Supplementary Material (ESI) for Organic & Biomolecular Chemistry

An efficient synthesis of benzodiazepinyl phosphonates as clostripain inhibitors via $FeCl_3$ catalyzed four-component reaction

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Supplementary Information

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Experimental section

General

The FT-IR spectra were recorded on an FT-IR-8300 Shimadzu spectrometer and microanalyses were carried out on a Carlo-Erba instrument. NMR spectra were recorded on Bruker ACF 200 and AV200 (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR) and AV400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR), using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR, respectively. Chemical shifts are expressed in parts per million (ppm). In case of NMR data of mixture of regioisomers, the peaks corresponding to the major isomer is given. Mass spectra were recorded on LC-MS/MS-TOF API QSTAR PULSAR spectrometer, samples introduced by infusion method using Electrospray Ionization Technique (ESI). Clostripain, *N*-α-benzoyl-DL-arginine-*p*-nitroanilide (BAPNA), dithiothreitol (DTT), dimethoxy sulfoxide (DMSO) and calcium chloride ($CaCl_2$) were purchased from Sigma Chem. Co. (USA). All other chemicals were of analytical grade.

Typical experimental procedure. To a mixture of *o*-phenylenediamine (1 mmol), acetone (0.5 mL) and molecular sieves (4 Å, 50 mg), $FeCl_3$ (10 mol%) and phosphite (1 mmol) were added. The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction (TLC), saturated aq. $NaHCO_3$ (10 mL) was added to the reaction mixture and the product was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to furnish the crude product which was purified by silica gel column chromatography (ethyl acetate: pet ether, 40-60%).

*Diethyl 2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5aa**).*

Pale yellow syrup; (Found: C, 58.95; H, 8.28; N, 8.63. Calc. for $C_{16}H_{27}N_2O_3P$: C, 58.88; H, 8.34; N, 8.58%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 3367, 3019, 1604, 1518, 1424, 1216, 1048 and 1031; δ_H (200 MHz; $CDCl_3$) 1.29-1.36 (12 H, m), 1.56 (3 H, d, $^3J_{PH}$ 17.2), 1.72-1.82 (1 H, m), 2.14-2.37 (1 H, m), 4.08-4.24 (4 H, m) and 6.62-6.81 (4 H, m); δ_C (50 MHz, $CDCl_3$) 16.5 (d, $^3J_{PC}$ 5.9), 16.6 (d, $^3J_{PC}$ 5.5), 23.5, 30.5, 33.6, 44.0 (d, $^2J_{PC}$ 2.6), 53.2 (d, $^3J_{PC}$ 14.6), 56.2 (d, $^1J_{PC}$ 148.2), 62.5 (d, $^2J_{PC}$ 7.7), 63.2 (d, $^2J_{PC}$ 7.0), 121.6, 121.8, 121.9, 122.0, 136.8 (d, $^3J_{PC}$ 12.4) and 137.5; δ_P (161 MHz, $CDCl_3$) 29.1; *m/z* (ESI): 327.29 $(M+H)^+$, 349.28 $(M+Na)^+$.

*Dibutyl 2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5ab**).*

Yellow syrup; (Found: C, 62.78; H, 9.34; N, 7.41. Calc. for $C_{20}H_{35}N_2O_3P$: C, 62.80; H, 9.22; N, 7.32%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3421, 3020, 2972, 1599, 1476, 1423, 1216 and 1030; δ_H (400 MHz, $CDCl_3$) 0.91 (6 H, t, *J* 7.3), 1.28 (3 H, s), 1.30 (3 H, s), 1.56 (3 H, d, $^3J_{PH}$ 17.2), 1.26-1.66 (8 H, m), 1.72-1.77 (1 H, m), 2.15-2.21 (1 H, m), 4.04-4.14 (4 H, m) and 6.60-6.76 (4 H, m); δ_C (100 MHz, $CDCl_3$) 13.6, 18.7, 23.6, 30.6, 32.6 (d, $^3J_{PC}$ 5.8), 32.7 (d, $^3J_{PC}$ 5.5), 33.4, 43.9 (d, $^2J_{PC}$ 2.6), 53.2 (d, $^3J_{PC}$ 14.6), 56.4 (d, $^1J_{PC}$ 147.8), 66.2 (d, $^2J_{PC}$ 8.0), 66.8 (d, $^2J_{PC}$ 7.3), 121.5, 121.6, 121.8, 121.9, 136.8 (d, $^3J_{PC}$ 11.7) and 137.4; δ_P (161 MHz, $CDCl_3$) 29.77; *m/z* (ESI) 383.32 $(M+H)^+$, 405.31 $(M+Na)^+$.

*Diallyl 2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5ac**).*

Yellow syrup; (Found: C, 61.76; H, 7.69; N, 7.92. Calc. for $C_{18}H_{27}N_2O_3P$: C, 61.70; H, 7.77; N, 7.99%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 3019, 2934, 1602, 1522, 1424, 1216 and 1045; δ_H (200 MHz, $CDCl_3$) 1.30 (3 H, s), 1.33 (3 H, s), 1.59 (3 H, d, $^3J_{PH}$ 17.4), 1.74-1.84 (1 H, m), 2.18-2.31 (1 H, m), 4.52-4.65 (4 H, m), 5.14-5.43 (4 H, m), 5.83-6.03 (2 H, m) and 6.61-7.01 (4 H, m); δ_C (50 MHz, $CDCl_3$) 23.7, 30.6, 33.5, 43.8 (d, $^2J_{PC}$ 2.2), 53.2 (d, $^3J_{PC}$ 14.6), 56.6 (d, $^1J_{PC}$ 147.1), 66.9 (d, $^2J_{PC}$ 7.7), 67.4 (d, $^2J_{PC}$ 6.9), 118.0 (d, $^4J_{PC}$ 2.2), 121.5, 121.8, 121.8, 122.0, 133.0 (d, $^3J_{PC}$ 5.9), 133.2 (d, $^3J_{PC}$ 5.9), 136.5 (d, $^3J_{PC}$ 11.7) and 137.5; δ_P (161 MHz, $CDCl_3$): 30.43; *m/z* (ESI) 351.27 $(M+H)^+$, 373.25 $(M+Na)^+$.

*Dimethyl 2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5ad**).*

Yellow syrup; (Found: C, 56.42; H, 7.70; N, 9.42. Calc. for $C_{14}H_{23}N_2O_3P$: C, 56.37; H, 7.77; N, 9.39%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 3019, 2934, 1614, 1502, 1216 and 1054; δ_H (400 MHz, $CDCl_3$) 1.30 (3 H, s), 1.31 (3 H, s), 1.56 (3 H, d, $^3J_{PH}$ 17.3), 1.75-1.80 (1 H, m), 2.04-2.37 (1 H, m), 3.79 (3 H, d, $^3J_{PH}$ 10.5), 3.81 (3 H, d, $^3J_{PH}$ 10.5), 6.64-6.66 (1 H, m), 6.72-6.74 (1 H, m) and 6.77-6.80 (2 H, m); δ_C (100 MHz, $CDCl_3$): 23.5, 30.3, 33.6, 44.0 (d, $^3J_{PC}$ 2.2), 53.1 (d, $^3J_{PC}$ 14.6), 53.2 (d, $^2J_{PC}$ 8.1), 54.3 (d, $^2J_{PC}$ 7.3), 56.6 (d, $^1J_{PC}$ 147.5), 121.6, 121.8, 121.9, 122.2, 136.6 (d, $^3J_{PC}$ 12.5) and 137.5; δ_P (161 MHz, $CDCl_3$) 32.27; *m/z* (ESI) 299.23 $(M+H)^+$, 321.20 $(M+Na)^+$.

*Diethyl 2,4,4,9-tetramethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5ba+5ba'**)* (1:6 regio-isomeric mixtures).

Yellow syrup; (Found: C, 59.83; H, 8.63; N, 8.34. Calc. for $C_{17}H_{29}N_2O_3P$: C, 59.98; H, 8.59; N, 8.23%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 3367, 3019, 1599, 1476, 1421, 1216 and 1029; δ_H (500 MHz, $CDCl_3$) 1.29-1.38 (12 H, m), 1.58 (3 H, d, $^3J_{PH}$ 17.9), 1.77-1.81 (1 H, m), 2.13-2.16 (1 H, m), 2.23 (3 H, s), 4.13-4.23 (4 H, m), 6.55 (1 H, d, *J* 7.6), 6.66-6.69 (1 H, m) and 6.74 (1 H, d, *J* 7.6); δ_C (125 MHz, $CDCl_3$): 16.5 (d, $^3J_{PC}$ 5.5), 18.0, 23.4, 30.4, 33.4, 43.6 (d, $^2J_{PC}$ 1.8), 52.8 (d, $^3J_{PC}$ 15.4), 56.0 (d, $^3J_{PC}$ 148.0), 62.7 (d, $^2J_{PC}$ 8.2), 62.8 (d, $^2J_{PC}$ 7.3), 120.4, 120.9, 124.1, 128.2, 136.0 (d, $^2J_{PC}$ 10.9 and 137.3; δ_P (202 MHz, $CDCl_3$) 30.30; *m/z* (ESI) 341.57 $(M+H)^+$, 363.57 $(M+Na)^+$.

*Dibutyl 2,4,4,9-tetramethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5bb+5bb'**)* (1:8 regio-isomeric mixtures).

Yellow syrup; (Found: C, 63.55, H, 9.50; N, 7.10. Calc. for $C_{21}H_{37}N_2O_3P$: C, 63.61; H, 9.41; N, 7.07%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 3360, 3019, 1599, 1518, 1476, 1424, 1215 and 1022; δ_H (200 MHz, $CDCl_3$): 0.88-0.98 (6 H, m), 1.25-1.73 (17 H, m), 1.76-1.83 (1 H, m), 2.08-2.28 (1 H, m), 2.23 (3 H, s), 4.02-4.18 (4 H, m) and 6.53-6.90 (3 H, m); δ_C (50 MHz, $CDCl_3$): 13.6, 18.1, 18.7, 23.6, 30.5, 32.7 (d, $^3J_{PC}$ 5.5), 33.3, 43.4 (d, $^2J_{PC}$ 2.2), 52.8 (d, $^3J_{PC}$ 15.0), 56.3 (d, $^1J_{PC}$ 147.5), 66.5 (d, $^2J_{PC}$ 7.7), 66.6 (d, $^2J_{PC}$ 7.7), 120.5, 120.9, 124.2, 128.2, 136.1 (d, $^3J_{PC}$ 10.6) and 137.1; δ_P (161 MHz, $CDCl_3$) 29.94; *m/z* (ESI) 397.64 $(M+H)^+$, 419.65 $(M+Na)^+$.

*Diallyl 2,4,4,9-tetramethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5bc+5bc'**)* (1:5 regio-isomeric mixtures).

Yellow syrup; (Found: C, 62.57; H, 8.09; N, 7.74. Calc. for $C_{19}H_{29}N_2O_3P$: C, 62.62; H, 8.02; N, 7.69%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3355, 3019, 1599, 1520, 1466, 1384, 1319, 1215 and 1029; δ_H (200 MHz, $CDCl_3$) 1.28 (3 H, s), 1.32 (3 H, s), 1.63 (3 H, d, $^3J_{PH}$ 17.6), 1.75-1.85 (1 H, m), 2.12-2.19 (1 H, m), 2.23 (3 H, s), 4.55-4.66 (4 H, m), 5.15-5.44 (4 H, m), 5.86-6.03 (2 H, m) and 6.53-6.90 (3 H, m); δ_C (50 MHz, $CDCl_3$) 18.1, 23.6, 30.5, 33.3, 43.3, 52.8 (d, $^3J_{PC}$ 15.0), 56.4 (d, $^1J_{PC}$ 147.1), 67.1 (d, $^2J_{PC}$ 7.7), 67.2 (d, $^2J_{PC}$ 7.7), 118.0, 118.1, 120.6, 121.1. 124.3, 128.4, 132.9 (d, $^3J_{PC}$ 5.9), 133.0 (d, $^3J_{PC}$ 5.9), 135.9 (d, $^3J_{PC}$ 10.6) and 137.3; δ_P (161 MHz, $CDCl_3$) 30.95; *m/z* (ESI) 365.62 $(M+H)^+$, 387.62 $(M+Na)^+$.

*Diethyl 7,8-dichloro-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5ca**).*

Pale yellow syrup; (Found: C, 48.77; H, 6.44; N, 7.16. Calc. for $C_{16}H_{25}Cl_2N_2O_3P$: C, 48.62; H, 6.38; N, 7.09%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3421, 3019, 1647, 1542, 1489, 1215 and 1048; δ_H (400 MHz, $CDCl_3$) 1.32-1.37 (12 H, m), 1.59 (3 H, d, $^3J_{PH}$ 16.8), 1.77-1.82 (1 H, m), 2.17-2.24 (1 H, m), 4.13-4.25 (4 H, m), 6.72 (1 H, s) and 6.79 (1 H, s); δ_C (100 MHz, $CDCl_3$): 16.5 (d, $^3J_{PC}$ 6.6), 16.6 (d, $^3J_{PC}$ 5.9), 23.8, 30.8, 33.2, 43.3, 53.5 (d, $^3J_{PC}$ 13.9), 56.2 (d, $^1J_{PC}$ 148.2), 62.7 (d, $^2J_{PC}$ 8.1), 63.2 (d, $^2J_{PC}$ 7.3), 121.7, 122.1, 123.7, 123.9, 136.4 (d, $^3J_{PC}$ 11.0) and 137.1; δ_P (161 MHz, $CDCl_3$): 29.1; *m/z* (ESI): 395.12 $(M+H)^+$, 417.10 $(M+Na)^+$.

*Dibutyl 7,8-dichloro-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5cb**).*

Yellow syrup; (Found: C, 53.25; H, 7.43; N, 6.24. Calc. for $C_{20}H_{33}Cl_2N_2O_3P$: C, 53.22; H, 7.37; N, 6.21%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3421, 3019, 2964, 1607, 1488, 1385, 1215 and 1028; δ_H (500 MHz, $CDCl_3$): 0.93 (6 H, 2t, *J* 7.3), 1.29 (3 H, s), 1.33-1.42 (4 H, m), 1.37 (3 H, s), 1.58 (3 H, d, $^3J_{PH}$ 16.8), 1.62-1.67 (4 H, m), 1.75-1.79 (1 H, m), 2.16-2.21 (1 H, m), 4.05-4.12 (4 H, m), 6.69 (1 H, s) and 6.76 (1 H, s); δ_C (125 MHz, $CDCl_3$): 13.6, 18.8, 24.1, 30.9, 32.6 (d, $^3J_{PC}$ 5.5), 32.7 (d, $^3J_{PC}$ 5.5), 33.2, 43.2, 53.5 (d, $^3J_{PC}$ 13.6), 56.5 (d, $^1J_{PC}$ 148.1), 66.5 (d, $^2J_{PC}$ 8.2), 66.8 (d, $^3J_{PC}$ 7.3), 121.5, 122.1, 123.6, 123.9, 136.3 (d, $^3J_{PC}$ 9.9) and 137.0; δ_P (202 MHz, $CDCl_3$) 28.91; *m/z* (ESI) 383.32 $(M+H)^+$, 405.31 $(M+Na)^+$.

*Diallyl 7,8-dichloro-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5cc**).*

Yellow syrup; (Found: C, 51.64; H, 6.15; N, 6.74. Calc. for $C_{18}H_{25}Cl_2N_2O_3P$: C, 51.56; H, 6.01; N, 6.68%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3421, 3019, 1611, 1423, 1215 and 1019; δ_H (400 MHz, $CDCl_3$) 1.29 (3 H, s), 1.36 (3 H, s), 1.61 (3 H, d, $^3J_{PH}$ 17.2), 1.74-1.84 (1 H, m), 2.16-2.35 (1 H, m), 4.53-4.62 (4 H, m), 5.23-5.38 (4 H, m), 5.83-6.02 (2 H, m), 6.69 (1 H, s) and 6.77 (1 H, s); δ_C (50 MHz, $CDCl_3$) 24.1, 30.9, 33.2, 43.2 (d, $^2J_{PC}$ 1.1), 53.5 (d, $^3J_{PC}$ 13.9), 56.5 (d, $^1J_{PC}$ 147.1), 67.1 (d, $^2J_{PC}$ 7.7), 67.4 (d, $^2J_{PC}$ 7.0), 118.3, 118.4, 121.6, 122.2, 123.5, 124.1, 132.8, 132.9, 135.6 (d, $^2J_{PC}$ 10.6) and 137.1; δ_P (161 MHz, $CDCl_3$) 29.68; *m/z* (ESI) 420.31 $(M+H)^+$.

*Dimethyl 7,8-dichloro-2,4,4-trimethyl-2,3,4,5-tetra-hydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5cd**).*

Yellow syrup; (Found: C, 45.83; H, 5.82, N, 7.66. Calc. for $C_{14}H_{21}Cl_2N_2O_3P$: C, 45.79; H, 5.76; N, 7.63%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3421, 3019, 2964, 1622, 1542, 1488, 1385, 1216 and 1031; δ_H (200 MHz, $CDCl_3$) 1.30 (3 H, s), 1.34 (3 H, s), 1.58 (3 H, d, $^3J_{PH}$ 17.2), 1.73-1.83 (1 H, m), 2.05-2.25 (1 H, m), 3.79 (3 H, d, $^3J_{PH}$ 10.4), 3.82 (3 H, d, $^3J_{PH}$ 10.3), 6.72 (1 H, s) and 6.81 (1 H, s); δ_C (50 MHz, $CDCl_3$) 23.9, 30.7, 33.2, 43.4, 53.4(d, $^2J_{PC}$ 7.7), 53.5 (d, $^3J_{PC}$ 13.9), 54.0 (d, $^2J_{PC}$ 7.0), 56.1 (d, $^1J_{PC}$ 148.6), 121.8, 122.2, 123.7, 124.1, 136.2 (d, $^3J_{PC}$ 10.9) and 137.1; δ_P (202 MHz, $CDCl_3$) 31.33; *m/z* (ESI) 367.17 $(M+H)^+$, 389.16 $(M+Na)^+$.

*Diethyl 2,4,4-trimethyl-8-nitro-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5da+5da'**)* (1:8 regio-isomeric mixtures).

Pale yellow semi-solid; (Found: 51.81; H, 7.17; N, 11.23. Calc. for $C_{16}H_{26}N_3O_5P$: C, 51.75; H, 7.06; N, 11.31%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3421, 3367, 3019, 1614, 1519, 1216 and 1054; δ_H (200 MHz, $CDCl_3$) 1.26 (6 H, t, *J* 7.0), 1.39 (3 H, s), 1.59 (3 H, d, $^3J_{PH}$ 16.7), 1.57 (3 H, s), 1.76-1.85 (1 H, m), 2.37-2.53 (1 H, m), 4.01-4.21 (4 H, m), 6.43 (1 H, d, *J* 8.7) and 7.58-7.90 (2 H, m); δ_C (50 MHz, $CDCl_3$) 16.4 (d, $^3J_{PC}$ 5.5), 16.5 (d, $^3J_{PC}$ 5.5), 25.0, 32.0, 33.5, 43.1, 54.3 (d, $^1J_{PC}$ 11.7), 55.2 (d, $^1J_{PC}$ 145.6), 62.5 (d, $^2J_{PC}$ 8.0), 62.7 (d, $^2J_{PC}$ 7.3), 116.5, 117.4, 119.3, 132.3 (d, $^3J_{PC}$ 7.0), 138.9 and 145.3; δ_P (161 MHz, $CDCl_3$) 28.35; *m/z* (ESI) 372.67 $(M+H)^+$, 394.73 $(M+Na)^+$.

*Dibutyl 2,4,4-trimethyl-8-nitro-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5db'**).*

Pale yellow semi-solid; (Found: C, 56.10; H, 8.14; N, 9.96 Calc. for $C_{20}H_{34}N_3O_5P$: C, 56.19; H, 8.02; N, 9.83%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 3367, 3019, 2964, 1593, 1518, 1319, 1216 and 1024; δ_H (400 MHz, $CDCl_3$) 0.87-0.95 (6 H, m), 1.27-1.61 (8 H, m), 1.38 (3 H, s), 1.57 (3 H, s), 1.60 (3 H, d, $^3J_{PH}$ 16.5), 1.78-1.83 (1 H, m), 2.40-2.48 (1 H, m), 3.74 (1 H, bs), 3.94-4.11 (4H, m), 4.18 (1 H, bs), 6.40 (1 H, d, *J* 8.7), 7.56 (1 H, d, *J* 2.4) and 7.66 (1 H, dd, *J* 8.7, 2.4); δ_C (100 MHz, $CDCl_3$) 13.6, 18.7, 18.8, 25.1 (d, $^4J_{PC}$ 1.10), 32.1, 32.6 (d, $^3J_{PC}$ 3.3), 32.7 (d, $^3J_{PC}$ 3.3), 33.6, 43.0, 54.3 (d, $^3J_{PC}$ 11.7), 56.9 (d, $^1J_{PC}$ 145.3), 66.3 (d, $^2J_{PC}$ 7.7), 66.5 (d, $^2J_{PC}$ 7.7), 116.5, 117.5, 119.3, 132.3 (d, $^3J_{PC}$ 6.7), 139.2 and 145.1; δ_P (161 MHz, $CDCl_3$) 25.7; *m/z* (ESI): 428.2 $(M+H)^+$, 450.2 $(M+Na)^+$.

*Diallyl 2,4,4-trimethyl-8-nitro-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5dc'**)*

Pale yellow semi-solid; (Found: C, 54.75, 6.53. N, 10.59 Calc. for $C_{18}H_{26}N_3O_5P$: C, 54.68; H, 6.63; N, 10.63%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3421, 3367, 3020, 1593, 1519, 1484, 1320, 1215 and 1030; δ_H (500 MHz, $CDCl_3$) 1.38 (3 H, s), 1.59 (3 H, s), 1.62 (3 H, d, $^3J_{PH}$ 16.6), 1.80-1.84 (1 H, m), 2.47-2.53 (1 H, m), 4.38-4.58 (4 H, m), 5.20-5.30 (4 H, m), 5.80-5.88 (2 H, m), 6.41 (1 H, d, *J* 8.7), 7.58 (1 H, d, *J* 2.5) and 7.66 (1 H, dd, *J* 8.7, 2.5); δ_C (125 MHz, $CDCl_3$): 25.2, 32.0, 33.6, 43.0, 54.2, 57.0 (d, $^1J_{PC}$ 143.5), 66.8 (d, $^2J_{PC}$ 7.3), 67.0 (d, $^2J_{PC}$ 7.3), 116.4, 117.5, 118.2, 118.4, 119.4, 132.1 (d, $^3J_{PC}$ 6.3), 132.7 (d, $^3J_{PC}$ 5.3), 132.8 (d, $^3J_{PC}$ 5.3), 139.0 and 145.3; δ_P (202 MHz, $CDCl_3$) 29.1; *m/z* (ESI) 396.48 $(M+H)^+$, 418.43 $(M+Na)^+$.

*Dimethyl 2,4,4-trimethyl-8-nitro-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5dd+5dd'**)* (1:1 regio-isomeric mixtures).

Yellow syrup; (Found: C, 49.87; H, 6.52; N, 12.22. Calc. for $C_{14}H_{22}N_3O_5P$: C, 49.98; H, 6.46; N, 12.24%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 3360, 3019, 2923, 1592, 1518, 1318, 1215 and 1046; δ_H (400 MHz, $CDCl_3$) 1.28 (3 H, s), 1.38 (3 H, s), 1.70 (3 H, d, $^3J_{PH}$ 16.6), 1.79-1.87 (1 H, m), 2.15-2.45 (1 H, m), 3.68 (3 H, d, $^3J_{PH}$ 10.3), 3.79 (3 H, d, $^3J_{PH}$ 10.3), 6.42 (1 H, d, *J* 8.8) and 7.53-7.64 (2 H, m); δ_C (100 MHz, $CDCl_3$): 25.1, 31.2, 32.4, 43.2, 53.6 (d, $^2J_{PC}$ 8.1), 54.1 (d, $^2J_{PC}$ 7.3), 53.7 (d, $^3J_{PC}$ 11.0), 57.0 (d, $^1J_{PC}$ 149.7), 116.4, 118.2, 119.4, 135.1, 140.9 and 145.2; δ_P (161 MHz, $CDCl_3$): 30.80; *m/z* (ESI) 344.28 $(M+H)^+$, 366.25 $(M+Na)^+$.

*Diethyl 7-benzoyl-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5ea+5ea'**)* (3:4 regio-isomeric mixtures).

Yellow syrup; (Found: C, 64.27; H, 7.30; N, 6.50. Calc. for $C_{23}H_{31}N_2O_4P$: C, 64.17; H, 7.26; N, 6.51%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 3368, 3019, 1730, 1620, 1515, 1446, 1319 and 1215; δ_H (200 MHz, $CDCl_3$) 1.24-1.48 (12 H, m), 1.58 (3 H, d, $^3J_{PH}$ 16.9), 1.77-1.89 (1 H, m), 2.14-2.46 (1 H, m), 4.05-4.24 (4 H, m), 6.52 (1 H, d, *J* 8.7), 7.21-7.28 (2 H, m), 7.40-7.57 (3 H, m) and 7.69-7.74 (2 H, m); δ_C (50 MHz, $CDCl_3$): 16.4 (d, $^3J_{PC}$ 4.4), 16.6 (d, $^3J_{PC}$ 4.4), 24.6, 31.9, 33.5, 43.5, 54.0 (d, $^3J_{PC}$ 13.5), 56.5 (d, $^1J_{PC}$ 146.7), 62.9 (d, $^2J_{PC}$ 7.0),

63.4 (d, $^2J_{PC}$ 7.0), 117.9, 123.9, 126.1, 128.1, 130.0, 129.5, 131.4, 135.5, 138.9, 143.0 and 195.2; δ_P (161 MHz, $CDCl_3$) 29.08; *m/z* (ESI) 431.76 $(M+H)^+$, 453.77 $(M+Na)^+$.

*Dibutyl 7-benzoyl-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5eb+5eb'**)* (1:3 regio-isomeric mixtures).

Yellow syrup; (Found: C, 66.70; H, 8.13; N, 5.68. Calc. for $C_{27}H_{39}N_2O_4P$: C, 66.65; H, 8.08; N, 5.76%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3421, 3392, 3018, 1641, 1593, 1480, 1320 and 1216; δ_H (200 MHz, $CDCl_3$) 0.94 (6 H, t, *J* 7.2), 1.19-1.75 (17 H, m), 1.82-2.41 (2 H, m), 4.00-4.15 (4 H, m), 6.52 (1 H, d, *J* 8.6), 7.23-7.30 (2 H, m), 7.40-7.56 (3 H, m) and 7.69-7.74 (2 H, m); δ_C (100 MHz, $CDCl_3$): 13.6, 18.7, 24.7, 31.2, 33.4, 32.6 (d, $^3J_{PC}$ 5.8), 32.6 (d, $^3J_{PC}$ 5.5), 43.5, 53.9 (d, $^3J_{PC}$ 13.5), 56.8 (d, $^1J_{PC}$ 146.4), 66.3 (d, $^2J_{PC}$ 8.0), 66.6 (d, $^2J_{PC}$ 7.7), 119.2, 123.9, 126.1, 128.1, 128.5, 129.5, 131.3, 135.4, 138.9, 143.0 and 195.5; δ_P (161 MHz, $CDCl_3$) 28.96; *m/z* (ESI) 487.94 $(M+H)^+$, 509.95 $(M+Na)^+$.

*Diallyl 7-benzoyl-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5ec+5ec'**)* (1:2 regio-isomeric mixture).

Yellow syrup; (Found: C, 66.13; H, 6.84; N, 6.21. Calc. for $C_{25}H_{31}N_2O_4P$: C, 66.07; H, 6.87; N, 6.16%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 3370, 3019, 1641, 1521, 1476, 1422 and 1215; δ_H (200 MHz, $CDCl_3$) 1.38 (3 H, s), 1.50 (3 H, s), 1.61 (3 H, d, $^3J_{PH}$ 17.1), 1.79-1.88 (1 H, m), 2.35-2.51 (1 H, m), 4.43-4.63 (4 H, m), 5.14-5.49 (4 H, m), 5.78-5.97 (2 H, m), 6.51 (1 H, d, *J* 8.6), 7.23-7.29 (1 H, m), 7.39-7.54 (4 H, m) and 7.67-7.78 (2 H, m); δ_C (50 MHz, $CDCl_3$) 24.8, 31.9, 33.5, 43.4, 54.0 (d, $^3J_{PC}$ 12.4), 56.9 (d, $^1J_{PC}$ 144.9), 66.9 (d, $^2J_{PC}$ 8.0), 67.2 (d, $^2J_{PC}$ 7.0), 117.8, 118,1, 118.2, 124.1, 128.2, 128.1, 128.7, 129.5, 131.4, 132.9, 133.2, 138.9, 142.9 and 195.1; δ_P (161 MHz, $CDCl_3$): 29.79; *m/z* (ESI) 455.44 $(M+H)^+$, 477.29 $(M+Na)^+$.

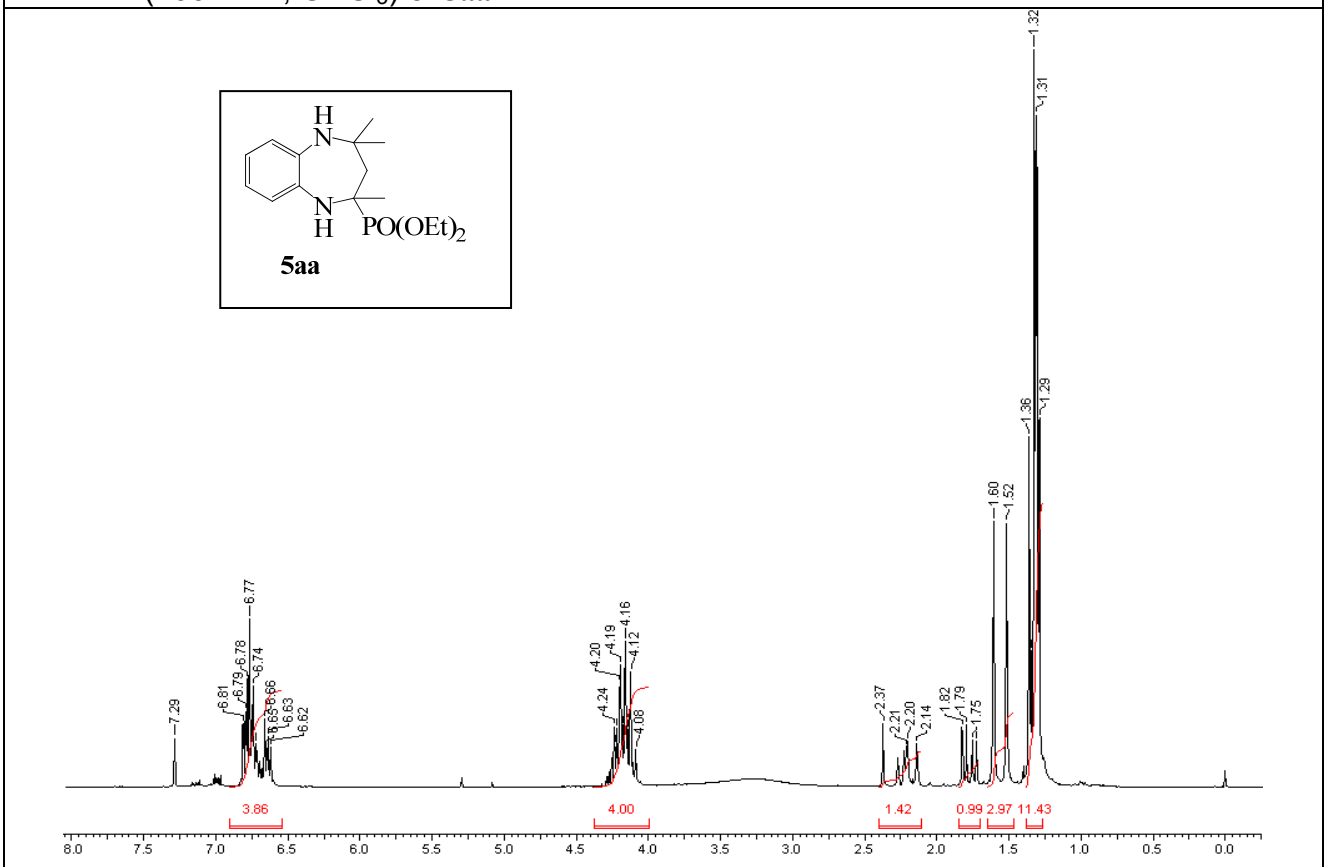
*Dimethyl 7-benzoyl-2,4,4-trimethyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-2-ylphosphonate (**5ed+5ed'**)* (1:1 regio-isomeric mixture).

Yellow syrup; (Found: C, 62.75; H, 6.72; N, 6.91. Calc. for $C_{21}H_{27}N_2O_4P$: C, 62.68; H, 6.76; N, 6.96%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 3018, 2956, 1653, 1641, 1593, 1508, 1338, 1217, 1132 and 1053; δ_H (400 MHz, $CDCl_3$) 1.37 (3 H, s), 1.39 (3 H, s), 1.70 (3 H, d, $^3J_{PC}$ 16.6), 1.78-1.88(1 H, m), 2.20-2.40 (1 H, m), 3.74-3.85 (6 H, m), 6.69 (1 H, d, *J* 8.6), 7.23-7.27 (2 H, m), 7.43-7.54 (3 H, m) and 7.72-7.82 (2 H, m); δ_C (100 MHz, $CDCl_3$): 24.6, 30.9, 32.7, 43.1, 53.2 (d, $^2J_{PC}$ 7.3), 53.4, 56.9 (d, $^1J_{PC}$ 149.6), 118.2, 123.9, 125.8, 128.1, 129.6, 130.3, 131.6, 133.4, 138.7, 141.9 and 195.2; δ_P (161 MHz, $CDCl_3$): 31.5; *m/z* (ESI): 403.62 $(M+H)^+$, 425.69 $(M+Na)^+$.

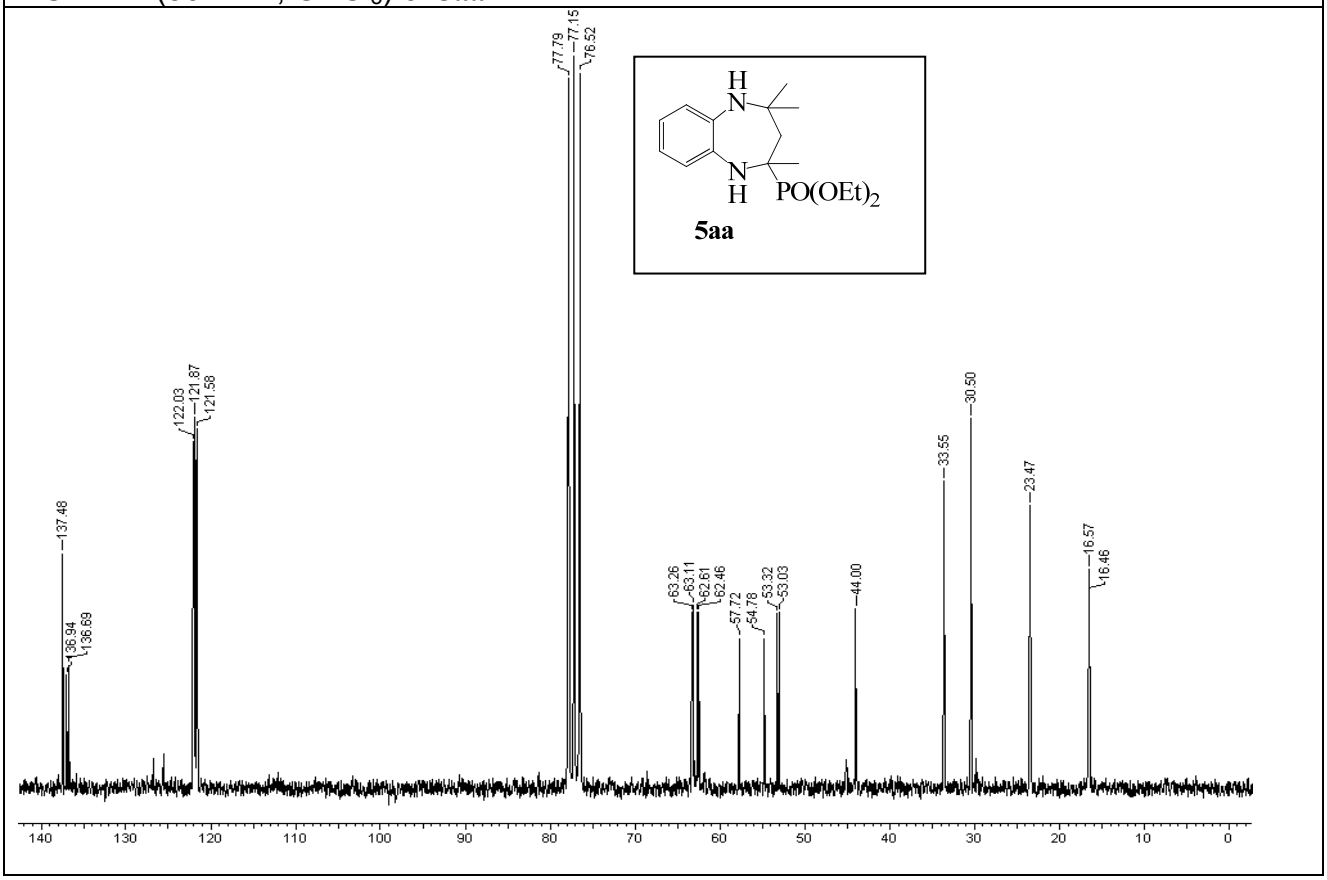
Bioassay of synthesized BDPs

The inhibitory activity of cysteine protease inhibitor (CPI) against clostripain was assayed spectrophotometrically. Clostripain was activated in 10 mM Tris HCL buffer, pH 7.4, containing 1 mM $CaCl_2$ and 2.5 mM DTT for 3 h at 37 ^oC. After activation, clostripain (25 nM) was added to enzyme buffer (100 mM Tris HCl buffer, pH 7.4) containing the substrate BAPNA (500 μM) in the presence and absence of CPI. Formation of product (*p*-nitroaniline) was monitored by the increase in absorbance at 410 nm.

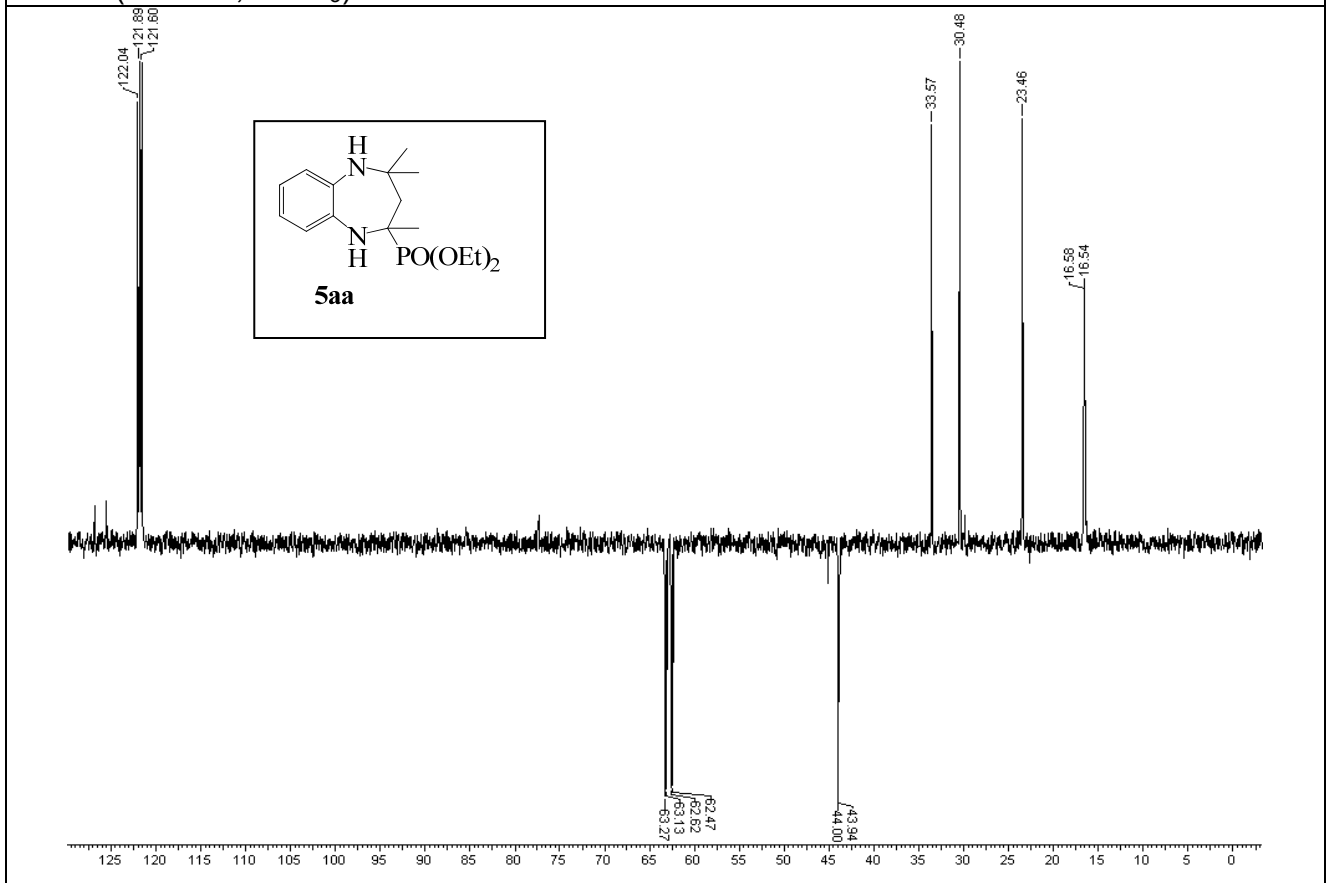
^{1}H NMR (200 MHz, $CDCl_3$) of **5aa**



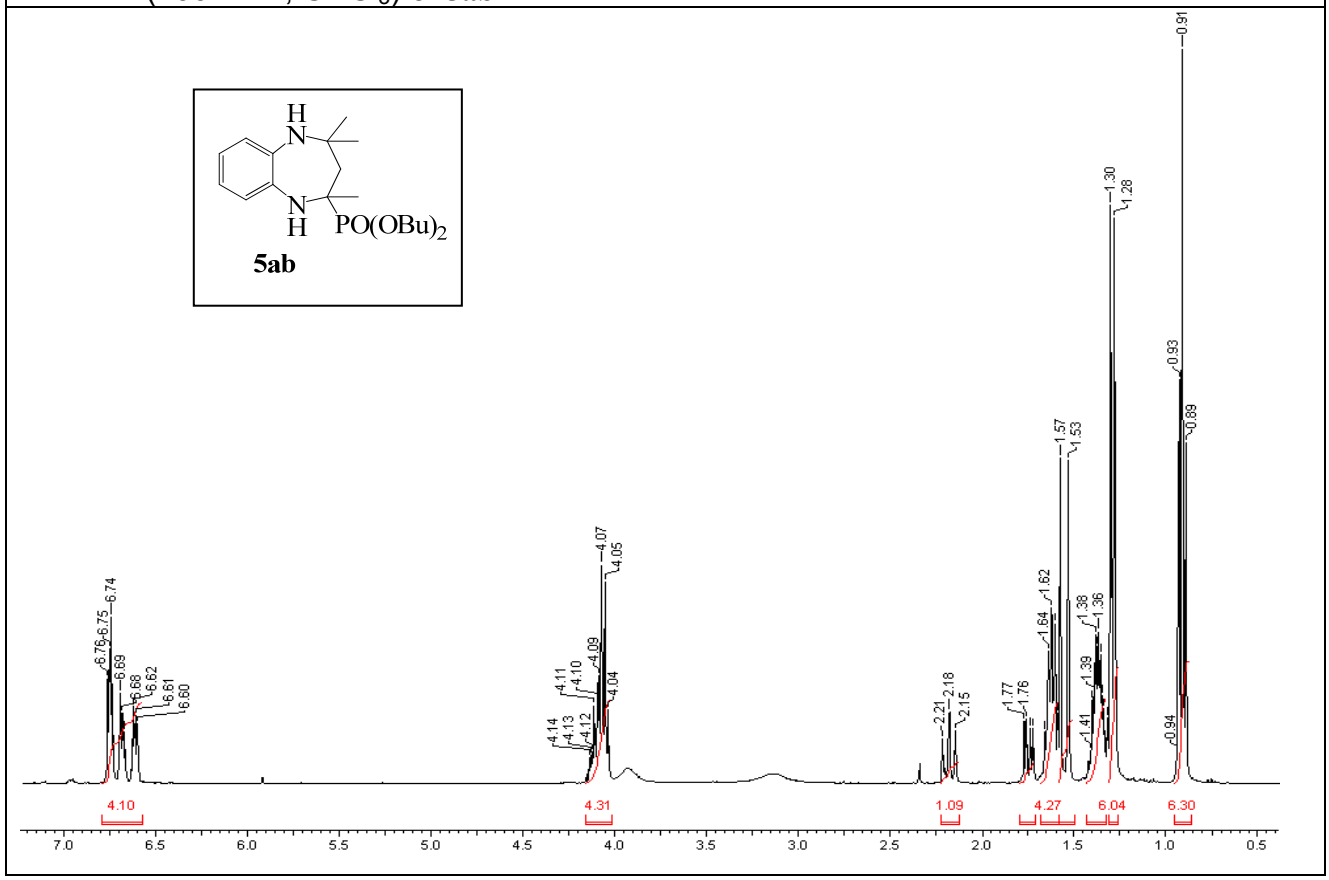
^{13}C NMR (50 MHz, $CDCl_3$) of **5aa**



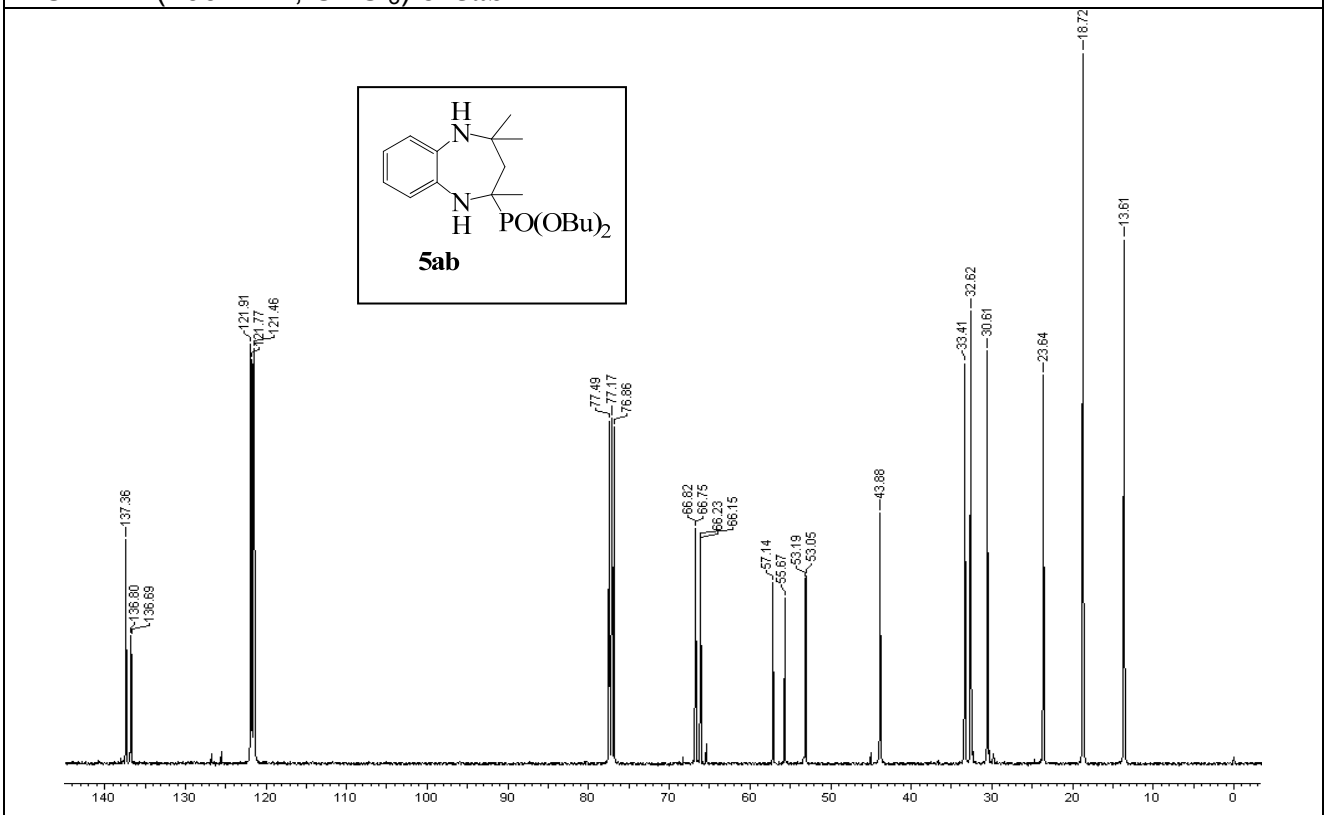
DEPT (50 MHz, $CDCl_3$) of **5aa**



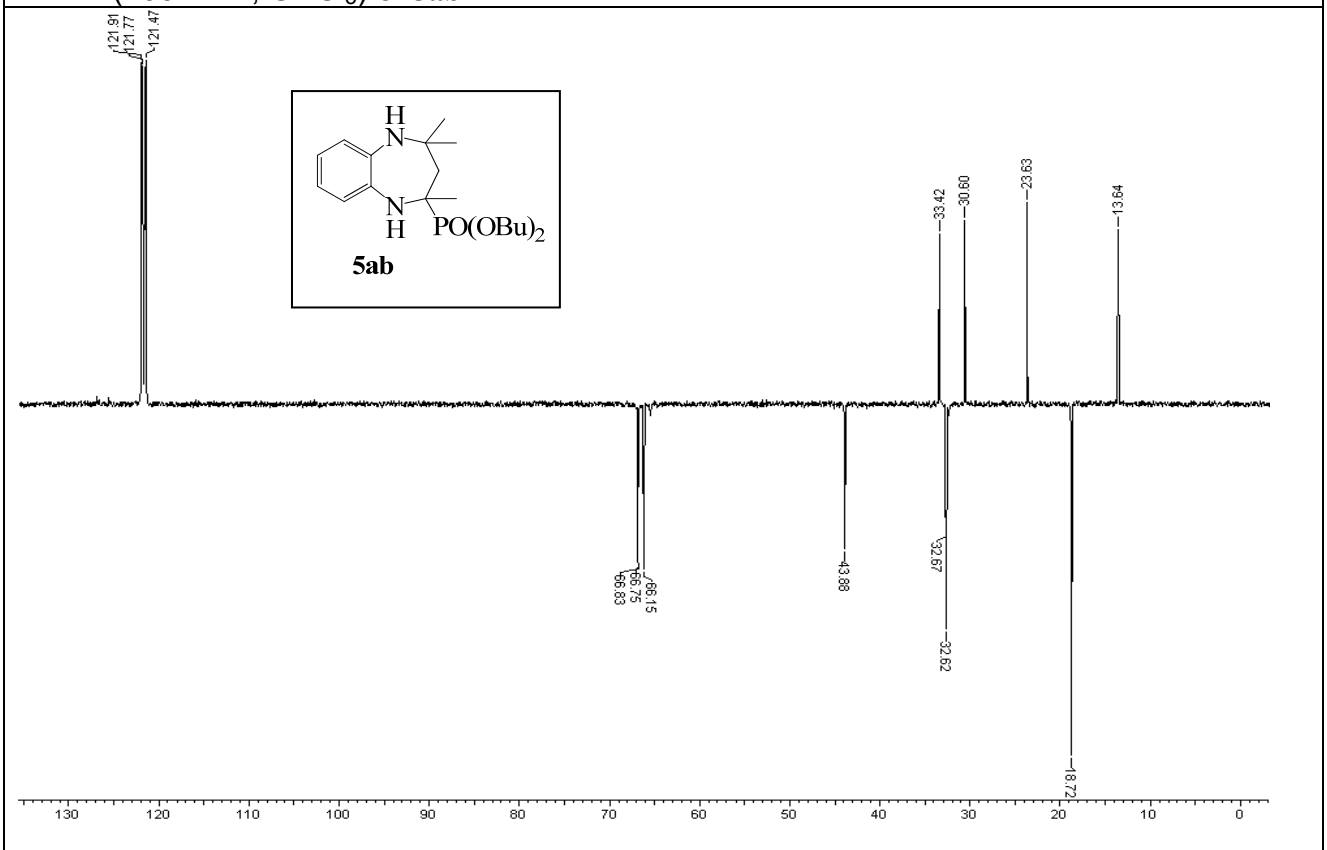
^{1}H NMR (400 MHz, $CDCl_3$) of **5ab**



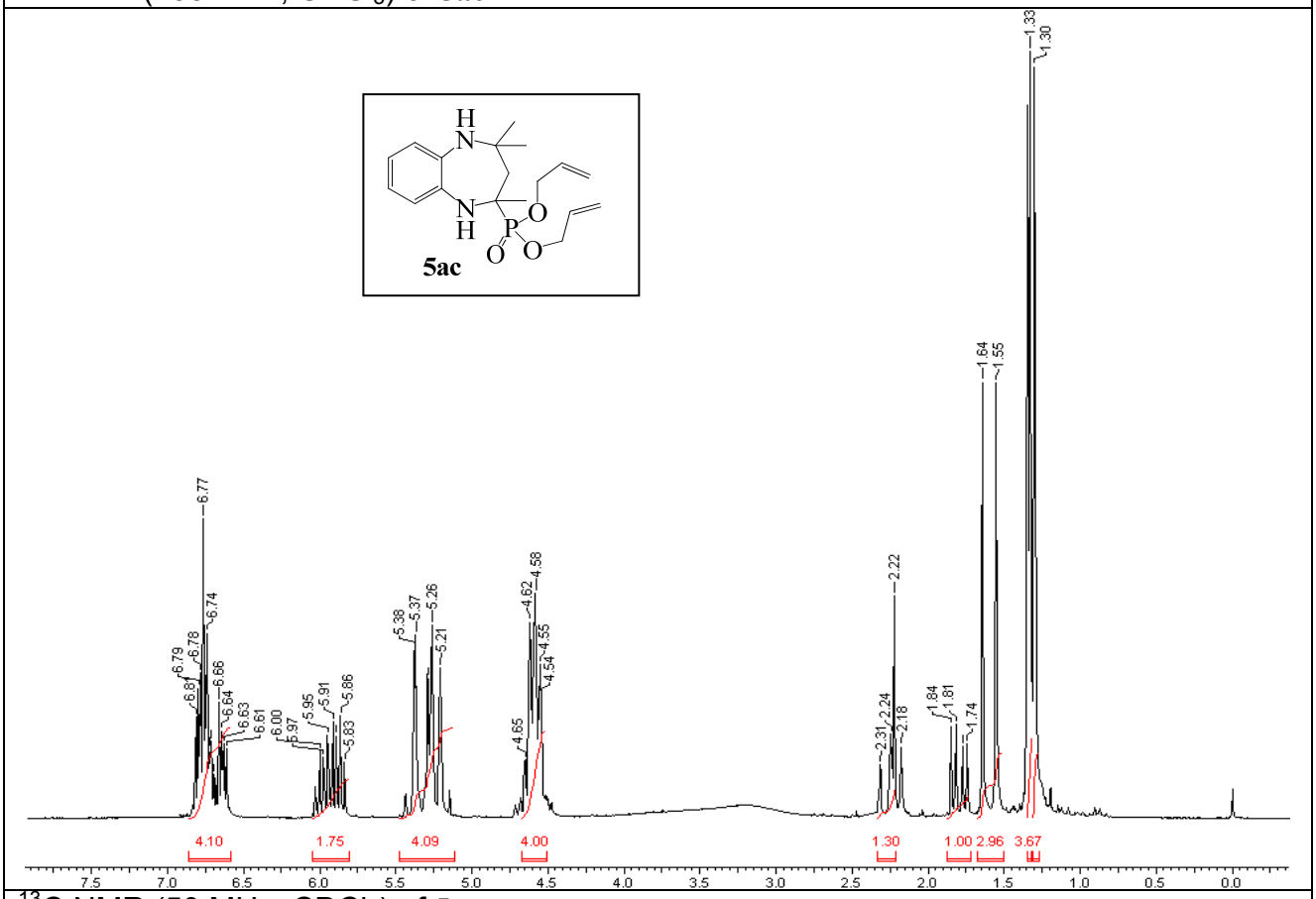
^{13}C NMR (100 MHz, $CDCl_3$) of **5ab**



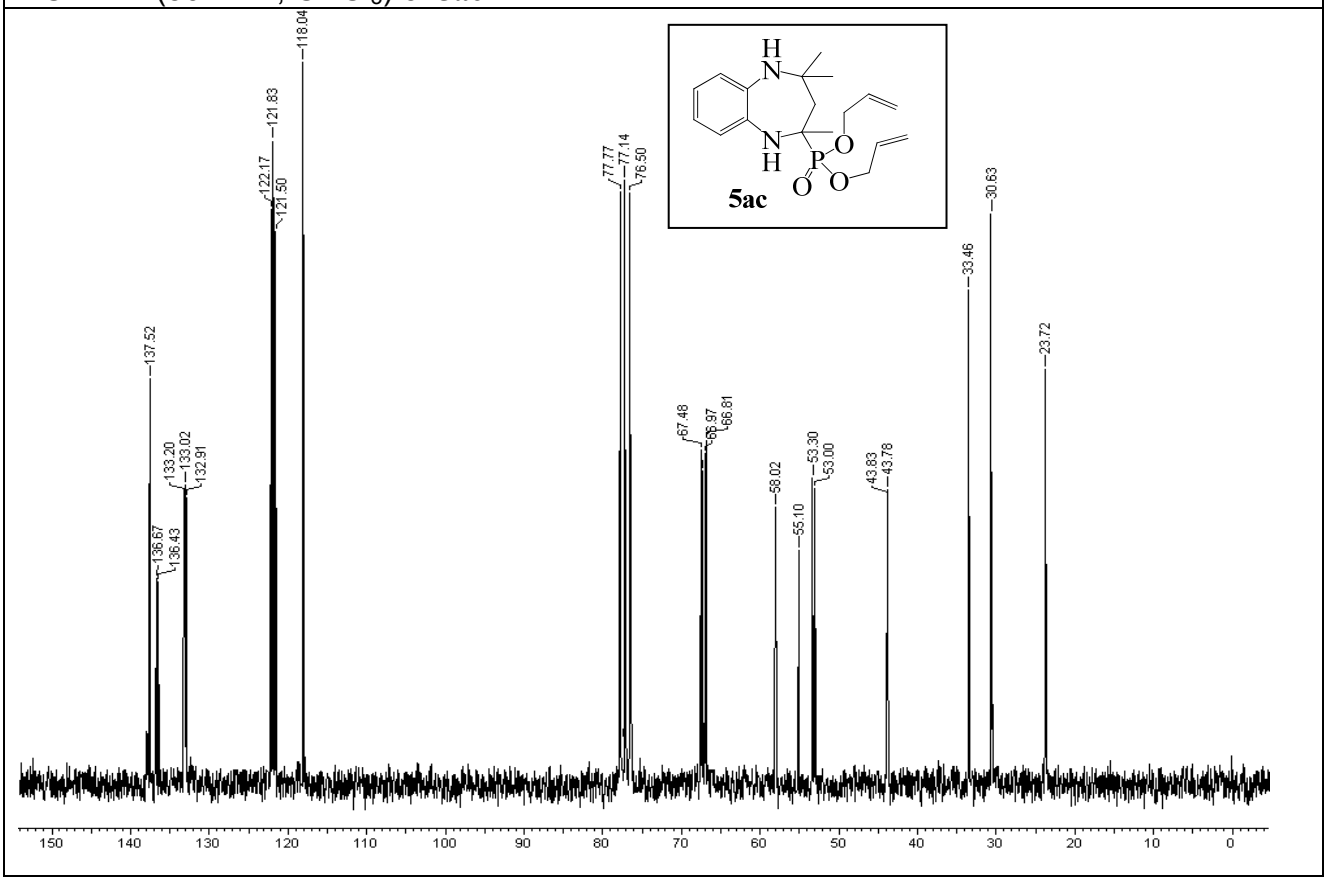
DEPT (100 MHz, $CDCl_3$) of **5ab**



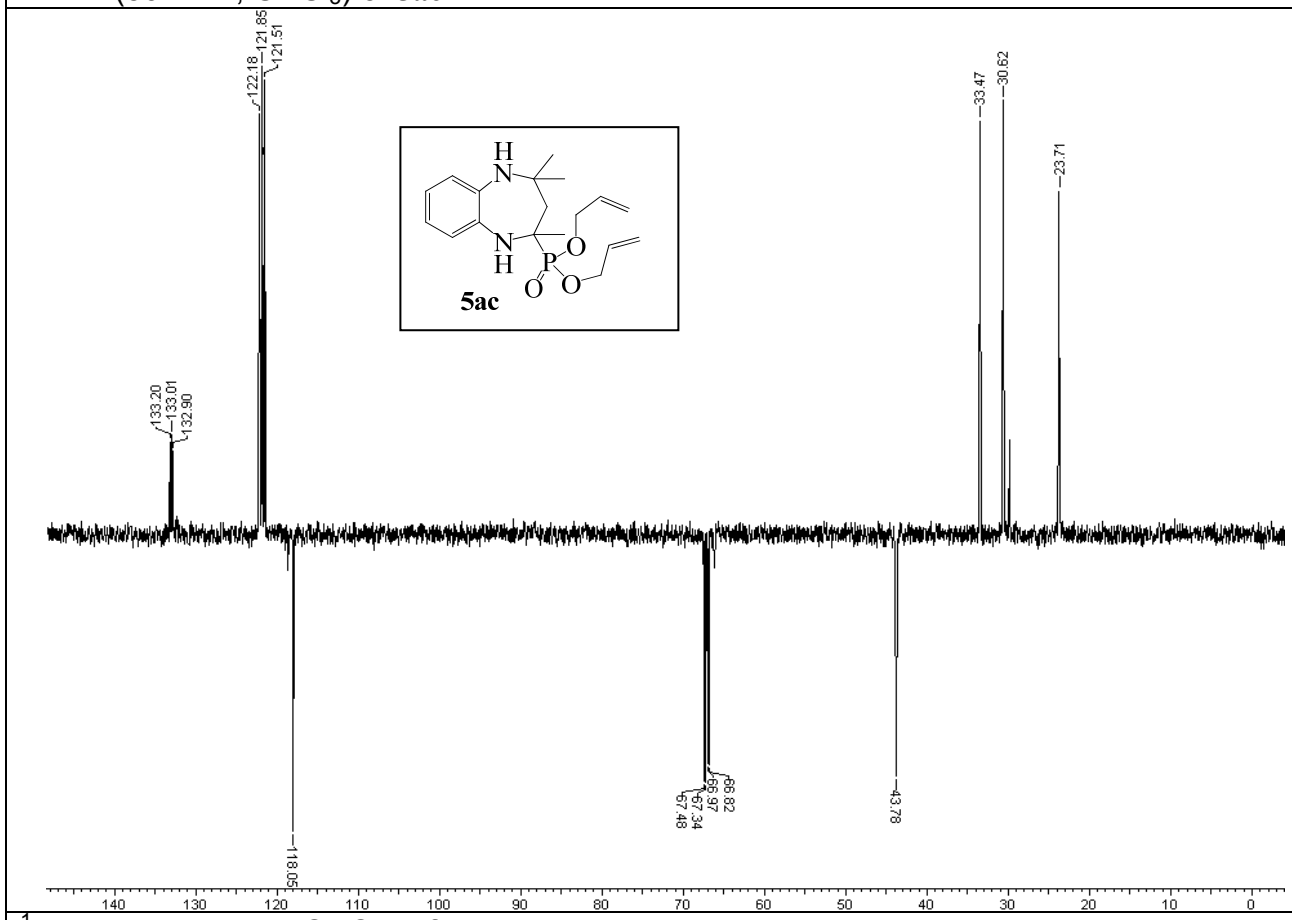
^{1}H NMR (200 MHz, $CDCl_3$) of **5ac**



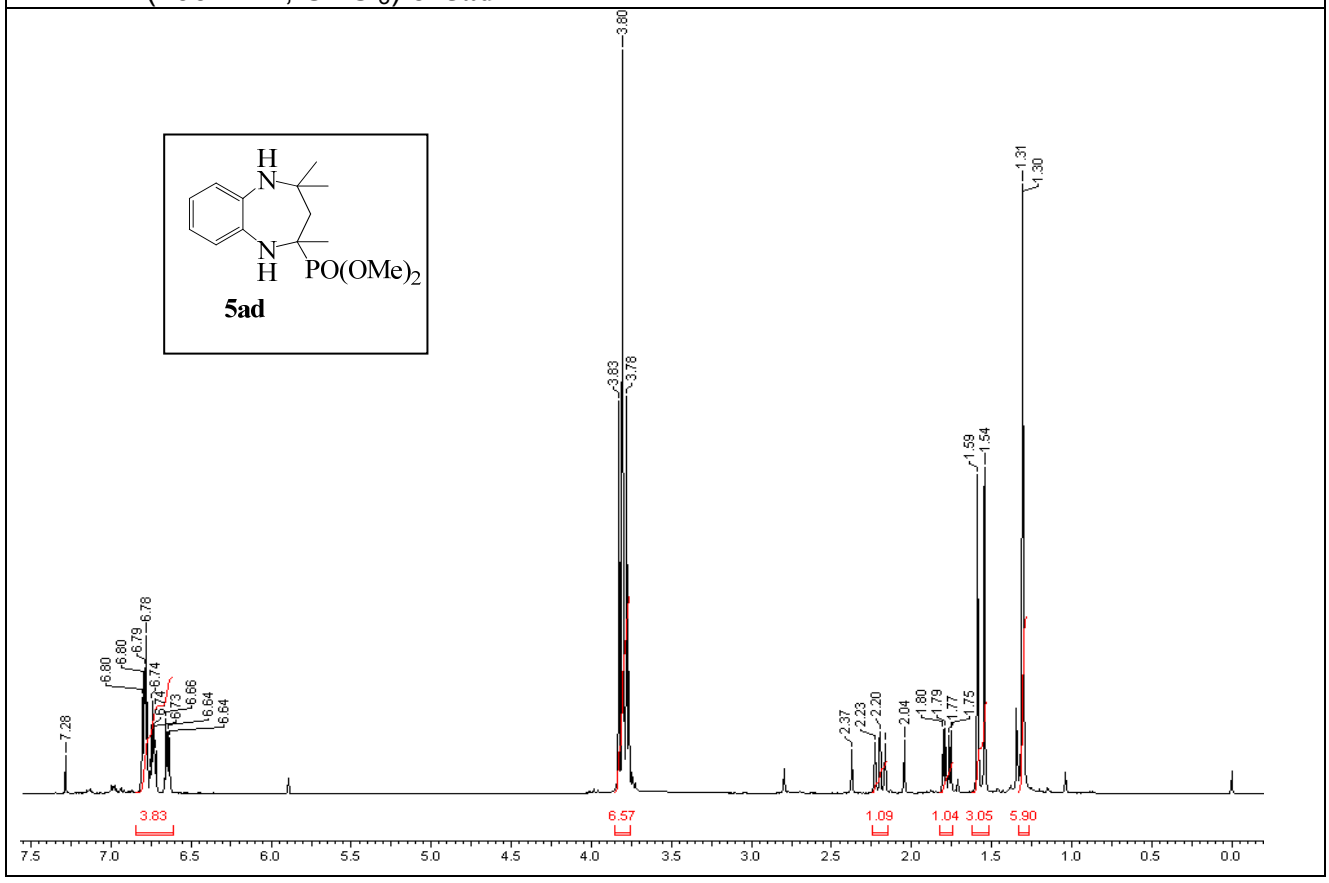
^{13}C NMR (50 MHz, $CDCl_3$) of **5ac**



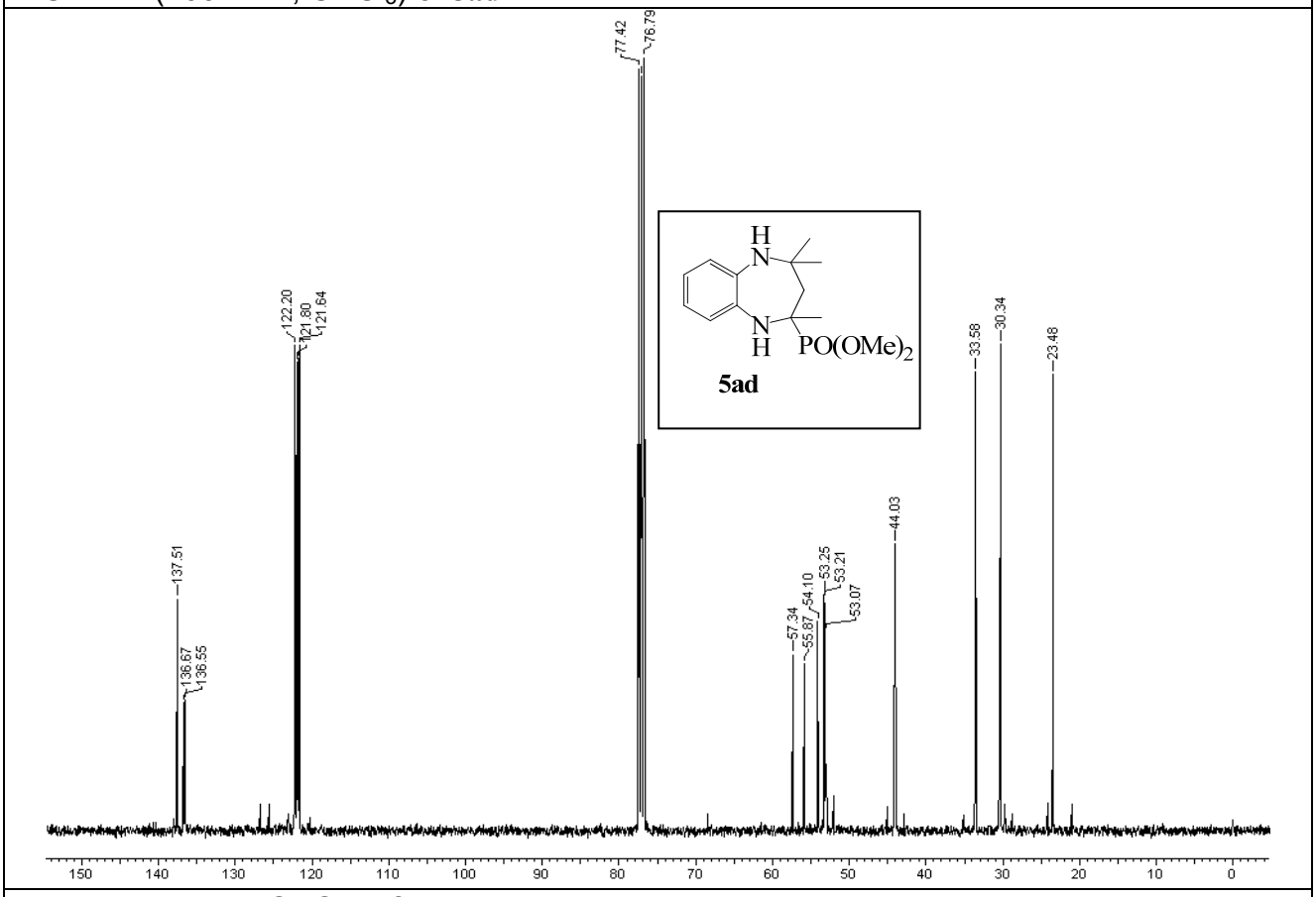
DEPT (50 MHz, $CDCl_3$) of **5ac**



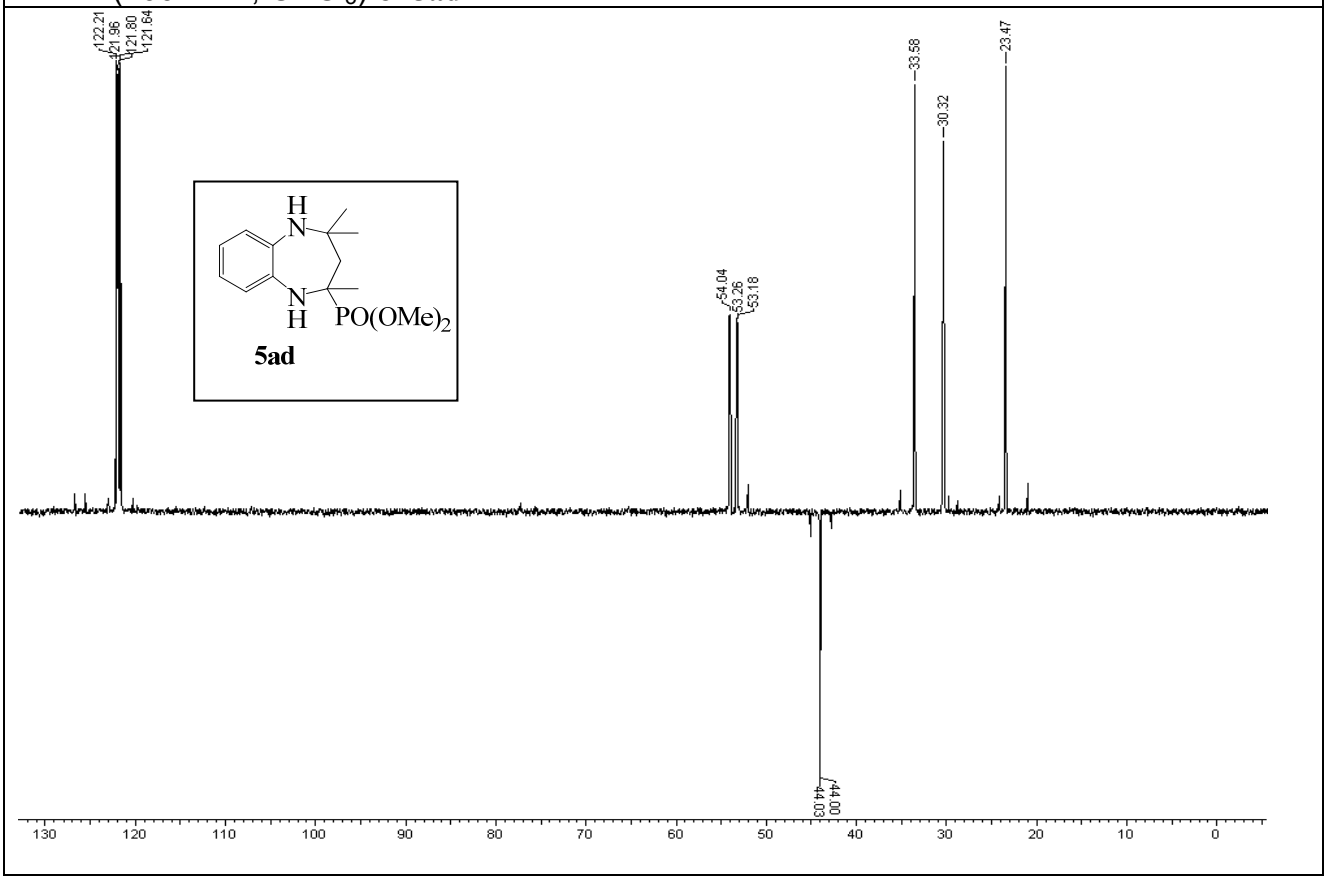
^{1}H NMR (400 MHz, $CDCl_3$) of **5ad**



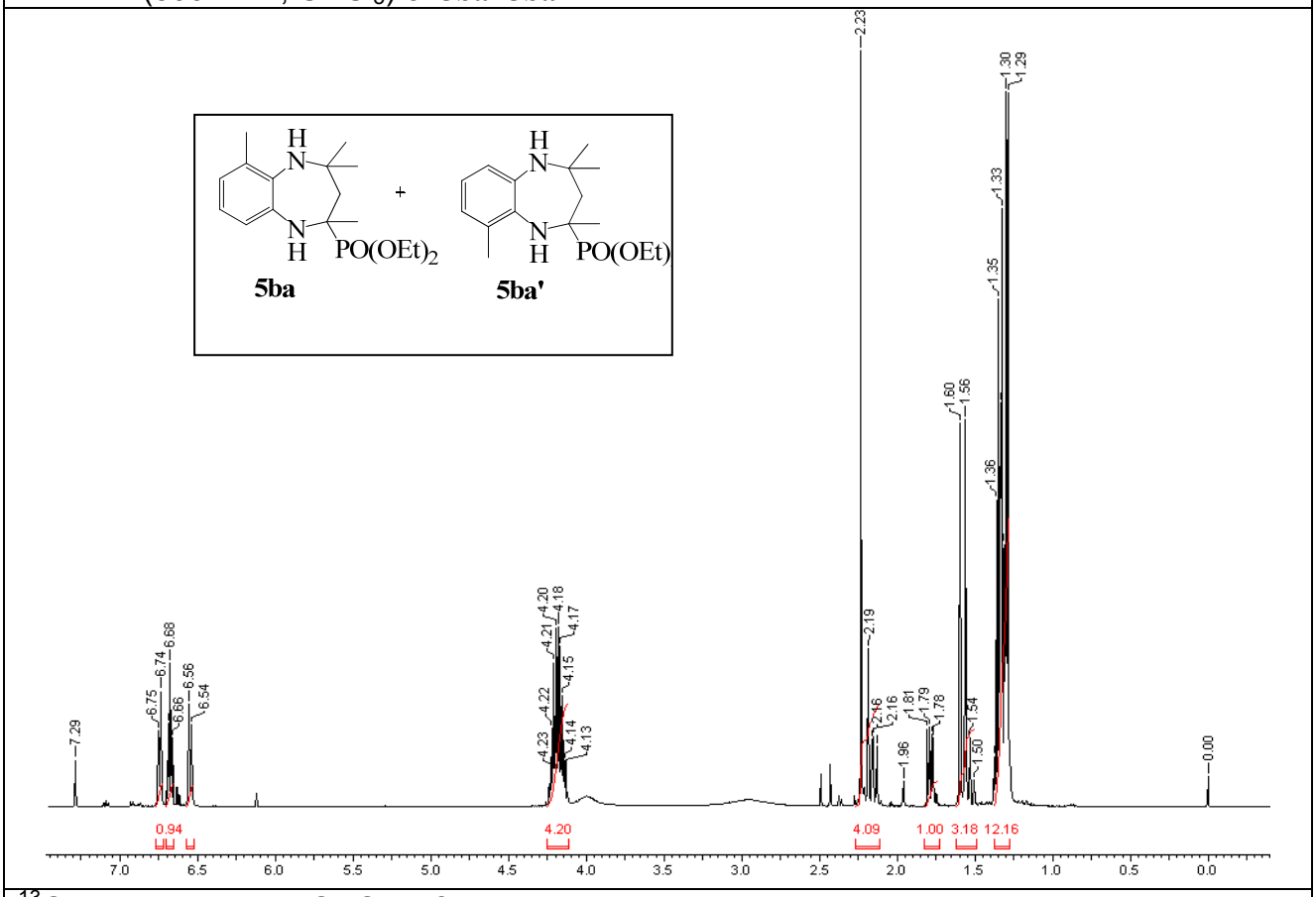
^{13}C NMR (100 MHz, $CDCl_3$) of **5ad**



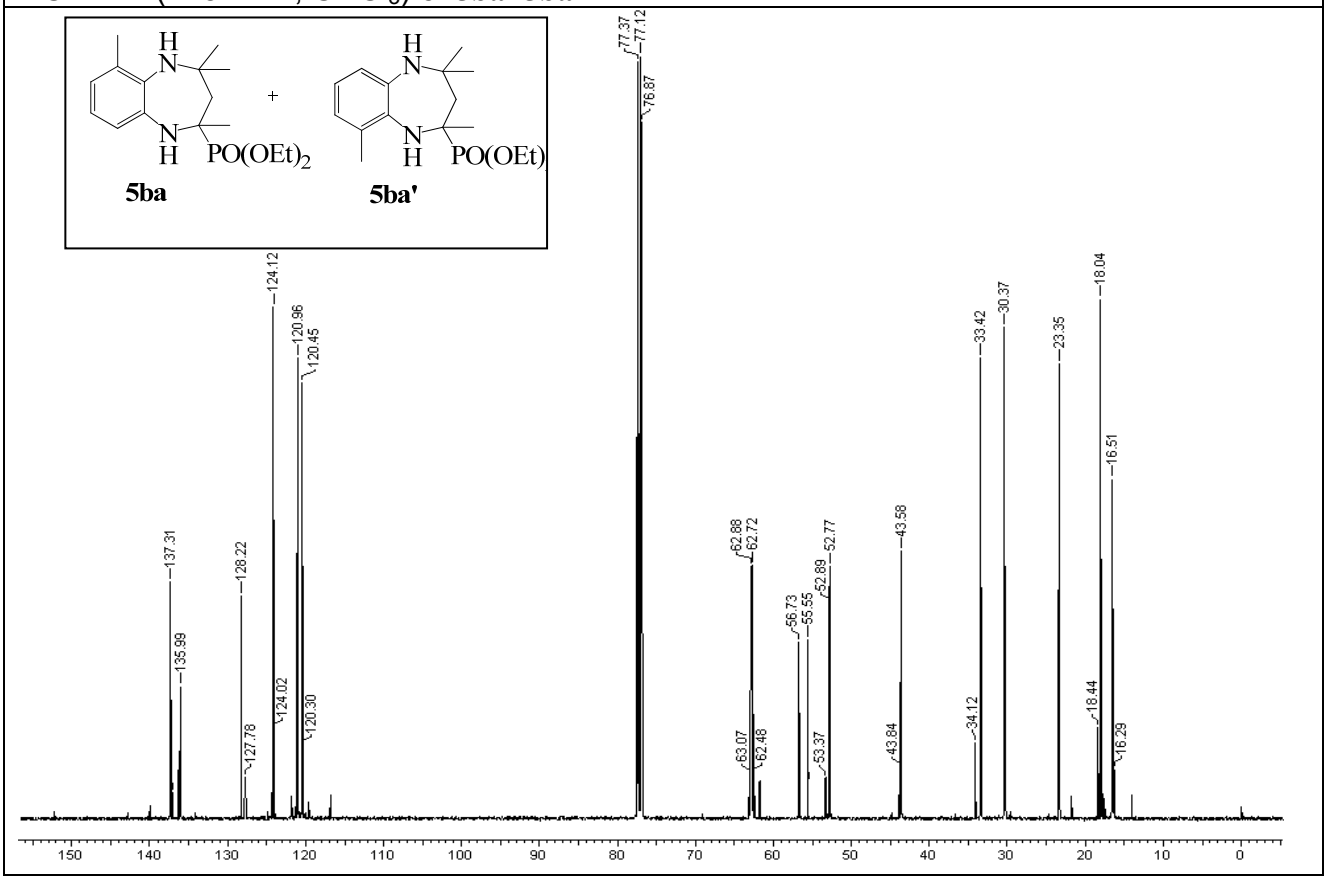
DEPT (100 MHz, $CDCl_3$) of **5ad**



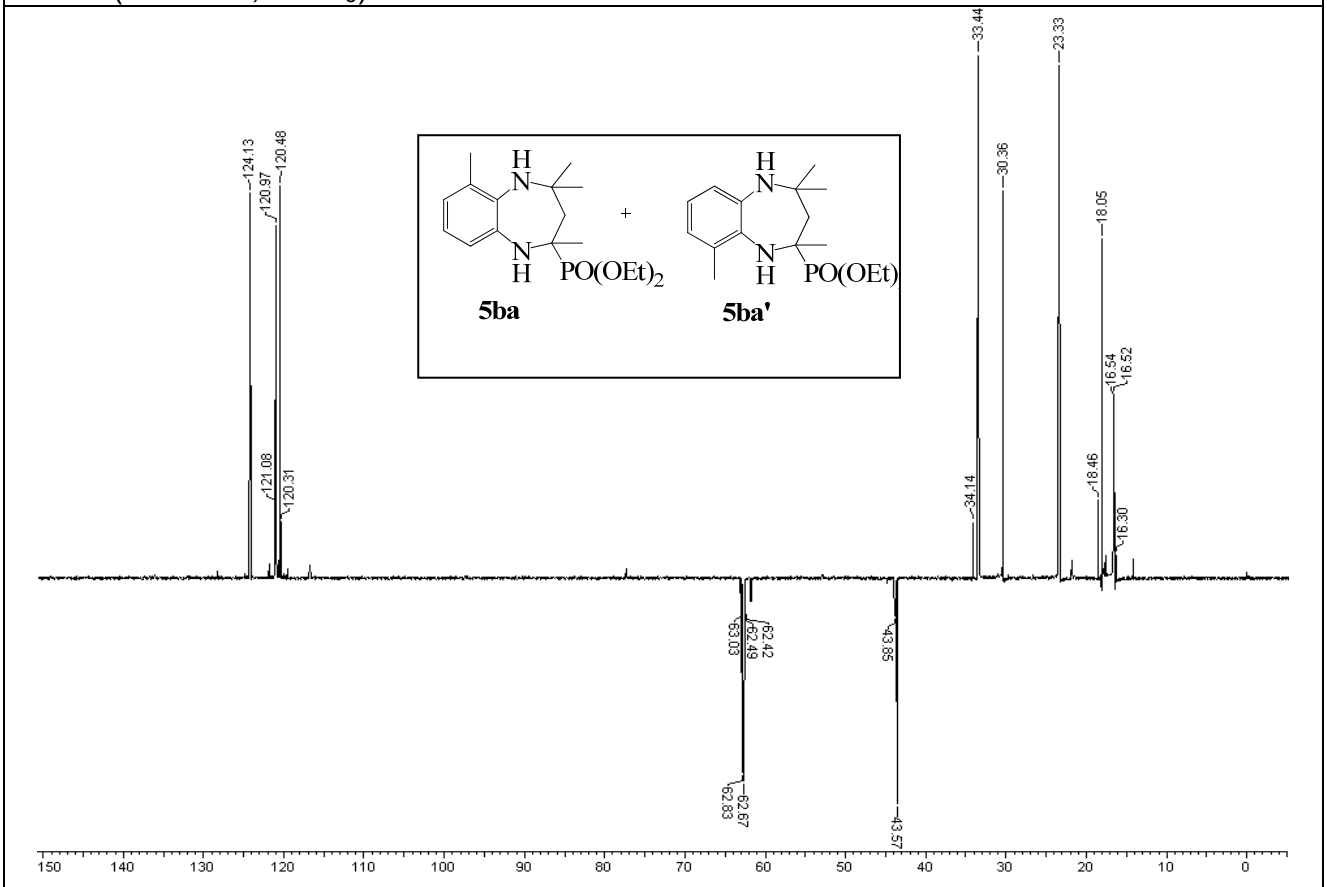
^{1}H NMR (500 MHz, $CDCl_3$) of **5ba+5ba'**



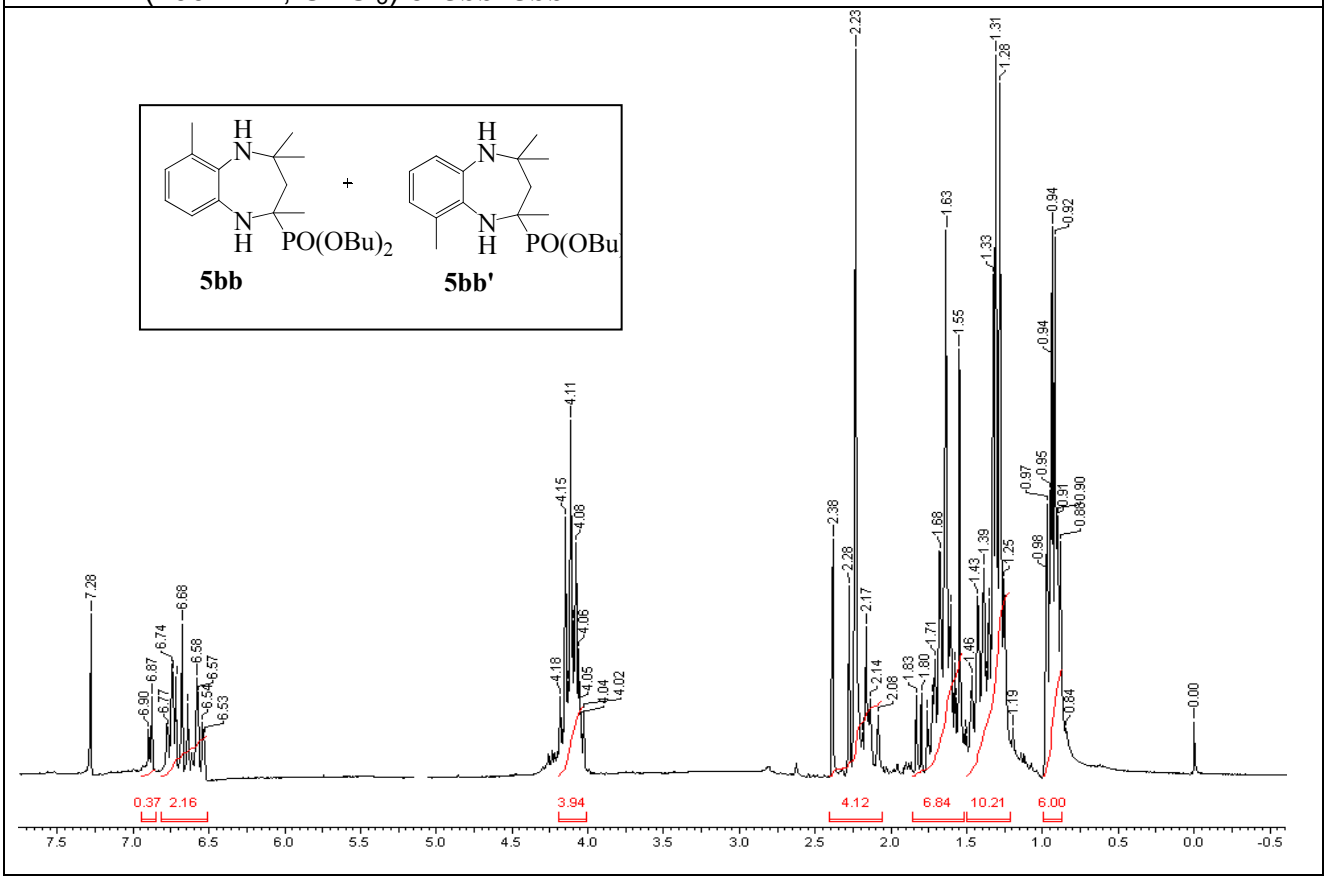
^{13}C NMR (125 MHz, $CDCl_3$) of **5ba+5ba'**



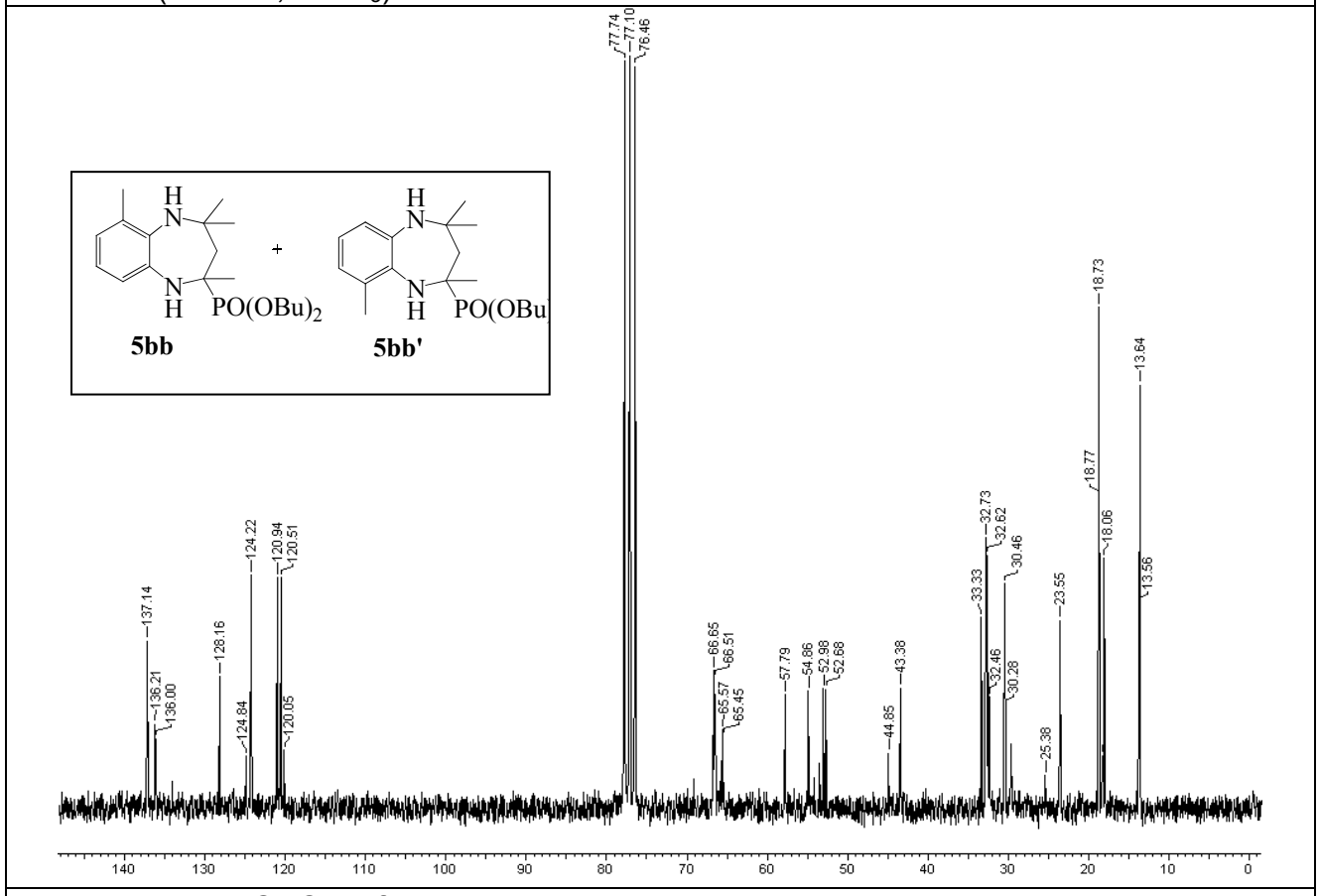
DEPT (125 MHz, $CDCl_3$) of **5ba+5ba'**



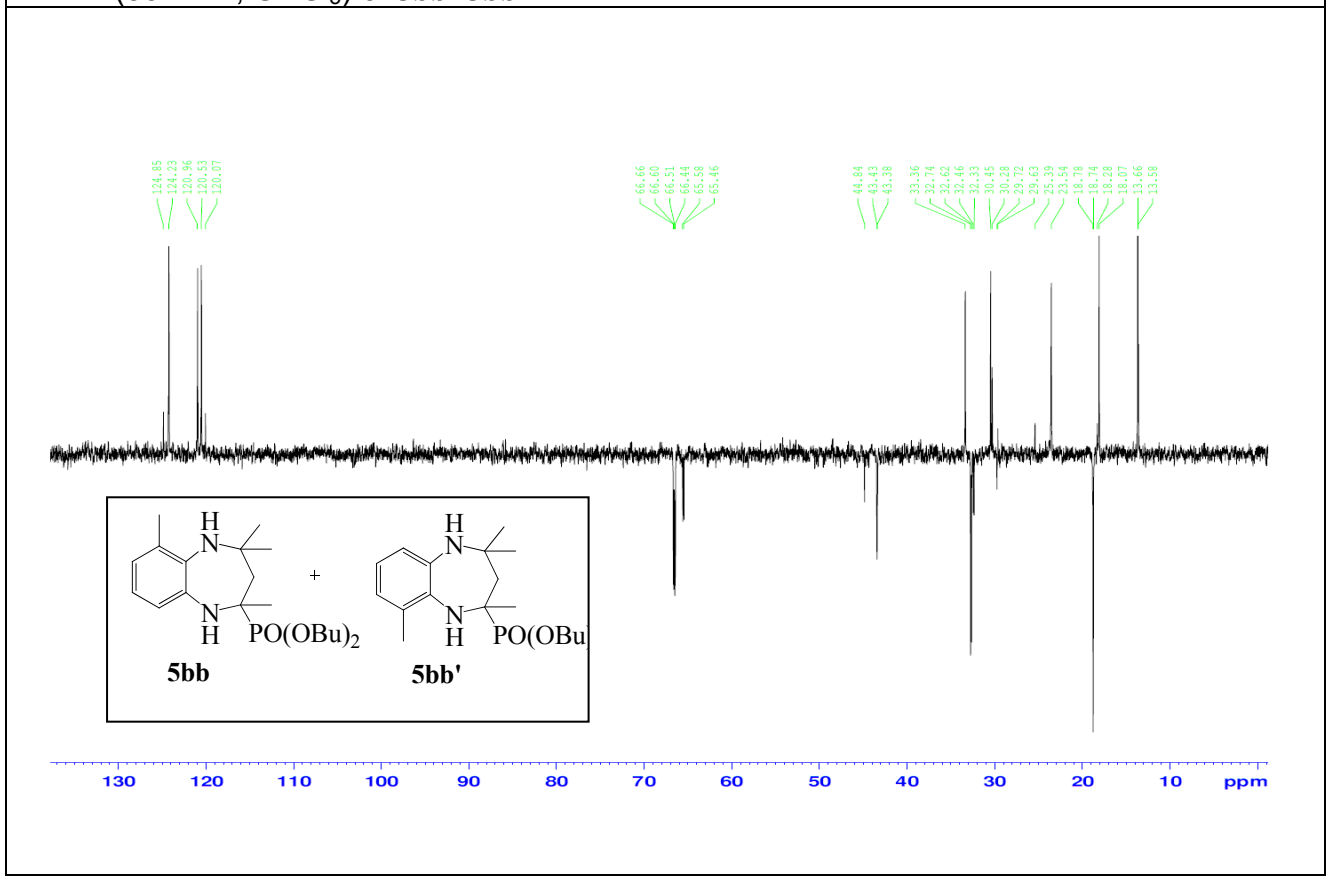
^{1}H NMR (200 MHz, $CDCl_3$) of **5bb+5bb'**



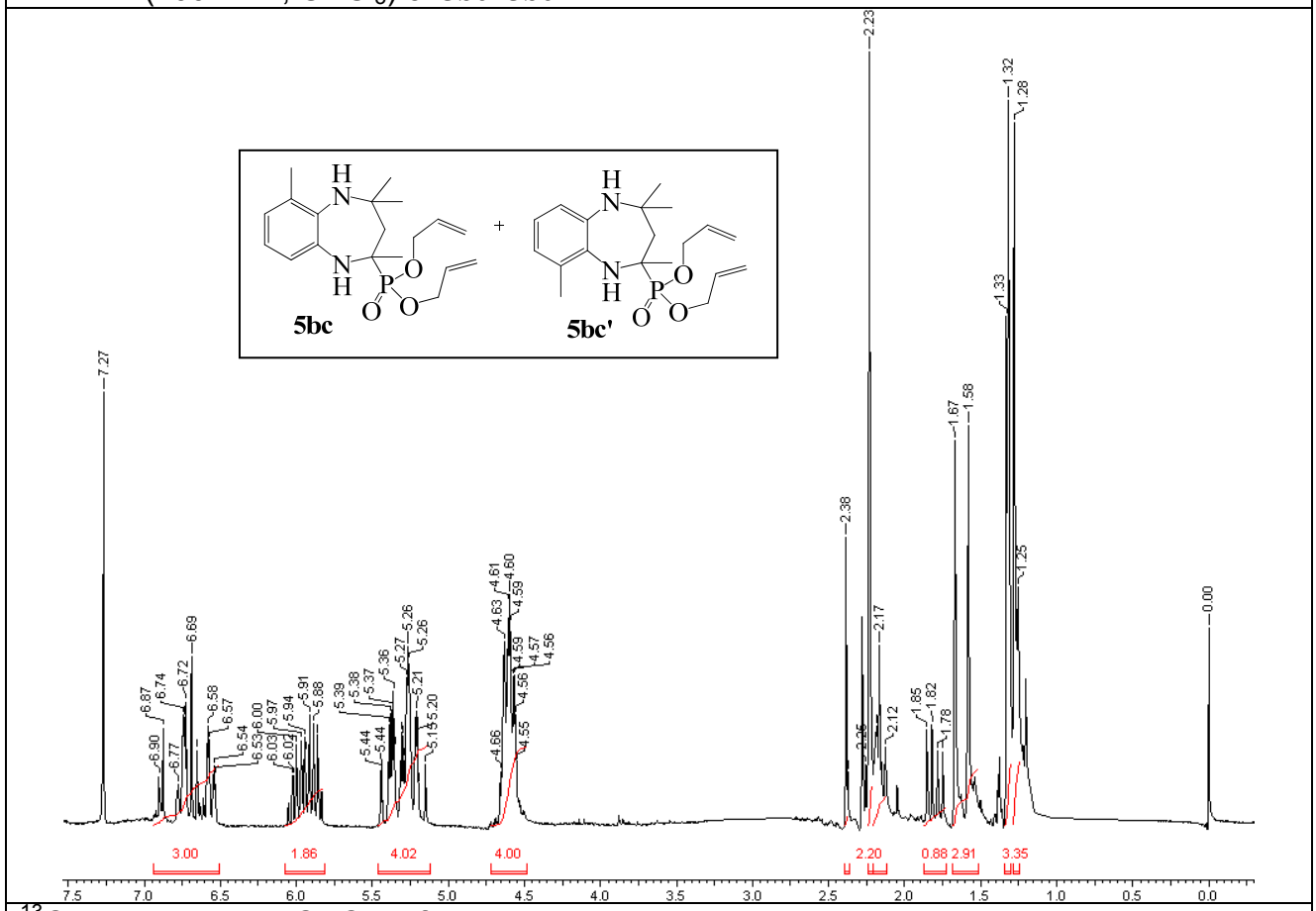
^{13}C NMR (50 MHz, $CDCl_3$) of **5bb**+**5bb'**



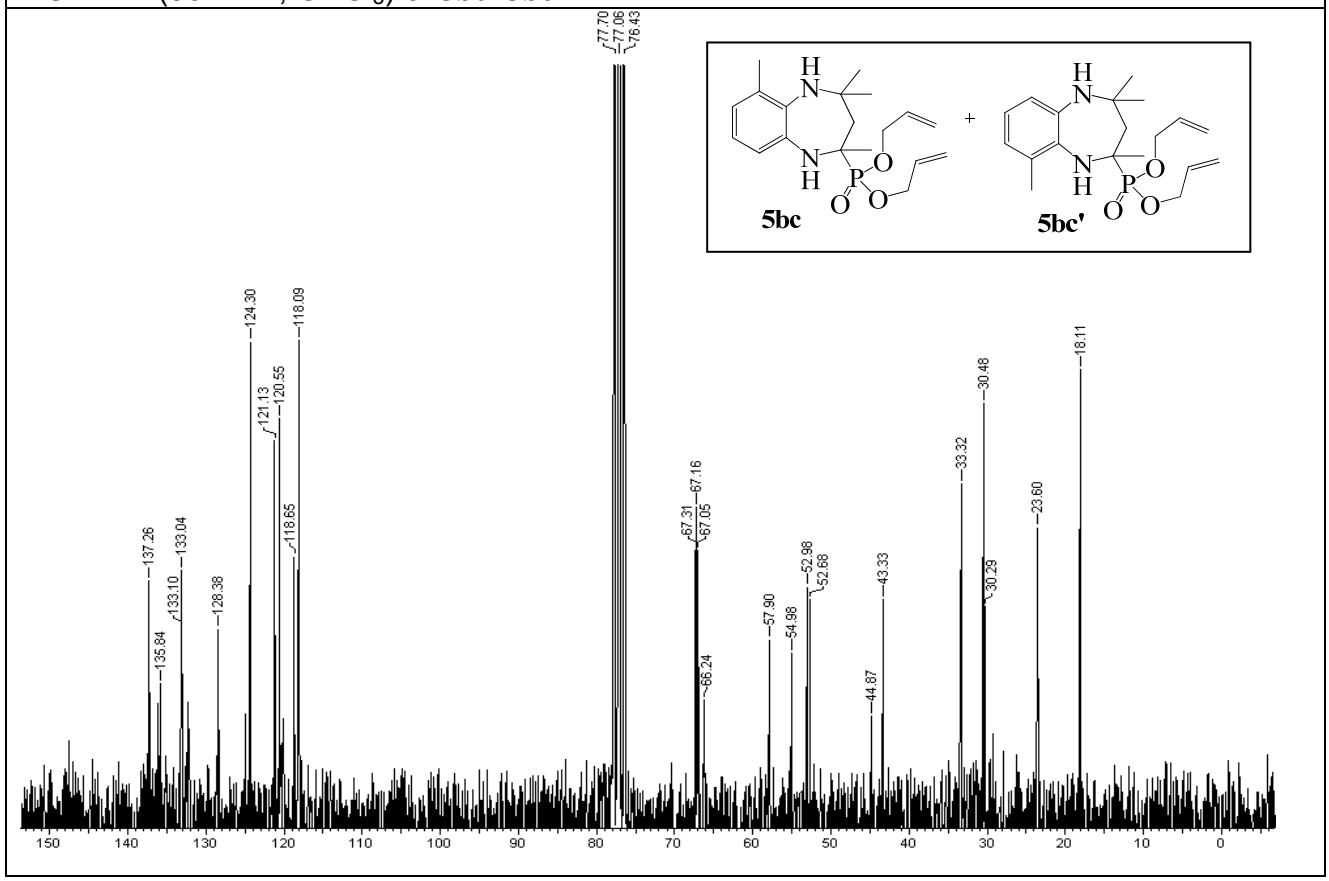
DEPT (50 MHz, $CDCl_3$) of **5bb**+**5bb'**



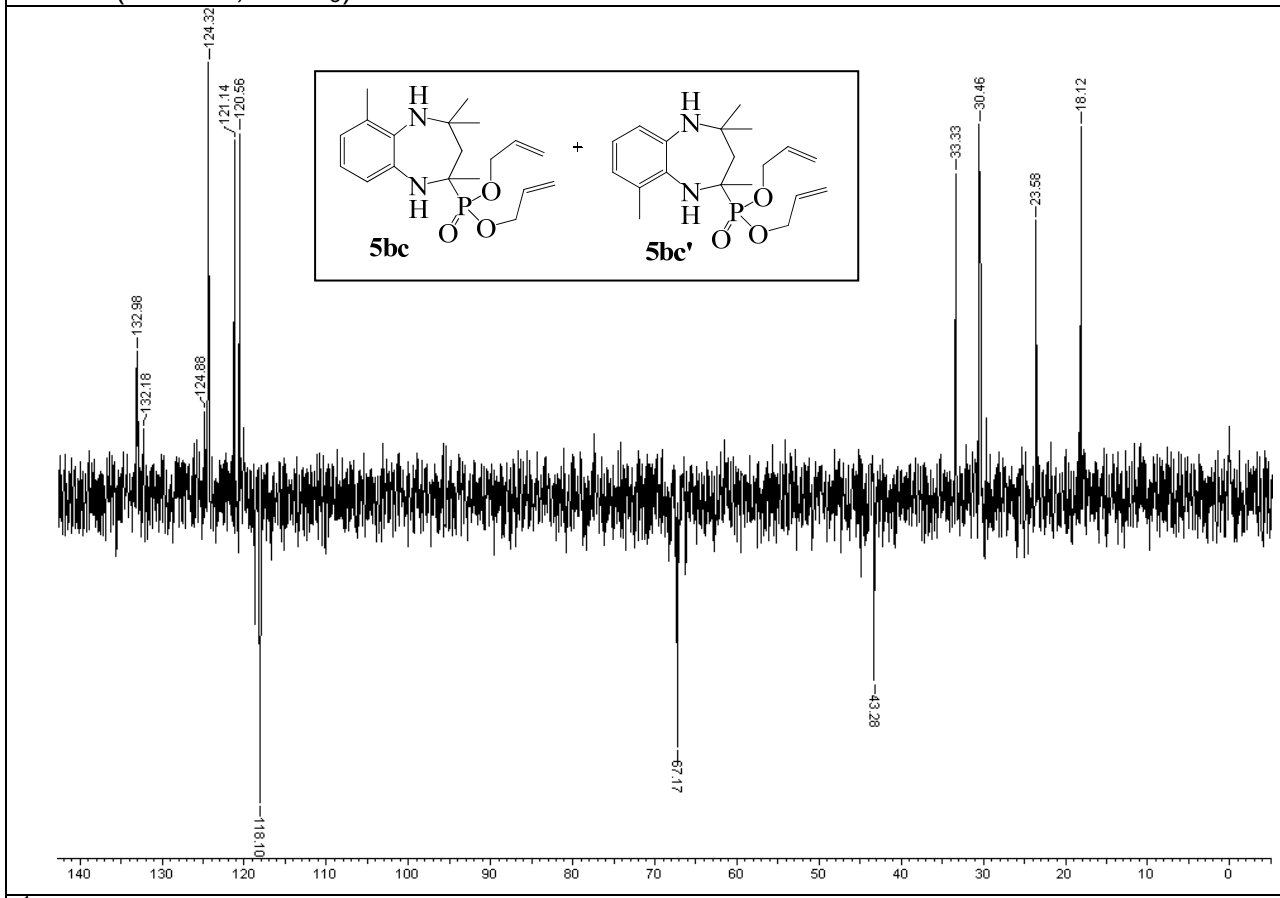
^{1}H NMR (200 MHz, $CDCl_3$) of **5bc+5bc'**



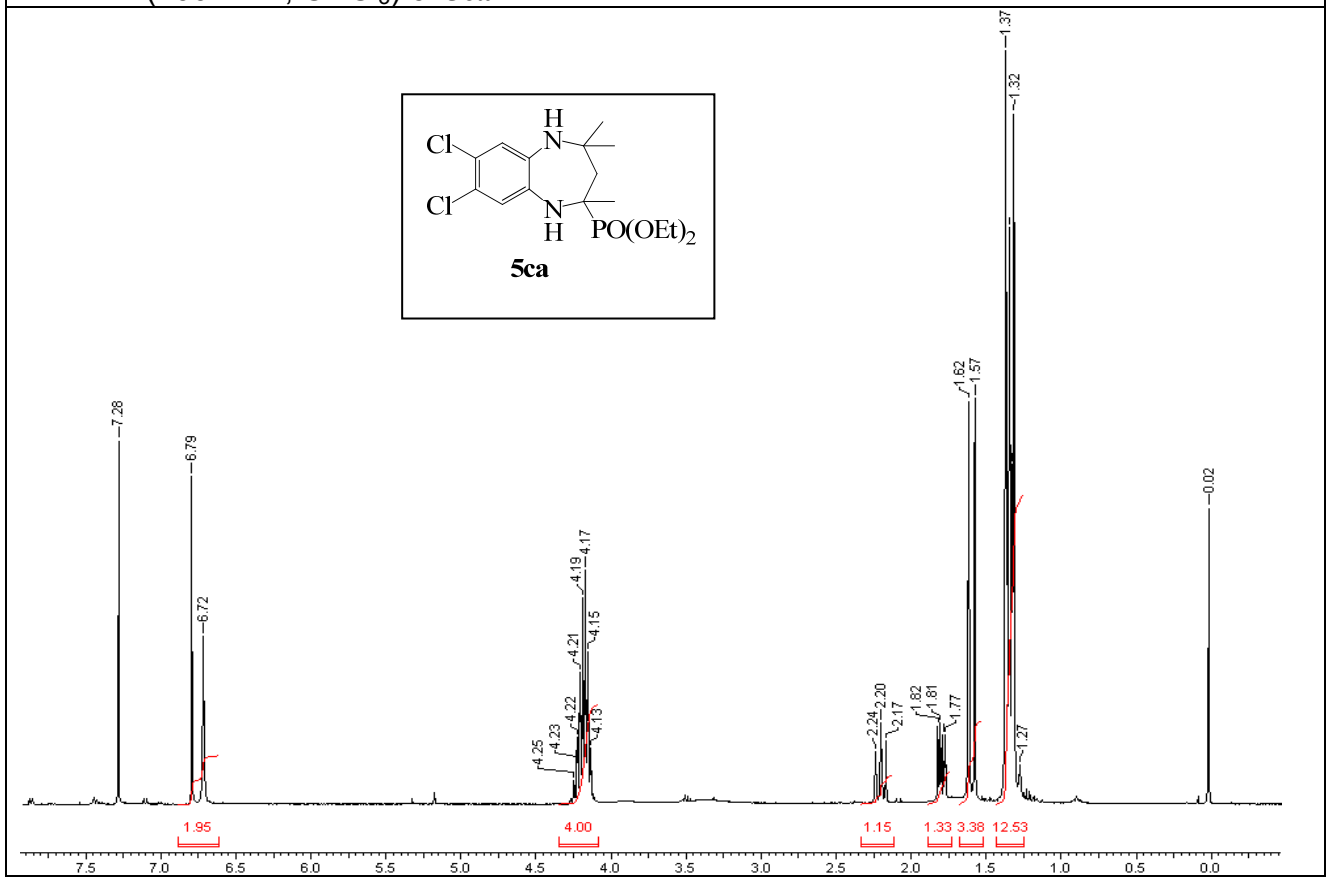
^{13}C NMR (50 MHz, $CDCl_3$) of **5bc+5bc'**



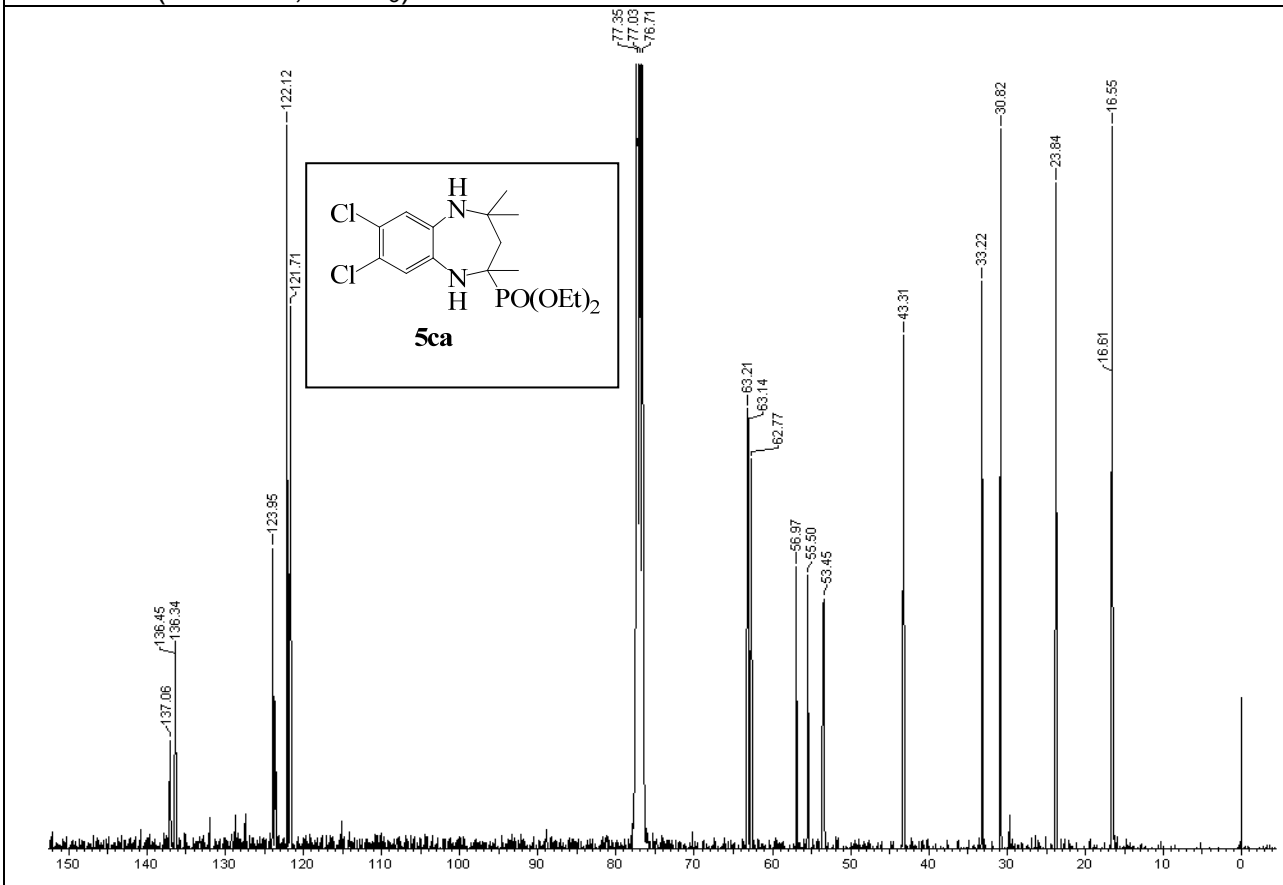
DEPT (50 MHz, $CDCl_3$) of **5bc+5bc'**



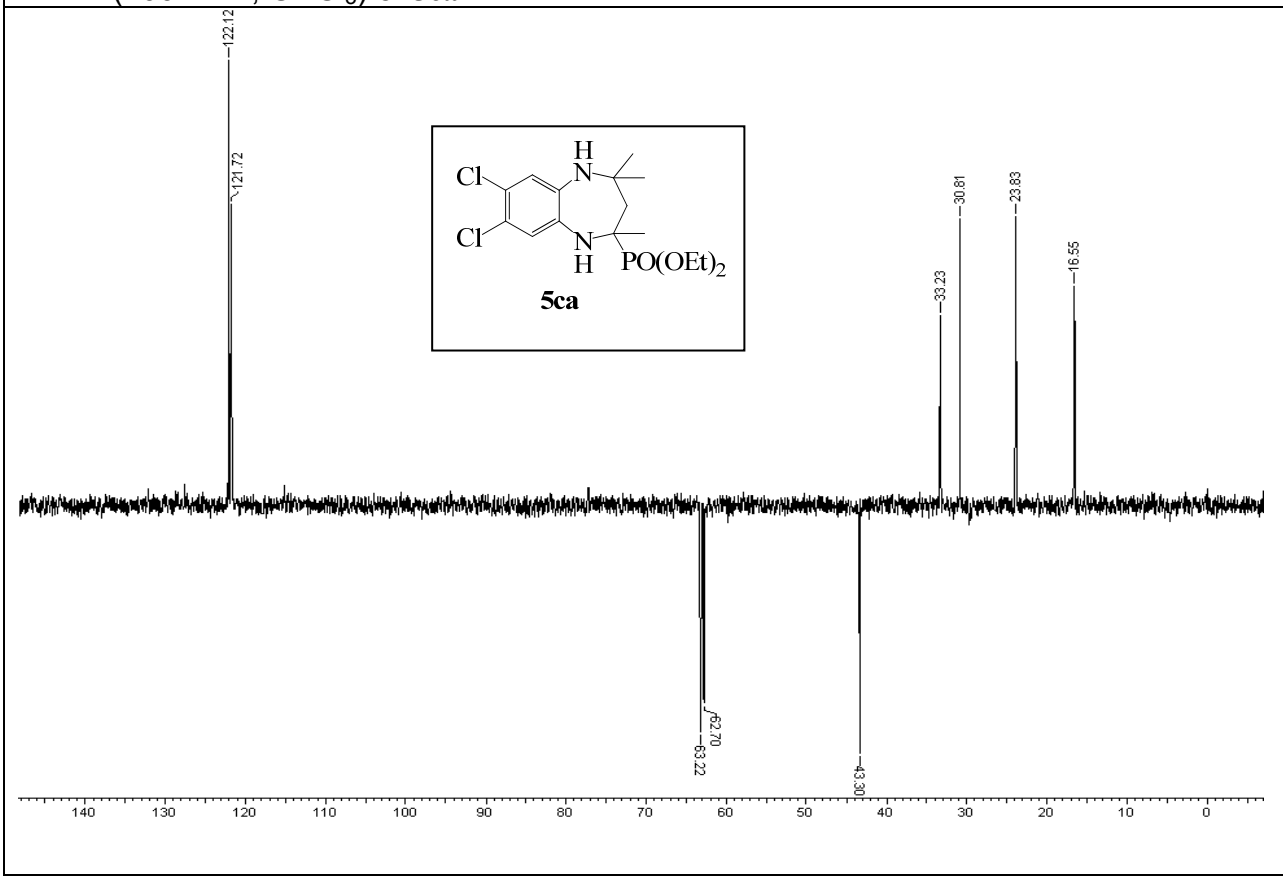
^{1}H NMR (400 MHz, $CDCl_3$) of **5ca**



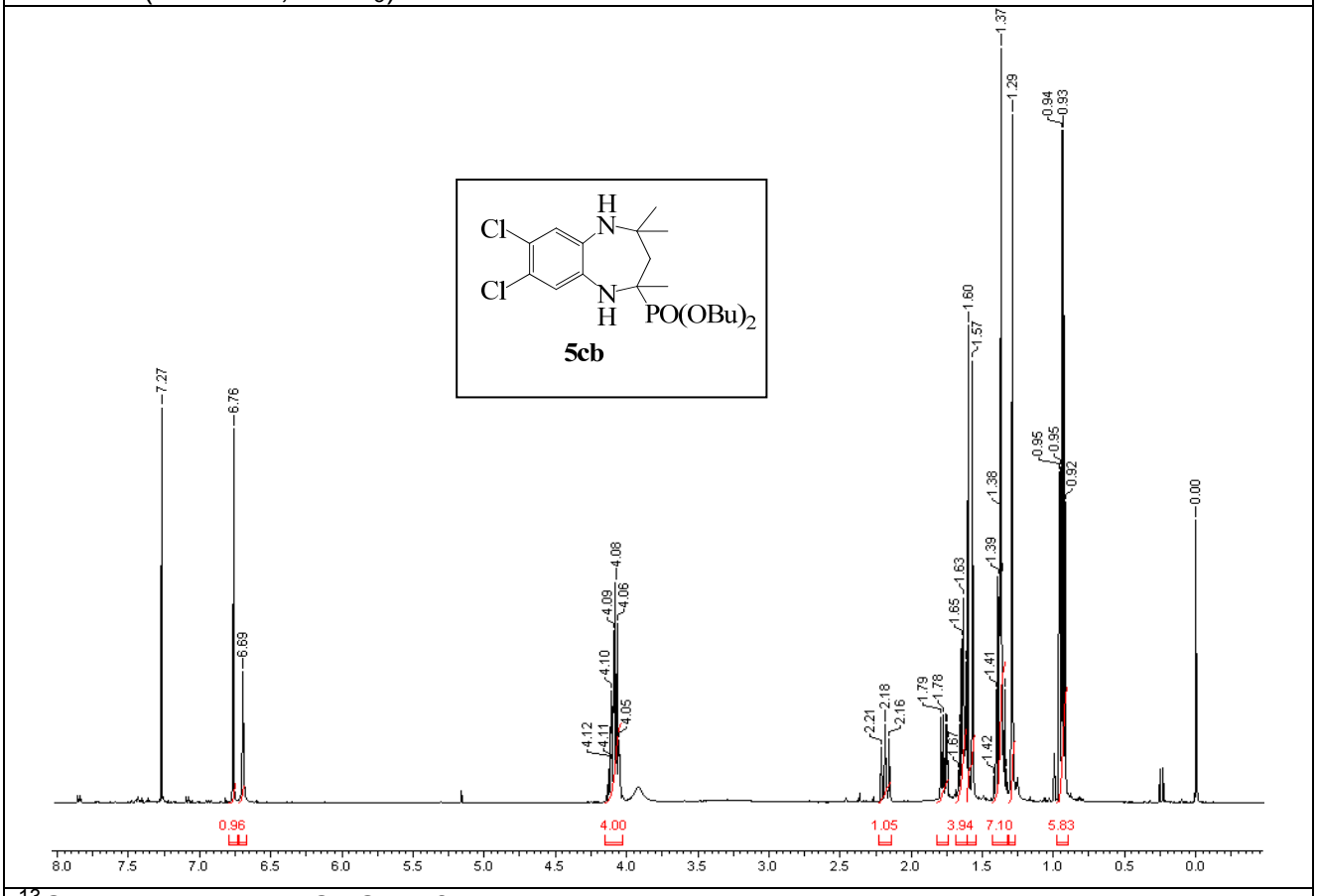
^{13}C NMR (100 MHz, $CDCl_3$) of **5ca**



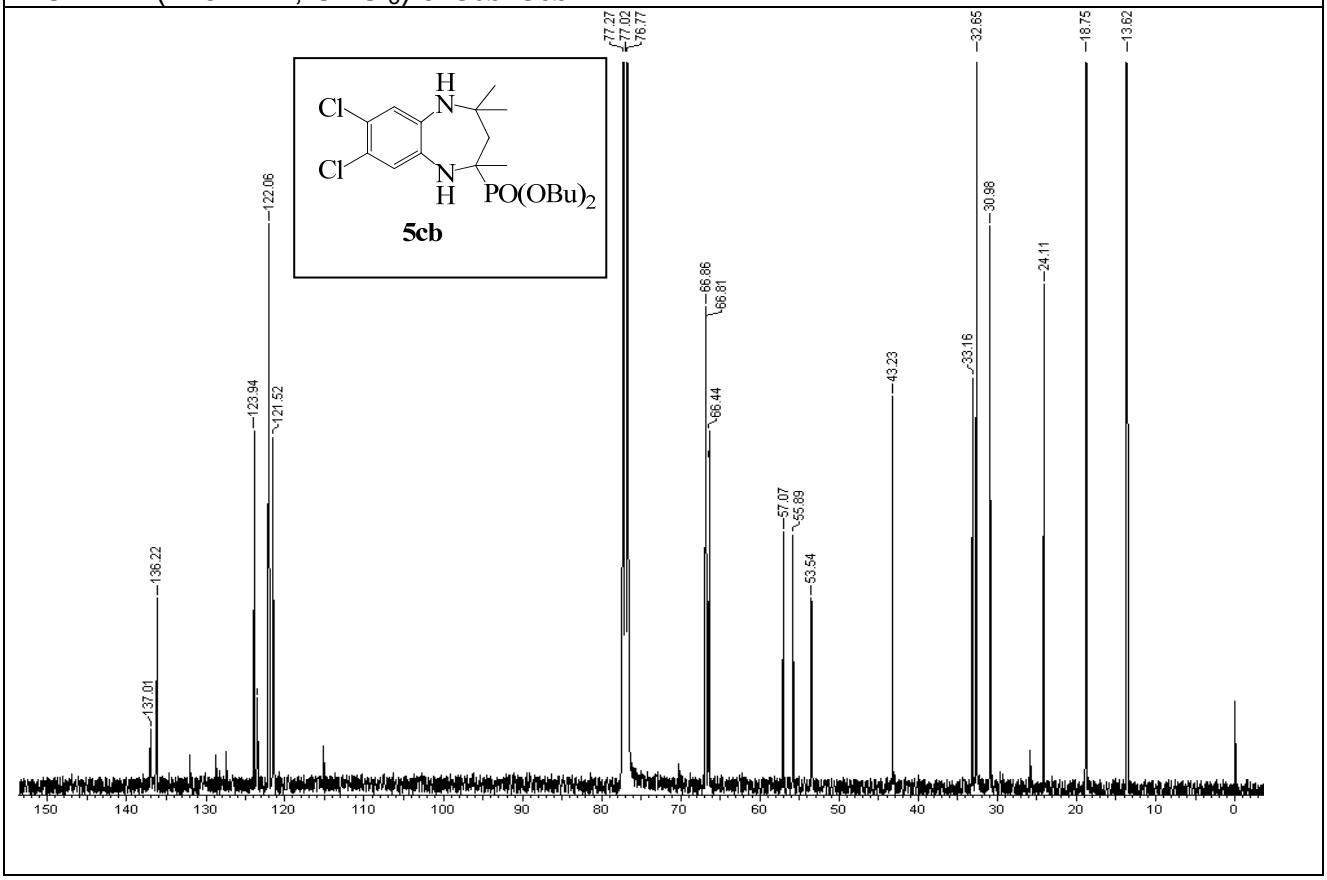
DEPT (100 MHz, $CDCl_3$) of **5ca**



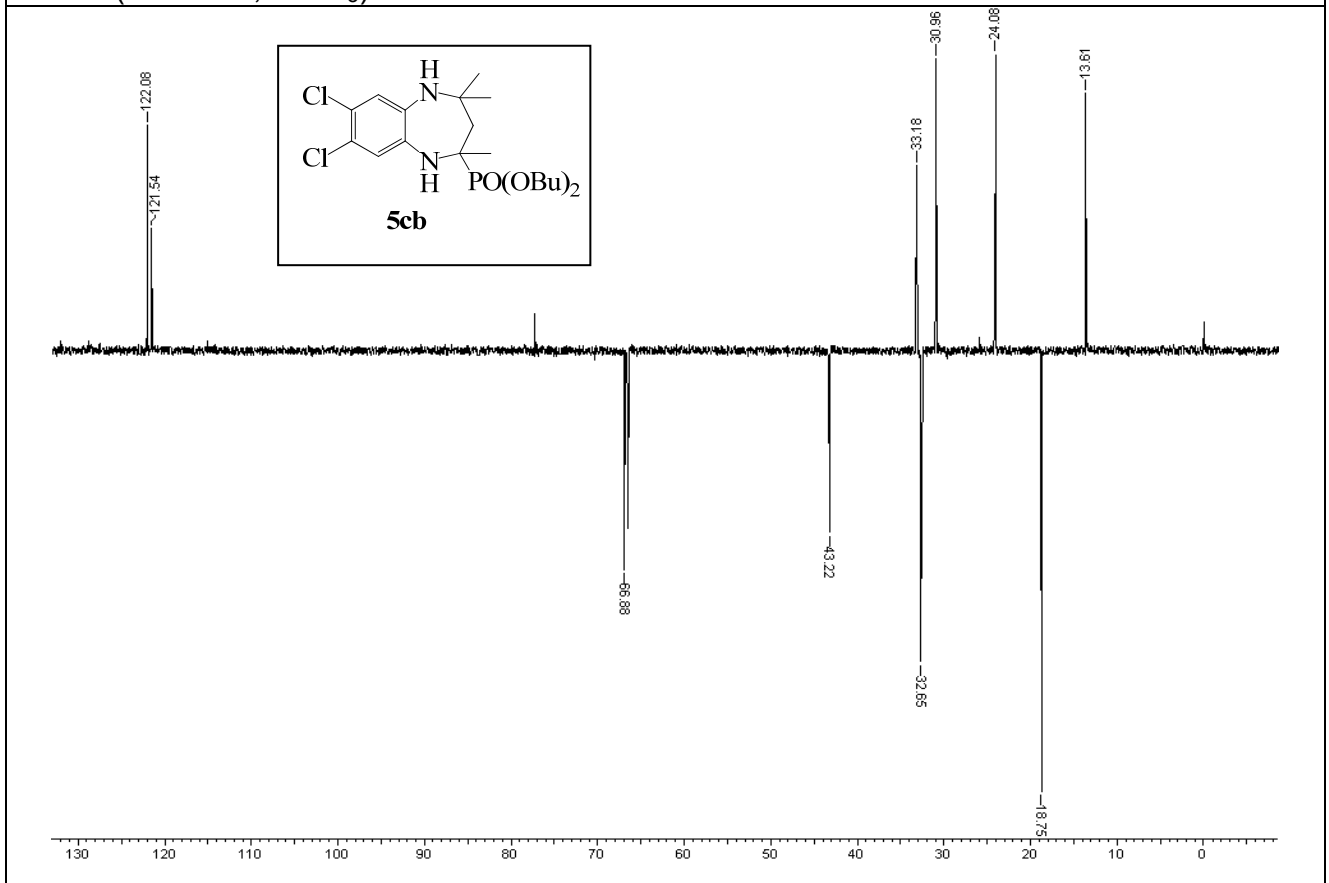
^{1}H NMR (500 MHz, $CDCl_3$) of **5cb+5cb'**



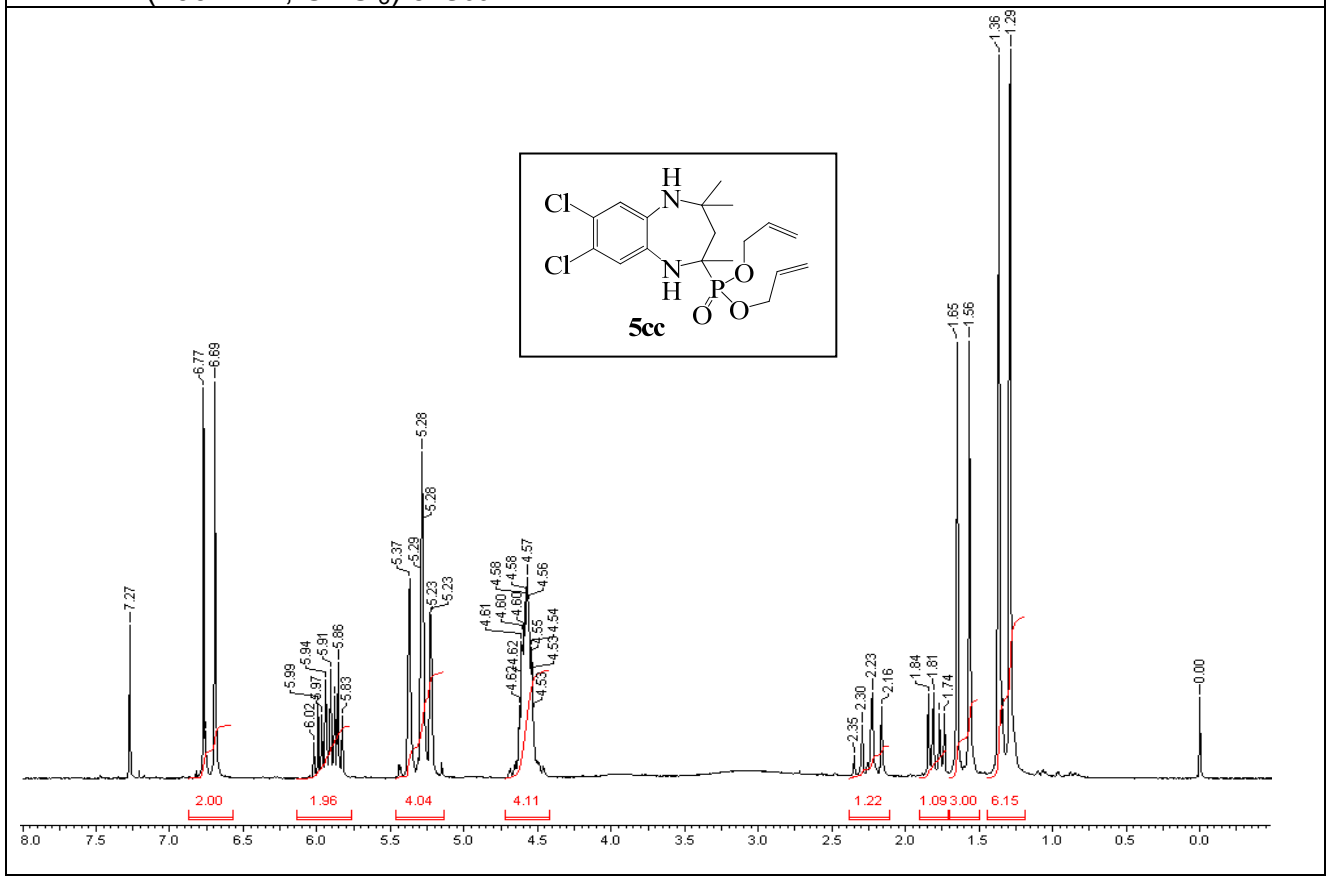
^{13}C NMR (125 MHz, $CDCl_3$) of **5cb+5cb'**



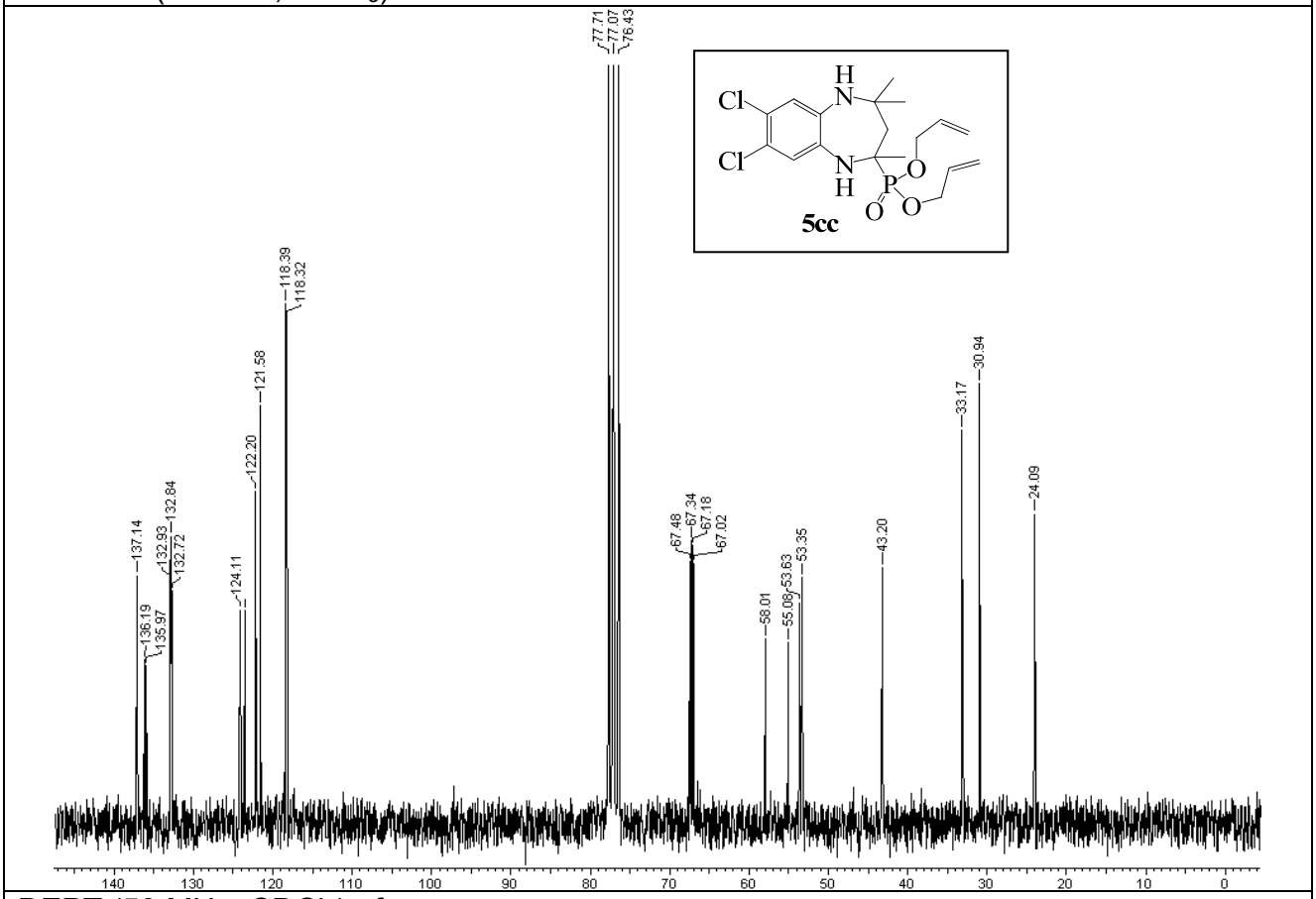
DEPT (125 MHz, $CDCl_3$) of **5cb+5cb'**



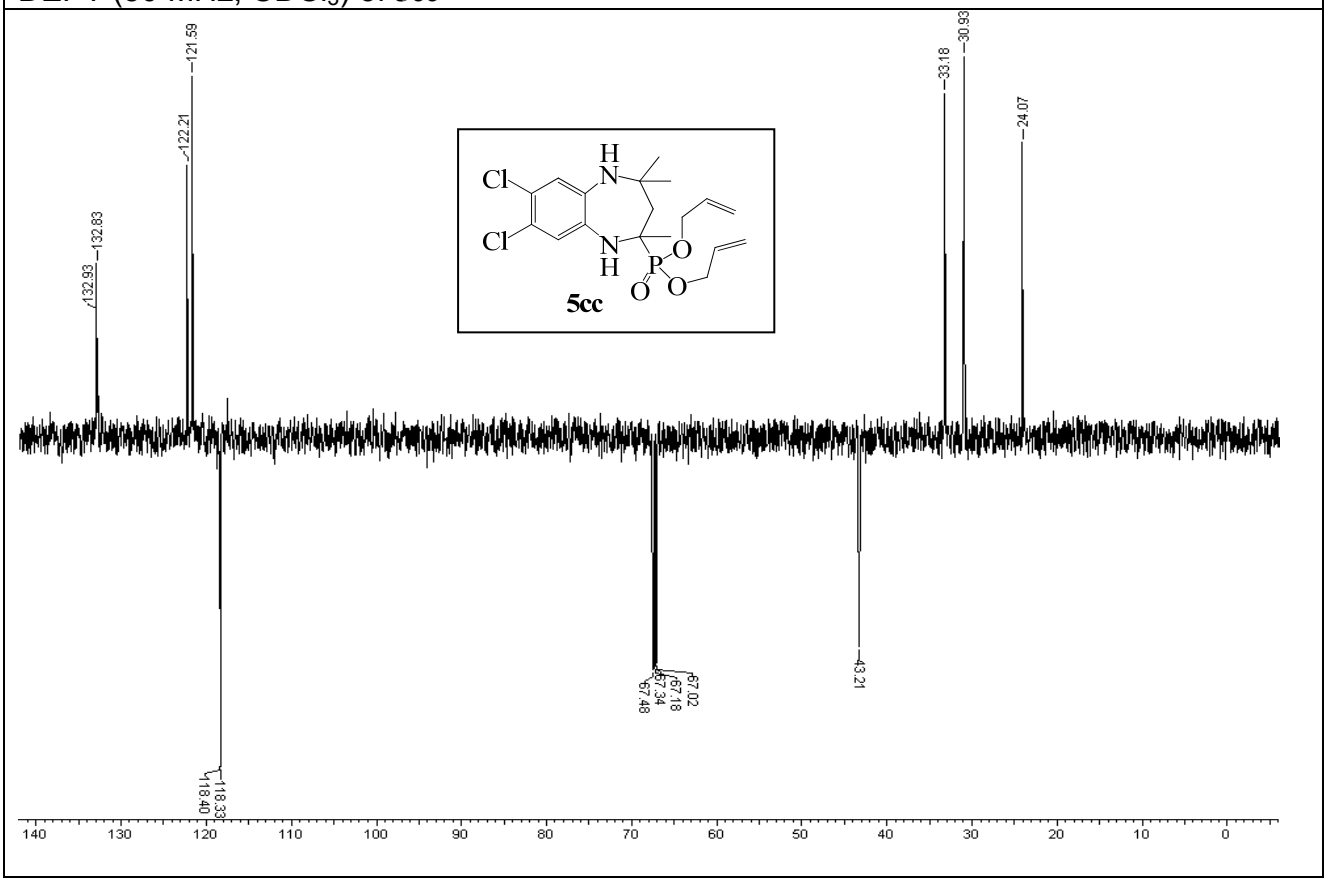
^{1}H NMR (400 MHz, $CDCl_3$) of **5cc**



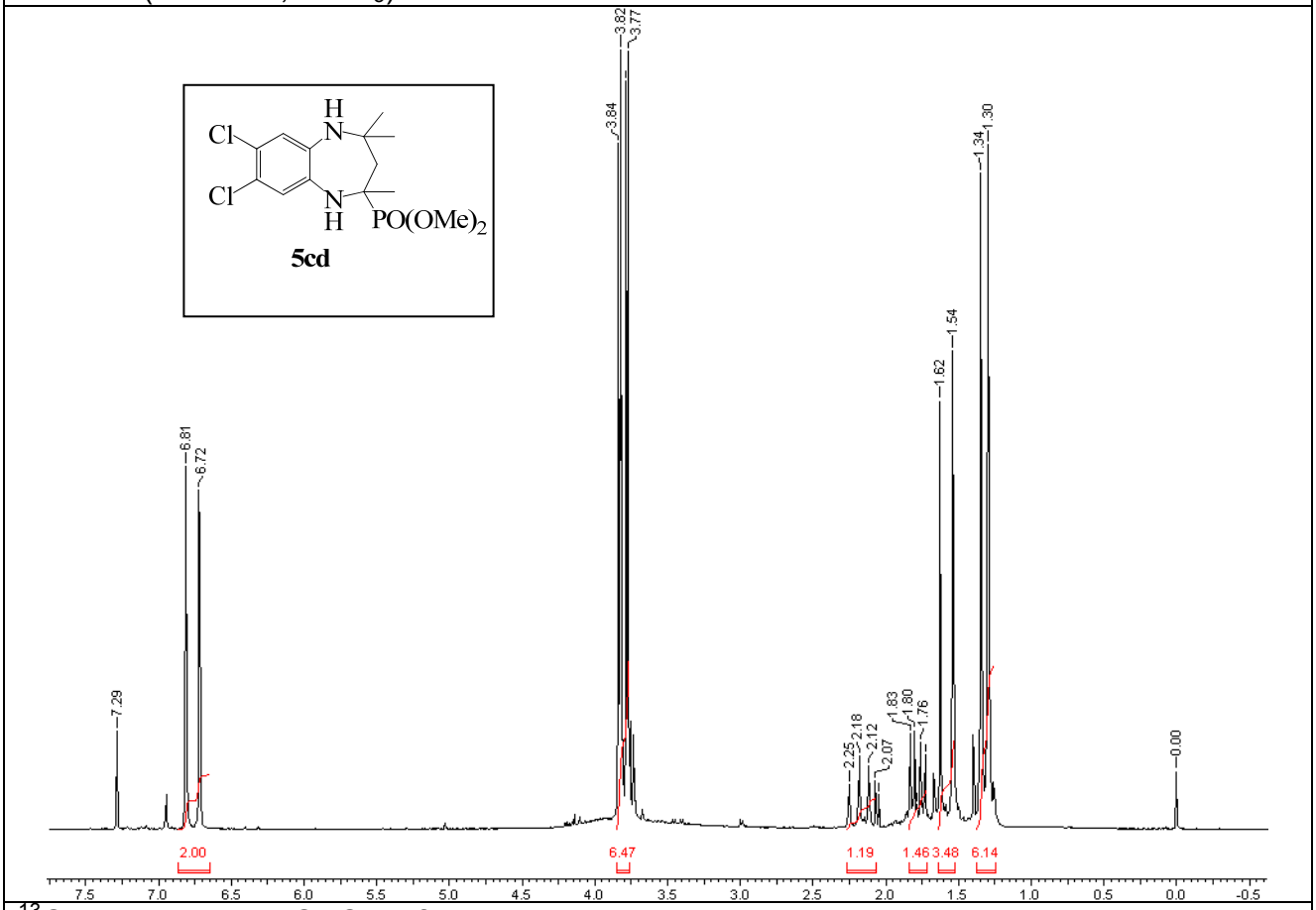
^{13}C NMR (50 MHz, $CDCl_3$) of **5cc**



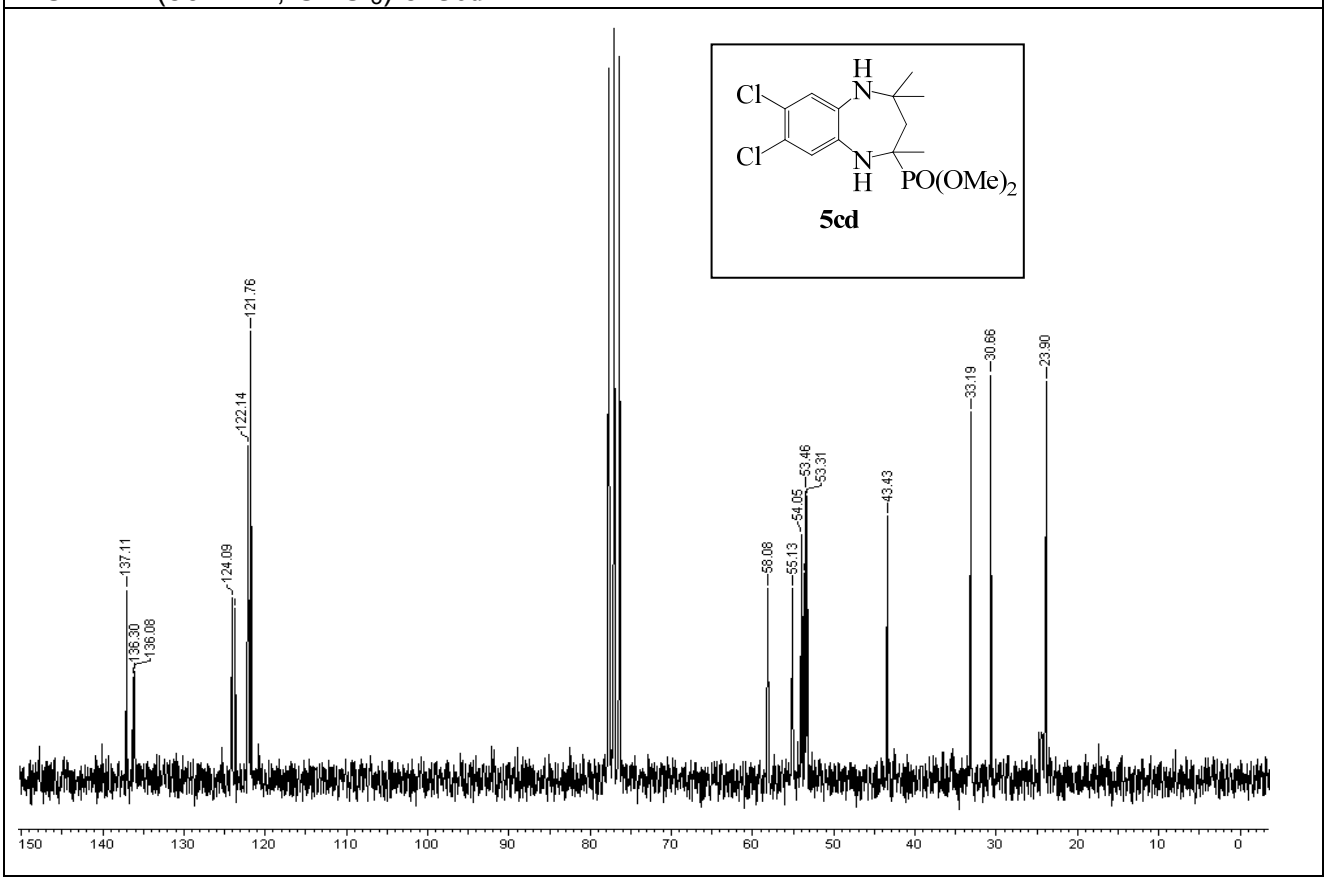
DEPT (50 MHz, $CDCl_3$) of **5cc**



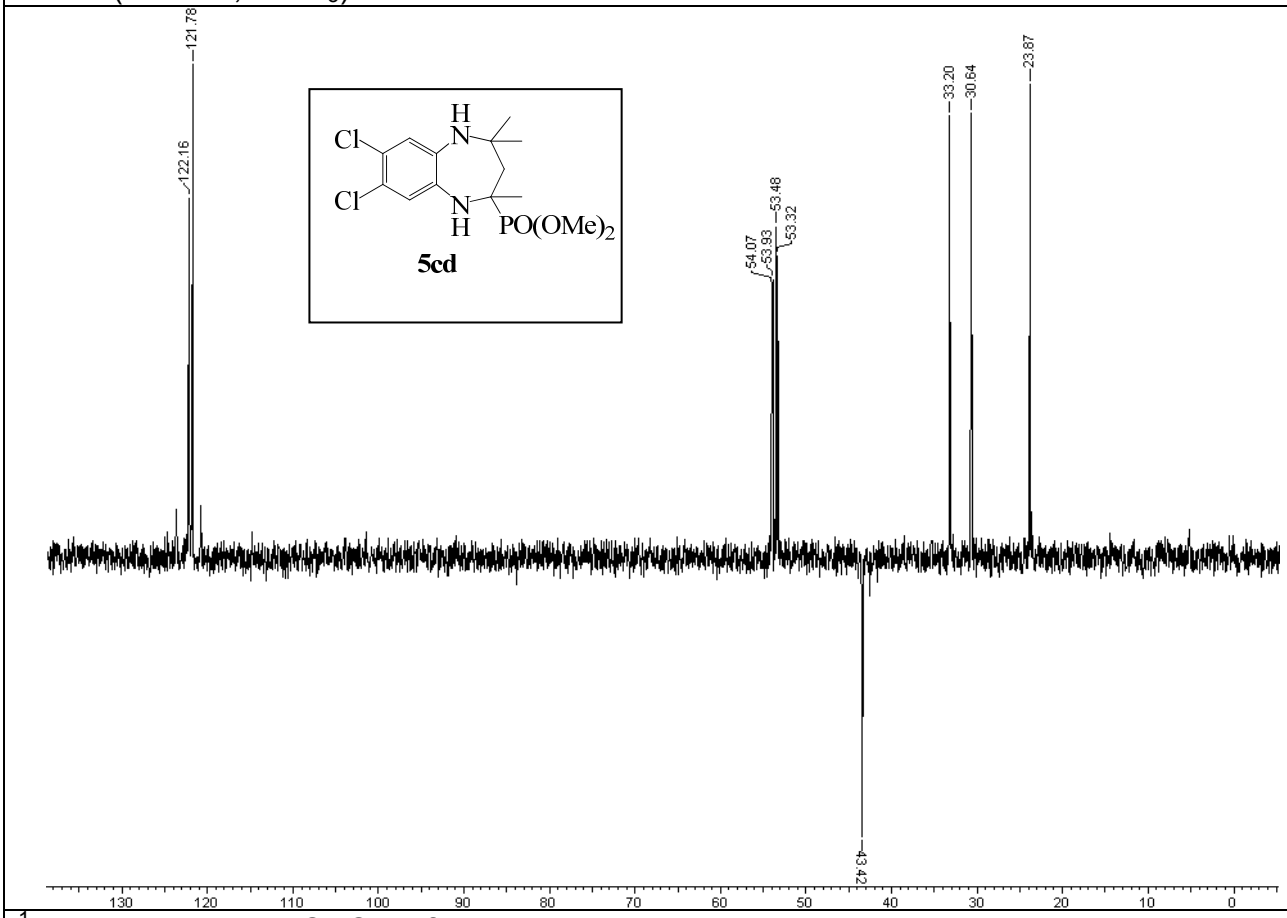
^{1}H NMR (200 MHz, $CDCl_3$) of **5cd**



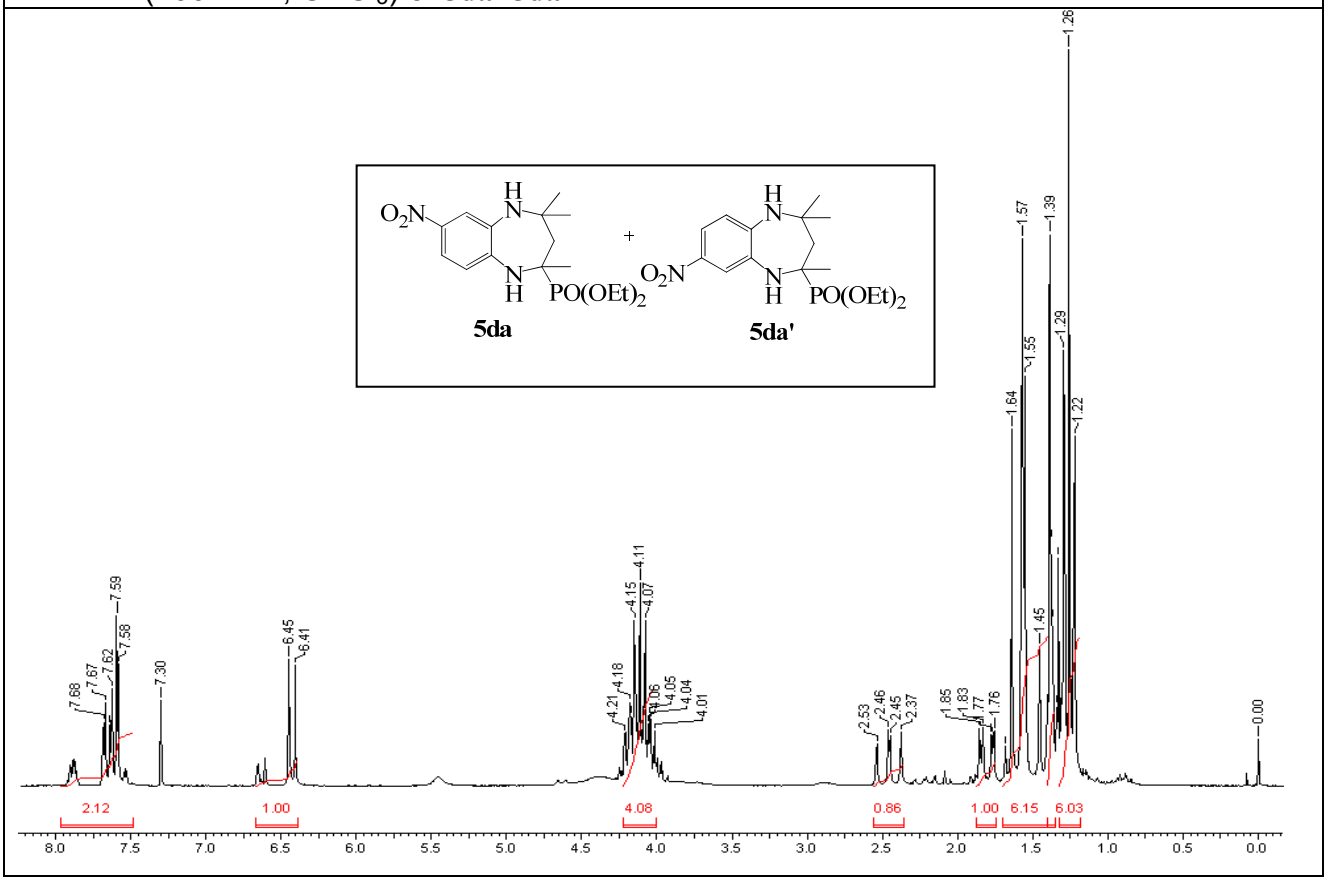
^{13}C NMR (50 MHz, $CDCl_3$) of **5cd**



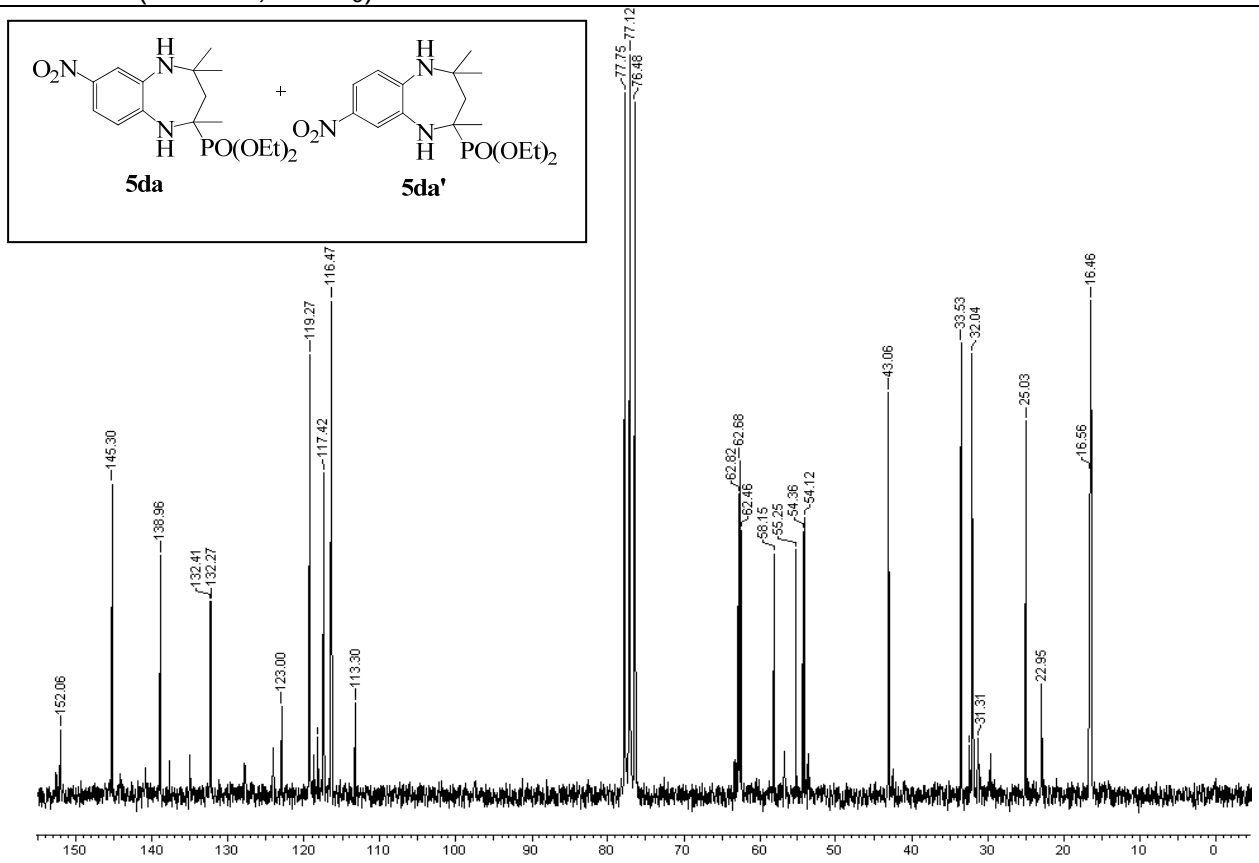
DEPT (50 MHz, $CDCl_3$) of **5cd**



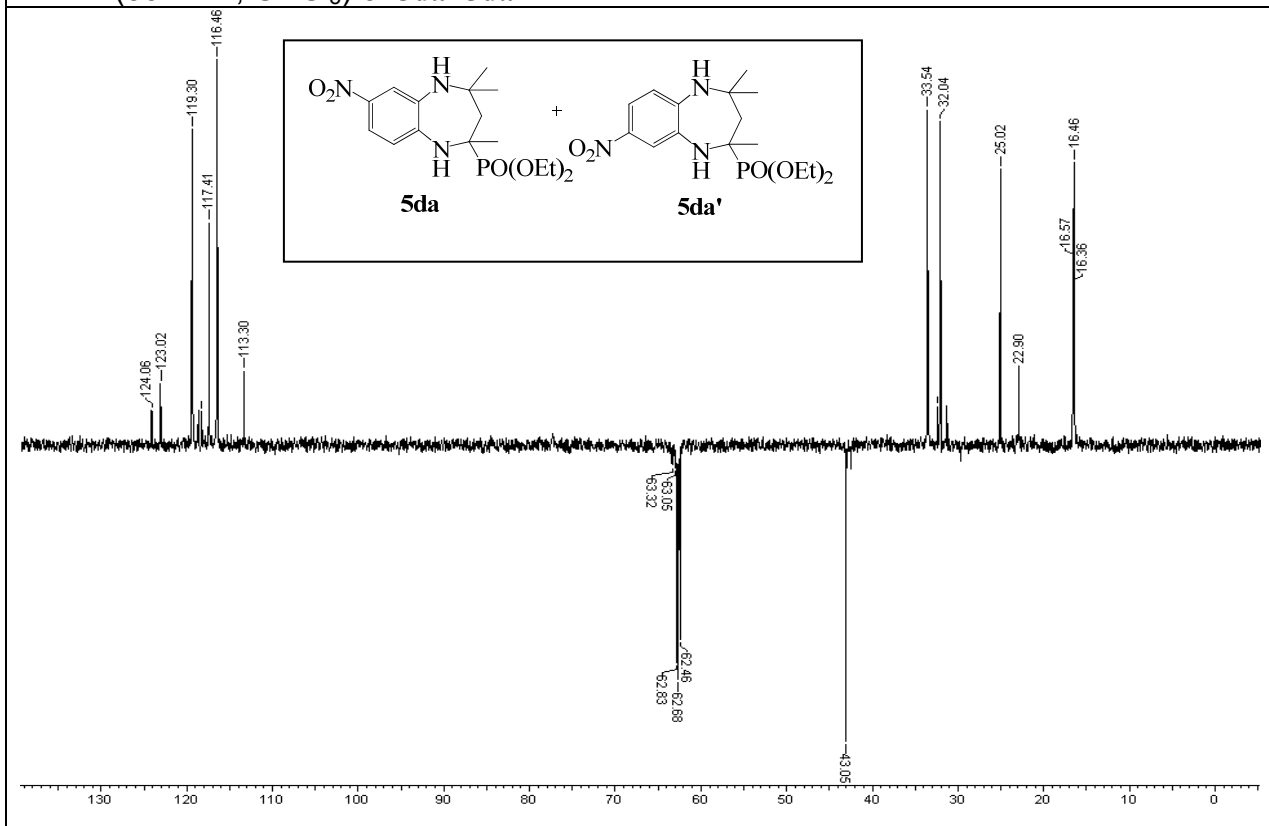
^{1}H NMR (200 MHz, $CDCl_3$) of **5da**+**5da'**



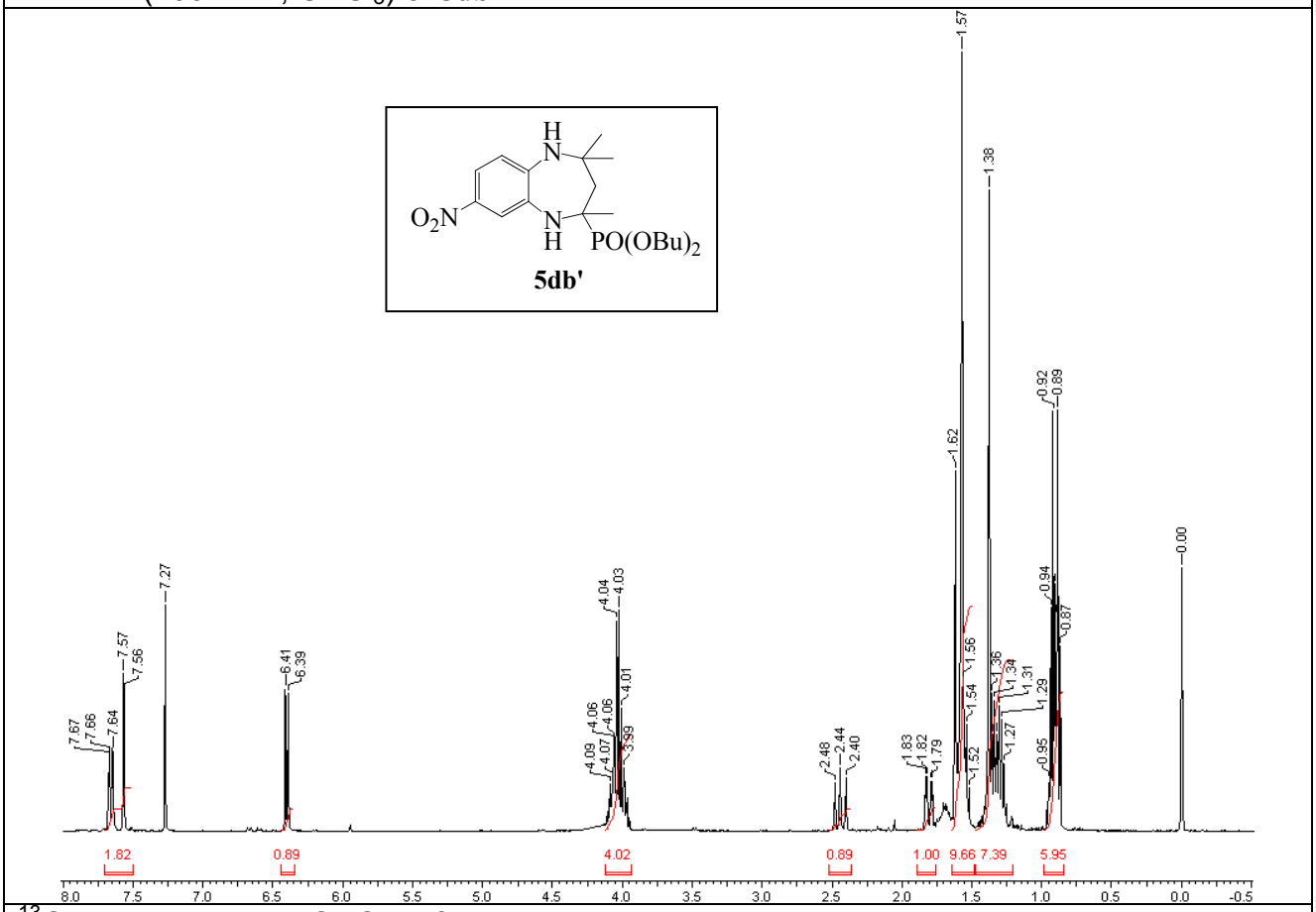
^{13}C NMR (50 MHz, $CDCl_3$) of **5da**+**5da'**



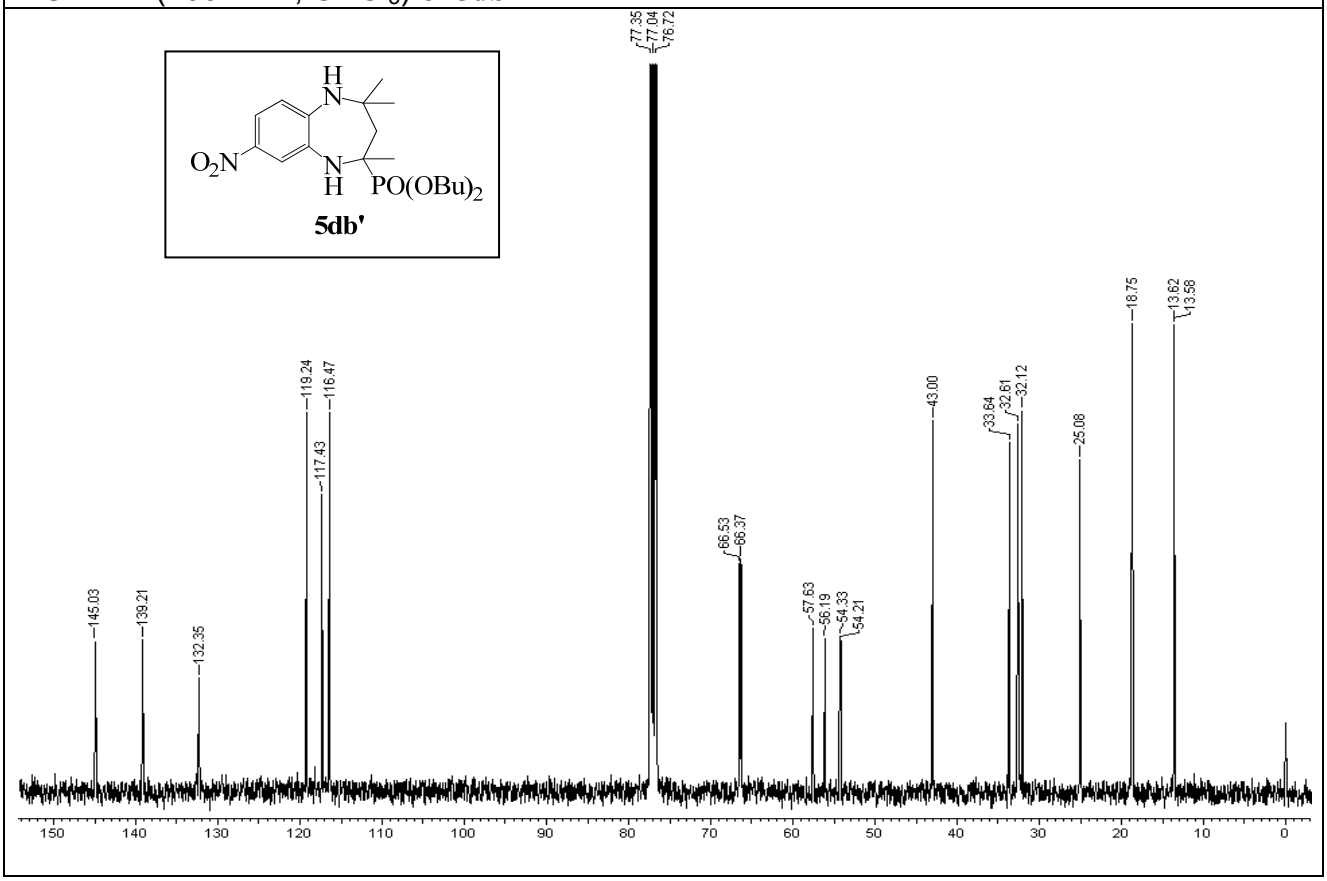
DEPT (50 MHz, $CDCl_3$) of **5da**+**5da'**



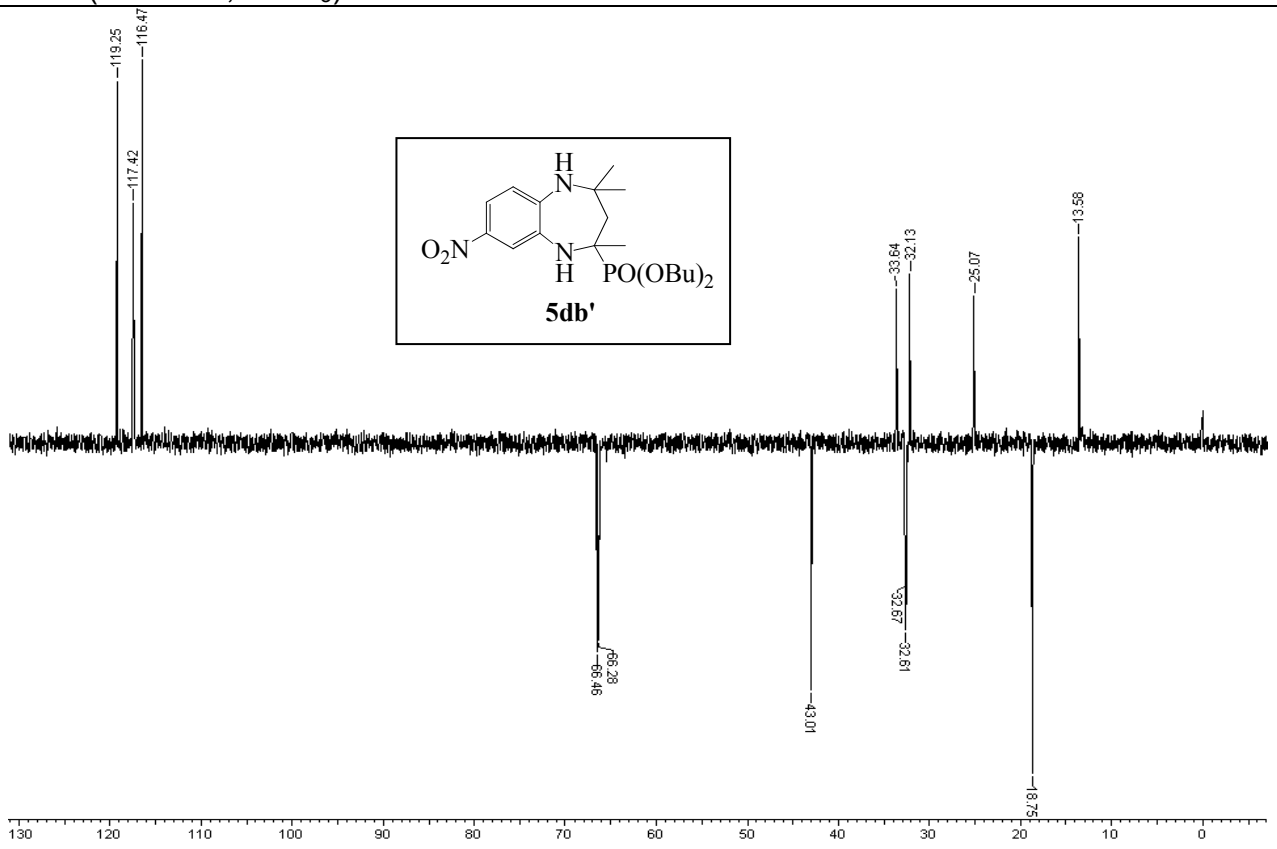
^{1}H NMR (400 MHz, $CDCl_3$) of **5db'**



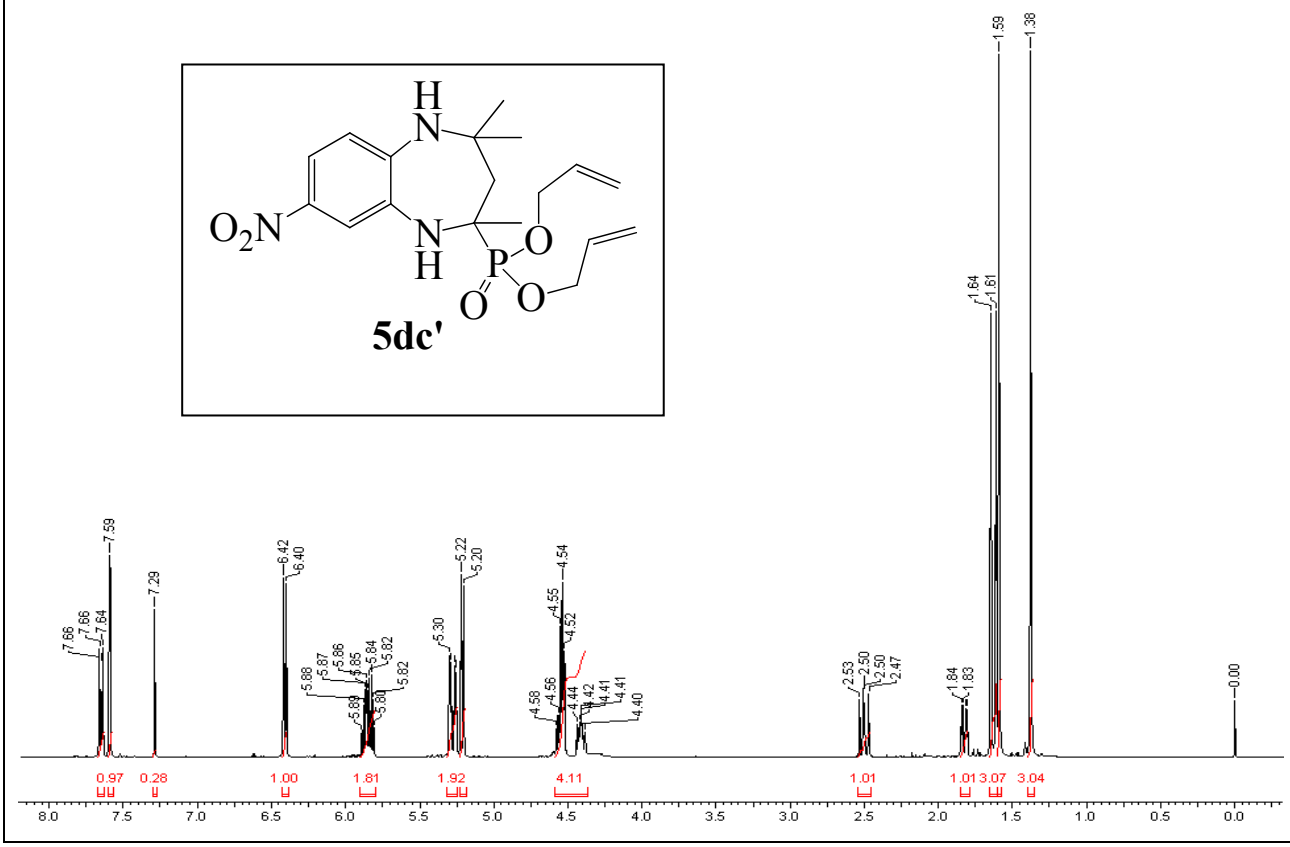
^{13}C NMR (100 MHz, $CDCl_3$) of **5db'**



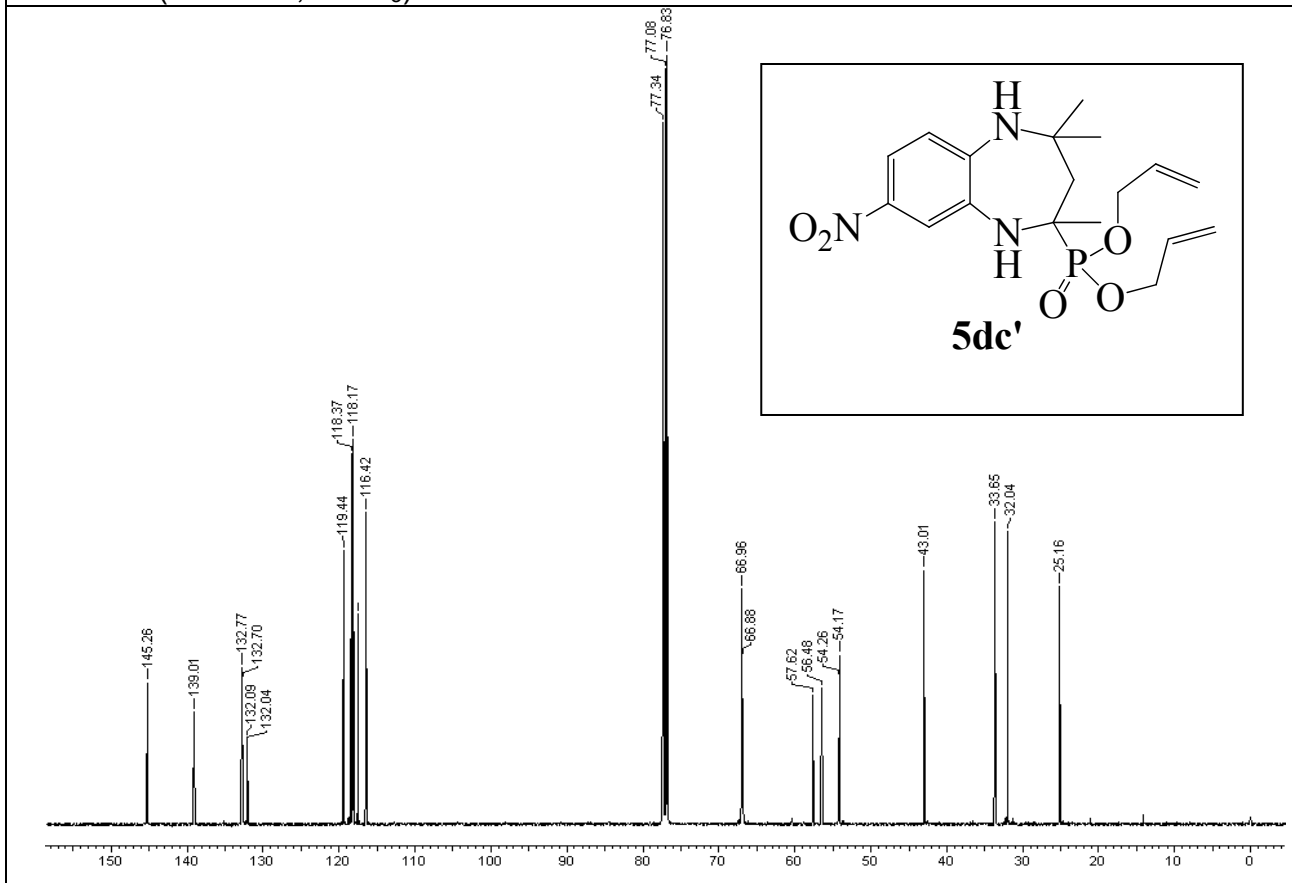
DEPT (100 MHz, $CDCl_3$) of **5db'**



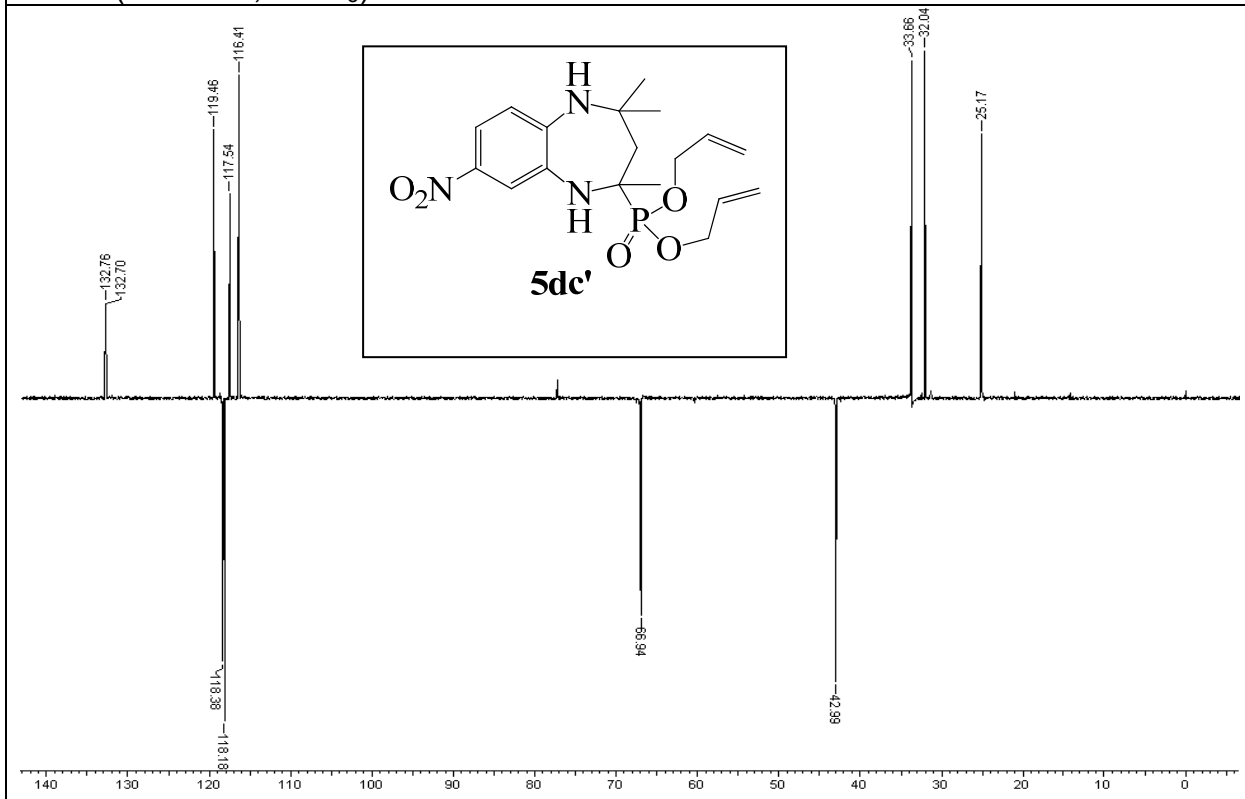
^{1}H NMR (500 MHz, $CDCl_3$) of **5dc'**



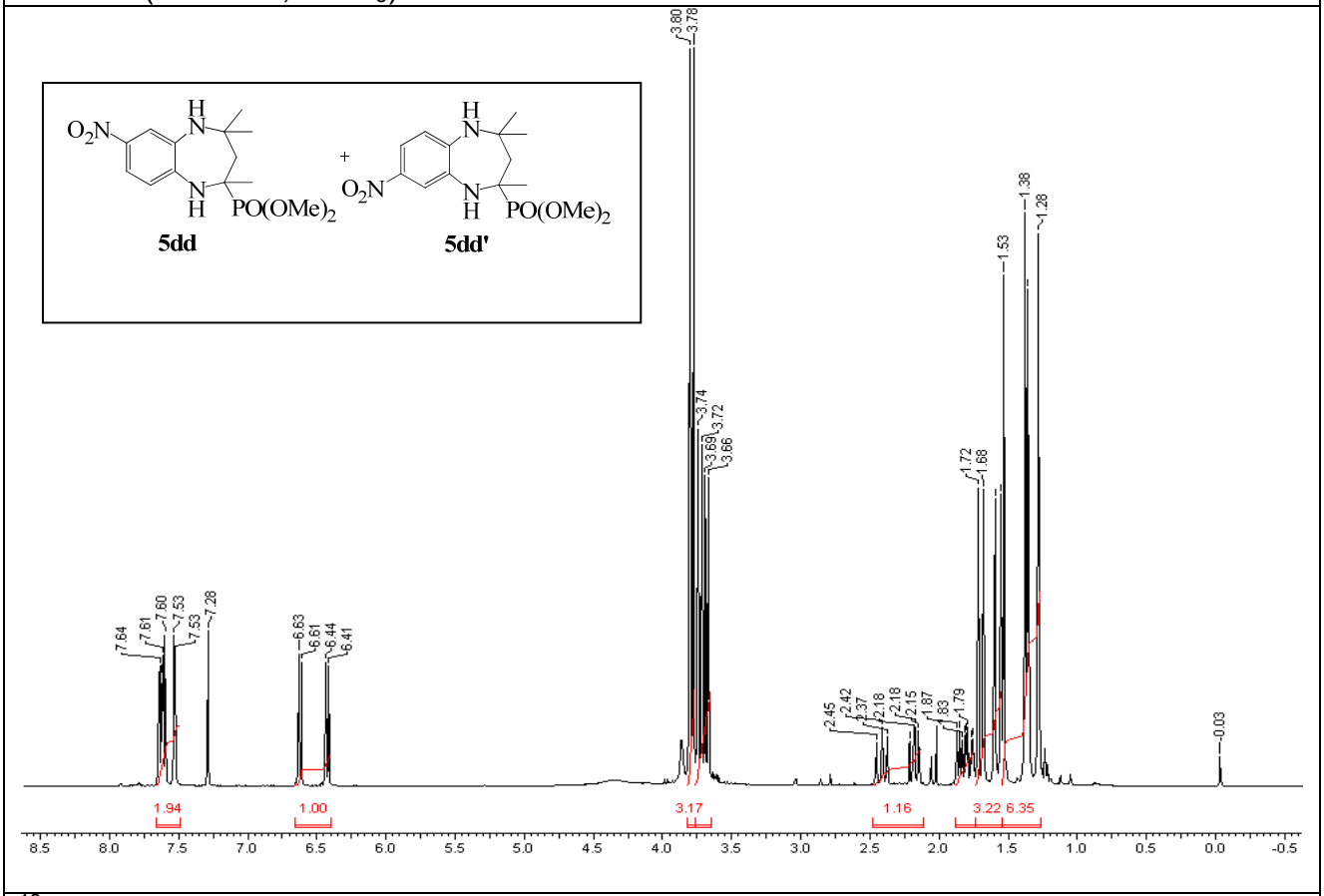
^{13}C NMR (125 MHz, $CDCl_3$) of **5dc'**



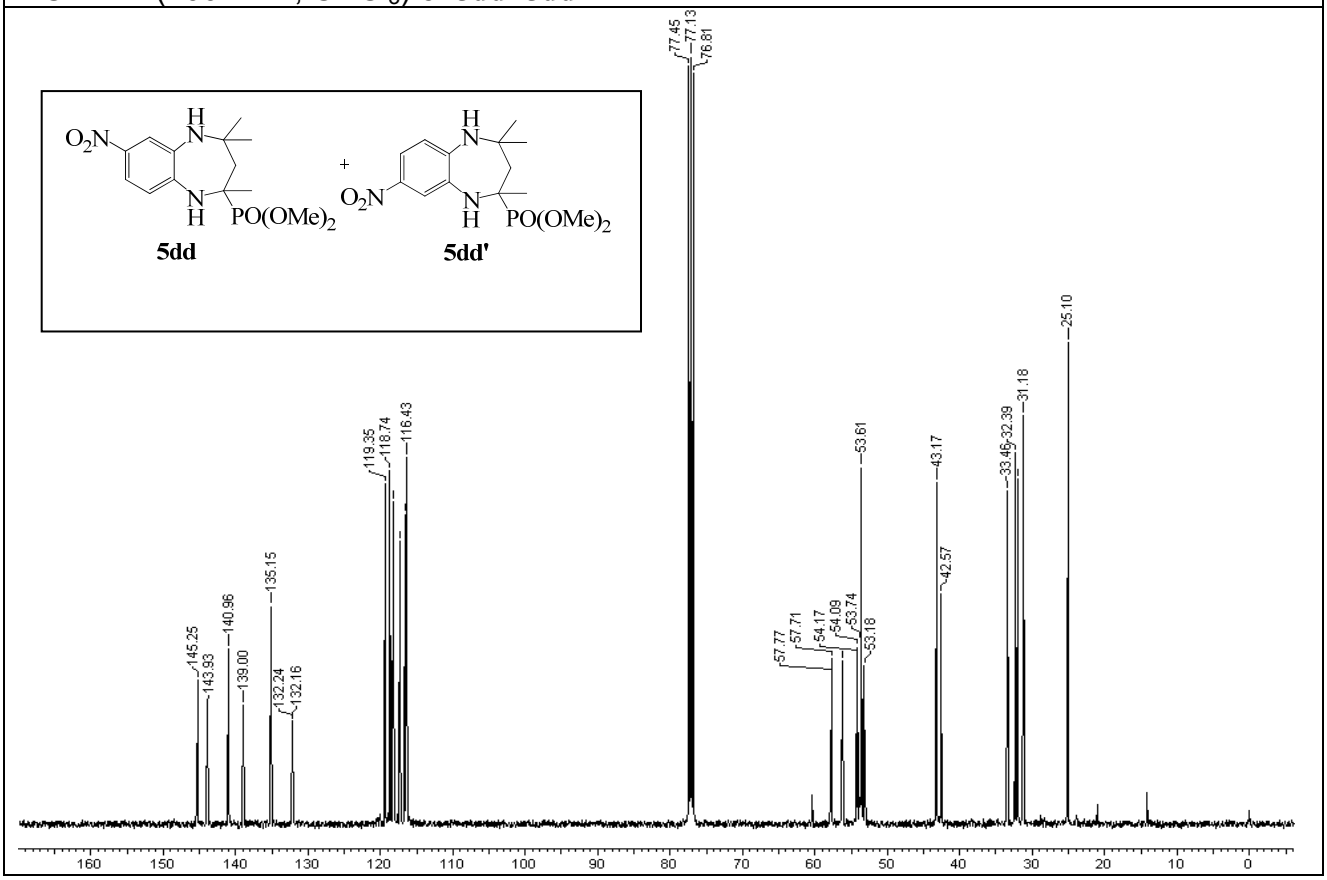
DEPT (125 MHz, $CDCl_3$) of **5dc'**



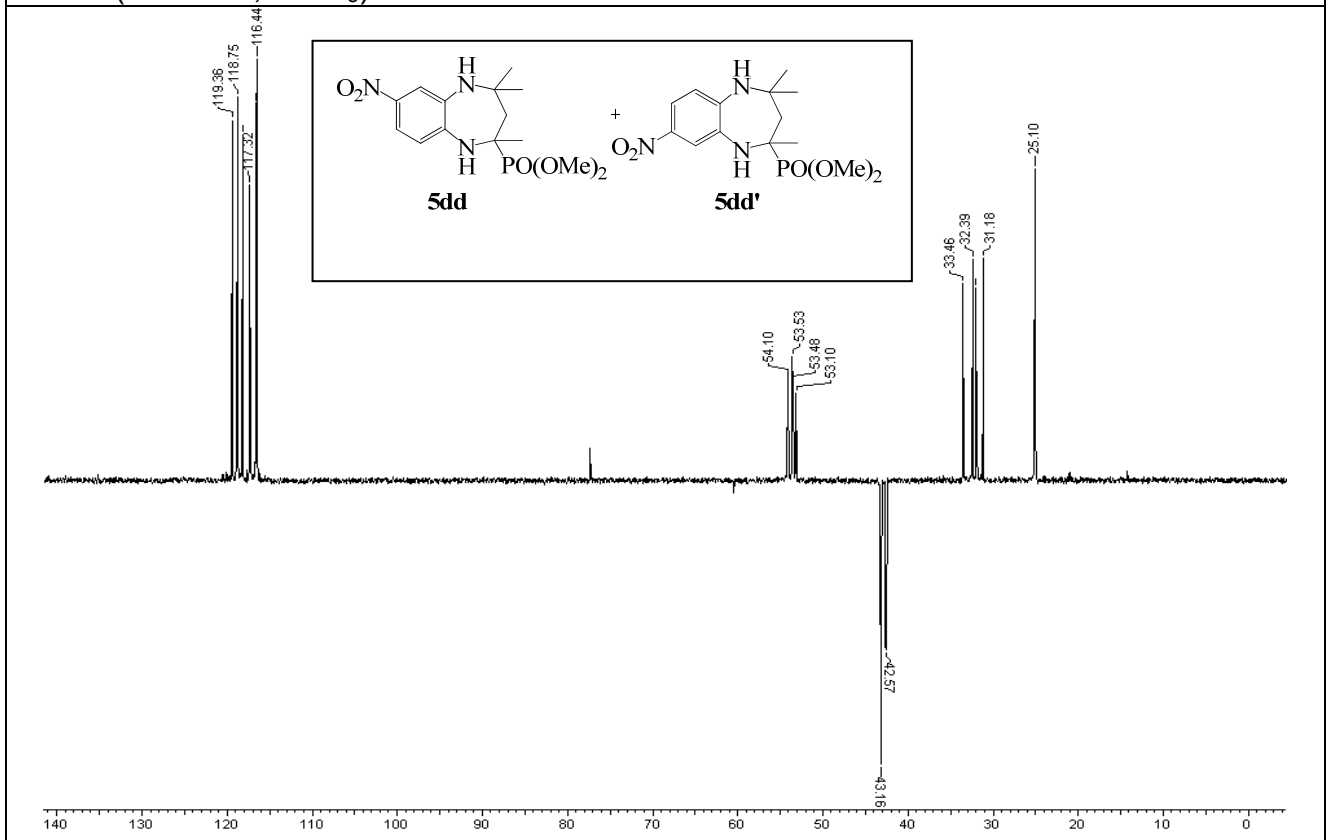
^{1}H NMR (400 MHz, $CDCl_3$) of **5dd+5dd'**



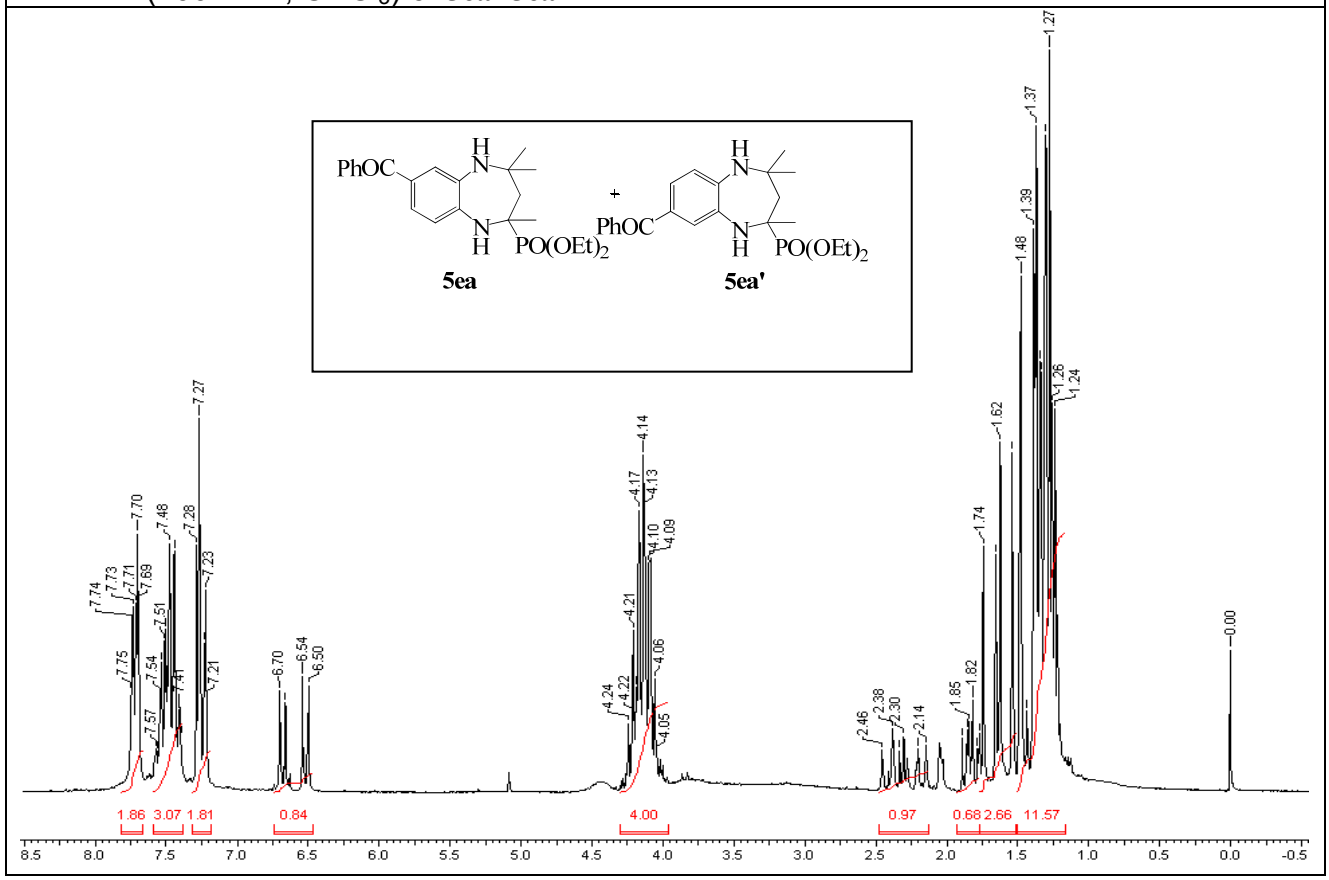
^{13}C NMR (100 MHz, $CDCl_3$) of **5dd+5dd'**



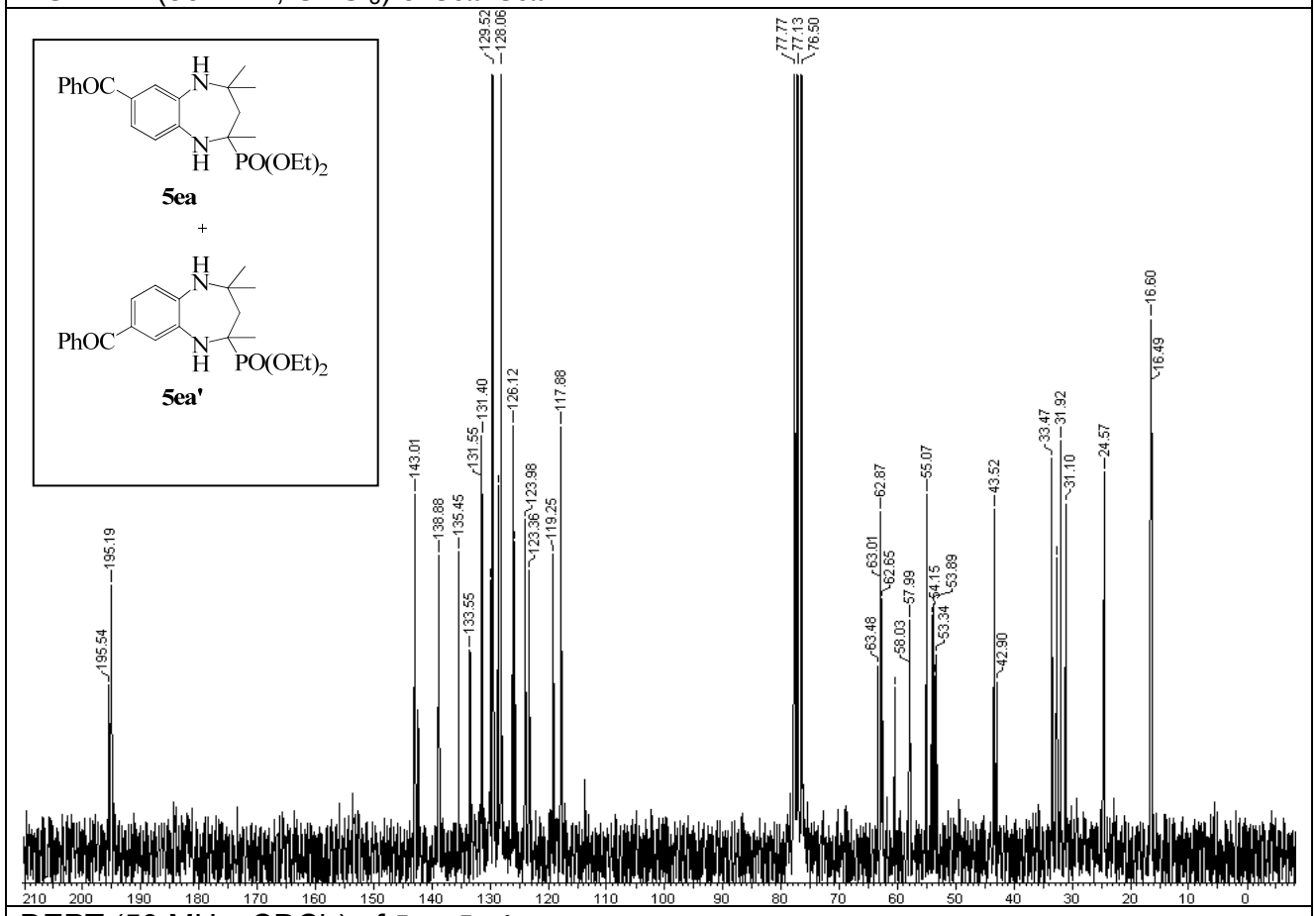
DEPT (100 MHz, $CDCl_3$) of **5dd+5dd'**



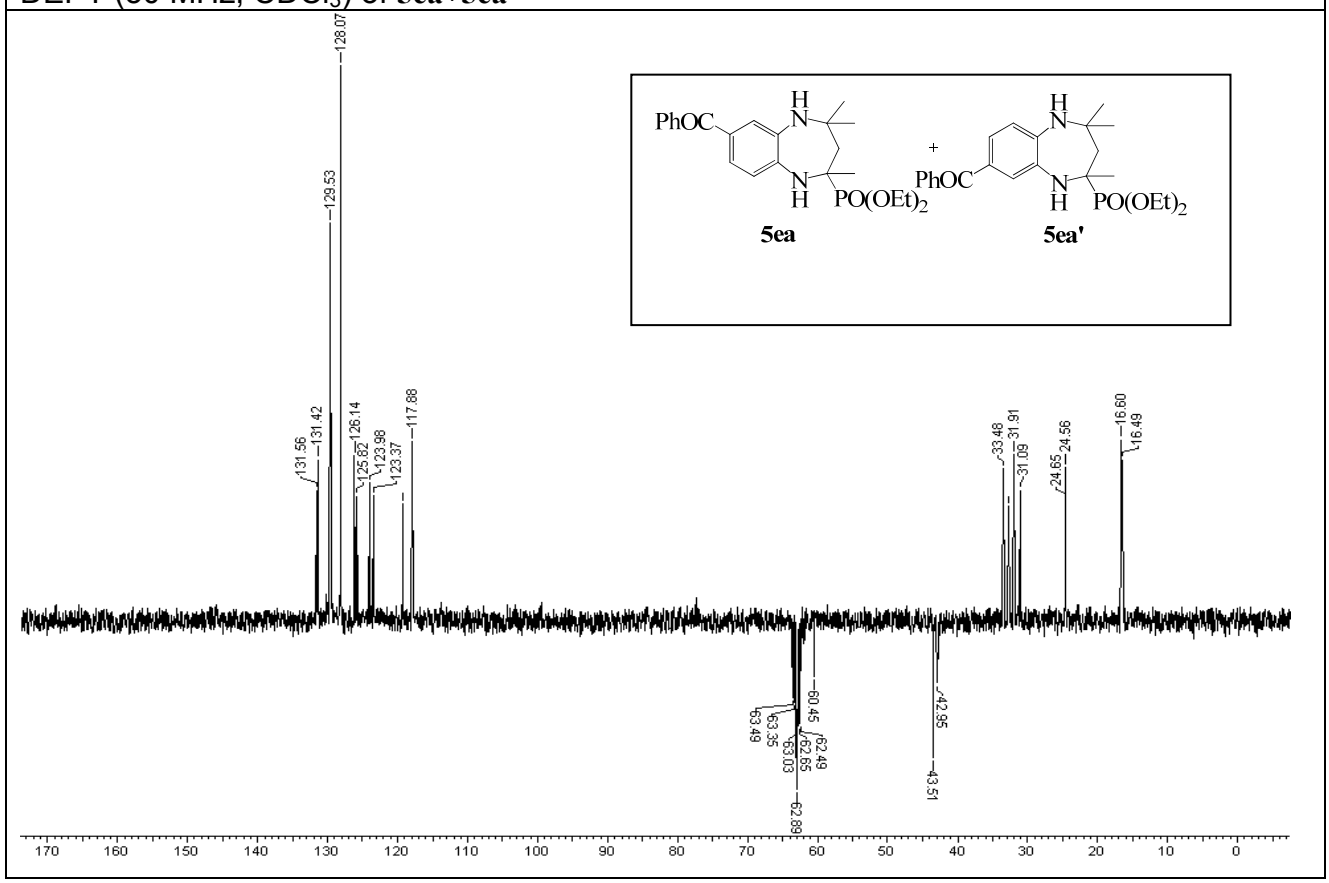
^{1}H NMR (200 MHz, $CDCl_3$) of **5ea+5ea'**



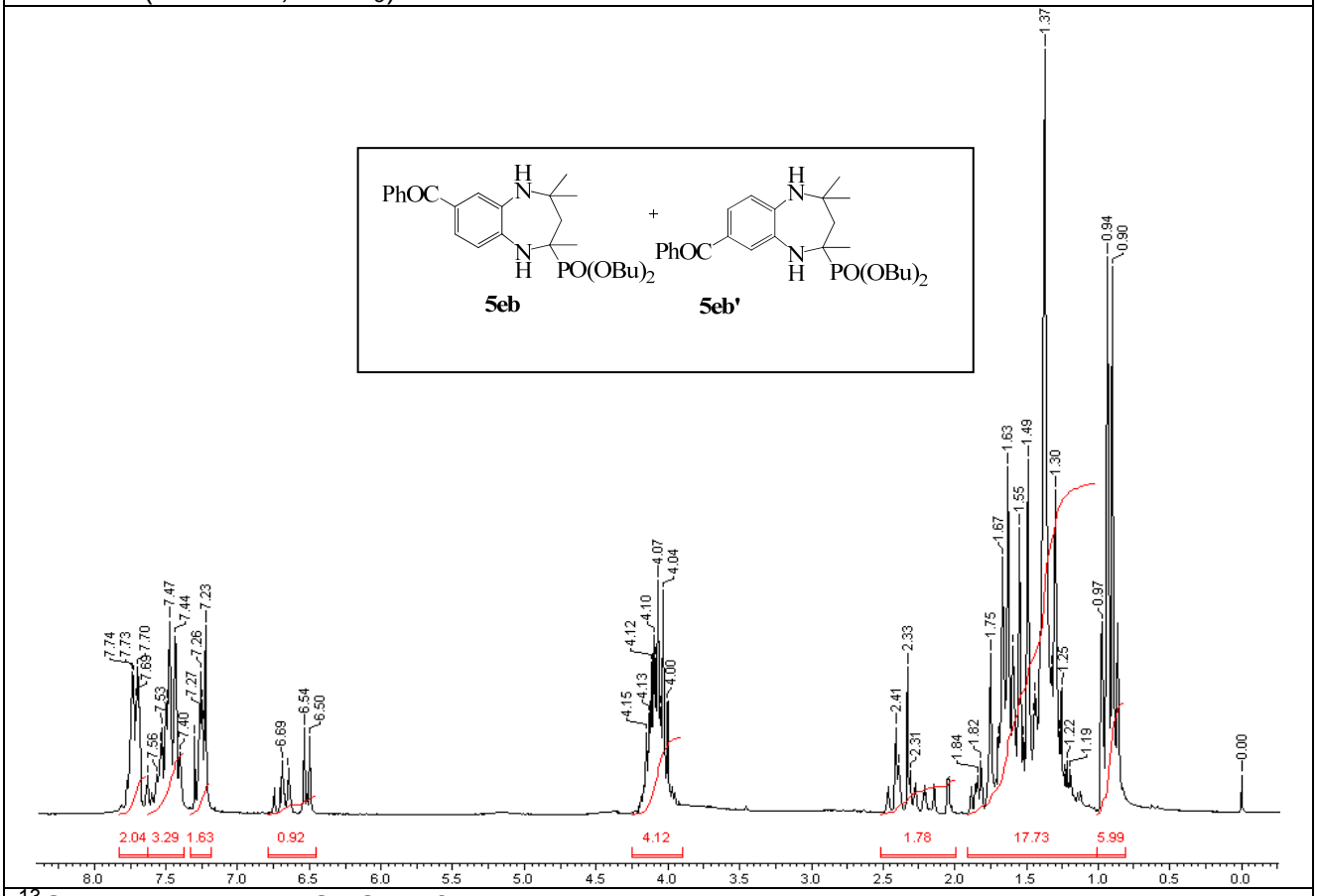
^{13}C NMR (50 MHz, $CDCl_3$) of **5ea**+**5ea'**



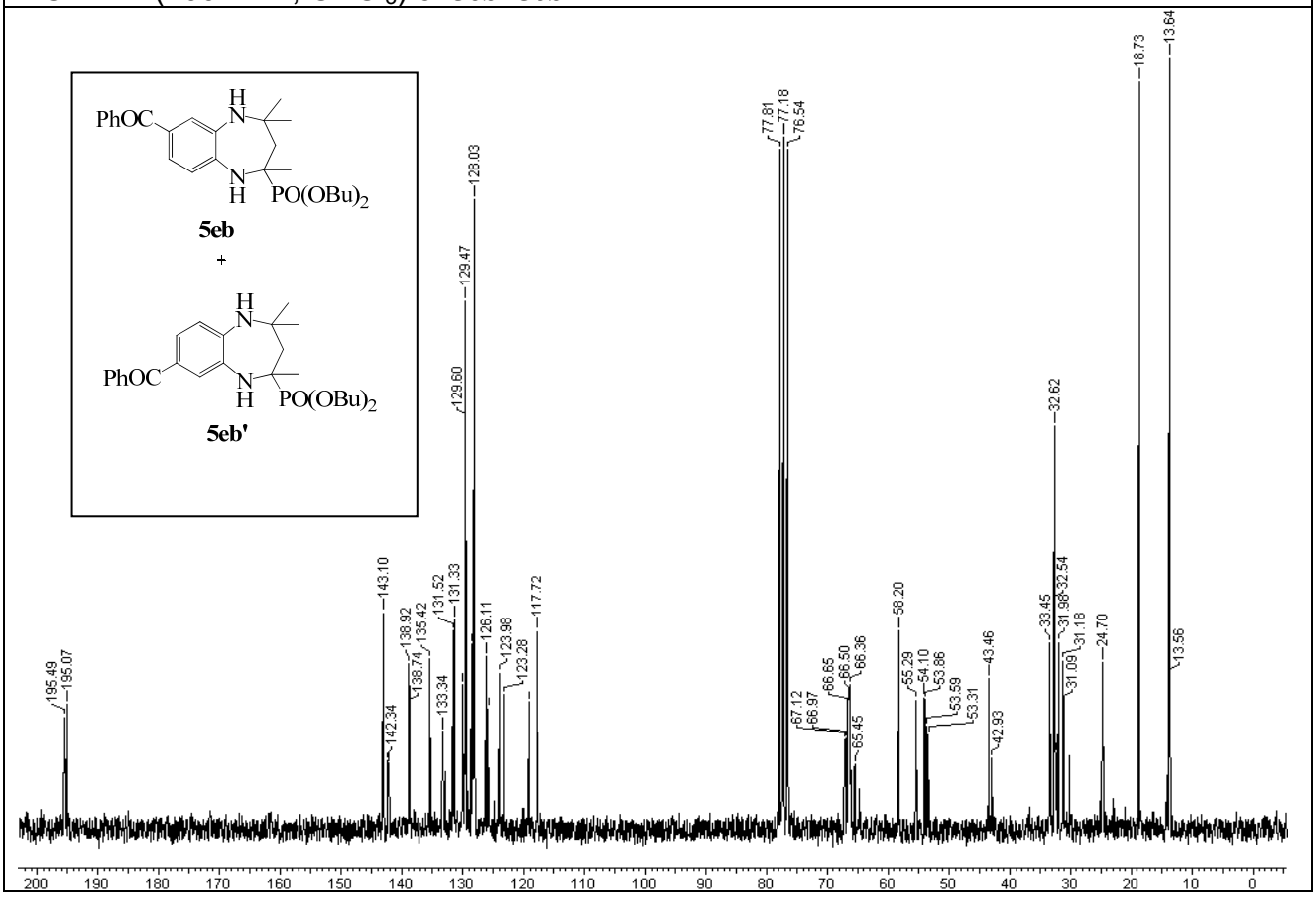
DEPT (50 MHz, $CDCl_3$) of **5ea**+**5ea'**



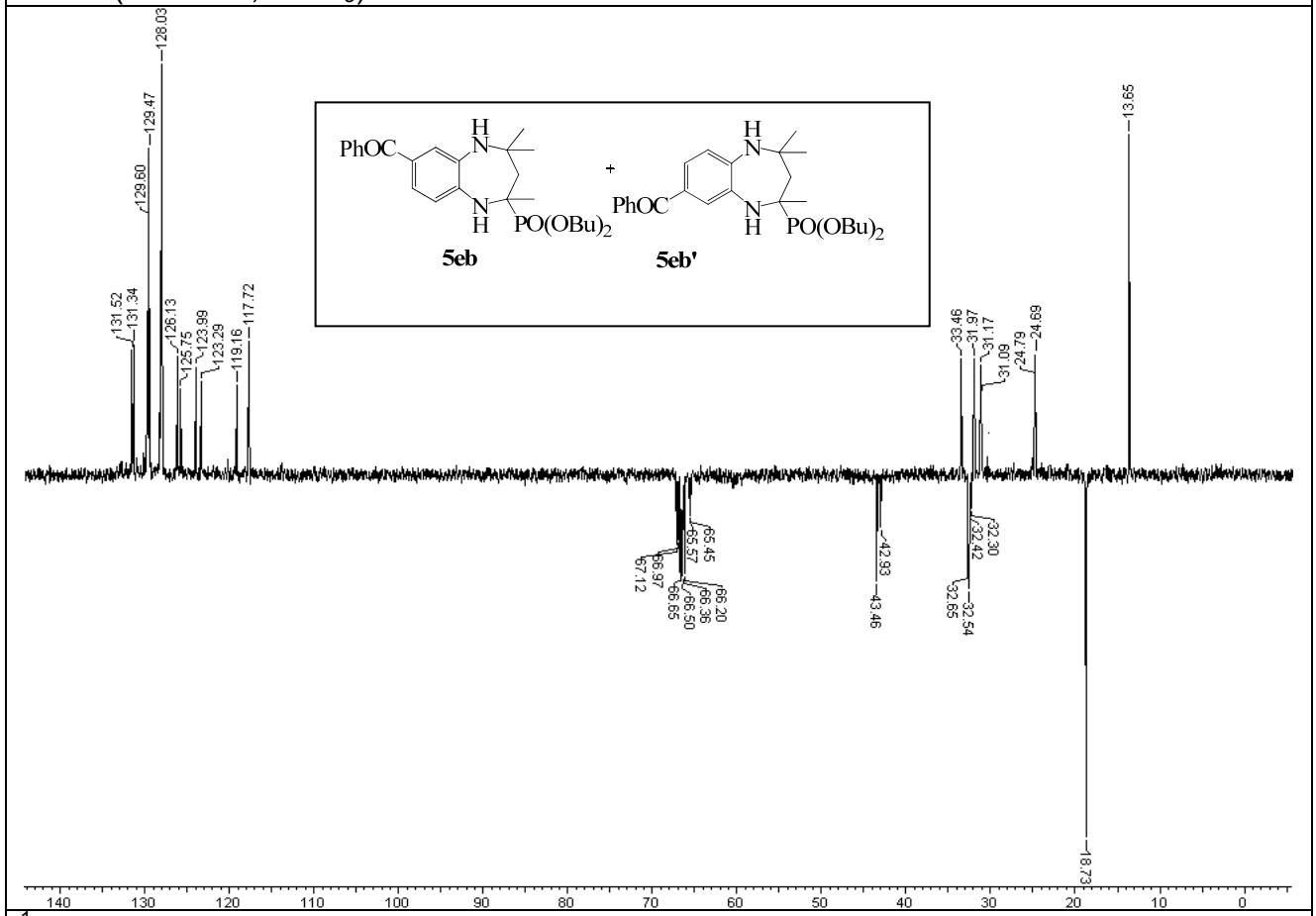
^{1}H NMR (200 MHz, $CDCl_3$) of **5eb+5eb'**



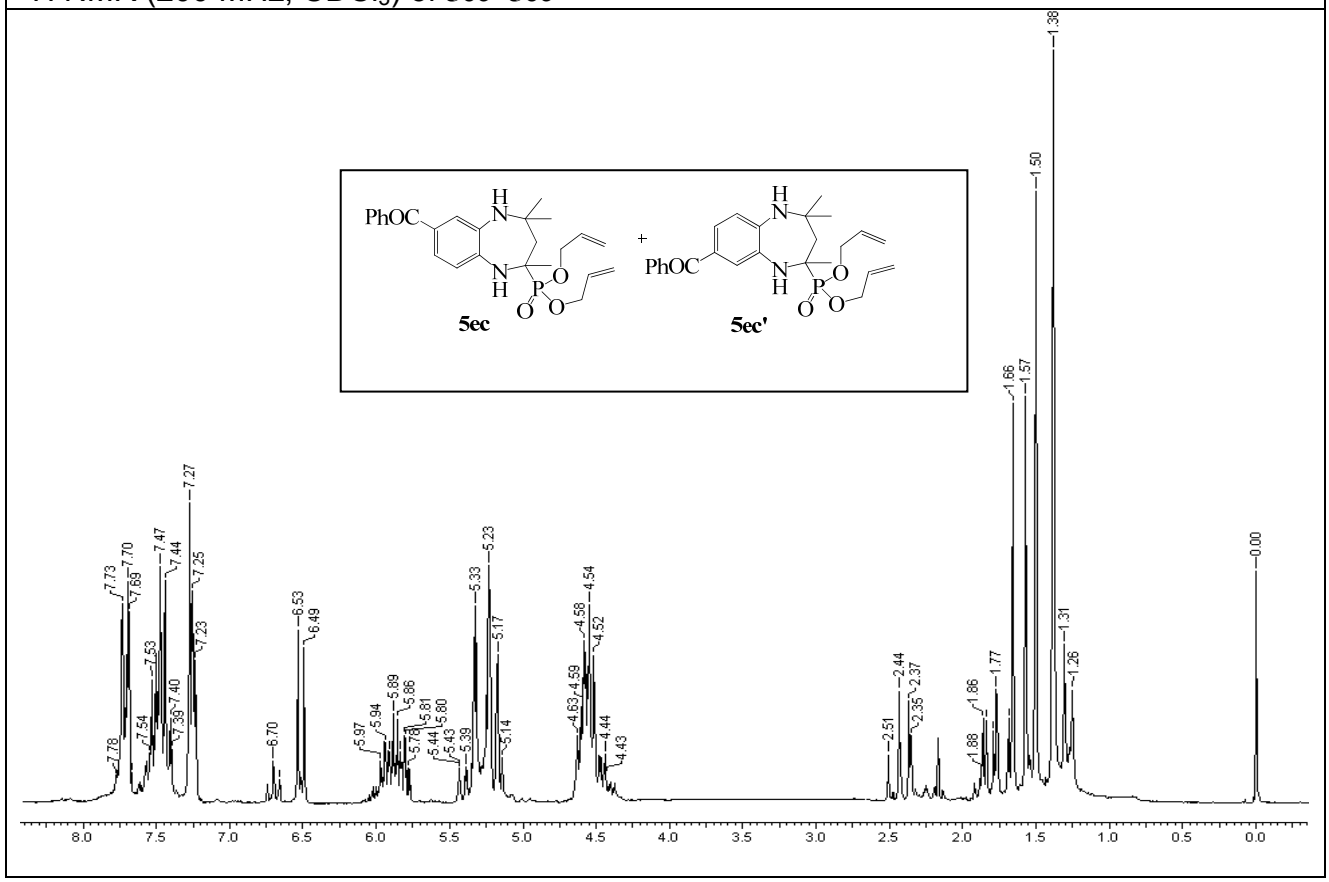
^{13}C NMR (100 MHz, $CDCl_3$) of **5eb+5eb'**



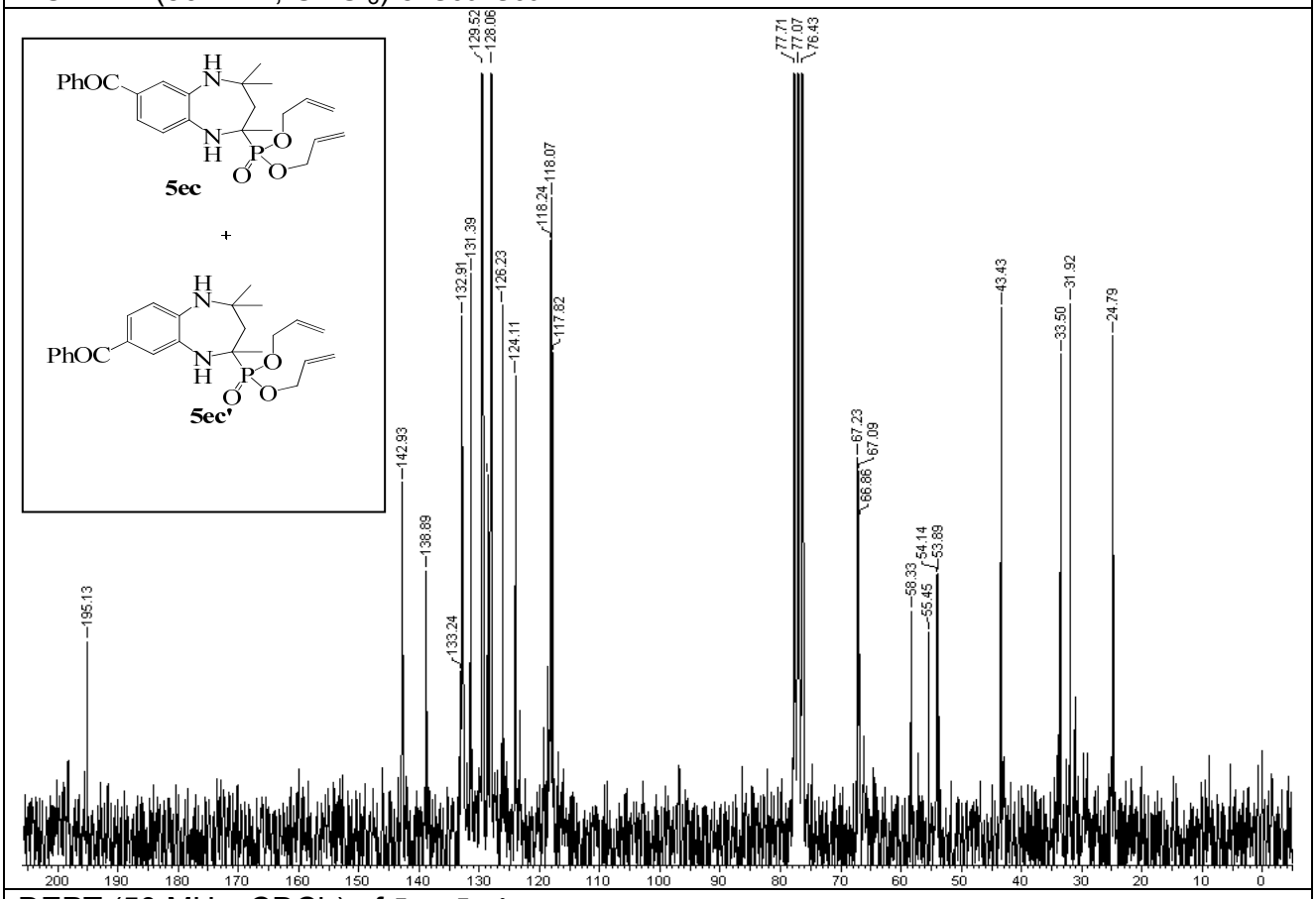
DEPT (100 MHz, $CDCl_3$) of **5eb**+**5eb'**



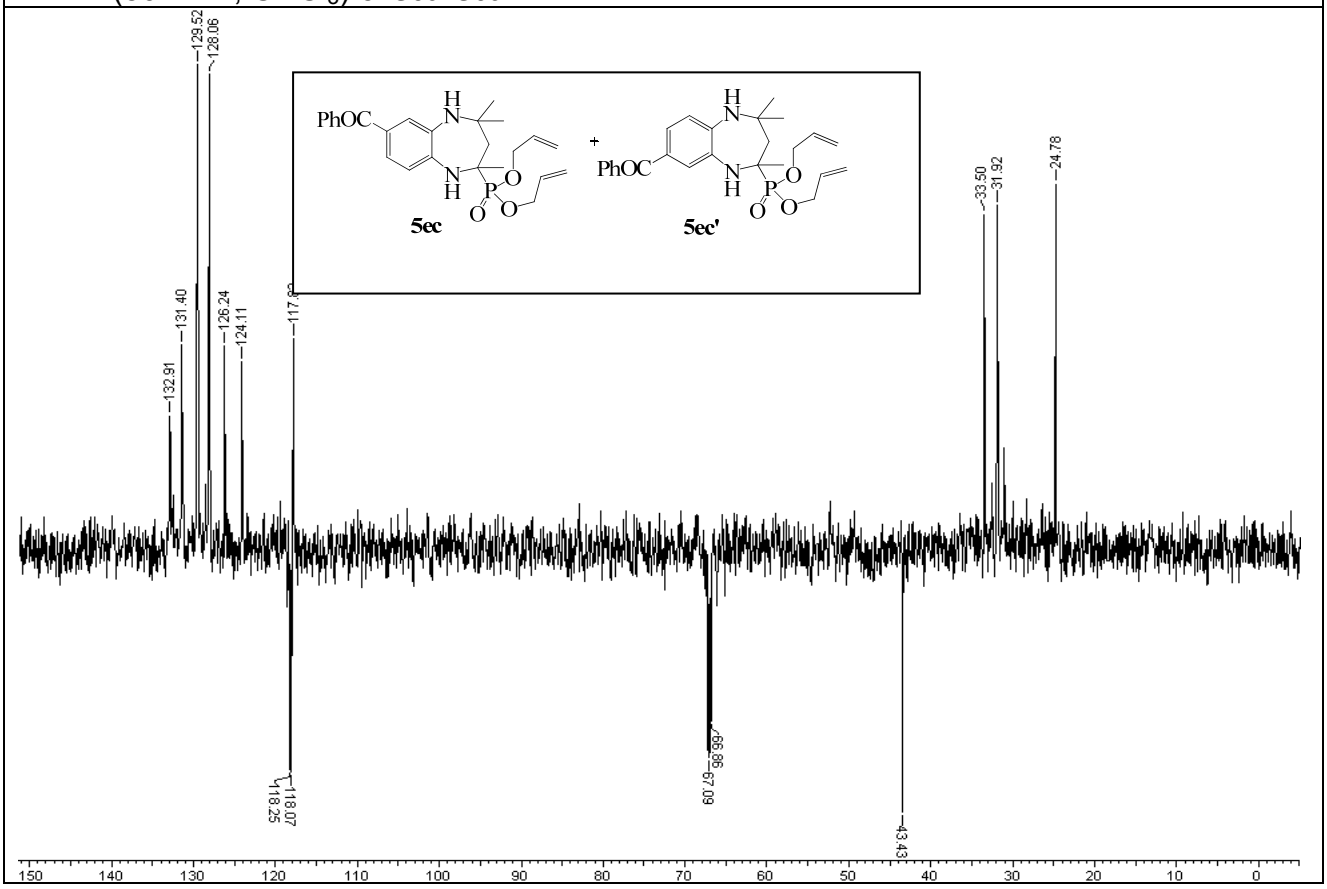
^{1}H NMR (200 MHz, $CDCl_3$) of **5ec**+**5ec'**



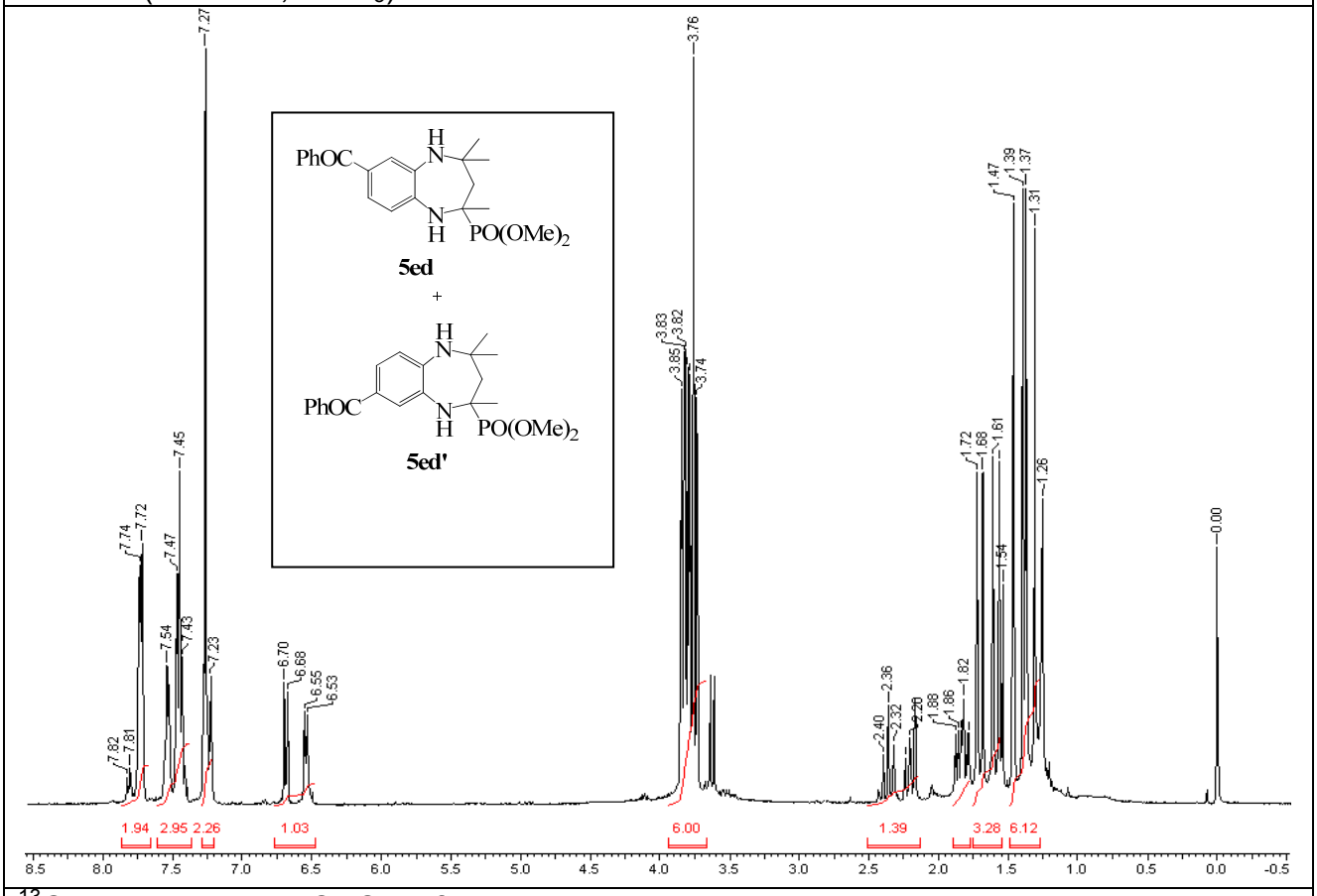
^{13}C NMR (50 MHz, $CDCl_3$) of **5ec+5ec'**



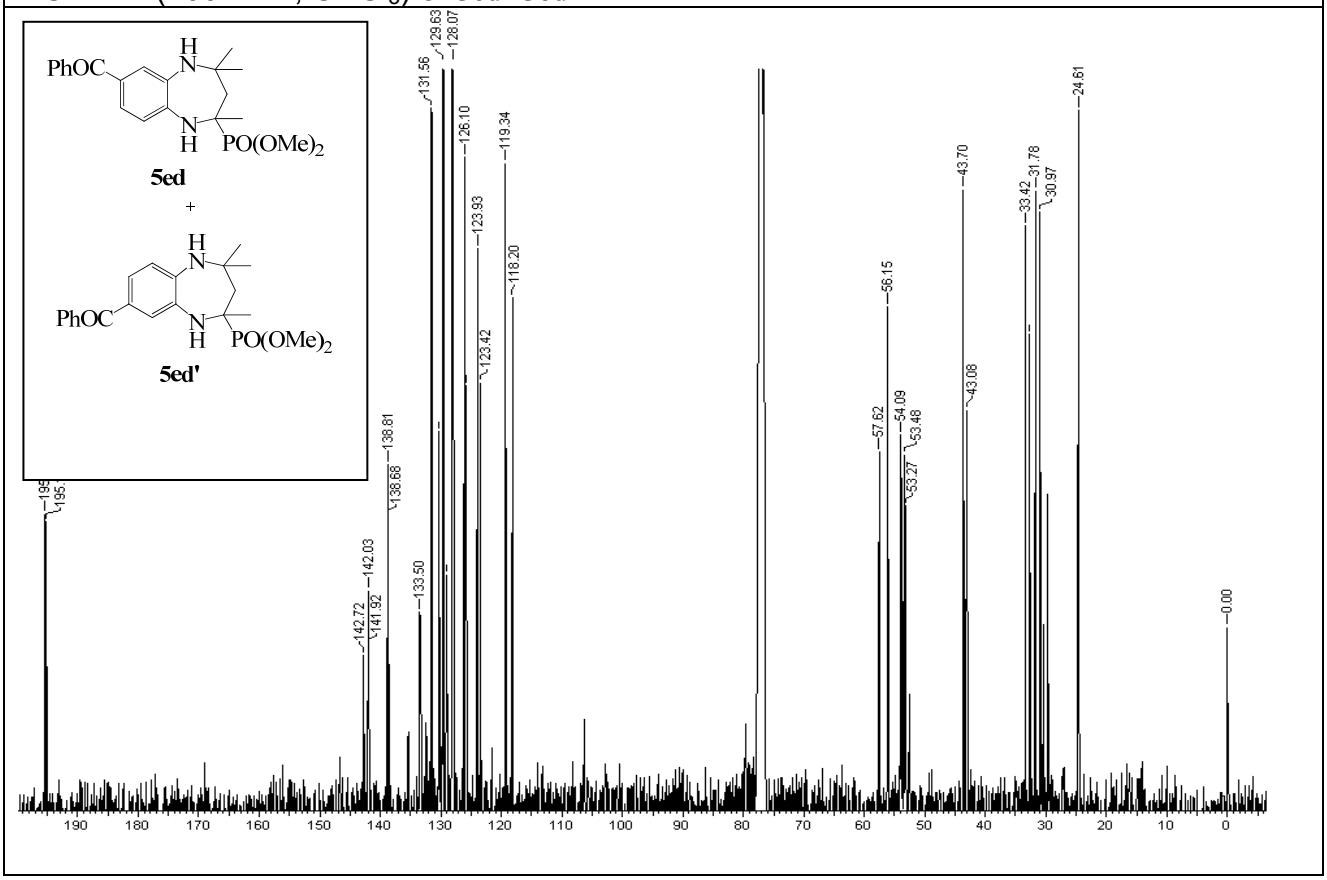
DEPT (50 MHz, $CDCl_3$) of **5ec+5ec'**



^{1}H NMR (400 MHz, $CDCl_3$) of **5ed+5ed'**



^{13}C NMR (100 MHz, $CDCl_3$) of **5ed+5ed'**



DEPT (100 MHz, $CDCl_3$) of **5ed**+**5ed'**