Article

Subscriber access provided by University of South Dakota

# Photoredox-catalyzed Deformylative 1,4-Addition of 2#-Deoxy-5#-O-phthalimidonucleosides for Synthesis of 5#-Carba Analogs of Nucleoside 5#-Phosphates

Yuta Ito, Airi Kimura, Takashi Osawa, and Yoshiyuki Hari

J. Org. Chem., Just Accepted Manuscript • DOI: 10.1021/acs.joc.8b00637 • Publication Date (Web): 23 Aug 2018 Downloaded from http://pubs.acs.org on August 23, 2018

# **Just Accepted**

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Photoredox-catalyzed Deformylative 1,4-Addition of 2'-Deoxy-5'-O-phthalimidonucleosides for Synthesis of 5'-Carba Analogs of Nucleoside 5'-Phosphates

Yuta Ito, Airi Kimura, Takashi Osawa, and Yoshiyuki Hari\*

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Nishihama,

Yamashiro-cho, Tokushima 770-8514, Japan.



**ABSTRACT:** A concise approach for the synthesis of the 5'-carba analogs of nucleoside 5'-phosphates from 2'-deoxy-5'-*O*-phthalimidonucleosides by a visible light-mediated deformylative 1,4-addition was developed. This method enabled rapid and facile generation of 4'-carbon radicals of nucleosides. Moreover, this synthetic strategy was applicable to the 5'-carba analogs of nucleoside 5'-phosphates as well as other 5'-carba nucleosides bearing methoxycarbonyl, cyano and *N*-methylsulfamoyl groups.

#### **INTRODUCTION**

Resistance of modified nucleotides against enzymatic degradation by phosphatase and phosphodiesterase is one of the most important requirements in the search for nucleoside drugs.<sup>1</sup> To improve the stability of nucleotides, various chemical modifications have been investigated to date.<sup>2</sup> In particular, the 5'-carba analogs of nucleoside 5'-phosphates are quite stable against chemical and enzymatic hydrolysis because the 5'-oxygen-phosphorus bond is replaced with a non-hydrolyzable carbon-phosphorus bond. Therefore, the 5'-carba analogs have recently attracted considerable attention as antiviral agents or as chemical modifications for short interfering RNA.<sup>3</sup>

In general, the synthesis of 5'-carba analogs is typically achieved via Horner-Wadsworth-Emmons (HWE) olefination (or Wittig olefination) of aldehydes with bisphosphonates followed by hydrogenation (Scheme 1a).<sup>3,4</sup> This conventional method has often been used for the synthesis of 2'-deoxyribonucleosides and ribonucleosides. However, multi-step reactions including several protection and deprotection steps are required due to the presence of highly reactive functional groups such as hydroxyl and amino groups. The selective protection of the secondary hydroxyl

group at the 3'-position in the synthesis of 5'-aldehyde intermediate from 2'-deoxyribonucleosides is particularly tedious. An alternative method for the synthesis of 5'-carba analogs, based on an approach using a 4'-carbon radical generated from a Barton ester, by Barton and co-workers is known (Scheme 1b).<sup>5</sup> However, this synthetic method has some drawbacks, e.g., (i) troublesome protection-deprotection processes is required for the preparation of the Barton ester, and (ii) a 2-thiopyridyl group remains after the reaction. Despite the drawbacks, the reports are quite impressive, and we considered that it would provide a convenient and efficient synthetic tool for the preparation of the 5'-carba analogs of nucleoside 5'-phosphates if the 4'-carbon radicals could be easily generated from readily available nucleoside derivatives. Very recently, Inoue and co-workers reported the generation of 4'-carbon radicals by radical decarbonylation from the 5'-acyl tellurides of 2'-O,3'-O-isopropylideneuridines and used it for the total synthesis of polyoxins J and L, and their fluorinated analogs.<sup>6</sup> As such, a new generation method of 4'-carbon radicals of nucleosides will contribute to development of useful nucleoside analogs.

Scheme 1. Strategies for the Synthesis of 5'-Carba Analogs of Nucleosides



Recently, Chen and co-workers demonstrated visible light-mediated selective  $C(sp^3)$ -H allylation and alkenylation reactions of *N*-alkoxyphthalimides through an intramolecular 1,5-hydrogen atom transfer (1,5-HAT) induced by alkoxy radicals (Scheme 2a, route A).<sup>7</sup> On the other hand, when the *N*-alkoxyphthalimide (R = Me) synthesized from a secondary alcohol was used, the  $\beta$ -fragmentation of the alkoxy radical involving the elimination of acetaldehyde partially proceeded to give an  $\alpha$ -alkoxy radical (Scheme 2a, route B). Thus, if a photoredox reaction of a 2'-deoxy-5'-*O*-phthalimidonucleoside, which can be prepared from natural nucleosides in one step by the Mitsunobu reaction,<sup>8</sup> preferentially undergoes  $\beta$ -fragmentation of the alkoxy radical, that is radical deformylation, 4'-carbon radicals might be easily generated (Scheme 2b). The 4'-carbon radicals would then add to vinylphosphonates to produce 5'-carba analogs of nucleosides. This straightforward strategy would offer significant advantages over the

 aforementioned methods with regard to ease of synthesis and handling. Herein, we report the concise synthesis of 5'-carba analogs of nucleosides from 2'-deoxy-5'-*O*-phthalimidonucleosides by a photoredox-catalyzed deformylative 1,4-addition reaction. In addition, this methodology can be successfully applied for the construction of various 5'-modified nucleosides.

Scheme 2. Novel Strategy for Synthesis of 5'-Carba Analogs of Nucleosides



(b) This work:



# **RESULTS AND DISCUSSION**

In the preliminary investigations, 5'-O-phthalimidothymidine 1a and diethyl

vinylphosphonate 2a were selected as model substrates for the optimization of the reaction conditions (Table 1). In the presence of fac-Ir(ppy)<sub>3</sub> as a photocatalyst and Hantzsch ester as a reductant and hydrogen source,<sup>9</sup> treatment of **1a** with 1.5 equiv. of 2a in DCM under irradiation with a 32 W compact fluorescent lamp (CFL) underwent reductive cleavage of an N-O bond in the N-alkoxyphthalimide moiety to afford thymidine 4 in 43% yield; the desired 5'-carba analog 3 was only detected in trace amounts (entry 1). Remarkably, the solvent played a crucial role in this reaction. The substrate 1a could not be dissolved in the tested solvents (entries 1-4) because of its polar nature. Although the reaction remained as a heterogeneous suspension in DCM, MeCN and MeOH even after 1 h (entries 1-3, and Figure S1), a homogeneous solution was formed in 1,4-dioxane (entry 4 and Figure S2). Prolonged reaction time to 24 h using MeOH as a solvent became homogeneous solution to afford not only desired **3** (<34%, including impurities) but also the N-O reduction product 4 (36%) with complete consumption of starting material 1a. In the conditions of entry 4, compound 3 was obtained in 53% yield as a mixture of 4'-epimers ( $\beta$ : $\alpha$  = 6:1), and interestingly, the reaction preferentially produced desired  $3\beta^{10}$ , the structure of which was determined by NOESY correlations (Figure S3). Using 2.0 or 1.0 equiv. of 2a somewhat reduced the yield of desired 3 with an increased production of 4 (entries 5 and 6). The yield was

only slightly improved though a large amount of 2a (10 equiv.) was used (entry 7). Increasing the reaction temperature resulted in lower diastereoselectivity (entries 8 and 9). In the absence of fac-Ir(ppy)<sub>3</sub>, the reaction did not proceed after 1 h and only 14% of 3 was observed with a recovery of 74% of 1a even after 24 h (entries 10 and 11). On the other hand, Chen's group very recently succeeded in the generation of an  $\alpha$ -alkoxy radical from N-alkoxyphthalimide using only the Hantzsch ester without any photocatalyst.<sup>11</sup> Thus, in the reaction using 5 equiv. of Hantzsch ester and 3 equiv. of 2a,<sup>11</sup> the desired 3 was afforded in 39% yield along with 38% of thymidine 4 and 22% of the recovered **1a** (entry 12). In the absence of the Hantzsch ester, the reaction did not proceed after 24 h (entry 13). These experiments indicated that the conditions shown in entry 4 gave the best results and that a combination of the photocatalyst and Hantzsch ester was important for the efficient reaction. Notably, this reaction could be performed on a gram scale without any loss in efficiency or diastereoselectivity (entry 14).





2	
2	
2	
4	
5	
6	
0	
7	
8	
0	
9	
10	
11	
10	
12	
13	
14	
17	
15	
16	
17	
17	
18	
19	
20	
20	
21	
22	
22	
23	
24	
25	
20	
26	
27	
28	
20	
29	
30	
21	
51	
32	
33	
24	
54	
35	
36	
27	
5/	
38	
39	
22	
40	
41	
42	
12	
43	
44	
45	
46	
47	
<u>4</u> 8	
+0	
49	
50	
51	
51	
52	
53	
- J J	
54	
55	
56	
5/	
58	
50	
22	

entry	solvent	2a	<i>T</i> (°C)	time (h)	yield of 3	yield of <b>4</b>
		(equiv.)			$(\beta:\alpha)^a$	
1	DCM	1.5	rt	1	trace (-)	43%
2	MeCN	1.5	rt	1	34% (4:1)	16%
3	МеОН	1.5	rt	1	33% (1:1)	_
4	1,4-dioxane	1.5	rt	1	53% (6:1)	24%
5	1,4-dioxane	2.0	rt	1	44% (7:1)	42%
6	1,4-dioxane	1.0	rt	1	45% (5:1)	47%
7	1,4-dioxane	10	rt	1	58% (5:1)	31%
8	1,4-dioxane	1.5	40	1	45% (4:1)	45%
9	1,4-dioxane	1.5	60	0.5	52% (4:1)	41%
$10^{b}$	1,4-dioxane	1.5	rt	1	_	_
$11^{b}$	1,4-dioxane	1.5	rt	24	14% (4:1)	11%
$12^{b,c}$	1,4-dioxane	3.0	rt	36	39% (5:1)	38%
13 <sup>d</sup>	1,4-dioxane	1.5	rt	24	_	_
14 <sup>e</sup>	1,4-dioxane	1.5	rt	1	57% (6:1)	31%

<sup>*a*</sup>Diastereomeric ratio was determined by <sup>1</sup>H NMR analysis. <sup>*b*</sup>No *fac*-Ir(ppy)<sub>3</sub>. <sup>*c*</sup>5 equiv. of Hantzsch ester. <sup>*d*</sup>No Hantzsch ester. <sup>*e*</sup>A gram-scale reaction (2.6 mmol scale). ppy =

The results of Table 1 and previous reports<sup>7,9</sup> suggest a reaction mechanism in which both Ir(ppy)<sub>3</sub> and Hantzsch ester work (Scheme 3). Single-electron transfer from Ir<sup>II</sup>(ppy)<sub>3</sub> to the *N*-alkoxyphthalimide **1a** proceeds to form the radical anion **A**, in which homolytic cleavage of the N-O bond gives the alkoxy radical **B**. The resulting **B** undergoes  $\beta$ -fragmentation with elimination of formaldehyde, as expected, and 4'-carbon radical **C** is generated. Then, the addition of **C** to the vinyl phosphonate **2a** yields  $\alpha$ -phosphonyl radical **D**. Finally, hydrogen atom abstraction from radical intermediate of Hantzsch ester provides desired **3**.

## Scheme 3. Plausible Reaction Mechanism



With the optimized conditions in hand, the photoredox-catalyzed deformylative

1,4-addition reaction was extended to some vinylphosphonates and 2'-deoxy-5'-O-phthalimidonucleosides (Scheme 4). When diphenyl (**2b**) and dibenzyl (**2c**) vinylphosphonates were used, the corresponding 5'-carba analogs **5** and **6** were isolated in moderate yields. The protecting groups of the phosphonates in **5** and **6** including **3** could be removed under different conditions.<sup>12-14</sup> Interestingly, the reaction proceeded with a protection-free purine analog, 2'-deoxy-5'-O-phthalimidoadenosine **1c**, to afford the corresponding phosphonate **7** in 61% yield and with a diastereoselectivity of 4:1.





5'-Modified thymidines bearing cyanomethyl and sulfamoylmethyl groups are inhibitors of thymidine monophosphate kinase and biotin protein ligase, respectively, in

*Mycobacterium tuberculosis*;<sup>15,16</sup> however, the synthesis required 6 steps in a similar way to that shown in Scheme 1a and the yields of the products were extremely low (<5.4%).<sup>15</sup> Thus, we next investigated the reactions using other electron-deficient olefins, instead of vinylphosphonates, as radical acceptors (Scheme 5). When **1a** was treated with methyl acrylate under the optimized conditions, the expected reaction proceeded to give **8**, possessing an ester functionality, in 43% yield with a diastereoselectivity of  $\beta$ : $\alpha$  = 10:1. The yield was improved to 61% upon increasing the reaction temperature to 80 °C. Gratifyingly, olefins with nitrile and sulfonamide moieties afforded **9**<sup>15</sup> and **10**<sup>15</sup> in 54% and 51% yields, respectively. Based on these results, the developed method would offer a highly efficient synthetic route for the preparation of 5'-modified nucleosides in a fewer number of steps as compared to previous methods.





<sup>a</sup>The reaction was carried out at 80 °C for 0.5 h. <sup>b</sup>The reaction was carried out at 70 °C

for 0.5 h.

Next, viable protecting groups for the 3'-hydroxyl groups were explored (Table 2). 3'-Protected analogs could be synthesized over two steps via the Mitsunobu reaction followed by 3'-*O*-protection. Treatment of TBS-protected **11** under the photoredox conditions afforded the  $\beta$ -adduct **15**<sup>10</sup> ( $\beta$ : $\alpha = >50$ :1) in 41% yield (entry 1). This improvement of the diastereoselectivity was likely due to the limited access of **2a** from the  $\alpha$ -side owing to the bulky nature of the 3'-*O*-protecting group. Using the acyl-protected compounds such as acetyl (**12**) and benzoyl (**13**) groups, improvements in the diastereoselectivity ( $\beta$ : $\alpha = 13$ :1 and *ca*. 40:1) were also observed to give **16** and **17**<sup>17</sup> in 32% and 34% yields, respectively (entries 2 and 3). Furthermore, 3'-*O*-benzyloxymethyl (BOM) protection gave desired product **18** as a sole isomer ( $\beta$ : $\alpha$ = >50:1) (entry 4).

Table 2. Effect of Protecting Groups at the 3'-Position on Diastereoselectivity



2	<b>12</b> ( $R^1 = Ac$ )	2a	16	32% (13:1)
3	<b>13</b> ( $R^1 = Bz$ )	2a	17	34% (ca. 40:1)
4	<b>14</b> (R <sup>1</sup> = BOM)	2c	18	35% (>50:1)

<sup>a</sup>Diastereomeric ratio was determined by <sup>1</sup>H NMR analysis.

To understand the high diastereoselectivity, the energy-minimized conformations of 4'-carbon radical intermediates (R = H and Bz) were calculated using the Hartree-Fock method with the 6-311G\* basis using Spartan'16 (Figure 1a). As a result, the 3'-hydroxyl group was determined to be in a pseudo-axial position, as shown in Figure 1a. Therefore, the addition of a 4'-carbon radical would preferentially occur from the less hindered  $\beta$ -side, which is opposite to the 3'-hydroxyl group (Figure 1b). Protecting groups in the 3'-position, like a benzoyl analog shown in Figure 1a, would lead to a more stereoselective reaction because of the steric hindrance. This theoretical finding was also supported by Barton and co-workers, which indicated that 4'-carbon radical with a TBDPS group on the 3'-hydroxyl group resulted in excellent diastereoselectivity.5a,5b



**Figure 1.** (a) Energy-minimized structures of 4'-carbon radical intermediates. (b) Possible mechanism for enhanced diastereoselectivity in the radical addition.

Finally, in order to demonstrate the practical utility of the developed method, the formal synthesis of 5'-carba analog of dUTP,<sup>4a</sup> which potently inhibits sterile alpha motif and histidine/aspartic acid domain-containing protein 1 (SAMHD1), was performed as shown in Scheme 6. Phosphonate **18** was obtained from commercially available 2'-deoxyuridine in 3 steps: (i) Mitsunobu reaction, (ii) BOM protection of the 3'-hydroxyl group, and (iii) the developed photocatalytic reaction, as shown in entry 4 in Table 2. Subsequently, both the benzyl and BOM protecting groups were simultaneously removed by hydrogenolysis to afford the 5'-carba analog of dUMP **19**, which is a key intermediate in the synthesis of the 5'-carba analog of dUTP. Although, in another method,<sup>4a</sup> the deprotection of methyl phosphonate and the TBS group with bromotrimethylsilane required microwave irradiation due to the suppression of anomerization, anomerization at the 1'-position was observed (the ratio of  $\beta$ - and

 $\alpha$ -anomer was 8:1). In contrast, our approach facilitated the facile deprotection under mild conditions without anomerization and the 5'-carba analog of dUMP was prepared in only 4 steps.

Scheme 6. Formal Synthesis of 5'-Carba Analog of dUTP<sup>a</sup>



<sup>a</sup>Reagents and conditions: (a) NHPI (1.1 equiv.),  $Ph_3P$  (1.1 equiv.), DIAD (1.3 equiv.), DMF, 0 °C to rt, 4 h, 73%; (b) BOMCI (10 equiv.), Ag<sub>2</sub>O (12 equiv.), DCE, reflux, 4.5 d, 47%; (c) see entry 4 in Table 2; (d) H<sub>2</sub>,  $Pd(OH)_2/C$ , MeOH, rt, 4 h, 99%; NHPI = *N*-hydroxyphthalimide; DIAD = diisopropyl azodicarboxylate; DMF = *N*,*N*'-dimethylformamide; BOM = benzyloxymethyl.

#### CONCLUSION

In conclusion, we developed a visible light-mediated deformylative 1,4-addition reaction with 2'-deoxy-5'-*O*-phthalimidonucleosides. This method enabled the rapid and facile generation of 4'-carbon radicals without protection of the 3'-hydroxyl group and provided concise access to the 5'-carba analogs of nucleoside 5'-phosphates as well as other 5'-modified nucleosides. In addition, the diastereoselectivity was dramatically improved upon protection of the 3'-hydroxyl group, and 3'-*O*-protected substrates could be synthesized from natural nucleosides in only 2 steps: (i) Mitsunobu reaction and (ii) protection at the 3'-position. We believe that, in terms of simplicity and availability, the

developed method will be a powerful tool for the synthesis of 5'-carba analogs of nucleosides. The synthesis of new and useful nucleosides using this procedure is currently underway in our laboratory.

## **EXPERIMENTAL SECTION**

General Information. All moisture-sensitive reactions were conducted in well-dried glassware under an Ar atmosphere. Anhydrous DCE, DCM, 1,4-dioxane, DMF, MeCN and MeOH were used as received. <sup>1</sup>H NMR, <sup>13</sup>C NMR, and <sup>31</sup>P NMR spectra were recorded on a Bruker AVANCE III HD 500 equipped with a BBO cryoprobe or Agilent 400-MR. All <sup>13</sup>C and <sup>31</sup>P NMR spectra were proton-decoupled. Chemical shift values were reported in ppm, relative to internal tetramethylsilane ( $\delta = 0.00$  ppm for CDCl<sub>3</sub>), acetone ( $\delta = 2.20$  ppm for D<sub>2</sub>O) and residual solvent signals ( $\delta = 2.50$  ppm for DMSO-*d*<sub>6</sub>) for <sup>1</sup>H NMR, solvent signals ( $\delta = 77.0$  ppm for CDCl<sub>3</sub> and  $\delta = 39.5$  ppm for DMSO-d<sub>6</sub>) for <sup>13</sup>C NMR, and external 5% H<sub>3</sub>PO<sub>4</sub> ( $\delta = 0.00$  ppm) for <sup>31</sup>P NMR. IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. High-resolution mass spectrometry was performed on a Waters SYNAPT G2-Si (quadrupole/TOF). For column chromatography, silica gel PSQ-60B (Fuji Silysia) was used. The progress of the reaction was monitored by analytical thin-layer chromatography (TLC) on

pre-coated aluminum sheets (silica gel 60  $F_{254}$  by Merck). 2'-Deoxy-5'-O-phthalimidonucleoside **1a-c**<sup>8</sup> and **11**<sup>18</sup>, dibenzyl vinylphosphonate **2c**<sup>19</sup> and *N*-methylethenesulfonamide<sup>20</sup> were synthesized according to previously reported procedures.

## Preparation of 3'-O-Protected 2'-Deoxy-5'-O-phthalimidonucleosides.

3'-O-Acetyl-5'-O-phthalimidothymidine (12).To solution of а 5'-O-phthalimidothymidine 1a (1.0 g, 2.58 mmol) in pyridine (10 mL), Ac<sub>2</sub>O (0.73 mL, 7.74 mmol) and DMAP (32.0 mg, 0.26 mmol) were added. After stirring for 2 h at room temperature, the reaction mixture was quenched with sat. NaHCO<sub>3</sub> aq. and extracted with AcOEt. The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The crude residue was purified by column chromatography (hexane/AcOEt = 1:2) to give compound 12 as a white solid (663 mg, 60%). <sup>1</sup>H NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  11.35 (s, 1H), 7.88-7.84 (m, 4H), 7.64 (q, J = 1.0 Hz, 1H), 6.19 (dd, J = 9.0, 6.0 Hz, 1H), 5.37 (d, J = 6.0 Hz, 1H), 4.46-4.39 (m, 2H), 4.34-4.32 (m, 1H), 2.36 (ddd, J = 15.0, 9.0, 6.0 Hz, 1H), 2.28 (ddd, J = 14.5, 6.0, 1.5 Hz, 1H), 2.09 (s, 3H), 1.81 (s, 3H). <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>): δ 170.0, 163.6, 163.0, 150.4, 135.6, 134.8, 128.6, 123.3, 110.1, 84.2, 81.4, 77.2, 74.3, 35.8, 20.8, 12.1. IR (ATR) cm<sup>-1</sup>: 3028, 1790, 1726, 1694, 1664, 1472, 1363, 1242. HRMS (ESI-TOF): calcd

of

for C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>NaO<sub>8</sub> [M + Na]<sup>+</sup> 452.1070, found 452.1065.

*3'-O-Benzoyl-5'-O-phthalimidothymidine* (13). To a solution

5'-O-phthalimidothymidine 1a (1.0 g, 2.58 mmol) in pyridine (15 mL), benzoyl chloride (0.36 mL, 3.10 mmol) was added at 0 °C. After stirring for 5 h at room temperature, the reaction mixture was quenched with sat. NaHCO<sub>3</sub> aq. and extracted with AcOEt. The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The crude residue was washed with Et<sub>2</sub>O to give compound 13 as a white solid (1.18 g, 93%). <sup>1</sup>H NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  11.36 (s, 1H), 8.03 (d, J = 7.5 Hz, 2H), 7.89-7.85 (m, 4H), 7.71 (dd, J = 7.5, 7.5 Hz, 1H), 7.69 (s, 1H), 7.56 (dd, *J* = 7.5, 7.5 Hz, 2H), 6.32 (dd, *J* = 8.0, 6.5 Hz, 1H), 5.65 (d, *J* = 4.0 Hz, 1H), 4.55-4.48 (m, 3H), 2.54-2.45 (m, 2H), 1.83 (s, 3H). <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>): δ 165.2, 163.6, 163.0, 150.4, 135.7, 134.8, 133.7, 129.4, 129.2, 128.8, 128.6, 123.3, 110.1, 84.4, 81.4, 77.2, 75.2, 36.0, 12.1. IR (ATR) cm<sup>-1</sup>: 3248, 1791, 1720, 1702, 1681, 1466, 1396, 1372, 1318, 1296, 1271. HRMS (ESI-TOF): calcd for C<sub>25</sub>H<sub>21</sub>N<sub>3</sub>NaO<sub>8</sub> [M + Na]<sup>+</sup> 514.1226, found 514.1225.

General Procedure for the Synthesis of 5'-Carba Analogs of Nucleosides. A suspension of 2'-deoxy-5'-O-phthalimidonucleoside (0.2 mmol), olefin (0.3 mmol), Hantzsch ester (76.0 mg, 0.3 mmol) and fac-Ir(ppy)<sub>3</sub> (1.3 mg, 0.002 mmol) in

1,4-dioxane (3 mL) was deaerated by Ar bubbling for 0.5 h. The mixture was stirred and then irradiated with a 32 W compact fluorescent lamp at room temperature. After stirring for 1 h, a yellow homogeneous solution was obtained. The crude solution was directly purified by flash column chromatography (CHCl<sub>3</sub>/MeOH) to obtain the pure product.

*I*-*[*(*3S*,*4R*/4*S*)-6-(*Diethoxyphosphinyl*)-2,5,6-trideoxy-β/α-hexofuranosyl]thymine (**3**)<sup>10</sup>. Purification of the crude solution by flash column chromatography (CHCl<sub>3</sub>/MeOH = 20:1 to 5:1) afforded compound **3** as a white solid (39.9 mg, 53%, β:α = 6:1). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): (major isomer) δ 11.29 (s, 1H), 7.40 (d, *J* = 1.0 Hz, 1H), 6.12 (dd, *J* = 7.0, 7.0 Hz, 1H), 5.29 (d, *J* = 4.5 Hz, 1H), 4.10-4.06 (m, 1H), 4.04-3.93 (m, 4H), 3.66-3.63 (m, 1H), 2.22 (ddd, *J* = 13.5, 7.0, 7.0 Hz, 1H), 2.04 (ddd, *J* = 13.5, 6.5, 4.0 Hz, 1H), 1.87-1.68 (m, 4H), 1.79 (d, *J* = 1.0 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 6H). <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>): δ 163.7, 150.5, 136.1, 109.9, 85.3 (d, *J* = 17.0 Hz), 83.3, 72.7, 61.0 (d, *J* = 6.0 Hz), 60.9 (d, *J* = 6.0 Hz), 38.3, 26.0 (d, *J* = 4.0 Hz), 21.1 (d, *J* = 140.5 Hz), 16.3 (d, *J* = 6.0 Hz), 12.1. <sup>31</sup>P NMR (202 MHz, DMSO-*d*<sub>6</sub>): δ 32.0. IR (ATR) cm<sup>-1</sup>: 3367, 2984, 1683, 1470, 1270, 1229, 1207. HRMS (ESI-TOF): calcd for C<sub>15</sub>H<sub>25</sub>N<sub>2</sub>NaO<sub>7</sub>P [M + Na]<sup>+</sup> 399.1297, found 399.1292.

 $1-[(3S,4R/4S)-6-(Diphenoxyphosphinyl)-2,5,6-trideoxy-\beta/\alpha-hexofuranosyl]thymine$  (5).

Purification of the crude solution by flash column chromatography (CHCl<sub>3</sub>/MeOH = 20:1 to 5:1) afforded compound **5** as a white solid (48.8 mg, 52%,  $\beta$ : $\alpha$  = 7:1). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): (major isomer)  $\delta$  11.31 (s, 1H), 7.43 (s, 1H), 7.39 (dd, *J* = 8.0, 7.5 Hz, 4H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.15 (dd, *J* = 7.0, 6.5 Hz, 1H), 5.34 (d, *J* = 4.5 Hz, 1H), 4.17-4.13 (m, 1H), 3.75-3.72 (m, 1H), 2.29-2.18 (m, 3H), 2.12-2.04 (m, 2H), 2.01-1.89 (m, 1H), 1.77 (s, 3H). <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  163.7, 150.5, 149.9 (d, *J* = 7.0 Hz), 136.2, 129.9, 125.2, 120.54 (d, *J* = 2.0 Hz), 120.50 (d, *J* = 2.0 Hz), 109.9, 85.0 (d, *J* = 17.5 Hz), 83.3, 72.6, 38.2, 25.8 (d, *J* = 5.0 Hz), 22.3 (d, *J* = 140.5 Hz), 12.1. <sup>31</sup>P NMR (162 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  26.8. IR (ATR) cm<sup>-1</sup>: 3388, 3188, 3061, 1681, 1591, 1489, 1266, 1210. HRMS (ESI-TOF): calcd for C<sub>23</sub>H<sub>25</sub>N<sub>2</sub>NaO<sub>7</sub>P [M + Na]<sup>+</sup> 495.1297, found 495.1296.

1-[(3S,4R/4S)-6-(Dibenzyloxyphosphinyl)-2,5,6-trideoxy-β/α-hexofuranosyl]uracil (6). Purification of the crude solution by flash column chromatography (CHCl<sub>3</sub>/MeOH = 20:1 to 5:1) afforded compound **6** as a white solid (49.6 mg, 51%,  $\beta$ :α = 6:1). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): (major isomer) δ 11.32 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.39-7.32 (m, 10H), 6.09 (dd, *J* = 7.0, 6.5 Hz, 1H), 5.59 (d, *J* = 8.0 Hz, 1H), 5.30 (d, *J* = 4.5 Hz, 1H), 5.01 (d, *J* = 4.5 Hz, 1H), 5.04 and 4.98 (ABq, *J* = 12.0 Hz, 2H), 5.02 and 4.97 (ABq, *J* = 12.0 Hz, 2H), 4.05-4.01 (m, 1H), 3.68-3.65 (m, 1H), 2.14 (ddd, *J* = 13.5, 1.55 (d, *J* = 12.0 Hz, 2H), 4.05-4.01 (m, 1H), 3.68-3.65 (m, 1H), 2.14 (ddd, *J* = 13.5, 1.55 (d, *J* = 12.0 Hz, 2H), 4.05-4.01 (m, 1H), 3.68-3.65 (m, 1H), 2.14 (ddd, *J* = 13.5).

7.0, 7.0 Hz, 1H), 2.07 (ddd, $J = 13.5$ , 6.5, 4.5 Hz, 1H), 1.99-1.67 (m, 4H). <sup>13</sup> C NMR
(126 MHz, DMSO- <i>d</i> <sub>6</sub> ): δ 163.0, 150.4, 140.7, 136.7 (d, <i>J</i> = 7.0 Hz), 128.5, 128.2 (d, <i>J</i> =
2.0 Hz), 127.7 (d, J = 6.0 Hz), 102.8, 85.4 (d, J = 18.0 Hz), 83.6, 72.5, 66.4 (d, J = 7.0
Hz), 66.3 (d, $J = 6.0$ Hz), 38.6, 25.9 (d, $J = 4.0$ Hz), 21.3 (d, $J = 139.5$ Hz). <sup>31</sup> P NMR
(202 MHz, DMSO- <i>d</i> <sub>6</sub> ): δ 33.1. IR (ATR) cm <sup>-1</sup> : 3355, 2955, 1678, 1456, 1379, 1212.
HRMS (ESI-TOF): calcd for $C_{24}H_{27}N_2NaO_7P [M + Na]^+$ 509.1454, found 509.1453.
$1-[(3S,4R/4S)-6-(Diethoxyphosphinyl)-2,5,6-trideoxy-\beta/\alpha-hexofuranosyl]adenine $ (7).
Purification of the crude solution by flash column chromatography (CHCl <sub>3</sub> /MeOH =
20:1 to 5:1) afforded compound <b>7</b> as a white solid (46.9 mg, 61%, $\beta$ : $\alpha$ = 4:1). <sup>1</sup> H NMR
(500 MHz, DMSO-d <sub>6</sub> ): (major isomer) δ 8.29 (s, 1H), 8.13 (s, 1H), 7.26 (s, 2H), 6.29
(dd, <i>J</i> = 7.0, 6.5 Hz, 1H), 5.35 (d, <i>J</i> = 4.5 Hz, 1H), 4.36-4.33 (m, 1H), 3.99-3.88 (m, 4H),
3.81-3.78 (m, 1H), 2.87 (ddd, J = 13.5, 6.5, 6.5 Hz, 1H), 2.27 (ddd, J = 13.5, 6.5, 4.5 Hz,
1H), 1.89-1.67 (m, 4H), 1.19 (t, $J = 7.0$ Hz, 6H). <sup>13</sup> C NMR (126 MHz, DMSO- $d_6$ ): $\delta$
156.1, 152.5, 149.1, 139.7, 119.2, 86.0 (d, <i>J</i> = 17.0 Hz), 82.9, 72.9, 60.9 (d, <i>J</i> = 6.0 Hz),
60.8 (d, J = 6.0 Hz), 38.4, 26.1 (d, J = 4.5 Hz), 21.0 (d, J = 140.0 Hz), 16.2 (d, J = 5.5
Hz). <sup>31</sup> P NMR (162 MHz, DMSO- $d_6$ ): $\delta$ 32.0. IR (ATR) cm <sup>-1</sup> : 3321, 3184, 2984, 1642,
1598, 1575, 1474, 1330, 1296, 1232, 1208. HRMS (ESI-TOF): calcd for
$C_{15}H_{24}N_5NaO_5P [M + Na]^+ 408.1413$ , found 408.1415.

$1-[(3S,4R/4S)-6-Methoxycarbonyl-2,5,6-trideoxy-\beta/\alpha-hexofuranosyl]thymine$ (8).
Purification of the crude solution by flash column chromatography (CHCl <sub>3</sub> /MeOH =
20:1 to 5:1) afforded compound <b>8</b> as a white solid (36.3 mg, 61%, $\beta$ : $\alpha$ = 7:1). <sup>1</sup> H NMR
(500 MHz, DMSO- $d_6$ ): (major isomer) $\delta$ 11.28 (br s, 1H), 7.38 (s, 1H), 6.11 (dd, $J = 7.0$
7.0 Hz, 1H), 5.28 (br s, 1H), 4.07-4.04 (m, 1H), 3.64-3.61 (m, 1H), 3.58 (s, 3H), 2.40
(ddd, J = 7.5, 7.5, 2.0 Hz, 1H), 2.18 (ddd, J = 13.5, 7.0, 7.0 Hz, 1H), 2.03 (ddd, J = 13.5
6.5, 4.0 Hz, 1H), 1.95-1.88 (m, 1H), 1.84-1.77 (m, 1H), 1.79 (s, 3H). <sup>13</sup> C NMR (126
MHz, DMSO- <i>d</i> <sub>6</sub> ): δ 173.1, 163.9, 150.6, 136.0, 109.8, 84.6, 83.3, 72.8, 51.3, 38.3, 29.9,
28.2, 12.1. IR (ATR) cm <sup>-1</sup> : 3452, 2931, 1707, 1656, 1628, 1474, 1366, 1267. HRMS
(ESI-TOF): calcd for $C_{13}H_{18}N_2NaO_6 [M + Na]^+ 321.1063$ , found 321.1062.

*1-[(3S,4R/4S)-6-Cyano-2,5,6-trideoxy-β/α-hexofuranosyl]thymine* (**9**)<sup>15</sup>. Purification of the crude solution by flash column chromatography (CHCl<sub>3</sub>/MeOH = 20:1 to 10:1) afforded compound **9** as a white solid (28.4 mg, 54%,  $\beta$ : $\alpha$  = 6:1). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): (major isomer) δ 11.30 (br s, 1H), 7.43 (s, 1H), 6.14 (dd, *J* = 7.0, 7.0 Hz, 1H), 5.34 (br s, 1H), 4.12-4.09 (m, 1H), 3.70-3.67 (m, 1H), 2.62-2.52 (m, 2H), 2.21 (ddd, *J* = 14.0, 7.0, 7.0 Hz, 1H), 2.05 (ddd, *J* = 14.0, 7.0, 4.0 Hz, 1H), 1.99-1.82 (m, 2H), 1.79 (s, 3H). <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>): δ 163.7, 150.5, 136.2, 120.4, 109.9, 84.0, 83.5, 72.6, 38.1, 28.5, 13.3, 12.1. IR (ATR) cm<sup>-1</sup>: 3378, 3190, 2926, 2246, 1718, 1650,

 1475, 1269. HRMS (ESI-TOF): calcd for  $C_{12}H_{15}N_3NaO_4$  [M + Na]<sup>+</sup> 288.0960, found 288.0957.

# $1-{(3S, 4R/4S)-6-[(Methylamino)sulfonyl]-2, 5, 6-trideoxy-\beta/\alpha-hexofuranosyl}thymine$

 $(10)^{15}$ . Purification of the crude solution by flash column chromatography (CHCl<sub>3</sub>/MeOH = 10:1 to 5:1) afforded compound **10** as a white solid (33.9 mg, 51%,  $\beta:\alpha = 6:1$ ). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): (major isomer)  $\delta$  11.30 (br s, 1H), 7.41 (q, J = 1.0 Hz, 1H), 6.93 (br s, 1H), 6.14 (dd, J = 7.0, 6.5 Hz, 1H), 5.40 (br s, 1H), 4.12-4.10 (m, 1H), 3.74-3.71 (m, 1H), 3.12-2.99 (m, 2H), 2.56 (s, 3H), 2.23 (ddd, J =14.0, 7.0, 7.0 Hz, 1H), 2.08-1.99 (m, 2H), 1.95-1.87 (m, 1H), 1.80 (d, J = 1.0 Hz, 3H). <sup>13</sup>C NMR (126 MHz, DMSO- $d_6$ ):  $\delta$  163.8, 150.5, 136.1, 110.0, 83.7, 83.4, 72.8, 46.1, 38.1, 28.6, 27.1, 12.1. IR (ATR) cm<sup>-1</sup>: 3371, 2950, 2502, 1716, 1650, 1632, 1477, 1305. HRMS (ESI-TOF): calcd for  $C_{12}H_{19}N_3NaO_6S [M + Na]^+ 356.0892$ , found 356.0891.  $1-[(3S,4R)-3-O-(tert-butyldimethylsilyl)-6-(diethoxyphosphinyl)-2,5,6-trideoxy-\beta-hexofu$ ranosyl]thymine  $(15)^{10}$ . Purification of the crude solution by flash column chromatography (hexane/AcOEt = 1:3 to  $CHCl_3/MeOH = 50:1$ ) afforded compound 15 as a colorless oil (40.1 mg, 41%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  8.57 (br s, 1H), 7.10 (d, *J* = 1.0 Hz, 1H), 6.20 (dd, *J* = 6.5, 6.5 Hz, 1H), 4.16-4.06 (m, 5H), 3.79-3.76 (m, 1H),

2.27 (ddd, J = 10.5, 6.5, 4.5 Hz, 1H), 2.08 (ddd, J = 13.5, 6.5, 6.5 Hz, 1H), 2.02-1.92 (m,

2H), 1.95 (d, J = 1.0 Hz, 3H), 1.87-1.77 (m, 2H), 1.34 (t, J = 7.0 Hz, 3H), 1.33 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.084 (s, 3H), 0.079 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  163.4, 150.0, 135.1, 111.3, 86.0 (d, J = 17.0 Hz), 84.6, 74.7, 61.74 (d, J = 6.0 Hz), 61.67 (d, J = 6.0 Hz), 40.4, 26.6 (d, J = 5.0 Hz), 25.7, 22.3 (d, J = 143.5 Hz), 17.9, 16.5 (d, J = 6.0 Hz), 12.6, -4.6, -4.9. <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>):  $\delta$  31.1. IR (ATR) cm<sup>-1</sup>: 2929, 1688, 1471, 1367, 1249. HRMS (ESI-TOF): calcd for C<sub>21</sub>H<sub>39</sub>N<sub>2</sub>NaO<sub>7</sub>PSi [M + Na]<sup>+</sup> 513.2162, found 513.2158.

 $1-[(3S,4R/4S)-3-O-Acetyl-6-(diethoxyphosphinyl)-2,5,6-trideoxy-\beta/\alpha-hexofuranosyl]thy$ 

*mine* (**16**). Purification of the crude solution by flash column chromatography (CHCl<sub>3</sub>/MeOH = 30:1 to 10:1) afforded compound **16** as a colorless oil (31.5 mg, 38%,  $\beta:\alpha = 13:1$ ). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): (major isomer)  $\delta$  11.29 (s, 1H), 7.49 (q, *J* = 1.0 Hz, 1H), 6.12 (dd, *J* = 8.5, 6.0 Hz, 1H), 5.08-5.05 (m, 1H), 4.03-3.95 (m, 4H), 3.92-3.89 (m, 1H), 2.53-2.47 (m, 1H), 2.21 (ddd, *J* = 14.5, 6.0, 2.5 Hz, 1H), 2.05 (s, 3H), 1.93-1.76 (m, 4H), 1.80 (d, *J* = 1.0 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 6H). <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  169.9, 163.5, 150.3, 136.0, 109.9, 83.6, 82.8 (d, *J* = 17.5 Hz), 75.8, 60.91 (d, *J* = 6.0 Hz), 60.86 (d, *J* = 6.0 Hz), 34.9, 25.9 (d, *J* = 4.5 Hz), 20.9 (d, *J* = 140.5 Hz), 20.7, 16.1 (d, *J* = 5.5 Hz), 11.9. <sup>31</sup>P NMR (202 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  31.7. IR (ATR) cm<sup>-1</sup>: 2983, 1737, 1685, 1469, 1369, 1233. HRMS (ESI-TOF): calcd for

 $C_{17}H_{27}N_2NaO_8P [M + Na]^+ 441.1403$ , found 441.1398.

 $1-[(3S, 4R/4S)-3-O-Benzoyl-6-(diethoxyphosphinyl)-2, 5, 6-trideoxy-\beta/\alpha-hexofuranosyl]th$ 

*vmine*  $(17)^{17}$ . Purification of the crude solution by flash column chromatography  $(CHCl_3/MeOH = 100:1 \text{ to } 50:1)$  afforded compound **17** as a colorless oil (32.7 mg, 34%,  $\beta:\alpha = ca. 40:1$ ). <sup>1</sup>H NMR (500 MHz,CDCl<sub>3</sub>): (major isomer)  $\delta$  8.91 (s, 1H), 8.04 (d, J =8.0, 1.5 Hz, 2H), 7.61 (td, J = 7.5, 1.5 Hz, 1H), 7.47 (dd, J = 8.0, 7.5 Hz, 1H), 7.19 (q, J = 1.0 Hz, 1H), 6.39 (dd, J = 8.5, 6.0 Hz, 1H), 5.30 (ddd, J = 6.5, 2.5, 2.5 Hz, 1H), 4.18-4.08 (m, 5H), 2.57 (ddd, J = 14.5, 6.0, 2.0 Hz, 1H), 2.30 (ddd, J = 14.5, 8.5, 6.5 Hz, 1H), 2.20-2.11 (m, 1H), 2.06-1.85 (m, 3H), 1.98 (d, *J* = 1.0 Hz, 3H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.33 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 165.9, 163.4, 150.3, 134.5, 133.6, 129.7, 129.1, 128.5, 111.9, 84.5, 83.8 (d, *J* = 18.0 Hz), 76.6, 61.81 (d, *J* = 7.0 Hz), 61.76 (d, J = 7.0 Hz), 36.8, 27.1 (d, J = 4.5 Hz), 22.0 (d, J = 143.5 Hz), 16.5 (d, J = 6.0 Hz), 12.6. <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>): δ 30.7. IR (ATR) cm<sup>-1</sup>: 2984, 1686, 1469, 1451, 1266, 1212. HRMS (ESI-TOF): calcd for  $C_{22}H_{29}N_2NaO_8P [M + Na]^+$  503.1559, found 503.1552.

## Formal Synthesis of the 5'-Carba Analog of dUTP.

2'-Deoxy-5'-O-phthalimidouridine  $(1b)^8$ . To a solution of 2'-deoxyuridine (1.89 g, 8.28 mmol), NHPI (1.49 g, 9.11 mmol) and Ph<sub>3</sub>P (2.53 g, 9.11 mmol) in DMF (20 mL),

DIAD (2.12 mL, 10.8 mmol) was slowly added at 0 °C. After stirring for 4 h at room temperature, the reaction mixture was concentrated *in vacuo*. The syrupy residue was dissolved in Et<sub>2</sub>O (10 mL) and poured into cold water (30 mL). After stirring for 1 h at 0 °C, the precipitate was filtered and washed with CHCl<sub>3</sub>. The precipitated product was dried to give compound **1b** as a white solid (2.25 g, 73%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  11.31 (s, 1H), 7.88-7.84 (m, 4H), 7.78 (d, *J* = 8.0 Hz, 1H), 6.19 (dd, *J* = 7.0, 7.0 Hz, 1H), 5.60 (d, *J* = 8.0 Hz, 1H), 5.47 (d, *J* = 4.5 Hz, 1H), 4.38-4.35 (m, 3H), 4.10-4.08 (m, 1H), 2.15 (dd, *J* = 6.5, 4.5 Hz, 2H). <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  163.0, 150.4, 140.6, 134.8, 128.6, 123.3, 102.0, 84.6, 84.1, 77.7, 70.5, 38.9. IR (ATR) cm<sup>-1</sup>: 3471, 3237, 1789, 1726, 1686, 1457, 1369, 1236. HRMS (ESI-TOF): calcd for C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>NaO<sub>7</sub> [M + Na]<sup>+</sup> 396.0808, found 396.0807.

3'-O-(Benzyloxymethyl)-2'-deoxy-5'-O-phthalimidouridine (14). To a suspension of compound 1b (200 mg, 0.53 mmol) in DCE (5 mL), BOMCl (371 µL, 2.68 mmol) and Ag<sub>2</sub>O (745 mg, 3.22 mmol) were added. After stirring for 24 h at reflux, the mixture was added to BOMCl (371 µL, 2.68 mmol) and Ag<sub>2</sub>O (745 mg, 3.22 mmol). After stirring for another 84 h at reflux, the heterogeneous reaction mixture was filtered through Celite. The filtrate was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography

(hexane/AcOEt = 1:1 to AcOEt) to give compound 14 as a white solid (123 mg, 47%).
<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ): $\delta$ 8.92 (br s, 1H), 8.04 (d, $J = 8.0$ Hz, 1H), 7.88-7.84 (m,
2H), 7.81-7.76 (m, 2H), 7.38-7.27 (m, 5H), 6.36 (dd, <i>J</i> = 8.0, 6.0 Hz, 1H), 5.84 (dd, <i>J</i> =
8.0, 2.0 Hz, 1H), 4.89 and 4.87 (ABq, J = 8.0 Hz, 2H), 4.75-4.73 (m, 1H), 4.68 and 4.65
(ABq, J = 8.0 Hz, 2H), 4.45-4.39 (m, 2H), 4.31-4.29 (m, 1H), 2.54 (ddd, J = 14.0, 5.5,
2.5 Hz, 1H), 2.15 (ddd, $J = 14.0$ , 8.0, 6.0 Hz, 1H). <sup>13</sup> C NMR (100 MHz, CDCl <sub>3</sub> ): $\delta$
163.5, 163.0, 150.4, 140.3, 137.3, 134.7, 128.6, 128.5, 127.9, 127.8, 123.7, 102.7, 94.0,
85.7, 82.8, 77.5, 77.0, 70.1, 38.6. IR (ATR) cm <sup>-1</sup> : 3025, 1790, 1731, 1681, 1456, 1375,
1274. HRMS (ESI-TOF): calcd for $C_{25}H_{23}N_3NaO_8$ [M + Na] <sup>+</sup> 516.1383, found
516.1384.

1-[(3S,4R)-3-O-(Benzyloxymethyl)-6-(dibenzyloxyphosphinyl)-2,5,6-trideoxy-β-hexofuranosyl]uracil (18). A suspension of compound 14 (89.2 mg, 0.18 mmol), dibenzylvinylphosphonate (78.1 mg, 0.27 mmol), Hantzsch ester (68.6 mg, 0.27 mmol) andfac-Ir(ppy)<sub>3</sub> (1.2 mg, 0.002 mmol) in 1,4-dioxane (3 mL) was deaerated by Ar bubblingfor 0.5 h. The mixture was stirred and then irradiated with a 32 W compact fluorescentlamp at room temperature. After stirring for 1 h, a yellow homogeneous solution wasobtained. The crude solution was directly purified by flash column chromatography(hexane/AcOEt = 1:5 to AcOEt) to give compound 18 as a colorless oil (38.2 mg, 35%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  9.15 (br s, 1H), 7.37-7.26 (m, 15H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.15 (dd, *J* = 6.5, 6.5 Hz, 1H), 5.67 (d, *J* = 8.0 Hz, 1H), 5.07 (d, *J* = 8.5 Hz, 2H), 5.07 (d, *J* = 8.5 Hz, 2H), 4.97 (dd, *J* = 8.5, 3.0 Hz, 2H), 4.94 (dd, *J* = 8.5, 3.0 Hz, 2H), 4.74 and 4.72 (ABq, *J* = 7.5 Hz, 2H), 4.59 and 4.55 (ABq, *J* = 8.0 Hz, 2H), 3.98 (ddd, *J* = 7.0, 3.5, 3.5 Hz, 1H), 3.89-3.86 (m, 1H), 2.40 (ddd, *J* = 14.0, 6.0, 3.5 Hz, 1H), 1.98-1.72 (m, 5H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  163.0, 150.0, 139.1, 137.2, 136.2 (d, *J* = 6.0 Hz), 128.62, 128.55, 128.51, 128.03, 127.96, 127.92, 127.86, 102.8, 93.7, 85.0, 83.9 (d, *J* = 18.0 Hz), 78.9, 70.0, 67.4 (d, *J* = 7.0 Hz), 67.3 (d, *J* = 7.0 Hz), 37.7, 26.8 (d, *J* = 5.0 Hz), 22.5 (d, *J* = 142.5 Hz). <sup>31</sup>P NMR (202 MHz, CDCl<sub>3</sub>):  $\delta$  32.0. IR (ATR) cm<sup>-1</sup>: 3031, 2945, 1686, 1455, 1379, 1271, 1244, 1209. HRMS (ESI-TOF): calcd for C<sub>32</sub>H<sub>35</sub>N<sub>2</sub>NaO<sub>8</sub>P [M + Na]<sup>+</sup> 629.2029, found 629.2031.

1-[(3S,4R)-6-(Dihydroxyphosphinyl)-2,5,6-trideoxy-β-hexofuranosyl]uracil (19)<sup>3f</sup>. Compound 18 (31.2 mg, 0.05 mmol) was treated in MeOH (3 mL) at room temperature under a hydrogen atmosphere in the presence of Pd(OH)<sub>2</sub>/C (30.0 mg). After stirring for 4 h, the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by Sep-Pak<sup>®</sup> Plus C18 cartridges (Waters, eluent: H<sub>2</sub>O to H<sub>2</sub>O/MeOH = 10:1). The obtained solution was concentrated *in vacuo* and lyophilized to give compound 19 as a white solid (15.5 mg, 99%). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O): δ 7.70 (d, *J* = 8.0 Hz, 1H),

6.24 (dd, J = 6.5, 6.5 Hz, 1H), 5.89 (d, J = 8.0 Hz, 1H), 4.35-4.32 (m, 1H), 4.00-3.97 (m, 1H), 2.40-2.37 (m, 2H), 2.01-1.75 (m, 4H). <sup>13</sup>C NMR (126 MHz, D<sub>2</sub>O):  $\delta$  166.9, 152.2, 142.5, 103.0, 87.1 (d, J = 18.0 Hz), 86.1, 73.9, 38.6, 27.2 (d, J = 4.0 Hz), 24.8 (d, J = 135.5 Hz). <sup>31</sup>P NMR (202 MHz, D<sub>2</sub>O):  $\delta$  24.6. IR (ATR) cm<sup>-1</sup>: 3194, 3088, 1721, 1659, 1476, 1434, 1270. HRMS (ESI-TOF): calcd for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>7</sub>P [M - H]<sup>-</sup> 305.0539, found 305.0538.

## **ASSOCIATED CONTENT**

## **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Photos of the reaction solution, NOESY spectrum of compound **3**, NMR spectra for compounds and *ab initio* quantum mechanical calculation data (PDF)

# **AUTHOR INFORMATION**

#### **Corresponding Author**

\*E-mail: hari@ph.bunri-u.ac.jp.

# ORCID

Yoshiyuki Hari: 0000-0002-3903-7340

## **Author Contributions**

Y.I. and Y.H. designed the experiments. Y.I., A.K., and T.O. performed experiments.

Y.I. and Y.H. co-wrote the paper. Y.H. supervised the project.

# Notes

The authors declare no competing financial interest.

#### ACKNOWLEDGMENT

This research was partially supported by a Grant from Tokushima Bunri University for Educational Reform and Collaborative Research (No. TBU2017-2-5).

#### REFERENCES

(1) (a) Pradere, U.; Garnier-Amblard, E. C.; Coats, S. J.; Amblard, F.; Schinazi, R. F.
 Synthesis of Nucleoside Phosphate and Phosphonate Prodrugs. *Chem. Rev.* 2014, *114*, 9154-9218.
 (b) Pertusati, F.; Serpi, M.; McGuigan, C. Medicinal Chemistry of Nucleoside Phosphonate Prodrugs for Antiviral Therapy. *Antiviral Chem. Chemother.* 2012, *22*, 181-203.

(2) (a) Wan, W. B.; Seth, P. P. The Medicinal Chemistry of Therapeutic Oligonucleotides. *J. Med. Chem.* 2016, *59*, 9645-9667. (b) Sharma, V. K.; Sharma, R. K.; Singh, S. K. Antisense Oligonucleotides: Modifications and Clinical Trials. *MedChemComm* 2014, *5*, 1454-1471.

(3) (a) Prakash, T. P.; Lima, W. F.; Murray, H. M.; Li, W.; Kinberger, G. A.; Chappell, A. E.; Gaus, H.; Seth, P. P.; Bhat, B.; Crooke, S. T.; Swayze, E. E. Identification of Metabolically Stable 5'-Phosphate Analogs that Support Single-stranded siRNA Activity. Nucleic Acids Res. 2015, 43, 2993-3011. (b) Song, L.; Risseeuw, M. D. P.; Karalic, I.; Barrett, M. O.; Brown, K. A.; Harden, T. K.; Van Calenbergh, S. Synthesis of Extended Uridine Phosphonates Derived from an Allosteric P2Y<sub>2</sub> Receptor Ligand. Molecules 2014, 19, 4313-4325. (c) Meurillon, M.; Marton, Z.; Hospital, A.; Jordheim, L. P.; Béjaud, J.; Lionne, C.; Dumontet, C.; Périgaud, C.; Chaloin, L.; Peyrottes, S. Structure-activity Relationships of  $\beta$ -Hydroxyphosphonate Nucleoside Analogues as Cytosolic 5'-Nucleotidase II Potential Inhibitors: Synthesis, in Vitro Evaluation and Molecular Modeling Studies. Eur. J. Med. Chem. 2014, 77, 18-37. (d) Parrish, J. P.; Lee, S. K.; Boojamra, C. G.; Hui, H.; Babusis, D.; Brown, B.; Shih, I.-H.; Feng, J. Y.; Ray, A. S.; Mackman, R. L. Evaluation of  $2'-\alpha$ -Fluorine Modified Nucleoside Phosphonates as Potential Inhibitors of HCV Polymerase. Bioorg. Med. Chem. Lett. 2013, 23, 3354-3357. (e) Van Poecke, S.; Barrett, M. O.; Kumar, T. S.; Sinnaeve, D.; Martins, J. C.; Jacobson, K. A.; Harden, T. K.; Van Calenbergh, S. Synthesis and P2Y<sub>2</sub> Receptor Agonist Activities of Uridine 5'-Phosphonate Analogues. Bioorg. Med. Chem. 2012, 20, 2304-2315. (f) Van Poecke, S.; Sinnaeve, D.; Martins, J. C.; Balzarini, J.; Van

> Calenbergh, S. Synthesis of 5-Substituted 2'-Deoxyuridine-5'-Phosphonate Analogues and Evaluation of their Antiviral Activity. *Nucleosides Nucleotides Nucleic Acids* **2012**, 31, 256-272. (g) Cosyn, L.; Van Calenbergh, S.; Joshi, B. V.; Ko, H.; Carter, R. L.; Harden, T. K.; Jacobson, K. A. Synthesis and P2Y Receptor Activity of Nucleoside 5'-Phosphonate Derivatives. Bioorg. Med. Chem. Lett. 2009, 19, 3002-3005. (4) (a) Seamon, K. J.; Hansen, E. C.; Kadina, A. P.; Kashemirov, B. A.; McKenna, C. E.; Bumpus, N. N.; Stivers, J. T. Small Molecule Inhibition of SAMHD1 dNTPase by Tetramer Destabilization. J. Am. Chem. Soc. 2014, 136, 9822-9825. (b) Pradere, U.; Amblard, F.; Coats, S. J.; Schinazi, R. F. Synthesis of 5'-Methylene-Phosphonate Furanonucleoside Prodrugs: Application to D-2'-Deoxy-2'-α-fluoro-2'-β-C-methyl Nucleosides. Org. Lett. 2012, 14, 4426-4429. (c) Nencka, R.; Sinnaeve, D.; Karalic, I.; Martins, J. C.; Van Calenbergh, S. Synthesis of C-6-Substituted Uridine Phosphonates through Aerobic Ligand-free Suzuki-Miyaura Cross-coupling. Org. Biomol. Chem. 2010, 8, 5234-5246.

> (5) (a) Barton, D. H. R.; Géro, S. D.; Quiclet-Sire, B.; Samadi, M. New Synthesis of Sugar, Nucleoside and α-Amino Acid Phosphonates. *Tetrahedron* 1992, 48, 1627-1636.
> (b) Barton, D. H. R.; Géro, S. D.; Quiclet-Sire, B.; Samadi, M. Stereoselectivity in Radical Reactions of 2'-Deoxynucleosides. A Synthesis of an Isostere of

3'-Azido-3'-deoxythymidine-5'-monophosphate (AZT-5' Monophosphate). *Tetrahedron Lett.* 1989, *30*, 4969-4972. (c) Barton, D. H. R.; Géro, S. D.; Quiclet-Sire,
B.; Samadi, M. Radical Addition to Vinyl Phosphonates. A New Synthesis of Isosteric
Phosphonates and Phosphonate Analogues of α-Amino Acids. *J. Chem. Soc., Chem. Commun.* 1989, 1000-1001.

(6) Fujino, H.; Nagatomo, M.; Paudel, A.; Panthee, S.; Hamamoto, H.; Sekimizu, K.; Inoue, M. Unified Total Synthesis of Polyoxins J, L, and Fluorinated Analogues on the Basis of Decarbonylative Radical Coupling Reactions. *Angew. Chem. Int. Ed.* **2017**, *56*, 11865-11869.

(7) Zhang, J.; Li, Y.; Zhang, F.; Hu, C.; Chen, Y. Generation of Alkoxyl Radicals by Photoredox Catalysis Enables Selective C(sp<sup>3</sup>)–H Functionalization under Mild Reaction Conditions. *Angew. Chem. Int. Ed.* **2016**, *55*, 1872-1875.

(8) Perbost, M.; Hoshiko, T.; Morvan, F.; Swayze, E.; Griffey, R. H.; Sanghvi, Y. S.
Synthesis of 5'-O-Amino-2'-deoxypyrimidine and Purine Nucleosides: Building-Blocks
for Antisense Oligonucleotides. J. Org. Chem. 1995, 60, 5150-5156.

(9) Wang, C.; Harms, K.; Meggers, E. Catalytic Asymmetric C<sub>sp3</sub> -H Functionalization under Photoredox Conditions by Radical Translocation and Stereocontrolled Alkene Addition. *Angew. Chem. Int. Ed.* **2016**, *55*, 13495-13498. (10) Garvey, E. P.; Lowen, G. T.; Almond, M. R. Nucleotide and Nucleoside Analogues as Inhibitors of Cytosolic 5'-Nucleotidase I from Heart. *Biochemistry* **1998**, *37*, 9043-9051.

(11) Zhang, J.; Li, Y.; Xu, R.; Chen, Y. Donor-Acceptor Complex Enables Alkoxyl Radical Generation for Metal-Free C(sp<sup>3</sup>)-C(sp<sup>3</sup>) Cleavage and Allylation/Alkenylation. *Angew. Chem. Int. Ed.* 2017, *56*, 12619-12623.

(12) (a) Kim, B.-S.; Kim, B.-T.; Hwang, K.-J. The Synthesis of Diverse Adenosine
5'-Phosphonate Analogues as Chain Terminators against Hepatitis C Virus (HCV). *Bull. Korean Chem. Soc.* 2010, *31*, 1643-1648. (b) Kim, B.-S.; Kim, B.-T.; Hwang, K.-J. A
Practical Method to Cleave Diphenyl Phosphonate Esters to Their Corresponding
Phosphonic Acids in One Step. *Bull. Korean Chem. Soc.* 2009, *30*, 1391-1393.

(13) Koh, Y.-H.; Shim, J. H.; Wu, J. Z.; Zhong, W.; Hong, Z.; Girardet, J.-L. Design, Synthesis, and Antiviral Activity of Adenosine 5'-Phosphonate Analogues as Chain Terminators against Hepatitis C Virus. *J. Med. Chem.* **2005**, *48*, 2867-2875.

(14) (a) McKenna, C. E.; Schmidhuser, J. Functional Selectivity in Phosphonate Ester
Dealkylation with Bromotrimethylsilane. *J. Chem. Soc., Chem. Commun.* 1979,
739-739. (b) McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M.-C. The Facile
Dealkylation of Phosphonic Acid Dialkyl Esters by Bromotrimethylsilane. *Tetrahedron*

Lett. 1977, 18, 155-158.

(15) Toti, K. S.; Verbeke, F.; Risseeuw, M. D. P.; Frecer, V.; Munier-Lehmann, H.; Van

Calenbergh, S. Synthesis and Evaluation of 5'-Modified Thymidines and 5-Hydroxymethyl-2'-deoxyuridines as *Mycobacterium tuberculosis* Thymidylate Kinase Inhibitors. *Bioorg. Med. Chem.* **2013**, *21*, 257-268.

(16) Shi, C.; Tiwari, D.; Wilson, D. J.; Seiler, C. L.; Schnappinger, D.; Aldrich, C. C.
Bisubstrate Inhibitors of Biotin Protein Ligase in *Mycobacterium tuberculosis* Resistant
to Cyclonucleoside Formation. *ACS Med. Chem. Lett.* 2013, *4*, 1213-1217.

(17) Hutter, D.; Blaettler, M. O.; Benner, S. A. From Phosphate to Bis(methylene)Sulfone: Non-Ionic Backbone Linkers in DNA. *Helv. Chim. Acta* 2002, 85, 2777-2806.

(18) Peyrat, S.; Xie J. Synthesis of Thymidine Dimers from 5'-O-Aminothymidine. *Synthesis* **2012**, *44*, 1718-1724.

(19) Veleti, S. K.; Petit, C.; Ronning, D. R.; Sucheck, S. J. Zwitterionic Pyrrolidene-phosphonates: Inhibitors of the Glycoside Hydrolase-like Phosphorylase *Streptomyces coelicolor* GlgEI-V279S. *Org. Biomol. Chem.* **2017**, *15*, 3884-3891.

(20) Molino, B. F.; Liu, S.; Sambandam, A.; Guzzo, P. R.; Hu, M.; Zha, C.; Nacro, K.; Manning, D. D.; Isherwood, M. L.; Fleming, K. N.; Cui, W.; Olson, R. E. Aryl- and Heteroaryl-substituted Tetrahydrobenzazepines and Use Thereof to Block Reuptake of Norepinephrine, Dopamine, and Serotonin. PCT Int. Appl. WO 2007011820, 2007;

Chem. Abstr. 2007, 184383.