Stereoselective Glycosylations via Selenium Intermediate: A Synthetic Route to 2'-Deoxynucleosides

Dong Hoon Lee, Joong Young Kim and Yong Hae Kim

Department of Chemistry, Korea Advanced Science and Technology, Kusong-dong, 373-1, Yousong-gu, Taejon 305-701, Korea

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Modified nucleosides often show very potent biological activity. 2,3'-Dideoxynucleosides (dd) and their 2',3'-unsaturated analogs (d4) are known to be potent anti-human immuno deficiency virus (HIV) agents. 2',3'-Dideoxyinosine (ddI, **1**), 2',3'-dideoxycytosine (ddC, **2**) and 3'-azido-3'-deoxythymidine (AZT, **3**) are the approved drugs for the treatment of Acquired Immune Deficiency Syndrome (AIDS). A number of other nucleocides, such as 3'-azido-2',3'-dideoxyuridine (AzddU, **4**) 2',3'-didehydro-2',3'-deoxythymidine (d4T, **5**) have been studied through the preliminary clinical test (Huryn and Okabe, 1992). Since most synthetic methods of dd or d4 nucleosides based on DNA nucleosides which are obtained from the limited natural sources are inimical to the broad applications of modified nucleosides, general and economical methods for the preparation of those substances from non-nucleoside material are of interest. Several efforts to prepare dd and d4 nucledsides have been performed by the use of either L-glutamic acid or a synthetic sugar as the starting materials to give poor stereoselectivity in the glycosylation step (Chu *et al.*, 1988; Farina and Benign, 1988; Okabe *et al.*, 1988; Jung and Gardiner, 1992). The β-isomers exhibit useful biological activity and the most important factor in the synthetic strategy from non-nucleoside material involves delivering the base from the β-face of the carbohydrate ring in the glycosylation reaction.

1. B = Hypoxanthin-9-yl, R = H
2. B = Cytosine-1-yl, R = H
3. B = Thymine-1-yl, R = N_3
4. B = Uracil-1-yl, R = N_3
5. B = Thymine-1-yl

Fig. 1. Approved or potent anti-viral agents.

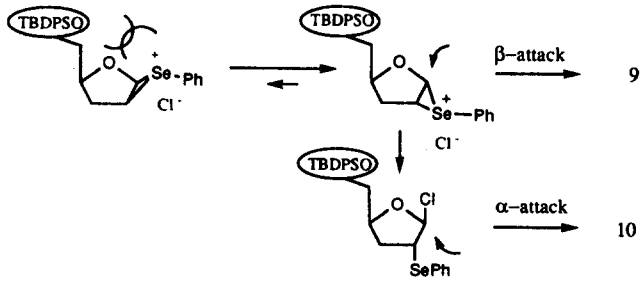
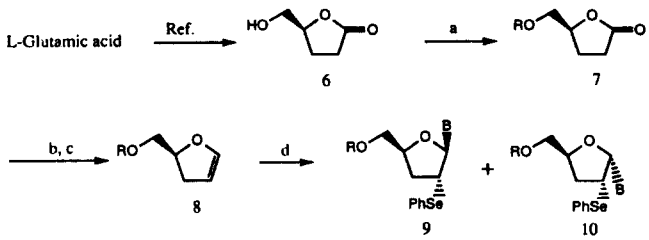


Fig. 2. Mechanistic aspect on stereoselectivity.



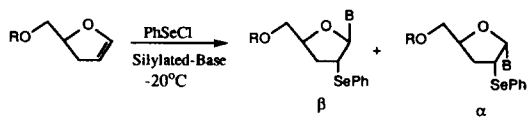
(a) t-$BuMe_2SiCl$ or t-$BuPh_2SiCl$, imidazole, CH_2Cl_2 (b) Dibal-H, CH_2Cl_2, -78 °C
(c) MsCl, Et_3N, CH_2Cl_2 (d) Trimethysilylated base, PhSeCl
R = TBDMS or TBDPS

Scheme 1

Recently, good stereoselectivity contol has been achieved by using furanoid glycal intermediate with N-iodosuccinimide (Kim and Misco, 1992) or ArSX (Wang *et al.*, 1993) as an electrophile. It has been reported that no glycosylation takes place by the reaction of silylated base with the 1-halo-2-phenylselenenyl furanoses obtained from glycal and selenium electrophile but that the glycosylation reaction of glycal in the presence of AgOTf activator gives relatively high

Correspondence to: Yong Hae Kim, Department of Chemistry, Korea Advanced Institute of Science and Technology, 373-1, Kusong-dong, Yousong-gu, Taejon, 305-701, Korea

Table I. Addtions of Phenylselenenyl Chloride and Silylated bases to glycals



Entry	R	Silylated Base[a]	Solvent	Ratio[b] (β : α)	Time (h)	Yield (%)[c]
1	TBDPS	Thymine	CH_2Cl_2	70 : 30	5	54
2	TBDPS	Thymine	THF	97 : 3	7	67
3	TBDMS	Thymine	THF	83 : 17	5	68
4	TBDPS	Uracil	THF	97 : 3	7	70

[a] Molar ratio; 1/1.5/2 glycal/PhSeCl/Pyrimidine base
[b] Ratios were determined by HPLC (normal phase, CH_2Cl_2 : MeOH = 15 : 1) after desilyation of 5'-protecting group.
[c] Isolated yields.

selectivity (β : α = 90 : 10) (El-Laghdach *et al.*, 1993).

In the present report we describe a straightforward synthetic method for dd or d4 nucleosides based on the highly stereoselective glycosylations to a furanoid glycal with phenylselenenyl chloride without using activator. The synthesis of the requisite furanoid glycal (**8**) was derived from the known lactone (**6**) which was readily prepared from L-glutamic acid (Taniguchi *et al.*, 1974). Lactone was converted to glycal by the 3-step sequences (Takle and Kocienski, 1990). Addition of PhSeCl to glycal in the presence of trimethylsilylated base produced the compound (**9**) and (**10**) in good yields and with high stereoselectivities as shown in Table 1. The observed stereoselectivity may be due to a consequence of the sterically favored α-face approach of the phenylselenenyl chloride to form a selenium cation intermediate in which is then attacked from the β-face by trimethylsilylated pyrimidine base as shown in Fig. 2. The choice of solvent is important in the stereochemical control : THF resulted in the better stereoselectivity (β : α = 97 : 3 in THF, 70 : 30 in CH_2Cl_2 in Table 1). The bulky protecting group of TBDPS gave also the better stereoselectivity (β : α = 97 : 3) than TBDMS (β : α = 87 : 13). 2'-Phenylselenenyl substituted nucleosides have been well known to be an intermediate for conversion to the corresponding dd or d4 nucleosides (Chu *et al.*, 1990). In conclusion, 2'-phenylselenenyl substituted nucleosides can be synthesized from glycal and PhSeCl in good yields and high stereoselectivities. This methodology can be applicable to the synthesis of dd or d4 derivatives in stereocontrolled manner from the non-nucleoside materials.

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