Synthesis and Conformational Analysis of Novel 2',3'-Didehydro-2',3'-dideoxy-4'-selenonucleosides

Yun Jung Ko, Won Jun Choi, Jung Ha Jun, Long Xuan Zhao, and Lak Shin Jeong

Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750

ABSTRACT
The structure of 2',3'-didehydro-2',3'-dideoxy-nucleosides (d4Ns) was applied to design the novel bioisosteric 4'-seleno-d4Ns as potential inhibitors of human immunodeficiency virus reverse transcriptase (HIV RT). Conversion of 2',3'-dihydroxy groups of 4'-selenoribofuranosyl pyrimidines into the olefin was accomplished by treatment of cyclic 2',3'-thiocarbonate with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine.

INTRODUCTION
2',3'-Didehydro-2',3'-dideoxy-nucleosides (1, d4Ns) have been developed as nucleoside reverse transcriptase (RT) inhibitors of human immunodeficiency virus (HIV) (Fig. 1), among which the thymine analogue d4T (stavudine) is being clinically used for the treatment of AIDS.

Since the discovery of d4Ns, bioisosteric nucleosides, 4'-carbonucleosides (2, 4'-carbo-d4Ns) and 4'-thionucleosides (3, 4'-thio-d4Ns) were also developed as potent HIV-1 inhibitors. However, because these cause unwanted side effects such as peripheral neuropathy and drug resistance, development of a new template to solve these problems has been highly desirable. 4'-Selenonucleoside could be a good candidate for that purpose because it is in the bioisosteric relationship with oxygen or sulfur and also acts as a chemical isostere of methylene (CH2). Therefore it was of great interest to synthesize the selenium analogues of d4Ns (4'-seleno-d4Ns) and to compare the conformations of d4Ns with those of 4'-seleno-d4Ns. Herein we present the stereoselective synthesis of 4'-seleno-d4Ns 4a-c and their conformational analysis based on X-ray crystal structures.

RESULTS AND DISCUSSION
To synthesize the target nucleosides 4a-c, 4'-selenoribofuranosyl pyrimidines 5a-c were chosen as starting materials, which have been published previously (Scheme 1).

Reagents and Conditions: (a) TBDMSCl, imidazole, DMF, 0 °C; (b) 1,1-thiocarbonyldimimidazole, CH2Cl2, rt; (c) 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine, THF, rt; (d) i. TBAF, THF, rt; ii. only for 8c: NH3/Methanol, rt.

Scheme 1. Synthesis of 4'-seleno-d4Ns

Protection of the primary hydroxyl groups of 5a-c with TBS group yielded 6a-c. In order to convert 2',3'-dihydroxy groups of 6a-c into the olefin, compounds 6a-c were treated with thiocarbonyl diimidazole (TCI) to give the cyclic 2',3'-thiocarbonates 7a-c, which were reacted with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine to give the protected 4'-seleno-d4Ns 8a-c, respectively. Removal of the protecting groups of 8a-c afforded the final 4'-seleno-d4Ns 4a-c. Structures of the final 4'-seleno-d4Ns 4a-c were confirmed by spectral and analytical data. Especially, the structure of 4'-seleno-d4T (4a) was further confirmed by its X-ray crystal structure (Fig. 2).
Anti-HIV activity of synthesized compounds was tested in MT-4 cells, but they did not show significant anti-HIV activity.

In order to compare the conformation of 4′-seleno-d4T (4a) with that of d4T, molecular modeling study was performed based on the X-ray crystal structures of d4T and 4′-seleno-d4T. From this study, it was revealed that the 5-membered selenosugar was completely flat when compared with the furanose ring which was slightly puckered up toward the thymine. The orientation of the 5′-hydroxyl group in 4′-seleno-d4T was also significantly different from that of d4T. These findings might explain the loss of anti-HIV activity of 4′-seleno-d4T, compared with that of d4T.

CONCLUSION

We have synthesized novel 2′,3′-didehydro-2′,3′-dideoxy-4′-selenonucleosides (4′-seleno-d4Ns) 4a-c from 4′-selenoribofuranosyl pyrimidines 5a-e. Conversion of 4′-selenoribofuranosyl moiety into 4′-seleno-2′, 3′-didehydro-2′, 3′-dideoxyribofuranosyl moiety was achieved using 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholindine. Superimposition of 4′-seleno-d4T and d4T revealed that their 5′-hydroxyl groups did not match each other. This information will provide valuable insights into the cellular phosphorylation by kinases.

REFERENCES


*Corresponding Author. E-mail: lakjeong@ewha.ac.kr