

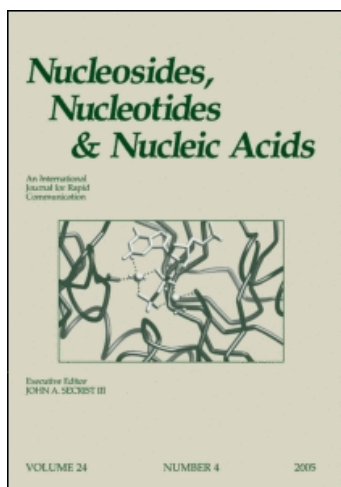
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Synthesis of Certain Heterodimers Expected as HIV-1 Reverse Transcriptase Inhibitors

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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-*N*piperazinyl-[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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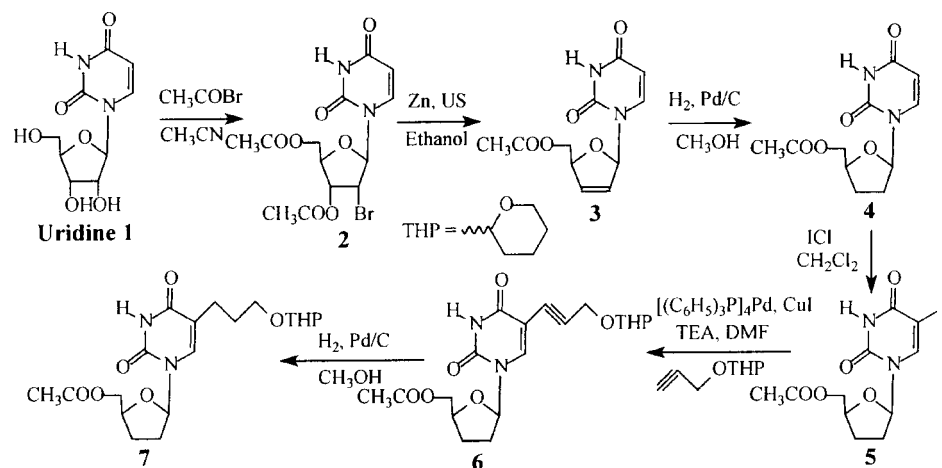


Figure 1. Synthesis of 5'-O-acetyl-5-[tetrahydro-2-(2-propynyloxy)-2H-pyran]-d₂U (6) and 5'-O-acetyl-5-[tetrahydro-2-(2-propyloxy)-2H-pyran]-d₂U (7).

compounds **6** and **7** by an acid medium (CF₃COOH) afforded the NRTI **10** and the NRTI **11** (Fig. 3).

At the same time, for the NNRTI, we have chosen a Troviridine 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.

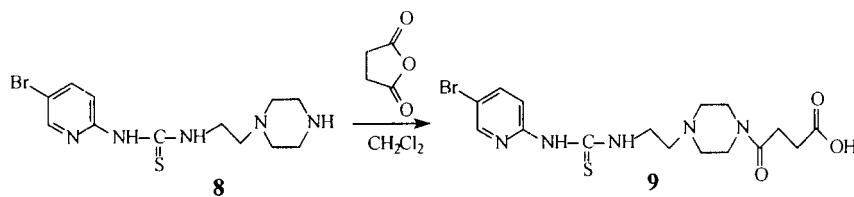


Figure 2.

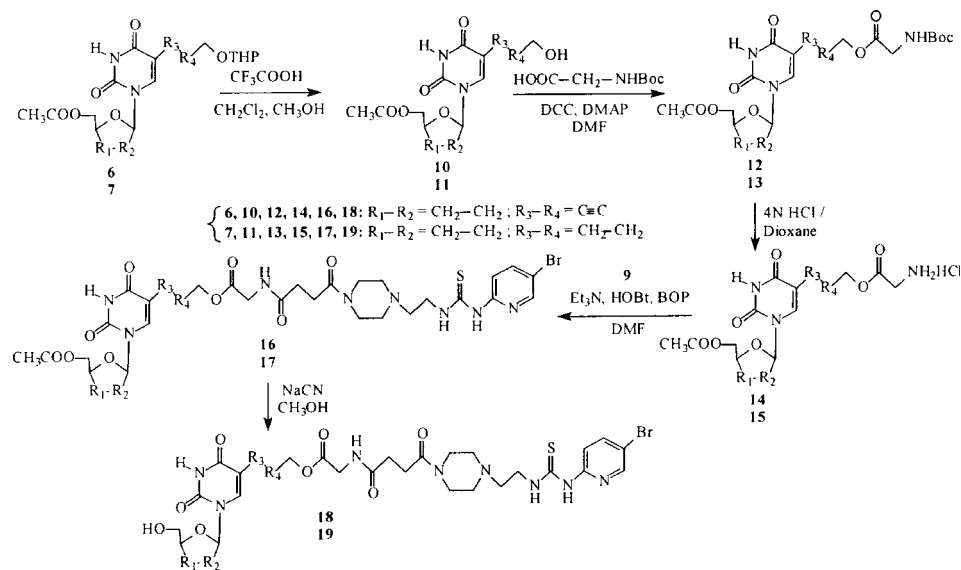


Figure 3. Synthesis of the heterodimers: [NRTI]-C5-GLY-SUCCINYL-Npiperazinyl-[NNRTI] (18 and 19).

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