Tetrahedron Letters, Vol. 34, No. 31, pp. 4997-5000, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

# A Novel Synthesis of "Double Headed" Nucleosides via "Reversed" Nucleosides

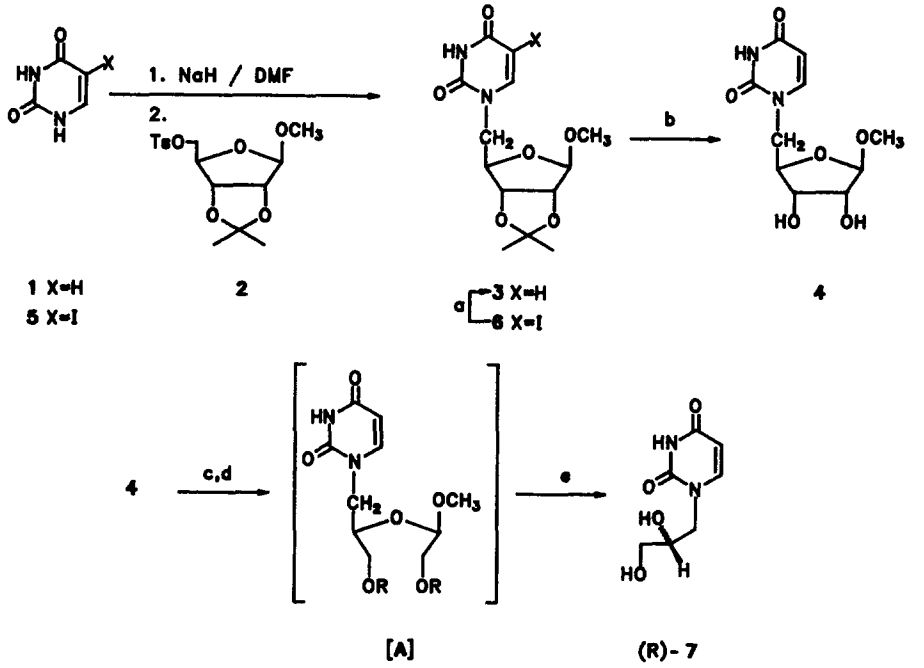
Biserka Kašnar*, Vinko Škarić, Branimir Klaić, and Mladen Žinić
Department of Organic Chemistry and Biochemistry, "Rudjer Bošković" Institute, 41000 Zagreb, P.O.B. 1016, Croatia

**Abstract:** The "double headed" nucleosides **10**, **11** and **13** bearing pyrimidine or purine bases attached on C-1 and C-5 positions of single ribose unit have been synthesized following a new synthetic strategy. The strategy rests on the introduction of the first nucleo base at C-5 position of the ribose unit giving "reversed" nucleoside and the subsequent attachment of the second base at C-1 position of the ribose, by classical glycosylation reaction. This order of the base attachments gave much better yields on the "double headed" nucleosides then previously known C-1 then C-5 order of attachments.

The intensive effort to find effective therapeutic agents with anti-tumor[1] and anti-viral[2] activity has reaffirmed the need for the efficient synthetic methods giving diverse modified nucleosides or their analogues. Among the enormous number of modified nucleosides and analogues synthesized to date, there are only a few publications reporting on the synthesis of the so called "double headed"[3-5] or "abbreviated"[6] nucleosides bearing two heterocyclic bases on C-1 and C-5 positions of the single deoxyribose unit. This type of modified nucleoside brings the potential of simultaneous binding and recognizing two complementary bases by Watson-Crick type base pairing.[7] Alternatively, "double headed" nucleosides may interact with a polynucleotide using one base for pairing and the second one as the intercalator stabilizing the base pair. A few "double headed" nucleosides of deoxyribose series have been prepared by (a) direct alkylation of the sodium salt of adenine or thymine with 5'-deoxy-5'-*O*-tosyl nucleosides in 10-30% yield[3,4] and (b) by the ring closure of 5'-*N*-(ß-methoxy-α-methylacryloyl)ureidodeoxynucleoside intermediate in the basic conditions giving 5'-deoxy-5'-(thymin-1-yl)thymidine in 78% yield (30% yield from thymidine).[6] In the more versatile method (a) the yields on "double headed" nucleosides are generally low and depend strongly whether purine or pyrimidine base is present at C-1' position in the starting nucleoside. Thus, with 5'-*O*-tosyl thymidine derivative the adenine was introduced at C-5' position in 31% yield, while with 2'-deoxyadenosine the 5'-(adenin-9-yl)-2',5'-dideoxyadenosine was obtained in only 14% yield as the multiple hydrate.[3] Apparently, the presence of the first base at C-1 position of the sugar makes the introduction of the second base at C-5 difficult, presumably due to steric reasons. We reasoned that the better synthetic strategy leading to "double headed" nucleosides may be the one based on the reversed order of the base attachments.

In this respect, the synthesis would start with appropriate "reversed" nucleoside derivative bearing the base at C-5 position[8] of the monosaccharide moiety. In the subsequent step the second base at C-1 position could be introduced by the classical glycosylation reaction.

In the present work we report on the synthesis of some "double headed" nucleosides in the ribo-series and demonstrate that reversed order of base introduction results with considerable yield improvements. Following the reported procedure for preparation of some "reversed" nucleosides,[9] the sodium salt of uracil **1** was reacted with suitably protected ribofuranoside **2** giving **3** (m.p. 187-188 °C; $[\alpha]_D^{22}$+67° , c 0.5 $CHCl_3$) in only 37% yield (Scheme 1). After the isopropylidene removal by using acidic ion-exchange resin in methanol, the "reversed" nucleoside **4** (foam; $[\alpha]_D^{21}$ +36°, c 1 MeOH)

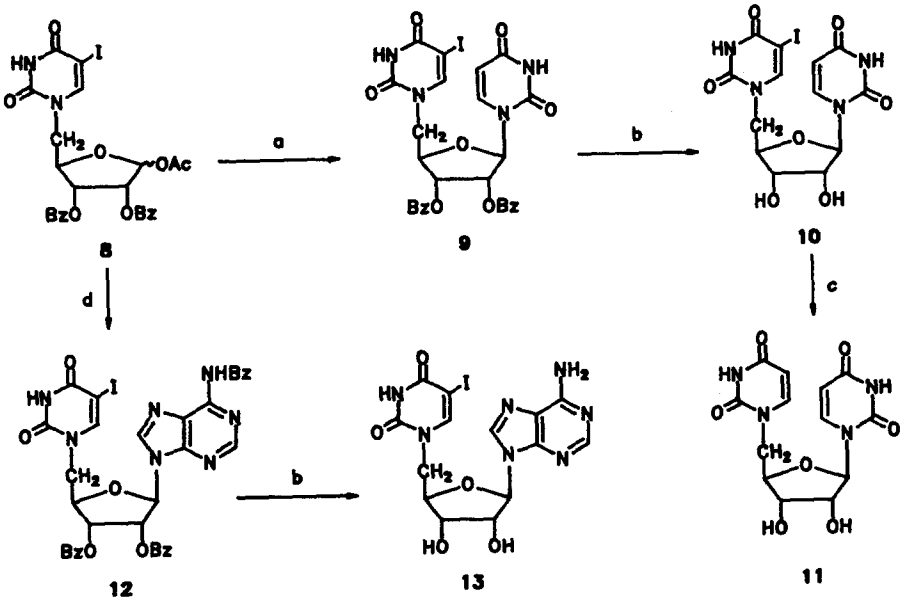



a) $H_2$, Pd/C, MeOH, 1 eq NaOH; b) Amberlite IR-120 ($H^+$)/MeOH; c) $NaIO_4$; d) $NaBH_4$; d) HOAc pH=2.

**SCHEME 1**

was obtained in 89% yield. The variations of the reaction conditions in the preparation of **3** (react. time, temperature, stoichiometry of reactants) failed to improve the yield. We have found, however, that the reaction of the sodium salt of 5-iodouracil **5** and **2** gave approximately 20% better yield on the "reversed" 5-iodouracil-1-yl nucleoside **6** (58% yield; m.p. 182-183 °C; $[\alpha]_D^{25}$ +16°, c 2 $CHCl_3$ ). The subsequent catalytic hydrogenolysis gave **3** in 82% yield. For both **3** and **4** the β-configuration at ribose C-1 position was assigned since their H's-1 appeared as singlets (**3** $\delta$ 5.00 ppm and **4** $\delta$ 4.83 ppm) in their $^1H$ NMR spectra. The attachment of the base at N-1' position for **3** also follows from

its $^1$H NMR spectrum since H-5' appeared as doublet of doublets due to the vicinal H-5'-H-6'




a) 1. uracil/BSA/$CH_3CN$; 2. TMSOTf; b) $NH_3$/MeOH; c) $H_2$, Pd/C/MeOH/1eq NaOH
d) 1. NHBz-adenine/BSA/$CH_3CN$, 2. TMSOTf.

**SCHEME 2**

coupling ($J_{5',6'}$=7.9 Hz) and the additional long-range H-5'-NH-3' coupling ($J_{5',NH-3'}$=2.0 Hz). The attachment of the base at N-1' position in **4** was also confirmed by its conversion to (*R*)-**7** *via* the unstable intermediate **[A]**. **[A]** whose structure was assigned from $^1$H and $^{13}$C spectra was quantitatively converted to (*R*)-**7** (80% yield from **4**, m.p. 142-143 °C; $[\alpha]_D^{25}$ +74° , c 1 EtOH), which was recently prepared by an independent route.[10] The synthesis of two novel "double headed" ribonucleosides **10** and **13** is shown in Scheme 2. The "reversed" nucleoside **6** was converted in **8** (63% yield; foam) which is suitably protected and functionalized for the glycosylation at C-1 by the Vorbrüggen method.[11,12] The reaction of trimethylsilylated uracil and **8** in the presence of trimethylsylyl trifluoromethanesulfonate gave after flash chromatography ($CH_2Cl_2$-MeOH 30:1) **9** (89% yield; m.p. 291-293 °C; $[\alpha]_D^{22}$ +2° , c 1 DMF). The removal of the benzoyl protecting groups gave 5"-iodo derivative **10** (92% yield, m.p. 190-192 °C; $[\alpha]_D^{22}$ +86° , c 1 DMF) which by catalytic hydrogenolysis afforded the "double headed" **11** (93% yield, m.p. 240 °C dec.; $[\alpha]_D^{24}$ +41°, c 0.5 DMF). Using the same set of reactions the protected derivative of the mixed "double headed" nucleoside **12** (56% yield, m.p. 188-190°C; $[\alpha]_D^{22}$ +47°, c 1 MeOH) has been prepared and

deprotected giving **13** (96% yield, m.p. 244-245 °C; $[\alpha]_D^{22}$ +128°, c 1 DMF). The assignments of the protons in **10** and **13** were based on the 2D NMR COSY spectra, and the stereochemistry about the anomeric centers was established from NOESY spectra. In the NOESY experiment with **10** a strong NOE interactions between H-6 ($\delta$ 7.77 ppm) and H-2' ($\delta$ 4.26 ppm), and H-2' and H-3' ($\delta$ 3.91 ppm) together with a smaller NOE effect between H-6 and H-6" ($\delta$ 8.07 ppm) support the ß-anomeric configuration. The NOESY spectrum of **13** showed strong NOE interactions between H-8 ($\delta$ 8.37 ppm) and H-6" ($\delta$ 8.06 ppm), H-1' ($\delta$ 5.92 ppm) and OH-2' ($\delta$ 5.51 ppm), H-1' and OH-3' ($\delta$ 5.39 ppm); and a smaller NOE effect between H-8 and H-1'. The observed NOE effects in **13** are in favour of its ß-anomeric configuration.

**Acknowledgements:** The funding from Ministry of Science of Croatia is gratefully acknowledged.

REFERENCES AND NOTES

1. Isono, K. *J. Antibiot.*, **1988**,41,1711.
2. a) MacCoss, M; Robins, M. J., *Chemistry of Antitumor Agents*; Wilman, D. E. V. Ed.; Blackie and Son: U.K. 1990; p. 261. b) Robins, R. K.; Kini, D. *ibid.* p. 299.
3. Fecher, R.; Boswell, K. H.; Wittick, J. J.; Shen, T. Y. *J. Am. Chem. Soc.* **1970**, 92, 1400.
4. Fecher, R.; Boswell, K. H.; Wittick, J. J.; Shen, T. Y., *Carbohyd. Res*, **1970**, 13, 105.
5. Utkina, E. A.; Mel'nik, S. Ya.; Preobrazhenskaya, M. N.; Suvorov, N. N., *Zh. Org. Khim.* **1975**, 11, 194.
6. Logue, M. W.; Leonard, N. J. *J. Am. Chem. Soc.* **1972**, 94, 2842.
7. Shen, T. Y., *Angew. Chem., Int. Ed. Engl.* **1970**, 9, 678.
8. The reversed nucleosides were denoted as 5-substituted derivatives of ribofuranose, while double headed nucleosides were denoted as 5'-substituted derivatives of nucleosides.
9. Holý. A., *Collect. Czech. Chem. Commu.* **1975**, 40, 187.
10. Škarić. V.; Kašnar, B., *Croat. Chem. Acta* **1985**, 58, 583.
11. Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B., *Chem. Ber.* **1981**, 114, 1234.
12. Vorbrüggen, H; Höfle, G., *Chem. Ber.* **1981**, 114, 1256.

(Received in UK 8 June 1993)