Supplementary material

Marcin Drop[a] Xavier Bantreil,[b] Katarzyna Grychowska,[a] Gilbert Umuhire Mahoro,[b] Evelina Colacino,[b] Maciej Pawłowski,[a] Jean Martinez,[b,c] Gilles Subra,[c] Pawel Zajdela and Frédéric Lamaty*[b]

[a] *Department of Medicinal Chemistry, Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Krakow, Poland.*
[b] *Institut des Biomolécules Max Mousseron (IBMM) UMR 5247, CNRS, Université de Montpellier, ENSCM, Université de Montpellier Campus Triolet Place Eugène Bataillon 34095 Montpellier cedex 5, France. E-mail: frederic.lamaty@umontpellier.fr*
[c] *Institut des Biomolécules Max Mousseron (IBMM) UMR 5247, CNRS, Université de Montpellier, ENSCM, Bâtiment E, Faculté de Pharmacie 15, avenue Charles Flahault BP14491 34093 Montpellier cedex 5, France.*

Table of contents

General considerations

Organic transformations were carried out at ambient temperature, unless indicated otherwise. Organic solvents used in this study were of reagent grade and were used without purification. All other commercially available reagents were of the highest purity (from Sigma Aldrich, Alfa Aesar, Fluorochem, TCI). Metathesis catalysts used were either purchased from Sigma Aldrich, Apeiron-Synthesis (NO_2-Grela) or given by Umicore AG & Co. KG and Materia Inc. All workup and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Substrates **1a-g** were prepared according to literature.[1]
Continuous flow experiments were performed using a Uniqsis Flowsyn Multi-X equipment connected to an automated fraction collector (Fig. 1). A 5 mL high temperature PTFE coil reactor was set-up. Flow rates were adapted to ensure an appropriate residence time in the reaction coil.

Figure 1. Flowsyn Multi-X equipment

HPLC analyses were performed with an Agilent model 1220 instrument at 214 nm using: column Phenomenex® Onyx Monolithic HD-C18, 2m, (50 x 4.6 mm), flow 3 ml/min, H_2O (0.1 % TFA)/CH_3CN (0.1 % TFA), gradient 0-0 % (30 s), 0-100 % (3 min) and 100 % (1 min).
^1H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 101 MHz (Bruker Avance III) or at 600 MHz and 150 MHz (Bruker Avance III) using $CDCl_3$, as solvent. Chemical shifts are given in ppm. The *J* values are reported in Hertz (Hz), and the splitting patterns are designated as follows: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet), bs (broad singlet).

General procedure

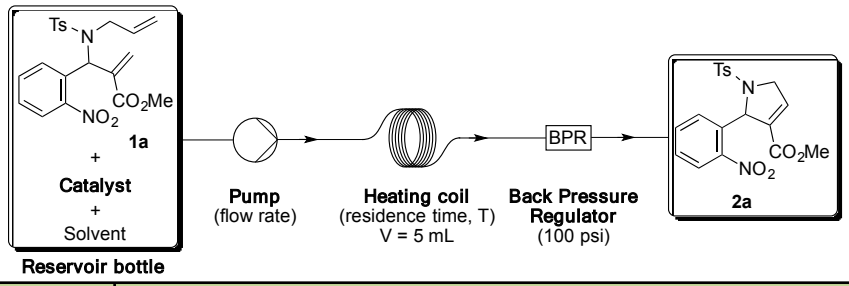
Flow Procedure using one pump. The mixture of substrate (1 mmol), catalyst (0.03 mmol, 3 mol%) and dimethylcarbonate (8 mL, 0.125 mmol) was prepared in a vial. After setting the temperature to 120°C, the valve position was switched to place the mixture inline. The reaction mixture was then flowed into the 5mL PTFE residence coil and then through a back-pressure-regulator (BPR) rated to 6.9 bars (100 psi). The collected sample was quenched with ethylvinyl ether to stop the reaction before drying under reduced pressure. Then the residue was diluted with dichloromethane and filtrated through a layer of silica gel (about 1g). The filtrate was evaporated and the obtained residue was treated with diethyl ether giving a grey-white precipitate, which was filtrated off and dried under reduced pressure.

Flow Procedure using two pumps. A solution of substrate **1a** (430.5 mg, 1 mmol) in dimethylcarbonate (4 mL) was prepared and connected to pump A. Similarly, a solution of **M2** (28.5 mg, 0.03 mmol) in dimethyl carbonate (4 mL) was prepared and connected to pump B. After setting the temperature to 120°C, both valve positions were switched to place the mixture inline. Solution A and B, pumped using pump A and pump B, respectively, were flowed in a T-shaped mixer, then into the 5mL PTFE residence coil and then through a back-pressure-regulator (BPR) rated to 6.9 bars (100 psi) at a flow rate ensuring a 1 min residence time (5 $mL.min^{-1}$). The collected sample was quenched with ethylvinyl ether to stop the reaction before drying under reduced pressure. Then the residue was

diluted with dichloromethane and filtrated through a layer of silica gel (about 1g). The filtrate was evaporated and the obtained residue was treated with diethyl ether giving a grey-white precipitate, which was filtrated off and dried under reduced pressure. Pure compound (334.0 mg, 83% yield) was obtained as a grey-white solid.

Optimization of the reaction conditions

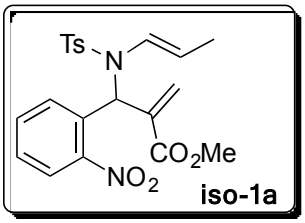
Table S1. Optimization of the reaction conditions[a]



Solvent	T (°C)	Residence Time (min)	HPLC Conv. (%)									
			G-II	NO_2-Grela	HG-II	$M5_1$	$M5_2$	M2		M20	$M3_1$	$M2_2$
			3mol%	*3mol%*	*3mol%*	*3mol%*	*3mol%*	*2mol%*	*3mol%*	*3mol%*	*3mol%*	*3mol%*
DCM	90	20							92 (0)			
		30	72 (2)	74 (2)	94 (3)	96 (<1)	14 (0)	84 (0)	98 (0)	94 (0)	25 (0)	35 (3)
		50						84 (0)	88 (0)			
	100	5	68 (3)	70 (2)		85 (0)	10 (0)		86 (<1)	93 (0)	25 (0)	
		10							93 (<1)	94 (0)		
		20							95 (<1)			
		30							84 (<1)			
	110	5						85 (0)	94 (0)	89 (0)		
		10							95 (0)			
		20							95 (0)			
AcOEt	90	30	75 (1)	73 (2)	95 (4)	85 (0)	22 (0)		23 (0)	60 (<1)	23 (0)	88 (<1)
	100	30							51 (2)			
		60							74 (1)			
	110	30							75 (1)			
DMC	90	30	74 (1)	84 (2)	94 (4)	82 (0)	10 (0)	77 (2)	98 (0)	50 (1)	21 (0)	75 (<1)
		50						85 (1)				
	100	10							92 (1)			
		20							98 (0)			
		30				73 (<1)			97 (0)			
	110	1							84 (2)			
		5	76 (1)	85 (3)	94 (5)	78 (0)	7 (0)		98 (0)	57 (1)	11 (0)	77 (3)
		10							97 (0)			
	120	1	71 (2)	73 (2)	85 (4)	69 (1)	5 (0)		96 (0)	46 (2)	19 (0)	53 (2)
		5							96 (0)			
		30										96 (<1)
	130	1										79 (3)
		5										92 (1)
		10										92 (1)

[a] Reaction conditions: **1a** (0.125 mmol), catalyst (3 mol%), solvent (1 mL), T, residence time. HPLC conversion of **1a** into **2a** is given. Ratio of isomer **iso-1a** is given in brackets.

Isomer **iso-1a** was isolated after 2.0 mmol scale RCM using **HG-II** (conditions from Table 1, entry 4 (DMC, 110°C, 5 min)) and fully characterized (see below).



Description of compounds

Methyl (*Z*)-2-(((4-methyl-*N*-(prop-1-en-1-yl)phenyl)sulfonamido)(2-nitrophenyl)methyl) acrylate (Iso-1a)

^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.94 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.64 (td, *J* = 7.7, 1.2 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.47 (td, *J* = 7.2, 1.2 Hz, 1H), 7.23 (d, *J* = 7.8 Hz 2H), 6.97 (s, 1H), 6.47 (s, 1H), 6.02 (dd, *J* = 13.8, 1.6 Hz, 1H), 5.53 (d, *J* = 1.2 Hz, 1H), 5.45 (dq, *J* = 13.5, 6.7 Hz, 1H), 3.56 (s, 3H), 2.41 (s, 3H), 1.62 (dd, *J* = 6.7, 1.6 Hz, 3H).
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 165.6, 148.1, 143.6, 137.8, 137.2, 134.2, 133.4, 131.0, 130.8, 129.4, 128.9, 127.9, 125.8, 125.4, 121.1, 58.9, 52.3, 21.7, 15.7.
HRMS calculated for $C_{21}H_{23}N_2O_6S$: 431.1277. Found: 431.1274.

Methyl 2,5-dihydro-2-(2-nitrophenyl)-1-tosyl-1*H*-pyrrole-3-carboxylate (2a)

White solid, 87% yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.90 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.61 – 7.51 (m, 2H), 7.41 (ddd, *J* = 8.5, 5.3, 3.5 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.75 (dd, *J* = 4.0, 2.0 Hz, 1H), 6.73 – 6.65 (m, 1H), 4.61 (ddd, *J* = 17.4, 6.0, 2.0 Hz, 1H), 4.36 (dt, *J* = 17.4, 2.7 Hz, 1H), 3.53 (s, 3H), 2.43 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 161.7, 148.9, 144.3, 136.7, 135.8, 135.2, 133.5, 133.3, 130.2, 129.8, 128.7, 127.9, 124.7, 62.4, 55.8, 52.2, 21.7.
Data in agreement with lit.[2]

Methyl 2-(2-chlorophenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (2b)

White solid, 91% yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (d, J = 8.2 Hz, 2H), 7.31 – 7.27 (m, 1H), 7.25 – 7.11 (m, 5H), 6.81 – 6.79 (m, 1H), 6.17 – 6.12 (m, 1H), 4.59 – 4.42 (m, 2H), 3.57 (s, 3H), 2.39 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 162.1, 143.7, 137.3, 136.5, 134.9, 134.86, 133.8, 130.0, 129.9, 129.8, 129.2, 127.5, 127.0, 65.5, 55.6, 52.0, 21.6.
Data in agreement with lit.[3]

Methyl 2-(2-methoxyphenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (2c)

White solid, 88% yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.17 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.88 (td, *J* = 7.5, 0.9 Hz, 1H), 6.76 (dd, *J* = 4.0, 2.0 Hz, 1H), 6.68 – 6.64 (m, 1H), 6.00 (dt, *J* = 6.0, 1.9 Hz, 1H), 4.51 (dt, *J* = 16.5, 2.4 Hz, 1H), 4.37 (ddd, *J* = 16.5, 6.1, 1.9 Hz, 1H), 3.56 (s, 6H), 2.36 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 162.5, 157.6, 142.9, 136.2, 135.9, 134.3, 130.5, 129.4, 129.3, 127.2, 126.9, 120.6, 111.1, 65.1, 55.5, 55.4, 51.8, 21.6.
Data in agreement with lit.[1]

Methyl 2-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3- carboxylate (2d)

White solid, 92% yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.18 (m, 5H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.78 (dd, *J* = 3.8, 2.0 Hz, 1H), 5.74 (dt, *J* = 5.7, 2.0 Hz, 1H), 4.51 (dt, *J* = 17.1, 2.4 Hz, 1H), 4.38 (ddd, *J* = 17.1, 5.8, 1.9 Hz, 1H), 3.58 (s, 3H), 2.37 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 162.3, 143.4, 139.5, 135.8, 135.7, 129.6, 128.4, 128.2, 127.9, 127.2, 69.1, 55.0, 51.9, 21.6.
Data in agreement with lit.[4]

Methyl 2-(3-methoxyphenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (2e)

White solid, 52% yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42 (d, *J* = 7.6 Hz, 2H), 7.20 – 7.07 (m, 3H), 6.84 (d, *J* = 7.3 Hz, 1H), 6.77 (s, 2H), 6.67 (s, 1H), 5.71 (s, 1H), 4.51 (d, *J* = 16.9 Hz, 1H), 4.37 (dd, *J* = 16.9, 4.5 Hz, 1H), 3.71 (s, 3H), 3.59 (s, 3H), 2.36 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 162.3, 159.6, 143.4, 140.8, 135.9, 135.8, 129.5, 129.4, 127.2, 120.5, 113.7, 113.4, 69.0, 55.2, 55.1, 52.0, 21.6.

Data in agreement with lit.[1]

Methyl 2-(4-chlorophenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (2f)
White solid, 68% yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45 (d, *J* = 8.1 Hz, 2H), 7.18 (q, *J* = 8.6 Hz, 6H), 6.78 (s, 1H), 5.68 (d, *J* = 5.3 Hz, 1H), 4.50 (d, *J* = 17.2 Hz, 1H), 4.39 (dd, *J* = 16.5, 5.0 Hz, 1H), 3.59 (s, 3H), 2.39 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 162.2, 143.8, 138.2, 136.1, 135.5, 135.4, 134.0, 129.7, 129.2, 128.6, 127.2, 68.4, 55.1, 52.0, 21.6.
Data in agreement with lit.[1]

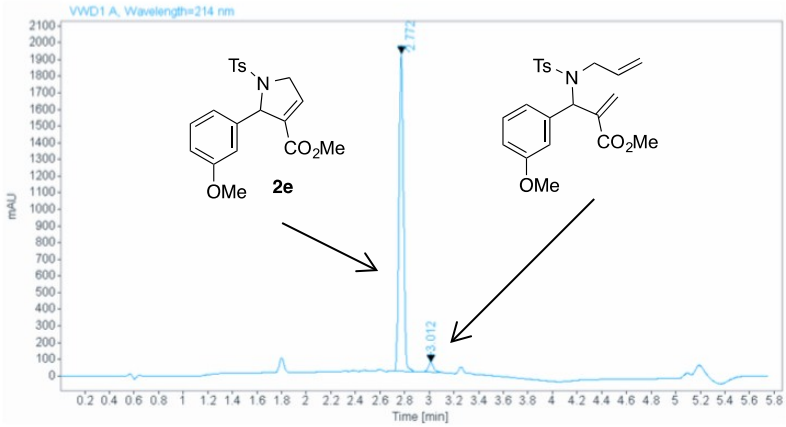
Methyl 2-(4-methoxyphenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (2g)
White solid, 81% yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43 (d, *J* = 8.2 Hz, 2H), 7.14 (t, *J* = 8.1 Hz, 4H), 6.76 (d, *J* = 8.5 Hz, 3H), 5.70 (d, *J* = 5.5 Hz, 1H), 4.48 (dt, *J* = 17.0, 2.3 Hz, 1H), 4.35 (ddd, *J* = 17.1, 5.7, 1.8 Hz, 1H), 3.77 (s, 3H), 3.59 (s, 3H), 2.37 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 162.4, 159.5, 143.3, 135.8, 135.5, 131.7, 129.6, 129.0, 127.2, 113.8, 68.6, 55.4, 54.9, 51.9, 21.6.
Data in agreement with lit.[1]

HPLC chromatograms for the synthesis of 2e and 2f

Since compounds **2e** and **2f** could not be isolated in high yields, HPLC chromatograms recorded after the reaction are provided to demonstrate that conversion was almost complete in both cases, with no degradation nor side-products.

Description:
Injection volume: 5.000

Instrument: Agilent1220
Injection date: 5/27/2016 11:42:20 AM
Acq. method: 0a100_3min_214nm.M

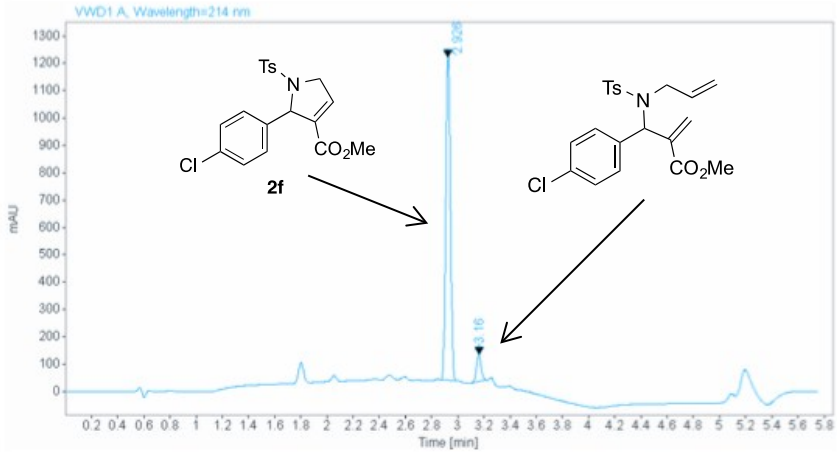


Signal: VWD1 A, Wavelength=214 nm

RT [min]	Area	Height	Peak Area Percent
2.772	4849.06787	1910.50439	96.74
3.012	163.26904	58.19406	3.26

Description:
Injection volume: 5.000

Instrument: Agilent1220
Injection date: 5/25/2016 5:56:25 PM
Acq. method: 0a100_3min_214nm.M

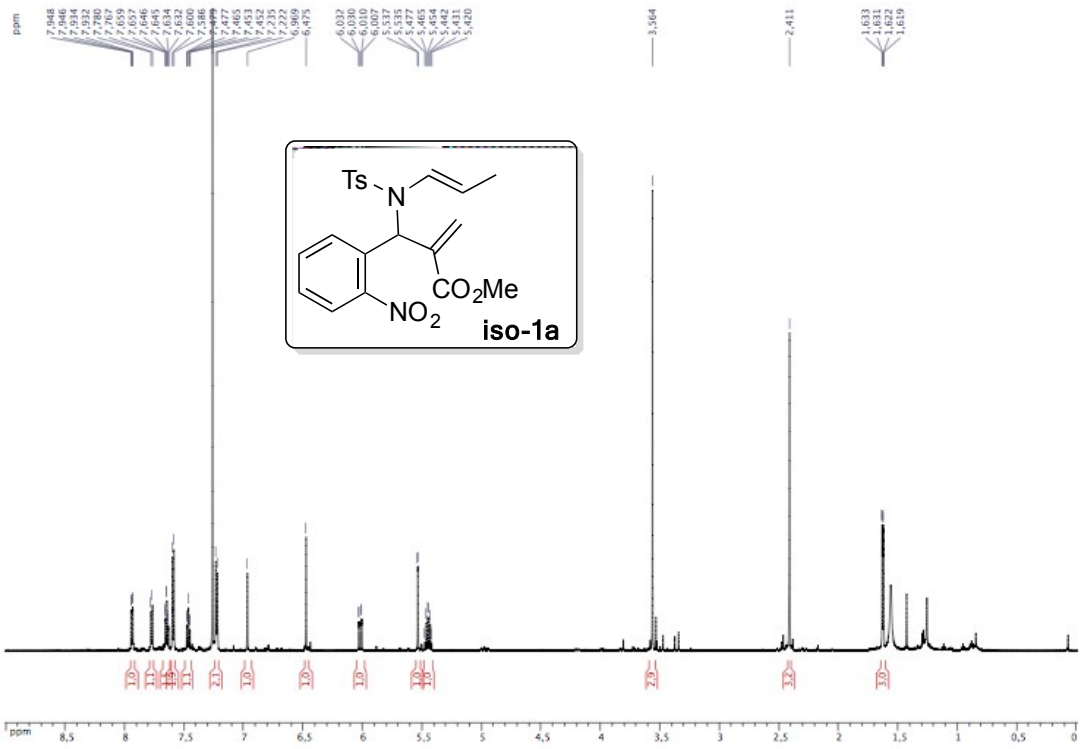


Signal: VWD1 A, Wavelength=214 nm

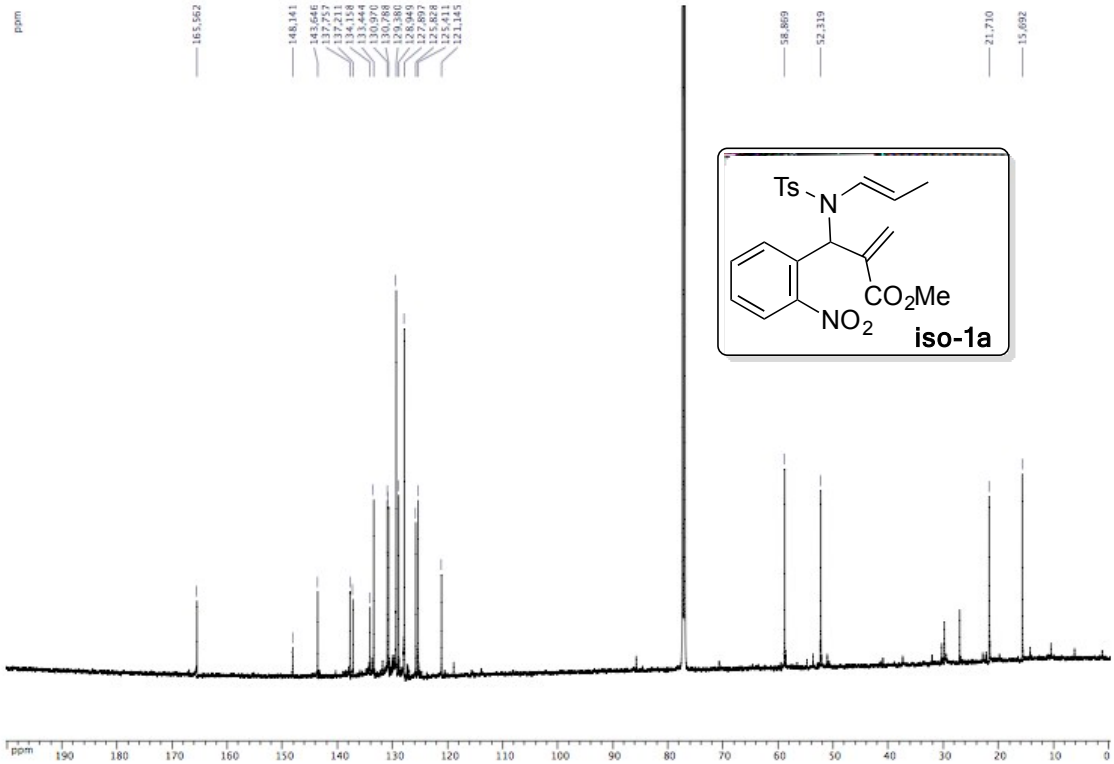
RT [min]	Area	Height	Peak Area Percent
2.926	2913.62500	1186.59692	92.46
3.160	237.46588	98.04047	7.54

NMR spectra of compounds iso-1a and 2a-g

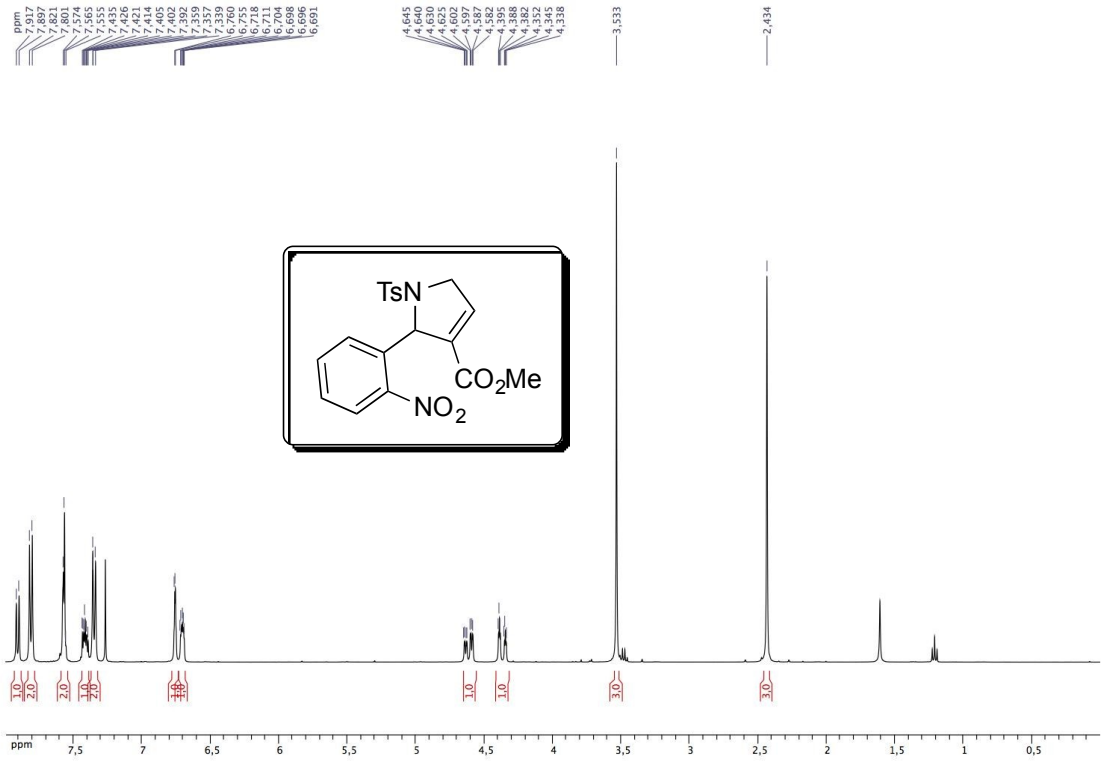
^{1}H NMR of Methyl (*E*)-2-(((4-methyl-*N*-(prop-1-en-1-yl)phenyl)sulfonamido)(2-nitrophenyl)methyl) acrylate **iso-1a**



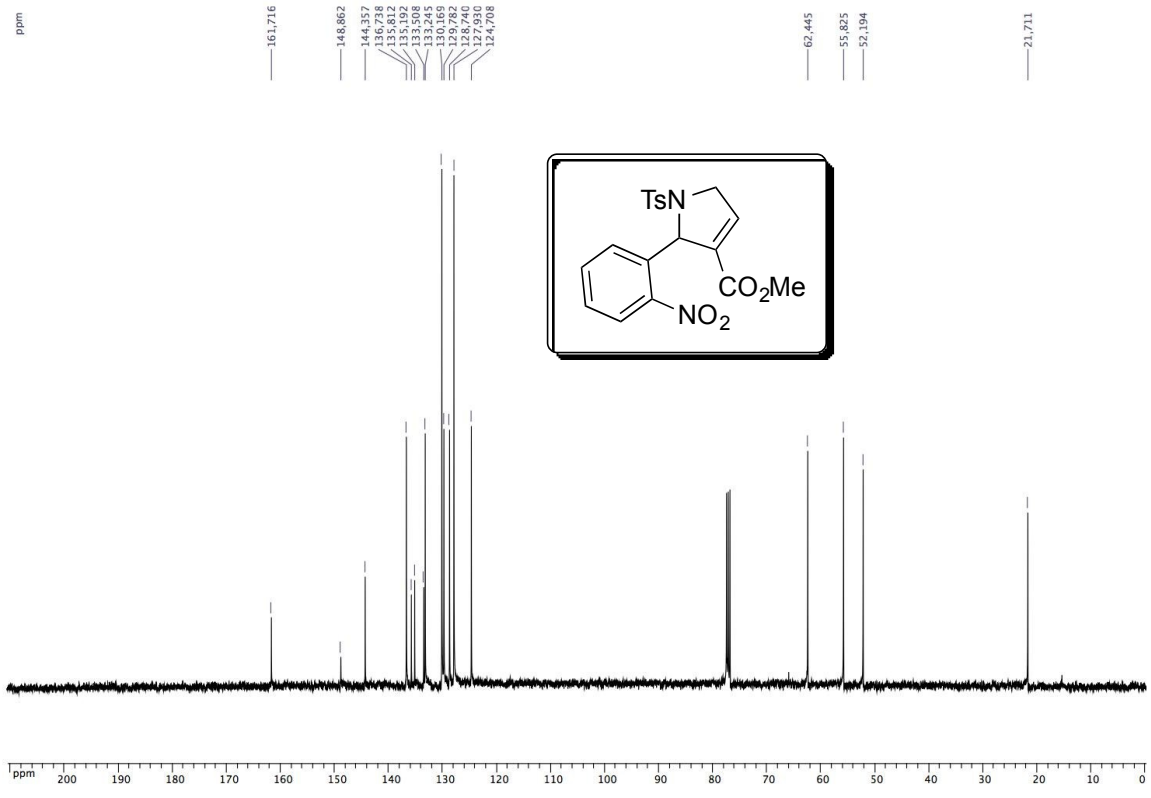
^{13}C NMR of Methyl (*E*)-2-(((4-methyl-*N*-(prop-1-en-1-yl)phenyl)sulfonamido)(2-nitrophenyl)methyl) acrylate **iso-1a**



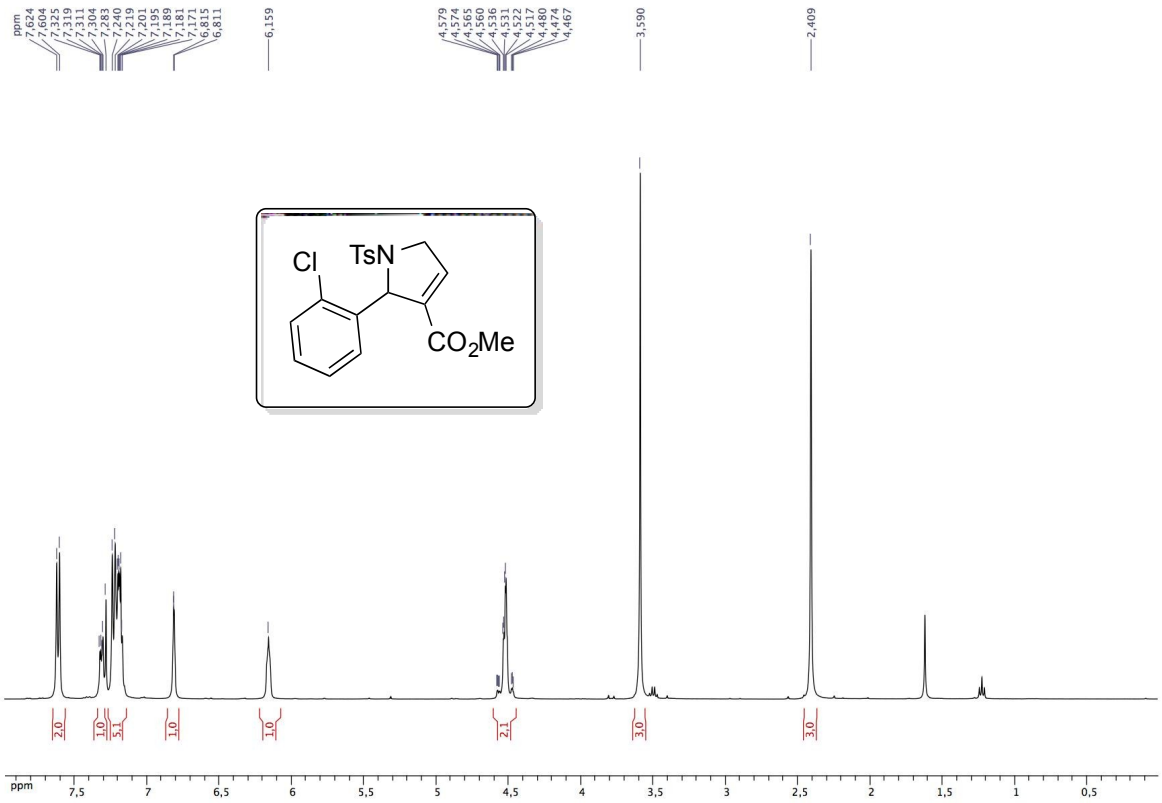
^{1}H NMR of Methyl 2,5-dihydro-2-(2-nitrophenyl)-1-tosyl-1*H*-pyrrole-3-carboxylate **2a**



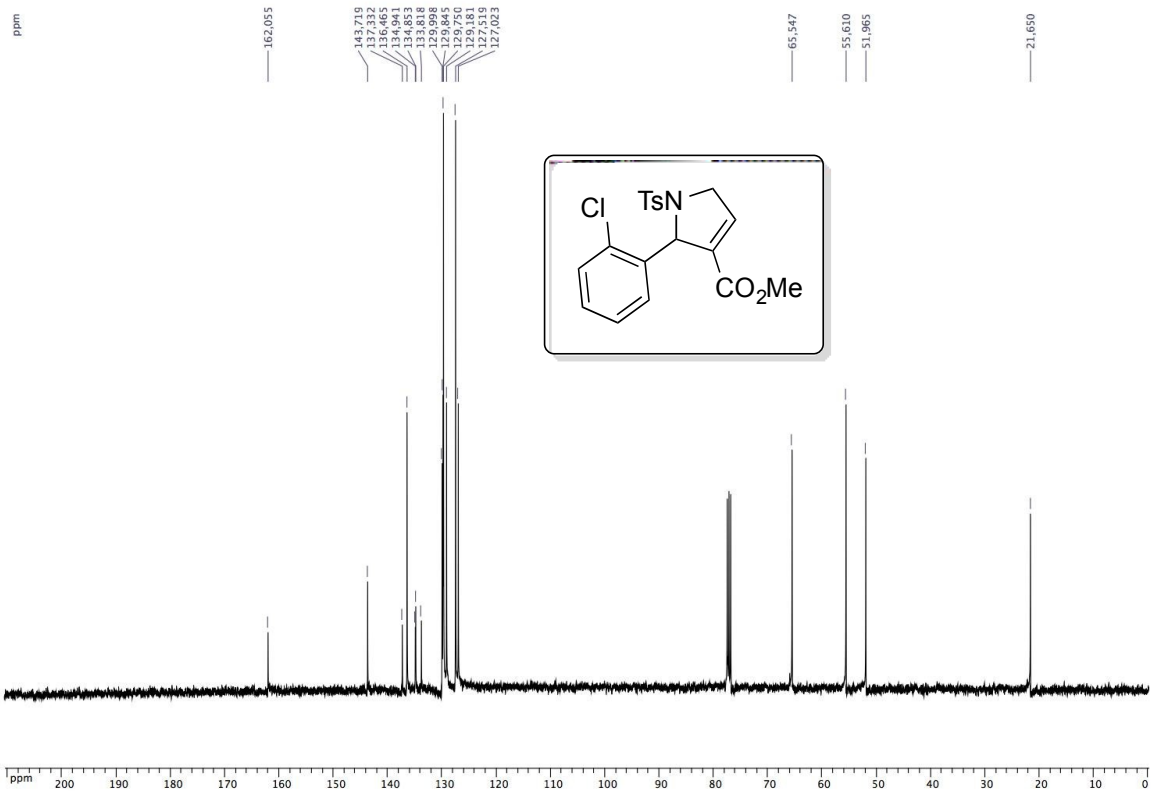
^{13}C NMR of Methyl 2,5-dihydro-2-(2-nitrophenyl)-1-tosyl-1*H*-pyrrole-3-carboxylate **2a**



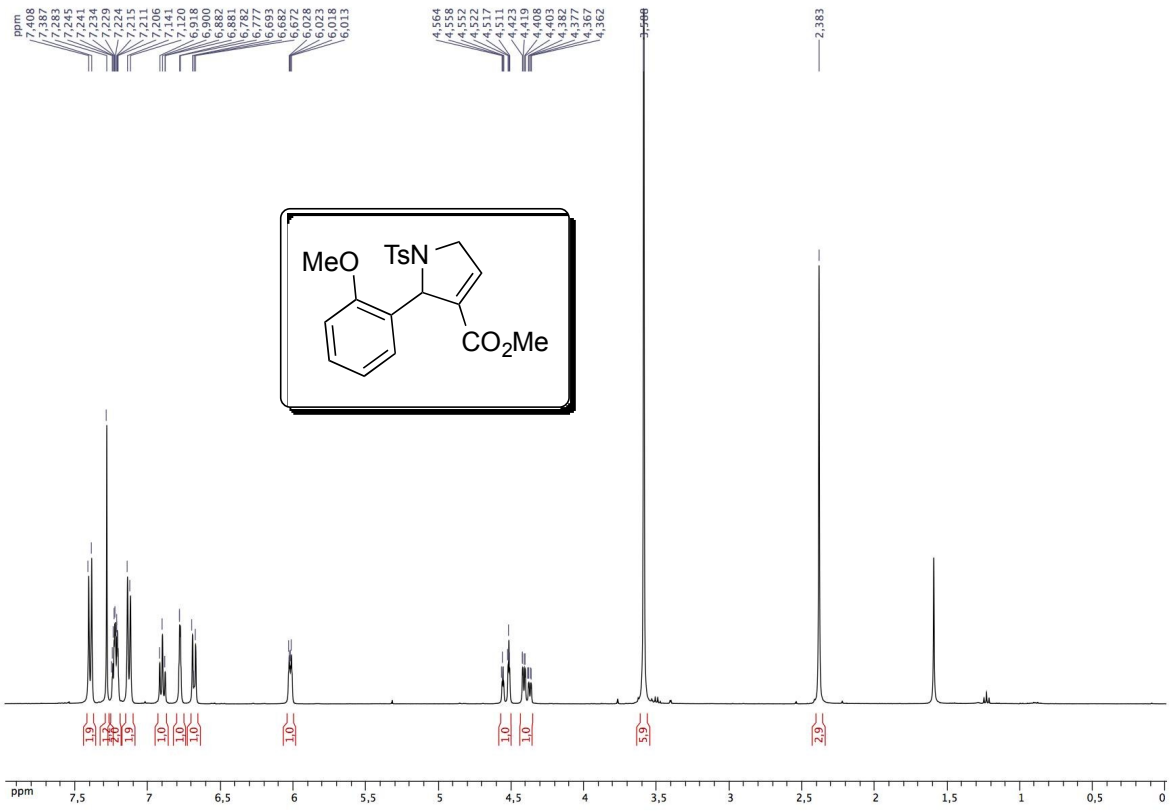
^{1}H NMR of Methyl 2-(2-chlorophenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **2b**



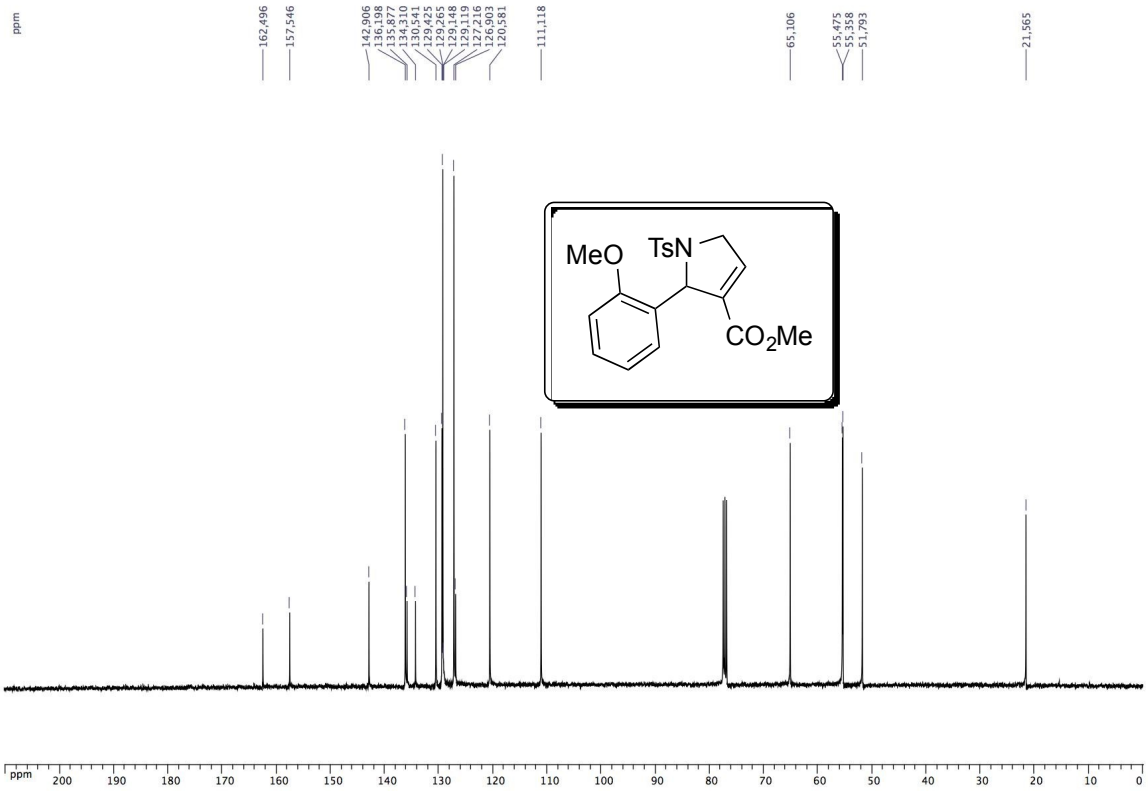
^{13}C NMR of Methyl 2-(2-chlorophenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **2b**



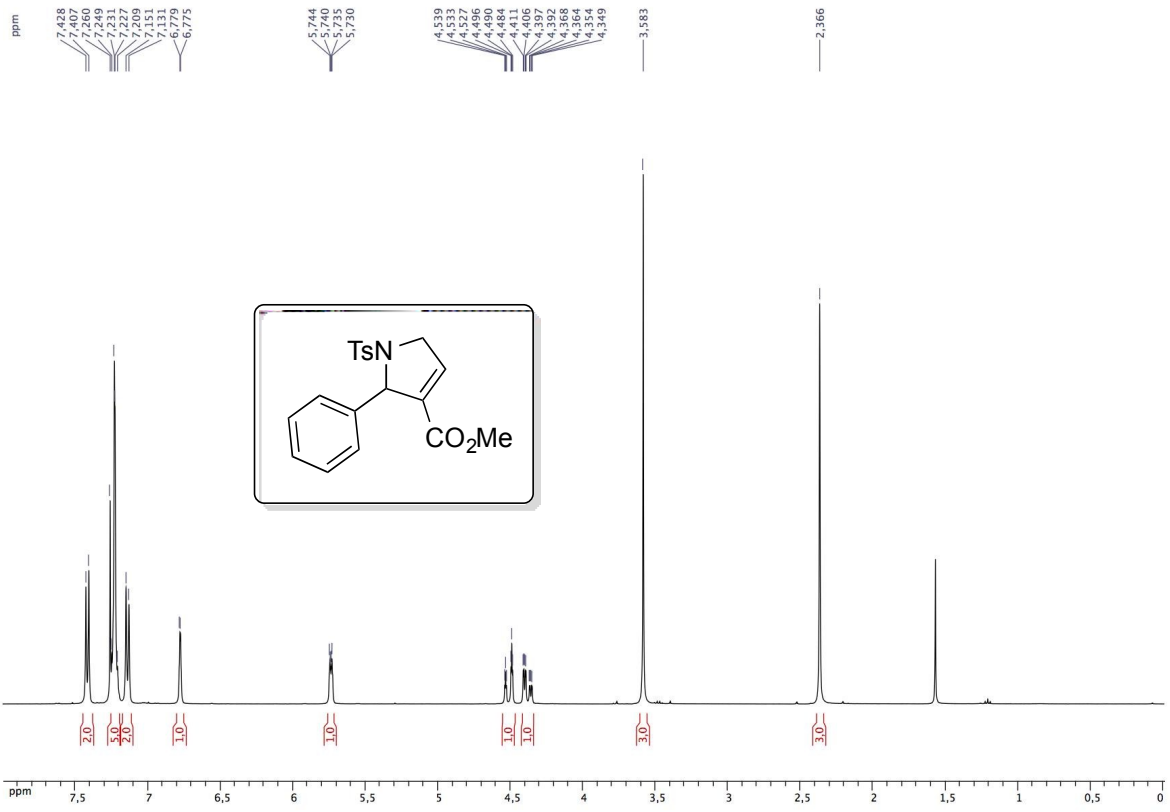
^{1}H NMR of Methyl 2-(2-methoxyphenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **2c**



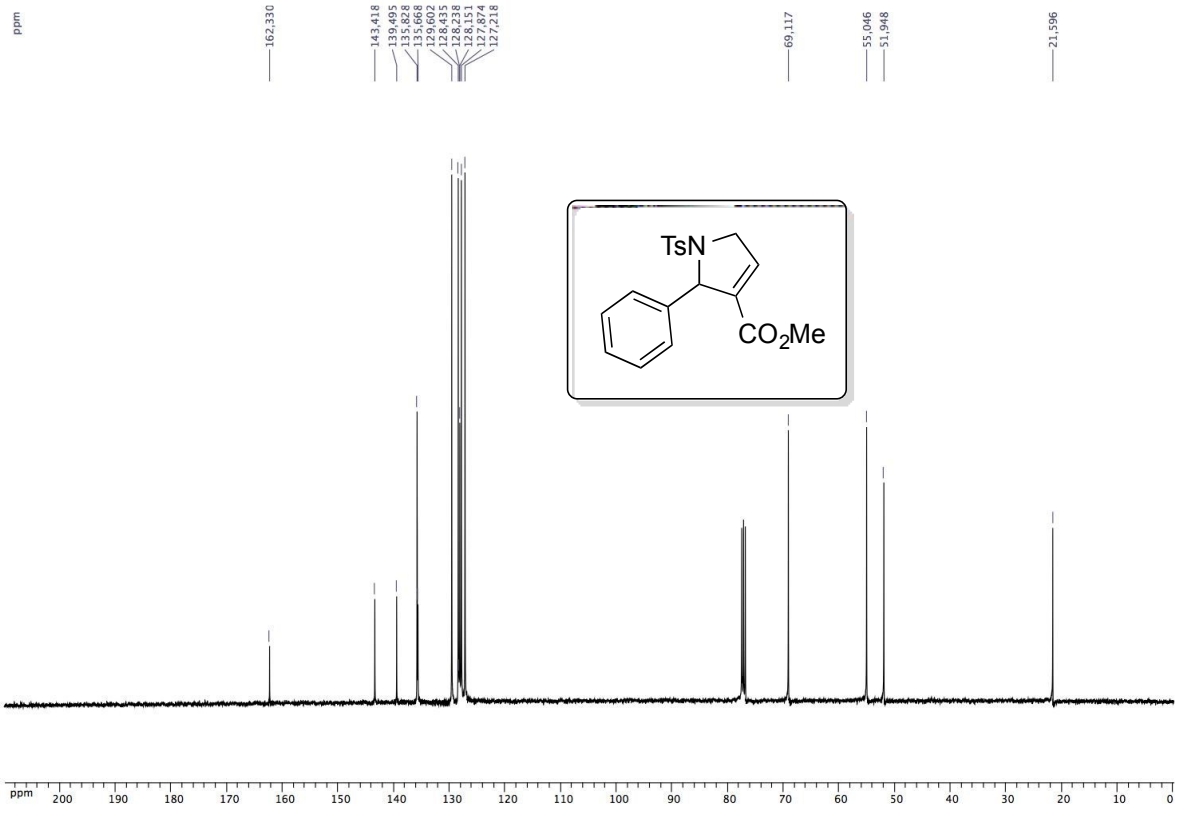
^{13}C NMR of Methyl 2-(2-methoxyphenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **2c**



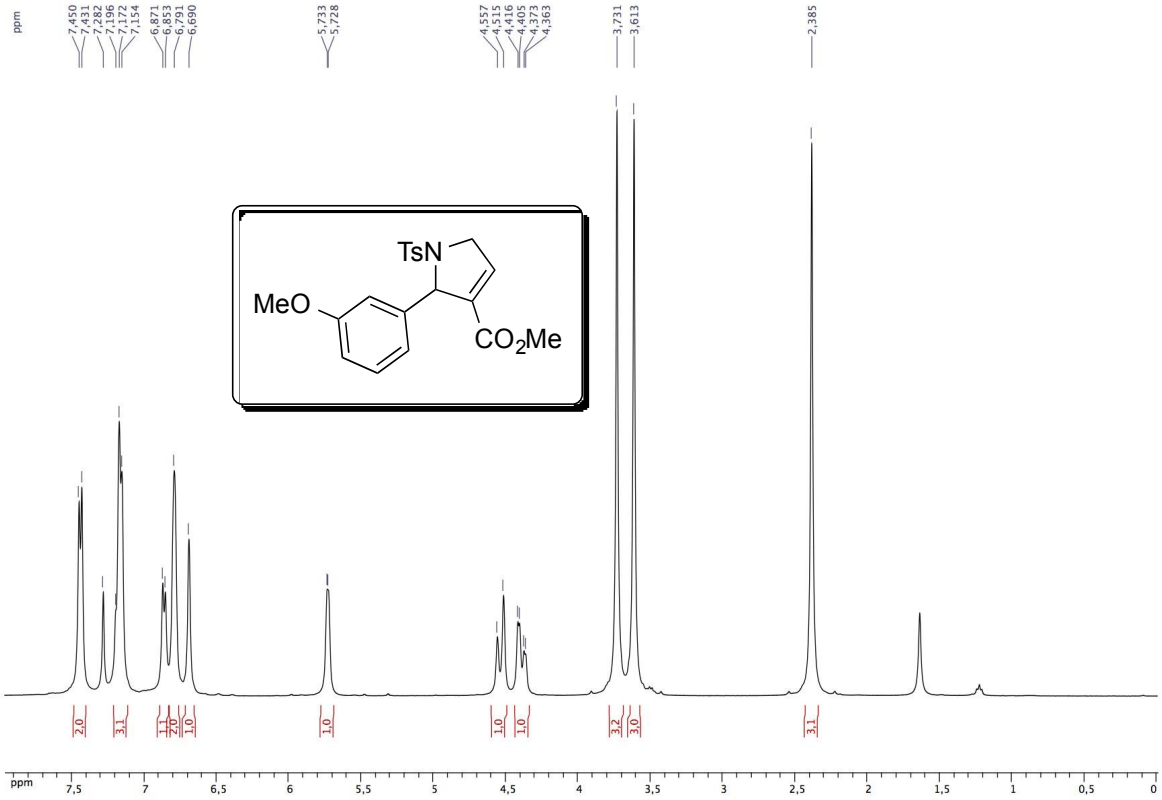
^{1}H NMR of Methyl 2-phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **2d**



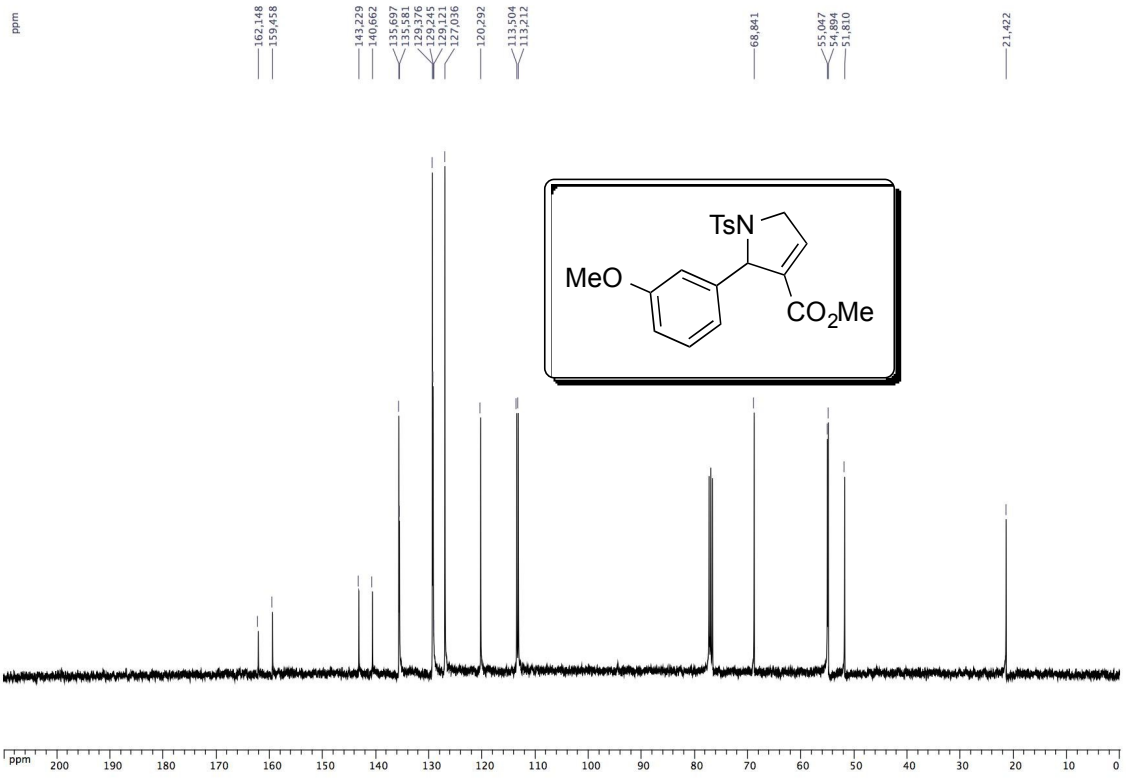
^{13}C NMR of Methyl 2-phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **2d**



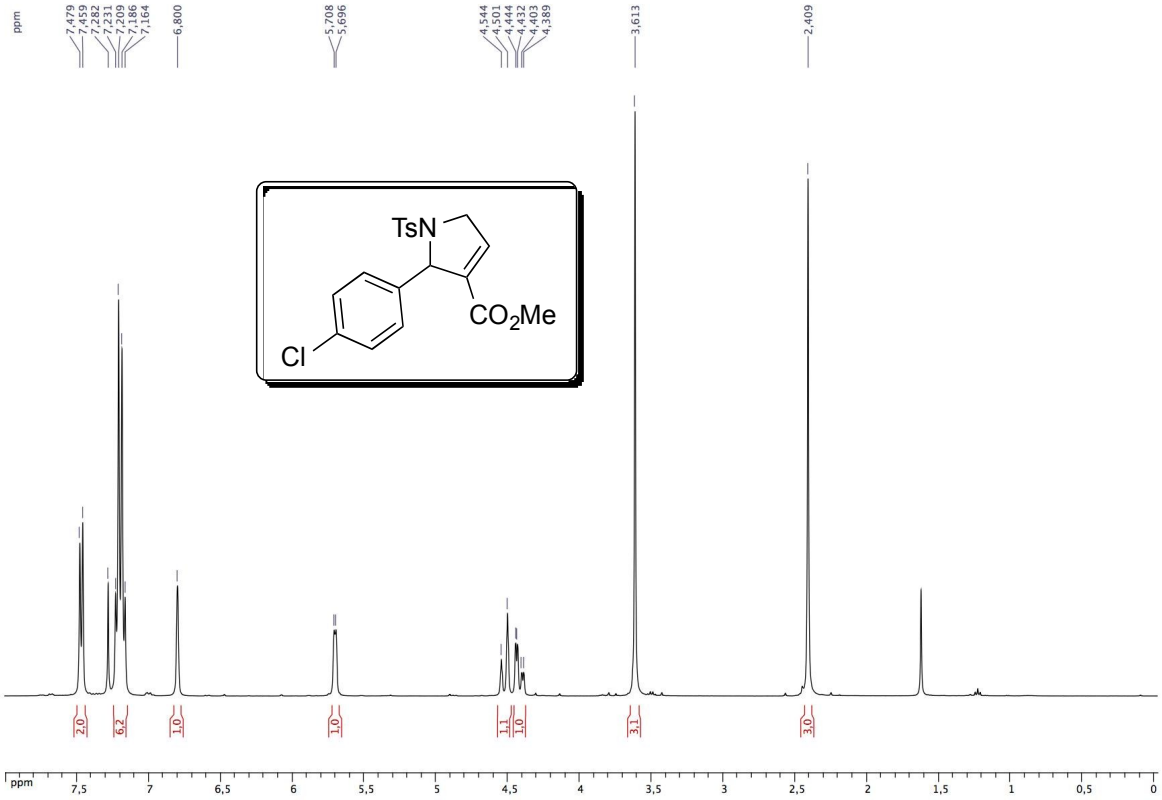
^{1}H NMR of Methyl 2-(3-methoxyphenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **2e**



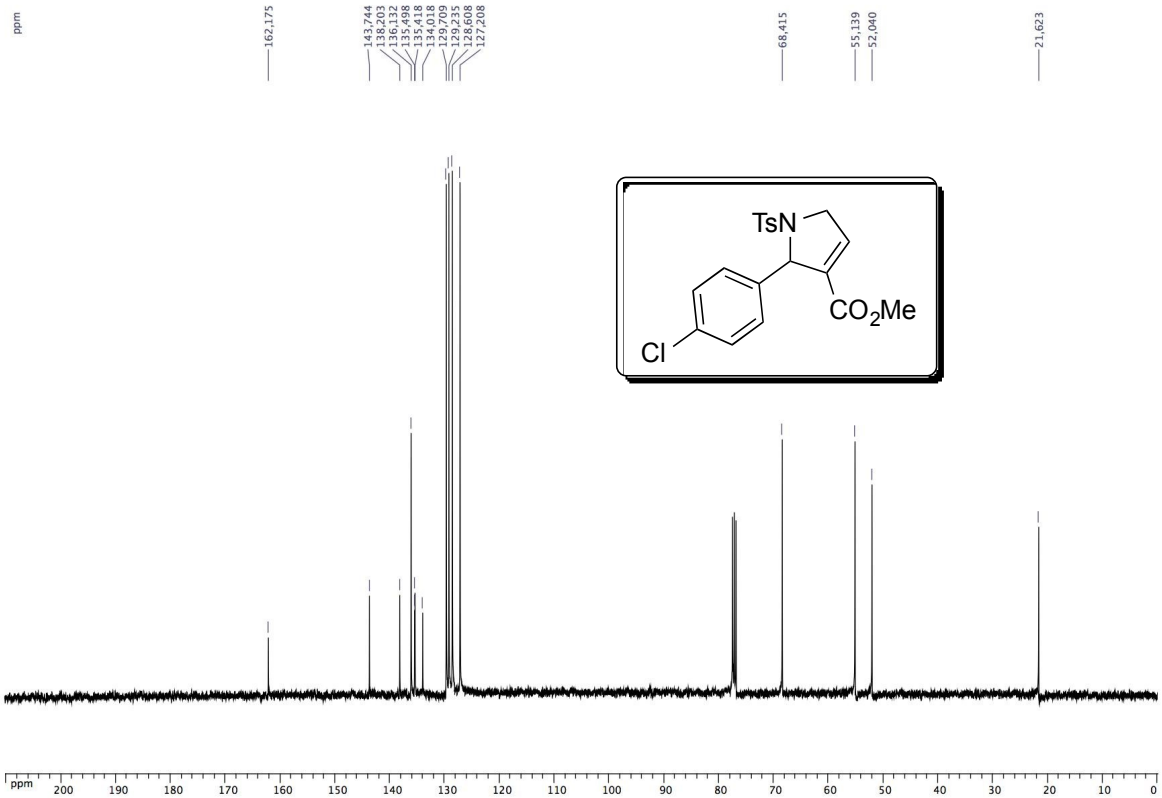
^{13}C NMR of Methyl 2-(2-methoxyphenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **2e**



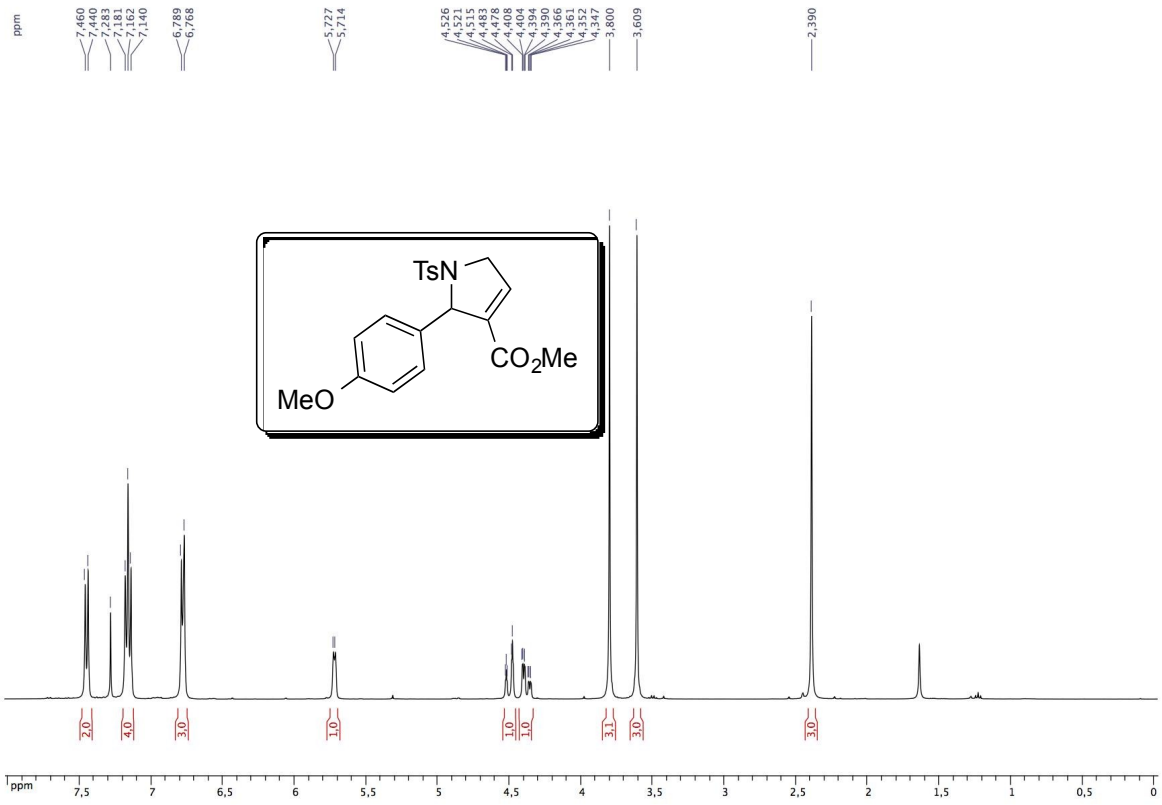
^{1}H NMR of Methyl 2-(4-chlorophenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **2f**



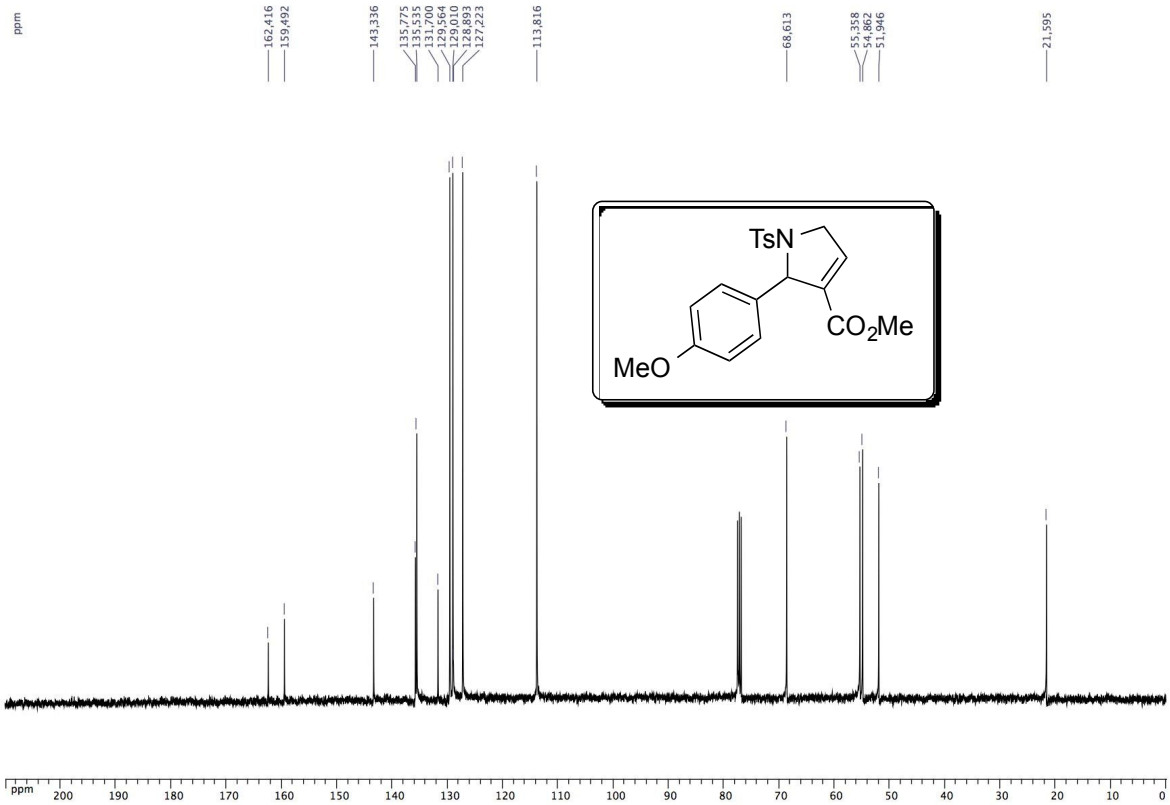
^{13}C NMR of Methyl 2-(4-chlorophenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **2f**



^{1}H NMR of Methyl 2-(4-methoxyphenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **2g**



^{13}C NMR of Methyl 2-(4-methoxyphenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **2g**



References

1. K. Grychowska, B. Kubica, M. Drop, E. Colacino, X. Bantreil, M. Pawłowski, J. Martinez, G. Subra, P. Zajdel and F. Lamaty, *Tetrahedron*, 2016, **72**, 7462.
2. (a) H. Benakki, E. Colacino, C. Andre, F. Guenoun, J. Martinez and F. Lamaty, *Tetrahedron*, 2008, **64**, 5949; (b) P. Zajdel, K. Grychowska, F. Lamaty, E. Colacino, X. Bantreil, J. Martinez, M. Pawlowski, G. Satala, A. J. Bojarski, A. Partyka, A. Wesolowska, T. Kos, P. Popik and G. Subra, WO2015012704A1, 29 January, 2015; (c) K. Grychowska, G. Satala, T. Kos, A. Partyka, E. Colacino, S. Chaumont-Dubel, X. Bantreil, A. Wesolowska, M. Pawlowski, J. Martinez, P. Marin, G. Subra, A. J. Bojarski, F. Lamaty, P. Popik and P. Zajdel, *ACS Chem. Neurosci.*, 2016, **7**, 972.
3. W. Sun, X. Ma, L. Hong and R. Wang, *J. Org. Chem.*, 2011, **76**, 7826.
4. D. J. Aldous, A. S. Batsanov, D. S. Yufit, A. J. Dalencon, W. M. Dutton and P. G. Steel, *Org. Biomol. Chem.*, 2006, **4**, 2912.