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Regioselective synthesis of 3-deazacarbovir and its 3-deaza-adenosine analogues

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ABSTRACT

We herein report the hitherto unknown synthesis of 3-deazacarbovir and its adenosine analogue. The major highlight in the synthesis of adenosine analogs is to use 6-*N*,*N*-diboc protected 3-deazapurines **9** and **11** for regioselective Mitsunobu coupling as well as unexplored palladium catalyzed coupling with these substrates. Synthesis of 3-deazacarbovir **1** has been accomplished by the regioselective palladium catalyzed coupling of 6-*N*,*N*-diphenylcarbamoyl protected 3-deazaguanine base **18** with dicarbonate **14**. All the target nucleosides were screened for anti-HIV-1 activity and none of them have significant activity as well as toxicity up to 100 μM.

1. Introduction

Carbocyclic nucleosides have emerged as the target of intense investigation due to their interesting biological activity and greater metabolic stability to nucleoside phosphorylase, than the corresponding carbohydrate counterpart.[1] Since the discovery of the naturally occurring aristeromycin and neplanocin A as biologically interesting carbocyclic nucleosides, a number of synthetic carbocyclic nucleosides have been synthesized and have shown interesting antiviral activity (Fig. 1).[2–9] Two carbocyclic nucleosides abacavir[10] and entecavir[11] have been approved by the US FDA for the treatment of HIV and HBV, respectively. The discovery of 2′,3′-olefinic carbocyclic nucleosides, such as carbovir and abacavir having potent anti-HIV activity, has increased interests in the search for novel nucleosides in

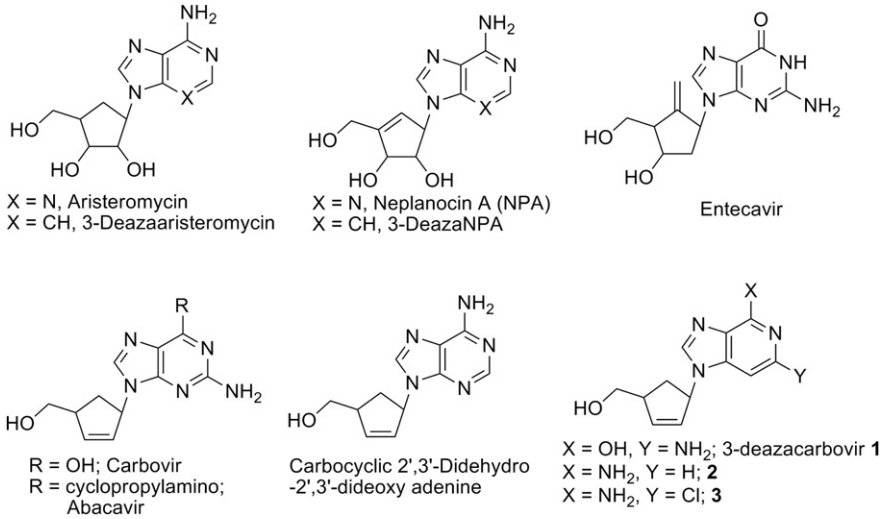

Figure 1. Some important carbocyclic nucleoside and its 3-deaza analogs.

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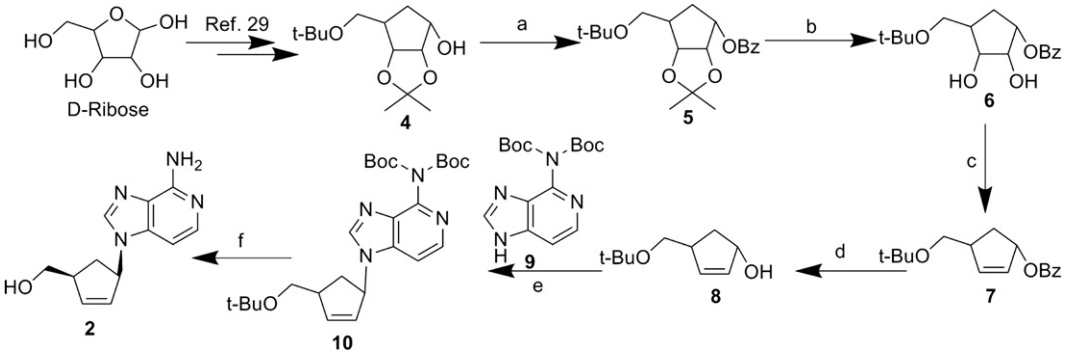
this class of compounds. Carbocyclic 2′,3′-didehydro-2′,3′-dideoxy adenosine has also shown potent anti-HIV-1 activity equivalent to dideoxyinosine (ddI) but one third to carbovir.[10,12]

Nucleoside analogs based on the 3-deazapurine (1*H*-imidazo[4,5-*c*]pyridine) framework have found significant usefulness in the design of antiviral agent and biochemical investigations.[13–15] Carbocyclic analogs of 3-deazapurines such as 3-deazaaristeromycin[16] and 3-deazaneplanocin A[17,18] are potent inhibitors of *S*-adenosylhomocysteine hydrolase, which display wide variety of antiviral activity against DNA and RNA viruses. In our efforts to further explore the carbocyclic 3-deazanucleoside, it was of interest to synthesize hitherto unknown 3-deazacarbovir **1** and carbocyclic 2′,3′-didehydro-2′,3′-dideoxy-3-deaza-adenosine analogs **2** and **3**.

Several synthetic methodologies have been reported for the synthesis of carbovir[19–28] among them palladium catalyzed coupling and convergent approach to construct base ring are most prominent. Our group has reported the synthesis of L-carbovir using Mitsunobu coupling.[29] Our aim was to explore the synthesis of carbocyclic 2′,3′-didehydro-2′,3′-dideoxy-3-deaza-adenosine analogs **2** and **3** using Mitsunobu coupling of suitable protected product (Scheme 1). Compound **6** was reacted with trimethyl orthoformate and pyridinium *p*-toluenesulfonate (PPTS) to obtain cyclic 2′,3′-orthoester followed by heating in acetic anhydride at 120 °C to obtain compound **7** in moderate yield. Finally, removal of the benzoyl group using LiOH gave compound **8**. Mitsunobu coupling of 3-deazapurine with 2′,3′-unsaturated carbocyclic alcohol has been recently reported to produce a mixture of N-7 and N-9 isomers.[31] Introduction of bulkier group at 6-amino group in adenine [32] shields the reaction at N-7 position and produce N-9 regioselectivity. However, the use *N*,*N*-diboc protected 3-deazapurines **9**[33] have not been much explored for the synthesis of carbocyclic 3-deaza nucleosides. Mitsunobu coupling of compound **8** with diboc protected nucleobase **9** gave the desired N-9 isomer **10** as major isolable product. On TLC, it appears another isomer may be present <5–7%, but could not be isolated pure. Removal of diboc and tert butyl groups using either TFA/H_2O (2:1 or 3:1) or 2 M HCl in methanol at 30–50° resulted in the cleavage of nucleosidic bond within 45 min. However, deprotection was finally effected with TFA in anhydrous DCM at rt for 3–4 h to get the target compound **2** in moderate yield (Scheme 1).



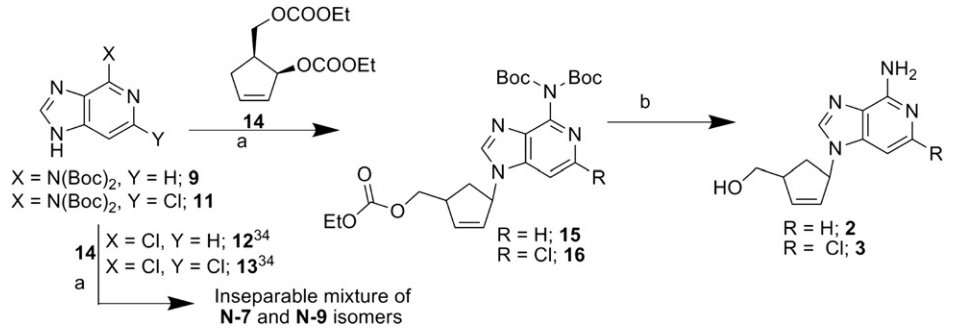
Scheme 1. Reagents and conditions: (a) BzCl, Pyr, rt, 12 h; (b) concentrated HCl/MeOH (1:70, v/v), rt, 2.5 h; (c) (i) $CH(OMe)_3$, pyridinium *p*-toluenesulfonate, rt, 2 h; (ii) Ac_2O, 120–130 °C, 6 h; (d) LiOH, MeOH/THF/H_2O (5:3:2) rt, 1.5 h (e) Ph_3P, DIAD, THF, 0 °C to rt; (f) DCM, TFA rt 3–4 h.

3-deaza bases **9** and **11** with cyclopentenol **8** as well as explore these bases for hitherto unknown palladium catalyzed coupling with dicarbonate **14**. For the regioselective synthesis of 3-deazacarbovir, we developed *N*,*N*-diphenylcarbamoyl protected 3-deazaguanine base **18**, which was found to be good substrate for the palladium catalyzed coupling with dicarbonate **14**.

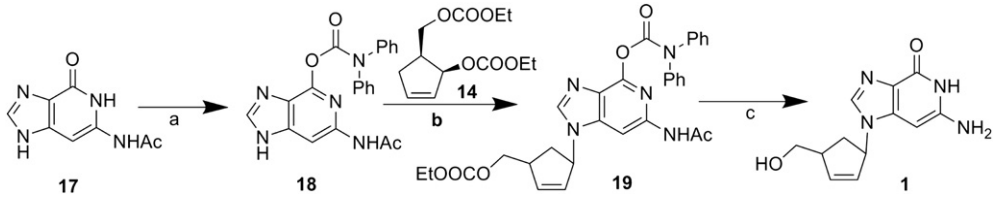
2. Chemistry

Intermediate **4** was prepared from D-ribose in 10 steps as reported previously.[30] Cyclopentanol **8** was prepared analogously to the reported method published for L-sugar from our group.[29] Protection of hydroxyl group in compound **4** using benzoyl chloride gave compound **5**, which was treated with MeOH/conc HCl to obtain compound **6** along with the 2-benzoyl migrated undesired

To explore the palladium catalyzed coupling to generate carbocyclic 3-deazanucleoside, we used Crimmins method[23] to obtain dicarbonate **14** in 5 steps (Scheme 2). Palladium catalyzed coupling of dicarbonate **14** with 4-chloro-1*H*-imidazo-[4,5-*c*]pyridine **12**[34] or 4,6-dichloro-1*H*-imidazo-[4,5-*c*]pyridine **13**[34] resulted in a difficult separable mixture of N-9 and N-7 isomers in moderate yields. Although the *N*,*N*-diboc protected adenine[31] have been explored for the regioselective Mitsunobu coupling in the synthesis of carbocyclic nucleoside, however, this base hasn't been explored for a palladium catalyzed coupling. Therefore, we focused our strategy to explore 6-*N*,*N*-diboc protected 3-deaza nucleobases[33] **9** and **11**, which underwent smooth regioselective Palladium catalyzed coupling with dicarbonate **14** using standard condition[23] to yield nucleosides **15** and **16**, respectively. Similar to the Mitsunobu coupling with compound **8**, the palladium catalyzed coupling reaction also indicates the



Scheme 2. Reagents and conditions: (a) $Pd(PPh_3)_4$, THF/DMSO (1:1), rt, 1 h; (b) (i) DCM, TFA, rt 5–7 h; (ii) K_2CO_3/MeOH, 1 h, rt.



Scheme 3. Reagents and conditions: (a) (i) Diphenyl carbamoyl chloride, diisopropyl amine, pyridine, 1 h, 85%; (ii) K_2CO_3, MeOH, 45 min; (b) $Pd(PPh_3)_4$, THF/DMSO (1:1), rt, 45 min–1 h; (c) NH_3 (*l*), MeOH, 80 °C, 16 h.

presence of another isomer <5–7% (by TLC). However, in the case of compound **11**, the N-9 isomer was the only isomer visible on TLC as well as isolable. Removal of protecting groups in compounds **15** and **16** were effected with TFA in anhyd DCM followed by treating the crude with K_2CO_3/MeOH yielded the smooth conversion to compounds **2** and **3**, respectively in good yield.

Carbocyclic 3-deazaguanosine analogs are hitherto unknown in literature and are difficult to synthesize due to the limited availability of synthetic methodology as well as the regioselectivity for N-7/N-9 isomers. Palladium catalyzed coupling of *N*-acetyl-3-deazaguanosine **17**[35] with dicarbonate **14** gave a complex reaction mixture. Finally, we aimed to prepare a novel *N*,*N*-diphenyl carbamoyl protected 3-dezaguanine base, similarly to the case of purines.[36] This may completely shield the reaction at N-7 position, moreover deprotection can also be effected in mild basic condition (Scheme 3). Reaction of *N*-acetyl-3-deazaguanosine **17** with *N*,*N*-diphenylcarbamoyl chloride gave the 6-(*O*),9-di-*N*,*N*-diphenyl carbamate protected *N*-acetyl-3-deazaguanosine, which was selectively deprotected to compound **18**. Palladium catalyzed coupling of base **18** with dicarbonate **14** proceeded smoothly to give exclusively N-9 product **19** as a white solid in good yield. All the protecting groups were removed with heating compound **19** using NH_3/MeOH in steel reaction vessel at 80 °C to obtain 3-deazacarbovir **1** in good yield, which was recrystallized in methanol/acetonitrile. It is worthwhile to mention that during deprotection increasing temperature >100 °C leads to the epimerization at C-1 in ~7–10% (by ^{1}H NMR) (Scheme 3).

The nucleosides obtained were characterized by spectroscopic methods, and the structure of 3-deazacarbovir **1** was further confirmed by a single-crystal X-ray diffraction study, and the ORTEP diagram[37] is shown in Figure 2 with their corresponding atomic numbering. The crystal structural studies show a planar conformation of cyclopentene ring with anti-base disposition.

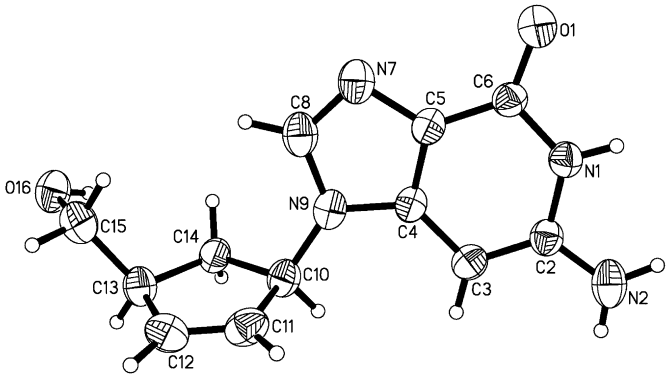


Figure 2. ORTEP diagram showing displacement ellipsoid plot (30% probability) of the X-ray crystal structure of compound **1**.

3. Conclusion

We have described the hitherto unknown synthesis of 3-deazacabovir **1** and 2′,3′-didehydro-2′,3′-dideoxy-3-deaza-adenosine analogs **2** and **3**. Exploration of palladium catalyzed coupling for 6-*N*,*N*-doboc protected bases **9**, **11** and 6-*N*,*N*-diphenylcarbamoyl 3-deazaguanosine **18**, with dicarbonate **14** was found to be highly regioselective. These bases can be explored further for the regioselective synthesis of various other carbocyclic as well as ribose-3-deazaguanosine analogs. Carbocyclic nucleosides **1**–**3** were tested for anti-HIV activity in human peripheral blood mononuclear (PBM) cells infected with HIV-1. Cytotoxicity was tested in three cell lines (PBM, CEM, and Vero). Unfortunately, all the compounds did not show anti-HIV-1 activity as well as cytotoxicity up to 100 μM.

4. Experimental

4.1. Materials and methods

NMR spectra were recorded on Varian Inova 500 MHz with tetramethylsilane as the internal standard. Chemical shifts (δ) are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or bs (broad singlet). Optical rotations were measured by a Jasco DIP-370 digital polarimeter. High-resolution mass spectra (HRMS) were recorded on a Micromass Autospec high-resolution mass spectrometer using electrospray ionization (ESI) in positive mode. Microanalyses have been performed at Atlantic microanalysis labs, Atlanta. Melting points were taken on Mel-Temp II melting point apparatus and were uncorrected. TLC was performed on 0.25 mm silica gel. Purifications were carried out using flash silica gel (60 Å, 32–63 mm) or C_{18} reversed silica gel (230–400 mesh).

*4.1.1. 6-(tert-Butoxymethyl)-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl benzoate (**5**).* To a solution of alcohol **4** (2.75 g, 11.18 mmol) in pyridine (10 mL) at 0 °C was added benzoyl chloride (2.0 mL, 17 mmol) dropwise and the reaction mixture was stirred at room temperature for 4 h. Reaction mixture was quenched by adding ice, and extracted by EtOAc, washed with aq $NaHCO_3$ (2×10 mL), followed by satd NH_4Cl soln The solvent was removed under reduced pressure and the residue purified by column chromatography (EtOAc/hexanes, 20:1) to afford compound **3** (3.5 g, 90%) as viscous oil: $[\alpha]^{25}_D$ −52.38 (c 1.60, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 5.24 (m, 1H), 4.80 (t, *J*=5.5, 8.5 Hz, 1H), 4.54 (d, *J*=5.5 Hz, 1H), 3.42 (dd, *J*=4.5, 8.5 Hz, 1H), 3.34 (dd, *J*=4.5, 8.5 Hz, 1H), 2.48 (m, 1H), 2.32 (m, 1H), 2.02 (m, 1H), 1.44 (s, 3H), 1.34 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 132.7, 130.4, 129.7, 128.2, 111.0, 83.6, 79.0, 74.7, 2.8, 63.0, 41.8, 32.1, 27.4, 26.3, 24.8. HRMS (ESI) calcd $[M+H]^+$ ($C_{20}H_{29}O_5$): 349.2015, found 349.2016.

*4.1.2. (1S,2R,3R,4R)-4-(tert-butoxymethyl)-2,3-dihydroxycyclopentyl benzoate (**6**).* To a solution of compound **5** (3.15 g, 9.04 mmol) in MeOH and conc HCl (100 mL, conc HCl/MeOH 1:70, v/v) was stirred at room temperature for 3 h. The reaction mixture was cooled using ice bath, neutralized with solid $NaHCO_3$, and filtered. The filtrate was concentrated to dryness, and the residue was purified by column chromatography (EtOAc/hexanes, 1:4) to afford **6** as well as 2-benzoyl migrated compound (7–10% by ^{1}H NMR) (1.9 g, 68%) as

syrup: ^{1}H NMR (500 MHz, CD_3OD) δ 8.12 (m, 2H), 7.62 (m, 1H), 7.5 (m, 2H), 5.24 (m, 1H), 4.20 (m, 1H), 3.95 (m, 1H), 3.50 (m, 2H), 2.37 (m, 1H), 2.18 (m, 1H), 1.99 (m, 1H), 1.23 (s, 9H). ^{13}C NMR (125 MHz, CD_3OD) δ 166.4, 132.7, 130.2, 129.3, 128.0, 74.9, 73.1, 72.9, 72.4, 62.5, 43.4, 30.2, 26.4. HRMS (ESI) calcd $[M+H]^+$ ($C_{17}H_{25}O_5$): 309.1702, found 309.1690.

*4.1.3. (1S,4S)-4-(tert-butoxymethyl)cyclopent-2-enyl benzoate (**7**).* A suspension of compound **6** (1.0 g, 5.48 mmol) and pyridinium *p*-toluenesulfonate (1.2 g, 6.0 mmol) in trimethyl orthoformate (12 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered, concentrated to dryness. The residue, after being co-evaporated with toluene (2×10 mL) treated with acetic anhydride (15 mL). The reaction mixture was heated at 120–130 °C for 8 h, after completion of reaction (monitored by TLC), it was concentrated under reduced pressure to dryness. The residue was purified by column chromatography (EtOAc/hexane, 1:50) to afford compound **7** as oil (0.48 g, 53.9%): $[\alpha]^{25}_D$ −215.0 (c 0.316, CH_2Cl_2) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.53 (m, 1H), 7.43 (m, 2H), 6.15 (m, 1H), 5.97 (m, 1H), 5.94 (m, 1H), 3.3 (d, *J*=7.0 Hz, 2H), 3.14 (m, 1H), 2.02–2.16 (m, 2H), 1.19 (S, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 140.0, 132.7, 130.6, 130.1, 129.5, 128.2, 80.6, 72.7, 65.5, 45.7, 34.3, 27.5. HRMS (ESI) calcd $[M+H]^+$ ($C_{17}H_{23}O_3$): 275.1647, found 275.1643.

*4.1.4. (1S,4S)-4-(tert-butoxymethyl)cyclopent-2-enol (**8**).* To a solution of (1*S*,4*S*)-4-(tert-butoxymethyl)cyclopent-2-enyl benzoate (**7**) (0.4 g, 1.45 mmol) in MeOH/THF/H_2O (5:3:2) was added $LiOH\cdot H_2O$ (0.1 g, 2.1 mmol) The reaction mixture was stirred at room temperature for 1.5 h, after completion of reaction, solvent was evaporated under reduced pressure and crude was extracted with EtOAc and washed with brine (2×10 mL). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the crude was purified by column chromatography (EtOAc/hexane, 1:5) to get the desired compound **8** as syrup (0.18 g, 73%): $[\alpha]^{25}_D$ −219.25 (c 0.234, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (m, 1H), 5.88 (m, 1H), 4.88 (m, 1H), 3.22 (m, 2H), 3.06 (m, 1H), 1.92 (m, 1H), 1.86 (m, 1H), 1.36 (bs, 1H, OH), 1.16 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 133.9, 77.1, 72.6, 65.8, 45.4, 37.6, 27.5. HRMS (ESI) calcd $[2M+H]^+$ ($C_{20}H_{38}O_4$) 341.2692, found 341.2838.

*4.1.5. (1S,4S)-4-N,N-Di tert butyl carbonyl-1-(4-(tert-butoxymethyl)-cyclopent-2-enyl)-1H-imidazo[4,5-c] pyridine (**10**).* To a solution of compound **8** (0.17 g, 1 mmol), diboc protected base **9**[33] (0.5 g, 1.5 mmol) and PPh_3 (0.78 g, 3.0 mmol) in THF was added DIAD (0.58 mL, 3.0 mmol) dropwise at 0 °C under inert condition. Reaction mixture was stirred at room temperature for 4–5 h, then concentrated and purified by column chromatography (EtOAc/hexane, 1:5) to afford compound **10** as light yellow oil (contaminated with DIAD by product): UV (MeOH), λ_{max}=278.0, 250. nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J*=6.0 Hz), 8.30 (s, 1H), 7.69 (d, *J*=6.0 Hz, 1H), 6.20 (m, 1H), 5.8 (m, 1H), 5.58 (m, 1H), 3.41 (d, *J*=5.0, 9.0 Hz, 1H), 3.33 (d, *J*=5.0, 9.0 Hz, 1H), 3.04 (m, 1H), 2.77 (m, 1H), 1.70 (m, 1H), 1.38 (s, 9H), 1.35 (s, 9H), 1.13 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 150.8, 150.6, 145.3, 140.3, 140.1, 136.7, 128.5, 127.2, 115.5, 83.5, 83.4, 72.9, 63.7, 61.7, 46.2, 35.8, 27.9, 27.5, 27.4. HRMS (ESI) calcd $[M+H]^+$ ($C_{26}H_{39}N_4O_5$): 487.2920, found 487.2927.

*4.1.6. ((1S,4S)-4-(4-amino-1H-imidazo[4,5-c]pyridin-1-yl)cyclopent-2-enyl)methanol (**2**).* To a solution of crude compound **10** in DCM was added TFA (0.7 mL, excess) and reaction mixture stirred at room temperature for 5 h. After complete consumption of starting material, solvent was evaporated under reduced pressure and dried under high vacuum to get the crude as foam. Crude was dissolved in methanol and neutralized with solid $NaHCO_3$ and purified by column chromatography (methanol/DCM/NH_4OH, 1:8.9:0.1) to get the compound **8** as white solid (80 mg, 34.7% over 2 steps): mp 206 °C. $[\alpha]^{24}_D$ −10.28 (*c*=0.35, MeOH). UV (pH 2.0) λ_{max}=264 (ε=35 600), (pH 7.4) λ_{max}=265 (ε=28 700), (pH 11) λ_{max}=266 (ε=31 000); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.69 (d, 1H, *J*=6.0 Hz), 6.90 (d, 1H, *J*=6.0 Hz), 6.20 (m, 1H), 6.15 (s, 2H, NH_2) 5.98 (m, 1H), 5.60 (m, 1H), 4.79 (t, 1H, *J*=5.0 Hz, OH), 3.48 (m, 2H), 2.91 (bs, 1H), 2.69–2.63 (m, 1H), 1.67–1.62 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6), 153.8, 141.8, 141.6, 139.8, 139.2, 131.4, 128.6, 99.1, 65.3, 62.8, 56.5, 49.3, 35.6. Anal. Calcd for $C_{12}H_{14}N_4O$ 0.15H_2O: C, 61.88; H, 6.01; N, 24.06. Found: C, 61.82; H, 6.06; N, 24.07.

*4.1.7. ((1S,4S)-(4-(4-(N,N′-Di-tert-butyloxycarbonyl)-amino-1H-imidazo[4,5-c]pyridin-1-yl)) cyclopent-2-enyl)methyl ethyl carbonate (**15**).* A solution of compound **9** (0.26 g, 0.775 mmol) and tetrakis (triphenylphosphine) palladium (0) (115 mg, 10 mol %) in 5 mL DMSO was degassed and stirred at room temperature for 5 min under nitrogen atmosphere. A solution of dicarbonate **14** (0.2 g, 0.775 mmol) in 5 mL THF was added dropwise and reaction mixture continued stirring for 1 h (color turns light yellow to orange color). It was quenched with water, extracted with EtOAc, washed with water, dried (Na_2SO_4) and concentrated. The crude was purified by column chromatography (EtOAc/hexane, 1:1) to afford the compound **15** as yellow syrup (337 mg; contaminated with 5–7% PPh_3O by ^{1}H NMR): UV (MeOH), λ_{max}=265 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, 1H, *J*=5.5 Hz), 8.00 (s, 1H), 7.45 (d, 1H, *J*=5.5 Hz), 6.21 (m, 1H), 5.99 (m, 1H), 5.54 (m, 1H), 4.29 (dd, 1H, *J*=5.5 Hz, 11.0 Hz), 4.20 (m, 3H, OCH+$OCOCH_2$), 3.23 (m, 1H), 2.85 (m, 1H), 1.86 (m, 1H), 1.43 (s, 18H), 1.32 (t, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 151.4, 150.0, 144.5, 143.0, 140.6, 139.9, 130.5, 106.5, 82.8, 69.0, 64.3, 61.9, 44.6, 34.2, 27.9, 14.2. HRMS (ESI) calcd $[M+H]^+$ ($C_{25}H_{35}ClN_4O_7$): 503.2506, found 503.2505.

*4.1.8. ((1S,4S)-4-(4-amino-1H-imidazo[4,5-c]pyridin-1-yl)cyclopent-2-enyl)methanol (**2**).* To a solution of **15** in DCM was added TFA (0.7 mL, excess) and reaction mixture stirred at room temperature for 5 h. After complete consumption of starting material, solvent was evaporated under reduced pressure and dried under high vacuum to get the crude as foam, which was dissolved in 10 mL methanol and added 0.2 mL of 10% aq K_2CO_3 and stirred for 1 h. Solvent was evaporated under reduced pressure and purified by column chromatography (methanol/DCM/NH_4OH, 1:8.9:0.1) to get the compound **2** as white solid. 80 mg (45% over 2 steps).

*4.1.9. ((1S,4S)-(4-(4-(N,N′-Di-tert-butyloxycarbonyl)-amino-6-chloro-1H-imidazo[4,5-c]pyridin-1-yl))cyclopent-2-enyl)methyl ethyl carbonate (**16**)*

*4.1.9.1. Experimental procedure same as for compound **15**.* White foam, 70.8%: $[\alpha]_D^{23}$ −19.67 (*c*=0.7, DCM). UV (MeOH), λ_{max}=278.0 nm, 262.0 nm (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.44 (s, 1H), 6.24 (m, 1H), 5.98 (m, 1H), 5.48 (m, 1H), 4.30 (dd, 1H, *J*=4.5 Hz, 5.5 Hz), 4.20 (m, 3H), 3.23 (bs, 1H), 2.81–2.88 (m, 1H), 1.82–1.88 (m, 1H), 1.43 (s, 9H), 1.31 (t, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 150.9, 144.1, 143.0, 141.7, 141.3, 137.9, 136.7, 130.0, 106.0, 83.2, 68.7, 64.3, 62.0, 44.6, 34.2, 27.9, 14.2. HRMS (ESI) calcd $[M+H]^+$ ($C_{25}H_{34}ClN_4O_7$): 537.2116, found 537.2123.

*4.1.10. ((1S,4S)-(4-(4-amino-6-chloro-1H-imidazo[4,5-c]pyridin-1-yl)cyclopent-2-enyl)) methanol (**3**)*

*4.1.10.1. Experimental procedure same as for compound **2** in 4.1.8.* White solid (81.8%), mp 190 °C: $[\alpha]^{24}_D$ −7.058 (*c*=0.19, MeOH): UV (pH 2.0) λ_{max}=286 (s), 269 (ε=18 600) (pH 7.4) λ_{max}=270 (ε=23 800), (pH 11) λ_{max}=271 (ε=23 200); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04 (s, 1H), 6.92 (s, 1H), 6.68 (s, 2H, NH_2),

6.16 (m, 1H), 5.94 (m, 1H), 5.56 (m, 1H), 4.80 (bs, 1H, OH), 3.49 (m, 2H, OCH_2), 2.90 (bs, 1H), 2.65 (m, 1H), 1.65 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 145.0, 142.6, 141.3, 141.0, 139.8, 138.7, 129.3, 95.9, 63.9, 61.7, 47.9, 33.9. Anal. Calcd for $C_{12}H_{14}N_4ClO$: C, 54.45; H, 4.95; N, 21.17. Found: C, 54.67; H, 4.95; N, 20.88.

*4.1.11. 6-Acetamido-1H-imidazo[4,5-c]pyridin-4-yl diphenylcarbamate (**18**).* Diphenyl carbamoyl chloride (1.72 g, 7.41 mmol) was added to a suspension of compound **17**[35] (570 mg, 2.96 mmol) in diisopropyl amine (1.03 mL, 5.92 mmol) and anhydrous pyridine (5 mL) and stirring was continued at room temperature for 1 h. The reaction was quenched with water and stirring was continued for 10 min and the volatiles were evaporated under reduced pressure. The residue was purified by column chromatography using 50% EtOAc/hexane to get 6-(*O*),9-di-*N*,*N*-diphenyl carbamate protected *N*-acetyl-3-deazaguanosine in 85% yield. ^1H NMR (500 MHz, DMSO-d_6): δ 10.72 (s, 1H, NH), 8.53 (s, 1H), 8.03 (s, 1H), 7.32–7.45 (m, 20H), 2.11 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): 167.5, 151.6, 150.0, 149.5, 146.9, 146.5, 144.2, 142.7, 142.6, 136.6, 130.2, 129.8, 128.0, 127.4, 127.3, 124.3, 97.1, 24.3. HRMS (ESI) calcd $[M+H]^+$ ($C_{34}H_{27}N_6O_4$): 583.2094, found 583.2073.

To a solution of di-*N*,*N*-diphenylcarbamoyl protected compound (600 mg, 1.03 mmol) in methanol and potassium carbonate (213 mg, 1.54 mmol) was added and the reaction was stirred at room temperature for 45 min. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (MeOH–CH_2Cl_2, 1:25) to afford compound **18** as light brown solid (0.31 g, 78%): ^1H NMR (500 MHz, DMSO-d_6): δ 12.93 (s, 1H, NH), 10.60 (s, 1H, NH), 8.38 (s, 1H), 8.25 (s, 1H), 7.37–7.52 (m, 10H), 2.14 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): 169.3, 152.0, 150.0, 146.8, 144.4, 144.3, 143.7, 142.4, 129.7, 128.4, 127.3, 95.1, 24.27. HRMS (ESI) calcd $[M+H]^+$ ($C_{21}H_{18}N_5O_3$): 388.1410, found 388.1396.

*4.1.12. 6-Acetamido-1-(4-((ethoxycarbonyloxy)methyl)cyclopent-2-enyl)-1H-imidazo[4,5-c]pyridin-4-yl diphenylcarbamate (**19**).* A solution of **18** (0.31 g, 0.8 mmol) and tetrakis (triphenylphosphine) palladium (0) (92 mg, 10 mol %) in 5 mL DMSO was degassed and stirred at room temperature for 5 min under nitrogen atmosphere. A solution of dicarbonate **14** (0.21 g, 0.8 mmol) in 5 mL THF was added dropwise and reaction mixture continued stirring for 2 h (color turns light yellow to orange color). It was quenched with water, extracted with EtOAc, washed with water, dried (Na_2SO_4) and concentrated. The crude was purified over flash silica gel (EtOAc/hexane, 2:3) to afford the compound, which was recrystallized with EtOAc/hexane to get the compound **19** as white solid. (330 mg, 64.8%), mp 192 °C: $[\alpha]^{26}_D$ −58.12 (c=0.31, MeOH), UV (MeOH), λ_{max}=269 nm. ^1H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.96 (s, 1H), 7.92 (s, 1H, NH), 7.46 (m, 4H), 7.36 (m, 4H), 7.22 (m, 2H), 6.23 (m, 1H), 5.98 (m, 1H), 5.51 (m, 1H), 4.17–4.24 (m, 4H, 2×OCH_2), 3.22 (bs, 1H), 2.89 (m, 1H), 2.18 (s, 3H), 1.71 (m, 1H), 1.30 (t, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 155.0, 151.9, 150.0, 147.5, 143.4, 142.8, 142.2, 137.6, 135.0, 132.1, 132.0, 131.9, 130.1, 129.4, 129.0, 128.5, 128.4, 128.0, 93.6, 69.3, 64.2, 61.3, 44.6, 34.7, 24.6, 14.2. HRMS (ESI) calcd $[M+H]^+$ ($C_{30}H_{30}N_5O_6$): 556.2196, found 556.2195.

*4.1.13. 6-Amino-1-(4-(hydroxymethyl)cyclopent-2-enyl)-1H-imidazo[4,5-c]pyridin-4(5H)-one (**1**).* To a solution of compound **19** (255 mg) in methanol was passed NH_3 (g) at −30 °C for 1 h in steel bomb. Sealed reaction vessel was then heated at 80 °C for 24 h. Solvent was evaporated and the crude solid was purified over amine functionalized silica gel (MeOH/DCM, 1:10). Compound **1** was further recrystallized with MeOH/acetonitrile to get the compound as transparent crystals. (95 mg, 84.8%), mp >260 °C: $[\alpha]_D^{23}$ −10.39 (c=0.41, MeOH). UV (pH 2.0) λ_{max}=313 (ε=28 700), 280 (ε=56 400), (pH 7.4) λ_{max}=299 (s, ε=32 000), 269 (ε=45 600), (pH 11) λ_{max}=303 (s), 271 (ε=55 800). ^1H NMR (CD_3OD) δ 7.75 (s, 1H), 6.23 (m, 1H, olefin-H), 5.99 (m, 1H, olefin-H), 5.76 (s, 1H), 5.41 (m, 1H), 3.64 (m, 2H), 3.03 (m, 1H), 2.76 (m, 1H), 1.72 (m, 1H). ^{13}C NMR (CD_3OD) δ 157.6, 147.4, 143.2, 138.4, 138.0, 129.5, 122.9, 72.7, 64.1, 61.5, 53.2, 33.8. Anal. Calcd for $C_{12}H_{14}N_4O_2$; C, 58.53; H, 5.73; N, 22.75. Found: C, 58.43; H, 5.76; N, 22.68.

4.2. X-ray data for compound 1

*4.2.1. Crystal data of **1**.* $C_{12}H_{14}N_4O_2$, M=246.27, monoclinic, space group P2, a=9.127(2), b=11.812(2), c=11.642(2) Å, β=106.37(3)°, V=1204.2(4) Å^3, T=293 K, Z=2, R1=0.0465 for 1610 Fo>4sig(Fo) and 0.0591 for all 1707 data. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 737517. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK; E-mail: deposit@ccdc.cam.ac.uk].

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Supplementary data

The supplementary data associated with this article can be found in the on-line version, at doi:10.1016/j.tet.2009.08.087.

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