Carbohydrate Research 343 (2008) 2530–2534

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

The diastereoselective synthesis of methyl 5-deoxy-5-(dialkylphosphono)-5-(dialkylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranosides

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ARTICLE INFO

Article history:
Received 31 March 2008
Received in revised form 5 June 2008
Accepted 6 June 2008
Available online 14 June 2008

Keywords:
Diastereoselective synthesis
α-Amino phosphonate
Mannich-type reaction
Acetyl chloride

ABSTRACT

A convenient method has been developed for the diastereoselective synthesis of methyl 5-deoxy-5-(dialkylphosphono)-5-(dialkylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranosides under mild conditions, namely the reaction of a dialkyl phosphoramidate with a dialkyl phosphite and methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside in acetyl chloride in a one-pot procedure.

1. Introduction

α-Amino phosphonates have received an increasing amount of attention since they are key substrates in the synthesis of phosphonopeptides. Their wide range of utilities as enzyme inhibitors, antibiotics, pharmacological agents, and haptens of catalytic antibodies have attracted the interest of chemists for a long time.[1] A number of synthetic methods for the synthesis of α-amino phosphonates have been developed during the past two decades.[2] Also a large number of phosphate–phosphonate derivatives, bearing a P–N–C–P bond structure have been synthesized, and their significant herbicidal, antiviral, and fungicidal activities are reported.[3]

In the course of our program aimed at searching for potential and selective organophosphorus inhibitors, virucids, and herbicides, methyl 5-deoxy-5-(dialkylphosphono)-5-(dialkylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranoside stimulated our interest. Forming this kind of organophosphorus compound can introduce a wide range of substituents at the α-position to the phosphorus atom, which can be applied for asymmetric synthesis of various chiral α-aminophosphorus acids. Carbohydrate residues are crucial in receptor recognition; antigens are recognized by the immune system in normal tissue,[4] and the isolation and careful structural identification of specific carbohydrate antigens overexpressed in cancer cells has inspired carbohydrate-based tumor immunotherapy.[5]

Diastereoselection in asymmetric reactions has been important for a very long time to organic chemists for constructing synthetic building blocks of high stereoisomeric purity. Carbohydrates contain several functional groups and stereogenic centers in one molecular unit, which allows their use as tools in stereochemical differentiation, as starting materials in ex-chiral pool syntheses of interesting enantiopure compounds, and as chiral templates in asymmetric transformations and stereoselective syntheses.[6] D-Ribose is very essential for life as some of the most important biological molecules contain D-ribose, including ATP (adenosine triphosphate), all the nucleotides and nucleotide coenzymes, and all forms of RNA (ribonucleic acid). D-Ribose can also improve diastolic function and quality of life in congestive heart failure patients. Herein, we reported the diastereoselective synthesis of methyl 5-deoxy-5-(dialkylphosphono)-5-(dialkylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranoside by the reaction of dialkyl phosphoramidate (**1**) with methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**2**) and dialkyl phosphate (**3**) in a one-pot procedure with the aid of acetyl chloride.

2. Results and discussion

The Mannich-type reaction has proved facile for the preparation of new phosphorus α-amino phosphonate compounds.[7] A number of Lewis acid catalysts such as $InCl_3$,[8] $TaCl_5$–SiO_2,[9] and $Mg(ClO_4)_2$[10] have been used in methylene chloride or other organic solvents to promote this addition. Our group has reported the synthesis of N-protected α-amino phosphonates under refluxing benzene.[11,12] As shown in Table 1, dialkyl phosphoramidate (**1**) was allowed to

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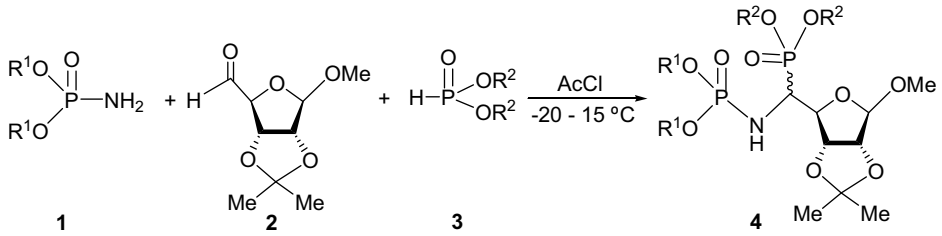
doi:10.1016/j.carres.2008.06.009

Table 1
Synthesis of compound **4**



1 **2** **3** **4**

4	R^1	R^2	Yield[a] (%)
4a	*n*-C_3H_7	CH_3	49
4b	*n*-C_3H_7	C_2H_5	56
4c	*n*-C_3H_7	*n*-C_3H_7	47
4d	*n*-C_3H_7	*i*-C_3H_7	45
4e	*n*-C_3H_7	*n*-C_4H_9	50
4f	C_2H_5	CH_3	50
4g	C_2H_5	C_2H_5	53
4h	C_2H_5	*n*-C_3H_7	49
4i	C_2H_5	*i*-C_3H_7	48
4j	C_2H_5	*n*-C_4H_9	51

[a] Isolated yield of the major diastereoisomer.

react with dialkyl phosphite (**3**) and methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**2**) in acetyl chloride to give the target methyl 5-deoxy-5-(dialkylphosphono)-5-(dialkylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranosides **4a–j** in moderate yields of about 50% (crude products). The reactions were carried out using a one-pot procedure. All the products were isolated from reaction mixture by column chromatography, and their structures were ascertained by ^{1}H NMR, ^{31}P NMR, and ^{13}C NMR spectroscopies and by mass spectrometry.

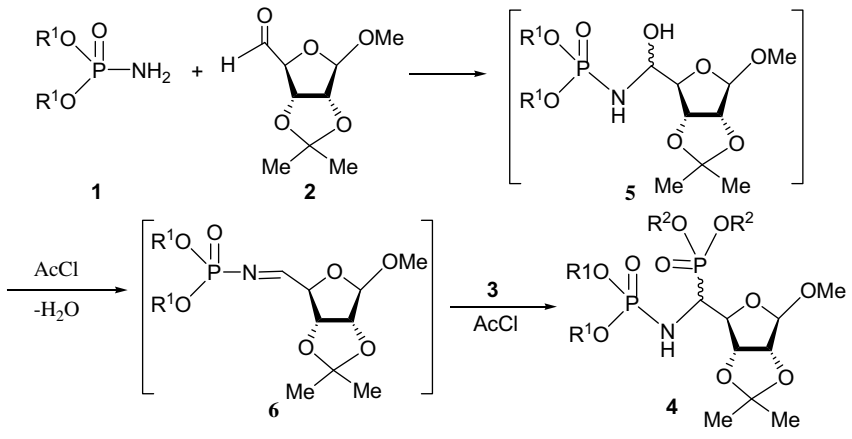
The reactions are aided by using acetyl chloride as the dehydrating agent. It is reasonable to postulate that carbonyl addition of **1** to **2** forms the unstable adduct **5**. Acetyl chloride[13] accelerates the process of intramolecular dehydration of **5** forming the corresponding Schiff's base **6** (Scheme 1).

Because one stereogenic center (a carbon atom at the α-position to the phosphorus atom) is created, two diastereoisomers should be found. In fact, only one diastereoisomer was separated as a pale-yellow oil to afford analytically pure product by column chromatography. Owing to the close values of R_f of the other diastereoisomer with an impurity, it appeared to be impossible to isolate it from the crude product by column chromatography. The ratios between the two diastereoisomers given in Table 2 were determined by integration of suitable signals in the ^{31}P NMR spectra of the crude products.

Table 2
^{31}P NMR data, chemical shift, and coupling constants

Product	Yield[a] (%)	^{31}P NMR/$CDCl_3$/H_3PO_4						Ratio[b]
		Major		*J* (Hz)	Minor		*J* (Hz)	
4a	49	24.31	7.44	18.7	26.71	6.81	16.1	69:31
4b	56	21.59	7.62	19.8	25.32	7.95	17.6	72:28
4c	47	24.51	7.03	17.5	22.01	7.56	18.3	68:32
4d	45	19.79	7.77	21.7	21.40	6.88	18.6	70:30
4e	50	21.97	7.55	20.1	27.75	6.66	17.5	84:16
4f	50	24.50	6.73	18.6	26.76	7.16	16.3	63:37
4g	53	21.72	6.85	19.4	24.00	7.22	17.3	75:25
4h	49	22.01	7.28	18.0	24.15	6.93	17.6	77:23
4i	48	19.81	7.61	21.5	21.66	6.75	19.1	78:22
4j	51	22.03	7.3	19.9	24.20	6.9	17.8	73:27

[a] Isolated yield of the major diastereoisomer.
[b] Determined by the integration of suitable signals in ^{31}P NMR spectra of the crude products.



1 **2** **5** **6** **4**

Scheme 1. Forming the corresponding Schiff's base **6**.

The ^{31}P NMR spectra of compound **4** showed four doublets due to the P–P splitting. Similar results have been reported by Yuan and others.[13,14] A comparison of the spectra of the diastereoisomers displayed differences in the chemical shifts of ^{31}P and in the P–P coupling constants. The chemical shifts in the ^{31}P NMR spectra of the two diastereoisomers are recognized by their identical coupling constants. For example, after flash column chromatography of **4c**, a mixture of two diastereoisomers was obtained as a pale-yellow oil exhibiting four doublets in the ^{31}P NMR spectrum (^{31}P NMR): δ 24.51 (d, ^3J = 17.5 Hz), 22.01 (d, ^3J = 18.3 Hz), 7.56 (d, ^3J = 18.3 Hz), 7.03 (d, ^3J = 17.5 Hz). The δ 24.51 and 22.01 were attributable to the P-atom of the diphenoxyphosphinyl group, and δ 7.56 and 7.03 to the P-atom of the *N*-phosphoryl group. The major diastereoisomer was separated as a pale-yellow oil from the crude product to afford analytically pure product by column chromatography. In the ^{13}C NMR spectra of **4a–j** (the major diastereoisomer), the NCP carbon atom appeared as a doublet (δ 48.94–53.24) due to the phosphorus atom with a coupling constant $^1J_{P,C}$ of about 160 Hz.

In conclusion, we have developed a convenient route for the diastereoselective synthesis of methyl 5-deoxy-5-(dialkylphosphono)-5-(dialkylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranosides with the aid of acetyl chloride. The reactions take place under mild conditions in moderate yields, and this makes it possible to introduce a wide range of substituents to the phosphorus atom. The intermolecular pathway of the formation of the P–C bond in the P–C–N fragment gives a good example of a Mannich-type reaction. Acetyl chloride accelerates the process of intramolecular dehydration of **5** forming the corresponding Schiff's base **6**.

3. Experimental

3.1. General experimental methods

All melting points were determined on a Yanaco apparatus, and are uncorrected. NMR spectra were measured on a Bruker AVANCE 300 NMR (300 MHz for ^1H, 75 MHz for ^{13}C and 121 MHz for ^{31}P) instrument in $CDCl_3$. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as the internal standard (δ = 0.0) for ^1H NMR, and the central line of $CDCl_3$ (δ = 77.0) for ^{13}C NMR spectra. Coupling constants (*J*) are given in Hertz. H_3PO_4 (85%) served as the external standard for ^{31}P NMR spectroscopy. High-resolution mass spectra (HRESIMS) were obtained on a Varian 7.0 T FTICR-MS spectrometer. IR spectra were recorded on a Equinox55 Spectrometer, and band positions are reported in wave numbers (cm^{-1}). Elemental analyses were obtained by Elementar Vario EL. Column chromatography was performed using silica gel H (100–200 μm, Ocean Chemical Factory of Qingdao). The solvent was dried with sodium and redistilled.

3.2. General procedure for synthesis of methyl 5-deoxy-5-(dialkylphosphono)-5-(dialkylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranosides

Methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**2**)[15] (303 mg, 1.5 mmol) was added dropwise to a stirred mixture of the dialkyl phosphoramidate **1** (1.5 mmol), the dialkyl phosphate **3** (1.5 mmol), and acetyl chloride (2 mL) at −20 °C. After 1 h stirring, the reaction mixture was allowed warm to 0 °C and stirring for another 6–8 h (TLC (silica gel) monitoring). The mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (silica gel, 6:1 AcOEt–petroleum ether (bp 60–90 °C)) to afford the pure mixtures of **4a–j**. One major diastereoisomer was isolated from the pure mixtures **4a–j** by further column chromatography (silica gel, 2:1 AcOEt–petroleum ether (bp 60–90 °C)).

3.2.1. Methyl 5-deoxy-5-(dimethylphosphono)-5-(di-*n*-propylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranoside (4a)

The product **4a** from the reaction of dipropyl phosphoramidate **1** (272 mg, 1.5 mmol) and dimethyl phosphate **3** (165 mg, 1.5 mmol) was obtained (349 mg, 49% yield) as a pale-yellow oil (major diastereoisomer): $[\alpha]_D^{20}$ −21 (*c* 1.0, $CHCl_3$). IR (KBr) ν cm^{-1}: 3147, 2973, 2225, 1726, 1402, 1043, 855, 747. ^1H NMR ($CDCl_3$): δ 4.86–4.83 (m, 1H, NCHP), 4.80 (s, 1H, C-1H), 4.49 (d, 1H, C-2H, *J* 5.6 Hz), 4.23 (d, 1H, C-3H, *J* 5.9 Hz), 4.07 (br, 1H, NH), 3.98–3.88 (m, 5H, C-4H, 2OCH_2CH$_2$CH$_3$), 3.77 (t, 6H, 2POCH$_3$), 3.25 (s, 3H, OCH$_3$), 1.67–1.56 (m, 4H, 2CH$_2$), 1.42–1.23 (m, 6H, CH$_3$CCH$_3$), 1.42 (s, 3H, OCH$_2$CH$_2$CH_3), 1.23 (s, 3H, OCH$_2$CH$_2$CH_3). ^{13}C NMR ($CDCl_3$): δ 112.73 (CH$_3$CCH$_3$), 106.78 (C-1), 85.11 (C-2), 80.97 (C-3), 75.49 (C-4, $^2J_{P-C4}$ 15.0 Hz), 68.13 (OCH$_2$, *J* 5.3 Hz), 67.91 (OCH$_2$, *J* 5.3 Hz), 54.69 (OCH$_3$), 53.64 (POCH$_3$, *J* 7.1 Hz), 53.17 (POCH$_3$, *J* 6.6 Hz), 49.10 (NCHP, *J* 160.3 Hz), 25.74, 24.32 (*C*H$_3$C*C*H$_3$), 23.61 (2OCH$_2$*C*H$_2$CH$_3$), 9.97 (2OCH$_2$CH$_2$*C*H$_3$). ^{31}P NMR ($CDCl_3$): δ 24.31 (d, ^3J 18.7 Hz), 7.44 (d, ^3J 18.7 Hz). ESIMS: [M+Na$^+$] *m*/*z* 498. HRESIMS: [M+Na]$^+$ calcd for $C_{17}H_{35}NO_{10}P_2Na^+$: 498.1628; found, 498.1623.

3.2.2. Methyl 5-deoxy-5-(diethylphosphono)-5-(di-*n*-propylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranoside (4b)

The product **4b** from the reaction of dipropyl phosphoramidate **1** (272 mg, 1.5 mmol) and diethyl phosphate **3** (207 mg, 1.5 mmol) was obtained (423 mg, 56% yield) as a pale-yellow oil (major diastereoisomer): $[\alpha]_D^{20}$ −24 (*c* 1.0, $CHCl_3$). IR (KBr): ν cm^{-1}: 350, 2978, 2225, 1728, 1476, 1400, 1055, 743. ^1H NMR (300 MHz, $CDCl_3$): δ 4.88–4.85 (m, 1H, NCHP), 4.80 (s, 1H, C-1H), 4.48 (d, 1H, C-2H, *J* 5.8 Hz), 4.18–4.09 (m, 6H, 2OCH$_2$, NH, C-3H), 3.99–3.90 (m, 5H, C-4H, 2OCH$_2$), 3.25 (s, 3H, OCH$_3$), 1.68–1.56 (m, 4H, 2CH$_2$), 1.42–1.232 (m, 12H, CH_3CCH_3, 2OCH$_2$CH_3), 0.88 (t, 6H, 2OCH$_2$CH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.59 (CH$_3$*C*CH$_3$), 106.71 (C-1), 85.24 (C-2), 81.20 (C-3), 75.34 (C-4, $^2J_{P-C4}$ 15.5 Hz), 67.95 (OCH$_2$, *J* 5.3 Hz), 67.68 (OCH$_2$, *J* 5.3 Hz), 62.81 (PO*C*H$_2$CH$_3$, *J* 7.4 Hz), 62.62 (PO*C*H$_2$CH$_3$, *J* 6.6 Hz), 54.64 (OCH$_3$), 49.75 (NCHP, *J* 159.8 Hz), 25.72, 24.24 (*C*H$_3$C*C*H$_3$), 23.59 (2OCH$_2$*C*H$_2$CH$_3$), 16.27 (2OCH$_2$*C*H$_3$), 9.94 (2OCH$_2$CH$_2$*C*H$_3$). ^{31}P NMR (121 MHz, $CDCl_3$): δ 21.59 (d, ^3J 19.8 Hz), 7.62 (d, ^3J 19.8 Hz). ESIMS: [M+Na$^+$] *m*/*z* 526. HRESIMS: [M+Na]$^+$ calcd for $C_{19}H_{39}NO_{10}P_2Na^+$: 526.1941; found, 526.1937.

3.2.3. Methyl 5-deoxy-5-(di-*n*-propylphosphono)-5-(di-*n*-propylphosphoryl amido)-2,3-*O*-isopropylidene-β-D-ribofuranoside (4c)

The product **4c** from the reaction of dipropyl phosphoramidate **1** (272 mg, 1.5 mmol) and dipropyl phosphate **3** (249 mg, 1.5 mmol) was obtained (375 mg, 47% yield) as a pale-yellow oil (major diastereoisomer): $[\alpha]_D^{20}$ −20 (*c* 1.0, $CHCl_3$). IR (KBr): ν cm^{-1}: 3161, 2965, 2356, 1728, 1402, 1239, 1058, 992, 869. ^1H NMR (300 MHz, $CDCl_3$): δ 5.09–5.07 (m, 1H, NCHP), 4.92 (s, 1H, C-1H), 4.51 (d, 1H, C-2H, *J* 6.1 Hz), 4.22 (d, 1H, C-3H, *J* 6.3 Hz), 4.08–3.98 (m, 6H, 2OCH$_2$, NH, C-4H), 3.94–3.90 (m, 4H, 2OCH$_2$), 3.36 (s, 3H, OCH$_3$), 1.68–1.58 (m, 4H, 2CH$_2$), 1.22 (s, 3H, CH$_3$CCH$_3$), 1.19 (s, 3H, CH$_3$CCH$_3$), 0.89 (t, 12H, 4OCH$_2$CH$_2$CH_3, *J* 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.48 (CH$_3$*C*CH$_3$), 110.16 (C-1), 84.46 (C-2), 81.67 (C-3), 75.39 (C-4, $^2J_{P-C4}$ 15.3 Hz), 69.26 (OCH$_2$, *J* 5.1 Hz), 69.14 (OCH$_2$, *J* 5.1 Hz), 68.15 (POCH$_2$CH$_2$CH$_3$, *J* 7.0 Hz), 68.00 (POCH$_2$CH$_2$CH$_3$, *J* 6.8 Hz), 55.84 (OCH$_3$), 51.13 (NCHP, *J* 156.6 Hz), 26.56, 26.38 (CH$_3$*C*CH$_3$), 26.04 (2OCH$_2$*C*H$_2$CH$_3$), 25.70 (2OCH$_2$*C*H$_2$CH$_3$), 23.55 (2OCH$_2$CH$_2$*C*H$_3$), 9.94 (2OCH$_2$CH$_2$*C*H$_3$). ^{31}P NMR (121 MHz, $CDCl_3$): δ 24.51 (d, ^3J 17.5 Hz), 7.03 (d, ^3J 17.5 Hz). ESIMS: [M+Na$^+$] *m*/*z* 554. HRESIMS: [M+Na]$^+$ calcd for $C_{21}H_{43}NO_{10}P_2Na^+$: 554.2254; found, 554.2249.

3.2.4. Methyl 5-deoxy-5-(diisopropylphosphono)-5-(di-*n*-propylphosphoryl amido)-2,3-*O*-isopropylidene-β-D-ribofuranoside (4d)

The product **4d** from the reaction of dipropyl phosphoramidate **1** (272 mg, 1.5 mmol) and diisopropyl phosphate **3** (249 mg, 1.5 mmol) was obtained (359 mg, 45% yield) as a pale-yellow oil (major diastereoisomer): $[\alpha]_D^{20}$ −21 (*c* 1.0, $CHCl_3$). IR (KBr): *ν* cm^{-1}: 3129, 2978, 2227, 2024, 1730, 1401, 1091, 1012. ^1H NMR ($CDCl_3$): *δ* 4.86–4.83 (m, 1H, NCHP), 4.79 (s, 1H, C-1H), 4.73 (d, 1H, C-2H, *J* 6.0 Hz), 4.47 (d, 1H, C-3H, *J* 5.8 Hz), 4.25–4.15 (m, 4H, $2CH_3CHCH_3$, NH, C-4H), 4.04–3.88 (m, 4H, $2OCH_2$), 3.25 (s, 3H, OCH_3), 1.67–1.58 (m, 4H, $2CH_2$), 1.41–1.18 (m, 18H, $2CH_3CHCH_3$, CH_3CCH_3), 0.92–0.84 (m, 6H, $2OCH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$): *δ* 112.60 (CH_3CCH_3), 106.75 (C-1), 85.23 (C-2), 81.10 (C-3), 75.32 (C-4, $^2J_{P-C4}$ 14.9 Hz), 70.01 (POCH, *J* 6.9 Hz), 69.70 (OCH_2, *J* 6.9 Hz), 63.02 ($POCH_2CH_2CH_3$, *J* 7.2 Hz), 62.69 ($POCH_2CH_2CH_3$, *J* 7.0 Hz), 54.21 (OCH_3), 53.24 (NCHP, *J* 159.6 Hz), 26.40, 26.19 (CH_3CCH_3), 23.50 ($2OCH_2CH_2CH_3$), 23.45 ($2CH_3CHCH_3$), 10.01 ($2OCH_2CH_2CH_3$). ^{31}P NMR ($CDCl_3$): *δ* 19.79 (d, ^3J 21.7 Hz), 7.77 (d, ^3J 21.7 Hz). ESIMS: $[M+Na^+]$ *m*/*z* 554. HRESIMS: $[M+Na]^+$ calcd for $C_{21}H_{43}NO_{10}P_2Na^+$: 554.2254; found, 554.2249. Anal. Calcd for $C_{21}H_{43}NO_{10}P_2$: C, 47.45; H, 8.15; N, 2.64. Found: C, 47.70; H, 8.26; N, 2.77.

3.2.5. Methyl 5-deoxy-5-(dibutylphosphono)-5-(di-*n*-propylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranosidephosphonate (4e)

The product **4e** from the reaction of dipropyl phosphoramidate **1** (272 mg, 1.5 mmol) and dibutyl phosphate **3** (291 mg, 1.5 mmol) was obtained (420 mg, 50% yield) as a pale-yellow oil (major diastereoisomer): $[\alpha]_D^{20}$ −21 (*c* 1.0, $CHCl_3$). IR (KBr): *ν* cm^{-1}: 3198, 2988, 1721, 1476, 1401, 1080, 855. ^1H NMR ($CDCl_3$): *δ* 4.85–4.83 (m, 1H, NCHP), 4.79 (s, 1H, C-1H), 4.48 (d, 1H, C-2H, *J* 5.7 Hz), 4.25 (d, 1H, C-3H, *J* 6.1 Hz), 4.14–4.00 (m, 6H, $2OCH_2$, NH, C-4H), 3.96–3.89 (m, 4H, $2OCH_2$), 3.25 (s, 3H, OCH_3), 1.97–1.95 (m, 4H, $2CH_2$), 1.65–1.57 (m, 4H, $2CH_2$), 1.44–1.32 (m, 6H, CH_3CCH_3), 1.23–1.15 (m, 4H, $2CH_2$), 0.92–0.84 (m, 12H, 4H, $4CH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$): *δ* 112.66 (CH_3CCH_3), 106.74 (C-1), 82.26 (C-2), 81.14 (C-3), 75.48 (C-4, $^2J_{P-C4}$ 14.8 Hz), 68.16 ($POCH_2$, *J* 5.5 Hz), 67.88 ($POCH_2$, *J* 5.1 Hz), 66.82 ($POCH_2$, *J* 7.2 Hz), 66.58 ($POCH_2$, *J* 7.2 Hz), 54.67 (OCH_3), 49.60 (NCHP, *J* 159.8 Hz), 25.76, 24.29 ($2CH_3CCH_3$), 23.62, 19.09, 18.64 ($6CH_2CH_3$), 13.53, 9.98 ($4CH_2CH_3$). ^{31}P NMR ($CDCl_3$): *δ* 21.97 (d, ^3J 20.1 Hz), 7.55 (d, ^3J 20.1 Hz). ESIMS: $[M+Na^+]$ *m*/*z* 582. HRESIMS: $[M+Na]^+$ calcd for $C_{23}H_{47}NO_{10}P_2Na^+$: 582.2567; found, 582.2563.

3.2.6. Methyl 5-deoxy-5-(dimethylphosphono)-5-(diethylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranoside (4f)

The product **4f** from the reaction of diethyl phosphoramidate **1** (230 mg, 1.5 mmol) and dimethyl phosphate **3** (165 mg, 1.5 mmol) was obtained (336 mg, 50% yield) as a pale-yellow oil (major diastereoisomer): $[\alpha]_D^{20}$ −25 (*c* 1.0, $CHCl_3$). IR (KBr): *ν* cm^{-1}: 3169, 2988, 1721, 1476, 1401, 1080, 855. ^1H NMR ($CDCl_3$): *δ* 5.13–5.11 (m, 1H, NCHP), 5.00 (s, 1H, C-1H), 4.92 (d, 1H, C-2H, *J* 5.7 Hz), 4.59 (d, 1H, C-3H, *J* 6.2 Hz), 4.28 (br, 1H, NH), 4.20–4.08 (m, 5H, $2OCH_2$, C-4H), 3.88–3.81 (m, 4H, $2POCH_3$), 3.33 (s, 3H, OCH_3), 1.36–1.26 (m, 12H, $2CH_3CHCH_3$, $2OCH_2CH_3$). ^{13}C NMR ($CDCl_3$): *δ* 110.39 (CH_3CCH_3), 106.76 (C-1), 85.01 (C-2), 80.86 (C-3), 75.57 (C-4, $^2J_{P-C4}$ 11.8 Hz), 62.53 ($POCH_2$, *J* 5.1 Hz), 62.34 ($POCH_2$, *J* 5.1 Hz), 54.61 (OCH_3), 53.50 ($POCH_3$, *J* 7.3 Hz), 53.12 ($POCH_3$, *J* 6.4 Hz), 48.94 (NCHP, *J* 159.6 Hz), 25.68, 24.27 (CH_3CCH_3), 16.00, 15.91 ($2OCH_2CH_3$). ^{31}P NMR ($CDCl_3$): *δ* 24.50 (d, ^3J 18.6 Hz), 6.73 (d, ^3J 18.6 Hz). ESIMS: $[M+Na^+]$ *m*/*z* 470. HRESIMS: $[M+Na]^+$ calcd for $C_{15}H_{31}NO_{10}P_2Na^+$: 470.1315; found, 470.1321. Anal. Calcd for $C_{15}H_{31}NO_{10}P_2$: C, 40.27; H, 6.98; N, 3.13. Found: C, 39.98; H, 7.26; N, 2.79.

3.2.7. Methyl 5-deoxy-5-(diethylphosphono)-5-(diethylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranoside (4g)

The product **4g** from the reaction of diethyl phosphoramidate **1** (230 mg, 1.5 mmol) and diethyl phosphate **3** (207 mg, 1.5 mmol) was obtained (378 mg, 53% yield) as a pale-yellow oil (major diastereoisomer): $[\alpha]_D^{20}$ −21 (*c* 1.0, $CHCl_3$). IR (KBr): *ν* cm^{-1}: 3190, 2981, 1725, 1400, 1210, 1101, 865. ^1H NMR ($CDCl_3$): *δ* 5.15–5.13 (m, 1H, NCHP), 4.98 (s, 1H, C-1H), 4.93 (d, 1H, C-2H, *J* 5.5 Hz), 4.55 (d, 1H, C-3H, *J* 5.9 Hz), 4.32–4.03 (m, 10H, $4OCH_2$, NH, C-4H), 3.33 (s, 3H, OCH_3), 1.50–1.45 (m, 6H, CH_3CCH_3), 1.38–1.26 (m, 12H, $4OCH_2CH_3$). ^{13}C NMR ($CDCl_3$): *δ* 112.43 (CH_3CCH_3), 106.63 (C-1), 84.97 (C-2), 80.85 (C-3), 75.45 (C-4, $^2J_{P-C4}$ 14.3 Hz), 62.90 (OCH_2, *J* 4.3 Hz), 62.62 (OCH_2, *J* 7.3 Hz), 62.33 (OCH_2CH_3, *J* 5.0 Hz), 62.62 (OCH_2CH_3, *J* 5.0 Hz), 54.44 (OCH_3), 49.37 (NCHP, *J* 160.1 Hz), 25.58, 24.13 (CH_3CCH_3), 16.15, 16.08, 15.89, 15.80 ($4OCH_2CH_3$). ^{31}P NMR ($CDCl_3$): *δ* 21.72 (d, ^3J 19.4 Hz), 6.85 (d, ^3J 19.4 Hz). ESIMS: $[M+Na^+]$ *m*/*z* 498. HRESIMS: $[M+Na]^+$ calcd for $C_{17}H_{35}NO_{10}P_2Na^+$: 498.1628; found, 498.1631. Anal. Calcd for $C_{17}H_{35}NO_{10}P_2$: C, 42.95; H, 7.42; N, 2.95. Found: C, 42.80; H, 7.10; N, 3.12.

3.2.8. Methyl 5-deoxy-5-(di-*n*-propylphosphono)-5-(diethylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranoside (4h)

The product **4h** from the reaction of diethyl phosphoramidate **1** (230 mg, 1.5 mmol) and dipropyl phosphate **3** (249 mg, 1.5 mmol) was obtained (370 mg, 49% yield) as a pale-yellow oil (major diastereoisomer): $[\alpha]_D^{20}$ −22 (*c* 1.0, $CHCl_3$). IR (KBr): *ν* cm^{-1}: 3212, 2973, 1716, 1636, 1389, 1092, 866. ^1H NMR (300 MHz, $CDCl_3$): *δ* 5.07–5.04 (m, 1H, NCHP), 4.91 (s, 1H, C-1H), 4.81 (d, 1H, C-2H, *J* 5.9 Hz), 4.22 (d, 1H, C-3H, *J* 6.0 Hz), 4.43 (br, 1H, NH), 4.25–3.95 (m, 9H, $4OCH_2$, C-4H), 3.34 (s, 3H, OCH_3), 2.06–1.95 (m, 4H, $2CH_2$), 1.39–1.18 (m, 12H, CH_3CCH_3, $2OCH_2CH_3$), 0.93–0.86 (m, 6H, $2OCH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 112.38 (CH_3CCH_3), 110.22 (C-1), 86.16 (C-2), 84.38 (C-3), 81.63 (C-4, $^2J_{P-C4}$ 14.9 Hz), 68.37 (OCH_2, *J* 8.4 Hz), 68.27 (OCH_2, *J* 8.3 Hz), 62.97 ($POCH_2CH_2CH_3$, *J* 6.5 Hz), 62.88 ($POCH_2CH_2CH_3$, *J* 6.3 Hz), 55.83 (OCH_3), 51.02 (NCHP, *J* 157.2 Hz), 26.48, 26.12 (CH_3CCH_3), 23.81 ($2OCH_2CH_2CH_3$), 16.03 ($2OCH_2CH_3$), 9.98 ($2OCH_2CH_2CH_3$). ^{31}P NMR (121 MHz, $CDCl_3$): *δ* 22.01 (d, ^3J 18.0 Hz), 7.28 (d, ^3J 18.0 Hz). ESIMS: $[M+Na^+]$ *m*/*z* 526. HRESIMS: $[M+Na]^+$ calcd for $C_{19}H_{39}NO_{10}P_2Na^+$: 5526.1941; found, 526.1938. Anal. Calcd for $C_{19}H_{39}NO_{10}P_2$: C, 45.33; H, 7.81; N, 2.78. Found: C, 45.58; H, 7.61; N, 3.12.

3.2.9. Methyl 5-deoxy-5-(diisopropylphosphono)-5-(diethylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranoside (4i)

The product **4i** from the reaction of diethyl phosphoramidate **1** (230 mg, 1.5 mmol) and diisopropyl phosphate **3** (249 mg, 1.5 mmol) was obtained (362 mg, 48% yield) as a pale-yellow oil (major diastereoisomer): $[\alpha]_D^{20}$ −18 (*c* 1.0, $CHCl_3$). IR (KBr): *ν* cm^{-1}: 3186, 2988, 1712, 1411, 1216, 1096, 858. ^1H NMR (300 MHz, $CDCl_3$): *δ* 4.94–4.90 (m, 1H, NCHP), 4.86 (s, 1H, C-1H), 4.78 (d, 1H, C-2H, *J* 6.2 Hz), 4.54 (d, 1H, C-3H, *J* 5.8 Hz), 4.24–4.02 (m, 8H, $2OCH_2$, $2CH_3CHCH_3$, NH, C-4H), 3.33 (s, 3H, OCH_3), 1.49 (s, 3H, CH_3CCH_3), 1.38–1.15 (m, 21H, $2CH_3CHCH_3$, CH_3CCH_3, $2OCH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 112.55 (CH_3CCH_3), 106.73 (C-1), 85.25 (C-2), 81.09 (C-3), 75.53 (C-4, $^2J_{P-C4}$ 14.8 Hz), 71.91 (POCH, *J* 7.2 Hz), 71.60 (OCH_2, *J* 7.6 Hz), 62.61 ($POCH_2CH_3$, *J* 4.8 Hz), 62.34 ($POCH_2CH_3$, *J* 5.8 Hz), 54.67 (OCH_3), 50.54 (NCHP, *J* 162.2 Hz), 25.75, 24.23 (CH_3CCH_3), 23.80, 23.45 ($2CH_3CCH_3$), 16.15, 15.99 ($2OCH_2CH_3$). ^{31}P NMR (121 MHz, $CDCl_3$): *δ* 19.81 (d, ^3J 21.5 Hz), 7.61 (d, ^3J 21.5 Hz). ESIMS: $[M+Na^+]$ *m*/*z* 526. HRESIMS: $[M+Na]^+$ calcd for $C_{19}H_{39}NO_{10}P_2Na^+$: 526.1941; found, 526.1940. Anal. Calcd for $C_{19}H_{39}NO_{10}P_2$: C, 45.33; H, 7.81; N, 2.78. Found: C, 45.01; H, 7.46; N, 3.02.

3.2.10. Methyl 5-deoxy-5-(dibutylphosphono)-5-(diethylphosphorylamido)-2,3-*O*-isopropylidene-β-D-ribofuranoside (4j)

The product **4j** from the reaction of diethyl phosphoramidate **1** (230 mg, 1.5 mmol) and diisopropyl phosphate **3** (291 mg, 1.5 mmol) was obtained (407 mg, 51% yield) as a pale-yellow oil (major diastereoisomer): $[\alpha]_D^{20}$ −19 (*c* 1.0, $CHCl_3$). IR (KBr): ν cm^{-1}: 3196, 2983, 1723, 1408, 1202, 1088, 861. ^1H NMR (300 MHz, $CDCl_3$): δ 5.08–5.06 (m, 1H, NCHP), 4.89 (s, 1H, C-1H), 4.84 (d, 1H, C-2H, *J* 5.8 Hz), 4.79 (d, 1H, C-3H, *J* 5.6 Hz), 4.48 (m, 2H, NH, C-4H), 4.22–3.95 (m, 8H, $4OCH_2$), 3.24 (s, 3H, OCH_3), 1.64–1.55 (m, 4H, $2CH_2$), 1.41–1.17 (m, 16H, $2CH_2$, $2OCH_2CH_3$, CH_3CCH_3), 0.86 (t, 6H, $2CH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.44 (CH_3CCH_3), 106.58 (C-1), 85.08 (C-2), 81.00 (C-3), 75.29 (C-4, $^2J_{P-C4}$ 14.9 Hz), 66.41 ($POCH_2$, *J* 6.1 Hz), 66.22 ($POCH_2$, *J* 6.9 Hz), 62.38 ($POCH_2$, *J* 4.9 Hz), 62.17 ($POCH_2$, *J* 4.8 Hz), 54.47 (OCH_3), 49.49 (NCHP, *J* 160.0 Hz), 32.27 ($2CH_2$), 25.61, 24.12 ($2CH_3CCH_3$), 18.49 ($2CH_2$), 15.75 ($2OCH_2CH_3$), 13.38 ($2CH_2CH_2CH_3$). ^{31}P NMR (121 MHz, $CDCl_3$): δ 22.03 (d, ^3J 19.9 Hz), 7.3 (d, ^3J 19.9 Hz). ESIMS: $[M+Na^+]$ *m*/*z* 554. HRESIMS: $[M+Na]^+$ calcd for $C_{21}H_{43}NO_{10}P_2Na^+$: 554.2254; found, 554.2248. Anal. Calcd for $C_{21}H_{43}NO_{10}P_2$: C, 47.45; H, 8.15; N, 2.64. Found: C, 47.40; H, 7.95; N, 2.84.

Acknowledgments

We thank the Committee of Science and Technology of Tianjin (07JCZDJC04800) and Nankai University (J02044 to Z. W. Miao) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.06.009.

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