Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

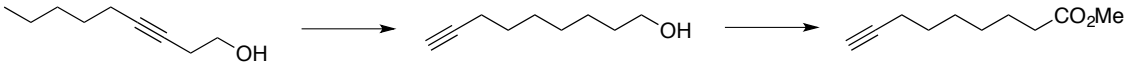
Asymmetric synthesis of 12-hydroxyheptadecatrienoic acid and its 5,6-dihydro- and 14,15-dehydro-derivatives

Yuichi Kobayashi,* Masao Morita, Narihito Ogawa, Daiki Kondo and Toshifumi Tojo

School of Life Science and Technology, Tokyo Institute of Technology
Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan

Synthesis of HHD

Methyl non-8-ynoate (7b)



17 **18** **7b**

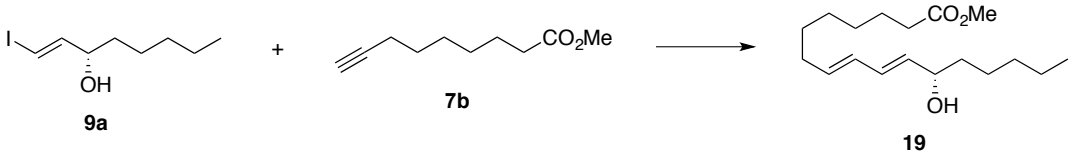
To an ice-cold solution of 1,3-diaminopropane (3.00 mL, 35.9 mmol) in THF (10 mL) was added *n*-BuLi (1.55 M in hexane, 23.0 mL, 35.7 mmol) dropwise. After 20 min of stirring at 0 °C, a solution of *t*-BuOK (3.20 g, 28.5 mmol) in THF (25 mL) and a solution of non-3-yn-1-ol (**17**) (997 mg, 7.11 mmol) in THF (7 mL) were added successively. After the addition, the mixture was warmed slowly to rt, stirred for 3 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed successively with 1 N HCl, saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford acetylene **18** (946 mg, 95%): R_f 0.46 (hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22–1.66 (m, 11 H), 1.94 (t, J = 2.7 Hz, 1 H), 2.18 (dt, J = 2.7, 6.9 Hz, 2 H), 3.64 (t, J = 6.6 Hz, 2 H).

To an ice-cold solution of CrO_3/H_2SO_4 (4.0 M in H_2O, 0.45 mL, 1.80 mmol) in acetone (3 mL) was added a solution of acetylene **18** (99 mg, 0.706 mmol) in acetone (4 mL) dropwise. After 20 min of stirring at 0 °C, the solution was diluted with *i*-PrOH and the resulting mixture was filtered through a pad of Celite with EtOAc. The filtrate was diluted with brine and the mixture was extracted with EtOAc twice. The combined extracts were dried over $MgSO_4$ and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the corresponding carboxylic acid (78 mg, 71%): R_f 0.41 (hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29–1.72 (m, 8 H), 1.94 (dt, J = 0.9, 2.7 Hz, 1 H), 2.14–2.23 (m, 2 H), 2.36 (t, J = 7.5 Hz, 2 H).

To an ice-cold solution of the above carboxylic acid (198 mg, 1.28 mmol) in Et_2O (4 mL) was added freshly prepared CH_2N_2 in Et_2O. After 5 min, the resulting mixture was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford ester **7b** (186 mg, 86%): R_f 0.86 (hexane/EtOAc 2:1); ^{1}H NMR

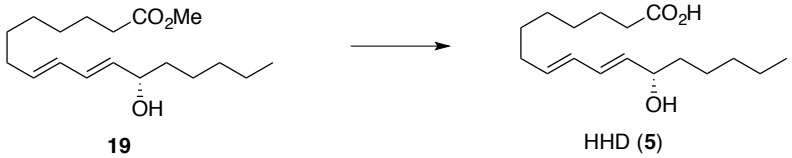
(300 MHz, $CDCl_3$) δ 1.24–1.70 (m, 8 H), 1.93 (t, J = 2.7 Hz, 1 H), 2.18 (dt, J = 2.7, 7.2 Hz, 2 H), 2.31 (t, J = 7.2 Hz, 2 H), 3.66 (s, 3 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 18.2 (–), 24.7 (–), 28.2 (–), 28.3 (–), 28.5 (–), 33.9 (–), 51.4 (+), 68.2 (–), 84.4 (–), 174.1 (–). The ^{1}H and ^{13}C NMR spectra were consistent with those reported.[S1]

Methyl (*S*,8*E*,10*E*)-12-hydroxyheptadeca-8,10-dienoate (19)



To an ice-cold solution of acetylene **7b** (68 mg, 0.404 mmol) in THF (3 mL) and Et_2O (4 mL) was added freshly prepared $(Sia)_2BH$ (0.50 M in THF, 1.40 mL, 0.70 mmol) slowly. After 1 h of stirring at 0 °C, 2 N NaOH (0.99 mL, 2.0 mmol) and a solution of iodide **9a** (50 mg, 0.197 mmol) in THF (2 mL) were added. After 5 min of argon bubbling, $Pd(PPh_3)_4$ (23 mg, 0.020 mmol) was added. The mixture was stirred at rt overnight and diluted with phosphate buffer (pH 5). The resulting mixture was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **19** (27 mg, 46%): R_f 0.30 (hexane/EtOAc 4:1); $[\alpha]_D^{20}$ +4 (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3 H), 1.20–1.70 (m, 17 H), 2.07 (q, J = 6.9 Hz, 2 H), 2.30 (t, J = 7.5 Hz, 2 H), 3.66 (s, 3 H), 4.10 (q, J = 6.8 Hz, 1 H), 5.57 (dd, J = 15.3, 6.8 Hz, 1 H), 5.67 (dt, J = 15.0, 6.9 Hz, 1 H), 6.01 (dd, J = 15.0, 10.5 Hz, 1 H), 6.16 (dd, J = 15.3, 10.5 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 14.1 (+), 22.7 (–), 24.9 (–), 25.2 (–), 28.8 (–), 29.0 (–), 31.9 (–), 32.6 (–), 34.1 (–), 37.3 (–), 51.6 (+), 73.0 (+), 129.6 (+), 131.0 (+), 133.8 (+), 135.4 (+), 174.4 (–); HRMS (FAB) calcd for $C_{18}H_{31}O_3$ [$(M–H)^+$] 295.2273, found 295.2276.

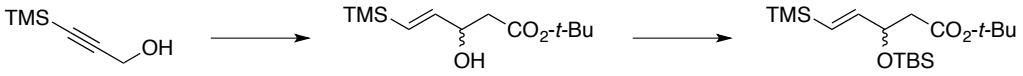
(*S*,8*E*,10*E*)-12-Hydroxyheptadeca-8,10-dienoic acid (5)



To a solution of methyl ester **19** (13 mg, 0.044 mmol) in THF (0.3 mL) was added 2 N LiOH (0.23 mL, 0.46 mmol). After 12 h of stirring at rt, the mixture was diluted with McIlvaine buffer (pH 5.0). The resulting mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford HHD (**5**) (8 mg, 65%): R_f 0.14 (hexane/EtOAc 1:1); $[\alpha]_D^{19}$ +7 (*c* 0.42, $CHCl_3$); UV (MeOH) λ_{max} 229 nm; IR (neat) 3412, 1710, 988 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3 H), 1.20–1.70 (m, 16 H), 2.07 (q, *J* = 6.8 Hz, 2 H), 2.34 (t, *J* = 7.2 Hz, 2 H), 4.11 (q, *J* = 6.6 Hz, 1 H), 5.0–7.0 (br s, 2 H), 5.57 (dd, *J* = 15.0, 7.2 Hz, 1 H), 5.68 (dt, *J* = 15.0, 6.8 Hz, 1 H), 6.01 (dd, *J* = 15.0, 10.5 Hz, 1 H), 6.16 (dd, *J* = 15.0, 10.5 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 14.1 (+), 22.7 (–), 24.7 (–), 25.2 (–), 28.8 (–), 28.9 (–), 29.0 (–), 31.8 (–), 32.6 (–), 34.0 (–), 37.3 (–), 73.1 (+), 129.7 (+), 131.0 (+), 133.7 (+), 135.3 (+), 179.5 (–); HRMS (FAB^-) calcd for $C_{17}H_{29}O_3$ $[(M–H)^-]$ 281.2117, found 281.2118.

Synthesis of HHTE

***tert*-Butyl (*E*)-3-((*tert*-butyldimethylsilyl)oxy)-5-(trimethylsilyl)pent-4-enoate (22)**



20 **21** **22**

To an ice-cold solution of alcohol **20** (1.00 g, 7.80 mmol) in Et_2O (20 mL) was added Red-Al (3.6 M in toluene, 4.80 mL, 17.3 mmol) dropwise. The mixture was stirred at rt for 3.5 h and the excess reagent was quenched by carefully adding 1 N HCl. The resulting mixture was extracted with Et_2O twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give the corresponding allylic alcohol, which was used for the next reaction without further purification.

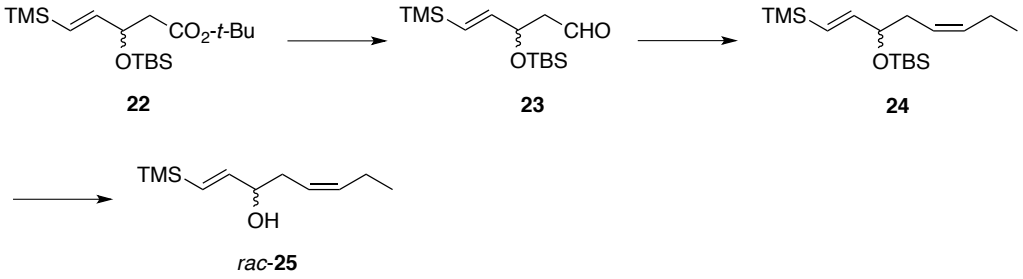
To a solution of the above alcohol in CH_2Cl_2 (26 mL) were added PCC (1.86 g, 8.63 mmol) and Celite (2.42 g). The mixture was stirred at rt for 2 h and diluted with petroleum ether. After 30 min of stirring at rt, the mixture was filtered through a pad of silica gel. The

filtrate was concentrated to give (*E*)-3-(trimethylsilyl)acrylaldehyde, which was used for the next reaction without further purification.

To a solution of *i*-Pr_2NH (1.65 mL, 11.7 mmol) in THF (10 mL) was added *n*-BuLi (1.63 M in hexane, 6.70 mL, 10.9 mmol) at –78 °C slowly. After 20 min, *tert*-butyl acetate (1.40 mL, 10.5 mmol) was added. The solution was stirred at –78 °C for 30 min and the above aldehyde in THF (8 mL) was added. The solution was stirred at –78 °C for 40 min and poured to saturated NH_4Cl with vigorous stirring. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol **21** (1.31 g, 69% over three steps): R_f 0.19 (hexane/EtOAc 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 9 H), 1.46 (s, 9 H), 2.42 (dd, *J* = 16.0, 8.1 Hz, 1 H), 2.52 (dd, *J* = 16.0, 4.2 Hz, 1 H), 3.14 (d, *J* = 4.8 Hz, 1 H), 4.41–4.52 (m, 1 H), 5.93 (dd, *J* = 18.9, 0.9 Hz, 1 H), 6.03 (dd, *J* = 18.9, 4.2 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –1.3 (+), 28.2 (+), 42.0 (–), 70.5 (+), 81.5 (–), 130.1 (+), 146.0 (+), 171.9 (–).

A mixture of alcohol **21** (917 mg, 3.75 mmol), imidazole (444 mg, 6.52 mmol) and TBSCl (801 mg, 5.31 mmol) in DMF (13 mL) was stirred at rt overnight and diluted with saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with saturated brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford TBS ether **22** (1.23 g, 91%): R_f 0.63 (hexane/EtOAc 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 15 H), 0.88 (s, 9 H), 1.43 (s, 9 H), 2.33 (dd, *J* = 14.5, 5.7 Hz, 1 H), 2.44 (dd, *J* = 14.5, 7.5 Hz, 1 H), 4.51 (ddt, *J* = 7.5, 0.9, 5.7 Hz, 1 H), 5.83 (dd, *J* = 18.6, 0.9 Hz, 1 H), 5.97 (dd, *J* = 18.6, 5.7 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –4.8 (+), –4.2 (+), –1.3 (+), 18.2 (–), 25.9 (+), 28.2 (+), 44.6 (–), 72.8 (+), 80.4 (–), 129.7 (+), 147.7 (+), 170.5 (–); HRMS (FAB^+) calcd for $C_{18}H_{39}O_3Si_2$ [$(M+H)^+$] 359.2438, found 359.2438. The ^{1}H NMR spectrum was consistent with that reported.[S2]

(1*E*,5*Z*)-1-(Trimethylsilyl)octa-1,5-dien-3-ol (*rac*-25)



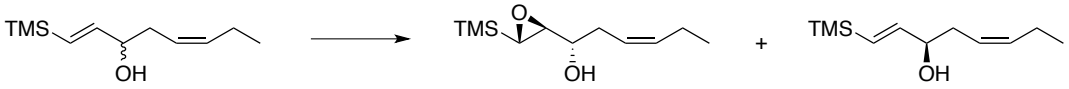
To a solution of TBS ether **22** (2.50 g, 6.97 mmol) in CH_2Cl_2 (30 mL) was added DIBAL (1.02 M in hexane, 8.20 mL, 8.36 mmol) at –78 °C. After 1 h of stirring at –78 °C, the reaction was terminated by adding MeOH (5 mL, 0.12 mol) at –78 °C. The solution was poured into a mixture of H_2O (20 mL, 1.1 mol) and NaF (2.5 g, 60 mmol) with vigorous stirring. The resulting mixture was filtered through a pad of Celite and extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford aldehyde **23** (1.59 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.07 (s, 9 H), 0.88 (s, 9 H), 2.50 (ddd, J = 15.6, 4.8, 2.5 Hz, 1 H), 2.60 (ddd, J = 15.6, 7.3, 2.5 Hz, 1 H), 4.58–4.68 (m, 1 H), 5.88 (dd, J = 18.7, 0.9 Hz, 1 H), 6.01 (dd, J = 18.7, 5.2 Hz,1 H), 9.77 (t, J = 2.5 Hz, 1 H).

To an ice-cold solution of propyl phosphonium bromide (2.76 g, 7.17 mmol) in THF (30 mL) was added $NaN(TMS)_2$ (1.0 M in THF, 6.69 mL, 6.69 mmol) dropwise. After 30 min of stirring at 0 °C, the solution was cooled to –90 °C (liquid N_2 and hexane). A solution of the above aldehyde (1.37 g, 4.78 mmol) in THF (10 mL) was added dropwise. After the addition, the solution was stirred at rt for 30 min and saturated NH_4Cl was added to the solution. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to afford olefin **24** (1.38 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3 H), 0.04 (s, 3 H), 0.05 (s, 9 H), 0.89 (s, 9 H), 0.95 (t, J = 7.4 Hz, 3 H), 2.03 (quint., J = 7.4 Hz, 2 H), 2.23 (t, J = 6.0 Hz, 2 H), 4.07 (ddt, J = 5.4, 1.3, 6.0 Hz, 1 H), 5.28–5.49 (m, 2 H), 5.77 (dd, J = 18.6, 1.2 Hz, 1 H), 5.98 (dd, J = 18.6, 5.4 Hz, 1 H).

To an ice-cold solution of olefin **24** (1.03 g, 3.28 mmol) in THF (10 mL) was added

Bu_4NF (1.0 M in THF, 4.9 mL, 4.9 mmol) dropwise. The solution was stirred at rt for 12 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol *rac*-**25** (641 mg, 98%): R_f 0.35 (hexane/EtOAc 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 9 H), 0.97 (t, J = 7.5 Hz, 3 H), 1.69 (d, J = 4.2 Hz, 1 H), 2.07 (quint., J = 7.5 Hz, 2 H), 2.30 (t, J = 7.2 Hz, 2 H), 4.08–4.18 (m, 1 H), 5.35 (dtt, J = 10.8, 7.5, 1.2 Hz, 1 H), 5.57 (dtt, J = 10.8, 7.2, 1.2 Hz, 1 H), 5.88 (dd, J = 18.9, 1.2 Hz, 1 H), 6.07 (dd, J = 18.9, 4.8 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –1.2 (+), 14.2 (+), 20.8 (–), 35.0 (–), 73.8 (+), 123.9 (+), 129.4 (+), 135.3 (+), 147.8 (+); HRMS (EI^+) calcd for $C_{11}H_{22}OSi$ (M^+) 198.1440, found 198.1437.

(*S*,*Z*)-1-((2*S*,3*S*)-3-(Trimethylsilyl)oxiran-2-yl)hex-3-en-1-ol (26) and (*R*,1*E*,5*Z*)-1-(trimethylsilyl)octa-1,5-dien-3-ol ((*R*)-25)



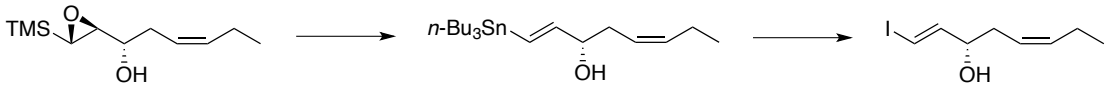
rac-**25** **26** (*R*)-**25**

To an ice-cold solution of Ti(O-*i*-Pr)$_4$ (1.29 mL, 4.40 mmol) in CH_2Cl_2 (22 mL) was added L-(+)-DIPT (1.10 mL, 5.26 mmol). After 30 min at 0 °C, the solution was cooled to –10 °C and a solution of allylic alcohol *rac*-**25** (869 mg, 4.38 mmol) in CH_2Cl_2 (2 mL) was added. The solution was stirred at –10 °C for 30 min and cooled to –40 °C. A solution of *t*-BuOOH (3.51 M in CH_2Cl_2, 1.88 mL, 6.60 mmol) was added dropwise. After the addition, the solution was stirred at –18 °C for 6 h, and then Me_2S (1.0 mL, 14 mmol), 10% tartaric acid (1.0 mL) and NaF (3.19 g, 76 mmol) were added. The resulting mixture was stirred at rt for 30 min and filtered through a pad of Celite with CH_2Cl_2. The filtrate was mixed with 10% NaOH (50 mL) and the mixture was stirred at rt for 1 h. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford epoxide **26** (419 mg, 45%) and allylic alcohol (*R*)-**25** (382 mg, 44%).

Epoxide **26**: 98% ee by Mosher analysis; R_f 0.62 (hexane/EtOAc 3:1); IR (neat) 3441, 1250, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 9 H), 0.97 (t, J = 7.5 Hz, 3 H), 1.97 (br s, 1 H), 2.07 (quint., J = 7.5 Hz, 2 H), 2.30–2.42 (m, 3 H), 2.90 (t, J = 3.5 Hz, 2 H), 3.79–3.89 (m, 1 H), 5.41 (dtt, J = 10.3, 7.5 Hz, 1 H), 5.54 (dt, J = 10.3, 7.1 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –3.6 (+), 14.3 (+), 20.8 (–), 31.7 (–), 47.7 (+), 58.1 (+), 69.3 (+), 123.3 (+), 134.9 (–); HRMS (FAB^+) calcd for $C_{11}H_{22}O_2SiNa$ [$(M+Na)^+$] 237.1287, found 237.1282.

Allylic alcohol (*R*)-**25**: 98% ee by Mosher analysis; R_f 0.68 (hexane/EtOAc 3:1). The ^1H NMR spectrum was consistent with that described above for the racemic allylic alcohol *rac*-**25**.

(*S*,1*E*,5*Z*)-1-Iodoocta-1,5-dien-3-ol (9b)



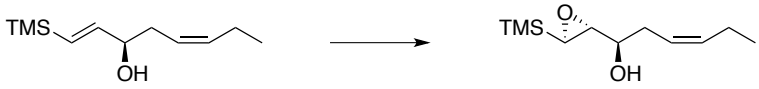
26 **27** **9b**

To an ice-cold solution of *i*-Pr_2NH (0.082 mL, 0.585 mmol) in THF (5 mL) was added *n*-BuLi (1.61 M in hexane, 0.31 mL, 0.499 mmol) dropwise. The solution was stirred at 0 °C for 30 min and added *n*-Bu_3SnH (0.068 mL, 0.253 mmol). After 30 min a solution of epoxide **26** (36 mg, 0.168 mmol) in THF (1 mL) was added. The solution was stirred at 0 °C for 1 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to leave an oil, which was passed through a short column of silica gel (hexane/EtOAc) to afford vinyl stannane **27**, which was used for the next reaction without further purification.

To a solution of the above stannane in Et_2O (5 mL) was added iodine (64 mg, 0.25 mmol). After 1 h of stirring at rt, the solution was diluted with aqueous $Na_2S_2O_3$. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford iodide **9b** (29 mg, 69% over two steps): R_f = 0.48 (hexane/EtOAc 5:1); $[\alpha]_D^{19}$ –22 (*c* 0.99, $CHCl_3$), cf. $[\alpha]_D^{20}$ +16.4

(*c* 1.2, $CHCl_3$) for the enantiomer[S3]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.5 Hz, 3 H), 1.77 (d, *J* = 4.2 Hz, 1 H), 2.06 (quint., *J* = 7.5 Hz, 2 H), 2.31 (t, *J* = 6.5 Hz, 2 H), 4.08–4.18 (m, 1 H), 5.32 (dtt, *J* = 10.8, 7.5, 1.5 Hz, 1 H), 5.60 (dtt, *J* = 10.8, 7.2, 1.5 Hz, 1 H), 6.37 (dd, *J* = 14.4, 1.2 Hz, 1 H), 6.59 (dd, *J* = 14.4, 5.7 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 14.3 (+), 20.8 (–), 34.6 (–), 73.9 (+), 77.4 (+), 122.8 (+), 136.1 (+), 147.8 (+). The ^{1}H and ^{13}C NMR spectra were consistent with that reported.[S3,S4] The structure was also supported by the ^{13}C–APT NMR spectrum.

(*R*,*Z*)-1-((2*R*,3*R*)-3-(Trimethylsilyl)oxiran-2-yl)hex-3-en-1-ol (*ent*-26)



(*R*)-**25** *ent*-**26**

To an ice-cold solution of Ti(O-*i*-Pr)$_4$ (1.47 mL, 5.04 mmol) in CH_2Cl_2 (30 mL) was added D-(–)-DIPT (1.27 mL, 6.05 mmol). After being stirred at 0 °C for 30 min, the solution was cooled to –30 °C and a solution of allylic alcohol (*R*)-**25** (1.00 g, 5.04 mmol) in CH_2Cl_2 (5 mL) was added to the solution, which was stirred at –30 °C for 15 min. To this solution was added *t*-BuOOH (2.88 M in CH_2Cl_2, 2.63 mL, 7.56 mmol) at –30 °C dropwise. The solution was stirred at –18 °C for 6 h and then Me_2S (1.12 mL, 15.1 mmol), 10% tartaric acid (40 mL) and NaF (2.12 g, 50.4 mmol) were added. The resulting mixture was stirred at rt for 30 min and filtered through a pad of Celite. A mixture of the filtrate and 1 N NaOH (30 mL, 30 mmol) was stirred at rt for 15 min vigorously and extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford epoxide *ent*-**26** (1.07 g, 99%). The ^{1}H NMR spectrum was identical with that for **26**.

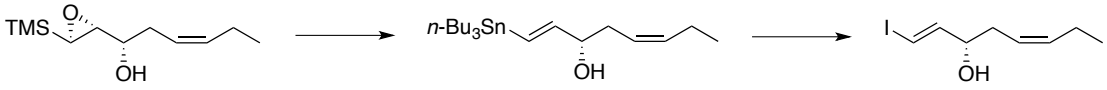
(*S*,*Z*)-1-((2*R*,3*R*)-3-(Trimethylsilyl)oxiran-2-yl)hex-3-en-1-ol (28)

ent-**26** **28**

To an ice-cold solution of epoxide *ent*-**26** (700 mg, 3.27 mmol) in THF (2 mL) were added 4-nitrobenzoic acid (821 mg, 4.91 mmol) and PPh_3 (1.27 g, 4.84 mmol). After 15 min at 0 °C, diisopropyl azodicarboxylate (0.94 mL, 4.83 mmol) was added. The mixture was stirred at 0 °C for 1 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was passed through a short column of silica gel (hexane/EtOAc) to give the corresponding ester, which was used for the next reaction without further purification.

To an ice-cold solution of the above ester in THF/MeOH (1:1, 8 mL) was added 1 N NaOH (16 mL, 16 mmol). After being stirred at rt for 15 min, the mixture was diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to afford epoxide **28** (568 mg, 81% over two steps): R_f 0.40 (hexane/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 9 H), 0.98 (t, J = 7.7 Hz, 3 H), 1.98 (d, J = 5.4 Hz), 2.08 (quint., J = 7.5 Hz, 2 H), 2.24 (d, J = 3.6 Hz, 1 H), 2.28–2.48 (m, 2 H), 2.85 (dd, J = 5.0, 3.6 Hz, 1 H), 3.40–3.52 (m, 1 H), 5.32–5.44 (m, 1 H), 5.48–5.62 (m, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ –3.7 (+), 14.2 (+), 20.7 (–), 32.5 (–), 49.4 (+), 58.7 (+), 72.6 (+), 123.3 (+), 134.9 (+); HRMS (FAB$^+$) calcd for $C_{11}H_{22}O_2SiNa$ [(M+Na)$^+$] 237.1287, found 237.1287.

(*S*,1*E*,5*Z*)-1-Iodoocta-1,5-dien-3-ol (9b)



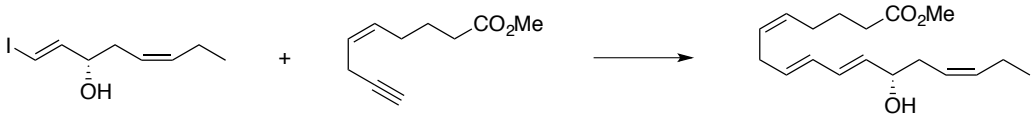
28 **27** **9b**

To an ice-cold solution of *i*-Pr_2NH (0.376 mL, 2.68 mmol) in THF (2 mL) was added *n*-BuLi (1.60 M in hexane, 1.26 mL, 2.02 mmol) dropwise. After 15 min of stirring at 0 °C, *n*-Bu_3SnH (0.36 mL, 1.34 mmol) was added. The solution was stirred at 0 °C for 15 min and a solution of epoxide **28** (150 mg, 0.670 mmol) in THF (1 mL) was added. The solution was stirred at 0 °C for 30 min and diluted with water. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over

$MgSO_4$ and concentrated. The residue was passed through a short column of silica gel (hexane/EtOAc) to give stannane **27**, which was used for the next reaction without further purification.

To a solution of iodine (207 mg, 0.816 mmol) in Et_2O (2 mL) was added a solution of the above stannane in Et_2O (1 mL) at –70 °C and the cooling bath was replaced by an ice-water bath. The solution was stirred for 1 h and diluted with aqueous $Na_2S_2O_3$ and saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc twice. The combined organic layers were washed brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on 10% w/w K_2CO_3-silica gel (hexane/EtOAc) to afford iodide **9b** (120 mg, 71% over two steps). The ^{1}H NMR spectrum was identical with iodide **9b** synthesized from **26**.

Methyl (*S*,5*Z*,8*E*,10*E*,14*Z*)-12-hydroxyheptadeca-5,8,10,14-tetraenoate (29)

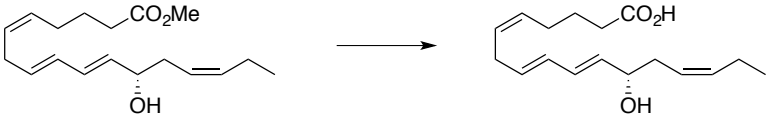


9b **7a** **29**

To an ice-cold solution of acetylene **7a** (23 mg, 0.138 mmol) in THF (3 mL) was added freshly prepared $(Sia)_2BH$ (0.50 M in THF, 0.46 mL, 0.23 mmol) dropwise. After 30 min of stirring at 0 °C, 2 N NaOH (0.56 mL, 1.12 mmol) and a solution of iodide **9b** (29 mg, 0.115 mmol) in Et_2O (3 mL) were added to the solution. The resulting mixture was bubbled gently with nitrogen at 0 °C for 10 min and $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) was added to the mixture, which was stirred at rt for 4 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc twice. The organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford methyl ester **29** (20 mg, 59%): R_f 0.18 (hexane/EtOAc 5:1); $[\alpha]_D^{19}$ –8 (*c* 0.72, $CHCl_3$); IR (neat) 3511, 1740, 1311, 1210, 989 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.5 Hz, 3 H), 1.56–1.82 (br s, 1 H), 1.69 (quint., *J* = 7.5 Hz, 2 H), 1.99–2.14 (m, 4 H), 2.21–2.40 (m, 4 H), 2.81 (t, *J* = 5.6 Hz, 2 H), 3.66 (s, 3 H), 4.16 (q, *J* = 6.5 Hz, 1 H), 5.28–5.72 (m, 6 H), 6.03 (dd, *J* = 15.1, 10.5 Hz, 1 H), 6.20 (dd, *J* = 15.1, 10.5 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 14.3 (+), 20.8 (–), 24.8 (–), 26.5 (–),

30.4 (–), 33.5 (–), 35.3 (–), 51.6 (+), 72.1 (+), 123.9 (+), 127.8 (+), 129.80 (+), 129.83 (+), 130.7 (+), 133.0 (+), 133.5 (+), 135.3 (+), 174.2 (–); HRMS (FAB^+) calcd for $C_{18}H_{28}O_3Na$ $[(M+Na)^+]$ 315.1936, found 315.1929.

(*S*,5*Z*,8*E*,10*E*,14*Z*)-12-Hydroxyheptadeca-5,8,10,14-tetraenoic acid (6)



29 HHTE (**6**)

A solution of methyl ester **29** (20 mg, 0.0684 mmol) and 2 N LiOH (0.20 mL, 0.40 mmol) in THF (1 mL) and MeOH (1 mL) was stirred at rt for 10 h and diluted with McIlvaine buffer (pH 5.0). The resulting mixture was extracted with Et_2O five times. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford HHTE (**6**) (12 mg, 63%): R_f 0.26 (hexane/EtOAc 1:4); $[\alpha]_D^{20}$ –11 (*c* 0.595, $CHCl_3$); UV (MeOH) λ_{max} 231 nm; IR (neat) 3364, 1709, 989, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.5 Hz, 3 H), 1.71 (quint., *J* = 7.3 Hz, 2 H), 2.00–2.16 (m, 4 H), 2.22–2.44 (m, 4 H), 2.82 (t, *J* = 5.7 Hz, 2 H), 4.17 (q, *J* = 6.5 Hz, 1 H), 5.28–5.73 (m, 6 H), 6.04 (dd, *J* = 15.2, 10.5 Hz, 1 H), 6.21 (dd, *J* = 15.2, 10.5 Hz, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 14.3 (+), 20.8 (–), 24.5 (–), 26.4 (–), 30.4 (–), 33.3 (–), 35.2 (–), 72.2 (+), 123.8 (+), 127.9 (+), 129.7 (+), 129.8 (+), 130.8 (+), 133.0 (+), 133.4 (+), 135.3 (+), 179.1 (–); HRMS (FAB^-) calcd for $C_{17}H_{25}O_3$ $[(M–H)^-]$ 277.1804, found 277.1806.

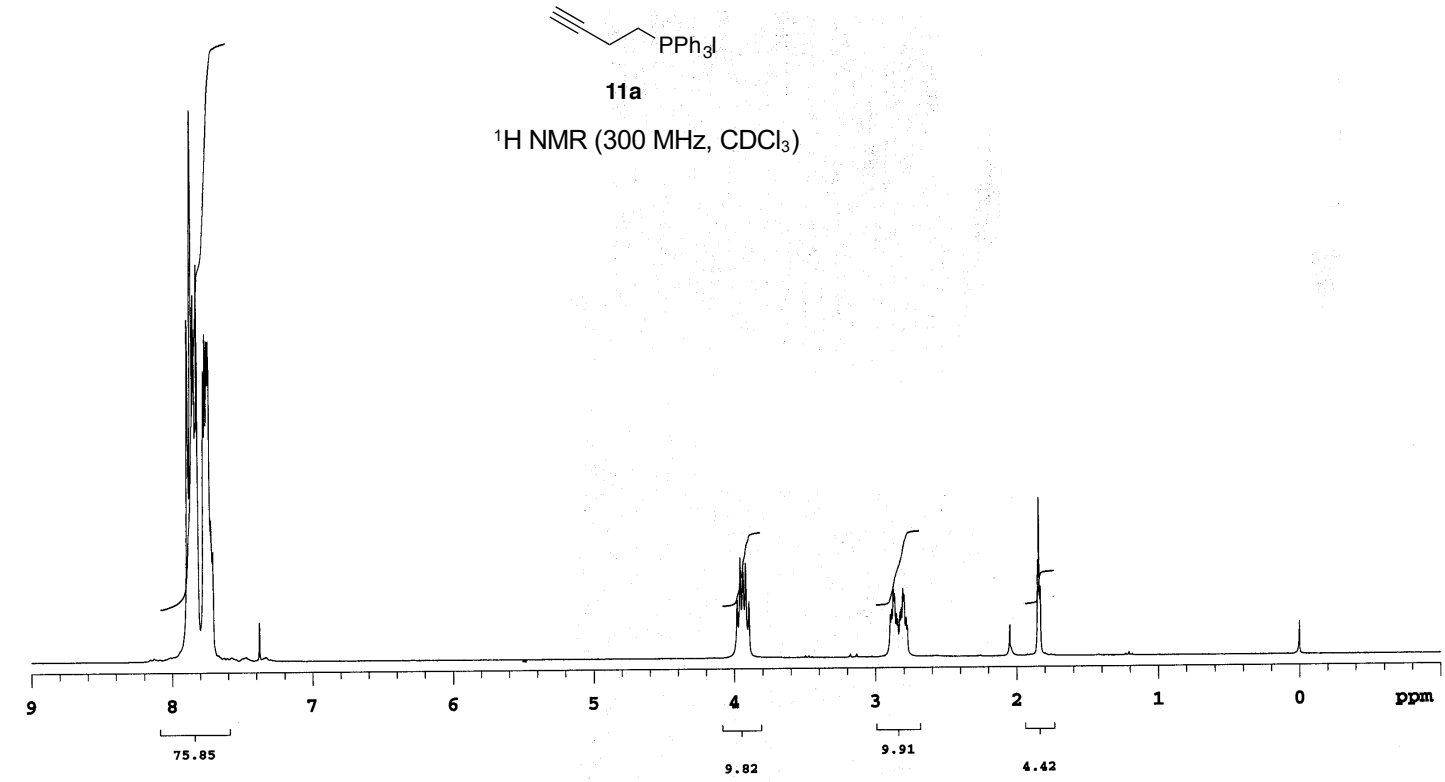
References

S1 (*a*) E. Quesada, J. Delgado, V. Hornillos, A. U. Acuña and F. Amat-Guerri, *Eur. J. Org. Chem*., **2007**, 2285; (*b*) B. M. Trost and A. B. Pinkerton, *J. Org. Chem*., 2001, **66**, 7714.

S2 K. Takeda, Y. Yamawaki and N. Hatakeyama, *J. Org. Chem*., 2002, **67**, 1786.

S3: M. Bischop, V. Doum, A. C. M. Nordschild, J. Pietruszka and D. Sandkuhl, *Synthesis*, 2010, 527.

S4: A. R. Rodriguez and B. W. Spur, *Tetrahedron Lett*., 2012, **53**, 6990.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7
6
5
4
3
2
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0
ppm
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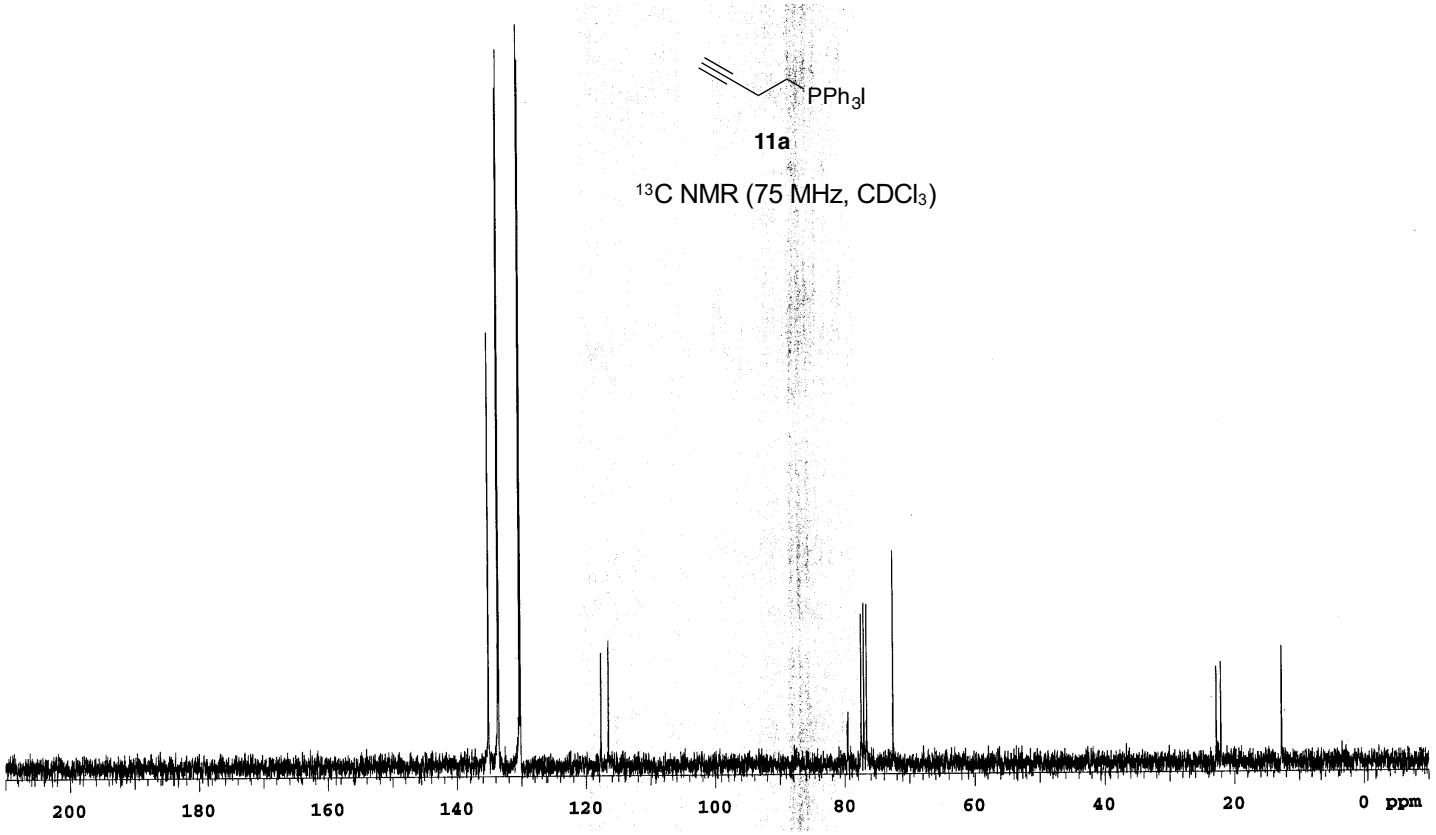
9.82
9.91
4.42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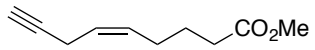
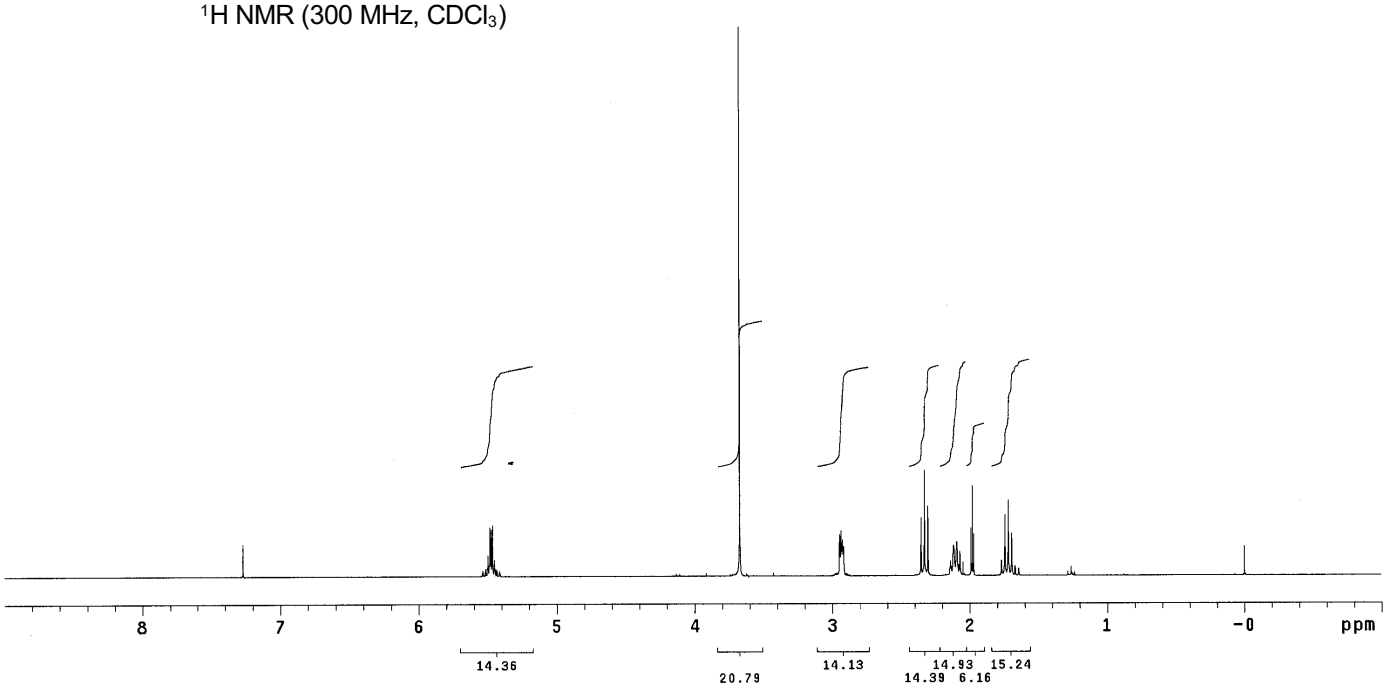
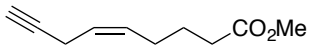
160
140
120
100
80
60
40
20
0
ppm



7a

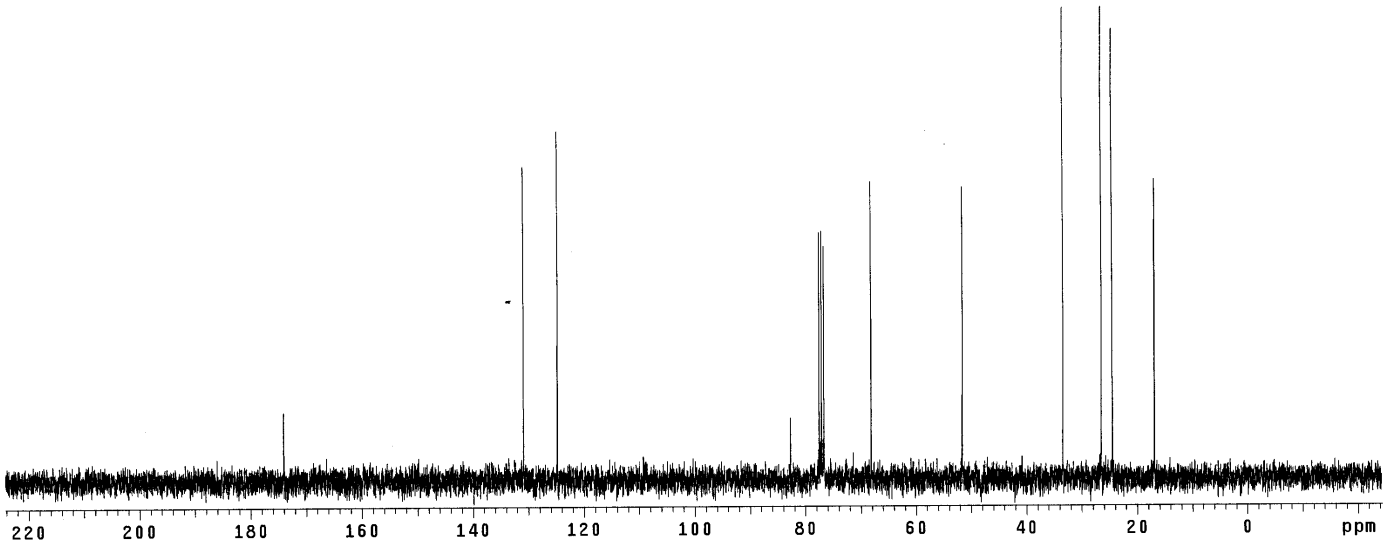
^{1}H NMR (300 MHz, $CDCl_3$)

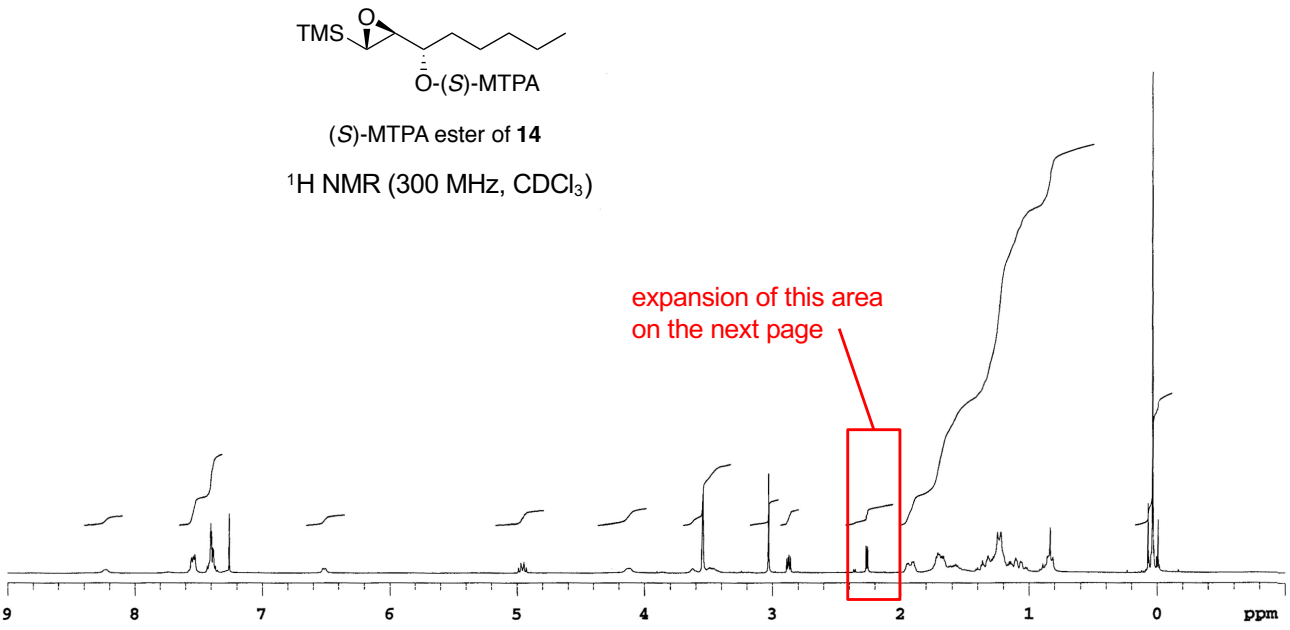


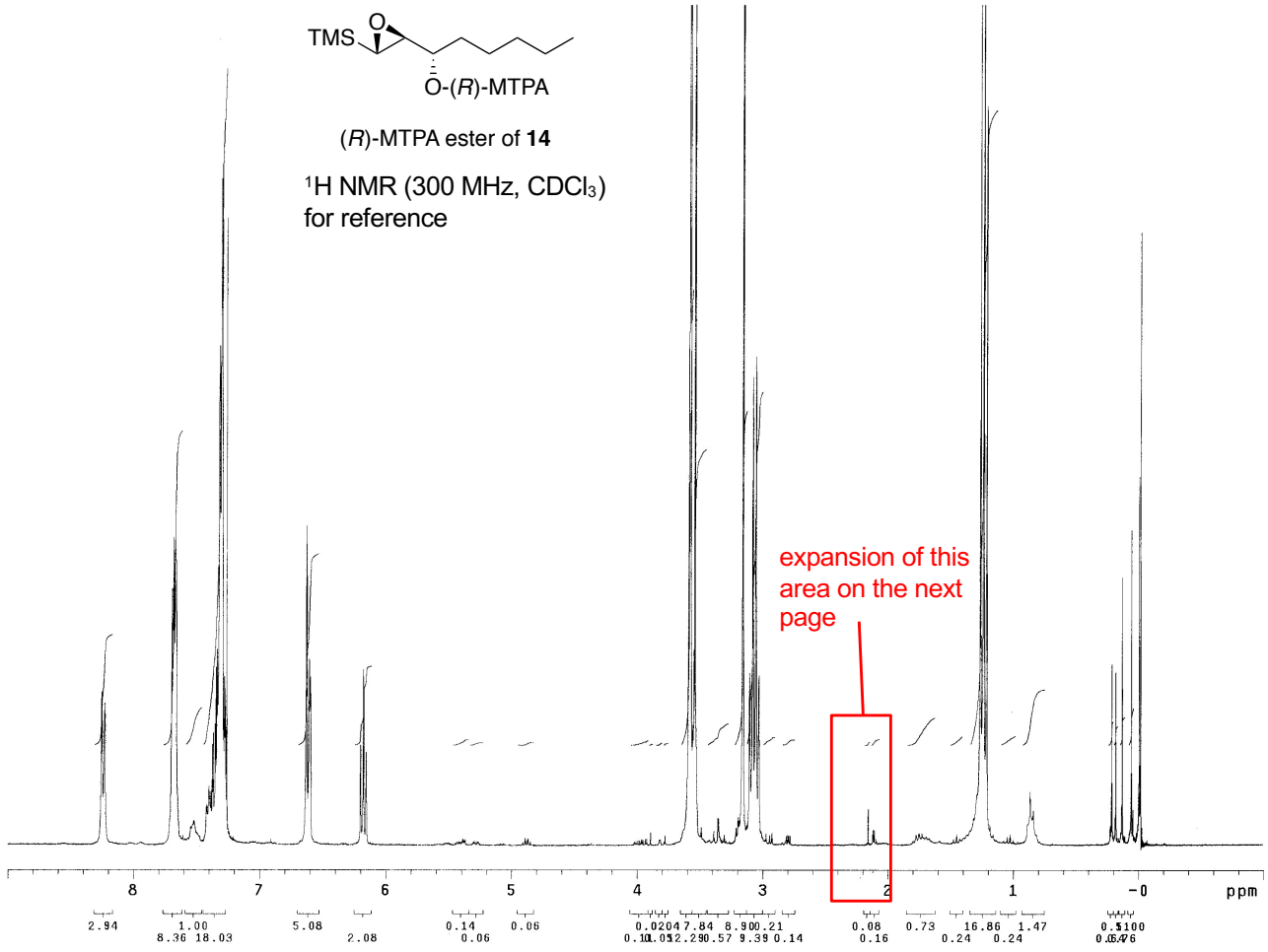


7a

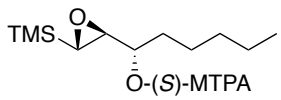
^{13}C NMR (75 MHz, $CDCl_3$)




TMS
O
O-(S)-MTPA
(S)-MTPA ester of 14
1H NMR (300 MHz, CDCl3)
expansion of this area
on the next page
9
8
7
6
5
4
3
2
1
0
ppm


TMS
O
O-(R)-MTPA
(R)-MTPA ester of 14
1H NMR (300 MHz, CDCl3)
for reference
expansion of this
area on the next
page
8
7
6
5
4
3
2
1
−0
ppm

(*S*)-MTPA isomer

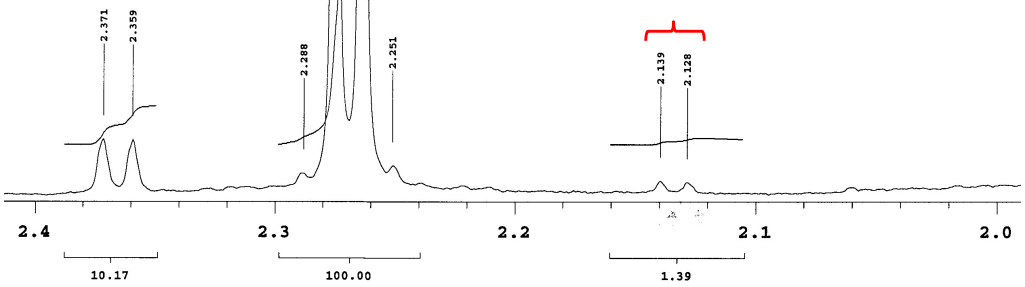


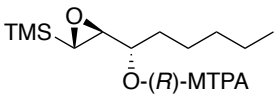
(*S*)-MTPA ester of **14**

^{1}H NMR (300 MHz, $CDCl_3$)

% ee of epoxy alcohol **14**
= {(100 – 1.39) / (100 + 1.39)} x 100
= 97.3
≈ 97

(*R*)-MTPA isomer



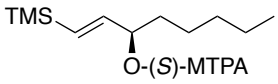


(*R*)-MTPA ester of **14**

^{1}H NMR (300 MHz, $CDCl_3$)
for reference

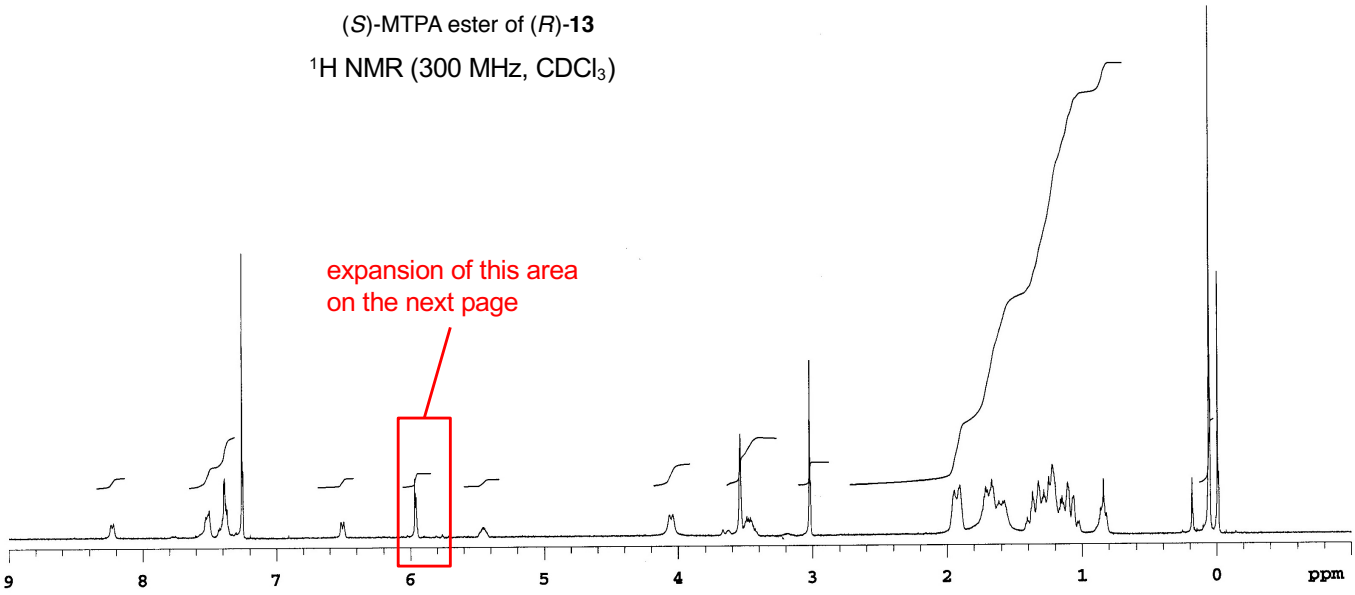
(*R*)-MTPA ester

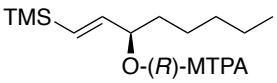
(*S*)-MTPA ester



(*S*)-MTPA ester of (*R*)-**13**

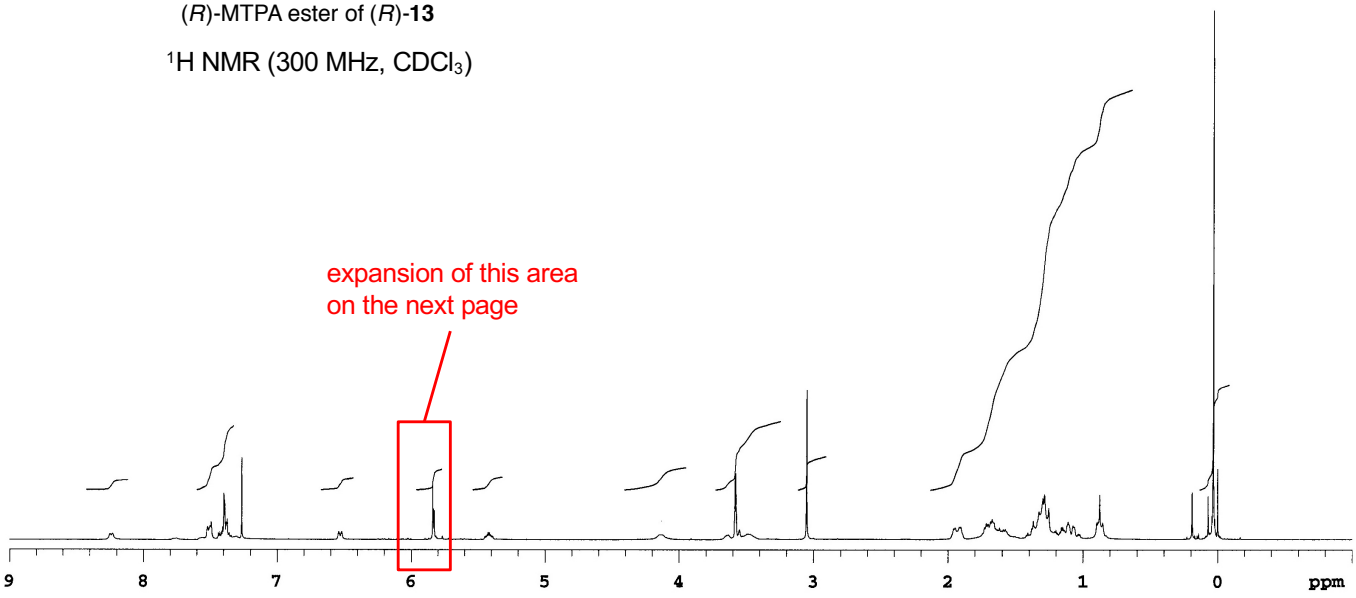
^{1}H NMR (300 MHz, $CDCl_3$)

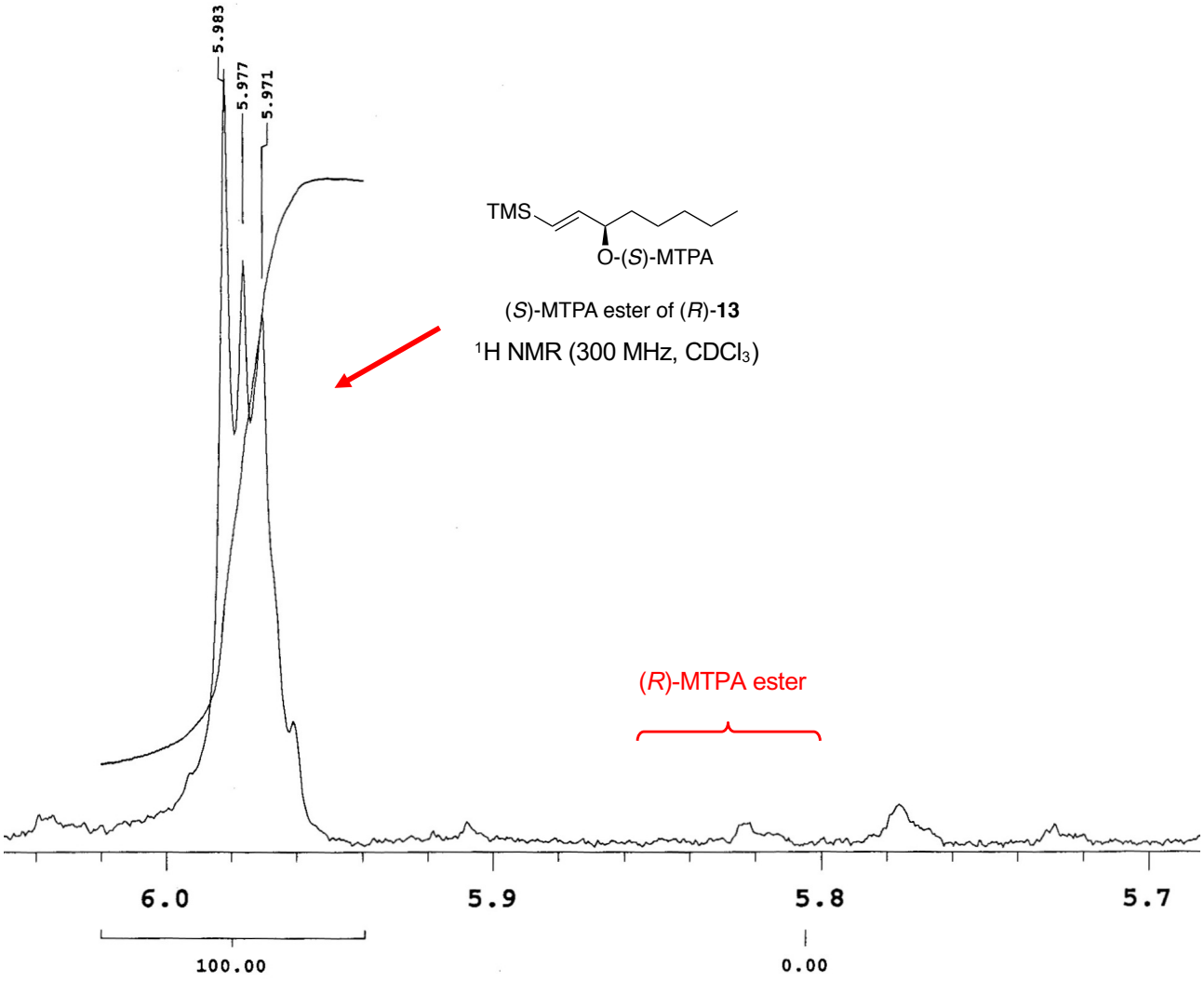




(*R*)-MTPA ester of (*R*)-**13**

^{1}H NMR (300 MHz, $CDCl_3$)

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(S)-MTPA ester of (R)-13
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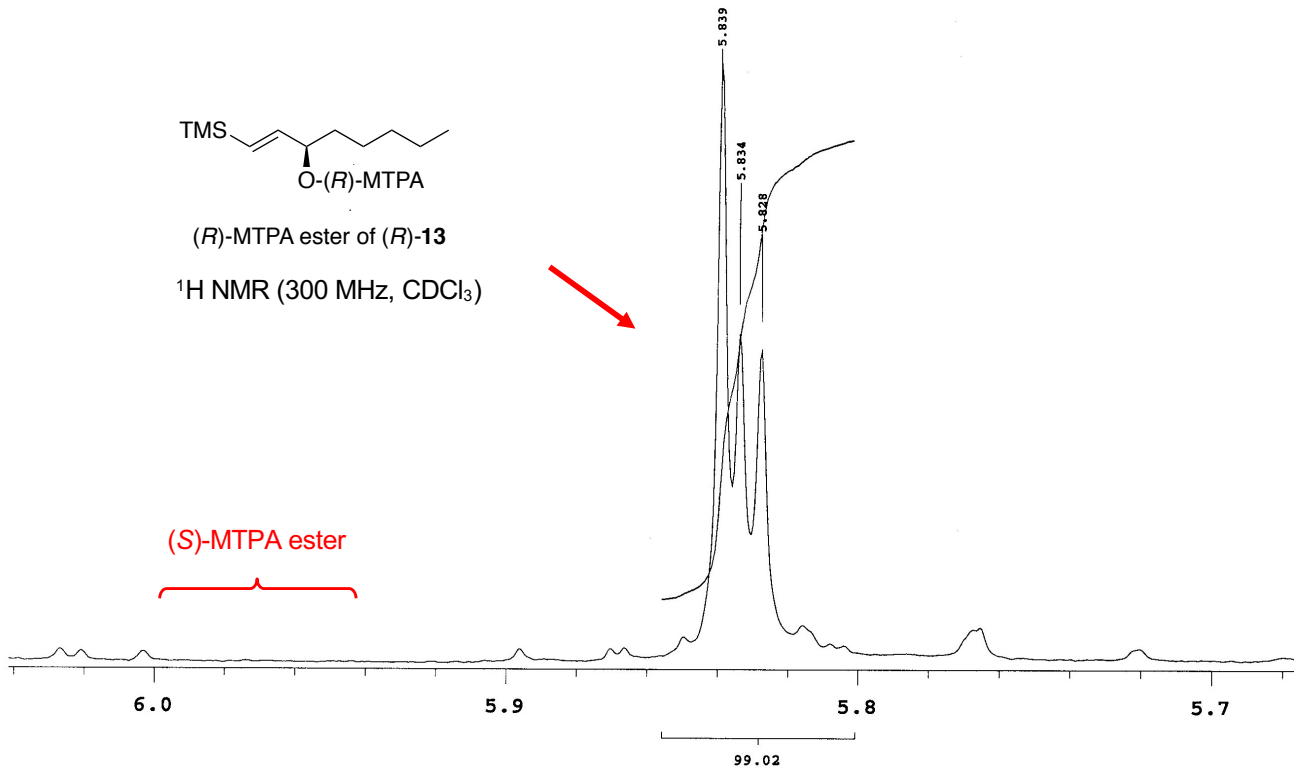
5.9
5.8
5.7
100.00
0.00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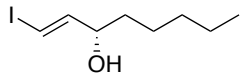
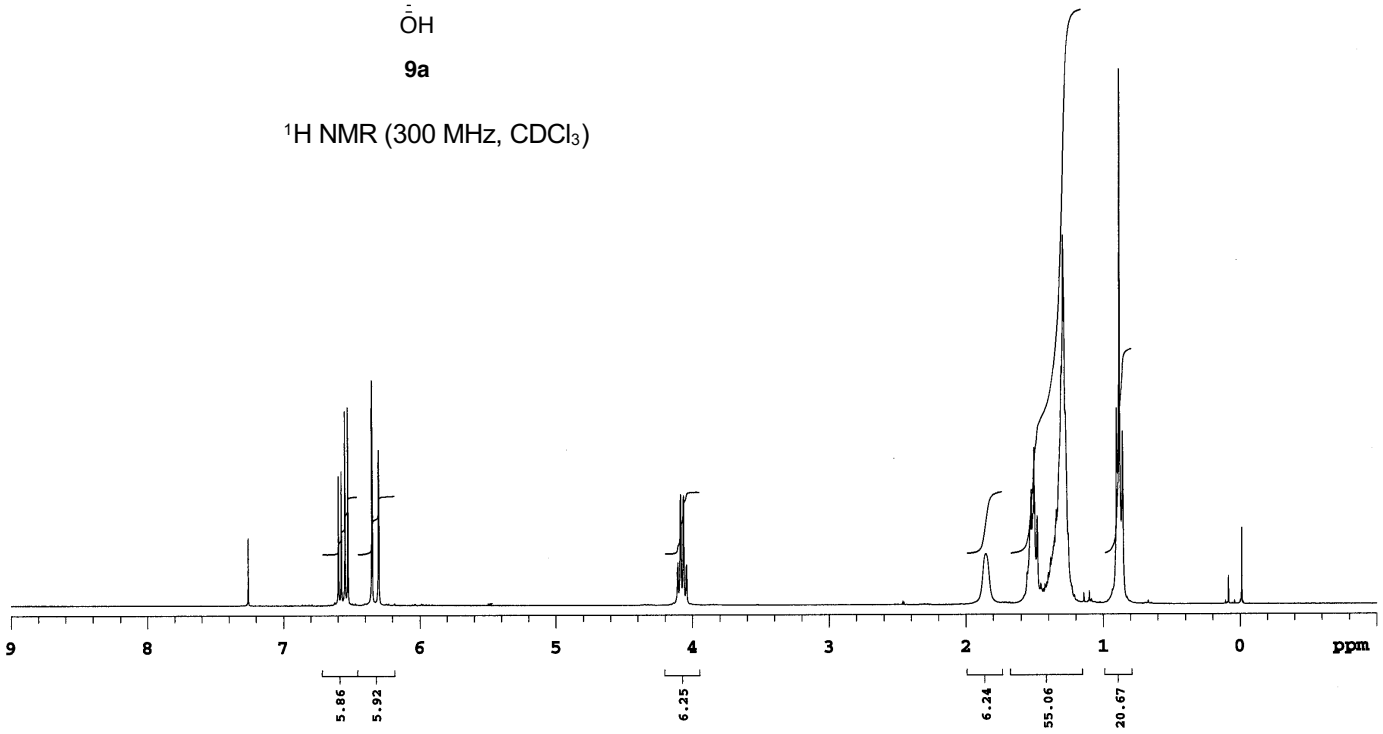
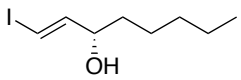
1H NMR (300 MHz, CDCl3)
(S)-MTPA ester
6.0
5.9
5.8
5.7
99.02



9a

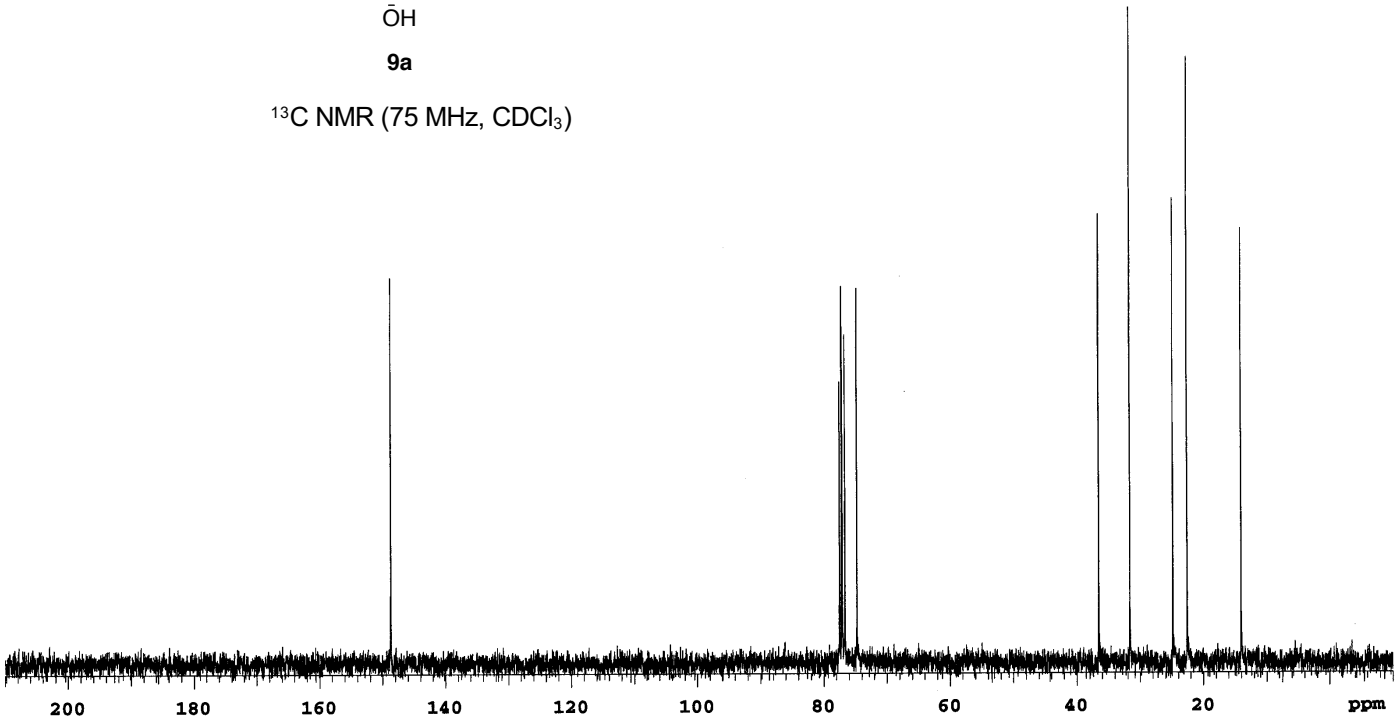
^{1}H NMR (300 MHz, $CDCl_3$)

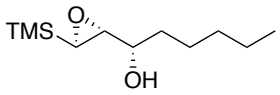




9a

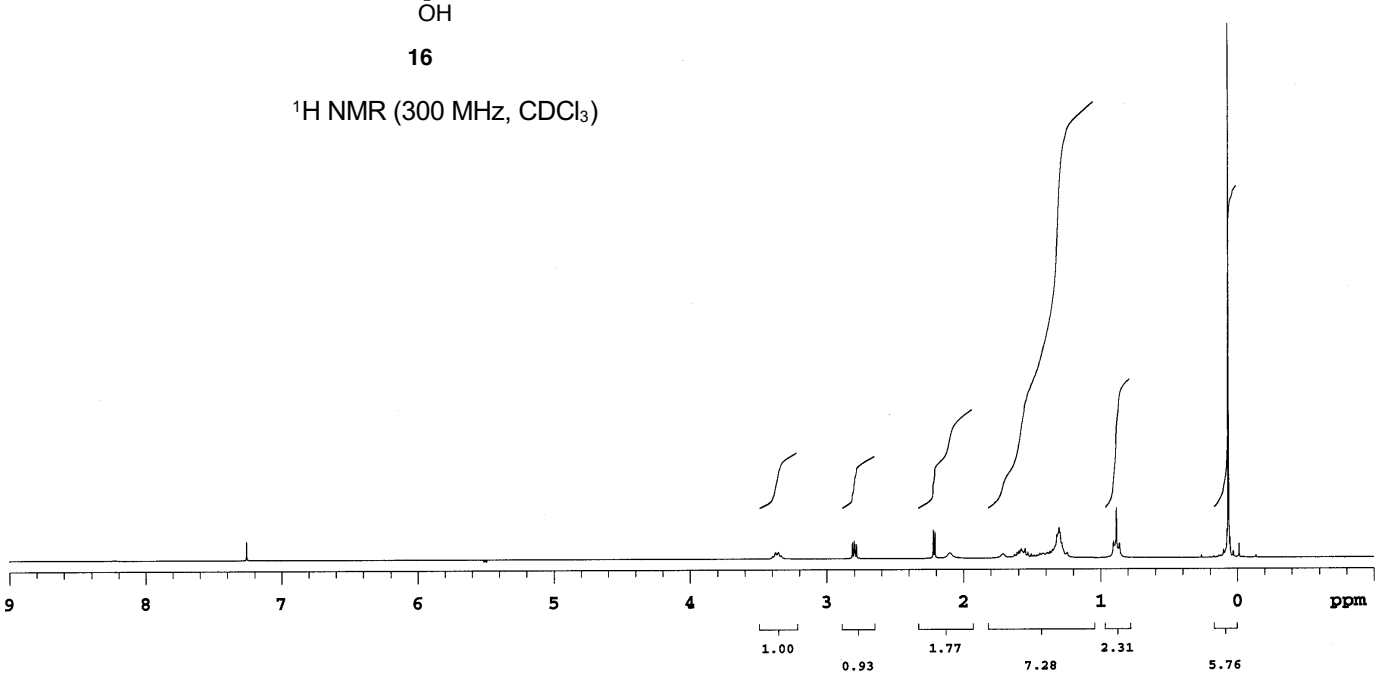
^{13}C NMR (75 MHz, $CDCl_3$)

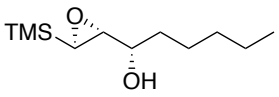




16

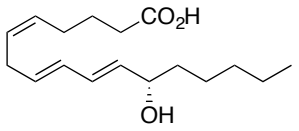
^{1}H NMR (300 MHz, $CDCl_3$)





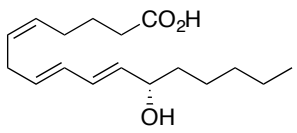
16

^{13}C NMR (75 MHz, $CDCl_3$)



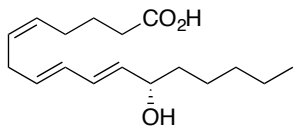
12-HHT (**4**)

^{1}H NMR (300 MHz, $CDCl_3$)



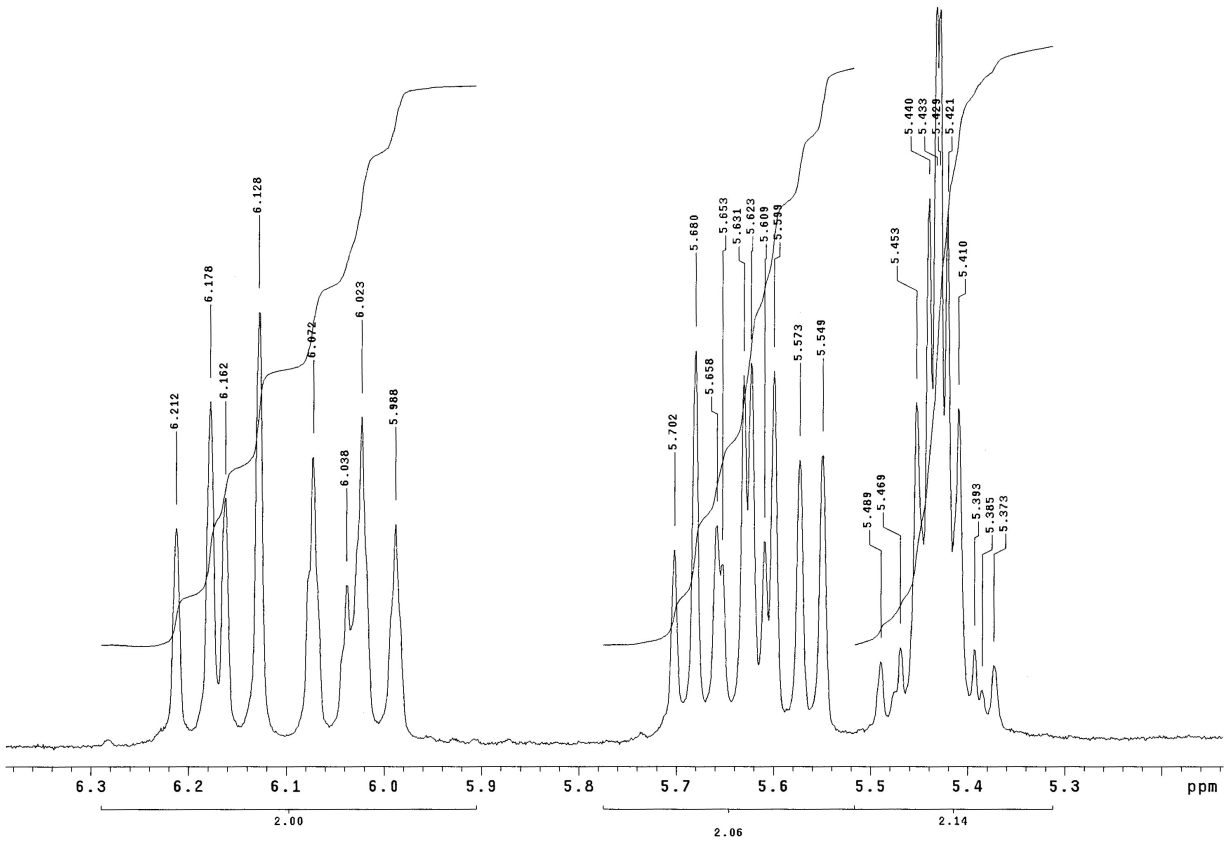
12-HHT (**4**)

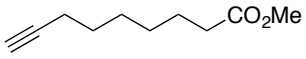
^{13}C NMR (75 MHz, $CDCl_3$)



12-HHT (**4**)

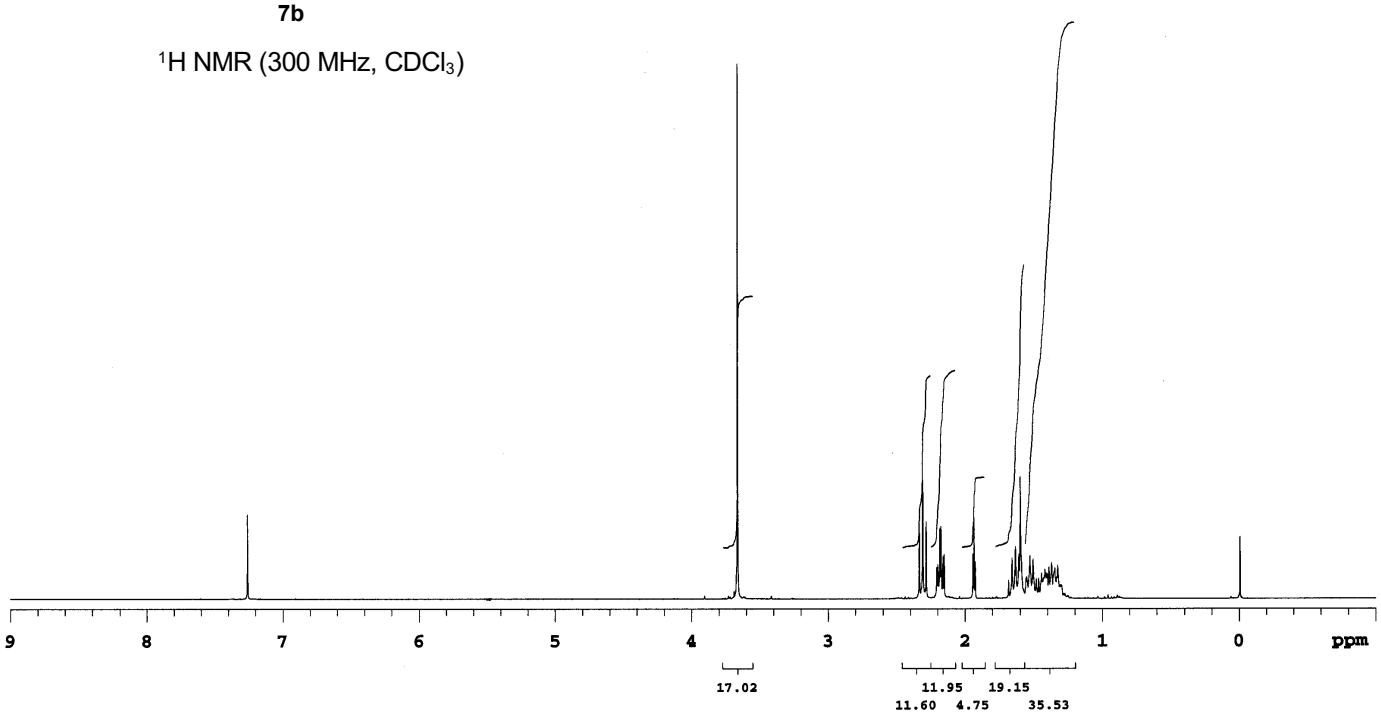
^{1}H NMR (300 MHz, $CDCl_3$)

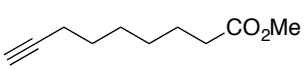




7b

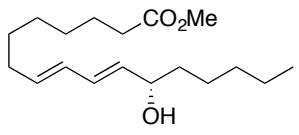
^{1}H NMR (300 MHz, $CDCl_3$)





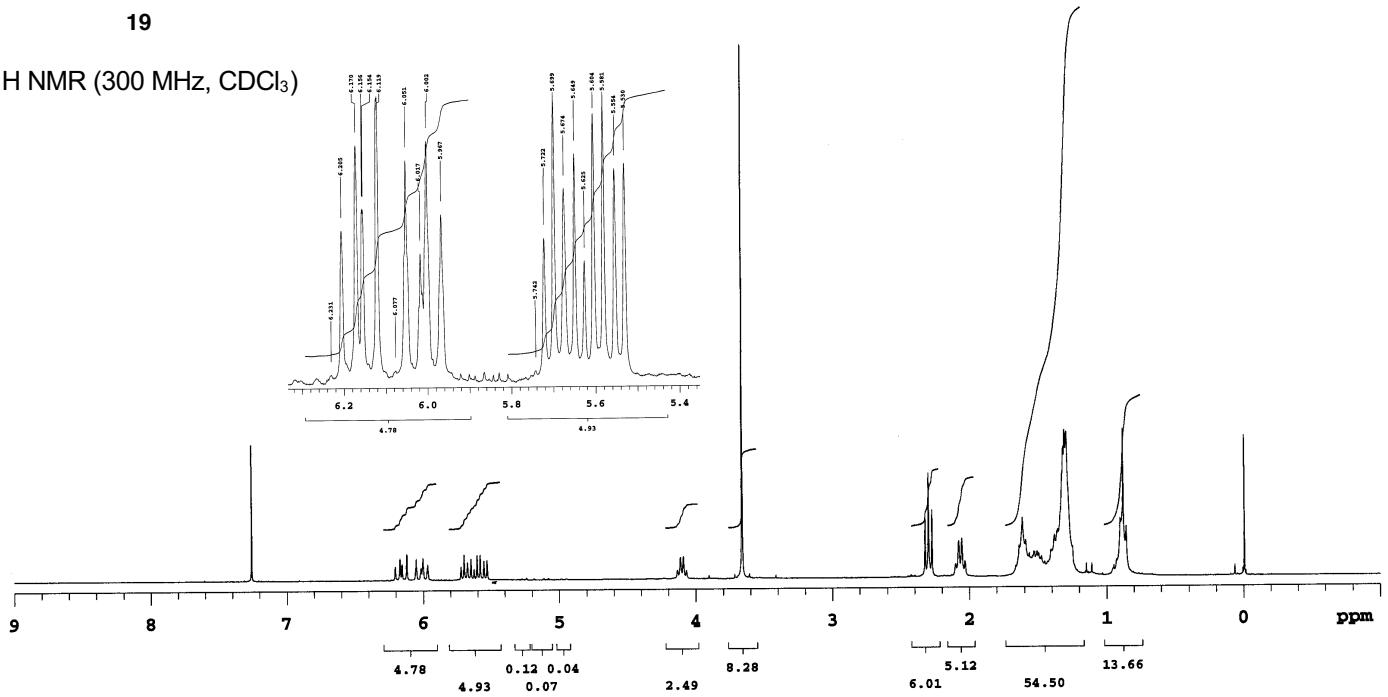
7b

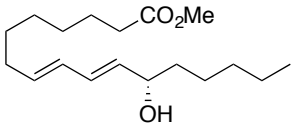
^{13}C NMR (75 MHz, $CDCl_3$)



19

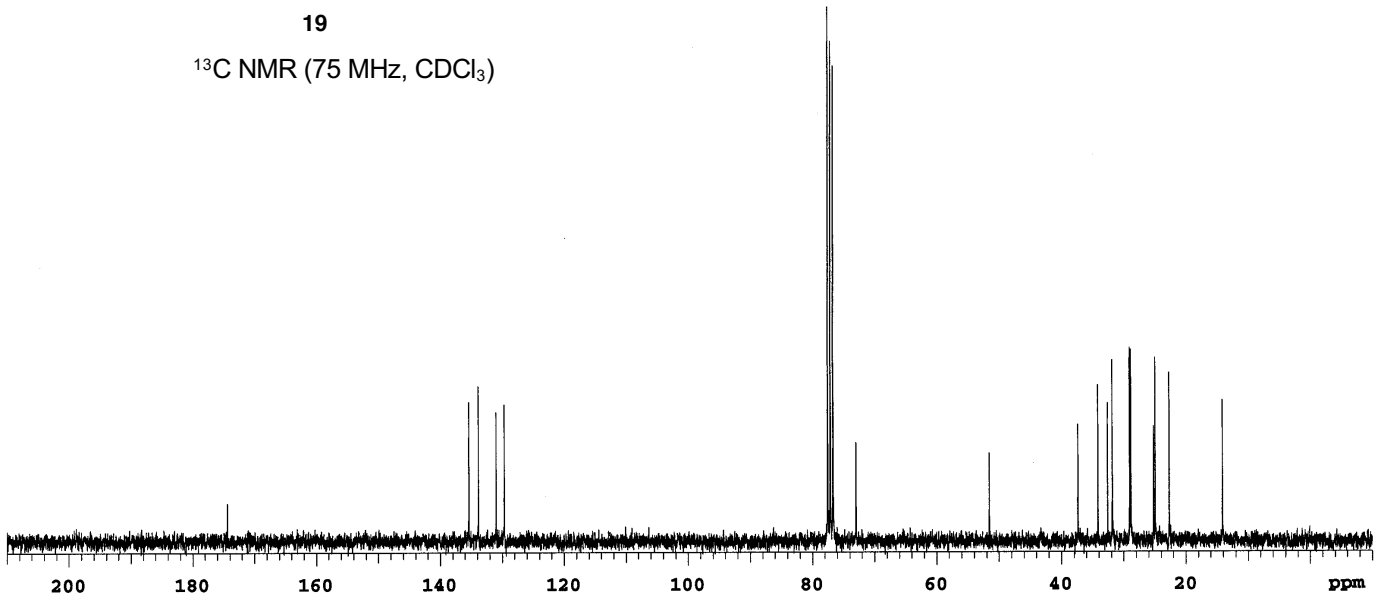
^{1}H NMR (300 MHz, $CDCl_3$)

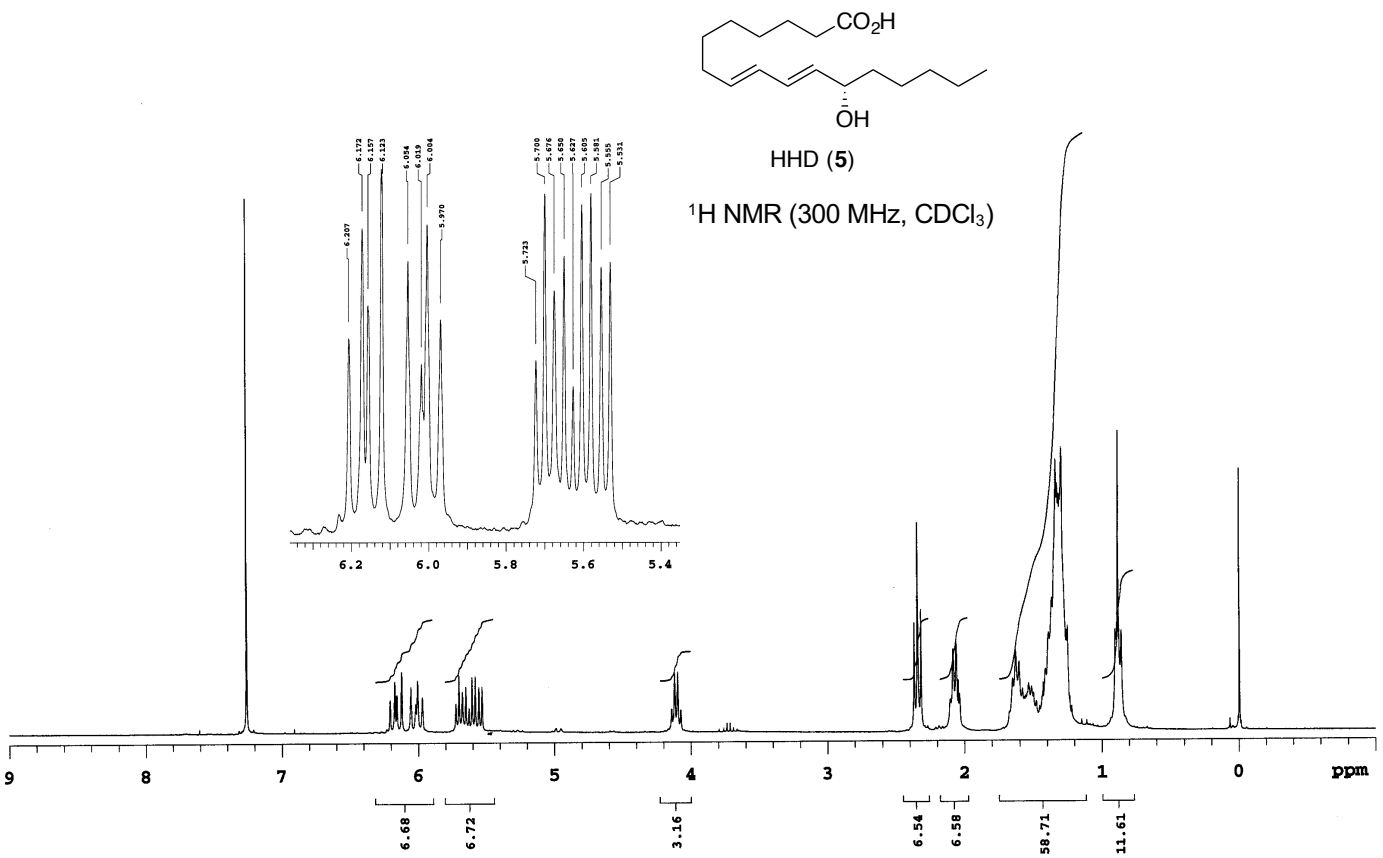


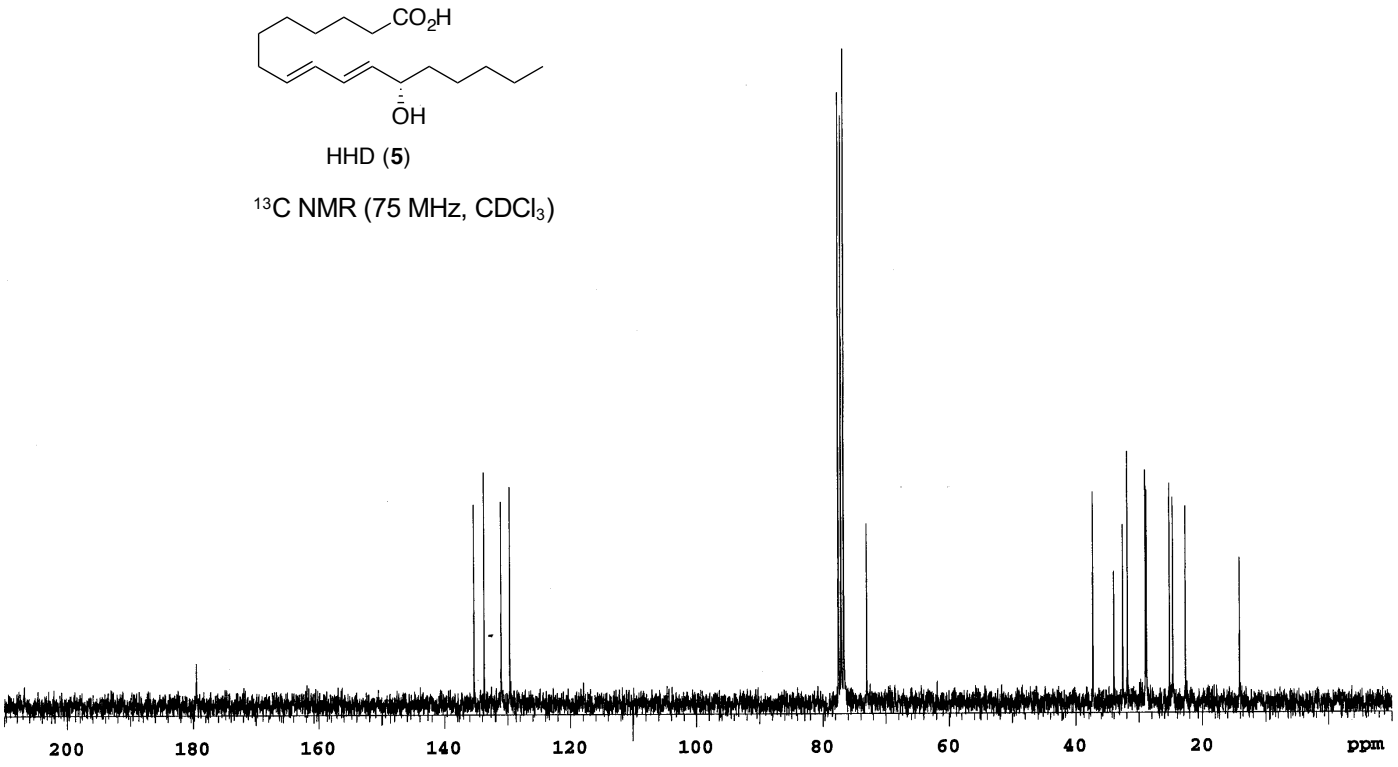


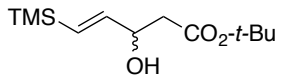
19

^{13}C NMR (75 MHz, $CDCl_3$)



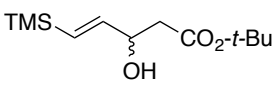

CO2H
OH
HHD (5)
1H NMR (300 MHz, CDCl3)
6.207
6.172
6.157
6.133
6.054
6.019
6.004
5.970
5.723
5.700
5.676
5.650
5.627
5.605
5.581
5.555
5.531
6.2
6.0
5.8
5.6
5.4
9
8
7
6
5
4
3
2
1
0
ppm
6.68
6.72
3.16
6.54
6.58
58.71
11.61


CO2H
OH
HHD (5)
13C NMR (75 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
ppm



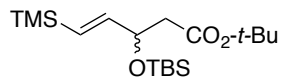
21

^{1}H NMR (300 MHz, $CDCl_3$)



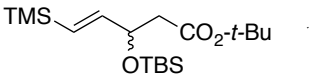
21

^{13}C NMR (75 MHz, $CDCl_3$)



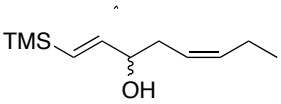
22

^{1}H NMR (300 MHz, $CDCl_3$)



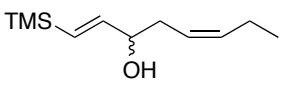
22

^{13}C NMR (75 MHz, $CDCl_3$)



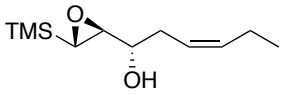
rac-**25**

^{1}H NMR (300 MHz, $CDCl_3$)



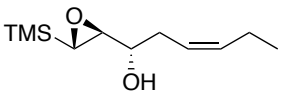
rac-**25**

^{13}C NMR (75 MHz, $CDCl_3$)



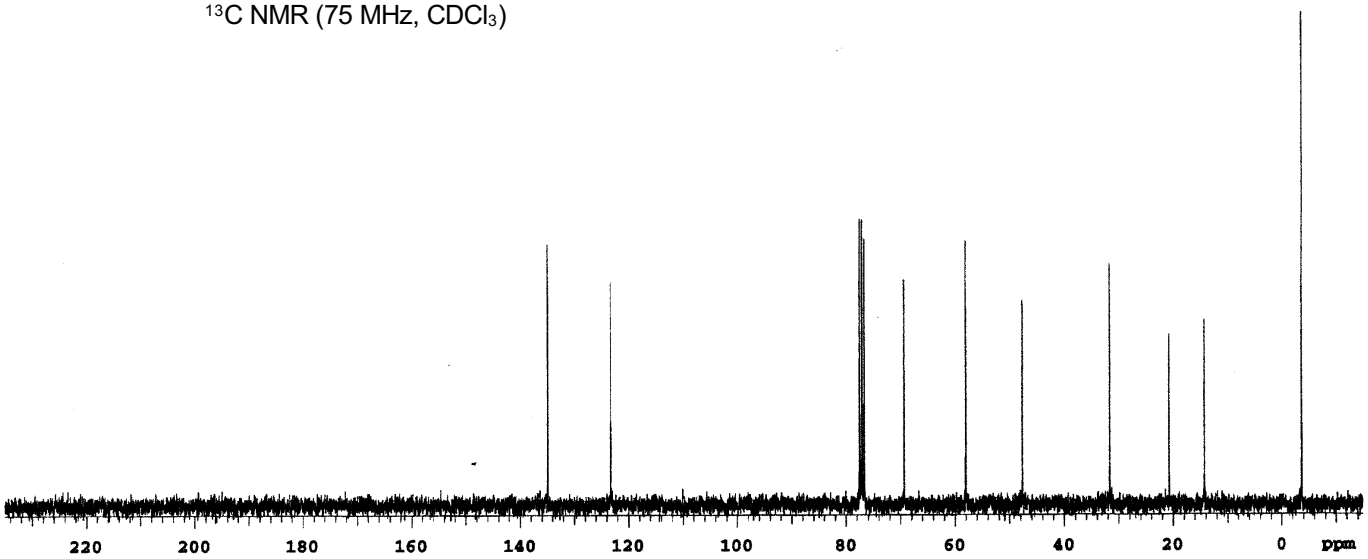
26

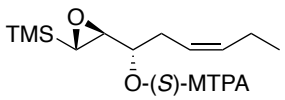
^{1}H NMR (300 MHz, $CDCl_3$)



26

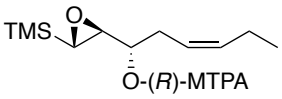
^{13}C NMR (75 MHz, $CDCl_3$)





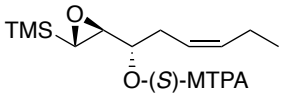
(*S*)-MTPA ester of **26**

^{1}H NMR (400 MHz, $CDCl_3$)



(*R*)-MTPA ester of **26**

^{1}H NMR (400 MHz, $CDCl_3$)

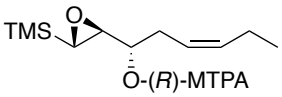


(*S*)-MTPA ester of **26**

^{1}H NMR (400 MHz, $CDCl_3$)

% ee of epoxy alcohol **14** by height
= {(120 – 1.4) / (120 + 1.4)} x 100
= 98.5

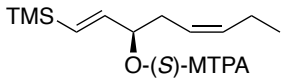
% ee of epoxy alcohol **14** by integration
= {(0.99 – 0.01) / (0.99 + 0.01)} x 100
= 98.0



(*R*)-MTPA ester of **26**

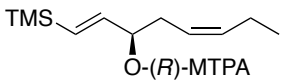
^{1}H NMR (400 MHz, $CDCl_3$)

% ee of epoxy alcohol **14** by integration
= {(1.00 – 0.01) / (1.00 + 0.01)} x 100
= 98.0



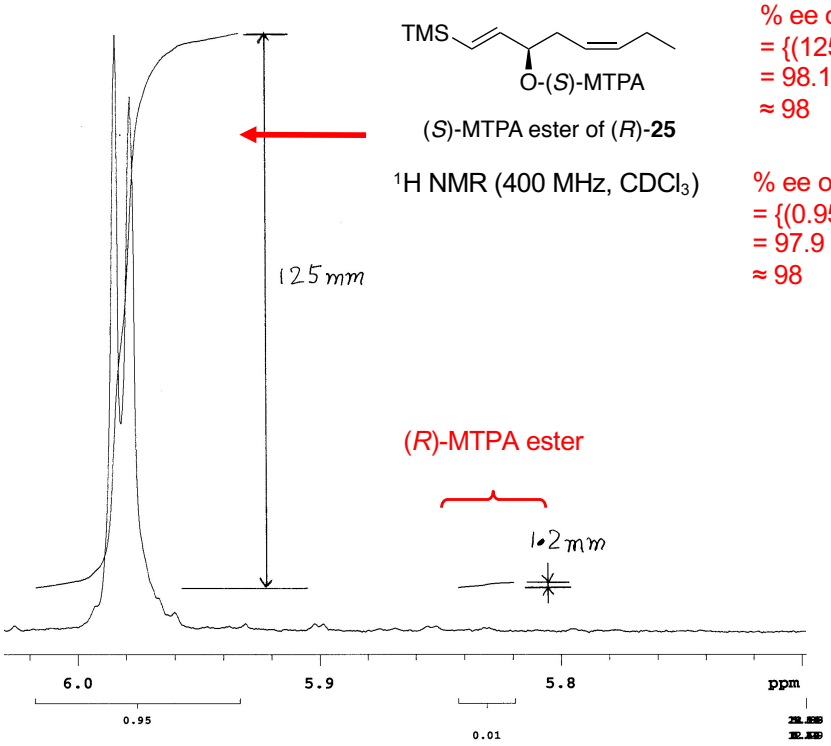
(*S*)-MTPA ester of (*R*)-**25**

^{1}H NMR (400 MHz, $CDCl_3$)



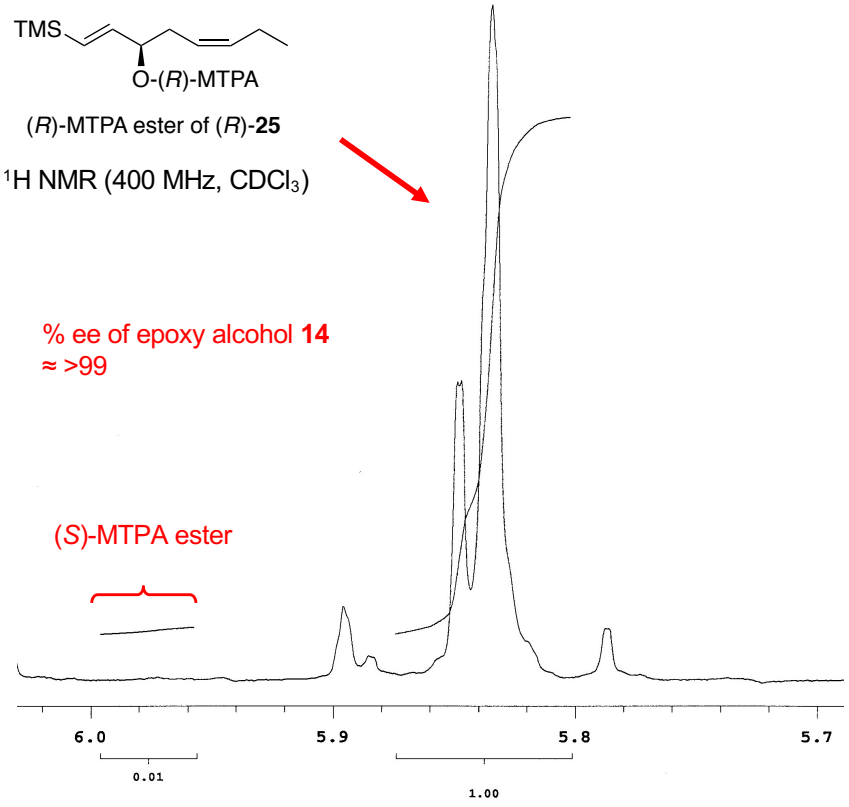
(*R*)-MTPA ester of (*R*)-**25**

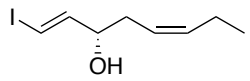
^{1}H NMR (400 MHz, $CDCl_3$)



% ee of epoxy alcohol **14** by height
= {(125 – 1.2) / (125 + 1.2)} x 100
= 98.1
≈ 98

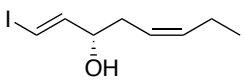
% ee of epoxy alcohol **14** by integration
= {(0.95 – 0.01) / (0.95 + 0.01)} x 100
= 97.9
≈ 98





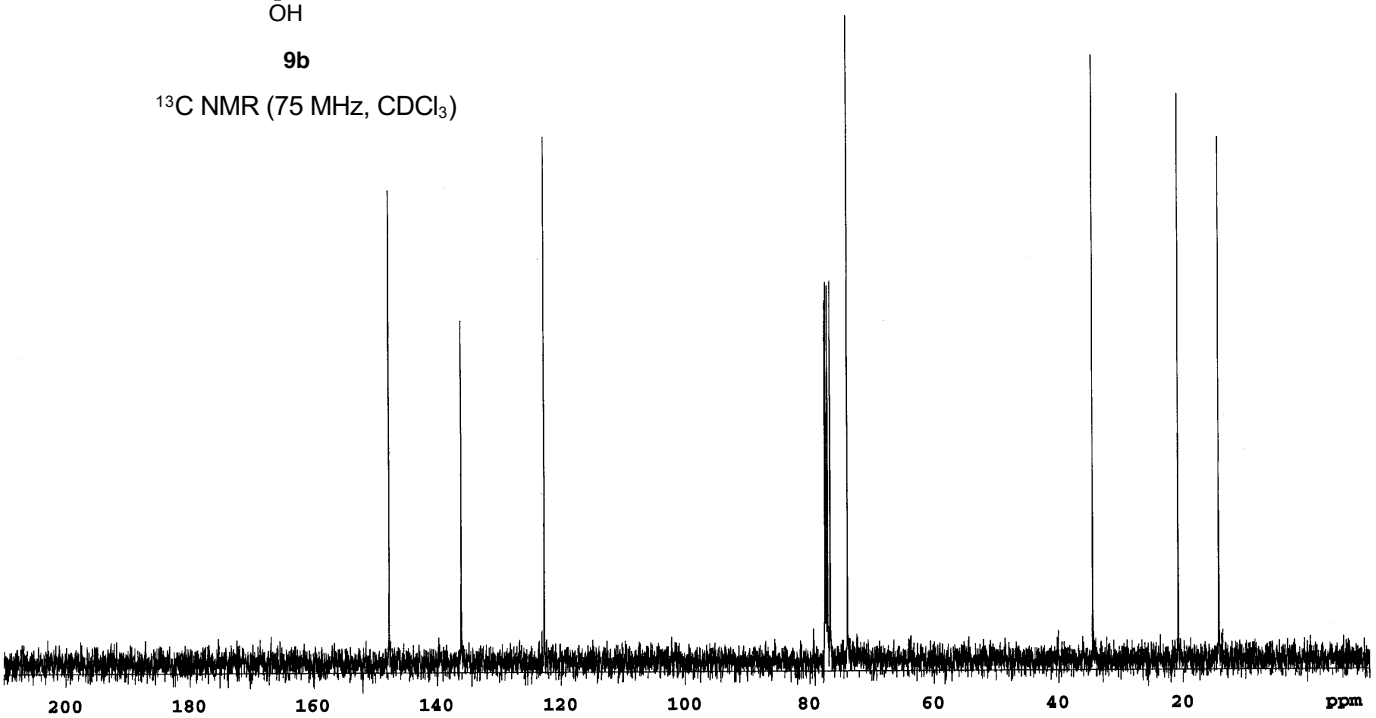
9b

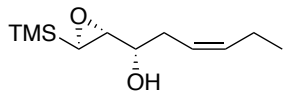
^{1}H NMR (300 MHz, $CDCl_3$)



9b

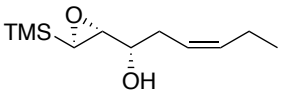
^{13}C NMR (75 MHz, $CDCl_3$)





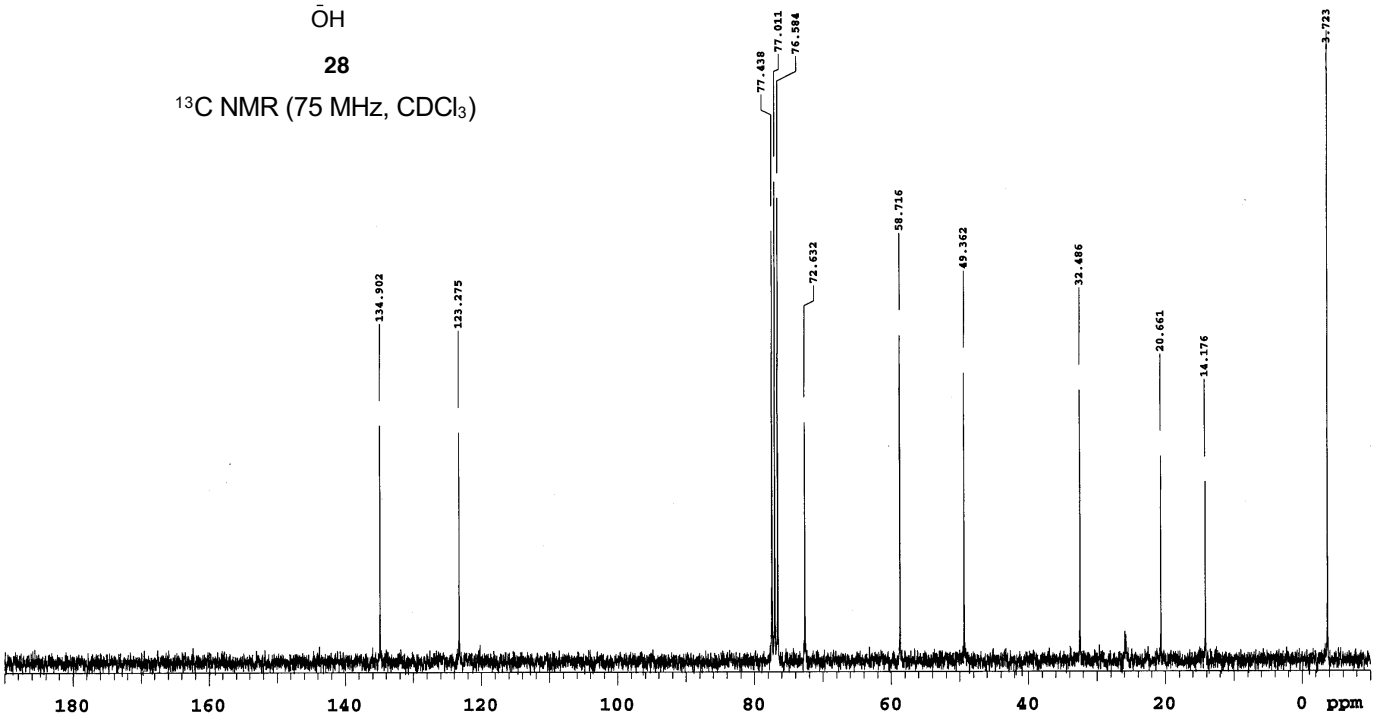
28

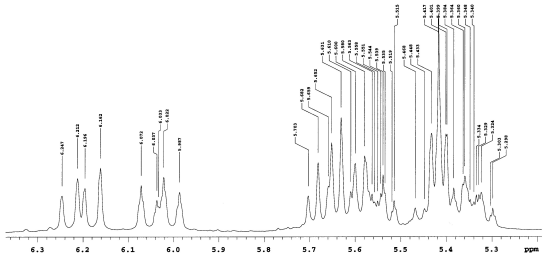
^{1}H NMR (300 MHz, $CDCl_3$)

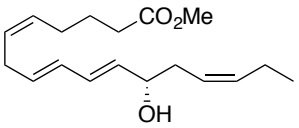


28

^{13}C NMR (75 MHz, $CDCl_3$)

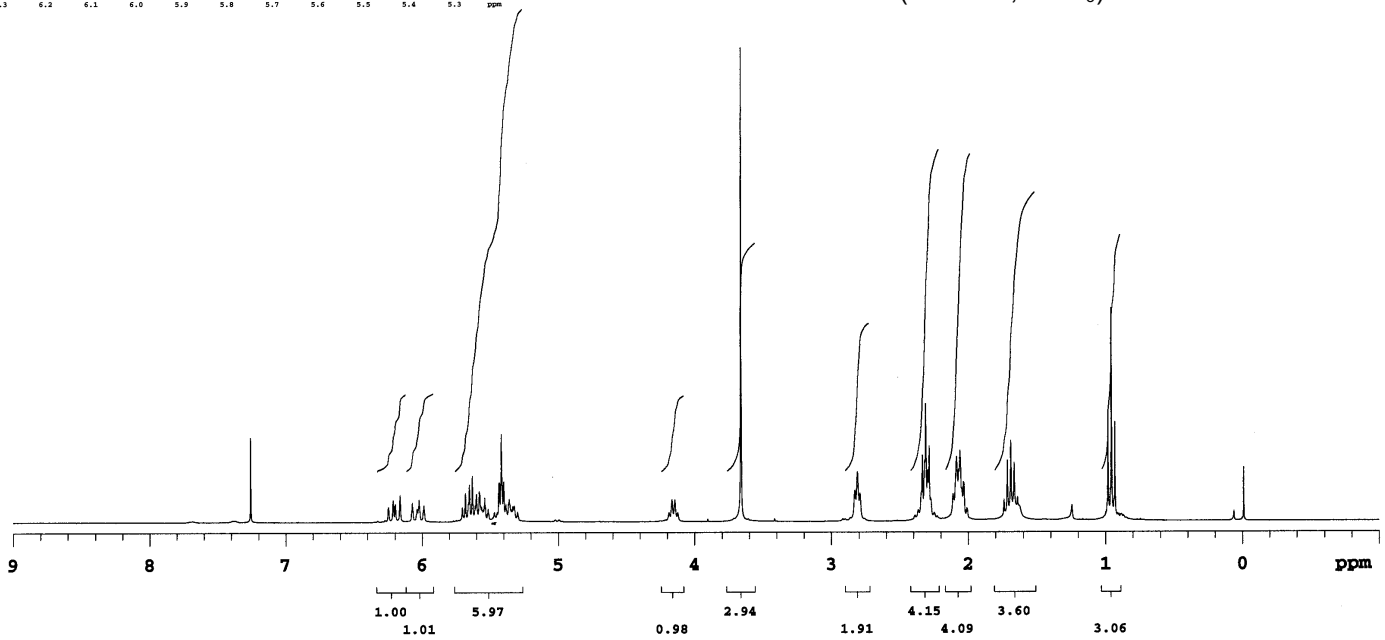


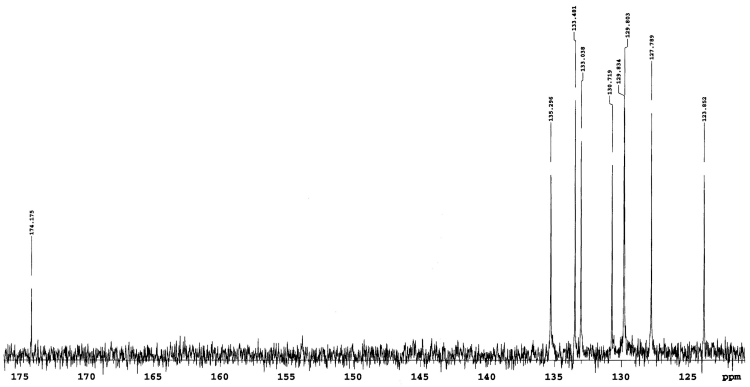


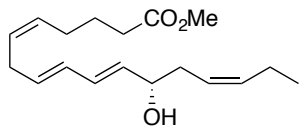


29

^{1}H NMR (300 MHz, $CDCl_3$)

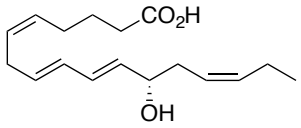






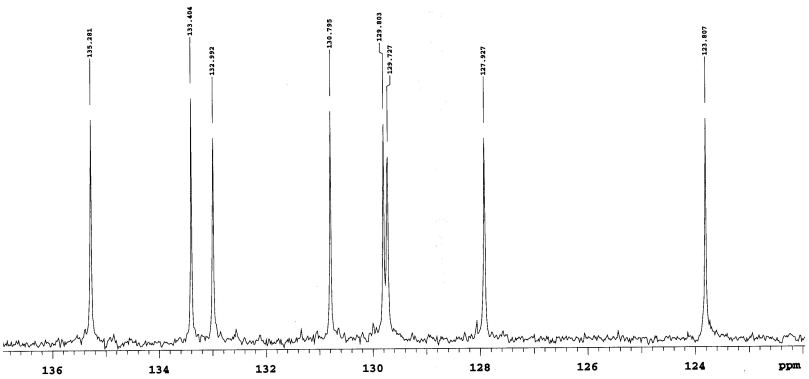
29

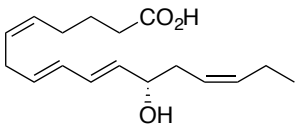
^{13}C NMR (75 MHz, $CDCl_3$)



HHTE (**6**)

^{1}H NMR (300 MHz, $CDCl_3$)





HHTE (**6**)

^{13}C NMR (75 MHz, $CDCl_3$)