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Enantiomeric Synthesis of 3'-Fluoro-Apionucleosides Using Claisen Rearrangement

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Abstracts: Enantiomeric synthesis of 3'-fluoro-apionucleosides was accomplished from 1,2-*O*-isopropylidene D-glyceraldehyde. The key intermediate, γ,δ-unsaturated *tert*-fluoro ethyl ester **7** from the fluoro allylic alcohol derivative **5** was achieved *via* Claisen rearrangement reaction with a 90.4% enantioselectivity. The condensation of the intermediate **10** with silylated N^4-benzoylcytosine and 6-chloropurine followed by deprotection gave the desired pyrimidine and purine apionucleosides, respectively.
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It has been well known that fluorinated compounds may profoundly influence biological and chemical properties.[1] The carbon-fluorine bond generally provide metabolic stability. Furthermore, the electronegativity of fluorine atom can significantly influence the overall electronic properties of a molecule.

Recently, there have been considerable interests in modification of nucleosides with a fluorine atom as potential antiviral agents.[2-6] While there have been numerous examples of modifications at the 2'- or 3'-position of nucleosides, much less is known about the modification at the 4'-position. Interestingly, nucleocidine, which is one of natural products containing a fluorine atom at 4'-position, has been isolated from *Streptomyces calvus* and was found to have antitrypanosomal activity.[7] Recently, 2',4'-difluorinated carbocyclic nucleosides have been found to have potent antiviral agents against herpes simplex viruses.[8] A number of apionucleosides (or isonucleosides), regioisomers of natural nucleosides by transposition of the hydroxy methyl group from the normal 4'-position to the 3'-position have been reported by Nair *et al.*[9] as potential antiviral agents. Some of these nucleosides have been found to possess potent anti-HIV activity.[10] Furthermore, recently, it was reported that racemic 3'-fluoro-apionucleosides showed potent anti-HBV activity.[11] In view of these interesting biological activities, it was of interest to synthesize enantiomeric 4-fluoro-apionucleosides as described below:

Optically active fluorinated compounds, where at least one of the asymmetric carbon atoms bears a fluorine are quite difficult to synthesize because the methodology for an asymmetric fluorination of tertiary carbon remains limited.[12] In order to introduce the required *tert*-fluorinated carbon, in this communication we successfully used the [3,3]-sigmatropic Claisen rearrangement reaction.[13] Due to the highly ordered transition state, generally a high level of stereochemical control can be achieved during this rearrangement.[14] Therefore, the judicious choice of precursor originated from an appropriate carbohydrate intermediate could allow us to create the desired fluorinated carbon center *via* the 1,3-chirality transfer in a stereochemically predictable fashion. Thus, 2,3-*O*-isopropylidene-D-glyceradehyde **1**, bearing an asymmetric secondary hydroxy group, was employed as the starting material (Scheme 1), which was reacted under the Horner-Wadsworth-Emmons condition with triethylfluorophosphonoacetate in tetrahydrofuran to give (*E*)-α,β-unsaturated fluroro ethyl ester.[15] The isopropylidene protection group was then hydrolyzed in 2 N HCl solution to give diol derivative **3**, which was treated with di-*n*-butyl tin oxide to give *in situ* di-*n*-butyl tin protected compound **4**.[16] The moisture sensitive intermediate **4** was treated with benzyl bromide to give the dibenzyl allylic alcohol derivative **5** with a high regioselectivity (10:1). This substrate **5**, which is suitable for the 1,3-chirality transfer, was subjected to the Claisen rearrangement condition in the presence of excess triethyl orthoacetate and catalytic amounts of propionic acid to give γ,δ-unsaturated tertiary fluoro ethyl ester **7** *via* possibly six-membered transition state **6** in 86% yield. The enantioselectivity of Claisen rearrangement reaction was determined at the final compound **13** to be 90.4% (ee) by chiral HPLC.[17] The double bond of **7** was ozonized to aldehydes **8**, which was subjected to

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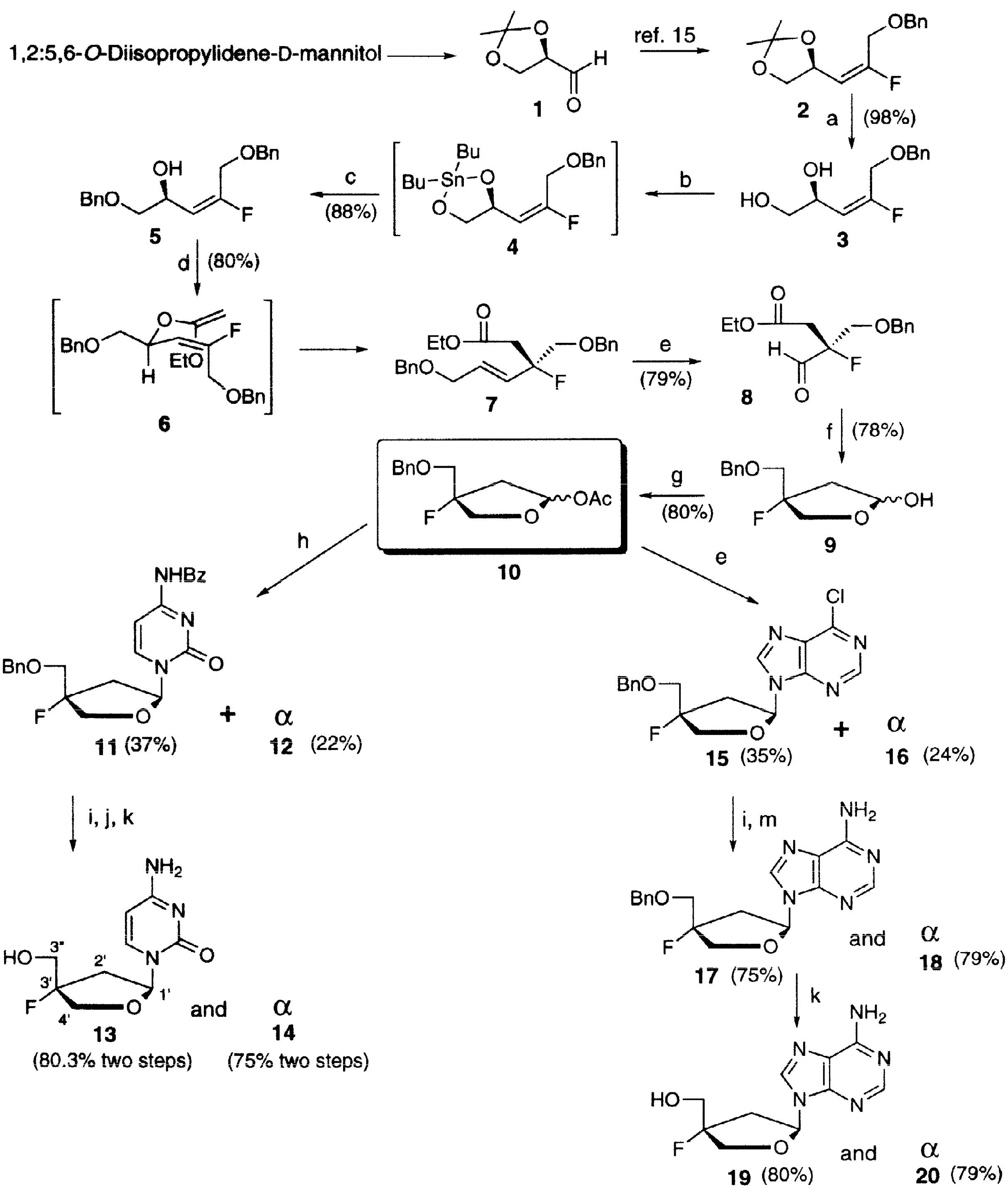
Scheme 1



Reagents: a) 2 N HCl solution, rt, 2 h. b) Di-*n*-butyl tin oxide, toluene, reflux. c) Benzyl bromide, tetrabutylammonium iodide, 70 °C, overnight. d) Triethyl orthoacetate, propionic acid, 130 °C, 7 h. e) O_3/DMS. f) DIBAL-H, toluene, -78 °C. g) Acetic anhydride, py. h) Silylated N^4-benzoylcytosine, TMSOTf, CH_3CN. i) Silica gel column chromatography. j) Ammonia in methanol. k) H_2/Pd$(OH)_2$, methanol. l) Silylated 6-chloropurine, TMSOTf, CH_3CN. m) Ammonia in methanol, steel bomb, 80-90 °C.

DIBAL-H reduction to give the lactol **9**. The apiose lactol **9** was then treated with acetic anhydride to give the intermediate **10**, which was condensed with silylated N^4-benzoyl cytosine under Vorbrüggen conditions[18] to afford glycosylate products **11** and **12** with an anomeric mixture (α/β = 1:2 determined by ^{1}H NMR). The separation of anomeric mixtures was readily accomplished by silica gel column chromatography. The free nucleosides **13**[20] and **14**[21] were obtained by the treatment of ammonia in methanol and subsequentely, $H_2/Pd(OH)_2$ in methanol,[19] and their stereochemical assignments were determined on the basis of ^{1}H NMR. There exist cross peaks in the NOESY spectrum for **13** between proximal hydrogen atoms (between H_β-4', H_β-2' and H-6), while no cross peak was observed in that of **14**. The 6-chloropurine analogues **15** and **16** were also obtained by the condensation with **10** under similar conditions as for cytosine to give an anomeric mixture (α/β = 1: 2 determined by ^{1}H NMR) and their anomeric mixtures were also readily separated by silica gel column chromatography to give the individual anomers. Compounds **15** and **16** were separately treated with NH_3/MeOH in a steel bomb at 80-90 °C to give **17** and **18**, respectively. In order to obtain free nucleosides, these compounds were subjected to $H_2/Pd(OH)_2$ in methanol to afford **19**[22] and **20**[23], respectively. Their stereochemical assignments were also made on the basis of X-ray crystallography[24] and NMR studies.

In summary, we successfully developed a novel synthetic method, which can provide enantiomeric apionucleosides with high enantioselectivity using [3,3]-sigmatropic Claisen rearrangement. This synthetic method can be applied for the synthesis of opposite optical isomers of apionucleosides reported here as well as apionucleosides having other substituents on the 3'-position. These synthetic efforts as well as biological evaluation of the synthesized nucleosides are in progress.

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20 **1-[3'-*C*-(Hydroxymethyl)-3'-deoxy-3'-fluoro-β-L-erythro-tetrafuranosyl] cytosine (13)** mp foam; $[\alpha]^{27}_D$ -40.7 (*c* 0.70, MeOH); UV (H_2O) λ_{max} 269.5 (ε 8329) (pH 7), 266 (ε 8010) (pH 11), 278.5 (ε 13091) (pH 2); ^1H NMR (DMSO-d_6) δ 2.21-2.53 (m, 2H), 3.70-3.78 (m, 2H), 4.06 (dd, *J* = 10.4, 21.7, 1H), 4.32 (dd, *J* = 10.4, 35.1, 1H), 5.33 (t, *J* = 5.7, 1H, D_2O exchangeable), 5.80 (d, *J* = 7.4, 1H), 6.18 (t, *J* = 6.9, 1H), 7.29 (br d, 2H, D_2O exchangeable), 7.70 (d, *J* = 7.4, 1H); Anal Calcd for $C_9H_{12}N_3O_3F{\cdot}0.3MeOH$: C, 46.77; H, 5.56; N, 17.59. Found: C, 46.64; H, 5.56; N, 17.33; MS (*m/z*): 230 $[M+H]^+$.

21 **1-[3'-*C*-(Hydroxymethyl)-3'-deoxy-3'-fluoro-α-L-erythro-tetrafuranosyl] cytosine (14)** mp 183-185 °C; $[\alpha]^{27}_D$ +74.5 (*c* 0.41, MeOH); UV (H_2O) λ_{max} 270 (ε 8543) (pH 7), 266 (ε 8017) (pH 11), 279 (ε 13469) (pH 2); ^1H NMR (DMSO-d_6) δ 2.05-2.14 (m, 2H), 2.44-2.64 (m, 1H), 3.60-3.66 (m, 2H), 3.90-4.31 (m, 2H), 5.29 (br s, 1H, D_2O exchangeable), 5.76 (d, *J* = 7.4, 1H), 6.05 (dd, *J* = 2.3, 7.5, 1H), 7.17 (br d, 2H, *J* = 7.4, 1H); Anal Calcd for $C_9H_{12}N_3O_3F{\cdot}0.7H_2O$: C, 44.70; H, 5.58; N, 17.37. Found: C, 44.76; H, 5.65; N, 17.06; MS (*m/z*): 230 $[M+H]^+$.

22 **9-[3'-*C*-(Hydroxymethyl)-3'-deoxy-3'-fluoro-β-L-erythro-tetrafuranosyl] adenine (19)** mp 196-199 °C; $[\alpha]^{27}_D$ +84.4 (*c* 0.18, DMF); UV (H_2O) λ_{max} 258.5 (ε 17107) (pH 7), 257 (ε 17396) (pH 2), 259 (ε 17179) (pH 11); ^1H NMR (DMSO-d_6) δ 2.65-2.76 (m, 1H), 2.91-3.00 (ddd, *J* = 6.9, 14.9, 34.6, 1H), 3.88 (dd, *J* = 5.5, 20.5, 2H), 4.02-4.09 (dd, *J* = 10.4, 20.1, 1H), 4.37-4.25 (dd, *J* = 10.5, 35.4, 1H), 5.37 (t, *J* = 5.7, 1H, D_2O exchangeable), 6.47 (t, *J* = 7.0, 1H), 7.32 (br s, 2H, D_2O exchangeable), 8.16 (s, 1H), 8.34 (s, 1H); Anal Calcd for $C_{10}H_{12}N_5O_2F$: C, 47.43; H, 4.77; N, 27.65. Found: C, 47.26; H, 4.86; N, 27.52; MS (*m/z*): 254 $[M+H]^+$.

23 **9-[3'-*C*-(Hydroxymethyl)-3'-deoxy-3'-fluoro-α-L-erythro-tetrafuranosyl] adenine (20)** mp 200-202 °C; $[\alpha]^{27}_D$ -53.4 (*c* 0.25, DMF); UV (H_2O) λ_{max} 260 (ε 17700) (pH 7), 257 (ε 17058) (pH 2), 259 (ε 17161) (pH 11); ^1H NMR (DMSO-d_6) δ 2.72-2.88 (m, 2H, H-2'),3.67-3.70 (m, 2H, H-5'), 4.11 (dd, *J* = 10.8, 30.8, 1H), 4.33 (dd, *J* = 10.7, 20.9, 1H), 5.39 (t, *J* = 5.3, 1H, D_2O exchangeable), 6.39 (dd, *J* = 3.0, 7.3, 1H), 7.30 (br s, 2H, D_2O exchangeable), 8.15 (s, 1H), 8.16 (s, 1H); Anal Calcd for $C_{10}H_{12}N_5O_2F$: C, 47.43; H, 4.77; N, 27.65. Found: C, 47.34; H, 4.77; N, 27.59; MS (*m/z*): 254 $[M+H]^+$.

24 Unpublished result.