

## Electronic supplementary information

### An easy entry to optically active $\alpha$ -amino phosphonic acid derivatives using phase transfer catalysis (PTC)

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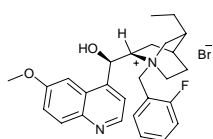
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#### Experimental details:

**General methods:** <sup>1</sup>H, <sup>13</sup>C, <sup>31</sup>P and <sup>19</sup>F NMR were recorded on a Varian AS 400 spectrometer running at 400, 100, 162 and 376 MHz, respectively, in CDCl<sub>3</sub> as the solvent, unless otherwise stated. Chemical shifts are reported in the  $\delta$  scale relative to residual solvent peaks for <sup>1</sup>H and <sup>13</sup>C NMR (<sup>1</sup>H NMR: 7.26 ppm for CDCl<sub>3</sub> and 4.79 ppm for D<sub>2</sub>O/NaOH, <sup>13</sup>C NMR: 77.0 ppm for CDCl<sub>3</sub>) or using an external reference for <sup>31</sup>P, <sup>19</sup>F NMR and <sup>13</sup>C in D<sub>2</sub>O (<sup>31</sup>P NMR: 0.0 ppm for K<sub>3</sub>PO<sub>4</sub> 85%, <sup>19</sup>F NMR: -163.0 ppm for C<sub>6</sub>F<sub>6</sub>, <sup>13</sup>C NMR in D<sub>2</sub>O/NaOH: 0.0 ppm for sodium 3-(trimethylsilyl)propionate). <sup>13</sup>C NMR, <sup>19</sup>F NMR and <sup>31</sup>P NMR spectra were recorded on a broad band decoupled mode. Coupling constants (*J*) are given in Hertz. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES) ionisation techniques. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC, using a UV detector operating at 215 nm. Melting points were measured on a Büchi smp-20 apparatus and are uncorrected. Chromatographic purifications were performed using 70-230 mesh silica.

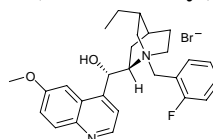
**Materials:** All commercially available solvents and reagents were used as received.  $\alpha$ -Amido sulfones **1a-l** were obtained following literature procedures.<sup>1</sup> Racemic samples were obtained at room temperature using tetrabutylammonium bromide as the catalyst.

**Preparation of N-(2-fluorobenzyl)-hydroquininium bromide (4f):** *o*-Fluorobenzyl bromide (289  $\mu$ L, 2.4 mmol) was



added to a suspension of hydroquinine (652 mg, 2.0 mmol) in toluene (6 mL). The resulting mixture was heated to 80 °C with stirring. After 4 h the reaction mixture was allowed to cool to room temperature and evaporated in vacuo. The residue was dissolved in the minimal amount of CH<sub>2</sub>Cl<sub>2</sub> (ca. 1 mL), and poured onto Et<sub>2</sub>O (ca. 20 mL) with stirring. The resulting precipitate was collected by suction filtration, washed several times with Et<sub>2</sub>O giving **4f** as a light pink solid (670 mg, 65% yield). mp >160 °C (dec.); [ $\alpha$ ]<sub>D</sub><sup>20</sup> -109 (c 0.20 in CHCl<sub>3</sub>);  $\delta$ <sub>H</sub> 0.78 (3 H, t, *J* 7.1), 1.22-1.33 (2 H, m), 1.41-1.50 (1 H, m), 1.67-1.85 (2 H, m), 1.90 (1 H, br s), 2.04 (1 H, br s), 2.30-2.45 (1 H, m), 2.73-2.80 (1 H, m), 3.08-3.18 (1 H, br dt, *J* 6.4 and 11.5), 3.33 (1 H, br t, *J* 11.5), 3.66 (1 H, dd, *J* 7.2 and 11.0), 3.96 (3 H, s), 4.51 (1 H, d, *J* 12.1), 5.15 (1 H, td, *J* 3.3 and 11.7), 6.48 (1 H, d, *J* 11.7), 6.53 (1 H, d, *J* 7.7), 6.76 (1 H, d, *J* 6.9), 7.10 (1 H, d, *J* 2.7), 7.16-7.21 (1 H, m), 7.33 (1 H, dt, *J* 1.1 and 7.7), 7.39 (1 H, dd, *J* 2.6 and 9.3), 7.49-7.57 (1 H, m), 7.81 (1 H, d, *J* 4.9), 8.06 (1 H, d, *J* 9.0), 8.27 (1 H, dt, *J* 1.8 and 7.8), 8.79 (1 H, d, *J* 4.8);  $\delta$ <sub>C</sub> 11.2, 21.0, 23.8, 25.2, 26.4, 36.1, 50.9, 55.8, 57.3, 63.2, 63.4, 71.3, 100.6, 114.5 (d, *J* 13), 115.9 (d, *J* 22), 120.6, 121.4, 125.8 (d, *J* 26), 126.0, 132.4, 133.4 (d, *J* 9), 136.2, 142.9, 144.2, 147.8, 158.2, 162.0 (d, *J* 248);  $\delta$ <sub>F</sub> -114.5; *m/z* (ESI) 435 [M<sup>+</sup>].

**N-(2-fluorobenzyl)-hydroquininidinium bromide (4g):** Following the procedure used for **4f**, the title compound was



obtained as a light pink solid (793 mg, 77% yield). mp >210 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +125 (c 0.33 in CHCl<sub>3</sub>);  $\delta$ <sub>H</sub> 0.89 (3 H, t, *J* 7.2), 1.03 (1 H, ddd, *J* 5.1, 9.6 and 13.9), 1.54-1.86 (4 H, m), 1.91 (1 H, br s); 2.07 (1 H, br s), 2.49 (1 H, br t, *J* 12.4), 2.91 (1 H, br q, *J* 10.0), 3.44 (1 H, br t, *J* 3.5), 3.71 (1 H, br t, *J* 10.3), 3.79 (1 H, br t, *J* 9.2), 3.93 (3 H, s), 4.39-4.47 (1 H, m), 4.81 (1 H, d, *J* 12.2), 6.24 (1 H, d, *J* 11.9), 6.61 (1 H, d, *J* 6.0), 6.72 (1 H, d, *J* 6.3), 7.13 (1 H, br t, *J* 8.9), 7.19 (1 H, d, *J* 2.6),

<sup>1</sup> (a) E. Bernacka, A. Kapacz and A. Zwierzak, *Tetrahedron Lett.*, 2001, **42**, 5093-5094; (b) A. G. Wenzel and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 12964-12965.

7.28 (1 H, dt,  $J$  1.2 and 7.6), 7.32 (1 H, dd,  $J$  2.6 and 9.2), 7.44-7.51 (1 H, m), 7.82 (1H, d,  $J$  4.5), 7.99 (1 H, d,  $J$  9.3), 8.12 (1 H, dt,  $J$  1.7 and 7.6), 8.70 (1 H, d,  $J$  4.5);  $\delta_{\text{C}}$  11.4, 21.0, 24.2, 24.3, 24.6, 36.1, 55.8, 55.9, 56.4, 56.9, 64.6, 69.6, 100.8, 114.7 (d,  $J$  13), 116.0 (d,  $J$  22), 120.5, 121.4, 125.5, 125.6, 132.1, 133.2 (d,  $J$  8), 136.3, 142.8, 144.2, 147.6, 158.1, 161.9 (d,  $J$  249);  $\delta_{\text{F}}$  -113.4;  $m/z$  (ESI) 435 [ $\text{M}^+$ ].

**General procedure for the catalytic reaction of dimethylphosphite 2e with  $\alpha$ -amido sulfones 1:** Dimethylphosphite **2b** (14  $\mu\text{L}$ , 0.15 mmol for N-Boc  $\alpha$ -amido sulfones **1a,c,e,g,i,j,l**, 28  $\mu\text{L}$ , 0.30 mmol for N-Cbz  $\alpha$ -amido sulfones **1b,d,f,h,k**) was added to a test tube containing a mixture of  $\alpha$ -amido sulfone **1** (0.10 mmol) and catalyst **4f** (2.6 mg, 0.005 mmol) in toluene (1 mL). After the resulting mixture had been cooled to  $-78\text{ }^\circ\text{C}$ , finely ground KOH (17 mg, 0.30 mmol), weighed in a oven-dried vial, was added in one portion. The reaction mixture was then vigorously stirred at the same temperature without any precaution to exclude moisture or air. After 60 h, sat.  $\text{NH}_4\text{Cl}$  (ca. 2 mL) was added, and the mixture was allowed to warm to room temperature. The toluene layer was separated, and the aqueous phase extracted twice with toluene (ca 1 mL). The combined organic extracts were then charged directly on a silica gel column, and the product was obtained using a *n*-hexane/EtOAc/acetone 5:3:2 mixture as eluent.

**(R)-tert-Butyl 1-(dimethoxyphosphoryl)-3-phenylpropylcarbamate (3b).** Following the general procedure and performing the reaction on a 1 mmol scale, the title compound was obtained as a colourless thick oil in 94% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{\text{maj}}$  10.7 min;  $t_{\text{min}}$  8.4 min; 88% ee).  $[\alpha]_{\text{D}}^{20}$  -19 (c 0.64 in  $\text{CHCl}_3$ );  $\delta_{\text{H}}$  [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.47 (9 H, s), 1.78-1.96 (1 H, m), 2.08-2.21 (1 H, m), 2.62-2.73 (1 H, m), 2.76-2.86 (1 H, m), 3.74 (3 H, d,  $J$  10.7), 3.77 (3 H, d,  $J$  10.7), 3.91 (0.1 H, br s), 4.04-4.16 (0.9 H, m), 4.48 (0.1 H, br s), 4.75 (1 H, d,  $J$  9.9), 7.16-7.22 (3 H, m), 7.25-7.31 (2 H, m);  $\delta_{\text{C}}$  28.2, 31.7, 32.0 (d,  $J$  14), 46.1 (d,  $J$  158), 52.9 (d,  $J$  6), 53.1 (d,  $J$  7), 80.1, 126.1, 128.4, 140.8, 155.3;  $\delta_{\text{P}}$  28.3;  $m/z$  (ESI) 366 [ $\text{M}^+$  + Na].

To verify the possibility of performing a Boc-deprotection CbzCl derivatisation sequence without affecting the enantiomeric excess of the products, necessary for the determination of the ee of products **3e,g,i,k,l** which could not be easily detected by the HPLC UV-detector, a sample of **3b** with 76% ee was treated as follows: TFA (39  $\mu\text{L}$ , 0.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) was added to a cooled ( $0\text{ }^\circ\text{C}$ ) solution of **3b** (18 mg, 0.05 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL). The resulting solution was then stirred at room temperature for 5 h, then sat.  $\text{NaHCO}_3$  (ca. 2 mL) and sat.  $\text{Na}_2\text{CO}_3$  (ca. 1 mL) were added at  $0\text{ }^\circ\text{C}$ , followed by EtOAc (2 mL) and CbzCl (11  $\mu\text{L}$ , 0.07 mmol). The resulting biphasic mixture was then vigorously stirred at room temperature overnight. The N-Cbz protected **3d** was then extracted with EtOAc, the organic phase dried on  $\text{MgSO}_4$ , filtered and evaporated under reduced pressure. The crude product was then purified by a short column chromatography on silica gel. HPLC analysis of thus obtained **3d** using a Daicel Chiralpak AD-H column (*n*-hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{\text{maj}}$  12.4 min;  $t_{\text{min}}$  14.7 min), revealed 75% ee, thus showing that racemisation did not occur to a considerable extent.

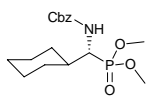
**(S)-tert-Butyl 1-(dimethoxyphosphoryl)-3-phenylpropylcarbamate (ent-3b).** Following the general procedure using catalyst **4g** derived from hydroquinidine (0.01 mmol, 10 mol%) and using 3 equiv. of dimethyl phosphite **2b**, the title compound was obtained as a colourless thick oil in 88% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{\text{maj}}$  8.4 min;  $t_{\text{min}}$  10.7 min; 34% ee).  $[\alpha]_{\text{D}}^{20}$  +6 (c 0.58 in  $\text{CHCl}_3$ ). Spectral data were identical to compound **3b**.

**(R)-Benzyl 1-(dimethoxyphosphoryl)-3-phenylpropylcarbamate (3d).** Following the general procedure the title compound was obtained as a white solid in 95% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{\text{maj}}$  12.4 min;  $t_{\text{min}}$  14.7 min; 84% ee). mp  $80\text{--}82\text{ }^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{20}$  -17 (c 0.62 in  $\text{CHCl}_3$ );  $\delta_{\text{H}}$  [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.83-1.97 (1 H, m), 2.11-2.23 (1 H, m), 2.61-2.72 (1 H, m), 2.76-2.85 (1 H, m), 3.70 (3 H, d,  $J$  10.1), 3.73 (3 H, d,  $J$  11.6), 3.99 (0.1 H, br s), 4.09-4.22 (0.9 H, m), 4.95 (0.1 H, br s), 5.12 (1 H, d,  $J$  11.7), 5.17 (0.9 H, br s), 5.17 (1 H, d,  $J$  11.7), 7.10-7.21 (3 H, m), 7.22-7.30 (2 H, m), 7.30-7.40 (5 H, m);  $\delta_{\text{C}}$  31.6 (d,  $J$  4), 32.0 (d,  $J$  14), 47.0 (d,  $J$  156), 52.0 (d,  $J$  6), 53.1 (d,  $J$  7), 67.2, 126.1, 128.0, 128.2, 128.4, 128.5, 136.2, 140.7, 155.9 (d,  $J$  5);  $\delta_{\text{P}}$  27.7  $m/z$  (ESI) 400 [ $\text{M}^+$  + Na].

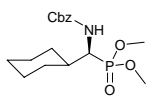
**(R)-tert-Butyl cyclohexyl(dimethoxyphosphoryl)methylcarbamate (3e).** Following the general procedure the title compound was obtained as a white solid in 94% yield. The ee of the product was determined by HPLC, after conversion into its Cbz derivative **3f** through Boc deprotection followed by CbzCl derivatisation (*vide supra*), using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{\text{maj}}$  10.8 min;  $t_{\text{min}}$  13.7 min; 82% ee). mp  $59\text{--}60\text{ }^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{20}$  -11 (c 0.47 in  $\text{CHCl}_3$ );  $\delta_{\text{H}}$  [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 0.99-1.33 (6

H, m), 1.45 (9 H, s), 1.60-1.91 (5 H, m), 3.76 (6 H, d,  $J$  10.4), 3.99 (1 H, ddd,  $J$  4.5, 10.7 and 18.4), 4.52 (0.1 H, br d,  $J$  12.1), 4.78 (0.9 H, d,  $J$  11.4);  $\delta_C$  25.8 (d,  $J$  12), 26.0, 27.9, 28.0, 28.2, 30.4 (d,  $J$  12), 38.5 (d,  $J$  5), 51.2 (d,  $J$  152), 52.3 (d,  $J$  7), 52.8 (d,  $J$  7), 80.0, 155.5 (d,  $J$  5);  $\delta_P$  28.1;  $m/z$  (ESI) 344 [ $M^+$  + Na].

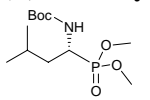
**(R)-Benzyl cyclohexyl(dimethoxyphosphoryl)methylcarbamate (3f).** Following the general procedure the title compound was obtained as a white solid in 93% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{maj}$  10.8 min;  $t_{min}$  13.7 min; 89% ee). mp 86-88 °C;  $[\alpha]_D^{20}$  -6 (*c* 0.54 in CHCl<sub>3</sub>);  $\delta_H$  0.97-1.31 (5H, m), 1.58-1.92 (6H, m), 3.69 (3H, d,  $J$  9.3), 3.74 (3H, d,  $J$  10.4), 3.87-3.97 (0.1 H, m), 4.03 (0.9H, ddd,  $J$  4.3, 10.7 and 18.9), 4.80 (0.1 H, br d,  $J$  11.3), 5.06 (0.9H, br d,  $J$  10.6), 5.09 (1H, d,  $J$  12.3), 5.15 (1H, d,  $J$  12.3), 7.30-7.37 (5H, m);  $\delta_C$  25.9 (d,  $J$  12), 26.0, 27.9, 28.0, 30.4 (d,  $J$  11), 38.5 (d,  $J$  4), 52.0 (d,  $J$  150), 52.8 (d,  $J$  6), 52.9 (d,  $J$  6), 67.2, 128.0, 128.2, 128.5, 136.2, 156.2;  $\delta_P$  27.5;  $m/z$  (ESI) 378 [ $M^+$  + Na].



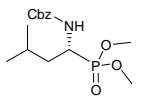
**(S)-Benzyl cyclohexyl(dimethoxyphosphoryl)methylcarbamate (ent-3f).** Following the general procedure using catalyst **4g** derived from hydroquinidine (0.010 mmol, 10 mol%), the title compound was obtained as a white solid in 99% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{maj}$  13.7 min;  $t_{min}$  10.8 min; 78% ee).  $[\alpha]_D^{20}$  +5 (*c* 0.68 in CHCl<sub>3</sub>). Spectral data were identical to compound **3f**.



**(R)-tert-Butyl 1-(dimethoxyphosphoryl)-3-methylbutylcarbamate (3g).** Following the general procedure the title compound was obtained as a colourless oil in 93% yield. The ee of the product was determined by HPLC, after conversion into its Cbz derivative **3h** through Boc deprotection followed by CbzCl derivatisation (*vide supra*), using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{maj}$  8.2 min;  $t_{min}$  10.3 min; 83% ee).  $[\alpha]_D^{20}$  -35 (*c* 0.60 in CHCl<sub>3</sub>);  $\delta_H$  [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 0.91 (3 H, d,  $J$  6.8), 0.93 (3 H, d,  $J$  6.8), 1.43 (9 H, s), 1.49-1.59 (2 H, m), 1.67-1.78 (1 H, m), 3.75 (3 H, d,  $J$  10.7), 3.76 (3 H, d,  $J$  10.5), 3.95-4.05 (0.1 H, m), 4.13 (0.9 H, ddd,  $J$  5.5, 10.4 and 20.7), 4.31 (0.1 H, d,  $J$  9.9), 4.57 (0.9 H, d,  $J$  10.4);  $\delta_C$  21.1, 23.2, 24.4 (d,  $J$  13), 28.2, 38.4, 44.7 (d,  $J$  156), 52.9 (d,  $J$  6), 53.1 (d,  $J$  6), 80.0, 155.2;  $\delta_P$  29.2;  $m/z$  (ESI) 318 [ $M^+$  + Na].



**(R)-Benzyl 1-(dimethoxyphosphoryl)-3-methylbutylcarbamate (3h).** Following the general procedure the title compound was obtained as a colourless oil in 66% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{maj}$  8.2 min;  $t_{min}$  10.3 min; 86% ee).  $[\alpha]_D^{20}$  -33 (*c* 0.63 in CHCl<sub>3</sub>);  $\delta_H$  [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 0.93 (3 H, d,  $J$  6.4), 0.94 (3 H, d,  $J$  6.6), 1.52-1.60 (2 H, m), 1.67-1.77 (1 H, m), 3.71 (3 H, d,  $J$  10.4), 3.75 (3 H, d,  $J$  10.4), 4.01-4.09 (0.1 H, m), 4.19 (0.9 H, ddd,  $J$  5.9, 10.4 and 25.7), 4.60 (0.1 H, d,  $J$  11.1), 4.88 (0.9 H, d,  $J$  10.2), 5.08 (1 H, d,  $J$  12.4), 5.15 (1 H, d,  $J$  12.2), 7.28-7.38 (5 H, m);  $\delta_C$  21.0, 23.3, 24.3 (d,  $J$  13), 38.4, 45.5 (d,  $J$  156), 52.9 (d,  $J$  7), 53.0 (d,  $J$  7), 67.1, 127.9, 128.2, 128.5, 136.2, 155.9;  $\delta_P$  28.6;  $m/z$  (ESI) 352 [ $M^+$  + Na].

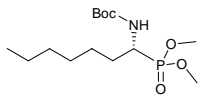


The absolute configuration of compound **3h** was determined to be R by comparison of its optical rotation with a literature value:

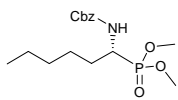
Measured optical rotation (86% ee):  $[\alpha]_D^{20}$  -33 (*c* 0.63 in CHCl<sub>3</sub>)

Lit.<sup>2</sup>  $[\alpha]_D^{20}$  -36.4 (*c* 1 in CHCl<sub>3</sub>) for the (R)-isomer.

**(R)-tert-Butyl 1-(dimethoxyphosphoryl)heptylcarbamate (3i).** Following the general procedure the title compound was obtained as a colourless oil in 84% yield. The ee of the product was determined by HPLC, after conversion into its Cbz derivative through Boc deprotection followed by CbzCl derivatisation (*vide supra*), using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{maj}$  7.4 min;  $t_{min}$  9.4 min; 87% ee).  $[\alpha]_D^{20}$  -25 (*c* 0.53 in CHCl<sub>3</sub>);  $\delta_H$  [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 0.86 (3 H, t,  $J$  6.4), 1.21-1.58 (8 H, m), 1.43 (9 H, s), 1.74-1.85 (2 H, m), 3.76 (3 H, d,  $J$  10.6), 3.77 (3 H, d,  $J$  10.6), 3.85-3.95 (0.1 H, m), 4.05 (0.9 H, dtd,  $J$  3.6, 10.9 and 19.4), 4.32 (0.1 H, br s), 4.62 (0.9 H, d,  $J$  9.8);  $\delta_C$  14.0, 22.5, 25.6 (d,  $J$  14), 28.2, 28.7, 29.8, 31.5, 46.6 (d,  $J$  155), 52.8 (d,  $J$  6), 53.0 (d,  $J$  7), 80.0, 155.3;  $\delta_P$  28.8;  $m/z$  (ESI) 346 [ $M^+$  + Na].



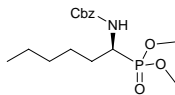
**(R)-Benzyl 1-(dimethoxyphosphoryl)hexylcarbamate (3j).** Following the general procedure the title compound was obtained as a colourless oil in 97% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{maj}$  7.9 min;  $t_{min}$  9.8 min; 95% ee).  $[\alpha]_D^{20}$  -25 (*c* 0.62 in CHCl<sub>3</sub>);  $\delta_H$  [some protons show multiple resonances for the



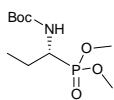
<sup>2</sup> P. A. Bartlett, J. E. Hanson and P. G. Giannousis, *J. Org. Chem.*, 1990, **55**, 6268-6274.

presence of different rotamers due to restricted rotation around the C-N bonds] 0.86 (3 H, t,  $J$  6.7), 1.19-1.52 (6 H, m), 1.76-1.93 (2 H, m), 3.71 (3 H, d,  $J$  10.4), 3.74 (3 H, d,  $J$  10.8), 3.91-4.02 (0.1 H, m), 4.08 (0.9 H, dtd,  $J$  3.8, 10.6 and 20.8), 4.73 (0.1 H, d,  $J$  9.2), 4.98 (0.9 H, d,  $J$  10.4), 5.09 (1 H, d,  $J$  12.2), 5.13 (1 H, d,  $J$  12.2), 7.27-7.37 (5 H, m);  $\delta_{\text{C}}$  13.9, 22.3, 25.3 (d,  $J$  13), 29.7, 31.2, 47.2 (d,  $J$  156), 52.9 (d,  $J$  7), 53.1 (d,  $J$  7), 67.1, 128.0, 128.2, 128.5, 136.3, 156.0;  $\delta_{\text{P}}$  28.2;  $m/z$  (ESI) 366 [ $\text{M}^+$  + Na].

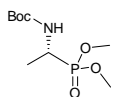
**(S)-Benzyl 1-(dimethoxyphosphoryl)hexylcarbamate (ent-3j).** Following the general procedure using catalyst **4g** derived from hydroquinidine (10 mol%) the title compound was obtained as a colourless oil in 94% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{\text{maj}}$  9.8 min;  $t_{\text{min}}$  7.9 min; 84% ee).  $[\alpha]_{\text{D}}^{20} +22$  (c 0.60 in  $\text{CHCl}_3$ ). Spectral data were identical to compound **3j**.



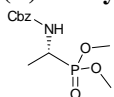
**(R)-tert-Butyl 1-(dimethoxyphosphoryl)propylcarbamate (3k).** Following the general procedure the title compound was obtained as a colourless oil in 78% yield. The ee of the product was determined by HPLC, after conversion into its Cbz derivative through Boc deprotection followed by CbzCl derivatisation (*vide supra*), using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{\text{maj}}$  8.2 min;  $t_{\text{min}}$  10.4 min; 80% ee).  $[\alpha]_{\text{D}}^{20} -27$  (c 0.40 in  $\text{CHCl}_3$ );  $\delta_{\text{H}}$  [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.01 (3 H, t,  $J$  7.6), 1.44 (9 H, s), 1.50-1.64 (1 H, m), 1.82-1.96 (1 H, m), 3.76 (3 H, d,  $J$  10.7), 3.77 (3 H, d,  $J$  10.5), 4.01 (1 H, dtd,  $J$  4.0, 10.3 and 20.5), 4.33 (0.1 H, br s), 4.65 (0.9 H, d,  $J$  10.5);  $\delta_{\text{C}}$  10.4 (d,  $J$  13), 23.3, 28.2, 47.9 (d,  $J$  156), 52.9 (d,  $J$  7), 53.1 (d,  $J$  7), 80.0, 155.5;  $\delta_{\text{P}}$  28.6;  $m/z$  (ESI) 290 [ $\text{M}^+$  + Na].



**(R)-tert-Butyl 1-(dimethoxyphosphoryl)ethylcarbamate (3l).** Following the general procedure the title compound was obtained as a colourless oil in 84% yield. The ee of the product was determined by HPLC, after conversion into its Cbz derivative **3m** through Boc deprotection followed by CbzCl derivatisation (*vide supra*), using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 90:10, flow rate 0.75 mL/min,  $t_{\text{maj}}$  13.8 min;  $t_{\text{min}}$  17.1 min; 79% ee).  $[\alpha]_{\text{D}}^{20} -17$  (c 0.30 in  $\text{CHCl}_3$ );  $\delta_{\text{H}}$  [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.36 (3 H, dd,  $J$  7.4 and 16.9), 1.44 (9 H, s), 3.77 (3 H, d,  $J$  10.6), 3.78 (3 H, d,  $J$  10.6), 4.04-4.21 (1 H, m), 4.46 (0.1 H, br s), 4.75 (0.9 H, d,  $J$  8.9);  $\delta_{\text{C}}$  15.9, 28.2, 42.2 (d,  $J$  158), 52.9 (d,  $J$  7), 53.2 (d,  $J$  7), 80.1, 155.0;  $\delta_{\text{P}}$  29.2;  $m/z$  (ESI) 276 [ $\text{M}^+$  + Na].



**(R)-Benzyl 1-(dimethoxyphosphoryl)ethylcarbamate (3m).** Following the general procedure the title compound was obtained as a colourless oil in 76% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 90:10, flow rate 0.75 mL/min,  $t_{\text{maj}}$  13.8 min;  $t_{\text{min}}$  17.1 min; 80% ee).  $[\alpha]_{\text{D}}^{20} -15$  (c 1.0 in  $\text{CHCl}_3$ );  $\delta_{\text{H}}$  [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.39 (3 H, dd,  $J$  7.4 and 16.6), 3.73 (3 H, d,  $J$  10.8), 3.75 (3 H, d,  $J$  10.8), 4.11-4.26 (1 H, m), 4.85 (0.1 H, br s), 5.09 (0.9 H, d,  $J$  11.0), 5.11 (2 H, s), 7.28-7.37 (5 H, m);  $\delta_{\text{C}}$  15.9, 42.8 (d,  $J$  158), 53.0 (d,  $J$  6), 53.2 (d,  $J$  6), 67.1, 128.1, 128.2, 128.5, 136.1, 155.6;  $\delta_{\text{P}}$  28.6;  $m/z$  (ESI) 310 [ $\text{M}^+$  + Na].

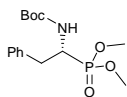


The absolute configuration of compound **3m** was determined to be R by comparison of its optical rotation with a literature value:

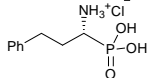
Measured optical rotation (80% ee):  $[\alpha]_{\text{D}}^{20} -15$  (c 1.0 in  $\text{CHCl}_3$ )

Lit.<sup>3</sup>  $[\alpha]_{\text{D}}^{20} -17.5$  (c 1 in  $\text{CHCl}_3$ ) for the (R)-isomer.

**(R)-tert-Butyl 1-(dimethoxyphosphoryl)-2-phenylethylcarbamate (3n).** Following the general procedure the title compound was obtained as a colourless oil in 83% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{\text{maj}}$  10.7 min;  $t_{\text{min}}$  8.3 min; 84% ee).  $[\alpha]_{\text{D}}^{20} -22$  (c 0.73 in  $\text{CHCl}_3$ );  $\delta_{\text{H}}$  [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.20 (2 H, s), 1.38 (7 H, s), 2.61-2.75 (0.2 H, m), 2.83 (0.8 H, td,  $J$  10.2 and 14.5), 3.20 (1 H, ddd,  $J$  5.1, 8.9 and 13.7), 3.76 (6 H, d,  $J$  10.9), 4.12-4.20 (0.2 H, m), 4.41 (0.8 H, dtd,  $J$  4.9, 10.6 and 21.2), 4.49 (0.2 H, br s), 4.68 (0.8 H, br s), 7.19-7.31 (5 H, m);  $\delta_{\text{C}}$  28.1, 36.0, 47.4 (d,  $J$  157), 52.9 (d,  $J$  7), 53.2 (d,  $J$  7), 80.0, 126.7, 128.4, 129.2, 136.5 (d,  $J$  12), 155.0;  $\delta_{\text{P}}$  27.8;  $m/z$  (ESI) 352 [ $\text{M}^+$  + Na].



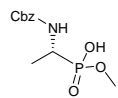
**Preparation of (R)-1-amino-3-phenylpropylphosphonic acid hydrochloride (5).** In a test tube equipped with magnetic stirrer bar was placed phosphonate **3b** (0.1 mmol) in HCl 10 M (1.8 mL). The solution was refluxed for 18 h, which was followed by removal of the solvent under reduced pressure. The title compound was obtained as a white solid in 84% yield. The ee of the product was determined by



<sup>3</sup> J. E. Hanson, A. K. Kaplan and P. A. Bartlett, *Biochemistry*, 1989, **28**, 6294-6305.

HPLC, after conversion into its N-Cbz dimethyl derivative **3d** according to literature procedure,<sup>4</sup> using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 80:20, flow rate 0.75 mL/min,  $t_{\text{maj}}$  12.4 min;  $t_{\text{min}}$  14.7 min; 85% ee). mp > 300 °C (dec.);  $[\alpha]_{\text{D}}^{20}$  -17 (*c* 0.48 in 1 N NaOH<sub>aq</sub>);  $\delta_{\text{H}}$  (D<sub>2</sub>O/NaOH) 1.64 (1 H, br s), 2.07 (1 H, br s), 2.47-2.76 (2 H, m), 2.82-3.00 (1 H, m), 7.27 (1 H, br s), 7.37 (4 H, br s);  $\delta_{\text{C}}$  (D<sub>2</sub>O/NaOH) 35.9 (d, *J* 13.5), 37.0, 52.7 (d, *J* 138), 128.8, 131.6, 146.2;  $\delta_{\text{P}}$  (D<sub>2</sub>O/NaOH) 22.0 *m/z* (ESI) 216 [ $\text{M}^+ + \text{H}$ ].

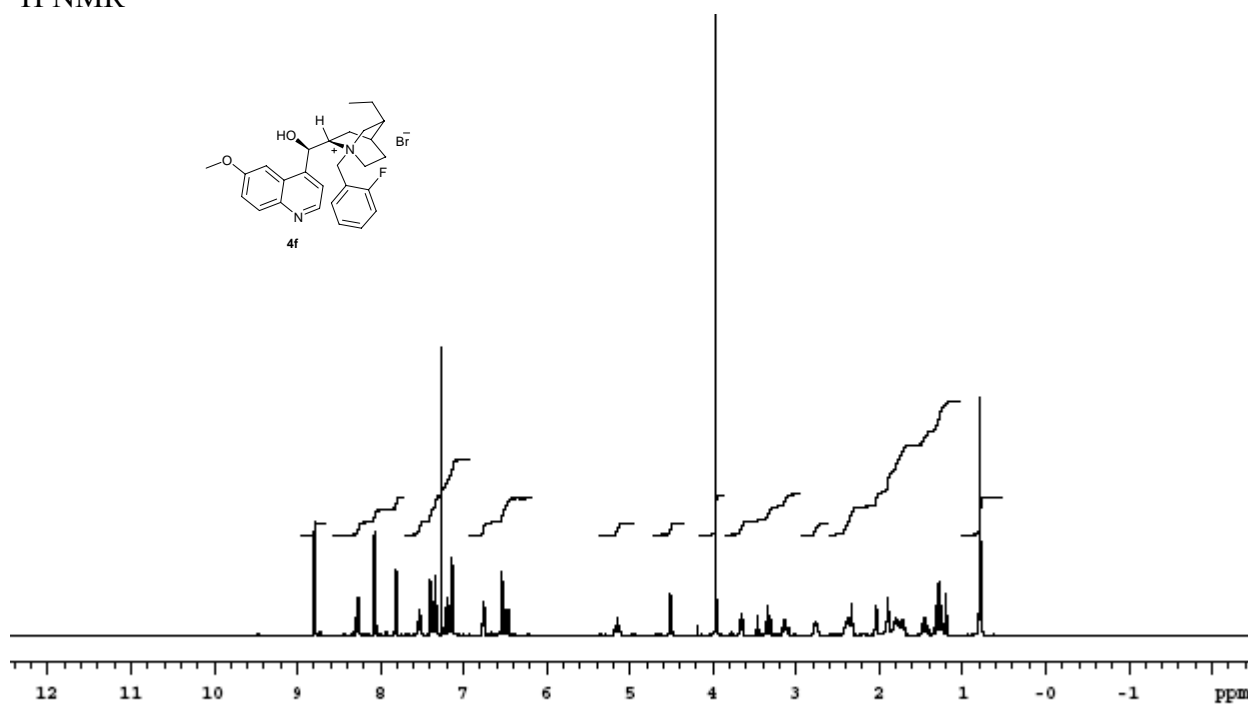
**Preparation of (R)-benzyl 1-(monomethoxyphosphoryl)ethylcarbamate (6).** In a test tube equipped with magnetic stirrer bar was placed phosphonate **3m** (0.076 mmol) in NaOH 2 M (0.1 ml). The mixture was stirred at 20 °C overnight. After dilution with H<sub>2</sub>O (5 mL), the solution was washed twice with CHCl<sub>3</sub>, acidified with 0.7 mL of concentrated HCl, and extracted 4 times with CHCl<sub>3</sub>. The combined CHCl<sub>3</sub> extracts were dried (MgSO<sub>4</sub>), filtered and the solvent was evaporated to give the title compound was obtained as a pale yellow waxy solid in 88% yield. The ee of the product was determined by HPLC, after conversion into its dimethyl derivative **3m** according to literature procedure,<sup>4</sup> using a Daicel Chiralpak AD-H column (hexane/*i*PrOH 90:10, flow rate 0.75 mL/min,  $t_{\text{maj}}$  13.8 min;  $t_{\text{min}}$  17.1 min; 80% ee).  $\delta_{\text{H}}$  [some protons show multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 1.35 (3 H, dd, *J* 7.4 and 17.4), 3.72 (3 H, d, *J* 11.2), 3.92-4.31 (1 H, m), 5.11 (1 H, s), 5.28 (0.85 H, br s), 5.67 (0.15 H, br s), 7.34 (5 H, br s) 8.30 (1 H, br s);  $\delta_{\text{C}}$  15.6, 43.0 (d, *J* 161), 52.6 (d, *J* 6), 67.2, 128.1, 128.2, 128.5, 136.1, 155.8;  $\delta_{\text{P}}$  [<sup>31</sup>P spectrum shows multiple resonances for the presence of different rotamers due to restricted rotation around the C-N bonds] 28.3 (0.15 P), 28.9 (0.85 P).



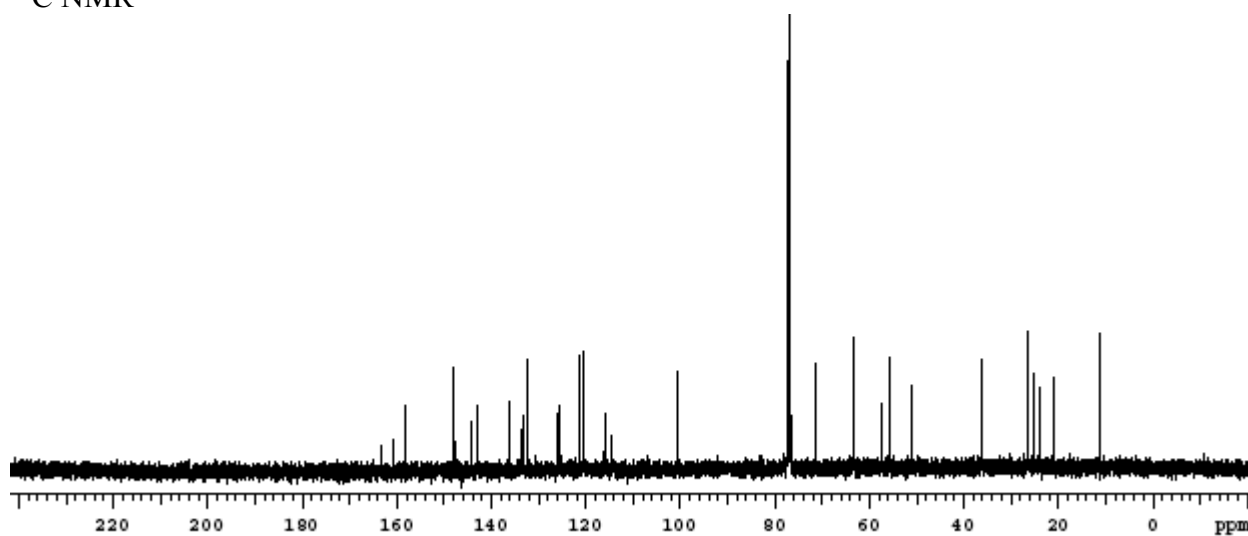
<sup>4</sup> G. D. Joly and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 4102-4103.

Copies of the  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$  and  $^{31}\text{P}$  NMR spectra for compounds **4f**, **4g**, **3b**, **3d-n**, **5** and **6**.

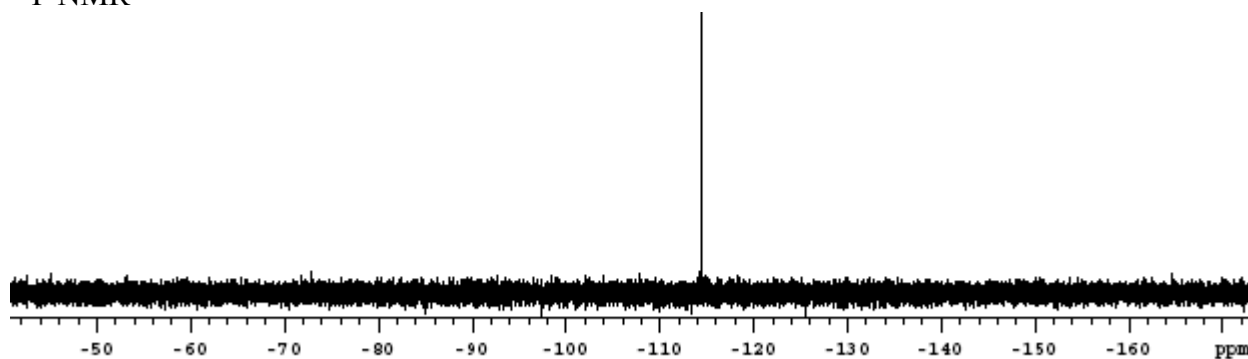
$^1\text{H}$  NMR



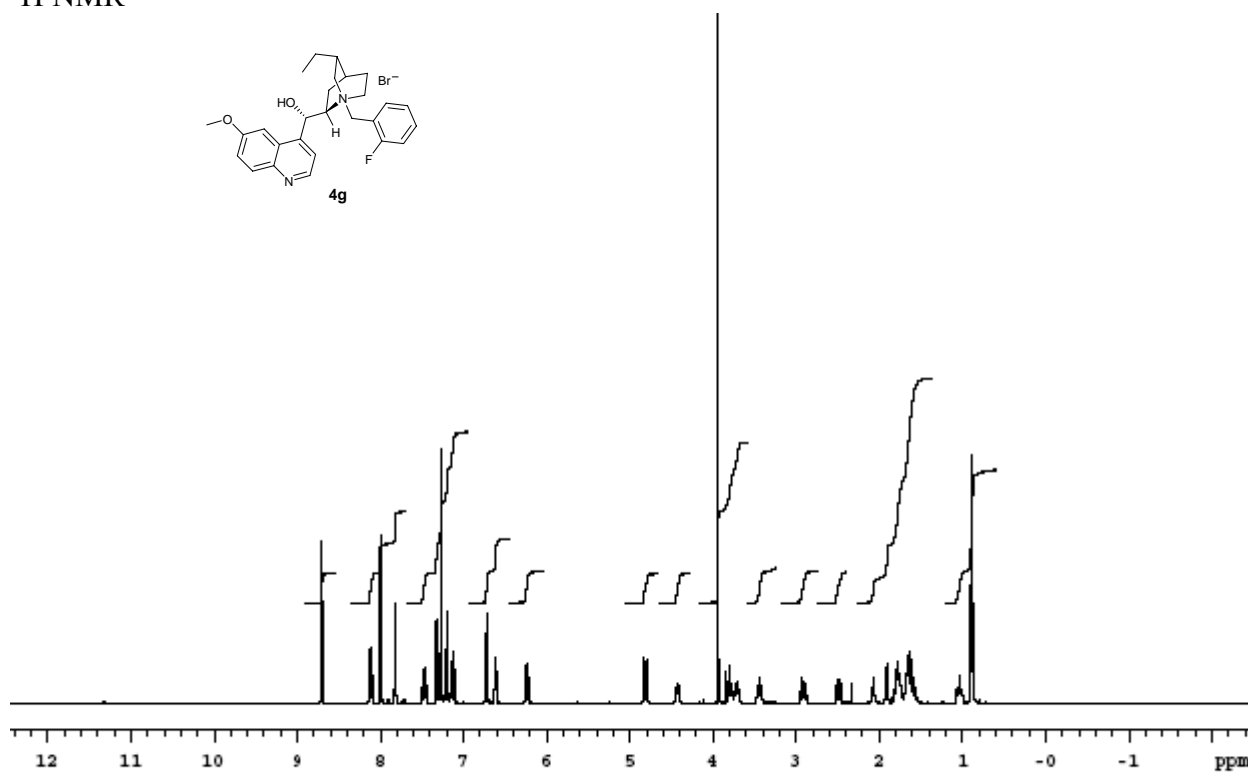
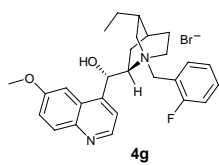
$^{13}\text{C}$  NMR



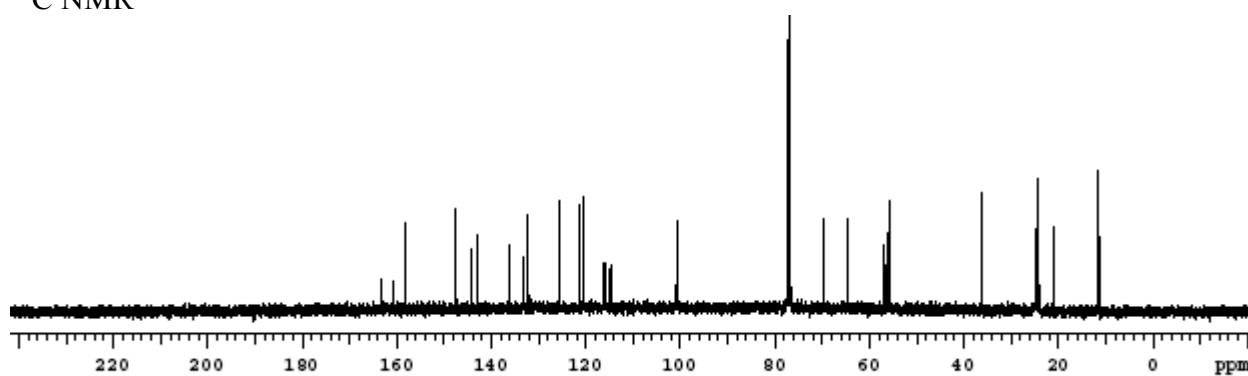
$^{19}\text{F}$  NMR



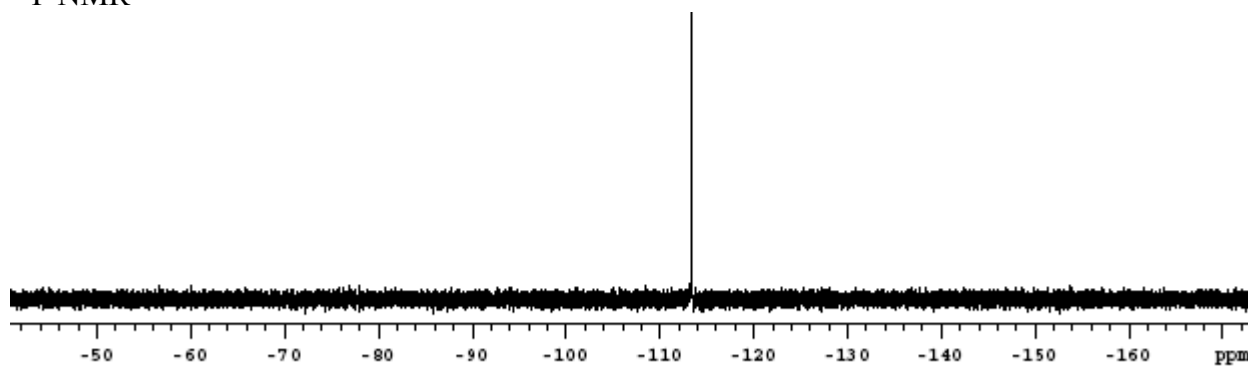
$^1\text{H}$  NMR



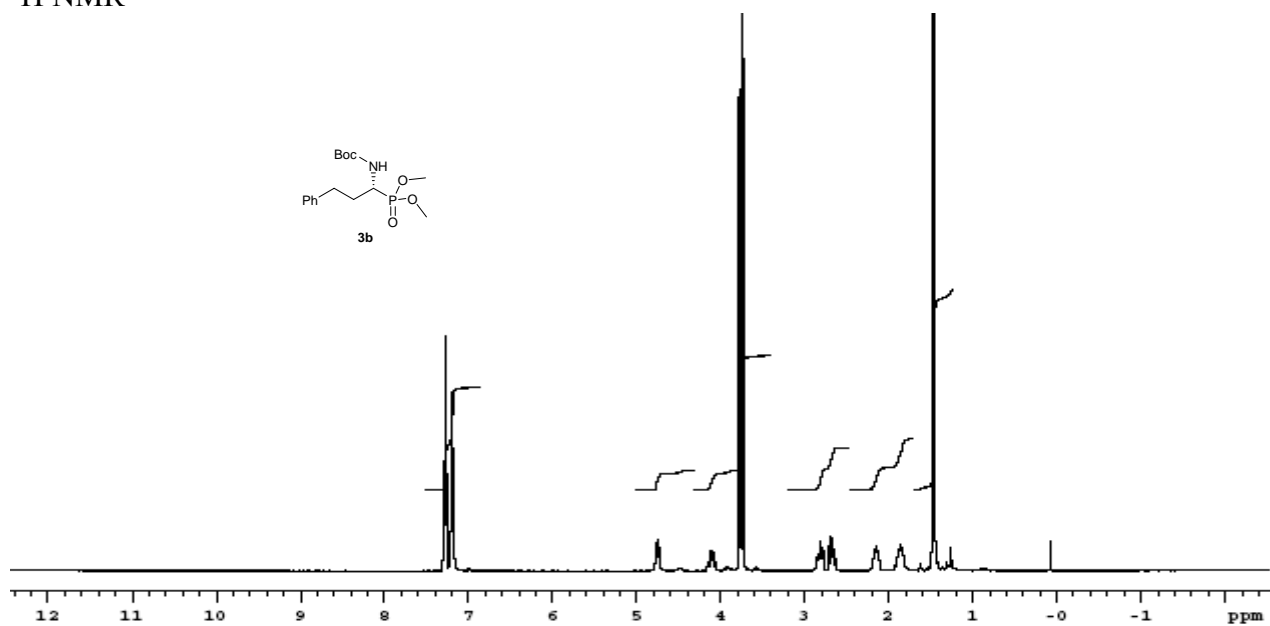
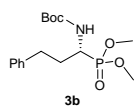
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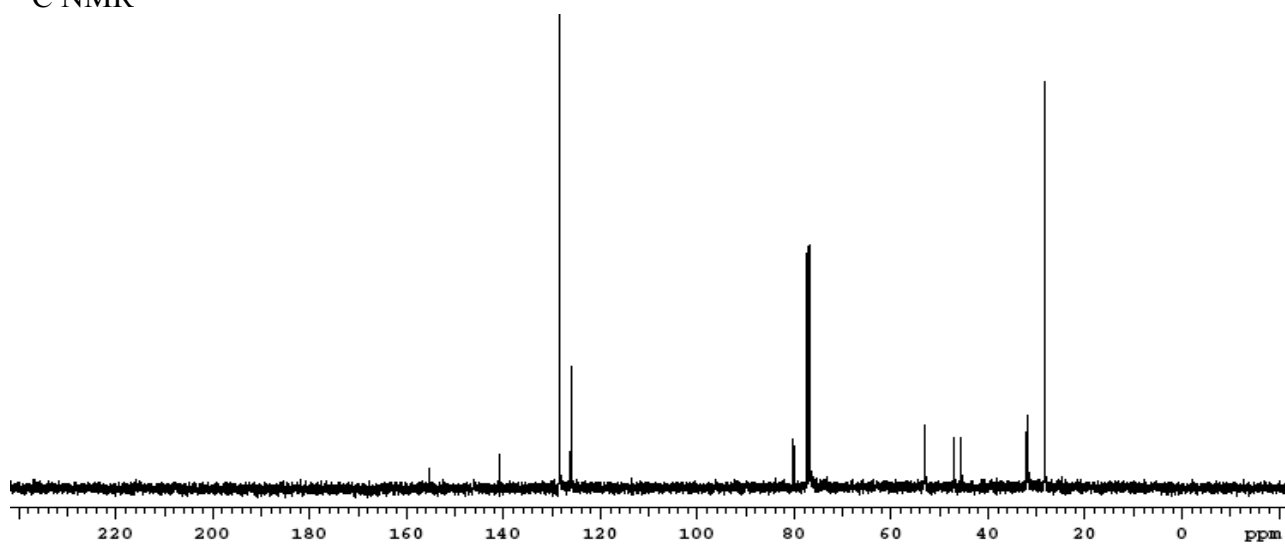
$^{19}\text{F}$  NMR



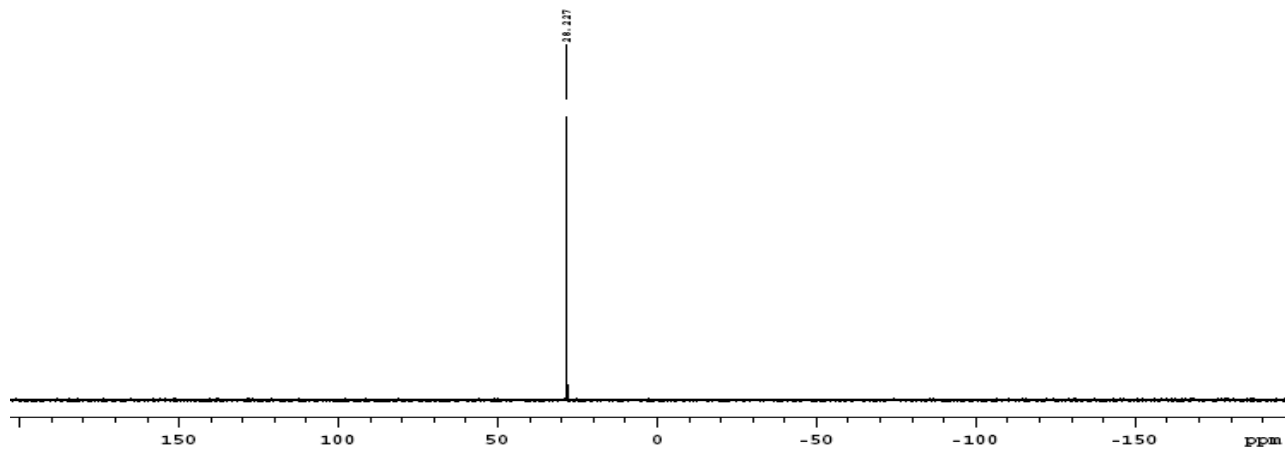
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$^{13}\text{C}$  NMR

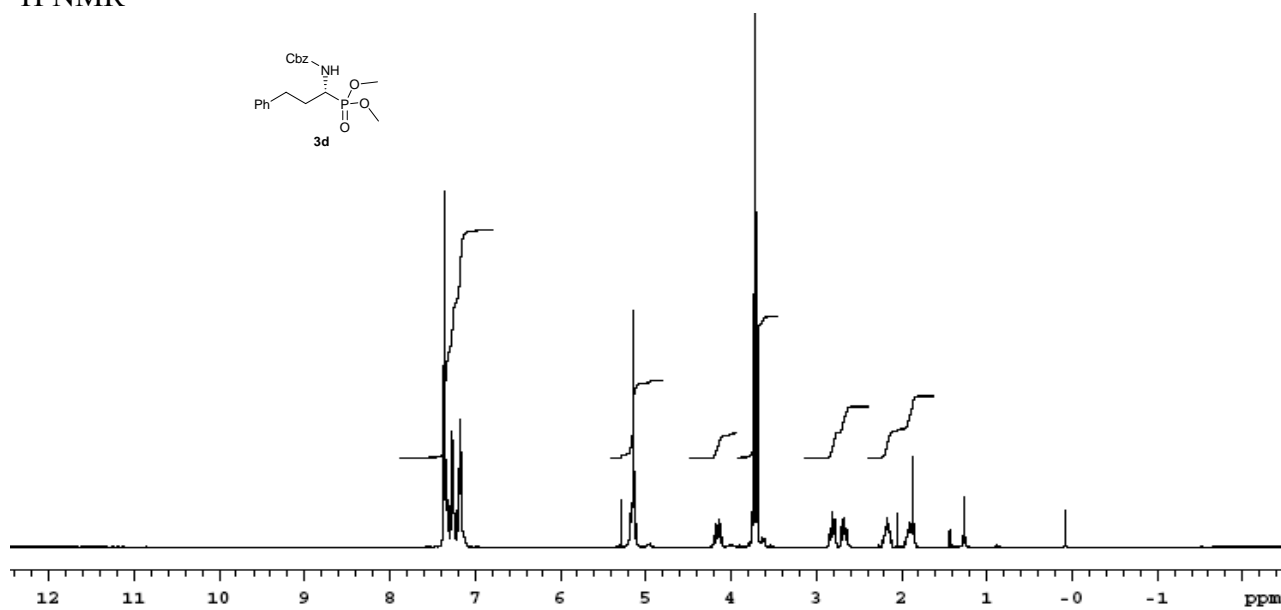
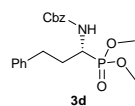


$^{31}\text{P}$  NMR

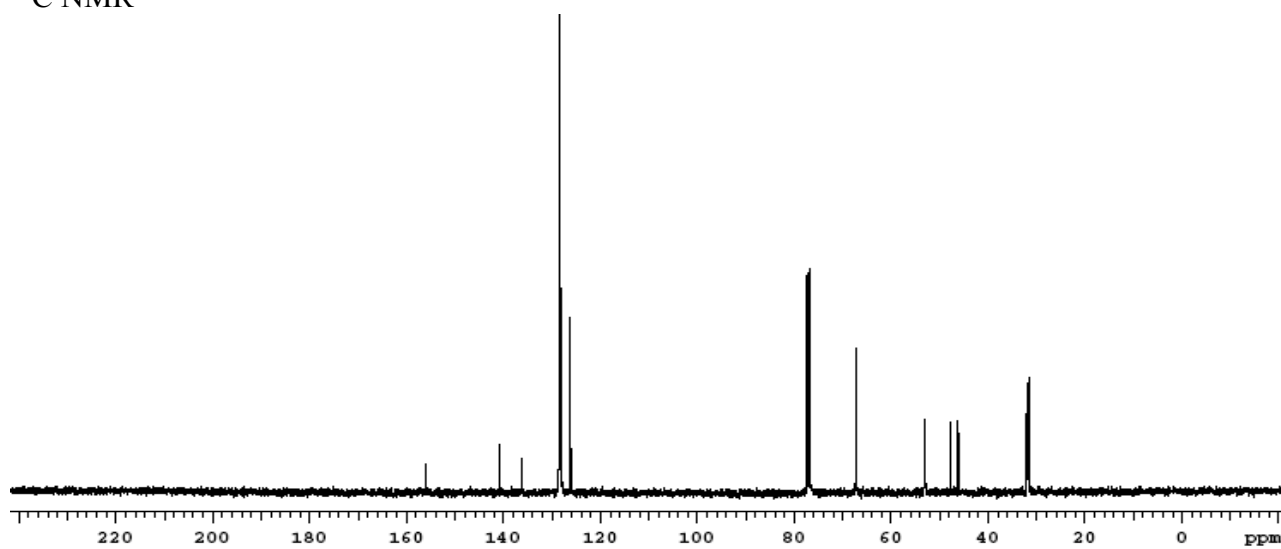




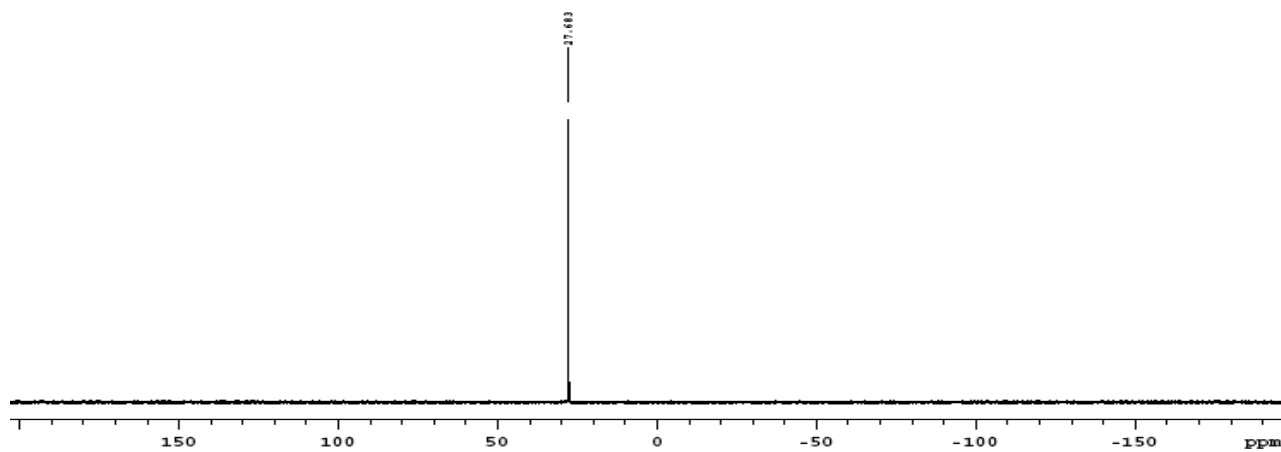
$^1\text{H}$  NMR



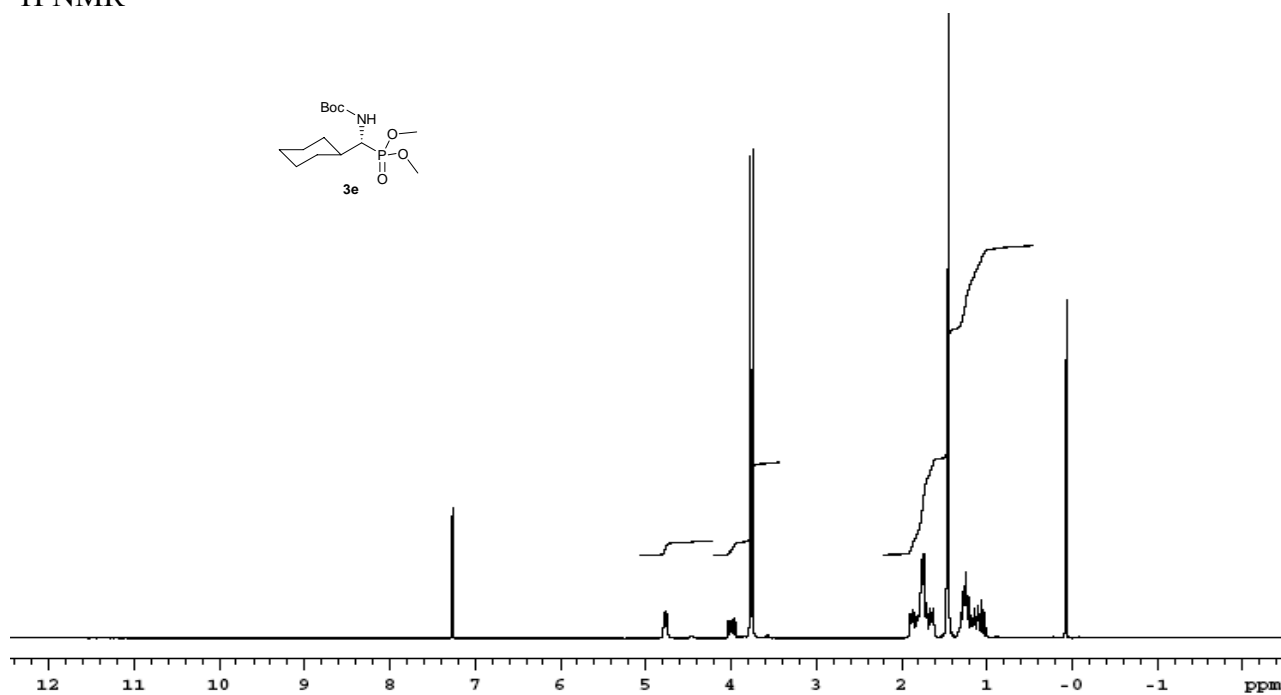
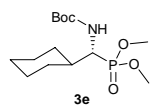
$^{13}\text{C}$  NMR



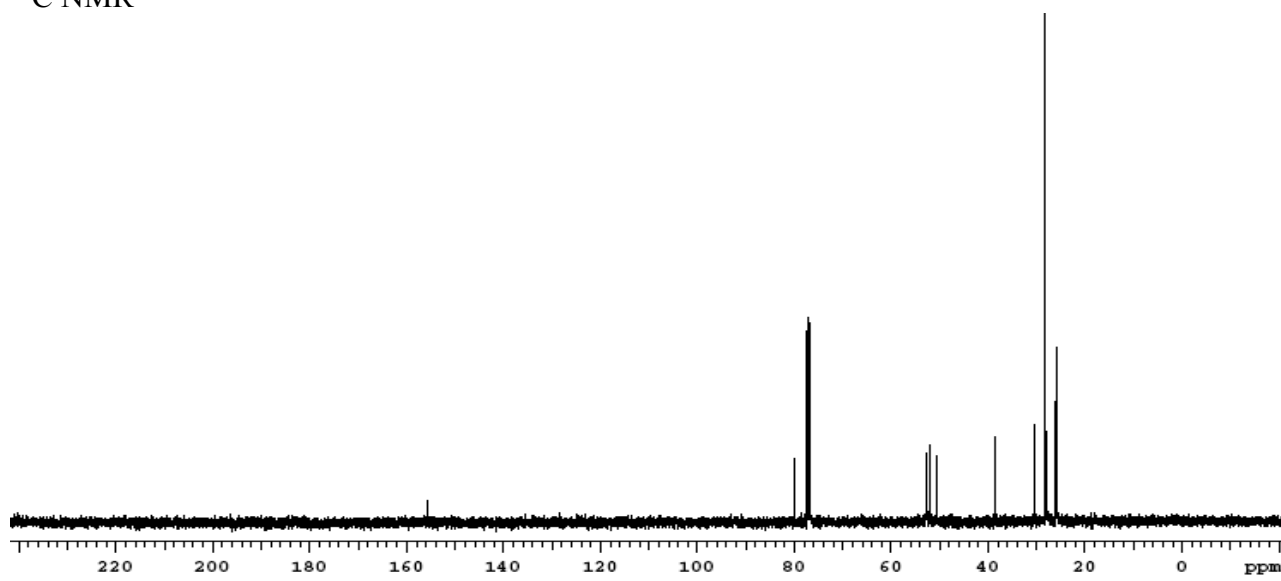
$^{31}\text{P}$  NMR



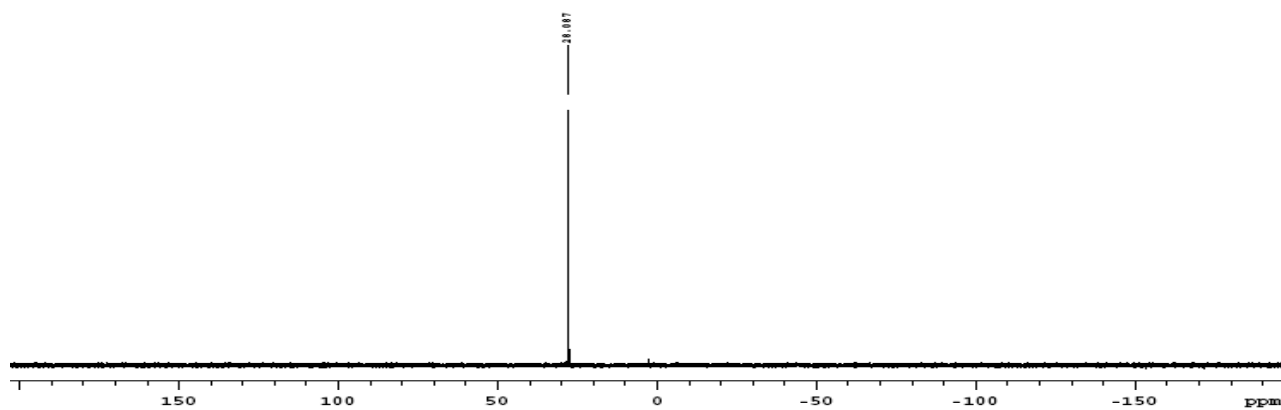
$^1\text{H}$  NMR



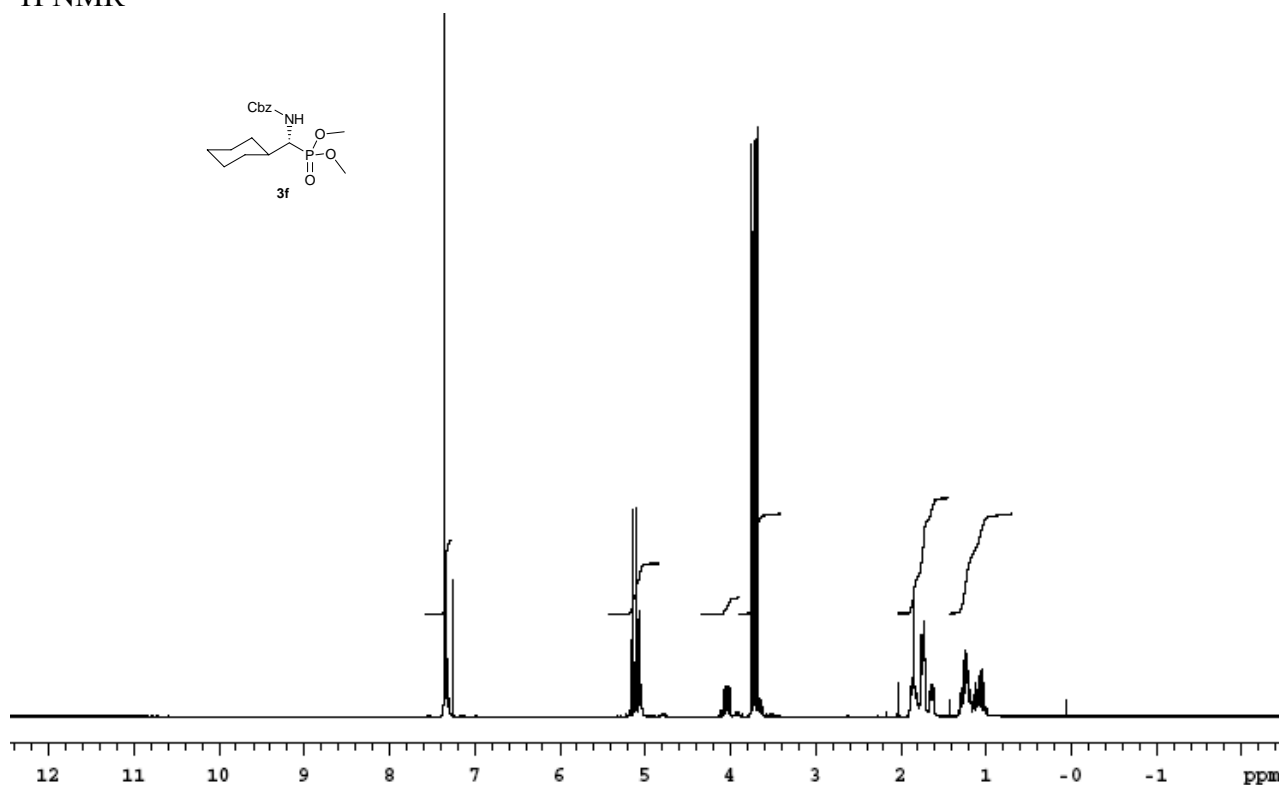
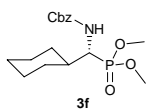
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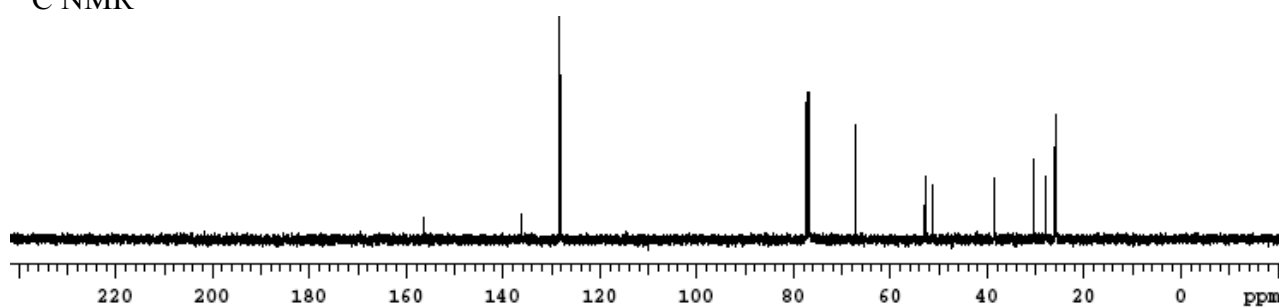
$^{31}\text{P}$  NMR



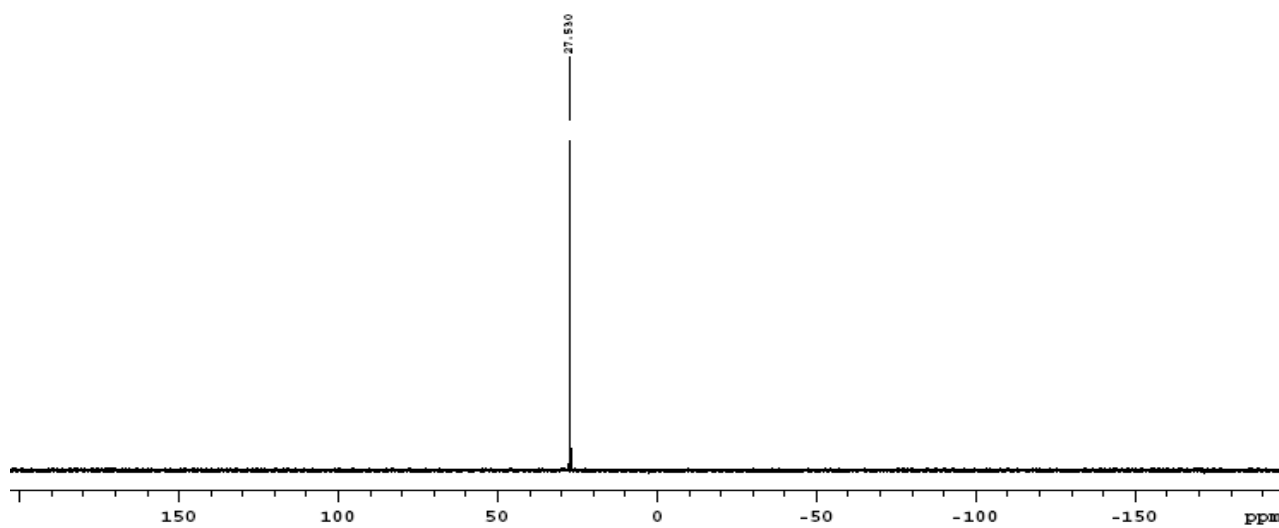
$^1\text{H}$  NMR



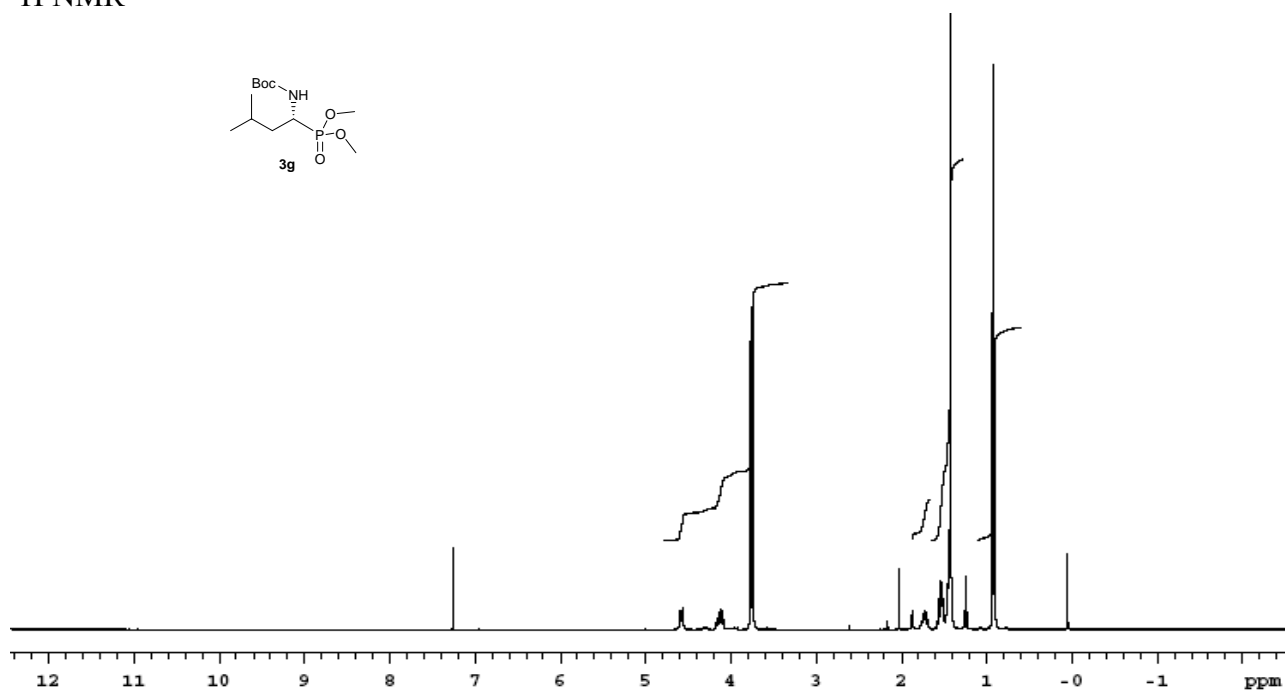
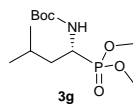
$^{13}\text{C}$  NMR



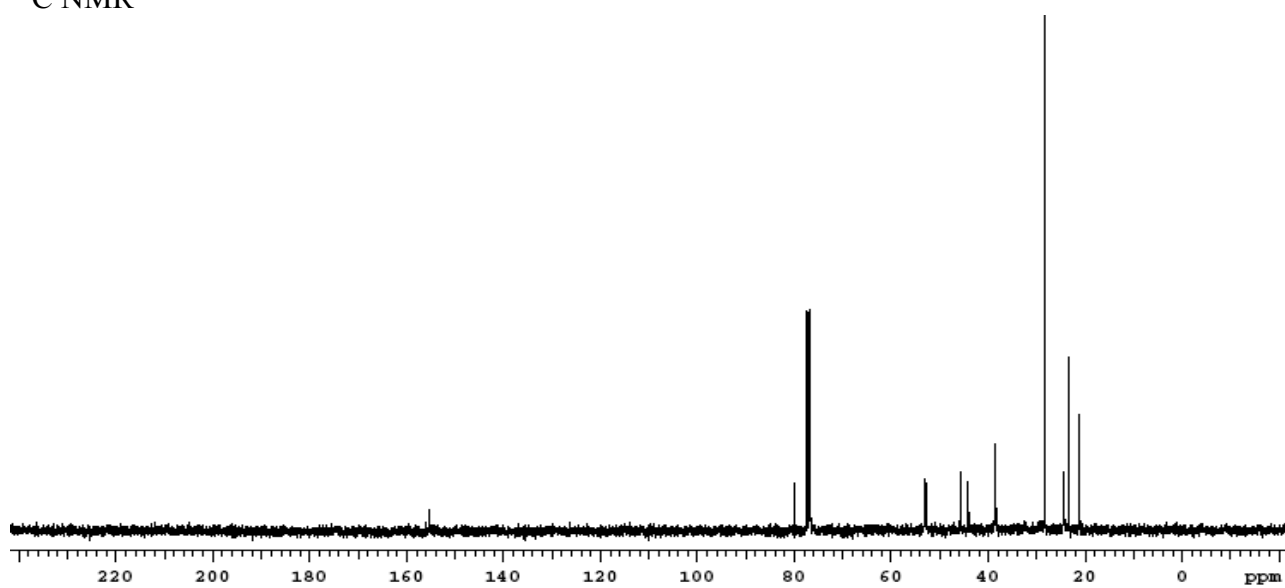
$^{31}\text{P}$  NMR



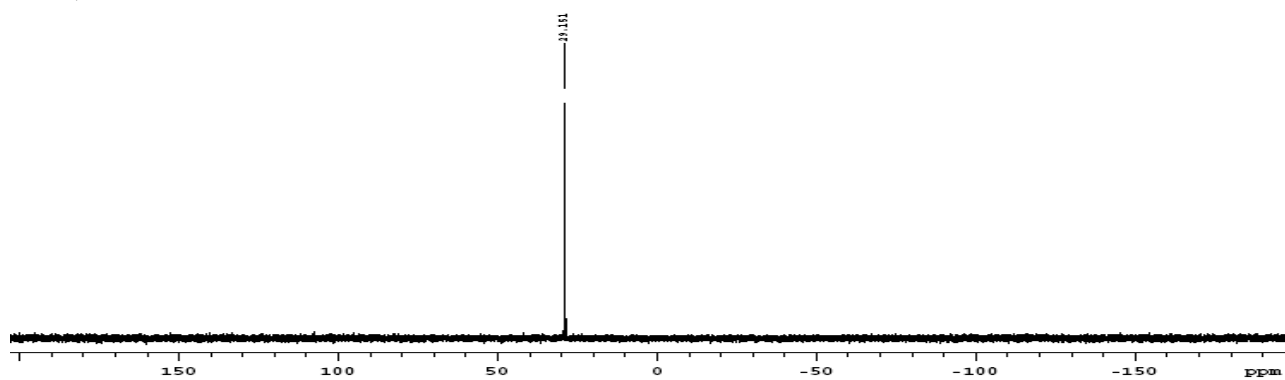
$^1\text{H}$  NMR



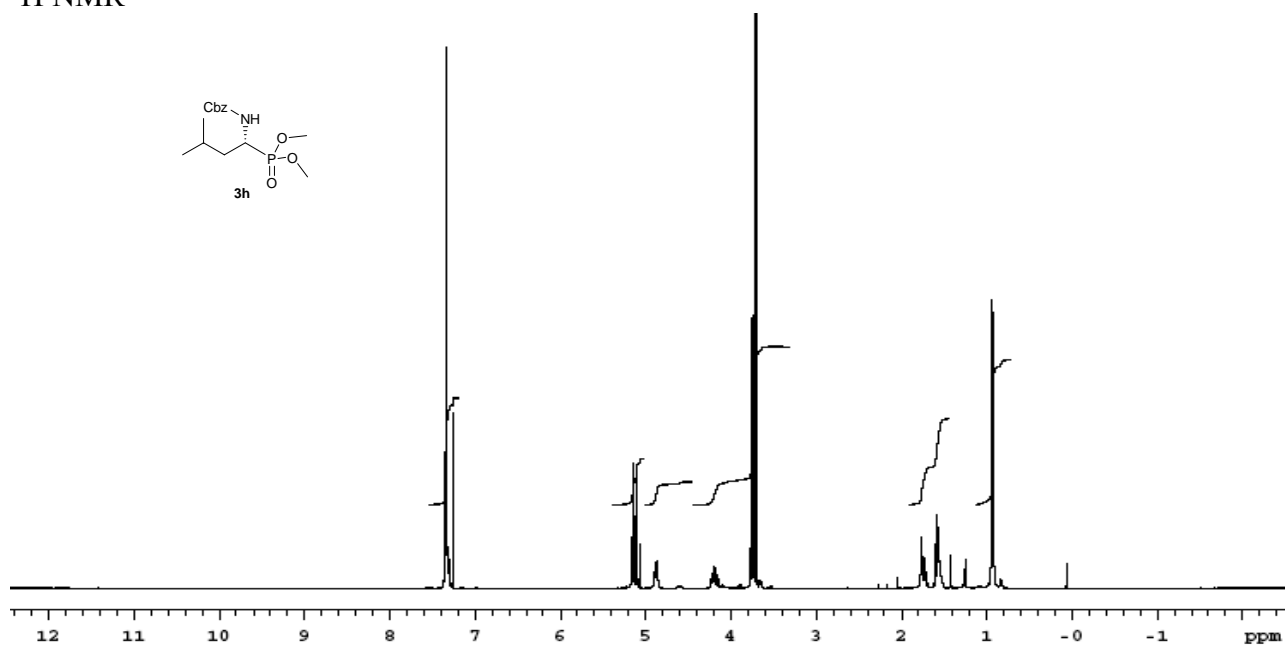
$^{13}\text{C}$  NMR



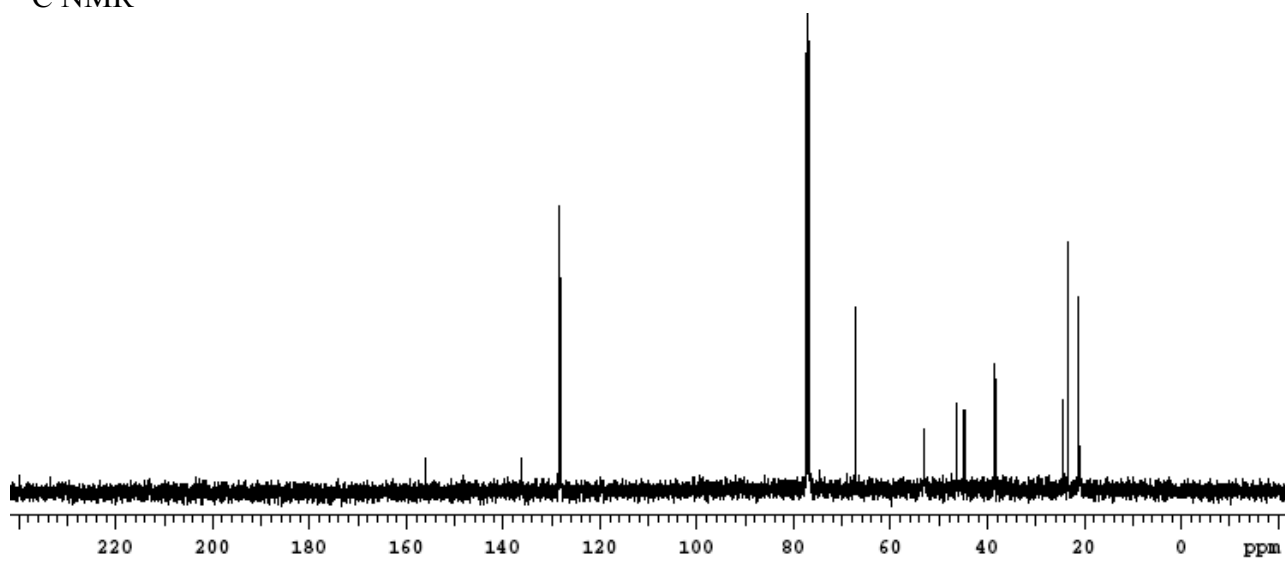
$^{31}\text{P}$  NMR



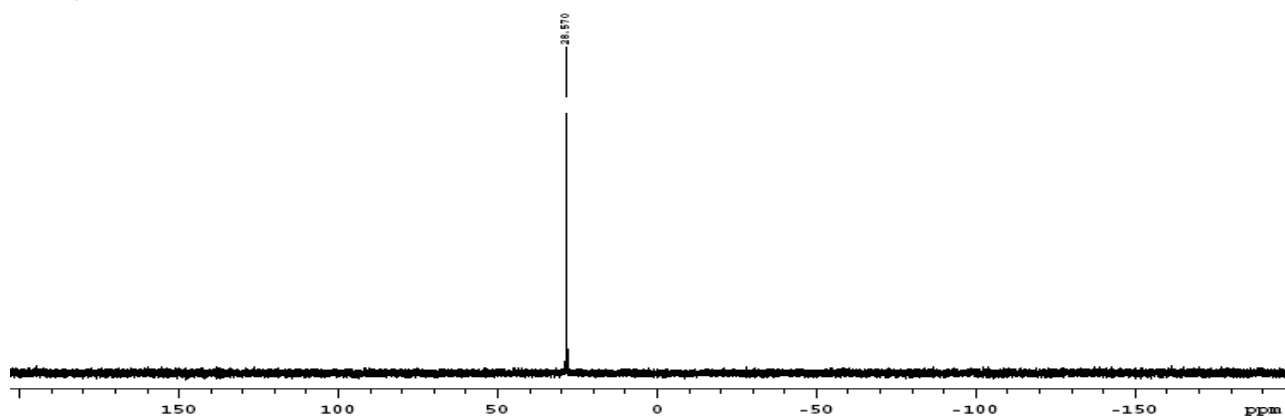
$^1\text{H}$  NMR



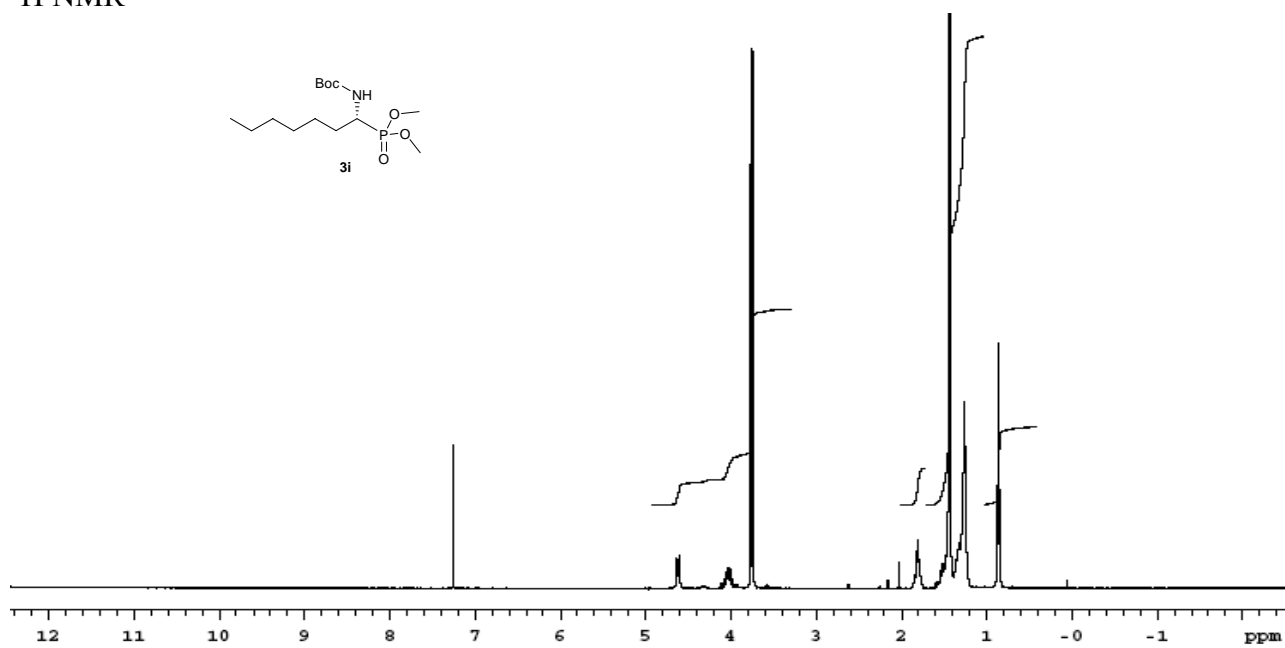
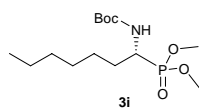
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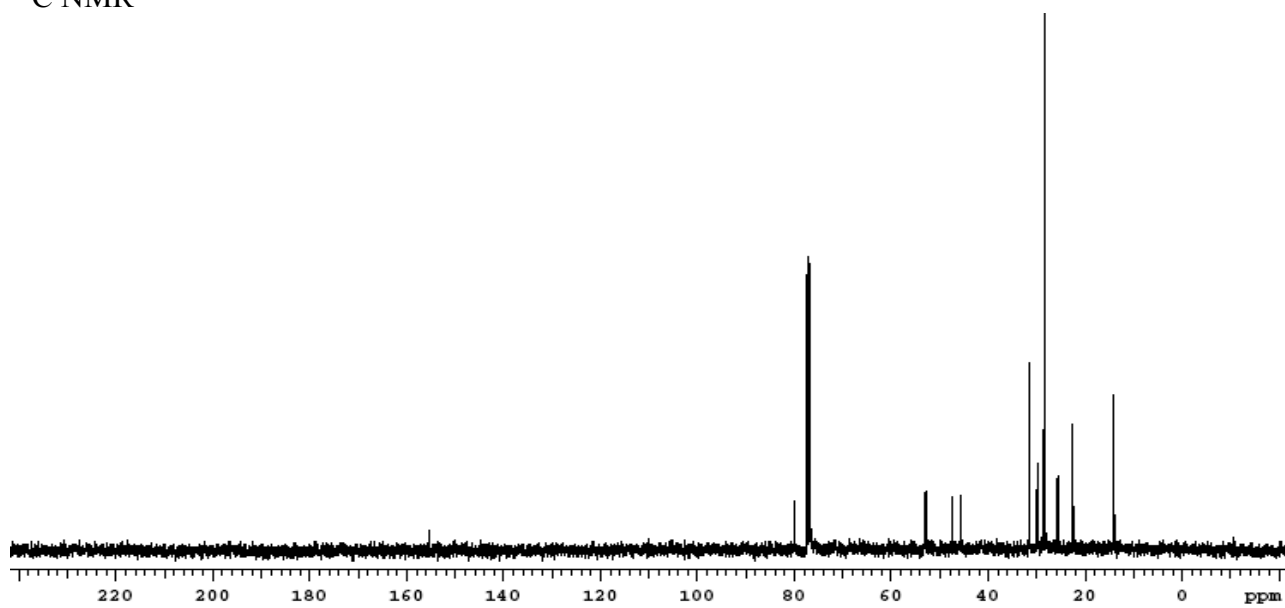
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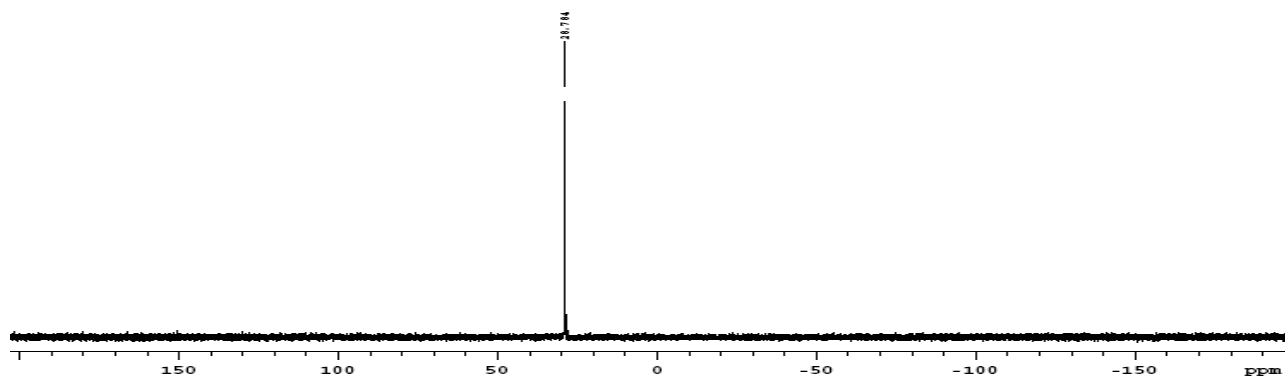
$^1\text{H}$  NMR



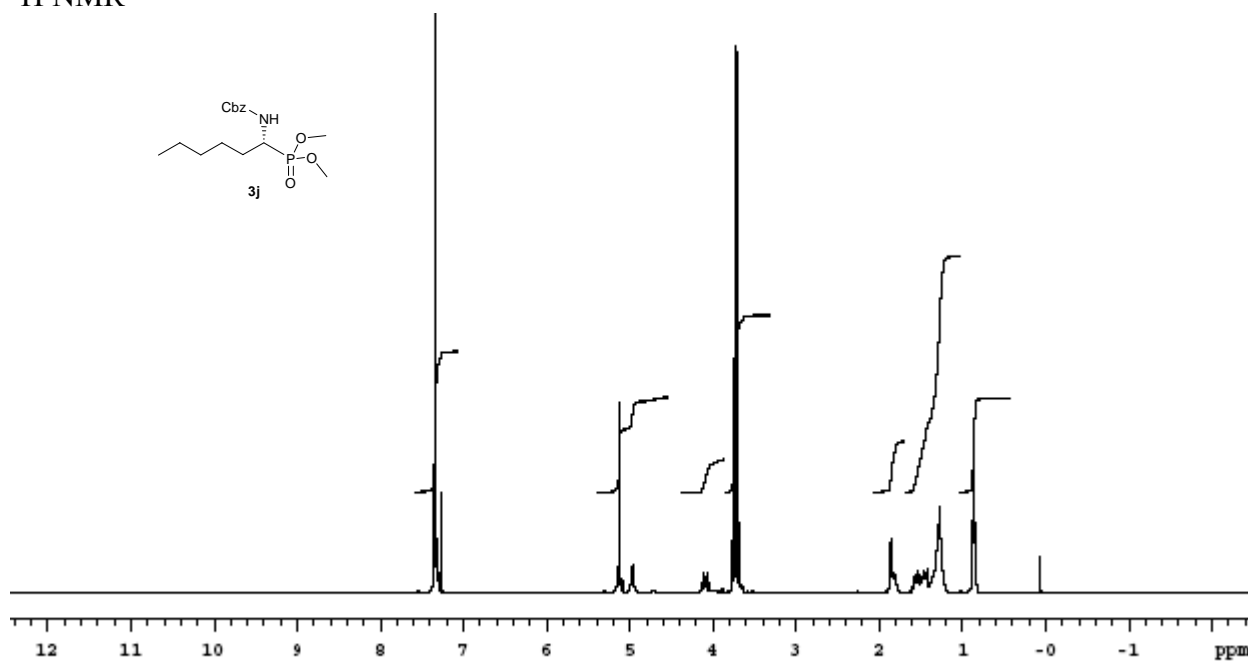
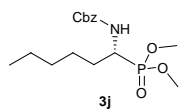
$^{13}\text{C}$  NMR



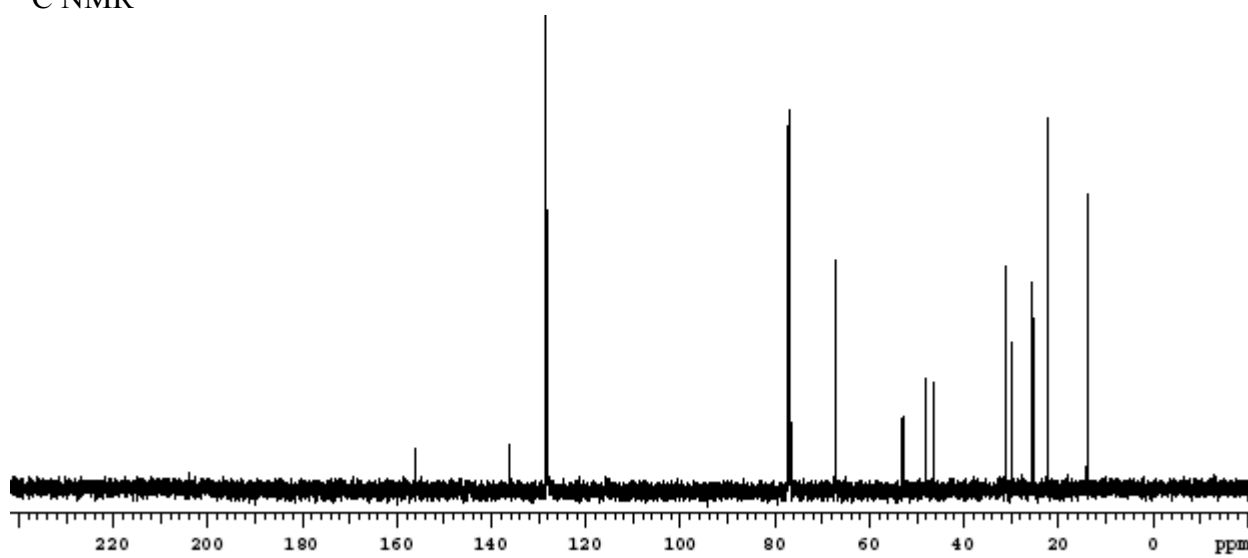
$^{31}\text{P}$  NMR



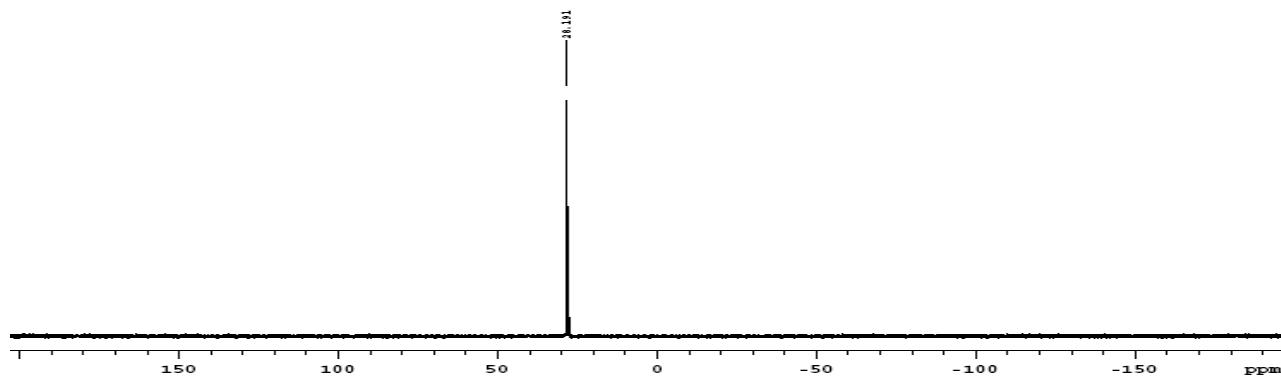
$^1\text{H}$  NMR



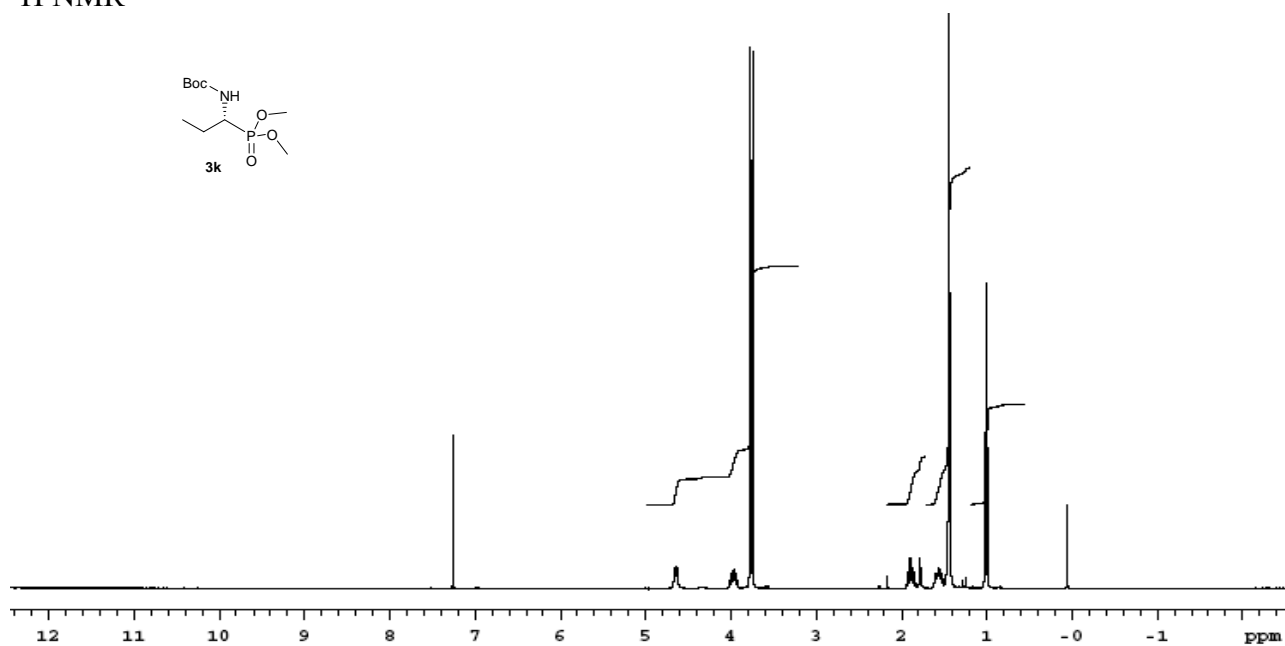
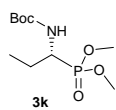
$^{13}\text{C}$  NMR



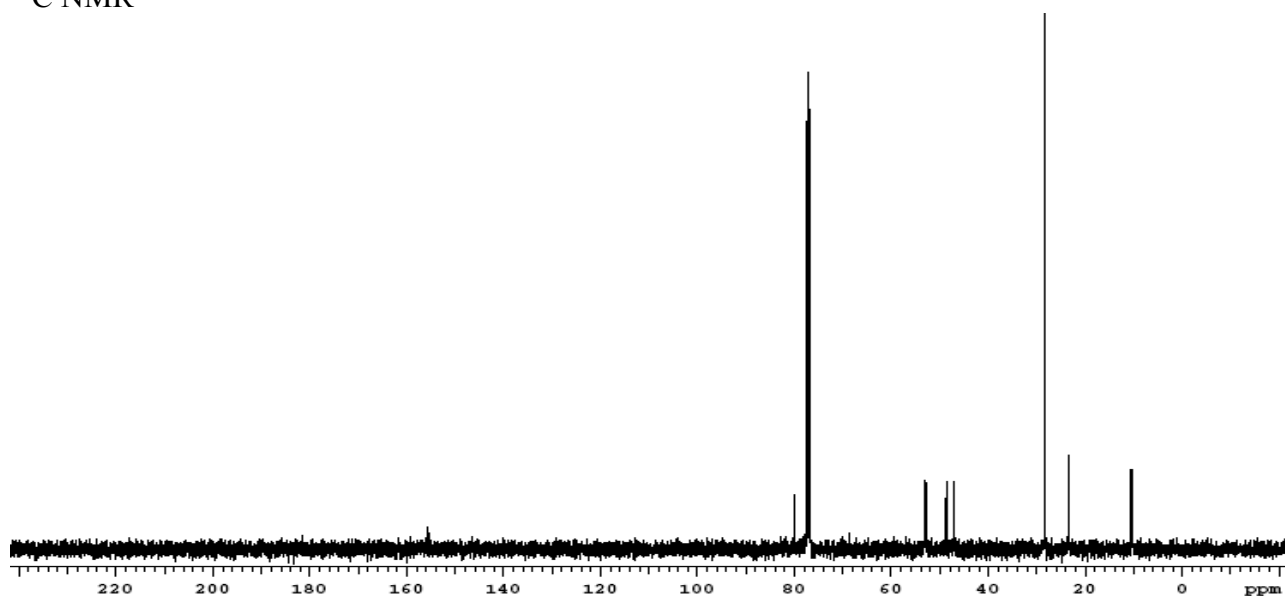
$^{31}\text{P}$  NMR



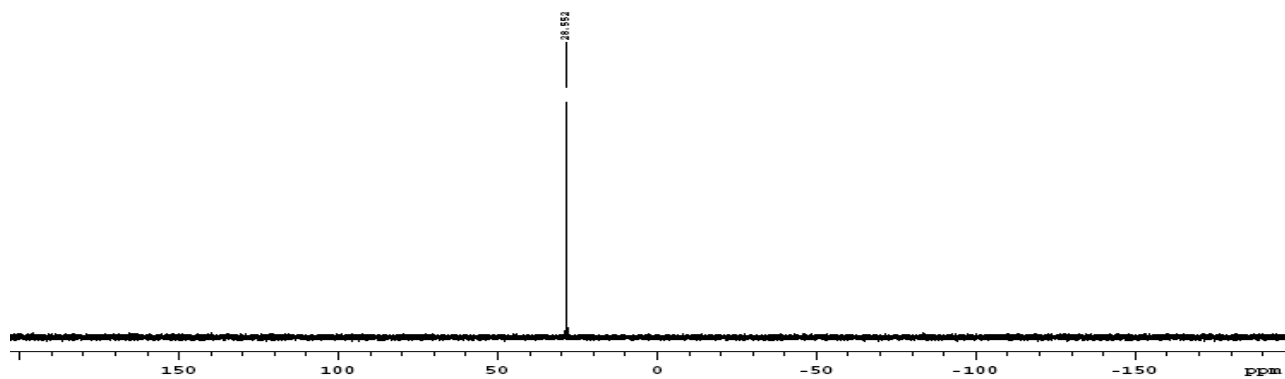
$^1\text{H}$  NMR



$^{13}\text{C}$  NMR

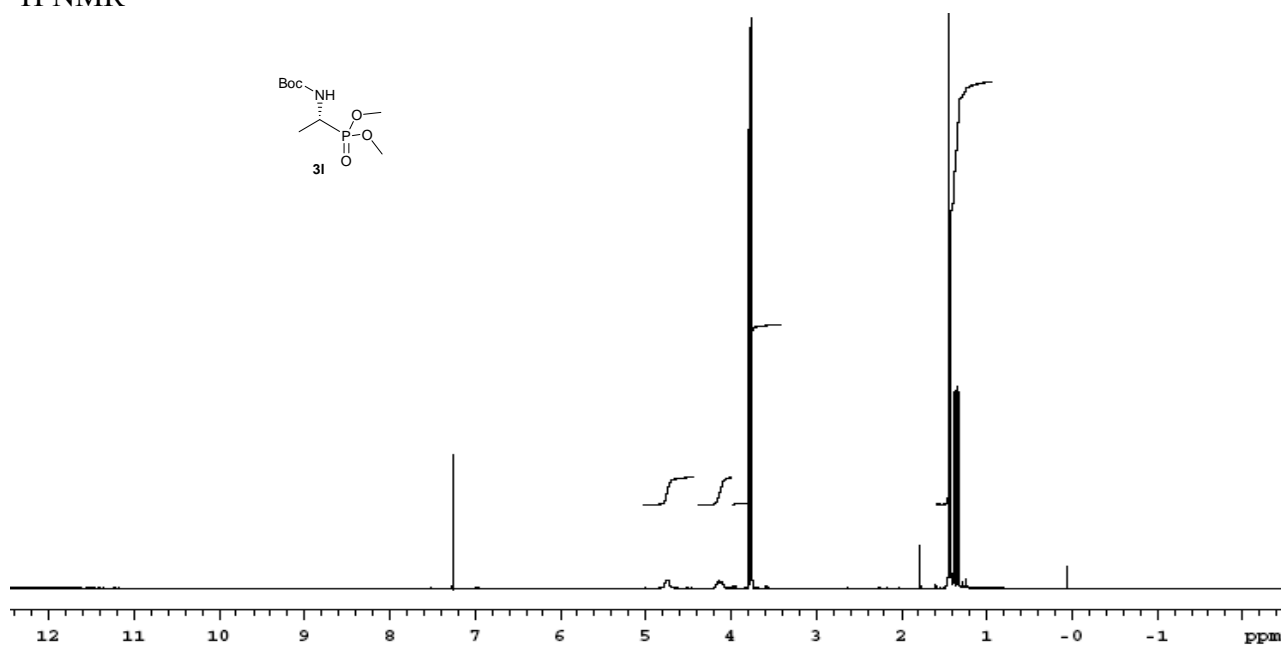
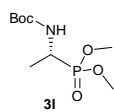


$^{31}\text{P}$  NMR

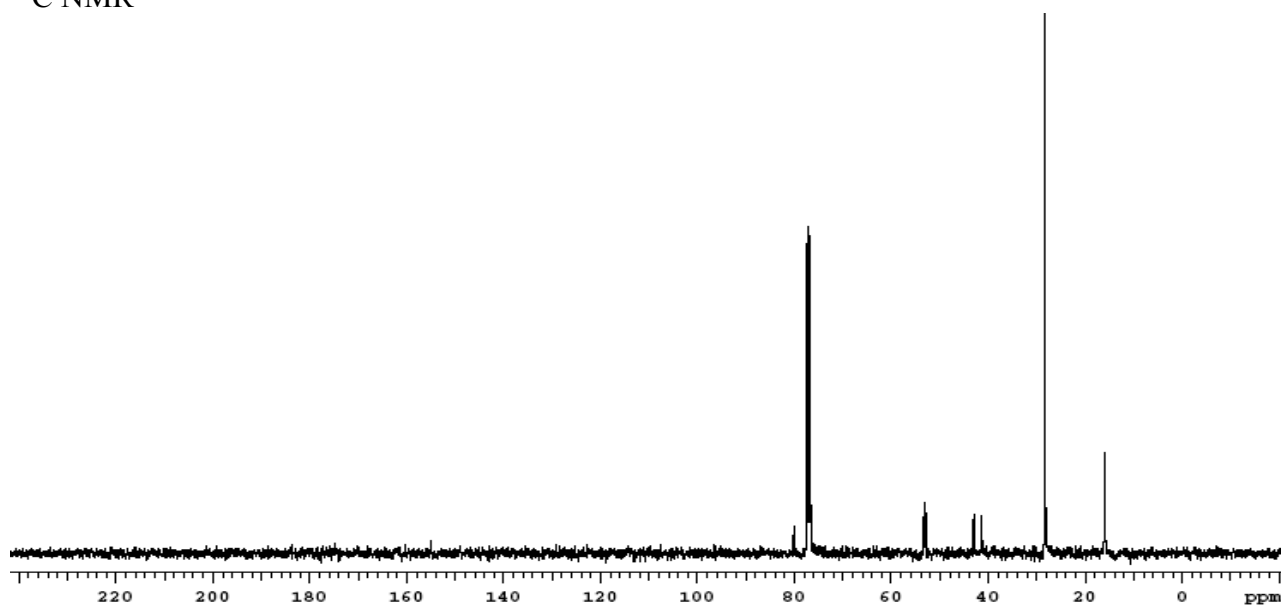




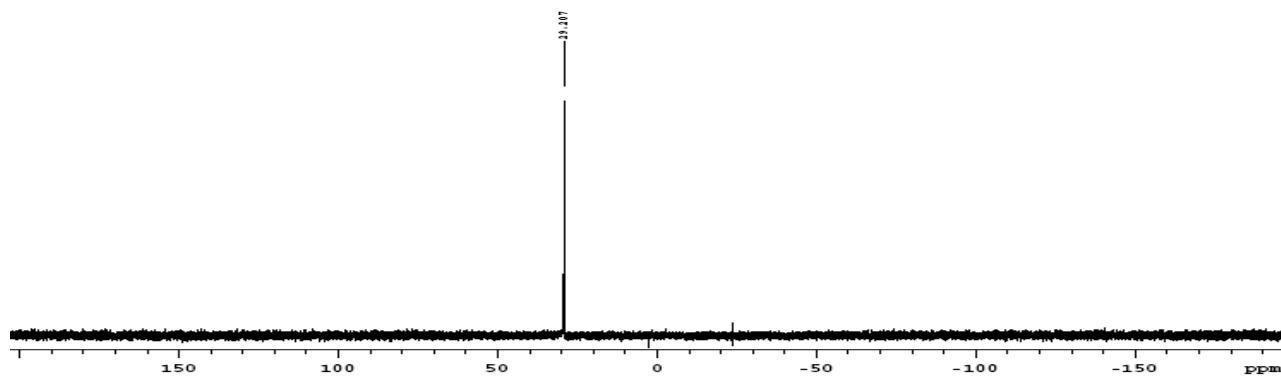
$^1\text{H}$  NMR



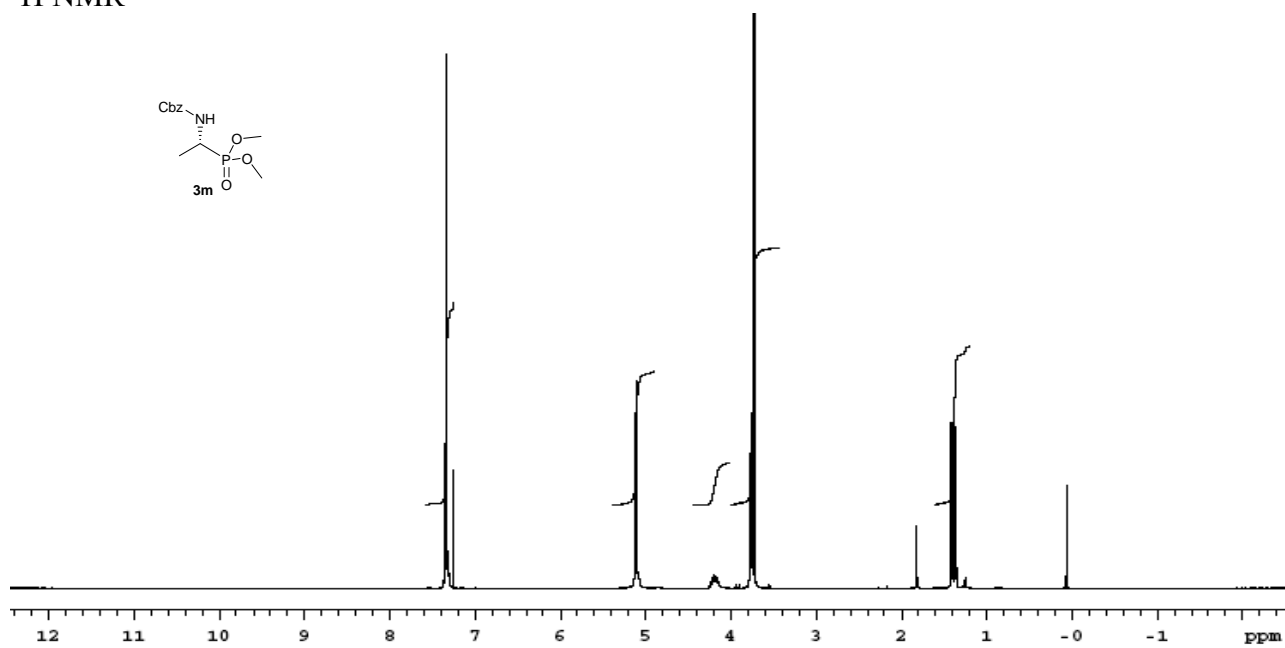
$^{13}\text{C}$  NMR



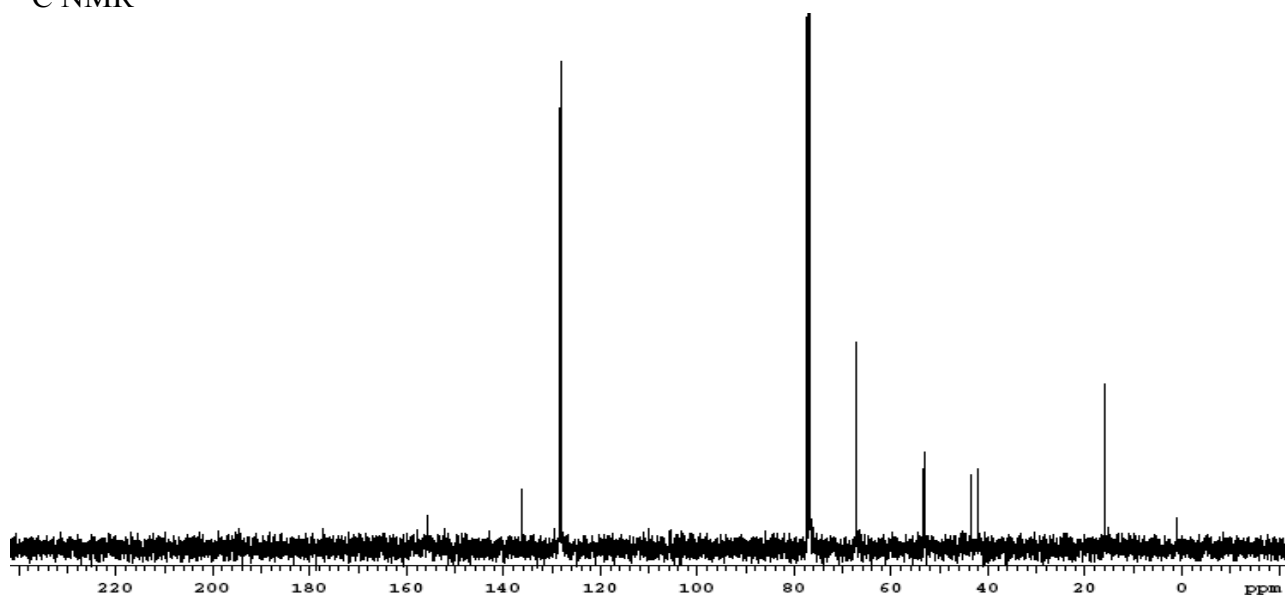
$^{31}\text{P}$  NMR



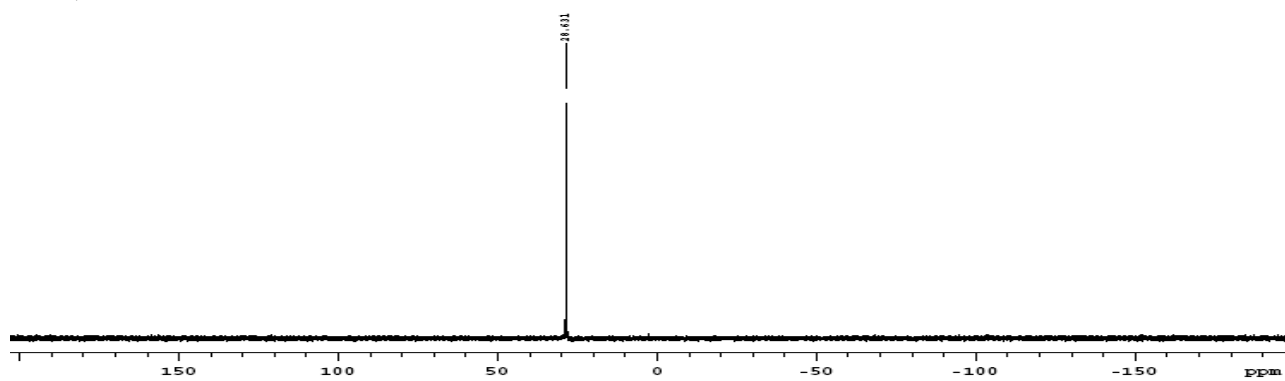
$^1\text{H}$  NMR



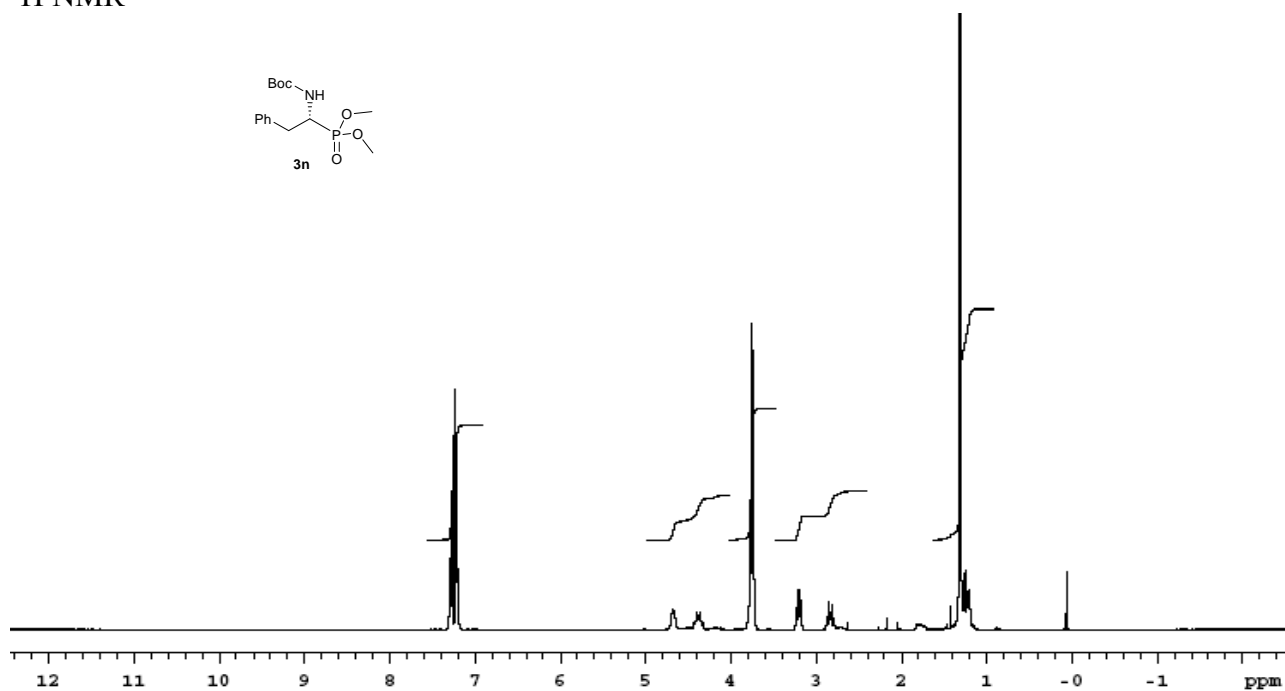
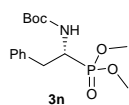
$^{13}\text{C}$  NMR



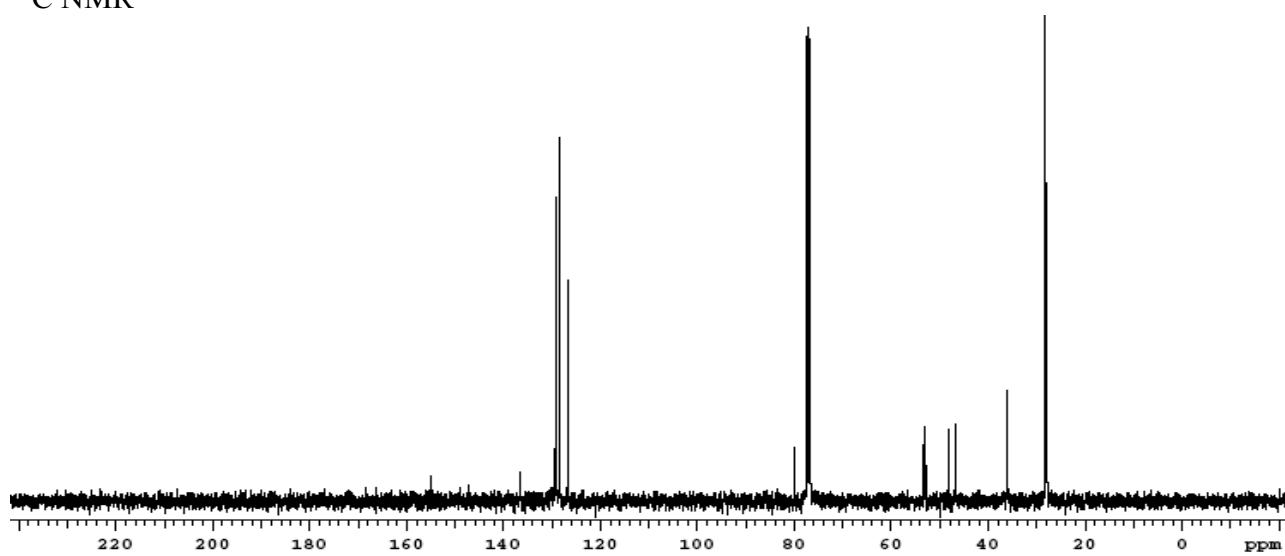
$^{31}\text{P}$  NMR



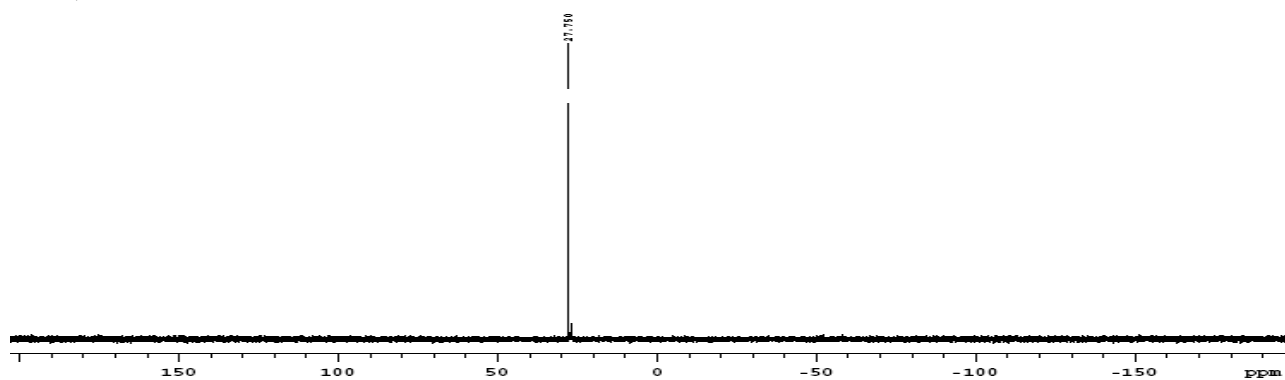
$^1\text{H}$  NMR



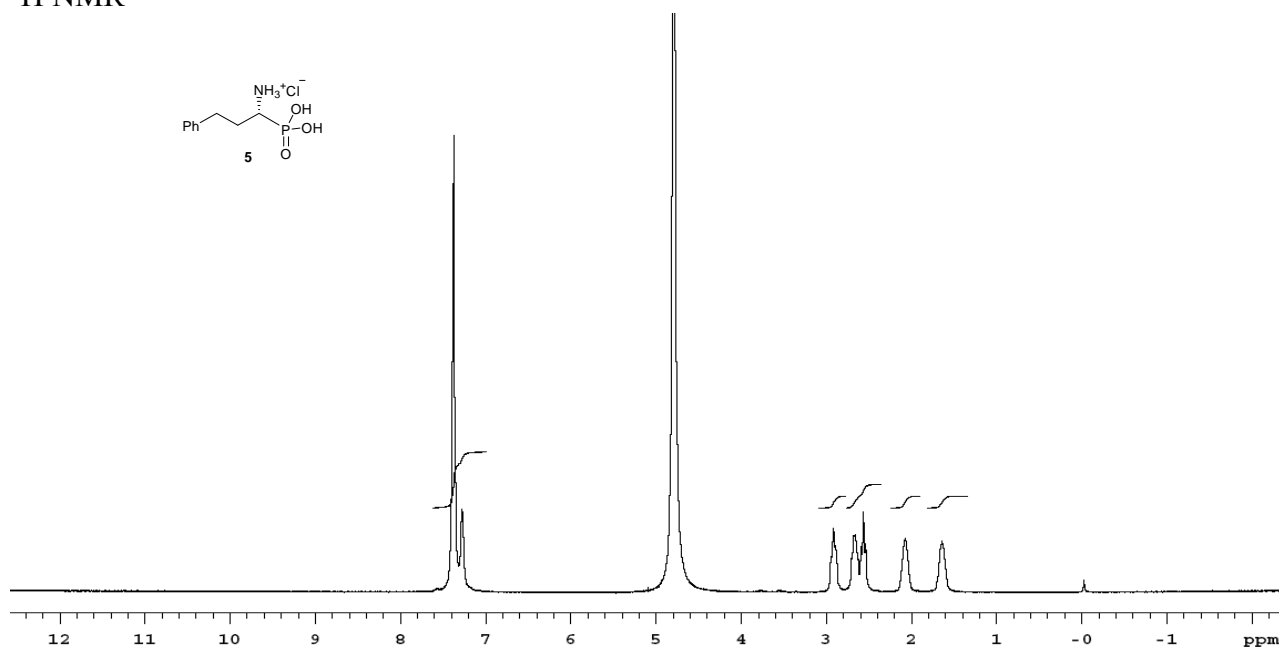
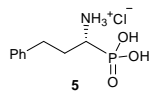
$^{13}\text{C}$  NMR



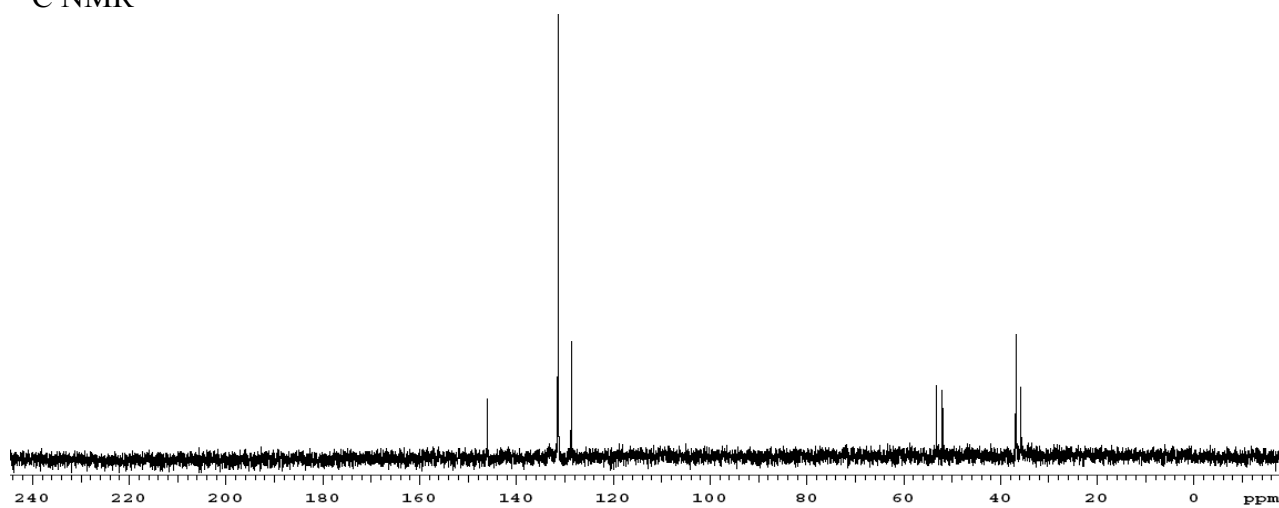
$^{31}\text{P}$  NMR



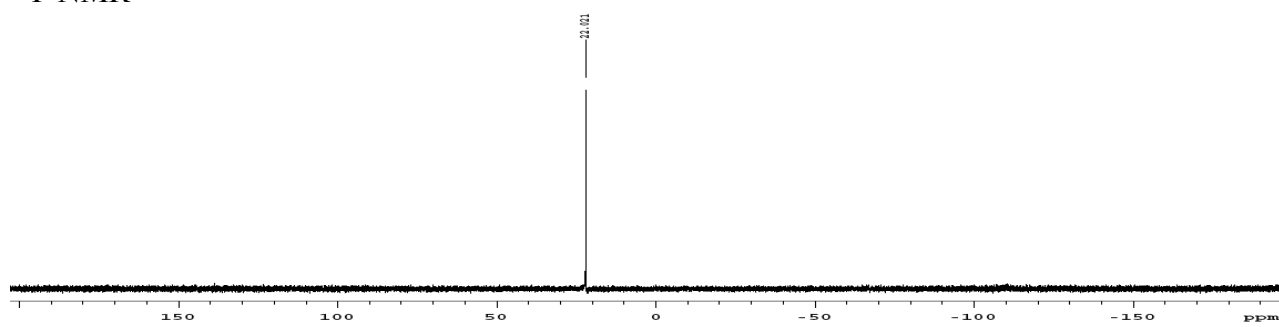
$^1\text{H}$  NMR



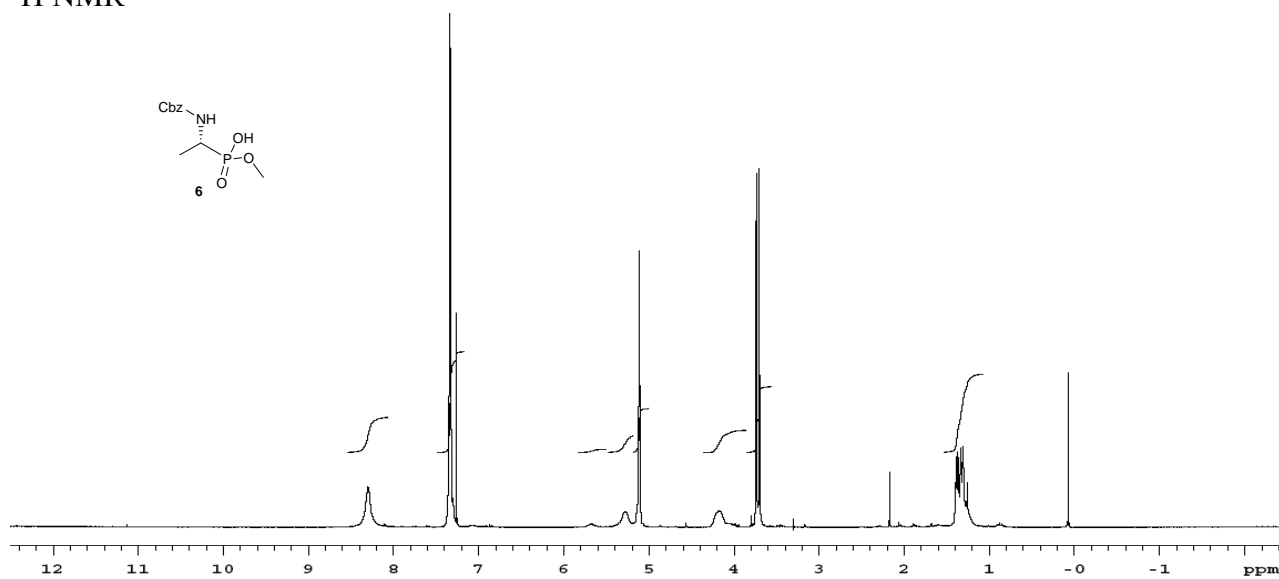
$^{13}\text{C}$  NMR



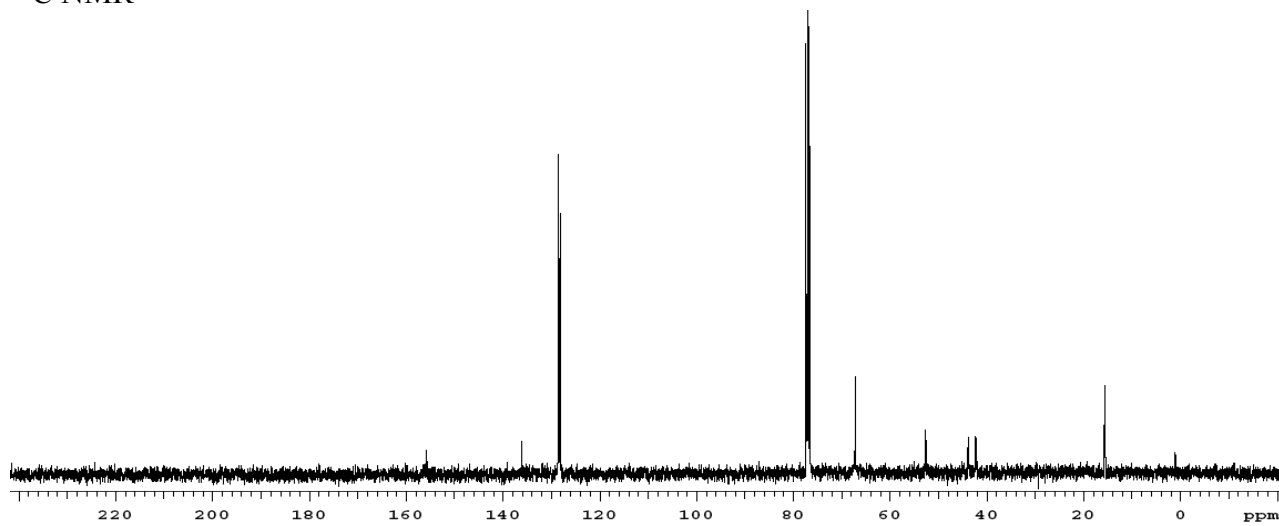
$^{31}\text{P}$  NMR



### $^1\text{H}$ NMR



### $^{13}\text{C}$ NMR



### $^{31}\text{P}$ NMR

