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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]

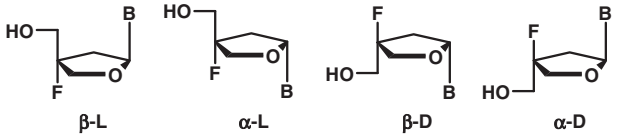

Figure 1. Stereoisomers of 1-(2,3-dideoxy-3-fluoroapiofuranosyl)-nucleosides.

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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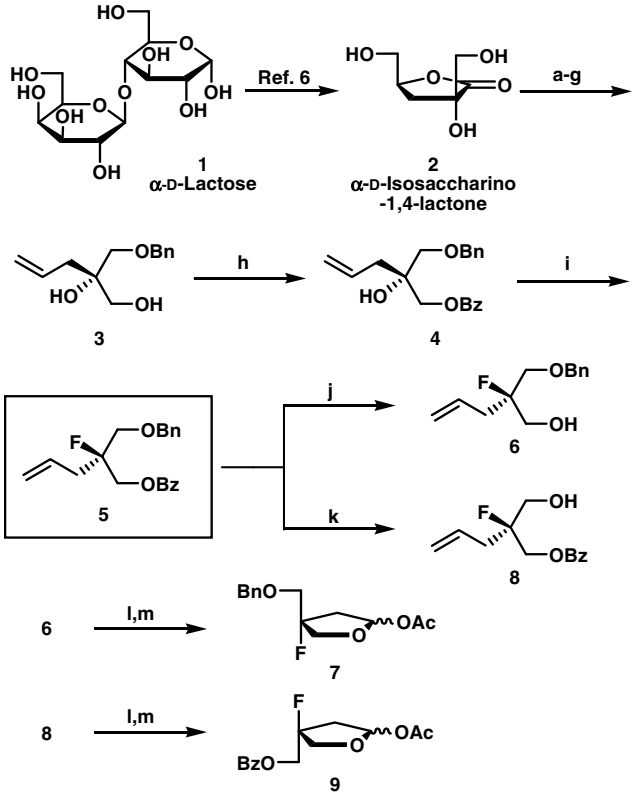


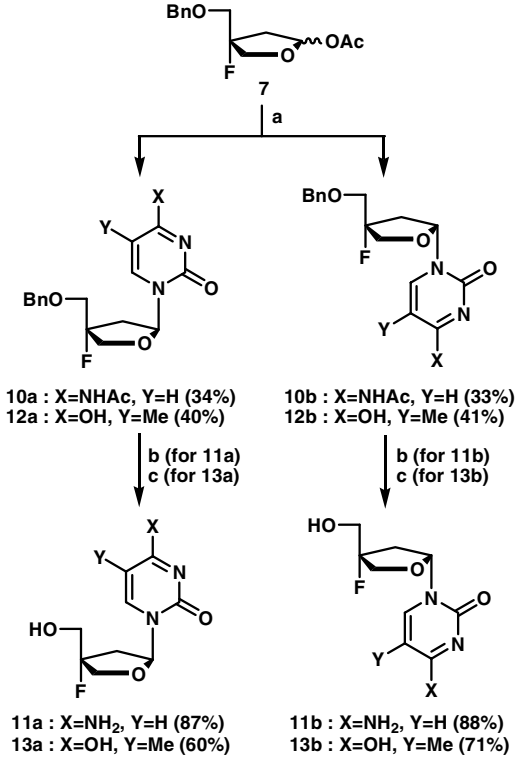
Scheme 1. Reagents and conditions: (a) $Me_2C(OMe)_2$, *p*-TsOH, Me_2CO, rt, 2 h, 90%; (b) TsCl, pyridine, $CHCl_3$, rt, 10 h, 84%; (c) NaI, 2-butanone, reflux, 12 h, 85%; (d) Zn, AcOH, THF–H_2O (30:1), 40 °C, 1 h, 72%; (e) LAH, THF, reflux, 6 h, 80%; (f) NaH, Bu_4NI, $PhCH_2Br$, THF, rt, 12 h, 80%; (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.

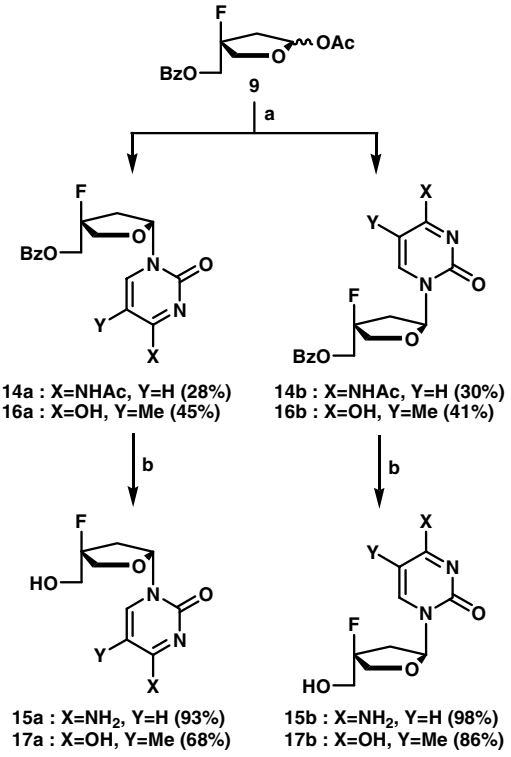
With the enantiomerically pure tertiary alcohol **4** in hand, we tried the fluorination of the tertiary hydroxyl group in **4** with DAST at −78 °C. It was found that the conversion of the hydroxyl to the corresponding fluoride **5** with complete inversion of stereochemistry was achieved in 81% yield. 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.



Scheme 3. Reagents and conditions: (a) silylated N^4-acetylcytosine or silylated thymine, TMSOTf, CH_2Cl_2, 0 °C, 0.5 h; (b) NaOMe, MeOH, rt, 1 h.

shown in Scheme 3. Deprotection was carried out with NaOMe to give enantiomerically pure D-nucleosides **15** and **17**, respectively.[12]

3. Conclusion

In summary, we have developed the efficient and convenient synthetic method for optically pure 2′,3′-dideoxy-3′-fluoroapiofuranosyl nucleosides in which the stereospecific fluorination and the orthogonal protection are the key steps. Asymmetric syntheses of other pyrimidine- and purine-analogs as well as evaluation of their antiviral activities are in progress.

4. Experimental

4.1. General

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Column chromatography was performed using silica gel 60 (70–230 mesh, Merck). Thin layer chromatography (TLC) was performed on Merck precoated $60F_{254}$ plates. Optical rotations were measured with a Rudolph Autopol IV polarimeter. Ultraviolet spectra were recorded with a Hewlett Packard HP8452 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard and coupling constants are in hertz. High Resolution Mass Spectra was measured with a VG70-VSEQ Mass Spectrometer using electron impact (EI, 70 eV) techniques.

4.2. Experimental procedure

4.2.1. (2*R*)-2-Hydroxy-2-(benzyloxymethyl)-4-penten-1-yl benzoate (4). To a solution of (2*S*)-2-hydroxy-2-(benzyloxymethyl)-4-penten-1-ol (**3**) (290 mg, 1.30 mmol), 4-dimethylaminopyridine (32 mg, 0.26 mmol), and triethylamine (0.3 ml) in CH_2Cl_2 was added benzoic anhydride (443 mg, 2.0 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2 and water. The organic layer was successively washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, and filtered. After the filtrate was concentrated under reduced pressure, the residue was purified with flash silica gel column chromatography (*n*-hexane/EtOAc = 8:1) to give **4** (425 mg, 99%) as a colorless syrup: $R_f = 0.27$ (*n*-hexane/EtOAc = 5:1); $[\alpha]_D^{20} = +4.0$ (*c* 1.68, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, 2H, $J = 10.4$ Hz), 7.59–7.55 (m, 1H), 7.46–7.42 (m, 2H), 7.32–7.25 (m, 5H), 5.96–5.86 (m, 1H), 5.16–5.13 (m, 2H), 4.59 (d, 1H, $J = 12$ Hz), 4.55 (d, 1H, $J = 12$ Hz), 4.35 (s, 2H), 3.53 (d, 1H, $J = 9.3$ Hz), 3.48 (d, 1H, $J = 9.3$ Hz), 2.46–2.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 138.2, 133.5, 132.8, 130.4, 130.1, 128.9, 128.8, 128.2, 128.1, 119.6, 73.9, 73.3, 73.1, 67.6, 39.9; HRMS (EI): calcd ($C_{20}H_{22}O_4$) 326.1519, found 326.1520.

4.2.2. (2*S*)-2-Fluoro-2-(benzyloxymethyl)-4-penten-1-yl benzoate 5. To a solution of **4** (7.04 mg, 2.16 mmol) in CH_2Cl_2 (5 ml) was added dropwise diethylaminosulfur trifluoride (DAST) (0.5 ml, 3.24 mmol) at −78 °C and the mixture stirred at −78 °C for 30 min. After the reaction was completed, the mixture was warmed to 0 °C and neutralized with saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with flash silica gel column chromatography (*n*-hexane/EtOAc = 20:1) to give **5** (574 mg, 81%) as a colorless syrup: $R_f = 0.5$ (*n*-hexane/EtOAc = 5:1); $[\alpha]_D^{20} = +10.6$ (*c* 0.58, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.03–8.01 (m, 2H), 7.57–7.53 (m, 1H), 7.47–7.44 (m, 2H), 7.32–7.26 (m, 5H), 5.88–5.82 (m, 1H), 5.20–5.16 (m, 2H), 4.59 (s, 2H), 4.50 (d, 2H, $J = 19.2$ Hz), 3.69 (dd, 1H, $J = 19.2$, 10.3 Hz), 3.65 (dd, 1H, $J = 20.4$, 10.2 Hz), 2.66–2.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 138.1, 133.6, 131.4, 131.4, 130.2, 130.1, 128.8, 128.2, 128.1, 120.2, 96.8, 95.0, 74.1, 70.8, 70.5, 65.7, 65.5, 38.1, 37.9; HRMS (EI): calcd ($C_{20}H_{21}FO_3$) 328.1478, found 328.1476.

4.2.3. (2*R*)-2-Fluoro-2-(benzyloxymethyl)-4-penten-1-ol 6. To a solution of **5** (240 mg, 0.73 mmol) in MeOH (4 ml) was added sodium methoxide (25 wt % solution in MeOH, 0.1 ml) and the mixture stirred at room temperature for 1 h. The reaction mixture was poured into EtOAc (50 ml) and neutralized with saturated NH_4Cl solution. The organic layer was washed with brine, dried

over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with flash silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **6** (180 mg, 97%) as a colorless syrup: $R_f = 0.14$ (*n*-hexane/EtOAc = 5:1); $[\alpha]_D^{20} = +3.6$ (*c* 0.72, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.31 (m, 5H), 5.85–5.79 (m, 1H), 5.18–5.14 (m, 2H), 4.60 (d, 1H, $J = 12$ Hz), 4.56 (d, 1H, $J = 12$ Hz), 3.76–3.72 (m, 2H), 3.68–3.58 (m, 2H), 2.55–2.47 (m, 2H), 2.17–2.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 131.9, 128.9, 128.3, 128.1, 119.7, 98.2, 96.4, 74.1, 71.5, 71.2, 65.3, 65.1, 37.8, 37.6; HRMS (EI): calcd ($C_{13}H_{17}FO_2$) 224.1213, found 224.1219.

4.2.4. 3′-*O*-Benzyl-2,3-dideoxy-3-fluoroapio-L-furanosyl acetate 7. To a stirred solution of **6** (180 mg, 0.80 mmol) in EtOAc (5 ml) at −78 °C was periodically added an EtOAc solution saturated with ozone over 2 h. After the reaction was completed, dimethyl sulfide (1.5 ml) was added and the mixture stirred at room temperature overnight. After concentrating the solution, the residue was diluted with CH_2Cl_2 (4 ml). To the solution were added 4-dimethylaminopyridine (17 mg, 0.16 mmol), triethylamine (0.1 ml), and acetic anhydride (0.1 ml, 1.20 mmol) at −10 °C and the mixture stirred at −10 °C for 1 h. The mixture was diluted with CH_2Cl_2 and water. The organic layer was successively washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, and filtered. After the filtrate was concentrated under reduced pressure, the residue was purified with silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give a 4:1 mixture of two diastereoisomers **7** (167 mg, 78%) as a colorless syrup. Major isomer: $R_f = 0.53$ (*n*-hexane/EtOAc = 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 6.44 (dd, 1H, $J = 6.0$, 2.3 Hz), 4.66–4.63 (m, 2H), 4.22–4.02 (m, 2H), 3.80–3.62 (m, 2H), 2.65–2.21 (m, 2H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 137.5, 128.6, 127.9, 127.0, 97.3, 92.6, 75.2, 74.5, 69.7, 38.5, 21.3; HRMS (EI): calcd ($C_{14}H_{17}FO_4$) 268.1111, found 268.1108.

4.2.5. (2*R*)-2-Fluoro-2-(hydroxymethyl)-4-penten-1-yl benzoate 8. To a solution of **5** (300 mg, 0.91 mmol) in CH_2Cl_2 (5 ml) was added boron trichloride (1 M solution in CH_2Cl_2, 4.5 ml) at −78 °C and the mixture stirred at −78 °C for 1 h. To the reaction mixture was added dropwise a mixture (10 ml) of CH_2Cl_2 and methanol (1:1) and the mixture warmed to 0 °C and diluted with *n*-hexane (10 ml). Impurities were removed by filtering the reaction mixture through short silica gel column. After evaporation of the filtrate was purified with silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **8** (167 mg, 77%) as a colorless syrup: $R_f = 0.43$ (*n*-hexane/EtOAc = 2:1); $[\alpha]_D^{20} = -15.7$ (*c* 0.67, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.07–8.05 (m, 2H), 7.61–7.57 (m, 1H), 7.48–7.44 (m, 2H), 5.90–5.83 (m, 1H), 5.23–5.19 (m, 2H), 4.58–4.44 (m, 2H), 3.78 (d, 1H, $J = 5.0$ Hz), 3.74 (d, 1H, $J = 5.0$ Hz), 2.64–2.57 (m, 2H), 2.28–2.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 133.8, 131.2, 130.1, 129.8, 128.9, 120.4, 97.4, 95.6, 64.9, 64.7, 64.1, 63.8, 37.6, 37.4; HRMS (EI): calcd ($C_{13}H_{15}FO_3$) 238.1006, found 238.1014.

4.2.6. 3′-*O*-Benzoyl-2,3-dideoxy-3-fluoroapio-D-furanosyl acetate 9. Compound **8** (166 mg, 0.697 mmol) was converted to a 5:1 mixture of two diastereoisomers **9** (153 mg, 74%) as a colorless syrup according to the same procedure used for the preparation of **7**. Major isomer: $R_f = 0.5$ (*n*-hexane/EtOAc = 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.07–8.03 (m, 2H), 7.62–7.58 (m, 1H), 7.49–7.45 (m, 2H), 6.51 (dd, 1H, $J = 6.0$, 2.0 Hz), 4.69–4.54 (m, 2H), 4.32–4.09 (m, 2H), 2.74–2.32 (m, 2H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 165.3, 133.5, 130.3, 129.6, 128.5, 97.3, 92.0, 71.4, 70.2 38.3, 21.2; HRMS (EI): calcd ($C_{14}H_{15}FO_5$) 282.0904, found 282.0906.

4.2.7. (−)-N^4-Acetyl-1-(3′-*O*-benzyl-2,3-dideoxy-3-fluoroapio-β-L-furanosyl)cytosine 10a and (+)-N^4-acetyl-1-(3′-*O*-benzyl-2,3-dideoxy-3-fluoroapio-α-L-furanosyl)cytosine 10b. A suspension of N^4-acetylcytosine (183 mg, 1.2 mmol) and ammonium sulfate (catalytic amount) in 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 10 ml) was stirred under reflux for 3 h. The reaction mixture was cooled to room temperature and HMDS was removed under reduced pressure. To this residue was added a solution of **7** (160 mg, 0.60 mmol) in anhydrous CH_2Cl_2 (15 ml) and the reaction mixture was cooled to 0 °C. Trimethylsilyl trifluoro-methanesulfonate (TMSOTf, 0.23 ml, 1.2 mmol) was added and stirred for 30 min. The reaction mixture was diluted with CH_2Cl_2 and neutralized with saturated $NaHCO_3$ solution. The organic layer was separated, washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **10a** (72 mg, 34%) and **10b** (70 mg, 33%) as a white solid. Compound **10a**: $R_f = 0.28$ (EtOAc only); $[\alpha]_D^{20} = -76.9$ (*c* 0.31, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (br s, 1H), 7.81 (d, 1H, $J = 7.5$ Hz), 7.39 (d, 1H, $J = 7.5$ Hz), 7.37–7.26 (m, 5H), 6.17 (t, 1H, $J = 6.4$ Hz), 4.58 (d, 1H, $J = 12$ Hz), 4.54 (d, 1H, $J = 12$ Hz), 4.29–4.19 (m, 2H), 3.74–3.60 (m, 2H) 3.05–2.94 (m, 1H), 2.31–2.18 (m, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 163.5, 155.3, 144.1, 137.5, 128.9, 128.5, 128.1, 103.6, 101.7, 97.1, 89.5, 76.1, 75.9, 74.1, 70.2, 69.9, 42.4, 42.2, 25.3; HRMS (EI): calcd ($C_{18}H_{20}O_4N_3F$) 361.1439, found 361.1435. Compound **10b**: $R_f = 0.17$ (EtOAc only); $[\alpha]_D^{20} = +65.2$ (*c* 0.42, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (br s, 1H), 7.92 (d, 1H, $J = 7.5$ Hz), 7.44 (d, 1H, $J = 7.5$ Hz), 7.38–7.26 (m, 5H), 6.18 (dd, 1H, $J = 7.1$, 1.1 Hz), 4.60 (d, 1H, $J = 12.1$ Hz), 4.55 (d, 1H, $J = 12.1$ Hz), 4.51–4.10 (m, 2H), 3.75–3.60 (m, 2H), 2.73–2.42 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 163.6, 155.5, 144.4, 137.5, 128.9, 128.4, 128.1, 103.2, 101.4, 96.8, 88.7, 77.2, 77.0, 74.1, 70.0, 69.8, 41.7, 41.5, 25.2; HRMS (EI): calcd ($C_{18}H_{20}O_4N_3F$) 361.1439, found 361.1434.

4.2.8. (+)-1-(3′-*O*-Benzyl-2,3-dideoxy-3-fluoroapio-β-L-furanosyl)thymine (12a) and (+)-1-(3′-*O*-Benzyl-2,3-dideoxy-3-fluoroapio-α-L-furanosyl)thymine 12b. A suspension of thymine (658 mg, 5.2 mmol) and ammonium sulfate (catalytic amount) in HMDS (25 ml) was

refluxed for 4 h. The reaction mixture was cooled to room temperature and HMDS then removed under reduced pressure. To this residue was added a solution of **7** (700 mg, 2.6 mmol) in anhydrous CH_2Cl_2 (40 ml) and the reaction mixture cooled to 0 °C. TMSOTf (0.76 ml, 4.0 mmol) was added and stirred for 30 min. After the same work-up as that for **10a**, purification by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) gave **12a** (345 mg, 40%) and **12b** (355 mg, 41%) as a white solid. Compound **12a**: R_f = 0.44 (*n*-hexane/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (br s, 1H), 7.39–7.31 (m, 5H), 7.12 (s, 1H), 6.22 (dd, 1H, J = 7.1, 6.5 Hz), 4.61 (s, 2H), 4.32–4.12 (m, 2H), 3.75–3.68 (m, 2H), 2.73–2.68 (m, 1H), 2.40–2.26 (m, 1H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 150.4, 137.5, 135.9, 129.0, 128.5, 128.2, 111.6, 103.6, 101.8, 87.5, 75.8, 75.5, 74.2, 70.4, 70.1, 40.8, 40.6, 12.9. Compound **12b**: R_f = 0.32 (*n*-hexane/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.40–7.31 (m, 5H), 7.36 (s, 1H), 6.24 (dd, 1H, J = 7.9, 2.6 Hz), 4.61 (d, 1H), 4.59 (d, 1H), 4.44–4.36 (m, 1H), 3.99 (dd, 1H, J = 34.9, 11.1 Hz), 3.76–3.63 (m, 2H), 2.73–2.58 (m, 1H), 2.36–2.30 (m, 1H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 150.5, 137.4, 135.7, 129.0, 128.5, 128.1, 111.1, 103.2, 101.4, 85.9, 76.2, 75.9, 74.2, 70.1, 69.8, 41.3, 41.1, 13.0.

4.2.9. (−)-1-(2,3-Dideoxy-3-fluoroapio-β-L-furanosyl)-cytosine 11a. To a cooled (−78 °C) solution of **10a** (72 mg, 0.20 mmol) in CH_2Cl_2 (5 ml) was added boron trichloride (1.0 M solution in CH_2Cl_2, 1 ml) and the mixture stirred at the same temperature for 1 h. A mixed solution (5 ml) of CH_2Cl_2 and methanol (1:1) was added dropwise to the reaction mixture and the mixture warmed to 0 °C. After the addition of $NaHCO_3$ (20 mg), the mixture was stirred for 10 min, filtered, and the filtrate concentrated. To the solution of the residue in methanol (4 ml) was added sodium methoxide (25 wt % solution in methanol, 0.05 ml) at room temperature and the mixture stirred for 1 h. The reaction mixture was neutralized with methanol saturated with HCl gas and purified by silica gel column chromatography (CH_2Cl_2/MeOH = 8:1) to give **11a** (40 mg, 87%) as a white solid: R_f = 0.11 (CH_2Cl_2/MeOH = 8:1); mp 82 °C; $[\alpha]_D^{20}$ = −44.4 (*c* 0.18, MeOH) {lit.[4] $[\alpha]_D^{27}$ = −40.7 (*c* 0.70, MeOH)}; UV (H_2O) λ_{max} 270.5 nm (pH 7), 279.1 nm (pH 2), 271.1 nm (pH 11); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, 1H, J = 7.4 Hz), 7.16–7.12 (m, 2H), 6.11 (t, 1H, J = 6.5 Hz), 5.70 (d, 1H, J = 7.4 Hz), 5.23 (t, 1H, J = 5.7 Hz), 4.19 (dd, 1H, J = 35.0, 10.6 Hz), 3.94 (dd, 1H, J = 21.0, 10.6 Hz), 3.71–3.63 (m, 2H), 2.48–2.20 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.7, 157.1, 141.5, 105.4, 103.6, 95.2, 88.6, 75.3, 75.1, 62.9, 62.7, 40.6, 40.4; HRMS (EI): calcd ($C_9H_{12}O_3N_3F$) 229.0864, found 229.0862.

4.2.10. (+)-1-(2,3-Dideoxy-3-fluoroapio-α-L-furanosyl)-cytosine 11b. Compound **10b** (70 mg, 0.19 mmol) was converted to **11b** (39 mg, 88%) as a white solid according to the same procedure used for the preparation of **11a**: R_f = 0.09 (CH_2Cl_2/MeOH = 8:1); mp 195 °C; $[\alpha]_D^{20}$ = +84.1 (*c* 0.37, MeOH) {lit.[4] $[\alpha]_D^{27}$ = +74.5 (*c* 0.41, MeOH)}; UV (H_2O) λ_{max} 270.8 nm (pH 7), 279.7 nm (pH 2), 270.8 nm (pH 11); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, 1H, J = 7.4 Hz), 7.12–7.03 (m, 2H), 6.03 (dd, 1H, J = 7.4, 2.3 Hz), 5.71 (d, 1H, J = 7.4 Hz), 5.25 (m, 1H), 4.30–4.27 (m, 1H), 3.95 (dd, 1H, J = 34.5, 10.9 Hz), 3.65–3.58 (m, 2H), 2.66–2.04 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.7, 157.2, 141.2, 141.1, 104.6, 102.9, 94.5, 87.9, 76.1, 75.9, 62.8, 62.5, 40.9, 40.7; HRMS (EI): calcd ($C_9H_{12}O_3N_3F$) 229.0864, found 229.0864.

4.2.11. (+)-1-(2,3-Dideoxy-3-fluoroapio-β-L-furanosyl)-thymine 13a. To a cooled (−78 °C) solution of **12a** (220 mg, 0.66 mmol) in CH_2Cl_2 (30 ml) was added boron trichloride (1.0 M solution in CH_2Cl_2, 4 ml) and the mixture stirred at the same temperature for 2 h. A mixed solution (10 ml) of CH_2Cl_2 and methanol (1:1) was added dropwise to the reaction mixture and the mixture was warmed to 0 °C. After the addition of $NaHCO_3$ (100 mg), the mixture was stirred for 10 min, filtered, and the filtrate concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1:10) to give **13a** (95 mg, 60%) as a white solid: R_f = 0.45 (CH_2Cl_2/MeOH = 10:1); mp 179 °C; $[\alpha]_D^{20}$ = +10.0 (*c* 0.18, MeOH); UV (H_2O) λ_{max} 266 nm (pH 7), 268 nm (pH 2), 268 nm (pH 11); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (br s, 1H), 7.56 (d, 1H, J = 1.0 Hz), 6.14 (dd, 1H, J = 8.1, 6.4 Hz), 5.26 (br t, 1H), 4.21 (dd, 1H, J = 35.0, 10.5 Hz), 3.98–3.90 (m, 1H), 3.73–3.66 (m, 2H), 2.50–2.27 (m, 2H), 1.78 (d, 3H, J = 1.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 165.4, 151.2, 137.3, 110.7, 105.4, 103.6, 87.6, 75.3, 75.0, 63.0, 62.7, 39.5, 39.3, 11.3; HRMS (EI): calcd ($C_{10}H_{13}N_2O_4F$) 244.0860, found 244.0859.

4.2.12. (+)-1-(2,3-Dideoxy-3-fluoroapio-α-L-furanosyl)-thymine (13b). Compound **12b** (230 mg, 0.69 mmol) was converted to **13b** (120 mg, 71.4%) as a white solid according to the same procedure used for the preparation of **13a**: R_f = 0.43 (CH_2Cl_2/MeOH = 10:1); mp 155 °C; $[\alpha]_D^{20}$ = +15.4 (*c* 0.10, MeOH); UV (H_2O) λ_{max} 266 nm (pH 7), 268 nm (pH 2), 268 nm (pH 11); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (br s, 1H), 7.39 (d, 1H, J = 1.0 Hz), 6.08 (dd, 1H, J = 7.8, 3.0 Hz), 5.27 (br t, 1H), 4.30–4.22 (m, 1H), 3.89 (dd, 1H, J = 33.9, 10.9 Hz), 3.68–3.59 (m, 2H), 2.64–2.49 (m, 1H), 2.23–2.17 (m, 1H), 1.77 (d, 3H, J = 1.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 165.4, 151.3, 136.5, 110.2, 104.6, 102.9, 86.4, 75.7, 75.4, 62.8, 62.5, 40.2, 40.0, 11.6; HRMS (EI): calcd ($C_{10}H_{13}N_2O_4F$) 244.0860, found 244.0858.

4.2.13. (+)-N^4-Acetyl-1-(3′-*O*-benzoyl-2,3-dideoxy-3-fluoroapio-β-D-furanosyl)cytosine 14a and (−)-N^4-acetyl-1-(3′-*O*-benzoyl-2,3-dideoxy-3-fluoroapio-α-D-furanosyl)cytosine 14b. Compound **9** (164 mg, 0.58 mmol) was converted to **14a** (60 mg, 28%) and **14b** (65 mg, 30%) as a white solid according to the same procedure used for the preparation of **10a** and **10b**. Compound **14a**: R_f = 0.25 (EtOAc only); $[\alpha]_D^{20}$ = +61.1 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (br s, 1H), 8.02–8.00 (m, 2H), 7.83 (d, 1H, J = 7.5 Hz), 7.62–7.58z

(m, 1H), 7.48–7.41 (m, 3H), 6.15 (t, 1H, $J = 6.5$ Hz), 4.69–4.54 (m, 2H), 4.43–4.29 (m, 2H), 3.22–3.12 (m, 1H), 2.44–2.31 (m, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 166.2, 163.6, 155.3, 144.3, 133.9, 130.1, 129.4, 128.9, 102.8, 101.0, 97.2, 90.1, 76.1, 75.9, 65.3, 65.0, 42.3, 42.1, 25.2; HRMS (EI): calcd ($C_{18}H_{18}O_5N_3F$) 375.1231, found 375.1229. Compound **14b**: $R_f = 0.15$ (EtOAc only); $[\alpha]_D^{20} = -72.9$ (c 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (br s, 1H), 8.04–8.02 (m, 2H), 7.94 (d, 1H, $J = 7.5$ Hz), 7.62–7.58 (m, 1H), 7.48–7.44 (m, 3H), 6.25 (dd, 1H, $J = 7.1$, 1.6 Hz), 4.67–4.53 (m, 3H), 4.22 (dd, 1H, $J = 35.0$, 11.1), 2.85–2.62 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 166.1, 163.6, 155.5, 144.2, 134.0, 130.1, 129.3, 128.9, 102.1, 100.3, 96.8, 88.6, 77.0, 76.7, 64.9, 64.6, 41.9, 41.7, 25.2; HRMS (EI): calcd ($C_{18}H_{18}O_5N_3F$) 375.1231, found 375.1232.

4.2.14. (−)-1-(3′-*O*-Benzoyl-2,3-dideoxy-3-fluoroapio-β-D-furanosyl)thymine (16a) and (−)-1-(3′-*O*-Benzoyl-2,3-dideoxy-3-fluoroapio-α-D-furanosyl)thymine 16b. Compound **9** (400 mg, 1.5 mmol) was converted to **16a** (221 mg, 45%) and **16b** (200 mg, 41%) as a white solid according to the same procedure used for the preparation of **12a** and **12b**. Compound **16a**: $R_f = 0.38$ (*n*-hexane/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (br s, 1H), 8.06–8.03 (m, 2H), 7.63–7.59 (m, 1H), 7.49–7.45 (m, 2H), 7.11 (d, 1H, $J = 0.96$ Hz), 6.14 (t, 1H, $J = 6.9$ Hz), 4.73–4.57 (m, 2H), 4.42–4.23 (m, 2H), 2.87–2.80 (m, 1H), 2.53–2.47 (m, 1H), 1.92 (d, 3H, $J = 0.96$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 164.3, 150.7, 136.5, 134.0, 130.1, 129.5, 128.9, 111.6, 103.0, 101.2, 88.9, 75.9, 75.7, 65.4, 65.1, 40.9, 40.6, 12.8. Compound **16b**: $R_f = 0.30$ (*n*-hexane/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 8.06–8.03 (m, 2H), 7.64–7.60 (m, 1H), 7.50–7.46 (m, 2H), 7.35 (d, 1H, $J = 1.1$ Hz), 6.32 (dd, 1H, $J = 7.8$, 2.6 Hz) 4.70–4.53 (m, 2H), 4.54–4.47 (m, 1H), 4.04 (dd, 1H, $J = 34.0$, 11.1 Hz) 2.80–2.53 (m, 1H), 2.53–2.47 (m, 1H), 1.95 (d, 3H, $J = 0.96$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 164.4, 150.9, 135.4, 134.1, 130.2, 129.3, 129.0, 111.5, 102.2, 100.4, 85.8, 75.9, 75.7, 64.9, 64.6, 41.5, 41.3, 13.1.

4.2.15. (+)-1-(2,3-Dideoxy-3-fluoroapio-β-D-furanosyl)-cytosine 15a. To a solution of **14a** (60 mg, 0.16 mmol) in MeOH (4 ml) was added sodium methoxide (25 wt % solution in methanol, 0.1 ml) at room temperature and the mixture was stirred for 2 h. The reaction mixture was neutralized with methanol saturated with HCl gas and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 8:1) to give **15a** (34 mg, 93%) as a white solid: $R_f = 0.11$ ($CHCl_2$/MeOH = 8:1); mp 85 °C; $[\alpha]_D^{20} = +48.7$ (c 0.17, MeOH) {lit.[5] $[\alpha]_D^{24} = +41.1$ (c 0.48, MeOH)}; UV (H_2O) λ_{max} 271.3 nm (pH 7), 278.6 nm (pH 2), 270.8 nm (pH 11); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (d, 1H, $J = 7.4$ Hz), 7.16–7.08 (m, 2H), 6.10 (t, 1H, $J = 7.5$ Hz), 5.70 (d, 1H, $J = 7.4$ Hz), 5.23 (t, 1H, $J = 5.8$ Hz), 4.19 (dd, 1H, $J = 35.0$, 10.4 Hz), 3.94 (dd, 1H, $J = 22.0$, 10.4 Hz), 3.71–3.63 (m, 2H), 2.48–2.18 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.5, 157.3, 141.5, 105.3, 103.6, 95.4, 88.4, 75.3, 75.0, 62.9, 62.6, 40.6, 40.4; HRMS (EI): calcd ($C_9H_{12}O_3N_3F$) 229.0864, found 229.0866.

4.2.16. (−)-1-(2,3-Dideoxy-3-fluoroapio-α-D-furanosyl)-cytosine 15b. Compound **14b** (65 mg, 0.17 mmol) was converted to **15b** (39 mg, 98%) as a white solid according to the same procedure used for the preparation of **15a**: $R_f = 0.09$ (CH_2Cl_2/MeOH = 8:1); mp 207 °C; $[\alpha]_D^{20} = -78.0$ (c 0.32, MeOH) {lit.[5] $[\alpha]_D^{24} = -75.8$ (c 0.50, MeOH)}; UV (H_2O) λ_{max} 270.3 nm (pH 7), 279.0 nm (pH 2), 270.6 nm (pH 11); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, 1H, $J = 7.4$ Hz), 7.11–7.03 (m, 2H), 6.03 (dd, 1H, $J = 7.6$, 2.5 Hz), 5.71 (d, H, $J = 7.4$ Hz), 5.24 (t, 1H, $J = 5.7$ Hz), 4.25 (dd, 1H, $J = 20.9$, 10.9 Hz), 3.94 (dd, 1H, $J = 34.5$, 10.9 Hz), 3.67–3.58 (m, 2H), 2.62–2.07 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.6, 157.2, 141.2, 141.1, 104.6, 102.8, 94.5, 87.9, 76.2, 75.9, 62.7, 62.5, 40.9, 40.7; HRMS (EI): calcd ($C_9H_{12}O_3N_3F$) 229.0864, found 229.0863.

4.2.17. (−)-1-(2,3-Dideoxy-3-fluoroapio-β-D-furanosyl)-thymine 17a. To a solution of **16a** (180 mg, 0.52 mmol) in MeOH (20 ml) was added sodium methoxide (25 wt % solution in methanol, 0.2 ml) at room temperature and the mixture was stirred for 3 h. The reaction mixture was neutralized by the addition of several pieces of dry ice and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 10:1) to give **17a** (85 mg, 68%) as a white solid: $R_f = 0.45$ (CH_2Cl_2/MeOH = 10:1); mp 181 °C $[\alpha]_D^{20} = -11.8$ (c 0.11, MeOH); UV (H_2O) λ_{max} 266 nm (pH 7), 268 nm (pH 2), 268 nm (pH 11); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (br s, 1H), 7.56 (d, 1H, $J = 1.0$ Hz), 6.14 (dd, 1H, $J = 8.1$, 6.4 Hz), 5.26 (br t, 1H), 4.21 (dd, 1H, $J = 35.0$, 10.5 Hz), 3.98–3.90 (m, 1H), 3.73–3.66 (m, 2H), 2.50–2.27 (m, 2H), 1.78 (d, 3H, $J = 1.0$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 165.4, 151.2, 137.3, 110.7, 105.4, 103.6, 87.6, 75.3, 75.0, 63.0, 62.7, 39.5, 39.3, 11.3; HRMS (EI): calcd ($C_{10}H_{13}N_2O_4F$) 244.0860, found 244.0860.

4.2.18. (−)-1-(2,3-Dideoxy-3-fluoroapio-α-D-furanosyl)-thymine 17b. Compound **16b** (100 mg, 0.29 mmol) was converted to **17b** (60 mg, 86%) as a white solid according to the same procedure used for the preparation of **17a**: $R_f = 0.43$ (CH_2Cl_2/MeOH = 10:1); mp 153 °C $[\alpha]_D^{20} = -14.8$ (c 0.11, MeOH); UV (H_2O) λ_{max} 268 nm (pH 7), 268 nm (pH 2), 266 nm (pH 11); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (br s, 1H), 7.39 (d, 1H, $J = 1.0$ Hz), 6.08 (dd, 1H, $J = 7.8$, 3.0 Hz), 5.27 (br t, 1H), 4.30–4.22 (m, 1H), 3.89 (dd, 1H, $J = 33.9$, 10.9 Hz), 3.68–3.59 (m, 2H), 2.64–2.49 (m, 1H), 2.23–2.17 (m, 1H), 1.77 (d, 3H, $J = 373$ 1.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 165.4, 151.2, 136.5, 110.2, 104.6, 102.9, 86.3, 75.7, 75.4, 62.8, 62.5, 40.2, 40.0, 11.6; HRMS (EI): calcd ($C_{10}H_{13}N_2O_4F$) 244.0860, found 244.0859.

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9. The specific rotations of the D-isomers {**13a** $[\alpha]_D^{20} = +48.7$ (*c* 0.17, MeOH), **13b** $[\alpha]_D^{20} = -78.0$ (*c* 0.32, MeOH)} were also in good agreement with the data reported by Kim and Hong {**13a** $[\alpha]_D^{24} = +41.1$ (*c* 0.48, MeOH), **13b** $[\alpha]_D^{24} = -75.8$ (*c* 0.50, MeOH)}.[5]
10. HPLC conditions: column: Chiral-AGP (Chirom Tech AB), 100×4.0 mm; eluent: 0.01 M phosphate buffer (pH 7); flow rate: 0.3 ml/min; concentration: 40 μg/100 ml; *retention times*: 5.2 min (**11a**), 7.9 min (**11b**), 4.5 min (**15a**), and 6.4 min (**15b**).
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