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One-step synthesis of novel tricyclic isomeric azidonucleosides

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Abstract—Several tricyclic azido-isonucleosides were formed in high yields by the treatment of pyrimidine isonucleosides with triphenylphosphine, tetrabromomethane, and sodium azide. The regioselective ring opening of these tricyclic azido-isonucleosides was also investigated.

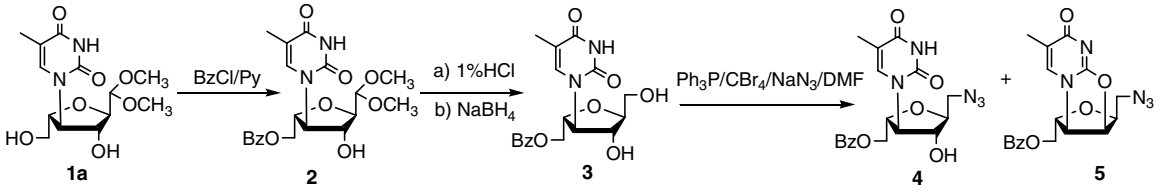
1. Introduction

The finding that 3′-azido-3′-deoxythymidine (AZT) is a therapeutic agent for the treatment of acquired immunodeficiency syndrome (AIDS) has triggered an explosive new development in the synthetic chemistry of nucleosides.[1] Many nucleoside analogues with anti-virus or anticancer activities have been developed, many of which are used in the current clinical condition including some tricyclic nucleosides, for example, 2,2′-anhydro-1-β-D-arabinosyl cytosine.[2] However, there still remain some problems with these drugs such as the development of drug resistance, cytotoxicity, and enzymatic instability in vivo, which led to the search for new nucleoside analogues with more potent activity and lower side-effects. Isonucleosides represent a novel class of carbohydrate modified nucleosides, in which the nucleobase is linked to various positions of ribose other than C-1′; some of these nucleosides showed interesting biological activities.[3–7] We have also reported a series of isonucleoside syntheses and their incorporation into oligonucleotides.[8–10] Therefore, it would be interesting to synthesize some isonucleosides with both azido groups and tricyclic structures and investigate their biological activities. Herein, we report the synthesis of tricyclic azido-isonucleosides.

2. Results and discussion

In order to regioselectively introduce an azido group to the 6′ or 1′ position of isonucleoside **1a** or **3**, we preferred to use the reagent triphenylphosphine/tetrabromomethane/sodium azide.[11] Isonucleoside **1a**[9] was protected with a benzoyl group to give compound **2**. After hydrolysis and reduction of the acetal group, compound **2** was then converted to compound **3** in 84% yield.

When compound **3** was treated with Ph_3P, CBr_4, and NaN_3 (compound **3**/Ph_3P:CBr_4:NaN_3 = 1.0/1.1:1.1:5.0) at room temperature in DMF for 12 h, compound **4** was obtained in 82% yield (Scheme 1). To study the influence of the ratio of isonucleoside substrate **3** and azido reagent on this one-step regioselective azidation, the ratio was increased from 1.0/1.1:1.1:5.0 to 1.0/1.5:1.5:5.0. In addition to compound



Scheme 1. Synthesis of azido-isonucleoside **4** and tricyclic azido-isonucleoside **5**.

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4, which was obtained in 65% yield, a novel tricyclic azido-isonucleoside **5** was also obtained in 22% yield. When the ratio of reagent was further changed into 1/2.5:2.5:5, compounds **4** and **5** were afforded in 5% and 83% yields, respectively (Table 1).

Table 1. The yields (%) of **4**, **5**, **6**, and **7** with different reactant ratios

Isonucleoside/Ph_3P:CBr_4:NaN_3	**4**	**5**	**6a**	**7a**	**6b**	**7b**
1/1.1:1.1:5	82	—	75	—	92	—
1/1.5:1.5:5	65	22	58	19		
1/2.5:2.5:5	5	83	8	74	24	62

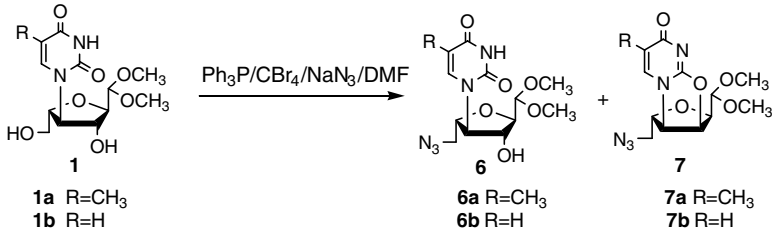
'—' Not observed.

The structure of compound **5** was identified by ^1H, ^{13}C NMR, and HRMS spectra. A comparison of the molecular weight of compound **5** with the molecular weight of compound **4** indicated that compound **5** was formed from compound **4** by the loss of a hydroxyl group. The ^1H NMR of compound **5** showed cis coupling constant between H-2′ and H-3′. HMBC gave a strong coupling effect of H-3′ with C-2 on thymine, which indicated the formation of the bond between the O-2 and C-3′. The azidation of compound **1a** or **1b** with this reagent is similar to that of compound **3** (Table 1). Compounds **6a**,**b** and **7a**,**b** were obtained, conveniently, by adjusting the ratio of the reactants and reaction time (Scheme 2).

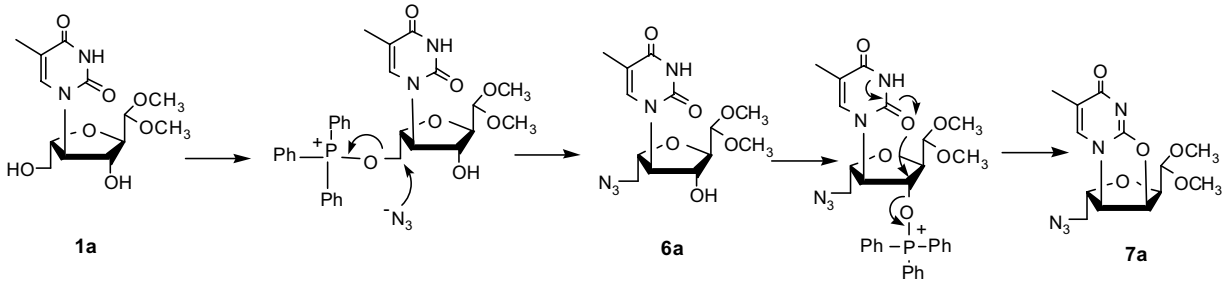
The triphenylphosphine-tetrahalomethane system has been used for the replacement of various hydroxyl groups in the sugar moiety of nucleosides by chlorine or bromine. An ionic mechanism was suggested for this nucleophilic substitution; $Ar_3P^+X\ CX_3^-$ was involved as an activator.[12,13] According to this mechanism, the formation of compounds **6a** and **7a** is proposed in Scheme 3.

Compound **5** was treated with methylamine in methanol at room temperature for 15 min; O-deprotected compound **8** was provided in 98% yield. Compound **8** could be further reacted with methylamine to give product **9** and the reaction was complete in several hours in 97% yield. Compound **5** was refluxed in 1 M sodium hydroxide or treated with aqueous ammonia at 100 °C in a sealed steel vessel to give compound **10** in 95% yield. ^1H NMR of compounds **9** and **10** showed a cis coupling constant between H-3′ and H-4′. The structures of compounds **9** and **10** were also identified by ^{13}C NMR and HRMS. In the case of 2,2′-anhydro-β-D-arabino-furanosylthymine, it was reported that 'hard' nucleophiles such as hydroxide ion or ammonia attack at C-2 on the pyrimidine, resulting in substitution at C-2 and leaving the hydroxyl on the 2′ position in the arabino configuration; while the 'soft' nucleophiles, such as thiophenolate and azide ions, attack at C-2′ of the ribose.[14] In this work, the 'hard' nucleophiles such as methylamine and hydroxide ion attack at C-2 on the pyrimidine of the 2,3′-anhydro-4′-pyrimidine-4′-azido-isonucleoside **5**, affording the corresponding regio- and stereospecific ring-opening products **9** and **10** in good yields (Scheme 4).

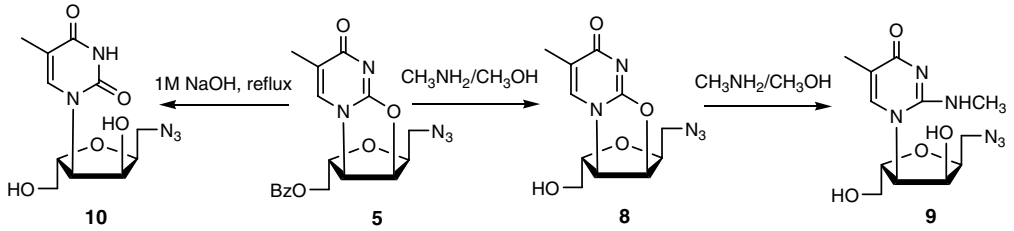
When compound **8** was treated with toluene-4-thiol in methanol in the presence of triethylamine, a new tricyclic isonucleoside **12** was formed, in which the C2–N1′ bond was formed instead of the C2–O3′ bond (Scheme 5). Compound **8** was refluxed with toluene-4-thiol in methanol or reduced by catalytic hydrogenation (H_2/Pd); the azido group was reduced to give amino derivative **11**. When **11** was refluxed further with triethylamine in methanol, the final tricyclic isonucleoside **12** was formed. The structure of tricyclic isonucleoside **12** was identified by ^1H, ^{13}C NMR, and HMBC.



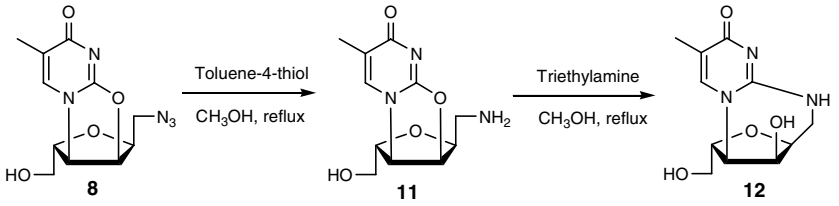
Scheme 2. Synthesis of azido-isonucleoside **6a**,**b** and tricyclic azido-isonucleoside **7a**,**b**.



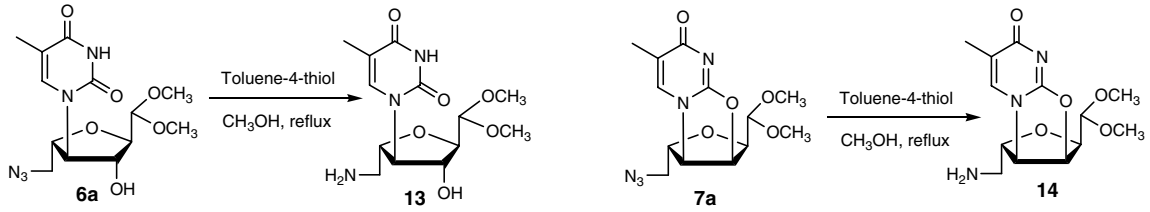
Scheme 3. Proposed mechanism for the formation of azido-isonucleoside **6a** and tricyclic azido-isonucleoside **7a**.



Scheme 4. Regio- and stereospecific ring-opening reaction of compound **5**.



Scheme 5. Formation of 1′-deoxy-1′-amino-4′-deoxy-4′-(thymin-1-yl)-2,1′:2′,5′-dianhydro-L-altritol **12**.



Scheme 6. The reduction of the azido group by toluene-4-thiol.

The azido group in compounds **6a** and **7a** can be easily reduced to an amino group by a similar reaction to give compounds **13** and **14**. Since the amino group in compound **14** is far from the C2 position of thymine ring, the further amino substitution did not take place (Scheme 6).

3. Conclusion

In conclusion, a convenient route has been achieved to the synthesis of tricyclic isomeric azidonucleosides in one-step; this kind of isonucleosides can easily be substituted by a regio-selective nucleophilic opening ring reaction.

4. Experimental

Unless specified otherwise, all starting materials and reagents were obtained from commercial suppliers and used without further purification. All anhydrous reactions were conducted in oven-dried glassware, under a dry argon atmosphere with anhydrous DMF, which was dried by P_2O_5 and distilled before use. Thin layer chromatography was performed using silica gel GF-254 (Qing-Dao Chemical Company, China) plates with detection by UV, or charting with 5% phosphomolybdic acid hydrate in ethanol. Column chromatography was performed on silica gel (200–300 mesh, purchased from Qing-Dao Chemical Company, China). Optical rotations were recorded on a Perkin–Elmer 243B polarimeter. ^{1}H NMR (500 Hz) and ^{13}C NMR (125.7 Hz) spectra were recorded on Varian Inova VXR-500 or Avance 500 Bruker spectrometer. When necessary, 2D experiments were performed to assist in structure elucidation. Infrared spectra were recorded on a NEXUS-470 FTIR (Nicolet) spectrometer and only the more representative frequencies are reported (cm^{-1}). Mass spectra (ESI-TOF$^+$ MS) and high-resolution mass spectra (ESI-TOF$^+$ HRMS) were obtained on a MDS SCLEX QSTAR instrument and only the most representative peaks are reported (m/z).

4.1. 6′-*O*-Benzoyl-1′-deoxy-1′-azido-4′-deoxy-4′-(thymin-1-yl)-2′,5′-anhydro-L-mannitol 4

To a mixture of compound **3** (280 mg, 0.74 mmol), triphenylphosphine (215 mg, 0.82 mmol), and sodium azide (240 mg, 3.7 mmol) in dry DMF (5 ml) was added carbon tetrabromide (271 mg, 0.82 mmol) at room temperature. The mixture was stirred at room temperature for 12 h and then methanol was added until the mixture turned into a clear solution. Stirring was continued for another h. After the usual work-up, the residue was purified by short-column chromatography using a gradient of MeOH in CH_2Cl_2 (2–2.5%) to yield **4** (245 mg, 82%). Compound **4**: $[\alpha]_D^{24} = -39.2$ (c 0.120, MeOH). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.78 (s, 3H, 5-CH_3), 3.46–3.59 (m, 2H, H-1′), 3.98 (m, 1H, H-2′), 4.35–4.41 (m, 4H, H-5′, H-3′, and H-6′), 4.84 (t, $J_{4',3'} = J_{4',5'} = 8.5$ Hz, 1H, H-4′), 5.80 (d,

$J = 5.5$ Hz, 1H, 3′-OH), 7.52 (t × d, $J = 2.0$ Hz, $J = 7.0$ Hz, 2H, Bz-3,5), 7.67 (m, 1H, Bz-4), 7.69 (s, 1H, H-6), 7.94 (dd, $J = 2.0$ Hz, $J = 7.0$ Hz, 2H, Bz-2,6), 11.32 (s, 1H, N-3). ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ 11.9 (5-CH_3), 51.5 (C-1′), 63.4 (C-6′), 64.6 (C-4′), 72.5 (C-3′), 75.0 (C-5′), 80.8 (C-2′), 109.6 (C-5), 128.7 (Bz-3,5), 129.1 (Bz-4), 129.3 (Bz-2,6), 133.4 (Bz-1), 138.4 (C-6), 151.2 (C-2), 163.6 (PhCO), 165.3 (C-4). IR 3212 (br), 2103, 1690. Anal. Calcd for $C_{18}H_{19}N_5O_6$ (401.1): C, 53.86; H, 4.77; N, 17.45. Found: C, 53.67; H, 4.61; N, 17.26.

4.2. 6′-*O*-Benzoyl-1′-deoxy-1′-azido-4′-deoxy-4′-(thymin-1-yl)-2,3′:2′,5′-dianhydro-L-altritol 5

To a mixture of compound **3** (376 mg, 1.0 mmol), triphenylphosphine (655 mg, 2.5 mmol), and sodium azide (325 mg, 5.0 mmol) in dry DMF (10 ml) was added carbon tetrabromide (827 mg, 2.5 mmol) at room temperature. The mixture was stirred at room temperature for 36 h and then methanol was added until the mixture turned into a clear solution. Stirring was continued for a further hour. After the usual work-up, the residue was purified by a short-column chromatography using a gradient of MeOH in CH_2Cl_2 (2–3.3%) to yield **4** (20 mg, 5%) and **5** (320 mg, 83%). Compound **5**: $[\alpha]_D^{24} = +28.9$ (c 0.127, MeOH). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.91 (d, $J = 1.0$ Hz, 3H, 5-CH_3), 3.60 (m, 2H, H-1′), 4.49 (m, 2H, H-6′), 4.65–4.69 (m, 2H, H-2′ and H-5′), 5.30 (d, $J_{4',3'} = 7.5$ Hz, 1H, H-4′), 5.62 (dd, $J_{3',2'} = 4.5$ Hz, $J_{3',4'} = 7.5$ Hz, 1H, H-3′), 7.34 (d, $J = 1.5$ Hz, 1H, H-6), 7.48 (t, $J = 8.0$ Hz, 2H, Bz-3,5), 7.61 (t, $J = 7.5$ Hz, 1H, Bz-4), 8.00 (m, 2H, Bz-2,6). ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 13.9 (5-CH_3), 49.2 (C-3′), 64.0 (C-6′), 65.3 (C-4′), 80.5 (C-1′), 81.6 (C-2′), 83.2 (C-5′), 119.3 (C-5), 128.6 (Bz-3,5), 128.9 (Bz-4), 129.5 (Bz-2,6), 130.9 (Bz-1), 133.7 (C-6), 159.7 (C-2), 165.9 (PhCO), 172.1 (C-4). IR: 2103, 1724. HRMS (ESI-TOF$^+$) calcd for $C_{18}H_{18}N_5O_5$ (M^++H): 384.1302; found: 384.1292.

4.3. 6′-Deoxy-6′-azido-4′-deoxy-4′-(thymin-1-yl)-2′,5′-anhydro-L-mannofuranose dimethyl acetal 6a

To a mixture of compound **1a** (4.41 g, 13.95 mmol), triphenylphosphine (4.02 g, 15.35 mmol), and sodium azide (5.00 g, 76.92 mmol) in dry DMF (100 ml) was added carbon tetrabromide (4.90 g, 14.80 mmol) at room temperature. The mixture was stirred at room temperature for 48 h and then methanol was added until the mixture turned into a clear solution. Stirring was continued for another hour. After the usual work-up, the residue was purified by a short-column chromatography using a gradient of MeOH in CH_2Cl_2 (2–2.5%) to yield **6a** (3.57 g, 75%). Compound **6a**: $[\alpha]_D^{24} = -19.6$ (c 0.160, MeOH). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.79 (s, 3H, 5-CH_3), 3.29–3.54 (m, 2H, H-6′), 3.34 (s, 3H, 1′-OCH_3), 3.35 (s, 3H, 1′-OCH_3), 3.81 (t, $J_{2',1'} = J_{2',3'} = 5.5$ Hz, 1H, H-2′), 4.16 (m, 1H, H-5′), 4.40 (m, 1H, H-3′), 4.49 (d, $J_{1',2'} = 5.5$ Hz, 1H, H-1′), 4.65 (dd, $J = 8$ Hz, $J = 9$ Hz, 1H, H-4′), 5.58 (d, $J = 5.5$ Hz, 1H, 3′-OH), 7.54 (d, $J = 1$ Hz, 1H, H-6), 11.30 (s, 1H, N-3). ^{13}C NMR (DMSO-d_6, 125.7 MHz): δ (5-CH_3), 51.2 (C-6′), 53.8 (1′-OCH_3), 54.3 (1′-OCH_3), 64.0 (C-4′), 73.5 (C-3′), 77.0 (C-5′), 81.6 (C-2′), 103.9 (C-1′), 109.5 (C-5), 138.1 (C-6), 151.1 (C-4), 163.6 (C-2). IR: 2105, 1691. HRMS (ESI-TOF$^+$) calcd for $C_{13}H_{20}N_5O_6$ (M^++H): 342.1408; found: 342.1424.

4.4. 6′-Deoxy-6′-azido-4′-deoxy-4′-(uracil-1-yl)-2′,5′-anhydro-L-mannofuranose dimethyl acetal 6b

To a mixture of compound **1b** (100 mg, 0.33 mmol), triphenylphosphine (95 mg, 0.36 mmol), and sodium azide (120 mg, 1.84 mmol) in dry DMF (5 ml) was added carbon tetrabromide (120 mg, 0.36 mmol) at room temperature. The mixture was stirred at room temperature for 16 h and then methanol was added until the mixture turned into a clear solution. Stirring was continued for a further hour. After the usual work-up, the residue was purified by a short-column chromatography using a gradient of MeOH in CH_2Cl_2 (2–2.5%) to yield **6b** (100 mg, 92%). Compound **6b**: $[\alpha]_D^{24} = -23.8$ (c 0.080, MeOH). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.17–3.56 (m, 2H, H-6′), 3.33 (s, 1′-OCH_3), 3.34 (s, 1′-OCH_3), 3.82 (t, $J_{2',1'} = J_{2',3'} = 5.5$ Hz, 1H, H-2′), 4.16 (m, 1H, H-5′), 4.41 (m, 1H, H-3′), 4.49 (d, $J_{1',2'} = 5.5$ Hz, 1H, H-1′), 4.65 (t, $J_{4',3'} = J_{4',5'} = 8$ Hz, 1H, H-4′), 5.66 (d, $J = 5.5$ Hz, 1H, 3′-OH), 5.67 (d, H-5), 7.66 (d, 1H, H-6), 11.33 (s, 1H, N-3). ^{13}C NMR (DMSO-d_6, 125.7 MHz): δ 51.7 (C-6′), 54.4 (1′-OCH_3), 55.1 (1′-OCH_3), 65.0 (C-4′), 74.1 (C-3′), 77.6 (C-5′), 82.3 (C-2′), 102.5 (C-1′), 104.5 (C-5), 143.0 (C-6), 151.6 (C-4), 163.5 (C-2). IR: 2107, 1722. HRMS (ESI-TOF$^+$) calcd for $C_{12}H_{18}N_5O_6$ (M^++H): 328.1251; found: 328.1265.

4.5. 6′-Deoxy-6′-azido-4′-deoxy-4′-(thymin-1-yl)-2,3′:2′,5′-dianhydro-L-altrofuranose dimethyl acetal 7a

To a mixture of compound **1a** (202 mg, 0.64 mmol), triphenylphosphine (335 mg, 1.28 mmol), and sodium azide (250 mg, 3.85 mmol) in dry DMF (5 ml) was added carbon tetrabromide (423 mg, 1.28 mmol) at room temperature. The mixture was stirred at room temperature for 36 h and then methanol was added until the mixture turned into a clear solution. Stirring was continued for another h. After the usual work-up, the residue was purified by short-column chromatography using a gradient of MeOH in CH_2Cl_2 (2–3.3%) to yield **6a** (18 mg, 8%) and **7a** (152 mg, 74%). Compound **7a**: $[\alpha]_D^{24} = +79.4$ (c 0.152, MeOH). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.78 (s, 3H, 5-CH_3), 3.30 (s, 3H, 1′-OCH_3), 3.38 (s, 3H, 1′-OCH_3), 3.31–3.76 (m, 2H, H-6′), 4.29 (dd, $J_{2',3'} = 4.0$ Hz, $J_{2',1'} = 7.5$ Hz, 1H, H-2′), 4.42–4.54 (m, 2H, H-5′ and H-1′), 4.87 (d, $J_{4',3'} = 7.0$ Hz, 1H, H-4′), 5.44 (dd, $J_{3',2'} = 4.0$ Hz, $J_{3',4'} = 7.0$ Hz, 1H, H-3′), 7.75 (s, 1H, H-6). ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ 13.6 (5-CH_3), 49.2 (C-3′), 52.7 (1′-OCH_3), 54.9 (1′-OCH_3), 64.7 (C-4′), 78.6 (C-6′), 82.4 (C-2′), 83.5 (C-5′), 101.4 (C-1′), 116.5 (C-5), 132.8 (C-6), 159.5 (C-2), 171.2 (C-4). HRMS (ESI-TOF$^+$) calcd for $C_{13}H_{18}N_5O_5$ (M^++H): 324.1302; found: 324.1289.

4.6. 6′-Deoxy-6′-azido-4′-deoxy-4′-(uracil-1-yl)-2,3′:2′,5′-dianhydro-L-altrofuranose dimethyl acetal 7b

To a mixture of compound **1b** (125 mg, 0.41 mmol), triphenylphosphine (265 mg, 1.01 mmol), and sodium azide (150 mg, 2.31 mmol) in dry DMF (5 ml) was added carbon

tetrabromide (340 mg, 1.02 mmol) at room temperature. The mixture was stirred at room temperature for 58 h and then methanol was added until the mixture turned into a clear solution. Stirring was continued for another hour. After the usual work-up, the residue was purified by short-column chromatography using a gradient of MeOH in CH_2Cl_2 (2–4%) to yield **6b** (32 mg, 24%) and **7b** (79 mg, 62%). Compound **7b**: $[\alpha]_D^{24} = +92.7$ (*c* 0.070, MeOH). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.32 (s, 3H, 1′-OCH_3), 3.39 (s, 3H, 1′-OCH_3), 3.35–3.78 (m, 2H, H-6′), 4.30 (dd, $J_{2',3'} = 4.0$ Hz, $J_{2',1'} = 7.5$ Hz, 1H, H-2′), 4.44–4.47 (m, 2H, H-5′ and H-1′), 4.90 (dd, $J_{4',5'} = 1.0$ Hz, $J_{4',3'} = 7.0$ Hz, 1H, H-4′), 5.47 (dd, $J_{3',2'} = 4.0$ Hz, $J_{3',4'} = 7.5$ Hz, 1H, H-3′), 5.88 (d, $J = 7.0$ Hz, 1H, H-5), 7.84 (d, $J = 7.0$ Hz, 1H, H-6). ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ 49.2 (C-3′), 52.7 (1′-OCH_3), 54.9 (1′-OCH_3), 64.6 (C-4′), 78.5 (C-6′), 82.6 (C-2′), 83.7 (C-5′), 101.4 (C-1′), 108.4 (C-5), 137.2 (C-6), 159.9 (C-2), 170.8 (C-4). IR: 2109, 1664, 1632. HRMS (ESI-TOF$^+$) calcd for $C_{12}H_{16}N_5O_5$ (M^++H): 310.1145; found: 310.1140.

4.7. 1′-Deoxy-1′-azido-4′-deoxy-4′-(thymin-1-yl)-2,3′:2′,5′-dianhydro-L-altritol 8

A solution of **5** (73 mg, 0.19 mmol) in 2 ml 25–30% methylamine alcohol solution was stirred at room temperature for 15 min. After this time, the solution was evaporated under reduced pressure until dryness and the residue purified by short-column chromatography using a gradient of MeOH in CH_2Cl_2 (2–5%) to yield **8** (52 mg, 98%). Compound **8**: $[\alpha]_D^{24} = +45.0$ (*c* 0.030, MeOH). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.80 (d, $J = 1$ Hz, 3H, 5-CH_3), 3.43–3.68 (m, 4H, H-1′ and H-6′), 4.30 (t, $J = 4.0$ Hz, 1H, H-5′), 4.48 (d × t, $J_{2',1'} = 8.0$ Hz, $J_{2',3'} = 4.5$ Hz, 1H, H-2′), 5.03 (d, $J_{4',3'} = 7.5$ Hz, 1H, H-4′), 5.17 (t, $J =$ 5 Hz, 1H, 6′-OH), 5.52 (dd, $J_{3',4'} = 7.5$ Hz, $J_{3',2'} = 4.5$ Hz, 1H, H-3′), 7.74 (d, $J = 1.0$ Hz, H-6). ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ 13.6 (5-CH_3), 49.3 (C-3′), 61.9 (C-6′), 64.9 (C-4′), 80.2 (C-4′), 83.5 and 83.6 (C-2′ and C-5′), 116.5 (C-5), 132.7 (C-6), 159.5 (C-2), 171.3 (C-4). HRMS (ESI-TOF$^+$) calcd for $C_{11}H_{14}N_5O_4$ (M^++H): 280.1040; found: 280.1044.

4.8. 1′-Deoxy-1′-azido-4′-deoxy-4′-(5-methyl-N^2-methyl-*iso*-cytosin-1-yl)-2′,5′-anhydro-L-altritol 9

A solution of **5** (68 mg, 0.18 mmol) in 2 ml 25–30% methylamine alcohol solution was stirred at room temperature overnight. After this time, the solution was evaporated under reduced pressure until dryness and the residue purified by short-column chromatography using MeOH in CH_2Cl_2 (50%) to yield **9** (55 mg, 97%). Compound **9**: $[\alpha]_D^{24} = -82.3$ (*c* 0.038, MeOH). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.71 (s, 3H, 5-CH_3), 2.73 (d, $J = 4.5$ Hz, 3H, –N–CH_3), 3.32–3.59 (m, 4H, H-6′ and H-1′), 4.15–4.18 (m, 1H, H-2′), 4.31 (m, 1H, H-3′), 4.44–4.46 (m, 1H, H-5′), 4.49 (dd, $J_{4',5'} = 9.0$ Hz, $J_{4',3'} = 4.0$ Hz, 1H, H-4′), 5.02 (t, $J = 5.5$ Hz, 1H, 6′-OH), 5.67 (d, $J = 5.5$ Hz, 1H, 3′-OH), 6.97 (q, $J =$ 4.0 Hz, 1H, –NH–), 7.31 (s, 1H, H-6). ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ 13.5 (5-CH_3), 50.3 (C-5′), 58.4 (C-4′), 59.7 (C-6′), 69.1 (C-2′), 77.0 (C-1′), 79.5 (C-3′), 111.6 (C-5), 136.6 (C-6), 153.9 (C-2), 169.7 (C-4). HRMS (ESI-TOF$^+$) calcd for $C_{12}H_{19}N_6O_4$ (M^++H): 311.1462; found: 311.1462.

4.9. 1′-Deoxy-1′-azido-4′-deoxy-4′-(thymin-1-yl)-2′,5′-anhydro-L-altritol 10

A solution of **5** (23 mg, 0.06 mmol) in 5 ml aqueous ammonia was heated to 100 °C in a sealed steel vessel for 10 h. After this time, the solution was evaporated under reduced pressure until dryness and the residue was purified by short-column chromatography using MeOH in CH_2Cl_2 (2.5–4%) to yield **10** (17 mg, 95%). Compound **10**: $[\alpha]_D^{24} = -38.5$ (*c* 0.040, MeOH). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.31–3.52 (m, 4H, 1′ and 6′), 4.15–4.20 (m, 2H, 2′ and 3′), 4.28–4.32 (m, 1H, H-5′), 4.85 (t, $J = 5.5$ Hz, 1H, 6′-OH), 4.91 (dd, $J_{4',3'} = 4.5$ Hz, $J_{4',5'} = 9.5$ Hz, 1H, H-4′), 5.57 (d, $J = 5.5$ Hz, 1H, 3′-OH), 7.51 (s, 1H, H-6), 11.25 (s, 1H, N-3). ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ 12.6 (5-CH_3), 50.8 (C-1′), 61.5 (C-6′), 70.4 (C-4′), 77.8 (C-5′), 80.3 (C-2′), 107.7 (C-5), 140.2 (C-6), 151.9 (C-2), 164.2 (C-4). HRMS (ESI-TOF$^+$) calcd for $C_{11}H_{16}N_5O_5$ (M^++H): 298.1145; found: 298.1152.

4.10. 1′-Deoxy-1′-amino-4′-deoxy-4′-(thymin-1-yl)-2,1′:2′,5′-dianhydro-L-altritol 12

To a solution of **8** (30 mg, 0.11 mmol) in 3 ml MeOH, toluene-4-thiol (68 mg, 0.55 mmol), and triethylamine (0.1 ml, 0.71 mmol) were added and the mixture refluxed for 8 h. After this time, the solution was evaporated under reduced pressure until dryness and the residue was purified by short-column chromatography using MeOH in CH_2Cl_2 (3.3–20%) to yield **12** (18 mg, 66%). Compound **12**: $[\alpha]_D^{24} = +40.8$ (*c* 0.105, MeOH). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.72 (s, 3H, 5-CH_3), 3.13–3.21 (m, 2H, H-1′), 3.37–3.47 (m, 2H, H-6′), 4.22–4.23 (m, 1H, H-4′), 4.28–4.30 (m, 1H, H-3′), 4.94–4.96 (t, $J = 5.0$ Hz, 1H, 6′-OH), 5.75 (s, 1H, 3′-OH), 6.85 (s, 1H, –NH–), 7.28 (s, 1H, H-6). ^{13}C NMR (DMSO-d_6, 125.7 MHz) δ 13.1 (5-CH_3), 4.9 (C-1′), 62.6 (C-6′), 67.4 and 67.5 (C-3′ and C-4′), 75.1 (C-2′), 82.0 (C-5′), 114.7 (C-5), 141.4 (C-6), 156.6 (C-2), 170.1 (C-4). IR: 3299 (br), 1662, 1571. MS (ESI-TOF$^+$) 254 (M+1,100), 276 (M+23).

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