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Synthesis of 3′-azido-4′-ethynyl-3′,5′-dideoxy-5′-norarabinouridine: a new anti-HIV nucleoside analogue

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ABSTRACT

3′-Azido-4′-ethynyl-3′,5′dideoxy-5′-norarabinouridine **10** was synthesized from commercial uridine **1** in which the key step is the opening of protected 2′,3′-epoxyuridine derivative **7** by sodium azide and the hydroxymethyl at 4-position of the ribose ring are replaced by ethynyl group.

1. Introduction

The continued interest in the synthesis of nucleoside analogues is reflected in the successful use of this class of compounds in viral cancerous diseases.[1] This interest has recently become more focused with the identification of the retrovirus HIV-1 as the causative agent of Acquired Immune Deficiency Syndrome (AIDS).[2] To date, eight nucleoside analogues, namely zidovudine (AZT), stavudine (d4T), didanosine (ddI), Abacavir, zalcitabine (ddC), lamivudine (3TC), emtricitabine (FTC), and tenofovir (PMPA) (Fig. 1) have been approved by the US Food and Drug Administration (FDA) for the treatment of human immunodeficiency virus (HIV) infection.[3,4] All these 2′,3′-dideoxynucleoside analogues share a common mechanism of action. They are metabolized by cellular kinases to their 5′-triphosphate forms, which then exert their biological effect as virus-specific polymerase (reverse transcriptase) competitive inhibitors or chain terminators because they lack a hydroxyl group at the C-3′ position.[5] The total syntheses of 3′,4′-diethynyl-2′,3′,5′-trideoxy-5′-norarabinouridine as a new self-polymerizable 2′-deoxyribonucleoside analogue (Fig. 2) and as an anti-HIV agent was prepared in our laboratory.[6]

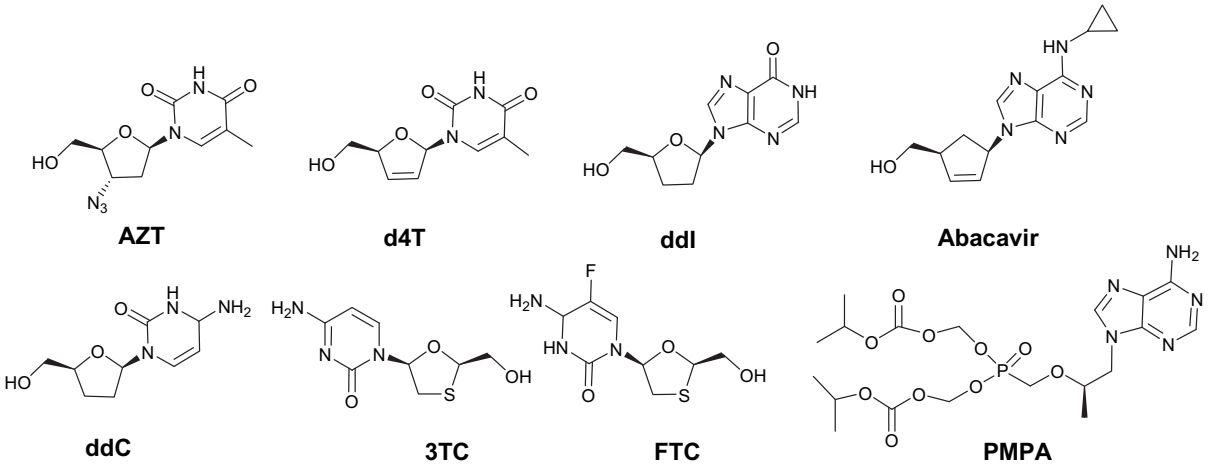

Fig. 1. Structure of the nucleoside analogues currently approved by US Food and Drug Administration (FDA) for the treatment of human immunodeficiency virus (HIV) infection.

The present work deals with the enantioselective synthesis of a derivative of uridine analogues, in which the hydroxymethyl and

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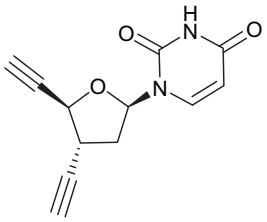


Fig. 2. Structure of 3′,4′-diethynyl-2′,3′,5′-trideoxy-5′-norarabinouridine nucleoside.

OH substituents at 4′- and 3′-positions of the ribose ring are replaced by ethynyl and azido groups, respectively. Although nucleoside analogues in which the ethynyl or azido group are bound to the positions C-2′, C-3′, C-4′or C-5′ of ribose moiety are known[7–24], **10** appears to be the first such analogue to be described in which ethynyl and azide groups are present in the same molecule.

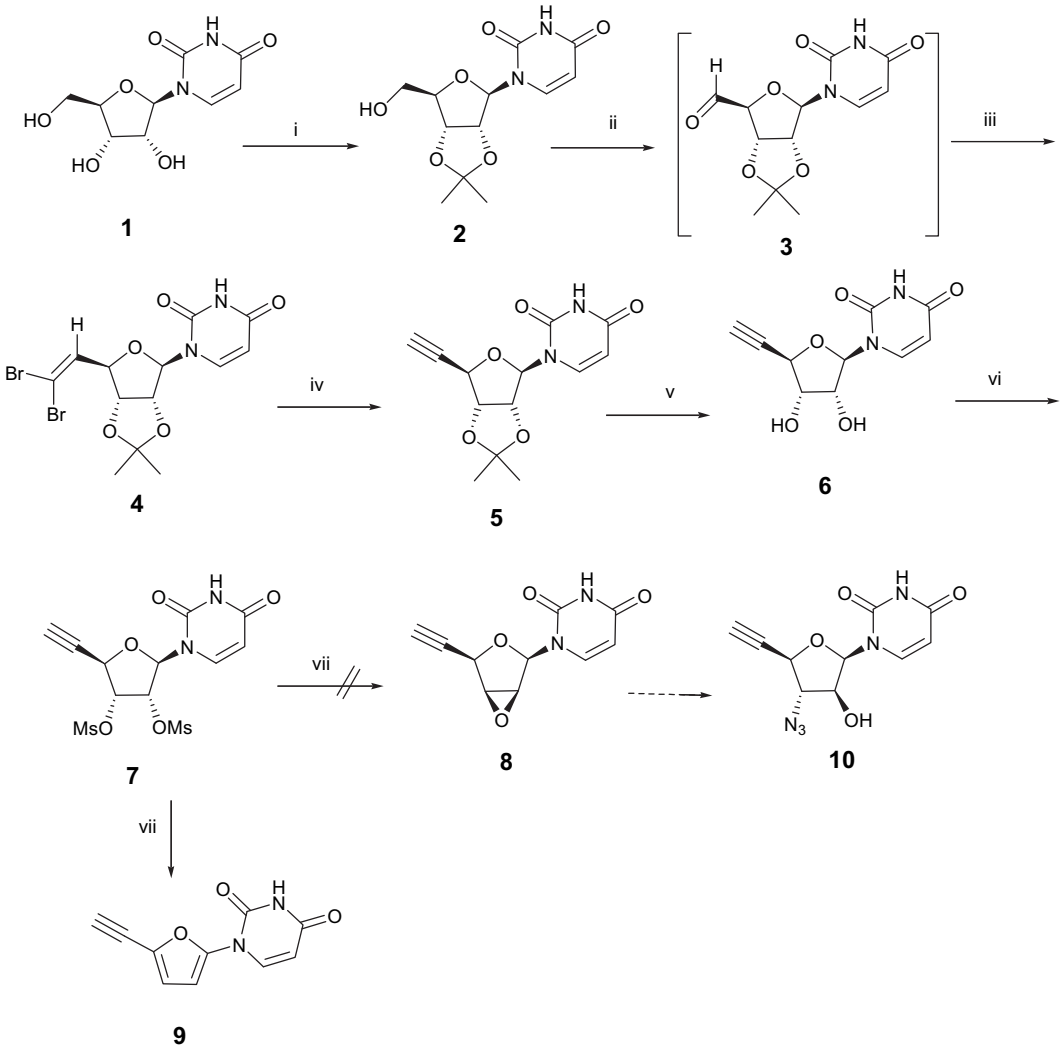
2. Results and discussion

2.1. Attempted synthesis of 10 from 2′,3′-epoxy-4′-ethynyl-lyxo-derivatives 8

This was readily accessible starting from uridine **1**. The transformation of $HOCH_2$-(5′) substituent into an ethynyl group was achieved by a Corey–Fuchs reaction on acetonide protected 2′,3′-*O*-isopropylideneuridine **2**. Oxidation of the primary hydroxyl compound **2** by using the *Moffatt* oxidation[25], using DMSO/DCC catalyzed by pyridine and trifluroacetic acid (TFA) followed by condensation of aldehyde **3** without purification, [(dibromomethylidene) triphenylphosphorane][14] gave 1-[5,6-dideoxy-6,6-dibromo-2,3-*O*-*iso*-propylidene-β-D-enofuranosyl]pyrimidine-2,4-(1*H*,3*H*)dione **4** in 60% yield from hydroxyl compound **2**. The base mediated dehydrohalogenation of **4** was achieved using *n*-butyllithium in THF at −78 °C, followed by neutralization with acetic acid affording 4′-ethynyl derivative **5**. The ^{1}H NMR spectrum of compound **5** showed the ethynyl proton as a doublet at δ 2.7 ppm (J=2.2 Hz) with a long-rang allylic coupling with the proton at C-4′. The isopropylidene group was removed by treatment with acetic acid to give **6**. Mesylation of **6** with methanesulfonyl chloride affords di-*O*-mesyl **7**, which was treated with sodium hydroxide solution but did not lead to the desired 2′,3′-epoxy derivative **8**, which could be used for the synthesis of 3′-azido compound **10**, but instead, by elimination, gave furanyl nucleoside **9** (Scheme 1).

2.2. Synthesis of 3′-azido-4′-ethynyl-3′,5′-dideoxy-5′-norarabinouridine 10

Despite the above mentioned failure, opening of epoxide was attempted again, this time before introduction of the ethynyl



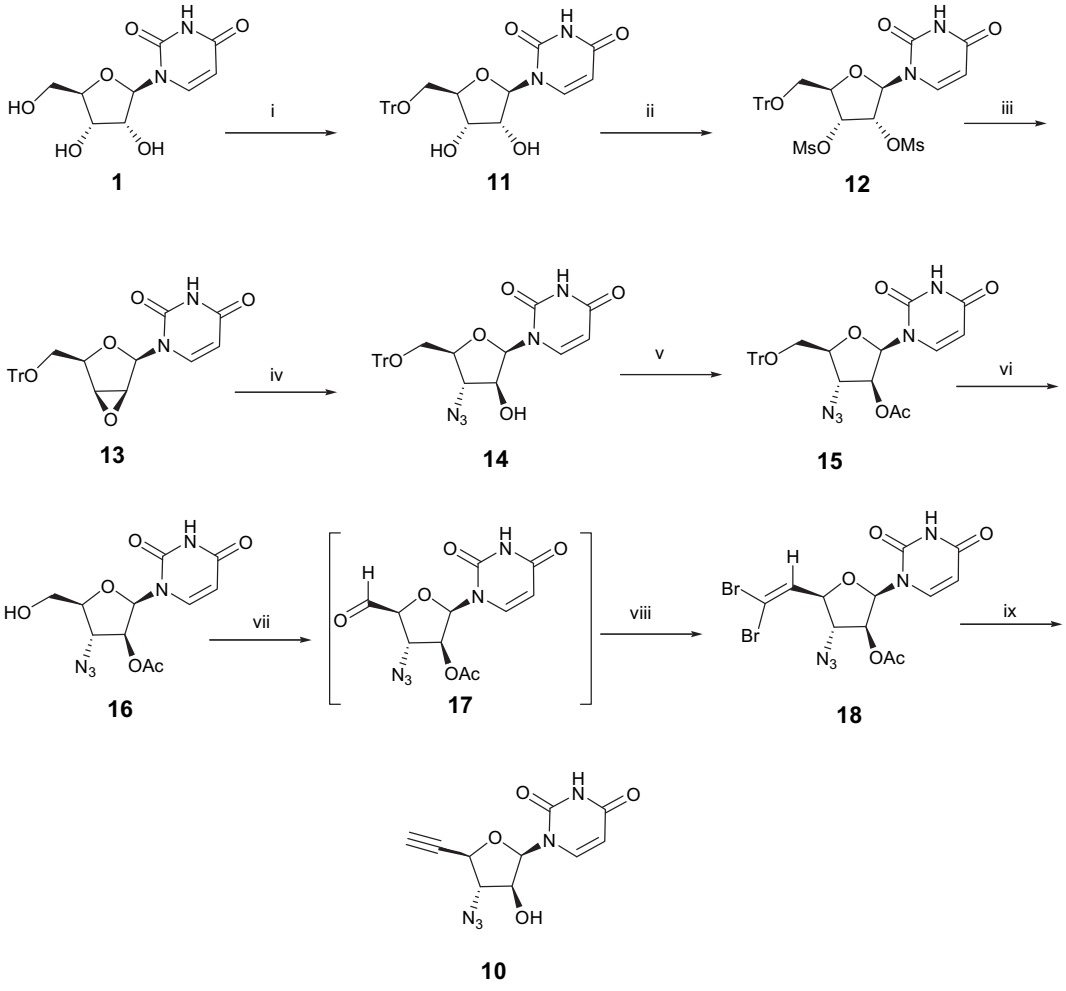
Scheme 1. Reagents and conditions (i) acetone, $CuSO_4$, H_2SO_4; (ii) DMSO, pyridine, TFA, DCC; (iii) CBr_4, Ph_3P, Zn, 60% from **2**; (iv) *n*-BuLi, THF, −78 °C, 63%; (v) AcOH (80%), 100 °C, 2 h, 91%; (vi) MsCl, pyridine, 0 °C, 96%; (vii) 1 M NaOH, 86%.

group in the molecule. The primary hydroxyl group of uridine (**1**) was protected as a trityl group using triphenylmethyl chloride in anhydrous pyridine to afford (**11**). Mesylation of (**11**) with methanesulfonyl chloride gave di-*O*-mesyl (**12**), which was treated with 1 M aq NaOH afforded 2′,3′-epoxy derivative (**13**). The epoxide (**13**) was opened by sodium azide in dimethylformamide to give the azide derivative (**14**). Acetyl was preferred as a protecting group for the hydroxyl at carbon-2′ because it is stable under the acidic conditions used in the next step.[6] The acetyl group was introduced by acetylation of (**14**) with acetic anhydride in pyridine to afford (**15**). Selective deprotection of the trityl group was achieved with aqueous acetic acid to yield (**16**). The primary hydroxyl group was oxidized by a *Moffatt* oxidation to the aldehyde (**17**), which was reacted without purification in a Corey–Fuchs reaction to give the dibromo derivative (**18**). Transformation of (**18**) to the ethynyl derivative (**10**) was achieved using *n*-butyllithium. *n*-Butyllithium in this reaction has two functions, the first is the generation of the ethynyl group and the second is the deprotection of the acetyl group,[6] Scheme 2.

4. Experimental part

4.1. General

All reagents were purchased from commercial sources and used without further purification. All air- and water-sensitive reaction were carried out under nitrogen. THF was freshly distilled from sodium/benzophenone. Thin-layer chromatography (TLC) was performed on precoated 0.2 mm Merck kiesilica gel 60 F_{254} silica plates and compounds were visualized under 245 nm ultraviolet irradiation and/or stained in I_2 vapor. Column chromatography (CC) was performed using Merck silica gel 60 (230–400 mesh) with the indicated solvents. Melting points were measured on a Kofler hot stage apparatus and uncorrected. Optical rotations were measured on a Perkin–Elmer polarimeter 241 and are given in 10^{-1} cm^2 g^{-1}. Infrared spectra were recorded on a Mattson 5000 FT-IR spectrophotometer. Absorption frequencies are given in wave numbers (cm^{-1}). NMR spectra were recorded on a Varian instrument. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR at 100 MHz. Data are expressed in parts per million downfield shift from tetramethylsilane as internal standard or relative to $CHCl_3$ or DMSO. All *J* values are given in hertz. Mass spectra were recorded using a Vacuum Generator Micromass 7070 E spectrometer operating in chemical ionization (CI), Electron ionization (EI) or fast atom bombardment (FAB). Elemental analyses were performed on a Heraus CHN-rapid analyzer.



Scheme 2. Reagents and conditions: (i) TrCl, pyridine; (ii) MsCl, pyridine, 0 °C, 95%; (iii) 1 M NaOH, 91%; (iv) NaN_3, DMF, 73%; (v) Ac_2O, pyridine, 90%; (vi) AcOH (80%), 92%; (vii) DMSO, pyridine, TFA, DCC; (viii) Ph_3P, CBr_4, Zn, 56% from **16**; (ix) *n*-BuLi, THF, −78 °C, 59%.

3. Conclusion

In conclusion, we synthesized the 3′-aziod-4′-ethynyl-3′,5′-dideoxy-5′-norarabinouridine **10** as the first nucleoside derivative in which ethynyl and azido groups are present in the same nucleoside at C-3′and C4′ of a sugar moiety.

4.2. 1-(5,6-Dideoxy-6,6-dibromo-2,3-*O*-isopropylidene-β-D-enofuranosyl)pyrimidine-2,4(1*H*-3*H*)-dione (4)

Oxidation of **2** (1.40 g, 4.93 mmol) to the corresponding aldehyde **3** was carried out in dimethyl sulfoxide (24 mL) containing pyridine (0.4 mL), trifluroacetic acid (0.2 mL), and *N*,*N*′-dicyclohexylcarbodiimide (3.06 g, 14.8 mmol), which was stirred under nitrogen for 24 h at room temperature. Thereafter, the mixture was added dropwise to a solution of (dibromomethylidene)triphenylphosphorane (prepared by the reaction of triphenylphosphine (2.62 g, 10.0 mmol)), carbon tetrabromide (3.32 g, 10.0 mmol), and zinc dust (0.65 g, 10.0 mmol) in CH_2Cl_2 (24 mL). After stirring for 24 h at room temperature, CH_2Cl_2 (100 mL) was added, the solution washed with water (3×100 mL), dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography on silica gel using EtOAc/CH_2Cl_2 (1:1) as an eluent to give the product, which contained dicyclohexylurea as impurity. The product was redissolved in CH_2Cl_2, the solid precipitate filtered off, and the solution evaporated to give **4** (1.30 g, 60% from **2**) as white solid, mp 330–331 °C. R_f (3:1 CH_2Cl_2/EtOAc) 0.42; IR (KBr) 3452, 3224, 3052, 2931, 1692, 1460, 1380, 1272, 1203, 1109, 1068, 1022, 889, 717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 and 1.50 (2×s, 6H, Me_2C), 4.61 (dd, *J*=8.2, 3.6, 1H, H-2′), 4.74 (dd, *J*=8.2, 7.4, 1H, H-3′), 5.15 (dd, *J*=7.4, 6.3, 1H, H-4′), 5.61 (d, *J*=8.0, 1H, H-5), 5.70 (d, *J*=3.6, 1H, H-1′), 6.84 (d, *J*=6.3, 1H, H-5′), 7.71 (d, *J*=8.0, 1H, H-6), and 11.53 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 25.7 (q, Me), 27.7 (q, Me), 84.3 (d, 2C, C-2′,3′), 87.6 (d, C-1′), 93.3 (s, C-6′), 94.3 (d, C-4′), 102.1 (d, C-5), 113.5 (s, Me_2C), 137.3 (d, C-5′), 144.0 (d, C-6), 150.0 (s, CO, C-4), 163.5 (s, CO, C-2). FAB: 461 ([M+Na]$^+$, 5), 460 (2), 459 (6), 441 (29), 440 (11), 439 (60), 438 (7), 437 (32), 423 (8), 380 (8), 327 (15), 113 (100). Anal. Calcd for $C_{13}H_{14}Br_2N_2O_5$: C 35.64, H 3.22, N 6.39. Found: C 36.49, H 3.41, N 6.27.

4.3. 1-[5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-ynofuranosyl]pyrimidine-2,4(1*H*,3*H*)-dione (5)

A solution of **4** (0.50 g, 1.14 mmol) in anhydrous THF was cooled to −78 °C before 6 mL (9.60 mmol) of 1.6 M butyllithium in hexane was added. The mixture was stirred for 5 h and then neutralized with acetic acid. The solvent was evaporated after addition of absolute ethanol and the residue purified by column chromatography using silica gel and CH_2Cl_2/EtOAc (1:1) as an eluent to give **5** (0.20 g, 63%) as a white solid, mp 171–174 °C. R_f (2:1 CH_2Cl_2/EtOAc) 0.46; IR (KBr) 3454, 3223, 3082, 2951, 2130, 1690, 1469, 1417, 1340, 1296, 1213, 1168, 1112, 1024, 814, 727, 711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 and 1.51 (2×s, 6H, Me_2C), 2.74 (d, *J*=2.2, 1H, CH≡C), 4.86–4.98 (m, 2H, H-2′,3′), 5.11–5.15 (m, 1H, H-4′), 5.74 (d, *J*=8.2, 1H, H-5), 5.82 (d, *J*=3.4, 1H, H-1′), 7.50 (d, *J*=8.2, 1H, H-6), and 9.33 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 25.5 (q, Me), 27.1 (q, Me), 71.1 (d, C-4′), 71.1 (d, HC≡C), 75.4 (s, HC≡C), 79.2 (d, C-5), 87.6 (d, C-2′), 92.5 (d, C-1′); 102.9 (d, C-5), 115.2 (s, Me_2C), 141.7 (d, C-6), 151.1 (s, CO, C-4), 164.2 (s, CO, C-2). EI: 279 ([M+H]$^+$, 4), 278 (M$^+$, 6), 263 (60) 220 (19), 169 ([M−uracil]$^+$, 49), 113 ([uracil+H]$^+$, 52). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C 56.11, H 5.07, N 10.07. Found: C 56.30, H 5.23, N 10.15.

4.4. 1-[5-Ethynyl-3,4-dihydroxy-tetrahydro-furan-2-yl]-1*H*-pyrimidine-2,4-dione (6)

Compound **5** (2.78 g, 10.0 mmol) was dissolved in acetic acid (80%, 20 mL). Reflux for 30 min and the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel using CH_2Cl_2/EtOAc (4:1) to give the **6** (2.16 g, 91%), as a white solid, mp 142–144 °C. R_f (5:1 CH_2Cl_2/EtOAc) 0.36; IR (KBr) 3509, 3415, 3172, 3082, 2921, 2129, 1697, 1465, 1413, 1380, 1340, 1291, 1211, 1169, 1110, 1024, 727, 711 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.70 (d, *J*=2.1, 1H, CH≡C), 4.35–4.47 (m, 2H, H-2′,3′), 4.89–4.93 (m, 1H, H-4′), 5.14–5.31 (m, 2H, 2OH), 5.83 (d, *J*=8.1, 1H, H-5), 6.10 (d, *J*=2.3, 1H, H-1′), 8.02 (d, *J*=8.1, 1H, H-6), and 11.42 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 71.3 (d, C, 3′), 73.2 (d,C-5′), 75.8 (d, HC≡C), 76.8 (d,C-4′), 81.4 (s, HC≡C), 83.9 (d, C-2′), 102.7 (d, C-5), 141.3 (d, C-6), 151.1 (s, CO, C-2), 163.9 (s, CO, C-4). EI: 261 ([M$^+$, 5), 207 (6), 179 (12) 178 (15), 113 (25), 112 (100). Anal. Calcd for $C_{10}H_{10}N_2O_5$: C 50.42, H 4.23, N 11.76. Found: C 50.59, H 4.3, N 11.65.

4.5. (2*R*,3*S*,4*S*,5*R*)-2-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-(ethynyl)tetrahydrofuran-3,4-diyl dimethane-sulfonate (7)

Methanesulfonyl chloride (6 mL) was added slowly to an ice-cooled solution of **6** (1.20 g, 5.00 mmol) in anhydrous pyridine (12 mL). After storage overnight at 0 °C, the reaction mixture was slowly poured into (500 mL) well stirred ice-water. The precipitate was filtered off, washed with water, dried, and purified by column chromatography using CH_2Cl_2/EtOH (95:5, v/v) as an eluent. The appropriate fractions were pooled and the solvent was removed by evaporation to give the product **7** (1.96 g, 96%) as white solid, mp 172–173 °C. A small portion was crystallized from hexane/CH_2Cl_2. R_f (9:1 CH_2Cl_2/EtOH) 0.51; $[\alpha]_D^{25}$ −19.5 (*c* 0.65, $CDCl_3$); IR (KBr) 3462, 3225, 3061, 2931, 2218, 1693, 1492, 1456, 1381, 1241, 1114, 1073, 1021, 987, 765, 707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (d, *J*=2.2, 1H, CH≡C), 3.01 (s, 3H, Me), 3.23 (s, 3H, Me), 5.19–5.24 (m, 1H, H-5), 5.49–5.54 (m, 2H, H-3, H-4), 5.70 (d, *J*=8.2, 1H, H-5-pyrimi), 5.94 (d, *J*=3.2, 1H, H-2), 7.81 (d, *J*=8.2, 1H, H-6), and 9.63 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 38.2 (2q), 74.8 (d, C-5), 78.3 (d, HC≡C), 80.2 (d, C-3), 83.4 (d, C-4), 82.1 (s, HC≡C), 90.5 (d, C-3), 102.4 (d, C-5-pyrimi), 141.8 (d, C-6), 150.7 (s, CO, C-2), 163.6 (s, CO, C-4). FAB: 417 ([M+Na]$^+$, 7), 395 ([M+H]$^+$, 11), 312 (7), 282 (27), 113 (100). Anal. Calcd for $C_{12}H_{14}N_2O_9S_2$: C 36.55, H 3.58, N 7.10. Found: C 36.30, H 3.83, N 7.25.

4.6. 1-(5-Ethynylfuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (9)

The di-*O*-mesyl compound **7** (7.88 g, 20.0 mmol) was dissolved in 1 M NaOH in acetone/water (1:1) (40 mL). The resulting solution was kept at room temperature for 18 h, and then poured in ice-water mixture (500 mL) neutralized with 1 M HCl. The resulting precipitate was filtered off and purified by column chromatography on silica gel using CH_2Cl_2/EtOAc (3:2), as eluent. The appropriate fractions were pooled and the solvent was evaporated, recrystallized form ethanol/petroleum ether (1:2, v/v) to give **9** (3.50 g, 86.6%), as white solid; mp 221–222 °C. R_f (8:2 EtOAc/CH_2Cl_2) 0.34; IR (KBr) 3448, 3284, 3061, 2933, 1691, 1487, 1455, 1382, 1269, 1204, 1113, 1063, 1024, 776, 702 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.13 (s, 1H, CH≡C), 5.89 (d, *J*=8.1, 1H, H-5), 6.50 (d, *J*=3.4, 1H, C-3′), 6.72 (d, *J*=3.4, 1H, C-2′), 7.84 (d, *J*=8.1, 1H, H-6), and 10.81 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 78.1 (s, HC≡C), 80.3 (d, HC≡C), 93.4 (d, C-3′), 102.8 (d, C-5), 121.7 (d, C, 4′), 134.2 (s, C-5′), 142.2 (d, C-6), 149.3 (s, CO, C-2), 149.9 (d, C-2′), 163.6 (s, CO, C-4). CI: 203 ([M+H]$^+$, 5), 135 (14), 108 (19), 107 (100). Anal. Calcd for $C_{10}H_6N_2O_3$: C 59.41, H 2.99, N 13.86. Found: C 59.53, H 3.12, N 13.79.

4.7. 1-[2,3-Di-*O*-(metanesulfonyl)-5-*O*-(triphenylmethyl)-β-D-ribofuranosyl]pyrimidine-2,4(1*H*,3*H*)-dione (12)

The di-mesyl compound **12** was obtained as a white crystals (8.80 g, 95.2%) from (9.72 g, 20.0 mmol) of **11** as described for **7**, mp 109–110 °C. The product crystallized from AcOEt. R_f (4:1 EtOAc/CH_2Cl_2) 0.46; IR (KBr) 3461, 3232, 3056, 2933, 1691, 1463, 1381, 1265, 1112, 1026, 775, 706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.02 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 3.54–3.68 (m, 2H, H-5′), 4.23–4.29 (m, 1H, H-4′), 5.34 (dd, *J*=8.1, 1.4, 1H, H-5), 5.36–5.48 (m, 2H, H-2′,3′), 6.01 (d, *J*=3.4, 1H, H-1′), 7.19-7.41 (m, 15H, Ph_3C), 7.73 (d, *J*=8.1, 1H, H-6), and 9.80 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 38.3 (2q, $2CH_3$); 61.8 (d,

C-5′), 74.4 (d, C-3′), 77.3 (d, C-2′), 80.3 (d, C-4′), 87.1 (s, Ph_3C), 88.4 (d, C-1′), 102.2 (d, C-5), 127.5, 127.8, 128.2, 128.6, 143.4 (Ph_3C), 141.3 (d, C-6), 150.6 (s, CO, C-4), 163.3 (s, CO, C-2). FAB: 665 ($[M+Na]^+$, 6), 643 ($[M+H]^+$, 7), 569 (8), 383 (10), 244 ($[Ph_3C+H]^+$, 100), 165 (100). Anal. Calcd for $C_{30}H_{30}N_2O_{10}S_2$: C 56.06, H 4.70, N 4.36. Found: C 56.21, H 4.84, N 4.28.

4.8. 1-[2,3-Epoxy-5-*O*-(triphenylmethyl)-β-D-lyxofurano-syl] pyrimidine-2,4(1*H*,3*H*)-dione (13)

The compound **13** was obtained (4.00 g, 91% yield) from 6.34 g (10.0 mmol) of **12** as described for **9**, mp 128–131 °C. The product was crystallized from ethanol. R_f (1:4 EtOH/CH_2Cl_2) 0.39; $[\alpha]_D^{25}$ −11.5 (*c* 2.5, MeOH); IR (KBr) 3462, 3200, 3058, 3034, 2929, 2879, 1693, 1613, 1490, 1449, 1384, 1223, 1074, 1032, 990, 827, 764,707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.31–3.39 (m, 2H, H-5′), 3.81 (dd, *J*=5.8, 3.0 1H, H-3′), 3.92 (d, *J*=3.0, 1H, H-2′), 4.23 (t, *J*=5.8, 1H, H-4′), 5.59 (d, *J*=8.2, H-5), 6.22 (d, *J*=3.0, 1H, H-1′), 7.21–7.48 (m, 15H, Ph_3C), 7.63 (d, *J*=8.2, 1H, H-6), 9.34 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 56.5 (d, C-2′), 56.7 (d, C-3′), 62.7 (t, C-5′), 77.3 (d, C-4′), 82.3 (d, C-′), 88.0 (s, Ph_3C), 102.9 (d, C-5), 127.7 128.4, 129.1, 144.0 (Ph_3C), 141.8 (d, C-6), 150.9 (s, CO, C-4), 163.5 (s, CO, C-2). FAB-Ms: 491 ($[M+Na]^+$, 20), 469 ($[M+H]^+$, 15), 243 (Ph_3C^+, 100), 209 (8), 165 (40). Anal. Calcd for $C_{28}H_{24}N_2O_5$: C 71.78, H 5.16, N 5.98. Found: C 71.69, H 5.31, N 6.11.

4.9. 1-[3-Azido-3-deoxy-5-*O*-(triphenylmethyl)-β-D-ara-binofuranosyl]pyrimidine-2,4-(1*H*,3*H*)-dione (14)

A mixture of 2,3-anhydro-nucleoside **13** (2.00 g, 4.30 mmol) and NaN_3 (1.30 g, 20.0 mmol) in 40 mL of dry DMF was stirred at 80 °C. After 24 h a second crop of NaN_3 (0.50 g) was added and the mixture was further stirred. TLC revealed completeness of the reaction after another 12 h. The reaction mixture was concentrated and partitioned between H_2O (200 mL) and ethyl acetate (150 mL). The water layer was washed with 100 mL of ethyl acetate (100 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated. Column chromatography (CH_2Cl_2/MeOH, 97:3) of the residue yielded (1.60 g, 73.4%) of the title compound **14** as a white solid; mp 212–213 °C. R_f (1:9 MeOH/CH_2Cl_2) 0.51; IR (KBr) 3441, 3284, 3057, 2929, 2143, 1691, 1463, 1380, 1274, 1114, 1071, 767, 707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.24 −3.29 (m, 1H, H-5′), 3.38–3.42 (m, 1H, H-5′), 4.23–4.29 (m, 1H, H-3′), 4.30–4.35 (m, 1H, H-4′), 4.51–4.54 (m, 1H, H-2′), 5.22 (s, 1H, HO-2′), 5.60 (d, *J*=5.3, 1H, H-1′), 5.94 (d, *J*=8.1, 1H, H-5), 7.21–7.53 (m, 15H, H–Ph_3C), 7.92 (d, *J*=8.1, 1H, H-6), 9.90 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 63.1 (t, C-5′), 72.9 (d, C-3′), 77.3 (d, C-2′), 85.3 (d, C-4′), 86.1 (d, C-1′), 87.2 (s, Ph_3C), 102.1 (d, C-5), 127.0, 128.1 and 128.6 (d, C–Ph_3), 142.9 (d, C-6), 144.2 (s, Ph_3C), 151.6 (s, CO, C-2), 165.3 (s, CO, C-4). FAB: 534 ($[M+Na]^+$, 8), 512 ($[M+H]^+$, 9), 252 ($[M-OPh_3C]^+$, 7), 243 (Ph_3C, 100), 140 (19), 113 ($[uracil+H]^+$, 15). Anal. Calcd for $C_{28}H_{25}N_5O_5$: C 65.41, H 4.93, N 13.69. Found: C 65.53, H 5.10, N 13.79.

4.10. (2*R*,3*R*,4*S*,5*S*)-4-Azido-2-(2,4-dioxo-3,4-dihydropyrimidine-1(2*H*)-yl)-5-(trityloxymethyl)-tetrahydro-furan-3-ylacetate (15)

Acetic anhydride (6 mL) was added to a solution of **14** (5.11 g, 10.0 mmol) in anhydrous pyridine (50 mL). After stirring for 3 h at room temperature, the reaction mixture was poured slowly into ice-water (500 mL). The precipitate was filtered off, washed with water, and dried in vacuum. The product was purified by column chromatography on silica gel using EtOAc to give **15** (5.00 g, 90%), small portion was crystallized from dichloromethane, mp 130–131 °C. R_f (4:3 EtOAc/CH_2Cl_2) 0.41; $[\alpha]_D^{25}$ −35.0 (*c* 1.0, $CDCl_3$); IR (KBr) 3463, 3286, 3058, 2928, 2256, 1753, 1692, 1633, 1505, 1448, 1376, 1221, 1113, 1071, 1003, 902, 767, 706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (s, 3H, Ac), 3.25–3.29 (m, 1H, H-6), 3.41–3.45 (m, 1H, H-6), 4.10–4.14 (m, 1H, H-4), 4.38–4.43 (m, 1H, H-5), 5.60–5.65 (m, 1H, H-3), 5.74 (d, *J*=5.3, 1H, H-2), 5.93 (d, *J*=8.1, 1H, H-5-pyrimi), 7.23-7.50 (m, 15H, H–Ph_3C), 7.94 (d, *J*=8.1, 1H, H-6-pyrimi), 9.91 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 63.1 (t, C-6), 72.9 (d, C-4), 77.3 (d, C-3), 85.3 (d, C-5), 86.1 (d, C-2), 87.2 (s, Ph_3C), 102.1 (d, C-5-pyrimi), 127.0, 128.1 and 128.6 (d, C–Ph_3), 142.9 (d, C-6-pyrimi), 144.2 (s, Ph_3), 151.6 (s, CO, C-2), 165.3 (s, CO, C-4). FAB: 534 ($[M+Na]^+$, 8), 512 ($[M+H]^+$, 9), 252 ($[M-OPh_3C]^+$, 7), 243 (Ph_3C, 100), 140 (19), 113 ($[uracil+H]^+$, 15). Anal. Calcd for $C_{30}H_{27}N_5O_6$: C 65.09, H 4.92, N 12.34. Found: C 65.15, H 5.12, N 12.38.

4.11. (2*R*,3*R*,4*S*,5*S*)-4-Azido-2-(2,4-dioxo-3,4-dihydro-pyrimidin-1(2*H*)-yl)-5-(hydroxymethyl)tetrahydrofura-3-yl acetate (16)

A solution of **15** (2.00 g, 3.61 mmol) in acetic acid/water (4:1,v/v) (20 mL) was refluxed 30 min. The solvent was removed by evaporation under vacuum, then absolute ethanol (10 mL) was added, evaporated, and the residue purified by column chromatography on silica gel using AcOEt. The product was crystallized from EtOH/CH_2Cl_2 (1:1) to give **16** (1.05 g, 92%), mp 205–206 °C. R_f (3:7 EtOH/CH_2Cl_2) 0.48; $[\alpha]_D^{25}$ −17.4 (*c* 0.65, $CDCl_3$); IR (KBr) 3387, 3255, 2925, 2882, 2239, 1739, 1714, 1665, 1470, 1414, 1379, 1312, 1243, 1115, 1074, 1034, 935, 856, 790, 706 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.23 (s, 3H, Ac), 3.49–3.53 (m, 1H, H-6), 3.81–3.85 (m, 1H, H-6), 3.98–4.04 (m, 1H, H-4), 4.28–4.32 (m, 1H, H-5), 5.34 (t, *J*=5.5, 1H, H-OH); 5.51 (d, *J*=8.0, 6.1, 1H, H-3), 5.70 (d, *J*=6.1, 1H, H-2), 5.89 (d, *J*=8.1, 1H, H-5-pyrimi), 7.91 (d, *J*=8.1, 1H, H-6-pyrimi), 11.22 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 20.5 (q), 60.8 (t, C-6), 70.2 (d, C-4), 75.8 (d, C-3), 82.2 (d, C-5), 83.3 (d, C-2), 101.4 (d, C-5-pyrimi), 141.2 (d, C-6-pyrimi), 150.3 (s, CO, C-2), 163.4 (s, CO, C-4), 169.0 (s, AcCO). Anal. Calcd for $C_{11}H_{13}N_5O_6$: C 42.45, H 4.21, N 22.50. Found: C 42.55, H 4.36, N 22.45.

4.12. (2*R*,3*R*,4*S*,5*R*)-4-Azido-5-(2,2-dibromovinyl)-2-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydro-furan-3-yl acetate (18)

The compound **18** was obtained as a white solid (0.41 g, 56%) from the hydroxyl compound **16** (0.50 g, 1.60 mmol) as described for **4**, mp 234–236 °C. R_f (4.5:0.5 CH_2Cl_2/EtOAc) 0.39; $[\alpha]_D^{25}$ −22.0 (*c* 0.33, $CDCl_3$); IR (KBr) 3461, 3220, 3055, 2932, 1691, 1462, 1381, 1275, 1206, 1113, 1071, 1027, 891, 711 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.12 (s, 3H, CH_3), 5.49 (t, *J*=7.3, 1H, H-4), 5.71 (d, *J*=7.3, 1H, H-2), 5.93 (d, *J*=8.2, 1H, H-5-pyrimi), 6.09 (dd, *J*=7.3, 3.8, 1H, H-5), 6.74 (d, *J*=7.3, 1H, H-3), 6.90 (d, *J*=3.8, 1H, H-6), 8.11 (d, *J*=8.2, 1H, H-6-pyrimi), and 11.32 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 21.0 (q, Me), 82.5 (d, C-4), 84.8 (d, C-2) 86.1 (s, C-3), 88.1 (d, C-5), 90.9 (d, C, 7), 101.7 (d, 5-pyrimi), 137.3 (d, C-6), 141.8 (d, C-6-pyrimi), 150.1 (s, CO, C-2), 163.4 (s, CO, C-2), 164.1 (s, CO, C-Ac). FAB: 488 ($[M+Na]^+$, 10), 466 ($[M+H]^+$, 26), 354 ($[M-B]^+$, 30), 294 (29), 242 (100). Anal. Calcd for $C_{12}H_{11}Br_2N_5O_5$: C 30.99, H 2.38, N 15.06. Found: C 30.87, H 2.46, N 15.13.

4.13. 3′-Azido-4′-ethynyl-3′,5′-dideoxy-5′-norarabinouridine (10)

The compound **10** was obtained as colorless crystals (0.10 g, 59%) from 0.30 g (0.65 mmol) of **18** as described for **5**, mp 193–195 °C. R_f (8:2 EtOAc/CH_2Cl_2) 0.34; $[\alpha]_D^{25}$ −31.0 (*c* 0.95, $CDCl_3$); IR (KBr) 3452, 3224, 3052, 2931, 1692, 1460, 1380, cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (d, *J*=2.2, 1H, CH≡C), 4.19 (s, 1H, OH-2′), 4.90 (dd, *J*=10.5, 7.3, 1H, H-3′), 5.63 (d, *J*=7.3, 1H, H-1′), 5.82 (dd, *J*=10.5. 2.2, 1H, H-4′), 5.90 (d, *J*=8.2, 1H, H-5), 6.01 (d, *J*=7.3, 1H, H-2′), 7.92 (d, *J*=8.2, 1H, H-6), and 9.89 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 69.6 (d, HC≡C), 78.8 (s, CH≡C), 84.1 (d, C-4′), 87.5 (d, C-3′), 88.5 (d, C-2′), 89.6 (d, C-1′), 101.6 (d, C-5), 143.1 (d, C-6), 151.1 (s, CO, C-2), 163.9 (s, CO, C-4). EI: 264 ($[M+H]^+$,8), 263 (M^+, 10), 245 (M–H_2O ,55), 221 (22), 150 ($[M-uracil]^+$, 45), 113

([uracil+H]$^+$,55). Anal. Calcd for $C_{10}H_9N_5O_4$: C 45.63, H 3.45, N 26.16; Found: C 45.78, H 3.61, N 26.40.

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