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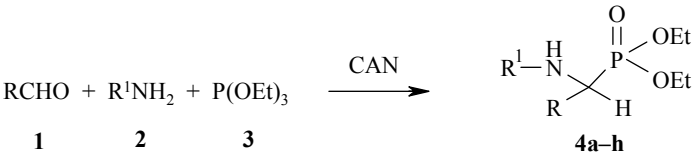
SYNTHESES OF SUBSTITUTED 8-(AMINOBENZYL)DINAPHTHO-DIOXAPHOSPHOCINE 8-OXIDES

M. F. Stephen Babu, B. Hari Babu, K. R. Kishore Kumar Reddy, C. Naga Raju, and C. Suresh Reddy

Substituted (8-aminobenzyl)dinaphthodioxaphosphocine 8-oxides were prepared in a two-step process. The first step of the reaction is one-pot synthesis of α-aminophosphonates by the reaction of aldehydes, amines, and trialkyl phosphite in the presence of ceric ammonium nitrate. The second step is cyclization of α-aminophosphonates with bis(2-hydroxy-1-naphthyl)methane in the presence of a catalytic amount of p toluenesulphonic acid under reflux conditions. Their structures were established by elemental analyses, IR, ^{1}H, ^{13}C, ^{31}P NMR, and mass spectral data.

Keywords: α-aminophosphonates, bis(2-hydroxy-1-naphthyl)methane, dinaphthodioxaphosphocine 8-oxides.

α-Aminophosphonates are a very important class in the chemistry of peptide mimics [1], enzyme inhibitors [2], antibiotics, and pharmacological agents [3]. Phosphonate-containing molecules showed a wide range of biological activities as inhibitors of HIV protease [4], renin [5], herbicides [6], and surrogates for α-aminocarboxylic acids [7].



1 **2** **3** **4a–h**

A versatile, straightforward, and relatively inexpensive solvent free *one-pot* synthesis of α-amino-phosphonates uses ceric ammonium nitrate (CAN) as a catalyst. The viability of this procedure and efficiency of CAN as a catalyst was tested with several structurally varied aldehydes and amines. The reaction was successfully completed with all of them, affording various yields depending on the nature of the reactants. A typical experimental procedure is that a mixture of aldehyde **1**, amine **2**, triethyl phosphite **3**, and a catalytic amount of CAN is refluxed with vigorous stirring to give α-aminophosphonates **4a-h**. The progress of the reaction was monitored by TLC. The crude α-aminophosphonates **4a-h** were purified by column chromatography.

Department of Chemistry, Sri Venkateswara University, Tirupati-517 502, India; e-mail: csureshsvu@yahoo.com Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, 1574-1580, September, 2007. Original article submitted August 17, 2006.

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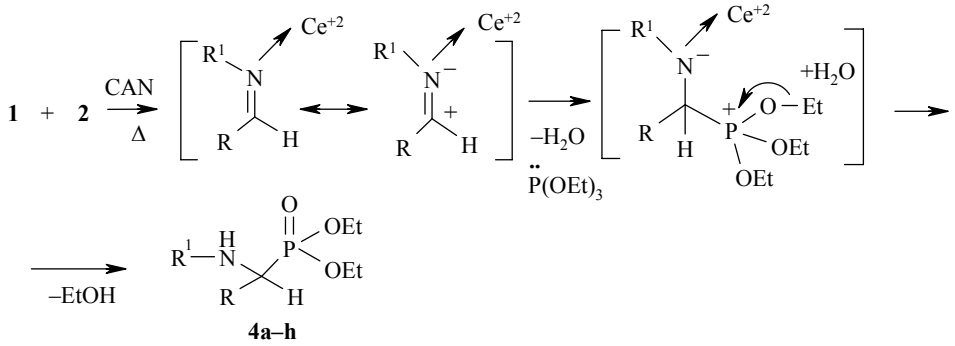
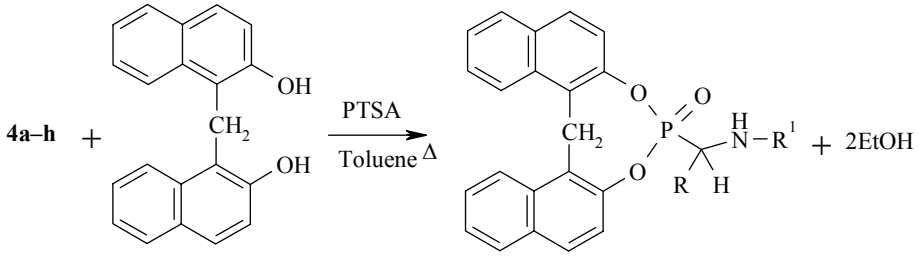
The success of this reaction is attributed to the catalytic role played by CAN, which owing to the ability of cerium(II) to stabilize imines and carbocations, facilitates nucleophilic attack of phosphorus at the imine carbon leading to the formation of ylide. The inherent tendency of ylide to break down to form more stable □-aminophosphonates drives the reaction to completion.



In the second step the cyclization of bis(2-hydroxy-1-naphthyl)methane (**5**) with α-aminophosphonates **4a–h** (Scheme 1) involves a nucleophilic attack of the two oxygen atoms of the two hydroxy groups of the binaphthol on the phosphorus of α-aminophosphonates.

Scheme 1



5 **6a–h**

6 a R = R^1 = Ph; **b** R = Ph, R^1 = $C_6H_4NO_2$-4; **c** R = C_6H_4Me-4, R^1 = Ph;
d R = C_6H_4Me-4, R^1 = C_6H_4I-4; **e** R = R^1 = C_6H_4Cl-4; **f** R = C_6H_4Br-4, R^1 = C_6H_4Cl-4;
g R = R^1 = C_6H_4Me-4; **h** R = R^1 = C_6H_4OMe-4

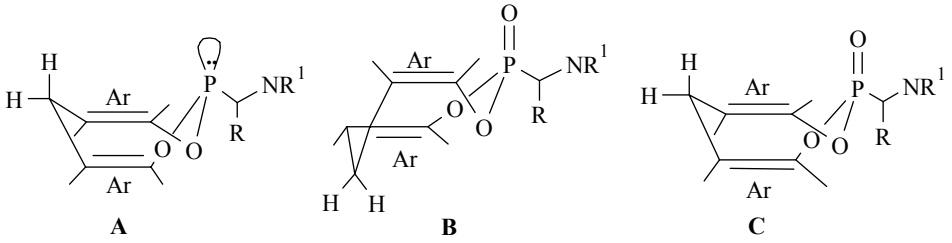
p-Toluenesulfonic acid (PTSA) catalyzes the reaction by protonation of the phosphoryl (P=O) oxygen and renders the phosphorus atom more electrophilic. Thus the nucleophilic attack of the two oxygens of the hydroxyl groups of bis(2-hydroxy-1-naphthyl)methane (**5**) is facilitated. Subsequently, electronic repolarization in the substrates facilitates cyclization of bis(2-hydroxy-1-naphthyl)methane with α-aminophosphonate to form the title compounds **6a-h** with the simultaneous elimination of ethanol. After work-up, the crude solid products obtained were purified by recrystallization from 2-propanol. The presence of characteristic infrared absorption bands for NH (3310–3375), P=O (1225–1290), P–O (945–976) and O–C (1192–1235 cm^{-1}) of P–O–$C_{(aromatic)}$ group confirmed their structures [8-11].

^{1}H NMR spectra of compounds **6a-h** exhibited signals of naphthalenic protons in the region of 6.74-8.24 ppm. A careful analysis of signal pattern revealed that the twelve naphthalene protons showed only six signals. This may be due to the symmetrical disposition of naphthalene moieties around the central dioxa-phosphocine ring. The aromatic protons of the two benzene rings of the substituted dinaphthodioxaphosphocine 8-oxide system in compounds **6a–h** showed a complex multiplet. The distinction of the signals for the protons of

dinaphthodioxaphosphocine moiety and 8-(phenylamino)benzyl moiety could not be made since separate signals for them did not occur due to their identical environment. The other methyl, methoxy, and methylene proton signals of the phenyl and benzyl moieties in compounds **6a-h** were observed in the expected region [12].

The bridged methylene protons of dioxaphosphocine 8-oxide resonated as two distinct doublets in the region of 3.68-4.10 ($^2J_{H,H}$ = 15.6–16.6) and 3.40–3.62 ppm ($^2J_{H,H}$ = 16.2-16.7 Hz) indicating their non-equivalence. A study of the signal pattern in dioxaphosphocines [13] revealed that there is a long-range coupling ($^5J_{H,P}$ = 2.9 Hz) between one of the methylene protons and phosphorus. The long-range coupling is attributed to the proximity of the protons of methy- lene and the lone electron pair on the phosphorus as shown in conformation **A**.

The absence of long-range coupling with phosphorus ($^5J_{H,P}$) in the present series of compounds and the examination of the molecular models suggested an unstrained rigid chair conformation **B** for these compounds. However, a boat-like conformation with increase in the distance between P=O and CH_2 as shown in conformation **C** may also be another possibility in which these compounds may exist. The change in the conformation of dioxaphosphocine ring in the dinaphtho compounds may, perhaps, be attributed to the steric strain due to the bulky naphthyl moiety [14].



The twenty carbons of the 16H-dinaphtho[2,1-*d*:1',2'-*g*][1,3,2]dioxaphosphocine 8-oxide moiety gave only ten resonances because of their symmetrical disposition with respect to the dioxaphosphocine moiety [15]. The carbons 6, 10, 6a, 9a, and 15a,b experienced coupling with phosphorus. The oxygen-bearing carbons 6a, 9a which are connected to phosphorus through oxygen exhibited chemical shifts down field at δ 149.9-151.0 [14], C-6,10 resonated at δ 119.1-120.0, and C-15a,b gave signals at δ 129.5-130.1 ppm [16]. Carbon chemical shifts of the phenylamino and benzyl moieties in compounds **6a-h** were observed downfield by 10-15 ppm. The aliphatic α-carbon was coupled with phosphorus atom and resonated in the region of 53.9-55.2 ppm (J_{P-C} = 123.0-142.0 Hz). Carbon signals of methyl and methoxy substituents are in the expected region [12]. ^{31}P NMR resonance signals appeared in the region 21.8-30.8 ppm [17].

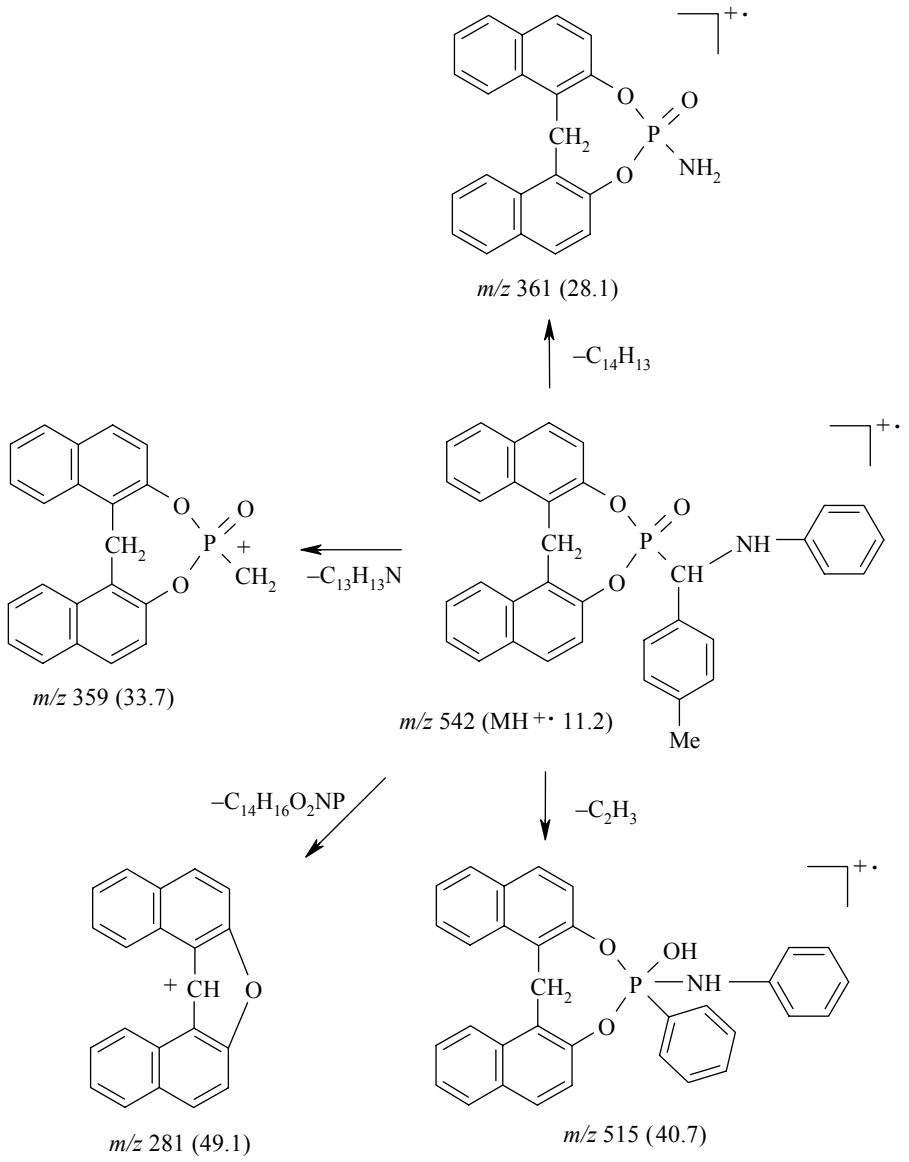
FAB mass spectrum of compound **6c** showed the protonated molecular ion peak at *m/z* 542 $[MH]^+$ with intensity of 20.2 percent and is rationalized in Scheme 2 as a representative of the series. The presence of $[M–C_2H_3]^+$, $[M–C_{13}H_{13}N]^+$, $[M–C_{14}H_{13}]^+$, and $[M–C_{14}H_{16}O_2NP]^+$ ions confirmed its assigned structure.

All compounds **6a–h** were screened for their antimicrobial activity [18, 19] against *Colletotrichum gloeosporiodes* and *Aspergillus flavus,* for antifungal activity and for antibacterial activity against *Xanthomonas citri* and *Pseudomonas solonarum* by using the poisoned food technique [20]. All compounds exhibited a moderate activity toward fungi and bacteria at 500 and 1000 ppm.

EXPERIMENTAL

The melting points are determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. IR spectra are recorded as KBr pellets on a Perkin–Elmer 1430 unit. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on AMX 400 MHz spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C and 162 for ^{31}P) in $CDCl_3$ The chemical shifts (δ) are referenced to TMS (^{1}H, ^{13}C) and 85% H_3PO_4 (^{31}P). FAB mass spectra are recorded on a JEOL DK, 102/DA/600 system using Argon/Xenon at 6 kV, 10 mA.

Scheme 2



Bis(2-hydroxy-1-naphthyl)methane (**5**) was prepared according to the reported procedure [21].

α-Substituted O,O'-Diethylphosphonates 4. A mixture of 4-methylbenzaldehyde (0.6 g, 5.0 mmol), aniline (0.46 g, 5.0 mmol), triethylphosphite (0.83 g, 5.0 mmol), and a catalytic amount of ceric ammonium nitrate (CAN) was stirred under reflux for 30 min. After completion of the reaction as indicated by TLC analysis the residue was purified by column chromatography using 60–120 mesh silica gel as adsorbent and ethyl acetate–hexane, 1:2, as an eluent to afford pure α-aminophosphonate **4b** as solid.

Other phosphonates were prepared analogously.

8-Chlorophenylaminochlorobenzyl-16H-dinaphtho[2,1-*d*:1',2'-*g*][1,3,2]dioxaphosphocine 8-oxide (**6b**). A mixture of α-aminophosphonate **4b** (0.79 g 2.0 mmol) and bis(2-hydroxy-1-naphthyl)methane **5** (0.6 g, 2.0 mmol), and a catalytic amount of *p*-toluene sulfonic acid in toluene (50 ml) was stirred under reflux. 50% of the reaction mixture was distilled off during the course of the reaction to remove ethanol formed in the condensation

reaction. After completion of the reaction as indicated by TLC analysis, the reaction mixture was cooled to room temperature and quenched by the addition of saturated $NaHCO_3$ solution. The reaction mixture was extracted with ethyl acetate and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness to obtain the crude solid product which on recrystallization from 2-propanol afforded an analytically pure compound **6b**, 0.64 g (60%), mp 219-220°C.

Other Members of the Series 6a–h were prepared by adopting the same procedure.

Compound 6a. Yield 62%; mp 198-199°C. IR spectrum, ν_{max}, cm^{-1}: 1262 (P=O), 964, 1210 (P–O–$C_{aromatic}$), 3312 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.80-8.00 (22H, m, H-Ar); 3.72 (d, *J* = 16.3, H_a CH_2); 3.50 (d, *J* = 16.2, H_b CH_2); 4.23 (d, *J* = 20.6, CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 127.9 (2C, C-1,15); 125.0 (2C, C-2,14); 123.4 (2C, C-3,13); 128.1 (2C, C-4,12); 128.5 (2C, C-5,11); 120.0 (2C, C-6,10); 149.9 (2C, C-6a,9a); 129.5 (2C, C-15b,16a); 122.6 (2C, C-15a,16b); 131.4 (2C, C-4a,11a); 26.4 (1C, CH_2); 54.6 (J_{P-C} = 123.0, C-17); 146.2 (C-1'); 126.8 (C-2'); 128.2 (C-3'); 126.2 (C-4'); 127.3 (C-5'); 126.8 (C-6'); 116.8 (C-2"); 130.1 (C-3"); 122.6 (C-4"); 130.1 (C-5"); 116.8 (C-6"). ^{31}P NMR spectrum, δ, ppm: 30.8. Found, %: C 77.35; H 4.94. $C_{34}H_{26}NO_3P$. Calculated, %: C 77.40; H 4.96.

Compound 6b. Yield 58%; mp 202-203°C. IR spectrum, ν_{max}, cm^{-1}: 1272 (P=O), 976, 1220 (P–O–$C_{aromatic}$), 3375 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.74-7.90 (21H, m, H-Ar); 3.68 (d, *J* = 15.6, H_a CH_2); 3.48 (d, *J* = 16.0, H_b CH_2); 5.62 (d, *J* = 9.8, NH); 4.62 (d, *J* = 22.0, CH). ^{31}P NMR spectrum, δ, ppm: 21.8. Found, %: C 73.19; H 4.30. $C_{34}H_{24}N_2O_5P$. Calculated, %: C 73.24; H 4.33.

Compound 6c. Yield 60%; mp 182-183°C. IR spectrum, ν_{max}, cm^{-1}: 1230 (P=O), 952, 1202 (P–O–$C_{aromatic}$), 3327 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.85–8.02 (21H, m, H-Ar); 3.77 (d, *J* = 16.6, H_a CH_2); 3.52 (d, *J* = 16.5, H_b CH_2); 6.46 (d, *J* = 10.2, NH); 4.46 (d, *J* = 22.6, CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 128.0 (2C, C-1,15); 124.5 (2C, C-2,14); 123.8 (2C, C-3,13); 128.0 (2C, C-4,12); 128.7 (2C, C-5,11); 119.1 (2C, C-6,10); 150.6 (2C, C-6a,9a); 130.1 (2C, C-15b,16a); 122.9 (2C, C-15a,16b); 131.2 (2C, C-4a,11a); 28.5 (1C, CH_2); 53.9 ($J_{P–C}$ = 136.0, C-17); 144.5 (C-1'); 126.6 (C-2'); 128.6 (C-3'); 134.1 (C-4'); 126.6 (C-5'); 128.8 (C-6'); 150.6 (C-1"); 112.3 (C-2"); 129.8 (C-3"); 123.1 (C-4"); 129.8 (C-5"); 117.4 (C-6"); 21.3 (C"). ^{31}P NMR spectrum, δ, ppm: 23.7. FAB mass spectrum, *m/z* (*I*, %): 542 $[MH]^{+\bullet}$, 515 (40.7), 420 (21.0), 406 (67.4), 391 (16.8), 361 (28.1), 359 (33.7), 281 (49.1), 252 (100), 216 (16.8), 176 (9.8), 154 (26.6), 138 (28.1), 111 (18.2), 91 (14.0). Found, %: C 77.58; H 5.19. $C_{35}H_{28}NO_3P$. Calculated, %: C 77.62; H 5.21.

Compound 6d. Yield 63%; mp 178–179°C. IR spectrum, ν_{max}, cm^{-1}: 1225 (P=O), 960, 1232 (P–O–$C_{aromatic}$), 3320 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.02–8.10 (21H, m, H Ar); 3.74 (d, *J* = 16.2, Ha CH_2); 3.60 (d, *J* = 16.4, Hb CH_2); 6.20 (1H, br. s, NH); 4.56 (d, *J* = 20.6, CH); 2.10 (3H, s, 4'-CH_3 Ar). ^{31}P NMR spectrum, δ, ppm: 31.6. Found, %: C 63.01; H 3.89. $C_{35}H_{26}INO_3P$. Calculated, %: C 63.07; H 3.93.

Compound 6e. Yield 64%; mp 160-161°C. IR spectrum, ν_{max}, cm^{-1}: 1242 (P=O), 968, 1212 (P–O–$C_{aromatic}$), 3310 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.94-8.20 (20H, m, H Ar); 3.90 (d, *J* = 16.1, H_a CH_2); 3.46 (d, *J* = 16.4, H_b CH_2); 4.80 (1H, br. s, NH); 4.70 (d, *J* = 24.3, CH). ^{31}P NMR spectrum, δ, ppm: 30.8. Found, %: C 68.41; H 4.02. $C_{34}H_{24}Cl_2NO_3P$. Calculated, %: C 68.46; H 4.05.

Compound 6f. Yield 60%; mp 186-187°C. IR spectrum, ν_{max}, cm^{-1}: 1276 (P=O), 945, 1235 (P–O–$C_{aromatic}$), 3324 (NH). ^1H NMR spectrum δ, ppm (*J*, Hz): 7.02-8.24 (20H, m, H-Ar); 4.10 (d, *J* = 16.1, H_a CH_2); 3.62 (d, *J* = 16.7, H_b CH_2); 4.68 (d, *J* = 22.4, CH). ^{31}P NMR spectrum, δ, ppm: 29.2. Found, %: C 63.66; H 3.74. $C_{34}H_{24}BrClNO_3P$. Calculated, %: C 63.71; H 3.77.

Compound 6g. Yield 58%; mp 170-171°C. IR spectrum, ν_{max}, cm^{-1}: 1290 (P=O), 956, 1192 (P–O–$C_{aromatic}$), 3368 (NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.80-7.98 (20H, m, H-Ar); 3.96 (d, *J* = 16.2, H_a CH_2); 3.42 (d, *J* = 16.5, H_b CH_2); 6.10 (1H, br. s, NH); 4.66 (d, *J* = 22.4, CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 128.2 (2C, C-1,15); 124.8 (2C, C-2,14); 123.2 (2C, C-3,13); 128.1 (2C, C-4, 12); 128.4 (2C, C-5,11); 119.8 (2C, C-6,10); 151.0 (2C, C-6a,9a); 129.6 (2C, C-15b,16a); 122.2 (2C, C-15a,16b); 131.4 (2C, C-4a,11a); 26.8 (1C,

CH_2); 55.2 (J_{p-c} = 142.0, C-17); 148.0 (C-1'); 126.4 (C-2'); 127.4 (C-3'); 136.6 (C-4'); 128.1 (C-5'); 126.3 (C-6'); 150.0 (C-1"); 114.2 (C-2"); 132.6 (C-3"); 136.2 (C-4"); 132.6 (C-5"). ^{31}P NMR spectrum, δ, ppm: 31.2. Found, %: C 82.50; H 5.75. $C_{36}H_{30}NO_3P$. Calculated, %: C 82.57; H 5.77.

Compound 6h. Yield 56%; mp 158-159°C. IR spectrum, ν_{max}, cm^{-1}: 1256 (P=O), 966, 1223 (P–O–$C_{aromatic}$), 3318 (NH). ^{1}H NMR spectrum, ™, ppm (*J*, Hz): 6.94–8.06 (20H, m, H-Ar); 3.62 (d, *J* = 16.2, $H_a CH_2$); 3.40 (d, *J* = 16.6, $H_b CH_2$); 4.80 (d, *J* = 23.4, CH). ^{31}P NMR spectrum, δ, ppm: 24.7. Found, %: C 80.07; H 5.58. $C_{36}H_{30}NO_2P$. Calculated, %: C 80.13; H 5.60.

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