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A short and highly stereoselective synthesis of α-(2-aminothiazolyl)-C-nucleosides

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Abstract—A short route to novel α-(2-aminothiazolyl)-C-nucleosides has been developed. The key step was the high diastereoselective reduction of the hemiacetal intermediates using L-Selectride, which afforded the corresponding *R*-diols in quantitative yields. These diols were converted, after C4–C1 ring closure and protecting groups cleavage, to their corresponding free α-C-nucleosides.

Numerous natural or synthetic nucleosides deriving from a five-membered-ring nucleobase and displaying a potent antitumoral or antiviral activity, have been described (Fig. 1).[1]

For example, thiazofurin is a C-nucleoside which has been shown to inhibit the inosine 5′-monophosphate dehydrogenase (IMPDH), thus inducing a shutdown of the guanine nucleotide synthesis and causing the apoptosis of human erythroleukemia cells.[2] Ribavirin, a synthetic nucleoside, in combination with the pegylated interferon-α (α-INF-peg), is the unique drug to date used for the treatment of hepatitis C virus (HCV) infection.[3] In the case of pyrazomycin, both α and β anomers were isolated from natural sources and formed the subject of extensive studies.[4]

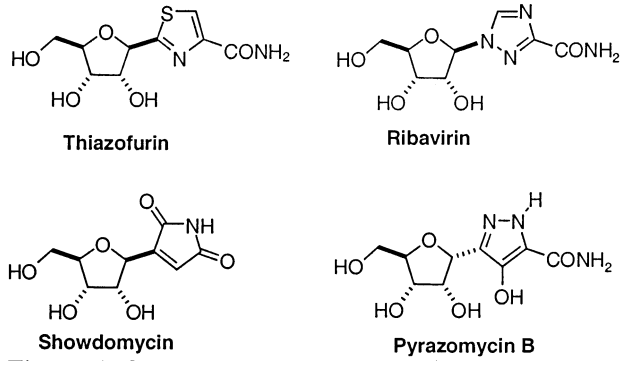

Figure 1. Structure of some potent five-membered ring nucleosides.

The chemical and enzymatic stability of the C–C glycosidic bond in the C-nucleosides is also an attractive feature of these analogues. Recently, several synthetic C-nucleosides have been studied not only as chemotherapeutic agents,[5] but also as building blocks in artificial DNA and RNA syntheses (antisens and anti-gene strategies)[6] and in a number of other biochemical applications.[7] Therefore, a large number of synthetic approaches to C-nucleosides have been recently reported.[8] However, synthetic difficulties in terms of yield and/or stereoselectivity have been frequently encountered.[9]

In a previous report, some of us described a useful stereocontrolled synthesis of imidazole and indole C-nucleosides.[10] This methodology, based on the neighboring protecting group effect and the assistance of NH-containing heterocycles to undergo an α-hydroxy elimination, cannot be applied to the synthesis of thiazole C-nucleosides. As an alternative route to this end, we describe herein a short, stereocontrolled and efficient strategy for the synthesis of α-(2-aminothiazolyl)-C-nucleosides starting from the ribonolactone **1**. The key step is the highly *syn*-diastereoselective reduction of the hydroxyketones (hydroxyketone in equi-

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Table 1.

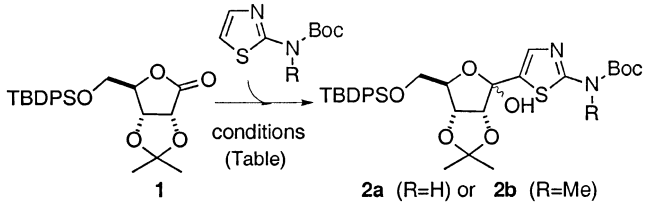
Entry	Substrate	Base (equiv.)	Temperature (°C)	Yield[a]
1	R = H	LDA (2 equiv.)	−78	**2a** (28)
2		– (4 equiv.)	−20	– (15)
3	R = H	BuLi (2 equiv.)	−78	**2a** (30)
4		–	−20	– (25)
5	R = H	*t*-BuLi (2 equiv.)	−78	**2a** (35)
6	R = Me	LDA (1.1 equiv.)	−78	**2b** (73)
7	–	– (2 equiv.)	–	– (68)

[a] Yield of pure isolated products.

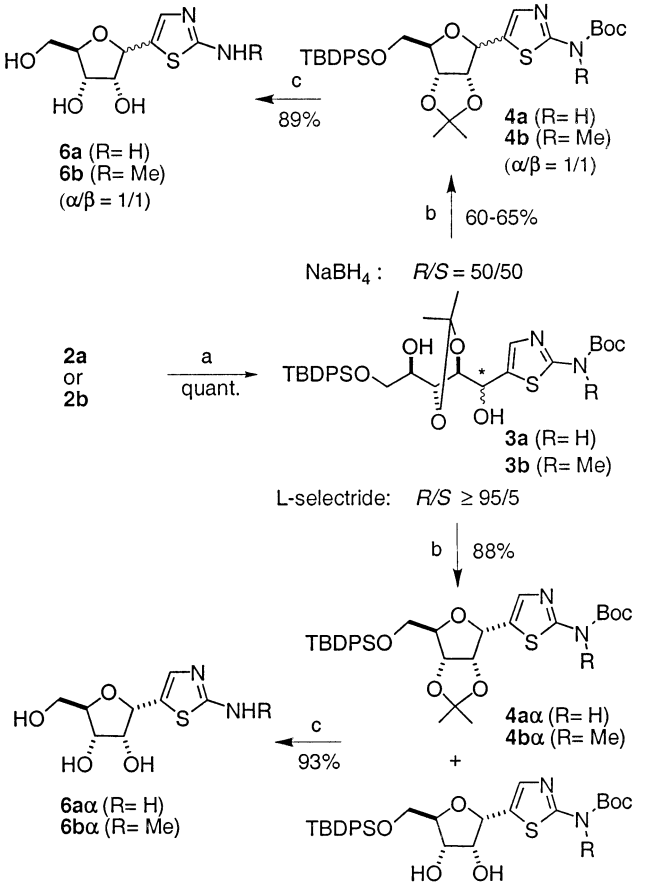
librium with the hemiacetal form, see Scheme 3) which afforded a quantitative yield of the corresponding diols. Then, sequential ring closure-protecting groups cleavage allowed access to C-nucleosides with a blocked α-configuration (Scheme 2).

Thus, the 2-Boc-aminothiazole was first subjected to the condensation conditions (LDA (2 equiv.)/THF/–78°C) with lactone **1**. Contrary to our previous experience with imidazole analogues, only low yields were obtained with 2-Boc-aminothiazole (Table 1). The hemiacetal **2a** was isolated as a mixture of two diastereoisomers (Scheme 1). Therefore, a careful optimization of base and base stoichiometry, temperature and time was carried out. Unfortunately, only a poor yield was obtained when using a large excess of LDA (entry 2), which results in part from the observed retro-aldol reaction. Moreover, we did not observe any improvement with other metalating agents such as BuLi or *t*-BuLi or when the reactions were performed at –20°C (Table 1). This result is probably due to a weakly reactive di-anion species, arising from a double deprotonation that occurs on NH-Boc and at C5-position, during the lithiation of the heterocycle. Indeed, the use of the *N*,*N*-Boc,*Me*-aminothiazole (R = Me)[11] under the same condensation conditions gave a satisfactory yield of the coupled product **2b** (entries 6 and 7).[12]

The next steps were then pursued with both hemiacetals **2a** and **2b** (Scheme 2).[13] Thus, the reduction of these hemiacetals using $NaBH_4$ in THF proceeded in quantitative yield to give an equimolar mixture of diastereomeric diols of **3a** and **3b** ($R/S = 1/1$), respectively. Moreover, treatment of compounds **2a** and **2b** with standard reducing agents such as $LiAlH_4$ or $LiBH_4$ had no significant impact on the diastereomeric ratio (data not shown). The absence of diastereofacial hydride differentiation is most probably due to the planar ketone-thiazole conformation which allowed hydride delivery on both faces. Hence, we envisioned the use of hindered reducing reagents to increase the facial selectivity of hydride addition. Interestingly, a high stereocontrol ($R/S \geq 95/5$)[14] was observed when the reduction of **2a**,**b** was performed with L-Selectride, a highly reactive and hindered reagent.[15] Indeed, only compounds **3a***R* and **3b***R* were isolated from this reaction. This result is, as expected, in accordance with the Felkin–Anh model (Scheme 3).[16]

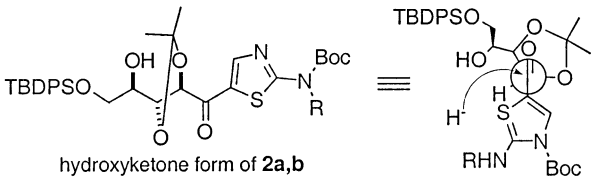


Scheme 1.



Scheme 2. *Reagents and conditions*: (a) reducing agent, THF (–30 to 0°C); (b) *p*TSA, toluene, 50°C; (c) H_2SO_4, dioxane.

Diols **3a**,**b***R* were then cyclized using *p*-toluenesulfonic acid. However, the C-nucleosides **4a**,**bα** were obtained together with their respective derivatives **5a**,**bα** as a result of isopropylidene cleavage (88% overall yield, ratio **4**/**5** = 3/1). The isopropylidene deprotection could be avoided by using a Dean–Stark water distillation during reaction. Otherwise, when the reaction was performed with an excess of *p*TSA, compounds **5a**,**bα** were only isolated. It should be mentioned that when the diols **3a**,**b***R* were cyclized using the standard DEAD/PPh_3 treatment, their respective protected C-nucleoside **4a**,**bα** were obtained in rather low yields together with other non-identified side products as attested by TLC analysis.



Scheme 3. Felkin–Anh model for the reduction step.

Acidic treatment of both **4aα**, **5aα** and **4bα**, **5bα** afforded the free α-C-nucleosides **6aα** and **6bα**, respectively (93%). Importantly, epimerization of the *C*1′-stereocenter in **4** and/or **5** was not observed after acidic (*p*-TSA or H_2SO_4) treatment.[15] In the same way, the 1/1 diastereomeric mixtures of diols **3a**,**b** (*R*/*S*) resulting from $NaBH_4$ reduction of **2a**,**b** were converted to their respective free C-nucleosides **6a**,**b**, isolated as an equimolar mixture of α and β anomers.

In summary, we have described a short, stereoselective and efficient synthesis of α-(2-aminothiazolyl)-C-nucleosides. The sequential cyclization–cleavage could be performed in one-pot and high yield, making the methodology quite attractive. This process also tolerates other sensitive functional groups and allows conventional post-synthetic modifications. Further investigations aimed at the synthesis of the β anomers following a chelation-based stereocontrolled process from the same intermediates, are in progress and will be reported in due course.

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11. The *N*,*N*-Boc,*Me*-aminothiazole was obtained in quantitative yield from Boc-aminothiazole (NaH, DMF, MeI). We failed to prepare the di-Boc protected aminothiazole by using standard conditions (low yields). However, when the *N*,*N*-*Benzyl*,Boc-aminothiazole was used in the condensation step with lactone **1**, the hemiacetal adduct was obtained in low yield, due to the observed side products resulting from the alkylation at the benzylic position (-$\underline{CH_2}$Ph).
12. **2a** (major diastereomer): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 9H, ^{t}Bu), 1.33 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.61 (s, 9H, Boc), 2.82 (br s, 1H, OH), 3.72–3.95 (m, 3H, H4′, 2H5′), 4.64 (t, J=5.8 Hz, H3′), 4.96 (d, 1H, J=5.5 Hz, H2′), 7.31–7.52 (m, 6H, H–Ar), 7.60–7.80 (m, 4H, H–Ar), 8.41 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.37, 26.10, 26.81, 26.92, 27.09, 28.31, 64.79, 72.80, 77.08, 81.16, 83.28, 111.34, 127.69, 127.83, 127.92, 128.05, 129.86, 130.10, 130.21, 133.08, 133.18, 135.52, 135.67, 146.22, 152.28, 166.20. MS (ESI$^+$) m/z=627 (MH^+). R_f= 0.70 (hexane/AcOEt: 50/50).
2b (major diastereomer): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 9H, ^{t}Bu), 1.34 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.60 (s, 9H, Boc), 2.90 (br s, 1H, OH), 3.60 (s, 3H, CH_3), 3.60–3.80 (m, 3H, H4′, 2H5′), 4.58 (t, 1H, J=5.8 Hz,

H3′), 4.96 (d, 1H, $J=5.7$ Hz, H2′), 7.25–7.45 (m, 6H, H–Ar), 7.53–7.50 (m, 4H, H–Ar), 8.45 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.04, 25.86, 26.59, 26.88, 27.89, 33.99, 64.55, 72.58, 76.20, 81.01, 86.18, 111.07, 127.51, 127.74, 129.53, 130.10, 130.15, 131.58, 132.80, 135.37, 135.86, 145.08, 146.65, 152.60, 166.30. MS (ESI$^+$) $m/z=$ 641 (MH^+). $R_f=0.15$ (hexane/AcOEt: 80/20). Mp = 63–64°C.

13. Spectral data of selected compounds:
(**3a***R*): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05 (s, 9H, ^{t}Bu), 1.33 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.56 (s, 9H, Boc), 3.65–4.00 (m, 4H, H3′, H4′, 2H5′), 4.29 (dd, 1H, $J=2.5$ and 7.5 Hz, H2′), 5.10 (d, 1H, $J=2$ Hz, H1′), 7.33 (s, 1H, H-thiazole), 7.35–7.45 (m, 6H, H–Ar), 7.61–7.71 (m, 4H, H–Ar). (**3a***S*) ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.08 (s, 9H, ^{t}Bu), 1.28 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.56 (s, 9H, Boc), 3.65–4.00 (m, 4H, H3′, H4′, 2H5′), 4.08 (t, 1H, $J=7.4$ Hz, H2′), 4.87 (d, 1H, $J=7.6$ Hz, H1′), 7.33 (s, 1H, H-thiazole), 7.35–7.45 (m, 6H, H–Ar), 7.61–7.71 (m, 4H, H–Ar). ^{13}C NMR (**3a** *R*/*S*) (50 MHz, $CDCl_3$) δ 19.28, 26.85, 27.00, 27.14, 28.33, 65.21, 65.33, 67.15, 70.18, 73.26, 75.93, 79.31, 82.57, 83.47, 109.84, 109.92, 127.84, 129.94, 131.37, 131.67, 132.74, 132.84, 132.93, 134.18, 134.41, 135.57, 152.91, 162.06. MS (**3a** *R*/*S*) (ESI$^+$) $m/z=629$ (MH^+). R_f (**3a** *R*/*S*) = 0.42 (hexane/AcOEt = 50/50).
(**3b***R*): ^{1}H NMR (200 MHz, $CDCl_3$–CD_3OD) δ 1.00 (s, 9H, ^{t}Bu), 1.26 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.50 (s, 9H, Boc), 3.44 (s, 3H, CH_3), 3.60–3.95 (m, 4H, H3′, H4′, 2H5′), 4.20 (dd, 1H, $J=3.0$ and 7.5 Hz, H2′), 5.10 (br s, 1H, H1′), 7.35–7.50 (m, 7H, H–Ar), 7.55–7.75 (m, 4H, H–Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.64, 27.23, 27.44, 27.52, 28.64, 34.37, 65.46, 67.81, 73.55, 76.26, 77.43, 83.18, 110.26, 128.21, 128.26, 130.31, 133.09, 133.30, 133.67, 135.07, 135.91, 135.97, 162.35. MS (ESI$^+$) $m/z=643$ (MH^+). $R_f=0.22$ (hexane/AcOEt = 70/30).
(**3b***S*): ^{1}H NMR (200 MHz, $CDCl_3$–CD_3OD) δ 0.99 (s, 9H, ^{t}Bu), 1.19 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.48 (s, 9H, Boc), 3.42 (s, 3H, CH_3), 3.60–3.80 (m, 4H, H3′, H4′, 2H5′), 4.00 (t, 1H, $J=7.1$ Hz, H2′), 4.78 (d, 1H, $J=7.3$ Hz, H1′), 7.25–7.45 (m, 7H, H–Ar), 7.50–7.70 (m, 4H, H–Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.69, 27.29, 28.64, 34.42, 65.71, 70.50, 73.65, 79.65, 83.85, 110.20, 128.21, 128.26, 130.34, 133.27, 133.36, 133.59, 135.78, 135.96, 135.99, 153.42, 162.60. MS (ESI$^+$) $m/z=643$ (MH^+). $R_f=0.25$ (hexane/AcOEt = 70/30).
(**4b**α): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.07 (s, 9H, ^{t}Bu), 1.26 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.57 (s, 9H, Boc), 3.51 (s, 3H, CH_3), 3.81 (m, 2H, 2H5′), 4.11 (m, 2H, H3′, H4′), 4.34 (dd, 1H, $J=6.7$ and 3.3 Hz, H2′), 6.04 (d, 1H, $J=3.3$ Hz, H1′), 7.25–7.45 (m, 6H, H–Ar), 7.49 (s, 1H, H–thiazole), 7.60–7.70 (m, 4H, H–Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.28, 19.37, 26.93, 27.77, 28.30, 34.10, 64.37, 64.82, 72.81, 73.36, 75.81, 81.76, 110.65, 127.91, 129.97, 133.06, 135.63, 137.93, 154.02, 163.20. MS (ESI$^+$) $m/z=625$ (MH^+). $R_f=0.26$ (hexane/AcOEt = 70/30).
14. The *R* and *S* configurations of diols were determined on the basis of the anomeric stereochemistry of their cyclized products (Cosy–Noesy experiments). The *R*/*S* ratio was obtained by both ^{1}H NMR and HPLC analyses.
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