Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 16 (2008) 5424–5433
Bioorganic & Medicinal Chemistry

Synthesis of 5′-functionalized nucleosides: *S*-Adenosylhomocysteine analogues with the carbon-5′ and sulfur atoms replaced by a vinyl or halovinyl unit

Stanislaw F. Wnuk,[a,*] Pablo R. Sacasa,[a] Elzbieta Lewandowska,[a,†] Daniela Andrei,[a] Sumin Cai[b] and Ronald T. Borchardt[b]

[a]*Department of Chemistry and Biochemistry, Florida International University, Miami, FL 33199, USA*
[b]*Departments of Molecular Biosciences and Pharmaceutical Chemistry, The University of Kansas, Lawrence, KS 66047, USA*

Received 28 December 2007; revised 5 April 2008; accepted 9 April 2008
Available online 12 April 2008

Abstract—Adenosine and uridine analogues functionalized with alkenyl or fluoroalkenyl chain at C5′ were prepared employing cross-metathesis, Negishi couplings, and Wittig reactions. Metathesis of the protected 5′-deoxy-5′-methyleneadenosine or uridine analogues with six-carbon amino acids (homoallylglycines) in the presence of Grubbs catalysts gave nucleoside analogues with the C5′–C6′ double bond. Alternatively, the Pd-catalyzed cross-coupling between the protected 5′-deoxy-5′-(iodomethylene) nucleosides and suitable alkylzinc bromides also provided analogues with alkenyl unit. Stereoselective Pd-catalyzed monoalkylation of 5′-(bromofluoromethylene)-5′-deoxyadenosine with alkylzinc bromides afforded adenosylhomocysteine analogues with a 6′-(fluoro)vinyl motif. The vinylic adenine nucleosides produced time-dependent inactivation of the *S*-adenosyl-L-homocysteine hydrolases.

1. Introduction

The enzyme *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase (EC 3.3.1.1) effects the hydrolytic cleavage of AdoHcy to adenosine (Ado) and L-homocysteine (Hcy).[1] The cellular levels of AdoHcy and Hcy are critical since AdoHcy is a potent feedback inhibitor of crucial methylation enzymes,[1,2] and elevated plasma levels of Hcy in humans have been shown to be a risk factor in coronary artery disease.[3] Therefore, the design of inhibitors of AdoHcy hydrolase provides a rational approach to mechanism-based chemotherapy of cancer and viral diseases.[1,2] Several inhibitors which function as substrates for the '3′-oxidative activity' of AdoHcy hydrolase and converts the enzyme from its active form (NAD^+) to its inactive form (NADH) have been prepared.[1] Inhibitors which function as substrates for the '5′/6′-hydrolytic activity' include the vinyl fluorides [9-(5-deoxy-5-fluoro-β-D-*erythro*-pent-4-enofuranosyl)adenine],[4] 5′-deoxy-5′-(halomethylene)adenosine,[5] 5′-(bromofluoromethylene)-5′-deoxyadenosine (i.e., **A**; Fig. 1),[6] 5′-*S*-allenyl(or propynyl)-5′-thioadenosine analogues,[7a] and 6-fluoroneplanocin,[7b] among others.[1c,7]

Addition of an enzyme-sequestered water molecule across the 5′,6′-double bond of **A** followed by the loss of bromide was proposed to generate the homoAdo 6′-carboxyl fluoride **B** at the active site of AdoHcy hydrolase.[6b] The nucleophilic attack by proximal amino acid functionalities caused the covalent binding inhibition of type **C**. Addition of water across the 5′,6′-triple bond of haloacetylenes was postulated to generate similar reactive electrophiles at the enzyme active site.[8]

The X-ray crystallographic analysis of the human AdoHcy hydrolase inactivated with 9-(dihydroxycyclopentene)-adenine,[9a] and neplanocin A,[9b] as well as AdoHcy hydrolase from rat liver[9c] established the presence of a water molecule in the active site of the enzyme. This made it a priority to prepare analogues of AdoHcy that closely resemble the natural substrate that bind tightly to the enzyme. Such compounds should form 'stable' complexes with the enzyme that would help to identify

Keywords: *S*-Adenosylhomocysteine hydrolase; Cross-coupling; Cross-metathesis; Nucleosides; Wittig reaction.
* Corresponding author. Tel.: +1 305 348 6195; fax: +1 305 348 3772; e-mail: wnuk@fiu.edu
† Faculty on leave from the Department of Chemistry, University of Agriculture, Poznan, Poland.

0968-0896/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2008.04.017

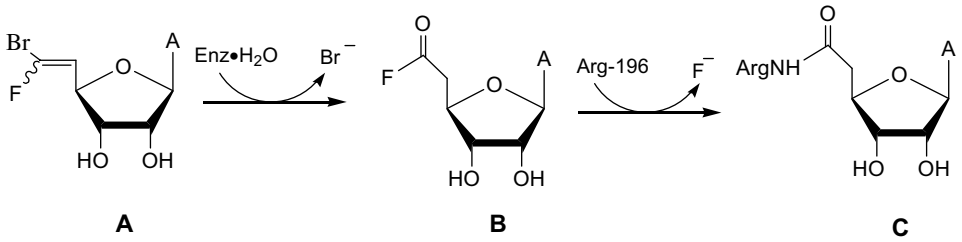


Figure 1. Generation of active intermediates from the (bromofluoro)vinyl analogue **A** by the 'hydrolytic activity' of AdoHcy hydrolase.[6b]

the key binding groups at the active site of the enzyme that interact with the Hcy moiety and participate in the subsequent elimination and 'hydrolytic' activity steps. We now describe syntheses of the adenosine and uridine[10] nucleosides modified with alkenyl or haloalkenyl chain at C5′. Adenosine analogues with the 5′,6′-vinyl **D** or halovinyl **E** motif incorporated in place of the carbon-5′ and sulfur atoms (Fig. 2) are expected to be the substrates for the 'oxidative' and/or 'hydrolytic' activity of AdoHcy hydrolase. Enzyme-mediated addition of water to **E** (X = F, Z = H or NH_2) might occur at C5′ or C6′. This would generate a new species bearing hydroxyl or keto (after β-elimination of HF) binding sites within the enzyme.

2. Chemistry

The retrosynthetic analysis indicated that AdoHcy analogue **D** can be targeted by the construction of new C5′–C6′ double bond via either a Wittig reaction employing adenosine 5′-aldehyde **H** or cross-metathesis reaction utilizing 5′-deoxy-5′-methyleneadenosine **I** as nucleoside precursors (Fig. 3). The subsequent bromination–dehydrobromination of **D** might afford bromovinyl analogue **E** (X = Br). It is also possible to use Pd-catalyzed cross-coupling approaches to form a new C6′–C7′ bond in a key step. For example, the alkylation of 5′-deoxy-5′-(iodomethylene)adenosine **G** with the suitable alkylzinc bromides should produce **D**. Alternatively, the selective monoalkylation of 5′-deoxy-5′-(dihalomethylene)adenosine **F** should afford **E** directly. Coupling approaches were tested on model compounds[11] and the reactions were performed on the pyrimidine[10] and purine nucleosides to generalize the synthetic approaches.

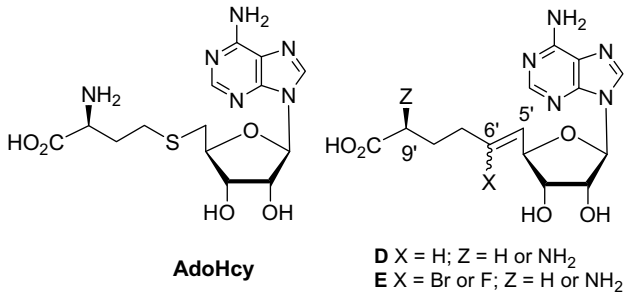


Figure 2. *S*-Adenosyl-L-homocysteine (AdoHcy) and analogues with the carbon-5′ and sulfur atoms replaced by a vinyl or halovinyl unit.

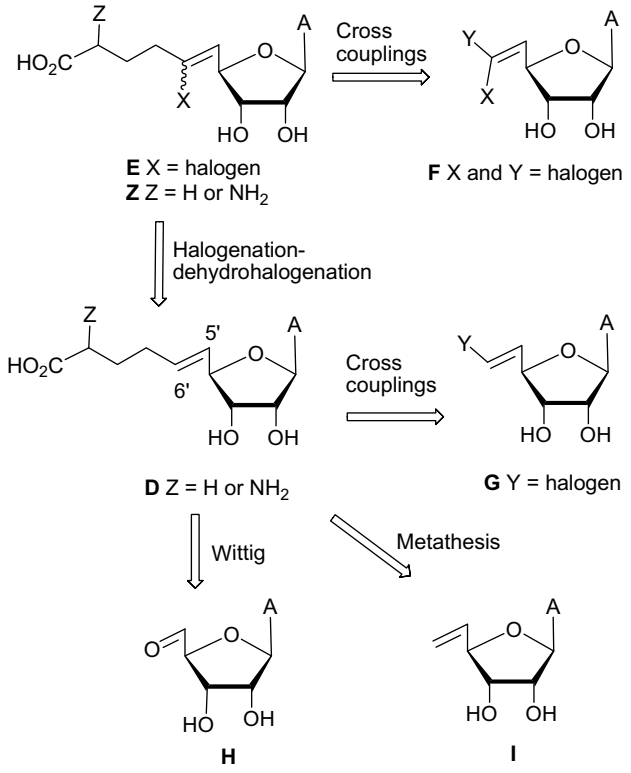
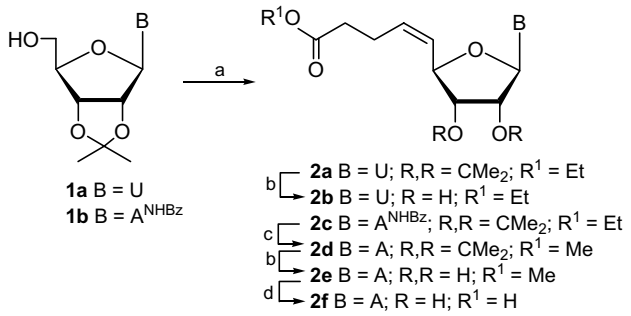


Figure 3. Retrosynthetic analysis for AdoHcy analogues with the carbon-5′ and sulfur atoms replaced by a vinyl or halovinyl unit.

Moffatt oxidation[12] of 2′,3′-*O*-isopropylideneuridine **1a** and treatment of the crude 5′-aldehyde with Wittig reagent, generated from the commercially available $EtO_2C(CH_2)_3PPh_3{\cdot}Br$ with lithium bis(trimethylsilyl)amide (LHMDS), gave ethyl 4(*Z*)-(5′-deoxy-2′,3′-*O*-isopropylideneuridin-5′-ylidene)butanoate **2a** in 16% yield. Deprotections [trifluoroacetic acid (TFA)/H_2O] of **2a** yielded **2b** (Scheme 1). The vicinal coupling constant (**2b**; $J_{5'-6'} = 9.8$ Hz) was diagnostic for the *Z* stereochemistry, as expected for the Wittig product derived from the non-stabilized ylide.[13] Analogous Wittig-treatment of 6-*N*-benzoyl-2′,3′-*O*-isopropylideneadenosine **1b** gave **2c**. Treatment of crude **2c** with NH_3/MeOH removed the benzoyl group and converted the ethyl ester into a methyl ester **2d** (18% from **1b**). Deacetonization of **2d** and saponification of the resulting **2e** afforded **2f**; a nine-carbon analogue of AdoHcy with the vinyl unit between C5′ and C6′. The low yields and notorious instability of 5′-aldehydes[14] toward the experimental conditions, that is required for the genera-



Scheme 1. Reagents: (a) i—DCC/DMSO/Cl_2CHCO_2H; ii—$EtO_2C(CH_2)_3PPh_3Br$/LHMDS/THF; (b) TFA/H_2O; (c) NH_3/MeOH; (d) NaOH/H_2O/MeOH.

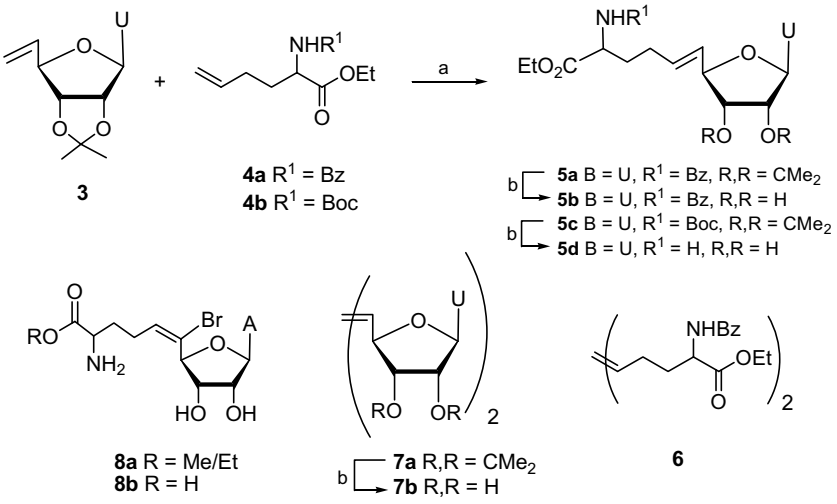
tion of non-stabilized Wittig reagents, prompted us to examine the metathesis approach for the synthesis of **D**.

In order to explore the metathesis route,[15,16] ethyl 2-amino-5-hexenoate (homoallylglycine) bearing a terminal double bond was prepared by the alkylation of glycine with 4-bromo-1-butene followed by protection of the α-amino group with benzoyl or Boc group to give racemic **4a** or **4b**, respectively.[17] Cross-metathesis between 2′,3′-*O*-isopropylidene-5′-deoxy-5′-methyleneuridine[18] **3** with **4a** in a CH_2Cl_2 solution containing 2nd generation (2-imidazolidinylidene-Ru) Grubbs catalyst[15] gave the desired product **5a** (72%) in addition to two dimers **7a** (5%) and **6** (7%) resulting from the self-metathesis of nucleoside[16,19] **3** and amino acid[17,20] **4b** substrates, respectively (Scheme 2). Deacetonization of **5a** and HPLC purification yielded **5b** (66%) as 5′*E* isomers ($J_{5'-6'} = 15.3$ Hz) of a 1:1 mixture of 9′*R*/*S* diastereomers. The ratio of diastereomers was determined based on the NMR spectra where a double set of peaks for several protons (^1H) and carbons (^{13}C) of similar intensities were observed. Analogous metathesis of **3** and **4b** gave **5c** as the sole product (74%). Aqueous TFA effected concomitant removal of Boc and isopropylidene protection groups to produce **5d**; a uracil analogue of AdoHcy with the amino group at C9′ and the carboxylic group at C10′.[21]

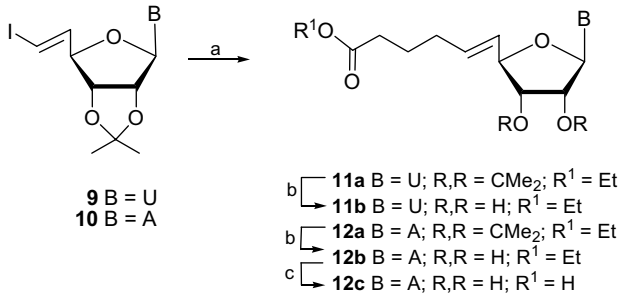
As previously reported, metathesis of 6-*N*,*N*-dibenzoyl-2′,3′-*O*-isopropylidene-5′-deoxy-5′-methyleneadenosine with **4b** in the presence of Hoveyda-Grubb's catalyst (*o*-isopropoxy-phenylmethylene-Ru) gave the protected AdoHcy analogue **D** (Z = NH_2) in 76% yield.[17,22] However, the treatment of the latter with pyridinium tribromide followed by the dehydrobromination with DBU yielded 5′-(bromo)vinyl AdoHcy analogue as a single isomer, which was deprotected to ester **8a** and acid **8b**.[17] Consequently, in order to prepare 6′-(halo)vinyl analogues **E**, we turned our attention to the Pd-catalyzed selective monoalkylation of 5′-deoxy-5′-(dihalomethylene)nucleoside precursors.

Although Pd-catalyzed cross-coupling reactions are powerful methods for the formation of carbon–carbon bonds under conditions that are compatible with a broad range of functional groups,[23a] couplings involving $C_{sp}3$ centers[23b] are less explored with the exception of couplings between $C_{sp}2$ as electrophiles and $C_{sp}3$ as nucleophiles.[23a,24] Therefore among other approaches,[25,26] we began with exploring Negishi coupling.[24] Treatment of the protected 5′-deoxy-5′-(iodomethylene)adenosine[5a] (*E*)-**10** with commercially available $EtO_2C(CH_2)_3ZnBr$ produced ethyl 5-(5′-deoxy-2′,3′-*O*-isopropylideneadenosin-5′-ylidene)pentanoate **12a** (68%) as a single *E* isomer ($J_{6'-5'} = 15.4$ Hz; Scheme 3). Deacetonization of **12a** with TFA/H_2O afforded ester **12b** (61%) and the subsequent saponification gave **12c** with a six-atom alkenyl chain attached to the furanosyl C4′ and the carboxylic group at C10′ as in AdoHcy. Subjection of the 5′-deoxy-5′-(iodomethylene)uridine[18] (*E*)-**9** to the analogous Negishi coupling and deacetonization of the resulting **11a** afforded **11b** (52% overall).

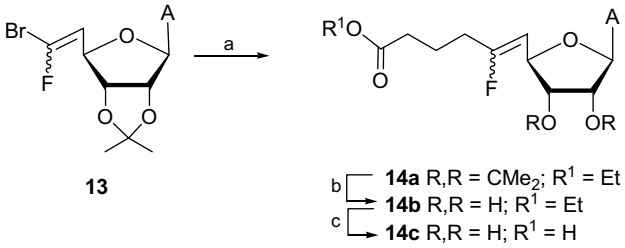
Encouraged by the results on the alkylation of iodo(vinyl) nucleosides **9** and **10** with alkylzinc bromides, we have explored a selective monoalkylation of dihalo(vinyl) nucleoside substrates (e.g., **13**), although the mono cross-coupling reactions of 1,1-dihalovinyl electrophiles with $C_{sp}3$ nucleophiles are very scarce.[24c,27] We recently



Scheme 2. Reagents and condition: (a) 2nd generation Grubbs catalyst/CH_2Cl_2/Δ; (b) TFA/H_2O.



Scheme 3. Reagents and condition: (a) $EtO_2C(CH_2)_3ZnBr/Pd_2(dba)_3$/benzene/Δ; (b) TFA/$H_2O$; (c) NaOH/$H_2O$.



Scheme 4. Reagents and condition: (a) $EtO_2C(CH_2)_3ZnBr/Pd(PPh_3)_4$/benzene/Δ; (b) TFA/$H_2O$; (c) NaOH/$H_2O$.

developed Pd-catalyzed Negishi coupling of 1-fluoro-1-(iodo, or bromo, or chloro)alkenes with alkylzincs, which provided stereoselective access to the internal fluoroalkenes.[11] We were gratified to find that treatment of the protected 5′-(bromofluoromethylene)-5′-deoxyadenosine[6a] **13** (*E*/*Z*, 3:2) with $EtO_2C(CH_2)_3ZnBr/Pd(PPh_3)_4$ produced **14a** (56%) as a mixture[28] of the geometric isomers (*E*/*Z*, 2:3; Scheme 4).[29] Acid-catalyzed deprotection of **14a** gave ester **14b**, and saponification afforded **14c**; a 10-carbon AdoHcy analogue with C5′ and sulfur atoms replaced by 6′-fluoro(vinyl) unit. Attempted monoalkylation of **13** with the zinc salt of enatiomerically pure *N*-Boc-γ-bromohomoalanine-OMe,[30] generated by Knochel's procedure[31] utilizing a Zn/LiCl combination, failed to give 6′-(fluoro)vinyl analogue **E** (X = F, Z = NH_2) bearing amino group at C9′.

3. Interactions with AdoHcy hydrolase

The 5′,6′-vinylic adenine nucleosides were tested against human AdoHcy hydrolase using a protocol involving a 0.5 or a 4 h preincubation with the enzyme followed by a 12 min incubation that measures the residual enzyme activity (Table 1). For esters **2e**, **8a**, **12b**, and **14b** only data for the 0.5 h preincubation are included since these esters are potentially unstable either chemically or enzymatically under the assay conditions. The compounds had similar activity toward the *Trypanosoma cruzi* AdoHcy hydrolase[32] (data not shown). The most active inhibitors were found to be the 9-carbon **2e** and **2f** as well as the 10-carbon **12b** and **12c** vinylic analogues. With a 30 min preincubation, esters **2e** and **12b** were found to be more active than the corresponding acids **2f** and **12c**. The 6′-fluoro vinylic analogues **14b** and **14c** showed a lower activity than the non-halogenated derivatives **12b** and **12c** perhaps in accord with the fact that 5′-deoxy-5′-(fluoromethylene)adenosine showed the lowest enzyme inactivation efficiency among all 5′-halomethylene derivatives.[5b,c] The 5′-(bromo)vinylic analogues **8a** and **8b** with the amino group at C9′ also showed a lower enzyme inhibition. The **2f**, **8b**, **12c**, and **14c** produced similar time-dependent inactivation of the human (Table 1) and *T. cruzi* (data not shown) AdoHcy hydrolases. Since esters **2e** and **12b** are less active than structurally related dienes[33a] (see Table 1, footnote a) and enynes,[33b] and **8a** and **14b** are significantly less active no further enzymatic studies were performed.

Table 1. Inhibition of AdoHcy hydrolase by 5′,6′-vinylic adenosine derivatives

Compound[a]	% of enzyme inhibition[b,c]	
	0.5 h[d]	4 h[d]
2e[e]	68.1	
2f	50.5	95.5
8a[e]	11.4	
8b	14.5	44.6
12b[e]	81	
12c	28.5	92.4
14b[e]	14.1	
14c	15.2	35.2

[a] Dienes, for example, ethyl (*E*/*E*)- and (*Z*/*E*)-4-(5′-deoxyadenosin-5′-ylidene)but-2-enoate caused 96.4% and 98.2% of the enzyme inhibition under nearly identical conditions with 20 min incubation time.[33a]

[b] AdoHcy hydrolase (204 nM) was incubated with the inhibitors (281 μM) at 37 °C for 12 min and the remaining enzyme activity was assayed as described in Section 5.

[c] Data are the average of duplicate determinations.

[d] Preincubation time of the inhibitors with the enzyme.

[e] Esters were not tested with 4 h preincubation time because of the chemical instability in the enzymatic assay.

4. Summary and conclusions

We have developed the synthesis of adenosine and uridine analogues functionalized at C5′ with alkenyl or 6′-fluoroalkenyl unit employing metathesis, coupling, and Wittig reactions. Cross-metathesis of the 5′-deoxy-5′-methyleneadenosine or uridine analogues with homoallylglycines gave a 10-carbon nucleoside analogues with the C5′–C6′ double bond. The Pd-catalyzed selective monoalkylation of the 5′-(bromofluoromethylene)-5′-deoxyadenosine with $EtO_2C(CH_2)_3ZnBr$ afforded AdoHcy analogues with 6′-(fluoro)vinyl unit. The vinylic adenine nucleosides were tested against human and *T. cruzi* AdoHcy hydrolases. The most active inhibitors were found to be 10- and 9-carbon non-halogenated vinylic analogues. The free carboxylic acids derivatives produced time-dependent inactivation of the enzyme.

5. Experimental

UV spectra were measured with solutions in MeOH. ^1H (400 or 600 MHz) and ^{13}C (100 MHz) NMR spectra were determined with solutions in $CDCl_3$ unless other-

wise noted. Mass spectra (MS) were obtained with atmospheric pressure chemical ionization (APCI) technique and HRMS in AP-ESI mode. TLC was performed with Merck kieselgel 60-F_{254} sheets with MeOH/$CHCl_3$ (1:19), EtOAc/hexane (2:1) or EtOAc/*i*-PrOH/H_2O (4:1:2, upper layer; S1) as developing systems and products were detected with 254 nm light. Merck kieselgel 60 (230–400 mesh) was used for column chromatography. HPLC purifications were performed using XTerra® preparative RP_{18} OBD™ column (5 μm 19 × 150 mm) with gradient program using CH_3CN/H_2O as a mobile phase. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN. Reagent grade chemicals were used, and solvents were dried by reflux over and distillation from CaH_2 (except THF/potassium) under argon.

5.1. Ethyl 4(*Z*)-(5′-deoxy-2′,3′-*O*-isopropylideneuridin-5′-ylidene)butanoate (2a). Procedure A

In flask A, Cl_2CHCO_2H (0.62 mL, 97 mg, 0.75 mmol) was added dropwise via syringe to a stirred solution of **1a** (426 mg, 1.5 mmol) and DCC (1.08 g, 5.25 mmol) in DMSO (4 mL) at ambient temperature under N_2. The stirring was continued for an additional 1 h to produce the corresponding aldehyde. In flask B, lithium bis(trimethylsilyl)amide (3.6 mL/1 M THF, 3.6 mmol) was added to a stirred solution of [3-(ethoxycarbonyl)propyl]triphenylphosphonium bromide (823 mg, 1.8 mmol) in anhydrous THF (6 mL) at ambient temperature under N_2 and stirring was continued until the reaction turned red (~2 h). The content of flask A was then transferred to flask B via syringe and the resulting mixture was stirred overnight (TLC analysis showed the formation of a less polar product). Oxalic acid dihydrate (378 mg, 3 mmol) dissolved in MeOH (3 mL) was added and after 20 min the reaction mixture was concentrated (to ~1/3 volume). Dicyclohexylurea was filtered, washed with cold MeOH, and the combined filtrates were evaporated. The residue was partitioned ($CHCl_3/NaHCO_3/H_2O$) and the organic layer was washed (3× H_2O, brine), dried ($MgSO_4$), and was evaporated. Column chromatography of the residue (40 → 60% EtOAc/hexane) gave **2a** (92 mg, 16%); ^{1}H NMR δ 1.23 (t, J = 7.1 Hz, 3, CH_3), 1.32 (s, 3, CH_3), 1.54 (s, 3, CH_3), 2.34–2.48 (m, 2, H7′,7″,8′,8″), 4.11 (q, J = 7.1 Hz, 2, CH_2), 5.14 (dd, J = 4.3, 6.3, Hz, 1, H3′), 4.85 (dd, J = 4.2, 8.5 Hz, 1, H4′), 4.98 (dd, J = 1.8, 6.3 Hz, 1, H2′), 5.51–5.68 (m, 3, H5,5′,6′), 5.81 (d, J = 2.0 Hz, 1, H1′), 7.45 (d, J = 8.1 Hz, 1, H6); MS *m*/*z* 381 (100, MH^+).

5.2. Ethyl 4(*Z*)-(5′-deoxyuridin-5′-ylidene)butanoate (2b). Procedure B

A solution of **2a** (140 mg, 0.37 mmol) in TFA/H_2O (9:1, 5 mL) was stirred at 0 °C (ice bath) for 1 h. The volatiles were evaporated under *vacuum* (<15 °C) and co-evaporated (3×) with toluene. The residue was column chromatographed (1 → 6% MeOH/$CHCl_3$) to give **2b** (48 mg, 38%): UV max 261 nm (ε 8800), min 230 (2200); ^{1}H NMR (MeOH-d_4, 600 MHz) δ 1.27 (t, J = 7.1 Hz, 3, CH_3), 2.41–2.58 (m, 4, H7′,7″,8′,8″), 3.95 (t, J = 5.8 Hz, 1, H3′), 4.15 (q, J = 7.2 Hz, 2, CH_2), 4.22 (dd, J = 3.7, 5.4 Hz, 1, H2′), 4.68 (dd, J = 6.6, 8.2 Hz, 1, H4′), 5.64 ('tt', $J_{5'-4'/6'}$ = 9.8 Hz,$J_{5'-7'/7''}$ = 1.2 Hz, 1, H5′), 5.73–5.78 (m, 2, H5,6′), 5.83 (d, J = 3.6 Hz, 1, H1′), 7.63 (d, J = 8.0 Hz, 1, H6); ^{13}C NMR (MeOH-d_4, 600 MHz) δ 14.52 (CH_3), 24.45 (C7′), 35.08 (C8′), 61.61 (CH_2), 75.31 (C3′), 75.81 (C3′), 80.38 (C4′), 92.17 (C1′), 102.84 (C5), 129.41 (C5′), 134.87 (C6′), 142.57 (C6), 152.55 (C2), 166.21 (C4), 174.66 (C9′); MS *m*/*z* 341 (100, MH^+). Anal. Calcd for $C_{15}H_{20}N_2O_7{\cdot}H_2O$ (358.35): C, 50.28; H, 6.19; N, 7.82. Found: C, 49.91; H, 5.82; N, 7.56.

5.3. Methyl 4(*Z*)-(5′-deoxy-2′,3′-*O*-isopropylideneadenosin-5′-ylidene)butanoate (2d)

Oxidation of **1b**[14] (205 mg, 0.5 mmol) with DMSO (2 mL)/DCC (395 mg, 1.75 mmol)/Cl_2CHCO_2H (0.044 mL, 65 mg, 0.5 mmol) and treatment with Wittig reagent (274 mg, 0.6 mmol) by the procedure A gave **2c** (~90 mg, ~36%; contaminated in ~20%, ^{1}H NMR): MS *m*/*z* 508 (100, MH^+). This material was dissolved in NH_3/MeOH and was stirred overnight at ambient temperature. The volatiles were evaporated in vacuo and the residue was partitioned ($CHCl_3$//H_2O/$NaHCO_3$). The organic layer was washed (brine), dried ($MgSO_4$), evaporated and purified on column chromatography (50 → 70% EtOAc/hexane) to give **2d** (35 mg, 18% from **1b**); ^{1}H NMR δ 1.41 (s, 3, CH_3), 1.64 (s, 3, CH_3), 2.42 (t, J = 6.8 Hz, 2, H8′,8″), 2.47–2.52 (m, 2, H7′,7″), 3.68 (s, 3, CH_3), 4.95 (dd, J = 3.3, 6.1 Hz, 1, H3′), 5.06–5.09 (m, 1, H4′), 5.52–5.68 (m, 3, H2′,5′,6′), 5.81 (br s, 2, NH_2), 6.15 (d, J = 1.9 Hz, 1, H1′), 7.92 (s, 1, H2), 8.37 (s, 1, H8); MS *m*/*z* 390 (100, MH^+). HRMS calcd for $C_{18}H_{24}N_5O_5$ $[M+H]^+$ 390.1772, found 390.1782.

5.4. Methyl 4(*Z*)-(5′-deoxyadenosin-5′-ylidene)butanoate (2e)

Treatment of **2d** (30 mg, 0.077 mmol) with TFA/H_2O (9:1, 5 mL) by procedure B gave **2e** (15 mg, 56%); ^{1}H NMR (MeOH-d_4) δ 2.35–2.58 (m, 4, H7′,7″,8′,8″), 3.67 (s, 3, CH_3), 4.22 (t, J = 5.3 Hz, 1, H3′), 4.72 ('t', J = 4.8 Hz, 1, H2′), 4.82–4.92 (m, 1, H4′), 5.62–5.78 (m, 2, H5′,6′), 6.02 (d, J = 4.3 Hz, 1, H1′), 8.18 (s, 1, H2), 8.21 (s, 1, H8); ^{13}C NMR (MeOH-d_4) δ 23.34 (C7′), 33.77 (C8′), 51.09 (CH_3), 74.27 (C3′), 75.23 (C2′), 80.19 (C4′), 89.42 (C1′), 119.63 (C5), 128.99 (C6′), 132.93 (C5′), 140.31 (C8), 149.57 (C4), 152.89 (C2), 156.33 (C6), 174.07 (C9′); MS *m*/*z* 350 (100, MH^+). HRMS calcd for $C_{15}H_{20}N_5O_5$ $[M+H]^+$ 350.1464, found 350.1460.

5.5. 4(*Z*)-(5′-Deoxyadenosin-5′-ylidene)butanoic acid (2f)

NaOH/H_2O (0.2 mL, 1 M) was added to a stirred solution of **2e** (13 mg, 0.037 mmol) in MeOH (2 mL) at ambient temperature. After 24 h, volatiles were evaporated in vacuo and the residue was partitioned [EtOAc/H_2O/CH_3COOH (pH ~ 4)]. Aqueous layer was extracted four times with EtOAc and the combined organic layer was dried ($MgSO_4$), evaporated, and purified on a column chromatography (EtOAc → 20% S1/EtOAc) to give **2f** (9 mg, 73%): mp 220–221 °C (MeOH);

^{1}H NMR (MeOH-d_4, 600 MHz) δ 1.92–2.18 (m, 4, H7′,7″,8′,8″), 3.91 (t, J = 4.9 Hz, 1, H3′), 4.46 (t, J = 4.9 Hz, 1, H2′), 4.53 (dd, J = 5.1, 8.0 Hz, 1, H4′), 5.39 (dt, J = 10.5, 7.9 Hz, 1, H6′), 5.44 (dd, J = 7.4, 10.6 Hz, 1, H5′), 5.71 (d, J = 4.7 Hz, 1, H1′), 7.99 (s, 1, H2), 8.08 (s, 1, H8); ^{13}C NMR (Me_2SO-d_6) δ 22.30 (C7′), 33.51 (C8′), 73.99 (C3′), 75.45 (C2′), 80.36 (C4′), 88.64 (C1′), 120.06 (C5), 130.05, 132.99 (C5′ and 6′), 140.78 (C8), 150.18 (C4), 153.50 (C2), 156.93 (C6), 175.89 (C9′), MS m/z 336 (100, MH$^+$). Anal. Calcd for $C_{14}H_{17}N_5O_5$ (335.32): C, 50.15; H, 5.11; N, 20.89. Found: C, 50.45; H, 5.47; N, 20.45.

5.6. Ethyl 2(*R*/*S*)-benzamido-5(*E*)-(5′-deoxy-2′,3′-*O*-isopropylideneuridin-5′-ylidene)pentanoate (5a). Procedure C

Compounds **3**[18] (90 mg, 0.3 mmol) and **4a**[17] (78 mg, 0.3 mmol) were added to a stirred solution of [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(phenylmethylene)(tricyclohexylphosphine)ruthenium (5 mg, 0.006 mmol) in dried CH_2Cl_2 (5 mL) at ambient temperature under an Ar atmosphere. The reaction mixture was stirred overnight at 55 °C in the Teflon cap closed vial, cooled down to ambient temperature, and was partitioned ($CHCl_3$/H_2O). The organic layer was washed (brine), dried ($MgSO_4$), and evaporated to give brown foam. Column chromatography (1 → 3% MeOH/$CHCl_3$) gave **5a** (111 mg, 72%; R/*S*, ~1:1); ^{1}H NMR δ 1.26 (t, J = 7.1 Hz, 3, CH_3), 1.31 (s, 3, CH_3), 1.36 (s, 3, CH_3), 1.81–1.95 (m, 2, H8′,8″), 2.02–2.25 (m, 2, H7′,7″), 4.23 (q, J = 7.1 Hz, 2, CH_2), 4.47–4.52 (m, 1, H4′), 4.69–4.74 (m, 1, H3′), 4.84 (‘q’, J = 6.5 Hz, 1, H9′), 5.01 (‘dm’, J = 6.4 Hz, 1, H2′), 5.61 (d, J = 2.8 Hz, 0.5, H1′), 5.62 (d, J = 2.8 Hz, 0.5, H1′) 5.64–5.75 (m, 2, H5,5′), 5.79–5.87 (m, 1, H6′), 6.84 (d, J = 7.8 Hz, 0.5, NH). 6.91 (d, J = 7.8 Hz, 0.5, NH), 7.26 (d, J = 8.1 Hz, 0.5, H6), 7.28 (d, J = 8.1 Hz, 0.5, H6), 7.45 (t, J = 7.7 Hz, 2, Ar), 7.52 (t, J = 7.9 Hz, 1, Ar), 7.82 (d, J = 8.0, 2, Ar), 9.38 (br s, 1, NH); ^{13} C NMR δ 13.18 (CH_3), 24.27 and 26.11 (CMe_2), 26.98 (C7′), 30.75 (C8′), 51.06 (C9′), 60.72 (CH_2), 83.15 and 83.24 (C3′), 83.71, 83.78 (C2′), 87.45 and 87.50 (C4′), 93.51 and 93.38 (C1′), 101.50 (C5), 113.46 (*C*Me$_2$), 126.10, 127.59, 130.78, 133.03 (Bz), 127.12 and 127.13 (C5′), 132.84 and 132.86 (C6′), 141.36 (C6), 148.94 (C2), 162.28 (C4), 166.08 and 166.11 (Bz), 171.50 and 171.54 (C10′); MS m/z 514 (100, MH$^+$).

Isolated also from column were self-metathesis dimers diethyl 2,9-bis(benzamido)dec-5-enedioate **6**[17] (10 mg, 7%, 14% consumption of **4a**; less polar then **5a**) and **7a** (8 mg, 5%, 10% consumption of **3**; more polar then **5a**). Compound **7a** had: ^{1}H NMR: δ 1.34 (s, 3, CH_3), 1.56 (s, 3, CH_3), 4.54 (‘dt’, J = 2.1, 3.8 Hz, 1, H4′), 4.76 (dd, J = 4.0, 6.3 Hz, 1, H3′), 5.05 (dd, J = 1.8, 6.4 Hz, 1, H2′), 5.52 (d, J = 1.7 Hz, H1′), 5.83 (d, J = 8.0 Hz, 1, H5), 5.97 (‘dd’, J = 1.7, 3.7 Hz, 1, H5′), 7.19 (d, J = 8.0 Hz, 1, H6), 9.73 (br s, 1, NH); ^{13}C NMR δ 25.63 and 27.49 (CMe_2), 84.88 (C2′ and C3′), 87.71 (C4′), 95.92 (C1′), 102.95 (C5), 114.88 (*C*Me$_2$), 130.99 (C5′), 143.45 (C6), 150.18 (C2), 164.66 (C4); MS m/z 533 (100, MH$^+$). Treatment of **7a** (8 mg, 0.015 mmol) with TFA/H_2O (9:1, 1.0 mL) by procedure B and HPLC purification (10 → 40% CH_3CN/H_2O for 50 min, t_R = 20 min) gave **7b** (4 mg, 60%); ^{1}H NMR (MeOH-d_4) δ 4.02 (t, J = 5.8 Hz, 1, H3′), 4.26 (dd, J = 3.8, 5.3 Hz, 1, H2′), 4.44 (‘ddd’, J = 1.8, 3.7, 5.8 Hz, 1, H4′), 5.75 (d, J = 8.1 Hz, 1, H5), 5.83 (d, J = 3.6 Hz, 1, H1′), 6.08 (dd, J = 1.8, 3.7 Hz, 1, H5′), 7.64 (d, J = 8.1 Hz, 1, H6); ^{13}C NMR (MeOH-d_4) δ 74.93 (C2′), 75.11 (C3′), 84.68 (C4′), 92.45 (C1′), 102.95 (C5), 132.23 (C5′), 142.80 (C6), 152.23 (C2), 166.15 (C4). HRMS calcd for $C_{18}H_{21}N_4O_{10}$ [M+H]$^+$ 453.1252, found 453.1260.

5.7. Ethyl 2(*R*/*S*)-benzamido-5(*E*)-(5′-deoxyuridin-5′-ylidene)pentanoate (5b)

Treatment of **5a** (25 mg, 0.05 mmol) with TFA/H_2O (9:1, 1.5 mL) by procedure B [column chromatography ($CHCl_3$/MeOH; 95:5)] gave **5b** (15 mg, 66%; *R*/*S*, ~1:1): UV max 260 nm (ε 14,500), min 233 nm (ε 9300); ^{1}H NMR (MeOH-d_4) δ 1.28 (t, J = 7.1 Hz, 3, CH_3), 1.93–2.22 (m, 2, H8′,8′), 2.24–2.33 (m, 2, H7′,7″), 3.92 (‘q’, J = 5.2 Hz, 1, H3′), 4.15–4.20 (m, 1, H2′) 4.22 (‘dq’, J = 2.0, 7.0 Hz, 2, CH_2), 4.35 (t, J = 7.1, 1, H4′), 4.62 (‘dd’, J = 4.9, 9.8 Hz, 1, H9′), 5.62–5.76 (m, 2, H5,5′), 5.81 (d, J = 3.4 Hz, 0.5, H1′), 5.83 (d, J = 3.4 Hz, 0.5, H1′), 5.90 (dt, J = 15.3, 6.7 Hz, 0.5, H6′), 5.91 (dt, J = 15.3, 6.6 Hz, 0.5, H6′), 7.51 (‘t’, J = 7.8 Hz, 2, Ar), 7.53–7.66 (m, 2, H6 and Ar), 7.91 (d, J = 8.1 Hz, 2, Ar); ^{13}C NMR (MeOH-d_4) δ 13.53 (CH_3), 28.82 and 28.89 (C7′), 30.45 and 30.48 (C8′), 52.69 (C9′), 62.44 (CH_2), 74.15 (C3′), 74.22 and 74.25 (C2′), 84.37 and 84.48 (C4′), 90.69 (C1′), 101.84 (C5), 127.54 and 127.56, 128.59, 131.95, 133.71 (Bz), 129.16 and 129.24 (C5′), 134.22 and 134.24 (C6′), 141.40 (C6), 151.25 (C2), 165.15 (C4), 169.51 (Bz), 172.85 (C10′); MS m/z 474 (100, MH$^+$). HRMS calcd for $C_{23}H_{28}N_3O_8$ [M+H]$^+$ 474.1871, found 474.1880.

5.8. Ethyl 2(*R*/*S*)-*tert*-butoxycarbonylamino-5(*E*)-(5′-deoxy-2′,3′-*O*-isopropylideneuridin-5′-ylidene)pentanoate (5c)

Metathesis of **3**[18] (40 mg, 0.14 mmol) and **4b**[17] (35 mg, 0.14 mmol) by procedure C [column chromatography ($CHCl_3$ → 2% MeOH)] gave **5c** (73 mg, 74%, *R*/*S*, 1:1); ^{1}H NMR δ 1.28 (t, J = 7.1 Hz, 3, CH_3), 1.36 (s, 3, CH_3), 1.45 (s, 9, *t*-Bu), 1.59 (s, 3, CH_3), 1.69–2.19 (m, 4, H7′,7″,8′,8″), 4.22 (q, J = 7.1 Hz, 2, CH_2), 4.27–4.34 (‘br q’, J = 8.0 Hz, 1, H9′), 4.51 (dd, J = 4.2, 8.1 Hz, 0.5, H4′), 4.52 (dd, J = 4.2, 8.1 Hz, 0.5, H4′), 4.75–4.80 (m, 1, H3′), 5.01–5.07 (m, 1, H2′), 5.15 (‘t’, J = 9.0 Hz, 1, NH), 5.58-5.85 (m, 4, H1′,5, 5′,6′), 7.25 (d, J = 8.0 Hz, 0.5, H6), 7.27 (d, J = 8.0 Hz, 0.5, H6), 9.45 (br s, 1, NH); MS m/z 510 (100, MH$^+$), 410 (97, MH$^+$-Boc). HRMS calcd for $C_{24}H_{36}N_3O_9$ [M+H]$^+$ 510.2452, found 510.2455.

5.9. Ethyl 2(*R*/*S*)-amino-5(*E*)-(5′-deoxyuridin-5′-ylidene)pentanoate (5d)

Treatment of **5c** (45 mg, 0.088 mmol) with TFA/H_2O (9:1, 3.5 mL) by procedure B [column chromatography

(5 → 12% MeOH/$CHCl_3$)] gave **5d** (20 mg, 61%; R/*S*, 1:1) as a white hygroscopic solid: UV max 260 nm (ε 10,500), min 233 nm (ε 3800); ^{1}H NMR (Me_2SO-d_6) δ 1.19 (t, *J* = 7.1 Hz, 3, CH_3), 1.48–1.56 (m, 1, H8′), 1.60–1.69 (m, 1, H8″), 2.10 ('q', *J* = 7.2 Hz, 2, H7′,7″), 3.29–3.31 (m, 1, H9′), 3.79 (m, 1, H3′), 4.05–4.18 (m, 4, H2′,4′ and CH_2), 5.21 (br s, 2, OH2′ and OH3′), 5.42–5.44 (m, 2, NH_2), 5.63 (dd, *J* = 7.8, 15.2 Hz, 1, H5′), 5.65 (d, *J* = 8.0 Hz, 1, H5), 5.72 (d, *J* = 4.1 Hz, 1, H1′), 5.74 (dt, *J* = 6.8, 15.2 Hz, 1, H6′), 7.59 (d, *J* = 8.0 Hz, 1, H6), 11.35 (br s, 1, NH); ^{13}C NMR (Me_2SO-d_6) δ 15.00 (CH_3), 28.78 (C7′), 34.55 and 34.60 (C8′), 54.22 (C9′), 60.91 (CH_2), 73.72 and 73.75 (C3′), 74.37 and 74.39 (C2′), 84.82 and 84.87 (C4′), 89.60 (C1′), 102.79 (C5), 129.31 (C5′), 134.58 (C6′), 141.88 (C6), 151.48 (C2), 163.96 (C4), 176.35 (C10′); MS *m*/*z* 370 (100, MH^+). HRMS calcd for $C_{16}H_{24}N_3O_7$ $[M+H]^+$ 370.1609, found 370.1618.

5.10. Ethyl 5(*E*)-(5′-deoxy-2′,3′-*O*-isopropylideneuridin-5′-ylidene)pentanoate (11a). Procedure D

Tris(dibenzylideneacetone)dipalladium (9.2 mg, 0.01 mmol) was added to a solution of (*E*)-**9**[18] (40 mg, 0.1 mmol) in benzene (2 mL) followed by dropwise addition of $EtO_2C(CH_2)_3ZnBr$ (0.5 M/THF, 0.3 mL, 0.15 mmol) via syringe at ambient temperature under N_2. The resulting mixture was heated at 55 °C for 8 h [additional $EtO_2C(CH_2)_3ZnBr$ (0.1 mL, 0.05 mmol) was added after 5 h] and progress of the reaction was monitored (TLC) by the formation of slightly more polar compound. The volatiles were evaporated and the brown residue was partitioned (EtOAc/H_2O). The organic layer was washed (brine), dried (Na_2SO_4), evaporated, and the residue was column chromatographed (EtOAc/hexane, 85:15) to give **11a** (28 mg, 72%); ^{1}H NMR δ 1.25 (t, *J* = 7.1 Hz, 3, CH_3), 1.38 (s, 3, CH_3), 1.58 (s, 3, CH_3), 1.72 (quint, *J* = 7.6 Hz, 2, H8′,8″), 2.12 (q, *J* = 7.1 Hz, 2, H7′,7″), 2.32 (t, *J* = 7.6 Hz, 2, H9′), 4.14 (q, *J* = 7.1 Hz, 2, CH_2), 4.50 (dd, *J* = 4.3, 7.8 Hz, 1, H4′), 4.74 (dd, *J* = 4.4, 6.2 Hz, 1, H3′), 5.02 (dd, *J* = 1.7, 6.5 Hz, 1, H2′), 5.60 (d, *J* = 1.6 Hz, 1, H1′), 5.62 (dd, *J* = 8.0, 14.6 Hz, 1, H5′), 5.73 (d, *J* = 8.2 Hz, 1, H5), 5.82 (dt, *J* = 6.8, 14.6 Hz, 1, H6′), 7.28 (d, *J* = 8.2 Hz, 1, H6), 9.40 (s, 1, NH); ^{13}C NMR δ 14.25 (CH_3), 24.03 (C8′), 25.32 and 27.16 (CMe_2), 31.53 (C7′), 33.62 (C9′), 60.35 (CH_2), 84.22 (C3′), 84.84 (C2′), 88.63 (C4′), 94.29 (C1′), 102.45 (C5), 114.57 (CMe_2), 128.57 (C6′), 131.96 (C5′), 142.23 (C6), 149.77 (C2), 163.03 (C4), 173.45 (C10′); MS *m*/*z* 395 (100, MH^+); HRMS calcd for $C_{19}H_{27}N_2O_7$ $[M+H]^+$ 395.1818, found 395.1811.

5.11. Ethyl 5(*E*)-(5′-deoxyuridin-5′-ylidene)pentanoate (11b)

Treatment of **11a** (70 mg, 0.78 mmol) with TFA/H_2O (9:1, 2.5 mL) by procedure B gave **11b** (45 mg, 72%): mp 102–104 °C dec; UV max 262 nm (ε 9200), min 230 nm (ε 2100); ^{1}H NMR (Me_2SO-d_6/D_2O) δ 1.18 (t, *J* = 7.1 Hz, 3, CH_3), 1.62 ('quint', *J* = 7.3 Hz, 2, H8′,8″), 2.08 (q, *J* = 6.8 Hz, 2, H7′,7″), 2.32 (t, *J* = 7.4 Hz, 2, H9′,9″), 3.81 (t, *J* = 5.3 Hz, 1, H3′), 4.04–4.10 (m, 3, H2′,CH_2), 4.15 ('t', *J* = 6.4 Hz, 1, H4′), 5.57–5.72 (m, 4, H1′,5,5′,6′), 7.58 (d, *J* = 8.1 Hz, 1, H6); ^{13}C NMR (Me_2SO-d_6) δ 14.91 (CH_3), 24.60 (C8′), 31.75 (C7′), 33.68 (C9′), 60.60 (CH_2), 73.73 (C3′), 74.40 (C2′), 84.81 (C4′), 89.62 (C1′), 102.79 (C5), 129.58 (C6′), 134.44 (C5′), 141.89 (C6), 151.49 (C2), 163.95 (C4), 173.61 (C10′); MS *m*/*z* 355 (100, MH^+). Anal. Calcd for $C_{16}H_{22}N_2O_7$ (354.36): C, 54.23; H, 6.26; N, 7.91. Found: C, 54.34; H, 6.28; N, 7.68.

5.12. Ethyl 5(*E*)-(5′-deoxy-2′,3′-*O*-isopropylideneadenosin-5′-ylidene)pentanoate (12a)

Coupling of (*E*)-**10**[5a] (41 mg, 0.1 mmol) with $EtO_2C(CH_2)_3ZnBr$ (0.5 M/THF, 0.4 mL, 0.2 mmol) by procedure D [column chromatography (1 → 2% MeOH/EtOAc)] gave **12a** (27 mg, 68%); ^{1}H NMR (600 MHz) δ 1.25 (t, *J* = 7.2 Hz, 3, CH_3), 1.28 (s, 3, CH_3), 1.42 (s, 3, CH_3), 1.68 (quint, *J* = 7.5 Hz, 2, H8′,8″), 2.04 (q, *J* = 7.2 Hz, 2, H7′,7″), 2.28 (t, *J* = 7.5 Hz, 2, H9′,9″), 4.08 (q, *J* = 7.1 Hz, 2, CH_2), 4.65 (dd, *J* = 3.3, 7.5 Hz, 1, H4′), 4.98 (dd, *J* = 3.5, 6.2 Hz, 1, H3′), 5.51 (dd, *J* = 1.9, 6.3 Hz, 1, H2′), 5.59 (ddt, *J* = 1.2, 7.6, 15.4 Hz, 1, H5′), 5.72 (dt, *J* = 15.4, 6.6 Hz, 1, H6′), 5.90 (br s, 2, NH_2), 6.09 (d, *J* = 1.9 Hz, 1, H1′), 7.91 (s, 1, H2), 8.38 (s, 1, H8); MS *m*/*z* 418 (100, MH^+); HRMS calcd for $C_{20}H_{28}N_5O_5$ $[M+H]^+$ 418.2090, found 418.2082.

5.13. Ethyl 5(*E*)-(5′-deoxyadenosin-5′-ylidene)pentanoate (12b)

Treatment of **12a** (27 mg, 0.065 mmol) with TFA/H_2O by procedure B gave **12b** (15 mg, 61%). Purification on HPLC (10 → 60% CH_3CN/H_2O for 1 h, t_R = 43 min) and recrystallization (MeOH) gave white crystals: mp 91–93 °C dec; UV max 260 nm (ε 12,700), min 230 nm (ε 1840); ^{1}H NMR (MeOH-d_6, 600 MHz) δ 1.05 (t, *J* = 7.2 Hz, 3, CH_3), 1.55 (quint, *J* = 7.3 Hz, 2, H8′,8″), 1.98 (q, *J* = 7.0 Hz, 2, H7′,7″), 2.16 (t, *J* = 7.4 Hz, 2, H9′,9″), 3.94 (q, *J* = 7.0 Hz, 2, CH_2), 4.04 (t, *J* = 5.2 Hz, 1, H3′), 4.25 (dd, *J* = 5.4, 6.6 Hz, 1, H4′), 4.59 (t, *J* = 4.8 Hz, 1, H2′), 5.58 (dd, *J* = 6.8, 15.4 Hz, 1, H5′), 5.65 (dt, *J* = 15.4, 6.4 Hz, 1, H6′), 5.84 (d, *J* = 4.5 Hz, 1, H1′), 8.08 (s, 1, H2), 8.10 (s, 1, H8); ^{13}C NMR (Me_2SO-d_6) δ 14.90 (CH_3), 24.46 (C8′), 31.57 (C7′), 33.62 (C9′), 60.74 (CH_2), 73.54 (C3′), 74.69 (C2′), 85.40 (C4′), 88.33 (C1′), 119.76 (C5), 129.64 (C6′), 133.98 (C5′), 140.95 (C8), 150.11 (C4), 153.53 (C2), 156.56 (C6), 173.97 (C10′); MS *m*/*z* 378 (100, MH^+). Anal. Calcd for $C_{17}H_{23}N_5O_5{\cdot}H_2O$ (395.41): C, 51.64; H, 6.37; N, 17.71. Found: C, 51.53; H, 6.42; N, 17.37.

5.14. 5(*E*)-(5′-Deoxyadenosin-5′-ylidene)pentanoic acid (12c)

NaOH/H_2O (1 M, 0.35 mL) was added to a solution of **12b** (10 mg, 0.026 mmol) in MeOH (2.5 mL) and stirring was continued at ambient temperature overnight. The resulting mixture was neutralized with AcOH to pH ~ 7. Volatiles were evaporated and the residue was

purified on HPLC (10 → 30% CH_3CN/H_2O for 50 min, t_R = 28 min) to give **12c** (7.5 mg, 82%); ^{1}H NMR (MeOH-d_4) δ 1.74 ('quint', J = 7.4 Hz, 2, H8′,8″), 2.15 (q, J = 7.1 Hz, 2, H7′,7″), 2.32 (t, J = 7.4 Hz, 2, H9′,9″), 4.21 (t, J = 5.2 Hz, 1, H3′), 4.43 (dd, J = 5.5, 6.8 Hz, 1, H4′), 4.72 (t, J = 4.9 Hz, 1, H2′), 5.75 (dd, J = 7.0, 15.4 Hz, 1, H5′), 5.83 (dt, J = 15.5, 6.5 Hz, 1, H6′), 6.01 (d, J = 4.5 Hz, 1, H1′), 8.16 (s, 1, H2), 8.22 (s, 1, H8); ^{13}C NMR (MeOH-d_4) δ 25.37 (C8′), 32.64 (C7′), 34.32 (C9′), 75.12 (C3′), 75.70 (C2′), 86.43 (C4′), 90.14 (C1′), 120.10 (C5), 129.76 (C6′), 135.18 (C5′), 141.28 (C8), 150.66 (C4), 153.93 (C2), 157.36 (C6), 177.59 (C10′); MS m/z 350 (100, MH^+); HRMS calcd for $C_{15}H_{20}N_5O_5$ $[M+H]^+$ 350.1464, found 350.1469.

5.15. Ethyl 5-fluoro-5-(5′-deoxy-2′,3′-*O*-isopropylideneadenosin-5′-ylidene)pentanoate (14a)

$Pd(PPh_3)_4$ (25.6 mg, 0.022 mmol) was added to a solution of **13**[6a] (*E*/*Z*, ~60:40; 80 mg, 0.2 mmol) in benzene (5 mL) followed by dropwise addition of $EtO_2C(CH_2)_3ZnBr$ (0.5 M/THF, 0.88 mL, 0.44 mmol) via syringe at ambient temperature under N_2. The resulting mixture was heated at 55 °C for 8 h. The volatiles were evaporated and the brown residue was partitioned (EtOAc/$NaHCO_3/H_2O$). The organic layer was washed (brine), dried (Na_2SO_4), evaporated, and the residue was column chromatographed (1 → 3% MeOH/$CHCl_3$) to give **14a** (49 mg, 56%; *E*/*Z*, ~40:60); ^{19}F NMR δ −95.78 ('q', $J_{F-H5',7',7''}$ = 21.8 Hz, 0.4, *E*), −101.80 (dt, $J_{F-H5'}$ = 35.5 Hz, $J_{F-H7',7''}$ = 17.3 Hz, 0.6, *Z*); MS m/z 436 (MH^+); HRMS calcd for $C_{20}H_{27}FN_5O_5$ $[M+H]^+$ 436.1996, found 436.1991. (*Z*)-**14a** had: ^{1}H NMR δ 1.23 (t, J = 7.1 Hz, 3, CH_3), 1.36 (s, 3, CH_3), 161 (s, 3, CH_3), 1.84 ('quint', J = 7.3 Hz, 2, H8′,8″), 2.15 (dt, J = 17.1, 7.7 Hz, 2, H7′,7″), 2.30 (t, J = 7.5 Hz, 2, H9′,9″), 4.09 (q, J = 7.2 Hz, 2, CH_2), 4.85 (dd, J = 9.2, 35.5 Hz, 1, H5′), 4.97 ('dd', J = 3.3, 6.2 Hz, 1, H3′), 5.15 (dd, J = 3.1, 9.2 Hz, 1, H4′), 5.54 (dd, J = 1.9, 6.2 Hz, 1, H2′), 5.88 (br s, 2, NH_2), 5.98 (d, J = 1.7 Hz, 1, H1′), 7.86 (s, 1, H2), 8.34 (s, 1, H8). (*E*)-**14a** had: ^{1}H NMR δ 1.21 (t, J = 7.1 Hz, 3, CH_3), 1.35 (s, 3, CH_3), 160 (s, 3, CH_3), 1.74 ('quint', J = 7.2 Hz, 2, H8′,8″), 2.26 (t, J = 7.4 Hz, 2, H9′,9″), 2.35 (dt, J = 23.3, 7.3 Hz, 2, H7′,7″), 4.11 (q, J = 7.2 Hz, 2, CH_2), 4.75 (ddd, J = 1.8, 3.2, 10.1 Hz, 1, H4′), 4.97 ('dd', J = 3.3, 6.2 Hz, 1, H3′), 5.30 (dd, J = 10.1, 19.6 Hz, 1, H5′), 5.50 (dd, J = 1.7, 6.3 Hz, 1, H2′), 5.88 (br s, 2, NH_2), 5.97 (d, J = 1.5 Hz, 1, H1′), 7.84 (s, 1, H2), 8.34 (s, 1, H8).

5.16. Ethyl 5-fluoro-5-(5′-deoxyadenosin-5′-ylidene)pentanoate (14b)

Treatment of **14a** (40 mg, 0.092 mmol; *E*/*Z*, 40:60) with TFA/H_2O by procedure B and HPLC purification (15 → 50% CH_3CN/H_2O, t_R = 49 min) gave **14b** (32 mg, 88%; *E*/*Z*, ~35:65): ^{19}F NMR (MeOH-d_4) δ −94.73 ('q', $J_{F-H5',7,7'}$ = 20.5 Hz, 0.35, *E*), −102.14 (dt, $J_{F-H5'}$ = 35.9 Hz, $J_{F-H7',7''}$ = 17.7 Hz, 0.65, *Z*); MS m/z 396 (100, MH^+); HRMS calcd for $C_{17}H_{23}FN_5O_5$ $[M+H]^+$ 396.1678, found 396.1680. (*Z*)-**14b** had: ^{1}H NMR (MeOH-d_4) δ 1.24 (t, J = 7.1 Hz, 3, CH_3), 1.86 ('quint', J = 7.4 Hz, 2, H8′,8″), 2.32 ('dt', J = 17.6, 7.3 Hz, 2, H7′,7″), 2.40 (t, J = 7.4 Hz, 2, H9′,9″), 4.13 (q, J = 7.1 Hz, 2, CH_2), 4.23 (t, J = 4.7 Hz, 1, H3′), 4.86 ('t', J = 4.4 Hz, 1, H2′), 4.94 (dd, J = 4.5, 9.2 Hz, 1, H4′), 5.20 (dd, J = 9.2, 36.5 Hz, 1, H5′), 5.99 (d, J = 4.8 Hz, 1, H1′), 8.24 (s, 1, H2), 8.26 (s, 1, H8); ^{13}C NMR (MeOH-d_4) δ 14.50 (CH_3), 22.34 (C8′), 31.99 (d, J = 27.2 Hz, C7′), 33.87 (C9′), 61.55 (CH_2), 74.89 (C2′), 76.29 (C3′), 79.34 (d, J = 6.5 Hz, C4′), 90.38 (C1′), 106.01 (d, J = 11.3 Hz, C5′), 120.82 (C5), 141.69 (C8), 150.62 (C4), 153.90 (C2), 157.37 (C6), 163.50 (d, J = 260.9 Hz, C6′), 174.86 (C10′). (*E*)-**14b** had: ^{1}H NMR (MeOH-d_4) δ 1.24 (t, J = 7.1 Hz, 3, CH_3), 1.84 ('quint', J = 7.4 Hz, 2, H8′,8″), 2.39 (t, J = 7.3 Hz, 2, H9′,9″), 2.43–2.55 (m, 2, H7′,7″), 4.12 (q, J = 7.1 Hz, 2, CH_2), 4.28 (t, J = 5.5 Hz, 1, H3′), 4.60 (ddd, J = 1.9, 5.8, 9.8 Hz, 1, H4′), 4.72 (dd, J = 4.0, 5.1 Hz, 1, H2′), 5.44 (dd, J = 9.7, 19.9 Hz, 1, H5′), 6.00 (d, J = 3.6 Hz, 1, H1′), 8.25 (s, 1, H2), 8.23 (s, 1, H8); ^{13}C NMR (MeOH-d_4) δ 14.50 (CH_3), 22.34 (C8′), 28.56 (d, J = 27.2 Hz, C7′), 33.78 (C9′), 61.55 (CH_2), 75.21 (C2′), 76.11 (C3′), 81.03 (d, J = 14.4 Hz, C4′), 90.57 (C1′), 106.83 (d, J = 24.4 Hz, C5′), 120.70 (C5), 141.31 (C8), 150.54 (C4), 153.94 (C2), 157.37 (C6), 165.42 (d, J = 255.3 Hz, C6′), 174.89 (C10′).

5.17. 5-Fluoro-5(*E*)-(5′-deoxyadenosin-5′-ylidene)pentanoic acid (14c)

Treatment of **14b** (8 mg, 0.020 mmol; *E*/*Z*, 35:65) with NaOH as described for **12c** and HPLC purification (5 → 50% CH_3CN/H_2O for 1 h, t_R = 42 min) gave **14c** (6 mg, 82%; *E*/*Z*, 45:55); ^{19}F NMR (MeOH-d_4) δ −97.8 ('q', $J_{F-H5',7',7''}$ = 23.9 Hz, 0.45, *E*), −105.0 ('dt', $J_{F-H5'}$ = 35.6 Hz, $J_{F-H7',7''}$ = 17.6 Hz, 0.55, *Z*); MS m/z 368 (100, MH^+); HRMS calcd for $C_{15}H_{19}FN_5O_5$ $[M+H]^+$ 368.1370, found 368.1375. (*Z*)-**14c** had: ^{1}H NMR (MeOH-d_4) δ 1.85 ('quint', J = 7.4 Hz, 2, H8′,8″), 2.32 (dt, J = 17.3, 7.4 Hz, 2, H7′,7″), 2.38 (t, J = 7.3 Hz, 2, H9′,9″), 4.23 (t, J = 4.8 Hz, 1, H3′), 4.83 ('t', J = 5.0 Hz, 1H, H2′), 4.92 (dd, J = 4.7, 9.3 Hz, 1, H4′), 5.20 (dd, J = 9.2, 36.0 Hz, 1, H5′), 6.01 (d, J = 5.2 Hz , 1, H1′), 8.24 (s, 1, H2), 8.27 (s, 1H, H8); ^{13}C NMR (MeOH-d_4) δ 23.02 (C8′), 32.05 (d, J = 27.4 Hz, C7′), 33.82 (C9′), 74.91 (C2′), 76.27 (C3′), 79.34 (d, J = 6.6 Hz, C4′), 90.27 (C1′), 105.90 (d, J = 11.0 Hz, C5′), 120.46 (C5), 141.36 (C8), 150.60 (C4), 153.88 (C2), 157.34 (C6), 163.30 (d, J = 258.6 Hz, C6′), 177.09 (C10′). (*E*)-**14c** had: ^{1}H NMR (MeOH-d_4) δ 1.84 ('quint', J = 7.4 Hz, 2H, H8′,8″), 2.39 (t, J = 7.3 Hz, 2, H9′,9″), 2.45 (dt, J = 23.7, 7.3 Hz, 1, H7′), 2.46 (dt, J = 23.7, 7.3 Hz, 1, H7″), 4.28 (t, J = 5.6 Hz, 1, H3′), 4.60 (ddd, J = 1.8, 5.8, 9.7 Hz, 1, H4′), 4.72 (dd J = 4.0, 5.2 Hz, 1, H2′), 5.44 (dd, J = 9.8, 19.9 Hz, 1, H5′), 6.00 (d, J = 3.7 Hz, 1, H1′), 8.23 (s, 1, H2), 8.25 (s, 1, H8); ^{13}C NMR (MeOH-d_4) δ 22.45 (C8′), 28.65 (d, J = 26.9 Hz, C7′), 33.82 (C9′), 75.17 (C2′), 76.12 (C3′), 81.04 (d, J = 14.8 Hz, C4′), 90.58 (C1′), 106.73 (d, J = 24.7 Hz, C5′), 120.53 (C5), 141.68 (C8), 150.49 (C4), 153.91 (C2), 157.34 (C6), 165.88 (d, J = 258.6 Hz, C6′), 177.09 (C10′).

5.18. Inactivation of AdoHcy hydrolase

Recombinant human placental AdoHcy hydrolase (204 nM) was incubated with 281 μM of **2e**, **2f**, **8a**, **8b**, **12b**, **12c**, **14b**, and **14c** in potassium-phosphate buffer [50.5 μL; 50 mM, pH 7.2, containing 1 mM EDTA (buffer A)] at 22 °C for 0.5 or 4 h. The remaining enzyme activity was assayed in the synthetic direction essentially as previously described.[8b] An aliquot (5 μL) of the enzyme/inhibitor was added to 995 μL of buffer A containing 0.5 mM Ado and 0.5 mM Hcy in buffer A and then incubated at 37 ° C for 12 min followed by the addition of $HClO_4$ (25 μL, 5 M) to terminate the reaction. The reaction product, AdoHcy, was quantitatively measured using RP-HPLC with the detector monitoring at 258 nm.[8b]

Acknowledgments

This investigation was supported by grants from the National Institutes of Health (S06GM08205 and GM29332). The support of US ARO (W911NF-04-1-0022) for the purchase of 600 MHz NMR spectrometer is acknowledged.

References and notes

1. (a) Yuan, C.-S.; Liu, S.; Wnuk, S. F.; Robins, M. J.; Borchardt, R. T.. In *Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI Press: Greenwich, 1996; Vol. 2, pp 41–88; (b) Turner, M. A.; Yang, X.; Yin, D.; Kuczera, K.; Borchardt, R. T.; Howell, P. L. *Cell Biochem. Biophys.* **2000**, *33*, 101; (c) Wnuk, S. F. *Mini-Rev. Med. Chem.* **2001**, *1*, 307.
2. (a) Ueland, P. M. *Pharmacol. Rev.* **1982**, *34*, 223; (b) Chiang, P. K. *Pharmacol. Ther.* **1998**, *77*, 115.
3. (a) Refsum, H.; Ueland, P. M.; Nygard, O.; Vollset, S. E. *Annu. Rev. Med.* **1998**, *49*, 31; (b) Schynder, G.; Roffi, M.; Pin, R.; Flammer, Y.; Lange, H.; Eberli, F. R.; Meier, B.; Turi, Z. G.; Hess, O. M. *N. Eng. J. Med.* **2001**, *345*, 1593.
4. (a) McCarthy, J. R.; Jarvi, E. T.; Matthews, D. P.; Edwards, M. L.; Prakash, N. J.; Bowlin, T. L.; Mehdi, S.; Sunkara, P. S.; Bey, P. *J. Am. Chem. Soc.* **1989**, *111*, 1127; (b) Yuan, C.-S.; Yeh, J.; Liu, S.; Borchardt, R. T. *J. Biol. Chem.* **1993**, *268*, 17030.
5. (a) Wnuk, S. F.; Yuan, C.-S.; Borchardt, R. T.; Balzarini, J.; De Clercq, E.; Robins, M. J. *J. Med. Chem.* **1994**, *37*, 3579; (b) Yuan, C.-S.; Wnuk, S. F.; Liu, S.; Robins, M. J.; Borchardt, R. T. *Biochemistry* **1994**, *33*, 12305; (c) Yuan, C.-S.; Liu, S.; Wnuk, S. F.; Robins, M. J.; Borchardt, R. T. *Biochemistry* **1994**, *33*, 3758.
6. (a) Wnuk, S. F.; Mao, Y.; Yuan, C.-S.; Borchardt, R. T.; Andrei, J.; Balzarini, J.; De Clercq, E.; Robins, M. J. *J. Med. Chem.* **1998**, *41*, 3078; (b) Yuan, C.-S.; Wnuk, S. F.; Robins, M. J.; Borchardt, R. T. *J. Biol. Chem.* **1998**, *273*, 18191.
7. (a) Guillerm, G.; Guillerm, D.; Vandenplas-Witkowski, C.; Roginaux, H.; Carte, N.; Leize, E.; Van Dorsselaer, A.; De Clercq, E.; Lambert, C. *J. Med. Chem.* **2001**, *44*, 2743; (b) Jeong, L. S.; Yoo, S. J.; Lee, K. M.; Koo, M. J.; Choi, W. J.; Kim, H. O.; Moon, H. R.; Lee, M. Y.; Park, J. G.; Lee, S. K.; Chun, M. W. *J. Med. Chem.* **2003**, *46*, 201; (c) Guillerm, G.; Muzard, M.; Glapski, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5799; (d) Guillerm, G.; Muzard, M.; Glapski, C.; Pilard, S.; De Clercq, E. *J. Med. Chem.* **2006**, *49*, 1223.
8. (a) Robins, M. J.; Wnuk, S. F.; Yang, X.; Yuan, C.-S.; Borchardt, R. T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1998**, *41*, 3857; (b) Yang, X.; Yin, D.; Wnuk, S. F.; Robins, M. J.; Borchardt, R. T. *Biochemistry* **2000**, *39*, 15234.
9. (a) Turner, M. A.; Yuan, C.-S.; Borchardt, R. T.; Hershfield, M. S.; Smith, G. D.; Howell, P. L. *Nat. Struct. Biol.* **1998**, *5*, 369; (b) Yang, X.; Hu, Y.; Yin, D. H.; Turner, M. A.; Wang, M.; Borchardt, R. T.; Howell, P. L.; Kuczera, K.; Schowen, R. L. *Biochemistry* **2003**, *42*, 1900; (c) Hu, Y.; Komoto, J.; Huang, Y.; Gomi, T.; Ogawa, H.; Takata, Y.; Fujioka, M.; Takusagawa, F. *Biochemistry* **1999**, *38*, 8323.
10. For recent examples on the importance and synthetic challenges associated with the synthesis of the uracil-nucleosides functionalized at C5′ see: (a) Zhang, X.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **2007**, *90*, 864; (b) Kurosu, M.; Narayanasamy, P.; Crick, D. C. *Heterocycles* **2007**, *72*, 339; (c) Hirano, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2008**, *73*, 569.
11. Andrei, D.; Wnuk, S. F. *J. Org. Chem.* **2006**, *71*, 405.
12. Pfitzer, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661.
13. (a) Maryanoff, B. E.; Duhl-Emswiler, B. A. *Tetrahedron Lett.* **1981**, *22*, 4185; (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
14. (a) Wnuk, S. F.; Robins, M. J. *Can. J. Chem.* **1991**, *69*, 334; (b) Wnuk, S. F.; Yuan, C.-S.; Borchardt, R. T.; Balzarini, J.; De Clercq, E.; Robins, M. J. *J. Med. Chem.* **1997**, *40*, 1610.
15. (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.
16. For application of metathesis towards synthesis of nucleoside analogues see: Amblard, F.; Nolan, S. P.; Agrofoglio, L. A. *Tetrahedron* **2005**, *61*, 7067.
17. Andrei, D.; Wnuk, S. F. *Org. Lett.* **2006**, *8*, 5093.
18. Wnuk, S. F.; Robins, M. J. *Can. J. Chem.* **1993**, *71*, 192.
19. For an example on self-metathesis reaction of carbohydrate derived terminal olefins (e.g., 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose) see: Hadwiger, P.; Stütz, A. E. *Synlett* **1999**, 1787.
20. Biagini, S. C. G.; Gibson, S. E.; Keen, S. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2485.
21. For unexpected inhibitory activity of carbocylic pyrimidine nucleosides against AdoHcy hydrolase see: Mosley, S. L.; Bakke, B. A.; Sadler, J. M.; Sunkara, N. K.; Dorgan, K. M.; Zhou, Z. S.; Seley-Radtke, K. L. *Bioorg. Med. Chem.* **2006**, *14*, 7967.
22. Attempted metathesis of uridine precursor **3** with **4a** or **4b** in the presence of Hoveyda-Grubb's catalyst failed to give products **5a** or **5c**. It seems that 2nd generation Grubbs catalyst is more compatible with pyrimidine bases, while Hoveyda-Grubbs catalyst gave better results with purine nucleosides.
23. (a)*Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; (b) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384.
24. (a) Negishi, E.-I.; Liu, F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 1–47, Chapter 1; (b) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719; (c) Negishi, E.-I.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichim. Acta* **2005**, *38*, 71.
25. (a) Attempted Ag(I)-promoted Suzuki-Miyaura coupling [$Pd(dppf)_2Cl_2/Ag_2O/K_2CO_3$/80 °C][25b] between boronic

acid $(HO)_2B(CH_2)_3CO_2Et$[25b] and vinyl iodides (*E*)-**9**[18] and (*E*)-**10**[5a] (or the corresponding bromides[5a,18]) produced desired **11a** and **12a** in low and irreproducible yields (~5–20%); (b) Falck, J. R.; Kumar, P. S.; Reddy, Y. K.; Zou, G.; Capdevila, J. H. *Tetrahedron Lett.* **2001**, *42*, 7211.

26. (a) Attempted Stille coupling of the readily available uridine[18] and adenosine[5a] vinyl 6′(*E*)-stannanes with *N*-Boc-γ-bromohomoalanine-OMe[30] [inactivated electrophile that contains C(sp^3)-Br bonds bearing β hydrogens] utilizing Fu's methodology {[(π-allyl)PdCl]$_2$/P(*t*-Bu)$_2$Me or [HP(*t*-Bu)$_2$Me]BF_4/NH_4F/THF}[26b] was unsuccessful; (b) Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718.
27. For successful Pd-catalyzed monoalkylation of vinyl dihalides via *trans*-selective monobutylation of 1,1-dichloro-2-phenylethene with *n*-C_4H_9ZnCl in 81% yield see: (a) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257; For studies on differentiation of two chlorine atoms in stepwise double alkylation reactions of 1,1-dichloroalkenes see: (b) Tan, Z.; Negishi, E.-I. *Angew. Chem., Int. Ed.* **2006**, *45*, 762; For Suzuki-Miyaura protocol to the selective monocoupling of 1,1-dichloroalkenes with 9-alkyl-9-BBN see: (c) Liron, F.; Fosse, C.; Pernolet, A.; Roulland, E. *J. Org. Chem.* **2007**, *72*, 2220.
28. (a) (a) Although monocoupling with *gem*-dihalovinyl substrates is considered to be *trans* selective,[11,24c,27b] Negishi alkylation of (*E*/*Z*)-3-benzyloxy-1-(bromo or iodo)-1-fluoropropene[11] and 5′-deoxy-5′-(iodofluoromethylene)ribose[28b] (which also has an oxygen atom at the γ-carbon from the halovinyl unit) also produced *E*/*Z* mixture of the coupling products; (b) Wnuk, S. F.; Lalama, J.; Garmendia, C. A.; Robert, J.; Zhu, J.; Pei, D. *Bioorg. Med. Chem.* **2008**. doi:10.1016/j.bmc.2008.03.028.
29. Attempted monoalkylation of 5′-(dibromomethylene)-5′-deoxy-2′,3′-*O*-isopropylideneadenosine[6a] failed to yield the 6′-bromo analogue of type **14a** but rather produced dialkylated and/or reduced[11,28b] byproducts.
30. (a) Bajgrowicz, J. A.; Hallaoui, A. E.; Jaqquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833; (b) Shah, V. J.; Kuntz, I. D.; Kenyon, G. L. *Bioorg. Chem.* **1996**, *24*, 194.
31. Krasnovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.
32. Parker, N. B.; Yang, X.; Hanke, J.; Mason, K. A.; Schowen, R. L.; Borchardt, R. T.; Yin, D. H. *Exp. Parasitol.* **2003**, *105*, 149.
33. (a) Wnuk, S. F.; Ro, B.-O.; Valdez, C. A.; Lewandowska, E.; Valdez, N. X.; Sacasa, P. R.; Yin, D.; Zhang, J.; Borchardt, R. T.; De Clercq, E. *J. Med. Chem.* **2002**, *45*, 2651; (b) Wnuk, S. F.; Lewandowska, E.; Sacasa, P. R.; Crain, L. N.; Zhang, J.; Borchardt, R. T.; De Clercq, E. *J. Med. Chem.* **2004**, *47*, 5251.