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APPLICATION OF GERMYLDESULFONYLATION REACTIONS TO THE SYNTHESIS OF GERMANIUM-CONTAINING NUCLEOSIDE ANALOGUES

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□ *Treatment of the protected (*E*)-5′-deoxy-5′-[(*p*-toluenesulfonyl)methylene]uridine and adenosine derivatives with tributyl- or triphenylgermane hydride (AIBN/toluene/*Δ*) effected radical-mediated germyldesulfonylations to give 5′-(tributyl- or triphenylgermyl)methylene-5′-deoxyuridine and adenosine derivatives as single (*E*)-isomers. Analogous treatment of 2′-deoxy-2′-[(phenylsulfonyl)methylene]uridine with Ph_3GeH afforded the corresponding vinyl triphenylgermane product. Stereoselective halodegermylation of the (*E*)-5′-(tributylgermyl)methylene-5′-deoxy nucleosides with* N*-iodosuccinimide or* N*-bromosuccinimide provided the Wittig-type (*E*)-5′-deoxy-5′-(halomethylene) nucleosides quantitatively, while no halodegermylations was observed with the 5′-deoxy-5′-(triphenylgermyl)methylene counterparts. Treatment of the vinyl trialkylgermanes with aqueous trifluoroacetic acid effected protiodegermylation, while vinyl triarylgermanes were stable under the acidic conditions.*

Keywords Germyldesulfonylation; germanonucleosides; vinyl germanes, vinyl sulfones

INTRODUCTION

Radical-mediated substitution of the arylsulfonyl group with tributylstannyl group at the vinylic carbon has been a critical step in the synthesis of the various nucleoside and amino acids analogues bearing a halo vinyl functionality. For example, McCarthy and coworkers employed a radical-mediated stannyldesulfonylation procedure (**1a** → **1b**) for the synthesis of (*E*)-fluorovinyl cytidine **1c** (Tezacitabine; an inhibitor

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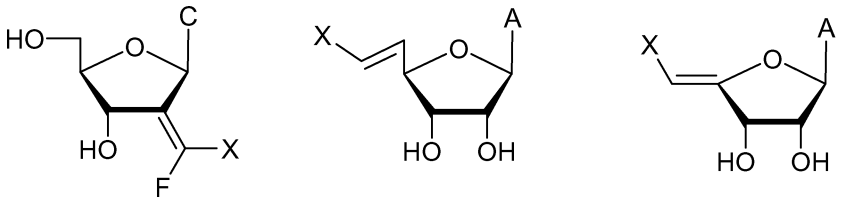


1a X = $PhSO_2$
1b X = Bu_3Sn
1c X = H

2a X = (4-CH_3)$PhSO_2$
2b X = Bu_3Sn
2c X = I, Br, Cl, or F

3a X = PhS
3b X = Bu_3Sn
3c X = I, Br, Cl, or F

FIGURE 1 Nucleoside analogues whose synthesis were accomplished by tin radical-mediated extrusion of sulfer atoms.

of ribonucleoside reductases with potent anticancer activity), from the protected (α-fluoro)vinyl sulfone **1a** (Figure 1).[1,2] Stannyldesulfonylation of the vinyl sulfone **2a** followed by halodestannylation of the resulting vinyl stannanes **2b** was a key step in the synthesis of 5′-deoxy-5′-(halomethylene)adenosines **2c**, which were found to be potent inhibitors of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase and valuable probes to study hydrolytic activity of the enzyme.[3–5] Stannyldesulfonylation/protiodestannylation of the (α-fluoro)vinyl sulfones and stannyldesulfonylation/halodestannylation of the vinyl sulfones procedures allowed synthesis of the various 5′-deoxy-5′-(halomethylene)nucleoside analogues derived from uridine,[6] L-adenosine,[7] 3′-deoxyadenosine,[8] and 6-*N*-cyclopropyladenosine[9] as well as 5′-deoxy-5′-(halomethylene)ribose derivatives,[10] among others.[11] The vinyl sulfone precursors have been conveniently prepared by treatment of the nucleoside 2′-keto or 5′-aldehyde derivatives with the sulfonyl-stabilized Wittig reagents.[1,12,13] The chemistry of the vinyl-sulfone modified carbohydrates and nucleosides has been reviewed.[14] Sulfur extrusion from nucleosidic vinyl sulfide **3a** with tributyltin hydride has been elaborated for the synthesis of the known AdoHcy hydrolase inhibitors **3c** via halodestannylation of the intermediary vinyl stannane **3b**.[15] The sequence involving introduction of the alkenes substituted with F/SO_2Ph, F/$SnBu_3$, F/I, F/C, or F/H into the synthesis of fluorovinyl analogues of amino acids has been developed by Berkowitz.[16,17]

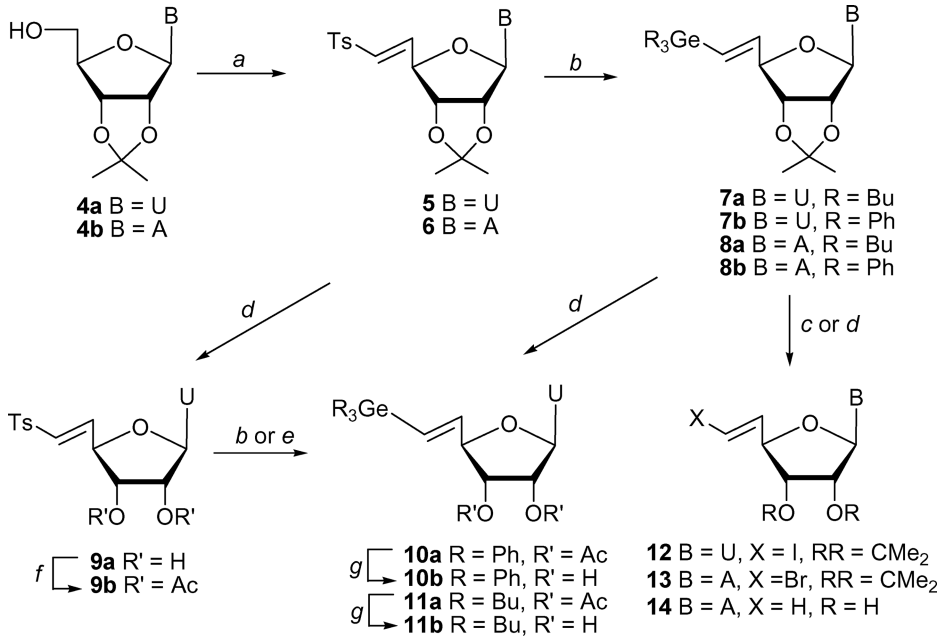
In order to eliminate toxicity factors associated with the necessity of using tributyltin hydride reagent in a stannyldesulfonylation reaction, we developed a stereoselective radical-mediated silyl- and germyldesulfonylations of vinyl and (α-fluoro)vinyl sulfones with tris(trimethylsilyl)silane (TTMSS) and germanium hydrides.[18] The germyldesulfonylation protocol tolerates some functional groups vulnerable to the radical hydrogenolysis with tributyltin hydride and TTMSS. For example, a chloro substituent was not affected by the mild conditions required for germyldesulfonylation with Ph_3GeH.[18]

Chemistry[19] and biological activity of the organogermanium compounds has been reviewed.[20,21] Germanium containing α-aminoacids and peptides have been incorporated into biologically active decapeptides.[22,23] The 6-trialkylgermyl-5-fluorouridine derivatives are one of the few known examples of germanium-containing nucleoside analogues[24] and 5-trimethylgermyl-2′-deoxyuridine was showed to inhibit HSV-1 replication in vitro and blocked incorporation of thymidine into DNA of cancer ovarian cells.[25] Herein, we report the application of germyldesulfonylation reactions to the synthesis of novel pyrimidine and purine nucleoside analogues modified in the sugar moieties with vinyl germane functionalities and their further application towards the synthesis of vinyl halides.

RESULTS AND DISCUSSION

Moffatt oxidation of 2′,3′-*O*-isopropylideneuridine **4a** or adenosine **4b** and Wittig treatment of the crude 5′-aldehydes with (*p*-toluenesulfonylmethylene)triphenylphosphorane gave (*E*)-vinyl sulfones **5**[13] and **6**,[12] respectively (Scheme 1). Treatment of the uridine-derived sulfone **5** with tributylgermane hydrides (AIBN/toluene/Δ) effected stereoselective radical-mediated germyldesulfonylation to give the 5′-(tributylgermyl)methylene-5′-deoxyuridine **7a** as a single (*E*)-isomer ($J_{5'\text{-}6'(\text{trans})} = 18.5$ Hz) in 57% yield. Adenosine-derived sulfone **6** also underwent germyldesulfonylation reaction with Bu_3GeH to afford the vinyl germane (*E*)-**8a** (46%). The analogous stannyldesulfonylation of **5** and **6** with Bu_3SnH afforded the corresponding (*E/Z*)-5′-(tributylstannyl)methylene-5′-deoxyuridine[6] and adenosine[3] derivatives in 87% and 61% yields, respectively. Treatment of **5** and **6** with triphenylgermane hydride gave (*E*)-5′-deoxy-5′-(triphenylgermyl)methylene nucleosides **7b** (72%) and **8b** (42%), respectively. Thus, both purine and pyrimidine nucleosides underwent desulfonylation with either trialkyl- or triarylgermanes. The yields were higher for the uridine substrates as was also observed in the case of the stannyldesulfonylation reactions.[3,6] It is noteworthy that contrary to the stannyldesulfonylation reactions,[3,6] the germyldesulfonylations of the vinyl sulfones derived from the sugar modified nucleosides are stereoselective since the corresponding (*Z*)-isomers of vinyl germanes **7** or **8** were not isolated from the crude reaction mixtures. Germyldesulfonylation reactions presumably occurred via the radical addition-elimination mechanism in analogy to the silyl- and stannyldesulfonylation processes.[11826]

Stereoselective iododegermylation[27,28] of tributylgermane **7a** with *N*-iodosuccinimide (NIS) provided the Wittig-type 5′-deoxy-5′-(iodomethylene)uridine (*E*)-**12** (92%). Analogous treatment of tributylgermane **8a** with *N*-bromosuccinimide (NBS) gave 5′-deoxy-5′-(bromomethylene)adenosine (*E*)-**13** (81%) with retention of the



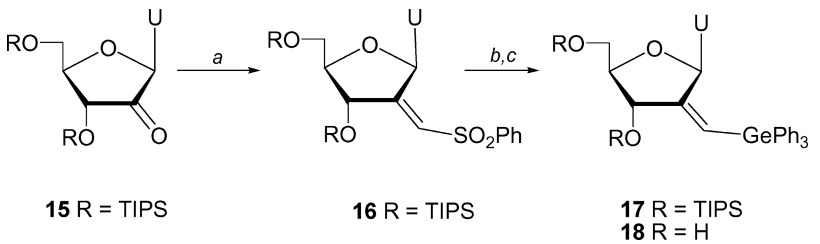
SCHEME 1 Reagents and conditions: (a) (i) DCC/DMSO/Cl_2CHCO_2H, (ii) pH_3P=CHTs; (b) Bu_3GeH or Ph_3GeH/AIBN/$PhCH_3$/heat; (c) NIS or NBS; (d) TFA/H_2O; (e) Bu_3GeH/ACCN/$HOCH_2CH_2SH$/$PhCH_3$/heat; (f) DMAP/Ac_2O; (g) NH_3/MeOH.

double-bond geometry.[27,28] It is noteworthy that substitution of the trialkylgermyl group on a sp^2 carbon with a halogen proceeded easier than the substitution of the corresponding trialkylsilyl group with the improved stereochemical outcome.[27] Interestingly, treatment of the triphenylgermanes **7b** and **8b** with NBS or NIS failed to afford the corresponding halomethylene nucleosides **12** or **13** resulting instead in the recovery of the vinyl triphenylgermanes. Also treatment of **7b** with iodine (CH_2Cl_2/-78°C to room temperature/14 hours) did not effect iododegermylations, although iododestannylation of the vinyl triaryltin derivatives is known.[29] Apparently, the strength of the Ge-C_{sp}^2 bond depends on the nature of the substituents at the germanium atom[19,30] and the stability of the C_{sp}^2-Ge(alkyl)$_3$ bonds is different than that of the C_{sp}^2-Ge(aryl)$_3$ bonds.

Different patterns of reactivity between vinyl triaryl- and trialkylgermanes were also observed for the protiodegermylation reactions. Thus, treatment of the tributylgermanes **8a** with aqueous trifluoroacetic acid (TFA) effected simultaneous protiodegermylation and deacetonization to afford 5′-deoxy-5′-methyleneadenosine **14**. On the other hand, treatment of the triphenylgermanes **7b** with TFA effected only removal of the isopropylidene protection group yielding germanonucleoside **10b**.

Deprotected trialkylgermane **11b** was synthesized using base-labile protection strategy. Thus, treatment of 2′,3′-*O*-diacetyl sulfone **9b** with Bu_3GeH/AIBN provided **11a** (49%), while germyldesulfonylation in the presence of a 2-mercaptoethanol, as a radical carrier,[31,32] and 1,1′-azobis(cyclohexanecarbonitrile; ACCN) afforded **11a** in 58% yield. Subsequent treatment of **11a** with methanolic ammonia effected deacylation yielding vinyl tributylgermane **11b** (72%). The vinyl triphenylgermane **10b** could be also prepared from the sulfone **9b** via **10a** (65% overall yield) utilizing the acetyl protection strategy.

Germyldesulfonylation reaction can also be applied for the removal of the sulfonyl group from the multi-substituted alkenes at C2′ position of the nucleosides. Horner-Wittig treatment of the protected 2′-ketouridine[33] **15** with sulfonyl-stabilized enolate derived from diethyl (phenylsulfonyl)methylphosphonate[18] gave vinyl 2′-phenylsulfone **16** as a single (*Z*)-isomer (Scheme 2). The *Z* stereochemistry was established using NOESY experiments and was also in agreement with McCarthy's work utilizing the fluoro(phenylsulfonyl)methylphosphonate reagent.[1] It is noteworthy that reaction between ketone **15** and sulfonyl-stabilized ylide, (*p*-toluenesulfonylmethylene)triphenylphosphorane,[12] failed to give the analogous *p*-tolylsulfone. Germyldesulfonylation of **16** with Ph_3GeH afforded 2′-deoxy-2′-[(triphenylgermyl)methylene]uridine **17** (51%) as a single (*Z*)-isomer. Desilylation of **17** with TBAF gave vinyl germane **18** (73%). Thus, germyldesulfonylation reaction has a general character and can effect removal of the sulfonyl group from the exomethylene and the isolated double bonds of the sugar moieties of nucleosides. Treatment of **17** (or **5**) with the more reactive tris(trimethylsilyl)germane [$(TMS)_3GeH$] provided the corresponding vinyl $(TMS)_3Ge$-uridine derivatives but in less than 15% yields (^1H NMR). Therefore, no further efforts were made to optimize germyldesulfonylation reactions utilizing $(TMS)_3GeH$ reagent, although the vinyl tris(trimethylsilyl)germanes could serve as precursors for the further modifications via Pd-catalyzed couplings with aryl/alkenyl halides.[18,34]



15 R = TIPS **16** R = TIPS **17** R = TIPS **18** R = H

SCHEME 2 Reagents and conditions: (a) $PhSO_2CH_2PO(OEt)_2$/LHMDS/THF; (b) Ph_3GeH/AIBN/$PhCH_3$/heat; (c) TBAF/THF.

In summary, we have developed a radical-mediated germyldesulfonylation procedure as a key step for the synthesis of 5′-deoxy-5′-(halomethylene) nucleosides. The method utilizes less toxic germane hydrides rather than the previously employed tin hydride reagents. The novel 5′-(tributylgermyl)methylene-5′-deoxyadenosine and uridine derivatives underwent efficient halo- and protiodegermylation reactions while the triphenyl counterparts were stable under acidic conditions and upon treatment with NBS or NIS.

EXPERIMENTAL

^{1}H NMR spectra at 400 MHz and ^{13}C NMR at 100.6 MHz were determined with solutions in $CDCl_3$, and mass spectra (MS) were obtained by atmospheric pressure chemical ionization (APCI) technique unless noted otherwise. Reagent grade chemicals were used and solvents were dried by reflux over and distillation from CaH_2 under an argon atmosphere. TLC was performed on Merck kieselgel 60-F_{254} and products were detected with 254 nm light. Merck kieselgel 60 (230–400 mesh) was used for column chromatography. Germane hydrides were purchased from Aldrich (Milwaukee, WI, USA) or Gelest (Morrisville, PA, USA) chemical corporations.

1-[6-(Tributylgermyl)-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-ribo-hex-5(*E*)-enofuranosyl]uracil (7a)

A suspension of **5**[13] (48 mg, 0.11 mmol) in toluene (2 mL) was deoxygenated (N_2, 1 hour), and then Bu_3GeH (49 mg, 0.052 mL, 0.20 mmol) was added. Deoxygenation was continued for 30 minutes, and AIBN (8.2 mg, 0.05 mmol) was added. The resulting solution was refluxed for 14 hours [additional AIBN (16.4 mg, 0.1 mmol) in degassed toluene (1 mL) was added to the reaction mixture periodically]. Volatiles were evaporated (TLC analysis showed a formation of the less polar product) and the residue was partitioned ($CHCl_3$//H_2O/$NaHCO_3$). The organic layer was washed with brine, dried ($MgSO_4$) and was evaporated. The residue was column chromatographed [EtOAc/hexane (7:3)] to give **7a** (33 mg, 57%) as a syrup: ^{1}H NMR δ 0.72–0.78 (m, 6H, Bu), 0.84–0.88 (m, 9H, Bu), 1.24–1.33 (m, 12H, Bu), 1.39 (s, 3, CH_3), 1.56 (s, 3, CH_3), 4.52 ("dd", J = 4.0, 6.0 Hz, 1, H4′), 4.69 (dd, J = 4.3, 6.4 Hz, 1, H3′), 4.92 (dd, J = 2.0, 6.4 Hz, 1, H2′), 5.70 (dd, J = 1.5, 8.2 Hz, 1, H5), 5.72 (d, J = 2.1 Hz, 1, H1′), 5.95 (dd, J = 6.3, 18.5 Hz, 1, H5′), 6.14 (dd, J = 1.1, 18.5 Hz, 1, H6′), 7.20 (d, J = 8.1 Hz, 1, H6), 8.75 (br s, 1, NH); ^{13}C NMR δ 12.71 (Bu), 13.77 (Bu), 25.37 (C*Me*$_2$), 26.42 (Bu), 27.15 (C*Me*$_2$), 27.29 (Bu), 83.99 (C3′), 84.83 (C2′), 89.79 (C4′), 93.47 (C1′), 102.41 (C5), 114.65 (*C*Me$_2$), 134.02 (C6′), 140.60 (C5′), 141.64 (C6), 149.77 (C2), 162.96 (C4); MS m/z 525

(100, MH^+, ^{74}Ge), 523 (70, MH^+, ^{72}Ge), 521 (50, MH^+, ^{70}Ge); HRMS calcd for $C_{25}H_{43}{}^{74}GeN_2O_5$ $[M+H]^+$ 525.2384, found 525.2385.

1-[5,6-Dideoxy-2,3-*O*-isopropylidene-6-(triphenylgermyl)-β-D-ribo-hex-5(*E*)-enofuranosyl]uracil (7b)

Treatment of **5**[13] (48 mg, 0.11 mmol) with Ph_3GeH (60 mg, 0.20 mmol; as described for **7a**) gave **7b** (46 mg, 72%) as a foam: ^1H NMR δ 1.26 (s, 3, CH_3), 1.50 (s, 3, CH_3), 4.61 (ddd, J = 1.2, 4.2, 5.6 Hz, 1, H4′), 4.71 (dd, J = 4.1, 6.3 Hz, 1, H3′), 4.90 (dd, J = 1.9, 6.4 Hz, 1, H2′), 5.55 (d, J = 8.1 Hz, 1, H5), 5.64 (d, J = 1.9 Hz, 1, H1′), 6.12 (dd, J = 5.7, 18.3 Hz, 1, H5′), 6.52 (dd, J = 1.3, 18.3 Hz, 1, H6′), 7.10 (d, J = 8.1 Hz, 1, H6), 7.26–7.33 (m, 9H, Ph), 7.36–7.42 (m, 6H, Ph), 8.65 (br s, 1, NH); ^{13}C NMR δ 25.34 & 27.11 (C*Me*$_2$), 84.14 (C3′), 84.69 (C2′), 89.48 (C4′), 93.92 (C1′), 102.61 (C5), 114.63 (*C*Me$_2$), 128.35, 128.53, 129.26, 135.03 (Ph), 135.64 (C6′), 141.80 (C5′), 145.00 (C6), 149.75 (C2), 162.99 (C4); MS m/z 585 (100, MH^+, ^{74}Ge), 583 (70, MH^+, ^{72}Ge), 581 (50, MH^+, ^{70}Ge); HRMS calcd for $C_{31}H_{31}{}^{74}GeN_2O_5$ $[M+H]^+$ 585.1485, found 585.1447.

9-[6-(Tributylgermyl)-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-ribo-hex-5(*E*)-enofuranosyl]adenine (8a)

Treatment of **6**[12] (50 mg, 0.11 mmol) with Bu_3GeH (47 mg, 0.050 mL, 0.19 mmol; as described for **7a**) gave **8a** (27 mg, 46%) as a syrup: ^1H NMR δ 0.66–0.71 (m, 6H, Bu), 0.85–0.89 (m, 9H, Bu), 1.26–1.34 (m, 12H, Bu) 1.42 (s, 3, CH_3), 1.62 (s, 3, CH_3), 4.71 (dd, J = 3.1, 5.0 Hz, 1, H4′), 5.02 (dd, J = 3.1, 6.2 Hz, 1, H3′), 5.57 (dd, J = 1.8, 6.3 Hz, 1, H2′), 5.64 (br s, 2, NH_2), 5.95 (dd, J = 5.1, 18.6 Hz, 1, H5′), 6.01 (d, J = 18.5 Hz, 1, H6′), 6.12 (d, J = 1.8 Hz, 1, H1′), 7.88 (s, 1, H2), 8.35 (s, 1, H8); ^{13}C NMR δ 12.69 (Bu), 13.85 (Bu), 26.54 (Bu), 26.63 & 27.26 (C*Me*$_2$), 27.38 (Bu), 84.70 (C3′), 85.39 (C2′), 90.63 (C4′), 91.27 (C1′), 114.97 (*C*Me$_2$), 120.99 (C5), 133.70 (C6′), 140.89 (C5′), 142.02 (C8), 150.44 (C4), 154.05 (C2), 156.36 (C6); MS m/z 548 (100, MH^+, ^{74}Ge), 546 (70, MH^+, ^{72}Ge), 544 (50, MH^+, ^{70}Ge); HRMS calcd for $C_{26}H_{44}{}^{74}GeN_5O_3$ $[M+H]^+$ 548.2656, found 548.2650.

9-[5,6-Dideoxy-2,3-*O*-isopropylidene-6-(triphenylgermyl)-β-D-ribo-hex-5(*E*)-enofuranosyl]adenine (8b)

Treatment of **6**[12] (50 mg, 0.11 mmol) with Ph_3GeH (57 mg, 0.19 mmol; as described for **7a**) gave **8b** (28 mg, 42%) as a foam: ^1H NMR δ 1.39 (s, 3, CH_3), 1.62 (s, 3, CH_3), 4.83 (ddd, J = 1.3, 3.2, 5.8 Hz, 1, H4′), 5.09 (dd, J = 3.2, 6.3 Hz, 1, H3′), 5.55 (dd, J = 1.9, 6.3 Hz, 1, H2′), 5.61 (br s, 2, NH_2), 6.11 (d, J = 1.9 Hz, 1, H1′), 6.20 (dd, J = 5.9, 18.3 Hz, 1, H5′), 6.46 (dd, J = 1.4, 18.3 Hz, 1, H6′), 7.31–7.40 (m, 15H, Ph), 7.85 (s, 1, H2), 8.11 (s, 1, H8);

^{13}C NMR δ 25.44 & 27.11 (C*Me*$_2$), 84.13 (C3′), 84.81 (C2′), 89.75 (C4′), 90.74 (C1′), 114.38 (*C*Me$_2$), 120.13 (C5), 127.96, 128.26, 129.13, 134.95 (Ph), 135.67 (C6′), 140.03 (C5′), 145.44 (C8), 149.44 (C4), 153.04 (C2), 155.31 (C6) MS *m/z* 608 (100, MH$^+$, ^{74}Ge), 606 (68, MH$^+$, ^{72}Ge), 604 (50, MH$^+$, ^{70}Ge); HRMS calcd for $C_{32}H_{32}{}^{74}GeN_5O_3$ [M+H]$^+$ 608.1717, found 608.1722.

1-[2,3-Di-*O*-acetyl-5,6-dideoxy-6-(*p*-toluenesulfonyl)-β-D-ribo-hex-5(*E*)-enofuranosyl]uracil (9b)

DMAP (5 mg, 0.04 mmol) was added to a stirred solution of **9a**[13] (80 mg, 0.18 mmol) in Ac_2O (4 mL) at ambient temperature. After 14 hours, MeOH (10 mL) was added and stirring was continued for 1 hour. Volatiles were evaporated and the residue was co-evaporated with MeOH (2 × 5 mL). The crude product was partitioned ($CHCl_3$//H_2O/HCl) and the organic layer was washed with $NaHCO_3/H_2O$, brine, dried ($MgSO_4$) and was evaporated to give **9b** (83 mg, 96%) of sufficient purity to be used in next step: ^{1}H NMR δ 2.05 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.38 (s, 3, CH_3), 4.64 (ddd, J = 1.6, 4.6, 6.0 Hz, 1, H4′), 5.24 (t, J = 6.1 Hz, 1, H3′), 5.36 (t, J = 5.5 Hz, 1, H2′), 5.70 (d, J = 8.1 Hz, 1, H5), 5.86 (d, J = 4.8 Hz, 1, H1′), 6.62 (dd, J = 1.6, 15.1 Hz, 1, H6′), 6.98 (dd, J = 4.4, 15.1 Hz, 1, H5′), 7.18 (d, J = 8.1 Hz, 1, H6), 7.28 (d, J = 8.2 Hz, 2H, Ar), 7.71 (d, J = 8.3 Hz, 2H, Ar), 9.45 (br s, 1, NH); ^{13}C NMR δ 20.39 (2×) & 21.65 (CH_3 & 2 × Ac), 72.16 (C3′), 72.39 (C2′), 79.17 (C4′), 89.35 (C1′), 103.68 (C5), 127.94 (Ar), 129.78 (Ar), 133.33 (C6′), 136.47 (Ar), 138.66 (C5′), 140.21 (C6), 145.01 (Ar), 149.98 (C2), 162.67 (C4), 169.44 & 169.58 (2 × Ac); MS *m/z* 479 (100, MH$^+$).

1-[2,3-Di-*O*-acetyl-5,6-dideoxy-6-(triphenylgermyl)-β-D-ribo-hex-5(*E*)-enofuranosyl]uracil (10a)

Treatment of **9b** (90 mg, 0.19 mmol) with Ph_3GeH (104 mg, 0.34 mmol; as described for **7a**) gave **10a** (81 mg, 68%) as an amorphous solid: ^{1}H NMR δ 2.09 (s, 3H, Ac), 2.11 (s, 3H, Ac), 4.66 (ddd, J = 1.5, 5.2, 5.4 Hz, 1, H4′), 5.27 (t, J = 5.2 Hz, 1, H3′), 5.32 (t, J = 5.4 Hz, 1, H2′), 5.65 (d, J = 8.1 Hz, 1, H5), 6.10 (d, J = 5.1 Hz, 1, H1′), 6.17 (dd, J = 5.4, 18.3 Hz, 1, H5′), 6.73 (dd, J = 1.4, 18.3 Hz, 1, H6′), 7.18 (d, J = 8.2 Hz, 1, H6), 7.37–7.43 (m, 9H, Ph), 7.45–7.50 (m, 6H, Ph), 8.98 (br s, 1, NH); ^{13}C NMR δ 20.43 & 20.54 (2 × Ac), 72.55 (C2′), 72.96 (C3′), 83.18 (C4′), 87.43 (C1′), 103.47 (C5), 128.48, 129.44, 134.96, 135.21 (Ph), 131.02 (C6′), 139.34 (C6), 142.87 (C5′), 150.22 (C2), 162.63 (C4), 169.61 (2 × Ac); MS *m/z* 629 (100, MH$^+$, ^{74}Ge), 627 (70, MH$^+$, ^{72}Ge), 625 (50, MH$^+$, ^{70}Ge); HRMS calcd for $C_{32}H_{31}{}^{74}GeN_2O_7$ [M+H]$^+$ 629.1343, found 629.1335.

1-[5,6-Dideoxy-6-(triphenylgermyl)-β-D-ribo-hex-5(*E*)-enofuranosyl]uracil (10b)

Method A. A solution of **10a** (32 mg, 0.05 mmol) in NH_3/MeOH (2 mL) was stirred at ~0°C for 2 hours, and was evaporated and co-evaporated (MeOH). The residue was column chromatographed (EtOAc/hexane, 4:1) to give **10b** (26 mg, 96%) as a white powder: ^{1}H NMR δ 4.01 (t, J = 5.5 Hz, 1, H3′), 4.19 (dd, J = 3.5, 5.0 Hz, 1, H2′), 4.62 ("t", J = 5.5 Hz, 1, H4′), 5.20 (br s, 2, 2 × OH), 5.58 (d, J = 8.1 Hz, 1, H5), 5.82 (d, J = 3.2 Hz, 1, H1′), 6.20 (dd, J = 5.3, 18.4 Hz, 1, H5′), 6.71 (dd, J = 1.4, 18.3 Hz, 1, H6′), 7.32–7.46 (m, 16H, Ph & H6), 8.92 (br s, 1, NH); ^{13}C NMR δ 73.82 (C3′), 75.10 (C2′), 85.81 (C4′), 91.11 (C1′), 102.52 (C5), 128.43, 128.87, 130.98, 134.85 (Ph), 136.36 (C6′), 139.54 (C6), 144.29 (C5′), 151.21 (C2), 163.69 (C4); MS m/z 545 (100, MH^+, ^{74}Ge), 543 (75, MH^+, ^{72}Ge), 541 (45, MH^+, ^{70}Ge); HRMS calcd for $C_{28}H_{27}{}^{74}GeN_2O_5$ $[M+H]^+$ 545.1132, found 545.1132.

Method B. A solution of **7b** (29 mg, 0.05 mmol) in TFA/H_2O (9:1, 1.5 mL) was stirred at ~0°C for 1 hour. The volatiles were evaporated, co-evaporated (3×) with toluene and the residue was column chromatographed (EtOAc) to give **10b** (18 mg, 66%) with data identical as above.

1-[2,3-Di-*O*-acetyl-6-(tributylgermyl)-5,6-dideoxy-β-D-ribo-hex-5-(*E*)-enofuranosyl]uracil (11a)

Method A. Treatment of **9b** (39 mg, 0.08 mmol) with Bu_3GeH (39 mg, 0.041 mL, 0.16 mmol; as described for **7a**) gave **11a** (22 mg, 49%) as a foam: ^{1}H NMR δ 0.78–0.92 (m, 15H, Bu), 1.26–1.38 (m, 12H, Bu), 2.08 (s, 3H, Ac), 2.10 (s, 3H, Ac), 4.52 ("t", J = 5.5 Hz, 1, H4′), 5.22 (t, J = 5.3 Hz, 1, H3′), 5.30 (t, J = 5.4 Hz, 1, H2′), 5.75 (d, J = 8.1 Hz, 1, H5), 5.95 (dd, J = 5.7, 18.5 Hz, 1, H5′), 6.02 (d, J = 5.2 Hz, 1, H1′), 6.26 (dd, J = 1.2, 18.5 Hz, 1, H6′), 7.26 (d, J = 8.1 Hz, 1, H6), 8.27 (s, 1, NH); ^{13}C NMR δ 12.71 (Bu), 13.73 (Bu), 26.35 (Bu), 27.32 (Bu), 20.42 & 20.49 (2 × Ac), 72.78 (C3′), 72.91 (C2′), 83.57 (C4′), 87.73 (C1′), 103.24 (C5), 135.65 (C6′), 138.84 (C5′), 139.50 (C6), 149.89 (C2), 162.27 (C4); 169.56 & 169.57 (2 × Ac); MS m/z 569 (100, MH^+, ^{74}Ge), 567 (72, MH^+, ^{72}Ge), 565 (51, MH^+, ^{70}Ge); HRMS calcd for $C_{26}H_{43}{}^{74}GeN_2O_7$ $[M+H]^+$ 569.2282, found 569.2289.

Method B. A suspension of **9b** (29 mg, 0.06 mmol) in toluene (4 mL) was degassed (N_2, 1 hour), and then Bu_3GeH (29 mg, 0.031 mL, 0.12 mmol) was added and deoxygenation was continued for an additional 1 hour. The 2-mercaptoethanol (2 mg, 2 μL, 0.02 mmol) and ACCN (14.5 mg, 0.06 mmol) were added and the resulting solution was refluxed for 20 hours. The aqueous work-up and column chromatography (as described for **7a**) gave **11a** (20 mg, 58%) with data as reported above.

1-[6-(Tributylgermyl)-5,6-dideoxy-β-D-ribo-hex-5-(*E*)-enofuranosyl]uracil (11b)

Treatment of **11a** (23 mg, 0.04 mmol) with NH_3/MeOH (2 mL; as described for **10a**) gave **11b** (14 mg, 72%) as a white powder: ^{1}H NMR (MeOH-d_4) δ 0.83–0.97 (m, 15H, Bu), 1.30–1.46 (m, 12H, Bu), 3.96 ("t", J = 5.7 Hz, 1, H3′), 4.18 (dd, J = 3.8, 5.3 Hz, 1, H2′), 4.35 (t, J = 5.8 Hz, 1, H4′), 5.69 (d, J = 8.1 Hz, 1, H5), 5.83 (d, J = 3.8 Hz, 1, H1′), 6.11 (dd, J = 5.3, 18.5 Hz, 1, H5′), 6.20 (d, J = 18.6 Hz, 1, H6′), 7.55 (d, J = 8.1 Hz, 1, H6); ^{13}C NMR (MeOH-d_4) δ 13.71 (Bu), 14.09 (Bu), 27.46 (Bu), 28.56 (Bu), 75.12 & 75.13 (C2′/3′), 87.08 (C4′), 92.09 (C1′), 102.78 (C5), 133.15 (C6′), 142.39 (C5′), 143.20 (C6), 152.22 (C2), 166.08 (C4); MS m/z 485 (100, MH^+, ^{74}Ge), 483 (77, MH^+, ^{72}Ge), 481 (52, MH^+, ^{70}Ge); HRMS calcd for $C_{22}H_{39}{}^{74}GeN_2O_5$ $[M+H]^+$ 485.2071, found 485. 2065.

1-[5,6-Dideoxy-6-iodo-2,3-*O*-isopropylidene-β-D-ribo-hex- 5(*E*)-enofuranosyl]uracil (12)

A solution of NIS (22 mg, 0.10 mmol) in $CHCl_3/CH_2Cl_2$ (1:1, 5 mL) was added dropwise to a stirred solution of **7a** (48 mg, 0.09 mmol) in $CHCl_3/CH_2Cl_2$ (1:1, 5 mL) at 0°C. After 1 hour (TLC showed exclusive formation of a more polar product), the pink reaction mixture was treated with $NaHSO_3/H_2O$ and the separated organic layer was washed with brine, dried ($MgSO_4$) and was evaporated. Purification on a short silica gel column ($CHCl_3$/MeOH, 30:1) gave **12** (34 mg, 92%) with data as reported.[6]

9-[6-Bromo-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-ribo-hex-5(*E*)-enofuranosyl]adenine (13)

A solution of NBS (18 mg, 0.10 mmol) in $CHCl_3/CH_2Cl_2$ (1:1, 5 mL) was added dropwise to a stirred solution of **8a** (50 mg, 0.09 mmol) in $CHCl_3/CH_2Cl_2$ (1:1, 5 mL) at 0°C. After 6 hours, the reaction mixture was washed with $NaHCO_3/H_2O$ and brine and the separated organic layer was dried (Na_2SO_4) and was evaporated. Purification on a short silica gel column ($CHCl_3$/MeOH, 20:1) gave **13** (28 mg, 81%) with data as reported.[3]

9-(5,6-Dideoxy-β-D-ribo-hex-5-enofuranosyl)adenine [5′-deoxy-5′-methyleneadenosine] (14)

A solution of **8a** (22 mg, 0.04 mmol) in CF_3CO_2H/H_2O (9:1, 1 mL) was stirred at 0°C for 1 hour. The volatiles were evaporated and the residue was co-evaporated (2×) with toluene. The residue was column chromatographed (1 → 5% MeOH/EtOAc) to give **14**[3,12] (8 mg, 76%): ^{1}H NMR (MeOH-d_4) δ 4.25 (t, J = 5.1 Hz, 1, H3′), 4.48 (dd, J = 5.3, 6.5 Hz, 1, H4′), 4.74 (t, J = 4.9 Hz, 1, H2′), 5.26 ("dt", J = 1.4, 10.5 Hz, 1, H6"), 5.41

("dt", J = 1.5, 17.1 Hz, 1, H6′), 6.04 (d, J = 5.0 Hz, 1, H1′), 6.11 ("ddd", J= 6.6, 10.5, 17.1 Hz, 1, H5′), 8.23 (s, 1, H2), 8.26 (s, 1, H8).

2′-Deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-2′-[(phenylsulfonyl)methylene]uridine [16(*Z*)]

Lithium bis(trimethylsilyl)amide (1 M/THF; 0.18 mL, 0.18 mmol) was added dropwise to a stirred solution of diethyl (phenylsulfonyl)methylphosphonate[18] (53 mg, 0.18 mmol) in THF (2 mL) at -78°C under nitrogen. After 30 minutes, ketone **15**[33] (78 mg, 0.16 mmol) was added and the resulting solution was allowed to warm up to -30°C over 2 hours and then to ~0°C over 15 minutes. NH_4Cl/H_2O (0.5 mL) was added and the volatiles were evaporated. The residue was partitioned ($CHCl_3//H_2O/NaHCO_3$) and the organic layer was washed with brine, dried ($MgSO_4$) and was evaporated. Column chromatography (30 → 40% EtOAc/hexane) gave **16** (62 mg, 62%) as a pale-yellow powder: ^{1}H NMR δ 0.97–1.05 (m, 28H, 4 × *i*-Pr), 3.62 (ddd, J = 3.0, 4.2, 8.7 Hz, 1, H4′), 3.99 (dd, J = 3.0, 12.8 Hz, 1, H5′), 4.06 (dd, J = 4.2, 12.8 Hz, 1, H5″), 5.35 (dt, J = 2.1, 8.5 Hz, 1, H3′), 5.70 (d, J = 8.0 Hz, 1, H5), 6.43 ("t", J = 1.8 Hz, 1, H1′), 6.48 ("t", J = 2.3 Hz, 1, H2"), 7.27 (d, J = 8.1 Hz, 1, H6), 7.51 ("t", J = 7.4 Hz, 2H, Ph), 7.60 ("tt", J = 1.3, 7.4 Hz, 1H, Ph), 7.68 ("dd", J = 1.4, 7.1 Hz, 2H, Ph), 8.30 (s, 1, NH); ^{13}C NMR δ 12.58 (CH), 16.86, 16.94, 17.05, 17.13, 17.20, 17.21, 17.23, 17.35 (CH_3), 61.21 (C5′), 73.02 (C3′), 81.38 (C4′), 85.83 (C1′), 102.06 (C5), 124.17 (C2"), 126.57, 129.56, 134.02, 140.57 (Ph), 145.08 (C6), 148.65 (C2), 156.65 (C2′), 162.91 (C4); MS m/z 623 (100, MH^+).

2′-Deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-2′-[(triphenylgermyl)methylene]uridine [17(*Z*)]

Treatment of **16** (43 mg, 0.07 mmol) with Ph_3GeH (40 mg, 0.13 mmol; as described for **7a**) gave **17** (28 mg, 51%) as a white powder: ^{1}H NMR δ 0.91–0.97 (m, 24H, 8 × CH_3), 1.03 (s, 4H, 4 × CH), 3.50 (dt, J = 3.2, 8.7 Hz, 1, H4′), 3.86 (dd, J = 3.2, 12.1 Hz, 1, H5′), 3.91 (dd, J = 3.6, 12.1 Hz, 1, H5″), 4.88 ("dt", J = 2.2, 8.4 Hz, 1, H3′), 5.15 (d, J = 8.1 Hz, 1, H5), 5.83 (t, J = 1.7 Hz, 1, H1′), 6.29 (d, J = 8.1 Hz, 1, H6), 6.77 (t, J = 2.1 Hz, 1, H2"), 7.20–7.26 (m, 9H, Ph), 7.30–7.36 (m, 6H, Ph), 8.28 (s, 1, NH); ^{13}C NMR δ 12.60, 12.66, 13.05, 13.65 (CH), 16.92, 17.02, 17.22, 17.24, 17.27, 17.31, 17.36 (CH_3), 61.31 (C5′), 73.50 (C3′), 82.12 (C4′), 85.37 (C1′), 102.24 (C5), 122.63 (C2"), 128.62, 129.53, 134.63, 135.29 (Ph), 141.17 (C6), 149.03 (C2), 155.27 (C2′), 162.21 (C4); MS m/z 787 (50, MH^+, ^{74}Ge), 785 (35, MH^+, ^{72}Ge), 783 (25, MH^+, ^{70}Ge); HRMS calcd for $C_{40}H_{53}{}^{74}GeN_2O_6Si_2$ $[M+H]^+$ 787.2654, found 787.2663.

2′-Deoxy-2′-[(triphenylgermyl)methylene]uridine [18(*Z*)]

Bu_4NF (1 M/THF, 0.12 mL, 0.12 mmol) was added to a solution of **17** (31 mg, 0.04 mmol) in THF (2 mL) and the resulting mixture was stirred at ~0°C for 3 hours. Volatiles were evaporated and the residue was partitioned between diethyl ether and water. The aqueous layer was evaporated and the oily residue was column chromatographed (EtOAc) to give **18** (16 mg, 73%) as an amorphous solid: ^{1}H NMR (MeOH-d_4) δ 3.66–3.73 (m, 2, H4′,5′), 3.83–3.89 (m, 1, H5"), 4.77 (dt, J = 2.2, 8.0 Hz, 1, H3′), 5.32 (d, J = 8.0 Hz, H5), 6.14 (t, J = 1.7 Hz, 1, H1′), 6.86 (t, J = 2.2 Hz, 1, H2"), 7.04 (d, J = 8.0 Hz, 1, H6), 7.37–7.43 (m, 9H, Ph), 7.49–7.52 (m, 6H, Ph); ^{13}C NMR (MeOH-d_4) δ 62.33 (C5′), 73.43 (C3′), 85.44 (C4′), 86.93 (C1′), 102.93 (C5), 124.67 (C2"), 129.65, 130.54, 135.76, 136.76 (Ph), 143.85 (C6), 151.61 (C2), 159.02 (C2′), 166.01 (C4); MS m/z 545 (50, MH^+, ^{74}Ge), 543 (35, MH^+, ^{72}Ge), 541 (25, MH^+, ^{70}Ge); HRMS (ESI) calcd for $C_{28}H_{26}{}^{74}GeN_2NaO_5$ $[M+Na]^+$ 567.0951, found 567.0960.

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