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Total Synthesis of (±)-Iso-d4T as Potential Antiviral Agent

Lak Shin Jeong,* **Young A Lee**, Hyung Ryong Moon, Su Jeong Yoo, and Su Youn Kim

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

Abstract : (±)-Iso-d4T which may act as a bioisostere of d4T was synthesized from 1,3-dihydroxyacetone using phenyl selenenium chemistry as a key step.

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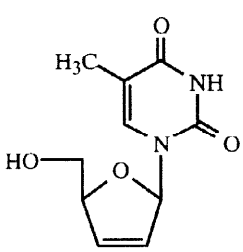
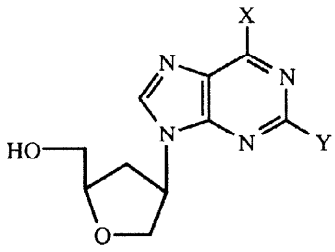
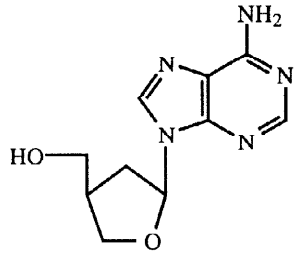
A number of 2′,3′-dideoxy- and 2′,3′-dideoxy-2′,3′-didehydronucleosides have been synthesized and evaluated for antiviral activities against human immunodeficiency virus (HIV)-1 and hepatitis B virus (HBV).[1-3] These compounds show antiviral activities by inhibiting reverse transcriptase which acts as a crucial enzyme for the replication of HIV-1 and also by inhibiting the reverse transcription process of the HBV replication.[1-3] Among these compounds, five nucleoside analogues have been approved for clinical use for the treatment of AIDS and AIDS-related complex (ARC).[1,2] 2′,3′-Dideoxy-2′,3′-didehydrothymidine (**1**, d4T, Starvudine) is one of five nucleosides which show potent anti-HIV activity, but it suffers from side effects like peripheral neuropathy.[4]



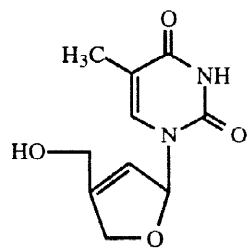
1



2a (X = NH_2, Y = H)
2b (X = OH, Y = NH_2)



3



4

On the other hand, isodideoxynucleosides in which oxygen of the furanose and C3-methylene were transposed were synthesized and evaluated for anti-HIV activity.[5] Among the synthesized compounds tested, iso-ddA (**2a**) and iso-ddG (**2b**) were found to be active against HIV-1 without apparent cytotoxicity. This class of compounds possess the metabolic advantages such as no hydrolysis of glycosidic linkage and resistance to adenosine deaminase. Apio dideoxynucleosides in which oxygen of the furanose and C2-methylene were transposed were also reported to show anti-HIV activity.[6] Adenine analogue **3** exhibited significant anti-HIV activity in MT-4 cells without cytotoxicity. These compounds also exhibit better profile about enzymatic deamination and glycosyl bond hydrolysis than 2′,3′-dideoxynucleosides.[7]

As a part of our ongoing efforts to search for new anti-HIV agents, we were interested in synthesizing iso-d4T (**4**) in which furanose oxygen and double bond of d4T were transposed and comparing its anti-HIV activity with that of parent nucleoside. Here, we report the synthesis of **4** starting from 1,3-dihydroxyacetone utilizing phenylselenenium chemistry as a key step.

Our first synthetic plan was to synthesize a cyclic allylic acetate **8** as a glycosyl donor and condense with thymine as an acceptor. As seen in Scheme 1, 1,3-dihydroxyacetone (**5**) was easily converted to α,β-unsaturated

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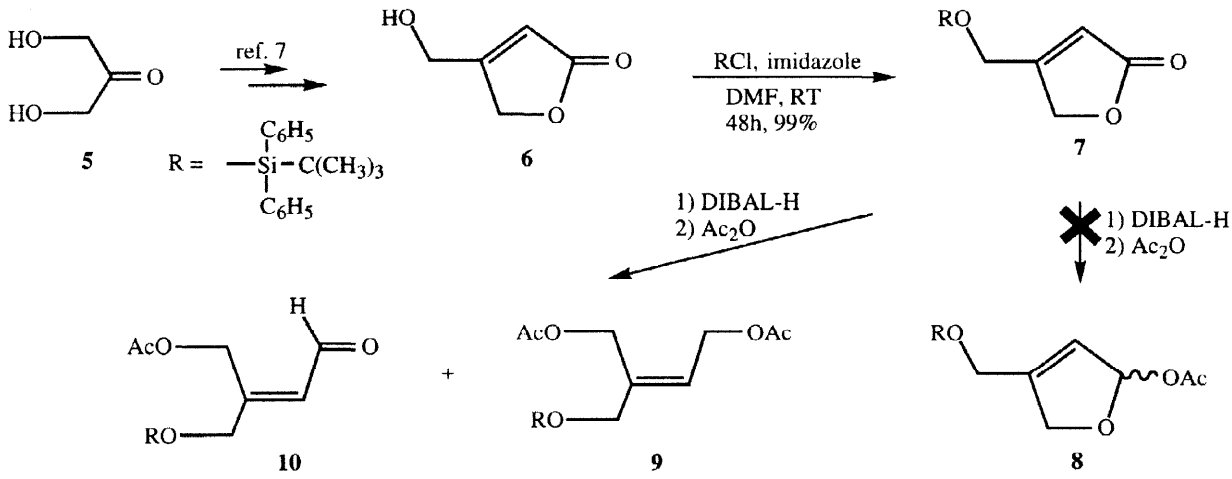
lactone **6** according to the known method.[8] The primary hydroxyl group of **6** was protected with t-butyldiphenylsilyl group to give **7** in 99% yield. Treatment of lactone **7** with DIBAL-H followed by addition of acetic anhydride did not give the desired cyclic allylic acetate **8**, but afforded the linear allylic acetates **9** and **10**. Since it was thought that failure to the formation of **8** is due to the double bond of the lactone, we decided to put double bond at the nucleoside level utilizing phenyl selenenium chemistry[9] as illustrated in Scheme 2.

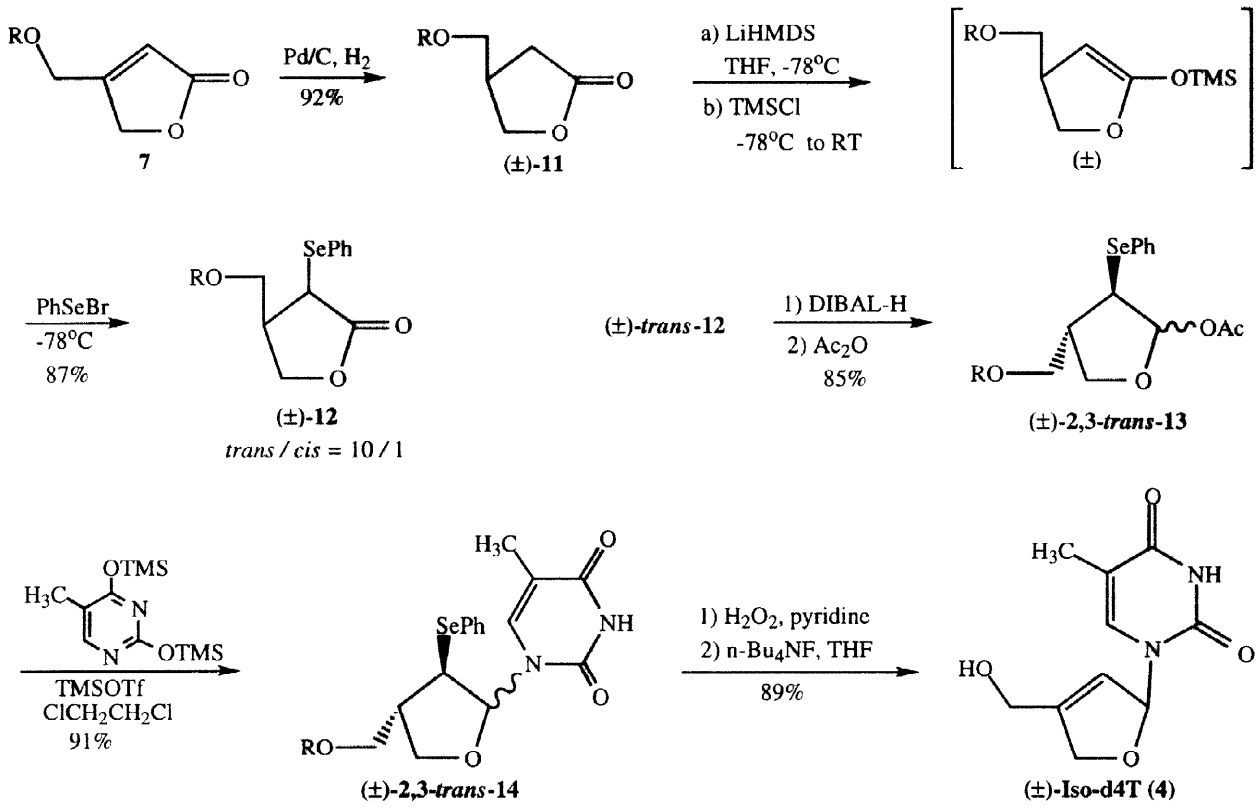
Scheme 1



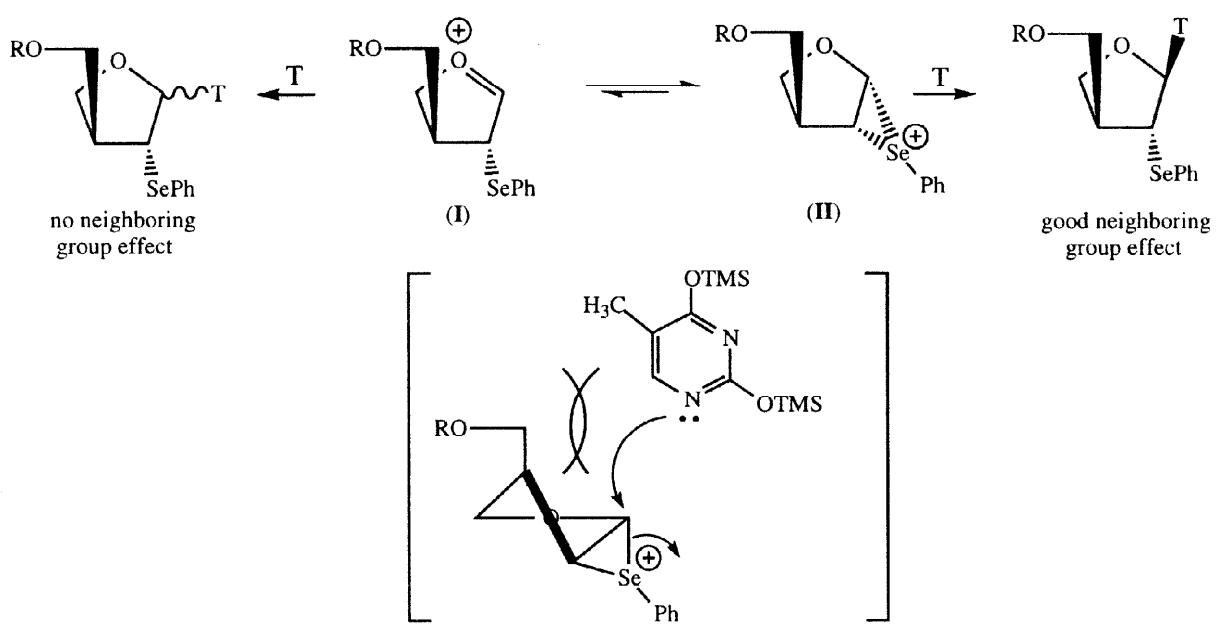
Double bond of the lactone **7** was reduced by catalytic hydrogenation (RT, 48 h) to give (±)-**11** (92%). Treatment of (±)-**11** with LiHMDS (-78°C, 1 h) followed by trapping of the resultant enolate with trimethylsilyl chloride (TMSCl) (RT, 30 min) afforded silyl enol ether which, without purification, was reacted with phenyl selenenyl bromide (-78°C, 2 h) to give (±)-**12** (*trans* / *cis* = 10 / 1).[10] It is well established that phenylselenenyl group was added at the opposite direction to the hydroxymethyl substituent to give the *trans*-isomer as the major product.[10] (±)-*Trans*-**12** was reduced with DIBAL-H to give the lactol (-78°C, 2 h) which, without purification, was treated with acetic anhydride (RT, 15 h) to give the (±)-2,3-*trans*-**13** as the glycosyl donor.

Condensation of the (±)-2,3-*trans*-**13** with silylated thymine in the presence of TMSOTf as the Lewis acid produced an inseparable anomeric mixture of (±)-2,3-*trans*-**14** (91%, β : α = 4 : 1). It was of interest to note that great neighboring group effect by phenylselenenyl group in glycosylation reaction was not observed unlike the excellent neighboring group effect (β : α = 99 : 1) by the participation of 2-phenylselenenyl group to the cation generated at the anomeric position during the glycosylation reaction of the 5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxyribosyl acetate.[10] This results indicate that glycosylation reaction still favors the formation of the episelenenium ion intermediate **II** as depicted in Scheme 3, giving the β isomer as major product by neighboring group effect. The reason for the increased formation of the α isomer could be explained by the repulsive effect between incoming thymine nucleophile and pseudoaxial hydroxymethyl substituent in the intermediate **II**, which moves the reaction equilibrium to the oxonium ion intermediate **I**, resulting in the formation of the anomeric mixture by no neighboring group effect. Phenylselenenyl group of (±)-2,3-*trans*-**14** was oxidatively removed with hydrogen peroxide and catalytic amount of pyridine to give the eliminated product without the formation of regioisomeric double bond, which was treated with *n*-tetrabutylammonium fluoride to afford the desired final (±)-iso-d4T (**4**).[11]

Scheme 2



Scheme 3



(±)-Iso-d4T was assayed for antiviral activities against several viruses such as HIV-1, HSV type-1, 2 and human cytomegalovirus (HCMV). This compound was found to exhibit very weak anti-HIV-1 activity

(EC_{50} = 35 μg/mL, CC_{50} = 100 μg/mL in MT-4 cells), but it showed significant anti-HCMV activity (EC_{50} = 15 μg/mL, CC_{50} > 33 μg/mL). However, this compound did not show anti-HSV activity.

In summary, we accomplished the total synthesis of (±)-iso-d4T which may act as a bioisostere starting from 1,3-dihydroxyacetone in which the double bond was inserted into the sugar ring using phenyl selenenium chemistry. It was observed that great neighboring group effect due to the steric replusion did not occur during the condensation reaction unlike the excellent anchimeric effect found in the synthesis of d4T. Systemic structure-activity relationship study of this class of nucleosides is in progress in our laboratory.

Acknowledgment

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11. Compound **4** : mp 320 °C; UV (MeOH) λ_{max} 264 nm; ^{1}H NMR (D_2O) δ 1.89 (s, 3 H), 3.56 (d, 1 H, *J* = 7.1 Hz), 3.62 (d, 1 H, *J* = 7.1 Hz), 4.41 (s, 2 H), 5.77 (d, 1 H, *J* = 1.6 Hz), 6.99 (m, 1 H), 7.34 (s, 1 H). Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.97; H, 5.67; N, 12.15.