Hydrogermylation of 5-Ethynyluracil Nucleosides: Formation of 5-(2-GermylvinyI)uracil and 5-(2-Germylacetyl)uracil Nucleosides

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ABSTRACT: A stereoselective radical-mediated hydrogermylation of the protected 5-ethynyluracil nucleosides with trialkyl-, triaryl-, or tris(trimethylsilyl)germanes gave (Z)-5-(2-germylvinyI)uridine, 2'-deoxyuridine, or ara-uridin as major products. Reaction of the β-triphenylgermyl vinyl radical intermediate with oxygen and fragmentation of the resulting peroxo radical provided also 5-[2-(tri phenylgermyI)acetyl]-pyrimidine nucleosides in low to moderate yields. Thermal isomerization of the latter in MeOH occurred via a four-centered activated complex, and subsequent hydrolysis of the resulting O-germyI substituted enol yielded 5-acetyluracil nucleosides in quantitative yield.

A broad spectrum of biological activity has been described for 5-substituted pyrimidine nucleosides. One especially potent and selective antiviral drug of this class is(E)-5-(2-bromovinyl)-2'-deoxyuridine (BDU). Pronounced cytotoxicity and significant antiviral activity have been reported for 1-(β-2'-arabinofuranosyl)-5-ethynyluracil and 5-ethynyl-2'-deoxyuridine. The synthesis of the numerous S-substituted pyrimidine nucleosides via Pd-assisted routes have been reviewed. The (E)-5-[2-(tributylstannyl)vinyl]uracil nucleosides, prepared by coupling of (E)-1,2-bis(tributylstannyl)ethene with 5-iodouracil precursors, have been developed as convenient substrates for a mild and rapid radiohalogenation via halodestannylation reactions. 6 However, the tendency of (E)-5-[2-(tributylstannyl)vinyl]arabinosyluridine and 5-trimethylgermylacetyl-araU to protiodestannylation was noted.

The 5-[2-(trimethylsilyI)ethyl]uracil nucleosides, prepared by Sonogashira coupling reactions between protected 5-iodouracil nucleosides with (trimethylsilyI)acetylene, have been hydrogenated to give (Z)-5-[2-(trimethylsilyI)vinyl]uracil products. Solvent-dependent isomerization of the latter into the E isomer was observed. The (E)-5-[2-(trimethylsilyI)vinyl]-2'-deoxyuridine has been also prepared by direct Pd-catalyzed coupling of (E)-2-[tributylstannyl]-1-(trimethylsilyI)ethene with protected 5-ido-2'-deoxyuridine. The 5-vinyl silanes were converted to S-(2-halovinyl)uracil products upon treatment with XeF2 and metal halides and were also utilized for the radioliodination via iododesilylations reactions.

The chemistry and biological activity of organogermainium compounds have been reviewed. A few biologically active germane-modified nucleoside analogues have been developed. Among them, the 5-trimethylgermyluracil and 1-(2-tetrahydrofuranyl)-5-trimethylgermyluracil exhibit cytotoxicity to melanoma B16 cells. The 1-(2-tetrahydrofuranyl)-6-triallylgermyl-5-fluorouracil derivatives have caused inhibition of DNA and RNA biosynthesis in Ptk cells almost twice as efficiently as the renowned antitumor drug FloraIur. The 5-trimethylgermyl-2'-deoxyuridine, which is one of the few known examples of germanium-containing nucleoside analogues, was shown to inhibit HSV-1 replication in vitro and block incorporation of thymidine into DNA of cancer ovarian cells. 18

Pd(0)-catalyzed, Lewis acid-promoted, and ultrasound- and microwave-accelerated hydrogermylation of alkynes provide vinyIgermanes with high regio- and stereoselectivity. Germyldesulfonylation protocols has been also developed for the synthesis of vinyl- and (α-fluoro)vinylgermanes. Herein, we report that hydrogermylation of the 5-ethynyluracil nucleosides with trialkyl-, triaryl-, and tris(trimethylsilyI)germanes in addition to the expected 5-(2-germylvinyI)uracil nucleosides provides also access to 5-(2-germylacetyl)uracil nucleosides which can be converted to 5-acetyluracil products. Several hydrogermylation approaches for the preparation of 5-(2-germylvinyI)uracil nucleosides of type 2 were initially tested. Thus, treatment of the acetyl protected 1-(β-2'-arabinofuranosyl)-5-ethynyluracil 1 with Ph3GeH in the presence of 1,1’-azobis(cyclohexanecarbonitrile) (ACCN), as radical initiator, in toluene at 90 °C (method A) produced predominantly the Z-vinyIgermanes 2a (E/Z, 9:5; Scheme 1). The 1H NMR spectra established the configuration for E-2a (J = 18.8 Hz) and Z-2a (J = 13.5 Hz) diastereomers. The formation of the Z isomer as the major product was in agreement with the expected anti-addition of germyl radical to the triple bond. Careful purification of the reaction mixture on a silica gel column gave not only pure Z-2a (47%) but also led to the isolation of a new product, whose structure was assigned (vide infra) as 5-[2-(triphenylgermyI)acetyl]uracil (β-germyl ketone) derivative 4a (12%; Table 1, entry 1).
Scheme 1. Hydrogermylation of 1-(β-D-Arabinofuranosyl)-5-ethenyluracil 1 with Germane Hydrides

![Diagram]

Compounds 2-4. Series: a R = Ph, b R = Me, c R = (Me3Si)3Ge

“Reagents and conditions: (a) R3GeH/(ACCN)/toluene/90 °C (method A), R3GeH/Et3B/THF/-78 °C (method B), or Pd(PPh3)4/THF/rt (method C); (b) NH3/MeOH/rt.

Analogous treatment of 1 with Ph3GeH without ACCN also yielded 2a and 4a (entry 2).

The Et3B-promoted addition27 of Ph3GeH to 1 in THF at low temperature (method B) gave Z-2a as the sole isolated product (55%, entry 3). However, analogous hydrogermylation of 1 at higher temperature (0 °C/6 h) afforded Z-2a and 4a (∼3:2, entry 4). Hydrogermylation of 1 with Ph3GeH in the presence of B(C6F5)322 in CH2Cl2 at ambient temperature produced 2a in lower than 10% yields (TLC, 1H NMR) while prolonged heating (48 h, reflux) produced a complex reaction mixture. The Pd(PPh3)4-catalyzed hydrogermylation19 of 1 with Ph3GeH in THF afforded a mixture of the expected E-isomer of 2a and the corresponding 5-[1-(triphenylgermyl)-ethenyl] regioisomer, produced by addition of germyl radical to α-carbon,3 in 3:2 ratio and 73% overall yield (entry 5; method C). The acyl product 4a was not isolated from the reaction catalyzed by Pd(PPh3)4.

At low temperature (∼78 °C), Et3B-promoted hydrogermylation27 of 1 with less reactive trimethylgermane failed to give vinylgermane 2b. However, at ambient temperature the hydrogermylation yielded 2b (E/Z, 15:85; entry 6) although in lower stereoselectivity. Moreover, no 5-[2-(trialkylgermyl)-acyetyl] product 4b was isolated from the reaction mixture.

Hydrogermylation of 1 with reactive (Me3Si)3GeH (ACCN/toluene/90 °C) stereoselectively produced the 5-[2-(TTMS-germyl)ethenyl]uracil analogue Z-2c (68%) in a shorter reaction time, though the acyl product 4c was also not isolated (30 min, entry 7). Deacetylation of Z-2a with NH3/MeOH afforded Z-3a (86%).

The Et3B-promoted hydrogermylation of the toluoyl protected of 5-ethenyluridine 5 with Ph3GeH/Et3B at −78 °C showed a slow conversion to 7a but warming of the reaction mixture to 0 °C afforded vinyl trimethylgermane Z-7a (40%) together with the 5-[2-(triphenylgermyl)acetyl] product 11a (13%, Scheme 2; entry 8). Analogous hydrogermylation of 5 with Me3GeH/Et3B at ambient temperature yielded only vinyl trimethylgermane 7b (E/Z, 45:55; entry 9). Deprotection of E/Z-7b with MeONa/MeOH afforded uridine analogue E/Z-

### Table 1. Hydrogermylation of 5-Ethenyluracil and Related Nucleosides with Germane Hydrides

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<th>entry</th>
<th>substrate</th>
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*Method A: R3GeH/(ACCN)/toluene/90 or 100 °C. Method B: R3GeH/Et3B/THF/-78 or 0 °C. Method C: Pd(PPh3)4/THF/rt.

**For the isolated products. &Crude reaction mixture (E/Z-2a, 5:95). $Without ACCN. °In addition to E-2a, the α-addition product was formed (∼3:2, 73% overall).

$Crude reaction mixture (E/Z-2c, 4:96). ‡Toluene/THF (20:1, v/v) was used as solvent. Oil bath. *With toluene/DMF/H2O (20:1:0.1, v/v) as solvents E-9a, Z-9a and 12a (∼2:2:1, 40% overall) were obtained. †With addition of 25 μL of H2O (14 equiv).
8b (71%), confirming stability38 of the C(sp^3)-Ge(alkyl)₃ bond in basic conditions.

Hydrogermylation of the toluoyl protected 5-ethyl-2'-deoxyuridine 6 with Ph₃GeH/Et₃B produced the vinyltriphénylgermane Z-9a (61%) along with the S-[2-(triphenylermyl)acetyl] product 12a (12%, entry 10). Treatment of 6 with Ph₃GeH/ACCN in toluene/THF (20:1, v/v) also yielded Z-9a and 12a (entry 11). Interestingly, analogous hydrogermylation of 6 in toluene/DMF with addition of a “measured” amount of water (14 equiv.) produced mixture of E/Z isomers of 9a (∼1:1) as well as 12a (entry 11, footnote i); DMF or THF were added to increase solubility of 6 in reaction mixture). Deprotection of Z-9a with NH₃/MeOH provided 2'-deoxyuridine analogue Z-10a (65%). Treatment of 6 with Me₃GeH/Et₃B gave E/Z-9b (entry 12), but once again hydrogermylation with alkyllgermanes did not yield the germyl ketone product.

Treatment of E/Z-9b (40:60) with N-bromosuccinimide (NBS) followed by deprotection (NH₃/MeOH) afforded a mixture of S-(2-bromovinyl)-2'-deoxyuridines (E/Z, ∼2:3; 70%) illustrating a potential application of vinyl 5-[2-(trimethylgermyl)vinyl]uracil nucleosides toward the synthesis of 5-(2-halovinyl) analogues with possible applications for radio labeling. Stereoselective halodegermylation of vinyl trilalkygermanes with NBS or NIS with retention of the double-bond geometry is known.22,28,29 It is also worth mentioning that substitution of the trilalkygermanyl group on an sp² carbon29,30 (as well as sp carbon30,31) with a halogen proceed not only more easily than the substitution of the corresponding trialkylsulfonyl group but also with improved stereochemical outcome.

It is noteworthy that hydrogermylation of the alkyl- or aryalkynes usually provides vinylgermanes in high yields, while the formation of the corresponding β-germyl ketones have not been observed.23,24,27,32 We reexamined the hydrogermylation of phenylacetylene with Ph₃GeH under conditions described in methods A and B and found no formation of the β-germyl ketones. We also found that hydrostannylation and hydro-silylation of alkyne 5 with Ph₃SnH and Ph₃SiH under analogous conditions failed to yield S-[2-(triphenylstannyl- or -silyl)acyl] products of type 11a suggesting that the formation of S-acyclural products is selective for germane hydrides. Intrigued by this interesting finding, we have examined the chemistry involving the formation of S-ketopyrimidine nucleosides (e.g., 4a, 11a, or 12a) employing 1-N-benzyl-5-ethyluracil 13 as a model substrate. Thus, hydrogermylation of the readily available33,34 13 with Ph₃GeH/ACCN in toluene (90 °C/2 h) produced the Z-vinylgermane 14 and germyl ketone 15 (∼2:1, entry 13; Scheme 3). Analogous treatment of 13 with Ph₃GeH in toluene without ACCN yielded Z-14 and 15 in 34% and 20% yields (entry 14), whereas similar reaction of 13 with Ph₃GeH in “moist” toluene interestingly yielded only the syn-addition product E-14 (86%, entry 15; see also entry 11, footnote i). Hydrogermylation of 13 with Ph₃GeH in the presence of Et₂B/THF at 0 °C produced Z-14 as a sole product (entry 16).

The structures of the (triphenylermyl)methyl ketone (β-germyl ketone) products were established by spectroscopic analysis. Thus, the 1H NMR spectrum of 11a confirmed the absence of the vinyl unit, whereas two upfield shifted doublets at 3.76 and 3.87 ppm (J = 9.0 Hz) supported the presence of the C(O)CH₂Ge moiety. The peak at 193.3 ppm in the 13C NMR spectrum of 11a confirmed the presence of the ketone. The HMBC and NOE correlations also supported the proposed structures (Figure S1, Supporting Information).

The (+)ESI-MS analyses of 15 produced the [M + Na]+ ion as the predominant peak. The (-)ESI-MS/MS product ion spectrum of [M – H]⁻ (m/z 547 [7⁴Ge]) showed a loss of 43u (CONH) as the most abundant product ion (m/z 504[7⁴Ge]). Formation of the β-germyl ketones (e.g., 15) probably involves an initial attack of the triphenylermyl radical at the triple bond of 13 to give a vinylic radical 16 (Figure 1).

Abstraction of hydrogen from triphenylermylgermane in an anti fashion would produce Z-vinylgermane 14 as a major product while the syn addition could produce the E isomer (path a). Reaction of radical 16 with residual oxygen present in the reaction mixture might lead to peroxyl radical 17 which should abstract hydrogen from germane hydride35 to produce hydroperoxide. The latter can be converted to enol 18, probably by radical mechanism, and undergo tautomerization to yield the conjugated β-germyl ketone 15 (path b).

Efforts have been made to further optimize conditions for the preparation of 15 (and 14) from the reaction of 13 with Ph₃GeH. Thus, experiments under Ar vs N₂ vs atmospheric conditions as well as using dry vs reagent-grade toluene vs “moist” toluene (with the added measured amount of H₂O or D₂O) did not improve the yield of 15. In fact, they led mainly to the formation of Z-14 or E/Z-14 and 15 albeit in different yields and ratios. It is noteworthy that treatment of 13 with

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**Scheme 3. Hydrogermylation of the 5-Ethynyluracil 13**

![Scheme 3](image)

“Reagents and conditions: (a) Ph₃GeH/(ACCN)/toluene/(H₂O)/100 or 90 °C or Ph₃GeH/Et₂B/THF/0 °C.
Ph₃GeH in oxygenated toluene resulted in the recovery of unchanged 13. Optimal conditions for the formation of β-germyl ketones would require very low rate of initiation and very low and nearly constant concentration of Ph₃GeH and oxygen, which would allow the germyl radical to react with the vinyl group rather than oxygen and the vinyl radical 16 to react with oxygen rather than germane. Still our experiments employing slow addition of Ph₃GeH via syringe-pump over 24 h did not improve the yield of 15.

During recrystallization of the crude 15 from MeOH, we noticed the formation of a new byproduct whose structure was established as 5-acetyl-1-N-benzyluracil 20 both spectroscopically and by comparison with a sample of 20 that was independently synthesized by acid-catalyzed hydration of 15 analogues with triphenylgermane in toluene at elevated temperatures. The yield of vinylgermanes in good yields and high stereoselectivity. The Et₃B-promoted hydrogermylation of 5-[(triphenylgermyl)acetyl]uracil nucleosides in yields up to 85% provided vinylgermanes in addition to vinylgermanes produced also 5-[(triphenylgermyl)ethenyl]uracil (2a) and 1-[(2,3,5-Triphenylgermyl)ethyl]uracil (4a).

### Method A

Nucleoside 1 (50 mg, 0.13 mmol) was added to freshly distilled toluene (6 mL) and the suspension was stirred and degassed with N₂ for 30 min. The mixture was then preheated at 80 °C, and Ph₃GeH (50 mg, 0.16 mmol) and ACCN (4 mg, 0.02 mmol) were added. The temperature was increased to 90 °C, and the solution was stirred until 1 was completely consumed (TLC; 14 h). The volatiles were removed in vacuo, and the residue was chromatographed (hexane/EtOAc 2:3) to give a separable mixture of Z-2a (43 mg, 47%) and 4a (11 mg, 12%). Z-2a: 1H NMR δ 1.99 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 3.70 (dd, J = 13.7, 7.7 Hz, 1H), 3.91–3.98 (m, 2H), 4.97 (dd, J = 3.2, 2.0 Hz, 1H), 5.27 (dd, J = 4.1, 1.9 Hz, 1H), 5.71 (d, J = 4.1 Hz, 1H), 6.56 (d, J = 13.5 Hz, 1H), 7.08 (d, J = 1.0 Hz, 1H), 7.36–7.52 (m, 16H), 8.30 (br s, 1H). 13C NMR δ 20.4, 20.6, 20.7, 62.3, 74.6, 76.1, 79.8, 84.4, 113.4, 128.4, 129.1, 131.7, 134.8, 136.3, 136.41, 138.2, 148.6, 161.3, 168.5, 169.4, 170.2; MS m/z: 701 (100, MH⁺), 699 (71, MH⁺), 698 (51, MH⁺). Anal. Calcld for C₃₅H₃₄O₂SbEnNaO₁₀ [M + Na]⁺: 739.1323, found 739.1311.

### Method B

Et₃B (1M/THF; 140 µL, 0.14 mmol) was added to a stirred solution of 1 (50 mg, 0.172 mmol) and Ph₃GeH (43 mg, 0.14 mmol) in anhydrous THF (5 mL) placed in screw-capped glass tube at −78 °C. After 3 h, when TLC showed appearance of less polar spot, the reaction mixture was warmed up to −60 °C and was stirred for 1.5 h. The volatiles were evaporated, and the residue was chromatographed (hexane/EtOAc, 2:3) to give Z-2a (49 mg, 55%) as a white powder after crystallization from hexane/EtOAc.

### Method C

Ph₃GeH (59 mg, 0.2 mmol) and Pd(PPh₃)₄ (8 mg, 0.017 mmol) were added to a stirred suspension of 1 (70 mg, 0.18 mmol) in THF (3 mL) in a flame-dried round bottle flask at rt under N₂. After 5 h, the volatiles were evaporated in vacuo, and the residue was chromatographed (hexane/EtOAc, 1:1) to give inseparable mixture of the E-isomer of 2a with the characteristic peaks. NMR δ 6.31 (d, J = 4.0 Hz, H1'), 6.69 (d, J = 18.8 Hz, CH).

### Analogous thermal rearrangements of the β-silylketones into S-silyl substituted enols have been reported. Heating 15 in MeOD or MeOH-d₄ provided quantitatively 1-deuteriomethyl ketone 21, which supports the proposed degradation pathway.

In summary, we have demonstrated that radical hydrogermylation of the S-acetylenic derivatives of protected uracil, uridine, 2'-deoxyuridine, and 1-(β-d-arabinofuranosyl)uracil analogues with triphenylgermane in toluene at elevated temperature provided vinylgermanes in good yields and high Z-stereoselectivity. The E isomers can be formed in the presence of an added “measured” amount of water. Hydrogermylation of S-ethynyluracil nucleosides with triphenylgermane in addition to vinylgermanes produced also S-[(2-triarylgermyl)acetyl]uracil nucleosides in yields up to 20%.

Thermolysis of the latter in MeOH afforded quantitatively S-acetylenyluracil nucleosides via hydrolysis of the O-germyl substituted enols. The Et₃B-promoted hydrogermylation of S-ethynyluracil nucleosides with trimethylgermane in THF at low temperature gave E/Z mixture of vinylgermanes. Bromodegradation of vinyl trimethylgermanes with NBS provides access to S-(2-bromovinyl) analogues.

### EXPERIMENTAL SECTION

1H (Me₄Si) NMR spectra at 400 MHz and 13C (Me₄Si) at 100.6 MHz were determined in CDCl₃ unless otherwise noted. Mass spectra (MS) were obtained with atmospheric pressure chemical ionization (APCI) technique and HRMS in ESI TOF mode unless otherwise noted.

1-2(2,3,5-Tri-O-acetyl-β-d-arabinofuranosyl)-5-[(E/Z)-2-(trimethylgermyl)ethenyl]uracil (2b). Nucleoside 1 (50 mg, 0.13 mmol) was treated with Me₃GeH (30 mg, 0.26 µL, 0.25 mmol) in dry THF (5 mL) as described in method B (with injection of Me₃GeH into the reaction mixture via syringe and progressive warming from 0 °C to rt) for 14 h. The volatiles were removed under reduced pressure, and the residue was chromatographed (hexane/EtOAc, 2:3) to give E/Z-2b (27 mg, 40%; E/Z; 15:85); 1H NMR δ 0.26 (s, 7.65H), 0.28 (s, 1.35H), 2.02 (s, 3H), 2.12 (s, 2.55H), 2.15 (s, 0.45H), 2.16 (s, 2.55H), 2.17 (s, 0.45H), 4.19–4.25 (m, 1H), 4.34 (dd, J = 11.9, 6.2 Hz, 0.85H), 4.37–4.45 (m, 0.15H), 4.44 (dd, J = 11.9, 4.2 Hz, 0.85H), 4.52 (dd, J = 11.9, 6.2 Hz, 0.15H), 5.11 (dd, J = 3.8, 1.4 Hz, 0.85H), 5.15 (dd, J = 3.4, 1.6 Hz, 0.15H), 5.44–5.48 (m, 1H), 6.10 (d, J = 3.8 Hz, 0.85H), 6.24 (d, J = 3.8 Hz, 0.85H), 6.33 (d, J = 4.0 Hz, 0.15H), 6.60 (d, J = 18.9 Hz, 0.15H), 6.80 (d, J = 19.0 Hz, 0.15H), 6.98 (dd, J = 13.8, 10.0 Hz, 0.85H), 7.45 (d, J = 1.0 Hz, 0.85H), 7.59 (s, 0.15H), 8.97 (br s, 0.15H), 9.09 (br s, 0.85H). 13C NMR δ 1.7–1.0, 20.5,...

![Figure 2. Plausible pathway for the thermal degradation of β-germyl ketone 15.](Image)
Note

20.6, 20.8, 20.87, 20.92, 62.7, 63.2, 74.7, 74.8, 76.4, 76.5, 80.4, 80.8, 84.6, 112.9, 114.2, 132.1, 133.6, 134.3, 136.1, 136.4, 137.6, 149.2, 149.6, 161.8, 162.2, 168.6, 168.7, 169.7, 169.8, 170.5; HRMS calcd for C74H53GeN2O9Si3 [M + Na]+ 951.2307, found 951.2315.

Compound 11a had: UV (MeOH) λmax = 282 nm; 1H NMR δ 0.32 (3H, 1H), 1.3H, 1.62 (1H, 1H), 6.28 (d, J = 13.5 Hz, 1H), 6.90 (d, J = 13.5, 1.4 Hz, 1H), 7.29 (d, J = 1.4 Hz, 1H), 8.27 (br s, 1H); 13C NMR δ 0.19, 20.7, 20.9, 21.0, 63.1, 75.0, 76.5, 80.7, 85.4, 116.1, 133.9, 134.1, 135.6, 146.2, 160.2, 168.9, 169.7, 170.6; HRMS calcd for C30H28GeN2O9Si3 [M + H]+ 689.1801, found 689.1798. 1H NMR of C53H46GeN2O9Na [M + Na]+ 537.1076. Found 537.1075. Anal. Calcld. for C30H28GeN2O9Si3 [M + Na]+ 689.1798.

The volatiles were evaporated and they were chromatographed (hexane/EtOAc, 3:2) to give Z-2c (152 mg, 68%): 1H NMR δ 0.20 (27H, 2H), 0.21 (3H, 2H), 2.14 (s, 1H), 4.17–4.24 (m, 1H), 4.34 (dd, J = 12.0, 5.5 Hz, 1H), 4.38 (dd, J = 12.0, 5.5 Hz, 1H), 5.14 (dd, J = 3.6, 1.6 Hz, 1H), 5.47 (dd, J = 3.8, 1.7 Hz, 1H), 6.16 (d, J = 3.9 Hz, 1H), 6.28 (d, J = 13.5 Hz, 1H), 6.90 (dd, J = 13.5, 1.4 Hz, 1H), 7.29 (d, J = 1.4 Hz, 1H), 8.27 (br s, 1H). 13C NMR δ 195.7, 20.7, 20.9, 21.0, 65.1, 75.0, 76.5, 80.7, 85.4, 116.1, 133.9, 134.1, 135.6, 146.2, 160.2, 168.9, 169.7, 170.6; HRMS calcd for C30H28GeN2O9Si3 [M + H]+ 689.1801, found 689.1798. 1H NMR of C30H28GeN2O9Na [M + Na]+ 537.1076. Found 537.1075. Anal. Calcld. for C30H28GeN2O9Si3 [M + Na]+ 689.1798.

The crude reaction mixture showed 4:96 mixture of 2c and 5a.

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2.40 (s, 6H), 2.42 (s, 3H), 2.44 (s, 3H), 4.34 (dd, J = 12.0, 5.5 Hz, 1H), 4.38 (dd, J = 12.0, 5.5 Hz, 1H), 5.14 (dd, J = 3.6, 1.6 Hz, 1H), 5.47 (dd, J = 3.8, 1.7 Hz, 1H), 6.16 (d, J = 3.9 Hz, 1H), 6.28 (d, J = 13.5 Hz, 1H), 6.90 (dd, J = 13.5, 1.4 Hz, 1H), 7.29 (d, J = 1.4 Hz, 1H), 8.27 (br s, 1H); 13C NMR δ 0.19, 20.7, 20.9, 21.0, 65.1, 75.0, 76.5, 80.7, 85.4, 116.1, 133.9, 134.1, 135.6, 146.2, 160.2, 168.9, 169.7, 170.6; HRMS calcd for C30H28GeN2O9Si3 [M + H]+ 689.1801, found 689.1798. 1H NMR of C30H28GeN2O9Na [M + Na]+ 537.1076. Found 537.1075. Anal. Calcld. for C30H28GeN2O9Si3 [M + Na]+ 689.1798.

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2.40 (s, 6H), 2.42 (s, 3H), 2.44 (s, 3H), 4.34 (dd, J = 12.0, 5.5 Hz, 1H), 4.38 (dd, J = 12.0, 5.5 Hz, 1H), 5.14 (dd, J = 3.6, 1.6 Hz, 1H), 5.47 (dd, J = 3.8, 1.7 Hz, 1H), 6.16 (d, J = 3.9 Hz, 1H), 6.28 (d, J = 13.5 Hz, 1H), 6.90 (dd, J = 13.5, 1.4 Hz, 1H), 7.29 (d, J = 1.4 Hz, 1H), 8.27 (br s, 1H); 13C NMR δ 0.19, 20.7, 20.9, 21.0, 65.1, 75.0, 76.5, 80.7, 85.4, 116.1, 133.9, 134.1, 135.6, 146.2, 160.2, 168.9, 169.7, 170.6; HRMS calcd for C30H28GeN2O9Si3 [M + H]+ 689.1801, found 689.1798. 1H NMR of C30H28GeN2O9Na [M + Na]+ 537.1076. Found 537.1075. Anal. Calcld. for C30H28GeN2O9Si3 [M + Na]+ 689.1798.
Note: Treatment of 6 (50 mg, 0.10 mmol) with Ph3GeH (36 mg, 0.12 mmol) in toluene (4 mL) as described in Method A [DMF (0.2 mL) and water (25 μL, 25 mg, 0.14 mmol) were added to the preheated reaction mixture] gave partially separated isomers, 9a and 9b. Compound 9a had characteristic peaks for vinyl protons at δ 6.63 (d, J = 18.8 Hz, 1H) and within the envelope of aromatic protons at δ 7.20–7.50 (Cosy).

1-[(2-Deoxy-3,5-di-B-D-erythro-pentofuranos-1-yl)alkynyl]uracil (10a).
A solution of 5′-[(2-Deoxy-3,5-di-B-D-erythro-pentofuranos-1-yl)alkynyl]uracil (9b). Nucleoside (6g) (45.0 mg, 0.092 mmol) was treated with Me3GeH (21.8 mg, 21.6 μL, 0.18 mmol) in dry THF (5 mL) as described in Method B with injection of Me3GeH into the reaction mixture via syringe and progressive warming from 0 °C to rt) for 10 h. The volatiles were evaporated, and the residue was chromatographed (hexane/EtOAc, 1:1) to give E/Z-9b (16.5 mg, 35%; E/Z: 40/60; 1H NMR δ 0.14 (s, 3.6H), 0.21 (s, 5.4H), 2.25–2.34 (m, 14H), 2.42, 2.43, 2.45 (singlets, 6H), 2.78 (dd, J = 14.2, 5.5, 1.6 Hz, 0.6H), 2.80 (dd, J = 14.3, 5.1, 1.2 Hz, 0.4H), 4.50–4.61 (m, 14H), 4.65 (dd, J = 12.2, 3.2 Hz, 0.6H, 4.73–4.77 (m, 0.8H), 4.75 (dd, J = 12.2, 3.8 Hz, 0.6H), 4.59 (dd, J = 4.9, 1.9 Hz, 0.6H), 4.63 (dd, J = 6.4 Hz, 0.4H), 6.00 (d, J = 13.7 Hz, 0.6H), 6.40 (d, J = 8.7, 5.4 Hz, 0.6H), 6.41 (d, J = 19.2 Hz, 0.4H), 6.46 (d, J = 8.9, 5.2 Hz, 0.4H), 6.72 (d, J = 19.0 Hz, 0.4H), 6.78 (dd, J = 13.7, 1.0 Hz, 0.6H), 7.22–7.32 (m, 4.4H), 7.48 (d, J = 1.0 Hz, 0.6H), 7.67 (s, 0.4H), 7.85–7.99 (m, 4.9H), 8.51 (br s, 0.4H), 8.57 (br s, 0.6H); 1C NMR δ −2.0, −0.22, 21.70, 21.73, 38.5, 64.1, 64.4, 74.7, 75.0, 82.9, 83.1, 85.6, 113.9, 115.4, 126.3, 126.5, 126.9, 129.30, 129.34, 129.50, 129.54 129.69, 129.8, 131.9, 133.2, 132.4, 134.2, 134.5, 135.1, 138.1, 144.4, 144.5, 146.2, 149.2, 149.7, 161.5, 161.9, 166.0, 166.1; HRMS calcd for C31H26N8GeO5 (539.1480): [C31H26N8GeO5] + 539.1483, found. Noted: Treatment of 9b (E/Z, 40:60; 12 mg; 0.02 mmol) with NBS (5 mg, 0.028 mmol) in CHCl3/CH2Cl2 (1:1.5, v/v; 2.5 mL) for 6 h at 0 °C followed by deprotection with NH4/MeOH (0 °C to rt) gave 5′-[(2-bromovinyl)-2′-(2,6-dimethylphenyl)ureido]uracil (10a).

1-(2-Deoxy-3,5-di-B-D-erythro-pentofuranos-1-yl)alkynyl]uracil (10b).
A saturated solution of NH4/MeOH (2 mL) was added to a suspension of Z-9a (33 mg, 0.042 mmol) in MeOH (2 mL), and the resulting mixture was stirred for 24 h at rt. The volatiles were evaporated, and the residue was chromatographed (EtOAc) to give Z-10a (15 mg, 65%); 1H NMR (MeOD-d4) δ 1.44 (d, J = 14.2, 7.9, 6.6 Hz, 1H), 1.87 (d, J = 13.6, 5.9, 2.7 Hz, 1.38 (d, J = 4.4 Hz, 2H), 3.70 (q, J = 3.8 Hz, 1.9H), 3.97 (d, J = 6.0, 3.3, 2.8 Hz, 1H), 5.81 (dd, J = 8.0, 6.0 Hz, 1H), 6.52 (dd, J = 13.3 Hz, 1.7H), 7.28 (d, J = 1.1 Hz, 1.7H), 7.31 (dd, J = 13.3, 1.1 Hz, 1.7H), 7.36–7.54 (m, 15H); 1C NMR (MeOD-d4) δ 40.3, 63.0, 72.3, 86.3, 88.6, 115.8, 129.5, 130.2, 131.8, 135.9, 138.1, 138.2, 140.8, 151.6, 164.7; MS (ESI) m/z 581 (100, M+Na), 579 (790, M+Na), 577 (49, M+Na), 575 (42, M+Na). Anal. Calcd for C16H12GeNaO3 (557.18): C, 52.1; H, 4.07; N, 0.93. Found: C, 52.1; H, 4.07; N, 0.93. Noted: Treatment of 9b (E/Z, 20:1; 75:210) for 15 mg, 91% (0.02 mmol) using MeOD or MeOD-d4, instead of MeOH gave 1-N-alkyldieno-5′-[(2-deuteriocytosinyl)uracil (21a, 4.2 mg, 94%); GC–MS (q, m/z 245 (20%, M1), 91 (100). 1H NMR spectrum of 21 corresponded to this of the above 20 with 1/3 reduction of the integrated intensity for the signal from methyl group at C21 ppm.

ASSOCIATED CONTENT
Supporting Information
NOE and HMBC interactions observed for 11a, and 1H and 13C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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References