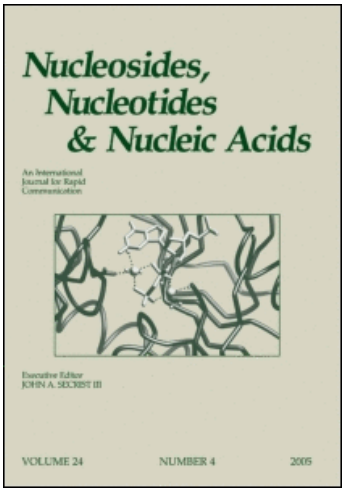

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SYNTHESIS OF 2′, 3′-UNSATURATED AND 2′, 3′-DIDEOXY ANALOGS OF 6-AZAPYRIMIDINE NUCLEOSIDES AS POTENTIAL ANTI-HIV AGENTS

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Abstract

Several 2′, 3′-unsaturated and 2′, 3′-dideoxy analogs of 6-azapyrimidine nucleosides, compounds 2′, 3′-dideoxy-6-azacytidine (12), 2′, 3′-dideoxy-6-azauridin-2′-ene (15a), 3′-deoxy-6-azathymidin-2′-ene (15b) and 3′-deoxy-6-azathymidine (16b), have been synthesized via a multi-step synthesis from 6-azauridine and 6-azathymidine, respectively. These compounds were evaluated against HIV-1 in vitro and found to be inactive.

Recently, a number of 2′, 3′-dideoxy and 2′, 3′-unsaturated nucleosides have been identified as potential anti-human immunodeficiency virus type 1 (HIV-1) agents. These include 2′, 3′-dideoxycytidine (d2C)[2], 2′, 3′-dideoxyadenosine (d2A)[2], 2′, 3′-dideoxycytidin-2′-ene (d4C)[3-6], and 3′-deoxythymidin-2′-ene (d4T)[7,8]. Based on these findings, the 2′, 3′-dideoxy analogs of 6-azacytidine and 6-azathymidine, and the 2′, 3′-unsaturated analogs of 6-azauridine and 6-azathymidine have been synthesized as potential anti-HIV agents.

Treatment of 6-azauridine (1) with 1, 3-dichloro-1,1,3,3-tetraisopropyldisiloxane in pyridine at room temperature gave the cyclic 3′, 5′-protected derivative 2, which was reacted with phenyl chlorothionocarbonate and 4-dimethylaminopyridine in dry acetonitrile under nitrogen[9] to yield the corresponding 2′-O-phenoxythiocarbonyl ester 3. Reductive deoxygenation[9] of compound 3 in the 2′-position by tri-n-butyltin hydride, in the presence

of 2′, 2′-azobis(2-methylpropionitrile) (AIBN), in toluene at 75-80°C produced the 2′-deoxy nucleoside 4. Deprotection of 4 with tetra-n-butylammonium fluoride in toluene under nitrogen afforded 2′-deoxy-6-azauridine (5a). Acetylation of 5a with acetyl anhydride in pyridine gave the diacetate 6. An attempt to convert 6 to 8, via the 4-(1,2,4-triazolyl) pyrimidone intermediate, by treatment[10] of 6 with 4-chlorophenyl phosphorodichloridate and 1,2,4-trazole in pyridine was unsuccessful and resulted in the recovery of the starting material, compound 6. Instead, treatment[11] of compound 6 with thionyl chloride in $CHCl_3$-DMF, followed by methanolic ammonia, yielded 2′-deoxy-6-azacytidine (8). Selective silylation of the 5′-hydroxy group in compound 8 with t-butyldimethylsilyl chloride in pyridine gave the 5′-protected nucleoside 9. Thioacylation of 9 with phenyl chlorothionocarbonate and 4-dimethylaminopyridine in acetonitrile afforded the 3′-0-phenoxythiocarbonyl ester 10 which was deoxygenated by treatment of tri-n-butyltin hydride in toluene to yield the protected 2′, 3′-dideoxy analog 11. Desilylation of compound 11 with tetra-n-butylammonium fluoride in THF produced the desired 2′, 3′-dideoxy-6-azacytidine (12). The synthetic sequence is illustrated in Scheme 1.

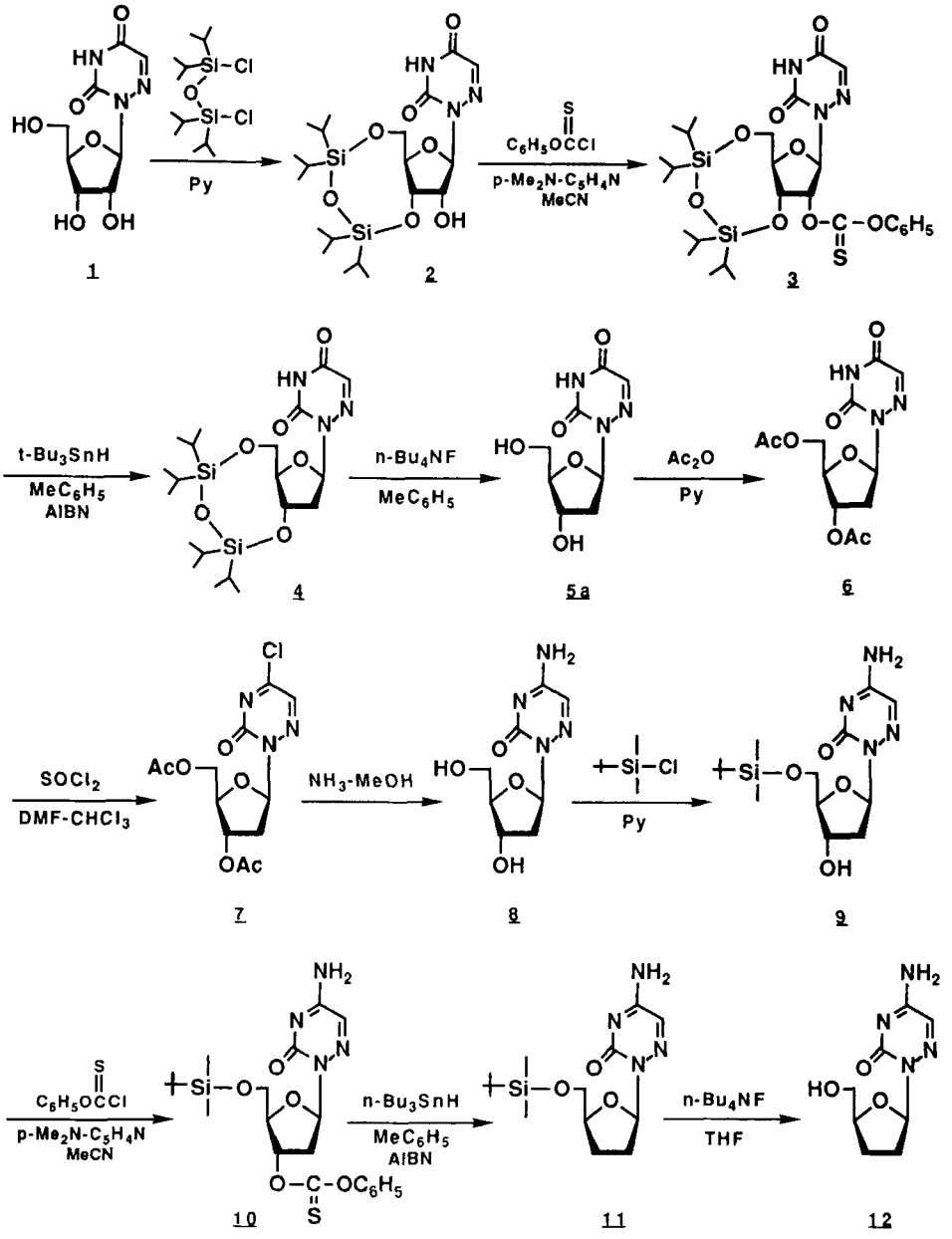
The 2′, 3′-unsaturated derivatives of 2′-deoxy-6-azauridine and 6-azathymidine, compounds 15a and 15b, were synthesized from 2′-deoxy-6-azauridine (5a) and 6-azathymidine (5b)[12], respectively, by the methodology of Horwitz et al.[13] with minor modifications as shown in Scheme 2. Treatment of 5a and 5b with two mole equavents of mesyl chloride in pyridine gave the dimesylates 13a and 13b. Refluxing 13a and 13b with 1 N NaOH solution yielded the cyclic ethers 14a and 14b which were then treated with t-butoxide in DMSO to produce the desired 2′, 3′-unsaturated nucleosides 15a and 15b. Catalytic (Pd/C) hydrogenation of compound 15b in EtOH afforded 3′-dideoxy-6-azathymidine (16b).

Compounds 12, 15a, 15b, and 16b were evaluated against HIV-1 in vitro using CEM-F cell line[14] and found to be inactive. It appears that the replacement of the 6-carbon in the pyrimidine base with a nitrogen in the nucleoside resulted in the loss of antiviral activity.

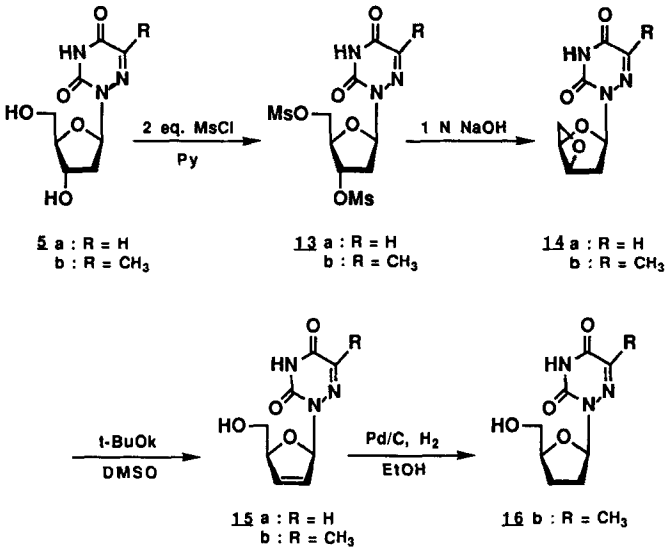
Experimental Section

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 500 MHz on a Brucker WM-500 spectrometer

Scheme 1



Scheme 2



5 a : R = H
b : R = CH_3

13 a : R = H
b : R = CH_3

14 a : R = H
b : R = CH_3

15 a : R = H
b : R = CH_3

16 b : R = CH_3

with Me_4Si as the internal reference. The UV spectra were recorded on a Beckman-25 spectrophotometer. IR spectra were taken on the Perkin-Elmer 21 spectrophotometer. The mass spectra(at 70 eV) were provided by Yale University Chemical Instrumentation Center. TLC was performed on EM precoated silica gel sheets containing a fluorescent indicator. Elemental analyses were carried out by the Baron Consulting Co., Orange, CT.

3′, 5′-0-(1,1,3,3-Tetraisopropyldisilox-1, 3-diyl)-6-azauridine (2).

1, 3-dichloro-1,1,3,3-tertraisopropyldisiloxane (6.3mL, 20mmol) was added dropwise to a solution of 6-azauridine (1, 4.9g, 20mmol) in 180mL of dry pyridine. The reaction mixture was stirred at room temperature for 3 days. The solvent was evaporated in vacuo until dry to yield a residue which was then partitioned between EtOAc-H_2O (150mL : 100mL). The organic phase was washed with cold 1 N HCl (2 x 20mL), water, aqueous saturated $NaHCO_3$ solution, water again, then dried (anhydrous $MgSO_4$) and filtered. The filtrate was evaporated to dryness in vacuo to afford a syrup (9.2g, 94%). This crude product was crystallized from hexane to yield the analytical sample : mp 125-126°C; UV (MeOH)λ_{max} 262nm (ε 6780), λ_{min} 224nm; UV (0.01 N NaOH)λ_{max} 257nm (ε 7630), λ_{min} 221nm; UV (0.01 N HCl)λ_{max} 263nm (ε 6630), λ_{min} 228nm. NMR ($CDCl_3$) δ 1.02-1.12 (m, 28H, i-Pr.), 3.04 (s, 1H, 2′-OH, D_2O exchangeable), 4.01 (m, 3H, 4′-H and 5′-H), 4.35 (t, 1H, 2′-H), 4.69 (m,

1H, 3′-H), 6.18 (s, 1H, 1′-H), 7.39 (s, 1H, 5-H), 9.08 (s, 1H, 3-NH, D_2O exchangeable); MS m/e 488 (M^+ + 1), 470 (M^+ - OH), 373 (M^+ - i-Pr_2Si). Anal. Calcd for $C_{20}H_{27}N_3O_7Si_2$: C, 49.25; H, 7.65; N, 8.62. Found: C, 48.99; H, 7.40; N, 8.76.

2′-0-Phenoxythiocarbonyl-3′, 5′-0-(1,1,3,3-tetraisopropyldisilox-1, 3-diyl)-6-azauridine (3).

Phenyl chlorothionocarbonate (2.8mL, 20mmol) and dimethylaminopyridine (3.96g, 32.4mmol) were added slowly to a stirred solution of compound 2 (5.85g, 12.0mmol) in 150mL of dried CH_3CN under nitrogen. The resulting solution was stirred at room temperature for 4 days. The solvent and excess reagents were removed in vacuo to yield a residue, which was dissolved in CH_2Cl_2 (150mL), washed with water, 0.5 N HCl solution, aqueous, saturated $NaHCO_3$ solution, brine, and then dried ($MgSO_4$). The solvent was evaporated to dryness to afford 7.35g (98%) of a glass, which was used immediately without further purification for the next preparation. The analytical sample was obtained as an amorphous solid by chromatographing the crude product on an Analtech preparative TLC plate ($CHCl_3$-MeOH, 100 : 2.5, v/v): mp 75-78°C; UV (MeOH) shoulder at 262 nm (ε 7310) and λ_{max} 242nm (ε 9500); UV (0.01 N NaOH) shoulder at 266nm (ε 9135) and λ_{max} 243nm (ε 12180); UV (0.01 N HCl) shoulder at 268nm (ε 12910) and λ_{max} 246nm (ε 14130); NMR ($CDCl_3$) δ 1.02-1.17 (m, 28H, i-Pr.), 3.99-4.01 (m, 2H, 5′-H), 4.09 (m, 1H, 4′-H), 4.85 (m, 1H, 3′-H), 6.00 (d, 1H, 2′-H), 6.35 (s, 1H, 1′-H), 7.42 (s, 1H, 5-H), 7.11-7.43 (m, 5H, C_6H_5); MS m/e 624 (M^+ + 1), 488 [M^+ - $C(S)OC_6H_5$]. Anal. Calcd for $C_{27}H_{41}N_3O_8SSi_2$: C, 51.98; H, 6.62; N, 6.74. Found: C, 51.69; H, 6.72; N, 6.62.

2′-Deoxy-3′, 5′-0-(1,1,3,3-tetraisopropyldisilox-1, 3-diyl)-6-azauridine (4).

Tri-n-butyltin hydride (1.35mL, 5.00mmol) was added dropwise to a stirred solution of compound 3 (1.54g, 2.47mmol) and 2, 2′-azobis(2-methylpropionitrile) (AIBN) (98mg, 0.6mmol) in 80mL of toluene under nitrogen. The reaction mixture was stirred at 75-80°C for 4 days. The solvent was then removed in vacuo to yield a syrup (2.1g), which was then chromatographed on a silica gel column (EtOAc-Hexane, 3:2, v/v) to afford 0.42g (36%) of product as a foam: UV (MeOH) λ_{max} 256nm (ε 5475), λ_{min} 239nm; UV (0.01 N NaOH) λ_{max} 258nm (ε 6512), λ_{min} 242nm; UV (0.01 N HCl) λ_{max} 264nm (ε 7442), λ_{min} 251nm; NMR ($CDCl_3$) δ 0.95-1.10 (m, 28H, i-Pr_2Si), 1.90 (m, 2H, 2′-H), 3.95 (m, 2H, 5′-H), 4.48 (m, 1H, 4′-H), 5.30 (m, 1H, 3′-H), 6.05 (t, 1H, 1′-H), 7.55 (s, 1H, 5-H); MS m/e 357 (M^+ - i-Pr_2Si).

Anal. Calcd for $C_{20}H_{37}N_3O_6Si_2$: C, 50.92; H, 7.91; N, 8.91. Found: C, 50.57; H, 8.14; N, 8.63.

2′-Deoxy-6-azauridine (5a).

To a stirred solution of compound 4 (7.06g, 15.0mmol) in 350mL of toluene, 30mL of tetra-n-butylammonium fluoride (1M solution in THF) was added under nitrogen. The reaction mixture was stirred at 75-80°C for 8h. The solvent was removed in vacuo. The residue was dissolved in water (100mL) and washed with ether (3 x 50mL). The aqueous layer was evaporated to dryness under reduced pressure to afford a syrup which was then absorbed in 25g of silica gel and chromatographed on a silica gel (250g) column (hexane-EtOAc-MeOH, 8 : 8 : 3.5, v/v) to yield 1.44g (42%) of product: mp 133-135°C (MeOH) (lit[13] mp 133.5-138°C); UV (MeOH) λ_{max} 260nm (ε 5820), λ 222nm (shoulder); UV (0.01 N NaOH) λ_{max} 257nm (ε 6340), λ 220nm (shoulder); UV (0.01 N HCl) λ_{max} 264nm (ε 6211), λ 226nm (shoulder); NMR (Me_2SO-d_6) δ 2.05 (m, 1H, 2′-H_a), 2.38 (m, 1H, 2′-H_b), 3.36 (m, 2H, 5′-H), 3.67 (m, 1H, 3′-H), 4.22 (m, 1H, 4′-H), 4.62 (br s, 1H, 5′-OH, D_2O exchangeable), 5.16 (br s, 1H, 3′-OH, D_2O exchangeable), 6.30 (m, 1H, 1′-H), 7.25 (s, 1H, 5-H), 12.5 (br s, 1H, 3-NH, D_2O exchangeable). Anal. Calcd for $C_8H_{11}N_3O_5$: C, 41.92; H, 4.84; N, 18.33. Found: C, 41.69; H, 4.72; N, 18.59.

3′,5′-Di-O-acetyl-2′-deoxy-6-azauridine (6)[11].

Acetyl anhydride (2.55g, 25mol) was added dropwise to a solution of 2′-deoxy-6-azauridine (5, 0.97g, 4.20mmol) in dry pyridine (10mL). The reaction mixture was stirred at 4°C overnight. The solution was evaporated to dryness in vacuo to give an oil, which was dissolved in 70mL of CH_2Cl_2, washed with water (2 x 20mL), and dried (anhydrous $MgSO_4$). The solvent was removed under reduced pressure to afford 0.94g (72%) of product as a syrup: NMR ($CDCl_3$) δ 2.00-2.09 (2s, 6H, $OCOCH_3$), 2.10-2.50 (m, 1H, 2′-H_a), 2.58-2.90 (m, 1H, 2′-H_b), 4.05-4.30 (m, 3H, 4′-H and 5′-H), 5.22 (m, 1H, 3′-H), 6.48 (t, 1H, 1′-H), 7.30 (s, 1H, 5-H).

2′-Deoxy-6-azacytidine (8).[11,15]

Thionyl chloride (10mL) and DMF (0.15mL) were added to a stirred solution of compound 6 (0.32g, 1.03mmol) in 10mL of $CHCl_3$. After the reaction mixture was refluxed

for 4h, three drops of DMF was then added to the reaction mixture, and the reflux was continued for an additional 3h. The solution was evaporated to dryness in vacuo. The residue was co-evaporated twice with benzene (2 X 15mL) and then treated with methanolic ammonia (15%) overnight. The solution was evaporated again to dryness under diminished pressure to give a syrup which was absorbed in 15g of silica gel and chromatographed on a silica gel (70g) column (EtOAc-hexane-MeOH, 4 : 4 : 1.5, v/v) to produce 0.1g (44% based on 6) of product mp 240-243°C (lit[11] mp 238-242°C); UV (MeOH) λ_{max} 266nm (8500), λ_{min} 231nm; NMR (Me_2SO-d_6-$CDCl_3$) δ 1.80 - 2.20 (m, 1H, 2′-H_a), 2.20 - 2.60 (m, 1H, 2′-H_b), 3.20 - 3.50 (m, 2H, 5′-H), 3.60 - 3.90 (m, 1H, 3′-H), 4.10 - 4.40 (m, 1H, 4′-H), 4.40 - 4.80 (t, 1H, 5′-OH, D_2O exchangeable), 4.90 - 5.20 (d, 1H, 3′-OH, D_2O exchangeable), 6.40 (t, 1H, 1′-H), 7.80 (br s, 2H, 4-NH_2, D_2O exchangeable).

2′-Deoxy-5′-0-tert-butyldimethylsilyl-6-azacytidine (9).

tert-Butyldimethylsilyl chloride (0.64g, 4.20mmol) was added to a stirred suspension of compound 8 (0.80g, 3.51mmol) in 100mL of dried pyridine. The reaction mixture was stirred at room temperature for 14h. The solvent was evaporated to dryness in vacuo to yield a residue, which was then partitioned between EtOAc-H_2O (150mL : 20mL). The aqueous layer was extracted with CH_2Cl_2-MeOH (10 : 1, v/v) (3 x 50mL). The organic phases were combined and dried over anhydrous $MgSO_4$. The solvents were removed under diminished pressure to afford a solid residue (1.14g, 95%) which was then recrystallized from acetone-hexane to yield the analytical sample: mp 219-221°C; UV (MeOH) λ_{max} 265nm (ε 6850), λ_{min} 228nm; UV (0.01 N NaOH) λ_{max} 264nm (ε 7490), λ_{min} 227nm; UV (0.01 N HCl) λ_{max} 267nm (ε 7020), λ_{min} 228nm; NMR (Me_2SO-d_6) δ 0.85 (m, 15H, t-BuSiMe_2), 1.99 (m, 1H, 2′-H_a), 2.35 (m, 1H, 2′-H_b), 3.52 (m, 1H, 3′-H), 3.64 (m, 2H, 5′-H), 4.22 (m, 1H, 4′-H), 5.15 (d, 1H, 3′-OH, D_2O exchangeable), 6.39 (m, 1H, 1′-H), 7.45 (s, 1H, 6-H), 7.81- 7.94 (br d, 2H, 4-NH_2, D_2O exchangeable). Anal. Calcd for $C_{14}H_{26}N_4O_4Si$: C, 49.10; H, 7.65; N, 16.36. Found: C, 48.80; H, 7.93; N, 16.09.

2′-Deoxy-3′-O-phenoxythiocarbonyl-5′-O-tert-butyldimethylsilyl-6-azacytidine (10).

To a stirred suspension of compound 9 (1.14g, 3.33mmol) and dimethylaminopyridine (1.10g, 9.00mmol) in 150mL of dried CH_3CN, phenyl chlorothionocarbonate (0.63mL, 4.5mmol) was added dropwise under nitrogen. The reaction mixture was stirred at room temperature

for 48h. The solvent and excess reagent were removed in vacuo to yield a residue, which was dissolved in 150mL of CH_2Cl_2, washed with H_2O, and dried (anhydrous $MgSO_4$). The solvent was evaporated to dryness under reduced pressure. The resultant residue was absorbed in 5g of silica gel and chromatographed on a silica gel (100g) column (EtOAc-MeOH, 100 : 5, v/v) to afford 0.83g (52%) of product: mp 201-202°C; UV (MeOH) shoulder at 262nm (ε 9533) and λ_{max} 242nm (ε 10254); NMR (Me_2SO-d_6) δ 0.84 (m, 15H, t-BuSiMe_2), 2.44 (m, 1H, 2′-H_a), 2.84 (m, 1H, 2′-H_b), 3.69 (m, 2H, 5′-H), 4.19 (m, 1H, 4′-H), 5.76 (m, 1H, 3′-H), 6.49 (t, 1H, 1′-H), 7.19 - 7.46 (m, 5H, aromatic), 7.50 (s, 1H, 6-H), 7.90- 8.06 (br d, 2H, 4-NH_2, D_2O exchangeable); MS m/e 479 (M^+ + 1), 367 (M^+-base), 325 [M^+-$OC(S)OC_6H_5$]. Anal. Calcd for $C_{21}H_{30}N_4O_5S$ Si: C, 52.69; H, 6.32; N, 11.72. Found: C, 52.40; H, 6.58; N, 11.75.

2′, 3′-Dideoxy-5′-0-tert-butyldimethysilyl-5-azacytidine (11).

Tri-n-butyltin hydride (0.55mL, 2.0mmol) was added to a stirred suspension of compound 10 (0.48g, 1.0mmol) and AIBN (0.49g, 3.0mmol) in 100mL of toluene under nitrogen. The reaction mixture was stirred at 90-95°C for 21h. The solvent was removed in vacuo to dryness yielding a residue, which then was absorbed in 6g of silica gel and chromatographed on a silica gel (100g) column (EtOAc-MeOH, 100 : 6, v/v) to afford 0.18g (55%) of product: mp 220-221°C (Me_2CO-hexane); UV (MeOH) λ_{max} 265 (ε 5405), λ_{min} 230nm; UV (0.01 N NaOH) λ_{max} 264nm (ε 6381), λ_{min} 231nm; UV (0.01 N HCl) λ_{max} 264nm (ε 5856), λ_{min} 229nm; NMR (Me_2SO-d_6) δ 0.83 (m, 15H, t-BuSiMe_2), 1.90 (m, 2H, 2′-H), 2.12 (m, 2H, 3′-H), 3.58 (m, 2H, 5′-H), 3.98 (m, 1H, 4′-H), 6.34 (t, 1H, 1′-H), 7.44 (s, 1H, 6′-H), 7.78 - 7.90 (br d, 2H, 4-NH_2, D_2O exchangeable); MS m/e 327 (M^+ + 1), 211 (M^+-t-BuSiMe_2). Anal. Calcd for $C_{14}H_{26}N_4O_3Si$: C, 51.53; H, 7.98; N, 17.18. Found: C, 51.91; H, 8.13; N, 16.92.

2′, 3′-Dideoxy-6-azacytidine (12).

To a stirred solution of compound 11 (0.095g, 0.29mmol) in 20mL of dried THF, tetra-n-butylammonium fluoride (1M in THF, 0.88mL, 0.87mmol) was added. The reaction mixture was stirred at room temperature for 1.5h. The solvent was removed in vacuo to yield a residue, which was then chromatographed on two preparative TLC plates (Analtech Uniplate, 2mm) (EtOAc-MeOH, 3 :1, v/v) to afford 0.035g (57%) of product: mp 133-135°C (Me_2CO); UV (MeOH) λ_{max} 267nm (ε 5452), λ_{min} 228nm; UV (0.01 N NaOH) λ_{max} 265nm (ε 5471),

λ_{min} 228nm; UV (0.01 N HCl) λ_{max} 264nm (ε 5218), λ_{min} 230nm; NMR (Me_2SO-d_6) δ 1.80 - 1.95 (m, 2H, 2′-H), 2.07 - 2.16 (m, 2H, 3′-H), 3.37 (m, 2H, 5′-H), 3.95 (m, 1H, 4′-H), 4.60 (t, 1H, 5′-OH, D_2O exchangeable), 6.28 (m, 1H, 1′-H), 7.46 (s, 1H, 6′-H), 7.79 - 7.83 (br d, 2H, 4-NH_2, D_2O exchangeable); MS m/e 213 (M^+ + 1), 113 (base + 2H). Anal. Calcd for $C_8H_{12}N_4O_3 \cdot 0.5\ H_2O$: C, 43.23; H, 5.89; N, 25.44. Found: C, 43.51; H, 6.14; N, 25.10.

2′-Deoxy-3′, 5′-0-dimethanesulfonyl-6-azauridine (13a)

Methanesulfonyl chloride (1.31g, 11.4mmol) was added dropwise to a stirred solution of 2′-deoxy-6-azauridine (5a, 0.87g, 3.8mmol) in 40mL of dried pyridine at 0°C (ice-water bath). The reaction mixture was stirred at 0° - 4°C overnight. The solvent was evaporated to dryness in vacuo and the resulting residue was then chromatographed on a silica gel (100g) column (CH_2Cl_2-MeOH, 20 : 1, v/v) to afford 0.87g (60%) of product: mp 1, v/v) to ~ pH 7. The solvents were evaporated again to dryness under diminished pressure. The resultant residue was then chromatographed on a silica gel (200g) column (EtOAc-MeOH, 100:7, v/v) to give 0.33g (55%) of product: mp 142-144°C (Me_2CO-hexane); UV (MeOH) λ_{max} 263nm (ε 5362), λ_{min} 216nm; UV (0.01 N NaOH) λ_{max} 258nm (ε 6272), λ_{min} 219nm UV (0.01 N HCl) λ_{max} 262 (ε 5665), λ_{min} 227nm; NMR (Me_2SO-d_6) δ 3.42 (m, 2H, 5′-H), 4.71 (m, 2H, 4′-H; 5′-OH D_2O exchangeable), 5.84 (m, 1H, 3′-H, vinyl), 6.33 (m, 1H, 2′-H, vinyl), 6.88 (dd, 1H, 1′-H) 7.49 (s, 1H, 5′-H), 12.2 (br s, 1H, 3-NH, D_2O exchangeable); MS m/e 212 (M^+ + 1). Anal. Calcd for $C_8H_9N_3O_4$: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.75; H, 4.46; N, 20.19.

Compounds 13b - 15b were synthesized from 6-azathymidine (5b) by the same methodology as described above.

3′, 5′-Di-0-methanesulfonyl-6-azathymidine (13b):

Yield, 96%; mp 65-67°C; R_f 0.73 (CH_2Cl_2-EtOH, 8: 1.5, v/v); UV (MeOH) λ_{max} 261nm (ε 7916), λ_{min} 224nm; UV (0.01 N NaOH) λ_{max} 254nm (ε 8167), λ_{min} 220nm UV (0.01 N HCl) λ_{max} 262 (ε 7107), λ_{min} 234nm; NMR (Me_2SO-d_6) δ 2.28 (s, 3H, 5′-CH_3), 2.57 - 2.62 (m, 1H, 2′-H_a), 2.89 -2.94 (m, 1H, 2′-H_b), 3.04 (s, 3H, 5′-OSO_2CH_3), 3.12 (s, 3H, 3′-OSO_2CH_3), 4.36 - 4.42 (m, 3H, 4′-H and 5′-H), 5.42 (m, 1H, 3′-H), 6.57 (m, 1H, 1′-H) 7.26 (s, 1H, 6′-H), 8.72 (br s, 1-H, 3-NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{17}N_3O_9S_2$: C, 33.07; H, 4.29; N, 10.52. Found: C, 33.36; H, 4.53; N, 10.77.

3′, 5′-Anhydro-6-azathymidine (14b):

Yield, 61%; mp 172-173°C; R_f 0.66 (CH_2Cl_2-EtOH, 8: 1.5, v/v); UV (MeOH) λ_{max} 265nm (ε 6350), λ_{min} 231nm; UV (0.01 N NaOH) λ_{max} 254nm (ε 8176), shoulder at 220nm, λ_{min} 206nm; UV (0.01 N HCl) λ_{max} 264 (ε 6080), λ_{min} 233nm; NMR (Me_2SO-d_6) δ 2.09 (s, 3H, 5′-CH_3), 2.35 163-165°C (Me_2CO-hexane); UV (MeOH) λ_{max} 263nm (ε 5202), shoulder at 216nm; UV (0.01 N NaOH) λ_{max} 253nm (ε 5980), shoulder at 218nm; UV (0.01 N HCl) λ_{max} 261nm (ε 5056), λ_{min} 225nm; NMR (Me_2SO-d_6) δ 2.57 (m, 1H, 2′-H_a), 2.75 (m, 1H, 2′-H_b), 3.16 (s, 6H, OSO_2CH_3), 4.24 (m, 1H, 4′-H), 4.34 (m, 2H, 5′-H) 5.28 (m, 1H, 3′-H), 6.40 (m, 1H, 1′-H), 7.57 (s, 1H, 5-H), 13.04 (br s, 3-NH, D_2O exchangeable); MS m/e 386 (M^+ + 1). Anal. Calcd for $C_{10}H_{15}N_3O_9S_2$: C, 31.17; H, 3.92; N, 10.90. Found: C, 31.44; H, 3.69; N,10.63.

2′-Deoxy-3′, 5′-anhydro-6-azauridine (14a)

A mixture of compound 13a (2.17g, 5.64mmol), 17.1mL of 1 N NaOH and 112mL of water was stirred and refluxed for 2.5h. The resultant solution was cooled to room temperature and neutralized with HOAc-MeOH to ~ pH 7. The solvent was evaporated to dryness in vacuo at 30-35°C to yield a residue, which was then chromatographed on a silica gel (210g) column (EtOAc-MeOH, 25 : 1, v/v) to produce 0.61g (38%) of product: mp 196-198°C (Me_2CO-hexane); UV (MeOH) λ_{max} 264nm (ε 5524), shoulder at 222nm; UV (0.01 N NaOH) λ_{max} 257nm (ε 6351), shoulder at 220nm; UV (0.01 N HCl) λ_{max} 263nm (ε 5505), λ_{min} 224nm; NMR (Me_2SO-d_6) δ 2.41 (m, 1H, 2′-H_a), 2.60 (m, 1H, 2′-H_b), 4.20 (m, 1H, 5′-H_a), 4.54 (m, 1H, 5′-H_b), 4.96 (dd, 1H, 4′-H) 5.35 (t, 1H, 3′-H), 6.54 (m, 1H, 1′-H), 7.57 (s, 1H, 5′-H), 12.9 (br s, 1-H, 3-NH, D_2O exchangeable); MS m/e 212 (M^+ + 1). Anal. Calcd for $C_8H_9N_3O_4$: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.13; H, 4.07; N, 19.52.

2′, 3′-Dideoxy-6-azauridin-2′-ene (15a).

A mixture of compound 14a (0.60g, 2.84mmol) and t-BuOK (0.80g, 7.1mmol) in dried Me_2SO (30mL) was stirred at 75-80°C for 2.5h. The solvent was removed in vacuo to yield a residue, which was dissolved in EtOH-H_2O (15mL : 5mL) and neutralized with HOAc-EtOH (1 : - 2.62 (m, 2H, 2′-H), 4.26 - 4.30 (m, 1H, 5′-H_a), 4.52 - 4.56 (m, 1H, 5′-H_b), 4.95 (m, 1H, 4′-H), 5.33 (m, 1H, 1′-H), 6.53 (m, 1H, 1′-H), 11.2 (br s, 1-H, 3-NH, D_2O exchangeable). Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.02; H, 4.88; N, 18.66. Found: C, 48.00; H, 5.10; N, 18.41.

3′-Deoxy-6-azathymidin-2′-ene (15b):

Yield, 51%; mp 126-128°C; R_f 0.5 (EtOH - MeOH, 10: 0.4, v/v); UV (MeOH) λ_{max} 264nm (ε 6510), λ_{min} 230nm; UV (0.01 N NaOH) λ_{max} 256nm (ε 8217), λ_{min} 210nm; UV (0.01 N HCl) λ_{max} 265 (ε 6324), λ_{min} 231nm; NMR (Me_2SO-d_6) δ 2.03 (s, 3H, 5′-CH_3), 3.40 - 3.49 (m, 2H, 5′-H), 4.69 - 4.71 (m, 2H, 4′-H; 5′-OH, D_2O exchangeable), 5.83 (m, 1H, 3′-H, vinyl), 6.33 (m, 1H, 2′-H, vinyl), 6.88 (m, 1H, 1′-H), 12.1 (br s, 1-H, 3-NH, D_2O exchangeable). Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.02; H, 4.88; N, 18.66. Found: C, 48.37; H, 5.02; N, 18.33.

3′-Deoxy-6-azathymidine (16b).

A solution of compound 15b (0.15g, 0.60mmol) in 15mL of MeOH, containing 40mg of 10% Pd/C was hydrogenated at 50 psi of hydrogen at room temperature for 3h. The catalyst was removed by filtration and the filtrate was evaporated to dryness in vacuo. The resulting residue was then purified by silica gel column chromatography (EtOAc-MeOH, 10: 0.5, v/v) to give 0.095g (63%) of product as a glass: R_f 0.63 (EtOH - MeOH, 10: 0.5, v/v); UV (MeOH) λ_{max} 265nm (ε 6480), λ_{min} 231nm; UV (0.01 N NaOH) λ_{max} 257nm (ε 8347), λ_{min} 212nm; UV (0.01 N HCl) λ_{max} 266 (ε 6512), λ_{min} 230nm; NMR (Me_2SO-d_6) δ 1.85 - 2.19 (m, 7H, 2′-H, 3′-H, and 5-CH_3), 3.39 (m, 2H, 5′-H), 3.97 (m, 1H, 4′-H), 4.62 (br s, 1H, 5′-OH, D_2O exchangeable), 6.18 (m, 1H, 1′-H), 12.04 (br s, 1-H, 3-NH, D_2O exchangeable); Ms m/e 227 (M^+), 228 ($M^+ + 1$), 229 ($M^+ + 2$), 128 (base + 1). Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.58; H, 5.73; N, 18.50. Found: C, 47.23; H, 5.98; N, 18.24.

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