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A Stepwise One-Pot Synthesis of Aryl *N*-Phosphonamidothionate Derivatives of Nucleosides

Zhi-Wei Miao,[1] Hua Fu,[1] Guang-Zhong Tu,[2] Ji-Gang Zhu,[1] Hui-Wang Ai,[1] and Yu-Fen Zhao[1]

[1]*The Key Laboratory of Bioorganic Phosphorus Chemistry, Ministry of Education, Department of Chemistry, School of Life Sciences and Engineering, Tsinghua University, Beijing 100084, People's Republic of China*

[2]*Beijing Institute of Microchemistry, Beijing 100091, People's Republic of China*

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ABSTRACT: *Novel aryl N-phosphonamidothionate derivatives of nucleosides as membrane-soluble prodrugs of bioactive free nucleotides have been prepared by phosphochloridothioate chemistry. Unprotected nucleosides, for example uridine and adenosine, were used; phosphorylation took place selectively at the 5′-position.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:62–66, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10080

INTRODUCTION

Phosphate triester derivatives of nucleosides have been prepared as membrane-soluble prodrugs of bioactive nucleotides and have been evaluated against HIV-1 in vitro. Nucleoside analogues act only after intracellular conversion to their 5′-triphosphate derivatives [1]. This dependence of nucleoside analogues on host kinase can be a major limitation that cannot be easily overcome by the use of simple nucleotides, as their charges greatly impede membrane penetration [2]. Consequently, there was much interest in the use of masked phosphate esters as membrane-soluble depot forms of the bioactive nucleotides for chemotherapeutic nucleoside analogues [3–6]. Recently, MeGuigan reported that phosphate triester derivatives of AZT bearing amino acid moieties did have anti-HIV activity [7].

The relative metabolic stability of nucleoside-5′-phosphorothioates is well documented; for instance, AMP-S is relatively resistant to enzymatic transformations by adenylate deaminase, adenylate kinase, and 5′-nucleotidase, and ATP-α-*S* diastereoisomers exhibit selective metabolic stability [8,9].

For developing a new type of prodrugs, herein we report an efficient method to synthesize different aryl thiophosphoramidate derivatives of nucleosides. The target compounds were synthesized as shown in Schemes 1 and 2, phenylphosphonothioic dichloride (**1**) being used as a starting material. The key step was the coupling of nucleosides or their analogues with aryl methoxyaminoacyl thiophosphorochloredates (**3**) to form new, conjugated compounds **5**.

RESULTS AND DISCUSSION

Reactions of the hydrochlorides of amino acid methyl esters **2** with phenylphosphonothioic

Correspondence to: Yu-Fen Zhao; e-mail: tp-dch@tsinghua.edu.cn.
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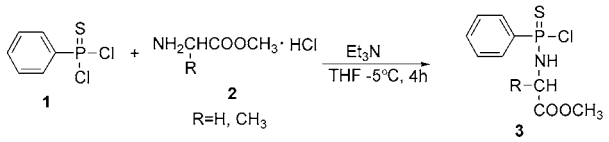


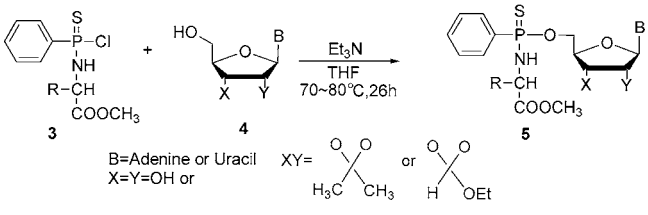
1 2 3

SCHEME 1

dichloride (**1**) were performed at −5°C under a nitrogen atmosphere (Scheme 1). Triethylamine was added via a syringe to the stirred solutions. Each reaction was monitored by ^{31}P NMR spectroscopy. It was found that phenylphosphonothioic dichloride (**1**) with a ^{31}P NMR shift at $\delta = 76$ was converted into **3** with $\delta = 57$, within approximately 4 h, then a solution of the nucleoside or its analogue **4** and triethylamine in pyridine or THF was added to the reaction solution (Scheme 2). After 26 h at 70–80°C the reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in chloroform and washed with 1 M hydrochloric acid solution, saturated sodium bicarbonate solution, and then water. The organic phase was dried ($MgSO_4$) and evaporated under a vacuum, and the residue was purified by chromatography on silica by elution with 5% methanol in chloroform. Pooling and evaporation of appropriate fractions gave the product **5** in 69–86% yields.

Although unprotected nucleosides, for example uridine and adenosine, were used, phosphorylation took place selectively at the 5′-position (^{1}H and ^{13}C NMR). Aryl thiophosphoramidate derivatives of the nucleosides **5** were obtained as a mixture of diastereoisomers because of the chirality at the phosphorus center. Hence the ^{31}P NMR chemical shifts appeared as a pair of peaks at about $\delta = 72$. The dissolution of the nucleoside is essential for the occurrence of the reaction. Table 1 lists the products of aryl thiophosphoramidate derivatives of nucleosides **5**.

Formation of **5b** was monitored by ^{31}P NMR spectroscopy, as shown in Figs. 1 and 2. The starting material phenylphosphonothioic dichloride (**1**) in THF shows a ^{31}P NMR resonates at $\delta = 76$. After the solution of amino acid methyl ester hydrochloride (**2**) and triethylamine had been added to the



3 4 5

SCHEME 2

TABLE 1 Products of Aryl Thiophosphoramidate Derivatives of Nucleosides

5	*R*	*Nucleoside 4*	*Yield (%)*
5a	H	Adenosine	71.2
5b	CH_3	Adenosine	68.8
5c	H	Uridine	74.6
5d	CH_3	Uridine	78.2
5e	H	2′,3′-O-Isopropylidene uridine	80.1
5f	CH_3	2′,3′-O-Isopropylidene uridine	81.4
5g	CH_3	2′,3′-O-Ethoxymethylidene adenosine	85.8

solution of **1**, the peak at ^{31}P NMR $\delta = 76$ disappeared in 4 h and a pair of new peaks at ^{31}P NMR $\delta = 57.91$ and 57.12 had emerged, corresponding to compound **3b** (Fig. 1). When a nucleoside or its analogue **4** was added, the double peaks at $\delta = 70.37$ and 71.05 appeared corresponding to compound **5b** (Fig. 2). After 26 h, only a pair of peaks at about ^{31}P NMR $\delta = 71$ were observed. Triethylamine acted both as a catalytic reagent and for neutralizing the hydrochloride produced in the reactions.

In this article, a convenient and efficient approach for the syntheses of aryl thiophosphoramidate derivatives of nucleosides under mild conditions has been developed. In the first step only one chloride of the phenylphosphonothioic dichloride is displaced by the amino acid ester to form a new phosphorus–nitrogen bond. Nucleoside thiophosphorylation with high selectivity takes place at the 5′-position rather than at 2′ or 3′-position. The reaction is a convenient two-step, one-pot synthesis, and the intermediate need not be separated in reaction. More detailed investigations into these compounds and their biological activity are currently underway.

EXPERIMENTAL

General Information

All glassware was dried in an oven for at least 3 h at 120°C prior to use. Air sensitive materials were

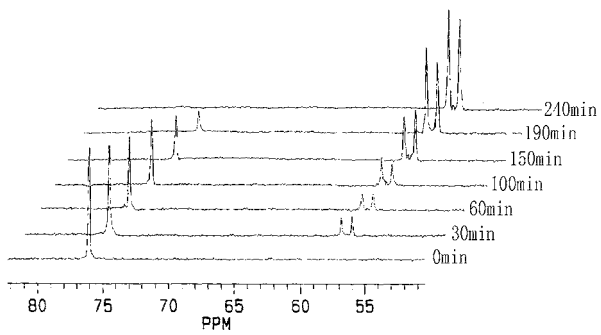


FIGURE 1 The stack ^{31}P NMR spectra of formation of compound **3b**.

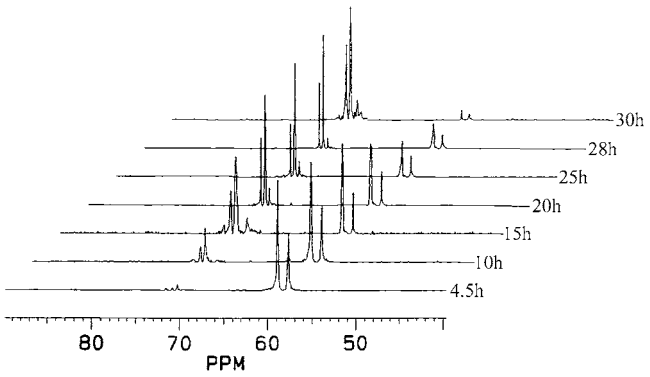


FIGURE 2 The stack ^{31}P NMR spectra of formation of compound **5b**.

transferred under a nitrogen atmosphere. THF and triethylamine were dried over Na and CaH_2, respectively. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 500 spectrometer. TMS ($\delta = 0.0$) and $CDCl_3$ ($\delta = 7.24$) were references for ^1H and ^{13}C NMR spectra, respectively. ^{13}C NMR spectra were all taken under ^1H decoupled and ^{31}P coupled conditions. ^{31}P NMR spectra were taken on a Bruker AC 200 spectrometer at 81 MHz under ^1H decoupled conditions. ^{31}P NMR chemical shifts are reported in ppm downfield (+) or upfield (−) from external 85% H_3PO_4 as a reference. Mass spectra were taken on a Bruker Esquire-LC mass spectrometer operated in positive and negative ion mode.

*Syntheses of Phenylphosphonothioic Dichloride (**1**), Amino Acid Methyl Ester Hydrochlorides (**2**), and Protected Nucleosides (**4**)*

The preparation of phenylphosphonothioic dichloride (**1**), amino acid methyl ester hydrochlorides (**2**), and protected nucleosides (**4**) were carried out according to the literature [10–13]. All physical constants and spectroscopic data of the products synthesized were in agreement with the literature.

General Procedure for Syntheses of Alkyl Thiophosphoramidate Derivatives of Nucleosides

A solution of triethylamine (1.4 ml, 1.0 g, 10.0 mmol) in THF (10 ml) was added dropwise with vigorous stirring to a solution of each amino acid methyl ester hydrochloride (**2**, 5.02 mmol) and phenylphosphonothioic dichloride (**1**, 1.06 g, 5.02 mmol) in THF (10 ml) at −5°C over a period of 15 min. The reaction mixture was slowly warmed to ambient temperature, with stirring over 4 h, and the solvent was then removed in vacuo. The residue was treated with THF (15 ml), the mixture was filtered, and the filtrate was evaporated in a vacuum to yield the product **3** as a colorless oil (5.02 mmol, 100%). A solution of each nucleoside **4** (5.02 mmol) was dissolved in pyridine (10 ml), and the selected alkyl methoxyalaninyl thiophosphorochloridate (**3**) (5.02 mmol) and triethylamine (0.7 ml, 0.5 g, 5.02 mmol) were added with vigorous stirring.

After 26 h at 70–80°C, the solvent was removed under a vacuum. The residue was dissolved in chloroform (10 ml) and washed with 1 M hydrochloric acid solution (2 × 15 ml), saturated sodium bicarbonate solution (2 × 10 ml), and then water (3 × 15 ml). The organic phase was dried ($MgSO_4$) and evaporated under a vacuum, and the residue was purified by chromatography on silica by elution with 5% methanol in chloroform. Pooling and evaporation of appropriate fractions gave each product **5**.

Compound **5a** *(Diastereoisomers).* MeOH: $CHCl_3$ (1:50) as eluent ($R_f = 0.71$ for TLC). 1.76 g (yield 71.2%). ^{31}P NMR ($CDCl_3$, δ, J: Hz): δ 71.47, 70.66; ^1H NMR (500 MHz, $CDCl_3$): δ 8.22 (1H, s, H-8), 8.07 (1H, s, H-2), 7.58–7.67 (2H, m, Ph), 7.36 (2H, bs, NH_2), 7.27 (3H, m, Ph), 6.61, 6.60 (1H, d, $^3J = 6.0$, H-1′), 5.59 (1H, br, 2′-OH), 5.44 (1H, br, 3′-OH), 5.16 (1H, s, P-NH), 4.69 (1H, m, H-2′), 4.41 (1H, m, H-3′), 4.16 (1H, m, H-4′), 3.80 (2H, m, H-5′), 3.66 (2H, m, H-α), 3.51 (3H, s, $OC\underline{H}_3$); ^{13}C NMR (500 MHz, $CDCl_3$): δ 173.54 ($\underline{C}OOMe$), 152.53 (C-2), 150.28 (C-6), 144.53 (Ph-jpso), 143.60 (C-4), 140.13 (Ph-para), 138.22 (C-8), 131.47 (Ph-ortho), 129.60 (Ph-meta), 121.07 (C-5), 91.28 (C-4′), 87.68 (C-1′), 82.35 (C-3′), 80.24 (C-2′), 64.15 (C-5′), 61.51 (C-α); ESI-MS (pos.): *m/z* 495 $(M+H)^+$; ESI-MS (neg.): *m/z* 493 $(M-H)^-$; HRMS (FAB) *m/z* calcd for $C_{19}H_{23}N_6O_6PS$ $(M+H)^+$ 495.4680, found 495.4683.

Compound **5b** *(Diastereoisomers).* MeOH: $CHCl_3$ (1:50) as eluent ($R_f = 0.76$ for TLC). 1.75 g (yield 68.8%). ^{31}P NMR ($CDCl_3$, δ, J: Hz): δ 71.05, 70.37; ^1H NMR (500 MHz, $CDCl_3$): δ 8.16 (1H, s, H-8), 8.01 (1H, s, H-2), 7.71–7.89 (2H, m, Ph), 7.35–7.62 (5H, m, Ph, NH_2), 6.44, 6.43 (1H, d, $^3J = 6.0$, H-1′), 5.57 (1H, br, 2′-OH), 5.41 (1H, br, 3′-OH), 5.24 (1H, s, P-NH), 4.64 (1H, m, H-2′), 4.31 (1H, m, H-3′), 4.18 (1H, m, H-4′), 3.83 (2H, m, H-5′), 3.78 (1H, m, H-α), 3.60 (3H, s, $OC\underline{H}_3$), 1.08, 1.07 (3H, d, $^3J = 6.0$, β-CH_3); ^{13}C NMR (500 MHz, $CDCl_3$): δ 174.24 ($\underline{C}OOMe$), 158.63 (C-2), 155.08 (C-6), 151.30 (C-4), 143.28, 143.16 (C-8), 141.91 (Ph-jpso), 139.36 (Ph-para), 130.71, 130.57 (Ph-ortho), 129.30, 129.21 (Ph-meta), 122.07 (C-5), 90.98 (C-4′), 88.38 (C-1′), 76.35 (C-3′), 73.24 (C-2′), 64.15 (C-5′), 63.70 (C-α), 52.07 ($O\underline{C}H_3$), 26.35 (C-β); ESI-MS (pos.):

m/z 509 $(M+H)^+$; ESI-MS (neg.): *m/z* 507 $(M-H)^-$; HRMS (FAB) *m/z* calcd for $C_{20}H_{25}N_6O_6PS$ $(M+H)^+$ 509.4951, found 509.4947.

Compound **5c** *(Diastereoisomers)*. MeOH: $CHCl_3$ (1:50) as eluent ($R_f = 0.64$ for TLC). 1.76 g (yield 74.6%). ^{31}P NMR ($CDCl_3$, δ, J: Hz): δ 71.85, 71.06; ^1H NMR (500 MHz, $CDCl_3$): δ 11.38 (1H, br, H-3), 7.86, 7.85 (1H, d, $^3J = 5$, H-6), 7.53–7.67 (2H, m, Ph), 7.18–7.27 (3H, m, Ph), 5.87 (2H, m, H-1′,5), 5.51 (1H, br, 3′-OH), 5.33 (1H, br, 2′-OH), 4.33 (2H, m, H-2′,3′), 4.21 (1H, m, H-4′), 4.07 (2H, m, H-5′), 3.80 (2H, m, H-α), 3.74 (3H, s, $OC\underline{H}_3$), 3.32 (1H, m, P-NH); ^{13}C NMR (500 MHz, $CDCl_3$): δ 173.24 ($\underline{C}OOMe$), 163.70 (C-2), 150.43 (C-4), 140.67, 140.52 (Ph-jpso), 139.65, 139.52 (Ph-para), 136.11 (C-6), 129.89, 129.80 (Ph-ortho), 128.23, 128.12 (Ph-meta), 109.36 (C-5), 87.23 (C-1′), 83.76 (C-4′), 82.36 (C-2′), 70.42 (C-3′), 61.33 (C-5′), 54.79 ($O\underline{C}H_3$), 46.82 (C-α); ESI-MS (pos.): *m/z* 472 $(M+H)^+$; ESI-MS (neg.): *m/z* 470 $(M-H)^-$; HRMS (FAB) *m/z* calcd for $C_{18}H_{22}N_3O_8PS$ $(M+H)^+$ 472.4285, found 472.4285.

Compound **5d** *(Diastereoisomers)*. MeOH: $CHCl_3$ (1:50) as eluent ($R_f = 0.70$ for TLC). 1.90 g (yield 78.2%). ^{31}P NMR ($CDCl_3$, δ, J: Hz): δ 72.31, 71.60; ^1H NMR (500 MHz, $CDCl_3$): δ 11.43 (1H, br, H-3), 8.00, 7.99 (1H, d, $^3J = 5$, H-6), 7.63–7.71 (2H, m, Ph), 7.31 (3H, m, Ph), 5.88 (2H, m, H-1′, 5), 5.51 (1H, br, 3′-OH), 5.37 (1H, br, 2′-OH), 4.86 (1H, m, $OC\underline{H}Me_2$), 4.37 (2H, m, H-2′,3′), 4.28 (1H, m, H-4′), 4.17 (2H, m, H-5′), 3.85 (2H, m, H-α), 3.64 (3H, s, $OC\underline{H}_3$), 3.33 (1H, m, P-NH), 1.29 (6H, m, $OCH(C\underline{H}_3)_2$), 1.08, 1.07 (3H, d, $^3J = 6.0$, β-CH_3); ^{13}C NMR (500 MHz, $CDCl_3$): δ 178.33 ($\underline{C}OOMe$), 165.26 (C-2), 148.33 (C-4), 145.77 (Ph-jpso), 136.53 (Ph-para), 134.61 (C-6), 128.63 (Ph-ortho), 121.33, 121.21 (Ph-meta), 111.46 (C-5), 87.25 (C-1′), 84.26 (C-4′), 83.86 (C-2′), 71.42 (C-3′), 64.83 (C-5′), 52.99 ($O\underline{C}H_3$), 46.82 (C-α), 26.45 (C-β); ESI-MS (pos.): *m/z* 486 $(M+H)^+$; ESI-MS (neg.): *m/z* 484 $(M-H)^-$; HRMS (FAB) *m/z* calcd for $C_{19}H_{24}N_3O_8PS$ $(M+H)^+$ 486.4551, found 486.4552.

Compound **5e** *(Diastereoisomers)*. MeOH: $CHCl_3$ (1:50) as eluent ($R_f = 0.85$ for TLC). 2.05 g (yield 80.1%). ^{31}P NMR ($CDCl_3$, δ, J: Hz): δ 71.23, 70.36; ^1H NMR (500 MHz, $CDCl_3$): δ 9.11, 9.10 (1H, d, $^3J = 5.5$, H-3), 7.82–8.10 (2H, m, Ph), 7.66–7.81 (3H, m, Ph), 7.59, 7.58 (1H, d, $^3J = 4.5$, H-6), 5.82 (2H, m, H-1′,5), 4.93 (2H, m, H-2′, 3′), 4.42 (1H, m, H-4′), 4.00 (2H, m, H-5′), 3.63 (3H, s, $OC\underline{H}_3$), 3.57 (2H, m, H-α), 3.35 (1H, m, P-NH), 1.53 (3H, s, $C\underline{H}_3$), 1.33 (3H, s, $C\underline{H}_3$); ^{13}C NMR (500 MHz, $CDCl_3$): δ 171.25 ($\underline{C}OOMe$), 169.02 (C-4), 145.39, 145.36 (C-6), 141.99 (C-2), 137.93, 137.82 (Ph-jpso), 135.94, 135.52 (Ph-para), 131.21, 131.13 (Ph-ortho), 128.98, 128.78 (Ph-meta), 117.02, 116.96 (>$\underline{C}Me_2$), 104.33, 104.22 (C-5), 95.83, 95.16 (C-1′), 87.97 (C-4′), 87.20, 87.13 (C-2′), 83.64, 83.51 (C-3′), 67.24 (C-5′), 55.09 ($O\underline{C}H_3$), 45.80, 45.73 (C-α), 28.63 (CH_3), 26.86 (CH_3); ESI-MS (pos.): *m/z* 512 $(M+H)^+$; ESI-MS (neg.): *m/z* 510 $(M-H)^-$; HRMS (FAB) *m/z* calcd for $C_{21}H_{26}N_3O_8PS$ $(M+H)^+$ 512.4930, found 512.4931.

Compound **5f** *(Diastereoisomers)*. MeOH: $CHCl_3$ (1:50) as eluent ($R_f = 0.88$ for TLC). 2.15 g (yield 81.4%). ^{31}P NMR ($CDCl_3$, δ, J: Hz): δ 71.90, 71.16; ^1H NMR (500 MHz, $CDCl_3$): δ 9.56 (1H, br, H-3), 7.88, 7.87 (1H, dd, $^3J = 5$, H-6), 7.71–7.88 (2H, m, Ph), 7.53–7.64 (3H, m, Ph), 5.89 (2H, m, H-1′,5), 4.98 (2H, m, H-2′,3′), 4.41 (1H, m, H-4′), 4.04 (2H, m, H-5′), 3.89 (1H, m, P-NH), 3.73 (4H, m, $OC\underline{H}_3$, H-α), 1.61 (3H, s, $C\underline{H}_3$), 1.42 (3H, s, $C\underline{H}_3$), 1.31, 1.30 (3H, d, $^3J = 6$, β-CH_3); ^{13}C NMR (500 MHz, $CDCl_3$): δ 174.27 ($\underline{C}OOMe$), 163.13 (C-4), 151.28 (C-2), 144.36, 144.32 (C-6), 142.68 (Ph-jpso), 138.79 (Ph-para), 126.47 (Ph-ortho), 122.30 (Ph-meta), 118.40, 117.59 (>$\underline{C}Me_2$), 107.62, 107.43 (C-5), 98.76, 98.41 (C-1′), 86.23 (C-4′), 85.71, 85.63 (C-2′), 82.70, 82.58 (C-3′), 65.44 (C-5′), 56.87 ($O\underline{C}H_3$), 50.73 (C-α), 48.66 (C-β), 26.53 (CH_3), 25.85 (CH_3); ESI-MS (pos.): *m/z* 526 $(M+H)^+$; ESI-MS (neg.): *m/z* 524 $(M-H)^-$; HRMS (FAB) *m/z* calcd for $C_{22}H_{28}N_3O_8PS$ $(M+H)^+$ 526.4866, found 526.4864.

Compound **5g** *(Diastereoisomers)*. MeOH: $CHCl_3$(1:50) as eluent ($R_f = 0.84$ for TLC). 2.43 g (yield 85.8%). ^{31}P NMR ($CDCl_3$, δ, J: Hz): δ 72.46, 71.90; ^1H NMR (500 MHz, $CDCl_3$): δ 8.67 (1H, s, H-8), 8.58 (1H, s, H-2), 7.68–7.77 (2H, m, Ph), 7.37–7.53 (5H, m, Ph, NH_2), 6.44, 6.43 (1H, d, $^3J = 5.0$, H-1′), 6.14 (1H, s, >C$\underline{H}$OEt), 5.52 (1H, m, H-2′), 5.14 (1H, m, H-3′), 4.41 (1H, m, H-4′), 3.74 (3H, m, H-5′, H-α), 3.50 (5H, m, $OC\underline{H}_3$, $OC\underline{H}_2CH_3$), 1.16, 1.15 (3H, d, $^3J = 6.0$, β-CH_3), 0.97 (3H, m, $OCH_2C\underline{H}_3$); ^{13}C NMR (500 MHz, $CDCl_3$): δ 171.54 ($\underline{C}OOMe$), 152.13 (C-2), 149.14 (C-6), 146.27 (Ph-jpso), 143.81 (C-4), 137.23 (Ph-para), 128.33 (Ph-ortho), 122.43, 122.31 (Ph-meta), 133.45 (C-8), 128.18 (C-5), 117.85 (>$\underline{C}$HOEt), 91.24 (C-4′), 86.70 (C-1′), 84.31 (C-3′), 81.78 (C-2′), 65.07 (C-5′), 64.77 ($O\underline{C}H_3$), 52.58 (>$CHO\underline{C}H_2CH_3$), 50.43 (C-α), 19.53 (C-β), 14.18 (>$CHOCH_2\underline{C}H_3$); ESI-MS (pos.): *m/z* 565 $(M+H)^+$; ESI-MS (neg.): *m/z* 563 $(M-H)^-$; HRMS (FAB) *m/z* calcd for $C_{23}H_{29}N_6O_7PS$ $(M+H)^+$ 565.5593, found 565.5590.

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