Organocatalytic Asymmetric Formal [3+2] Cycloaddition with In Situ Generated *N*-Carbamoyl Nitrones

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Supporting Information

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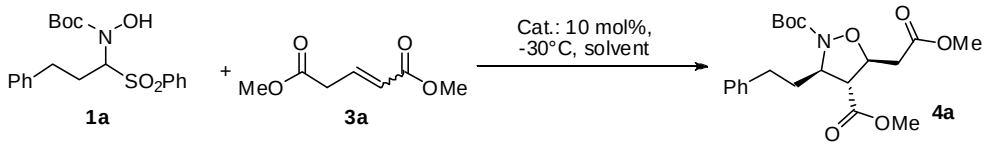
Screening of different catalysts and reaction conditions[a]



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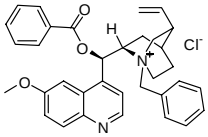
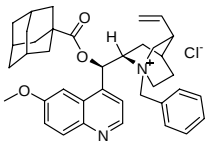
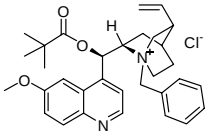
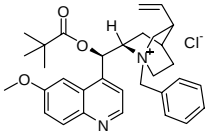
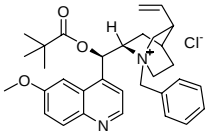
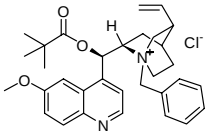
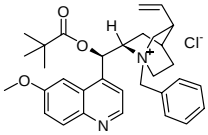
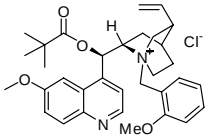
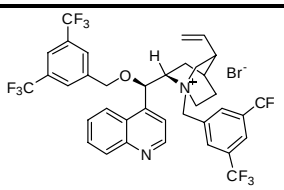
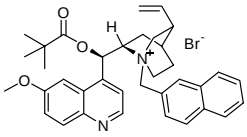
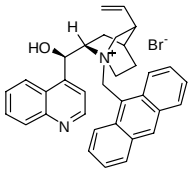
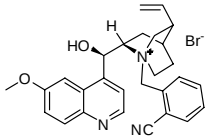
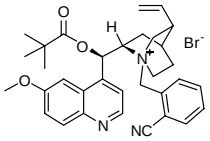
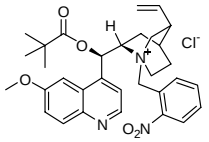
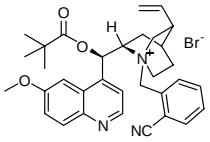
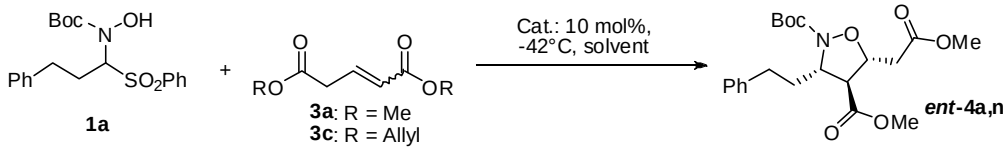
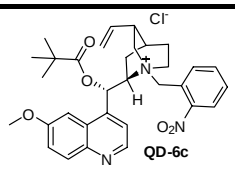
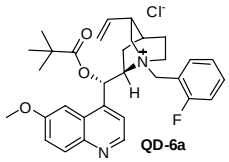
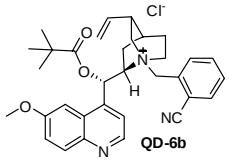
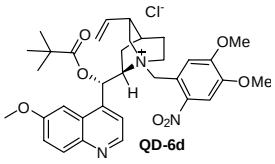
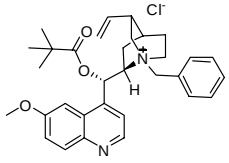
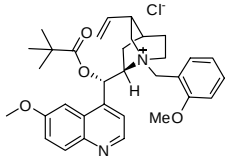
1		K_2CO_3 (s), 5 eq.	Tol.	24	80	34
2		K_2CO_3 (s), 5 eq.	Tol.	24	85	44
3		K_2CO_3 (s), 5 eq.	Tol.	22	85	55
4		K_2CO_3 (s), 5 eq.	CH_2Cl_2	21	<5	--
5		K_2CO_3 (s), 5 eq.	Tol./CH_2Cl_2 10/1	21	55	68
6		K_2CO_3 (s), 5 eq.	o-, m-xilene mixture	21	60	46
7		K_2CO_3 (s), 5 eq.	TBME	21	60	68
8		K_2CO_3 (s), 5 eq.	Tol.	21	65	61

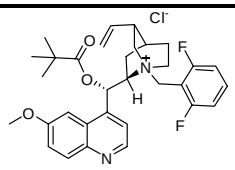
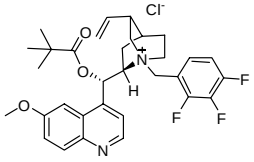
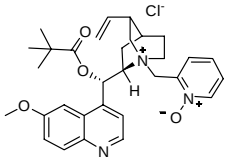
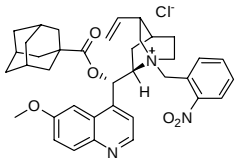
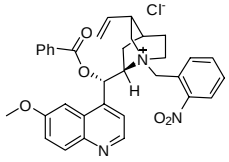
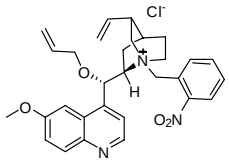
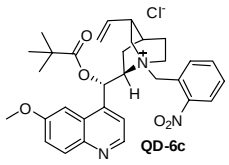
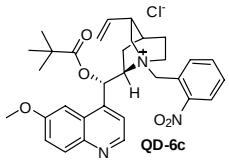
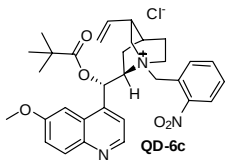
9		K_2CO_3 (s), 5 eq.	Tol.	22	35	42
10		K_2CO_3 (s), 5 eq.	Tol.	21	65	61
11		K_2CO_3 (s), 5 eq.	Tol.	18	50	20
12		K_2CO_3 (s), 5 eq.	Tol.	18	85	15
13	 **6b**	K_2CO_3 (s), 5 eq.	Tol.	21	65	70
14	 **6c**	K_2CO_3 (s), 5 eq.	Tol.	21	65	72
15	 **6b**	K_2CO_3 (aq) 50% $^{w}/_{w}$, 5 eq.	Tol.	21	90	70

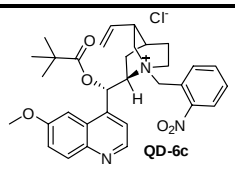
[a] Reaction performed at -30°C on a 0.1 mmol scale, using 2 eq. of **3a**, 10 mol% of the catalyst in 1 mL of the solvent (0.1 M). [b] Conversion determined by ^{1}H NMR analysis. [c] Enantiomeric excess determined by using chiral HPLC analysis.

Screening of different quinidine catalysts and reaction conditions[a]



entry	catalyst	3	solvent	t (h)	conv. (%)[b]	ee (%)[c]
1	 QD-6c	**3a**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	24	>90	60[d]
2	 QD-6a	**3a**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	24	>90	30[d]
3	 QD-6b	**3a**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	24	>90	55[d]
4	 QD-6d	**3a**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	24	>90	21[d]
5		**3a**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	24	>90	25[d]
6		**3a**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	24	>90	27[d]

7		**3a**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	24	>90	5[d]
8		**3a**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	24	>90	50[d]
9		**3a**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	24	>90	60[d]
10		**3a**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	24	>90	67[d]
11		**3a**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	24	>90	63[d]
12		**3a**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	24	>90	31[d]
13		**3c**	Tol/TBME/CH_2Cl_2 3.5/3.5/3	96	>99[e]	65
14		**3c**	Tol	96	70[e]	70
15		**3c**	Tol/CH_2Cl_2 10/1	96	95[e]	70

16	 QD-6c	**3c**	Tol/CH_2Cl_2 7/3	96	98[e]	66

[a] Reaction performed at -42 °C on a 0.10 mmol scale, using 2 eq. of **3a,c**, 10 mol% of the catalyst in 1 mL of the solvent (0.1 M), K_2CO_3 (aq) 50% $^{w}/_{w}$, 0.50 mmol. [b] Conversion determined by ^{1}H NMR analysis. [c] Enantiomeric excess determined by using chiral HPLC analysis. [d] Determined by using chiral HPLC analysis after Boc deprotection CbzCl derivatization. [e] Isolated yield.

General methods and materials.

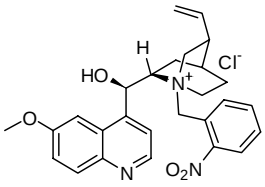
^{1}H NMR and ^{13}C NMR were recorded on a Varian Mercury 400 or Inova 600 MHz spectrometer, in $CDCl_3$, CD_3OD, CD_3CN as solvents. Chemical shifts are reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm), CHD_2OD (3.34 ppm), CHD_2CN (1.96 ppm) for ^{1}H NMR and to the central line of $CDCl_3$ (77.0 ppm) CD_3OD (49.86 ppm), CD_3CN (1.79 ppm) for ^{13}C NMR. ^{13}C NMR were recorded with ^{1}H broadband decoupling. Unless otherwise noted all the NMR spectra were performed in $CDCl_3$. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES+) ionisation techniques. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC. ECD spectra were recorded on a Jasco J-810 dichrograph at 25°C in acetonitrile solutions, using path lengths of 1.0 cm, in the range 190-400 nm; reported $\Delta\varepsilon$ values are expressed as L mol^{-1}cm^{-1}.

Unless otherwise noted all commercially available solvents and reagents were used as received. THF was distilled from Na/benzophenone. *N*-carbamoyl-*N*-hydroxy-α-amido sulfones **1a-l**, **2a-d** were obtained following literature procedures.[1] Racemic samples were obtained using tetrabutylammonium bromide as the catalyst.

[1] (a) Guinchard, X.; Vallée, Y.; Denis, J.-N. *Org. Lett.* **2005**, *7*, 5147. (b) Guinchard, X.; Denis, J.-N. *J. Org. Chem.* **2008**, *73*, 2028.

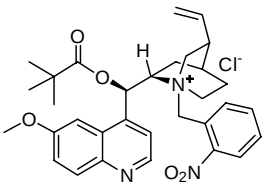
Synthesis of catalysts

N-2-Nitrobenzyl quininium chloride



To a stirred suspension of quinine (694 mg, 2.0 mmol) in toluene/THF 1:1 (6 mL), 2-nitrobenzyl chloride (445 mg, 2.6 mmol) was added. The resulting mixture was then heated up to 70°C and stirred for 20 h at the same temperature. After cooling to r.t., the precipitate was collected by Bückner filtration and washed with tol/THF 1:1 (circa 20 ml) and several times with Et_2O, affording the title compound as a pale yellow solid in 80% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.79 (d, J = 4.7 Hz, 1H), 8.66 (d, J = 7.5 Hz, 1H), 8.13 (d, J = 8.6 Hz, 1H), 8.06 (d, J = 9.6 Hz, 1H), 7.87-7.84 (m, 2H), 7.73 (t, J = 8.3 Hz, 1H), 7.41-7.38 (m, 2H), 7.04 (d, J = 2.6 Hz, 1H), 6.89 (d, J = 12.5 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 5.52 (ddd, J_1 = 18.5 Hz, J_2 = 11.4 Hz, J_3 = 7.6 Hz, 1H), 5.46 (d, J = 12.0 Hz, 1H), 5.34 (t, J = 12.5 Hz, 1H), 5.05 (d, J = 10.3 Hz, 1H), 4.97 (d, J = 17.1 Hz, 1H), 4.01 (s, 3H), 3.74-3.70 (m, 1H), 3.14-3.06 (m, 2H), 3.03-2.99 (m, 1H), 2.58-2.53 (m, 1H), 2.46-2.40 (m, 1H), 2.29-2.25 (m, 1H), 2.05 (s, 1H), 1.80 (t, J = 14.5 Hz, 1H), 1.44 (t, J = 12.7 Hz, 1H); ^{13}C NMR δ 158.5, 150.5, 147.5, 144.1, 142.8, 138.1, 135.8, 134.8, 132.4, 126.0, 125.4, 122.3, 121.6, 120.8, 118.3, 99.4, 72.4, 63.5, 60.6, 59.1, 55.7, 51.8, 38.0, 26.3, 24.9, 21.7; ESIMS: 460 [Q^+]; $[\alpha]^{20}_D$ -115 (c = 0.5, $CHCl_3$)

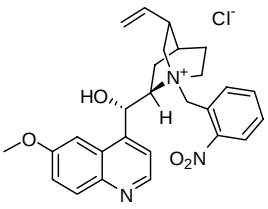
O-1-Pivaloyl-*N*-2-nitrobenzyl quininium chloride (6c)



To a stirred suspension of *N*-2-nitrobenzyl quininium chloride (0.5 mmol) in CH_2Cl_2 (5 mL), were sequentially added pivaloyl chloride (2.5 mmol) and a 30% w/w NaOH solution (0.7 mL, 5.3 mmol). After 30 min of vigorous stirring, H_2O and CH_2Cl_2 were added. The two layers were separated and the aqueous layer extracted with CH_2Cl_2, the combined extracted phases were dried over $MgSO_4$, filtered off and evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (ca 5.0 ml), poured onto Et_2O (100 mL) with stirring. The resulting precipitate was collected and washed several times with Et_2O, giving **6c** as a white solid in 75% yield; ^{1}H NMR (CD_3OD, 600 MHz) δ 8.79 (d, J = 4.9 Hz, 1H), 8.30 (dd, J_1 = 8.3 Hz, J_2 = 1.3 Hz, 1H), 8.06 (d, J = 9.4 Hz, 1H), 8.00 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 7.94 (dt, J_t = 7.5 Hz, J_d = 1.3 Hz, 1H), 7.87 (dt, J_t = 7.7 Hz, J_d = 1.5 Hz, 1H), 7.72 (d, J = 4.6 Hz, 1H), 7.58 (dd, J_1 = 9.2 Hz, J_2 = 2.6 Hz, 1H), 7.48 (s, 1H), 7.44 (d, J = 2.6 Hz, 1H), 5.90 (d, J = 13.4 Hz, 1H), 5.74 (ddd, J_1 = 17.4 Hz, J_2 = 10.3 Hz, J_3 = 7.1 Hz, 1H), 5.14 (bd, J = 3.8 Hz, 1H), 5.10 (d, J = 7.0 Hz, 1H), 5.03 (d, J = 10.8 Hz, 1H), 4.21 (t, J = 8.3 Hz, 1H), 4.07 (s, 3H), 3.95 (tt, J_1 = 11.7

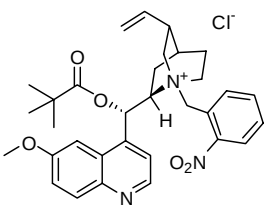
Hz, J_2 = 3.9 Hz, 1H), 3.75 (ddd, J_1 = 12.5 Hz, J_2 = 5.6 Hz, J_3 = 3.4 Hz, 1H), 3.63 (t, J = 12.0 Hz, 1H), 3.38 (dt, J_t = 11.3 Hz, J_d = 5.4 Hz, 1H), 2.78-2.73 (m, 1H), 2.54 (dd, J_1 = 13.3 Hz, J_2 = 7.7 Hz, 1H), 2.28 (m, 1H), 2.18 (d, J = 3.8 Hz, 1H), 2.01 (bt, J = 12.6 Hz, 1H), 1.84 (dt, J_t = 13.9 Hz, J_d = 2.9 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR δ 176.5, 159.7, 150.9, 145.8, 142.3, 141.9, 137.1, 137.0, 134.4, 132.8, 129.8, 126.7, 129.1, 123.4, 121.1, 119.4, 116.9, 101.1, 67.8, 67.6, 61.6, 60.1, 55.5, 51.3, 39.0, 37.9, 26.5, 26.2, 24.9, 22.6; ESIMS: 544 [Q^+]; $[\alpha]^{20}_D$ -400 (c = 0.2, $CHCl_3$).

_N_-2-Nitrobenzyl quinidinium chloride



To a stirred suspension of quinidine (649 mg, 2.0 mmol) in THF (6 mL), 2-nitrobenzyl chloride (445 mg, 2.6 mmol) was added. The resulting mixture was then heated to reflux, and stirred for 20 h at the same temperature. After cooling to r.t., the precipitate was collected by Bückner filtration and washed several times with Et_2O and pentane, affording the title compound as a yellow solid in 62% yield.; mp = 170-172 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.78 (d, J = 4.7 Hz, 1H), 8.28 (dd, J = 7.9, 1.2 Hz, 1H), 8.06-8.00 (m, 2H), 7.97-7.91 (m, 2H), 7.88 (dt, J_t = 7.9 Hz, J_d = 1.4 Hz, 1H), 7.51 (dd, J = 9.2, 2.5 Hz, 1H), 7.46 (d, J = 2.5 Hz, 1H), 6.66 (br s, 1H), 6.14-6.03 (m, 1H), 5.61 (d, J = 13.3 Hz, 1H), 5.51 (d, J = 13.2 Hz, 1H), 5.32-5.25 (m, 2H), 4.50 (ddd, J = 12.3, 8.4, 2.5 Hz, 1H), 4.17 (s, 3H), 4.09 (br t, J = 8.6 Hz, 1H), 3.87-3.78 (m, 1H), 3.56 (br t, J = 11.4 Hz, 1H), 3.20-3.12 (m, 1H), 2.67 (br q, J = 7.9 Hz, 1H), 2.54 (br dd, J = 13.2, 10.6 Hz, 1H), 1.97 (br s, 1H), 1.94-1.85 (m, 2H), 1.17-1.08 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 160.3, 152.6, 148.1, 145.7, 144.7, 138.2, 137.7, 135.3, 133.7, 131.7, 127.6, 127.4, 123.8, 122.8, 121.5, 118.0, 102.1, 70.0, 67.1, 60.2, 57.6, 57.0, 56.7, 39.1, 28.2, 24.8, 22.4; ESIMS: 460 [Q^+]; $[\alpha]_D^{20}$ = +224 (c = 0.36 in CH_3OH).

_O_-1-Pivaloyl-_N_-2-nitrobenzyl quinidinium chloride (QD–6c)

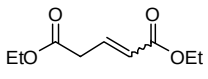


To a stirred suspension of *N*-2-nitrobenzyl quinidinium chloride (0.5 mmol) in CH_2Cl_2 (5 mL), were sequentially added pivaloyl chloride (2.5 mmol) and a 30% w/w NaOH solution (0.7 mL, 5.3 mL). After 30 min of vigorous stirring, H_2O and CH_2Cl_2 were added. The two layers were separated and the aqueous layer extracted with CH_2Cl_2, the combined extracted phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (ca 5 mL, poured onto Et_2O (100 mL) with stirring. The resulting precipitate was collected and washed several times with Et_2O, giving **QD–6c** as a white solid in 74% yield; ^{1}H NMR (CD_3Cl, 600 MHz) δ

8.97 (d, J = 8.1 Hz, 1H), 8.73 (d, J = 4.6 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.83 (t, J = 7.5 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.69 (d, J = 1.9 Hz, 1H), 7.50 (s, 1H), 7.46 (bs, 1H), 7.43 (dd, J_1 = 9.1 Hz, J_2 = 2.5 Hz, 1H), 6.53 (d, J = 10.7 Hz, 1H), 6.15 (t, J = 10.7 Hz, 1H), 5.92 (ddd, J_1 = 17.2 Hz, J_2 = 10.5 Hz, J_3 = 7.0 Hz, 1H), 5.48 (d, J = 11.8 Hz, 1H), 5.48 (d, J = 11.8 Hz, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.19 (d, J = 16.8 Hz, 1H), 4.99 (t, J = 9.4 Hz, 1H), 4.35 (s, 3H), 3.86 (t, J = 11.8 Hz, 1H) 3.07 (t, J = 11.8 Hz, 1H), 2.77 (q, J = 10.2 Hz, 1H), 2.62 (t, J = 12.2 Hz, 1H), 2.54 (q, J = 8.6 Hz, 1H), 2.16-2.04 (m, 2H), 1.85-1.80 (m, 1H), 1.67-1.61 (m, 1H), 1.37 (s, 9H); ^{13}C NMR δ 176.5, 159.9, 150.8, 145.8, 144.9, 139.1, 138.6, 134.8, 134.7, 132.4, 131.5, 126.7, 126.0, 124.4, 121.7, 119.4, 101.2, 67.6, 65.8, 57.2, 56.7, 56.2, 55.9, 39.4, 38.4, 27.3, 26.8, 23.7, 23.6; ESIMS: 544 [Q^+]; $[\alpha]^{20}_D$ +318 (c = 0.25, $CHCl_3$).

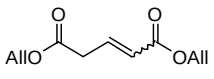
Synthesis of the glutaconates 3b-f

Diethyl glutaconate (3b).



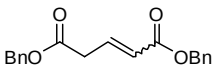
To a stirred solution of glutaconic acid (325 mg, 2.5 mmol) in EtOH (2.5 mL), H_2SO_4 (1 drop) was added. The mixture was refluxed overnight with stirring, then cooled to r.t. and the solvent evaporated. The residue was purified by chromatography on silica gel (*n*-hexane/EtOAc 85:15), giving the title compound as a colorless liquid in 85% yield (*E*/*Z* 90:10). ^{1}H NMR (600 MHz) δ 6.99 (dt, J_d = 15.8 Hz, J_t = 7.4 Hz, 1H$_E$), 6.47 (dt, J_d = 11.6 Hz, J_t = 4.5 Hz, 1H$_Z$), 5.92 (dt, J_d = 15.6 Hz, J_t = 1.5 Hz, 1H$_E$, 1H$_Z$), 4.21-4.13 (m, 4H$_Z$, 4H$_E$), 3.74 (dd, J = 6.9, 2.0 Hz, 2H$_Z$), 3.21 (dd, J = 7.3, 1.6 Hz, 2H$_E$), 1.29-1.24 (m, 6H$_E$, 6H$_Z$); ^{13}C NMR δ [signals of the *E* isomer] 169.8, 165.8, 139.6, 124.7, 61.1, 60.5, 37.5, 14.2, 14.1; ESIMS m/z 209 [M + Na$^+$].

Diallyl glutaconate (3c).



Following the procedure used for **3b**, the title compound was obtained as a colorless liquid in 77% yield (*E*/*Z* 89:11). ^{1}H NMR (600 MHz) δ 7.04 (dt, J_d = 15.8 Hz, J_t = 7.3 Hz, 1H$_E$), 6.51 (dt, J_d = 11.6 Hz, J_t = 4.9 Hz, 1H$_Z$), 5.98-5.87 (m, 3H$_E$, 3H$_Z$), 5.34-5.29 (m, 2H$_E$, 2H$_Z$), 5.26-5.22 (m, 2H$_E$, 2H$_Z$), 4.64 (dt, J_d = 5.7 Hz, J_t = 1.5 Hz, 2H$_E$, 2H$_Z$), 4.60 (dt, J_d = 5.8 Hz, J_t = 1.4 Hz, 2H$_E$), 4.58 (dt, J_d = 5.9 Hz, J_t = 1.2 Hz, 2H$_Z$), 3.80 (dd, J = 7.0, 2.0 Hz, 2H$_Z$), 3.26 (dd, J = 7.1, 1.6 Hz, 2H$_E$); ^{13}C NMR δ [signals of the *E* isomer] 169.4, 165.3, 139.9, 132.1, 131.7, 124.5, 118.8, 118.3, 65.8, 65.2, 37.4; ESIMS m/z 233 [M + Na$^+$].

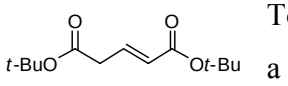
Dibenzyl glutaconate (3d).



In a round bottom flask equipped with a Dean-Stark apparatus, to a suspension of glutaconic acid (650 mg, 5.0 mmol) in toluene (5.0 mL), benzyl alcohol (0.99 mL, 9.5 mmol) and TsOH·H_2O (few mg) were added. The mixture was refluxed with stirring for 2 h, then cooled to r.t. and the solvent evaporated. The residue was purified by chromatography on silica gel (*n*-hexane/EtOAc 85:15), giving the title compound as a colorless liquid in 72% yield (*E*/*Z* 90:10). ^{1}H NMR (600 MHz) δ 7.37-7.29 (m, 5H$_E$, 5H$_Z$), 7.06 (dt, J_d = 15.7 Hz, J_t = 7.0 Hz, 1H$_E$), 6.52 (dt, J_d = 11.6 Hz, J_t = 4.5 Hz, 1H$_Z$), 6.00-5.95 (m, 1H$_E$, 1H$_Z$), 5.17 (s, 2H$_E$, 2H$_Z$), 5.14 (s, 2H$_Z$), 5.14 (s, 2H$_E$), 3.83 (dd, J = 6.7, 1.9 Hz, 2H$_Z$), 3.27 (dd, J = 7.0, 1.4 Hz, 2H$_E$); ^{13}C NMR δ [signals of the *E* isomer]

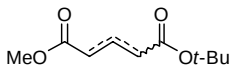
169.6, 165.5, 140.0, 135.9, 135.4, 128.6, 128.6, 128.4, 128.3, 128.2, 128.1, 124.6, 66.9, 66.3, 37.4; ESIMS m/z 333 [M + Na^+].

Di-*tert*-butyl glutaconate (3e).[2]



To a stirred solution of glutaconic acid (130 mg, 1.0 mmol) in dry THF (2.0 mL), a solution of *tert*-butyl 2,2,2-trichloroacetimidate (874 mg, 4.0 mmol) in cyclohexane (4.0 mL) was added under a N_2 atmosphere, followed by $BF_3{\cdot}OEt_2$ (40 µL, 0.24 mmol). The reaction mixture was stirred at r.t. overnight, then the solvents were evaporated, and the residue purified by chromatography on silica gel (*n*-hexane/EtOAc 90:10), giving the title compound as a colorless liquid in 45% yield (*E*/*Z* > 98:2). ^{1}H NMR (600 MHz) δ 6.86 (dt, J_d = 15.7 Hz, J_t = 7.6 Hz, 1H), 5.83-5.78 (m, 1H), 3.10 (dd, *J* = 7.3, 1.5 Hz, 2H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C NMR δ 169.3, 165.2, 139.0, 126.1, 81.4, 80.4, 38.6, 28.1, 28.0. ESIMS m/z 265 [M + Na^+].

***tert*-Butyl methyl glutaconate (3f).**[3]



Glutaconic acid (650 mg, 5.0 mmol) was dissolved in acetic anhydride (1.4 mL) and heated to 150 °C. After 25 minutes at the same temperature, the dark mixture was allowed to cool to r.t., then acetic anhydride was removed by stripping with toluene under reduced pressure, leaving crude glutaconic anhydride as a brown residue. This brown solid was dissolved in MeOH (10 mL) and stirred overnight. The solvent was then removed under reduced pressure, and the residue purified by chromatography on silica gel (*n*-hexane/EtOAc 1:1), giving the glutaconic acid monomethyl ester in 34% yield as a colorless oil (*Z*/*E* >95:5). ^{1}H NMR (600 MHz) δ 6.64 (dt, J_d = 11.4 Hz, J_t = 4.9 Hz, 1H), 5.95 (br d, *J* = 10.8 Hz, 1H), 3.76 (dd, *J* = 6.9, 1.6 Hz, 2H), 3.72 (s, 3H); ^{13}C NMR δ 171.2, 170.9, 143.2, 121.2, 52.1, 34.0. The thus obtained monomethyl ester was treated with *tert*-butyl 2,2,2-trichloroacetimidate following the procedure used for **3e**, giving after chromatography on silica gel (*n*-hexane/EtOAc 90:10) a mixture of the two regioisomeric diesters and the stereoisomer of one of these as a colorless oil in 56% overall yield. Separation of these compounds was not attempted, as they were assumed to give the same anionic species under the conditions used for the catalytic asymmetric cycloaddition reactions. ^{1}H NMR (600 MHz) δ [signals of the major component]

[2] Procedure adapted from: Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483.

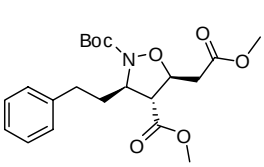
[3] Procedure for the preparation of the crude glutaconic anhydride taken from: Briggs, S. P.; Davies, D. I.; Newton, R. F.; Reynolds, D. P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 146.

6.36 (dt, J_d = 11.6 Hz, J_t = 4.8 Hz, 1H), 5.80 (dt, J_d = 11.5 Hz, J_t = 2.1 Hz, 1H), 3.72 (dd, J = 7.0, 2.0 Hz, 2H), 3.68 (s, 3H), 1.46 (s, 9H); ^{13}C NMR δ [signals of the major component] 171.6, 165.4, 138.7, 123.8, 80.6, 51.9, 33.7, 28.0; ESIMS m/z 223 [M + Na^+].

General procedure for the catalytic reactions

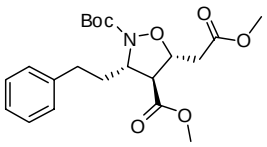
In a test tube equipped with a magnetic stirring bar were added in sequence the *N*-carbamoyl-*N*-hydroxy-α-amido sulfones **1a-l** or **2a-d** (0.10 mmol), catalyst **6c** (5.8 mg, 0.01 mmol) a toluene/MTBE/CH_2Cl_2 mixture (2.0 mL, 3.5:3.5:3) and glutaconate **3a-f** (0.20 mmol), giving a white suspension which was cooled to -42° C. K_2CO_3 50% $^{w}/_{w}$ (0.10 mL, 5.0 mmol) was then added, resulting in two liquid layers, with solid materials suspended in the organic solvent. After the reaction was vigorously stirred at the same temperature for 24 h, giving a solid/liquid biphasic mixture, with the solid being presumably constituted by the sulfinate salt formed, Na_2CO_3 10% $^{w}/_{w}$ (2 mL) was added and the thus obtained two clear layers were allowed to warm to room temperature. The crude product was extracted with AcOEt (3x2 mL), the combined organic phases were filtered on a plug of silica to remove the catalyst, dried in vacuo and analyzed by means of ^{1}H NMR spectroscopy, which always showed the presence of a single diastereoisomer. The crude mixtures of compounds **4b-e** showed the presence of the corresponding linear not-cyclized compound not exceeding 7 mol%. The product was finally obtained after column chromatography on silica gel (*n*-hexane/AcOEt 90:10 then 80:20). Due to their very low UV absorbance which prevented the direct determination of their ee by HPLC-UV, the *N*-Boc protected cycloadducts **4a-j** were converted as follows to the corresponding *N*-Cbz derivatives. Pure compounds **4a-j** were dissolved in CH_2Cl_2 (0.5 mL), cooled to 0°C and treated with TFA (0.2 mL, 25 equiv.) After 5 h stirring at room temperature, Na_2CO_3 10% $^{w}/_{w}$ (2 mL) was added, followed by EtOAc (2 mL) and CbzCl (0.1 mL, 7 equiv.). The reaction was vigorously stirred at room temperature overnight. The phases were separated, the aqueous layer extracted with AcOEt (3x2 mL), and the combined organic phases filtered on a plug of silica. The solvents were evaporated and the pure *N*-Cbz product was obtained after chromatography on silica gel (*n*-hexane/AcOEt 90:10 then 80:20).

(3*R*,4*R*,5*S*)-2-(*tert*-Butyl 4-methyl 5-(2-methoxy-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate (4a).



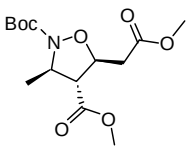
Following the general procedure and performing the reaction on a 1.0 mmol, scale, compound **4a** was obtained as a colorless oil in 86% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/i-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 19.8 min, τ_{min} = 24.1 min); ^{1}H NMR (400 MHz) δ 7.30-7.25 (m, 2H), 7.22-7.15 (m, 3H), 4.55-4.43 (m, 2H), 3.72 (s, 3H), 3.69 (s, 3H), 2.89 (dd, J_1 = 8.3 Hz, J_2 = 3.9 Hz, 1H), 2.85-2.65 (m, 4H), 2.02-1.83 (m, 2H), 1.51 (s, 9H); ^{13}C NMR δ 171.7, 169.8, 157.9, 141.2, 128.4, 128.3, 125.9, 82.5, 80.0, 65.0, 58.4, 52.5, 52.0, 37.6, 36.9, 32.7, 28.2; ESIMS m/z 430 [M + Na^+]; $[\alpha]^{20}_D$ – 13.0 (c = 0.6, $CHCl_3$), 91% ee.

(3*R*,4*R*,5*S*)-2-(*tert*-Butyl 4-methyl 5-(2-methoxy-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate (*ent*-4a).



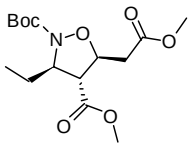
Following the general procedure and using cat **QD-6c** compound ***ent*-4a** was obtained as a colorless oil in 86% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 24.1 min, τ_{min} = 19.8 min); spectral data were identical to compound **4a**; $[\alpha]^{20}_D$ +8 (c = 0.6, $CHCl_3$), 60% ee.

(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 5-(2-methoxy-2-oxoethyl)-3-methylisoxazolidine-2,4-dicarboxylate (4b).



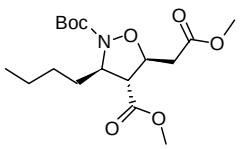
Following the general procedure, but performing the reaction in a toluene/MTBE/CH_2Cl_2 mixture (2.0 mL, 4.5:4.5:1.0), at -40 °C for 48 h compound **4b** was obtained as a colorless oil in 53% yield. The ee of the product was determined on the corresponding Cbz, derivative obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 14.0 min, τ_{min} = 17.0 min); ^{1}H NMR (400 MHz) δ 4.55-4.48 (m, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 2.88-2.83 (m, 2H), 2.73 (dd, J_1 = 16.3 Hz, J_2 = 6.9 Hz, 1H), 1.50 (s, 9H), 1.38 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 171.4, 169.8, 157.4, 82.4, 79.7, 60.7, 59.6, 52.4, 52.0, 37.0, 28.0, 21.7; ESIMS m/z 340 [M + Na^+]; $[\alpha]^{20}_D$ -31 (c = 0.5, $CHCl_3$), 60% ee.

(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 3-ethyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (4c).



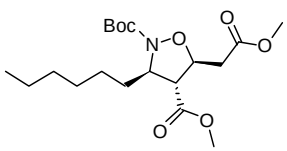
Following the general procedure, compound **4c** was obtained as a colorless oil in 80% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 13.0 min, τ_{min} = 16.0 min); ^{1}H NMR (400 MHz) δ 4.49 (dt, J_d = 8.5 Hz, J_t = 6.5 Hz, 1H), 4.30 (dd, J_1 = 7.9 Hz, J_2 = 4.3 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.88-2.81 (m, 2H), 2.72 (dd, J_1 = 16.1 Hz, J_2 = 6.8 Hz, 1H), 1.72-1.57 (m, 2H), 1.50 (s, 9H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 171.8, 169.8, 158.0, 82.3, 79.9, 66.7, 58.1. 52.4, 52.0, 36.9, 28.8, 28.0, 10.7; ESIMS m/z 354 [M + Na$^+$]; $[\alpha]^{20}_D$ -43 (c = 0.6, $CHCl_3$), 88% ee.

(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 3-butyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (4d).



Following the general procedure, compound **4d** was obtained as a colorless oil in 70% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 12.0 min, τ_{min} = 14.0 min); ^{1}H NMR (400 MHz) δ 4.49 (dt, J_d = 8.3 Hz, J_t = 6.8 Hz, 1H), 4.15 (dd, J_1 = 7.9 Hz, J_2 = 4.3 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.88-2.82 (m, 2H), 2.72 (dd, J_1 = 16.1 Hz, J_2 = 6.8 Hz, 1H), 1.68-1.29 (m, 6H), 1.50 (s, 9H), 0.90 (bt, J = 6.9 Hz, 3H); ^{13}C NMR δ 171.8, 169.8, 157.9, 82.3, 79.9, 65.3, 58.5, 52.4, 52.0, 37.0, 35.5, 28.4, 28.1, 22.1, 13.9; ESIMS m/z 382 [M + Na$^+$]; $[\alpha]^{20}_D$ -37 (c = 0.6, $CHCl_3$), 92% ee.

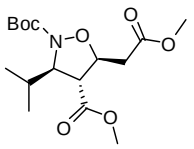
(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 3-hexyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (4e).



Following the general procedure, compound **4e** was obtained as a colorless oil in 72% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 11.5 min, τ_{min} = 13.0 min); ^{1}H NMR (400 MHz) δ 4.49 (dt, J_d = 8.3 Hz, J_t = 6.2 Hz, 1H), 4.38 (dd, J_1 = 9.0 Hz, J_2 = 4.0 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.88-2.82 (m, 2H), 2.71 (dd, J_1 = 15.9 Hz, J_2 = 6.6 Hz, 1H), 1.70-1.23 (m, 10H), 1.50 (s, 9H), 0.87 (bt, J = 6.8 Hz, 3H); ^{13}C NMR δ 171.8, 169.8, 157.9, 82.3, 79.9, 65.3, 58.5, 52.4,

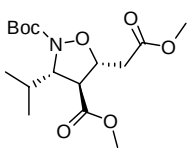
52.0, 37.0, 35.8, 31.7, 28.7, 28.1, 26.2, 22.5, 14.0; ESIMS m/z 410 [M + Na^+]; $[\alpha]^{20}_D$ -25 (c = 0.6, $CHCl_3$), 94% ee.

(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 3-isopropyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (4f).



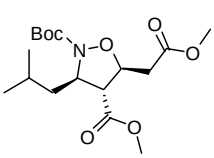
Following the general procedure, compound **4f** was obtained as a colorless oil in 93% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 11.5 min, τ_{min} = 14.5 min); ^{1}H NMR (400 MHz) δ 4.46 (dt, J_d = 9.2 Hz, J_t = 6.1 Hz, 1H), 4.15 (dd, J_1 = 7.9 Hz, J_2 = 4.3 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.96 (dd, J_1 = 8.8 Hz, J_2 = 5.2 Hz, 1H), 2.84 (dd, J_1 = 16.1 Hz, J_2 = 6.1 Hz, 1H), 2.71 (dd, J_1 = 15.7 Hz, J_2 = 6.0 Hz, 1H), 1.80 (oct, J = 7.5 Hz, 1H), 1.50 (s, 9H), 0.96 (d, J = 6.8 Hz, 6H); ^{13}C NMR δ 172.0, 169.8, 158.2, 82.3, 80.5, 71.1, 56.3, 52.5, 52.0, 36.6, 32.8, 28.1, 19.0, 18.9; ESIMS m/z 368 [M + Na^+]; $[\alpha]^{20}_D$ -37 (c = 0.6, $CHCl_3$), 99% ee.

(3*S*,4*S*,5*R*)-2-*tert*-Butyl 4-methyl 3-isopropyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (*ent*-4f).



Following the general procedure and using cat **QD-6c** compound ***ent*-4f** was obtained as a colorless oil in 87% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 14.5 min, τ_{min} = 11.5 min); spectral data were identical to compound **4f**; $[\alpha]^{20}_D$ +35 (c = 0.5, $CHCl_3$), 80% ee.

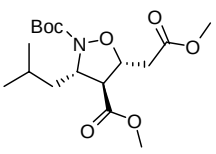
(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 3-isobutyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (4g).



Following the general procedure, compound **4g** was obtained as a colorless oil in 97% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 11.0 min, τ_{min} = 12.5 min); ^{1}H NMR (400 MHz) δ 4.49 (m, 2H), 3.72 (s, 3H), 3.68 (s, 3H), 2.85 (dd, J_1 = 16.4 Hz, J_2 = 6.1 Hz, 1H), 2.80 (dd, J_1 = 8.1 Hz, J_2 = 3.7 Hz, 1H), 2.70 (dd, J_1 = 16.0 Hz, J_2 = 7.2 Hz, 1H), 1.70 (oct, J = 6.9 Hz, 1H), 1.65-1.58 (m, 1H), 1.50 (s, 9H), 1.32-1.24 (m, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H);

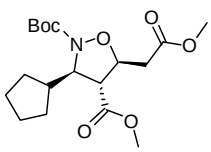
^{13}C NMR δ 172.2, 170.0, 158.1, 82.6, 80.2, 64.1, 59.1, 52.6, 52.2, 45.2, 37.3, 28.3, 25.5, 23.1, 21.8; ESIMS m/z 382 [M + Na^+]; $[\alpha]^{20}_D$ - 22 (c = 0.6, $CHCl_3$), 98% ee.

(3*S*,4*S*,5*R*)-2-*tert*-Butyl 4-methyl 3-isobutyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (*ent*-4g).



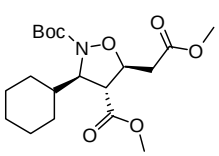
Following the general procedure and using cat **QD-6c** compound ***ent*-4g** was obtained as a colorless oil in 83% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 12.5 min, τ_{min} = 11.0 min); spectral data were identical to compound **4g**; $[\alpha]^{20}_D$ +10 (c = 0.5, $CHCl_3$), 57% ee.

(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 3-cyclopentyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (4h).



Following the general procedure, compound **4h** was obtained as a colorless oil in 97% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 12.7 min, τ_{min} = 18.2 min); ^{1}H NMR (400 MHz) δ 4.48 (dt, J_d = 8.3 Hz, J_t = 6.2 Hz, 1H), 4.26 (dd, J_1 = 8.8 Hz, J_2 = 4.0 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 2.94 (dd, J_1 = 8.5 Hz, J_2 = 4.1 Hz, 1H), 2.85 (dd, J_1 = 15.9 Hz, J_2 = 6.1 Hz, 1H), 2.70 (dd, J_1 = 16.1 Hz, J_2 = 6.9 Hz, 1H), 2.08 (sext, J = 8.4 Hz, 1H), 1.77-1.24 (m, 8H), 1.50 (s, 9H); ^{13}C NMR δ 172.0, 169.8, 158.2, 82.3, 80.4, 69.4, 57.7, 52.4, 52.0, 44.8, 36.9, 29.6, 29.0, 28.1, 25.3, 25.0; ESIMS m/z 394 [M + Na^+]; $[\alpha]^{20}_D$ -27 (c = 0.6, $CHCl_3$), 99% ee.

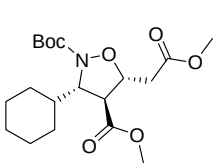
(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 3-cyclohexyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (4i).



Following the general procedure and performing the reaction on a 5.0 mmol scale, compound **4i** was obtained as a colorless oil in quantitative yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 12.8 min, τ_{min} = 17.5 min); ^{1}H NMR (400 MHz) δ 4.45 (dt, J_d = 8.4 Hz, J_t = 6.6 Hz, 1H), 4.16 (dd, J_1 = 7.8 Hz, J_2 = 4.3 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 2.97 (dd, J_1 = 8.5 Hz, J_2 = 4.4 Hz,

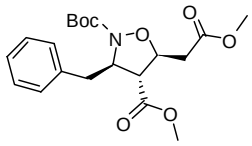
1H), 2.83 (dd, J_1 = 16.2 Hz, J_2 = 6.3 Hz, 1H), 2.70 (dd, J_1 = 16.2 Hz, J_2 = 6.8 Hz, 1H), 1.86-0.96 (m, 11H), 1.50 (s, 9H); ^{13}C NMR δ 172.1, 169.8, 158.3, 82.2, 80.4, 70.3, 56.2, 52.4, 52.0, 42.2, 36.7, 29.5, 29.4, 28.1, 26.2, 25.9, 25.7; ESIMS m/z 408 [M + Na^+]; $[\alpha]^{20}_D$ -34 (c = 0.6, $CHCl_3$), >99% ee.

(3*S*,4*S*,5*R*)-2-*tert*-Butyl 4-methyl 3-cyclohexyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (*ent*-4i).



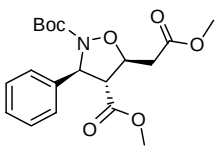
Following the general procedure and using cat **QD-6c** compound ***ent*-4i** was obtained as a colorless oil in 98% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 17.5 min, τ_{min} = 12.8 min); spectral data were identical to compound **4i**; $[\alpha]^{20}_D$ +17 (c = 0.5, $CHCl_3$), 83% ee.

(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 3-benzyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (4j).



Following the general procedure, compound **4j** was obtained as a colourless oil in 81% yield. The ee of the product was determined on the corresponding Cbz derivative, obtained as described above, by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 19.5 min, τ_{min} = 22.0 min); ^{1}H NMR (400 MHz) δ 7.30-7.20 (m, 5H), 4.70 (dt, J_d = 4.7 Hz, J_t = 6.9 Hz, 1H), 4.48 (dt, J_d = 8.3 Hz, J_t = 6.6 Hz, 1H), 3.68 (s, 3H), 3.62 (s, 3H), 3.05 (dd, J_1 = 13.7 Hz, J_2 = 7.8 Hz, 1H), 2.98 (dd, J_1 = 8.4 Hz, J_2 = 4.6 Hz, 1H), 2.87 (dd, J_1 = 13.7 Hz, J_2 = 6.8 Hz, 1H), 2.80 (dd, J_1 = 16.1 Hz, J_2 = 6.0 Hz, 1H), 2.66 (dd, J_1 = 15.9 Hz, J_2 = 6.6 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR δ 171.4, 169.7, 157.2, 137.1, 129.6, 128.4, 126.7, 82.4, 80.1, 65.7, 57.5, 52.4, 52.0, 41.2, 36.6, 28.0; ESIMS m/z 416 [M + Na^+]; $[\alpha]^{20}_D$ -10 (c = 0.6, $CHCl_3$), 95% ee.

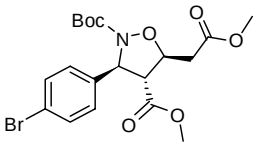
(3*S*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 5-(2-methoxy-2-oxoethyl)-3-phenylisoxazolidine-2,4-dicarboxylate (4k).



Following the general procedure and using a toluene/CH_2Cl_2 10/1 mixture as the solvent, compound **4k** was obtained as a colourless oil in quantitative yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 12.0 min, τ_{min} = 13.1 min); ^{1}H

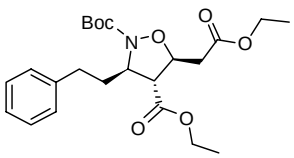
NMR (600 MHz) δ 7.38-7.35 (m, 2H), 7.34-7.31 (m, 2H), 7.27-7.24 (m, 1H), 5.55 (d, J = 4.8 Hz, 1H), 4.62 (dt, J_d = 8.3 Hz, J_t = 6.4 Hz, 1H), 3.77 (s, 3H), 3.65 (s, 3H), 3.26 (dd, J_1 = 8.6 Hz, J_2 = 5.0 Hz, 1H), 2.83 (dd, J_1 = 16.3 Hz, J_2 = 6.4 Hz, 1H), 2.71 (dd, J_1 = 16.1 Hz, J_2 = 6.0 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR δ 171.3, 169.9, 157.4, 141.1, 128.9, 127.8, 126.1, 83.0, 80.3, 67.4, 61.8, 52.9, 52.2, 37.0, 28.3; ESIMS m/z 402 [M + Na^+]; $[\alpha]^{20}_D$ -7 (c = 0.5, CH_3OH), 67% ee.

(3*S*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 3-(4-bromophenyl)-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (4l).



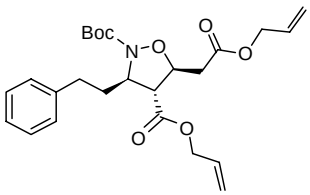
Following the general procedure, compound **4l** was obtained as a colourless oil in 63% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column cooled to 0° C (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, τ_{maj} = 42.6 min, τ_{min} = 46.3 min); ^{1}H NMR (400 MHz) δ 7.49-7.45 (m, 2H), 7.28-7.24 (m, 2H), 5.51 (d, J = 5.1 Hz, 1H), 4.61 (dt, J_d = 8.3 Hz, J_t = 6.4 Hz, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.23 (dd, J_1 = 8.6 Hz, J_2 = 5.1 Hz, 1H), 2.82 (dd, J_1 = 16.2 Hz, J_2 = 6.1 Hz, 1H), 2.72 (dd, J_1 = 16.5 Hz, J_2 = 6.5 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR δ 171.0, 169.8, 157.3, 140.2, 132.1, 127.9, 121.8, 83.3, 80.3, 66.8, 61.6, 53.0, 52.2, 36.8, 28.3; ESIMS m/z 480-482 [M + Na^+]; $[\alpha]^{20}_D$ +2 (c = 0.5, $CHCl_3$), 60% ee.

(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-ethyl 5-(2-ethoxy-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate (4m).



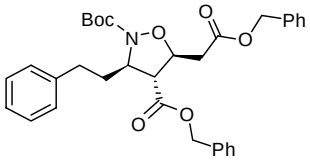
Following the general procedure (96 h reaction time), compound **4m** was obtained as a colorless oil in 60% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, τ_{maj} = 11.4 min, τ_{min} = 12.1 min); ^{1}H NMR (600 MHz) δ 7.28-7.24 (m, 2H), 7.20-7.15 (m, 3H), 4.52 (dd, J_1 = 14.2 Hz, J_2 = 6.7 Hz, 1H), 4.44 (quint, J_1 = 4.6 Hz, 1H), 4.20-4.11 (m, 4H), 2.86 (dd, J_1 = 8.1 Hz, J_2 = 3.9 Hz, 1H), 2.82 (dd, J_1 = 15.9 Hz, J_2 = 5.8 Hz, 1H), 2.79-2.74 (m, 1H), 2.72-2.66 (m, 2H), 2.01-1.93 (m, 1H), 1.90-1.84 (m, 1H), 1.49 (s, 9H), 1.24 (t, J = 7.7 Hz, 6H); ^{13}C NMR δ 171.4, 169.6, 158.1, 141.5, 128.7, 128.6, 126.2, 82.7, 80.3, 65.2, 61.6, 61.2, 58.8, 37.8. 37.5, 32.9, 28.3, 14.4, 14.3; ESIMS m/z 458 [M + Na^+]; $[\alpha]^{20}_D$ -11 (c = 0.5, $CHCl_3$), 91% ee.

(3*R*,4*R*,5*S*)-4-Allyl 2-*tert*-butyl 5-(2-(allyloxy)-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate (4n).



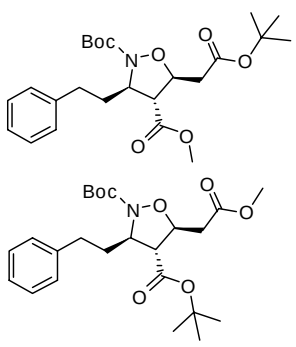
Following the general procedure (96 h reaction time), compound **4n** was obtained as a colorless oil in 76% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 90:10, flow rate 0.75 mL/min, τ_{maj} = 7.0 min, τ_{min} = 6.7 min); ^{1}H NMR (600 MHz) δ 7.28-7.24 (m, 2H), 7.21-7.15 (m, 3H), 5.91-5.83 (m, 2H), 5.32-5.26 (m, 2H), 5.23 (dd, J_1 = 10.0 Hz, J_2 = 7.4 Hz, 2H), 4.63-4.52 (m, 5H), 4.46 (quint, J = 4.8 Hz, 1H), 2.91 (dd, J_1 = 8.3 Hz, J_2 = 4.0 Hz, 1H), 2.87 (dd, J_1 = 15.9 Hz, J_2 = 5.8 Hz, 1H), 2.80-2.65 (m, 3H), 2.03-1.94 (m, 1H), 1.91-1.84 (m, 1H), 1.50 (s, 9H); ^{13}C NMR δ 171.1, 169.2, 158.1, 141.4, 131.9, 131.7, 128.7, 128.6, 126.2, 119.1, 118.9, 82.8, 80.2, 66.2, 65.9, 65.2, 58.7, 37.8, 37.3, 32.9, 28.3; ESIMS m/z 482 [M + Na^+]; $[\alpha]^{20}_D$ -10 (c = 0.5, $CHCl_3$), 94% ee.

(3*R*,4*R*,5*S*)-4-Benzyl 2-*tert*-butyl 5-(2-(benzyloxy)-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate (4o).



Following the general procedure (96 h reaction time), compound **4o** was obtained as a colorless oil in 73% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, τ_{maj} = 30.1 min, τ_{min} = 28.8 min); ^{1}H NMR (600 MHz) δ 7.36-7.24 (m, 12H), 7.19-7.15 (m, 3H), 5.14-5.05 (m, 4H), 4.58 (dd, J_1 = 13.8 Hz, J_2 = 7.0 Hz, 1H), 4.46 (quint, J = 4.8 Hz, 1H), 2.95 (dd, J_1 = 8.3 Hz, J_2 = 4.1 Hz, 1H), 2.90 (dd, J_1 = 16.3 Hz, J_2 = 6.0 Hz, 1H), 2.78-2.72 (m, 2H), 2.71-2.64 (m, 1H), 2.00-1.92 (m, 1H), 1.90-1.82 (m, 1H), 1.45 (s, 9H); ^{13}C NMR δ 171.0, 169.1, 157.8, 141.1, 135.4, 135.3, 128.6, 128.5, 128.4, 128.3, 128.2, 125.9, 82.5, 80.0, 67.2, 66.7, 65.0, 58.5, 37.4, 37.0, 32.6, 28.0; ESIMS m/z 582 [M + Na^+]; $[\alpha]^{20}_D$ -9 (c = 0.5, $CHCl_3$), 95% ee.

(3*R*,4*R*,5*S*)-2-*tert*-Butyl 4-methyl 5-(2-*tert*-butoxy-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate and (3*R*,4*R*,5*S*)-di-*tert*-butyl 5-(2-methoxy-2-oxoethyl)-3-phenethylisoxazolidine-2,4-dicarboxylate (4q).



Following the general procedure (96 h reaction time, 0 °C), compounds **4q** were obtained as a colorless oil in 25% yield and as a regioisomeric mixture (60:40 favouring the 4-methyl carboxylate isomer) as determined by ^{1}H NMR

analysis from the integration of the signals relative to the methyl ester protons. The ee of the major regioisomer was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, τ_{maj} = 10.5 min, τ_{min} = 13.1 min; minor regioisomer, τ = 9.5 min, not separated); ^{1}H NMR (400 MHz) δ 7.30-7.16 (m, $5H_{maj}$, $5H_{min}$), 4.54-4.40 (m, $2H_{maj}$, $2H_{min}$), 3.71 (s, $3H_{maj}$), 3.69 (s, $3H_{min}$), 2.89-2.56 (m, $5H_{maj}$, $5H_{min}$), 2.04-1.81 (m, $2H_{maj}$, $2H_{min}$) 1.51 (s, $9H_{maj}$), 1.50 (s, $9H_{min}$), 1.44 (s, $9H_{maj}$), 1.43 (s, $9H_{min}$); ^{13}C NMR δ [signals of both isomers] 172.0, 170.3, 170.0, 168.8, 158.1, 141.6, 141.5, 128.7, 128.6, 126.2, 82.7, 82.6, 82.2, 81.8, 80.7, 80.0, 65.3, 65.0, 59.6, 58.6, 52.6, 52.2, 38.7, 37.8, 37.7, 37.3, 33.0, 32.9, 28.3, 28.2, 28.1; ESIMS m/z 472 [M + Na^+], 73% ee (major regioisomer).

Small amounts of the two compounds as single regioisomers were obtained by extensive column chromatography on silica gel (petroleum ether/Et_2O/CH_2Cl_2 8/1.5/0.5), and were used for the determination of their structure by means of NMR experiments as follows:

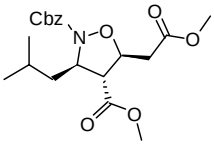
Major regiosiomer: R_f 0.14 (petroleum ether/Et_2O/CH_2Cl_2 8.0/1.5/0.5); ^{1}H NMR (CD_3CN, 600 MHz) δ 7.36-7.12 (m, 5H), 4.44-4.40 (m, 1H), 4.39-4.36 (m, 1H), 3.67 (s, 3H), 2.93 (dd, J = 7.7, 3.6 Hz, 1H), 2.73-2.68 (m, 2H), 2.68 (dd, J = 15.7, 9.4 Hz, 1H), 2.64 (dd, J = 15.7, 6.7 Hz, 1H), 1.93-1.82 (m, 2H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (CD_3CN) δ [deduced from the gHSQC and gHMBC experiments, Boc carbonyl missing] 172.3, 169.0, 141.7, 128.7, 128.6, 126.1, 82.1, 81.0, 80.8, 65.3, 58.0, 52.2, 38.4, 37.3, 32.5, 27.5, 27.4.

A gHMBC NMR experiment showed a relation between the ^{1}H signal at 3.67 ppm (OCH_3) and the ^{13}C signal at 172.3 ppm, which could thus be assigned to the carbonyl carbon of the methyl ester. The same experiment showed a relation between the ^{1}H signal at 4.44-4.40 ppm and the ^{13}C signals of both carbonyl groups at 172.3 and 169.0 ppm, thus allowing the assignment of this ^{1}H signal to the C^5H of the isoxazolidine cycle (CHO), and consequently of the ^{1}H signal at 4.39-4.36 ppm to the C^2H of the isoxazolidine (CHN). As the gHMBC spectrum presented a relation between this latter ^{1}H signal and the ^{13}C signal at 172.3 ppm, the quaternary carbon of the methyl ester, it was possible to conclude that in this isomer the methyl ester moiety is at the C^4 position of the isoxazolidine ring.

Minor regioisomer: R*f* 0.13 (petroleum ether/Et_2O/CH_2Cl_2 8/1.5/0.5); ^{1}H NMR (CD_3CN, 600 MHz) δ 7.32-7.28 (m, 2H), 7.27-7.24 (m, 2H), 7.22-7.18 (m, 1H), 4.43-4.38 (m, 1H), 4.38-4.33 (m, 1H), 3.66 (s, 3H), 2.85-2.82 (m, 1H), 2.78-2.73 (m, 2H), 2.73-2.68 (m, 2H), 1.93-1.81 (m, 2H), 1.45 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (CD_3CN) δ [signals deduced from a gHMBC experiment, Boc carbonyl missing] 170.6, 170.3, 155.0, 141.8, 128.7, 128.6, 126.1, 82.1, 81.7, 80.1, 65.0, 59.0, 52.5, 38.2, 37.1, 32.3, 27.6, 27.3.

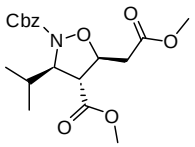
A gHMBC NMR experiment showed a relation between the ^{1}H signal at 3.66 ppm (OCH_3) and the ^{13}C signal at 170.3 ppm, which could therefore be assigned to the carbonyl carbon of the methyl ester. The remaining ^{13}C carbonyl signal at 170.6 ppm could thus be assigned to the carbonyl of the *tert*-butyl ester. As the gHMBC spectrum presented relations between both ^{1}H signals at 4.43-4.38 and 4.38-4.33 ppm (C^2H and C^4H of the isoxazolidine cycle) and the ^{13}C signal at 170.6 ppm, the carbonyl carbon of the *tert*-butyl ester, it was possible to conclude that in this isomer the *tert*-butyl ester moiety is at the C^4 position of the isoxazolidine ring.

(3*R*,4*R*,5*S*)-2-Benzyl 4-methyl 3-isobutyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (5a).



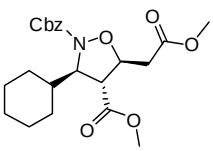
Following the general procedure, compound **5a** was obtained as a colourless oil in 60% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 11.0 min; τ_{min} = 12.5 min); ^{1}H NMR (600 MHz) δ 7.40-7.29 (m, 5H), 5.25 (d, J = 12.3 Hz, 1H), 5.18 (d, J = 12.3 Hz, 1H), 4.58-4.49 (m, 2H), 3.67 (s, 6H), 2.90-2.84 (m, 2H), 2.73 (dd, J_1 = 16.5 Hz, J_2 = 7.0 Hz, 1H), 1.78-1.68 (m, 1H), 1.66-1.60 (m, 1H), 1.34-1.29 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 171.8, 169.9, 158.0, 135.9, 128.7, 128.5, 128.3, 80.6, 68.5, 63.8, 58.8, 52.7, 52.2, 45.0, 37.2, 25.5, 23.1, 21.8; ESIMS m/z 416 [M + Na^+]; $[\alpha]^{20}_D$ -25 (c = 0.5, $CHCl_3$), 75% ee.

(3*R*,4*R*,5*S*)-2-Benzyl 4-methyl 3-isopropyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (5b).



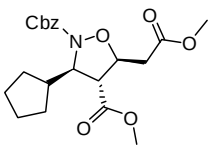
Following the general procedure, compound **5b** was obtained as a colorless oil in 72% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/i-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 11.5 min, τ_{min} = 14.5 min);^{1}H NMR (600 MHz) δ 7.38-7.29 (m, 5H), 5.28-5.15 (m, 2H), 4.47 (dt, J_d = 8.6 Hz, J_t = 6.5 Hz, 1H), 4.23 (dd, J_1 = 7.7 Hz, J_2 = 4.5 Hz, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 3.01 (dd, J_1 = 8.6 Hz, J_2 = 4.9 Hz, 1H), 2.84 (dd, J_1 = 16.6 Hz, J_2 = 5.9 Hz, 1H), 2.72 (dd, J_1 = 16.2 Hz, J_2 = 6.8 Hz, 1H), 1.83 (oct, J = 6.8 Hz, 1H), 0.97 (bd, J = 6.8 Hz, 3H), 0.95 (bd, J = 6.8 Hz, 3H); ^{13}C NMR δ 171.9, 169.9, 159.1, 136.0, 128.7, 128.4, 128.2, 81.1, 71.0, 68.4, 56.2, 52.7, 52.2, 36.7, 32.9, 19.1, 18.9; ESIMS m/z 402 [M + Na^+]; $[\alpha]^{20}_D$ -37 (c = 0.25, $CHCl_3$), 80% ee.

(3*R*,4*R*,5*S*)-2-Benzyl 4-methyl 3-cyclohexyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (5c).



Following the general procedure, compound **5c** was obtained as a colourless oil in quantitative yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 12.8 min, τ_{min} = 17.5 min); ^{1}H NMR (600 MHz)δ 7.38-7.29 (m, 5H), 5.23 (d, J = 12.9 Hz, 1H), 5.18 (d, J = 12.6 Hz, 1H), 4.46 (dt, J_d = 9.0 Hz, J_t = 5.7 Hz, 1H), 4.24 (dd, J_1 = 8.5 Hz, J_2 = 4.5 Hz, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.02 (dd, J_1 = 8.9 Hz, J_2 = 4.3 Hz, 1H), 2.84 (dd, J_1 = 15.7 Hz, J_2 = 5.9 Hz, 1H), 2.71 (dd, J_1 = 16.0 Hz, J_2 = 6.8 Hz, 1H), 1.82-0.97 (m, 11H); ^{13}C NMR δ 171.9, 169.9, 159.2, 136.0, 128.7, 128.4, 128.2, 81.0, 70.2, 68.4, 56.2, 52.7, 52.2, 42.3, 36.8, 29.6, 29.5, 26.4, 26.0, 25.9; ESIMS m/z 442 [M + Na^+]; $[\alpha]^{20}_D$ -39 (c = 0.5, $CHCl_3$), 94% ee.

(3*R*,4*R*,5*S*)-2-Benzyl 4-methyl 3-cyclopentyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-2,4-dicarboxylate (5d).

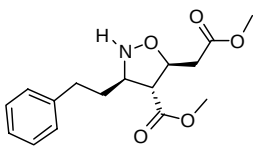


Following the general procedure, compound **5d** was obtained as a colourless oil in 68% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 12.7 min; τ_{min} = 18.2 min); ^{1}H NMR (400 MHz) δ 7.40-7.29 (m, 5H), 5.25 (d, J = 12.7 Hz, 1H), 5.18 (d, J = 12.7 Hz, 1H), 4.50 (dt, J_d = 7.9 Hz, J_t = 6.8 Hz, 1H), 4.36 (dd, J_1 = 9.1 Hz, J_2 = 4.0 Hz, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.01 (dd, J_1 = 8.9 Hz, J_2 = 4.0 Hz, 1H), 2.87 (dd, J_1 = 16.4 Hz, J_2 = 6.3 Hz, 1H), 2.73 (dd, J_1 = 16.1 Hz, J_2 = 6.8 Hz, 1H), 2.11 (sext, J = 7.5 Hz, 1H), 1.79-1.19 (m, 8H);^{13}C NMR δ 171.9, 169.9, 159.1, 136.0, 128.7, 128.4, 128.2, 81.0, 69.4, 68.5, 57.7, 52.7, 52.2, 45.0, 37.0, 29.8, 29.2, 25.5, 25.3; ESIMS m/z 428 [M + Na^+]; $[\alpha]^{20}_D$ -34 (c = 0.5, $CHCl_3$), 85% ee.

Product elaborations.

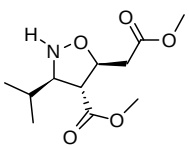
Deprotection of the product.

(3*R*,4*R*,5*S*)-Methyl 5-(2-methoxy-2-oxoethyl)-3-phenethylisoxazolidine-4-dicarboxylate (7a).



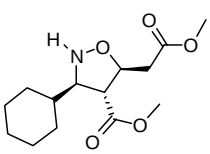
In a test tube were added the cycloadduct **4a** (0.30 mmol, 122 mg), 1.5 mL CH_2Cl_2, was cooled to 0°C and TFA (0.6 ml 7.8 mmol) was added. The mixture was allowed to wart to room temperature and stirred for 4 h then was quenched with 2 mL Na_2CO_3 10% w/w, extracted with AcOEt (3x2 mL), the combined organic phases were dried on $MgSO_4$, filtered and evaporated in vacuo. The product was obtained as a colorless oil after column cromatography on silica gel (*n*-hexane/ AcOEt mixture) in 85% yield. No epimerization of the chiral centers was observed by ^{1}H NMR analysis of the crude product;^{1}H NMR (400 MHz) δ 7.30-7.25 (m, 2H), 7.20-7.16 (m, 3H), 4.44 (q, J = 6.4 Hz, 1H), 3.98 (bs, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.61-3.55 (m, 1H), 2.87-2.65 (m, 5H), 1.99-1.78 (m, 2H); ^{13}C NMR δ 173.2, 170.7, 141.4, 115.9, 128.7, 126.2, 82.5, 65.5, 59.3, 52.6, 52.2, 38.2, 36.2, 33.2; ESIMS m/z 330 [M + Na^+]; $[\alpha]^{20}_D$ +34 (c = 0.5, $CHCl_3$), 91% ee (determined on the Cbz derivative).

(3*R*,4*R*,5*S*)-Methyl 3-*iso*-propyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-4-carboxylate (7f).



Following the above procedure the cycloadduct **7f** could be obtained in 77% yield. No epimerization of the chiral centers was observed by ^{1}H NMR analysis of the crude product; ^{1}H NMR (600 MHz) δ 5.67 (bs, 1H), 4.39 (q, J = 6.7 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.30 (dd, J_1 = 8.4 Hz, J_2 = 4.0 Hz, 1H), 2.90 (dd, J_1 = 7.0 Hz, J_2 = 5.0 Hz, 1H), 2.78 (dd, J_1 = 16.8 Hz, J_2 = 6.4 Hz, 1H), 2.70 (dd, J_1 = 18.8 Hz, J_2 = 6.4 Hz, 1H), 1.73 (oct, J = 6.6 Hz, 1H), 0.98 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 173.6, 83.2, 72.2, 57.2, 52.6, 37.8, 29.9, 19.9, 19.5; ESIMS m/z 268 [M + Na^+]; $[\alpha]^{20}_D$ +12 (c = 0.5, $CHCl_3$), 99% ee (determined on the Cbz derivative).

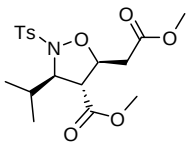
(3*R*,4*R*,5*S*)-Methyl 3-cyclohexyl-5-(2-methoxy-2-oxoethyl)isoxazolidine-4-dicarboxylate (7i).



Following the above procedure the cycloadduct **7i** could be obtained in 70% yield. No epimerization of the chiral centers was observed by ^{1}H NMR analysis of the crude product; ^{1}H NMR (600 MHz) δ 4.38 (q, J = 5.6 Hz, 1H), 3.71 (s, 3H), 3.67 (s,

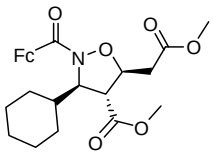
3H), 3.32 (dd, J_1 = 8.4 Hz, J_2 = 5.1 Hz, 1H), 2.90 (dd, J_1 = 7.2 Hz, J_2 = 5.0 Hz, 1H), 2.77 (dd, J_1 = 16.2 Hz, J_2 = 6.3 Hz, 1H), 2.68 (dd, J_1 = 16.2 Hz, J_2 = 6.3 Hz, 1H), 1.92 (bd, J = 12.8 Hz, 1H) 1.75-1.61 (m, 4H), 1.41-1.34 (m, 1H), 1.25-1.09 (m, 4H), 1.00-0.92 (m, 2H); ^{13}C NMR δ 173.5, 170.7, 82.9, 71.2, 57.0, 52.6, 52.1, 41.6, 37.9, 30.3, 30.0, 26.5, 26.2, 26.0; ESIMS m/z 308 [M + Na^+]; $[\alpha]^{20}_D$ +28 (c = 0.5, $CHCl_3$), 99% ee (determined on the Cbz derivative).

(3*R*,4*R*,5*S*)-Methyl 3-*iso*-propyl-5-(2-methoxy-2-oxoethyl)-2-tosylisoxazolidine-4-carboxylate (8).



To a solution of cycloadduct **7f** (0.10 mmol) in EtOAc (2 mL), Na_2CO_3 10% w/w (2 mL) was added, followed by TsCl (0.266g, 14 equiv.). The reaction was vigorously stirred at room temperature overnight. The phases were separated, the aqueous layer extracted with AcOEt (3x2 mL), and the combined organic phases filtered on a plug of silica. The pure *N*-Ts product **8** was obtained after chromatography on silica gel (*n*-hexane/AcOEt 90:10 then 80:20) as a pale yellow oil in 70% yeld. No epimerization of the chiral centers was observed by ^{1}H NMR analysis of the crude product; ^{1}H NMR (600 MHz) δ 7.85 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 4.86-4.82 (m, 1H), 4.45 (t, J = 6.5 Hz, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 3.04 (dd, J_1 = 9.1 Hz, J_2 = 5.6 Hz, 1H), 2.72 (dd, J_1 = 15.8 Hz, J_2 = 4.4 Hz, 1H), 2.59 (dd, J_1 = 16.1 Hz, J_2 = 7.9 Hz, 1H), 2.42 (s, 3H), 1.92 (oct, J = 6.4, 1H), 1.00 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 170.2, 169.8, 145.2, 133.4, 129.8, 129.6, 80.2, 67.8, 55.4, 52.9, 52.1, 37.3, 33.4, 21.9, 19.0, 18.8; ESIMS m/z 422 [M + Na^+]; $[\alpha]^{20}_D$ -135 (c = 0.5, $CHCl_3$).

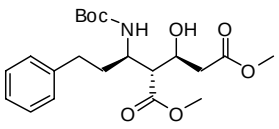
(3*R*,4*R*,5*S*)-Methyl 3-*iso*-propyl-5-(2-methoxy-2-oxoethyl)-2-ferrocenoylisoxazolidine-4-carboxylate (9).



To a solution of cycloadduct **7i** (1.0 mmol) in EtOAc (20 mL), Na_2CO_3 10% w/w (20 mL) was added, followed by FcCOCl (992 mg, 4.0 equiv.). The reaction was vigorously stirred at room temperature overnight. The phases were separated, the aqueous layer extracted with AcOEt (3x10 mL), and the combined organic phases filtered on a plug of silica. Pure product **9** was obtained in 69% yield after chromatography on silica gel (CH_2Cl_2/Et_2O 95:5) as a red solid; ^{1}H NMR (400 MHz) δ 5.01 (bd, J = 7.4 Hz, 2H), 4.70 (dd, J_1 = 7.7 Hz, J_2 = 5.6 Hz, 1H), 4.62-4.55 (m, 1H), 4.38 (bd, J = 11.4 Hz, 2H), 4.21 (s, 5H), 3.75 (s, 3H), 3.73 (s, 3H), 3.04 (dd, J_1 = 8.6 Hz, J_2 = 4.9 Hz, 1H), 2.89-2.77 (m, 2H), 1.84-1.72 (m, 4H), 1.69-1.53 (m, 2H), 1.31-1.02 (m, 5H); ^{13}C NMR δ 173.4, 171.5, 169.9, 81.2, 72.5, 71.6, 71.4, 71.3, 71.2, 70.1, 66.4, 55.5, 52.8, 52.3, 42.7, 37.5, 29.6, 29.5, 26.5, 26.1, 26.0; ESIMS m/z 520 [M + Na^+]; $[\alpha]^{20}_D$ -78 (c = 0.5, $CHCl_3$).

Reductive cleavage of the N-O bond with $Mo(CO)_6$.

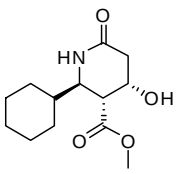
(2*R*,3*S*)-Dimethyl 2-((*R*)-1-(*tert*-butoxycarbonyl-3-phenylpropyl)-3-hydroxypentanedioate (10).



To a solution of the cycloadduct **4a** (0.10 mmol) in CH_3CN/H_2O (1.0 mL, 10:1, degassed under argon) $Mo(CO)_6$ (0.12 mmol) was added at 0 °C. The reaction was allowed to warm to room temperature under argon and then heated at reflux for 24 h. The crude reaction mixture was filtered through a short column of silica gel (AcOEt). The pure product was obtained after column cromatography on silica gel (mixture of *n*-hexane/ AcOEt) as a colorless oil in 75% yield. No epimerization of the chiral centers was observed by ^{1}H NMR analysis of the crude product. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 28.9 min, τ_{min} = 16.6 min); ^{1}H NMR (400 MHz) δ 7.30-7.25 (m, 2H), 7.20-7.15 (m, 3H), 4.75 (bd, J = 11.1 Hz, 1H), 4.37 (bt, J = 7.1 Hz, 1H), 4.18-4.09 (m, 1H), 3.69 (s, 6H), 3.36 (bs, 1H), 2.80-2.58 (m, 4H), 2.51 (dd, J_1 = 16.7 Hz, J_2 = 9.4 Hz, 1H), 1.98-1.89 (m, 1H), 1.72-1.60 (m, 1H), 1.45 (s, 9H); ^{13}C NMR δ 173.5, 172.6, 155.7, 141.7, 128.6, 126.2, 79.8, 66.9, 55.2, 52.2, 52.1, 49.7, 38.9, 35.4, 32.8, 28.5; ESIMS m/z 432 [M + Na^+]; $[\alpha]^{20}_D$ +6 (c = 0.5, $CHCl_3$), 90% ee.

Cleavage of the N-O bond and deprotection.[4]

(2*R*,3*R*,4*S*)-Methyl 2-cyclohexyl-4-hydroxy-6-oxopiperidine-3-carboxylate (11).



The cycloadduct **5c** (0.06 mmol) was dissolved in MeOH (3 mL) and hydrogenated (H_2 1 atm, balloon) in the presence of 10% w/w Pd/C (6 mg) at room temperature for 3 h. The catalyst was filtered off on a celite pad, the solvent evaporated and the pure product **11** was obtained as a colorless oil in 75% yield after cromatography on silica gel (*n*-hexane/AcOEt). The product observed derives from an intramolecular cyclization with the formation of the relative δ-lactam. No epimerization of the chiral centers was observed by ^{1}H NMR analysis of the crude product. The ee of the product was determined by HPLC using a Daicel Chiralpak OJH column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 7.6 min, τ_{min} = 9.1 min); ^{1}H NMR (CD_3OD, 600 MHz) δ 4.41-4.38 (m, 1H), 3.84-3.81 (m, 1H), 3.72 (s, 3H), 2.83 (bd, J = 9.5 Hz, 1H), 2.54 (d, J = 17.9 Hz, 1H), 2.39 (d, J = 18.0 Hz, 1H), 1.81-1.75 (m, 2H), 1.67-1.59 (m, 3H), 1.49-1.43 (m, 1H), 1.30-1.12 (m, 4H), 0.97 (dq, J_q = 12.3 Hz, J_d = 3.3 Hz, 1H); ^{13}C NMR δ 172.3, 171.9, 65.4, 54.4, 51.4, 45.5, 42.0, 39.4, 29.2, 26.7, 26.4, 26.2, 26.1; ESIMS m/z 278 [M + Na^+]; $[\alpha]^{20}_D$ +16 (c = 0.5, $CHCl_3$), 99% ee.

[4] Palmisano, G.; Danieli, B.; Lesma, G.; Trupiano, F.; Pilati, T. *J. Org. Chem.* **1988**, *53*, 1056.

Assignment of the relative and absolute configuration of compounds 4.

Compounds **4c** and **4f** were selected in order to determine the relative and absolute configuration. Full assignment of ^{1}H and ^{13}C NMR signals was obtained by HSQC and HMBC bi-dimensional sequences. For both molecules, NOE spectra were acquired in order to establish the relative stereochemistry. In particular, in the case of compound **4c**, saturation of the H-5 line showed similar NOE effects on the H-4 and H-3 lines, and saturation of the H-4 line showed similar effects on H-5 and H-3. These NOE constraints imply that H-5 and H-3 are at the same distance with respect to H-4, and that H-3 and H-4 are at the same distance from H-5 (Figure S1). The relative stereochemistry is therefore trans-trans (i.e. 3*R**,4*R**,5*S**), and the DFT calculated structure matches very well the experimental NOE ratios.

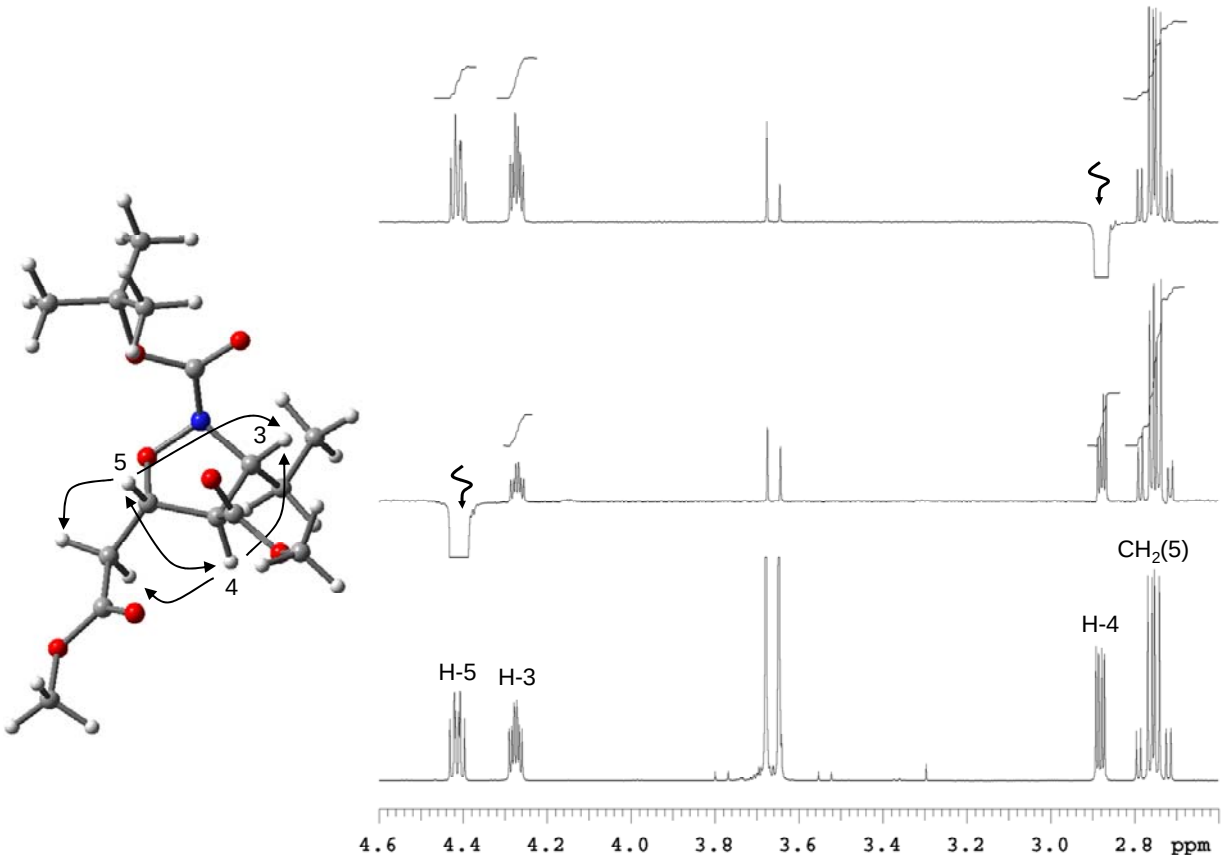


Figure S1: DPFGSE-NOE spectra obtained for **4c**. bottom trace: control spectrum, middle trace: NOE spectrum obtained on saturation of H-5; top trace: NOE spectrum obtained on saturation of H-4. Observed NOE are indicated as arrows in the DFT optimized structure.

Conformational analysis and absolute configuration determination

All compounds **4** and **5** are viscous oils, therefore the use of the Bijovet method, based on anomalous X-ray dispersion to unambiguously assign the absolute configuration (AC) is precluded. Recently, the determination of the absolute configurations (ACs) of chiral molecules using the chiroptical techniques of optical rotation (OR), electronic circular dichroism (ECD), and vibrational circular dichroism (VCD) has been revolutionized by the development of Time-Dependent Density Functional Theory (TD-DFT) methods for the prediction of these properties. In the present case, theoretical calculation of ECD spectra and optical rotations was carried out by means of the TD-DFT method, since this technique has been successfully employed several times to predict ECD spectra and to assign the AC of organic molecules.[5] It is worth to note that the relative stereochemistry has been already fixed by the NOE analysis, therefore only the conformation of the molecule can modify the shape of the ECD spectrum.

A preliminary conformational search, starting from the relative configuration derived from NOE spectra of **4c** has been carried out using Monte Carlo searching together with the MMFF94 molecular mechanics force field (as implemented in Titan 1.0.5). frequencies of each conformation were calculated at the same level to confirm their stability (no imaginary frequencies observed), and to evaluate the free energy of each conformation. After DFT minimization, the MMFF structures fall into four stable conformations; in all the optimized structures, the dihedral angle O1-N2-C=O is close to 0° (about -12°).

It seemed strange to us that conformations with the same dihedral close to 180° were not identified by MM search. Therefore, four more conformations were built by 180° rotation of the BOC group around the O1-N2-C=O dihedral. When subjected to DFT minimization, four new energy minima were located, with very similar energies to the first four conformations. In summary, 8 stable conformations, named **a-h** were located by DFT calculation, and six of them are enclosed in a 1 kcal/mol range. (see Table S1). The same theoretical approach was used for **4f**, in which the ethyl group in position 3 is All

[5] For recent examples of this method to assign the absolute configurations of organic molecules, see: (a) Diedrich, C.; Grimme, S. *J. Phys. Chem. A* **2003**, *107*, 2524. (b) Casarini, D.; Lunazzi, L.; Mancinelli, M.; Mazzanti, A.; Rosini, C. *J. Org. Chem.* **2007**, *72*, 7667. (c) Goel, A.; Singh, F. V.; Kumar, V.; Reichert, M.; Goulder, T. A. M.; Bringmann, G. *J. Org. Chem.* **2007**, *72*, 7765. (d) Stephens, P. J.; Pan, J. J.; Devlin, F. J.; Cheeseman, J. R. *J. Nat. Prod.* **2008**, *71*, 285. (e) Penon, O.; Carlone, A.; Mazzanti, A.; Locatelli, M.; Sambri, L; Bartoli, G.; Melchiorre, P. *Chem. Eur. J.* **2008**, *14*, 4788. (f) Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2008**, *47*, 8703. (g) Shaikh, R.R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2008**, *47*, 8707. For a review: (h) Berova, N.; Di Bari, L.; Pescitelli, G. *Chem. Soc. Rev.* **2007**, *36*, 914.

conformations within a 3 kcal/mol window were then optimized using DFT at the B3LYP/6-31G(d) level,[6] and the harmonic vibrational replaced by a bulkier isopropyl group, with results similar to that obtained for **4c**. Results of the conformational analysis and calculated ECD spectra are shown in Table S1 and Figure S2.

Table S1: Calculated relative energies (ΔE) and free energies (ΔG) of the conformations of **4c** (in kcal/mol, B3LYP/6-31G(d) level). Populations percentages (P) are calculated assuming Boltzmann statistics at T=25°C.

Molecule	Conf	ΔE	ΔG	Pop (ΔG)
4c	**a**	0.00	0.11	34
	b	0.14	0.00	41
	c	0.53	0.87	9
	d	0.80	1.05	7
	e	0.91	0.94	8
	f	0.96	0.52	17
	g	1.20	1.57	-
	h	2.32	2.77	-
4f	**a**	0.00	0.00	43
	b	0.45	0.13	35
	c	0.88	0.96	8
	d	0.98	0.69	14
	e	1.12	1.45	-
	f	1.32	1.23	-
	g	1.50	1.42	-
	h	2.34	2.18	-

[6] Program Gaussian 03, Revision E.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

Unfortunately, these results confirm that compound **4c** (and **4f** as well) are very flexible molecules. The only active chromophores are the carbonyl groups, therefore the ECD spectra are compressed in a very small interval and, more important, the relative disposition of the carbonyl groups greatly affect the shape of the calculated spectrum. Being six conformations enclosed in a small energy range, any error in the evaluation of the relative energies causes relevant modifications in the shape of the resulting weighted ECD spectrum, up to the point of reversing its shape.

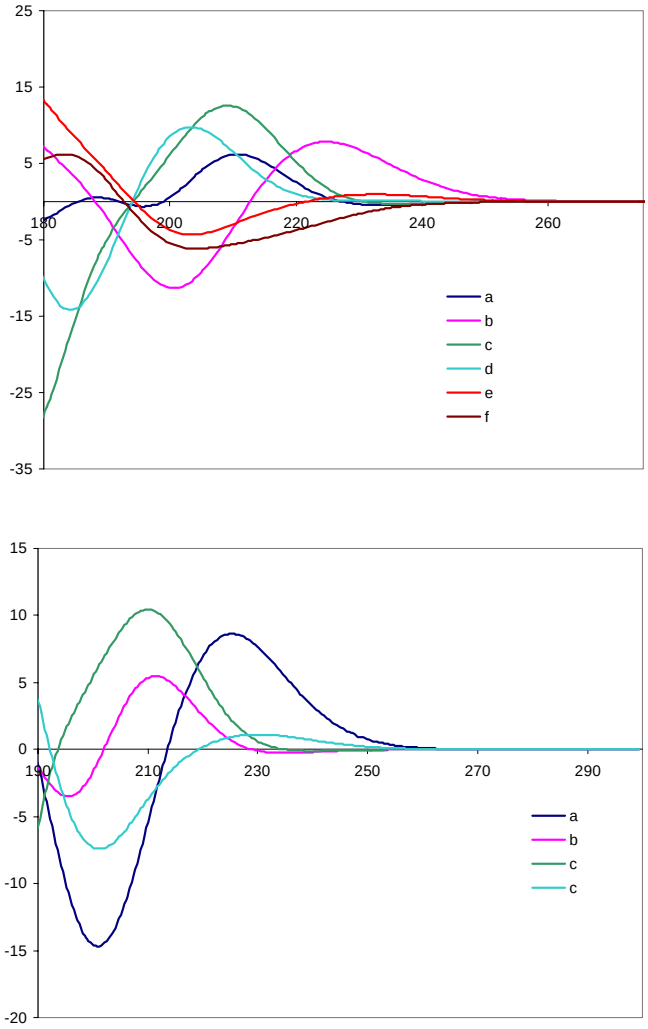


Figure S2. Calculated ECD spectra (B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level) for the first six conformations of **4c** (top) and for the first four conformation of **4f** (bottom)

In the present cases, therefore, an assignment based on the ECD spectrum is not appropriate, due to the extreme uncertainty of the results. Also theoretical calculation of the optical rotation $[\alpha]_D$ is not an option, since the experimental values are too small to be reliably reproduced by calculations (-43° and

-37° for **4c** and **4f**, respectively).[7]

In order to reduce the conformational flexibility of the molecule, the same chiroptical approach was applied to **7f**, in which the Boc group was removed. For this molecule, MMFF conformational search followed by DFT optimization finds only three energy minima (**a**-**c**) within a 1.5 kcal/mol window (Table S2). The two more stable conformations (separated by 0.2 kcal/mol) agree well with NOE data about the conformation of the CH_2COOMe and isopropyl group.

Table S2: Calculated relative energies (ΔE) and free energies (ΔG) of the conformations of 7f (in kcal/mol, B3LYP/6-31G(d) level). Populations percentages (P) are calculated assuming Boltzmann statistics at T=25°C.

Molecule	Conf.	ΔE	P(%)	ΔG	P(%)
7f	**a**	0.00	70	0.00	56
	b	0.89	16	0.20	40
	c	0.91	14	1.52	4

Electronic excitation energies and rotational strengths have been calculated for the three conformation of **7f** using TD-DFT at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) and supposing 3*R*,4*R*,5*S* AC, with the results given in Figure S3. Rotational strength were calculated in both length and velocity representation. Since the resulting values are very similar, errors due to basis set incompleteness are very small, or negligible. The final simulated ECD spectra was obtained taking into account the 56:40:4 population ratios determined assuming Boltzmann statistics from the calculated free energies at the B3LYP/6-31G(d) level (left in Figure S3), or by taking into account the 70:16:14 population ratios determined from the calculated total energies (without any thermochemical correction) at the same level of theory. It is quite interesting to note that in the latter case, the agreement with the experimental spectrum is much better than in the former. The agreement between calculated and experimental spectra is whatever fairly good, over the relatively limited spectral range of the experimental CD spectrum.

The CD simulation thus supports the conclusion that the AC of **7f** is 3*R*, 4*R*, 5*S*. As correctly suggested

[7] (a) Stephens, P. J.; McCann, D. M.; Devlin, F. J., Smith III, A. B. *J. Nat. Prod.* **2006**, *69*, 1055; (b) Stephens, P. J; McCann, D. M.; Cheeseman, J. R.; Frisch, M. J. *Chirality* **2005**, *17*, S52.

by some authors,[8] use of more than one chirooptic method is always desirable; in the present compound, however, calculation of the $[\alpha]_D$ is not feasible, due to the very small experimental value (+16°).

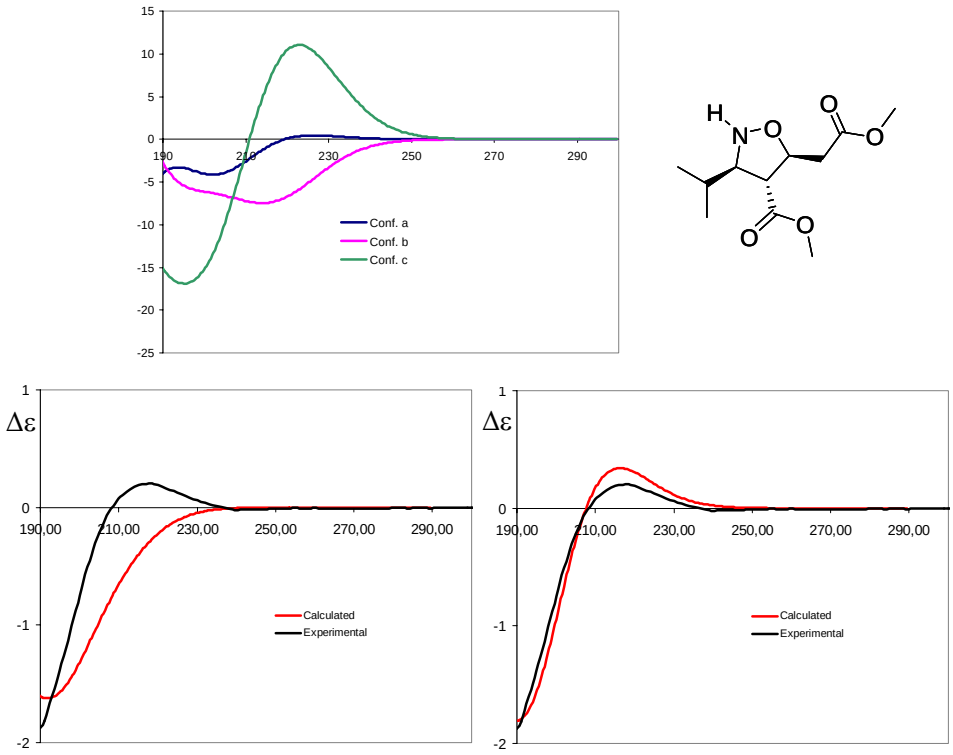


Figure S3: Top: calculated ECD spectra for the three most stable conformation of **7f**. Bottom left: experimental (black) and calculated ECD spectra (red) based on calculated free energies (ΔG). Bottom right: experimental (black) and calculated ECD spectra (red), based on total energies (ΔE). Molecular CD (Δε) are expressed in L $mol^{-1}cm^{-1}$.

In order to enhance reliability of our AC analysis, we envisaged that derivatization of **7f** with a chromophore group, like tosylate, could confirm the assignment in three ways: a more intense ECD spectrum, a larger $[\alpha]_D$, and possibly the use of anomalous dispersion X-ray diffraction. Unfortunately, the tosylate **8** did not yield crystals at all (it is still an oil), but its $[\alpha]_D$ grows to -135°, thus a coupled theoretical approach, i.e. calculation of ECD spectrum and $[\alpha]_D$, can be applied. Also in this case, NOE NMR spectra greatly helped in determining the conformation of the exocylic moieties (see Figure S4). In particular, the two diastereotopic hydrogens of the CH_2COOMe are well separated (2.55 and 2.78

[8] (a) Polavarapu, P. L. *Chirality*, **2008**, *20*, 664; (b) Stephens, P. J.; Pan, J. J.; Devlin, F. J.; Krohn, K.; Kurtn, T. *J. Org. Chem* **2007**, *72*, 3521.

ppm), and show very different vicinal J-coupling with H-5 (8.3 and 4.0 Hz, respectively). These values indicate that one hydrogen is anti to H-5, and the other is gauche. On saturation of the H-5 signal, the NOE effect on the low field gauche hydrogen (J = 4.0 Hz) is larger than that on the high field anti hydrogen (J = 8.3 Hz), as expected for the gauche/anti disposition. Saturation of the H-4 signal (top trace), shows large NOEs for the diastereotopic hydrogens, showing that they are *both* near to H-4. The latter observation implies that the COOMe group places itself in position gauche to the cyclic oxygen, otherwise only a very small NOE should be observed on the gauche hydrogen on saturation of H-4.

The conformation of the isopropyl group can be deduced from the saturation of the H-4 signal. A very strong NOE is observed on the CH when H-4 is saturated, hence the isopropilyc CH is anti to the cyclic nitrogen, and near to H-4.

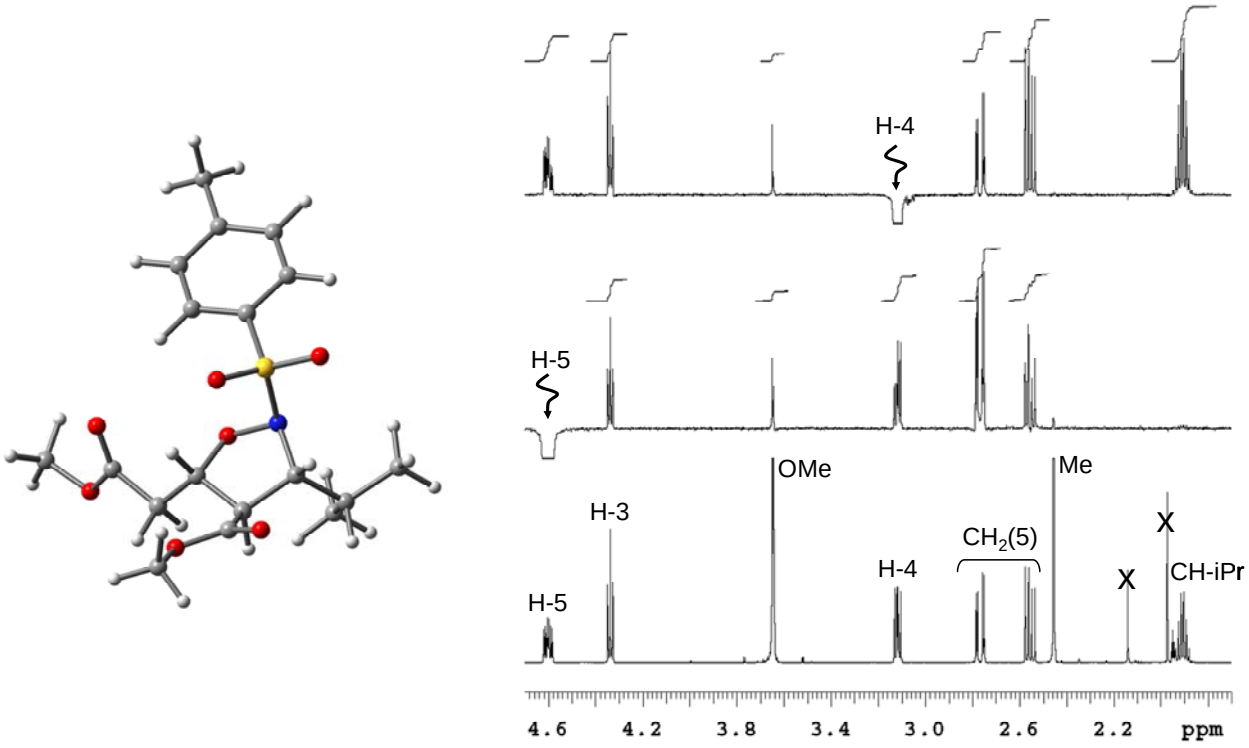


Figure S4: DPFGSE-NOE spectra obtained for **8**. Bottom trance: control spectrum. Middle trace: NOE spectrum obtained on saturation of H-5. Top trace: NOE spectrum obtained on saturation of H-4. Also the best structure obtained by DFT optimization is shown.

Conformational search was performed by MM methods starting from the NOE-constrained structure, and the best minimum is shown in Figure S4. It is worth to note that this structure, when optimized at the B3LYP/6-31G(d) level, is calculated to be very close in energy (+0.12 kcal/mol) to the global minimum calculated by the unrestricted MMFF conformational search followed by DFT optimization.

The latter structure, however, is not compatible with the NOE constrains because of the conformation of the CH_2COOMe group, in which the COOMe is placed in an anti relationship with H-5, and both the diastereotopic protons occupy the gauche positions. Here probably the solvent plays an important role on the conformational preferences of the exocylic groups (NOE and ECD were recorded both in acetonitrile, calculations were performed without solvents effect). It is also well known that DFT calculations occasionally fail in the determination of the relative energies of isomers[9] and conformations.[10]

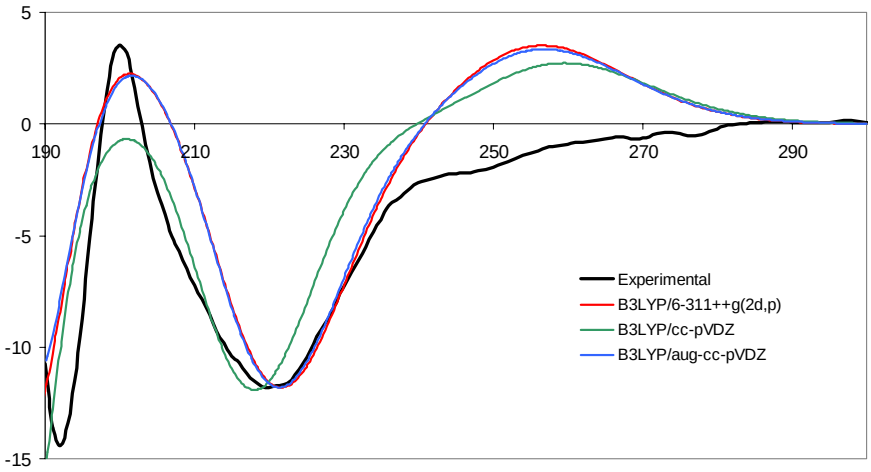


Figure S5: Top: experimental (Black line) and calculated ECD spectra for the most stable conformation of **8**, derived from NOE constrains coupled with MMFF conformational search.

Calculation of ECD was performed at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d), B3LYP/cc-pVDZ//B3LYP/6-31G(d), and B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d) levels on the NOE-derived structure, showing results in good agreement with the experimental spectrum (Figure S5). Rotational

[9] (a) Check, C. E.; Gilbert, T. M. *J. Org. Chem*. **2005**, *70*, 9828; (b) Wodrich, M. D.; Corminbouef, C.; Schleyer, P. v. R. *Org. Lett*. **2006**, *8*, 3631. (c) Shreiner, P. R.; Fokin, A. A.; Pascal, J. R. A.; De Mejere, A. *Org. Lett.* **2006**, *8*, 3635. (d) Grimme, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 4460. (e) Zhao, Y.; Truhlar, D. G. *Org. Lett*. **2006**, *8*, 5753. (f) Shreiner, P. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 4217. (g) Wodrich, M. D.; Wannere, C. S.; Mo, Y.; Jarowski, P. D.; Houk, K. N.; Schleyer, P. v. R. *Chem. Eur. J.* **2007**, *13*, 7731. (h) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157. (i) Schwabe, T.; Grimme, S. *Acc. Chem. Res.* **2008**, *41*, 569. (j) Wodrich, M. D.; Jana, D. F.; Schleyer, P. v. R.; Corminbouef, C. *J. Phys. Chem. A*, **2008**, *112*, 11495.

[10] Casarini, D.; Lunazzi, L.; Mazzanti, A. *Org. Biomol. Chem*. **2009**, *8*, 1619.

strengths were calculated in both length and velocity representation. Since the resulting values are very similar in all the three cases, errors due to basis set incompleteness are very small, or negligible.

In the case of **8**, the experimental $[\alpha]_D$ (-135°) is out of the "uncertainty zone"[3b], and calculation of the optical rotation is feasible. Calculations using rotational lengths[11] at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d) level yields -134°, in very good agreement with the -135° experimental value, (-113° for B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d) and -236° for B3LYP/cc-pVDZ//B3LYP/6-31G(d), respectively).

Table S3: Calculated relative energies (ΔE) and free energies (ΔG) of the conformations of 8 (in kcal/mol, B3LYP/6-31G(d) level). Populations percentages (P) are calculated assuming Boltzmann statistics at T=25°C.

Molecule	Conf.	ΔE	P(%)	ΔG	P(%)
8	**a**	0.00	38	0.00	41
	b	0.65	13	0.71	12
	c	1.97	1	0.96	8
	d	0.48	17	1.26	5
	e(NOE)	0.30	31	0.12	34

Using the results from the unrestricted MMFF conformational search, five conformations are enclosed in a 1 kcal/mol windows, one of which is that obtained by NOE constraints (Table S3).

Electronic excitation energies and rotational strengths have been calculated for these conformation at the B3LYP/6-311++G(2d,p)//B3LYP/6-31G(d), with the results given in Figure S6. Except for conformation **a**, all the others have similar shape, with some differences in the intensity of the CD bands. The final simulated ECD spectra was obtained taking into account the 41:12:8:5:34 population ratios determined assuming Boltzmann statistics from the calculated free energies at the B3LYP/6-31G(d) level. The final agreement is still in good agreement with the experimental spectrum.

All these data agree with the 3*R*,4*R*,5*S* absolute configuration of **8**, and reliably confirm the AC already deduced for its precursor **7f**.

[11] (a) Stephens, P. J.; McCann, D. M. *J. Org. Chem.* **2006**, *71*, 6074. (b) Stephens, P. J. McCann, D. M.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 7514.

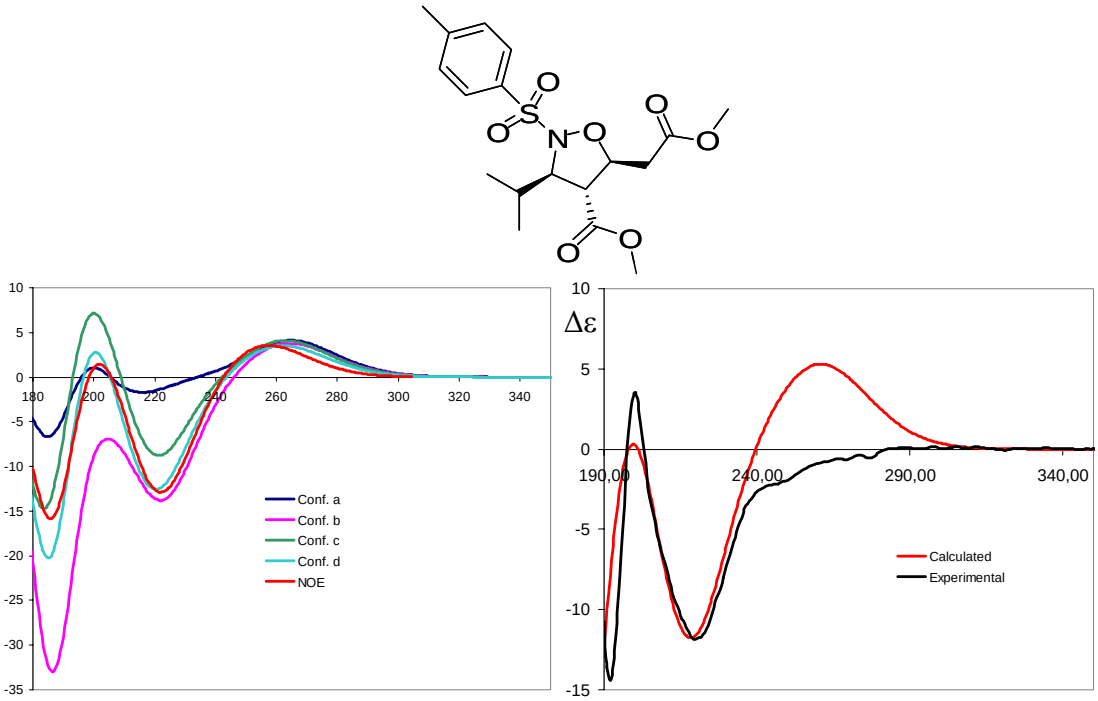


Figure S6: Left: calculated ECD spectra for the five most stable conformation of **8**.
Right: experimental (black) and calculated ECD spectra (red) based on calculated free energies. Molecular CD (Δε) are expressed in L $mol^{-1}cm^{-1}$.

Finally, to overcome the residual ambiguity of the absolute configuration determination based on chiroptical methods[12], and to further confirm the reliability of the method, some compounds were deprotected from Boc and reacted with ferrocenoyl chloride[13] in order to have solid compounds containing the heavy atom required for the X-ray analysis. Only in the case of **9**, obtained from compound **4i** *via* **7i**, some good crystals were serendipitously obtained by slow evaporation of a wet hexane/Et_2O solution.

The absolute configuration deduced from X-ray diffraction confirms the assignment made by the TD-DFT approach (3*R*,4*R*,5*S*). The unit cell contains molecules bonded together by an hydrogen bond with a molecule of co-crystallized water.

[12] This update was explicitly requested by two reviewers.

[13] Aguilar-Aguilar, A.; Allen, A.D.; Peña Cabrera, E.; Fedorov, A. Fu, N.; Henry-Riyad, H. Leuninger, J. Schmid, U.; Tidwell,T. T.; Verma, R. *J. Org. Chem.* **2005**, *70*, 9556.

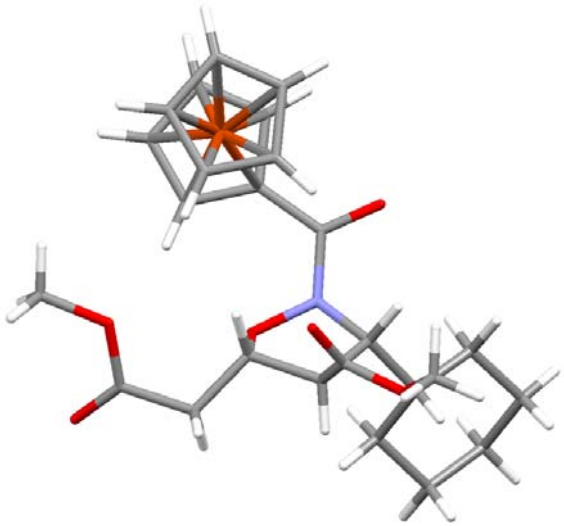
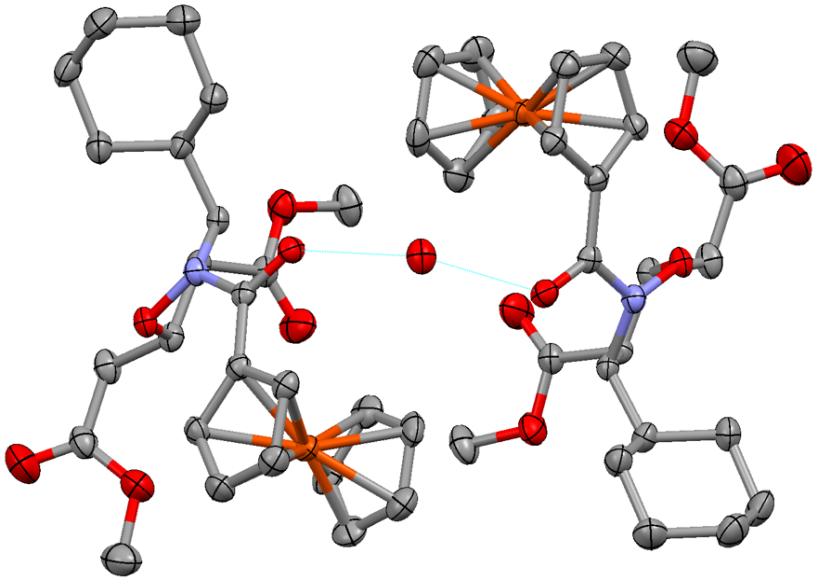


Figure S7: X-ray structure of compound **9**.

Crystal data for compound 9

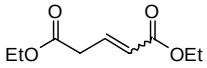


Crystals were obtained from a wet hexane/Et_2O mixture by slow evaporation. Molecular formula: $2(C_{25}H_{11}FeNO_6)\cdot H_2O$, M_r = 1012.73, Orthorhombic, space group $C222_1$ (No. 20), a = 14.0007(16), b = 15.3289(16), c = 45.317(5), V = 9725.8(18) Å^3, T = 298(2) K, Z = 8, ρ_c = 1.383 g cm^{-3}, $F(000)$ = 4272, graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), $\mu(Mo_{K\alpha})$ = 0.663 mm^{-1}, orange brick (0.4 × 0.3 × 0.3 mm^3), empirical absorption correction with SADABS (transmission factors: 0.8260 – 0.7775), 2400 frames, exposure time 15 s, 1.80 ≤ θ ≤ 27.50, –18≤ h ≤ 17, –19 ≤ k ≤ 19, –58 ≤ l ≤ 58, 54768 reflections collected, 11160 independent reflections (R_{int} = 0.0339), solution by direct methods (SHELXS97) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELX97), hydrogen atoms refined with a riding model, data / restraints / parameters = 11160/ 251 / 704, $S(F^2)$ = 1.069, $R(F)$ = 0.0663 and $wR(F^2)$ = 0.1414 on all data, $R(F)$ = 0.0538 and $wR(F^2)$ = 0.1337 for 9352 reflections with $F_0 > 4\sigma(F_0)$, weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0634P)^2 + 12.306P]$ where $P = (F_o^2 + 2F_c^2)/3$, largest difference peak and hole 0.412 and –0.404 e Å^{-3}. Flack parameter:[14] 0.047(17). The asymmetric unit contains two independent molecules and a molecule of water. Disorder was observed and modelled on the cyclohexane ring of one molecule, and on one COOMe moiety of the same molecule. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-

[14] Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876-881.

735613. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Copies of the ^{1}H NMR and ^{13}C NMR spectra



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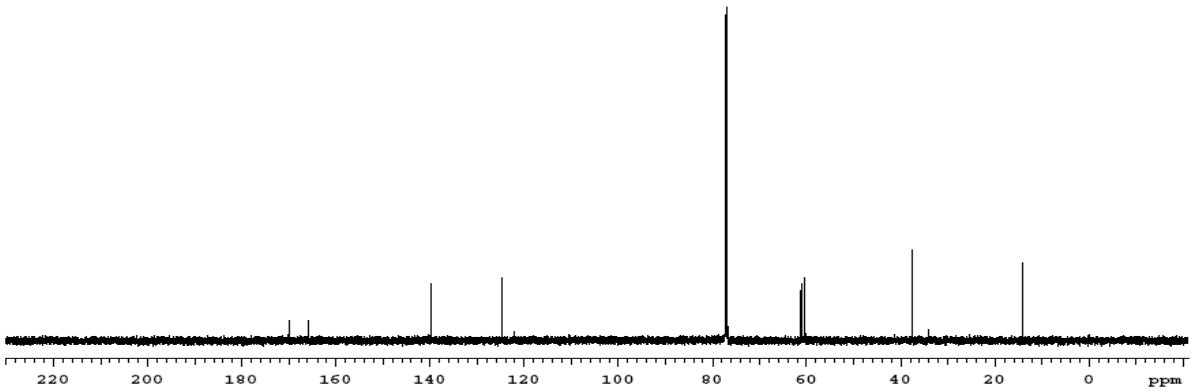

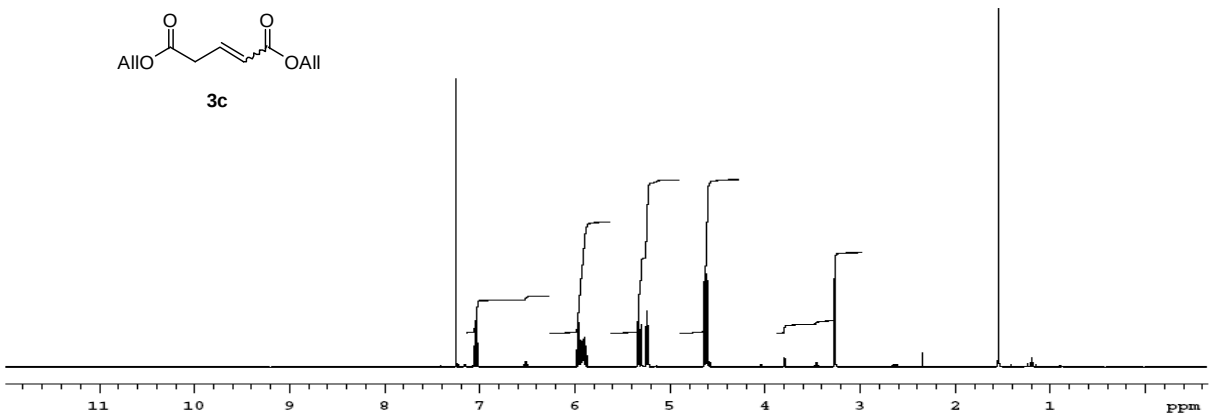
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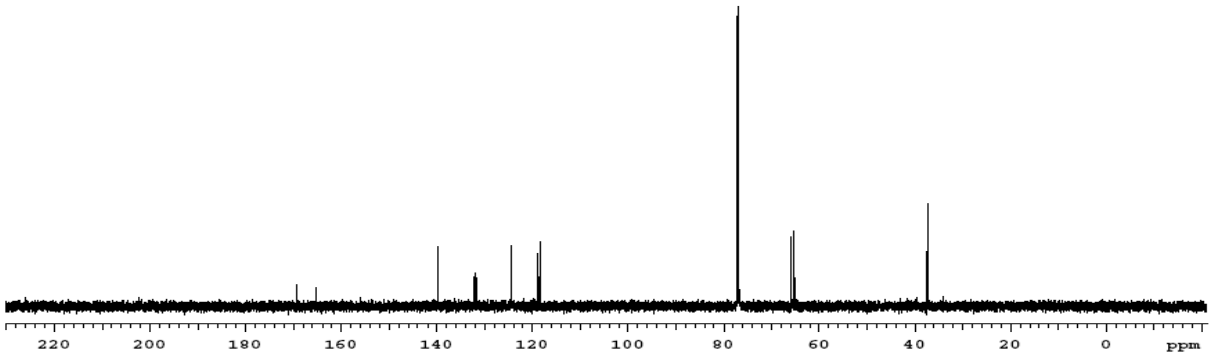
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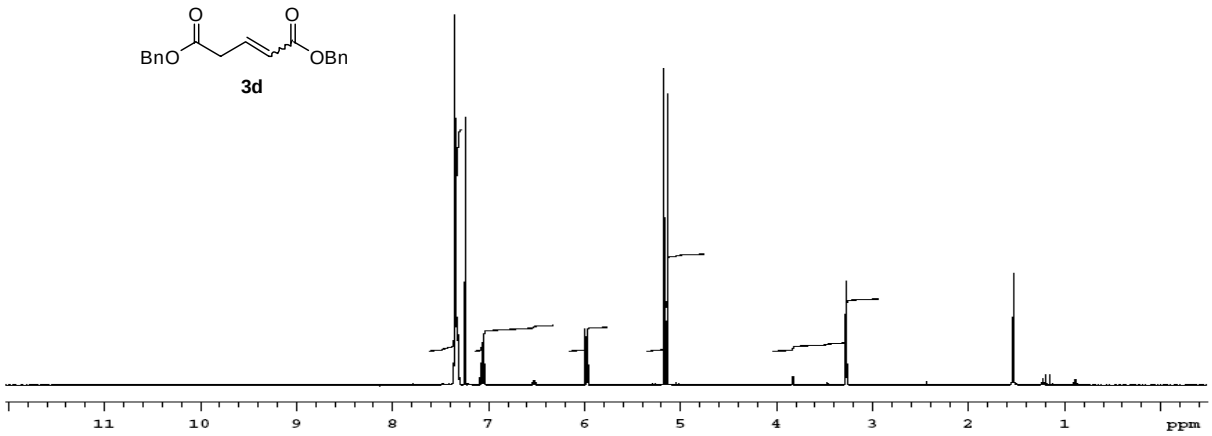
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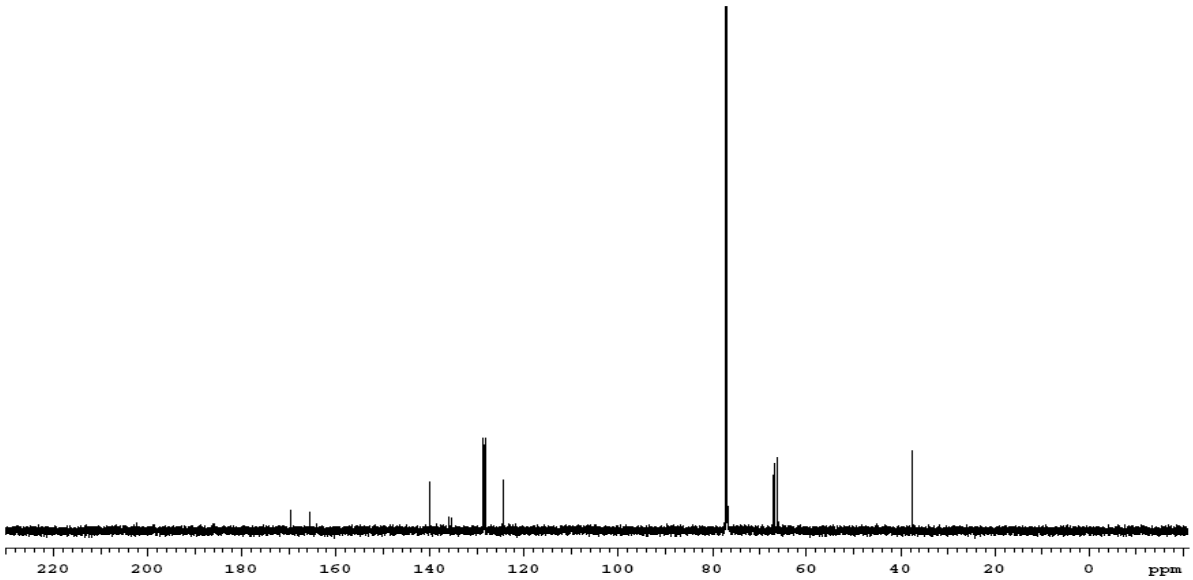
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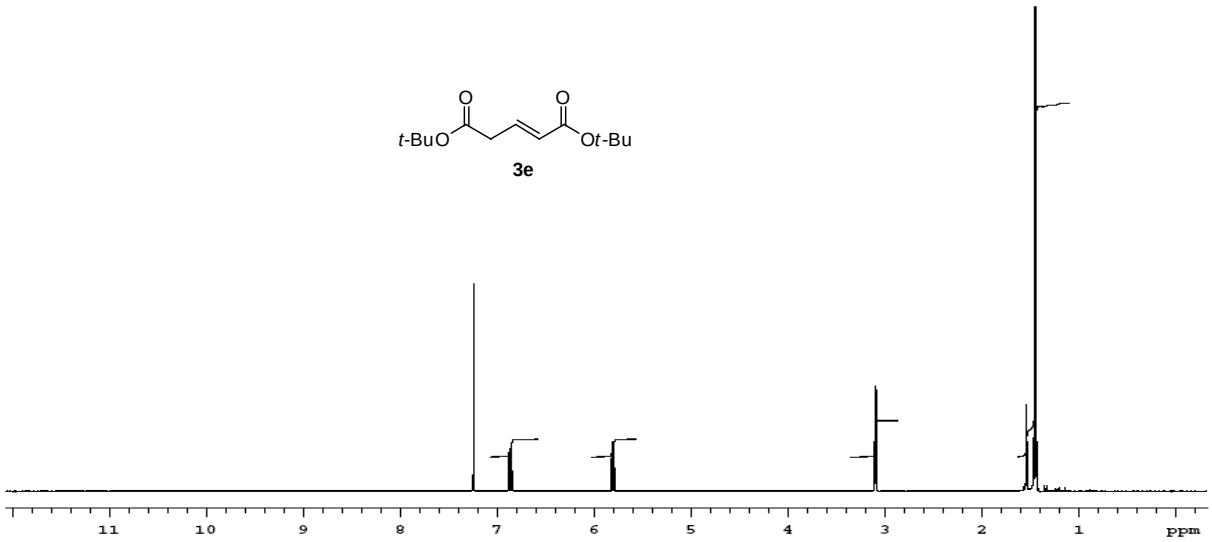
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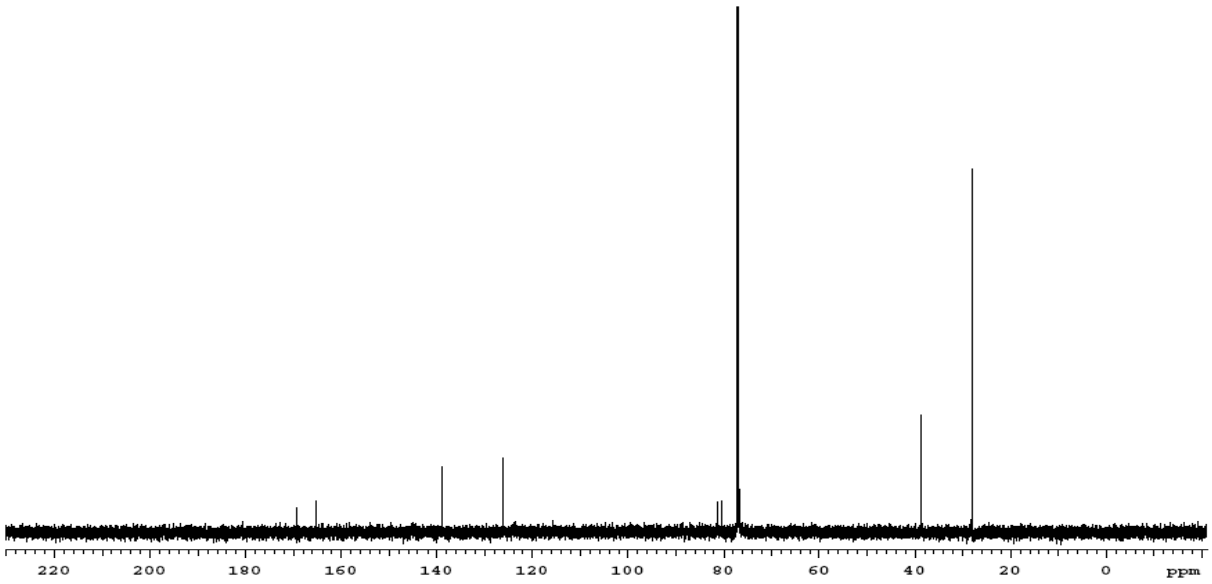
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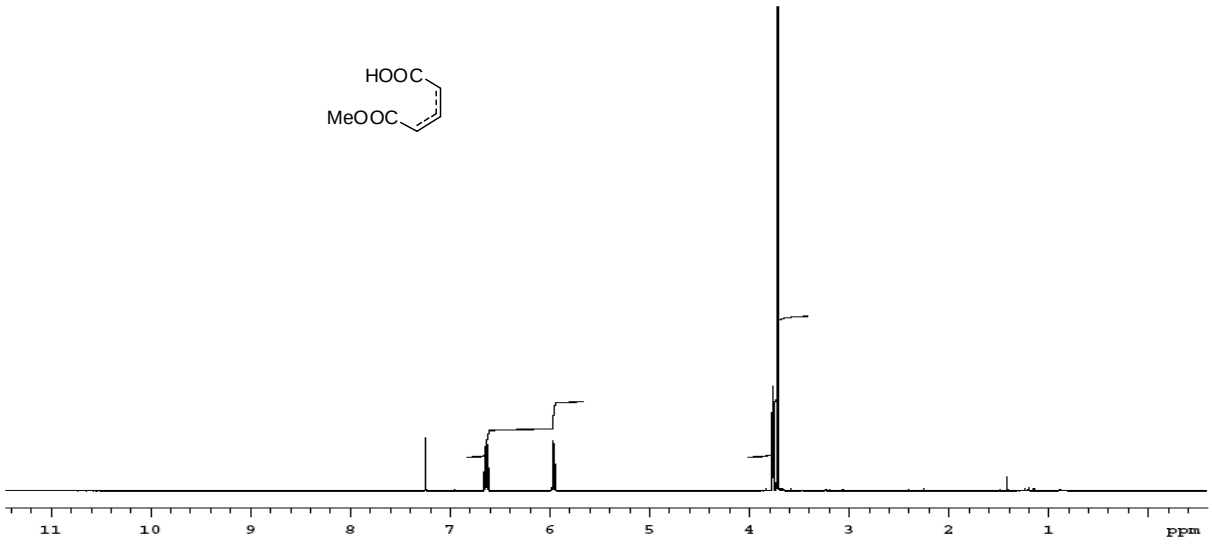
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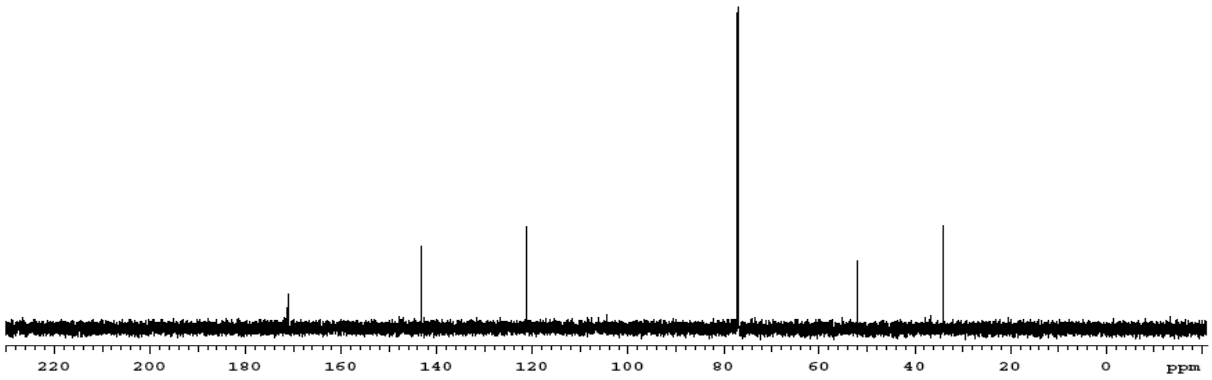
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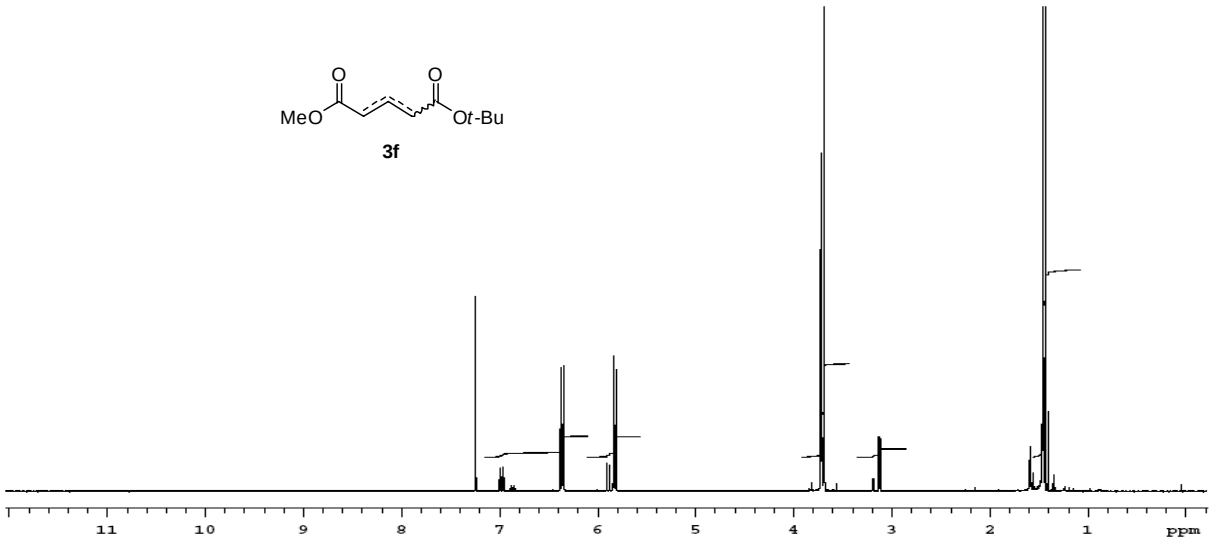
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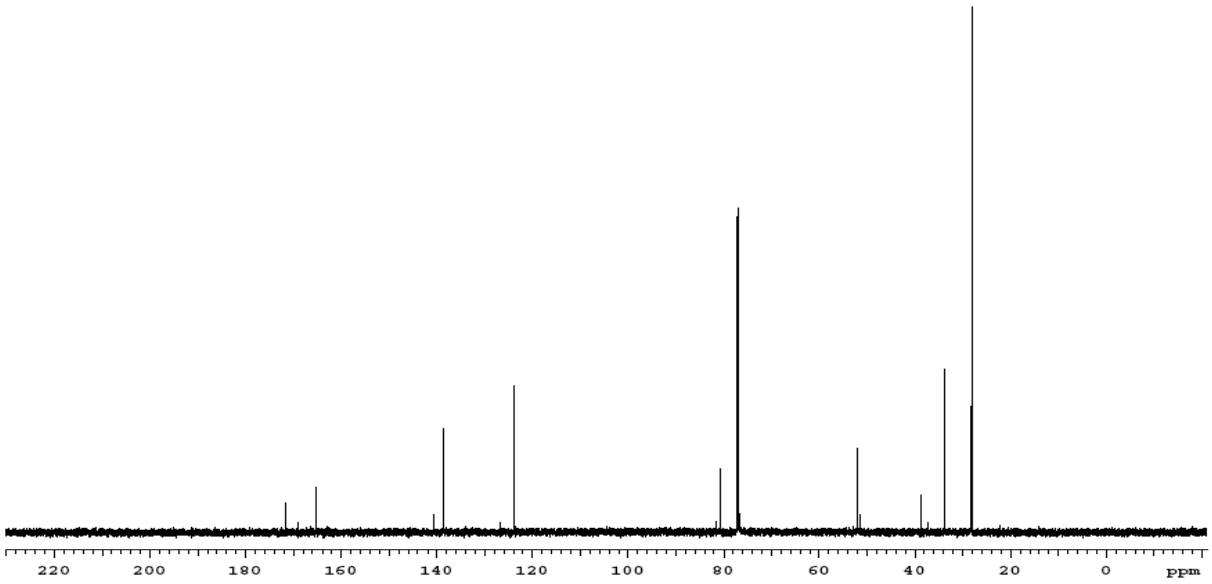
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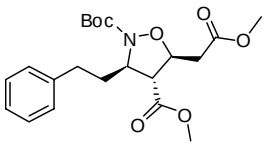
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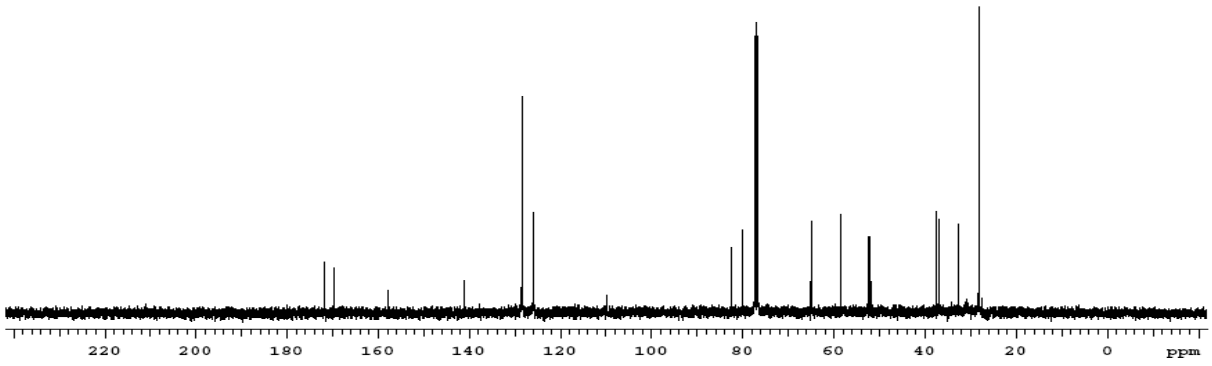
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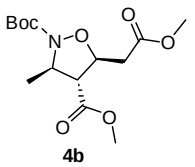
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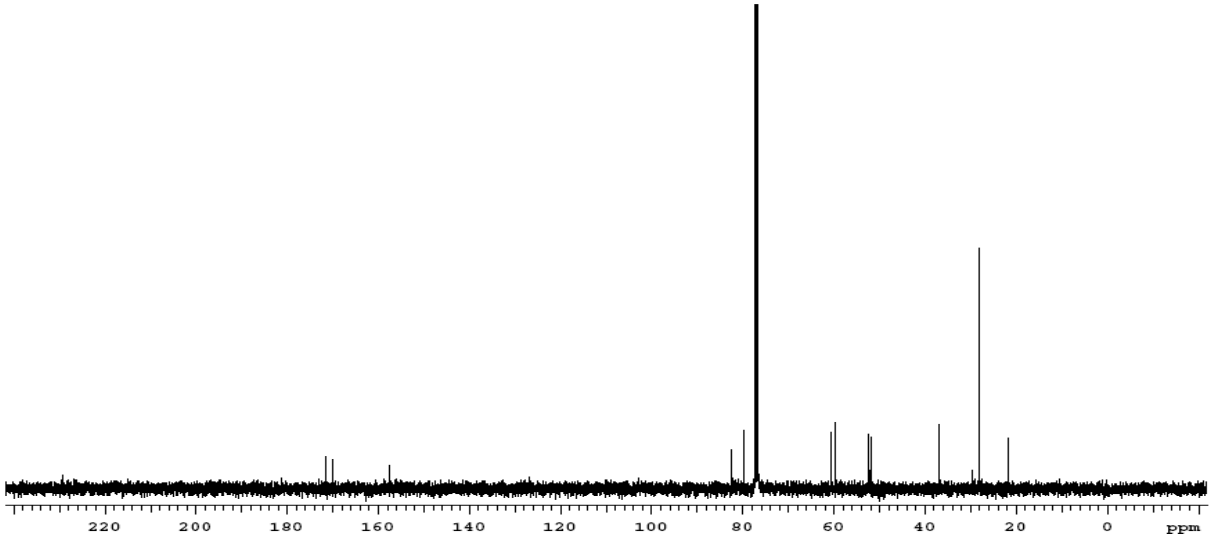
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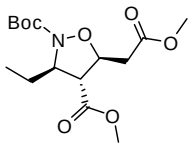
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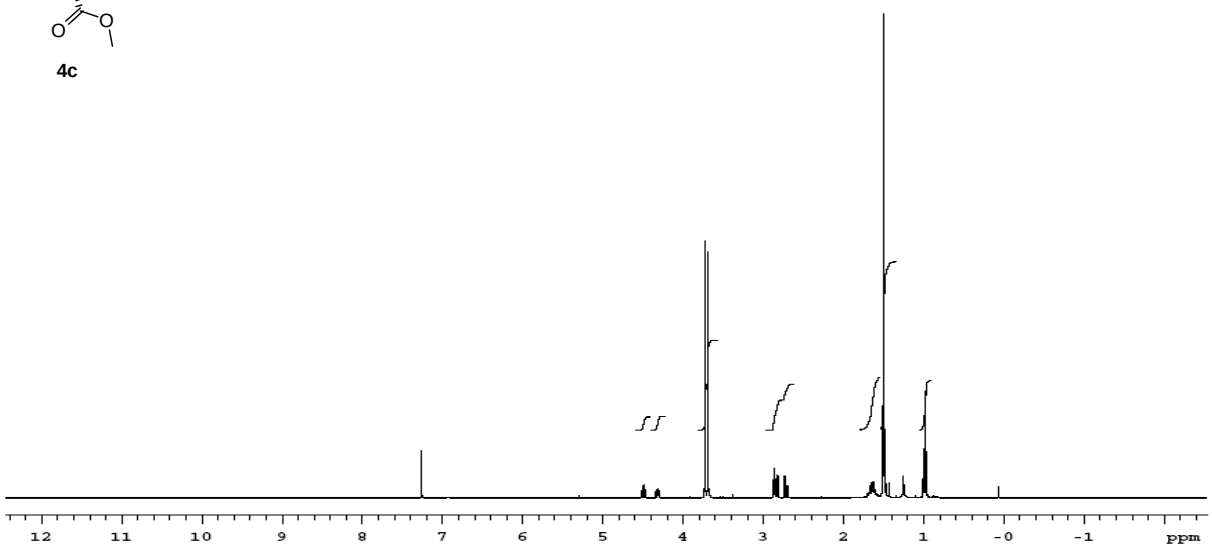
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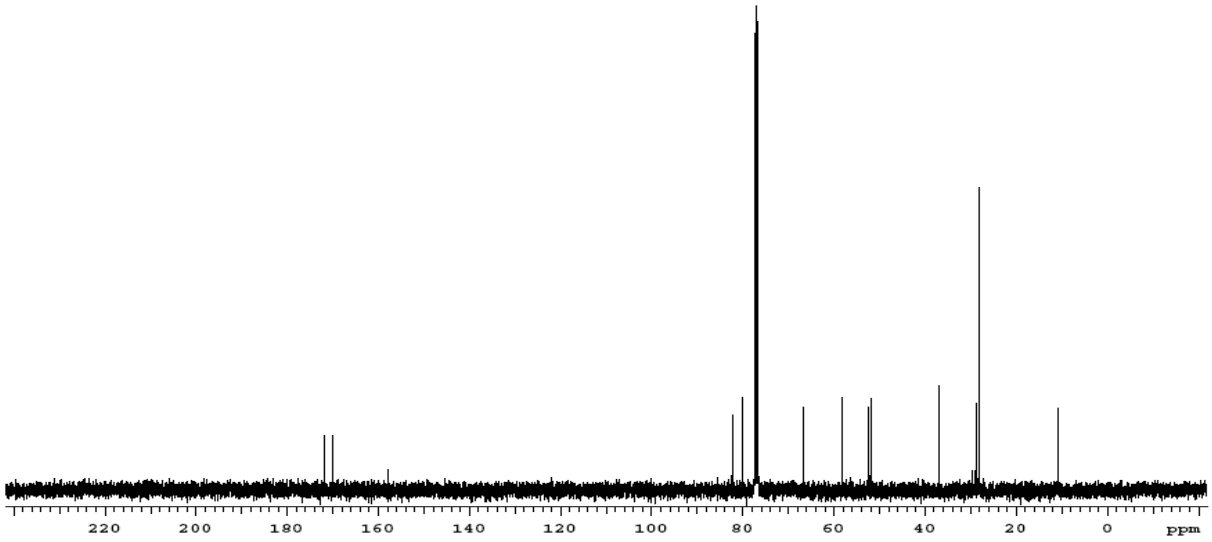
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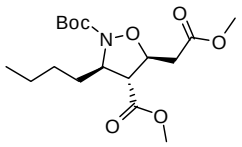
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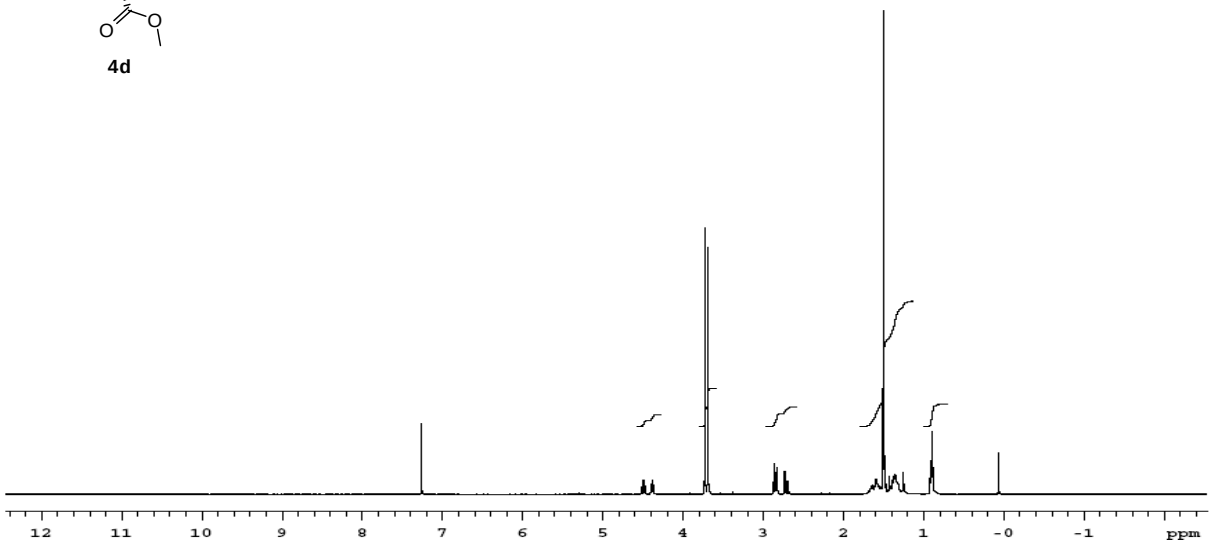
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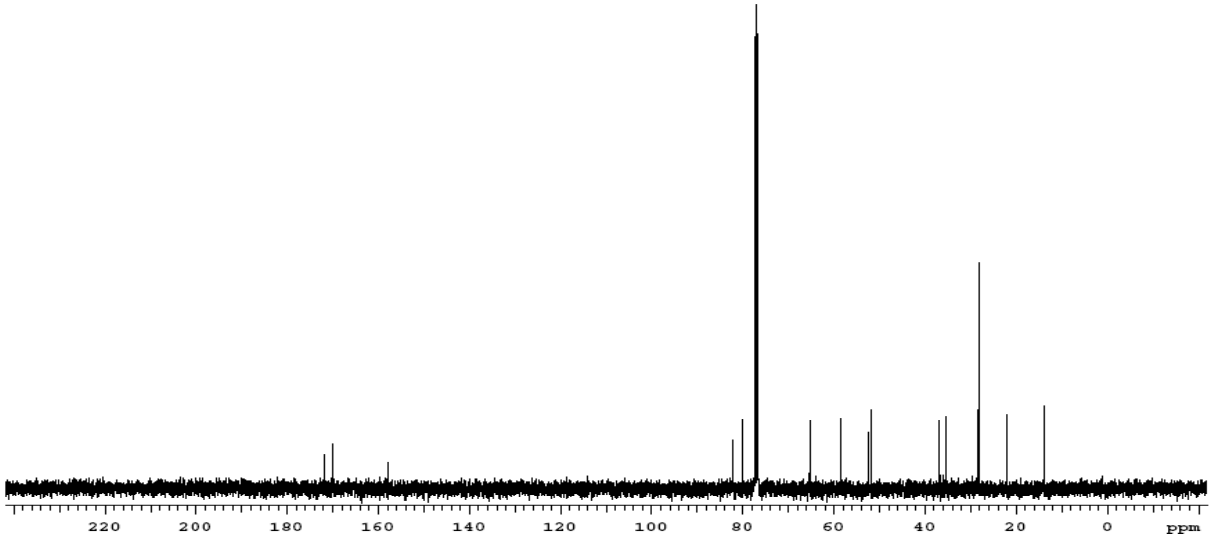
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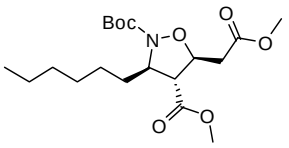
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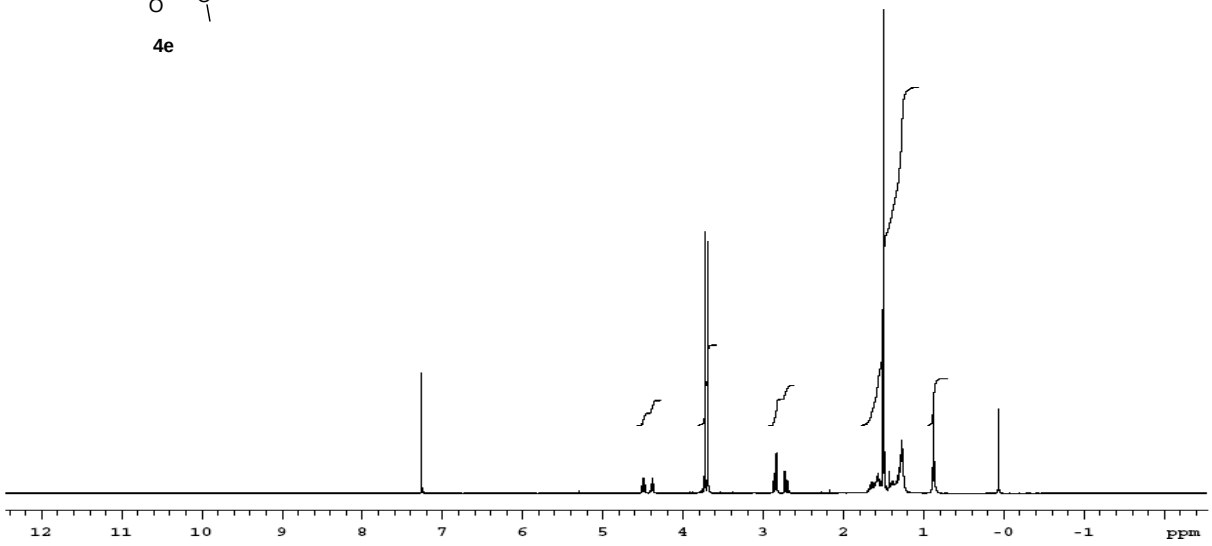
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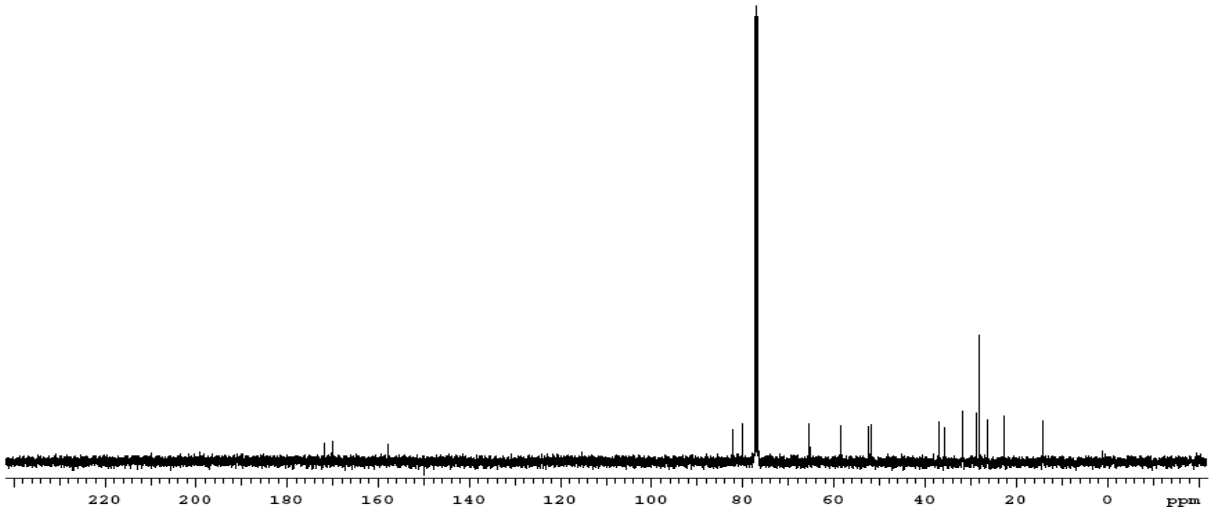
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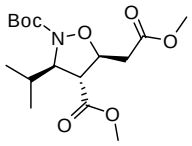
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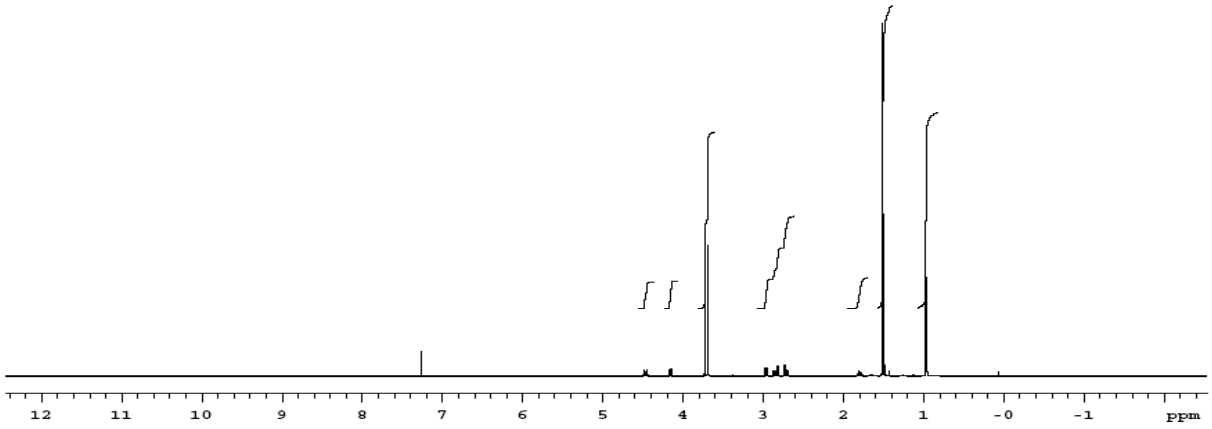
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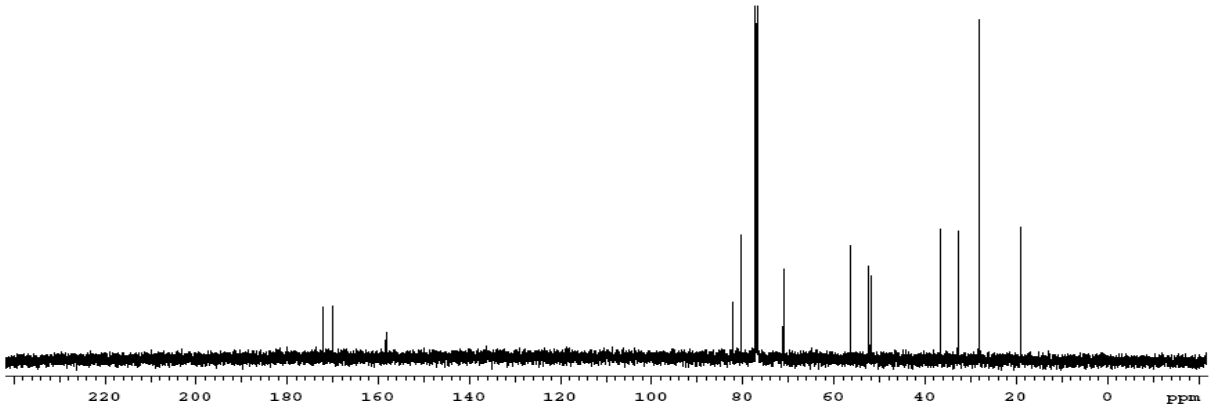
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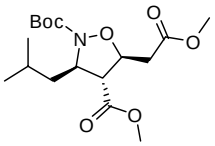
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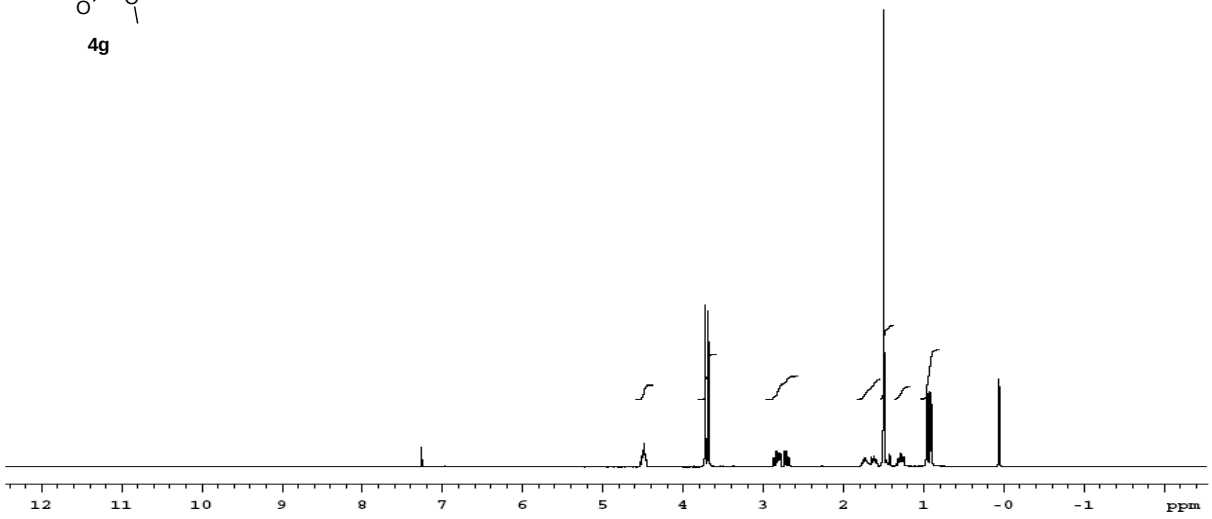
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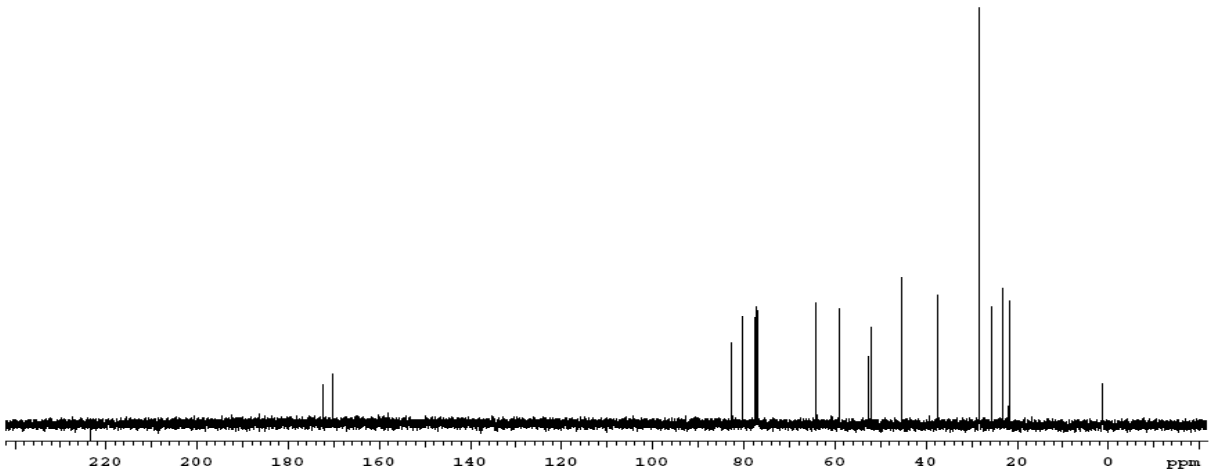
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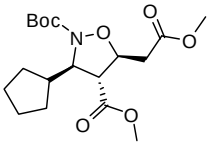
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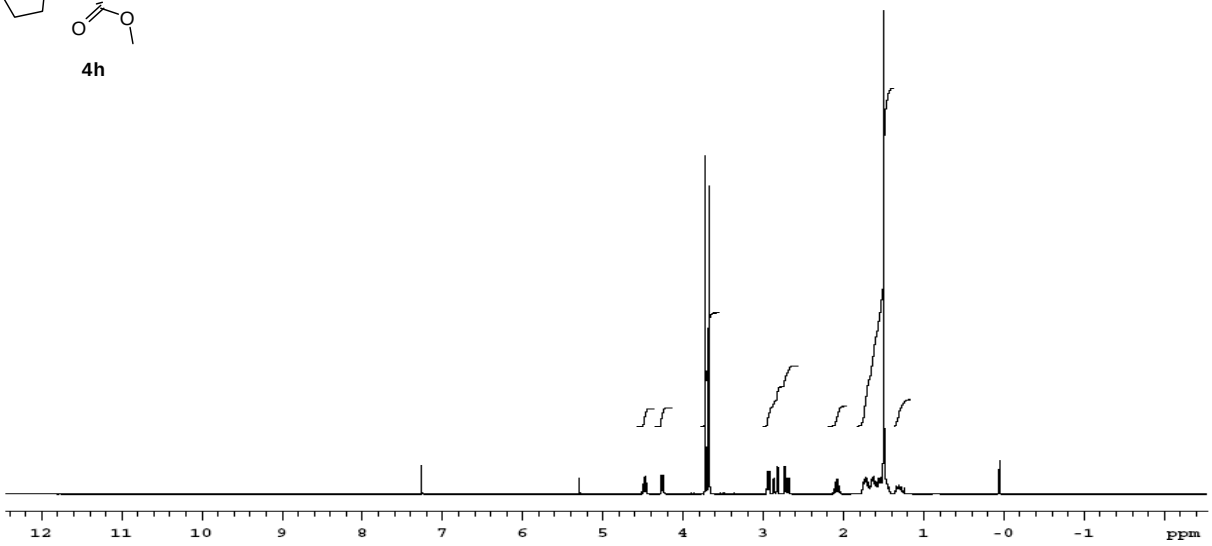
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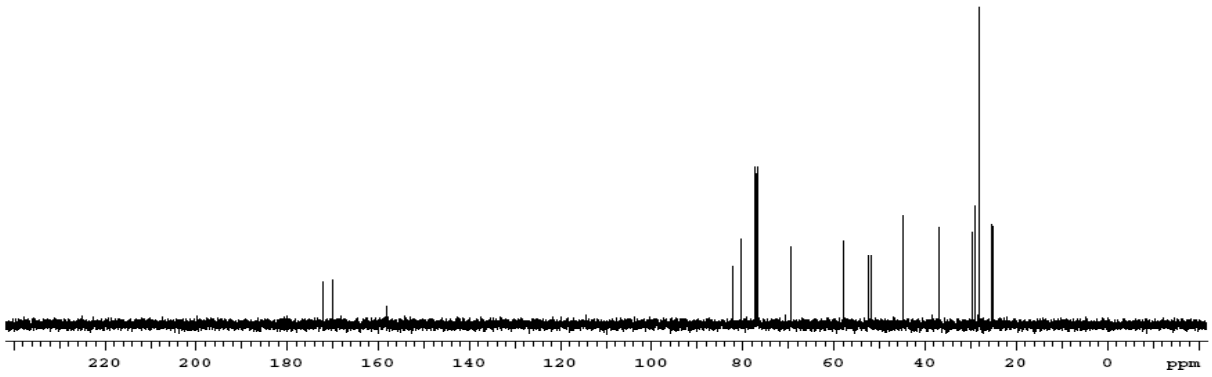
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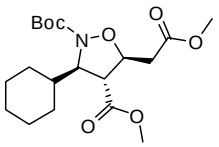
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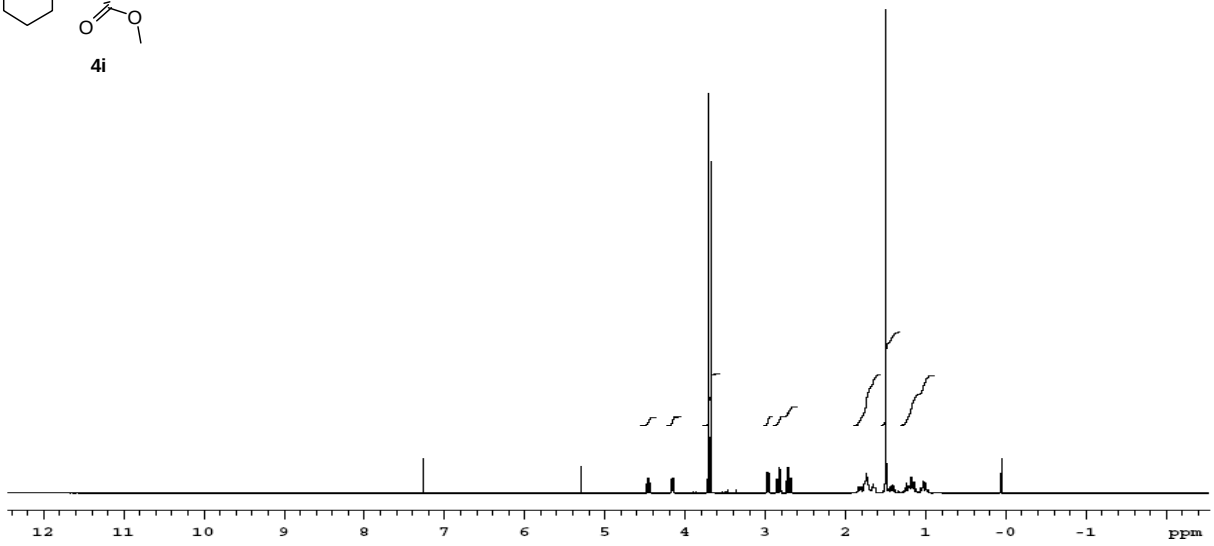
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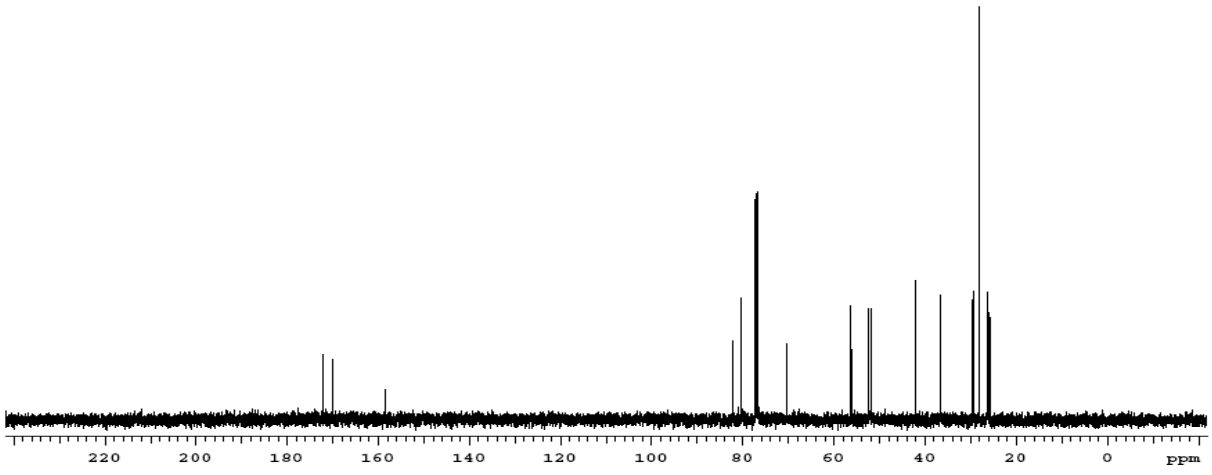
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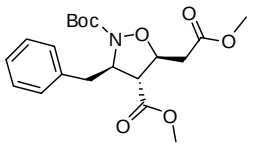
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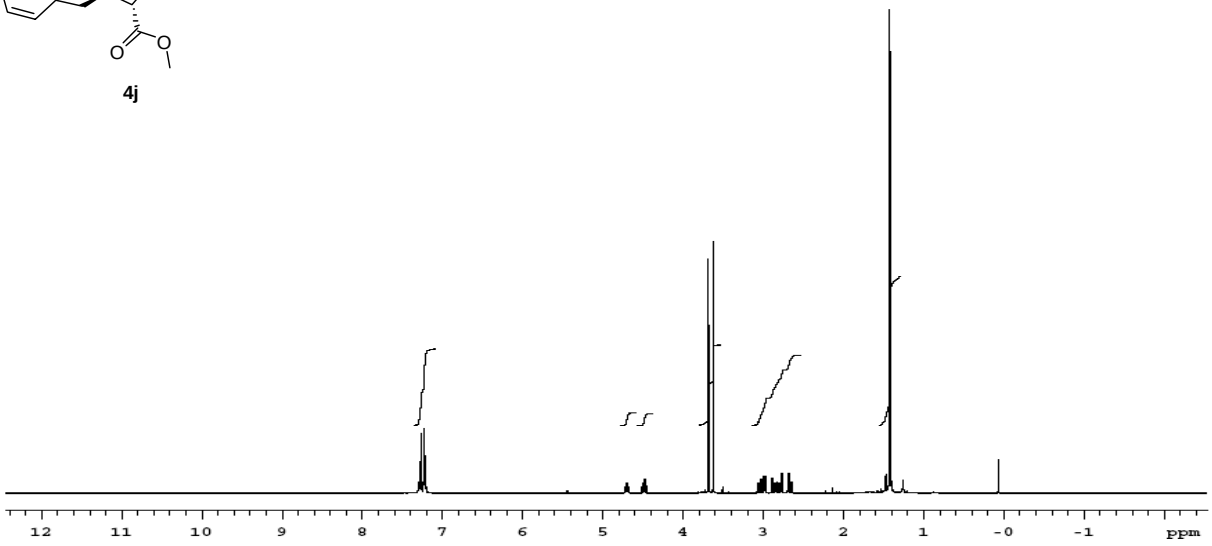
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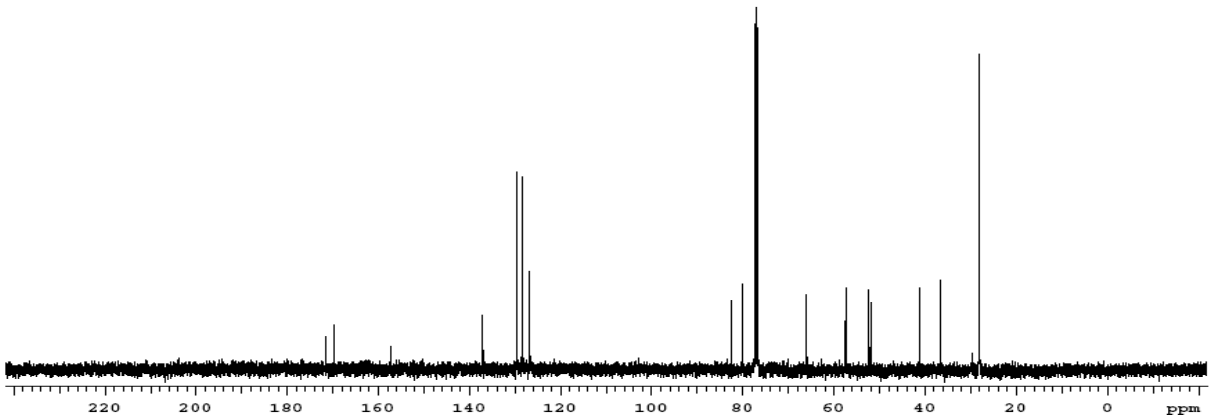
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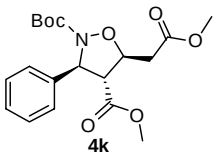
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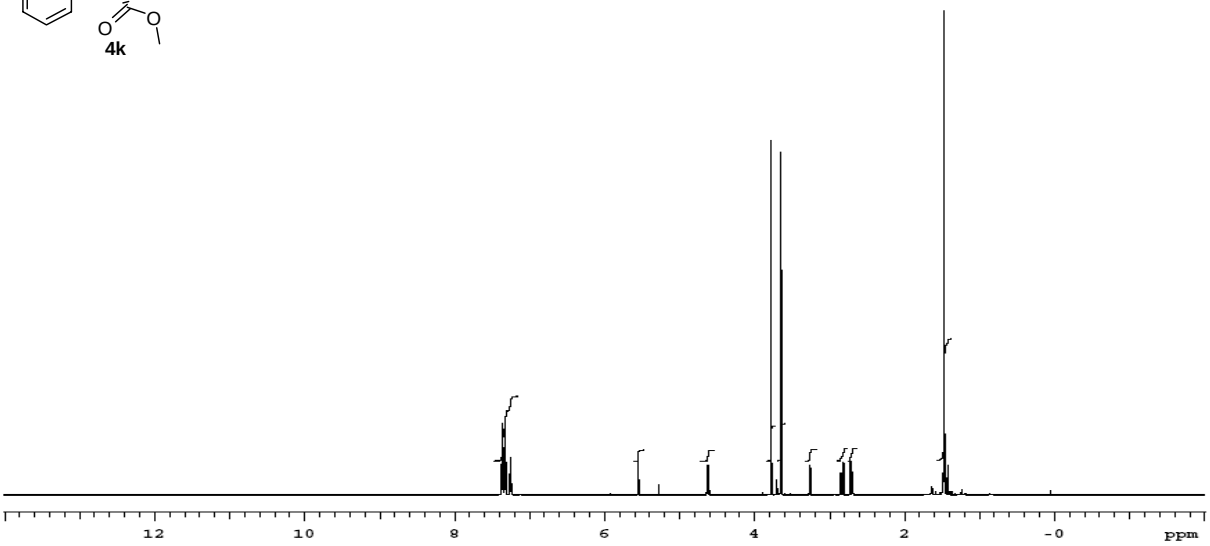
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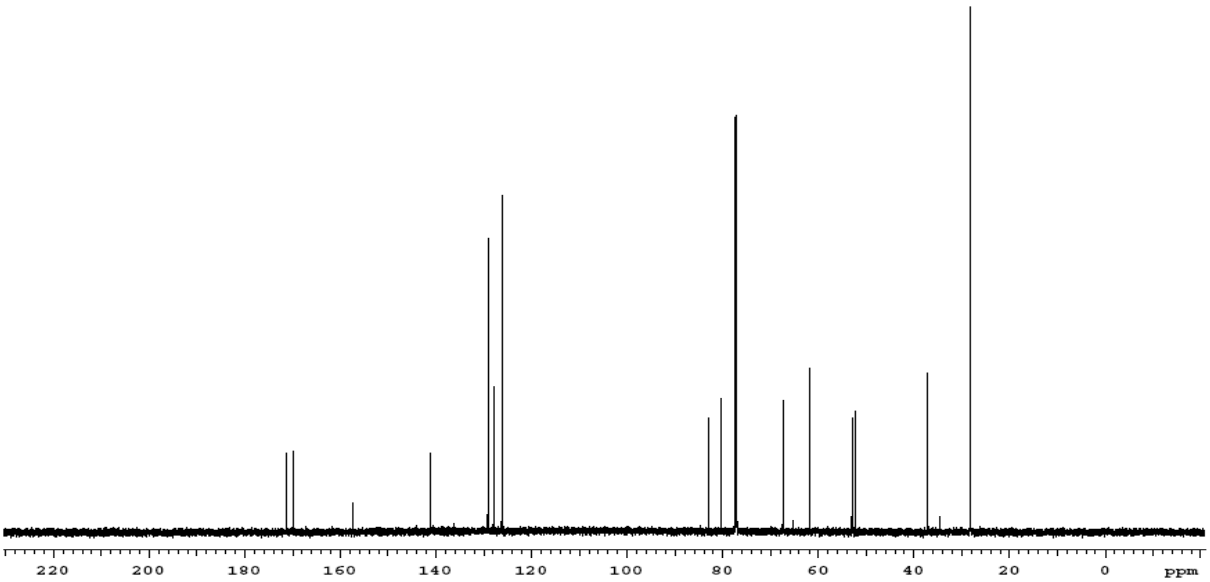
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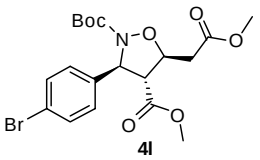
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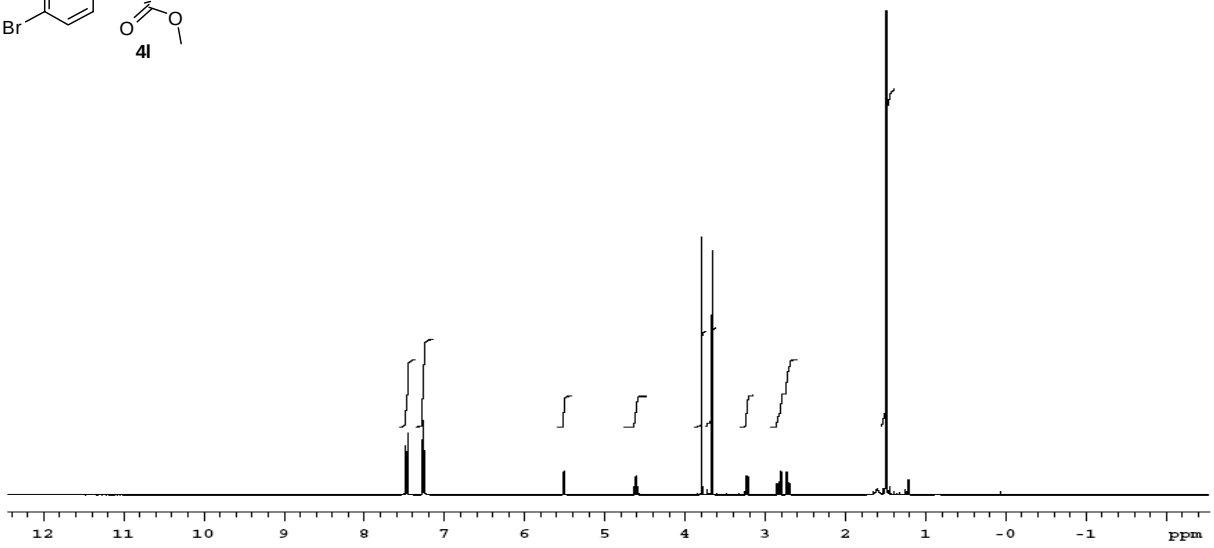
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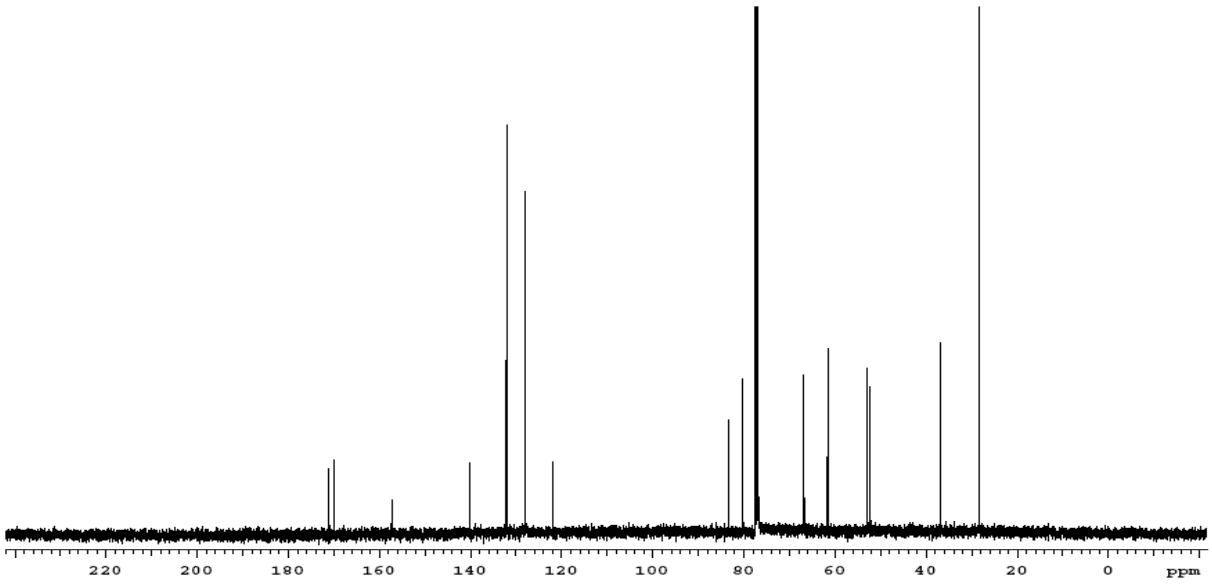
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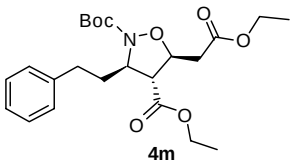
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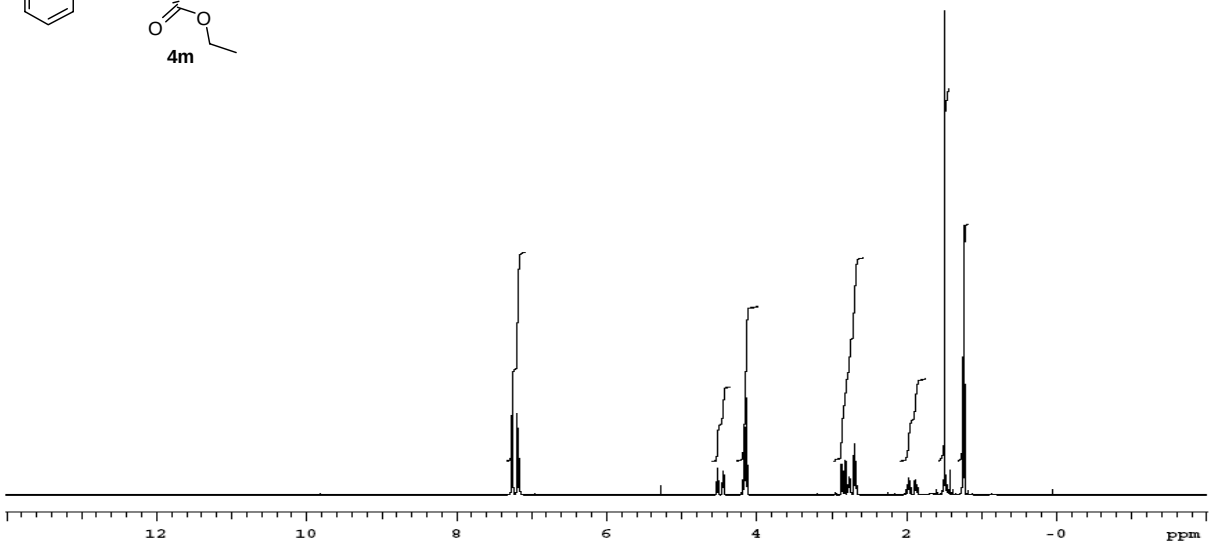
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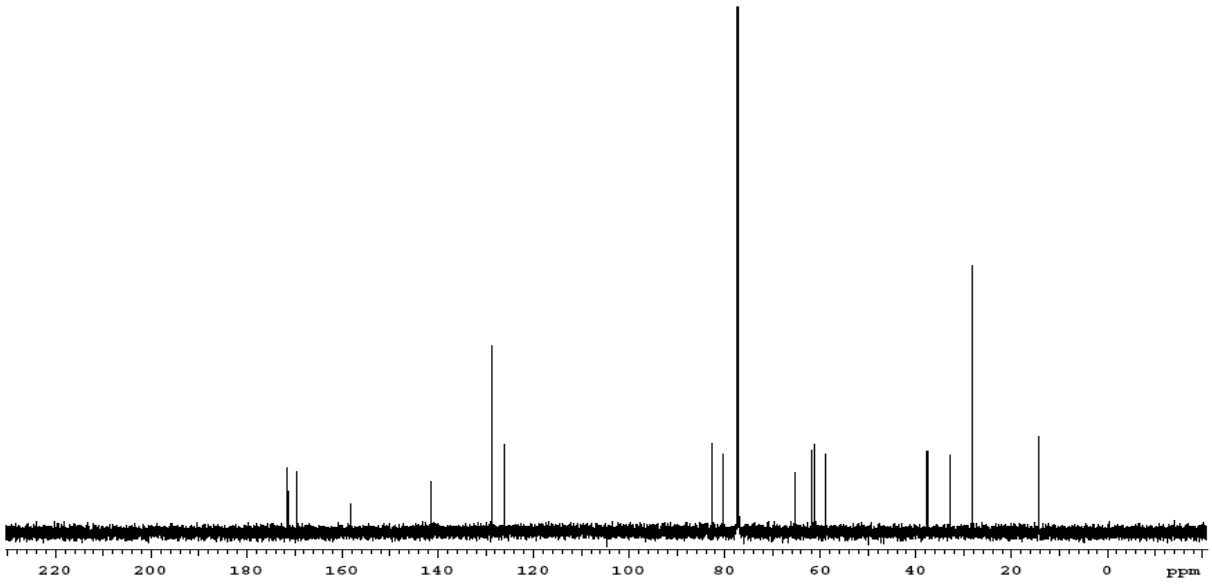
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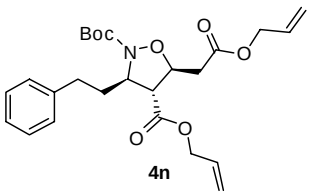
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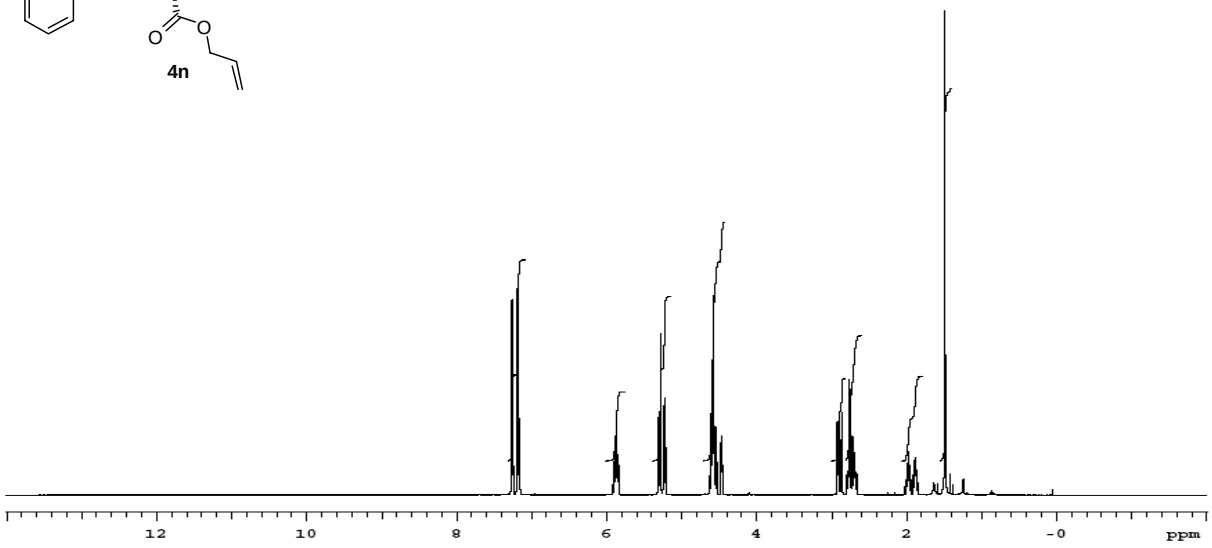
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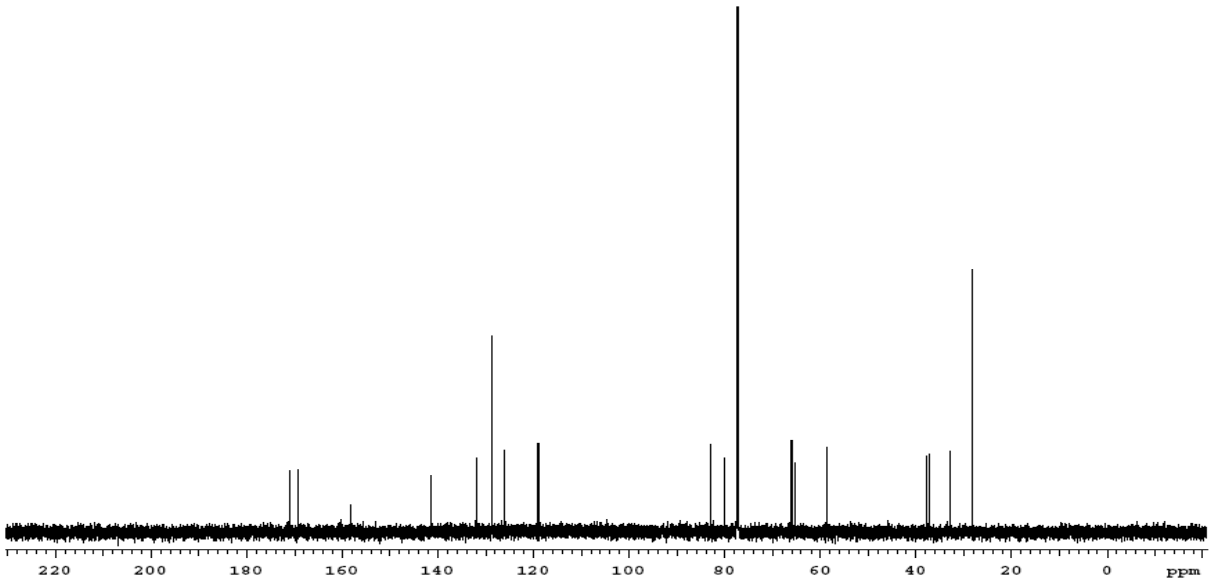
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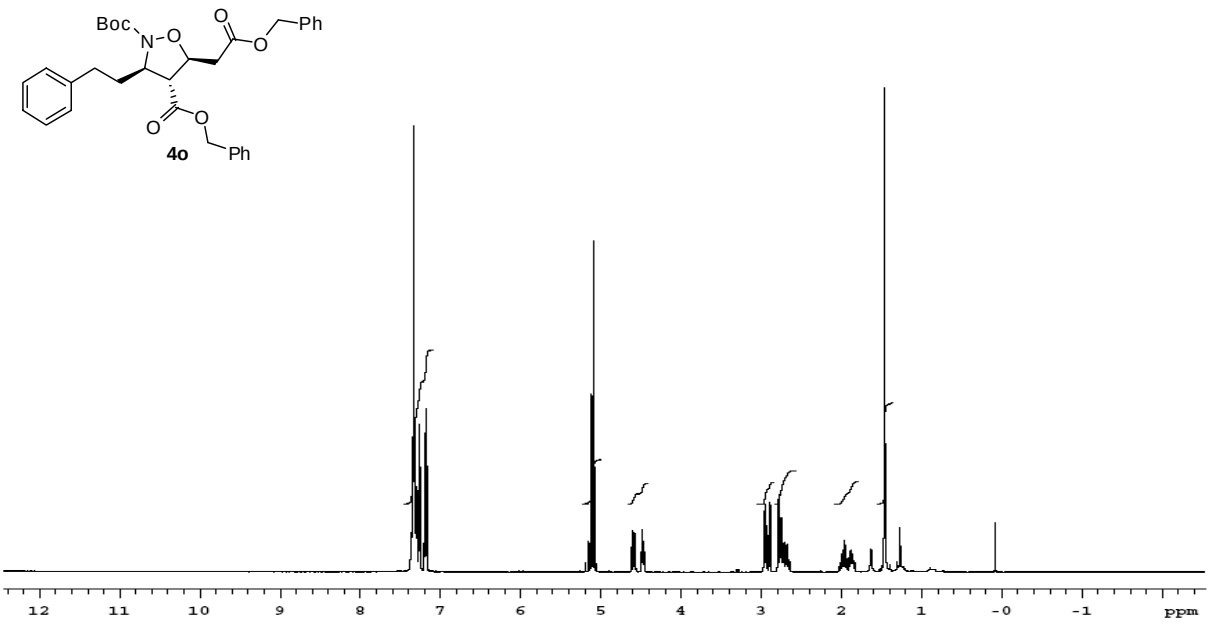
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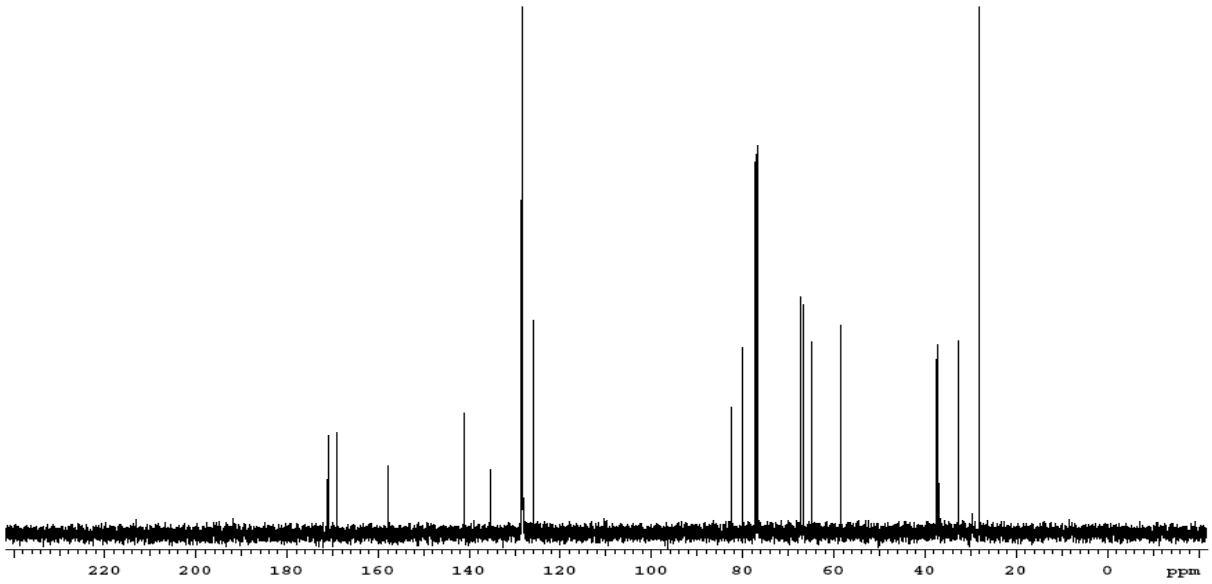
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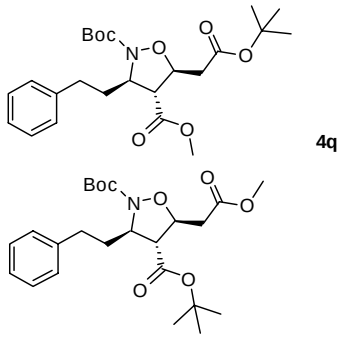
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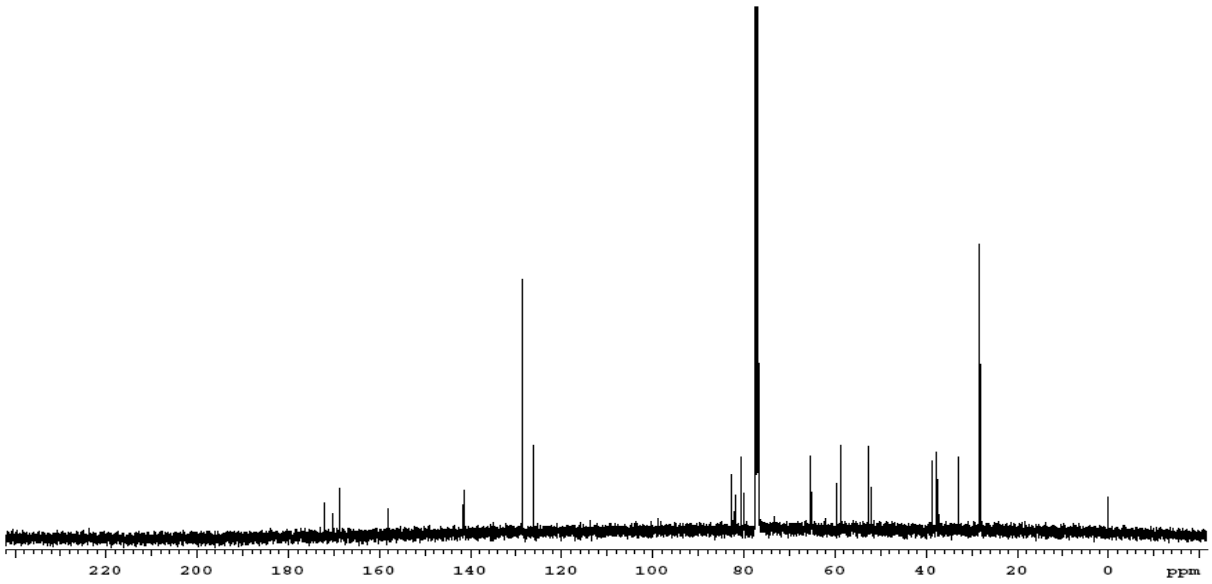
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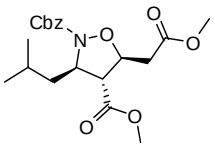
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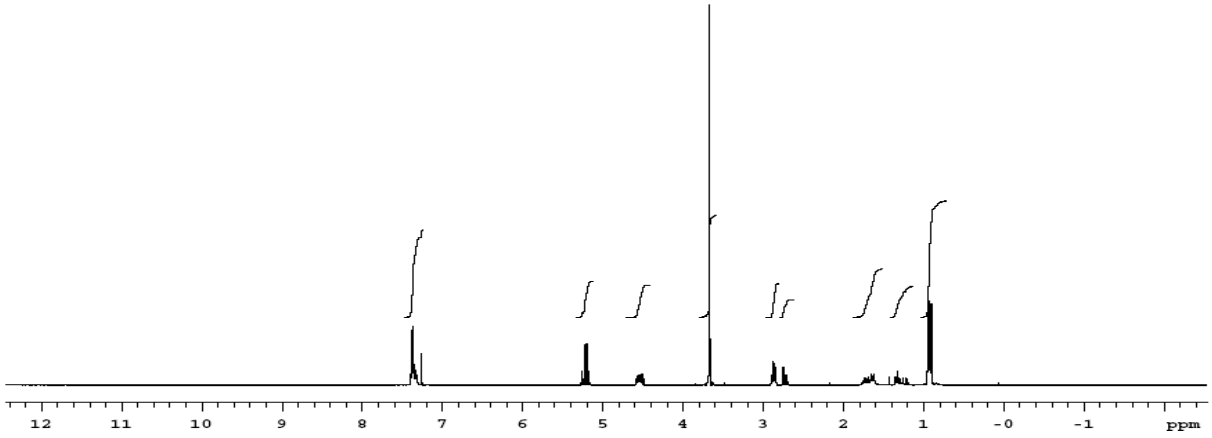
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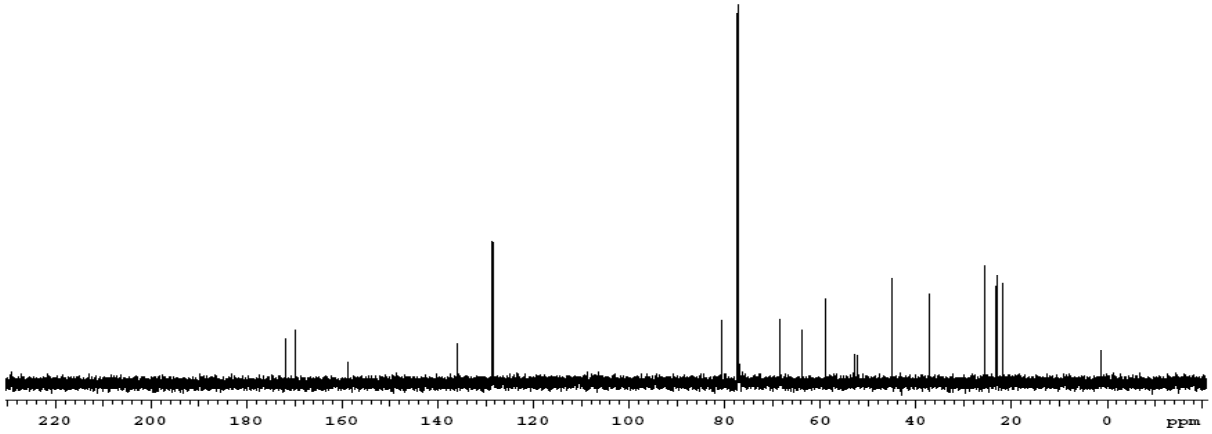
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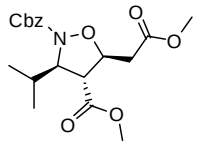
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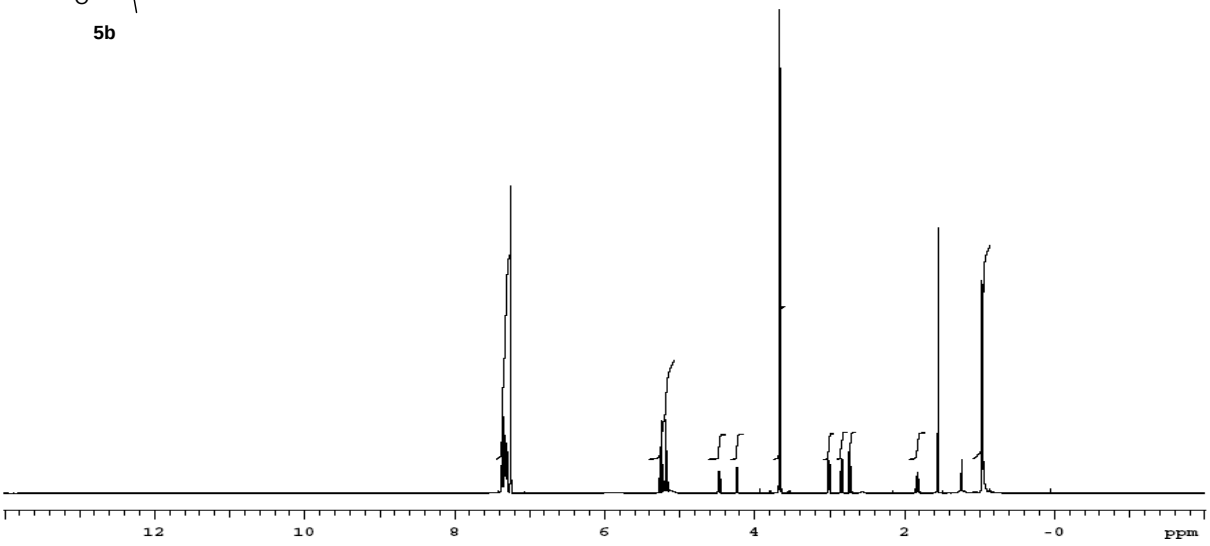
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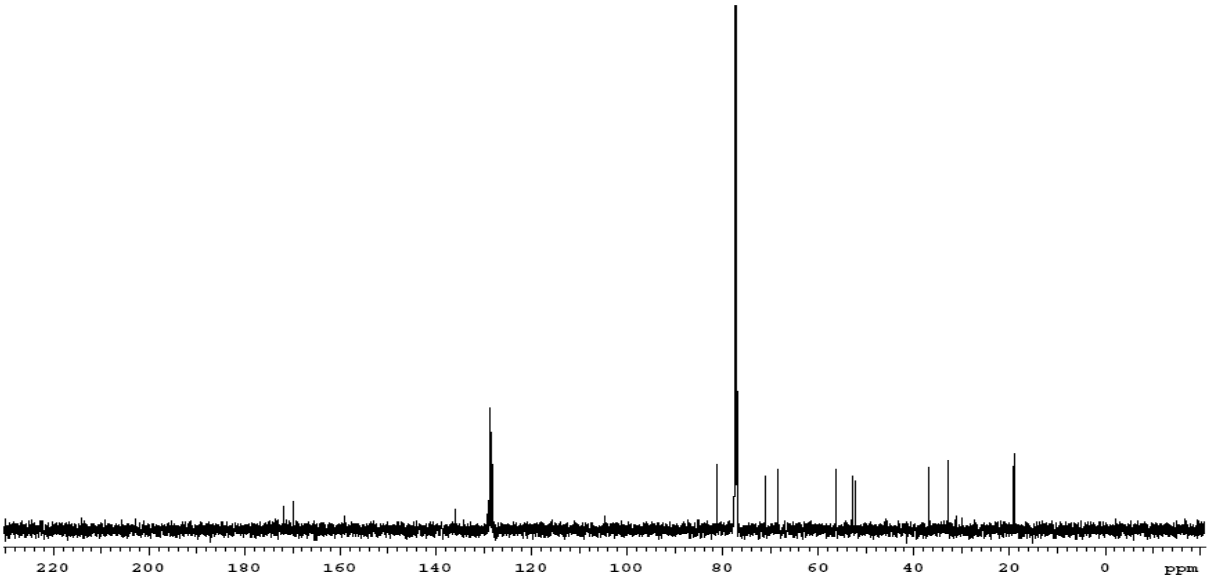
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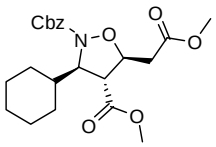
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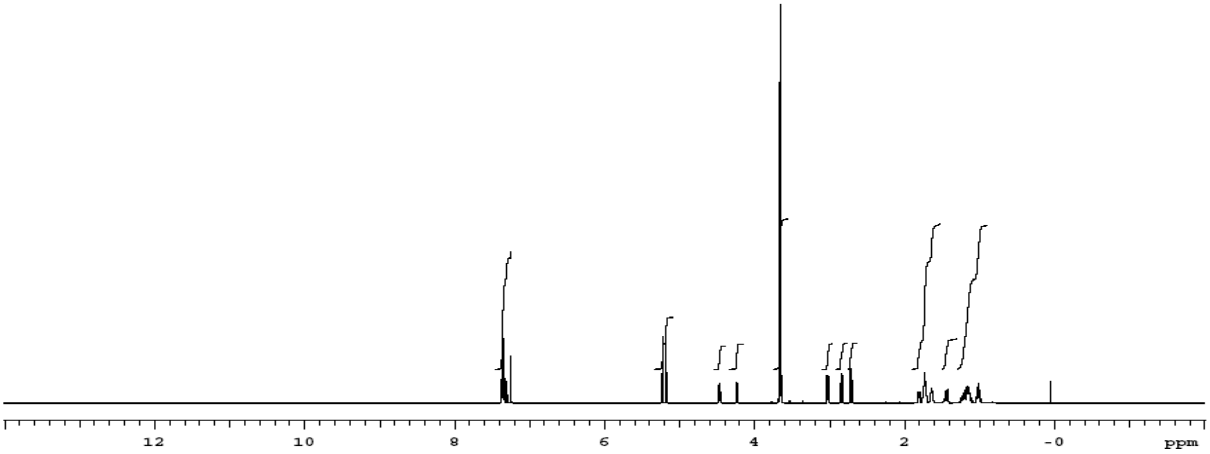
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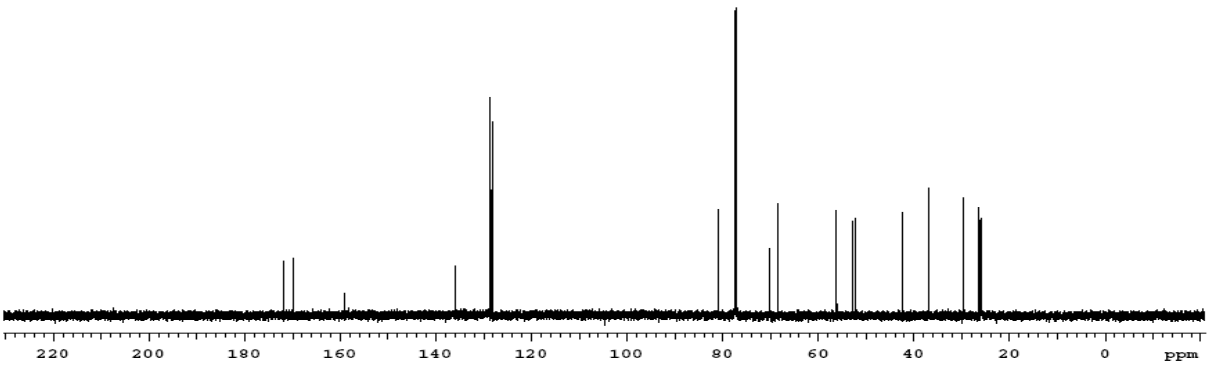
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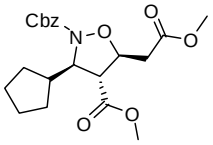
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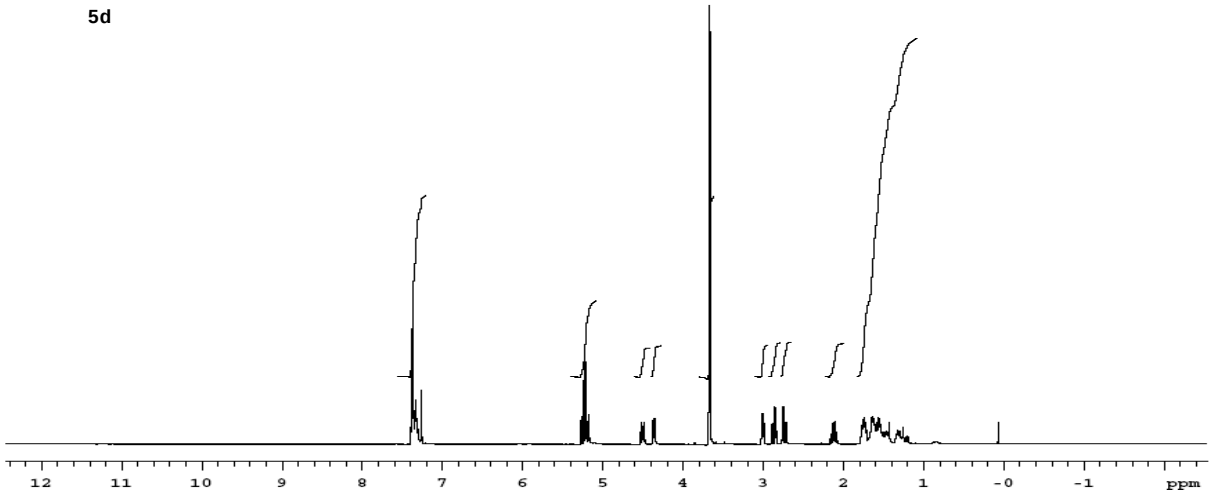
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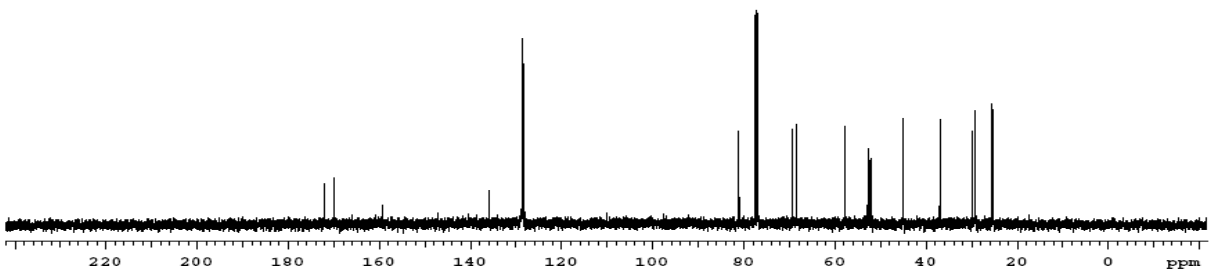
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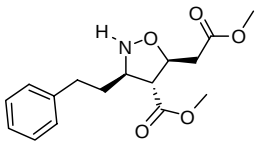

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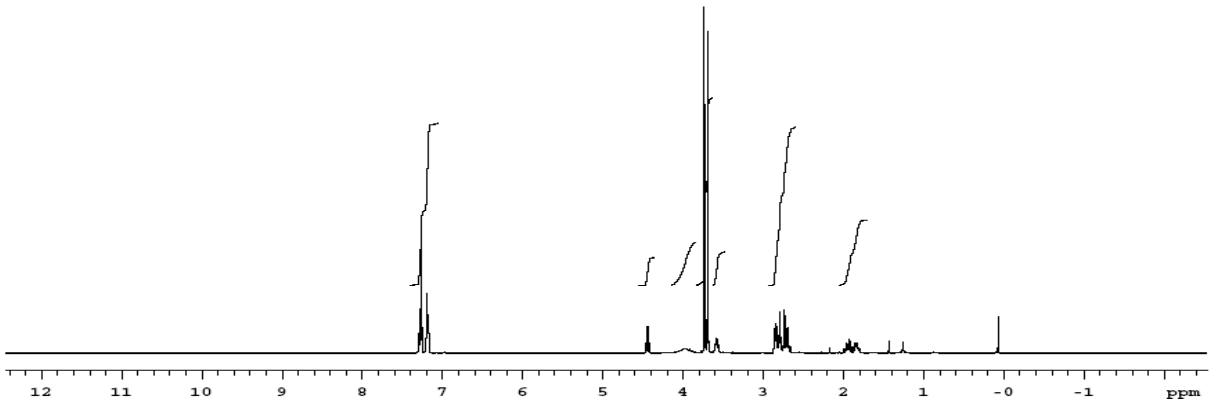
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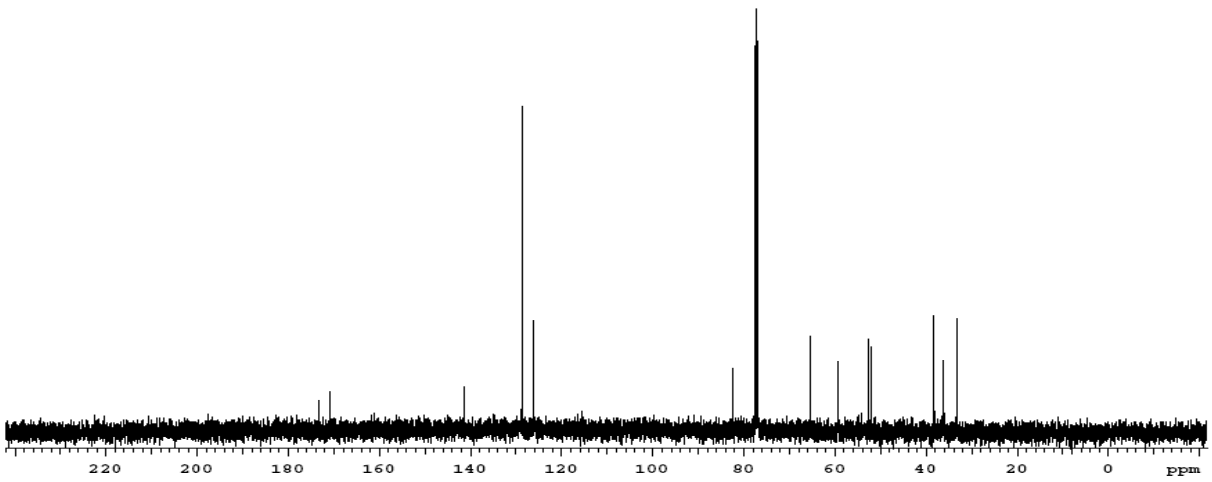
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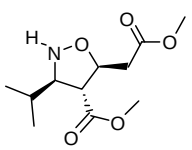

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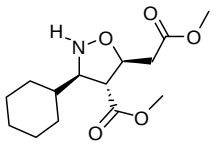

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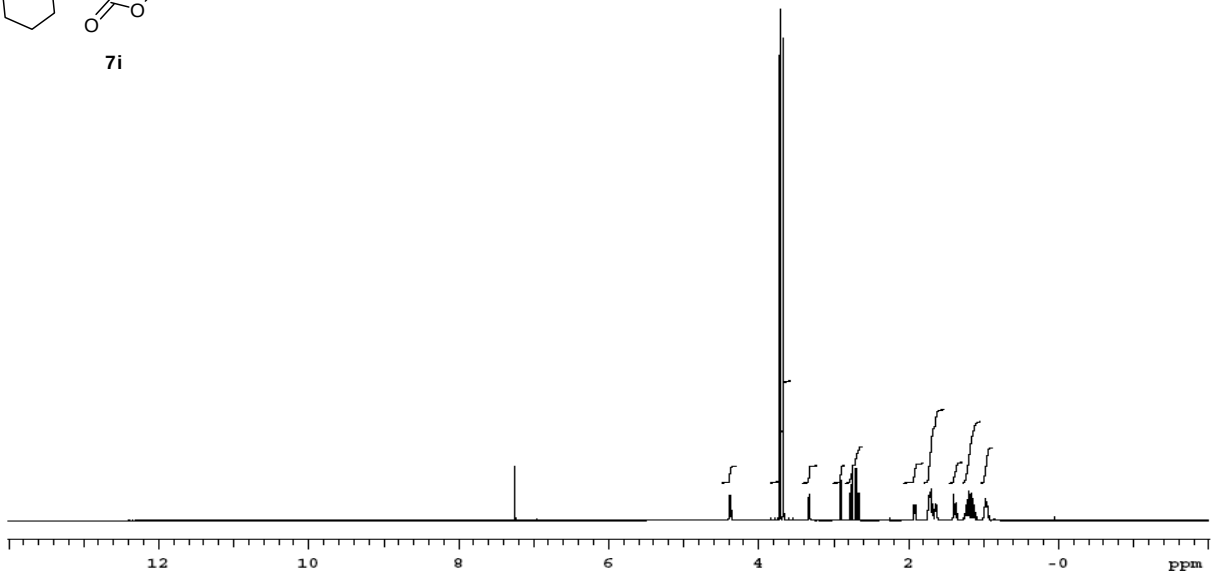

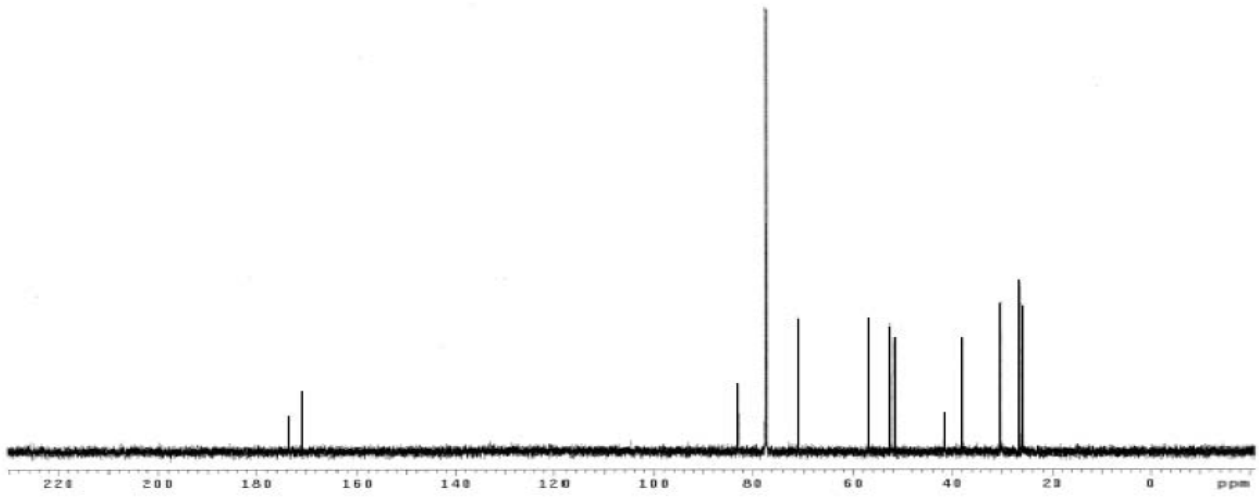

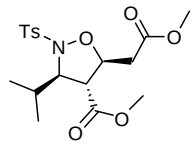

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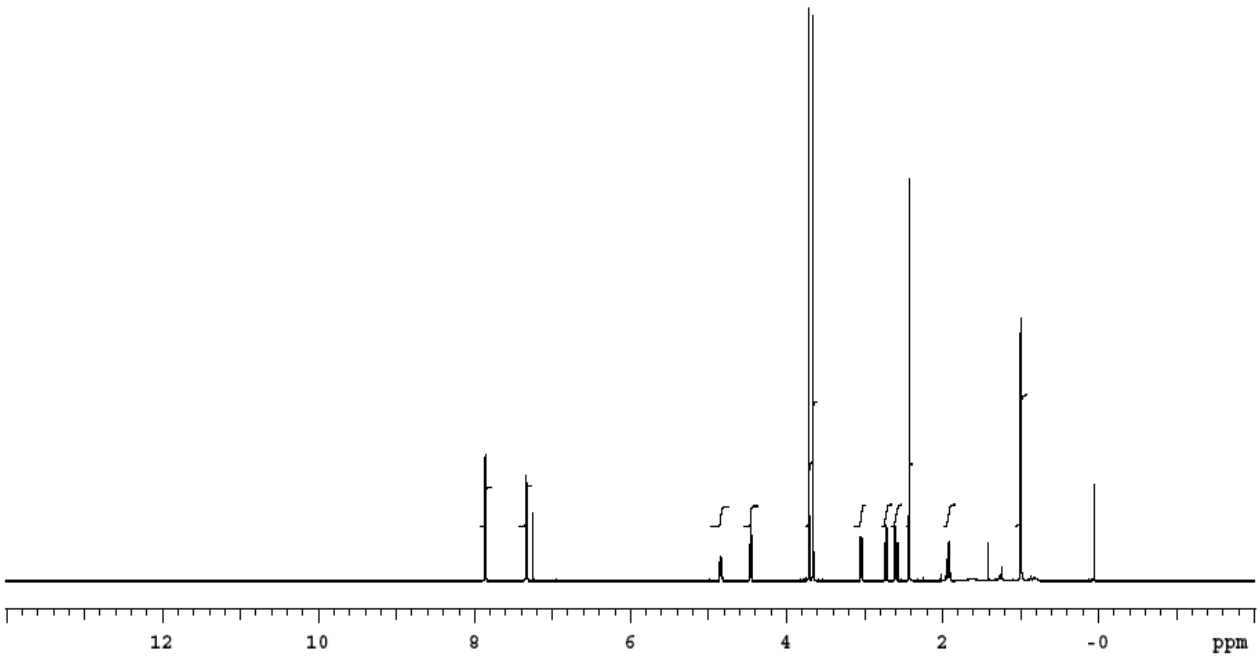

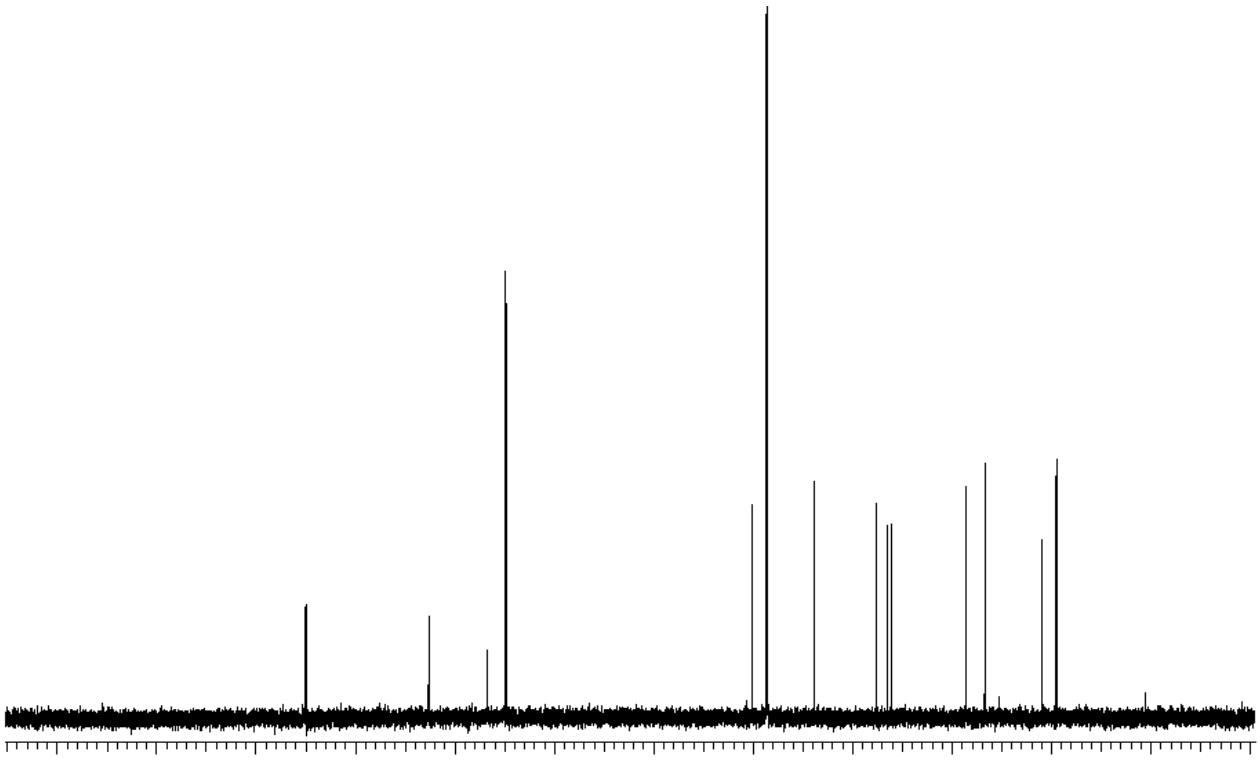

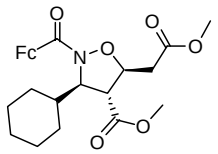
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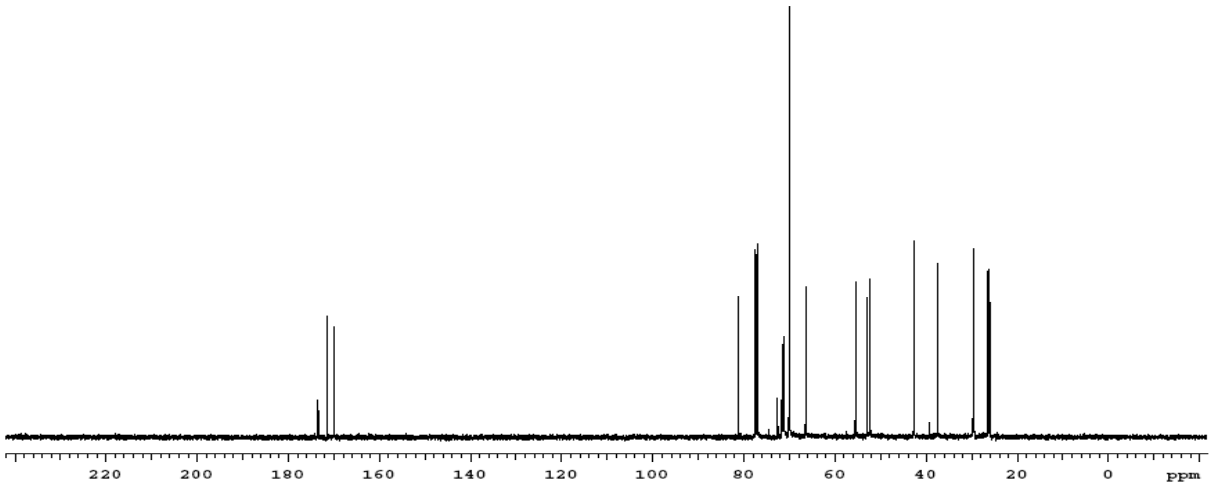
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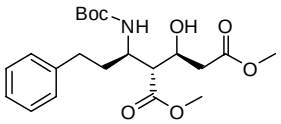
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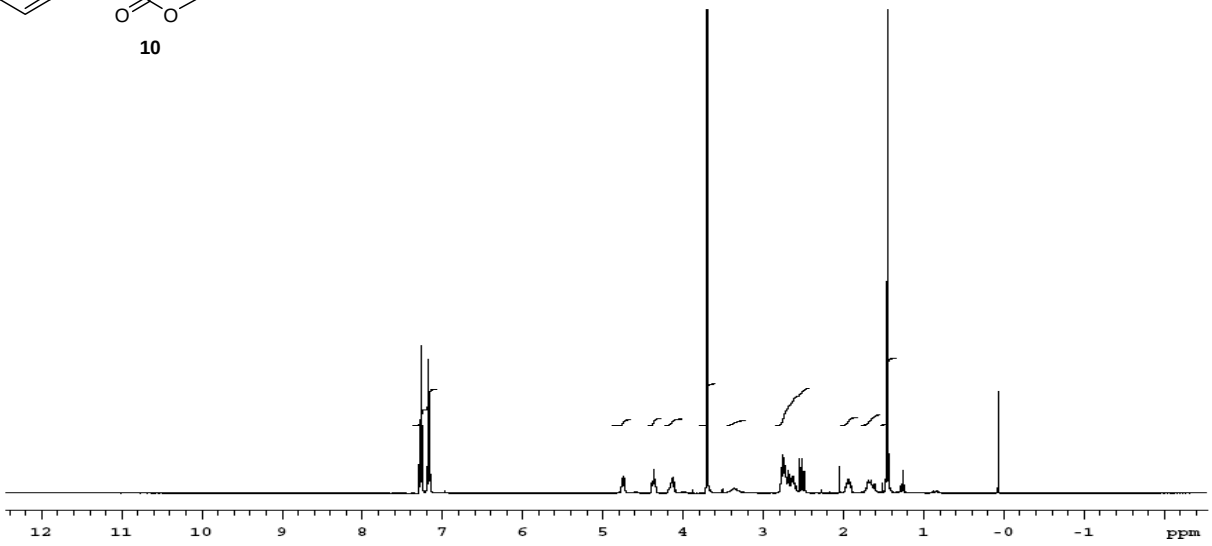
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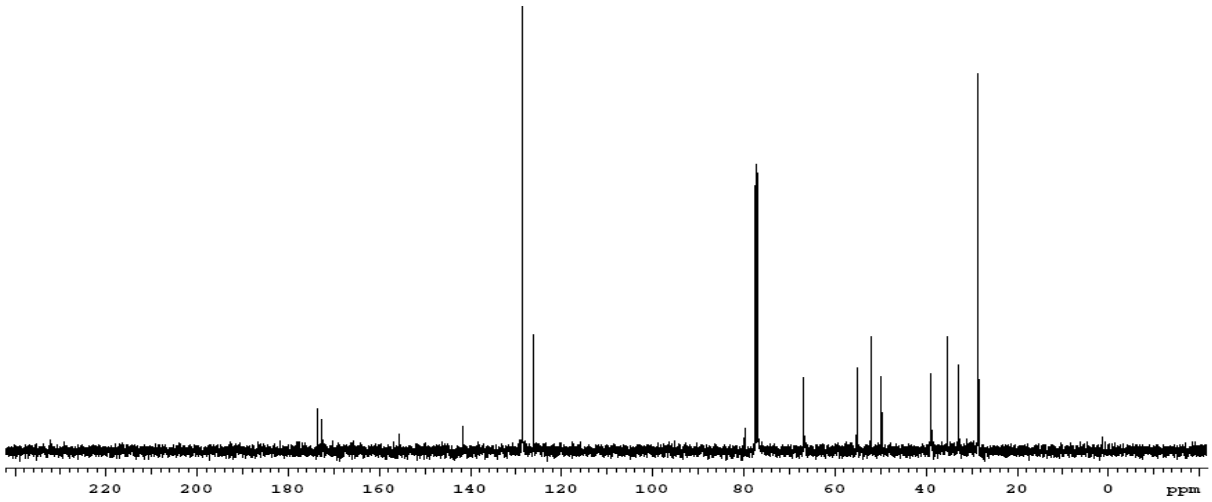
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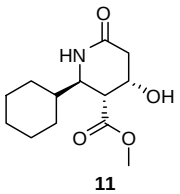
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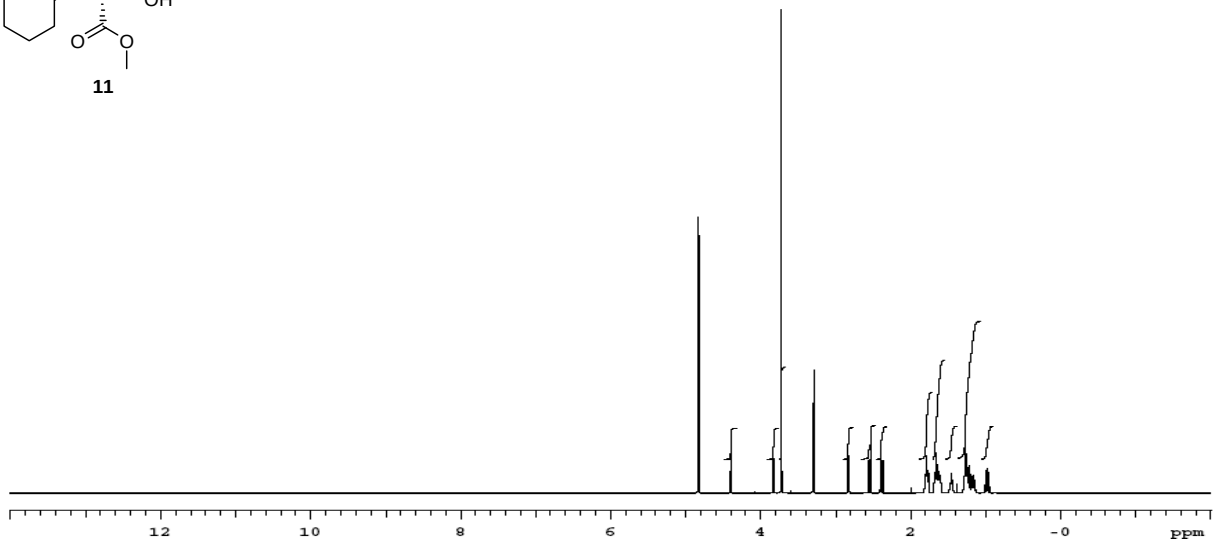
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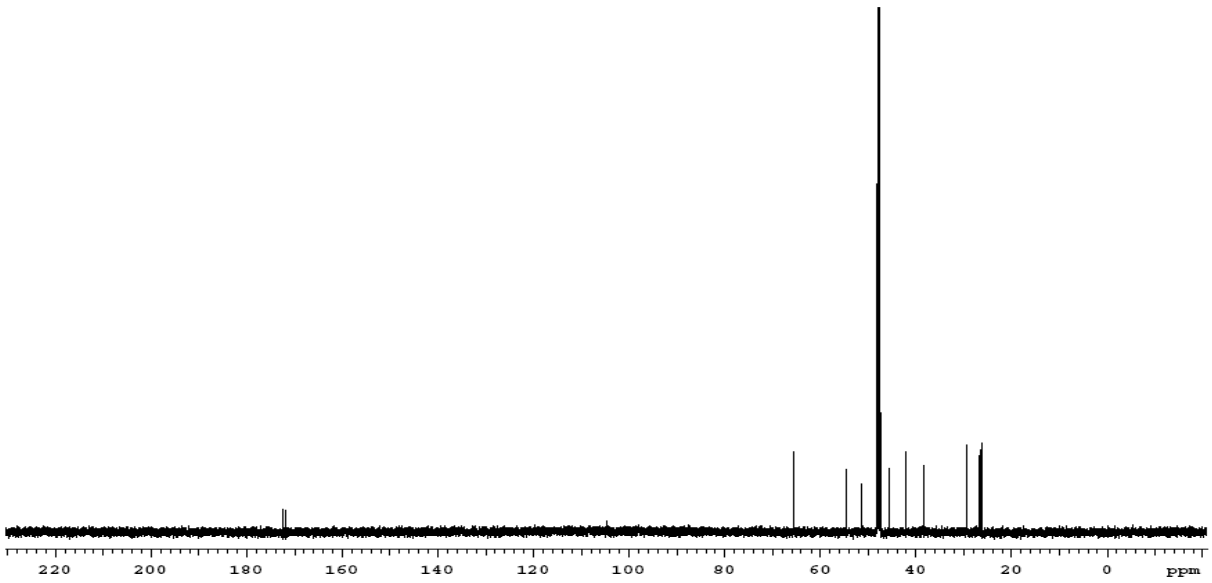
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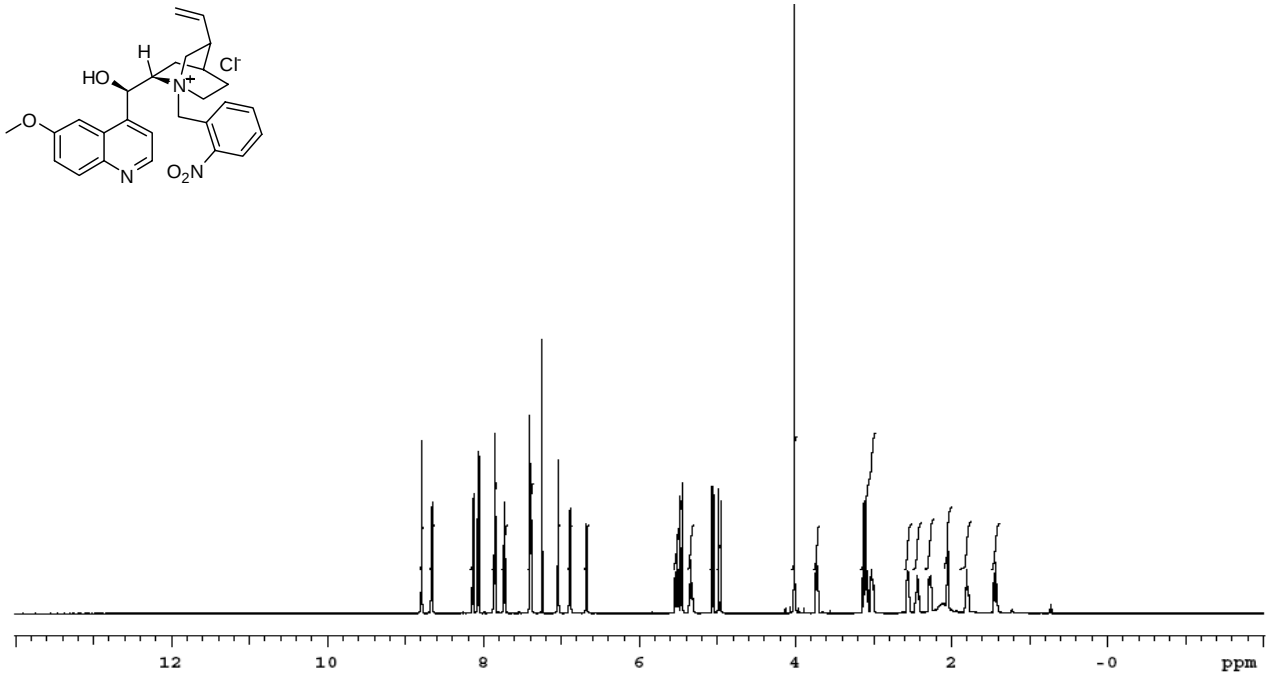
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HO
Cl-
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N
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12
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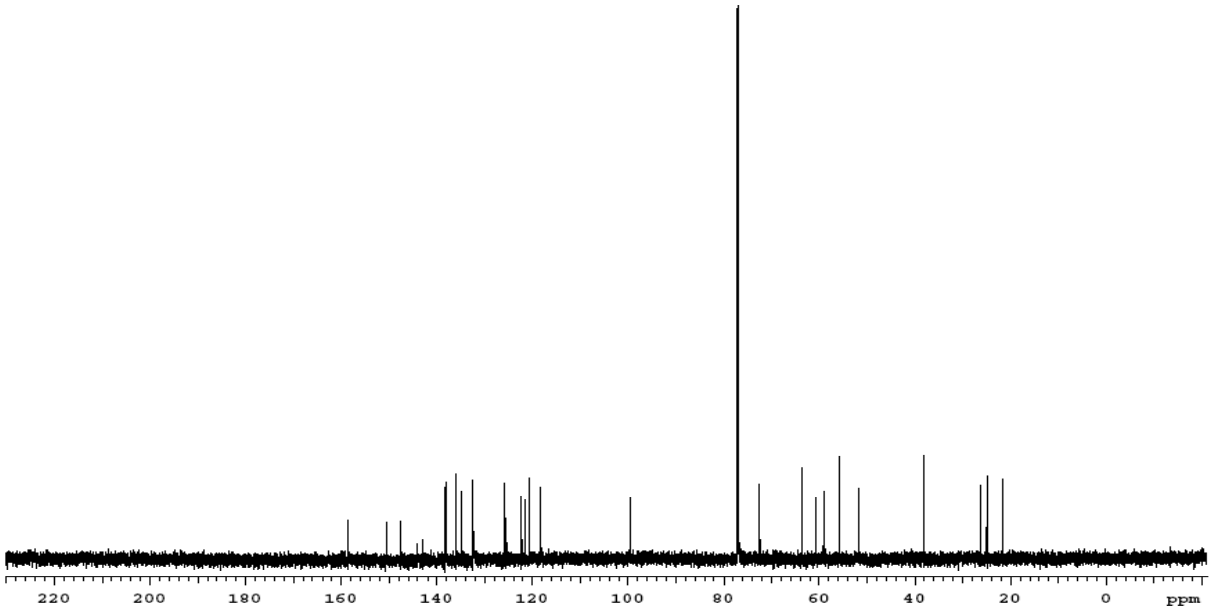
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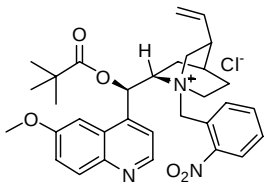
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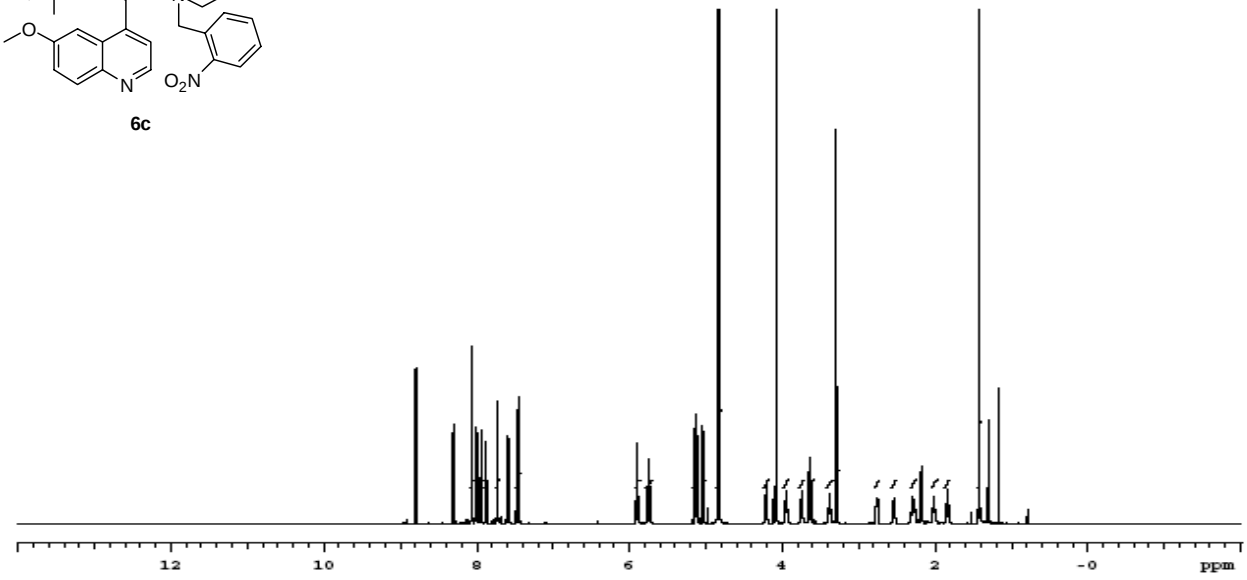
Cl-
O
N+
O
N
O2N

6c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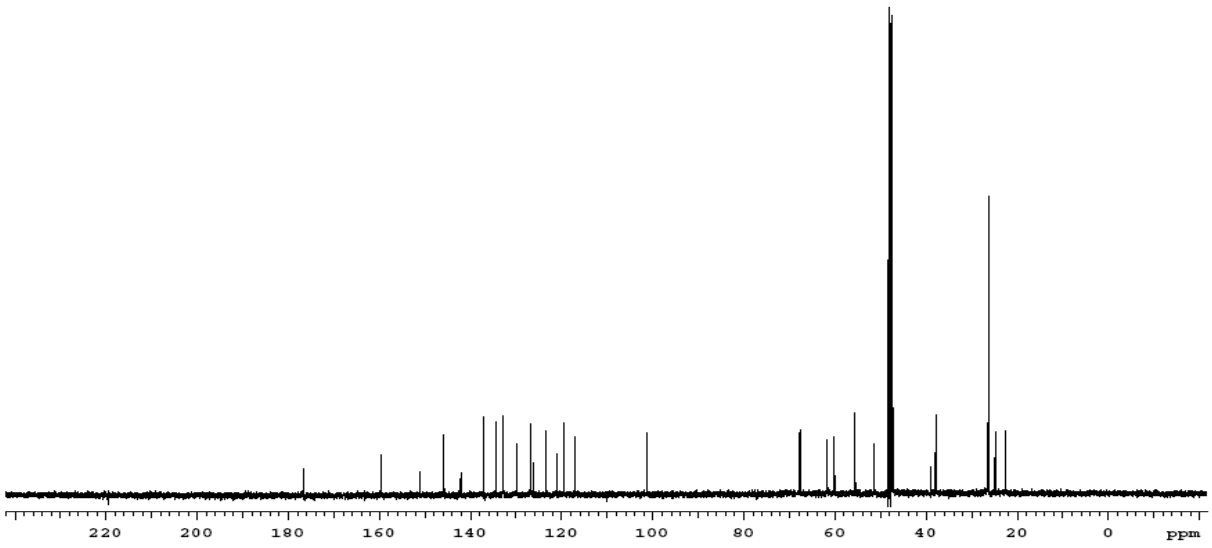
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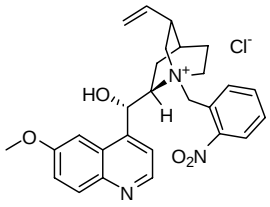
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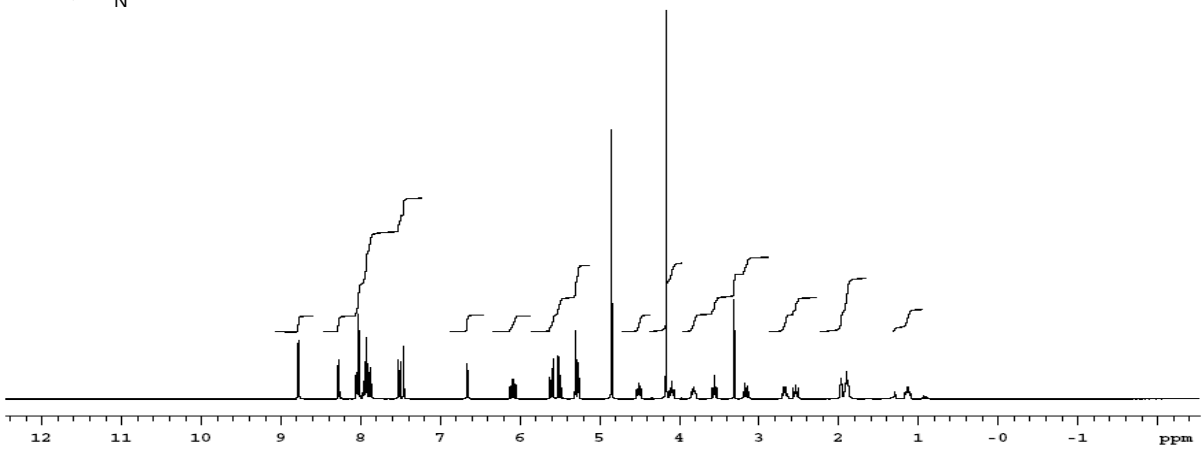
HO
H
O
O2N
N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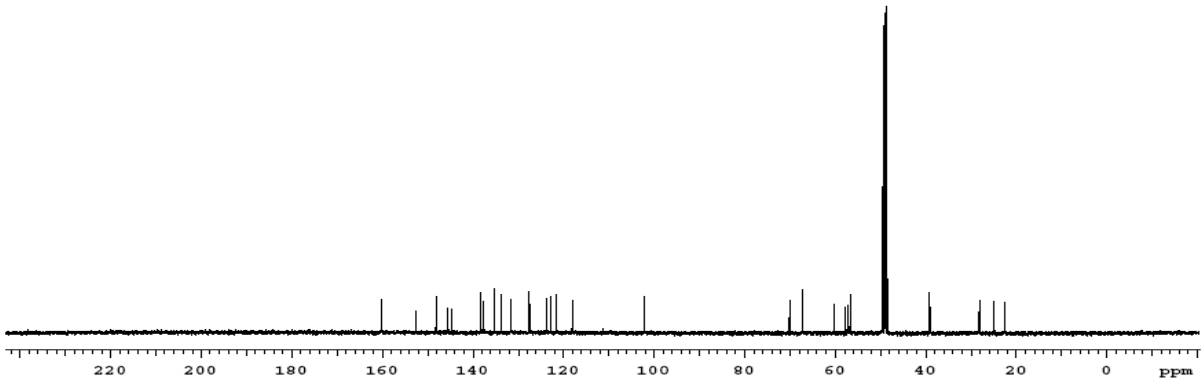
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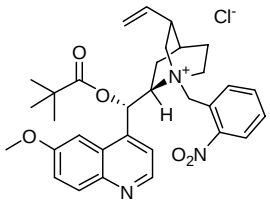
Cl-
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O
N+
H
O
O2N
N

QD-6c

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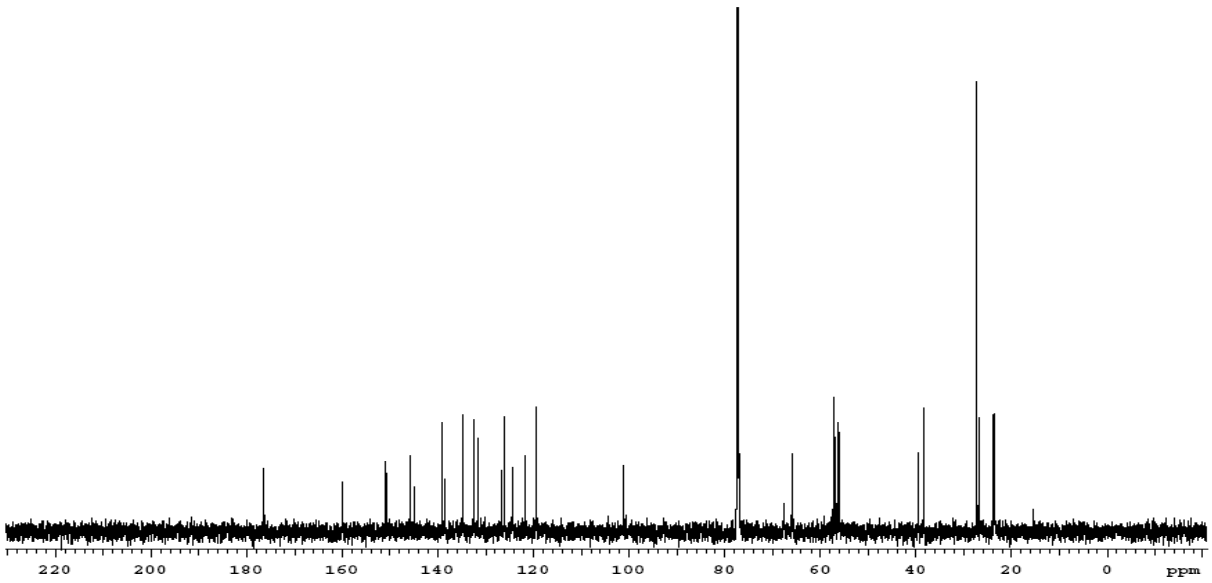
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ppm