SYNTHESIS AND BIOACTIVITY OF NOVEL BISPHOSPHONATE DERIVATIVES

B. Hari Babu,a G. Syam Prasad,a M. F. Stephen Babu,a Pallamreddy Haranath,a S. Hemadri Reddy,b and C. Naga Raju*a

aDepartment of Chemistry, Sri Venkateswara University, Tirupati-517502, India
bDepartment of Biotechnology, Sri Venkateswara University, Tirupati, India
E-mail: naga_raju04@yahoo.co.in

Abstract – Synthesis of novel bis-(2,10-dimethyl-4,8-di-t-butyl-12H-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 PCl3 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 osteoporosis2 and as radio imaging agents3 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 al7 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 al9 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) IC50 of 6.8 µM. The most potent bisphosphonates are found10 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 acid10 is the most potent derivative and it has an ED50 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.\textsuperscript{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-\textit{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.\textsuperscript{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\textsuperscript{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).

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.\textsuperscript{14} The presence of two forms in the solution state is further evidenced by the presence of two phosphorus chemical shifts in the \textsuperscript{31}P NMR spectra of all the
synthesized compounds 6a-j.

All the title compounds showed IR absorption bands in the region 1276-1262 (P=O), 769-761 (P-C\textsubscript{aliph}), 1219-1201 [O-C of P-O-C\textsubscript{aromatic}] and 956-931 [P-O of P-O-C\textsubscript{aromatic}] cm\textsuperscript{-1}. In the \textsuperscript{31}P-NMR, all the compounds 6a-j exhibited two distinct \textsuperscript{31}P chemical shifts for the two phosphorus (P\textalpha and P\textbeta) 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.\textsuperscript{18,19}

The aromatic protons of the title compounds showed multiplets at \(\delta\) 7.82-6.08. The bridged methyne (P-CH-P) proton resonated as a triplet due to coupling with phosphorous\textsuperscript{20} in the region 3.61-3.66 ppm (t, \(J\textsubscript{P-C-H}=14.5-14.7\) Hz). The chemical shifts of other protons are observed in the expected regions for the compounds 6a-j. Interpretation of the \textsuperscript{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(4a') & C(7a') resonated as doublets in the downfield region at \(\delta\) 149.98 – 149.61 (\(^{2}J\textsubscript{POC} = 5.3-6.9\) Hz). The chemical shifts of the bridged C(11a) & C(12a) and C(11a') & C(12a') appeared as low intensity signals at \(\delta\) 126.25-125.26.\textsuperscript{21} The bulky t-butyl groups attached to C(4) & C(8) and C(4') & C(8') showed signals in the region \(\delta\) 136.79-136.40. The singlet at \(\delta\) 131.86-130.85 is assigned to C(2) & C(10) and C(2') & C(10'). The signals in the regions \(\delta\) 20.96-20.94 and 31.27-30.53 were ascribed to methyl carbons [-C(CH\textsubscript{3})] and t-butyl group [-C(CH\textsubscript{3})\textsubscript{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 \(\delta\) 48.25-44.76.\textsuperscript{20} Mass spectral data for 6b, 6g and 6i were recorded. All the three compounds exhibited M+1 and M\textsuperscript{*} 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 \(\mu\)g / disc) for their antifungal activity on *Aspergillus niger* and *Fusarium solani*, Nystatin (25 \(\mu\)g / disc) is used as standard according to disc-diffusion method.\textsuperscript{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\textsuperscript{5} cell / mL) on nutrient agar plates at 37 °C for 24 hours.\textsuperscript{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)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Bacteria</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus (µg/disc)</td>
<td>Escherichia coli (µg/disc)</td>
</tr>
<tr>
<td>6a</td>
<td>25  75</td>
<td>25  75</td>
</tr>
<tr>
<td>6b</td>
<td>5   6</td>
<td>3   5</td>
</tr>
<tr>
<td>6c</td>
<td>2   3</td>
<td>-   -</td>
</tr>
<tr>
<td>6d</td>
<td>3   5</td>
<td>5   5</td>
</tr>
<tr>
<td>6e</td>
<td>5   9</td>
<td>4   7</td>
</tr>
<tr>
<td>6f</td>
<td>4   5</td>
<td>3   5</td>
</tr>
<tr>
<td>6g</td>
<td>-   -</td>
<td>2   -</td>
</tr>
<tr>
<td>6h</td>
<td>3   5</td>
<td>4   5</td>
</tr>
<tr>
<td>6i</td>
<td>3   7</td>
<td>3   6</td>
</tr>
<tr>
<td>6j</td>
<td>6   9</td>
<td>5   8</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nystatin</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ 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$_3$PO$_4$ ($^{31}$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-12H-6-oxidobenzo[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 PCl₃ (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 triethylamine (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-12H-6-oxidodibenzo[d,g][1,3,2]dioxaphosphocin-6-yl)-4-methylphenylmethanol (4b). In step 3, compound 1 was treated with PCl₃ 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, ³¹P NMR (CDCl₃, 161.9 MHz) δ: 0.77, 4.94, ¹H NMR (CDCl₃, 400 MHz) δ: 6.38-7.25 (m, 8H, Ar-H), 4.39-4.43 (m, 4H, 2x-CH₂), 3.62-3.65(t, J=14.7 Hz, 1H, P-CH-P), 2.25 (s, 12H, CH₃), 1.39 (s, 36H, C(CH₃)₃); ¹³C NMR (CDCl₃, 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 (-CH₂-12&12’), 20.9 ((CH₃), 2,10&12,10’ 34.6 (t-C(CH₃)₃), 4.8/4’8’), 30.5 (t-C(CH₃)₃), 4.8/4’8’), 48.3 (P-CH-P) 106.8 (-CCl₃). Anal. Calcd for C₄₈H₆₁O₆P₂Cl₃: 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) cm⁻¹, ³¹P NMR (CDCl₃, 161.9 MHz) δ: 0.77, 4.94, ¹H NMR (CDCl₃, 400 MHz) δ: 6.36-7.24 (m, 12H, Ar-H), 4.39- 4.58 (m, 4H, 2x-CH₂), 3.61-3.65 (t, J=14.7 Hz, 1H, P-CH-P), 2.28 (s, 12H, CH₃), 1.37 (s, 36H, C(CH₃)₃); ¹³C NMR (CDCl₃, 100 MHz) δ: 129.4 (C-1&11/ C-1’&C11’), 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 (-CH2-12&12’), 20.9 ((CH3), 2,10/2’,10’) 34.6 (\(t\)-C(CH3), 4,8/4’8’), 31.3(\(t\)-C(CH3), 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”-CH3) FAB-MS, m/z (%): 875 (M* + 1, 16), 874 (M*, 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 C54H68O6P2: C 74.14; H 7.78. Found: C 74.07; H 7.74 %.

6c ; Yield 81%, mp 151-153 °C (EtOH). IR (KBr): \(\nu_{max}\) 1276 (P=O), 1218, 931 P-O-C (aromatic) 769 (P-C) cm⁻¹, 31P NMR (CDCl3, 161.9 MHz) \(\delta\): 0.77, 4.94, \(^1\)H NMR (CDCl3, 400 MHz) \(\delta\): 6.31-7.18 (m, 12, Ar-H), 4.32-4.41 (m, 4H, 2x-CH2-), 3.61-3.64 (t, \(J=14.7\) Hz, 1H, P-CH-P), 2.25 (s, 12H, CH3), 1.33 (s, 36H, (CH3)3 ). Anal. Calcd for C53H61O6P2Cl: C 71.10; H 7.26. Found: C 71.07; H 7.22 %.

6d ; Yield 76%, mp 139-141 °C (EtOH). IR (KBr): \(\nu_{max}\) 1270(P=O), 1211, 943 P-O-C (aromatic) 763 (P-C) cm⁻¹, 31P NMR (CDCl3, 161.9 MHz) \(\delta\): 0.77, 4.94, \(^1\)H NMR (CDCl3, 400 MHz) \(\delta\): 6.37-7.38 (m, 12H, Ar-H), 4.38-4.41 (m, 4H, 2x-CH2-), 3.61-3.65 t, \(J=14.7\) Hz, 1H, P-CH-P), 2.28 (s, 12H, CH3), 1.38 (s, 36H, C(CH3)3). Anal. Calcd for C53H65O6P2Br: C 67.73; H 6.92. Found: C 67.69; H 6.89 %.

6e ; Yield 77%, mp 115-117 °C (EtOH). IR (KBr): \(\nu_{max}\) 1276 (P=O), 1219, 934 P-O-C(aromatic) 766 (P-C) cm⁻¹, 31P NMR (CDCl3, 161.9 MHz) \(\delta\): 0.77, 4.94, \(^1\)H NMR (CDCl3, 400 MHz) \(\delta\): 6.38-7.66 (m, 12H, Ar-H), 4.39-4.43 (m, 4H, 2x-CH2-), 3.62-3.66 t, \(J=14.7\) Hz, 1H, P-CH-P), 2.29 (s, 12H, CH3), 1.39 (s, 36H, C(CH3)3); 13C NMR (CDCl3, 100 MHz) \(\delta\): 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(-CH2-12&12’), 20.3 ((CH3), 2,10/2’,10’) 34.6(t-(CH3)3, 4,8/4’8’),30.5 (t-(CH3)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 C53H65NO8P2: C 70.72; 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): \(\nu_{max}\) 1273 (P=O), 1207, 933 P-O-C(aromatic) 761 (P-C) cm⁻¹, 31P NMR (CDCl3, 161.9 MHz) \(\delta\): 4.88, \(^1\)H NMR (CDCl3, 400 MHz) \(\delta\): 6.37-7.24 (m, 12H, Ar-H), 4.38-4.43 (m, 4H, 2x-CH2-), 3.61-3.65 t, \(J=14.7\) Hz, 1H, P-CH-P), 2.25 (s, 12H, CH3), 1.37 (s, 36H, C(CH3)3). Anal. Calcd for C53H66O2P2: C 72.60; H 7.53. Found: C 72.54; H 7.48 %.

6g ; Yield 68%, mp 109-111 °C (EtOH). IR (KBr): \(\nu_{max}\) 1269 (P=O), 1213, 940 P-O-C(aromatic) 765 (P-C) cm⁻¹, 31P NMR (CDCl3, 161.9 MHz) \(\delta\): 0.77, 4.94 \(^1\)H NMR (CDCl3, 400 MHz) \(\delta\): 6.38-7.26 (m, 12H,
Ar-H), 4.39-4.43 (m, 4H, 2x-CH2-), 3.62-3.66 (t, J=14.7 Hz, 1H, P-CH-P), 2.29 (s, 12H, CH3), 1.39 (s, 36H, C(CH3)3); FAB-MS m/z (%):906 (M+ +1, 28), 905 (M+, 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 C54H68O7P2: C 72.80; H 7.64; Found: C 72.85; H 7.59 %.

6h ; Yield 63%, mp 120-122 °C (EtOH). IR (KBr): νmax 1271 (P=O), 1215, 941 P-O-C (aromatic) 764(P-C) cm-1, 31P NMR (CDCl3, 161.9 MHz) δ: 0.77, 4.94, 1H NMR (CDCl3, 400 MHz) δ: 6.08-7.82 (m, 11H, Ar-H), 4.32-4.39 (m, 4H, 2x-CH2-), 3.63-3.66 (t, J=14.7 Hz, 1H, P-CH-P), 2.17 (s, 12H, CH3), 1.45 (s, 36H, C(CH3)3). Anal. Calcd for C51H64O7P2: C 72.00; H 7.52. Found: C 72.06; H 7.48 %.

6i ; Yield 65%, mp 134-136 °C (EtOH). IR (KBr): νmax 1276 (P=O), 1218, 934 P-O-C (aromatic) 769(P-C) cm-1, 31P NMR (CDCl3, 161.9 MHz) δ: 0.77, 4.94, 1H NMR (CDCl3, 400 MHz) δ: 6.38-7.25 (m, 11H, Ar-H), 4.39-4.43 (m, 4H, 2x-CH2-), 3.62-3.65 (t, J=14.7 Hz, 1H, P-CH-P), 2.29 (s, 12H, CH3), 1.39 (s, 36H, C(CH3)3); FAB-MS m/z (%): 867 (M+ +1, 23), 866 (M+, 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 C51H64O8P2S: C 70.66; H 7.39. Found: C 70.63 H 7.44 %.

6j ; Yield 74%, mp 129-131 °C (EtOH). IR (KBr): νmax 1274 (P=O), 1219, 934 P-O-C (aromatic) 769(P-C) cm-1, 31P NMR (CDCl3, 161.9 MHz) δ: 0.77, 4.94, 1H NMR (CDCl3, 400 MHz) δ: 6.38-7.26 (m, 12H, Ar-H), 4.37-4.40 (m, 4H, 2x-CH2-), 3.61-3.65 (t, J=14.7 Hz, 1H, P-CH-P), 2.28 (s, 12H, CH3), 1.38 (s, 36H, C(CH3)3); 13C NMR (CDCl3, 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-4a&7a/ C-4a’&7a’), 126.3 (d, J=4.2 Hz, C-11a&12a/ C-11a’&12a’), 131.1 (-CH2-12&12’), 20.9 ((-CH3, 2,10’2’, 10’2’) 34.6 (t-C(CH3)3, 4,8/4’8’), 30.5 (t-C(CH3)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 C52H65NO6P2: C 72.47; H 7.54; N 1.62. Found: C 72.50; H 7.49; N 1.58 %.

ACKNOWLEDGEMENTS
The authors express thanks to the director of Central Drug Research Institute, Lucknow and Sophisticated Instrumentation Facility, IISc, Bangalore for the elemental analyses and spectral data.

REFERENCES


