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Practical synthesis of 1′-substituted Tubercidin C-nucleoside analogs

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ABSTRACT

Several 1′-substituted analogs of Tubercidin C-nucleosides were prepared using a highly convergent synthesis. Good to high diastereoselectivity was achieved using a variety of nucleophiles targeting the 1′-position. The source for this stereoselectivity is herein proposed. It is thought to be attributed to a temperature-dependent chelation of the incoming nucleophile to either the 2′- or 3′-benzyloxy ether of the ribose core.

Introduction

There are many C-nucleosides that exhibit antibacterial, antiviral, and antitumor properties, however only a few have been investigated for drug discovery.[1] Perhaps, this has been due to a lack of practical, stereo-controlled syntheses of C-nucleosides that take advantage of the convergent coupling similar to those available in the synthesis of N-nucleosides.[2]

Tubercidin **1** (7-deazaadenosine, Fig. 1) is an adenosine mimic that is highly cytotoxic, capable of interfering with numerous biological processes.[3] Compound **2**, the C-nucleoside analog of Tubercidin, has previously been synthesized by Klein and co-workers albeit in low yield.[4] It has a nearly equipotent cytotoxicity compared to **1**. Klein's approach entailed the coupling of the ribose lactol with pyrrolemagnesium bromide as a synthon that was used to eventually access 7,9-dideaza-4-aza-adenosine. However, this synthesis, not only suffers from a low yield, but also does not allow for an efficient access to various 1′-substitutions, a position that we have become interested in for biological evaluation.[5]

Chemistry

In recent years there has been an extensive variety of syntheses of compounds modeled on C-nucleosides.[6] Three approaches have been primarily used for the synthesis of C-nucleosides: (i) construction of the heterocycle on the preformed carbohydrate,[7] (ii) construction of a sugar moiety onto a preformed heterocycle unit,[8] and (iii) direct coupling of a preformed sugar moiety onto a preformed heterocyclic unit.[9]

We were particularly attracted to the last method as it was a convergent and synthetically practical strategy that we envisioned would allow access to 1′-substituted nucleosides. High β

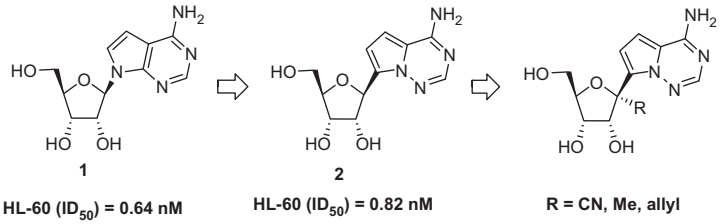

Figure 1. Tubercidin **1**, Tubercidin-C-nucleoside **2** and 1′-substituted C-nucleoside analogs.

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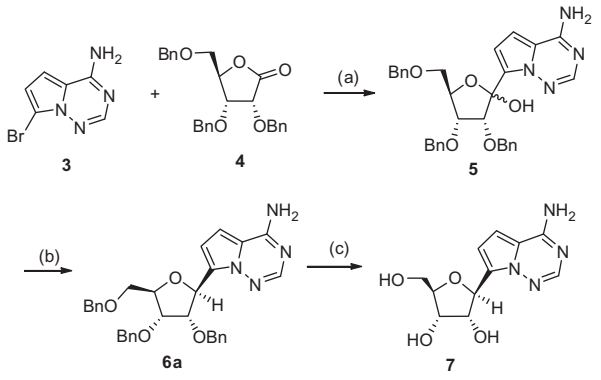


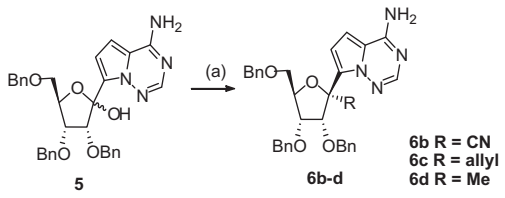
Scheme 1. Reagents and conditions: (a) Method A: (i) compound **3**, *n*-BuLi (3.3 equiv), THF, −78 °C (ii) add **4**; 3 h, 38% yield. Method B: (i) **3**, 1,1,4,4-tetramethyl-1,4-dichlorodisilylethylene (1.2 equiv), NaH (2.2 equiv, 60% mineral oil), *n*-BuLi (3.3 equiv), THF, −78 °C (ii) add **4**; 1 h, 60% yield. (b) $BF_3{\cdot}OEt_2$ (3 equiv), triethylsilane (4 equiv), CH_2Cl_2, 0 °C, 2 h. ratio of anomers 95:5 (β:α) yield 82%. (c) BCl_3, CH_2Cl_2, −78 °C, 2 h, 78% yield.

stereoselectivity has been achieved by the anomeric reduction of the hemiacetal intermediates prepared by coupling of aryl lithium reactants to protected ribonolactones.[10] Further, this synthetic approach allowed for practical iterations of either the heterobase or furanose moieties.

Our approach began with lithiating a fully elaborated bromo heterocycle **3** (Scheme 1).[11] Though compound **3** possess an acidic amino group and is sparingly soluble in THF, the addition of *n*-butyl lithium at −78 °C, afforded the lithio species, which was reacted with the tribenzyl lactone **4**.[12] This generated hemiacetal **5** as an inconsequential 3:1 anomeric mixture in a 38% yield. The absolute stereochemistry was not determined. Our yield was improved to 60% when the 6-amino group of **3** was transiently protected as its stabase adduct.[13,14] The resulting hemiacetal **5** was then subjected to anomeric reduction using triethylsilane and boron trifluoride etherate to furnish **6a**.[15] The reaction was carried out at 0 °C to yield a 95:5 ratio of β:α anomers (determined by ^{1}H NMR and NOESY spectroscopy). The benzyl protecting groups were then globally removed using boron trichloride to provide the corresponding nucleoside **7** in a 40% yield over three steps.

We surmised that compound **5** could serve as an intermediate for the synthesis of various 1′-substituted nucleosides (Scheme 2).[16]

The stereochemical outcome upon the addition of various nucleophiles to **5** was explored. Nitrile **6b** was obtained using trimethylsilyl cyanide in the presence of boron trifluoride etherate. Unlike the results obtained from the anomeric reductions with triethylsilane, when the reaction was carried out at 0 °C, no stereoselectivity was observed (Table 1). When the reaction was run at -78 °C, the anomeric stereoselectivity was 89:11 β:α in a 64%



Scheme 2. Reagents and conditions: **6b**: TMSCN (4 equiv), TMSOTf (3 equiv), CH_2Cl_2, 0 °C. ratio of anomers 57:43 (β:α), 76%. At −78 °C, 5 h, 89:11 (β:α), 65%. TMSCN (4 equiv), $BF_3{\cdot}OEt_2$ (3 equiv), CH_2Cl_2, −78 °C, 5 h, 85:15 (β:α), 58 %. **6c**: allyltrimethylsilane (3 equiv), $BF_3{\cdot}OEt_2$ (3 equiv), CH_2Cl_2, 0 °C 74:26 (β:α), 76%. At −78 °C, 87:13 (β:α), 70 %. **6d**: $AlMe_3$ (5 equiv), $BF_3{\cdot}OEt_2$ (4 equiv), CH_2Cl_2, 0 °C, 12 h, 45% 52:48 (β:α).

Table 1
Diastereoselective substitutions of hemiacetal **5** with various nucleophiles

Nucleophile	R	Lewis acid	Temp (°C)	Time (h)	Yield (%)	α/β
Triethylsilane	**H**	$BF_3{\cdot}OEt_2$	0	1	82	5/95
TMSCN	CN	TMSOTf	0	2	76	43/57
		TMSOTf	−78	3	65	15/85
		$BF_3{\cdot}OEt_2$	−78	3	58	11/89
AllylTMS	**Allyl**	$BF_3{\cdot}OEt_2$	−78	2	55	13/87
$AlMe_3$	Me	$BF_3{\cdot}OEt_2$	0	3	45	
AllylTMS	Allyl	$BF_3{\cdot}OEt_2$	0	2	75	26/74

yield. Nitrile **6b** was also synthesized using trimethylsilyl trifluoromethanesulfonate as a Lewis acid without any significant erosion of selectivity or yield. Allyl **6c**, was obtained using allyltrimethylsilane in the presence of boron trifluoride etherate. When the reaction was carried out at 0 °C, a ratio of 74:26 β:α in a 76% yield. At -78 °C, the ratio improved modestly to 87:13 β:α in a 70% yield.

When the reaction was carried out at 0 °C, the 1′-Me analog **6d** was obtained using trimethyl aluminum and boron trifluoride etherate in a 45% yield approximately a 1:1 mixture of the two anomers. However, when the reaction temperature was lowered to less than 5% conversion to product was observed.

Discussion

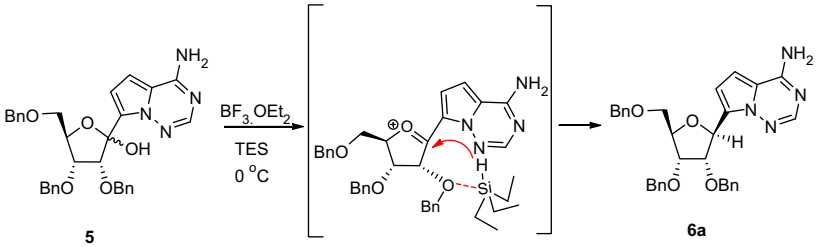
There is a considerable volume of work in the literature intended to explain and predict the stereochemical outcome of nucleophilic substitutions to various ribono-oxocarbenium ions.[18] Reissig and Schmitt proposed a Felkin–Ahn model for the selectivity seen in γ-lactols.[19] More recently, Guindon has proposed a S_N2 'exploded model' that puts forth evidence that substituents at C-2 are more likely to influence the stereochemical outcome of nucleophilic addition to the C-1 than substituent's at C-3.[20] Woerpel has provided empirical evidence to support the 'inside-attack' model. Specifically it is proposed addition takes place toward the concave face of the envelope conformation of the transition state oxocarbenium ion.[21]

In our work, it is clear there is a temperature effect influencing the stereoisomeric ratio when **5** is subjected to certain nucleophiles. To explain this, a mechanism for the stereoselective anomeric reduction is postulated below (Scheme 3).

In the case of **6a**, at 0 °C, the chelation of silicon to either a 2′- or 3′-benzyl ether oxygen electron lone pair results in delivery of the hydride anion from a favored face to furnish only the β anomer almost exclusively. For **6b**, at 0 °C, this proposed chelation is compromised, as evidenced by the loss of selectivity. At −78 °C, chelation of the silicon atom of the trimethylsilyl cyanide to the benzyloxy group is effective and the result is that the cyanation occurs stereoselectively (Fig. 2).This coordination results in the delivery of the cyanide from the α-face preferentially.

It should be noted that there is no evidence as to which of the 2′- or 3′-benzyl ethers are responsible for the observed stereoselectivity. Woerpel and co-workers has reported that the 3′-benzyloxy group plays a bigger role in determining the stereochemical outcome of substitution at the 1′-position, though he also found that 2′-benzyl ethers also contribute.[22]

Methyl addition to the 1′-position failed to proceed stereoselectively yielding a 1:1 β:α anomeric mixture. This might be due to weak chelation of aluminum to the 2′- or 3′-benzyl ether oxygen at 0 °C. At temperatures that gave good selectivity for the addition of cyano and allyl moieties (−78 °C), there was no appreciable product formed with trimethylaluminum. Carrying out the reaction at 0 °C in order to effect conversion resulted in a complete loss of stereoselectivity.



Scheme 3. Proposed mechanism for stereoselective dehydroxylation of **5**.

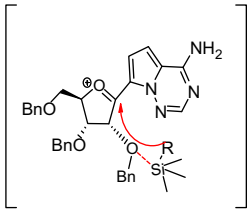


Figure 2. Proposed transition states for cyanation and allyation at −78 °C. O–Si coordination preferentially delivers nucleophile from α phase.

Conclusion

A practical and convergent synthetic approach to 1′-substituted C-nucleoside analogs is described. The hemiacetal obtained from the coupling of the bromo heterocycle **3** and ribonolactone **4**, is a versatile intermediate en route to this novel class of nucleosides. In the case of some nucleophiles, addition to the 1′-position, resulted in good stereoselectivity at reduced temperature. This protocol appears to be general and should allow for the facile access to various C-nucleosides.

Biological evaluation for this new class of nucleosides will be reported shortly.

Acknowledgments

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14. *Spectral data for compound* ***5***: 7-Bromo-pyrrolo[2,1-*f*]triazine-4-ylamine **3** (2.78 gm, 1.1 equiv 13.2 mmol, prepared according to WO2007056170) was suspended in anhydrous THF (70 mL). Under inert atmosphere, 1,1,4,4-tetramethyl-1,4-dichlorodisilyethylene (2.83 gm, 1,1 equiv, 13.2 mmol) was added along with sodium hydride (1.05 gm, 26.3 mmol, 2.2 equiv) was added and the mixture was stirred for 20 min at room temperature. The reaction was then cooled to −78 °C before *n*-BuLi (27.4 mL, 43.89 mmol, 1.6 M in Hexanes) slowly over 5 min. The reaction was allowed to stir for a further 15 min before lactone **4** (dissolved in 3 mL was added dropwise). When the reaction was complete by LCMS, the reaction was quenched with acetic acid. The reaction was concentrated in vacuo before being diluted in EtOAc and washing with water, saturated NH_4Cl and brine. The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The material was purified by silica chromatography (0–50% EtOAc/Hexanes) provided a 3:1 mixture of **5** anomers. 4.38 gm (y. 60%) of a white solid was obtained.
^{1}H NMR (400 MHz) $(CD_3)_2CO$ 8.00 (s, 1H), 7.30–7.47 (m, 15H), 7.20 (d, 8.4 Hz, 1H), 6.87 (d, 8.4 Hz, 1H), 5.40 (d, 8.2 Hz, 1H), 4.65–4.4.0 (m, 3 H), 3.65 (dd, 8.8, 4.3.2, 1 H), 3.55 (dd, 8.8, 4.3.2, 1 H) LC–MS (*m*/*z* 553.01, $M+H^+$).
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