

*Supporting Information for*

# Conjugate reduction of vinyl bisphosphonates

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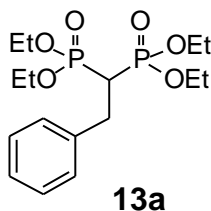
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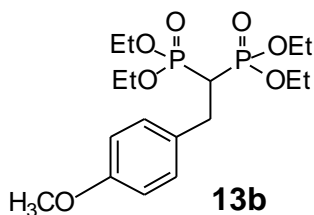
**General procedure for synthesis of vinylbisphosphonates.** To a Schlenk flask with a magnetic stirrer at 0 °C was added carbon tetrachloride (2.6 eq) and titanium tetrachloride (2 eq). Tetrahydrofuran (2.0 M) was added dropwise as the mixture was stirred carefully, and a yellow precipitate formed. The selected aldehyde (1 eq) was added dropwise, followed by tetraethyl methylenebisphosphonate (1 eq). *N*-Methylmorpholine (1.5 eq) in THF (0.3 M) was added dropwise over the course of 1 h. The reaction mixture then was stirred and allowed to warm to room temperature overnight. The reaction was quenched carefully by addition of aqueous sodium bicarbonate (sat) and the THF was removed under reduced pressure. The resulting residue was diluted with ethyl acetate and water, the layers were separated, and the aqueous layer was extracted five times with ethyl acetate. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified *via* flash chromatography (typically 2% NEt<sub>3</sub> and 10% EtOH, in EtOAc).

**General Procedure for catalytic conjugate reduction.** To a flask containing Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (5 mol %) and the phosphine ligand (5 mol %) under a nitrogen atmosphere, <sup>t</sup>BuOH (3.0 eq) and toluene were added and the solution was stirred for 30 minutes until it turned a light blue color. Poly(methylhydrosiloxane) (0.665 mL/1 mmol of the vinyl bisphosphonate) was added and the solution was stirred for 5 minutes. The appropriate vinyl bisphosphonate (typically 1 mmol) was added to the stirring solution and the solution was allowed to stir for ~1 h. At this time, reaction progress could be confirmed by <sup>31</sup>P NMR on an aliquot of the reaction mixture: the symmetry of the product results in only one phosphorus resonance while the vinyl bisphosphonates show two resonances with slightly different shifts and each is a doublet. The reaction was quenched by addition sat. NH<sub>4</sub>Cl, the aqueous layer was washed with EtOAc (3x), and the combined organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered. After concentration of the filtrate

in vacuo, final purification via flash column chromatography (2%  $\text{NEt}_3$  in EtOAc to 2%  $\text{NEt}_3$  and 5% EtOH in EtOAc) provided the desired geminal bisphosphonate.

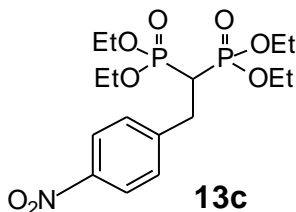


**Tetraethyl (2-phenylethane-1,1-diyl)bis(phosphonate) (13a).** Following the general procedure for conjugate reduction,  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (49 mg, 10 mol %), DPPBZ (88 mg, 8 mol %), and  $^t\text{BuOH}$  (0.7 mL, 3.0 eq), were added to toluene (12 mL) and the solution was stirred until it turned a light blue color. Poly(methylhydrosiloxane) (1.64 mL) was added and the solution was stirred for 5 minutes. The vinyl bisphosphonate **14a** (930 mg, 2.47 mmol) was added to the stirring solution and the reaction was allowed to stir for 1 h, when complete reaction was confirmed via  $^{31}\text{P}$  NMR analysis. Standard workup and final purification via flash column chromatography (5% EtOH in EtOAc) provided the reduced bisphosphonate **15a** (99% via NMR analysis, 680 mg, 74%). The  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{31}\text{P}$  NMR spectra matches data for the known compound.<sup>1</sup>

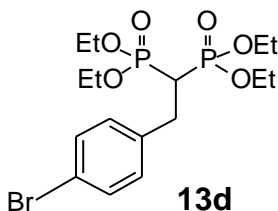


**Tetraethyl (2-(4-methoxyphenyl)ethane-1,1-diyl)bis(phosphonate) (13b).** Following the general procedure for catalytic conjugate reduction,  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (10 mg, 5 mol %), DPPBZ (23 mg, 5 mol %),  $^t\text{BuOH}$  (3.0 eq), and toluene (5 mL) were combined and the solution was stirred for 30 minutes until it turned a light blue color. Poly(methylhydrosiloxane) (0.665 mL/1 mmol VBP) was added and the solution was stirred for 5 minutes. After vinyl bisphosphonate **12b** (406 mg, 1 mmol, 1.0 eq) was added, the solution was allowed to stir for 1 h when complete reaction

was confirmed via  $^{31}\text{P}$  NMR analysis. Standard workup and final purification via flash column chromatography (2%  $\text{NEt}_3$  in EtOAc to 2%  $\text{NEt}_3$  and 5% EtOH in EtOAc) provided the geminal bisphosphonate **13b** (404 mg, 99%). The  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{31}\text{P}$  NMR spectra match reported data.<sup>1</sup>

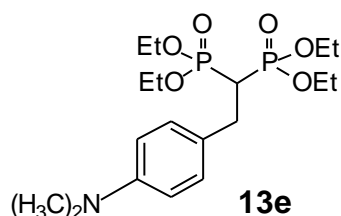


**Tetraethyl (2-(4-nitrophenyl)ethane-1,1-diyl)bis(phosphonate) (13c).** Following the general procedure for catalytic conjugate reduction,  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (10 mg, 5 mol %), DPPBZ (23 mg 5 mol %),  $^t\text{BuOH}$  (3.0 eq), and toluene (5 mL) were combined and the resulting solution was stirred for 30 minutes until it turned a light blue color. Poly(methylhydrosiloxane) (0.665 mL/1 mmol VBP) was added and the solution was stirred for 5 minutes. After the vinyl bisphosphonate **12c** (421 mg, 1 mmol, 1.0 eq) was added, the reaction was allowed to stir for 1 h, when complete reaction was confirmed via  $^{31}\text{P}$  NMR analysis. Standard workup and final purification via flash column chromatography (2%  $\text{NEt}_3$  in EtOAc to 2%  $\text{NEt}_3$  and 5% EtOH in EtOAc) provided the geminal bisphosphonate **13c** (364 mg, 86%). The  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{31}\text{P}$  NMR spectra match reported data.<sup>2</sup>



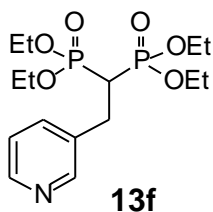
**Tetraethyl (2-(4-bromophenyl)ethane-1,1-diyl)bis(phosphonate) (13d).** Following the general procedure for catalytic conjugate reduction,  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (10 mg, 5 mol %), DPPBZ (23 mg, 5 mol %),  $^t\text{BuOH}$  (3.0 eq), and toluene (5 mL) were combined and the solution was stirred

for 30 minutes until it turned a light blue color. Poly(methylhydrosiloxane) (0.665 mL/1 mmol VBP) was added and the solution was stirred for 5 minutes. After vinyl bisphosphonate **12d** (455 mg, 1.0 mmol, 1.0 eq) was added to the solution, it was stirred for 1 h when complete reaction was confirmed via  $^{31}\text{P}$  NMR analysis. Standard workup and final purification via flash column chromatography (2%  $\text{NEt}_3$  in EtOAc – 2%  $\text{NEt}_3$  and 5% EtOH in EtOAc) provided the geminal bisphosphonate **13d** (438 mg, 96%). The  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{31}\text{P}$  NMR spectra match known data.<sup>1</sup>

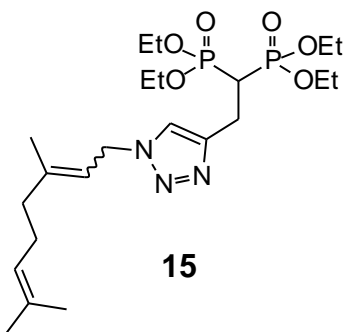


**Tetraethyl (2-(4-(dimethylamino)phenyl)ethane-1,1-diyl)bis(phosphonate) (13e).**

Following the general procedure for catalytic conjugate reduction,  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (10 mg, 5 mol %) and DPPBZ (23 mg, 5 mol %),  $^t\text{BuOH}$  (3.0 eq), and toluene (5 mL, 0.2 M) were combined and the solution was stirred for 30 minutes until it turned a light blue color. Poly(methylhydrosiloxane) (0.665 mL/1 mmol VBP) was added and the solution was stirred for 5 minutes. The vinyl bisphosphonate **12e** (419 mg, 1 mmol, 1.0 eq) was added and the solution was allowed to stir for 2 h, when complete reaction was confirmed via  $^{31}\text{P}$  NMR analysis. Standard workup and final purification via flash column chromatography (2%  $\text{NEt}_3$  in EtOAc to 2%  $\text{NEt}_3$  and 5% EtOH in EtOAc) provided the geminal bisphosphonate **13e** (404 mg, 99%). The  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{31}\text{P}$  NMR spectra match known data.<sup>1</sup>



**Tetraethyl (2-(pyridin-3-yl)ethane-1,1-diyl)bis(phosphonate) (13f).** Following the general procedure for catalytic conjugate reduction, Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (20 mg, 10 mol %), DPPBZ (36 mg, 8 mol %), <sup>t</sup>BuOH (3.0 eq), and toluene (~5 mL) were combined and the solution was stirred until it turned a light blue color. Poly(methylhydrosiloxane) (0.665 mL/1 mmol) was added and the resulting solution was stirred for 5 minutes. After the vinyl bisphosphonate **12f** (380 mg, 1.0 mmol, 1.0 eq) was added, the solution was allowed to stir for 1 h when analysis revealed that the reaction was complete. Standard workup and purification via flash column chromatography (5% EtOH in EtOAc to 20% EtOH in EtOAc) provided the geminal bisphosphonate **13f** (270 mg, 71%). The <sup>1</sup>H, <sup>13</sup>C, and <sup>31</sup>P NMR spectra match reported data.<sup>1</sup>



**(E/Z)-Tetraethyl (2-(1-(3,7-dimethylocta-2,6-dien-1-yl)-1H-1,2,3-triazol-4-yl)ethane-1,1-diyl)bis(phosphonate) (15).** Following the general procedure for catalytic conjugate reduction, Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (12 mg, 10 mol %), DPPBZ (21 mg, 8 mol %), and <sup>t</sup>BuOH (0.17 mL, 3.0 eq) were added to toluene (10 mL) and the solution was stirred until it turned a light blue color. After poly(methylhydrosiloxane) (0.4 mL) was added, the solution was stirred for 5 minutes and vinyl bisphosphonate **14** (300 mg, 0.6 mmol) was added. The solution was allowed to stir for ~2 h at 50° C, when complete reaction completion was confirmed via <sup>31</sup>P NMR analysis of an aliquot from the reaction mixture. The reaction was quenched by addition of brine, extracted with EtOAc (3x) and the combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. Final purification

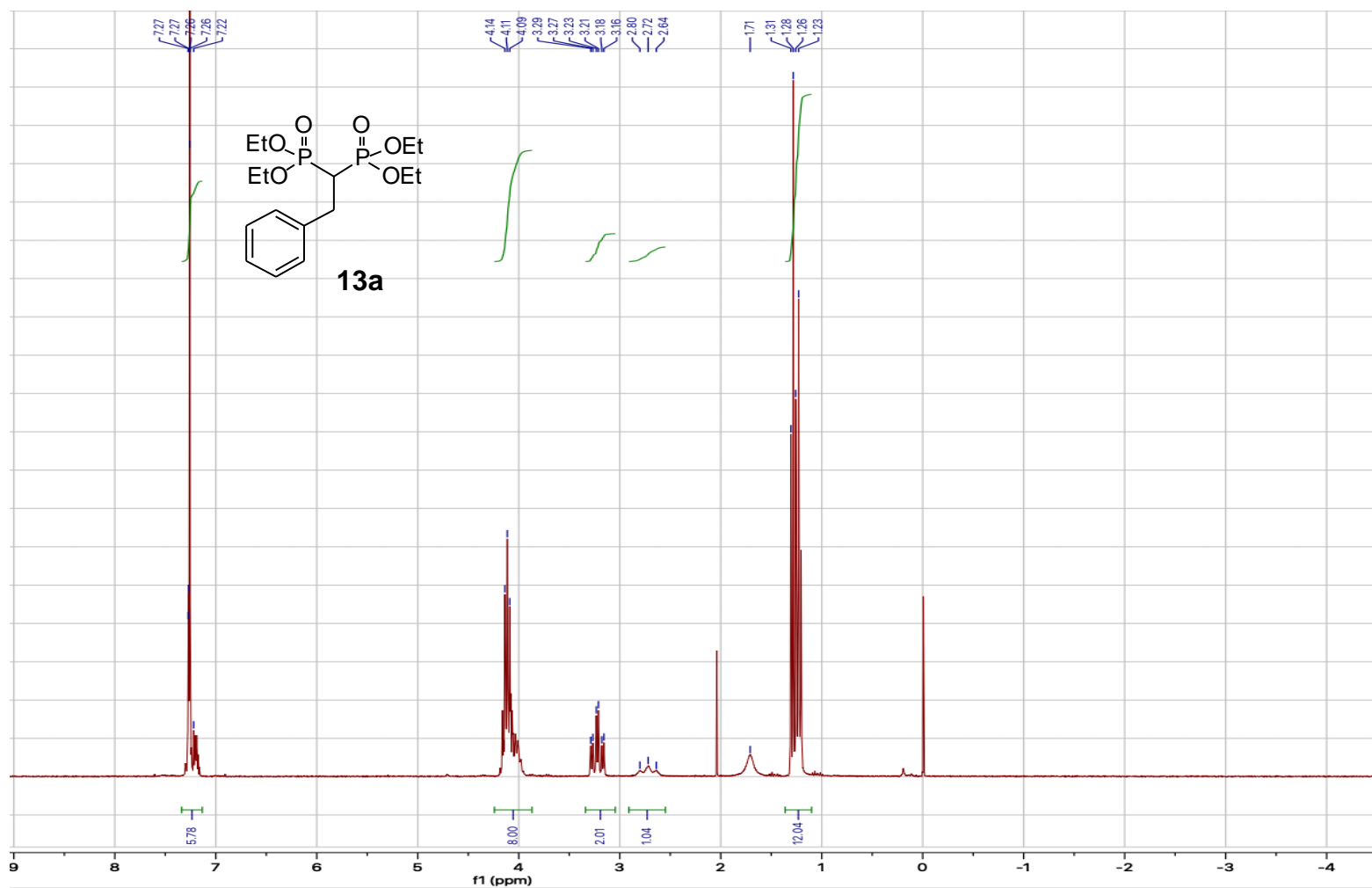
via flash column chromatography (5% EtOH in EtOAc to 10% EtOH in EtOAc) provided the reduced bisphosphonate **15** (99% via NMR analysis; 230 mg, 76%). The  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{31}\text{P}$  NMR spectra matched known data.<sup>3</sup>

## References

1. Bianchini, G.; Scarso, A.; Chiminazzo, A.; Sperti, L.; Strukul, G., Water enhanced synthesis of gem-bisphosphonates via Rh(I) mediated 1,4-conjugate addition of aryl boronic acids to vinylidenebisphosphonate esters. *Green Chemistry* **2013**, *15* (3), 656-662.
2. Chiminazzo, A.; Sperti, L.; Damuzzo, M.; Strukul, G.; Scarso, A., Copper-mediated 1,4-Conjugate Addition of Boronic Acids and Indoles to Vinylidenebisphosphonate leading to gem-Bisphosphonates as Potential Antiresorption Bone Drugs. *ChemCatChem* **2014**, *6* (9), 2712-2718.
3. Zhou, X.; Hartman, S. V.; Born, E. J.; Smits, J. P.; Holstein, S. A.; Wiemer, D. F., Triazole-based inhibitors of geranylgeranyltransferase II. *Bioorg Med Chem Lett* **2013**, *23* (3), 764-6.

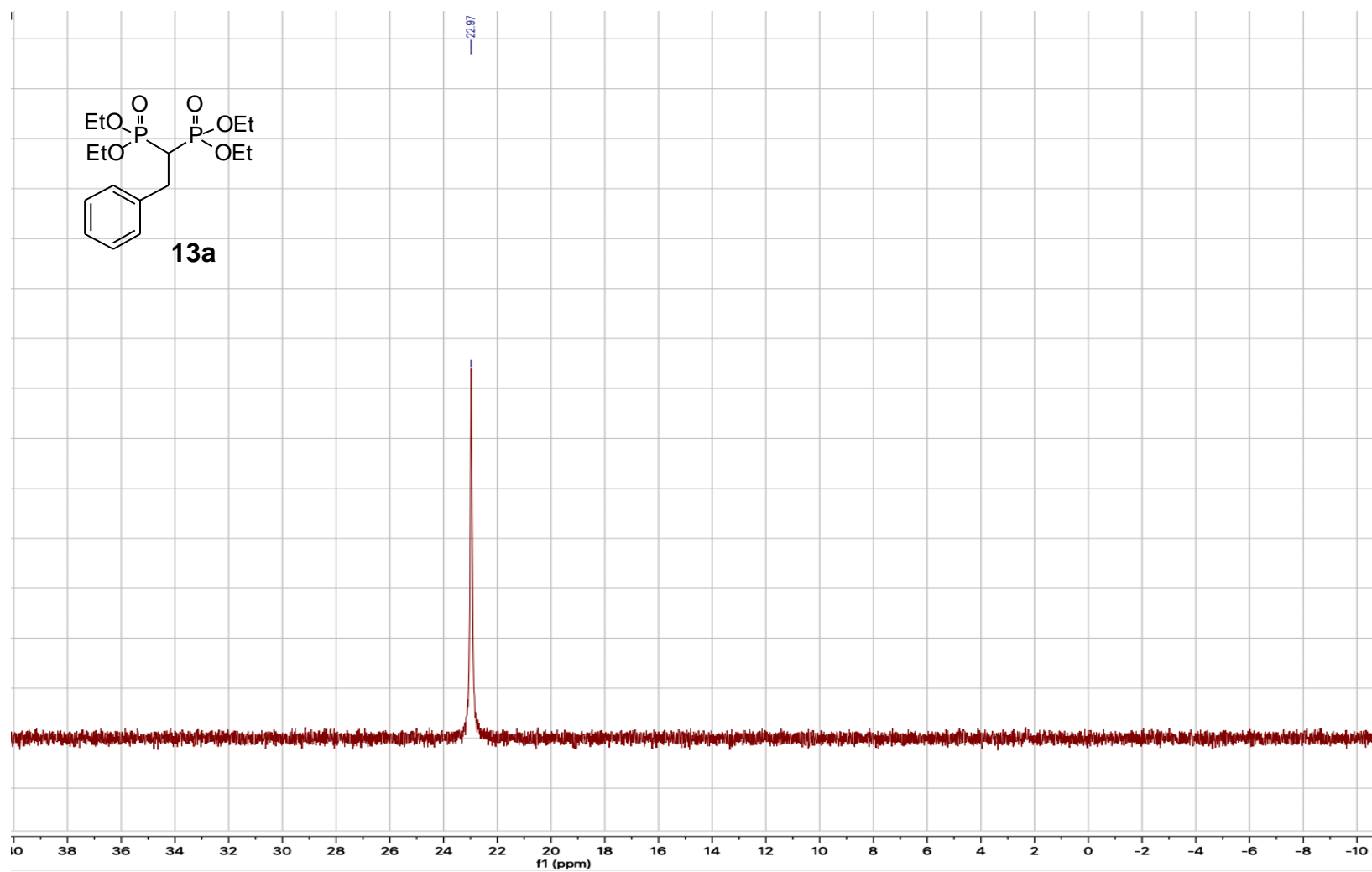
# NMR Spectra

$^1\text{H}$  NMR spectrum of compound 13a ( $\text{CDCl}_3$ , 300 MHz).

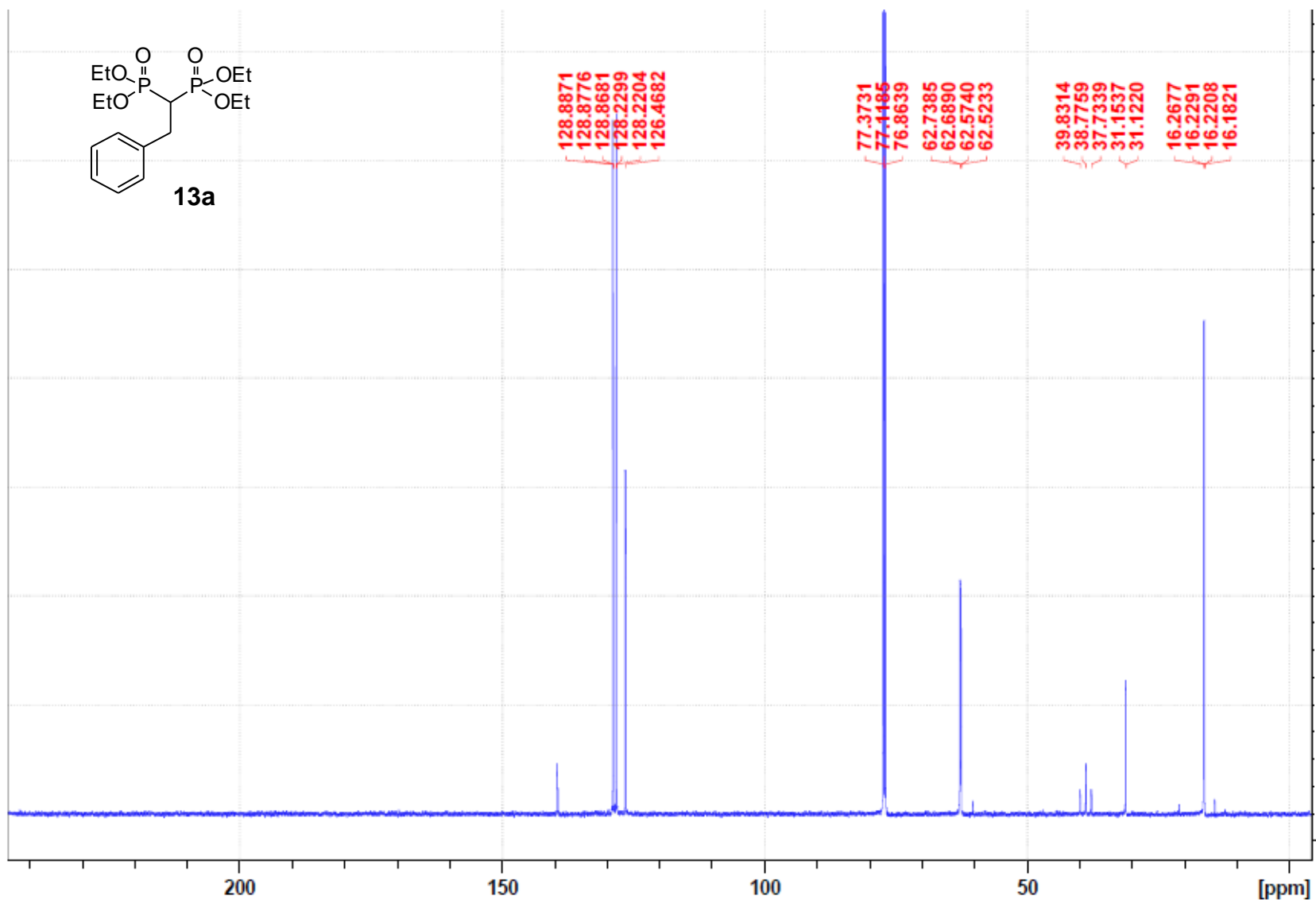




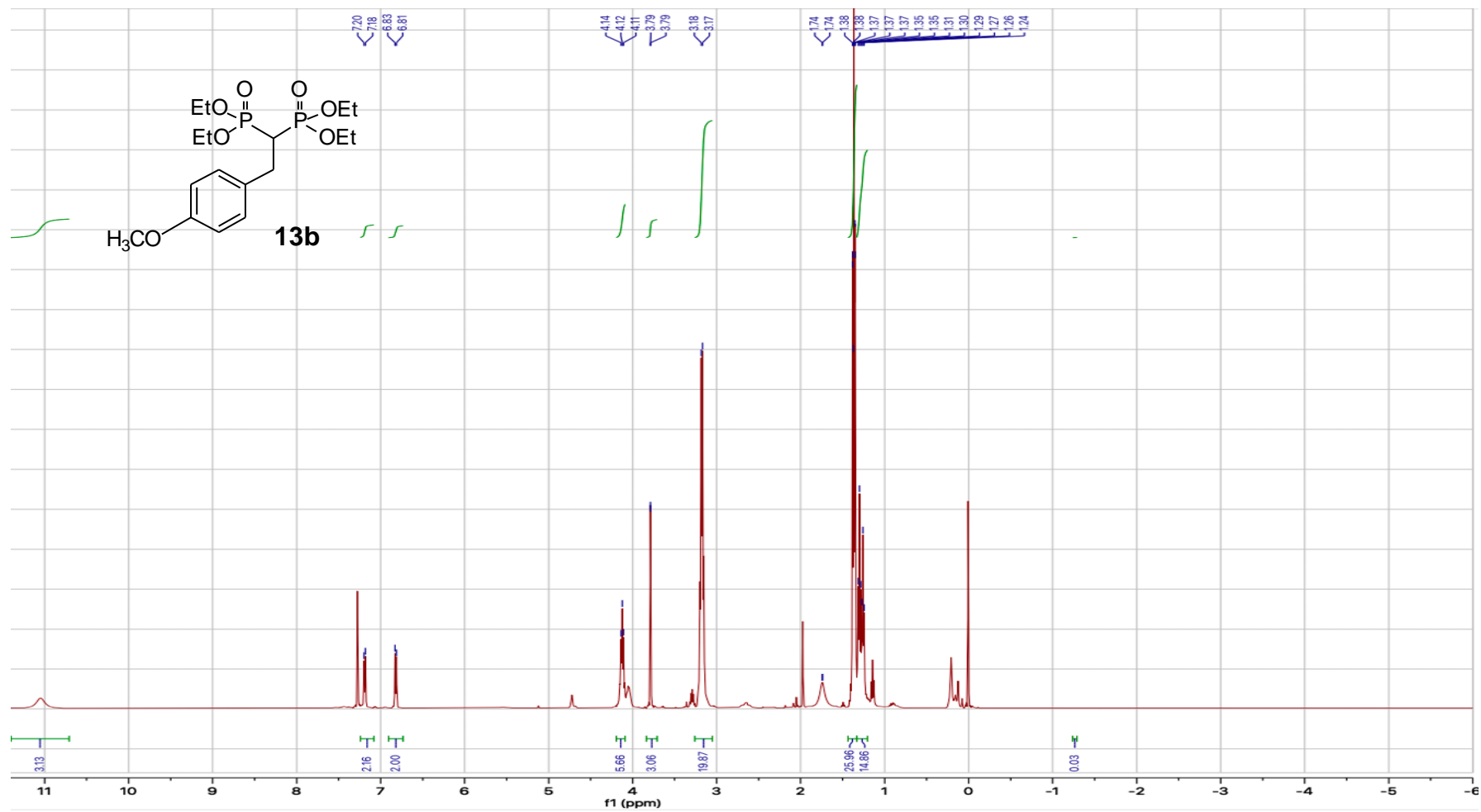
**<sup>31</sup>P NMR spectrum of compound 13a (CDCl<sub>3</sub>, 121 MHz).**



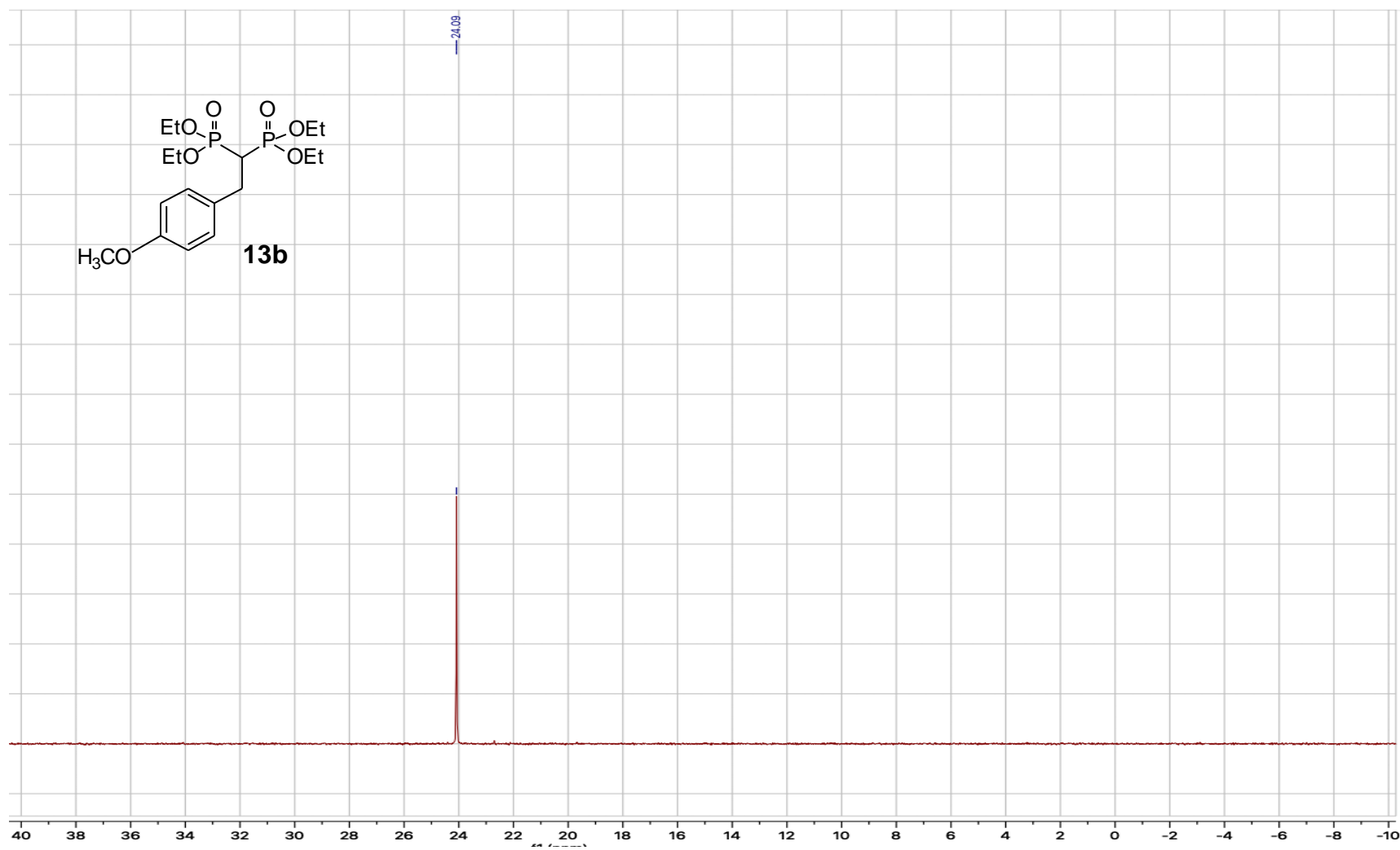
<sup>13</sup>C NMR spectrum of compound 13a (CDCl<sub>3</sub>, 125 MHz).



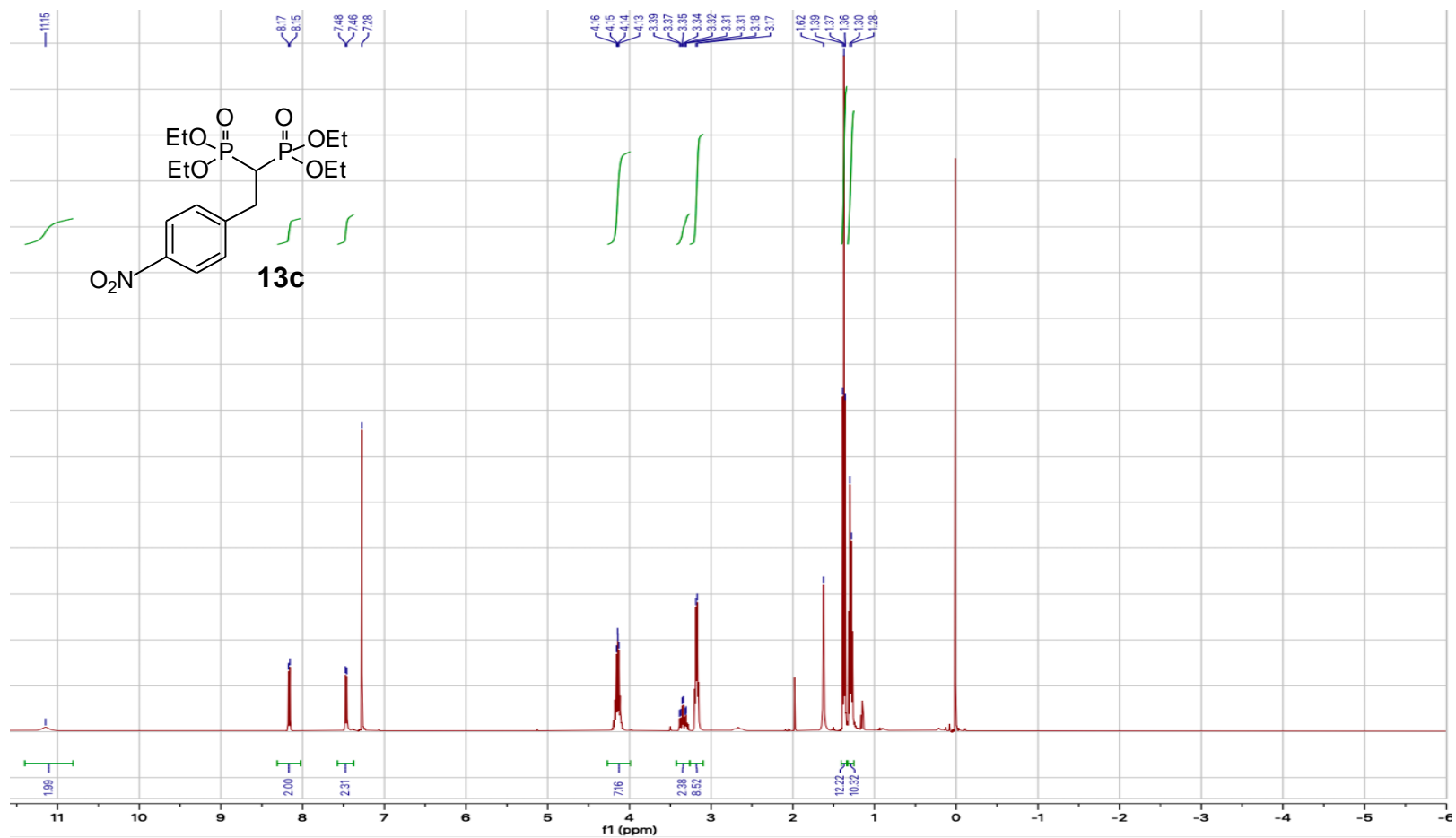
<sup>1</sup>H NMR spectrum of compound 13b (CDCl<sub>3</sub>, 400 MHz).



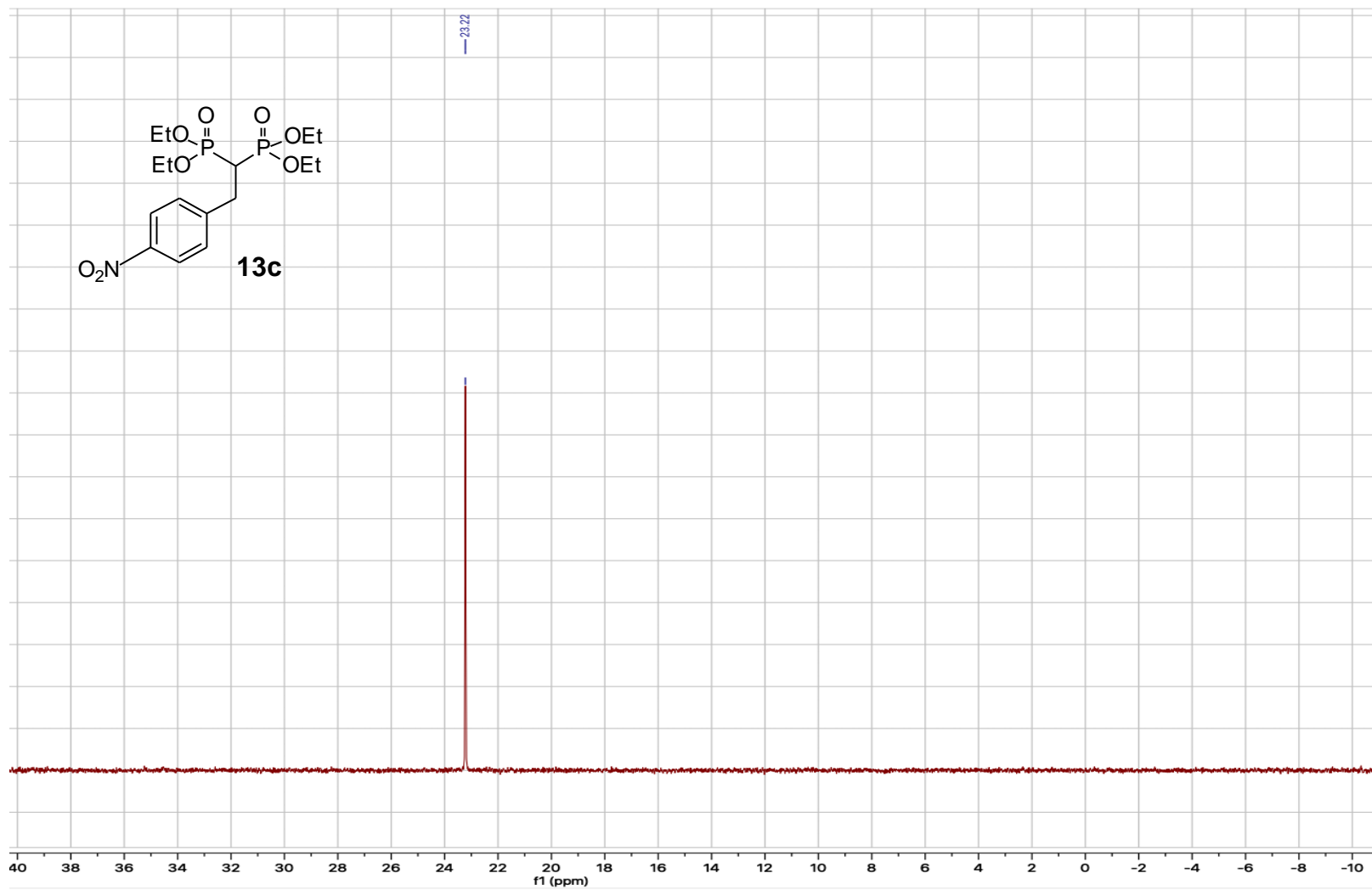
**$^{31}\text{P}$  NMR spectrum of compound 13b ( $\text{CDCl}_3$ , 162 MHz).**



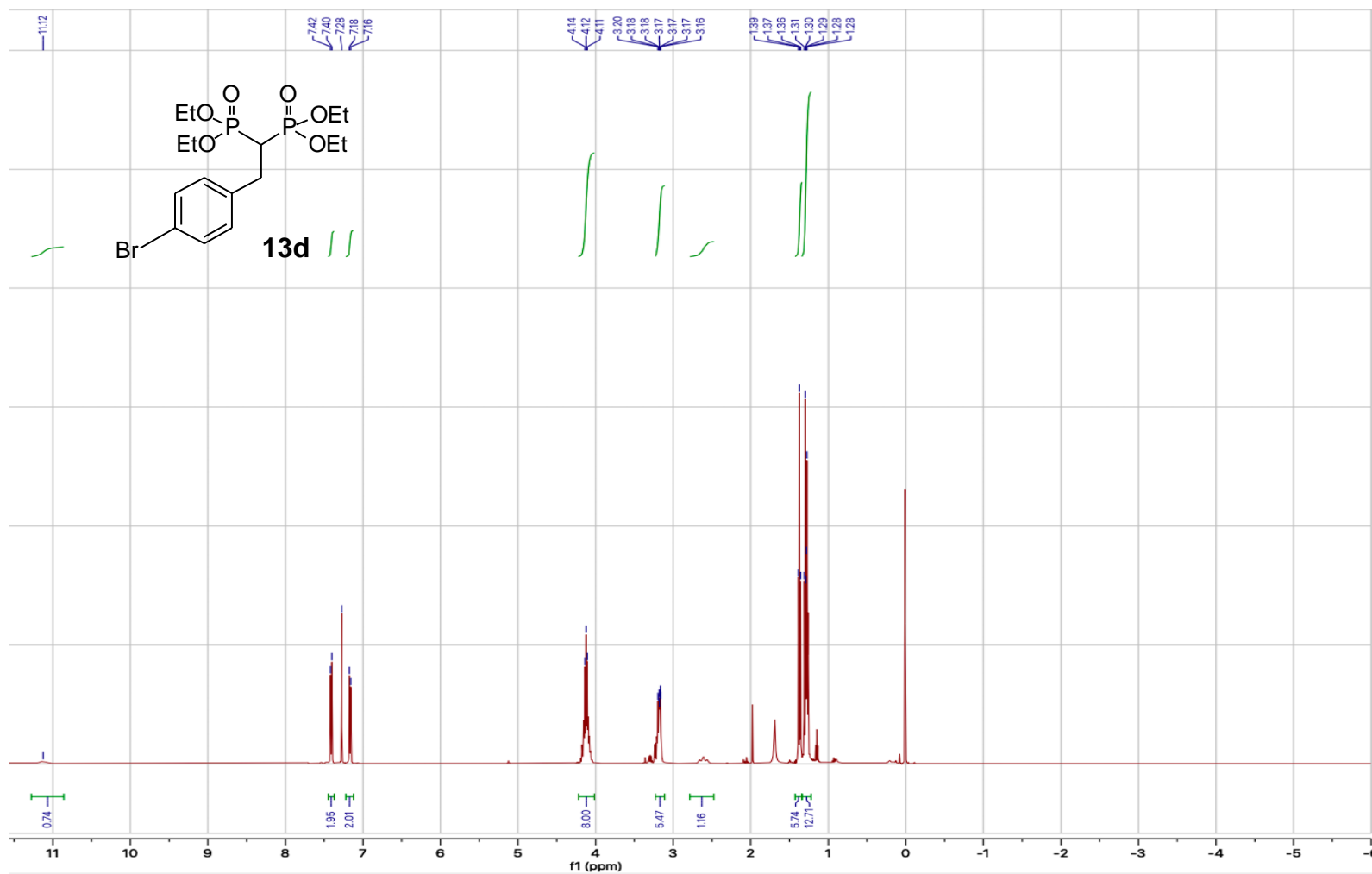
$^1\text{H}$  NMR spectrum of compound **13c** ( $\text{CDCl}_3$ , 300 MHz).



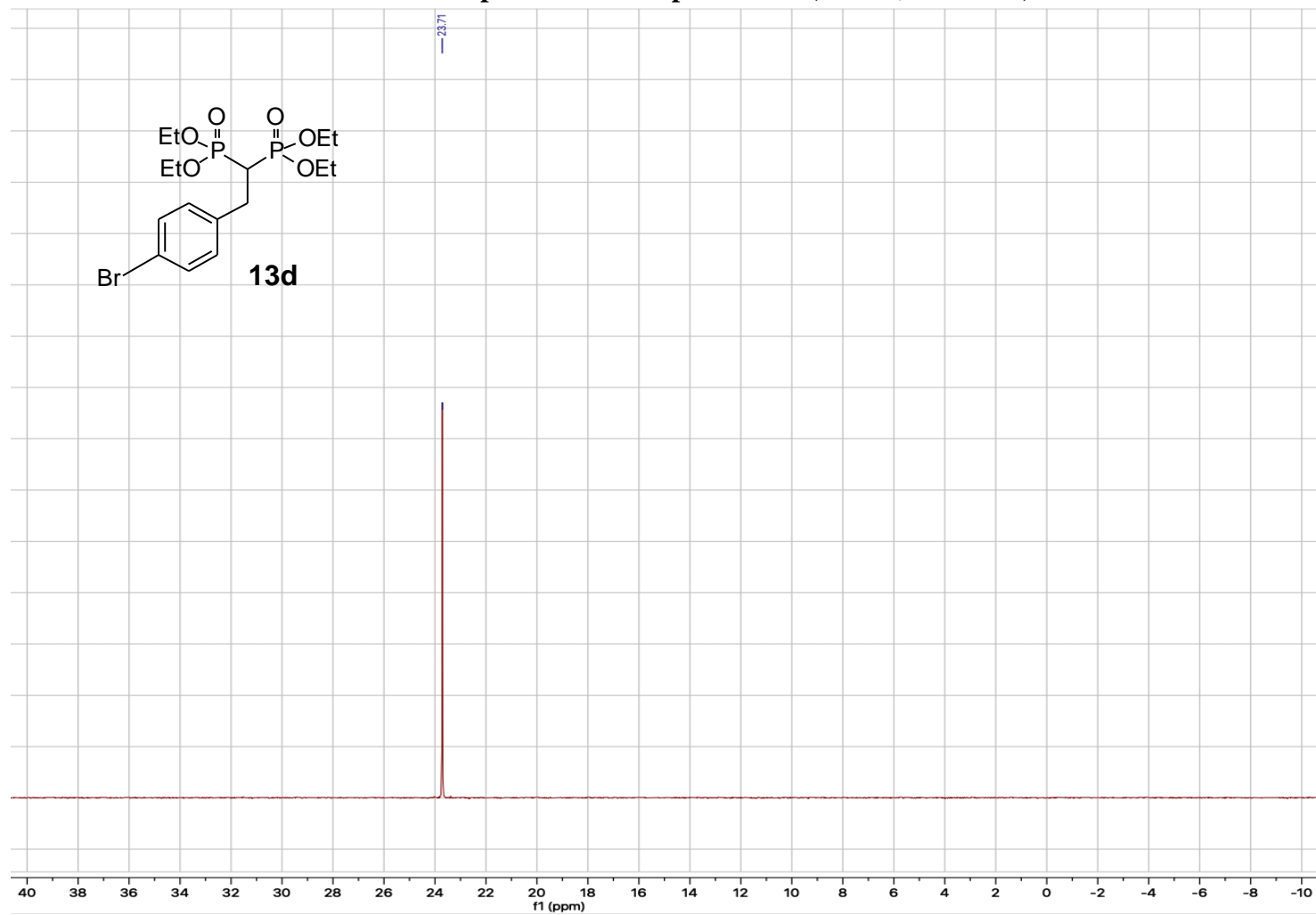
<sup>31</sup>P NMR spectrum of compound 13c (CDCl<sub>3</sub>, 121 MHz).



**<sup>1</sup>H NMR spectrum of compound 13d (CDCl<sub>3</sub>, 400 MHz).**

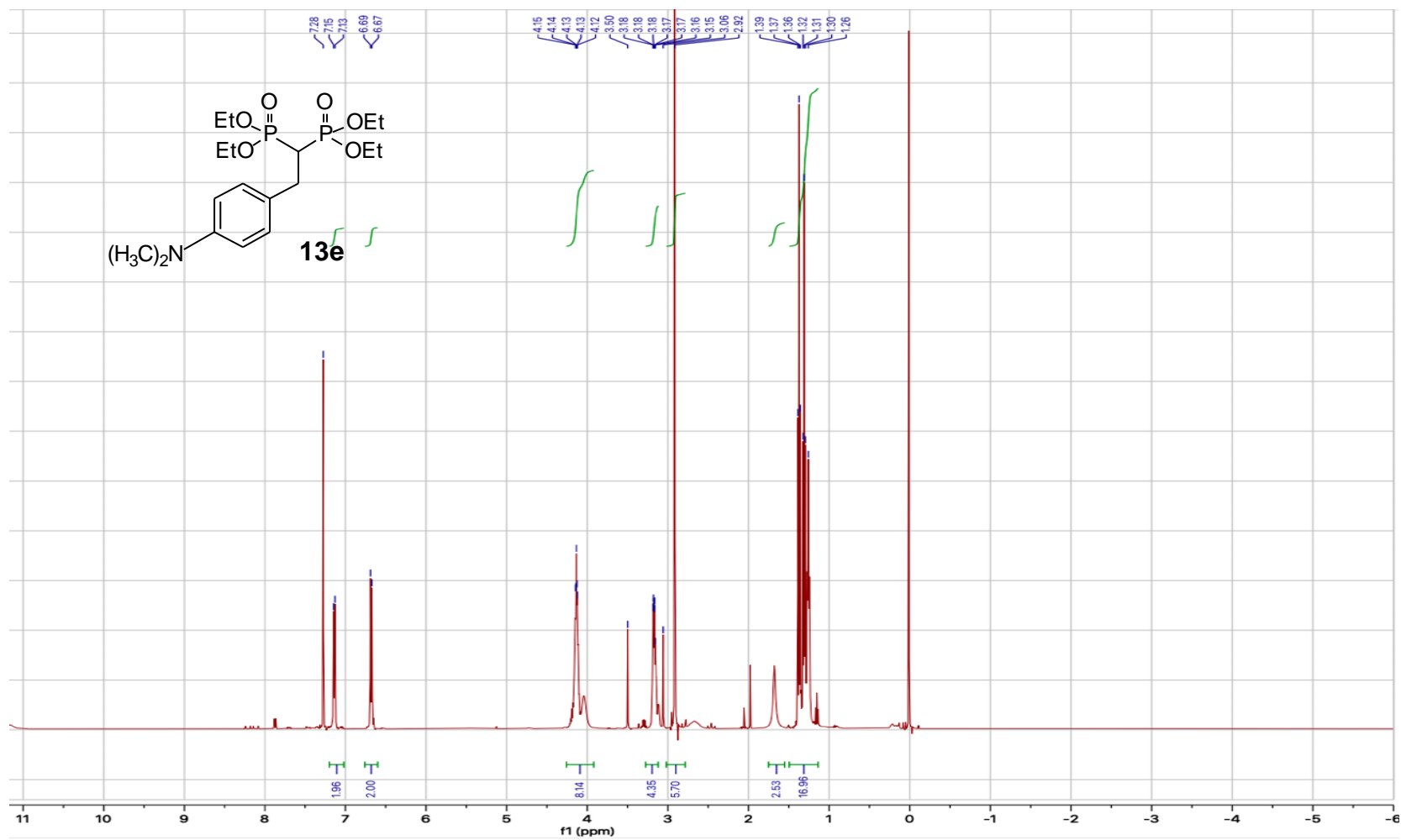


**<sup>31</sup>P NMR spectrum of compound 13d (CDCl<sub>3</sub>, 162 MHz).**

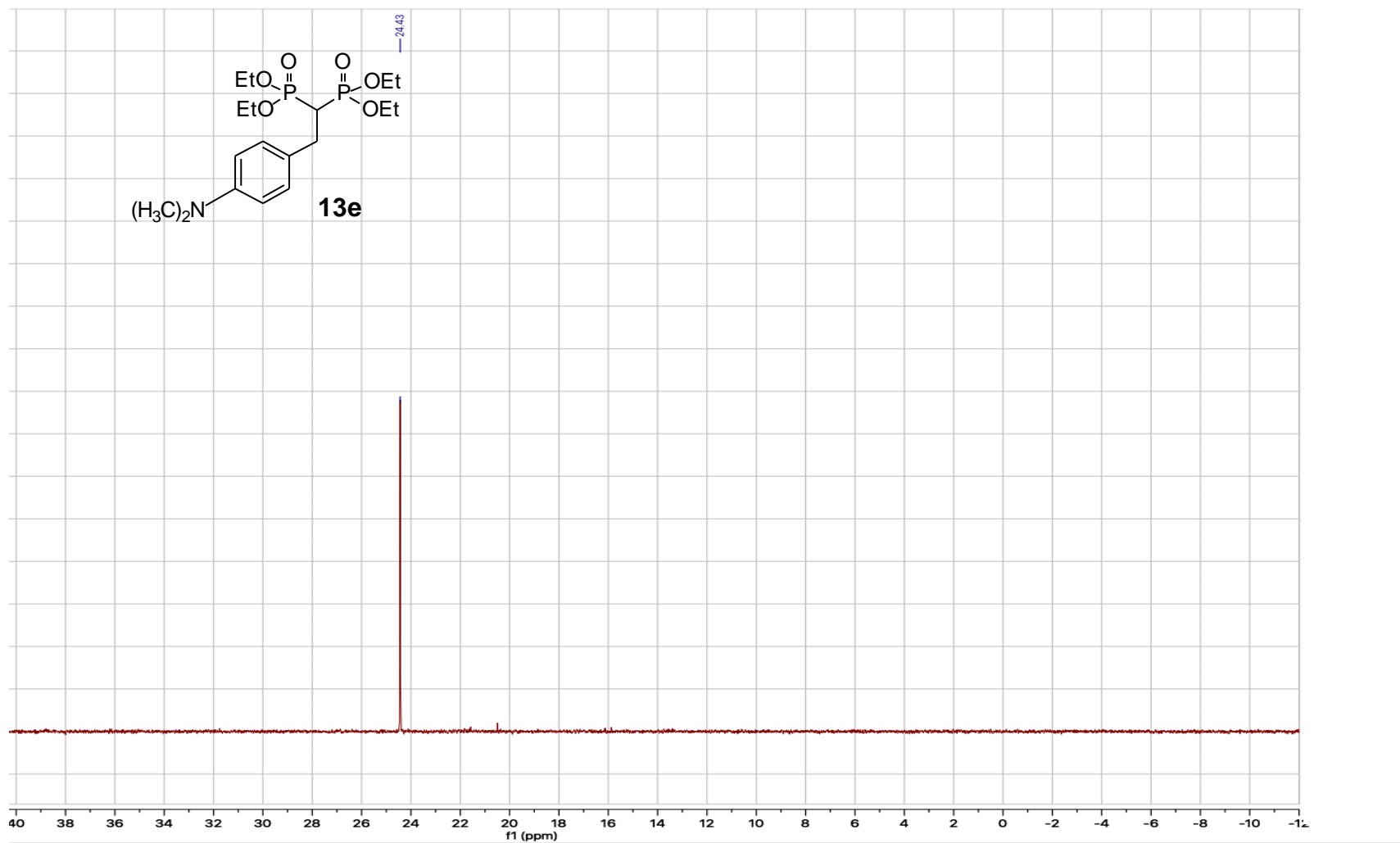




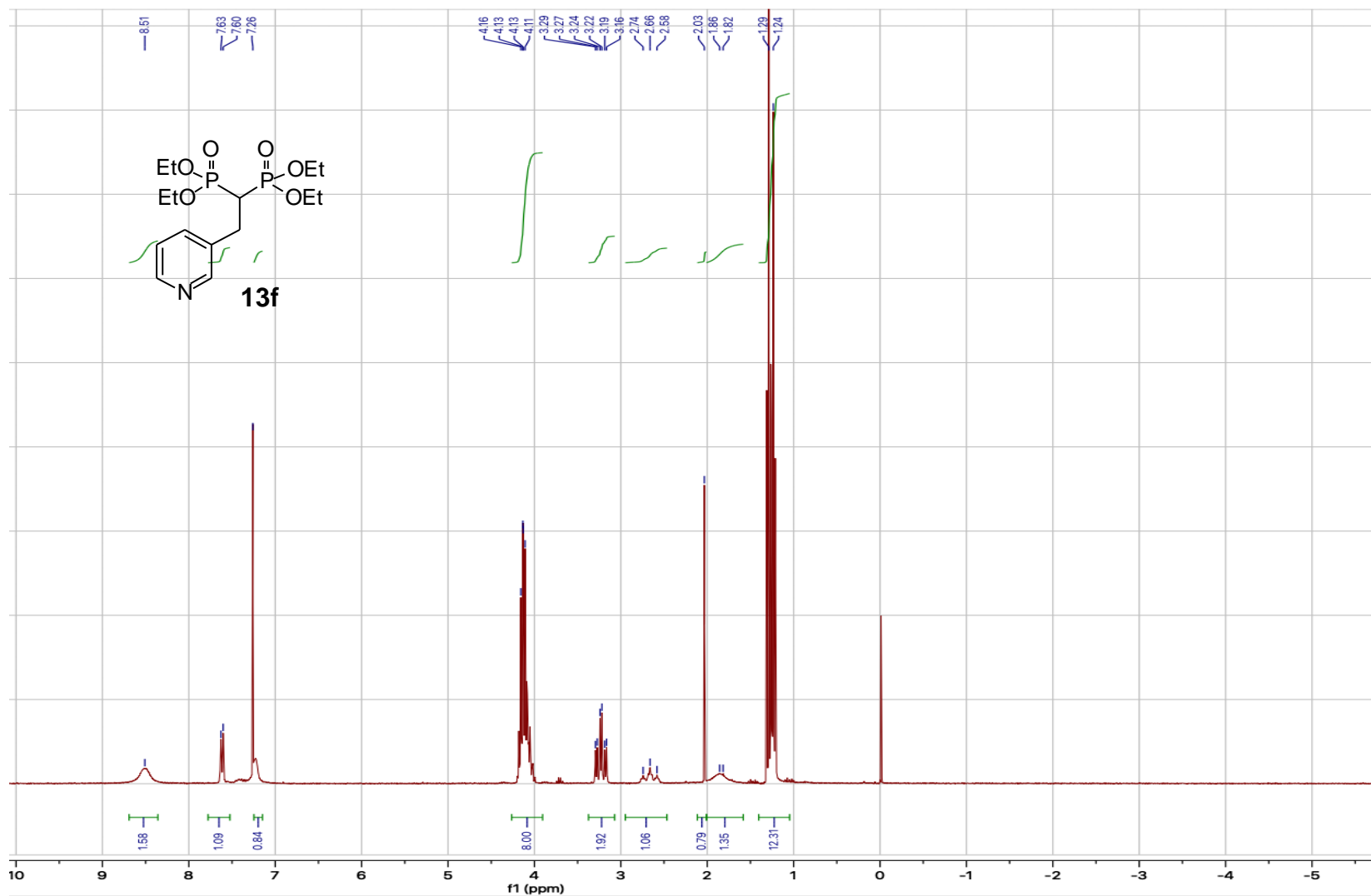
<sup>1</sup>H NMR spectrum of compound 13e (CDCl<sub>3</sub>, 400 MHz).



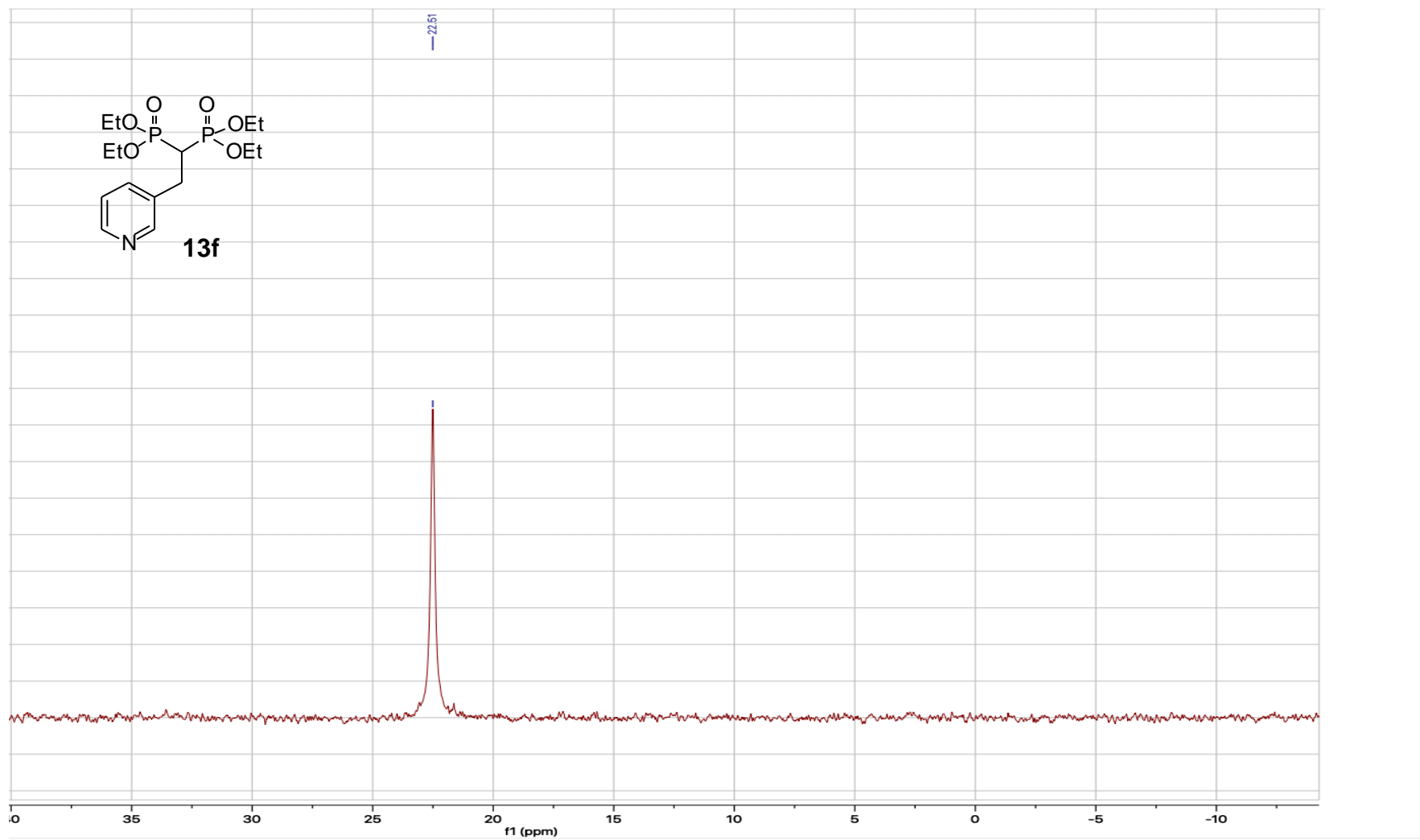
<sup>31</sup>P NMR spectrum of compound 13e (CDCl<sub>3</sub>, 162 MHz).



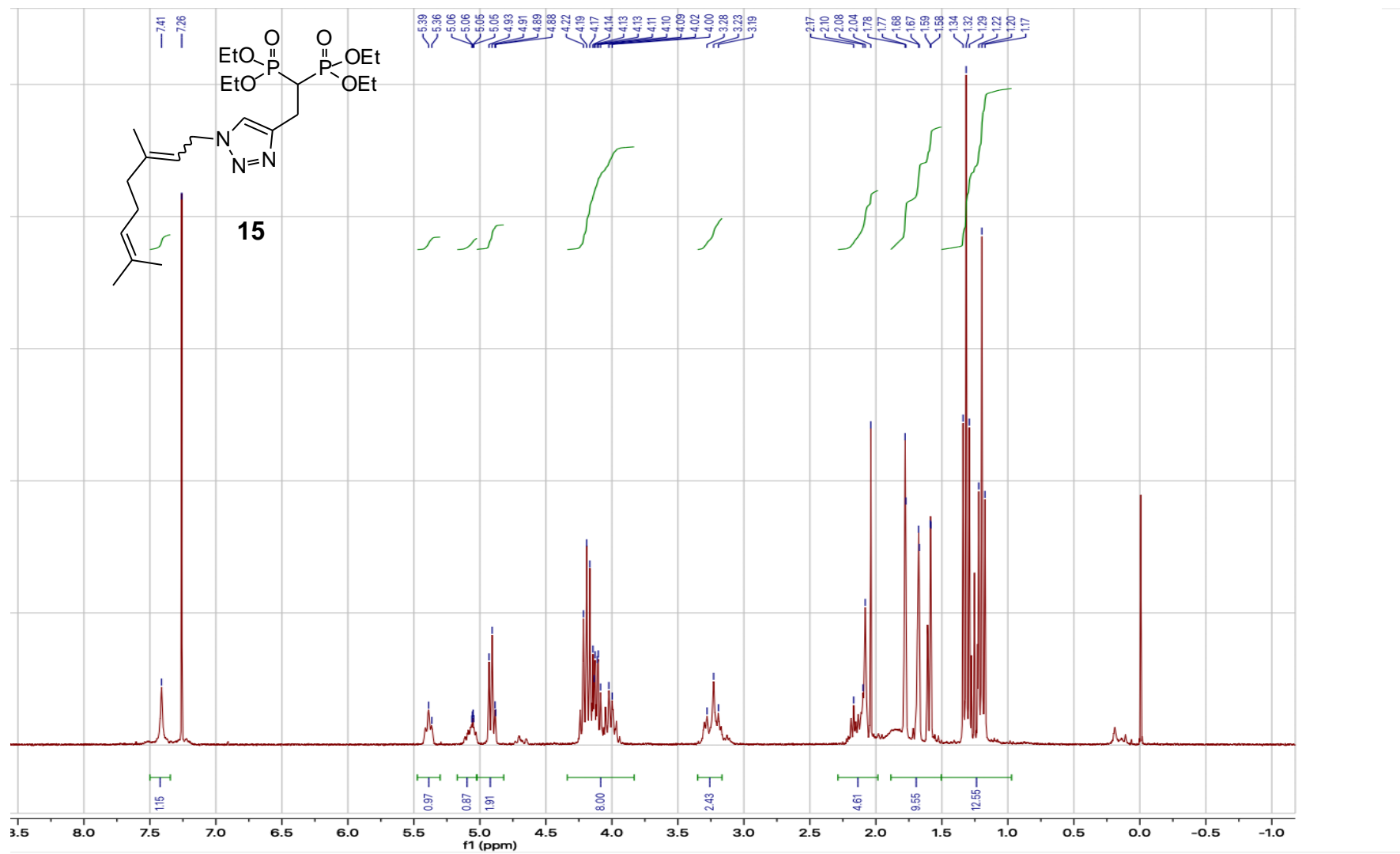
**<sup>1</sup>H NMR spectrum of compound 13f (CDCl<sub>3</sub>, 300 MHz).**



**$^{31}\text{P}$  NMR spectrum of compound 13f ( $\text{CDCl}_3$ , 121 MHz).**



<sup>1</sup>H NMR spectrum of triazole 15 (CDCl<sub>3</sub>, 300 MHz).



<sup>31</sup>P NMR spectrum of triazole 15 (CDCl<sub>3</sub>, 121 MHz).

