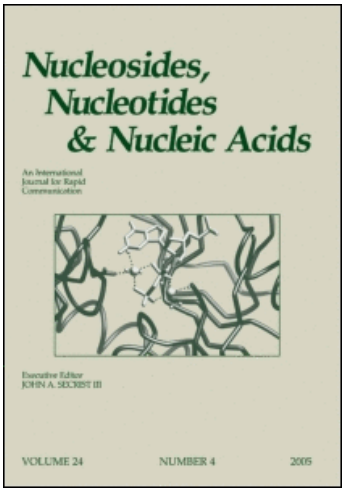

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A General Synthetic Method for 2',3'-Dideoxynucleosldes: Total Synthetic Approach

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A GENERAL SYNTHETIC METHOD FOR 2',3'-DIDEOXYNUCLEOSIDES: TOTAL SYNTHETIC APPROACH

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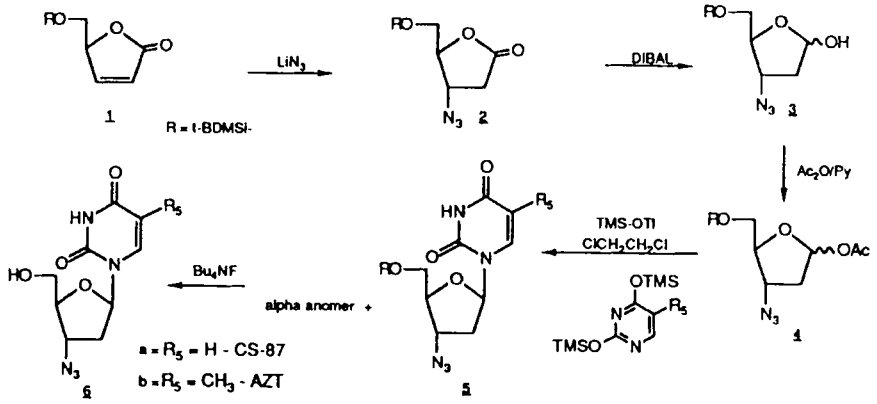
Abstract: A general method for the total synthesis of 2',3'-dideoxynucleosides is described.

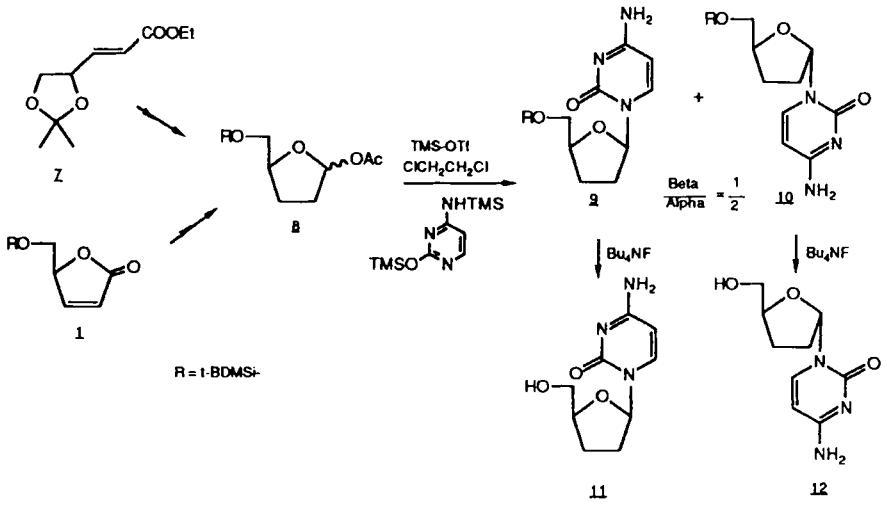
Nucleosides that lack 3'-hydroxy group are being studied extensively as potential chemotherapeutic agents for acquired immune deficiency syndrome (AIDS). Among them, a number of 2',3'-dideoxynucleosides have been shown to be effective inhibitors of human immunodeficiency virus type-1(HIV-1),[1,2] the causative agent of AIDS. In 1987, 3'-azido-3'-deoxythymidine (AZT) was approved by the FDA for the treatment of AIDS and AIDS-related complex. Other 2',3'-dideoxynucleosides that are currently undergoing clinical trials are 2',3'-dideoxycytidine (DDC) and 2',3'-dideoxyadenosine (DDA)[3]. Although the exact mechanism by which these nucleosides inhibit HIV is not fully understood, they are generally believed to inhibit, as their triphosphates, the viral specific enzyme, reverse transcriptase. Furthermore, these nucleosides cause a premature chain termination of the growing viral DNA chain[4].

We have synthesized a number of pyrimidine- and purine-2',3'-dideoxynucleosides for the study of structure-activity relationships as anti-HIV agents. From these studies we have identified 3'-azido-2',3'-dideoxyuridine(CS-87), 3'-azido-2',3'-dideoxy-5-ethyluridine (CS-85), 3'-azido-2',3'-dideoxy-5-methylcytidine(CS-92), and 2',3'-dideoxy-N^6-methyladenosine (CS-176) as potent antiviral agents against HIV-1 in vitro[5,6]. As part of our continuing efforts to study the structure-activity relationships, we have developed a total synthetic approach for the preparation of new anti-HIV agents that are not easily accessible through modification of preformed nucleosides.

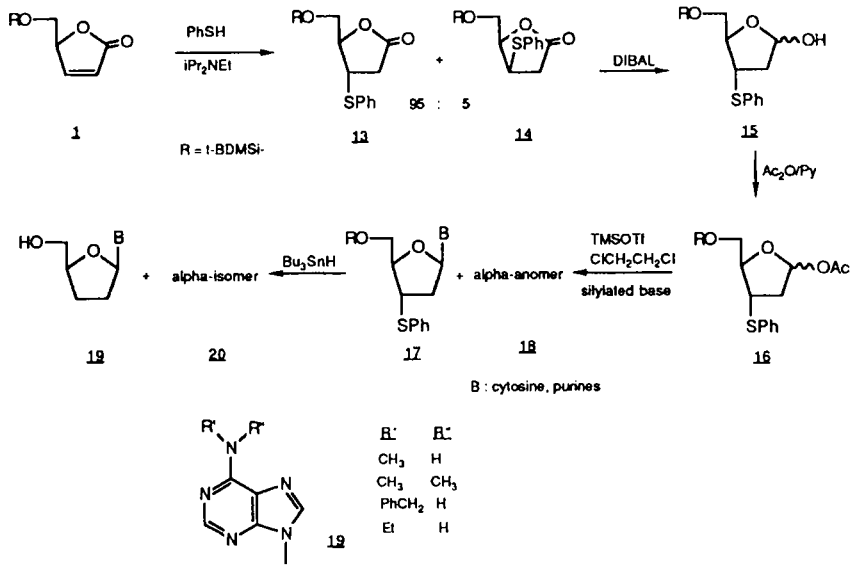
Recently, we have utilized the lactone 1, prepared from D-mannitol, for the synthesis of AZT and CS-87 (SCHEME 1)[7]. This lactone appeared to be an ideal key intermediate for the



SCHEME 1



SCHEME 2



SCHEME 3

synthesis of 2',3'-dideoxynucleosides, thus eliminating the use of expensive nucleosides and sugar derivatives as starting materials. In this communication we report a general synthesis of 2',3'-dideoxypyrimidine and purine nucleosides from key carbohydrate intermediates. Attempted condensation of dideoxyribose derivative 8 with silylated cytosine in the presence of trimethylsilyl triflate[8] gave more alpha anomer than the beta anomer (SCHEME 2). Therefore, the procedure was modified as shown in SCHEME 3. The lactone 1 was reacted with thiophenol in a Michael-type addition[9], to obtain the desired intermediate 13 as the major isomer (alpha:beta = 95:5). The strategy was to enhance the stereoselectivity by introducing a bulky group at 3-position of the sugar moeity and thereby directing the glycosylation, leading to the desired beta isomer. Reduction of 13 to 15 with DIBAL followed by acetylation gave 16, which was condensed with various pyrimidine and purines in the presence of trimethylsilyl triflate to obtain 17 and 18. In this case the ratio between the alpha and beta isomer was 1:1, as determined by ^{1}H-NMR. Chromatographically 17 and 18 could not be separated. However, after desilylation beta and alpha anomers could be separated by silica gel chromatography and individually desulfurized using tributyltin hydride to give the desired nucleosides 19 and 20.

This method promises to be a general route for the synthesis of variously substituted nucleosides, otherwise not easily accessible through modifications of preformed nucleosides.

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