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One-Pot Synthesis of Novel 2′-Deoxyuridine Derivatives Containing α-Aminophosphonate Moieties

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ABSTRACT: *A series of α-aminophosphonate derivatives of 2′-deoxyuridine (**8a–k**) have been prepared from 5′-O-tert-butyldimethylsilyl-3′-amino-2′, 3′-dideoxyuridine in good yields. The structures of all the products were confirmed by ^{1}H NMR, ^{31}P NMR, ^{31}C NMR, and IR spectroscopy, and mass spectrometry and elemental analyses.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:230–235, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20288

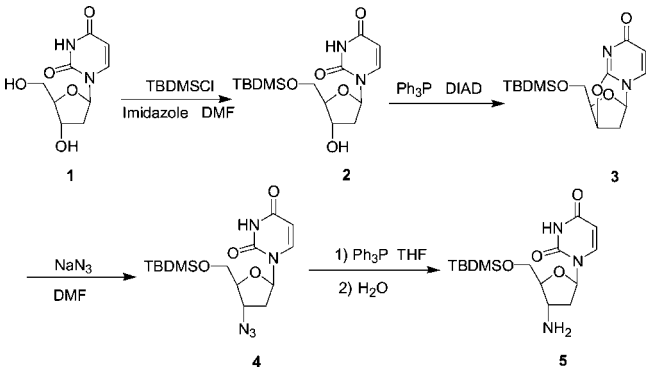
INTRODUCTION

Nucleoside analogues have figured prominently in the search for effective antiviral agents despite concerns over the toxicity generally associated with this class of compounds [1]. To date, a number of modifications of the sugar moiety in nucleosides have been carried out. Especially, various attempts have been made to synthesize the 2′- and 3′-sites of nucleosides in connection with AZT, a potent anti-HIV agent [2]. On the other hand, α-amino phosphonic acid and phosphonate esters have attracted attention because not only are they biologically attractive peptide mimics of α-amino acid but they also exhibit intriguing biological activities [3]. They have been employed as antibiotics [4], herbicides [5], antitumor agents [6], or enzyme inhibitors [7], with a broad application in many areas of agriculture and medicine [8]. Their synthesis has therefore been the subject of much interest. A variety of methods are available, but the nucleophilic addition reaction of phosphites with imines is the most direct and efficient one among them.

To search for novel anticancer drugs, a series of α-aminophosphonate derivatives of 2′-deoxyuridine were synthesized by the addition reactions of phosphite and imines, which were produced from 3′-amino-2′,3′-dideoxyuridine and aromatic aldehydes.

RESULTS AND DISCUSSION

The individual steps are summarized in Schemes 1 and 2. 2′-Deoxyuridine (**1**) was first converted into



SCHEME 1

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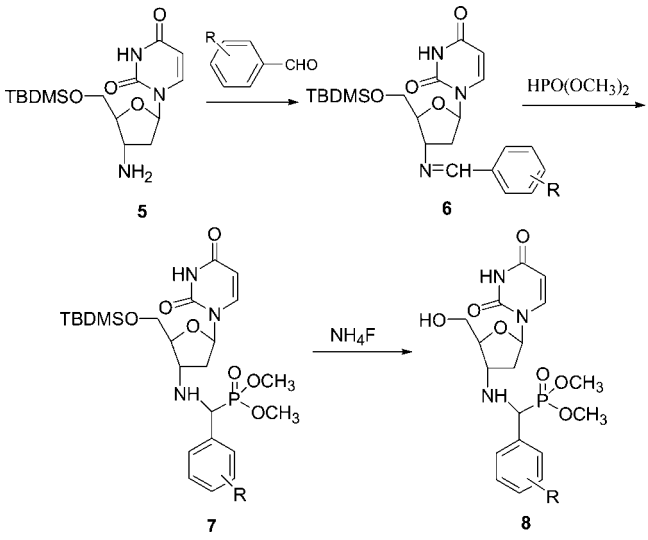


SCHEME 2

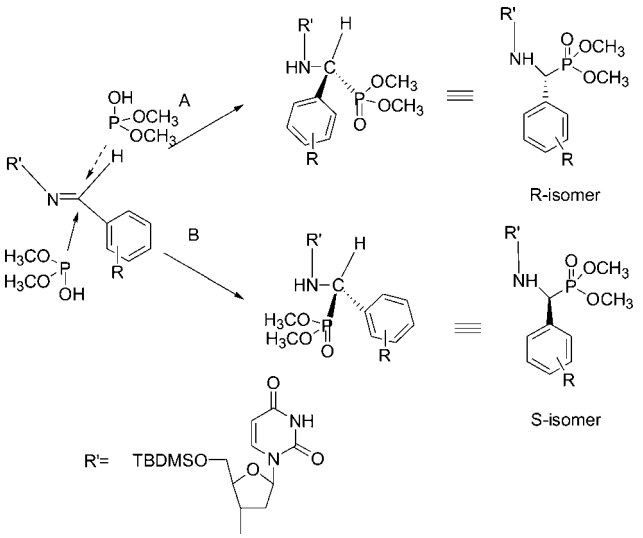
its 5′ -*O*-*tert*-butyldimethylsilyl derivative **2** in 68% yield by treatment with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in DMF below −10°C [9]. When **2** was treated with triphenylphosphine-diisopropyl azodicarboxylate at room temperature, a cyclonucleoside derivative **3** is obtained in 68% yield [10]. Conversion of **3** into the AzddUrd **4** in 87% yield was attempted by a nucleophilic opening reaction with sodium azide in DMF at 120°C [11]. The P—N ylide obtained by the Staudinger reaction was treated with 25% ammonia solution at 50°C to give the key intermediate **5** in 75% yield [12]. When the amino nucleoside **5** was heated under reflux with aromatic aldehydes in EtOH, imines **6** were obtained. The nucleophilic addition of phosphites to imines catalyzed by a base or an acid is the most convenient method to synthesize α-aminophosphonates. A variety of metal halides such as $TiCl_4$ [13], $SnCl_4$ [14], and $ZnCl_2$ [15] have been used as Lewis catalysts in methylene chloride or other organic solvents to promote this addition. However, organic solvents, particularly chlorinated hydrocarbons, are high on the list of damaging chemicals because of their volatile nature, considerable toxicity, and their use in large quantities for a reaction. On the other hand, the metal halides utilized as catalysts in these procedures are not all eco-friendly, and often entail severe environmental pollution during the waste disposal process. To avoid these disadvantages, imines **6** with dimethyl phosphite were heated at 80°C in neat without any solvent and in the presence of a catalyst to give the corresponding α-aminophosphonates **7**. Deprotection of 5′-TBDMS group with ammonium fluoride at 50°C in MeOH provided the title compounds **8** in good yields [16]. The results are summarized in Table 1.

The configurations of the three chiral carbon atoms of **5** are known, but the newly formed chiral carbon atom resulting from the addition reaction might have two configurations. The phosphorus atom may attack the carbon atom from the back (mode A) or the front (mode B) of the imine. Accordingly, the configuration of the chiral carbon atom formed by the reaction is either *R* or *S* (Scheme 3). Thus, there may be a mixture of diastereoisomers for compound **8**. In the ^1H, ^{31}P, and ^{13}C NMR spectra of compound **8**, two diastereoisomers were clearly observed, because some of H, P, and C atoms of **8** gave two sets of signals. Moreover, the H and C atoms in CHP exhibit "dd" peaks due to the phosphorus coupling $^2J_{PH} = 18.0–22.0$ Hz and $^1J_{PC} = 155.1–163.0$ Hz, respectively. The product obtained in each synthesis was a mixture of two diastereomers in roughly 2:3 ratio (determined from ^1H NMR spectra). The attempts

TABLE 1 Physical and Chemical Data of Compounds **8**

				Analysis Found (Calculated)		
Compound	*R*	*Yield[a] (%)*	*Formula*	*C*	*H*	*N*
8a	H	70	$C_{18}H_{24}N_3O_7P$	50.58 (50.82)	5.46 (5.69)	10.02 (9.88)
8b	2,4-Cl	61	$C_{18}H_{22}Cl_2N_3O_7P$	43.92 (43.74)	4.67 (4.49)	8.63 (8.50)
8c	4-CH_3	65	$C_{19}H_{26}N_3O_7P$	51.86 (51.94)	5.90 (5.96)	9.30 (9.56)
8d	4-Cl	68	$C_{18}H_{23}ClN_3O_7P$	46.91 (47.02)	5.31 (5.04)	8.91 (9.14)
8e	4-F	66	$C_{18}H_{23}FN_3O_7P$	48.73 (48.76)	5.32 (5.23)	9.27 (9.48)
8f	4-NO_2	60	$C_{18}H_{23}N_4O_9P$	45.72 (45.96)	5.09 (4.93)	11.86 (11.91)
8g	4-OCH_3	70	$C_{19}H_{26}N_3O_8P$	49.90 (50.11)	5.66 (5.75)	9.30 (9.23)
8h	3,4-OCH_2O	62	$C_{19}H_{24}N_4O_9P$	48.56 (48.62)	5.22 (5.15)	8.81 (8.95)
8i	3-NO_2	55	$C_{18}H_{23}N_4O_9P$	46.02 (45.96)	5.07 (4.93)	11.87 (11.91)
8j	2-Cl	63	$C_{18}H_{23}ClN_3O_7P$	46.92 (47.02)	5.20 (5.04)	9.14 (9.14)
8k	3-Cl	65	$C_{18}H_{23}ClN_3O_7P$	47.04 (47.02)	5.24 (5.04)	9.10 (9.14)

[a]Isolated yield on the basis of compound **5** in three steps.



SCHEME 3

to obtain single diastereomer using fractional crystallization and column chromatography also failed. Owing to the overlap of peaks, H-5 proton signal of all compounds and H on the carbon connecting to phosphorus signal of **8a** appear as a triplet. The IR spectra of compounds **8** show normal stretching absorption bands, indicating the existence of groups N—H (~3400 cm^{-1}), C=O (1670–1708 cm^{-1}), P=O (1264–1272 cm^{-1}), and P—O—C (1021–1055 cm^{-1}).

In summary, we provide a new synthetic method of 2-deoxyuridine derivatives containing α-aminophosphonate moieties at the 3-position of the deoxyribose ring. It is also important to mention that hydrophosphonylation of imines with dimethyl phosphite without any solvent and in the presence of a catalyst is a simple and green method to cater the need of academia as well as industries. Further studies on the separation and application of title products are in progress.

EXPERIMENTAL

Melting points were determined with a model YANACO MP-500 apparatus, and are uncorrected. IR spectra were recorded on a Bruker Equinox 55 spectrometer. Elemental analyses were carried on a Yanaco CHN Corder MT-3 apparatus. ^{1}H, ^{31}P, and ^{13}C NMR spectra were measured by using Varian 400 Mercury plus spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 162 MHz for ^{31}P) with TMS and 85% H_3PO_4 as the internal and external references, respectively, and with $CDCl_3$ as the solvent. Mass spectra were obtained using a Bruker ESQUIRE~LC™ ESI ion trap spectrometry equipped with a gas nebulizer probe. All reagents were purchased from commercial sources and used without further purification unless specified. All solvents were dried and distilled according to standard procedures. In ^{1}H NMR analysis, J_1 and J_2 represent coupling constants of each diastereomer, respectively. In ^{13}C NMR analysis: A, value for one diastereomer; B, value for two diastereomers.

General Procedure for the Synthesis of **8a–k**

Aromatic aldehyde (1 mmol) was added to a solution of **5** (1 mmol) in ethanol (10 mL), and then heated under reflux for 4 h. The solvent was removed under reduced pressure, and then dimethyl phosphite (4 mmol) was added. The mixture was stirred for 2 h at 80°C, and then 10 mL of methanol and ammonium fluoride (10 mmol) were added. The solution was heated at 50°C for 2 h, and then the solvent was evaporated in vacuo. The crude residue was dissolved in $CHCl_3$ and extracted with water (3 × 15mL). The organic layer was dried with Na_2SO_4, filtered off, and the solvent was removed under reduced pressure. The crude was purified by chromatography column (7% MeOH/CH_3Cl), affording a white foamy solid after vacuum drying.

^{1}H, ^{31}P, ^{13}C NMR, and IR Spectra and Mass Spectrometry of Compounds **8a–k**. Compound **8a** (diastereoisomers): IR υ_{max} (KBr)/cm^{-1} 3628, 3388, 3162, 1697, 1464, 1397, 1272, 1052; ^{31}P NMR ($CDCl_3$) $\delta = 25.54$ and 25.60 ppm; ^{1}H NMR ($CDCl_3$) $\delta = 8.97$ and 8.93 (s each, 1H together, N*H*), 7.80 and 7.60 (d each, $J_1 = J_2 = 8.0$ Hz, 1H together, H-6,), 7.36–7.41 (m, 5H, Ar*H*), 6.20 and 6.11 (t each, $J_1 = J_2 = 5.20$ Hz, 1H together, H-1′), 5.67 (t, 1H, H-5), 4.09–4.19 (t, 1H, C*H*P), 3.40–3.93 (m, 10H, H-3′, 4′, 5′, POCH_3), 2.05–2.32 (m, 3H, H-2′, O*H*,); ^{13}C NMR ($CDCl_3$) $\delta = 164.51$ (C-4, A), 164.45 (C-4, A), 150.83 (C-2, B), 140.97 (C-6, A), 140.82 (C-6, A), 136.14 (Ar*C*, B), 135.10 (Ar*C*, B), 128.96 (Ar*C*, B), 128.57 (Ar*C*, B), 102.35 (C-5, A), 102.23 (C-5, A), 85.87 (A), 85.78 (A), 85.66 (A), 85.50 (C-1′, 4′, A), 62.12 (C-5′, A), 61.94 (C-5′, A), 59.47 (d, $^{1}J_{PC} = 158.1$ Hz, *C*HP, A), 58.78 (d, $^{1}J_{PC} = 155.1$ Hz, *C*HP, A), 56.54 (d, $^{2}J_{PC} = 15.0$ Hz, POCH_3, B), 55.49 (d, $^{2}J_{PC} = 13.9$ Hz, POCH_3, B), 54.19 (d, $^{3}J_{PC} = 5.4$ Hz, C-3′, A), 53.98 (d, $^{3}J_{PC} = 6.1$ Hz, C-3′, A), 39.74 (C-2′, A), 38.25 (C-2′, A); ESI-MS (positive) *m/z* 426 $(M + H)^+$, *m/z* 448 $(M + Na)^+$; (negative) *m/z* 424 $(M - H)^-$.

Compound **8b** (diastereoisomers): IR υ_{max} (KBr)/cm^{-1} 3624, 3306, 3147, 1681, 1466, 1396, 1272, 1038; ^{31}P NMR ($CDCl_3$) $\delta = 25.11$ and 25.17 ppm; ^{1}H NMR ($CDCl_3$) $\delta = 9.82$ and 9.72 (s, 1H together, N*H*), 7.74 and 7.28–7.64 (d and m, $J_1 = 8.40$ Hz, 4H together, H-6 and Ar*H*), 6.16–6.22 (m, 1H,

H-1′), 5.68 (t, 1H, H-5), 4.71 and 4.68 (d each, $^2J_{PH1} = 22.0$ Hz $^2J_{PH2} = 21.6$ Hz, 1H together, C*H*P), 3.68–3.91 (m, 3H, H-5′, 4′), 3.85 (d, $^3J_{PH} = 10.4$ Hz, 3H, POCH_3), 3.57 (d, $^3J_{PH} = 10.8$ Hz, 3H, POCH_3), 3.25–3.39 (m, 1H, H-3′), 3.19 (bs, 1H, N*H*, B), 1.98–2.32 (m, 1H, H-2′); ^{13}C NMR ($CDCl_3$) $\delta = 164.45$ (C-4, A), 164.36 (C-4, A), 150.89 (C-2, B), 140.94 (C-6, A), 140.79 (C-6, A), 135.16 (Ar*C*, B), 134.77 (Ar*C*, B), 133.10 (Ar*C*, B), 130.76 (Ar*C*, B), 129.57 (Ar*C*, B), 128.11 (Ar*C*, B), 102.50 (C-5, A), 102.41 (C-5, A), 85.81 (A), 85.63 (A), 85.47 (C-1′, 4′, A), 62.45 (C-5′, A), 62.18 (C-5′, A), 59.47 (d, $^1J_{PC} = 158.1$ Hz, *C*HP, A), 58.78 (d, $^1J_{PC} = 155.1$ Hz, *C*HP, A), 56.54 (d, $^2J_{PC} = 15.0$ Hz, POCH_3, B), 55.49 (d, $^2J_{PC} = 13.9$ Hz, POCH_3, B), 54.19 (d, $^3J_{PC} = 5.4$ Hz, C-3′, A), 53.98 (d, $^3J_{PC} = 6.1$ Hz, C-3′, A), 39.74 (C-2′, A), 38.25 (C-2′, A); ESI-MS (positive) *m/z* 494 $(M+H)^+$, *m/z* 516 $(M+Na)^+$; (negative) *m/z* 492 $(M-H)^-$.

Compound **8c** (diastereoisomers): IR υ_{max} (KBr)/cm^{-1} 3657, 3446, 3191, 1702, 1464, 1396, 1272, 1032; ^{31}P NMR ($CDCl_3$) $\delta = 26.00$ and 26.14 ppm; ^{1}H NMR ($CDCl_3$) $\delta = 9.53$ and 9.50 (s each, 1H together, N*H*), 7.80 and 7.60 (d each, $J_1 = J_2 = 8.0$ Hz, 1H together, H-6), 7.15–7.28 (m, 4H, Ar*H*), 6.20 and 6.11 (t each, $J_1 = J_2 = 6.0$ Hz, 1H together, H-1′), 5.66 (t, 1H, H-5), 4.10 and 4.06 (d, $^2J_{PH1} = 20.4$ Hz and $^2J_{PH2} = 17.6$ Hz, 1H together, C*H*P), 3.53–3.91 (m, 10H, H-3′, 4′, 5′, POCH_3), 2.33 (s, 3H, CH_3), 2.00–2.16 (m, 2H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 164.31$ (C-4, A), 164.26 (C-4, A), 150.81 (C-2, B), 140.91 (C-6, A), 140.73 (C-6, A), 139.38 (Ar*C*, B), 132.30 (Ar*C*, B), 131.93 (Ar*C*, B), 129.73 (Ar*C*, B), 128.40 (d, $^3J_{PC} = 8.1$ Hz, Ar*C*, B), 102.42 (C-5, A), 102.26 (C-5, A), 85.89 (A), 85.72 (A), 85.70 (A), 85.54 (C-1′, 4′, A), 62.23 (C-5′, A), 61.93 (C-5′, A), 59.35 (d, $^1J_{PC} = 155.9$ Hz, *C*HP, A), 58.53 (d, $^1J_{PC} = 155.0$ Hz, *C*HP, A), 56.46 (d, $^2J_{PC} = 14.9$ Hz, POCH_3, B), 55.37 (d, $^2J_{PC} = 15.6$ Hz, POCH_3, B), 54.13 (d, $^3J_{PC} = 7.7$ Hz, C-3′, A), 53.98 (d, $^3J_{PC} = 7.4$ Hz, C-3′, A), 39.91 (C-2′, A), 38.32 (C-2′, A), 21.35 (*C*H$_3$, B); ESI-MS (positive) *m/z* 440 $(M+H)^+$, *m/z* 462 $(M+Na)^+$; (negative) *m/z* 438 $(M-H)^-$.

Compound **8d** (diastereoisomers): IR υ_{max} (KBr)/cm^{-1} 3577, 3388, 3155, 1692, 1473, 1399, 1272, 1047; ^{31}P NMR ($CDCl_3$) $\delta = 23.78$ and 24.02 ppm; ^{1}H NMR ($CDCl_3$) $\delta = 9.27$ and 9.46 (s each, 1H together, N*H*), 7.66–7.77 (m, 2H, H-6, Ar*H*), 7.27–7.46 (m, 3H, Ar*H*), 6.24 and 6.14 (t each, $J_1 = J_2 = 6.0$ Hz, 1H together, H-1′), 5.69 (t, 1H, H-5), 4.26 and 4.06 (d, $^2J_{PH1} = 20.4$ Hz and $^2J_{PH2} = 18.4$ Hz, 1H together, C*H*P), 3.34–3.94 (m, 10H, H-3′, 4′, 5′, POCH_3), 1.86–2.27 (m, 3H, H-2′, O*H*); ^{13}C NMR ($CDCl_3$) $\delta = 164.40$ (C-4, B), 150.86 (C-2, B), 140.88 (C-6, A), 140.79 (C-6, A), 134.82 (Ar*C*, B), 134.18 (Ar*C*, B), 123.83 (Ar*C*, B), 128.95 (Ar*C*, B), 129.09 (Ar*C*, B), 102.36 (C-5, A), 102.23 (C-5, A), 85.75 (A), 85.63 (A), 85.47 (C-1′, 4′, A), 62.00 (C-5′, B), 58.80 (d, $^1J_{PC} = 155.7$ Hz, *C*HP, A), 58.13 (d, $^1J_{PC} = 156.5$ Hz, *C*HP, A), 56.75 (d, $^2J_{PC} = 15.2$ Hz, POCH_3, B), 55.46 (d, $^2J_{PC} = 16.3$ Hz, POCH_3, B), 54.28 (d, $^3J_{PC} = 4.8$ Hz, C-3′, A), 54.00 (d, $^3J_{PC} = 6.7$ Hz, C-3′, A), 39.69 (C-2′, A), 38.21 (C-2′, A); ESI-MS (positive) *m/z* 460 $(M+H)^+$, *m/z* 482 $(M+Na)^+$; (negative) *m/z* 458 $(M-H)^-$.

Compound **8e** (diastereoisomers): IR υ_{max} (KBr)/cm^{-1} 3610, 3349, 3133, 1695, 1465, 1398, 1227, 1055; ^{31}P NMR ($CDCl_3$) $\delta = 25.43$ ppm; ^{1}H NMR ($CDCl_3$) $\delta = 9.38$ (bs, 1H, N*H*), 7.78 and 7.60 (d each, $J_1 = 8.4$ Hz and $J_2 = 8.0$ Hz, 1H together, H-6), 7.36–7.39 (t, 2H, Ar*H*), 7.04–7.08 (t, 2H, Ar*H*), 6.21 and 6.12 (t each, $J_1 = 6.2$ Hz and $J_2 = 6.0$ Hz, 1H together, H-1′), 5.67 (t, 1H, H-5), 4.14 and 4.11 (d each, $^2J_{PH1} = 19.2$ Hz and $^2J_{PH2} = 18.0$ Hz, 1H together, C*H*P), 3.34–3.92 (m, 10H, H-3′, 4′, 5′, POCH_3), 2.04–2.33 (m, 3H, H-2′, O*H*); ^{13}C NMR ($CDCl_3$) $\delta = 164.45$ (C-4, B), 162.69 (d, $^1J_{CF} = 243.3$ Hz, Ar*C*, B), 150.86 (C-2, B), 140.82 (C-6, B), 132.06 (Ar*C*, A), 131.00 (Ar*C*, A), 130.33 (d, $^3J_{CF} = 6.1$ Hz, Ar*C*, B), 105.87 (d, $^2J_{CF} = 21.3$ Hz, Ar*C*, B), 102.29 (C-5, A), 102.17 (C-5, A), 85.78 (A), 85.60 (A), 85.44 (C-1′, 4′, A), 61.97 (C-5′, B), 59.12 (d, $^1J_{PC} = 158.2$ Hz, *C*HP, A), 57.94 (d, $^1J_{PC} = 155.1$ Hz, *C*HP, A), 56.57 (d, $^2J_{PC} = 15.2$ Hz, POCH_3, B), 55.38 (d, $^2J_{PC} = 15.2$ Hz, POCH_3, B), 54.24 (d, $^3J_{PC} = 6.1$ Hz, C-3′, A), 53.93 (d, $^3J_{PC} = 6.1$ Hz, C-3′, A), 39.68 (C-2′, A), 38.22 (C-2′, A); ESI-MS (positive) *m/z* 444 $(M+H)^+$, *m/z* 466 $(M+Na)^+$; (negative) *m/z* 442 $(M-H)^-$.

Compound **8f** (diastereoisomers): IR υ_{max} (KBr)/cm^{-1} 3636, 3388, 3100, 1699, 1463, 1397, 1270, 1047; ^{31}P NMR ($CDCl_3$) $\delta = 24.30$ and 24.32 ppm; ^{1}H NMR ($CDCl_3$) $\delta = 9.09$ (bs, 1H, N*H*), 8.23 (d, $J = 8.4$ Hz, 2H, Ar*H*), 7.73 and 7.56–7.62 (d and m, $J = 8.0$ Hz, 3H together, H-6 and Ar*H*), 6.20 and 6.12 (t each, $J_1 = J_2 = 6.0$ Hz, 1H together, H-1′), 5.67 (t, 1H, H-5), 4.28 and 4.26 (d each, $^2J_{PH1} = 21.6$ Hz and $^2J_{PH} = 19.6$ Hz, 1H together, C*H*P), 3.35–3.93 (m, 10H, H-3′, 4′, 5′, POCH_3), 2.04–2.33 (m, 3H, H-2′, O*H*); ^{13}C NMR ($CDCl_3$) $\delta = 163.76$ (C-4, B), 150.59 (C-2, B), 147.46 (Ar*C*, B), 144.51 (Ar*C*, A), 143.61 (Ar*C*, A), 140.18 (C-6, A), 140.10 (C-6, A), 129.48 (d, $^3J_{CP} = 5.2$ Hz, Ar*C*, A), 129.36 (d, $^3J_{CP} = 7.4$ Hz, Ar*C*, A), 123.52 (Ar*C*, B), 102.00 (C-5, B), 85.47 (A), 84.88 (A), 84.82 (C-1′, 4′, A), 61.62 (C-5′, A), 61.37 (C-5′, A), 58.44 (d, $^1J_{PC} = 156.8$ Hz, *C*HP, A), 58.00 (d, $^1J_{PC} = 149.0$ Hz, *C*HP, A), 56.71 (d, $^2J_{PC} = 16.4$ Hz, POCH_3, B), 55.70 (d, $^2J_{PC} = 15.1$ Hz, POCH_3, B), 54.39 (d, $^3J_{PC} = 6.3$ Hz, C-3′, A), 54.14 (d, $^3J_{PC} = 6.3$ Hz, C-3′, A), 39.50 (C-2′, A), 38.16 (C-2′, A); ESI-MS (positive) *m/z* 493 $(M+Na)^+$; (negative) *m/z* 469 $(M-H)^-$.

Compound **8g** (diastereoisomers): IR υ_{max} (KBr)/cm^{-1} 3631, 3378, 3183, 1630, 1470, 1398, 1264,

1027; ^{31}P NMR ($CDCl_3$) $\delta = 26.09$ and 26.20 ppm; ^{1}H NMR ($CDCl_3$) $\delta = 9.49$ and 9.46 (s each, 1H together, N*H*), 7.80 and 7.61 (d each, $J_1 = 8.0$ Hz and $J_2 = 8.4$ Hz, 1H together, H-6), 7.31 (d, 2H, Ar*H*), 6.88 (d, 2H, Ar*H*), 6.20 and 6.11 (t each, $J_1 = J_2 = 6.0$ Hz, 1H together, H-1′), 5.66 (t, 1H, H-5), 4.08 and 4.04 (d each, $^2J_{PH1} = 20.0$ Hz and $^2J_{PH2} = 17.6$ Hz, 1H together, C*H*P), 3.35–3.88 (m, 10H, H-3′, 4′, 5′, POCH_3), 3.79 (s, 3H, OCH_3), 2.00–2.28 (m, 3H, H-2′, O*H*); ^{13}C NMR ($CDCl_3$) $\delta = 164.23$ (C-4, A), 164.18 (C-4, A), 159.53 (Ar*C*, B), 150.62 (C-2, B), 140.73 (C-6, A), 140.59 (C-6, A), 129.53 (d, $^3J_{PC} = 4.9$ Hz, Ar*C*, B), 127.74 (Ar*C*, A), 126.65 (Ar*C*, A), 114.21 (Ar*C*, B), 102.12 (C-5, A), 101.99 (C-5, A), 85.68 (A), 85.57 (A), 85.46 (A), 85.30 (C-1′, 4′, A), 61.94 (C-5′, A), 61.77 (C-5′, A), 58.58 (d, $^1J_{PC} = 157.1$ Hz, *C*HP, A), 57.82 (d, $^1J_{PC} = 155.6$ Hz, *C*HP, A), 56.31 (d, $^2J_{PC} = 15.4$ Hz, POCH_3, B), 55.19 (OCH_3, B), 55.16 (POCH_3, B), 53.91 (d, $^3J_{PC} = 7.0$ Hz, C-3′, A), 53.74 (d, $^3J_{PC} = 7.1$ Hz, C-3′, A), 39.58 (C-2′, A), 38.07 (C-2′, A); ESI-MS (positive) m/z 456 $(M + H)^+$, m/z 478 $(M + Na)^+$.

Compound **8h** (diastereoisomers): IR υ_{max} (KBr)/cm^{-1} 3617, 3465, 3270, 1670, 1491, 1390, 1268, 1021; ^{31}P NMR ($CDCl_3$) $\delta = 25.79$ and 25.82 ppm; ^{1}H NMR ($CDCl_3$) $\delta = 9.27$ (bs, 1H, N*H*), 7.80 and 7.61 (d each, $J_1 = 8.0$ Hz and $J_2 = 8.4$ Hz, 1H together, H-6), 6.92 (d, $J = 8.4$ Hz, 1H, Ar*H*), 6.77–6.83 (m, 2H, Ar*H*), 6.20 and 6.12 (t each, $J_1 = J_2 = 6.0$ Hz, 1H together, H-1′), 5.98 (s, 2H, OCH_2O), 5.68 (t, 1H, H-5), 4.06 and 4.03 (d each, $^2J_{PH1} = 20.0$ Hz and $^2J_{PH2} = 21.6$ Hz, 1H together, C*H*P), 3.38–3.92 (m, 10H, H-3′, 4′, 5′, POCH_3), 2.09–2.30 (m, 3H, H-2′, OH); ^{13}C NMR ($CDCl_3$) $\delta = 164.42$ (C-4, B), 150.86 (C-2, B), 148.21 (Ar*C*, B), 147.82 (Ar*C*, B), 140.82 (C-6, B), 129.84 (Ar*C*, B), 128.78 (Ar*C*, B), 122.24 (Ar*C*, B), 108.59 (Ar*C*, B), 102.29 (C-5, A), 102.12 (C-5, A), 101.47 (O*C*H$_2$O, B), 85.90, 85.72, 85.54 (C-1′, 4′, A), 62.00 (C-5′, B), 59.08 (d, $^1J_{PC} = 158.2$ Hz, *C*HP, A), 58.36 (d, $^1J_{PC} = 155.1$ Hz, *C*HP, A), 56.45 (d, $^2J_{PC} = 15.2$ Hz, POCH_3, B), 55.23 (d, $^2J_{PC} = 15.2$ Hz, POCH_3, B), 54.22 (d, $^3J_{PC} = 4.5$ Hz, C-3′, A), 53.95 (d, $^3J_{PC} = 4.1$ Hz, C-3′, A), 39.80 (C-2′, A), 38.25 (C-2′, A); ESI-MS (positive) m/z 470 $(M + H)^+$, m/z 492 $(M + Na)^+$; (negative) m/z 468 $(M - H)^-$.

Compound **8i** (diastereoisomers): IR υ_{max} (KBr)/cm^{-1} 3630, 3363, 3178, 1691, 1468, 1399, 1273, 1050; ^{31}P NMR ($CDCl_3$) $\delta = 24.44$ and 24.58 ppm; ^{1}H NMR ($CDCl_3$) $\delta = 9.09$ (bs, 1H, N*H*), 8.23 (d, $J = 8.4$ Hz, 2H, Ar*H*), 7.73 and 7.56–7.62 (d and m, $J = 8.0$ Hz, 3H together, H-6 and Ar*H*), 6.20 and 6.12 (t each, $J_1 = J_2 = 6.0$ Hz, 1H together, H-1′), 5.67 (t, 1H, H-5), 4.28 and 4.26 (d each, $^2J_{PH1} = 21.6$ Hz and $^2J_{PH} = 19.6$Hz, 1H, C*H*P), 3.35–3.93 (m, 10H, H-3′, 4′, 5′, POCH_3), 2.04–2.33 (m, 3H, H-2′, O*H*); ^{13}C NMR ($CDCl_3$) $\delta = 164.05$ (C-4, B), 150.77 (C-2, B), 148.70 (Ar*C*, B), 140.73 (C-6, B) 139.02 (Ar*C*, B), 138.13 (Ar*C*, B), 134.80 (Ar*C*, B), 129.90 (Ar*C*, B), 123.42 (Ar*C*, B), 102.36 (C-5, A), 102.30 (C-5, A), 85.83 (A), 85.76 (A), 85.62 (C-1′, 4′, A), 62.00 (C-5′, A), 61.82 (C-5′, A), 59.05 (d, $^1J_{PC} = 154.0$ Hz, *C*HP, A), 58.30 (d, $^1J_{PC} = 151.2$ Hz, *C*HP, A), 56.79 (d, $^2J_{PC} = 13.6$ Hz, POCH_3, B), 55.37 (d, $^2J_{PC} = 16.2$ Hz, POCH_3, B), 54.63 (d, $^3J_{PC} = 5.4$ Hz, C-3′, A), 54.11 (d, $^3J_{PC} = 5.3$ Hz, C-3′, A), 39.67 (C-2′, A), 38.43 (C-2′, A); ESI-MS (positive) m/z 471 $(M + H)^+$, m/z 493 $(M + Na)^+$; (negative) m/z 469 $(M - H)^-$.

Compound **8j** (diastereoisomers): IR υ_{max} (KBr)/cm^{-1} 3640, 3381, 3198, 1680, 1446, 1394, 1272, 1028; ^{31}P NMR ($CDCl_3$) $\delta = 25.51$ ppm; ^{1}H NMR ($CDCl_3$) $\delta = 9.27$ and 9.16 (s each, 1H together, N*H*), 7.66–7.77 (m, 2H, H-6, Ar*H*), 7.27–7.46 (m, 3H, Ar*H*), 6.16 (t, $J = 6.0$ Hz, H-1′), 5.69 (m, 1H, H-5), 4.77 (t, $^2J_{PH} = 21.6$ Hz, 1H, C*H*P), 3.34–3.94 (m, 10H, H-3′, 4′, 5′, POCH_3), 1.86–2.27 (m, 3H, H-2′, O*H*); ^{13}C NMR ($CDCl_3$) $\delta = 164.45$ (C-4, A), 164.39 (C-4, A), 150.83 (C-2, B), 140.97 (C-6, A), 140.82 (C-6, A), 134.50 (d, $^2J_{PC} = 9.1$ Hz, Ar*C*, B), 134.21 (Ar*C*, B), 129.82 (Ar*C*, B), 129.69 (Ar*C*, B), 127.68 (Ar*C*, B), 102.41 (C-5, A), 102.35 (C-5, A), 85.84 (A), 85.75 (A), 85.63 (A), 85.47 (C-1′, 4′, A), 62.42 (C-5′, A), 62.18 (C-5′, A), 56.95 (d, $^2J_{PC} = 13.4$ Hz, POCH_3, B), 55.65 (d, $^2J_{PC} = 14.9$ Hz, POCH_3, B), 54.47 (d, $^1J_{PC} = 159.4$ Hz, *C*HP, A), 53.79 (d, $^1J_{PC} = 132.2$ Hz, *C*HP, A), 54.63 (d, $^3J_{PC} = 14.2$ Hz, C-3′, A), 53.80 (d, $^3J_{PC} = 6.2$ Hz, C-3′, A), 39.61 (C-2′, A), 38.30 (C-2′, A); ESI-MS (positive) m/z 460 $(M + H)^+$, m/z 482 $(M + Na)^+$; (negative) m/z 458 $(M - H)^-$.

Compound **8k** (diastereoisomers): IR υ_{max} (KBr)/cm^{-1} 3608, 3375, 3134, 1690, 1467, 1400, 1272, 1051; ^{31}P NMR ($CDCl_3$) $\delta = 24.97$ and 25.11ppm; ^{1}H NMR ($CDCl_3$) $\delta = 9.29$ (bs, 1H, N*H*), 7.78 and 7.62 (d each, $J_1 = J_2 = 8.0$ Hz, 1H together, H-6), 7.31–7.39 (m, 4H, Ar*H*), 6.21 and 6.13 (t each, $J_1 = 5.6$ Hz and $J_2 = 5.2$ Hz, 1H together, H-1′), 5.68 (t, 1H, H-5), 4.12 and 4.09 (d each, $^2J_{PH1} = 20.8$ Hz and $^2J_{PH2} = 18.0$ Hz, 1H together, C*H*P), 3.36–3.89 (m, 10H, H-3′, 4′, 5′, POCH_3), 2.03–2.31 (m, 3H, H-2′, O*H*); ^{13}C NMR ($CDCl_3$) $\delta = 164.05$ (C-4, B), 159.53 (Ar*C*, B), 150.77 (C-2, B), 148.70 (Ar*C*, B), 140.73 (C-6, A),139.04 (Ar*C*, A), 138.12 (Ar*C*, A), 134.78 (d, $^3J_{PC} = 9.5$ Hz, Ar*C*, B), 129.90 (Ar*C*, B), 123.46 (Ar*C*, B), 102.41 (C-5, A), 102.32 (C-5, A), 85.68 (A), 85.87 (A), 85.78 (A), 85.66 (C-1′, 4′, A), 62.03 (C-5′, A), 61.85 (C-5′, A), 59.05 (d, $^1J_{PC} = 153.9$ Hz, *C*HP, A), 58.30 (d, $^1J_{PC} = 151.2$ Hz, *C*HP, A), 56.79 (d, $^2J_{PC} = 13.6$ Hz, POCH_3, B), 55.37 (d, $^2J_{PC} = 16.2$ Hz, POCH_3, B), 54.35 (d, $^3J_{PC} = 8.9$ Hz, C-3′, A), 53.99 (d, $^3J_{PC} = 8.3$ Hz, C-3′, A), 39.68 (C-2′, A), 38.22 (C-2′, A); ESI-MS (positive) m/z 460 $(M + H)^+$, m/z 482 $(M + Na)^+$; (negative) m/z 458 $(M - H)^-$.

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