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A Novel Route to 3'-Azido-3'-deoxythymidine

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The preparation of 3'-azido-3'-deoxythymidine was first described by J.P. Horwitz et al.[1] in 1964. To date, 3'-azido-3'-deoxythymidine, AZT or zidovudine, remains the only drug approved for the treatment of AIDS. We wish to report herein a novel synthesis of zidovudine involving a readily available starting material, a cyclic sulfite intermediate, and a photochemical deoxygenation. Starting from 1,2-O-isopropylidene-α-D-xylofuranose **1**, 3,5-di-O-pivaloyl-α-D-xylofuranose **2** was synthesized in an 80% yield. The cyclic sulfite **3** was synthesized according to the method of C.H. Gagnieu et al.[2] in a 94% yield. The cyclic sulfite was next fused with 2,4-bis-O-trimethylsilylthymine yielding nucleoside **4** in a 62% yield. Recently, Gagnieu[3] has reported on the successful synthesis of nucloesides via cyclic sulfites. Treatment of **4** with sodium methoxide lead to 1-(β-D-xylofuranosyl)thymine which was converted to **5** 1-(3'-5'-O-isopropylidene-β-D-xylofuranosyl)thymine in a 44% yield after recrystallization. Compound **5** was derivatized and deoxygenated to **6** according to the method of Saito[4] in a 65% overall yield. Hydrolysis of **6** lead to 1-(2'-deoxy-β-D-threo-pentofuranosyl)thymine **7**. From **7**, zidovudine was obtained in 4 additional steps by known procedures.

1) J.P. Horwitz et al., J. Org. Chem., 29, 2076-2078 (1964)
2) A. Guiller, C.H. Gagnieu, H. Pacheco, J. Carb. Chem., 5, 153-160 (1986)
3) C.H. Gagnieu, A. Guiller, H. Pacheco, Carb. Res., 180, 233-242 (1988)
4) J. Saito et al., JACS, 108, 3115-3117 (1986)

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The mechanism of action of Ro 31-8959 on HIV infected cells.

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Ro 31-8959 is a potent inhibitor of both HIV-1 and HIV-2 proteases (Ki 0.12 and <0.1nM respectively). At nanomolar concentrations it inhibits the production of both HIV-1 encoded p24 and HIV-1 induced syncytia in cultures of CD4+ cell lines. Experiments with both acutely and chronically infected cells demonstrate the antiviral activity of Ro 31-8959, and show that the compound inhibits breakdown of the viral protein precursor p55 and prevents virion maturation.