Microwave-Assisted Synthesis of α-Amino Phosphonates Derived from Formylporphyrins of Natural Origin

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Abstract: The first synthesis of α-amino phosphonates comprising porphyrin core was accomplished. Three methods of obtaining α-amino phosphonates **5**–**8** were compared. Conventional heating of formylporphyrins **1**–**4** with *t*-$BuNH_2$ and $(EtO)_2P(O)H$ in various solvents was ultimately unsuccessful for preparing **5**–**8** whereas the use of microwave irradiation made it possible to obtain **5**–**8** in good yields. Regioselective preparation of **5**–**8** in excellent yields was achieved by combining microwave-assisting conditions and catalysis with CdI_2. Efficient synthetic procedures of obtaining formylporphyrins **3**,**4** in large scale were also proposed.

Key words: α-amino phosphonates, photodynamic therapy, protoporphyrin IX, regioselectivity, Schiff bases

Extensive substituent manipulations on porphyrins derived from naturally occurring tetrapyrroles (e.g. heme and chlorocruoroheme) produce a number of phototherapeutic agents efficiently utilized in diverse medical fields including ophthalmology, oncology, gynecology, dermatology, urology, cardiology and immunology.[1–4] The method allowing tetrapyrroles to be used as photosensitizers (PSs) is called photodynamic therapy (PDT). Due to the basic concept of PDT, the combination of two therapeutic agents, a PS and light, which have low toxicity by themselves and being combined in the presence of oxygen lead to ultimate tissue destruction.[1–4]

In order to construct porphyrin-based PSs capable of accumulating selectively in neoplastic (e.g. tumor) tissues a variety of synthetic approaches were elaborated.[1,2] Promising results were achieved by introducing pharmacophor units (e.g. alkoxy-, amino-, α-amino acid residues) into the side-chain positions of porphyrins.[1,2,5]

An intriguing class of biologically active compounds are α-amino phosphonates. Due to their structural analogy with α-amino acids and transition state mimicking of peptides, α-amino phosphonates act as potent antibiotics,[6] peptide mimics,[6,7] enzyme inhibitors[6,8] and pharmacological agents.[9]

With the aim of combining in one molecule phototherapeutic potential of porphyrins and unique biological activity of α-amino phosphonates, we report the first synthesis of α-amino phosphonates comprising porphyrin moiety. It is well documented[10–14] that heterocyclic α-amino phosphonates could be efficiently prepared by the addition of phosphites to aldimine, generated from the corresponding amines and heterocyclic aldehydes. Although there is a broad variety of formylporphyrins derived from natural tetrapyrrols,[2,15] we chose to utilize namely **1**–**4**[15,16] as aldehyde components since formyl group of **1**–**4** was reported to be an optimum site for designing potent pharmacological agents.[1,2,17–20] $(EtO)_2P(O)H$ and *t*-$BuNH_2$ were employed because they have been successfully used in obtaining various α-amino phosphonates and their motif could be easily detected by NMR.[21–23] Thus, this paper describes the synthesis of α-amino phosphonates **5**–**8** and synthetic approach to them is shortly depicted in Scheme 1.

Our synthesis began from protoporphyrin IX dimethyl ester **9**, obtained in excellent yield (89%) from commercially available hemin **10** via a Grinstein's method.[24] Further light-mediated Diels–Alder-type reaction of **9** with singlet oxygen initially produced labile endoperoxides **11**,**12** which underwent rearrangement into the mixture of stable γ-hydroxyaldehydes **1**,**2** (the so called photoprotoporphyrins).[1,16] Individual aldehydes **1**,**2** were isolated in 32% and 30% yields, respectively, by repeated column chromatography on alumina with 30% recovery of **9**[25] and each isomer was processed separately through the rest of sequences (Schemes 1, 2, 4).

The next phase of our project required facile access to gram quantities of individual isomeric aldehydes **3**,**4**. *Spirographis* porphyrin dimethyl ester **3** owes its name to its origin from the prosthetic group of the oxygen-carrying pigment of the polychaete worm *Spirographis spallanzanii*[26] and has been the subject of numerous syntheses.[16,27–32] However, the procedure describing convenient large scale preparation of **3** as well as **4** has not been published yet.

Logically, formylporphyrins **3**,**4** can be prepared by direct vinyl group oxidation of **9**. In practice, direct synthesis of **3**,**4** from **9** proceeds with low yield. In addition, direct

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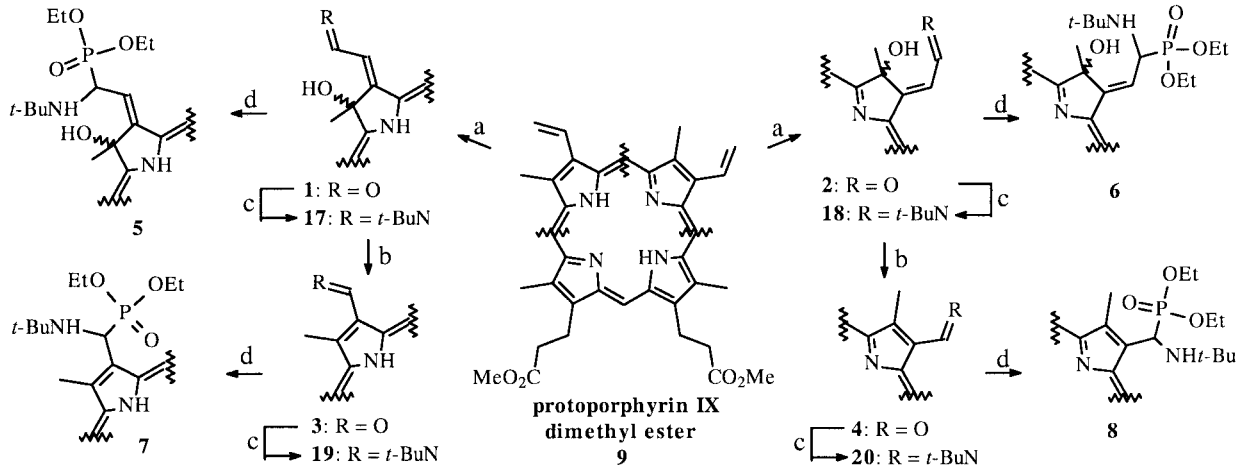
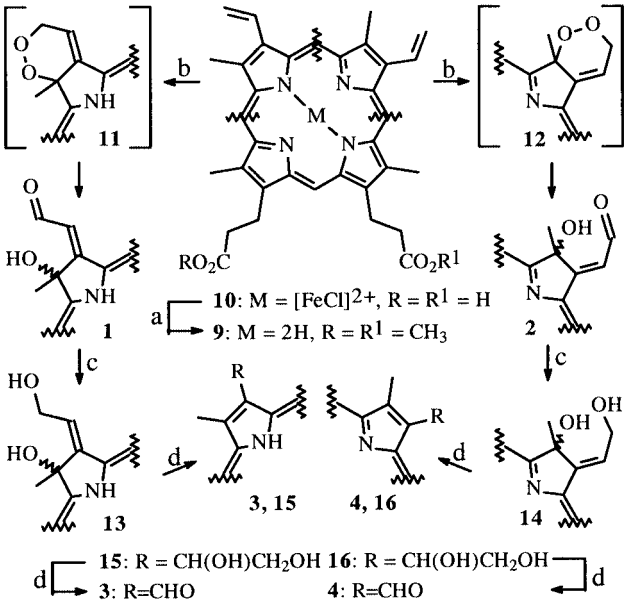


Scheme 1 (a) O_2, CH_2Cl_2, r.t., stirring with irradiation, (2 × 950W high-pressure mercury lamps), 22 h, 32% of **1**, 30% of **2** and 30% recovery of **9**. (b) $NaBH_4$, $CHCl_3$, MeOH, r.t., 10 min, then H_5IO_6, 1,4-dioxane, r.t., 45 min, 65% of **3** from **1**, 66% of **4** from **2**. (c) *t*-$BuNH_2$, $ClCH_2CH_2Cl$, reflux, 2–3 min, quant. (d) *t*-$BuNH_2$, $(EtO)_2P(O)H$, $ClCH_2CH_2Cl$, MW (102 W), CdI_2, 9–10 min, 82% of **5** from **1**, 85% of **6** from **2**, 80% of **7** from **3** and 84% of **8** from **4**.

route implies the formation of an equimolar mixture of **3**,**4**, which could only be separated into individual **3**,**4** on milligram scale.[28,30,32]

Photoprotoporphyrins **1**,**2**, accessible in gram quantities from **9** as individual isomers,[25] were recognized to be useful starting materials in obtaining **3**,**4** with good yields in 400 mg scale.[16] Following this route, we found that large scale (1–1.5 g) reduction of aldehydes **3**,**4** by brief (10 min) treatment with $NaBH_4$ in $CHCl_3$/MeOH at room temperature[33] provided diols **13**,**14** quantitatively whereas the previously applied conditions ($NaBH_4$/CH_2Cl_2/MeOH/steam bath/60 min)[16] gave rise to decomposition products (Schemes 1, 2).

The principle of converting diols **13**,**14** into target aldehydes **3**,**4** is based on acid-catalyzed rearrangement of **13**,**14** to *vic*-diols **15**,**16** followed by their in situ oxidation to **3**,**4**.[16] According to literature report, aldehydes **3**,**4** could be efficiently (80% yield) prepared by treating diols **13**,**14** with H_2SO_4/$NaIO_4$ in two phase system (CH_2Cl_2/benzene/water) for 2 h followed by column chromatography.[16] In our hands, the above procedure led to **3**,**4** in low yields (5–8%), which were increased to 15–20% by esterification of the crude product with 5% H_2SO_4 in MeOH.[34] Thus, it became evident that the above conditions favored hydrolysis of ester groups. To solve the problem, we turned to the utility of anhydrous H_5IO_6, thus excluding the possibility of acid-catalyzed hydrolysis of ester groups. Actually, the yields of aldehydes **3**,**4** were dramatically enhanced (up to 65–66%) by treating diols **13**,**14** with H_5IO_6 in 1,4-dioxane for 45 min. Moreover, H_5IO_6 acts as selective reagent even when large quantities (1–1.5 g) of diols **13**,**14** were loaded and only subsequent flash chromatography on alumina was required to obtain pure **3**,**4**[33] (Scheme 2).



Scheme 2 (a): $FeSO_4$, $CHCl_3$, MeOH, pyridine, stream of dry HCl (20 min), then flash chromatography on alumina, 89%. (b) O_2, CH_2Cl_2, r.t., stirring with irradiation, (2 × 950W high-pressure mercury lamps), 22 h, then chromatographic separation on alumina, 32% of **1**, 30% of **2** and 30% recovery of **9**. (c) $NaBH_4$, $CHCl_3$, MeOH, r.t., 10 min, then AcOH, quant. (d) H_5IO_6, 1,4-dioxane, r.t., 45 min, then $NaHCO_3$ and flash chromatography on alumina, 65% of **3** from **1**, 66% of **4** from **2**.

Keeping a facile access to formylporphyrins **1**–**4** in hand, a comparative study of obtaining α-amino phosphonates **5**–**8** by utilizing various procedures became real. Two methods of producing heterocyclic α-amino phosphonates from heterocyclic aldehydes are most popular: a) aldimine, preliminarily obtained by reacting aldehyde with amine, is heated with respective phosphite,[10,11] b) aldimine, generated in situ from corresponding aldehyde and amine, is heated with appropriate phosphite.[12,13]

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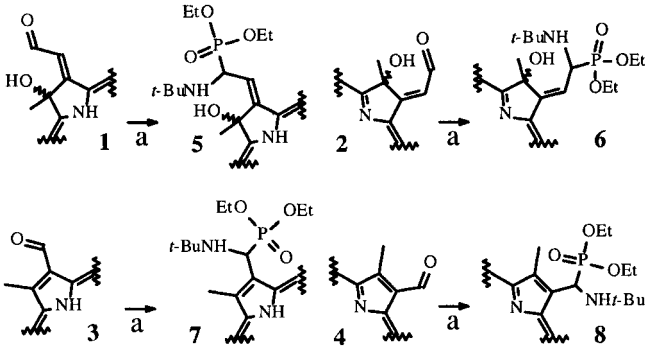
It has been previously reported[35] that porphyrin–aldimines are formed in nearly quantitative yield but could not be isolated as single compounds due to their instability. In trial experiments we observed that brief (2–3 min) heating of aldehydes **1**–**4** with excess of *t*-$BuNH_2$ led to aldimines **17**–**20** which turned back to **1**–**4** either when *t*-$BuNH_2$ was evaporated or under TLC-control (Scheme 1). So, method a) was rejected as a possibility of obtaining **5**–**8**.

Regioselective conversion of **1**–**4** to α-amino phosphonates **5**–**8** in accordance with method b) proved problematic, since vinyl and ester groups of porphyrins are prone to react with aliphatic amines under heating.[36] Actually, numerous attempts to obtain **5**–**8** by conventional heating[12,13] of **1**–**4** with *t*-$BuNH_2$ and $(EtO)_2P(O)H$ in toluene under reflux as well as under milder thermal regime (30–60°C/toluene or $ClCH_2CH_2Cl$) led to complex mixture of unidentified products with no eventual formation of **5**–**8** (Table 1).

Very recently, the use of microwave irradiation was demonstrated to have a beneficial effect in obtaining α-amino phosphonates as compared with the conventional methods.[23,37,38] By applying microwave assistance we actually solved the very problem of producing α-amino phosphonates **5**–**8**. Thus, the reaction of **1**–**4** with *t*-$BuNH_2$ and $(EtO)_2P(O)H$ in $ClCH_2CH_2Cl$ gave **5**–**8** in 62–65% yield after 25 minutes irradiation in domestic oven (102 W) with 15–17% recovery of **1**–**4**. Further attempts to enhance the yields of **5**–**8** by extending the reaction time led to decomposition products (Scheme 3, Table 1).

The final objective of our studies was to optimize the yields of **5**–**8**. Due to our latest findings[23] a broad variety of α-aminophosphonates were obtained in excellent yields by utilizing a combined effect of microwave assistance and catalysis with Lewis acid (CdI_2). Gratifyingly, with a combined assistance of microwaves and CdI_2 the reaction proceeded faster (9–10 min) to give **5**–**8** in substantially enhanced yields (80–84%). The utility of the above system provides the crude **5**–**8** of very high quality and the usual workup requires only evaporation of the solvents and subsequent filtration through a small column equipped with alumina[39] (Schemes 1, 3, Table 1).



Scheme 3 (a) *t*-$BuNH_2$, $(EtO)_2P(O)H$, $ClCH_2CH_2Cl$, MW (102 W), 25 min, then thick layer chromatography on silica gel plates or *t*-$BuNH_2$, $(EtO)_2P(O)H$, $ClCH_2CH_2Cl$, MW (102 W), CdI_2, 9–10 min and subsequent filtration through alumina.

Table 1 Microwave Assisted Synthesis of α-Amino Phosphonates **5**–**8**

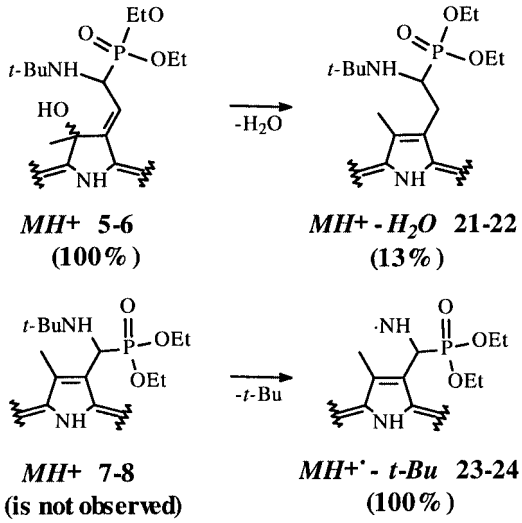
Substrate	Product	Microwave irradiation		Microwave irradiation and CdI_2	
		Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]
1	**5**	25	64	9	82
2	**6**	25	65	10	85
3	**7**	25	60	10	80
4	**8**	25	64	9	84

[a] Yields refer to isolated products.

It should be also stressed that attempts to obtain **5**–**8** by conventional heating of **1**–**4** with *t*-$BuNH_2$ and $(EtO)_2P(O)H$ in $ClCH_2CH_2Cl$ in the presence of CdI_2 were ultimately unsuccessful (Table 1), although the use of CdI_2 in preparing 'usual' heterocyclic α-amino phosphonates had been shown to be efficient.[21] These experiments proved that a synergistic effect of microwaves and CdI_2 is responsible for regioselective conversion of **1**–**4** to **5**–**8**.

In ^{31}P NMR spectra of **5**–**8** signals of phosphorous atoms appeared in the region typical of P-atoms in α-amino phosphonates.[21–23] ^1H NMR spectrum of **5**–**8** confirmed that chemical shifts of protons in ethoxy- and *t*-Bu-groups are in accordance with the data reported for usual α-amino phosphonates.[21–23]

MS spectra of **5**,**6** show a very intense (100%) [MH^+] peak and a daughter peak [MH^+ – 18] (13%). This daughter peak presumably arises from loss of water from **5**,**6**. A possible mechanism for this process is the rearrangement of **5**,**6** into **21**,**22**. In the MS spectra of **7**,**8** molecular ion was absent, the base peak being of [MH^+ – 57] units (100%). The appearance of this peak is attributed to the expulsion of labile *t*-Bu-group from **7**,**8** to give **23**,**24** (Scheme 4).



Scheme 4

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In summary, the first and highly efficient synthesis of α-amino phosphonates **5**–**8** bearing porphyrin nucleus is reported. The final step of constructing **5**–**8** was accomplished regioselectively in excellent yield within a few minutes by utilizing domestic oven and CdI_2 as a catalyst thus unambiguously demonstrating the advantages of this method in comparison with conventional procedures. We are currently investigating the flexibility of this method for obtaining novel α-amino phosphonates by means of varying formylporphyrins, amines and phosphites. Biological studies of **5**–**8** are also underway. The results will be reported in due course.

Acknowledgment

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(25) **Preparation of Photoprotoporphyrins 1**,**2**: Porphyrin **9** (7.083 g, 12.000 mmol) was dissolved in CH_2Cl_2 (2 l) and placed into a 2.5 L two-necked flask fitted with oxygen inlet and effective condenser. Stream of O_2 was passed slowly through the mixture for 40 min. The solution was irradiated for 22 h by using two high-pressure mercury lamps with total capacity of 1.9 kW. Further repeated chromatography on alumina[16] with gradient elution [Et_2O/CH_2Cl_2, 3–12% (v/v)] finally provided **1** (2.391 g, 32%) and **2** (2.244 g, 30%) with recovery of unreacted **9** (2.124 g, 30**%**).
Photoprotoporphyrin IX Dimethyl Ester 1: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.13–10.12 (d, 1 H, CHO, *J* = 6.2 Hz), 9.63, 9.62, 8.29, 7.64 (all s, 4 H, *meso*-H), 7.98–7.90 (dd, J_{trans} = 17.7 Hz, J_{cis} = 11.3 Hz, 1 H, 8-C*H*=CH_2), 6.25–6.21 (dd, J_{gem} = 0.3 Hz, 1H, *trans*-8-CH=CH_2), 6.15–6.12 (dd, 1 H, *cis*-8-CH=CH_2), 6.07–6.05 (d, 1 H, 3-C*H*CHO), 4.37–4.12 (m, 4 H, 2 × C$H_2$$CH_2CO_2CH_3$), 3.71 and 3.70 (2 s, 6 H, 2 × $CH_2CH_2CO_2CH_3$), 3.38, 3.28 and 2.78 (all s, 9 H, 3 × CH_3-ring), 3.27–3.18 (m, 4 H, 2 × CH_2C$H_2CO_2CH_3$), 1.47 (s, 3 H, 2-CH_3), –3.64 and –3.99 (2 br s, 2 H, 2 × NH). MS (ESI$^+$): 623.4 [$C_{36}H_{38}N_4O_6$ + H]. UV–VIS ($CHCl_3$): $\lambda_{max/nm}$ (ε) = 395 (88700), 422 (81800), 570 (13100), 610 (10200), 669 (37100). Anal. Calcd for $C_{36}H_{38}N_4O_6$: C, 69.43; H, 6.15; N, 8.99. Found: C, 69.28; H, 6.21; N, 8.90.
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(33) **Preparation of 3-Formyl-8-vinyldeuteroporphyrin IX Dimethyl Ester 3 and 8-Formyl-3-vinyldeuteroporphyrin IX Dimethyl Ester 4**: Photoprotoporphyrin IX dimethyl ester **1** (1.555 g, 2.500 mmol) was dissolved in $CHCl_3$–MeOH [300 mL, 1:1 (v/v)] and $NaBH_4$ (1.555 g, 41.104 mmol) was added to the solution with stirring. After 10 min reaction mixture was carefully diluted with 10% aq AcOH (400 mL) to decompose the excess of $NaBH_4$. Stirring was continued for 15 min. The reaction mixture was diluted with $CHCl_3$ (250 mL). The organic phase was washed with sat. aq solution of $NaHCO_3$ (500 mL) and then with water until pH of the water phase become neutral. Organic layer was separated and evaporated to dryness. The residue was dissolved in freshly distilled 1,4-dioxane (200 mL) and poured into 200 mL of dioxane containing H_5IO_6 (2.945 g, 12.920 mmol). Reaction mixture was protected from light and stirred vigorously for 45 min at ambient temperature. Wet $NaHCO_3$, prepared by mixing 6 g of $NaHCO_3$ with 2 mL of water, was added and stirring was continued for 5 min. Then inorganic salts were removed on a glass filter under reduced pressure and 1,4-dioxane was evaporated. The remaining solid was dissolved in $CHCl_3$ and flashed on a short column equipped with 150 g of alumina (Merck, 230–400 mesh, Brockmann Grade IV, elution with 2% Et_2O in $CHCl_3$) to yield 962 mg (65%) of porphyrin **3**. Following the above method, *iso*-photoprotoporphyrin IX dimethyl ester **2** was converted into porphyrin **4** in 66% yield.

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3-Formyl-8-vinyldeuteroporphyrin IX dimethyl ester 3: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.30 (s, 1 H, CHO), 10.67, 9.92, 9.85, 9.79 (all s, 4 H, *meso*-H), 8.23–8.16 (dd, J_{trans} = 17.7 Hz, J_{cis} = 11.5 Hz, 1 H, 8-C*H*=CH_2), 6.42–6.38 (d, 1 H, *trans*-8-CH=C*H*$_2$), 6.24–6.21 (d, 1 H, *cis*-8-CH=C*H*$_2$), 4.41–4.37 and 4.29–4.25 (2 t, 4 H, 2 × C*H*$_2$$CH_2CO_2CH_3$), 3.76, 3.67, 3.65, 3.63, 3.57, 3.50 (all s, 18 H, 2 × $CH_2CH_2CO_2$C*H*$_3$ and 4 × CH_3-ring), 3.26–3.21 (2 overlapping t, 4 H, 2 × CH_2C*H*$_2$$CO_2CH_3$), –4.01 (br s, 2 H, 2 × NH). MS (ESI^+): 593.4 [$C_{35}H_{36}N_4O_5$ + H]. UV–VIS ($CHCl_3$): $\lambda_{max/nm}$ (ε) = 419 (155200), 517 (11400), 557 (15100), 583 (9900), 641 (2300). Anal. Calcd for $C_{35}H_{36}N_4O_5$: C, 70.92; H, 6.12; N, 9.45. Found: C, 70.84; H, 6.20; N, 9.48.

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(39) **Microwave irradiation:**
Appropriate aldehyde (**1**/**2**, 20.5 mg, 0.033 mmol; **3**/**4**, 19.5 mg, 0.033 mmol), absolute $ClCH_2CH_2Cl$ (4.0 mL), anhyd *t*-$BuNH_2$ (0.9 mL), CdI_2 (5.1 mg, 0.014 mmol) and freshly distilled $(EtO)_2P(O)H$ (0.9 mL) were placed into 25 mL flask and exposed to microwave irradiation at 102 W using domestic oven (Daewoo KOR-4125G) for 9–10 min. Solvents were completely removed at 0.1 mmHg; the residue was dissolved in CH_2Cl_2 and flashed on a small alumina column (Merck, 230–400 mesh, Brockmann Grade IV) eluting with CH_2Cl_2/Et_2O/pyridine (100:5:0.5). Solvents were evaporated under reduced pressure and the respective α-amino phosphonate **5**–**8** was precipitated from CH_2Cl_2/hexane. ^{1}H NMR, ^{31}P NMR and microanalytical data for some newly obtained α-amino phosphonates **5**–**8** are as follows:

α-Amino Phosphonate Derived from Photoprotoporphyrin IX Dimethyl Ester 5: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.86, 9.67, 9.29, 9.22 (all s, 4 H, *meso*-H), 8.23–8.15 (dd, J_{trans} = 17.7 Hz, J_{cis} = 11.5 Hz, 1 H, 8-C*H*=CH_2), 7.08–7.04 (dd, 1 H, 3^1-CH), 6.38–6.33 (dd, J_{gem} = 1.4 Hz, 1 H, *trans*-8-CH=C*H*$_2$), 6.17–6.14 (dd, 1 H, *cis*-8-CH=C*H*$_2$), 5.36–5.27 (dd, 1 H, 3^2-CH), 4.33–4.27 [q, 4 H, 3^2-P(O)(O*CH*$_2$$CH_3$)$_2$], 4.19–4.08 (2 t, 4 H, 2 × C*H*$_2$$CH_2CO_2CH_3$), 3.66 and 3.64 (2 s, 6 H, 2 × $CH_2CH_2CO_2$C*H*$_3$), 3.59, 3.48, 3.40 (all s, 9 H, 3 × CH_3-ring), 3.21–3.14 (2 overlapping t, 4 H, 2 × CH_2C*H*$_2$$CO_2CH_3$), 2.14 (s, 3 H, 2-$CH_3$), 1.46 [s, 9 H, 3^2-NHC(C*H*$_3$)$_3$], 1.35–1.31 [t, 6 H, 3^2-P(O)(OC*H*$_2$C*H*$_3$)$_2$], –2.41 –2.54 (2 br s, 2 H, 2 × NH-ring). ^{31}P NMR (32 MHz, $CDCl_3$): δ = 24.00 [s, 3^2-*P*(O)$(OCH_2CH_3)_2$]. MS (ESI^+): 816.1 [$C_{44}H_{58}N_5O_8P$ + H]. UV–VIS ($CHCl_3$): $\lambda_{max/nm}$ (ε) = 407 (168400), 502 (13400), 538 (11100), 604 (4300), 664 (32900). Anal. Calcd for $C_{44}H_{58}N_5O_8P$: C, 64.76; H, 7.16; N, 8.58. Found: C, 64.51; H, 7.09; N, 8.54.

α-Amino Phosphonate Derived from 3-Formyl-8-vinyldeuteroporphyrin IX Dimethyl Ester 7: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.24, 9.99, 9.85, 9.84 (all s, 4 H, *meso*-H), 8.25–8.17 (dd, J_{trans} = 17.7 Hz, J_{cis} = 11.8 Hz, 1 H, 8-C*H*=CH_2), 6.37–6.33 (dd, J_{gem} = 0.5 Hz, 1 H, *trans*-8-CH=C*H*$_2$), 6.20–6.16 (m, 2 H, *cis*-8-CH=C*H*$_2$ and 3^1-C*H*), 4.34–4.28 (2 overlapping t, 4 H, 2 × C*H*$_2$$CH_2CO_2CH_3$), 4.22–4.12 [2 overlapping q, 4 H, 3^1-P(O)(OC*H*$_2$$CH_3$)$_2$], 3.65, 3.65, 3.64, 3.57, 3.55, 3.52 (all s, 18 H, 2 × $CH_2CH_2CO_2$C*H*$_3$ and 4 × CH_3-ring), 3.23–3.19 (2 overlapping t, 4 H, 2 × CH_2C*H*$_2$$CO_2CH_3$), 1.30–1.26 [t, 6 H, 3^1-P(O)(OCH$_2$C*H*$_3$)$_2$], 1.24 and 1.23 [2 s, 9 H, 3^1-NHC(C*H*$_3$)$_3$], –4.21 (br s, 2 H, 2 × NH-ring). ^{31}P NMR (32 MHz, $CDCl_3$): δ = 19.49 [s, 3^2-*P*(O)$(OCH_2CH_3)_2$]. MS (ESI^+): 729.2 [$C_{43}H_{56}N_5O_7P$ – *t*-Bu + H]. UV–VIS ($CHCl_3$): $\lambda_{max/nm}$ (ε) = 407 (164100), 503 (11500), 539 (10300), 575 (8900), 628 (3300). Anal. Calcd for $C_{43}H_{56}N_5O_7P$: C, 65.71; H, 7.18; N, 8.91. Found: C, 65.64; H, 7.11; N, 8.89.

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