One-Pot Conversion of N-allyl a-cyano esters to a-allyl-a-cyano lactams through a hydrolysis/ketene formation/cyclization/Claisen Rearrangment Sequence

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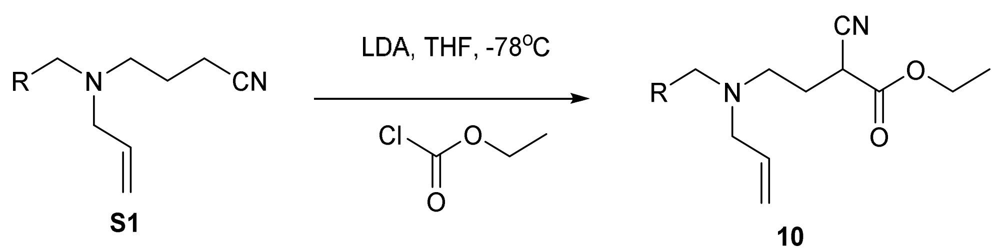
Supporting Information Contents

I. General Information and Materials

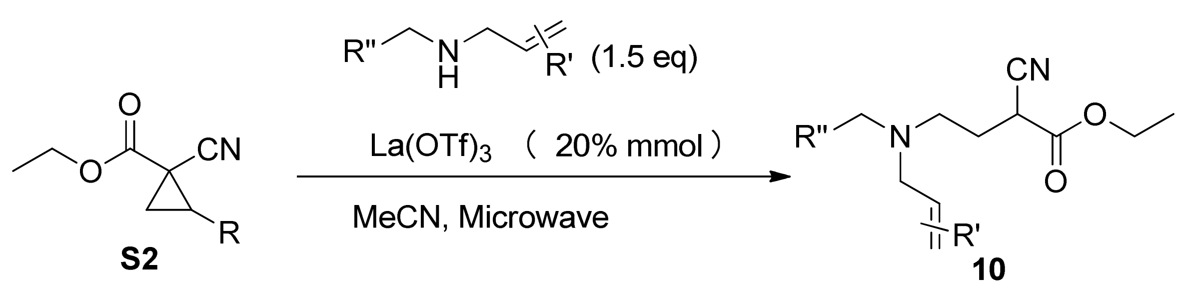
NMR spectra were recorded using Bruker AV-400 / AV-500 spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High resolution mass spectra were acquired on an agilent 6230 spectrometer and were obtained by peak matching. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator and/or by exposure to phosphormolybdic acid/cerium (IV) sulfate/ninhydrine followed by brief heating with a heat gun. Liquid chromatography (flash chromatography) was performed on 200-300 Å mesh silica gel (SiO_2). All reactions were carried out under nitrogen or argon with anhydrous solvents in oven-dried glassware, unless otherwise noted. Commercially available reagents were used without further purification.

II. A: Preparation of amino ester (10a, 10i, 10m, 10n)

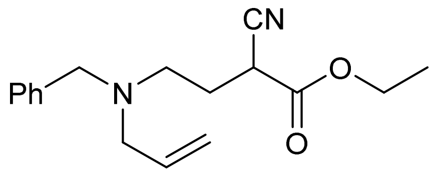


A solution of **S1**[1] (5.0 mmol, 1.0 eq) in 15 mL THF is added dropwise to a solution of LDA (12.5 mmol, 2.5 eq) in THF cooled to -78°C.The reaction mixture is allowed to stir at -78°C for 30 min. and then at room temperature for an additional 30 minutes.The reaction mixture is then cooled -78°C and a solution of ethyl chloroformate in 10 ml THF is added via syringe. The reaction mixture is stirred at -78°C for 2.5 hours. The reaction mixture is quenched with 10 mL saturated ammonium chloride and extracted with 75 mL diethyl ether. The ether is washed with 10% HCl (2 x 30 mL), brine (30 mL) and dried with $MgSO_4$. The solvent is removed under reduced pressure and the resulting crude oil is purified using silica gel chromatography (3% EtOAc in PE) to yield the desired cyanoesters **10a, 10i, 10m , 10n**.

B: Synthesis of amino ester (10b-h, j, k, l)

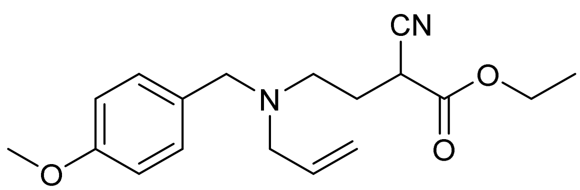


The mixture of **S2**[2,3] (2.0 mmol, 1.0 eq), N-allylamine (3.0 mmol, 1.5 eq) and La(OTf)$_3$ (0.2 eq) in MeCN (5 ml) in a sealed reaction vessel was stirred and heated at 100 ^{o}C in microwave reactor (Anton Paar Monowave 300). The reaction was filtered through a glass funnel, the filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (10% EtOAc in PE) to yield corresponding amino ester **(10b-h, j, k)**.



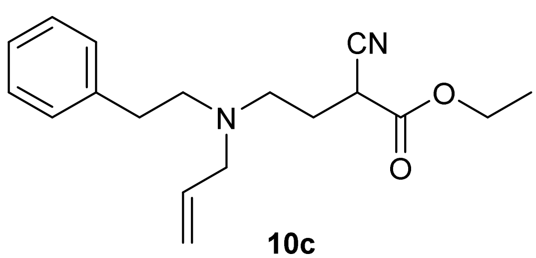
10a

10a: 1.11 g, 78%, colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.26 – 7.16 (m, 5H), 5.84-5.74 (m, 1H), 5.13 (d, *J* = 4.9 Hz, 1H), 5.09 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.68 (t, 1H), 3.51 (q, *J* = 13.5 Hz, 2H), 3.06-2.95 (m, 2H), 2.64 – 2.51 (m, 2H), 2.11-2.03(m, 1H), 1.97-1.89 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 163.7, 138.2, 134.9, 129.2, 128.2, 127.1, 118.2, 114.8, 63.8, 57.9, 56.0, 54.1, 48.9, 31.5, 13.8. HRMS(ESI) m/z calculated for $C_{17}H_{23}N_2O_2^+$ $[M+H]^+$ 287.1754, found 287.1750.



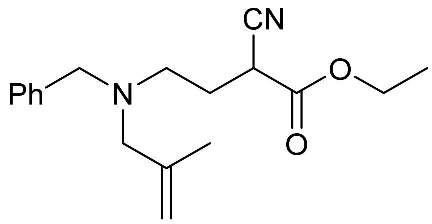
10b

10b: 391 mg, 62%, colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.86 – 6.84 (m, 2H), 5.89-5.79 (m, 1H), 5.20 – 5.18 (m, 1H), 5.15 (s, 1H), 4.26 – 4.15 (q, J=8.0Hz,2H), 3.79 (s, 3H), 3.76 – 3.73(t, J=12.0Hz,1H), 3.52 (q, *J* = 12.0 Hz, 2H), 3.12-3.00 (m, 2H), 2.66-2.58 (m, 2H), 2.17-2.08 (m, 1H), 2.04-1.97 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 166.3, 158.7, 135.0, 130.1, 118.1, 116.7, 113.7, 62.6, 57.5, 56.4, 55.2, 49.6, 34.8, 27.9, 13.9. HRMS(ESI) m/z calculated for $C_{18}H_{24}N_2O_2Na^+$ $[M+Na]^+$ 339.1679, found 339.1680.



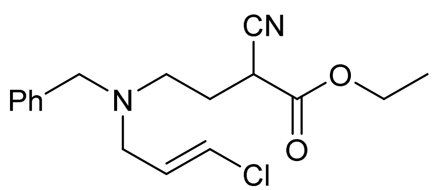
10c

10c: 300 mg, 50%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.4 Hz, 2H), 7.18 (t, *J* = 7.7 Hz, 3H), 5.88-5.78 (m, 1H), 5.19 (t, *J* = 12.0 Hz, 2H), 4.22 (q, *J* = 8.0 Hz, 2H), 3.57-3.53 (t, J = 7.0Hz, 1H), 3.21 (dd, *J* = 13.8, 5.9 Hz, 1H), 3.13 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.73 – 2.66 (m, 6H), 2.11-2.04 (m, 1H), 1.99-1.92 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 140.3, 134.9, 128.8, 128.4, 126.1, 118.0, 116.8, 62.6, 56.8, 55.3, 49.9, 34.6, 33.4, 29.7, 27.9, 14.0. HRMS(ESI) m/z calculated for $C_{18}H_{25}N_2O_2^+$ $[M+H]^+$ 301.1911, found 301.1902.



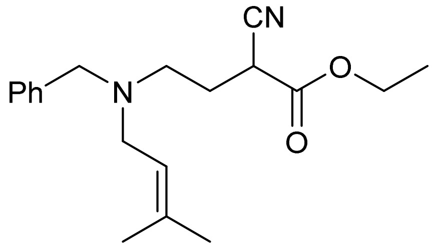
10d

10d: 270 mg, 45%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 5H), 4.92 (d, *J* = 15.0 Hz, 2H), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.24(m, 5H), 4.94 (s, 1H), 4.90 (s, 1H), 4.18 (q,J=7.2Hz, 2H), 3.73 (dd, *J* = 8.0, 5.6 Hz, 1H), 3.58 (d, *J* = 13.6 Hz, 1H), 3.46 (d, *J* = 13.2 Hz, 1H), 2.95 (q, *J* = 13.2 Hz, 2H), 2.64-2.59 (m, 1H), 2.55 – 2.49 (m, 1H), 2.18-2.10 (m, 1H), 2.03-1.92 (m, 1H), 1.77 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 166.2, 142.9, 138.7, 128.8, 128.2, 127.0, 116.5, 113.6, 62.5, 61.3, 58.3, 50.0, 34.6, 27.9, 20.7, 13.8. HRMS(ESI) m/z calculated for $C_{18}H_{25}N_2O_2^+$ $[M+H]^+$ 301.1911, found 301.1921.



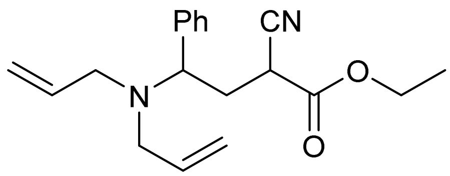
10e

10e: 256 mg, 40%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 5H), 6.09 (d, *J* = 13.6 Hz, 1H), 5.97 (dd, *J* = 13.6, 6.8 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.72 (dd, *J* = 7.6, 6.0Hz, 1H), 3.58 (q, *J* = 13.6 Hz, 2H), 3.08 (d, *J* = 6.8 Hz, 2H), 2.67 – 2.64 (m, 2H), 2.17-2.08 (m, 1H), 2.05-1.97 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 166.1, 138.0, 129.6, 128.7, 128.3, 127.2, 120.6, 116.4, 62.6, 57.9, 52.9, 49.7, 34.7, 27.7, 13.8. HRMS(ESI) m/z calculated for $C_{17}H_{22}ClN_2O_2^+$ $[M+H]^+$ 321.1364, found 321.1363.



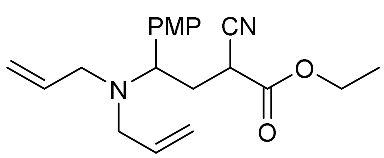
10f

10f: 270 mg, 43%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 5H), 5.24 (t, J = 6.8 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 3.82 – 3.78 (t, J=7.0Hz,1H), 3.56 (q, J = 12.8 Hz, 2H), 3.01 (d, J = 5.9 Hz, 2H), 2.65 – 2.58 (m, 2H), 2.14 – 2.11 (m, 1H), 2.01– 1.97 (m, 1H), 1.73 (s, 3H), 1.58 (s, 3H), 1.28 (t, J=7.2Hz,3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 166.5, 135.8, 128.9, 128.3, 127.1, 120.9, 116.8, 62.6, 58.6, 51.2, 49.9, 34.9, 29.7, 25.9, 18.1, 14.0. HRMS(ESI) m/z calculated for $C_{19}H_{27}N_2O_2^+$ $[M+H]^+$ 315.2067, found 315.2060.



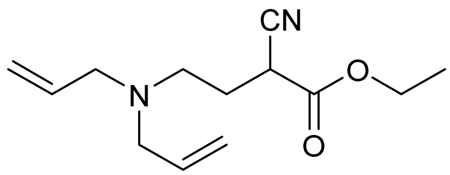
10g

10g: 343 mg, 55%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 3H), 7.25 – 7.18 (m, 2H), 5.86 – 5.76 (m, 2H), 5.20-5.14 (m, 4H), 4.27-4.21 (m, 2H), 4.09-4.01 (m, 1H), 3.59 (s, 1H), 3.32 – 3.29(m, 2H), 2.77 – 2.57 (m, 3H), 2.28 (d, J = 14.8 Hz, 1H), 2.09 (t, J = 9.9 Hz, 1H), 1.34-1.29 (m, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 166.6, 165.9, 137.9, 136.36, 128.7, 128.5, 128.3, 128.1, 127.7, 127.1, 117.5, 116.6, 77.3, 77.0, 76.7, 62.6, 59.1, 52.7, 52.4, 35.0, 34.8, 32.1, 31.9, 31.4, 19.2, 13.9. HRMS(ESI) m/z calculated for $C_{19}H_{25}N_2O_2^+$ $[M+H]^+$ 313.1911, found 313.1918.



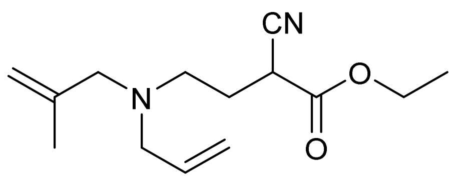
10h

10h: 383 mg, 56%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.06 (m, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.79 – 5.73 (m, 2H), 5.16 – 5.10 (m, 4H), 4.19 (q, J = 7.1 Hz, 2H), 4.01– 3.97, 3.62-3.58 (m, 2H), 3.73 (s, 3H), 3.60 (t, J = 6.4 Hz, 1H), 3.27 – 3.23(m, 2H), 2.73 – 2.50 (m, 3H), 2.23-1.97 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 166.3, 165.7, 158.7, 136.3, 129.3, 128.1, 127.8, 116.9, 116.4, 113.1, 77.3, 77.2, 77.0, 76.7, 62.1, 59.1, 58.2 54.7, 52.3, 52.1, 34.8, 34.6, 31.9, 31.7, 13.5. HRMS(ESI) m/z calculated for $C_{20}H_{27}N_2O_3^+$ $[M+H]^+$ 343.2016, found 343.2019.



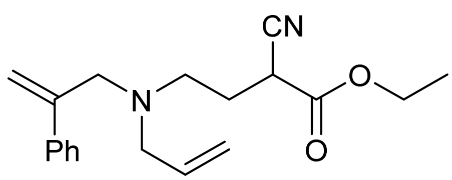
10i

10i: 944 mg, 80%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 – 5.73 (m, 2H), 5.15 – 5.11 (m, 4H), 4.21 (q, J = 7.0 Hz, 2H), 3.73 (t, J = 6.7 Hz, 1H), 3.15 – 2.95 (m, 4H), 2.59 (d, J = 5.1 Hz, 2H), 2.11 – 2.08 (m, 1H), 2.02– 1.99 (m, 1H), 1.28 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 166.3, 134.8, 117.9, 116.6, 62.5, 56.6, 49.2, 34.9, 27.7, 13.8. HRMS(ESI) m/z calculated for $C_{13}H_{20}N_2O_2Na^+$ $[M+Na]^+$ 259.2016, found 259.2019.



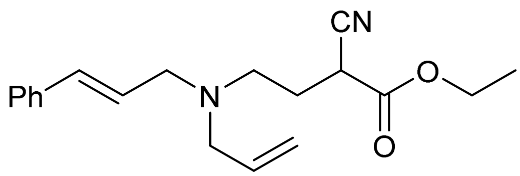
10j

10j: 190 mg, 38%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 – 5.70(m, 1H), 5.10 (dd, J = 14.0, 6.0 Hz, 2H), 4.81 (d, J = 7.9 Hz, 2H), 4.19 (q, J=6.4Hz, 2H), 3.74 (t, J=7.0Hz ,1H), 3.02 (dd, J = 14.1, 6.0 Hz, 1H), 2.95 – 2.91 (m, 2H), 2.84 (d, J = 13.4 Hz, 1H), 2.62 – 2.55 (m, 1H), 2.52 – 2.46 (m, 1H), 2.13 – 2.06 (m, 1H), 1.99-1.91 (m, 1H), 1.67 (s, 3H), 1.26(t, J=7.2Hz,3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 166.2, 142.9, 134.9, 117.6, 116.5, 113.1, 77.3, 77.0, 76.7, 62.4, 60.7, 56.2, 49.6, 34.6, 27.7, 20.5, 13.7. HRMS(ESI) m/z calculated for $C_{14}H_{23}N_2O_2^+$ $[M+H]^+$ 251.1754, found 251.1768.



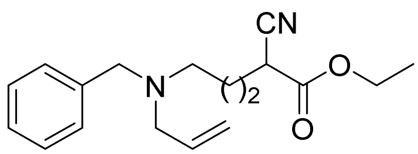
10k

10k: 299 mg, 48%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.40 (m, 2H), 7.34 – 7.25 (m, 3H), 5.84 – 5.74 (m, 1H), 5.42 (s, 1H), 5.24 (d, J = 1.0 Hz, 1H), 5.17 (s, 1H), 5.17 – 5.13 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.52 (d, J = 13.9 Hz, 1H), 3.54 – 3.37 (m, 2H), 3.13 (dd, J = 14.0, 6.2 Hz, 1H), 3.02 (dd, J = 14.1, 7.0 Hz, 1H), 2.69 – 2.63(m, 1H), 2.61 – 2.55 (m, 1H), 2.14– 2.08 (m, 1H), 1.93– 1.86 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 166.5, 145.5, 139.9, 134.8, 128.2, 127.6, 126.5, 118.2, 116.9, 115.6, 62.5, 58.5, 56.7, 49.6, 34.4, 28.0, 13.9. HRMS(ESI) m/z calculated for $C_{19}H_{25}N_2O_2^+$ $[M+H]^+$ 313.1911, found 313.1907.



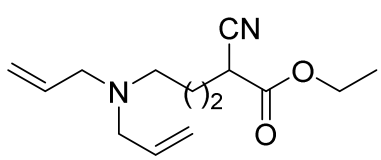
10l

10l: 218 mg, 35%, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.15 (m, 5H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.18-6.09(m, 1H), 5.84-5.70 (m, 1H), 5.15-5.09 (m, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.71(t,J=6.9Hz 1H), 3.18 – 3.16 (m, 2H), 3.06 (t, *J* = 5.8 Hz, 2H), 2.63 – 2.58 (m, 2H), 2.13 – 1.95 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 136.8, 134.9, 132.9, 128.5, 127.4, 126.4, 126.2, 118.1, 116.7, 62.6, 56.7, 55.9, 49.4, 34.9, 27.7, 13.9. HRMS(ESI) m/z calculated for $C_{19}H_{24}N_2O_2Na^+$ $[M+Na]^+$ 335.1730, found 335.1727.



10m

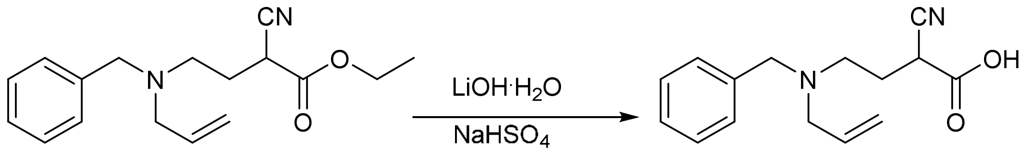
10m: 1.12 g, 75%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 5H), 5.90 – 5.81(m, 1H), 5.18 (dd, *J* = 24.0, 6.2 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.54 (d, *J* = 5.4 Hz, 2H), 3.50 – 3.45 (m, 1H), 3.06 (d, *J* = 5.7 Hz, 2H), 2.46 (t, *J* = 6.6 Hz, 2H), 1.99-1.88 (m, 2H), 1.69 – 1.63 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 166.1, 139.2, 135.4, 128.7, 128.1, 126.9, 117.5, 116.5, 62.5, 58.1, 56.6, 51.5, 36.9, 27.5, 23.8, 13.9. HRMS(ESI) m/z calculated for $C_{17}H_{23}N_2O_2^+$ $[M+H]^+$ 301.1911, found 301.1897.



10n

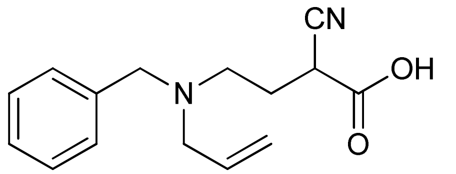
10n: 1.03 g, 83%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.74 (m, 2H), 5.16-5.09 (m, 4H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.59 (dd, *J* = 7.8, 6.4 Hz, 1H), 3.03 (d, *J* = 6.5 Hz, 4H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.00-1.88 (m, 2H), 1.66-1.58 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 166.2, 135.5, 117.5, 116.6, 62.6, 56.6, 51.8, 37.3, 27.9, 23.9, 14.0. HRMS(ESI) m/z calculated for $C_{13}H_{21}N_2O_2^+$ $[M+H]^+$ 251.1754, found 251.1753.

III. Preparation of α-cyano N-allyl amino acid



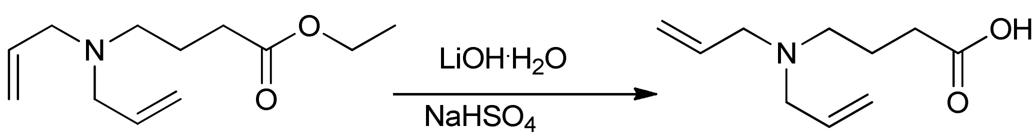
10 **8**

To a solution of **10** (1.0 eq) in MeOH/THF (1:1) was added LiOH·H_2O (1.2 eq), The mixture was reacted overnight .Then the lithium salt was acidized in $NaHSO_4$ (1.2 eq) and stirred 30 minutes. Then the solid was filtered and the filtrate is removed under reduced pressure, the remaining sticky liquid was redissolved in dried THF and concentrated under reduced pressure. Repeat this process three times. The remaining oily residue was the corresponding acid product **8**.



8a

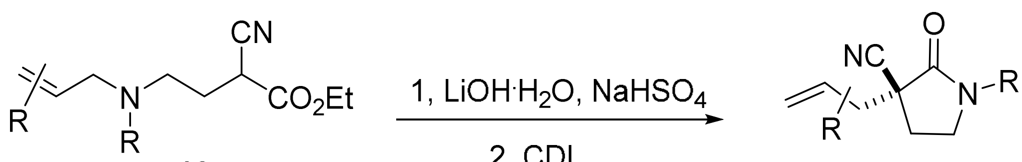
8: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.10 (s, 1H), 7.45 – 7.36 (m, 2H), 7.36 – 7.28 (m, 3H), 5.97 – 5.83 (m, 1H), 5.38 (t, *J* = 13.5 Hz, 2H), 4.11 – 3.98 (m, 2H), 3.58 (t, *J* = 6.2 Hz, 1H), 3.44 (t, *J* = 5.7 Hz, 2H), 3.09 (t, *J* = 7.0 Hz, 2H), 2.36-2.23 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 131.0, 130.4, 129.1, 128.9, 127.9, 124.1, 119.1, 56.5, 54.2, 49.9, 37.6, 25.1. HRMS(ESI) m/z calculated for $C_{15}H_{19}N_2O_2^+$ $[M+H]^+$ 259.1441, found 259.1441.



S3 **1-H**

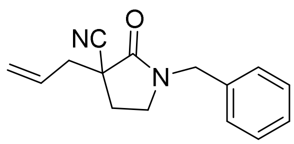
1-H was prepared from **S3**[1] according to the general procedure similar to **8a**.
1-H: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.07 (s, 1H), 5.99-5.85 (m, 2H), 5.37 – 5.29 (m, 4H), 3.40 (d, *J* = 7.0 Hz, 4H), 2.82 (t, *J* = 6.7 Hz, 2H), 2.42 (t, J = 8.0Hz, 2H), 1.91 – 1.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 129.4, 122.9, 55.2, 52.4, 34.6, 20.4. HRMS(ESI) m/z calculated for $C_{10}H_{18}NO_2^+$ $[M+H]^+$ 184.1332, found 184.1332.

IV. The preparation of α-allyllactam 9



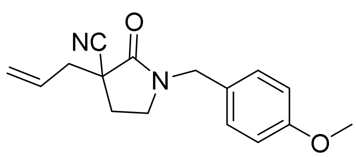
10 **9**

To a solution of **10** (0.59 mmol, 1.0 eq) in MeOH/THF(1:1) was added $LiOH{\cdot}H_2O$ (0.71 mmol , 1.2 eq), the mixture was reacted overnight. Then the lithium salt was acidized with $NaHSO_4$ (0.71 mmol, 1.2 eq) and stirred for 30 minutes. The reaction mixture was concentrated and dried in vacuum. Then the residue was dissolved in DCM (5 ml) and carbonyl diimidazole (CDI) (1.06 mmol, 1.5 eq) was added and stirred overnight. The reaction mixture was concentrated in vacuum and the residue was purified directly by column chromatography (20% EtOAc in PE) to yield corresponding α-allyllactam **9**.



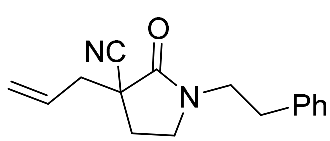
9a

9a: 114 mg, 81%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27– 7.18 (m, 3H), 7.13 – 7.11 (m, 2H), 5.76-5.65 (m, 1H), 5.19-5.14 (m, 2H), 4.37 (q, *J* = 14.8 Hz, 2H), 3.27-3.21 (m, 1H), 3.13-3.07 (m, 1H), 2.70-2.64 (m, 1H), 2.41 – 2.28 (m, 2H), 2.09-2.02 (m, 1H). ^{13}C NMR (100MHz, $CDCl_3$) δ 168.0, 135.1, 130.4, 128.7, 127.9, 127.9, 121.0, 119.1, 77.3, 77.0, 76.7, 47.2, 44.1, 43.2, 38.9, 28.6. HRMS(ESI) m/z calculated for $C_{15}H_{17}N_2O^+$ $[M+H]^+$ 241.1335, found 241.1332.



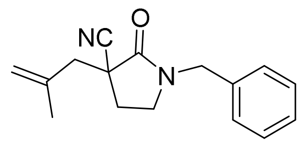
9b

9b: 135 mg, 85%, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.88– 6.83 (m, 2H), 5.86-5.72 (m, 1H), 5.28-5.22 (m, 2H), 4.40 (q, *J* = 19.2 Hz, 2H), 3.78 (s, 3H), 3.36-3.28 (m, 1H), 3.21-3.14 (m, 1H), 2.78-2.71 (m, 1H), 2.49 – 2.34 (m, 2H), 2.17-2.07 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 159.2, 130.4, 129.4, 127.1, 121.0, 119.2, 114.1, 55.1, 46.6, 44.2, 43.0, 38.9, 28.6. HRMS(ESI) m/z calculated for $C_{16}H_{18}N_2O_2Na^+$ $[M+Na]^+$ 293.1260, found 293.1274.



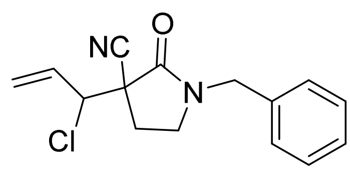
9c

9c: 131 mg, 88%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.3 Hz, 2H), 7.21 – 7.16(m, 3H), 5.71 – 5.61 (m, 1H), 5.20-5.15(m, 2H), 3.66 – 3.59 (m, 1H), 3.51-3.44 (m, 1H), 3.27-3.21 (m, 1H), 3.14-3.08 (m, 1H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.63-2.58 (m, 1H), 2.32-2.26 (m, 2H), 2.06 – 1.99 (m, 1H). ^{13}C NMR (100MHz, CDCl3) δ 167.7, 137.7, 130.4, 128.4, 126.4, 120.7, 119.0, 44.4, 44.1, 43.9, 38.8, 33.1, 28.7. HRMS(ESI) m/z calculated for $C_{12}H_{19}N_2O^+$ $[M+H]^+$ 255.1492, found 255.1478.



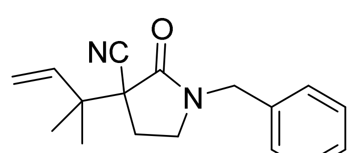
9d

9d: 124 mg, 83%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 3H), 7.20 (d, *J* = 6.9 Hz, 2H), 4.97 (s, 1H), 4.86 (s, 1H), 4.45 (s, 2H), 3.37-3.30 (m, 1H), 3.21-3.16 (m, 1H), 2.80 (d, *J* = 14.3 Hz, 1H), 2.44-2.35 (m, 2H), 2.20 – 2.13 (m, 1H), 1.82 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 168.4, 139.2, 135.1 128.8, 128.0, 127.9, 119.5, 116.5, 47.4, 43.6, 43.2, 42.1, 29.3, 23.0. HRMS(ESI) m/z calculated for $C_{16}H_{18}N_2ONa^+$ $[M+Na]^+$ 277.1311 , found 277.1299.



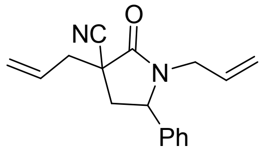
9e

9e: 132 mg, 82%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29(m, 3H), 7.21 – 7.19 (m, 2H), 5.91-5.82 (m, 1H), 5.53 (d, *J* = 16.8 Hz, 1H), 5.34 (d, *J* = 10.2 Hz, 1H), 4.91 (d, *J* = 7.4 Hz, 1H), 4.53 (d, *J* = 14.6 Hz, 1H), 4.37 (d, *J* = 14.6 Hz, 1H), 3.38-3.32 (m, 1H), 3.23-3.17 (m, 1H), 2.51 – 2.38 (m, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 165.3, 134.7, 130.7, 128.8, 128.2, 128.1, 122.2, 117.9, 62.5, 51.3, 47.5, 43.5, 25.7. HRMS(ESI) m/z calculated for $C_{15}H_{16}ClN_2O^+$ $[M+H]^+$275.0946, found 275.0946.



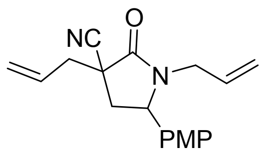
9f

9f: 139 mg, 88%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 3H), 7.21 – 7.19 (m, 2H), 5.89 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.15 (d, *J* = 2.3 Hz, 1H), 5.11 (d, *J* = 3.1 Hz, 1H), 4.44 (dd, *J* = 40.6, 14.6 Hz, 2H), 3.28 – 3.22 (m, 1H), 3.13 – 3.07 (m, 1H), 2.31-2.25 (m, 1H), 2.22-2.15 (m, 1H), 1.34 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 167.2, 141.0, 135.2, 128.7, 128.0, 127.8, 119.1, 115.4, 51.2, 47.3, 43.1, 41.9, 27.3, 23.1, 22.4. HRMS(ESI) m/z calculated for $C_{17}H_{21}N_2O^+$ $[M+H]^+$ 269.1648, found 269.1644.



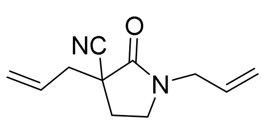
9g

9g: 117 mg, 75%, colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 – 7.33 (m, 3H), 7.22– 7.20(m, 2H), 5.87-5.76 (m, 1H), 5.59 – 5.54 (m, 1H), 5.32 – 5.28 (m, 2H), 5.13 (d, J = 10.1 Hz, 1H), 4.94 (d, J = 17.1 Hz, 1H), 4.52 (t, J = 7.6Hz, 1H), 4.34 (dd, J = 15.0, 4.8 Hz, 1H), 3.07 (dd, J = 15.0, 8.0 Hz, 1H), 2.78-2.73 (m, 1H), 2.69-2.64 (m, 1H), 2.58-2.53 (m, 1H), 2.38-2.33 (m, 1H). ^{13}C NMR (100MHz, CDCl$_3$) δ 168.5, 138.3, 130.6, 130.2, 129.2, 128.8, 126.9, 121.5, 119.6, 119.4, 58.8, 43.9, 43.6, 39.9, 37.8. HRMS(ESI) m/z calculated for $C_{17}H_{19}N_2O^+$ $[M+H]^+$ 267.1492, found 267.1508.



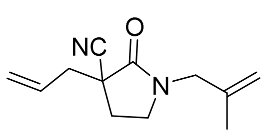
9h

9h: 122 mg, 70%, colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.13 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.86-5.76 (m, 1H), 5.61-5.51 (m, 1H), 5.31-5.27 (m, 2H), 5.12 (d, J = 10.0 Hz, 1H), 4.94 (d, J = 17.1 Hz, 1H), 4.48 (t, J = 7.3 Hz, 1H), 4.29 (dd, J=15.0,4.7Hz,1H), 3.78 (s, 3H), 3.05 (dd, J = 15.0, 8.0 Hz, 1H), 2.76-2.71 (m, 1H), 2.66-2.61 (m, 1H), 2.56-2.51 (m, 1H), 2.35-2.30 (m, 1H). ^{13}C NMR (100MHz, CDCl$_3$) δ 168.3, 159.8, 130.7, 130.2, 129.9, 128.2, 121.4, 119.6, 119.2, 114.4, 58.2, 55.2, 43.7, 43.6, 39.7, 37.9. HRMS(ESI) m/z calculated for $C_{18}H_{20}N_2O_2Na^+$ $[M+Na]^+$ 319.1417, found 319.1412.



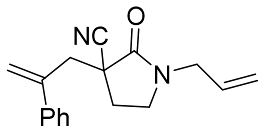
9i

9i: 87 mg, 78%, colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.83 – 5.64 (m, 2H), 5.27 – 5.17 (m, 4H), 3.95 – 3.84 (m, 2H), 3.45-3.39 (m, 1H), 3.31-3.25 (m, 1H), 2.75-2.70 (m, 1H), 2.47 – 2.39 (m, 2H), 2.20-2.13 (m, 1H). ^{13}C NMR (100MHz, CDCl$_3$) δ 167.8, 131.0, 130.5, 121.1, 119.2, 118.9, 45.9, 44.2, 43.4, 39.1, 28.8. HRMS(ESI) m/z calculated for $C_{11}H_{15}N_2O^+$ $[M+H]^+$191.1179, found 191.1181.



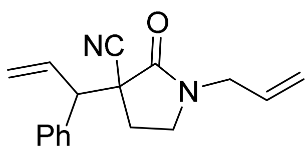
9j

9j: 96 mg, 80%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 – 5.74 (m, 1H), 5.28 – 5.23 (m, 2H), 4.92 (s, 1H), 4.81 (s, 1H), 3.84 (s, 2H), 3.43-3.37 (m, 1H), 3.27-3.22 (m, 1H), 2.78-2.72 (m, 1H), 2.49 – 2.40 (m, 2H), 2.20-2.13 (m, 1H), 1.66 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 167.9, 139.0, 130.6, 121.1, 119.2, 113.8, 49.4, 44.2, 43.4, 39.0, 28.9, 19.8. HRMS(ESI) m/z calculated for $C_{12}H_{16}N_2ONa^+$ $[M+Na]^+$ 227.1155, found 227.1169.



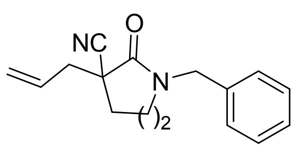
9k

9k: 134 mg, 86%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.66 – 5.53 (m, 1H), 5.46 (d, J = 0.8 Hz, 1H), 5.35 (s, 1H), 5.22-5.14 (m, 2H), 3.84-3.71 (m, 2H), 3.34 – 3.24 (m, 1H), 3.13-3.08 (m, 1H), 3.00 (d, J = 14.4, 1H), 2.24-2.17(m, 1H), 2.04 – 1.97 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 142.6, 140.3, 131.2, 128.6, 128.2, 126.5, 126.2, 119.0, 118.9, 45.9, 44.9, 43.6, 39.8, 29.5. HRMS(ESI) m/z calculated for $C_{17}H_{19}N_2O^+$ $[M+H]^+$267.1492, found 267.1488.



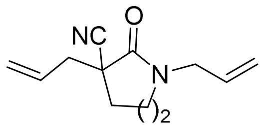
9l

9l: 128 mg, 82%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (m, 5H), 6.30 – 6.21 (m, 1H), 5.66-5.58 (m, 1H), 5.29 – 5.13 (m, 4H), 3.92 (d, J = 8.3 Hz, 1H), 3.87-3.80 (m, 2H), 3.29-3.23 (m, 1H), 2.83-2.77 (m, 1H), 2.43 (t, J = 6.7 Hz, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 167.1, 137.2, 134.2, 131.1, 128.9, 128.7, 128.0, 120.1, 119.2, 118.9, 53.9, 49.6, 46.0, 43.5, 27.6. HRMS(ESI) m/z calculated for $C_{17}H_{18}N_2ONa^+$ $[M+Na]^+$289.1311, found 289.1305.



9m

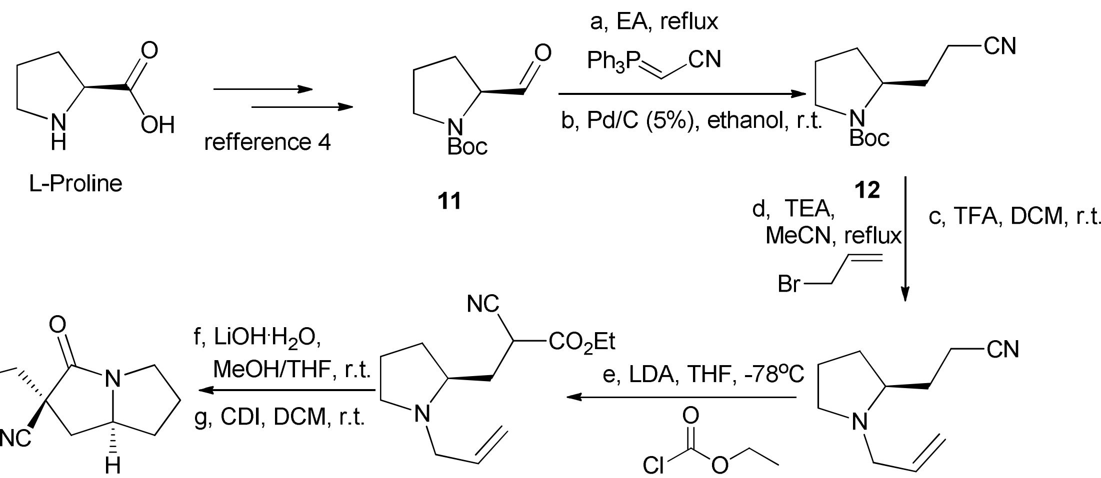
9m: 59 mg, 40%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (m, 3H), 7.22 (d, J = 7.2 Hz, 2H), 5.86-5.76 (m, 1H), 5.26 – 5.21 (m, 2H), 4.58 (s, 2H), 3.29 – 3.17 (m, 2H), 2.95-2.90 (m, 1H), 2.70-2.64 (m, 1H), 2.20 – 2.15 (m, 1H), 2.04 – 1.97 (m, 1H), 1.93 – 1.87 (m, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 164.5, 136.2, 131.3, 128.8, 128.0, 127.8, 120.9, 120.5, 51.2, 47.1, 43.9, 40.8, 30.5, 19.4. HRMS(ESI) m/z calculated for $C_{15}H_{17}N_2O^+$ $[M+H]^+$ 255.1492, found 255.1476.



9n

9n: 36 mg, 30%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 – 5.69(m, 2H), 5.25 – 5.14 (m, 4H), 3.98 (dd, *J* = 6.0, 1.3 Hz, 2H), 3.36 – 3.24 (m, 2H), 2.91-2.86 (m, 1H), 2.65-2.60 (m, 1H), 2.21-2.16 (m, 1H), 2.09 – 2.00 (m, 1H), 1.98 – 1.86 (m, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 164.0, 131.7, 131.3, 120.8, 120.5, 118.1, 50.4, 47.2, 43.7, 40.8, 30.5, 19.5. HRMS(ESI) m/z calculated for $C_{11}H_{15}N_2O^+$ $[M+H]^+$ 205.1335, found 205.1334.

Ⅴ. Synthesis of highly functionalized bicyclic amides 15



15 **14** **13**

(Triphenylphosphoranylidene)acetonitrile (4.5 g, 15 mmol, 1.5 eq) was added a solution of **11** {$[\alpha]^D{}_{25}$ = - 87.4 (c = 1.0, EA), 1.99 g, 10 mmmol, 1.0 eq} in EA (40 ml) and the mixture was refluxed overnight. The reaction mixture was concentrated in vacuum and the residue was purified directly by column chromatography (20% EtOAc in PE) to yield the corresponding alkene: $[\alpha]^D{}_{25}$ = - 85.1 (c = 1.1, EA) (green liquid, 1.87 g, 84%).

A reactor (50 ml) was charged with the precursor of **12** (1.0 g, 4.5 mmol, 1.0 eq), Pd/C (5%) (47 mg, 0.45 mmol, 0.1 eq), absolute EtOH (20 ml), the mixture was blowed with hydrogen and stirred overnight at room temperature. Then the solid was filtered and washed with EA (5 ml) three times. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (20% EtOAc in PE) to yield corresponding **12**$[\alpha]^D{}_{25}$ = - 50.0 (c = 0.3, EA) (colorless liquid , 850 mg, 85%).

To a solution of **12** (850 mg, 3.8 mmol, 1.0 eq) in DCM (15 ml) was added TFA (1.15 ml, 15.2 mmol, 4.0 eq) at 0 ºC. After stirring at ambient temperature for 3 h, the reaction mixture was concentrated *in vacuum* and the crude product was used immediately without further purification. The crude salt was dissolved in MeCN (3 mL); then to this solution was introduced TBAI (0.38 mmol, 140 mg, 0.1 eq), TEA (2.6 ml, 18.9 mmol, 5.0 eq), allyl bromide (0.35 ml, 4.16 mmol, 1.1 eq). Then the resulting reaction mixture was refluxed overnight and concentrated in vacuum; the residue was purified directly by column chromatography (40% EtOAc in PE) to yield corresponding tertiary amine **13** $[\alpha]^{D}_{25}$ = - 82.8 (c = 0.14, EA) as a yellow oil (360 mg, 58% for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 – 5.82 (m, 1H), 5.18 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.09 (d, *J* = 10.1 Hz, 1H), 3.36 (dd, *J* = 13.5, 5.5 Hz, 1H), 3.08 – 3.04 (m, 1H), 2.83 (dd, *J* = 13.4, 7.4 Hz, 1H), 2.51-2.44 (m, 1H), 2.43 – 2.39 (m, 1H), 2.34-2.27 (m, 1H), 2.20 (dd, *J* = 17.7, 8.8 Hz, 1H), 1.95 – 1.90 (m, 2H), 1.75 – 1.63 (m, 3H), 1.48 – 1.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 120.0, 117.0, 62.1, 57.4, 54.0, 29.7, 29.5, 22.4, 13.5. HRMS (ESI) m/z calculated for $C_{10}H_{17}N_2^+$ $[M+H]^+$ 165.1386, found 165.1389.

(−)−**14** $[\alpha]^{D}_{25}$ = - 66.3 (c = 0.16, EA) was prepared according to general procedure **A**. yellow oil, 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (m, 5.87-5.86, 1H), 5.18 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 10.1 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.62 (t, *J* = 6.9 Hz, 1H), 3.38 (dd, *J* = 13.5, 5.5 Hz, 1H), 3.07 – 3.02 (m, 1H), 2.88 (s, 1H), 2.71 – 2.65 (m, 1H), 2.31-2.25 (m, 1H), 2.19 – 2.12 (m, 1H), 2.04-1.95 (m, 2H), 1.77 - 1.72 (m, 2H), 1.55-1.53 (m, 1H), 1.32 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 135.8, 135.5, 117.5, 117.2, 117.0, 116.8, 63.2, 62.7, 62.2, 61.0, 60.7, 57.4, 53.9, 53.6, 53.4, 34.3, 30.0, 22.8, 13.9. HRMS(ESI) m/z calculated for $C_{13}H_{21}N_2O_2^+$ $[M+H]^+$ 237.1598, found 237.1599.

(−)−**15** $[\alpha]^{D}_{25}$ = - 44.7 (c = 0.16, EA) was prepared according to general procedure similar to **9**. colorless oil, 75%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 – 5.85 (m, 1H), 5.56-5.51 (m, 2H), 4.01-3.90 (m, 2H), 3.88-3.79 (m, 1H), 3.55 (dd, *J* = 13.1, 8.4 Hz, 1H), 3.03-2.93 (m, 1H), 2.84 (dd, *J* = 12.9, 8.0 Hz, 1H), 2.39-2.28 (m, 2H), 1.2.07-1.88 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 126.4, 126.3, 120.4, 63.5, 61.0, 58.0, 33.4, 30.8, 23.5. HRMS(ESI) m/z calculated for $C_{11}H_{15}N_2O^+$ $[M+H]^+$ 191.1179, found 191.1176.

Enantiomeric excess was determined to be 97% (determined by HPLC using chiral IC-H column, n-Hexane/EtOH/Diethylamine = 60/40/0.1, λ = 254 nm, 35 ^{o}C, 0.8mL/min, t_{major} = 24.54 min, t_{minor} = 26.63 min).

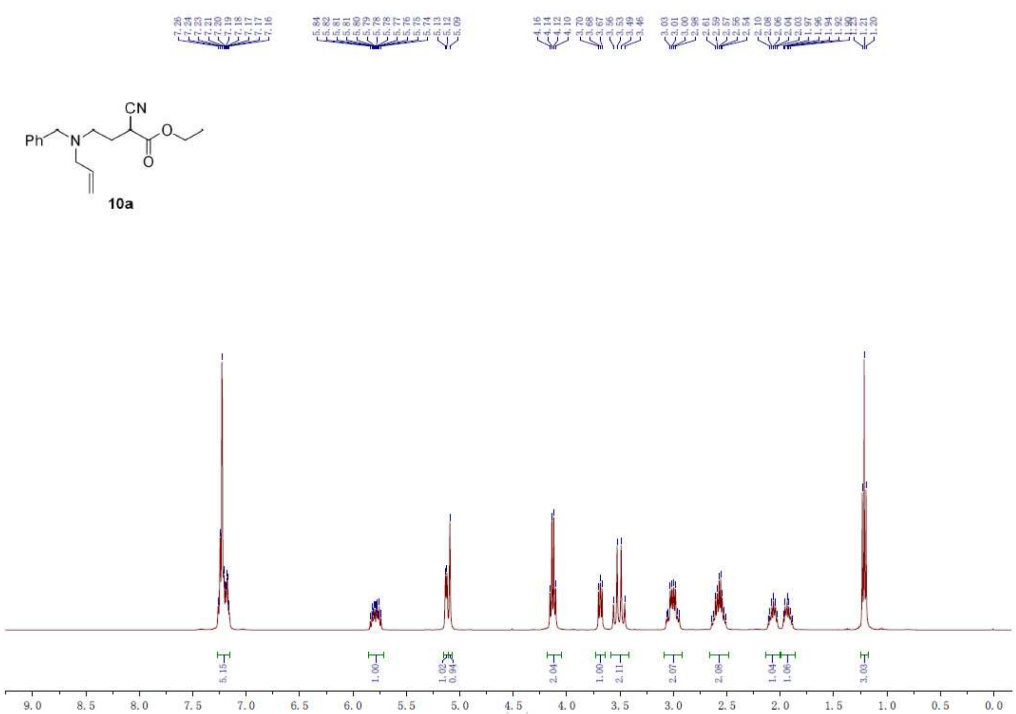
Note，the racemic compound (+/-)-**15** was made by using the same route for (-)-**15** and using (D/L)-proline as starting materials.

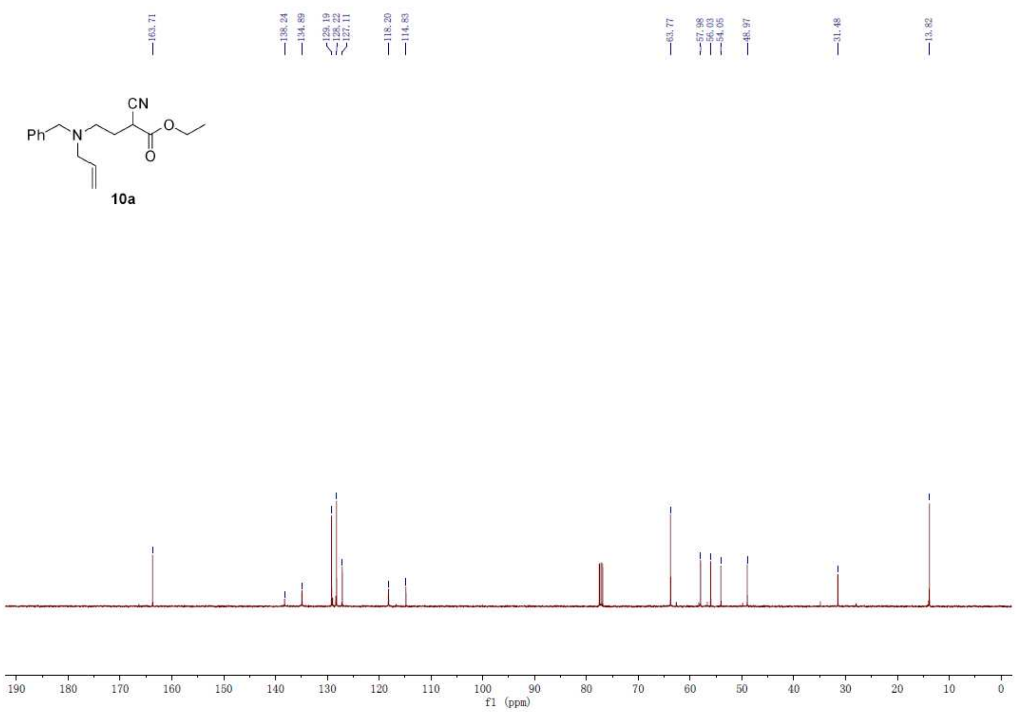
VI. Reference

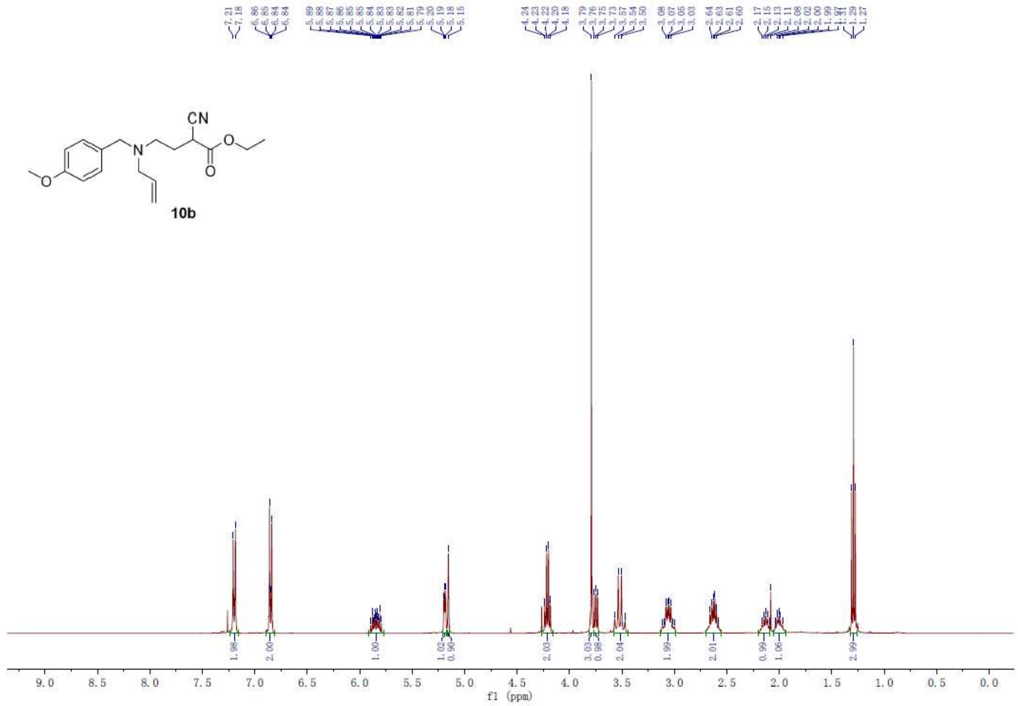
1. Couty, Francois.; Prim, Damien. *Tetrahedron: Asymmetry*. **2002**, 13, 2619-2624.

2. Xue, Yong-Lai. *Asian Journal of Chemistry*. **2012**, 24, 3016-3018.
3. You-Yun Zhou.; Yong Tang. *J. Am. Chem. Soc*. **2012**, 134, 9066-9069.
4. Chinmay Bhat.; Santosh G. Tilve. *Tetrahedron Lett.* **2011**, 52, 6566-6568.

VII. ^{1}H and ^{13}C NMR spectra of compounds



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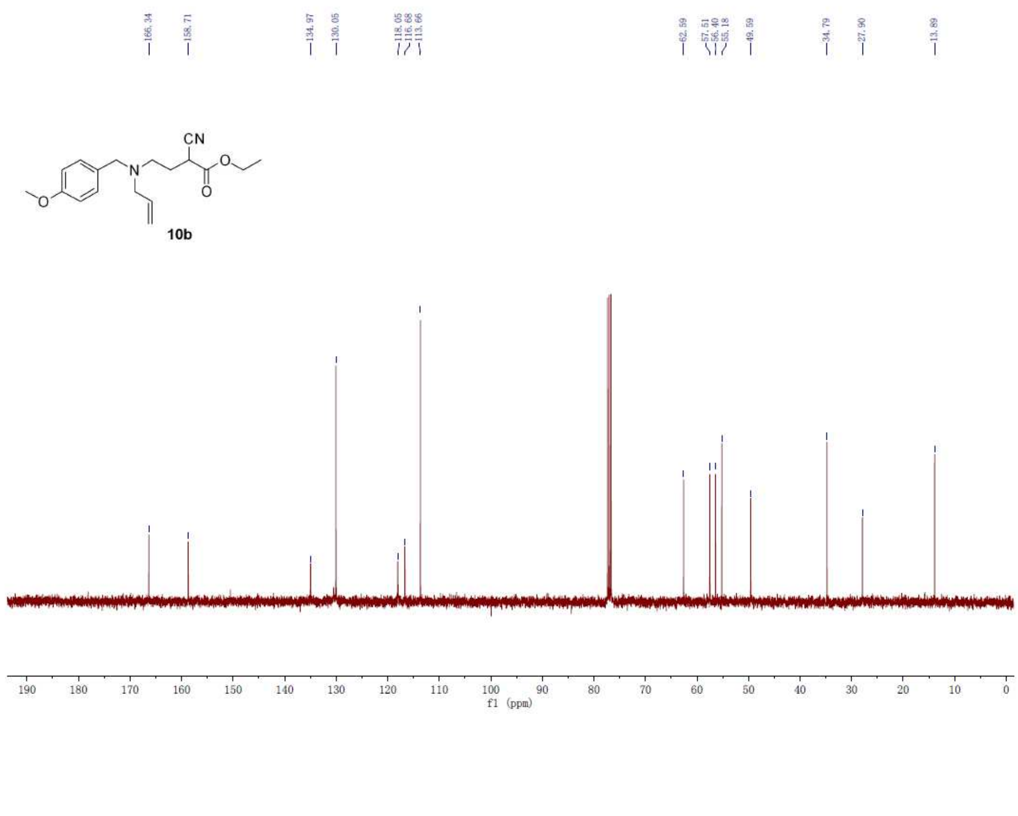
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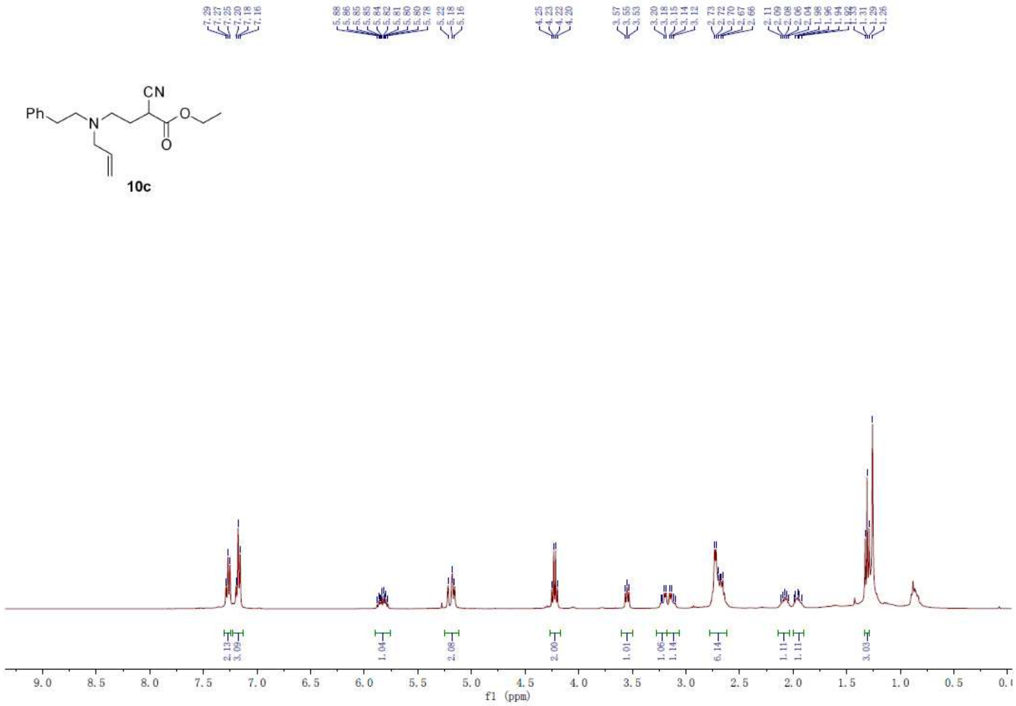
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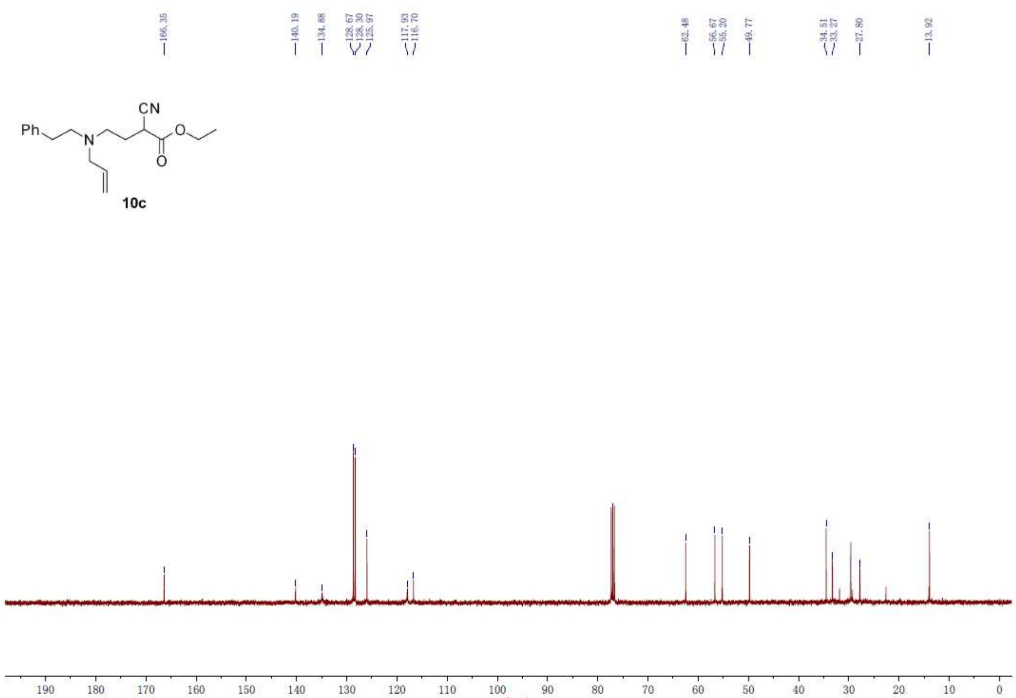
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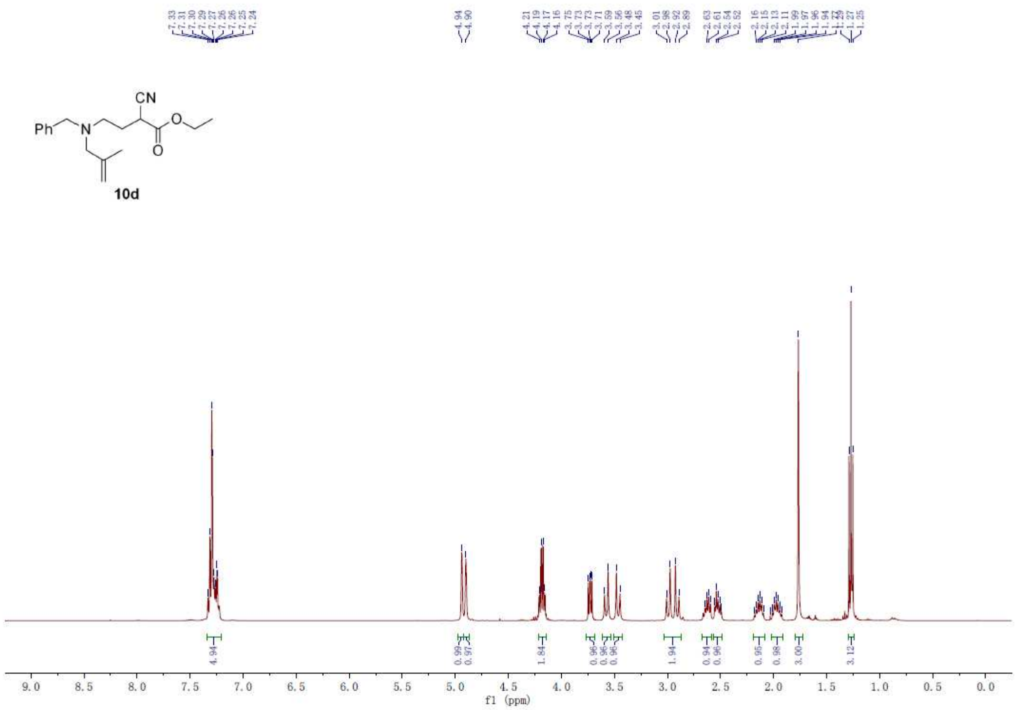

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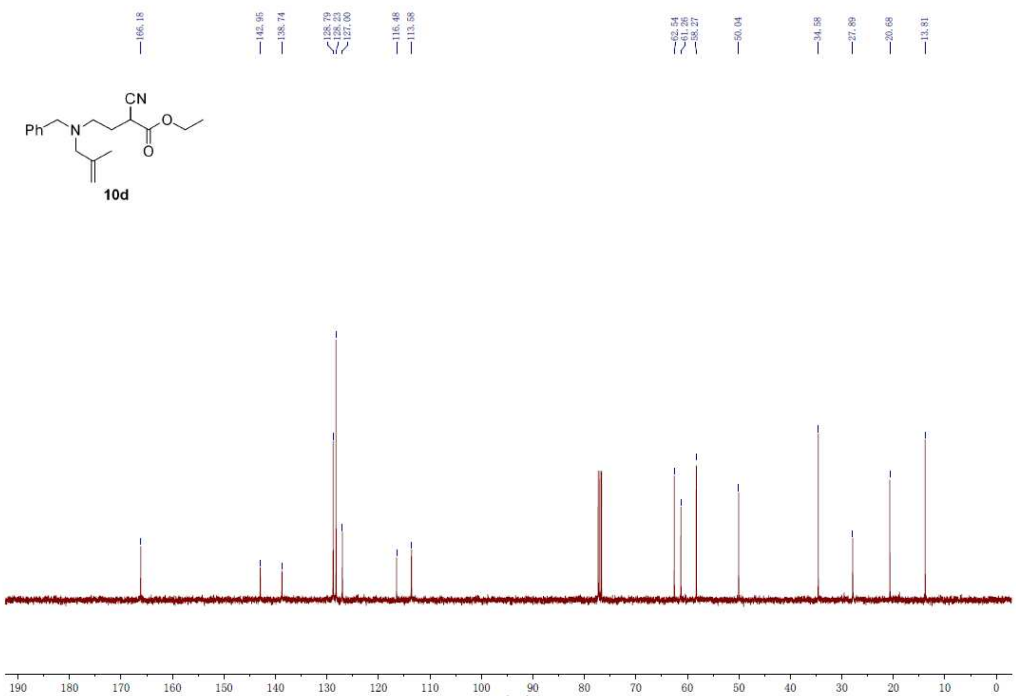

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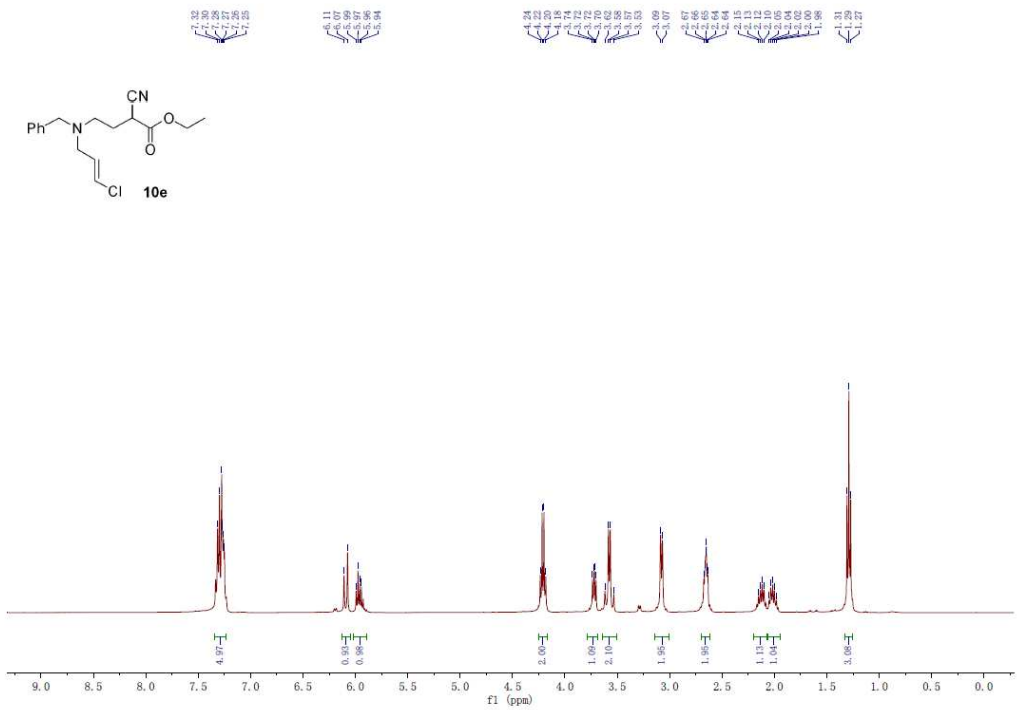

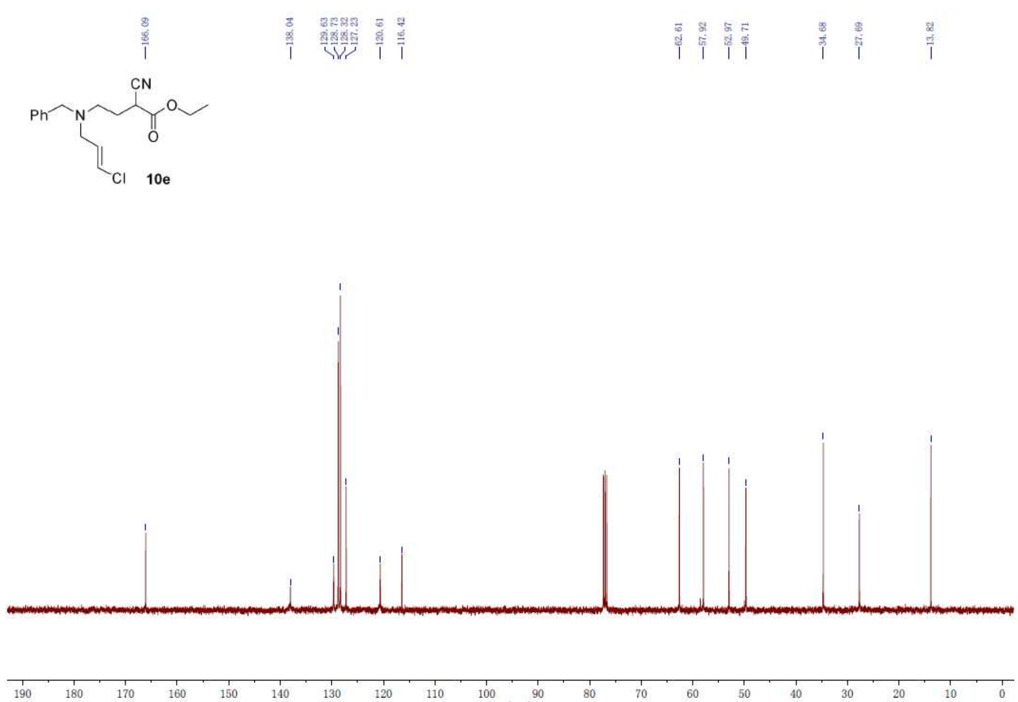

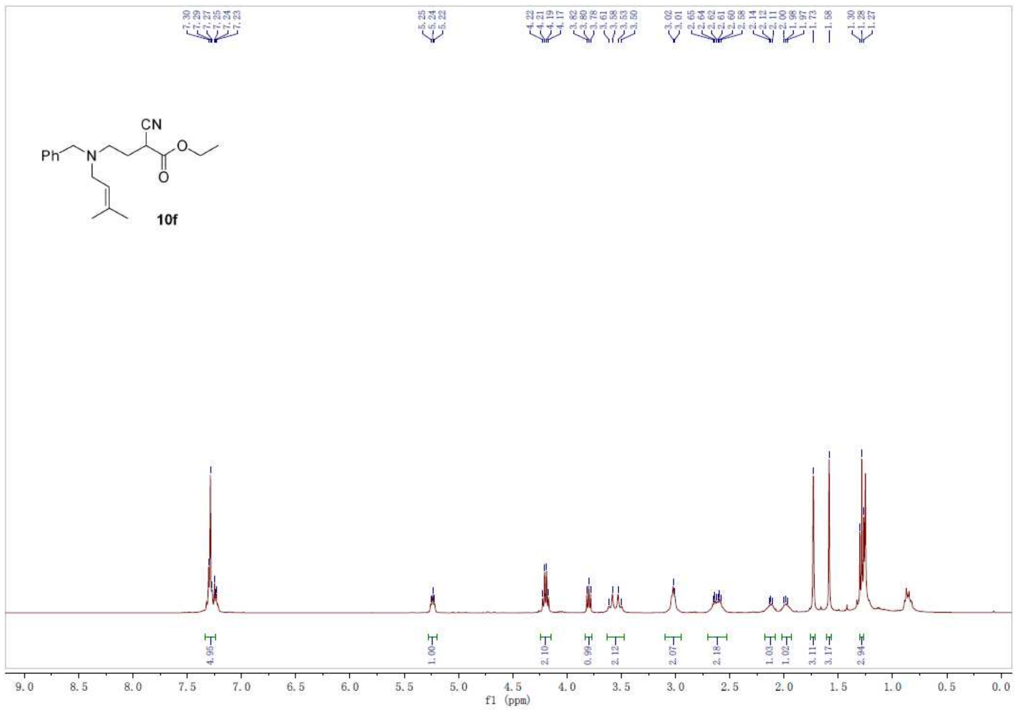

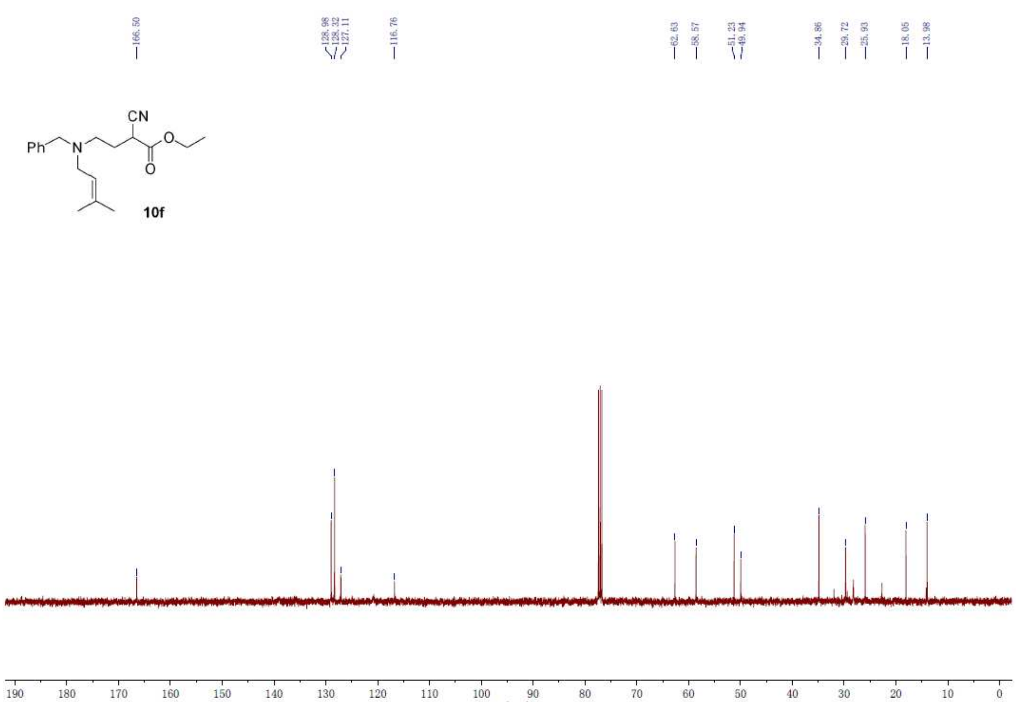

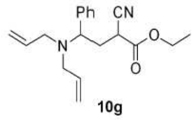

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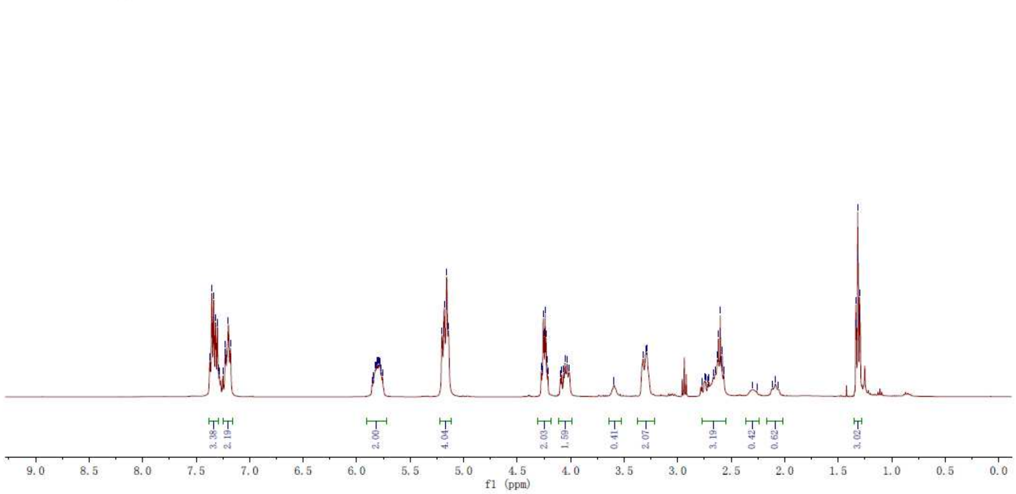

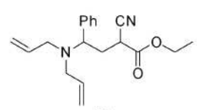

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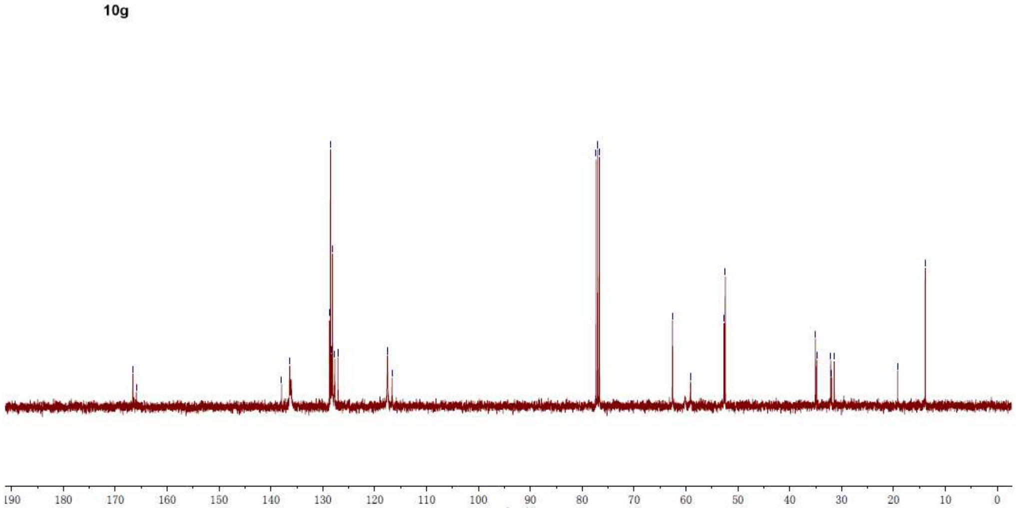

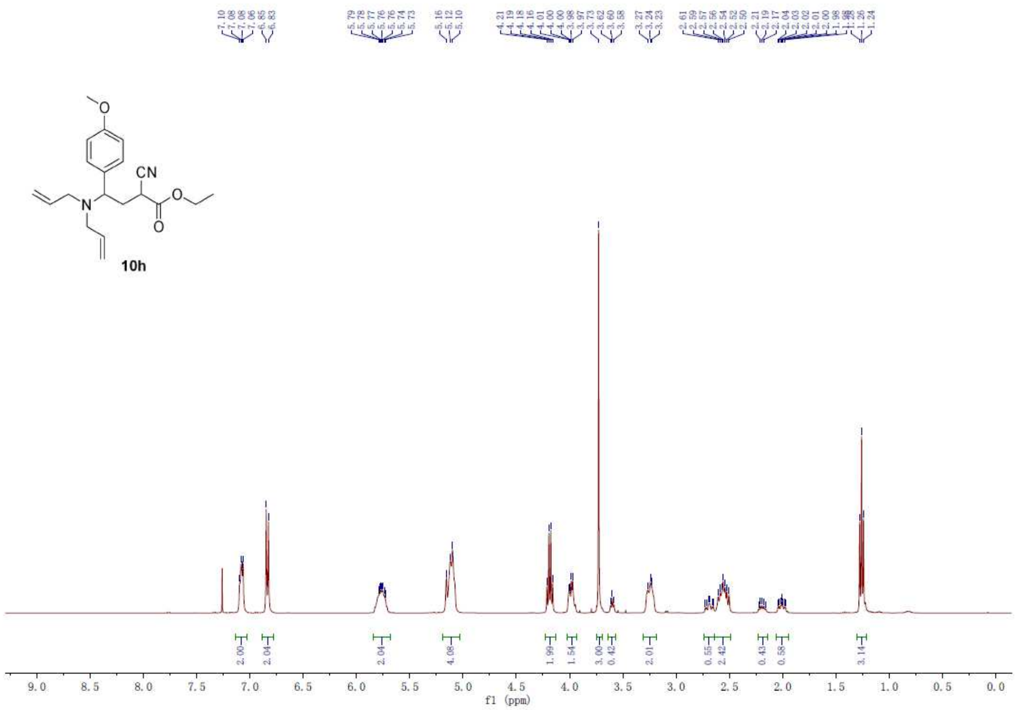
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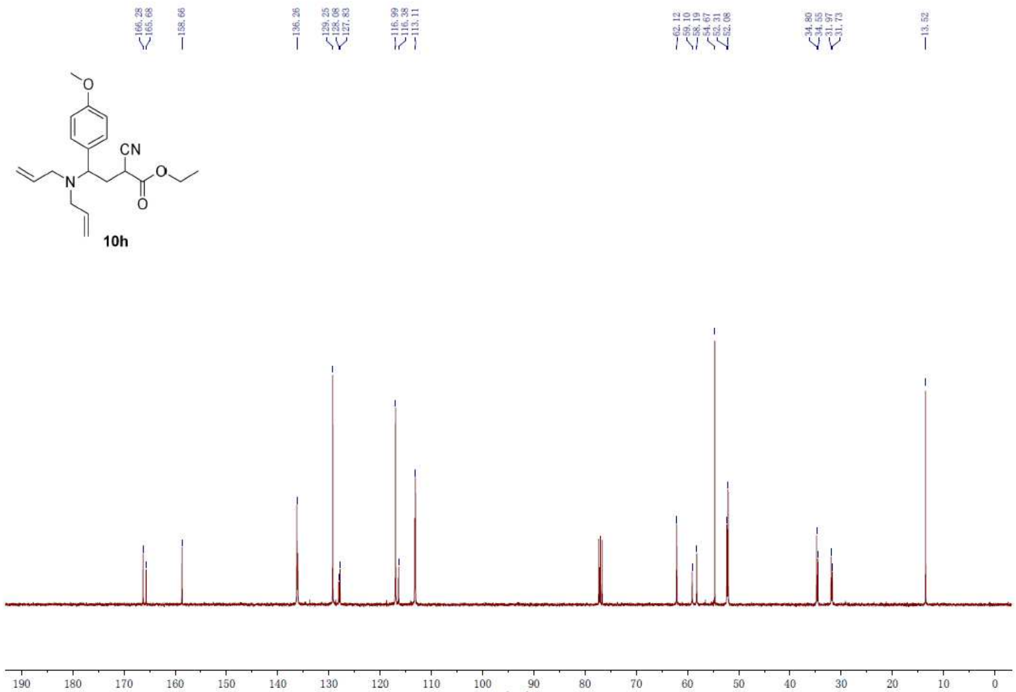
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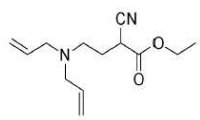

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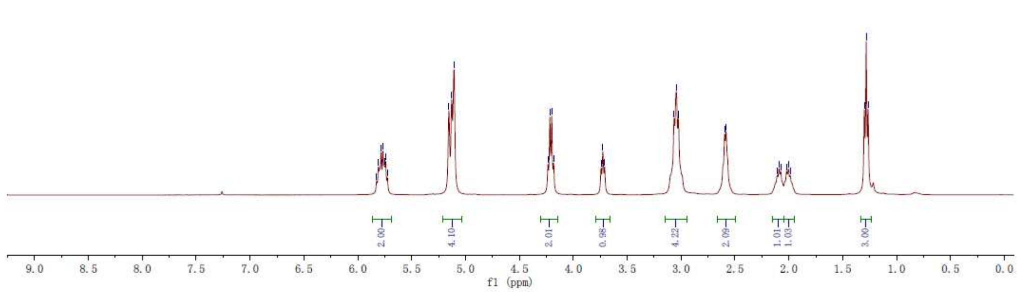

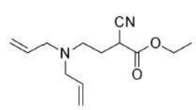

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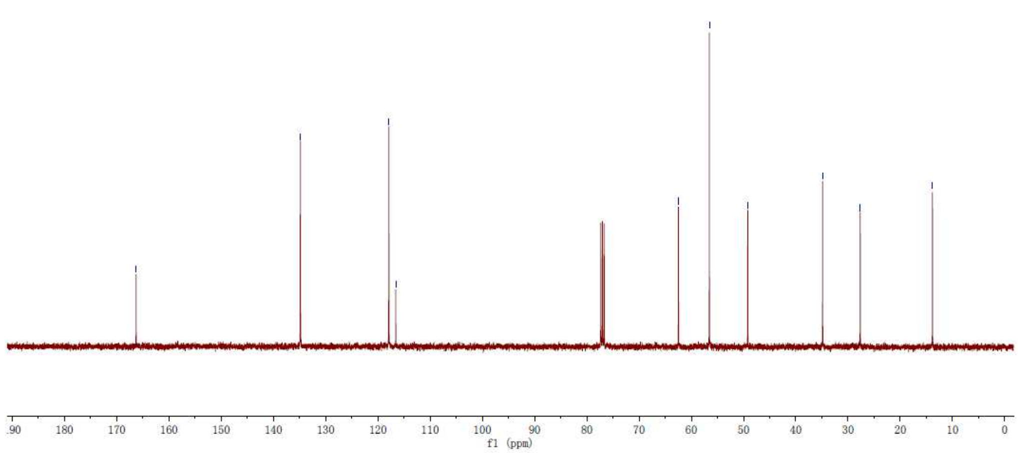

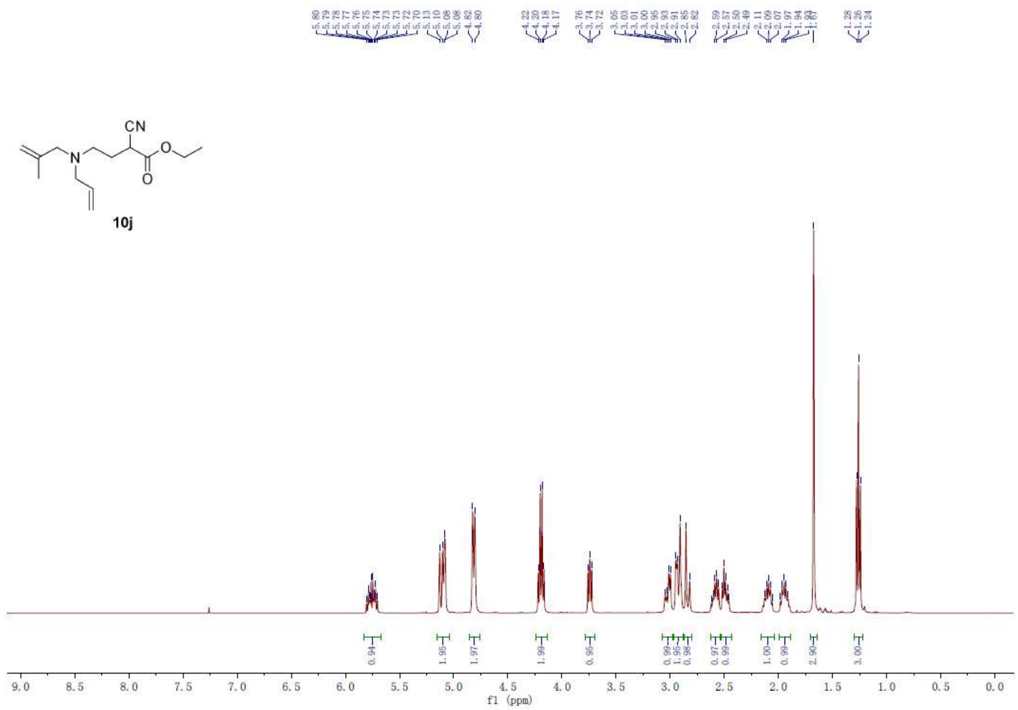
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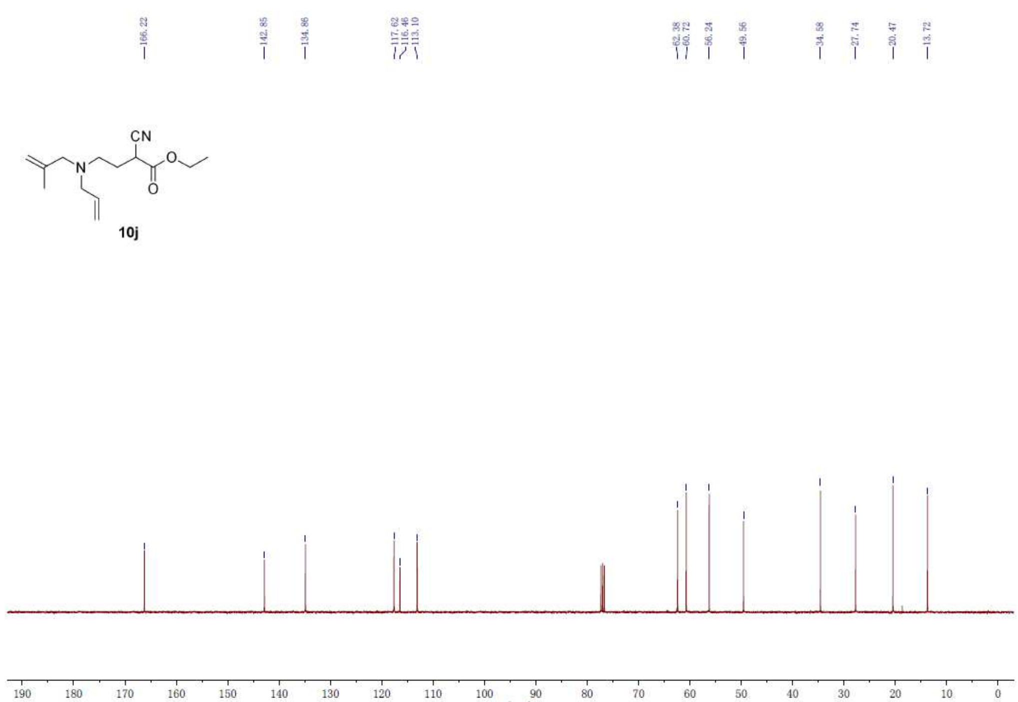
O
N
10j
f1 (ppm)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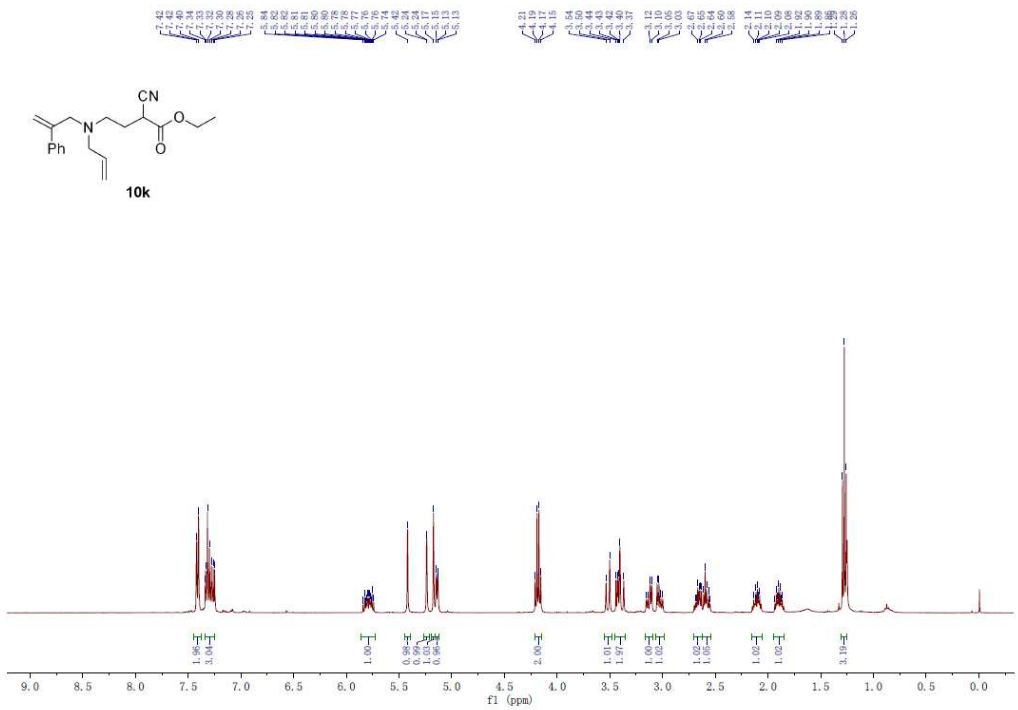
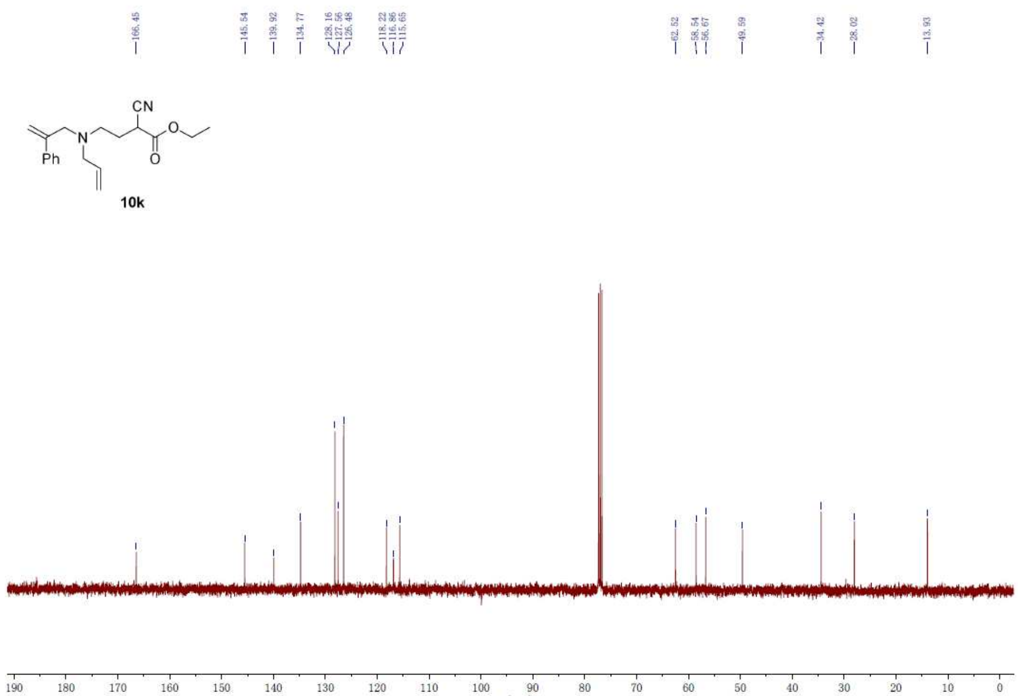
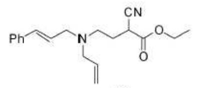
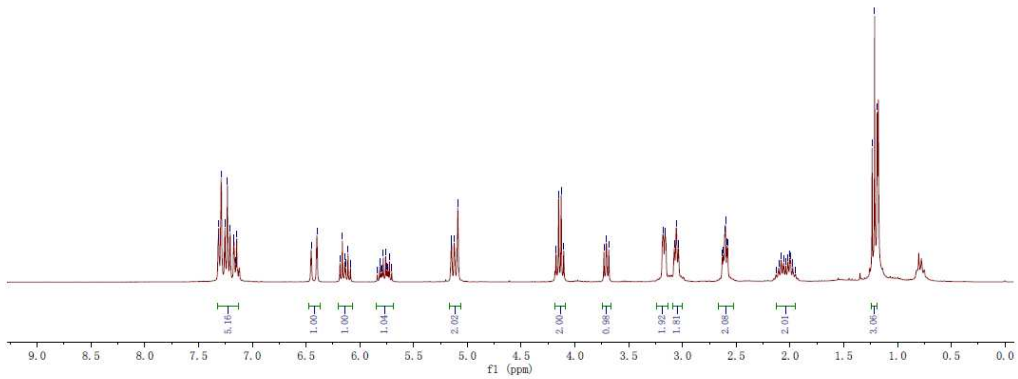
CN
O
O
N
10j
f1 (ppm)

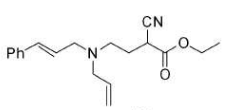






10l





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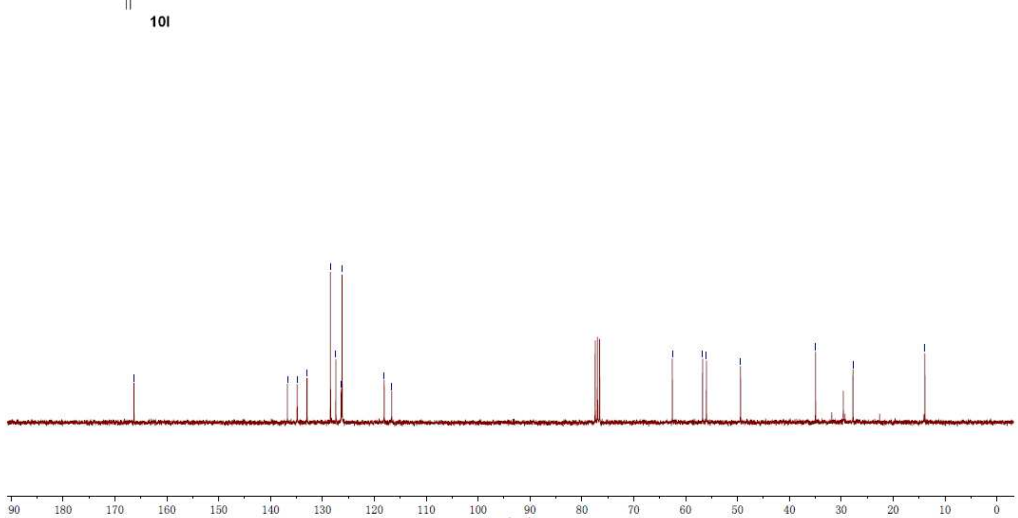

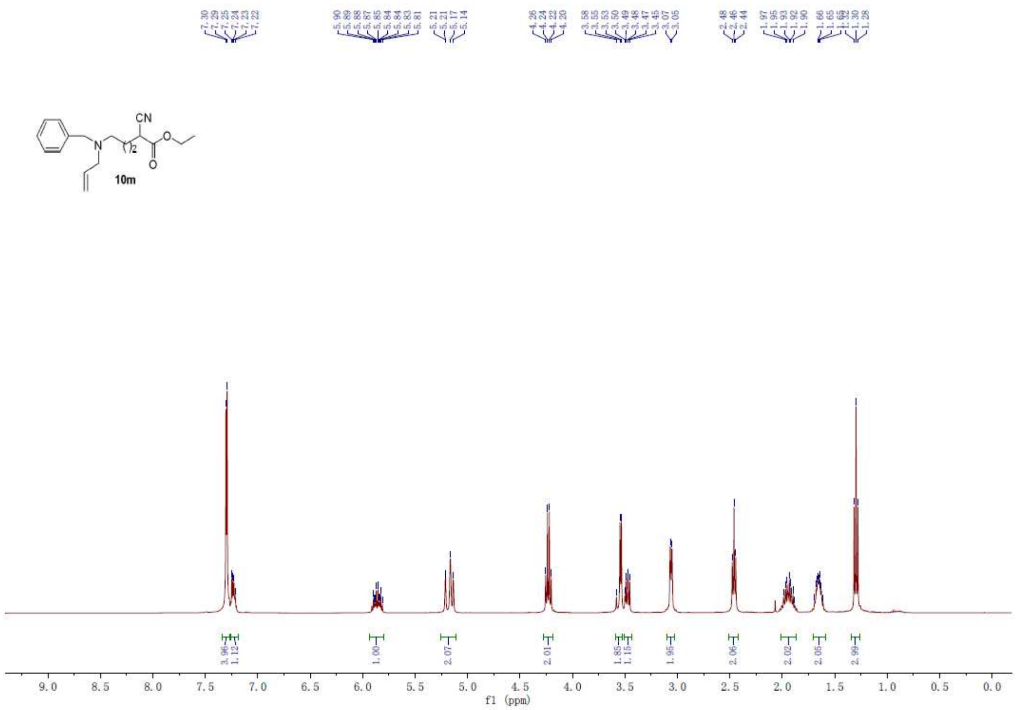
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N
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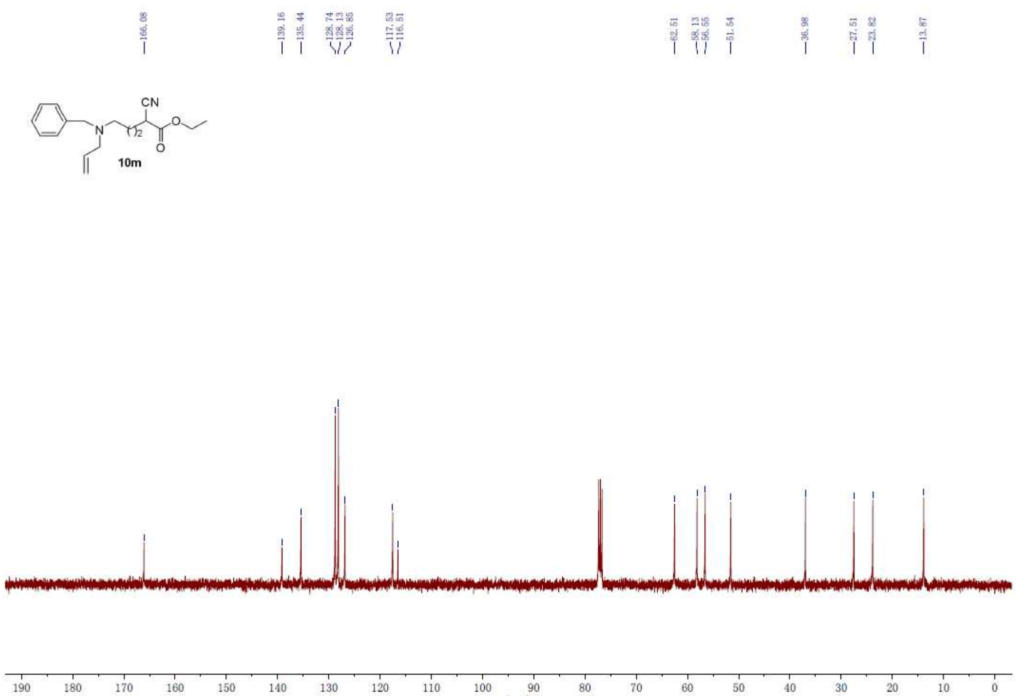
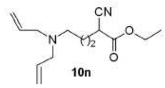
O
O
10m
f1 (ppm)


CN
N
2
O
O
10m
f1 (ppm)



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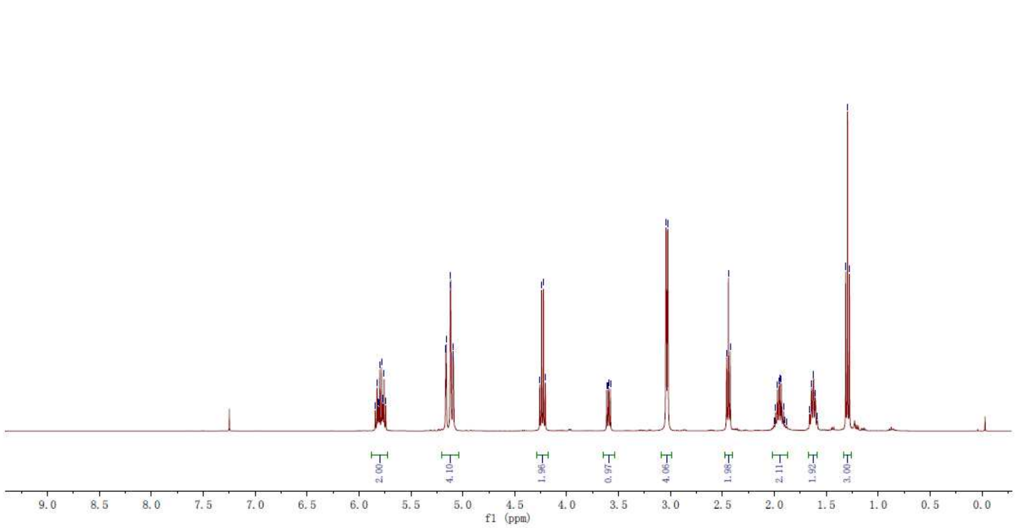
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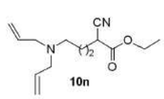
4.26 4.24 4.22 4.21
3.61 3.60 3.59 3.58
3.04 3.03
2.46 2.44 2.43
1.97 1.95 1.95 1.93 1.91
1.64 1.62 1.62 1.29 1.28
2.00 4.10 1.96 0.97 4.06 1.98 2.11 1.92 3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



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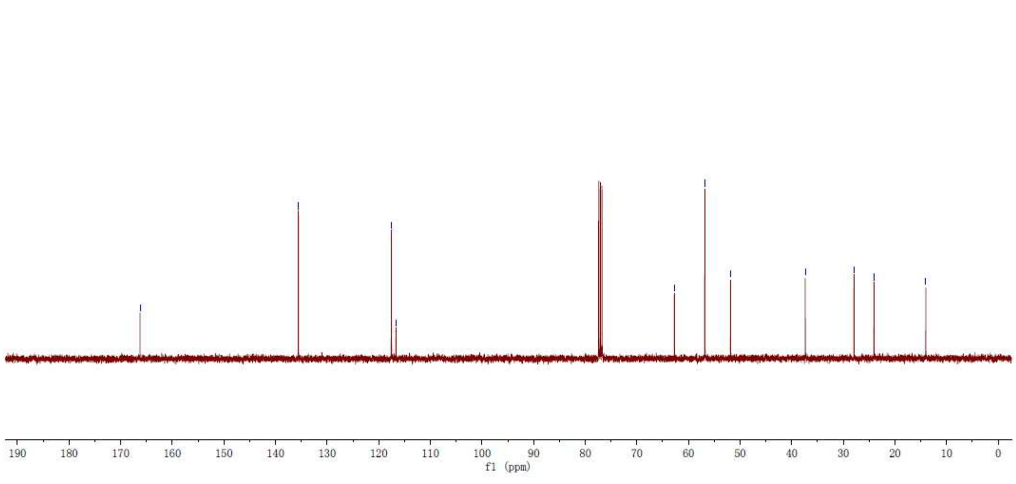
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135.57
117.56 116.65
62.72
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37.37
27.92
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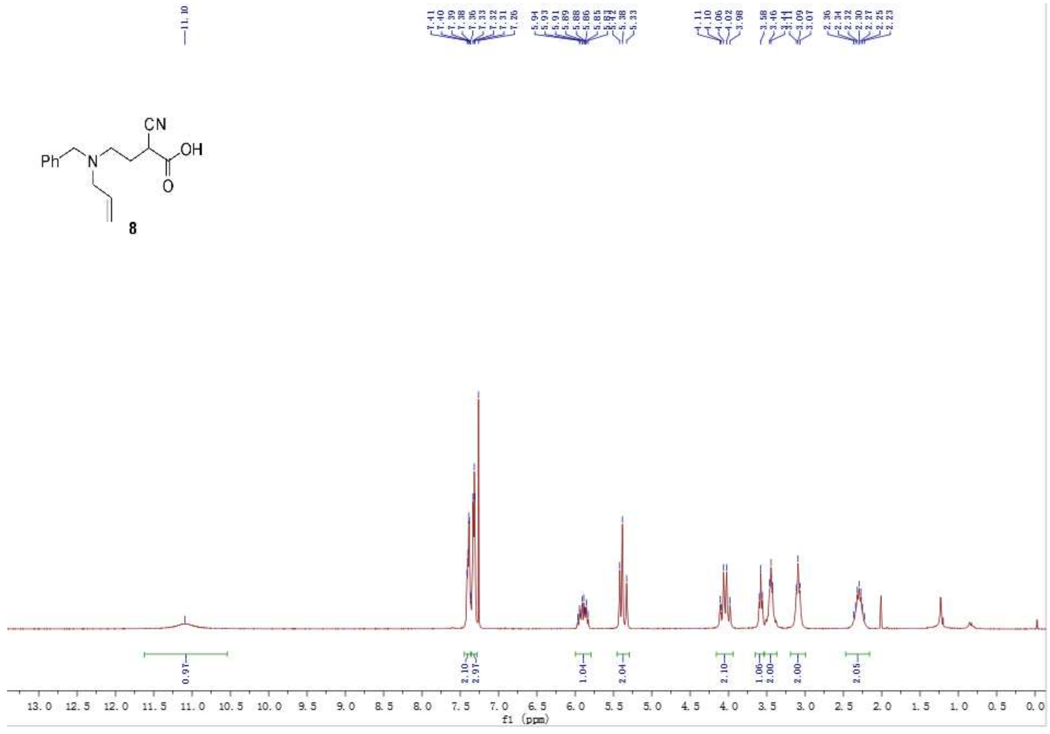
f1 (ppm)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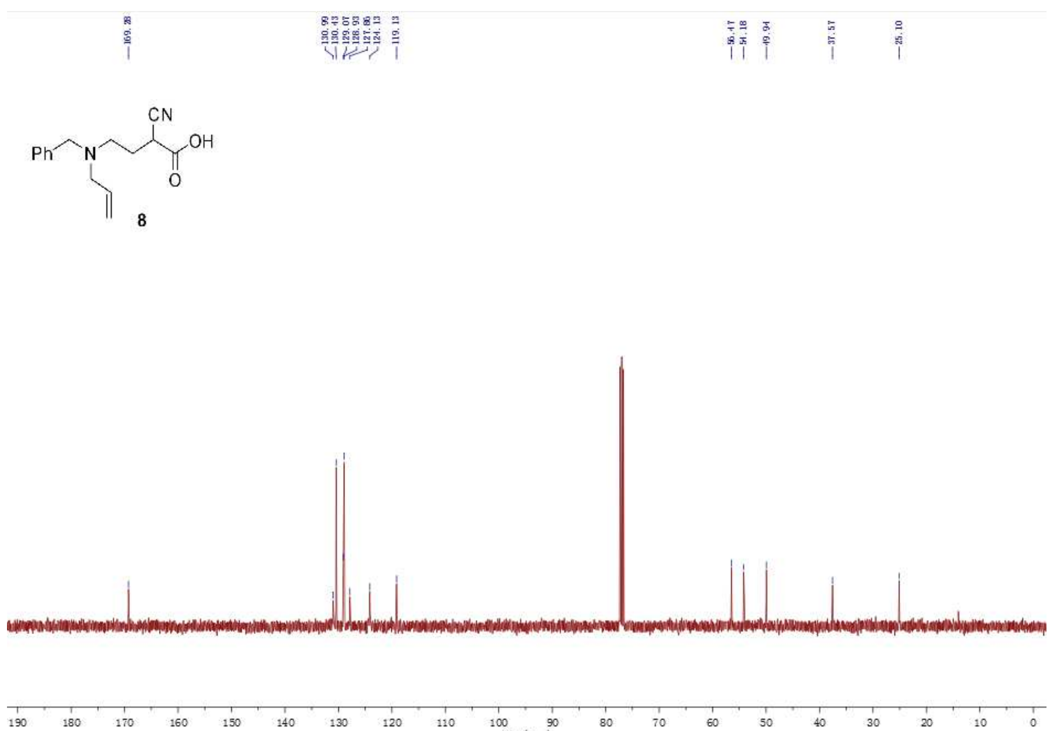
Ph
N
OH
O
8
f1 (ppm)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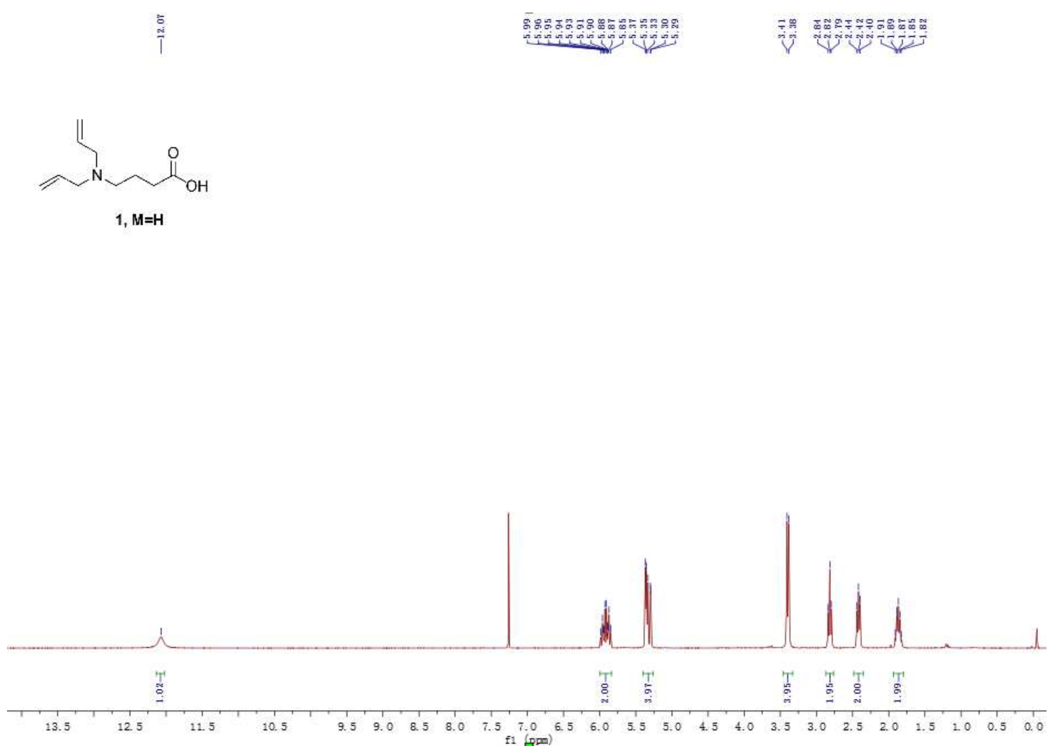
Ph
N
OH
O
8
f1 (ppm)



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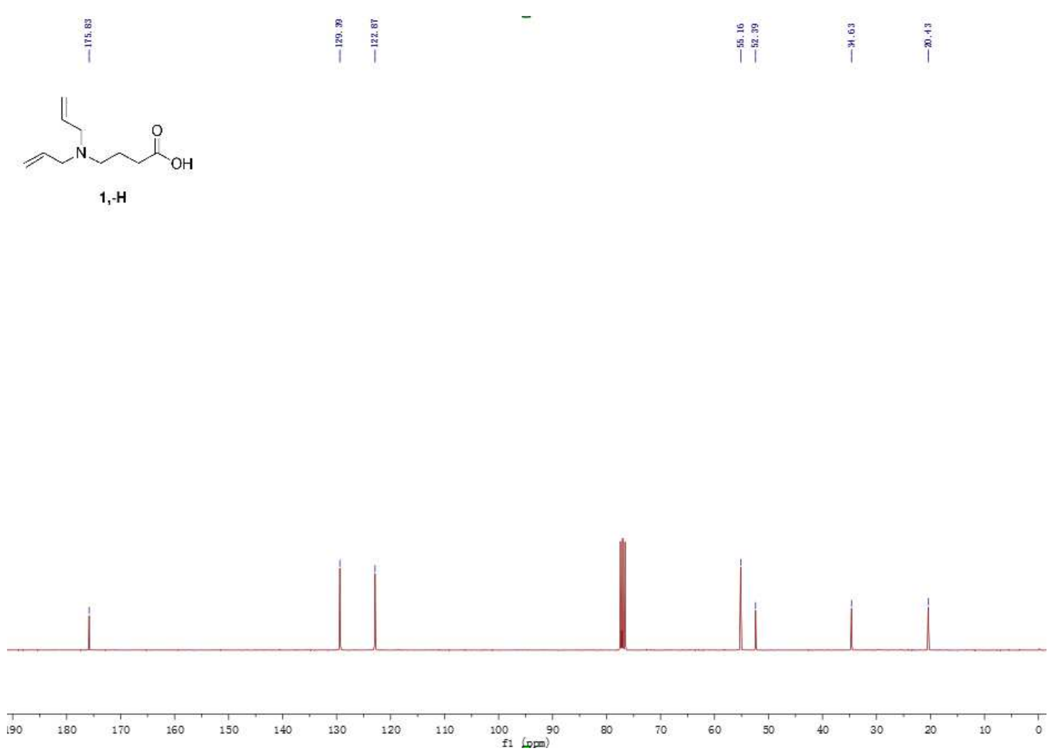
5.96
5.95
5.94
5.93
5.91
5.90
5.88
5.87
5.85
5.37
5.35
5.33
5.30
5.29
3.41
3.38
2.84
2.82
2.79
2.44
2.42
2.40
1.91
1.89
1.87
1.85
1.82
1.02
2.00
3.91
3.95
1.95
2.00
1.99
f1 (ppm)

1, M=H



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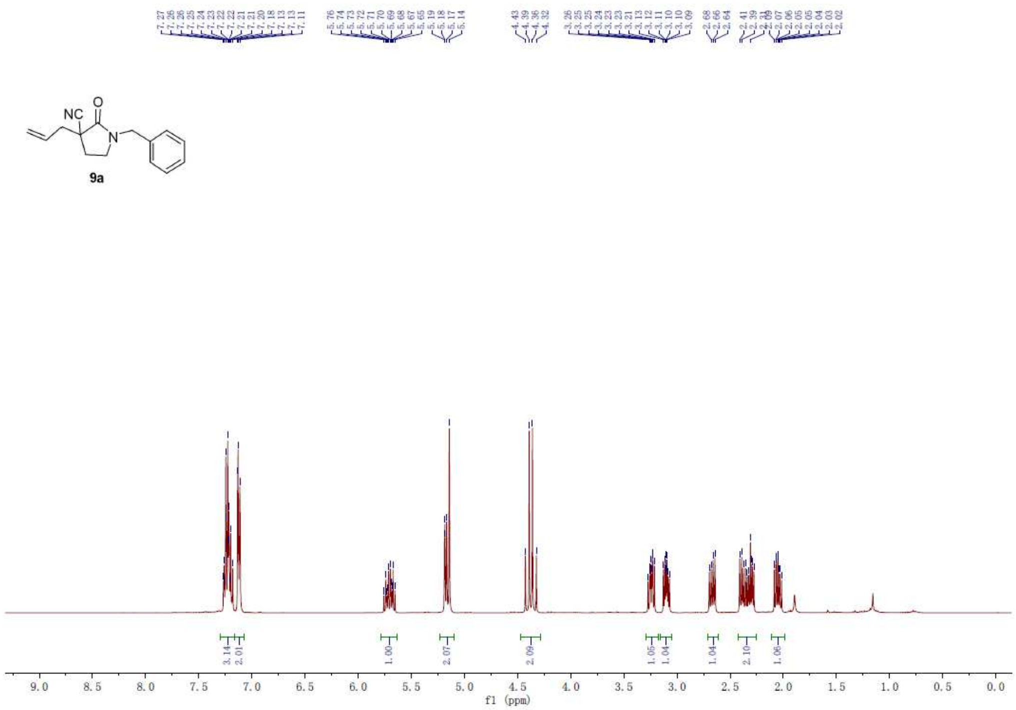
122.87
55.16
52.39
34.63
20.43
f1 (ppm)

1,-H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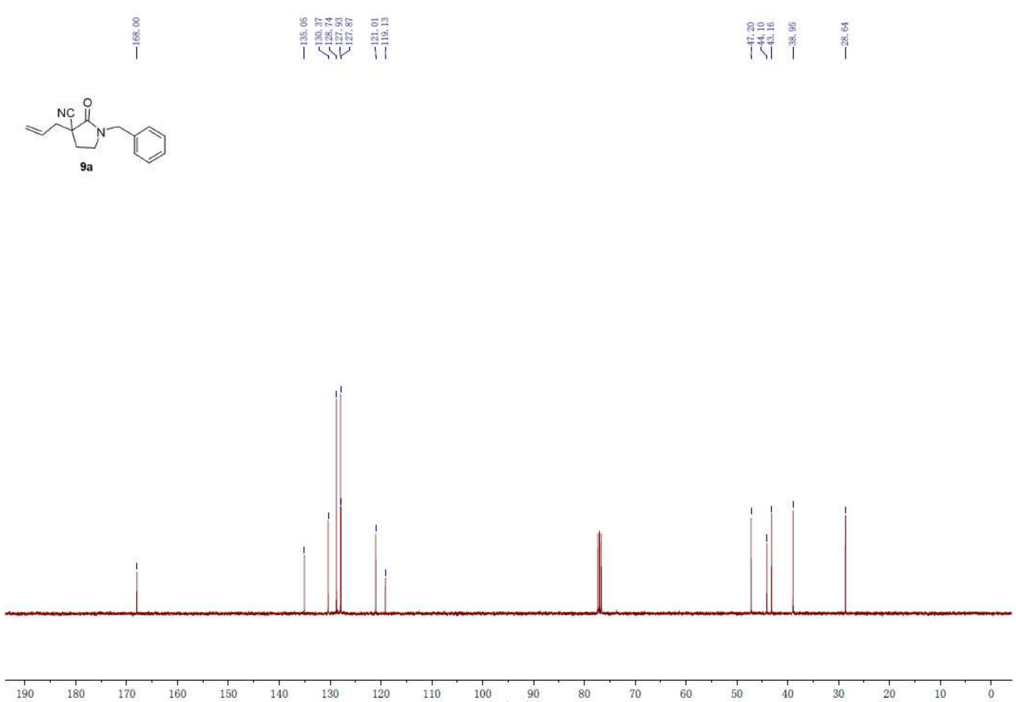
N
9a
f1 (ppm)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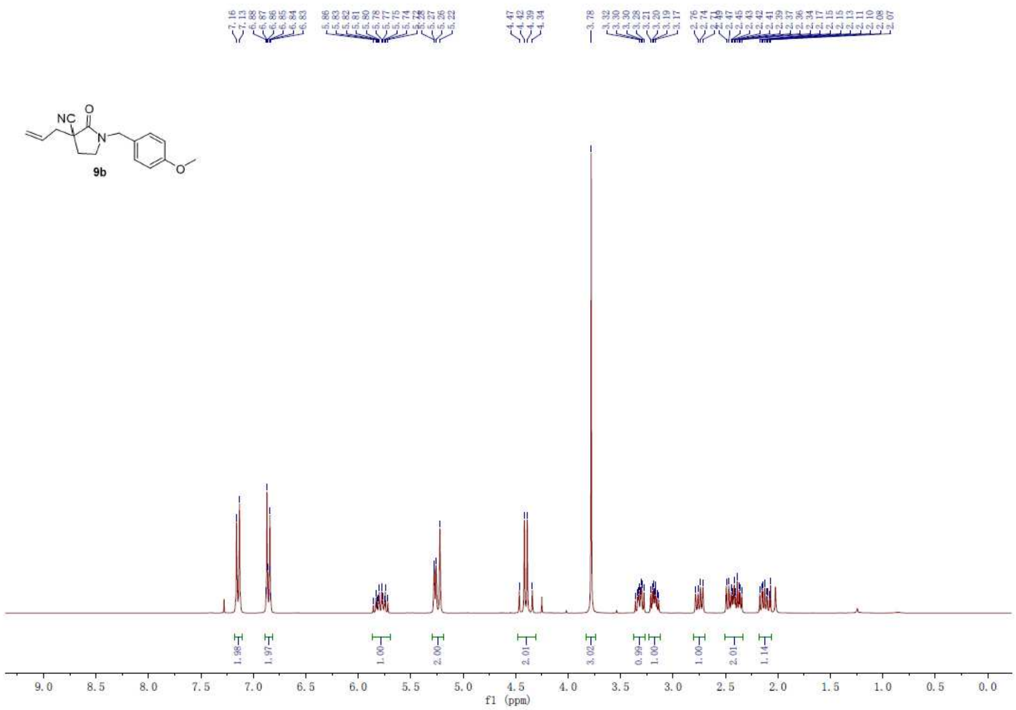
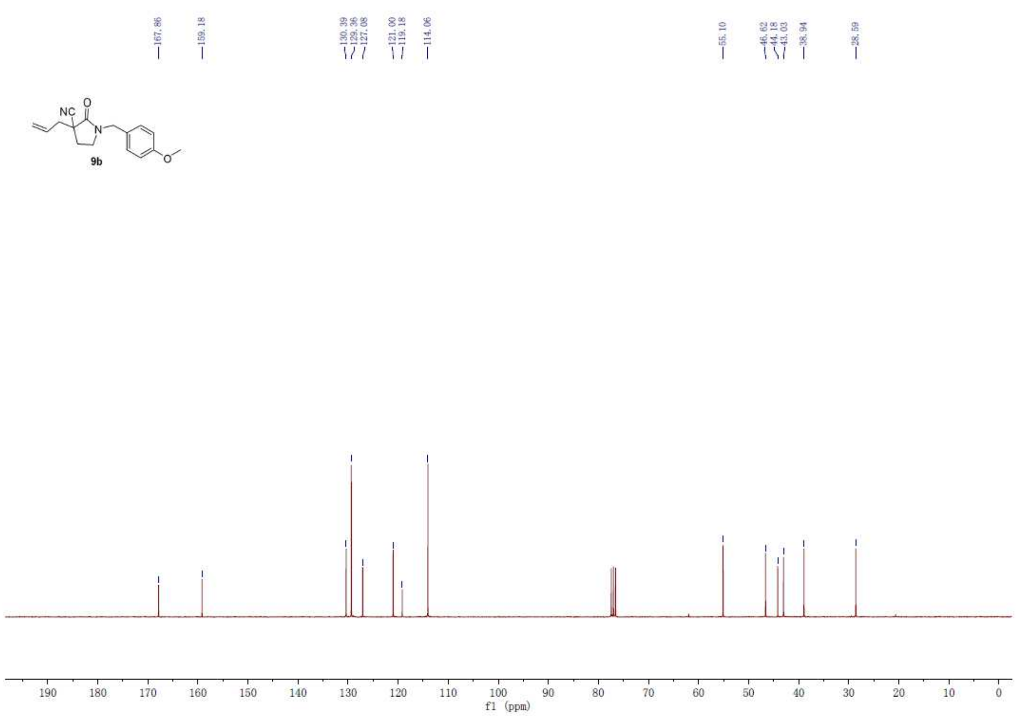
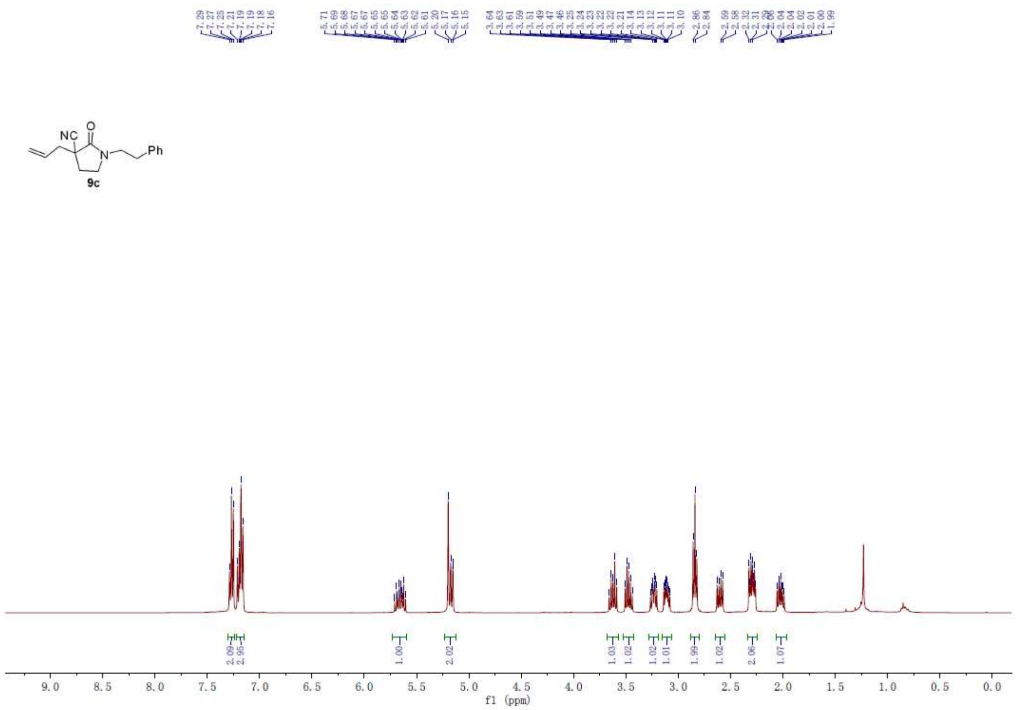
28.64
NC
O
N
9a
f1 (ppm)







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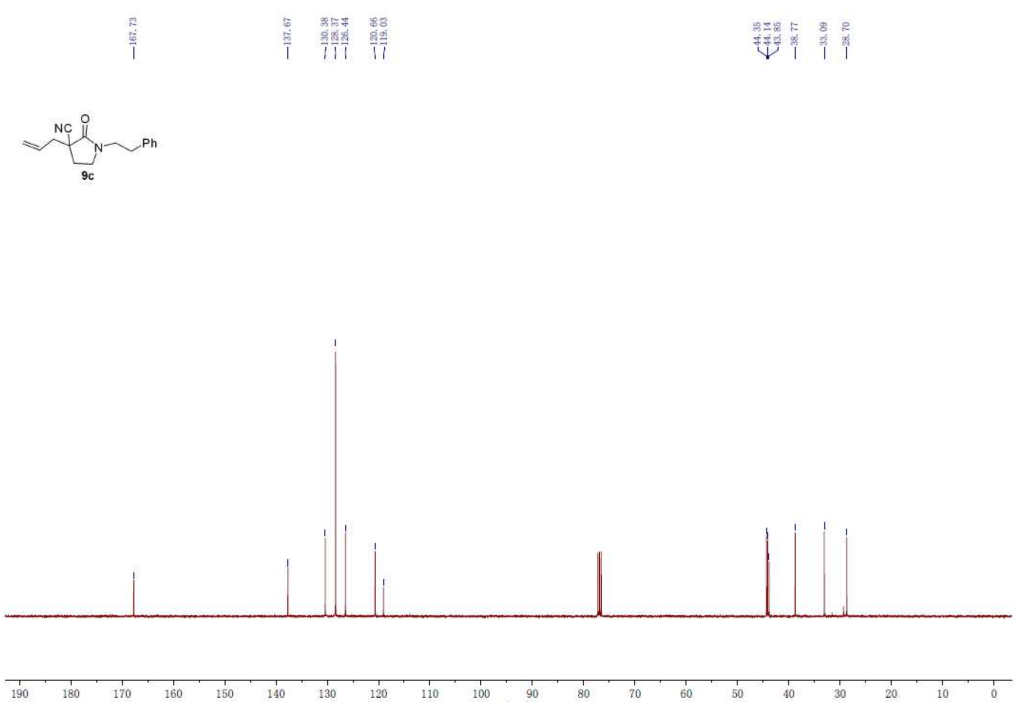

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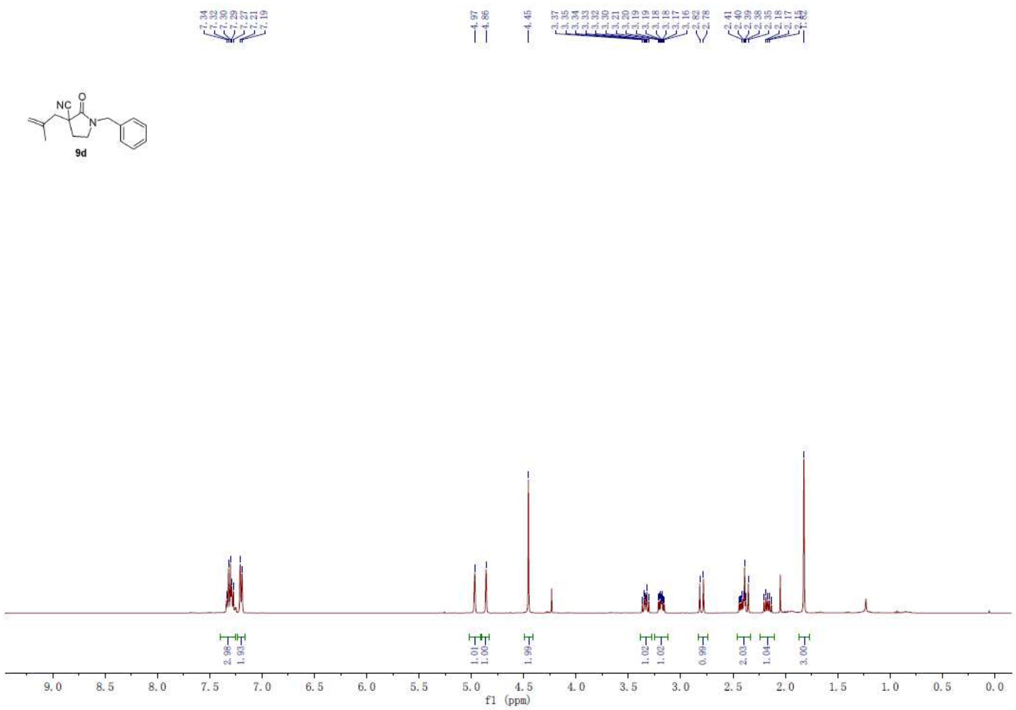
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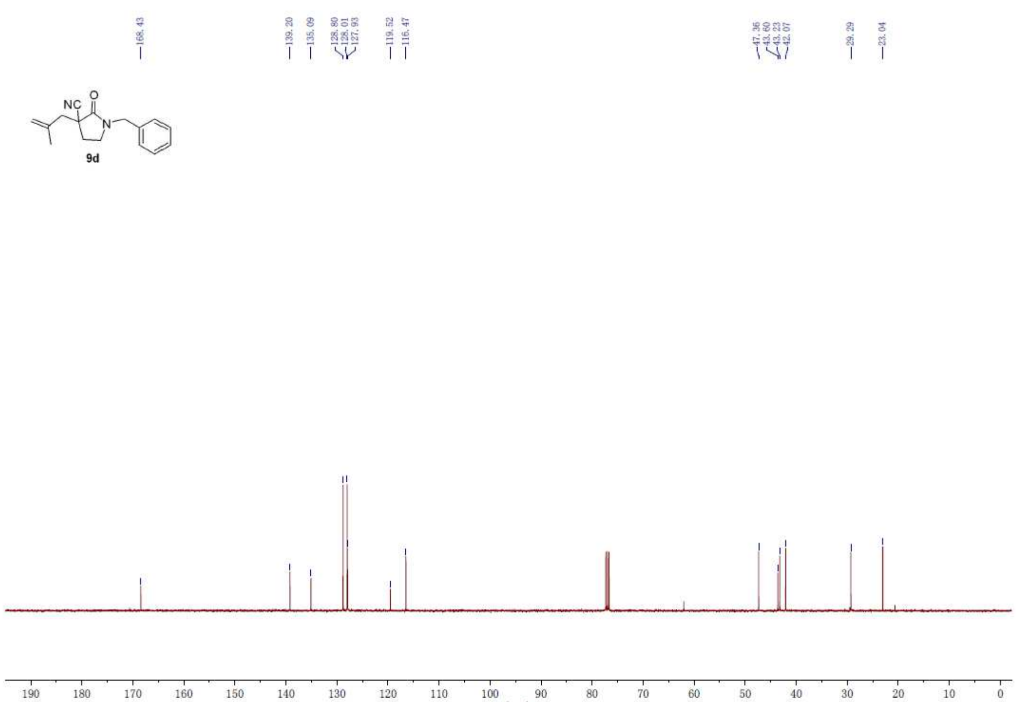
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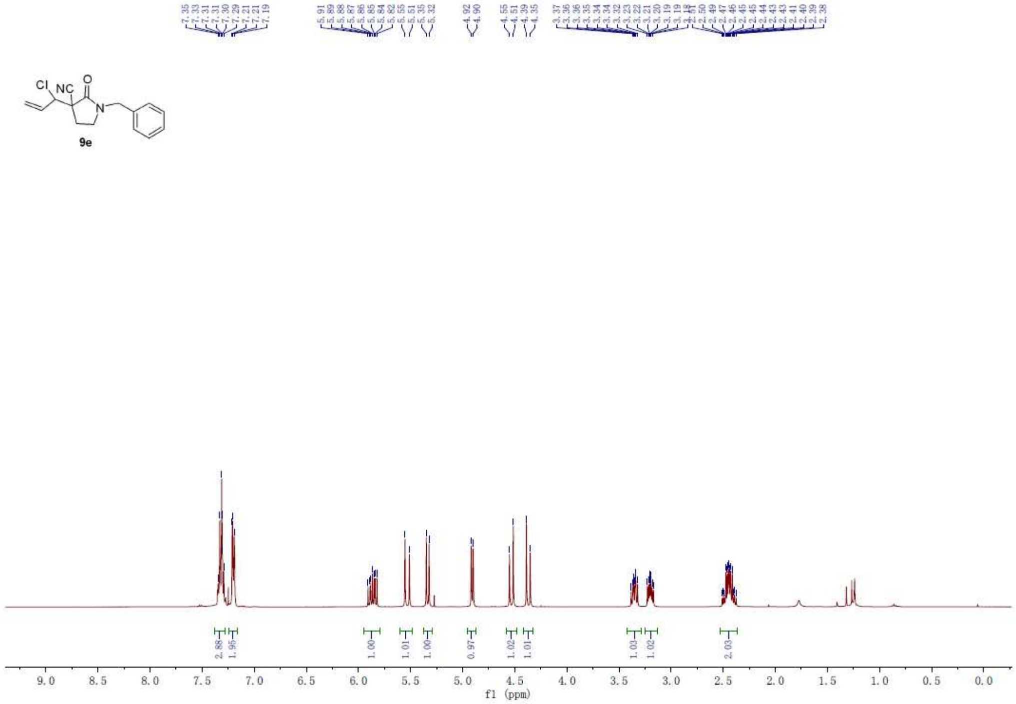
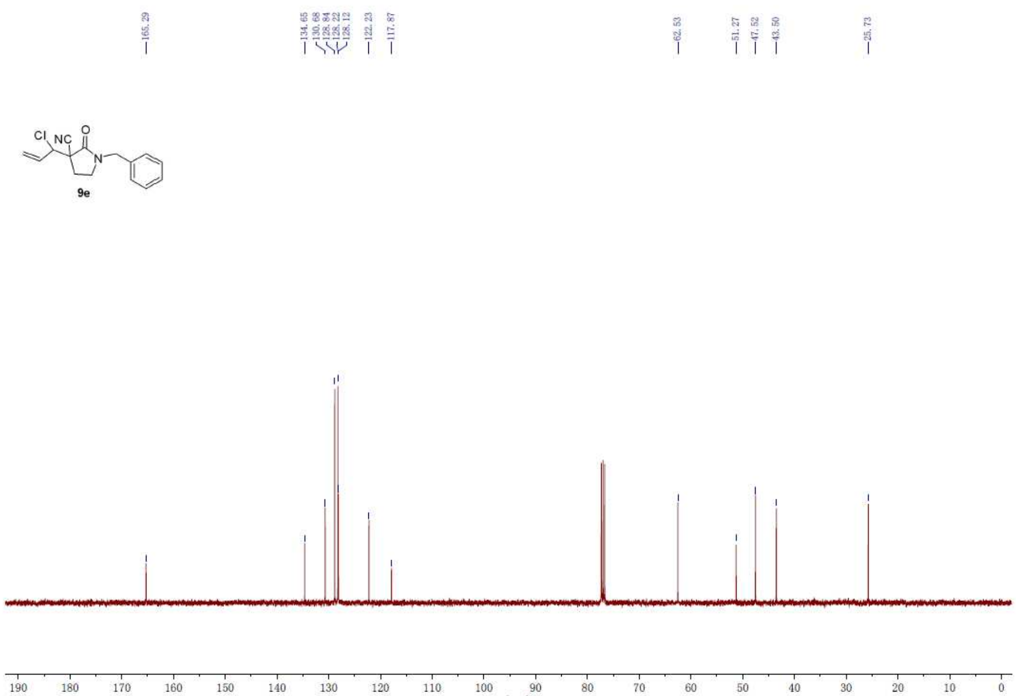
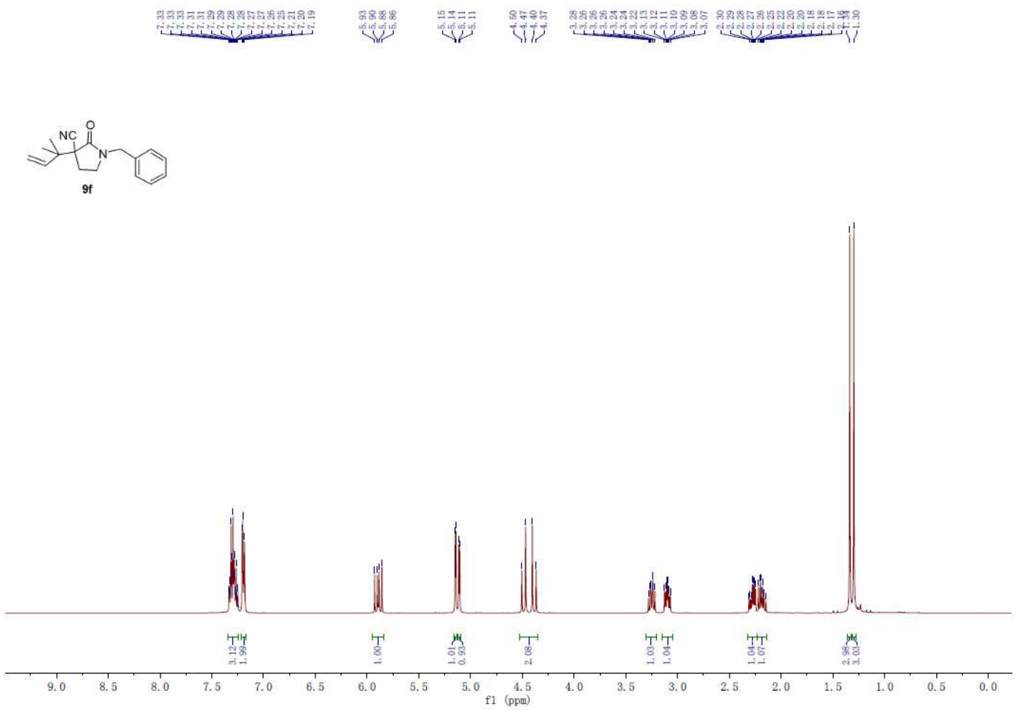
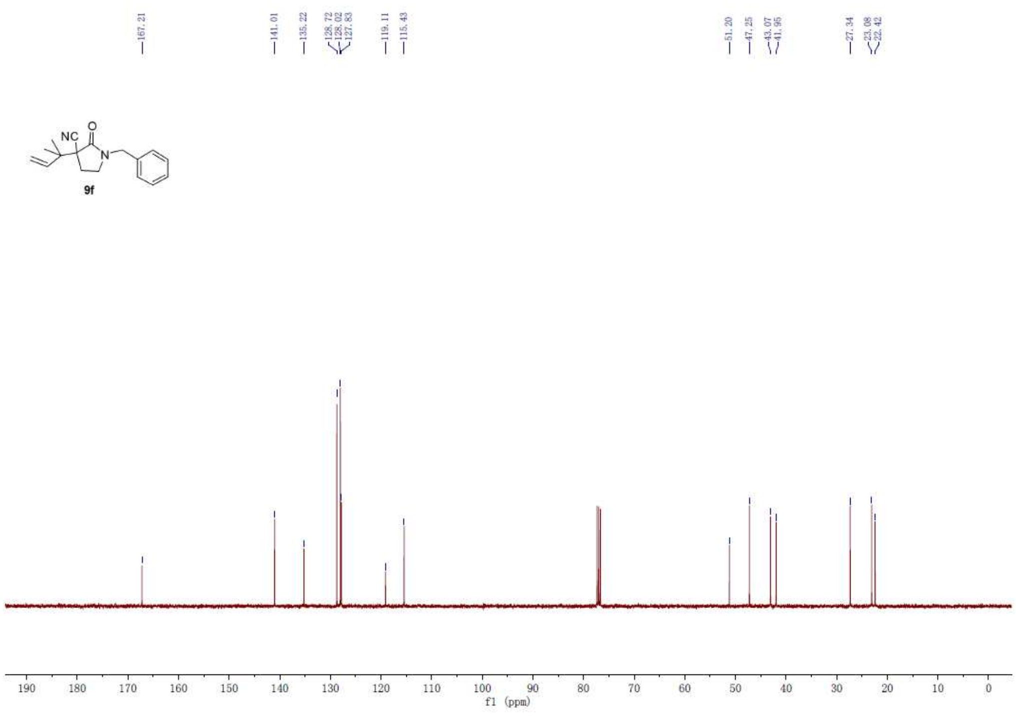





9f
f1 (ppm)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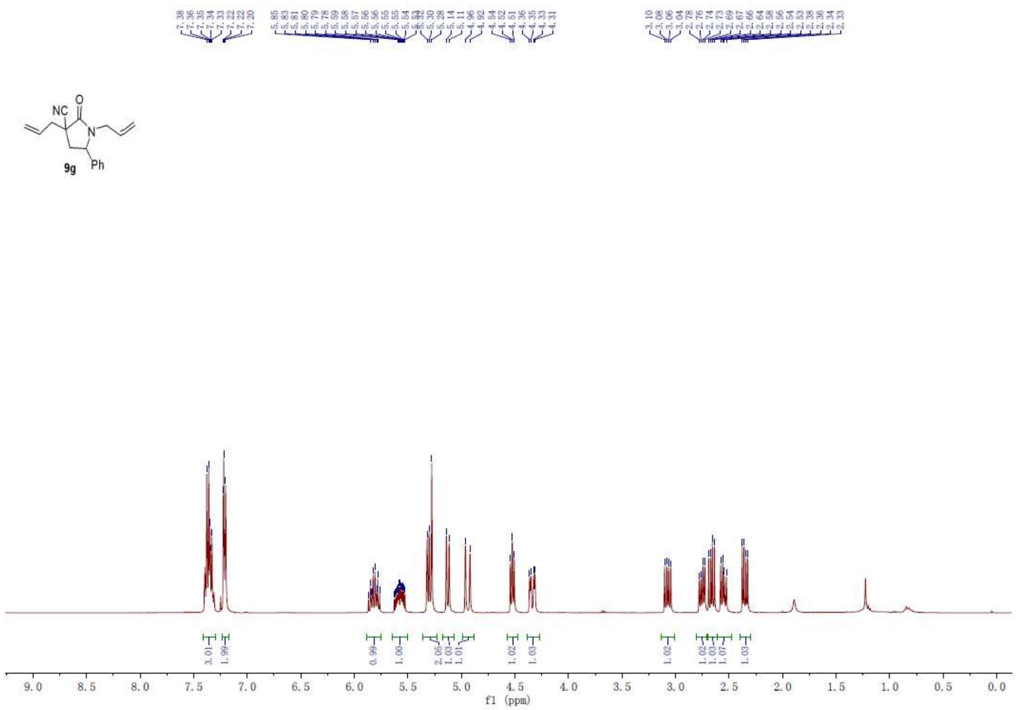
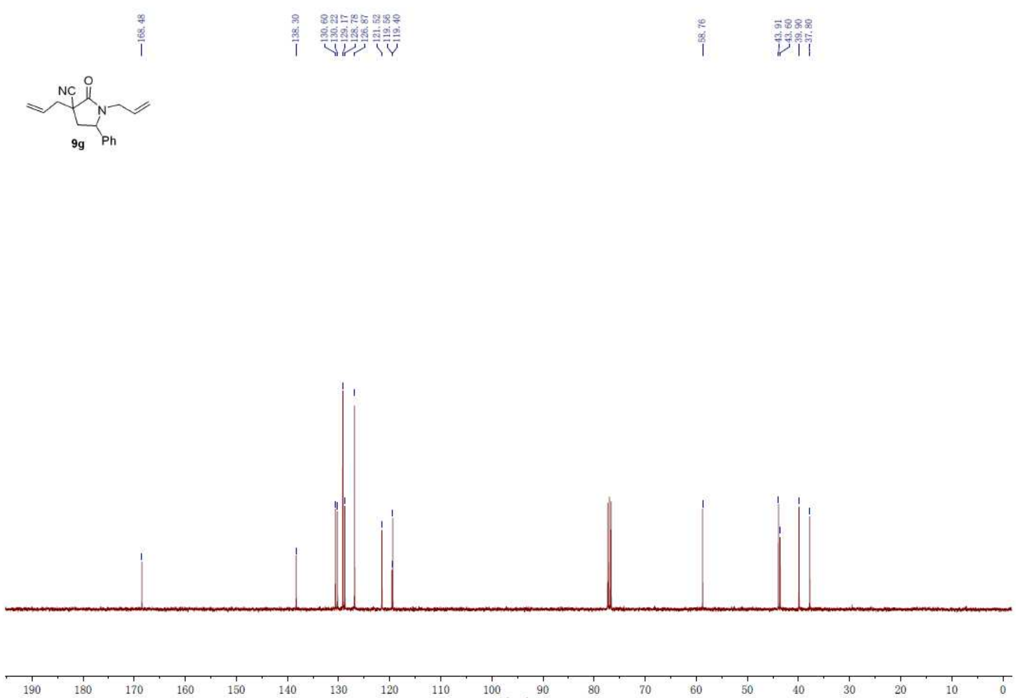
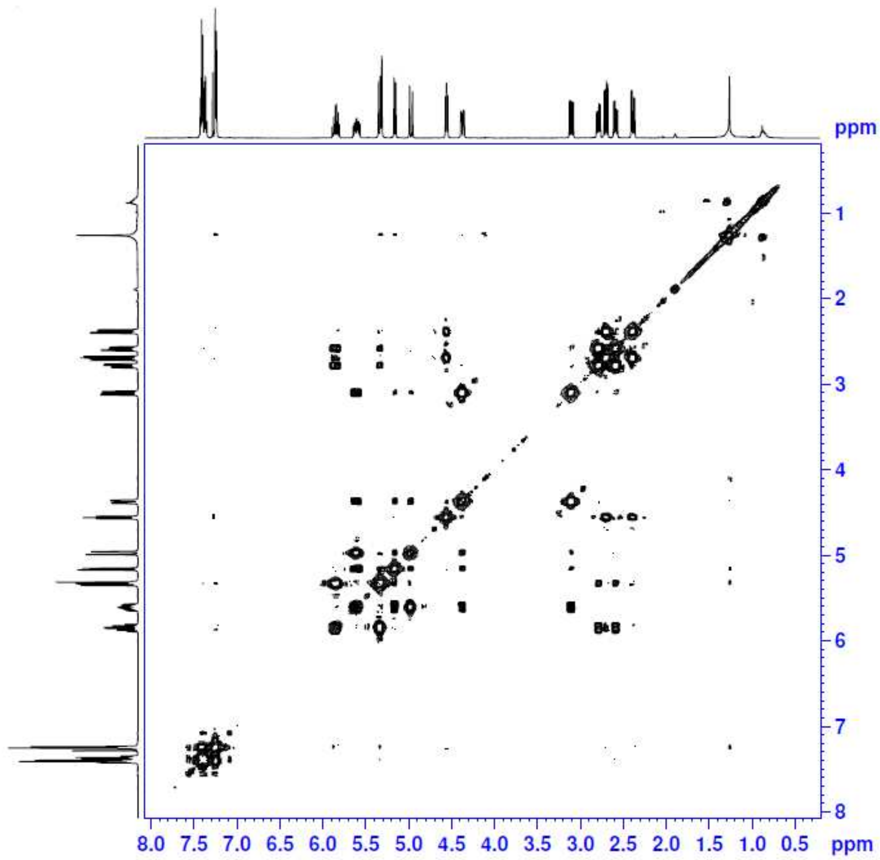
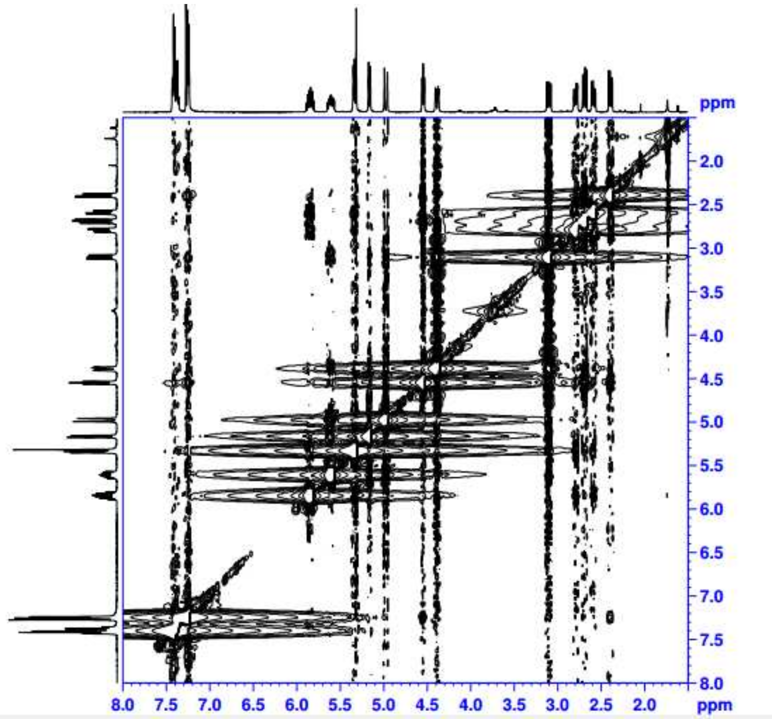


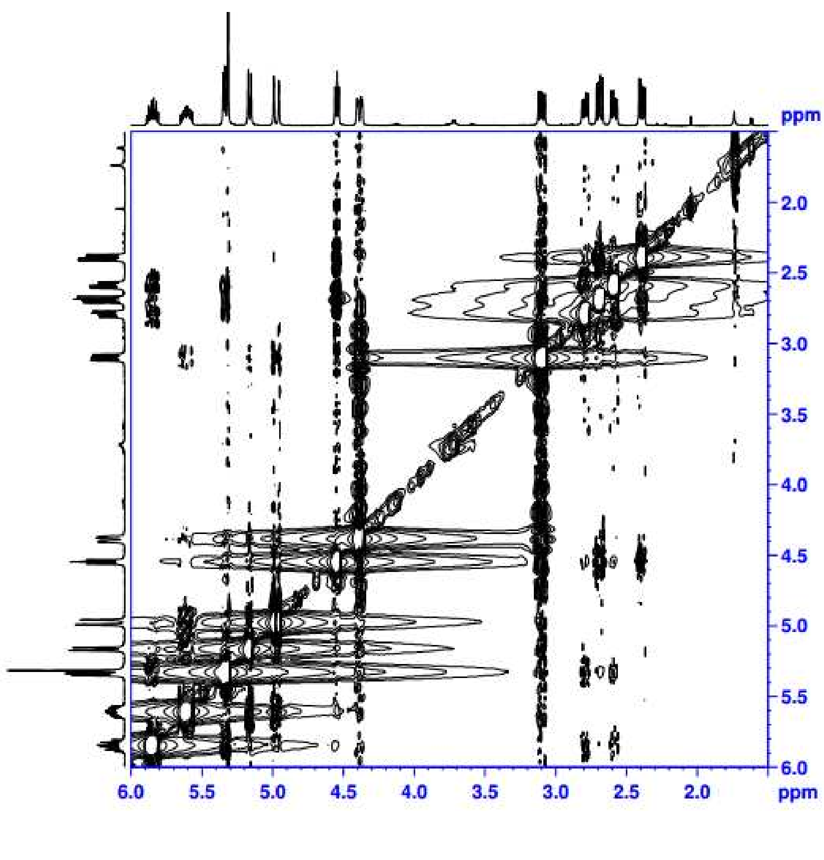


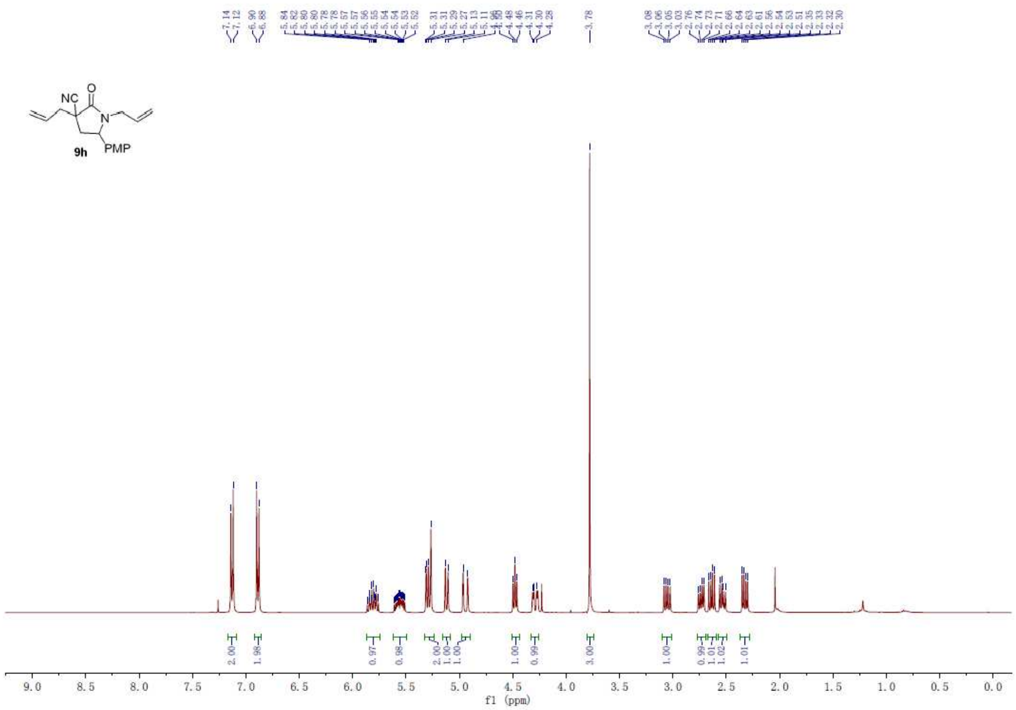
^{1}H-^{1}H Cosy spectra of 9g



^1H-^1H Noesy spectra of 9g



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O
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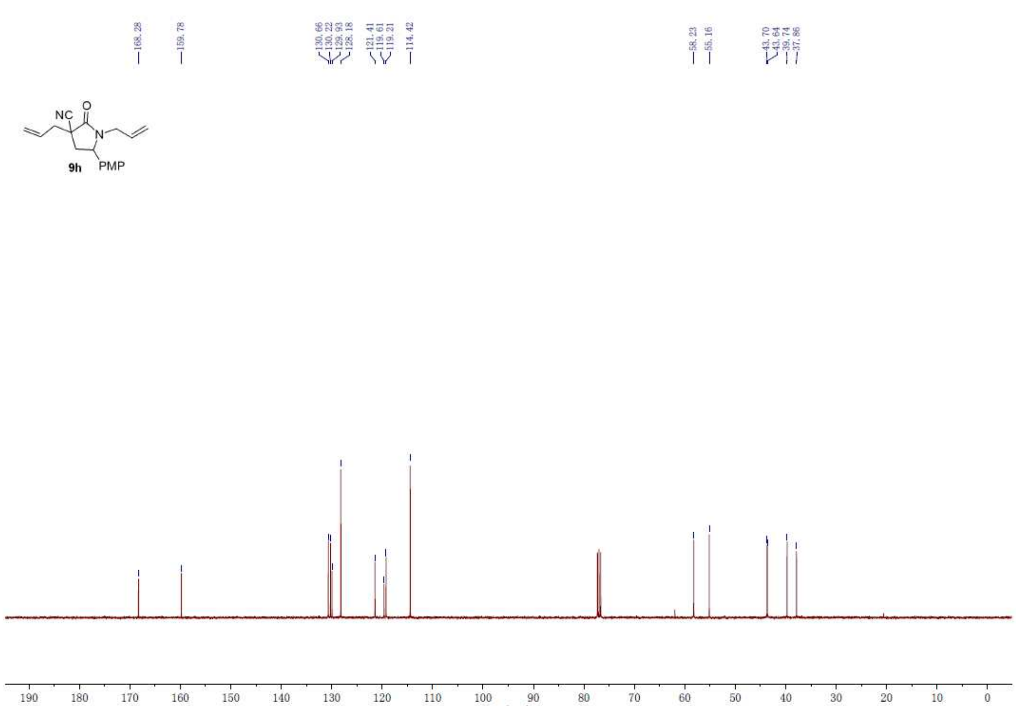
9h
PMP
f1 (ppm)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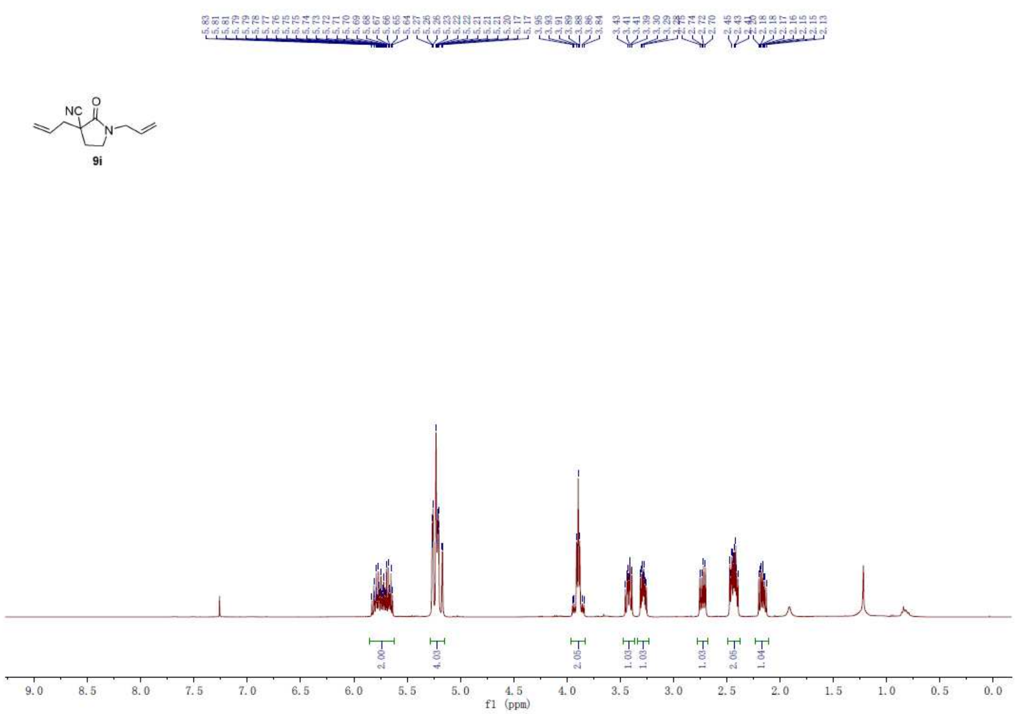
N
9h
PMP
f1 (ppm)



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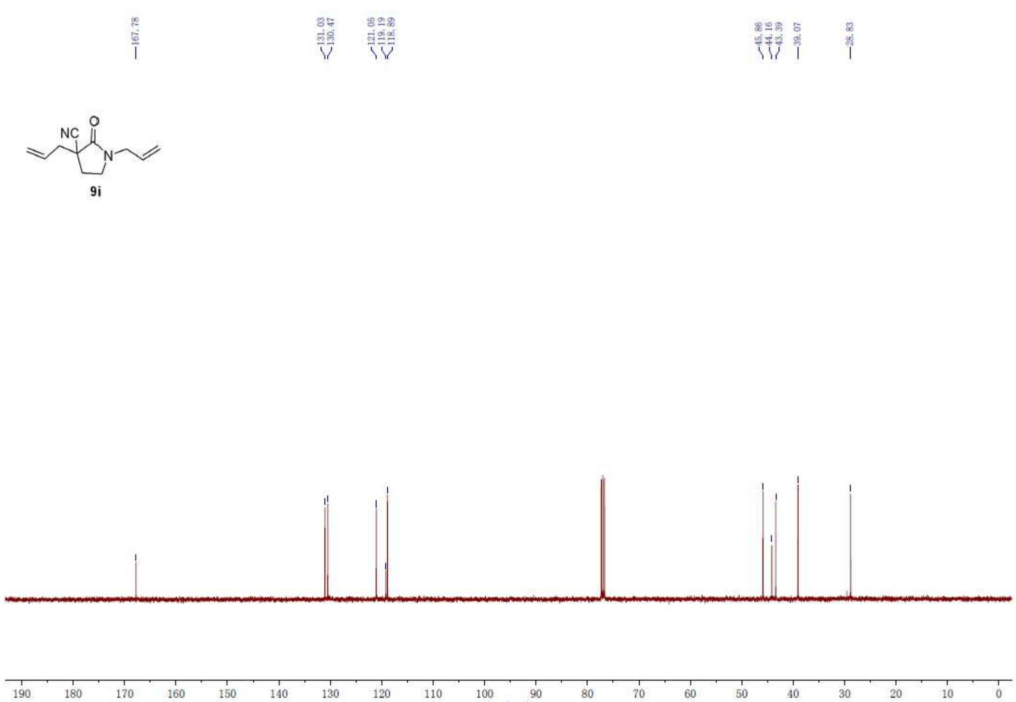

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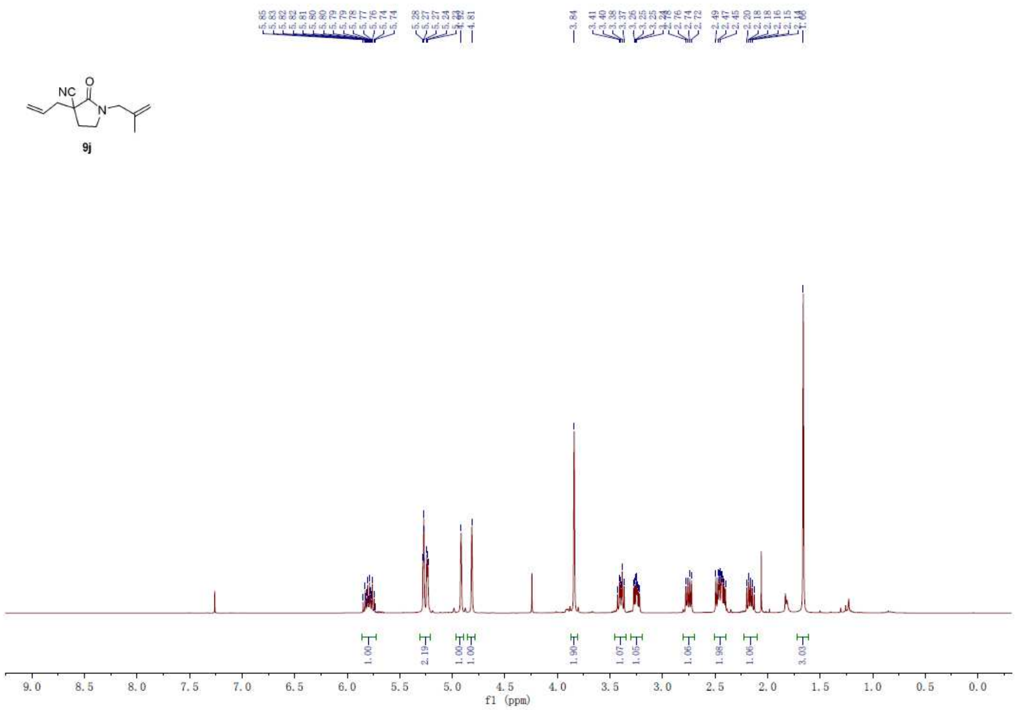

NC
O
N
1.00
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1.00
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1.05
1.06
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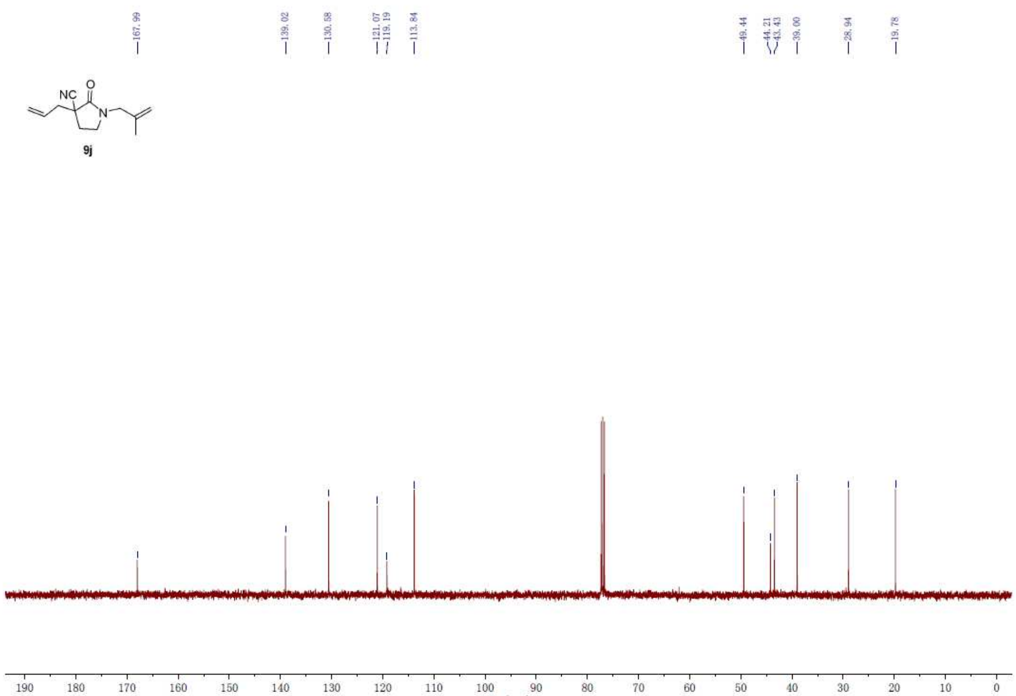
1.06
3.03
f1 (ppm)

9j



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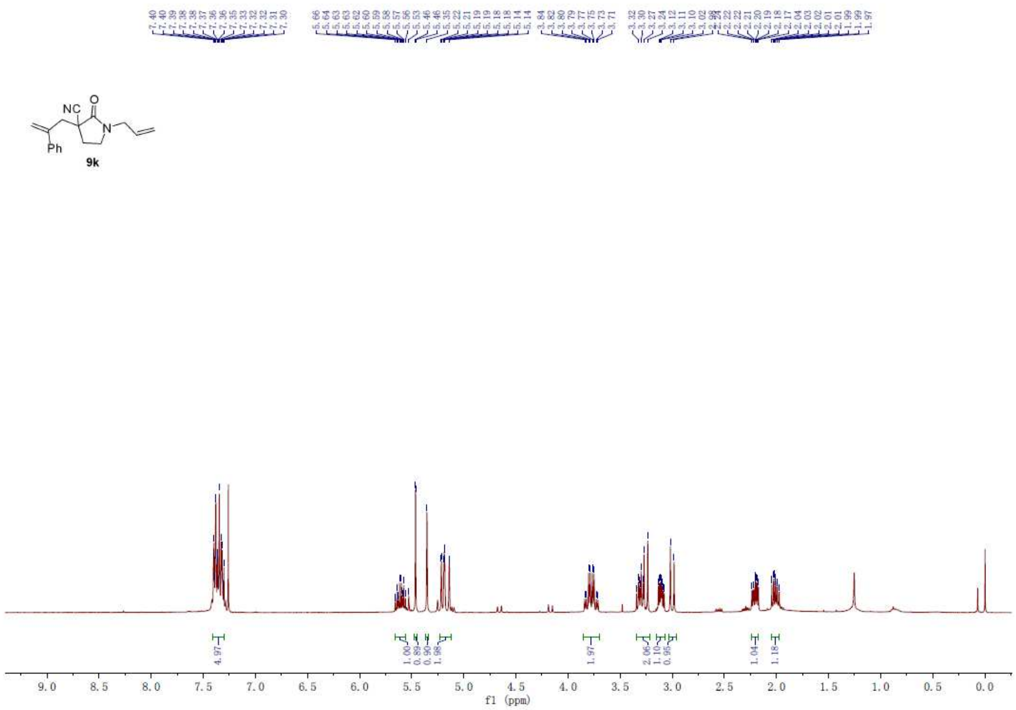
NC
O
N
f1 (ppm)

9j



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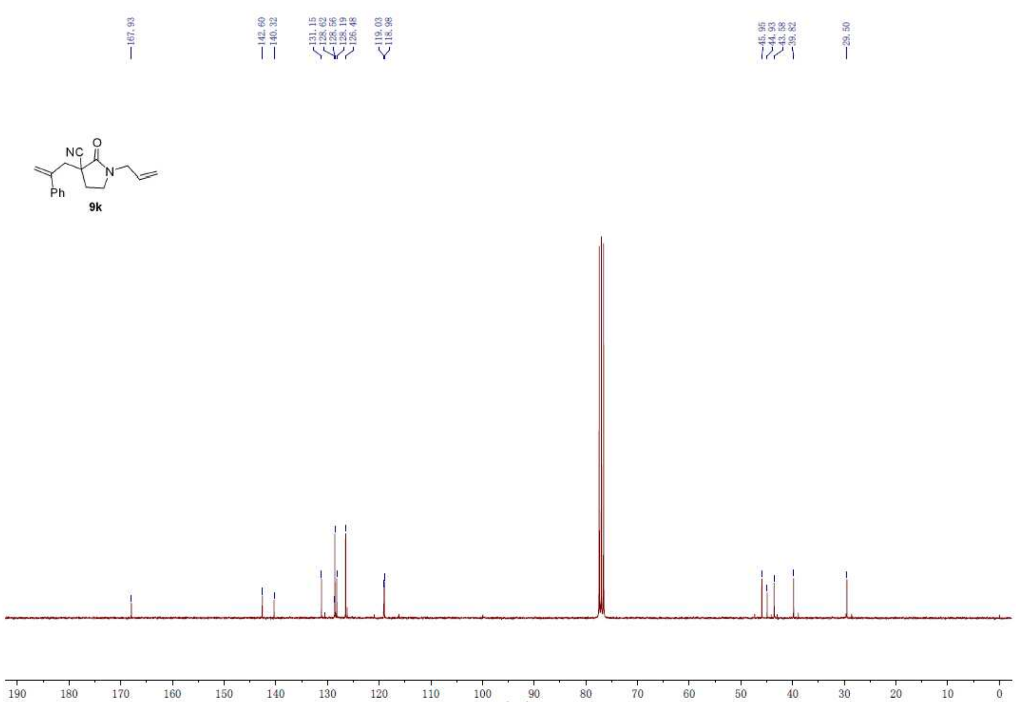

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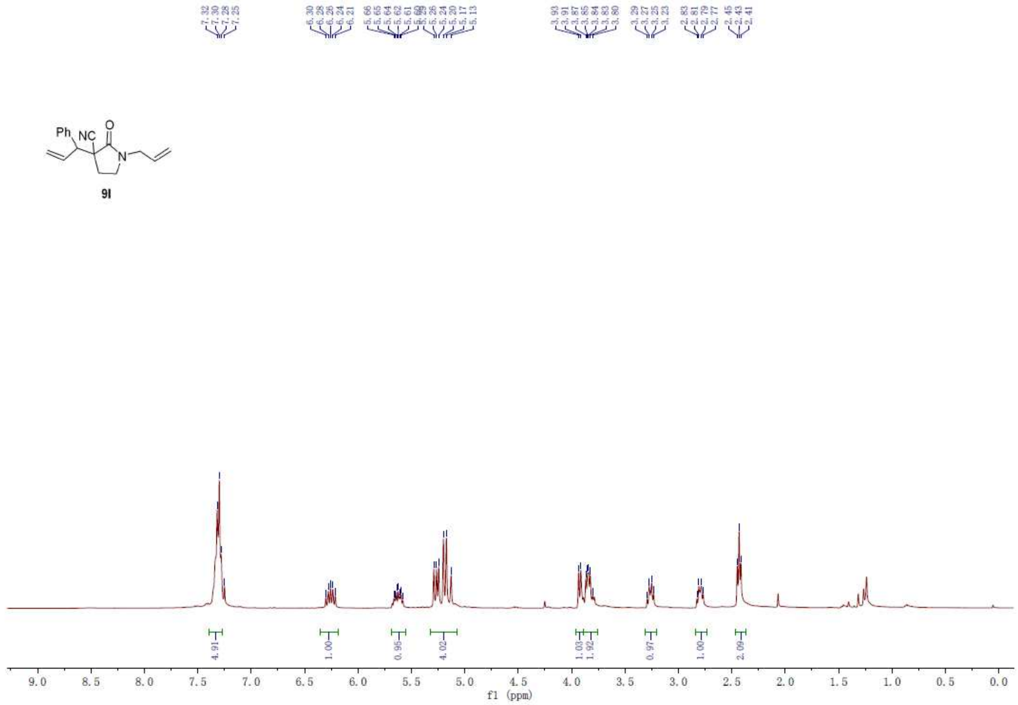
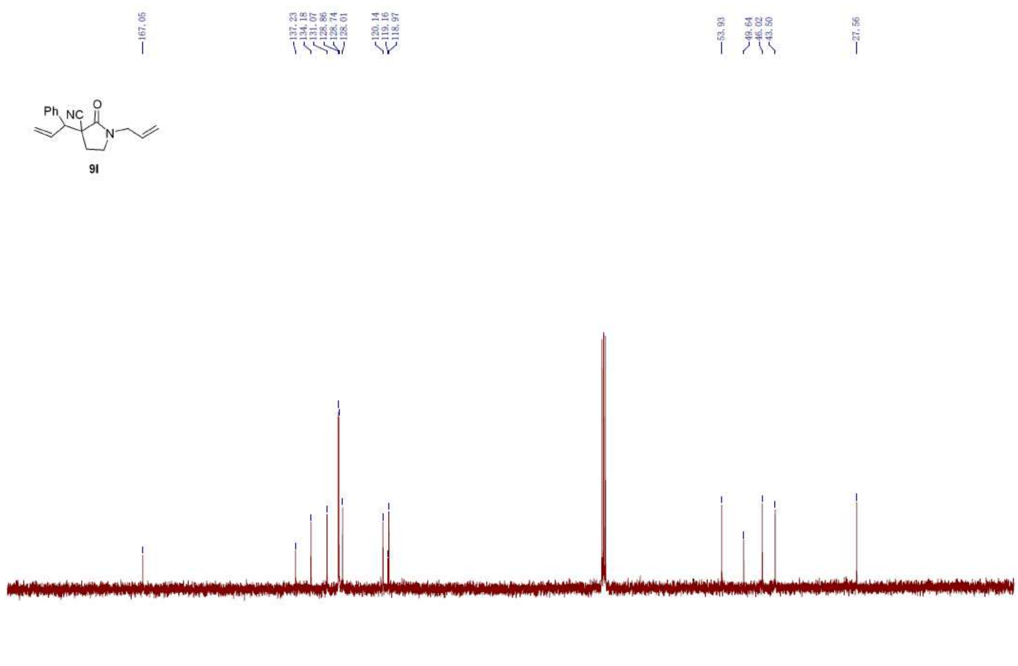
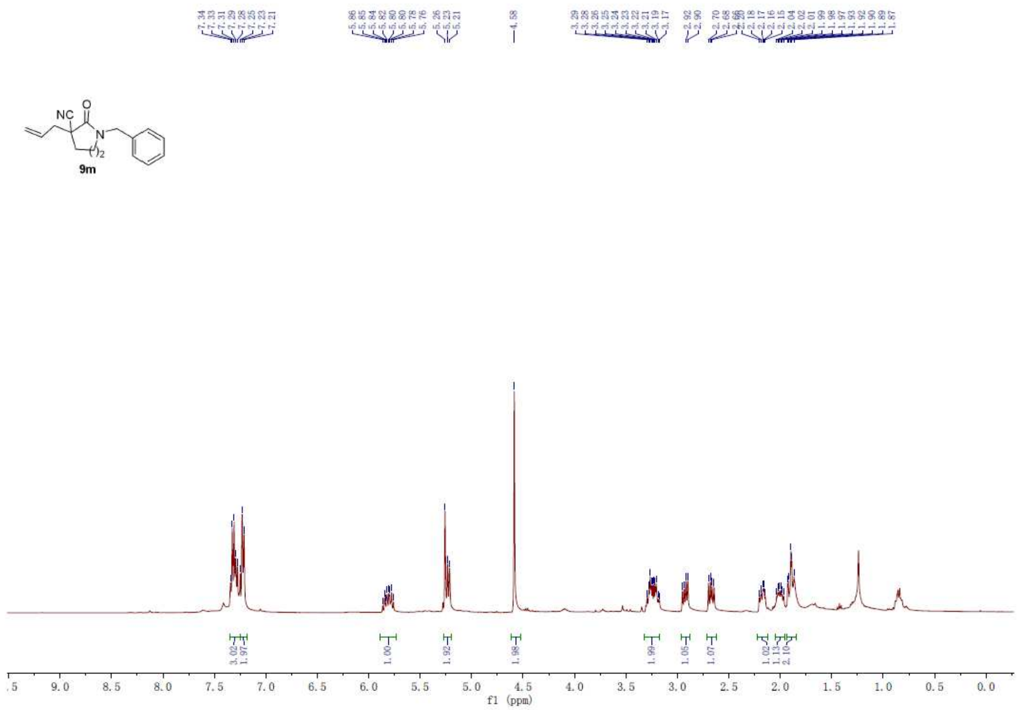
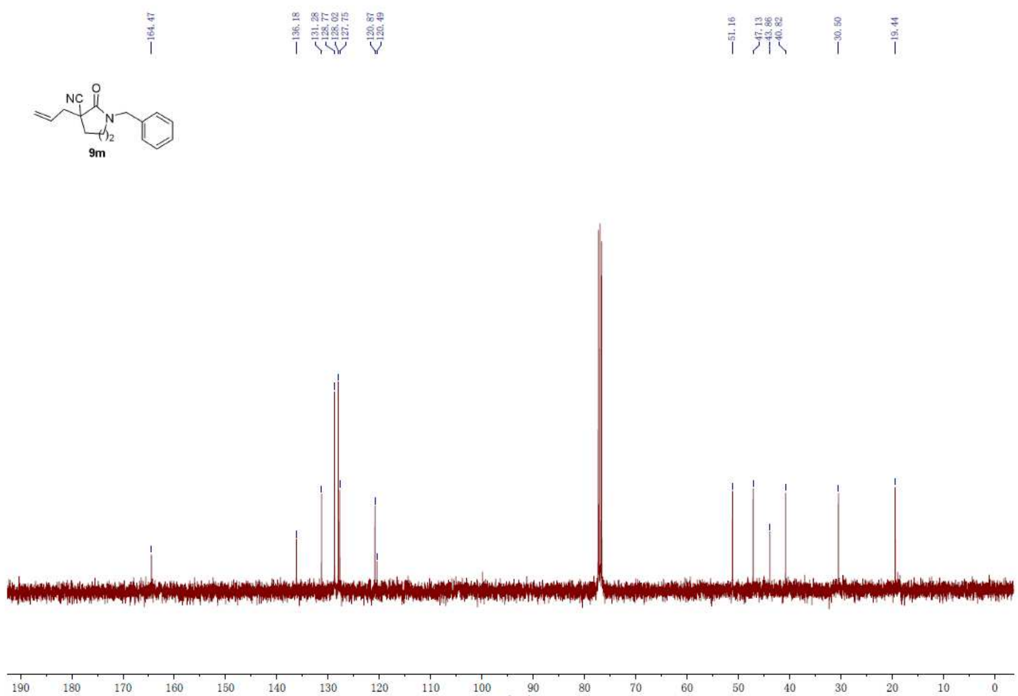
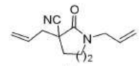


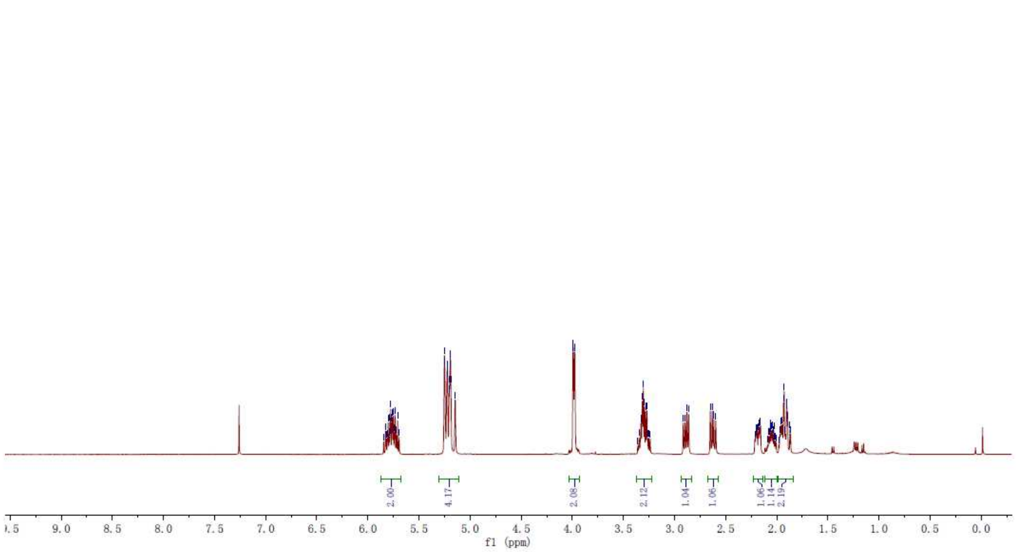


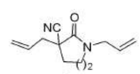




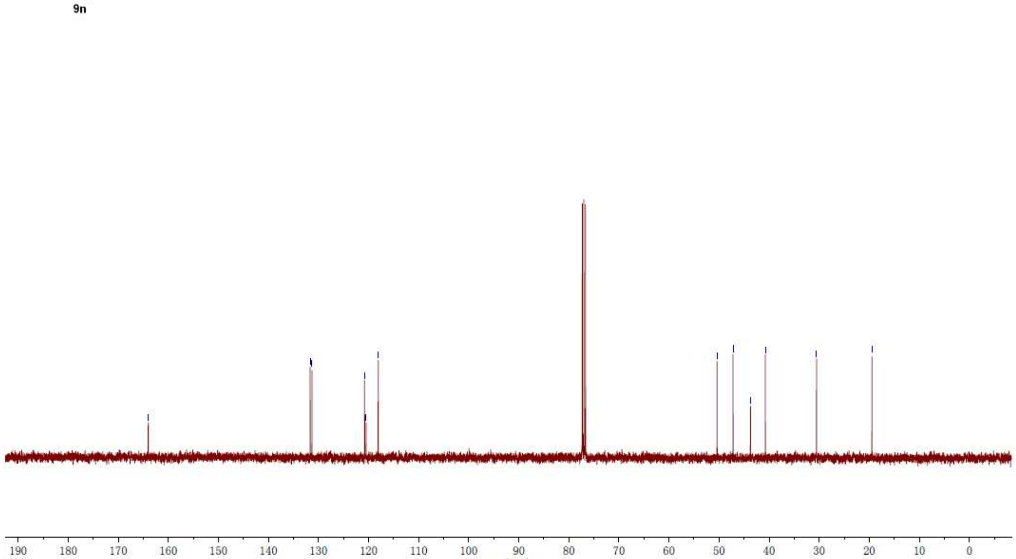

NC
O
N
2

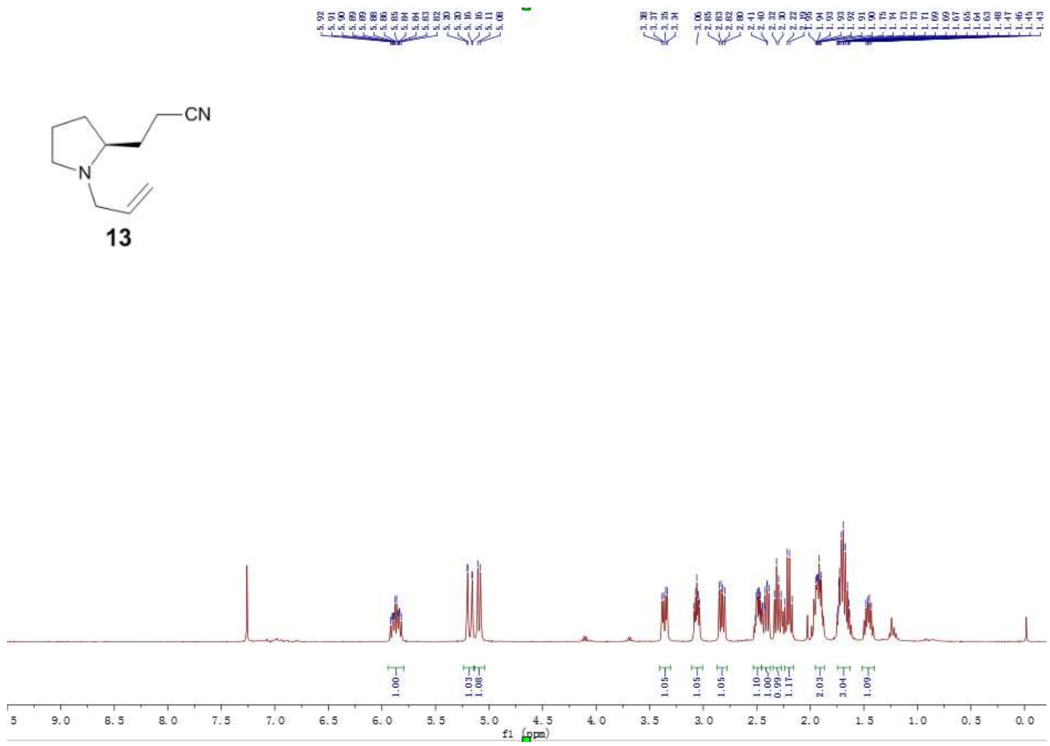
9n

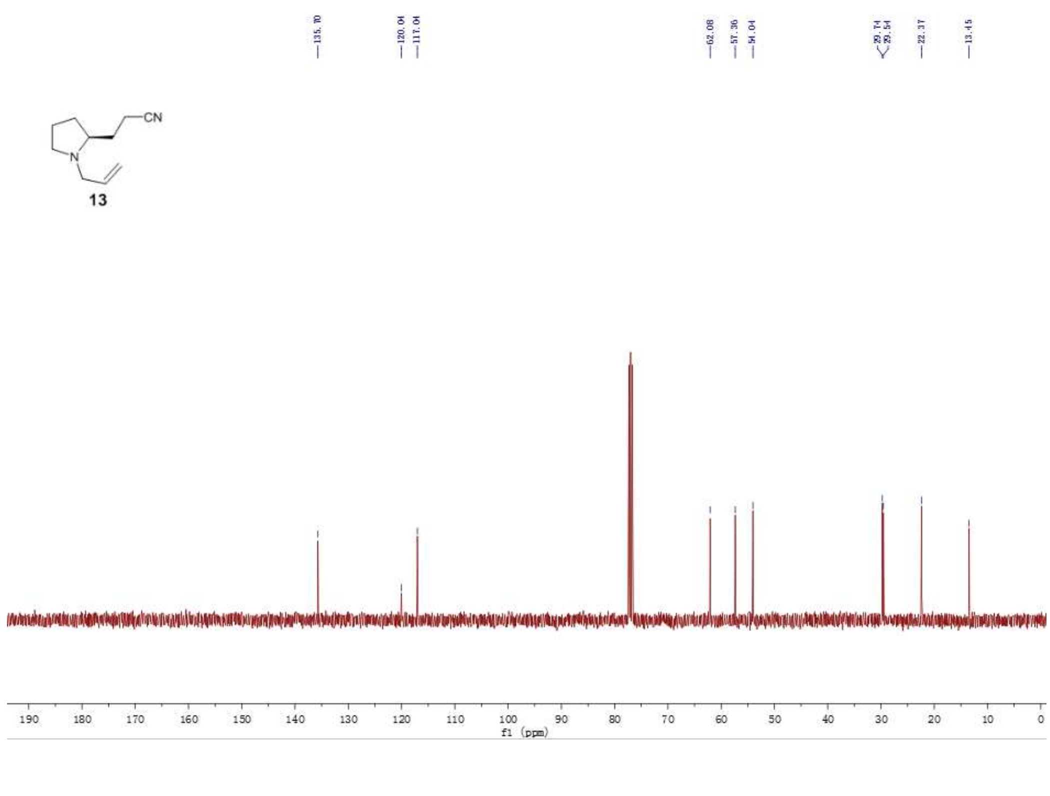

2.00
4.17
2.08
2.12
1.04
1.06
1.06
1.14
2.19
f1 (ppm)

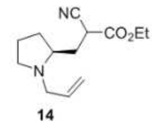

NC
O
N
2

9n

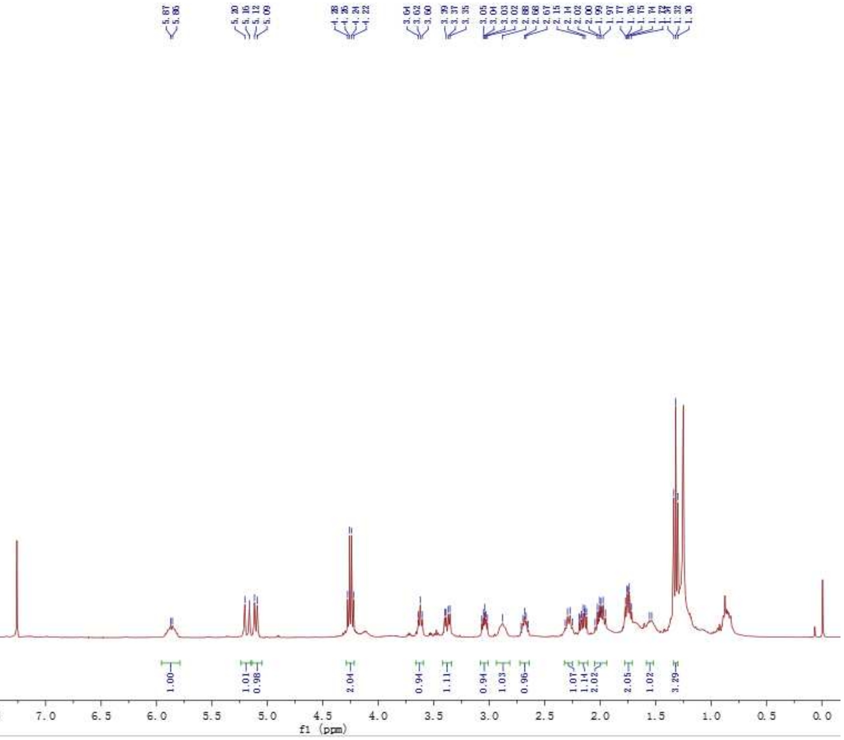

164.01
131.66
131.30
120.80
120.49
118.08
50.40
47.20
43.72
40.75
30.53
19.47
f1 (ppm)

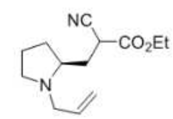

CN
N
13
f1 (ppm)


135.70
120.04
117.04
62.08
57.36
54.04
29.74
29.54
22.37
13.45
CN
N
13
f1 (ppm)

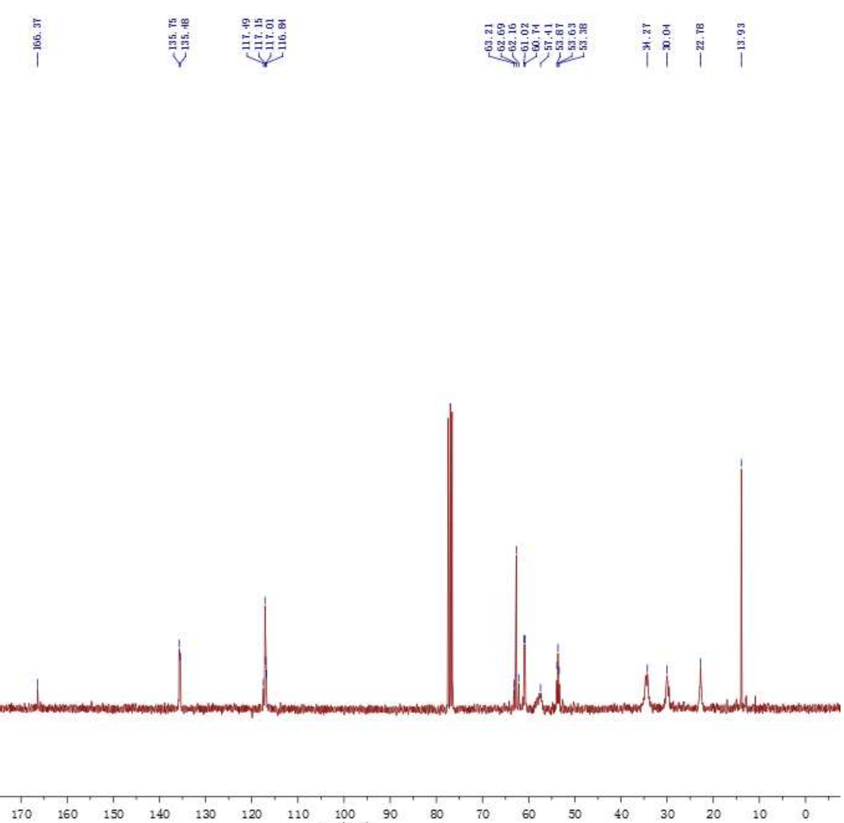


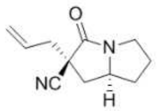
14



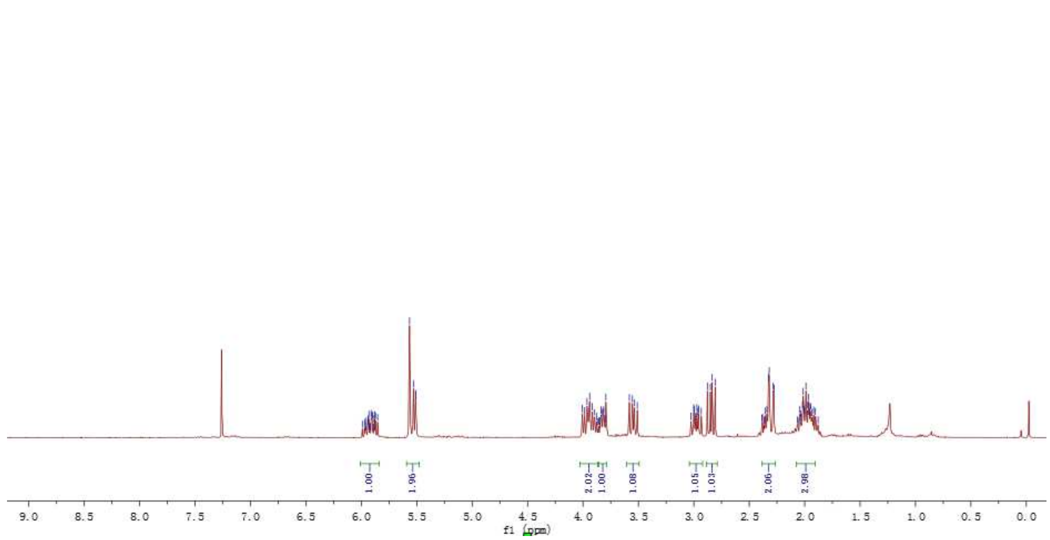


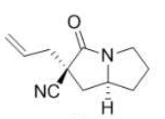
14



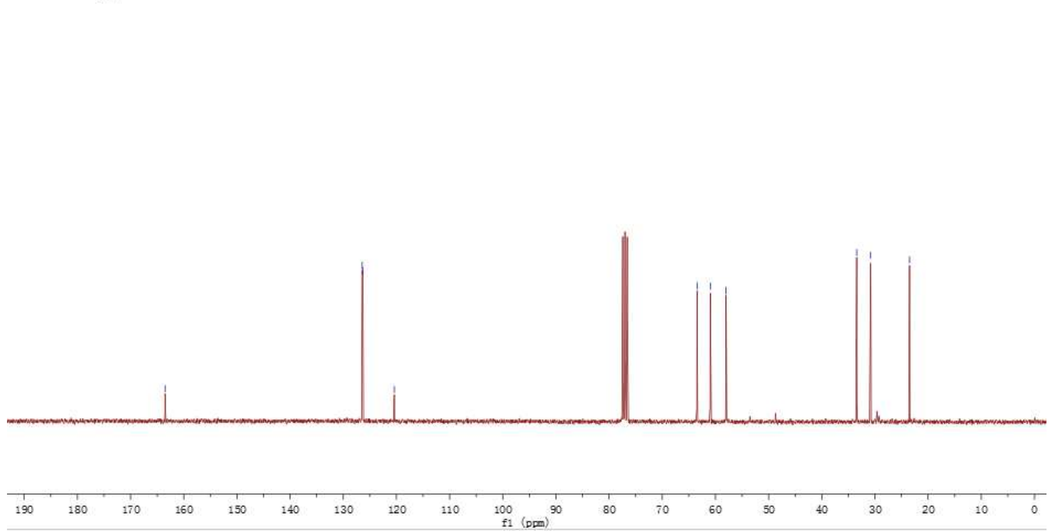


15

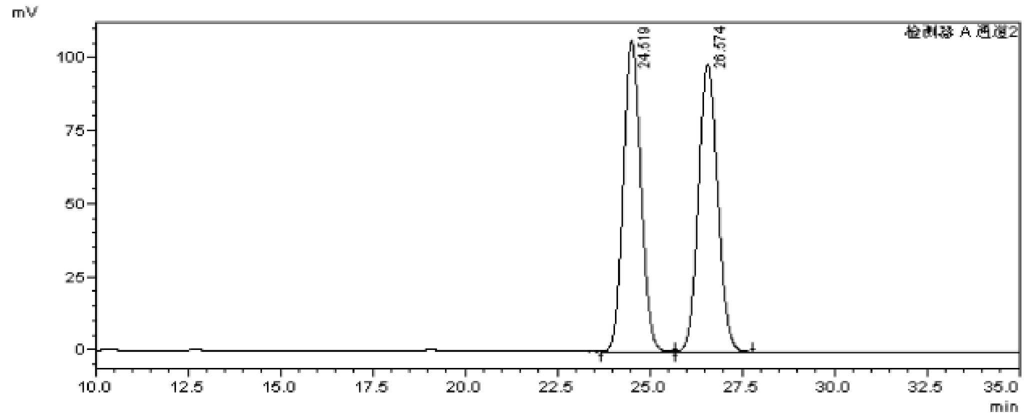




15

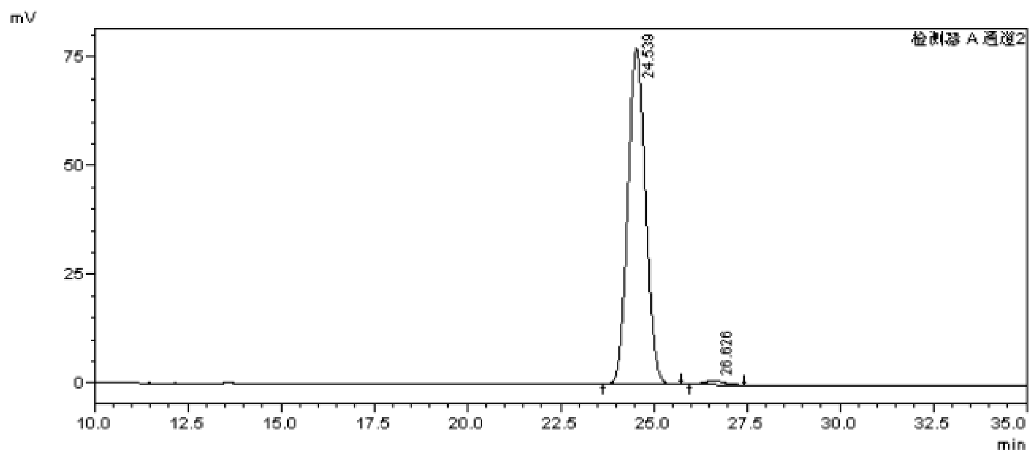


VIII HPLC spectra for (+/-)-15 and (-)-15



Racemic 15

Pea	Time	Area	Area %	Plate number	Tailing	Resolution
1	24.519	3525002	49.6750	12411.563	1.081	--
2	26.574	3571128	50.3250	12119.459	1.082	2.227



Enantiomerically enriched 15

Peak	Time	Area	Area %	Plate number	Tailing	Resolution
1	24.539	2571162	98.5958	12369.166	1.077	--
2	26.626	36618	1.4042	12475.546	1.043	2.274

Enantiomeric excess was determined to be 97% (determined by HPLC using chiral IC-H column, n-Hexane/EtOH/Diethylamine = 60/40/0.1, λ = 254 nm, 35 ^{o}C, 0.8mL/min, t_{major} = 24.54 min, t_{minor} = 26.63 min).