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Asymmetric synthesis of 2′,3′-dideoxy-3′-fluoroapiofuranosyl nucleosides

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Abstract—An efficient stereoselective synthetic method for each stereoisomer of enantiomerically pure 2′,3′-dideoxy-3′-fluoroapiofuranosyl nucleosides was developed. The key features of this strategy are the enantiospecific fluorination of the *tert*-alcohol and the orthogonal protection/deprotection of the diol.

1. Introduction

It is well known that fluorine substituted compounds show remarkable differences in biological activities and pharmacological properties compared to their parent molecules.[1] The development of a preparative method for enantiomerically pure fluorine-containing compounds has been of great interest in medicinal and organic chemistry. Despite there being many examples for the asymmetric synthesis of fluoro-compounds, there is still a need to develop more efficient synthetic methods for enantiomerically pure fluorine containing compounds.[2]

We have reported the synthesis of the racemic 1-(2,3-dideoxy-3-fluoroapiofuranosyl)cytosine and determination of its relative configuration by NMR and X-ray crystallography.[3] A short time later, Chu et al. accomplished the synthesis of the enantiomerically enriched (−)-1-(2,3-dideoxy-3-fluoroapio-β-L-furanosyl)cytosine **11a** in 90% ee where the 1,3-chirality transfer using a Claisen rearrangement was employed as the key step.[4] They also reported the determination of the absolute configuration of **11a** by NMR and X-ray crystallographic studies.[4] An application of this synthetic strategy to the enantiomeric synthesis of the D-isomers **15a** and **15b** has recently been reported by Kim and Hong.[5]

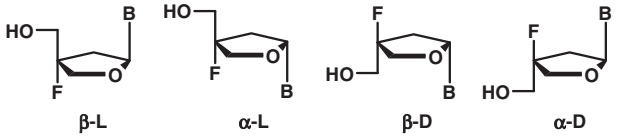

Figure 1. Stereoisomers of 1-(2,3-dideoxy-3-fluoroapiofuranosyl)-nucleosides.

Over the course of the asymmetric synthesis of enantiomerically pure fluoroapiofuranosyl nucleosides shown in Figure 1, we needed to prepare the enantiomerically pure tertiary fluoride **5** from the chiral tertiary alcohol **4** (Scheme 1). Amongst the many reports on the preparation of fluoro compounds by treatment of alcohols with diethylaminosulfur trifluoride (DAST), we found only a few examples on the conversion of a tertiary alcohol to a tertiary fluoride with DAST.[6] Herein, we report an efficient method for the asymmetric synthesis of each stereoisomer of enantiomerically pure 2′,3′-dideoxy-3′-fluoroapio-β/α-L/D-furanosyl nucleosides, shown in Figure 1, through an unprecedented enantiospecific conversion of chiral tertiary alcohol to the corresponding fluoride with inversion of stereochemistry using DAST as a key step.

2. Results and discussion

The asymmetric synthesis of the key intermediates, L- and D-2,3-dideoxy-3-fluoroapiofuranoses **7** and **9**, is described in Scheme 1. Our synthesis commenced with commercially available α-D-lactose **1**, which was

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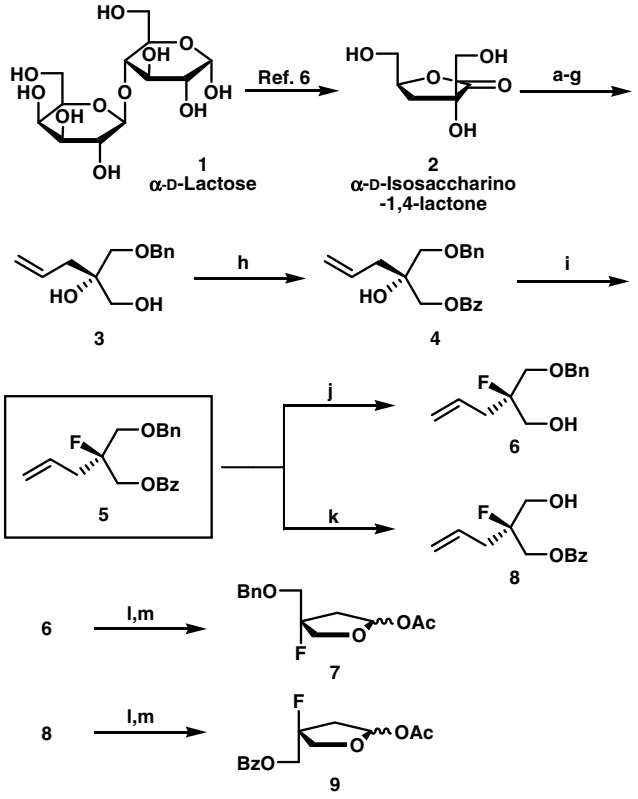


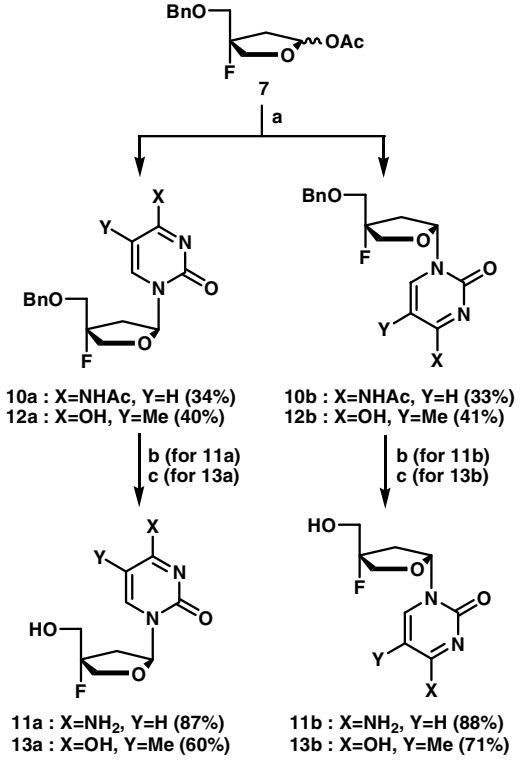
Scheme 1. Reagents and conditions: (a) $Me_2C(OMe)_2$, *p*-TsOH, Me_2CO, rt, 2 h, 90%; (b) TsCl, pyridine, $CHCl_3$, rt, 10 h, 84%; (c) NaI, 2-butanone, reflux, 12 h, 85%; (d) Zn, AcOH, THF–H_2O (30:1), 40 °C, 1 h, 72%; (e) LAH, THF, reflux, 6 h, 80%; (f) NaH, Bu_4NI, $PhCH_2Br$, THF, rt, 12 h, 80%; (g) HCl, MeOH, rt, 20 h, 82%; (h) $(PhCO)_2O$, Et_3N, DMAP, CH_2Cl_2, rt, 2 h, 99%; (i) Et_2NSF_3, CH_2Cl_2, −78 to 0 °C, 0.5 h, 81%; (j) NaOMe, MeOH, rt, 1 h, 97%; (k) BCl_3, CH_2Cl_2, −78 °C, 1 h, 77%; (l) O_3, EtOAc, −78 °C, 2 h; (m) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h, 78% for **7** (for two steps) and 74% for **9** (for two steps), respectively.

transformed to α-D-isosaccharino-1,4-lactone **2** by the known procedure.[7] Preparation of the enantiomerically pure diol **3** was accomplished from **2** in seven steps developed by Monneret et al.[8] The primary hydroxyl group of **3** was selectively benzoylated with benzoic anhydride and DMAP to give **4** quantitatively.

With the enantiomerically pure tertiary alcohol **4** in hand, we tried the fluorination of the tertiary hydroxyl group in **4** with DAST at −78 °C. It was found that the conversion of the hydroxyl to the corresponding fluoride **5** with complete inversion of stereochemistry was achieved in 81% yield. The absolute configuration of **5** was confirmed by the comparison of specific rotations of **11a** $\{[\alpha]_D^{20} = -44.4$ (*c* 0.18, MeOH)$\}$ and **11b** $\{[\alpha]_D^{20} = +84.1$ (*c* 0.37, MeOH)$\}$ with the literature data reported by the Chu group {**11a**: $[\alpha]_D^{27} = -40.7$ (*c* 0.70, MeOH), **11b**: $[\alpha]_D^{27} = +74.5$ (*c* 0.41, MeOH)}.[4,9] The enantiopurity of **5** was confirmed by the determination of the enantiomeric excesses of the final nucleosides, **11a** (β-L), **11b** (α-L), **15a** (β-D), and **15b** (α-D), by chiral HPLC analysis. All compounds showed >99% enantiomeric excesses.[10] All these results consistently demonstrate the complete inversion of stereochemistry in the fluorination step (**4**→**5**). To the best of our knowledge, this is the first example of an enantiospecific inversion of a tertiary alcohol to a tertiary fluoride with DAST in an acyclic system.

The advantage of our synthesis lies in the versatility of the orthogonally protected fluorodiol **5**. Depending on the deprotection method of the two protective groups (benzyl vs benzoyl) of the diol in **5**, either the L- or D-form of the apiofuranosyl acetates, **7** or **9**, was selectively obtained. For the preparation of the L-isomer, NaOMe treatment to **5** in methanol gave the mono-benzylated alcohol **6**. Ozonolysis of the double bond in **6**, followed by reductive treatment gave the lactol, which was acetylated to afford the L-fluoroapiofuranosyl acetate **7**. On the other hand, treatment of **5** with BCl_3 in CH_2Cl_2 afforded the *mono*-benzoylated alcohol **8**, which was treated with the same method mentioned above to give the D-fluoroapiofuranosyl acetate **9**.

Syntheses of enantiomerically pure 1-(2,3-dideoxy-3-fluoroapio-L-furanosyl)pyrimidine nucleosides are depicted in Scheme 2. Coupling of L-apiosyl acetate **7** with silylated N^4-acetylcytosine or thymine under Vorbrüggen reaction conditions gave a 1:1 mixture of β- and α-isomers, which were readily separated by column chromatography.[11,12] The protecting groups in **10** and **12** were removed to afford enantiomerically pure L-nucleosides **11** and **13**, respectively. In a similar manner, D-isomers were prepared from D-apiosyl acetate **9**



Scheme 2. Reagents and conditions: (a) silylated N^4-acetylcytosine or silylated thymine, TMSOTf, CH_2Cl_2, 0 °C, 0.5 h; (b) (i) BCl_3, CH_2Cl_2, −78 °C, 1 h, (ii) NaOMe, MeOH, rt, 1 h; (c) BCl_3, CH_2Cl_2, −78 °C, 2 h.