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

Yong Liang, Jean-Philippe Pitteloud[†], and Stanislaw F. Wnuk

Department of Chemistry and Biochemistry, Florida International University, Miami, Florida, 33199, USA

Stanislaw F. Wnuk: wnuk@fiu.edu

Abstract

A stereoselective radical-mediated hydrogermylation of the protected 5-ethynyluracil nucleosides with trialkyl-, triaryl-, or tris(trimethylsilyl)-germanes gave (*Z*)-5-(2-germylvinyl)-uridine, 2'-deoxyuridine or *ara*-uridine as major products. Reaction of the β -triphenylgermyl vinyl radical intermediate with oxygen and fragmentation of the resulting peroxyradical provided also 5-[2-(triphenylgermyl)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*-germyl substituted enol yielded 5-acetyluracil nucleosides in quantitative yield.

A broad spectrum of biological activity has been described for 5-substituted pyrimidine nucleosides.¹ One especially potent and selective antiviral drug of this class is (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU).² Pronounced cytotoxicity and significant antiviral activity have been reported for 1-(β -D-arabinofuranosyl)-5-ethynyluracil³ and 5-ethynyl-2'-deoxyuridine.⁴ The synthesis of the numerous 5-substituted pyrimidine nucleosides *via* Pd-assisted routes have been reviewed.⁵

The (*E*)-5-[2-(tributylstannyl)vinyl]uracil nucleosides, prepared by coupling of (*E*)-1,2-bis(tributylstannyl)ethene with 5-iodouracil precursors⁶ or via radical hydrostannylation of 5-ethynyluracil precursors,^{7,8} have been developed as convenient substrates for a mild and rapid radiohalogenation via halodestannylation reactions.^{6–9} However, the tendency of (*E*)-5-[2-(tributylstannyl)vinyl]arabinosyl uridine⁸ and 5-trimethylstannyl araU⁹ to protiodestannylation was noted.

The 5-[2-(trimethylsilyl)ethynyl]uracil nucleosides, prepared by Sonogashira coupling reactions between protected 5-iodouracil nucleosides with (trimethylsilyl)acetylene,^{5,10} have been hydrogenated to give (*Z*)-5-[2-(trimethylsilyl)vinyl]uracil products.¹¹ Solvent dependent isomerization of the latter into the *E* isomer was observed.¹⁰ The (*E*)-5-[2-(trimethylsilyl)vinyl]-2'-deoxyuridine has been also prepared by direct Pd-catalyzed coupling of (*E*)-2-(tributylstannyl)-1-(trimethylsilyl)ethene with protected 5-iodo-2'-deoxyuridine.¹² The 5-vinyl silanes were converted to 5-(2-halovinyl)uracil products upon treatment with XeF₂ and metal halides,¹¹ and were also utilized for the radioiodination via iododesilylations reactions^{10,12}

Correspondence to: Stanislaw F. Wnuk, wnuk@fiu.edu.

[†]Present address: Torrey Pines Institute for molecular studies, FL, USA

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>.

The chemistry¹³ and biological activity of organogermanium compounds have been reviewed.^{14,15} A few biologically active germane-modified nucleoside analogues have been developed. Among them, the 5-trimethylgermyluracil and 1-(2-tetrahydrofuryl)-5-trimethylgermyluracil exhibit cytotoxicity to melanoma B16 cells.¹⁶ The 1-(2-tetrahydrofuryl)-6-trialkylgermyl-5-fluorouracil derivatives have caused inhibition of DNA and RNA biosynthesis in *Frh*k cells almost twice as efficiently as the renowned antitumor drug Ftorafur.¹⁷ 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,^{19,20} Lewis acid-promoted,^{21,22} radical-mediated,²³ and ultrasound- and microwave-accelerated²⁴ hydrogermylation of alkynes provide vinyl germanes with high regio and stereoselectivity. Germyldesulfonylation protocols has been also developed for the synthesis of vinyl and (α -fluoro)vinyl germanes.²⁵ Herein, we report that hydrogermylation of the 5-ethynyluracil nucleosides with trialkyl-, triaryl-, and tris(trimethylsilyl)germanes in addition to the expected 5-(2-germylvinyl)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-germylvinyl)uracil nucleosides of type **2** were initially tested. Thus, treatment of the acetyl protected 1-(β -D-arabinofuranosyl)-5-ethynyluracil²⁶ **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*-vinyl germanes **2a** (*E/Z*, 5:95; 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 expected²³ *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-(triphenylgermyl)acetyl]uracil (β -germylketone) derivative **4a** (12%; Table 1, entry 1). 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,¹⁹ 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 vinyl germane **2b**. However, at ambient temperature the hydrogermylation yielded **2b** (*E/Z*, 15:85; entry 6) although in lower stereoselectivity. Moreover, no 5-[2-(trialkylgermyl)acetyl] 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-ethynyluridine **5** with Ph₃GeH/Et₃B at –78 °C showed a slow conversion to **7a** but warming of the reaction mixture to 0 °C afforded vinyl triphenylgermane **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-8b* (71%), confirming stability²⁸ of the C(*sp*²)-Ge(alkyl)₃ bond in basic conditions.

Hydrogermylation of the toluoyl protected 5-ethynyl-2'-deoxyuridine **6** with Ph₃GeH/Et₃B produced the vinyl triphenylgermane **Z-9a** (61%) along with the 5-[2-(triphenylgermyl)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 "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 alkyl germanes 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 5-(2-bromovinyl)-2'-deoxyuridines (*E/Z*, ~2:3; 70%) illustrating a potential application of vinyl 5-[2-(trimethylgermyl)vinyl]uracil nucleosides towards the synthesis of 5-(2-halovinyl) analogues with possible applications for radiolabeling. Stereoselective halodegermylation of vinyl trialkylgermanes 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 trialkylgermyl group on a *sp*² carbon^{29,30} (as well as *sp* carbon^{30,31}) with a halogen proceed not only more easily than the substitution of the corresponding trialkylsilyl group but also with improved stereochemical outcome.

It is noteworthy that hydrogermylation of the alkyl or aryl alkynes usually provides vinyl germanes in high yields, while the formation of the corresponding β-germylketones have not been observed.^{23,24,27,32} We reexamined the hydrogermylation of phenylacetylene with Ph₃GeH under conditions described in Method A and B and found no formation of the β-germylketones. We also found that hydrostannylation and hydrosilylation of alkyne **5** with Ph₃SnH and Ph₃SiH under analogous conditions failed to yield 5-[2-(triphenylstannyl-, or silyl)acetyl] products of type **11a** suggesting that the formation of 5-acyluracil products is selective for germane hydrides. Intrigued by this interesting finding, we have examined the chemistry involving the formation of 5-keto pyrimidine nucleosides (e.g. **4a**, **11a** or **12a**) employing 1-*N*-benzyl-5-ethynyluracil **13** as a model substrate. Thus, hydrogermylation of the readily available^{33,34} **13** with Ph₃GeH/ACCN in toluene (90 °C/2 h) produced the *Z*-vinyl germane **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 Et₃B/THF at 0 °C produced **Z-14** as a sole product (entry 16).

The structures of the (triphenylgermyl)methyl ketone (β-germylketone) products were established by spectroscopic analysis. Thus, 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 in SI section). 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 [^{74}Ge]) showed loss of 43u (CONH) as the most abundant product ion (m/z 504 [^{74}Ge]).

Formation of the β -germylketones (e.g., **15**) probably involves an initial attack of the triphenylgermyl radical at the triple bond of **13** to give a vinylic radical **16** (Figure 1). Abstraction of hydrogen from triphenylgermane in an *anti* fashion would produce *Z*-vinyl germane **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 peroxy 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 -germylketone **15** (path *b*).

Efforts have been made to further optimize conditions for the preparation of **15** (and **14**) from the reaction of **13** with Ph_3GeH . Thus, experiments under Ar vs N_2 vs atmospheric conditions as well as using dry vs reagent-grade toluene vs "moist" toluene (with the added measured amount of H_2O or D_2O) 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 Ph_3GeH in oxygenated toluene resulted in the recovery of unchanged **13**. Optimal conditions for the formation of β -germylketones would require very low rate of initiation and very low and nearly constant concentration of Ph_3GeH and oxygen, which would allow the germyl radical to react with the vinyl group rather than oxygen and the vinylic radical **16** to react with oxygen rather than germane. Still our experiments employing slow addition of Ph_3GeH via syringe-pump over 24 hours 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 hydration³⁶ of **13**. We found that heating of **15** in MeOH gave the 5-acetyl product **20** quantitatively. Conversion of (triphenylgermyl)methyl ketone **15** to methyl ketone **20** most probably involves intramolecular thermal isomerization which proceeds via a four-centered activated complex. Hydrolysis of the resulting *O*-germyl substituted enol **19** led to ketone **20** (Figure 2). Analogous thermal rearrangements of the β -silylketones into *O*-silyl substituted enols have been reported.³⁷ Heating **15** in MeOD or MeOH- d_4 provided quantitatively 1-deuteriomethyl ketone **21**, which supports the proposed degradation pathway.

In summary, we have demonstrated that radical hydrogermylation of the 5-acetylenic derivatives of protected uracil, uridine, 2'-deoxyuridine, and 1-(β -D-arabinofuranosyl)uracil analogues with triphenylgermane in toluene at elevated temperature provided vinyl germanes in good yields and high *Z*-stereoselectivity. The *E* isomers can be formed in the presence of added "measured" amount of water. Hydrogermylation of 5-ethynyluracil nucleosides with triphenylgermane in addition to vinyl germanes produced also 5-[2-(triphenylgermyl)acetyl]uracil nucleosides in yields up to 20%. Thermolysis of the latter in MeOH afforded quantitatively 5-acetyluracil nucleosides via hydrolysis of the *O*-germyl substituted enols. The Et_3B -promoted hydrogermylation of 5-ethynyluracil nucleosides with trimethylgermane in THF at low temperature gave *E/Z* mixture of vinyl germanes. Bromodegermylation of vinyl trimethylgermanes with NBS provides access to 5-(2-bromovinyl) analogues.

Experimental Part

^1H (Me_4Si) NMR spectra at 400 MHz and ^{13}C (Me_4Si) at 100.6 MHz were determined in CDCl_3 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-(2,3,5-Tri-*O*-acetyl- β -D-arabinofuranosyl)-5-(*E/Z*)-[2-(triphenylgermyl)ethenyl]uracil (**2a**) and 1-(2,3,5-tri-*O*-acetyl- β -D-arabinofuranosyl)-5-[2-(triphenylgermyl)acetyl]uracil (**4a**)

Method A. Nucleoside **1**²⁶ (50 mg, 0.13 mmol) was added to freshly distilled toluene (6 mL) and the suspension was stirred and degassed with N_2 for 30 min. The mixture was then preheated at 80 °C and Ph_3GeH (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); ^{13}C 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, 136.38, 136.41, 138.2, 148.6, 161.3, 168.5, 169.4, 170.2; MS m/z 701 (100, MH^+ , ^{74}Ge), 699 (71, MH^+ , ^{72}Ge), 698 (51, MH^+ , ^{70}Ge). Anal. Calcd for $\text{C}_{35}\text{H}_{34}\text{GeN}_2\text{O}_9 \cdot 0.25 \text{ EtOH}$ (710.81): C, 59.99; H, 5.03; N, 3.94. Found: C, 59.63; H, 4.92; N, 4.00.

^1H NMR of the crude reaction mixture also showed presence (~5%) of the *E*-**2a** with the characteristic peaks at δ 6.31 (d, J = 4.0 Hz, H^1), 6.69 (d, J = 18.8 Hz, CH).

Compound **4a** had: ^1H NMR δ 1.90 (s, 3H), 2.14 (s, 3H), 2.15 (s, 3H), 3.48 (d, J = 9.3 Hz, 1H), 4.16–4.19 (m, 1H), 4.17 (d, J = 9.3 Hz, 1H), 4.33 (dd, J = 12.1, 4.5 Hz, 1H), 4.44 (dd, J = 12.1, 4.9 Hz, 1H), 5.12 (dd, J = 3.3, 1.6 Hz, 1H), 5.33 (dd, J = 4.1, 1.6 Hz, 1H), 6.23 (d, J = 4.1 Hz, 1H), 7.21–7.55 (m, 15H), 8.08 (s, 1H), 8.49 (br. s, 1H); ^{13}C NMR δ 20.4, 20.7, 20.8, 33.0, 62.4, 74.6, 76.6, 80.8, 83.9, 113.3, 128.4, 129.5, 135.1, 135.3, 146.6, 148.8, 160.4, 168.8, 169.6, 170.8, 194.2; HRMS calcd for $\text{C}_{35}\text{H}_{34}^{74}\text{GeN}_2\text{NaO}_{10} [\text{M}+\text{Na}]^+$ 739.1323, found 739.1311.

Method B. Et_3B (1M/THF; 140 μL , 0.14 mmol) was added to a stirred solution of **1** (50 mg, 0.127 mmol) and Ph_3GeH (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/ Et_2O .

Method C. Ph_3GeH (59 mg, 0.2 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (8 mg, 0.08) were added to a stirred suspension of **1** (70 mg, 0.18 mmol) in THF (3 mL) in a flamed dried round bottle flask at rt under N_2 . 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** and the α -addition product (90 mg, 73%; *E*-**2a**/ α -addition product, 3:2): MS (ESI) m/z 701 (100, MH^+ , ^{74}Ge), 699 (70, MH^+ , ^{72}Ge), 697 (50, MH^+ , ^{70}Ge). *E*-**2a**: ^1H NMR δ 1.88 (s, 3H), 1.98 (s, 3H), 2.14 (s, 3H), 4.23 (m, 2H), 4.35–4.39 (m, 1H), 5.09 (dd, J = 3.4, 1.5 Hz, 1H), 5.43 (dd, J = 3.9, 1.5 Hz, 1H), 6.31 (d, J = 4.0 Hz, 1H), 6.69 (d, J = 18.8 Hz, 1H), 7.33–7.55 (m, 16H), 7.60 (s, 1H), 9.29 (br. s, 1H). The α -addition product 1-(2,3,5-tri-*O*-acetyl- β -D-arabinofuranosyl)-5-[1-(triphenylgermyl)-ethenyl]uracil: ^1H NMR δ 1.80 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 4.00–4.23 (m, 2H), 4.45–4.49 (m, 1H), 4.98 (dd, J = 3.5, 1.9 Hz, 1H), 5.35

(dd, $J = 4.1, 1.5$ Hz, 1H), 5.72 (d, $J = 2.0$ Hz, 1H), 6.17 (d, $J = 4.1$ Hz, 1H), 6.41 (d, $J = 2.0$ Hz, 1H), 7.33–7.55 (m, 16H), 8.98 (br. s, 1H).

1-(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, 29.6 μ L, 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, $J = 13.8$ 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, $J = 13.8, 1.0$ 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, -0.2, 20.5, 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 C₂₀H₂₈⁷⁴GeNaN₂O₉ [M+Na]⁺ 537.0899, found 537.0888.

1-(2,3,5-Tri-*O*-acetyl- β -D-arabinofuranosyl)-5-(*Z*)-[2-(tris(trimethylsilyl)germyl)ethenyl]uracil (**2c**)

Nitrogen gas was bubbled through a heterogeneous mixture of **1** (127 mg, 0.32 mmol) in dry toluene (10 mL) for 30 min. The suspension was pre-heated up to 90 °C (~5 min) and (Me₃Si)₃GeH (115 mg, 123 μ L, 0.39 mmol) was added via syringe followed by ACCN (8 mg, 0.04 mmol) dissolved in degassed toluene (1 mL). The reaction mixture was heated at 90 °C for 30 min. Volatiles were evaporated and the residue was chromatographed (hexane/EtOAc, 3:2) to give *Z*-**2c** (152 mg, 68%): ¹H NMR δ 0.20 (s, 27H), 2.01 (s, 3H), 2.10 (s, 3H), 2.14 (s, 3H), 4.17–4.24 (m, 1H), 4.34 (dd, $J = 12.0, 5.5$ Hz, 1H), 4.38 (dd, $J = 12.0, 5.2$ Hz, 1H), 5.14 (dd, $J = 3.8, 1.6$ 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 1.95, 20.7, 20.9, 21.0, 63.1, 75.0, 76.5, 80.7, 85.4, 116.1, 133.9, 134.1, 136.2, 149.6, 162.0, 168.9, 169.7, 170.6; HRMS calcd for C₂₆H₄₇⁷⁴GeN₂O₉Si₃ [M+H]⁺ 689.1801, found 689.1798.

¹H NMR of the crude reaction mixture showed 4:96 mixture of *E/Z* isomers of **2c**. The *E*-**2c** had the characteristic peaks on the ¹H NMR spectrum at: δ 6.36 (d, $J = 3.5$ Hz, H1'), 6.63 (d, $J = 18.7$ Hz, CH), 6.86 (d, $J = 18.5$ Hz, CH).

1-(β -D-Arabinofuranosyl)-5-(*Z*)-[2-(triphenylgermyl)ethenyl]uracil (**3a**)

A saturated solution of NH₃/MeOH (3 mL) was added to a suspension of *Z*-**2a** (40.0 mg, 0.057 mmol) in MeOH (2 mL) and the reaction mixture stirred for 6 h at 0 °C and then for 2 h at rt. Volatiles were evaporated and the residue was chromatographed (EtOAc/MeOH, 98:2) to give *Z*-**3a** (28.2 mg, 86%): ¹H NMR (MeOH-*d*₄) δ 3.28 (dd, $J = 11.3, 4.0$ Hz, 1H), 3.37 (dd, $J = 11.3, 5.6$ Hz, 1H), 3.76 (ddd, $J = 5.8, 4.1, 2.1$ Hz, 1H), 3.98–4.02 (m, 2H), 5.59 (d, $J = 3.3$ Hz, 1H), 6.50 (d, $J = 13.2$ Hz, 1H), 7.30 (d, $J = 13.3$ Hz, 1H), 7.35–7.51 (m, 16H); ¹³C NMR (MeOH-*d*₄) δ 62.6, 76.6, 78.4, 87.0, 88.3, 113.8, 129.3, 130.0, 131.5, 136.0, 138.2, 139.9, 140.7, 151.3, 165.0; HRMS calcd for C₂₉H₂₈⁷⁴GeNaN₂O₆ [M+Na]⁺ 597.1051, found 597.1076. Anal. Calcd for C₂₉H₂₈GeN₂O₆•CH₃OH•H₂O (623.24): C, 57.81; H, 5.50; N, 4.49. Found: C, 57.84; H, 5.41; N, 4.69.

5-Ethynyl-2',3',5'-tri-*O*-*p*-toluoyluridine (**5**)

The *p*-toluoyl chloride (86 μ L, 101 mg, 0.65 mmol) was added to a stirred solution of 5-ethynyluridine³⁸ (50 mg, 0.19 mmol) in pyridine (5 mL). After 24 h, volatiles were evaporated and the residue was partitioned (NaHCO₃/H₂O/CHCl₃). The organic layer was washed with HCl/H₂O, NaHCO₃/H₂O, brine, and was dried (MgSO₄), and evaporated. The residue was chromatographed (hexane/EtOAc, 7:3 $\rightarrow$ 6:4) to give **5** (85 mg, 73%): ¹H NMR δ 2.40 (s, 3H), 2.44 (s, 6H, 2 $\times$ Me), 2.94 (s, 1H), 4.69–4.76 (m, 2H), 4.78–4.84 (m, 1H), 5.70 ("t", J = 6.0 Hz, 1H), 5.84 (dd, J = 5.9, 3.6 Hz, 1H, H3), 6.37 (d, J = 6.1 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.81 (s, 1H), 7.84 (d, J = 8.2 Hz, 2H), 7.91 (d, J = 8.2 Hz, 2H), 8.02 (d, J = 8.2 Hz, 2H), 8.18 (s, 1H); ¹³C NMR δ 21.8, 21.9, 63.8, 71.5, 73.76, 73.77, 81.4, 82.5, 87.9, 100.6, 125.7, 126.1, 126.5, 129.4, 129.5, 129.7, 129.9, 130.1, 130.2, 143.2, 144.6, 144.8, 144.9, 148.8, 160.6, 165.4, 165.5, 166.3; HRMS calcd for C₃₅H₃₁N₂O₉ [M+H]⁺ 623.2024, found 623.2033.

5-(*Z*)-[2-(Triphenylgermyl)ethenyl]-2',3',5'-tri-*O*-*p*-toluoyluridine (**7a**) and 5-[2-(triphenylgermyl)acetyl]-2',3',5'-tri-*O*-*p*-toluoyluridine (**11a**)

Nucleoside **5** (49 mg, 0.08 mmol) was treated with Ph₃GeH (26 mg, 0.085 mmol) in dry THF (5 mL) as described in Method B. After 6 h at –78 °C, the reaction mixture was slowly warmed to 0 °C (~24 h). The volatiles were evaporated and the residue was chromatographed (hexane/EtOAc, 1:1) to give a separable mixture of **Z-7a** (29 mg, 40%) and **11a** (10 mg, 13%). **Z-7a**: ¹H NMR δ 2.40 (s, 6H), 2.42 (s, 3H), 4.34 (dd, J = 12.2, 5.4 Hz, 1H), 4.40 (dd, J = 12.2, 3.4 Hz, 1H), 4.47 (ddd, J = 5.8, 5.4, 3.5 Hz, 1H), 5.38 (dd, J = 6.2, 4.5 Hz, 1H), 5.51 ("t", J = 6.0 Hz, 1H), 5.52 (d, J = 4.4 Hz, 1H), 6.50 (d, J = 13.6 Hz, 1H), 7.11 (d, J = 0.9 Hz, 1H), 7.16 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.22 (dd, J = 13.5, 0.9 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.31–7.55 (m, 15H), 7.80 (d, J = 8.2 Hz, 4H), 7.96 (d, J = 8.2 Hz, 2H), 8.09 (br. s, 1H); ¹³C NMR δ 21.67, 21.69, 21.72, 63.5, 70.5, 73.6, 79.9, 89.8, 115.0, 125.9, 126.0, 126.7, 128.5, 129.1, 129.2, 129.3, 129.7, 129.8, 129.9, 131.4, 134.7, 136.6, 137.0, 138.2, 144.2, 144.4, 144.5, 148.8, 161.4, 165.0, 165.1, 166.1; HRMS calcd for C₅₃H₄₆⁷⁴GeN₂NaO₉ [M+Na]⁺ 951.2307, found 951.2315.

Compound **11a** had: UV (MeOH) $\lambda_{\max}$ = 282 nm; ¹H NMR δ 2.35 (s, 3H), 2.40 (s, 3H), 2.42 (s, 3H), 3.76 (d, J = 9.0 Hz, 1H), 3.87 (d, J = 9.0 Hz, 1H), 4.67–4.75 (m, 3H), 5.66 (dd, J = 5.9, 5.1 Hz, 1H), 5.83 ("t", J = 5.7 Hz, 1H), 6.01 (d, J = 5.0 Hz, 1H), 7.16–7.55 (m, 21H), 7.83 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H), 8.02 (d, J = 8.2 Hz, 2H), 8.05 (s, 1H); ¹³C NMR δ 21.7, 33.0, 63.5, 71.0, 73.9, 80.9, 90.4, 113.7, 125.7, 126.0, 126.6, 128.2, 129.21, 129.24, 129.3, 129.4, 129.8, 129.9, 135.0, 135.1, 144.1, 144.5, 144.7, 146.6, 148.5, 160.2, 165.19, 165.21, 166.3, 193.3; HRMS calcd for C₅₃H₄₇⁷⁴GeN₂O₁₀ [M+H]⁺ 945.2437, found 945.2456.

5-(*E/Z*)-[2-(Trimethylgermyl)ethenyl]-2',3',5'-tri-*O*-*p*-toluoyluridine (**7b**)

Nucleoside **5** (50.0 mg, 0.08 mmol) was treated with Me₃GeH (19.0 mg, 18.8 μ L 0.16 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, 3:2) to give **E/Z-7b** (24.5 mg, 41%; *E/Z*, 45:55). ¹H NMR δ 0.12 (s, 4.05H), 0.20 (s, 4.95H), 2.40, 2.43, 2.44 (singlets, 9H), 4.68–4.82 (m, 3H), 5.72 ("t", J = 6.0 Hz, 0.55H), 5.78 ("t", J = 6.3 Hz, 0.45H), 5.82 (dd, J = 6.1, 3.9 Hz, 0.55H), 5.88 (dd, J = 5.8, 2.8 Hz, 0.45H), 5.98 (d, J = 13.7 Hz, 0.55H), 6.34 (d, J = 5.9 Hz, 0.55H), 6.37 (d, J = 19.0 Hz, 0.45H), 6.50 (d, J = 6.8 Hz, 0.45H), 6.69 (d, J = 19.0 Hz, 0.45H), 6.72 (dd, J = 13.7, 1.0 Hz, 0.55H), 7.16–7.32 (m, 6H), 7.34 (d, J = 1.0 Hz, 0.55H), 7.54 (s, 0.45H), 7.83–8.04 (m, 6H), 8.24 (br. s, 0.45H), 8.27 (br. s, 0.55H); ¹³C NMR δ –2.0, –0.2, 21.7, 63.7, 64.2, 71.1, 71.5, 73.45, 73.53, 80.7, 81.0, 86.9, 88.0, 114.4, 116.0, 125.65, 125.70, 125.96, 125.97, 126.3, 126.5, 129.24, 129.25, 129.29,

129.4, 129.6, 129.71, 129.73, 129.88, 129.9, 129.95, 130.0, 131.8, 134.1, 134.4, 135.1, 135.8, 138.7, 144.3, 144.5, 144.57, 144.63, 144.64, 144.7, 149.3, 149.7, 161.3, 161.7, 165.3, 165.35, 165.38, 165.5, 166.1; MS (ESI⁺) *m/z* 765 (100, MNa⁺, ⁷⁴Ge), 763 (71, MNa⁺, ⁷²Ge), 762 (52 MNa⁺, ⁷⁰Ge); Anal. Calcd for C₃₈H₄₀GeN₂O₉ • H₂O (759.39): C, 60.10; H, 5.57; N, 3.69. Found: C, 60.39; H, 5.38; N, 3.87.

5-(*E/Z*)-[2-(Trimethylgermyl)ethenyl]uridine (**8b**)

A 0.1 N solution of MeONa in MeOH (2.5 mL) was added to **7b** (18.8 mg, 0.025 mmol; *E/Z*, ~45:55) and the resulting mixture was stirred at rt for 12 h. The reaction mixture was neutralized to pH ~6.2 by addition of Dowex 50WX2-200(H⁺). Dowex resin was filtered off and the filtrate was evaporated and residue partitioned between Et₂O/H₂O. The organic layer was extensively washed with water and the combined aqueous layer was evaporated to yield *E/Z*-**8b** (7 mg, 71%; *E/Z*, ~40:60): ¹H NMR (D₂O) δ 0.27 (s, 5.4H), 0.32 (s, 3.6H), 3.84–3.91 (m, 1H), 3.95 (dd, *J* = 12.7, 2.7 Hz, 0.6H), 4.05 (dd, *J* = 12.9, 2.4 Hz, 0.4H), 4.18–4.24 (m, 1H), 4.29 (“t”, *J* = 5.0 Hz, 0.6H), 4.34 (“t”, *J* = 5.7 Hz, 0.4H), 4.39–4.44 (m, 1H), 6.00 (d, *J* = 3.8 Hz, 0.4H), 6.05 (d, *J* = 5.3 Hz, 0.6H), 6.36 (d, *J* = 13.6 Hz, 0.6H), 6.70 (d, *J* = 19.0 Hz, 0.4H), 6.83 (d, *J* = 19.0 Hz, 0.4H), 6.93 (d, *J* = 13.6 Hz, 0.6H), 7.77 (s, 0.6H), 8.20 (s, 0.4H); ¹³C NMR (MeOH-*d*₄) δ -2.9, -1.2, 60.1, 61.0, 68.9, 69.8, 73.7, 74.1, 84.0, 84.7, 88.8, 89.7, 113.8, 115.7, 132.1, 134.1, 134.7, 137.6, 137.8, 140.8, 151.1, 151.6, 164.6, 165.3; HRMS calcd for C₁₄H₂₃⁷⁴GeN₂O₆ [M+H]⁺ 389.0762, found 389.0775.

1-(2-Deoxy-3,5-di-*O-p*-toluoyl-β-D-erythro-pentofuranosyl)-5-(*Z*)-[2-(triphenylgermyl)ethenyl]uracil (**9a**) and 1-(2-Deoxy-3,5-di-*O-p*-toluoyl-β-D-erythro-pentofuranosyl)-5-[2-(triphenylgermyl)acetyl]uracil (**12a**)

Nucleoside **6**¹⁰ (44 mg, 0.09 mmol) was treated with Ph₃GeH (30 mg, 0.1 mmol) in dry THF (5 mL) as described in Method B. After 6 h at -78 °C, the reaction mixture was slowly warmed to 0 °C and stirred for 3 h. The volatiles were evaporated and the residue was chromatographed (hexane/EtOAc, 3:2) to give a separable mixture of *Z*-**9a** (43 mg, 61%) and **12a** (9 mg, 12%). *Z*-**9a**: ¹H NMR δ 1.68 (ddd, *J* = 14.9, 8.1, 7.0 Hz, 1H), 2.31 (ddd, *J* = 14.5, 5.7, 1.8 Hz, 1H), 2.41 (s, 3H), 2.45 (s, 3H), 4.16 (dd, *J* = 11.1, 3.5 Hz, 1H), 4.26–4.30 (m, 1H), 4.32 (dd, *J* = 11.1, 5.0 Hz, 1H), 5.15 (“dt”, *J* = 6.8, 1.8 Hz, 1H), 5.84 (dd, *J* = 8.1, 5.7 Hz, 1H), 6.51 (d, *J* = 13.5 Hz, 1H), 7.11 (d, *J* = 1.0 Hz, 1H), 7.21–7.56 (m, 20H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 2H); ¹³C NMR δ 21.68, 21.72, 37.3, 63.9, 74.5, 82.3, 85.5, 114.8, 126.4, 126.7, 128.5, 129.2, 129.25, 129.28, 129.6, 129.8, 131.0, 134.8, 135.6, 136.6, 138.8, 144.2, 144.5, 149.3, 161.7, 165.8, 166.0; HRMS calcd for C₄₅H₄₁⁷⁴GeN₂O₇ [M+H]⁺ 795.2120, found 795.2131.

Compound **12a** had: ¹H NMR δ 2.18–2.27 (m, 1H), 2.36 (s, 3H), 2.45 (s, 3H), 2.64 (ddd, *J* = 14.3, 5.7, 1.8 Hz, 1H), 3.81 (d, *J* = 9.1 Hz, 1H), 3.85 (d, *J* = 9.1 Hz, 1H), 4.53–4.60 (m, 2H), 4.74–4.80 (m, 1H), 5.54 (“d”, *J* = 6.6 Hz, 1H), 6.16 (dd, *J* = 8.3, 5.7 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.32–7.57 (m, 15H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.95 (d, *J* = 8.2 Hz, 2H), 8.15 (s, 1H); ¹³C NMR δ 21.70, 21.73, 32.8, 38.4, 63.8, 74.5, 83.2, 86.2, 113.6, 126.3, 126.6, 128.2, 129.25, 129.28, 129.3, 129.8, 135.1, 135.2, 144.1, 144.5, 145.2, 148.8, 160.3, 165.8, 166.2, 193.5; HRMS calcd for C₄₅H₄₁⁷⁴GeN₂O₈ [M+H]⁺ 811.2075, found 811.2063.

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, 1.4 mmol) were added to the pre-heated reaction mixture] gave partially separated *E*-**9a** (13 mg, 16%), **12a** (6.5 mg, 8%) and *Z*-**9a** (13 mg, 16%). Compound *E*-**9a** had characteristic peaks for vinylic 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-*O*-*p*-toluoyl- β -D-erythro-pentofuranosyl)-5-(*E/Z*)-[2-(trimethylgermyl)ethenyl]uracil (9b)

Nucleoside **6**¹⁰ (45.0 mg, 0.092 mmol) was treated with Me₃GeH (21.8 mg, 21.6 μ L, 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, 1H), 2.42, 2.43, 2.45 (singlets, 6H), 2.78 (ddd, *J* = 14.2, 5.5, 1.6 Hz, 0.6H), 2.80 (ddd, *J* = 14.3, 5.1, 1.2 Hz, 0.4H), 4.56–4.61 (m, 1H), 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 (“dt”, *J* = 4.9, 1.9 Hz, 0.6H), 4.63 (“d”, *J* = 6.4 Hz, 0.4H), 6.00 (d, *J* = 13.7 Hz, 0.6H), 6.40 (dd, *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, 4H), 7.48 (d, *J* = 1.0 Hz, 0.6H), 7.67 (s, 0.4H), 7.85–7.99 (m, 4H), 8.51 (br. s, 0.4H), 8.57 (br. s, 0.6H); ¹³C NMR δ –2.0, –0.2, 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, 126.4, 126.5, 129.30, 129.34, 129.50, 129.54, 129.6, 129.8, 131.9, 133.9, 134.2, 134.9, 135.1, 138.3, 144.4, 144.5, 144.6, 149.2, 149.7, 161.5, 161.9, 166.0, 166.1; HRMS calcd for C₃₀H₃₄⁷⁴GeN₂NaO₇ [M+Na]⁺ 631.1470, found 631.1482.

Note—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 deprotections with NH₃/MeOH (0 °C to rt, 12 h) gave 5-(2-bromovinyl)-2'-deoxyuridine^{39,40} (*E/Z*, 2:3; 70% from **9b**).

1-(β -D-Erythro-pentofuranosyl)-5-(*Z*)-[2-(triphenylgermyl)ethenyl]uracil (10a)

A saturated solution of NH₃/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 (MeOH-*d*₄) δ 1.44 (ddd, *J* = 14.2, 7.9, 6.6 Hz, 1H), 1.87 (ddd, *J* = 13.6, 5.9, 2.7 Hz, 1H), 3.38 (“d”, *J* = 4.4 Hz, 2H), 3.70 (“q”, *J* = 3.8 Hz, 1H), 3.97 (ddd, *J* = 6.0, 3.3, 2.8 Hz, 1H), 5.81 (dd, *J* = 8.0, 6.0 Hz, 1H), 6.52 (d, *J* = 13.3 Hz, 1H), 7.28 (d, *J* = 1.1 Hz, 1H), 7.31 (dd, *J* = 13.3, 1.1 Hz, 1H), 7.36–7.54 (m, 15H); ¹³C NMR (MeOH-*d*₄) 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, MNa⁺, ⁷⁴Ge), 579 (70, MNa⁺, ⁷²Ge), 577 (49, MNa⁺, ⁷⁰Ge); Anal. Calcd for C₂₉H₂₈GeN₂O₅ (557.18): C, 62.51; H, 5.07; N, 5.03. Found: C, 62.14; H, 5.28; N, 4.86.

1-*N*-Benzyl-5-(*Z*)-[2-(triphenylgermyl)ethenyl]uracil (14)

Alkyne **13**^{33,34} (50 mg, 0.22 mmol) was dissolved in anhydrous THF (5 mL) and the resulting solution was stirred for 20 min under N₂ at 0 °C. Ph₃GeH (73 mg, 0.24 mmol) and Et₃B (1M/THF 265 μ L, 0.265 mmol,) were added and the resulting solution was stirred at 0 °C for 7 h. The volatiles were evaporated and the residue was chromatographed (hexane/EtOAc, 1:1) to give *Z*-**14** (61 mg, 52%) as a white powder: M.p. 202–204 °C (MeOH); UV (MeOH) max 296 nm (ϵ 11 000), min 255 (ϵ 3500); ¹H NMR δ 4.03 (s, 2H), 6.30 (d, *J* = 13.5 Hz, 1H), 6.69 (“d”, *J* = 7.0 Hz, 2H), 6.84 (s, 1H), 7.09 (“t”, *J* = 7.5 Hz, 2H), 7.16 (“t”, *J* = 7.1 Hz, 1H), 7.23–7.35 (m, 10H), 7.37–7.46 (m, 6H), 8.51 (br. s, 1H); ¹³C NMR δ 51.2, 113.7, 128.3, 128.3, 128.4, 128.8, 129.1, 129.5, 134.8, 135.0, 136.7, 138.7, 141.0, 150.1, 162.4; HRMS calcd for C₃₁H₂₆⁷⁴GeN₂NaO₂ [M+Na]⁺ 555.1105, found 555.1113.

1-*N*-Benzyl-5-(*E*)-[2-(triphenylgermyl)ethenyl]uracil (**14**)

Ph₃GeH (118.6 mg, 0.38 mmol) and H₂O (25 μL, 25 mg, 1.4 mmol) were added to a stirred solution of **13** (80 mg, 0.35 mmol) in toluene (5 mL) at rt. The resulting mixture was heated at 100 °C for 12 h. The volatiles were evaporated and the residue was chromatographed (CH₂Cl₂/EtOAc, 10:1) to give *E*-**14** (126 mg, 86%) as white solid. Recrystallization (MeOH) gave white crystals: M.p. 185–186 °C; UV (MeOH) max 300 nm (ε 13 900), 251 nm (ε 15 500), min 272 (ε 7100); ¹H NMR δ 4.92 (s, 2H), 6.56 (d, *J* = 18.7 Hz, 1H), 7.21 (s, 1H), 7.28–7.30 (m, 2H), 7.33 (d, *J* = 18.7 Hz, 1H), 7.35–7.51 (m, 18H), 8.78 (br. s, 1H); ¹³C NMR δ 51.5, 113.8, 127.2, 127.9, 128.3, 128.6, 129.1, 129.2, 135.1, 135.2, 136.1, 136.9, 141.7, 150.1, 161.8; HRMS calcd for C₃₁H₂₆GeN₂O₂ [M+Na]⁺ 555.1105, found 555.1111. Anal. Calcd for C₃₁H₂₆GeN₂O₂ (531.19): C, 70.09; H, 4.93; N, 5.27. Found: C, 69.82; H, 4.64; N, 5.35.

1-*N*-Benzyl-5-[2-(triphenylgermyl)acetyl]uracil (**15**)

Alkyne **13** (50 mg, 0.22 mmol) was suspended in dry toluene (5 mL) and the suspension was degassed with N₂ for 45 min at ambient temperature. Ph₃GeH (73 mg, 0.24 mmol) and ACCN (10 mg, 0.041 mmol) were added and the suspension was heated at 90 °C for 2 h. The volatiles were evaporated and residue was chromatographed (hexane/EtOAc, 3:2) to give **15** (15 mg, 13%) followed by *Z*-**14** (31 mg, 27%). Compound **15** was recrystallized (MeOH) to give colorless crystals: M.p. 205–207 °C; UV (MeOH) max 294 nm (ε 10 600), min 255 (ε 3800); ¹H NMR δ 3.81 (s, 2H), 4.77 (s, 2H), 7.24–7.54 (m, 20H), 7.79 (br. s, 1H), 7.85 (s, 1H); ¹³C NMR δ 33.1, 52.4, 113.3, 128.3, 128.5, 129.1, 129.3, 129.5, 134.5, 135.2, 135.3, 149.7, 149.9, 160.7, 194.3; HRMS calcd for C₃₁H₂₆⁷⁴GeN₂NaO₃ [M+Na]⁺ 571.1054, found 571.1068. Anal. Calcd for C₃₁H₂₆GeN₂O₃ (547.2): C, 68.04; H, 4.79; N, 5.12. Found: C, 68.26; H, 4.60; N, 4.81.

1-*N*-Benzyl-5-acetyluracil (**20**)

A solution of **15** (15 mg, 0.03 mmol) in CH₃OH (3 mL) was heated for 12 h at 65 °C. Volatiles were evaporated and the residue was chromatographed (CH₂Cl₂/EtOAc, 2:1) to give **20**⁴¹ (6.5 mg, 95%) as a white powder: UV (MeOH) max 290 nm (ε 12 200), 226 nm (ε 8100), min 249 (ε 1400); ¹H NMR δ 2.61 (s, 3H), 5.01 (s, 2H), 7.33–7.41 (m, 5H), 8.28 (s, 1H), 8.59 (br. s, 1H); ¹³C NMR δ 30.6, 52.5, 112.8, 128.3, 129.0, 129.3, 134.3, 150.2, 150.6, 161.2, 193.9; GC-MS (*t*_R 26.87 min) *m/z* 244 (20, M⁺), 91 (100); HRMS calcd for C₁₃H₁₂N₂NaO₃ [M+Na]⁺ 267.0740, found 267.0739.

Analogous treatment of **15** (10 mg, 0.02 mmol) using MeOD or MeOH-*d*₄ instead of MeOH gave 1-*N*-benzyl-5-(2-deuterioacetyl)uracil (**21**; 4.2 mg, 94%): GC-MS (*t*_R 26.87 min) *m/z* 245 (20, M⁺), 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 2.61 ppm.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A plausible pathway for the formation of β -germylketone **15** during radical hydrogermylation of alkyne **13** with Ph_3GeH

Figure 2.
A plausible pathway for the thermal degradation of β -germylketone **15**

Compounds **2-4**, Series: **a** $R = \text{Ph}$, **b** $R = \text{Me}$, **c** $R = (\text{Me}_3\text{Si})_3$

Scheme 1.

Hydrogermylation of 1-(β-D-arabinofuranosyl)-5-ethynyluracil **1** with germane hydrides
 Reagents and conditions: (a) $\text{R}_3\text{GeH}/(\text{ACCN})/\text{toluene}/90^\circ\text{C}$ (Method A) or $\text{R}_3\text{GeH}/\text{Et}_3\text{B}/\text{THF}/-78^\circ\text{C}$ (Method B) or $\text{Pd}(\text{PPh}_3)_4/\text{THF}/\text{rt}$ (Method C); (b) $\text{NH}_3/\text{MeOH}/\text{rt}$.

Compounds **7-12**, Series: **a** R = Ph, **b** R = Me

Scheme 2.

Hydrogermylation of 5-ethenyluridine **5** and 2'-deoxy-5-ethenyluridine **6** with germane hydrides.

Reagents and conditions: (a) Ph₃GeH/(ACCN)/toluene/(THF or DMF)/90 °C or R₃GeH/Et₃B/THF/−78 °C; (b) MeONa/MeOH/rt; (c) NH₃/MeOH/rt.

Scheme 3. Hydrogermylation of the 5-ethynyluracil **13**Reagents and conditions: (a) $\text{Ph}_3\text{GeH}/(\text{ACCN})/\text{toluene}/(\text{H}_2\text{O})/100$ or 90°C or $\text{Ph}_3\text{GeH}/\text{Et}_3\text{B}/\text{THF}/0^\circ\text{C}$

Table 1

Hydrogermylation of 5-ethynyluracil and related nucleosides with germane hydrides

Entry	Substrate	Method ^a	Temp (°C)	R ₃ GeH	Vinyl Germanes			Germynyl Ketones	
					Product	Yield ^b (%)	Ratio ^b (E/Z)	Product	Yield ^b (%)
1	1	A	90	Ph ₃ GeH	2a ^c	47	0:100	4a	12
2	1	A ^d	90	Ph ₃ GeH	2a	60	3:97	4a	15
3	1	B	-78 → -60	Ph ₃ GeH	2a	55	0:100	-	-
4	1	B	0	Ph ₃ GeH	2a	28	0:100	4a	19
5	1	C	25	Ph ₃ GeH	2a ^e	45	100:0	-	-
6	1	B	0 → 25	Me ₃ GeH	2b	40	15:85	-	-
7	1	A	90	(Me ₃ Si) ₃ GeH	2c ^f	68	0:100	-	-
8	5	B	-78 → 0	Ph ₃ GeH	7a	40	0:100	11a	13
9	5	B	0 → 25	Me ₃ GeH	7b	41	45:55	-	--
10	6	B	-78 → 0	Ph ₃ GeH	9a	61	0:100	12a	12
11	6	A ^g	100 ^h	Ph ₃ GeH	9a ⁱ	33	0:100	12a	17
12	6	B	0 → 25	Me ₃ GeH	9b	35	40:60	-	-
13	13	A	90	Ph ₃ GeH	14	27	0:100	15	13
14	13	A ^d	100	Ph ₃ GeH	14	34	0:100	15	20
15	13	A ^{d,j}	100	Ph ₃ GeH	14	86	100:0	-	-
16	13	B	0	Ph ₃ GeH	14	52	0:100	-	-

^aMethod A: R₃GeH/ACCN/toluene/90 or 100 °C; Method B: R₃GeH/Et₃B/THF/-78 or 0 °C; Method C: Pd(PPh₃)₄/THF/rt.^bFor the isolated products.^cCrude reaction mixture (E/Z **2a**, 5:95).^dWithout ACCN.^eIn addition to **E-2a** the α-addition product was formed (~3:2, 73% overall).^fCrude reaction mixture (E/Z **2c**, 4:96).

g Toluene/THF (20:1, v/v) was used as solvent.

h Oil-bath.

i With toluene/DMF/H₂O (20:1:0.1, v/v/v) as solvents **E-9a**, **Z-9a** and **12a** (~2:2:1, 40% overall) were obtained.

j With addition of 25 μ L H₂O (14 equiv.).