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Synthesis and Antiviral Activity of Novel Phenyl Branched Apiosyl Nucleosides

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Novel phenyl branched apiosyl nucleosides were synthesized in this study. The introduction of phenyl group in the 4'-position was accomplished by a [3,3]-sigmatropic rearrangement. Apiosyl sugar moiety was constructed by sequential ozonolysis and reductions. The natural bases (cytosine and adenine) were efficiently coupled with an apiosyl sugar by classical glycosyl condensation procedure (persilyated base and TMSOTf). The antiviral activities of the synthesized compounds were evaluated against the HIV-1, HSV-1, HSV-2 and HCMV.

Key words: Apiosyl nucleoside, Antiviral agents, Ozonolysis

INTRODUCTION

Since the emergence of the HIV pandemic, extensive efforts have been concentrated on various modifications in the sugar moiety of nucleosides, resulting in FDA approved anti-HIV agents such as AZT (Furman *et al.*, 1986), ddC (Yarchoan *et al.*, 1988), ddI (Yarchoan *et al.*, 1989), d4T (Lin *et al.*, 1987), 3TC (Schinazi *et al.*, 1992) and abacavir (Daluge *et al.*, 1997). However, side effects and the emergence of drug-resistant mutants continue to be a problem with these antiviral agents. Therefore, the development of structurally new nucleoside derivatives, which have potent antiviral activities and low toxicity as well as novel resistant profiles, is urgently needed to provide better choices for the combination chemotherapy. Recently, the compounds synthesized, 4'α-*C*-ethenylthymidine **1** (Sugimoto *et al.*, 1999), 4'α-*C*-ethynylthymidine **2** (Ohrui *et al.*, 2000) and 4'α-*C*-cyanothymidine **3** (O-Yang *et al.*, 1992) are of particular interest as they represent a new class of compounds and exhibit significant biological activity. Furthermore, more fundamental modifications of pentofuranose moiety, such as isonucleosides and apionucleosides, have been reported to be compatible with antiviral activities. Apiosyl nucleosides are a group of compounds that are structurally similar to natural nucleosides in which the 4¢-hydroxymethyl group of the classical nucleosides moves to the *C*3' position (Nair *et al.*, 1995). Among this type of nucleosides adenine analogue (apio-ddA, **4**) was reported to exhibit anti-HIV activity comparable to parent 2',3'-dideoxy adenosine (Nair *et al.*, 1994). The glycosyl bond of apio-ddA also appears to possess metabolic resistance to adenosine deaminase (Sells *et al.*, 1993). Nevertheless, since systematic structure-activity relationship study in apio dideoxy nucleosides has not been fulfilled so far, it is thought that much more effort should be made in this class of nucleosides to search for new antiviral agents. Based on these interesting observations of branched and apiosyl nucleoside we have synthesized novel 4'-phenyl branched apiosyl nucleosides.

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MATERIALS AND METHODS

All the chemicals were of reagent grade and were used without further purification. All the moisture-sensitive reactions were performed in an inert atmosphere with either N_2 or Ar using distilled dry solvents. The melting points were determined using a Mel-temp II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL JNM-LA 300 spectrometer. The chemical shifts are reported in parts per million (δ) and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). The UV spectra were obtained using a Beckman DU-7 spectrophotometer. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. The dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

(±)-4-(*tert*-Butyldimethylsilanyloxy)-3-formyl-3-phenyl-butyric acid ethyl ester (7)

A solution of compound **6** (3.44 g, 12.0 mmol) in anhydrous CH_2Cl_2 (120 mol) was cooled down to -78°C, and ozone gas was then bubbled into the reaction mixture until a blue color persisted for an additional 5 min. The reaction mixture was degassed with nitrogen, and methyl sulfide (4.3 mol, 60.1 mmol) was slowly added at -78°C. The mixture was stirred for 1 h at rt under nitrogen. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:35) to give compound **7** (3.03 g, 72%) as a colorless oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.60 (s, 1H), 7.39-7.16 (m, 5H), 4.26 (dd, *J* = 10.4, 2.1 Hz, 2H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.14 (d, *J* = 16.8 Hz, 1H), 3.00 (d, *J* = 16.8 Hz, 1H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 200.19, 171.15, 135.94, 133.13, 129.71, 128.40, 128.27, 84.66, 64.40, 60.42, 57.11, 25.67, 18.43, 13.98, -5.75.

(±)-4-(*tert*-Butyldimethylsilanyloxymethyl)-4-phenyl-tetrahydrofuran-2-ol (8)

To a solution of compound **7** (1.87 g, 5.35 mmol) in anhydrous toluene (60 mL), 1.5 M solution of DIBAL-H (7.46 mL, 11.2 mmol) in toluene was added drop wise at -78°C under nitrogen, and the mixture was then stirred for 15 min at -78°C. The reaction mixture was quenched by MeOH (12 mL), and the temperature was elevated to rt. After stirring at rt for 3 h, the resulting solid was removed by Celite filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **8** (1.02 g, 62%) as a colorless oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.26-7.04 (m, 5H), 5.41 (dd, *J* = 9.9, 5.4 Hz, 1H), 4.91 (d, *J* = 10.2 Hz, 1H), 4.29 (d, *J* = 8.7 Hz, 1H), 4.18 (d, *J* = 8.7 Hz, 1H), 3.60 (dd, *J* = 17.4, 9.9 Hz, 2H), 2.48 (m, 2H), 2.25 (d, *J* = 13.5 Hz, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 128.48, 127.94, 127.49, 126.76, 126.39, 99.02, 74.05, 71.93, 71.30, 69.08, 53.35, 51.81, 44.56, 42.30, 25.90, 18.45, -5.63.

(±)-4-[(*tert*-Butyldimethylsilanyloxymethyl)-4-phenyl-tetrahydrofuran-2-yl] acetate (9)

To a solution of compound **8** (1.44 g, 4.67 mmol) in anhydrous pyridine (30 mL), Ac_2O (0.71 g, 7.0 mmol) was slowly added, and the mixture was stirred overnight under nitrogen. The pyridine was evaporated under reduced pressure and co-evaporated with toluene. The residue was extracted with EtOAc/H_2O, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give compound **9** (1.36 g, 83%) as a colorless oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.55-7.31 (m, 5H), 6.59-6.54 (m, 1H), 4.59 (d, *J* = 8.4 Hz, 1H), 4.33 (d, *J* = 8.4 Hz, 1H), 3.84 (d, *J* = 9.6 Hz, 1H), 3.73 (d, *J* = 9.6 Hz, 1H), 2.89 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.50 (dd, *J* = 14.1, 3.0 Hz, 1H), 2.27 (s, 3H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 171.34, 128.21, 127.78, 126.64, 126.39, 98.65, 73.45, 63.56, 62.98, 50.95, 37.56, 25.76, 21.12, 18.42, -5.72.

(*rel*)-N^4-Benzoyl-1-[(2*S*,4*R*)-4-*C*-(*t*-butyldimethylsilyloxymethyl)-4-phenyl-tetrahydrofuran-2-yl] cytosine (10β) and (*rel*)-N^4-Benzoyl-1-[(2*R*,4*R*)-4-*C*-(*t*-butyldimethylsilyloxymethyl)-4-phenyl-tetrahydrofuran-2-yl] cytosine (10α)

N^4-Benzoyl cytosine (178.6 mg, 0.83 mmol), anhydrous HMDS (10 mL), and a catalytic amount of ammonium sulfate (20 mg) were refluxed to a clear solution, and the solvent was distilled under anhydrous conditions. The residue was dissolved in anhydrous 1,2-dichloroethane (5 mL). To this mixture, a solution of **9** (234 mg, 0.667 mmol) in dry DCE (5 mL) and TMSOTf (0.24 mL, 1.33 mmol) was added, and the resulting mixture was stirred at rt for 2 h. The reaction mixture was quenched with 3 mL of saturated $NaHCO_3$ and stirred for 20 min. The resulting solid was filtered through a Celite pad, and the filtrate was extracted with CH_2Cl_2 two times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 3:1) to give compound **10**β (85.86 mg, 32%) and **10**α (75.13 mg, 28%): Spectroscopical data for **10**b: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.76 (br s, 1H), 8.01-7.21 (m, 12H), 6.30 (t, *J* = 6.3 Hz, 1H), 4.74 (d, *J* = 8.4 Hz, 1H), 4.42 (d, *J* = 8.4 Hz, 1H), 3.86 (d, *J* = 9.6 Hz, 1H), 3.74 (d, *J* = 9.6 Hz, 1H), 3.39 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.42 (dd, *J* = 13.8, 5.7 Hz, 1H), 0.85 (s, 9 H), 0.03 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 191.08, 161.45, 142.06, 133.06, 129.03, 128.25, 127.13, 127.02, 89.09, 74.89, 68.84, 53.31, 41.60, 25.76, 18.22, -5.88. Spectroscopical data for **10**α: ^{1}H-NMR ($CDCl_3$, 300 MHz) d 9.72 (br s, 1H), 7.95 (m, 4H), 7.76-7.61 (m, 3H), 7.39 (m, 4H), 7.24 (d, *J* = 7.2 Hz, 1H), 6.28 (t, *J* = 6.0 Hz, 1H), 4.77 (d, *J* = 8.6 Hz, 1H), 4.43 (d, *J* = 8.6 Hz, 1H), 3.89 (d, *J* = 9.4 Hz, 1H), 3.76 (d, *J* = 9.4 Hz, 1H), 3.30 (dd, *J* = 12.8, 6.4 Hz, 1H), 2.52 (dd, *J* = 12.8, 5.8 Hz, 1H), 0.87 (s, 9 H), 0.02 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 191.12, 161.76, 141.87, 133.23, 128.71, 128.11, 127.34, 126.67, 88.81, 75.75, 69.32, 53.38, 40.98, 25.34, 18.65, -5.71.

(*rel*)-1-[(2*S*,4*R*)-4-*C*-(*t*-Butyldimethylsilyloxymethyl)-4-phenyl-tetrahydrofuran-2-yl] cytosine (11)

Compound **10**β (88 mg, 0.174 mmol) was treated with saturated methanolic ammonia overnight at rt. The solvent was evaporated under reduced pressure. The residue

was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:15) to give compound **11** (63.6 mg, 91%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.60-7.22 (m, 6H), 6.33 (t, *J* = 6.3 Hz, 1H), 5.76 (d, *J* = 6.9 Hz, 1H), 4.69 (d, *J* = 8.7 Hz, 1H), 4.34 (d, *J* = 8.4 Hz, 1H), 3.86 (d, *J* = 9.6 Hz, 1H), 3.74 (d, *J* = 9.6 Hz, 1H), 3.29 (dd, *J* = 14.1, 6.6 Hz, 1H), 2.35 (dd, *J* = 13.5, 6.0 Hz, 1H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 165.42, 155.72, 142.53, 140.11, 128.16, 127.24, 126.84, 93.45, 88.22, 74.57, 68.76, 53.32, 41.58, 41.58, 25.78, 18.20, -5.88.

(*rel*)-1-[(2*S*,4*R*)-4-*C*-(Hydroxymethyl)-4-phenyl-tetrahydrofuran-2-yl] cytosine (12)

To a solution of **11** (230 mg, 0.573 mmol) in tetrahydrofuran (10 mL), tetrabutylammonium fluoride (1.0 mL, 1.0 M solution in THF) was added at 0°C. The mixture was stirred overnight at rt, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:5) to give compound **12** (123.5 mg, 75%): mp 161-163°C; UV (H_2O) λ_{max} 262.5 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.61-7.13 (m, 6H), 6.17 (t, *J* = 6.6 Hz, 1H), 5.70 (d, *J* = 7.8 Hz, 1H), 5.08 (t, *J* = 5.2 Hz, 1H), 4.37 (d, *J* = 8.7 Hz, 1H), 4.22 (d, *J* = 8.1 Hz, 1H), 2.89 (dd, *J* = 12.9, 6.0 Hz, 1H), 2.09 (dd, *J* = 13.2, 7.2 Hz, 1H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ 165.59, 155.09, 143.46, 140.98, 127.90, 127.15, 126.22, 93.99, 86.85, 74.08, 67.04, 59.74, 53.14.

(*rel*)-6-{Chloro-9-[(2*S*,4*R*)-4-*C*-(*t*-Butyldimethylsilyloxymethyl)-4-phenyl-tetrahydrofuranosyl]} purine (13β) and (*rel*)-6-{Chloro-9-[(2*R*,4*R*)-4-*C*-(*t*-Butyldimethylsilyloxymethyl)-4-phenyl-tetrahydrofuranosyl]} purine (13α)

Compound (**13**β) and (**13**α) was prepared from 6-Chloropurine using the similar method as described for **10**β (30%) and **10**α (34%): Spectroscopical data for **13**β: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.60 (s, 1H), 8.05 (s, 1H), 6.05 (t, *J* = 5.8 Hz, 1H), 4.61 (d, *J* = 8.6 Hz, 1H), 4.32 (d, *J* = 8.6 Hz, 1H), 3.72 (d, *J* = 10.2 Hz, 1H), 3.65 (d, *J* = 10.2 Hz, 1H), 3.20 (dd, *J* = 12.0, 8.4 Hz, 1H), 2.25 (dd, *J* = 12.0, 6.4 Hz, 1H), 0.90 (s, 9H), 0.02 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 155.65, 152.34, 149.71, 148.75, 130.32, 128.83, 127.65, 126.53, 126.22, 92.17, 88.36, 75.65, 69.23, 52.44, 41.26, 25.65, 18.21, -5.44. Spectroscopical data for **13**a: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.62 (s, 1H), 8.08 (s, 1H), 6.00 (d, *J* = 6.2 Hz, 1H), 4.67 (d, *J* = 8.8 Hz, 1H), 4.40 (d, *J* = 8.8 Hz, 1H), 3.70 (d, *J* = 9.6 Hz, 1H), 3.54 (d, *J* = 9.6 Hz, 1H), 3.23 (dd, *J* = 10.6, 6.4 Hz, 1H), 2.29 (dd, *J* = 10.6, 8.4 Hz, 1H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 156.19, 153.21, 149.73, 149.30, 129.89, 127.65, 126.87, 126.54, 91.34, 88.24, 75.34, 69.23, 53.29, 42.73, 25.77, 18.82, -5.70.

(*rel*)-9-[(2S,4R)-4-*C*-(*t*-Butyldimethylsilyloxymethyl)-4-phenyl-tetrahydrofuranosyl]] adenine (14)

Compound **13**β (64 mg, 0.145 mmol) was treated with saturated methanolic ammonia overnight at 90-100°C in a steel bomb. After removal of the solvent, the residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:12) to give compound **14** (47.5 mg, 77%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 7.91 (s, 1H), 7.66-7.38 (m, 5H), 6.11 (t, *J* = 5.8 Hz, 1H), 4.56 (d, *J* = 8.8 Hz, 1H), 4.23 (d, *J* = 8.8 Hz, 1H), 3.79 (d, *J* = 9.4 Hz, 1H), 3.65 (d, *J* = 9.4 Hz, 1H), 3.21 (dd, *J* = 10.4, 6.4 Hz, 1H), 2.25 (dd, *J* = 10.4, 8.2 Hz, 1H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 155.72, 153.69, 148.43, 147.27, 128.28, 127.34, 126.80, 92.12, 89.67, 74.28, 68.29, 52.31, 43.22, 25.91, 18.80, -5.74.

(*rel*)-9-[(2*S*,4*R*)-4-*C*-(Hydroxymethyl)-4-phenyl-tetrahydrofuran-2-yl] adenine (15)

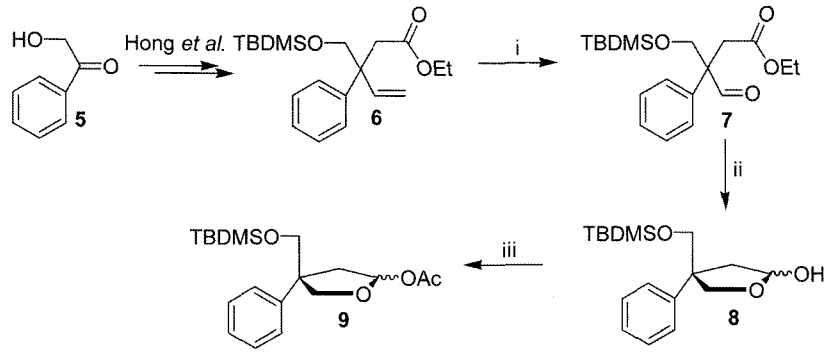
Compound **15** was synthesized from **13**β using the similar procedure as described for **12**: yield 72%; mp 178-180°C; UV (H_2O) λ_{max} 262.0 nm; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.45 (s, 1H), 8.27 (s, 1H), 7.30 (br s, 2H), 6.09 (t, *J* = 6.0 Hz, 1H), 5.12 (t, *J* = 5.4 Hz, 1H), 4.64 (d, *J* = 8.4 Hz, 1H), 4.30 (d, *J* = 8.4 Hz, 1H), 3.75 (d, *J* = 9.0 Hz, 1H), 3.61 (d, *J* = 9.0 Hz, 1H), 3.23 (dd, *J* = 10.6, 6.8 Hz, 1H), 2.34 (dd, *J* = 10.6, 8.4 Hz, 1H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ 155.69, 152.36, 148.77, 146.90, 128.61, 127.89, 127.12, 126.88, 126.21, 91.45, 88.80, 73.23, 68.72, 53.66, 43.28.

RESULTS AND DISCUSSION

As shown in Scheme 1, the γ,δ-unsaturated ester derivative **6**, which was readily synthesized from 2-hydroxy acetophenone **5** by a previously reported method (Hong *et al.*, 2003), was selected as the starting compound for the synthesis of target nucleosides.

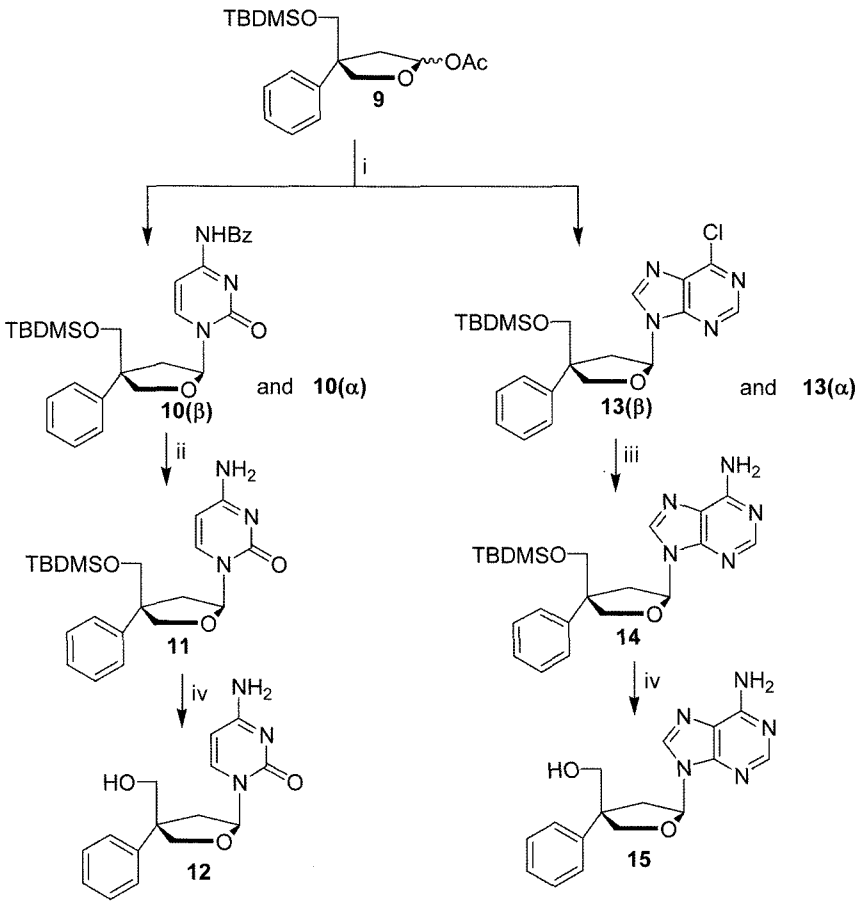
Ester **6** was treated with ozone in methylene chloride at -78°C, followed by decomposition of the ozonide by dimethylsulfide (DMS) to give the aldehyde **7** and subsequently reduced using DIBAL-H in toluene at -78°C to give lactol **8**. The apiose lactol **8** was acetylated in pyridine to furnish the key intermediate **9** as glycosyl donor (Scheme 1). For the preparation of the cytosine nucleoside, compound **9** was condensed with per-*O*-silylated N^4-benzoyl cytosine using trimethylsilyl trifluoromethanesulfonates (TMSOTf) as the catalyst in 1,2-dichloroethane (DCE) to give protected nucleosides **10**β and **10**α, respectively. Desired β-configuration cytosine nucleoside **12** was obtained *via* methanolic ammonolysis and desilylation from the corresponding nucleoside analogue **10**β. Stereochemical assignments of the synthesized compounds were determined on the basis of ^{1}H-NMR

spectroscopy. A cross peak (0.9%) was found in the NOESY spectrum for **10**α between proximal hydrogen atoms (anomeric H & CH_2OH). However, there were weak cross peak (0.3%) in the spectrum for **10**β. The synthesis of adenine nucleoside was carried out by condensation of compound **9** with silylated 6-chloropurine using TMSOTf as a catalyst in DCE to give protected 6-chloropurine derivatives **13**β and **13**α. Stereochmical determinations of **13**β and **13**α were similarly made as described for **10**β and **10**α. Target adenine nucleoside **15** was similarly prepared from **13**β by sequential methanolysis reaction in a steel bomb at 90-100°C followed by desilylation.



Reagents: i) O_3, dimethylsulfide, CH_2Cl_2, -78 °C; ii) DIBAL-H, toluene, -78 °C; iii) Ac_2O, pyridine

Scheme 1. Synthesis of apiosyl acetate



Reagents: i) (a) Bases, HMDS, $(NH_4)_2SO_4$, reflux, overnight; (b) silylated bases, TMSOTf;
ii) NH_3/MeOH, rt, overnight; iii) NH_3/MeOH, steel bomb, 90-100 °C, overnight; iv) TBAF, THF.

Scheme 2. Synthesis of phenyl branched apiosyl nucleosides

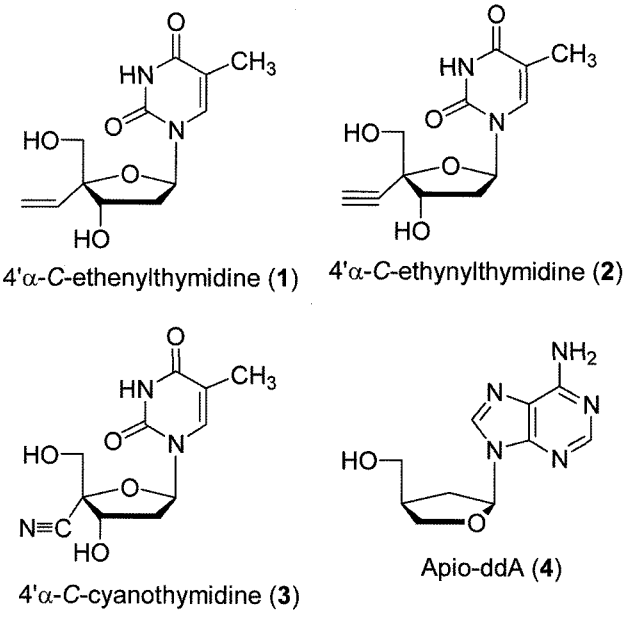


Fig. 1. Synthesis rationale of target 4'-branched nucleosides

In summary, the first synthetic method for novel phenyl branched nucleosides starting from commercially available 2-hydroxy acetophenone was developed. The synthesized compounds were tested against several viruses such as HIV (MT-4 cells), HSV-1,2 (CCL18 cells) and HCMV (AD-169). However, none of these compounds had any significant activity up to 100 mM. The lack of antiviral activity of these compounds is presumably associated with their unfavorable conformations for the phosphorylation occurring during the nucleotide activation process. However, the information obtained in the present study will be useful for the development of novel nucleoside antiviral agents.

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