Supplementary Material

Synthesis of the TNF inhibitor, flurbiprofen and an *i*-Pr analogue in enantioenriched forms by using the copper-catalyzed propargylic substitution with Grignard reagents

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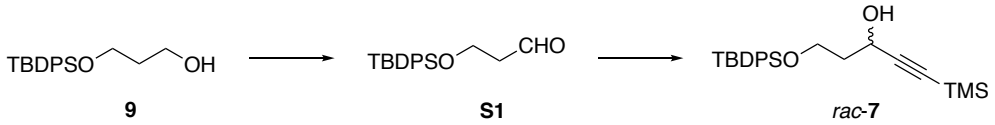
Table of Contents

1. General information

The ^{1}H, ^{13}C and ^{13}C-attached proton test (^{13}C–APT) NMR spectroscopic data were recorded in $CDCl_3$ using Me_4Si (δ = 0 ppm) and the centerline of the triplet (δ = 77.1 ppm) as internal standards, respectively. The ^{19}F NMR data were measured in $CDCl_3$ with $PhCF_3$ (δ = –63.72 ppm). Signal patterns are indicated as br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Coupling constants (J) are given in Hertz (Hz). Chemical shifts of carbons are accompanied by ^{13}C–APT signal patterns as minus (downward for C and CH_2) and plus (upward for CH and CH_3). The solvents that were distilled prior to use are THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). Crude products were purified by column chromatography on silica gel (Merck, silica gel 60 and KANTO, silica gel 60N).

2. Experimental procedures and characterization data

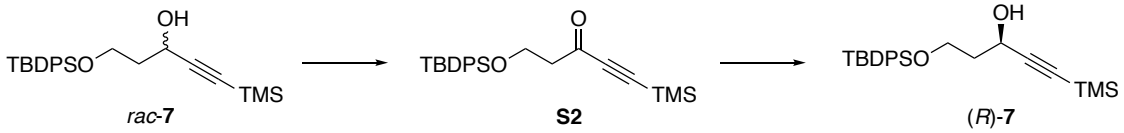


5-(*tert*-Butyldiphenylsilyloxy)-1-(trimethylsilyl)pent-1-yn-3-ol (*rac*-7)

To an ice-cold solution of alcohol **9**[S1,S2] (1.64 g, 5.21 mmol) in CH_2Cl_2 (10 mL) were added DMSO (1.48 mL, 20.8 mmol) and Et_3N (2.18 mL, 15.6 mmol). The solution was stirred at 0 °C for 1 h, and SO_3·pyridine (1.66 g, 10.4 mmol) was added. The solution was stirred at room temperature for 1 h and diluted with H_2O and brine. The mixture was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was passed through a short column of silica gel (hexane/EtOAc) to give aldehyde **S1**, which was dissolved in THF (5 mL) for the next reaction. Liquid. R_f = 0.59 (hexane/EtOAc = 3:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9 H), 2.61 (dt, J = 2.1, 6.0 Hz, 2 H), 4.02 (t, J = 6.0 Hz, 2 H), 7.32–7.48 (m, 6 H), 7.62–7.69 (m, 4 H), 9.82 (t, J = 2.1 Hz, 1 H). The spectrum was coincident with the reported data.[S2]

To the above THF solution cooled to 0 °C was added *n*-BuLi (1.60 M in hexane, 4.24 mL, 6.78 mmol) dropwise. The solution was stirred at 0 °C for 30 min and cooled to –78

ºC. The above aldehyde in THF was added to the solution, which was then stirred at –78 °C for 1 h and poured to a mixture of saturated NH_4Cl and EtOAc with vigorous stirring. The organic phase was separated, and the aqueous phase was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give alcohol *rac*-**7** (1.65 g, 77% over two steps). Liquid. R_f = 0.35 (hexane/EtOAc = 19:1, two-development) (cf. the above aldehyde, R_f = 0.43). IR (neat) 3429, 2170, 1251, 1112, 844 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 9 H), 1.05 (s, 9 H), 1.84–1.97 (m, 1 H), 1.98–2.10 (m, 1 H), 3.28 (d, J = 6.0 Hz, 1 H), 3.83 (ddd, J = 10.5, 6.0, 4.5 Hz, 1 H), 4.05 (ddd, J = 10.5, 7.8, 3.9 Hz, 1 H), 4.70 (dt, J = 4.5, 6.3 Hz, 1 H), 7.36–7.48 (m, 6 H), 7.64–7.72 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ –0.0 (+), 19.1 (–), 26.8 (+), 38.8 (–), 61.8 (–), 61.9 (+), 89.4 (–), 106.3 (–), 127.8 (+), 129.9 (+), 133.00 (–), 133.04 (–), 135.53 (+), 135.56 (+). HRMS (FAB) calcd for $C_{24}H_{35}O_2Si_2$ [$(M+H)^+$] 411.2176, found 411.2172. The ^1H NMR and ^{13}C NMR spectral data were consistent with the reported data,[S3] while the ^{13}C NMR spectrum was updated.

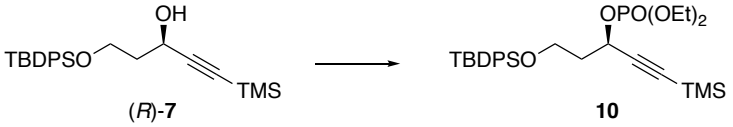


(*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-(trimethylsilyl)pent-1-yn-3-ol [(*R*)-7]

To an ice-cold solution of *rac*-**7** (1.65 g, 4.02 mmol) in CH_2Cl_2 (16 mL) were added Celite (2.60 g) and PCC (1.30 g, 6.03 mmol). The mixture was stirred at room temperature for 18 h, diluted with hexane and filtered through a pad of Celite with hexane. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/EtOAc) to give ketone **S2** (1.23 g, 75%). Liquid. R_f = 0.57 (hexane/EtOAc = 9:1). IR (neat) 2151, 1681, 1113, 847, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 9 H), 1.03 (s, 9 H), 2.78 (t, J = 6.2 Hz, 2 H), 4.01 (t, J = 6.2 Hz, 2 H), 7.34–7.47 (m, 6 H), 7.62–7.74 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ –0.7 (+), 19.2 (–), 26.8 (+), 48.0 (–), 59.4 (–), 98.2 (–), 102.0 (–), 127.7 (+), 129.8 (+), 133.4 (–), 135.6 (+), 186.2 (–). The ^1H NMR and ^{13}C NMR spectral data were coincident with the reported data.[S4]

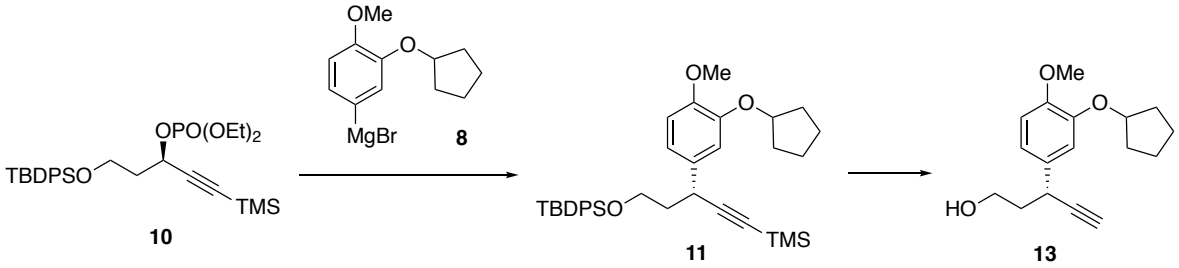
A mixture of RuCl[(*R*,*R*)-TsDPEN](*p*-cymene) (39.6 mg, 0.0622 mmol) and KOH (ca. 7.5 mg, 0.13 mmol) in CH_2Cl_2 (2.5 mL) was stirred at room temperature for 5 min and

washed with H_2O twice. The remaining CH_2Cl_2 layer was transferred to another flask, dried over CaH_2 and concentrated to afford solids, which was dissolved in *i*-PrOH (3 mL) for the next reaction. To an ice-cold solution of the above ketone (254 mg, 0.621 mmol) in *i*-PrOH (3 mL) was added the above *i*-PrOH solution of the catalyst. The solution was stirred at 30 °C for 15 h and diluted with H_2O and saturated $NaHCO_3$. The product was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was passed through a short column of silica gel (hexane/EtOAc) to give alcohol (*R*)-**7** (247 mg, 97%). 97.5% ee by HPLC analysis of the corresponding benzoate (Chiralcel OD-H, hexane/*i*-PrOH = 99.9:0.1, 0.3 mL/min, 25 °C, t_R = 30.9 and 40.7 min for (*R*)-isomer (major) and (*S*)-isomer (minor), respectively. The ^1H and ^{13}C NMR spectra were identical with those of the racemic alcohol *rac*-**7**.



(*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-(trimethylsilyl)pent-1-yn-3-yl diethyl phosphate (10)

To a solution of (*R*)-**7** (234 mg, 0.570 mmol) in CH_2Cl_2 (2.3 mL) were added *N*-methylimidazole (0.117 mL, 1.48 mmol) and diethyl chlorophosphate (0.205 mL, 1.43 mmol). The solution was stirred at room temperature for 2 h and diluted with 1 N HCl. The mixture was extracted with CH_2Cl_2 twice. The combined organic layers were washed with saturated $NaHCO_3$ and then with brine. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give phosphate **10** (266 mg, 85%). Liquid. R_f = 0.21 (hexane/EtOAc = 5:1). $[\alpha]_D^{24}$ +19 (*c* 0.24, $CHCl_3$). IR (neat) 2178, 1112, 1035, 846 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9 H), 1.05 (s, 9 H), 1.32 (dq, *J* = 0.9, 7.2 Hz, 6 H), 1.94–2.22 (m, 2 H), 3.81 (t, *J* = 6.2 Hz, 2 H), 4.00–4.21 (m, 4 H), 5.24 (q, *J* = 7.2 Hz, 1 H), 7.33–7.46 (m, 6 H), 7.60–7.70 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ –0.3 (+), 16.1 (d, *J* = 7 Hz) (+), 19.2 (–), 26.8 (+), 39.4 (d, *J* = 6 Hz) (–), 59.6 (–), 63.7 (d, *J* = 6 Hz) (–), 63.8 (d, *J* = 6 Hz) (–), 65.7 (d, *J* = 6 Hz) (+), 91.8 (–), 102.3 (d, *J* = 3 Hz) (–), 127.7 (+), 129.6 (+), 133.46 (–), 133.49 (–), 135.5 (+). HRMS (FAB) calcd for $C_{28}H_{44}O_5PSi_2$ $[(M+H)^+]$ 547.2465, found 547.2449.

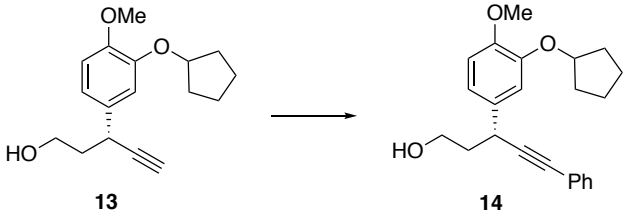


(*S*)-3-[3-(Cyclopentyloxy)-4-methoxyphenyl]pent-4-yn-1-ol (13)

The Grignard reagent **8** in THF was prepared as usual from 4-bromo-2-(cyclopentyloxy)-1-methoxybenzene (1.36 g, 5.02 mmol) and Mg (182 mg, 7.49 mmol) in THF (ca. 5 mL), and a part of the solution (0.95 M, 1.01 mL, 0.960 mmol) was added to an ice-cold solution of CuCN (8.6 mg, 0.096 mmol) in THF (2 mL) and DME (2 mL). The solution was stirred at 0 °C for 30 min, and a solution of phosphate **10** (262 mg, 0.479 mmol) in THF (7 mL) was added dropwise. The solution was stirred at 0 °C for 1.5 h and diluted with saturated NH_4Cl and NH_4OH with vigorous stirring. The mixture was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was passed through a short column of silica gel (hexane/EtOAc) to give a mixture of acetylene **11** and the reagent residue, which was diluted with THF (5 mL) for the next reaction. The product **11** was synthesized again and purified by chromatography on silica gel (hexane/EtOAc). Liquid. R_f = 0.74 (hexane/EtOAc = 5:1). $[\alpha]_D^{25}$ +27 (*c* 1.20, $CHCl_3$). IR (neat) 2169, 1507, 1258, 1112, 843 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9 H), 1.07 (s, 9 H), 1.50–1.66 (m, 2 H), 1.74–2.02 (m, 8 H), 3.68 (dt, *J* = 9.9, 6.0 Hz, 1 H), 3.74–3.98 (m, 2 H), 3.83 (s, 3 H), 4.66–4.84 (m, 1 H), 6.75–6.97 (m, 3 H), 7.32–7.46 (m, 6 H), 7.61–7.72 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.2 (+), 19.4 (–), 24.1 (–), 27.0 (+), 32.8 (–), 32.9 (–), 34.5 (+), 41.5 (–), 56.2 (+), 61.4 (–), 80.3 (+), 87.0 (–), 108.6 (–), 111.9 (+), 114.4 (+), 119.5 (+), 127.7 (+), 129.6 (+), 133.9 (–), 134.0 (–), 134.1 (–), 135.57 (+), 135.62 (+), 147.6 (–), 148.7 (–).

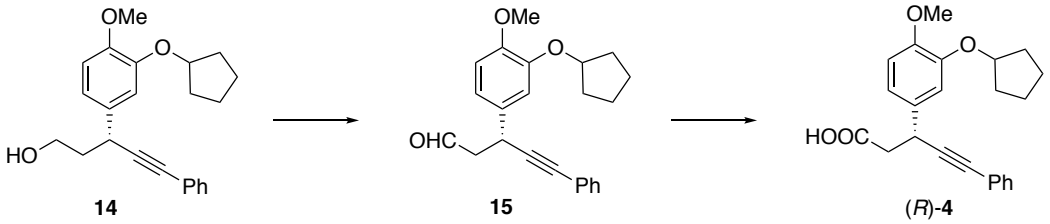
The above THF solution was cooled to 0 °C and mixed with TBAF (1.0 M in THF, 2.90 mL, 2.90 mmol) and AcOH (0.160 mL, 2.81 mmol). The solution was stirred at room temperature for 24 h and diluted with saturated NH_4Cl and EtOAc. The organic phase was separated, and the aqueous phase was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give alcohol **13** (122 mg, 93% over two

steps). Liquid. R_f = 0.55 (hexane/EtOAc = 1:1). $[\alpha]_D^{22}$ +13 (*c* 1.14, $CHCl_3$). IR (neat) 3400, 3288, 1507, 1259, 1136 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.46–1.69 (m, 3 H), 1.75–2.04 (m, 8 H), 2.31 (d, *J* = 2.4 Hz, 1 H), 3.69–3.92 (m, 3 H), 3.83 (s, 3 H) 4.74–4.83 (m, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 6.87–6.93 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1 (–), 32.7 (–), 32.8 (–), 33.6 (+), 40.8 (–), 56.1 (+), 60.4 (–), 71.3 (–), 80.4 (+), 85.8 (–), 112.0 (+), 114.2 (+), 119.2 (+), 133.3 (–), 147.6 (–), 148.9 (–). HRMS (FAB) calcd for $C_{17}H_{22}O_3$ (M^+) 274.1569, found 274.1568.



(*R*)-3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-5-phenylpent-4-yn-1-ol (14)

To a solution of alcohol **13** (111 mg, 0.405 mmol), PhI (0.090 mL, 0.81 mmol) and *t*-$BuNH_2$ (0.43 mL, 4.06 mmol) in benzene (4 mL) were added $Pd(PPh_3)_4$ (45.0 mg, 0.039 mmol) and CuI (23.1 mg, 0.121 mmol). The mixture was stirred at room temperature for 13 h under dark and diluted with saturated NH_4Cl with vigorous stirring. The product was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford Ph acetylene **14** (128 mg, 90%). Liquid; R_f = 0.64 (hexane/EtOAc = 1:1). 96.9% ee by HPLC analysis (Chiralcel OJ-H, hexane/*i*-PrOH = 90:10, 0.5 mL/min, 25 °C, t_R = 25.3 and 30.7 min for (*S*)-isomer (minor) and (*R*)-isomer (major), respectively. $[\alpha]_D^{24}$ +7 (*c* 0.27, $CHCl_3$). IR (neat) 3406, 1513, 1259, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.50–1.72 (m, 3 H), 1.76–2.00 (m, 6 H), 2.02–2.12 (m, 2 H), 3.75–3.96 (m, 2 H), 3.84 (s, 3 H), 4.01 (t, *J* = 7.4 Hz, 1 H), 4.76–4.84 (m, 1 H), 6.84 (d, *J* = 8.1 Hz, 1 H), 6.93–7.01 (m, 2 H), 7.27–7.33 (m, 3 H), 7.40–7.46 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1 (–), 32.8 (–), 32.9 (–), 34.5 (+), 41.1 (–), 56.2 (+), 60.8 (–), 80.4 (+), 83.6 (–), 91.2 (–), 112.0 (+), 114.4 (+), 119.3 (+), 123.5 (–), 127.9 (+), 128.3 (+), 131.6 (+), 134.0 (–), 147.7 (–), 148.9 (–). HRMS (FAB) calcd for $C_{23}H_{26}O_3$ (M^+) 350.1882, found 350.1884.

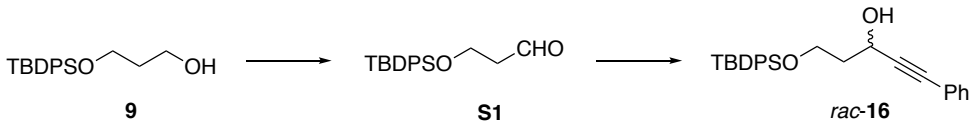


(*R*)-3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-5-phenylpent-4-ynoic acid (4)

To an ice-cold solution of alcohol **14** (128 mg, 0.366 mmol) in CH_2Cl_2 (1.5 mL) were added DMSO (0.104 mL, 1.46 mmol), Et_3N (0.153 mL, 1.10 mmol) and SO_3·pyridine (117 mg, 0.733 mmol). The mixture was stirred at room temperature for 20 h and diluted with H_2O and CH_2Cl_2. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic layers were washed sequentially with citrate-phosphate buffer (pH = 5.0) and brine, dried over $MgSO_4$ and concentrated. The residue was passed through a short column of silica gel (hexane/EtOAc) to give aldehyde **15**, which was dissolved in acetone (1.5 mL) for the next reaction. The aldehyde was synthesized again and purified by chromatography on silica gel (hexane/EtOAc). Liquid. R_f = 0.52 (hexane/EtOAc = 2:1). $[\alpha]_D^{24}$ +1 (*c* 1.02, $CHCl_3$). IR (neat) 1724, 1512, 1260 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.46–1.70 (m, 2 H), 1.76–2.04 (m, 6 H), 2.89 (ddd, *J* = 16.8, 6.3, 1.8 Hz, 1 H), 2.98 (ddd, *J* = 16.8, 7.5, 1.8 Hz, 1 H), 3.84 (s, 3 H), 4.37 (dd, *J* = 7.5, 6.3 Hz, 1 H), 4.74–4.84 (m, 1 H), 6.84 (d, *J* = 8.1 Hz, 1 H), 6.94–7.01 (m, 3 H), 7.27–7.34 (m, 3 H), 7.39–7.46 (m, 2 H), 9.86 (t, *J* = 1.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1 (–), 32.1 (+), 32.8 (–), 32.9 (–), 51.4 (–), 56.1 (+), 80.4 (+), 84.2 (–), 89.7 (–), 112.1 (+), 114.2 (+), 119.3 (+), 123.1 (–), 128.2 (+), 128.3 (+), 131.7 (+), 132.5 (–), 147.8 (–), 149.2 (–), 200.5 (+).

To the above acetone solution cooled to 0 °C was added Jones reagent (10 drops). After being stirred at 0 °C for 10 min, the mixture was diluted with *i*-PrOH and H_2O. The product was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish acid (*R*)-**4** (83.1 mg, 62% over two steps). Liquid. R_f = 0.12 (hexane/EtOAc = 3:1). $[\alpha]_D^{24}$ –7 (*c* 0.97, $CHCl_3$). Cf. lit.[S5] $[\alpha]_D^{23}$ –3.5 (*c* 0.75, $CHCl_3$). IR (neat) 3000, 1711, 1515, 1260, 1136 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.42–1.68 (m, 2 H), 1.72–2.01 (m, 6 H), 2.83 (dd, *J* = 15.8, 7.2 Hz, 1 H), 2.95 (dd, *J* = 15.8, 8.4 Hz, 1 H), 3.83 (s, 3 H), 4.31 (t, *J* = 7.3 Hz, 1 H), 4.72–4.84 (m, 1 H), 6.83 (d, *J* = 7.8 Hz, 1 H), 6.94–

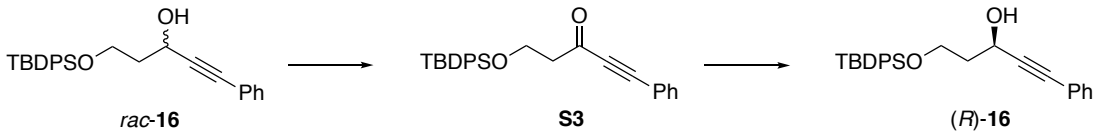
7.01 (m, 2 H), 7.24–7.33 (m, 3 H), 7.37–7.46 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1 (–), 32.8 (–), 32.9 (–), 34.1 (+), 43.3 (–), 56.1 (+), 80.4 (+), 83.6 (–), 89.9 (–), 112.1 (+), 114.3 (+), 119.4 (+), 123.3 (–), 128.1 (+), 128.3 (+), 131.7 (+), 132.6 (–), 147.7 (–), 149.2 (–), 176.9 (–). HRMS (FAB) calcd for $C_{23}H_{24}O_4Na$ [$(M+Na)^+$] 387.1572, found 387.1567. The ^{1}H NMR spectral data except the undetected COO*H* were consistent with those reported,[S5] while the ^{13}C NMR spectral data were updated. The ^{13}C–APT NMR spectrum also supported the structure.



5-(*tert*-Butyldiphenylsilyloxy)-1-phenylpent-1-yn-3-ol (*rac*-16)

According to the procedure described above, alcohol **9** (2.99 g, 9.51 mmol) was subjected to oxidation with SO_3·pyridine (3.03 g, 19.0 mmol), DMSO (2.70 mL, 38.0 mmol) and Et_3N (4.0 mL, 29 mmol) in CH_2Cl_2 (20 mL) at room temperature overnight to afford aldehyde **S1**, which was passed through a short column of silica gel (hexane/EtOAc) for the next reaction.

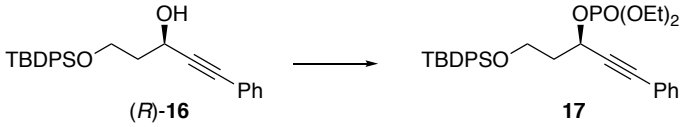
To a solution of phenylacetylene (1.67 mL, 15.2 mmol) in THF (10 mL) was added *n*-BuLi (1.60 M in hexane, 7.73 mL, 12.4 mmol) dropwise at –78 °C. After 30 min at –78 °C, the above aldehyde dissolved in THF (10 mL) was added. The solution was stirred at –78 °C for 1 h and diluted with saturated NH_4Cl. The mixture was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give alcohol *rac*-**16** (3.13 g, 80% over two steps). Liquid. R_f = 0.13 (hexane/EtOAc = 19:1). IR (neat) 3410, 1428, 1112, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9 H), 1.93–2.07 (m, 1 H), 2.08–2.21 (m, 1 H), 3.49 (d, J = 5.1 Hz, 1 H), 3.89 (ddd, J = 10.2, 6.0, 4.2 Hz, 1 H), 4.13 (ddd, J = 10.2, 8.0, 4.2 Hz, 1 H), 4.88–4.98 (m, 1 H), 7.26–7.47 (m, 11 H), 7.66–7.75 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1 (–), 26.8 (+), 38.8 (–), 62.0 (–), 62.2 (+), 85.1 (–), 89.7 (–), 122.8 (–), 127.9 (+), 128.3 (+), 128.4 (+), 129.88 (+), 129.91 (+), 131.8 (+), 132.9 (–), 135.6 (+). HRMS (FAB) calcd for $C_{27}H_{31}O_2Si$ [$(M+H)^+$] 415.2093, found 415.2088. The ^{1}H and ^{13}C NMR spectral data and their spectra reported in the literature[S4] were updated.



(*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-phenylpent-1-yn-3-ol [(*R*)-16]

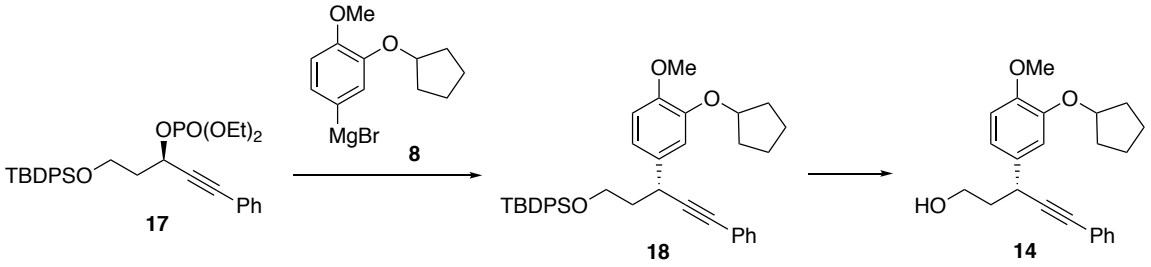
To an ice-cold solution of *rac*-**16** (139 mg, 0.335 mmol) in CH_2Cl_2 (3 mL) were added Celite (220 mg) and PCC (108 mg, 0.503 mmol). The mixture was stirred at room temperature for 26 h, diluted with hexane and filtered through a pad of Celite with hexane. The filtrate was concentrated and the residue was purified by chromatography on silica gel (hexane/EtOAc) to give ketone **S3** (94.6 mg, 68%). Liquid. R_f = 0.63 (hexane/EtOAc = 5:1). IR (neat) 2200, 1674, 1112 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 2.89 (t, J = 6.1 Hz, 2 H), 4.10 (t, J = 6.1 Hz, 2 H), 7.29–7.57 (m, 11 H), 7.62–7.74 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (–), 26.8 (+), 48.3 (–), 59.5 (–), 87.9 (–), 91.2 (–), 120.0 (–), 127.8 (+), 128.6 (+), 129.8 (+), 130.8 (+), 133.1 (+), 133.4 (–), 135.6 (+), 186.4 (–). The ^1H NMR spectrum was coincident with those reported, while the ^{13}C NMR spectral data and spectrum were updated.[S4]

A mixture of RuCl[(*R*,*R*)-TsDPEN](*p*-cymene) (31.3 mg, 0.049 mmol) and KOH (ca. 9 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 5 min, and washed with H_2O twice. The organic layer was transferred to another flask, dried over CaH_2 and concentrated to afford a residue, which was diluted with *i*-PrOH (6 mL) for the next reaction. To an ice-cold solution of the above ketone (338 mg, 0.819 mmol) in *i*-PrOH (1 mL) was added the above *i*-PrOH solution. The mixture was stirred at 30 °C for 21 h, and diluted with H_2O and saturated $NaHCO_3$. The mixture was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was passed through a short column of silica gel (hexane/EtOAc) to give alcohol (*R*)-**16** (286 mg, 84%). $[\alpha]_D^{23}$ –11 (*c* 0.524, $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical with those for the racemic alcohol *rac*-**16**.



(*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-phenylpent-1-yn-3-yl diethyl phosphate (17)

To a solution of (*R*)-**16** (280 mg, 0.675 mmol) in CH_2Cl_2 (2.7 mL) were added *N*-methylimidazole (0.138 mL, 1.75 mmol) and diethyl chlorophosphate (0.243 mL, 1.69 mmol). The solution was stirred at room temperature for 4 h and diluted with 1 N HCl. The mixture was extracted with CH_2Cl_2 twice. The combined organic layers were washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give phosphate **17** (347 mg, 93%). Liquid. R_f = 0.14 (hexane/EtOAc = 5:1). $[\alpha]_D^{24}$ +33 (*c* 0.56, $CHCl_3$). IR (neat) 1276, 1112, 1033, 997, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9 H), 1.28–1.36 (m, 6 H), 2.03–2.18 (m, 1 H), 2.20–2.34 (m, 1 H), 3.88 (t, *J* = 6.2 Hz, 2 H), 4.03–4.23 (m, 4 H), 5.49 (q, *J* = 7.0 Hz, 1 H), 7.27–7.45 (m, 11 H), 7.62–7.72 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1 (d, *J* = 7 Hz) (+), 19.1 (–), 26.7 (+), 39.5 (d, *J* = 7 Hz) (–), 59.6 (–), 63.7 (d, *J* = 6 Hz) (–), 63.8 (d, *J* = 6 Hz) (–), 66.0 (d, *J* = 6 Hz) (+), 86.1 (d, *J* = 3 Hz) (–), 86.8 (–), 122.0 (–), 127.64 (+), 127.65 (+), 128.2 (+), 128.7 (+), 129.60 (+), 129.63 (+), 131.7 (+), 133.4 (–), 135.5 (+). HRMS (FAB) calcd for $C_{31}H_{40}O_5PSi$ [$(M+H)^+$] 551.2383, found 551.2376.

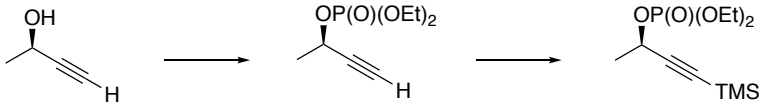


(*R*)-*tert*-Butyl[3-[3-(cyclopentyloxy)-4-methoxyphenyl]-5-phenylpent-4-ynyloxy]diphenylsilane (14)

The Grignard reagent **8** (0.90 M in THF) was prepared by the method described above, and a part of the solution (0.77 mL, 0.69 mmol) was added to an ice-cold solution of CuCN (6.2 mg, 0.069 mmol) in THF (1.4 mL) and DME (1.4 mL). The solution was stirred at 0 °C for 30 min, and phosphate **17** (190 mg, 0.345 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at 0 °C for 1.5 h and diluted with saturated NH_4Cl and EtOAc with vigorous stirring. The organic phase was separated, and the aqueous phase was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was passed through a short column of silica gel (hexane/EtOAc) to afford acetylene **18**, which was dissolved in THF (3.5 mL) for the next reaction. The

product was synthesized again and purified by chromatography on silica gel (hexane/EtOAc). Liquid. R_f = 0.65 (hexane/EtOAc = 5:1). $[\alpha]_D^{24}$ +17 (*c* 1.17, $CHCl_3$). IR (neat) 1513, 1427, 1260, 1112, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9 H), 1.50–1.66 (m, 2 H), 1.74–1.97 (m, 6 H), 1.99–2.10 (m, 2 H), 3.76 (dt, *J* = 10.2, 5.7 Hz, 1 H), 3.84 (s, 3 H), 3.87–3.99 (m, 1 H), 4.14 (t, *J* = 7.5 Hz, 1 H), 4.73–4.82 (m, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 6.91–7.01 (m, 3 H), 7.25–7.44 (m, 11 H), 7.64–7.74 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (–), 24.1 (–), 26.9 (+), 32.8 (–), 32.9 (–), 34.1 (+), 41.5 (–), 56.2 (+), 61.4 (–), 80.4 (+), 83.2 (–), 91.7 (–), 112.0 (+), 114.5 (+), 119.5 (+), 123.8 (–), 127.7 (+), 128.2 (+), 129.6 (+), 131.7 (+), 133.8 (–), 133.9 (–), 134.3 (–), 135.59 (+), 135.65 (+), 147.6 (–), 148.8 (–).

To the above THF solution cooled to 0 °C were added TBAF (1.0 M in THF, 1.04 mL, 1.04 mmol) and AcOH (0.059 mL, 1.0 mmol). The solution was stirred at room temperature for 18 h and diluted with saturated NH_4Cl. The product was extracted with EtOAc twice, and 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 give alcohol **14** (104 mg, 86% over two steps). 95.6% ee by HPLC analysis (Chiralcel OJ-H, hexane/*i*-PrOH = 90:10, 0.5 mL/min, 25 °C, t_R = 28.1 and 33.4 min for (*S*)-isomer (minor) and (*R*)-isomer (major), respectively. The ^1H NMR spectral data of **14** were identical with those synthesized from acetylene **13** by the Sonogashira coupling reaction (vide supra).



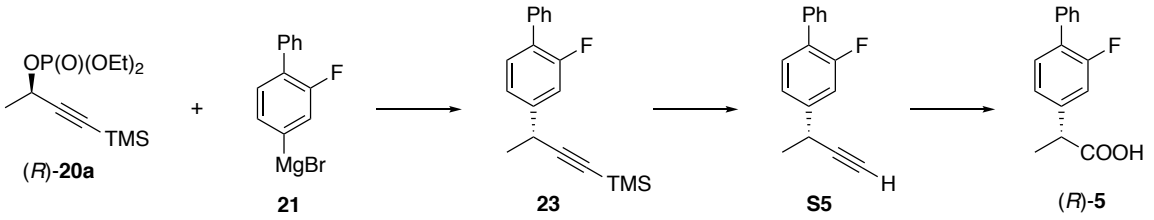
22 **S4** (*R*)-**20a**

(*R*)-Diethyl 4-(trimethylsilyl)but-3-yn-2-yl phosphate [(*R*)-20a]

To an ice-cold mixture of alcohol **22** (98.2% ee,[S6,S7] 503 mg, 7.18 mmol) and *N*-methylimidazole (1.22 mL, 14.3 mmol) in CH_2Cl_2 (20 mL) was added diethyl chlorophosphate (1.53 mL, 10.7 mmol). The mixture was stirred at room temperature for 3 h and poured to brine. The product was extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to obtain phosphate **S4** (1.42 g, 96%). Pale yellow liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (tm, *J* = 7.2 Hz, 6

H), 1.60 (d, J = 6.6 Hz, 3 H), 2.56 (d, J = 2.4 Hz, 1 H), 4.06–4.22 (m, 4 H), 5.04–5.16 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1 (d, J = 7 Hz) (+), 23.3 (d, J = 6 Hz) (+), 63.9 (d, J = 5 Hz) (+), 64.0 (d, J = 6 Hz) (–), 74.0 (–), 81.9 (d, J = 5 Hz) (–). The spectral data were in agreement with those reported.[S8]

To a solution of the above phosphate (1.00 g, 4.85 mmol) in THF (50 mL) was added $NaN(TMS)_2$ (1.0 M in THF, 6.30 mL, 6.30 mmol) dropwise at –78 °C. After 30 min, a solution of TMSCl (0.86 mL, 6.8 mmol) in THF (10 mL) was added. The solution was stirred at –78 °C for 2 h and poured to 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 afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford TMS phosphate (*R*)-**20a** (1.19 g, 88%). Liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 9 H), 1.346 (dt, J = 1.0, 7.0 Hz, 3 H), 1.355 (dt, J = 1.0, 7.0 Hz, 3 H), 1.56 (d, J = 6.6 Hz, 3 H), 4.06–4.22 (m, 4 H), 5.09 (dq, J = 7.8, 6.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ –0.3 (+), 16.1 (d, J = 7 Hz) (+), 23.4 (d, J = 6 Hz) (+), 63.8 (d, J = 6 Hz) (–), 63.9 (d, J = 7 Hz) (–), 64.6 (d, J = 5 Hz) (+), 90.6 (–), 103.4 (d, J = 5 Hz) (–). The spectra were consistent with those reported.[S9]



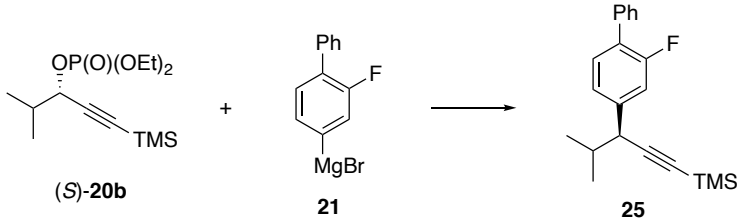
(*R*)-Flurbiprofen [(*R*)-5]

To an ice-cold solution of $CuBr{\cdot}Me_2S$ (14.9 mg, 0.0725 mmol) in THF (1 mL) and DME (1 mL) was added the Grignard reagent **21** (0.90 M in THF, 0.82 mL, 0.74 mmol) dropwise. The resulting mixture was stirred at 0 °C for 30 min and phosphate (*R*)-**20a** (80.3 mg, 0.288 mmol) in THF (4 mL) was added dropwise. 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 extracts were dried over $MgSO_4$ and concentrated to afford an oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alkyne **23** (75.4 mg, 88%). Liquid. R_f = 0.55 (hexane/EtOAc = 10:1). 98.1% ee by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 99.9:0.1, 0.3 mL/min, 25 °C, t_R = 29.9 and 39.1 min for (*R*)-isomer

(major) and (*S*)-isomer (minor), respectively). $[\alpha]_D^{23}$ –2 (*c* 1.51, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 9 H), 1.51 (d, *J* = 7.2 Hz, 3 H), 3.81 (q, *J* = 7.2 Hz, 1 H), 7.17–7.57 (m, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.2 (+), 24.4 (+), 32.4 (+), 86.9 (–), 108.6 (–), 114.7 (d, *J* = 24 Hz) (+), 122.9 (d, *J* = 3 Hz) (+), 127.3 (d, *J* = 14 Hz) (–), 127.6 (+), 128.5 (+), 129.0 (d, *J* = 3 Hz) (+), 130.8 (d, *J* = 4 Hz) (+), 135.7 (–), 144.7 (d, *J* = 7 Hz) (–), 159.8 (d, *J* = 246 Hz) (–). ^{19}F NMR (376 MHz, $CDCl_3$) δ 119.0 (s).

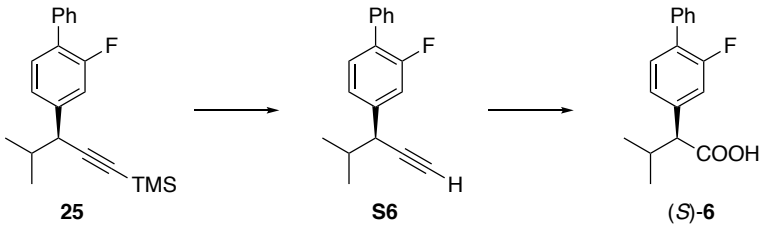
To a solution of the above alkyne in MeOH (2 mL) was added K_2CO_3 (53.3 mg, 0.386 mmol). The mixture was stirred at room temperature for 4 h, diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated to afford an oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford acetylene **S5** (41.8 mg, 73%). Liquid. R_f = 0.45 (hexane/EtOAc = 10:1).

To an ice-cold solution of the above acetylene in MeCN (1 mL), CCl_4 (1 mL) and H_2O (0.3 mL) were added $RuCl_3 \cdot nH_2O$ (ca. 2 mg) and $NaIO_4$ (106 mg, 0.496 mmol). The mixture was stirred at room temperature for 90 min, diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated to afford an oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*R*)-**5** (30.0 mg, 66%). $[\alpha]_D^{25}$ –37 (*c* 0.60, $CHCl_3$). Cf. lit. $[\alpha]_D^{20}$ –29.5 (*c* 1.10, $CHCl_3$) for (*R*)-isomer of 90% ee (calcd $[\alpha]_D$ –32.8 for 100% ee);[S10a] $[\alpha]_D^{31}$ –44.0 (*c* 1.00, $CHCl_3$) for (*R*)-isomer of 97% ee;[S10b] $[\alpha]_D^{22}$ +33.5 (*c* 1.0, $CHCl_3$) for (*S*)-isomer of 85% ee (calcd $[\alpha]_D$ +39.4 for 100% ee).[S10c] ^1H NMR (300 MHz, $CDCl_3$) δ 1.56 (d, *J* = 7.2 Hz, 3 H), 3.79 (q, *J* = 7.2 Hz, 1 H), 7.12–7.20 (m, 2 H), 7.33–7.48 (m, 4 H), 7.50–7.56 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (+), 44.9 (+), 115.5 (d, *J* = 24 Hz) (+), 123.8 (d, *J* = 3 Hz) (+), 127.8 (+), 128.2 (d, *J* = 13 Hz) (–), 128.5 (+), 129.0 (d, *J* = 3 Hz) (+), 131.0 (d, *J* = 4 Hz) (+), 135.5 (–), 141.0 (d, *J* = 8 Hz) (–), 159.8 (d, *J* = 247 Hz) (–), 180.1 (–). The ^1H NMR spectrum except the undetected COO*H* and the ^{13}C NMR spectrum were consistent with those reported.[S10c,S11a–f] The ^{13}C–APT spectrum was coincident with that reported.[S11d]



(*S*)-[3-(2-Fluoro-[1,1'-biphenyl]-4-yl)-4-methylpent-1-yn-1-yl]trimethylsilane (25)

To an ice-cold solution of CuBr·Me_2S (7.9 mg, 0.038 mmol) in THF (0.5 mL) and DME (0.5 mL) was added the Grignard reagent **21** (0.90 M in THF, 0.41 mL, 0.37 mmol) dropwise. The solution was stirred at 0 °C for 1 h and phosphate (*S*)-**20b**[S12] (96.6% ee, 46.0 mg, 0.150 mmol) in THF (2 mL) was added dropwise. After 1 h at 0 °C, the reaction was quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with EtOAc twice. The combined extracts were dried over $MgSO_4$ and concentrated to afford an oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alkyne **25** (40.5 mg, 83%). Liquid. R_f = 0.83 (hexane/EtOAc = 3:1). 96.8% ee by HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 99.9:0.1, 0.3 mL/min, 25 °C, t_R = 22.6 and 27.1 min for (*R*)-isomer (minor) and (*S*)-isomer (major), respectively). $[\alpha]_D^{25}$ +6 (*c* 0.81, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 9 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 1.93–2.06 (m, 1 H), 3.58 (d, *J* = 5.7 Hz, 1 H), 7.15 (d, *J* = 10.5 Hz, 2 H), 7.31–7.48 (m, 4 H), 7.52–7.58 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.2 (+), 18.4 (+), 21.2 (+), 35.0 (+), 45.6 (+), 89.0 (–), 106.1 (–), 115.9 (d, *J* = 23 Hz) (+), 124.2 (d, *J* = 3 Hz) (+), 127.2 (d, *J* = 14 Hz) (–), 127.6 (+), 128.5 (+), 129.0 (d, *J* = 3 Hz) (+), 130.4 (d, *J* = 4 Hz) (+), 135.8 (–), 142.4 (d, *J* = 7 Hz) (–), 159.6 (d, *J* = 246 Hz) (–). ^{19}F NMR (376 MHz, $CDCl_3$) δ 119.5 (s). HRMS (FD) calcd for $C_{21}H_{25}FSi$ [M^+] 324.17095, found 324.17018.



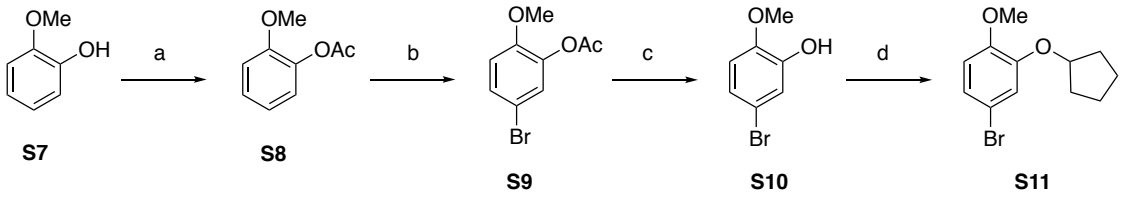
(*S*)-2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutanoic acid [(*S*)-6]

A mixture of alkyne **25** (40.1 mg, 0.124 mmol) and K_2CO_3 (24.4 mg, 0.177 mmol) in MeOH (1 mL) was stirred at room temperature for 3 h, diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated to afford an oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford acetylene **S6** (29.3 mg, 94%). Liquid. R_f = 0.63 (hexane/EtOAc = 20:1) (cf. **25**, R_f = 0.76).

To an ice-cold solution of the above acetylene in MeCN (0.7 mL), CCl_4 (0.7 mL) and H_2O (0.25 mL) were added $RuCl_3 \cdot nH_2O$ (ca. 1 mg) and $NaIO_4$ (66.9 mg, 0.313 mmol). The

mixture was stirred at room temperature for 1.5 h, diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated to afford an oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford acid (*S*)-**6** (17.1 mg, 51% from **25**). Solids. Mp 158–160 °C. R_f = 0.12 (hexane/EtOAc = 3:1). $[\alpha]_D^{20}$ +38 (*c* 0.266, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, *J* = 6.8 Hz, 3 H), 1.11 (d, *J* = 6.8 Hz, 3 H), 2.26–2.42 (m, 1 H), 3.21 (d, *J* = 10.4 Hz, 1 H), 7.15–7.21 (m, 2 H), 7.33–7.47 (m, 4 H), 7.50–7.56 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2 (+), 21.5 (+), 31.9 (+), 59.3 (+), 116.2 (d, *J* = 24 Hz) (+), 124.8 (+), 127.8 (+), 128.3 (d, *J* = 13 Hz) (–), 128.5 (+), 129.0 (+), 130.8 (d, *J* = 3 Hz) (+), 135.5 (–), 139.1 (d, *J* = 8 Hz) (–), 159.7 (d, *J* = 248 Hz) (–), 178.6 (–). HRMS (FD) calcd for $C_{17}H_{17}FO_2$ (M^+) 272.12126, found 272.12146. The carboxylic proton (COO*H*) was not observed in the ^1H NMR spectrum.

3. Synthesis of the precursor of the Grignard reagent 8



S7 **S8** **S9** **S10** **S11**

The following synthesis of the precursor **S11** of the reagent **8** was carried out according to the published procedure[S13] with modification to step a. The spectral data were identical with the reported data.[S13] Conversion of **S11** to the Grignard reagent **8** was described in the propargylic substitution mentioned above.

4-Bromo-2-(cyclopentyloxy)-1-methoxybenzene (S11)

Step a. A solution of the commercially available alcohol **S7** (5.02 g, 40.4 mmol) and Ac_2O (5.68 mL, 60.4 mmol) in pyridine (9.7 mL, 120 mmol) was stirred at room temperature for 18 h and diluted with saturated $NaHCO_3$ with vigorous stirring. The mixture was extracted with EtOAc three times. The combined organic layers were washed successively with 1 N HCl and brine, dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give acetate **S8** (6.69 g, 100%). Liquid.

R_f = 0.37 (hexane/EtOAc = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3 H), 3.83 (s, 3 H), 6.91–7.00 (m, 2 H), 7.04 (dd, J = 8.0, 2.0 Hz, 1 H), 7.21 (ddd, J = 8.4, 7.2, 1.8 Hz, 1 H).

Step b. A solution of **S8** (1.08 g, 6.50 mmol) and NBS (1.27 g, 7.14 mmol) in MeCN (13 mL) was heated at 60 °C overnight under nitrogen, cooled to room temperature and diluted with Na_2SO_3 solution. The product was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by column chromatography on silica gel (hexane/EtOAc) to afford bromide **S9** (1.54 g, 97%). Liquid. R_f = 0.37 (hexane/EtOAc = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 3.82 (s, 3 H), 6.84 (d, J = 8.8 Hz, 1 H), 7.19 (d, J = 2.5 Hz, 1 H), 7.31 (dd, J = 8.8, 2.5 Hz, 1 H).

Step c. A mixture of acetate **S9** (1.54 g, 6.28 mmol) and $NaHCO_3$ (789 mg, 9.39 mmol) in MeOH (6 mL) and H_2O (8 mL) was heated for 4 h under reflux, cooled to room temperature and extracted with EtOAc several times. The combined organic extracts were washed with brine and concentrated to give crude phenol **S10** (1.27 g), which was used for the next reaction without further purification. Liquid. R_f = 0.26 (hexane/EtOAc = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3 H), 5.65 (s, 1 H), 6.71 (d, J = 8.4 Hz, 1 H), 6.96 (dd, J = 8.4, 2.4 Hz, 1 H), 7.06 (d, J = 2.4 Hz, 1 H).

Step d. A mixture of the above phenol, cyclopentyl bromide (1.01 mL, 9.42 mmol) and K_2CO_3 (1.73 g, 12.5 mmol) in DMF (25 mL) was heated to 50 °C for 14 h with vigorous stirring, coolded to room temperature and diluted with brine. The product was extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to give a residue, which was purified by column chromatography on silica gel (hexane/EtOAc) to afford ether **S11** (1.62 g, 95% over two steps). Liquid. R_f = 0.57 (hexane/EtOAc = 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52–1.69 (m, 2 H), 1.75–2.02 (m, 6 H), 3.82 (s, 3 H), 4.70–4.77 (m, 1 H), 6.73 (d, J = 8.4 Hz, 1 H), 6.96–7.02 (m, 2 H).

4. References

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S6 This alcohol used herein was previously prepared with 98.2% ee. See ref. S7, the Supporting Information, pages S6 and S24.

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S8 Y. Imada, M. Yuasa, I. Nakamura and S. Murahashi, *J. Org. Chem*., 1994, **59**, 2282.

S9 (*a*) Ref. S7, page S6; (*b*) C. F. Bender, C. L. Paradise, V. M. Lynch, F. K. Yoshimoto and J. F. De Brabander, *Tetrahedron*, 2018, **74**, 909.

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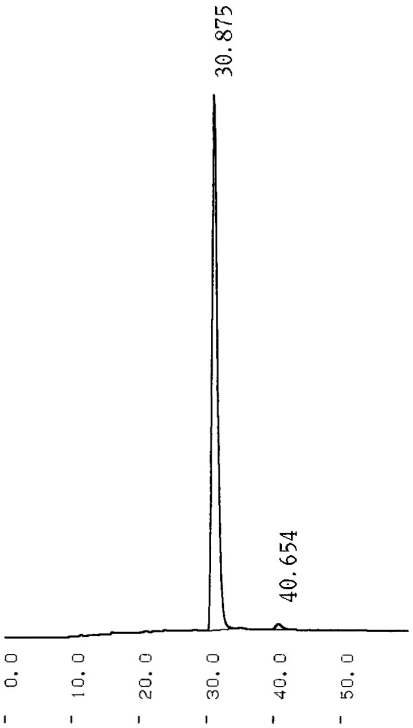
S12 This phosphate was previously prepared with 96.6% ee in: Y. Kobayashi, Y. Takashima, Y. Motoyama, Y. Isogawa, K. Katagiri, A. Tsuboi and N. Ogawa, *Chem. Eur. J*., 2021, **27**, 3779 (the Supporting Information, pages S8–S9 and S47).

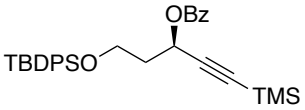
S13 A. S. Paraskar and A. Sudalai, *Tetrahedron*, 2006, **62**, 4907.

5. Calculation of ratios by ^{1}H NMR spectroscopy and HPLC analysis

Enantiomeric excess of (*R*)-**7**

Chiralcel OD-H; hexane/*i*-PrOH 99.9:0.1; flow 0.3 mL/min; temp. 25 °C



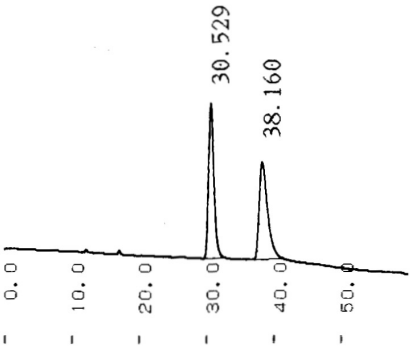


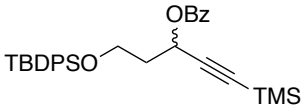
benzoate of (*R*)-**7**

% ee
= (98.7696 – 1.2304) x 100/(98.7696 + 1.2304)
= 97.539
≈ 97.5

** CALCULATION REPORT **

CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC
1	5	30.875	4521100	80422			98.7696
	7	40.654	56319	857			1.2304
		TOTAL	4577420	81279			100



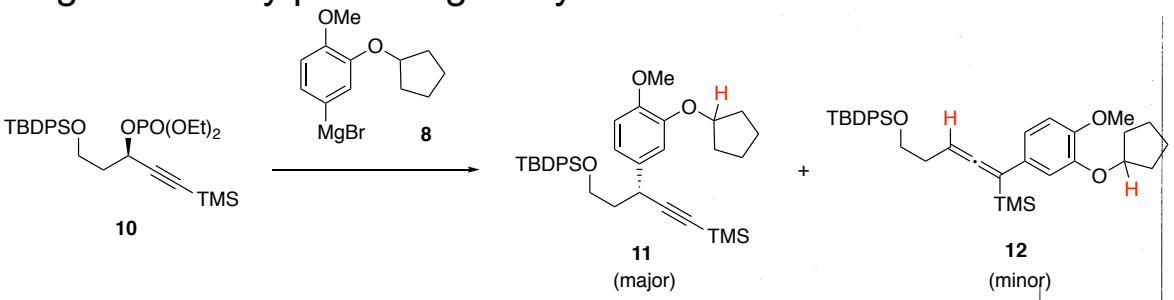


benzoate of *rac*-**7**

** CALCULATION REPORT **

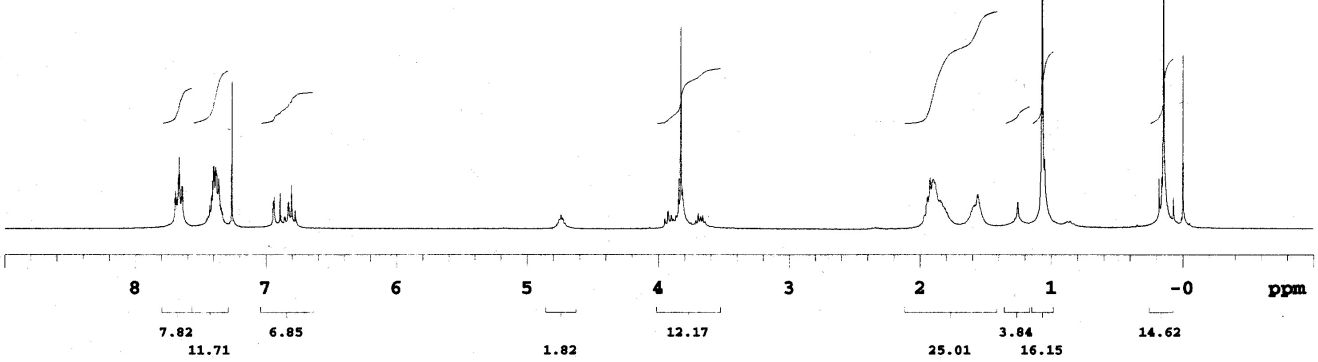
CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC
1	4	30.529	588226	10606	V		50.2987
	5	38.16	581239	6623			49.7013
		TOTAL	1169465	17229			100

Regioselectivity producing acetylene **11** over allene **12**

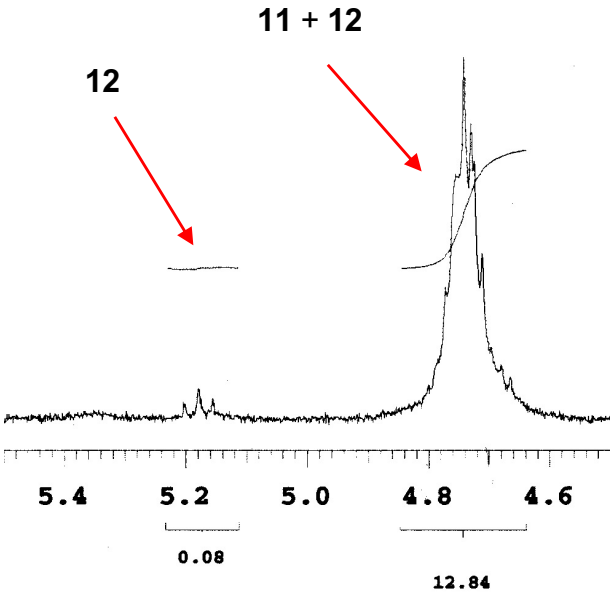


Purified products

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



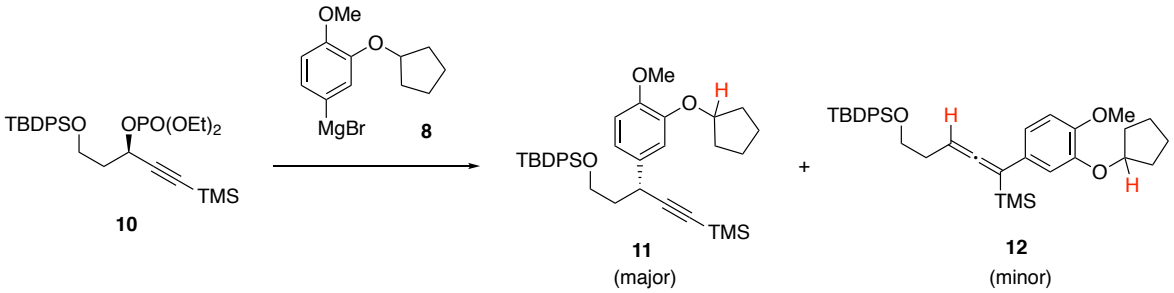
Expansion of the above NMR spectrum



regioselectivity giving **11** (%)

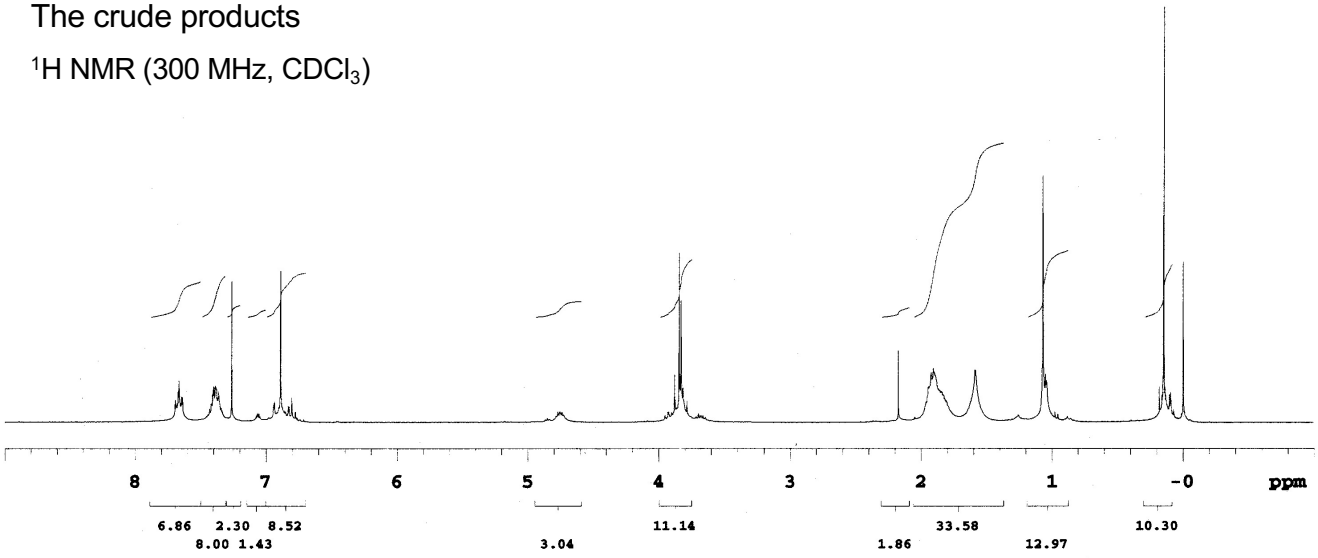
= (12.84 – 0.08) x 100/12.84
= 99.377
≈ 99

Cf. the ^{1}H NMR spectrum of the crude substitution products

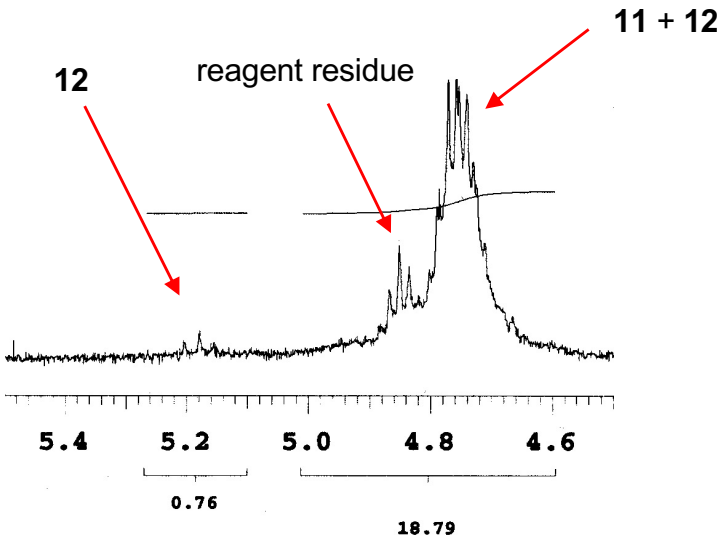


The crude products

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



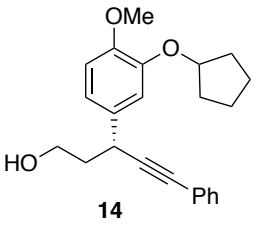
Expansion of the above NMR spectrum



Calculation of **11**/**12**: see the previous page

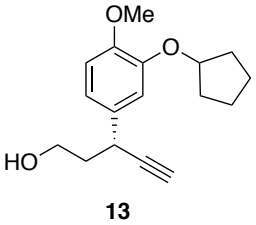
Enantiomeric excess of **14** derived from **13**

Chiralcel OJ-H; hexane/*i*-PrOH 90:10; flow 0.5 mL/min; temp. 25 °C

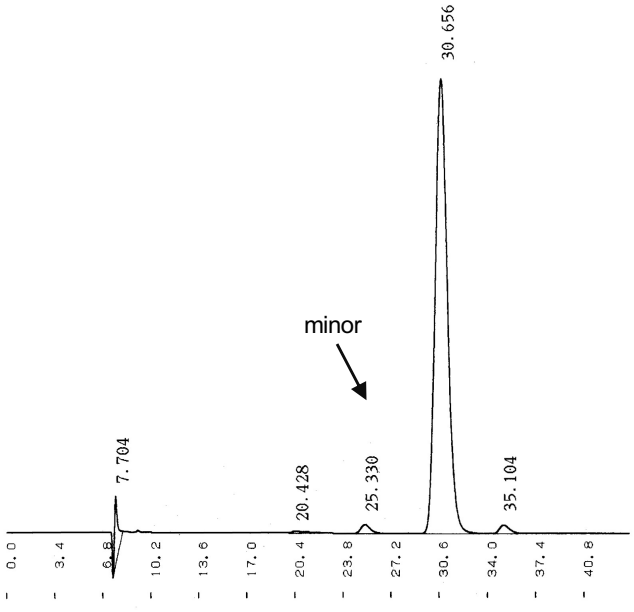


14

from



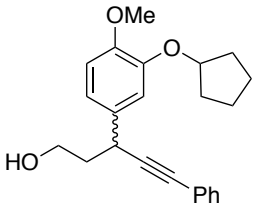
13



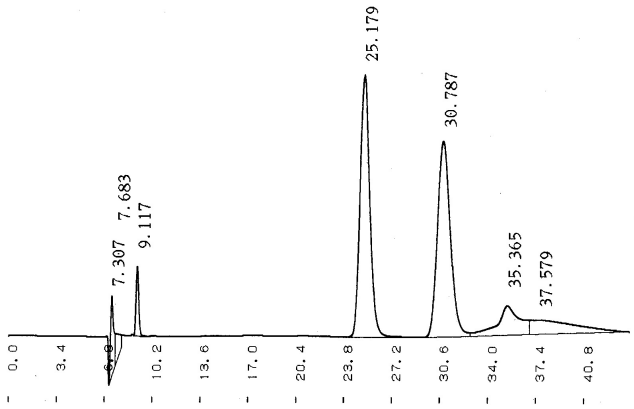
** CALCULATION REPORT **

CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC
1	1	7.704	112419	6791			3.9308
	20	20.428	15196	236	V		0.5313
	21	25.33	42273	896			1.4781
	24	30.656	2646546	44315	V		92.5377
	25	35.104	43530	867			1.5221
		TOTAL	2859964	53104			100

% ee
= (92.5377 – 1.4781) x 100/(92.5377 + 1.4781)
= 96.856
≈ 96.9



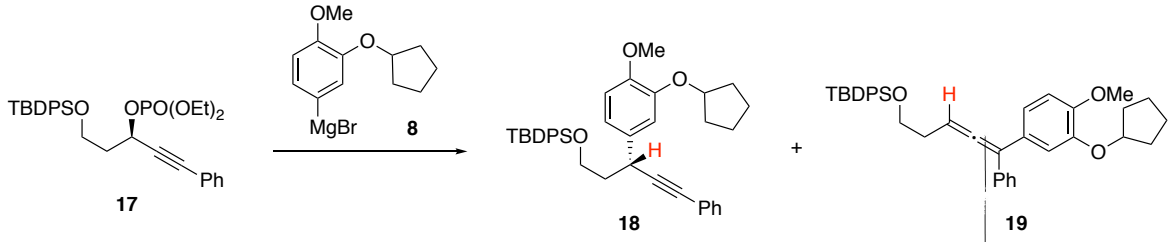
the racemate corresponding to **14**



** CALCULATION REPORT **

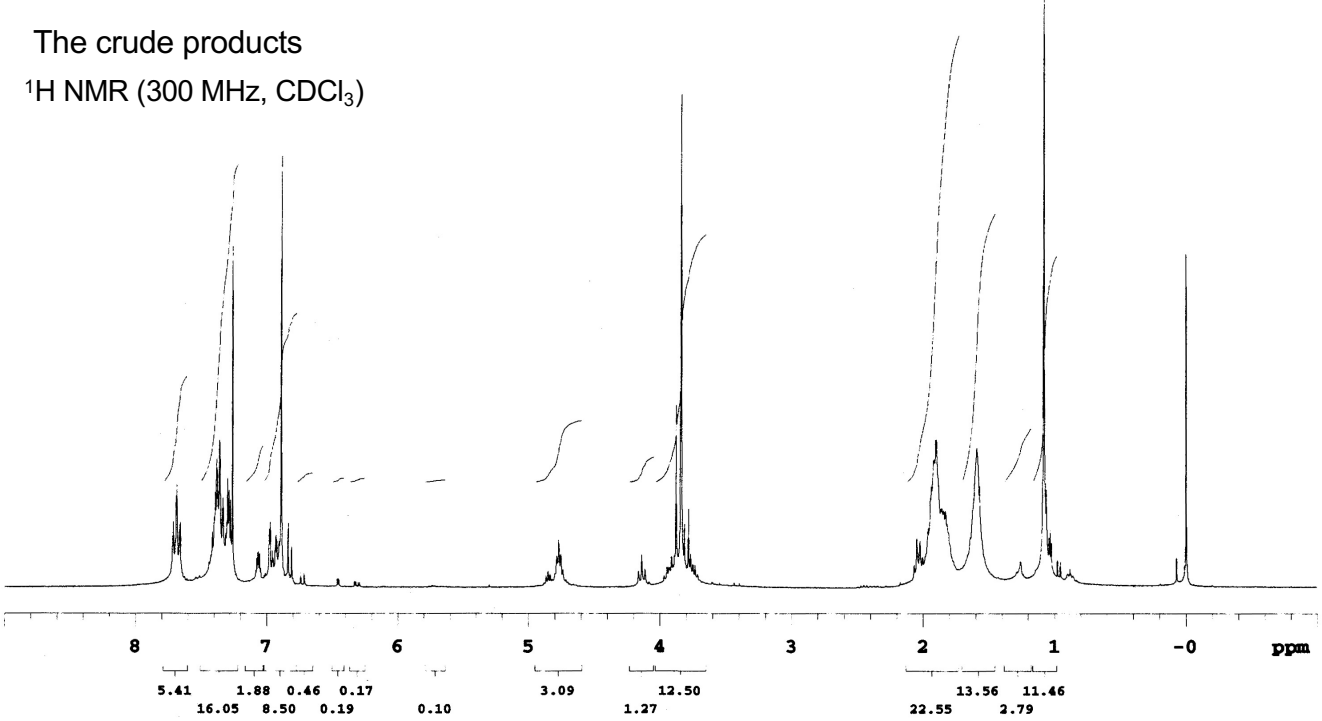
CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC
1	2	7.307	124467	7976			3.7513
	3	7.683	60208	2800	V		1.8146
	7	9.117	92561	6834	V		2.7897
	37	25.179	1220759	25529			36.7919
	38	30.787	1202571	19044			36.2438
	39	35.365	323554	2832	V		9.7515
	40	37.579	293887	1355	V		8.8573
		TOTAL	3318008	66370			100

Regioselectivity producing acetylene **18** over allene **19**



The crude products

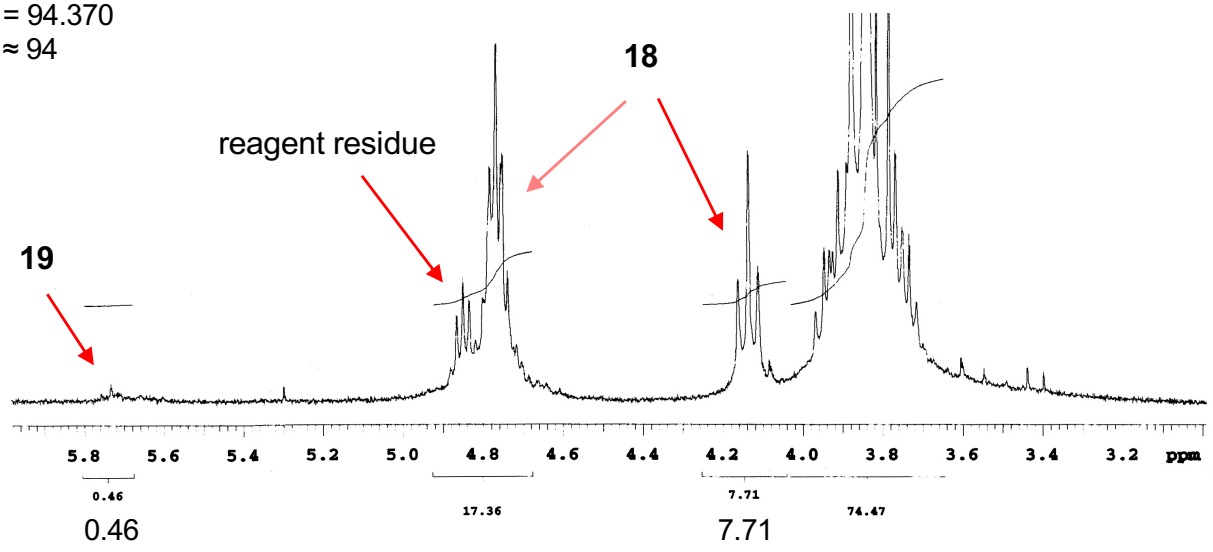
^{1}H NMR (300 MHz, $CDCl_3$)



Expansion of the above NMR spectrum

regioselectivity giving **18** (%)

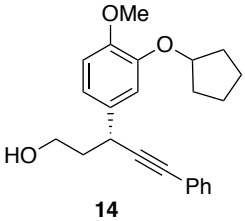
= 7.71 x 100/(7.71 + 0.46)
= 94.370
≈ 94



0.46 7.71

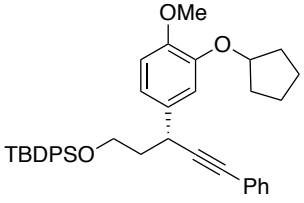
Enantiomeric excess of **14** derived from **18**

Chiralcel OJ-H; hexane/*i*-PrOH 90:10; flow 0.5 mL/min; temp. 25 °C



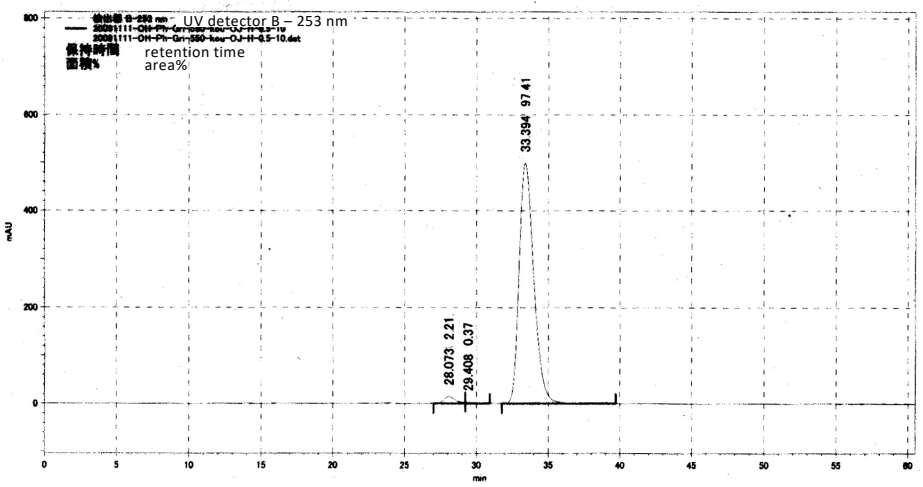
14

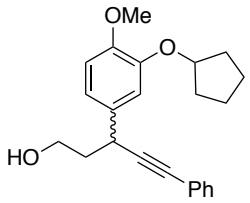
from



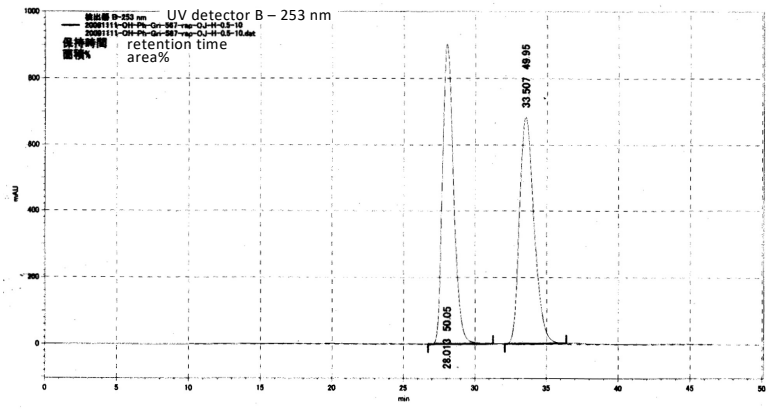
18

% ee
= (97.41 – 2.21) x 100/(97.41 + 2.21)
= 95.563
≈ 95.6

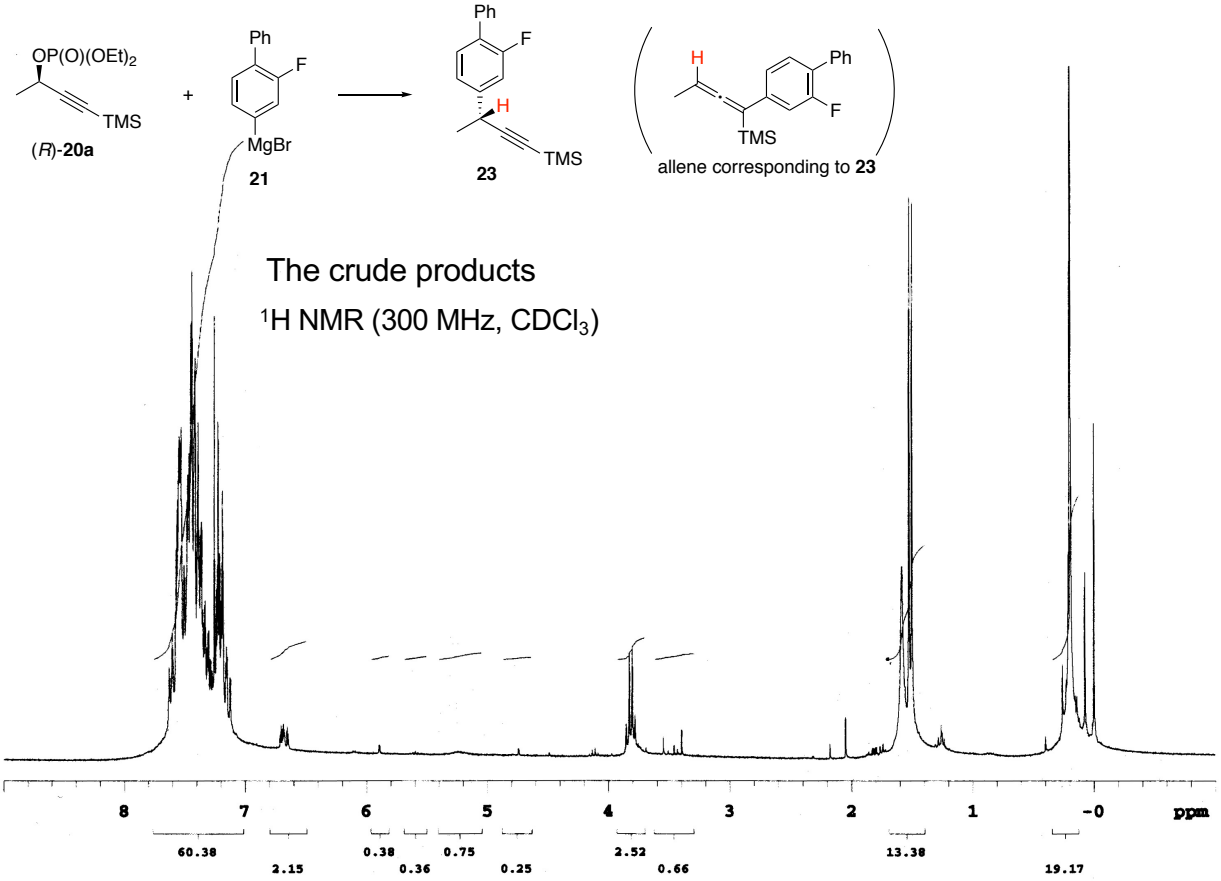




the racemate
corresponding to **14**

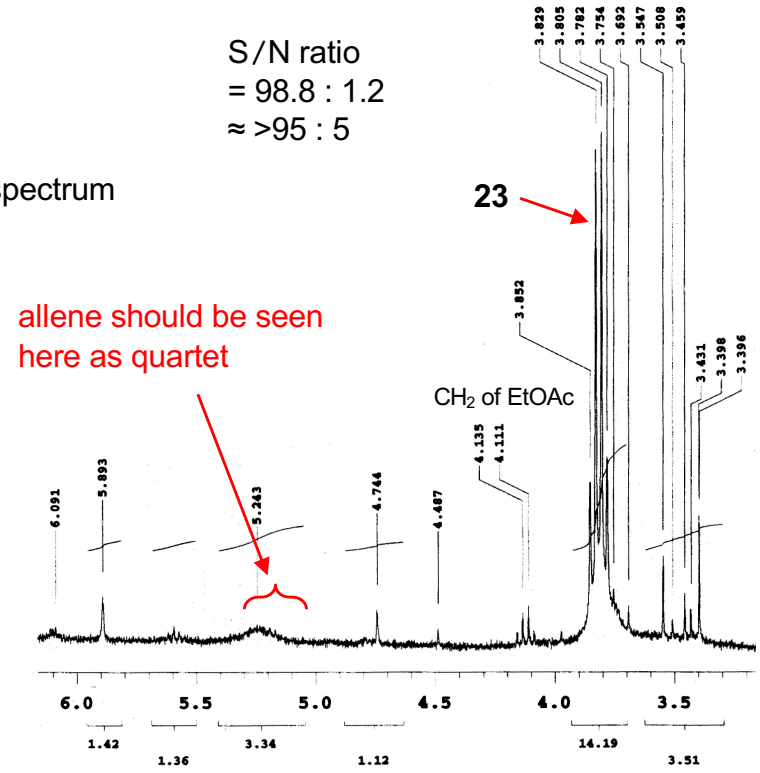


Regioisomeric purity of **23** over the allene
by the S/N ratio of the ^{1}H NMR spectrum of **23**



Expansion of
the above NMR spectrum

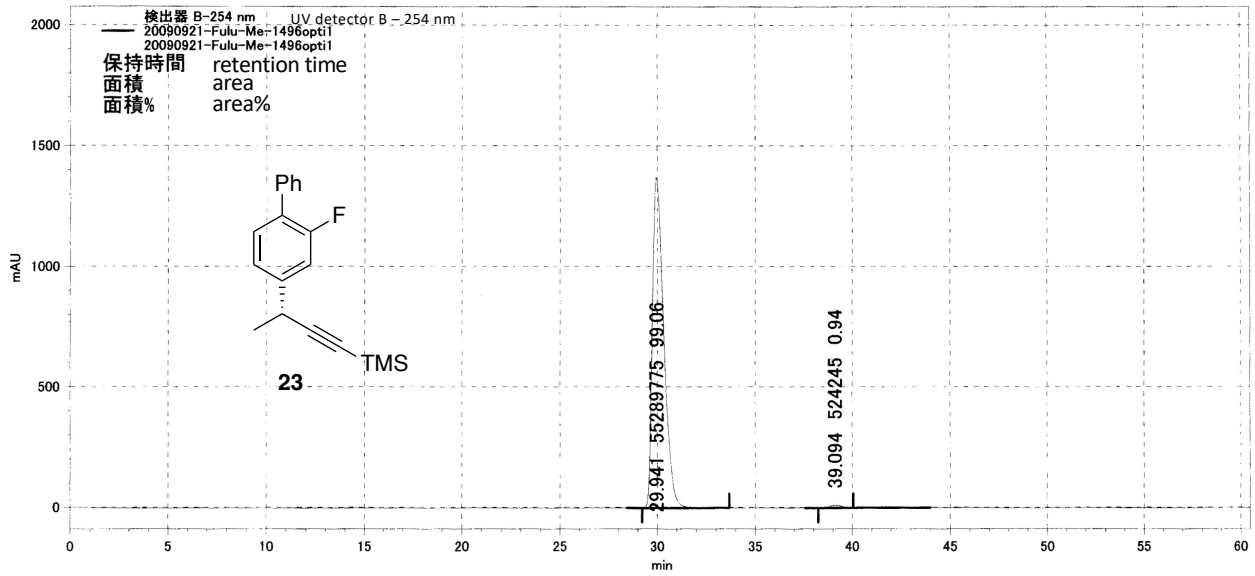
S/N ratio
= 98.8 : 1.2
≈ >95 : 5

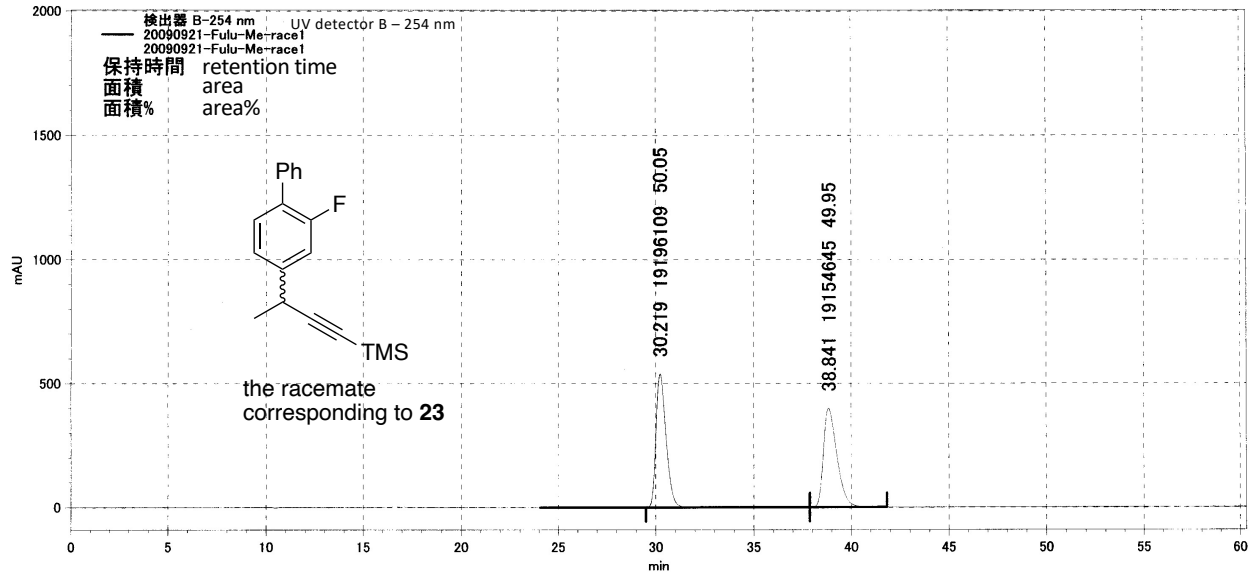


Enantiomeric excess of **23**

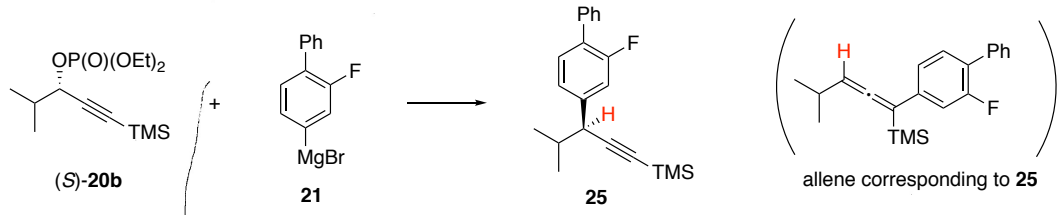
Chiralcel OD-H; hexane/*i*-PrOH 99.9:0.1; flow 0.3 mL/min; temp. 25 °C

% ee
= (99.06 – 0.94) x 100/(99.06 + 0.94)
= 98.12
≈ 98.1



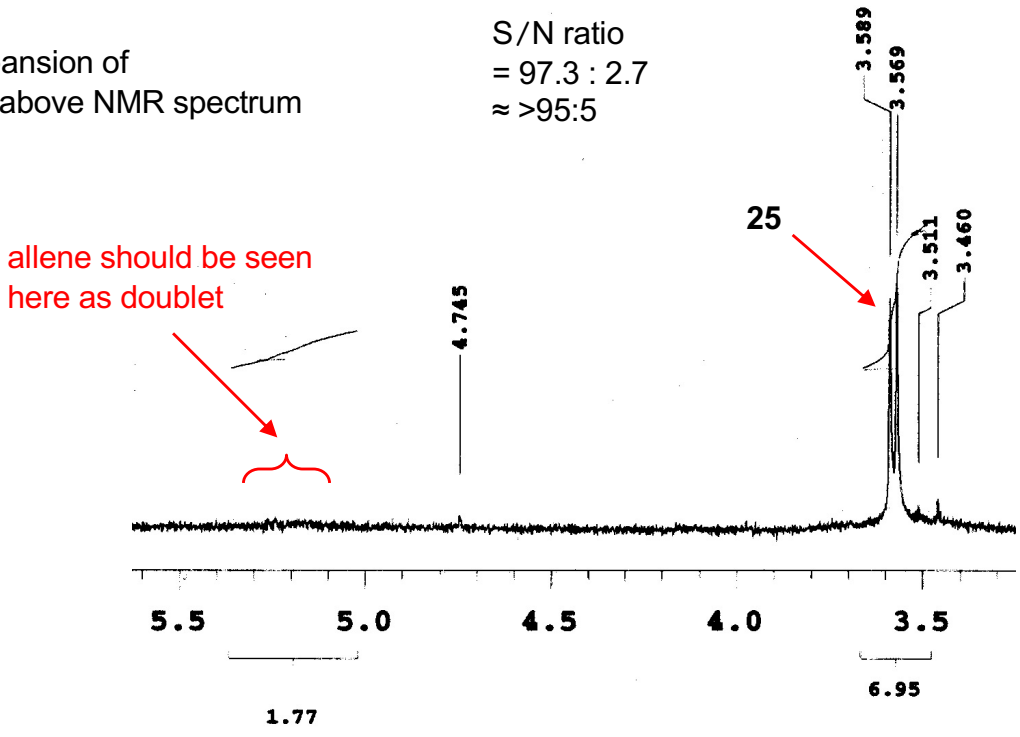


Regioisomeric purity of **25** over the allene
by the S/N ratio of the ^{1}H NMR spectrum of **25**



Expansion of
the above NMR spectrum

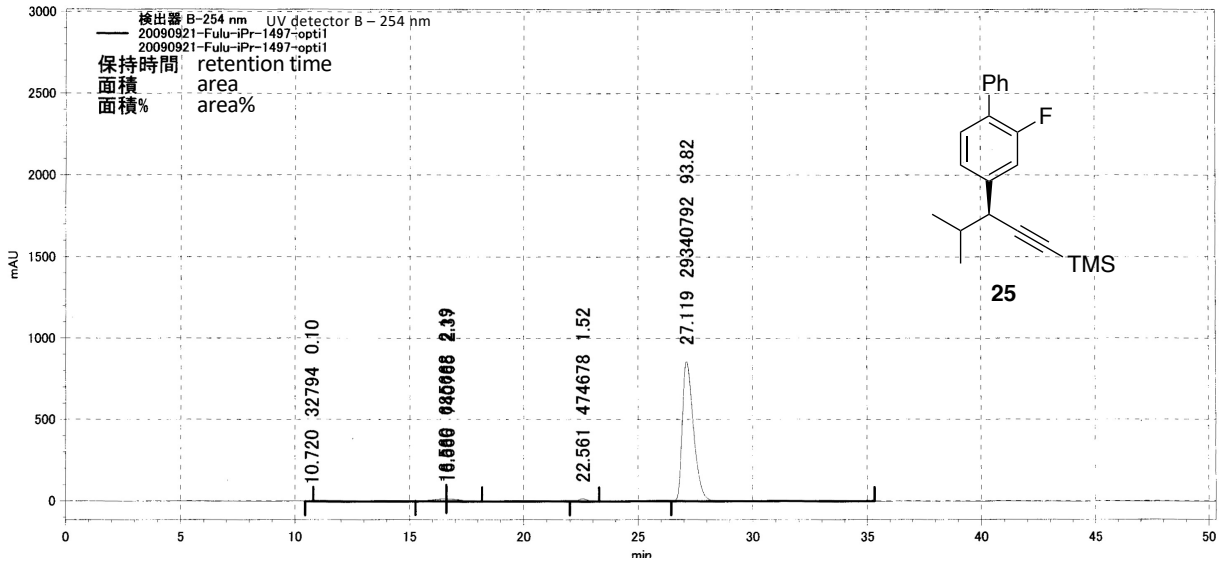
S/N ratio
= 97.3 : 2.7
≈ >95:5

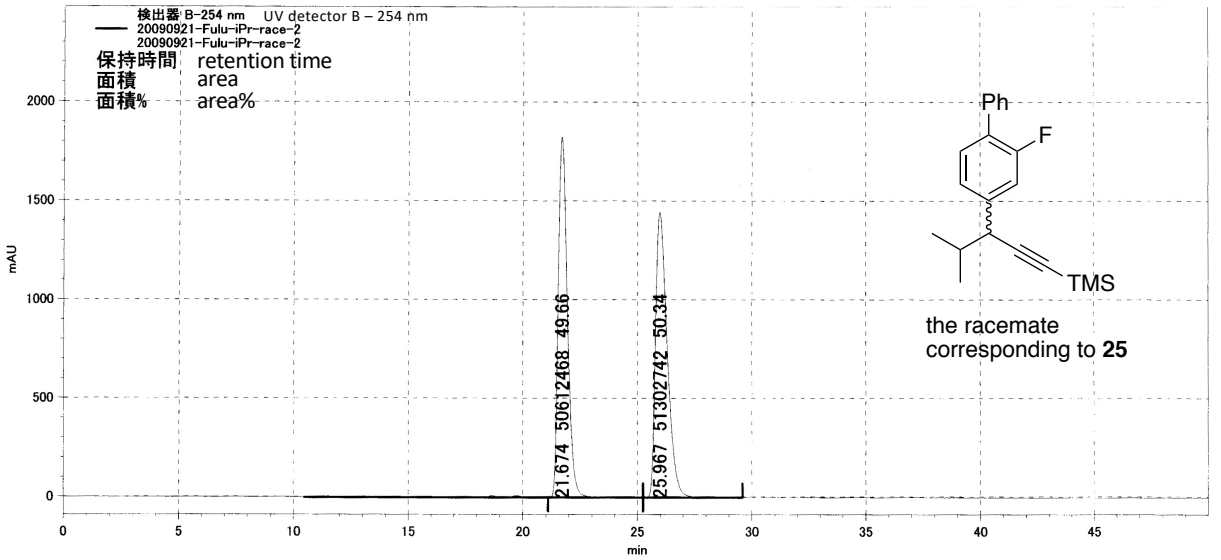


Enantiomeric excess of **25**

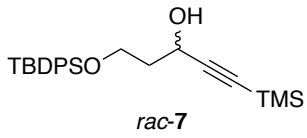
Chiralcel OD-H; hexane/*i*-PrOH 99.9:0.1; flow 0.3 mL/min; temp. 25 °C

% ee
= (93.82 – 1.52) x 100/(93.82 + 1.52)
= 96.83
≈ 96.8



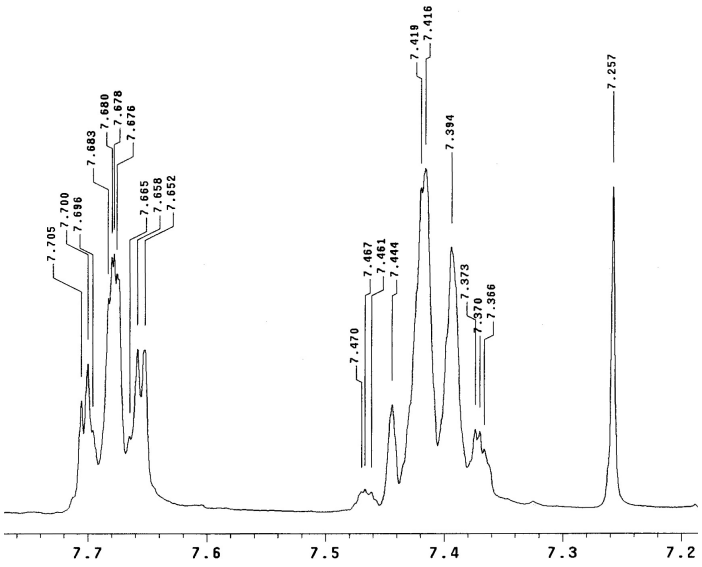


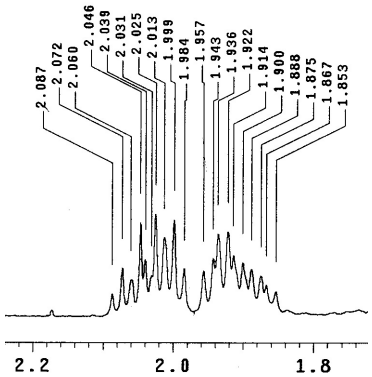
6. ^{1}H, ^{13}C and ^{13}C–APT NMR spectra

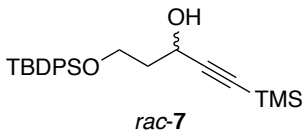


rac-**7**

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

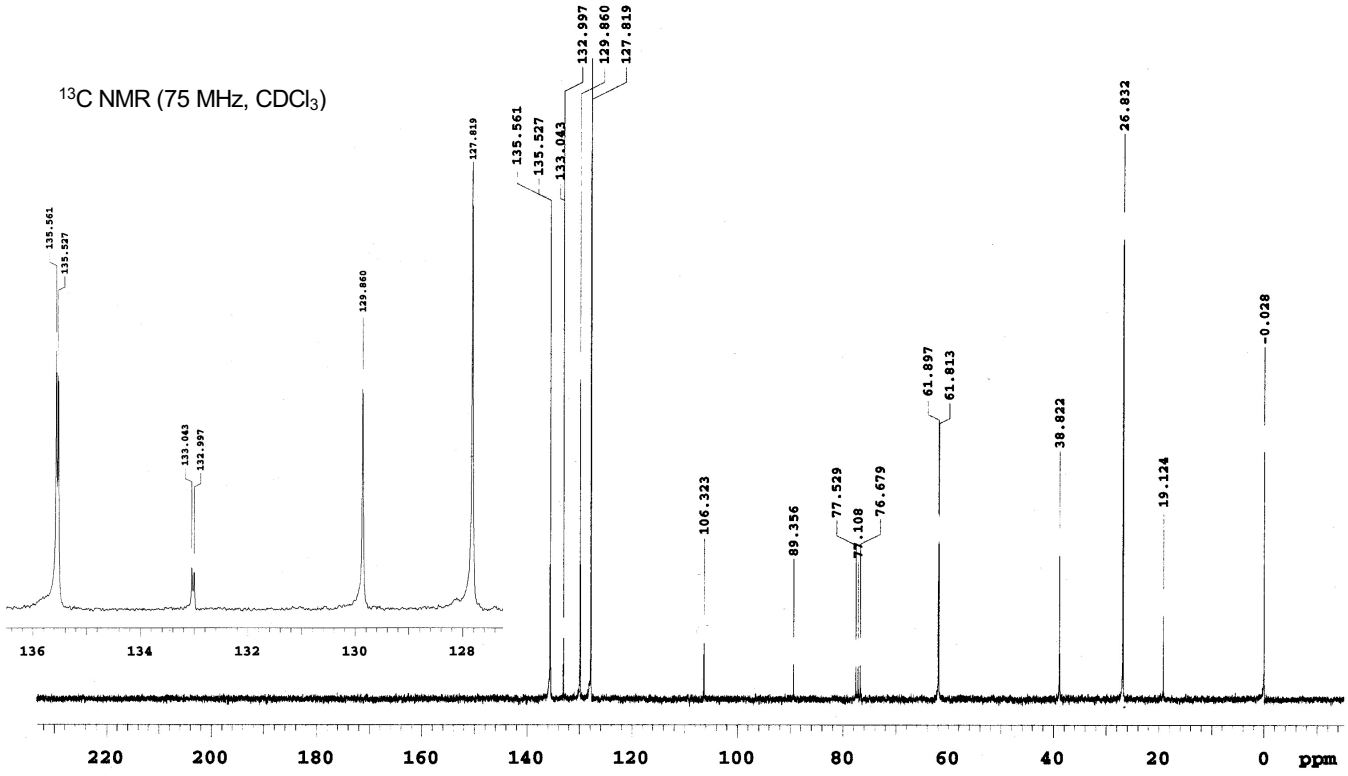




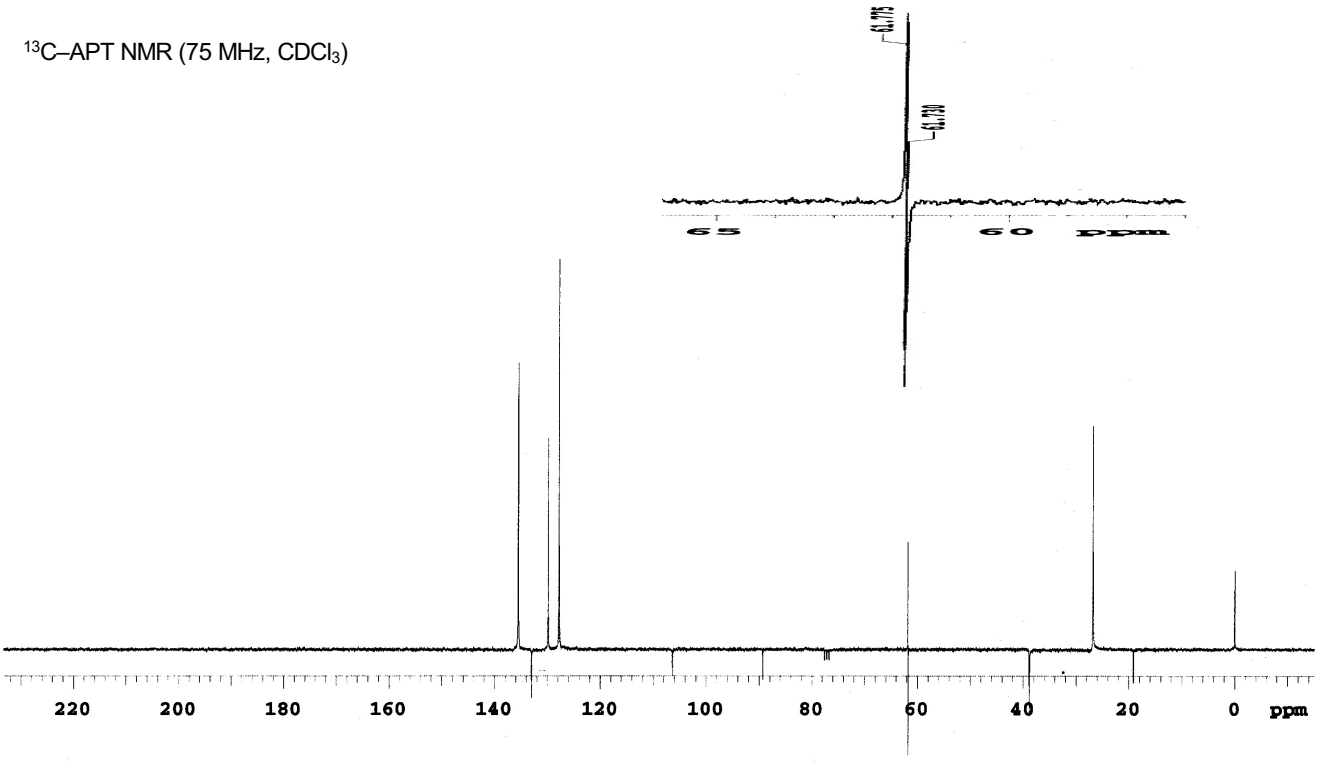


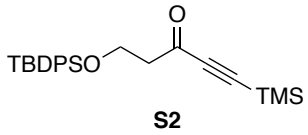
rac-**7**

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



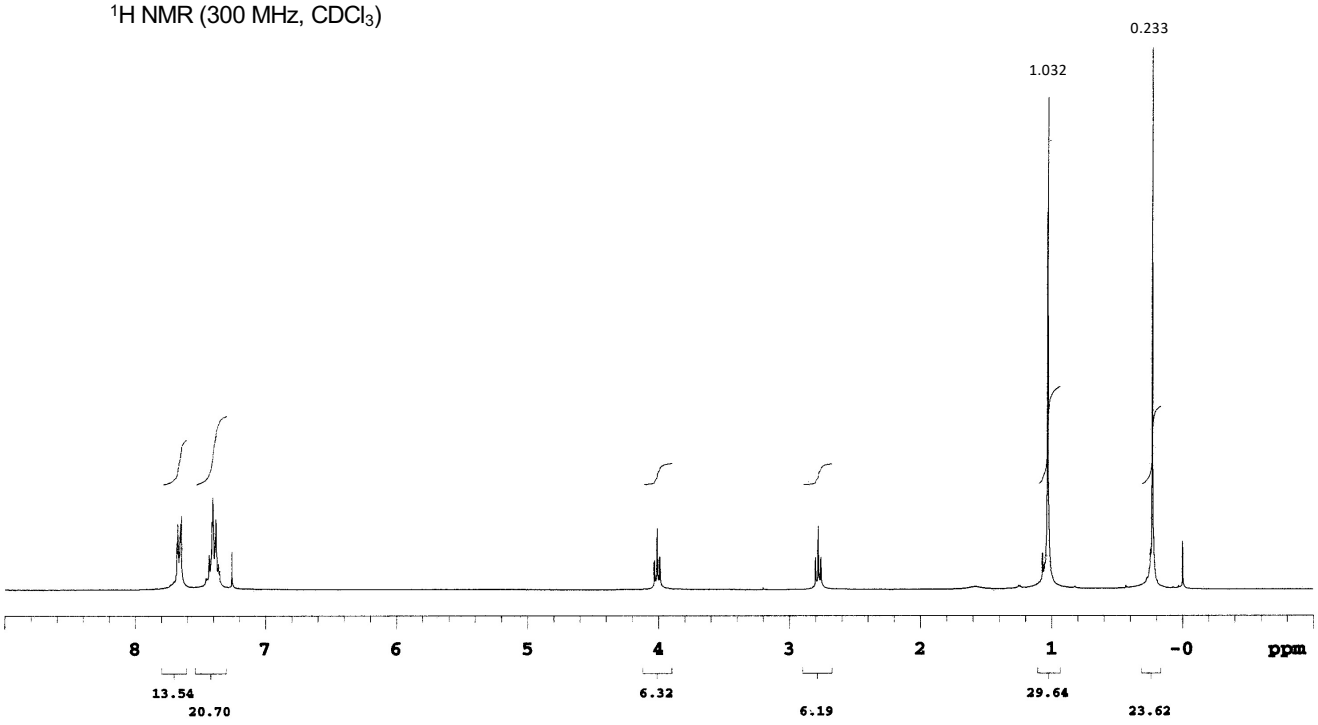
^{13}C–APT NMR (75 MHz, $CDCl_3$)

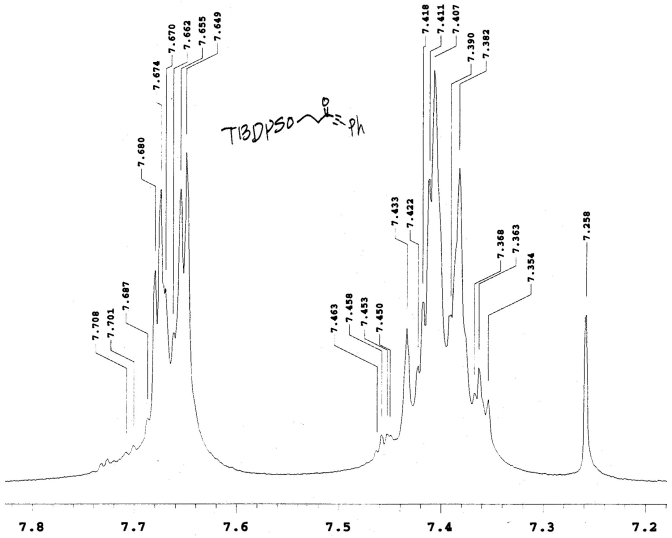


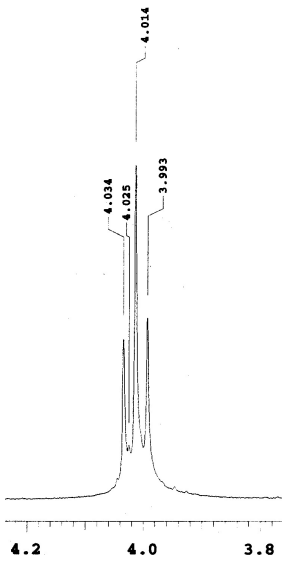


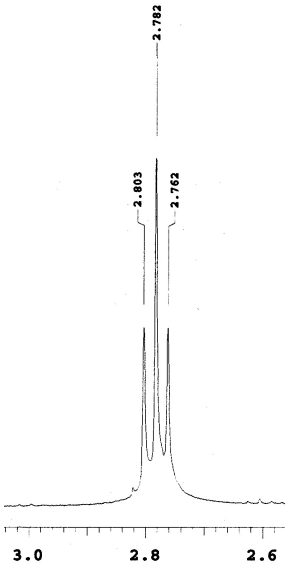
S2

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

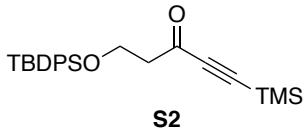




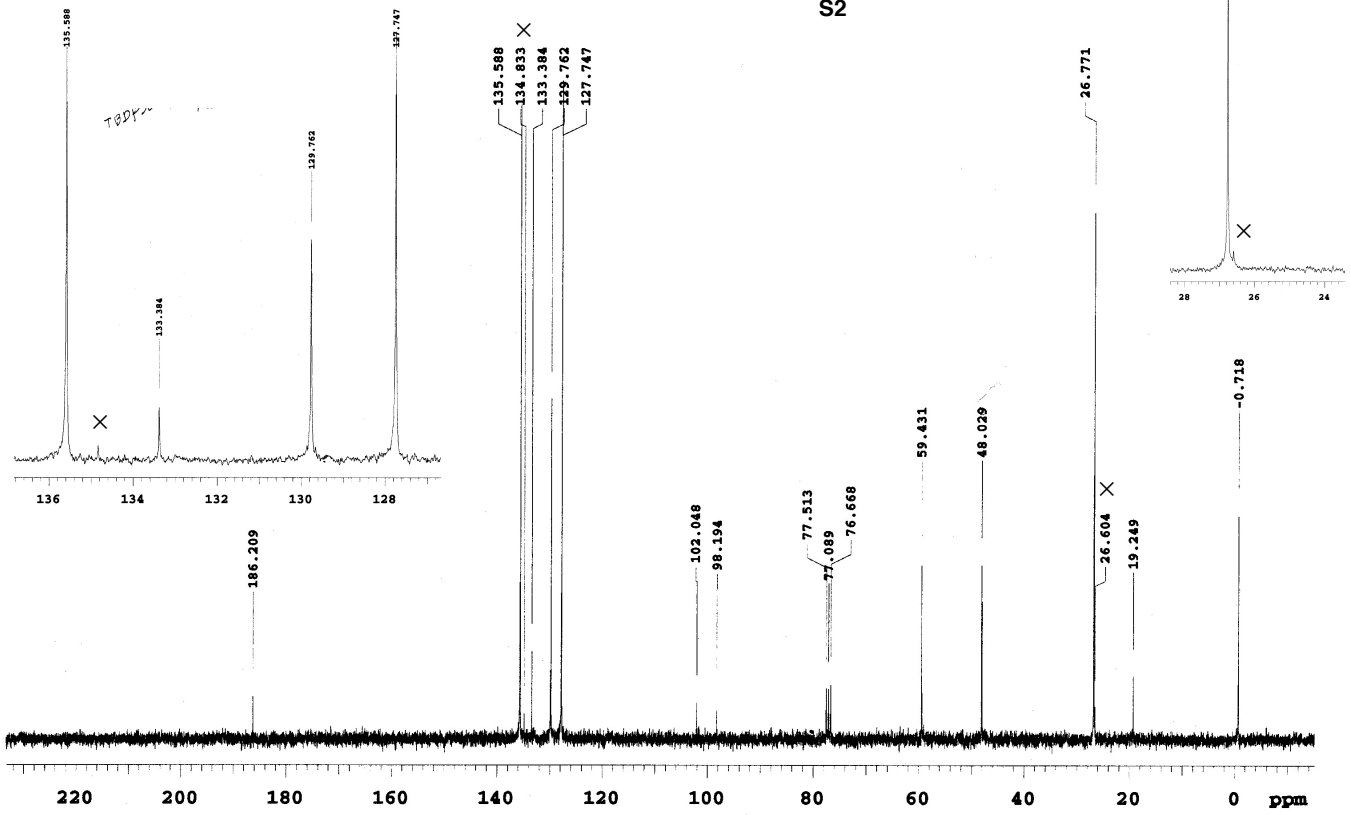




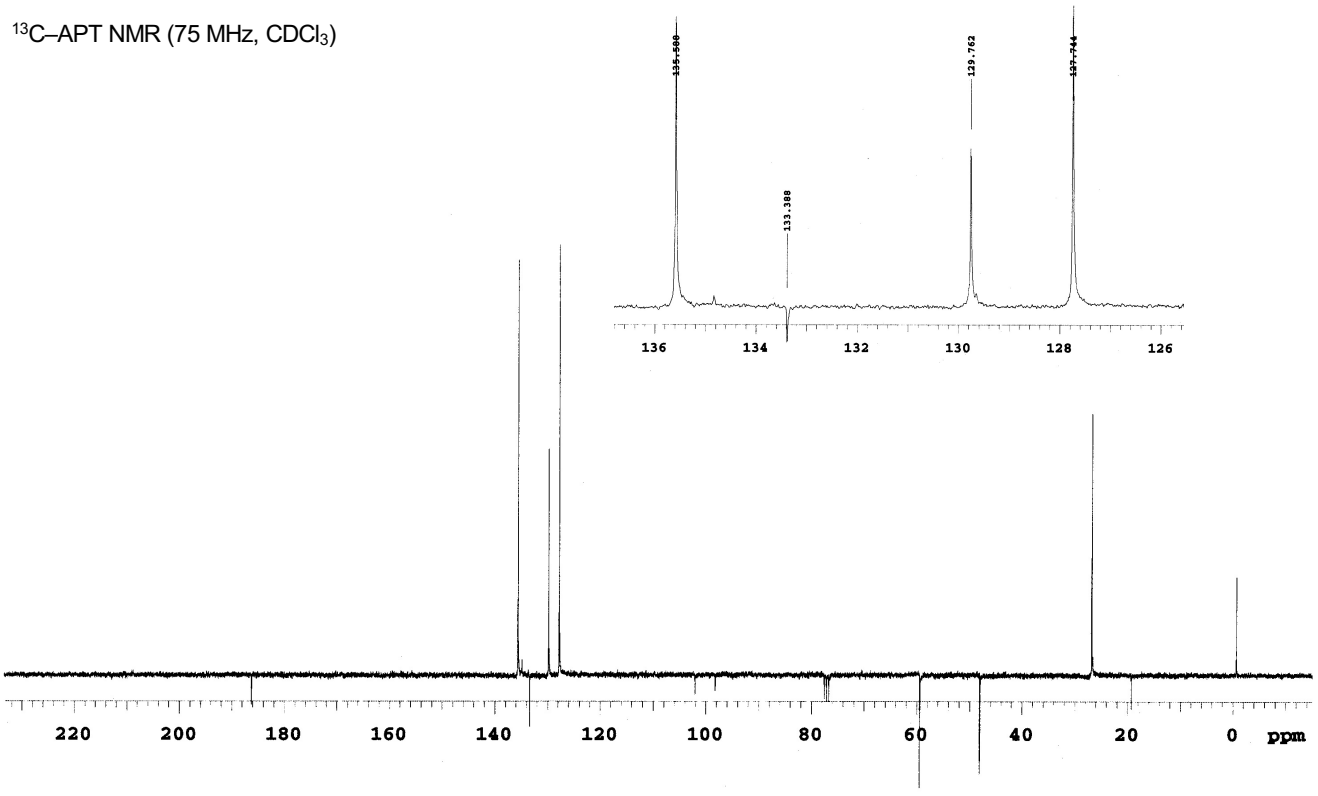
^{13}C NMR (75 MHz, $CDCl_3$)

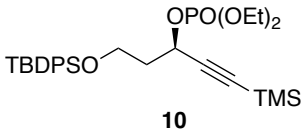


S2



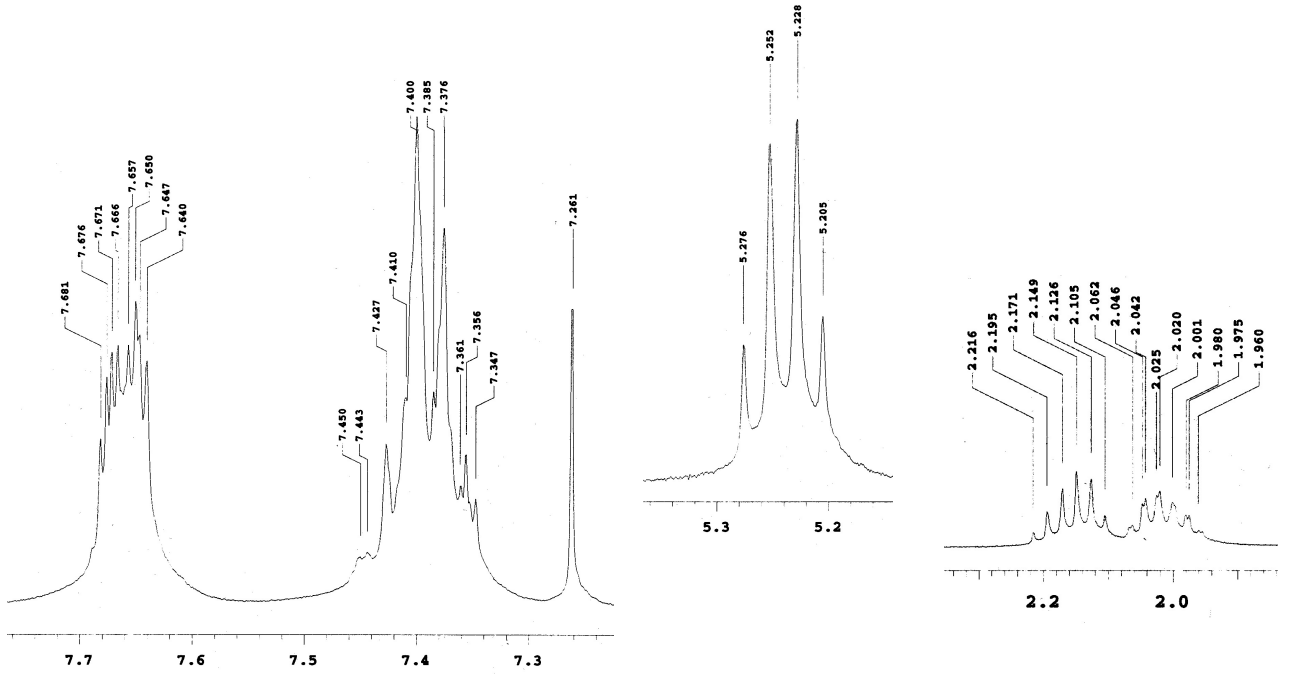
^{13}C–APT NMR (75 MHz, $CDCl_3$)



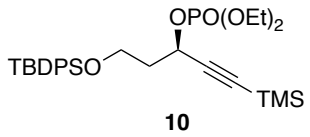


10

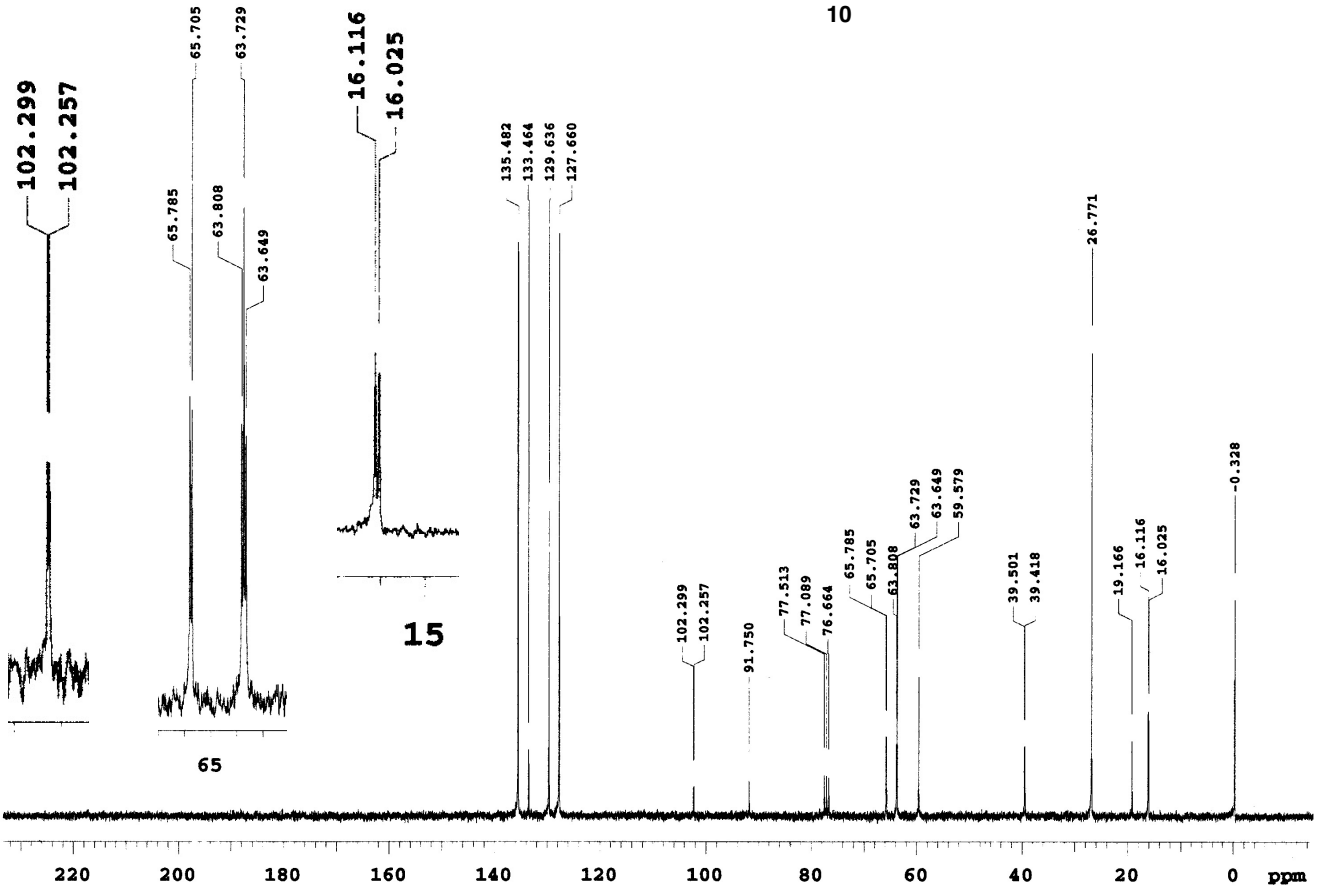
^{1}H NMR (300 MHz, $CDCl_3$)



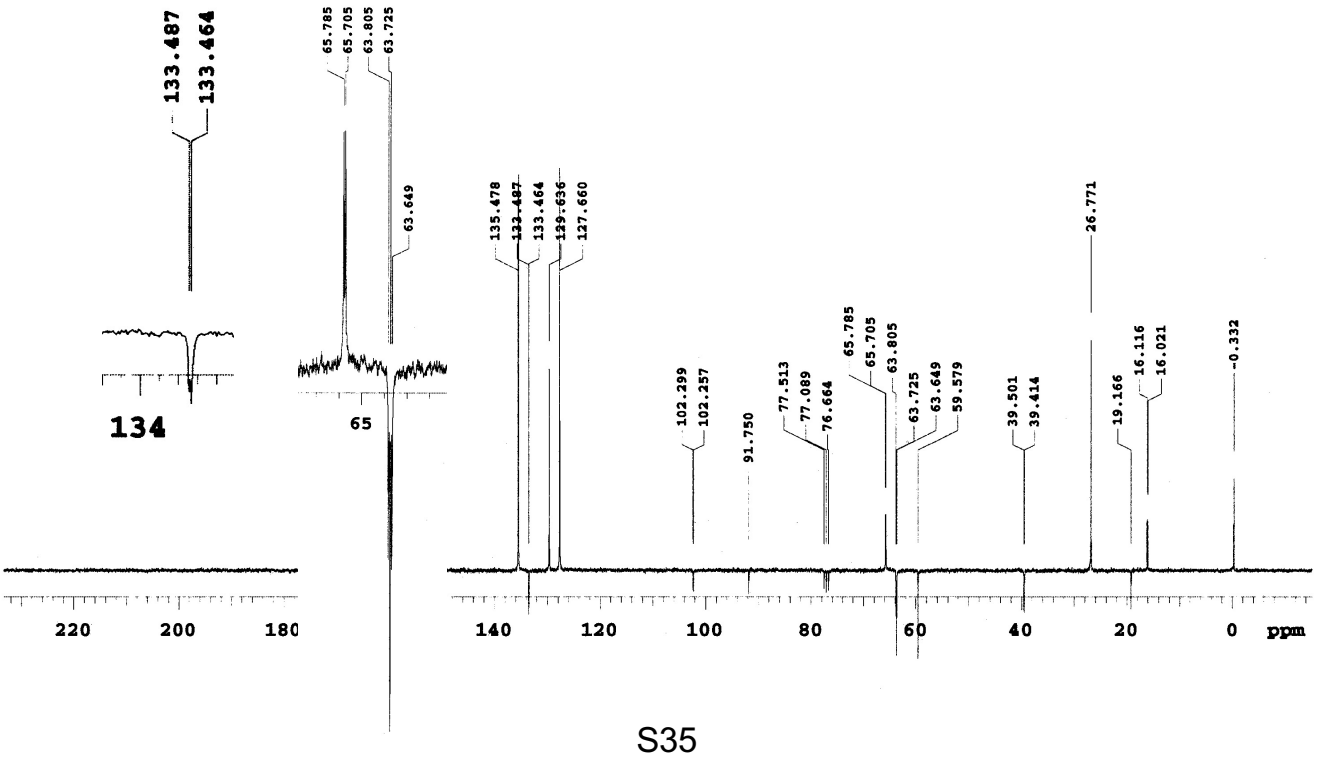
^{13}C NMR (75 MHz, $CDCl_3$)

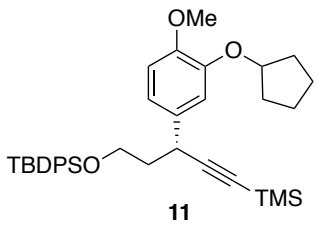


10



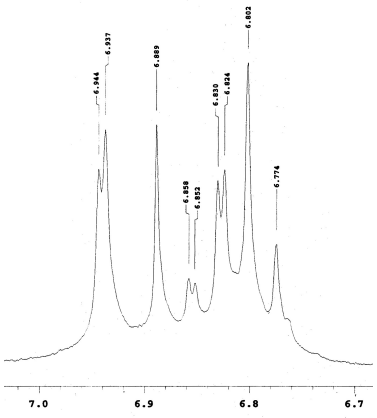
^{13}C–APT NMR (75 MHz, $CDCl_3$)

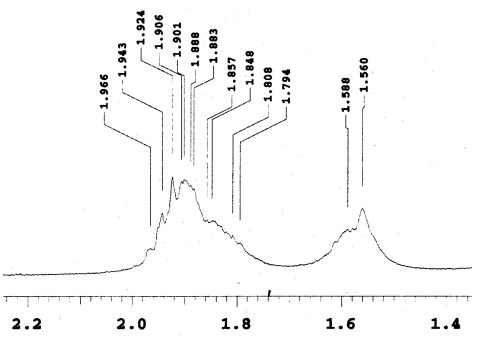


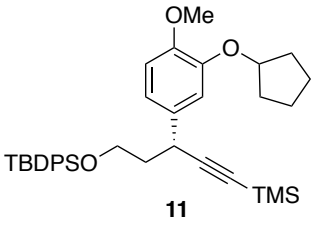


11

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



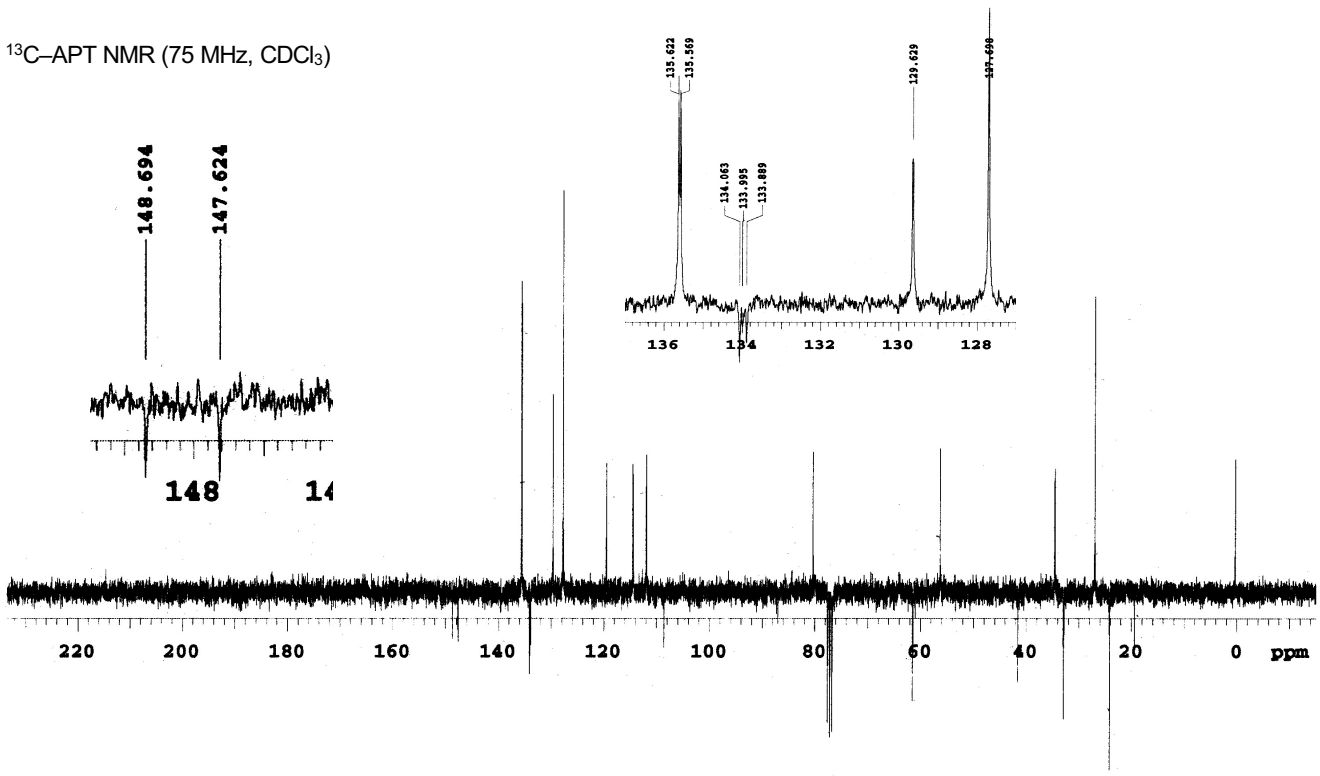


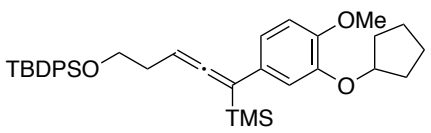


11

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

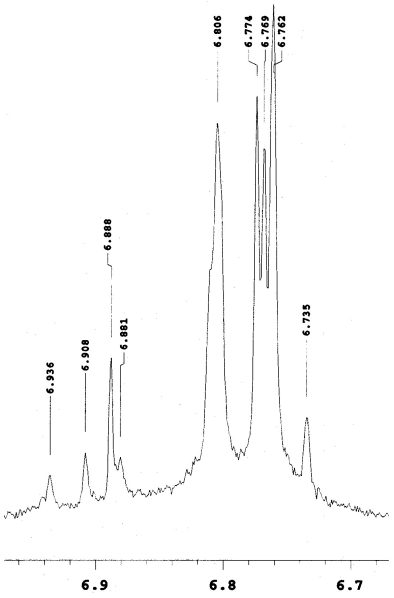
^{13}C–APT NMR (75 MHz, $CDCl_3$)

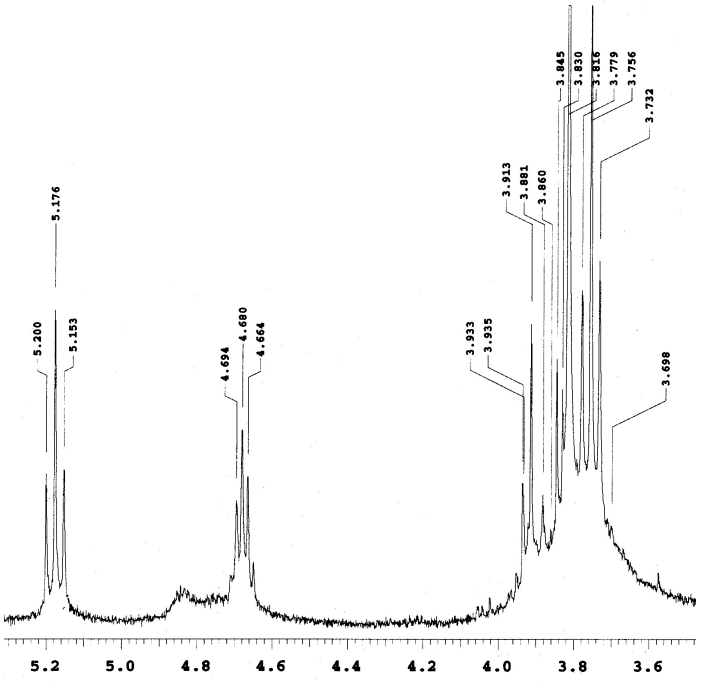


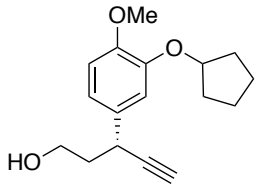


12

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

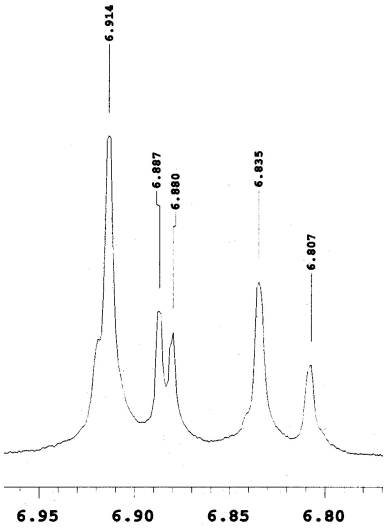


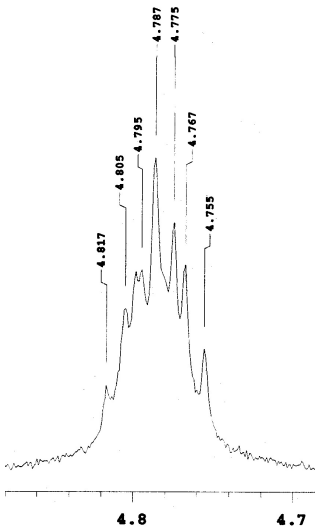


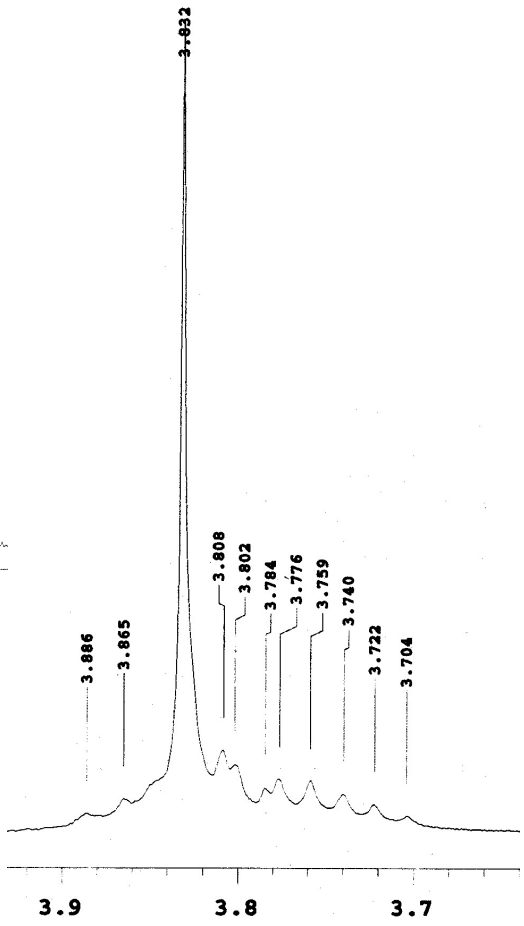


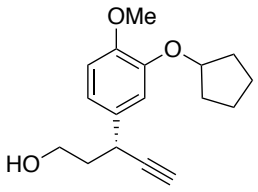
13

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



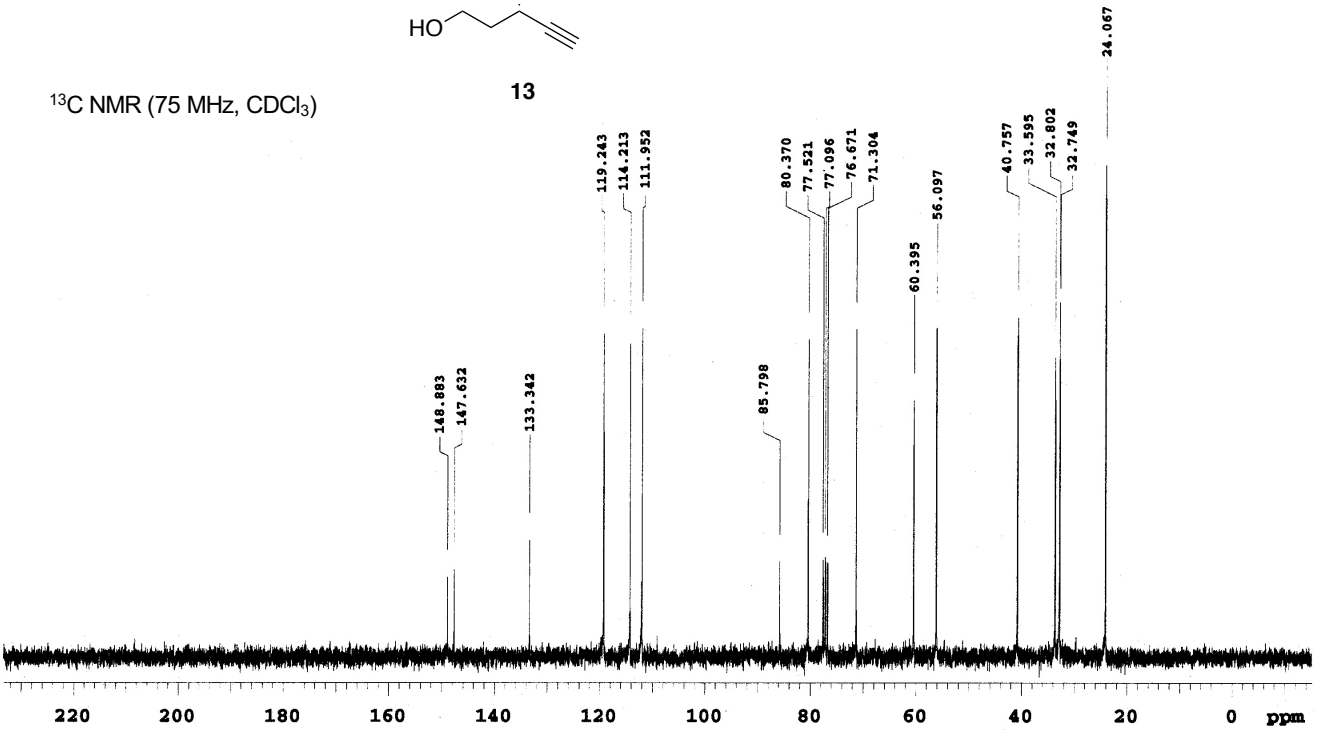




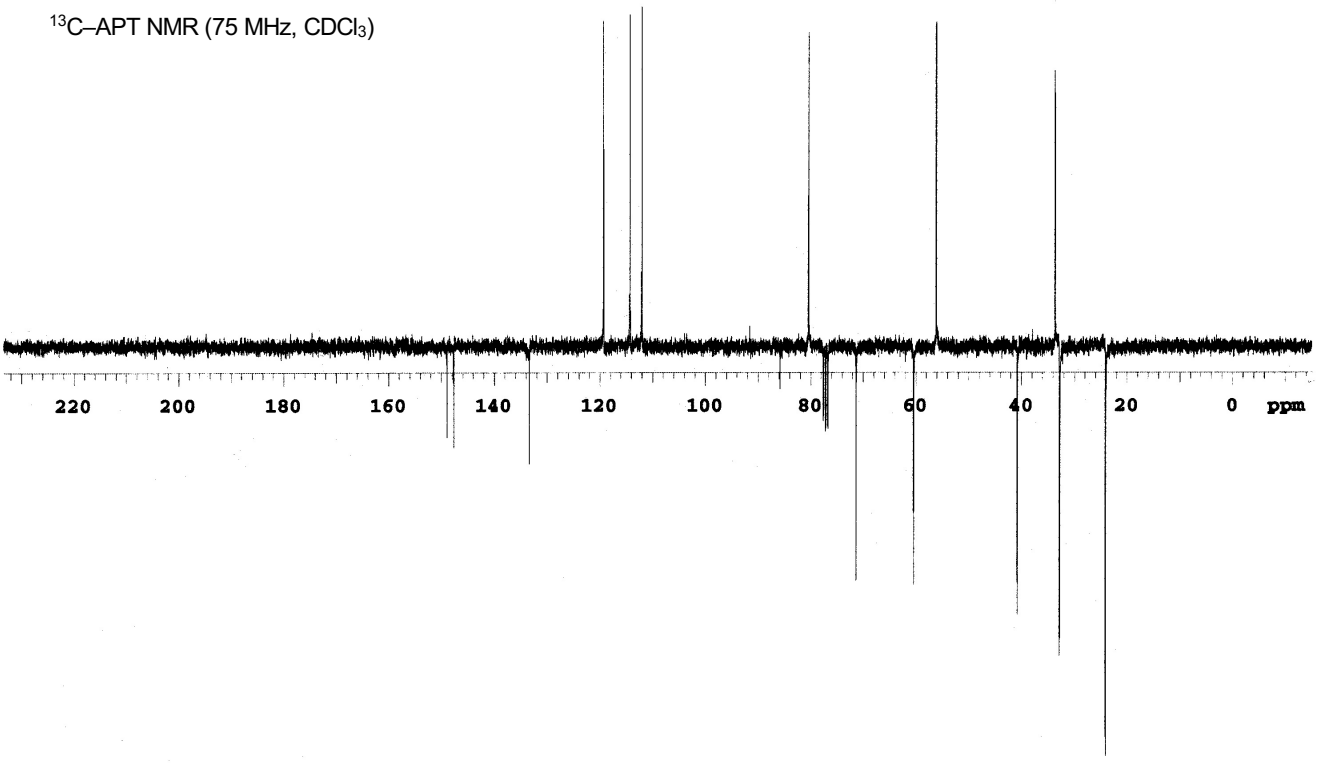


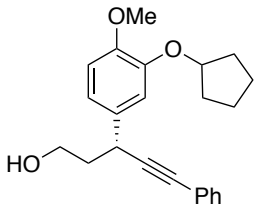
13

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



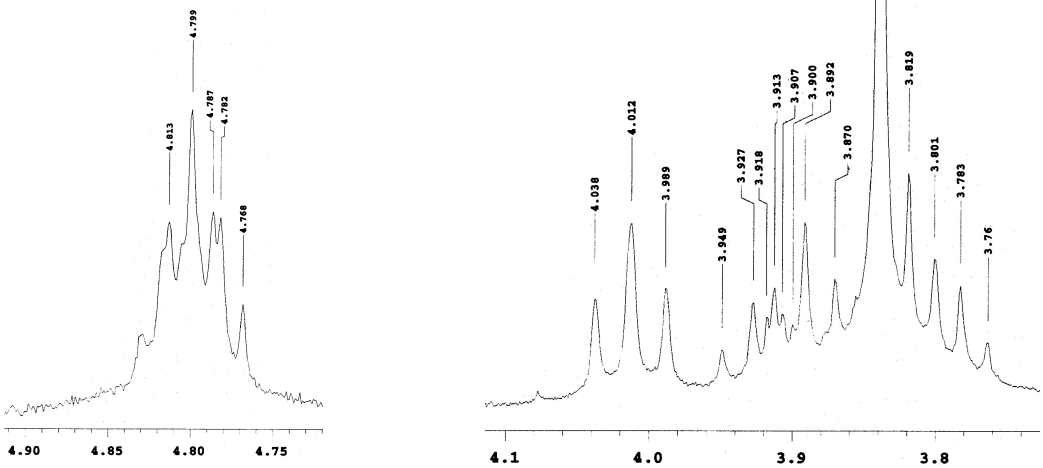
^{13}C–APT NMR (75 MHz, $CDCl_3$)



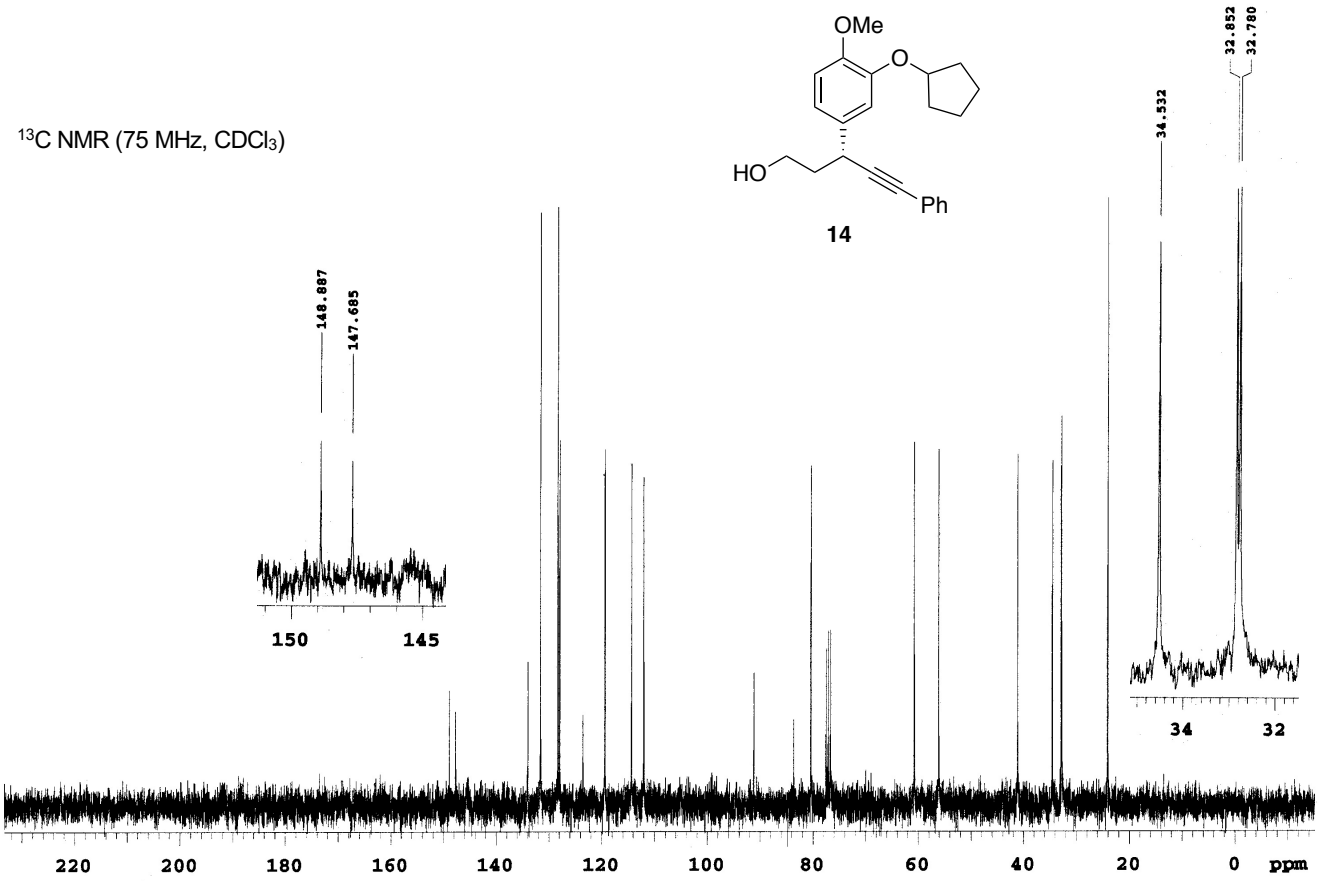


14

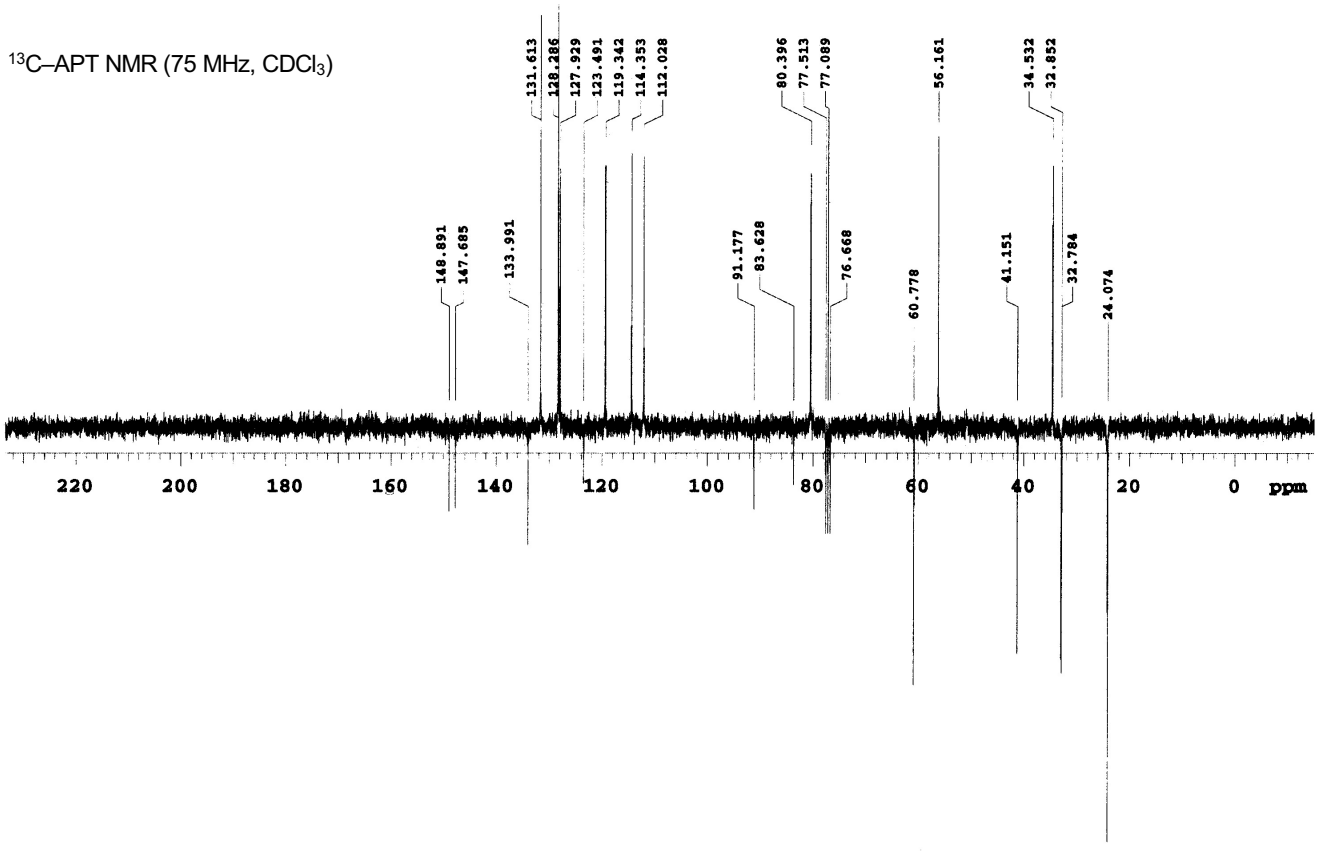
^{1}H NMR (300 MHz, $CDCl_3$)

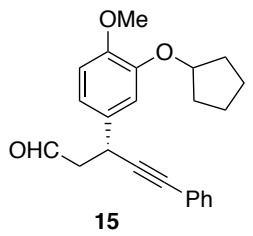


^{13}C NMR (75 MHz, $CDCl_3$)



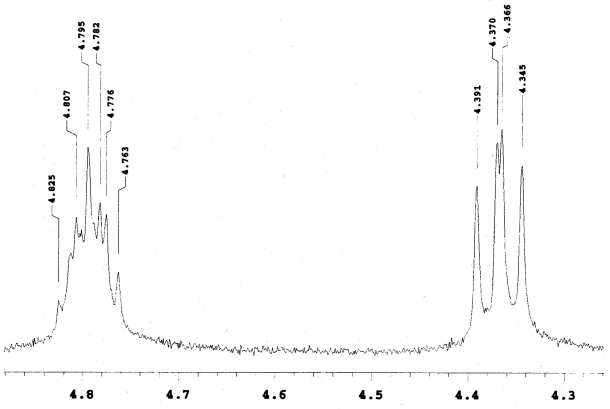
^{13}C–APT NMR (75 MHz, $CDCl_3$)

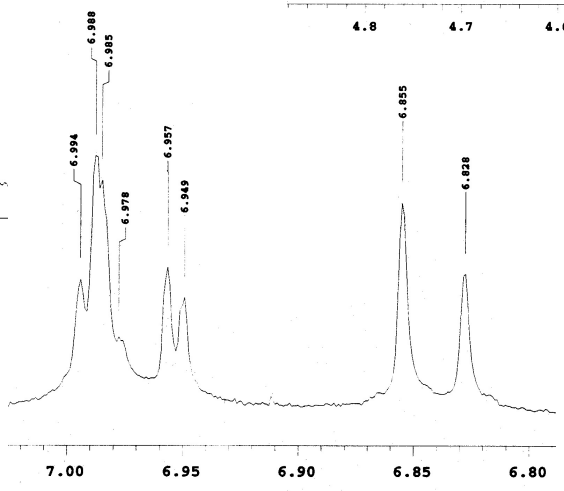


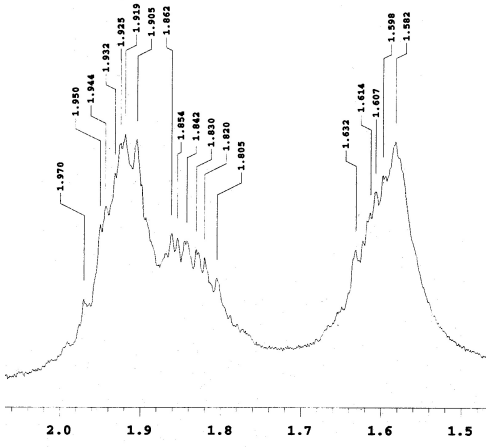


15

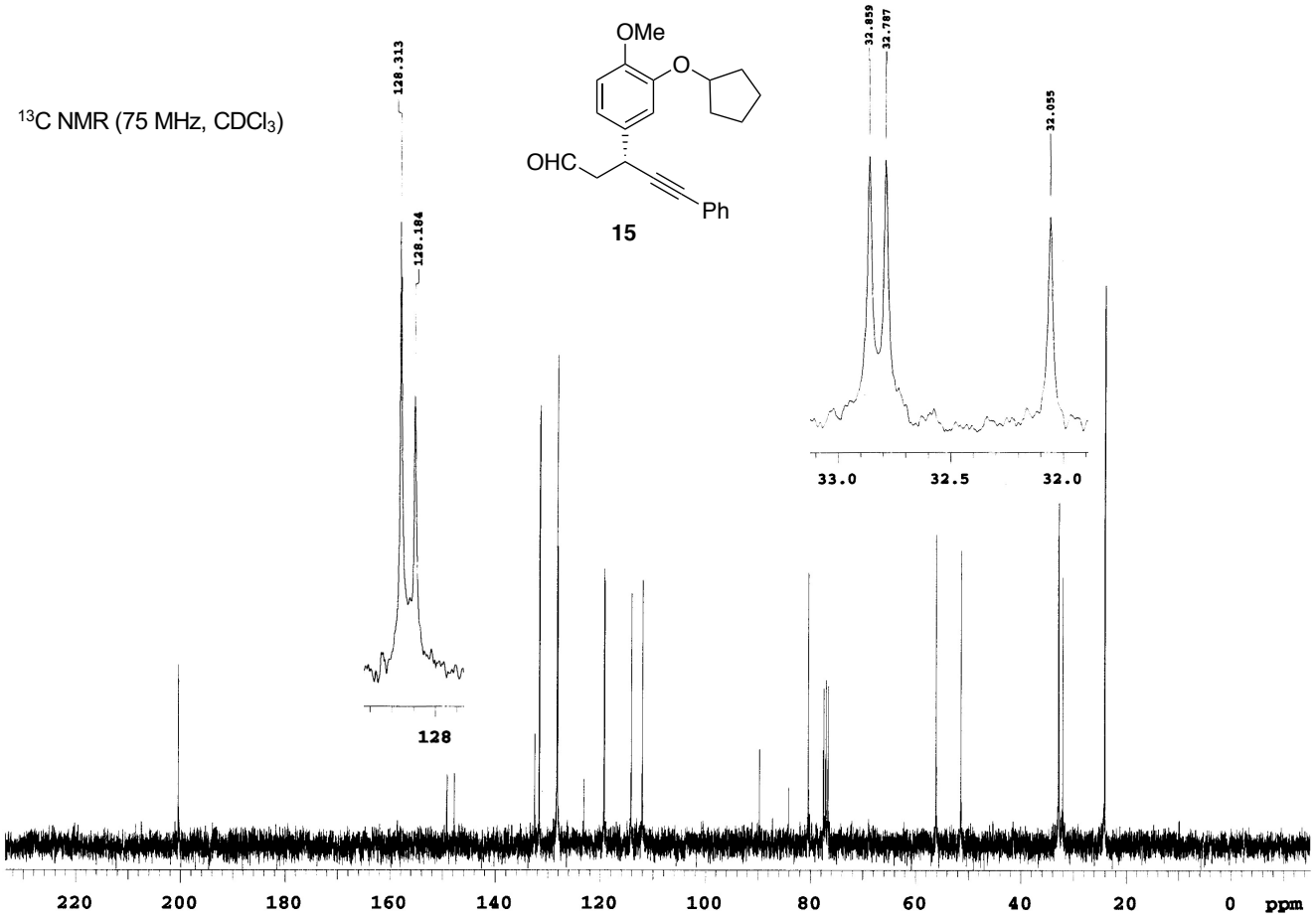
^{1}H NMR (300 MHz, $CDCl_3$)



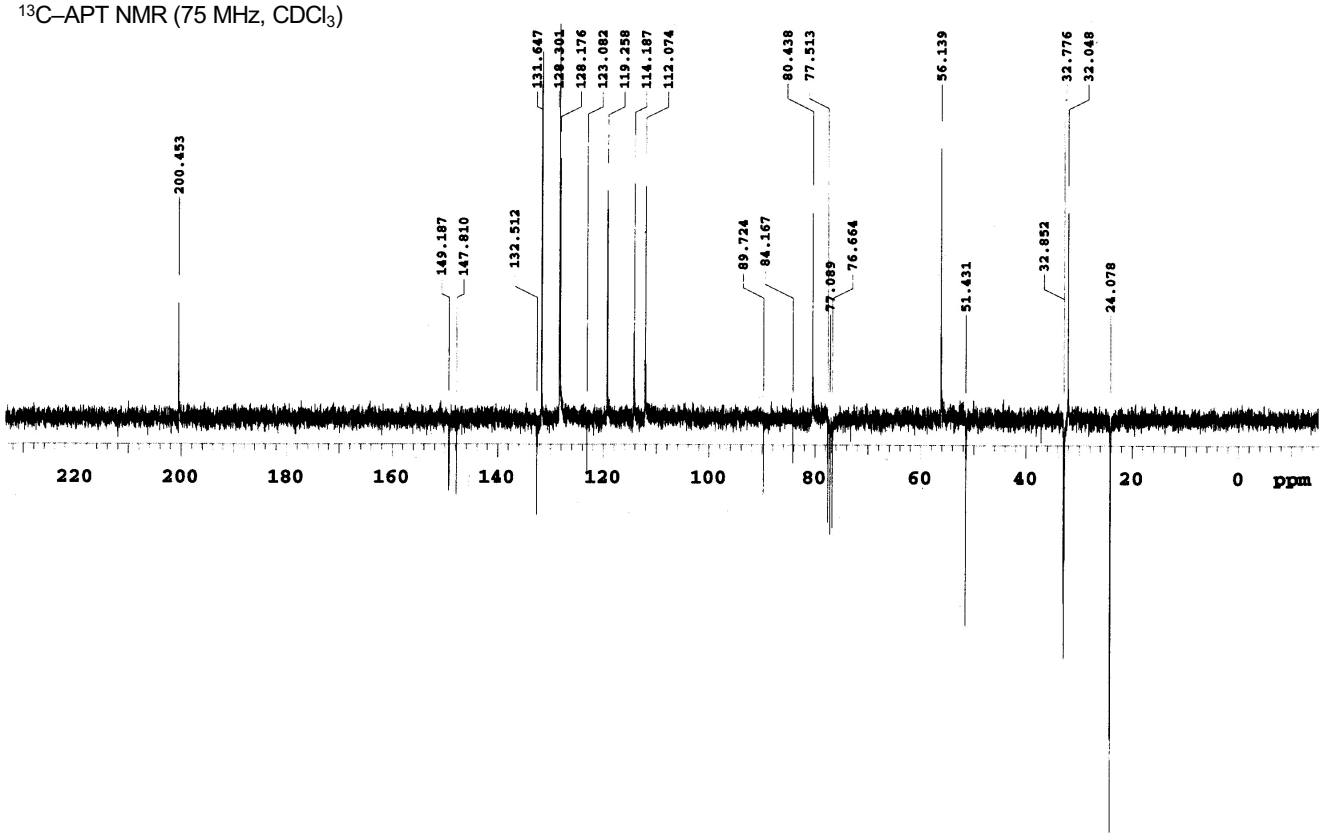


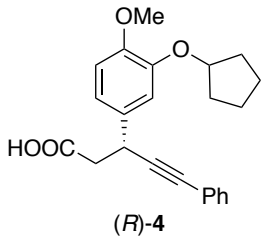


^{13}C NMR (75 MHz, $CDCl_3$)



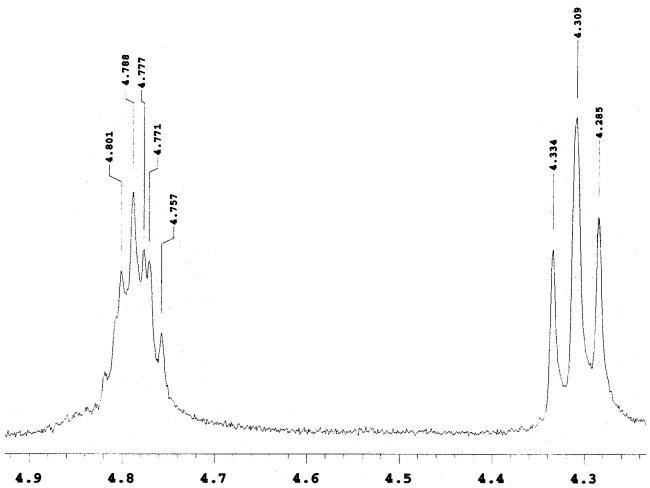
^{13}C–APT NMR (75 MHz, $CDCl_3$)

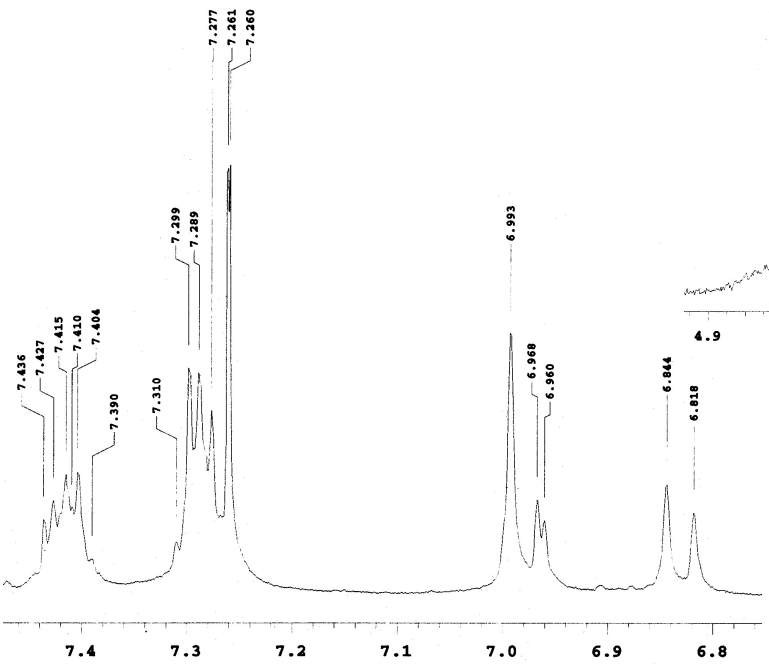


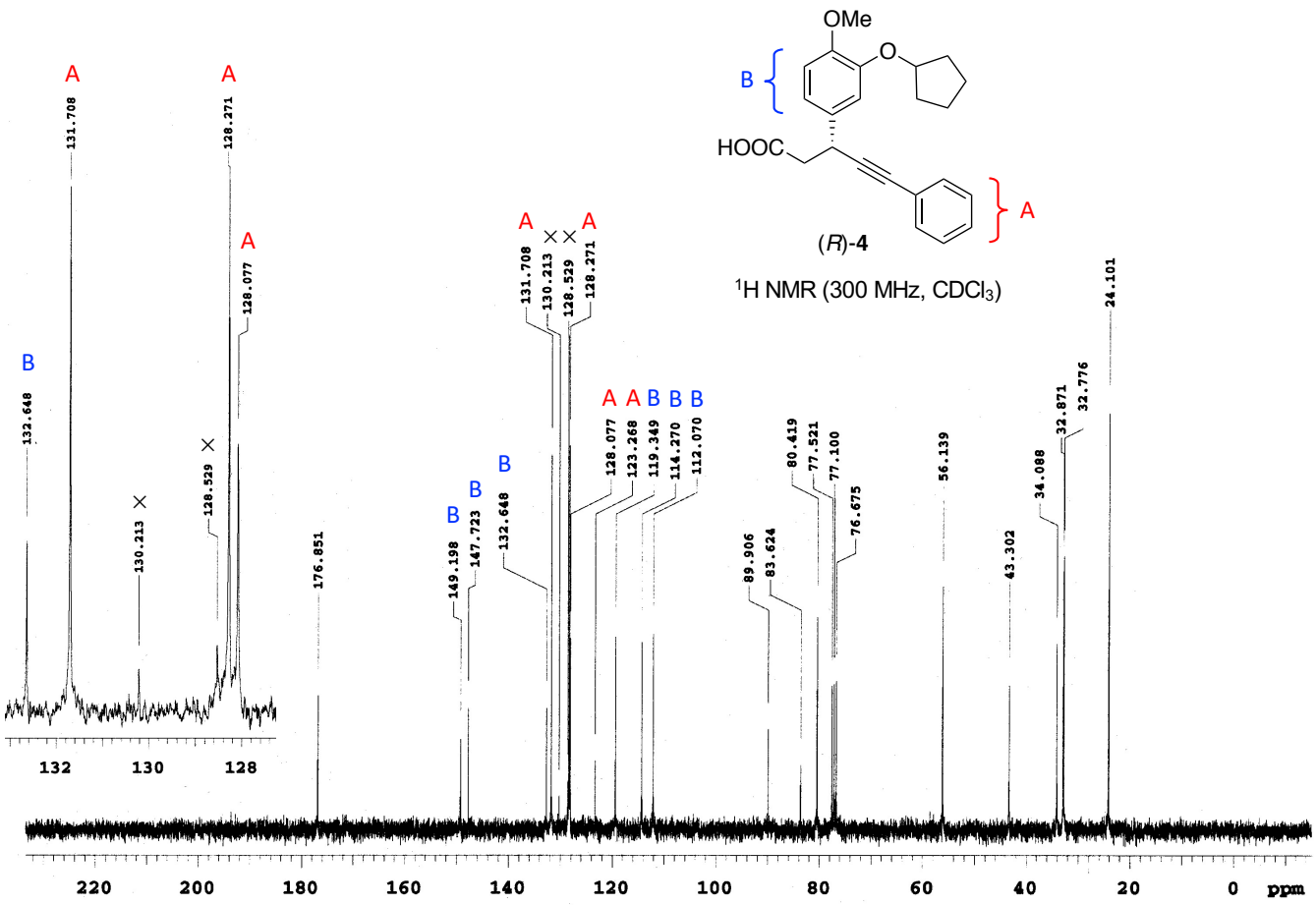


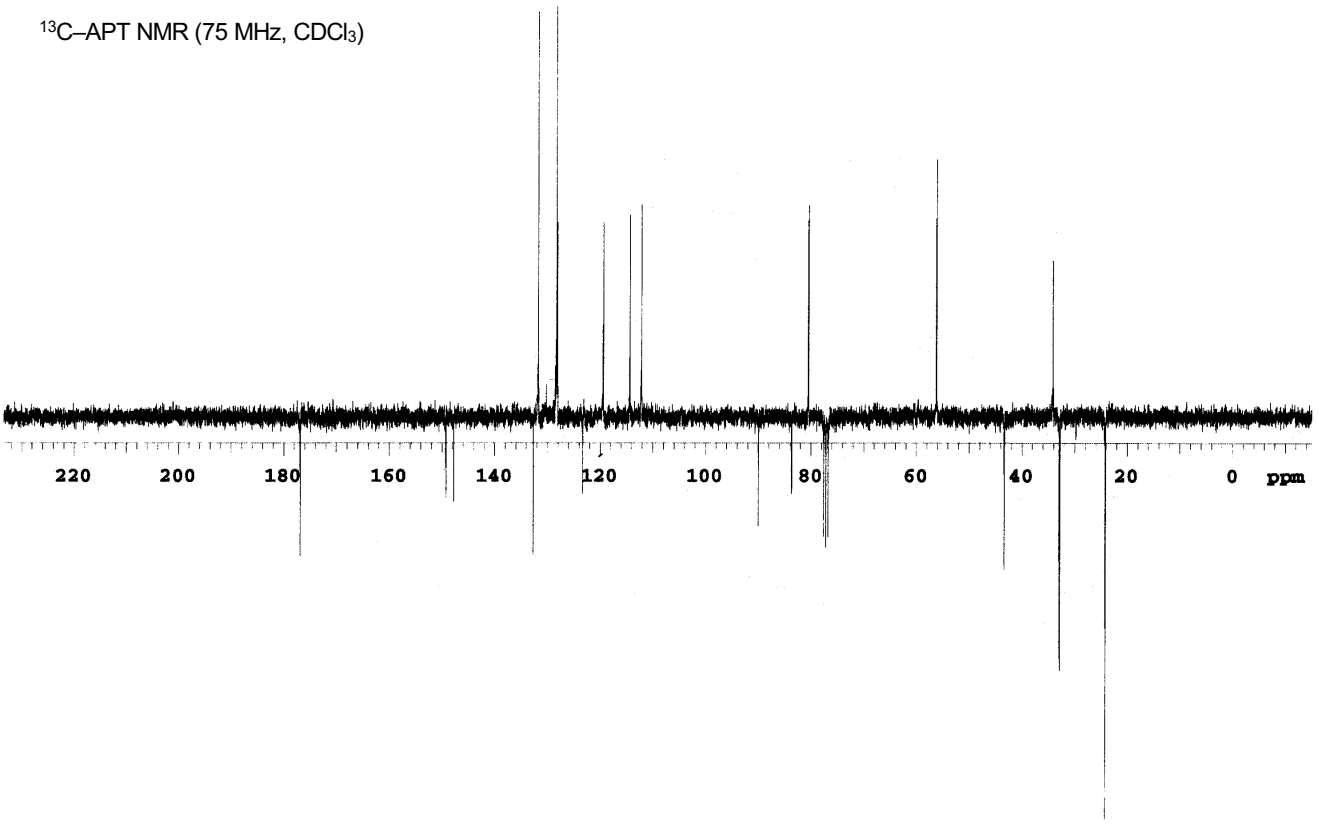
(*R*)-**4**

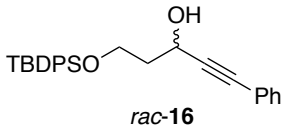
^{1}H NMR (300 MHz, $CDCl_3$)





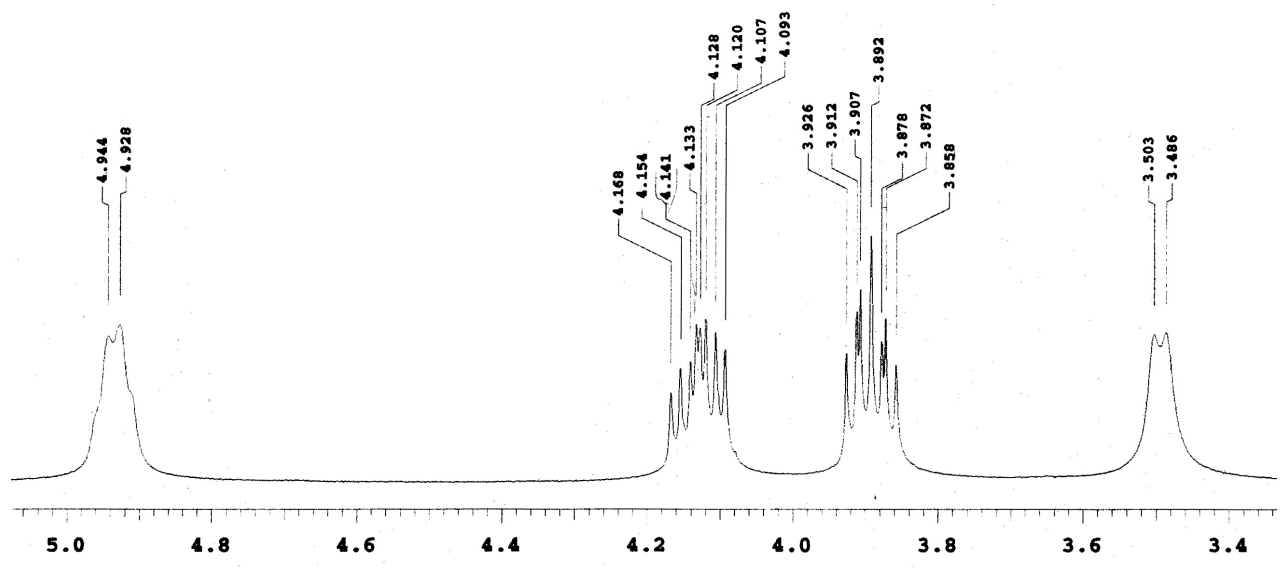

OMe
O
B
HOOC
A
(R)-4
1H NMR (300 MHz, CDCl3)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

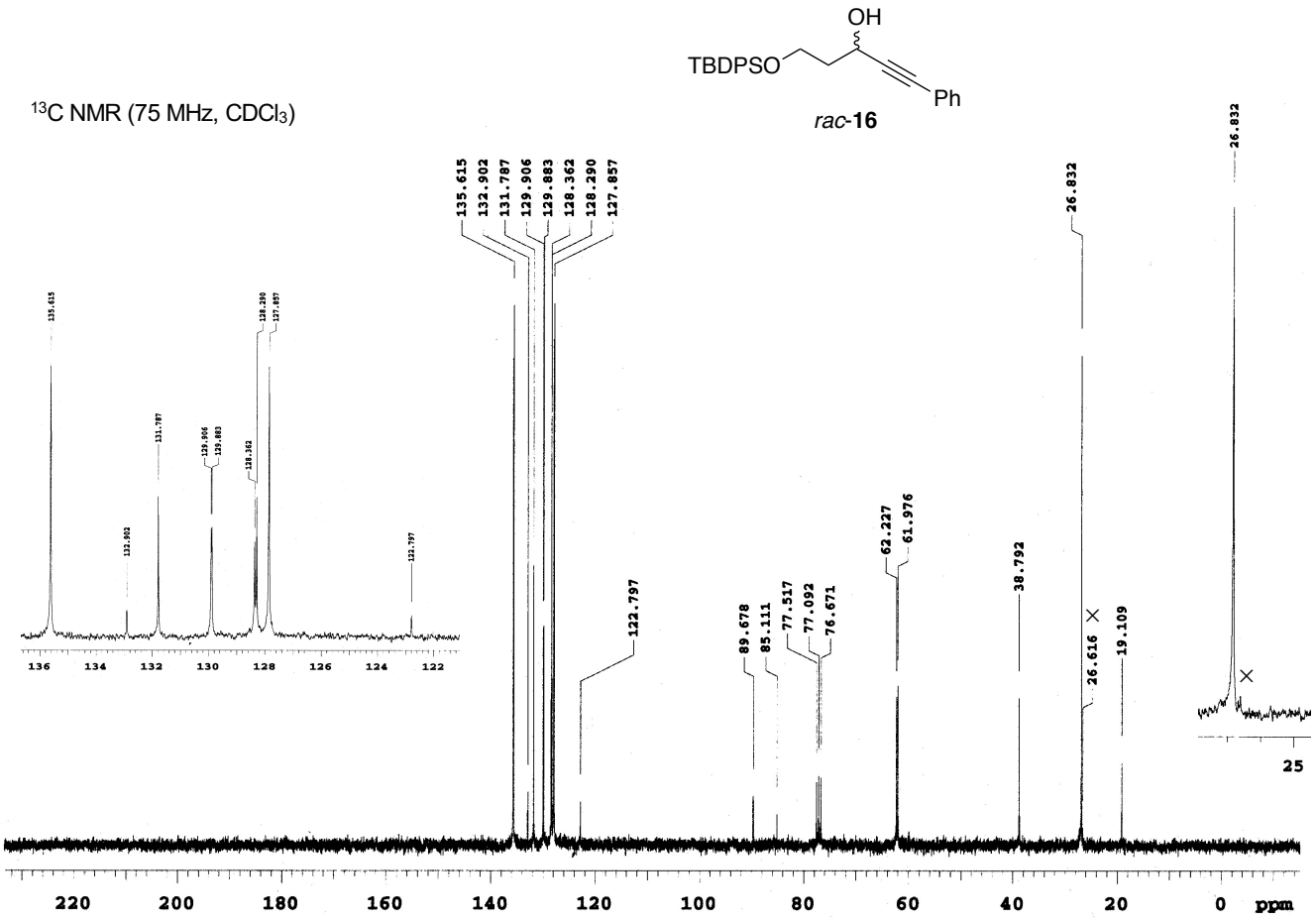

13C–APT NMR (75 MHz, CDCl3)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

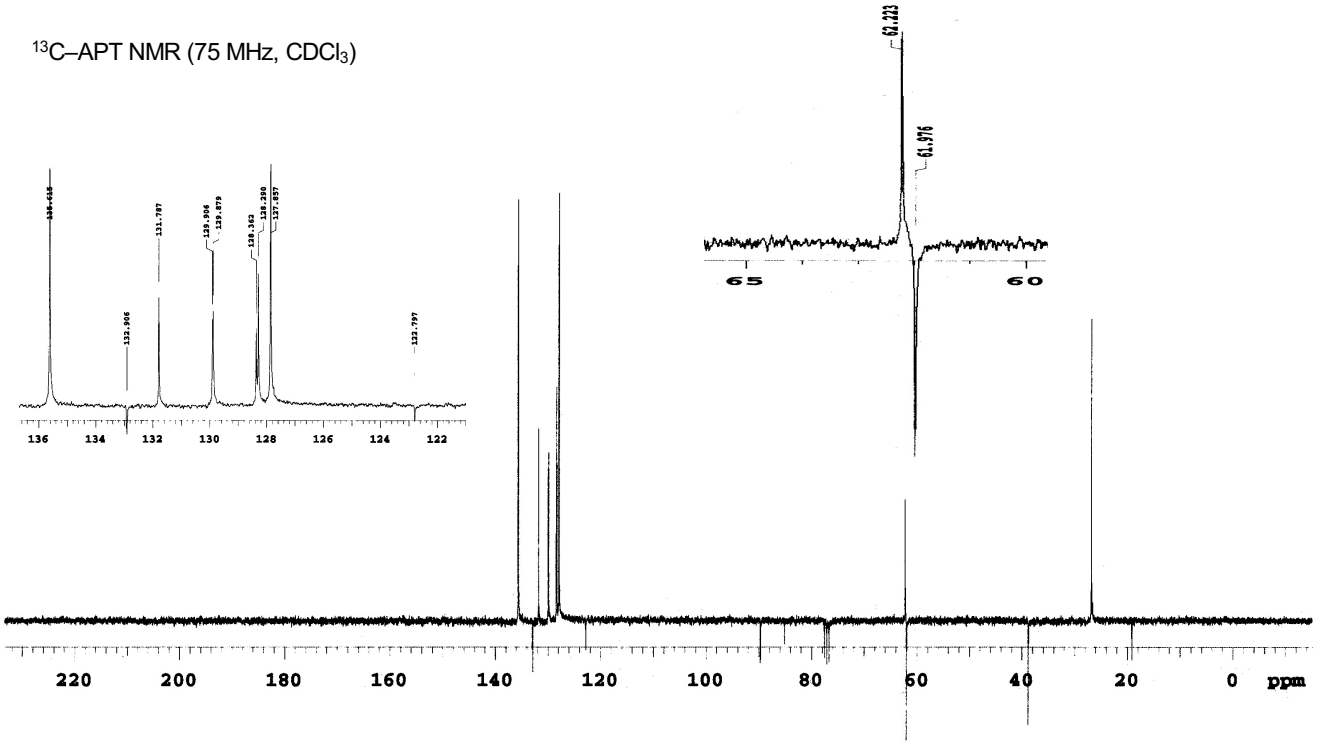


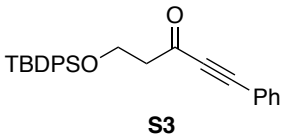
rac-**16**

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



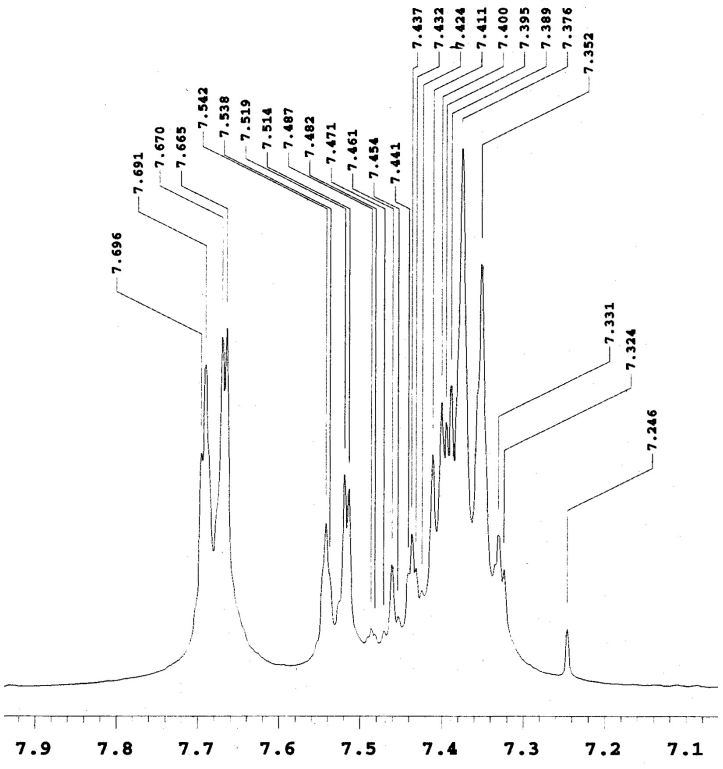

OH
TBDPSO
Ph
rac-16
13C NMR (75 MHz, CDCl3)
135.615
132.902
131.787
129.906
129.883
128.362
128.290
127.857
122.797
89.678
85.111
77.517
77.092
76.671
62.227
61.976
38.792
26.832
26.616
19.109
ppm


13C–APT NMR (75 MHz, CDCl3)
ppm

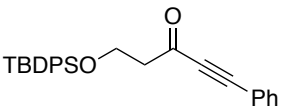


S3

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

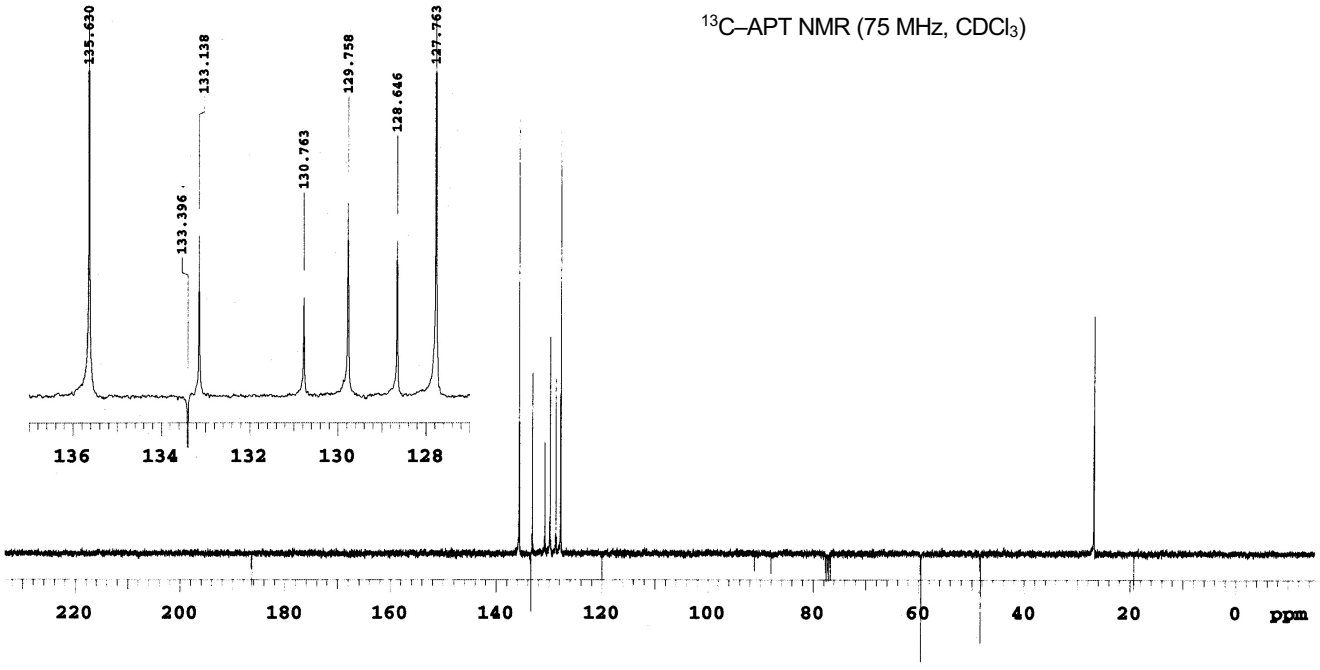


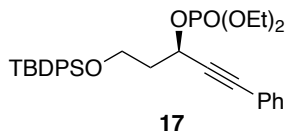
^{13}C NMR (75 MHz, $CDCl_3$)



S3

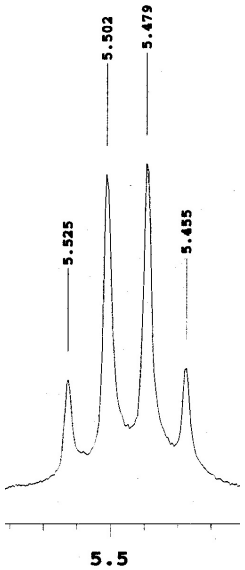
^{13}C–APT NMR (75 MHz, $CDCl_3$)

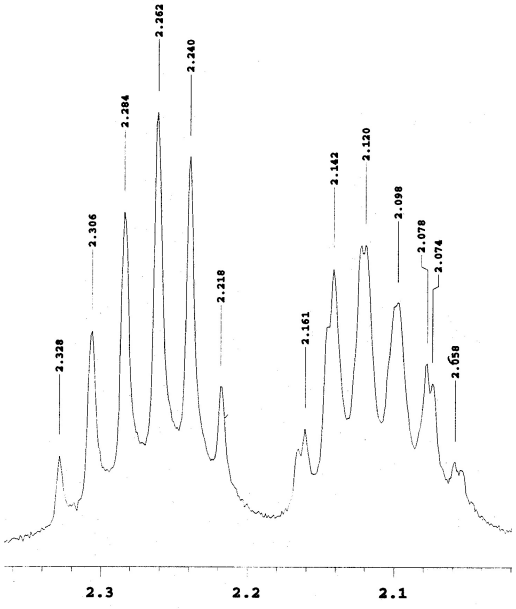


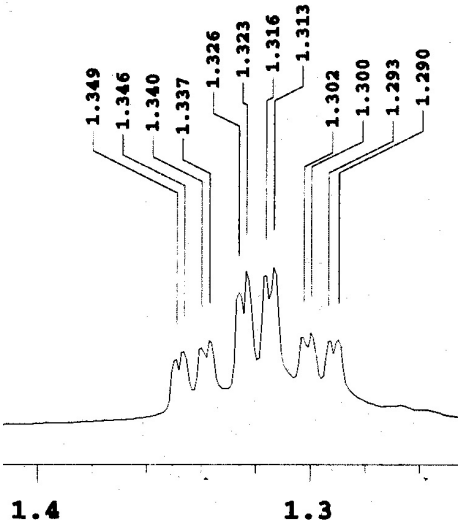


17

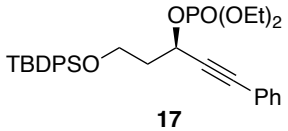
^{1}H NMR (300 MHz, $CDCl_3$)



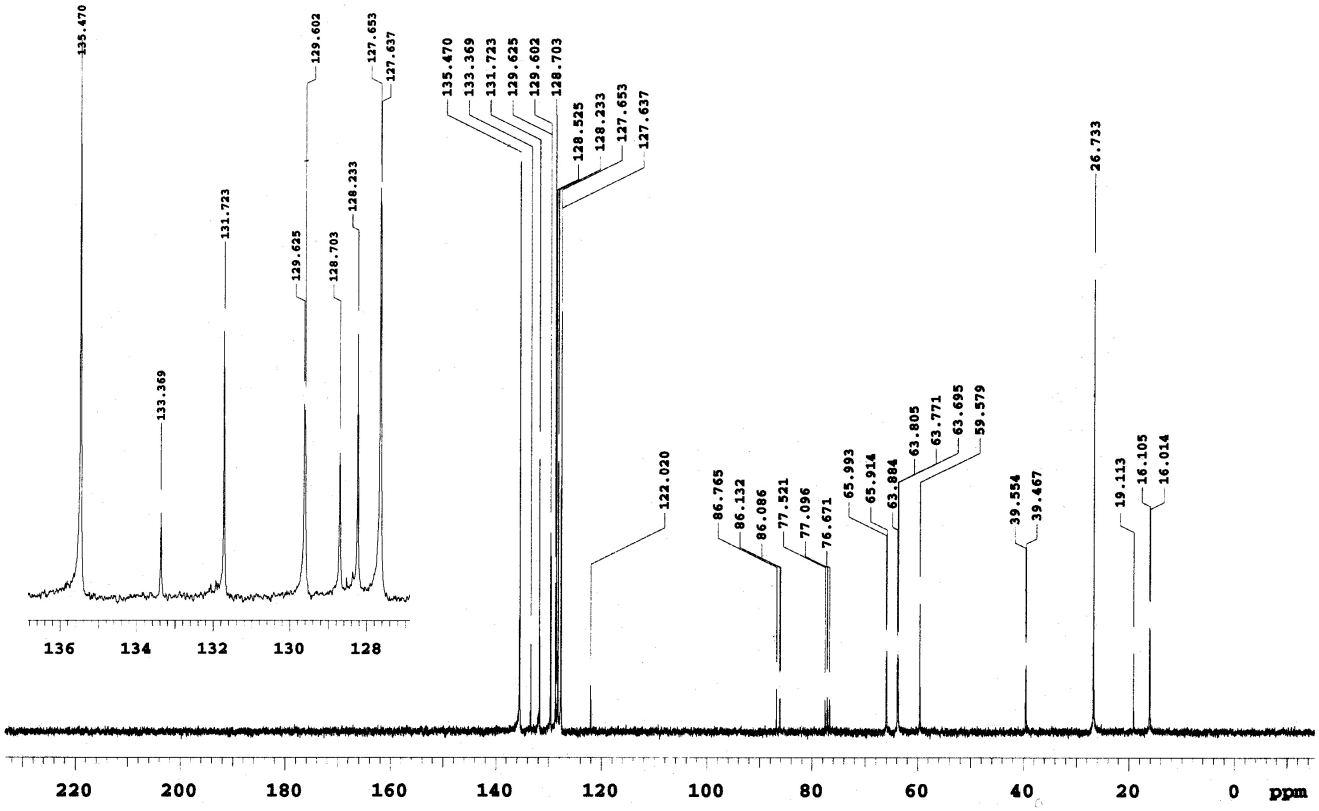




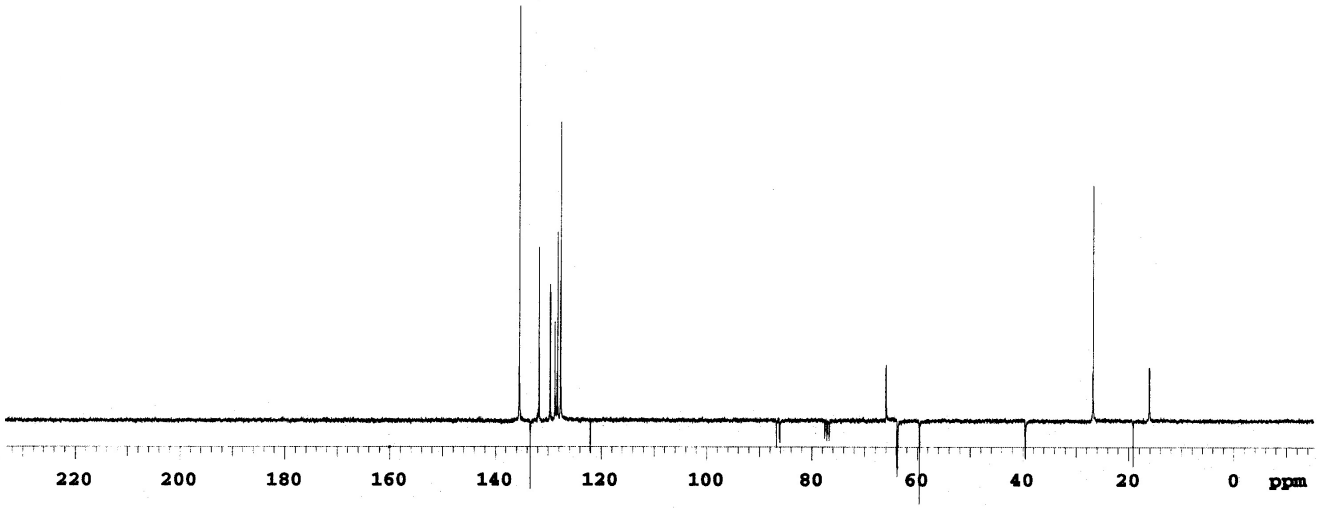
^{13}C NMR (75 MHz, $CDCl_3$)

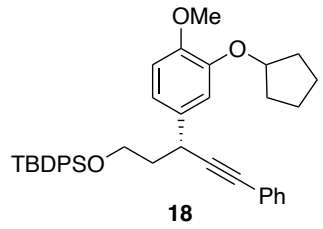


17



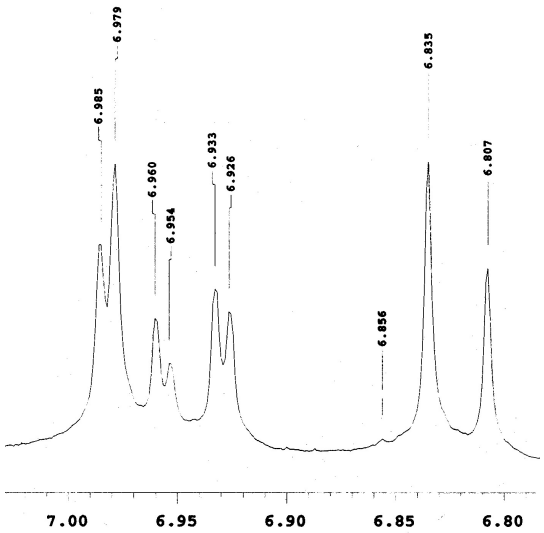
^{13}C–APT NMR (75 MHz, $CDCl_3$)

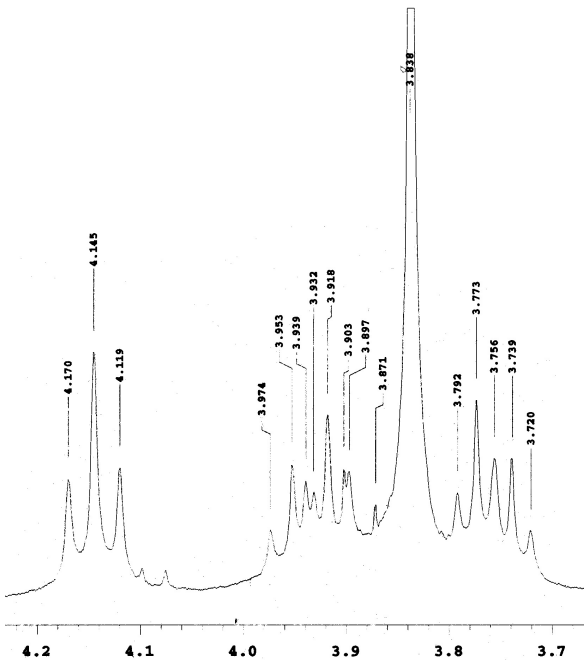




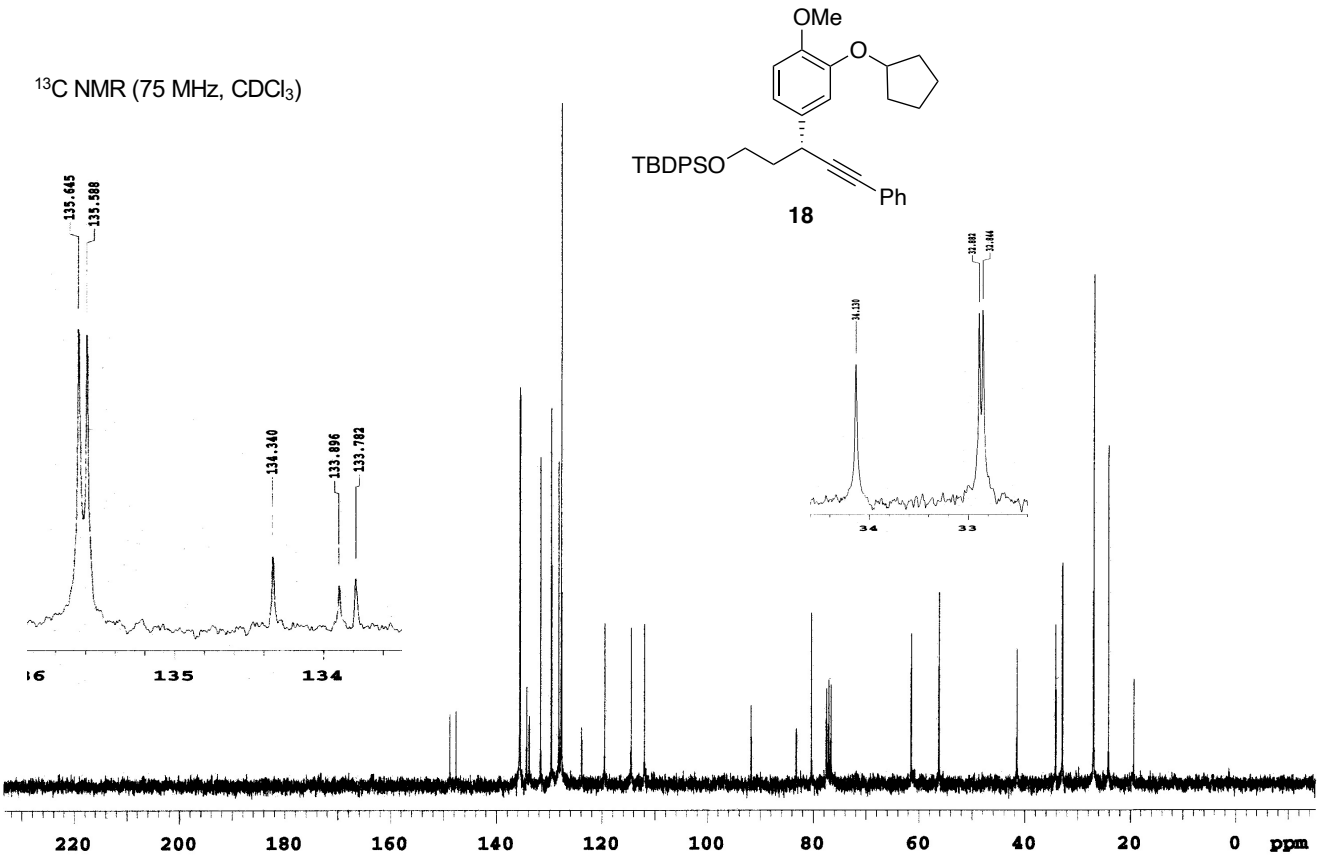
18

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

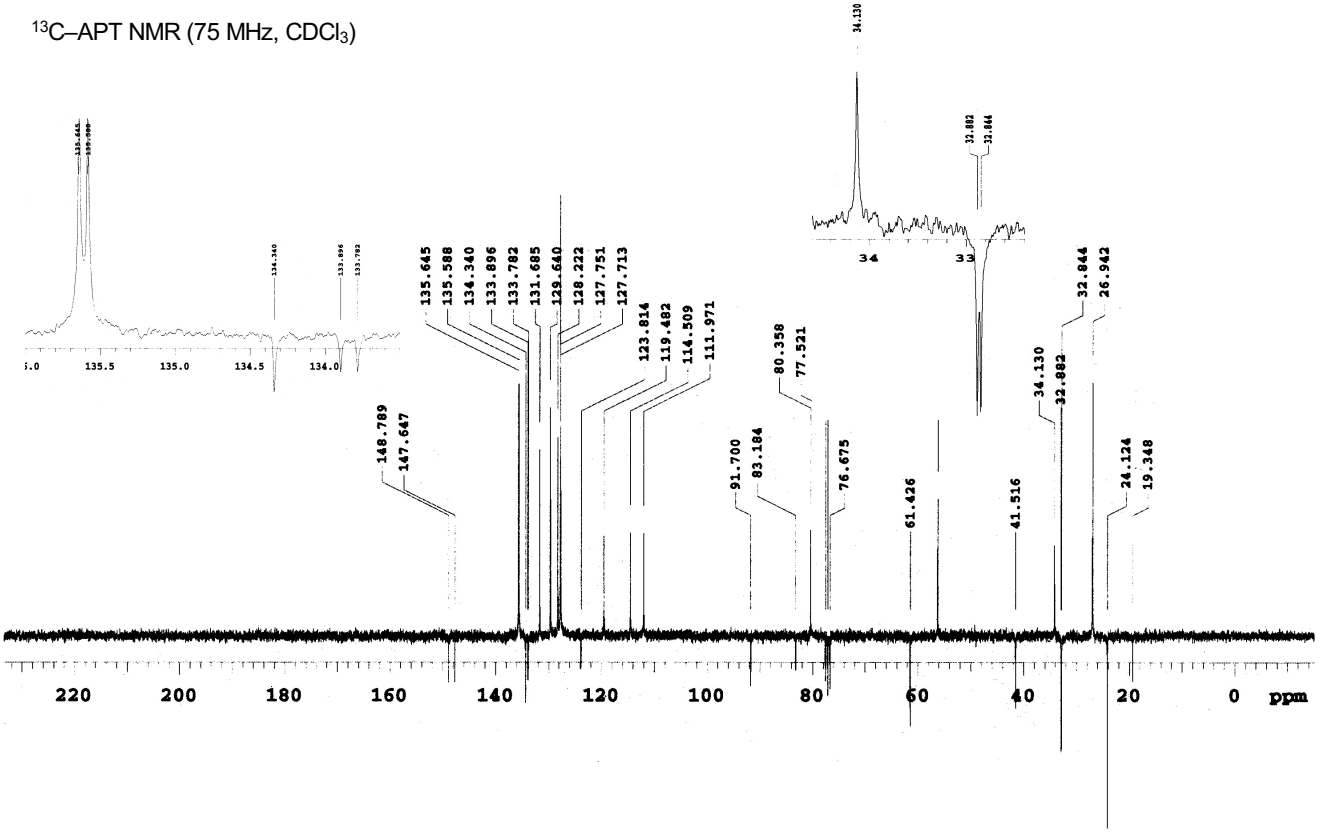


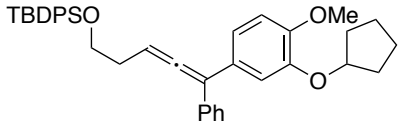


^{13}C NMR (75 MHz, $CDCl_3$)



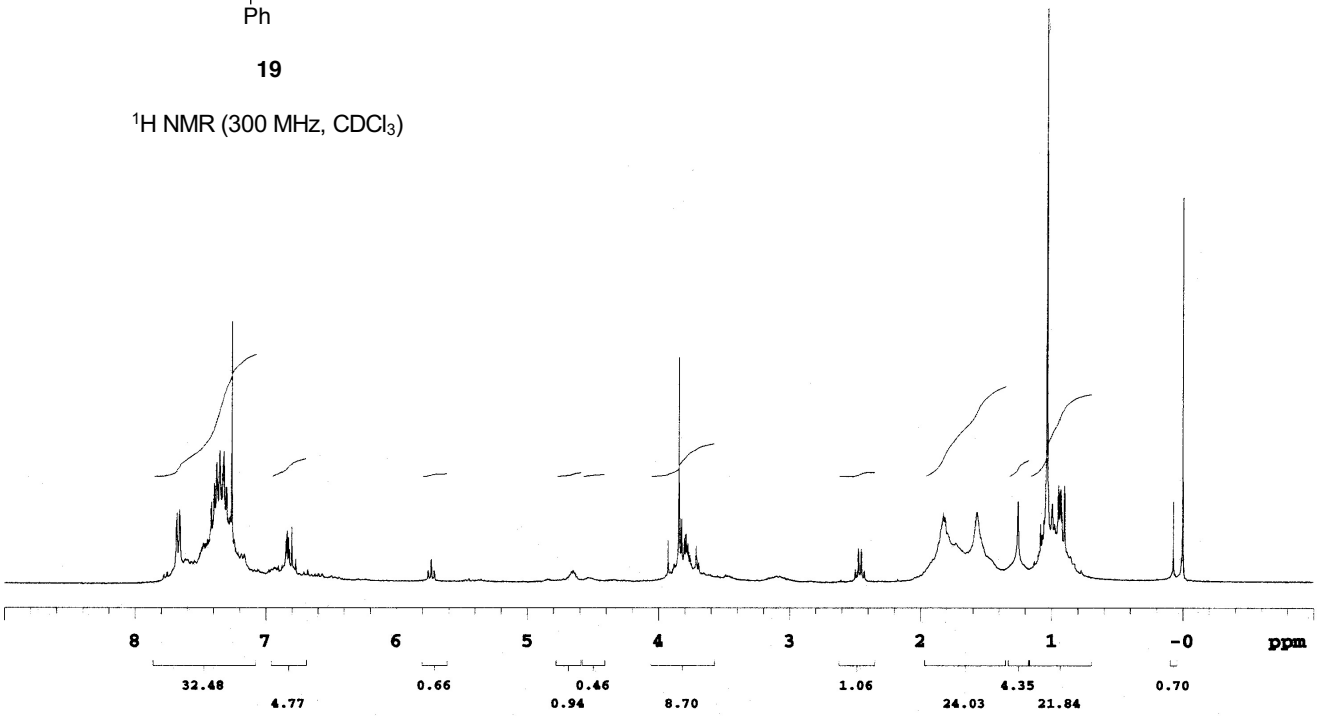
^{13}C–APT NMR (75 MHz, $CDCl_3$)

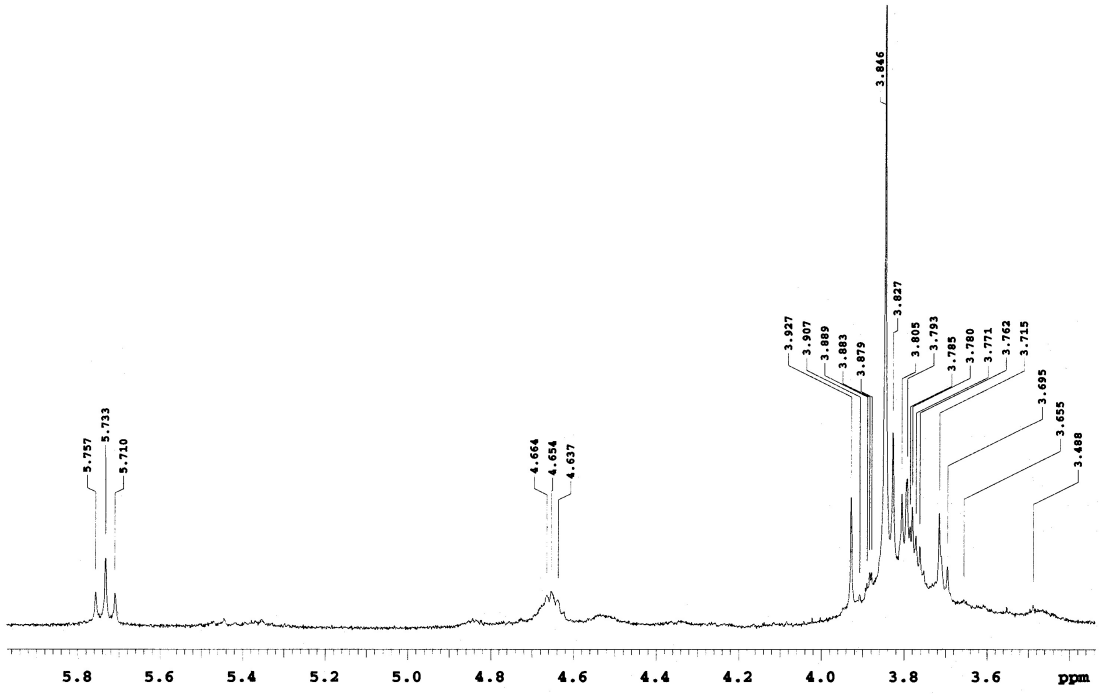


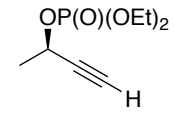


19

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

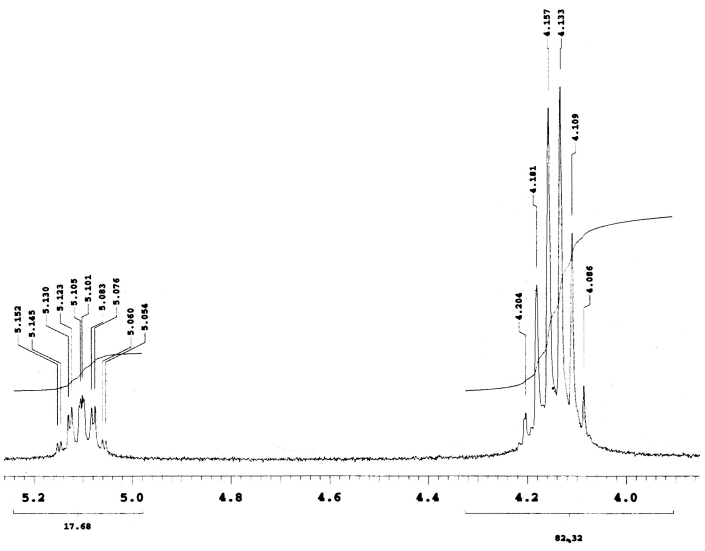


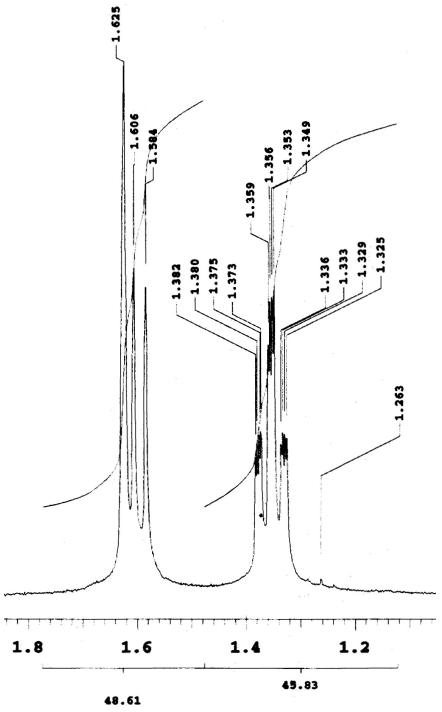


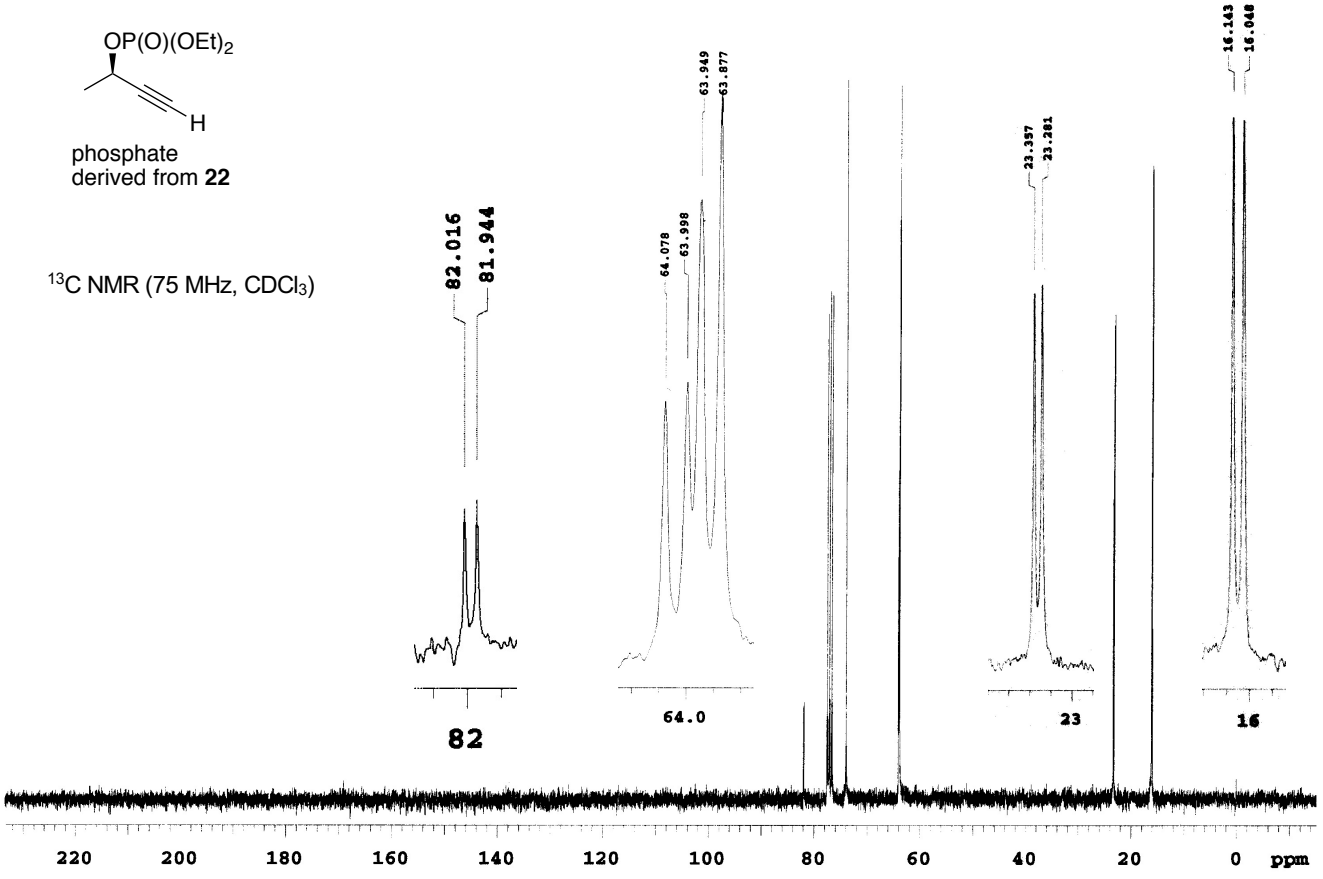


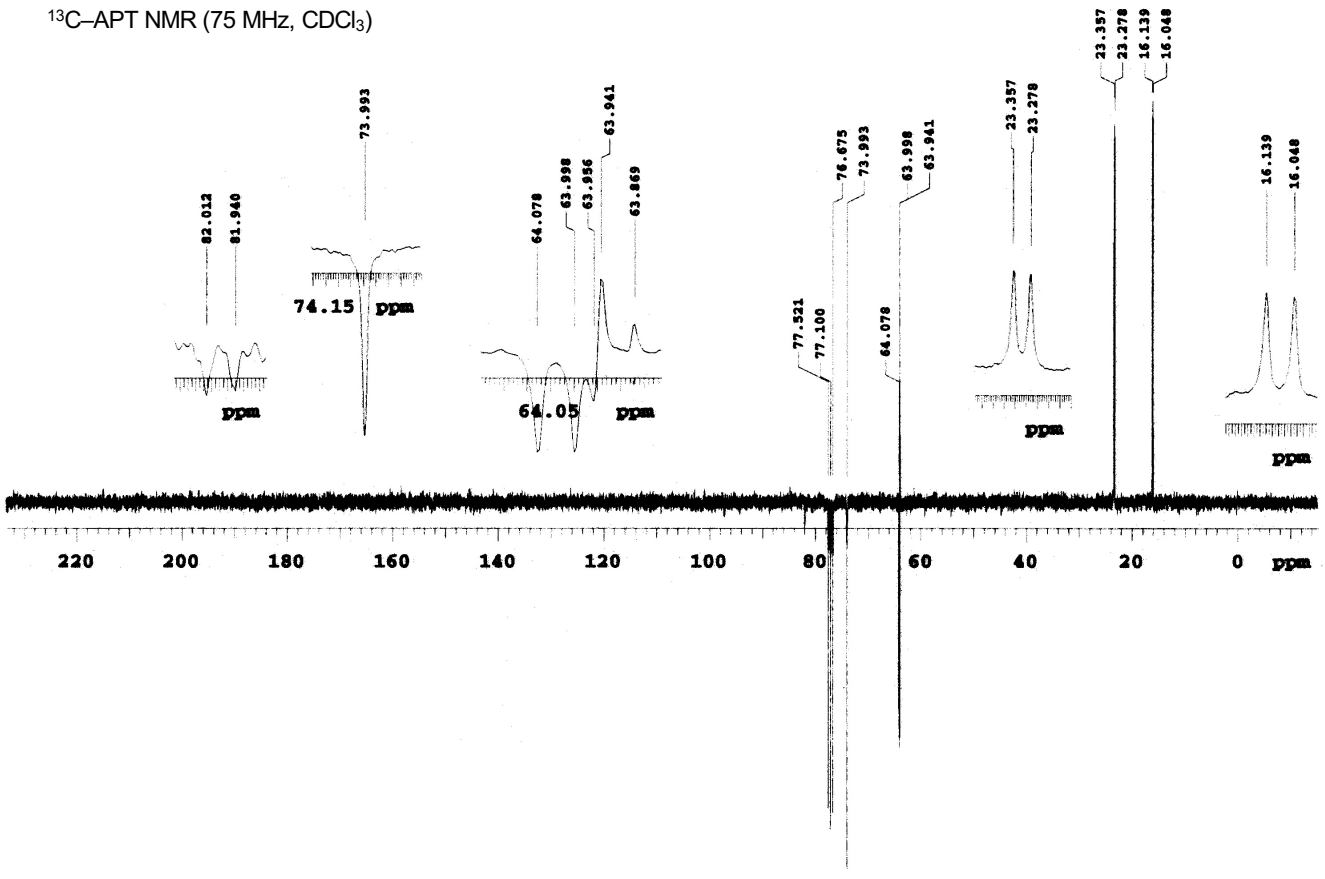
phosphate
derived from **22**

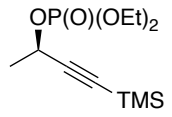
^{1}H NMR (300 MHz, $CDCl_3$)





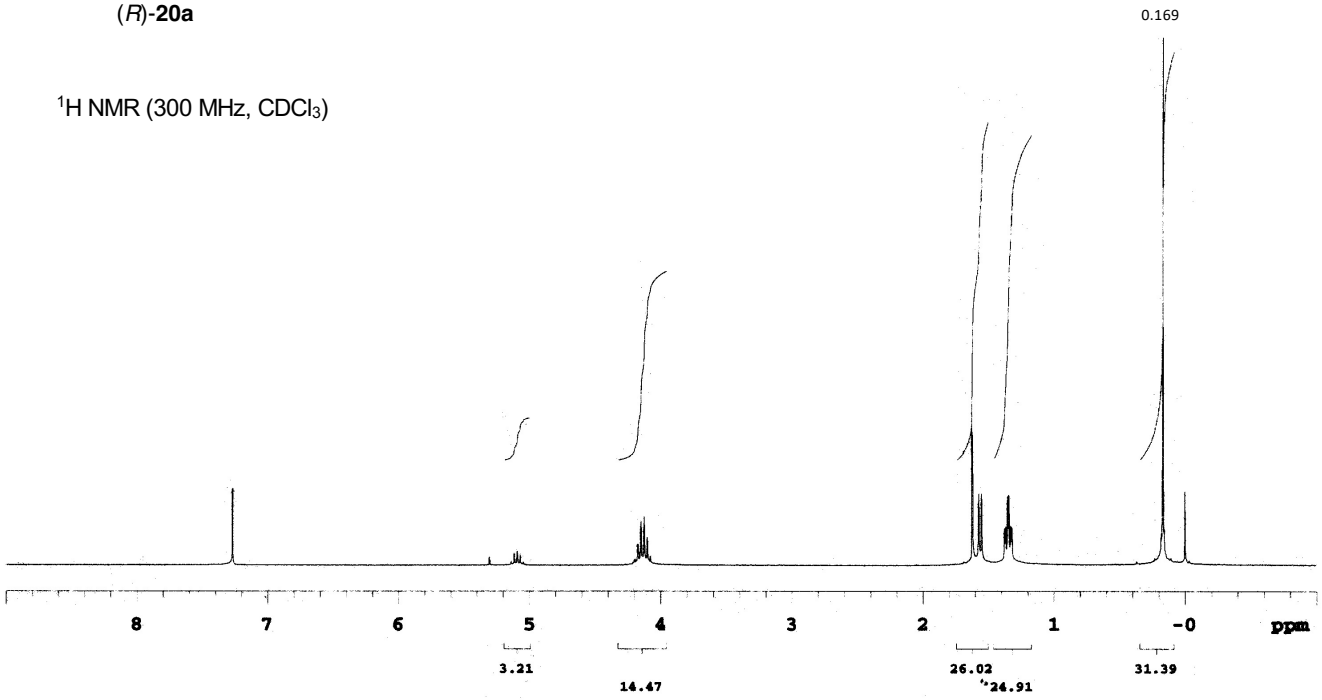

OP(O)(OEt)2
H
phosphate
derived from 22
13C NMR (75 MHz, CDCl3)
82.016
81.944
64.078
63.998
63.949
63.877
23.357
23.281
16.143
16.048
82
64.0
23
16
220
200
180
160
140
120
100
80
60
40
20
0
ppm

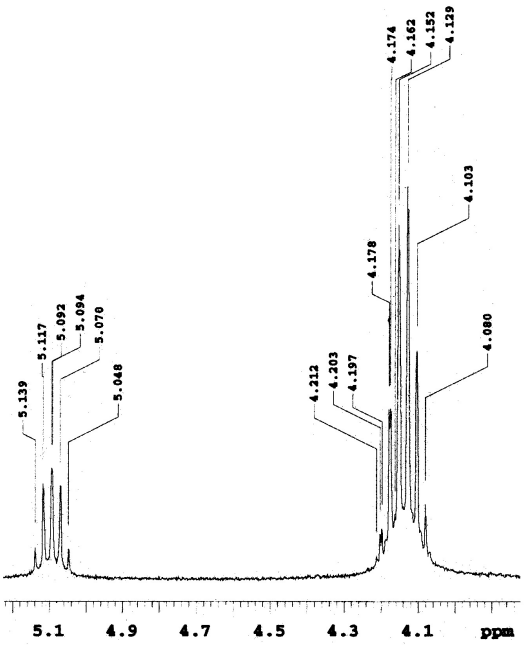

13C–APT NMR (75 MHz, CDCl3)
82.012
81.940
73.993
74.15 ppm
64.078
63.998
63.956
63.941
63.869
64.05 ppm
77.521
77.100
76.675
73.993
63.998
63.941
64.078
23.357
23.278
16.139
16.048
ppm
220
200
180
160
140
120
100
80
60
40
20
0
ppm

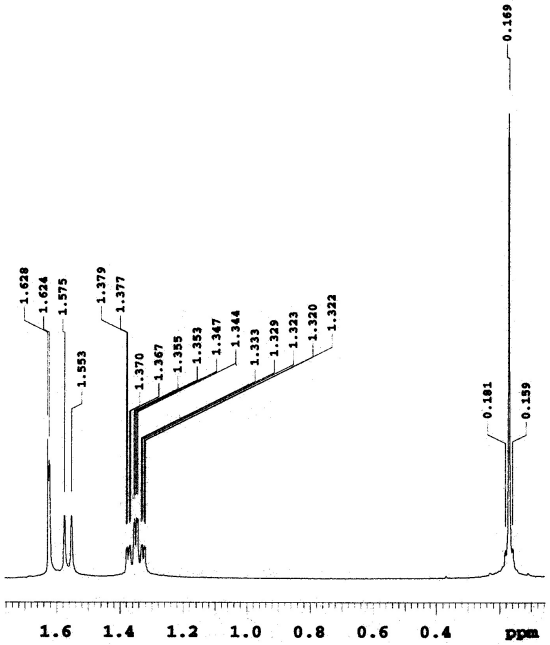


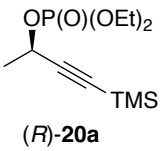
(*R*)-**20a**

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





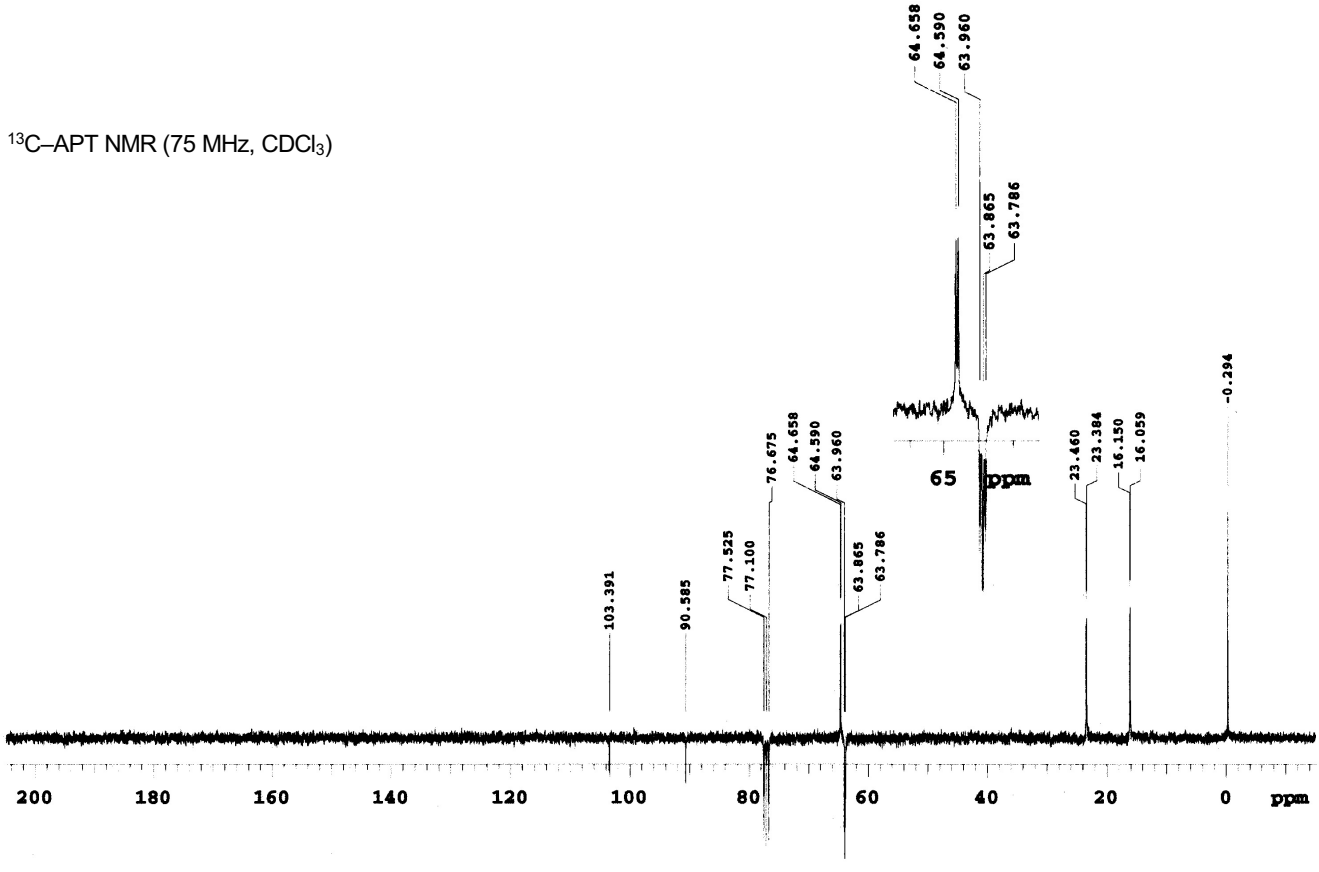


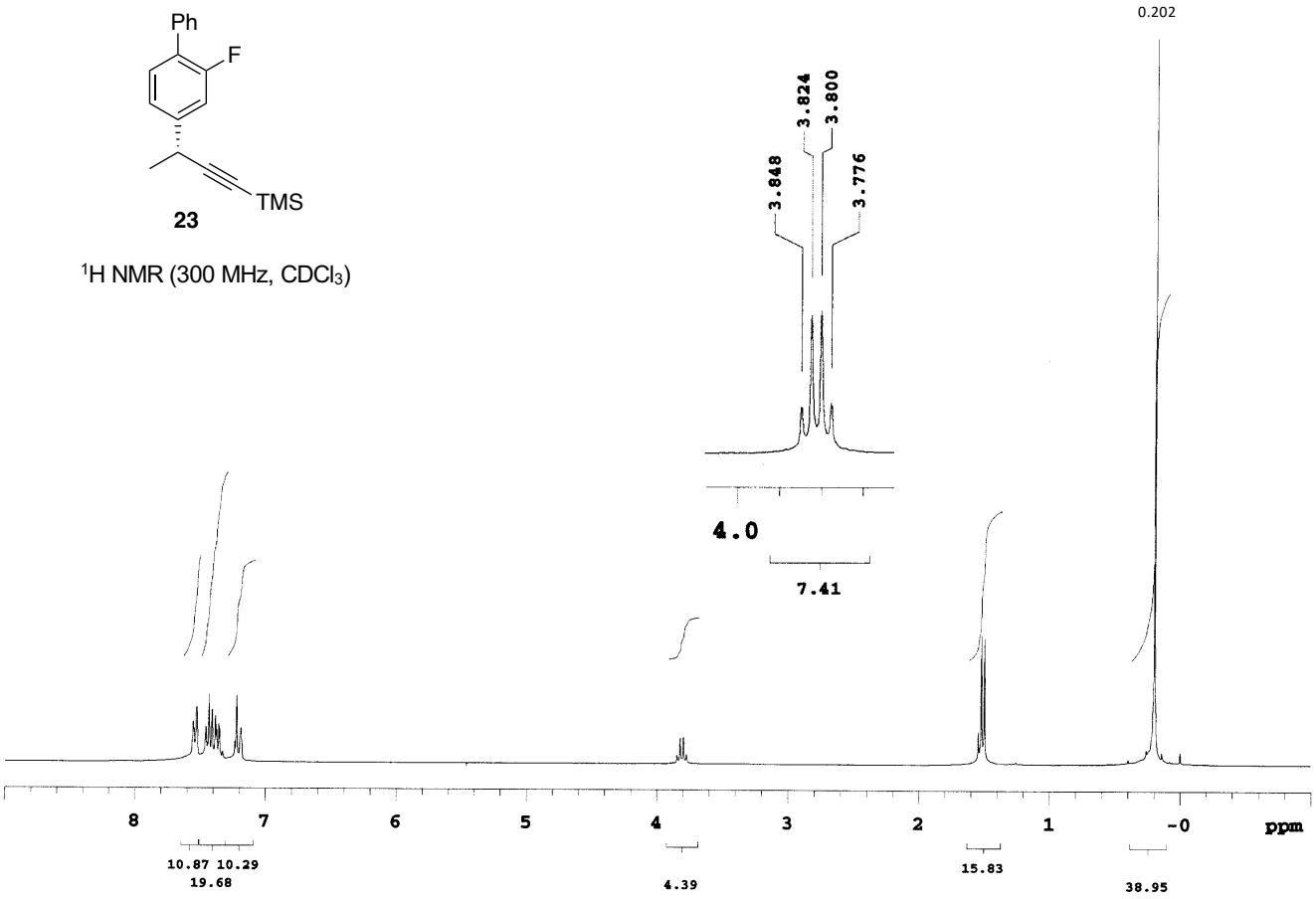


(*R*)-**20a**

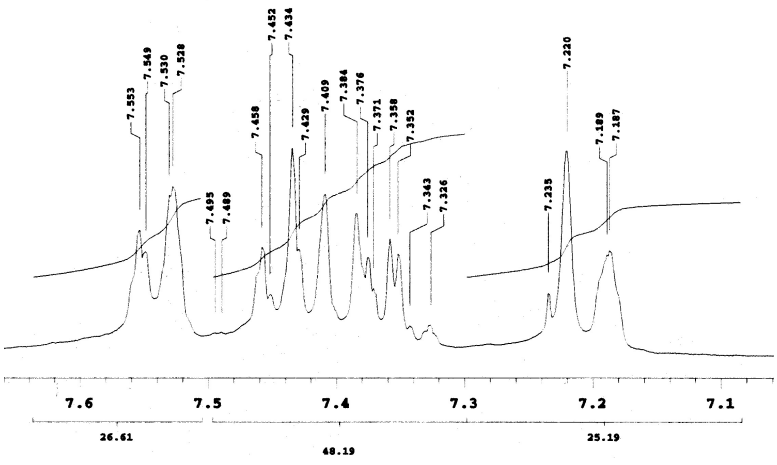
^{13}C NMR (75 MHz, $CDCl_3$)

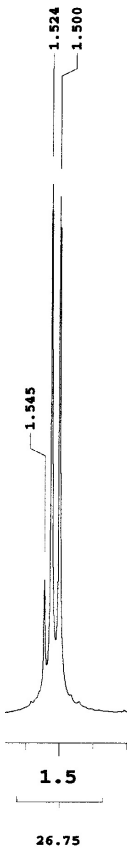
^{13}C–APT NMR (75 MHz, $CDCl_3$)

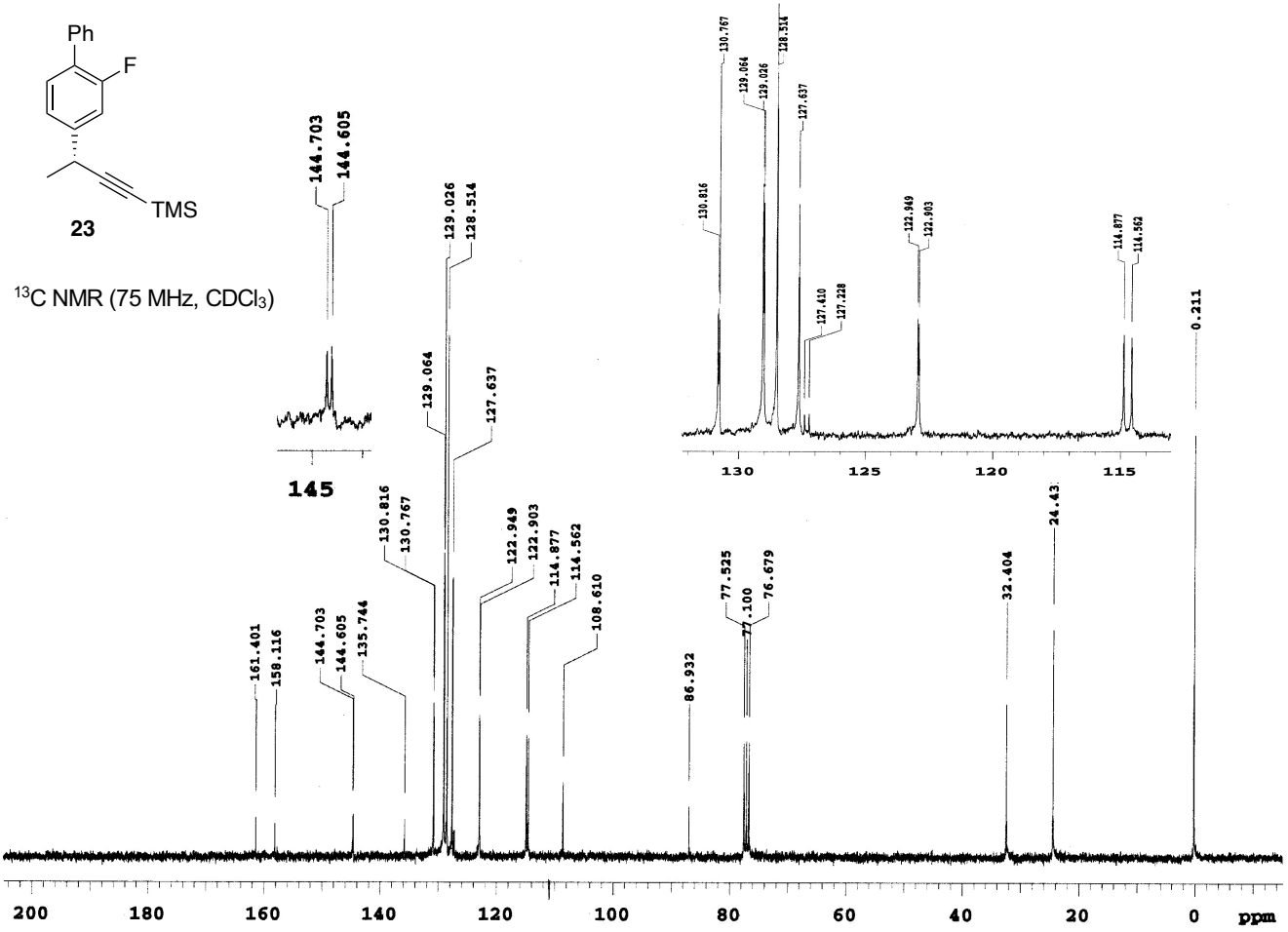


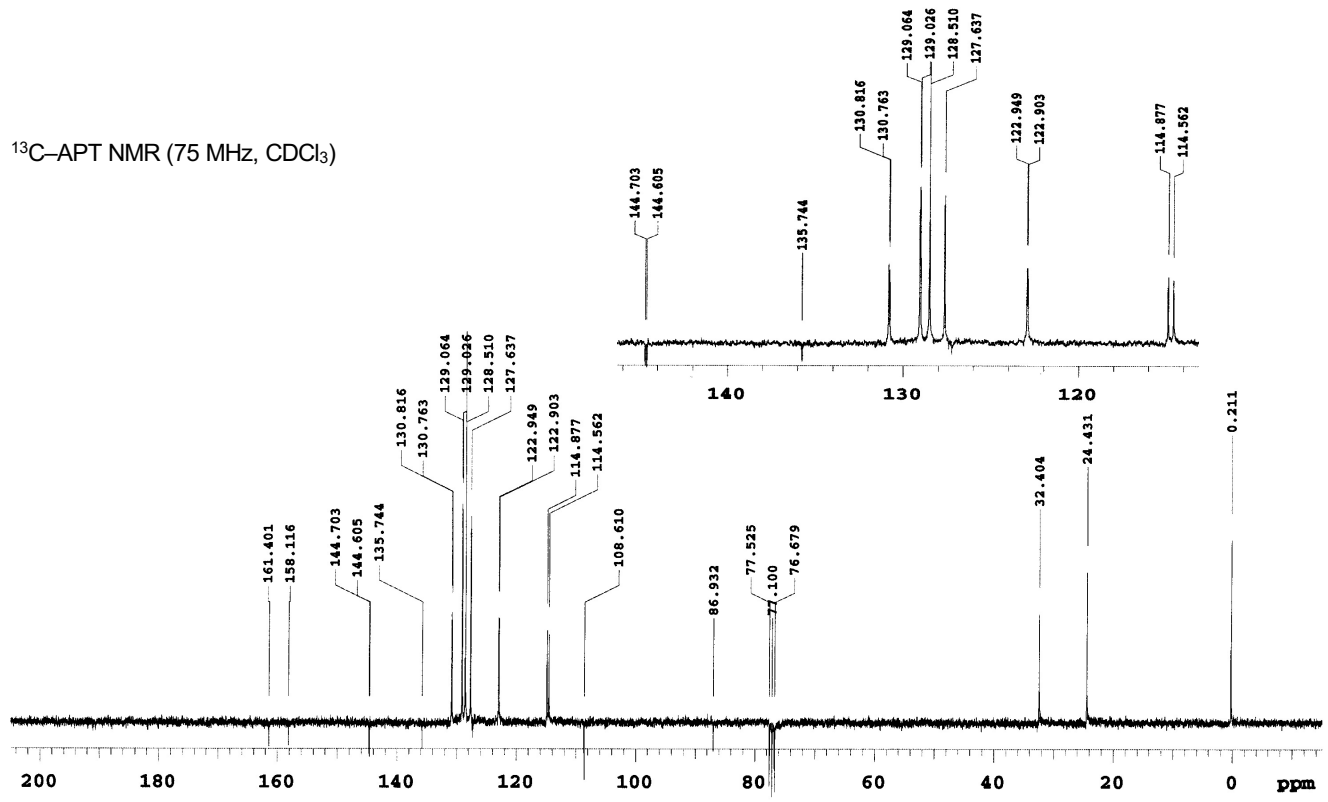


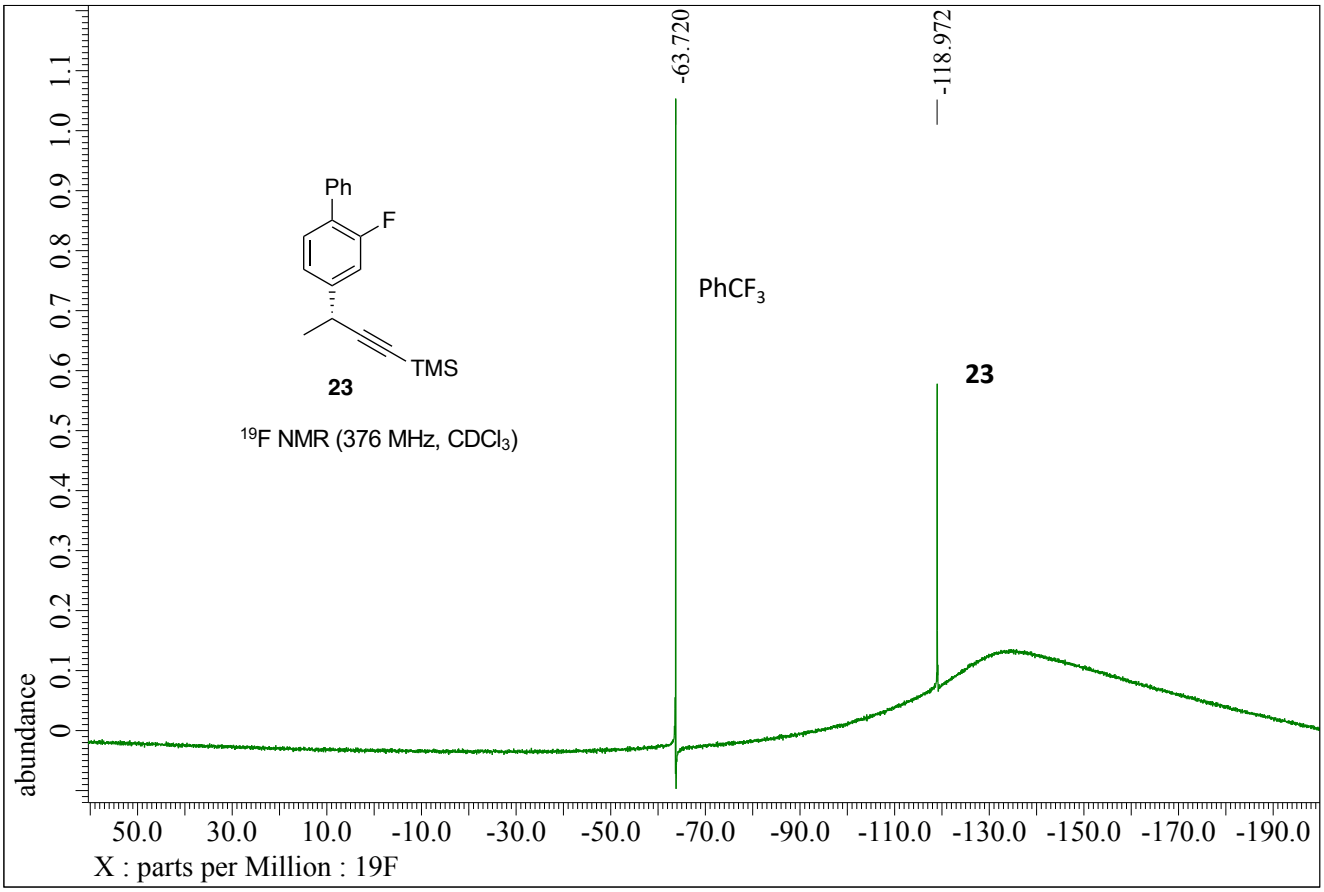
^{1}H NMR (300 MHz, $CDCl_3$)

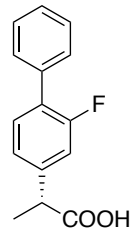





Ph
F
TMS
23
^{13}C NMR (75 MHz, CDCl$_3$)
144.703
144.605
129.026
128.514
129.064
127.637
145
130.816
130.767
122.949
122.903
114.877
114.562
108.610
161.401
158.116
144.703
144.605
135.744
86.932
77.525
77.100
76.679
32.404
24.43
0.211
200
180
160
140
120
100
80
60
40
20
0
ppm

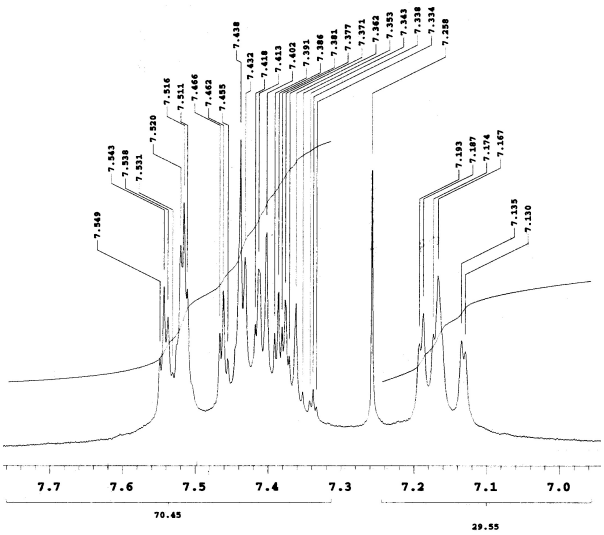

^{13}C–APT NMR (75 MHz, CDCl$_3$)
144.703
144.605
135.744
130.816
130.763
129.064
129.026
128.510
127.637
122.949
122.903
114.877
114.562
161.401
158.116
108.610
86.932
77.525
77.100
76.679
32.404
24.431
0.211
200
180
160
140
120
100
80
60
40
20
0
ppm

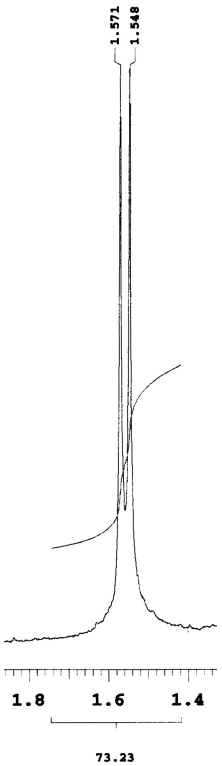

-63.720
-118.972
Ph
F
TMS
23
PhCF3
23
19F NMR (376 MHz, CDCl3)
abundance
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1
50.0 30.0 10.0 -10.0 -30.0 -50.0 -70.0 -90.0 -110.0 -130.0 -150.0 -170.0 -190.0
X : parts per Million : 19F



(*R*)-**5**

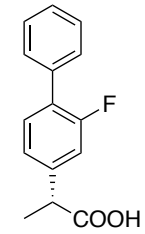
^{1}H NMR (300 MHz, $CDCl_3$)





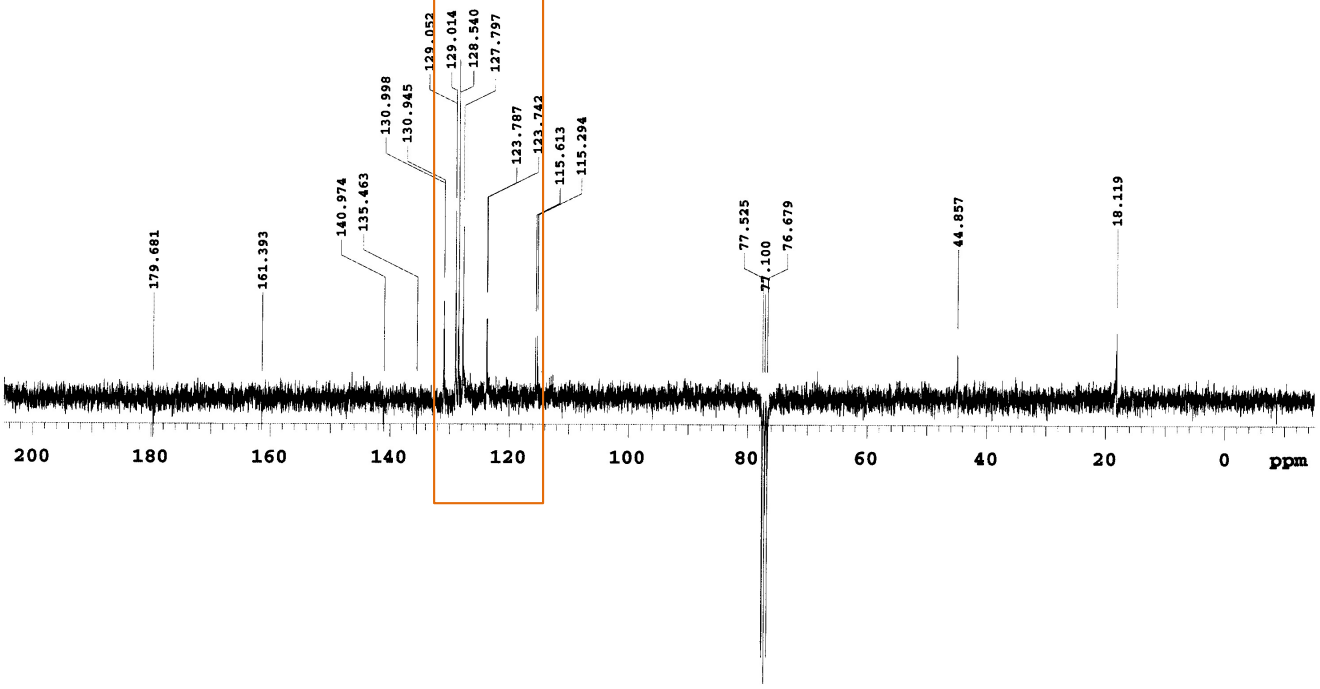
^{13}C NMR (75 MHz, $CDCl_3$)

Expansion,
see the next page

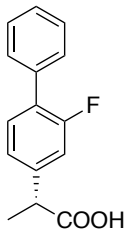


(*R*)-**5**

^{13}C–APT NMR (75 MHz, $CDCl_3$)



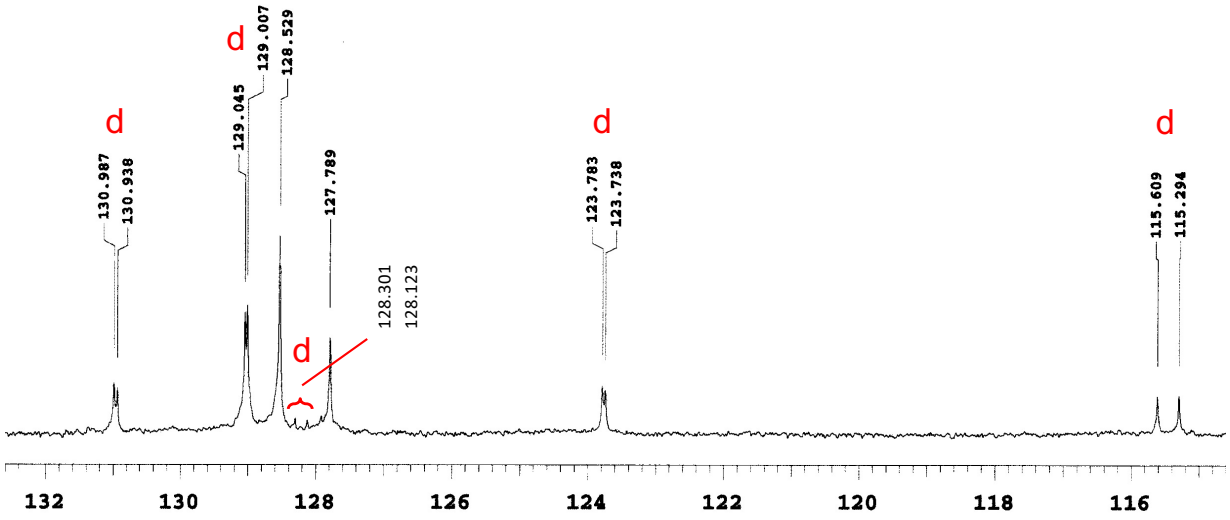
Expansion



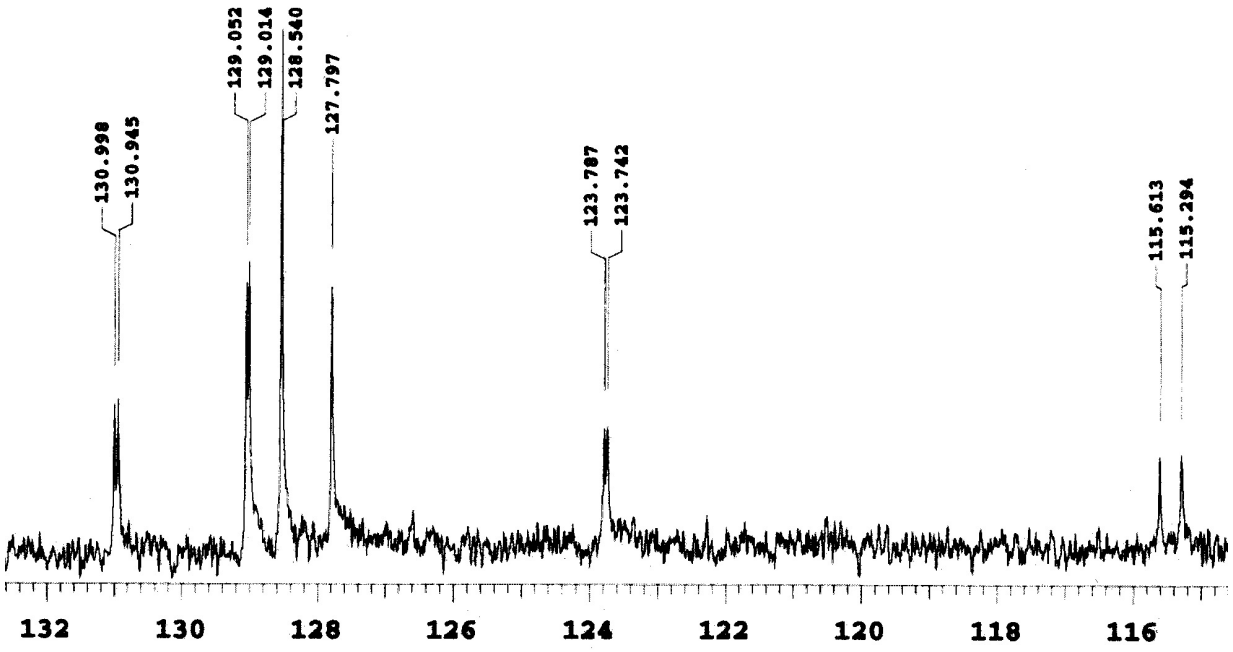
(*R*)-**5**

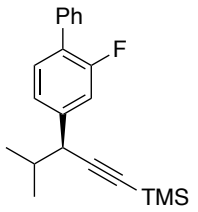
^{13}C NMR (75 MHz, $CDCl_3$)

d: doublet



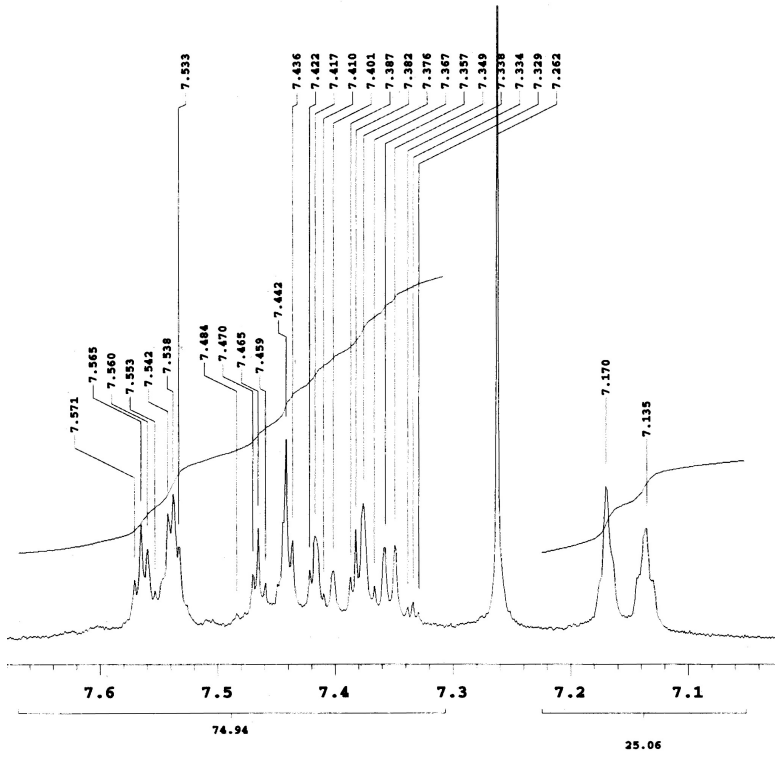
^{13}C–APT NMR (75 MHz, $CDCl_3$)

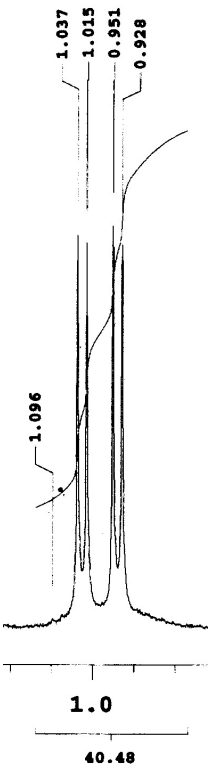


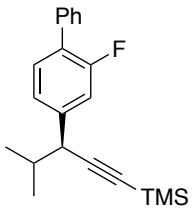


25

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



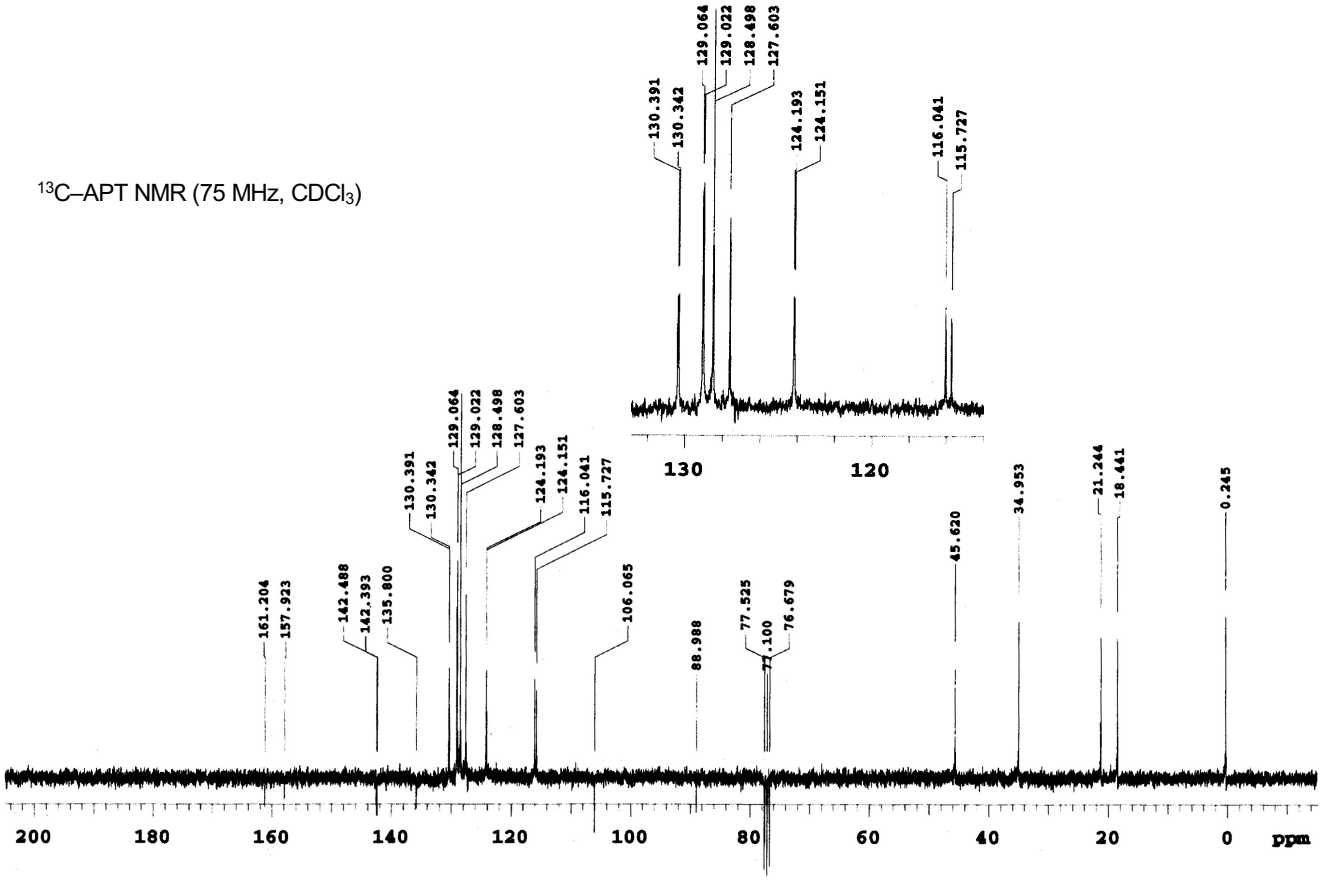


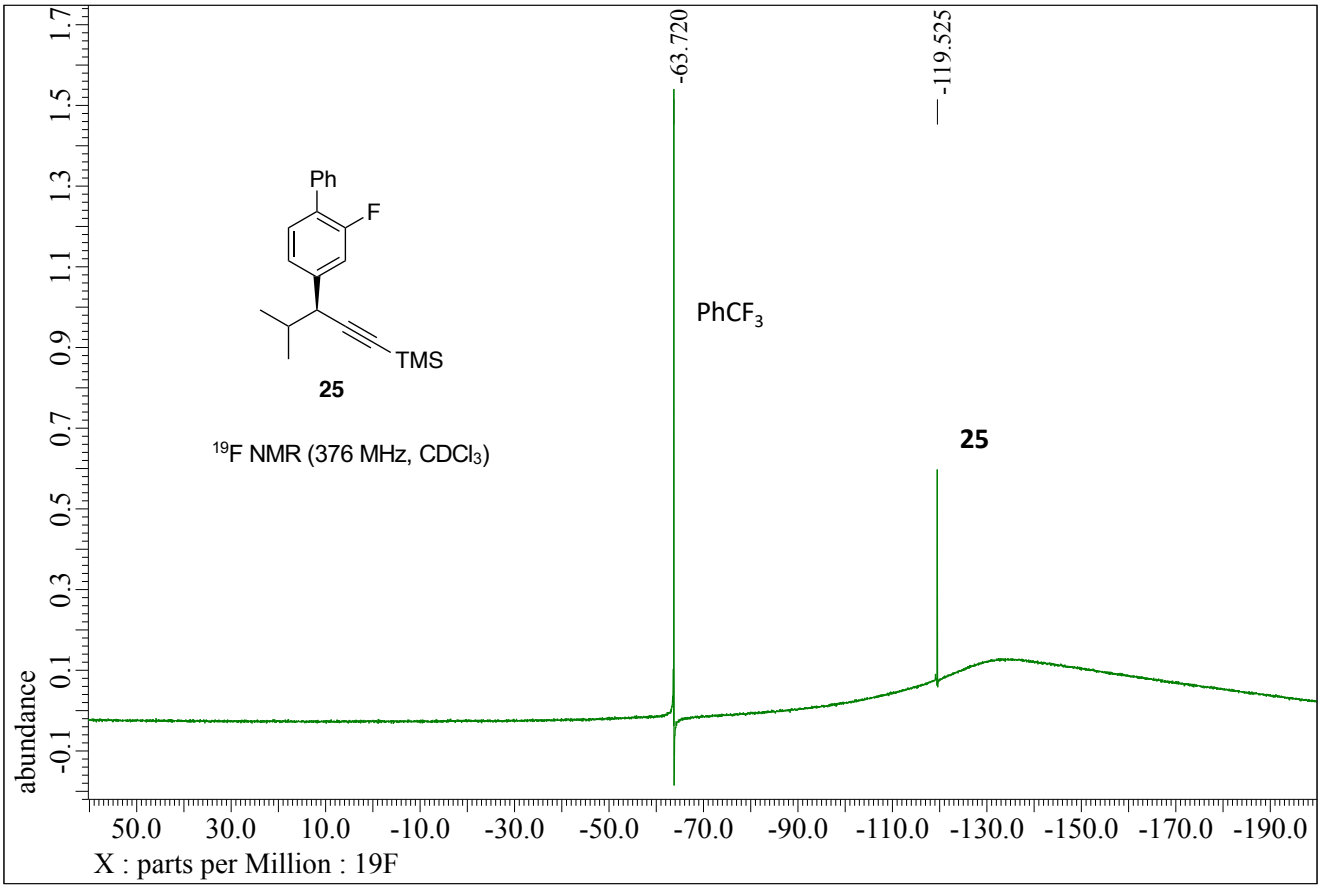


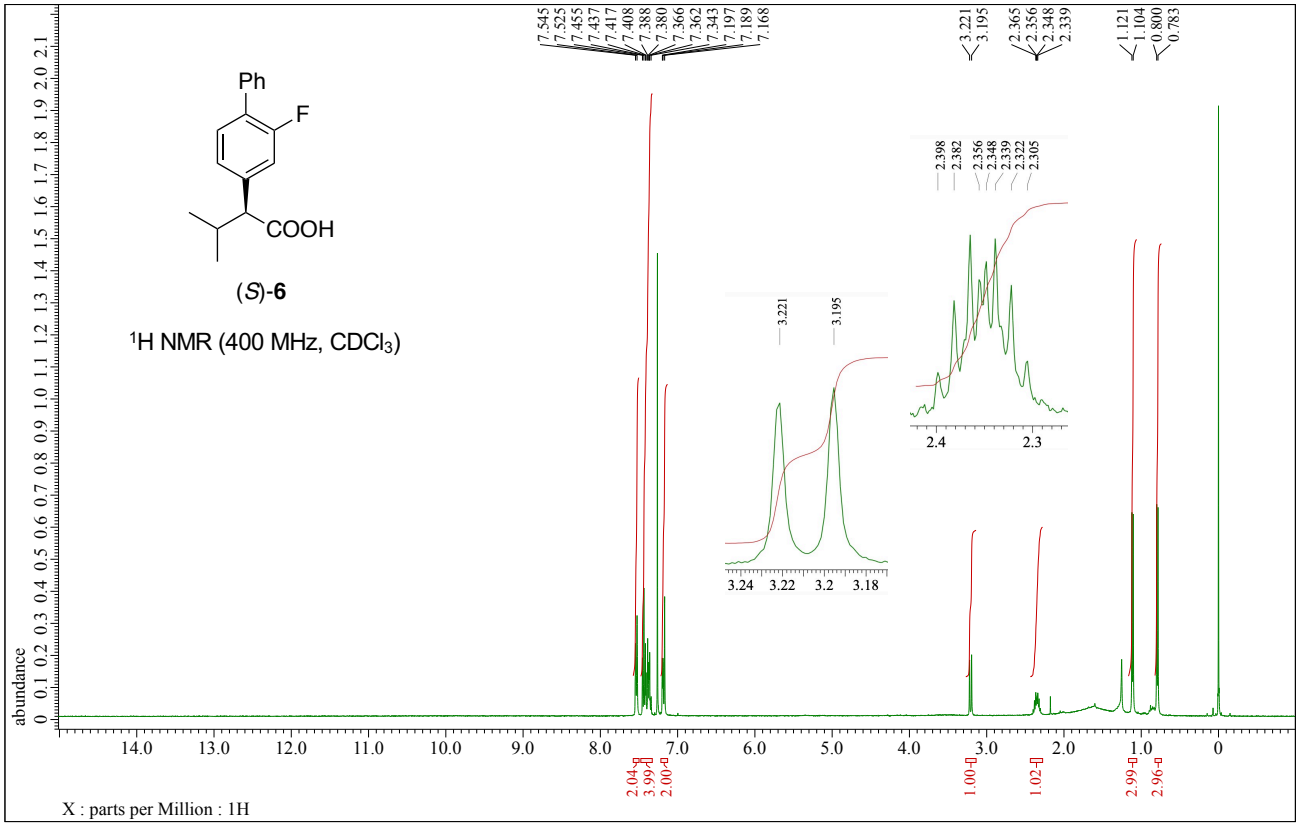
25

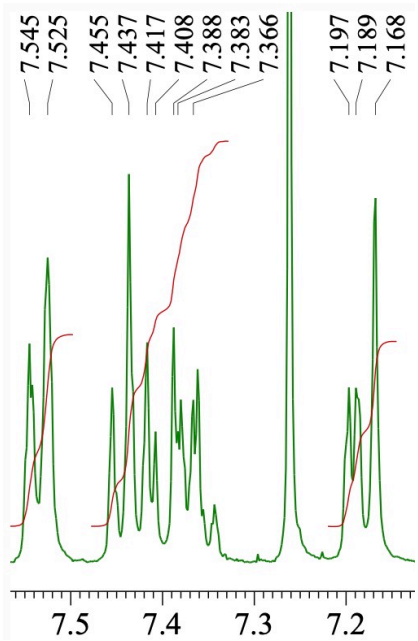
^{13}C NMR (75 MHz, $CDCl_3$)

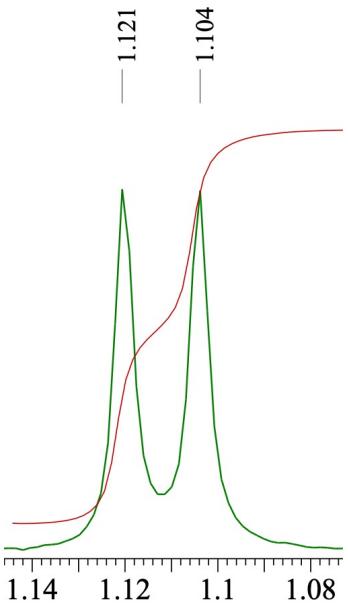
^{13}C–APT NMR (75 MHz, $CDCl_3$)

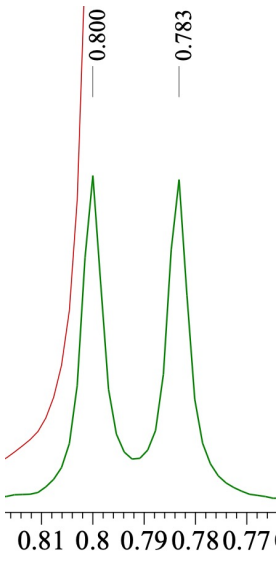


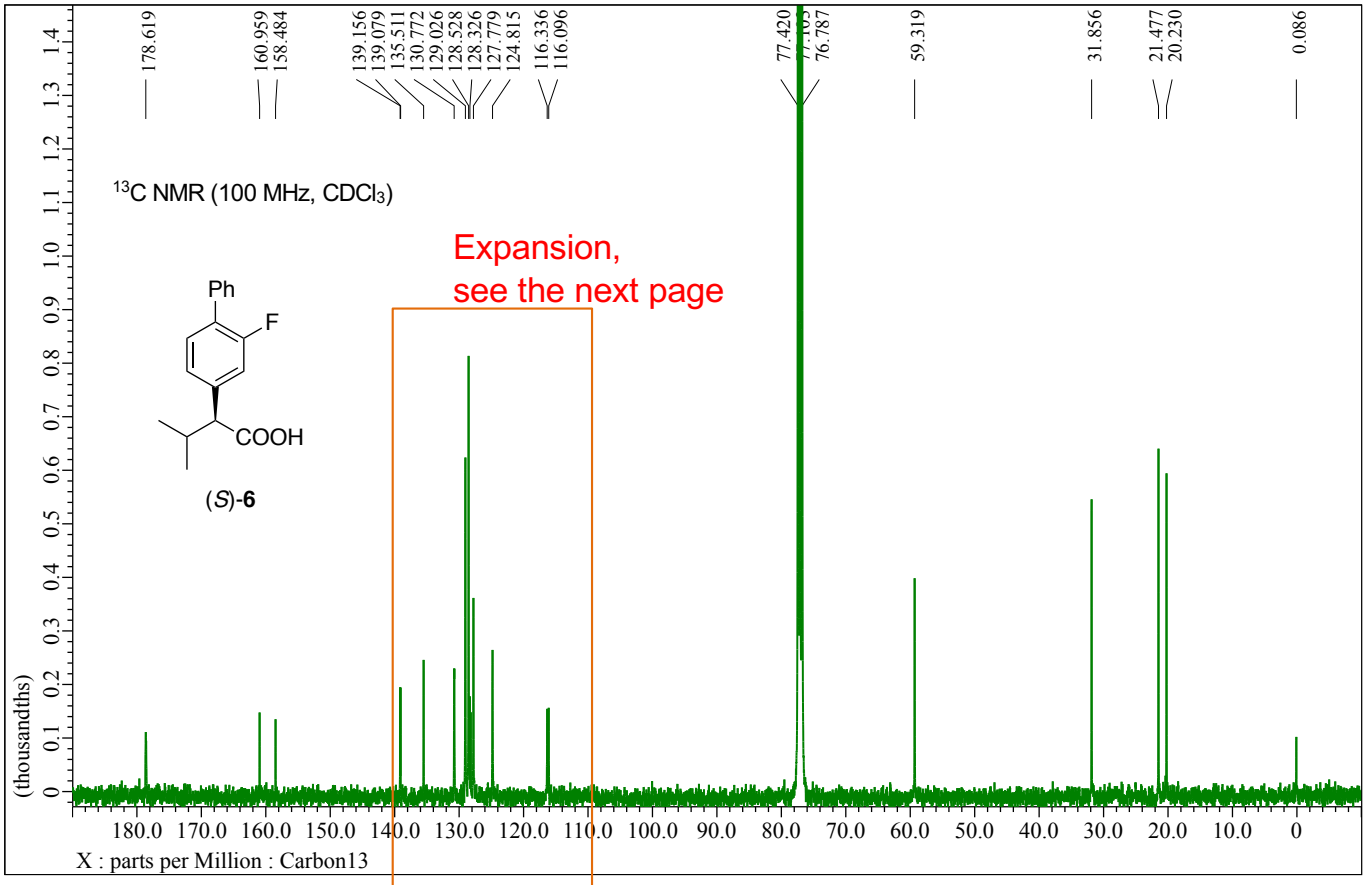

-63.720
-119.525
Ph
F
TMS
25
PhCF3
25
19F NMR (376 MHz, CDCl3)
abundance
1.7
1.5
1.3
1.1
0.9
0.7
0.5
0.3
0.1
-0.1
50.0
30.0
10.0
-10.0
-30.0
-50.0
-70.0
-90.0
-110.0
-130.0
-150.0
-170.0
-190.0
X : parts per Million : 19F

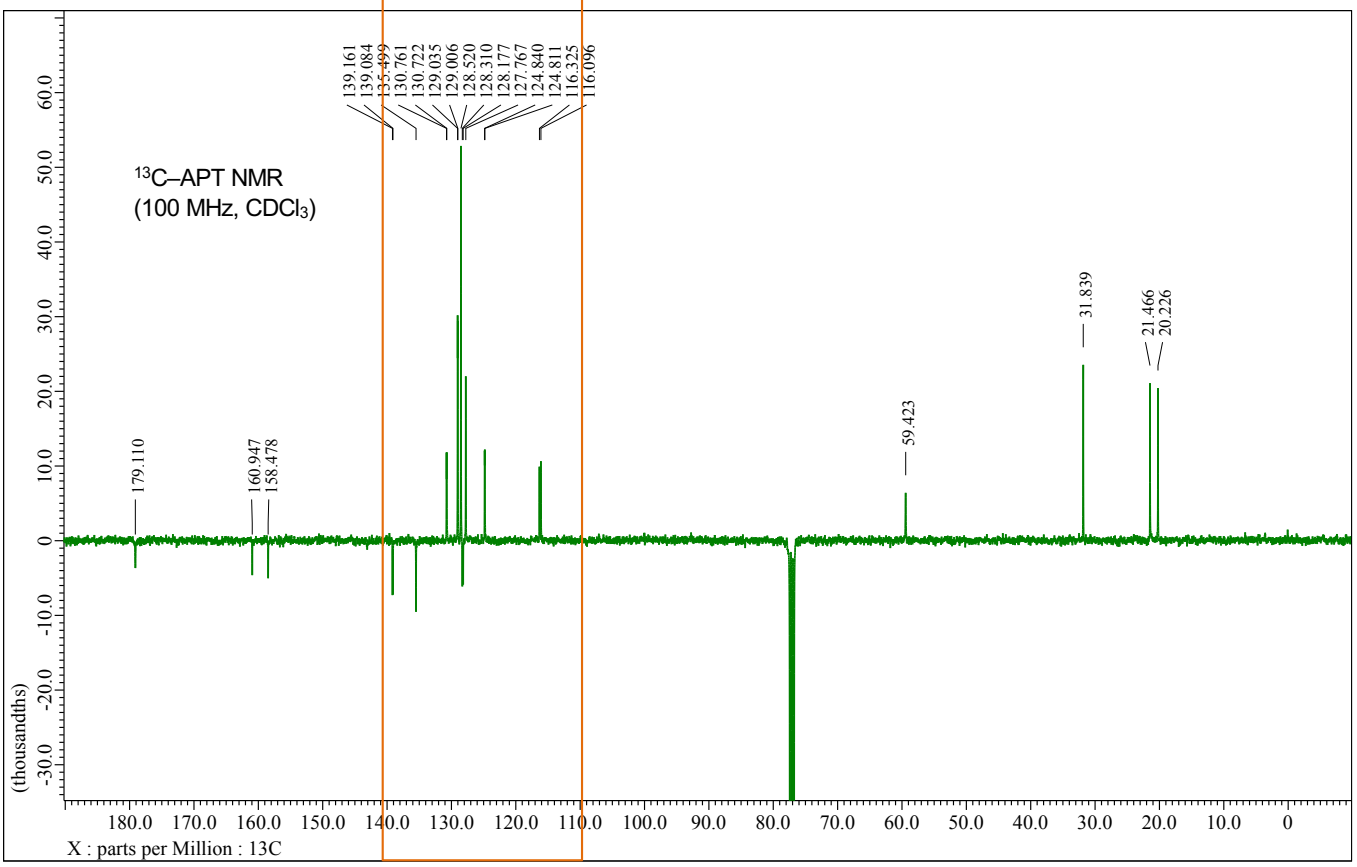

Ph
F
COOH
(S)-6
1H NMR (400 MHz, CDCl3)
abundance
X : parts per Million : 1H


7.545
7.525
7.455
7.437
7.417
7.408
7.388
7.383
7.366
7.197
7.189
7.168

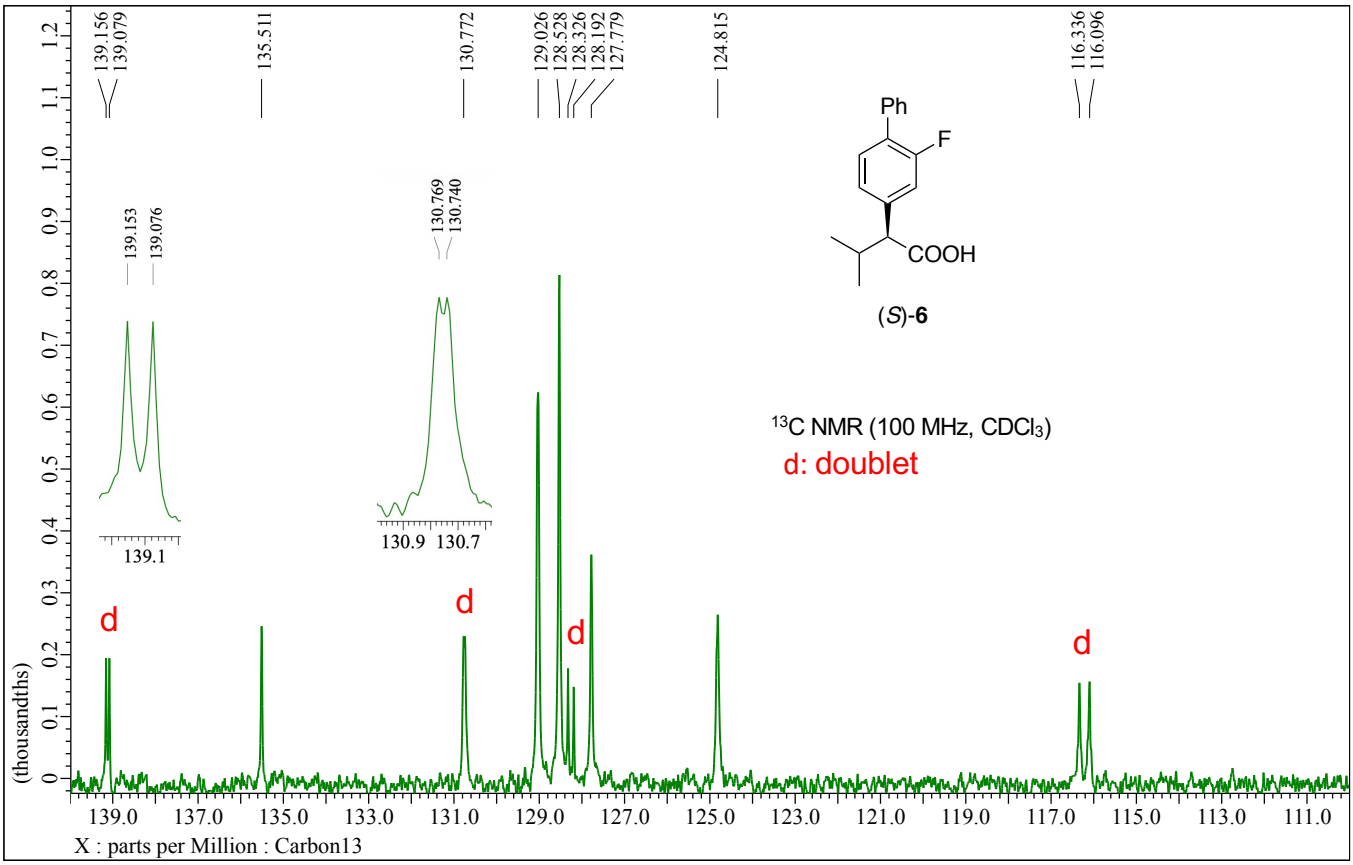

1.121
1.104

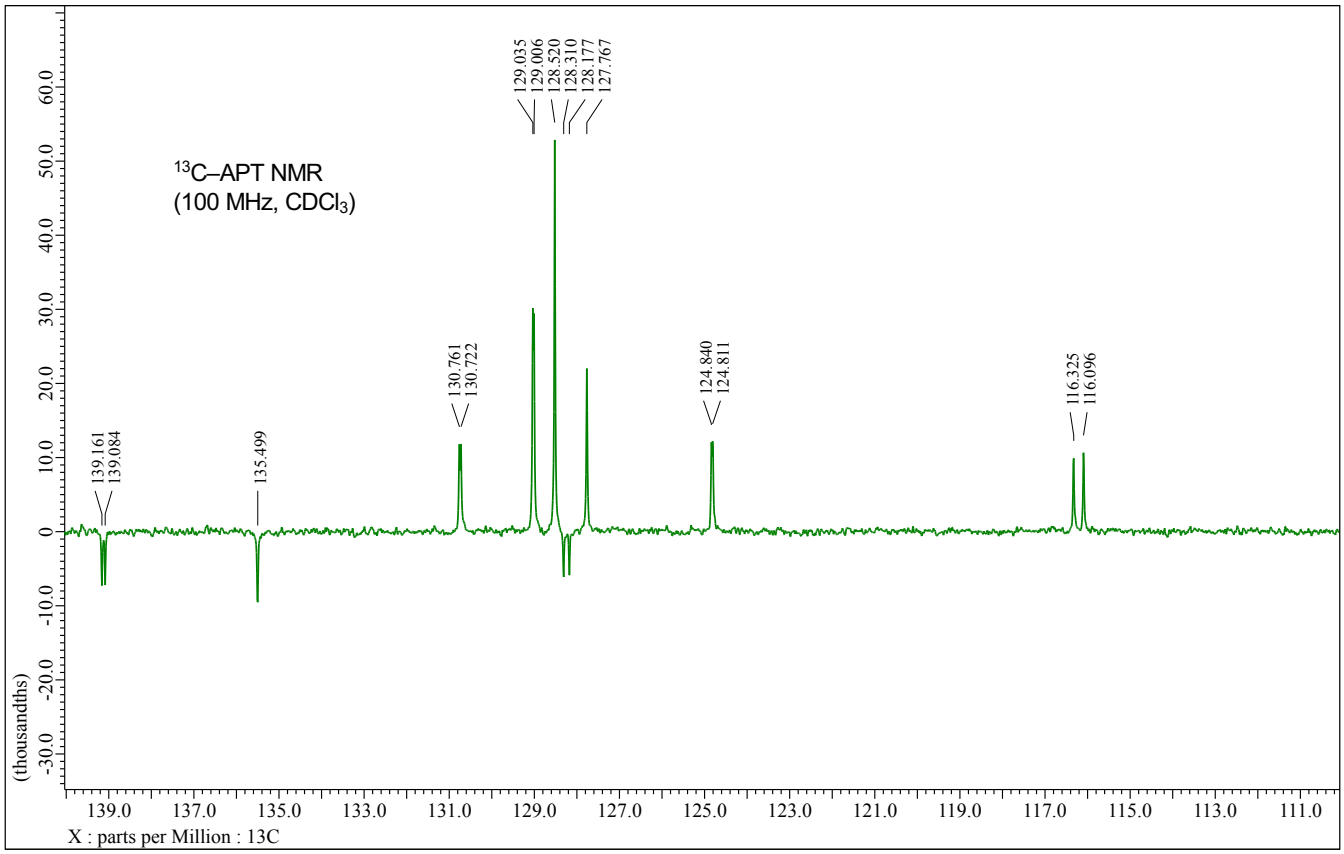

0.800
0.783


178.619
160.959
158.484
139.156
139.079
135.511
130.772
129.026
128.528
128.326
127.779
124.815
116.336
116.096
77.420
76.787
59.319
31.856
21.477
20.230
0.086
13C NMR (100 MHz, CDCl3)
Expansion,
see the next page
Ph
F
COOH
(S)-6
(thousandths)
X : parts per Million : Carbon13


139.161
139.084
135.499
130.761
130.722
129.035
129.006
128.520
128.310
128.177
127.767
124.840
124.811
116.325
116.096
13C–APT NMR
(100 MHz, CDCl3)
179.110
160.947
158.478
59.423
31.839
21.466
20.226
(thousandths)
X : parts per Million : 13C

Expansion


139.156
139.079
135.511
130.772
129.026
128.528
128.326
128.192
127.779
124.815
116.336
116.096
139.153
139.076
130.769
130.740
Ph
F
COOH
(S)-6
13C NMR (100 MHz, CDCl3)
d: doublet
d
d
d
d
139.1
130.9 130.7
(thousandths)
X : parts per Million : Carbon13


129.035
129.006
128.520
128.310
128.177
127.767
13C–APT NMR
(100 MHz, CDCl3)
130.761
130.722
124.840
124.811
116.325
116.096
139.161
139.084
135.499
(thousandths)
X : parts per Million : 13C