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A short and efficient synthesis of 2′-deoxybenzo- and pyridoimidazole *C*-nucleosides

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Abstract—A short route to a series of 2′-deoxy-*C*-nucleosides featuring substituted nucleobases has been developed. The key step is the formation of the cyclized products following Mukaiyama's type amide coupling and a simple dehydration, starting from readily accessible synthons. The epimerization of the C1′-stereogenic center was avoided under mild and controlled conditions.

C-Nucleosides are important targets in organic synthesis due to their potential value as therapeutic agents and biochemical probes. They have been also found in a number of natural and synthetic products (such as thiazofurin, showdomycin, pyrazomycin, etc...) with potent antiviral or antitumor activities.[1] Recently, several synthetic *C*-nucleosides have been studied as chemotherapeutic agents,[1,2] as potential universal bases,[3] or as building blocks in artificial DNA and RNA syntheses[4] for the control of gene expression. Their properties were also investigated in a number of other biochemical applications.[5] Another attractive feature of *C*-nucleosides arises from the presence of the C–C glycosidic bond which confers to these analogs a greater resistance towards chemical and enzymatic hydrolysis than to the *N*-nucleosides. Therefore, a large number of synthetic approaches to *C*-ribofuranosyl nucleosides have recently been explored.[6] However, less attention has been focused on their 2′-deoxy analogs.[7] One of the most well known strategy is the conversion of the *C*-nucleosides to their 2′-deoxy derivatives by using the radical 2′-deoxygenation process (Barton–McCombie reaction) which, however, requires additional steps and, thus, decreases the overall yield.[8] The standard nucleophilic substitution of an appropriate halogenated sugar has also been largely used but was in some cases low yielding.[9]

In the continuation of our studies aimed at overcoming the chemical limitations of triple helix formation by using modified synthetic oligonucleotides,[10] we report herein a short synthesis (three key steps) of 2′-deoxy-*C*-nucleosides **6** featuring a heterocyclic nucleobase, starting from the readily accessible *O*-Tol protected 2′-deoxyribonic acid **3** with a given α or β anomeric configuration (Scheme 1). These three steps consist into (i) a Mukaiyama's type coupling between 2′-deoxyribonic acid **3** and *ortho*-aryl disubstituted diamines (**a**–**d**) to give the conjugates **4** followed by sequential (ii) acid catalyzed ring-closure, and (iii) *O*-Tol deprotection to afford the target 2′-deoxybenzimidazole or pyridoimidazole *C*-nucleosides **6**.

The starting known 2′-deoxyribonic acids **3**α and **3**β were best obtained in two steps from the *O*-Tol protected α-chlorosugar **1** by using TMSCN and BF_3Et_2O as catalyst (Scheme 1), followed by the hydrolysis of the resulting cyano-derivative **2**α and **2**β, respectively (∼90% overall yields). The cyano-derivative **2** was obtained as a mixture of α/β diastereomers (α/β molar ratio = 1/3) which were easily separated by standard silica gel column chromatography. It should be noted that, when we performed the Cl/CN substitution as

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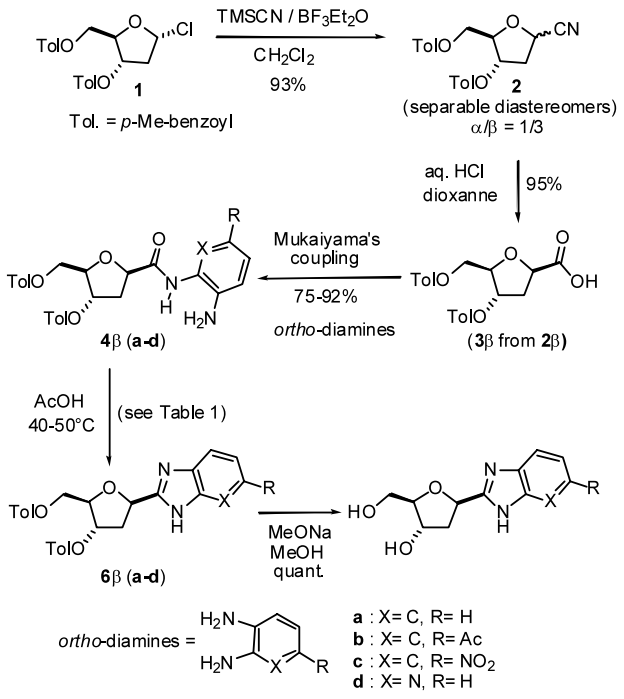


Scheme 1. Synthetic strategy to the 2′-deoxy-*C*-nucleosides **6**β.

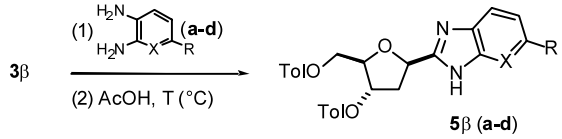
described in literature, i.e. by using NaCN in different solvents[11] or Et_2AlCN in toluene,[12] we isolated **2** in much lower yields (below 45%) and with a non-controlled α/β anomeric ratio. These lower yields were due in part to the observed 3′- and 5′-toluoyl cleavage side reaction.

The coupling of **3**β with the *ortho*-diamines (**a**–**d**) using Mukaiyama's reagent (chloromethylpyridinium iodide)[13] in CH_2Cl_2 afforded the corresponding β-conjugates **4a**–**d**β in good yields (75–92%). These compounds, apart from the pyridine analog **4d**β (vide infra), were then cleanly cyclized by simple heating in AcOH, yielding the protected 2′-deoxy-*C*-nucleoside derivatives **5**β (Table 1, entries 1, 3 and 5), providing however that the temperature was kept at 40–45°C. Indeed, epimerization at the C1′-stereocenter occurred when this reaction was performed in AcOH at 95–110°C (see Table 1, entries 2 and 4).[14] This epimerization likely took place before or during cyclization. That it did not occur from the cyclized **5**β anomer (β→α) is strongly supported by the fact that no epimerization was observed when the pure β-anomers (and also the α-anomers) of **5a** or **5b** were heated in AcOH, the starting materials remaining unchanged (although partial degradation was detected). These results are further in line with our recent findings in the *ribo*-series with similar analogs[15] and outline that the epimerization process in *C*-nucleosides is highly dependent on the nature of the aglycone part.[9,16] In the case of the pyridine analog **4d**β, the cyclization was very slow at 40°C and gave a much lower yield of the desired compound **5d**β (25%), the starting material being mainly recovered (70%). Conversion of **4d**β into **5d**β could be improved by heating at higher temperature (110°C) or by using additional TFA (1 equiv.) (entries 7 and 8, respectively). However, partial epimerization was observed under these more drastic conditions.

The *O*-Tol-deprotection in **5a**–**d**β was performed with MeONa in MeOH and afforded quantitatively the target 2′-deoxy-*C*-nucleosides **6a**–**d**β (Scheme 1).

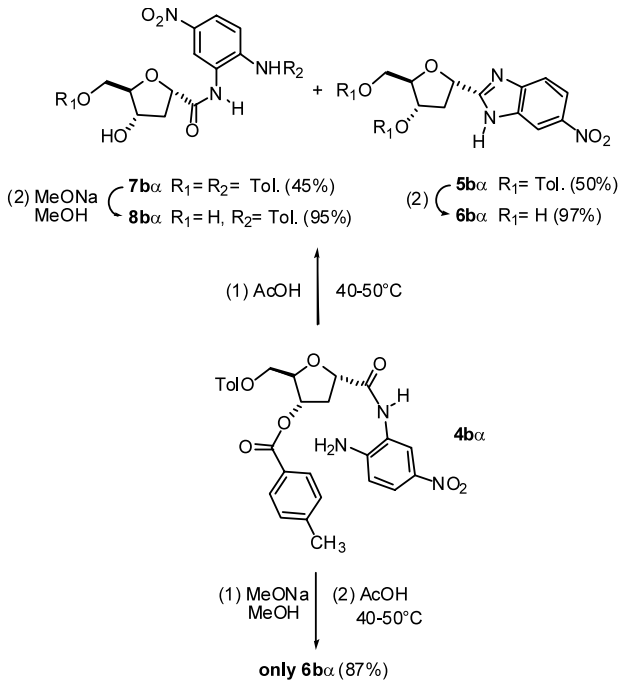
Where the synthesis sequence of the α anomers was concerned, the coupling step **3(a**–**d)**α→**4(a**–**d)**α was accomplished in a similar way as for their β-analogs, but required longer reaction times. Unfortunately, when **4(a**–**d)**α were heated in AcOH, we observed not only the cyclization into their respective derivatives **5(a**–**d)**α but also the intramolecular migration of the toluoyl group from the 3′-position to the *ortho*-NH_2 group. Indeed, and as shown in Scheme 2, derivative **7b**α together with the expected **5b**α (in nearly 1/1 molar ratio) was also isolated after AcOH treatment of **4b**α.

Table 1.



Entry	*ortho*-Diamine (**a**–**d**)	Temp. (°C)/time (h)		**5** α/β ratio (yield %)[a]
1	X = C, R = Ac	40/12	**5a**	0/100 (60)
2	X = C, R = Ac	95/16	**5a**	50/50 (67)
3	X = C, R = NO_2	40/12	**5b**	0/100 (61)
4	X = C, R = NO_2	95/16	**5b**	45/55 (50)
5	X = C, R = H	45/12	**5c**	0/100 (55)
6	X = N, R = H	45/12	**5d**	0/100 (25)
7	X = N, R = H	110/14	**5d**	25/75 (51)
8	X = N, R = H	50/14	**5d**	20/80 (50)[b]

[a] Yield of pure isolated products (two steps).
[b] 1 equiv. of TFA was added.



Scheme 2. Cyclization/cleavage steps of the α-derivative.

The *O*- to *N*-toluoyl migration, which was not detected in the case of the β-anomers, is probably favored in the case of α-analogs by (i) the close *cis* relationship of the two substituents in 1′- and 3′-positions (Scheme 2) and (ii) the known 2′-*endo* sugar conformation of such analogs. This migration could be avoided by reversing the order of the reaction sequence. Thus, when **4b**α was first submitted to MeONa/MeOH (deprotection) and then cyclized (AcOH/40°C), the desired product **6b**α was obtained in 87% overall yield.[17]

In summary, we have developed a short and straightforward synthesis of 2′-deoxy-*C*-nucleosides featuring substituted benzimidazole or pyridoimidazole nucleobases. The sequential coupling–cyclization steps could be performed in one operation making the methodology more attractive. Furthermore, this process is highly flexible and does not require the protection of the heterocycles and allows conventional post-synthetic transformations.

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4aβ. Mp (AcOEt) = 181–183°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.28–2.41 (m, 1H), 2.37 (s, 3H), 2.43 (s, 3H), 2.46 (s, 3H), 2.71–2.86 (m, 1H), 4.20 (br s, 2H), 4.55–4.93 (m, 4H), 5.56 (d, 1H, J = 4.8 Hz), 6.75 (d, 1H, J = 8.5 Hz), 7.18 (d, 2H, J = 7.9 Hz), 7.28 (d, 2H, J = 7.9 Hz), 7.71 (dd, 1H, J = 2.0 and 8.5 Hz), 7.85 (d, 1H, J = 2.0 Hz), 7.87 (d, 2H, J = 8.2 Hz), 7.95 (d, 2H, J = 8.2 Hz), 8.53 (br s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.98, 26.43, 37.83, 64.60, 76.24, 79.38, 85.48, 116.83, 126.93, 128.58, 129.62, 129.68, 130.07, 144.83, 145.92, 166.6, 167.40, 170.47. MS (ES^+) m/z = 531 $[M+H]^+$, 553 $[M+Na]^+$, 569 $[M+K]^+$.

5aβ. Mp (AcOEt) = 129–131°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.30–2.50 (m, 1H), 2.37 (s, 3H), 2.44 (s, 3H), 2.68 (s, 3H), 2.88 (ddd, 1H, J = 13.9, 5.8 and 1.2 Hz), 4.59–4.88 (m, 3H), 5.59 (m, 1H), 5.68 (dd, 1H, J = 10.1 and 5.8 Hz), 7.18 (d, 2H, J = 7.9 Hz), 7.29 (d, 2H, J = 7.9 Hz), 7.61 (d, 1H, J = 8.5 Hz), 7.74 (br s, 1H), 7.91 (d, 2H, J = 8.5 Hz), 7.93 (dd, 1H, J = 8.5 and 1.6 Hz), 7.97 (d, 2H, J = 8.5 Hz), 8.24 (d, 1H, J = 1.6 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.69, 21.75, 26.79, 39.15, 64.77, 76.03, 76.15, 84.58, 114.69, 123.29, 126.35, 126.47, 128.28, 129.68, 132.34, 144.54, 144.70, 156.79, 166.25, 167.84. MS (IC) m/z = 513 $[M+H]^+$, 119 $[Tol]^+$.

6aβ. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.30 (m, 1H), 2.43 (m, 1H), 2.65 (s, 3H), 3.65–3.85 (2dd, 2H, J = 12.0, 6.4 and 4.8 Hz), 4.05 (m, 1H), 4.32 (m, 1H), 5.40 (dd, 1H, J = 9.6 and 6.3 Hz), 7.59 (d, 1H, J = 8.5 Hz), 7.92 (dd, 1H, J = 8.5 and 1.5 Hz), 8.21 (d, 1H, J = 1.5 Hz). ^{13}C NMR (CD_3OD, 50 MHz) δ 26.95, 42.81, 63.63, 73.68, 75.90, 89.80, 128.85, 130.12, 130.23, 130.65, 133.44, 159.87. MS (ES^-) m/z = 275 $[M-H]^-$.

4aα. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.24 (s, 3H), 2.26 (s, 3H), 2.34 (s, 3H), 2.73 (m, 2H), 4.29 (br s, 2H), 4.44 (d, 2H, J = 4.6 Hz), 4.70 (t, 1H, J = 4.6 Hz), 4.83 (t, 1H, J = 6.5 Hz), 5.49 (br t, 1H, J = 3.2 Hz), 6.67 (d, 1H, J = 8.5 Hz), 6.99 (d, 2H, J = 7.9 Hz), 7.19 (d, 2H, J = 7.9 Hz), 7.60–7.67 (m, 2H), 7.74 (d, 2H, J = 8.2 Hz), 7.88 (d, 2H, J = 8.2 Hz), 8.40 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.97, 22.02, 26.27, 36.09, 64.40, 76.04, 79.28, 84.54, 116.98, 122.07, 126.58, 126.94, 127.01, 128.59, 129.51, 129.64, 130.03, 130.11, 144.56, 144.78, 146.22, 166.21, 166.55, 171.69. MS (ES^+) m/z = 531 $[M+H]^+$, 553 $[M+Na]^+$.

5aα. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.25 (s, 3H), 2.41 (s, 3H), 2.67 (s, 3H), 2.92–3.13 (m, 2H), 4.53 (m, 2H), 4.68 (m, 1H), 5.62 (m, 1H), 5.76 (dd, 1H, J = 6.5 and 4.4 Hz), 6.83 (d, 2H, J = 8.0 Hz), 7.10–7.40 (m, 6H), 7.59 (d, 1H, J = 8.5 Hz), 7.95 (d, 2H, J = 8.0 Hz), 8.23 (br s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.84, 21.97, 27.07, 37.96, 64.43, 76.10, 76.35, 83.93, 123.38, 126.50, 126.91, 129.22, 129.58, 129.63, 129.95, 132.39, 144.58, 144.54, 158.69, 166.06, 166.73. MS (ES^+) m/z = 513 $[M+H]^+$.

6aα. ^{1}H NMR (CD_3OD, 200 MHz) δ (ppm) 2.30 (ddd, 1H, J = 12.9, 5.0 and 4.7 Hz), 2.64 (s, 3H), 2.78 (ddd, 1H, J = 13.3, 6.3 and 8.2 Hz), 3.65 (dd, 1H, J = 12.6 and 5.0 Hz), 3.74 (dd, 1H, J = 12.6 and 4.0 Hz), 4.17 (dd, 1H, J = 8.3 and 4.1 Hz), 4.42 (m, 1H), 5.40 (dd, 1H, J = 8.3 and 5.0 Hz), 7.57 (d, 1H, J = 8.6 Hz), 7.90 (dd, 1H, J = 8.6 and 1.5 Hz), 8.19 (d, 1H, J = 1.5 Hz). ^{13}C NMR (CD_3OD, 50 MHz) δ 27.28, 42.12, 63.83, 73.93, 76.22, 89.32, 124.52, 133.53. MS (ES^-) m/z = 275 $[M-H]^-$.

4bα. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.33 (s, 3H), 2.41 (s, 3H), 2.80 (dd, 2H, J = 5.7 and 2.9 Hz), 4.49 (d, 2H, J = 4.6 Hz), 4.68 (br s, 2H), 4.77 (t, 1H, J = 4.6 Hz), 4.89 (t, 1H, J = 6.0 Hz), 5.54 (t, 1H, J = 2.9 Hz), 6.70 (d, 1H, J = 8.8 Hz), 7.10 (d, 2H, J = 8.1 Hz), 7.25 (d, 2H, J = 8.2 Hz), 7.80 (d, 2H, J = 8.2 Hz), 7.92 (dd, 1H, J = 8.8 and 2.5 Hz), 7.93 (d, 2H, J = 8.1 Hz), 8.01 (d, 1H, J = 2.4 Hz), 8.56 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 21.64; 21.69, 35.81, 64.27, 75.93, 79.03, 84.19, 111.71, 115.31, 120.77, 120.86, 122.87, 124.00, 126.22, 126.66, 129.75, 129.78, 138.11, 144.59, 144.86, 148.48, 166.36, 166.78, 172.39.

6bα. ^{1}H NMR (CD_3OD, 200 MHz) δ (ppm) 2.34 (ddd, 1H, J = 13.0, 8.2 and 4.9 Hz), 2.80 (ddd, 1H, J = 13.0, 6.2 and 5.0 Hz), 3.70 (m, 2H), 4.19 (dd, 1H, J = 4.3 and 8.2 Hz), 4.38–4.50 (m, 1H), 5.42 (dd, 1H, J = 5.0 and 8.2 Hz), 7.60 (d, 1H, J = 8.9 Hz), 8.11 (dd, 1H, J = 8.9 and 2.0 Hz), 8.39 (d, 1H, J = 2.0 Hz). ^{13}C NMR (50 MHz, CD_3OD) δ (ppm) 42.08, 63.86, 73.95, 76.23, 89.84, 119.52, 145.18, 163.52. MS (ES^-) m/z 278 $[M-H]^-$.

8bα. ^{1}H NMR (DMSO-d_6, 200 MHz) δ (ppm) 2.08 (dt, 1H, J = 12.8 and 3.1 Hz), 2.40 (ddd, 1H, J = 13.3, 9.0 and 5.4 Hz), 2.50 (s, 3H), 3.70 (s, 2H), 3.90–3.99 (m, 1H), 4.05–4.17 (m, 1H), 4.54 (dd, 1H, J = 9.0 and 3.7 Hz), 4.96 (br s, 1H), 6.39 (t, 1H, J = 6.8 Hz), 7.01 (d, 1H, J = 8.9 Hz), 7.17 (d, 1H, J = 8.9 Hz), 7.45 (m, 1H), 7.86 (dd, 1H, J = 2.8 and 8.9 Hz), 7.94 (d, 1H, J = 5.7 Hz), 9.20 (d, 1H, J = 3.0 Hz), 10.08 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 26.70, 41.11, 62.08, 71.26, 78.31, 88.84, 107.92, 112.38, 112.90, 117.12, 120.07, 131.24, 131.32, 139.46, 139.71, 141.63, 146.64, 154.23, 171.85, 171.92. MS (ES^-) m/z = 414 $[M-H]^-$.