

Copper Phosphoramidite Catalyzed Enantioselective Desymmetrization of Meso Cyclic Allylic Bisdiethylphosphates

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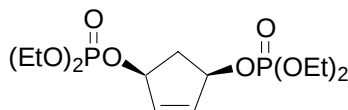
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Supporting Information

General procedures. All reactions were carried out in flame-dried glassware with magnetic stirring under argon atmosphere. All commercially available reagents were used as received. The solvents were dried by distillation over the following drying agents and were transferred under nitrogen: CH₂Cl₂ (CaH₂), THF (Na), Et₂O (Na), toluene (Na). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F₂₅₄ precoated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a ceric ammonium molybdate (CAM) solution. Flash column chromatography was performed using silica gel 60Å, particle size 40–64 µm. Proton NMR spectra were recorded on a 400 MHz spectrometer. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard (CDCl₃ δ 7.26 ppm). Carbon NMR spectra were recorded on a 400 MHz (100 MHz) spectrometer with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard (CDCl₃, δ 77.0). ³¹P NMR spectra were recorded on a 400 MHz (162 MHz) spectrometer with complete proton decoupling. Infrared spectra were recorded on a standard Infrared Spectrophotometer; peaks are reported in cm⁻¹. Optical rotation values were measured on an automatic polarimeter with a 1 dm cell at the sodium D line. Gas chromatography was performed on a GC instrument equipped with a flame ionization detector, temperature and pressure control. Enantiomeric excesses were determined by chiral GC using a MEGADEX DMEPEB, OV 1701 capillary column (25 m, film 0.25 µm) in comparison with a racemic sample.

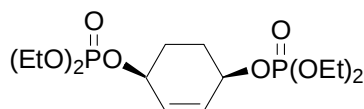
General procedure for the preparation of meso-bisdiethylphosphates 2a, 2b, 2c, 6. *n*-Butyllithium (1.6 M in *n*-hexane, 3.94 mL, 6.3 mmol) was added dropwise to a cooled (–40 °C) solution of the meso-diol (3.00 mmol) in THF/TMEDA (4:1, 20 mL). The solution was stirred for 15 min and then diethyl chlorophosphate (1.087 g, 6.3 mmol) was added. The resulting mixture was stirred at –40 °C for 1 hour and slowly warmed to 0 °C, quenched with brine, and extracted with dichloromethane. The organic phase was dried over Na₂SO₄ and volatiles were removed under reduced pressure. The crude residue was purified by flash chromatography (eluant: ethyl acetate / methanol 94/6) to give meso-bisdiethylphosphates 2a, 2b, 2c, 6.

meso-4-Cyclopentene-1,3-bisdiethylphosphate (2a)



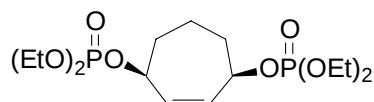
Yield: 1.027 g (90 %). IR (film) ν_{max} 2985, 1645, 1373, 1261, 1164, 1027, 989, 804 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.17–6.16 (m, 2H), 5.25–5.19 (m, 2H), 4.16–4.08 (m, 8H), 2.98–2.88 (m, 1H), 2.04 (dt, 1H, *J* = 14.6 Hz, *J* = 4.3 Hz), 1.35 (t, 12H, *J* = 7.0 Hz); ³¹P NMR (162 MHz, CDCl₃) δ 0.81; ¹³C NMR (100 MHz, CDCl₃) δ 134.9 (CH), 134.8 (CH), 79.0 (CH), 78.9 (CH), 63.7 (2CH₂), 63.6 (2CH₂), 39.4 (CH₂), 15.9 (4CH₃); MS (FAB, glycerol) *m/z* (%) 373 (60) [M+H]⁺, 219 (100) [M-(EtO)₂P(O)OH+H]⁺, 191 (25) [M-(EtO)₂P(O)OH-(C₂H₄)+H]⁺, 163 (45) [M-(EtO)₂P(O)OH-2(C₂H₄)+H]⁺; HRMS (EI, 70 eV) *m/z* calcd for C₁₃H₂₆O₈P₂: 372.1103 [M]⁺; found: 372.1111.

meso-2-Cyclohexene-1,4-bisdiethylphosphate (2b)



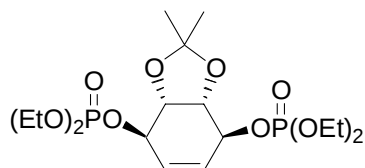
Yield: 0.996 g (86 %). IR (film) $\nu_{\max}$ 2985, 1644, 1396, 1261, 1164, 1027, 989, 817 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.93 (m, 2H), 4.78-4.72 (m, 2H), 4.06 (dq, $J = 7.3$ Hz, $J = 7.3$ Hz, 8H), 2.04-1.94 (m, 2H), 1.93-1.83 (m, 2H), 1.29 (t, 12 H $J = 7.1$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ 0.24; ^{13}C NMR (100 MHz, CDCl_3) δ 130.6 (2CH), 77.7 (2CH), 63.7 (4CH₂), 26.0 (2CH₂), 16.1 (4CH₃); MS (FAB, glycerol) m/z (%) 409 (10) $[\text{M}+\text{Na}]^+$, 387 (40) $[\text{M}+\text{H}]^+$, 233 (100) $[\text{M}-(\text{EtO})_2\text{P}(\text{O})\text{OH}+\text{H}]^+$, 155 (95) $[(\text{EtO})_2\text{P}(\text{O})\text{OH}+\text{H}]^+$, 127 (50) $[(\text{EtO})\text{P}(\text{O})(\text{OH})_2+\text{H}]^+$, 99 (90) $[\text{P}(\text{O})(\text{OH})_3+\text{H}]^+$; HRMS (EI, 70 eV) m/z calcd for $\text{C}_{14}\text{H}_{29}\text{O}_8\text{P}_2$: 387.1338 $[\text{M}+\text{H}]^+$; found: 387.1378.

meso-2-Cycloheptene-1,4-bisdiethylphosphate (2c)



Yield: 1.057 g (88 %). IR (film) $\nu_{\max}$ 2985, 1646, 1396, 1263, 1164, 1027, 989, 804 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.79 (bs, 2H), 4.91-4.82 (m, 2H), 4.12-4.04 (m, 8H), 2.04-1.94 (m, 2H), 1.72-1.63 (m, 2H), 1.31 (t, 12H, $J = 8.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -0.53; ^{13}C NMR (100 MHz, CDCl_3) δ 132.9 (2CH), 77.4 (2CH), 63.7 (4CH₂), 33.8 (2CH₂), 22.4 (CH₂), 16.0 (4CH₃); MS (FAB, glycerol) m/z (%) 401 (20) $[\text{M}+\text{H}]^+$, 247 (50) $[\text{M}-(\text{EtO})_2\text{P}(\text{O})\text{OH}+\text{H}]^+$, 155 (100) $[(\text{EtO})_2\text{P}(\text{O})\text{OH}+\text{H}]^+$, 127 (25) $[(\text{EtO})\text{P}(\text{O})(\text{OH})_2+\text{H}]^+$, 99 (45) $[\text{P}(\text{O})(\text{OH})_3+\text{H}]^+$; HRMS (EI, 70 eV) m/z calcd for $\text{C}_{15}\text{H}_{30}\text{O}_8\text{P}_2$: 400.1316 $[\text{M}]^+$; found: 400.1446.

meso -1,4-bisdiethylphosphate 6

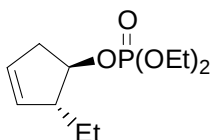


Yield: 1.224 g (89 %). IR (film) $\nu_{\max}$ 2986, 2935, 2911, 1735, 1717, 1445, 1396, 1384, 1263, 1165, 1028, 972 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.93 (bs, 2H), 4.78-4.72 (m, 2H), 4.31-4.23 (m, 2H), 4.20-4.11 (m, 8H), 1.51 (s, 3H) 1.39-1.36 (m, 15 H); ^{31}P NMR (162 MHz, CDCl_3) δ -0.55; ^{13}C NMR (100 MHz, CDCl_3) δ 128.6 (2CH), 109.6 (C), 76.5 (2CH), 75.4 (2CH), 64.1 (4CH₂, $J_{\text{PC}} = 4$ Hz), 27.0 (CH₃), 24.9 (CH₃), 26.0 (2CH₂), 16.0 (4CH₃, $J_{\text{PC}} = 7$ Hz); MS (FAB, glycerol) m/z (%) 459 (45) $[\text{M}+\text{H}]^+$, 305 (100) $[\text{M}-(\text{EtO})_2\text{P}(\text{O})\text{OH}+\text{H}]^+$, 155 (65) $[(\text{EtO})_2\text{P}(\text{O})\text{OH}+\text{H}]^+$, 127 (30) $[(\text{EtO})\text{P}(\text{O})(\text{OH})_2+\text{H}]^+$, 99 (60) $[\text{P}(\text{O})(\text{OH})_3+\text{H}]^+$; HRMS (EI, 70 eV) m/z calcd for $\text{C}_{17}\text{H}_{32}\text{O}_{10}\text{P}_2$: 459.1549 $[\text{M}+\text{H}]^+$; found: 459.1563.

Small scale screening of ligands 5. General procedure for the copper phosphoramidite catalyzed enantioselective desymmetrization of meso-bisdiethylphosphates 2a, 2b, 2c, 6. A solution of $[\text{Cu}(\text{OTf})_2] \cdot \text{C}_6\text{H}_6$ (1.5 mg, 5.4 μmol) and chiral ligand 5 (10.8 μmol) in anhydrous toluene (1.5 mL) was stirred at rt for 45 min. The colorless solution was cooled to the required temperature and a solution of meso-bisdiethylphosphate (54.0 μmol) in toluene (0.5 mL) was slowly added. After 5 min, R_2Zn ($\text{R} = \text{Et}$, 1.1 M in toluene, 98 μL , 108 μmol ; $\text{R} = \text{Me}$, 2.0 M in toluene, 54 μL , 108 μmol) was added and the resulting solution was stirred at that temperature for 16 h. The mixture was quenched with a saturated aqueous NH_4Cl solution (1.0 mL). After extraction with Et_2O , the organic phase was dried over Na_2SO_4 , volatiles were removed under reduced pressure and the crude reaction mixture was purified by flash chromatography (eluant: petroleum ether / ethyl acetate 55/45).

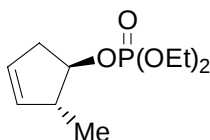
Preparative procedure for the copper phosphoramidite catalyzed enantioselective desymmetrization of *meso*-bisdiethylphosphates **2a, **2b**, **2c**, **6**.** Under the optimized conditions (ligand, temperature), the reactions reported in Table 1 (entry 7, 10), Table 2 (entry 10), Table 3 (entries 4,5), and Scheme 2 were repeated on a larger scale (1.08 mmol). A solution of [Cu(OTf)₂·C₆H₆] (30.0 mg, 0.108 mmol) and chiral ligand **5** (0.216 mmol) in anhydrous toluene (30.0 mL) was stirred at rt for 45 min. The colorless solution was cooled to the required temperature and a solution of *meso*-bisdiethylphosphate (1.08 mmol) in toluene (10 mL) was slowly added. After 5 min, R₂Zn (R = Et, 1.1 M in toluene, 1.96 mL, 2.16 mmol; R = Me, 2.0 M in toluene, 1.08 mL, 2.16 mmol) was added and the resulting solution was stirred at that temperature for 16 h. The mixture was quenched with a saturated aqueous NH₄Cl solution (20.0 mL). After extraction with Et₂O, the organic phase was dried over Na₂SO₄, volatiles were removed under reduced pressure and the crude reaction mixture was purified by flash chromatography (eluant: petroleum ether / ethyl acetate 55/45). The results (%yield and %e.e.) were identical (within the experimental error, ± 1%) to those obtained in the small scale screening experiments (see above).

(1*R*,2*R*)- Phosphoric acid diethyl ester 2-ethyl-cyclopent-3-enyl ester (3a**, R=Et)**



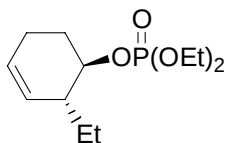
Yield: 264 mg (98 %). IR (film) ν_{max} 2963, 2932, 2876, 1459, 1445, 1393, 1370, 1263, 1167, 1028, 821 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.69-5.62 (m, 2H), 4.70-4.64 (m, 1H), 4.14-4.04 (m, 4H), 2.79-2.67 (m, 2H), 2.53-2.45 (m, 1H), 1.53-1.29 (m, 8H), 0.94 (t, 3H, *J* = 7.4 Hz); ³¹P NMR (162 MHz, CDCl₃) δ -0.35; ¹³C NMR (100 MHz, CDCl₃) δ 132.4 (CH), 127.2 (CH), 82.7 (CH), 63.5 (2CH₂), 54.5 (CH), 39.8 (CH₂), 25.4 (CH₂), 16.0 (2CH₃), 11.6 (CH₃); [α]_D²⁹⁸ = -84 (c 1.2, CHCl₃); MS (EI, 70 eV) *m/z* (%) 249 (40) [M+H]⁺, 155 (100) [(EtO)₂P(O)OH+H]⁺, 95 (10) [M-(EtO)₂P(O)OH+H]⁺; HRMS (EI, 70 eV) *m/z* calcd for C₁₁H₂₂O₄P: 249.1256 [M+H]⁺; found: 249.1260. The e.e. was determined by GC on a chiral stationary phase [column: see General Procedures; carrier: H₂ (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C, 0.8 °C/min to 130 °C]. *t*_R = 1.81 min (*n*-decane), 34.1 min (1*R*,2*R* enantiomer), 34.6 min (1*S*,2*S* enantiomer), 54.6 min (**2a**).

(1*R*,2*R*)- Phosphoric acid diethyl ester 2-methyl-cyclopent-3-enyl ester (3a**, R=Me)**



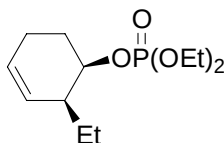
Yield: 137 mg (54 %). IR (film) ν_{max} 2960, 2927, 2892, 1465, 1458, 1393, 1370, 1262, 1167, 1029, 824 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.59 (bs, 2H), 4.69-4.54 (m, 1H), 4.15-4.05 (m, 4H), 2.84-2.72 (m, 2H), 2.54-2.45 (m, 1H), 1.37-1.31 (m, 6H), 1.05 (d, 3H, *J* = 7.2 Hz); ³¹P NMR (162 MHz, CDCl₃) δ -0.35; ¹³C NMR (100 MHz, CDCl₃) δ 134.3 (CH), 126.4 (CH), 84.6 (CH), 63.5 (2CH₂), 47.2 (CH), 39.4 (CH₂), 17.6 (CH₃), 16.1 (2CH₃); [α]_D²⁹⁸ = -56 (c 0.92, CHCl₃); MS (EI, 70 eV) *m/z* (%) 155 (60) [(EtO)₂P(O)OH+H]⁺, 127 (45) [(EtO)P(O)(OH)₂+H]⁺, 99 (65) [P(O)(OH)₃+H]⁺, 80 (30) [M-(EtO)₂P(O)OH+H]⁺, 43 (90), 28 (100). The e.e. was determined by GC on a chiral stationary phase [column: see General Procedures; carrier: H₂ (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C, 0.8 °C/min to 130 °C]. *t*_R = 1.81 min (*n*-decane), 25.2 min (1*R*,2*R* enantiomer), 25.5 min (1*S*,2*S* enantiomer), 54.6 min (**2a**).

(1*R*,2*R*)- Phosphoric acid diethyl ester 2-ethyl-cyclohex-3-enyl ester (3b)



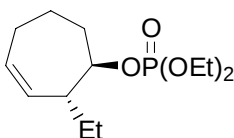
Yield: 167 mg (59 %). IR (film) $\nu_{\max}$ 2964, 2873, 1655, 1515, 1465, 1250, 1022, 805 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.71-5.64 (m, 1H), 5.57-5.50 (m, 1H), 4.40-4.29 (m, 1H), 4.17-4.07 (m, 4H), 2.26-2.01 (m, 4H), 1.87-1.76 (m, 1H), 1.67-1.56 (m, 1H), 1.45-1.31 (m, 7H) 0.95 (t, 3H, $J = 7.4$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -0.47; ^{13}C NMR (100 MHz, CDCl_3) δ 127.8 (CH), 126.4 (CH), 77.8 (CH), 63.5 (2CH₂), 43.2 (CH), 27.7 (CH₂), 25.0 (CH₂), 23.3 (CH₂), 16.1 (2CH₃), 10.5 (CH₃); $[\alpha]_{\text{D}}^{298} = -63$ (c 0.95, CHCl_3); MS (EI, 70 eV) m/z (%) 262 (2) $[\text{M}]^+$, 155 (100) $[(\text{EtO})_2\text{P}(\text{O})\text{OH}+\text{H}]^+$, 127 (95) $[(\text{EtO})\text{P}(\text{O})(\text{OH})_2+\text{H}]^+$, 108 (40) $[\text{M}-(\text{EtO})_2\text{P}(\text{O})\text{OH}]^+$, 99 (98) $[\text{P}(\text{O})(\text{OH})_3+\text{H}]^+$, 79 (80) $[\text{M}-(\text{EtO})_2\text{P}(\text{O})\text{OH}-\text{Et}]^+$; HRMS (EI, 70 eV) m/z calcd for $\text{C}_{12}\text{H}_{23}\text{O}_4\text{P}$: 262.1334 $[\text{M}]^+$; found: 262.1314.

(1*R,2*S**)- Phosphoric acid diethyl ester 2-ethyl-cyclohex-3-enyl ester (4b)**



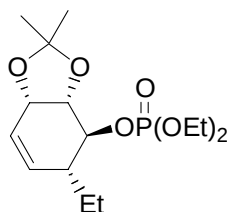
Yield: 28 mg (10 %). IR (film) $\nu_{\max}$ 2966, 2876, 1648, 1508, 1458, 1259, 1027, 802 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.71-5.64 (m, 1H), 5.57-5.50 (m, 1H), 4.40-4.29 (m, 1H), 4.17-4.07 (m, 4H), 2.26-2.01 (m, 4H), 1.87-1.76 (m, 1H), 1.67-1.56 (m, 1H), 1.45-1.31 (m, 7H) 0.95 (t, 3H, $J = 7.4$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -0.47; ^{13}C NMR (100 MHz, CDCl_3) δ 127.8 (CH), 126.4 (CH), 77.8 (CH), 63.5 (2CH₂), 43.2 (CH), 27.7 (CH₂), 25.0 (CH₂), 23.3 (CH₂), 16.1 (2CH₃), 10.5 (CH₃); MS (EI, 70 eV) m/z (%) 262 (2) $[\text{M}]^+$, 155 (100) $[(\text{EtO})_2\text{P}(\text{O})\text{OH}+\text{H}]^+$, 127 (95) $[(\text{EtO})\text{P}(\text{O})(\text{OH})_2+\text{H}]^+$, 108 (50) $[\text{M}-(\text{EtO})_2\text{P}(\text{O})\text{OH}]^+$, 99 (98) $[\text{P}(\text{O})(\text{OH})_3+\text{H}]^+$, 79 (95) $[\text{M}-(\text{EtO})_2\text{P}(\text{O})\text{OH}-\text{Et}]^+$; HRMS (EI, 70 eV) m/z calcd for $\text{C}_{12}\text{H}_{23}\text{O}_4\text{P}$: 262.1334 $[\text{M}]^+$; found: 262.1304.

(1*R*,2*R*)- Phosphoric acid diethyl ester 2-ethyl-cyclohept-3-enyl ester (3c)



Yield: 256 mg (86 %). IR (film) $\nu_{\max}$ 2978, 1653, 1392, 1262, 1166, 1033, 997, 870 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.87 (ddt, 1H, $J = 11.3$ Hz, $J = 6.2$ Hz, $J = 1.7$), 5.47-5.38 (m, 1H), 4.31-4.22 (m, 1H), 4.15-4.05 (m, 4H), 2.52-2.43 (m, 1H), 2.29-2.20 (m, 1H), 2.34-2.25 (m, 2H), 1.98-1.87 (m, 1H), 1.80-1.61 (m, 2H), 1.52-1.37 (m, 2H), 1.36-1.29 (m, 6H), 0.93 (t, 3H, $J = 7.0$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -0.68; ^{13}C NMR (100 MHz, CDCl_3) δ 132.9 (CH), 131.0 (CH), 79.2 (CH), 63.4 (2CH₂), 45.8 (CH), 36.4 (CH₂), 27.9 (CH₂), 24.5 (CH₂), 23.0 (CH₂), 16.1 (2CH₃), 11.0 (CH₃); $[\alpha]_{\text{D}}^{298} = -34$ (c 0.95, CHCl_3); MS (FAB, glycerol) m/z (%) 277 (25) $[\text{M}+\text{H}]^+$, 155 (100) $[(\text{EtO})_2\text{P}(\text{O})\text{OH}+\text{H}]^+$, 127 (55) $[(\text{EtO})\text{P}(\text{O})(\text{OH})_2+\text{H}]^+$, 123 (70) $[\text{M}-(\text{EtO})_2\text{P}(\text{O})\text{OH}+\text{H}]^+$, 99 (85) $[\text{P}(\text{O})(\text{OH})_3+\text{H}]^+$.

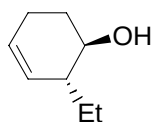
Phosphoric acid diethyl ester (1*S, 2*R**,5*S**, 6*S**)-2-ethyl-5,6-isopropylidendioxy-cyclohex-3-enyl ester (7)**



Yield: 188 mg (52 %). IR (film) $\nu_{\max}$ 2986, 2935, 2876, 1457, 1381, 1372, 1259, 1219, 1170, 1026, 976 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.88 (dt, 1H, $J = 12$ Hz, $J = 4$ Hz), 5.79-5.74 (m, 1H), 4.63-4.61 (m, 1H), 4.33-4.26 (m, 1H), 4.23-4.10 (m, 5H), 2.25-2.20 (m, 1H), 1.87-1.77 (m, 1H), 1.52 (s, 3H), 1.51-1.43 (m, 1H), 1.48 (s, 3H), 1.47-1.43 (m, 6H) 0.91 (t, 3H, $J = 7.4$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ -0.43; ^{13}C NMR (100 MHz, CDCl_3) δ 133.0 (CH), 123.6 (CH), 109.7 (C), 79.2 (CH), 77.6 (CH), 63.7 (2CH₂, $J_{\text{CP}} = 6$ Hz), 28.1 (CH₃), 26.1 (CH₃), 22.8 (CH₂), 16.1 (2CH₃), 10.7 (CH₃); $[\alpha]_{\text{D}}^{298} = -21$ (c 1.3, CHCl_3); MS (EI, 70 eV) m/z (%) 335 (1) $[\text{M}+\text{H}]^+$, 319 (40) $[\text{M}-\text{CH}_3]^+$, 155 (100) $[(\text{EtO})_2\text{P}(\text{O})\text{OH}+\text{H}]^+$, 127 (55) $[(\text{EtO})\text{P}(\text{O})(\text{OH})_2+\text{H}]^+$, 99 (25) $[\text{P}(\text{O})(\text{OH})_3+\text{H}]^+$; HRMS (EI, 70 eV) m/z calcd for $\text{C}_{15}\text{H}_{28}\text{O}_6\text{P}$: 335.1624 $[\text{M}+\text{H}]^+$; found: 335.1668.

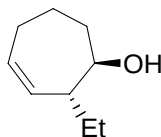
General procedure for the reduction of phosphate esters 3b, 4b, 3c, 7. To a stirred solution of phosphate ester (0.10 mmol) in dry Et_2O (1.66 mL), LAH (22.17 mg, 0.60 mmol) was added portionwise at rt. The solution was stirred for 20 min before quenching with water (SLOWLY !). The solution was filtered over a small cotton plug and volatiles were removed under reduced pressure.

(1*R*,2*R*)- 2-ethyl-cyclohex-3-enol (8)



Yield: quantitative. Spectral data were in complete agreement with literature data.¹ The e.e. was determined by GC on a chiral stationary phase [see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C 10 min, 10 °C/min to 200 °C]. $t_R = 7.9$ min and 8.3 min (*cis*-2-ethyl-cyclohexen-3-ol enantiomers, 1:1), 8.4 min (1*S*,2*S* enantiomer), 8.9 min (1*R*,2*R* enantiomer).

(1*R*,2*R*)- 2-ethyl-cyclohept-3-enol (9)

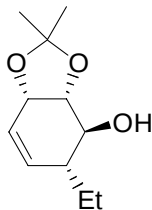


Yield: quantitative. IR (film) $\nu_{\max}$ 3367, 2963, 2930, 2874, 1648, 1445, 1378, 1259, 1024, 908 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.92-5.85 (m, 1H), 5.49-5.45 (m, 1H), 3.58-3.54 (m, 1H), 2.36-2.28 (m, 1H), 2.13-2.05 (m, 3H), 1.80-1.61 (m,

¹ Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2001**, 40, 930-932.

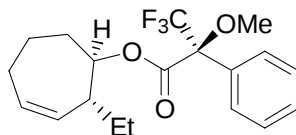
3H), 1.54-1.41 (m, 3H) 0.96 (t, 3H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 133.0 (CH), 132.0 (CH), 71.3 (CH), 47.3 (CH), 38.3 (CH_2), 28.1 (CH_2), 24.4 (CH_2), 23.2 (CH_2), 11.1 (CH_3); $[\alpha]_{\text{D}}^{298} = -41$ (c 0.93, CHCl_3).

(1*S, 2*R**, 5*S**, 6*S**)-2-ethyl-5,6-isopropylidendioxy-cyclohex-3-enol (10)**



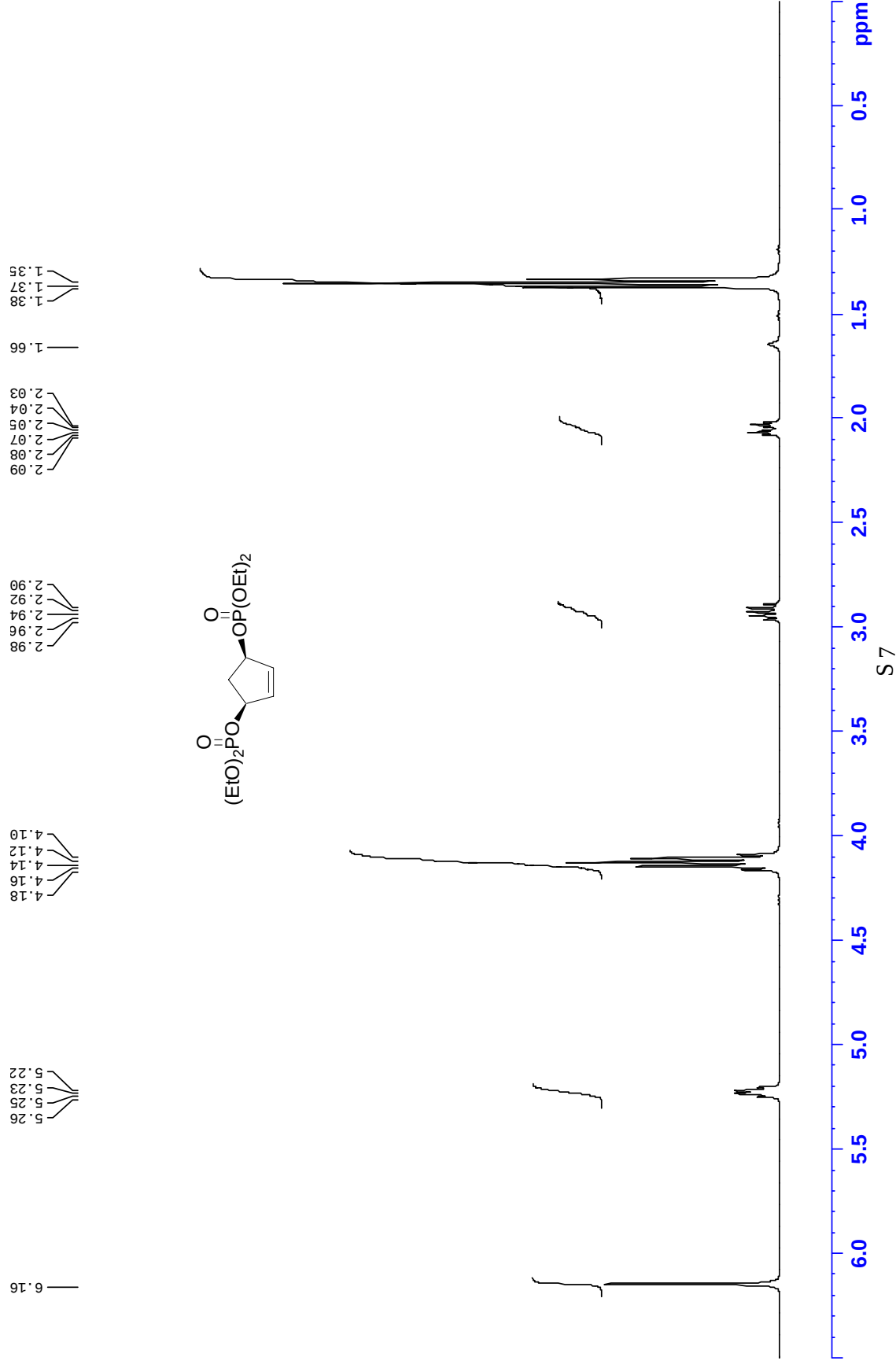
Yield: quantitative. IR (film) ν_{max} 3589, 3046, 2960, 1433, 1380, 1258, 1216, 1057, 865, 824 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.87 (dt, 1H, $J = 10$ Hz, $J = 3.2$ Hz), 5.82-5.80 (m, 1H), 4.63-4.60 (m, 1H) 3.96 (dd, 1H, $J = 9.3$ Hz, $J = 6.4$ Hz), 3.36 (t, 1H, $J = 9.3$ Hz), 2.06-1.97 (m, 1H), 1.90-1.80 (m, 1H), 1.52 (s, 3H), 1.43-1.33 (m, 1H), 1.40 (s, 3H), 0.98 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 134.6 (CH), 123.7 (CH), 80.4 (CH), 73.1 (CH), 73.0 (CH), 42.1 (CH), 28.6 (CH_3), 26.0 (CH_3), 23.3 (CH_2), 10.4 (CH_3); $[\alpha]_{\text{D}}^{298} = -33$ (c 0.4, CH_2Cl_2); MS (EI, 70 eV) m/z (%) 198 (2) $[\text{M}]^+$, 197 (5) $[\text{M}-\text{H}]^+$, 183 (100) $[\text{M}-\text{CH}_3]^+$, 123 (85), 111 (30), 95 (65); HRMS (EI, 70 eV) m/z calcd for $\text{C}_{11}\text{H}_{18}\text{O}_3$: 198.1256 $[\text{M}]^+$; found: 198.1276. The e.e. was determined by GC on a chiral stationary phase [see General Procedures; carrier: H_2 (70 kPa); injector: 250 $^\circ\text{C}$; detector: 250 $^\circ\text{C}$; oven temperature: 90 $^\circ\text{C}$]. $t_R = 23.1$ min (7%), 23.4 min (93%).

(1*R*, 2*R*)- 2-ethyl-cyclohept-3-enol (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid ester (11)

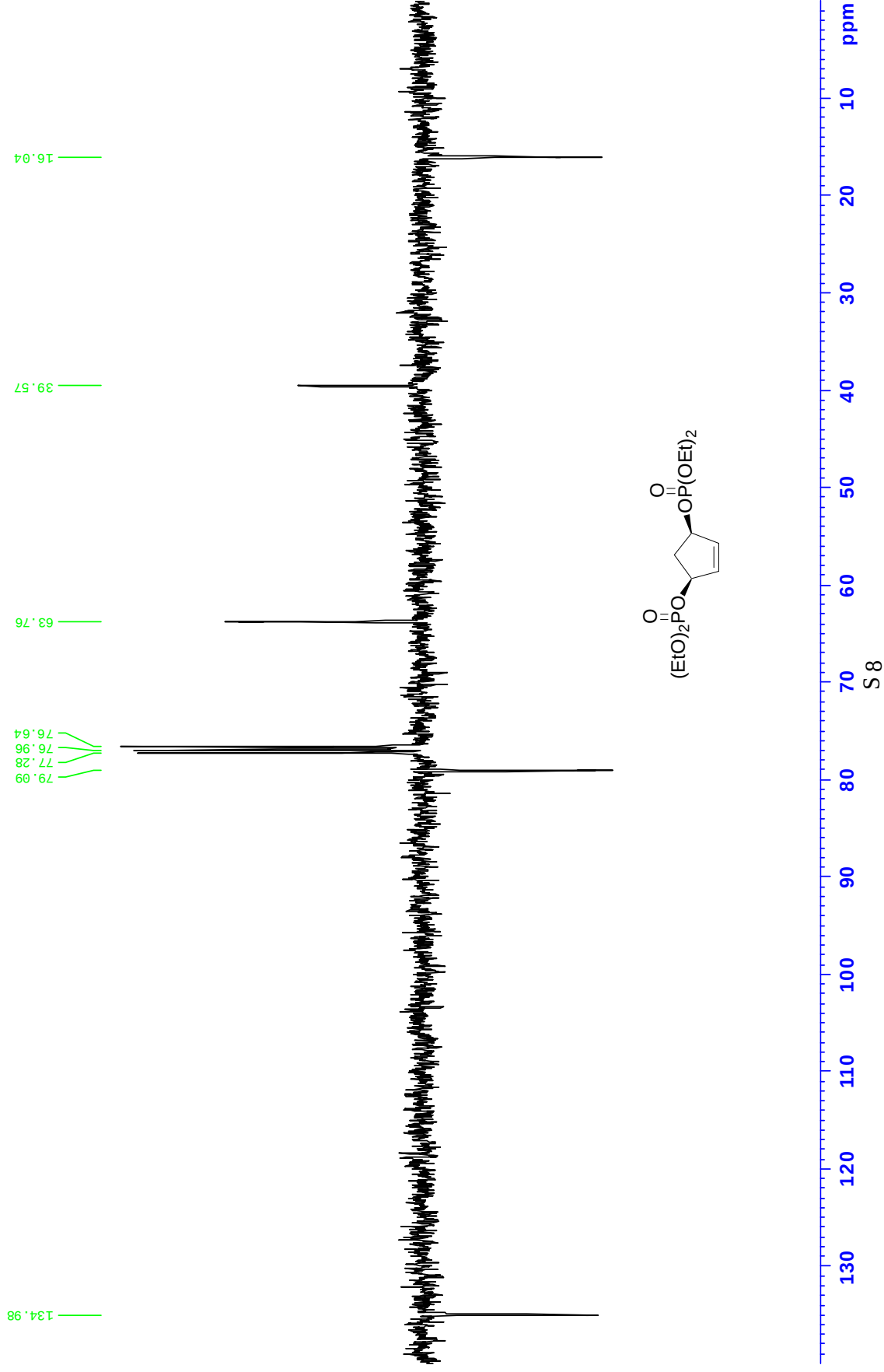


To a stirred solution of alcohol **9** (5 mg, 0.036 mmol) in dry CH_2Cl_2 (1 mL) was added 4-DMAP (8.7 mg, 0.07 mmol), (*R*)-(+)- α -methoxy- α -(trifluoromethyl)phenylacetic acid (16.4 mg, 0.07 mmol) and DCC (45 mg, 0.22 mmol). The solution was stirred overnight at rt. The solvent was evaporated under reduced pressure and the crude reaction mixture was subjected to column chromatography (petroleum ether/ethyl acetate 98/2) to deliver the Mosher ester (12.0 mg, 94%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.58-7.56 (m, 2H), 7.43-7.39 (m, 3H), 5.91-5.85 (m, 1H), 5.40-5.36 (m, 1H), 4.98-4.90 (m, 1H), 3.59-3.58 (m, 1H), 2.26-2.02 (m, 2H), 1.90-1.70 (m, 2H), 1.56-1.43 (m, 1H) 1.41-1.18 (m, 2H), 0.88 (t, $J = 7.4$ Hz, 3H).

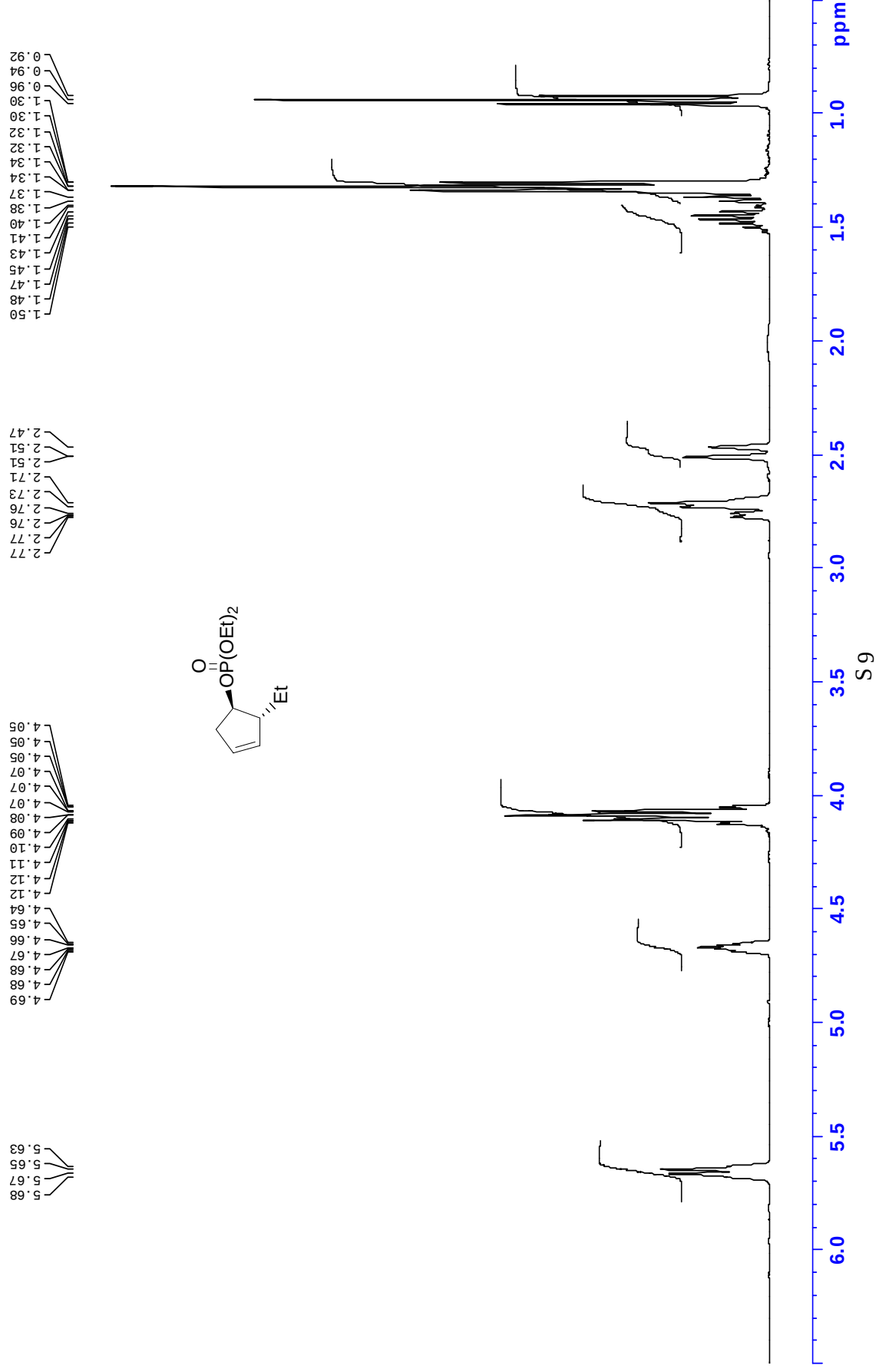
2a: ^1H NMR, 400 MHz, CDCl_3



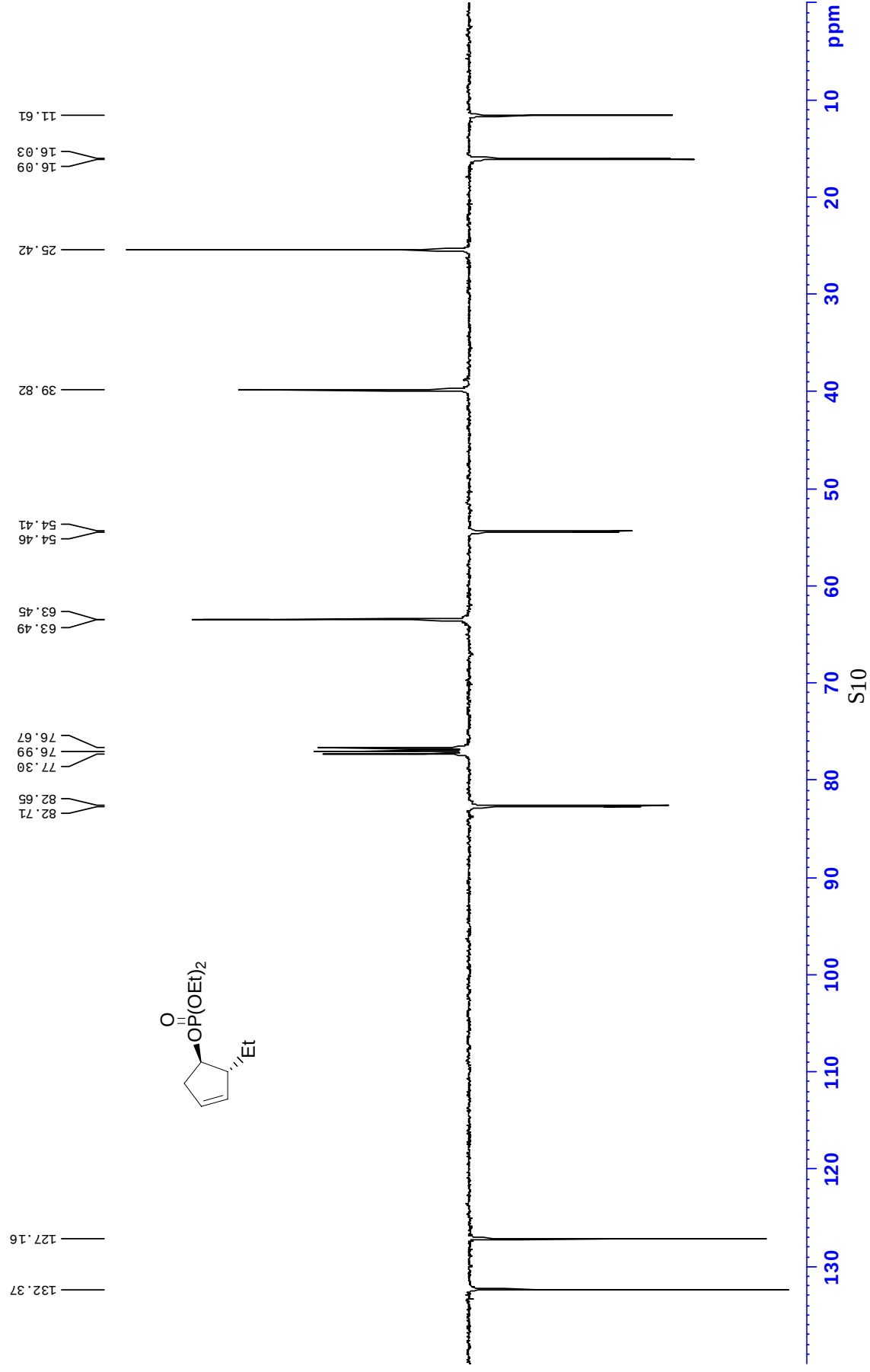
2a: ^{13}C NMR, 100 MHz, CDCl_3



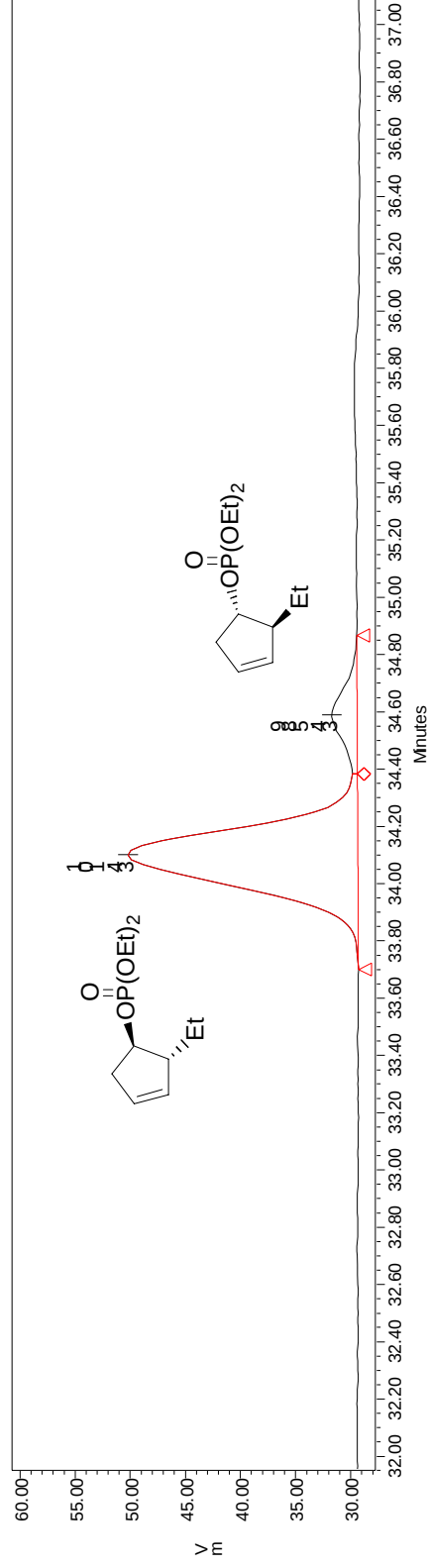
3a, R=Et: ^1H NMR, 400 MHz, CDCl_3



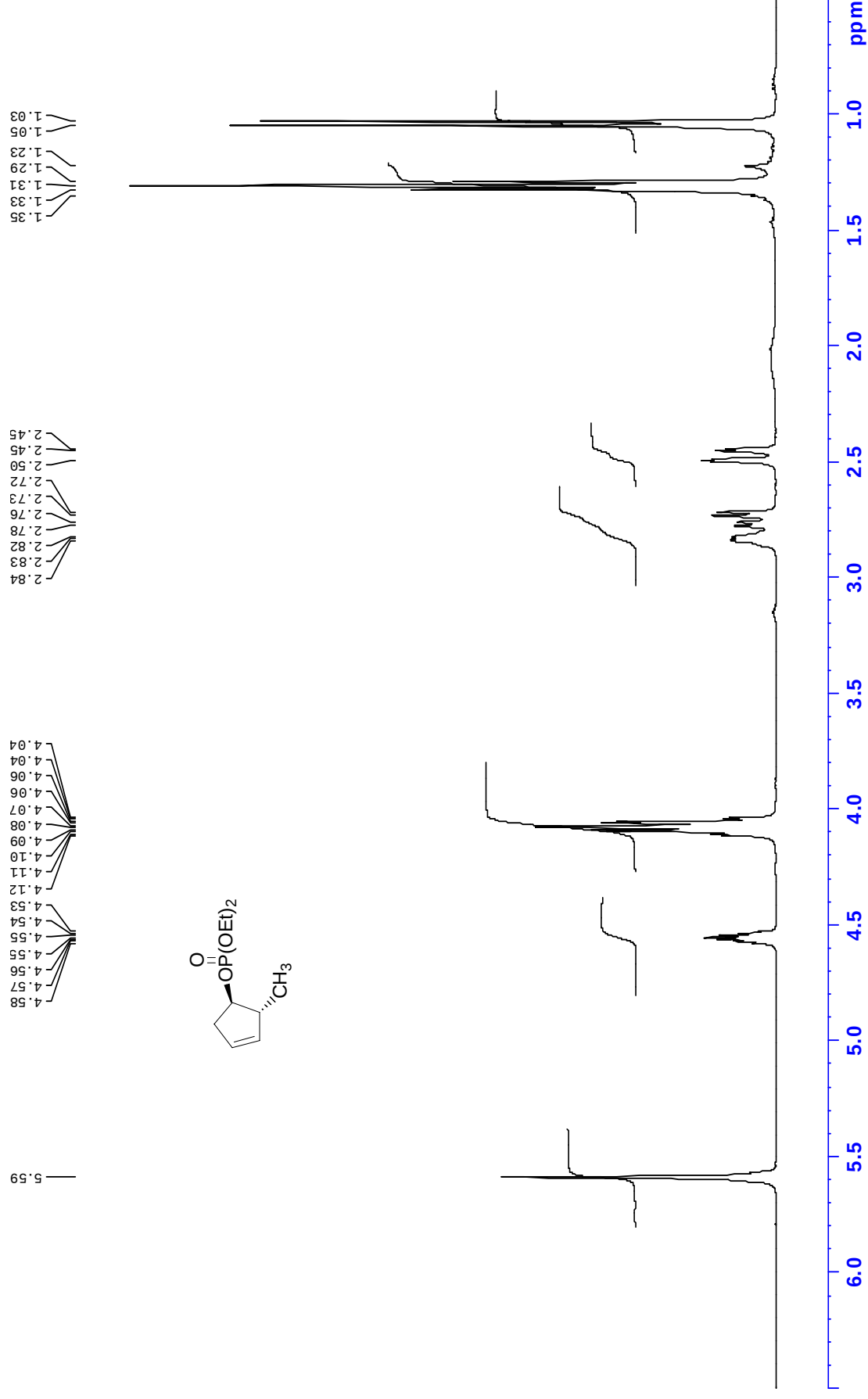
3a, R=Et: ^{13}C NMR, 100 MHz, CDCl_3



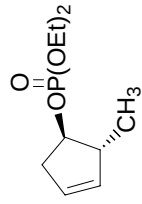
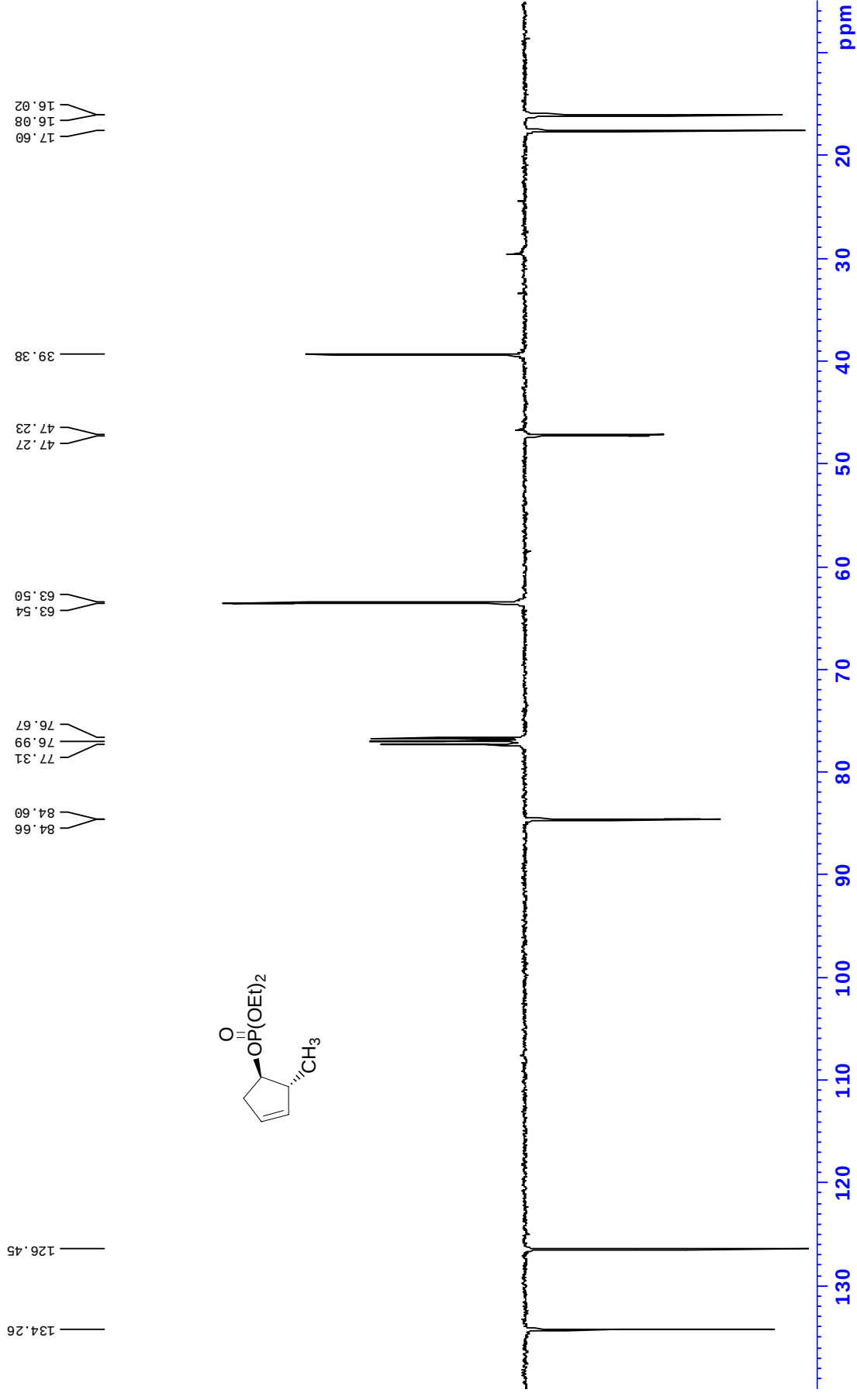
GC Trace of the two enantiomers of 3a (R=Et). Chiral stationary phase, see General Procedures; carrier: H₂ (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C, 0.8 °C/min to 130 °C. *t_R* = 1.81 min (*n*-decane), 34.1 min (1*R*,2*R* enantiomer), 34.6 min (1*S*,2*S* enantiomer), 54.6 min (2a).



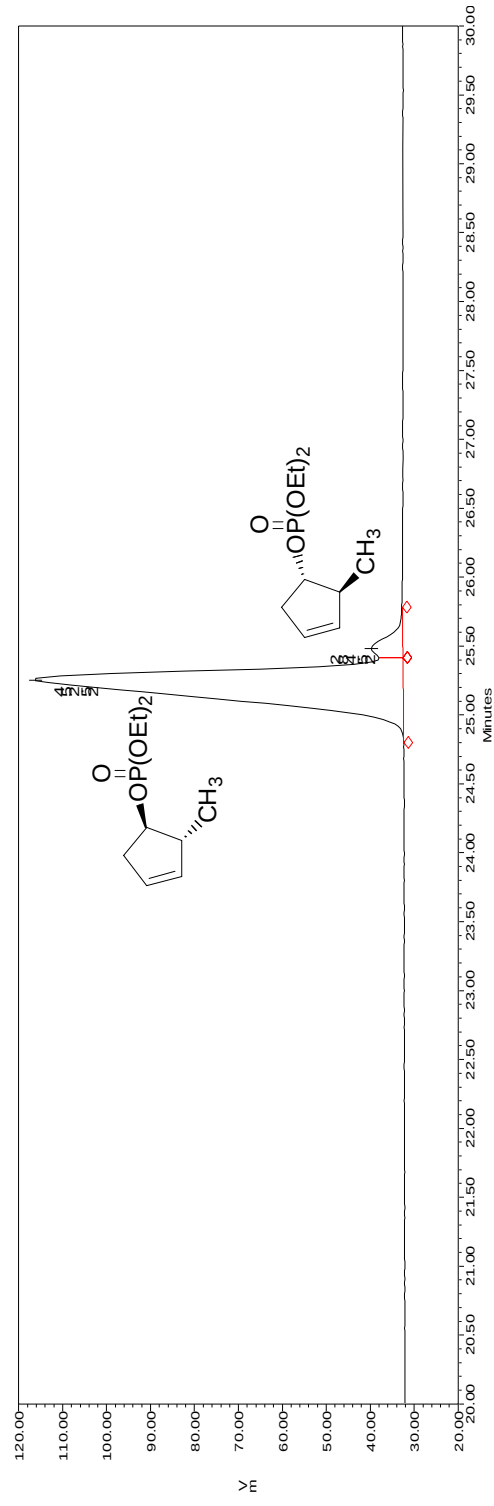
3a, R=Me: ^1H NMR, 400 MHz, CDCl_3



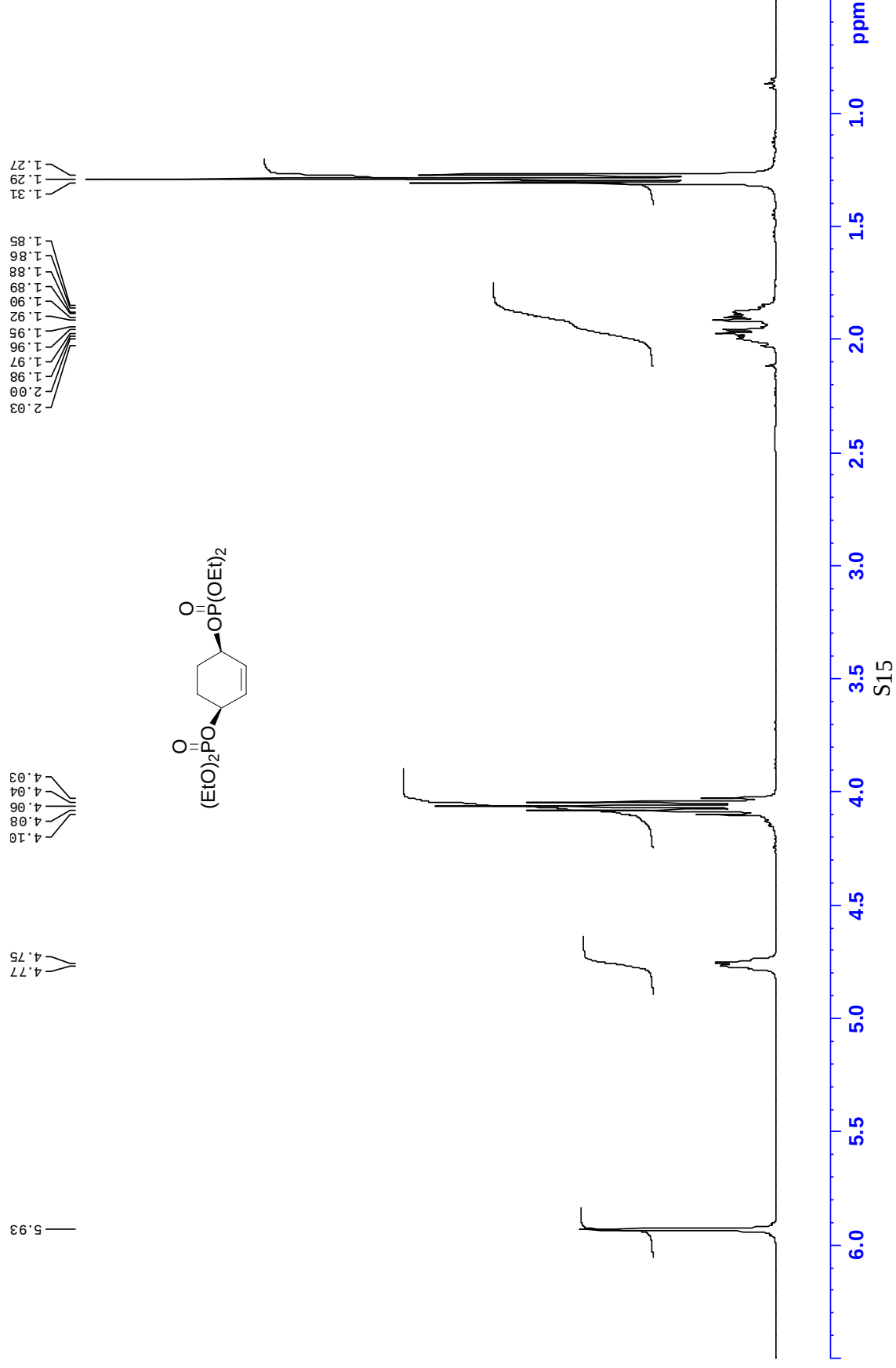
3a, R=Me: ^{13}C NMR, 100 MHz, CDCl_3



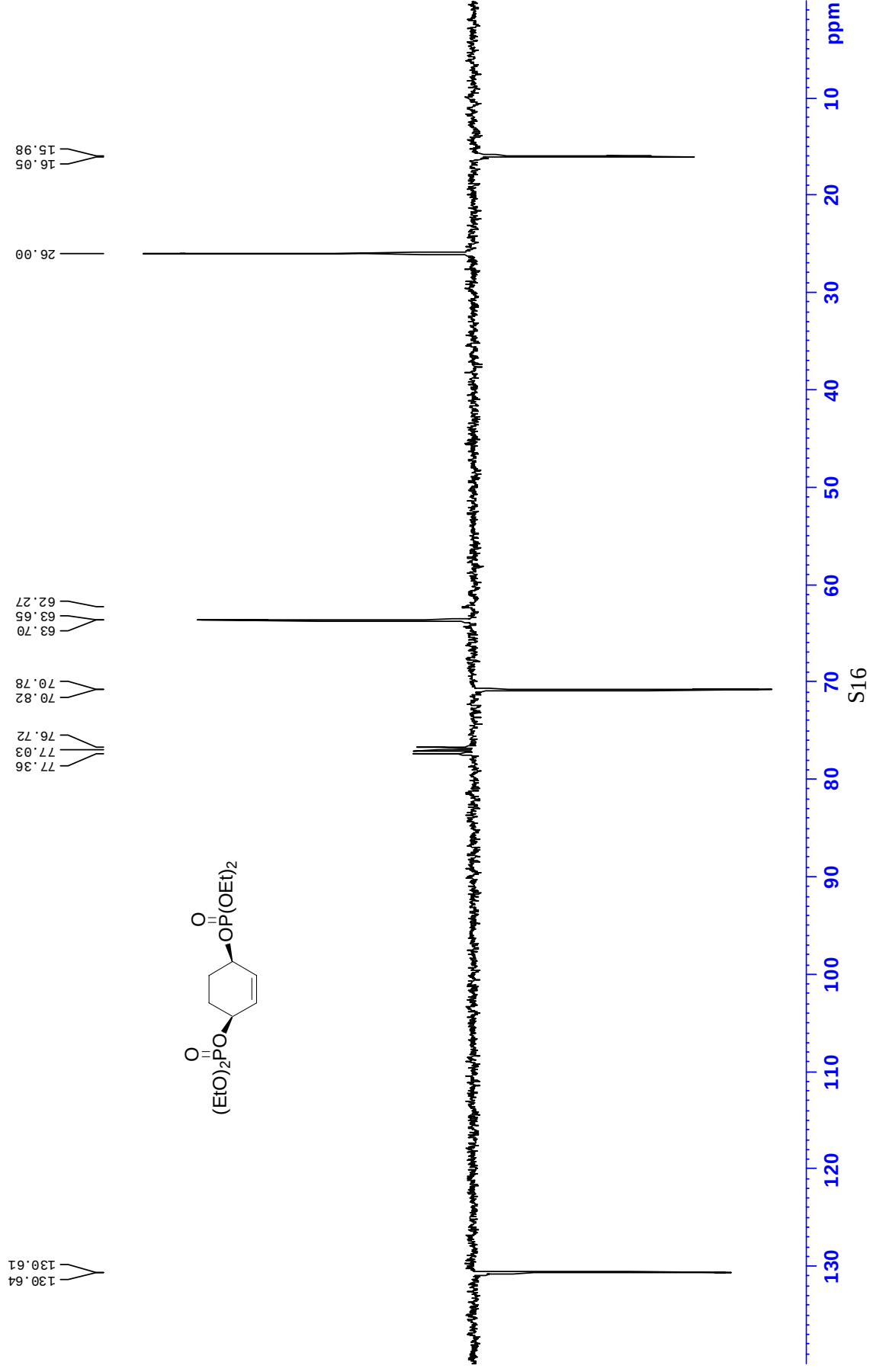
GC Trace of the two enantiomers of 3a (R = Me). Chiral stationary phase, see General Procedures; carrier: H₂ (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C, 0.8 °C/min to 130 °C. *t_R* = 1.81 min (*n*-decane), 25.2 min (1*R*,2*R* enantiomer), 25.5 min (1*S*,2*S* enantiomer), 54.6 min (2a).



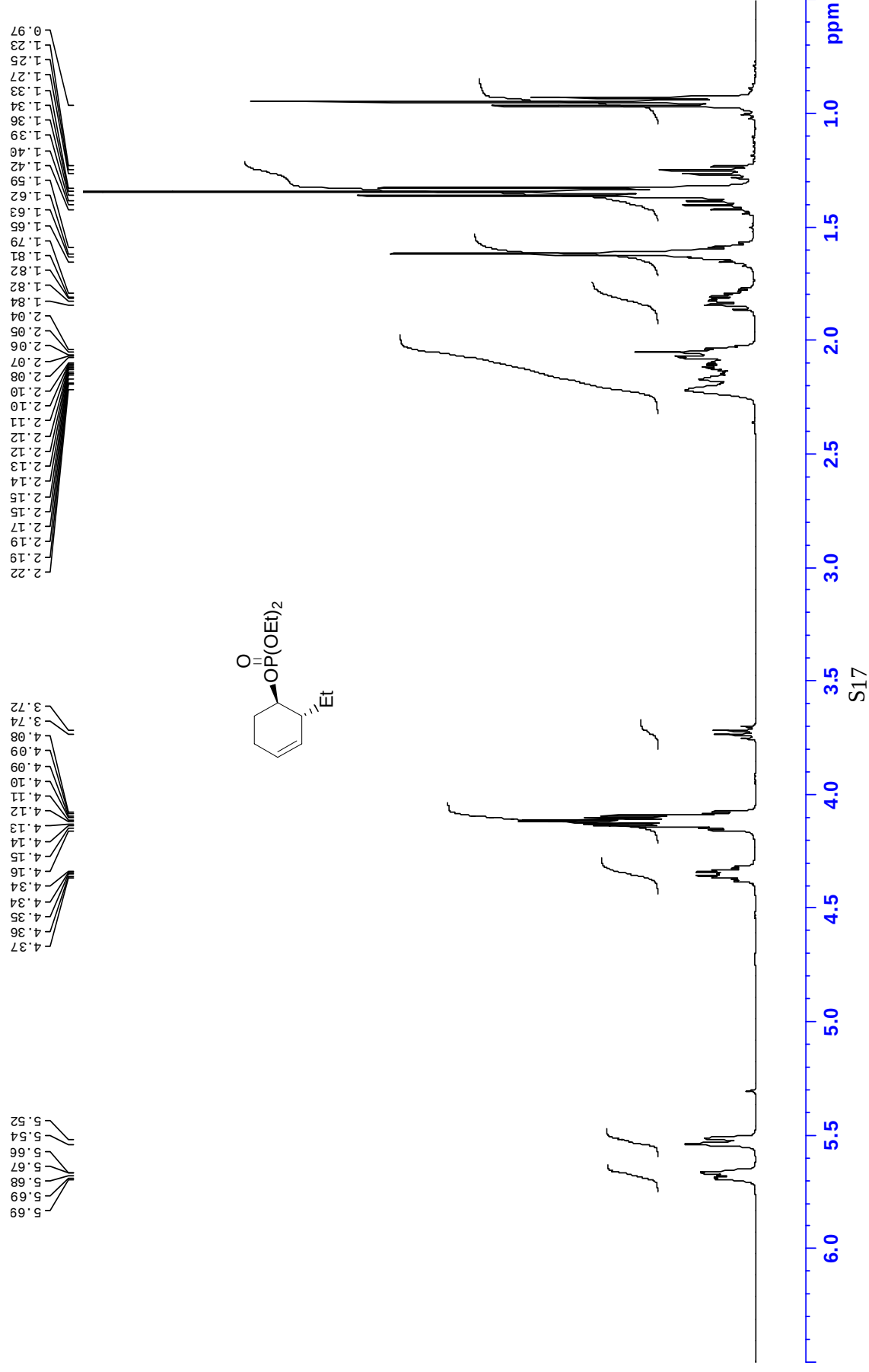
2b: ^1H NMR, 400 MHz, CDCl_3



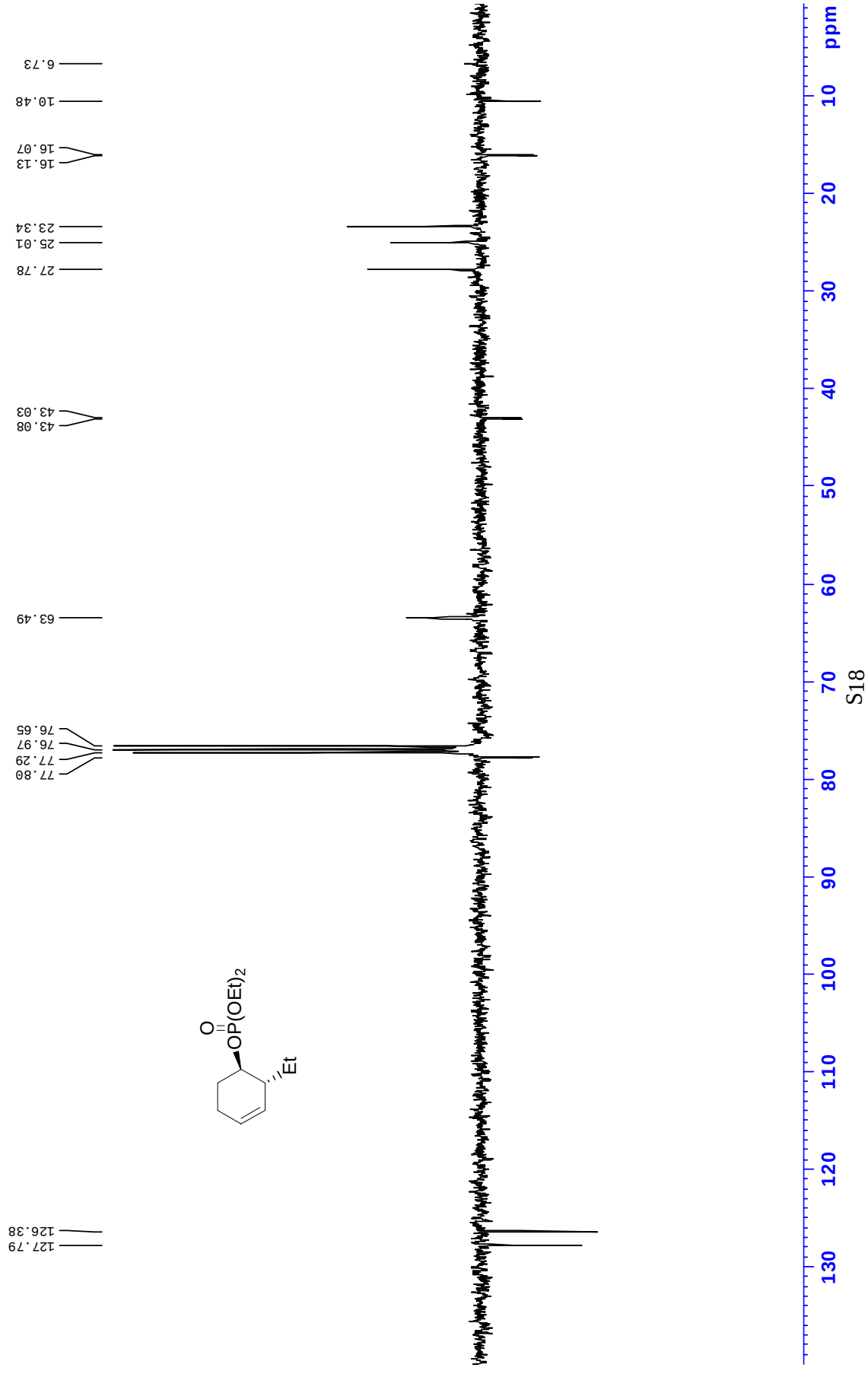
2b: ^{13}C NMR, 100 MHz, CDCl_3



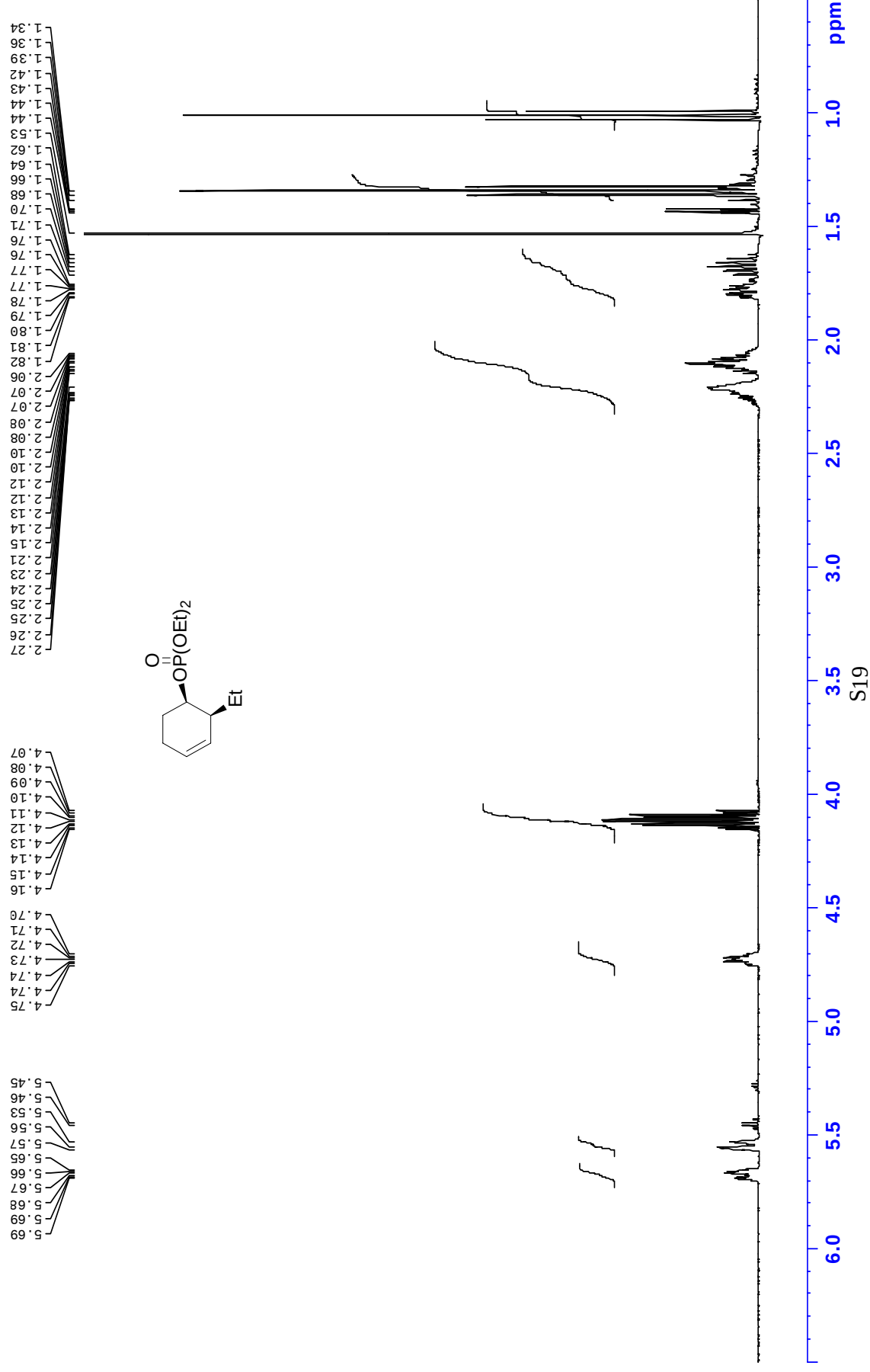
3b: ^1H NMR, 400 MHz, CDCl_3



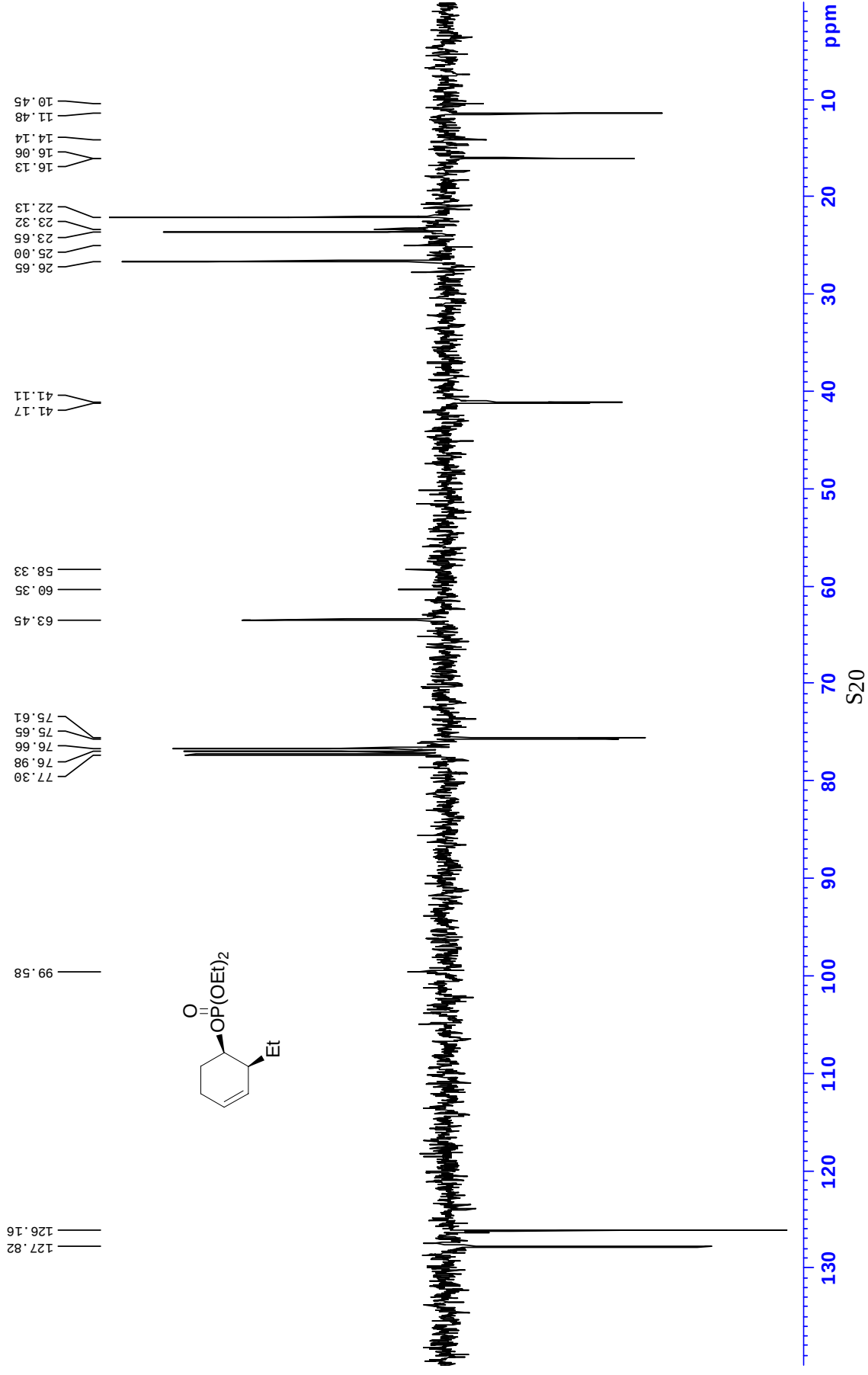
3b: ^{13}C NMR, 100 MHz, CDCl_3



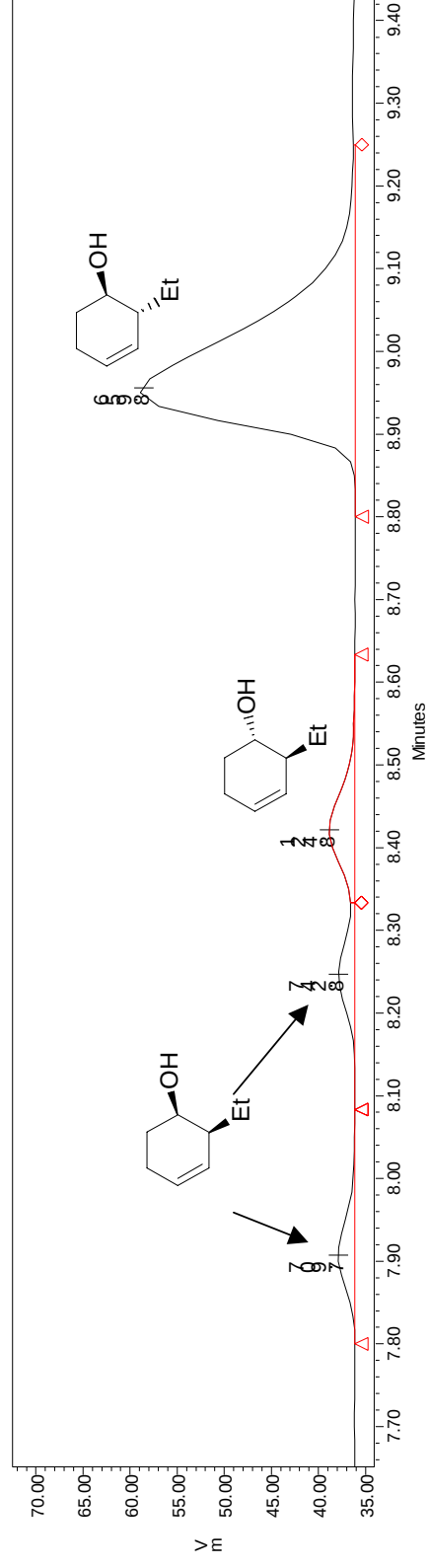
4b: ^1H NMR, 400 MHz, CDCl_3



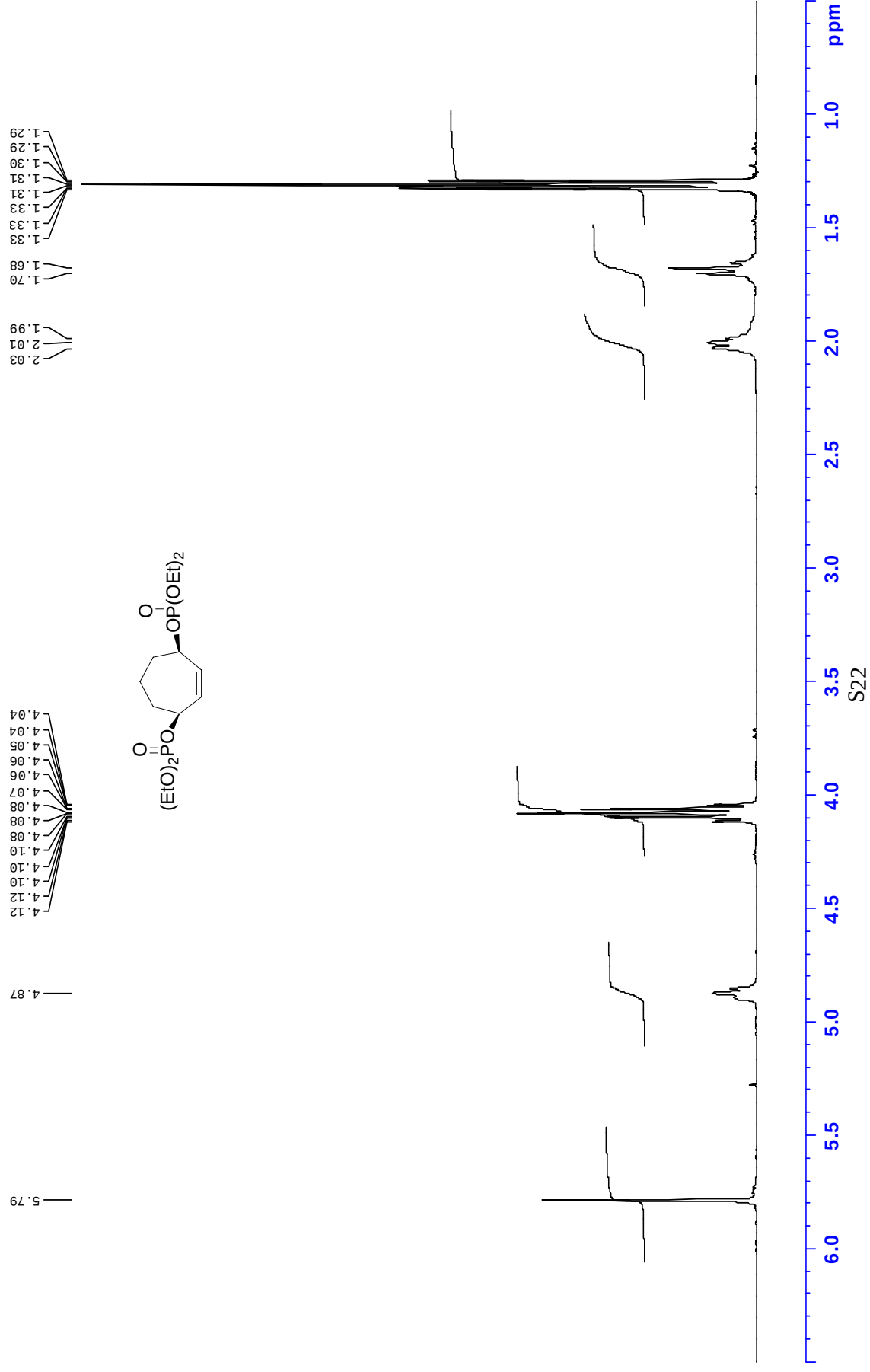
4b: ^{13}C NMR, 100 MHz, CDCl_3



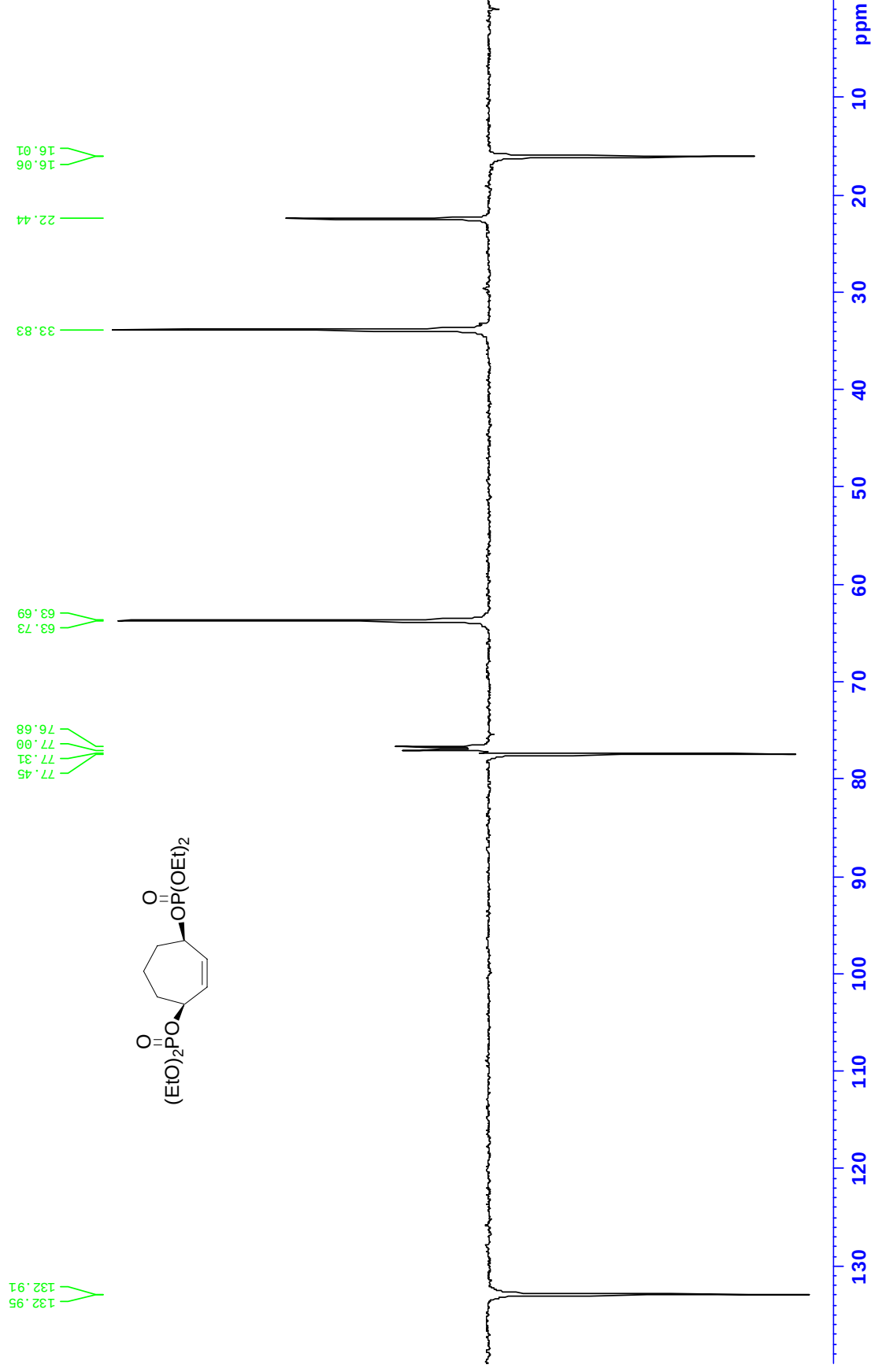
GC Trace of the two enantiomers of 8. Chiral stationary phase, see General Procedures; carrier: H₂ (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C 10 min, 20°C/min to 200 °C. *t_R* = 0.91 min (*n*-decane), 7.9 min and 8.3 min (*cis*-2-ethyl-cyclohexen-3-ol enantiomers, 1:1), 8.4 min (1*S*,2*S* enantiomer), 8.9 min (1*R*,2*R* enantiomer).



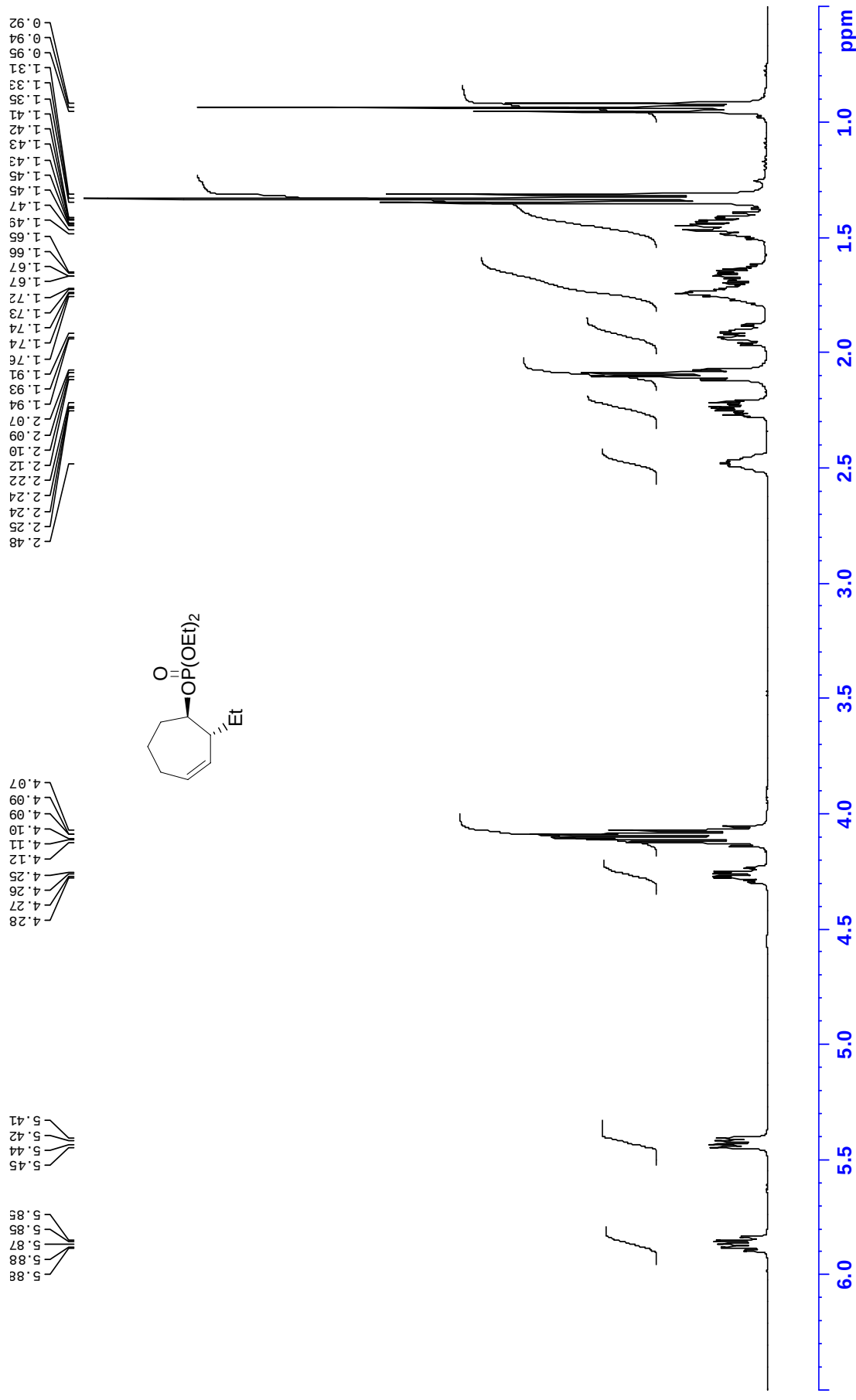
2c: ^1H NMR, 400 MHz, CDCl_3



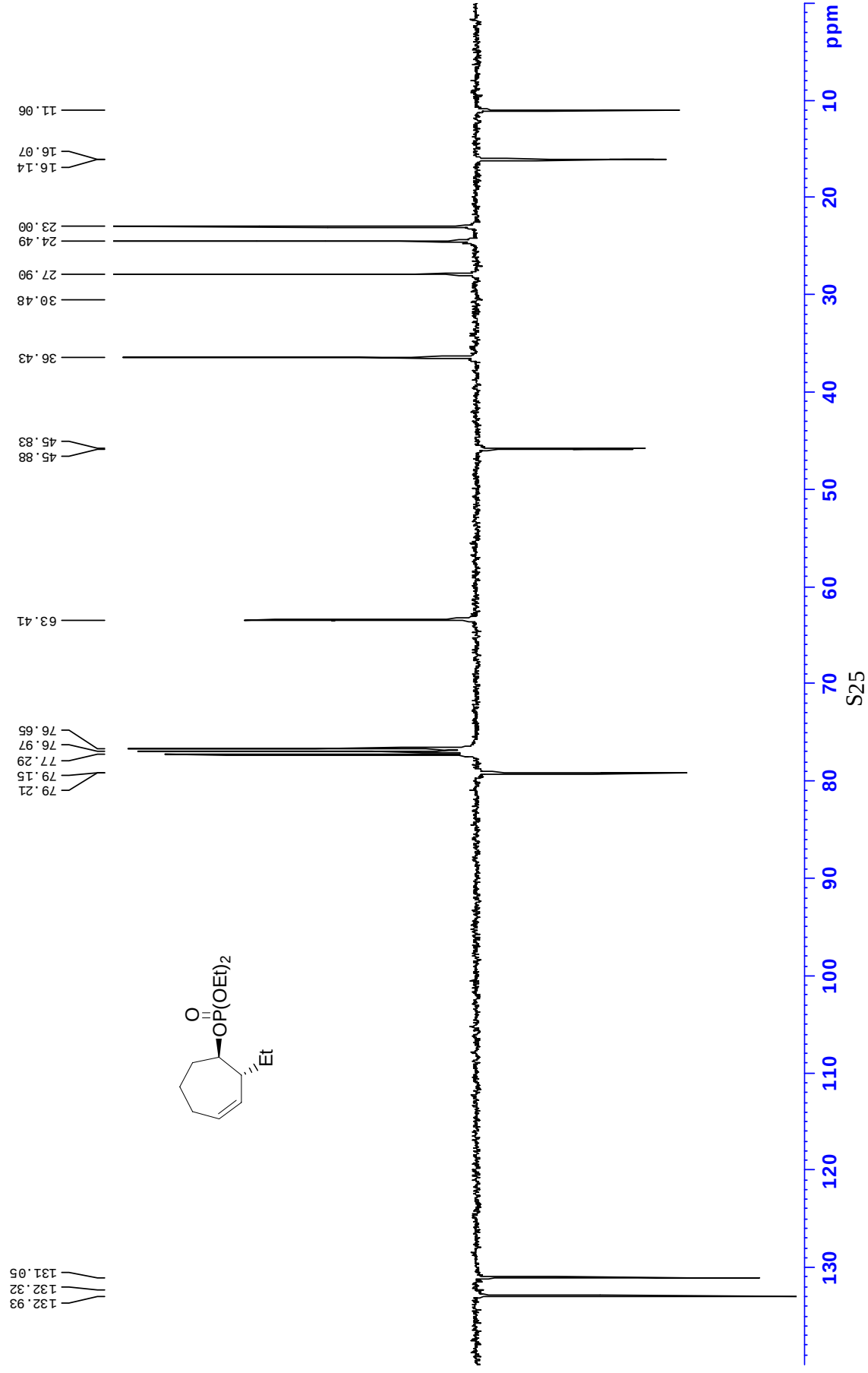
2c: ^{13}C NMR, 100 MHz, CDCl_3



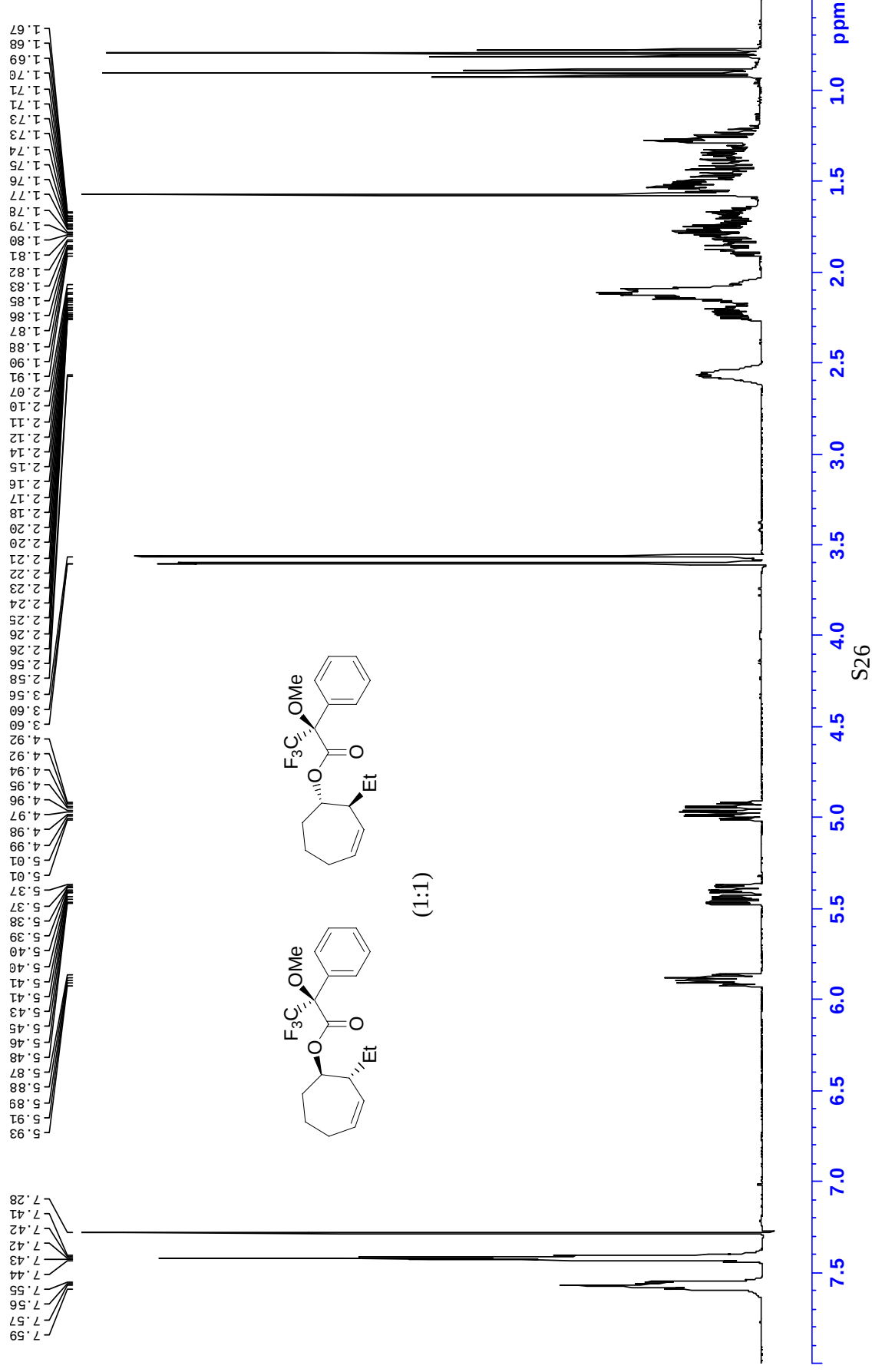
3c: ^1H NMR, 400 MHz, CDCl_3



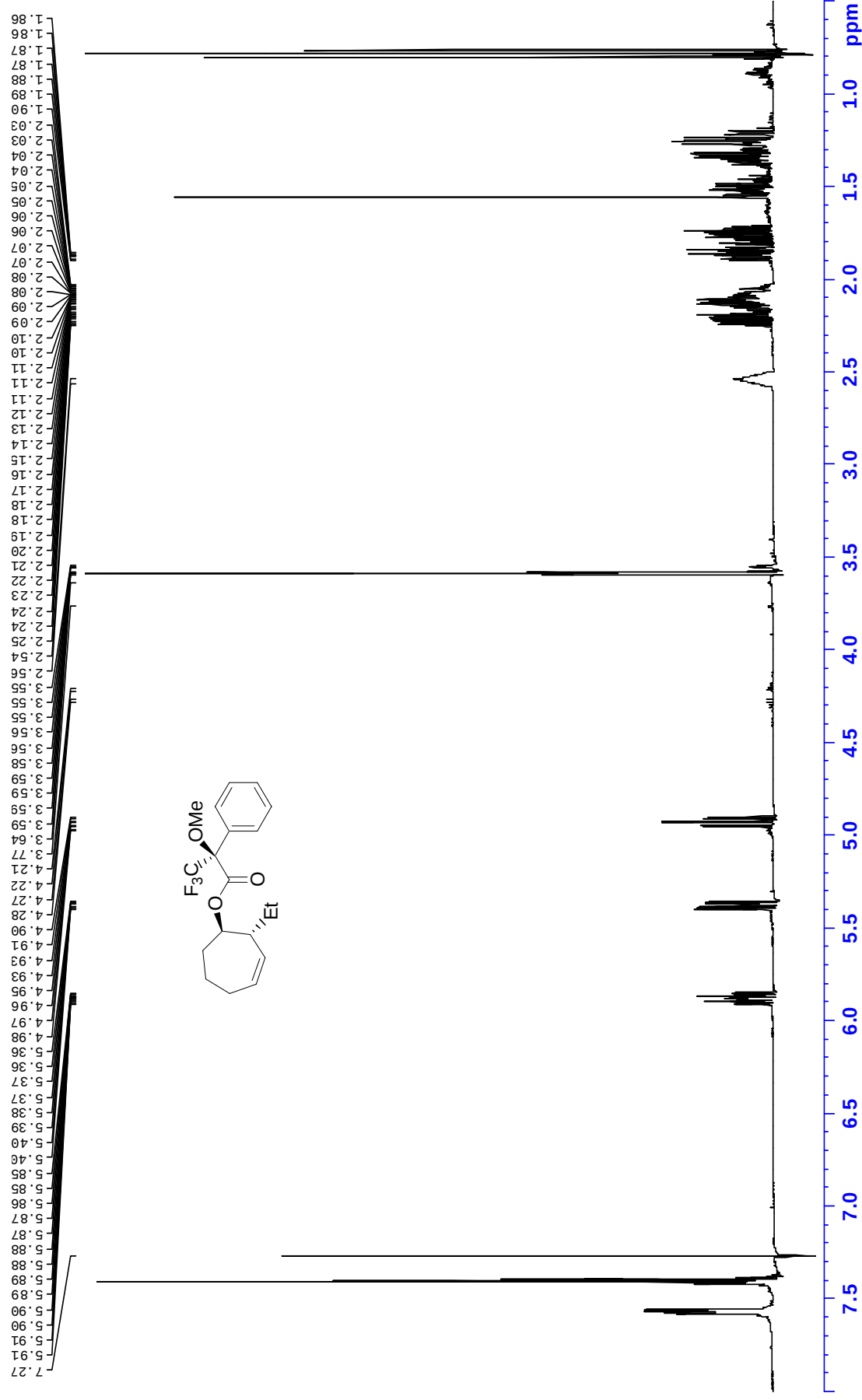
3c: ^{13}C NMR, 100 MHz, CDCl_3



(1*R*,2*R*)-2-ethyl-cyclohept-3-enol (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid ester and (1*S*,2*S*)-2-ethyl-cyclohept-3-enol (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid ester (1:1): ^1H NMR, 400 MHz, CDCl_3



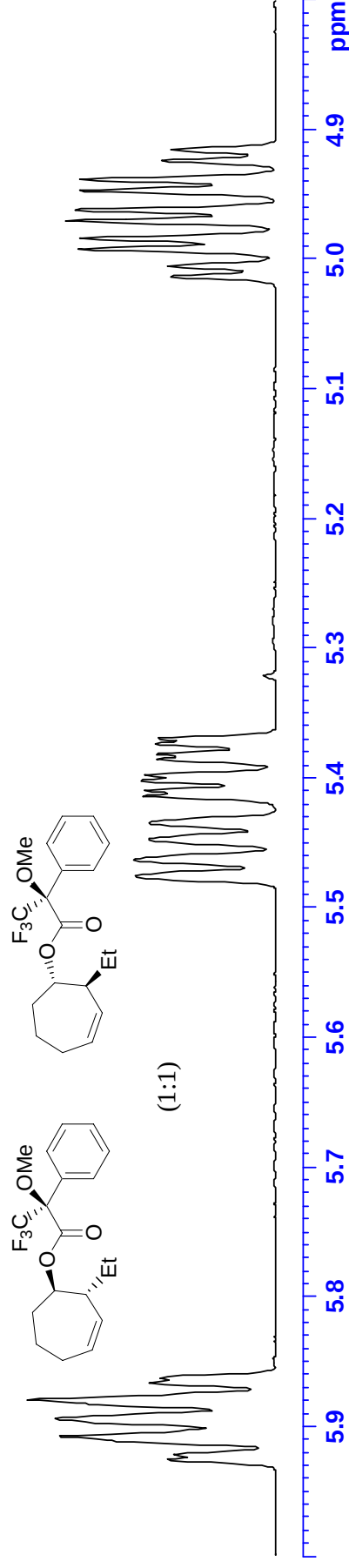
(1*R*,2*R*)-2-ethyl-cyclohept-3-enol (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid ester (**11**): ^1H NMR, 400 MHz, CDCl_3



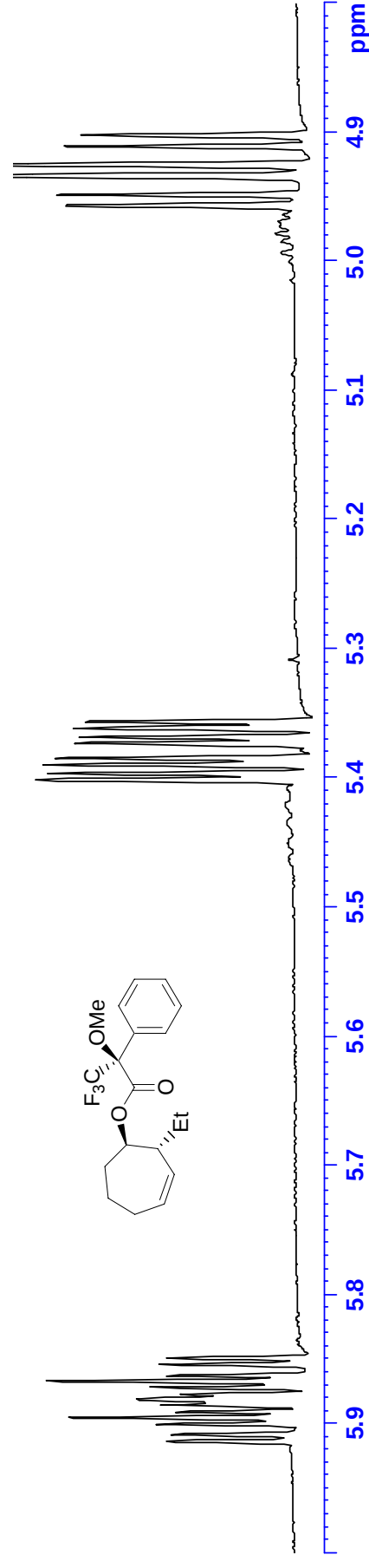
a) (1*R*,2*R*)- 2-ethyl-cyclohept-3-enol (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid ester and (1*S*,2*S*)- 2-ethyl-cyclohept-3-enol (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid ester (1:1): ^1H NMR, 400 MHz, CDCl_3 (expanded region, 6.0-4.8 ppm)

b) (1*R*,2*R*)- 2-ethyl-cyclohept-3-enol (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid ester (**11**): ^1H NMR, 400 MHz, CDCl_3 (expanded region, 6.0-4.8 ppm)

a)

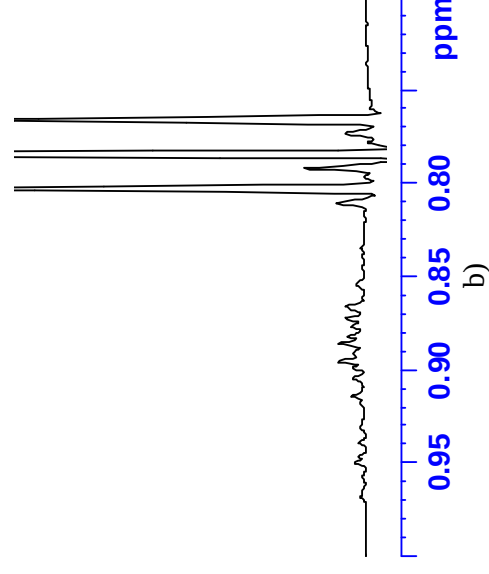
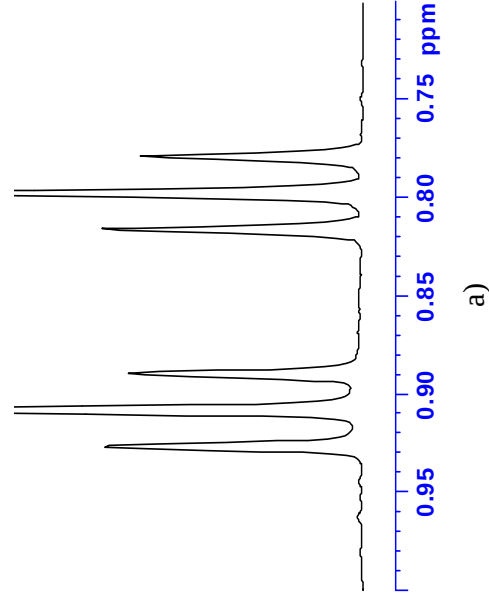


b)

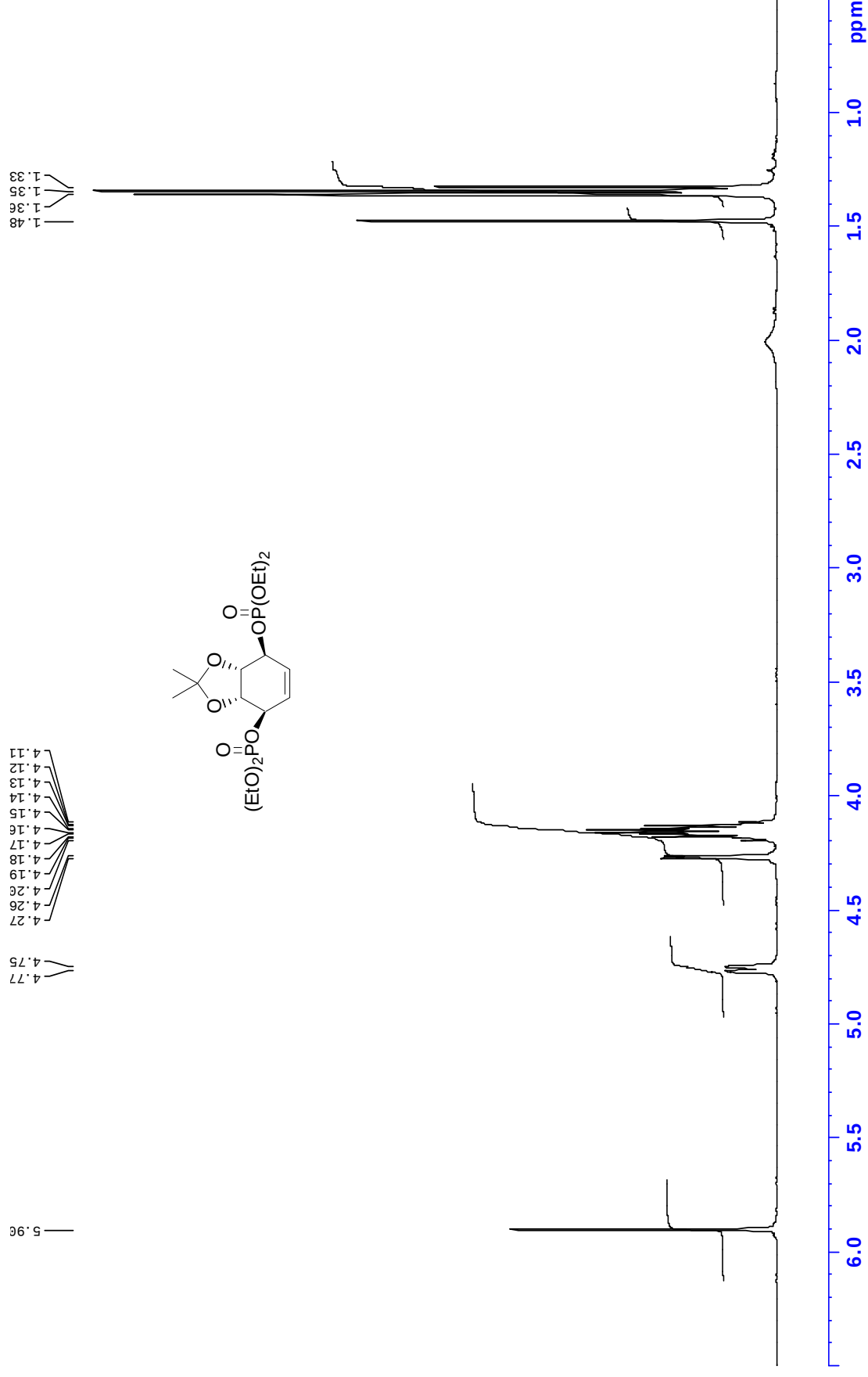


a) (1*R*,2*R*)- 2-ethyl-cyclohept-3-enol (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid ester and (1*S*,2*S*)- 2-ethyl-cyclohept-3-enol (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid ester (1:1): ^1H NMR, 400 MHz, CDCl_3 (expanded region, 1.0-0.7 ppm)

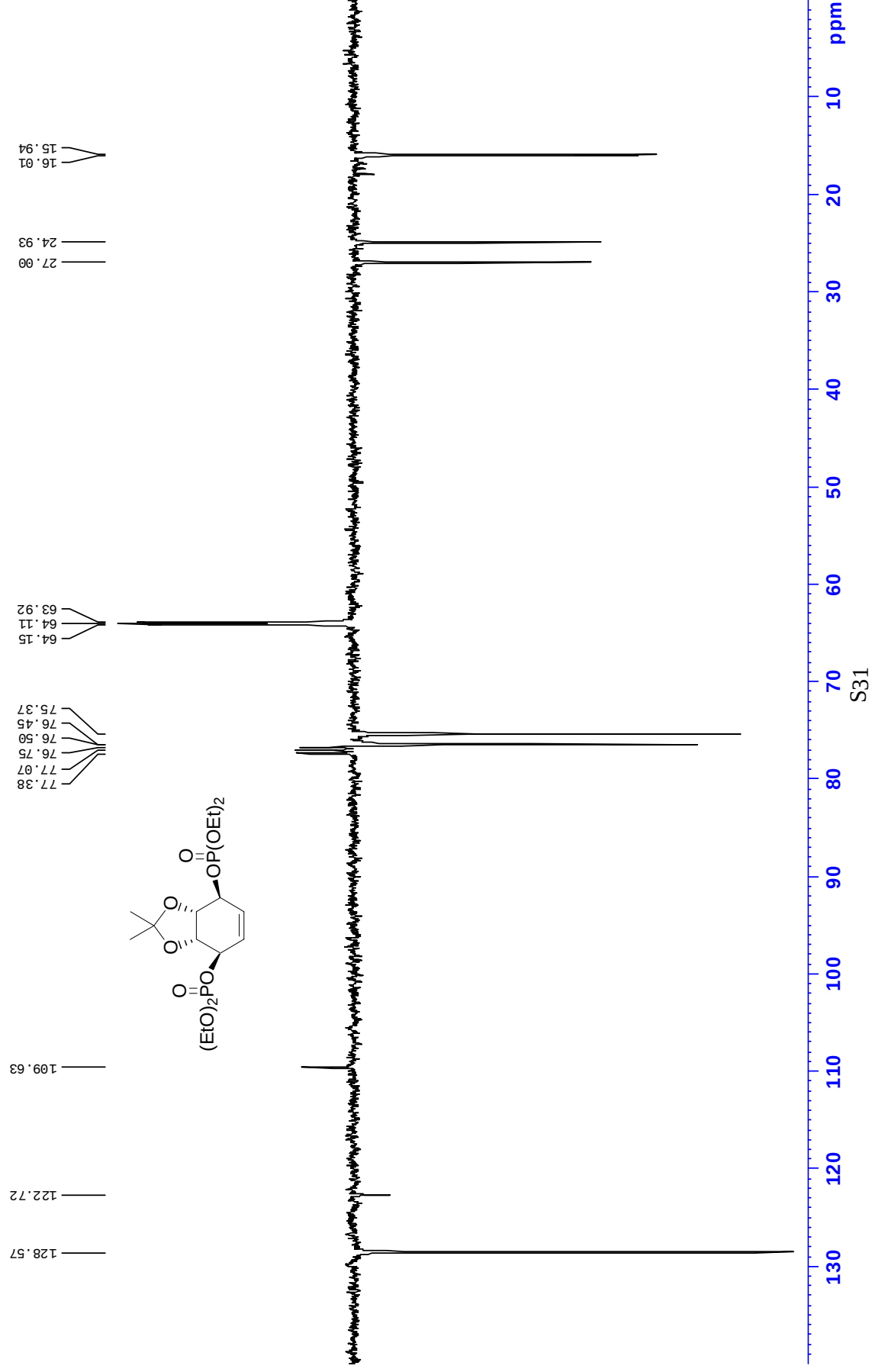
b) (1*R*,2*R*)- 2-ethyl-cyclohept-3-enol (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid ester (**11**): ^1H NMR, 400 MHz, CDCl_3 (expanded region, 1.0-0.7 ppm)



6: ^1H NMR, 400 MHz, CDCl_3



6: ^{13}C NMR, 100 MHz, CDCl_3

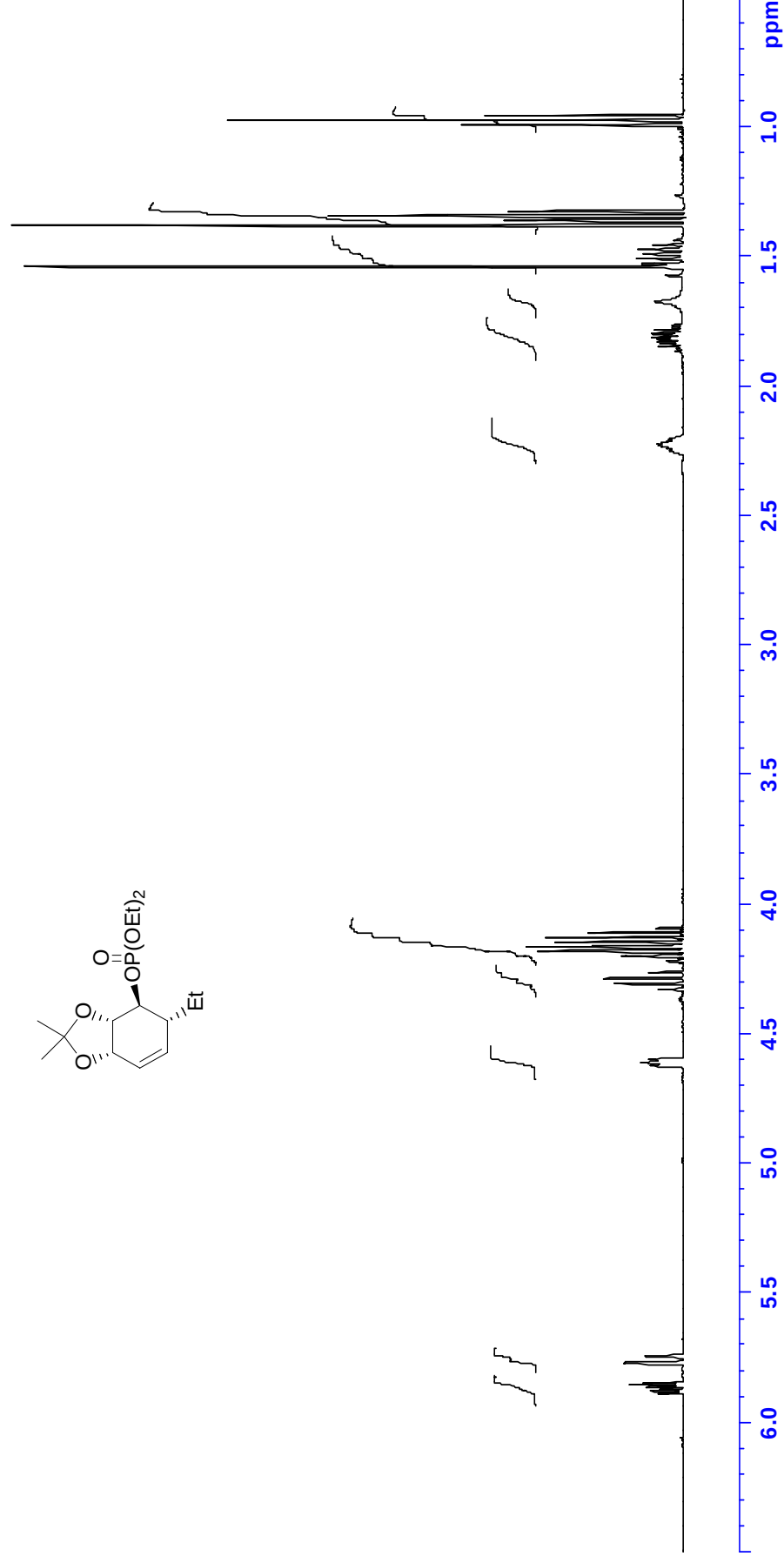
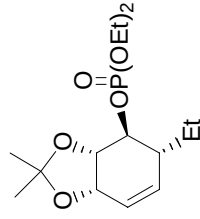


7: ^1H NMR, 400 MHz, CDCl_3

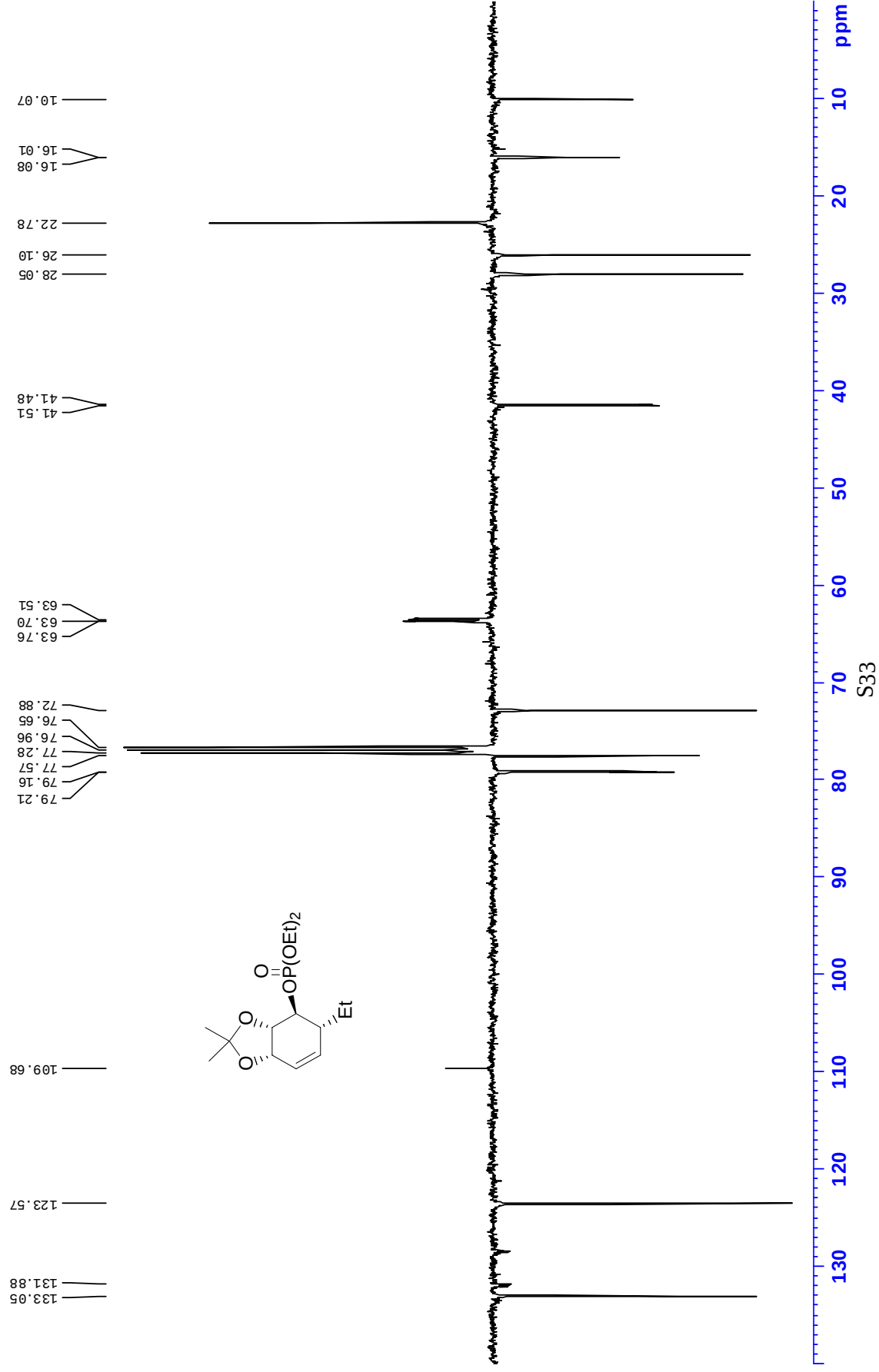
5.89
5.88
5.87
5.86
5.85
5.77
5.75

4.62
4.61
4.60
4.33
4.31
4.29
4.26
4.22
4.22
4.20
4.18
4.17
4.16
4.15
4.13
4.11
4.09

2.25
2.25
2.24
2.23
2.22
2.21
2.21
1.87
1.86
1.85
1.84
1.83
1.82
1.81
1.80
1.79
1.78
1.77
1.68
1.58
1.54
1.53
1.51
1.49
1.47
1.46
1.44
1.38
1.36
1.34
1.33
1.27
0.99
0.98
0.96



7: ^{13}C NMR, 100 MHz, CDCl_3



GC Trace of the two enantiomers of 10. Chiral stationary phase, see General Procedures; carrier: H₂ (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C. *t_R* = 23.1 min (7%), 23.4 min (93%).

