

Efficient Synthesis of 40- and 48-Membered Tetraether Macrocyclic Bisphosphocholines (SUPPORTING INFORMATION)

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Spectral Data for Compounds 1-15b

1: ^1H (CDCl₃; 200 MHz): 2.9 (s, 1H, OH), 3.45-4.45 (m, 5H, CH₂O, CHO), 5.55 (s, 1H, O-CH-Ph), 7.35-7.58 (m, 5H, C₆H₅).

2a: ^1H (CDCl₃; 200MHz) : 1.3-1.8 (m, 8H, CH₂), 1.95 (t, 1H, C≡C-H), 2.22 (td, 2H, CH₂-C≡C), 3.28 (m, 1H, CH-O [acetal]), 3.55 (t, 2H, CH₂-O), 4.05 (dd, 2H, CH₂-O [acetal]), 4.35 (dd, 2H, CH₂-O [acetal]), 5.55 (s, 1H, O-CH-Ph), 7.32-7.64 (m, 5H, C₆H₅).

2b: ^1H (CDCl₃; 200MHz) : 1.25-1.7 (m, 12H, CH₂), 1.95 (t, 1H, C≡C-H), 2.22 (td, 2H, CH₂-C≡C), 3.28 (m, 1H, CH-O [acetal]), 3.55 (t, 2H, CH₂-O), 4.05 (dd, 2H, CH₂-O [acetal]), 4.35 (dd, 2H, CH₂-O [acetal]), 5.55 (s, 1H, O-CH-Ph), 7.32-7.64 (m, 5H, C₆H₅).

3a: ^1H (CDCl₃; 200MHz) : 1.25-1.69 (m, 16H, CH₂), 1.93 (s, 2H, -OH), 2.22 (t, 4H, CH₂-C≡C), 3.43-3.79 (m, 14H, CH₂O, CHO), 4.53 (s, 4H, O-CH₂-Ph), 7.35 (m, 10H, C₁₂H₁₀).

3b: ^1H (CDCl₃; 200MHz) : 1.25-1.69 (m, 24H, CH₂), 1.93 (s, 2H, -OH), 2.22 (t, 4H, CH₂-C≡C), 3.43-3.79 (m, 14H, CH₂O, CHO), 4.53 (s, 4H, O-CH₂-Ph), 7.35 (m, 10H, C₁₂H₁₀). ^{13}C (CDCl₃; 50MHz): 19.161, 26.011, 28.271, 28.743, 29.003, 29.248, 29.994, 62.836, 65.238, 69.947, 70.339, 73.477, 77.636, 78.409, 127.606, 127.689, 128.392, 137.966.

4a: ^1H (CDCl₃; 200MHz): 1.25-1.67 (m, 32H, CH₂), 2.22 (t, 8H, CH₂-C≡C), 3.4-3.68 (m, 18H, CH₂O, CHO), 4.55 (s, 4H, O-CH₂-Ph), 7.34 (m, 10H, C₁₂H₁₀). ^{13}C (CDCl₃; 50MHz): 18.927, 25.385, 25.456, 28.090, 28.325, 28.438, 29.289, 29.676, 65.298, 69.999, 70.164, 71.034, 71.147, 73.128, 77.639, 77.823, 127.322, 127.374, 128.116, 138.171.

4b: ^1H (CDCl₃; 200MHz): 1.20-1.62 (m, 48H, CH₂), 2.22 (t, 8H, CH₂-C≡C), 3.4-3.68 (m, 18H, CH₂O, CHO), 4.55 (s, 4H, O-CH₂-Ph), 7.34 (m, 10H, C₁₂H₁₀). ^{13}C (CDCl₃; 50MHz): 19.175, 25.999, 26.050, 28.276, 28.705, 29.040, 29.220, 29.291, 29.600, 30.001, 65.322, 70.223, 70.514, 71.122, 71.496, 73.326, 77.643, 77.971, 127.495, 127.560, 128.296, 138.383.

5a: ^1H (CDCl₃; 300 MHz): 1.3-1.6 (m(b), 32H, CH₂), 2.2(t, 8H, CH₂-C≡C), 3.4-4.45 (m(b), 44H (CH₃)₃-N⁺, CH₂-O, CH-O, O-CH₂-CH₂-NMe₃). ^{13}C (CD₃OD: 50MHz): 26.982, 27.053, 29.876, 30.907, 31.287, 54.931, 55.004, 55.077, 60.680, 61.225, 61.274, 66.873, 67.453, 67.619, 67.692, 67.764, 71.592, 72.629, 78.333, 79.870. ^{31}P (CDCl₃; 124MHz): 0.670; **Positive Electrospray MS:** Calculated: m/z 942.55; Found: m/z (M+H) 943.5

5b: ^1H (CDCl₃; 300 MHz): 1.3-1.6 (m, 48H, CH₂), 2.22 (t, 4H, CH₂-C≡C),), 3.4-4.45 (m(b), 44H (CH₃)₃-N⁺, CH₂-O, CH-O, O-CH₂-CH₂-NMe₃) ^{13}C (CD₃OD: 50MHz): 20.211, 27.549, 27.635, 29.951, 30.207, 30.262, 30.606, 30.751, 31.141, 31.507, 55.040, 60.781, 60.882, 61.377, 61.959, 62.067, 66.563, 67.004, 67.611, 67.688, 71.687, 72.316, 72.773, 78.446, 79.663. **Positive Electrospray MS:** Calculated: m/z 1054.68; Found: m/z (M+H) 1055.5

6a: ^1H (CDCl₃; 200MHz): 1.2-1.5 (bs, 8H, CH₂), 1.57-1.8 (m, 2H, CH₂), 1.97-2.15 (m, 2H, CH₂-CH=CH₂), 3.25 (m, 1H, OCH), 3.53 (t, 2H, OCH₂), 4.05 (dd, 2H, CH₂-O [acetal]), 4.35 (dd, 2H, CH₂-O [acetal]), 4.89-5.05 (td, 2H, CH₂=CH), 5.55 (s, 1H, O-CH-Ph), 5.71-5.92 (m, 1H, CH=CH₂), 7.3-7.58 (m, 5H, C₆H₅). ^{13}C (CDCl₃; 75MHz): 26.157, 28.935, 29.155, 29.384, 29.846, 33.866, 69.003, 69.117, 70.660, 101.365, 114.234, 126.265, 128.206, 128.884, 138.260, 139.226.

6b: ^1H (CDCl₃; 200MHz): 1.2-1.5 (bs, 12H, CH₂), 1.75-1.93 (m, 2H, CH₂), 1.97-2.1 (m, 2H, CH₂-CH=CH₂), 3.25 (m, 1H, OCH), 3.53 (t, 2H, OCH₂), 4.05 (dd, 2H, CH₂-O

[acetal]), 4.35 (dd, 2H, $\text{CH}_2\text{-O}$ [acetal]), 4.89-5.05 (td, 2H, $\text{CH}_2\text{=CH}$), 5.55 (s, 1H, O-CH-Ph), 5.71-5.92 (m, 1H, CH=CH_2), 7.3-7.58 (m, 5H, C_6H_5). ^{13}C (CDCl_3 ; 50 MHz): 26.097, 28.901, 29.106, 29.419, 29.534, 29.761, 33.792, 68.955, 69.034, 70.565, 101.298, 114.075, 126.167, 128.129, 128.804, 138.135, 139.215.

7a: ^1H (CDCl_3 ; 300MHz): 1.2-1.4 (bs, 16H, CH_2), 2.35 (m, 4H, $\text{CH}_2\text{-CH}_2\text{-O}$), 1.95 (m, 4H, $\text{CH}_2\text{-CH=CH-}$), 2.17 (t, 2H, -OH), 3.35-3.8 (m, 14H, CH_2O , CHO), 4.55 (s, 4H, $\text{O-CH}_2\text{-Ph}$), 5.4 (t-like, 2H, CH=CH), 7.35 (s, 10H, $\text{C}_{12}\text{H}_{10}$). ^{13}C (CDCl_3 ; 75MHz): 26.033, 29.046, 29.284, 29.526, 30.021, 32.530, 62.830, 69.944, 70.384, 73.465, 78.405, 127.595, 127.673, 128.383, 130.292, 137.975.

7b: ^1H (CDCl_3 ; 200MHz): 1.2-1.5 (bs, 24H, CH_2), 1.75-1.93 (m, 4H, CH_2), 1.97-2.1 (m, 4H, $\text{CH}_2\text{-CH=CH}$), 3.4-3.8 (m, 14H, CHO , CH_2O), 4.52 (s, 4H, $\text{O-CH}_2\text{-Ph}$), 5.35 (t-like, 2H, CH=CH), 7.32 (s, 10H, $\text{C}_{12}\text{H}_{10}$).

8a: ^1H (CDCl_3 ; 300MHz): 1.2-1.6 (m, 40H, CH_2), 2.0 (m, 8H, $\text{CH}_2\text{-CH=CH}$), 3.35-3.78 (m, 18H, CH_2O , CHO), 4.55 (s, 4H, $\text{O-CH}_2\text{-Ph}$), 5.34 (t-like, 4H, CH=CH), 7.35 (s, 10H, $\text{C}_{12}\text{H}_{10}$). ^{13}C (CDCl_3 ; 75MHz): 26.621, 26.717, 28.329, 28.420, 28.864, 29.537, 29.624, 29.725, 30.151, 30.325, 32.193, 32.248, 69.804, 70.427, 71.343, 71.718, 73.330, 77.793, 127.579, 128.325, 130.916, 130.967.

8b: ^1H (CDCl_3 ; 200MHz): 1.2-1.5 (bs, 48H, CH_2), 1.75-1.93 (m, 8H, CH_2), 1.97-2.1 (m, 8H, $\text{CH}_2\text{-CH=CH}$), 3.4-3.8 (m, 18H, CHO , CH_2O), 4.52 (s, 4H, $\text{O-CH}_2\text{-Ph}$), 5.35 (t-like, 4H, CH=CH), 7.32 (s, 10H, $\text{C}_{12}\text{H}_{10}$). ^{13}C (CDCl_3 ; 50MHz): 26.297, 26.428, 26.823, 26.861, 28.276, 28.889, 29.348, 29.394, 29.485, 29.550, 29.696, 29.833, 30.074, 32.134, 69.946, 70.057, 70.476, 71.357, 71.721, 73.298, 77.886, 77.989, 127.509, 127.544, 128.290, 129.999, 130.063, 130.797, 138.262.

9a: ^1H (CDCl_3 ; 300 MHz): 1.15-1.32 (bs, 48H, CH_2), 1.45 (m, 8H, $\text{CH}_2\text{-CH}_2\text{-O}$), 3.1-4.2 (m, 44H, $(\text{CH}_3)_3\text{-N}^+$, $\text{CH}_2\text{-O}$, CH-O , $\text{O-CH}_2\text{-CH}_2\text{-NMe}_3$). ^{13}C (CD_3OD ; 75MHz): 26.845, 27.917, 28.448, 28.521, 28.626, 29.263, 29.354, 29.734, 29.775, 30.627, 31.016, 54.604, 54.650, 54.700, 60.460, 66.119, 71.347, 72.002, 72.405, 79.318. ^{31}P (CDCl_3 ; 124MHz): 2.566. **Positive Electrospray MS:** Calculated: m/z 958.68; Found: m/z (M+H) 959.5

9b: ^1H (CDCl_3 ; 300 MHz): 1.2-1.35 (bs, 68H, CH_2), 1.5 (m, 8H, $\text{CH}_2\text{-CH}_2\text{-O}$), 3.4-4.40 (m(b), 44H, $(\text{CH}_3)_3\text{-N}^+$, $\text{CH}_2\text{-O}$, CH-O , $\text{O-CH}_2\text{-CH}_2\text{-NMe}_3$). ^{13}C (CD_3OD ; 50MHz): 25.470, 25.527, 26.965, 27.266, 27.329, 27.496, 27.844, 27.963, 28.242, 28.348, 28.532, 28.671, 29.088, 29.470, 53.482, 53.551, 58.523, 59.069, 64.435, 64.550, 65.901, 65.951, 70.029, 70.466, 71.083, 77.488. ^{31}P (CDCl_3 ; 124MHz): 0.400. **Positive Electrospray MS:** Calculated: m/z 1070.80; Found: m/z (M+H) 1071.6

11a: ^1H (CDCl_3 ; 200 MHz): 1.55 (m, 6H, CH_2), 1.78 (m, 2H, CH_2), 1.95 (t, 1H, $\text{C}\equiv\text{C-H}$); 2.22 (td, 2H, $\text{CH}_2\text{-C}\equiv\text{C}$); 3.02 (s, 3H, $\text{CH}_3\text{-OSO}_3$); 4.24 (t, 2H, $\text{CH}_2\text{-OMs}$)

11b: ^1H (CDCl_3 ; 200 MHz): 1.2-1.6(m, 10H, CH_2), 1.78 (m, 2H, CH_2), 1.95 (t, 1H, $\text{C}\equiv\text{C-H}$); 2.22 (td, 2H, $\text{CH}_2\text{-}$

$\text{C}\equiv\text{C}$); 3.02 (s, 3H, $\text{CH}_3\text{-OSO}_3$); 4.24 (t, 2H, $\text{CH}_2\text{-OMs}$). ^{13}C (CDCl_3 ; 50MHz): 18.303, 25.307, 28.312, 28.504, 28.819, 29.040, 37.313, 68.143, 70.105, 84.594.

12a: ^1H (CDCl_3 ; 200 MHz): 1.3-1.6 (m, 6H, CH_2), 2.8 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-Br}$), 1.9 (t, 1H, $\text{C}\equiv\text{C-H}$), 2.22 (td, 2H, $\text{CH}_2\text{-C}\equiv\text{C}$), 3.45 (t, $\text{CH}_2\text{-Br}$).

12b: ^1H (CDCl_3 ; 200 MHz): 1.2-1.6 (m, 10H, CH_2), 1.85 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-Br}$), 1.95 (t, 1H, $\text{C}\equiv\text{C-H}$), 2.22 (td, 2H, $\text{CH}_2\text{-C}\equiv\text{C}$), 3.45 (t, 2H, $\text{CH}_2\text{-Br}$).

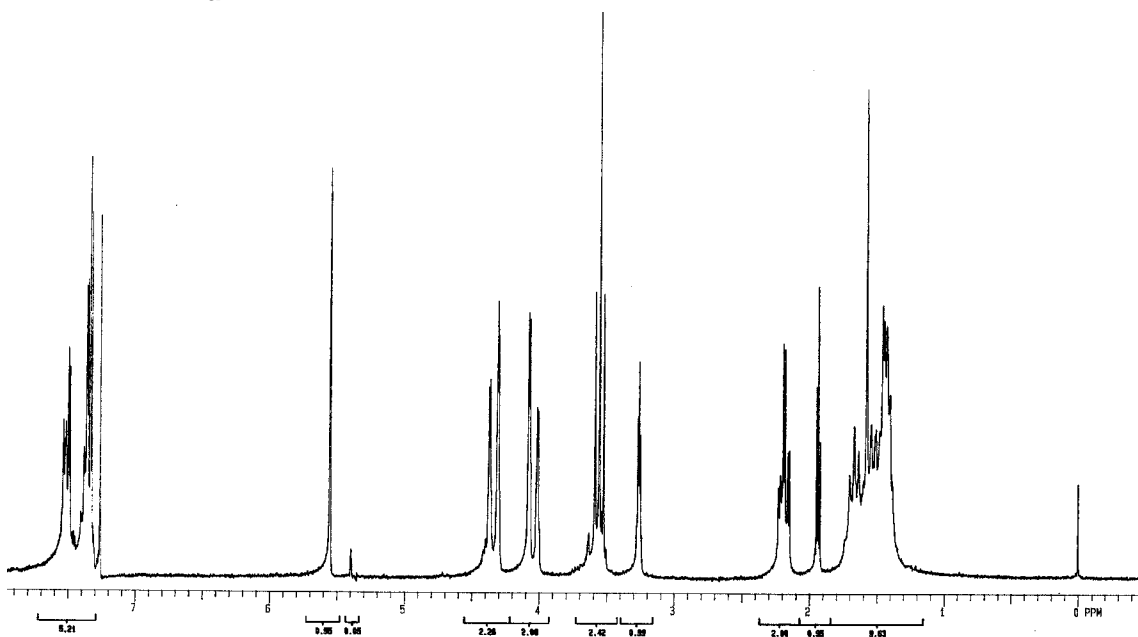
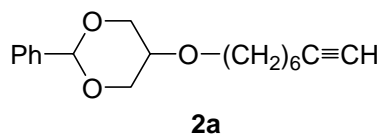
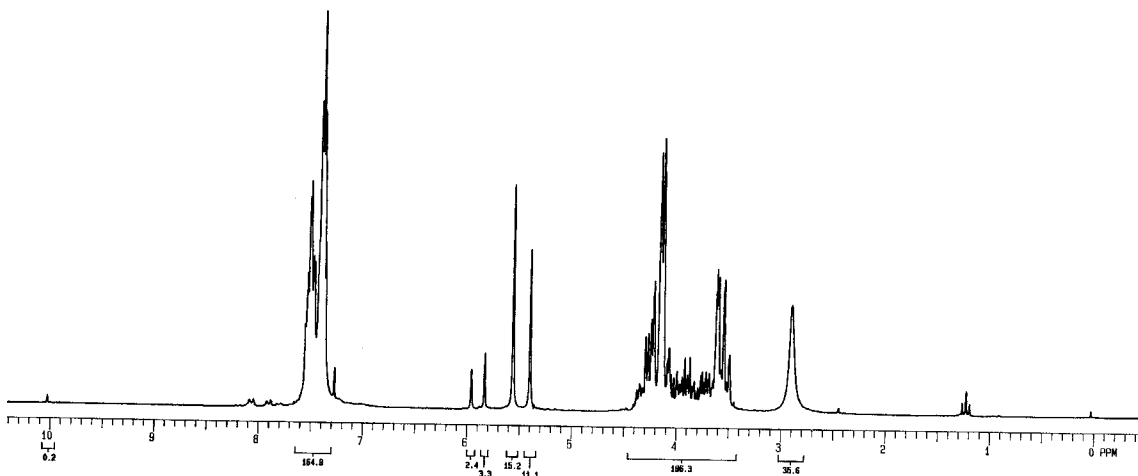
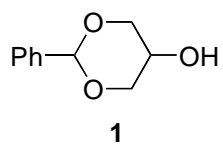
14a: ^1H (CDCl_3 ; 300 MHz): 1.2-1.42 (bs, 8H, CH_2), 1.74 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-OMs}$), 2.02 (m, 2H, $\text{CH}_2\text{-CH=CH}_2$), 3.0 (s, 3H, $\text{CH}_3\text{-OSO}_3$), 4.2 (t, 2H, $\text{CH}_2\text{-OMs}$), 4.87-5.05 (td, 2H, $\text{CH}_2\text{=CH}$), 5.7-5.9 (m, 1H, $\text{CH}_2\text{=CH}$). ^{13}C (CDCl_3 ; 75MHz): 25.398, 28.768, 28.892, 29.125, 33.736, 37.353, 70.262, 114.356, 139.011

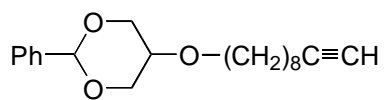
14b: ^1H (CDCl_3 ; 200 MHz): 1.2-1.47 (bs, 12H, CH_2), 1.74 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-OMs}$), 2.02 (m, 2H, $\text{CH}_2\text{-CH=CH}_2$), 3.0 (s, 3H, $\text{CH}_3\text{-OSO}_3$), 4.2 (t, 2H, $\text{CH}_2\text{-OMs}$), 4.87-5.05 (td, 2H, $\text{CH}_2\text{=CH}$), 5.7-5.9 (m, 1H, $\text{CH}_2\text{=CH}$).

15a: ^1H (CDCl_3 ; 200 MHz): 1.2-1.47 (bs, 8H, CH_2), 1.74-1.9(m, 2H, $\text{CH}_2\text{-CH}_2\text{-Br}$), 1.95-2.02 (m, 2H, $\text{CH}_2\text{-CH=CH}_2$), 3.4 (t, 2H, $\text{CH}_2\text{-Br}$), 4.87-5.05 (td, 2H, $\text{CH}_2\text{=CH}$), 5.7-5.9 (m, 1H, $\text{CH}_2\text{=CH}$).

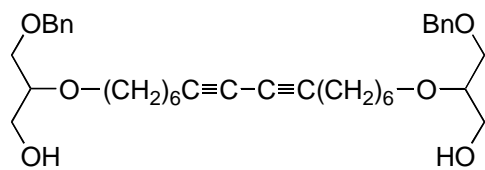
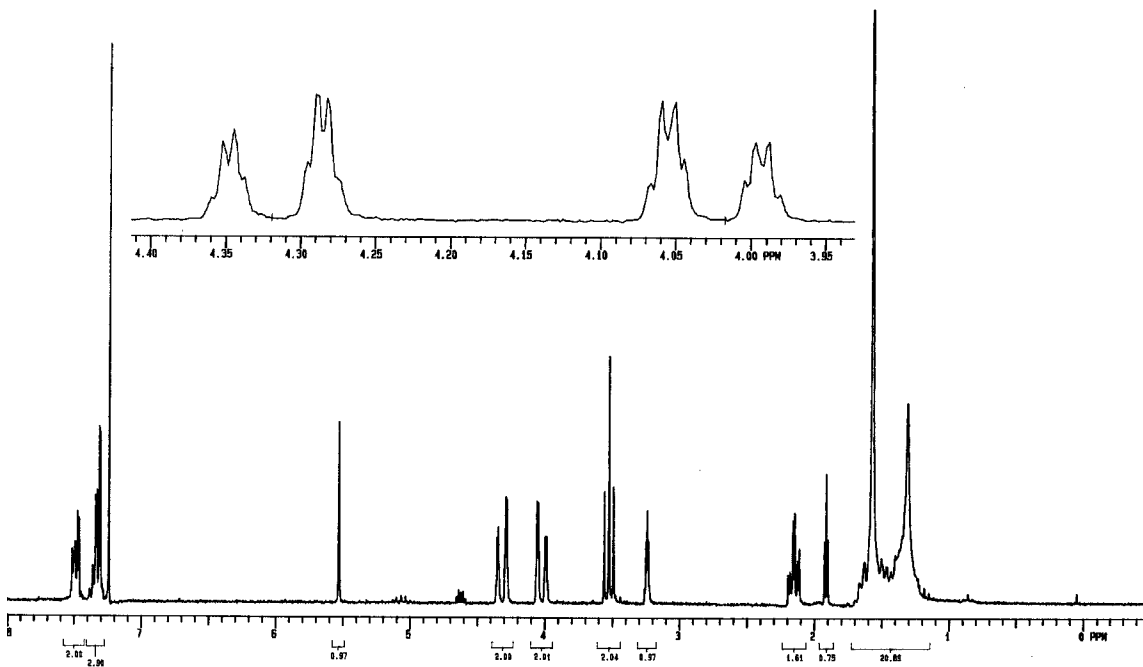
15b: ^1H (CDCl_3 ; 200 MHz): 1.2-1.47 (bs, 12H, CH_2), 1.74-1.9(m, 2H, $\text{CH}_2\text{-CH}_2\text{-Br}$), 1.95-2.02 (m, 2H, $\text{CH}_2\text{-CH=CH}_2$), 3.4 (t, 2H, $\text{CH}_2\text{-Br}$), 4.87-5.05 (td, 2H, $\text{CH}_2\text{=CH}$), 5.7-5.9 (m, 1H, $\text{CH}_2\text{=CH}$). ^{13}C (CDCl_3 ; 50MHz): 28.089, 28.576, 28.758, 28.867, 32.772, 33.702, 33.942, 114.226, 138.979.

NMR Supporting Information

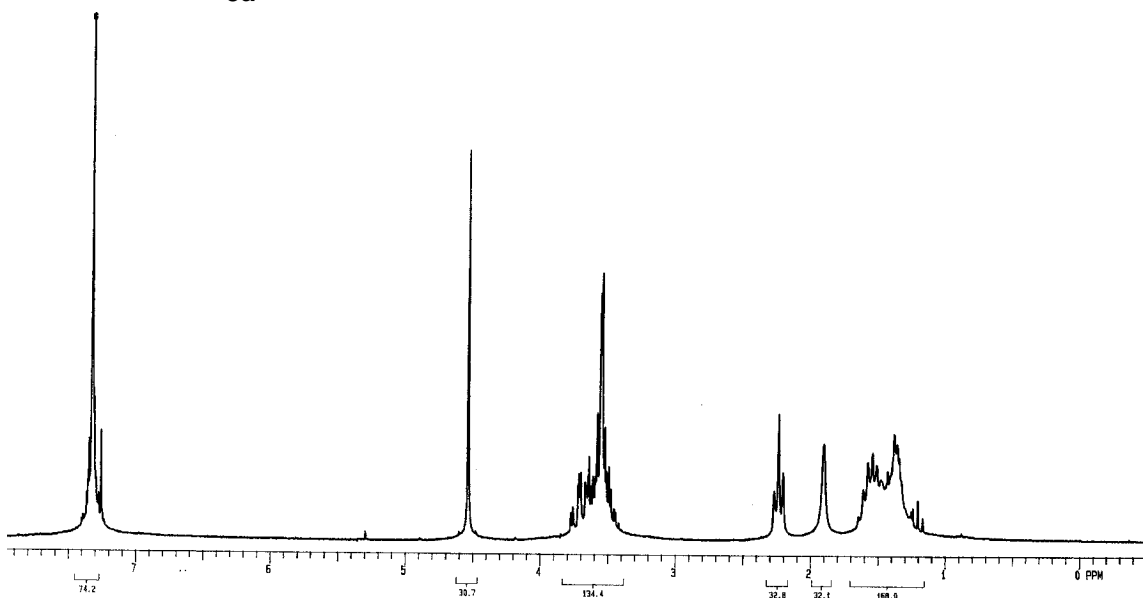


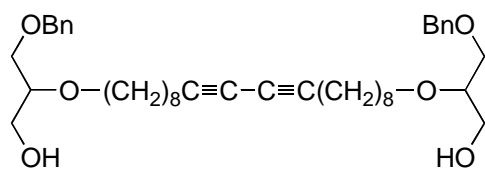


2b

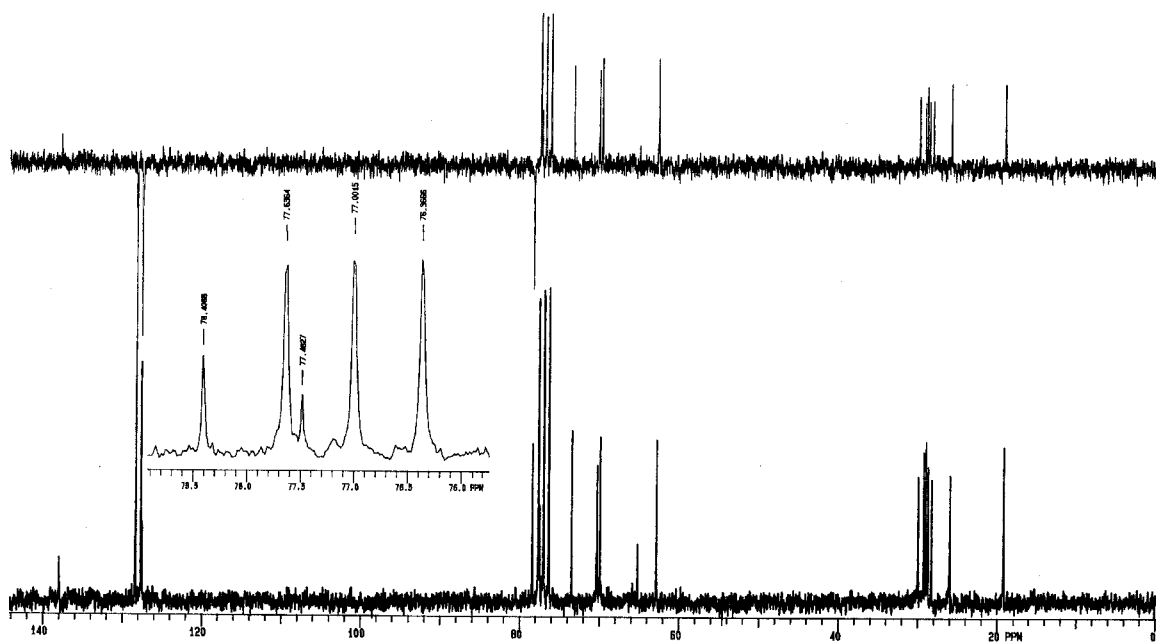
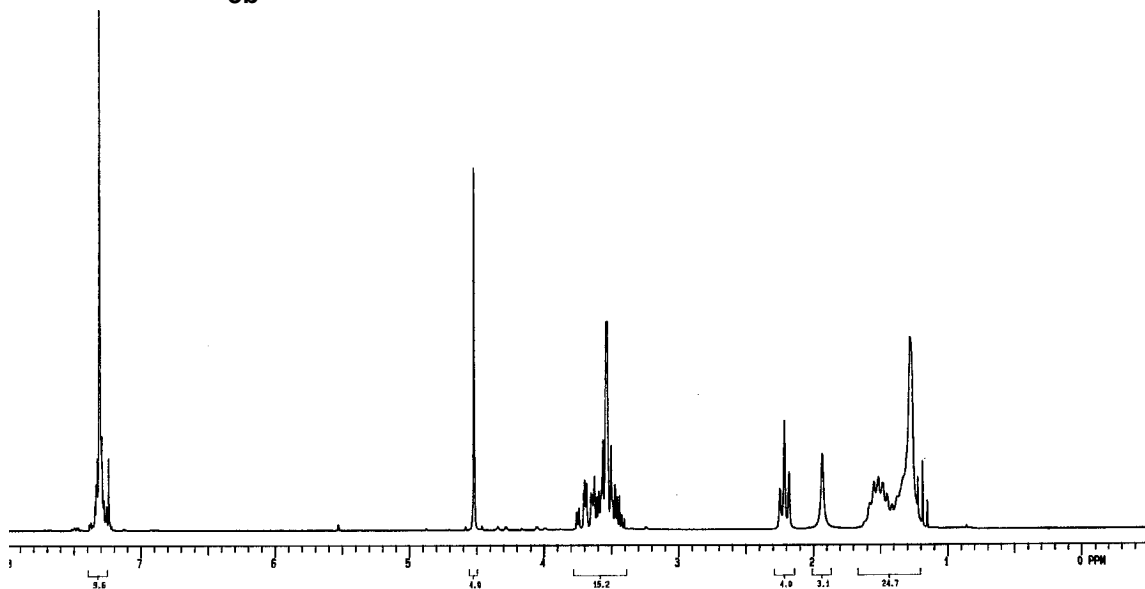


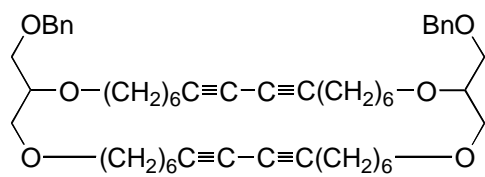
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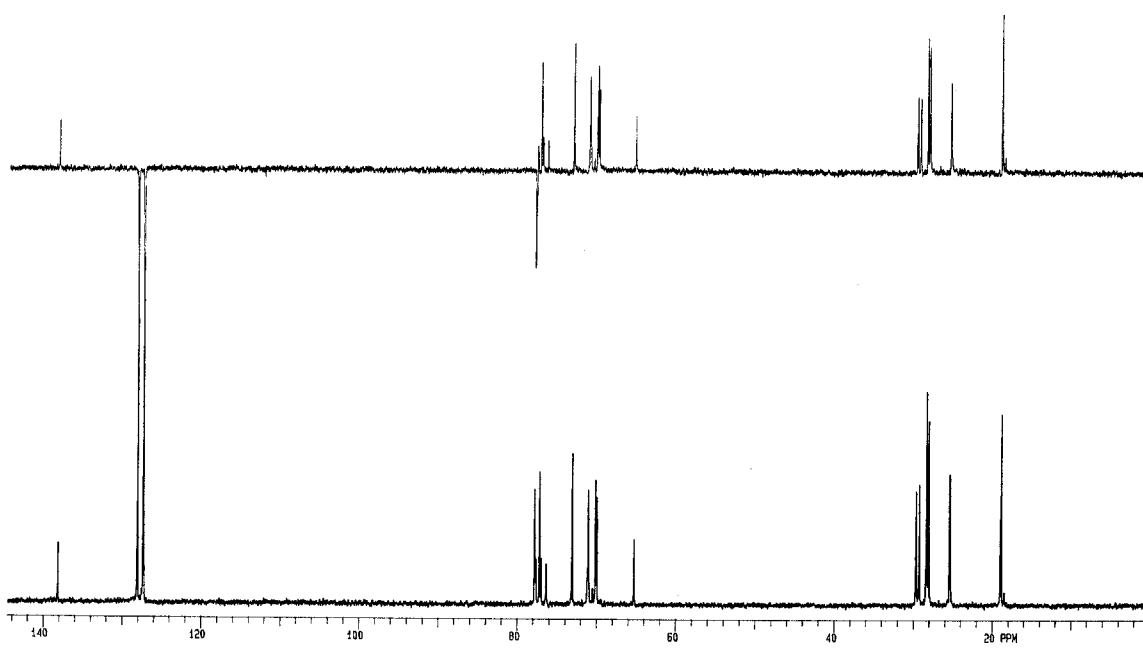
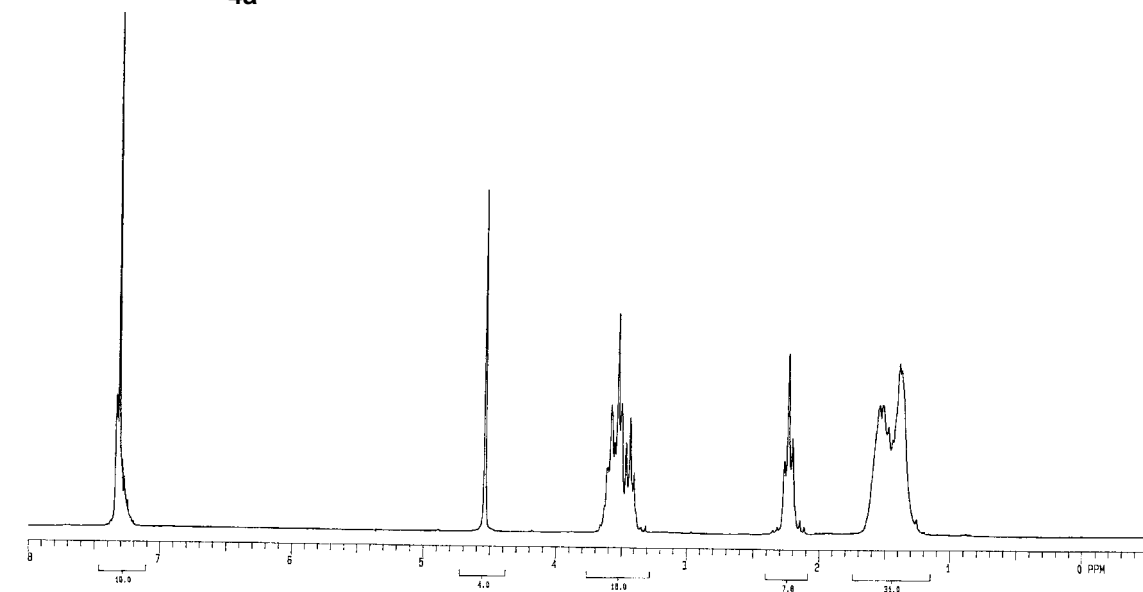


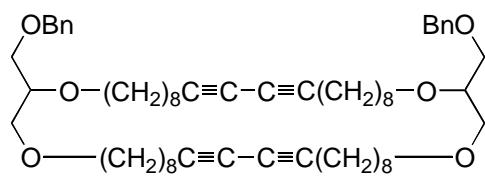
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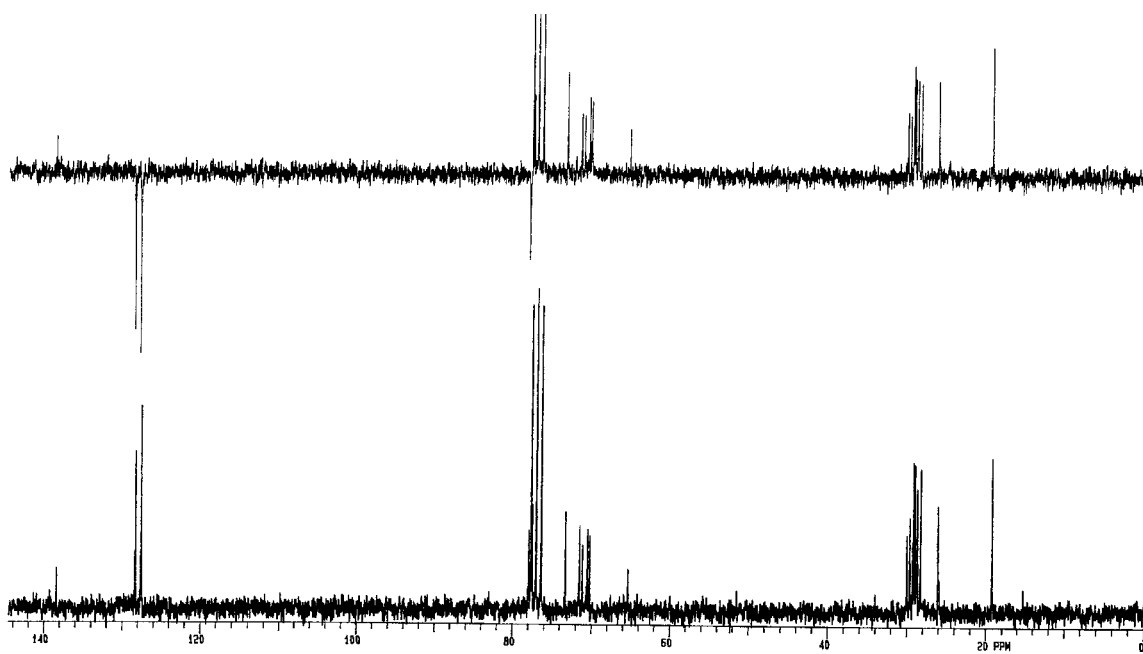
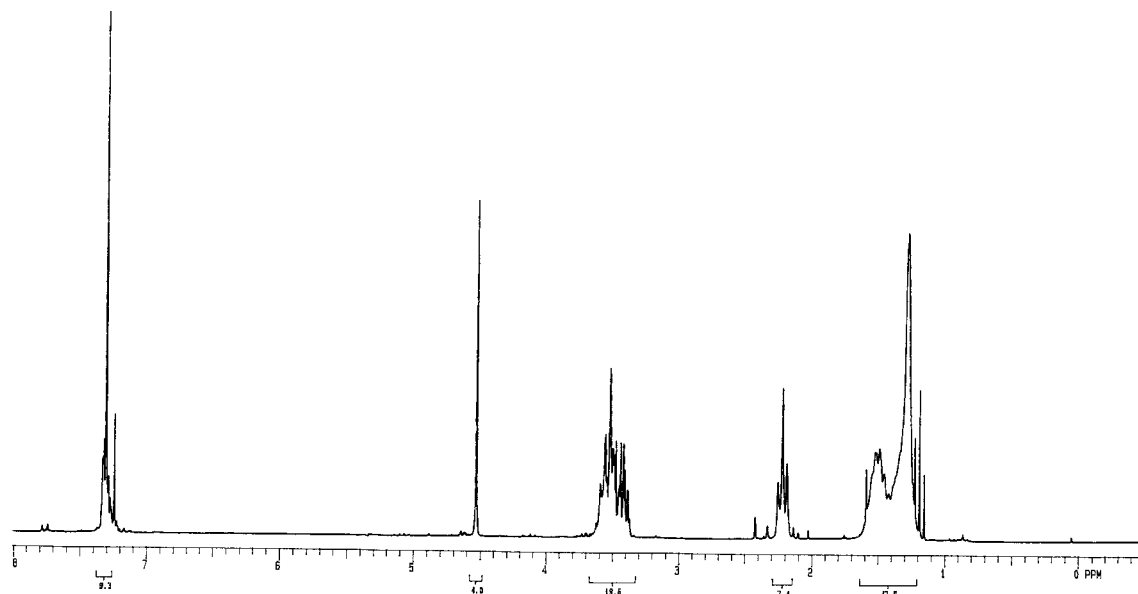


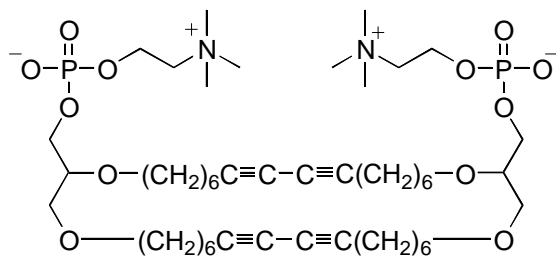
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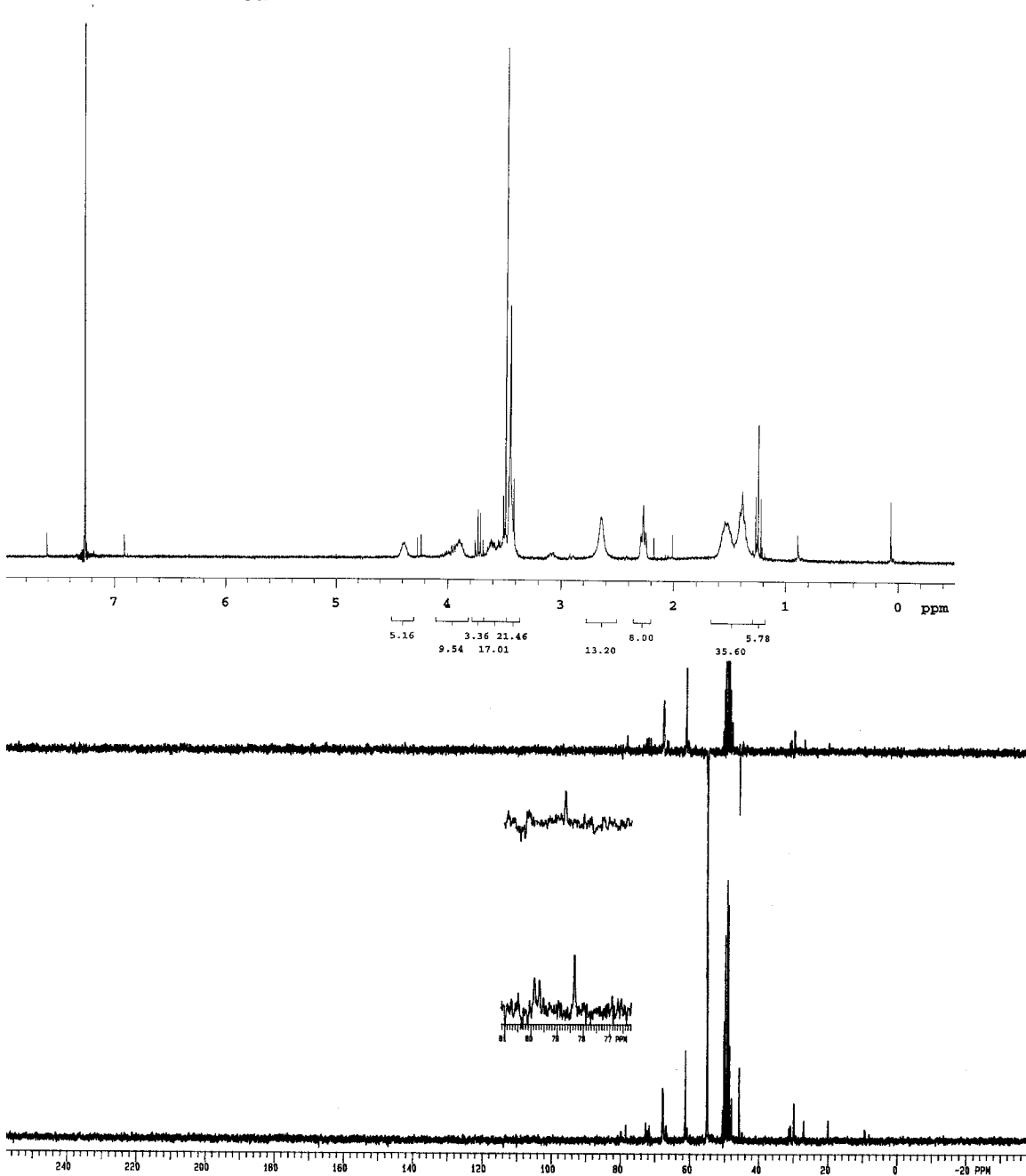


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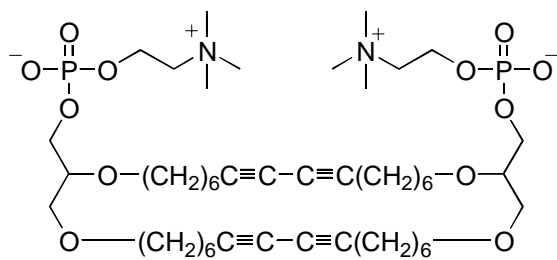




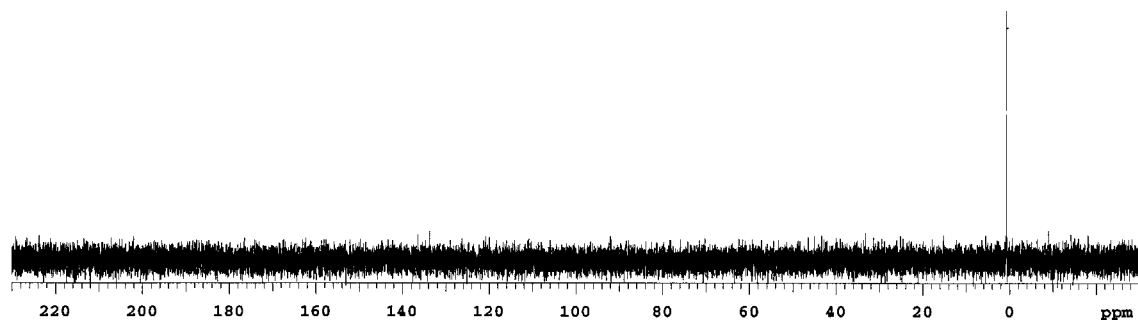
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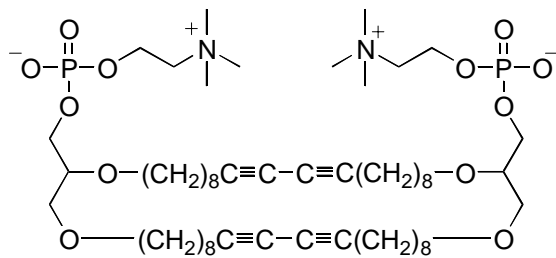


³¹P NMR OF

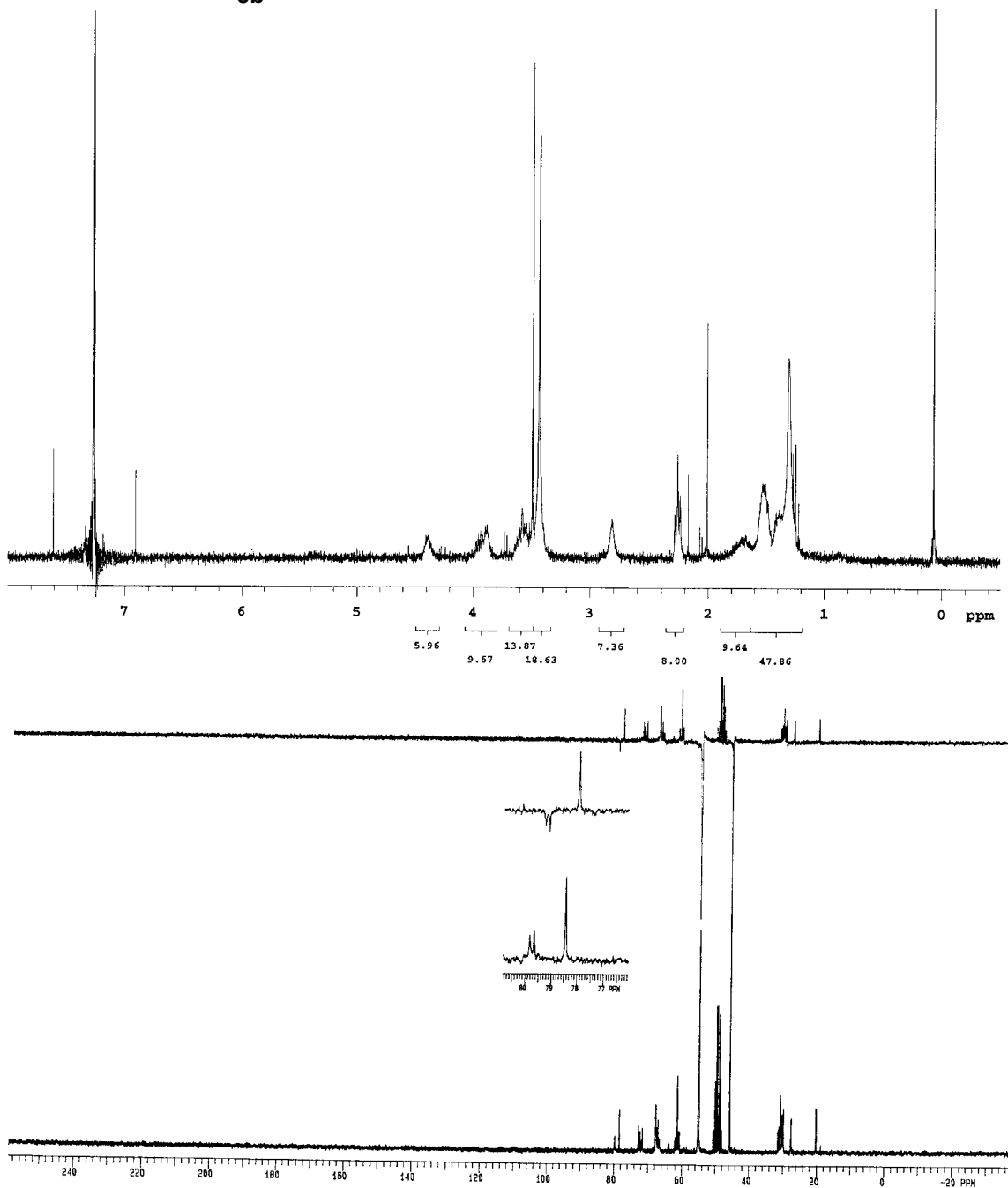


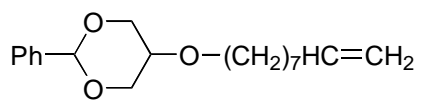
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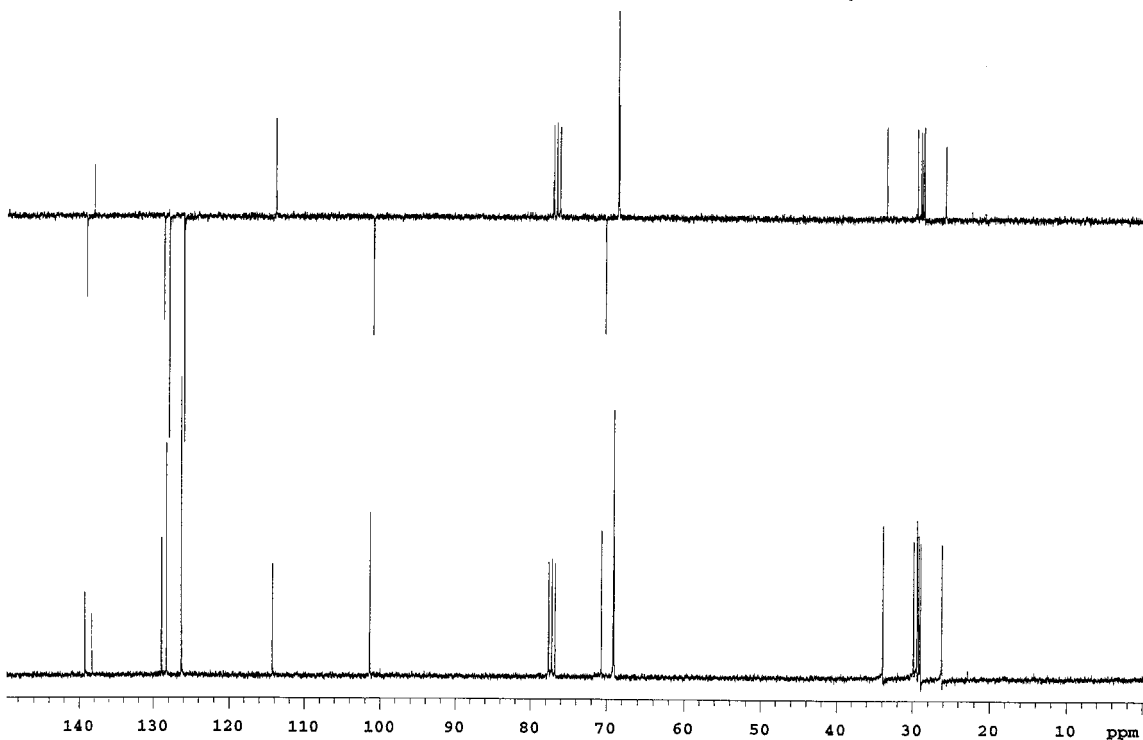
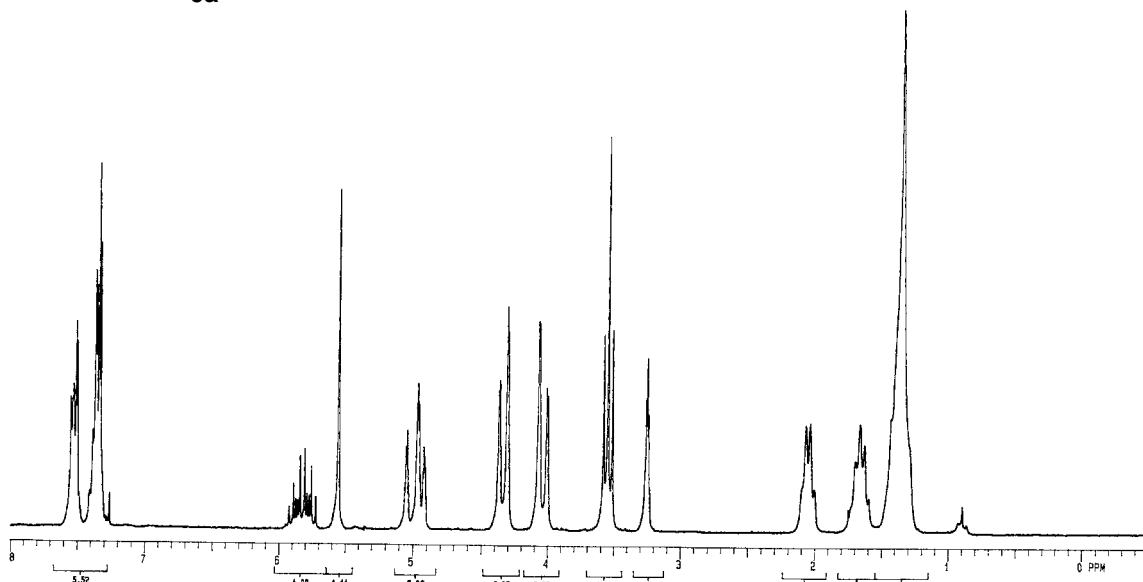


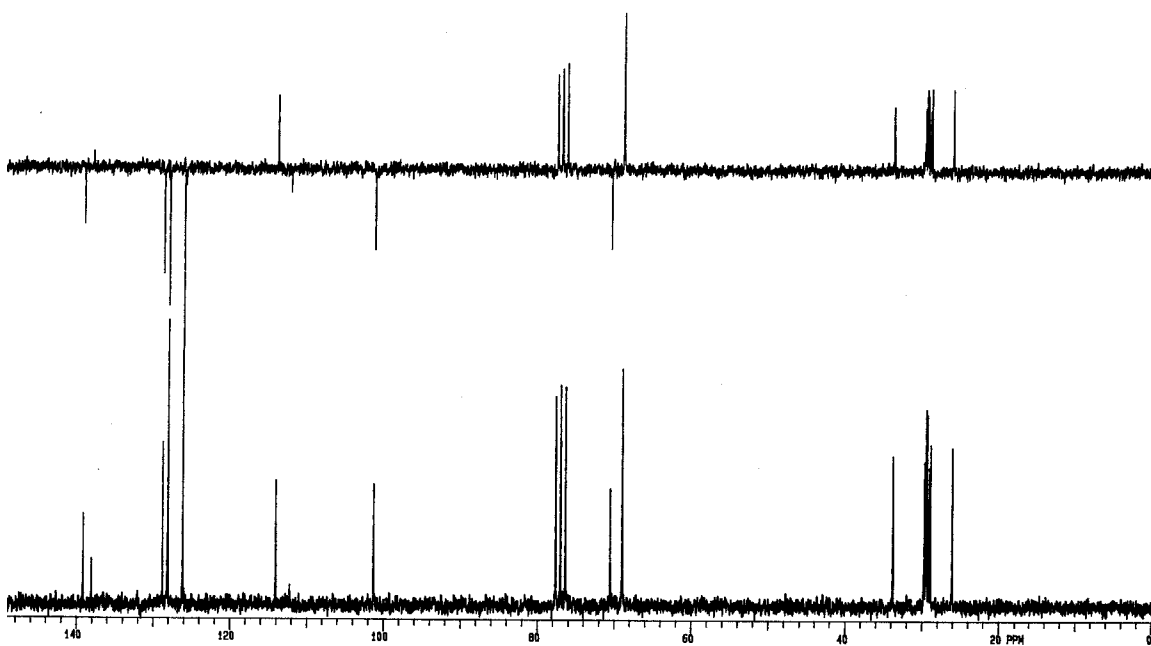
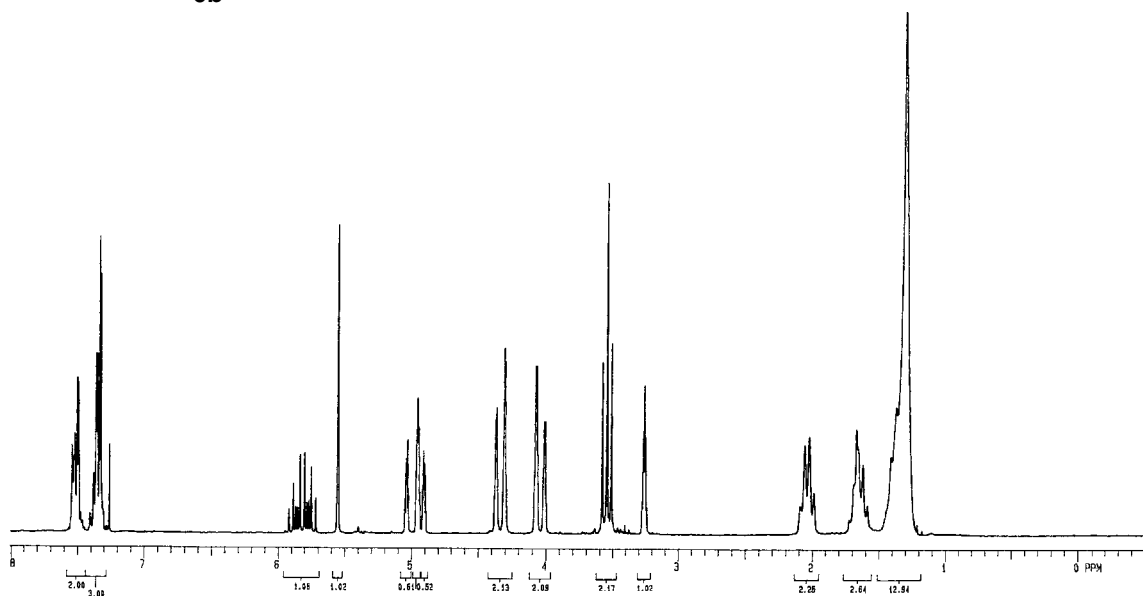
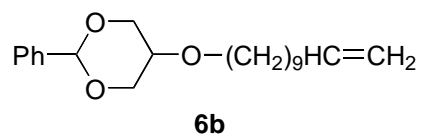
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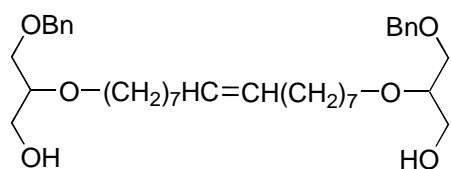




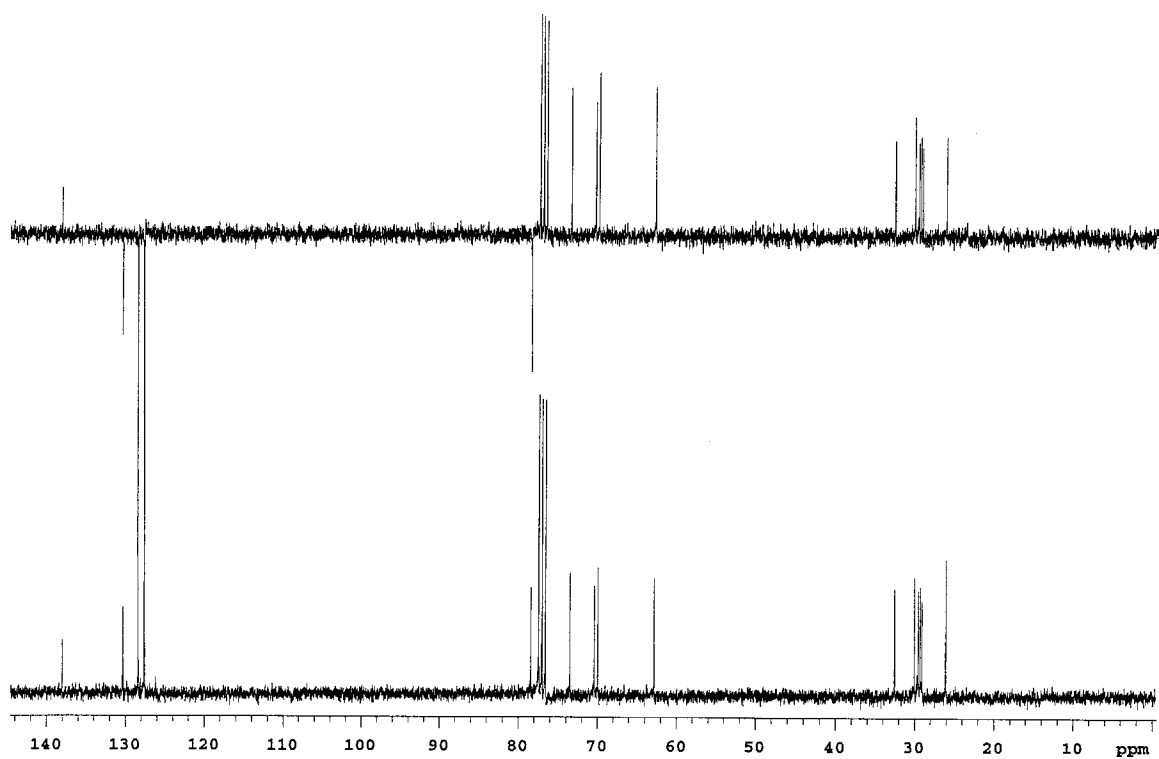
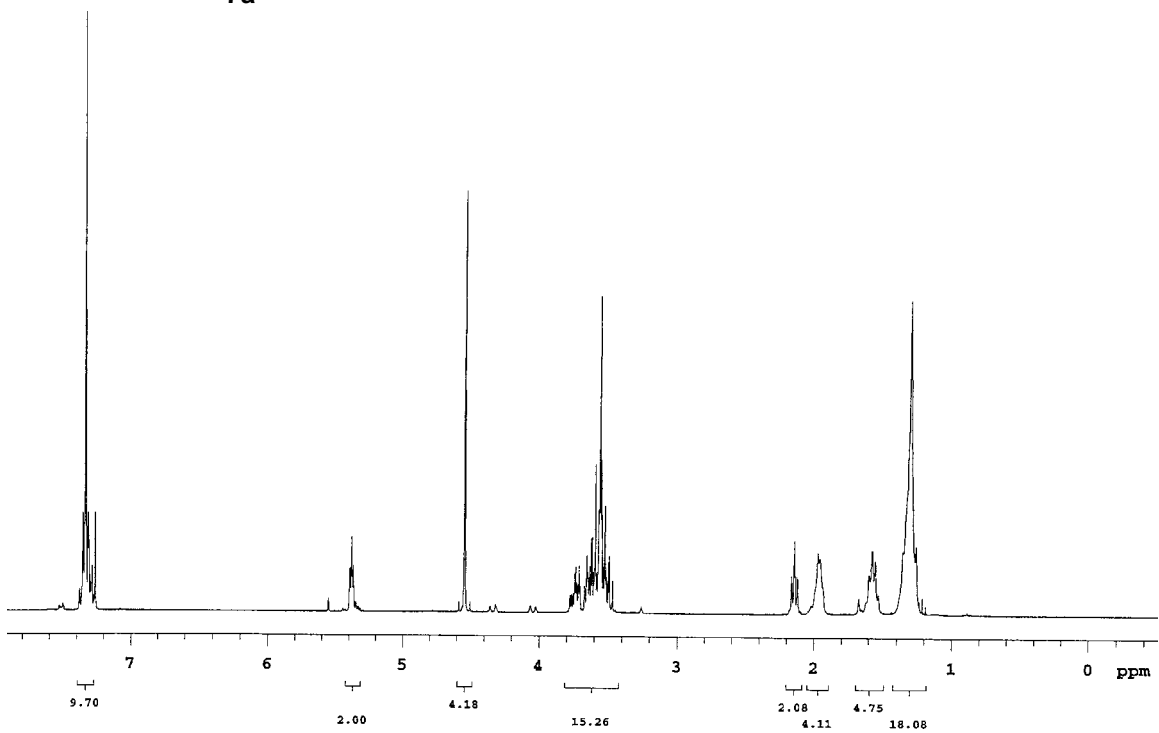
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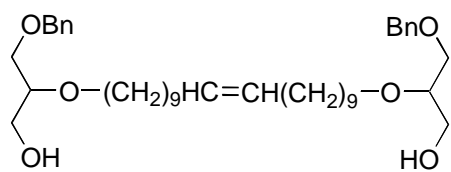




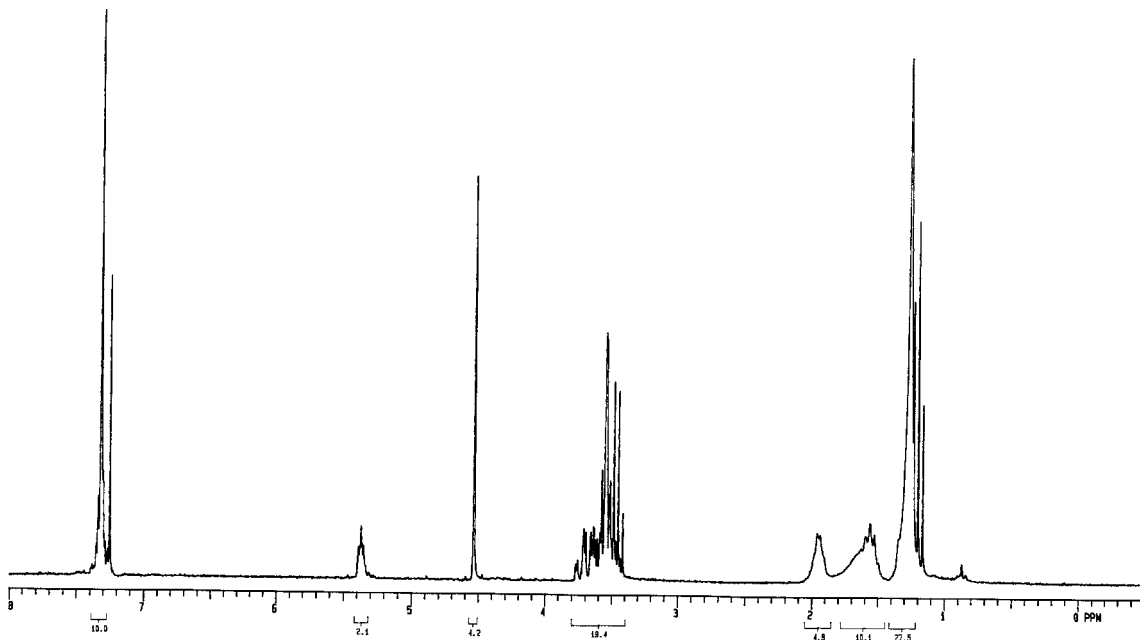


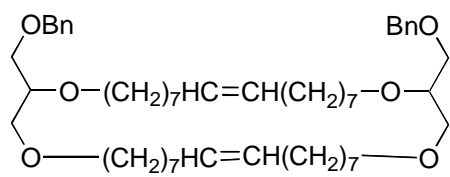
7a



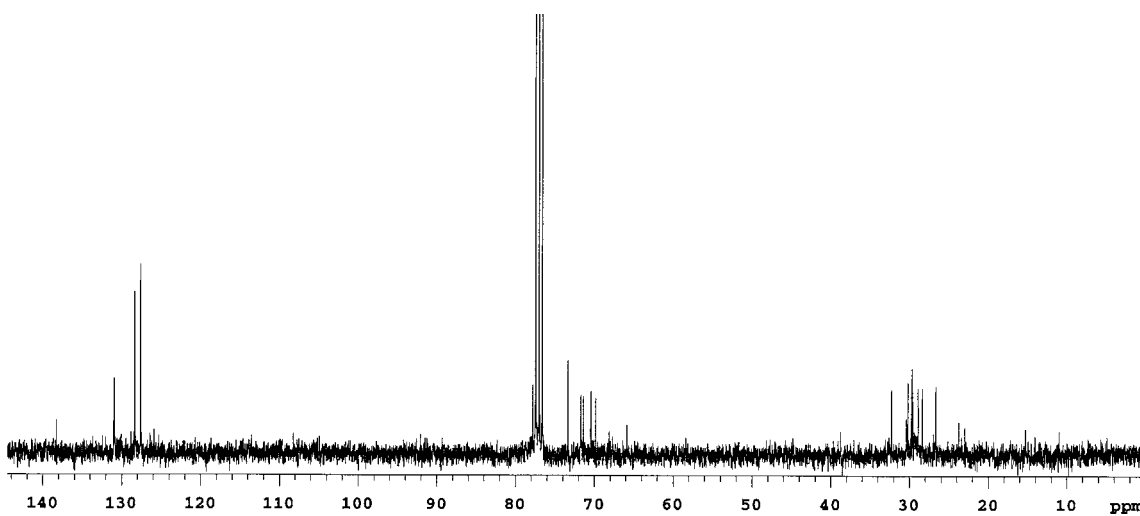
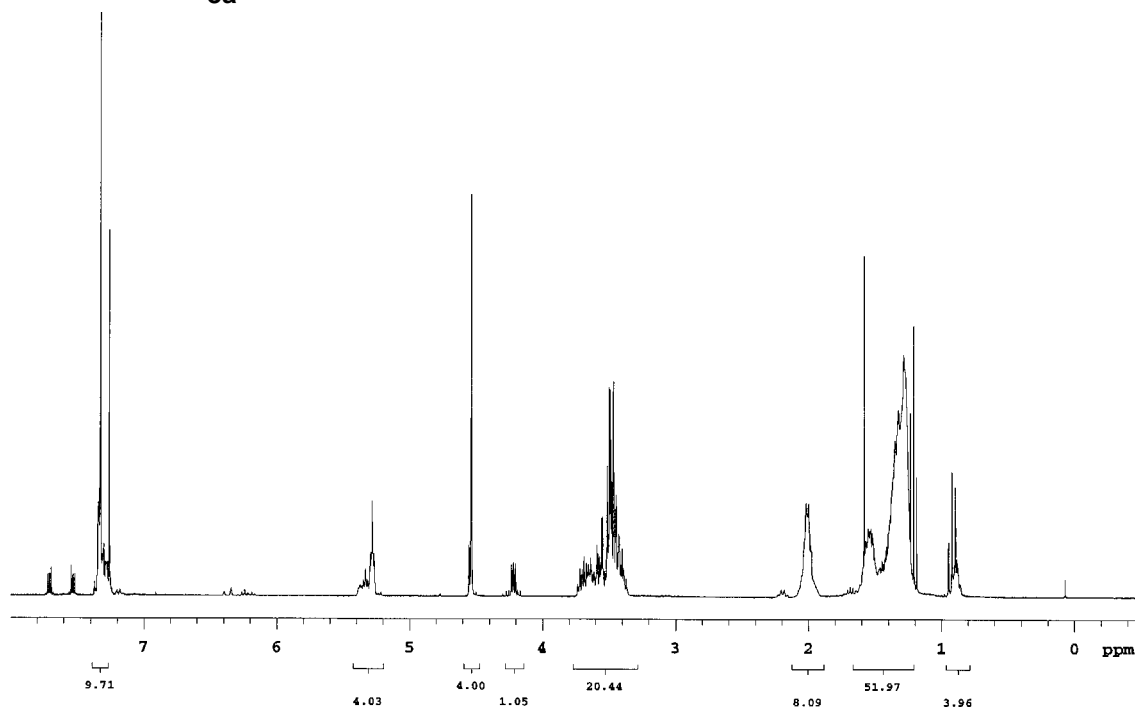


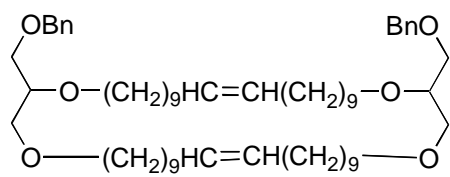
7b



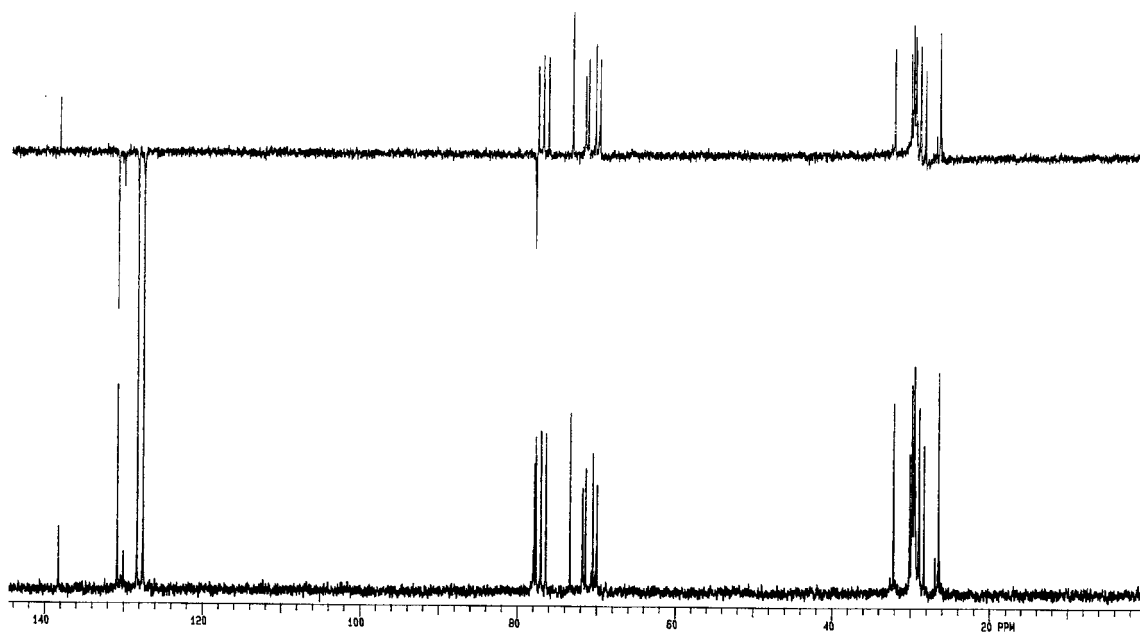
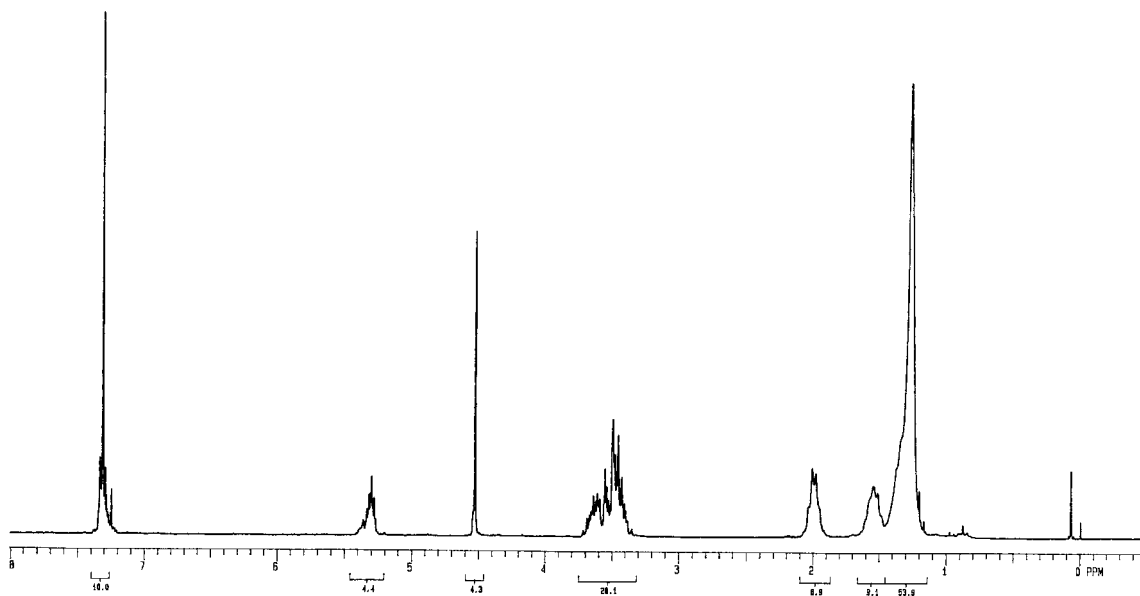


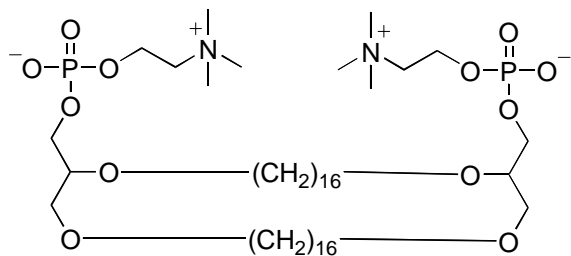
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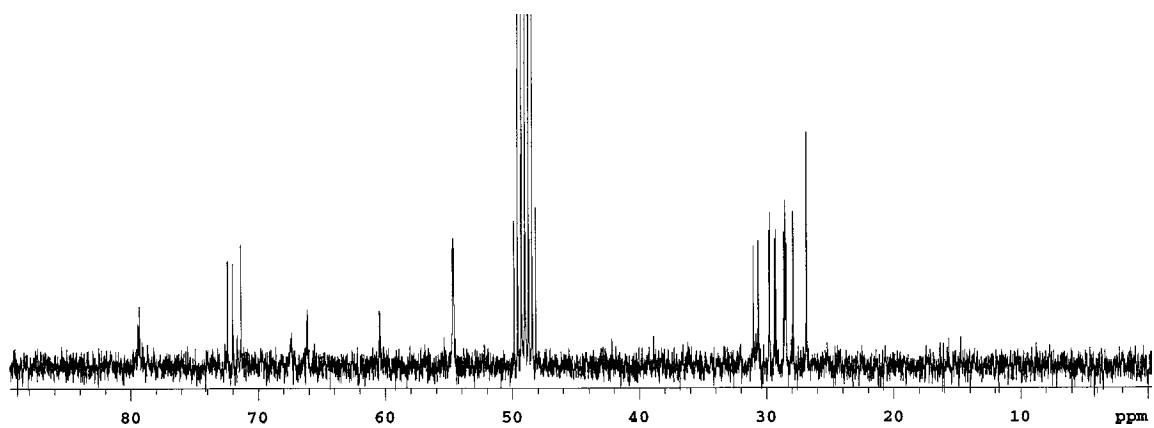
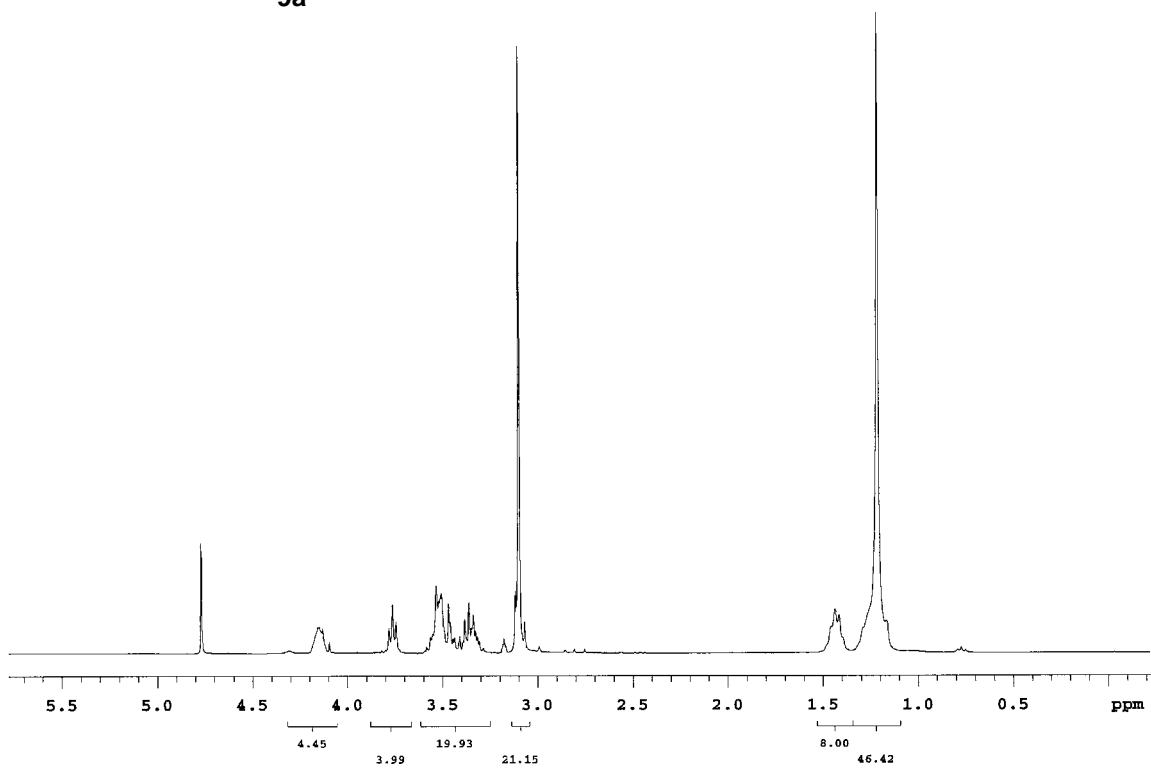


8b

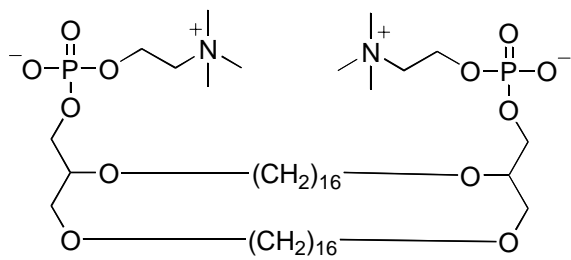




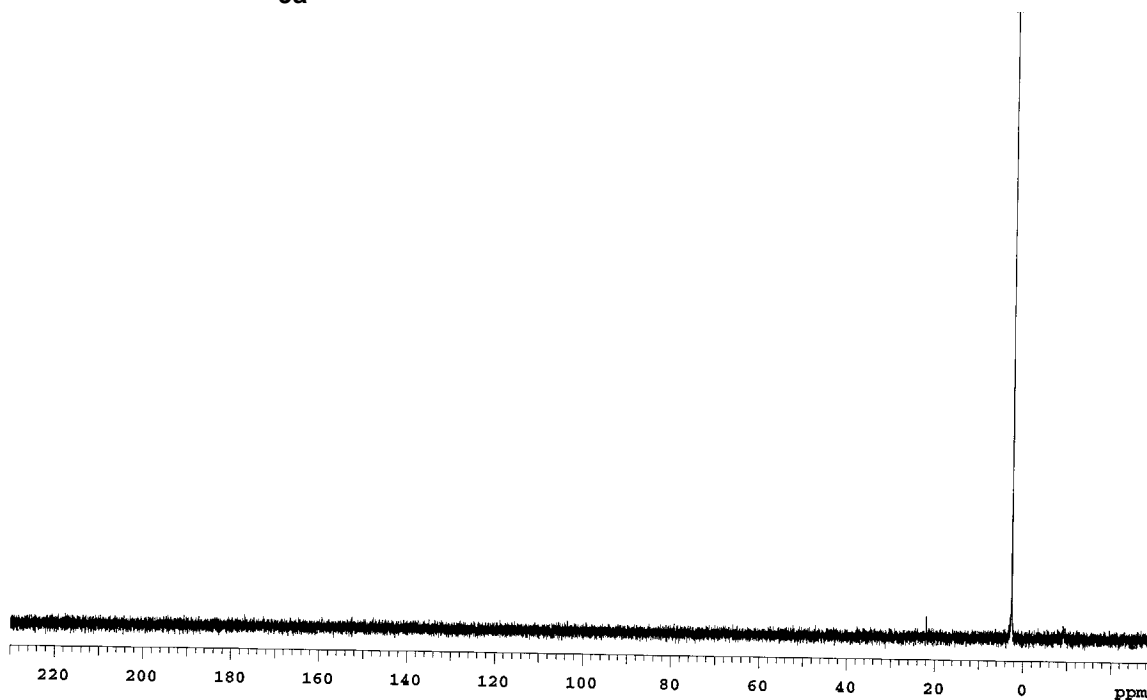
9a

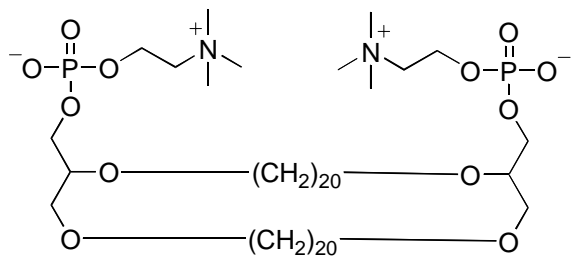


³¹P NMR OF

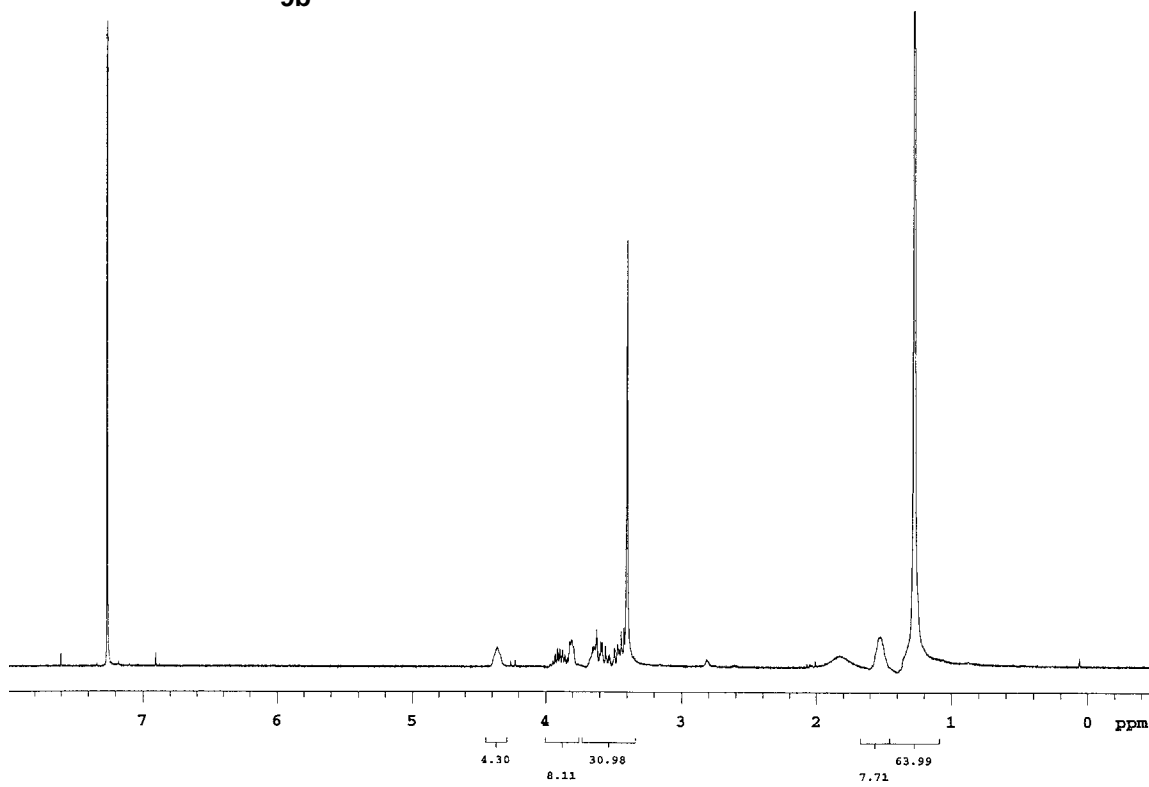


9a

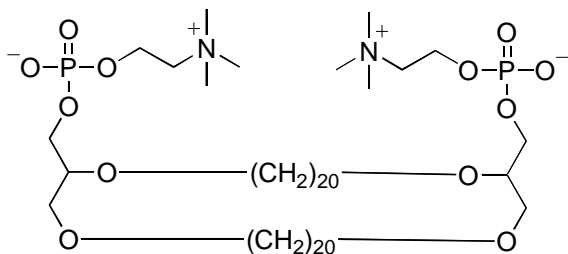




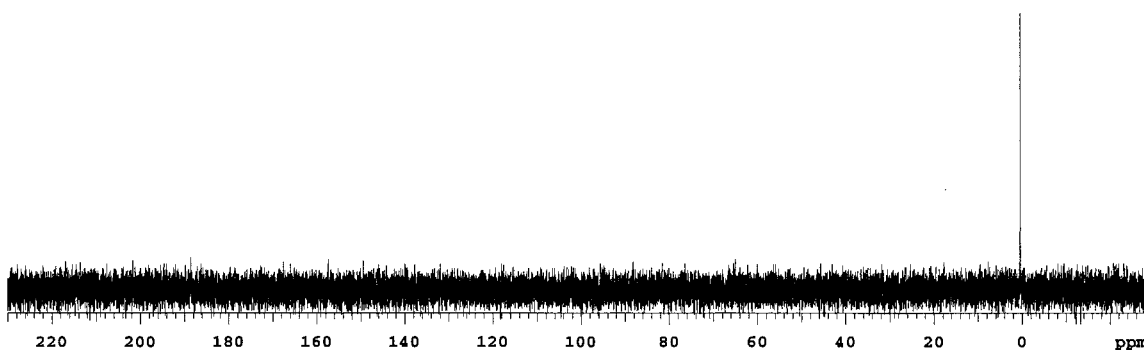
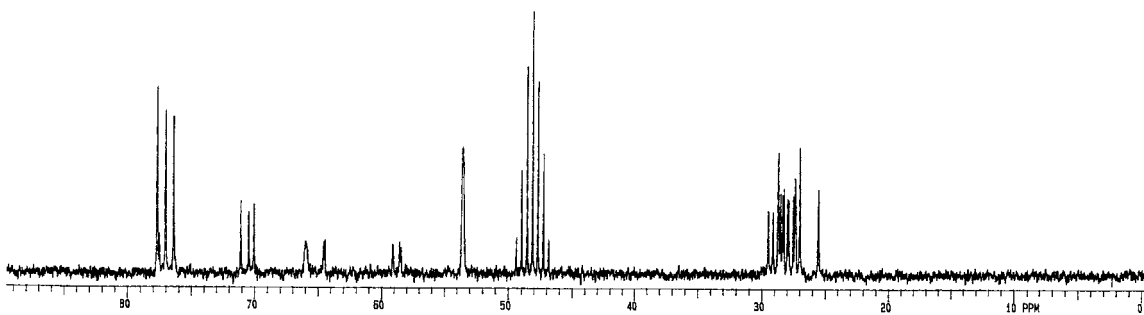
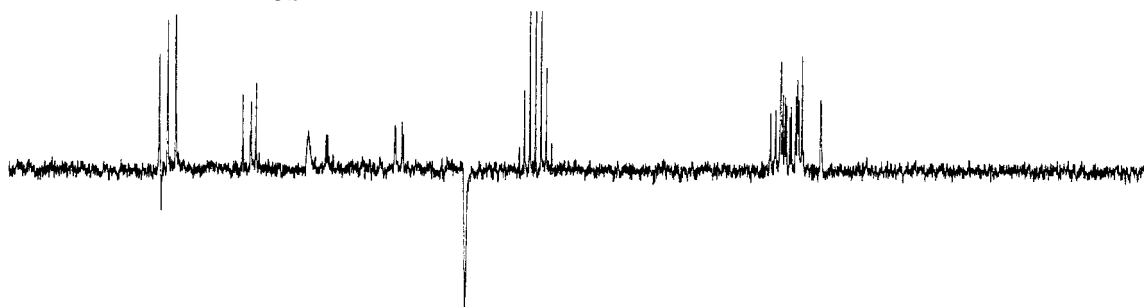
9b



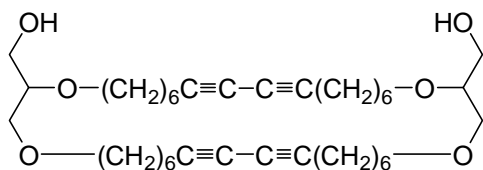
¹³C and ³¹P NMR of



9b

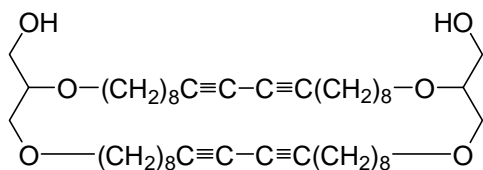


Elemental Analysis: Elemental Analysis for the following diols (bisphosphocholine precursors) was obtained.



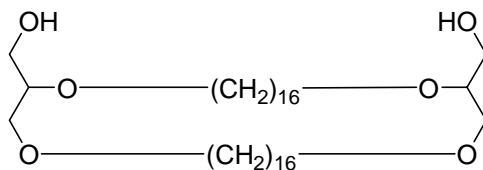
Calculated: C, 72.34; H 9.91 (Calculated as a Monohydrate)

Found : C, 72.59; H, 9.33



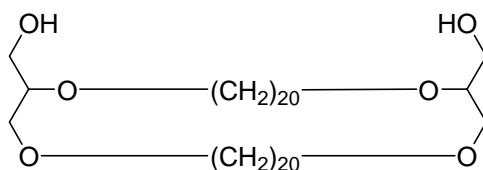
Calculated: C, 72.64; H, 10.89 (Calculated as a Dihydrate)

Found : C, 72.26; H, 9.87



Calculated: C, 72.56; H, 12.18

Found : C, 72.93; H, 12.40



Calculated: C, 74.54; H, 12.51

Found : C, 73.67; H, 12.37