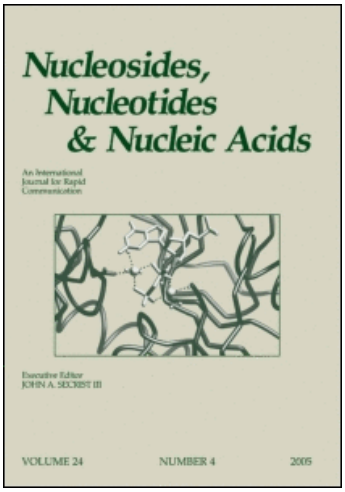

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Synthesis of Certain Heterodimers Expected as HIV-1 Reverse Transcriptase Inhibitors

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ABSTRACT

Expected for the ability to inhibit HIV replication, we report the synthesis of two heterodimers of the general formula: [2NRTI]-*C5*-GLY-SUCCINYL-*Npiperazinyl*-[NNRTI] (**18, 19**) containing both a Nucleoside Reverse Transcriptase Inhibitor (**10, 11**) and a Non-Nucleoside Reverse Transcriptase Inhibitor (**8**) [Trovirdine Analogue belonging of the phenethyl thiazolyl thiourea class] connected through the "succinyl-glycine" spontaneously cleavable linker.

Firstly, we have realized the synthesis of the NRTI (**10, 11**). The required key intermediary is: 5′-O-acetyl, 5-iodo-2′,3′-dideoxy-uridine **5** and it was obtained in four steps starting from the uridine **1**[1] (Fig. 1). A strategy based on the Sonogashira reaction[2] gave the 5-propynyl derivative **6**. The catalytic hydrogenation of **6** gave the 5-propyl derivative **7**. The following deprotection of the "THP" group of these

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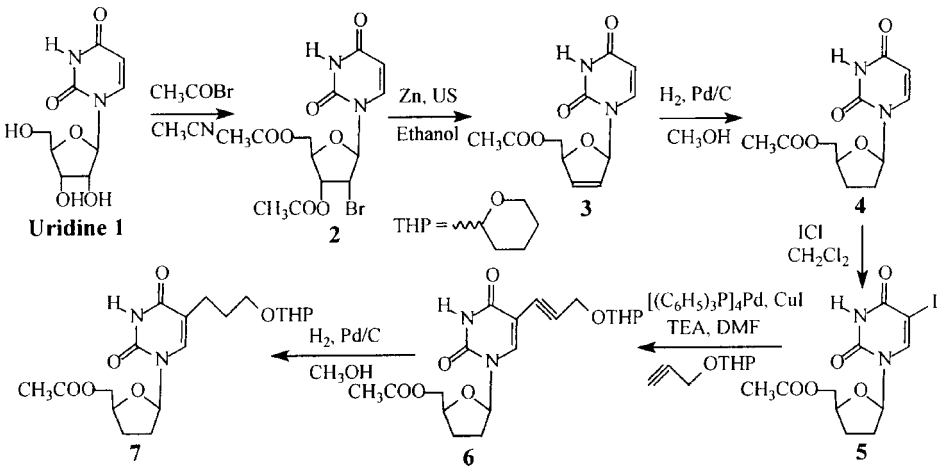

Figure 1. Synthesis of 5′-O-acetyl-5-[tetrahydro-2-(2-propynyloxy)-2H-pyranyl]-d_2U (6) and 5′-O-acetyl-5-[tetrahydro-2-(2-propyloxy)-2H-pyranyl]-d_2U (7).

compounds **6** and **7** by an acid medium (CF_3COOH) afforded the NRTI **10** and the NRTI **11** (Fig. 3).

At the same time, for the NNRTI, we have chosen a Trovirdine Analogue **8**,[3] which was coupled with succinic anhydride (Fig. 2).

Secondly, we have realized the synthesis of the heterodimers **18** and **19** (Fig. 3). Therefore, for the conjugation of the two different inhibitors (NRTI and NNRTI) we have used the "succinyl-glycine"as a spontaneously cleavable linker.

The antiviral activity of these compounds **18** and **19** is tested in present on the systems HIV-1 LAI/CEM-SS and HIV-1 IIIB/MT4 at I.N.S.E.R.M. U74 of Strasbourg.

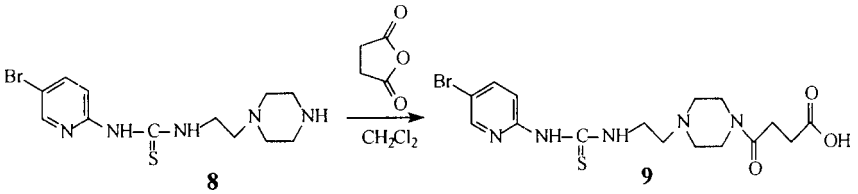

Figure 2.

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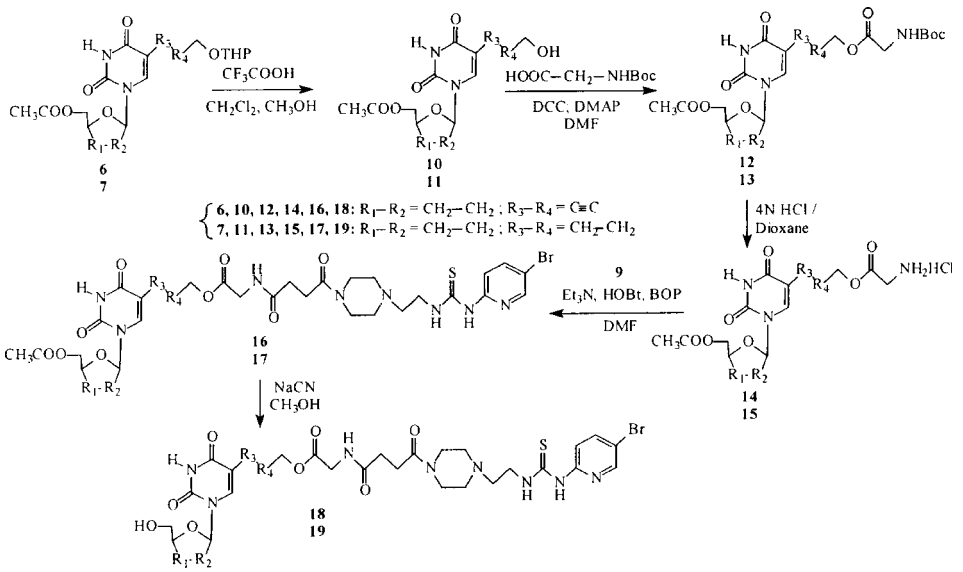

Figure 3. Synthesis of the heterodimers: [NRTI]-*C5*-GLY-SUCCINYL-*Npiperazinyl*-[NNRTI] (18 and 19).

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REFERENCES

1. Shiragami, H.; Irie, Y.; Shirae, H.; Yokozeki, K.; Yasuda, N. J. Org. Chem. **1998**, *53*, 5173.
2. Graham, D.; Parkinson, J.A.; Brown, T. J. Chem. Soc. Perkin. Trans. 1 **1998**, 1131–1138.
3. Vig, R.; Coll. Bioorg. Med. Chem. **1998**, *6*, 1789–1797.

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