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An efficient approach to 2,5-anhydro-glucitol-based 1′-homo-*N*-nucleoside mimetics

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ABSTRACT

This Letter describes an efficient synthesis of a range of 1′-homo-*N*-nucleoside mimetics with a series of 4-substituted 1,2,3-triazoles replacing the natural nucleobase. The synthesis of 6-*O*-monosulfated 1′-homo-*N*-nucleoside mimetic derivatives is also discussed.

Viral infections are a major cause of human disease and mortality; nearly one thousand different types of virus are known to infect humans, accounting for approximately 60% of all human infections.[1] It has been possible to control many viral infections, such as smallpox, poliomyelitis, and yellow fever, by safe and effective vaccines, but a plethora of viral diseases can neither be prevented nor treated by vaccination. There has been considerable interest in the design and preparation of novel nucleoside analogues as they form an important class of biologically active compounds.[2–4] The nucleoside inhibitors exert their biological effect mainly by targeting viral polymerases. These enzymes play an essential role in virus genome replication.[5,6] Many nucleosides have proven to be therapeutically useful agents for the treatment of viral infections.[2,7,8] A major concern, however, is inherent drug resistance[9] and toxicity[10] of the currently marketed inhibitors, therefore, making a compelling case for the search of new potent broad-spectrum anti-viral agents. We were, therefore, interested in exploring a convenient synthesis of compounds that would provide a library of novel 1′-homo-*N*-nucleoside mimetics that may target viral polymerases.

For the design and synthesis of novel nucleoside analogues (Fig. 1) as antiviral agents, much attention[7,11] has been focused on modifications of the sugar ring in nucleosides **1**. In 1′-homo-*N*-nucleosides **2**, the nucleobase and the sugar residues are separated by a carbon bridge.[12] The additional methylene group between the base and the anomeric center of the sugar makes these nucleosides more resistant to hydrolytic or enzymatic cleavage and also provides higher conformational flexibility.[12–14]

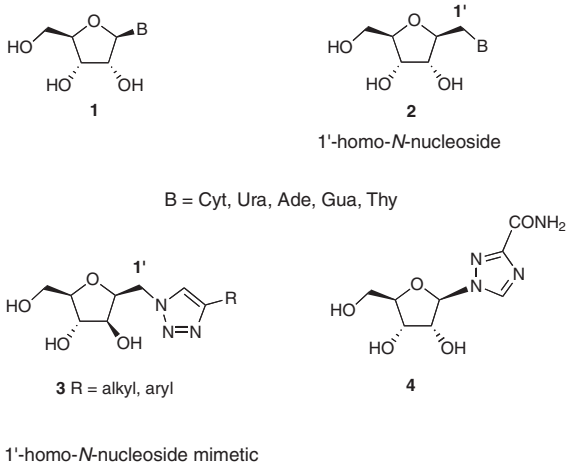

Figure 1. Nucleoside and nucleoside mimetic structures.

Syntheses of 1′-homo-*N*-nucleosides have been reported,[12] however, these methods have been utilized with varying degrees of success due to side-reactions. In 2003, Hanessian and co-workers reported an improved synthesis that involved nucleophilic ring-opening of 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-D-mannitol with purine and pyrimidine nucleophiles followed by *O*-heterocyclization to 1′-homo-*N*-nucleosides.[13]

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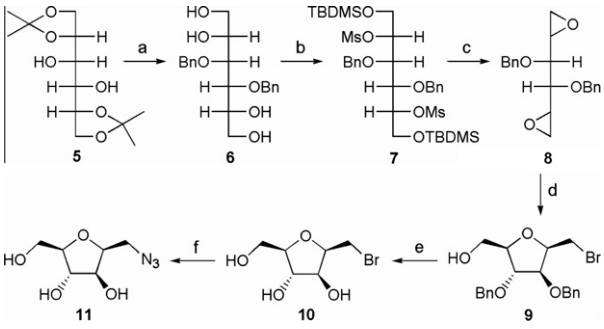
Herein we describe the synthesis of a series of triazole-containing 1′-homo-*N*-nucleoside mimetics (Fig. 1) based on the 2,5-anhydro-glucitol scaffold of general structure **3** utilizing azide–alkyne 'click' chemistry.[15] We chose a 2,5-anhydro-glucitol template, where the stereochemistry at C-3 (equivalent to C-2 of the ribose unit of the RNA nucleosides **1**) is reversed from the natural configuration. With the glucitol stereochemistry at C-3/C-4, introduction of modifications at these position should be simple, for example, through epoxide formation,[16] including inversion of the C-3 configuration to give the ribose-based mimetic. Our preference for the five-membered heterocycles, 1,2,3-triazoles, was based on a number of factors including their higher stability toward acidic and basic hydrolysis as well as harsh reductive/oxidative conditions.[15] It is also known that triazoles are capable of actively participating in hydrogen bonding, as well as dipole–dipole and π-stacking interactions.[17] Moreover, the apparent general antiviral activity of ribavirin (**4**), which is a 1,2,4-triazole-containing nucleoside,[18] provides a further validation for the preparation of 1′-homo-*N*-nucleoside mimetics bearing a triazole moiety. A ribavirin-based 1′-homo-*N*-nucleoside has also been reported, although to the best of our knowledge, no biological data has been published to date.[19]

Our initial study toward the preparation of 1′-homo-*N*-nucleoside mimetics **3** involved the synthesis of the 2,5-anhydro-glucitol derivative with a C-1 azide. The C-1 azide building block could then undergo a 1,3-dipolar cycloaddition with substituted alkynes possessing lipophilic, hydrophilic, acidic or basic functionalities. The synthesis of 1-azido-2,5-anhydro-glucitol is shown in Scheme 1.

The key intermediate 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-D-mannitol **8** was prepared from commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**5**), as described by Le Merrer et al.[20] Based on the work of Kuszmann in which brominated hexitols were prepared from protected 1,2:5,6-bisepoxides,[21] compound **8** was then treated with HBr in acetic acid to afford 1-bromo-2,5-anhydro-glucitol intermediate **9** (Scheme 1) through 2,5-*O*-heterocyclization. The high regioselectivity of the *O*-heterocyclization in favor of the *5-exo-tet* process[22,23] leads to ring closure at the more substituted atom of the second epoxide resulting in the facile formation of 2,5-anhydro-D-glucitol **9**. Thus, the intermediate 1-bromo-glucitol derivative **9** could be readily synthesized from the commercially available starting material **5** in 45% yield over seven steps. Successful de-*O*-benzylation was achieved by treatment of **9** with formic acid in the presence of Pd/C under a hydrogen gas atmosphere and resulted in the isolation of the desired deprotected 1-bromo derivative **10** in a satisfactory 87% yield. This was followed by nucleophilic displacement of the C-1 bromide by azide providing the key C-1 azide derivative **11** in 73% yield. Importantly, each step in Scheme 1 was optimized to obtain **11** from **5**, in a reaction sequence amenable to scale-up for generating a library of 1′-homo-*N*-nucleoside mimetics.



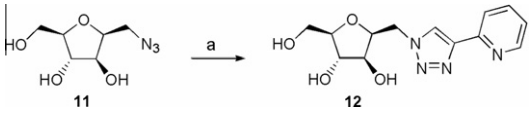
Scheme 1. Reagents and conditions: (a) (i) NaOH (50% aq soln), BnBr, nBu$_4$NI, THF, 50–60 °C, 12 h (90%); (ii) 70% AcOH, 55 °C, 1.5 h (88%; 79% over two steps); (b) (i) TBDMSCl, DMAP, imidazole, pyridine, 0 °C rt, 2 h, N_2; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min, N_2; (c) (i) HCl, MeOH, 0–20 °C, 2 h; (ii) KOH (20% aq soln) 0–20 °C, 3 h; (d) 33% w/v HBr in glacial AcOH, acetone, 0 °C, 30 min, N_2 (57% over five steps from **6**); (e) Pd/C, HCOOH, MeOH, H_2, rt, 2 h, (87%); (f) NaN_3, DMF:H_2O, 90–100 °C, 12 h, (73%).

Having established an efficient synthesis of the versatile building block **11**, we next examined the model copper-catalyzed 'click' reaction between unprotected azide **11** and the alkyne, 2-ethynylpyridine, in aqueous isopropanol (Scheme 2). The reaction went smoothly, however, purification of triazole derivative **12** proved problematic and the triazole product was isolated in 34% yield only, with some impurities still present.

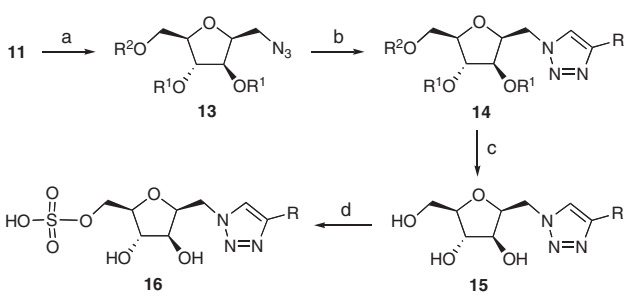
With compound **12**, aqueous work-up was not possible and even column purification was problematic. Therefore, acetylation of 1-azido derivative **11** was carried-out using standard acetylation conditions (Ac_2O, pyridine) to give pure acetylated derivative **13** in 90% yield (Scheme 3). The tri-*O*-acetylated C-1 azide **13** was then utilized as the starting material for 'click' chemistry with different alkynes to prepare a series of 18 differently substituted triazole derivatives **14a**–**r** (Table 1).

The triazole derivatives were obtained in excellent yields generally after purification. The only exception was the synthesis of compound **14l**, with the free amino group on the alkyne, which resulted in formation of a complex mixture. Subsequently, the 3,4,6-tri-*O*-acetylated triazole derivatives **14a**–**l** were deacetylated using 1 M sodium methoxide solution at room temperature. As indicated by TLC analysis, the reaction in each case was complete within 15 min and the final products **15a**–**l** (Table 1) were obtained in yields ranging from 71% to 89%.

It was found that the triazole derivatives with large hydrophobic substituents on the triazole ring (e.g., **15a** and **15b**) had limited aqueous solubility. It was anticipated that the introduction of a charged moiety at the primary C-6 hydroxy group on the carbohydrate residue would improve this solubility. Furthermore, it was thought that *O*-sulfation at C-6 would introduce an appropriate negative charge that would in part mimic the corresponding 6-*O*-phosphate group of nucleosides. Therefore, selective sulfation of the C-6 hydroxy group of the triazole derivatives was performed using sulfur trioxide–pyridine complex.[24] By way of example, compound **15a** was treated with two molar equivalents of sulfur trioxide–pyridine complex in anhydrous pyridine solution for 12 h

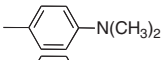
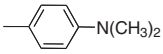
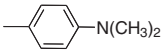
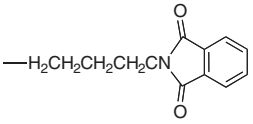
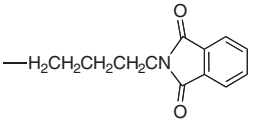
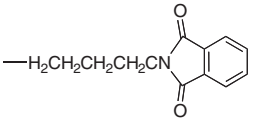
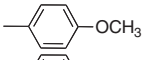
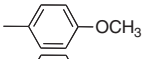
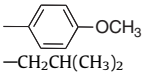
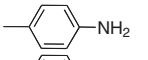
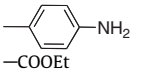
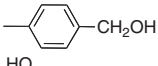


Scheme 2. Reagents and conditions: (a) 2-ethynylpyridine, $CuSO_4{\cdot}H_2O$, sodium ascorbate, iPrOH:H_2O, 40–50 °C, 1 h (34%).



Scheme 3. Reagents and conditions: (a) Ac_2O, pyridine, rt, 3 h, N_2 (90%); (b) alkyne, $CuSO_4{\cdot}H_2O$, sodium ascorbate, iPrOH:H_2O, 40–50 °C, 2 h; (c) NaOMe (1 M), MeOH, rt, 15 min; (d) SO_3·pyridine complex, pyridine, 0–4 °C, 16 h.

Table 1
1′-Homo-N-nucleoside mimetics and derivatives produced via Scheme 3

Product	R	R^1	R^1	R^2	Yield[a] (%)
14a		Ac	Ac	Ac	95
15a		H	H	H	72
16a		H	H	SO_3H	57
14b		Ac	Ac	Ac	91
15b		H	H	H	89
16b		H	H	SO_3H	33
14c		Ac	Ac	Ac	92
15c		H	H	H	74
16c		H	H	SO_3H	72
14d	$-CH_2CH(CH_3)_2$	Ac	Ac	Ac	93
15d	$-CH_2CH(CH_3)_2$	H	H	H	86
16d	$-CH_2CH(CH_3)_2$	H	H	SO_3H	27
14e	$-CH_2N(CH_2CH_3)_2$	Ac	Ac	Ac	91
15e	$-CH_2N(CH_2CH_3)_2$	H	H	H	82
16e	$-CH_2N(CH_2CH_3)_2$	H	H	SO_3H	46
14f		Ac	Ac	Ac	93
15f		H	H	H	88
16f		H	H	SO_3H	37
14g		Ac	Ac	Ac	92
15g		H	H	H	84
16g		H	H	SO_3H	44
14h	$-CH(OH)CH_2(CH_2)_3CH_3$	Ac	Ac	Ac	90
15h	$-CH(OH)CH_2(CH_2)_3CH_3$	H	H	H	86
16h	$-CH(OH)CH_2(CH_2)_3CH_3$	H	H	SO_3H	52
14i	$-CH(OH)CH_3$	Ac	Ac	Ac	94
15i	$-CH(OH)CH_3$	H	H	H	85
16i	$-CH(OH)CH_3$	H	H	SO_3H	42
14j	$-CH_2OAc$	Ac	Ac	Ac	92
15j	$-CH_2OAc$	H	H	H	71
14k	$-CH_2OCH_3$	Ac	Ac	Ac	90
15k	$-CH_2OCH_3$	H	H	H	72
14l		Ac	Ac	Ac	66[b]
15l		H	H	H	79
14m	$-COOEt$	Ac	Ac	Ac	91
14n	$-CH_2CH(COOCH_3)_2$	Ac	Ac	Ac	91
14o	$-COO^tBu$	Ac	Ac	Ac	91
14p		Ac	Ac	Ac	91
14q		Ac	Ac	Ac	91
14r	$-CH_2CH_2OH$	Ac	Ac	Ac	92

[a] Yield after purification by flash chromatography.
[b] Several components by TLC, other products not analyzed.

(Scheme 3). The reaction was then quenched, as the sulfation reaction was attempted on unprotected starting material, unlike literature procedures in which sulfation was performed on fully-protected nucleosides.[24] The 6-*O*-monosulfated derivative **16a** was obtained in 33% yield (or 57% yield based on recovered starting material **15a**) after purification by HPLC. The formation of the 6-*O*-sulfated 1′-homo-*N*-nucleoside derivative **16a** was confirmed by ^{1}H NMR spectroscopy. A multiplet at δ 4.11–4.17 was assigned to H-6 and H-6′ of **16a** and was shifted ~0.5 ppm downfield compared with H-6 and H-6′ of the starting material **15a**. The sulfation reaction was subsequently extended to other triazoles to generate a series of 6-*O*-sulfated 1′-homo-*N*-nucleoside derivatives **16a–i** (Table 1) containing a hydrophobic side chain on the triazole unit. The corrected yields (unoptimized), based on recovered starting material, ranged between 27% and 72%.

In conclusion, the synthesis of a library of 1′-homo-*N*-nucleoside mimetics with 4-substituted 1,2,3-triazoles that replace the natural nucleobase, from inexpensive starting materials, is described. These compounds may provide a new direction in novel antiviral inhibitor discovery and are now under biological investigation as potential inhibitors of a range of viruses.

Acknowledgments

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Supplementary data

Supplementary data (including full experimental details and data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.090.

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