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# New Telluride-Mediated Elimination for Novel Synthesis of 2′,3′-Didehydro-2′,3′-dideoxynucleosides

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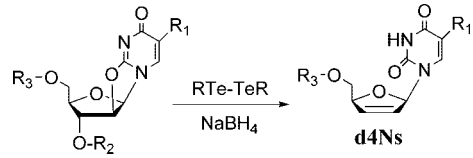


Several 2′,3′-dideoxynucleosides (ddNs) and 2′,3′-didehydro-2′,3′-dideoxynucleosides (d4Ns) are FDA-approved anti-HIV drugs. Via conveniently synthesized 2,2′-anhydronucleosides, we have developed a novel synthesis of d4Ns by discovering and applying a new telluride-mediated elimination reaction. Our experiment results show that after substitution of 2,2′-anhydronucleosides with a telluride monoanion, a telluride intermediate is formed, and its elimination leads to formation of the olefin products (d4Ns). Our mechanistic study indicates that this telluride-assisted reaction consists of two steps: substitution (or addition) and elimination. By using dimethyl ditelluride (0.1 equiv) as the reagent, d4Ns can be synthesized with yields up to 90% via this telluride-mediated elimination. Our novel strategy has great potential to simplify synthesis of these drugs and to further reduce cost of AIDS treatment and will also facilitate development of novel d4N and ddN analogues.

## Introduction

2′,3′-Dideoxynucleosides (ddNs) and 2′,3′-didehydro-2′,3′-dideoxynucleosides (d4Ns) are an important type of antiviral compounds, which terminate viral DNA polymerization after their incorporation by reverse transcriptase.[1] Several of them (Figure 1), including 2′,3′-dideoxycytidine (ddC, **1**), 2′,3′-didehydro-3′-deoxythymidine (d4T, Stavudine, **2**), 3′-azido-3′-deoxythymidine (AZT, **3**), ddI (2′,3′-dideoxyinosine, **4**), 3TC ($\beta$-3′-deoxy-3′-thiocytidine, **5**), ABC (Abacavir, **6**), and FTC (Emtricitabine, **7**), have been approved and permitted for marketing by the FDA as potent anti-HIV therapeutics.[2] Since the finding of the ddNs and d4Ns with high efficacy against HIV, tremendous attention has been directed toward the development of new chemistry for synthesizing these compounds as well as exploring novel analogues in order to reduce cost and better treat AIDS, one of the most deadly diseases caused by HIV.[3]

Extensive research has been conducted in this area, and the field has been reviewed.[4] In general, the ddNs can be synthesized from hydrogenation of d4Ns, and d4Ns are synthesized from well-developed strategies, including Corey−Winter reaction through the cyclic thionocarbonates,[5] Eastwood olefination through the cyclic orthoformates,[6] Mattocks reaction through the bromoacetates,[7] and olefin metathesis via the ring-closure reaction.[8] In addition, 2′,3′-anhydro-2′-deoxyuridine and -thymidine can be converted to d4Ns via base-catalyzed elimination.[9] Furthermore, syntheses of d4Ns via oxidative elimination

(1) For a review, see: Chu, C. K., Baker, D. C., Eds. *Nucleosides and Nucleotides as Antitumor and AntiViral Agents*; Plenum Press: New York, 1993.

(2) (a) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491. (b) Doong, S. L.; Tsai, C. H.; Schinazi, R. F.; Liotta, D. C.; Cheng, Y. C. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 8495. (c) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17.

(3) (a) Ogilvie, K. K.; Iwacha, D. J. *Can. J. Chem.* **1974**, *52*, 1787. (b) Saito, Y.; Zevaco, T. A; Agrofoglio, L. A. *Tetrahedron* **2002**, *58*, 9593. (c) Wiley, C. A.; Grafe, M.; Kennedy, C.; Nelson, J. A. *Acta Neuropathol. (Berlin)* **1988**, *76*, 338. (d) Kikyoya, T. Jpn. Kokai Tokkyo Koho 1988, JP 63241356-A-19881006. (e) Luzzio, F. A.; Menes, M. E. *J. Org. Chem.* **1994**, *59*, 7267.

(4) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745.

(5) (a) Dudycz, L. W. *Nucleosides Nucleotides* **1989**, *8*, 35. (b) Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; Van Roey, P. V. *J. Org. Chem.* **1989**, *54*, 2217.

(6) (a) Josan, J. S.; Eastwood, F. W. *Aust. J. Chem.* **1968**, *21*, 2013. (b) Crank, G.; Eastwood, F. W. *Aust. J. Chem.* **1964**, *17*, 1392.

(7) (a) Robins, M. J.; Wilson, J. S.; Madej, D.; Low, N. H.; Hansske, F.; Wnuk, S. F. *J. Org. Chem.* **1995**, *60*, 7902. (b) Mansuri, M. M.; Starrett, J. E.; Wos, J. A.; Tortolani, D. R.; Brodfuehrer, P. R.; Howell, H. G.; Martin, J. C. *J. Org. Chem.* **1989**, *54*, 4780. (c) Robins, M. J.; Hansske, F.; Low, N. H.; Park, J. I. *Tetrahedron Lett.* **1984**, *25*, 367.

(8) (a) Gillaizeau, I.; Lagoja, I. M.; Nolan, S. P.; Aucagne, V.; Rozenski, J.; Herdewijn, P; Agrofoglio, L. A. *Eur. J. Org. Chem.* **2003**, 666. (b) Ewing, D.; Glacon, V.; Mackenzie, G.; Postel, D.; Len, C. *Tetrahedron Lett.* **2002**, *43*, 3503.

(9) Horwitz, J. P.; Chua, J.; Rooge, M. A. D.; Noel, R.; Klundt, I. L. *J. Org. Chem.* **1966**, *31*, 205.

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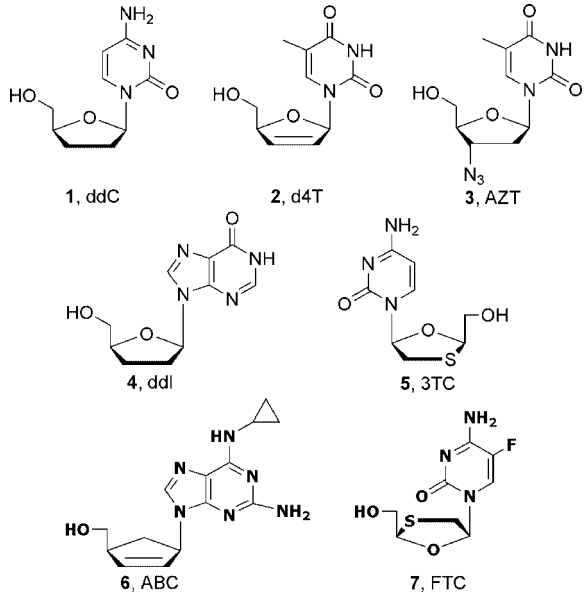



**FIGURE 1.** Structure of FDA-approved anti-HIV drugs.

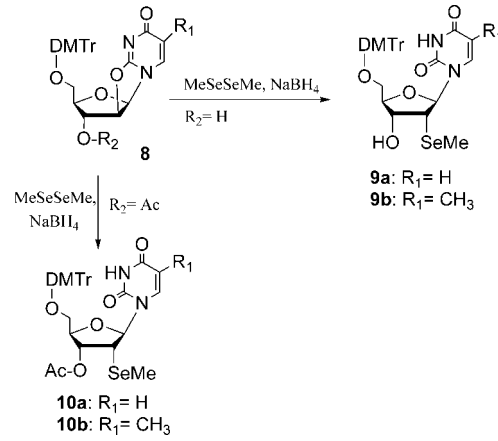
of nucleoside α-phenyl selenoxides[10] and via substitution of nucleoside dimesylates by selenide and telluride dianions[11] were reported.

Despite enormous efforts in developing synthetic routes for these d4Ns and ddNs, new methodology development will lead to disease treatment cost reduction as well as novel analogue/drug discovery. In our chemogenetic research of nucleic acid structure and function using atomic probes, we have pioneered atom-specific replacement of oxygen with selenium.[12] Selenium functionality can be successfully introduced to the α-2′-position via reacting sodium methyl selenide (reduced from dimethyl diselenide with $NaBH_4$) with 2,2′-anhydronucleosides, which gives the 2′-SeMe-nucleosides (Scheme 1).[12a,g] Surprisingly, when the corresponding telluride was used (Scheme 2), instead of the expected 2′-Te-nucleosides (**11**), we observed the formation of eliminated 2′,3′- and 1′,2′-olefin products (**12** and **13**). Interestingly, by tailoring the SN2 leaving ability of the 3′-moieties (such as acetylation), we are able to steer the telluride-mediated elimination to the 2′,3′-olefins (or d4Ns, **12**) exclusively. We report here the new telluride-mediated elimination reaction, its mechanistic study, and our novel methodology for d4N synthesis.

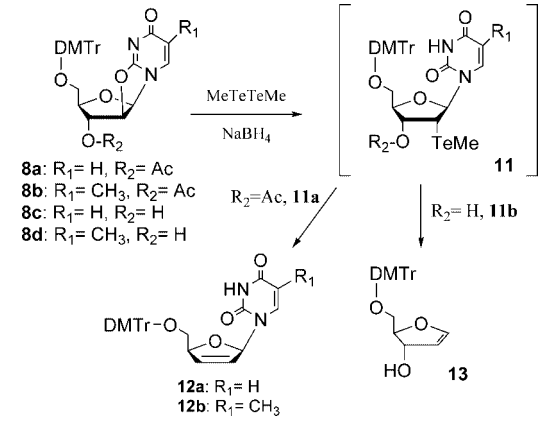
## Results and Discussion

Compound **8** was conveniently prepared via the well-established 2,2′-anhydronucleoside synthesis from the readily

**SCHEME 1. Synthesis of 2′-Se-nucleosides**




**SCHEME 2. Telluride-Mediated Elimination of Nucleosides**




available ribonucleosides,[12a,g,13] followed by protection of the 5′- and 3′-hydroxyl groups using conventional methodologies. On the basis of our observation of the telluride-mediated elimination, we hypothesized a two-step mechanism: substitution (or addition) and elimination. In this reaction, dimethyl ditelluride is first reduced to methyl telluride monoanion. Via a $S_N2$ reaction, this strong telluride nucleophile attacks the α-2′-position of 2,2′-anhydronucleosides by substituting the 2-oxide as the intramolecular leaving group, which leads to formation of a substitution (or addition) intermediate (**11**). This intermediate undergoes elimination to give 2′,3′-olefin (**12**, d4N) and 1′,2′-olefin (**13**). This hypothesis has guided our investigation. When dimethyl ditelluride ($Me_2Te_2$) was used as the reagent, however, the expected intermediate **11** could not be isolated. The instability of the intermediate was probably caused by the highly reactive alkyl telluride. Thus, we reasoned that a less reactive aryl telluride might allow us to isolate the intermediate for a mechanistic study.

As expected, when diphenyl ditelluride was used as the reagent, we were indeed able to successfully isolate the telluride intermediate. Due to the 3′-deacetylation under basic conditions in ethanol, however, intermediate **15** with the 2′-Ph-Te functionality was isolated instead of the 3′-Ac intermediate (**14**, Scheme 3). Similar to oxidative elimination of the nucleoside phenylselenides,[9,10a] phenyltelluride **15** can also undergo oxida-

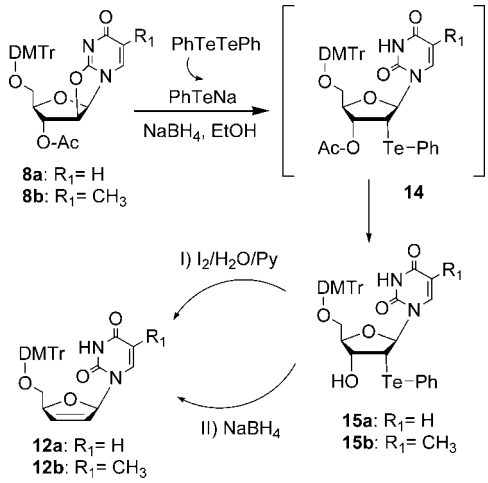
(10) (a) Diaz, Y.; El-Laghdach, A.; Matheu, M. I.; Castillon, S. *J. Org. Chem.* **1997**, *62*, 1501. (b) Beach, J. W.; Kim, H. O.; Jeong, L. S.; Nampalli, S.; Islam, Q.; Ahn, S. K.; Babu, J. R.; Chu, C. K *J. Org. Chem.* **1992**, *57*, 3887. (c) Haraguchi, K.; Tanaka, H.; Maeda, H.; Itoh, Y.; Saito, S.; Miyasaka, T. *J. Org. Chem.* **1991**, *56*, 5401.

(11) Clive, D. L. J.; Wickens, P. L.; Sgarbi, P. W. M. *J. Org. Chem.* **1996**, *61*, 7426.

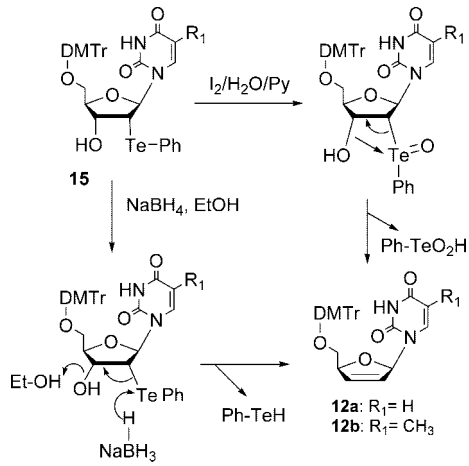
(12) (a) Sheng, J.; Jiang, J.; Salon, J.; Huang, Z. *Org. Lett.* **2007**, *9*, 749. (b) Salon, J.; Sheng, J.; Jiang, J.; Chen, G.; Caton, W, J.; Huang, Z. *J. Am. Chem. Soc.* **2007**, *129*, 4862. (c) Jiang, J.; Sheng, J.; Carrasco, N.; Huang, Z. *Nucleic Acids Res.* **2007**, *35*, 477. (d) Carrasco, N.; Caton-Williams, J.; Brandt, G.; Wang, S.; Huang, Z. *Ang. Chem., Int. Ed.* **2006**, *45*, 94. (e) Salon, J; Chen, G.; Portilla, Y.; Germann, M. W.; Huang, Z. *Org. Lett.* **2005**, *7*, 5645. (f) Carrasco, N.; Huang, Z. *J. Am. Chem. Soc.* **2004**, *126*, 448. (g) Carrasco, N.; Buzin, Y.; Tyson, E.; Halpert, E.; Huang, Z. *Nucleic Acids Res.* **2004**, *32*, 1638. (h) Du, Q.; Carrasco, N.; Teplova, M.; Wilds, C. J.; Egli, M.; Huang, Z. *J. Am. Chem. Soc.* **2002**, *124*, 24. (i) Carrasco, N.; Ginsburg, D.; Du, Q.; Huang, Z. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 1723.

(13) (a) Ogilvie, K. K.; Iwacha, D. J. *Can. J. Chem.* **1974**, *52*, 1787. (b) Shi, J.; Du, J.; Ma, T.; Pankiewicz, K. W.; Patterson, S. E.; Tharnish, P. M.; McBrayer, T. R.; Stuyver, L. J.; Otto, M. J.; Chu, C. K.; Schinazi, R. F.; Watanabe, K. A. *Bioorg. Med. Chem.* **2005**, *13*, 1641.

**SCHEME 3. Mechanism of d4N Synthesis Assisted by the Telluride Elimination**




**SCHEME 4. Mechanism of the Telluride-Mediated Elimination**




tive elimination when treated with iodine/water (Scheme 4). Furthermore, the cis-2′,3′-elimination of **15** can also happen when it is treated with $NaBH_4$, which explains the formation of a significant amount of **12** formed during the synthesis of phenyltelluride nucleoside **15**. Under the oxidative condition, this cis-elimination is probably caused by convenient transfer of the 3′-OH to the tellurium functionality in the same face. Under the $NaBH_4$ reduction, the telluride is probably reduced first by hydride, thereby generating a carbanion at the 2′-position and followed by elimination via an E1cb mechanism. Moreover, it is worth mentioning that, to the best of our knowledge, this is the first synthesis and isolation of tellurium-modified nucleosides.

To further explore the elimination mechanism and synthesis, the d4N formation has been further investigated with dimethyl ditelluride (Scheme 5). The advantages of using $Me_2Te_2$ are that (i) the substitution−elimination reaction is fast and (ii) we are able to control the exclusive formation of the 2′,3′-elimination products (d4Ns) without isolation of the telluride intermediate. In addition, by placing acyl groups on the 3′-positions of **8** and **17**, we are able to form **12** and **18** (5′-protected d4Ns) exclusively with reaction yield up to 90%, when $Me_2Te_2$ (0.1 equiv) is used (Table 1). Further lower amounts of $Me_2Te_2$ did not work well, presumably due to the consumption of MeTeH by minor side reactions. Furthermore, when a

**SCHEME 5. Telluride-Mediated Synthesis of d4Ns**

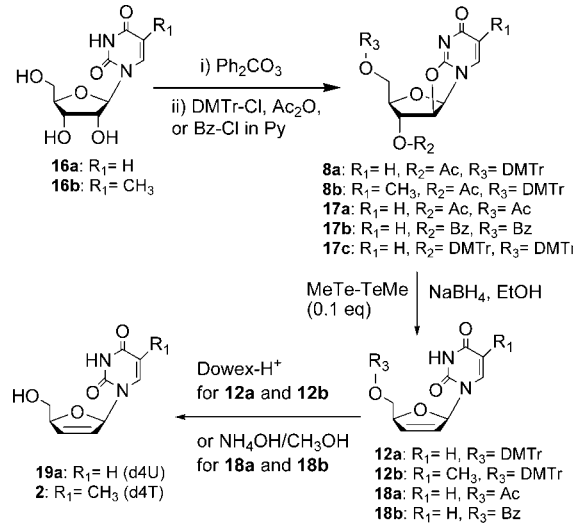



**TABLE 1. Synthesis of d4Ns via Te-Assisted Elimination (for Scheme 5**

| substrates | $R_1$ | $R_2$ | $R_3$ | products | yield (%) |
|---|---|---|---|---|---|
| **8a** | H | Ac | DMTr[a] | **12a** | 90 |
| **8b** | $CH_3$ | Ac | DMTr | **12b** | 85 |
| **17a** | H | Ac | Ac | **18a** | 80 |
| **17b** | H | Bz | Bz | **18b** | 69 |
| **17c** | H | DMTr | DMTr | **None** | |

[a] DMTr: dimethoxytrityl.

ditelluride reagent was not used in this reaction, only deacylated products were observed instead of the eliminated products. Moreover, no chemical reactions were observed in the absence of $NaBH_4$. Apparently, the telluride nucleophile may work as a catalyst in this elimination reaction. The telluride nucleophile (R-TeNa or R-TeH) is first generated by $NaBH_4$ reduction of the ditelluride reagent (RTe-TeR) and regenerated by reductive elimination of the telluride intermediate, such as **15**. Since the methyl-telluro group at the 2′-position is more reactive than the phenyl-telluro group and offers high yield, it is better to use MeTe-TeMe for the elimination reaction, where longer reaction time and the Te-intermediate isolation are not necessary.

In addition, we have incorporated a bulky DMTr group to the 3′-position of **17c** (Scheme 5). Probably due to the steric hindrance of this protecting group, which prevents the attack of the bulky telluride at the 2′-α-position, no elimination reaction was observed (Table 1). Furthermore, when the 3′-OH of **8c** was not activated, **13** was formed via 1′, 2′-elimination (Scheme 2). Moreover, when both the 3′- and 5′-positions of **17** were protected with the same acyl group for convenient synthesis (e.g., Ac- or Bz-), satisfactory elimination yields of d4Ns were also obtained. Thus, our experimental results reveal that a moderate leaving group at the 3′-positions can provide sufficient regioselectivity for the d4N synthesis, and that the 5′-position is not involved in the Te-assisted substitution-elimination reaction. Our experimental results suggest that this Te-mediated elimination consists of a two-stage mechanism: substitution and elimination.

## Conclusions

We have successfully developed a novel synthetic strategy for d4Ns via a new telluride-mediated elimination reaction.

Substitution of 2,2′-anhydronucleosides with a telluride monoanion leads to formation of a telluride intermediate. When the 3′-OH of the 2, 2′-anhydronucleosides is acylated, this Te-intermediate is eliminated to give d4Ns exclusively. The synthesis of d4Ns can reach up to 90% yield when dimethyl ditelluride (0.1 eq) is used. Furthermore, our mechanistic studies suggest that this telluride-mediated elimination reaction consists of two steps: the substitution (or addition) and elimination.

## Experimental Section

**5-Methyluridine or ribothymidine (16b).** was synthesized from thymine and the acylated ribose via glycosidation by following minor modifications of the literatures.[7c,12a]

**2,2′-Anhydro-1-[2′-deoxy-3′-acetyl-5′-*O*-(4,4-dimethoxytrityl)-β-D-arabinofuranosyl]uracil (8a) or -5-methyluracil (8b).** 2,2′-Anhydrouridine[3a,b,12g] and 2,2′-anhydro-5-methyuridine[12a,13] were first synthesized by following slight modifications of the literatures. Then, to a suspension of 2,2′-anhydrouridine or 2,2′-anhydrothymidine (2.85 or 3.02 g, 12.6 mmol) in dry pyridine (25 mL) was added dimethoxytrityl chloride (DMT-Cl, 2.36 g, 6.95 mmol), and the mixture was stirred at room temperature. One hour later, additional DMT-Cl (2.36 g, 6.95 mmol) was added, and the mixture was stirred for another 1 h (the 5′- and 3′-ditritylated products can be isolated as **8c** or **8d**). Acetic anhydride (1.89 mL, 20 mmol) was then added, and the mixture was stirred for 20 min at room temperature. The reaction was quenched by the addition of methanol (4 mL), and the solvents were removed under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (40 mL), and the suspension was washed with sodium bicarbonate (sat., 2 × 15 mL) and saturated brine (2 × 15 mL). The organic layer was dried over $MgSO_4$(s) and concentrated under reduced pressure, and the resulting residue was subjected to silica gel chromatography (0−5% MeOH in $CH_2Cl_2$) which gave pure **8a** (5.8 g, 87% yield) and **8b** (5.9 g, 85% yield) as white solids.

**8a:** $^1$H NMR ($CDCl_3$) $\delta$ 2.14 (s, 3H), 2.99−3.06 (m, 2H), 3.81 (s, 6H), 4.45 (m, 1H), 5.30−5.32 (m, 1H), 5.40 (m, 1H), 5.86 (d, $J$ = 7.6 Hz, 1H), 6.27 (d, $J$ = 5.6 Hz, 1H), 6.80−6.83 (m, 4H), 7.21−7.35 (m, 10H); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.7, 55.3, 62.6, 77.0, 85.8, 86.3, 86.6, 90.4, 110.2, 113.3, 127.1, 128.0, 129.8, 135.2, 144.1, 158.6, 134.5, 159.1, 169.4, 171.2; ESI-TOF $m/z$ calcd for $C_{32}H_{31}N_2O_7$ $(M+H)^+$ 571.2080, found 571.2080; mp 126.1−127.2 °C.

**8b:** $^1$H NMR ($CDCl_3$) $\delta$ 1.86 (s, 3H), 2.23 (s, 3H), 2.94−3.04 (m, 2H), 3.80 (s, 6H), 4.42−4.45 (m, 1H), 5.27−5.28 (m, 1H), 5.38 (m, 1H), 6.22 (d, $J$ = 5.6 Hz, 1H), 6.76−6.81 (m, 4H), 7.12−7.35 (m, 10H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.1, 20.7, 55.2, 62.8, 77.1, 85.8, 86.0, 86.6, 90.3, 119.0, 113.2, 127.9, 128.2, 129.8, 135.1, 144.1, 157.1, 130.0, 158.7, 169.6, 171.8; ESI-TOF $m/z$ calcd for $C_{33}H_{33}N_2O_7$ $(M+H)^+$ 585.2237, found 585.2255; mp 130.5−131.3 °C.

**2,2′-Anhydro-1-(2′-deoxy-3′,5′-di-*O*-acety-β-D-arabinofuranosyl)uracil (17a), 2,2′-Anhydro-1-(2′-deoxy-3′,5′-di-*O*-benzoyl-β-D-arabinofuranosyl)uracil (17b), and 2,2′-Anhydro-1-[2′-deoxy-3′,5′-di-(4,4-dimethoxytrityl)-β-D-arabinofuranosyl]uracil (17c).** To the pyridine suspension (10 mL) of 2,2′-anhydrouridine (0.62 g, 2.75 mmol) at room temperature was added acetic anhydride (for **17a**, 0.8 mL, 8.25 mmol), benzoyl chloride (for **17b**, 0.95 mL, 8.25 mmol), or the pyridine solution of dimethoxytrityl chloride (for **17c**, 1.86 g, 5.5 mmol). The reactions were stirred overnight before quenching with methanol (5 mL) and water (5 mL). The solvents were evaporated under reduced pressure, and the residue of **17a**, **17b**, or **17c** was dissolved in dichloromethane and washed with saturated sodium dicarbonate, brine, and water. The organic layers were combined, dried over $MgSO_4$(s), and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (gradient, 0−3% of methanol in $CH_2Cl_2$). The yields were generally high (88−95%) for the synthesis of **17a**−**c**.

**17a:** $^1$H NMR ($CDCl_3$, identical to literature)[14] $\delta$ 2.03 (s, 3H), 2.19 (s, 3H), 4.03−4.07 (dd, 1H, $J_1$ = 3.6 Hz, $J_2$ = 12.4 Hz), 4.33−4.37 (dd, 1H, $J_1$ = 3.6 Hz, $J_2$ = 12.4 Hz), 4.52−4.54 (m, 1H), 5.41−5.42 (m, 1H), 5.44−5.45 (m, 1H), 6.09 (d, $J$ = 7.2 Hz, 1H), 6.30 (d, $J$ = 6.4 Hz, 1H), 7.37 (d, $J$ = 7.2 Hz, 1H); ESI-TOF $m/z$ calcd for $C_{13}H_{15}N_2O_7$ $(M+H)^+$ 311.0879, found 311.0883.

**17b:** $^1$H NMR (DMSO-$d_6$, identical to literature)[15] $\delta$ 4.34−4.39 (m, 2H), 4.89 (m, 1H), 5.72 (m, 1H), 5.75−5.78 (m, 1H), 5.90 (d, 1H, $J$ = 7.2 Hz), 6.49 (d, 1H, $J$ = 5.6 Hz), 7.49−8.07 (m, 11H); ESI-TOF $m/z$ calcd for $C_{23}H_{19}N_2O_7$ $(M+H)^+$ 435.1192, found 435.1177.

**17c:** $^1$H NMR ($CDCl_3$, identical to literature)[16] $\delta$ 2.79−2.92 (m, 2H), 3.74 (s, 3H), 3.78 (s, 3H), 3.84 (s, 12H), 3.94−3.96 (m, 1H), 4.32 (m, 1H), 4.77−4.81 (m, 1H), 5.90 (d, $J$ = 7.2 Hz, 1H), 5.95 (d, $J$ = 5.6 Hz, 1H), 6.78−6.85 (m, 8H), 7.13−7.42 (m, 19H); ESI-TOF $m/z$ calcd for $C_{51}H_{47}N_2O_9$ $(M+H)^+$ 831.3282, found 831.3277.

**(*R*)-5-(4,4′-Dimethoxytrityloxymethyl)-2,3-dihydrofuran-4-ol (13).** To a stirred suspension of $NaBH_4$ (12 mg) in anhydrous THF (5 mL), under argon, was added dimethyl ditelluride (50 μL, 0.3 mmol), followed by several drops of dry ethanol until bubbles formed. The suspension was heated to 50 °C, and then the THF solution of starting material **8c** (0.32 g, 0.6 mmol) was added dropwise. The mixture was heated for 3 h at this temperature under argon. The solvent was evaporated under reduced pressure, and the residue was then dissolved in $CH_2Cl_2$ (20 mL). The solution was washed with water (3 × 20 mL). The $CH_2Cl_2$ layer was dried over $MgSO_4$(s) and evaporated under reduced pressure, and the residue was purified by silica gel column chromatography with pure $CH_2Cl_2$ to give compound **13** as a white solid (230 mg, 92% yield).

**13**: $^1$H NMR ($CDCl_3$) $\delta$ 3.18−3.22 (m, 2H), 3.81 (s, 6H), 4.44−4.49 (m, 1H), 4.79−4.81 (m, 1H), 5.20−5.21 (m, 1H), 6.62−6.63 (m, 1H), 6.84−6.86 (m, 4H), 7.23−7.46 (m, 9H,), 7.85 (d, $J$ = 7.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.2, 63.7, 76.2, 86.0, 88.3, 103.3, 113.1, 126.8, 127.8, 128.1, 130.1, 136.0, 144.8, 150.3, 158.5; ESI-TOF $m/z$ calcd for $C_{26}H_{25}O_5$ $(M-H)^-$ 417.1702, found 417.1708; mp 142.4−143.7 °C.

**5′-*O*-(4,4′-Dimethoxytrityl)-2′-phenyltelluro-2′-deoxyuridine (15a) or -thymidine (15b).** To a stirred suspension of $NaBH_4$ (6.2 mg) in anhydrous THF (5 mL), under argon at 0 °C, was added the THF solution of diphenylditelluride (0.2 g, 0.5 mmol in 5 mL), followed by several drops of dry ethanol until bubbles formed and the solution turned colorless. To this solution was added the starting material **8a** (0.285 g, 0.5 mmol, dissolved in 5 mL of THF), and the reaction was slowly warmed to room temperature and allowed to progress for 3 h at 50 °C, monitored by TLC. The solvent was then evaporated under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (20 mL) and washed with water (3 × 20 mL). The $CH_2Cl_2$ solution was dried over $MgSO_4$(s), and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (gradient, 0−3% methanol in $CH_2Cl_2$) to give compound **15a** as slight yellow solid (163 mg, 42% yield). Compound **15b** was synthesized analogously to **15a**.

**15a:** $^1$H NMR ($CDCl_3$) $\delta$ 3.45−3.46 (m, 2H), 3.82 (s, 6H), 3.92−3.95 (m, 1H), 4.24 (m, 1H), 4.54−4.57 (m, 1H), 5.12 (d, $J$ = 8 Hz, 1H), 6.63 (d, $J$ = 9.2 Hz, 1H), 6.81−6.86 (m, 4H), 7.19−7.37 (m, 12H), 7.45 (d, $J$ = 8 Hz, 1H), 7.82 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 36.9, 55.3, 63.9, 75.1, 85.5, 87.2, 91.6, 102.5, 109.6, 113.3, 127.2, 127.8, 128.0, 128.1, 128.7, 129.5, 130.1, 135.2, 140.2, 144.2, 150.2, 158.7, 162.7; ESI-TOF $m/z$ calcd for $C_{36}H_{34}N_2O_7TeNa$ $(M+Na)^+$ 759.1326, found 759.1316; mp 135.2−136.3 °C.

**15b:** $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (s, 3H), 2.71−2.83 (m, 1H), 3.36 and 3.51 (2xd, $J$ = 10 and 10 Hz, 2H), 3.81 (s, 6H), 3.95−4.06

(14) Logue, M. W.; Han, B, H. *J. Org. Chem.* **1980**, *45*, 5000.
(15) Sasaki, T.; Minamoto, K.; Sugiura, T.; Niwa, M. *J. Org. Chem.* **1976**, *41*, 3138.
(16) Dunkel, M.; Cook, P. D.; Acevedo, O. L. *J. Heterocycl.Chem.* **1993**, *30*, 1421.

(m, 1H), 4.21−4.27 (m, 1H), 4.54−4.62 (m, 1H), 6.70 (d, $J$ = 10 Hz, 1H), 6.81−6.86 (m, 4H), 7.19−7.41 (m, 12H), 7.84 (m, 2H), 8.18 (s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 11.47, 36.8, 55.3, 63.9, 75.4, 85.2, 87.2, 91.0, 109.5, 111.3, 113.3, 127.2, 128.0, 128.1, 128.6, 129.5, 129.6, 130.1, 135.0, 135.1, 140.3, 144.2, 150.4, 158.8, 163.1; ESI-TOF *m*/*z* calcd for $C_{37}H_{36}N_2O_7TeNa$ $(M + Na)^+$ 773.1477, found 773.1475; mp 138.3−140.0 °C.

**5′-*O*-(4,4-Dimethoxytrityl)-2′,3′-didehydro-2′,3′-dideoxyuridine (12a), 5′-*O*-(4,4-dimethoxytrityl)-2′,3′-didehydro-2′,3′-dideoxy-5-methyluridine (12b), 5′-*O*-acetyl-2′,3′-didehydro-2′,3′-dideoxyuridine (18a), and 5′-*O*-benzoyl-2′,3′-didehydro-2′,3′-dideoxyuridine (18b).** To a stirred suspension of $NaBH_4$ (12 mg) in anhydrous THF (5 mL), under argon, was added dimethyl ditelluride (50 $\mu$L, 0.3 mmol), followed by several drops of dry ethanol until bubbles were formed. The suspension was heated to 50 °C, and then the THF solution or suspension (5 mL) of the starting material (anhydronucleosides **8a**, **8b**, **17a**, **17b**, or **17c**, 3 mmol) was added. These reactions completed in 3−5 h, which was monitored by TLC. All of the solvents were evaporated under reduced pressure. The residues were then dissolved in $CH_2Cl_2$ and washed with water. Each $CH_2Cl_2$ solution was dried over $MgSO_4$ (s) and evaporated under reduced pressure. Each crude product was purified individually by silica gel column chromatography (gradient, 0−3% methanol in $CH_2Cl_2$) to give 69−90% yields of **12a**, **12b**, **18a**, or **18b** (Table 1).

**12a:** $^1$H NMR ($CDCl_3$)[3d] $\delta$ 3.47−3.48 (m, 2H), 3.82 (s, 6H), 4.97−4.98 (m, 1H), 5.06 (d, 1H, $J$ = 7.6 Hz), 5.89−5.91 (m, 1H), 6.35−6.37 (m, 1H), 6.84−6.86 (m, 4H), 7.05 (d, $J$ = 2.0 Hz, 1H), 7.27−7.38 (m, 9H), 7.85 (d, $J$ = 7.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.4, 64.2, 86.1, 86.9, 89.6, 102.2, 113.2, 127.1, 127.8, 127.4, 129.1, 130.20, 150.6, 127.1, 134.6, 141.4, 150.6, 158.6, 163.2; ESI-TOF *m*/*z* calcd for $C_{30}H_{27}N_2O_6$ $(M - H)^-$ 512.1869, found 511.1861.

**12b:** $^1$H NMR ($CDCl_3$, identical to literature)[17] $\delta$ 1.34 (s, 3H), 3.36−3.48 (m, 2H), 3.81 (s, 6H), 5.00 (m, 1H), 5.91−5.93 (m, 1H), 6.38−6.40 (m, 1H), 6.83−6.85 (m, 4H), 7.06 (m, 1H), 7.26−7.41 (m, 9H), 7.50 (s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.1, 55.3, 64.6, 85.8, 86.4, 89.7, 111.8, 113.2, 127.1, 127.7, 127.4, 129.2, 130.2, 150.6, 133.1, 134.6, 141.4, 150.5, 158.7, 163.4; ESI-TOF *m*/*z* calcd for $C_{31}H_{29}N_2O_6$ $(M - H)^-$ 525.2026, found 525.2048.

**18a:** $^1$H NMR ($CDCl_3$, identical to literature)[7b] $\delta$ 2.01 (s, 3H), 4.13−4.38 (m, 2H), 5.04 (m, 1H), 5.74 (d, $J$ = 7.6 Hz, 1H), 5.91 (m, 1 H), 6.51 (m, 1 H), 7.02 (m, 1 H), 7.67 (d, $J$ = 8.6 Hz, 1H); ESI-TOF *m*/*z* calcd for $C_{11}H_{11}N_2O_5$ $(M - H)^-$ 251.0668, found 251.0670.

**18b:** $^1$H NMR (DMSO-$d_6$, identical to literature)[18] $\delta$ 4.43−4.51 (m, 2H), 5.15 (m, 1H), 5.18 (d, $J$ = 7.6 Hz, 1H), 6.02 (m, 1H), 6.51 (m, 1 H), 6.89 (m, 1 H), 7.25−7.85 (m, 5H), 7.92 (d, $J$ = 7.6 Hz, 1H). ESI-TOF *m*/*z* calcd for $C_{16}H_{13}N_2O_5$ $(M-H)^-$ 313.0824, found 313.0825.

**1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (19a, d4U) and 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (2, d4T).** From **12a** and **12b**: Activated Dowex 50 w ($H^+$ form, 100 mg) was added to a methanol solution (3 mL) of **12a** or **12b** (0.1 mmol), and the mixture was stirred for 10 min. The insoluble solid was filtered out and washed with methanol several times. The organic solution was evaporated to a small volume under reduced pressure and the residue was precipitated with pentane. The precipitate was collected by filtration and washed with ether to give pure d4U and d4T in 90% yield.

From **18a** and **18b**: Ammonia solution (conc, 0.5 mL) was added to a methanol solution (3 mL) of **18a** or **18b** (0.1 mmol). The reaction was stirred for 1 h to complete the deprotection. The solvent was evaporated under reduced pressure. The crude product d4U or d4T was purified by silica gel column chromatography (gradient: 5−10% methanol in $CH_2Cl_2$) to offer a satisfactory yield (80−90%).

**19a (d4U):** $^1$H NMR (DMSO-$d_6$, identical to literature)[10b] $\delta$ 3.58−3.60 (m, 2H), 4.79−4.80 (m, 1H), 4.98 (m, 1H), 5.59 (d, $J$ = 8.0 Hz, 1H), 5.93−5.94 (m, 1 H), 6.40−6.42 (m, 1H), 6.81 (m, 1H), 7.75 (d, $J$ = 8.0 Hz, 1H), 11.3 (m, 1H); ESI-TOF *m*/*z* calcd for $C_9H_9N_2O_4$ $(M-H)^-$ 209.0562, found 209.0563.

**2 (d4T):** $^1$H NMR (DMSO-$d_6$, identical to literature)[7c] $\delta$ 1.72 (s, 3H), 3.60−3.61 (m, 2H), 4.76−4.78 (m, 1H), 4.98 (br, 1H), 5.91−5.92 (m, 1H), 6.39−6.41 (m, 1H), 6.82 (m, 1H), 7.65 (s, 1H), 11.3 (m, 1H); ESI-TOF $C_{10}H_{11}N_2O_4$, $(M-H)^-$ 223.0719, found 223.0721.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra for compound **8**, **12**, **13**, **15**, and **17**−**19** and the HRMS spectra for compound **15a** and **15b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Chambert, S.; Gautier-Luneau, I.; Fontecave, M.; Decout, J. L. *J. Org. Chem.* **2000**, *65*, 249.

(18) Palomino, E.; Meltsner, B, R.; Kessel, D.; Horwitz, J. P. *J. Med. Chem.* **1990**, *33*, 258.