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Efficient and green syntheses of novel γ -aminophosphonate and phosphine oxide derivatives

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Two synthetic protocols leading to novel γ -aminophosphonate and phosphine oxide derivatives, by reductive amination of γ -phosphonylketones, are reported. The first method involved a two-step procedure. Imine intermediates were first isolated from the *p*-toluenesulfonic acid-catalyzed reaction of primary amines with γ -ketophosphonates and phosphine oxides, then reduced with NaBH_4 in refluxing ethanol. The second method consists of a one-pot procedure which includes the condensation of γ -ketophosphonates and phosphine oxides with primary amines, in the presence of molecular sieves, followed by reduction with NaBH_4 . These methods offer significant advantages over prior reports, such as efficiency, generality, and good yields. Furthermore, they are green protocols avoiding hazardous hydrides and solvents.

Keywords: γ -aminophosphonates; phosphine oxides; reductive amination; sodium borohydride; green synthesis

Introduction

In recent years, the synthesis of aminophosphonates has received an increasing amount of attention due to their promising pharmacological activities. For instance, α -aminophosphonates, which are structural analogs of α -amino acids and transition state mimics of peptide hydrolysis (1, 2), are an important class of compounds in medicinal chemistry with potential biological effects as enzyme inhibitors (3), HIV protease (4), antibiotics (5), anticancer (6), and antithrombotic agents (7). On the other hand, β -aminophosphonates are known for their interesting biological activities as antibacterial agents (8), enzyme inhibitors (3), haptens for catalytic antibodies (9), and anti-HIV agents (10).

Although α - and β -aminophosphonates are well described in the literature, their γ -aminophosphonate homologues did not receive sufficient attention despite their structural resemblance to γ -amino butyric acid (GABA) and glutamates, which is responsible for their important therapeutic potential as GABA and glutamate receptor agonists and antagonists (11–13). Besides, one of the most promising γ -aminophosphonate derivatives, fosmidomycin, which is isolated from *Streptomyces lavendulae*, showed strong antimalarial activity (14).

Varied synthetic methods (15–26) have been developed in order to obtain γ -aminophosphonate

derivatives. Among them, the reductive amination of γ -ketophosphonates using hydride reducing agents is one of the most used methods (19, 23), but the hydrides used (NaBH_3CN , $\text{NaBH}(\text{OAc})_3$) suffer from some drawbacks which have limited the exploitation of these methods in high throughput synthesis. Indeed, reducing reagents including cyanide group are highly toxic and produce toxic products such as HCN and NaCN upon work-up. On the other hand, $\text{NaBH}(\text{OAc})_3$ and related acyloxyborohydrides are compatible with benzene, toluene, tetrahydrofuran (THF), dioxane, CH_2Cl_2 , or $\text{ClCH}_2\text{CH}_2\text{Cl}$ as solvent, but are sensitive to green solvents such as H_2O and EtOH. Furthermore, these hydrides are mild reducing agents giving low to moderate product yield.

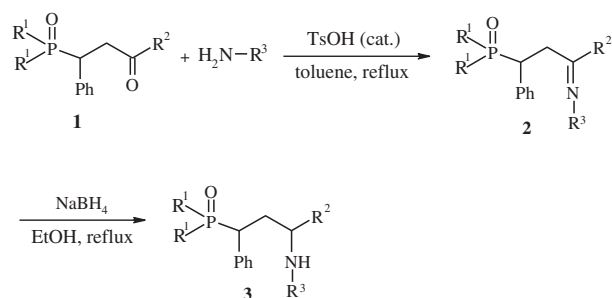
Therefore, additional synthetic methods, giving better yields and avoiding hazardous hydrides and solvents, are required to obtain a wider variety of γ -aminophosphonates for biological screening.

With this in mind, and in the continuation of our interest to develop efficient protocols for the synthesis of biologically active phosphonates (27–30), we report herein two simple and convenient methodologies for the synthesis of γ -aminophosphonates and phosphine oxides, by reductive amination of γ -phosphonylketones, which use inexpensive and environmentally friendly sodium borohydride as reducing agent, in ethanol as solvent.

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Results and discussion

For the synthesis of γ -aminophosphonates and phosphine oxides **3**, we have used two different approaches. The first one (Method A) involved a two-step procedure (Scheme 1). γ -phosphonylimines **2** were first prepared and isolated from the *p*-toluenesulfonic acid-catalyzed reaction of primary amines with γ -ketophosphonates and phosphine oxides **1** (31). The reduction of imines **2** was initially carried out with one hydride equivalent of LiAlH₄ in anhydrous THF, at various temperatures. Unfortunately, the expected γ -aminophosphonates were not obtained. Although the starting materials were completely consumed, the ³¹P NMR analysis of the reaction mixture showed complete dephosphonylation due to C–P bond cleaving (27, 32). It was gratifying to observe that performing the reduction with NaBH₄ as reducing agent, in refluxing ethanol, for 24 h, afforded the corresponding γ -aminophosphonates and phosphine oxides **3** in good overall yields (Table 1). These compounds, presenting two stereocenters, were obtained as a mixture of two unseparable diastereoisomers in an approximate 3:2 ratio.



Scheme 1. Synthesis of γ -aminophosphonates and phosphine oxides **3** (Method A).

The second method (Method B) that we developed to access compounds **3** consists of a simple one-pot protocol which can be useful for the generation of compound libraries of aminophosphonates **3** with diverse substitutions for biological screenings (Scheme 2). This convenient technique includes the condensation of γ -ketophosphonates and phosphine oxides **1** with primary amines, in the presence of molecular sieves (4 Å MS), at refluxing ethanol, for 24 h, leading to the imine intermediates. A subsequent reduction carried out, in a one-pot protocol, by treating with NaBH₄ at 0–78°C, furnished the γ -aminophosphonates and phosphine oxides **3** as a mixture of two unseparable diastereoisomers, in an approximate 3:2 ratio and satisfactory yields (Table 2).

Compounds **3** were characterized on the basis of their infrared (IR), NMR (¹H, ³¹P, ¹³C), and mass spectral data, which indicate that they were obtained as a mixture of two diastereoisomers. Their relative proportions were estimated from the ³¹P NMR spectra where a singlet for each isomer is present (Table 1). The IR spectra revealed the presence of absorption bands toward 1200 and 3350 cm⁻¹ corresponding, respectively to the P=O and N–H vibrators. The ¹H NMR spectrum of each compound **3** showed, in particular, a broad singlet in the region included between 2 and 5 ppm, ascribable to the N–H group. The protons of the CH₂–CH–P motif resonate as two multiplets between 2.0 and 3.5 ppm, probably consisting in an ABMX spin system. Such a multiplicity can be rationalized taking into account that the methylene protons are diastereotopic due to the neighboring asymmetric carbon. Other evidence of structure for compounds **3** is provided by ¹³C NMR. We observed in particular a doublet at 30–44 ppm, ascribable to the CH–P carbon. Such a doublet is characteristic of the coupling with phosphorus with a

Table 1. Substrate scope for the synthesis of compounds **3** (Method A).

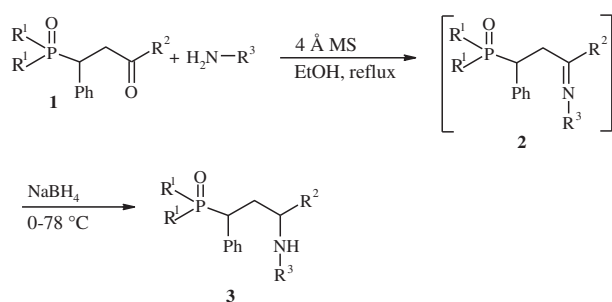
| Entry | R ¹ | R ² | R ³ | Product | $\delta^{31}\text{P}^{\text{a,b}}$ (maj) | $\delta^{31}\text{P}$ (min) | Percentage (maj/min) ^c | Yield ^d (%) |
|-------|----------------|----------------|---|-----------|--|-----------------------------|-----------------------------------|------------------------|
| 1 | EtO | Me | CH ₂ -Ph | 3a | 30.0 | 29.0 | 62/38 | 81 |
| 2 | EtO | Ph | CH ₂ -Ph | 3b | 29.6 | 28.5 | 68/32 | 84 |
| 3 | EtO | Me | 3-MeC ₆ H ₄ CH ₂ | 3c | 30.0 | 29.0 | 52/48 | 73 |
| 4 | EtO | Me | <i>i</i> Pr | 3d | 29.7 | 28.6 | 61/39 | 87 |
| 5 | EtO | Ph | <i>i</i> Pr | 3e | 29.5 | 28.3 | 62/38 | 86 |
| 6 | Ph | Ph | CH ₂ -Ph | 3f | 32.4 | 32.7 | 52/48 | 63 |
| 7 | Ph | Me | CH ₂ -Ph | 3g | 34.2 | 33.4 | 71/29 | 65 |
| 8 | Ph | Me | 3-MeC ₆ H ₄ CH ₂ | 3h | 34.6 | 34.3 | 57/43 | 61 |
| 9 | Ph | Me | Ph | 3i | 34.6 | 34.0 | 59/41 | 63 |
| 10 | Ph | Ph | <i>i</i> Pr | 3j | 33.4 | 33.0 | 51/49 | 66 |

Notes: ^a121.5 MHz, CDCl₃.

^b δ in ppm.

^cDetermined from the ³¹P NMR spectra.

^dIsolated yield.



Scheme 2. Synthesis of γ -aminophosphonates and phosphine oxides **3** (Method B).

Table 2. Substrate scope for the synthesis of compounds **3** (Method B).

| Entry | R ¹ | R ² | R ³ | Product | Percentage (maj/min) | Yield ^a (%) |
|-------|----------------|----------------|---------------------|-----------|----------------------|------------------------|
| 1 | EtO | Me | CH ₂ -Ph | 3a | 66/34 | 70 |
| 2 | EtO | Ph | CH ₂ -Ph | 3b | 69/31 | 76 |
| 3 | EtO | Me | <i>i</i> Pr | 3d | 51/49 | 65 |
| 4 | EtO | Ph | <i>i</i> Pr | 3e | 57/43 | 78 |
| 5 | Ph | Ph | CH ₂ -Ph | 3f | 56/44 | 68 |
| 6 | Ph | Me | CH ₂ -Ph | 3g | 73/27 | 61 |

Note: ^aIsolated yield.

¹J_{CP} coupling constant of about 60–160 Hz. We observed, on the other hand, a doublet (³J_{CP} = 11–17 Hz) at 45–70 ppm corresponding to the CH-NH carbon. Structures of compounds **3** were supported additionally by the mass spectra which showed the correct molecular ion peaks.

Conclusion

We successfully developed two efficient methodologies for the synthesis of γ -aminophosphonates and phosphine oxides, by reductive amination of γ -phosphonylketones, which use inexpensive and environmentally friendly sodium borohydride as reducing agent, in ethanol as solvent. By comparison with the existing procedures, these new syntheses have the advantages of efficiency, generality, and good yields. Furthermore, they are greener protocols avoiding hazardous hydrides and solvents. This is very beneficial for safely obtaining γ -aminophosphonate derivatives of pharmacological interest.

Experimental

¹H, ³¹P, and ¹³C NMR spectra were recorded with CDCl₃ as the solvent, on a Bruker-300 spectrometer. The chemical shifts are reported in ppm relative to tetramethylsilane (internal reference) for ¹H and ¹³C NMR and relative to 85% H₃PO₄ (external reference)

for ³¹P NMR. The coupling constants are reported in Hz. For the ¹H NMR, the multiplicities of signals are indicated by the following abbreviations: s – singlet; d – doublet; t – triplet; q – quartet; m – multiplet. Mass spectra were determined on a VOYAGER DE STR spectrometer under MALDI ionization conditions, or on an Agilent 5975B spectrometer, under electronic impact (EI) conditions. IR spectra were recorded on a Nicolet IR200 spectrometer. The progress of the reactions was monitored by thin layer chromatography. Purification of products was performed by column chromatography using silica gel 60 (Fluka).

General procedure for the synthesis of γ -aminophosphonates and phosphine oxides **3**

Method A

Synthesis of γ -phosphonylimine **2.** A mixture of γ -ketophosphonate or phosphine oxide **1** (33, 34) (0.005 mol), primary amine (0.01 mol), and *p*-toluene sulfonic acid (0.1 g) in dry toluene (40 mL) was heated at reflux, with Dean-Stark separation of water, for 48 h. The reaction mixture was then concentrated under vacuum. The residue obtained was washed with petroleum ether.

Reduction of imines **2.** A mixture of γ -phosphonylimine **2** (0.005 mol) and NaBH₄ (0.01 mol, 378 mg) in dry ethanol (30 mL) was stirred at reflux, under nitrogen atmosphere, for 24 h. The solvent was then removed under reduced pressure. The residue obtained was diluted with water (30 mL) and extracted with an equal volume of CHCl₃. The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The obtained residue was chromatographed on a silica gel column using ether as eluent.

Method B

A mixture of γ -phosphonylketone **1** (0.01 mol), primary amine (0.02 mol), and 4 Å molecular sieve (10 g) in dry ethanol (20 mL) was stirred at reflux, under nitrogen atmosphere, for 24 h. The mixture was cooled to 0°C and NaBH₄ (0.02 mol, 756 mg) was added, then the reaction was warmed and stirred at reflux for 24 h. The molecular sieve was filtered and the solvent was evaporated under vacuum. The residue obtained was diluted with 2 N aqueous HCl solution (40 mL) and extracted with CHCl₃ (2 × 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The crude product was chromatographed on a silica gel column using ether as eluent.

Spectral data of compounds 3. **3a:** Red oil; ^1H NMR (300 MHz, CDCl_3): δ = 0.90 (d, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}$); 0.93 (t, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 1.11 (t, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 1.71 (br s, 1H, NH, maj); 2.18 (br s, 1H, NH, min); 1.86–2.53 (m, 2H, $\text{CH}_2\text{-CH}$); 3.30–3.56 (m, 1H, CH-P); 3.60 (s, 2H, $\text{CH}_2\text{-Ph}$, min); 3.63 (s, 2H, $\text{CH}_2\text{-Ph}$, maj); 3.70–3.79 (m, 1H, CH-NH); 3.82–4.02 (m, 4H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); 7.05–7.17 (m, 10H, arom-H); ^{13}C NMR (75.5 MHz, CDCl_3): δ = 16.2 (d, $^3J_{\text{CP}} = 5.3$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 16.4 (d, $^3J_{\text{CP}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 19.9 (s, $\text{CH}_3\text{-CH}$, min); 20.9 (s, $\text{CH}_3\text{-CH}$, maj); 41.1 (d, $^1J_{\text{CP}} = 138.1$ Hz, CH-P, maj); 41.9 (d, $^1J_{\text{CP}} = 128.3$ Hz, CH-P, min); 43.5 (s, $\text{CH}_2\text{-CH}$, min); 46.3 (s, $\text{CH}_2\text{-CH}$, maj); 49.3 (d, $^3J_{\text{CP}} = 14.3$ Hz, CH-NH , maj); 50.5 (d, $^3J_{\text{CP}} = 15.1$ Hz, CH-NH , min); 53.1 (s, $\text{CH}_2\text{-Ph}$, min); 53.7 (s, $\text{CH}_2\text{-Ph}$, maj); 61.6 (d, $^2J_{\text{CP}} = 6.8$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 62.4 (d, $^2J_{\text{CP}} = 6.8$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); phenyl carbons: δ = 125.3; 126.7; 126.9; 127.0; 127.1; 128.0; 128.1; 128.2; 128.3; 128.4; 129.0; 129.4; 129.5; 136.2; 136.4; 136.5; 137.7; 140.3; 140.6; 140.9; IR (neat): $\nu_{\text{P=O}} = 1215$ cm^{-1} ; $\nu_{\text{NH}} = 3371$ cm^{-1} ; MALDI-MS: $m/z = 376.132$ ($[\text{M} + \text{H}]^+$); EI-HRMS: calculated for $\text{C}_{21}\text{H}_{30}\text{NO}_3\text{P}$: 375.1963 (M^+); found: 375.1961.

3b: Yellow oil; ^1H NMR (300 MHz, CDCl_3): δ = 0.98 (t, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 1.11 (t, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 1.74 (br s, 1H, NH); 2.20–2.55 (m, 2H, $\text{CH}_2\text{-CH}$); 3.14–3.33 (m, 1H, CH-P); 3.40–3.52 (m, 1H, CH-NH); 3.64 (s, 2H, $\text{CH}_2\text{-Ph}$, min); 3.66 (s, 2H, $\text{CH}_2\text{-Ph}$, maj); 3.70–4.02 (m, 4H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); 7.06–7.19 (m, 15H, arom-H); ^{13}C NMR (75.5 MHz, CDCl_3): δ = 16.3 (d, $^3J_{\text{CP}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 16.5 (d, $^3J_{\text{CP}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 39.7 (d, $^1J_{\text{CP}} = 150.9$ Hz, CH-P, min); 41.6 (d, $^1J_{\text{CP}} = 138.1$ Hz, CH-P, maj); 43.5 (s, $\text{CH}_2\text{-CH}$, min); 46.4 (s, $\text{CH}_2\text{-CH}$, maj); 53.2 (s, $\text{CH}_2\text{-Ph}$, maj); 53.8 (s, $\text{CH}_2\text{-Ph}$, min); 59.0 (d, $^3J_{\text{CP}} = 14.3$ Hz, CH-NH , maj); 60.6 (d, $^3J_{\text{CP}} = 17.4$ Hz, CH-NH , min); 61.8 (d, $^2J_{\text{CP}} = 7.5$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 62.5 (d, $^2J_{\text{CP}} = 6.8$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); phenyl carbons: δ = 125.8; 126.0; 126.2; 126.8; 127.0; 127.2; 127.4; 127.6; 127.9; 128.1; 128.2; 128.4; 128.9; 129.0; 129.5; 130.8; 131.1; 136.2; 136.3; 136.8; 137.5; 140.4; 140.5; 140.6; 140.8; 142.1; 143.1; 144.1; IR (neat): $\nu_{\text{P=O}} = 1248$ cm^{-1} ; $\nu_{\text{NH}} = 3319$ cm^{-1} ; MALDI-MS: $m/z = 438.163$ ($[\text{M} + \text{H}]^+$); EI-HRMS: calculated for $\text{C}_{26}\text{H}_{32}\text{NO}_3\text{P}$: 437.2120 (M^+); found: 437.2115.

3c: Red oil; ^1H NMR (300 MHz, CDCl_3): δ = 0.90 (d, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}$, min); 0.91 (d, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}$, maj); 0.93 (t, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 1.13 (t, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 2.16 (s, 3H, $\text{CH}_3\text{-Ph}$, min); 2.18 (s, 3H, $\text{CH}_3\text{-Ph}$, maj); 2.11–2.54 (m, 2H, $\text{CH}_2\text{-CH}$); 3.28 (br s, 1H, NH, min); 3.32 (br s, 1H, NH, maj); 3.34–3.56 (m, 1H, CH-P); 3.58 (s, 2H, $\text{CH}_2\text{-Ph}$, min); 3.61

(s, 2H, $\text{CH}_2\text{-Ph}$, maj); 3.69–3.76 (m, 1H, CH-NH); 3.87–3.98 (m, 4H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); 6.87–7.15 (m, 9H, arom-H); ^{13}C NMR (75.5 MHz, CDCl_3): δ = 16.2 (d, $^3J_{\text{CP}} = 5.3$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 16.4 (d, $^3J_{\text{CP}} = 5.3$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 18.5 (s, $\text{CH}_3\text{-CH}$, min); 19.9 (s, $\text{CH}_3\text{-CH}$, maj); 20.9 (s, $\text{CH}_3\text{-Ph}$, min); 21.4 (s, $\text{CH}_3\text{-Ph}$, maj); 41.2 (d, $^1J_{\text{CP}} = 138.1$ Hz, CH-P, maj); 41.9 (d, $^1J_{\text{CP}} = 137.4$ Hz, CH-P, min); 43.5 (s, $\text{CH}_2\text{-CH}$, min); 46.2 (s, $\text{CH}_2\text{-CH}$, maj); 49.4 (d, $^3J_{\text{CP}} = 15.1$ Hz, CH-NH , maj); 50.6 (d, $^3J_{\text{CP}} = 15.8$ Hz, CH-NH , min); 53.2 (s, $\text{CH}_2\text{-Ph}$, min); 53.7 (s, $\text{CH}_2\text{-Ph}$, maj); 61.6 (d, $^2J_{\text{CP}} = 7.5$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 62.4 (d, $^2J_{\text{CP}} = 6.8$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); phenyl carbons: δ = 124.2; 125.1; 125.2; 125.3; 126.9; 127.0; 127.1; 127.6; 127.7; 128.2; 128.3; 128.4; 128.5; 128.9; 129.2; 129.3; 129.4; 129.5; 137.7; 137.8; 138.0; 140.0; 140.8; 142.8; IR (neat): $\nu_{\text{P=O}} = 1249$ cm^{-1} ; $\nu_{\text{NH}} = 3383$ cm^{-1} ; MALDI-MS: $m/z = 390.153$ ($[\text{M} + \text{H}]^+$).

3d: Red oil; ^1H NMR (300 MHz, CDCl_3): δ = 0.60 (d, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}$, maj); 0.74 (d, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}$, min); 0.81 (d, 6H, $^3J_{\text{HH}} = 9.0$ Hz, $(\text{CH}_3)_2\text{CH}$); 0.84 (t, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 1.14 (t, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 1.87–2.74 (m, 2H, $\text{CH}_2\text{-CH}$); 2.95–3.10 (m, 1H, $\text{CH}(\text{CH}_3)_2$); 3.40–3.60 (m, 1H, CH-P); 3.71–3.76 (m, 1H, CH-NH); 3.88–3.96 (m, 4H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); 5.12 (br s, 1H, NH); 7.03–7.42 (m, 5H, arom-H); ^{13}C NMR (75.5 MHz, CDCl_3): δ = 15.9 (d, $^3J_{\text{CP}} = 5.3$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 16.1 (d, $^3J_{\text{CP}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 20.0 (s, $(\text{CH}_3)_2\text{CH}$, min); 21.2 (s, $(\text{CH}_3)_2\text{CH}$, maj); 22.3 (s, $\text{CH}_3\text{-CH}$, min); 24.1 (s, $\text{CH}_3\text{-CH}$, maj); 40.7 (d, $^1J_{\text{CP}} = 138.1$ Hz, CH-P, maj); 41.6 (d, $^1J_{\text{CP}} = 137.4$ Hz, CH-P, min); 44.7 (s, $\text{CH}_2\text{-CH}$, min); 44.8 (s, $\text{CH}_2\text{-CH}$, maj); 46.7 (d, $^3J_{\text{CP}} = 15.1$ Hz, CH-NH , maj); 47.3 (d, $^3J_{\text{CP}} = 15.8$ Hz, CH-NH , min); 53.4 (s, $(\text{CH}_3)_2\text{CH}$, maj); 56.9 (s, $(\text{CH}_3)_2\text{CH}$, min); 61.3 (d, $^2J_{\text{CP}} = 7.5$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 61.9 (d, $^2J_{\text{CP}} = 7.5$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); phenyl carbons: δ = 126.4; 127.9; 128.6; 129.2; 130.4; 132.5; 135.2; 135.4; 136.4; 139.7; 141.8; 142.4; IR (neat): $\nu_{\text{P=O}} = 1252$ cm^{-1} ; $\nu_{\text{NH}} = 3457$ cm^{-1} ; MALDI-MS: $m/z = 328.120$ ($[\text{M} + \text{H}]^+$).

3e: Yellow oil; ^1H NMR (300 MHz, CDCl_3): δ = 0.57 (d, 6H, $^3J_{\text{HH}} = 6.0$ Hz, $(\text{CH}_3)_2\text{CH}$, min); 0.74 (d, 6H, $^3J_{\text{HH}} = 6.0$ Hz, $(\text{CH}_3)_2\text{CH}$, maj); 0.87 (t, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 1.10 (t, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 2.02–2.42 (m, 2H, $\text{CH}_2\text{-CH}$); 2.49–2.67 (m, 1H, $\text{CH}(\text{CH}_3)_2$); 3.15–3.41 (m, 1H, CH-NH); 3.44–3.69 (m, 1H, CH-P); 3.71–3.98 (m, 4H, 2 $\text{CH}_3\text{-CH}_2\text{-O}$); 4.72 (br s, 1H, NH, min); 4.74 (br s, 1H, NH, maj); 6.72–7.37 (m, 10H, arom-H); ^{13}C NMR (75.5 MHz, CDCl_3): δ = 16.1 (d, $^3J_{\text{CP}} = 5.3$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 16.3 (d, $^3J_{\text{CP}} = 5.3$ Hz, $\text{CH}_3\text{-CH}_2\text{-O}$); 21.8 (s, $(\text{CH}_3)_2\text{CH}$, min); 24.3 (s, $(\text{CH}_3)_2\text{CH}$, maj); 40.0 (d, $^1J_{\text{CP}} = 169.8$ Hz, CH-P, maj); 41.4 (d, $^1J_{\text{CP}} = 138.1$ Hz, CH-P, min); 45.0 (s, $\text{CH}_2\text{-CH}$, maj); 45.3

(s, $\underline{\text{CH}}_2\text{-CH}$, min); 56.5 (d, $^3J_{\text{CP}} = 14.3$ Hz, $\underline{\text{CH}}\text{-NH}$, maj); 58.0 (d, $^3J_{\text{CP}} = 14.3$ Hz, $\underline{\text{CH}}\text{-NH}$, min); 59.5 (s, $(\underline{\text{CH}}_3)_2\text{CH}$); 61.6 (d, $^2J_{\text{CP}} = 6.8$ Hz, $\underline{\text{CH}}_3\text{-}\underline{\text{CH}}_2\text{-O}$); 62.2 (d, $^2J_{\text{CP}} = 6.8$ Hz, $\underline{\text{CH}}_3\text{-}\underline{\text{CH}}_2\text{-O}$); phenyl carbons: $\delta = 125.0$; 125.4; 125.9; 126.7; 127.3; 128.0; 128.3; 128.6; 129.4; 130.7; 130.9; 134.3; 135.7; 136.1; 136.6; 140.0; 143.0; 144.3; 144.8; 145.9; IR (neat): $\nu_{\text{P=O}} = 1249$ cm^{-1} ; $\nu_{\text{NH}} = 3439$ cm^{-1} ; MALDI-MS: $m/z = 390.154$ ($[\text{M} + \text{H}]^+$).

3f: White solid; mp 153–155°C; ^1H NMR (300 MHz, CDCl_3): $\delta = 1.96\text{--}2.56$ (m, 2H, $\underline{\text{CH}}_2\text{-CH}$); 3.22 (s, 2H, $\underline{\text{CH}}_2\text{-Ph}$, min); 3.33 (s, 2H, $\underline{\text{CH}}_2\text{-Ph}$, maj); 3.17–3.37 (m, 1H, $\underline{\text{CH}}\text{-P}$); 3.48 (br s, 1H, NH, maj); 3.52 (br s, 1H, NH, min); 4.27–4.33 (m, 1H, $\underline{\text{CH}}\text{-NH}$); 7.13–7.97 (m, 25H, arom-H); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 37.0$ (s, $\underline{\text{CH}}_2\text{-CH}$, maj); 38.1 (s, $\underline{\text{CH}}_2\text{-CH}$, min); 42.9 (d, $^1J_{\text{CP}} = 67.9$ Hz, $\underline{\text{CH}}\text{-P}$, maj); 42.3 (d, $^1J_{\text{CP}} = 67.2$ Hz, $\underline{\text{CH}}\text{-P}$, min); 50.8 (s, $\underline{\text{CH}}_2\text{-Ph}$, maj); 50.6 (s, $\underline{\text{CH}}_2\text{-Ph}$, min); 60.3 (d, $^3J_{\text{CP}} = 13.6$ Hz, $\underline{\text{CH}}\text{-NH}$, maj); 58.5 (d, $^3J_{\text{CP}} = 13.4$ Hz, $\underline{\text{CH}}\text{-NH}$, min); phenyl carbons: $\delta = 126.4$; 126.5; 126.6; 126.8; 127.4; 127.6; 127.7; 127.8; 127.9; 128.0; 128.2; 128.3; 128.4; 128.5; 128.6; 128.7; 129.6; 129.7; 129.8; 130.4; 130.5; 130.6; 130.7; 130.8; 130.9; 131.1; 131.5; 131.7; 131.9; 132.0; 132.1; 132.2; 132.4; 132.7; 132.8; 132.9; 133.0; 133.1; 133.2; 133.4; 135.1; 135.2; 135.7; 135.8; 140.1; 140.2; 140.3; 142.1; 142.2; 144.0; IR (neat): $\nu_{\text{P=O}} = 1268$ cm^{-1} ; $\nu_{\text{NH}} = 3335$ cm^{-1} ; MALDI-MS: $m/z = 502.173$ ($[\text{M} + \text{H}]^+$); EI-HRMS: calculated for $\text{C}_{34}\text{H}_{32}\text{NOP}$: 501.2221 (M^+); found: 501.2220.

3g: Brown solid; mp 150–152°C; ^1H NMR (300 MHz, CDCl_3): $\delta = 0.78$ (d, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\underline{\text{CH}}_3\text{-CH}$, maj); 0.91 (d, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\underline{\text{CH}}_3\text{-CH}$, min); 1.60–2.24 (m, 2H, $\underline{\text{CH}}_2\text{-CH}$); 2.78 (br s, 1H, NH); 3.24–3.46 (m, 1H, $\underline{\text{CH}}\text{-P}$); 3.56 (s, 2H, $\underline{\text{CH}}_2\text{-Ph}$, maj); 3.58 (s, 2H, $\underline{\text{CH}}_2\text{-Ph}$, min); 3.88–3.94 (m, 1H, $\underline{\text{CH}}\text{-NH}$); 6.95–8.14 (m, 20H, arom-H); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 21.0$ (s, $\underline{\text{CH}}_3\text{-CH}$, maj); 22.7 (s, $\underline{\text{CH}}_3\text{-CH}$, min); 37.4 (s, $\underline{\text{CH}}_2\text{-CH}$, min); 43.3 (d, $^1J_{\text{CP}} = 67.9$ Hz, $\underline{\text{CH}}\text{-P}$, maj); 44.2 (d, $^1J_{\text{CP}} = 67.9$ Hz, $\underline{\text{CH}}\text{-P}$, min); 45.9 (s, $\underline{\text{CH}}_2\text{-CH}$, maj); 49.8 (d, $^3J_{\text{CP}} = 12.8$ Hz, $\underline{\text{CH}}\text{-NH}$, min); 50.62 (s, $\underline{\text{CH}}_2\text{-Ph}$, min); 51.1 (d, $^3J_{\text{CP}} = 18.8$ Hz, $\underline{\text{CH}}\text{-NH}$, maj); 53.1 (s, $\underline{\text{CH}}_2\text{-Ph}$, maj); phenyl carbons: $\delta = 126.8$; 126.9; 127.3; 127.5; 127.6; 127.7; 127.9; 128.0; 128.2; 128.3; 128.4; 128.5; 128.6; 128.7; 128.8; 129.2; 129.7; 129.8; 129.9; 130.0; 130.1; 130.7; 130.8; 131.1; 131.1; 131.2; 131.3; 131.4; 131.5; 131.6; 131.7; 131.8; 132.0; 132.2; 132.4; 132.8; 133.2; 136.2; 139.4; 140.3; 141.0; 142.1; IR (neat): $\nu_{\text{P=O}} = 1200$ cm^{-1} ; $\nu_{\text{NH}} = 3382$ cm^{-1} ; MALDI-MS: $m/z = 440.145$ ($[\text{M} + \text{H}]^+$).

3h: Brown solid; mp 139–142°C; ^1H NMR (300 MHz, CDCl_3): $\delta = 0.80$ (d, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\underline{\text{CH}}_3\text{-CH}$, maj); 0.90 (d, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\underline{\text{CH}}_3\text{-CH}$,

min); 1.90–2.20 (m, 2H, $\underline{\text{CH}}_2\text{-CH}$); 2.10 (s, 3H, $\underline{\text{CH}}_3\text{-Ph}$, maj); 2.20 (s, 3H, $\underline{\text{CH}}_3\text{-Ph}$, min); 3.20–3.50 (m, 1H, $\underline{\text{CH}}\text{-P}$); 3.56 (s, 2H, $\underline{\text{CH}}_2\text{-Ph}$); 3.88–3.94 (m, 1H, $\underline{\text{CH}}\text{-NH}$); 4.56 (br s, 1H, NH); 6.50–8.10 (m, 19H, arom-H); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 14.3$ (s, $\underline{\text{CH}}_3\text{-CH}$, min); 15.2 (s, $\underline{\text{CH}}_3\text{-CH}$, maj); 21.3 (s, $\underline{\text{CH}}_3\text{-Ph}$, maj); 22.3 (s, $\underline{\text{CH}}_3\text{-Ph}$, min); 28.2 (d, $^1J_{\text{CP}} = 96.6$ Hz, $\underline{\text{CH}}\text{-P}$, maj); 34.0 (s, $\underline{\text{CH}}_2\text{-CH}$, min); 34.2 (d, $^1J_{\text{CP}} = 96.0$ Hz, $\underline{\text{CH}}\text{-P}$, min); 37.7 (s, $\underline{\text{CH}}_2\text{-CH}$, maj); 41.3 (s, $\underline{\text{CH}}_2\text{-Ph}$, maj); 43.7 (s, $\underline{\text{CH}}_2\text{-Ph}$, min); 45.0 (d, $^3J_{\text{CP}} = 13.6$ Hz, $\underline{\text{CH}}\text{-NH}$, maj); 50.0 (d, $^3J_{\text{CP}} = 13.6$ Hz, $\underline{\text{CH}}\text{-NH}$, min); phenyl carbons: $\delta = 119.6$; 123.8; 124.7; 125.9; 126.2; 126.3; 126.8; 127.1; 127.3; 127.9; 128.0; 128.2; 128.3; 128.4; 128.5; 128.6; 128.7; 128.8; 129.4; 129.5; 129.7; 129.8; 128.9; 129.0; 129.4; 129.5; 129.8; 129.9; 130.0; 130.8; 130.8; 130.9; 131.2; 131.4; 131.5; 131.6; 132.0; 132.5; 132.7; 134.7; 134.8; 137.8; 137.9; 138.1; 138.3; 141.3; IR (neat): $\nu_{\text{P=O}} = 1225$ cm^{-1} ; $\nu_{\text{NH}} = 3400$ cm^{-1} ; MALDI-MS: $m/z = 454.156$ ($[\text{M} + \text{H}]^+$).

3i: Brown solid; mp 146–148°C; ^1H NMR (300 MHz, CDCl_3): $\delta = 0.99$ (d, 3H, $^3J_{\text{HH}} = 5.7$ Hz, $\underline{\text{CH}}_3\text{-CH}$, min); 1.07 (d, 3H, $^3J_{\text{HH}} = 6.0$ Hz, $\underline{\text{CH}}_3\text{-CH}$, maj); 2.10–2.39 (m, 2H, $\underline{\text{CH}}_2\text{-CH}$); 3.45–3.65 (m, 1H, $\underline{\text{CH}}\text{-P}$); 3.80 (br s, 1H, NH); 4.10–4.30 (m, 1H, $\underline{\text{CH}}\text{-NH}$); 6.67–8.02 (m, 20H, arom-H); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 23.8$ (s, $\underline{\text{CH}}_3\text{-CH}$, min); 24.5 (s, $\underline{\text{CH}}_3\text{-CH}$, maj); 30.4 (d, $^1J_{\text{CP}} = 78.3$ Hz, $\underline{\text{CH}}\text{-P}$, min); 32.7 (d, $^1J_{\text{CP}} = 71.5$ Hz, $\underline{\text{CH}}\text{-P}$, maj); 37.8 (s, $\underline{\text{CH}}_2\text{-CH}$, min); 38.8 (s, $\underline{\text{CH}}_2\text{-CH}$, maj); 46.5 (d, $^3J_{\text{CP}} = 11.2$ Hz, $\underline{\text{CH}}\text{-NH}$, min); 47.1 (d, $^3J_{\text{CP}} = 11.2$ Hz, $\underline{\text{CH}}\text{-NH}$, maj); phenyl carbons: $\delta = 118.2$; 123.4; 123.5; 125.5; 126.0; 126.5; 127.0; 128.1; 128.2; 128.4; 128.6; 128.8; 129.3; 129.5; 129.7; 129.9; 130.0; 130.9; 131.0; 131.1; 131.4; 131.4; 131.6; 131.7; 131.8; 132.0; 132.3; 132.4; 132.6; 133.1; 133.9; 134.0; 134.5; 134.8; 135.5; 135.7; 135.9; 136.0; 136.1; 136.2; 137.1; 137.8; IR (neat): $\nu_{\text{P=O}} = 1288$ cm^{-1} ; $\nu_{\text{NH}} = 3357$ cm^{-1} ; MALDI-MS: $m/z = 426.115$ ($[\text{M} + \text{H}]^+$).

3j: White solid; mp 158–160°C; ^1H NMR (300 MHz, CDCl_3): $\delta = 0.66$ (d, 6H, $^3J_{\text{HH}} = 6.0$ Hz, $(\underline{\text{CH}}_3)_2\text{CH}$, min); 0.85 (d, 6H, $^3J_{\text{HH}} = 6.0$ Hz, $(\underline{\text{CH}}_3)_2\text{CH}$, maj); 1.80–2.36 (m, 2H, $\underline{\text{CH}}_2\text{-CH}$); 2.51–2.58 (m, 1H, $\underline{\text{CH}}(\underline{\text{CH}}_3)_2$); 3.03–3.09 (m, 1H, $\underline{\text{CH}}\text{-P}$); 3.24 (br s, 1H, NH); 4.16–4.18 (m, 1H, $\underline{\text{CH}}\text{-NH}$); 6.86–7.83 (m, 20H, arom-H); ^{13}C NMR (75.5 MHz, CDCl_3): $\delta = 21.4$ (s, $(\underline{\text{CH}}_3)_2\text{CH}$, maj); 24.0 (s, $(\underline{\text{CH}}_3)_2\text{CH}$, min); 42.0 (s, $\underline{\text{CH}}_2\text{-CH}$, min); 42.1 (d, $^1J_{\text{CP}} = 69.4$ Hz, $\underline{\text{CH}}\text{-P}$, min); 42.5 (d, $^1J_{\text{CP}} = 56.6$ Hz, $\underline{\text{CH}}\text{-P}$, maj); 44.6 (s, $\underline{\text{CH}}_2\text{-CH}$, maj); 56.1 (s, $\underline{\text{CH}}(\underline{\text{CH}}_3)_2$, maj); 57.5 (s, $\underline{\text{CH}}(\underline{\text{CH}}_3)_2$, min); 69.1 (d, $^3J_{\text{CP}} = 12.1$ Hz, $\underline{\text{CH}}\text{-NH}$, min); 71.2 (d, $^3J_{\text{CP}} = 14.3$ Hz, $\underline{\text{CH}}\text{-NH}$, maj); phenyl carbons: $\delta = 125.0$; 125.8; 126.0; 126.3; 126.4; 127.2; 127.3; 127.5; 127.6; 127.7;

127.8; 127.9; 128.1; 128.2; 128.3; 128.4; 129.4; 129.5; 128.6; 129.7; 129.8; 129.9; 130.1; 130.2; 130.3; 130.4; 130.5; 130.6; 130.7; 130.8; 130.9; 131.0; 131.5; 132.0; 133.0; 134.0; 135.1; 135.2; 142.0; 143.0; 144.0; 145.1; IR (neat): $\nu_{\text{P=O}} = 1269 \text{ cm}^{-1}$; $\nu_{\text{NH}} = 3258 \text{ cm}^{-1}$; MALDI-MS: $m/z = 454.170$ ($[\text{M} + \text{H}]^+$).

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