Construction of Chiral α-*tert*-Amine Scaffolds via Amine-catalyzed Asymmetric Mannich Reactions of Alkyl-substituted Ketimines

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1. General Information

^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer and a JEOL JNM-ECA500 (500 MHz) spectrometer. Chemical shifts were reported in ppm from tetramethylsilane as an internal standard. Data were reported as follow: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, td = triplet of doublet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and integration. ^{13}C NMR spectra were measured on a JEOL JNM-FX400 (100 MHz) and a JEOL JNM-FX500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 20A instruments using Daicel CHIRALPAK AD-3, IA-3, IB-3, IC-3, IC, ID and IG 4.6 mm × 25 cm columns. High-resolution mass spectra (HRMS) were performed on Thermo SCIENTIFIC Exactive Plus. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60N (Kanto Chemical Co. Inc., 40-50 μm). Solvents were removed under reduced pressure using Büchi Rotavapor apparatus. X-ray diffraction analysis was carried out with a RIGAKU Saturn70 CCD(system) with VariMax Mo Optic.

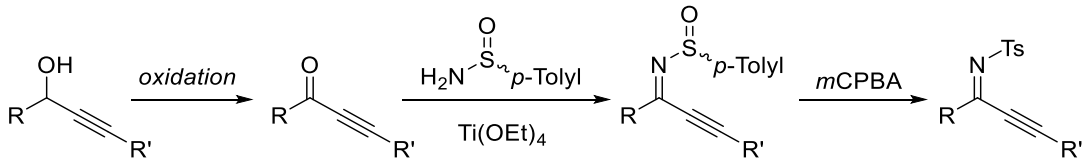
In experiments requiring dry solvents, tetrahydrofuran (THF) was purchased from Kanto Chemical Co. Inc. as “Dehydrated”. All other solvents were purchased from FUJIFILM Wako Pure Chemical Corporation, Ltd. Chloroform ($CHCl_3$) and tetrahydrofuran (THF) were stored over 4Å molecular sieves. Acetonitrile (MeCN) was stored over 3Å molecular sieves. Ethyl acetate (EtOAc), hexane, diethyl ether (Et_2O), dioxane, methanol (MeOH), ethanol (EtOH), 2-propanol (*i*PrOH), isobutylalcohol (*i*BuOH), *tert*-butyl alcohol (*t*BuOH), dichloromethane (CH_2Cl_2) and dichloroethane (DCE) were used without further purification. Reagents were purchased from Aldrich, Tokyo Chemical Industry Co., Ltd. (TCI), Nacalai Tesque, Inc., FUJIFILM Wako Pure Chemical Corporation, Ltd. or Peptide Institute, Inc. and used without purification except for aldehydes. The commercially available aldehydes were distilled and stored under a nitrogen atmosphere at 5 °C.

Non-2-yn-4-ol[1], *tert*-Butyl pent-3-yn-2-ylcarbamate[2], 4-(benzyloxy)butanal[3], 2,2,2-trifluoro-*N*-(4-oxobutyl)acetamide[4] were synthesized according to the literature procedures.

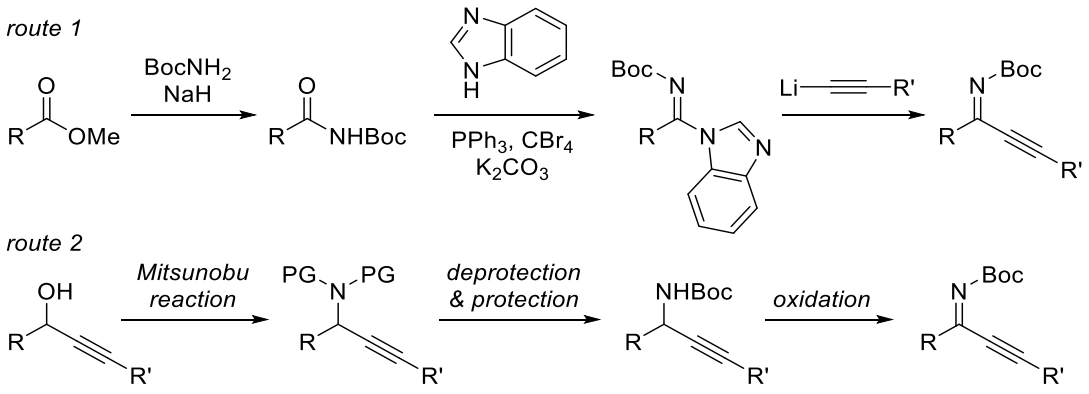
2. Preparation of *Z*-Ketimines

◆ Overview of synthesis of *Z*-ketimines

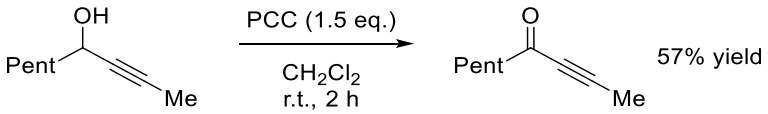
***N*-Sulfinyl or *N*-Ts-protected Ketimine**



***N*-Boc-protected Ketimines**



◆ Synthesis of non-2-yn-4-one



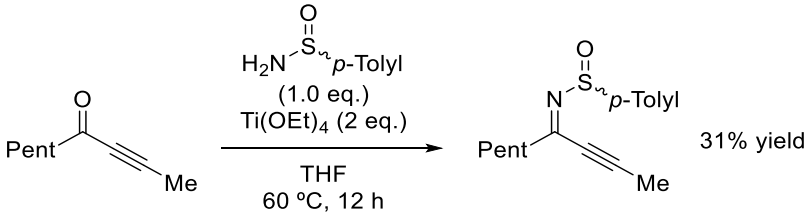
To a solution of non-2-yn-4-ol (776 mg, 5.5 mmol, 1.0 eq.) in CH_2Cl_2 (4 mL) was added pyridinium chlorochromate (PCC) (1.8 g, 8.3 mmol, 1.5 eq.) at room temperature. After stirring for 2 h, the mixture was filtered through a Celite pad and washed with CH_2Cl_2. The filtrate was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane/EtOAc = 15/1 as eluent) to give the corresponding ketone as a yellow oil (438 mg, 3.1 mmol, 57% yield).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.51 (t, J = 7.5 Hz, 2H), 2.02 (s, 3H), 1.69-1.63 (m, 2H), 1.37-1.26 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 188.3, 89.7, 80.1, 45.3, 31.0, 23.6, 22.3, 13.7, 3.9

HRMS (ESI): calcd. for $C_9H_{14}ONa^+$ ([M+Na]$^+$): 161.0937, found: 161.0936 ([M+Na]$^+$)

◆ Synthesis of (*Z*)-4-methyl-*N*-(non-2-yn-4-ylidene)benzenesulfinamide



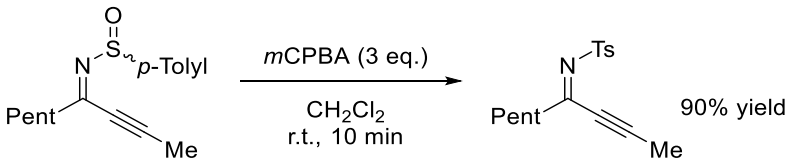
To a solution of non-2-yn-4-one (553 mg, 4 mmol, 1 eq.) and 4-methylbenzenesulfinamide (621 mg, 1.0 mmol, 1 eq.) in THF (8 mL) was added $Ti(OEt)_4$ (1.7 mL, 2 mmol, 2 eq.) at room temperature. After stirring for 12 h at 60 °C, the reaction mixture was cooled to room temperature and quenched by adding brine. After stirring for 30 min at the same temperature, insoluble materials were filtered through celite and washed with EtOAc thoroughly. The filtrate was concentrated and then purified by column chromatography on silica gel to afford the (*Z*)-4-methyl-*N*-(non-2-yn-4-ylidene)benzenesulfinamide (343 mg, 1.25 mmol, 31%) as a brown oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 2.47 (t, J = 7.8 Hz, 2H), 2.41 (s, 3H), 2.17 (s, 3H), 1.64-1.62 (m, 2H), 1.29-1.21 (m, 4H), 0.84 (t, J = 7.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 164.1, 143.4, 142.0, 129.6, 124.5, 102.6, 75.4, 41.8, 30.8, 25.8, 22.1, 21.4, 13.7, 4.6

HRMS (ESI): calcd. for $C_{16}H_{21}ONNaS^+$ ([M+Na]$^+$): 298.1236, found: 298.1237 ([M+Na]$^+$)

◆ Synthesis of (*Z*)-4-methyl-*N*-(non-2-yn-4-ylidene)benzenesulfonamide



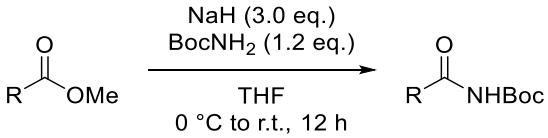
To a solution of (*Z*)-4-methyl-*N*-(non-2-yn-4-ylidene)benzenesulfinamide (220.3 mg, 0.8 mmol, 1 eq.) in CH_2Cl_2 (4 mL) was added *m*-chloroperoxybenzoic acid (*m*CPBA) (690.3 mg, 2.4 mmol, 3 eq.) at room temperature and the solution was stirred for 10 min at the same temperature. The mixture was then quenched with saturated $Na_2S_2O_3$ aq. and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was passed through a short silica gel/Na_2SO_4 plug, eluting with a solution of CH_2Cl_2 to afford the (*Z*)-4-methyl-*N*-(non-2-yn-4-ylidene)benzenesulfonamide (211 mg, 0.72 mmol, 90%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.84 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 2.51 (t, J = 7.8 Hz, 2H), 2.43 (s, 3H), 2.16 (s, 3H), 1.69-1.62 (m, 2H), 1.33-1.23 (m, 4H), 0.86 (t, J = 6.8 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.5, 143.7, 137.1, 129.2, 127.6, 108.0, 75.8, 43.0, 30.8, 25.9, 22.1, 21.5, 13.7, 5.3

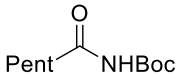
HRMS (ESI): calcd. for $C_{16}H_{21}O_2NNaS^+$ ([M+Na]$^+$): 314.1185, found: 314.1189 ([M+Na]$^+$)

◆ General procedure for preparation of *N*-Boc protected amides



To a mixture of *tert*-butyl carbamate ($BocNH_2$) (1.2 eq.) and NaH (60% in mineral oil, 3.0 eq.) in THF (0.2 M) was added an ester (1.0 eq.) at 0 °C and the mixture was warmed up to room temperature. After stirring for 12 h, the mixture was poured on ice, neutralized with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/EtOAc = 1/0 ~ 1/2 as eluent) to give the corresponding *N*-Boc protected amide.

tert-Butyl hexanoylcarbamate



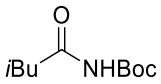
Was obtained as a colorless oil (3.1 g, 14 mmol, 72%), following the general procedure with methyl hexanoate (3.0 mL, 20 mmol).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.22 (br s, 1H), 2.72 (t, J = 7.5 Hz, 2H), 1.68-1.62 (m, 2H), 1.49 (s, 9H), 1.36-1.31 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.0, 150.6, 82.1, 36.0, 31.2, 27.9, 23.8, 22.3, 13.8

HRMS (ESI): calcd. for $C_{11}H_{21}O_3NNa^+$ ($[M+Na]^+$): 238.1414, found: 238.1413 ($[M+Na]^+$)

tert-Butyl (3-methylbutanoyl)carbamate



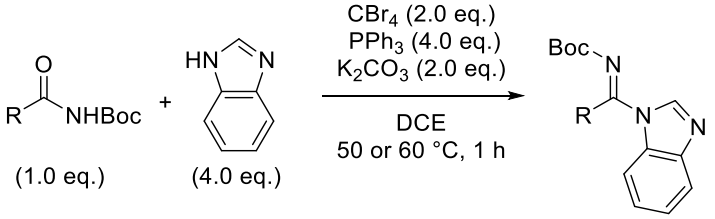
Was obtained as a white solid (719.9 mg, 3.6 mmol, 36%), following the general procedure with methyl isovalerate (1.3 g, 10 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.16 (br s, 1H), 2.61 (d, J = 7.2 Hz, 2H), 2.20-2.13 (m, 1H), 1.49 (s, 9H), 0.98 (d, J = 6.8 Hz, 6H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 174.0, 150.4, 82.3, 44.7, 28.0, 24.9, 22.5

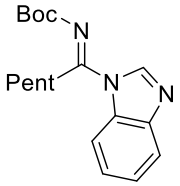
HRMS (ESI): calcd. for $C_{10}H_{19}O_3NNa^+$ ($[M+Na]^+$): 224.1257, found: 224.1257 ($[M+Na]^+$)

◆ General procedure for preparation of amidines



To a mixture of an *N*-Boc-protected amide (1.0 eq.), triphenylphosphine (PPh_3) (4.0 eq.), K_2CO_3 (2.0 eq.) and benzimidazole (4.0 eq.) in DCE (0.5 M) was added CBr_4 (2.0 eq.) at room temperature. After stirring for 1 h at 50 or 60 ºC, the mixture was filtered through a Celite pad and washed with CH_2Cl_2. The filtrate was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography with dry ice jacket (hexane/EtOAc = 7/1 ~ 2/1 as eluent) to give the desired product.

tert-Butyl (*E*)-(1-(1H-benzo[*d*]imidazol-1-yl)hexylidene)carbamate



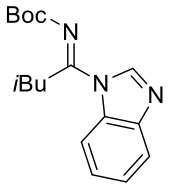
Was obtained as a white solid (1.6 g, 5.1 mmol, 51%), following the general procedure with *tert*-butyl hexanoylcarbamate (2.2 g, 10 mmol) at 60 ºC.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.34-8.32 (m, 1H), 8.29 (s, 1H), 7.81-7.79 (m, 1H), 7.42-7.35 (m, 2H), 2.90 (t, *J* = 8.2 Hz, 2H), 1.88-1.80 (m, 2H), 1.60 (s, 9H), 1.50-1.34 (m, 4H), 0.92 (t, *J* = 7.4 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.3, 157.0, 144.3, 141.1, 131.7, 125.4, 124.6, 120.3, 116.5, 82.6, 32.6, 31.7, 28.1, 27.6, 22.1, 13.8

HRMS (ESI): calcd. for $C_{18}H_{26}O_2N_3^+$ ([M+H]$^+$): 316.2020, found: 316.2025 ([M+H]$^+$)

tert-Butyl (*E*)-(1-(1H-benzo[*d*]imidazol-1-yl)-3-methylbutylidene)carbamate



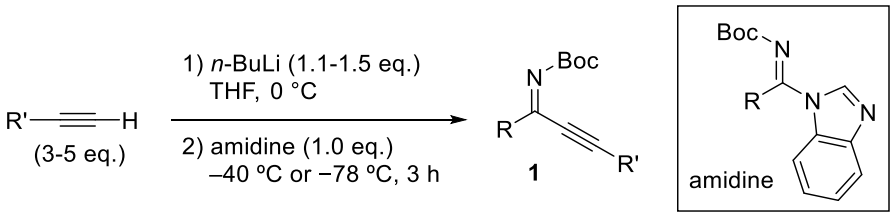
Was obtained as a white solid (326.0 mg, 1.1 mmol, 54%), following the general procedure with *tert*-butyl (3-methylbutanoyl)carbamate (406 mg, 2 mmol) at 50 ºC.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.32 (d, *J* = 7.5 Hz, 1H), 8.28 (s, 1H), 7.80 (d, *J* = 7.0 Hz, 1H), 7.42-7.36 (m, 2H), 2.85 (d, *J* = 8.0 Hz, 2H), 2.20-2.15 (m, 1H), 1.60 (s, 9H), 1.06 (d, *J* = 7.0 Hz, 6H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.1, 156.1, 144.2, 141.3, 131.7, 125.3, 124.6, 120.3, 116.4, 82.6, 40.7, 28.1, 27.8, 22.6

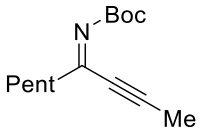
HRMS (ESI): calcd. for $C_{17}H_{24}O_2N_3^+$ ([M+H]$^+$): 302.1863, found: 302.4866 ([M+H]$^+$)

◆ General procedure for preparation of *Z*-ketimines



To a solution of a terminal alkyne (3-5 eq.) in THF was added *n*-butyllithium (*n*-BuLi) (1.56 M in hexane, 1.1-1.6 eq.) at 0 °C dropwise under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added dropwise the amidine (1.0 eq.) in THF (1.0 M) at –40 °C or −78 ºC, and the solution was stirred for 3 h at the same temperature. The mixture was then quenched with saturated NH_4Cl aq. and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel with dry ice jacket (hexane/EtOAc = 40/1 ~ 20/1 cooled by ice as eluent) to afford the corresponding ketimine. All of *N*-Boc protected ketimines were stored under a nitrogen atmosphere at −78 °C because they gradually decompose at room temperature.

tert-Butyl (*Z*)-non-2-yn-4-ylidenecarbamate (1a)



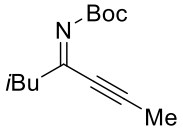
Was obtained as a colorless oil (405 mg, 1.7 mmol, 57%), following the general procedure with propyne (1 M in THF, 15 mL, 5.0 mmol, 5 eq.), *n*-BuLi (1.56 M in hexane, 2.9 mL, 4.5 mmol, 1.5 eq.), THF (15 mL) and the corresponding amidine (946 mg, 3.0 mmol) at –40 ºC.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.39 (t, J = 7.8 Hz, 2H), 2.02 (s, 3H), 1.70-1.62 (m, 2H), 1.53 (s, 9H), 1.37-1.31 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.7, 158.4, 95.6, 81.9, 74.7, 40.0, 31.1, 27.9, 25.4, 22.3, 13.9, 4.2

HRMS (ESI): calcd. for $C_{14}H_{24}O_2N$ ([M+H]$^+$): 238.1802, found: 238.1799 ([M+H]$^+$)

tert-Butyl (*Z*)-(6-methylhept-2-yn-4-ylidene)carbamate



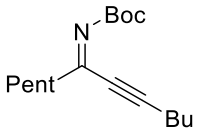
Was obtained as an colorless oil (127.2 mg, 0.57 mmol, >99%), following the general procedure with propyne (1 M in THF, 1.8 mL, 1.8 mmol, 3.2 eq.), *n*-BuLi (1.56 M in hexane, 577 µL, 0.9 mmol, 1.6 eq.), THF (4.2 mL) and the corresponding amidine (173 mg, 0.57 mmol) at –40 ºC.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.27 (d, J = 6.8 Hz, 2H), 2.21-2.11 (m, 1H), 2.02 (s, 3H), 1.53 (s, 9H), 0.97 (d, J = 6.8 Hz, 6H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.6, 157.7, 95.6, 81.8, 74.9, 48.9, 28.0, 26.2, 22.3, 4.2

HRMS (ESI): calcd. for $C_{13}H_{22}O_2N^+$ ($[M+H]^+$): 224.1645, found: 224.1645 ($[M+H]^+$)

tert-Butyl (*Z*)-dodec-7-yn-6-ylidenecarbamate



Was obtained as a colorless oil (125.3 mg, 0.45 mmol, 45%), following the general procedure with 1-hexyne (342 µL, 3.0 mmol, 3 eq.), *n*-BuLi (1.56 M in hexane, 705 µL, 1.1 mmol, 1.1 eq.), THF (10 mL) and the corresponding amidine (315 mg, 1.0 mmol) at –40 ºC.

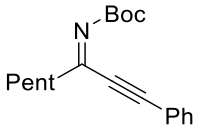
^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.42-2.31 (4H, m), 1.68-1.66 (2H, m), 1.57-1.52 (1H, m), 1.53 (s, 9H), 1.46-1.41 (3H, m), 1.33-1.31 (4H, m), 0.95-0.88 (6H, m)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.7, 158.5, 100.1, 81.9, 75.5, 40.3, 31.1, 29.9, 28.0, 25.5, 22.4, 21.9, 18.9, 13.9, 13.4

HRMS (ESI): calcd. for $C_{17}H_{30}O_2N^+$ ($[M+H]^+$): 280.2271, found: 280.2270 ($[M+H]^+$)

The geometrical configuration of this ketimine was determined by comparison with ^{1}H-NMR spectra of the one prepared by the literature procedure.[5]

tert-Butyl (*Z*)-(1-Phenyloct-1-yn-3-ylidene)carbamate



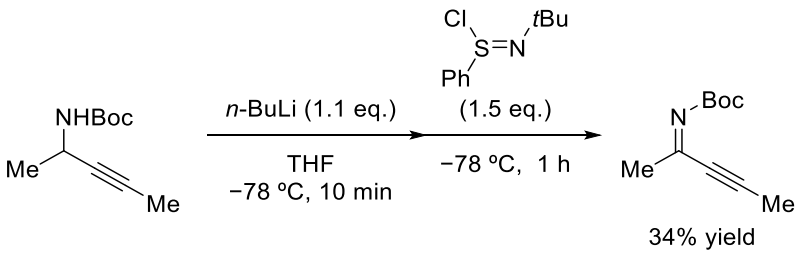
Was obtained as a pale yellow oil (362.5 mg, 1.2 mmol, 40%), following the general procedure with ethynylbenzene (990 µL, 9.0 mmol, 3 eq.), *n*-BuLi (1.56 M in hexane, 2.9 mL, 4.5 mmol, 1.5 eq.), THF (30 mL) and the corresponding amidine (946 mg, 3.0 mmol, 1 eq.) at –78 ºC.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.48 (app d, J = 7.0 Hz, 2H), 7.44-7.40 (m, 1H), 7.38-7.35 (m, 2H), 2.54 (t, J = 7.8 Hz, 2H), 1.78-1.72 (m, 2H), 1.56 (s, 9H), 1.41-1.32 (m, 4H), 0.92 (t, J = 7.3 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.4, 157.7, 132.2, 130.1, 128.4, 120.5, 96.7, 82.7, 82.1, 39.9, 31.0, 27.9, 25.4, 22.3, 13.8

HRMS (ESI): calcd. for $C_{19}H_{26}O_2N^+$ ($[M+H]^+$): 300.1958, found: 300.1956 ($[M+H]^+$)

◆ Synthesis of *tert*-butyl (*Z*)-pent-3-yn-2-ylidenecarbamate



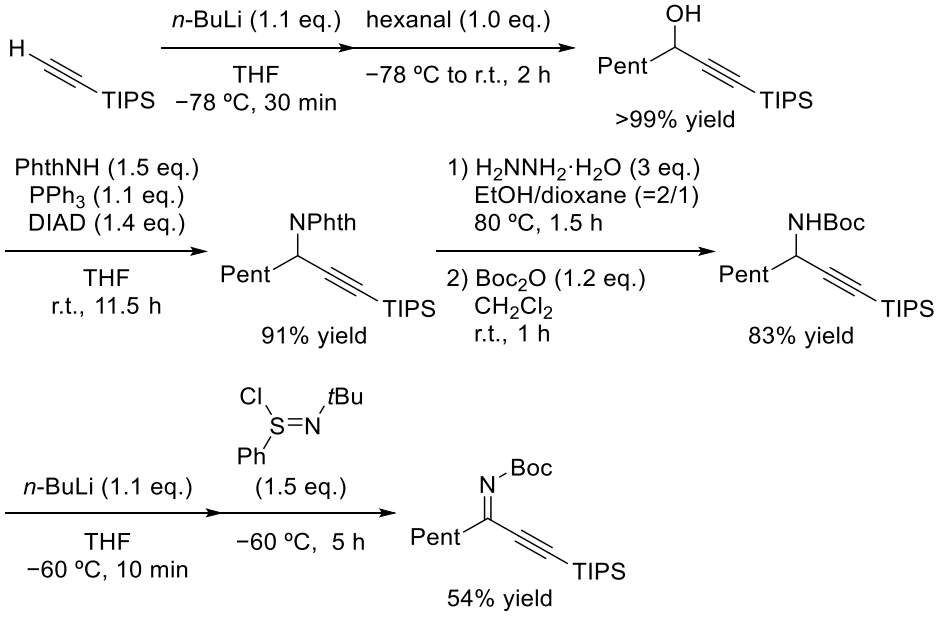
To a stirred solution of *tert*-butyl pent-3-yn-2-ylcarbamate (550 mg, 3 mmol) in THF (12 mL) was added *n*-BuLi (1.56 M in hexane, 2.1 mL, 3.3 mmol, 1.1 eq.) at –78 °C dropwise under a nitrogen atmosphere. The reaction mixture was stirred at –78 °C for 10 min. To the reaction mixture was added dropwise *N*-*tert*-butylbenzenesulfinimidoyl chloride[6] (971 mg, 4.5 mmol, 1.5 eq.) at –78 °C, and the solution was stirred for 1 h at –78 °C. The mixture was then quenched with saturated NH_4Cl aq. and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel with dry ice jacket (hexane/EtOAc = 20/1 ~ 3/1 as eluent) to afford the ketimine as an orange oil (187.5 mg, 0.97 mmol, 32% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.19 (s, 3H), 2.01 (s, 3H), 1.53 (s, 9H)

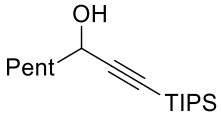
^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.3, 154.6, 95.6, 82.1, 75.3, 28.0, 27.2, 4.3

HRMS (ESI): calcd. for $C_{10}H_{15}O_2NNa^+$ ([M+Na]$^+$): 204.0995, found: 204.0997 ([M+Na]$^+$)

◆ Synthesis of *tert*-butyl (*Z*)-(1-(triisopropylsilyl)oct-1-yn-3-ylidene)carbamate



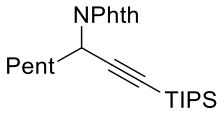
1-(Triisopropylsilyl)oct-1-yn-3-ol



To a solution of triisopropylsilylacetylene (3.4 mL, 15 mmol, 1.0 eq.) in THF (30 mL) was added *n*-BuLi (1.56 M in hexane, 10.6 mL, 16.5 mmol, 1.1 eq.) at –78 ºC. After stirring at −78 ºC for 30 min, a solution of hexanal (1.8 mL, 15 mmol, 1.0 eq.) in THF (20 mL) was added to the reaction mixture at –78 °C, and the solution was stirred for 5 h at room temperature. The mixture was then poured on ice, neutralized with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/EtOAc = 1/0 ~ 1/3 as eluent) to give the corresponding alcohol as a colorless oil (4.2 g, 15 mmol, 99% yield).

Spectroscopic data were in agreement with the ones previously reported in literature.[7]

2-(1-(Triisopropylsilyl)oct-1-yn-3-yl)isoindoline-1,3-dione



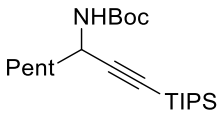
To a solution of the obtained alcohol (2.8 g, 10 mmol, 1.0 eq.), phthalimide (PhthNH) (2.2 g, 15 mmol, 1.5 eq.) and PPh_3 (2.9 g, 11 mmol. 1.1 eq.) in THF (75 mL) was added diisopropyl azodicarboxylate (DIAD) (2.7 mL, 14 mmol, 1.4 eq.) at room temperature. After stirring for 11.5 h, the mixture was poured on ice, neutralized with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in EtOH. $ZnCl_2$ (excess) was added to the solution, initiating the formation of a white precipitate.[8] The precipitate was separated by filtration and washed with EtOH. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (hexane/EtOAc = 1/0 ~ 1/3 as eluent) to give the corresponding phthaloyl protected amine as a colorless oil (3.7 g, 9.0 mmol, 90% yield).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.87-7.84 (m, 2H), 7.73-7.71 (m, 2H), 5.04 (t, J = 8.0 Hz, 1H), 2.18-2.13 (m, 1H), 2.01-1.93 (m, 1H), 1.50-1.47 (m, 1H), 1.34-1.29 (m, 5H), 1.09-1.00 (m, 21H), 0.87 (t, J = 7.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.9, 133.9, 131.9, 123.3, 103.7, 84.7, 42.5, 33.8, 31.0, 26.0, 22.4, 18.5, 13.9, 11.1

HRMS (ESI): calcd. for $C_{25}H_{37}O_2NNaSi^+$ ($[M+Na]^+$): 434.2486, found: 434.2491 ($[M+Na]^+$)

tert-Butyl (1-(triisopropylsilyl)oct-1-yn-3-yl)carbamate



To a solution of the phthaloyl protected amine (3.7 g, 9 mmol, 1.0 eq.) in EtOH/dioxane (18/9 mL) was added hydrazine monohydrate (1.3 mL, 27 mmol, 3 eq.) at room temperature. After stirring for 1.5 h at 80 ºC, the mixture was cooled to room temperature and extracted with EtOAc. The combined organic layers were washed with 1 M NaOH aq. and brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and di-*tert*-butyl dicarbonate (Boc_2O) (2.5 mL, 10.8 mmol, 1.2 eq.) was added to the solution.

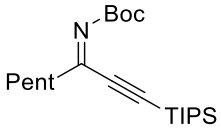
After stirring for 1 h at room temperature, 1-methylpiperazine (excess) was added.[9] After stirring for 1 h at room temperature, the mixture was then quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with 1 N HCl aq. and brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/EtOAc = 1/0 ~ 1/3 as eluent) to give the corresponding carbamate as a colorless oil (2.9 g, 7.6 mmol, 84% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.66 (br s, 1H), 4.41 (br s, 1H), 1.72-1.58 (m, 2H), 1.53-1.40 (m, 2H), 1.45 (s, 9H), 1.30-1.28 (m, 4H), 1.12-0.98 (m, 21H), 0.88 (t, J = 6.8 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.8, 107.5, 83.2, 79.5, 43.8, 36.4, 31.2, 28.3, 25.2, 22.5, 18.5, 13.9, 11.1

HRMS (ESI): calcd. for $C_{22}H_{43}O_2NNaSi^+$ ([M+Na]$^+$): 404.2955, found: 404.2956 ([M+Na]$^+$)

tert-Butyl (*Z*)-(1-(triisopropylsilyl)oct-1-yn-3-ylidene)carbamate



To a stirred solution of the obtained carbamate (169 mg, 0.44 mmol) in THF (1.8 mL) was added *n*-BuLi (1.56 M in hexane, 310 µL, 0.48 mmol, 1.1 eq.) at –60 °C dropwise under a nitrogen atmosphere. The reaction mixture was stirred at –60 °C for 10 min. To the reaction mixture was added *N*-*tert*-butylbenzenesulfinimidoyl chloride[6] (142 mg, 0.66 mmol, 1.5 eq.) dropwise at –60 °C, and the solution was stirred for 5 h at –60 °C. The mixture was then quenched with saturated NH_4Cl aq. and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel with dry ice jacket (hexane/EtOAc = 40/1 as eluent) to afford the ketimine as a colorless oil (88.8 mg, 0.24 mmol, 54% yield).

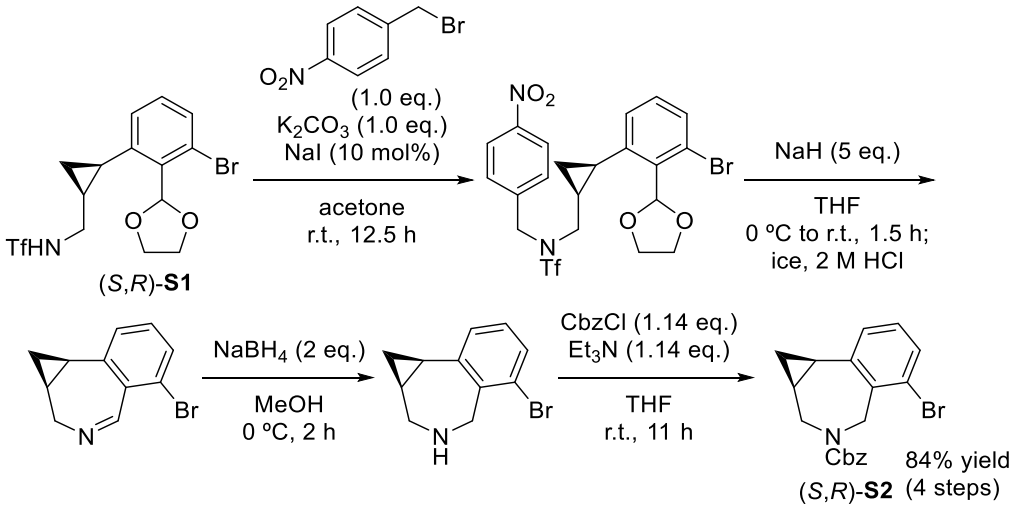
^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.45 (t, J = 7.8 Hz, 2H), 1.73-1.67 (m, 2H), 1.53 (s, 9H), 1.35-1.33 (m, 4H), 1.13-1.03 (m, 21H), 0.90 (t, J = 7.3 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 161.0, 157.4, 101.5, 99.1, 82.0, 40.4, 31.0, 28.0, 25.5, 22.3, 18.4, 13.8, 10.9

HRMS (ESI): calcd. for $C_{22}H_{41}O_2NNaSi^+$ ([M+Na]$^+$): 402.2799, found: 402.2801 ([M+Na]$^+$)

3. Synthesis of Phenylcyclopropane-Based Catalyst (*S*,*R*)-7

◆ Improved synthesis of catalyst intermediate (*S*,*R*)-S2



(*S*,*R*)-**S1** was synthesized according to the literature procedures.[10]

To a mixture of (*S*,*R*)-**S1** (860 mg, 2.0 mmol, 1.0 eq.), K_2CO_3 (276 mg, 2.0 mmol, 1.0 eq.) and NaI (29 mg, 0.2 mmol, 10 mol%) in acetone (10 mL) was added 4-nitrobenzyl bromide (432 mg, 2.0 mmol, 1.0 eq.). The reaction mixture was stirred at room temperature for 12.5 h. Water was added to quench the reaction, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The product was used for the next reaction without purification.[11]

To a solution of the obtained crude intermediate in THF (10 mL) was added NaH (60% in mineral oil, 400 mg, 10 mmol, 5 eq.) at 0 ºC. The mixture was warmed at room temperature, stirred for 1.5 h and then poured on ice. The mixture was then acidified with 2 M HCl aq. and washed with EtOAc. The aqueous layer was basified with Na_2CO_3 and 1 M NaOH aq. and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was used for the next reaction without purification.

To a solution of the crude intermediate in MeOH (10 mL) was added $NaBH_4$ (151 mg, 4 mmol, 2 eq.) at 0 °C. After stirring at 0 ºC for 2 h, the reaction mixture was quenched with H_2O, and then extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was used for the next reaction without purification.

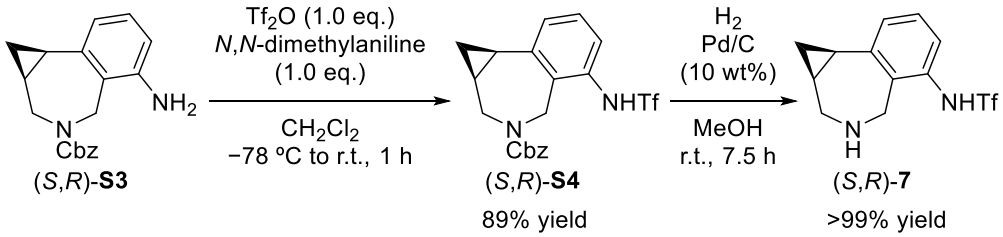
To a solution of the obtained crude intermediate in THF (6 mL) were added triethylamine (Et_3N) (318 µL, 2.3 mmol, 1.14 eq.) and benzyl chloroformate (CbzCl) (321 µL, 2.3 mmol, 1.14 eq.). After stirring at room temperature for 11 h, the mixture was quenched with H_2O and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 7/1 as eluent) to give (*S*,*R*)-**S2** as colorless oil (628.0 mg, 1.68 mmol, 84% yield for 4 steps).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.30-7.45 (m, 7H), 7.10 (t, J = 7.8 Hz, 1H), 5.69 (d, J = 12.8 Hz, 0.4H), 5.57

(d, *J* = 13.9 Hz, 0.6H), 5.10-5.24 (m, 2H), 4.61-4.65 (m, 1H), 4.50-4.53 (m, 0.6H), 4.45 (d, *J* = 14.2 Hz, 0.4H), 2.29 (app br s, 1H), 2.05-2.13 (m, 1H), 1.30 (app br s, 1H), 1.12 (app br s, 1H), 0.36 (app br s, 1H)

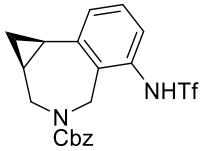
Spectroscopic data were in agreement with the ones previously reported in literature.[10]

◆ Synthesis of phenylcyclopropane-based catalyst (*S*,*R*)-7 from (*S*,*R*)-S3



(*S*,*R*)-**S3** was synthesized from (*S*,*R*)-**S2** according to the literature procedures.[10]

Triflamide (*S*,*R*)-S4

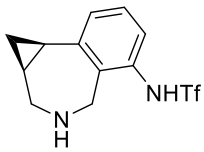


To a stirred solution of amine (*S*,*R*)-**S3** (320 mg, 1.04 mmol) in CH_2Cl_2 (50 mL) were added *N*,*N*-dimethylaniline (132 μL, 1.04 mmol, 1.0 eq.) and trifluoromethanesulfonic anhydride (Tf_2O) (174 μL, 1.04 mmol, 1.0 eq.) at −78 °C. The reaction mixture was stirred at room temperature for 1 h. The mixture was then quenched with saturated $NaHCO_3$ aq. and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 2/1 as eluent). The obtained product was dissolved in CH_2Cl_2 and washed with 4 N HCl aq. The organic layer was concentrated to afford (*S*,*R*)-**S4** as pale yellow solid (408 mg, 0.93 mmol, 89% yield).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.47 (br s, 1H), 7.43 (app d, *J* = 7.7 Hz , 1H), 7.27-7.38 (m, 7H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.06 (d, *J* = 14.7, 1H), 5.03 (d, *J* = 12.5, 1H), 4.72 (d, *J* = 14.7 Hz, 1H), 4.25 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.37 (app dd, *J* = 14.5, 8.2 Hz, 1H), 2.22 (dd, *J* = 13.6, 10.8 Hz, 1H), 1.34-1.41 (m, 1H), 1.22-1.27 (m, 1H), 0.40 (dd, *J* = 10.5, 5.1 Hz, 1H)

Spectroscopic data were in agreement with the ones previously reported in literature.[10]

Phenylcyclopropane-based catalyst (*S*,*R*)-7



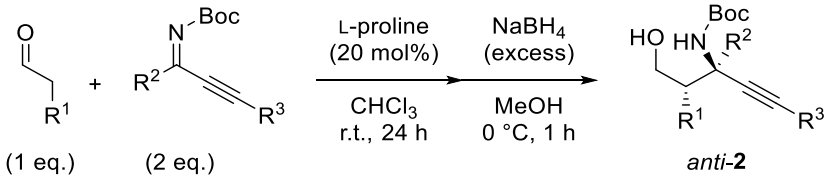
To a stirred solution of (*S*,*R*)-**S4** (315 mg, 0.71 mmol) in MeOH (7.1 mL) was added 10% palladium on carbon (31.5 mg, 10 wt%) at room temperature. The mixture was then hydrogenated under H_2 (balloon) at room

temperature for 7.5 h and filtered through a Celite pad. The solvent was removed under reduced pressure to afford (*S*,*R*)-**7** as a white solid (218 mg, 0.71 mmol, >99% yield).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.22 (app t, J = 7.8 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 4.82 (d, J = 13.0 Hz, 1H), 4.66 (d, J = 12.8 Hz, 1H), 3.79 (dd, J = 13.5, 4.7 Hz, 1H), 2.34 (dd, J = 13.6, 8.2 Hz, 1H), 2.23 (app t, J = 12.8 Hz, 1H), 1.41-1.49 (m, 1H), 1.23-1.27 (m, 1H), 0.51 (q, J = 5.1 Hz, 1H)

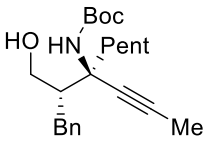
Spectroscopic data were in agreement with the ones previously reported in literature.[10]

4. General Procedure for *anti*-Selective Mannich Reaction of *Z*-Ketimines Catalyzed by L-Proline



To a mixture of L-proline (2.3 mg, 0.02 mmol, 20 mol%) and a ketimine (0.2 mmol, 2 eq.) in $CHCl_3$ (100 μL) was added an aldehyde (0.1 mmol, 1.0 eq.) at room temperature. After stirring for 24 h, the mixture was diluted with MeOH (ca. 2 mL) and cooled to 0 ºC. $NaBH_4$ (excess) was added to the mixture. After stirring for 1 h, the reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layers were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/EtOAc = 15/1 ~ 1/1 or hexane/Et_2O/EtOAc = 4/2/1 as eluent) to give the *anti*-**2**.

tert-Butyl ((*R*)-4-((*S*)-1-hydroxy-3-phenylpropan-2-yl)non-2-yn-4-yl)carbamate (*anti*-2a)



Was obtained as an oil (25.0 mg, 0.067 mmol, 67%, dr = >20/1, 97% ee), following the general procedure with 3-phenylpropanal (13 μL, 0.1 mmol) and the corresponding ketimine (47 mg, 0.2 mmol).

$[\alpha]_D^{30}$: 1.6 (*c* 1.0, $CHCl_3$)

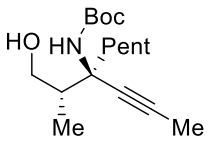
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29-7.24 (m, 4H), 7.20-7.16 (m, 1H), 4.97 (br s, 1H), 3.85 (dt, *J* = 12.5, 3.0 Hz, 1H), 3.55-3.49 (m, 1H), 2.97 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.76 (dd, *J* = 14.0, 11.5 Hz, 1H), 2.47 (br d, *J* = 8.0 Hz, 1H), 2.30 (br t, *J* = 10.8 Hz, 1H), 2.06 (br s, 1H), 1.87 (s, 3H), 1.73 (td, *J* = 12.6, 4.3 Hz, 1H), 1.59-1.51 (m, 1H), 1.47-1.40 (m, 1H), 1.45 (s, 9H), 1.35-1.33 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.0, 141.1, 129.2, 128.4, 125.9, 81.2, 80.3, 79.4, 61.2, 58.0, 49.3, 36.7, 32.8, 31.7, 28.4, 24.3, 22.6, 14.0, 3.5

HRMS (ESI): calcd. for $C_{23}H_{35}O_3NNa^+$ ($[M+Na]^+$): 396.2509, found: 396.2508 ($[M+Na]^+$)

HPLC analysis: Daicel Chiralpak IA-3-IA-3 (connected two columns), hexane/*i*PrOH = 20/1, flow rate = 0.3 mL/min, retention time; major diastereomer 43.0 min (major) and 50.0 min, minor diastereomer 41.0 min and 52.6 min (major)

tert-Butyl ((*R*)-4-((*S*)-1-hydroxypropan-2-yl)non-2-yn-4-yl)carbamate (*anti*-2b)



Was obtained as an oil (14.6 mg, 0.049 mmol, 49%, dr = 8/1), following the general procedure with propanal

(7.2 μL, 0.1 mmol) and the corresponding ketimine (47 mg, 0.2 mmol).

$[\alpha]_D^{23}$: 4.64 (*c* 1.0, $CHCl_3$)

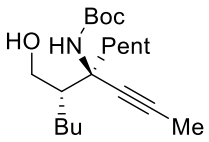
^{1}H-NMR (500 MHz, $CDCl_3$): (major diastereomer) δ 4.79 (br s, 1H), 3.73 (br t, *J* = 5.0 Hz, 2H), 2.34-2.30 (m, 1H), 2.15 (br t, *J* = 13.0 Hz, 1H), 2.02 (br s, 1H), 1.83 (s, 3H), 1.62 (td, *J* = 12.5, 4.2 Hz, 1H), 1.52-1.46 (m, 1H), 1.43 (s, 9H), 1.41-1.25 (m, 5H), 1.06 (d, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): (major diastereomer) δ 154.1, 80.7, 79.8, 79.3, 65.2, 57.6, 42.3, 36.9, 31.8, 28.4, 24.2, 22.6, 14.0, 12.4, 3.5

HRMS (ESI): calcd. for $C_{17}H_{31}O_3NNa^+$ ([M+Na]$^+$): 320.2196, found: 320.2203 ([M+Na]$^+$)

The ee was determined after benzoylation (*vide infra*).

tert-Butyl ((5*S*,6*R*)-5-(hydroxymethyl)-6-(prop-1-yn-1-yl)undecan-6-yl)carbamate (*anti*-2c)



Was obtained as an oil (24.9 mg, 0.073 mmol, 73%, dr = >20/1), following the general procedure with hexanal (12.3 μL, 0.1 mmol) and the corresponding ketimine (47 mg, 0.2 mmol).

$[\alpha]_D^{26}$: 0.45 (*c* 0.5, $CHCl_3$)

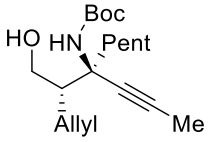
^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.86 (br s, 1H), 3.93 (br d, *J* = 12.4 Hz, 1H), 3.76-3.70 (m, 1H), 2.24-2.18 (m, 2H), 2.06-1.99 (m, 1H), 1.83 (s, 3H), 1.70-1.62 (m, 1H), 1.53-1.49 (m, 3H), 1.43 (s, 9H), 1.40-1.20 (m, 9H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.2, 80.7, 80.6, 79.4, 62.0, 57.9, 47.0, 36.9, 31.8, 30.2, 28.4, 25.8, 24.2, 22.9, 22.6, 14.1, 14.0, 3.5

HRMS (ESI): calcd. for $C_{20}H_{37}O_3NNa^+$ ([M+Na]$^+$): 362.2666, found: 362.2667 ([M+Na]$^+$)

The ee was determined after benzoylation (*vide infra*).

tert-Butyl ((4*S*,5*R*)-4-(hydroxymethyl)-5-(prop-1-yn-1-yl)dec-1-en-5-yl)carbamate (*anti*-2d)



Was obtained as an oil (14.7 mg, 0.045 mmol, 45%, dr = >20/1), following the general procedure with 4-pentenal (9.9 μL, 0.1 mmol) and the corresponding ketimine (47 mg, 0.2 mmol). The diastereomeric ratio was determined by ^{1}H-NMR spectroscopy in CD_3CN.

$[\alpha]_D^{24}$: 4.1 (*c* 1.0, $CHCl_3$)

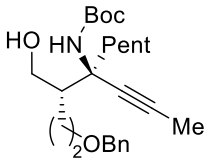
^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.91-5.83 (m, 1H), 5.12 (d, *J* = 17.0 Hz, 1H), 5.04 (d, *J* = 10.5 Hz, 1H), 4.89 (br s, 1H), 3.90 (br d, *J* = 12.0 Hz, 1H), 3.74-3.73 (m, 1H), 2.39-2.38 (m, 1H), 2.30-2.24 (m, 3H), 2.14 (br s, 1H), 1.83 (s, 3H), 1.66 (td, *J* = 12.6, 4.2 Hz, 1H), 1.51-1.30 (m, 6H), 1.43 (s, 9H), 0.90 (t, *J* = 7.3 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.1, 137.7, 116.3, 80.9, 80.1, 79.4, 62.2, 57.7, 47.0, 36.8, 31.8, 31.6, 28.4, 24.2, 22.6, 14.0, 3.5

HRMS (ESI): calcd. for $C_{19}H_{33}O_3NNa^+$ ([M+Na]$^+$): 346.2353, found: 346.2366 ([M+Na]$^+$)

The ee was determined after benzoylation (*vide infra*).

tert-Butyl ((*R*)-4-((*S*)-4-(benzyloxy)-1-hydroxybutan-2-yl)non-2-yn-4-yl)carbamate (*anti*-2e)



Was obtained as an oil (19.0 mg, 0.045 mmol, 45%, dr = >20/1, 96% ee), following the general procedure with 4-(benzyloxy)butanal (18 mg) and the corresponding ketimine (47 mg, 0.1 mmol).

$[\alpha]_D^{26}$: 16.0 (*c* 1.0, $CHCl_3$)

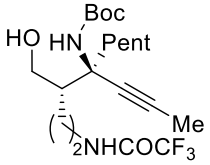
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.35-7.33 (m, 4H), 7.30-7.28 (m, 1H), 5.13 (br s, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 3.84-3.82 (m, 1H), 3.78-3.75 (m, 1H), 3.67-3.65 (m, 1H), 3.55-3.52 (m, 1H), 3.14 (dd, *J* = 7.3, 5.3 Hz, 1H), 2.23-2.22 (m, 1H), 2.16 (br s, 1H), 1.99-1.98 (m, 1H), 1.88-1.82 (m, 1H), 1.81 (s, 3H), 1.67 (td, *J* = 12.5, 4.3 Hz, 1H), 1.41 (s, 9H), 1.37-1.26 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.2, 137.8, 128.5, 127.8, 127.7, 80.1, 80.0, 79.2, 73.2, 69.6, 62.8, 57.7, 45.4, 36.4, 31.8, 28.4, 27.7, 24.1, 22.6, 14.0, 3.5

HRMS (ESI): calcd. for $C_{25}H_{39}NNaO_4^+$ ([M+Na]$^+$): 440.2771, found: 440.2770 ([M+Na]$^+$)

HPLC analysis: Daicel Chiralpak IA-3, hexane/*i*PrOH = 40/1, flow rate = 0.75 mL/min, retention time; major diastereomer 23.7 (major) min and 25.8 min , minor diastereomer 20.5 min and 28.3 min (major)

tert-Butyl ((*R*)-4-((*S*)-1-hydroxy-4-(2,2,2-trifluoroacetamido)butan-2-yl)non-2-yn-4-yl) carbamate (*anti*-2f)



Was obtained as an oil (25.9 mg, 0.061 mmol, 61%, dr = 17/1), following the general procedure with 2,2,2-trifluoro-*N*-(4-oxobutyl)acetamide (18 mg, 0.1 mmol) and the corresponding ketimine (47 mg, 0.2 mmol).

$[\alpha]_D^{30}$: 17.5 (*c* 0.63, $CHCl_3$)

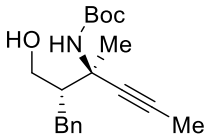
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.68 (br s, 1H), 4.80 (br s, 1H), 3.86-3.78 (m, 1H), 3.61-3.55 (m, 1H), 3.34-3.28 (m, 1H), 2.40 (br s, 2H), 2.11 (br t, *J* = 11.3 Hz, 1H), 2.05-1.98 (m, 1H), 1.82 (s, 3H), 1.80-1.73 (m, 1H), 1.62-1.57 (m, 1H), 1.53-1.47 (m, 1H), 1.42 (s, 9H), 1.37-1.28 (m, 5H), 0.90 (t, *J* = 7.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 157.4 (q, *J* = 36.7 Hz), 154.2, 116.0 (q, *J* = 288.8 Hz), 81.4, 80.0, 79.1, 62.8, 57.9, 45.2, 39.1, 37.1, 31.7, 28.3, 26.6, 24.3, 22.5, 14.0, 3.4

HRMS (ESI): calcd. for $C_{20}H_{33}N_2NaO_3F_3^+$ ([M+Na]$^+$): 445.2285, found: 445.2285 ([M+Na]$^+$)

The ee was determined after benzoylation (*vide infra*).

tert-Butyl ((2*S*,3*R*)-2-benzyl-1-hydroxy-3-methylhex-4-yn-3-yl)carbamate (*anti*-2g)



Was obtained as an oil (19.3 mg, 0.061mmol, 61%, dr = 13/1, 98% ee), following the general procedure with 3-phenylpropanal (26 μL, 0.2 mmol) and the corresponding ketimine (18 mg, 0.1 mmol).

$[\alpha]_D^{25}$: 3.4 (*c* 1.0, $CHCl_3$)

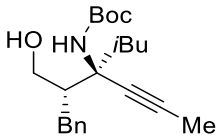
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29-7.25 (m, 4H), 7.21-7.18 (m 1H), 5.38 (br s, 1H), 3.89 (br d, *J* = 12.0 Hz, 1H), 3.57-3.52 (m, 1H), 3.01 (dd, *J* = 13.8, 3.3 Hz, 1H), 2.67 (dd, *J* = 13.5, 11.5 Hz, 1H), 2.36-2.34 (m, 1H), 1.93 (br s, 1H), 1.86 (s, 3H), 1.73 (s, 3H), 1.46 (s, 9H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.4, 140.9, 129.2, 128.4, 126.0, 81.7, 79.7, 79.5, 61.3, 54.1, 50.4, 32.7, 28.4, 26.0, 3.6

HRMS (ESI): calcd. for $C_{19}H_{27}O_3NNa^+$ ([M+Na]$^+$): 340.1883, found: 340.1891 ([M+Na]$^+$)

HPLC analysis: Daicel Chiralpak IC-3, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min, retention time; major diastereomer 30.8 min and 33.2 min (major), minor diastereomer 27.5 min (major) and 40.0 min

tert-Butyl ((*R*)-4-((*S*)-1-hydroxy-3-phenylpropan-2-yl)-6-methylhept-2-yn-4-yl)carbamate (*anti*-2h)



Was obtained as an oil (23.0 mg, 0.061 mmol, 64%, dr = >20/1, 96% ee), following the general procedure with 3-phenylpropanal (13 μL, 0.1 mmol) and the corresponding ketimine (45 mg, 0.2 mmol).

$[\alpha]_D^{29}$: −7.7 (*c* 1.0, $CHCl_3$)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.28-7.24 (m, 4H), 7.19-7.16 (m, 1H), 4.97 (br s, 1H), 3.82 (br d, *J* = 12.0 Hz, 1H), 3.53-3.50 (m, 1H), 2.97 (dd, *J* = 13.8, 2.8 Hz, 1H), 2.75 (dd, *J* = 13.5, 11.5 Hz, 1H), 2.57 (br s, 1H), 2.24 (br d, *J* = 10.0 Hz, 1H), 2.01 (br s, 1H), 1.95-1.91 (m, 1H), 1.87 (s, 3H), 1.68 (dd, *J* = 14.0, 6.5 Hz, 1H), 1.45 (s, 9H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H)

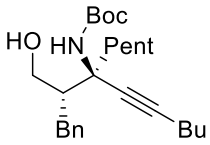
^{13}C-NMR (125 MHz, $CDCl_3$): δ 153.9, 141.1, 129.3, 128.4, 125.9, 82.0, 80.6, 79.5, 61.3, 57.5, 49.8, 44.6, 32.9, 28.4, 25.2, 24.4, 24.1, 3.5

HRMS (ESI): calcd. for $C_{22}H_{33}O_3NNa^+$ ([M+Na]$^+$): 382.2353, found: 382.2356 ([M+Na]$^+$)

HPLC analysis: Daicel Chiralpak IC-3-IC-3 (connected two columns), hexane/*i*PrOH = 40/1, flow rate = 0.9 mL/min, retention time; major diastereomer 26.3 min and 48.9 min (major), minor diastereomer 39.3 min

(major) and 44.7 min

tert-Butyl ((_R_)-6-((_S_)-1-hydroxy-3-phenylpropan-2-yl)dodec-7-yn-6-yl)carbamate (_anti_-2i)



Was obtained as an oil (25.9 mg, 0.062 mmol, 62%, dr = >20/1, 97% ee), following the general procedure with 3-phenylpropanal (13 μL, 0.1 mmol) and the corresponding ketimine (56 mg, 0.2 mmol).

$[\alpha]_D^{31}$: –0.76 (*c* 1.0, $CHCl_3$)

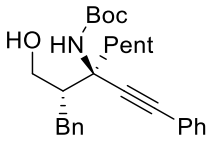
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29-7.24 (m, 4H), 7.19-7.16 (m, 1H), 4.94 (br s, 1H), 3.85 (dd, *J* = 12.0, 2.5 Hz, 1H), 3.52 (br d, *J* = 10.5 Hz, 1H), 2.97 (dd, *J* = 13.3, 2.8 Hz, 1H), 2.77 (dd, *J* = 13.8, 11.8 Hz, 1H), 2.49 (br d, *J* = 8.0 Hz, 1H), 2.32 (br t, *J* = 14.0 Hz, 1H), 2.23 (t, *J* = 7.0 Hz, 2H), 2.11 (br s, 1H), 1.73 (td, *J* = 12.6, 3.8 Hz, 1H), 1.61-1.48 (m, 3H), 1.46 (s, 9H), 1.46-1.38 (m, 3H), 1.36-1.33 (m, 4H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.0, 141.1, 129.3, 128.4, 125.9, 86.0, 81.2, 79.5, 61.3, 58.0, 49.4, 36.7, 32.9, 31.8, 30.7, 28.4, 24.3, 22.6, 22.0, 18.3, 14.0, 13.6

HRMS (ESI): calcd. for $C_{26}H_{41}O_3NNa^+$ ([M+Na]$^+$): 438.2979, found: 438.2978 ([M+Na]$^+$)

HPLC analysis: Daicel Chiralpak IB-3-IB-3 (connected two columns), hexane/*i*PrOH = 50/1, flow rate = 0.3 mL/min, retention time; major diastereomer 36.0 min and 36.8 (major) min, minor diastereomer 39.4 min and 41.1 min (major)

tert-Butyl ((_R_)-3-((_S_)-1-hydroxy-3-phenylpropan-2-yl)-1-phenyloct-1-yn-3-yl)carbamate (_anti_-2j)



Was obtained as an oil (33.5 mg, 0.077 mmol, 77%, dr = >20/1, 99% ee), following the general procedure with 3-phenylpropanal (13 μL, 0.1 mmol) and the corresponding ketimine (60 mg, 0.2 mmol).

$[\alpha]_D^{30}$: 13.1 (*c* 1.0, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44-7.43 (m, 2H), 7.31-7.26 (m, 7H), 7.22-7.19 (m, 1H), 5.17 (br s, 1H), 3.95 (br d, *J* =12.4 Hz, 1H), 3.63-3.59 (m, 1H), 3.06 (dd, *J* = 13.2, 2.8 Hz, 1H), 2.83 (dd, *J* = 13.2, 11.6 Hz, 1H), 2.57 (br d, *J* = 8.0 Hz, 1H), 2.43 (br t, *J* = 11.2 Hz, 1H), 2.04 (br s, 1H), 1.87 (td, *J* = 12.8, 4.4 Hz, 1H), 1.69-1.55 (m, 1H), 1.56-1.49 (m, 1H), 1.47 (s, 9H), 1.41-1.31 (m, 4H), 0.92 (t, *J* = 6.8 Hz, 3H)

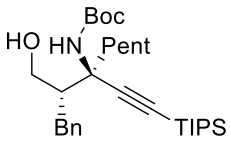
^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.2, 140.9, 131.7, 129.3, 128.5, 128.5, 128.4, 126.0, 122.4, 90.2, 85.2, 79.7, 61.4, 58.6, 49.6, 36.6, 32.9, 31.8, 28.4, 24.4, 22.6, 14.0

HRMS (ESI): calcd. for $C_{28}H_{37}O_3NNa^+$ ([M+Na]$^+$): 458.2666, found: 458.2662 ([M+Na]$^+$)

HPLC analysis: Daicel Chiralpak IC, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min, retention time; major

diastereomer 9.9 min (major) and 11.7 min, minor diastereomer 13.0 min (major) and 17.8 min

tert-Butyl ((_R_)-3-((_S_)-1-hydroxy-3-phenylpropan-2-yl)-1-(triisopropylsilyl)oct-1-yn-3-yl) carbamate (_anti_-2k)



Was obtained as a white solid (21.7 mg, 0.042 mmol, 42%, dr = >20/1, 96% ee), following the general procedure with 3-phenylpropanal (13 μL, 0.1 mmol) and the corresponding ketimine (113 mg, 0.2 mmol).

$[\alpha]_D^{24}$: −1.2 (*c* 0.5, $CHCl_3$)

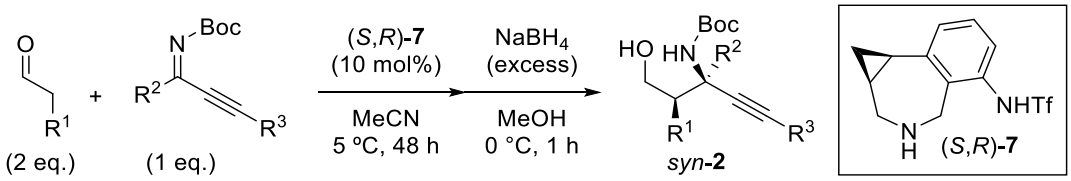
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29-7.23 (m, 4H), 7.18 (t, *J* = 7.0 Hz, 1H), 4.96 (br s, 1H), 3.89 (br d, *J* = 12.0 Hz, 1H), 3.55 (br s, 1H), 2.99 (br d, *J* = 13.0 Hz, 1H), 2.81 (dd, *J* = 13.5, 11.5 Hz, 1H), 2.52 (br s, 1H), 2.37 (br s, 1H), 2.15 (br s, 1H), 1.78 (td, *J* = 12.8, 3.7 Hz, 1H), 1.62-1.59 (m, 1H), 1.46 (s, 9H), 1.35-1.21 (m, 5H), 1.09 (s, 21H), 0.90 (t, *J* = 7.3 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 153.9, 140.9, 129.3, 128.4, 126.0, 108.7, 86.1, 79.6, 61.3, 58.7, 49.3, 36.8, 33.0, 31.8, 28.4, 24.4, 22.6, 18.6, 14.0, 11.2

HRMS (ESI): calcd. for $C_{31}H_{53}O_3NNaSi^+$ ($[M+Na]^+$): 538.3687, found: 538.3689 ($[M+Na]^+$)

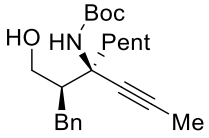
HPLC analysis: Daicel Chiralpak IG, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min, retention time; major diastereomer 6.9 min (major) and 8.0 min, minor diastereomer 5.7 min (major) and 6.3 min

5. General Procedure for *syn*-Selective Mannich Reaction of *Z*-Ketimines Catalyzed (*S*,*R*)-7



To a mixture of (*S*,*R*)-**7** (3.1 mg, 0.01 mmol, 10 mol%) and a ketimine (0.1 mmol, 1 eq.) in MeCN (100 μL) was added an aldehyde (0.2 mmol, 2 eq.) at 5 ºC. After stirring for 48 h, the mixture was diluted with MeOH (ca. 2 mL) and $NaBH_4$ (excess) was added to the mixture. After stirring for 1 h, the reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layers were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/Et_2O/EtOAc = 4/2/1 or hexane/EtOAc = 40/1 as eluent) to give the *syn*-**2**.

tert-Butyl ((*R*)-4-((*R*)-1-hydroxy-3-phenylpropan-2-yl)non-2-yn-4-yl)carbamate (*syn*-2a)



Was obtained as a colorless oil (31.5 mg, 0.084 mmol, 84%, dr = 13/1, 99% ee), following the general procedure with 3-phenylpropanal (26 μL, 0.2 mmol) and the corresponding ketimine (24 mg, 0.1 mmol).

$[\alpha]_D^{27}$: 8.0 (*c* 1.0, $CHCl_3$)

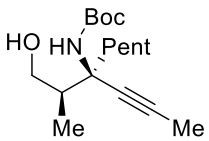
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29-7.26 (m, 4H), 7.19-7.18 (m, 1H), 5.15 (s, 1H), 3.81 (d, *J* = 12.0 Hz, 1H), 3.55-3.52 (m, 1H), 2.92 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.77 (app t, *J* = 12.8 Hz, 1H), 2.33-2.32 (m, 2H), 2.19 (br s, 1H), 1.89-1.86 (m, 1H), 1.88 (s, 3H), 1.53-1.50 (m, 1H), 1.43 (s, 9H), 1.34-1.33 (m, 5H), 0.91 (t, *J* = 6.8 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.4, 140.8, 129.2, 128.3, 125.9, 80.8, 80.4, 79.5, 60.8, 57.9, 49.4, 36.5, 33.2, 31.7, 28.3, 23.9, 22.6, 14.0, 3.5.

HRMS (ESI): calcd. for $C_{23}H_{35}O_3NNa^+$ ($[M+Na]^+$): 396.2509, found: 396.2508 ($[M+Na]^+$)

HPLC analysis: Daicel Chiralpak IA-3-IA-3 (connected two columns), hexane/*i*PrOH = 20/1, flow rate = 0.3 mL/min, retention time; major diastereomer 40.7 min (major) and 52.5 min, minor diastereomer 43.1 min and 50.0 min (major)

tert-Butyl ((*R*)-4-((*R*)-1-hydroxypropan-2-yl)non-2-yn-4-yl)carbamate (*syn*-2b)



Was obtained as an oil (24.5 mg, 0.084 mmol, 84%, dr = >20/1), following the general procedure with 1-

propanal (14 µL, 0.2 mmol) and the corresponding ketimine (24 mg, 0.1 mmol).

$[\alpha]_D^{28}$: 10.4 (*c* 1.0, $CHCl_3$)

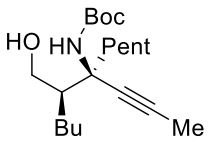
^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.04 (s, 1H), 3.81-3.77 (m, 1H), 3.72-3.69 (m, 1H), 2.32 (br s, 1H), 2.03 (br s, 2H), 1.82 (s, 3H), 1.76 (td, *J* = 12.6, 3.8 Hz, 1H), 1.43 (s, 9H), 1.31 (br s, 5H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.2, 80.5, 79.6, 79.3, 65.5, 58.2, 41.5, 36.3, 31.7, 28.4, 23.5, 22.6, 14.0, 13.1, 3.4

HRMS (ESI): calcd. for $C_{17}H_{31}O_3NNa^+$ ([M+Na]$^+$): 320.2196, found: 320.2197 ([M+Na]$^+$)

The ee was determined after benzoylation (*vide infra*).

tert-Butyl ((5*R*,6*R*)-5-(hydroxymethyl)-6-(prop-1-yn-1-yl)undecan-6-yl)carbamate (*syn*-2c)



Was obtained as a colorless oil (27.4 mg, 0.081 mmol, 81%, dr = >20/1), following the general procedure with hexanal (25 µL, 0.2 mmol) and the corresponding ketimine (24 mg, 0.1 mmol).

$[\alpha]_D^{26}$: 13.2 (*c* 1.0, $CHCl_3$)

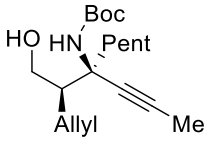
^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.08 (br s, 1H), 3.87 (d, *J* = 11.5 Hz, 1H), 3.76-3.75 (m, 1H), 2.35 (br s, 1H), 2.02 (br s, 2H), 1.82 (s, 3H), 1.80-1.74 (m, 1H), 1.51-1.45 (m, 3H), 1.42 (s, 9H), 1.40-1.23 (m, 8H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.3, 80.5, 80.3, 79.3, 62.0, 58.1, 46.9, 36.2, 31.7, 30.3, 28.3, 26.6, 23.7, 22.9, 22.6, 14.1, 14.0, 3.4

HRMS (ESI): calcd. for $C_{20}H_{37}O_3NNa^+$ ([M+Na]$^+$): 362.2666, found: 362.2670 ([M+Na]$^+$)

The ee was determined after benzoylation (*vide infra*).

tert-Butyl ((4*R*,5*R*)-4-(hydroxymethyl)-5-(prop-1-yn-1-yl)dec-1-en-5-yl)carbamate (*syn*-2d)



Was obtained as an oil (24.9 mg, 0.077 mmol, 77%, dr = >20/1), following the general procedure with 4-pentenal (19 µL, 0.2 mmol) the corresponding ketimine (24 mg, 0.1 mmol). The diastereomeric ratio was determined by ^{1}H-NMR spectroscopy in CD_3CN.

$[\alpha]_D^{28}$: 4.1

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.90-5.82 (m, 1H), 5.12 (br s, 1H), 5.11 (d, *J* = 17.0 Hz, 1H), 5.04 (d, *J* = 10.5 Hz, 1H), 3.86 (d, *J* = 12.5 Hz, 1H), 3.79-3.74 (m, 1H), 2.34-2.21 (m, 3H), 2.17-2.16 (m, 1H), 2.08 (br t, *J* = 12.5 Hz, 1H), 1.83 (s, 3H), 1.82-1.76 (m, 1H), 1.49-1.48 (m, 1H), 1.43 (s, 9H), 1.33-1.28 (m, 5H), 0.89 (t, *J* = 7.0

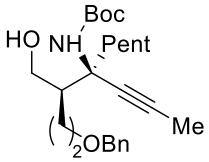
Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.3, 137.4, 116.3, 80.6, 80.0, 79.4, 61.9, 57.8, 46.7, 36.3, 31.9, 31.7, 28.3, 23.7, 22.5, 14.0, 3.5

HRMS (ESI): calcd. for $C_{19}H_{33}O_3NNa^+$ ([M+Na]$^+$): 346.2353, found: 346.2360 ([M+Na]$^+$)

The ee was determined after benzoylation (*vide infra*).

tert-Butyl ((*R*)-4-((*R*)-4-(benzyloxy)-1-hydroxybutan-2-yl)non-2-yn-4-yl)carbamate (*syn*-2e)



Was obtained as an oil (28.4 mg, 0.068 mmol, 68%, dr = >20/1, 99% ee), following the general procedure with 4-(benzyloxy)butanal (18 mg, 0.2 mmol) and the corresponding ketimine (24 mg, 0.1 mmol).

$[\alpha]_D^{27}$: 3.3 (*c* 1.00, $CHCl_3$)

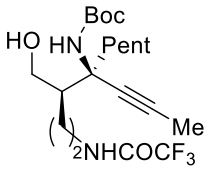
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 5.10 (br s, 1H), 4.52 (q, *J* = 12.0 Hz, 2H), 3.81-3.78 (m, 2H), 3.66-3.64 (m, 1H), 3.57-3.53 (m, 1H), 3.00 (br t, *J* = 6.0 Hz, 1H), 2.21-2.20 (m, 1H), 2.07 (br s, 1H), 1.98-1.92 (m, 1H), 1.89-1.83 (m, 1H), 1.81 (s, 3H), 1.71 (td, *J* = 12.6, 3.6 Hz, 1H), 1.67 (br s, 1H), 1.42 (s, 9H), 1.37-1.26 (m, 5H), 0.89 (*t*, *J* = 7.8 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.2, 138.0, 128.4, 127.8, 127.7, 80.2, 80.0, 79.3, 73.2, 69.4, 62.2, 57.8, 45.2, 36.4, 31.8, 28.4, 27.9, 23.9, 22.6, 14.0, 3.5

HRMS (ESI): calcd. for $C_{25}H_{39}O_4NNa^+$ ([M+Na]$^+$): 440.2771, found: 440.2781 ([M+Na]$^+$)

HPLC analysis: Daicel Chiralpak IA-3, hexane/*i*PrOH = 40/1, flow rate = 0.75 mL/min, retention time; major diastereomer 20.4 min (major) and 28.6 min, minor diastereomer 24.3 min and 26.0 min (major)

tert-Butyl ((*R*)-4-((*R*)-1-hydroxy-4-(2,2,2-trifluoroacetamido)butan-2-yl)non-2-yn-4-yl) carbamate (*syn*-2f)



Was obtained as an oil (25.8 mg, 0.061 mmol, 61%, dr = >20/1), following the general procedure with 2,2,2-trifluoro-*N*-(4-oxobutyl)acetamide (37 mg, 0.2 mmol) and the corresponding ketimine (24 mg, 0.1 mmol) at 0 ^{o}C.

$[\alpha]_D^{30}$: 4.2 (*c* 1.0, $CHCl_3$)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.68 (br s, 1H), 4.88 (s, 1H), 3.85 (br s, 2H), 3.60-3.57 (m, 1H), 3.35-3.31 (m, 1H), 2.71 (br s, 1H), 2.27-2.26 (m, 1H), 2.07 (t, *J* = 11.8 Hz, 1H), 2.00-1.93 (m, 1H), 1.82 (s, 3H), 1.80-1.73 (m, 1H), 1.62-1.59 (m, 1H), 1.52-1.47 (m, 1H), 1.42 (s, 9H), 1.33-1.29 (m, 5H), 0.90 (t, *J* = 7.0 Hz, 3H)

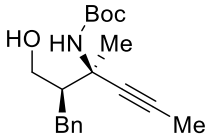
^{13}C-NMR (125 MHz, $CDCl_3$): δ 157.3 (q, *J* = 37.1 Hz), 154.3, 116.0 (q, *J* = 298.8 Hz), 81.0, 80.0, 79.7, 62.0, 57.7, 45.9, 39.1, 36.0, 31.6, 28.3, 26.9, 23.9, 22.6, 14.0, 3.4

^{19}F-NMR (466 MHz, $CDCl_3$): δ –75.9

HRMS (ESI): calcd. for $C_{20}H_{33}N_2NaO_3F_3^+$ ($[M+Na]^+$): 445.2285, found: 445.2285 ($[M+Na]^+$)

The ee was determined after benzoylation (*vide infra*).

tert-Butyl ((2*R*,3*R*)-2-benzyl-1-hydroxy-3-methylhex-4-yn-3-yl)carbamate (*syn*-2g)



Was obtained as an oil (28.6 mg, 0.063 mmol, 63%, dr = 10/1, 99% ee), following the general procedure with 3-phenylpropanal (26 μL, 0.2 mmol) and the corresponding ketimine (18 mg, 0.1 mmol).

$[\alpha]_D^{25}$: 11.6 (*c* 1.0, $CHCl_3$)

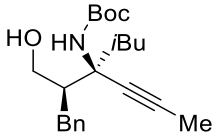
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.28-7.25 (m, 4H), 7.21-7.18 (m, 1H), 5.45 (s, 1H), 3.80 (d, *J* = 12.0 Hz, 1H), 3.63-3.59 (m, 1H), 2.95 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.67 (app t, *J* = 12.9 Hz, 1H), 2.28-2.26 (m, 1H), 2.15 (br s, 1H), 1.87 (d, *J* = 1.0 Hz, 3H), 1.70 (s, 3H), 1.45 (s, 9H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.5, 140.7, 129.2, 128.4, 126.0, 81.1, 79.62, 79.56, 61.2, 53.9, 50.5, 33.2, 28.4, 26.5, 3.6

HRMS (ESI): calcd. for $C_{19}H_{27}O_3NNa^+$ ($[M+Na]^+$): 340.1883, found: 340.1892 ($[M+Na]^+$)

HPLC analysis: Daicel Chiralpak IC-3, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min, retention time; major diastereomer 27.3 min and 40.0 min (major), minor diastereomer 30.8 min (major) and 33.5 min

tert-Butyl ((*R*)-4-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-6-methylhept-2-yn-4-yl)carbamate (*syn*-2h)



Was obtained as an oil (21.5 mg, 0.060 mmol, 60%, dr = >20/1, 99% ee), following the general procedure with 3-phenylpropanal (26 μL, 0.2 mmol) and the corresponding ketimine (22 mg, 0.1 mmol) at 0 °C.

$[\alpha]_D^{26}$: 10.3 (*c* 1.0, $CHCl_3$)

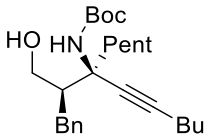
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29-7.26 (m, 5H), 7.18 (tt, *J* = 6.6, 2.3 Hz, 1H), 5.14 (s, 1H), 3.81 (d, *J* = 12.0 Hz, 1H), 3.53-3.50 (br m, 1H), 2.89 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.78 (dd, *J* = 13.5, 11.5 Hz, 1H), 2.41-2.36 (m, 1H), 2.32 (br s, 1H), 2.17 (br s, 1H), 1.97-1.92 (m, 1H), 1.88 (s, 3H), 1.79 (dd, *J* = 14.0, 6.0 Hz, 1H), 1.43 (s, 9H), 1.02 (dd, *J* = 19.0, 6.5 Hz, 6H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.3, 140.9, 129.3, 128.4, 125.9, 81.5, 80.6, 79.6, 60.8, 57.6, 49.9, 44.2, 33.4, 28.4, 25.0, 24.3, 24.1, 3.5.

HRMS (ESI): calcd. for $C_{22}H_{33}O_3NNa^+$ ([M+Na]$^+$): 382.2353, found: 382.2358 ([M+Na]$^+$)

HPLC analysis: Daicel Chiralpak IC-3-IC-3 (connected two columns), hexane/*i*PrOH = 40/1, flow rate = 0.9 mL/min, retention time; major diastereomer 39.3 min and 44.1 min (major), minor diastereomer 26.3 min (major) and 50.5 min

tert-Butyl ((*R*)-6-((*R*)-1-hydroxy-3-phenylpropan-2-yl)dodec-7-yn-6-yl)carbamate (*syn*-2i)



Was obtained as an colorless oil (31.6 mg, 0.076 mmol, 76%, dr = 16/1, 98% ee), following the general procedure with 3-phenylpropanal (26 μL, 0.2 mmol) and the corresponding ketimine (28 mg, 0.1 mmol).

$[\alpha]_D^{30}$: 7.8 (*c* 1.0, $CHCl_3$)

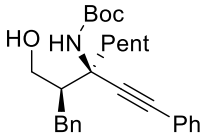
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.30-7.25 (m, 4H), 7.20-7.18 (m, 1H), 5.11 (s, 1H), 3.81 (dt, *J* = 12.3, 3.0 Hz, 1H), 3.54-3.51 (m, 1H), 2.92 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.78 (dd, *J* = 13.3, 11.8 Hz, 1H), 2.35-2.34 (m, 2H), 2.25 (t, *J* = 7.0 Hz, 2H), 2.22 (br s, 1H), 1.86 (td, *J* = 12.6, 3.7 Hz, 1H), 1.54-1.48 (m, 3H), 1.45-1.42 (m, 2H), 1.43 (s, 9H), 1.37-1.32 (m, 5H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.6, 141.1, 129.4, 128.5, 126.1, 85.7, 81.5, 79.7, 60.9, 58.1, 49.6, 36.6, 33.4, 31.9, 31.0, 28.5, 24.1, 22.8, 22.1, 18.5, 14.2, 13.7

HRMS (ESI): calcd. for $C_{26}H_{41}O_3NNa^+$ ([M+Na]$^+$): 438.2979, found: 438.2983 ([M+Na]$^+$)

HPLC analysis: Daicel Chiralpak IB-3-IB-3 (connected two columns), hexane/*i*PrOH = 50/1, flow rate = 0.3 mL/min, retention time; major diastereomer 39.1 min (major) and 41.1 min, minor diastereomer 36.0 min (major) and 36.9 min

tert-Butyl ((*R*)-3-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-1-phenyloct-1-yn-3-yl)carbamate (*syn*-2j)



Was obtained as a white solid (31.0 mg, 0.071 mmol, 71%, dr = 15/1, 99% ee), following the general procedure with 3-phenylpropanal (26 μL, 0.2 mmol) and the corresponding ketimine (30 mg, 0.1 mmol) at 0 ºC.

$[\alpha]_D^{27}$: 5.2 (*c* 1.0, $CHCl_3$)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.47-7.42 (m, 2H), 7.35-7.31 (m, 3H), 7.29-7.26 (m, 4H), 7.21-7.19 (m, 1H), 5.37 (br s, 1H), 3.86 (br dt, *J* = 12.3, 2.9 Hz, 1H), 3.63-3.61 (m, 1H), 3.04 (dd, *J* = 13.8, 3.3 Hz, 1H), 2.86 (t, *J* = 12.5 Hz, 1H), 2.40-2.26 (m, 3H), 2.04 (td, *J* = 13.0, 4.2 Hz, 1H), 1.57-1.52 (m, 3H), 1.46 (s, 9H), 1.41-1.33 (m, 3H), 0.92 (t, *J* = 7.0 Hz, 3H)

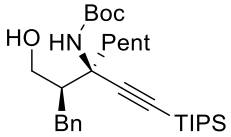
^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.8, 140.7, 131.7, 129.3, 128.42, 128.37, 128.3, 126.0, 122.6, 90.4, 85.0,

79.9, 60.7, 58.4, 49.8, 36.5, 33.3, 31.7, 28.4, 23.9, 22.6, 14.0

HRMS (ESI): calcd. for $C_{28}H_{37}O_3NNa^+$ ([M+Na]$^+$): 458.2666, found: 458.2668 ([M+Na]$^+$)

HPLC analysis: Daicel Chiralpak IC, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min, retention time; major diastereomer 13.5 min and 17.2 min (major), minor diastereomer 10.4 min and 11.5 min (major)

tert-Butyl ((*R*)-3-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-1-(triisopropylsilyl)oct-1-yn-3-yl) carbamate (*syn*-2k)



Was obtained as a white solid (41.3 mg, 0.080 mmol, 80%, dr = 20/1, >99% ee), following the general procedure with 3-phenylpropanal (26 μL, 0.2 mmol) and the corresponding ketimine (38 mg, 0.1 mmol).

$[\alpha]_D^{29}$: 5.6 (*c* 1.0, $CHCl_3$)

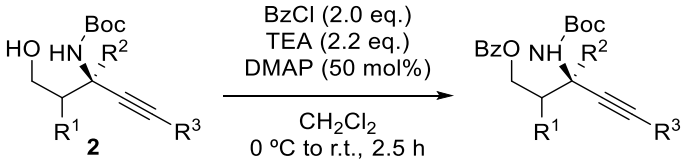
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.30-7.24 (m, 4H), 7.19 (t, *J* = 7.5 Hz, 1H), 5.11 (s, 1H), 3.82 (d, *J* = 12.0 Hz, 1H), 3.55 (br s, 1H), 2.96 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.84 (t, *J* = 12.5 Hz, 1H), 2.39 (app d, *J* = 11.0 Hz, 2H), 2.25 (br s, 1H), 1.93 (td, *J* = 12.9, 4.2 Hz, 1H), 1.59 (br s, 1H), 1.47-1.39 (m, 1H), 1.44 (s, 9H), 1.35-1.33 (m, 4H), 1.10 (app br s, 21H), 0.90 (t, *J* = 6.5 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 154.3, 140.7, 129.3, 128.4, 126.0, 108.7, 85.9, 79.8, 60.8, 58.5, 49.4, 36.5, 33.5, 31.7, 28.4, 24.0, 22.6, 18.6, 14.0, 11.2

HRMS (ESI): calcd. for $C_{31}H_{53}O_3NNaSi^+$ ([M+Na]$^+$): 538.3687, found: 538.3688 ([M+Na]$^+$)

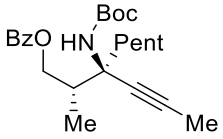
HPLC analysis: Daicel Chiralpak IG, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min, retention time; major diastereomer 5.7 min (major) and 6.2 min, minor diastereomer 6.9 min (major) and 8.0 min

6. General Procedure for Benzoylation of Mannich Products



To a solution of **2** in CH_2Cl_2 (0.1 M) were added benzoyl chloride (2.0 eq.), triethylamine (TEA) (2.2 eq.) and DMAP (50 mol%) at 0 ºC. After stirring the mixture for 1-2.5 h at room temperature, the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by preparative thin layer chromatography (hexane/EtOAc = 7/1 or 3/1).

(2*S*,3*R*)-3-((*tert*-Butoxycarbonyl)amino)-2-methyl-3-(prop-1-yn-1-yl)octyl benzoate



Was obtained as an oil (9.7 mg, 0.024 mmol, 78%, dr = 8/1, 99% ee), following the general procedure with *anti*-**2b** (9.2 mg, 0.031 mmol, dr = 8/1).

$[\alpha]_D^{28}$: 7.9 (*c* 1.0, $CHCl_3$)

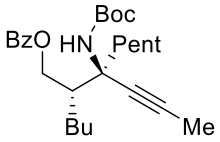
^{1}H-NMR (500 MHz, $CDCl_3$): (major diastereomer) δ 8.05 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 4.81 (br s, 1H), 4.47 (dd, *J* = 11.5, 5.0 Hz, 1H), 4.26 (dd, *J* = 11.0, 7.5 Hz, 1H), 2.84 (br s, 1H), 2.30 (br s, 1H), 1.81 (s, 3H), 1.70 (dt, *J* = 12.8, 4.0 Hz, 1H), 1.53-1.51 (m, 1H), 1.43 (s, 9H), 1.32-1.26 (m, 5H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): (major diastereomer) δ 166.6, 153.6, 132.9, 130.4, 129.6, 128.3, 80.7, 79.2, 78.7, 67.3, 58.4, 39.3, 36.4, 31.7, 28.4, 24.3, 22.6, 14.0, 13.4, 3.4

HRMS (ESI): calcd. for $C_{24}H_{35}O_4NNa^+$ ($[M+Na]^+$): 424.2458, found: 424.2458 ($[M+Na]^+$)

HPLC analysis: Daicel Chiralpak ID-AD-3 (connected two columns), hexane/*i*PrOH = 20/1, flow rate = 0.3 mL/min, retention time; major diastereomer 33.9 min (major) and 39.1 min, minor diastereomer 37.3 min (major) and 46.9 min

(2*S*,3*R*)-3-((*tert*-Butoxycarbonyl)amino)-2-butyl-3-(prop-1-yn-1-yl)octyl benzoate



Was obtained as an oil (15.8 mg, 0.016 mmol, 38%, dr = >20/1, 98% ee), following the general procedure with *anti*-**2c** (14.3 mg, 0.042 mmol, dr = >20/1).

$[\alpha]_D^{30}$: 17.5 (*c* 0.63, $CHCl_3$)

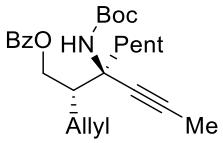
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.0 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 4.87 (br s, 1H), 4.45 (d, *J* = 4.5 Hz, 2H), 2.62 (br s, 1H), 2.32 (br s, 1H), 1.77 (s, 3H), 1.73-1.67 (m, 2H), 1.53-1.48 (m, 3H), 1.42 (s, 9H), 1.40-1.26 (m, 8H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.6, 153.6, 132.8, 130.4, 129.7, 128.3, 80.1, 79.6, 79.1, 65.2, 58.8, 43.8, 36.4, 31.8, 30.1, 28.4, 27.5, 24.3, 22.8, 22.6, 14.03, 14.00, 3.5

HRMS (ESI): calcd. for $C_{27}H_{41}O_4NNa^+$ ([M+Na]$^+$): 466.2928, found: 466.2930 ([M+Na]$^+$)

HPLC analysis: Daicel Chiralpak IG, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min, retention time; major diastereomer 7.2 min (major) and 10.0 min, minor diastereomer 7.9 min and 8.6 min (major)

(2*S*,3*R*)-2-Allyl-3-((*tert*-butoxycarbonyl)amino)-3-(prop-1-yn-1-yl)octyl benzoate



Was obtained as an oil (12.8 mg, 0.030 mmol, 67%, dr = >20/1, 99% ee), following the general procedure with *anti*-**2d** (14.7 mg, 0.045 mmol, dr = >20/1).

$[\alpha]_D^{26}$: 4.5 (*c* 1.00, $CHCl_3$)

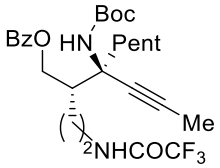
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 5.93-5.84 (m, 1H), 5.07 (d, *J* = 17.0 Hz, 1H), 5.02 (d, *J* = 10.5 Hz, 1H), 4.86 (br s, 1H), 4.47-4.40 (m, 2H), 2.79 (br s, 1H), 2.58-2.53 (m, 1H), 2.33 (br s, 1H), 2.25 (dt, *J* = 14.3, 9.1 Hz, 1H), 1.78 (s, 3H), 1.74-1.68 (m, 1H), 1.54-1.46 (m, 1H), 1.43 (s, 9H), 1.34-1.25 (m, 5H), 0.87 (t, *J* = 7.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.5, 153.6, 137.0, 132.8, 130.3, 129.6, 128.3, 116.4, 80.6, 79.2, 64.6, 58.5, 43.8, 36.4, 32.8, 31.7, 28.4, 24.2, 23.9, 22.6, 14.0, 3.4

HRMS (ESI): calcd. for $C_{26}H_{37}O_4NNa^+$ [(M+Na)$^+$]: 450.2615, found: 450.2617 [(M+Na)$^+$]

HPLC analysis: Daicel Chiralpak IG, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min, retention time; major diastereomer 7.9 min (major) and 11.5 min, minor diastereomer 9.2 min (major) and 9.9 min

(2*S*,3*R*)-3-((*tert*-Butoxycarbonyl)amino)-3-(prop-1-yn-1-yl)-2-(2-(2,2,2-trifluoroacetamido)-ethyl)octyl benzoate



Was obtained as an oil (16.1 mg, 0.031 mmol, 73%, dr = >20/1, 99% ee), following the general procedure with *anti*-**2f** (17.6 mg, 0.042 mmol, dr = >20/1).

$[\alpha]_D^{32}$: 1.3 (*c* 1.00, $CHCl_3$)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.27 (br s, 1H), 4.88 (br s, 1H), 4.48-4.40 (m, 2H), 3.57 (app q, *J* = 6.2 Hz, 2H), 2.90 (br s, 1H), 2.20 (t, *J* = 11.8 Hz, 1H), 2.11-2.05 (m, 1H), 1.79 (s, 3H), 1.77-1.71 (m, 2H), 1.53 (m, 1H), 1.41 (s, 9H), 1.34-1.26 (m, 5H), 0.88 (t, *J* = 6.8 Hz, 3H)

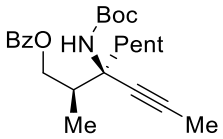
^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.7, 157.4 (q, *J* = 37.1 Hz), 154.2, 133.2, 129.9, 129.6, 128.4, 115.9 (q, *J* = 288.9 Hz), 81.4, 80.1, 78.3, 65.5, 58.9, 41.5, 38.4, 37.1, 31.6, 28.3, 27.3, 24.2, 22.5, 14.0, 3.4

^{19}F-NMR (466 MHz, $CDCl_3$): δ –75.7

HRMS (ESI): calcd. for $C_{27}H_{37}O_5N_2F_3Na^+$ [$(M+Na)^+$]: 549.2547, found: 549.2554 [$(M+Na)^+$]

HPLC analysis: Daicel Chiralpak IC, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min, retention time; major diastereomer 25.7 min and 42.2 min (major), minor diastereomer 17.4 min and 22.6 min (major)

(2*R*,3*R*)-3-((*tert*-Butoxycarbonyl)amino)-2-methyl-3-(prop-1-yn-1-yl)octyl benzoate



Was obtained as an oil (8.8 mg, 0.022 mmol, 26%, dr = >20/1, 99% ee), following the general procedure with *syn*-**2b** (24.5 mg, 0.85 mmol, dr = >20/1).

$[\alpha]_D^{28}$: 7.1 (*c* 1.0, $CHCl_3$)

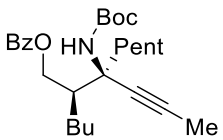
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.5 Hz, 2H), 7.57-1.53 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 4.92 (br s, 1H), 4.53 (dd, *J* = 11.0, 4.5 Hz, 1H), 4.32 (dd, *J* = 11.0, 7.5 Hz, 1H), 2.79 (br s, 1H), 2.17 (br s, 1H), 1.79 (s, 3H), 1.71 (td, *J* = 12.6, 5.0 Hz, 1H), 1.53-1.46 (m, 1H), 1.40 (s, 9H), 1.37-1.25 (m, 5H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 6.5 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.8, 153.7, 132.8, 130.4, 129.6, 128.3, 80.6, 79.2, 78.6, 67.6, 58.0, 38.7, 35.8, 31.7, 28.4, 23.7, 22.6, 14.0, 13.5, 3.4

HRMS (ESI): calcd. for $C_{24}H_{35}O_4NNa^+$ ([M+Na]$^+$): 424.2458, found: 424.2468 ([M+Na]$^+$)

HPLC analysis: Daicel Chiralpak ID-AD-3 (connected two columns), hexane/*i*PrOH = 20/1, flow rate = 0.3 mL/min, retention time; major diastereomer 37.3 min (major) and 47.3 min, minor diastereomer 34.1 min (major) and 39.3 min

(2*R*,3*R*)-3-((*tert*-Butoxycarbonyl)amino)-2-butyl-3-(prop-1-yn-1-yl)octyl benzoate



Was obtained as an oil (10.6 mg, 0.02 mmol, 52%, dr = >20/1, 99% ee), following the general procedure with *syn*-**2c** (15.6 mg, 0.046 mmol, dr = >20/1).

$[\alpha]_D^{26}$: 14.6 (*c* 1.0, $CHCl_3$)

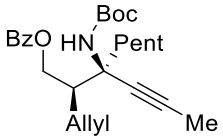
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.5 Hz, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 5.00 (br s, 1H), 4.54 (d, *J* = 12.0, 2.5 Hz, 2H), 4.50 (d, *J* = 12.0, 3.5 Hz, 2H), 2.52 (br s, 1H), 2.17 (br s, 1H), 1.77-1.76 (m, 1H), 1.73 (s, 3H), 1.54-1.52 (m, 4H), 1.39 (s, 9H), 1.37-1.26 (m, 8H), 0.90 (t, *J* = 9.0 Hz, 3H), 0.89 (t, *J* = 6.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.7, 153.7, 132.8, 130.5, 129.7, 128.3, 80.0, 79.5, 79.2, 65.3, 58.1, 44.0, 36.0, 31.8, 30.2, 28.4, 27.7, 23.9, 23.0, 22.6, 14.0 (2 peaks overlap), 3.5

HRMS (ESI): calcd. for $C_{27}H_{41}O_4NNa^+$ ($[M+Na]^+$): 466.2928, found: 466.2929 ($[M+Na]^+$)

HPLC analysis: Daicel Chiralpak IG, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min, retention time; major diastereomer 7.9 min (major) and 8.6 min, minor diastereomer 7.2 min and 10.0 min (major)

(2*R*,3*R*)-2-Allyl-3-((*tert*-butoxycarbonyl)amino)-3-(prop-1-yn-1-yl)octyl benzoate



Was obtained as an oil (15.7 mg, 0.037 mmol, 67%, dr = >20/1, 99% ee), following the general procedure with *syn*-**2d** (18.1 mg, 0.056 mmol, dr = >20/1).

$[\alpha]_D^{25}$: 5.1 (*c* 1.00, $CHCl_3$)

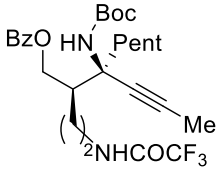
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 9.0 Hz, 2H), 7.55 (t, *J* = 9.5 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 5.93-5.83 (m, 1H), 5.08 (d, *J* = 17.2 Hz, 1H), 5.03 (d, *J* = 10.0 Hz, 1H), 4.99 (br s, 1H), 4.53-4.49 (m, 2H), 2.68 (br s, 1H), 2.44-2.40 (m, 1H), 2.34-2.17 (m, 2H), 1.74 (s, 3H), 1.51 (br s, 1H), 1.39 (s, 9H), 1.32-1.25 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.6, 153.7, 136.7, 132.8, 130.5, 129.7, 128.3, 116.6, 80.5, 79.2, 64.7, 57.8, 43.8, 36.2, 32.6, 31.7, 29.7, 28.4, 23.9, 22.6, 14.0, 3.5

HRMS (ESI): calcd. for $C_{26}H_{37}O_4NNa^+$ $[(M+Na)^+]$: 450.2615, found: 450.2621 $[(M+Na)^+]$

HPLC analysis: Daicel Chiralpak IG, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min, retention time; major diastereomer 9.2 min (major) and 9.7 min, minor diastereomer 7.8 min and 11.4 min (major)

(2*R*,3*R*)-3-((*tert*-Butoxycarbonyl)amino)-3-(prop-1-yn-1-yl)-2-(2-(2,2,2-trifluoroacetamido)-ethyl)octyl benzoate



Was obtained as an oil (22.1 mg, 0.042 mmol, 69%, dr = >20/1, 99% ee), following the general procedure with *syn*-**2f** (25.8 mg, 0.061 mmol, dr = >20/1).

$[\alpha]_D^{28}$: 11.1 (*c* 1.00, $CHCl_3$)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.04 (d, J = 8.0 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 8.0 Hz, 2H), 7.04 (br s, 1H), 4.93 (br s, 1H), 4.60 (dd, J = 12.0, 4.5 Hz, 1H), 4.49 (dd, J = 11.8, 4.8 Hz, 1H), 3.64-3.62 (m, 1H), 3.57-3.47 (m, 1H), 2.75 (br s, 1H), 2.10 (br s, 1H), 1.99-1.92 (m, 1H), 1.79-1.73 (m, 1H), 1.77 (s, 3H), 1.67 (td, J = 12.0, 4.0 Hz, 1H), 1.54-1.50 (m, 1H), 1.37 (s, 9H), 1.31-1.25 (m, 5H), 0.89 (t, J = 6.7 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.9, 157.3 (q, J = 37.0 Hz), 154.0, 133.2, 129.9, 129.7, 128.5, 115.9 (q, J = 287.7 Hz), 80.9, 79.7, 78.8, 65.4, 57.9, 42.1, 38.7, 35.9, 31.7, 28.3, 27.6, 23.9, 22.6, 14.0, 3.4

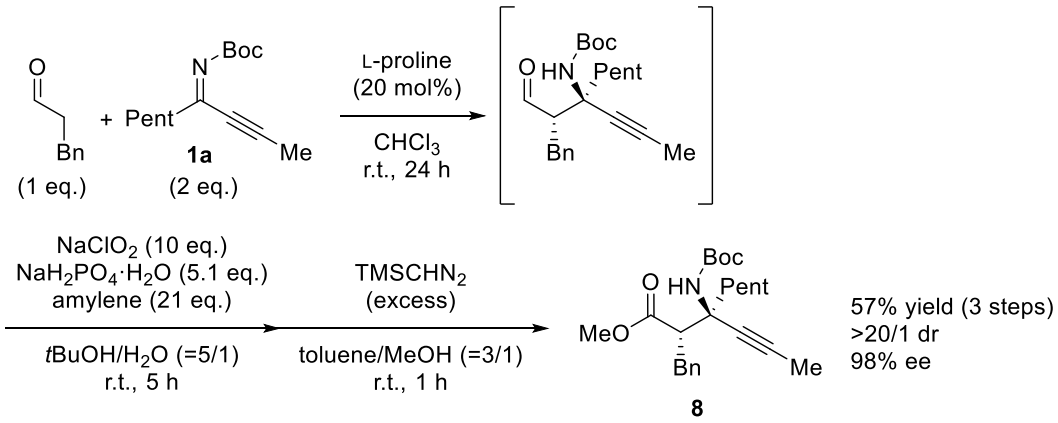
^{19}F-NMR (466 MHz, $CDCl_3$): δ –75.7

HRMS (ESI): calcd. for $C_{27}H_{37}O_5N_2F_3Na^+$ [$(M+Na)^+$]: 549.2547, found: 549.2554 [$(M+Na)^+$]

HPLC analysis: Daicel Chiralpak IC, hexane/*i*PrOH = 40/1, flow rate = 1.0 mL/min, retention time; major diastereomer 16.8 min (major) and 22.6 min, minor diastereomer 25.5 min (major) and 42.5 min

7. Transformation of Mannich Product

◆ Pinnick oxidation of a Mannich adduct



To a mixture of L-proline (2.3 mg, 0.02 mmol, 20 mol%) and **1a** (47 mg, 0.2 mmol, 2 eq.) in $CHCl_3$ (100 µL) was added 3-phenylpropanal (13 µL, 0.1 mmol, 1.0 eq.) at room temperature. After stirring for 24 h, the mixture was filtered through silica gel with EtOAc and the filtrate was evaporated under reduced pressure. The product was used for the next reaction without further purification.

To a solution of the obtained crude intermediate in *t*BuOH/H_2O (1.67/0.33 mL) were added NaH_2PO_4 (80 mg, 0.51 mmol, 5.1 eq.), amylene (220 µL, 2.1 mmol, 21 eq.) and $NaClO_2$ (92 mg, 1.0 mmol, 10 eq.) at room temperature. After stirring at room temperature for 5 h, the reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The product was used for the next reaction without further purification.

To a solution of the obtained crude intermediate in toluene/MeOH (1.5/0.5 mL) was added trimethylsilyldiazomethane ($TMSCHN_2$) (2 M solution in Et_2O) until the colorless solution turned to yellow. After stirring at room temperature for 1 h, the reaction was quenched by acetic acid and H_2O and extracted with EtOAc. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by preparative thin layer chromatography (hexane/EtOAc = 3/1) to afford **8** as colorless oil (22.8 mg, 0.057 mmol, 57% yield for 3 steps, dr = >20/1, 98% ee).

$[\alpha]_D^{24}$: −6.4 (*c* 1.0, $CHCl_3$)

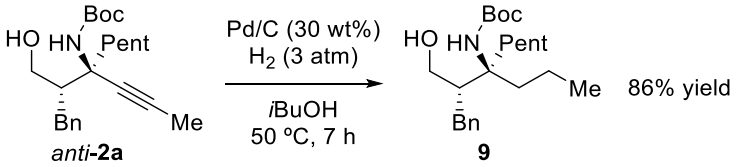
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.24 (t, *J* = 7.8 Hz, 2H), 7.18-7.15 (m, 3H), 4.94 (br s, 1H), 3.66 (br s, 1H), 3.49 (s, 3H), 3.07-3.03 (m, 2H), 2.34 (br s, 1H), 1.89 (s, 3H), 1.59-1.46 (m, 2H), 1.45 (s, 9H), 1.42-1.25 (m, 5H), 0.90 (t, *J* = 7.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 173.4, 153.6, 139.6, 128.9, 128.4, 126.2, 81.1, 79.5, 78.3, 57.1, 54.1, 51.4, 35.7, 34.6, 31.7, 28.4, 24.2, 22.6, 14.0, 3.6

HRMS (ESI): calcd. for $C_{24}H_{35}O_4NNa^+$ ($[M+Na]^+$): 424.2458, found: 424.2461 ($[M+Na]^+$)

HPLC analysis: Daicel Chiralpak AD-3, hexane/*i*-PrOH = 60/1, flow rate = 1.0 mL/min, retention time; 6.1 min (major) and 6.9 min

◆ Hydrogenation of Mannich adduct *anti*-2a



To a stirred solution of *anti*-**2a** (17.0 mg, 0.046 mmol, dr = >20/1) in *i*BuOH (1 mL) was added 10% palladium on carbon (5.1 mg, 30 wt%) at room temperature.[12] The mixture was then hydrogenated under H_2 (balloon) at 50 ºC for 7 h and filtered through a Celite pad. The filtrate was evaporated under reduced pressure. The crude mixture was purified by preparative thin layer chromatography (hexane/EtOAc = 3/1) to afford **9** as white solid (14.7 mg, 0.039 mmol, 86% yield).

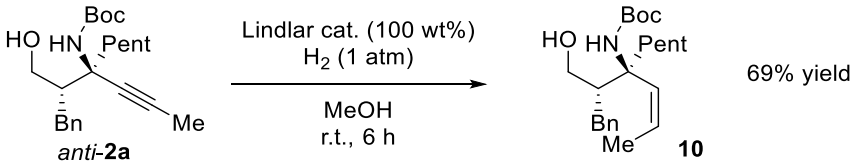
$[\alpha]_D^{27}$: 8.0 (*c* 1.0, $CHCl_3$)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29-7.27 (m, 2H), 7.24-7.23 (m, 2H), 7.20-7.16 (m, 1H), 4.60 (br s, 1H), 3.75 (d, *J* = 12.0 Hz, 1H), 3.53 (br s, 1H), 3.38 (br t, *J* = 9.0 Hz, 1H), 2.75-2.71 (m, 2H), 2.07 (br t, *J* = 11.5 Hz, 1H), 1.85 (d, *J* = 10.0 Hz, 1H), 1.81-1.75 (m, 1H), 1.65-1.62 (m, 2H), 1.45 (s, 9H), 1.37-1.22 (m, 8H), 0.95 (t, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 155.8, 141.6, 129.2, 128.4, 125.8, 79.5, 59.5, 59.1, 49.4, 36.9, 35.5, 32.3, 32.2, 28.4, 23.4, 22.6, 16.9, 14.6, 14.1

HRMS (ESI): calcd. for $C_{23}H_{39}O_3NNa^+$ ($[M+Na]^+$): 400.2822, found: 400.2826 ($[M+Na]^+$)

◆ Semi-hydrogenation of Mannich adduct *anti*-2a



To a stirred solution of *anti*-**2a** (16.4 mg, 0.044 mmol, dr = >20/1) in MeOH (440 µL) was added Lindlar catalyst (16.4 mg, 100 wt%) at room temperature.[12] The mixture was then hydrogenated under H_2 (balloon) at room temperature for 6 h and filtered through a Celite pad. The solvent was removed under reduced pressure. The crude mixture was purified by preparative thin layer chromatography (hexane/EtOAc = 3/1) to afford **10** as white solid (11.3 mg, 0.03 mmol, 69% yield).

$[\alpha]_D^{27}$: 0.3 (*c* 1.0, $CHCl_3$)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29-7.27 (m, 2H), 7.23-7.22 (m, 2H), 7.20-7.17 (m, 1H,), 5.60 (dq, *J* = 12.4, 7.2 Hz, 1H), 5.52 (d, *J* = 12.0 Hz, 1H), 5.07 (br s, 1H), 3.75 (ddd, *J* = 12.3, 4.8, 2.8 Hz, 1H), 3.48-3.43 (m, 1H), 2.83 (br d, *J* = 12.0 Hz, 1H), 2.72 (br s, 1H), 2.62 (app t, *J* = 12.5 Hz, 1H), 2.19-2.15 (m, 2H), 1.80 (d, *J* = 7.0 Hz, 3H), 1.76-1.72 (m, 1H), 1.46 (s, 9H), 1.39-1.25 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 155.2, 141.2, 133.3, 129.1, 128.4, 125.9, 125.4, 79.3, 61.7, 60.9, 50.6, 38.0, 32.4, 32.2, 28.4, 23.8, 22.6, 14.5, 14.0

HRMS (ESI): calcd. for $C_{23}H_{37}O_3NNa^+$ ($[M+Na]^+$): 398.2666, found: 398.2668 ($[M+Na]^+$)

8. Crystal Structure Analysis of *syn*-2k

Single crystals of *syn*-**2k** were grown from Et_2O and hexane at room temperature. The data were collected at –170 °C on a Rigaku Saturn Saturn70 CCD(system) with VariMax Mo Optics using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The crystal structure was solved by direct methods using SHELXT[13] and refined in SHELXL-2018[14] by full matrix least-squares using anisotropic thermal displacement parameters for all non-hydrogen atoms. Crystallographic data for *syn*-**2k**: $C_{31}H_{53}NO_3Si$, colorless needle, 0.40×0.10×0.06 mm^3, orthorhombic, $P2_12_12_1$, a = 13.1243(3), b = 15.2075(3), c = 16.3433(3) Å, V = 3261.92(12) $Å^3$, ρcalcd = 1.050 gcm^{-3}, Z = 4, 2θmax = 50.5, μ = 0.100 mm^{-1}. A total of 38852 reflections were measured. R = 0.0275, and Rw = 0.0667 for 5670 observed reflection with I > 2.0σ (I). Flack parameter = –0.05(4). CCDC-1979814 (*syn*-**2k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

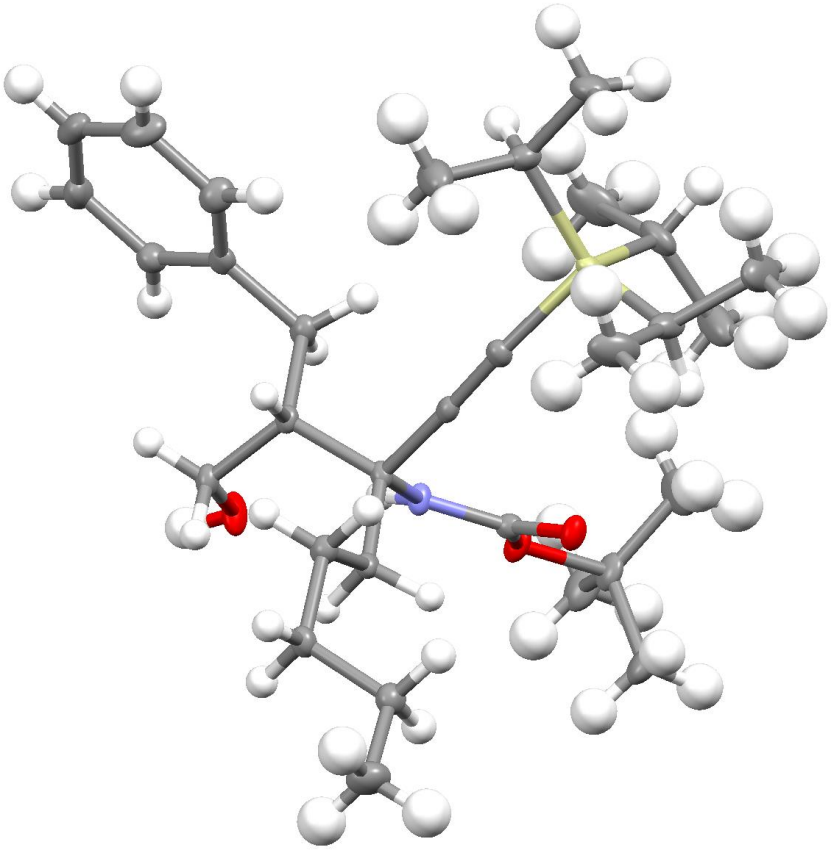
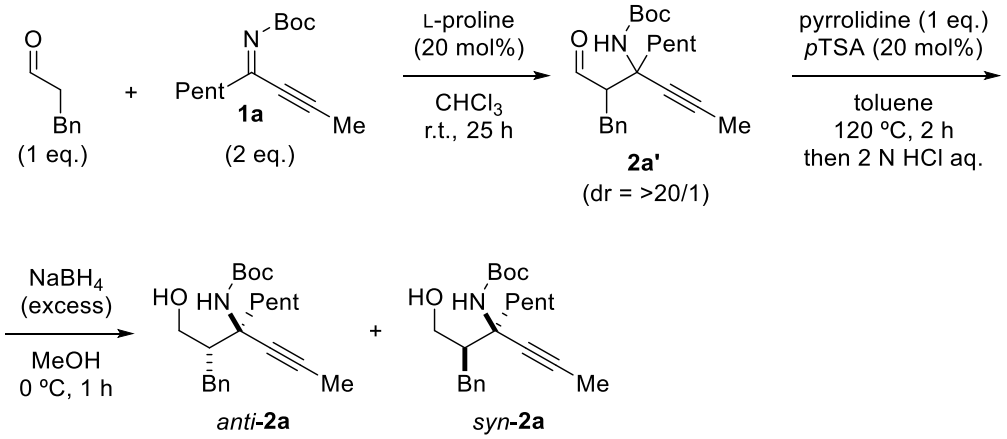


Figure S1. X-ray crystal structure of *syn*-**2k**.

9. Determination of Absolute Configuration of Mannich Product 2a



To determine the absolute configuration of the Mannich product catalyzed by L-proline, Mannich product **2a'** was epimerized.

To a mixture of L-proline (2.3 mg, 0.02 mmol, 20 mol%) and **1a** (47 mg, 0.2 mmol, 2 eq.) in $CHCl_3$ (100 μL) was added 3-phenylpropanal (13 μL, 0.1 mmol, 1.0 eq.) at room temperature. After stirring for 25 h, the reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layers were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was roughly purified by silica gel chromatography (hexane/EtOAc = 7/1 as eluent) to give the Mannich product **2a'** with impurities.

To a mixture of obtained **2a'** with impurities and pyrrolidine (8.2 μL, 0.1 mmol, 1 eq.) in CH_2Cl_2 was added *p*-toluenesulfonic acid monohydrate (3.8 mg, 0.02 mmol, 20 mol%). After stirring at 120 °C for 2 h, 2 M HCl aq. (excess) was added. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The product was used for the next reaction without purification.

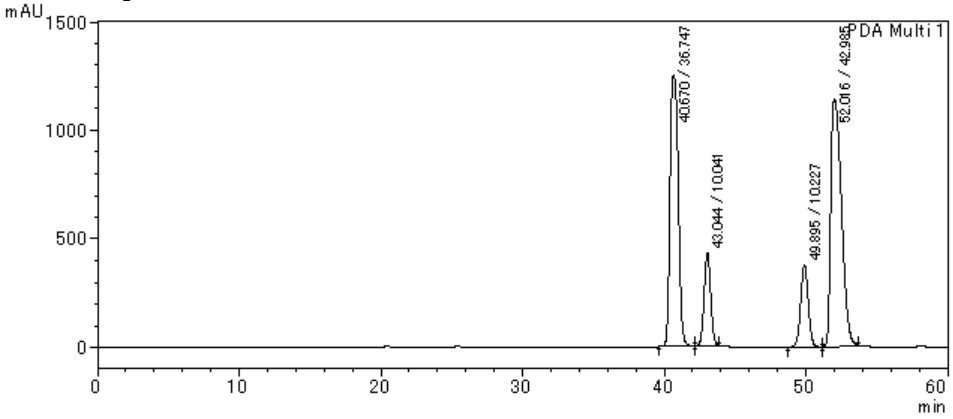
To the mixture of the obtained product in MeOH (ca. 2 mL) was added $NaBH_4$ (excess) at 0 °C. After stirring for 1 h, the reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layers were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*.

The crude mixture was purified by preparative thin layer chromatography (hexane/EtOAc = 3/1) to afford *anti*-**2a** and its epimer, *syn*-**2a**.

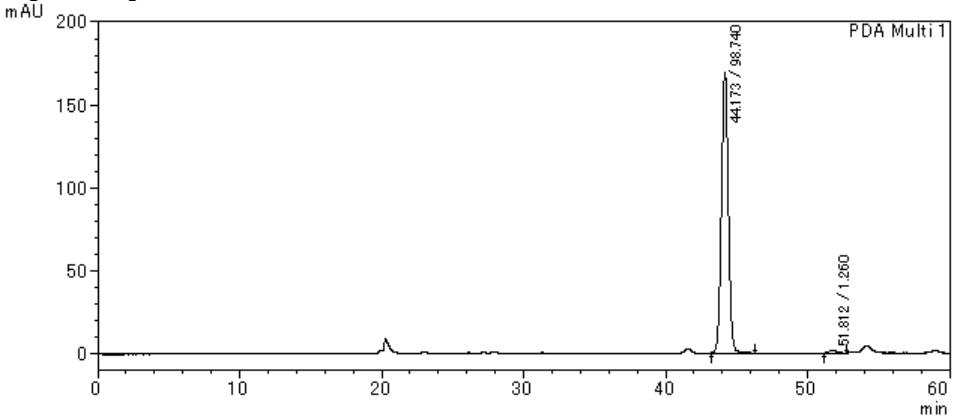
The absolute configuration of the obtained *syn*-**2a** was determined by comparison with *syn*-**2a** which is obtained from the reaction catalyzed by (*S*,*R*)-**7**.

HPLC trace

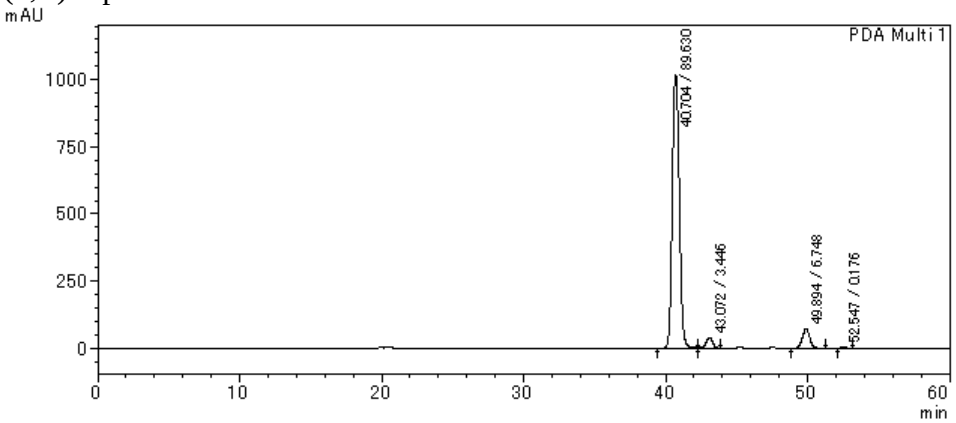
Racemic product



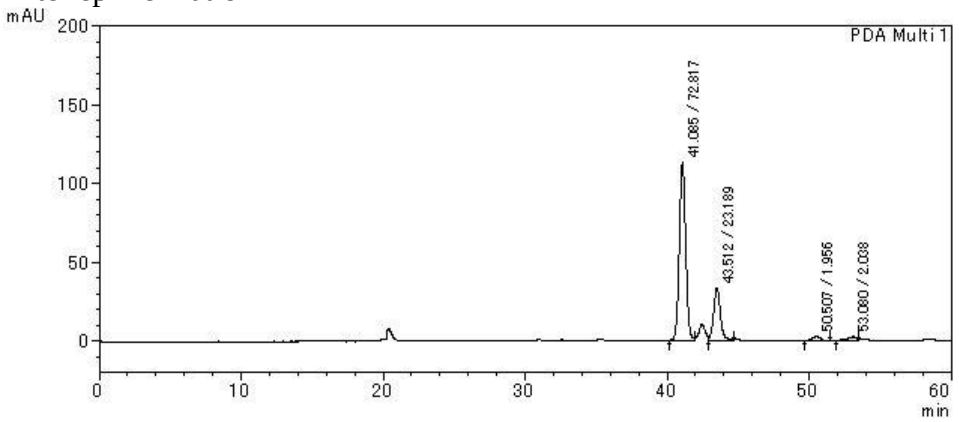
L-proline product



(*S*,*R*)-**7** product



After epimerization

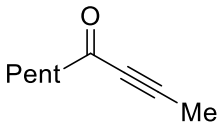


10. References

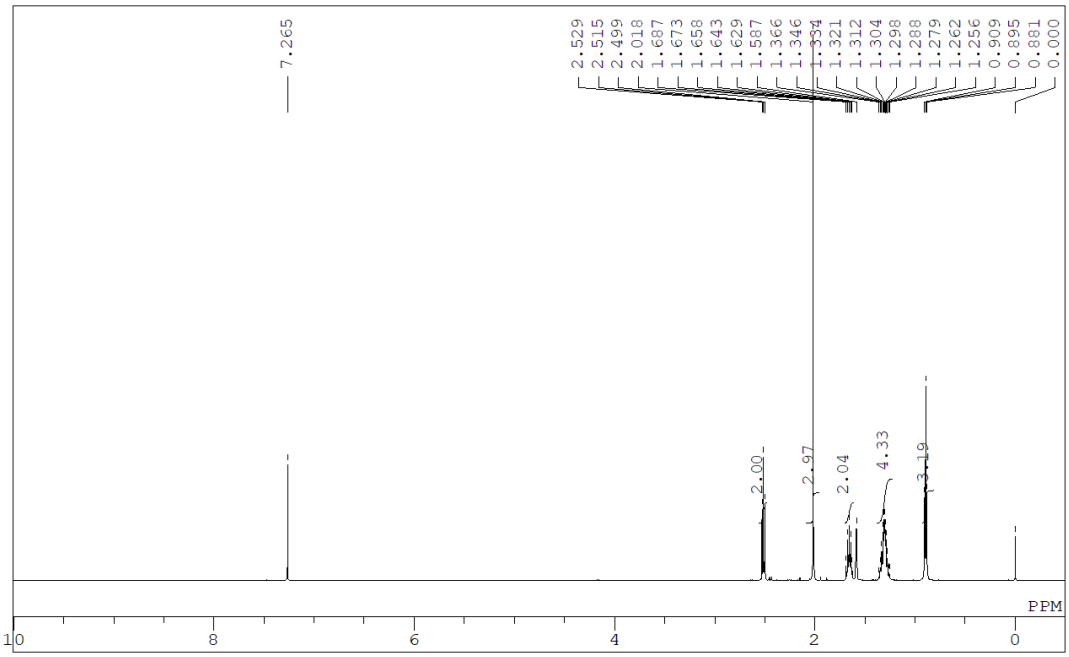
(1) M. C. Pacheco and V. Gouverneur, *Org. Lett.*, 2005, **7**, 1267−1270.
(2) J. Taguchi, T. Ikeda, R. Takahashi, I. Sasaki, Y. Ogasawara, T. Dairi, N. Kato, Y. Yamamoto, J. W. Bode and H. Ito, *Angew. Chem., Int. Ed.*, 2017, **56**, 13847−13851.
(3) M. A. Brimble, I. Haym, J. Sperry and D. P. Furkert, *Org. Lett.*, 2012, **14**, 5820−5823.
(4) C. Quinet, L. Sampoux and I. E. Marko, *Eur. J. Org. Chem.*, 2009, 1806−1811.
(5) B. M. Trost and B. Biannic, *Org. Lett.*, 2015, **17**, 1433−1436.
(6) T. Mukaiyama, J. Matsuo and M. Yanagisawa, *Chem. Lett.*, 2000, **29**, 1072−1073.
(7) C. J. Helal, P. A. Magriotis and E. J. Corey, *J. Am. Chem. Soc.*, 1996, **118**, 10938−10939.
(8) D. C. Batesky, M. J. Goldfogel and D. J. Weix, *J. Org. Chem.*, 2017, **82**, 9931−9936.
(9) M. S. Anson, H. F. Clark, P. Evans, M. E. Fox, J. P. Graham, N. N. Griffiths, G. Meek, J. A. Ramsden, A. J. Roberts, S. Simmonds, M. D. Walker and M. Willets, *Org. Process Res. Dev.*, 2011, **15**, 389−397.
(10) A. Takeshima, T. Kano and K. Maruoka, *Org. Lett.*, 2019, **21**, 8071−8074.
(11) A. E. Bosnidou and K. Muñiz, *Angew. Chem., Int. Ed.*, 2019, **58**, 7485−7489.
(12) T. Kano, Y. Aota and K. Maruoka, *Angew. Chem., Int. Ed.*, 2017, **56**, 16293−16296.
(13) G. M. Sheldrick, *Acta Cryst.* 2008, **A64,** 112−122.
(14) G. M. Sheldrick, *Acta Cryst.*, 2015, **A71**, 3−8.

11. ^{1}H and ^{13}C NMR Spectra

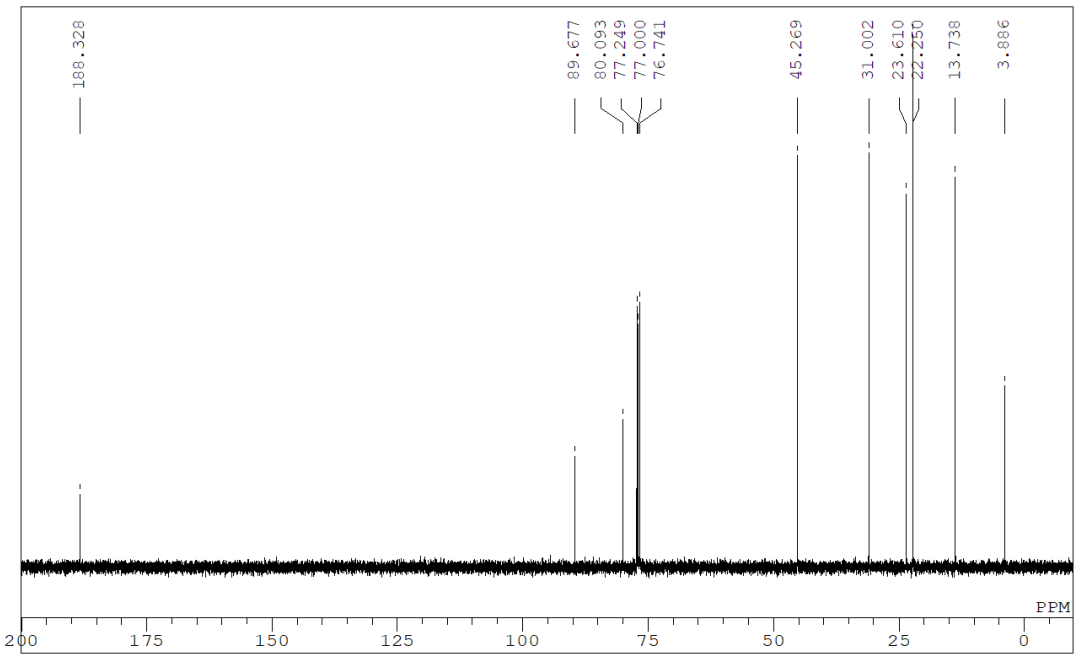
Non-2-yn-4-one



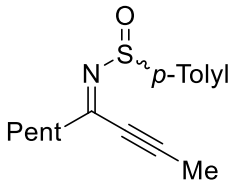
^{1}H-NMR (500 MHz, $CDCl_3$)



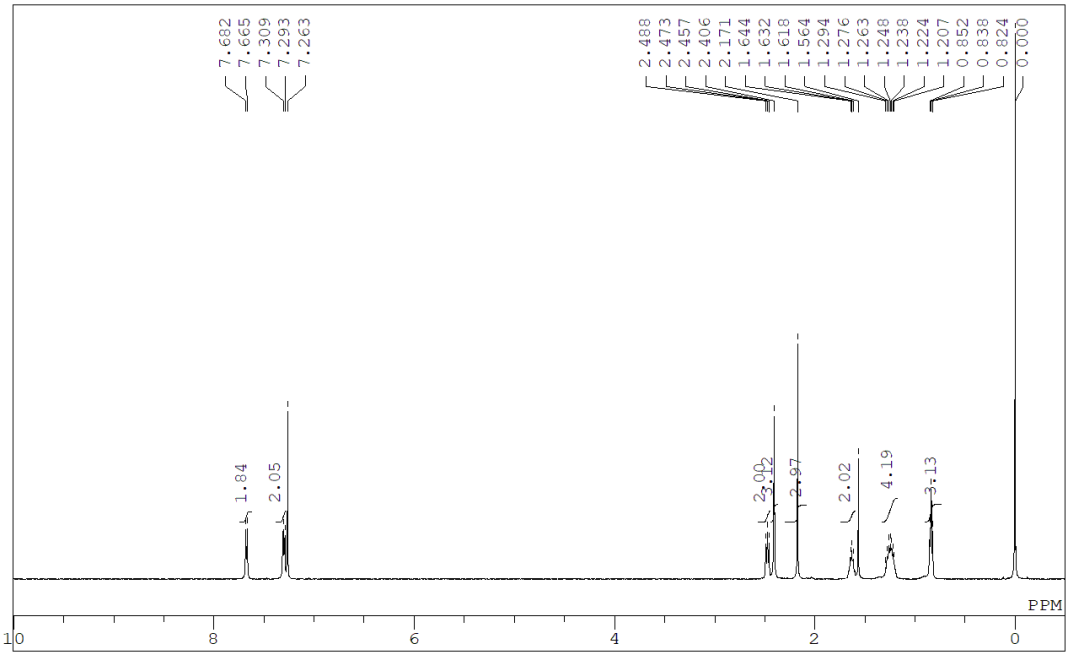
^{13}C-NMR (125 MHz, $CDCl_3$)



(*Z*)-4-Methyl-*N*-(non-2-yn-4-ylidene)benzenesulfinamide



^{1}H-NMR (500 MHz, $CDCl_3$)



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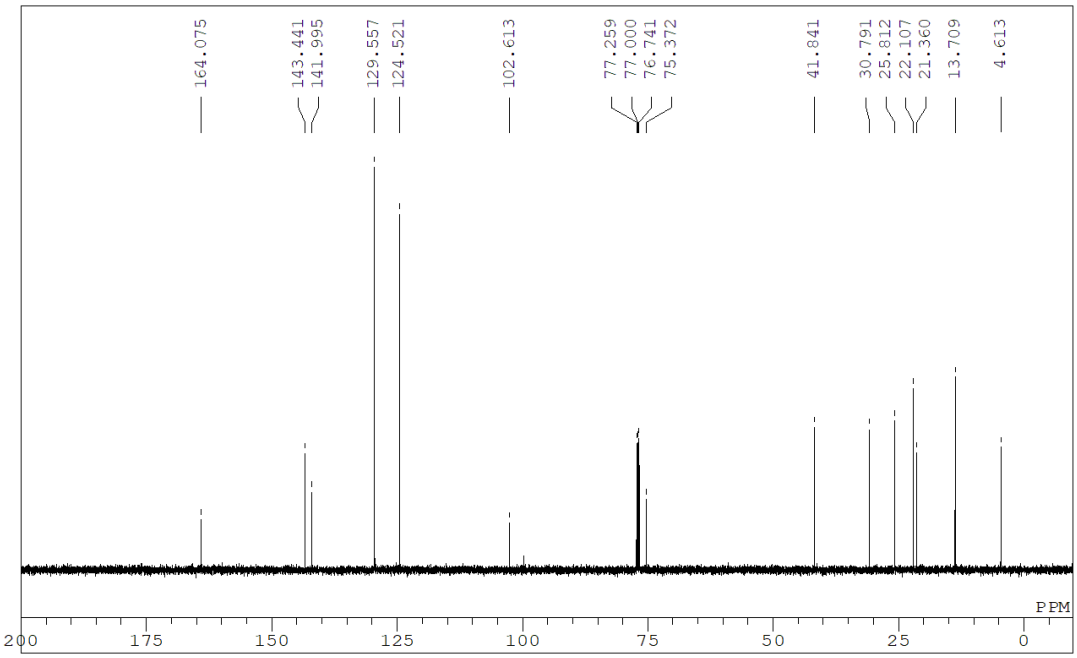
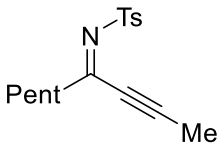
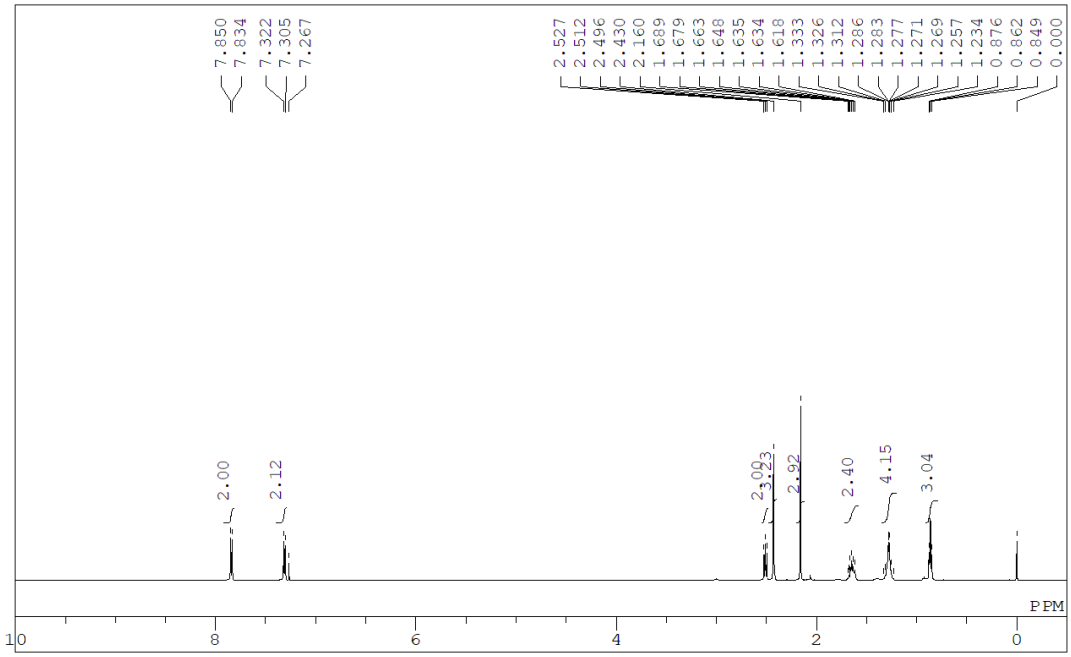


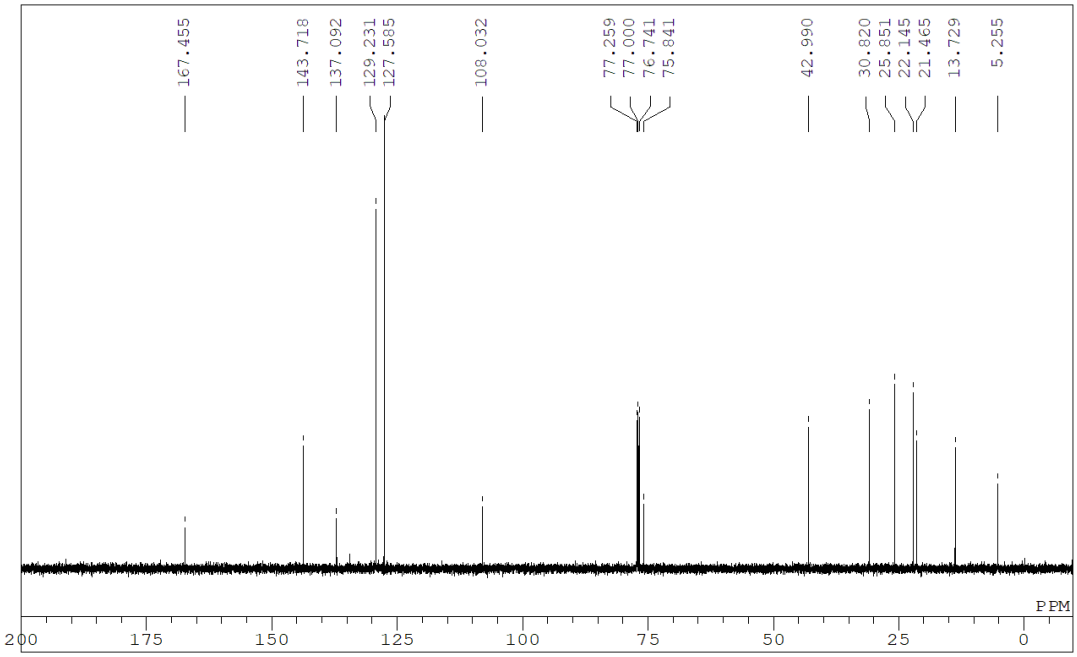
(*Z*)-4-Methyl-*N*-(non-2-yn-4-ylidene)benzenesulfonamide



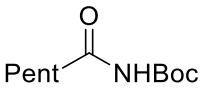
^{1}H-NMR (500 MHz, $CDCl_3$)



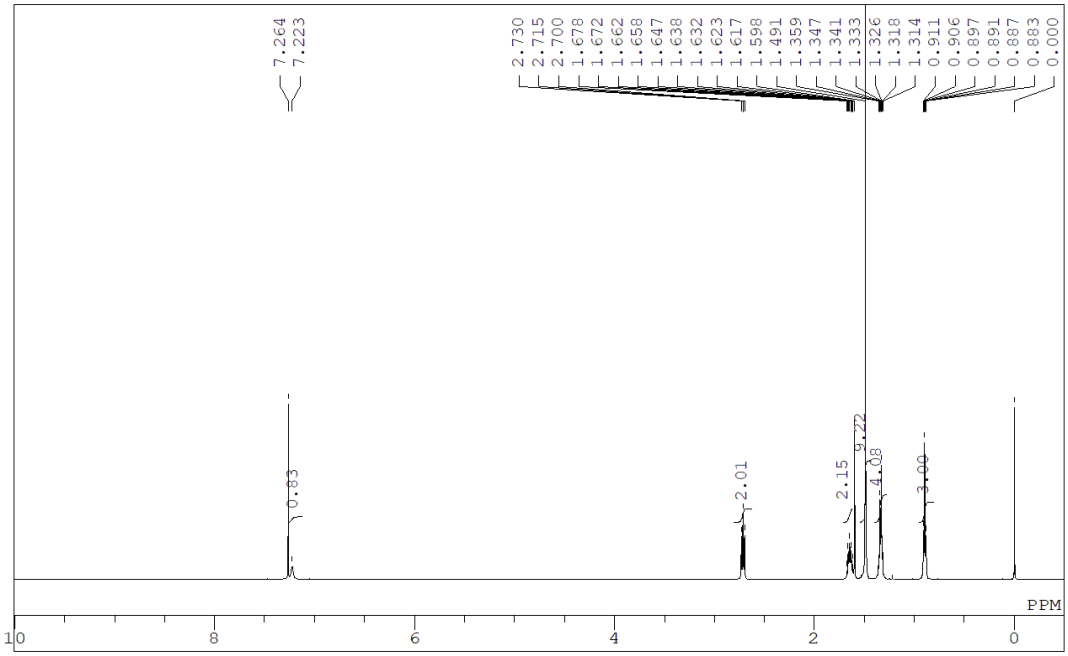
^{13}C-NMR (125 MHz, $CDCl_3$)



***tert*-Butyl hexanoylcarbamate**



^{1}H-NMR (500 MHz, $CDCl_3$)



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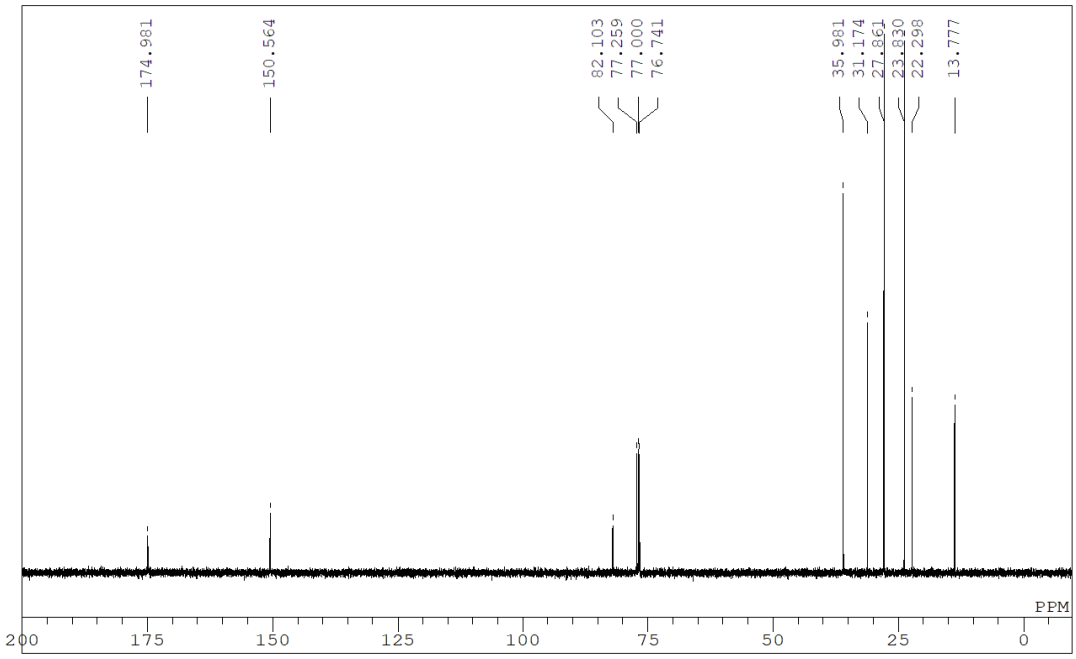
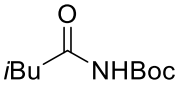
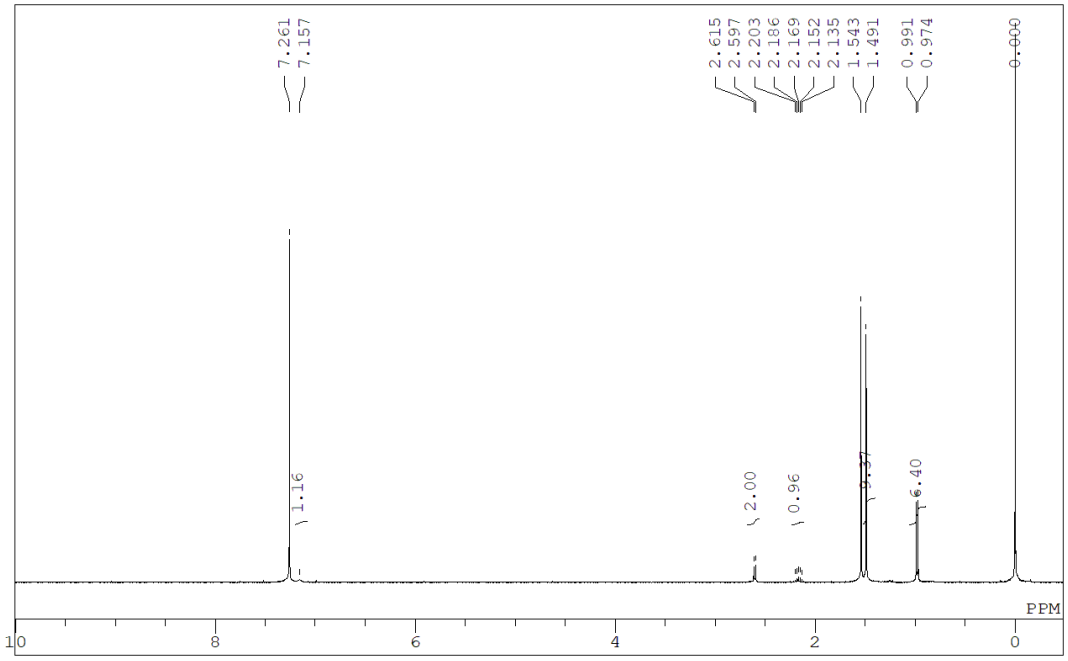


tert-Butyl (3-methylbutanoyl)carbamate



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



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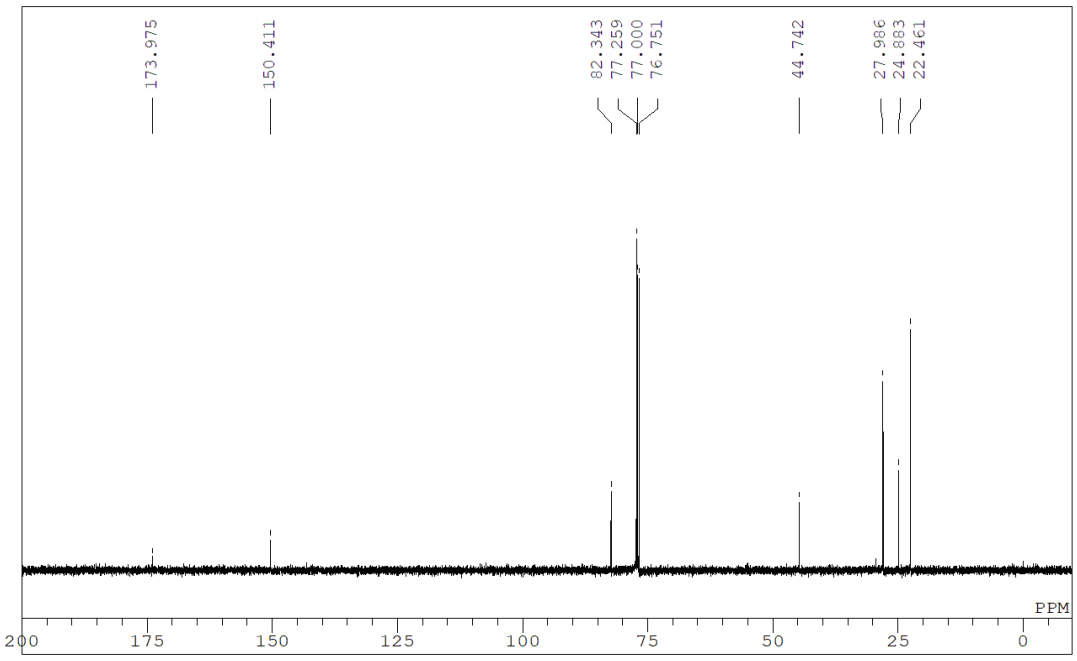
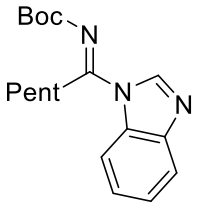


***tert*-Butyl (*E*)-(1-(1H-benzo[*d*]imidazol-1-yl)hexylidene)carbamate**



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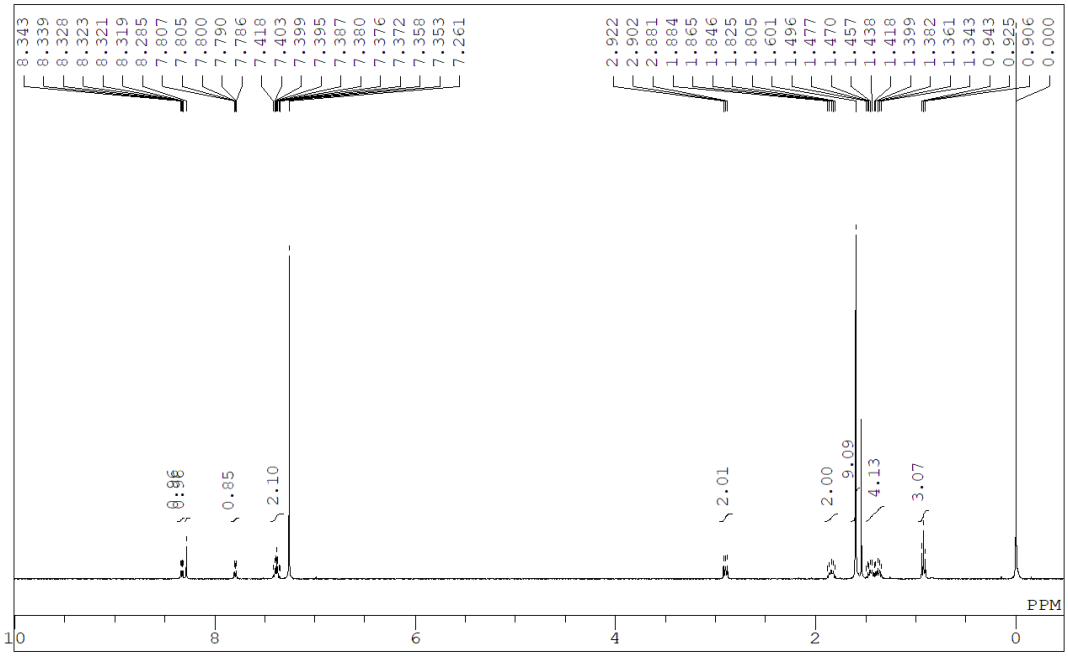

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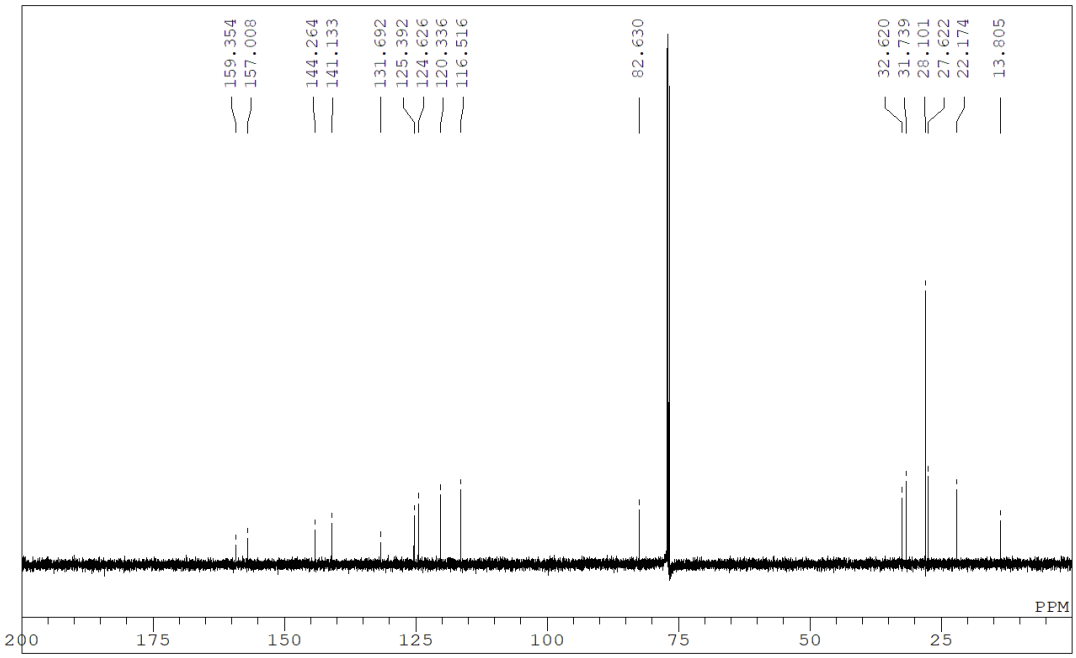
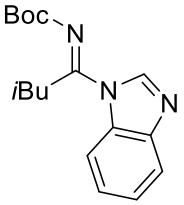


***tert*-Butyl (*E*)-(1-(1H-benzo[*d*]imidazol-1-yl)-3-methylbutylidene)carbamate**



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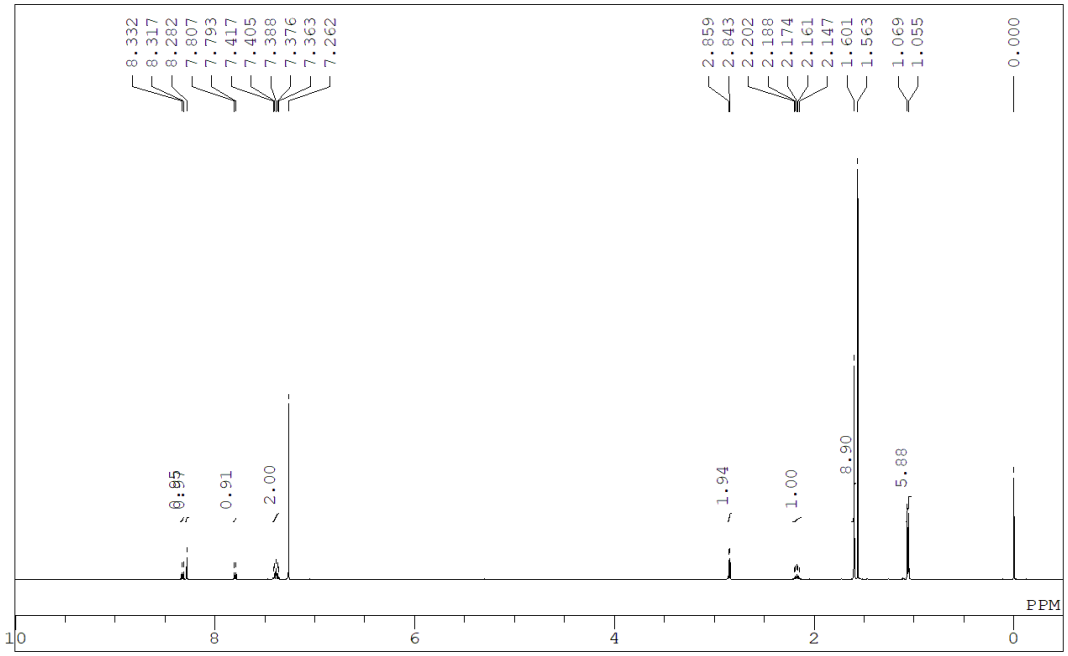

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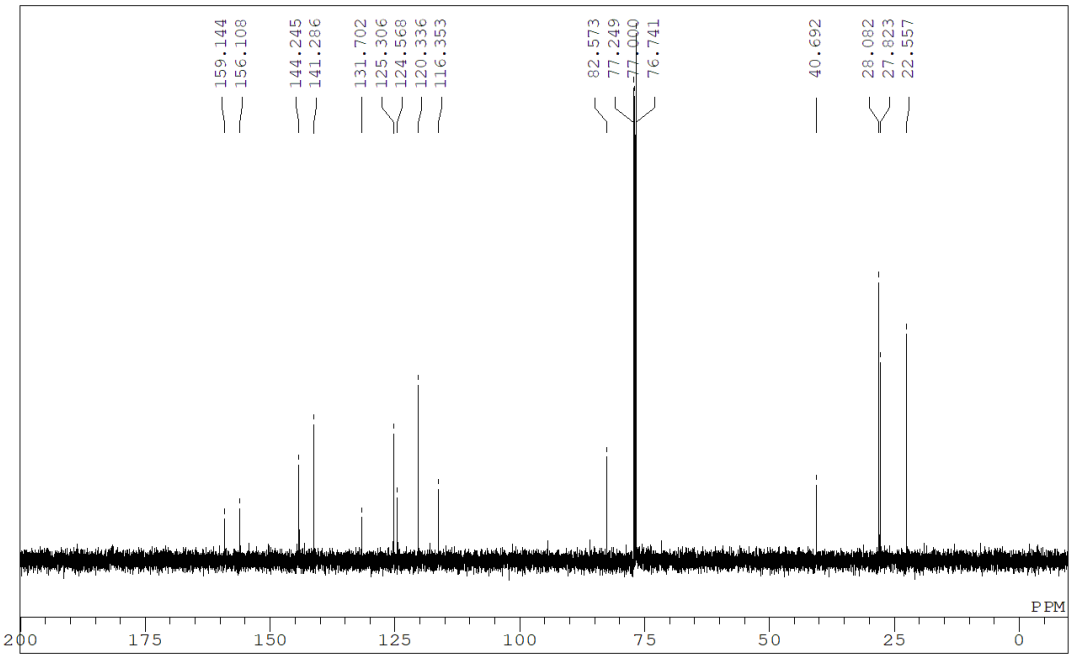

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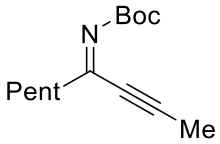

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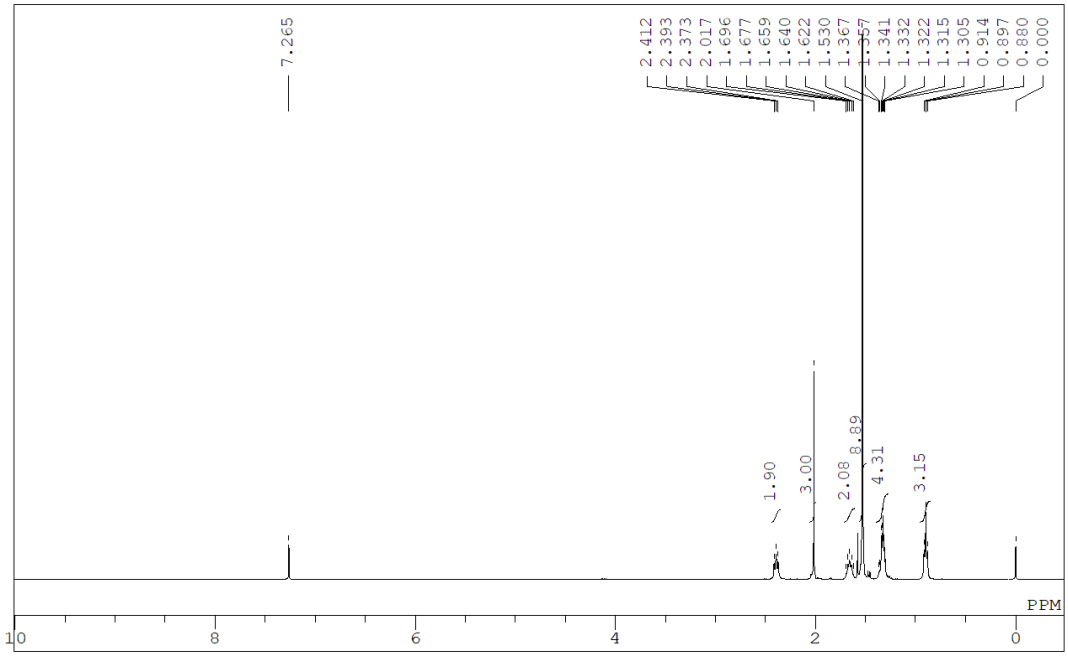

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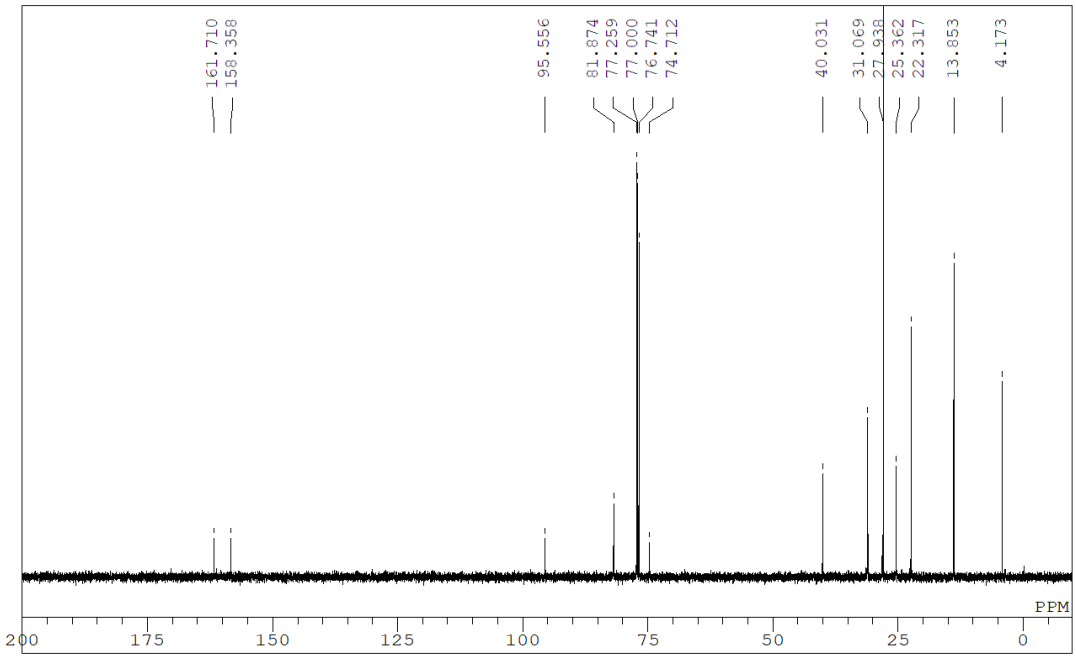
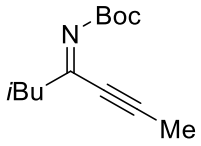


***tert*-Butyl (*Z*)-(6-methylhept-2-yn-4-ylidene)carbamate**



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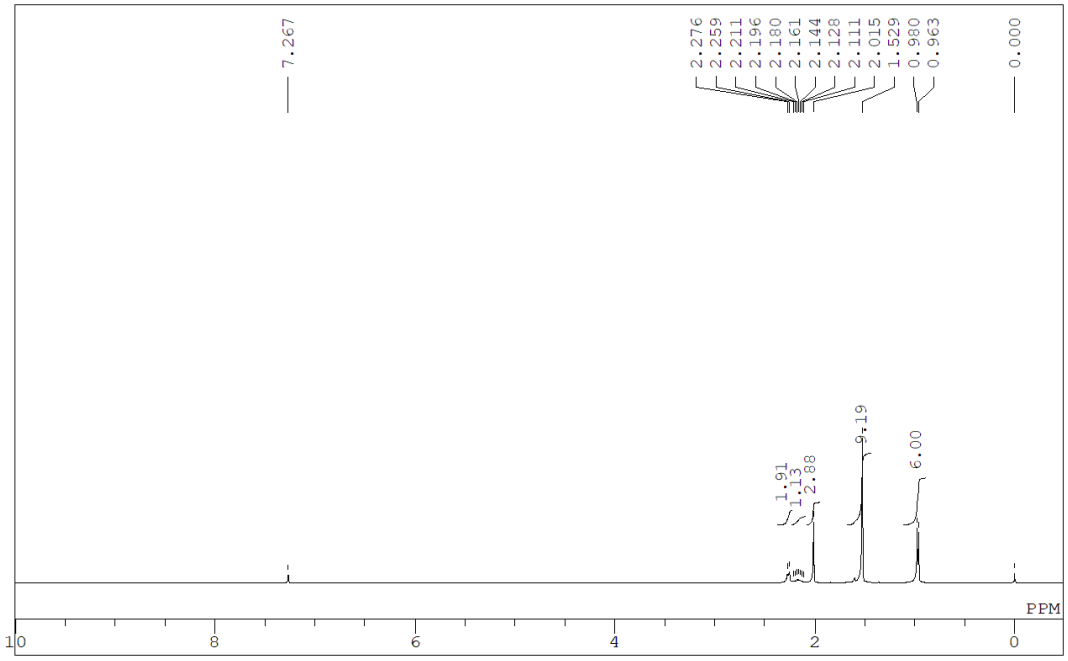

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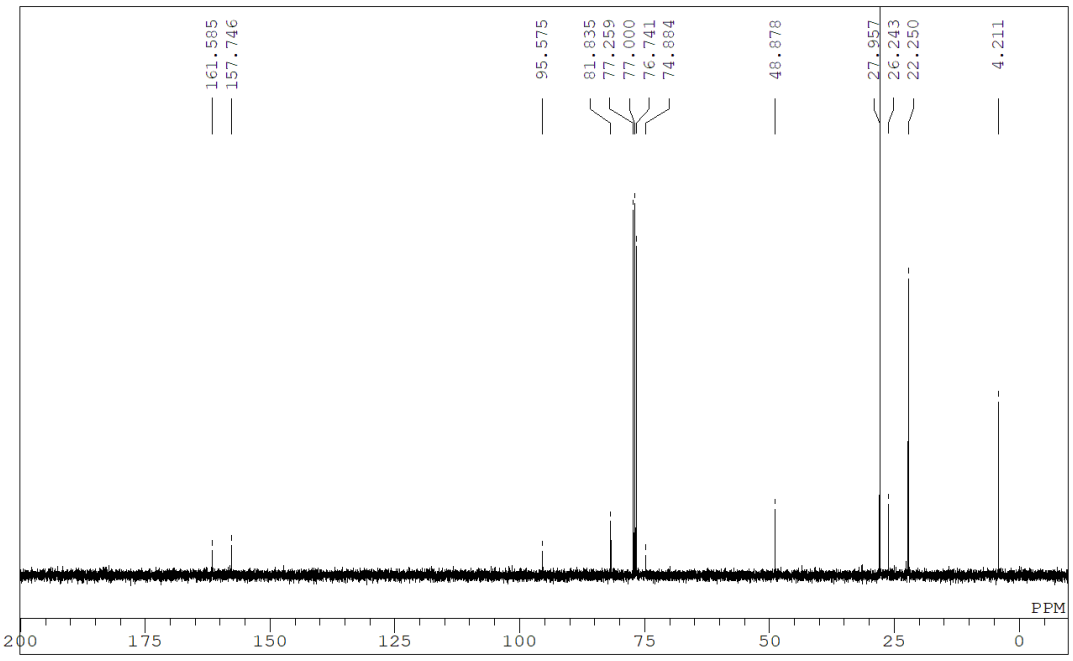
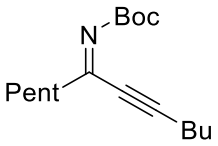


tert-Butyl (_Z_)-dodec-7-yn-6-ylidenecarbamate



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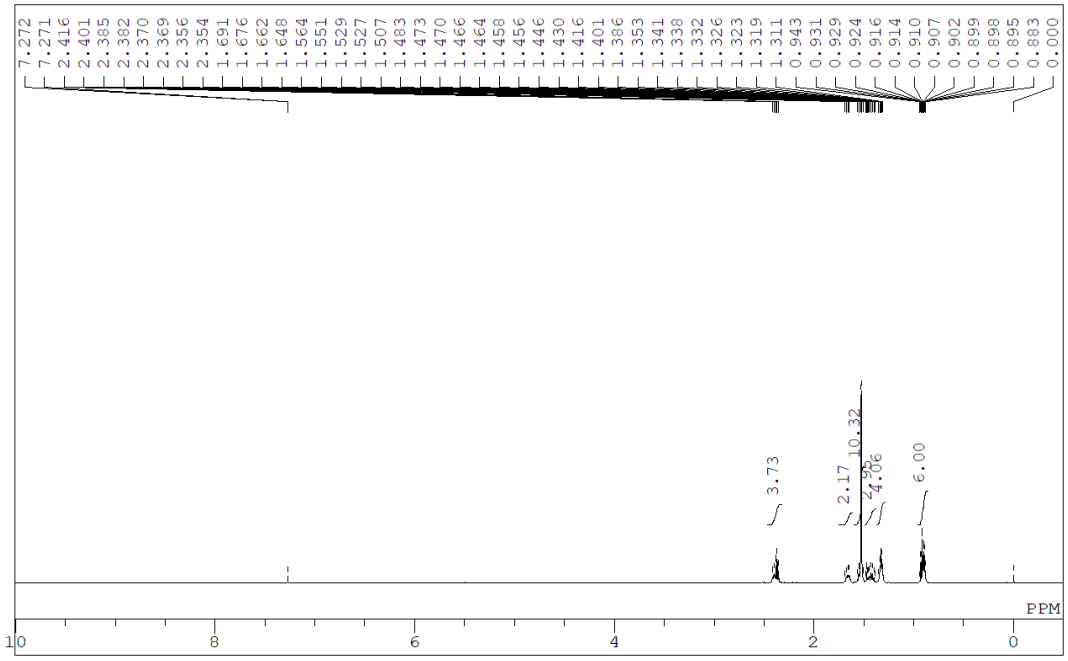

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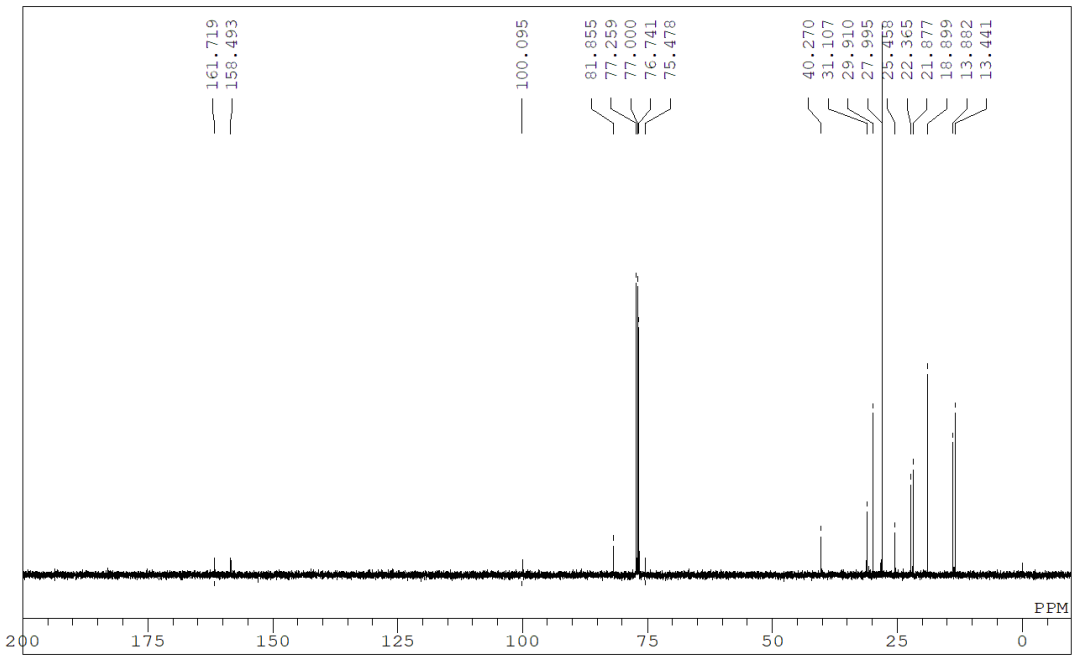
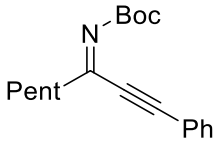
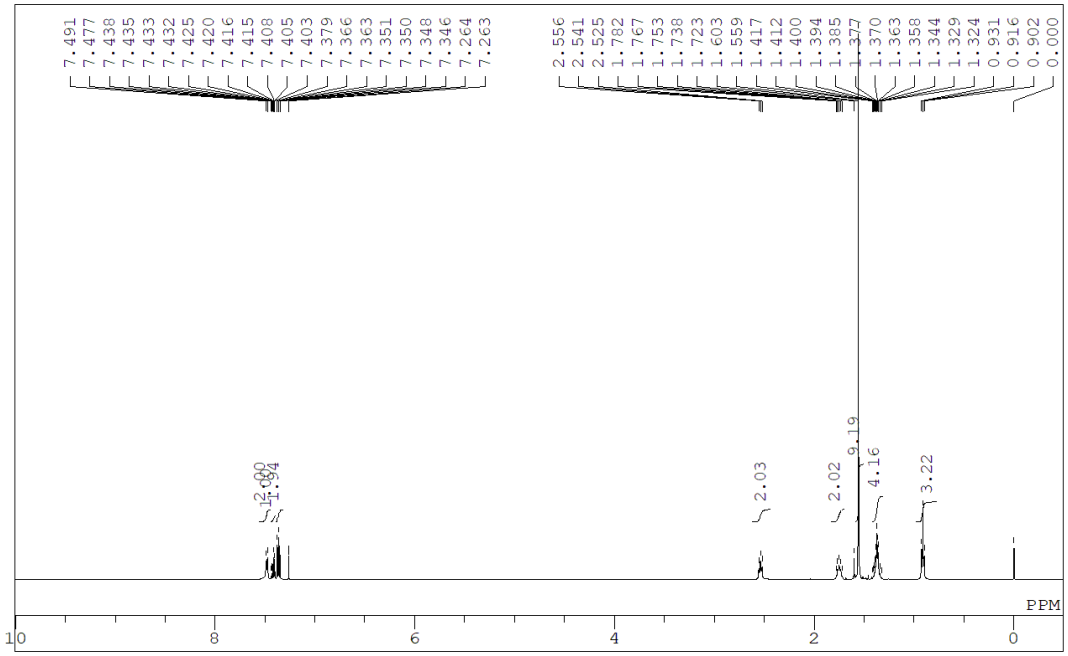


***tert*-Butyl (*Z*)-(1-phenyloct-1-yn-3-ylidene)carbamate**



^{1}H-NMR (500 MHz, $CDCl_3$)



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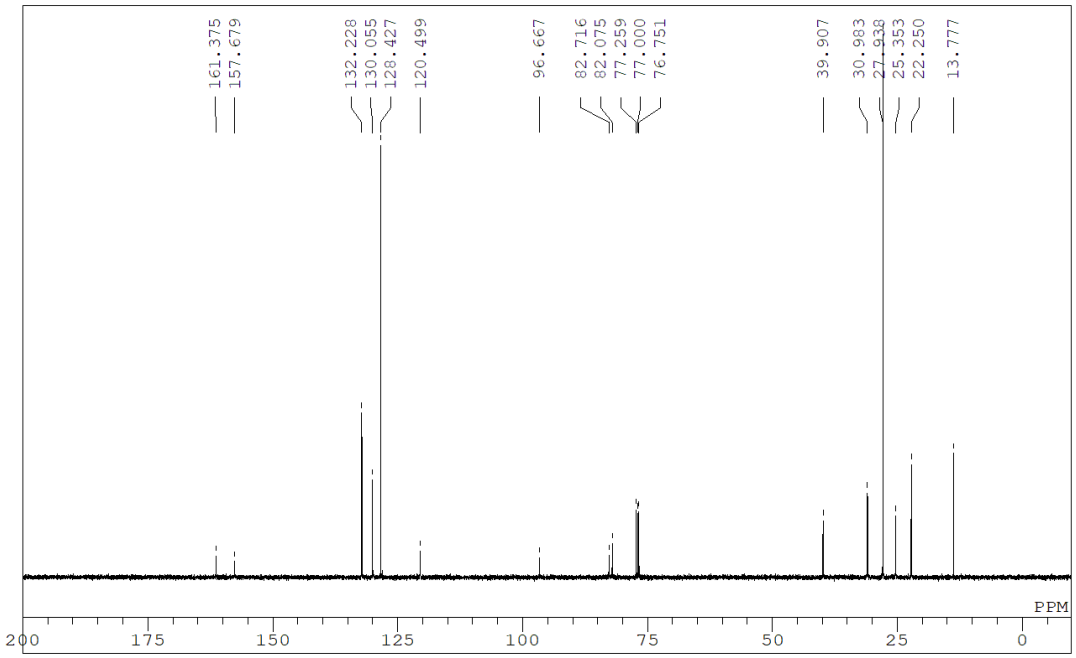
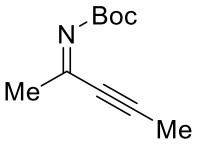


***tert*-Butyl (*Z*)-pent-3-yn-2-ylidenecarbamate**



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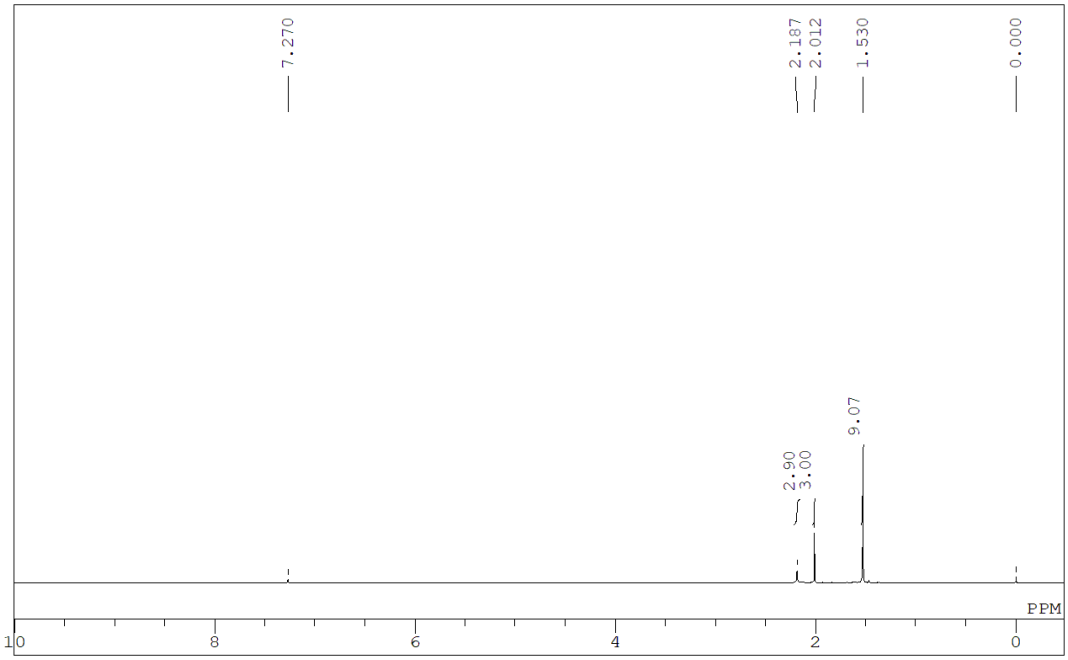

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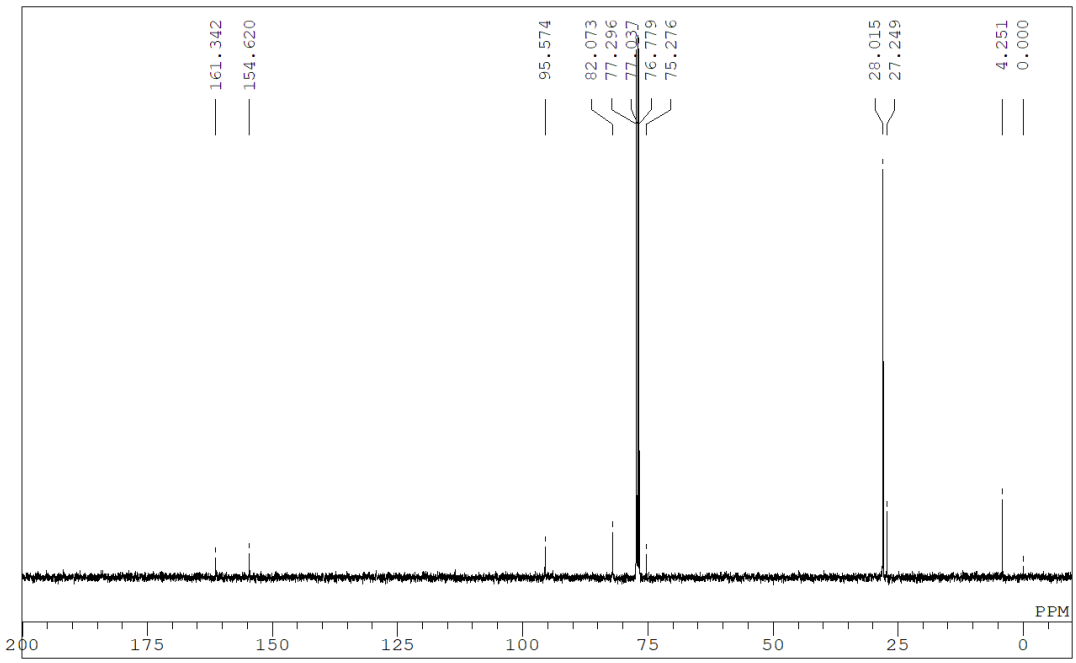
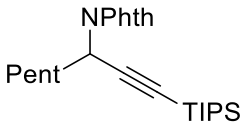
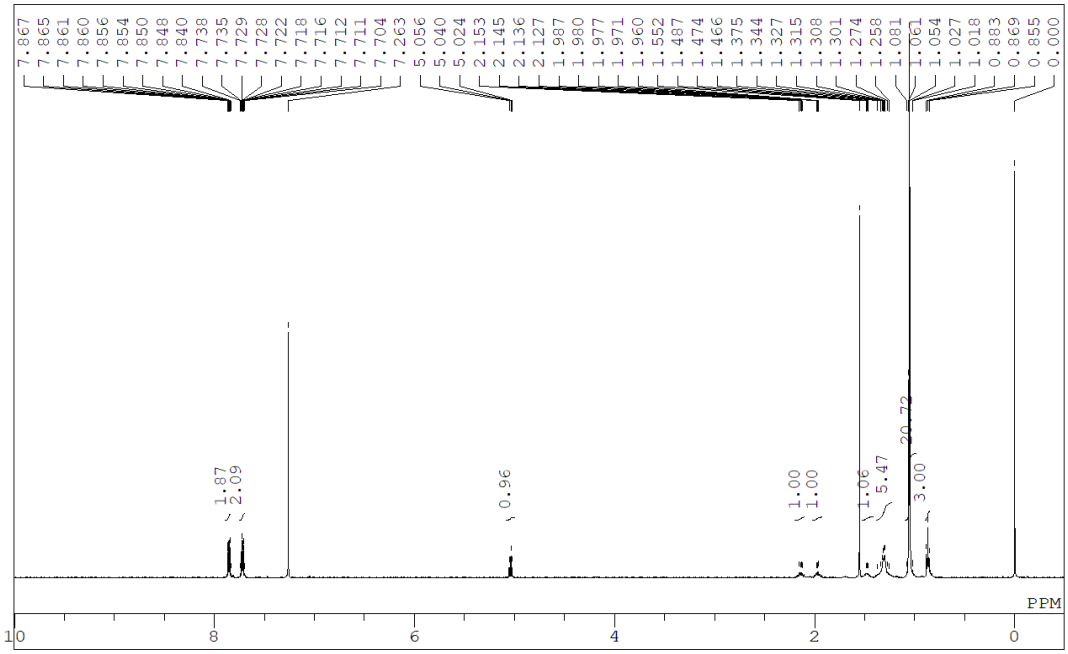


2-(1-(Triisopropylsilyl)oct-1-yn-3-yl)isoindoline-1,3-dione



^{1}H-NMR (500 MHz, $CDCl_3$)



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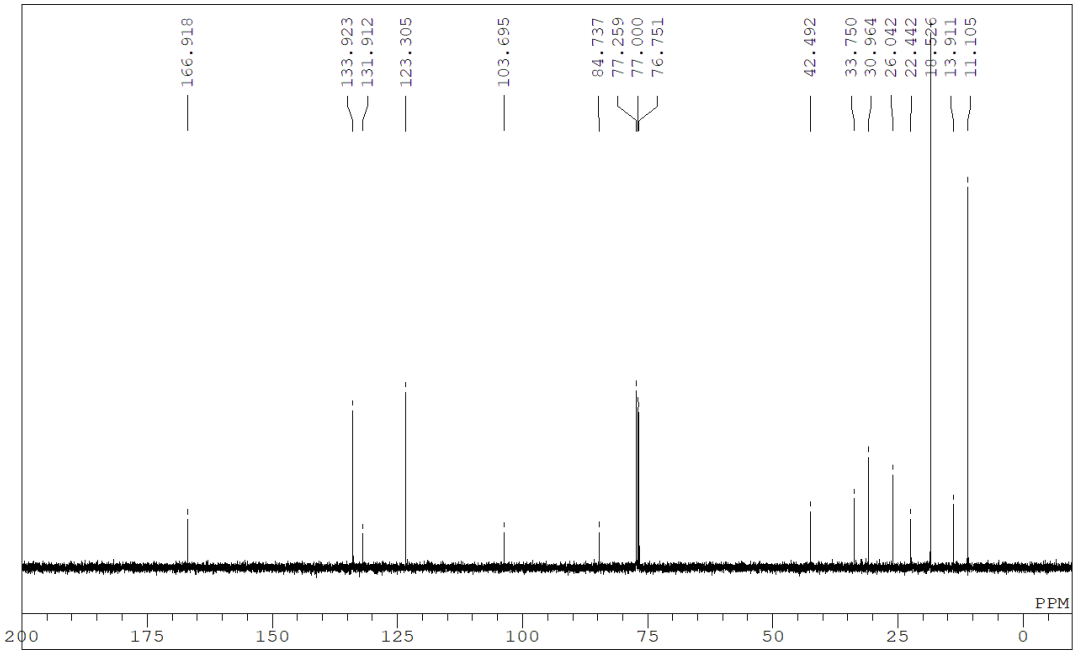
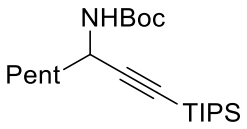
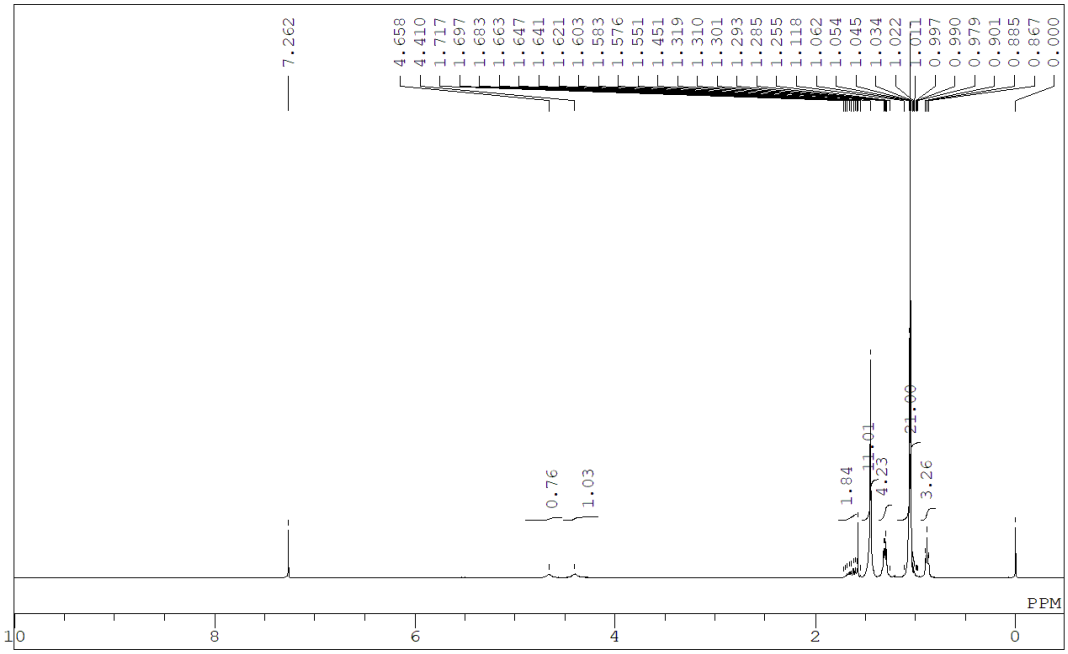


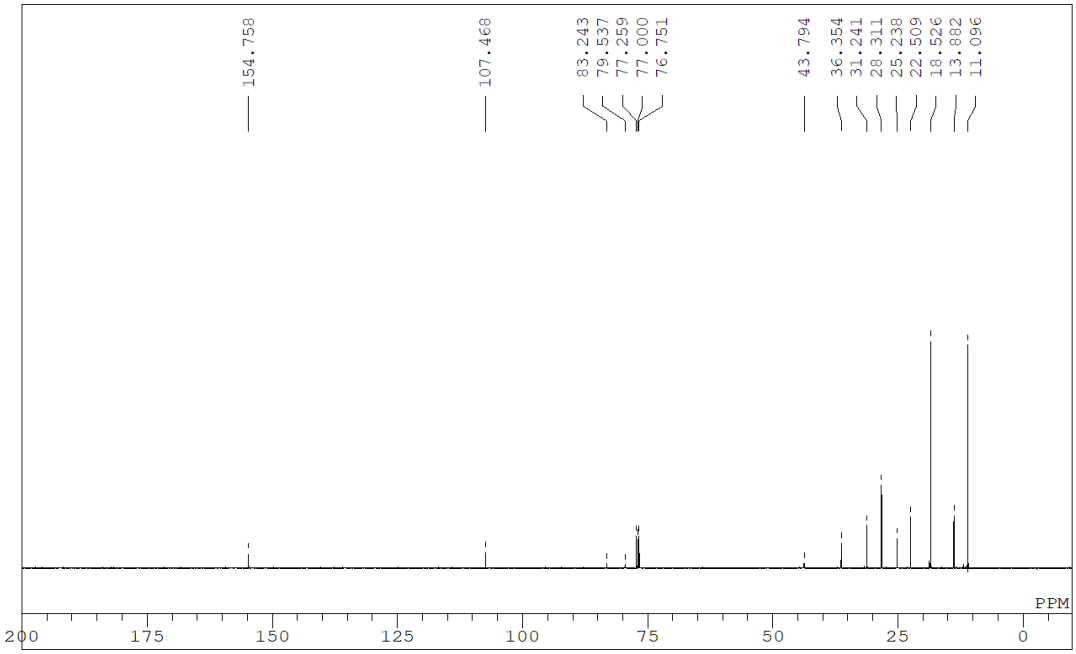
***tert*-Butyl (1-(triisopropylsilyl)oct-1-yn-3-yl)carbamate**



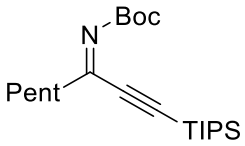
^{1}H-NMR (400 MHz, $CDCl_3$)



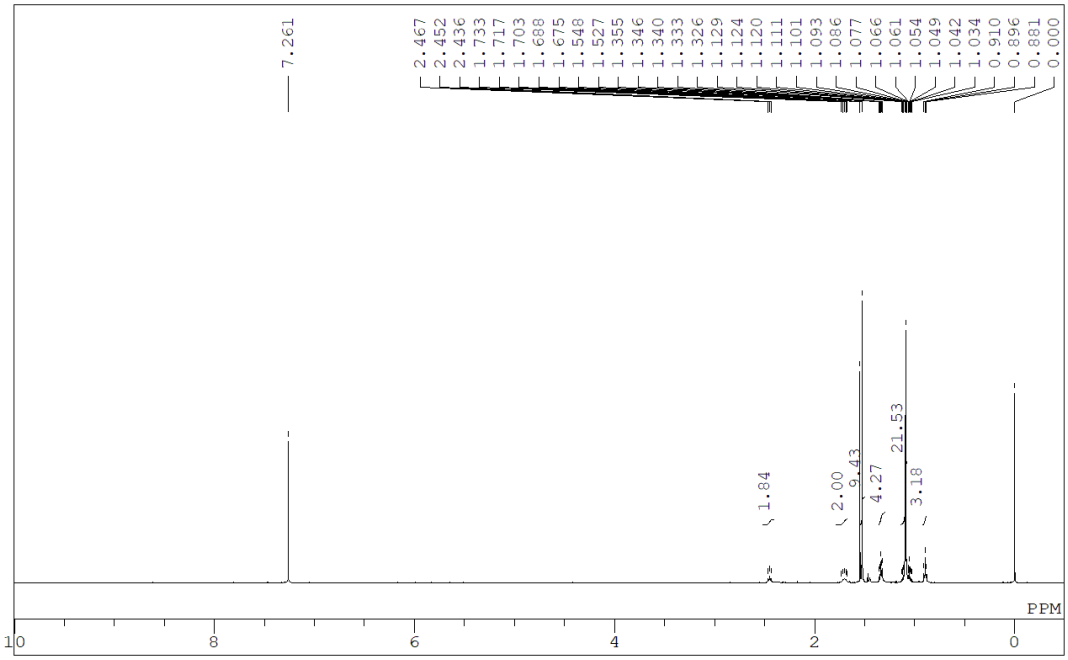
^{13}C-NMR (125 MHz, $CDCl_3$)



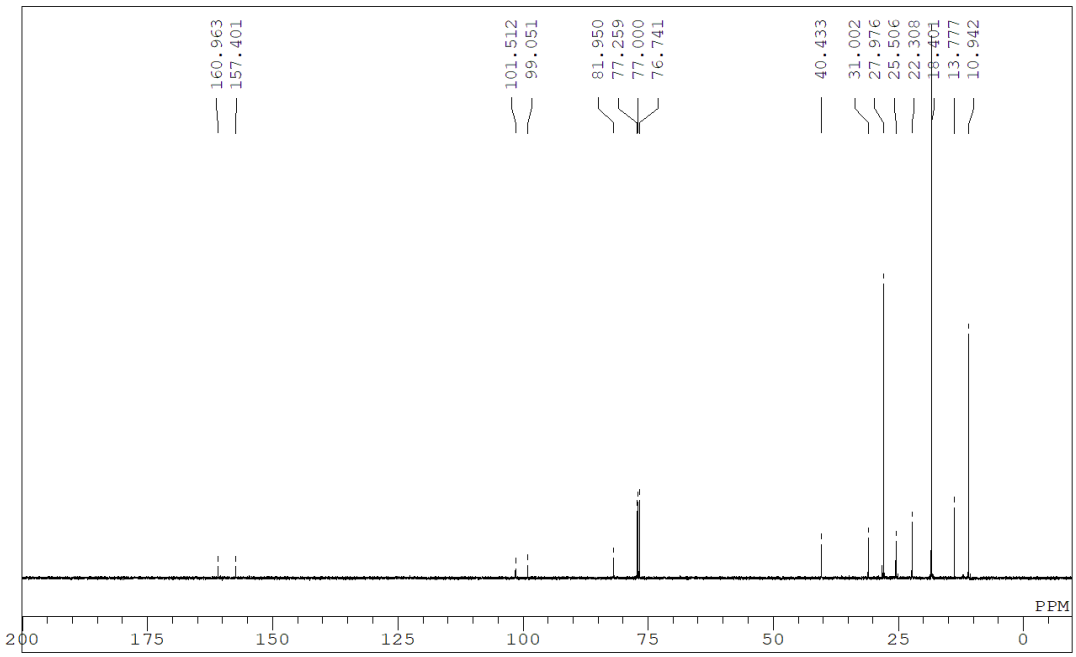
tert-Butyl (_Z_)-(1-(triisopropylsilyl)oct-1-yn-3-ylidene)carbamate



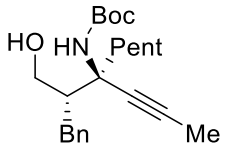
^{1}H-NMR (500 MHz, $CDCl_3$)



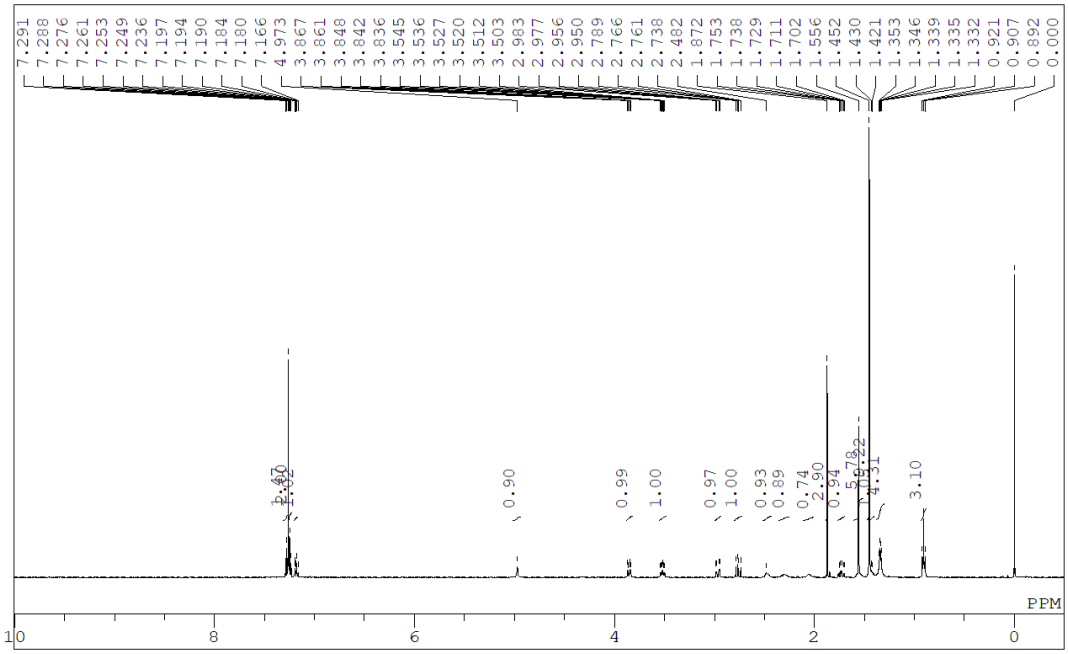
^{13}C-NMR (125 MHz, $CDCl_3$)



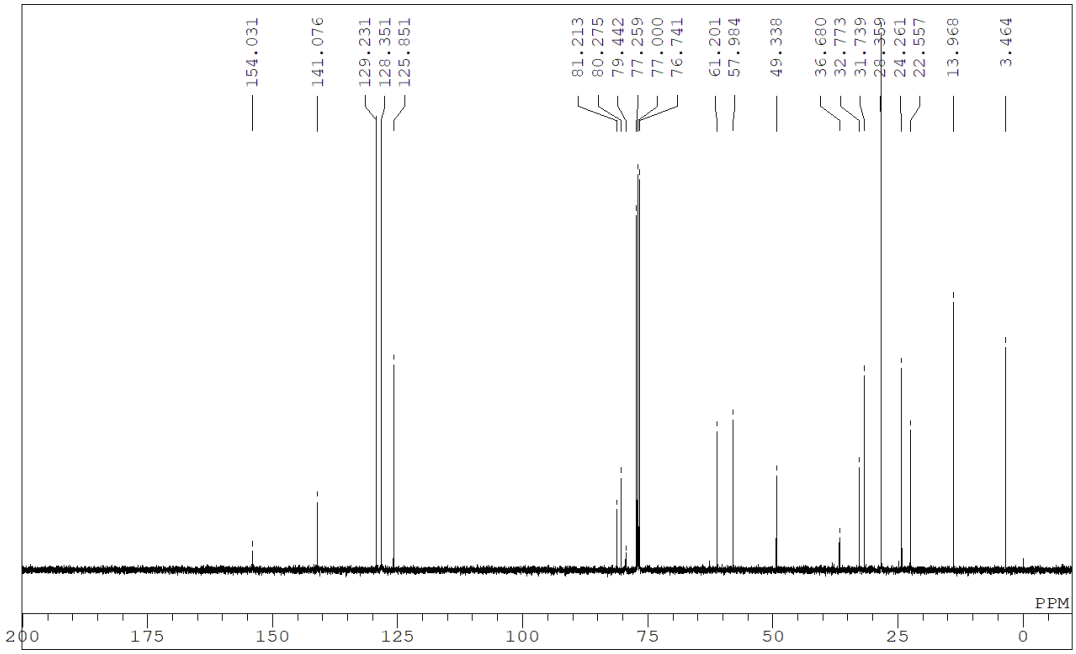
***tert*-Butyl ((*R*)-4-((*S*)-1-hydroxy-3-phenylpropan-2-yl)non-2-yn-4-yl)carbamate (*anti*-2a)**



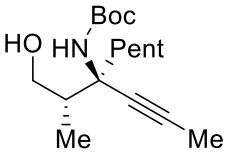
^{1}H-NMR (500 MHz, $CDCl_3$)



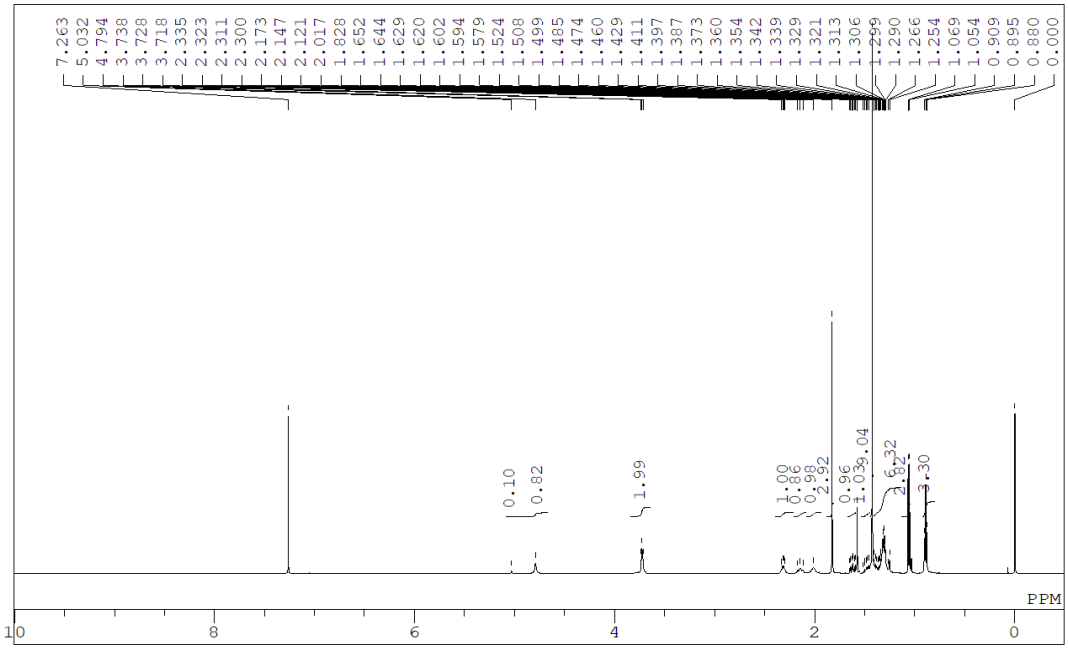
^{13}C-NMR (125 MHz, $CDCl_3$)



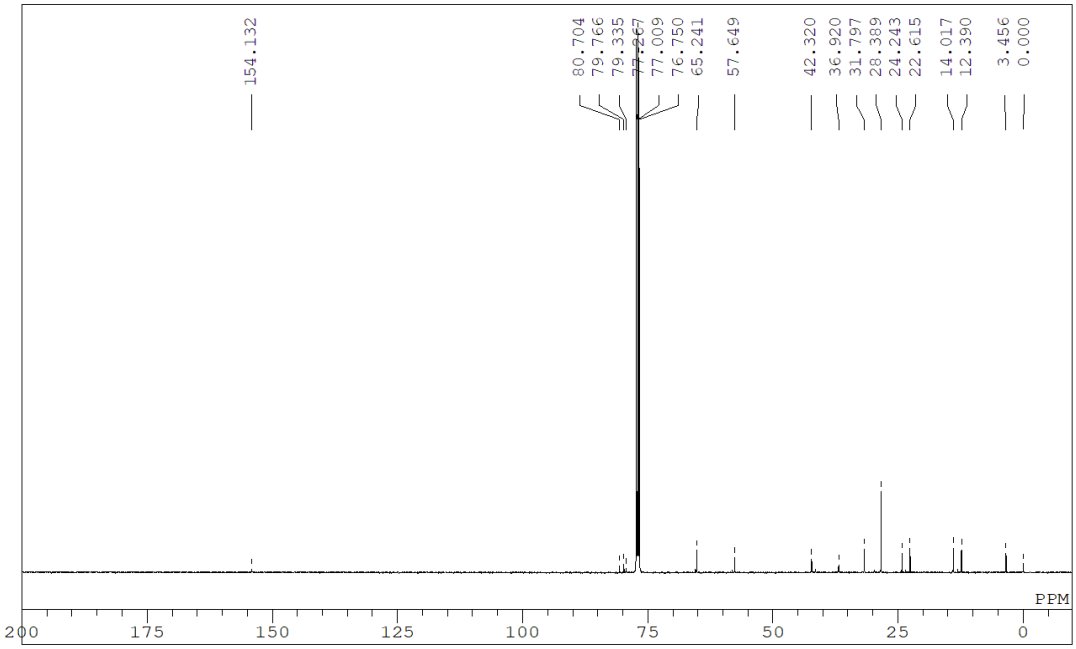
***tert*-Butyl ((*R*)-4-((*S*)-1-hydroxypropan-2-yl)non-2-yn-4-yl)carbamate (*anti*-2b)**



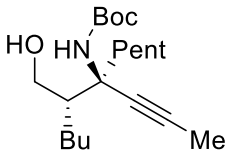
^{1}H-NMR (500 MHz, $CDCl_3$)



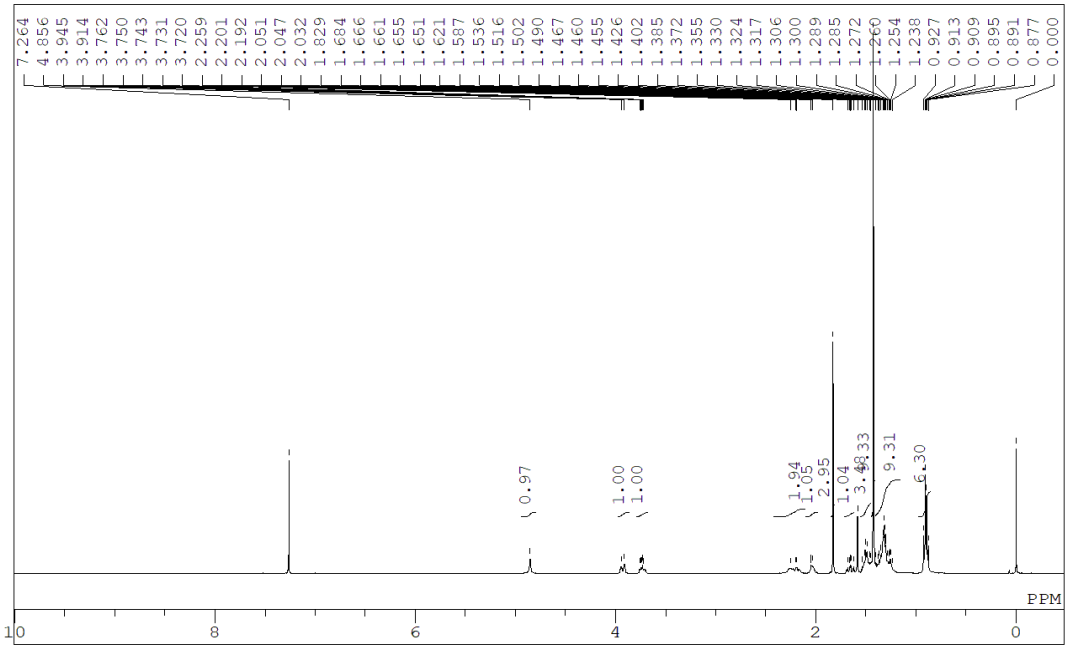
^{13}C-NMR (125 MHz, $CDCl_3$)



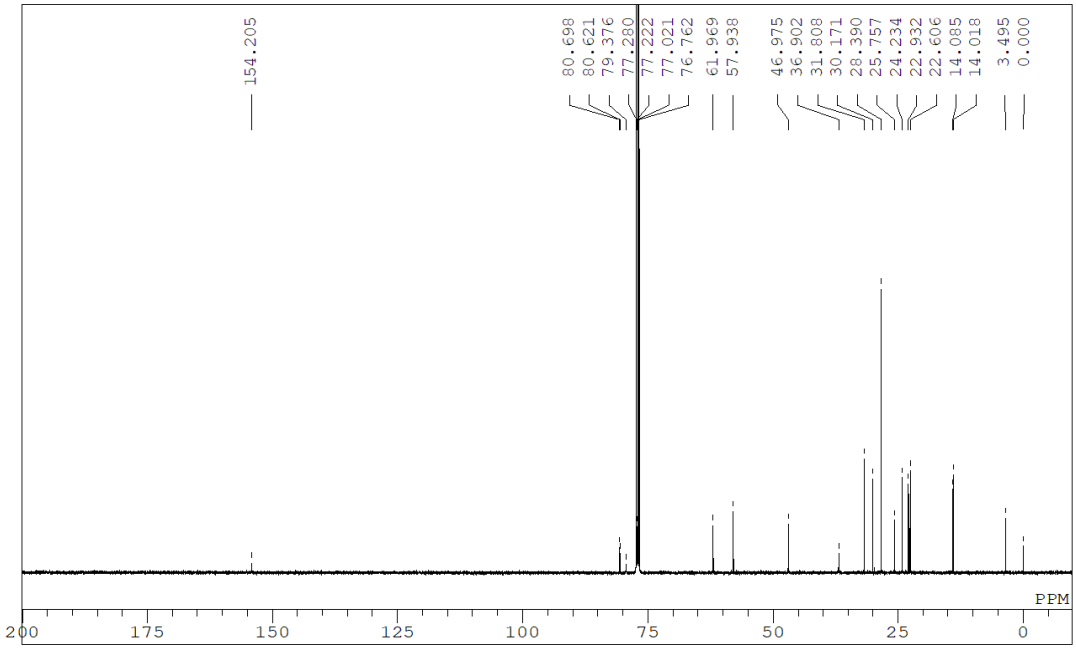
***tert*-Butyl ((5*S*,6*R*)-5-(hydroxymethyl)-6-(prop-1-yn-1-yl)undecan-6-yl)carbamate (*anti*-2c)**



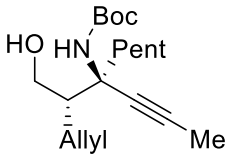
^{1}H-NMR (400 MHz, $CDCl_3$)



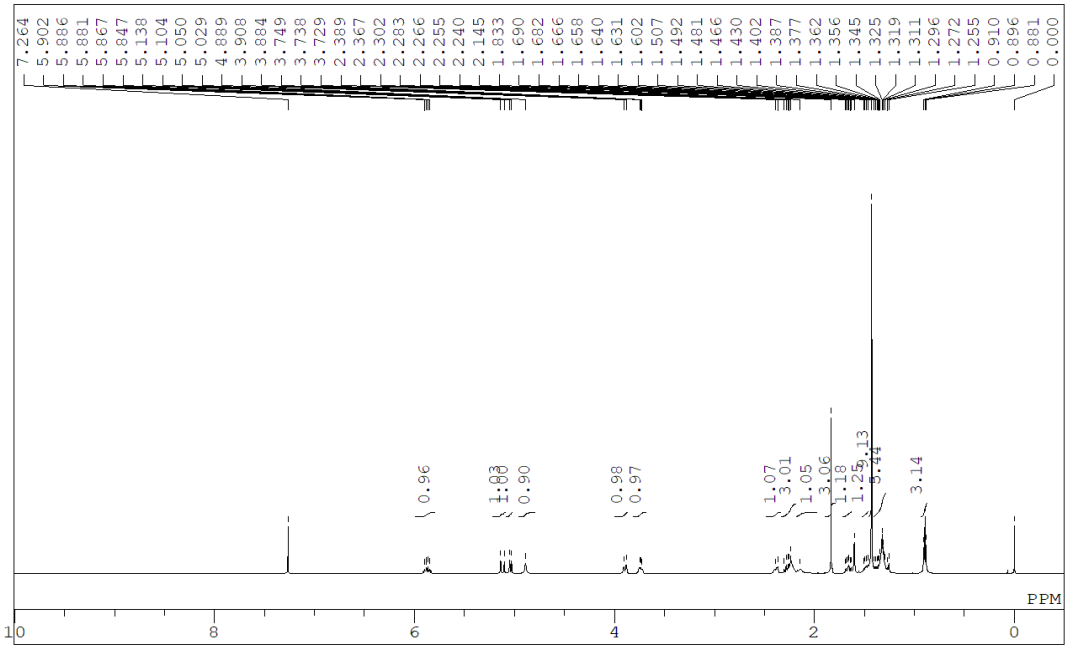
^{13}C-NMR (125 MHz, $CDCl_3$)



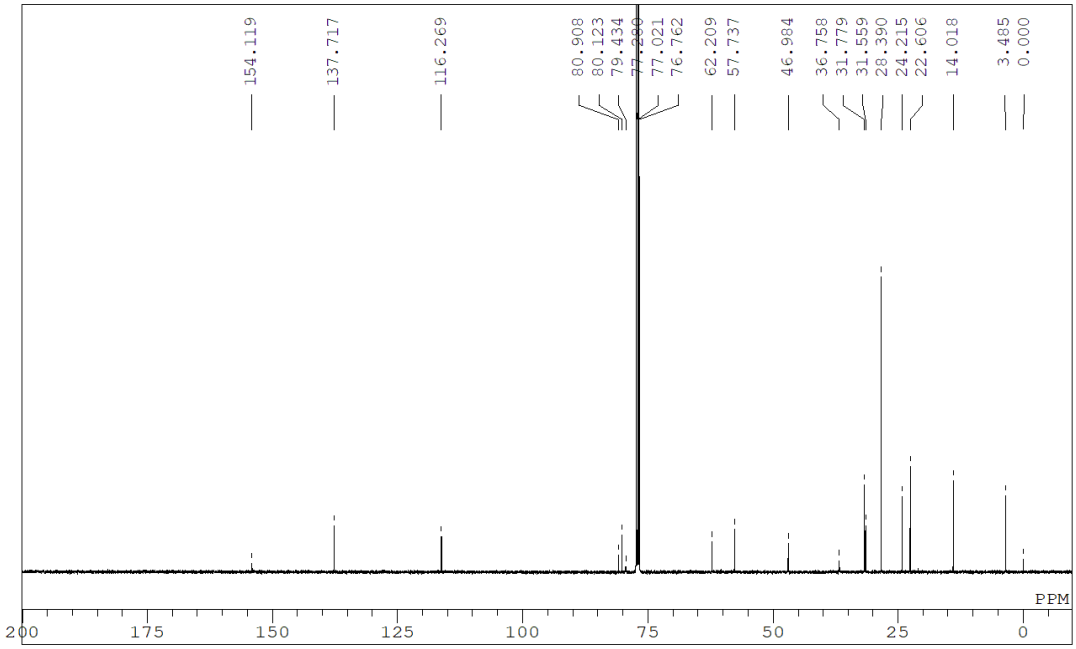
***tert*-Butyl ((4*S*,5*R*)-4-(hydroxymethyl)-5-(prop-1-yn-1-yl)dec-1-en-5-yl)carbamate (*anti*-2d)**



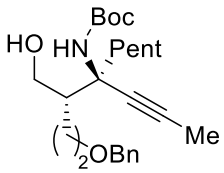
^{1}H-NMR (500 MHz, $CDCl_3$)



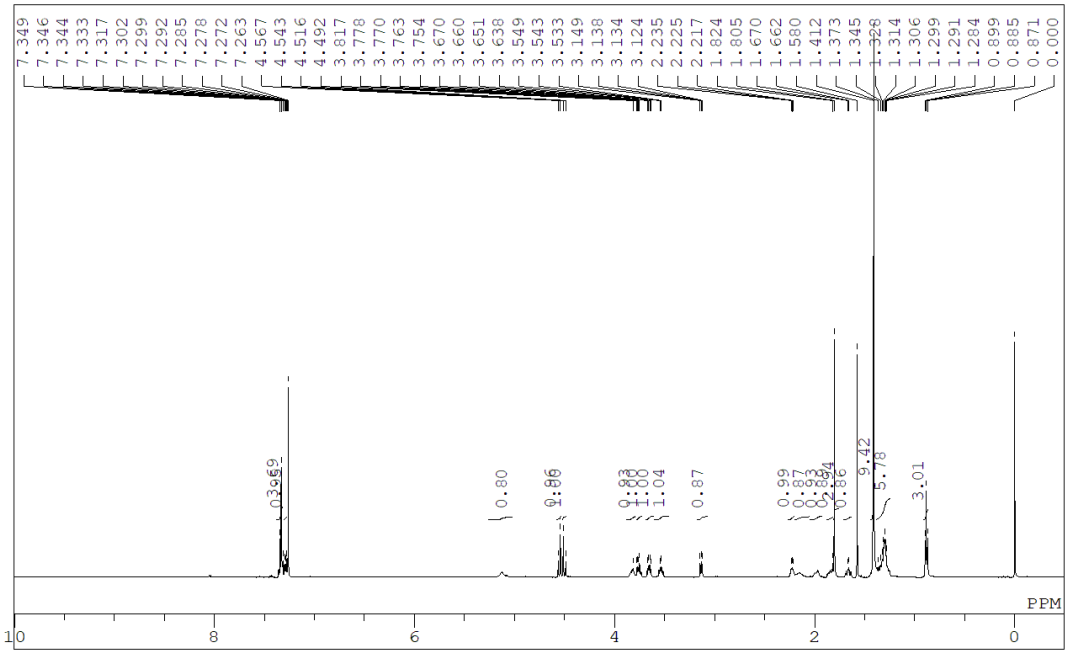
^{13}C-NMR (125 MHz, $CDCl_3$)



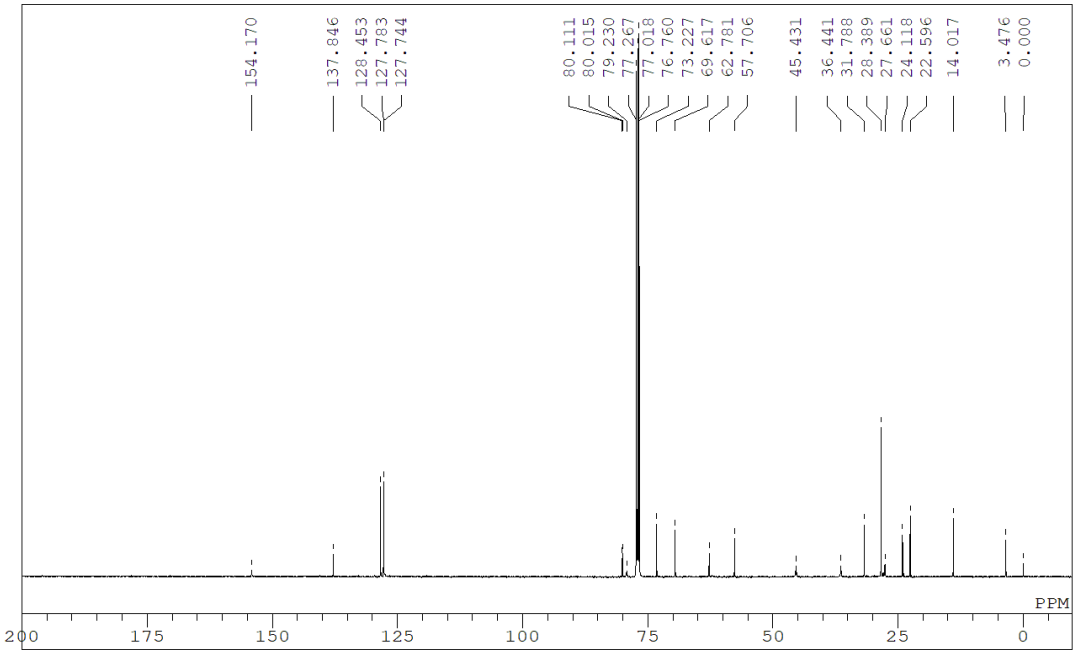
tert-Butyl ((_R_)-4-((_S_)-4-(benzyloxy)-1-hydroxybutan-2-yl)non-2-yn-4-yl)carbamate (_anti_-2e)



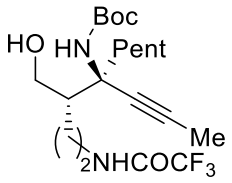
^{1}H-NMR (500 MHz, $CDCl_3$)



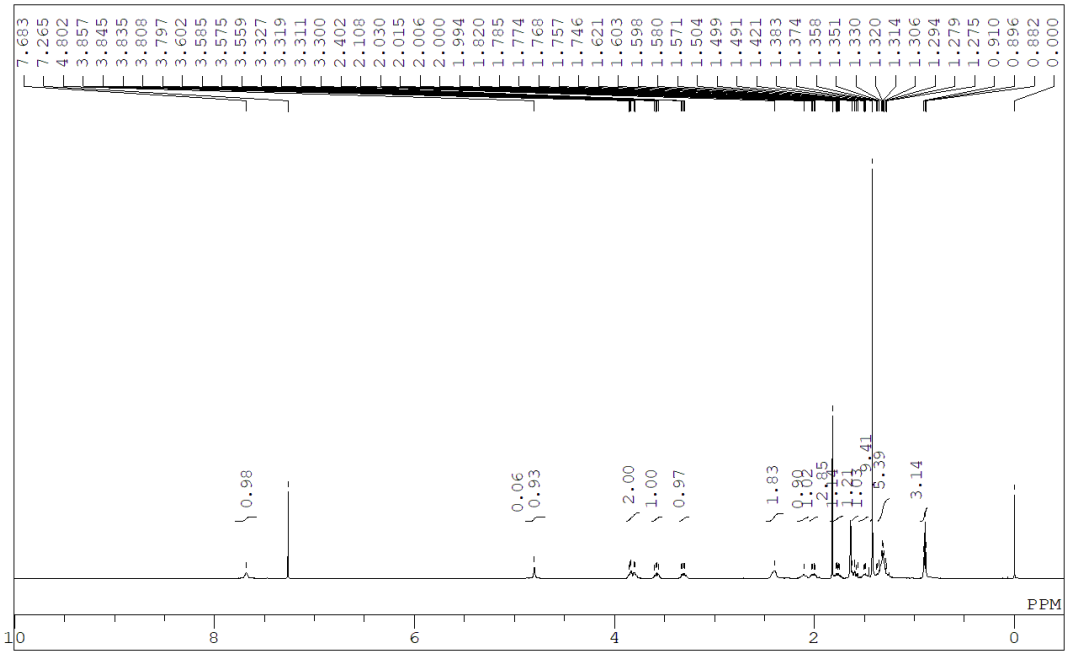
^{13}C-NMR (125 MHz, $CDCl_3$)



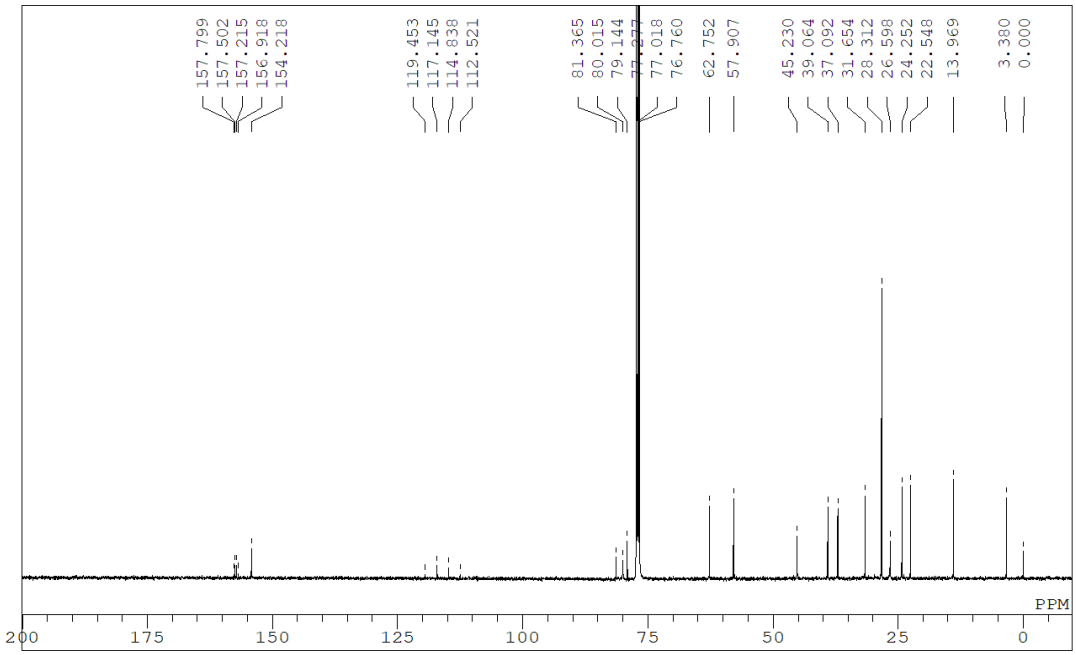
***tert*-Butyl ((*R*)-4-((*S*)-1-hydroxy-4-(2,2,2-trifluoroacetamido)butan-2-yl)non-2-yn-4-yl) carbamate(*anti*-2f)**



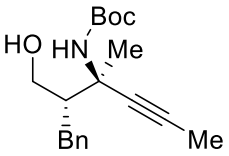
^{1}H-NMR (500 MHz, $CDCl_3$)



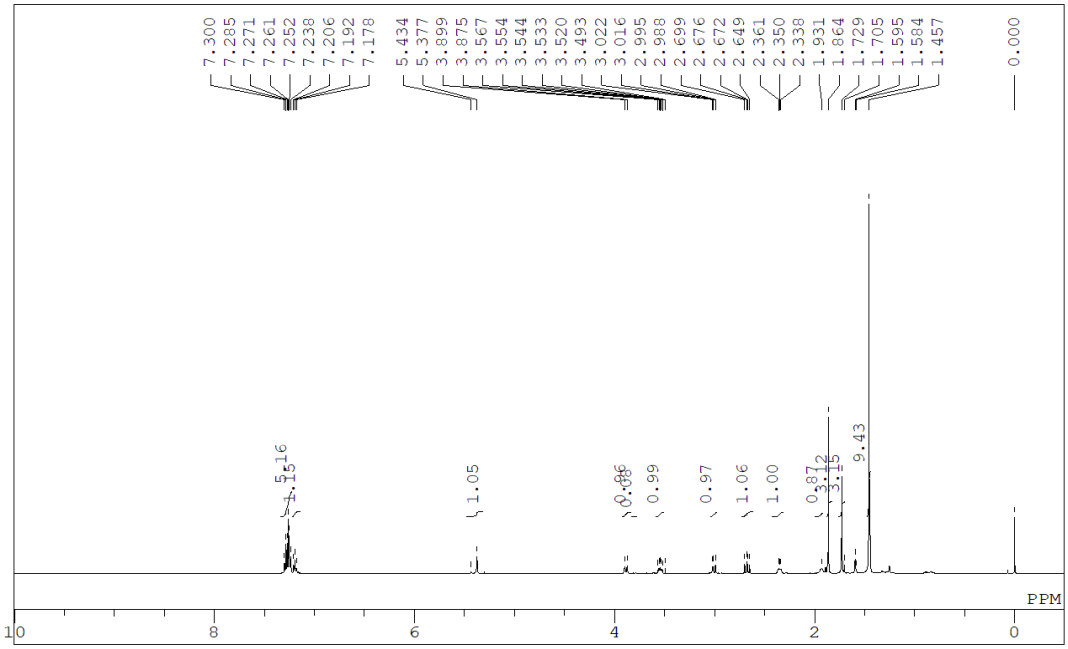
^{13}C-NMR (125 MHz, $CDCl_3$)



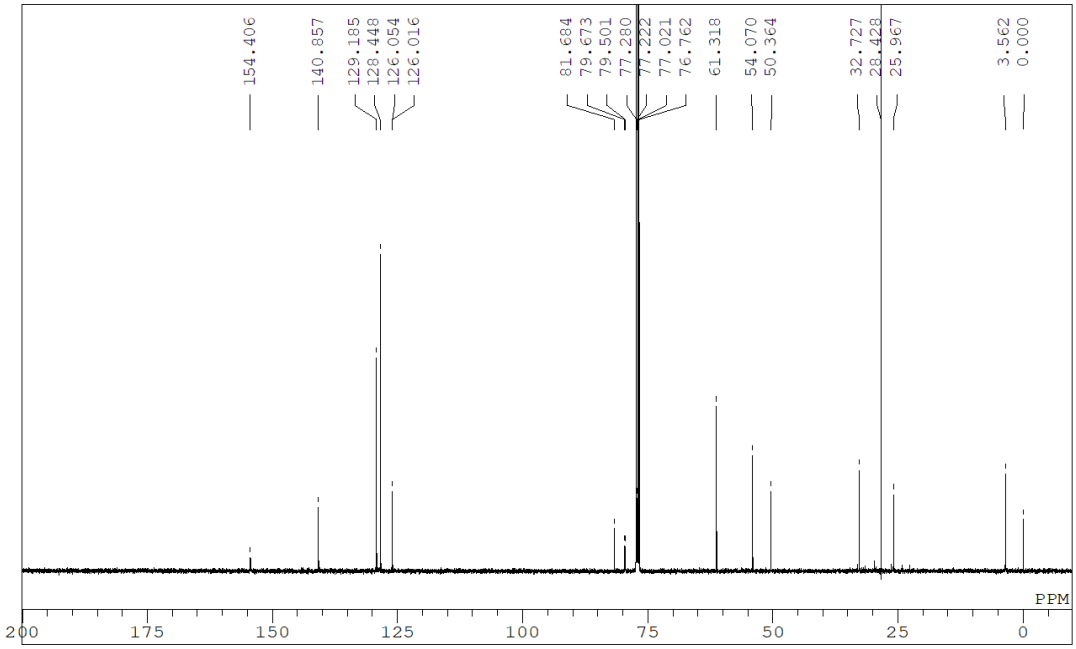
tert-Butyl ((2*S*,3*R*)-2-benzyl-1-hydroxy-3-methylhex-4-yn-3-yl)carbamate (_anti_-2g)



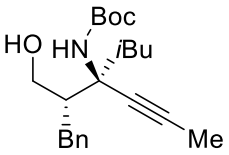
^{1}H-NMR (500 MHz, $CDCl_3$)



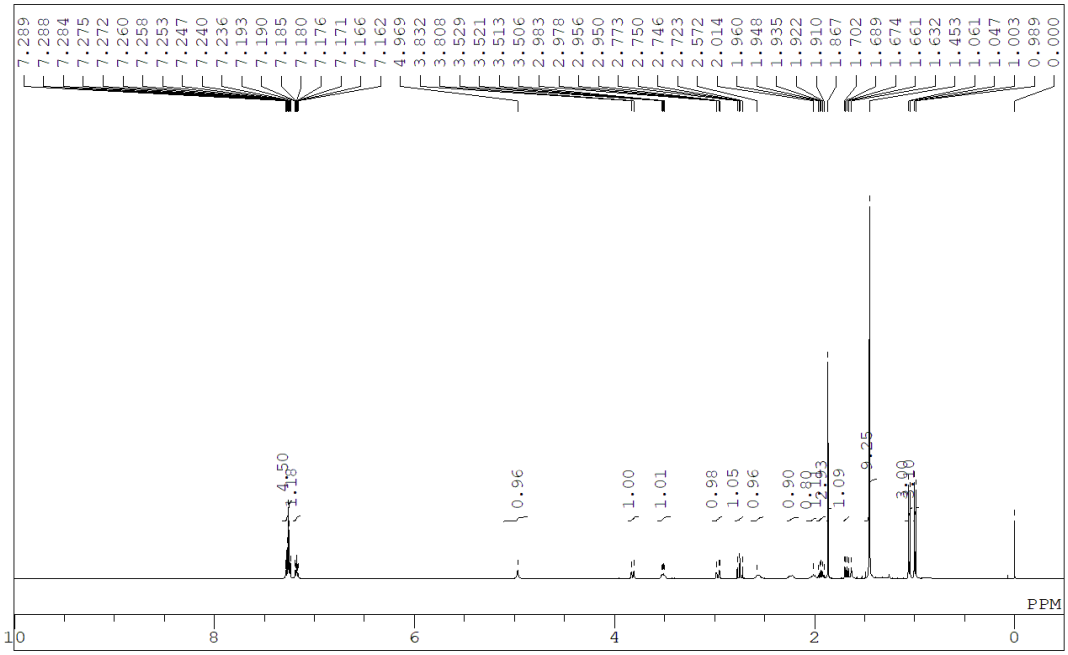
^{13}C-NMR (125 MHz, $CDCl_3$)



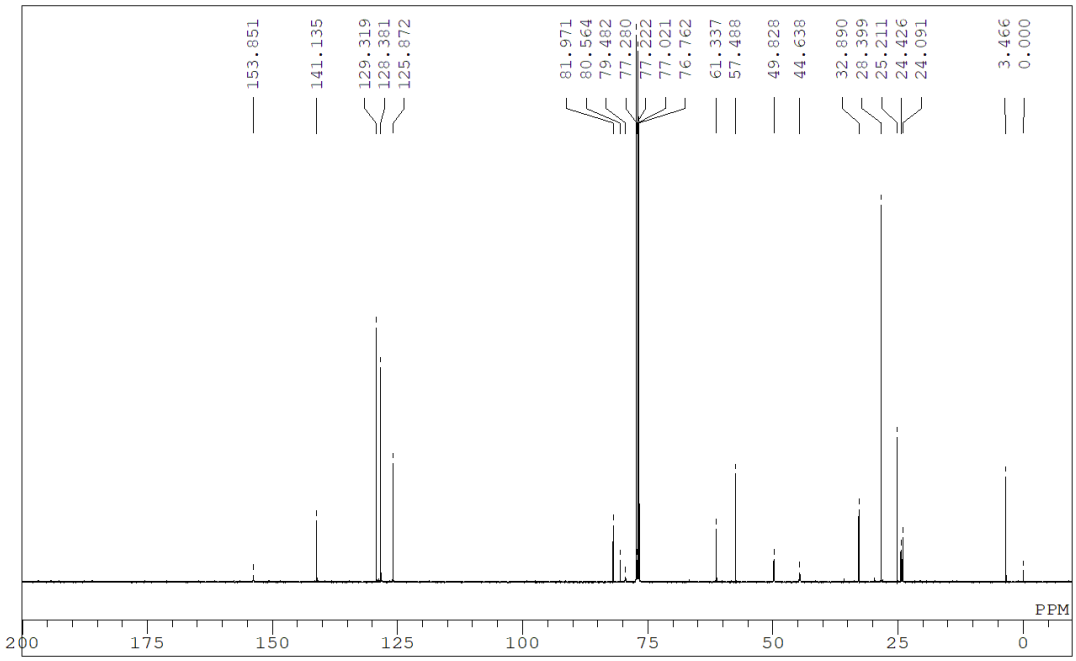
***tert*-Butyl ((*R*)-4-((*S*)-1-hydroxy-3-phenylpropan-2-yl)-6-methylhept-2-yn-4-yl)carbamate (*anti*-2h)**



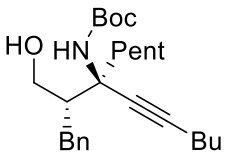
^{1}H-NMR (500 MHz, $CDCl_3$)



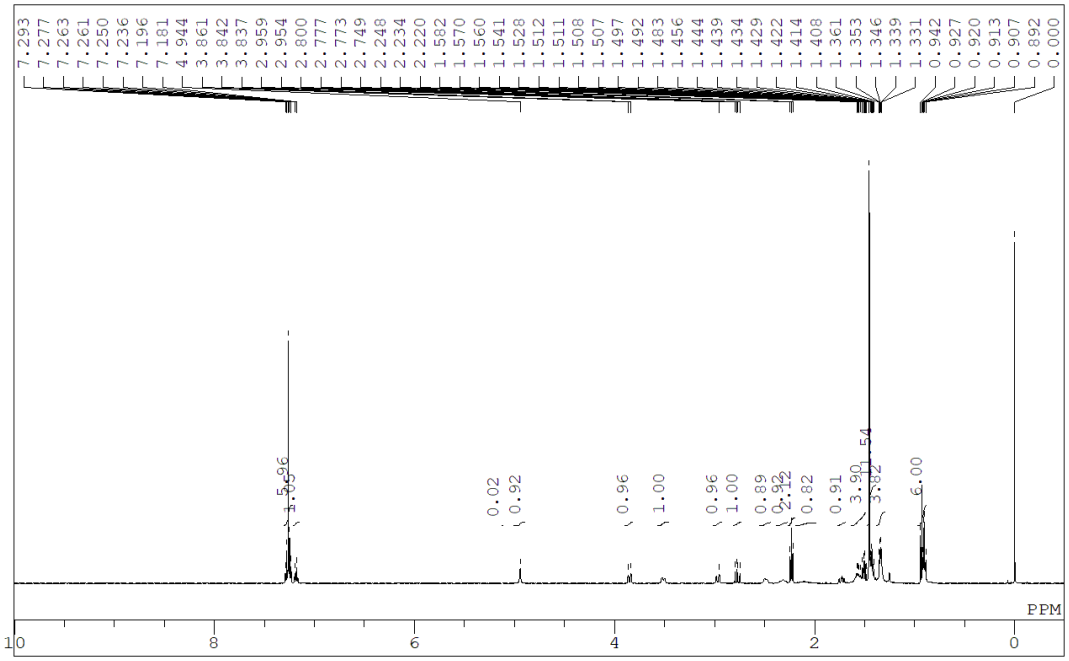
^{13}C-NMR (125 MHz, $CDCl_3$)



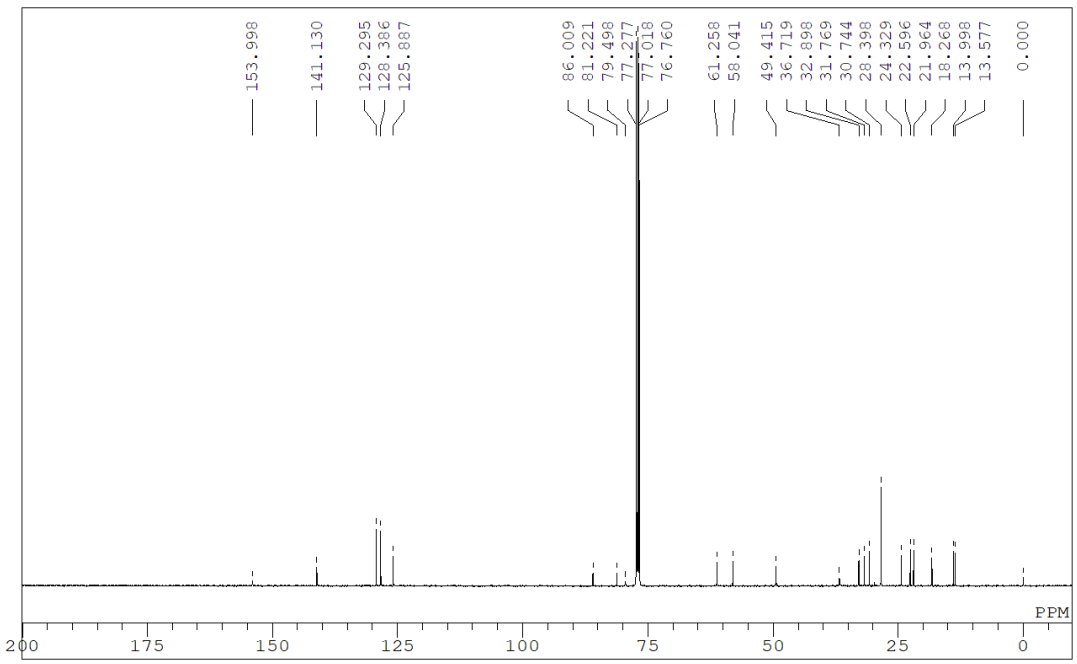
***tert*-Butyl ((*R*)-4-((*S*)-1-hydroxy-3-phenylpropan-2-yl)-6-methylhept-2-yn-4-yl)carbamate (*anti*-2i)**



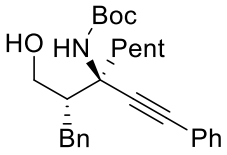
^{1}H-NMR (500 MHz, $CDCl_3$)



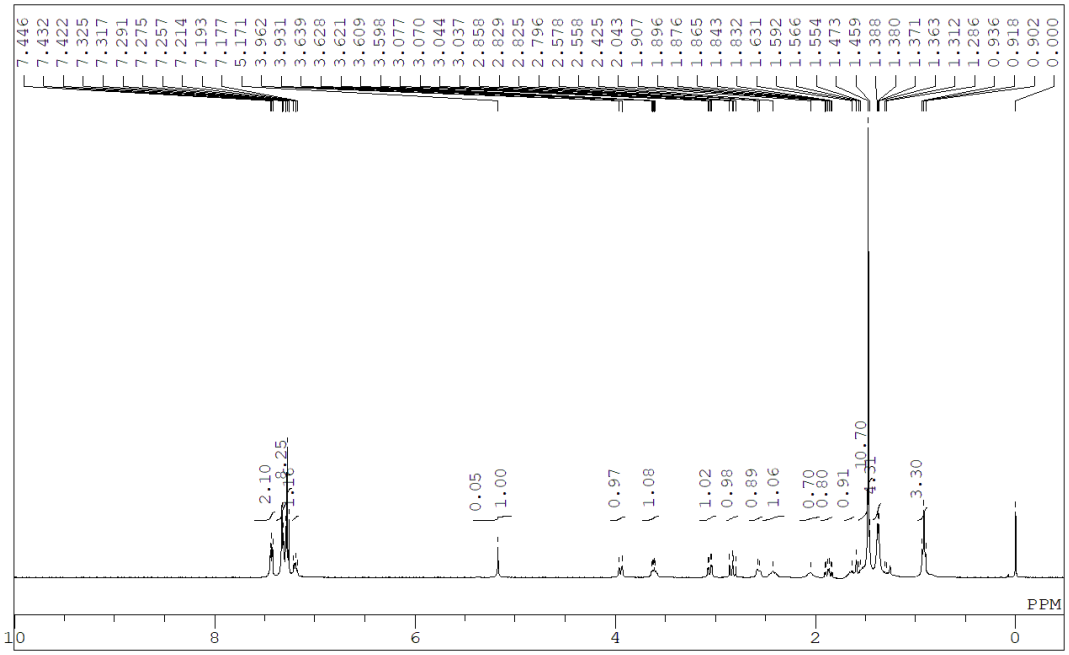
^{13}C-NMR (125 MHz, $CDCl_3$)



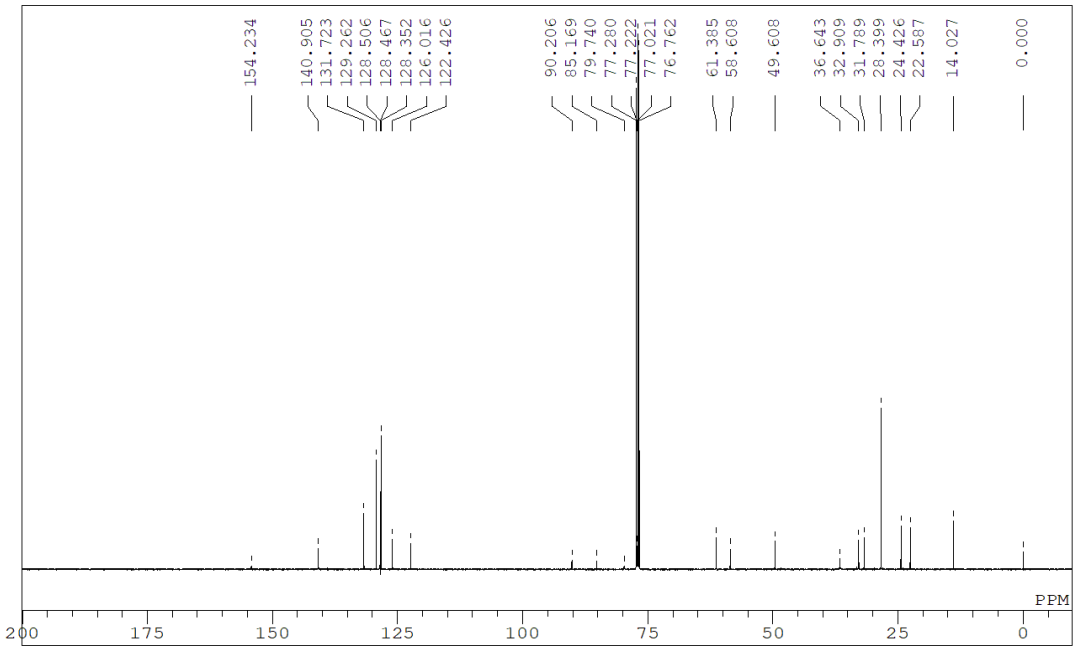
***tert*-Butyl ((*R*)-3-((*S*)-1-hydroxy-3-phenylpropan-2-yl)-1-phenyloct-1-yn-3-yl)carbamate (*anti*-2j)**



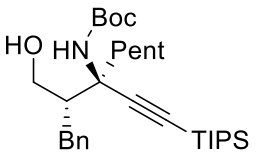
^{1}H-NMR (400 MHz, $CDCl_3$)



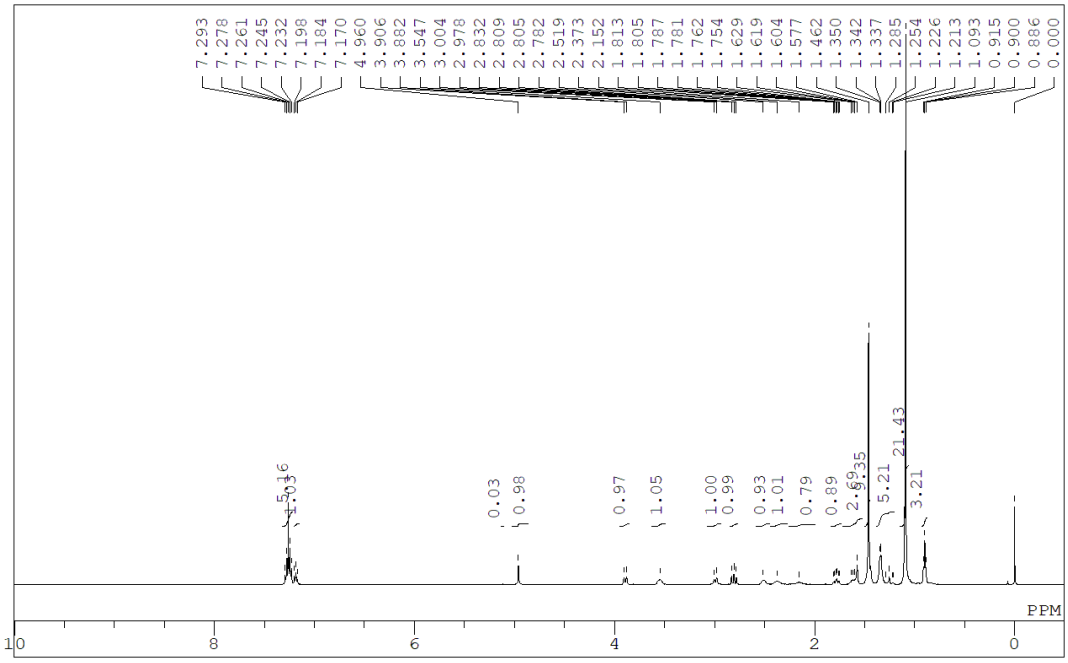
^{13}C-NMR (125 MHz, $CDCl_3$)



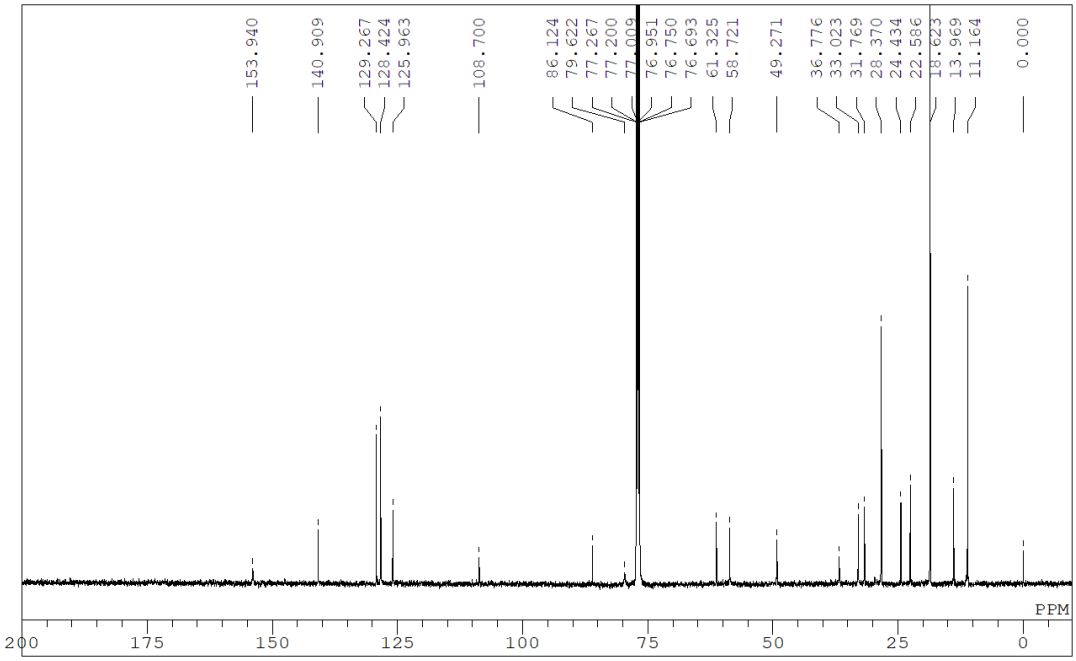
***tert*-Butyl ((*R*)-3-((*S*)-1-hydroxy-3-phenylpropan-2-yl)-1-(triisopropylsilyl)oct-1-yn-3-yl) carbamate (*anti*-2k)**



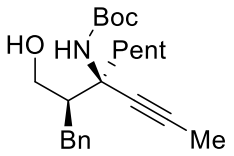
^{1}H-NMR (400 MHz, $CDCl_3$)



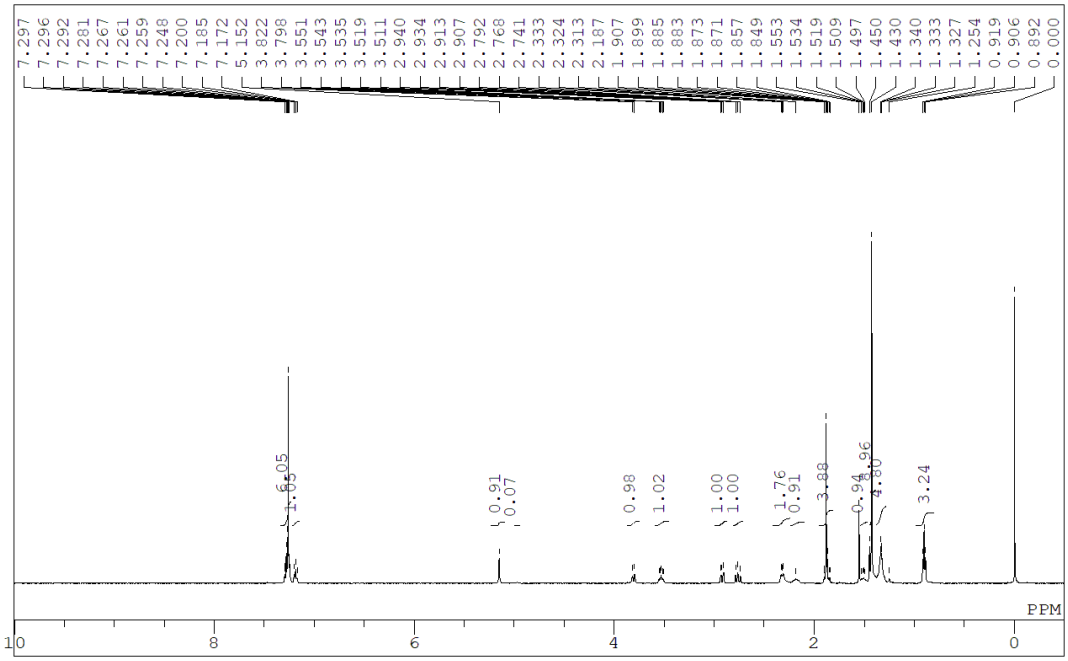
^{13}C-NMR (125 MHz, $CDCl_3$)



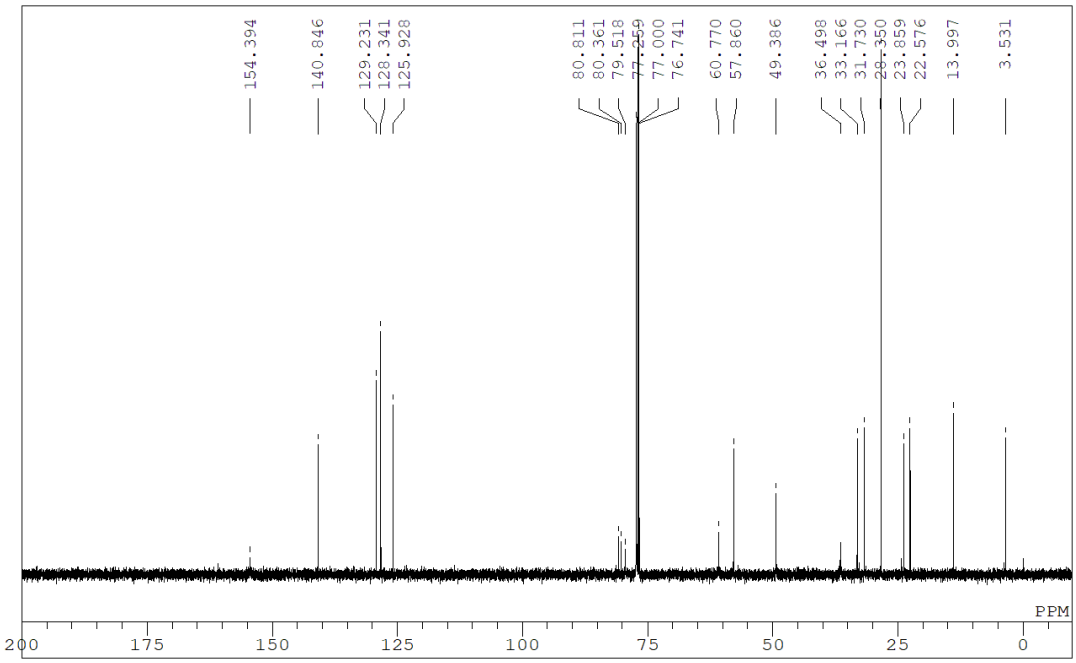
***tert*-Butyl ((*R*)-4-((*R*)-1-hydroxy-3-phenylpropan-2-yl)non-2-yn-4-yl)carbamate (*syn*-2a)**



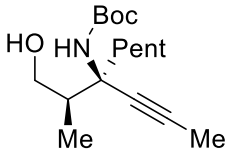
^{1}H-NMR (500 MHz, $CDCl_3$)



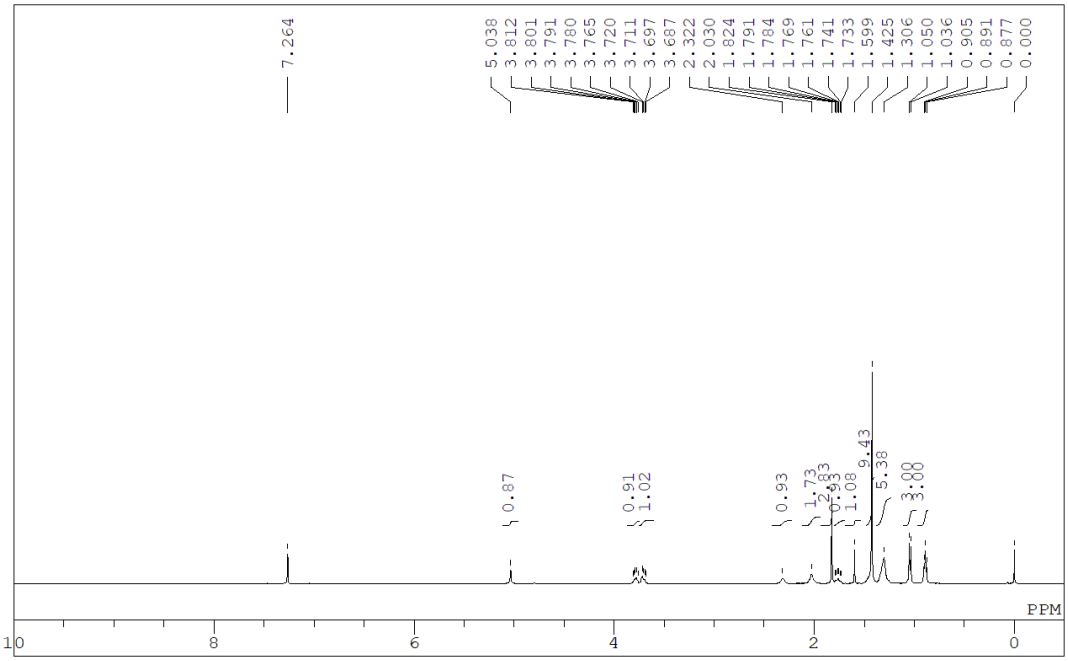
^{13}C-NMR (125 MHz, $CDCl_3$)



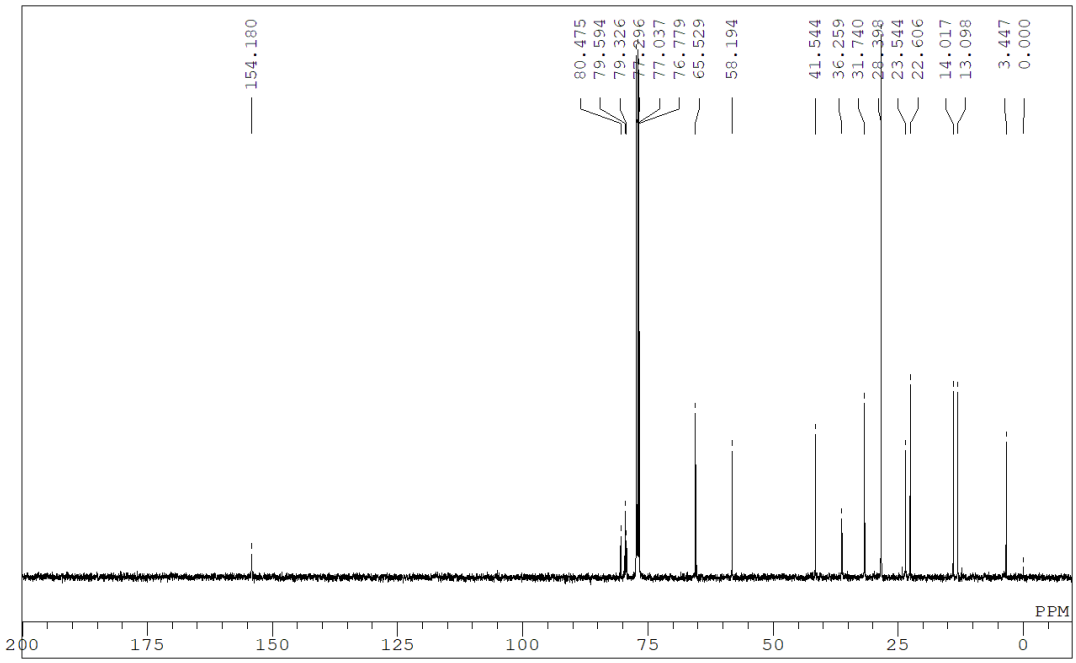
***tert*-Butyl ((*R*)-4-((*R*)-1-hydroxypropan-2-yl)non-2-yn-4-yl)carbamate (*syn*-2b)**



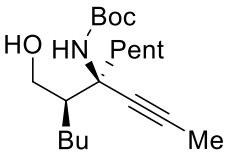
^{1}H-NMR (500 MHz, $CDCl_3$)



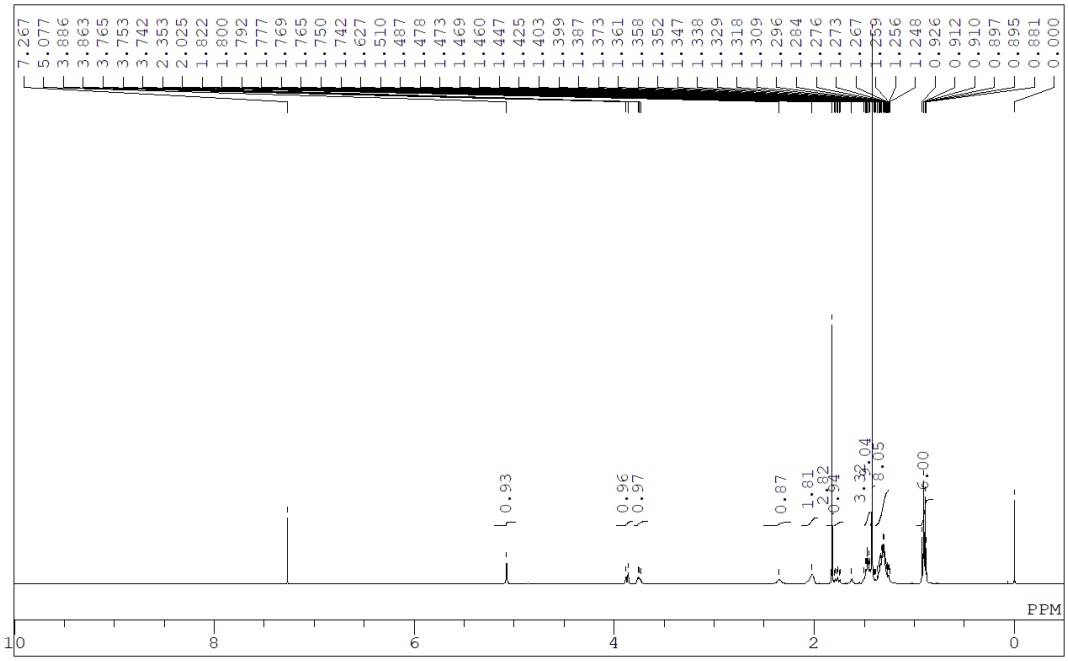
^{13}C-NMR (125 MHz, $CDCl_3$)



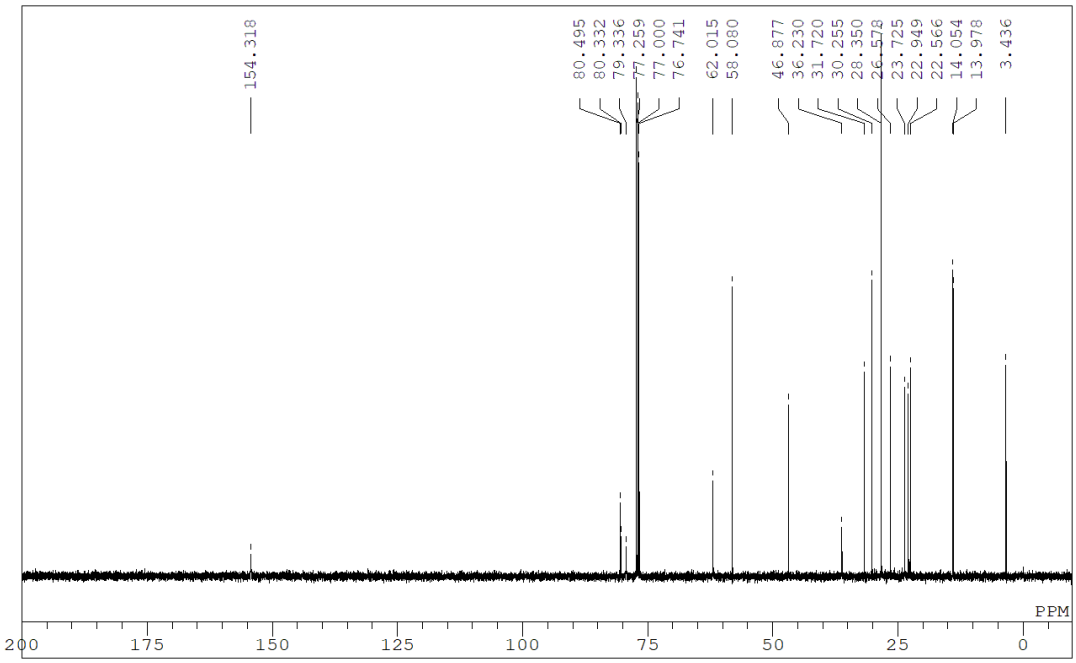
***tert*-Butyl ((5*R*,6*R*)-5-(hydroxymethyl)-6-(prop-1-yn-1-yl)undecan-6-yl)carbamate (*syn*-2c)**



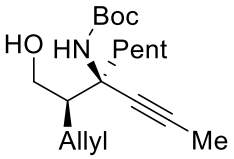
^{1}H-NMR (500 MHz, $CDCl_3$)



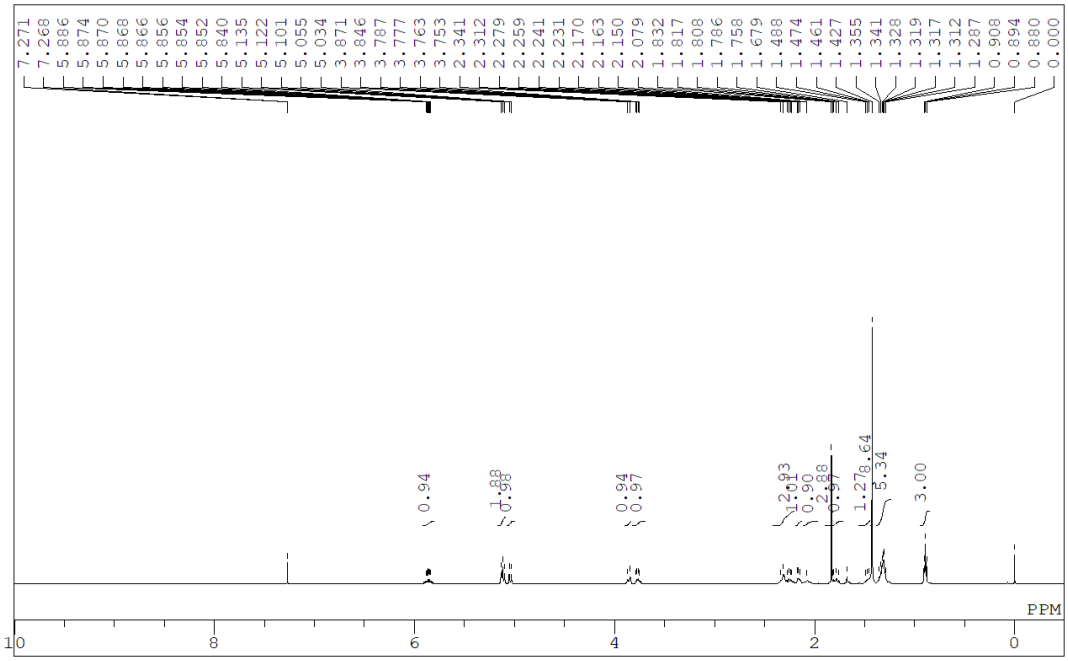
^{13}C-NMR (125 MHz, $CDCl_3$)



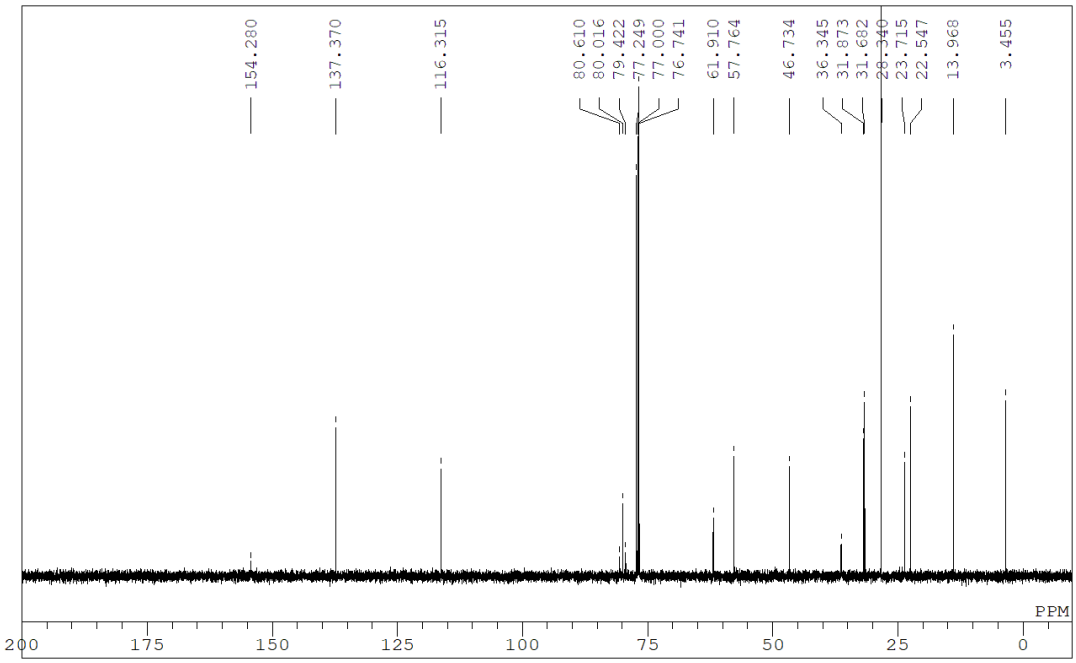
***tert*-Butyl ((4*R*,5*R*)-4-(hydroxymethyl)-5-(prop-1-yn-1-yl)dec-1-en-5-yl)carbamate (*syn*-2d)**



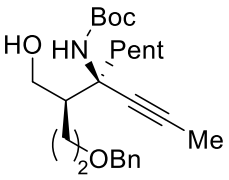
^{1}H-NMR (500 MHz, $CDCl_3$)



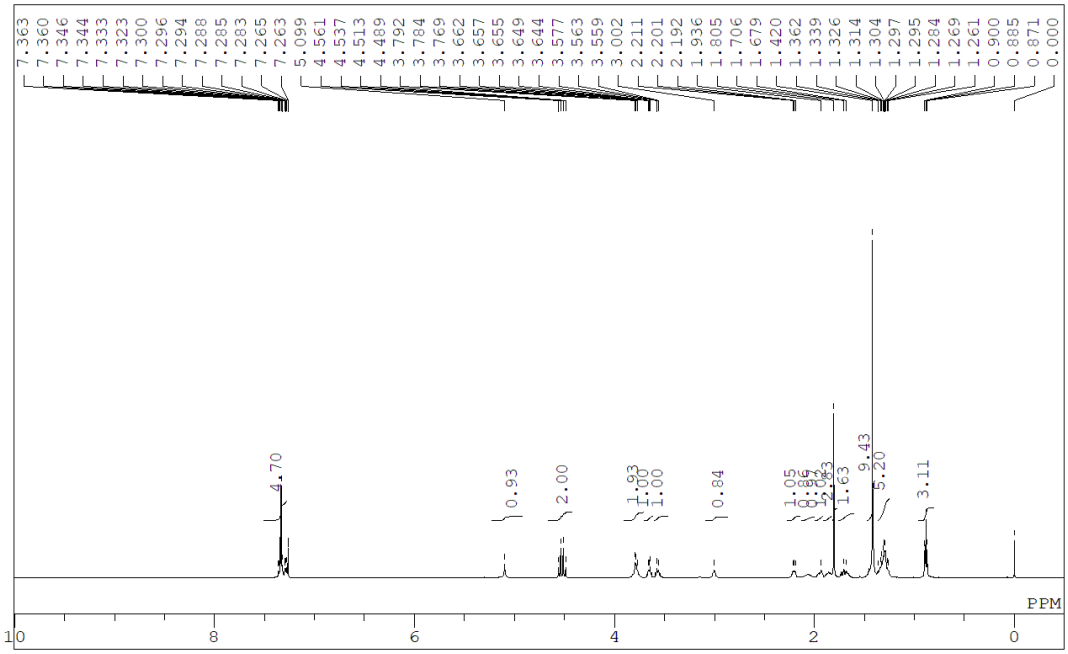
^{13}C-NMR (125 MHz, $CDCl_3$)



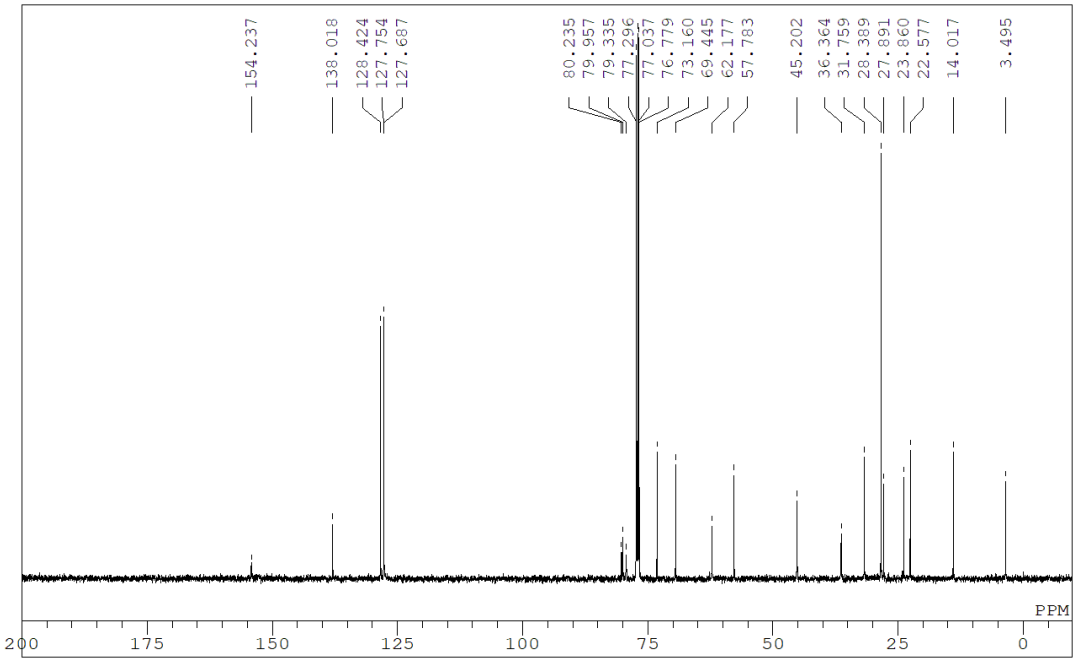
***tert*-Butyl ((*R*)-4-((*R*)-4-(benzyloxy)-1-hydroxybutan-2-yl)non-2-yn-4-yl)carbamate (*syn*-2e)**



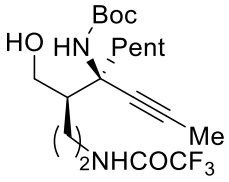
^{1}H-NMR (500 MHz, $CDCl_3$)



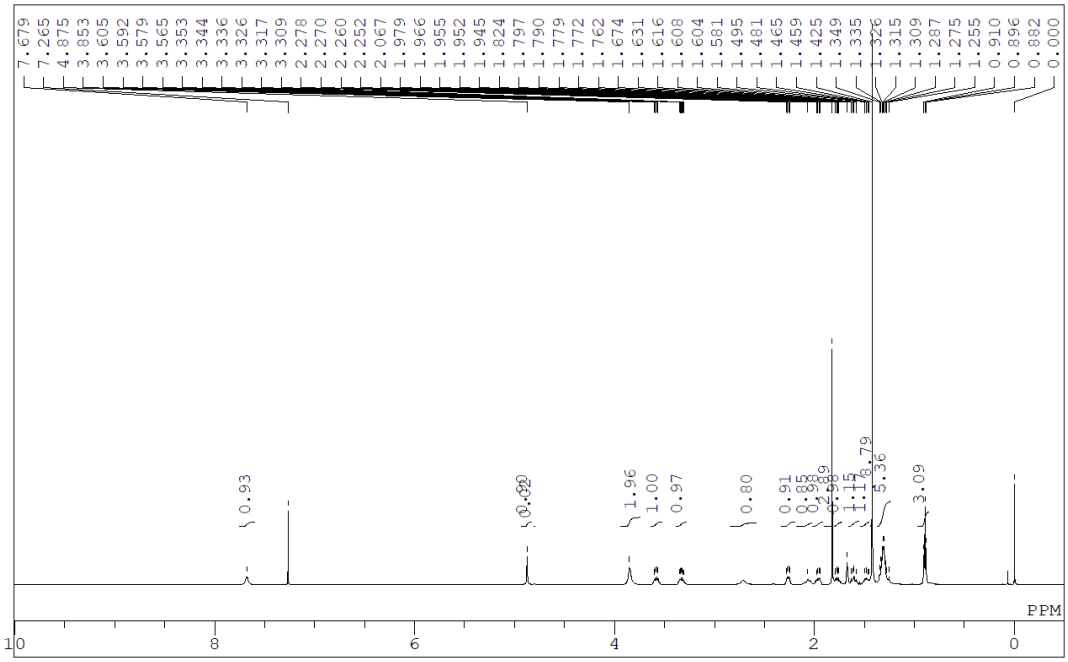
^{13}C-NMR (125 MHz, $CDCl_3$)



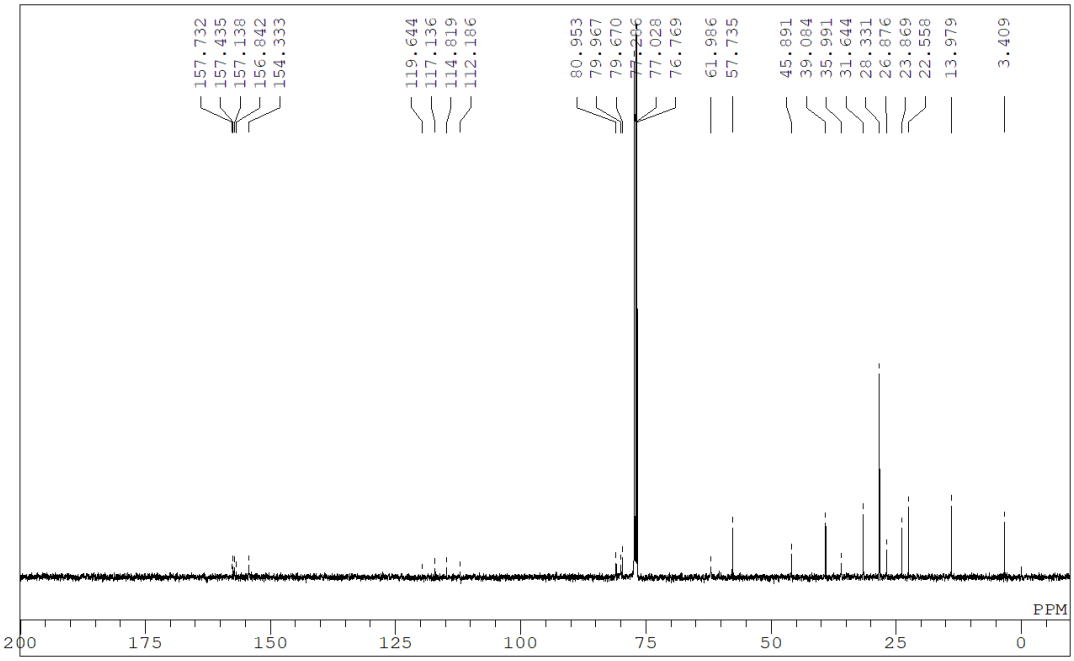
***tert*-Butyl ((*R*)-4-((*R*)-1-hydroxy-4-(2,2,2-trifluoroacetamido)butan-2-yl)non-2-yn-4-yl) carbamate (*syn*-2f)**



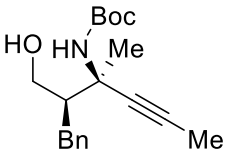
^{1}H-NMR (500 MHz, $CDCl_3$)



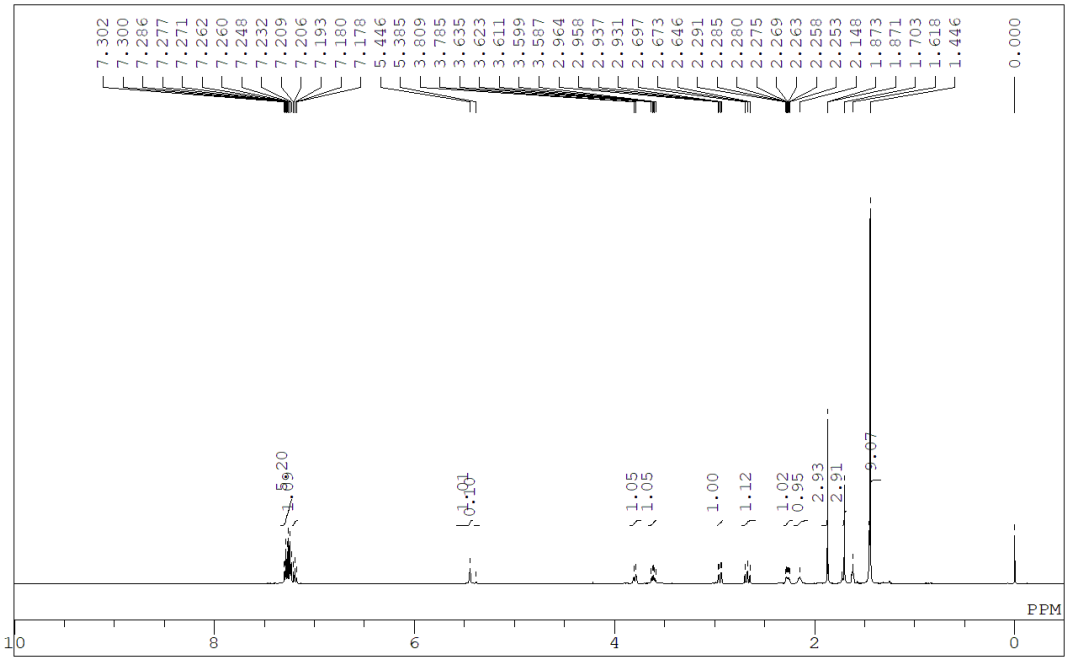
^{13}C-NMR (125 MHz, $CDCl_3$)



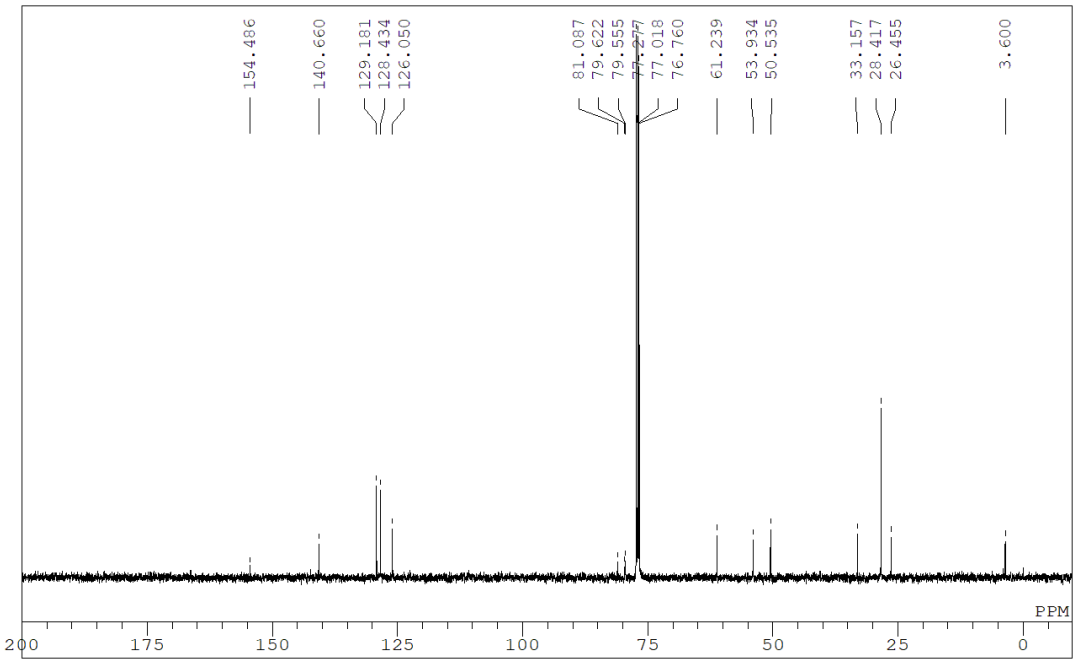
***tert*-Butyl ((2*R*,3*R*)-2-benzyl-1-hydroxy-3-methylhex-4-yn-3-yl)carbamate (*syn*-2g)**



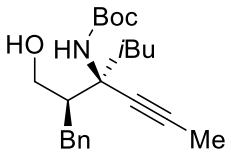
^{1}H-NMR (500 MHz, $CDCl_3$)



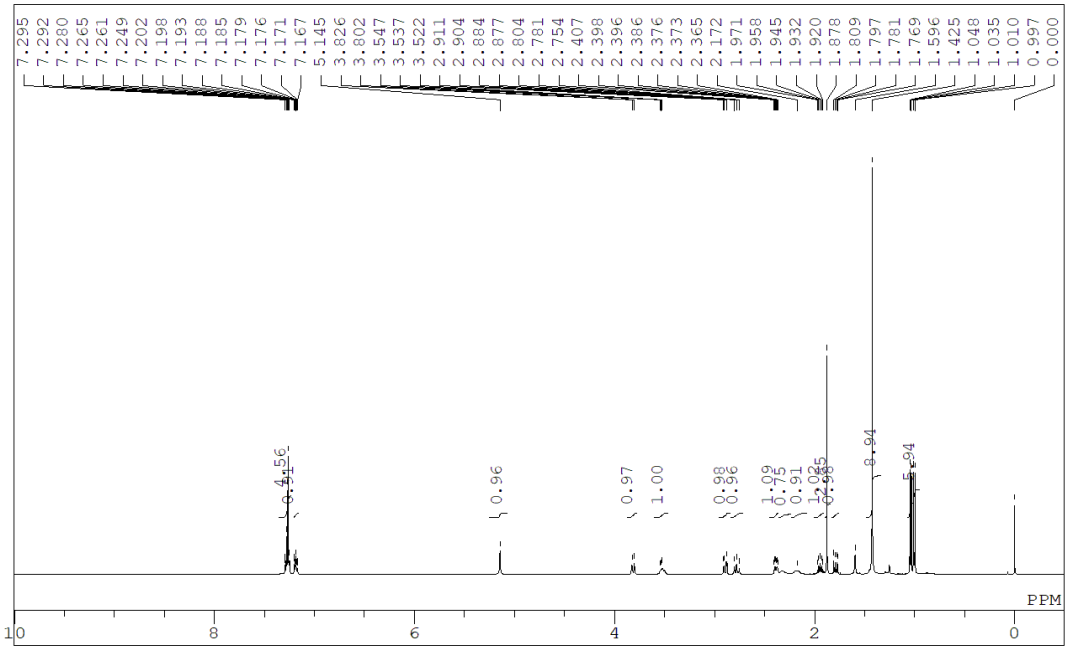
^{13}C-NMR (125 MHz, $CDCl_3$)



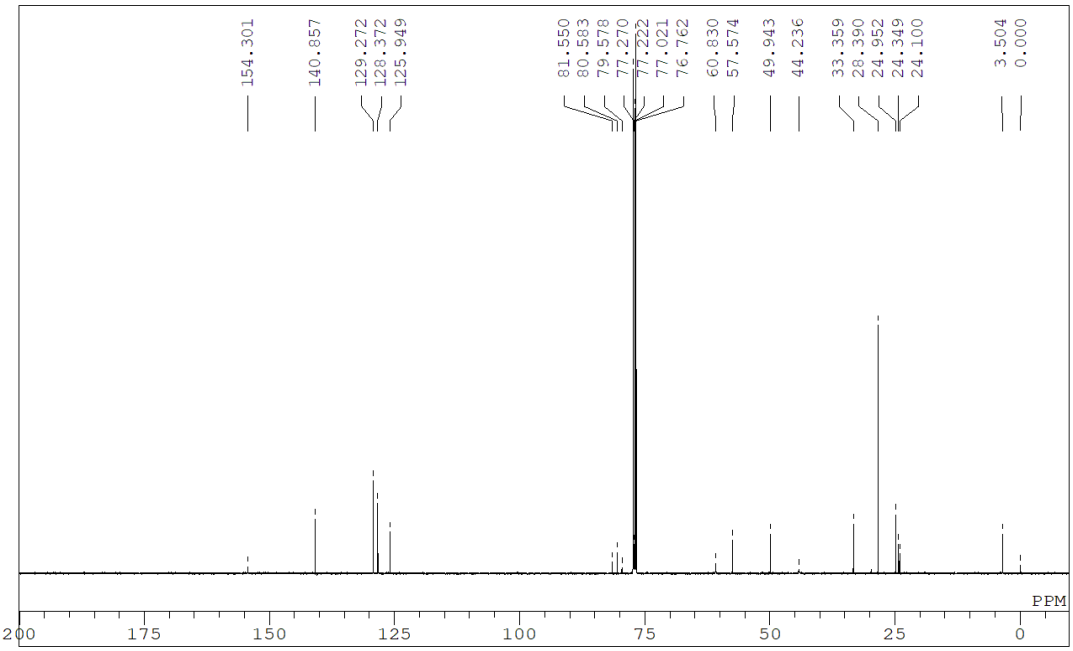
***tert*-Butyl ((*R*)-4-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-6-methylhept-2-yn-4-yl)carbamate (*syn*-2h)**



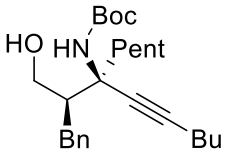
^{1}H-NMR (500 MHz, $CDCl_3$)



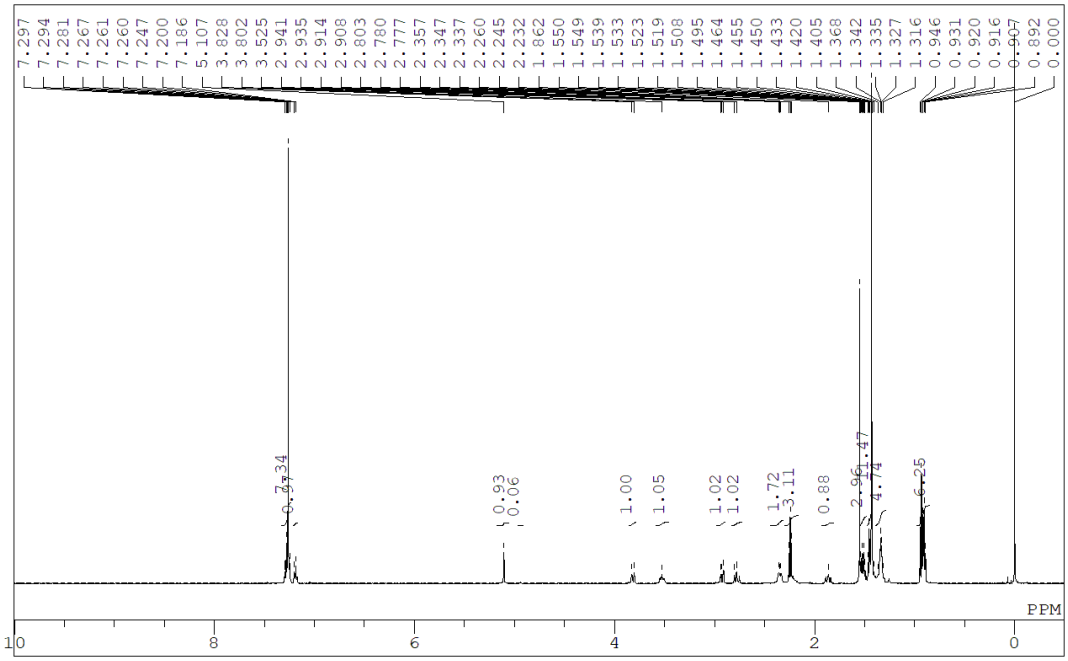
^{13}C-NMR (125 MHz, $CDCl_3$)



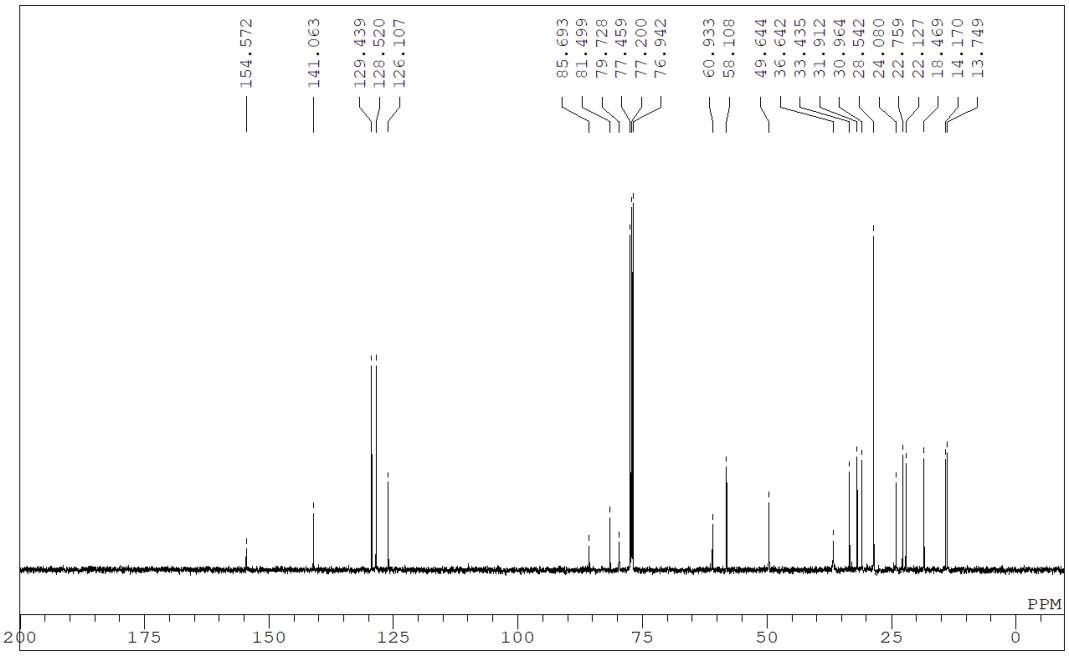
***tert*-Butyl ((5*R*,6*R*)-5-(hydroxymethyl)-6-(prop-1-yn-1-yl)undecan-6-yl)carbamate (*syn*-2i)**



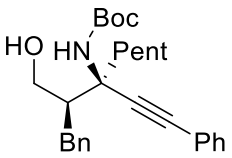
1H-NMR (500 MHz, $CDCl_3$)



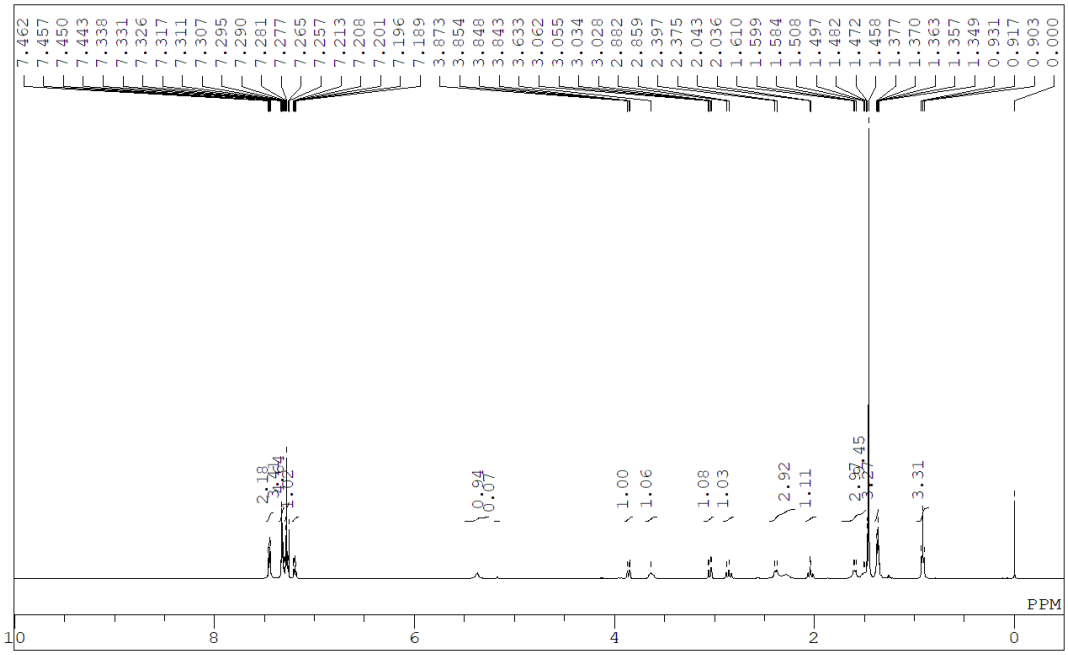
13C-NMR (125 MHz, $CDCl_3$)



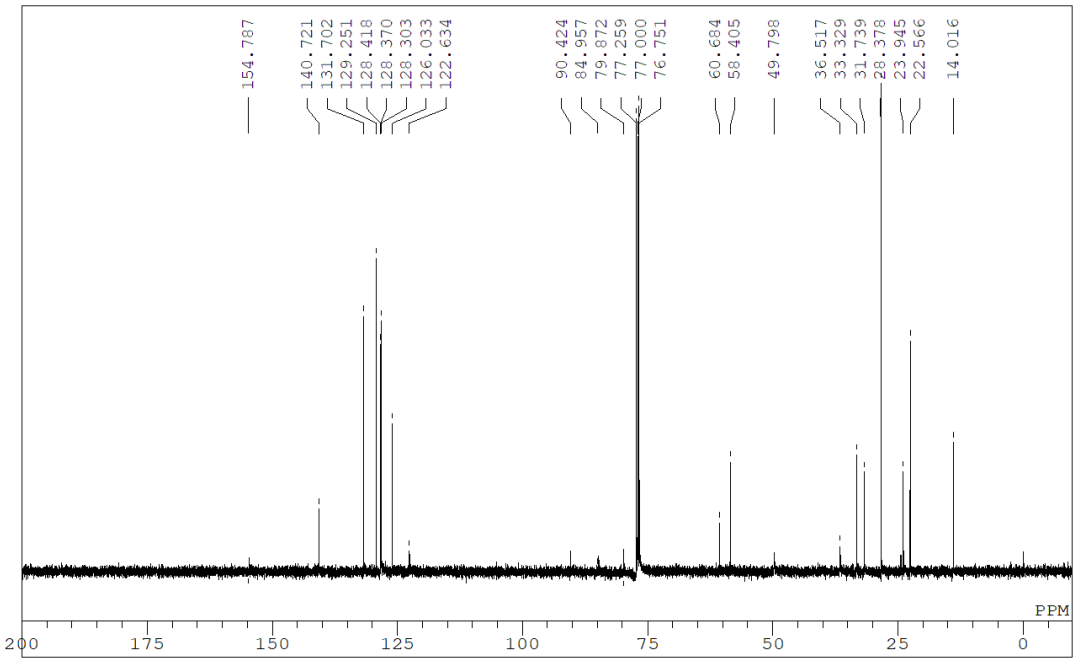
***tert*-Butyl ((*R*)-3-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-1-phenyloct-1-yn-3-yl)carbamate (*syn*-2j)**



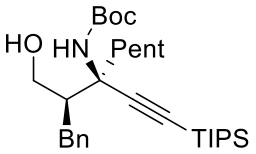
^{1}H-NMR (500 MHz, $CDCl_3$)



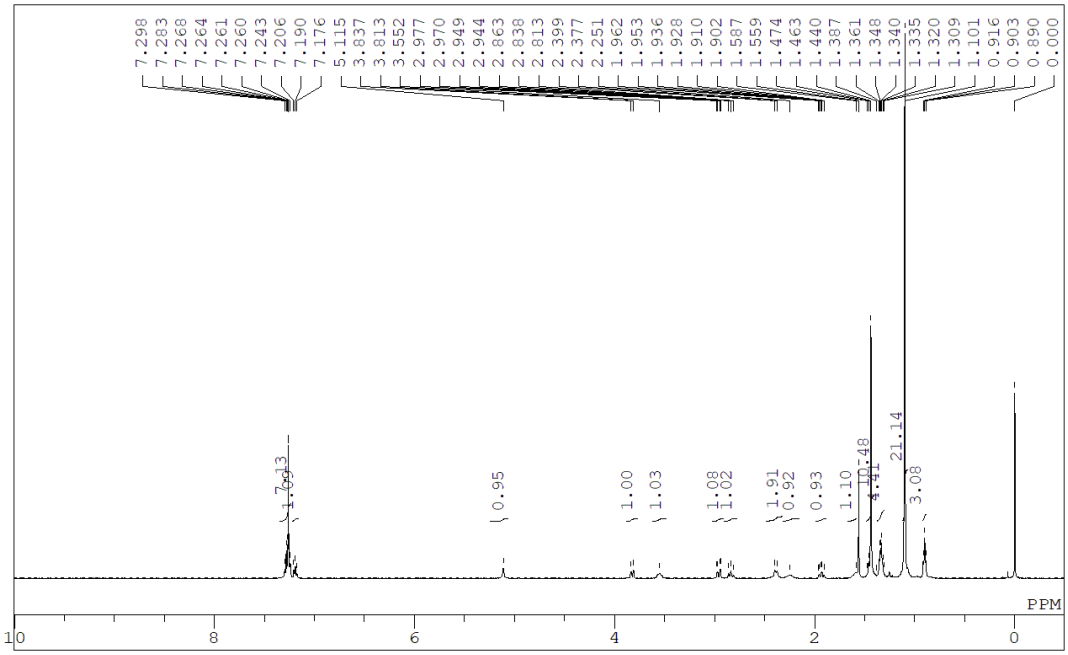
^{13}C-NMR (125 MHz, $CDCl_3$)



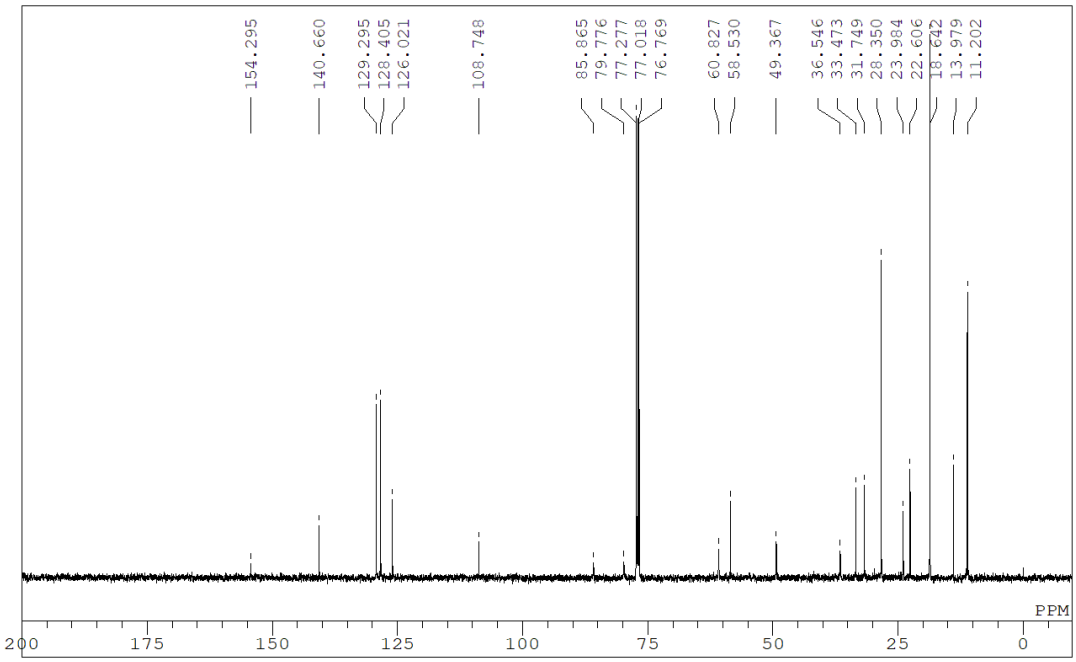
***tert*-Butyl ((*R*)-3-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-1-(triisopropylsilyl)oct-1-yn-3-yl) carbamate (*syn*-2k)**



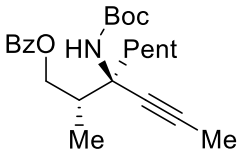
^{1}H-NMR (500 MHz, $CDCl_3$)



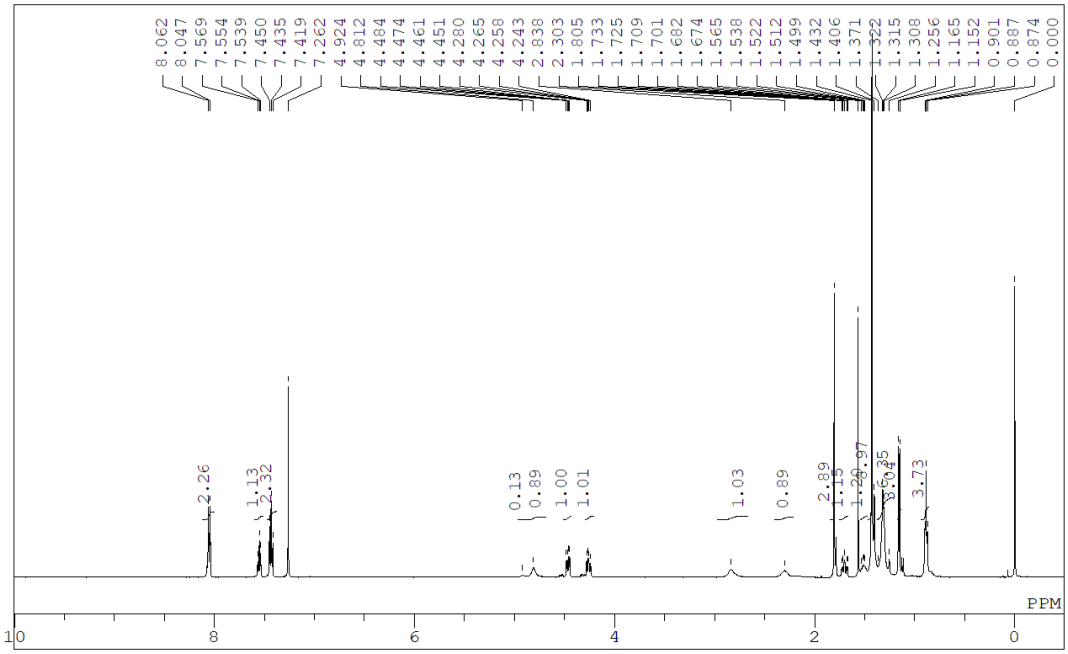
^{13}C-NMR (125 MHz, $CDCl_3$)



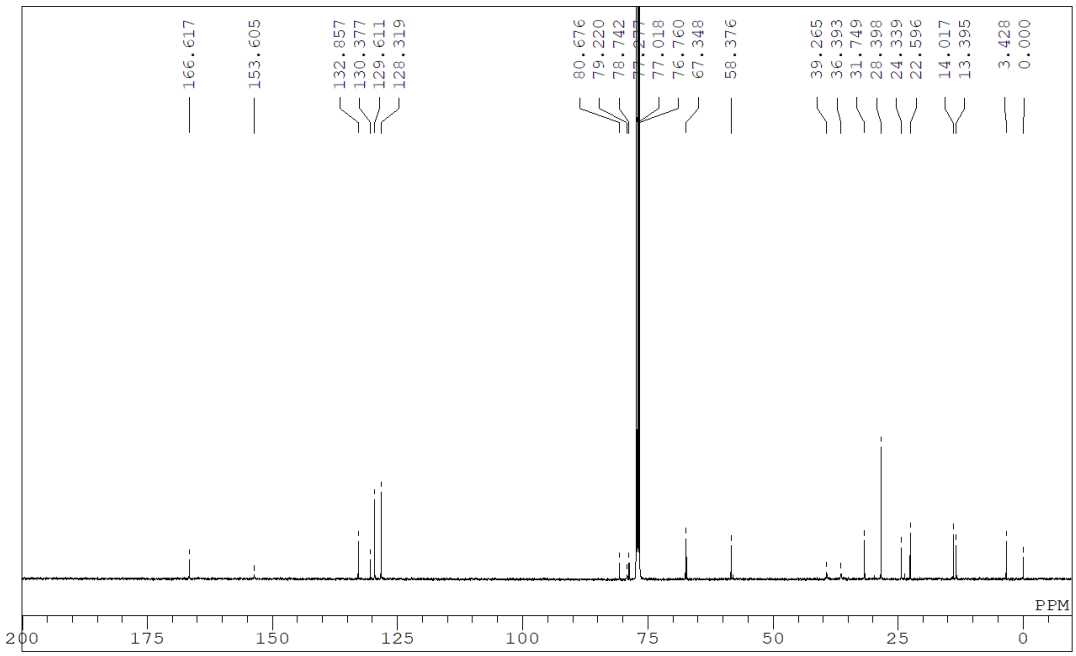
(2*S*,3*R*)-3-((*tert*-Butoxycarbonyl)amino)-2-methyl-3-(prop-1-yn-1-yl)octyl benzoate



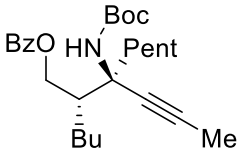
^{1}H-NMR (500 MHz, $CDCl_3$)



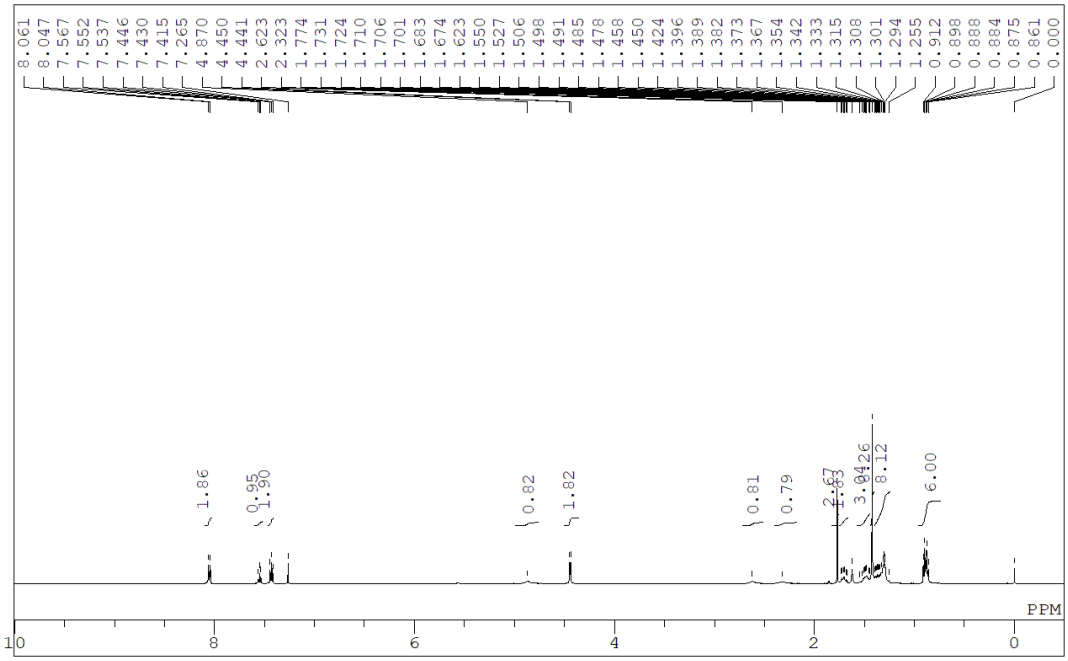
^{13}C-NMR (125 MHz, $CDCl_3$)



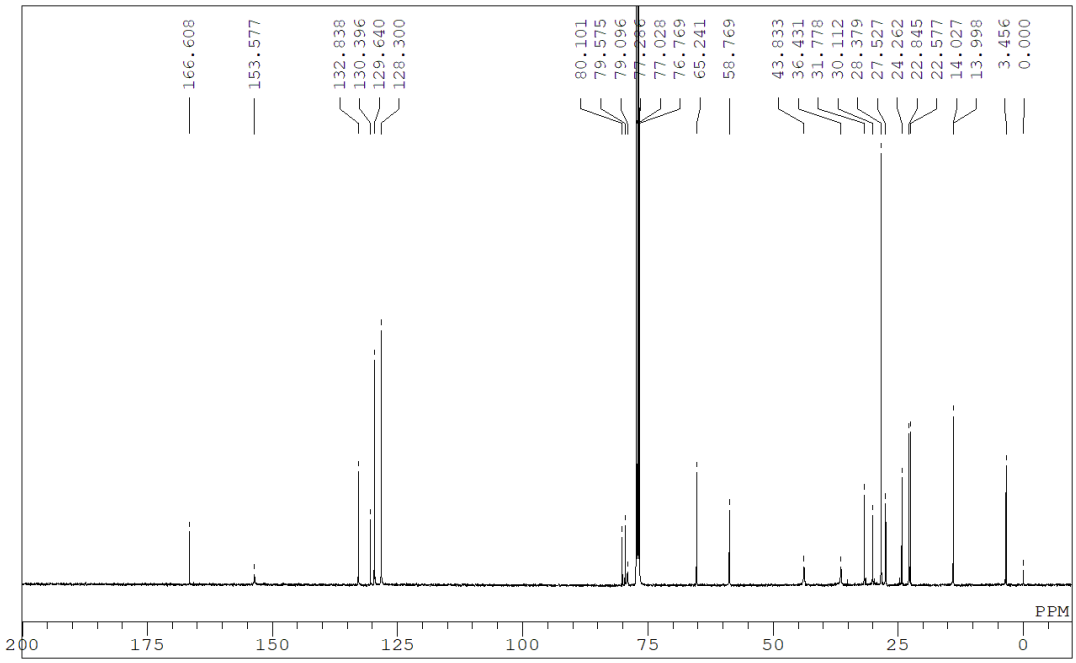
(2*S*,3*R*)-3-((*tert*-Butoxycarbonyl)amino)-2-butyl-3-(prop-1-yn-1-yl)octyl benzoate



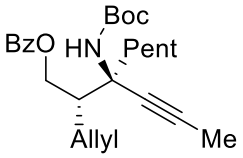
^{1}H-NMR (500 MHz, $CDCl_3$)



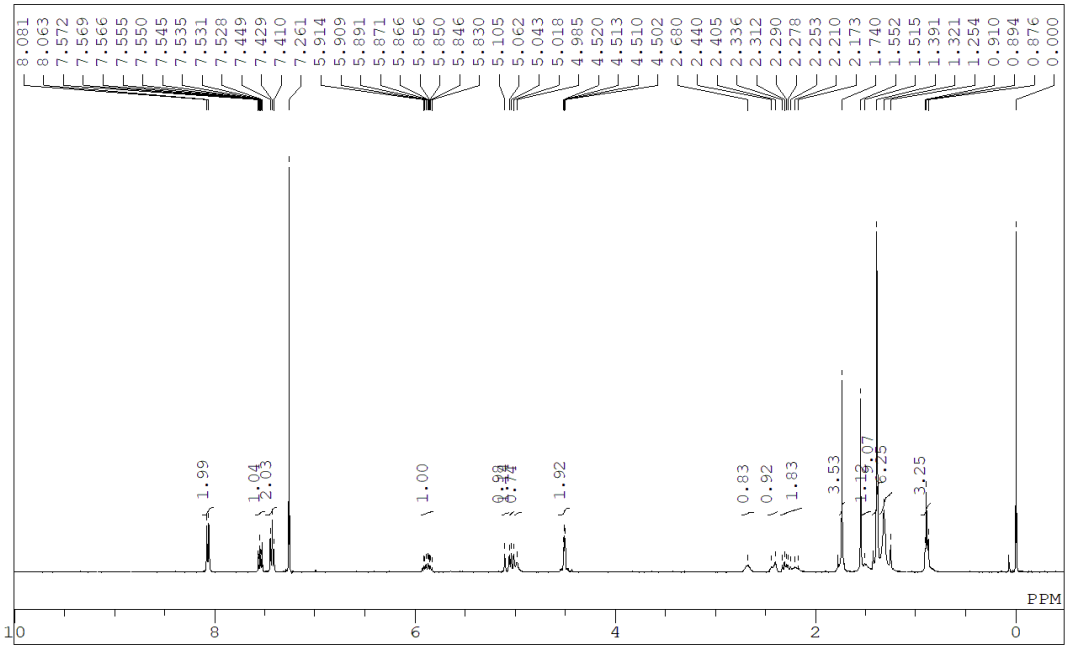
^{13}C-NMR (125 MHz, $CDCl_3$)



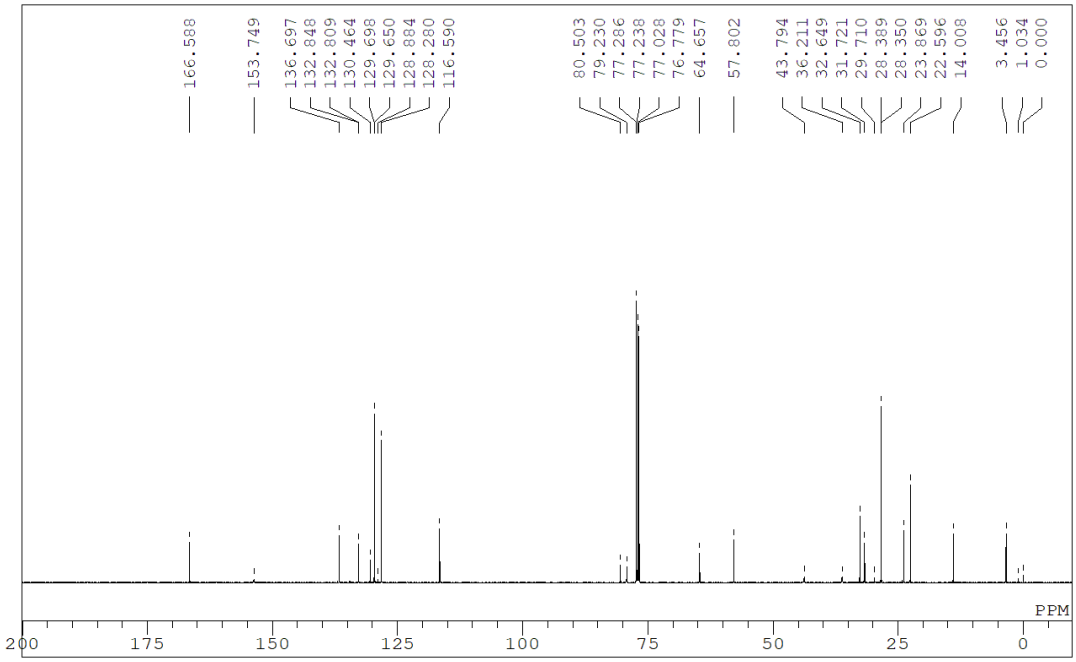
(2*R*,3*R*)-2-Allyl-3-((*tert*-butoxycarbonyl)amino)-3-(prop-1-yn-1-yl)octyl benzoate



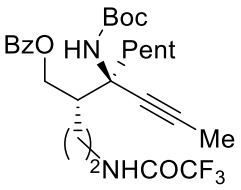
^{1}H-NMR (500 MHz, $CDCl_3$)



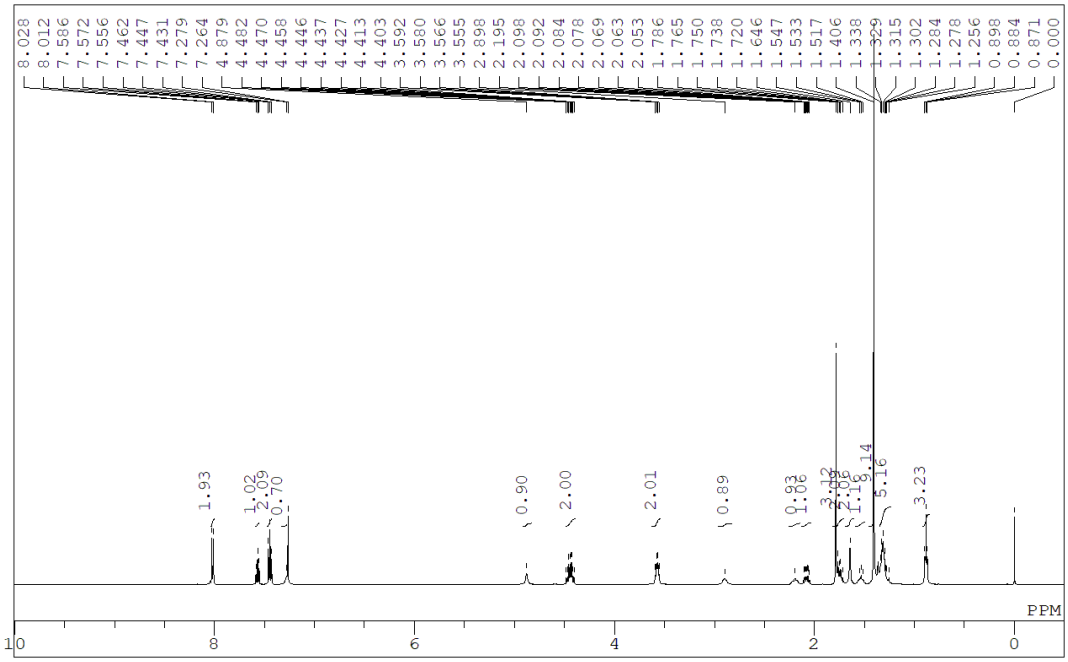
^{13}C-NMR (125 MHz, $CDCl_3$)



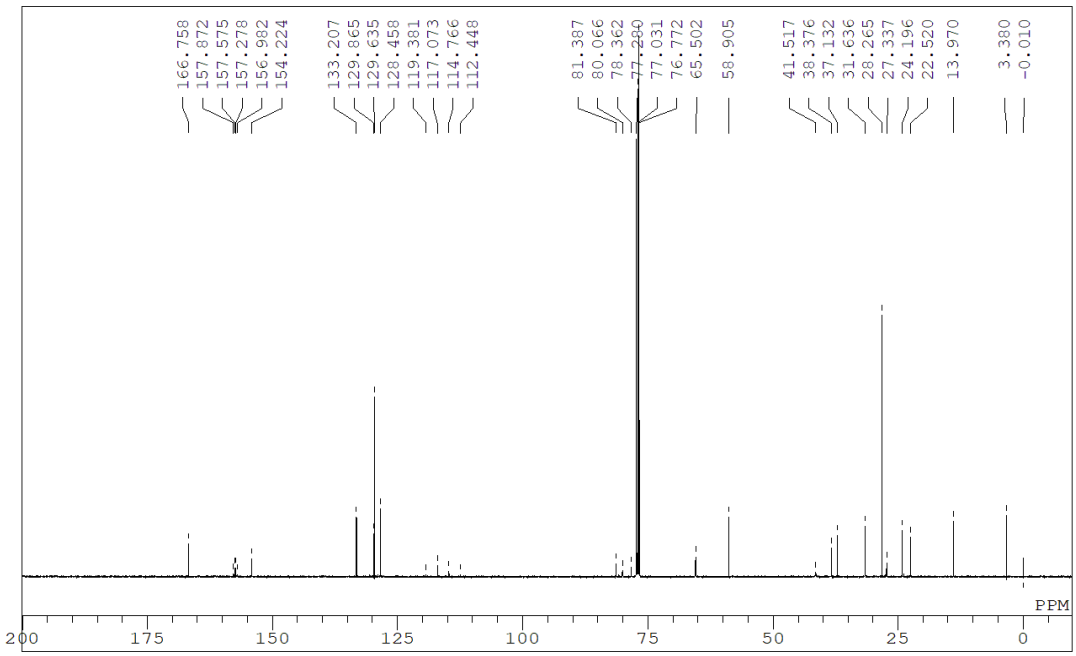
(2*S*,3*R*)-3-((*tert*-Butoxycarbonyl)amino)-3-(prop-1-yn-1-yl)-2-(2-(2,2,2-trifluoroacetamido)-ethyl)octyl benzoate



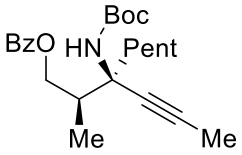
^{1}H-NMR (500 MHz, $CDCl_3$)



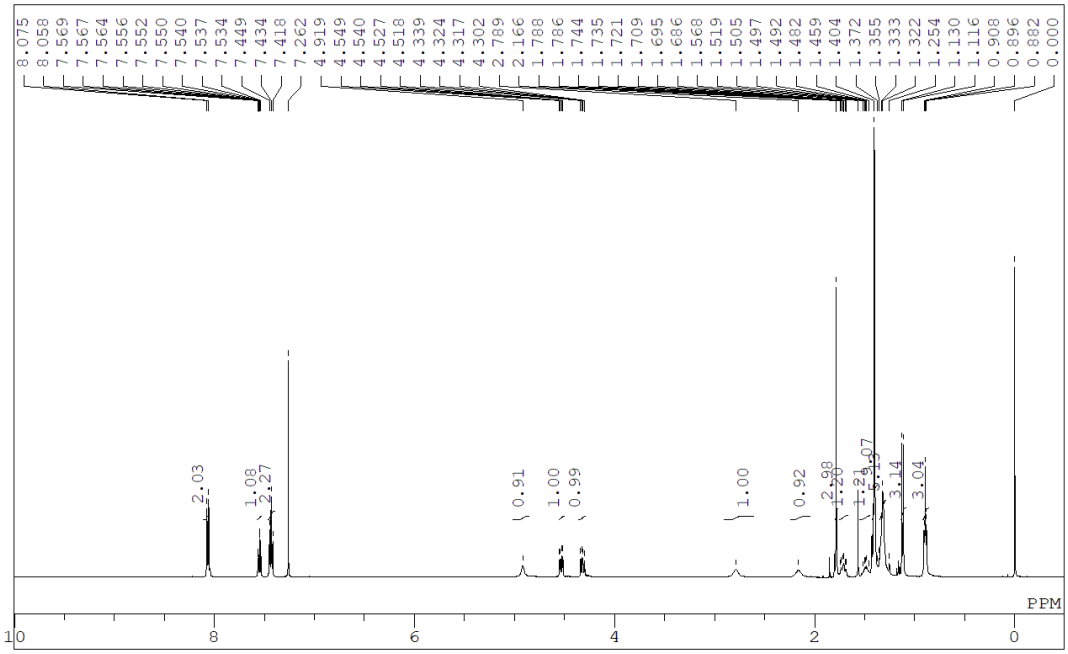
^{13}C-NMR (125 MHz, $CDCl_3$)



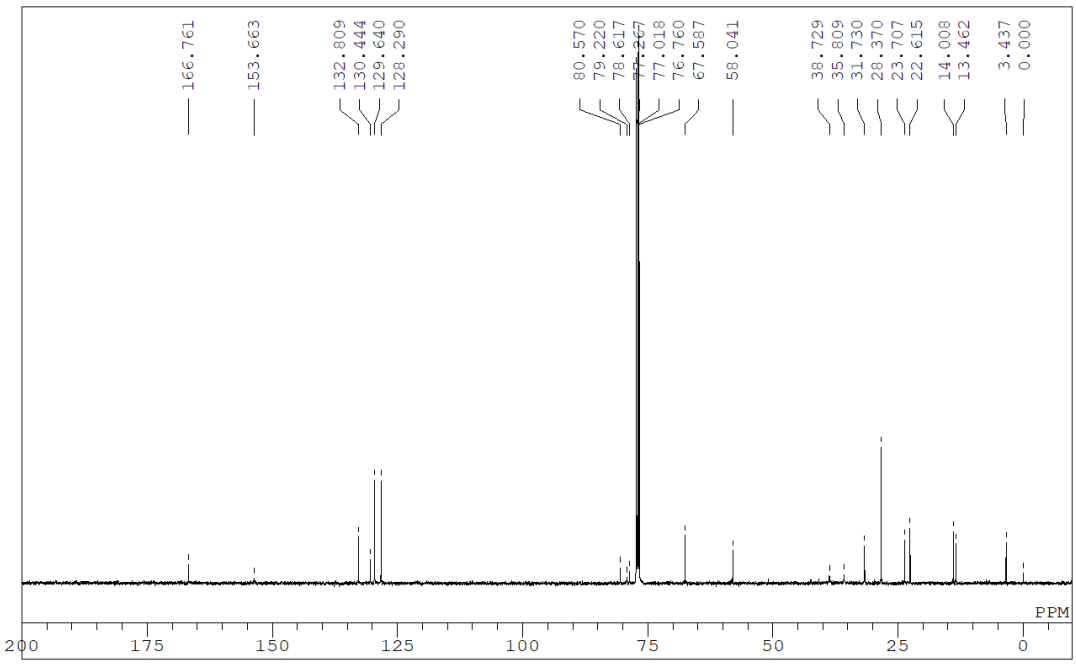
(2*R*,3*R*)-3-((*tert*-Butoxycarbonyl)amino)-2-methyl-3-(prop-1-yn-1-yl)octyl benzoate



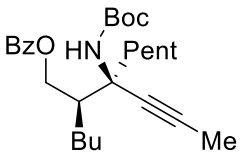
^{1}H-NMR (500 MHz, $CDCl_3$)



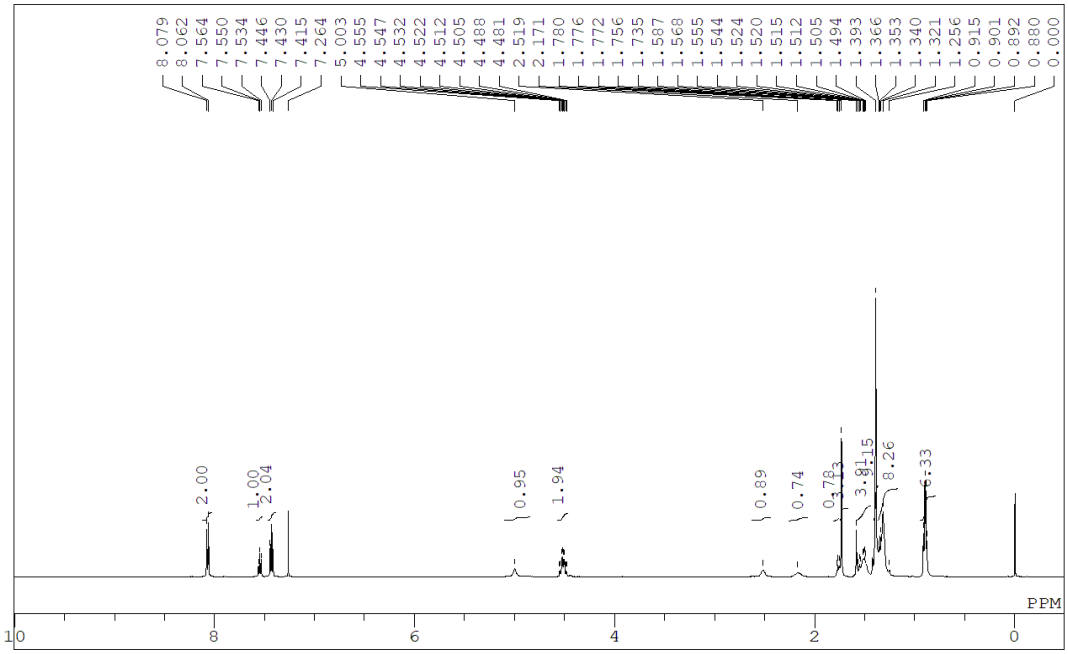
^{13}C-NMR (125 MHz, $CDCl_3$)



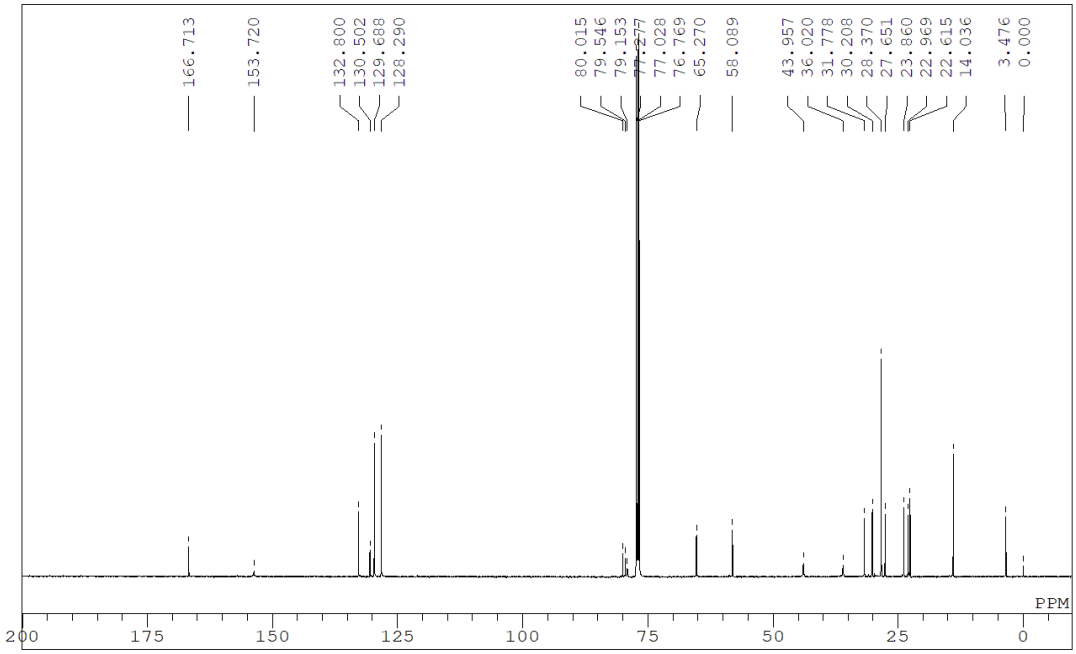
(2*R*,3*R*)-3-((*tert*-Butoxycarbonyl)amino)-2-butyl-3-(prop-1-yn-1-yl)octyl benzoate



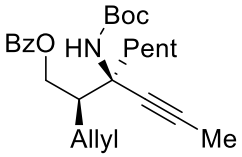
^{1}H-NMR (500 MHz, $CDCl_3$)



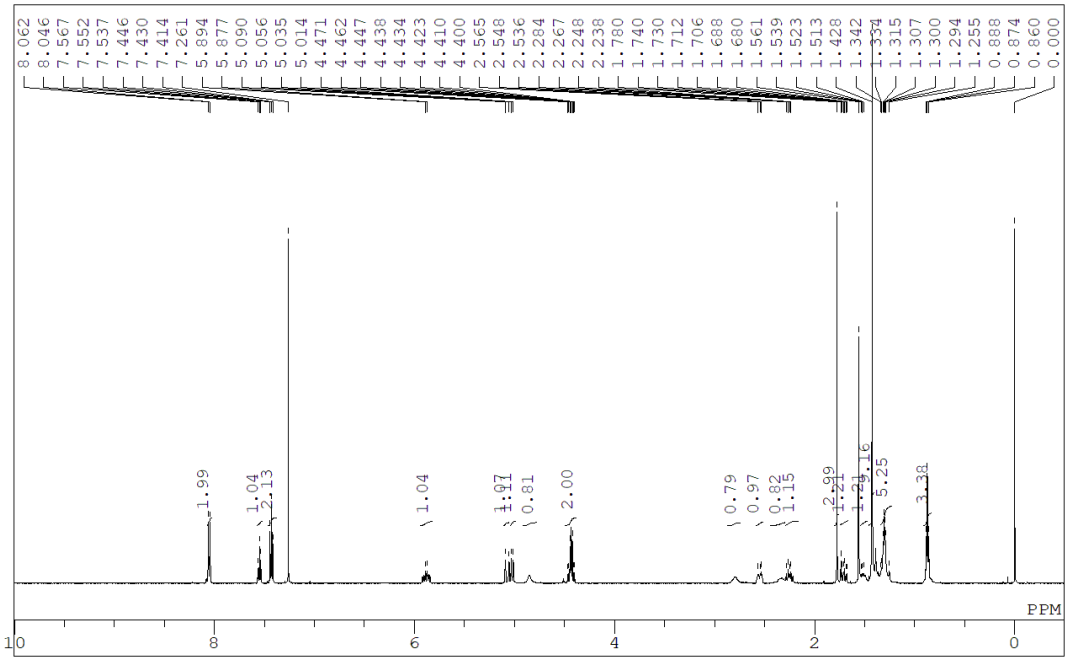
^{13}C-NMR (125 MHz, $CDCl_3$)



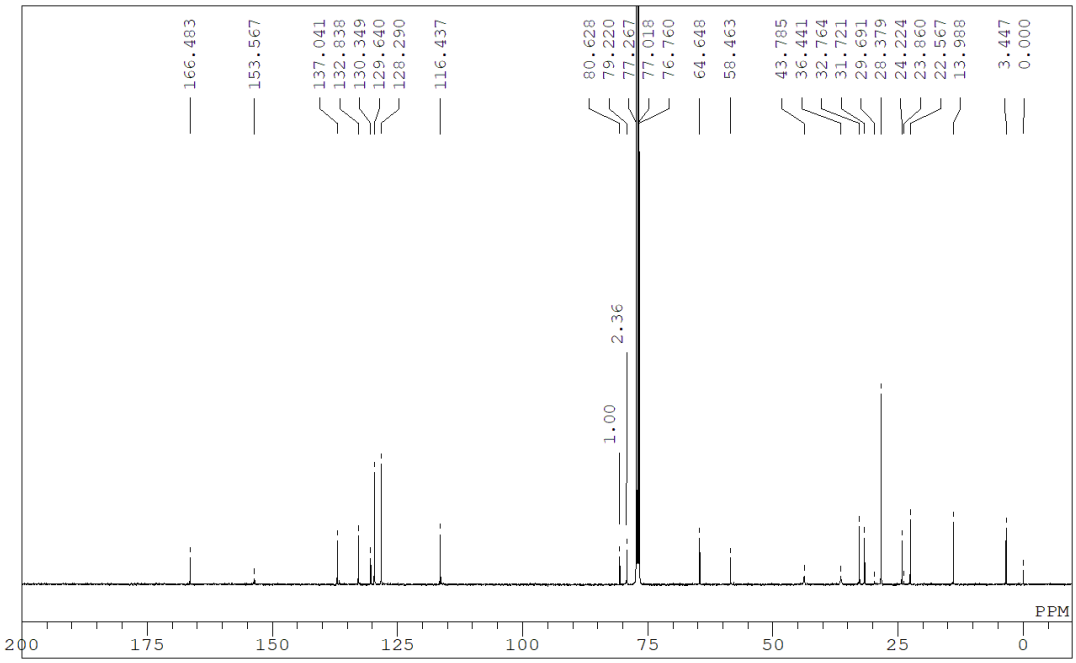
(2*R*,3*R*)-2-Allyl-3-((*tert*-butoxycarbonyl)amino)-3-(prop-1-yn-1-yl)octyl benzoate



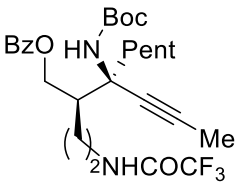
^{1}H-NMR (500 MHz, $CDCl_3$)



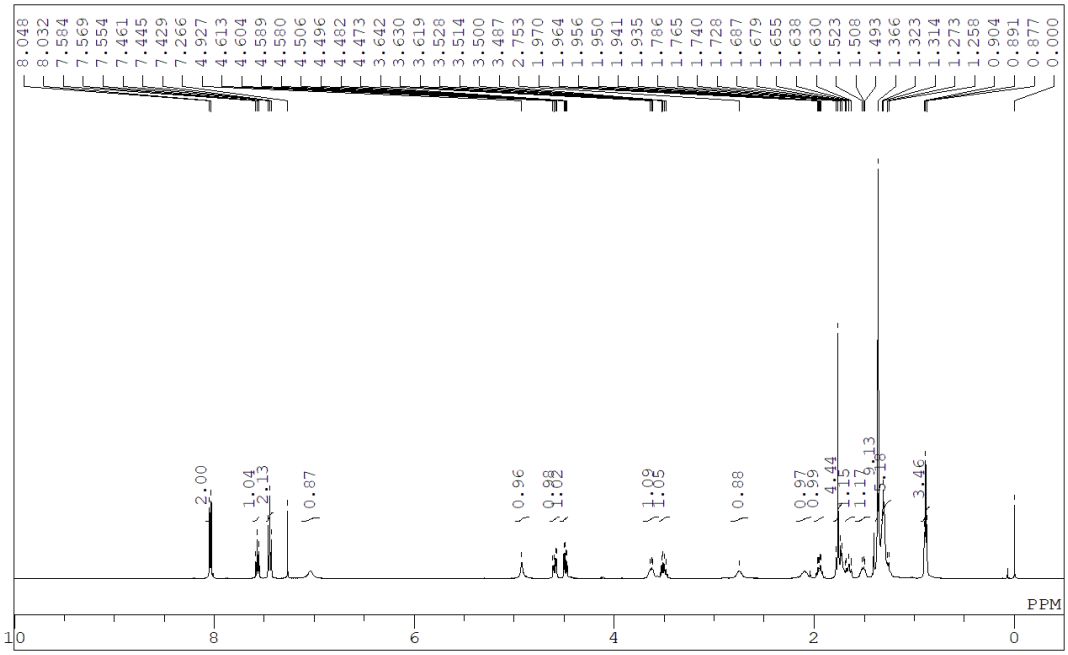
^{13}C-NMR (125 MHz, $CDCl_3$)



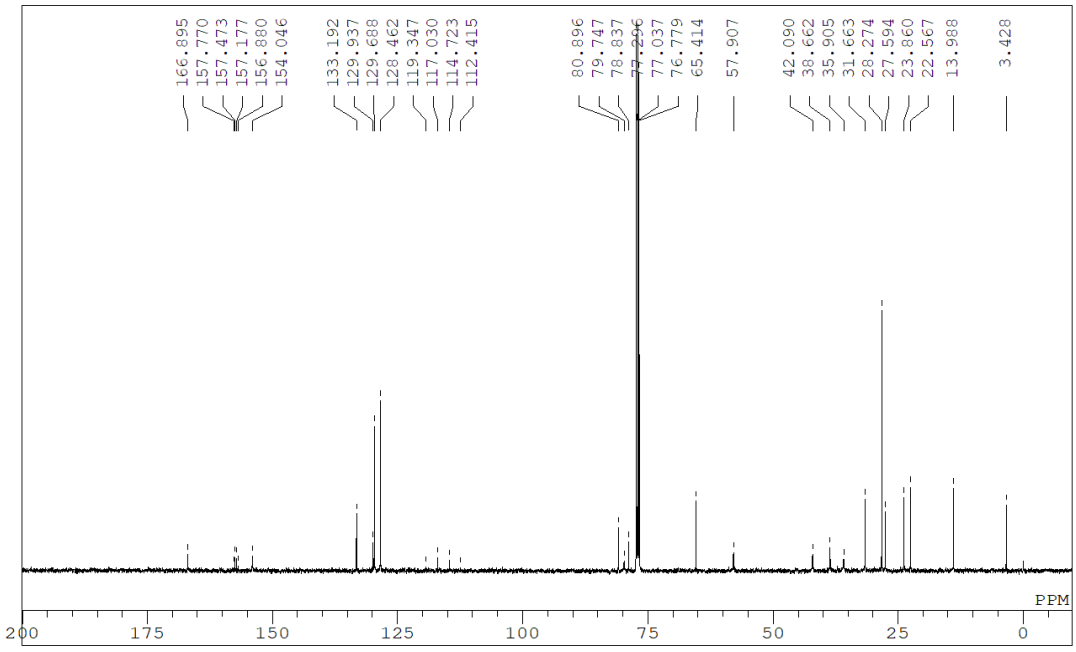
(2*R*,3*R*)-3-((*tert*-Butoxycarbonyl)amino)-3-(prop-1-yn-1-yl)-2-(2-(2,2,2-trifluoroacetamido)-ethyl)octyl benzoate



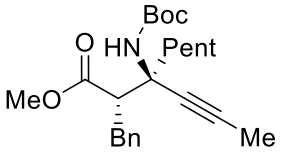
^{1}H-NMR (500 MHz, $CDCl_3$)



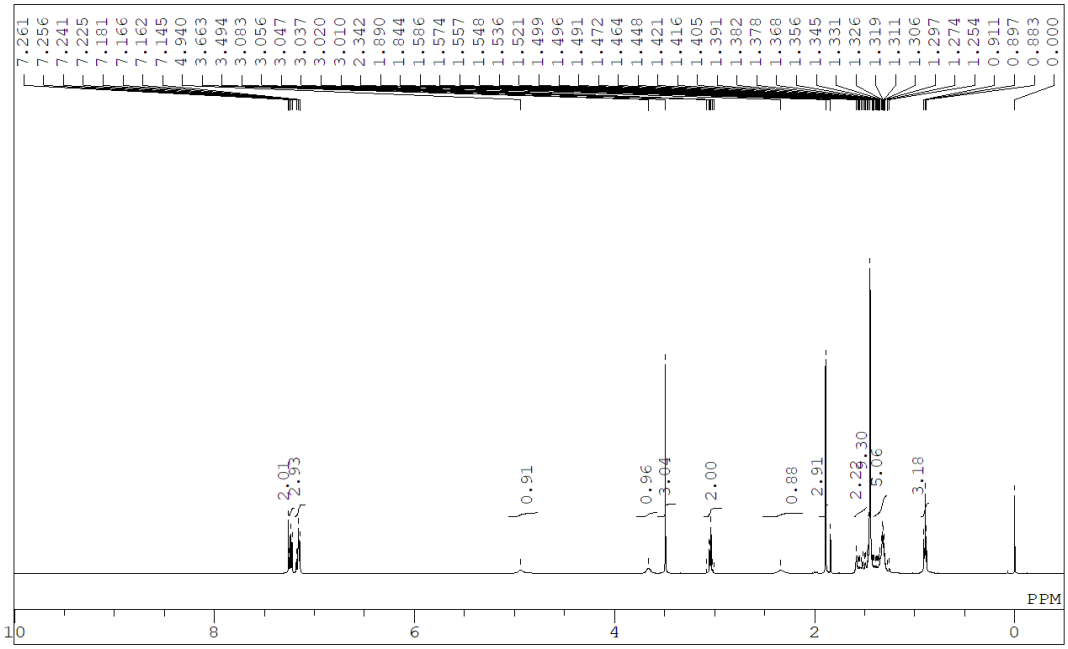
^{13}C-NMR (125 MHz, $CDCl_3$)



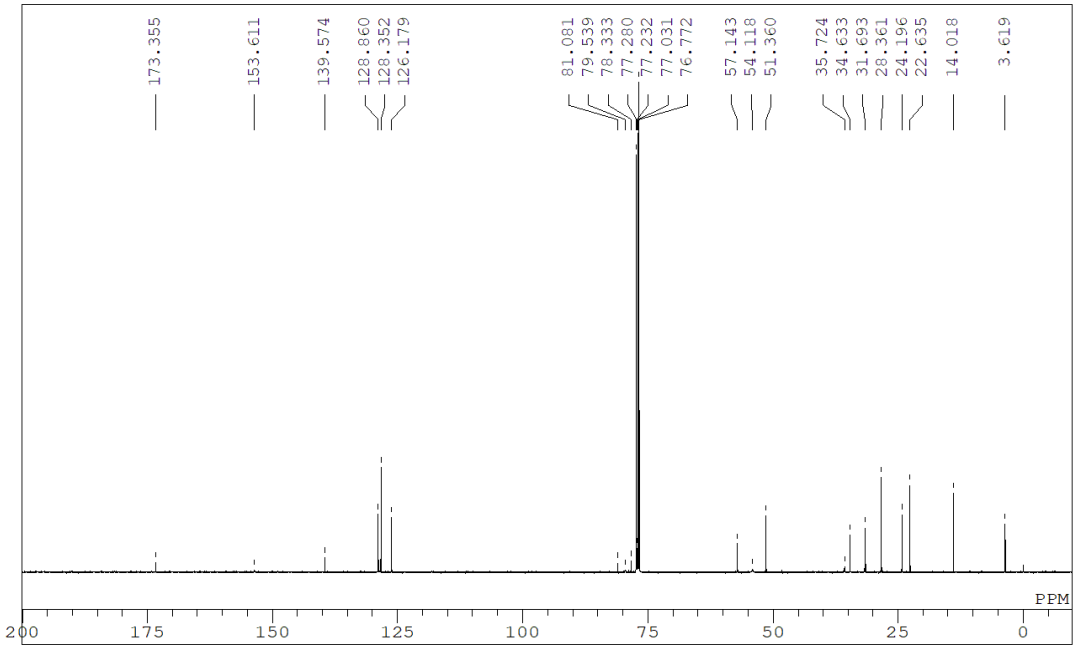
Methyl (2*S*,3*R*)-2-benzyl-3-((tert-butoxycarbonyl)amino)-3-(prop-1-yn-1-yl)octanoate (8)



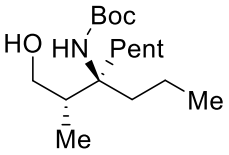
^{1}H-NMR (500 MHz, $CDCl_3$)



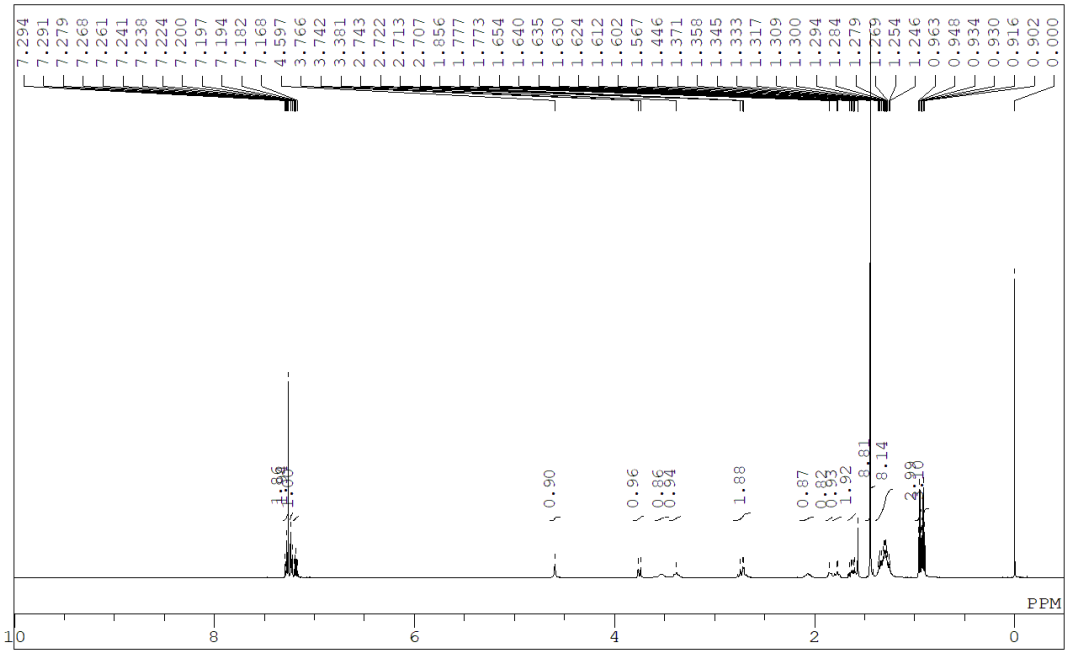
^{13}C-NMR (125 MHz, $CDCl_3$)



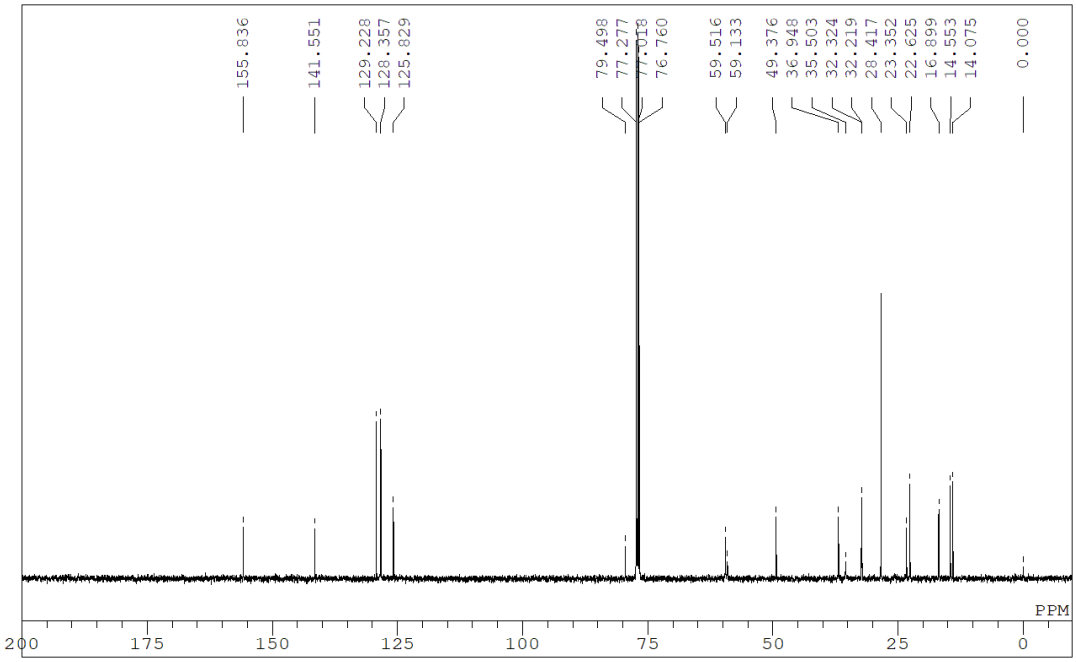
***tert*-Butyl ((*R*)-4-((*S*)-1-hydroxy-3-phenylpropan-2-yl)nonan-4-yl)carbamate (9)**



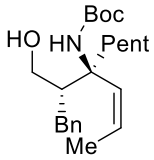
^{1}H-NMR (500 MHz, $CDCl_3$)



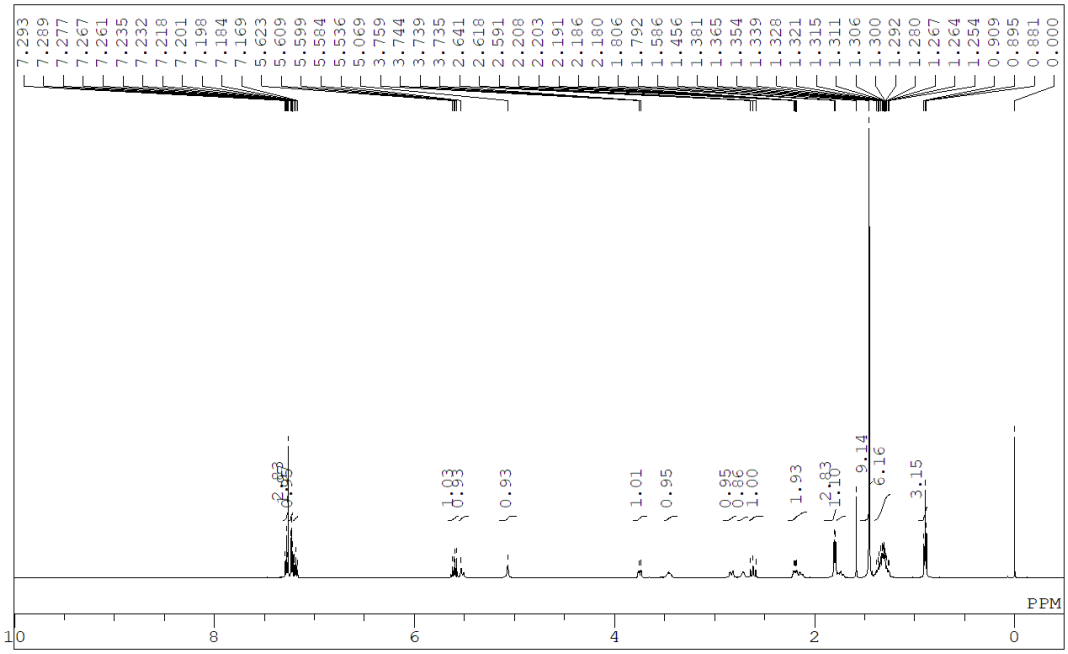
^{13}C-NMR (125 MHz, $CDCl_3$)



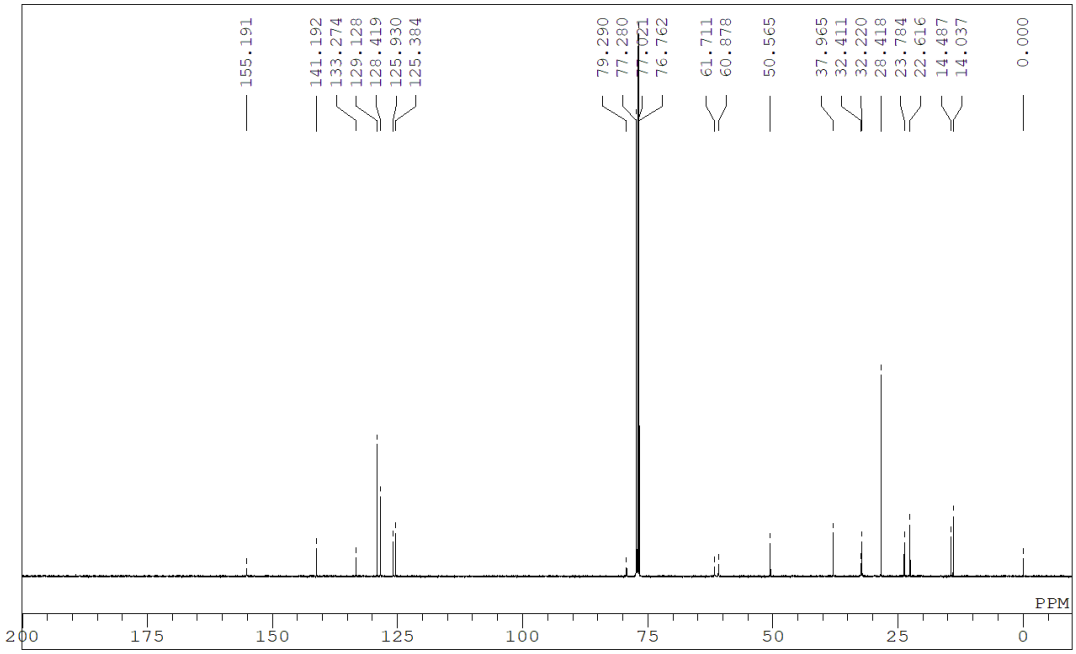
***tert*-Butyl ((*S*,*Z*)-4-((*S*)-1-hydroxy-3-phenylpropan-2-yl)non-2-en-4-yl)carbamate (10)**



^{1}H-NMR (500 MHz, $CDCl_3$)

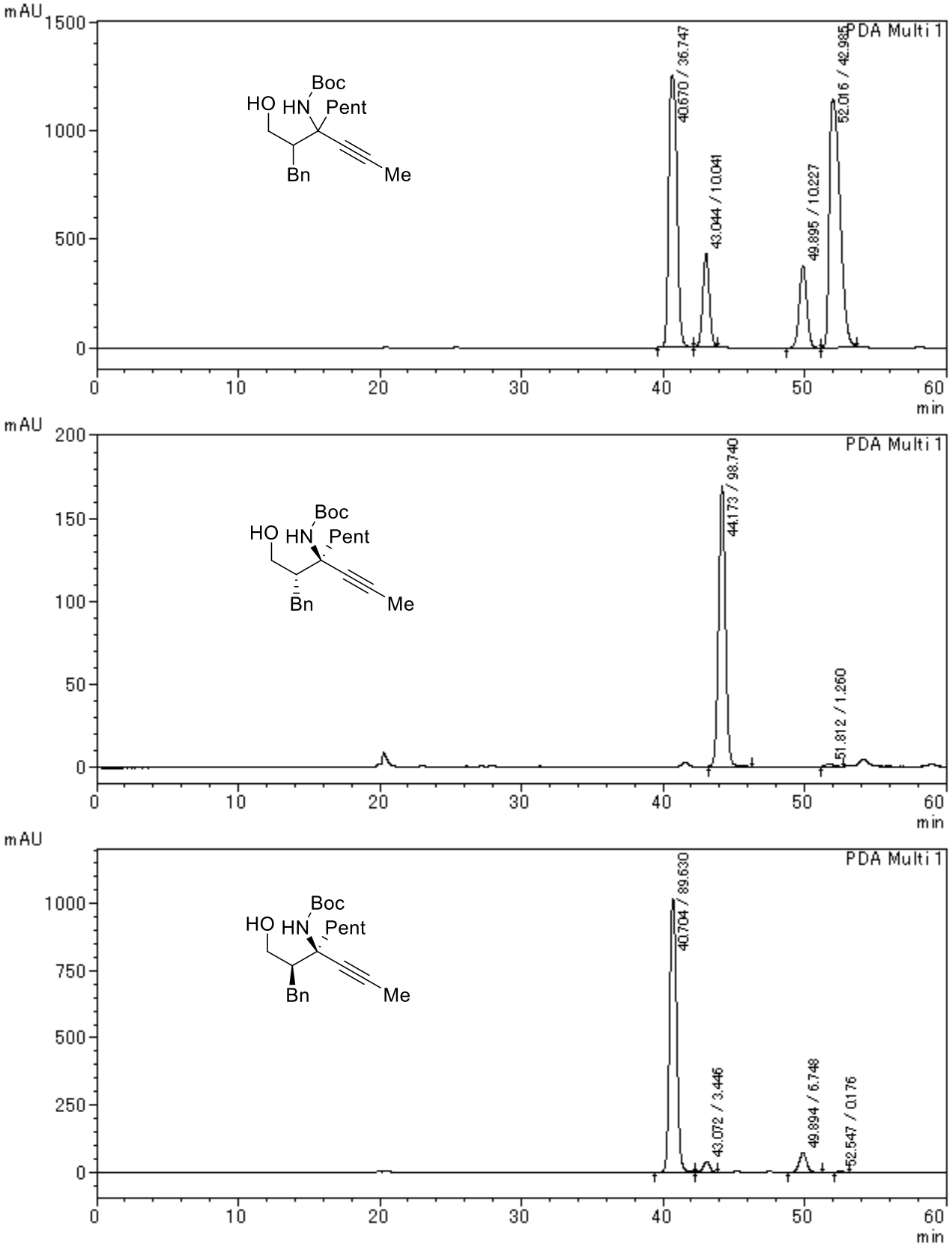


^{13}C-NMR (125 MHz, $CDCl_3$)

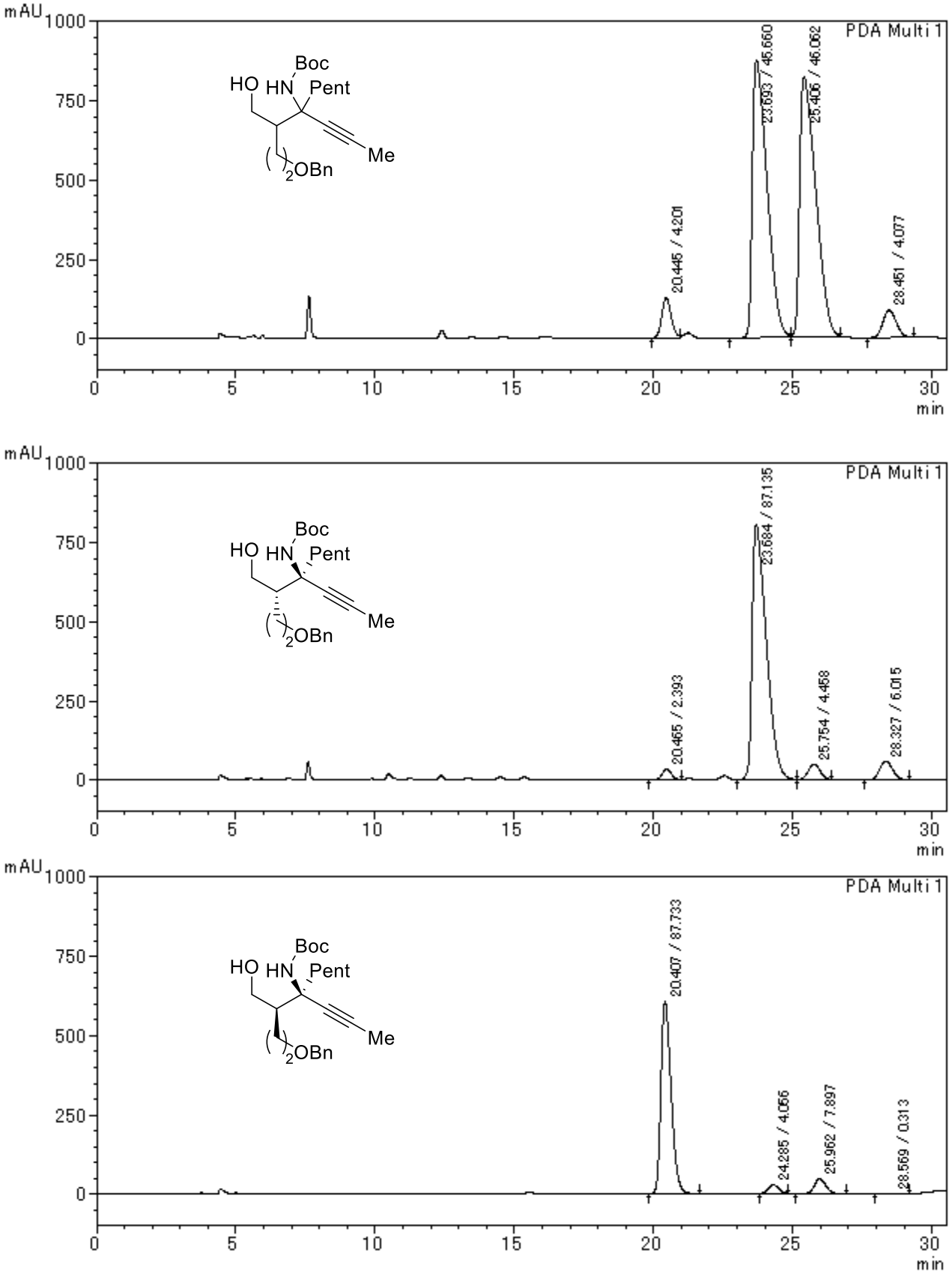


12. HPLC Trace

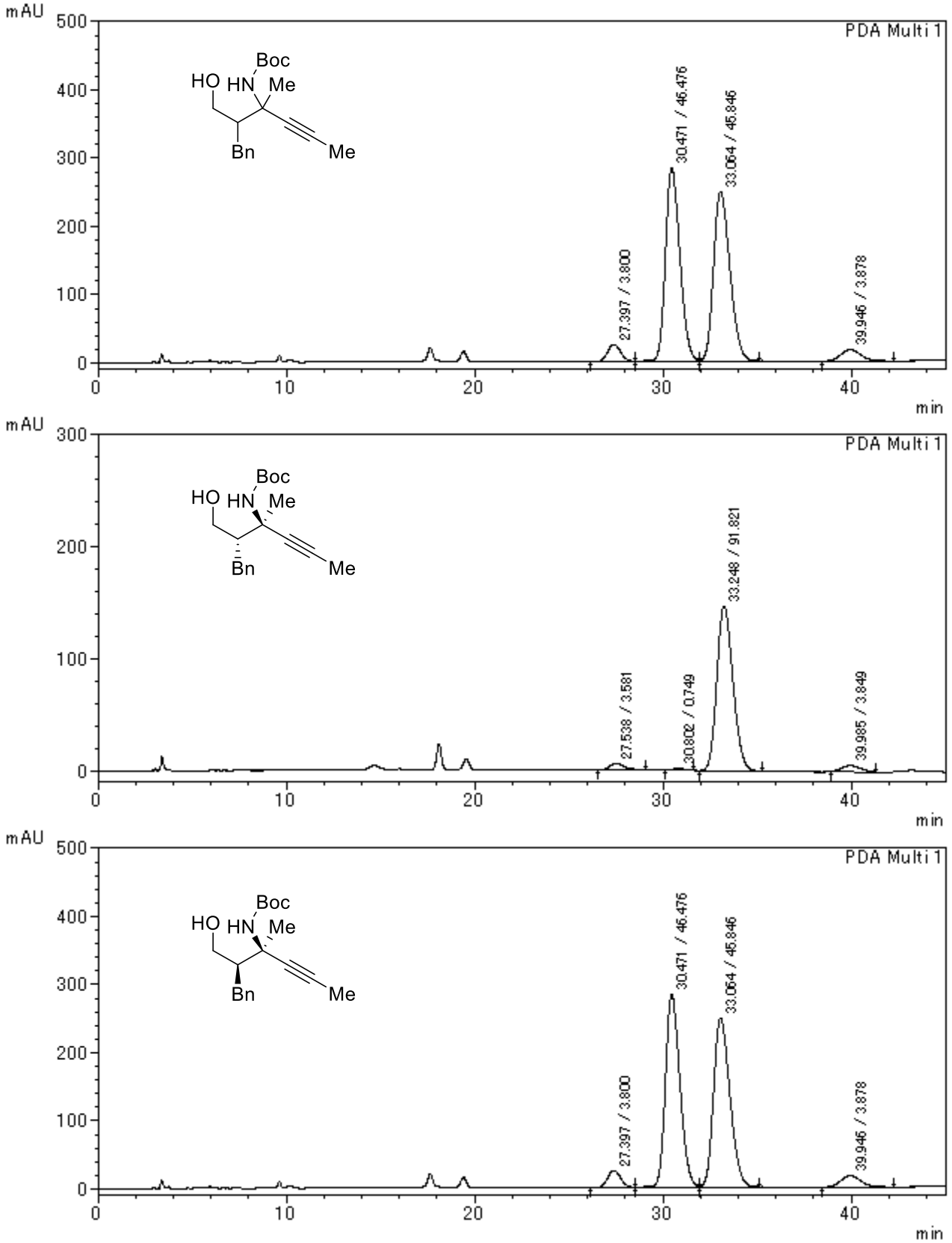
***tert*-Butyl (4-(1-hydroxy-3-phenylpropan-2-yl)non-2-yn-4-yl)carbamate (2a)**



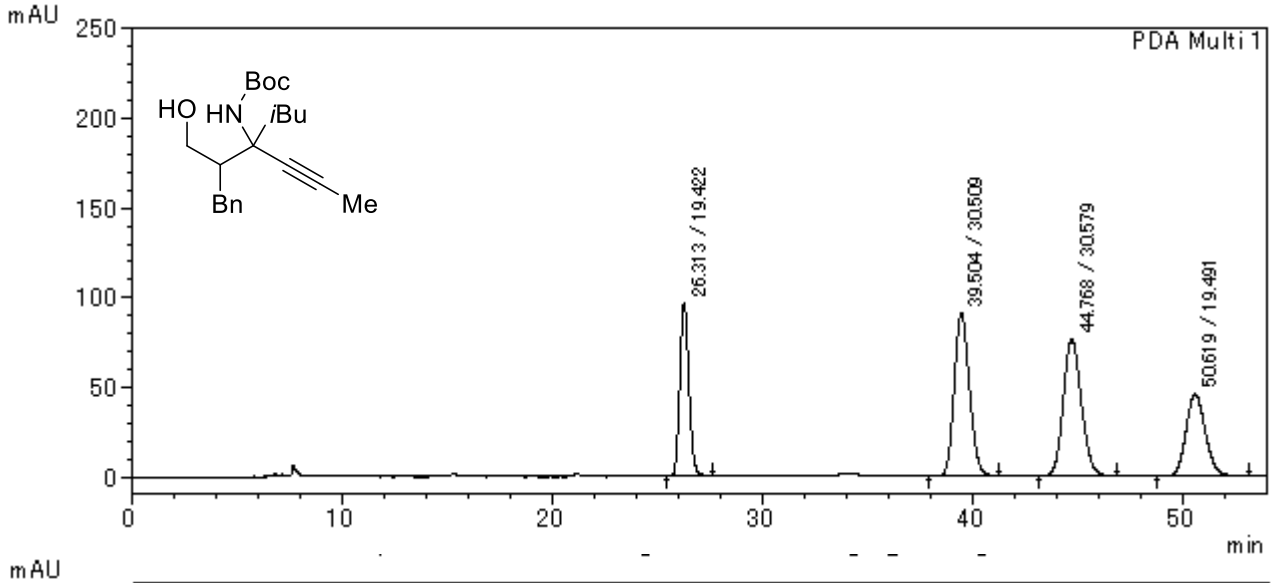
***tert*-Butyl (4-(4-(benzyloxy)-1-hydroxybutan-2-yl)non-2-yn-4-yl)carbamate (2e)**

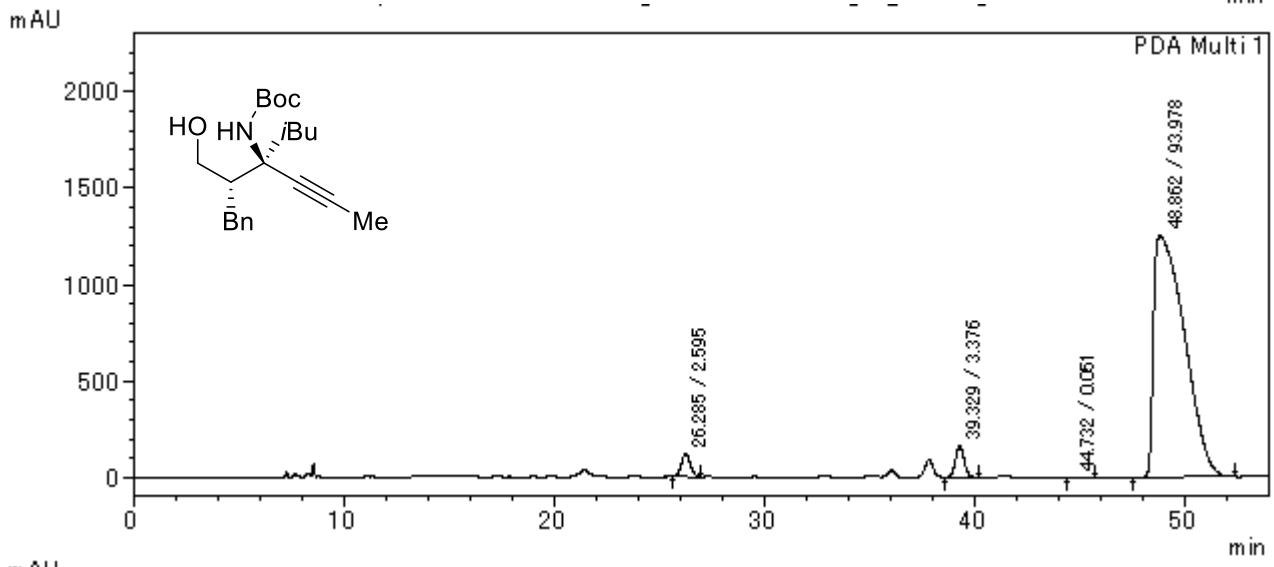


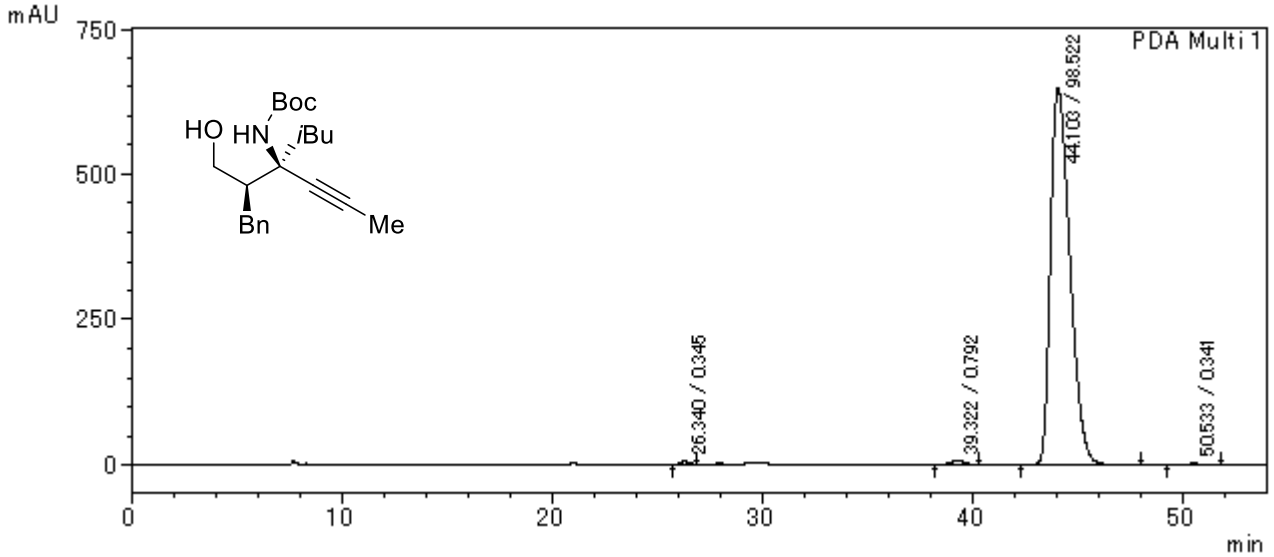
***tert*-Butyl (2-benzyl-1-hydroxy-3-methylhex-4-yn-3-yl)carbamate (2g)**



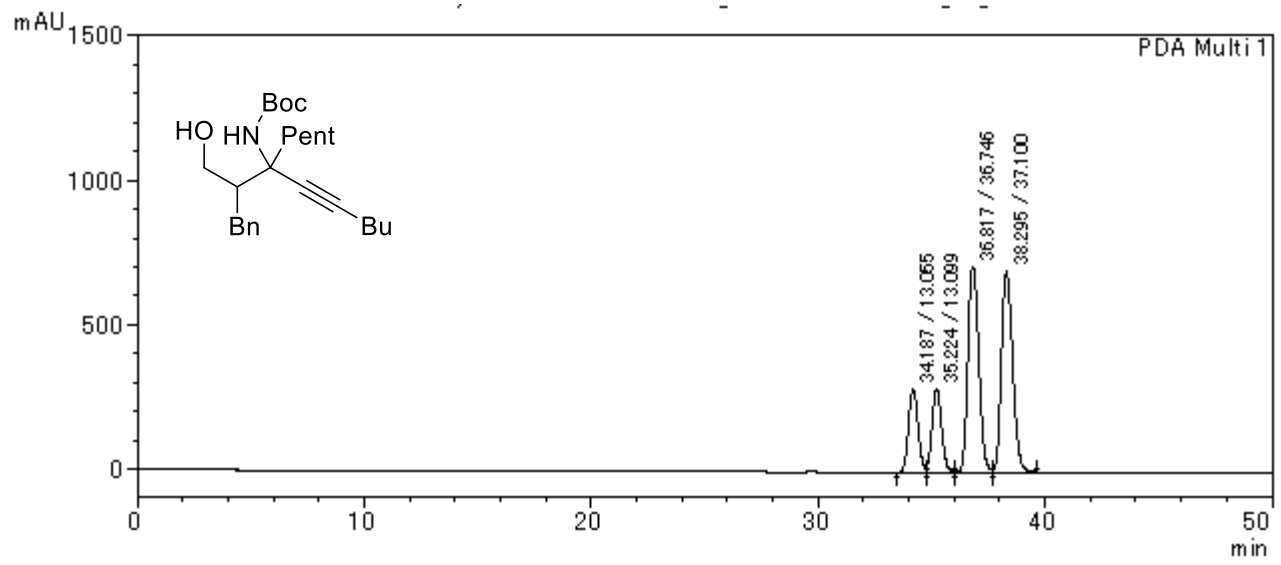
***tert*-Butyl (4-(1-hydroxy-3-phenylpropan-2-yl)-6-methylhept-2-yn-4-yl)carbamate (2h)**

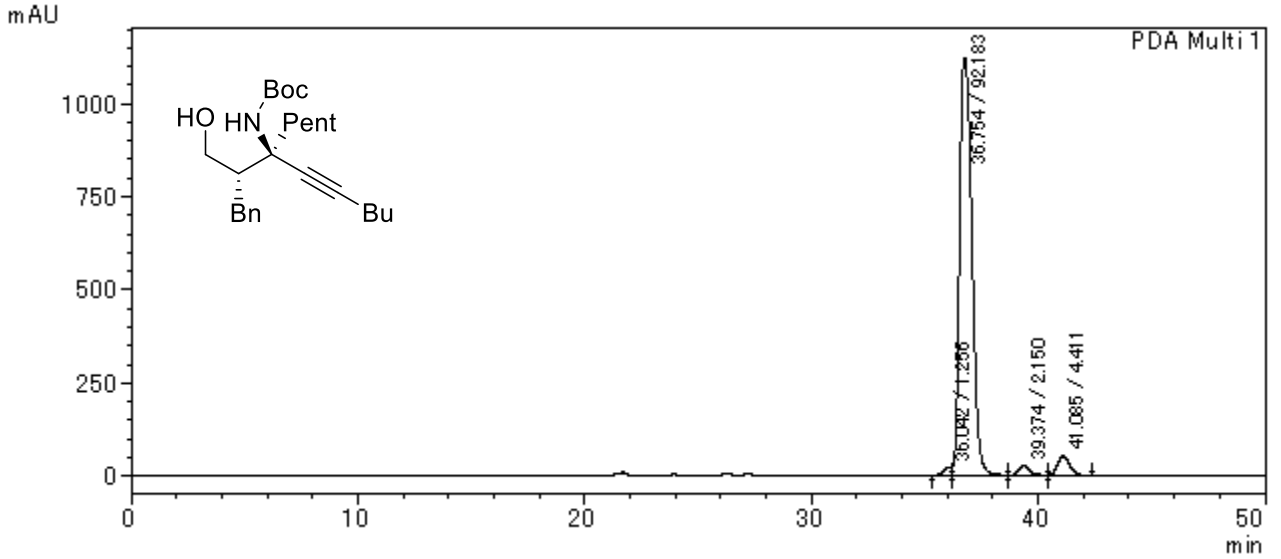


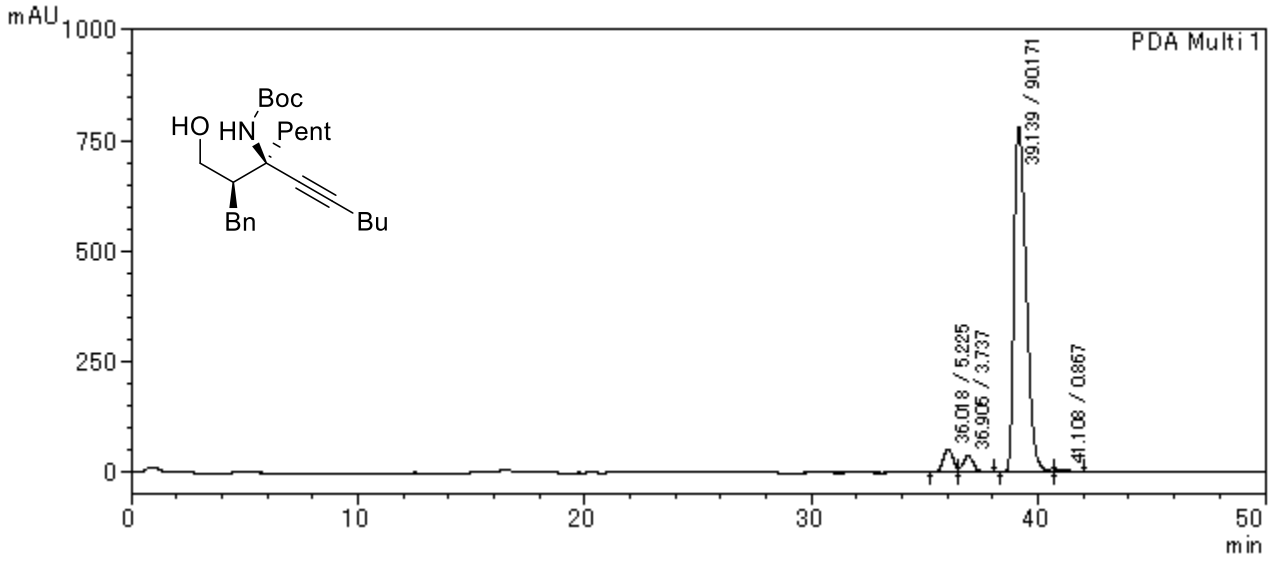




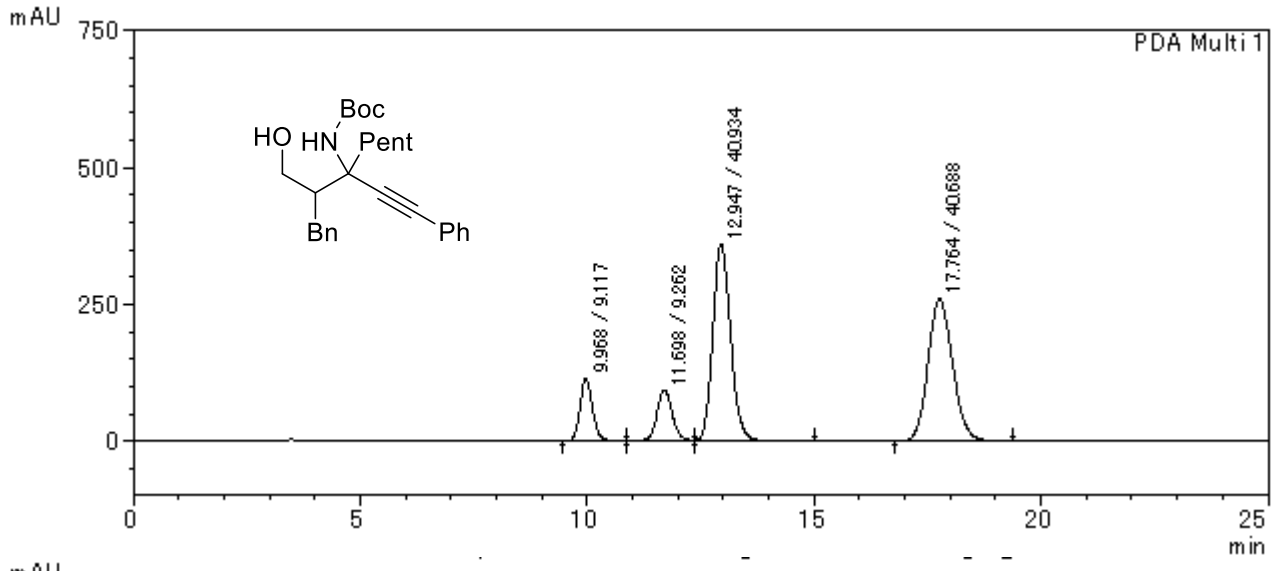
***tert*-Butyl (6-(1-hydroxy-3-phenylpropan-2-yl)dodec-7-yn-6-yl)carbamate (2i)**

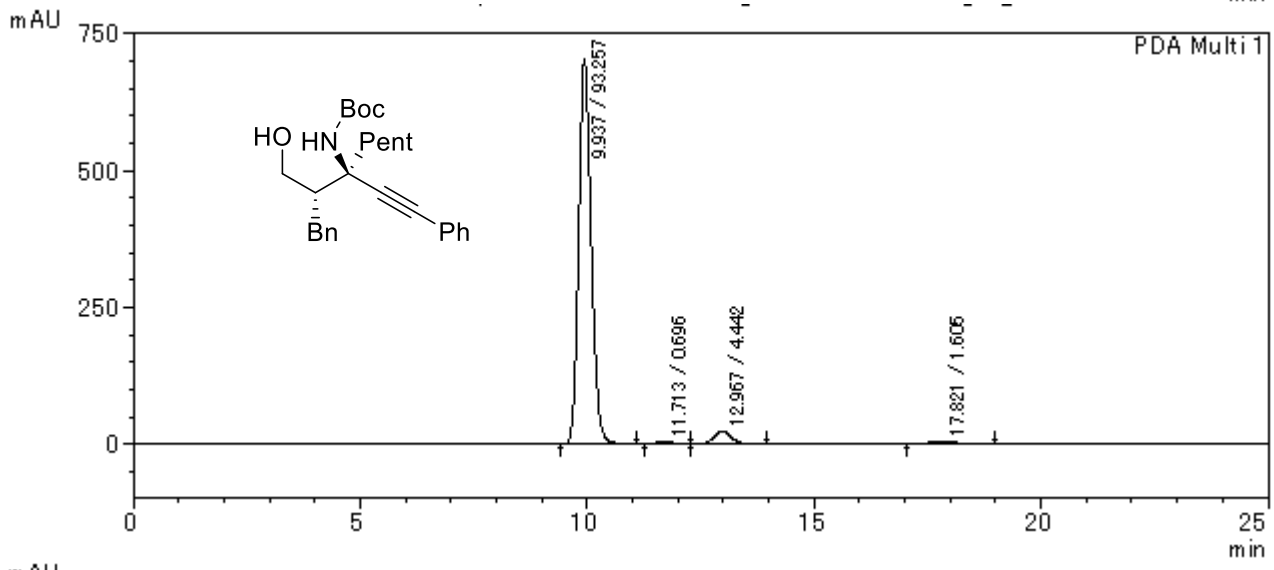


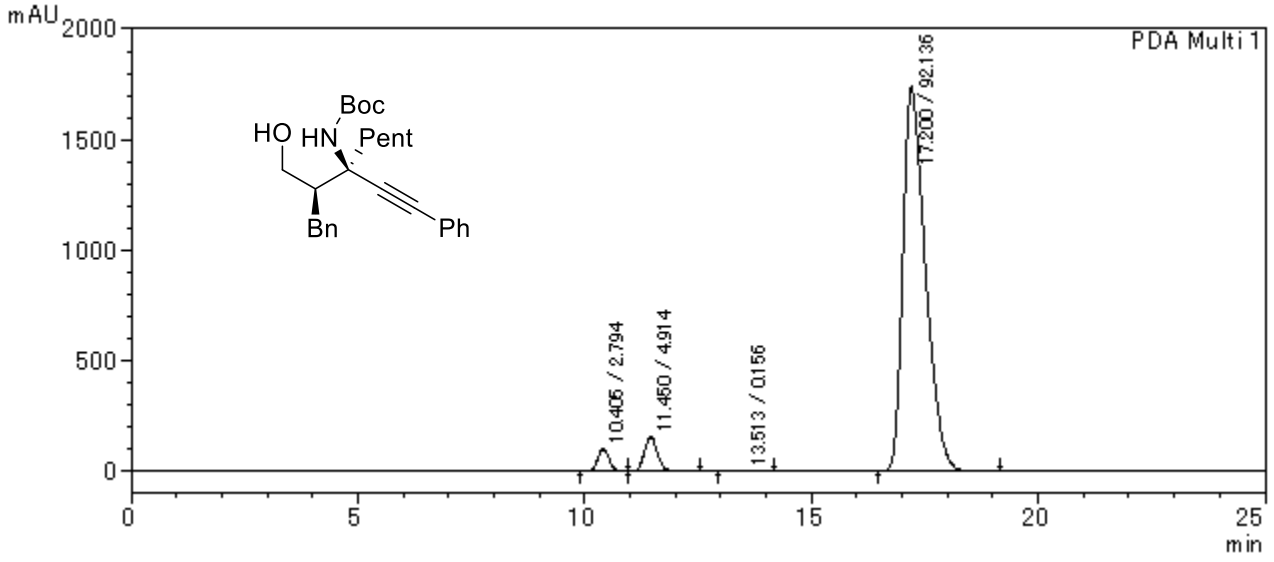




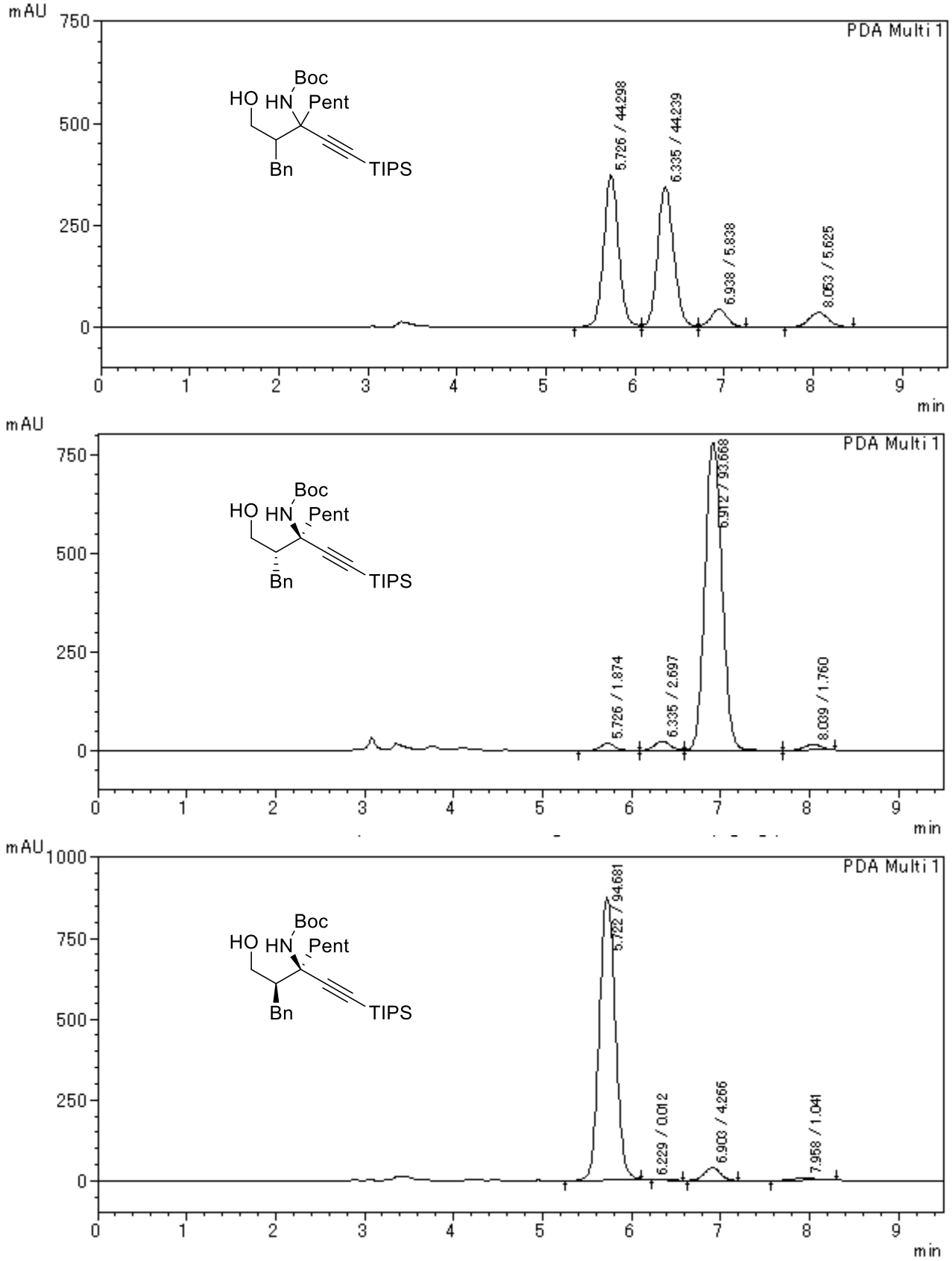
***tert*-Butyl (3-(1-hydroxy-3-phenylpropan-2-yl)-1-phenyloct-1-yn-3-yl)carbamate (2j)**



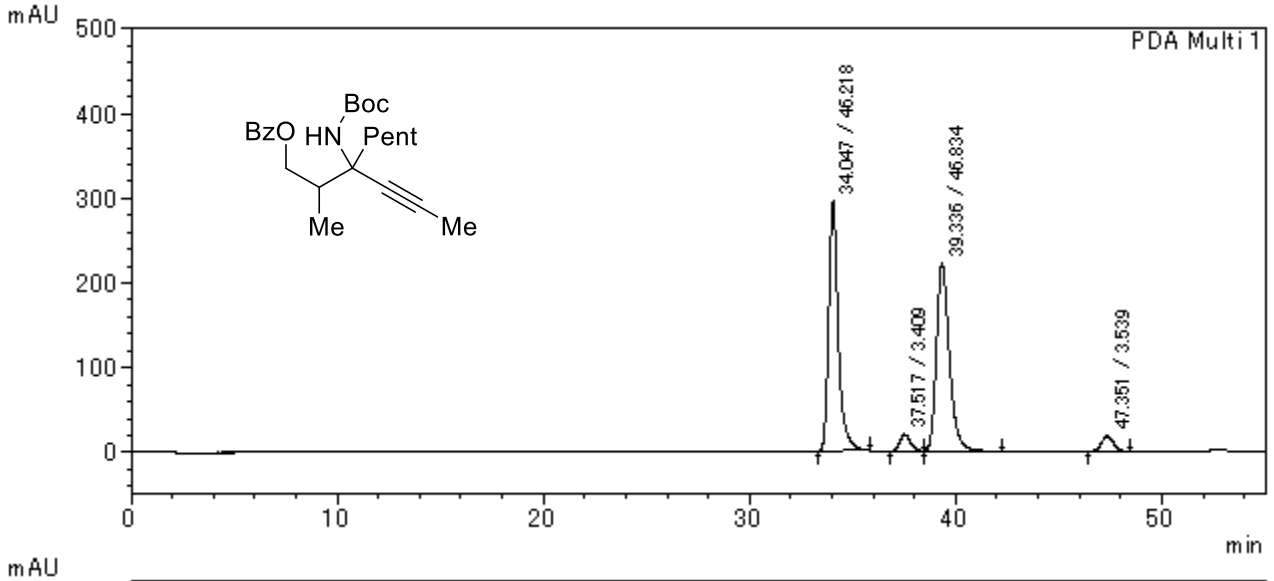


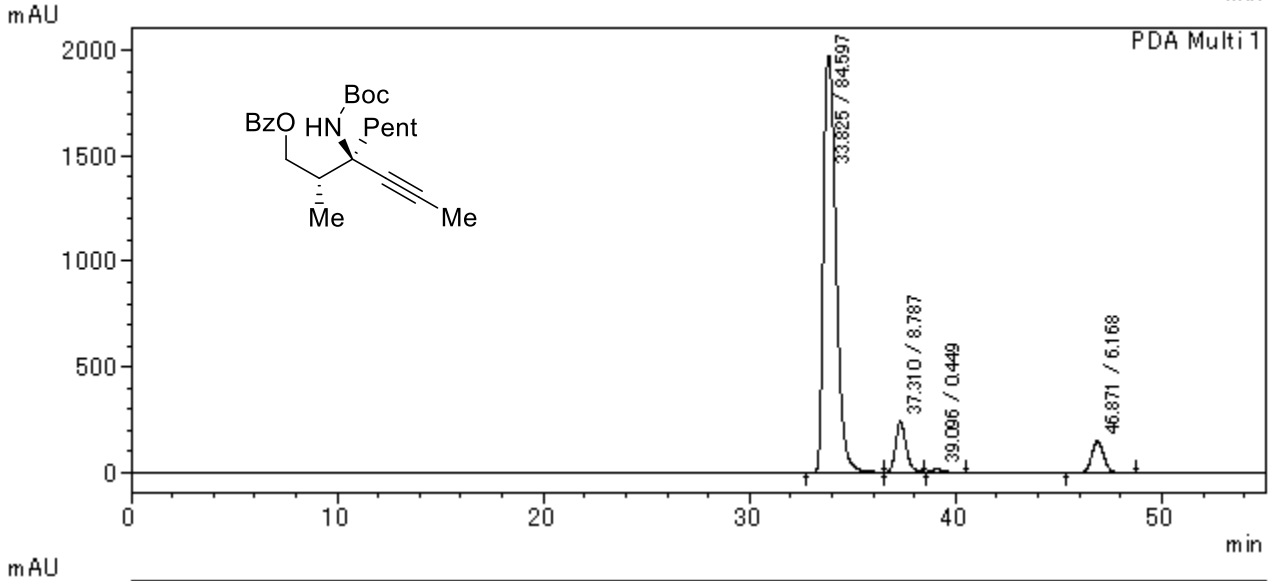


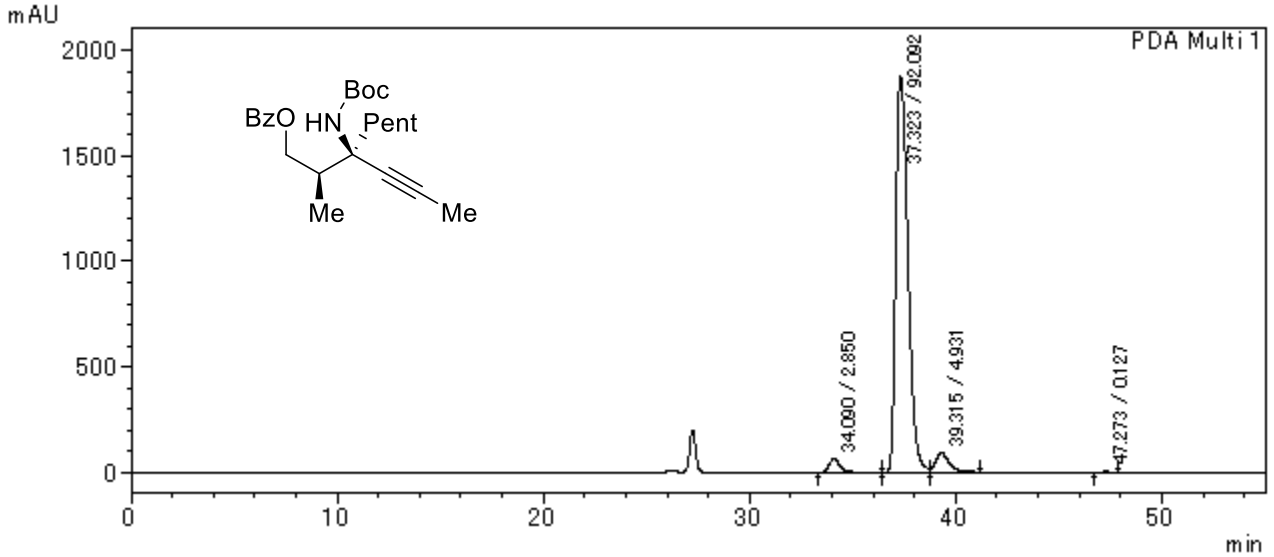
***tert*-Butyl (3-(1-hydroxy-3-phenylpropan-2-yl)-1-(triisopropylsilyl)oct-1-yn-3-yl)carbamate (2k)**



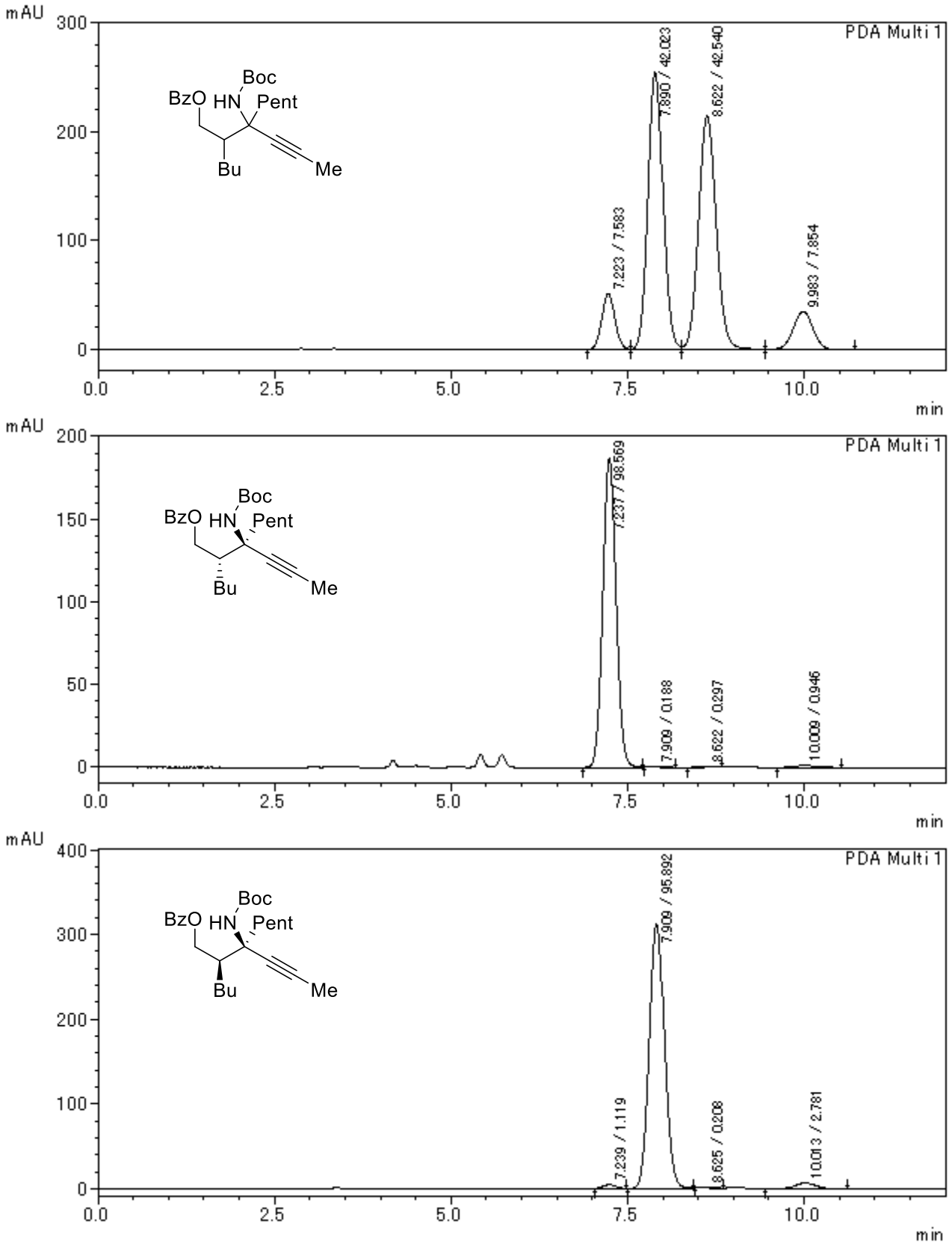
3-((*tert*-Butoxycarbonyl)amino)-2-methyl-3-(prop-1-yn-1-yl)octyl benzoate



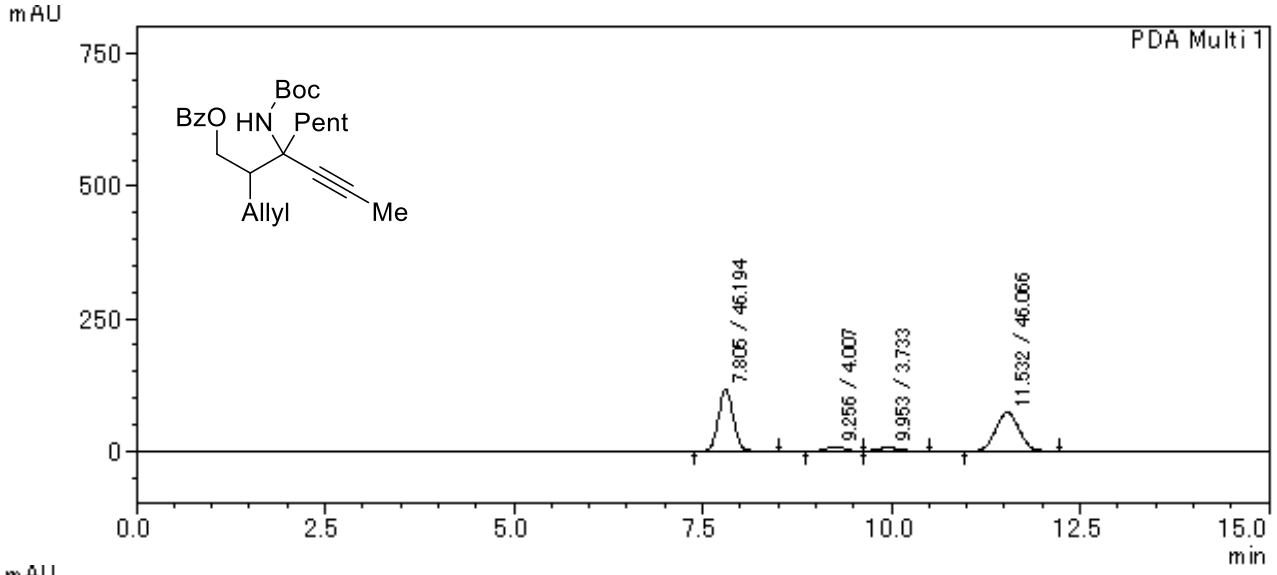


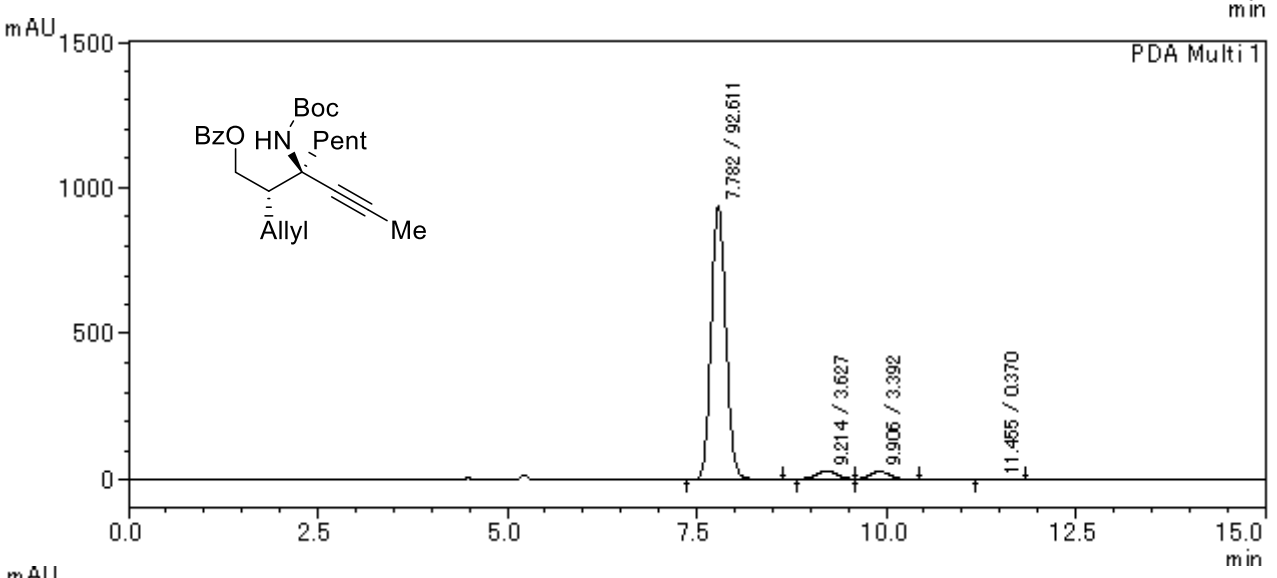


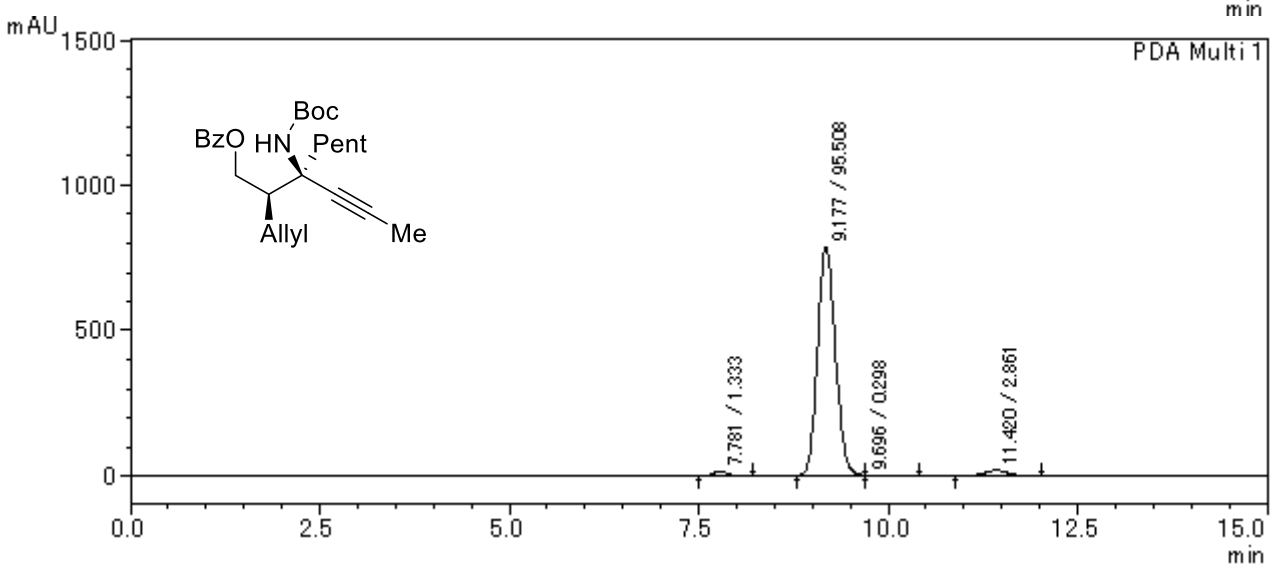
3-((*tert*-Butoxycarbonyl)amino)-2-butyl-3-(prop-1-yn-1-yl)octyl benzoate



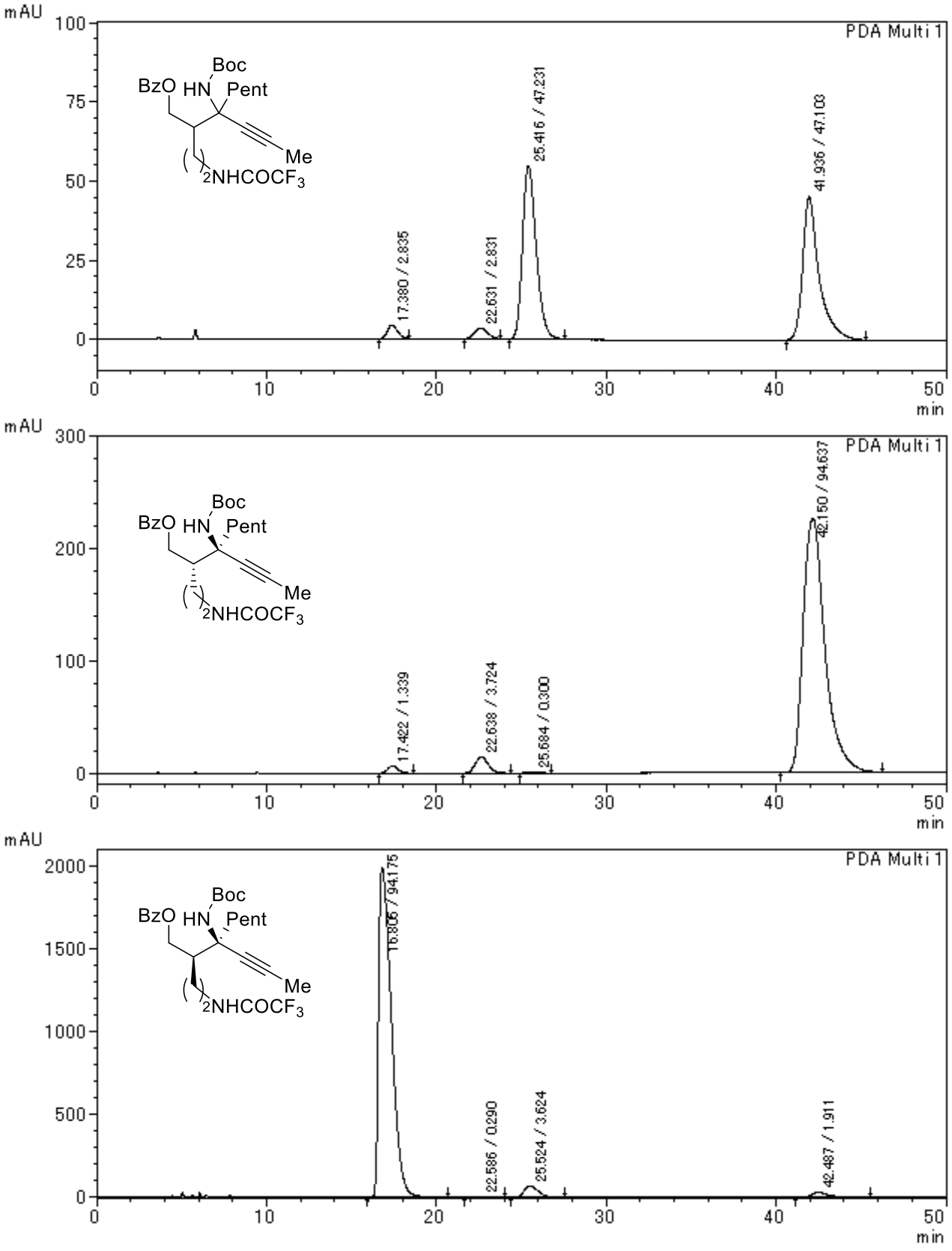
2-Allyl-3-((*tert*-utoxycarbonyl)amino)-3-(prop-1-yn-1-yl)octyl benzoate







3-((*tert*-Butoxycarbonyl)amino)-3-(prop-1-yn-1-yl)-2-(2-(2,2,2-trifluoroacetamido)ethyl)octyl benzoate



Methyl 2-benzyl-3-((tert-butoxycarbonyl)amino)-3-(prop-1-yn-1-yl)octanoate (8)