Pergamon

Tetrahedron 58 (2002) 4865–4871

TETRAHEDRON

Nucleosides with furanyl scaffolds

Sanjib Bera and Vasu Nair*

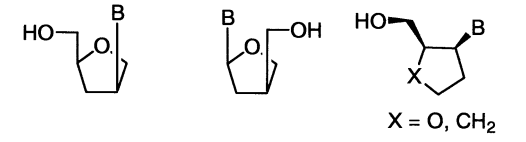
Department of Chemistry, The University of Iowa, Iowa City, IA 52242, USA

Received 28 January 2002; accepted 18 April 2002

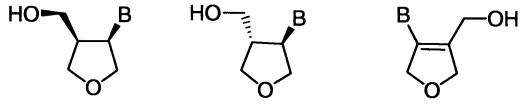
Abstract—Synthesis of purine and pyrimidine nucleosides with furanyl scaffolds is described. The 2-functionalized tetrahydrofuranol derivatives **12** and **15** were coupled with nucleobases through the Mitsunobu reaction. The methodology developed is general and can also be applied for an efficient synthesis of apionucleosides. In addition, the methodology was used for the synthesis of the unsaturated purine nucleoside **22**. However, when the elimination reaction used to produce **22** was applied to the pyrimidine case, the stable anhydro compound **24** was produced. The structures of **18** and **22** were confirmed by single-crystal X-ray data. Antiviral evaluation was performed.

1. Introduction

The anti-HIV activity of unusual dideoxynucleosides, where the base or the 5′-CH_2OH are transposed from their normal 1′ or 4′ position to non-natural or isomeric positions, has generated much interest in the synthesis of other related non-natural nucleosides. 2′-Isomeric dideoxynucleosides (**1**) synthesized in our laboratory,[1] have anti-HIV activity against HIV-1 and HIV-2. Dideoxynucleosides of the apiose family (**2**)[2] show anti-HIV activity in MT-4 cells. 1,2-Disubstituted carba- and iso-nucleosides (**3**) also show some antiviral activity.[3] Based on these findings, we designed and synthesized novel dideoxynucleosides with furanyl scaffolds (**4**–**6**) as potential antiviral agents. In the process of this work, we also discovered an excellent synthesis of an isomer of (±)-apioadenosine[4] that can be applied to the synthesis of apioadenosine itself.



1 **2** **3**



4 **5** **6**

Keywords: nucleosides; furanyl scaffolds; pyrimidine.

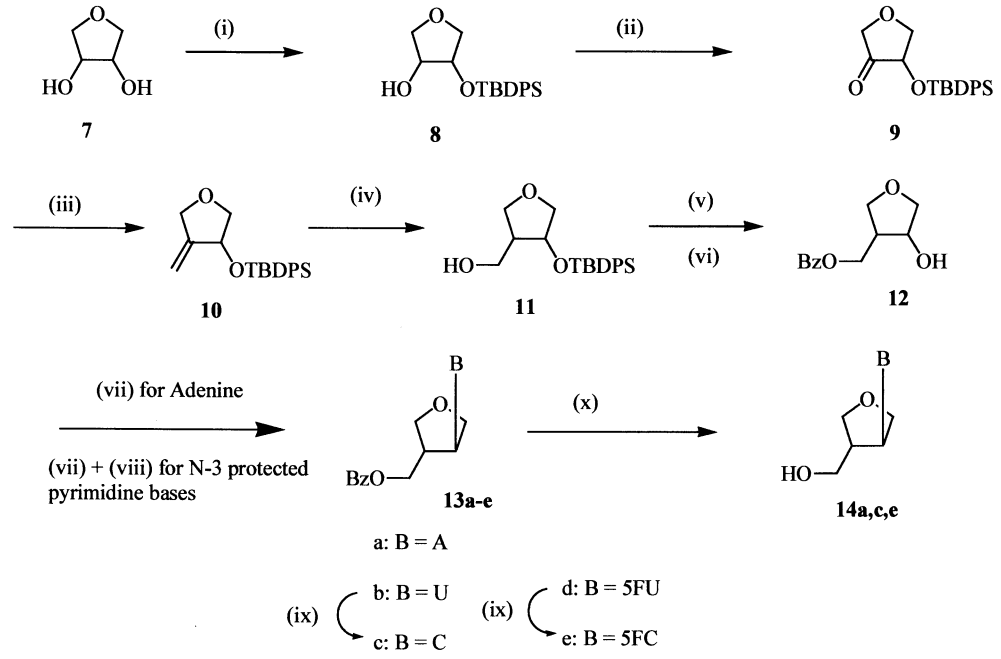
* Corresponding author. Tel.: +1-319-335-1364; fax: +1-319-353-2621; e-mail: vasu-nair@uiowa.edu

2. Results and discussion

Commercially available *meso*-1,4-anhydroerythritol **7** was chosen as a starting material for the synthesis of the hydroxymethyl nucleosides. Protection of one of the hydroxyl groups of **7** by treatment with one equivalent of TBDPSCl in DMF[5] gave the racemic monosilyl protected derivative **8**. The free hydroxyl group of **8** was oxidized[6] to the keto derivative **9**. Wittig reaction[7] of **9** with Ph_3PCH_3I and Bu^{t}OK in dry benzene afforded the olefin **10** in 60% overall yield from **8**. Hydroboration[8] of the protected allyl alcohol **10** with 9-BBN in THF produced the (±)-*cis*-hydroxymethyl derivative **11** as the major product in 70% yield. The (±)-*cis*-derivatives could easily be separated from the (±)-*trans* derivatives by silica gel column chromatography. Protection of the primary hydroxyl group with benzoyl chloride in pyridine followed by deprotection of the silyl protecting group afforded (±)-**12** (Scheme 1).

Compound **12**, on treatment with adenine under Mitsunobu conditions,[9a–c] afforded the *trans* 1,2-disubstituted adenine derivative, (±)-**13a**. Similar treatment of **12** with N-3 protected pyrimidine bases afforded coupling products that were partially deprotected (N-3 benzoyl deprotection) by treatment with aqueous ammonia to give **13b**,**d**. The uracil derivatives **13b** and **d** were converted to their corresponding cytidine derivatives **13c** and **e**. Compounds **13** on treatment with CH_3ONa in MeOH produced racemic 1,2-disubstituted *trans*-hydroxymethyl nucleosides **14**. The stereochemistry of **14c** was confirmed by difference NOE spectroscopy. For example, the α configuration of the hydroxymethyl group at C-4′ was confirmed by the NOE observed for H-6 and H-2′ when H-4′ was irradiated. Similarly, a strong NOE was observed for H-4′ when H-6 was irradiated. The absence of an NOE correlation between H-3′ and H-4′

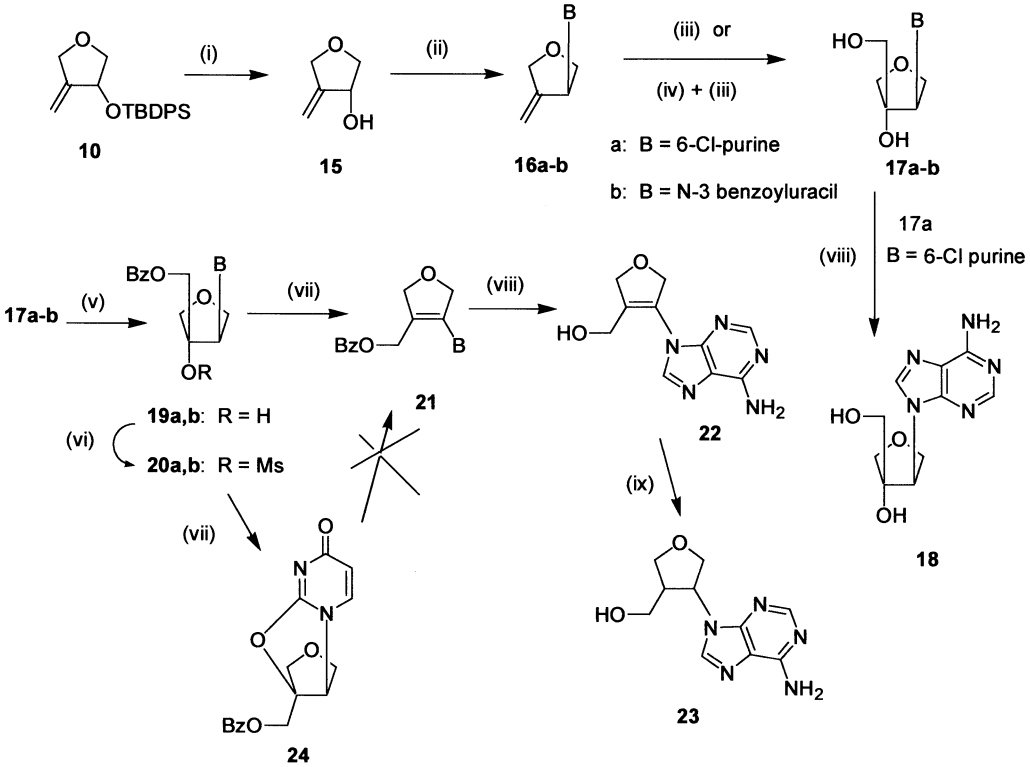
0040–4020/02/$ - see front matter
PII: S0040-4020(02)00430-1



Scheme 1. *Reagents and conditions*: (i) TBDPSCl, imidazole, DMF; (ii) CrO_3, Ac_2O, pyridine, CH_2Cl_2; (iii) CH_3PPh_3I, Bu^{t}OK, benzene; (iv) (a) 9-BBN, THF, room temperature; (b) H_2O_2, NaOH; (v) BzCl, pyridine; (vi) NH_4F, MeOH; (vii) Ph_3P, DEAD, dioxane; (viii) aqueous NH_3 and MeOH; (ix) (a) TIPSCl, DMAP, TEA, CH_3CN, (b) aqueous NH_3; (x) CH_3ONa, MeOH.

indicates that hydroxymethyl group and nucleobase are in a *trans* configuration in the target molecules (Fig. 1).

For compounds of the *cis*-series, the starting material was the unsaturated alcohol, (±)-**15**, derived from deprotection of **10**. Reaction of **15** with adenine under Mitsunobu conditions[9d,e] gave poor yields. However, the Mitsunobu condensation of **15** with 6-chloropurine proceeded smoothly to give nucleoside **16a** bearing the exocyclic methylene group. Similarly, the Mitsunobu reaction of **15**



Scheme 2. *Reagents and conditions*: (i) NH_4F, MeOH; (ii) 6-chloropurine or N-3 benzoyluracil, Ph_3P, DEAD; (iii) OsO_4, acetone; (iv) aqueous NH_3 in MeOH; (v) BzCl, pyridine, −10°C; (vi) MsCl, CH_2Cl_2, TEA, 0°C; (vii) NH_4F, THF; (viii) NH_3/MeOH, 80°C; (ix) H_2/Pd–C.

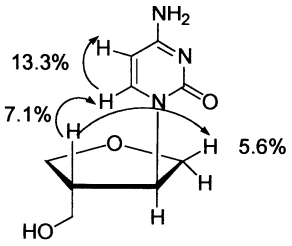


Figure 1. NOE NMR correlations of compound **14c**.

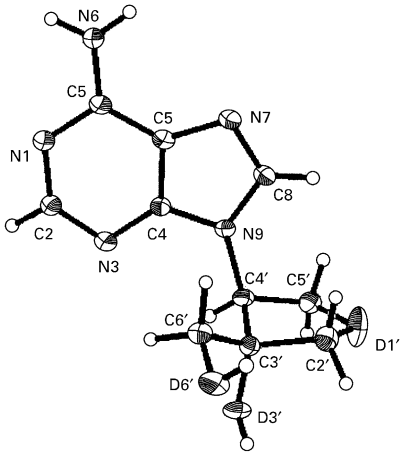


Figure 2. ORTEP plot of crystal structure of **18**.

with N-3 benzoyluracil produced **16b** in good yields (Scheme 2).

Dihydroxylation[10] of compound **16a** through treatment with OsO_4 in the presence of *N*-methylmorpholine-*N*-oxide gave **17a** in 41% overall yield from **15**. Similarly, deprotection of the N-3 benzoyl group of **16b**, followed by dihydroxylation of the deprotected compound afforded **17b**. Compound **17a**, on treatment with saturated methanolic ammonia in a steel bomb, afforded (±)-(isoapiofuranosyl)-adenine **18** in 75% yield. The structure, regiochemistry and stereochemistry of **18** was confirmed by single crystal X-ray data (Fig. 2).

For the synthesis of unsaturated nucleoside **22**, the primary hydroxyl group of **17a** was benzoylated by treatment with benzoyl chloride in pyridine to produce **19a** (84%). The *tert*-hydroxy group of **19a** was then mesylated by treatment with mesyl chloride in the presence of triethylamine to give **20a**. *cis*-Elimination[11] of **20a** with tetrabutylammonium fluoride at 0°C afforded the unsaturated derivative **21**, which on treatment with methanolic ammonia in a steel bomb at 80°C, afforded the 1,2-disubstituted unsaturated adenine derivative **22** (23% yield from **19a**). The structure of **22** was confirmed by single crystal X-ray data (Fig. 3).

Interestingly, the X-ray data also showed that the compound crystallized out in the dimeric form depicted in Fig. 2 with hydrogen bonding between N-7 (of molecule 1) and NH (of NH_2 of molecule 2), and NH (of NH_2 of molecule 1) and N-1 of molecule 2. Catalytic hydrogenation of **22** produced the racemic saturated derivative **23**. Unlike **20a**, treatment of **20b** with Bu_4NF did not produce the unsaturated elimination product, but the 2,3′-*O*-anhydro compound **24**. Formation of **24** is unlikely through an S_N2 mechanism because of the β-stereochemistry of the benzyloxymethyl group. Thus, it is likely that compound **24** arises from an S_N1 pathway in which a carbocation formed at C-3′ is attacked by O-2 of uracil. This type of anhydro compound has not been reported previously in nucleoside chemistry. Various attempts to convert the anhydro compound to the unsaturated derivative failed.

In summary, new furanyl nucleosides in which the base and $-CH_2OH$ have a 1,2-relationship have been synthesized and their structures confirmed by HRMS, NMR and X-ray crystal structure data. The methodology developed is general and can be applied to the synthesis of apio- as well as normal nucleoside analogs. Antiviral studies (HIV-1, HSV, VZV, CMV) revealed that the compounds were marginally active or inactive.

3. Experimental

3.1. General

Melting points reported were uncorrected and were determined on an Electrothermal Engineering Ltd. Melting point apparatus. Ultraviolet (UV) spectra were recorded on a Cary 3 UV–Vis spectrophotometer. ^1H and ^{13}C NMR were recorded on a AC-300 and WM-360 instruments. Chemical

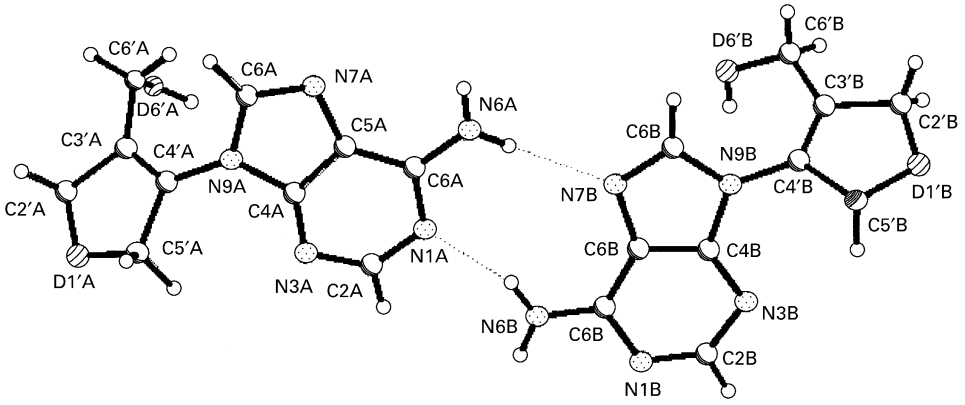


Figure 3. ORTEP plot of crystal structure of **22** showing dimeric form and intermolecular hydrogen bonding.

shifts are referenced to an internal TMS standard for ^{1}H NMR spectra and to solvent ($CDCl_3$, d_6-DMSO, d_6-Acetone or CD_3OD) for ^{13}C NMR spectra. Column chromatographic separations were carried out using 230–400 mesh silica gel. High resolution FAB mass spectral data were obtained on a VG ZAB-HF high resolution mass spectrometer.

3.1.1. (±)-4-(*tert*-Butyldiphenylsilyloxy)-tetrahydrofuran-3-ol 8. To a solution of **7** (1.04 g, 10 mmol) and imidazole (1.02 g, 15 mmol) in DMF (50 mL), TBDPSCl (2.6 mL, 11 mmol) was added. The reaction mixture was then heated at 85°C overnight. DMF was removed under reduced pressure and the residue was taken in EtOAc (100 mL) and washed with water (2×100 mL). The EtOAc part was dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel column to give the silyl derivative **8** (3.3 g, 83%) as a colourless gum. ^{1}H NMR ($CDCl_3$) δ 7.69–7.38 (m, 10H, phenyl), 4.30 (q, J=5.8 Hz, 1H, H-3), 4.08 (m, 1H, H-4), 3.82 (ddd, J=3.4, 4.7, 9.8 Hz, 2H, H-5), 3.60 (d, J=6.2 Hz, 2H, H-2), 1.12 (s, 9H, *t*-butyl); ^{13}C NMR ($CDCl_3$) δ 135.4, 135.3, 132.6, 132.3, 130.1, 130.0, 127.8, 127.7 (phenyl), 73.2 (C-2), 73.0 (C-3), 71.3 (C-5), 70.8 (C-4), 26.7 (*t*-butyl), 19.0 (*t*-butyl); HRMS (FAB): $(M+H)^+$ calcd for $C_{20}H_{27}O_3Si$: 343.1729, found 343.1728.

3.1.2. (±)-3-(*tert*-Butyldiphenylsilyloxy)-tetrahydro-4-methylidene furan 10. To a stirred suspension of CrO_3 (8.25 g), pyridine (13.7 mL) and Ac_2O (8.25 mL) in CH_2Cl_2 (75 mL) was added the solution of **8** (9 g, 26 mmol) in CH_2Cl_2 (75 mL). After the addition the reaction mixture was stirred at room temperature for 1 h. Poured into EtOAc (300 mL) and filtered through a silica gel column. The eluent was evaporated to dryness, coevaporated with toluene to give the keto product which after drying was used for Wittig reaction.

A suspension of Bu^{t}OK (4.68 g) and CH_3PPh_3I (17.1 g) in benzene (150 mL) was heated under reflux for 1 h. The yellow turbid solution was evaporated to dryness and the solution of the keto derivative in benzene (150 mL) was added to the residue. The reaction mixture was then heated at 65°C for 2.5 h. Water (150 mL) was added and extracted with EtOAc (3×80 mL). The organic part was dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel to afford the methylene derivative **10** (60% yield in two steps) as viscous liquid. ^{1}H NMR ($CDCl_3$) δ 7.74–7.40 (m, 10H, phenyl), 5.10 (d, J=1.1 Hz, vinyl), 5.02 (s, 1H, vinyl), 4.66 (bs, 1H, H-3), 4.46 (d, J=13.2 Hz, 1H, H-2a), 4.28 (d, J=13.1 Hz, 1H, H-2b), 3.71–3.60 (m, 2H, H-5). ^{13}C NMR ($CDCl_3$) δ 149.5 (C-4), 135.8, 133.7, 133.4 (phenyl), 106.7 (vinyl), 74.1 (C-2), 73.6 (C-3), 69.9 (C-5), 26.8 (*t*-butyl), 19.2 (*t*-butyl). HRMS (FAB): $(M+Na)^+$ calcd for $C_{21}H_{26}O_2NaSi$: 361.1599, found 361.1614.

3.1.3. (±)-3-(*tert*-Butyldiphenylsilyloxy)-4-(hydroxymethyl)-tetrahydrofuran 11. To a solution of **10** (1.01 g, 3 mmol) in THF (30 mL) was added 9-BBN (0.5 M, 8 mL) and the reaction mixture was stirred at room temperature for 24 h. Another 8 ml of 9-BBN was added and stirred for another 48 h. NaOH (2 N, 10 mL) was added followed by 30% H_2O_2 (1.5 mL) at 0°C. The turbid solution was then stirred at room temperature for 2 h. Saturated $Na_2S_2O_3$ (10 mL) was added to destroy excess of peroxide. Extracted with EtOAc (3×30 mL), the combined EtOAc part was dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel to give the hydroxymethyl derivative **11** (0.65 g, 61%) as gum. ^{1}H NMR ($CDCl_3$) δ 7.67–7.35 (m, 10H, phenyl), 4.52 (m, 1H, H-3), 3.86 (m, 4H, H-2, H-5), 3.53 (ddd, J=3.8, 4.8, 9.6 Hz, 2H), 2.31 (m, 1H, H-4), 1.08 (s, 9H, *t*-butyl). ^{13}C NMR ($CDCl_3$) δ 135.7, 135.6, 133.3, 132.7, 130.0, 127.9, 127.8 (phenyl), 74.8 (C-3), 74.6 (C-2), 69.2 (C-5), 60.5 (CH_2OH), 45.6 (C-4), 26.9 (*t*-butyl), 19.1 (*t*-butyl); HRMS (FAB): $(M+H)^+$ calcd for $C_{21}H_{29}O_3Si$: 357.1886, found 357.1889.

3.1.4. (±)-4-(Benzoyloxymethyl)-tetrahydrofuran-3-ol 12. To a solution of **11** (1.0 g, 2.8 mmol) in pyridine (30 mL), benzoyl chloride (1.64 mL, 14 mmol) was added dropwise at 0°C. After the addition the reaction mixture was stirred at 0°C for 4 h. The reaction was quenched with water (5 mL) and evaporated to dryness and coevaporated with toluene. The residue was taken in EtOAc (100 mL) and washed with water (2×100 mL). The EtOAc part was dried over Na_2SO_4, evaporated to dryness and purified over silica gel to give the benzoyl derivative (1.08 g, 2.35 mmol). The benzoyl derivative was dissolved in MeOH (60 mL) and to the solution NH_4F (0.8 g) was added. The solution was heated under reflux for 40 h and cooled down to room temperature. It was adsorbed directly on silica gel and purified on silica gel column to give **12** (0.49 g, 79%). ^{1}H NMR ($CDCl_3$) δ 8.00–7.37 (m, 5H, phenyl), 4.67 (dd, J=8.3 Hz, 1H), 4.36 (bs, 1H), 4.28 (dd, J=6.2, 11.3 Hz, 1H), 4.00–3.82 (m, 3H), 3.69 (m, 1H), 2.58 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 166.9 (ester CO), 133.1, 129.6, 128.5, 128.3 (phenyl), 75.7 (C-2), 71.2 (C-3), 68.4 (C-5), 61.6 (CH_2OBz), 44.5 (C-4). HRMS (FAB): $(M+H)^+$ calcd for $C_{12}H_{15}O_4$: 223.0970, found 223.0970

3.2. General methods for the synthesis of 13b,d

To a suspension of **12** (0.18 g, 0.81 mmol), PPh_3 (0.425 g, 1.62 mmol) and N-3 benzoyl pyrimidine base (1.6 mmol) in dioxane (25 mL) was added DEAD (0.26 mL, 1.62 mmol) dropwise. After the addition the reaction mixture was stirred at room temperature for 3 days. The solution was directly adsorbed on silica gel and purified over silica gel column to give the protected nucleosides which were characterized after N-3 benzoyl deprotection. The protected nucleosides were dissolved in MeOH (20 mL) and to this was added aqueous ammonia (4 mL, 28%). The solution was stirred at room temperature for 2–3 h and evaporated to dryness under reduced pressure. The residue was purified over silica gel to give **13b** (43%), **d** (40%). The uracil derivatives **13b** and **d** were converted to the corresponding cytidine derivatives **13c** and **e**, respectively, following the literature procedure.[12] These cytidine derivatives **13c** and **e** were characterized as their deprotected form **14c** and **e**.

3.2.1. Compound 13b. ^{1}H NMR ($CDCl_3$) δ 10.01 (s, 1H, NH), 7.96–7.35 (m, 6H, H-6, phenyl), 5.72 (d, J=8.1 Hz, 1H, H-5), 5.14 (m, 1H, H-3′), 4.40 (d, J=6.5 Hz, 2H, CH_2OBz), 4.28 (dd, J=8.3, 9.4 Hz, 1H, H-2′a), 3.95 (d, J=4.6 Hz, 2H, H-5′), 3.61 (dd, J=7.4, 9.5 Hz, 1H, H-2′b), 2.73 (m, 1H, H-4′). ^{13}C NMR ($CDCl_3$) δ 166.1 (ester CO), 163.3 (C-4), 150.8 (C-2), 140.8 (C-6), 133.1, 129.4, 129.3,

128.3 (phenyl), 103.3 (C-5), 71.6 (C-2′), 70.1 (C-5′), 64.1 (CH_2OBz), 58.4 (C-3′), 46.1 (C-4′); HRMS (FAB): $(M+H)^+$ calcd for $C_{16}H_{17}N_2O_5$: 317.1137, found 317.1153.

3.2.2. Compound 13d. ^1H NMR ($CDCl_3$) δ 7.99–7.39 (m, 6H, H-6, phenyl), 5.18 (m, 1H, H-3′), 4.44 (d, J=6.5 Hz, 2H, CH_2OBz), 4.35 (dd, J=8.5, 9.4 Hz, 1H, H-2′a), 3.99 (m, 2H, H-5′), 3.62 (dd, J=7.6, 9.5 Hz, 1H, H-2′b), 2.75 (m, 1H, H-4′). ^{13}C NMR ($CDCl_3$) δ 166.2 (ester CO), 156.7 (d, J=26.9 Hz, C-4), 149.4 (C-2), 141.2 (d, J=239 Hz, C-5), 133.3, 129.6, 129.3, 128.5 (phenyl), 125.1 (d, J=33.4 Hz, C-6), 71.7 (C-2′), 70.1 (C-5′), 63.9 (CH_2OBz), 58.8 (C-3′), 46.4 (C-4′).

3.3. General method for the synthesis of 14 from 13

To a solution of **13** (1 mmol) in anhydrous MeOH (10 ml) was added NaOMe (0.15 g) and the reaction mixture was stirred at room temperature for 3 h. The solution was neutralized with 10% aqueous acetic acid and evaporated to dryness under reduced pressure. The residue was purified over silica gel to give **14**.

3.3.1. (±)-*trans*-6-Amino-9-[4-(hydroxymethyl)-tetrahydrofuran-3-yl]-9H-purin 14a. To a suspension of **12** (0.16 g, 0.72 mmol), PPh_3 (0.38 g, 1.4 mmol) and adenine (0.15 g) in dioxane (15 mL) was added DEAD (0.23 mL, 1.4 mmol) dropwise. After the addition the reaction mixture was stirred at room temperature for 5 days. The solution was directly adsorbed on silica gel and purified over silica gel column to give **13a** (0.06 g, 24%) as white solid. Compound **13a** (0.05 g) was dissolved in MeOH (10 mL) and to the solution sodium methoxide (0.02 g) was added. The reaction mixture was stirred at room temperature for 3 h. The solution was neutralized with 10% aqueous acetic acid and evaporated to dryness. The residue was purified over silica gel column to give **14a** (0.03 g, 86%) as white powder. Mp: 194°C; UV (MeOH) λ_{max} 261 (ϵ 14,500); ^1H NMR (d_4-MeOH) δ 8.20 (s, 1H, H-2), 8.19 (s, 1H, H-8), 5.06 (m, 1H, H-3′), 4.34 (t, J=8.5 Hz, 1H), 4.09 (m, 2H), 3.71 (m, 3H), 2.82 (m, 1H); ^{13}C NMR (d_4-MeOH) δ 157.0 (C-6), 153.6 (C-2), 150.1 (C-4), 141.0 (C-8), 119.8 (C-5), 73.1 (C-2′), 71.2 (C-5′), 62.5 (CH_2OH), 58.8 (C-3′), 49.6 (C-4′). HRMS (FAB): $(M+H)^+$ calcd for $C_{10}H_{14}N_5O_2$: 236.1147, found 236.1147;

3.3.2. (±)-*trans*-4-Amino-1-[4-(hydroxymethyl)-tetrahydrofuran-3-yl]-pyrimidine-2(1H)-one 14c. Mp: 200°C; UV (MeOH) λ_{max} 276 (ϵ 9300); ^1H NMR (d_4-MeOH) δ 7.62 (d, J=7.4 Hz, 1H, H-6), 5.90 (d, J=7.4 Hz, 1H, H-5), 4.94 (m, 1H, H-3′), 4.22 (t, J=8.0 Hz, 1H, H-2′a), 3.91 (m, 2H, H-5′), 3.67–3.56 (m, 3H, H-2′b, CH_2OH), 2.48 (m, 1H, H-4′); ^{13}C NMR (d_4-MeOH+D_2O 4:1) δ 167.1 (C-4), 158.8 (C-2), 144.1 (C-6), 96.9 (C-5), 72.7/71.5, C-2′/C-5′, 63.0, CH_2OH, 61.1, C-3′, 49.0, C-4′; HRMS (FAB): $(M+H)^+$ calcd for $C_9H_{14}N_3O_3$: 212.1035, found 212.1038.

3.3.3. (±)-*trans*-4-Amino-1-[4-(hydroxymethyl)-tetrahydrofuran-3-yl]-5-fluoro-pyrimidine-2(1H)-one 14e. UV (MeOH) λ_{max} 286 (ϵ 6,700); 241 nm; ^1H NMR (d_4-MeOH+D_2O) δ 7.75 (m, 1H, H-6), 4.92 (bs, 1H, H-3′), 4.23 (t, J=7.8 Hz, 1H, H-2′a), 3.91 (m, 2H, H-5′), 3.65 (m, 2H, CH_2OH), 3.58 (t, J=7.8 Hz, 1H, H-2′b), 2.48 (m, 1H, H-4′); ^{13}C NMR (d_4-MeOH+D_2O) δ 159.1 (d, J=13.8 Hz, C-4), 157.2 (C-2), 136.5 (d, C-5), 128.2 (d, J=32.0 Hz, C-6), 72.7 (C-2′), 71.4 (C-5′), 63.1 (CH_2OH), 61.8 (C-3′), 50.3 (C-4′) HRMS (FAB): $(M+H)^+$ calcd for $C_{10}H_{13}FN_3O_3$: 230.0940, found 230.0944.

3.3.4. (±)-Tetrahydrofuran-4-methylidene-3-ol 15. To a solution of **10** (1.69 g, 5 mmol) in methanol (100 mL) was added NH_4F (1 g) and the reaction mixture was heated under reflux for 4 h. The solution was adsorbed directly on silica gel and purified over silica gel to produce the allyl alcohol derivative **15** (0.43 g, 86%) as an oil. ^1H NMR ($CDCl_3$) δ 5.24 (m, 1H, vinyl), 5.05 (m, 1H, vinyl), 4.47 (bs, 1H, H-3), 4.39 (m, 1H, H-2a), 4.19 (m, 1H, H-2b), 3.83 (dd, J=5.2, 9.6 Hz, 1H, H-5a), 3.65 (dd, J=3.9, 9.6, 1H, H-5b). ^{13}C NMR ($CDCl_3$) δ 150.2 (C-4), 107.7 (vinyl), 74.9 (C-2), 72.5 (C-3), 69.8 (C-5).

3.3.5. (±)-4-(6-Chloro-9H-purin-9-yl)-3-(hydroxymethyl)-tetrahydrofuran-3-ol 17a. To a suspension of **15** (0.45 g, 4.5 mmol), PPh_3 (1.8 g) and 6-chloro purine (0.77 g) in THF (70 mL) was added DEAD (1.5 mL) dropwise at 0°C. After the addition the reaction mixture was stirred at 0°C for 5 h. The solution was directly adsorbed on silica gel and purified over silica gel column to give **16a**. Compound **16a** was dissolved in acetone–water (50 mL, 4:1) and to the solution *N*-methylmorpholine-*N*-oxide (0.6 g) and OsO_4 (0.05 g) were added. The reaction mixture was then stirred at room temperature for 24 h. Solvent was evaporated to dryness under reduced pressure and the residue was purified over silica gel to produce the dihydroxylated derivative **17a** (0.5 g, 41% from **15**) as white solid. Mp: 202°C; UV (MeOH) λ_{max} 265 (ϵ 11,500); ^1H NMR (d_6-DMSO) δ 8.76 (s, 1H, H-2), 8.48 (s, 1H, H-8), 5.59 (s, 1H, –OH), 5.07 (m, 1H, H-4′), 4.50 (t, J=5.0 Hz, 1H, –OH), 4.36 (dd, J=5.5, 9.9 Hz, 1H), 4.24 (dd, J=1.5, 9.9 Hz, 1H), 4.12 (d, J=9.7 Hz, 1H), 3.71 (d, J=9.8 Hz, 1H) 3.17 (m, 2H); ^{13}C NMR (d_6-DMSO) δ 152.4 (C-6), 151.4 (C-2), 148.9 (C-4), 145.9 (C-8), 130.4 (C-5), 82.2 (C-3′), 74.9 (C-2′), 71.2 (C-5′), 62.8 (CH_2OH), 62.2 (C-4′); HRMS (FAB): $(M+H)^+$ calcd for $C_{10}H_{12}ClN_4O_3$: 271.0597, found 271.0598.

3.3.6. (±)-4-[Pyrimidine-2,4(1H,3H)-dione-1-yl]-3-(hydroxy-methyl)-tetrahydrofuran-3-ol 17b. To a suspension of **15** (0.2 g, 2 mmol), PPh_3 (1.05 g, 4 mmol) N-3 benzoyl uracil (0.8 g, 3.7 mmol) in THF (50 mL) was added DEAD (0.66 mL, 4 mmol) dropwise at −60°C. After the addition the reaction mixture was stirred at −45°C for 24 h. The solution was directly adsorbed on silica gel and purified over silica gel column to give **16b**. Compound **16b** was dissolved in MeOH (75 mL) and NaOMe (0.9 g) was added into it. The reaction mixture was stirred at room temperature for 20 h. Neutralized with 10% acetic acid and evaporated to dryness. The residue was purified over silica gel. The deprotected nucleoside was dissolved in acetone acetone–water (75 mL, 4:1) and to the solution were added *N*-methylmorpholine-*N*-oxide (0.35 g, 3 mmol) and OsO_4 (0.03 g). The reaction mixture was then stirred at room temperature for 24 h. Solvent was evaporated to dryness under reduced pressure and the residue was purified over silica gel to produce the dihydroxylated derivative **17b** (0.28 g, 68% overall yield

from **15**) as hygroscopic solid. UV (MeOH) λ_{max} 267 (ϵ 9700); ^{1}H NMR (d_6-DMSO) δ 11.23 (s, 1H, NH), 7.38 (d, J=8.0 Hz, 1H, H-6), 5.57 (d, J=8.0 Hz, 1H, H-5), 4.75 (d, J=5.0 Hz, 1H, H-4′), 4.73 (t, J=5.4 Hz, 1H, OH), 4.18 (dd, J=5.6, 10.4 Hz, 1H, H-2′a), 3.96 (d, J=10.4 Hz, 1H, H-2′b), 3.90 (d, J=9.9 Hz, 1H, H-5′a), 3.61 (d, J=9.8 Hz, 1H, H-5′b), 3.27 (m, 2H, CH_2OH); ^{13}C NMR (d_4-MeOH) δ 166.2 (C-4), 153.4 (C-2), 144.0 (C-6), 103.3 (C-5), 84.2 (C-3′), 76.4 (C-2′), 71.9 (C-5′), 64.9 (C-4′), 63.8 (CH_2OH); HRMS (FAB): $(M+H)^+$ calcd for $C_9H_{13}N_2O_5$: 229.0824, found 229.0828.

3.3.7. (±)-4-(6-Amino-9H-purin-9-yl)-3-(hydroxymethyl)-tetrahydrofuran-3-ol 18. A solution of **17a** (0.1 g) in saturated methanolic ammonia (15 mL) was heated at 80°C for 20 h. Solvent was removed and the residue was purified over silica gel column to give **18** (0.07 g, 75%) as white powder. Mp: 234°C; UV (MeOH) λ_{max} 260.6 (ϵ 15,500); ^{1}H NMR (d_6-DMSO) δ 8.14 (s, 1H, H-2), 7.97 (s, 1H, H-8), 7.26 (s, 2H, $-NH_2$), 4.89 (m, 1H, H-4′), 4.61 (t, J=6.0 Hz, 1H, –OH), 4.34 (dd, J=5.6, 9.8 Hz, 1H), 4.19 (dd, J=2.1, 9.8 Hz, 1H), 4.03 (d, J=9.7 Hz, 1H), 3.73 (d, J=9.7 Hz, 1H), 3.17 (dd, J=4.9, 11.0 Hz, 1H), 2.98 (dd, J=6.1, 11.2, 1H). ^{13}C NMR (d_6-DMSO) δ 156.0 (C-6), 152.4 (C-2), 149.8 (C-4), 138.9 (C-8), 118.2 (C-5), 82.5 (C-3′), 75.2 (C-2′), 71.3 (C-5′), 62.5 (CH_2OH), 61.7 (C-4′); HRMS (FAB): $(M+H)^+$ calcd for $C_{10}H_{14}N_5O_3$: 252.1096, found 252.1100.

3.3.8. (±)-4-(6-Chloro-9H-purin-9-yl)-3-(benzoyloxymethyl)-tetrahydrofuran-3-ol 19a. Benzoyl chloride (0.22 mL, 1.87 mmol) in pyridine (5 mL) was added dropwise at 0°C to a solution of **17a** (0.44 g, 1.63 mmol) in pyridine (25 mL) for a period of 1 h. After the addition the reaction mixture was stirred for another 2 h at 0°C. Saturated aqueous $NaHCO_3$ (25 mL) was added and the solution was extracted with CH_2Cl_2 (3×25 mL). The combined organic part was evaporated under reduced pressure, coevaporated with toluene. The residue was purified over silica gel column to give **19a** (0.59 g. 84%) as solid white foam. Mp: 202°C; ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H, H-2), 8.41 (s, 1H, H-8), 7.69–7.27 (m, 5H, phenyl), 5.32 (d, J=4.2 Hz, 1H, H-4′), 4.68 (bs, 1H, –OH), 4.61 (dd, J=4.8, 10.2 Hz, 1H), 4.32–4.06 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 166.06 (carbonyl), 152.2 (C-2), 151.9/ 151.4 (C-4/C-6), 143.7 (C-8), 133.7 (phenyl), 131.1 (C-5), 129.6, 128.5 (phenyl), 82.5 (C-3′), 75.7 (C-2′), 72.1 (C-5′), 64.9 (CH_2OBz), 62.9 (C-4′); HRMS (FAB): $(M+H)^+$ calcd for $C_{17}H_{16}ClN_4O_4$: 375.0860, found 375.0867.

3.3.9. (±)-4-[Pyrimidine-2,4(1H,3H)-dione-1-yl]-3-(benzoyloxymethyl)-tetrahydrofuran-3-ol 19b. Compound **19b** was prepared following the same method as described for **19a** in 71% yield. Mp: 182°C; ^{1}H NMR ($CDCl_3$+d_4-MeOH) δ 7.99–7.41 (m, 6H, H-6, phenyl), 5.68 (d, J=8.1 Hz, 1H, H-5), 5.07 (d, J=5.3 Hz, 1H, H-4′), 4.41 (m, 3H), 4.12 (2×d, J=5.5, 4.6 Hz, 2H), 3.95 (d, J=10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$+d_4-MeOH) δ 165.9 (CO), 163.6 (C-4), 151.1 (C-2), 141.2 (C-6), 132.8, 129.1, 128.6, 127.8 (phenyl), 102.6 (C-5), 81.1 (C-3′), 75.0 (C-2′), 70.6 (C-5′), 64.5 (CH_2OBz), 63.1 (C-4′); HRMS (FAB): $(M+H)^+$ calcd for $C_{16}H_{17}N_2O_6$: 333.1087, found 229.0828.

3.3.10. (±)-6-Amino-9-(4-hydroxymethyl-2,5-dihydrofuran-3-yl)-purine 22. To a solution of **19a** (0.3 g, 0.85 mmol) in CH_2Cl_2 (30 mL) were added Et_3N (0.83 mL, 6 mmol) and mesyl chloride (0.33 mL, 4.2 mmol) at 0°C. The reaction mixture was then stirred at 0°C for 2 h. The reaction was quenched with water (2 mL). Organic part was washed with saturated aqueous $NaHCO_3$ (30 mL) and water (30 mL), dried over Na_2SO_4 and evaporated to dryness to give the mesyl derivative **20a**. Crude mesyl product (0.4 g) was dissolved in THF (40 mL) and to this was added Bu_4NF (1 M, 15 ml) at 0°C and the solution was stirred at 0°C for 1.5 h. The reaction mixture was diluted with ethyl acetate (100 mL). The organic part was washed with $NaHCO_3$ (25 mL) and brine (30 mL), dried over Na_2SO_4 and purified over silica gel column to give the elimination product **21**. Compound **21** was always contaminated with unidentified impurities, so it was characterized after converting it to amino derivative **22**. A solution of **21** in methanolic ammonia (12 mL) was heated in a steel bomb for 20 h. Solvent was evaporated and the residue was purified over silica gel to give **22** (0.045 g, 23% from **19**) as a pale yellow coloured solid powder. Mp: 246°C; UV (MeOH) λ_{max} 259 (ϵ 13,700); ^{1}H NMR (d_6-DMSO) δ 8.23 (s, 1H, H-2), 8.15 (s, 1H, H-8), 7.39 (s, 2H, $-NH_2$), 5.12 (bs, 1H, –OH), 5.00 (m, 2H, H-5′), 4.82 (m, 2H, H-5′), 4.15 (s, 2H, $-CH_2OH$); ^{13}C NMR (d_6-DMSO) δ 156.2 (C-6), 153.0 (C-2), 149.3 (C-4), 139.9 (C-8), 130.7 (C-3′), 124.7 (C-4′), 118.4 (C-5); 75.6 (C-2′), 73.3 (C-5′), 54.2 (CH_2OH); HRMS (FAB): $(M+H)^+$ calcd for $C_{10}H_{12}N_5O_2$: 234.0991, found 234.0989.

3.3.11. (±)-*cis*-6-Amino-9-(4-hydroxymethyl-tetrahydrofuran-3-yl)-purine 23. A suspension of **22** (0.03 g) and Pd–C (10% Pd, 0.01 g) in MeOH–EtOAc (10 ml, 1:1) was stirred under hydrogen pressure (25 PSI) for 16 h. The solution was filter and evaporated to dryness. The residue was purified over silica gel column to give **23** (0.022 g, 73%) as white powder. Mp: 225°C; UV (MeOH) λ_{max} 261 (ϵ 14,700) ^{1}H NMR ($CDCl_3$+d_4-MeOH, 1:1) δ 8.01 (s, 1H, H-2), 7.80 (s, 1H, H-8), 5.02 (t, J=4.9 Hz, 1H, H-3′), 4.09 (d, J=10.5 Hz, 1H), 3.95 (m, 2H), 3.46 (t, J=9.1 Hz, 1H), 3.00 (dd, J=6.2, 11.4 Hz, 1H), 2.87 (dd, J=7.8, 11.4 Hz, 1H), 2.77 (m, 1H). ^{1}H NMR ($CDCl_3$+d_4-MeOH, 1:1) δ 155.4 (C-6), 152.4 (C-2), 149.5 (C-4), 139.0 (C-8), 117.9 (C-5), 72.5 (C-2′), 68.2 (C-5′), 58.4 (CH_2OH), 55.6 (C-3′), 46.3 (C-4′); HRMS (FAB): $(M+H)^+$ calcd for $C_{10}H_{14}N_5O_2$: 236.1147, found 236.1152.

3.3.12. Compound 24. As described for **19a**, compound **19b**, (0.12 g, 0.36 mmol) on treatment with mesyl chloride in CH_2Cl_2 gave the mesylated derivative **20b** (0.1 g, 67%). The mesylated derivative **20b** (0.1 g, 0.24 mmol) was dissolved in THF (15 mL) and to this solution was added Bu_4NF (5 mL, 1 M solution) at 0°C. The reaction mixture was stirred at 0°C for 3 h. Saturated $NaHCO_3$ (50 mL) solution was added to the reaction mixture and the extracted with EtOAc (3×20 mL). The combined EtOAc part was dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel column to produce **24** (0.05 g, 66%) as pale yellow solid. Mp: 233°C; UV (MeOH) λ_{max} 253, 229 nm; ^{1}H NMR ($CDCl_3$+d_4-MeOH) δ 7.85–7.34 (m, 6H, H-6, phenyl), 6.02 (d, J=7.4 Hz, 1H, H-5), 4.94

(d, J=4.0 Hz, 1H, H-4′), 4.34 (d, J=11.4 Hz, 1H, CH_2O), 4.17 (d, J=11.4 Hz, 1H, CH_2O), 3.81 (dd, J=4.1, 11.3 Hz, 1H, H-5′a), 3.73 (d, J=11.2 Hz, 1H, H-5′b); ^{13}C NMR ($CDCl_3$+d_4-MeOH) δ 172.6 (C-4), 165.6 (ester CO), 160.2 (C-2), 135.8 (C-6), 133.8, 129.5, 128.6, 128.2 (phenyl), 110.0 (C-5), 94.2 (C-3′), 74.6 (C-5′), 72.8 (C-2′), 65.5 (C-4′), 63.0 (CH_2OBz) HRMS (FAB): $(M+H)^+$ calcd for $C_{16}H_{15}N_2O_5$: 315.0980, found 315.0983.

3.4. X-Ray crystallographic data

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 178196 and 178197.

Acknowledgements

This research work was supported by the NIH (NIAID). Single-crystal X-ray structure determinations were carried out by Dr Dale Swenson. We thank Professors Erik De Clercq and Jan Balzarini for antiviral evaluations.

References

1. (a) Nair, V.; Clair, M. H. St.; Reardon, J.; Krasny, H. C.; Hazen, R. C.; Paff, M. T.; Boone, L. R.; Tisdale, M.; Najera, I.; Dornsife, R. E.; Averett, D. R.; Borroto-Esoda, K.; Yale, J. L.; Zimmerman, T. P.; Rideout, J. L. *Antimicrob. Agents Chemother.* **1995**, *39*, 1993–1999. (b) Nair, V.; Nuesca, Z. M. *J. Am. Chem. Soc.* **1992**, *114*, 7951–7953.
2. (a) Sells, T. B.; Nair, V. *Tetrahedron Lett.* **1992**, *33*, 7639–7642. (b) Terao, Y.; Akamatsu, M.; Achiwa, K. *Chem. Pharm. Bull.* **1991**, *39*, 823–825.
3. (a) Santana, L.; Uriarte, E. T.; Balzarini, J.; Clercq, E. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1349–1352. (b) Nuesca, M. Z.; Nair, V. *Tetrahedron Lett.* **1994**, *35*, 2485–2488.
4. (a) Sells, T. B.; Nair, V. *Tetrahedron* **1994**, *50*, 117–138. (b) Tronchet, J. M. J.; Tronchet, J. *Helv. Chim. Acta.* **1971**, *54*, 1466–1479. (c) Parikh, D. K.; Watson, R. R. *J. Med. Chem.* **1978**, *21*, 706–709. (d) Tronchet, J. M. J.; Tronchet, J.; Graf, R. *J. Med. Chem.* **1974**, *17*, 1055–1056.
5. Wenzel, T.; Nair, V. *Biocongugate Chem.* **1998**, *9*, 683–690.
6. Du, J.; Choi, Y.; Lee, K.; Chun, B. K.; Hong, J. H.; Chu, C. K. *Nucleosides Nucleotides* **1999**, *18*, 187–195.
7. Chao, Q.; Zhang, J.; Pickering, L.; Jahnke, T. S.; Nair, V. *Tetrahedron* **1998**, *54*, 3113–3124.
8. (a) Action, E. M.; Goerner, R. N.; Uh, H. S.; Ryan, K. J.; Henry, D. W. *J. Med. Chem.* **1979**, *22*, 518–525. (b) Wengel, J.; Schinazi, R. F.; Caruthers, M. V. *Bioorg. Med. Chem.* **1995**, *3*, 1223–1229.
9. (a) Jenny, T. F.; Previsani, N.; Benner, S. A. *Tetrahedron Lett.* **1991**, *32*, 7029–7032. (b) Bonnal, C.; Chavis, C.; Lucas, M. *J. Chem. Soc. Parkin Trans 1.* **1994**, 1401–1410. (c) Jenny, T. F.; Horlacher, J.; Previsani, N.; Benner, S. A. *Helv. Chim. Acta* **1992**, *75*, 1944–1954. (d) Jeong, L. S.; Yoo, S. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 847–852. (e) Bera, S.; Nair, V. *Helv. Chim. Acta* **2000**, *83*, 1398–1407.
10. (a) Mesmaeker, A. D.; Lesueur, C.; Bevierre, M.-O.; Waldner, A.; Fritsch, V.; Wolf, R. M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2790–2794. (b) Sanghvi, Y. S.; Bharadwaj, R.; Debart, F.; Mesmaeker, A. D. *Synthesis* **1994**, 1163–1166.
11. Seela, F.; Bourgeois, W. *Synthesis* **1990**, 945–950.
12. Kakefuda, A.; Shuto, S.; Nagahata, T.; Seki, J.; Sasaki, T.; Matsuda, A. *Tetrahedron* **1994**, *50*, 10167–10182.