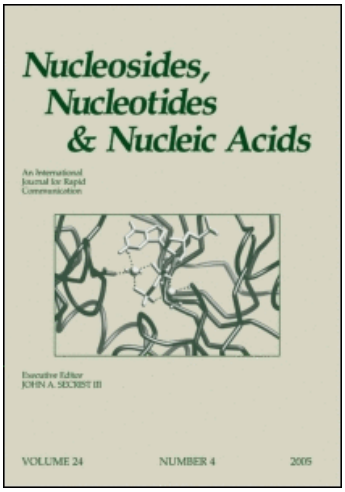

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

New and One Pot Chemoselective Synthesis of Nucleoside 5'-H-Phosphonate Diesters

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To cite this Article Guo, Xin , Jiang, Peng , Fu, Hua , Jiang, Yuyang and Zhao, Yufen(2005) 'New and One Pot Chemoselective Synthesis of Nucleoside 5'-H-Phosphonate Diesters', Nucleosides, Nucleotides and Nucleic Acids, 24: 9, 1325 — 1331
To link to this Article: DOI: 10.1080/15257770500230467
URL: http://dx.doi.org/10.1080/15257770500230467

Nucleosides, Nucleotides, and Nucleic Acids, 24 (9):1325–1331, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1080/15257770500230467

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NEW AND ONE POT CHEMOSELECTIVE SYNTHESIS OF NUCLEOSIDE 5′-H-PHOSPHONATE DIESTERS

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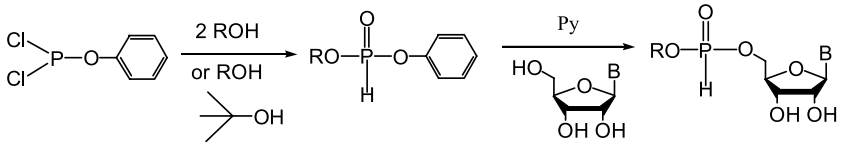
▫ *Arbuzov reaction of phenyl phosphorodichloridite with two equiv of alcohol, or mixture of one equiv of alcohol and one equiv of tert-butyl alcohol, led to the corresponding aryl H-phosphonate diesters. Following displacement of the H-phosphonate diesters with unprotected nucleosides chemoselectively produced nucleoside 5′-H-phosphonate diesters in good yields, respectively.*



Keywords H-Phosphonate Diester, Nucleoside, Chemoselective, Arbuzov Reaction

INTRODUCTION

H-Phosphonates are useful intermediates in chemistry, and finding new synthetic routes to these compounds constitutes a valuable target. In the past two

Received 16 February 2005, accepted 2 May 2005.
The program is supported from the Excellent Dissertation Foundations by the Chinese Ministry of Education (No. 200222), the Excellent Young Teacher Program of MOE, P.R. China, and the National Natural Science Foundation of China (Grand No. 20472042).
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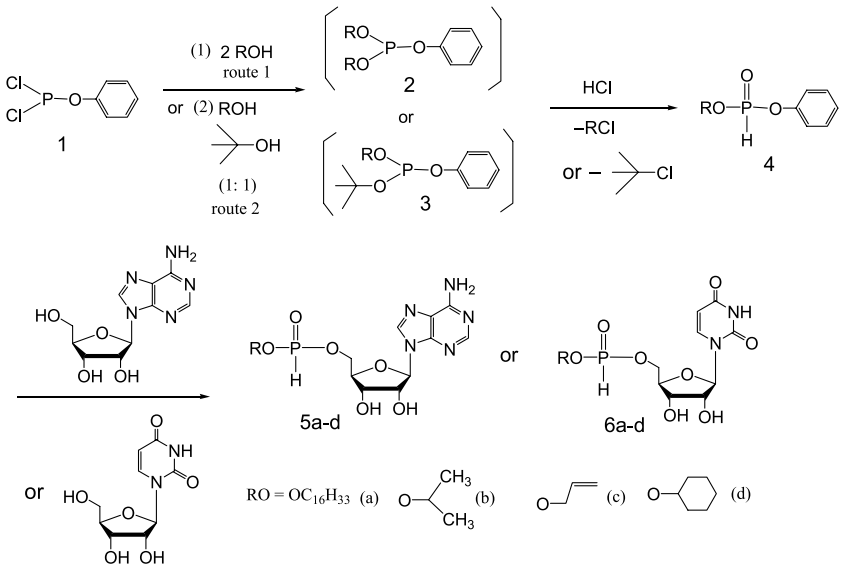
decades, studies on H-phosphonate derivatives have greatly progressed;[1–4] a more complete picture of synthetic potential of these compounds unfolded.[5,6] H-phosphonates were widely used as synthetic intermediates in nucleotide,[1–6] carbohydrate,[7,8] peptide,[9,10] lipid,[11,12] and general phosphorus chemistry.[13,14] Advances on the development of a comprehensive H-phosphonate methodology and the underlying chemistry for the preparation of biologically important phosphate esters and their analogues have been discussed by Stawinski and Kraszewski.[15] Preparation of H-phosphonate monoesters mainly comes from the following systems: PCl_3/imidazole,[16] salicylchlorophosphite,[17] H-pyrophosphonate,[18] and diphenyl H-phosphonate.[19] Synthesis of H-phosphonate diesters includes transesterification of easily available members of the family,[20] acidolysis or hydrolysis of phosphorochloridites or mixed anhydrides,[21–23] addition of phosphonic acid to oxiranes,[24] alcoholysis of *bis*(*N*,*N*-dimethylamino)phosphonate,[25] or condensation of alcohols with phosphonic acid by dicyclohexylcarbodiimide (DCC).[26] However, most of the methods require protection of amino and hydroxyl groups in the starting materials.

Since chemistry on uncharged and stable H-phosphonates appears to combine the advantages of two other phosphorus chemistries, that of P(V) phosphoryl compounds and that of tervalent P(III) derivatives, their synthetic potential certainly is worth further exploration.[15] In this article, we would like to report a simple, general, and efficient method for preparation of nucleoside H-phosphonate diesters, preferably based on inexpensive, commercial reagents.

RESULTS AND DISCUSSION

There are two routes to nucleoside H-phosphonate diesters, as shown in Scheme 1. In route 1, two equiv of alcohol was added to phenyl phosphorodichloridite in CH_2Cl_2 at 0°C under nitrogen atmosphere, the corresponding phenyl dialkyl phosphite triester (**2**) intermediate was obtained. The following Arbuzov rearrangement reaction of the phosphite triester with HCl produced phenyl alkyl H-phosphonate diester (**4**) with minor dialkyl H-phosphonate diester appearing. The displacement reaction of **4** with adenosine or uridine in dry pyridine at room temperature led to **5** or **6** in 58–67% (see Table 1). Route 2 is similar to route 1; however, mixture of one equiv of alcohol and one equiv of *tert*-butyl alcohol replaced two equiv of alcohol in the Arbuzov reaction, and the reaction yields are 61–70%. For example, in route 1, two equiv of isopropyl alcohol in CH_2Cl_2 was added dropwise to phenyl phosphorodichloridite at 0°C under nitrogen atmosphere. Thirty minutes later, the ^{31}P NMR showed that phenyl phosphorodichloridite at 177.58 ppm transferred into phenyl isopropyl H-phosphonate diester at 3.24 ppm with a minor peak at 4.96 ppm, corresponding to diisopropyl H-phosphonate diester (12% relative to phenyl isopropyl H-phosphonate diester). The solvent and HCl in the reaction solution were removed by distillation, the residue was dissolved in dry pyridine, and adenosine in pyridine was added dropwise to the



SCHEME 1 Synthetic routes of nucleoside H-phosphonate diesters.

solution at 20°C under nitrogen atmosphere. Six hours later, phenyl isopropyl H-phosphonate diester almost quantitatively transferred into a pair of diastereomers adenosine isopropyl H-phosphonate diester at ^{31}P NMR 8.92, 8.58 ppm (peak area ratio 1:1). After evaporation of pyridine, the crude product was purified by column chromatography using $CHCl_3$ and CH_3OH (8:1 to 6:1) as eluent, and adenosine isopropyl H-phosphonate diester was obtained in 67% yield, its structure was determined by ^{31}P, ^{1}H, ^{13}C NMR, and ESI-MS. The regioselectivity was proved by

TABLE 1 Yields and ^{31}P NMR of the Synthesized Compounds

Entry	Nucleoside	Alcohol	Product	Yield %	^{31}P NMR (ppm)
1	A	$C_{16}H_{33}OH$	5a	59	10.05, 9.62
2	A	$C_{16}H_{33}OH$:*tert*-butyl alcohol	5a	62	
3	A	Isopropyl alcohol	5b	67	8.92, 8.57
4	A	Isopropyl alcohol:*tert*-butyl alcohol	5b	70	
5	A	Allyl alcohol	5c	58	10.21, 9.94
6	A	Allyl alcohol:*tert*-butyl alcohol	5c	61	
7	A	Cyclohexanol	5d	60	8.77, 8.22
8	A	Cyclohexanol:*tert*-butyl alcohol	5d	68	
9	U	$C_{16}H_{33}OH$	6a	58	10.13, 9.70
10	U	$C_{16}H_{33}OH$:*tert*-butyl alcohol	6a	64	
11	U	Isopropyl alcohol	6b	64	8.83, 7.77
12	U	Isopropyl alcohol:*tert*-butyl alcohol	6b	68	
13	U	Allyl alcohol	6c	61	10.37, 10.02
14	U	Allyl alcohol:*tert*-butyl alcohol	6c	63	
15	U	Cyclohexanol	6d	65	8.46, 7.82
16	U	Cyclohexanol:*tert*-butyl alcohol	6d	70	

^{1}H NMR spectra during phosphonylation of nucleosides. ^{1}H NMR spectrum of 5′-CH_2 for a free nucleoside should show a pair of doublet peaks and two pair of doublet peaks for 2′ or 3′-monophosphonylated nucleoside because of existence of a pair of diastereomers. However, we found multiplet peaks of 5′-CH_2 in ^{1}H NMR spectra of nucleoside alkyl 5′-H-phosphonates, which showed the coupling ($^3J_{P\text{-}H}$) between P and 5′-CH_2.

In route 2, mixture of one equiv of alcohol and one equiv of *tert*-butyl alcohol was added dropwise to phenyl phosphorodichloridite at 0°C under nitrogen atmosphere, and the ^{31}P NMR showed alkyl phenyl H-phosphonate diester with minor dialkyl H-phosphonate diester appearing (8–12% relative to alkyl phenyl H-phosphonate diester). The following reaction and work-up is similar to the procedure in route 1. The advantage of route 2 is to reduce use of one equiv of alcohol, which is important for expensive alcohols such as preparation of dinucleotides, and the study on this project is in progress.

Displacement reaction of **4** with free nucleosides chemoselectively produced nucleoside 5′-phosphonate diesters. This is due to the difference in reactivity among amino of base, 5′, 2′ and 3′-OH, and 5′-OH is of high reactivity and small steric hindrance compared with other active groups. In addition, we believe that the similar regioselectivity can also be observed for other nucleosides and the corresponding deoxyribonucleosides with good solubility in pyridine.

EXPERIMENTAL

General procedure for preparation of nucleoside 5′-H-phosphonate diesters. 2 mmol of alcohol (primary or secondary alcohol) or mixture of 1 mmol of alcohol (primary or secondary alcohol) and 1 mmol of tert-butyl alcohol (74 mg) in 5 mL of $CHCl_3$ was added dropwise to phenyl phosphorodichloridite in 5 mL of dichloromethane at 0°C under nitrogen atmosphere, and the solution was stirred for 30 min at this temperature. The solvent was removed under reduced pressure, and the residue was dissolved in 5 mL of dry pyridine. One mmol of adenosine or uridine in 5 mL of dry pyridine was added dropwise to the above solution at room temperature. Six hours later, the reaction solution was evaporated by rotary evaporation, and the residue was purified by silica gel column chromatography using $CHCl_3$:MeOH (8:1 to 6:1) as eluent to give the target products. The target products were identified by ^{31}P, ^{1}H, ^{13}C NMR, and HRESI-MS.

Adenosine hexadecyl 5′-H-phosphonate (5a). ^{31}P NMR (122 MHz, DMSO-d_6, ppm): δ 10.05, 9.62 (a pair of diastereomers, peak area ratio 1:1); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.30 (1H, s, H-2), 8.13 (1H, d, H-8, $^3J_{H\text{-}H}$ = 1.38 Hz), 7.30 (2H, s, NH_2), 6.81 (0.5 H, d, P-H, $^1J_{P\text{-}H}$ = 701 Hz), 6.75 (0.5H, d, P-H, $^1J_{P\text{-}H}$ = 702 Hz), 5.93 (1H, q, H-1′, $^3J_{H\text{-}H}$ = 4.80 Hz), 5.59 (1H, br, 3′-OH), 5.39 (1H, br, 2′-OH), 4.65 (1H, m, H-2′), 4.25–4.22 (1H, m, H-3′), 4.08 (1H, m, H-4′),

3.92–3.89 (2H, m, H-5′), 3.44–3.37 (2H, m, $-CH_2OP$), 1.52 (2H, m, $-CH_2CH_2OP$), 1.30–1.19 (26H, m, $-CH_2-$), 0.83 (3H, t, CH_3, $^3J_{H\text{-}H}$ = 6.18 Hz); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 156.05 (C-6), 152.59 (C-2), 149.33 (C-4), 139.62 (C-8), 119.17 (C-5), 87.63 (C-1′), 82.41 (C-4′), 72.97 (C-2′), 69.89 (C-3′), 65.04 ($-CH_2-OP$), 56.03 (C-5′), 31.31 ($CH_3CH_2CH_2-$), 29.78 ($-CH_2CH_2OP$), 29.07–28.91 ($-CH_2-$), 24.91 ($-CH_2CH_2CH_2OP$), 22.11 (CH_3CH_2-), 13.94 (CH_3-); HRESI-MS: Calcd for $C_{26}H_{47}N_5O_6P$ $[M + H]^+$ (m/z) 556.3264, Found 556.3252.

Uridine hexadecyl 5′-H-phosphonate (6a). ^{31}P NMR (122 MHz, $CDCl_3$, ppm): δ 10.13, 9.70 (a pair of diastereomers, peak area ratio 1:1); ^1H NMR (300 MHz, $CDCl_3$, ppm): δ10.48 (1H, br, H-3), 7.62 (1H, d, H-6, $^3J_{H\text{-}H}$ = 7.89 Hz), 6.92 (0.5H, d, P-H, $^1J_{P\text{-}H}$ = 705 Hz), 6.90 (0.5H, d, P-H, $^1J_{P\text{-}H}$ = 708 Hz), 5.86 (1H, d, H-1′), 5.74 (1H, d, H-5, $^3J_{H\text{-}H}$ = 9.27 Hz), 4.40–4.36 (1H, m, H-2′), 4.22–4.26 (2H, m, H-3′, 4′), 4.13–4.07 (2H, m, H-5′), 3.77 (2H, m, $-CH_2OP$), 1.68 (2H, m, $-CH_2CH_2OP$), 1.30–1.21 (26H, m, $-CH_2-$), 0.88 (3H, t, CH_3-, $^3J_{H\text{-}H}$ = 6.51 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.88 (C-4), 153.87 (C-2), 143.34 (C-6), 105.34 (C-5), 92.85 (C-1′), 85.02 (C-4′), 77.00 (C-2′), 72.39 (C-3′), 69.37 ($-CH_2OP$), 67.55 (C-5′), 34.67 $CH_3CH_2CH_2-$), 33.13 ($-CH_2CH_2OP$), 32.70–31.92 ($-CH_2-$), 28.22 ($-CH_2CH_2CH_2OP$), 25.43 (CH_3CH_2-), 16.86 (CH_3-); HRESI-MS: Calcd for $C_{25}H_{46}N_2O_8P$ $[M + H]^+$ (m/z) 533.2992, Found m/z 533.2973.

Adenosine isopropyl 5′-H-phosphonate (5b). ^{31}P NMR (122 MHz, CD_3OD, ppm): δ 8.92, 8.57 (a pair of diastereomers, peak area ratio 1:1); ^1H NMR (300 MHz, CD_3OD, ppm): δ 8.27 (1H, d, H-2), 8.20 (1H, d, H-8, $^3J_{H\text{-}H}$ = 1.74 Hz), 7.24–7.21 (2H, m, NH_2), 6.83 (0.5H, d, P-H, $^1J_{P\text{-}H}$ = 714 Hz), 6.77 (0.5H, d, P-H, $^1J_{P\text{-}H}$ = 714 Hz), 6.03 (1H, q, H-1′, $^3J_{H\text{-}H}$ = 4.47 Hz), 4.76–4.71 (1H, m, H-2′), 4.47–4.42 (1H, m, H-3′), 4.38–4.30 (2H, m, H-5′), 4.28–4.22 (1H, m, H-4′), 3.30 (1H, m, >CH-O-P), 1.28 (6H, m, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 156.07 (C-6), 152.66 (C-2), 149.37 (C-4), 139.70 (C-8), 119.18 (C-5), 87.72 (C-1′), 82.46 (C-4′), 79.19 (C-2′), 70.51 (>CHOP), 69.98 (C-3′), 64.95 (C-5′), 23.55 (CH_3-); HRESI-MS: Calcd. for $C_{13}H_{21}N_5O_6P$ $[M + H]^+$ (m/z) 374.1229, Found 374.1236.

Uridine isopropyl 5′-H-phosphonate (6b). ^{31}P NMR (122 MHz, $CDCl_3$, ppm): δ 8.83, 7.77 (a pair of diastereomers, peak area ratio 1:1); ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 10.43 (1H, br, H-3), 7.62 (1H, q, H-6, $^3J_{H\text{-}H}$ = 4.47 Hz), 6.93 (0.5H, d, P-H, $^1J_{P\text{-}H}$ = 702 Hz), 6.92 (0.5H, d, P-H, $^1J_{P\text{-}H}$ = 705 Hz), 5.87 (1H, d, H-1′), 5.74 (1H, d, H-5, $^3J_{H\text{-}H}$ = 8.58 Hz), 4.77 (1H, m, H-2′), 4.34–4.31 (2H, m, H-3′, 4′), 4.26–4.20 (2H, m, H-5′), 3.76 (1H, m, >CH-OP), 1.36 (6H, d, CH_3-, $^3J_{H\text{-}H}$ = 1.71 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 164.21 (C-4), 151.04 (C-2), 136.18 (C-6), 102.52 (C-5), 89.95 (C-1′), 82.22 (C-4′), 74.16 (C-2′), 72.17 (>CH-OP), 69.62 (C-3′), 64.61 (C-5′), 23.86 (CH_3-); HRESI-MS: Calcd for $C_{12}H_{20}N_2O_8P$ $[M + H]^+$ (m/z) 351.0957, Found 351.0946.

Adenosine allyl 5′-H-phosphonate (5c). ^{31}P NMR (122 MHz, DMSO-d_6, ppm): δ 10.21, 9.94 (a pair of diastereomers, peak area ratio 1:1); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.31 (1H, d, H-2, $^{3}J_{H\text{-}H}$ = 1.38 Hz), 8.13 (1H, d, H-8, $^{3}J_{H\text{-}H}$ = 4.41 Hz), 7.33–7.30 (2H, s, NH_2), 6.88 (0.5H, d, P-H, $^{1}J_{P\text{-}H}$ = 702 Hz), 6.81 (0.5H, d, P-H, $^{1}J_{P\text{-}H}$ = 708 Hz), 5.91–5.82 (2H, m, H-1′, CH_2 = C*H*–), 5.58 (1H, d, 3′-OH), 5.41 (1H, d, 2′-OH), 5.30–5.20 (2H, m, CH_2 = CH-), 4.68–4.60 (1H, m, H-2′), 4.48–4.46 (1H, m, H-3′), 4.25–4.15 (4H, m, H-5′,–CH_2–OP), 4.08 (m, 1H, H-4′); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 156.06 (C-6), 152.49 (C-2), 149.34 (C-4), 139.73 (C-8), 133.01 (CH_2 = *C*H–), 118.56 (C-5), 115.20 (*C*H_2 = CH–), 87.57 (C-1′), 82.33 (C-4′), 72.79 (C-2′), 69.91 (C-3′), 65.41 (–CH_2–OP), 64.88 (C-5′); HRESI-MS: Calcd. for $C_{13}H_{19}N_5O_6P$ $[M + H]^+$ (m/z) 372.1073, Found 372.1081.

Uridine allyl 5′-H-phosphonate (6c). ^{31}P NMR (122 MHz, DMSO-d_6, ppm): δ 10.37, 10.02 (a pair of diastereomers, peak area ratio 1:1); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 11.37 (1H, s, H-3), 7.63 (1H, q, H-6, $^{3}J_{H\text{-}H}$ = 7.62 Hz), 6.94 (0.5H, d, P-H, $^{1}J_{P\text{-}H}$ = 705 Hz), 6.92 (0.5H, d, P-H, $^{1}J_{P\text{-}H}$ = 708 Hz), 6.00–5.90 (1H, m, H-1′), 5.77–5.74 (2H, m, H-5, CH_2 = C*H*–), 5.65–5.61 (1H, d, 3′-OH), 5.51–5.48 (1H, d, 2′-OH), 5.37–5.29 (2H, m, CH_2 = CH–), 4.53 (1H, m, H-2′), 4.22–4.17 (3H, m, H-3′, –CH_2–OP), 4.07 (1H, m, H-4′), 3.97 (2H, m, H-5′); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 163.07 (C-4), 150.71 (C-2), 140.58 (C-6), 133.08 (CH_2 = *C*H–), 117.91 (*C*H_2 = CH–), 102.07(C-5), 88.48 (C-1′), 81.96 (C-4′), 72.50 (C-2′), 69.48 (C-3′), 65.58 (–CH_2–OP), 64.79 (C-5′); HRESI-MS: Calcd. for $C_{12}H_{18}N_2O_8P$ $[M + H]^+$ (m/z) 349.0801, Found 349.0812.

Adenosine cyclohexyl 5′-H-phosphonate (5d). ^{31}P NMR (122 MHz, DMSO-d_6, ppm): δ 8.77, 8.22 (a pair of diastereomers, peak area ratio 1:1); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.30 (1H, d, H-2, $^{3}J_{H\text{-}H}$ = 1.71 Hz), 8.14 (1H, d, H-8, $^{3}J_{H\text{-}H}$ = 1.38 Hz), 7.29 (2H, s, NH_2), 6.84 (0.5H, d, P-H, $^{1}J_{P\text{-}H}$ = 702 Hz), 6.78 (0.5H, d, P-H, $^{1}J_{P\text{-}H}$ = 699 Hz), 5.91 (1H, d, H-1′, $^{3}J_{H\text{-}H}$ = 5.16 Hz), 5.57 (1H, d, 3′-OH), 5.38 (1H, d, 2′-OH), 4.66 (1H, m, H-2′), 4.29–4.18 (3H, m, H-3′, H-5′), 4.07 (1H, m, H-4′), 3.57–3.55 (1H, m, H-5′), 1.76 (2H, br, cyclohexyl), 1.57 (2H, br, cyclohexyl), 1.40 (3H, m, cyclohexyl), 1.17 (3H, m, cyclohexyl); ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 156.08 (C-6), 152.64 (C-2), 149.35 (C-4), 139.65 (C-8), 119.13 (C-5), 87.64 (C-1′), 82.45 (C-4′), 79.17 (C-2′), 74.85 (C-3′), 72.86 (>CH-OP), 69.85 (C-5′), 38.67 (cyclohexyl), 24.52 (cyclohexyl), 22.86 (cyclohexyl); HRESI-MS: Calcd. for $C_{16}H_{27}N_5O_6P$ $[M + H]^+$ (m/z) 414.1542, Found 414.1560.

Uridine cyclohexyl 5′-H-phosphonate (6d). ^{31}P NMR (122 MHz, $CDCl_3$, ppm): δ 8.46, 7.82 (a pair of diastereomers, peak area ratio 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.40 (1H, br, H-3), 7.63 (1H, q, H-6, $^{3}J_{H\text{-}H}$ = 7.92 Hz), 6.94 (0.5H, d, P-H, $^{1}J_{P\text{-}H}$ = 708 Hz), 6.93 (0.5H, d, P-H, $^{1}J_{P\text{-}H}$ = 711 Hz), 5.87 (1H, d, H-1′), 5.76 (1H, d, H-5, $^{3}J_{H\text{-}H}$ = 6.87 Hz), 4.52–4.48 (1H, m, H-2′), 4.35–4.30 (2H, m,

H-3′, H-4′), 4.26–4.23 (3H, m, H-5′, >CH-OP), 1.91 (2H, br, cyclohexyl), 1.72 (2H, br, cyclohexyl), 1.57–1.50 (3H, m, cyclohexyl), 1.35–1.29 (3H, m, cyclohexyl); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 164.12 (C-4), 150.24 (C-2), 136.19 (C-6), 102.49 (C-5), 89.90 (C-1′), 82.22 (C-4′), 76.83 (C-2′), 74.18 (>CH-OP), 69.54 (C-3′), 64.44 (C-5′), 33.50 (cyclohexyl), 24.83 (cyclohexyl), 23.38 (cyclohexyl); HRESI-MS: Calcd. for $C_{15}H_{24}N_2O_8P$ $[M + H]^+$ (m/z) 391.1270, Found 391.1258.

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