4′-*C*-Cyano-2-deoxyguanosine (14a). To a solution of **12a** (70.0 mg, 0.24 mmol) in 50 mM Tris-HCl buffer (pH, 7.50, 13.3 mL) was added adenosine deaminase (0.13 mL, 58.5 units) and stirred for 1 h at 40°C. The precipitate formed was collected by filtaration and recrystallized from water to give **14a** (56.0 mg, 0.19 mmol, 79.2%).

^{1}H-NMR (DMSO-d_6) δ 10.68 (1H, s, NH), 7.93 (1H, s, H-8), 6.53 (2H, s, NH_2), 6.29 (1H, t, H-1′, J = 6.8), 6.27 (1H, d, 3′-OH, J = 4.9), 5.73 (1H, t, 5′-OH, J = 5.8), 4.60 (1H, dd, H-3′, J = 4.9, 10.8), 3.75 (1H, dd, H-5′a, J = 5.8, 11.7), 3.64 (1H, dd, H-5′b, J = 5.9, 11.7), 2.80, 2.40 (each 1H, m, H-2′). FABMS m/z: 293 (MH^+). Anal. Found: C, 41.54; H, 4.37; N, 26.58. Calcd. for $C_{11}H_{12}N_6O_4 \cdot 0.6H_2O$: C, 41.41; H, 4.17; N, 26.34.

N^6-Benzoyl-3′-*O*-*tert*-butyldimethylsilyl-2′-deoxyadenosine (4b). To a solution of **3b** (2.00 g, 3.04 mmol) in DMF (6.00 mL) was added imidazole (0.83 g, 12.2 mmol) and *tert*-butylchlorodimethylsilane (0.92 g, 6.10 mmol) and the solution was stirred at room temperature overnight. After addition of MeOH, the reaction mixture was diluted with AcOEt and washed with water. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure.

The residue was dissolved in $CHCl_3$ (70.0 mL) and added dropwise toluenesulfonic acid hydrate (0.60 g) in MeOH (30.0 mL) at 0°C. After addition, the solution was stirred for 30 min at same temperature. The reaction mixture was neutralized by addition of saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (Eluent: AcOEt/*n*-hexane, 3:1) to give **4b** (1.20 g, 2.56 mmol, 84.2%).

^{1}H-NMR ($CDCl_3$) δ 9.02 (1H, s, NH), 8.79, 8.10 (each 1H, s, H-2 and H-8), 8.03–7.52 (5H, m, aromatic), 6.37 (1H, dd, H-1′, J = 5.5, 9.5), 5.78 (1H, dd, 5′-OH, J = 1.5, 11.5), 4.74 (1H, d, H-3′, J = 6.5), 4.17 (1H, s, H-4′), 4.00–3.74 (2H, m, H-5′), 3.07, 2.27 (each 1H, m, H-2′), 0.94 (9H, s, t-Bu), 0.13 (6H, s, Me). FABMS m/z: 470 (MH^+). Anal. Found: C, 58.45; H, 6.56; N, 14.76. Calcd. for $C_{23}H_{31}N_5O_4Si$: C, 58.83; H, 6.65; N, 14.91.

N^6-Benzoyl-3′-*O*-*tert*-butyldimethylsilyl-2′-deoxy-4′-*C*-hydroxymethyladenosine (5b). The solution of **4b** (2.55 g, 5.43 mmol) in toluene (10.0 mL) and DMSO (15.0 mL) was suspended 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.12 g, 16.3 mmol). The mixture was added pyridine (0.41 mL) and trifluoroacetic acid (0.21 mL) and stirred for 2 h at room temperature. The reaction mixture was diluted with AcOEt and washed with water. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure.

The residue was dissolved in dioxane (15.0 mL) and added 37% aqueous formaldehyde solution (2.86 mL) and 2 N sodium hydroxide (2.86 mL). After stirring for 1 h at room temperature, the reaction mixture was neutralized by addition of AcOH, diluted with AcOEt and washed with water. The organic layer was dried over $MgSO_4$ and evaporated under reduce pressure.

The residue was dissolved in EtOH (25.0 mL) and added $NaBH_4$ (0.21 g, 5.55 mmol) at 0°C. After stirring for 30 min, the reaction mixture was neutralized by addition of AcOH. The mixture was diluted with AcOEt and washed with water. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (Eluent: AcOEt/*n*-hexane, 3:1–4:1–5:1) to give **5b** (1.68 g, 3.36 mmol, 61.9%).

^{1}H-NMR ($CDCl_3$) δ 9.03 (1H, s, NH), 8.79, 8.08 (each 1H, s, H-2 and H-8), 8.03–7.52 (5H, m, aromatic), 6.45 (1H, dd, H-1′, J = 6.0, 9.0), 5.61 (1H, dd, OH, J = 2.0, 11.0), 4.94 (1H, dd, H-3′, J = 1.5, 6.0), 3.87–3.66 (4H, m, H-5′ and H-6′), 3.24 (1H, m, H-2′a), 2.68 (1H, dd, OH, J = 4.0, 9.0), 2.37 (1H, m, H-2′b), 0.96 (9H, s, *tert*-Bu), 0.19, 0.18 (each 3H, s, Me). FABMS m/z: 500 (MH^+). Anal. Found: C, 55.41; H, 6.50; N, 13.32. Calcd. for $C_{24}H_{33}N_5O_5Si \cdot 1.1H_2O$: C, 60.63; H, 7.15; N, 11.46.

N^6-Benzoyl-3′-*O*-*tert*-butyldimethylsilyl-2′-deoxy-4′-*C*-dimethoxytrityloxymethyladenosine (6b). To a solution of **5b** (0.84 g, 1.68 mmol) in CH_2Cl_2 (17.0 mL) was added triethylamine (0.47 mL, 3.37 mmol) and dimethoxytrityl chloride (0.85 g, 2.51 mmol) and stirred for 30 min at 0°C. After addition of MeOH, the reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (Eluent: *n*-hexane/AcOEt, 2:1–1:1) to give **6b** (0.91 g, 1.13 mmol, 67.3%).

^{1}H-NMR ($CDCl_3$) δ 9.17 (1H, s, NH), 8.96, 8.24 (each 1H, s, H-2 and H-8), 8.23–6.94 (18H, m, aromatic), 6.41 (1H, dd, H-1′, J = 6.0, 8.5), 5.44 (1H, dd, 5′-OH, J = 2.5, 11.0), 4.84 (1H, dd, H-3′, J = 1.5, 5.5), 4.43 (1H, dd, H-5′a, J = 3.0, 12.5), 3.92 (6H, s, OMe), 3.78 (1H, t, H-5′b, J = 12.0), 3.67 (1H, d, H-6′a, J = 11.0), 3.30 (1H, m, H-2′a), 3.20 (1H, d, H-6′b, J = 11.0), 2.39 (1H, m, H-2′b), 0.90 (9H, s, *tert*-Bu), 0.13, 0.11, (each 3H, s, Me). FABMS m/z: 802 (MH^+). Anal. Found: C, 67.02; H, 6.52; N, 8.55. Calcd. for $C_{45}H_{51}N_5O_7Si$: C, 67.39; H, 6.41; N, 8.73.

N^6-Benzoyl-3′,5′-di-*O*-*tert*-butyldimethylsilyl-2′-deoxy-4′-*C*-hydroxymethyladenosine (7b). To a solution of **6b** (1.61 g, 2.01 mmol) in DMF (8.00 mL) was added imidazole (0.41 g, 6.02 mmol) and *tert*-butylchlorodimethylsilane (0.45 g, 2.99 mmol) and stirred at room temperature overnight. After addition of MeOH, the reaction mixture was diluted with AcOEt and washed with water. The organic layer was dried over $MgSO_4$ and evaporated.

The residue was dissolved to $CHCl_3$ (70.0 mL) and added dropwise 1% TsOH hydrate in MeOH (30.0 mL) at 0°C. After addition, the solution was stirred for 30 min at same temperature. The reaction mixture was neutralized by addition of saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (Eluent: *n*-hexane/AcOEt, 3:1) to give **7b** (1.00 g, 1.63mmol, 81.1%).

^{1}H-NMR ($CDCl_3$) δ 9.04 (1H, s, NH), 8.81, 8.28 (each 1H, s, H-2 and H-8), 8.04–7.52 (5H, m, aromatic), 6.52 (1H, t, H-1′, J = 6.5), 5.78, 4.88 (1H, dd, H-3′, J = 4.5, 6.5), 3.89–3.73 (4H, m, H-5′ and H-6′), 3.04, 2.58 (each 1H, m, H-2′), 2.48 (1H, dd, 6′-OH, J = 5.5, 8.5) 0.95, 0.89 (each 9H, s, *tert*-Bu), 0.16, 0.06 (each 6H, s, Me). FABMS m/z: 614 (MH^+). Anal. Found: C, 58.33; H, 7.80; N, 11.14. Calcd. for $C_{30}H_{47}N5O5Si2$: C, 58.69; H, 7.72; N, 11.41.

N^6-Benzoyl-3′,5′-di-*O*-*tert*-butyldimethylsilyl-4′-*C*-cyano-2′-deoxyadenosine (10b). The solution of **7b** (1.00 g, 1.63 mmol) in toluene (3.00 mL) and DMSO (6.00 mL) was suspended 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.94 g, 4.90 mmol). Pyridine (0.13 mL) and trifluoroacetic acid (62.8 μL) were added and stirred for 1 h at room temperature. The reaction mixture was diluted with

AcOEt and washed with water. The organic layer was dried over $MgSO_4$ and evaporated to give crude aldehyde **8b**.

To a solution of crude aldehyde **8b** in pyridine (10.0 mL) was added hydroxylamine hydrochloride (0.17 g, 2.45 mmol) and stirred for 30 min at room temperature. The reaction mixture was evaporated and the residue was partitioned between AcOEt and water. The organic layer was dried over $MgSO_4$ and evaporated to give crude oxime **9b**.

To a solution of crude oxime **9b** in CH_2Cl_2 (10.0 mL) was added triethylamine (0.45 mL, 3.23 mmol) and methanesulfonyl chloride (0.19 mL, 2.45 mmol) at 0°C and stirred for 30 min at same temperature. The reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by silica-gel column chromatography (Eluent: $CHCl_3$/MeOH, 100:1) to give **10b** (0.87 g, 1.41 mmol, 87.7%).

^{1}H-NMR ($CDCl_3$) δ 9.10 (1H, s, NH), 8.79, 8.14 (each 1H, s, H-2 and H-8), 8.04–7.52 (5H, m, aromatic), 6.52 (1H, dd, H-1′, J = 6.0, 6.5), 5.02 (1H, t, H-3′, J = 6.0), 4.05, 3.89 (each 1H, d, H-5′, J = 11), 3.22, 2.62 (each 1H, m, H-2′), 0.98, 0.87 (each 9H, s, *tert*-Bu), 0.21, 0.19, 0.08, 0.03 (each 3H, s, Me). FABMS m/z: 609 (MH^+). Anal. Found: C, 58.64; H, 7.38; N, 13.60. Calcd. for $C_{30}H_{44}N_6O_4Si_2 \cdot 0.2H_2O$: C, 58.83; H, 7.31; N, 13.72.

4′-*C*-Cyano-2′-deoxyadenosine (12b). The mixture of **10b** (0.70 g, 1.15 mmol) in MeOH (10.5 mL) and conc. NH_4OH (3.50 mL) was stirred at room temperature overnight. Precipitate formed was collected by filtration to give crude debenzoylated product **11b** (0.50 g).

To a solution of crude **11b** (0.50 g) in THF (7.80 mL) was added tetra-*n*-butylammonium fluoride (1 M solution of THF, 2.18 mL, 2.18 mmol) and stirred for 15 min at room temperature. The reaction mixture was evaporated and the residue was purified by silica-gel column chromatography (Eluent: $CHCl_3$/MeOH, 20:1–10:1). The residue was recrystallized from water to give **12b** (0.21 g, 0.76 mmol, 66.1% from **10b**).

^{1}H-NMR (DMSO-d_6) δ 8.34 (1H, s, H-8), 8.16 (1H, s, H-2), 7.36 (2H, s, NH_2), 6.52 (1H, t, H-1′, J = 6.5), 6.32 (1H, d, 3′-OH, J = 5.0), 5.83 (1H, t, 5′-OH, J = 6.0), 4.74 (1H, dd, H-3′, J = 5.5, 11.5), 3.82 (1H, dd, H-5′a, J = 5.0, 11.5), 3.66 (1H, dd, H-5′b, J = 6.0, 12), 3.01, 2.47 (each 1H, m, H-2′). FABMS m/z: 277 (MH^+). Anal. Found: C, 45.90; H, 4.42; N, 29.12. Calcd. for $C_{11}H_{12}N_6O_3 \cdot 0.6H_2O$: C, 46.02; H, 4.63; N, 29.28.

4′-*C*-Cyano-2′-deoxyinosine (14b). To a solution of **12b** (0.15 g, 0.54 mmol) in Tris-HCl buffer (pH, 7.50, 30.0 mL) was added adenosine deaminase (0.30 mL, 135 units) and stirred for 2 h at 40°C. The reaction mixture was concentrated and purified reverse phase column chromatography (0–2.5% EtOH). The residue was recrystalized from water to give **14b** (90.0 mg, 0.32 mmol, 59.3%).

^{1}H-NMR (DMSO-d_6) δ 12.46 (1H, s, NH), 8.32 (1H, s, H-8), 8.10 (1H, s, H-2), 6.49 (1H, t, H-1′, J = 6.5), 6.36 (1H, d, 3′-OH, J = 5.0), 5.76 (1H, t, 5′-OH, J = 6.0), 4.69 (1H, dd, H-3′, J = 5.5, 11.5), 3.78 (1H, dd, H-5′a, J = 6.0, 12.0), 3.66 (1H, dd, H-5′b, J = 6.0, 12.0), 2.92, 2.49 (each 1H, m, H-2′). FABMS m/z: 278 (MH^+). Anal. Found: C, 44.91; H, 4.06; N, 24.06. Calcd. for $C_{11}H_{11}N_5O_4 \cdot 1H_2O$: C, 44.75; H, 4.44; N, 23.72.

9-(3,5-Di-*O*-*tert*-Butyldimethylsilyl-2-*deoxy*-4-C-ethynyl-*ribo*-pentofuranosyl)-2,6-dibenzamidopurine (16a). The solution of **7a** (2.00 g, 2.73 mmol) in toluene

(6.00 mL) and DMSO (12.0 mL) was suspended 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.57 g, 8.19 mmol). Pyridine (0.22 mL) and trifluoroacetic acid (0.11 mL) were added and stirred for 90 min at room temperature. The reaction mixture was diluted with AcOEt and washed with water. The organic layer was dried over $MgSO_4$ and evaporated to give crude aldehyde **8a**.

To a suspension of bromomethyltriphenylphosphonium bromide (2.40 g, 5.50 mmol) in THF (32.0 mL) was added potassium *tert*-butoxide (0.93 g, 8.29 mmol) at −40°C and stirred for 90 min at same temperature to prepare bromomethylene triphenylphosphorane. The solution was added crude aldehyde **8a** in THF (32.0 mL) and stirred for 2 h at −40°C. The reaction mixture was added saturated NH_4Cl and stirred. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (Eluent: *n*-hexane/AcOEt, 3:1–2:1–1:1) to give crude bromoethene **15a** (1.96 g).

To a solution of crude **15a** (1.96 g) in THF (50.0 mL) was added potassium *tert*-butoxide (0.91 g, 8.11 mmol) at −40°C and the solution was stirred for 1 h at same temperature. After addition of saturated NH_4Cl, the mixture was stirred at room temperature. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (Eluent: *n*-hexane/AcOEt, 2:1) to give **16a** (1.21 g, 1.66 mmol, 60.8% from **7a**).

^{1}H-NMR ($CDCl_3$) δ 9.38, 9.37 (each 1H, s, NH), 8.19 (1H, s, H-8), 8.04–7.49 (10H, m, aromatic), 6.54 (1H, dd, H-1', J = 4.5, 7.0), 4.84 (1H, t, H-3', J = 6.5), 4.03, 3.83 (each 1H, d, H-5', J = 11.0), 2.86, 2.66 (each 1H, m, H-2'), 2.55 (1H, s, ethynyl), 0.94, 0.90 (each 9H, s, *tert*-Bu), 0.14, 0.13, 0.08, 0.06 (each 3H, s, Me). FABMS m/z: 727 (MH^+). Anal. Found: C, 61.91; H, 6.94; N, 11.21. Calcd. for $C_{38}H_{50}N_6O_5Si_2 \cdot 0.5H_2O$: C, 62.01; H, 6.98; N, 11.42.

9-(2-Deoxy-4-*C*-ethynyl-*ribo*-pentofuranosyl)-2,6-diaminopurine (18a). To a solution of **16a** (1.24 g, 1.71 mmol) in THF (30.0 mL) was added tetra-*n*-butylammonium fluoride (1 M solution of THF, 4.30 mL, 4.30 mmol) and stirred for 30 min at room temperature. The reaction mixture was evaporated and the residue was purified by silica-gel column chromatography (Eluent: $CHCl_3$/MeOH, 20:1) to give **17a** (0.70 g, 1.40 mmol).

The mixture of **17a** (0.65 g, 1.30 mmol) in MeOH (15.0 mL) and 40% $MeNH_2$ aqueous solution (30.0 mL) was stirred at room temperature overnight. The reaction mixture was evaporated and the residue was purified by silica-gel column chromatography (Eluent: $CHCl_3$/MeOH, 10:1). The residue was recrystallized from water to give **18a** (0.33 g, 1.14 mmol, 87.7%), whose structure was confirmed by comparing spectroscopic data of **18a** with these of previously reported 9-(2-deoxy-4-*C*-ethynyl-*ribo*-pentofuranosyl)-2,6-diaminopurine.[6]

***N*^{6}-Benzoyl-3',5'-di-*O*-*tert*-butyldimethylsilyl-4'-*C*-ethynyl-2'-deoxyadenosine (16b).** The solution of **7b** (1.80 g, 2.93 mmol) in toluene (6.00 mL) and DMSO (12.0 mL) was suspended 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.69 g, 8.82 mmol). Pyridine (0.24 mL) and trifluoroacetic acid (0.12 mL) were added and stirred for 3 h at room temperature. The reaction mixture was diluted with AcOEt and washed with water. The organic layer was dried over $MgSO_4$ and evaporated to give crude aldehyde **8b**.

To a suspension of bromomethyltriphenylphosphonium bromide (2.56 g, 5.87 mmol) in THF (35.0 mL) was added potassium *tert*-butoxide (1.00 g, 8.91 mmol) at −40°C and stirred for 2 h at same temperature to prepare bromomethylene triphenylphosphorane. The solution was added crude aldehyde **8b** in THF (35.0 mL) and stirred for 2 h at −40°C. The reaction mixture was added saturated NH_4Cl and stirred. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (Eluent: *n*-hexane/AcOEt, 3:1–2:1–1:1) to give crude bromoethene **15b**.

To a solution of crude **15b** in THF (70.0 mL) was added potassium *tert*-butoxide (1.00 g, 8.91 mmol) at −40°C and the solution was stirred for 2 h at same temperature. After addition of saturated NH_4Cl, the mixture was stirred at room temperature. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (Eluent: *n*-hexane/AcOEt, 2:1–1:1) to give **16b** (1.21 g, 1.99 mmol, 67.9% from **7b**).

^{1}H-NMR ($CDCl_3$) δ 8.99 (1H, s, NHBz), 8.81, 8.30 (each 1H, s, H-2 and H-8), 8.04–7.51 (5H, m, aromatic), 6.54 (1H, dd, H-1′, J = 4.9, 7.3), 4.83 (1H, t, H-3′, J = 6.8), 3.97 (1H, d, H-5′a, J = 11.2), 3.81 (1H, d, H-5′b, J = 11.2), 2.79, 2.68 (each 1H, m, H-2′), 2.57 (1H, s, ethynyl), 0.94, 0.89 (each 9H, s, *tert*-Bu), 0.14, 0.13, 0.08, 0.04 (each, 3H, s, Me). FABMS m/z: 608 (MH^+). Anal. Found: C, 60.25; H, 7.50; N, 11.10. Calcd. for $C_{31}H_{45}N_5O_4Si_2 \cdot 0.5H_2O$: C, 60.36; H, 7.52; N, 11.35.

2′-Deoxy-4′-*C*-ethynyladenosine (18b). To a solution of **16b** (0.118 g, 0.235 mmol) in THF (3.2 mL) was added tetra-*n*-butylammonium fluoride (1 M solution of THF, 0.7 mL, 0.7 mmol) and stirred for 30 min at room temperature. The reaction mixture was evaporated and the residue was purified by silica-gel column chromatography (Eluent: $CHCl_3$/MeOH, 20:1) to give crude **17b** (0.122 g).

The mixture of **17b** (0.122 g) in MeOH (2.1 mL) and conc. NH_4OH (0.7 mL) was stirred at room temperature overnight. The reaction mixture was evaporated and the residue was purified by silica-gel column chromatography (Eluent: $CHCl_3$/MeOH, 20:1–10:1). The residue was recrystallized from water to give **18b** (0.057 g, 0.207 mmol, 88.1% from **16b**), whose structure was confirmed by comparing spectroscopic data of **18b** with these of previously reported 2′-deoxy-4′-*C*-ethynyladenosine.[6]

Antiviral Evaluation

Antiviral Agents. 3′-Azido-3′-deoxythymidine (AZT or zidovudine), 2′,3′-dideoxyinosine (ddI or didanosine), and 2′,3′-dideoxycytidine (ddC or zalcitabine) were purchased from Sigma (St. Louis, MO). (-)-2′,3′-Dideoxy-3′-thiacytidine (3TC or lamivudine) was a kind gift from Dr. R. F. Schinazi (Atlanta, GA). A series of 4′-position substituted nucleosides were designed and synthesized as described by us.

Determination of Drug Susceptibility of HIV-1. The inhibitory effects of test compounds on HIV-1 replication were monitored by the inhibition of virally induced cytopathicity in MT-4 cells. Briefly, MT-4 cells were suspended at 10^5 cells/mL and exposed to HIV-1_{LAI} at 100 50% tissue culture infectious doses ($TCID_{50}$s). Immediately after viral exposure, the cell suspension (10^4 cells in 100 μL) was brought into each well of a 96-well flat microtiter culture plate (Costar, Cambridge,

Mass.) containing various concentrations of test compounds. After incubation for 5 days, the number of viable cells was determined by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] method as previously described.[13,14]

The sensitivity of infectious clones to various RTIs was determined in the multinuclear activation of the galactosidase indicator (MAGI) assay,[17] with some modifications using the viral preparations titrated as previously described.[18] Briefly, target cells (HeLa CD4-LTR/β-gal; 104/well) were plated in 96-well flat microtiter culture plates. On the following day, the medium was aspirated and the cells were inoculated with HIV-1 clones (70 MAGI units/well, which gave 70 blue cells after 48 h of incubation) and cultured in the presence of various concentrations of drug in fresh medium. Forty-eight hours after viral exposure, all blue cells in each well were counted. The cytotoxicity of the compound was determined by the MTT method as previously described.[13] All experiments were performed in triplicate.

Preliminary Toxicity Test for Mice. Six-week-old, random-bred, Swiss albino ICR male mice, (Jcl:ICR) were purchased from Clea Japan. The drugs were dissolved in saline and administered once to the mice either orally (*p.o.*) or intravenously (*i.v.*). The mice were observed twice daily for 7 days for their death.

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Indium-Mediated Atom-Transfer and Reductive Radical Cyclizations of Iodoalkynes: Synthesis and Biological Evaluation of HIV-Protease Inhibitors

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Novel indium-mediated radical cyclization reactions of aliphatic iodoalkynes have been studied. Treatment of iodoalkynes with a catalytic amount of In (0.1 equiv) and I_2 (0.05 equiv) promotes atom-transfer 5-exo cyclization to give five-membered alkenyl iodides. In contrast, reaction with In (2 equiv) and I_2 (1 equiv) yields reductive 5-exo cyclization products via the same 5-exo cyclization. Both processes are most likely initiated by low-valent indium species. To demonstrate versatility of these reactions, optically active HIV protease inhibitors were synthesized by this reductive cyclization method. Among them, several products, which contain a hydroxyethylamine dipeptide isostere as a transition state-mimicking substructure, proved to possess potent activity (IC_{50} = 5−39 nM) against a wide spectrum of HIV strains, including multidrug-resistant variants.

Introduction

The use of radicals in organic synthesis has increased over the last two decades.[1] Tributyltin hydride has played an important role despite its neurotoxicity and the difficulty of complete removal of tin species from the reaction mixture.[2] Therefore, substantial efforts have been invested in the development of more convenient and useful reagents to replace tributyltin hydride.[3] Indium (In)-mediated reactions have gained increasing popularity over the past decade as environmentally benign[4] tools in organic synthesis.[5] Since the first ionization potential of In is 5.8 eV, which is as low as those of Li and Na, it would be easy for In to promote SET (single-electron-transfer) processes. In addition, In is comparatively stable in air and, unlike many metals, has no apparent toxicity.[6] We report herein the indium-mediated atom-transfer 5-exo cyclization (Kharasch-type reaction) and reductive 5-exo cyclization reaction of aliphatic iodoalkynes. In contrast to reductive radical cyclizations,[3,4c] there are few reports on atom-transfer radical cyclizations.[7,8]

We also have synthesized optically active furopyran P_2-ligands that are potent against a variety of HIV strains, including multidrug-resistant variants, by combining optically active hexahydrofuropyran derivatives, synthesized using our indium-mediated reductive cyclization method, and substructural units of previously published HIV protease inhibitors.

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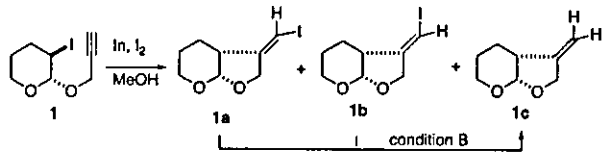
TABLE 1. Radical Cyclization of Iodoalkyne 1[a]



run	condition	In (equiv)	I_2 (equiv)	time (h)	yield (%) 1a	1b	1c	total
1		1	0.0	17	46	4	5	55
2	A	1	0.5	5	76	4	3	83
3		0.1	0.05	32	69	8	3	80
4	B	2	1.0	17	0	0	85	85

[a] Conditions A: **1** (2 mmol), In (2 mmol), I_2 (1 mmol), MeOH (4 mL). Conditions B: **1** (2 mmol), In (4 mmol), I_2 (2 mmol), MeOH (4 mL).

Atom-Transfer Cyclizations and Reductive Cyclizations of Iodoalkynes. We first investigated cyclization reactions of iodoalkyne **1** under various conditions. The results are summarized in Table 1. Iodoalkyne **1** was treated with In (1 equiv) in MeOH at room temperature to give 5-exo cyclized atom-transfer products **1a** (*Z*) and **1b** (*E*) in 50% yield (*Z*:*E* = 11.5:1, run 1). The *Z*-selectivity is in agreement with results reported by Curran et al.[9] They analyzed the formation of (*Z*)- and (*E*)-vinyl iodides with the aid of a Curtin–Hammett kinetic scheme. In the case of compound **1**, high stereoselectivity was observed and the cis-fused products **1a–c** were obtained as shown by NMR spectroscopy (^1H–^1H NOESY and NOE spectra). Trans-fused products and 6-endo cyclization products were not observed. It is well-known that In reacts with I_2 in aromatic solvent under reflux to produce In^{1+}, In^{2+}, and In^{3+}.[10] I_2 (0.5 equiv) was therefore added to In (1 equiv) in MeOH (condition A). The reaction proceeded smoothly to yield atom-transfer products **1a** and **1b** in 80% yield within 5 h (19:1, run 2). This atom-transfer-type reaction could be initiated by a catalytic amount of In and I_2. The reaction using In (0.1 equiv) and I_2 (0.05 equiv) gave the expected iodoolefins in 77% yield (**1a**:**1b** = 8.6:1, run 3), but the reaction took a long time.

Next, we used an excess amount of In. In (2 equiv) and I_2 (1 equiv) (condition B) gave only a reductive 5-exo cyclization product **1c** in 85% yield (run 4). Compound **1c** was also obtained from atom-transfer products **1a** and **1b** in 71% yield under condition B. Atom-transfer radical cyclization and reductive radical cyclization reactions were achieved for the first time by only controlling the quantities of In and I_2.

Next, we examined radical cyclizations to various aliphatic iodoalkynes (**2–9**) under conditions A and B. As can be seen from Table 2, iodoalkynes **2** and **4–6**[11] predominantly gave atom-transfer cyclization products **2a**, **4a**, **5a**, and **6a**[11,12] under conditions A and gave reductive cylization products **2b**, **4b**,[13] **5b**,[14] and **6b**[15] under conditions B (runs 1 and 3–5). Even under conditions A, the use of substrates **3** and **7** bearing an electron-delocalizing phenyl group on the sp carbon resulted in smooth reductive radical cyclization reactions to produce compounds **3b**[16] and **7b** (runs 2 and 6). In general, it is thought that the reduction of vinyl radical intermediates (Scheme 1, **D**) to a vinyl-indium compound (**E**) is slower than the addition of iodine from compound **1** to give atom-transfer cyclization products (**1a** and **1b**) under conditions A. On the other hand, vinylic radicals bearing phenyl groups (electrophilic radicals) might result in subsequent rapid electron transfer to produce a reductive radical cyclization product even under condition A. The atom-transfer cyclization or reductive cyclization may be realized by a subtle balance of reaction rates. We tried this reductive cyclization as an approach to synthesis of bicyclic sugars via radical cyclization (runs 7 and 8). Bicyclic sugars are interesting compounds because of their utility as building blocks for synthesis of natural products and because of their biological activities.[17] The sugar iodides **8** and **9** were prepared from glucal and galactal with propargyl alcohol in the presence of *N*-iodosuccinimide in CH_3CN.[18] Cyclization reactions with indium were carried out under conditions B using compounds **8** and **9**.[19] The reductive cyclization products **8b** and **9b** were obtained in 74 and 75% yields, respectively.

Intermolecular coupling reactions of alkyl iodide with electron-deficient olefins are well-known. To confirm the presence of radical intermediate **D** (Scheme 1), we investigated In-mediated cyclization of **1** in the presence of electron-deficient olefins such as α,β-unsaturated

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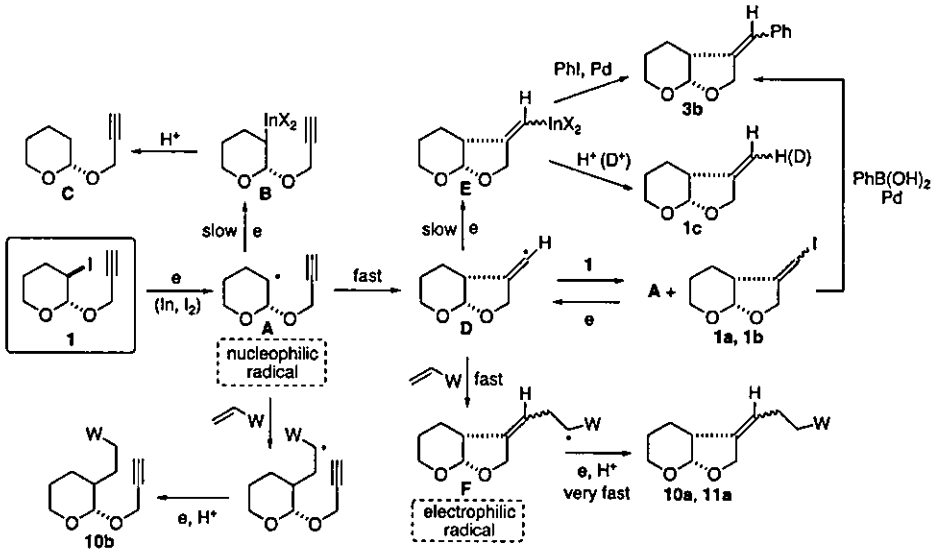
(18) α-Isomers **8** and **9** were obtained predominantly (**8**: 75% yield, α:β = 13:1; **9**: 74% yield, α:β = 14:1). (a) Audin, C.; Lancelin, J.-M.; Beau, J.-M. *Tetrahedron Lett.* **1988**, *29*, 3691–3694. (b) De Mesmaeker, A.; Hoffmann, P.; Ernst, B. *Tetrahedron Lett.* **1989**, *30*, 57–60.

(19) Cyclization products **8b** and **9b** were probably deacetylated by $InX_n(OMe)_{3-n}$. Thus, reacetylation with acetic anhydride and (dimethylamino)pyridine in THF was done.

TABLE 2. Radical Cyclizations of Various Iodoalkynes 2–9

Run	Substrate	Time (h)	Condition	Solvent	Product	Yield (%) Atom-transfer **a**	Yield (%) Reductive **b**	(*E*/*Z* ratio)
1	**2**	5	A	MeOH	**2a**	60	0	(1 : 3.6)
		5	B	MeOH	**2b**	0	65	(1 : 1)
2	**3**	8	A	MeOH	**3b**	0	73	(8.1 : 1)
3	**4**	18	A	MeOH	**4a**	67	0	(1 : 1.3)
		48	B	DMF	**4b**	0	86	
4	**5**	18	A	MeOH	**5a**	70	8	(1 : 1.5)
		48	B	DMF	**5b**	0	82	
5	**6**	24	A	DMF	**6a**	41	0	(1 : 3.4)
		48	B	DMF	**6b**	0	21	(1.3 : 1)
6	**7**	30	A	MeOH	**7b**	0	57	(2 : 1)
7	**8**	20	B	DMF	**8b**	0	74	
8	**9**	20	B	DMF	**9b**	0	75	

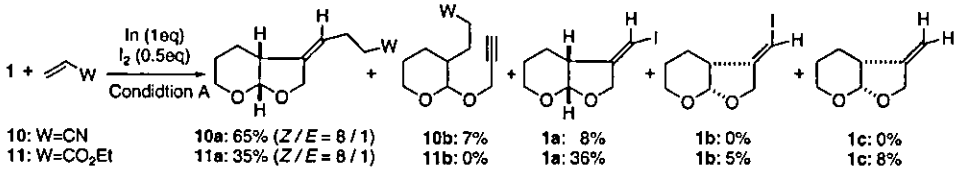
SCHEME 1. Mechanism of Indium-Mediated Radical Cyclization Reaction



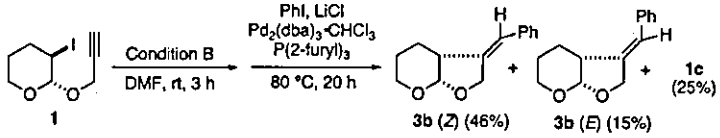
nitrile and ester in a protic solvent, MeOH (Scheme 2). When **1** was subjected to conditions A with acrylonitrile or ethyl acrylate (2 equiv), the desired compounds **10a** or **11a** were obtained in 65 and 35% yields, respectively, with or without compounds **10b**, **1a**, **1b**, and **1c**.

Furthermore, we carried out palladium-catalyzed cross-coupling reaction (Oshima's reaction)[21] in order to confirm that vinyl indium intermediate **E** is generated from compound **1** (Scheme 3). After treatment of compound **1** under conditions B in DMF, iodobenzene (0.9 equiv),

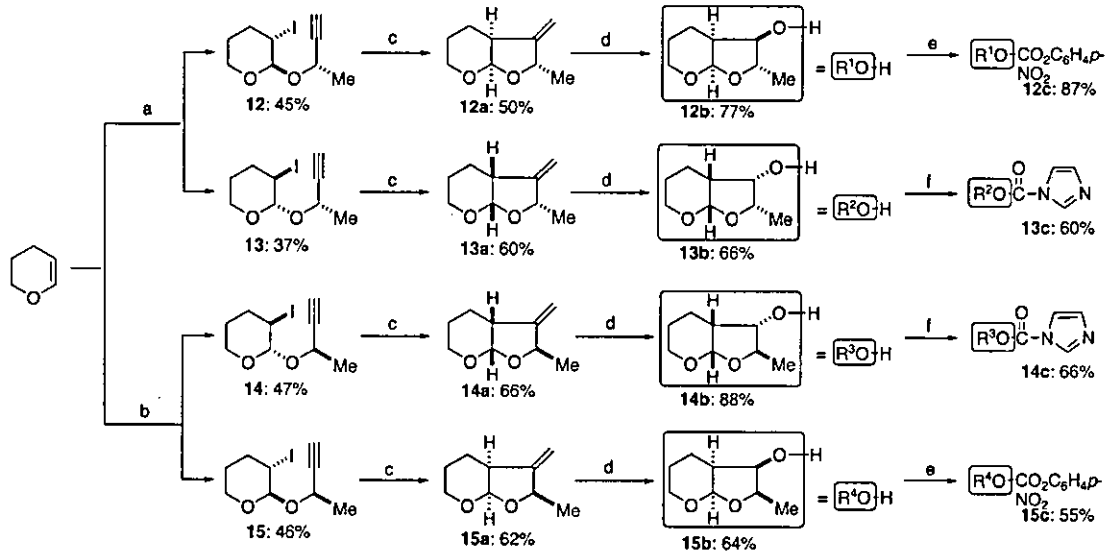
SCHEME 2. Intermolecular 1,4-Addition to Electron-Deficient Olefins



SCHEME 3. Application to Oshima's Reaction



SCHEME 4. Synthesis of Optically Active Bicyclic Ligands[a]



[a] Conditions: (a) *N*-Iodosuccinimide, (*S*)-(−)-3-butyn-2-ol, CH_2Cl_2, 0 °C-rt. (b) *N*-Iodosuccinimide, (*R*)-(+)-3-butyn-2-ol, CH_2Cl_2, 0 °C–rt. (c) In, I_2, MeOH, rt. (d) (1) O_3, MeOH, rt; (2) $NaBH_4$, rt. (e) 4-Nitrophenyl chloroformate, Et_3N, CH_2Cl_2, rt. (f) 1,1′-Carbonyldiimidazole, KOH (cat), toluene.

palladium−trifurylphosphine complex, prepared from $Pd_2(dba)_3$·$CHCl_3$ (0.02 equiv) and trifurylphosphine (0.12 equiv) in THF, and lithium chloride[22] (3 equiv) were added to the reaction mixture. Then, the reaction mixture was heated at 80 °C for 20 h to provide the corresponding coupling products **3b** in 61% yield (*Z*:*E* = 3:1) accompanied with the reductive cyclization product **1c** (25% yield). The geometrical chemistry of compounds **3b** (*Z* and *E*) was determined by NOE experiments of ^{1}H NMR. The results showed the presence of vinyl indium intermediate **E**.

On the basis of the above-described results, we propose the following reaction mechanism (Scheme 1). Treatment of compound **1** with low-valent indium (In, In^{1+}, and/or In^{2+}), produced by In and I_2 in MeOH, provides alkyl radical **A** (nucleophilic radical). In general, it is not easy for radical **A** to be reduced to compound **C** through alkyl indium intermediate **B**.[23] Alkyl radical **A** smoothly undergoes a radical cyclization reaction to produce vinyl radical **D**. This radical is readily reduced to vinyl indium compound **E**[24] when there are enough low-valent indium species. Protonation of **E** produces **1C**, whereas the Oshima reaction of **E** produces **3b**. When there is only a small amount of reducing agent, radical **D** abstracts the iodine radical from compound **1** to produce vinyl iodides **1a** and **1b** and to reproduce alkyl radical **A**. In the presence of α,β-unsaturated compounds, intermolecular addition of radical **D** to the activated olefins occurred to give radical **F** (electrophilic radical). Sequential addition of one electron and one proton proceeded smoothly to give

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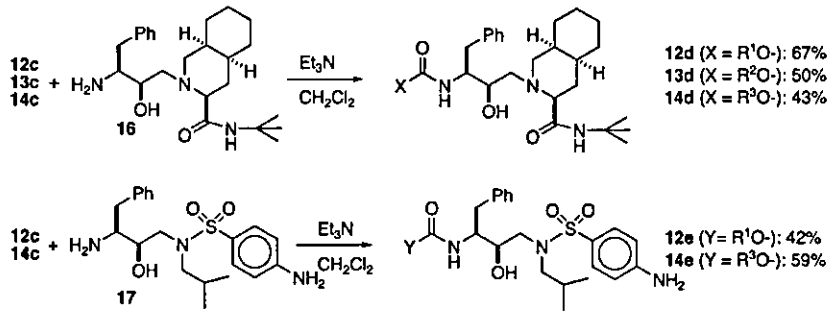
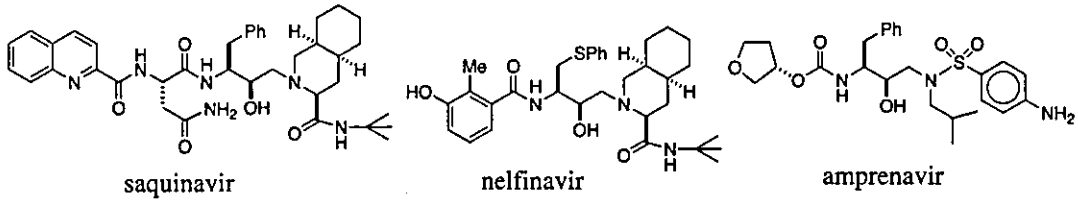
(24) Quenching with DCl in MeOD under Conditions B yielded the deuterated compound **1c** (89% D, *Z*:*E* = 19:1).

SCHEME 5. Synthesis of Various Inhibitors with Bicyclic Ethers as P_2 Ligands



SCHEME 6. Structures of Saquinavir, Nelfinavir, and Amprenavir



saquinavir nelfinavir amprenavir

heterocyclic compounds **10a** and **11a** in moderate yields. The reduction of an alkenyl radical **D** to an alkenyl indium compound **E** is slower than 1,4-addition of the radical **D** to α,β-unsaturated compounds. However, one-electron transfer to the resulting radical **F** having electron-withdrawing groups proceeds faster than addition to a different unsaturated bond.

Synthesis of Optically Active HIV Protease Inhibitors and Biological Evaluation. Ghosh et al.[25] reported that stereochemically defined hexahydrofuropyrans play a crucial role as the replacement of asparagine side chain of Ro 31−8959-based HIV protease inhibitors.[26] They also reported that a fused bicyclic ligand with oxygens properly positioned could effectively form a hydrogen bond to the NH of Asp 29 and 30 residues corresponding to the quinardic amide−asparagine amide fragment of the Ro 31−8959 inhibitor.[27]

We applied the indium-mediated reductive cyclization to the synthesis of optically active hexahydrofuropyran derivatives as HIV protease inhibitors with novel P_2-pharmacophores (Schemes 4 and 5). As shown in Scheme 4, the reaction of dihydropyran with *N*-iodosuccinimide and (*S*)- or (*R*)-3-butyn-2-ol gave optically active iodo ethers **12**−**15** in good yields. Radical cyclizations of **12**−**15** with In and I_2 under conditions B afforded the bicyclic acetals **12a**−**15a** (50−66%). Ozonolytic cleavage followed by the reduction of the resulting ketones with sodium borohydride in methanol at −78 °C furnished stereoselectively the optically active endo alcohols **12b**−**15b** in 64−88% yields. The stereochemical assignments of these alcohols **12b**−**15b** were determined by NOE experiments of ^{1}H NMR. The reaction of hexahydrofuropyran ligands **12b** and **15b** with 4-nitrophenyl chloroformate and triethylamine in methylene chloride afforded the active carbonates **12c** and **15c** in good yields. The compounds **13c** and **14c** could not be obtained by the same reaction. We therefore used 1,1′-carbonyldiimidazole instead of 4-nitrophenyl chloroformate. The ligands **13b** and **14b** with 1,1′-carbodiimidazole and potassium hydroxide in toluene afforded the active carbonates **13c** and **14c** in good yields.

Novel optically active hydroxyethylamine isosteres **12d**−**14d** bearing decahydroisoquinoline unit **16**[28,29] and **12e** and **14e** bearing sulfonamide unit **17**[30] were synthesized according to Ghosh's methods[31] (42−67% yields).

TABLE 3. Anti-HIV Activities, Cytotoxicities, and HIV Protease Inhibitory Activities of the Synthetic Compounds

run	compd	IC_{50} (nM)[a]	CC_{50} (μM)[b]	SI[c]
1	**12d**	39 ± 15	36.4 ± 3.5	930
2	**13d**	6 ± 2	32.9 ± 3.3	5480
3	**14d**	5 ± 3	27.8 ± 2.1	5560
4	**12e**	26 ± 4	30.3 ± 4.9	1170
5	**14e**	30 ± 10	40.0 ± 5.2	1330
6	saquinavir	17 ± 3	11 ± 3	650
7	amprenavir	36 ± 11	>100	>2780

[a] IC_{50} values are based on the inhibition of HIV-induced cytopathogenicity in MT-2 cells. [b] CC_{50} values are based on the reduction of the viability of mock-infected MT-2 cells (±1 standard deviation). All values represent the means from at least three independent experiments. [c] Selectivity index (SI) is shown as CC_{50}/IC_{50}.

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TABLE 4. Anti-HIV Activities of the Synthetic Compounds against HIV-1 Clinical Isolates

run	compd	$HIV_{ERS104pre}$	IC_{50} (nM) (fold change)[a] MDR[b]		
			HIV_{TM}	HIV_{MM}	HIV_{JSL}
1	**12d**	230 ± 30	>1000 (>4 x)	>1000 (>4 x)	NT
2	**13d**	24 ± 0.1	>1000 (>42 x)	>1000 (>42 x)	NT
3	**14d**	33 ± 5	>1000 (>32 x)	>1000 (>32 x)	NT
4	**12e**	24 ± 4	240 ± 190 (10 x)	100 ± 80 (5 x)	290 ± 70 (12 x)
5	**14e**	34 ± 13	260 ± 190 (8 x)	340 ± 20 (10 x)	410 ± 80 (11 x)
6	saquinavir	19 ± 4	230 ± 20 (12 x)	320 ± 2 (17 x)	550 ± 160 (29 x)
7	amprenavir	20 ± 3	480 ± 120 (24 x)	530 ± 80 (27 x)	800 ± 70 (40 x)

[a] IC_{50} values are based on inhibition of HIV p24 antigen expression in PBMC. All values represent the means from at least three independent experiments. Data without standard deviations are derived from the value for one experiment. [b] Amino acid substitutions in the protease-encoding region are shown in Supporting Information.

Among the compounds synthesized by using our method, **12d−14d** each have a decahydroisoquinoline unit, which is present in saquinavir[30,32] and nelfinavir,[33] at the $P_{1'}-P_{2'}$ position (Scheme 6). Compounds **12e** and **14e** also each have a sulfonamide unit, which is present in amprenavir,[34] at the $P_{1'}-P_{2'}$ position.

The anti-HIV activity of compounds **12d−14d**, **12e**, and **14e** was determined on the basis of inhibition of HIV-1-induced cytopathogenicity in MT-2 cells (described in Supporting Information).[35] Compounds **13d** and **14d** showed potent anti-HIV activity (Table 3, runs 2 and 3). They proved to be more potent than saquinavir (run 6) and amprenavir (run 7), which have currently been used clinically. It was noted that compounds **12d−14d**, **12e**, and **14e** (runs 1−5) exhibited greater selectivity indices (SIs) than saquinavir (run 6).

Next, we determined the anti-HIV activity of compounds **12d−14d**, **12e**, and **14e** against multidrug-resistant (MDR) strains as measured by the inhibition of HIV p24 antigen expression in peripheral blood mononuclear cells (PBMC) (described in Supporting Information).[35] The efficacy against $HIV_{ERS104pre}$ and three MDR strains of compounds **12e** and **14e** was similar to that of saquinavir and amprenavir (Table 4, runs 4−7).

Conclusion

In summary, we have found a novel indium-mediated atom-transfer radical cyclization reaction using a catalytic amount of In with I_2 and reductive radical cyclization reaction using an excess amount of In and I_2 without the use of a radical initiator such as AIBN or Et_3B/O_2. The protocol described above provides a new methodology for multibond formation and enables division of geometrical isomers. Novel HIV protease inhibitors, **12d−14d**, **12e**, and **14e**, were synthesized using the indium-mediated reductive radical cyclization method. They all inhibited HIV-induced cytopathogenicity in MT-2 cells and were all as effective as saquinavir and amprenavir against MDR strains. The present results will be useful for developing new attractive aspects of indium chemistry.

Experimental Section

General. Indium-Mediated Atom-Transfer Cyclization of Iodoalkyne (1) (condition A). The mixture of iodoalkyne **1** (2 mmol), In (2 mmol), and I_2 (1 mmol) in MeOH (4 mL) was stirred for 5 h at room temperature under nitrogen. MeOH was evaporated, and the residue was filtered with Celite using chloroform as an eluent. The filtrate was concentrated. The residue was purified by flash silica gel column chromatography to afford compound **1a** (404 mg, 76%), **1b** (21 mg, 4%), and **1c** (8 mg, 3%).

Indium-Mediated Reductive Radical Cyclization of Iodoalkyne (1) (condition B). The mixture of iodoalkyne **1** (2 mmol), In (4 mmol), and I_2 (2 mmol) in MeOH (4 mL) was stirred for 17 h at room temperature under nitrogen. MeOH was evaporated, and the residue was filtered with Celite using chloroform as an eluent. The filtrate was concentrated. The residue was purified by flash silica gel column chromatography to afford compound **1c** (238 mg, 85%) as an yellow oil.

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Supporting Information Available: Experimental procedures and characterization data of synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035482M

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Review

Potential of 4′-C-substituted nucleosides for the treatment of HIV-1

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Extensive efforts have been made to identify nucleoside reverse transcriptase inhibitors (NRTIs). Eight NRTIs have now been approved for clinical use; however, variants of HIV-1 resistant to these antiviral agents have emerged in patients even when they are treated with combinations [highly active antiretroviral therapy (HAART)]. Thus, the development of novel compounds that are active against drug-resistant HIV-1 variants and that prevent or delay the emergence of resistant HIV-1 variants is urgently needed. Previously, 4′-C-substituted nucleosides (4′-SNs) were designed as new types of NRTIs. They were synthesized and examined as potential therapeutic agents against HIV infection. Among them, several 4′-substituted-2′-deoxynucleosides (4′-SdNs), especially those that bear an ethynyl group, were shown to be active against various laboratory and clinical HIV-1 strains including known drug-resistant variants. These results were recently reported by our collaborators. In this review, we summarize the design, synthesis and demonstrations of the anti-HIV activity of 4′-SNs, and then consider 4′-SNs as potential therapeutic agents for HIV-1.

Keywords: NRTIs, 4′-SNs, anti-HIV-1 agents, HAART, drug-resistant HIV-1 variants

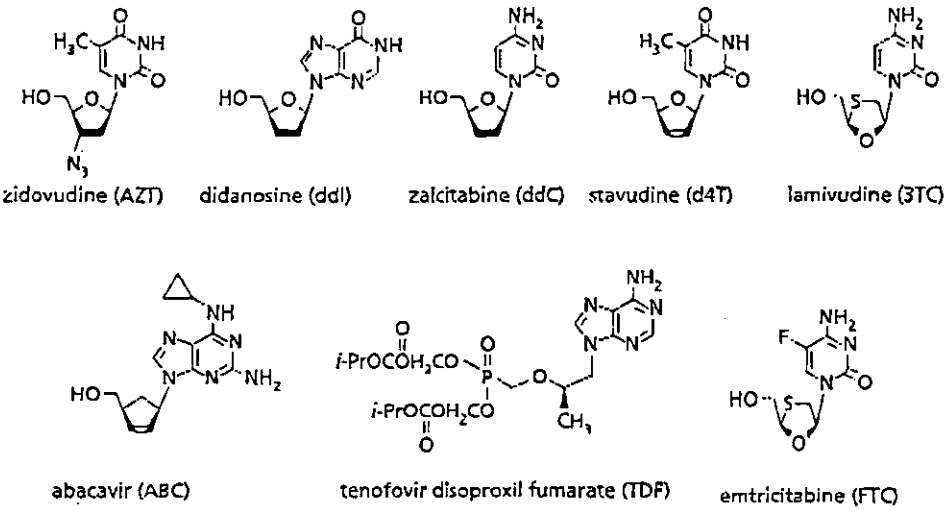
Introduction

The development of novel antiviral agents is essential in the battle against viruses such as HIV, because drug-resistant variants emerge. For the treatment of acquired immunodeficiency syndrome (AIDS), eight NRTIs have been approved for clinical use to date: 3′-azido-3′-deoxythymidine [zidovudine (AZT)], 2′,3′-dideoxyinosine [didanosine (ddI)], 2′,3′-dideoxycytidine [zalcitabine (ddC)], 2′,3′-dehydro-2′,3′-dideoxythymidine [stavudine (d4T)], L-1,3-oxathiolanylcytosine [lamivudine (3TC)], abacavir (ABC), tenofovir disoproxil fumarate (TDF), and L-1,3-oxathiolanyl-5-fluorocytosin [emtricitabine (FTC)] (Figure 1).

HAART using two, or more, NRTIs and protease inhibitors (PIs) has dramatically improved the quality of life and survival of patients infected with HIV-1. But the emergence of drug-resistant mutants has been a critical problem in using these chemotherapeutic agents; furthermore, some of these mutants show high levels of cross-resistance. Consequently, the development of structurally new nucleoside derivatives that are active against HIV-1 variants resistant to the existing 2′,3′-dideoxy nucleosides is urgently needed.

There are six classes of chemotherapeutic agent against HIV-1 so far: 1) NRTIs, mentioned above; 2) non-nucleoside reverse transcriptase inhibitors (NNRTIs); 3) protease inhibitors (PIs); 4) integrase inhibitors (INIs); 5) fusion inhibitors (FIs) and 6) chemokine receptor antagonists (CRAs). A number of NRTIs, NNRTIs and PIs are currently used clinically. Much progress has been made in the classes of FIs and CRAs, but INIs are still in the pre-clinical stage.

Figure 1. Structures of clinically used nucleoside analogues as NRTIs



During our exploration of novel NRTIs, we recently designed and synthesized a series of 4′-SdNs derivatives. Among these, 4′-*C*-ethynyl-2′-deoxynucleosides (4′-EdNs) showed promising features in both their biological activities and their structures (Kodama *et al.*, 2001). They inhibited the replication of multidrug-resistant clinical HIV-1 strains carrying a wide variety of drug resistance-related amino acid substitutions isolated from HIV-1-infected individuals, for whom 10 or 11 different anti-HIV-1 agents had failed. These 4′-EdNs have a 2′-deoxyribose moiety, unlike all of the currently available NRTIs. Additionally, all of these 4′-EdNs blocked the replication of a wide spectrum of laboratory and clinical HIV-1 strains *in vitro* with low cellular toxicities. Therefore, we set out to search for promising new candidates.

Synthesis and anti-HIV activity of 4′-SNs

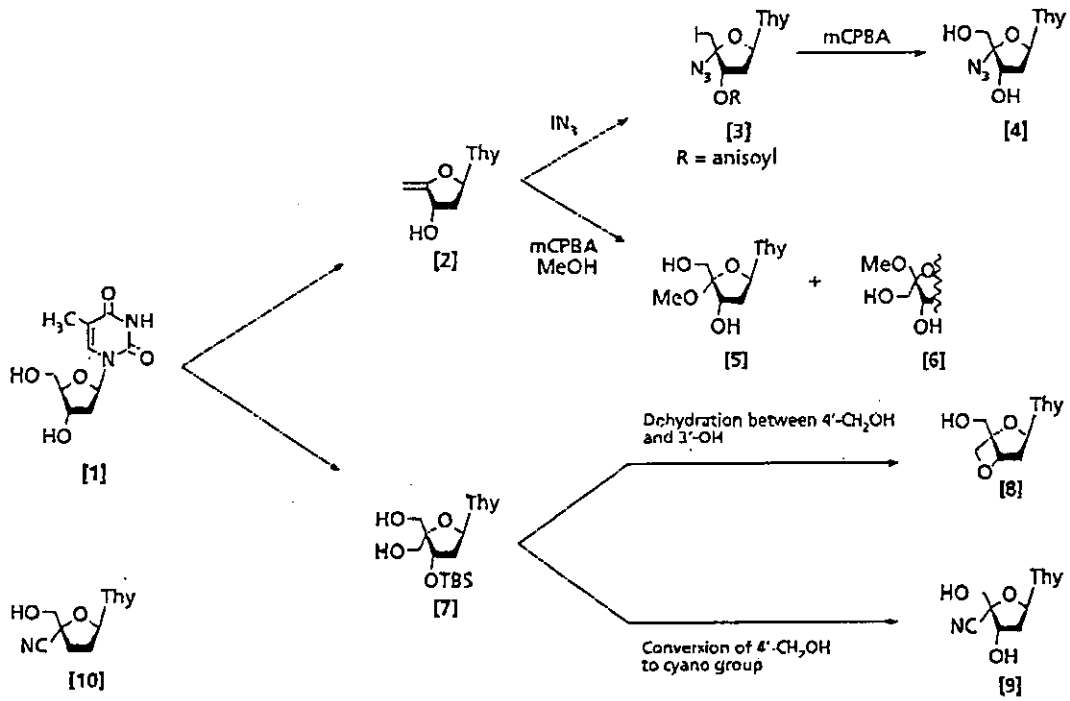
4′-Substituted nucleosides have been under development since JG Moffatt's group accomplished the synthesis of 4′-*C*-fluoro-5′-*O*-sulphamoyladenosine, the antibiotic nucleocidin and related nucleosides (Verheyden *et al.*, 1975, Jenkins *et al.*, 1976, Owen *et al.*, 1976, Youssefyeh *et al.*, 1977 & 1979, Jones *et al.*, 1979).

Compared with 2′- and 3′-substituted nucleoside derivatives, methods for the synthesis of 4′-SNs were very difficult. However, since the 1990s, several research groups have attempted the synthesis of 4′-SNs and the results, including biological activities, published.

Initially, the Syntex group, led by JG Moffat, pioneered the exploration for an improved method (Figure 2). Maag *et al.* reported the synthesis and anti-HIV activity of 4′-*C*-azidothymidine (4′-AZT 4) and 4′-*C*-methoxynucleosides (5) (Maag *et al.*, 1992). The key steps in the synthesis of the 4′-azido analogues were the stereo- and regioselective addition of iodine azido to a 4′,5′-unsaturated nucleoside precursor [2] followed by an oxidatively assisted displacement of the 5′-iodo group. 4′-AZT [4] led to potent activity against HIV-1 *in vitro*, especially its activity against HIV mutants which were resistant to AZT. IC_{50} was 0.01 μM against HIV-1 (LAV-IIIb) replication in A301 cells. Structure–activity relationships among HIV inhibitory 4′-*C*-substituted nucleosides were published by the Syntex research group (Prisbe *et al*, 1993).

O-Yang, of Syntex, also reported two interesting findings: that 1) the fused oxetane derivative of thymidine [8] inhibited HIV replication in A301 cells with remarkably low bone marrow toxicity (O-Yang *et al.*, 1992); and

Figure 2. Synthesis of various 4'-SNs by Syntex research groups



2) 4'-*C*-cyanothymidine (4'-CNT [9]) inhibited HIV in A301 cells with an IC_{50} of 0.002 μM (O-Yang *et al.*, 1992). 4'-*C*-cyano-3'-deoxythymidine [10] was also synthesized from 3'-deoxythymidine, but it was not active against HIV (O-Yang *et al.*, 1992). Additionally, both oxetane fused [8] and 4'-*C*-cyano [9] derivatives were prepared via similar intermediates [7] bearing a hydroxymethyl group at the *C*-4' position of the sugar moiety.

Subsequently, Chen and colleagues reported the mechanism of action of 4'-AZT [4] against HIV-1 to be through its DNA chain-terminating activity (Chen *et al.*, 1993).

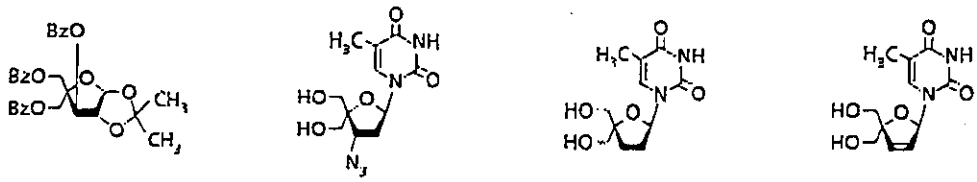
Results similar to those of the Syntex research group were published by A Holy's group (Hrebabecky *et al.*, 1993). They reported the synthesis of 4'α-*C*-hydroxymethyl thymidine derivatives of AZT [12], ddT [13] and d4T [14] related Ns starting from 1,2-*O*-isopropylidene-3,5-di-*O*-benzoyl-4-*C*-benzoyloxymethyl-β-L-arabinofuranose [11] (Figure 3).

JG Moffatt's group introduced a hydroxymethyl group at the 4'α-position of nucleosides using the Cannizzaro reaction 25 years ago, using an appropriately protected ribose 5-aldehyde [15] (Figure 4) (Youssefyeh *et al.*, 1979).

Since oxetane-fused derivatives of thymidine [8] and 4'-CNT [9] showed potent anti-HIV activity as mentioned in the Syntex report, A Matsuda's group reported that they adopted Moffatt's method to synthesize their target nucleosides via 4'-*C*-formyl derivatives [19]: 4'-*C*-ethynyl, -vinyl, -ethyl, -chlorovinyl, -cyano, and -methyl derivatives of pyrimidine nucleosides [20–28] (Figure 5) (Nomura *et al.*, 1999), (Sugimoto *et al.*, 1999). Moreover, they have recently reported the synthesis of 4'-*C*-branched thymidine [31–34] by the use of an intramolecular radical cyclization reaction (Figure 5) (Sugimoto *et al.*, 1999). They showed that 4'-*C*-substituted thymidine [31–34] including 4'-ET [28] exhibited potent activity against not only HIV-1 but also herpes simplex type 1. Besides the foregoing, the biological activities of these derivatives have also been reported in a 2'-deoxycytidine, cytidine and uridine series (Nomura *et al.*, 1999).

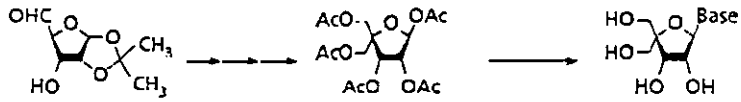
A new synthetic method leading to a series of 4'-*C*-branched 2',3'-didehydro-2',3'-dideoxyuridine (4'-Sd4U

Figure 3. Structures of 4-hydroxymethyl sugar [11] and nucleosides [12–14]



[11] [12] [13] [14]

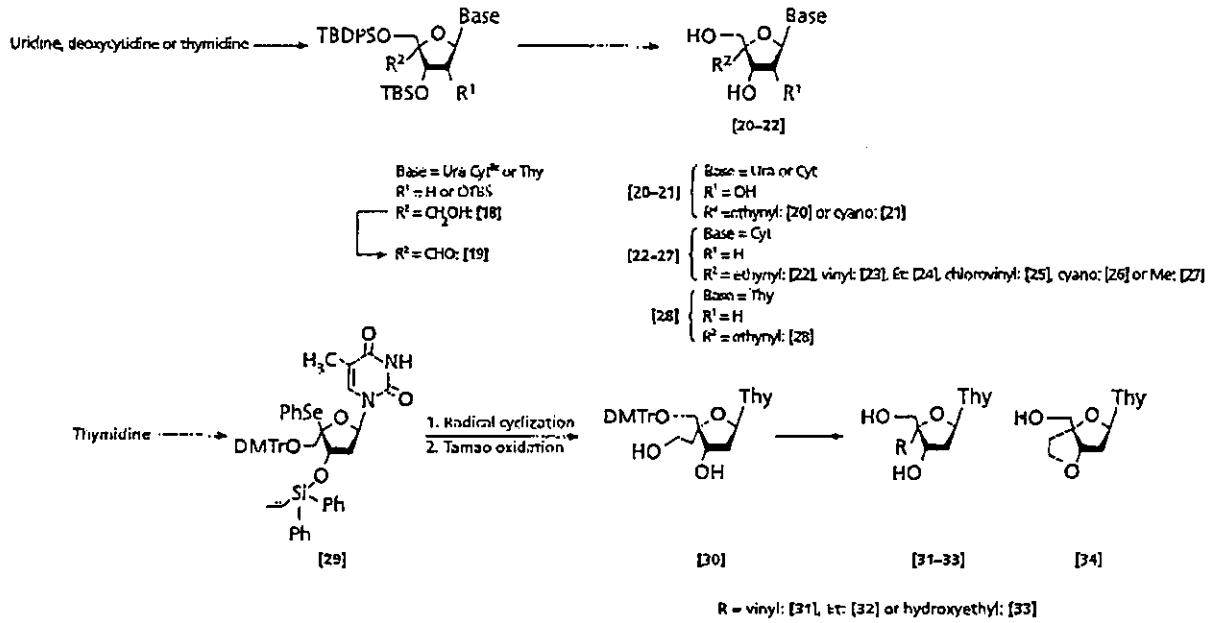
Figure 4. Synthesis of 4′-*C*-hydroxymethyl nucleosides by Cannizzaro reaction aldehyde [15] with formaldehyde



[15] [16] [17]

[36–42] was developed (Haraguchi *et al.*, 1992). This method was based on $SnCl_4$-promoted allylic rearrangement to give 4′-Sd4U [36–42] (Figure 6). However, they did not mention the biological activities of these derivatives. H Tanaka's group also very recently published a paper describing the synthesis and activity of 2′,3′-didehydro-3′-deoxy-4′-ethynyl-thymidine (4′-Ed4T) [47] (Haraguchi *et al.*, 2003). The key step of this reaction consisted of the ring-opening of 4′,5′-epoxy precursors [43] with aluminium reagents resulting in the formation of 4′-*C*-substituted nucleoside analogues [45–47] (Figure 6). In this reaction, the 3′-configuration of 4′,5′-epoxide [43] was very important to form 4′-SNs having the expected 4′-configuration. Very interestingly, 4′-Ed4T [47] was active against HIV-1 with an EC_{50} value of 0.20 μM, which was 14-fold more potent than that of d4T (EC_{50}=2.8 μM); 4′-Ed4T's cytotoxicity was low in comparison. In order to determine SAR, H Tanaka's group went on to prepare 4′-*C*-cyano-2′,3′-didehydro-3′-deoxythymidine (4′-CNd4T) [42] (Haraguchi *et al.*, 2003) by allylic substitution of the

Figure 5. Synthesis of 4′-*C*-substituted nucleosides by conversion of 4′-*C*-formyl derivatives and by radical cyclization reaction



3′,4′-unsaturated nucleoside **[35]**, having a leaving group at the 2′-position, with cyanotrimethylsilane in the presence of stannic chloride ($SnCl_4$) (Figure 6). Unfortunately, 4′-CNd4T **[42]**' s activity was only one-fifth that of d4T. One of their derivatives, 4′-Ed4T **[47]**, is expected to become a promising new NRTI candidate

4′-Trifluoromethylthymidine derivatives **[52, 53, 55]** and related purine nucleosides **[54, 56, 57]** were synthesized by Johnson (Figure 7) (Johnson *et al.* 1998). A strategy based on the use of (trifluoromethyl)trimethylsilane for introduction of a trifluoromethyl group at the *C*-4 of ribose was developed. Unfortunately, these nucleosides were not active against HIV.

Compared to 4′-*C*-substituted nucleosides, there are few reports on the synthesis of 4′α-carbon substituted carbocyclic nucleosides, the most common method being transformation from a natural product. The functionalization of the cyclopentene moiety is restricted in these cases. Interestingly, Kato reported that enantio- and diastereoselective synthesis of 4′-α-alkylcarbovir derivatives was achieved based on Sakai's asymmetric alkylation of β-keto esters (Kato *et al.*, 1998). This method and the related papers cited in his report will enable us to make many carobocyclic derivatives.

For the readers' reference, we cite related reports known to us for the synthesis of various 4′-*C*-substituted nucleosides: (Secrist III *et al.*, 1978; Johnson *et al.*, 1994; Thrane *et al.*, 1995; Marx *et al.*, 1996; Wang *et al.*, 1996; Kozak *et al.*, 1998; Singh *et al.*, 1998; Imanishi *et al.*, 1998; Wang *et al.*, 1999; Crich *et al.*, 1999; Jung *et al.*, 2001: Summerer *et al.*, 2001).

Chemistry and biological activity of 4′-SNs

Two principle methods were employed for the preparation of 4′-SNs: 1) condensation and 2) modification starting from natural nucleosides. The first approach used for the preparation of 4′-SNs was the condensation method; this is an efficient route to various derivatives. Modification starting from natural nucleosides readily scaled up, creating several candidates.

Therefore, initially we started our chemistry by the condensation method to explore the seeds, and then we utilized

Figure 6. Synthesis of 4'-*C*-substituted nucleosides by $SnCl_4$-promoted allylic rearrangement reaction and by ring-opening reaction of 4',5'-epoxy nucleosides [43]

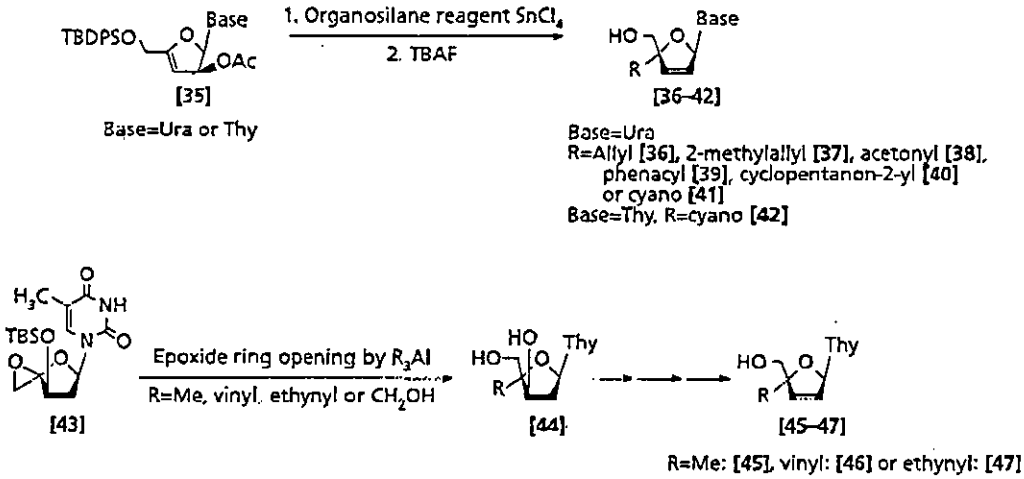
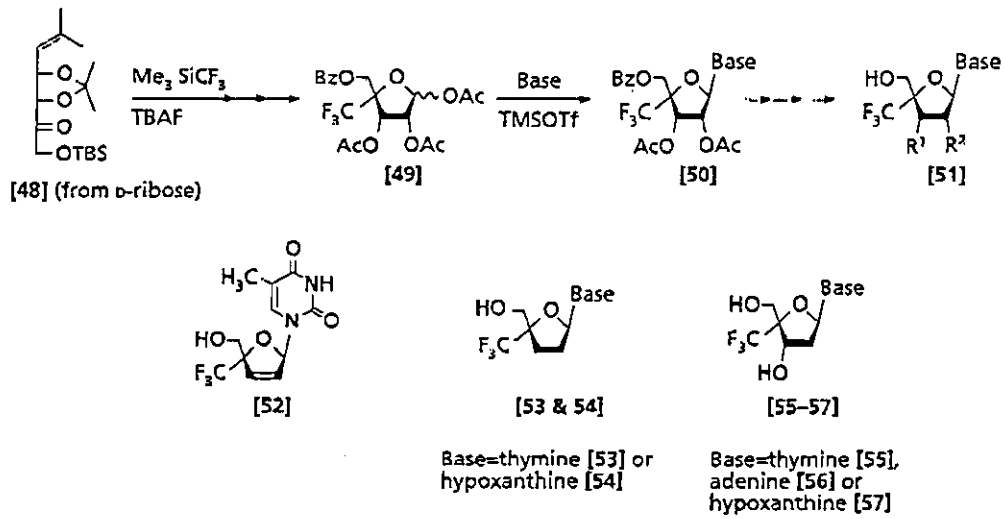


Figure 7. Synthesis of 4'-*C*-trifluoromethyl nucleosides [52–57]



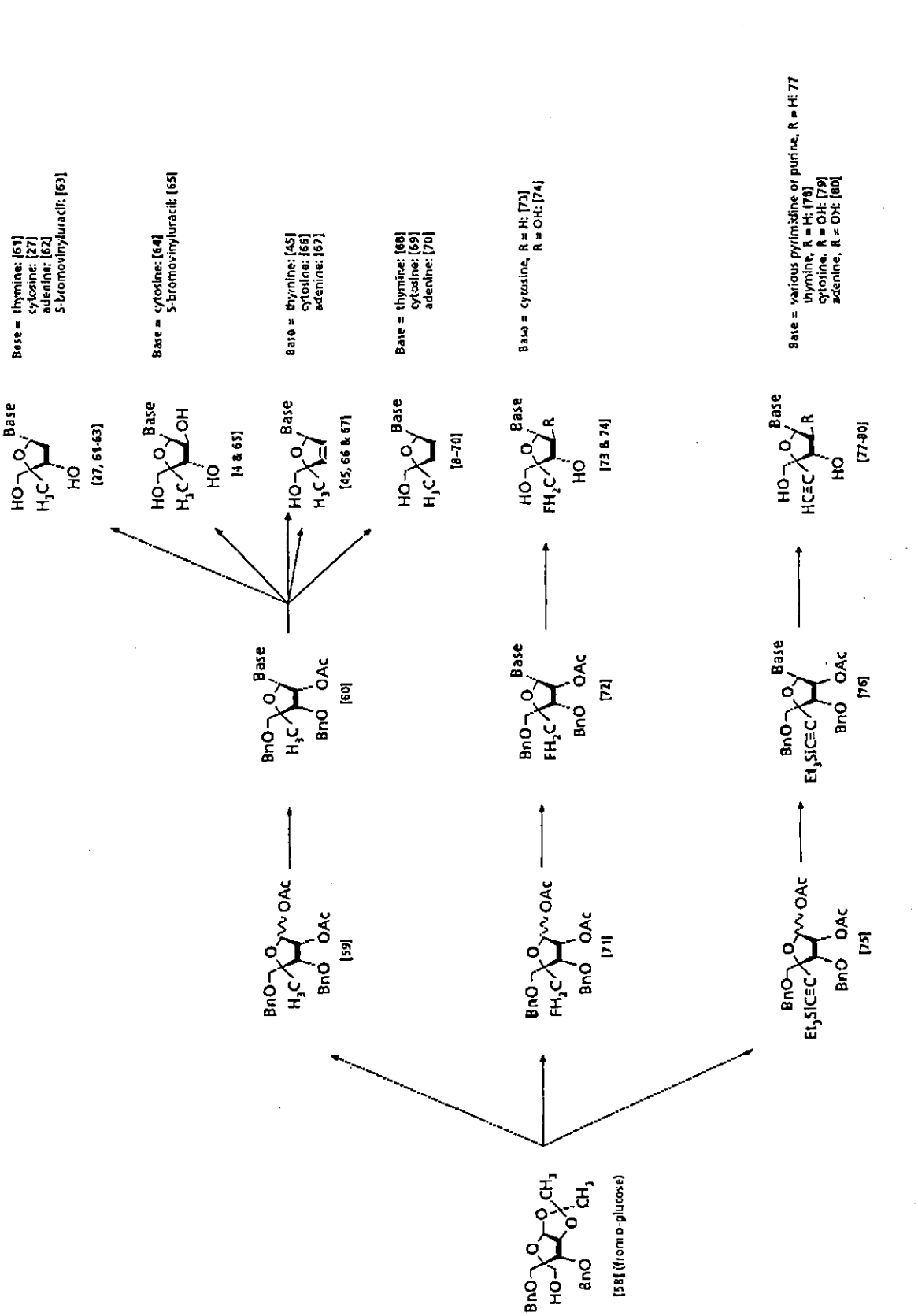


Figure 8. Synthesis of 4'-C-methyl, fluoromethyl and ethynyl nucleosides by condensation of sugars with bases