Supporting Information

for

Chemical and chemoenzymatic routes to bridged homoarabinofuranosylpyrimidines: Bicyclic AZT analogues

Sandeep Kumar, Jyotirmoy Maity, Banty Kumar, Sumit Kumar and Ashok K. Prasad

*Beilstein J. Org. Chem.* **2022**, *18*, 95–101. doi:10.3762/bjoc.18.10

Experimental part and NMR spectra
Table of contents

Experimental S2
Synthesis of anomeric mixture of 12a,b S2
General method for synthesis of 13a,b S3–4
General method for synthesis of 14a,b S5–6
General method for synthesis of 15a,b S6–7
General method for synthesis of 16a,b S7–8
General method for synthesis of 18 S8–9
General method for synthesis of 19a,b S9–10
General method for synthesis of 20a,b S10–11
General method for synthesis of 21a,b S12–13
General method for synthesis of 22a,b S13–14
General method for synthesis of 9a,b S14–15

1H and 13C NMR spectra of compound 12a,b S16
1H and 13C NMR spectra of compound 13a S17
1H and 13C NMR spectra of compound 13b S18
1H and 13C NMR spectra of compound 14a S19
1H and 13C NMR spectra of compound 14b S20
1H and 13C NMR spectra of compound 15a S21
1H and 13C NMR spectra of compound 15b S22
1H and 13C NMR spectra of compound 16a S23
1H and 13C NMR spectra of compound 16b S24
1H and 13C NMR spectra of compound 18 S25
1H and 13C NMR spectra of compound 19a,b S26
1H and 13C NMR spectra of compound 20a S27
1H and 13C NMR spectra of compound 20b S28
1H and 13C NMR spectra of compound 21a S29
1H and 13C NMR spectra of compound 21b S30
1H and 13C NMR spectra of compound 22a S31
1H and 13C NMR spectra of compound 22b S32
1H and 13C NMR spectra of compound 9a S33
DEPT-135 and COSY-NMR spectra of compound 9a S34
HETCOR and NOESY spectra of compound 9a

1H and 13C NMR spectra of compound 9b

Mass spectrum of intermediates detected during the conversion of 22b to 9b

**Experimental**

All reagents and chemicals were purchased from Sigma-Aldrich Chemicals Pvt. Limited, India or from local commercial sources and were used without any further purification unless otherwise specified. Rf values of compounds are reported for analytical TLC using the specified solvents and 0.25 mm silica gel 60 F254 plates that were visualized by UV irradiation or by charring with 5% alcoholic sulfuric acid solution. Melting points were determined on a Büchi M-560 instrument and are uncorrected. Column chromatography was performed on silica gel (100–200 mesh). The IR spectra of compounds were recorded on a Perkin-Elmer model 2000 FT-IR spectrometer and are expressed as wavenumber (cm⁻¹). Specific rotation was measured on Rudolph Autopol II polarimeter. The 1H, 13C, 1H-1H COSY, HETCOR, NOESY and DEPT NMR spectra were recorded on Jeol alpha-400 spectrometer by using tetramethylsilane (TMS) as internal standard. The solvents were removed under reduced pressure using rotary evaporator, followed by further removal of the residual solvent under high vacuum. The chemical shift values are on δ scale and the coupling constant (J) are in Hz. HRMS analysis was carried out using Agilent G6530AA LC Q-TOF mass spectrometer using the ESI method.

**Synthesis of 1,2,5,6-tetra-O-acetyl-3-azido-3-deoxy-α,β-D-allofuranose (12a,b)**

To a solution of 1,2:5,6-di-O-isopropylidene-3-azido-3-deoxy-α-D-allofuranose (11, 3.0 g, 10.52 mmol) in acetic acid (60.12 mL, 1052 mmol) at 0 °C, acetic anhydride (9.94 ml, 105.2 mmol) and conc. sulfuric acid (0.056 mL, 1.05 mmol) were added. The reaction mixture was stirred for 3 h at room temperature and on completion, as indicated by TLC examination, quenched by adding cold water and neutralized with sodium bicarbonate. The compound was extracted with chloroform (3 × 80 mL) and the combined organic layer was washed with brine solution (2 × 80 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product thus obtained was purified by column chromatography using ethyl acetate in petroleum ether as gradient solvent system to afford anomeric mixture 12a,b (α:β = 1:3.5 based on integration of the anomeric proton in 1H NMR).
It was obtained as colourless viscous material oil (3.69 g) in 94% yield. $R_f = 0.48$ (20% ethyl acetate in petroleum ether); $[\alpha]_D^{24} = +138.02$ (c 0.1, MeOH); IR (thin film) $\nu_{\text{max}}$: 3024, 2112, 1744, 1434, 1371, 1212, 1098, 959, 755 and 668; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 6.15 (1H, s), 5.34 (1H, d, $J = 4.9$ Hz), 5.15-5.17 (1H, m), 4.48 (1H, dd, $J = 12.2, 3.2$ Hz), 4.23 (1H, d, $J = 7.2$ Hz), 4.18 (1H, d, $J = 4.8$ Hz), 4.11 (1H, dd, $J = 12.2, 5.6$ Hz), 2.19 (3H, s), 2.15 (3H, s), 2.11 (3H, s) and 2.09 (3H, s); $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 170.6, 170.1, 169.5, 168.7, 98.1, 79.8, 75.8, 71.8, 62.3, 61.6, 21.0, 20.9, 20.8 and 20.6; HRMS (ESI): $m/z$ cal. for C$_{14}$H$_{23}$N$_4$O$_9$ [M+NH$_4$]$^+$ = 391.1460; found: 391.1465.

**General method for synthesis of 2',5',6'-tri-O-acetyl-3'-azido-3'-deoxy-β-D-allofuranosylpyrimidines 13a,b.**

To the anomeric mixture of tetra-O-acetylated sugar derivative (12a,b, 1.5 g, 4.02 mmol) and thymine/uracil (6.03 mmol) in anhydrous acetonitrile (60 mL), N,O-bis(trimethylsilyl)acetamide (3.93 mL, 16.08 mmol) was added dropwise. The reaction mixture was stirred at reflux for 1 h and then cooled to 0 °C. In the cooled reaction mixture trimethylsilyltrifluoromethane sulfonate (1.23 mL, 6.83 mmol) was added slowly and the solution was refluxed for 3–4 h. On completion, the reaction was quenched with cold saturated aq. sodium bicarbonate solution (160 mL) and extracted with chloroform ($3 \times 120$ mL). The combined organic layer was washed with saturated aq. sodium bicarbonate solution ($2 \times 120$ mL), brine solution ($2 \times 120$ mL) and then dried over anhydrous sodium sulfate to afford the crude product. The crude residue thus obtained was purified by silica gel column chromatography using ethyl acetate in petroleum ether as eluent to afford pure nucleosides 13a/13b in good yields.

**2',5',6'-Tri-O-acetyl-3'-azido-3'-deoxy-β-D-allofuranosylthymine (13a).**
It was obtained as colourless viscous oil (1.62 g) in 92% yield. $R_f = 0.45$ (5 % MeOH in CHCl$_3$); $[\alpha]_D^{24} = +137.04$ (c 0.1, MeOH); IR (KBr, cm$^{-1}$): 2110, 1739, 1687, 1462, 1371, 1211, 1043, 894, 785, 599 and 484 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.45 (1H, s), 6.98 (1H, s), 5.63 (1H, d, J = 4.2 Hz), 5.51 (1H, dd, J = 9.0, 5.5 Hz), 4.53 (1H, d, J = 6.9 Hz), 4.48-4.50 (1H, m), 4.14 (1H, dd, J = 12.2, 5.4 Hz), 4.08 (1H, t, J = 6.3 Hz), 2.20 (3H, s), 2.16 (3H, s), 2.10 (3H, s) and 1.93 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.6, 170.1, 170.0, 163.8, 150.1, 137.0, 111.9, 90.8, 79.9, 74.7, 70.7, 62.1, 60.5, 20.9, 20.8, 20.5 and 12.5; HRMS (ESI): m/z calcd for C$_{17}$H$_{22}$N$_5$O$_9$ [M+H]$^+$ = 440.1412; found: 440.1420.

2',5',6'-Tri-O-acetyl-3'-azido-3'-deoxy-β-D-allofuranosyluracil (13b).

It was obtained as colourless viscous oil (1.59 g) in 93% yield. $R_f = 0.50$ (5% MeOH/chloroform); $[\alpha]_D^{24} = +122.58$ (c 0.1, MeOH); IR (KBr, cm$^{-1}$): 3024, 2113, 1742, 1692, 1457, 1375, 1218, 1053, 814, 755 and 668; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.38 (1H, s), 7.17 (1H, d, J = 8.1 Hz), 5.78 (1H, d, J = 8.1 Hz), 5.61 (1H, d, J = 4.1 Hz), 5.53 (1H, dd, J = 6.5, 4.1 Hz), 5.33 (1H, td, J = 5.6, 3.5 Hz), 4.52 (1H, d, J = 6.8 Hz), 4.49 (1H, dd, J = 9.5, 2.8 Hz), 4.14 (1H, dd, J = 12.3, 5.5 Hz), 4.09 (1H, t, J = 6.4 Hz), 2.20 (3H, s), 2.15 (3H, s) and 2.10 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.6, 170.1, 170.0, 163.0, 149.9, 141.4, 103.4, 91.4, 80.0, 74.8, 70.6, 62.1, 60.5, 20.9, 20.8 and 20.6; HRMS (ESI): m/z calcd for C$_{16}$H$_{20}$N$_5$O$_9$ [M+H]$^+$ = 426.1256; found: 426.1274.

**General method of synthesis of 3'-azido-3'-deoxy-β-D-allofuranosylpyrimidines 14a, b.** To a solution of compound 13a (1.5 g, 3.41 mmol)/13b (1.5 g, 3.53 mmol) in methanol:water (9:1, 140 mL), K$_2$CO$_3$ (1.65 g, 11.94 mmol for 13a)/(1.71 g, 12.36 mmol for 13b) was added portion wise at 0 °C and the reaction mixture was stirred at 25 °C for 1 h. On completion of the reaction, solvent was removed under reduced pressure. The residue thus obtained was purified by column chromatography with a gradient solvent system of methanol in chloroform to afford trihydroxy nucleoside 14a/14b in quantitative yields.
3'-Azido-3'-deoxy-β-D-allofuranosylthymine (14a).

It was obtained as white solid (1.05 g) in 98% yield. Rf = 0.38 (10% MeOH/chloroform); [α]D24 = +63.97 (c 0.1, MeOH); m/p: 167-170°C; IR (KBr, cm⁻¹): 2108, 1691, 1645, 1475, 1390, 1344, 1280, 1220, 1055, 1008, 918, 781, 607, 547 and 480; 1H NMR (400 MHz, DMSO-d6): δ 11.37 (1H, s), 7.68 (1H, d, J = 1.1 Hz), 6.07 (1H, d, J = 5.4 Hz), 5.76 (1H, d, J = 6.6 Hz), 5.46 (1H, d, J = 4.7 Hz), 4.76 (1H, d, J = 5.0 Hz), 4.41 (1H, dd, J = 11.9, 5.8 Hz), 4.18 (1H, dd, J = 5.7, 3.1 Hz), 3.89 (1H, t, J = 3.3 Hz), 3.67-3.69 (1H, m), 3.41 (2H, t, J = 5.1 Hz) and 1.78 (3H, d, J = 0.9 Hz); 13C NMR (100 MHz, DMSO-d6): δ 163.7, 150.9, 136.0, 109.8, 86.4, 82.0, 73.7, 71.5, 62.4, 60.7 and 12.2; HRMS (ESI): m/z calcd for C11H16N5O6 [M+H]+ = 314.1095; found: 314.1100.

3'-Azido-3'-deoxy-β-D-allofuranosyluracil (14b).

It was obtained as white solid (1.02 g) in 97% yield. Rf = 0.40 (10% MeOH/chloroform); [α]D24 = +124.50 (c 0.1, MeOH); m/p: 146-148°C; IR (KBr, cm⁻¹): 3392, 2114, 1693, 1468, 1421, 1392, 1262, 1108, 1070, 817, 718 and 649; 1H NMR (400 MHz, DMSO-d6): δ 11.37 (1H, s), 7.81 (1H, d, J = 8.1 Hz), 6.11 (1H, d, J = 5.3 Hz), 5.76 (1H, d, J = 6.5 Hz), 5.67 (1H, d, J = 8.1 Hz), 5.37 (1H, s), 4.74 (1H, s), 4.41 (1H, dd, J = 11.6, 5.8 Hz), 4.18 (1H, dd, J = 5.6, 3.2 Hz), 3.91 (1H, t, J = 3.3 Hz), 3.67 (1H, s) and 3.42 (2H, s); 13C NMR (100 MHz, DMSO-d6): δ 163.0, 150.8, 140.5, 102.2, 86.6, 82.2, 73.9, 71.4, 62.3 and 60.6; HRMS (ESI): m/z calcd for C10H14N3O6 [M+H]+ = 300.0939; found: 300.0952.

General method for lipase-assisted synthesis of 6'-O-acetyl-3'-azido-3'-deoxy-β-D-allofuranosylpyrimidines 15a,b. To a solution of trihydroxy azidoallofuranosyl-pyrimidines
14a (1.0 g, 3.19 mmol)/14b (1.0 g, 3.34 mmol) in 2-Me-THF (60 mL) was added vinyl acetate (0.35 mL, 3.83 mmol for 14a)/(0.37 mL, 4.01 mmol for 14b) followed by addition of Lipozyme® TL IM (0.1 g, 10% w/w). The reaction mixture was stirred at 40 °C in an incubator shaker at 200 rpm for 2 h. On completion of the reaction as indicated by TLC examination, the reaction was quenched by filtering off the enzyme. The solvent was removed under reduced pressure and the residue thus obtained was purified by silica gel column chromatography using methanol in chloroform as gradient solvent system to afford the monoacetylated nucleosides 15a/15b in quantitative yields.

6'-O-Acetyl-3'-azido-3'-deoxy-β-D-allofuranosylthymine (15a).

It was obtained as white solid (1.12g) in 98% yield. Rf = 0.45 (10% MeOH/chloroform); [α]D<sup>24</sup> = +93.76 (c 0.1, MeOH); m/p:155-158°C; IR (KBr, cm<sup>-1</sup>): 3369, 2108, 1664, 1471, 1376, 1253, 1228, 1076, 1043, 908, 790, 594 and 549; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 11.37 (1H, s), 7.61 (1H, d, J = 1.1 Hz), 6.12 (1H, d, J = 5.4 Hz), 5.76 (2H, dd, J = 8.4, 4.5 Hz), 4.46 (1H, dd, J = 11.8, 5.8 Hz), 4.23 (1H, dd, J = 5.8, 3.3 Hz), 4.07 (1H, dd, J = 11.2, 4.4 Hz), 3.99 (1H, dd, J = 11.3, 6.3 Hz), 3.88-3.93 (1H, m), 3.80 (1H, dd, J = 4.7, 3.4 Hz), 2.03 (3H, s) and 1.79 (3H, d, J = 0.9 Hz); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): δ 170.3, 163.6, 150.8, 136.1, 109.9, 86.8, 81.5, 73.1, 68.3, 64.9, 60.9, 20.7 and 12.1; HRMS (ESI): m/z calcd for C<sub>13</sub>H<sub>18</sub>N<sub>5</sub>O<sub>7</sub> [M+H]<sup>+</sup> = 356.1201; found: 356.1213.

6'-O-Acetyl-3'-azido-3'-deoxy-β-D-allofuranosyluracil (15b).
It was obtained as white solid (1.13 g) in 97% yield. \( R_f = 0.46 \) (10% MeOH/chloroform); 
\([\alpha]_D^{24} = +108.24 \) (c 0.1, MeOH); m/p: 128-130°C; IR (KBr, cm\(^{-1}\)) : 3394, 1682, 1466, 1385, 1260, 1082, 1049, 816, 770, 715 and 647; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 11.40 (1H, s), 7.77 (1H, d, \( J = 8.1 \) Hz), 6.18 (1H, d, \( J = 5.0 \) Hz), 5.75 (2H, d, \( J = 6.4 \) Hz), 5.67 (1H, d, \( J = 8.1 \) Hz), 4.45 (1H, dd, \( J = 11.0, 5.6 \) Hz), 4.22 (1H, dd, \( J = 5.5, 3.3 \) Hz), 4.05 (1H, dd, \( J = 11.3, 4.6 \) Hz), 3.99 (1H, dd, \( J = 11.3, 6.0 \) Hz), 3.90 (1H, s), 3.80-3.82 (1H, m) and 2.03 (3H, s); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta \) 170.3, 163.0, 150.8, 140.7, 102.2, 87.1, 81.6, 73.3, 68.3, 64.8, 60.9 and 20.7; HRMS (ESI): \( m/z \) calcd for C\(_{12}\)H\(_{16}\)N\(_5\)O\(_7\) [M+H]\(^+\) = 342.1044; found: 342.1057.

**General method for synthesis of 6'-O-acetyl-3'-azido-3'-deoxy-2',5'-di-O-methanesulfonyl-\(\beta\)-D-allofuranosylpyrimidines 16a,b.** To the stirred solution of 15a (0.9 g, 2.53 mmol)/15b (0.9 g, 2.64 mmol) in anhydrous pyridine (10 mL), methanesulfonyl chloride (0.49 mL, 6.33 mmol) for 15a and (0.51 mL, 6.60 mmol) for 15b) was added slowly at 0 °C and further stirred at 25 °C for 3-4 h. On completion of the reaction as indicated by TLC examination, the reaction mixture was poured over 10% ice cold hydrochloric acid solution (80 mL) to neutralize pyridine and the product was extracted with chloroform (3 × 80 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (2 × 120 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue thus obtained was purified over silica gel column chromatography using methanol in chloroform as gradient to afford dimesylated nucleoside 16a/16b in pure form.

**6'-O-Acetyl-3'-azido-3'-deoxy-2',5'-di-O-methanesulfonyl-\(\beta\)-D-allofuranosylthymine (16a).**

\[
\text{AcO} \quad \text{MsO} \quad \text{N}_3 \quad \text{OMs}
\]

It was obtained as white solid (1.20 g) in 93% yield. \( R_f = 0.35 \) (5% MeOH/chloroform); 
\([\alpha]_D^{24} = +109.96 \) (c 0.1, MeOH); m/p: 103-105°C; IR (KBr, cm\(^{-1}\)): 2117, 1685, 1467, 1417, 1340, 1261, 1230, 1172, 1047, 964, 910, 835, 800, 677, 590, 522 and 484; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 9.77 (1H, s), 7.23 (1H, s), 5.72 (1H, d, \( J = 3.3 \) Hz), 5.54-5.56 (1H, m), 5.17 (1H, s), 4.69 (1H, t, \( J = 6.4 \) Hz), 4.55 (1H, dd, \( J = 12.6, 2.7 \) Hz), 4.22 (1H, dd, \( J = 12.7, 6.4 \) Hz), 4.13 (1H, dd, \( J = 4.46 \) Hz), 3.76 (1H, dd, \( J = 11.5, 3.7 \) Hz), 3.49 (1H, dd, \( J = 10.8, 3.7 \) Hz), 3.22 (1H, m) and 2.22 (3H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 170.3, 163.0, 150.8, 140.7, 126.1, 1230, 1172, 1047, 964, 910, 835, 800, 677, 590, 522 and 484; HRMS (ESI): \( m/z \) calcd for C\(_{12}\)H\(_{16}\)N\(_5\)O\(_7\) [M+H]\(^+\) = 342.1044; found: 342.1057.
= 6.4, 4.6 Hz), 3.34 (3H, s), 3.17 (3H, s), 2.14 (3H, s) and 1.92 (3H, s); 13C NMR (100 MHz, CDCl₃): δ 170.4, 163.9, 150.6, 137.5, 112.3, 91.5, 79.8, 78.6, 77.1, 62.1, 59.4, 39.0, 38.5, 20.8 and 12.2; HRMS (ESI): m/z calcd for C₁₅H₂₂N₅O₁₁S₂ [M+H]+ = 512.0752; found: 512.0770.

6'-O-Acetyl-3'-azido-3'-deoxy-2',5'-di-O-methanesulfonyl-β-D-allofuranosyluracil (16b).

It was obtained as white solid (1.23 g) in 94% yield. Rf = 0.36 (5% MeOH/chloroform); [α]D²⁴ = +146.35 (c 0.1, MeOH; m/p: 133–135°C; IR (KBr, cm⁻¹): 2117, 1690, 1458, 1354, 1263, 1231, 1175, 1050, 916, 813 and 758; 1H NMR (400 MHz, CDCl₃): δ 10.00 (1H, s), 7.42 (1H, d, J = 8.1 Hz), 5.79 (1H, d, J = 8.0 Hz), 5.73 (1H, d, J = 3.1 Hz), 5.58 (1H, dd, J = 6.1, 3.3 Hz), 5.16 (1H, t, J = 6.9 Hz), 4.68 (1H, t, J = 6.7 Hz), 4.54 (1H, dd, J = 12.6, 2.8 Hz), 4.23 (1H, dd, J = 12.7, 6.5 Hz), 4.15 (1H, dd, J = 7.1, 4.8 Hz), 3.25 (3H, s), 3.17 (3H, s) and 2.13 (3H, s); 13C NMR (100 MHz, DMSO-d₆): δ 170.5, 163.5, 150.5, 142.2, 103.3, 92.1, 79.6, 78.9, 77.1, 62.1, 59.4, 38.9, 38.4 and 20.8; HRMS (ESI): m/z calcd for C₁₄H₂₀N₅O₁₁S₂ [M+H]+ = 498.0595; found: 498.0611.

**Synthesis of 6-C-(tert-butyldiphenylsilyloxymethyl)-1,2-O-isopropylidene-3-azido-3-deoxy-α-D-allofuranose (18)**

To a solution of 1,2-O-isopropylidene-3-azido-3-deoxy-α-D-allofuranose (17, 6.0 g, 24.46 mmol) in pyridine (5.91 mL, 73.40 mmol) at 0°C, tert-butyldiphenylsilane, i.e., TBDPS-Cl (6.91 mL, 26.91 mmol) and Tetra-n-butylammonium bromide (TBAB) (1.57 g, 4.89 mmol) were added. The reaction mixture was stirred for 12 h at room temperature and on completion, as indicated by TLC examination, quenched by adding cold water and neutralized with 10% hydrochloric acid solution. The compound was extracted with ethyl acetate (3 × 110 mL) and the combined organic layer was washed with brine solution (2 × 90 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product thus obtained was purified by column chromatography using ethyl acetate in petroleum ether as gradient solvent system to afford 18 in pure form.
It was obtained as colourless viscous material (10.88 g) in 92% yield. \( R_f = 0.53 \) (30% ethyl acetate in petroleum ether); \([\alpha]_D^{24} = +25.36 \) (c 0.1, MeOH); IR (thin film) \( \nu_{\text{max}} \): 3040, 2117, 1695, 1313, 1118, 998, 959 and 750; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.67 (4H, d, \( J = 6.8 \) Hz), 7.38-7.46 (6H, m), 5.77 (1H, d, \( J = 3.6 \) Hz), 4.72 (1H, t, \( J = 4.2 \) Hz), 4.18 (1H, dd, \( J = 9.2, 5.4 \) Hz), 3.86-3.91 (1H, m), 3.76-3.84 (2H, m), 3.59 (1H, dd, \( J = 9.2, 4.8 \) Hz), 2.62 (1H, d, \( J = 4.7 \) Hz), 1.56 (3H, s), 1.36 (3H, s) and 1.07 (9H, s); \(^{13}\)C NMR (CDCl\(_3\), 100.6 MHz): \( \delta \) 135.6, 135.5, 132.9, 132.8, 130.0, 129.9, 127.9, 113.2, 104.0, 80.7, 77.2, 72.1, 64.5, 61.8, 26.9, 26.6, 26.5 and 19.3; HRMS (ESI): m/z cal. for C\(_{23}\)H\(_{34}\)N\(_3\)O\(_5\)Si [M+H]\(^+\) = 484.2262; found: 484.2268.

**Synthesis of 6-C-(tert-butyldiphenylsilyloxyethyl)-1,2,5-tri-O-acetyl-3-azido-3-deoxy-\( \alpha,\beta \)-D-allofuranose (19a,b)**

To a solution of 6-C-(tert-Butyldiphenylsilyloxyethyl)-1,2-O-isopropylidene-3-azido-3-deoxy-\( \alpha \)-D-allofuranose (18, 8.5 g, 17.57 mmol) in acetic acid (100.51 mL, 1757.54 mmol) at 0° C, acetic anhydride (16.61 ml, 175.75 mmol) and conc. sulfuric acid (0.09 mL, 1.76 mmol) were added. The reaction mixture was stirred for 4h at room temperature and on completion, as indicated by TLC examination, quenched by adding cold water and neutralized with sodium bicarbonate. The compound was extracted with ethyl acetate (3 × 120 mL) and the combined organic layer was washed with brine solution (2 × 100 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product thus obtained was purified by column chromatography using ethyl acetate in petroleum ether as gradient solvent system to afford anomeric mixture 19a,b (\( \alpha:\beta = 1:5 \) based on integration of anomeric proton in \(^1\)H NMR).

It was obtained as colourless viscous material oil (8.0 g) in 80% yield. \( R_f = 0.45 \) (30% ethyl acetate in petroleum ether); \([\alpha]_D^{24} = +46.01 \) (c 0.1, MeOH); IR (thin film) \( \nu_{\text{max}} \): 2940, 2115, 1745, 1311, 1112, 1098, 959 and 757; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.64-7.67 (4H, m), 7.37-7.44
(6H, m), 6.14 (1H, s), 5.32 (1H, d, J = 5.0 Hz), 5.09 (1H, dd, J = 11.0, 4.7 Hz), 4.39 (1H, t, J = 6.8 Hz), 4.19 (1H, dd, J = 7.1, 5.1 Hz), 3.84 (2H, d, J = 4.6 Hz), 2.17 (3H, s), 2.08 (3H, s), 2.01 (3H, s) and 1.06 (9H, s); 13C NMR (CDCl3, 100.6 MHz): δ 170.1, 169.6, 168.8, 135.6, 135.5, 133.0, 132.9, 130.0, 129.9, 127.9, 127.8, 98.2, 80.1, 76.2, 74.3, 62.4, 61.1, 26.8, 26.7, 21.0, 20.9, 20.5, and 19.3; HRMS (ESI): m/z cal. for C28H36N6O8Si [M+H]+ = 570.2266; found: 570.2270.

**General method of synthesis of 6'-C-(tert-butyldiphenylsilyloxyethyl)-2',5'-di-O-acetyl-3'-azido-3'-deoxy-β-D-allofuranosylpyrimidines (20a,b).** To the anomeric mixture of tri-O-acetylated sugar derivative (19a, b, 2.5 g, 4.38 mmol) and thymine/uracil (6.58 mmol) in anhydrous acetonitrile (90 mL), N,O-bis(trimethylsilyl)acetamide (4.29 mL, 17.55 mmol) was added dropwise. The reaction mixture was stirred at reflux for 1 h and then cooled to 0 °C. In the cooled reaction mixture trimethylsilyl trifluoromethane sulfonate (1.35 mL, 7.46 mmol) was added slowly and the solution was refluxed for 12–16 h. On completion, the reaction was quenched with cold saturated aq. sodium bicarbonate solution (180 mL) and extracted with chloroform (3 × 110 mL). The combined organic layer was washed with saturated aq. sodium bicarbonate solution (2 × 100 mL), brine solution (2 × 100 mL) and then dried over anhydrous sodium sulfate to afford the crude product. The crude residue thus obtained was purified by silica gel column chromatography using ethyl acetate in petroleum ether as eluent to afford pure nucleosides 20a/20b in good yields.

**6'-C-(tert-Butyldiphenylsilyloxyethyl)-2',5'-di-O-acetyl-3'-azido-3'-deoxy-β-D-allofuranosylthymine (20a).**

It was obtained as colourless viscous oil (2.51 g) in 90% yield. Rf = 0.45 (2% MeOH in CHCl3); [α]D24 = +68.05 (c 0.1, MeOH); IR (thin film) νmax: 3240, 2195, 1740, 1210, 1095, 970 and 760; 1H NMR (400 MHz, CDCl3): δ 9.25 (1H, s), 7.64–7.66 (4H, m), 7.38–7.45 (6H, m), 6.91 (1H, s), 5.80 (1H, d, J = 5.2 Hz), 5.38 (1H, t, J = 5.9 Hz), 5.21 (1H, q, J = 4.7 Hz), 4.51 (1H, t, J = 6.1 Hz), 4.24 (1H, t, J = 5.1 Hz), 3.84 (2H, d, J = 4.6 Hz), 2.19 (3H, s), 2.10 (3H, s), 1.90 (3H,
s) and 1.07 (9H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 170.1, 170.0, 163.6, 150.1, 135.8, 135.6, 135.5, 132.7, 130.0, 127.9, 111.9, 88.4, 80.3, 74.7, 73.2, 62.2, 60.0, 26.8, 21.0, 20.5, 19.3 and 12.6; HRMS (ESI): m/z calcd for C$_{31}$H$_{38}$N$_5$O$_8$Si [M+H]$^+$ = 636.2484; found: 636.2491.

6'-C-(tert-Butyldiphenylsilyloxyethyl)-2',5'-di-O-acetyl-3'-azido-3'-deoxy-β-D-allofuranosyluracil (20b).

It was obtained as colourless viscous oil (2.51 g) in 92% yield. R$_f$ = 0.46 (2% MeOH/chloroform); [$\alpha$]$^2$$_D$ = +68.05 (c 0.1, MeOH); IR (thin film) $\nu$$_{max}$: 3145, 2190, 1742, 1205, 1120, 965 and 790; $^1$H NMR (400 MHz, CDCl$_3$): δ 9.42 (1H, s), 7.64–7.66 (4H, m), 7.38–7.45 (6H, m), 7.11 (1H, d, J = 8.1 Hz), 5.78 (1H, d, J = 4.9 Hz), 5.73 (1H, d, J = 8.1 Hz), 5.37-5.40 (1H, m), 5.20 (1H, q, J = 4.7 Hz), 4.48 (1H, t, J = 6.1 Hz), 4.24 (1H, t, J = 5.3 Hz), 3.84 (2H, d, J = 4.7 Hz), 2.19 (3H, s), 2.09 (3H, s) and 1.07 (9H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 170.1, 170.0, 163.0, 150.0, 140.2, 135.6, 135.5, 132.7, 132.6, 130.1, 130.0, 127.9, 103.4, 88.9, 80.3, 74.8, 73.1, 62.2, 60.0, 26.8, 21.0, 20.5 and 19.2; HRMS (ESI): m/z calcd for C$_{30}$H$_{36}$N$_5$O$_8$Si [M+H]$^+$ = 622.2328; found: 622.2336.

General method of synthesis of 6'-C-(tert-butyldiphenylsilyloxyethyl)-3'-azido-3'-deoxy-β-D-allofuranosylpyrimidines (21a,b). To a solution of compound 20a (1.9 g, 2.98 mmol)/20b (1.9 g, 3.05 mmol) in methanol/water (7:3, 120 mL), K$_2$CO$_3$ (0.82 g, 5.96 mmol for 20a)/(0.84 g, 6.1 mmol for 20b) was added portion wise at 0 °C and the reaction mixture was stirred at 25 °C for 4–6 h. On completion of the reaction, solvent was removed under reduced pressure. The residue thus obtained was purified by column chromatography with a gradient solvent system of methanol in chloroform to afford trihydroxy nucleoside 21a/21b in quantitative yields.
6′-C-(tert-Butyldiphenylsilyloxymethyl)-3′-azido-3′-deoxy-β-D-allofuranosylthymine (21a).

It was obtained as white solid (1.61 g) in 98% yield. \( R_f = 0.46 \) (10% MeOH/chloroform); \( [\alpha]_D^{24} = +67.12 \) (c 0.1, MeOH); m/p: 112-114°C; IR (KBr, cm\(^{-1}\)): 2912, 2135, 1680, 1642, 1320, 1260, 1205, 998, 870, 547 and 481; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 11.38 (1H, s), 7.64-7.67 (5H, m), 7.42-7.47 (6H, m), 6.12 (1H, d, \( J = 5.4 \) Hz), 5.82 (1H, d, \( J = 6.7 \) Hz), 5.63 (1H, d, \( J = 5.1 \) Hz), 4.47 (1H, dd, \( J = 12.0, 5.9 \) Hz), 4.28 (1H, dd, \( J = 5.5, 2.8 \) Hz), 4.07 (1H, s), 3.83-3.85 (1H, m), 3.68 (1H, d, \( J = 5.4 \) Hz), 3.17 (1H, d, \( J = 5.2 \) Hz), 1.78 (3H, s) and 1.00 (9H, s); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta \) 163.7, 150.9, 135.1, 135.0, 132.8, 129.9, 127.9, 109.8, 86.4, 82.1, 73.7, 70.8, 65.0, 60.6, 26.5, 18.8 and 12.2; HRMS (ESI): \( m/z \) calcd for C\(_{27}\)H\(_{34}\)N\(_{5}\)O\(_6\)Si \([M+H]^+ = 552.2273\); found: 552.2280.

6′-C-(tert-Butyldiphenylsilyloxymethyl)-3′-azido-3′-deoxy-β-D-allofuranosyluracil (21b).

It was obtained as white solid (1.59 g) in 97% yield. \( R_f = 0.47 \) (10% MeOH/chloroform); \( [\alpha]_D^{24} = +105.22 \) (c 0.1, MeOH); m/p: 123-125 °C; IR (KBr, cm\(^{-1}\)): 3092, 2120, 1690, 1460, 1405, 1301, 1222 1021, 815, 712 and 641; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 11.40 (1H, s), 7.79 (1H, d, \( J = 8.1 \) Hz), 7.63-7.67 (4H, m), 7.41-7.47 (6H, m), 6.15 (1H, d, \( J = 5.4 \) Hz), 5.81 (1H, d, \( J = 6.6 \) Hz), 5.67 (1H, dd, \( J = 8.1, 1.9 \) Hz), 5.57 (1H, d, \( J = 5.0 \) Hz), 4.46 (1H, dd, \( J = 11.8, 5.8 \) Hz), 4.27 (1H, dd, \( J = 5.5, 2.9 \) Hz), 4.08 (1H, t, \( J = 2.9 \) Hz), 3.81-3.83 (1H, m), 3.67 (1H, d, \( J = 5.5 \) Hz), 3.17 (1H, d, \( J = 3.7 \) Hz) and 1.00 (9H, s); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta \) 162.9, 150.8, 140.5, 135.1, 135.0, 132.8, 129.9, 127.9, 102.2, 86.6, 82.1, 73.9, 70.8, 64.9, 60.6, 26.5 and 18.8; HRMS (ESI): \( m/z \) calcd for C\(_{26}\)H\(_{32}\)N\(_{5}\)O\(_6\)Si \([M+H]^+ = 538.2116\); found: 538.2125.
General method for synthesis of 6′-C-(tert-butyldiphenylsilyloxymethyl)-3′-azido-3′-deoxy-2′,5′-di-O-methanesulfonyl-β-D-allofuranosylpyrimidines (22a,b). To the stirred solution of 21a (1.3 g, 2.35 mmol) / 21b (1.3 g, 2.42 mmol) in anhydrous pyridine (18 mL), methanesulfonyl chloride (0.402 mL, 5.17 mmol for 21a) and (0.414 mL, 5.32 mmol for 21b) was added slowly at 0 °C and further stirred at 25 °C for 8–10 h. On completion of the reaction as indicated by TLC examination, the reaction mixture was poured over 10% ice cold hydrochloric acid solution (90 mL) to neutralize pyridine and the product was extracted with chloroform (3 × 90 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (2 × 100 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue thus obtained was purified over silica gel column chromatography using methanol in chloroform as gradient to afford dimesylated nucleoside 22a/22b in pure form.

6′-C-(tert-Butyldiphenylsilyloxymethyl)-3′-azido-3′-deoxy-2′,5′-di-O-methanesulfonyl-β-D-allofuranosylthymine (22a).

It was obtained as white solid (1.51 g) in 91% yield. Rf = 0.42 (5% MeOH/chloroform); [α]D24 = +107.21 (c 0.1, MeOH); m/p: 90-92 °C; IR (KBr, cm⁻¹): 2992, 2117, 1680, 1521, 1317, 1303, 1271, 912, 830, 800 and 490; ¹H NMR (400 MHz, CDCl₃): δ 9.35 (1H, s), 7.64-7.68 (4H, m), 7.40-7.47 (6H, m), 7.33 (1H, s), 5.85 (1H, d, J = 4.7 Hz), 5.34-5.37 (1H, m), 5.02 (1H, dd, J = 8.3, 4.7 Hz), 4.57 (1H, t, J = 6.0 Hz), 4.17 (1H, dd, J = 5.7, 3.3 Hz), 3.86-3.94 (2H, m), 3.19 (3H, s), 3.01 (3H, s), 1.92 (3H, s) and 1.09 (9H, s); ¹³C NMR (100 MHz, CDCl₃): δ 163.7, 150.5, 136.4, 135.6, 135.5, 132.2, 132.0, 130.4, 130.3, 128.1, 128.0, 112.4, 88.6, 80.2, 79.9, 78.1, 62.6, 58.9, 39.0, 38.5, 26.9, 19.2 and 12.2; HRMS (ESI): m/z calcld for C₂₉H₉₉N₅O₁₀S₂Si [M+H]⁺ = 708.1824; found: 708.1826.
\textit{6'-C-(tert-Butyldiphenylsilyloxymethyl)-3'-azido-3'-deoxy-2',5'-di-O-methanesulfonyl-\beta-D-allofuranosyluracil (22b).}

![Chemical Structure](image)

It was obtained as white solid (1.54 g) in 92\% yield. R$_f$ = 0.43 (5\% MeOH/chloroform); $[\alpha]_D^{24}$ = +132.12 (c 0.1, MeOH); m/p: 102-103 °C; IR (KBr, cm$^{-1}$): 3011, 2116, 1692, 1457, 1260, 1110, 1032, 915, 812 and 757; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.62 (1H, s), 7.66 (4H, t, $J$ = 7.5 Hz), 7.41-7.48 (7H, m), 5.78 (2H, dd, $J$ = 11.2, 6.1 Hz), 5.39-5.42 (1H, m), 5.01 (1H, d, $J$ = 4.0 Hz), 4.56 (1H, t, $J$ = 6.1 Hz), 4.18-4.20 (1H, m), 3.89-3.92 (2H, m), 3.20 (3H, s), 3.01 (3H, s) and 1.08 (9H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 163.1, 150.4, 141.1, 135.6, 135.5, 132.3, 132.1, 130.3, 130.2, 128.1, 128.0, 103.5, 89.5, 80.0, 79.7, 78.4, 62.6, 58.9, 38.9, 38.5, 26.9 and 19.2; HRMS (ESI): m/z calcd for C$_{28}$H$_{36}$N$_5$O$_{10}$S$_2$Si [M+H]$^+$ = 694.1667; found: 694.1672.

**General method for synthesis of (5'R)-3'-azido-3'-deoxy-2'-O,5'-C-bridged-\beta-D-homoarabinofuranosylpyrimidines (9a,b).** To a solution of compound 16a/16b and 22a/22b (0.9 g, 1.76 mmol) in dioxane/water (1:1, 30 mL), 2 M NaOH (0.9 mL) was added at 0 °C and the reaction mixture was stirred for 12–24 h at 25 °C. On completion, acetic acid (10 mL) was added to neutralize the reaction followed by co-evaporated of the reaction solvent with toluene under reduced pressure. The residue thus obtained was purified by silica gel column chromatography using methanol in chloroform as gradient solvent system to afford nucleoside 9a/9b in pure form.

\textit{(5'R)-3'-Azido-3'-deoxy-2'-O,5'-C-bridged-\beta-D-homoarabinofuranosylthymine (9a).}

![Chemical Structure](image)

It was obtained as white solid (0.43 g) in 82\% yield. R$_f$ = 0.29 (5\% MeOH/chloroform); $[\alpha]_D^{24}$ = +164.00 (c 0.1, MeOH); m/p: 178-180°C; IR (KBr, cm$^{-1}$): 3353, 2110, 1676, 1462, 1421, 1261,
1101, 1031, 962, 844, 731, 599 and 489; ¹H NMR (400 MHz, DMSO- d₆): δ 11.40 (1H, s), 7.67 (1H, s), 5.80 (1H, s), 4.96 (1H, t, J = 5.6 Hz), 4.75 (1H, d, J = 2.3 Hz), 4.73 (1H, s), 4.59 (1H, d, J = 1.6 Hz), 4.15 (1H, t, J = 5.2 Hz), 3.41 (2H, t, J = 5.1 Hz) and 1.81 (3H, s); ¹³C NMR (100 MHz, DMSO-d₆): δ 163.9, 150.4, 136.0, 108.3, 88.2, 83.9, 80.7, 75.4, 63.6, 61.0 and 12.2; HRMS (ESI): m/z calcd for C₁₁H₁₄N₅O₅ [M+H]+ = 296.0989; found: 296.0998.

(5'R)-3'-Azido-3'-deoxy-2'-O,5'-C-bridged-β-D-homoarabinofuranosyluracil (9b).

It was obtained as white solid (0.43 g) in 84% yield. Rₐ = 0.30 (5% MeOH/chloroform); [α]D⁲⁴ = +147.92 (c 0.1, MeOH); m/p: 163-165°C; IR (KBr, cm⁻¹): 3443, 2117, 1706, 1461, 1420, 1266, 1223, 1101, 1053, 911, 815, 754 and 664; ¹H NMR (400 MHz, DMSO-d₆): δ 11.41 (1H, s), 7.82 (1H, d, J = 8.1 Hz), 5.83 (1H, s), 5.59 (1H, d, J = 8.1 Hz), 4.97 (1H, t, J = 5.1 Hz), 4.75 (2H, d, J = 7.9 Hz), 4.60 (1H, s), 4.08 (1H, t, J = 5.0 Hz) and 3.40 (2H, s); ¹³C NMR (100 MHz, DMSO-d₆): δ 163.2, 150.4, 140.7, 100.6, 88.3, 84.0, 80.7, 75.4, 63.7 and 61.0; HRMS (ESI): m/z calcd for C₁₀H₁₂N₅O₅ [M+H]+ = 282.0833; found: 282.0842.
Figure S1: $^1$H NMR spectrum of compound 12a, b (400 MHz, CDCl$_3$).

Figure S2: $^{13}$C NMR spectrum of compound 12a, b (100.6 MHz, CDCl$_3$).
Figure S3: $^1$H NMR spectrum of compound 13a (400 MHz, CDCl$_3$).

Figure S4: $^{13}$C NMR spectrum of compound 13a (100.6 MHz, CDCl$_3$).
Figure S5: $^1$H NMR spectrum of compound 13b (400 MHz, CDCl$_3$).

Figure S6: $^{13}$C NMR spectrum of compound 13b (100.6 MHz, CDCl$_3$).
Figure S7: $^1$H NMR spectrum of compound 14a (400 MHz, DMSO-$d_6$).

Figure S8: $^{13}$C NMR spectrum of compound 14a (100.6 MHz, DMSO-$d_6$).
Figure S9: $^1$H NMR spectrum of compound 14b (400 MHz, DMSO-$d_6$).

Figure S10: $^{13}$C NMR spectrum of compound 14b (100.6 MHz, DMSO-$d_6$).
Figure S11: $^1$H NMR spectrum of compound 15a (400 MHz, DMSO-$d_6$).

Figure S12: $^{13}$C NMR spectrum of compound 15a (100.6 MHz, DMSO-$d_6$).
Figure S13: $^1$H NMR spectrum of compound 15b (400 MHz, DMSO-$d_6$).

Figure S14: $^{13}$C NMR spectrum of compound 15b (100.6 MHz, DMSO-$d_6$)
Figure S15: $^1$H NMR spectrum of compound 16a (400 MHz, CDCl$_3$).

Figure S16: $^{13}$C NMR spectrum of compound 16a (100.6 MHz, CDCl$_3$).
Figure S17: $^1$H NMR spectrum of compound 16b (400 MHz, CDCl$_3$).

Figure S18: $^{13}$C NMR spectrum of compound 16b (100.6 MHz, CDCl$_3$).
**Figure S19:** $^1$H NMR spectrum of compound 18 (400 MHz, CDCl$_3$).

**Figure S20:** $^{13}$C NMR spectrum of compound 18 (100.6 MHz, CDCl$_3$).
Figure S21: $^1$H NMR spectrum of compound 19a, b (400 MHz, CDCl$_3$).

Figure S22: $^{13}$C NMR spectrum of compound 19a, b (100.6 MHz, CDCl$_3$).
Figure S23: $^1$H NMR spectrum of compound 20a (400 MHz, CDCl$_3$).

Figure S24: $^{13}$C NMR spectrum of compound 20a (100.6 MHz, CDCl$_3$).
Figure S25: $^1$H NMR spectrum of compound 20b (400 MHz, CDCl$_3$).

Figure S26: $^{13}$C NMR spectrum of compound 20b (100.6 MHz, CDCl$_3$).
Figure S27: $^1$H NMR spectrum of compound 21a (400 MHz, DMSO-$d_6$).

Figure S28: $^{13}$C NMR spectrum of compound 21a (100.6 MHz, DMSO-$d_6$).
Figure S29: $^1$H NMR spectrum of compound 21b (400 MHz, DMSO-$d_6$).

Figure S30: $^{13}$C NMR spectrum of compound 21b (100.6 MHz, DMSO-$d_6$).

S30
Figure S31: $^1$H NMR spectrum of compound 22a (400 MHz, CDCl$_3$).

Figure S32: $^{13}$C NMR spectrum of compound 22a (100.6 MHz, CDCl$_3$).
Figure S33: $^1$H NMR spectrum of compound 22b (400 MHz, CDCl₃).

Figure S34: $^{13}$C NMR spectrum of compound 22b (100.6 MHz, CDCl₃).
Figure S35: $^1$H NMR spectrum of compound 9a (400 MHz, DMSO-$d_6$).

Figure S36: $^{13}$C NMR spectrum of compound 9a (100.6 MHz, DMSO-$d_6$).
Figure S37: DEPT-135 NMR spectrum of compound 9a (100.6 MHz, DMSO-d6).

Figure S38: $^1$H, $^1$H COSY NMR spectrum of compound 9a (DMSO-d6).
Figure S39: $^1$H-$^{13}$C HETCOR NMR spectrum of compound 9a (DMSO-$d_6$).
Figure S40: NOESY NMR spectrum of compound 9a.

Figure S41: $^1$H NMR spectrum of compound 9b (400 MHz, DMSO-$d_6$).
**Figure S42:** $^{13}$C NMR spectrum of compound 9b (100.6 MHz, DMSO-$d_6$).

**Figure S43.** Mass spectrum of reaction mixture (conversion of 22b to 9b).