Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Organocatalysed synthesis of isoxazolines initiated by a chemoselective oxa-Michael reaction of *N*-BocNHOH

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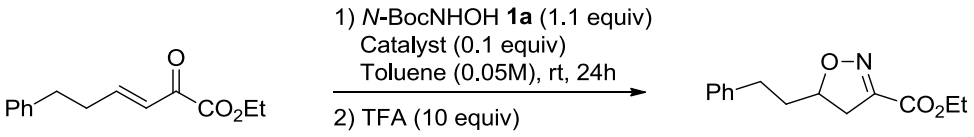
I General information

Solvents were purchased as dehydrated ones, and toluene or CH_2Cl_2 was distilled on CaH_2. All reagents were used as received unless otherwise indicated. Chromatographic purification of compounds was achieved with 60 silica gel (40-63 μm).[1] Thin layer chromatography was carried out on silica gel 60 F_{254} (1.1 mm) with spot detection under UV light or phosphomolybdic acid or ninhydrine or $KMnO_4$ oxidation. ^{1}H NMR spectra were recorded on a Bruker AVANCE 300 at 300 MHz. Data appear in the following order: chemical shifts in ppm, number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant *J* in Hz. ^{13}C NMR spectra were acquired at 75.4 MHz operating with broad band ^{1}H decoupling. The hydrogen multiplicity was obtained by DEPT135. IR spectra were recorded on a Perkin Elmer IRTF 100 spectrometer using an ATR (Attenuated Total Reflectance) sampling with solid dispersed or neat or on a Perkin Elmer IRFT 1650 with solid dispersed on KBr pastille. Mp's stand uncorrected. HRMS analyses were measured on a Q-TOF Micro WATERS spectrometer. HPLC analyses were performed with Daicel Chiralpack® or Daicel ChiralCel® columns (4.6 mm × 25 cm). A spectrosystem UV 1000 thermofisher detector and a chiral detector (polarimeter) JACSCO OR-1590 were used.

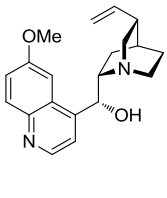
[1] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

II Optimization

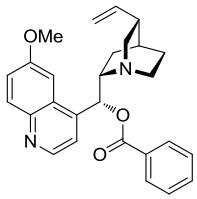
II-1 Screening of organocatalysts



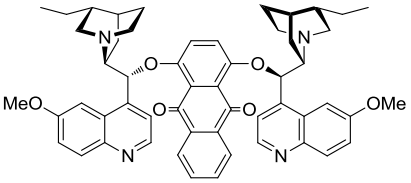
2a **4a**



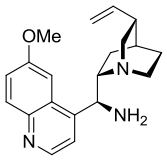
5% ee, 86%



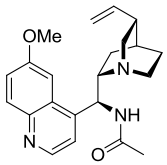
6% ee, 61%



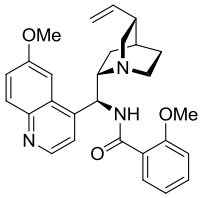
17% ee, 93%



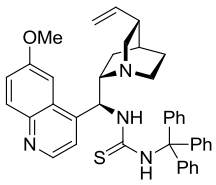
1% ee, 90%



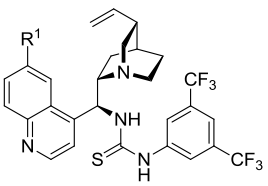
0% ee, 98%



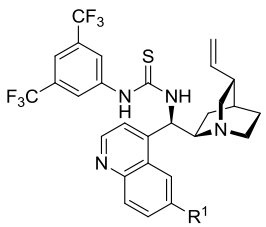
2% ee, 70%



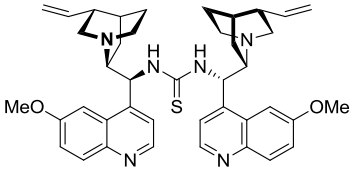
24% ee, 39%



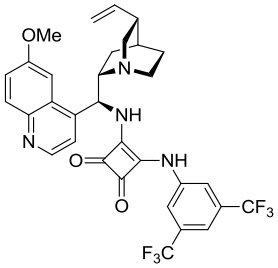
R^1 = OMe 34% ee, 82%
R^1 = H 28% ee, 95%



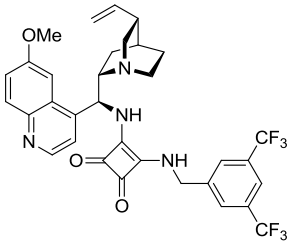
R^1 = OMe 27% ee, 98%
R^1 = H 28% ee, 86%



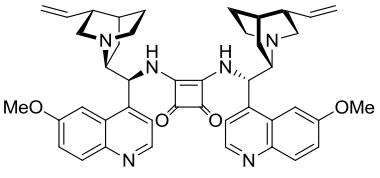
28% ee, 90%



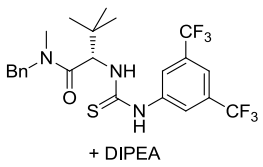
55% ee, 82%



4% ee, 86%

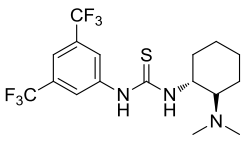


40% ee, 68%

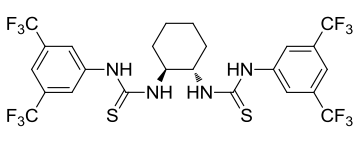


+ DIPEA

5% ee, 38%

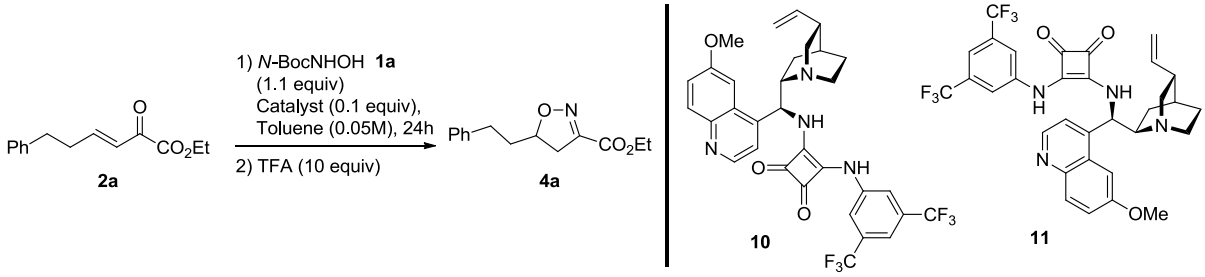


8% ee, 90%



31% ee, 19%

II-2 Representative optimizations: solvent, concentration and temperature

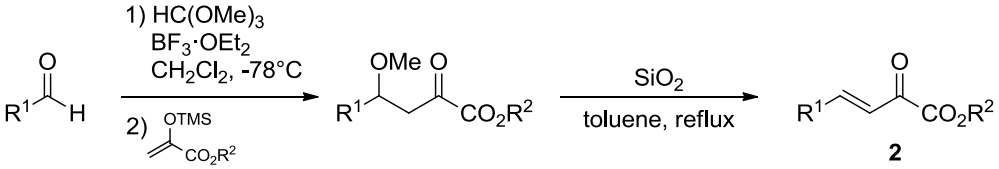


Entry	Catalyst	Solvent	Temp (°C)	Yield (%)[b]	ee (%)[c]
1	**11**	Toluene	rt	93	69
2	**11**	CH_2Cl_2	rt	77	45
3	**11**	THF	rt	86	55
4	**11**	Et_2O	rt	82	58
5	**11**	MeC_6H_{11}	rt	88	45
6	**11**	*m*-xylene	rt	62	66
7	**11**	$PhCF_3$	rt	82	63
8	**11**	MeCN	rt	82	55
9	**11**	DMF	rt	79	55
10	**11**	EtOH	rt	79	61
11	**11**	Toluene[d]	rt	86	70
12	**11**	Toluene (0.1 M)	rt	86	59
14	**11**	Toluene (0.025 M)	rt	82	70
17	**11** (5 mol%)	Toluene	rt	82	57
15	**11**	Toluene	rt	82	76[e]
16	**11**	Toluene	0°C	93	69[e]
17	**10**	Toluene	rt	82	55[f]
18	**10**	Toluene	rt	87	60
19	**10**	Toluene	rt	87	73[e]

[a] Unsaturated ketoester **2a** (0.10 mmol, 1 equiv), catalyst (0.01 mmol, 0.1 equiv), toluene (2.0 mL, 0.05 M), *N*-Boc hydroxylamine **1** (0.11 mmol, 1.1 equiv) was added in solution (0.37 M in toluene) in one-portion; then TFA (1.0 mmol, 10 equiv). [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] DMAc (1 equiv) was used as additive. [e] *N*-Boc hydroxylamine **1a** (0.11 mmol, 1.1 equiv) was added dropwise in solution (0.37 M in toluene) over 4 hours. [f] *N*-Boc hydroxylamine **1a** (0.11 mmol, 1.1 equiv) was added as a solid in one-portion (remark: the reaction is completed after 2 hours).

III Experimental procedures

III.1 unsaturated ketoesters 2

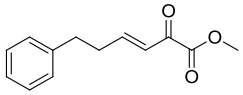


Typical procedure for unsaturated ketoester 2 preparation

To a solution of aldehyde (1.0 equiv) and trimethyl orthoformate (1.05 equiv) in anhydrous CH_2Cl_2 (0.4 M) was added dropwise $BF_3{\cdot}0Et_2$ (1.05 equiv) under Ar at -78°C. After 30 min, a solution of silyl enol ether (1.0 equiv) in CH_2Cl_2 (3.2 M) was added dropwise into the mixture at the same temperature with stirring. After 30 min, the reaction mixture was warmed to -30°C over 2 h and stirred for an additional 1 h at 0°C. The reaction was then quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in toluene (0.2 M) and silica gel for chromatography (1 g/mmol) was added to the solution, and then the mixture was refluxed with vigorous stirring for 3 h. After being cooled to room temperature, the silica gel was filtered off and washed with diethyl ether several times. The filtrate was combined and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give the expected compound.

Compound **2a**,[2] **2d**,[3] **2e**,[4] **2f**,[4] **2h**[5] and **2j**[6] have previously been reported and spectral data are in accordance with the literature.

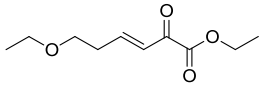
(E)-Methyl 2-oxo-6-phenylhex-3-enoate **2c**



[2] H. Sugimura and K. Yoshida, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 3209.
[3] R. P. Herrera, D. Monge, E. Martin-Zamora, R. Fernandez and J. M. Lassaletta, *Organic Letters*, 2007, **9**, 3303.
[4] L. Gremaud and A. Alexakis, *Angew. Chem. Int. Ed.*, 2012, **51**, 794.
[5] D. Bonnaffe, H. Simon, *Tetrahedron*, 1992, **48**, 9695.
[6] E. D. Stecher, M. J. Incorvia, B. Kerben, D. Lavine, M. Cen, E. Suhl, *J. Org. Chem.*, 1973, **38**, 4453.

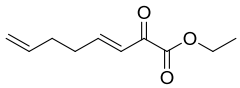
Following the general procedure A with 3-phenylpropionaldehyde (7.7 mL, 58.5 mmol), the title compound **2c** was obtained as pale yellow oil (3.61 g, 28%). R_f = 0.28 (Petroleum ether/EtOAc: 9/1). IR (neat) ν_{max} 3027, 2954, 1734, 1675, 1622, 1100, 1140, 1079, 971, 748, 699 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.34-7.17 (5H, m), 6.69 (1H, dt, J = 1.5, 15.9 Hz), 3.89 (3H, s), 2.86-2.81 (2H, m), 2.68-2.60 (2H, m). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 182.9 (C), 162.7 (C), 154.0 (CH), 140.4 (C), 128.7 (CH), 128.4 (CH), 126.5 (CH), 125.5 (CH), 53.0 (CH3), 34.9 (CH2), 34.1 (CH2).

(E)-Ethyl 6-ethoxy-2-oxohex-3-enoate **2g**



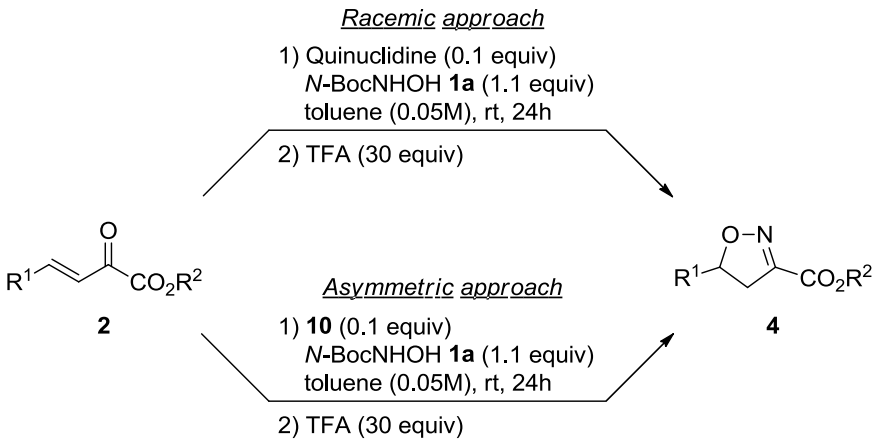
Following the general procedure A with 1,1,3-triethoxypropane (1.25 g, 7.09 mmol), the title compound **2g** was obtained as pale yellow oil (225 mg, 16%). R_f = 0.25 (Petroleum ether/EtOAc: 9/1). IR (neat) ν_{max} 2978, 2869, 1730, 1701, 1677, 1625, 1150, 1109, 1074, 1014, 976 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.18 (1H, dt, J = 6.8, 15.9 Hz), 6.72 (1H, dt, J = 1.5, 15.9 Hz), 4.33 (2H, q, J = 7.1 Hz), 3.56 (2H, t, J = 6.4 Hz), 3.48 (2H, q, J = 7.0 Hz), 2.60-2.53 (2H, m), 1.36 (3H, t, J = 7.1 Hz), 1.18 (3H, t, J = 7.0 Hz). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 183.3 (C), 162.4 (C), 151.6 (CH), 126.4 (CH), 68.2 (CH2), 66.5 (CH2), 62.5 (CH2), 33.1 (CH2), 15.2 (CH3), 14.2 (CH3).

(E)-ethyl 2-oxoocta-3,7-dienoate **2i**



Following the general procedure A with 4-pentenal (600 mg, 7.13 mmol), the title compound **2i** was obtained as pale yellow oil (485 g, 37%). R_f = 0.16 (Petroleum ether/EtOAc: 95/5). IR (neat) ν_{max} 2982, 2939, 1730, 1701, 1677, 1623, 1262, 1146, 1088, 989 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.17 (1H, dt, J = 6.7, 15.9 Hz), 6.66 (1H, dt, J = 1.5, 15.9 Hz), 5.79 (1H, ddt, J = 6.5, 10.2, 16.7 Hz), 5.09-4.99 (2H, m), 4.33 (2H, q, J = 7.1 Hz), 2.45-2.37 (2H, m), 2.29-2.22 (2H, m), 1.37 (3H, t, J = 7.1 Hz). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 183.4 (C), 162.5 (C), 154.0 (CH), 136.7 (CH), 125.6 (CH), 116.0 (CH2), 62.4 (CH2), 32.4 (CH2), 31.8 (CH2), 14.1 (CH3).

III.2 Isoxazolidine 4

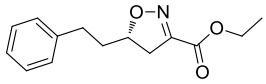


Typical procedure B for racemic isoxazolidinine preparation. A solution of unsaturated ketoester **2** (0.25 mmol), *N*-Boc hydroxylamine (36.6 mg, 0.275 mmol, 1.1 equiv) and quinuclidine (2.8 mg, 0.025 mmol, 0.1 equiv) in toluene (5 mL, 0.05 M) into a Schlenk flask was stirred at room temperature. After stirring for 24h, TFA (580 µL, 7.57 mmol, 30 equiv) was added and the resulting solution was stirred for 1h. The reaction mixture was partitioned between a saturated aqueous $NaHCO_3$ solution (10 mL) and Et_2O (10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to give the expected compound.

Representative procedure for compound 4a

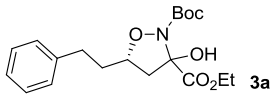
To a solution of unsaturated ketoester **2a** (0.25 mmol) and catalyst **10** (15.8 mg, 0.025 mmol, 0.1 equiv) in toluene (5 mL, 0.05M) into a Schlenk flask was added dropwise over 4h a solution of *N*-Boc hydroxylamine (36.6 mg, 0.275 mmol, 1.1 equiv) in toluene (750 µL). After stirring for 24h at 20°C, TFA (580 µL, 7.57 mmol, 30 equiv) was added and the resulting solution was stirred for 1h. The reaction mixture was partitioned between a saturated aqueous $NaHCO_3$ solution (10 mL) and Et_2O (10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to give the expected **4a** as a pale yellow oil (54 mg, 87%).

Ethyl 5-phenethyl-4,5-dihydroisoxazole-3-carboxylate **4a**



R_f = 0.25 (Petroleum ether/EtOAc: 9/1). $[\alpha]_D^{20}$ = - 104.5 (*c* 1.01, $CHCl_3$, 74% ee). IR (neat) ν_{max} 3026, 2982, 2938, 2862, 1738, 1721, 1715, 1588, 1454, 1380, 1257, 1125, 1018, 934, 749, 701 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.32-7.27 (2 H, m), 7.23-7.18 (3 H, m), 4.85-4.74 (1H, m), 4.35 (2 H, q, *J* = 7.1 Hz), 3.25 (1 H, dd, *J* = 11.0, 17.5 Hz), 2.85 (1 H, dd, *J* = 8.3, 17.5 Hz), 2.84-2.67 (2 H, m), 2.17-2.03 (1 H, m), 1.96-1.84 (1 H, m), 1.37 (3 H, t, *J* = 7.1 Hz). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 161.0 (C), 151.5 (C), 140.8 (C), 128.7 (2 x CH), 128.5 (2 x CH), 126.3 (CH), 83.2 (CH), 62.2 (CH2), 38.6 (CH2), 36.9 (CH2), 31.5 (CH2), 14.3 (CH3). HRMS (ESI^+): calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$: 248.1281; Found: 248.1278. HPLC analysis: Daicel Chiralpak® AD-H (heptane/iPrOH=98:2, flow rate 1.0 mL/min, UV 254 nm, t_{minor} = 15.0 min for *R* enantiomer; t_{major} = 19.9 min for *S* enantiomer, 74% ee).

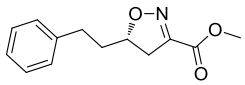
The intermediate could be isolated as a rather stable compound:



3a

With respect to the previous procedure, after stirring for 24h at 20°C, the reaction mixture was partitioned between a saturated aqueous $NaHCO_3$ solution (10 mL) and Et_2O (10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was rapidly purified by silica gel chromatography to give a mixture of two epimers **3a** as a pale yellow oil. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.32-7.19 (5 H, m), 4.55 (0.4 H, s), 4.45 (s), 4.47-4.26 (m), 4.31 (q, J = 7.1 Hz), 4.29 (q, J = 7.1 Hz), 2.87-2.69 (2.2 H, m), 2.44-2.38 (0.8 H, m), 2.28-2.12 (1.2 H, m), 1.98-1.86 (0.8 H, m), 1.49 (9 H, s), 1.35-1.28 (3 H, m). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 14.1 (CH3), 14.2 (CH3), 28.3 (CH3), 32.1 (CH2), 32.1 (CH2), 47.0 (CH2), 47.5 (CH2), 63.2 (CH2), 63.3 (CH2), 78.2 (CH), 79.2 (CH), 82.1 (C), 83.2 (C), 88.5 (C), 88.7 (C), 126.2 (C), 126.2 (C), 128.5 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 141.0 (C), 141.1 (C), 152.1 (C), 128.6 (C), 170.6 (C), 170.6 (C). MS (ESI^+): $[M+Na]^+$: 388.

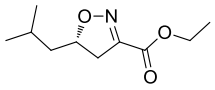
Methyl 5-phenethyl-4,5-dihydroisoxazole-3-carboxylate **4c**



Following the general procedure with unsaturated ketoester **2c** (54.6 mg, 0.250 mmol), the title compound **4c** was obtained as pale yellow oil (51 mg, 87%). R_f = 0.19 (Petroleum

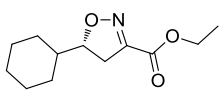
ether/EtOAc: 9/1). IR (neat) ν_{max} 3027, 2952, 2860, 1742, 1721, 1715, 1588, 1443, 1260, 1128, 932, 749, 701 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.32-7.27 (2 H, m), 7.23-7.18 (3 H, m), 4.86-4.75 (1 H, m), 3.89 (3 H, s), 3.26 (1 H, dd, J = 11.0, 17.5 Hz), 2.86 (1 H, J = 8.4, 17.5 Hz), 2.84-2.67 (2 H, m), 2.17-2.03 (1 H, m), 1.96-1.85 (1 H, m). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 161.4 (C), 151.3 (C), 140.7 (C), 128.7 (2 x CH), 128.6 (2 x CH), 126.4 (CH), 83.3 (CH), 52.9 (CH3), 38.5 (CH2), 36.9 (CH2), 31.5 (CH2). HRMS (ESI^+): calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$: 234.1125; Found: 234.1128. HPLC analysis: Daicel Chiralpak® AD-H (heptane/iPrOH=95:5, flow rate 1.0 mL/min, UV 254 nm, t_{minor} = 10.4 min for *R* enantiomer; t_{major} = 11.6 min for *S* enantiomer, 72% ee).

Ethyl 5-isobutyl-4,5-dihydroisoxazole-3-carboxylate **4d**



Following the general procedure with unsaturated ketoester **2d** (46.1 mg, 0.250 mmol), the title compound **4d** was obtained as pale yellow oil (41 mg, 82%). R_f = 0.19 (Petroleum ether/EtOAc: 95/5). IR (neat) ν_{max} 2958, 2873, 1742, 1721, 1715, 1587, 1470, 1380, 1255, 1174, 1126, 1020, 934, 750 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 4.84 (1 H, m), 4.33 (2 H, q, J = 7.1 Hz), 3.26 (1 H, dd, J = 10.8, 17.4 Hz), 2.79 (1 H, dd, J = 8.7, 17.4 Hz), 1.85-1.67 (2 H, m), 1.45-1.32 (1 H, m), 1.35 (3 H, t, J = 7.1 Hz), 0.94 (6 H, t, J = 6.3 Hz). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 161.1 (C), 151.5 (C), 82.9 (CH), 62.1 (CH2), 44.4 (CH2), 39.1 (CH2), 25.2 (CH), 22.9 (CH3), 22.4 (CH3), 14.2 (CH3). HRMS (ESI^+): calcd for $C_{10}H_{18}NO_3$ $[M+H]^+$: 200.1281; Found: 200.1287. HPLC analysis: Daicel Chiralpak® AD-H (heptane/iPrOH=99:1, flow rate 0.5 mL/min, UV 254 nm, t_{minor} = 12.2 min for *R* enantiomer; t_{major} = 17.4 min for *S* enantiomer, 68% ee).

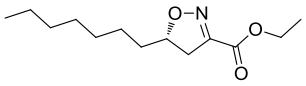
Ethyl 5-cyclohexyl-4,5-dihydroisoxazole-3-carboxylate **4e**



Following the general procedure with unsaturated ketoester **2e** (42.0 mg, 0.200 mmol), the title compound **4e** was obtained as white solid (33 mg, 73%). mp = 54-56°C (Et_2O). R_f = 0.23

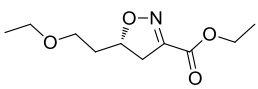
(Petroleum ether/EtOAc: 95/5). IR (neat) ν_{max} 2920, 2856, 1708, 1256, 1113, 930 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 4.54 (1 H, ddd, J = 6.7, 9.1, 11.2 Hz), 4.33 (2 H, q, J = 7.1 Hz), 3.13 (1 H, dd, J = 11.2, 17.7 Hz), 2.92 (1 H, dd, J = 9.1, 17.7 Hz), 1.87 (1 H, br d, J = 1.9 Hz), 1.79-1.50 (5 H, m), 1.35 (3 H, t, J = 7.1 Hz), 1.29-0.92 (5 H, m). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 161.1 (C), 151.5 (C), 88.5 (CH), 62.1 (CH2), 42.3 (CH), 35.9 (CH2), 28.3 (CH2), 28.1 (CH2), 26.3 (CH2), 25.8 (CH2), 25.7 (CH2), 14.3 (CH3). HRMS (ESI^+): calcd for $C_{12}H_{20}NO_3$ $[M+H]^+$: 226.1438; Found: 226.1438. HPLC analysis: Daicel Chiralpak® IC (heptane/iPrOH=80:20, flow rate 1.0 mL/min, UV 254nm, t_{minor} = 9.5 min for *R* enantiomer; t_{major} = 10.8 min for *S* enantiomer, 31% ee).

Ethyl 5-heptyl-4,5-dihydroisoxazole-3-carboxylate **4f**



Following the general procedure with unsaturated ketoester **2f** (56.6 mg, 0.250 mmol), the title compound **4f** was obtained as a pale yellow oil (52 mg, 86%). R_f = 0.29 (Petroleum ether/EtOAc: 95/5). IR (neat) ν_{max} 2925, 2857, 1742, 1721, 1715, 1587, 1254, 1125, 935 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 4.78 (1 H, ddt, J = 6.5, 8.5, 10.9 Hz), 4.33 (2 H, q, J = 7.1 Hz), 3.23 (1 H, dd, J = 10.9, 17.5 Hz), 2.82 (1 H, dd, J = 8.5, 17.5 Hz), 1.81-1.70 (1 H, m), 1.64-1.52 (1 H, m), 1.47-1.20 (10 H, m), 1.35 (3 H, t, J = 7.1 Hz), 0.87 (3 H, t, J = 6.7 Hz). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 161.1 (C), 151.5 (C), 84.3 (CH), 62.1 (CH2), 38.5 (CH2), 35.2 (CH2), 31.8 (CH2), 29.4 (CH2), 29.2 (CH2), 25.2 (CH2), 22.7 (CH2), 14.3 (CH3), 14.2 (CH3). HRMS (ESI^+): calcd for $C_{13}H_{24}NO_3$ $[M+H]^+$: 242.1751; Found: 242.1753. HPLC analysis: Daicel Chiralpak® IC (heptane/iPrOH=95/5, flow rate 1.0 mL/min, UV 254 nm, t_{minor} = 12.9 min for *R* enantiomer; t_{major} = 14.0 min for *S* enantiomer, 77% ee).

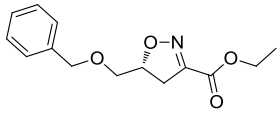
Ethyl 5-(2-ethoxyethyl)-4,5-dihydroisoxazole-3-carboxylate **4g**



Following the general procedure with unsaturated ketoester **2g** (50.1 mg, 0.250 mmol), the title compound **4g** was obtained as a pale yellow oil (43 mg, 80%). R_f = 0.25 (Petroleum

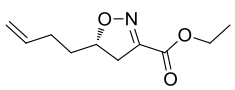
ether/EtOAc: 90/10). IR (neat) ν_{max} 2977, 2870, 1717, 1248, 1108, 927 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 4.94 (1H, dtd, J = 5.7, 7.6, 11.0 Hz), 4.32 (2H, q, J = 7.1 Hz), 3.58-3.44 (2H, m), 3.45 (2H, q, J = 7.0 Hz), 3.26 (1H, dd, J = 11.0, 17.6 Hz), 2.93 (1H, dd, J = 8.1, 17.6 Hz), 2.03-1.79 (2H, m), 1.34 (3H, t, J = 7.1 Hz), 1.16 (3H, t, J = 7.0Hz). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 160.9 (C), 151.7 (C), 81.6 (CH), 66.5 (CH2), 66.4 (CH2), 62.1 (CH2), 38.7 (CH2), 35.3 (CH2), 15.2 (CH3), 14.2 (CH3). HRMS (ESI^+): calcd for $C_{10}H_{18}NO_4$ $[M+K]^+$: 254.0789; Found: 254.0796. HPLC analysis: Daicel Chiralpak® IA (heptane/iPrOH=98/2, flow rate 1.0 mL/min, UV 254 nm, t_{minor} = 11.8 min for *R* enantiomer; t_{major} = 15.1 min for *S* enantiomer, 67% ee).

Ethyl 5-((benzyloxy)methyl)-4,5-dihydroisoxazole-3-carboxylate **4h**



Following the general procedure with unsaturated ketoester **2h** (58.6 mg, 0.250 mmol), the title compound **4h** was obtained as a pale yellow oil (45 mg, 68%). R_f = 0.19 (Petroleum ether/EtOAc: 85/15). IR (neat) ν_{max} 2983, 2865, 1715, 1252, 1118, 1017, 927, 739, 698 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.38-7.27 (5H, m), 5.01-4.91 (1H, m), 4.58 (2H, d, J = 1.2 Hz), 4.34 (2H, q, J = 7.1 Hz), 3.61 (2H, d, J = 4.6), 3.24 (1H, dd, J = 11.1, 17.7 Hz), 3.13 (1H, dd, J = 8.4, 17.7 Hz), 1.36 (3H, t, J = 7.1 Hz). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 160.8 (C), 151.7 (C), 137.1 (C), 128.6 (2 x CH), 128.0 (CH), 127.9 (2 x CH), 82.6 (CH), 73.8 (CH2), 70.4 (CH2), 62.2 (CH2), 35.7 (CH2), 14.3 (CH3).HRMS (ESI^+): calcd for $C_{14}H_{17}NO_4$ $[M+K]^+$: 302.0789; Found: 302.0780. HPLC analysis: Daicel Chiralpak® IC (heptane/iPrOH=90/10, flow rate 1.0 mL/min, UV 254 nm, t_{minor} = 25.5 min for *R* enantiomer; t_{major} = 32.2 min for *S* enantiomer, 72% ee).

Ethyl 5-(but-3-en-1-yl)-4,5-dihydroisoxazole-3-carboxylate **4i**

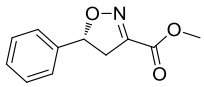


Following the general procedure with unsaturated ketoester **2i** (45.6 mg, 0.250 mmol), the title compound **4i** was obtained as a pale yellow oil (39 mg, 79%). R_f = 0.29 (Petroleum

ether/EtOAc: 9/1). IR (neat) ν_{max} 2981, 2938, 1738, 1721, 1715, 1588, 1259, 1126, 934 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 5.79 (1 H, ddt, *J* = 6.6, 10.2, 16.9 Hz), 5-08-4.97 (2 H, m), 4.80 (1 H, dddd, *J* = 6.1, 7.1, 8.3, 11.0 Hz), 4.32 (2 H, q, *J* = 7.1 Hz), 3.25 (1 H, dd, *J* = 11.0, 17.5 Hz), 2.84 (1 H, dd, *J* = 8.3, 17.5 Hz), 2.19-2.13 (2 H, m), 1.85 (1 H, ddd, *J* = 7.0, 11.0, 13.9 Hz), 1.73-1.62 (1 H, m), 1.35 (3 H, t, *J* = 7.1 Hz). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 160.9 (C), 151.4 (C), 137.0 (CH), 115.7 (CH2), 83.4 (CH), 62.0 (CH2), 38.4 (CH2), 34.2 (CH2), 29.3 (CH2), 14.1 (CH3). HRMS (ESI^+): calcd for $C_{10}H_{16}NO_3$ $[M+H]^+$: 198.1125; Found: 198.1126. HPLC analysis: Daicel Chiralpak® IC (heptane/MTBE=80:20, flow rate 1.0 mL/min, UV 254 nm, t_{major} = 48.1 min for *R* enantiomer; t_{min} = 53.4 min for *S* enantiomer, 78% ee).

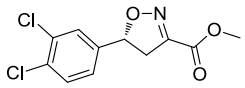
MTBE has been used as eluent because isopropanol failed to separate peaks with a return to baseline. Unfortunately, the inversion of peaks was then observed in this case.

Methyl 5-phenyl-4,5-dihydroisoxazole-3-carboxylate **4j**



Following the general procedure with unsaturated ketoester **2j** (47.6 mg, 0.250 mmol), the title compound **4j** was obtained as a yellow oil (11 mg, 21%). R_f = 0.20 (Petroleum ether/EtOAc: 9/1). $[\alpha]_D^{20}$ = +12.1 (*c* 0.96, $CHCl_3$, 5% ee). IR (neat) ν_{max} 2955, 1721, 1589, 1441, 1244, 1122, 913, 744, 698 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.42-7.30 (5H, m), 5.79 (1H, dd, *J* = 8.9, 11.6 Hz), 3.90 (3H, s), 3.64 (1H, dd, *J* = 11.6, 17.8 Hz), 3.22 (1H, dd, *J* = 8.9, 17.8 Hz). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 161.1 (C), 151.0 (C), 139.5 (C), 129.0 (CH), 128.8 (CH), 126.0 (CH), 85.2 (CH), 53.0 (CH3), 41.5 (CH2). HRMS (ESI^+): calcd for $C_{11}H_{12}NO_3$ $[M+H]^+$: 206.0812; Found: 206.0809. HPLC analysis: Daicel Chiralpak® IA (heptane/iPrOH=80:20, flow rate 1.0 mL/min, UV 254 nm, t_{minor} = 6.8 min for *R* enantiomer; t_{major} = 7.8 min for *S* enantiomer, 5% ee).

Methyl 5-(3,4-dichlorophenyl)-4,5-dihydroisoxazole-3-carboxylate **4k**

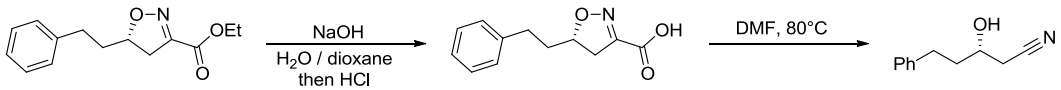


Following the general procedure with unsaturated ketoester **2k** (64.8 mg, 0.250 mmol), the title compound **4k** was obtained as a yellow solid (29 mg, 36%). mp = 98-100°C. R_f = 0.09

(Petroleum ether/EtOAc: 9/1). IR (*KBr*) ν_{max} 2959, 1715, 1589, 1442, 1375, 1254, 1272, 1123, 1029, 944, 914, 750 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.44 (1 H, d, J = 8.3 Hz), 7.41 (1 H, d, J = 2.1 Hz), 7.14 (1 H, dd, J = 2.1, 8.3 Hz), 5.74 (1 H, dd, J = 8.3, 11.6 Hz), 3.89 (3 H, s), 3.66 (1 H, dd, J = 11.6, 17.8 Hz), 3.16 (1 H, dd, J = 8.3, 17.8 Hz). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 160.7 (C), 151.0 (C), 139.8 (C), 133.2 (C), 132.9 (C), 131.0 (CH), 127.9 (CH), 125.2 (CH), 83.4 (CH), 53.1 (CH3), 41.6 (CH2). HRMS (ESI^+): calcd for $C_{11}H_9Cl_2NO_3$ $[M+H]^+$: 274.0032; Found: 274.0041. HPLC analysis: Daicel Chiralpak® IC (heptane/iPrOH=80:20, flow rate 1.0 mL/min, UV 254 nm, t_{major} = 10.2 min for *S* enantiomer; t_{minor} = 12.2 min for *R* enantiomer, 8% ee).

III.3 β-hydroxy acetonitrile 13

(*S*)-3-hydroxy-5-phenylpentanenitrile **13**



4a **12** **13**

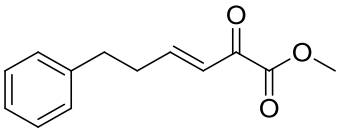
4a (38 mg, 0.154mmol) was dissolved in a mixture of a 1M aqueous NaOH solution (2 mL) and dioxane (0.8 mL). The reaction mixture was stirred vigorously at room temperature overnight and then concentrated under reduced pressure. The resulting solution was acidified with a 1M solution of HCl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the compound **12** (33 mg, M = 219.24 $g.mol^{-1}$, 98%) as a yellow solid which was used without further purification. R_f = 0.20 (Petroleum ether/EtOAc: 9/1). ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.91 (1H, br s), 7.33-7.19 (5H, m), 4.92-4.81 (1H, m), 3.26 (1H, dd, J = 11.1, 17.6 Hz), 2.86 (1H, dd, J = 8.6, 17.7 Hz), 2.85-2.68 (2H, m), 2.18-2.06 (1H, m), 1.99-1.87 (1H, m). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 164.2 (C), 151.2 (C), 140.6 (C), 128.7 (CH), 128.6 (CH), 126.4 (CH), 84.3 (CH), 37.9 (CH2), 36.9 (CH2), 31.5 (CH2).

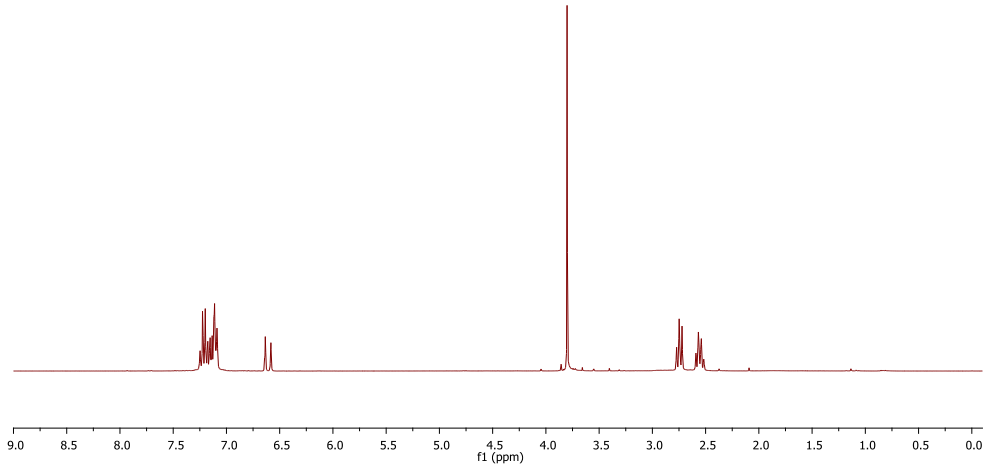
12 (33.8 mg, 0.154mmol) was dissolved in DMF and the mixture was stirred at 80°C for 18h. The mixture was then concentrated under reduced pressure and the crude residue was purified by silica gel chromatography to give the title compound **13** as a pale yellow oil (21 mg, 78%). $[\alpha]_D^{20}$ -11.1 (*c* 1.05, CH_2Cl_2, 74% ee).[7] HPLC analysis: Daicel Chiralcel® OD-H (heptane/iPrOH=90/10, flow rate 0.7 mL/min, UV 259 nm, t_{major} = 19.4 min for *S* enantiomer; t_{min} = 23.2 min for *R* enantiomer).

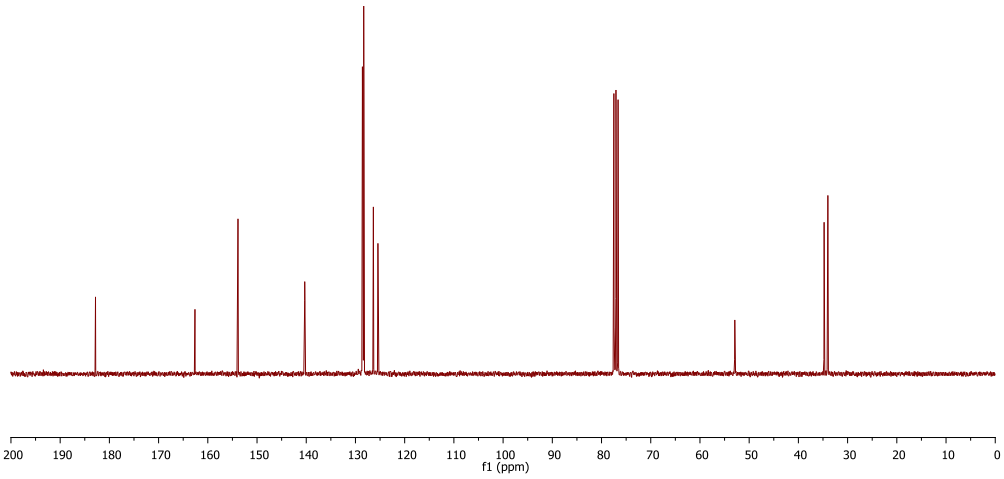
[7] A. Pohjakallio, P. M. Pihko, J. Liu, *J. Org. Chem.*, 2010, **75**, 6712.

IV NMR spectra and HPLC data of compound 13

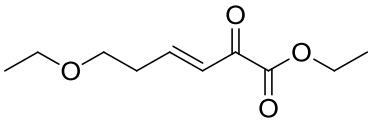
IV-1 (E)-Methyl 2-oxo-6-phenylhex-3-enoate (2c)

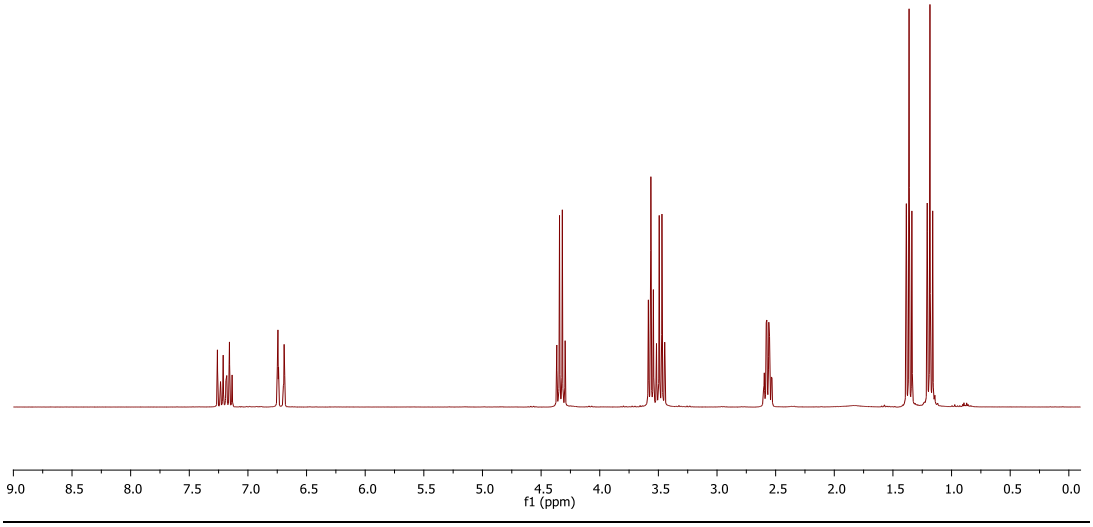


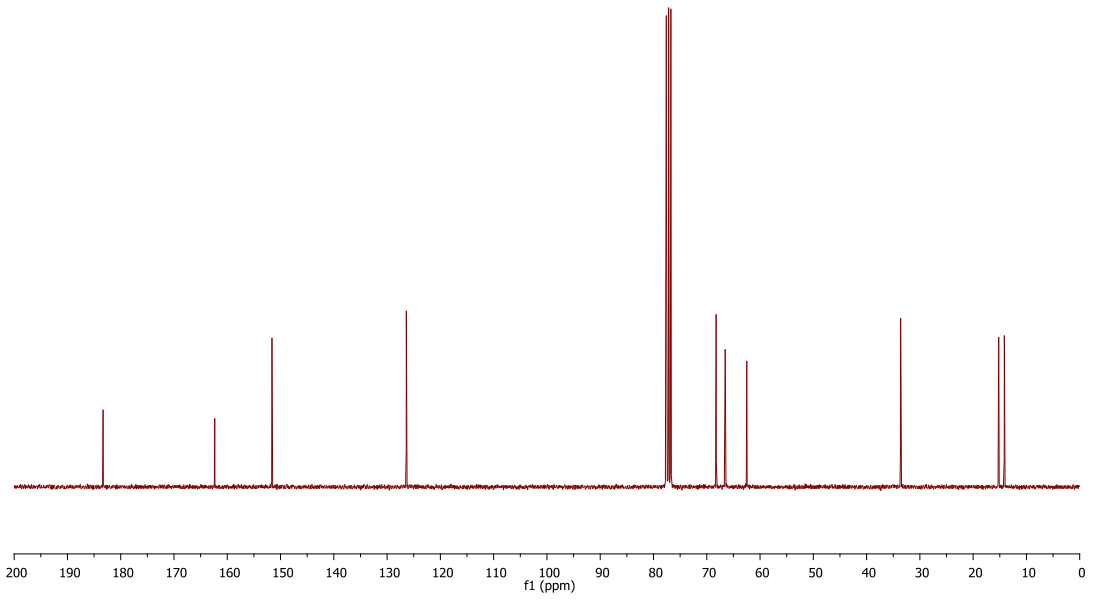




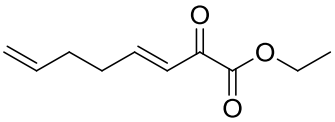
IV-2 (E)-Ethyl 6-ethoxy-2-oxohex-3-enoate (2g)

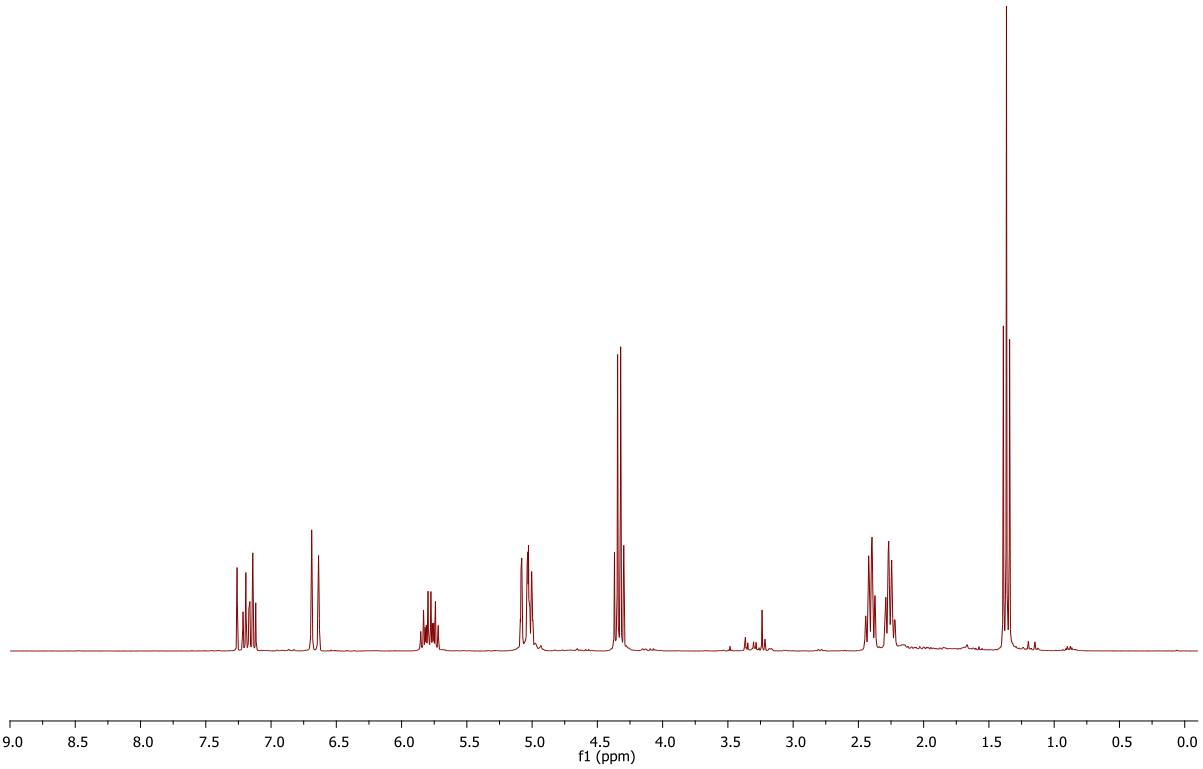


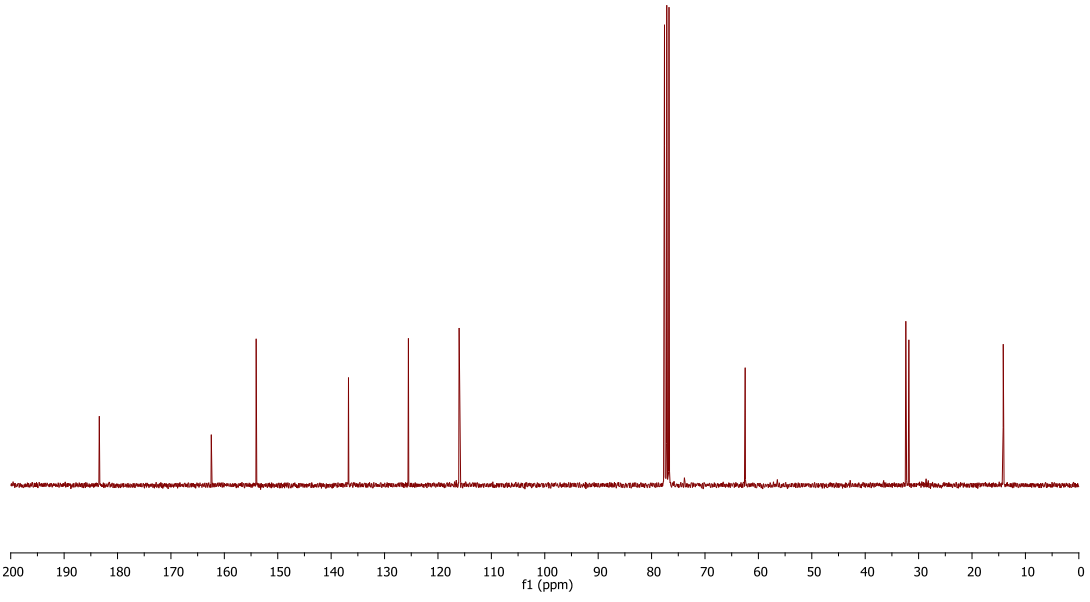




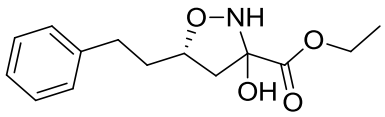
IV-3 (E)-Ethyl 2-oxoocta-3,7-dienoate (2i)

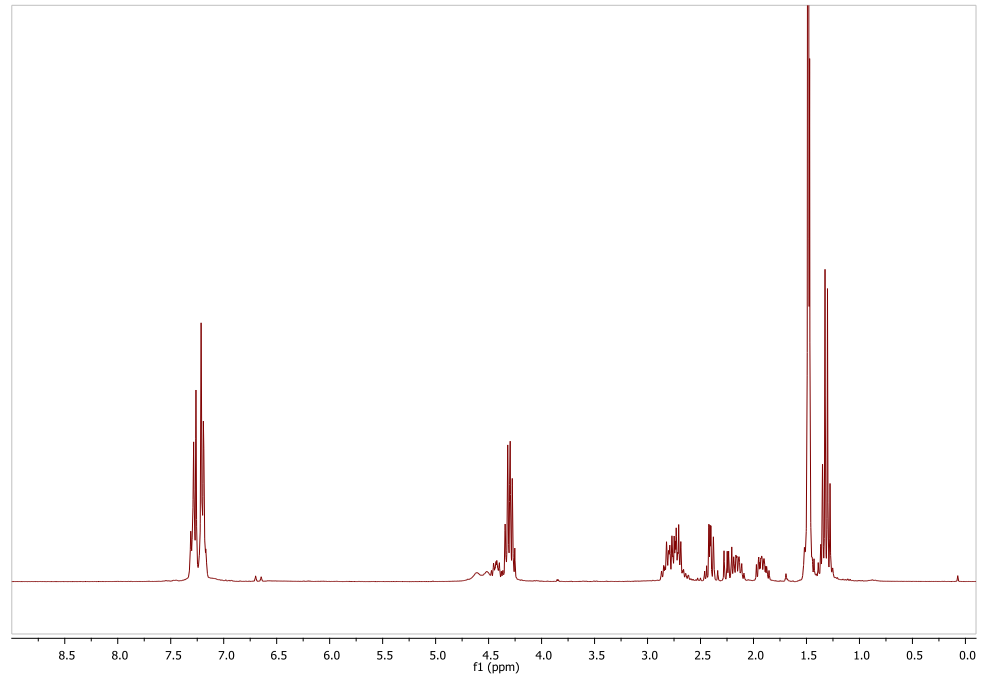


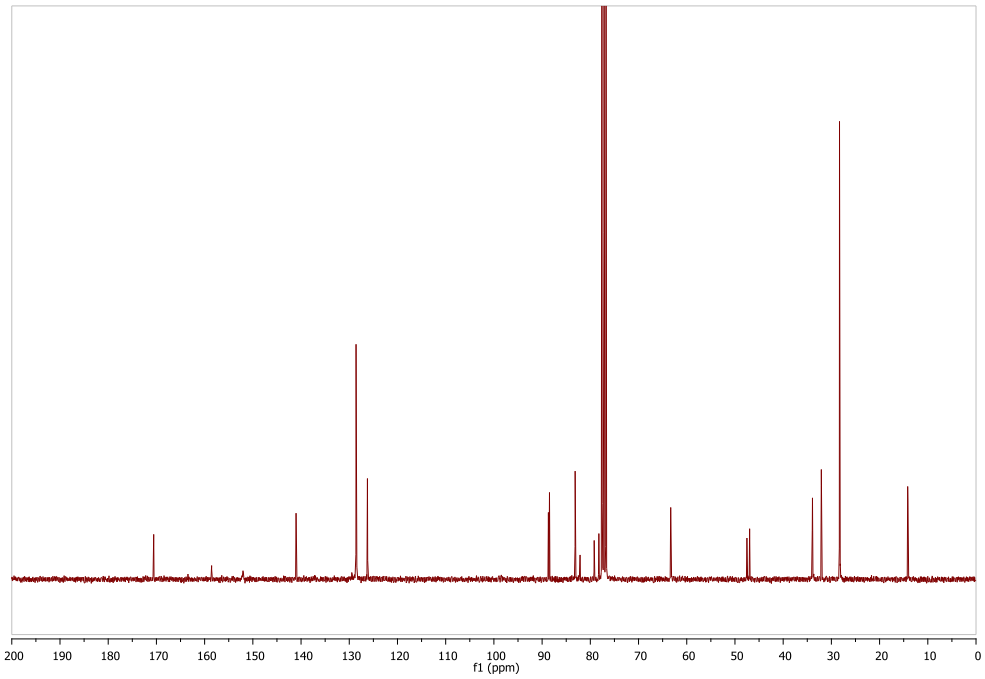




IV-4 2-tert-butyl 3-ethyl 3-hydroxy-5-phenethylisoxazolidine-2,3-dicarboxylate (3a)

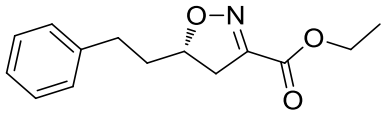


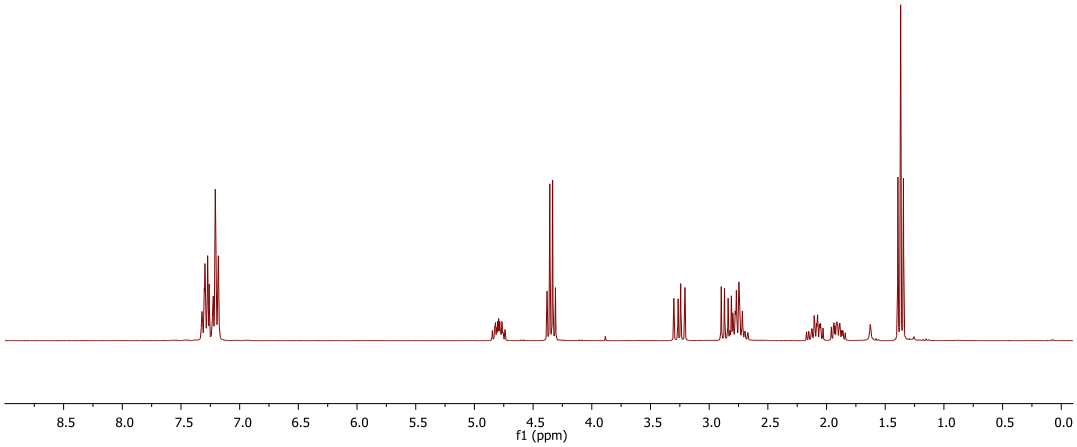


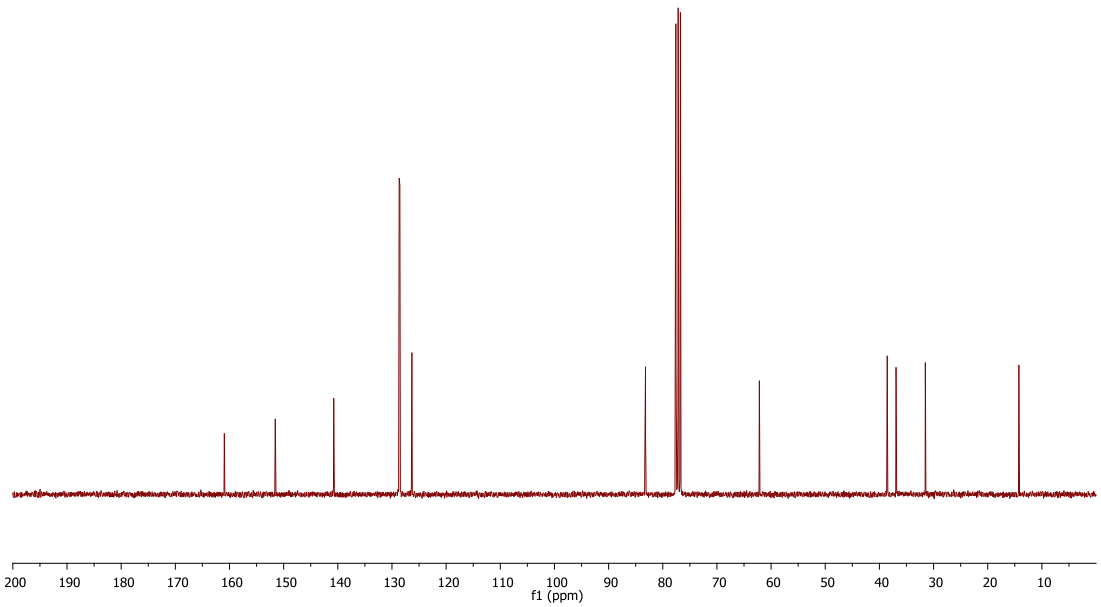


Remarcq : The NMR spectra has to be achieved rapidedly because it was observed some decomposition into the NMR tube ($CDCl_3$) after several hours of analysis.

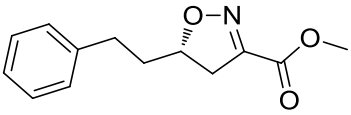
IV-5 Ethyl 5-phenethyl-4,5-dihydroisoxazole-3-carboxylate (4a)

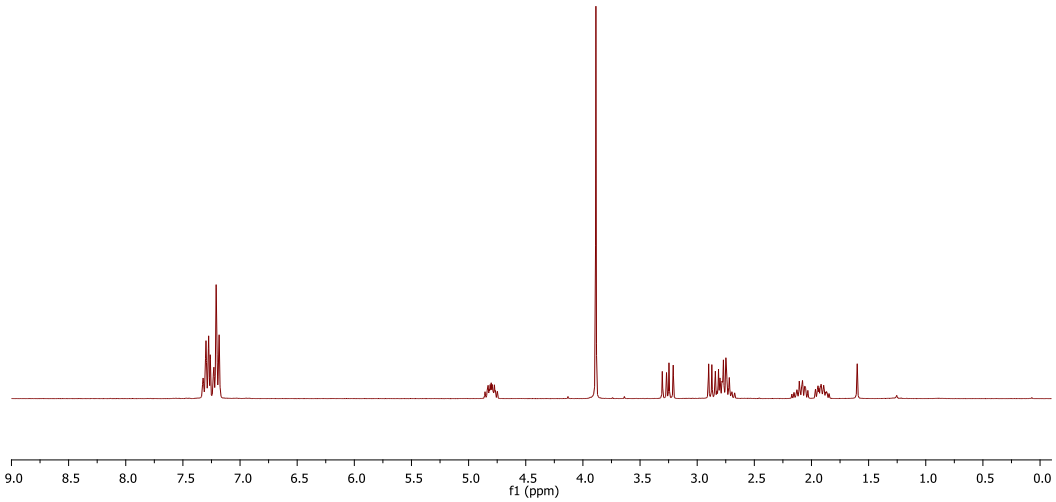


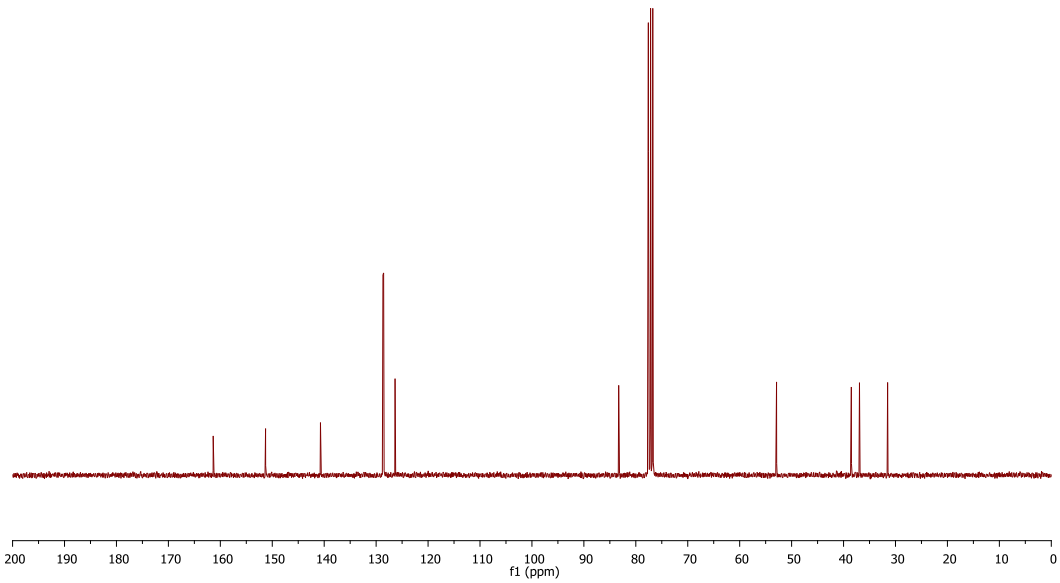




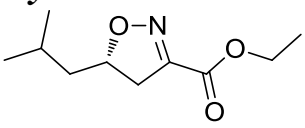
IV-6 Methyl 5-phenethyl-4,5-dihydroisoxazole-3-carboxylate (4c)

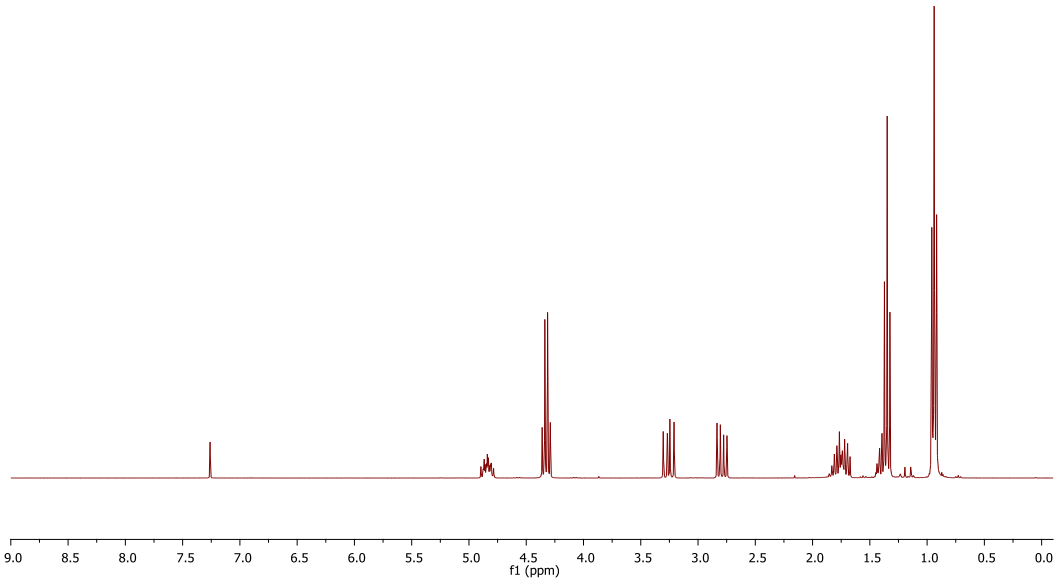


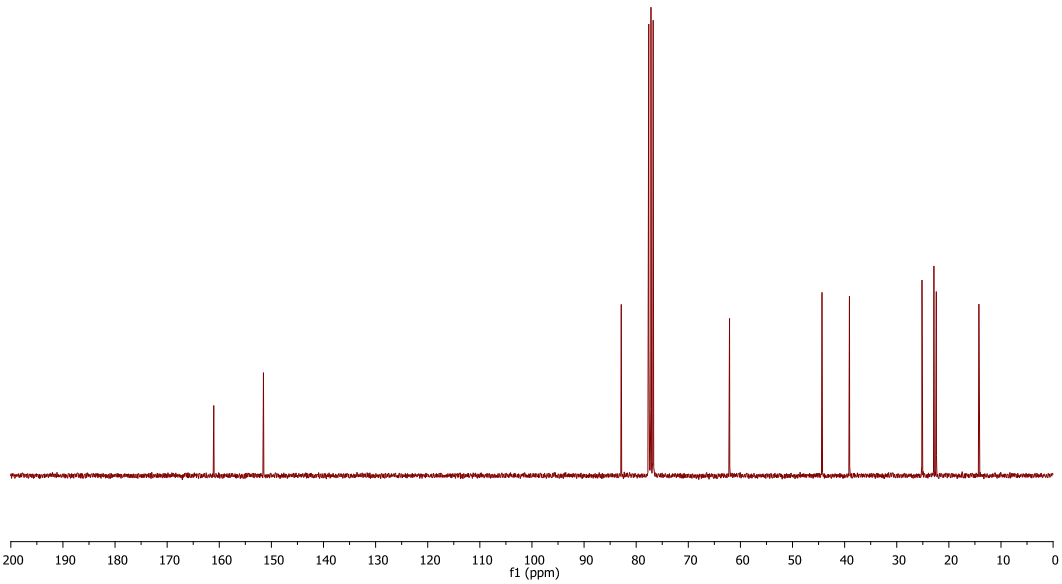




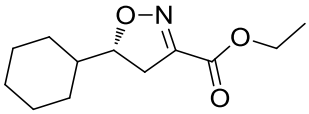
IV-7 Ethyl 5-isobutyl-4,5-dihydroisoxazole-3-carboxylate (4d)

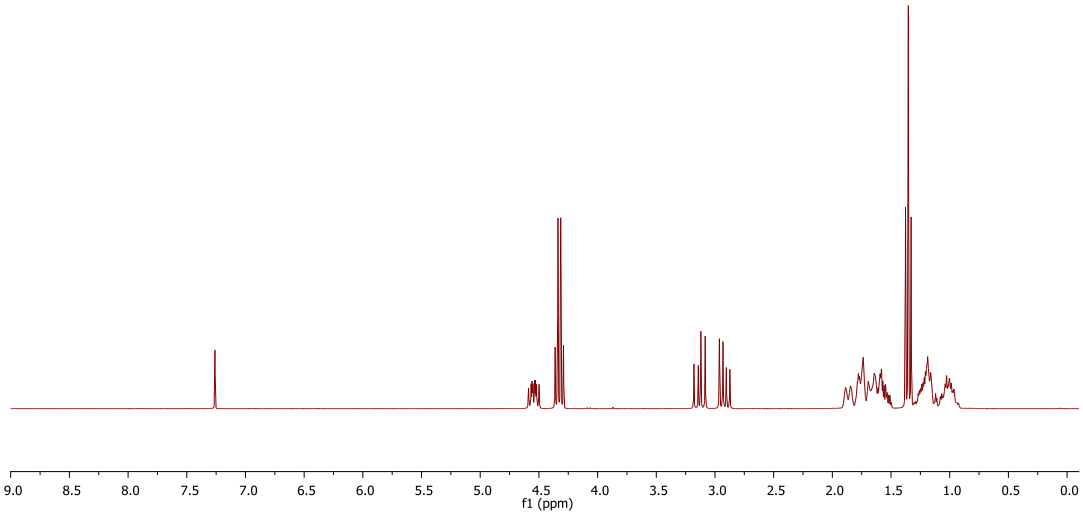


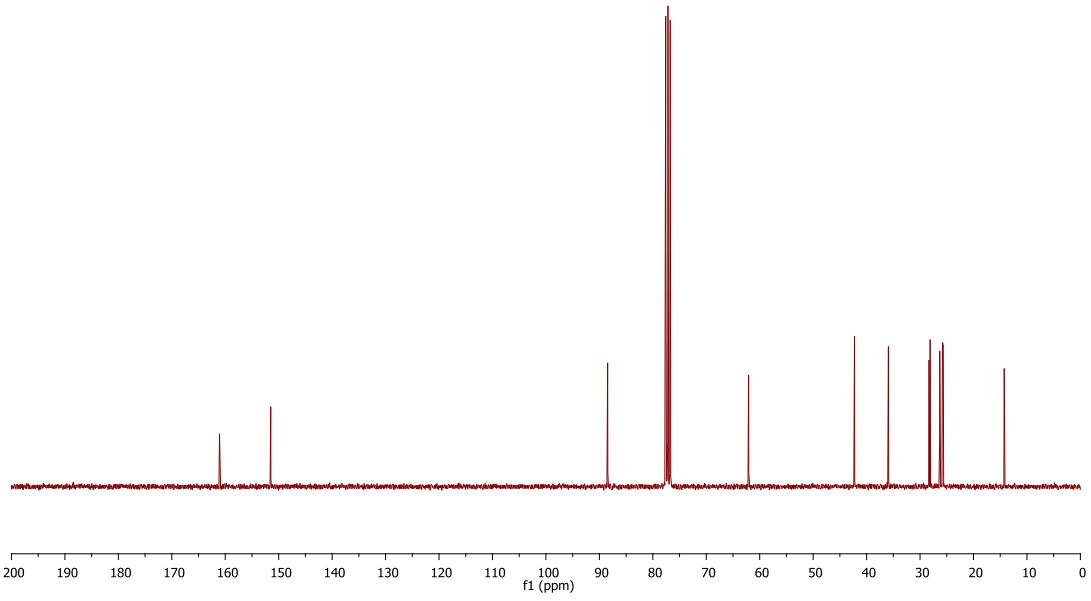




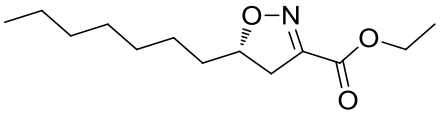
IV-8 Ethyl 5-phenethyl-4,5-dihydroisoxazole-3-carboxylate (4e)

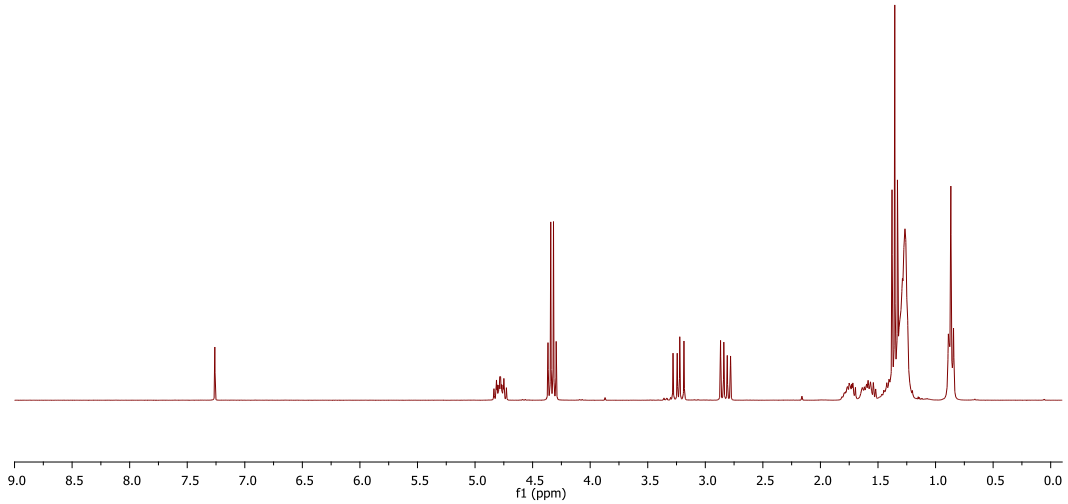


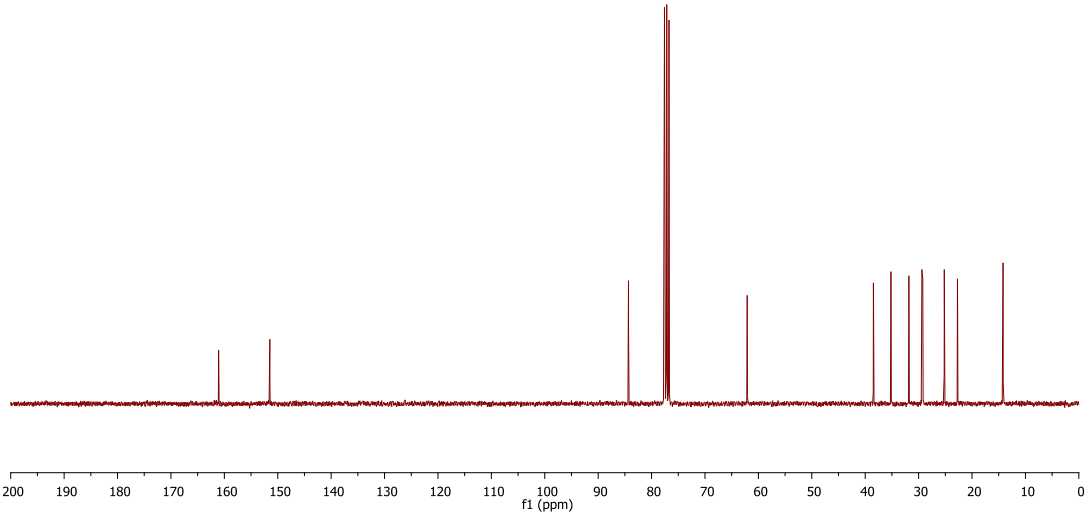




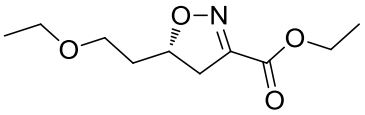
IV-9 Ethyl 5-heptyl-4,5-dihydroisoxazole-3-carboxylate (4f)

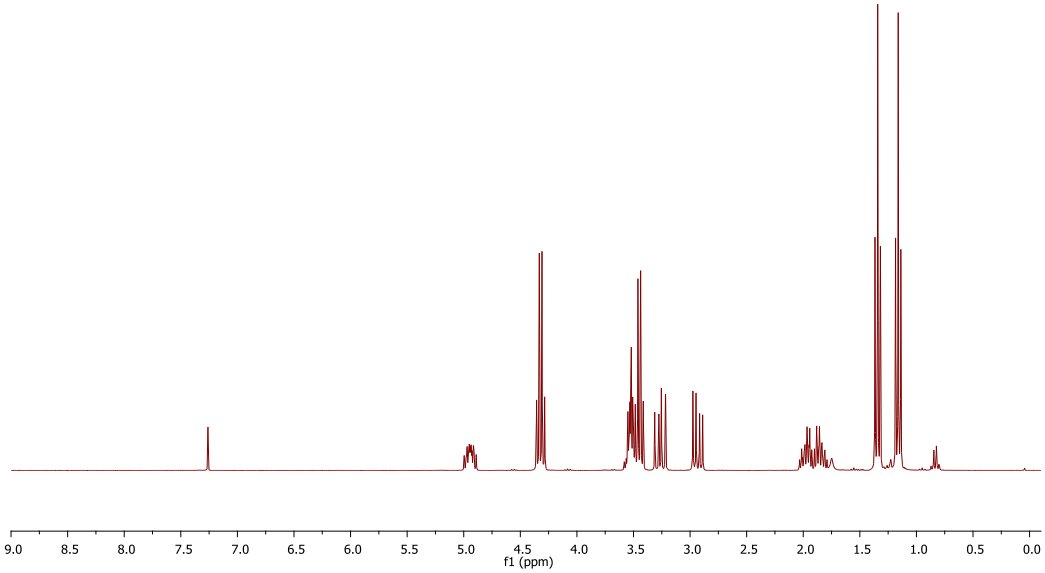


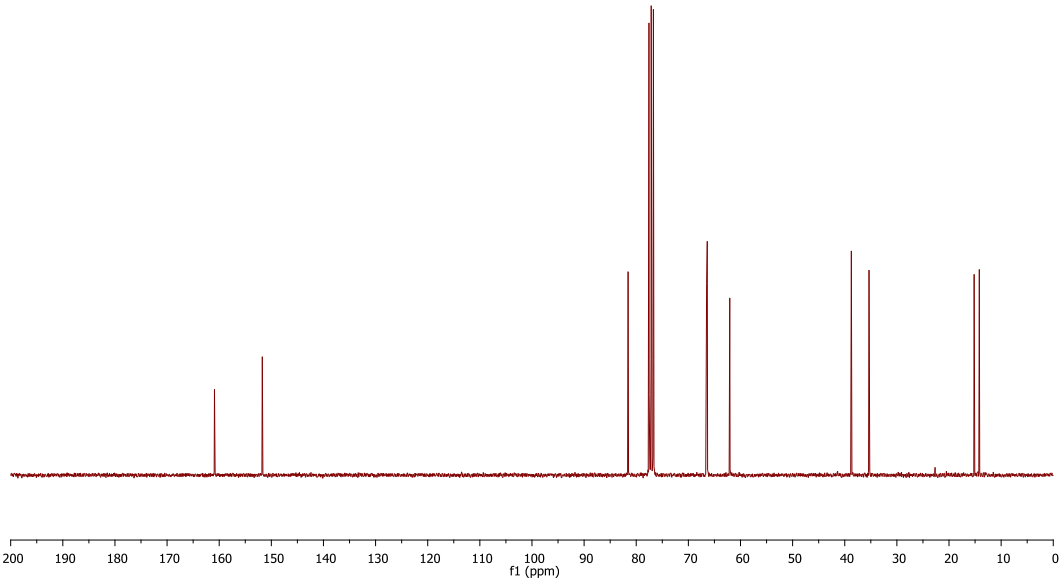




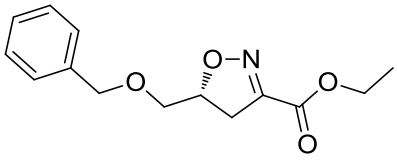
IV-10 Ethyl 5-(2-ethoxyethyl)-4,5-dihydroisoxazole-3-carboxylate (4g)

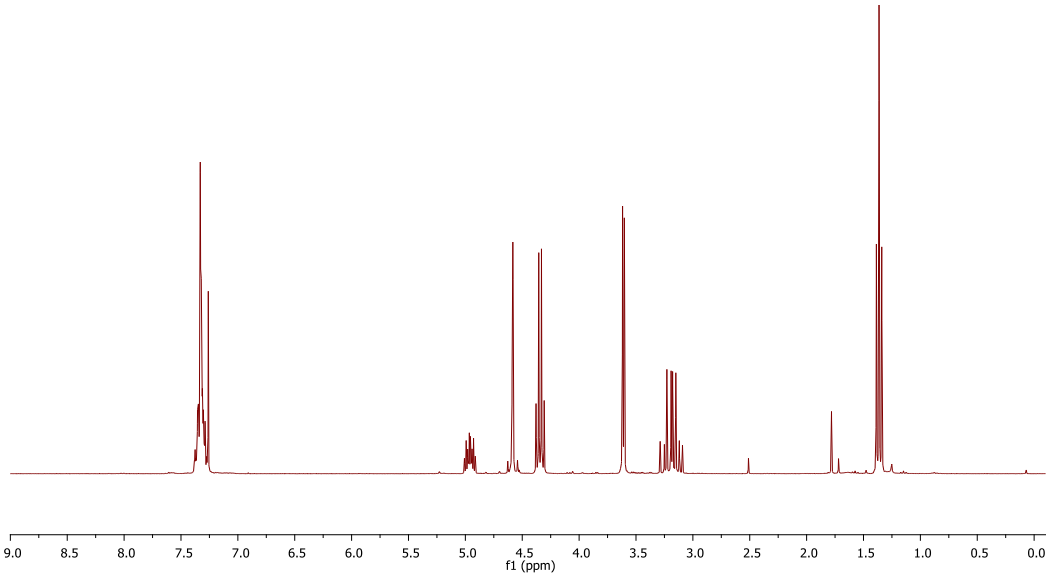


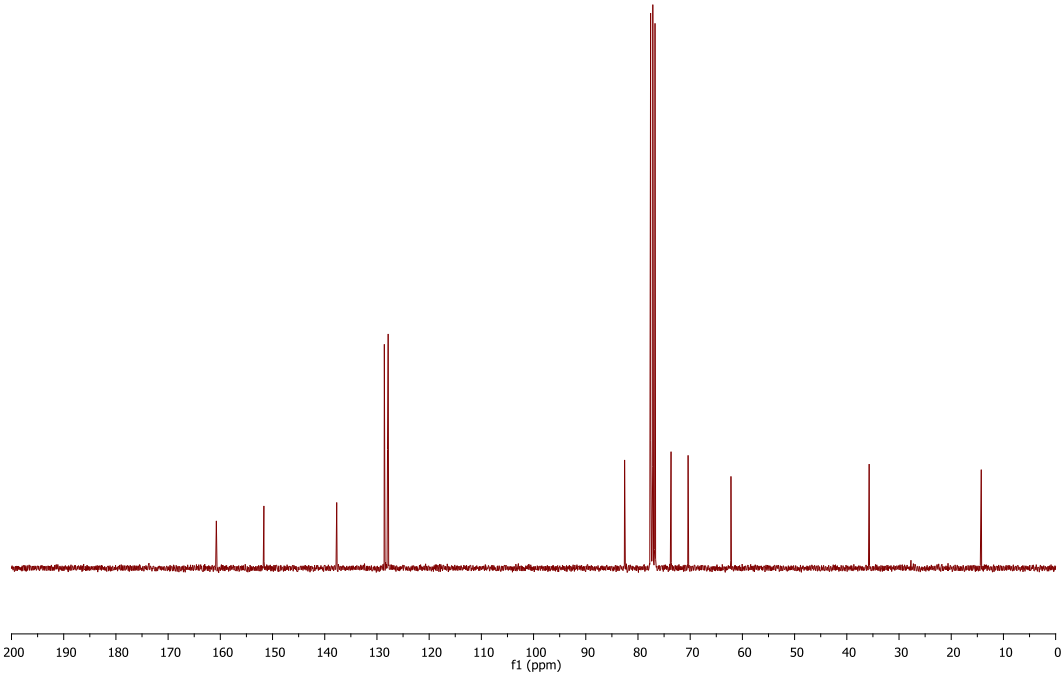




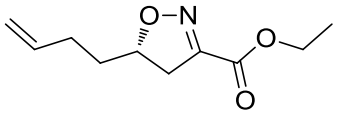
IV-11 Ethyl 5-((benzyloxy)methyl)-4,5-dihydroisoxazole-3-carboxylate (4h)

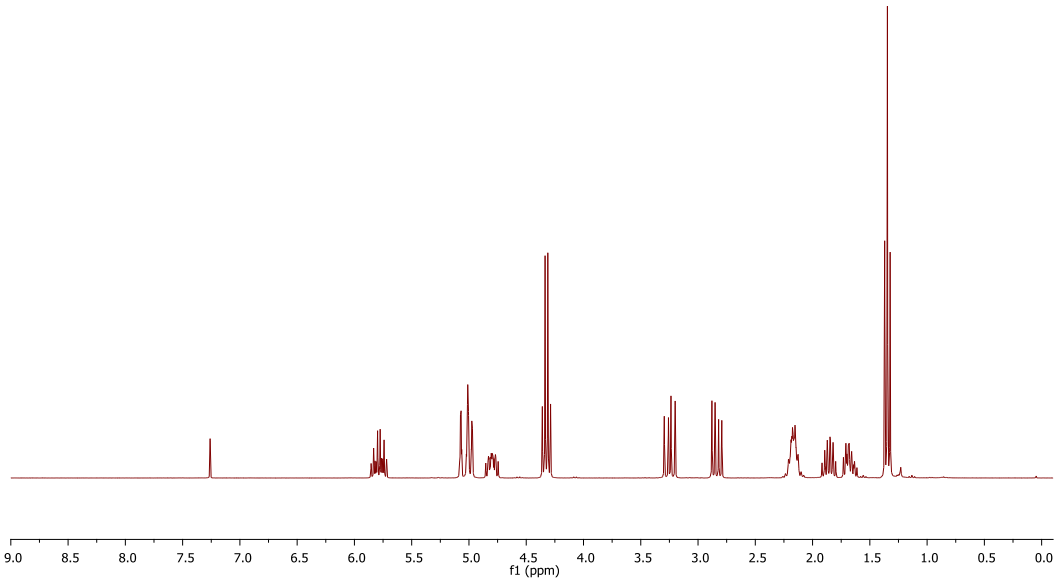


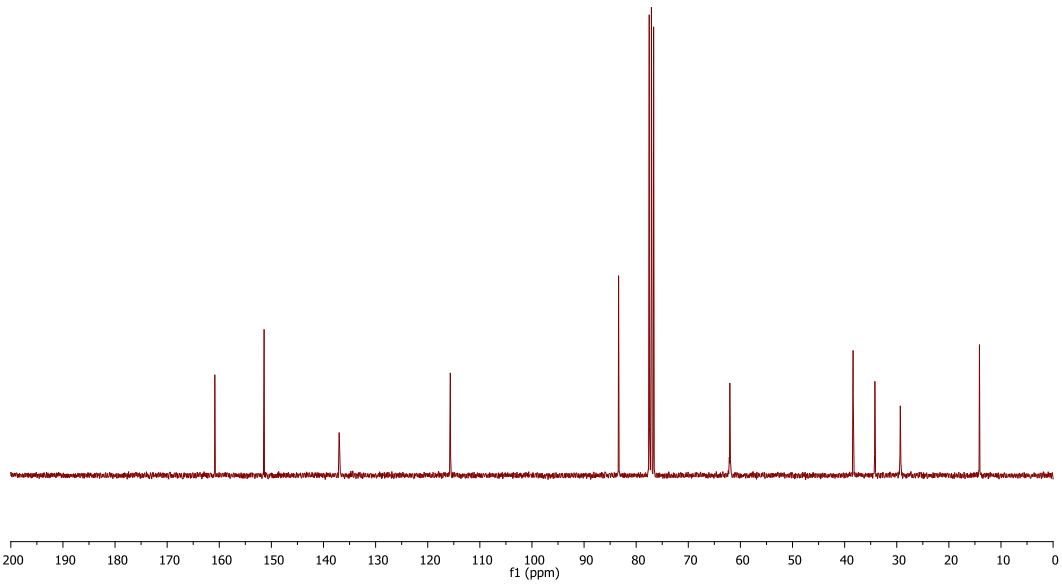




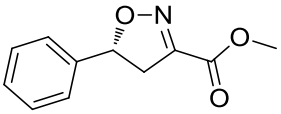
IV-12 Ethyl 5-(but-3-en-1-yl)-4,5-dihydroisoxazole-3-carboxylate (4i)

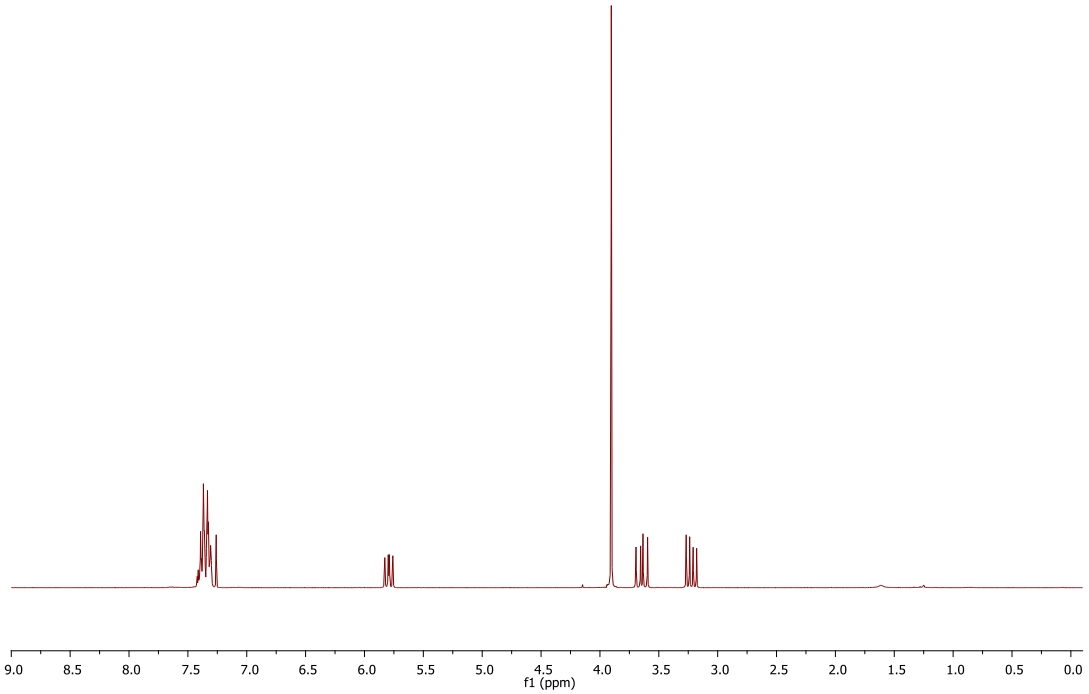


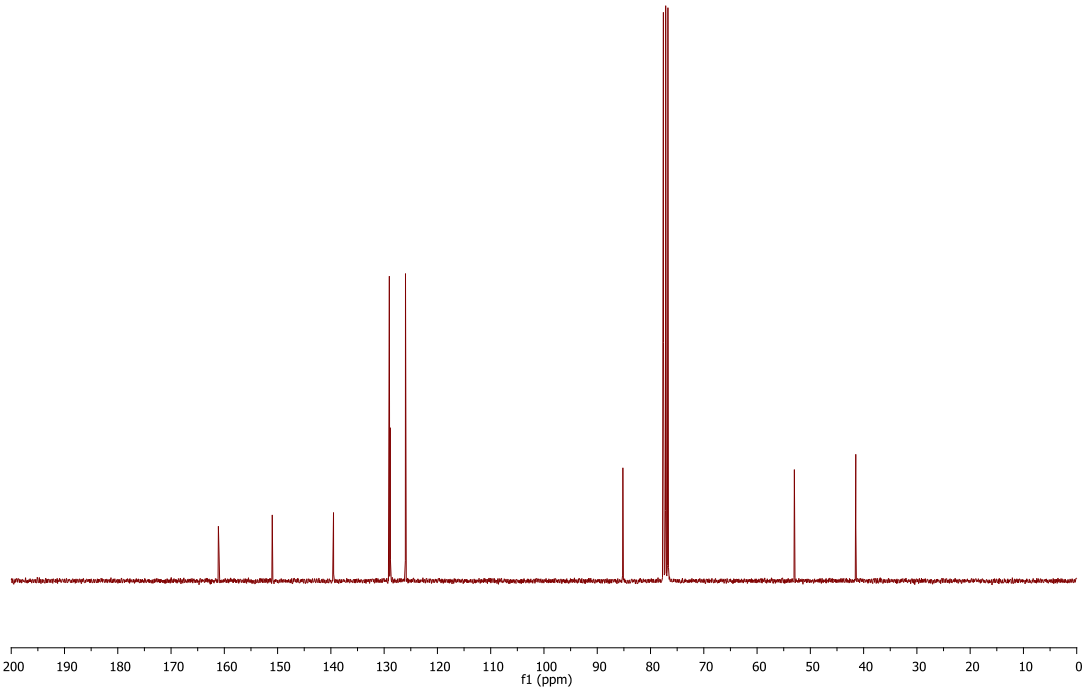




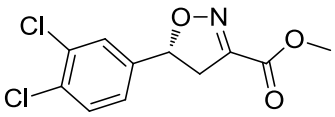
IV-13 Methyl 5-phenyl-4,5-dihydroisoxazole-3-carboxylate (4j)

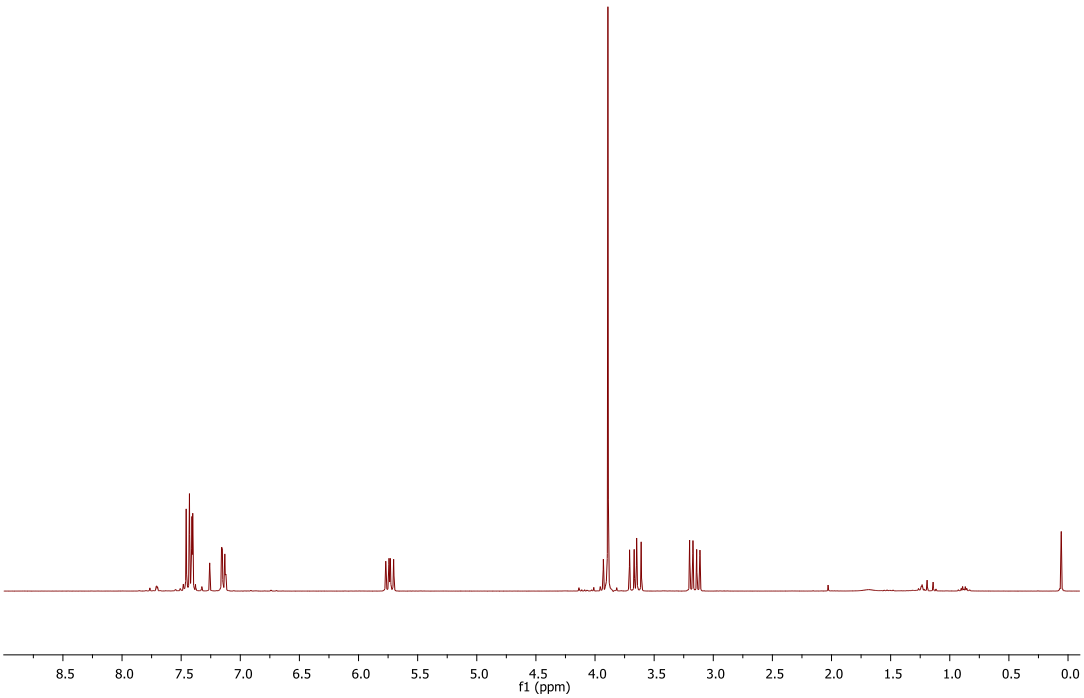


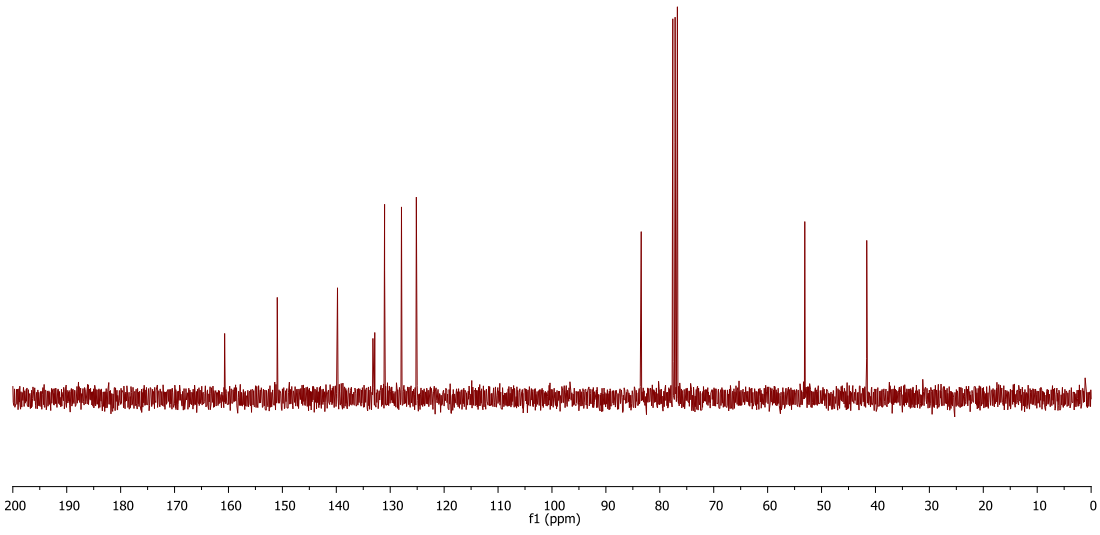




IV-14 Methyl 5-(3,4-dichlorophenyl)-4,5-dihydroisoxazole-3-carboxylate (4k)







IV-15 Methyl 5-(3,4-dichlorophenyl)-4,5-dihydroisoxazole-3-carboxylate (HPLC - 13)