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SYNTHESIS AND BIOACTIVITY OF NOVEL BISPHOSPHONATE DERIVATIVES

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Abstract – Synthesis of novel bis-(2,10-dimethyl-4,8-*di*-*t*-*butyl*-12*H*-6-oxido-dibenzo[d,g][1,3,2]dioxaphosphocin -6-yl)2/3/4-substituted phenyl / heteroaryl-methanes were accomplished by Pudovic reaction. Addition of an equimolar quantities of 2,2′-methylene-bis(6-*tert*-butyl-4-methylphenol) **1** and EtOH to PCl_3 afforded cyclic condensation product. This on reaction with respective aldehydes followed by treatment with phosphorus(III) monochloride of **1,** corresponding bisphosphonate intermediates were formed which on subsequent stirring at reflux temperature rearranged from P(III) to P(V) state.

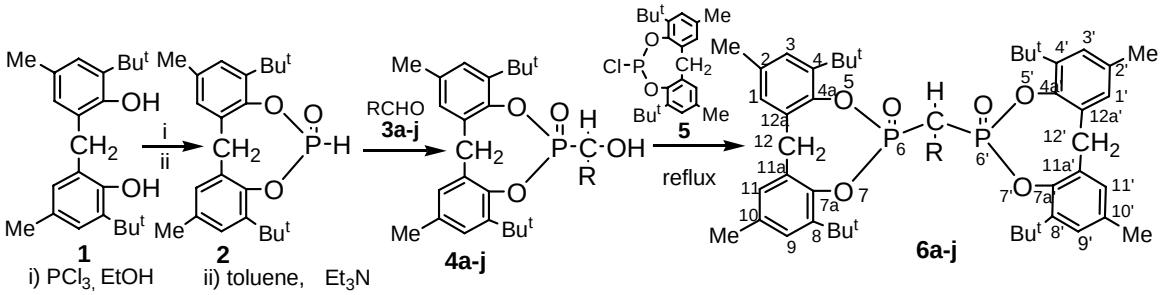
INTRODUCTION

Bisphosphonates, carbon analogues of pyrophosphate, strongly chelate metal ions and adsorb to bone.[1] They have been used to treat osteoporosis[2] and as radio imaging agents[3] and have reduced metastases in breast cancer.[4] Bisphosphonates as anticancer drugs is receiving further attention following the reports that clodronate exhibited antimetastatic activity in cancer patients, decreasing the tumor burden in the bone.[5] Even simple carbonyl bisphosphonates are reported to inhibit HIV-1 replication *in vitro.*[6] Another interesting use is in nuclear medicine as ligands for radiometals as bone-seeking diagnostic and therapeutic agents. Nugent *et al*[7] synthesised a few pyrazoline bisphosphonate esters and studied their anti-inflammatory and antiarthritic activity. Bisphosphonates find application in the prevention and treatment of bone metastases in breast cancer.[8] Oldfield *et al*[9] synthesised nitrogen containing bisphosphonates and tested for their activity in inhibiting the growth of three human cell lines, and found the most active species being a tetrakispivaloylmethyl (POM) ester, having an (average) IC_{50} of 6.8 μM. The most potent bisphosphonates are found[10] in the series containing a heteroaromatic moiety (with at least one nitrogen atom), which is linked via a single methylene group to the geminal bisphosphonate unit. Zoledronic acid[10] is the most potent derivative and it has an ED_{50} of 0.07 mg/kg. However, full potential

of bisphosphonates in chemotherapy is yet to be exploited and it remains to be work of the future.[10-11] In view of the above reports, we have synthesized new bisphosphonates and studied their antimicrobial activity.

RESULTS AND DISCUSSION

Synthesis of novel bis-(2,10-dimethyl-4,8-di-t-butyl-12*H*-6-oxidodibenzo [d,g] [1,3,2] dioxaphosphocin-6-yl) 2/3/4-substituted phenyl / heteroaryl methanes (**6a-j**) were accomplished by Pudovic reaction. Addition of an equimolar amount of 2,2′-methylene-bis (6-*tert*-butyl-4-methylphenol) (**1**) and EtOH to PCl_3 in toluene afforded cyclic condensation product **2**. It is a better procedure to get cyclic hydrogen phosphonates (**2**) when compared to the method of reaction of **1** directly with PCl_3 followed by addition of water in which acid-catalyzed reversible reaction occurs giving back the starting compounds.[12] Phosphonate **2**, was treated with respective aldehydes **3a-j** to get corresponding (2,10-dimethyl-4,8 -di-t-butyl-12*H*-6-oxidodibenzo [d,g] [1,3,2] dioxaphosphocin- 6-yl) 2/3/4 substituted phenyl / heteroaryl methanols (**4a-j**) (Pudovic reaction). Reaction of **4a-j** with 6-chloro-2,10-dimethyl-4,8-di-t-butyl -12*H*-dibenzo[d,g] [1,3,2] dioxaphosphocin (**5**), which was prepared by reacting **1** with PCl_3 in N_2 atmosphere corresponding bisphosphonate intermediates were obtained. These on subsequent stirring at reflux temperature for about 6 hrs rearranged from P(III) to P(V) state[12-13] and afforded bis(2,10-dimethyl-4,8-di-t-butyl-12*H*-6-oxidodibenzo[d,g][1,3,2]dioxaphosphocin-6-yl) 2/3/4 substituted phenyl / heteroaryl methanes (**6a-j**).



Compd.	R	Compd.	R	Compd.	R
a	$-CCl_3$	**e**	3"-NO_2-C_6H_4	**h**	
b	4"-Me-C_6H_4	**f**	4"-HO-C_6H_4	**i**	
c	4"-Cl-C_6H_4	**g**	4"-MeO-C_6H_4	**j**	
d	4"-Br-C_6H_4				

The structures of all the compounds are confirmed by elemental analysis, multi NMR and FAB mass spectrometry. The compounds **6a-j** were obtained as isomeric products. Their separation could not be effected by fractional crystallization. A few carbon NMR signals were split into two signals due to the presence of diastereoisomers in the sample.[14] The presence of two forms in the solution state is further evidenced by the presence of two phosphorus chemical shifts in the ^{31}P NMR spectra of all the

synthesized compounds **6a-j**.

All the title compounds showed IR absorption bands[15-17] in the region 1276-1262 (P=O), 769-761 (P-C_{aliph}), 1219-1201 [O-C of P-O-$C_{(aromatic)}$] and 956-931 [P-O of P-O-$C_{(aromatic)}$] cm^{-1}.In the ^{31}P-NMR, all the compounds **6a-j** exhibited two distinct ^{31}P chemical shifts for the two phosphorus (P_α and P_β) atoms present in them. This indicates their high magnitude of non-equivalence which might be arising due to their existence in two different isomers because of the restricted rotation between them.[18-19]

The aromatic protons of the title compounds showed multiplets at δ 7.82-6.08. The bridged methyne (P-C<u>H</u>-P) proton resonated as a triplet due to coupling with phosphorous[20] in the region 3.61-3.66 ppm (t, $J_{P\text{-}C\text{-}H}$=14.5-14.7 Hz). The chemical shifts of other protons are observed in the expected regions for the compounds **6a-j**. Interpretation of the ^{13}C NMR data was based on additivity rules, computed chemical shifts of starting compound **1**, carbon couplings with phosphorus and intensity of signals. The oxygen bearing C(4a) & C(7a) and C(4′) & C(7′) resonated as doublets in the downfield region at δ 149.98 – 149.61 ($^2J_{POC}$ = 5.3-6.9 Hz). The chemical shifts of the bridged C(11a) & C(12a) and C(11′) & C(12′) appeared as low intensity signals at δ 126.25-125.26.[21] The bulky t-butyl groups attached to C(4) & C(8) and C(4′) & C(8′) showed signals in the region δ 136.79-136.40. The singlet at δ 131.86-130.85 is assigned to C(2) & C(10) and C(2′) & C(10′). The signals in the regions δ 20.96-20.94 and 31.27-30.53 were ascribed to methyl carbons [-C(<u>C</u>H_3)] and t-butyl group [-<u>C</u>$(CH_3)_3$] attached to C-2 & 10 / C-2′ & 10′ and C-4 & 8 / C-4′ & 8′ respectively. The bridged chiral carbon in these compounds gave the signal in the region δ 48.25-44.76.[20] Mass spectral data for **6b, 6g** and **6i** were recorded. All the three compounds exhibited M+1 and $M^{+\bullet}$ ions in their mass spectra. Multinuclear NMR and mass spectral data conclusively confirm the structures of **6a- j**.

ANTIMICROBIAL ACTIVITY

The compounds **6a-j** were screened at two different concentrations (25, 75 μg / disc) for their antifungal activity on *Aspergillus niger* and *Fusarium solani*, Nystatin (25 μg / disc) is used as standard according to disc-diffusion method.[22] The fungal cultures were grown on potato dextrose broth at 25 °C for 3 hours and finally spore suspension was adjusted to 10^6 spores/ disc. Their antibacterial activity was evaluated against *Staphylococcus aureus* and *Escherichia coli* (10^5 cell / mL) on nutrient agar plates at 37 °C for 24 hours.[23] Ciprofloxacin is used as standard antibiotic. The title compounds were potent against tested bacteria. The compounds showed promising antibacterial activity against the bacteria when compared with that of standard, whereas their antifungal activity is moderate. It is interesting to observe that the nitrogen containing analogues **6e** and **6j** possess significant antibacterial activity (Table 1).

Table 1: Antibacterial and antifungal activities[a] of compounds **6a-j** in terms of zone of inhibition (mm)

Compd.	Bacteria				Fungi			
	Staphylococcus aureus(μg/disc)		*Escherichia coli* (μg/disc)		*Aspergillus niger*(μg/disc)		*Fusarium solani* (μg/disc)	
	25	75	25	75	25	75	25	75
6a	5	6	3	5	3	5	4	5
6b	2	3	-	3	-	2	3	-
6c	3	5	5	5	5	4	5	4
6d	-	3	2	-	2	-	-	-
6e	5	9	4	7	4	5	4	6
6f	4	5	3	5	2	3	5	-
6g	-	3	-	2	-	2	-	-
6h	3	5	4	5	3	2	5	3
6i	3	7	3	6	2	3	3	5
6j	6	9	5	8	4	5	4	6
Ciprofloxacin	-	8	-	6	-	-	-	-
Nystatin	-	-	-	-	-	6	-	4

[a] concentrations expressed in ppm, '-' indicates no activity.

In summary, we have adopted an effective and simple route for the synthesis of novel bisphosphonates, whose structures were supported by elemental and spectral analyses. The reaction can be performed smoothly in dry toluene in the presence of a base and the products are relatively easy to isolate and purify.

EXPERIMENTAL

The melting points were determined on a Mel-Temp apparatus and were uncorrected. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. All IR spectra were 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, operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P as solutions in $CDCl_3$ and the chemical shifts were referenced to TMS (^{1}H & ^{13}C) and 85% H_3PO_4 (^{31}P). 2,2′-methylene-bis (6-*tert*-butyl-4-methyl) phenol (**1**) was procured from Aldrich chemical company, USA.

Synthesis of Bis (2,10-dimethyl-4,8-di-t-butyl-12*H*-6-oxidodibenzo[d,g] [1,3,2] dioxaphosphocin-6-yl)-4-methylphenylmethane (6b).

It is obtained in 4 steps. In step 1,2,2′-methylene-bis(6-*tert*-butyl-4-methylphenol)(**1**, 0.68 g, 0.002

mol) was dissolved in 25 mL of dry toluene and to this EtOH (0.09 g, 0.002 mol) was added. The mixture was cooled to 5-10 °C. To this PCl_3 (0.27 g, 0.002 mol) was added dropwise taken in 10 mL of dry toluene. The reaction flask was cooled extremely so that the temperature did not rise above 25 °C. The reaction mixture was stirred at 25 °C for 4 h. Finally the reaction mixture was warmed on the steam bath to complete the removal of the by-products, 2,2′-methylene-bis(6-*tert-butyl*-4-methyl) hydrogen phosphonate (**2**) was obtained after removal of toluene at reduced pressure as white crystalline solid, mp 155-157 °C.

In step 2,4-methylbenzaldehyde (**3b**, 0.12 g, 0.001 mol) and trietylamine (0.50 g, 0.005 mol) in dry toluene was added at 5-8 °C to **2** (0.38 g, 0.001 mol) in toluene and mixture was stirred for 4 h to get 2,10-dimethyl-4,8-di-*t*-butyl-12*H*-6-oxidodibenzo[d,g][1,3,2]dioxaphosphocin-6-yl)-4-methylphenylmethanol (**4b**). In step 3, compound **1** was treated with PCl_3 in toluene under nitrogen atmosphere in the presence of triethylamine to get **5**.

In step 4, to the cold (5-7 °C) solution of **4b** (0.50 g, 0.001 mol) and triethylamine (0.1 g, 0.001 mol) taken in a new reaction flask in toluene, **5** (0.38 g, 0.001 mol) was added. Temperature was slowly raised to 50°C and stirring was continued for 6 h and then at refluxing temperature for 6 more h. Triethylamine hydrochloride was separated by filtration and the solvent from the filtrate was removed under reduced pressure. The residue was recrystallised from EtOH to afford the title compound **6b**. The title compounds **6a** and **6c-j** were prepared by adopting the same procedure.

Physical, Analytical and Spectral Data for the Compounds 6a-j

6a ;Yield 73%, mp 112-114 °C (EtOH). IR (KBr): ν_{max} 1276 (P=O), 1219, 934 P-O-$C_{(aromatic)}$ 768 (P-C) cm^{-1}, ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 0.77, 4.94, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.38-7.25 (m, 8H, Ar-H), 4.39-4.43 (m, 4H, 2x-CH_2-), 3.62-3.65(t, *J*=14.7 Hz, 1H, P-CH-P), 2.25 (s, 12H, CH_3), 1.39 (s, 36H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 129.4 (C-1&11/ C-1'&C11'), 131.9 (C-2&10/ C-2'&10'), 127.1 (C-3&9/ C-3'&9'), 136.4 (d, *J*=4.2 Hz, C-4&8/ C-4'&8'), 149.9 (d, *J*=6.3 Hz, C-4a&7a/ C-4a'& 7a'), 126.3 (d, *J*=4.2 Hz, C-11a&12a/ C-11a'&12a'), 32.1 (-CH_2-12&12'), 20.9 ((CH_3), 2,10/2',10') 34.6 (*t*-$\underline{C}(CH_3)_3$, 4,8/4'8'), 30.5 (*t*-$\underline{C}(CH_3)_3$, 4,8/4'8') , 48.3 (P-CH-P) 106.8 (-CCl_3). Anal. Calcd for $C_{48}H_{61}O_6P_2Cl_3$: C 63.89; H 6.76. Found: C 63.85; H 6.79 %.

6b ;Yield 71%, mp 118-120 °C (EtOH). IR (KBr): ν_{max} 1262 (P=O), 1201, 956 P-O-$C_{(aromatic)}$ 768 (P-C) ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 0.77, 4.94, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.36-7.24 (m, 12H, Ar-H), 4.39- 4.58 (m, 4H, 2x-CH_2-), 3.61-3.65 (t, *J*=14.7 Hz, 1H, P-CH-P), 2.28 (s, 12H, CH_3), 1.37 (s, 36H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 129.4 (C-1&11/ C-1'&11'), 130.9 (C-2&10/ C-2'& 10'), 127.7 (C-3&9/ -3'&9'), 136.5(d, *J*=4.1 Hz, C-4&8/ C-4'&8'), 149.9 (d, *J*=6.9 Hz, C-4a&7a/ C-4a'& 7a'), 125.3

(d, *J*=4.2 Hz, C-11a&12a/ C-11a'&12a'), 32.0 (-CH_2-12&12'), 20.9 ((CH_3), 2,10/2',10') 34.6 (*t*-C(CH_3)$_3$, 4,8/4'8'), 31.3(*t*-C(CH_3)$_3$, 4,8/4'8'), 46.1 (P-CH-P), 126.3 (C-1"), 129.6(C-2"&6"), 131.9 (C-3"&5"), 140.7(C-4"), 29.9(4"-CH_3) FAB-MS, m/z (%): 875 ($M^{+\bullet}$ + 1, 16), 874 ($M^{+\bullet}$, 14), 845 (19), 790 (23), 774(41), 725 (11), 664 (5), 660 (4), 609 (4), 562 (8), 387 (100), 340 (53), 331 (12), 275 (28), 265 (8), 223 (6),77 (48), 161 (27), 136 (21), 105 (11), 91 (9). Anal. Calcd for $C_{54}H_{68}O_6P_2$: C 74.14;H 7.78. Found: C 74.07;H 7.74 %.

6c ; Yield 81%, mp 151-153 °C (EtOH). IR (KBr): ν_{max} 1276 (P=O), 1218, 931 P-O-$C_{(aromatic)}$ 769 (P-C) cm^{-1}, ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 0.77, 4.94, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.31-7.18 (m, 12, Ar-H), 4.32-4.41 (m, 4H, 2x-CH_2-), 3.61-3.64 (t, *J*=14.7 Hz, 1H, P-CH-P), 2.25 (s, 12H, CH_3), 1.33 (s, 36H, (CH_3)$_3$). Anal. Calcd for $C_{53}H_{61}O_6P_2Cl$: C 71.10; H 7.26. Found: C 71.07; H 7.22 %.

6d ; Yield 76%, mp 139-141 °C (EtOH). IR (KBr): ν_{max} 1270(P=O), 1211, 943 P-O-$C_{(aromatic)}$ 763 (P-C) cm^{-1}, ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 0.77, 4.94, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.37-7.38 (m, 12H, Ar-H), 4.38- 4.41 (m, 4H, 2x-CH_2-), 3.61-3.65 t, *J*=14.7 Hz, 1H, P-CH-P), 2.28 (s, 12H, CH_3), 1.38 (s, 36H, C(CH_3)$_3$). Anal. Calcd for $C_{53}H_{65}O_6P_2Br$: C 67.73; H 6.92. Found: C 67.69; H 6.89 %.

6e ; Yield 77%, mp 115-117 °C (EtOH). IR (KBr): ν_{max} 1276 (P=O), 1219, 934 P-O-$C_{(aromatic)}$ 768 (P-C) cm^{-1}, ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 0.77, 4.94, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.38-7.66 (m, 12H, Ar-H), 4.39-4.43 (m, 4H, 2x-CH_2-), 3.62-3.66 (t, *J*=14.7 Hz, 1H, P-CH-P), 2.29 (s, 12H, CH_3), 1.39 (s, 36H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 128.3 (C-1&11/ C-1'&11'), 131.7 (C-2&10/ C-2'&10'), 127.8 (C-3&9/ C-3'&9'), 135.6 (d, *J*=4.8 Hz, C-4&8/ C-4'&8'), 149.6 (d, *J*=6.3 Hz, C-4a&7a/ C-4a'& 7a'), 125.3 (d, *J*=4.2 Hz, C-11a&12a/ C-11a'&12a'), 31.3(-CH_2-12&12'), 20.3 ((CH_3), 2,10/2',10') 34.6(*t*-C(CH_3)$_3$, 4,8/4'8'),30.5 (*t*-C(CH_3)$_3$, 4,8/4'8') 44.8 (P-CH-P), 126.8(C-1"),129.6(C-2"), 142.6 (C-3"), 128.7(C-4"), 129.4 (C-5"), 136.6(C-6"). Anal. Calcd for $C_{53}H_{65}NO_8P_2$: C 70.27; H 7.18; N 1.54. Found: C 70.23; H 7.15; N 1.51 %.

6f ; Yield 73%, mp 124-126 °C (EtOH). IR (KBr): ν_{max} 1273(P=O), 1207, 933 P-O-$C_{(aromatic)}$ 761 (P-C) cm^{-1}, ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 4.88, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.37-7.24 (m, 12H, Ar-H), 4.38-4.43 (m, 4H, 2x-CH_2-), 3.61-3.65 (t, *J*=14.7 Hz, 1H, P-CH-P), 2.25 (s, 12H, CH_3), 1.37 (s, 36H, C(CH_3)$_3$). Anal. Calcd for $C_{53}H_{66}O_7P_2$: C 72.60; H 7.53. Found: C 72.54; H 7.48 %.

6g ; Yield 68%, mp 109-111 °C (EtOH). IR (KBr): ν_{max} 1269 (P=O), 1213, 940 P-O-$C_{(aromatic)}$ 765 (P-C) cm^{-1}, ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 0.77, 4.94^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.38-7.26 (m, 12H,

Ar-H), 4.39-4.43 (m, 4H, 2x-CH_2-), 3.62-3.66 (t, *J*=14.7 Hz, 1H, P-CH-P), 2.29 (s, 12H, CH_3), 1.39 (s, 36H, $C(CH_3)_3$); FAB-MS m/z (%):906 ($M^{+\bullet}$+1, 28), 905 ($M^{+\bullet}$, 21), 845 (5), 844 (3), 774 (97), 727 (18), 725 (16), 708 (9), 595 (2), 572 (3), 562 (16), 516 (38), 488 (42), 460 (9), 387 (99), 386 (51), 340 (100), 339 (33), 275 (41), 265 (12), 223 (16), 177 (97), 161 (67), 102 (69), 91 (11). Anal. Calcd for $C_{54}H_{68}O_7P_2$: C 72.80; H 7.64; Found: C 72.85; H 7.59 %.

6h ; Yield 63%, mp 120-122 °C (EtOH). IR (KBr): ν_{max} 1271 (P=O), 1215, 941 P-O-$C_{(aromatic)}$ 764(P-C) cm^{-1}, ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 0.77, 4.94, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.08-7.82 (m, 11H, Ar-H), 4.32-4.39 (m, 4H, 2x-CH_2-), 3.63-3.66 (t, *J*=14.7 Hz, 1H, P-CH-P), 2.17 (s, 12H, CH_3), 1.45 (s, 36H, $C(CH_3)_3$). Anal. Calcd for $C_{51}H_{64}O_7P_2$: C 72.00; H 7.52. Found: C 72.06; H 7.48 %.

6i ; Yield 65%, mp 134-136 °C (EtOH). IR (KBr): ν_{max} 1276 (P=O), 1218, 934 P-O-$C_{(aromatic)}$ 769 (P-C) cm^{-1}, ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 0.77, 4.94, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.38-7.25 (m, 11H, Ar-H), 4.39-4.43 (m, 4H, 2x-CH_2-), 3.62-3.65 (t, *J*=14.7 Hz, 1H, P-CH-P), 2.29 (s, 12H, CH_3), 1.39 (s, 36H, $C(CH_3)_3$); FAB-MS m/z (%): 867 ($M^{+\bullet}$ +1, 23), 866 ($M^{+\bullet}$, 21), 845 (4), 808 (4), 774 (23), 727 (6), 658 (3), 562 (6), 387 (100), 340 (57), 331 (13), 275 (21), 239 (7), 223 (9), 177 (43), 161 (23), 154 (21), 136 (18), 105 (11), 91 (9). Anal. Calcd for $C_{51}H_{64}O_6P_2S$: C 70.66; H 7.39. Found: C 70.63 H 7.44 %.

6j ; Yield 74%, mp 129-131 °C (EtOH). IR (KBr): ν_{max} 1274 (P=O), 1219, 934 P-O-$C_{(aromatic)}$ 769 (P-C) cm^{-1}, ^{31}P NMR ($CDCl_3$, 161.9 MHz) δ: 0.77, 4.94, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.38-7.26 (m, 12H, Ar-H), 4.37-4.40 (m, 4H, 2x-CH_2-), 3.61-3.65 (t, *J*=14.7 Hz, 1H, P-CH-P), 2.28 (s, 12H, CH_3), 1.38 (s, 36H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 129.4 (C-1&11/ C-1'&11'), 131.9 (C-2&10/ C-2'&10'), 127.1 (C-3&9/ C-3'&9'), 136.7 (d, *J*=3.8, Hz, C-4&8/ C-4'&8'), 149.6(d, *J*=5.3 Hz, C-4a&7a/ C-4a'&7a'), 126.3 (d, *J*=4.2 Hz, C-11a&12a/ C-11a'&12a'), 31.1 (-CH_2-12&12'), 20.9 ((CH_3), 2,10/2',10') 34.6 (*t*-$\underline{C}(CH_3)_3$, 4,8/4'8'), 30.5 (*t*-$C(\underline{C}H_3)_3$, 4,8/4',8'),46.3 (P-CH-P), 181.7(C-2"&6"), 128.7(C-3"&5"), 178.6(C-4"). Anal. Calcd for $C_{52}H_{65}NO_6P_2$: C 72.47; H 7.54; N 1.62. Found: C 72.50; H 7.49; N 1.58 %.

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