Supplementary Material (ESI) for Chemical Communications

Electronic Supplementary Information

A Convenient Approach to Acyclic Unsaturated Amino Acids *via* Ring-Closing Metathesis

Hani Mutlak A. Hassan*‡ and Fraser K. Brown

Contents:

Manchester Interdisciplinary Biocentre (MIB), University of Manchester, 131 Princess Street, Manchester, M1 7DN, UK.
‡ Current address: Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, S3 7HF, UK.
E-mail: h.hassan@sheffield.ac.uk.

General Experimental.

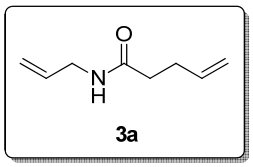
Unless otherwise noted, all air and moisture sensitive reactions were carried out under a positive pressure of nitrogen atmosphere in oven-dried glassware using anhydrous solvents. Reagents were purchased from commercial sources and used without further purification. Reactions were magnetically stirred and examined by thin layer chromatography (TLC) using ultraviolet light (254 nm) and/or aqueous potassium permanganate solution for visualization. All lactams, macrolactam, unsaturated amino acids, and unsaturated amino esters were treated as light sensitive.

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX-300 or 400 instruments. Chemical shifts are reported in parts per million (ppm) relative to chloroform (δ 7.26) or methanol (δ 3.31) for ^{1}H NMR and chloroform (δ 77.0) for ^{13}C NMR. Multiplicities and other abbreviations are expressed as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu), multiplet (m), broad (br), and apparent (app). Coupling constants are recorded in Hertz (Hz). High resolution mass spectrometry fast atom bombardment (HRMS FAB) was conducted using a Kratos MS50TC instrument. All microwave-based reactions were carried out using CEM Discover Microwave Synthesizer with Explorer Carousel.

Experimental.

N-allylpent-4-enamide (3a):[1]

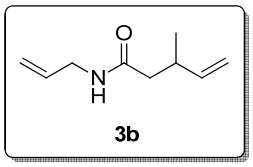
To a MW reaction tube was added allylamine **1** (732 μL, 9.78 mmol) and 4-pentenoic acid **2a** (1 mL, 9.78 mmol). The tube was sealed and placed in the MW reactor (300 W, 150 ºC, 250 psi pressure, 30 min with continuous stirring while cooling the vessel) in solvent-free conditions. Purification by silica gel column chromatography (25% EtOAc in CH_2Cl_2) afforded 1.30 g (96%) of **3a** as a yellow oil (TLC: R_f = 0.49): ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 6.62 (br s, 1H) 5.75–5.67 (m, 2H), 5.11–4.89 (m, 4H), 3.79–3.75 (m, 2H), 2.31–2.20 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 172.3, 136.9, 134.1, 115.8, 115.2, 41.6, 35.4, 29.4; HRMS (FAB) calcd for $C_8H_{13}NO$ (MNa^+) 162.0889, found 162.0887.



3a

N-allyl-3-methylpent-4-enamide (3b):

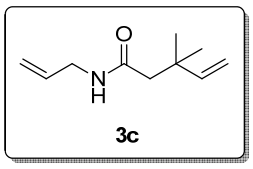
Experimental procedure for **3a** was followed, with allylamine **1** (925 μL, 12.36 mmol) and 3-methyl-4-pentenoic acid **2b** (1 mL, 8.24 mmol). Purification by silica gel column chromatography (10% EtOAc in CH_2Cl_2) afforded 1.25 g (99%) of **3b** (TLC: R_f = 0.42) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 6.57 (br s, 1H), 5.75–5.64 (m, 2H), 5.12–4.86 (m, 4H), 3.78 (m, 2H), 2.66–2.58 (m, 1H), 2.19 (dd, J = 15.0, 9.0 Hz, 1H), 2.08 (dd, J = 15.0, 9.0 Hz, 1H), 0.97 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 171.9, 142.6, 134.2, 115.8, 113.1, 43.3, 41.6, 34.5, 19.4; HRMS (FAB) calcd for $C_9H_{15}NO$ (MNa^+) 176.1045, found 176.1040.



3b

N-allyl-3,3-dimethylpent-4-enamide (3c):

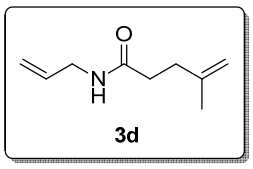
Experimental procedure for **3a** was followed, with allylamine **1** (1.12 mL, 15.0 mmol) and 3,3-methyl-4-pentenoic acid **2c** (960 mg, 7.5 mmol). Purification by silica gel column chromatography (10% EtOAc in CH_2Cl_2) afforded 784 mg (63%) of **3c** as a yellow oil (TLC: R_f = 0.27): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.91 (dd, J = 17.2, 10.8 Hz, 1H), 5.85–5.76 (m, 1H), 5.61 (br s, 1H), 5.16 (dd, J = 17.2, 1.2 Hz, 1H), 5.10 (dd, J = 10.8, 1.2 Hz, 1H), 5.01 (dd, A_2X system, J = 17.2, 10.8 Hz, 2H), 3.84 (t, J = 5.6 Hz, 2H), 2.20 (s, 2H), 1.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.8, 147.2, 134.3, 116.1, 111.4, 49.3, 41.7, 36.2, 26.9 (2 C); HRMS (FAB) calcd for $C_9H_{15}NO$ (MNa^+) 190.1202, found 190.1201.



3c

N-allyl-4-methylpent-4-enamide (3d):

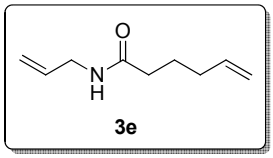
Experimental procedure for **3a** was followed, with allylamine **1** (329 μL, 4.39 mmol) and ethyl-4-methyl-4-pentenoate **2d** (700 μL, 4.39 mmol). Purification by silica gel column chromatography (10% EtOAc in CH_2Cl_2) afforded 391 mg of **3d** (58%) as a yellow oil (TLC: R_f = 0.23): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.69 (br s, 1H), 5.77–5.68 (m, 1H), 5.07 (d, J = 17.2 Hz, 1H), 5.00 (d, J = 10.0, 1H), 4.65 (s, 1H), 4.60 (s, 1H), 3.76 (m, 2H), 2.31–2.22 (m, 4H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.6, 144.2, 134.1, 115.7, 110.1, 41.6, 34.4, 33.1, 22.2; HRMS (FAB) calcd for $C_9H_{15}NO$ (MNa^+) 176.1045, found 176.1047.



3d

N-allylhex-5-enamide (3e):

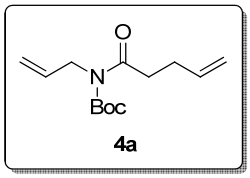
Experimental procedure for **3a** was followed, with allylamine **1** (315 μL, 4.21 mmol) and 5-hexenoic acid **2e** (500 μL, 4.21 mmol). Purification by silica gel column chromatography (8% EtOAc in CH_2Cl_2) afforded 586 mg (91%) of **3e** as a pale yellow oil (TLC: R_f = 0.32): ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 6.52 (br s, 1H), 5.77–5.63 (m, 2H), 5.11–4.87 (m, 4H), 3.79–3.75 (m, 2H), 2.15 (t, J = 7.8 Hz, 2H), 2.04–1.97 (m, 2H), 1.66 (qu, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 172.9, 137.7, 134.1, 115.8, 114.9, 41.6, 35.5, 32.9, 24.6; HRMS (FAB) calcd for $C_9H_{15}NO$ (MNa^+) 176.1045, found 176.1045.



3e

Tert-butyl-allylpent-4-enoylcarbamate (4a):[2]

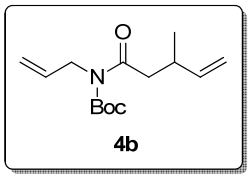
To an oven-dried round-bottomed flask was added *N*-allylpent-4-enamide **3a** (1.23 g, 8.85 mmol), Boc_2O (3.858 g, 17.7 mmol; added as liquid), DMAP (432 mg, 3.54 mmol), and CH_3CN (8 mL). The 1 M reaction mixture was stirred at rt for 2 h, under nitrogen atmosphere. The resulting deep red reaction mixture was concentrated *in vacuo* to give a deep red oil. Purification by silica gel column chromatography (3:10:87, Et_3N/EtOAc/hexane) afforded 2.11 g of **4a** (100%) as a yellow oil (TLC: R_f = 0.76): ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.81–5.67 (m, 2H), 5.09–4.90 (m, 4H), 4.23 (d, J = 5.7 Hz, 2H), 2.92 (t, J = 7.8 Hz, 2H), 2.37–2.30 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 174.7, 152.8, 137.3, 133.4, 116.2, 114.9, 82.7, 46.3, 37.4, 28.9, 27.8 (3 C); HRMS (FAB) calcd for $C_{13}H_{21}NO_3$ (MNa^+) 262.1413, found 262.1408.



4a

Tert-butyl-3-methylpent-4-enoylallylcarbamate (4b).

Experimental procedure for **4a** was followed, with *N*-allyl-3-methylpent-4-enamide **3b** (200 mg, 1.31 mmol), Boc_2O (685 mg, 3.14 mmol), DMAP (64 mg, 0.524 mmol), and

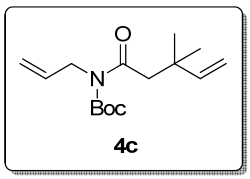


4b

CH_3CN (1 mL). Purification by silica gel column chromatography (3:10:87, Et_3N/EtOAc/hexane) afforded 320 mg of **4b** (97%) as a yellow oil (TLC: R_f = 0.70): ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.84–5.70 (m, 2H), 5.12–4.89 (m, 4H), 4.25 (d, J = 5.7 Hz, 2H), 2.95–2.69 (m, 3H), 1.48 (s, 9H), 1.03 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 174.3, 152.9, 143.1, 133.5, 116.3, 112.9, 82.8, 46.4, 44.7, 34.1, 27.9 (3 C), 19.7; HRMS (FAB) calcd for $C_{14}H_{23}NO_3$ (MNa^+) 276.1570, found 276.1568.

Tert-butyl-3,3-dimethylpent-4-enoylallylcarbamate (4c):

Experimental procedure for **4a** was followed, with *N*-allyl-3,3-dimethylpent-4-enamide **3c** (714 mg, 4.27 mmol), Boc_2O (2.33 g, 10.67 mmol), DMAP (260 mg, 2.13 mmol), and

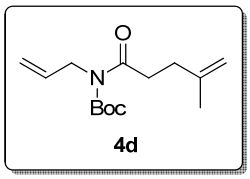


4c

CH_3CN (4 mL). Purification by silica gel column chromatography (3:10:87, Et_3N/EtOAc/hexane) afforded 915 mg of **4c** (80%) as a yellow oil (TLC: R_f = 0.76): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.94 (dd, J = 17.2, 10.8 Hz, 1H), 5.82–5.75 (m, 1H), 5.14–5.07 (m, 2H), 4.95–4.89 (m, 2H), 4.23 (d, J = 5.6 Hz, 2H), 2.97 (s, 2H), 1.49 (s, 9H), 1.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 173.6, 153.2, 147.3, 133.6, 116.4, 110.4, 82.7, 48.5, 46.5, 36.8, 27.9 (3 C), 27.1 (2 C); HRMS (FAB) calcd for $C_{15}H_{25}NO_3$ (MNa^+) 290.1726, found 290.1725.

Tert-butyl-4-methylpent-4-enoylallylcarbamate (4d):

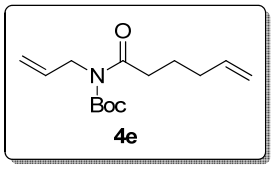
Experimental procedure for **4a** was followed, with *N*-allyl-4-methylpent-4-enamide **3d** (198 mg, 1.29 mmol), Boc_2O (676 mg, 3.10 mmol), DMAP (63 mg, 0.516 mmol), and CH_3CN (1 mL). Purification by silica gel column chromatography (3:8:89, Et_3N/EtOAc/hexane) afforded 311 mg of **4d** (95%) as a yellow oil (TLC: R_f = 0.71): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.81–5.72 (m, 1H), 5.11–5.06 (m, 2H), 4.70 (s, 1H), 4.66 (s, 1H), 4.25 (d, *J* = 5.6 Hz, 2H), 2.98 (t, *J* = 8.0 Hz, 2H), 2.31 (t, *J* = 8.0 Hz, 2H), 1.72 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 175.1, 152.8, 144.6, 133.4, 116.3, 109.9, 82.8, 46.4, 36.5, 32.7, 27.9 (3 C), 22.6; HRMS (FAB) calcd for $C_{14}H_{23}NO_3$ (MNa^+) 276.1570, found 276.1564.



4d

Tert-butyl-allylhex-5-enoylcarbamate (4e):

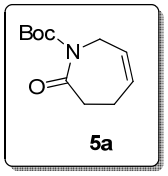
Experimental procedure for **4a** was followed, with *N*-allylhex-5-enaminde **3e** (360 mg, 2.35 mmol), Boc_2O (1.229 g, 5.64 mmol), DMAP (115 mg, 0.94 mmol), and CH_3CN (2 mL). Purification by silica gel column chromatography (3:10:87, Et_3N/EtOAc/hexane) afforded 565 mg of **4e** (95%) as a yellow oil (TLC: R_f = 0.71): ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 5.82–5.71 (m, 2H), 5.06–4.92 (m, 4H), 4.25 (d, *J* = 5.7 Hz, 2H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.11–2.04 (m, 2H), 1.72 (qu, *J* = 7.5, 2H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 175.4, 152.9, 138.1, 133.4, 116.2, 114.9, 82.8, 46.4, 37.5, 33.1, 27.9 (3 C), 24.2; HRMS (FAB) calcd for $C_{14}H_{23}NO_3$ (MNa^+) 276.1570, found 276.1567.



4e

(*Z*)-*tert*-butyl-3,4-dihydro-2-oxo-2*H*-azepine-1(7*H*)-carboxylate (5a):[2]

To an oven-dried round-bottomed flask fitted with a condenser was added *tert*-butyl-allylpent-4-enoylcarbamate **4a** (100 mg, 4.18 mmol) and deoxygenated CH_2Cl_2 (418

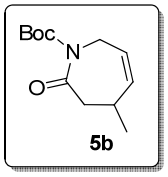


5a

mL). Grubbs' second-generation ruthenium catalyst **A** (18 mg, 2.09 mmol, 5 mol %) was then added in one aliquot. The 1 mM reaction mixture was heated to reflux (50 ºC) with stirring for 24 h in the absence of light, under a stream of nitrogen atmosphere. Following removal of the solvent, Ru scavenger (SiO_2-$Si(CH_2)_3NH_2$,[3] 10 equiv w/w relative to catalyst) and hexane (10 mL) were added and the resulting mixture was stirred vigorously at rt for 2 h. The crude product was passed through a pad of silica gel (100 mg per approximately 100 mg crude product) using a fritted filtration column, eluting with 3% Et_3N in hexane (20 mL) and further with 3:10:87 Et_3N/EtOAc/hexane (10 mL). The filtrate was then concentrated to dryness to obtain 85 mg (97%) of **5a** as a yellow oil without the need for further purification: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.85–5.74 (m, 2H), 4.34–4.32 (m, 2H), 2.87 (t, J = 6.4 Hz, 2H), 2.48 (m, 2H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 174.2, 152.2, 131.7, 124.3, 82.8, 41.9, 36.1, 27.9 (3 C), 25.6; HRMS (FAB) calcd for $C_{11}H_{17}NO_3$ (MNa^+) 234.1101, found 234.1102.

(*Z*)-*tert*-butyl-3,4-dihydro-4-methyl-2-oxo-2*H*-azepine-1(7*H*)-carboxylate (5b):

Experimental procedure for **5a** was followed, with *tert*-butyl-3-methylpent-4-



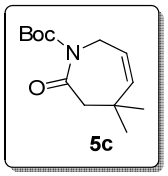
5b

enoylallylcarbamate **4b** (108 mg, 0.426 mmol), Grubbs' second-generation ruthenium catalyst **A** (18 mg, 0.0213 mmol, 5 mol %), and deoxygenated CH_2Cl_2 (427 mL). The crude product **5b** was obtained as a yellow oil (87 mg, 91%)

without the need for further purification: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.75 (ddd, *J* = 11.2, 6.0, 1.6 Hz, 1H), 5.64 (dd, *J* = 11.2, 3.2 Hz, 1H), 4.29 (m, 2H), 2.83–2.73 (m, 2H), 2.67 (m, 1H), 1.51 (s, 9H), 1.12 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 173.1, 152.1, 137.8, 123.0, 82.9, 43.3, 41.9, 31.5, 27.9 (3 C), 21.5; HRMS (FAB) calcd for $C_{12}H_{19}NO_3$ (MNa^+) 248.1257, found 248.1257.

(*Z*)-*tert*-butyl-3,4-dihydro-4,4-dimethyl-2-oxo-2*H*-azepine-1(7*H*)-carboxylate (5c):

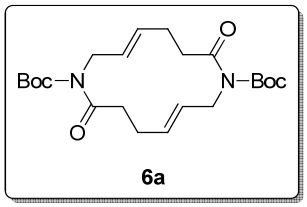
Experimental procedure for **5a** was followed, with *tert*-butyl 3,3-dimethylpent-4-enoylallylcarbamate **4c** (107 mg, 0.40 mmol), Grubbs' second-generation ruthenium catalyst **A** (17 mg, 0.02 mmol, 5 mol %), and deoxygenated CH_2Cl_2 (400 mL). The crude product **5c** was obtained as a yellow oil (94 mg, 98%) without the need for further purification: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 5.65 (dt, *J* = 11.2, 6.0 Hz, 1H), 5.50 (d, *J* = 11.2 Hz, 1H), 4.26 (d, *J* = 6.0 Hz, 2H), 2.72 (s, 2H), 1.49 (s, 9H), 1.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 172.4, 152.1, 142.4, 121.1, 82.9, 49.1, 41.9, 35.2, 29.7 (2 C), 27.9 (3 C); HRMS (FAB) calcd for $C_{13}H_{21}NO_3$ (MNa^+) 262.1413, found 262.1411.



5c

Macrolactam 6a:

Experimental procedure for **5a** was followed, with *tert*-butyl-allylpent-4-enoylcarbamate **4a** (200 mg, 0.836 mmol), Grubbs' second-generation ruthenium catalyst **A** (35 mg, 0.0418 mmol, 5 mol %), and deoxygenated CH_2Cl_2 (21 mL). Reaction mixture concentration

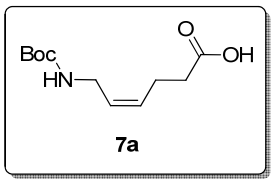


6a

= 40 mM. Ru scavenger (SiO_2-$Si(CH_2)_3NH_2$, 20 equiv w/w relative to catalyst) was used for catalyst byproducts removal and a pad of silica gel (200 mg per approximately 100 mg crude product) was used to pass the crude product through, eluting with 3% Et_3N in hexane (40 mL) and further with 3:10:87 Et_3N/EtOAc/hexane (20 mL). Purification by silica gel column chromatography (3% Et_3N in hexane) afforded 94 mg of **6a** (53%) as a colourless oil, which crystallized overtime to give a white solid (TLC: R_f = 0.15): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.53–5.29 (m, 4H, 2 C*H*=C*H*), 4.22 (m, 4H), 2.86–2.82 (m, 4H), 2.33 (m, 4H), 1.52 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm; presence of rotamers) δ 174.4, 174.2, 153.3, 153.1, 131.3, 129.2, 127.8, 125.8, 82.9, 82.8, 45.8, 45.5, 37.4, 37.2, 28.0 (6 C), 27.6, 27.4; HRMS (FAB) calcd for $C_{22}H_{34}N_2O_6$ (MNa^+) 445.2309, found 445.2305.

(*Z*)-6-(*tert*-butoxylcarbonyl)-hex-4-enoic acid (7a):

2 M 1:1 LiOH in THF/H_2O (220 μL × 2) were independently added to lactam **5a** (33 mg, 0.156 mmol). The 0.35 M biphasic reaction mixture was stirred at 30 ºC for 2 h in the absence of light. Water (2 mL) was added and the crude product was extracted with EtOAc (5 mL). The pH of the aqueous phase was acidified by a dropwise addition of 1 M HCl. The crude product was extracted three times with EtOAc (10 mL) and further with CH_2Cl_2 (10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated *in vacuo* to give a yellow oil. Purification by silica gel column chromatography (6% CH_3OH in CH_2Cl_2) afforded 35 mg of **7a** (97%) as a yellow oil (TLC: R_f = 0.17): ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 5.49–5.39 (m, 2H), 3.70 (d, *J* =

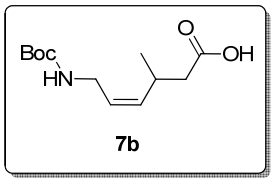


7a

6.0 Hz, 2H), 2.37 (m, 4H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.1, 155.9, 130.3, 127.5, 79.4, 37.4, 33.7, 28.3 (3 C), 22.4; HRMS (FAB) calcd for $C_{11}H_{19}NO_4$ (MH^+) 230.1387, found 230.1392.

(*Z*)-6-(*tert*-butoxylcarbonyl)-3-methylhex-4-enoic acid (7b).

Experimental procedure for **7a** was followed, with lactam **5b** (55 mg, 0.244 mmol) and 2 M 1:1 LiOH in THF/H_2O (350 μL × 2). Purification by silica gel column chromatography

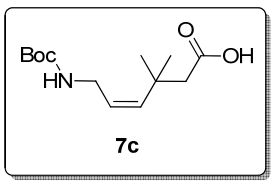


7b

(6% CH_3OH in CH_2Cl_2) afforded 55 mg of **7b** (93%) as a colourless oil (TLC: R_f = 0.24): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.39 (dt, *J* = 10.8, 6.8 Hz, 1H), 5.28 (app t, *J* = 10.4 Hz, 1H), 4.75 (br s, 1H), 3.76 (m, 2H), 3.03–2.94 (m, 1H), 2.36 (dd, *J* = 15.2, 6.0 Hz, 1H), 2.25 (dd, *J* = 15.2, 8.8 Hz, 1H), 1.43 (s, 9H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.3, 155.9, 136.4, 125.9, 79.4, 41.6, 37.6, 28.8, 28.4 (3 C), 20.9; HRMS (FAB) calcd for $C_{12}H_{21}NO_4$ (MH^+) 244.1543, found 244.1554.

(*Z*)-6-(*tert*-butoxylcarbonyl)-3,3-dimethylhex-4-enoic acid (7c):

Experimental procedure for **7a** was followed, with lactam **5c** (50 mg, 0.209 mmol) and 2 M 1:1 LiOH in THF/H_2O (300 μL × 2). The crude product **7c** was obtained as a yellow



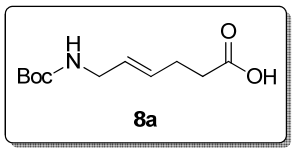
7c

oil (50 mg, 93%) without the need for further purification: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.47 (d, *J* = 12.0 Hz, 1H), 5.27 (dt, 12.0, 6.8 Hz, 1H), 4.75 (br s, 1H), 3.89 (m, 2H), 2.43 (s, 2H),

1.44 (s, 9H), 1.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 176.5, 155.9, 138.9, 126.8, 79.5, 47.4, 38.5, 35.5, 29.2 (2 C), 28.4 (3 C); HRMS (FAB) calcd for $C_{13}H_{23}NO_4$ (MH^+) 258.1699, found 258.1692.

(*E*)-6-(*tert*-butoxylcarbonyl)hex-4-enoic acid (8a):

Experimental procedure for **7a** was followed, with macrolactam **6a** (20 mg, 0.047 mmol) and 2 M 1:1 LiOH in THF/H_2O (700 μL × 2). The product **8a** was obtained as a yellow

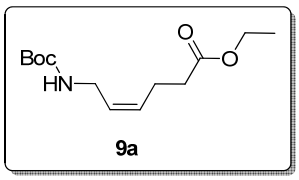


8a

oil (20 mg, 93%): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.64–5.57 (m, 1H), 5.54–5.49 (m, 1H), 4.61 (br s, 1H), 3.69 (m, 2H), 2.44–2.32 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.1, 155.9, 130.3, 127.5, 79.4, 42.4, 33.7, 28.3 (3 C), 27.1; HRMS (FAB) calcd for $C_{11}H_{19}NO_4$ (MH^+) 230.1387, found 230.1383.

(*Z*)-*tert*-butyl-5-(ethoxycarbonyl)pent-2-enylcarbamate (9a):

To lactam **5a** (47 mg, 0.222 mmol) in absolute EtOH (634 μL) at 0 ºC, was added Cs_2CO_3 (108 mg, 0.333 mmol). The 0.35 M reaction mixture was stirred at 30 ºC for 2 h



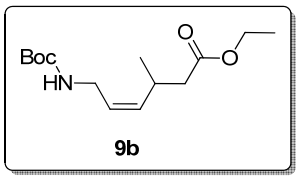
9a

in the absence of light. EtOH was removed *in vacuo* and the resulting residue was filtered through a short plug of Celite, eluting with Et_2O. The filtrate was concentrated to dryness to give 57 mg of **9a** (100%) as a yellow oil without the need for further purification: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.52–5.43 (m, 2H), 4.62 (br s, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.76 (m, 2H), 2.37 (m, 4H), 1.44 (s, 9H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100

MHz, $CDCl_3$, ppm) δ 172.9, 155.8, 130.6, 127.4, 79.3, 60.4, 37.4, 33.9, 28.4 (3 C), 22.7, 14.2; HRMS (FAB) calcd for $C_{13}H_{23}NO_4$ (MNa^+) 280.1519, found 280.1523.

(*Z*)-*tert*-butyl-5-(ethoxycarbonyl)-4-methylpent-2-enylcarbamate (9b):

Experimental procedure for **9a** was followed, with lactam **5b** (63 mg, 0.28 mmol), Cs_2CO_3 (136 mg, 0.42 mmol), and EtOH (800 μL). The crude product **9b** was obtained as

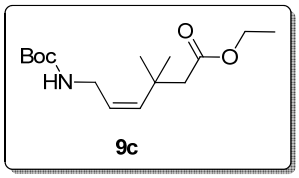


9b

a yellow oil (100%, 76 mg) without the need for further purification: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.39 (dt, J = 10.8, 6.8 Hz, 1H), 5.27 (app t, J = 10.4 Hz, 1H), 4.69 (br s, 1H), 4.16–4.04 (m, 2H), 3.86–3.68 (m, 2H), 3.06–2.95 (m, 1H), 2.31 (dd, J = 15.2, 6.0 Hz, 1H), 2.21 (dd, J = 15.2, 8.8 Hz, 1H), 1.43 (s, 9H), 1.22 (t, J = 7.2 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.4, 155.8, 136.7, 125.7, 79.2, 60.3, 41.8, 37.5, 28.9, 28.4 (3 C), 20.9, 14.2; HRMS (FAB) calcd for $C_{14}H_{25}NO_4$ (MNa^+) 294.1675, found 294.1682.

(*Z*)-*tert*-butyl-5-(ethoxycarbonyl)-4,4-dimethylpent-2-enylcarbamate (9c):

Experimental procedure for **9a** was followed, with lactam **5c** (30 mg, 0.125 mmol), Cs_2CO_3 (61 mg, 0.187 mmol), and 1:1 EtOH/CH_2Cl_2 (180 μL × 2). Purification by silica



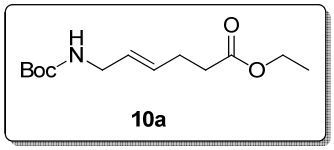
9c

gel column chromatography (2% EtOAc in CH_2Cl_2) afforded 31 mg of **9c** (86%) as a yellow oil (TLC: R_f = 0.19): ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.46 (d, J = 12.0 Hz, 1H), 5.27 (dt, J = 12.0, 6.8 Hz, 1H), 4.68 (br s, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.89 (m, 2H), 2.37 (s, 2H), 1.44 (s, 9H), 1.26–1.23 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.7, 155.7,

139.3, 126.3, 79.3, 60.1, 47.6, 38.4, 35.8, 29.2 (2 C), 28.4 (3 C), 14.3; HRMS (FAB) calcd for $C_{15}H_{27}NO_4$ (MNa^+) 308.1832, found 308.1829.

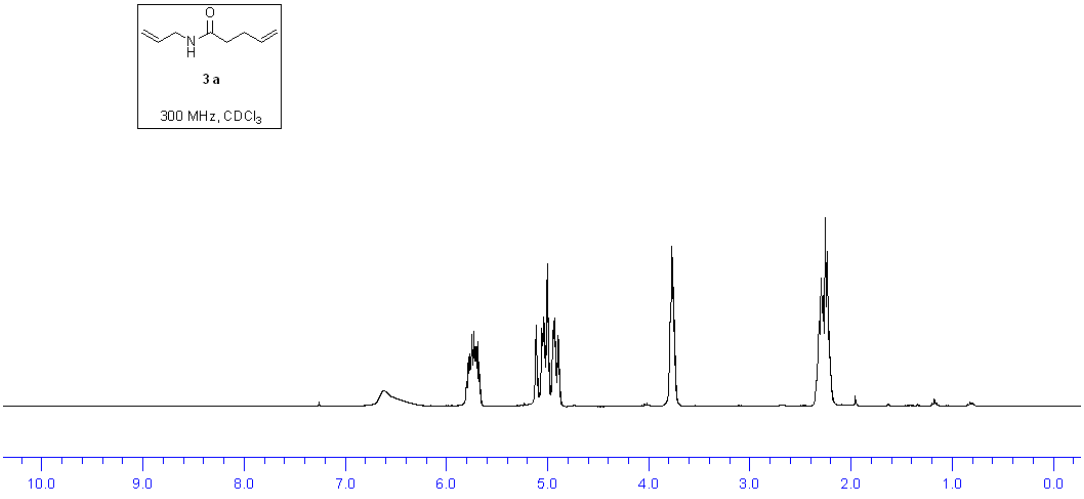
(*E*)-*tert*-butyl-5-(ethoxycarbonyl)pent-2-enylcarbamate (10a):

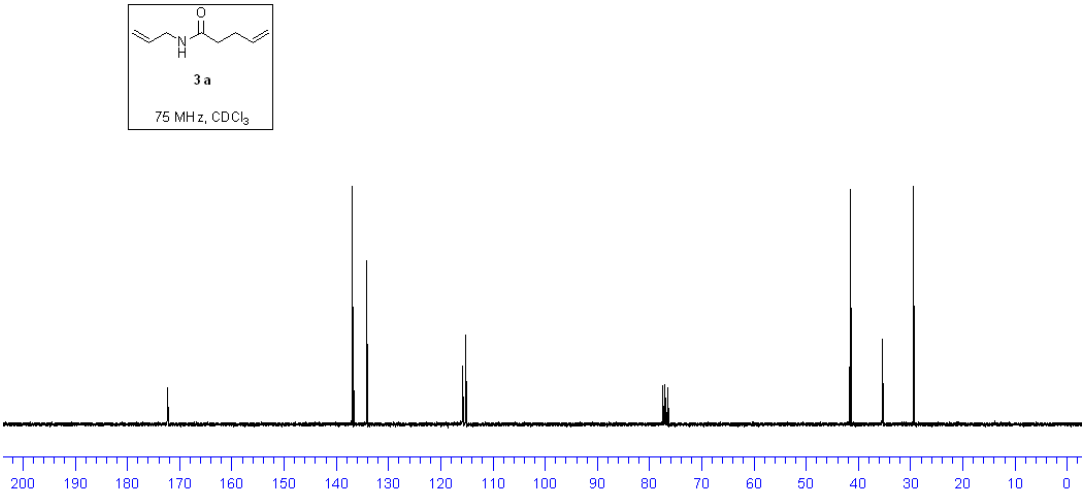
Experimental procedure for **9a** was followed, with macrolactam **6a** (21 mg, 0.0497 mmol), Cs_2CO_3 (24 mg, 0.0745 mmol), and EtOH (142 μL). The crude product **10a** was obtained as a yellow oil (25 mg, 98%) without the need for further purification: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.58 (dt, *J* = 15.2, 6.0 Hz, 1H), 5.49 (dt, *J* = 15.2, 5.6 Hz, 1H), 4.52 (br s, 1H), 4.15–4.09 (m, 2H), 3.67 (m, 2H), 2.39–2.28 (m, 4H), 1.43 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 173.1, 155.7, 130.5, 127.7, 79.3, 60.3, 42.4, 33.8, 28.4 (3 C), 27.4, 14.2; HRMS (FAB) calcd for $C_{13}H_{23}NO_4$ (MNa^+) 280.1519, found 280.1526.

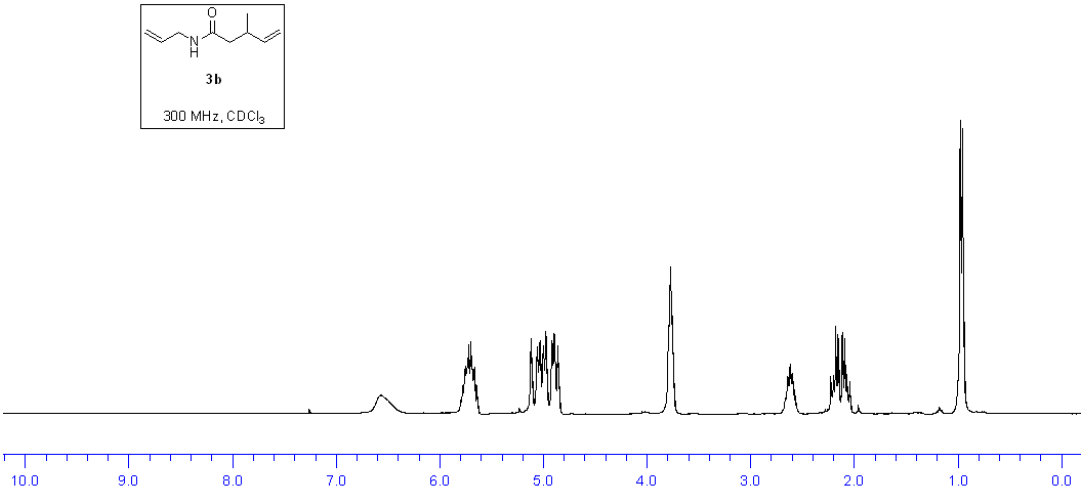


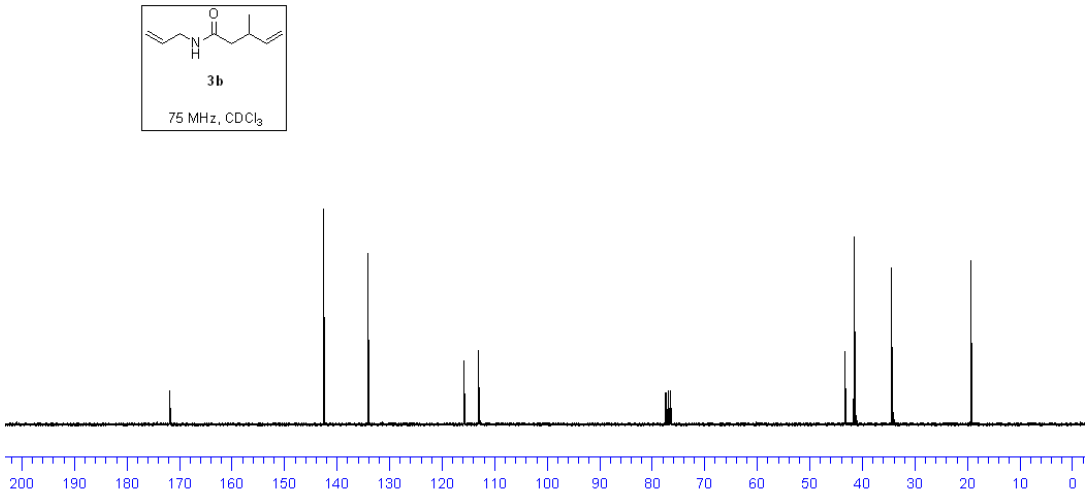
10a

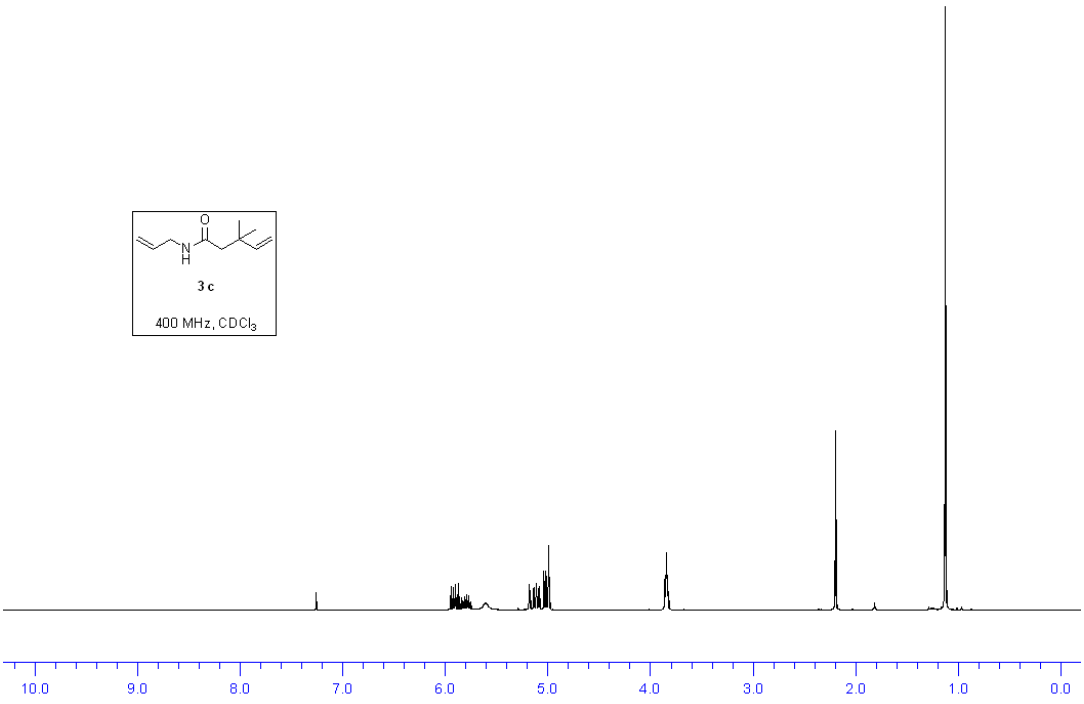
^{1}H and ^{13}C NMR Spectra

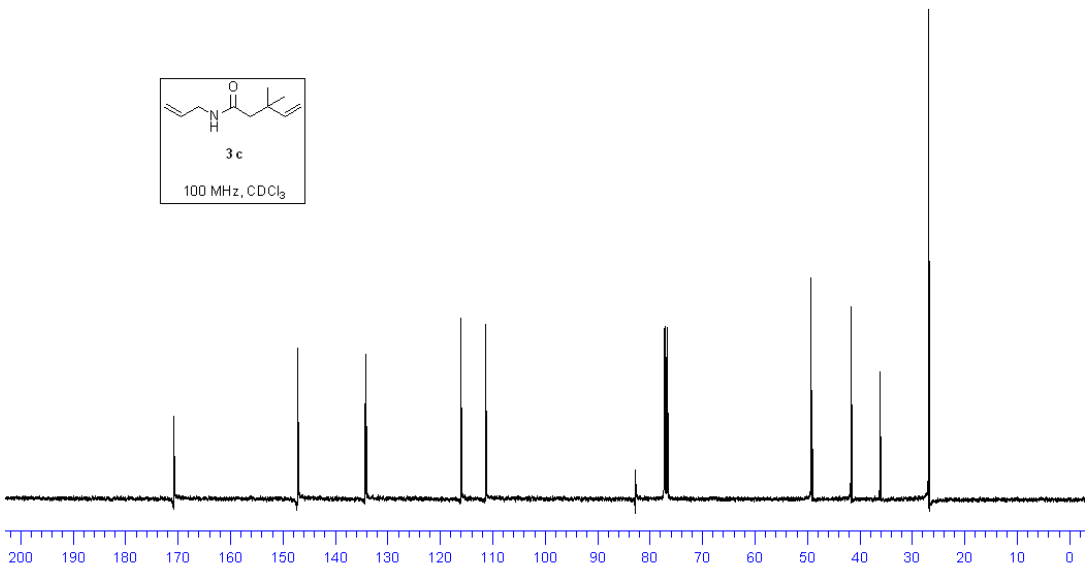

3a
300 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

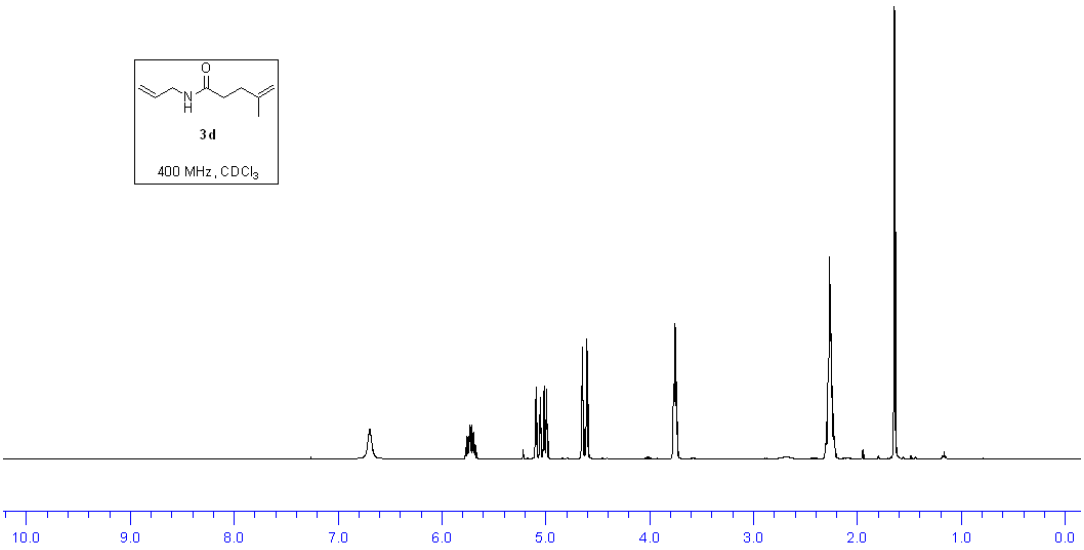

3a
75 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

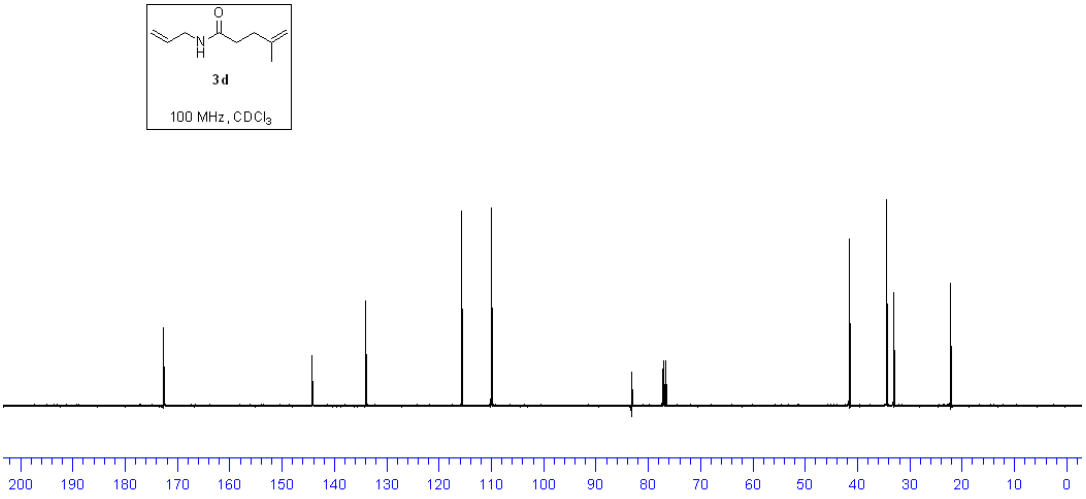

3b
300 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

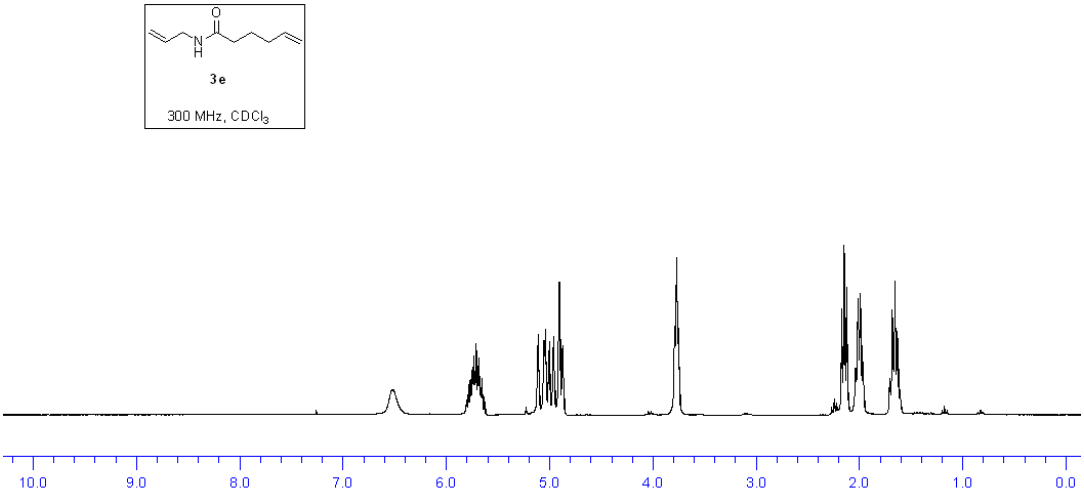

3b
75 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

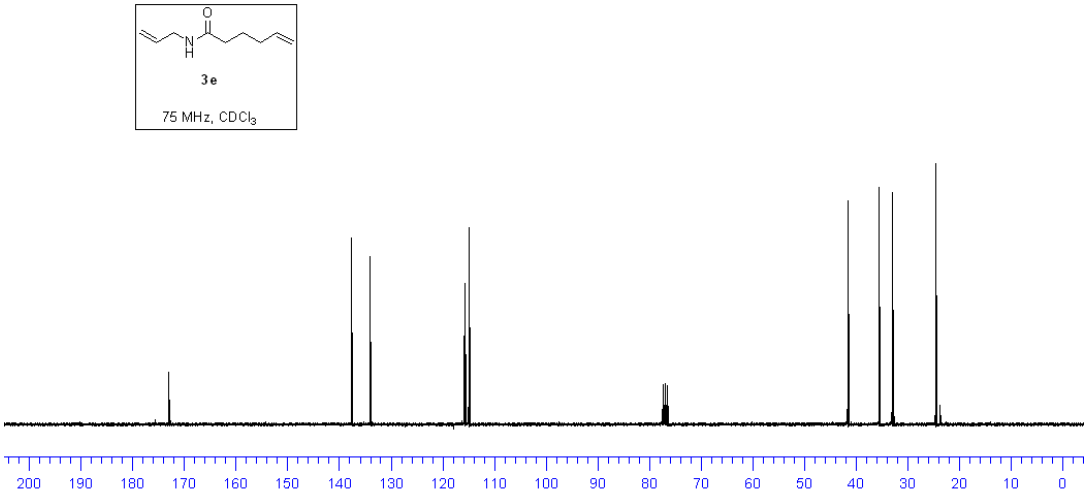

3c
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

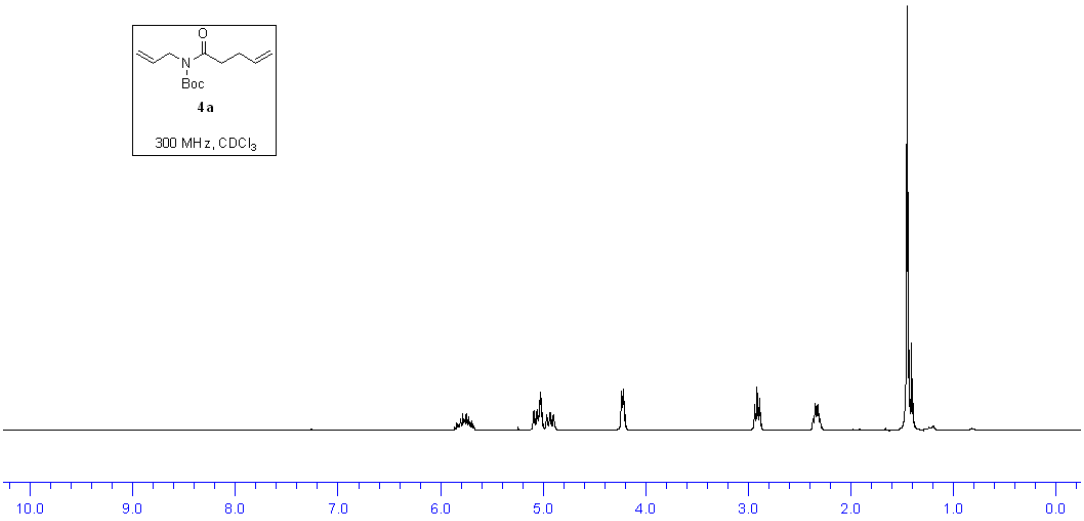

3c
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

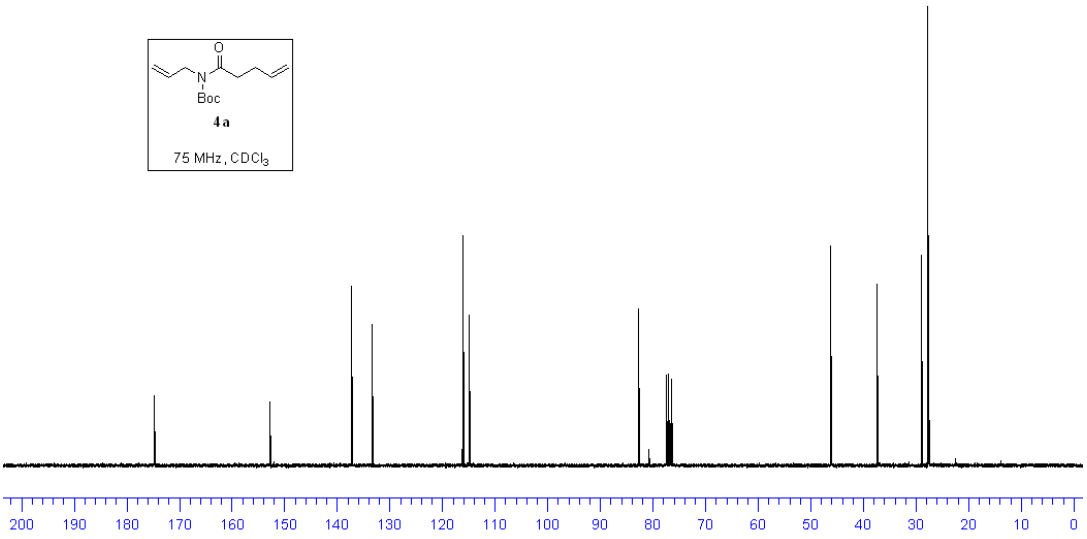

3d
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

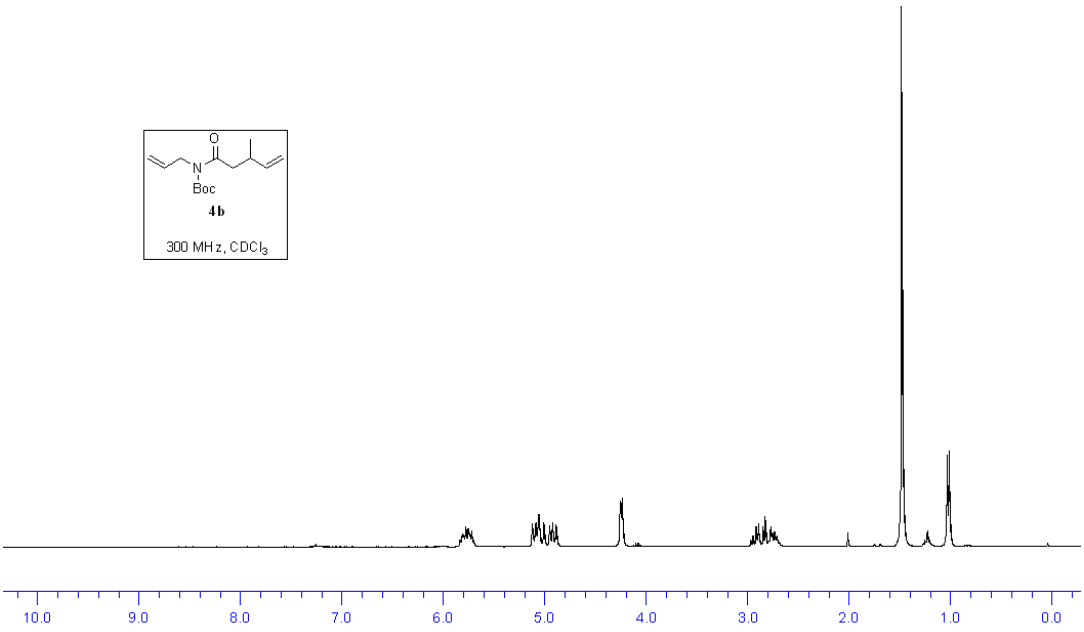

3d
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

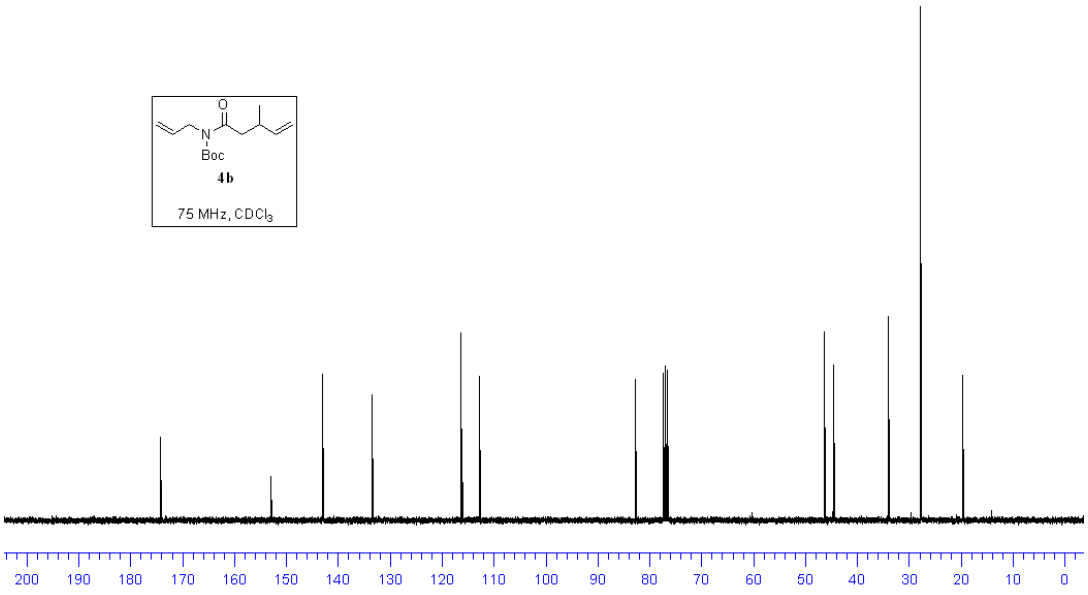

3e
300 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

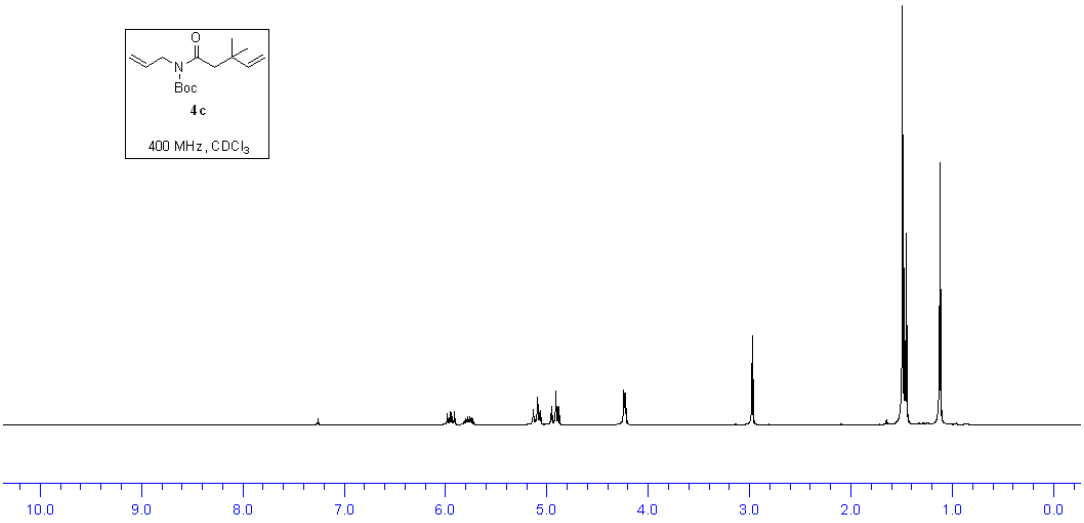

3e
75 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

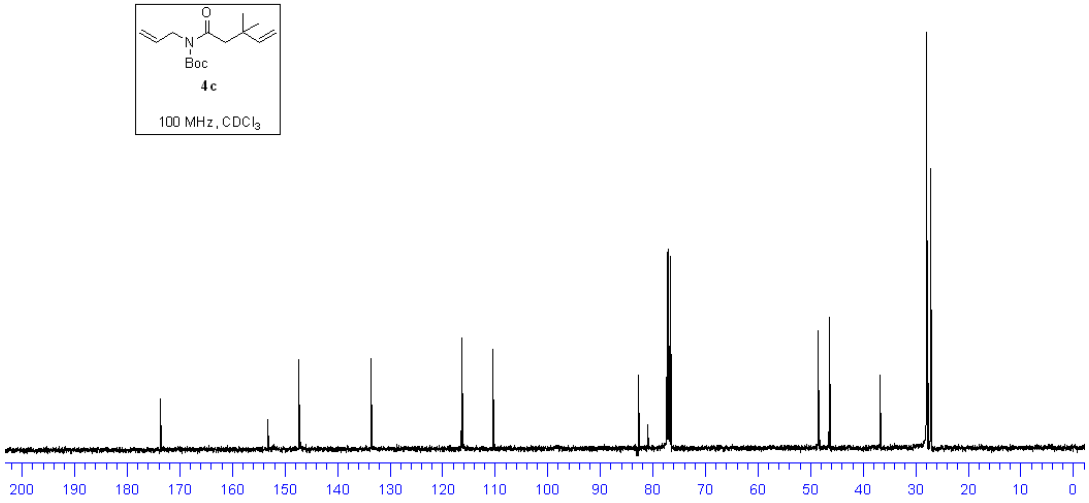

O
N
Boc
4a
300 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

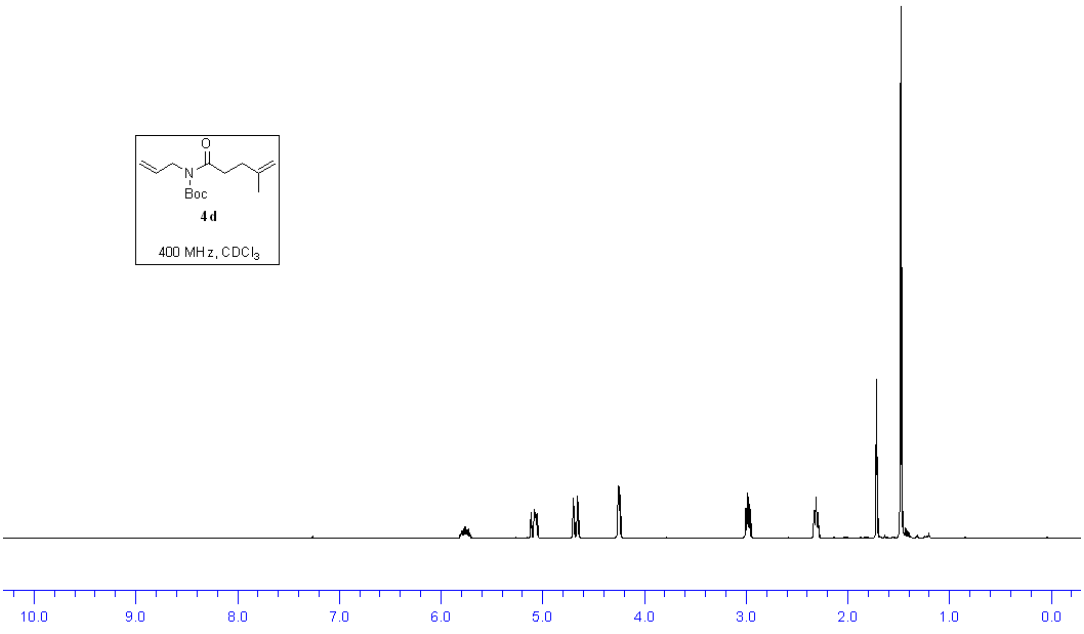

O
N
Boc
4a
75 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

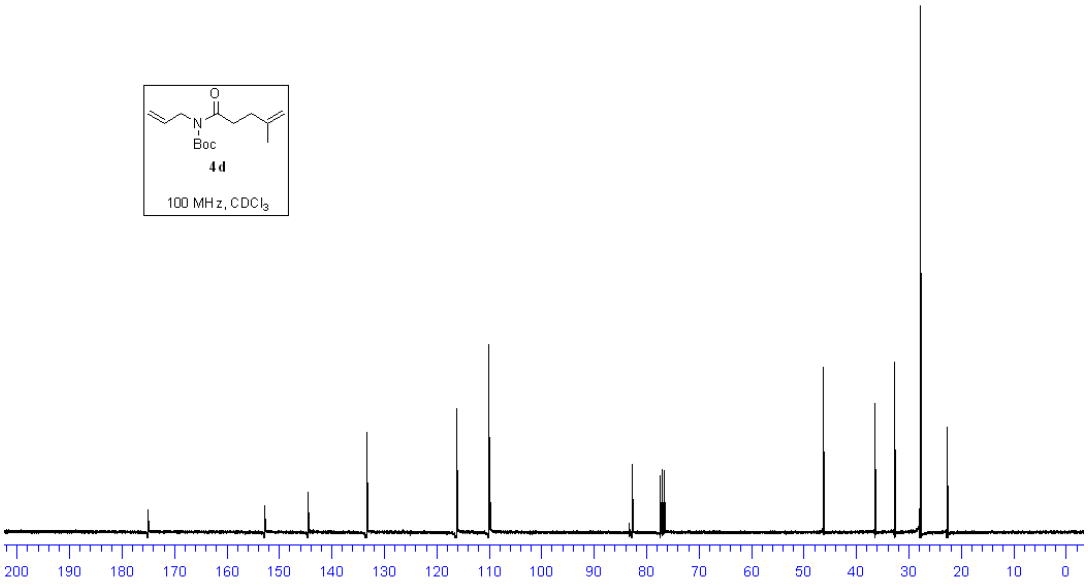

O
N
Boc
4b
300 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

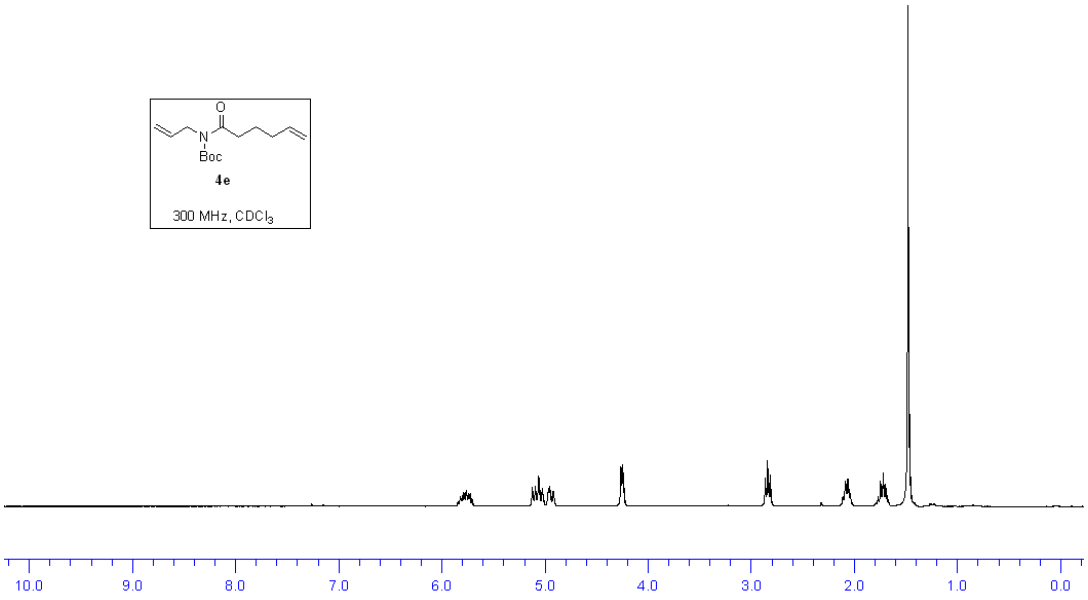

O
N
Boc
4b
75 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

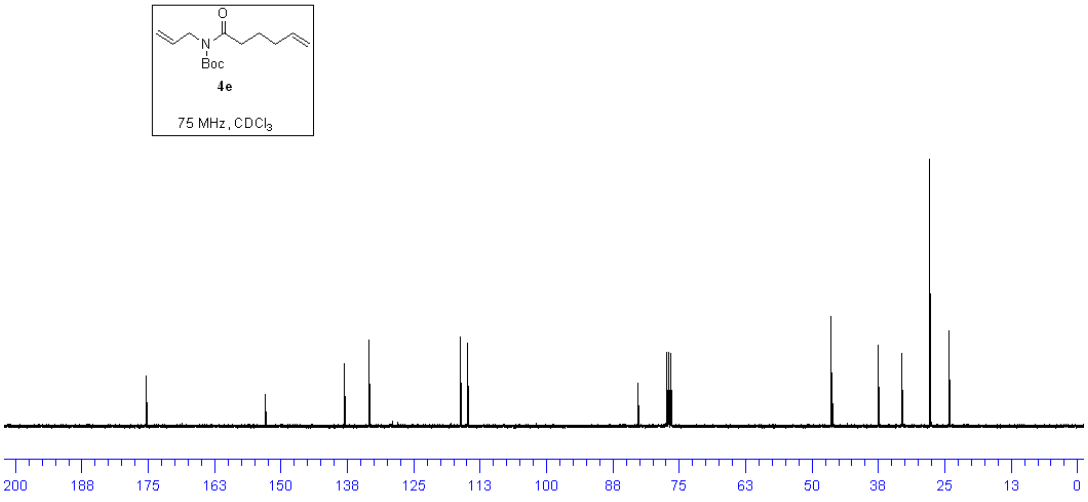

Boc
4c
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

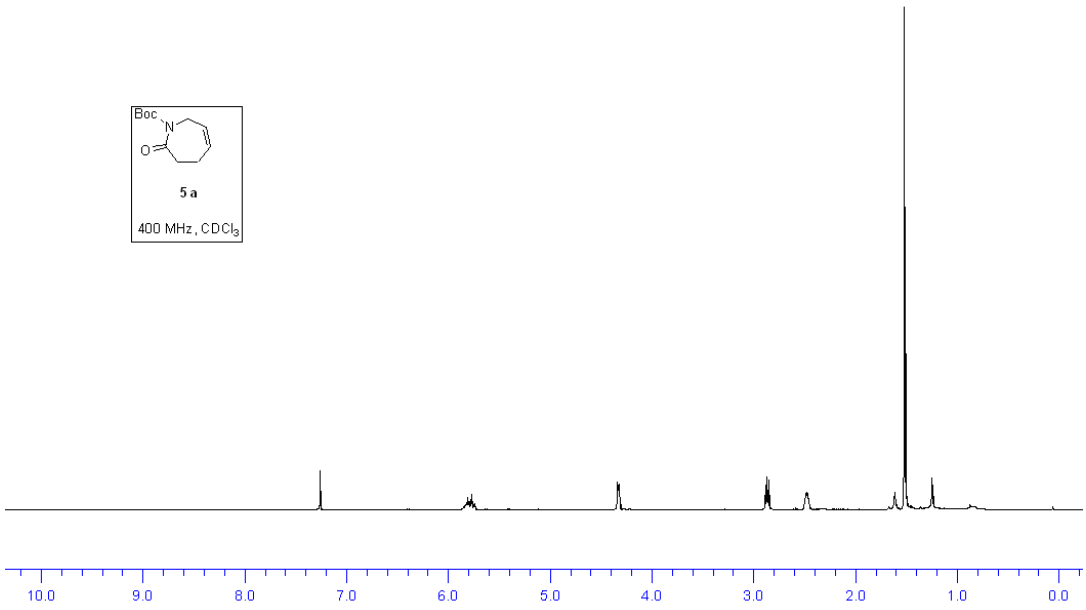

Boc
4c
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

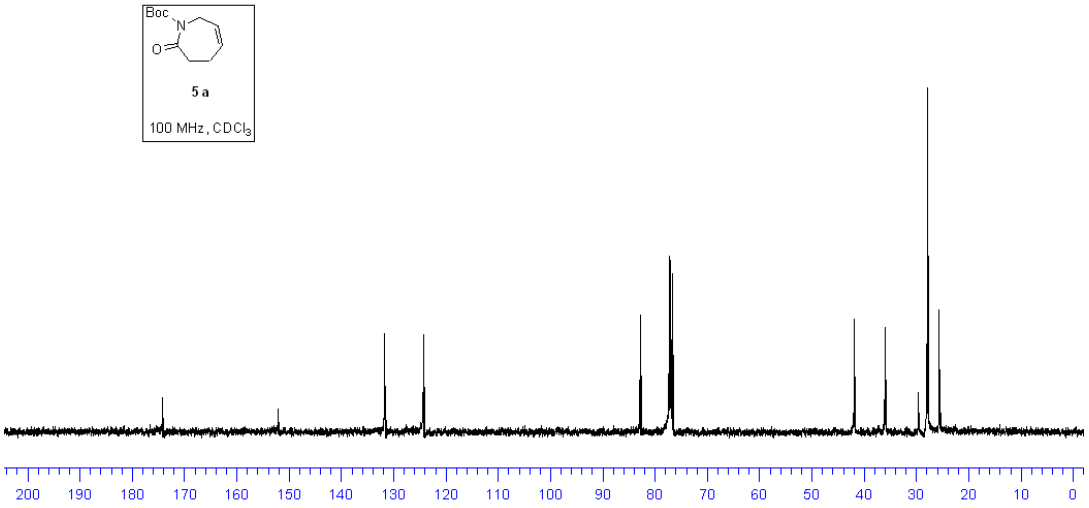

O
N
Boc
4d
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

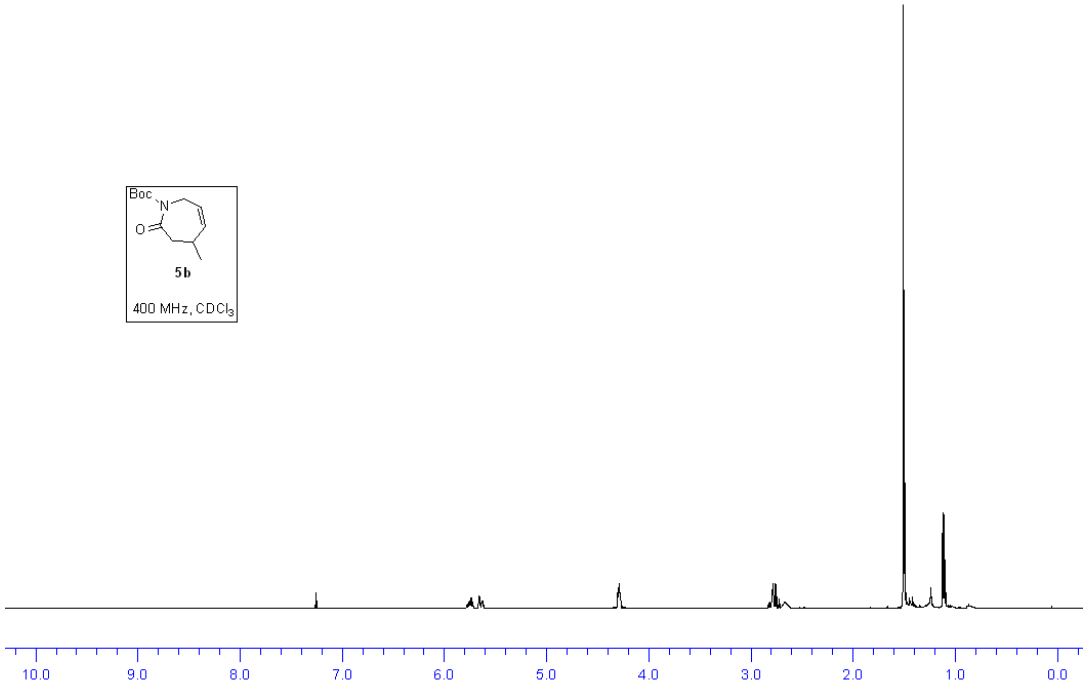

O
N
Boc
4d
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

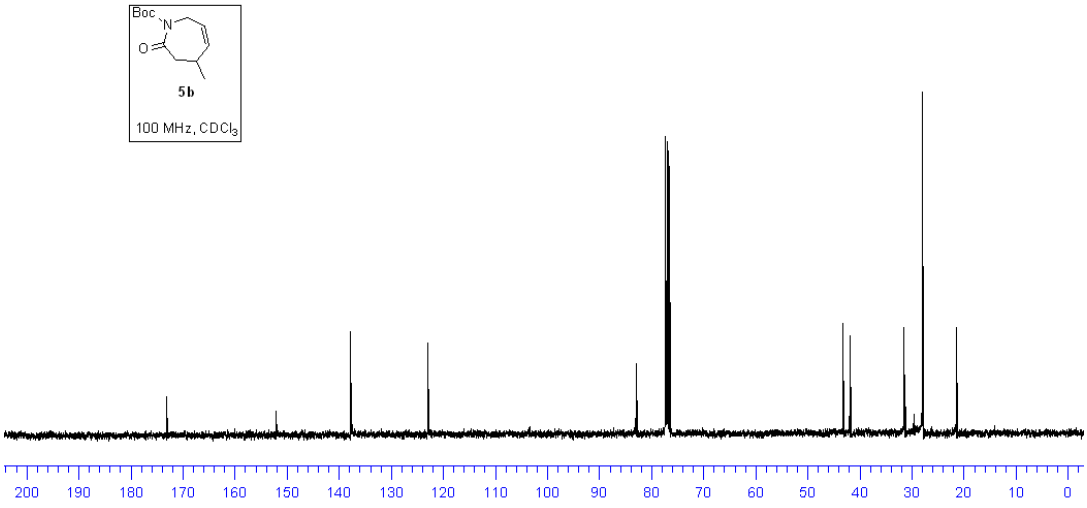

O
N
Boc
4e
300 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

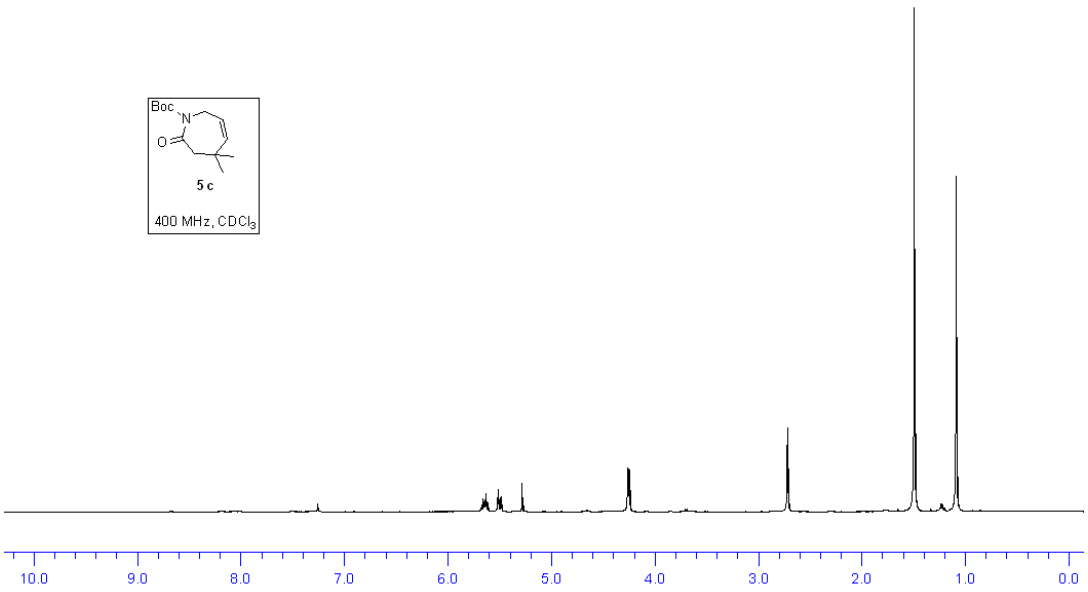

O
N
Boc
4e
75 MHz, CDCl3
200
188
175
163
150
138
125
113
100
88
75
63
50
38
25
13
0

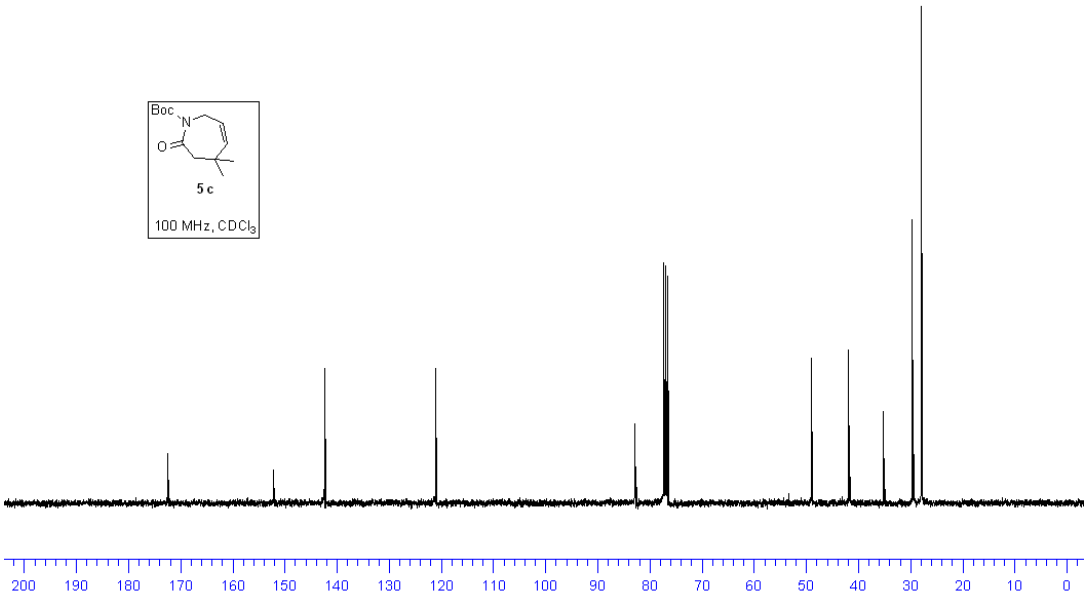

Boc
N
O
5a
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

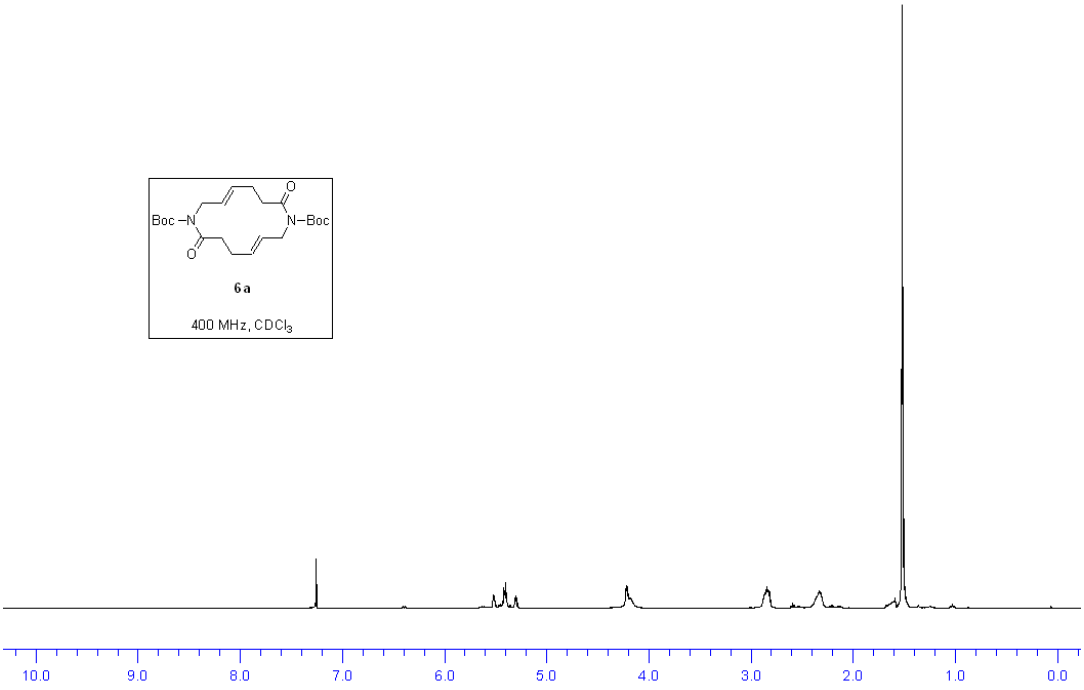

Boc
N
O
5a
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

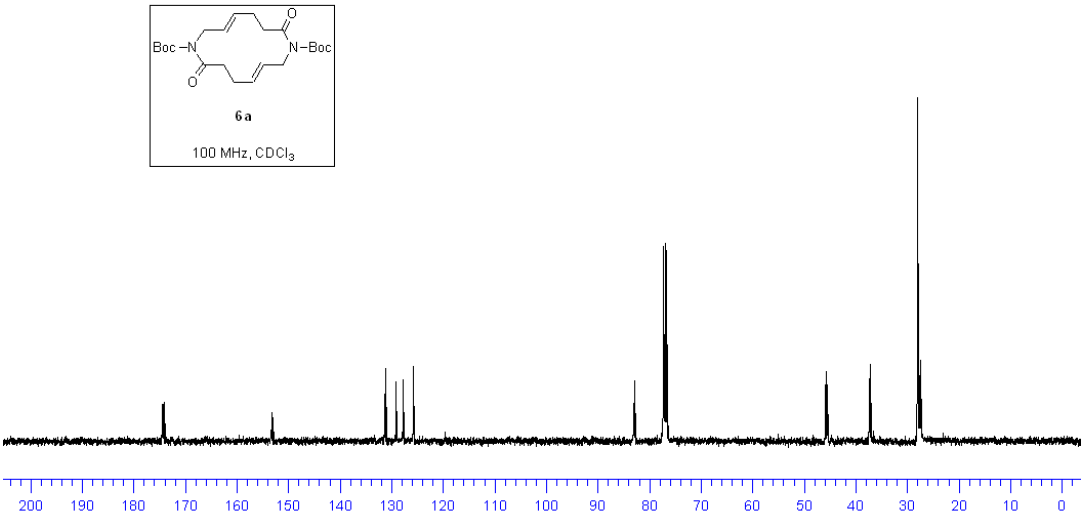

Boc
N
O
5b
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

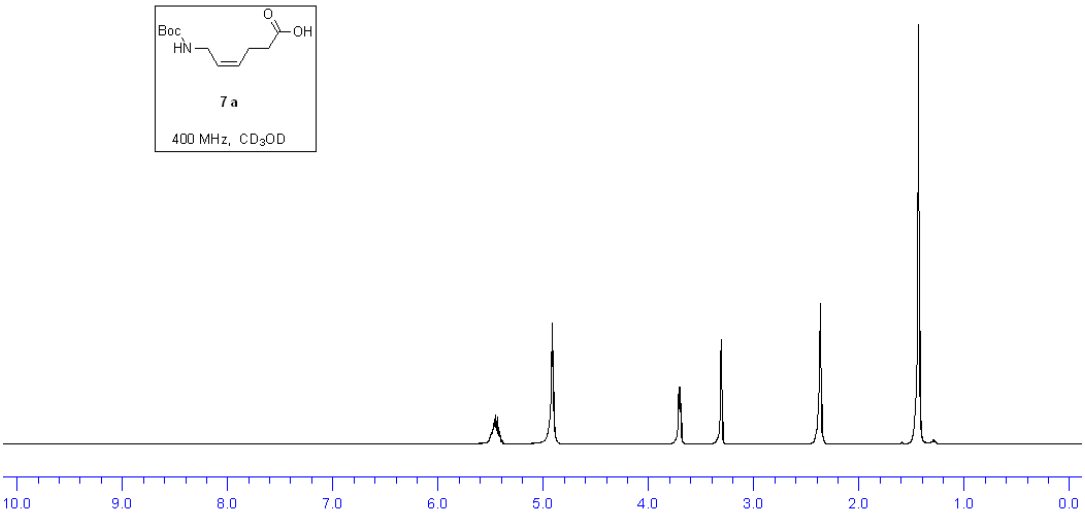

Boc
N
O
5b
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

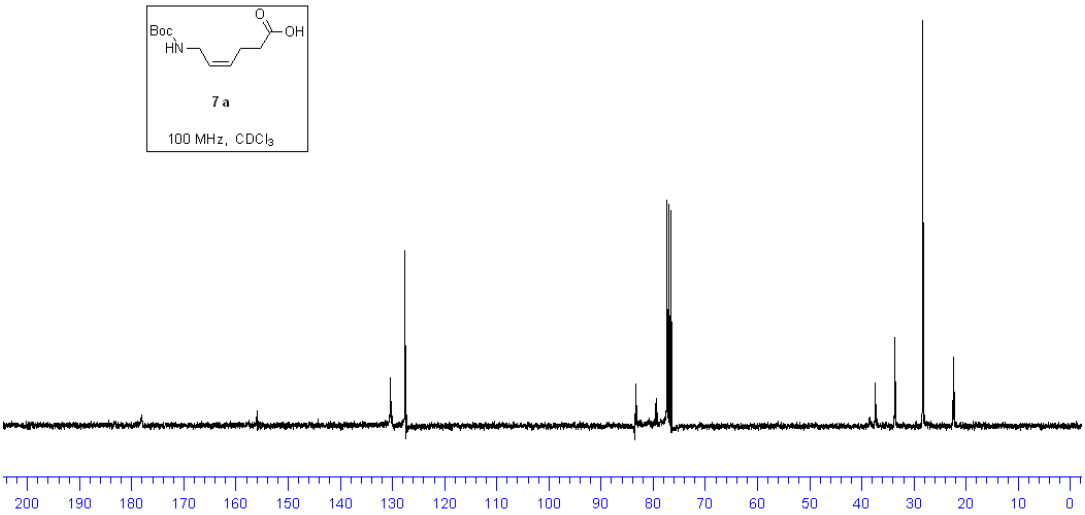

Boc
N
O
5 c
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

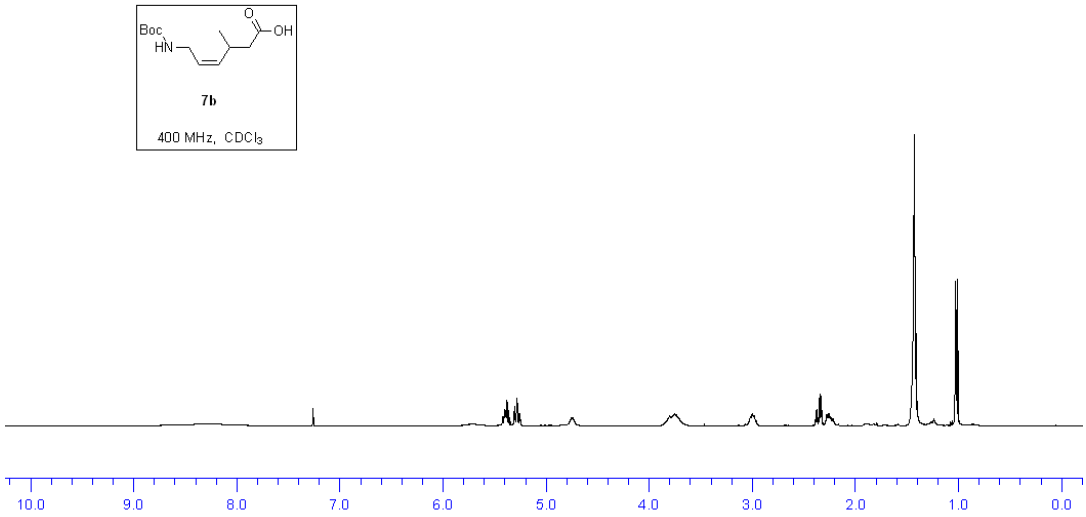

Boc
N
O
5 c
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

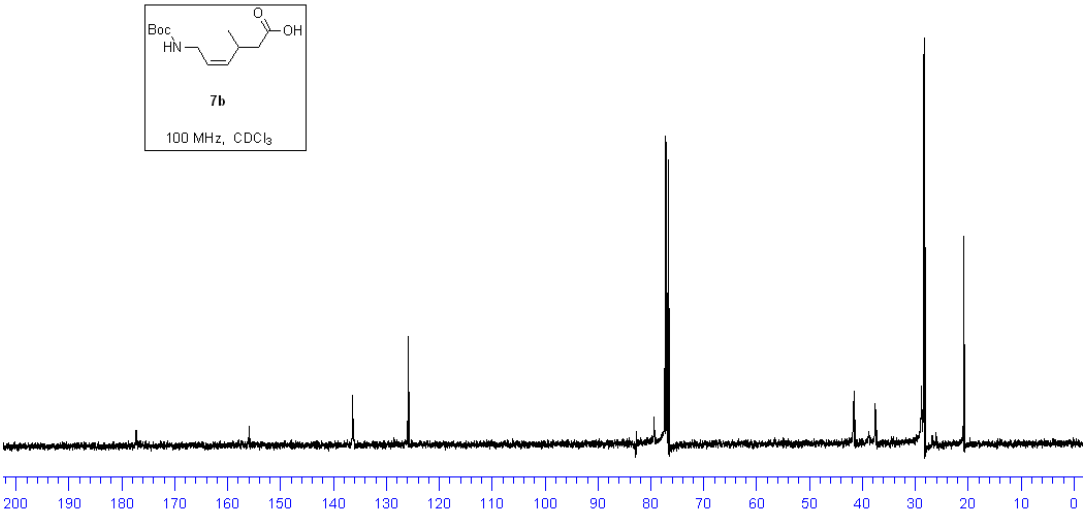

Boc–N
N–Boc
O
O
6a
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

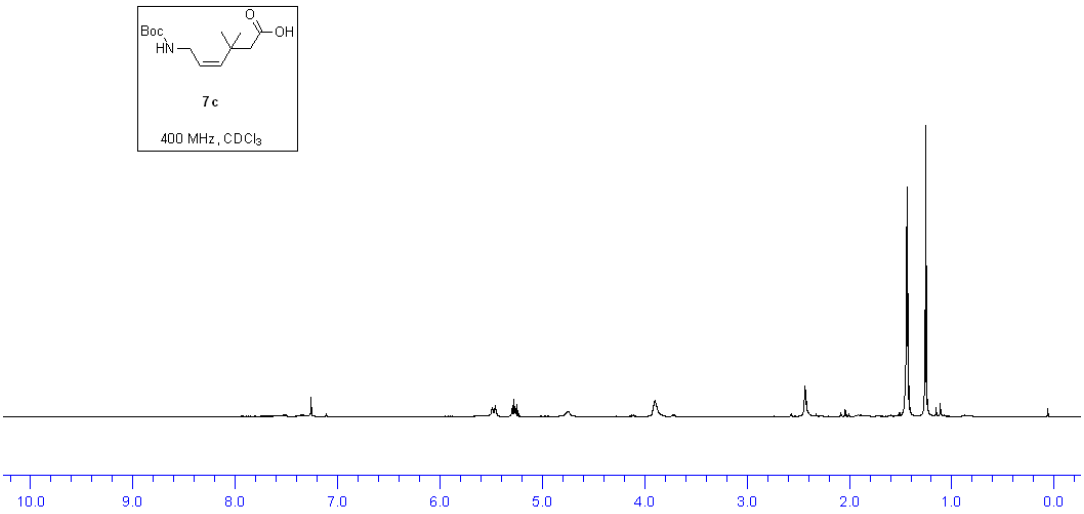

Boc–N
N–Boc
O
O
6a
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

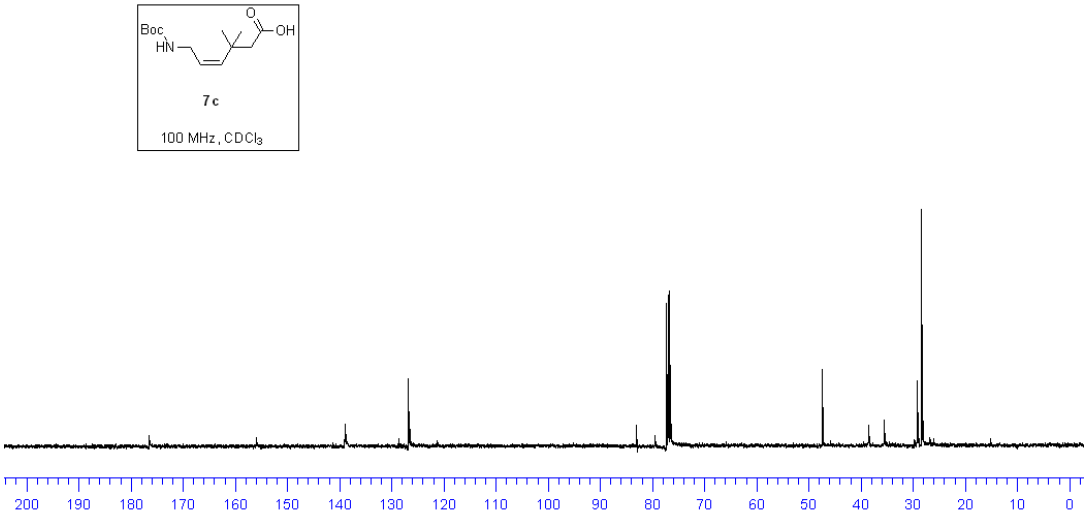

Boc
HN
O
OH
7a
400 MHz, CD3OD
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

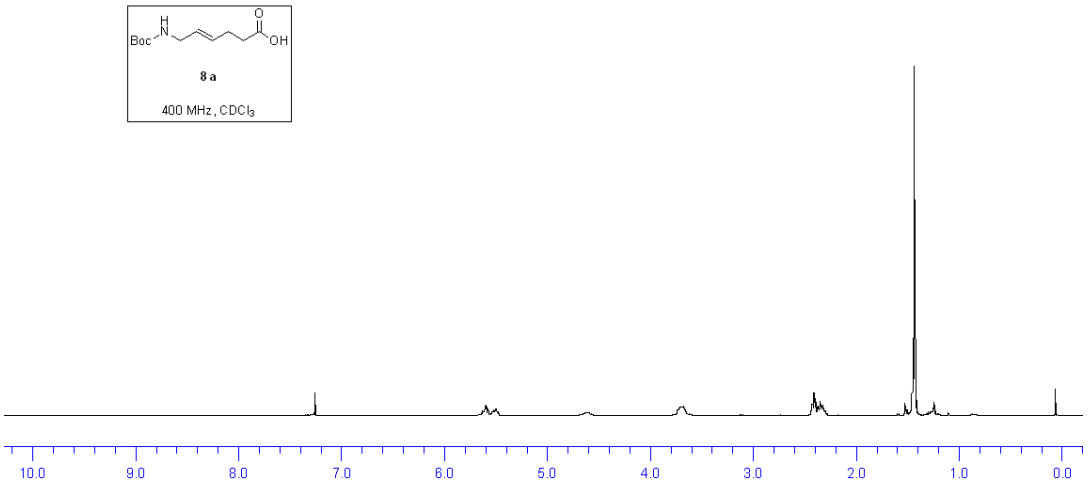

Boc
HN
O
OH
7a
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

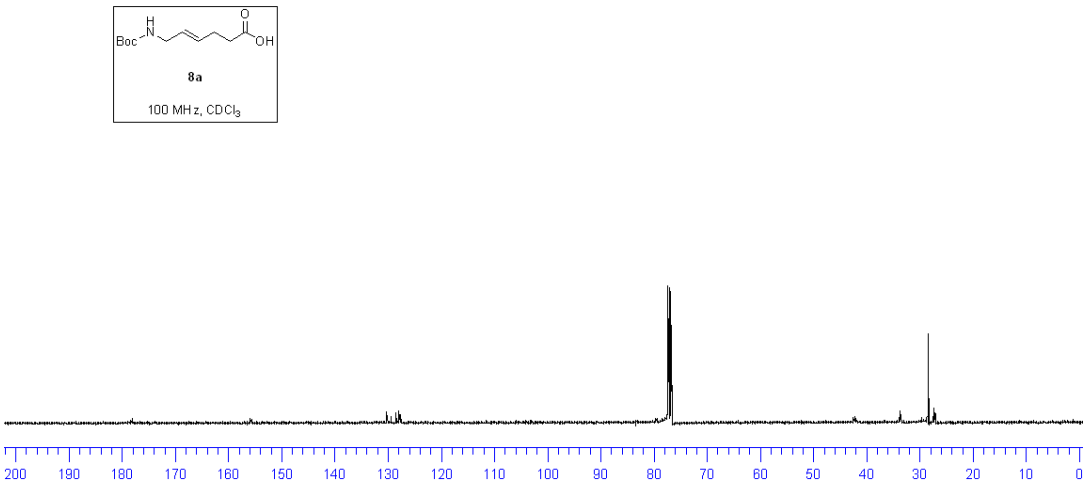

Boc
HN
O
OH
7b
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

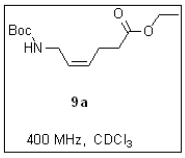

Boc
HN
O
OH
7b
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

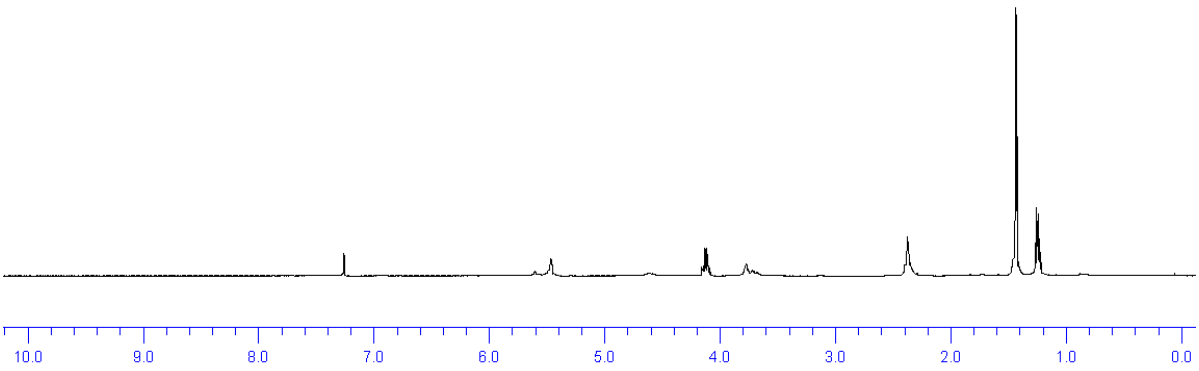

Boc
HN
O
OH
7c
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

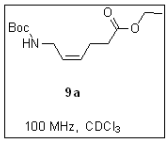

Boc
HN
O
OH
7c
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

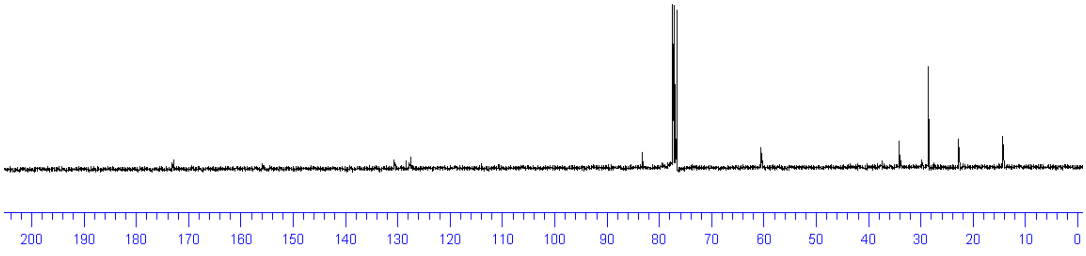

Boc
H
N
O
OH
8 a
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

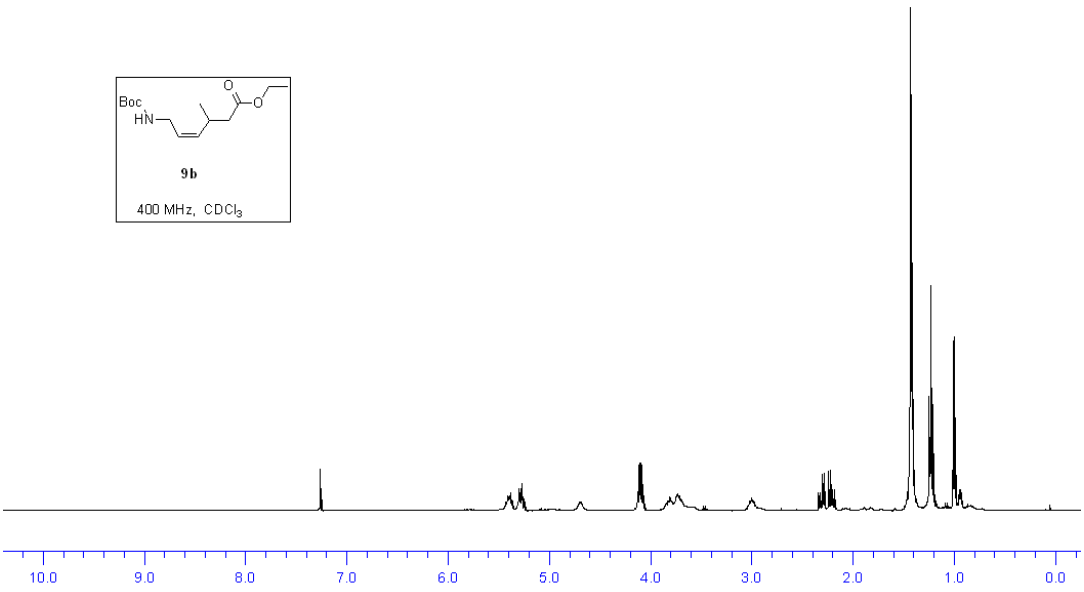

Boc
H
N
O
OH
8a
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

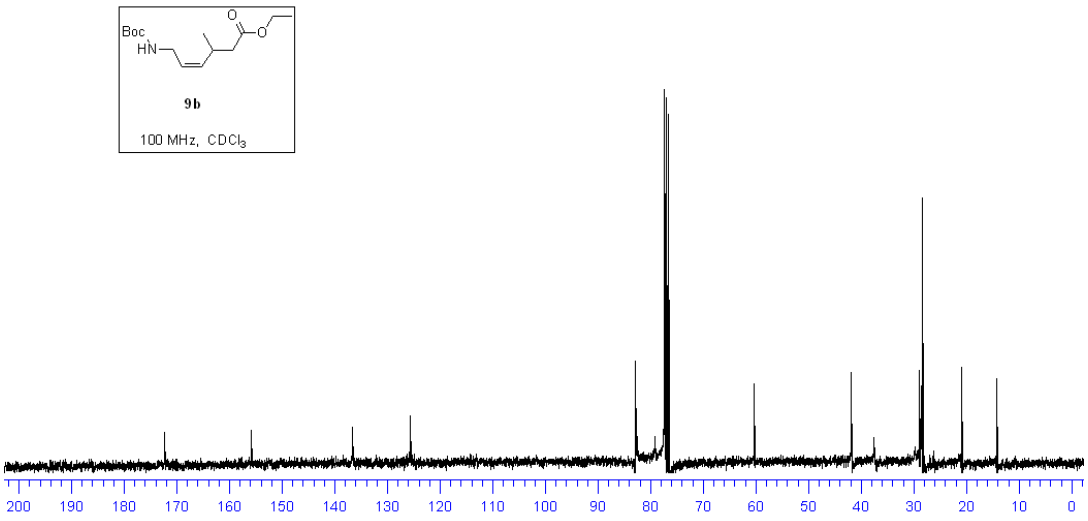

Boc
HN
O
O
9a
400 MHz, CDCl3

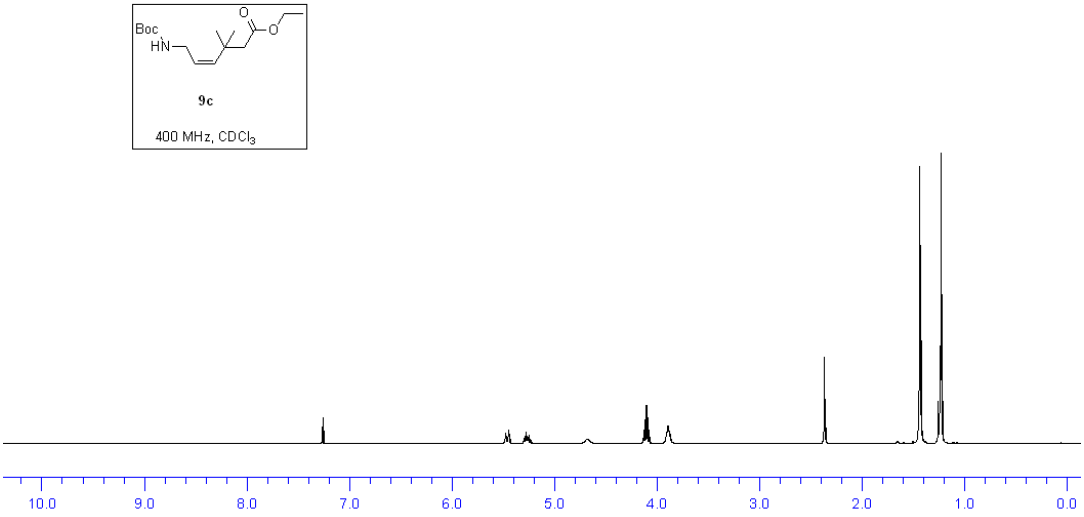

10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

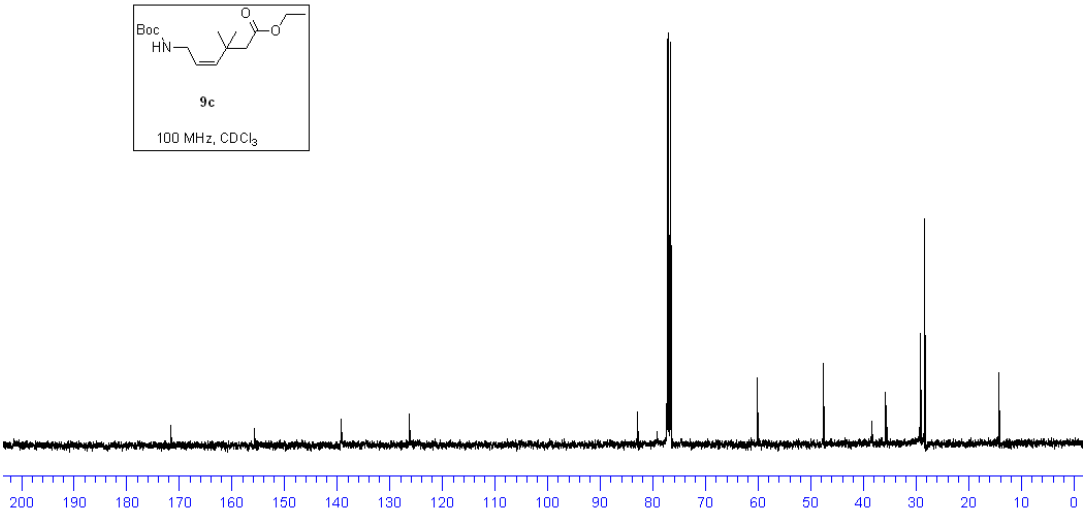

Boc
HN
O
O
9a
100 MHz, CDCl3

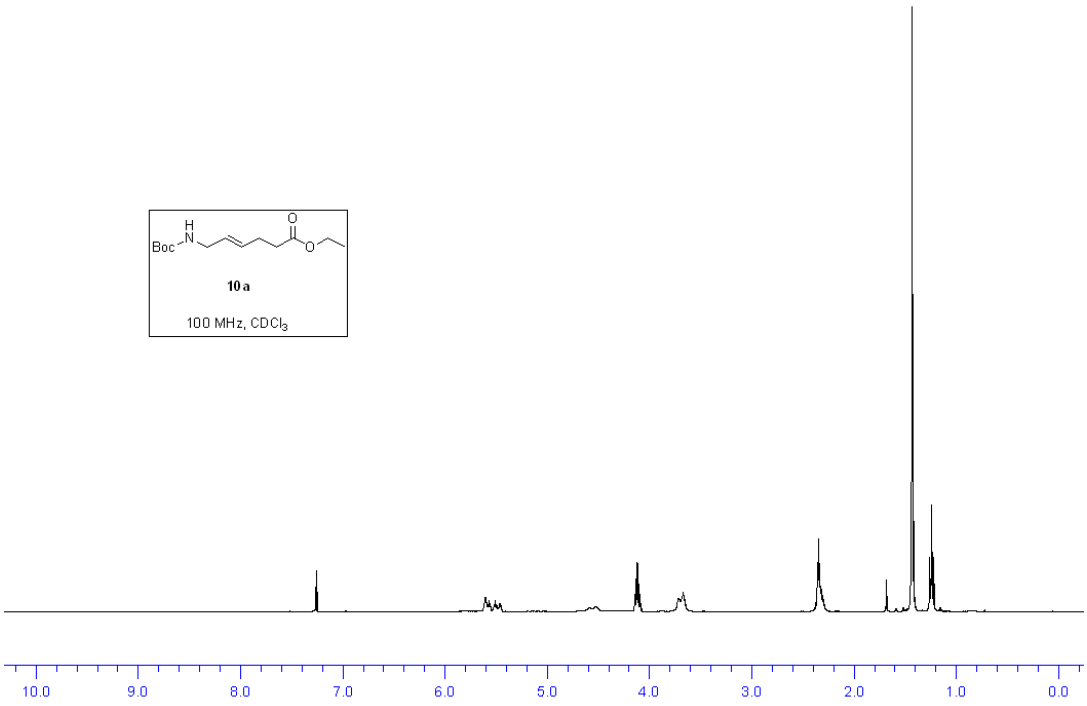

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

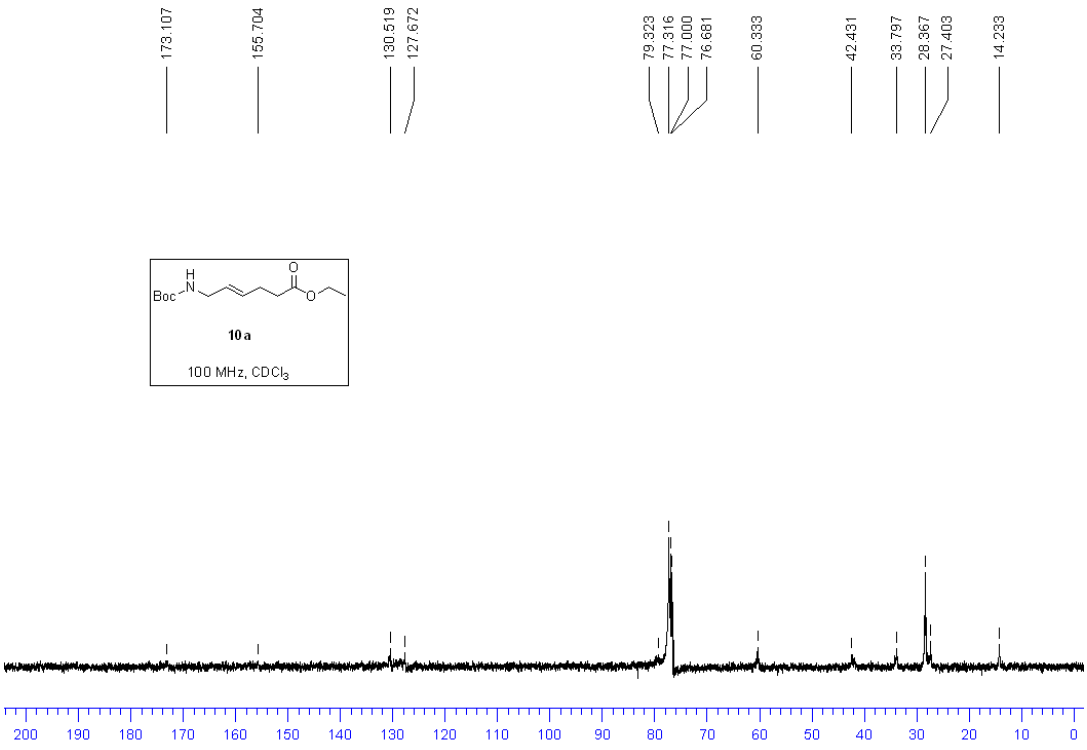

Boc
HN
O
O
9b
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


Boc
HN
O
O
9b
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Boc
HN
O
O
9c
400 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


Boc
HN
O
O
9c
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Boc
H
N
O
O
10 a
100 MHz, CDCl3
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


173.107
155.704
130.519
127.672
79.323
77.316
77.000
76.681
60.333
42.431
33.797
28.367
27.403
14.233
Boc
H
N
O
O
10 a
100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

References for Supplementary Information

(1) F. Gagosz, C. Moutrille and S. Z. Zard, *Org*. *Lett*., 2002, **4**, 2707–2709.

(2) A. Kamimura, K. Tanaka, T. Hayashi and Y. Omata, *Tetrahedron Lett*., 2006, **47**, 3625–3627.

(3) K. McEleney, D. P. Allen, A. E. Holliday and C. M. Crudden, *Org*. *Lett*., 2006, **8**, 2663–2666.