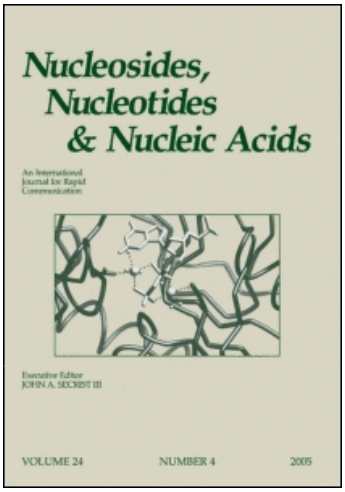

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Stereoselective Synthesis of 2',3'-Dideoxy-and 2,3'-Didehydro-2',3'-dideoxy-nucleosides

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STEREOSELECTIVE SYNTHESIS OF 2',3'-DIDEOXY- AND 2,3'-DIDEHYDRO-2',3'-DIDEOXY-NUCLEOSIDES

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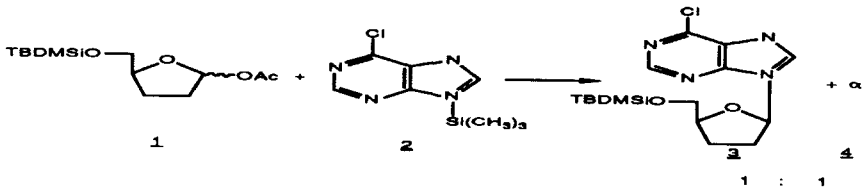
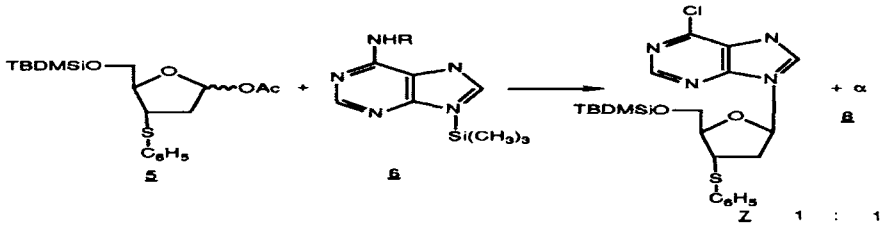
Abstract: A general highly stereoselective synthetic method for 2',3'-dideoxy- and 2',3'-didehydro-2',3'-dideoxynucleosides is described.

A number of 2',3'-dideoxy- and 2',3'-didehydro-2',3'-dideoxynucleosides have been found to be potent antiviral agents against human immunodeficiency virus (HIV). These include AZT,[1] AZDU,[2,3] DDA,[4] DDC,[4] DDI,[4] D4T,[5-7] N^6-methyl-DDA,[8] N^6-methyl-2'-fluoro-ara-DDA,[8] etc.

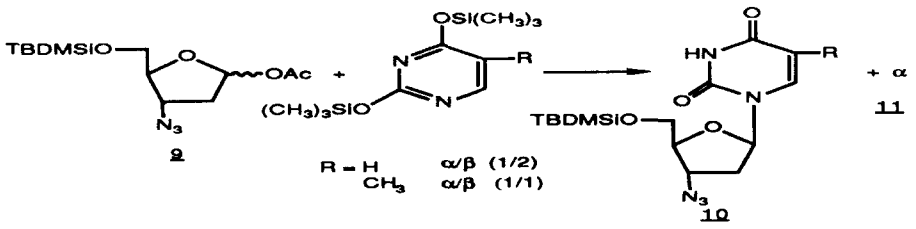
The synthesis of ribonucleosides from the condensation of acetyl or benzoyl protected ribose with aglycones yields mainly β-isomers due to the neighboring group effect of the acyl group. Furthermore, p-toluoyl protected 2'-deoxyribose gives 3:1 ratio in favor of β-isomer from the condensation with thymine.[9] Due to the limited availability of 2'-deoxynucleosides, there have been numerous efforts to develop a practical synthetic method to prepare 2',3'-dideoxynucleosides as anti-HIV agents by a condensation method from an appropriate carbohydrate and aglycone.[10] However, none of the published methods are satisfactory as a practical method for the synthesis of these anti-HIV agents, producing a mixture of α and β-isomers, which is normally difficult to separate by column chromatography. For example, we have recently published the synthesis of 2',3'-dideoxypurine analogues, in which a condensation of 2',3'-dideoxyribose derivative with 6-chloropurine yielded 1:1 mixture of α and β-isomers (Scheme 1).[8]



SCHEME 1



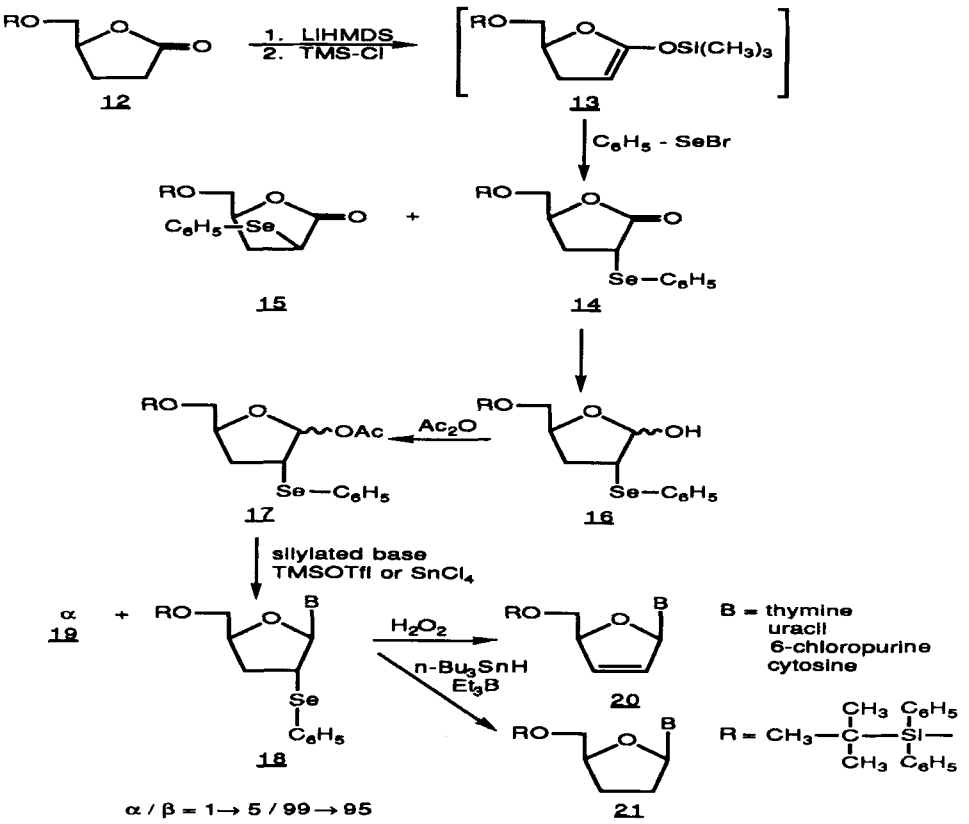
SCHEME 2



SCHEME 3

Even 3-substituted carbohydrate analogue 5 did not give any favorable stereoselectivity for β- isomer during the condensation (Scheme 2).[11] Additionally, condensation with 3-azido-sugar 9 with thymine gave a 1 : 1 mixture of α and β isomers under various conditions uracil produced some stereoselectivity yielding a 1 : 2 (α/β) mixture (Scheme 3).[12]

In order to overcome this non-stereoselectivity during the synthesis of 2',3'dideoxynucleosides, the approach shown in Scheme 4 has been tried. The strategy is to substitute a group at the 2-position, which can give astereoelectronic assistance to exclusively yield the β-isomer 18. Thus, the



SCHEME 4

lactone 12 was treated with LiHMDS at -78°C followed by the addition of TMS-Cl yielded silylether 13, which, without isolation, was treated with phenylselenium bromide to give 14 (68%) and 15 (30%). However, it was found that 15 can be readily converted to 14 in 61% by treating 15 with diethylamine or DBU at room temperature. The separation of 14 and 15 can be readily accomplished by silica gel column using a gradient mixture of ethyl acetate in hexane (0-6%) as the eluent. The lactone 14 was reduced by DIBAL to 16 and then acetylation to give 17 in an excellent yield. Condensation of 17 with silylated bases (thymine, uracil, 6-chlorpurine, cytosine, etc) in the presence of TMSOTfl or $SnCl_4$ as a catalyst gave a highly stereoselective β-isomer 18 and a trace amount of α-isomer 19. The αβ–ratio is depending on

the heterocyclic base, ranging between 95% to 99% in favor of β-isomer 18, which can be readily converted to 2',3'-didehydro-2',3'-dideoxynucleosides 20 as well as 2',3'-dideoxynucleosides 21 by the oxidation of 18 with H_2O_2 and reduction with n-Bu_3SnH/Et_3B at room temperature, respectively.

In summary, a highly stereoselective method of glycosylation has been developed by the condensation of 2-(phenylselenyl)-2,3-dideoxyribose derivative and silylated heterocyclic base in the presence of catalyst, which can be readily converted into the anti-HIV nucleosides, 2',3'-dideoxynucleosides and 2',3'-didehydro-2',3'-dideoxynucleosides.

Acknowledgements

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References Cited

1. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. Proc. Natl. Acad. Sci. USA., 1985, 82, 7096.
2. Chu, C. K.; Schinazi, R. F.; Ahn, M. K.; Ullas, G. V.; Gu, J. P. J. Med. Chem., 1989, 32, 612.
3. Eriksson, B. F. H.; Chu, C. K.; Schinazi, R. F. Antimicrob. Agents Chemother., 1989, 33, 1729.
4. Mitsuya, H.; Broder, S. Proc. Natl. Acad.Sci. USA., 1986, 83, 1911.
5. Lin, T. S.; Schinazi, R. F.; Prusoff, W. H. Biochem. Pharmacol., 1987, 36, 2613.
6. Hammamoto, Y.; Nakashima, H.; Matsui, T.; Matsuda, A.: Ueda, T. Antimicrob. Agents Chemother., 1987, 31, 907.
7. Balzarini, J.; Pauwels, R.; Herdewijn, P.; De Clercq, E.; Cooney, D. A.; Kang, G. J.; Dalil, M.; Johns, D. G.; Broder, S. Biochem. Biophys. Res. Commun., 1987, 140, 735.
8. Chu, C. K.; Babu, J. R.; Beach, J. W.; Ahn. S. K. ; Huang, H.; Jeong, L. S.; Lee, S. J. J. Org. Chem., 1990, 55, 1418.
9. Wierenga, W.; Skulnick, H. I. Carbohydr. Res., 1981, 90, 41.
10. Okabe, M.; Sun, R. -C.; Tam, S. Y. -K.; Todaro, J. J.; and Coffen, D. L. J. Org. Chem., 1988, 53, 4780; Farina, V.; Benigni, D. A. Tett. Lett., 1988, 29, 1239.
11. Chu, C. K.; Raghavachari, R.; Beach, J. W.; Kosugi, Y.; Ullas, G. V. Nucleosides and Nucleotides, 1989, 8, 903.
12. Chu, C.K.; Beach, J.W.; Ullas, G.V. and Kosugi, Y. Tett Lett., 1988, 29, 5349.