Copper Phosphoramidite Catalyzed Enantioselective Desymmetrization of Meso Cyclic Allylic Bisdiethylphosphates

Umberto Piarulli,*[,†,‡] Christelle Claverie,[‡] Philippe Daubos,[‡] Cesare Gennari,*[,‡] Adriaan J. Minnaard,[¶] and Ben L. Feringa[¶]

†) Dipartimento di Scienze Chimiche, Fisiche e Matematiche, Università dell'Insubria, via Valleggio 11, I-22100 Como, Italy

‡) Dipartimento di Chimica Organica e Industriale, Centro di Eccellenza C.I.S.I., Università di Milano, via G. Venezian 21, I-20133 Milano, Italy

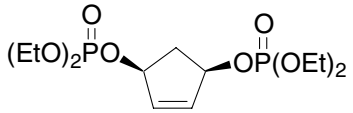
¶) Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

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: CH_2Cl_2 (CaH_2), THF (Na), Et_2O (Na), toluene (Na). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} 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 ($CDCl_3$ 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 ($CDCl_3$, δ 77.0). ^{31}P 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 DMEPEβ, OV 1701 capillary column (25 m, film 0.25 μm) in comparison with a racemic sample.

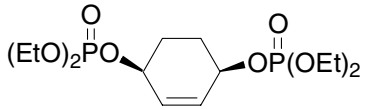
General procedure for the preparation of *meso*-bisdiethylphosphates 2a, **2b**, **2c, 6**. *n*-Butyllithium (1.6 M in *n*-hexane, 3.94 mL, 6.3 mmol) was added dropwise to a cooled (-40 °C) solution of the *meso*-diol (3.00 mmol) in THF/TMEDA (4:1, 20 mL). The solution was stirred for 15 min and then 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 Na_2SO_4 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)**



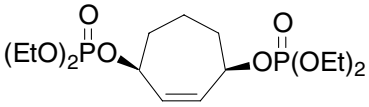
Yield: 1.027 g (90 %). IR (film) ν_{max} 2985, 1645, 1373, 1261, 1164, 1027, 989, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.17-6.16 (m, 2H), 5.25-5.19 (m, 2H), 4.16-4.08 (m, 8H), 2.98-2.88 (m, 1H), 2.04 (dt, 1H, *J* = 14.6 Hz, *J* = 4.3 Hz), 1.35 (t, 12H, *J* = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.81; ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9 (CH), 134.8 (CH), 79.0 (CH), 78.9 (CH), 63.7 ($2CH_2$), 63.6 ($2CH_2$), 39.4 (CH_2), 15.9 ($4CH_3$); MS (FAB, glycerol) *m/z* (%) 373 (60) $[M+H]^+$, 219 (100) $[M-(EtO)_2P(O)OH+H]^+$, 191 (25) $[M-(EtO)_2P(O)OH-(C_2H_4)+H]^+$, 163 (45) $[M-(EtO)_2P(O)OH-2(C_2H_4)+H]^+$; HRMS (EI, 70 eV) *m/z* calcd for $C_{13}H_{26}O_8P_2$: 372.1103 $[M]^+$; found: 372.1111.

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



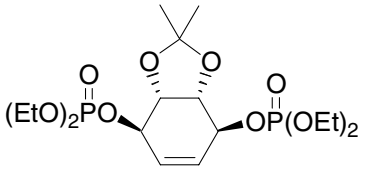
Yield: 0.996 g (86 %). IR (film) ν_{max} 2985, 1644, 1396, 1261, 1164, 1027, 989, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (m, 2H), 4.78-4.72 (m, 2H), 4.06 (dq, *J* = 7.3 Hz, *J* = 7.3 Hz, 8H), 2.04-1.94 (m, 2H), 1.93-1.83 (m, 2H), 1.29 (t, 12 H *J* = 7.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 0.24; ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.6 (2CH), 77.7 (2CH), 63.7 ($4CH_2$), 26.0 ($2CH_2$), 16.1 ($4CH_3$); MS (FAB, glycerol) *m/z* (%) 409 (10) $[M+Na]^+$, 387 (40) $[M+H]^+$, 233 (100) $[M-(EtO)_2P(O)OH+H]^+$, 155 (95) $[(EtO)_2P(O)OH+H]^+$, 127 (50) $[(EtO)P(O)(OH)_2+H]^+$, 99 (90) $[P(O)(OH)_3+H]^+$; HRMS (EI, 70 eV) *m/z* calcd for $C_{14}H_{29}O_8P_2$: 387.1338 $[M+H]^+$; found: 387.1378.

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



Yield: 1.057 g (88 %). IR (film) ν_{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 ($4CH_2$), 33.8 ($2CH_2$), 22.4 (CH_2), 16.0 ($4CH_3$); MS (FAB, glycerol) *m/z* (%) 401 (20) $[M+H]^+$, 247 (50) $[M-(EtO)_2P(O)OH+H]^+$, 155 (100) $[(EtO)_2P(O)OH+H]^+$, 127 (25) $[(EtO)P(O)(OH)_2+H]^+$, 99 (45) $[P(O)(OH)_3+H]^+$; HRMS (EI, 70 eV) *m/z* calcd for $C_{15}H_{30}O_8P_2$: 400.1316 $[M]^+$; found: 400.1446.

***meso* -1,4-bisdiethylphosphate 6**

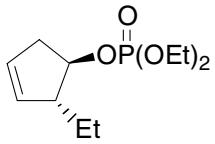


Yield: 1.224 g (89 %). IR (film) ν_{max} 2986, 2935, 2911, 1735, 1717, 1445, 1396, 1384, 1263, 1165, 1028, 972 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (bs, 2H), 4.78-4.72 (m, 2H), 4.31-4.23 (m, 2H), 4.20-4.11 (m, 8H), 1.51 (s, 3H) 1.39-1.36 (m, 15 H); ^{31}P NMR (162 MHz, $CDCl_3$) δ -0.55; ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.6 (2CH), 109.6 (C), 76.5 (2CH), 75.4 (2CH), 64.1 ($4CH_2$, J_{PC} = 4 Hz), 27.0 (CH_3), 24.9 (CH_3), 26.0 ($2CH_2$), 16.0 ($4CH_3$, J_{PC} = 7 Hz); MS (FAB, glycerol) *m/z* (%) 459 (45) $[M+H]^+$, 305 (100) $[M-(EtO)_2P(O)OH+H]^+$, 155 (65) $[(EtO)_2P(O)OH+H]^+$, 127 (30) $[(EtO)P(O)(OH)_2+H]^+$, 99 (60) $[P(O)(OH)_3+H]^+$; HRMS (EI, 70 eV) *m/z* calcd for $C_{17}H_{32}O_{10}P_2$: 459.1549 $[M+H]^+$; 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 $[Cu(OTf)]_2 \cdot C_6H_6$ (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 (R = Et, 1.1 M in toluene, 98 μL, 108 μmol; R = 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).

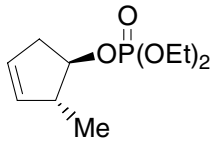
Preparative procedure for the copper phosphoramidite catalyzed enantioselective desymmetrization of *meso*-bisdiethylphosphates 2a, **2b**, **2c**, **6**. Under the optimized conditions (ligand, temperature), the reactions reported in Table 1 (entry 7, 10), Table 2 (entry 10), Table 3 (entries 4,5), and Scheme 2 were repeated on a larger scale (1.08 mmol). A solution of $[Cu(OTf)]_2 \cdot C_6H_6$ (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, R_2Zn (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 NH_4Cl solution (20.0 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). The results (%yield and %e.e.) were identical (within the experimental error, ± 1%) to those obtained in the small scale screening experiments (see above).

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



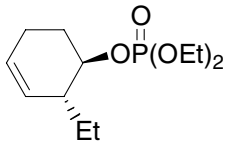
Yield: 264 mg (98 %). IR (film) ν_{max} 2963, 2932, 2876, 1459, 1445, 1393, 1370, 1263, 1167, 1028, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.69-5.62 (m, 2H), 4.70-4.64 (m, 1H), 4.14-4.04 (m, 4H), 2.79-2.67 (m, 2H), 2.53-2.45 (m, 1H), 1.53-1.29 (m, 8H), 0.94 (t, 3H, *J* = 7.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -0.35; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4 (CH), 127.2 (CH), 82.7 (CH), 63.5 ($2CH_2$), 54.5 (CH), 39.8 (CH_2), 25.4 (CH_2), 16.0 ($2CH_3$), 11.6 (CH_3); $[\alpha]_D^{298}$ = -84 (c 1.2, $CHCl_3$); 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 $C_{11}H_{22}O_4P$: 249.1256 $[M+H]^+$; found: 249.1260. The e.e. was determined by GC on a chiral stationary phase [column: see General Procedures; carrier: H_2 (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**).

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



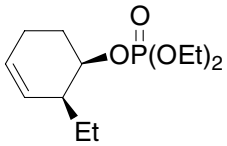
Yield: 137 mg (54 %). IR (film) ν_{max} 2960, 2927, 2892, 1465, 1458, 1393, 1370, 1262, 1167, 1029, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.59 (bs, 2H), 4.69-4.54 (m, 1H), 4.15-4.05 (m, 4H), 2.84-2.72 (m, 2H), 2.54-2.45 (m, 1H), 1.37-1.31 (m, 6H), 1.05 (d, 3H, *J* = 7.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -0.35; ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3 (CH), 126.4 (CH), 84.6 (CH), 63.5 ($2CH_2$), 47.2 (CH), 39.4 (CH_2), 17.6 (CH_3), 16.1 ($2CH_3$); $[\alpha]_D^{298}$ = -56 (c 0.92, $CHCl_3$); 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: H_2 (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**).

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



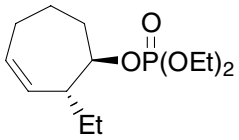
Yield: 167 mg (59 %). IR (film) ν_{max} 2964, 2873, 1655, 1515, 1465, 1250, 1022, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71-5.64 (m, 1H), 5.57-5.50 (m, 1H), 4.40-4.29 (m, 1H), 4.17-4.07 (m, 4H), 2.26-2.01 (m, 4H), 1.87-1.76 (m, 1H), 1.67-1.56 (m, 1H), 1.45-1.31 (m, 7H) 0.95 (t, 3H, *J* = 7.4 Hz); ^{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 ($2CH_2$), 43.2 (CH), 27.7 (CH_2), 25.0 (CH_2), 23.3 (CH_2), 16.1 ($2CH_3$), 10.5 (CH_3); $[\alpha]_D^{298}$ = -63 (c 0.95, $CHCl_3$); MS (EI, 70 eV) *m/z* (%) 262 (2) $[M]^+$, 155 (100) $[(EtO)_2P(O)OH+H]^+$, 127 (95) $[(EtO)P(O)(OH)_2+H]^+$, 108 (40) $[M-(EtO)_2P(O)OH]^+$, 99 (98) $[P(O)(OH)_3+H]^+$, 79 (80) $[M-(EtO)_2P(O)OH-Et]^+$; HRMS (EI, 70 eV) *m/z* calcd for $C_{12}H_{23}O_4P$: 262.1334 $[M]^+$; found: 262.1314.

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



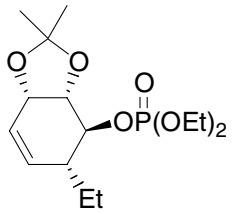
Yield: 28 mg (10 %). IR (film) ν_{max} 2966, 2876, 1648, 1508, 1458, 1259, 1027, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71-5.64 (m, 1H), 5.57-5.50 (m, 1H), 4.40-4.29 (m, 1H), 4.17-4.07 (m, 4H), 2.26-2.01 (m, 4H), 1.87-1.76 (m, 1H), 1.67-1.56 (m, 1H), 1.45-1.31 (m, 7H) 0.95 (t, 3H, *J* = 7.4 Hz); ^{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 ($2CH_2$), 43.2 (CH), 27.7 (CH_2), 25.0 (CH_2), 23.3 (CH_2), 16.1 ($2CH_3$), 10.5 (CH_3); MS (EI, 70 eV) *m/z* (%) 262 (2) $[M]^+$, 155 (100) $[(EtO)_2P(O)OH+H]^+$, 127 (95) $[(EtO)P(O)(OH)_2+H]^+$, 108 (50) $[M-(EtO)_2P(O)OH]^+$, 99 (98) $[P(O)(OH)_3+H]^+$; 79 (95) $[M-(EtO)_2P(O)OH-Et]^+$; HRMS (EI, 70 eV) *m/z* calcd for $C_{12}H_{23}O_4P$: 262.1334 $[M]^+$; found: 262.1304.

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



Yield: 256 mg (86 %). IR (film) ν_{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, 1 H), 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 ($2CH_2$), 45.8 (CH), 36.4 (CH_2), 27.9 (CH_2), 24.5 (CH_2), 23.0 (CH_2), 16.1 ($2CH_3$), 11.0 (CH_3); $[\alpha]_D^{298}$ = -34 (c 0.95, $CHCl_3$); MS (FAB, glycerol) *m/z* (%) 277 (25) $[M+H]^+$, 155 (100) $[(EtO)_2P(O)OH+H]^+$, 127 (55) $[(EtO)P(O)(OH)_2+H]^+$, 123 (70) $[M-(EtO)_2P(O)OH+H]^+$, 99 (85) $[P(O)(OH)_3+H]^+$.

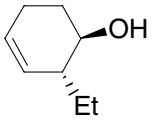
Phosphoric acid diethyl ester (*1S*, 2R*,5S*, 6S)-2-ethyl-5,6-isopropylidendioxy-cyclohex-3-enyl ester (7)**



Yield: 188 mg (52 %). IR (film) ν_{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 ($2CH_2$, J_{CP} = 6 Hz), 28.1 (CH_3), 26.1 (CH_3), 22.8 (CH_2) 16.1 ($2CH_3$), 10.7 (CH_3); $[\alpha]_D^{298}$ = -21 (c 1.3, $CHCl_3$); MS (EI, 70 eV) *m/z* (%) 335 (1) $[M+H]^+$, 319 (40) $[M-CH_3]^+$, 155 (100) $[(EtO)_2P(O)OH+H]^+$, 127 (55) $[(EtO)P(O)(OH)_2+H]^+$, 99 (25) $[P(O)(OH)_3+H]^+$; HRMS (EI, 70 eV) *m/z* calcd for $C_{15}H_{28}O_6P$: 335.1624 $[M+H]^+$; found: 335.1668.

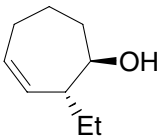
General procedure for the reduction of phosphate esters 3b, **4b**, **3c**, **7**. To a stirred solution of phosphate ester (0.10 mmol) in dry Et_2O (1.66 mL), LAH (22.17 mg, 0.60 mmol) was added portionwise at rt. The solution was stirred for 20 min before quenching with water (SLOWLY !). The solution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

(*1R,2R*)- 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).

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

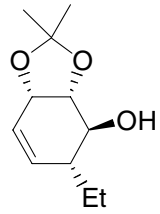


Yield: quantitative. IR (film) ν_{max} 3367, 2963, 2930, 2874, 1648, 1445, 1378, 1259, 1024, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92-5.85 (m, 1H), 5.49-5.45 (m, 1H), 3.58-3.54 (m, 1H), 2.36-2.28 (m, 1H), 2.13-2.05 (m, 3H), 1.80-1.61 (m,

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

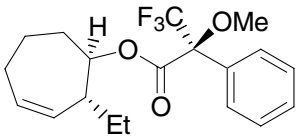
3H), 1.54-1.41 (m, 3H) 0.96 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.0 (CH), 132.0 (CH), 71.3 (CH), 47.3 (CH), 38.3 (CH_2), 28.1 (CH_2), 24.4 (CH_2), 23.2 (CH_2), 11.1 (CH_3); $[\alpha]_D^{298}$ = -41 (c 0.93, $CHCl_3$).

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



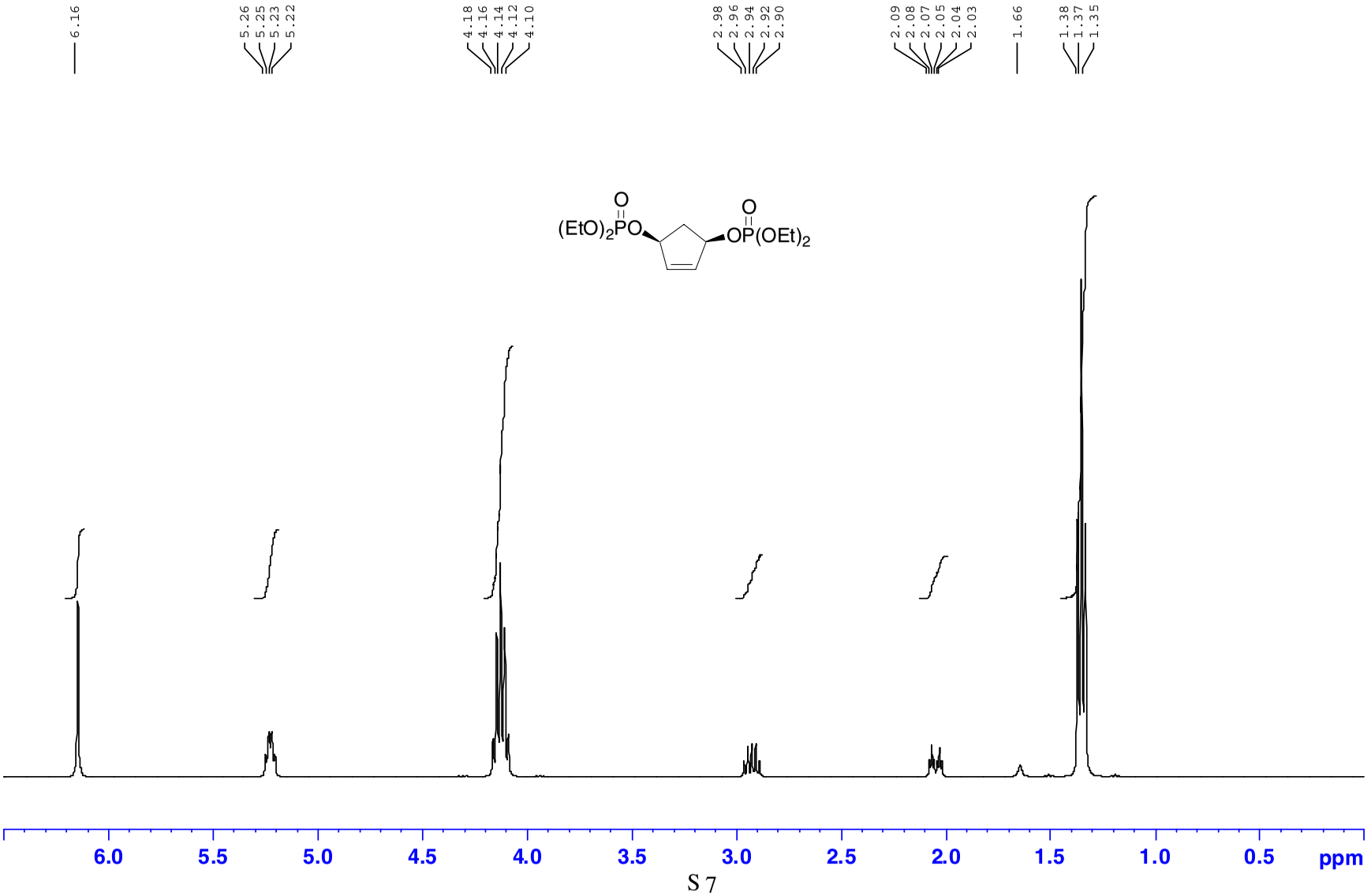
Yield: quantitative. IR (film) ν_{max} 3589, 3046, 2960, 1433, 1380, 1258, 1216, 1057, 865, 824 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (dt, 1H, *J* = 10 Hz, *J* = 3.2 Hz), 5.82-5.80 (m, 1H), 4.63-4.60 (m, 1H) 3.96 (dd, 1H, *J* = 9.3 Hz, *J* = 6.4 Hz), 3.36 (t, 1H, *J* = 9.3 Hz), 2.06-1.97 (m, 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); $[\alpha]_D^{298}$ = -33 (c 0.4, CH_2Cl_2); MS (EI, 70 eV) *m/z* (%) 198 (2) $[M]^+$, 197 (5) $[M-H]^+$, 183 (100) $[M-CH_3]^+$, 123 (85), 111 (30), 95 (65); HRMS (EI, 70 eV) *m/z* calcd for $C_{11}H_{18}O_3$: 198.1256 $[M]^+$; 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 °C; detector: 250 °C; oven temperature: 90 °C]. t_R = 23.1 min (7%), 23.4 min (93%).

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

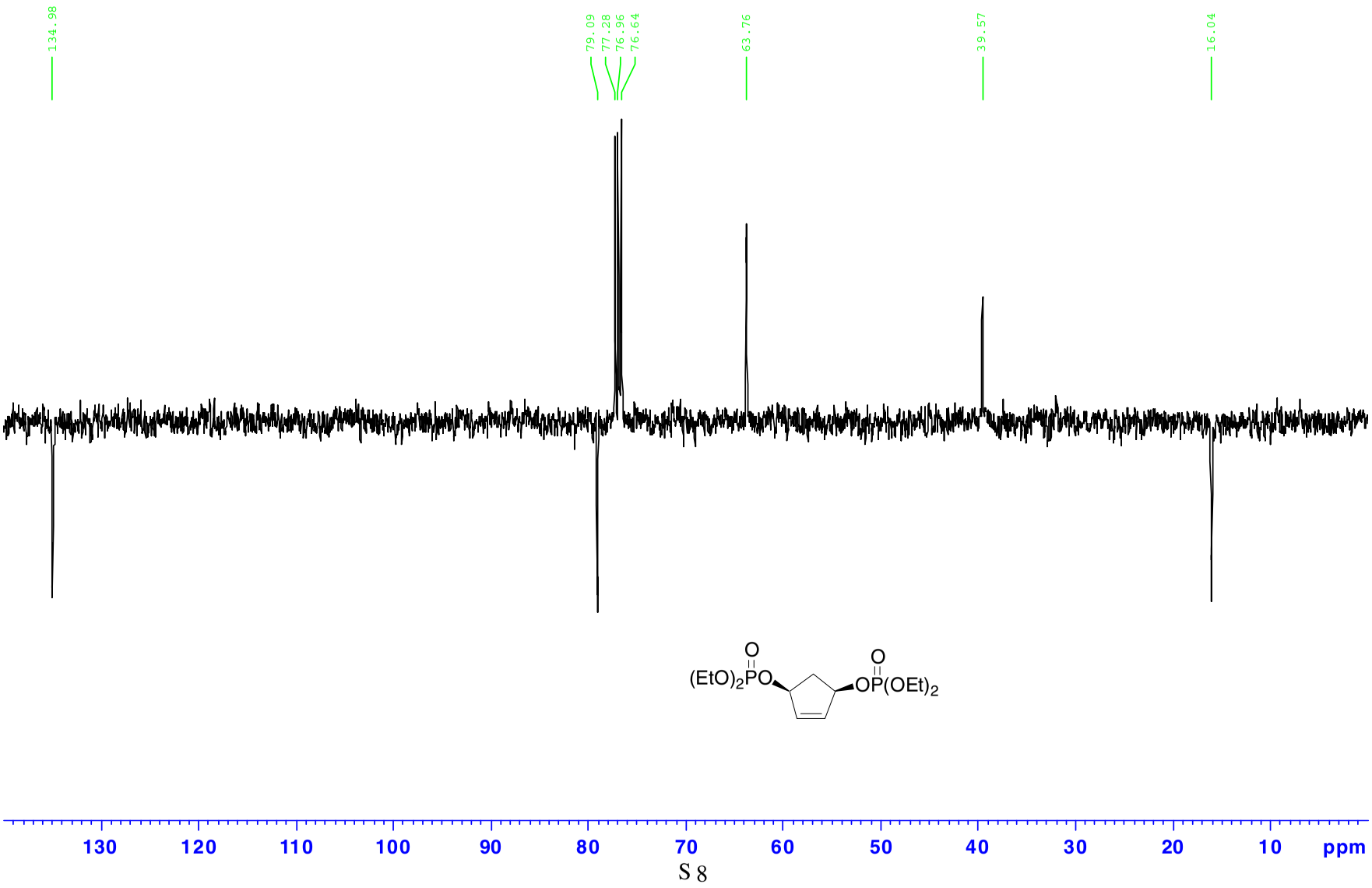


To a stirred solution of alcohol **9** (5 mg, 0.036 mmol) in dry CH_2Cl_2 (1 mL) was added 4-DMAP (8.7 mg, 0.07 mmol), (*R*)-(+)-α-methoxy- α -(trifluoromethyl)phenylacetic acid (16.4 mg, 0.07 mmol) and DCC (45 mg, 0.22 mmol). The solution was stirred overnight at rt. The solvent was evaporated under 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. ^{1}H 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).

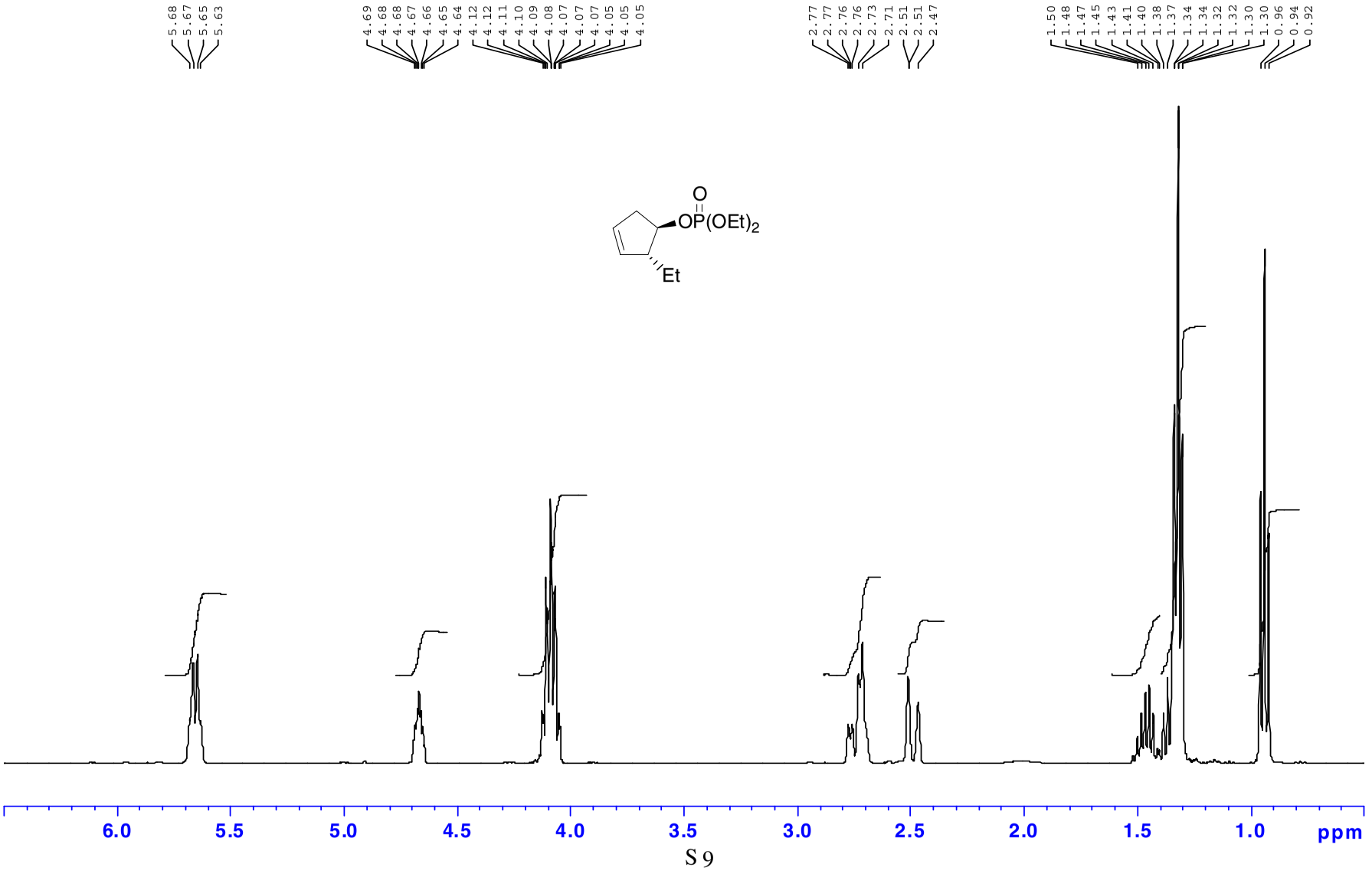
2a: ^{1}H NMR, 400 MHz, $CDCl_3$



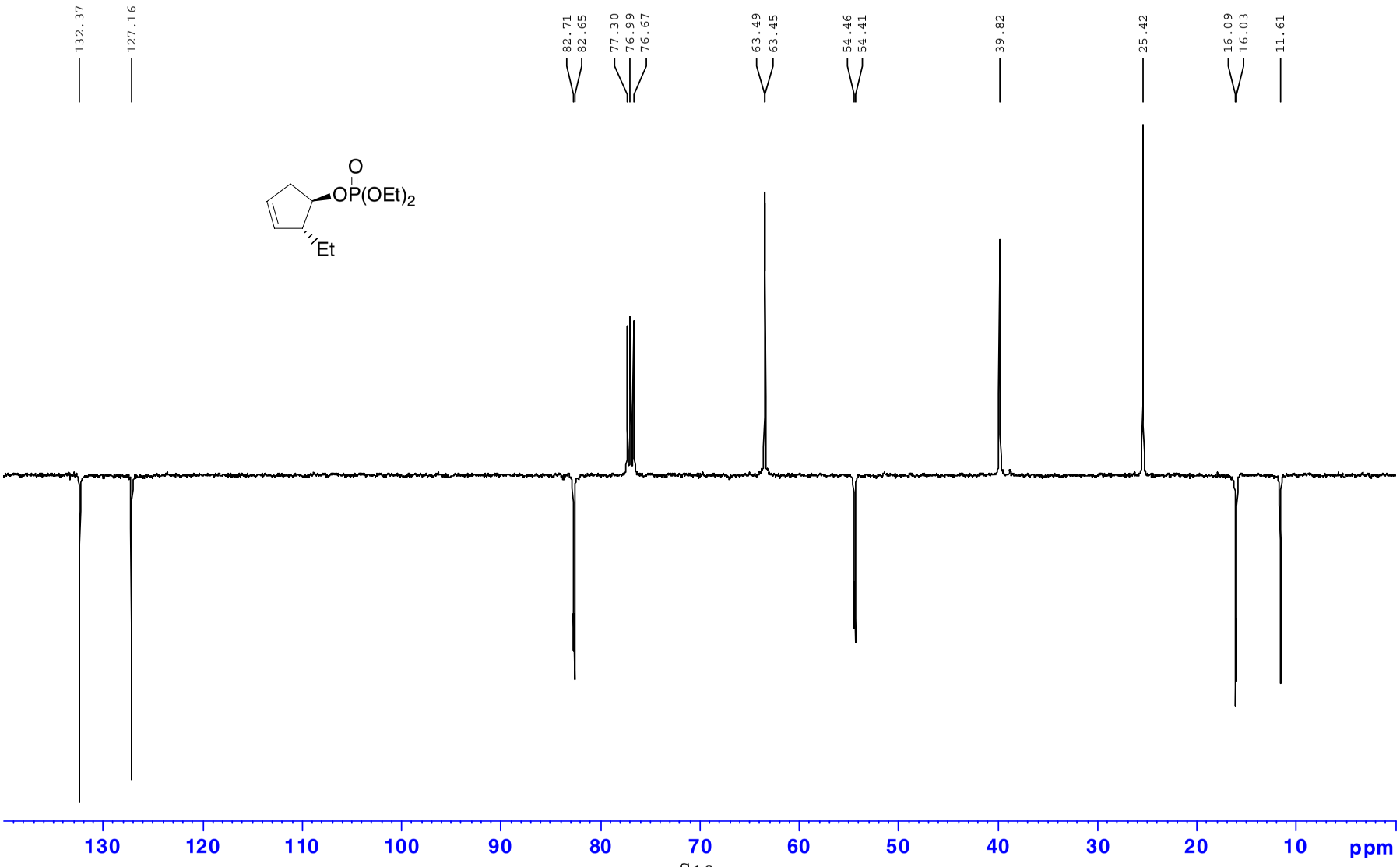
2a: ^{13}C NMR, 100 MHz, $CDCl_3$



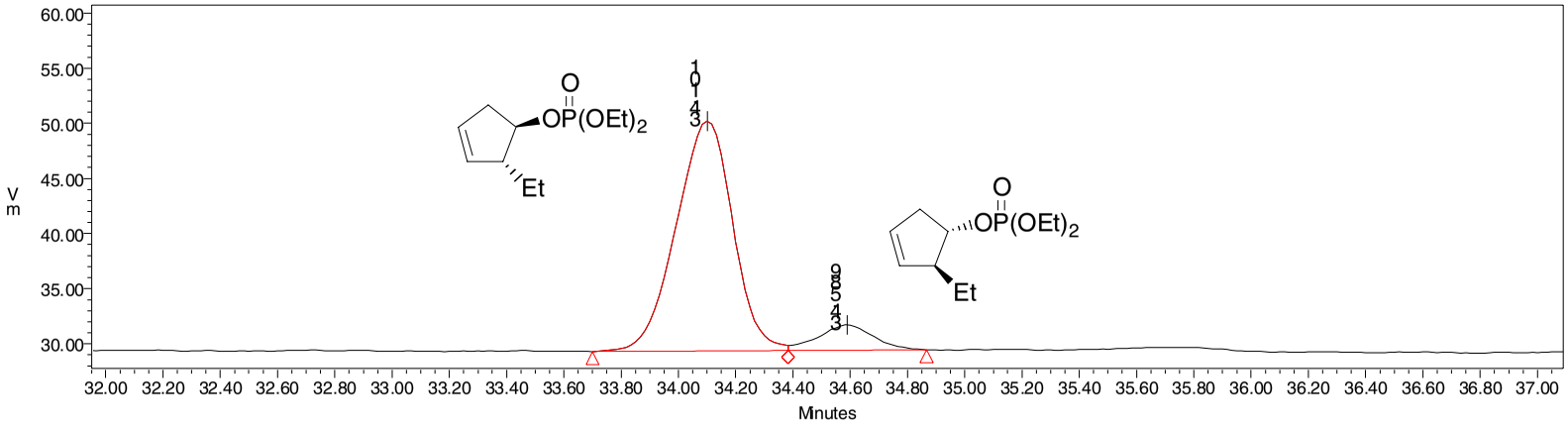
3a, R=Et: ^{1}H NMR, 400 MHz, $CDCl_3$



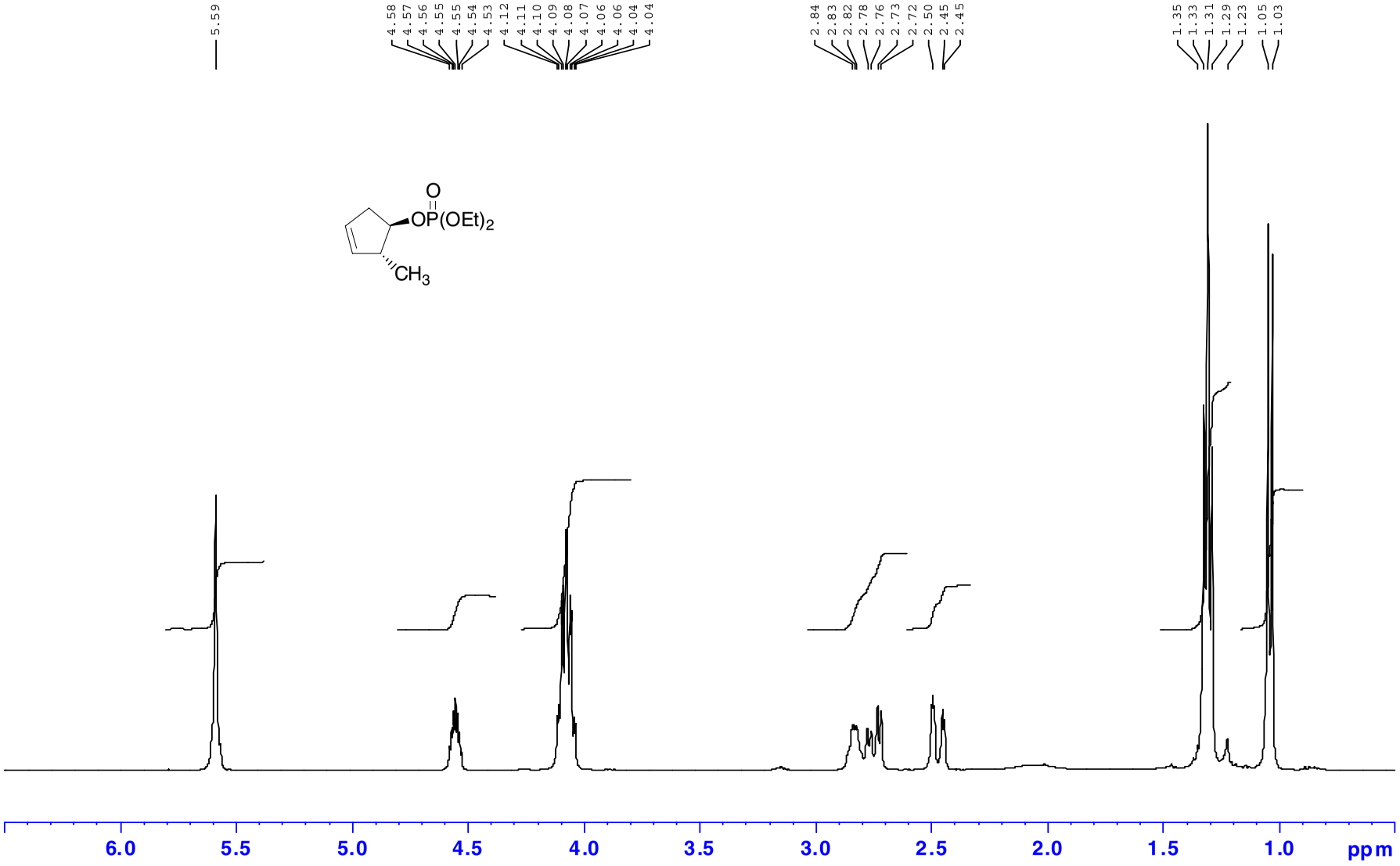
3a, R=Et: ^{13}C NMR, 100 MHz, $CDCl_3$



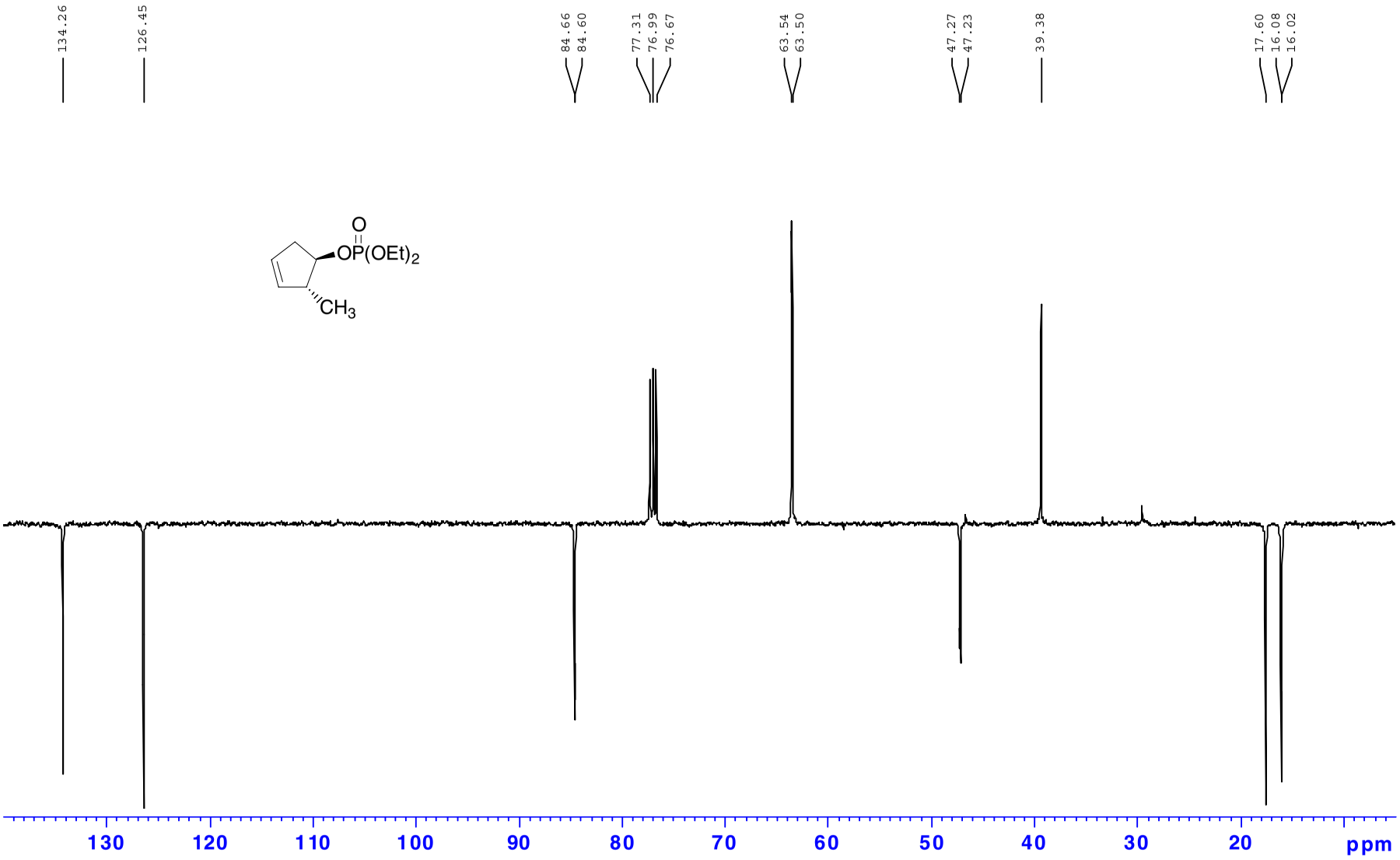
GC Trace of the two enantiomers of 3a (R=Et). Chiral stationary phase, see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C, 0.8 °C/min to 130 °C. t_R = 1.81 min (*n*-decane), 34.1 min (1*R*,2*R* enantiomer), 34.6 min (1*S*,2*S* enantiomer), 54.6 min (**2a**).



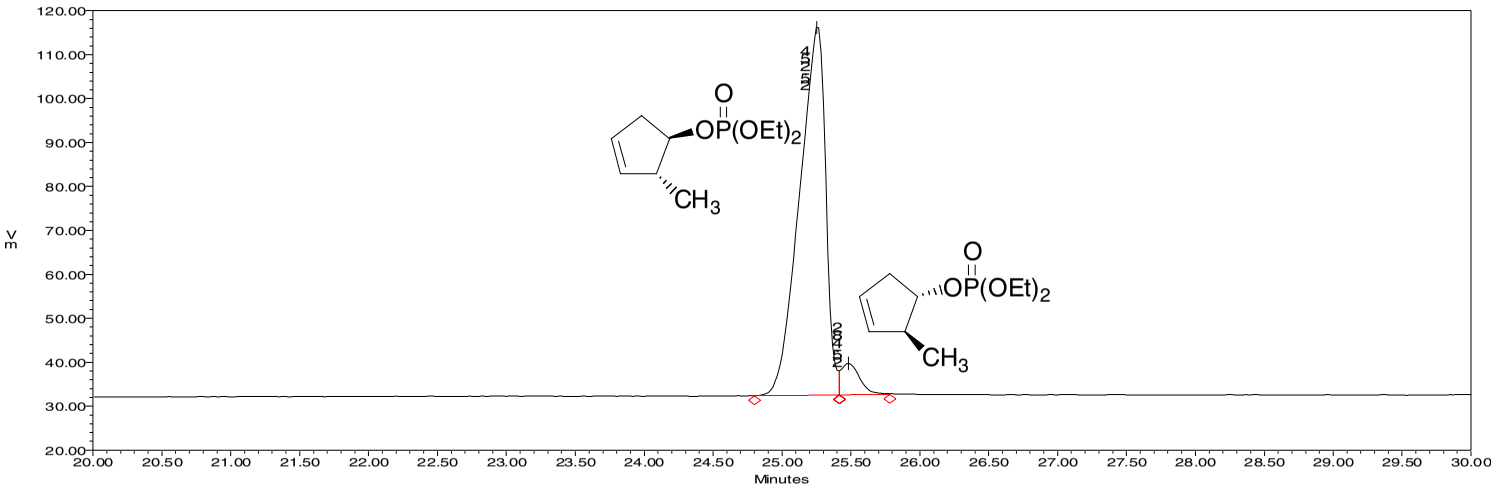
3a, R=Me: ^{1}H NMR, 400 MHz, $CDCl_3$



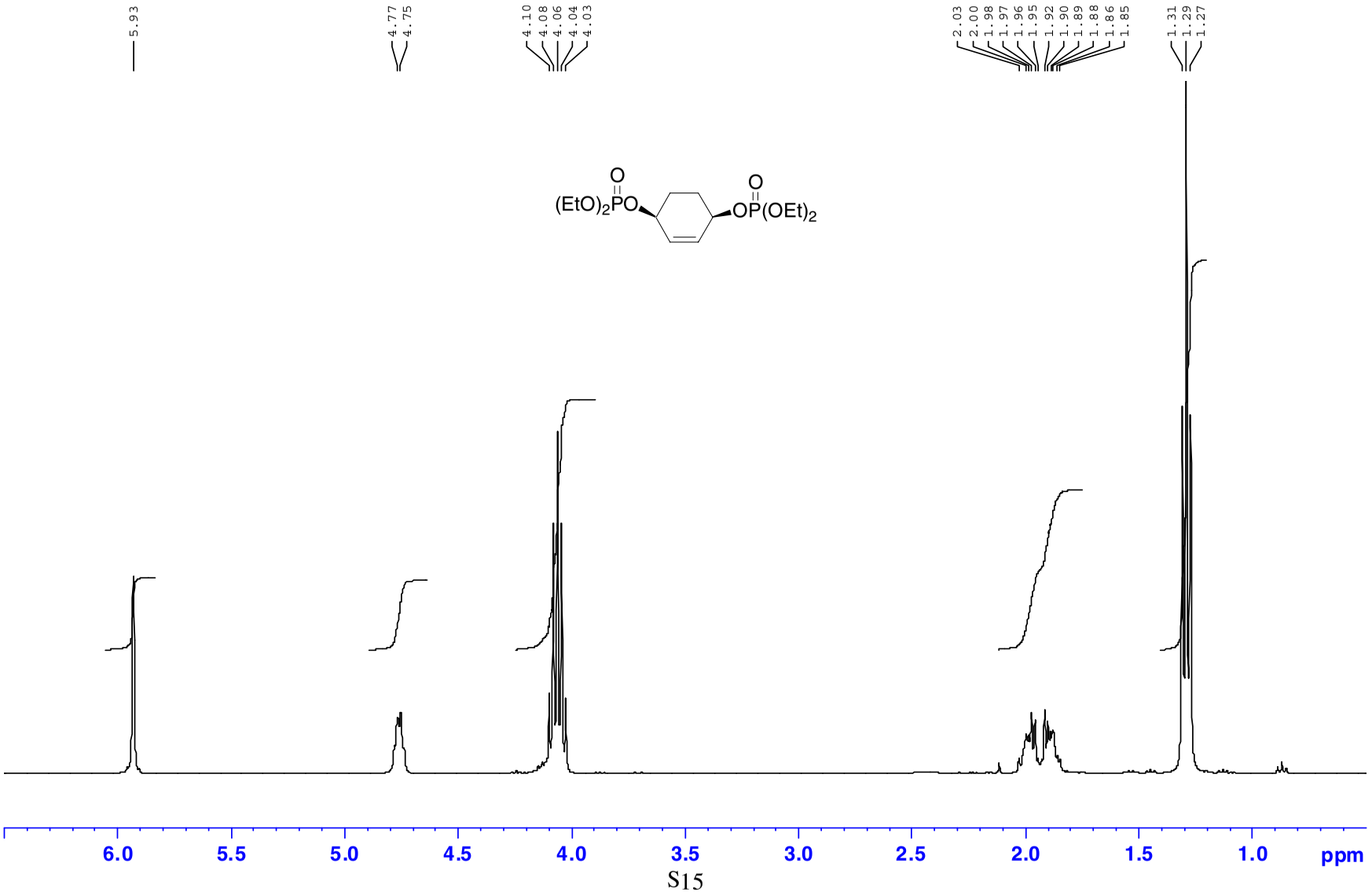
3a, R=Me: ^{13}C NMR, 100 MHz, $CDCl_3$



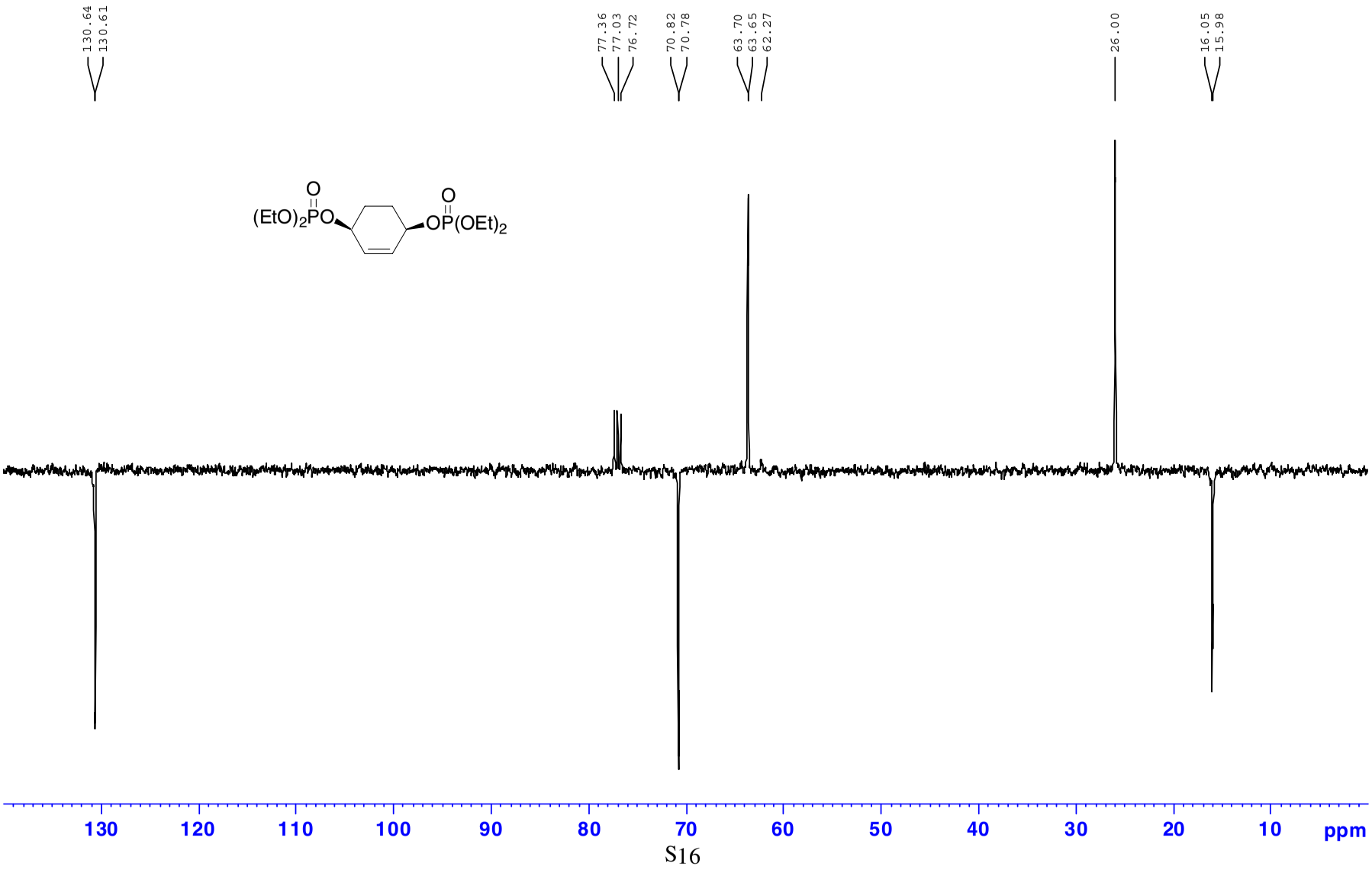
GC Trace of the two enantiomers of 3a (R = Me). Chiral stationary phase, see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C, 0.8 °C/min to 130 °C. t_R = 1.81 min (*n*-decane), 25.2 min (1*R*,2*R* enantiomer), 25.5 min (1*S*,2*S* enantiomer), 54.6 min (**2a**).



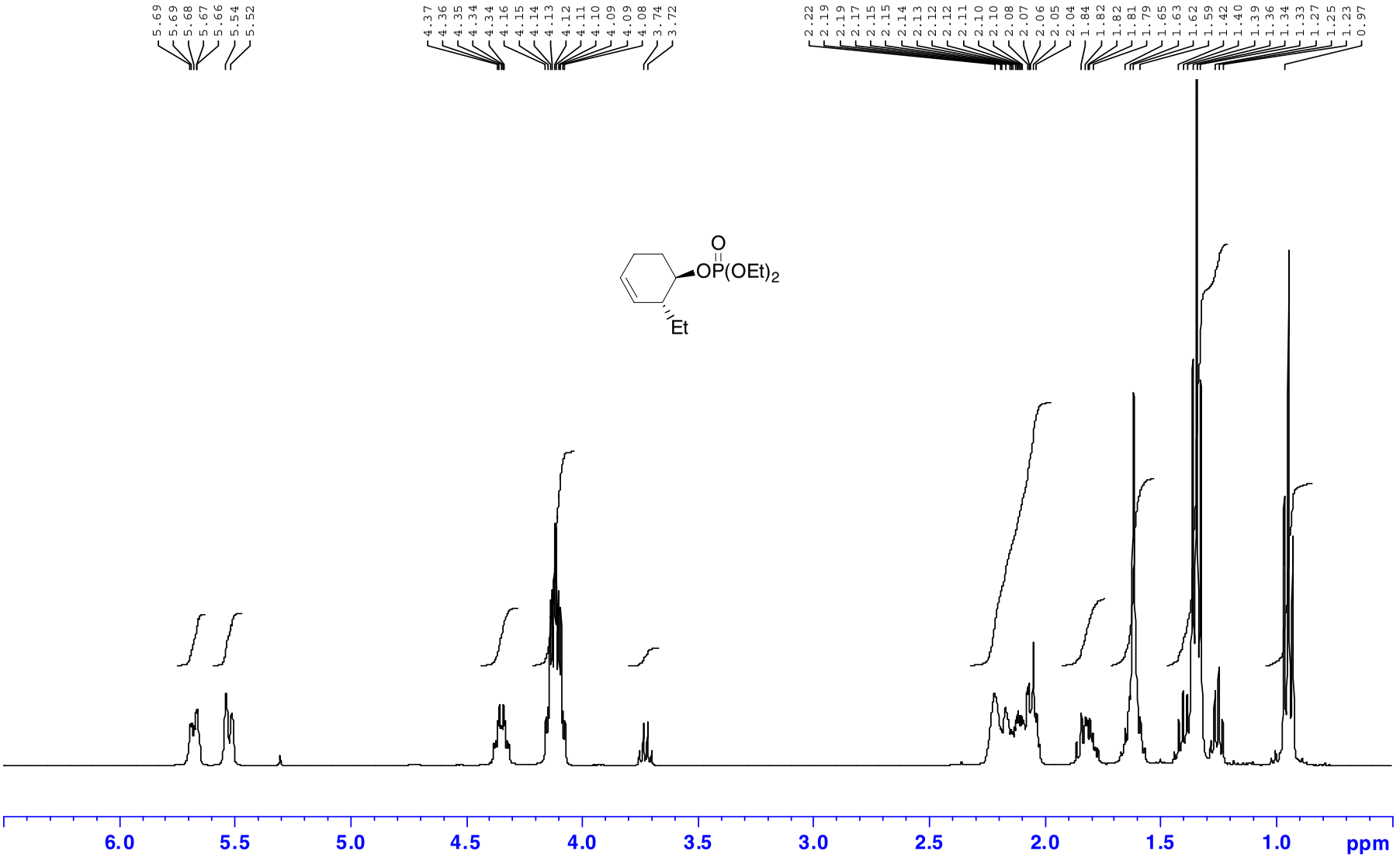
2b: ^{1}H NMR, 400 MHz, $CDCl_3$



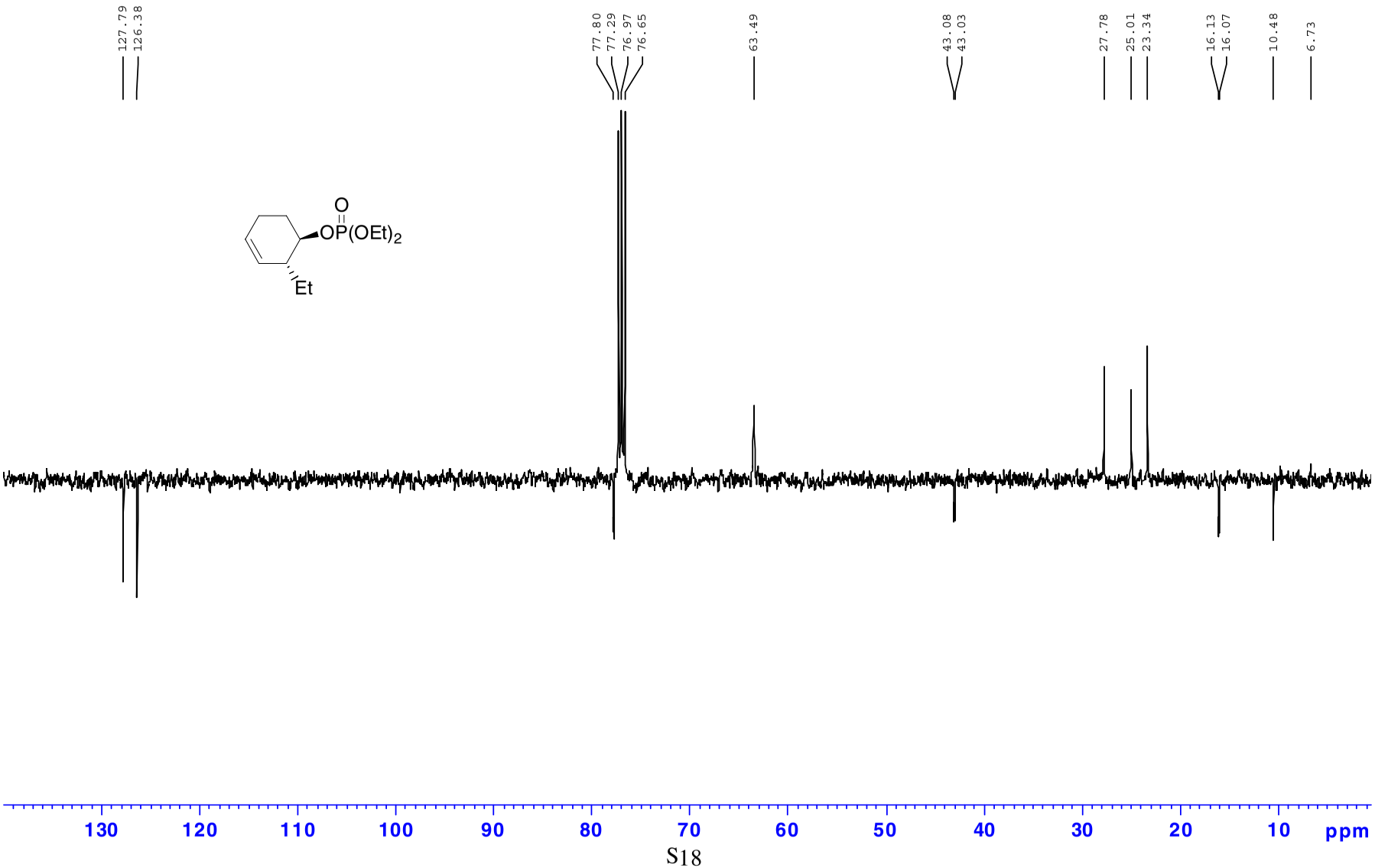
2b: ^{13}C NMR, 100 MHz, $CDCl_3$



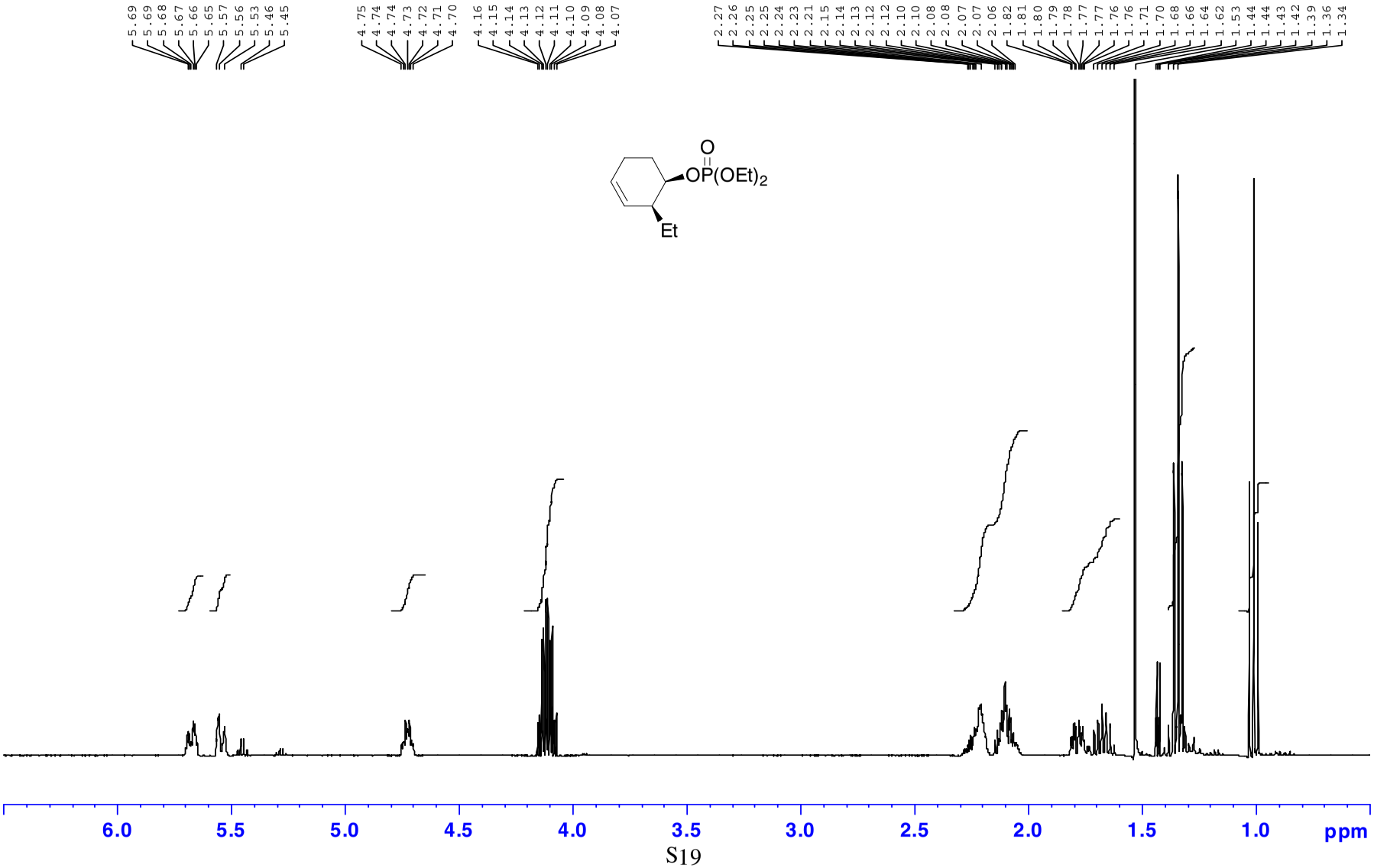
3b: ^{1}H NMR, 400 MHz, $CDCl_3$



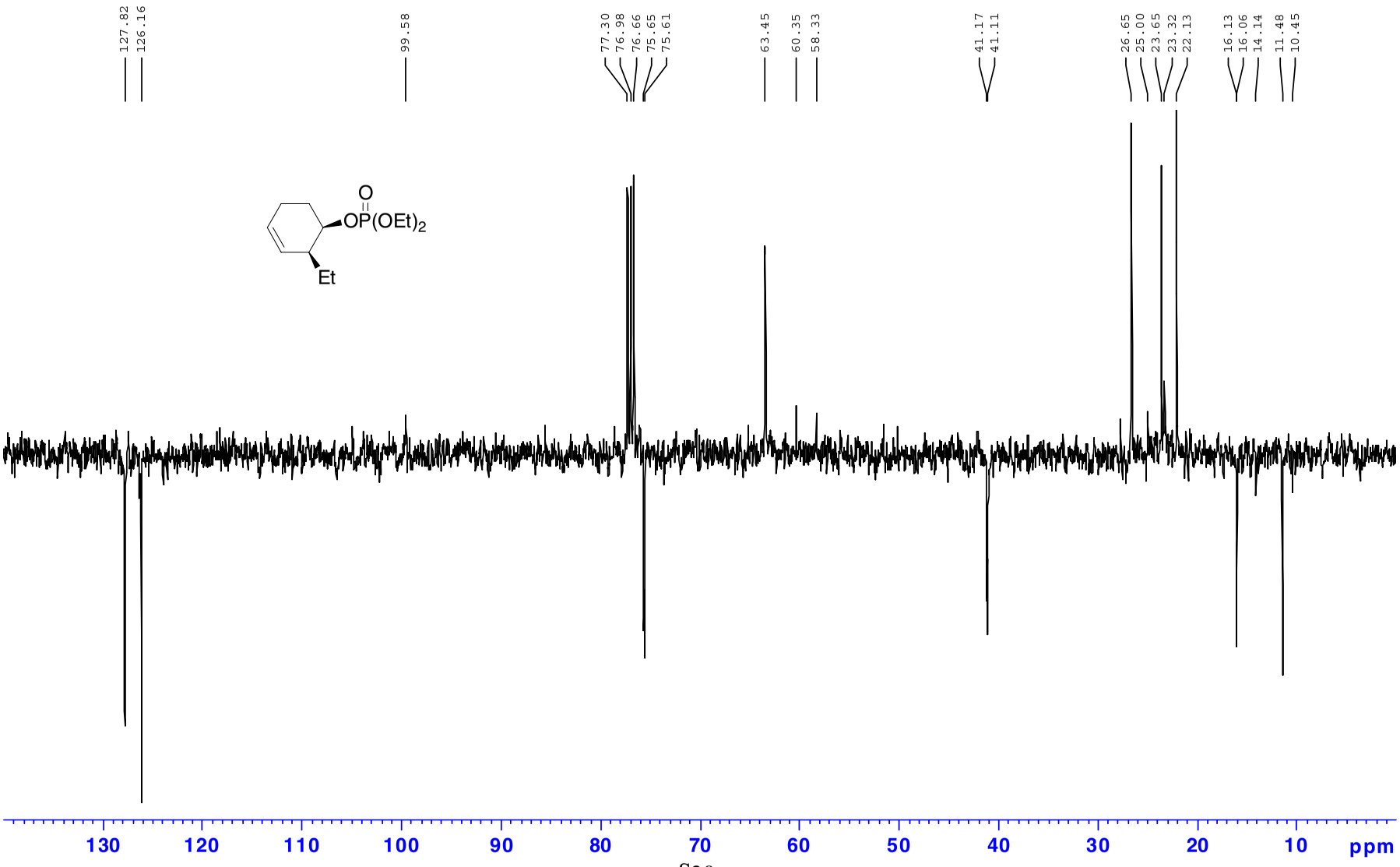
3b: ^{13}C NMR, 100 MHz, $CDCl_3$



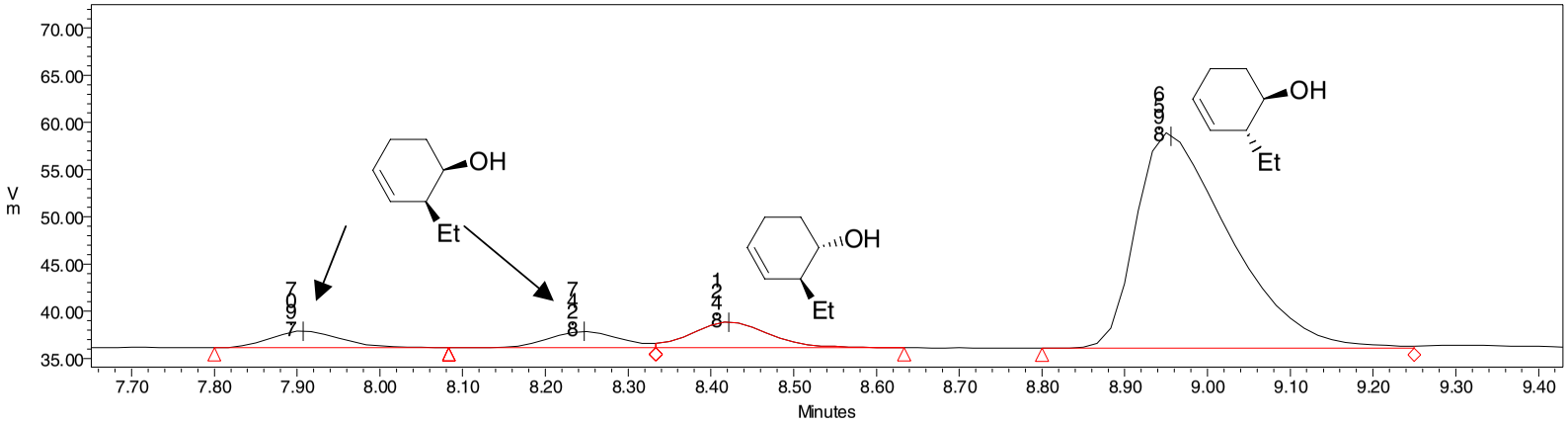
4b: ^{1}H NMR, 400 MHz, $CDCl_3$



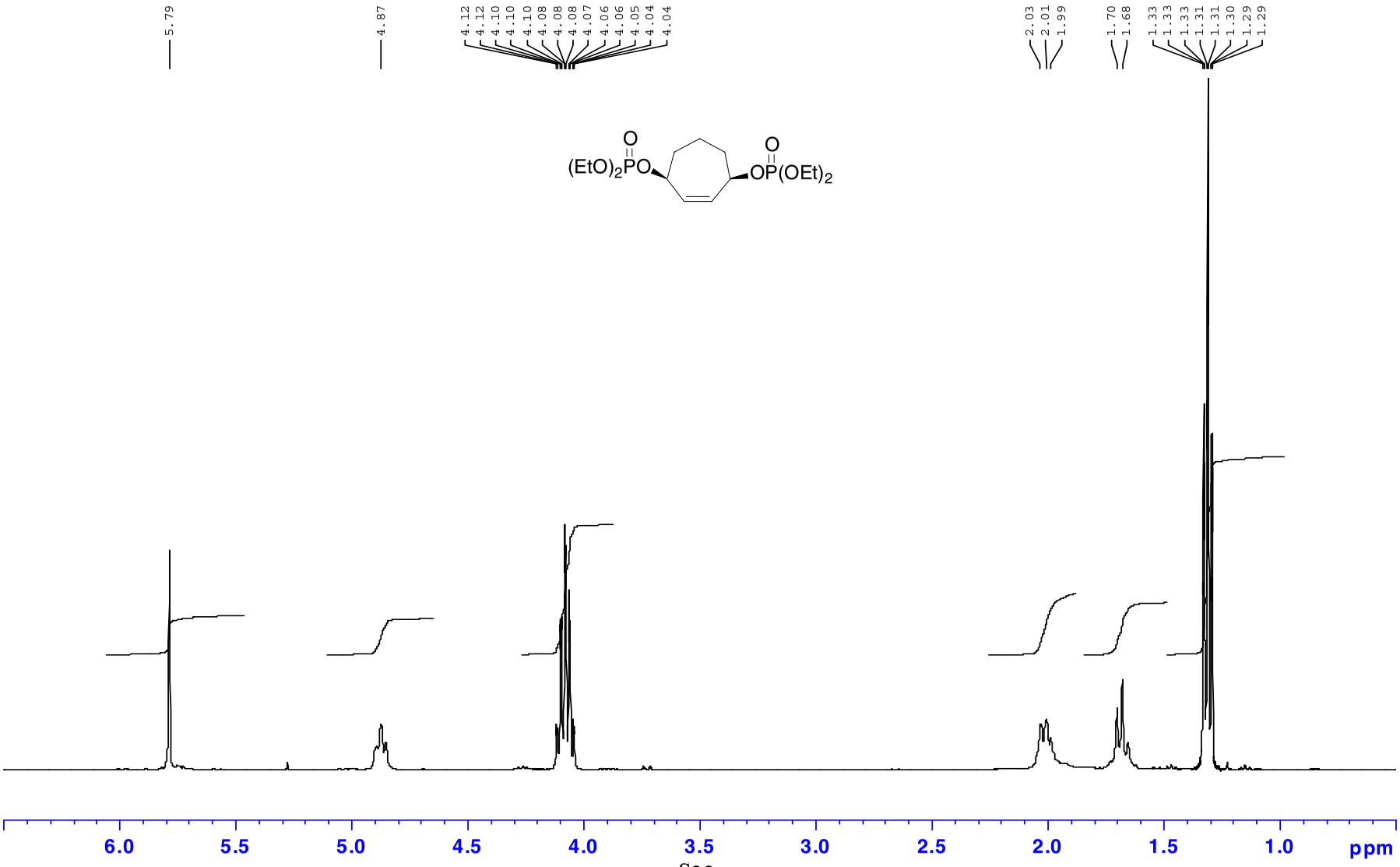
4b: ^{13}C NMR, 100 MHz, $CDCl_3$



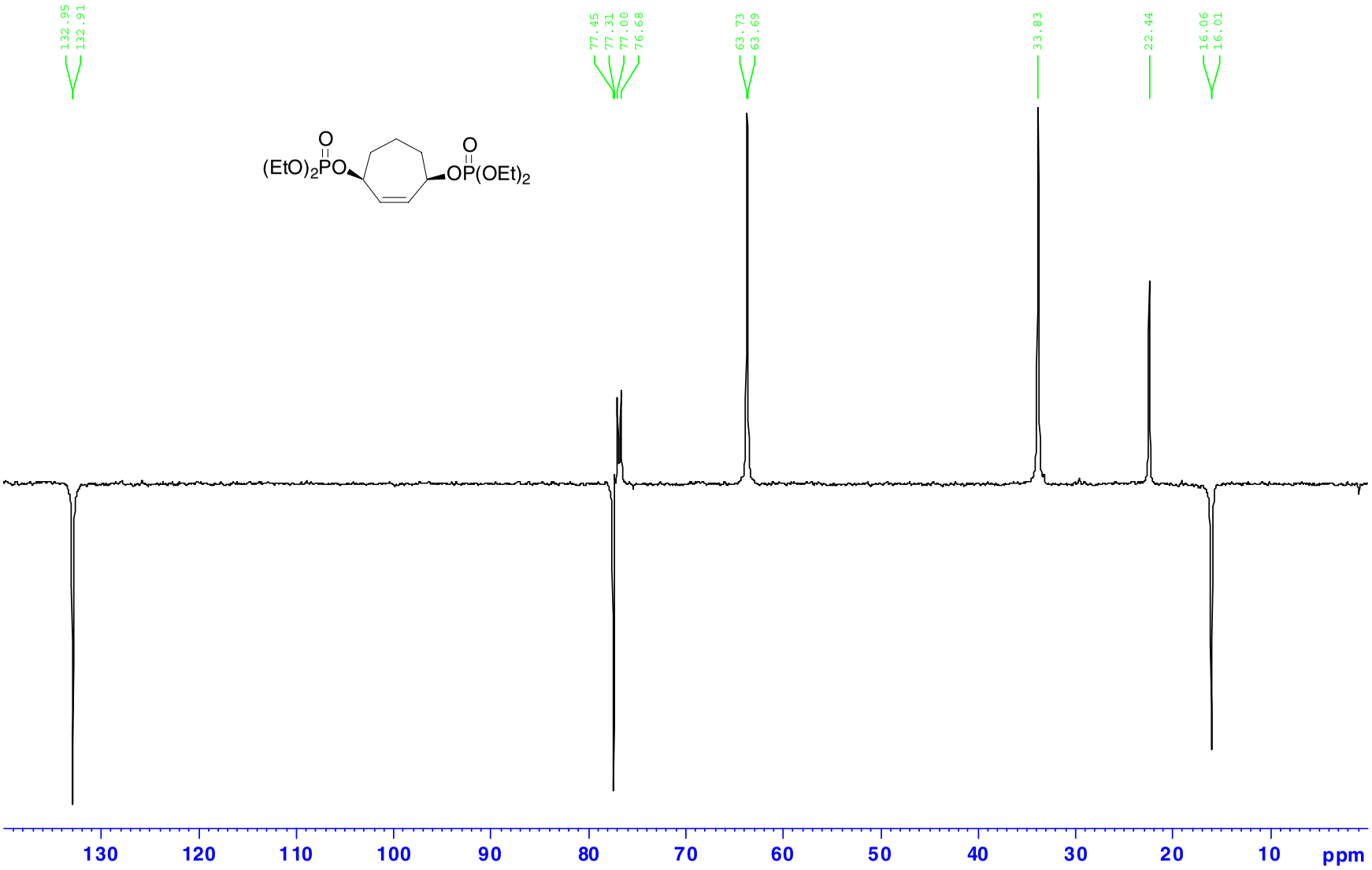
GC Trace of the two enantiomers of 8. Chiral stationary phase, see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C 10 min, 20°C/min to 200 °C. t_R = 0.91 min (*n*-decane), 7.9 min and 8.3 min (*cis*-2-ethyl-cyclohexen-3-ol enantiomers, 1:1), 8.4 min (1*S*,2*S* enantiomer), 8.9 min (1*R*,2*R* enantiomer).



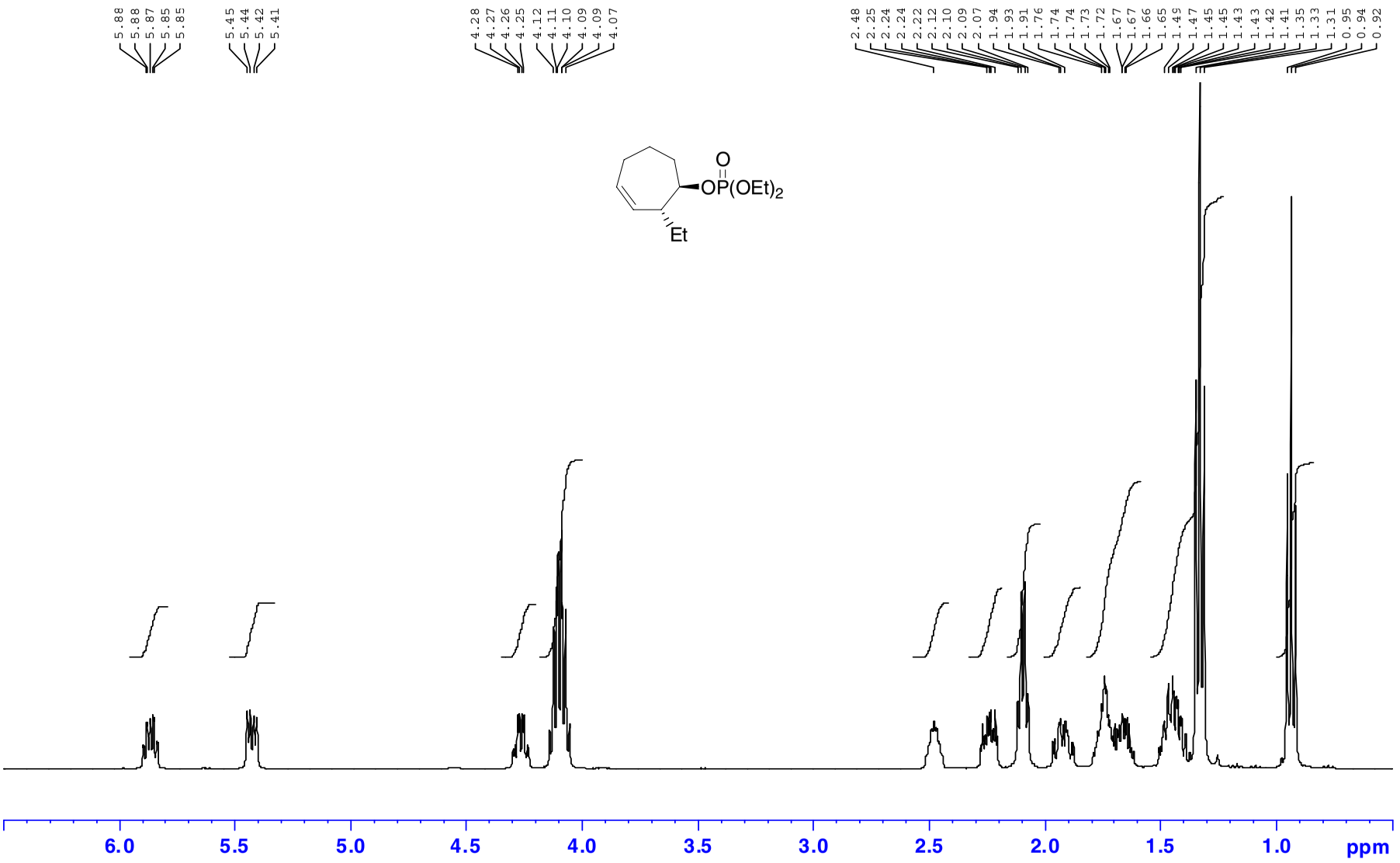
2c: ^{1}H NMR, 400 MHz, $CDCl_3$



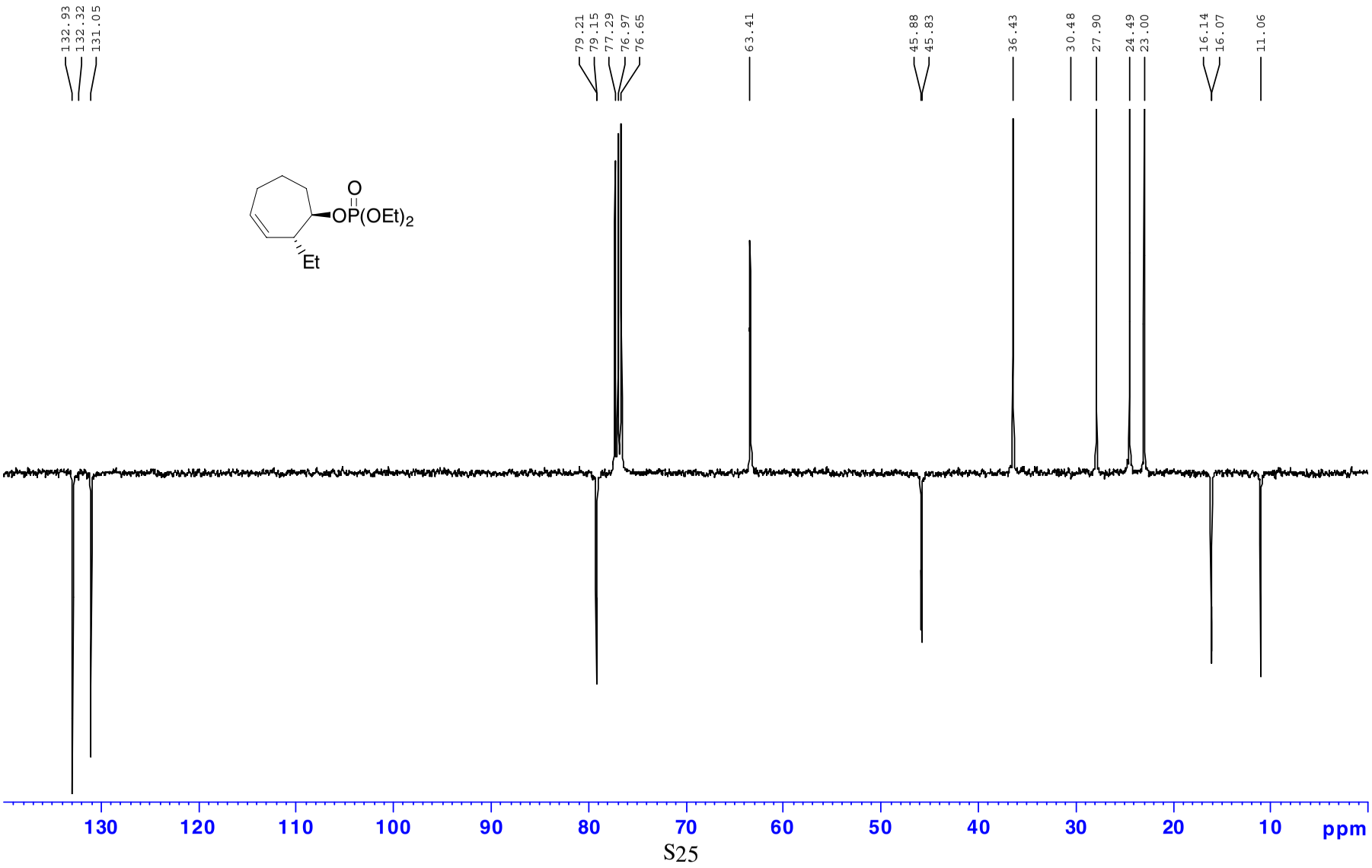
2c: ^{13}C NMR, 100 MHz, $CDCl_3$



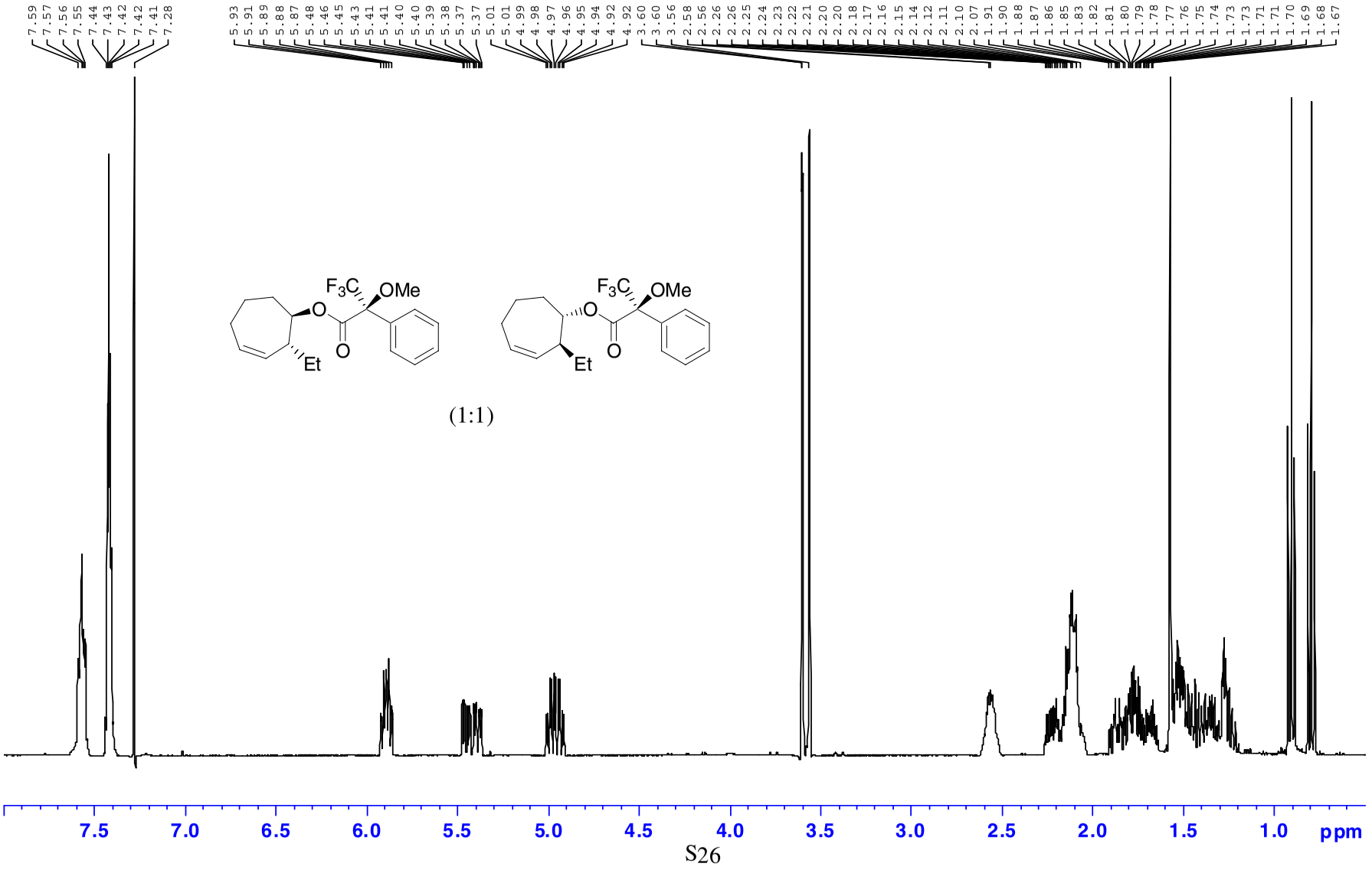
3c: ^{1}H NMR, 400 MHz, $CDCl_3$



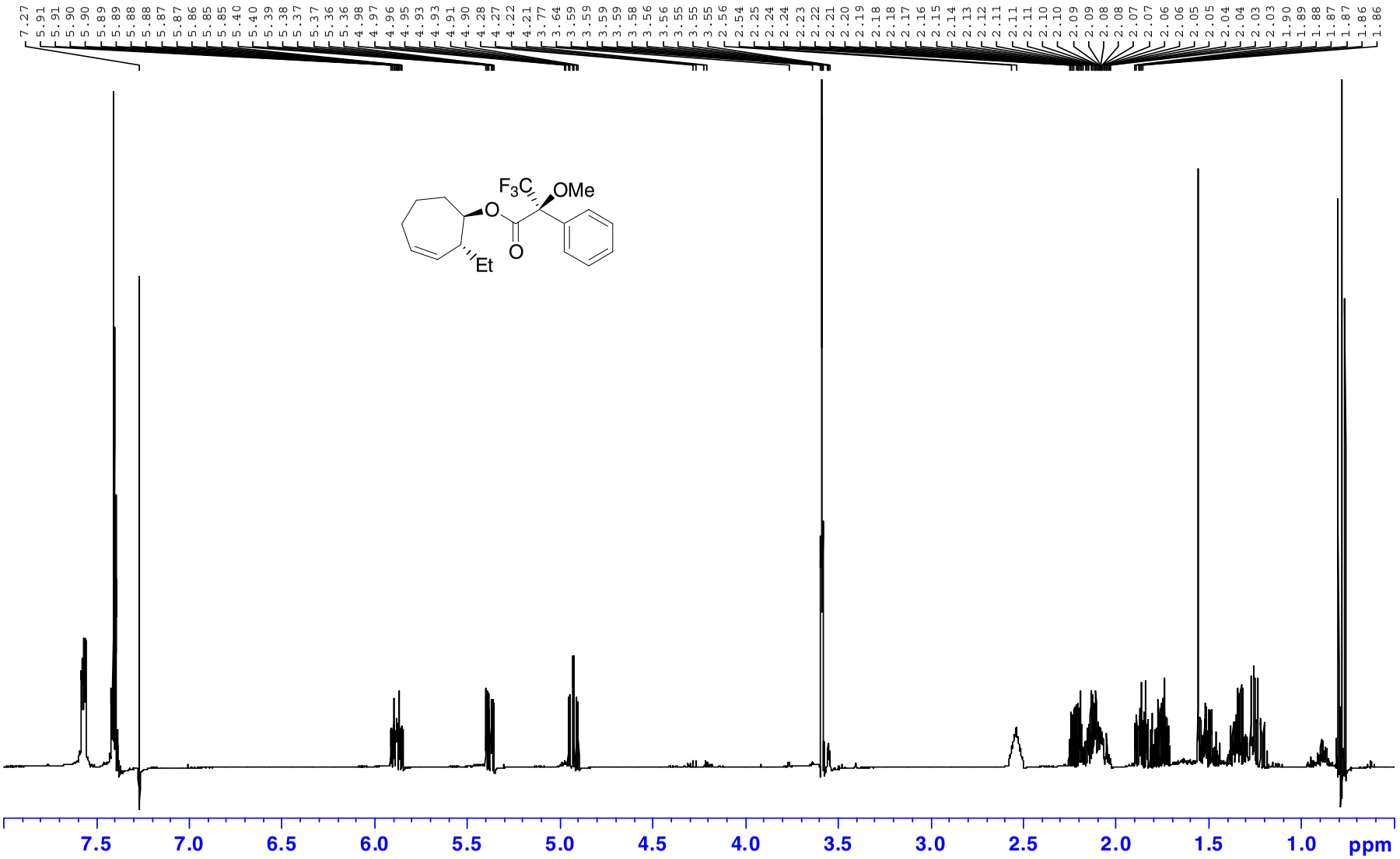
3c: ^{13}C NMR, 100 MHz, $CDCl_3$



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

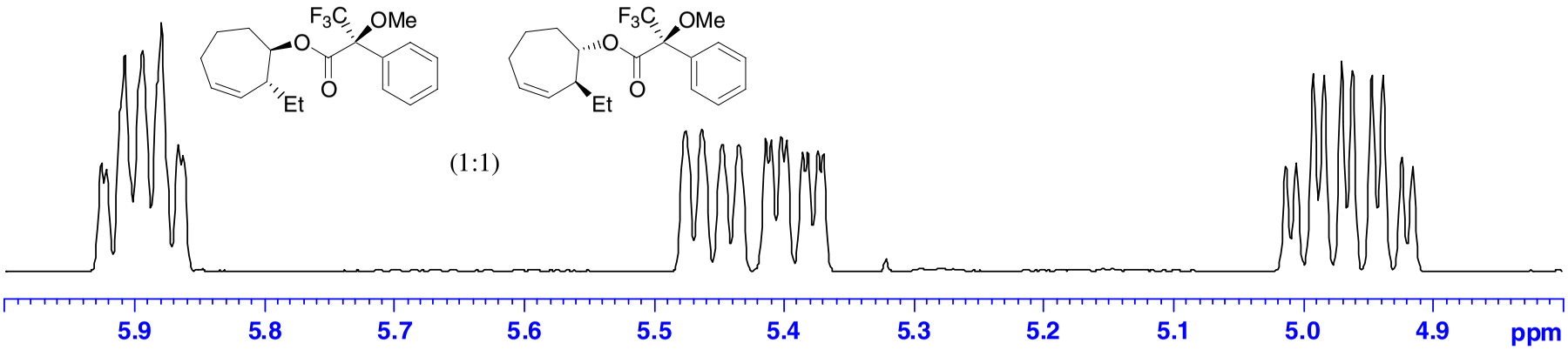


(*1R,2R*)- 2-ethyl-cyclohept-3-enol (*R*)-α-methoxy- α -(trifluoromethyl)phenylacetic acid ester (**11**): ^{1}H NMR, 400 MHz, $CDCl_3$

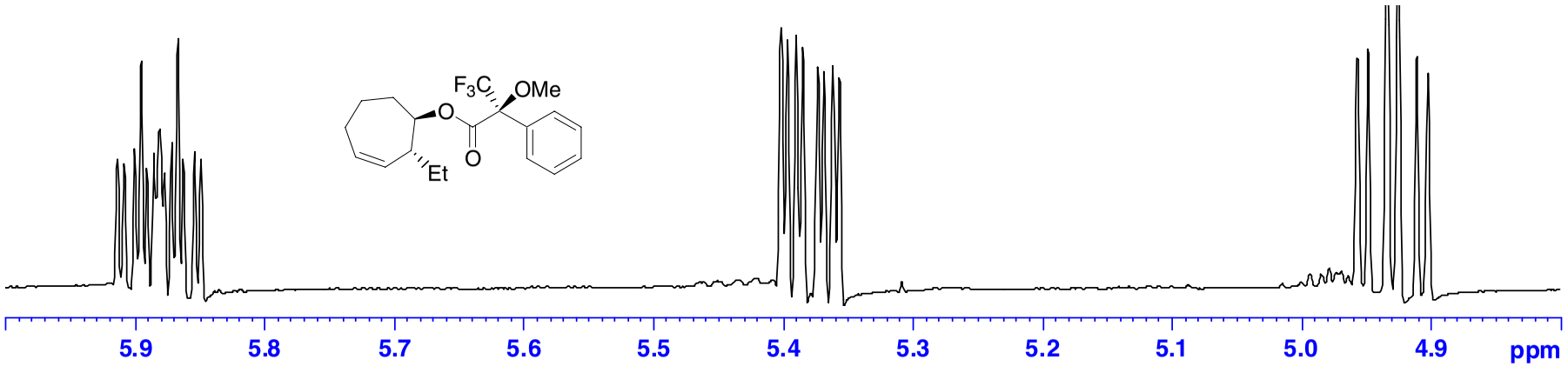


a) (*1R,2R*)- 2-ethyl-cyclohept-3-enol (*R*)-α-methoxy- α -(trifluoromethyl)phenylacetic acid ester and (*1S,2S*)- 2-ethyl-cyclohept-3-enol (*R*)-α-methoxy- α -(trifluoromethyl)phenylacetic acid ester (1:1): ^{1}H NMR, 400 MHz, $CDCl_3$ (expanded region, 6.0-4.8 ppm)
b) (*1R,2R*)- 2-ethyl-cyclohept-3-enol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

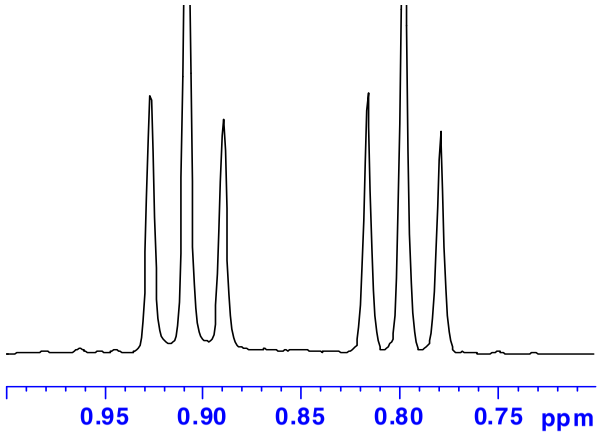
a)



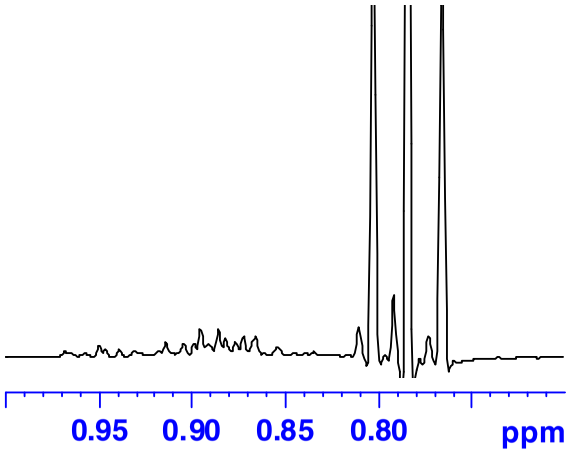
b)



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

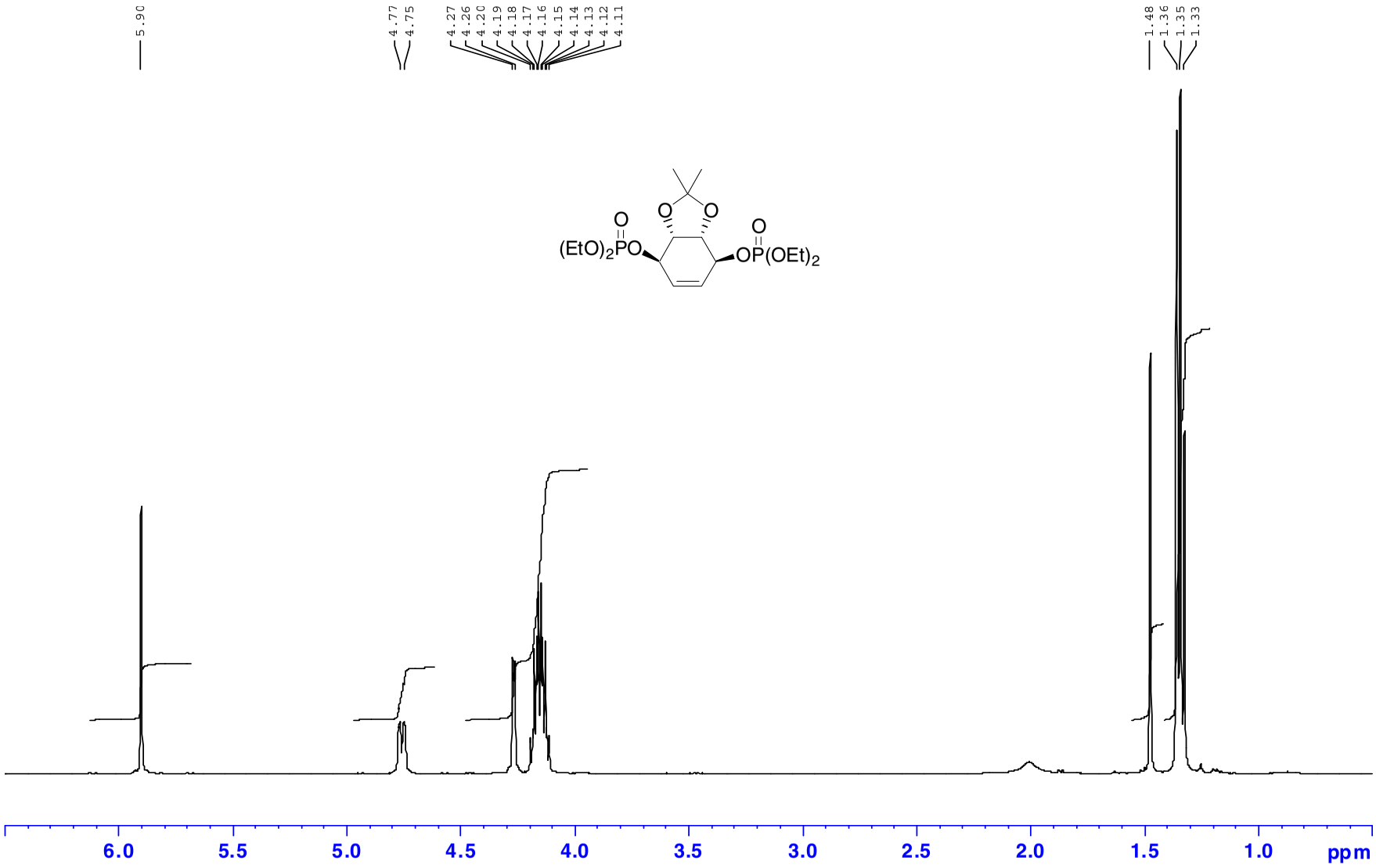


a)

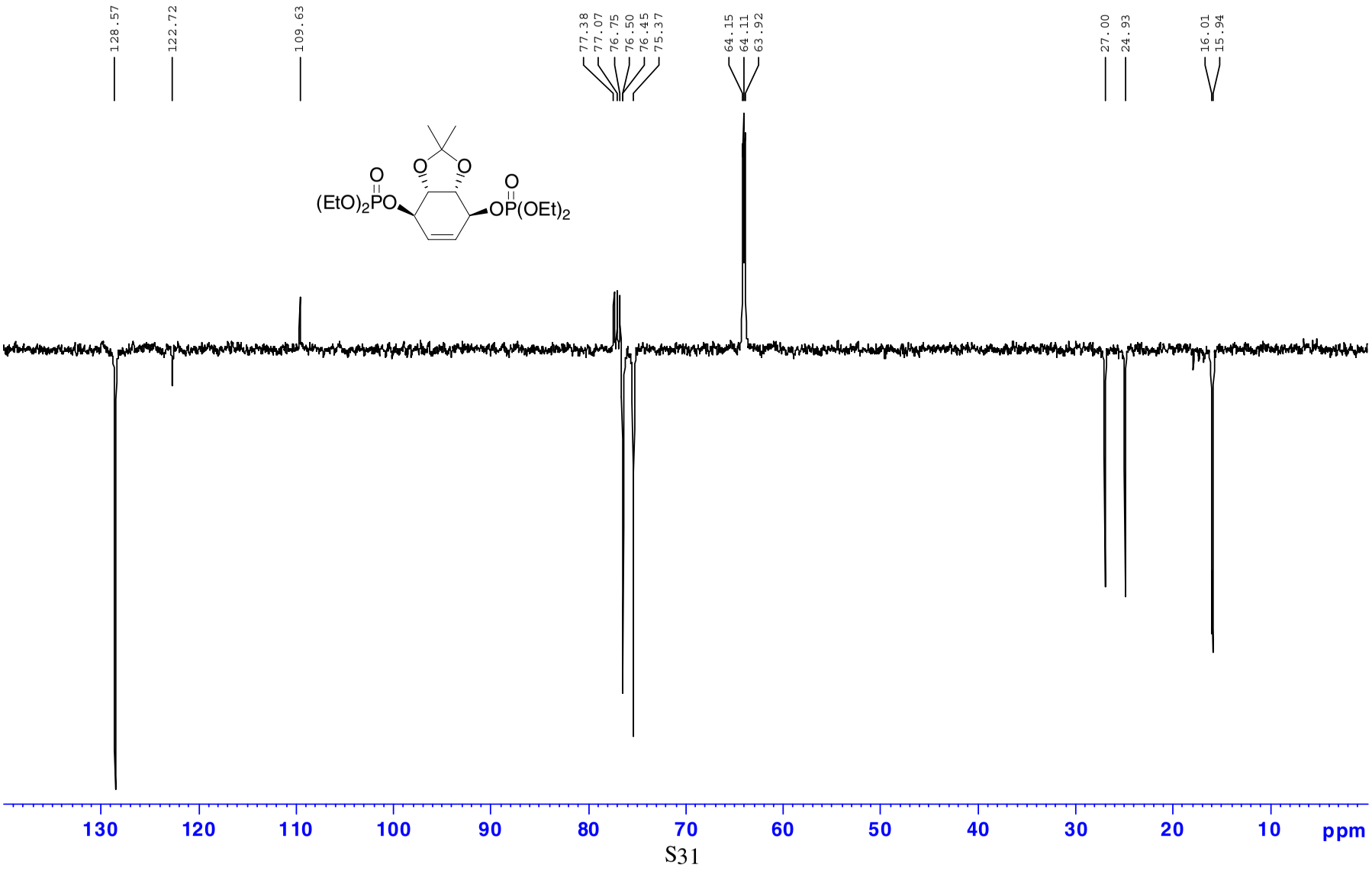


b)

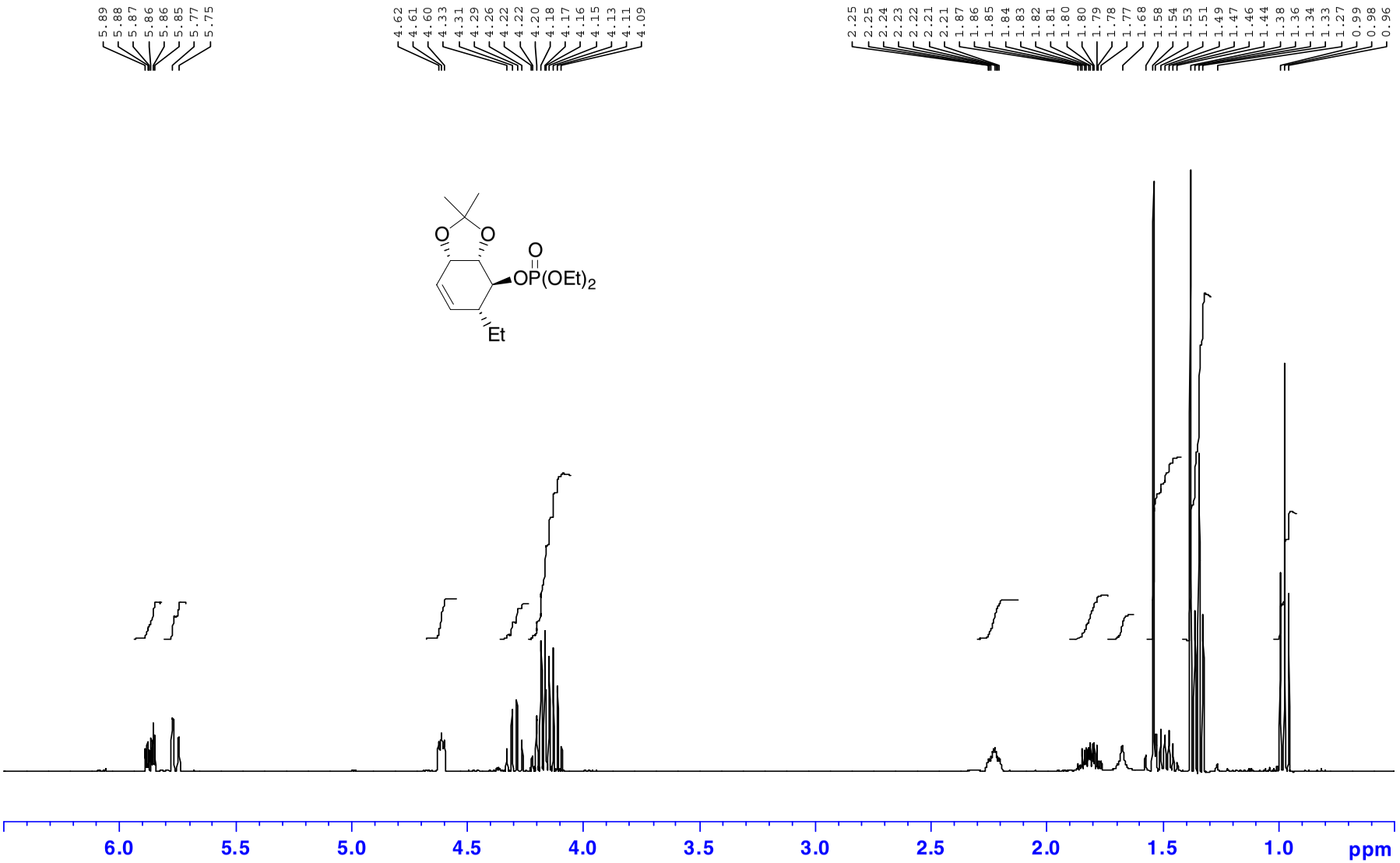
6: ^{1}H NMR, 400 MHz, $CDCl_3$



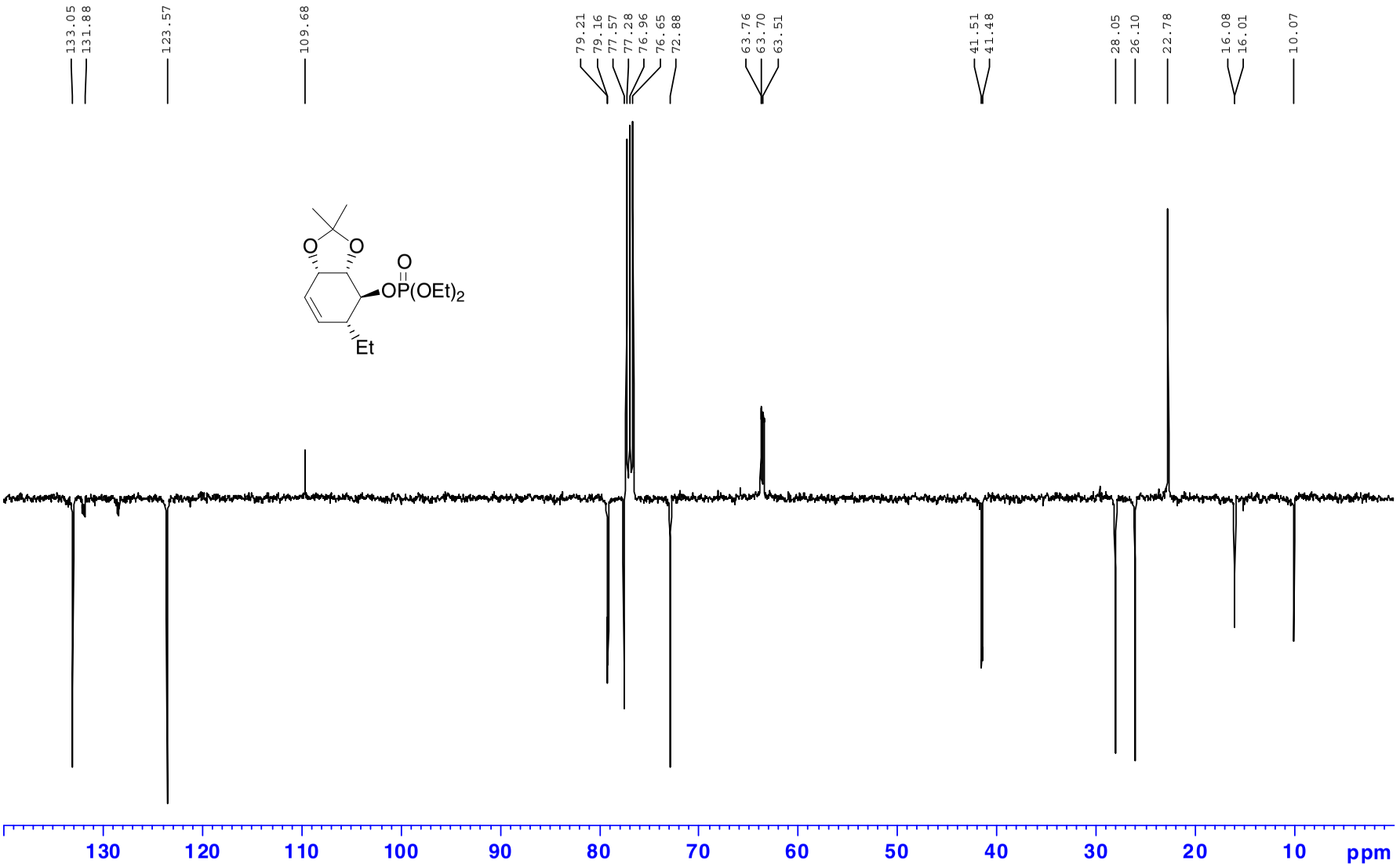
6: ^{13}C NMR, 100 MHz, $CDCl_3$



7: ^{1}H NMR, 400 MHz, $CDCl_3$



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



GC Trace of the two enantiomers of 10. Chiral stationary phase, see General Procedures; carrier: H_2 (70 kPa); injector: 250 °C; detector: 250 °C; oven temperature: 90 °C. t_R = 23.1 min (7%), 23.4 min (93%).