

Asymmetric Synthesis of 2-Substituted Azetidin-3-ones
via Metalated SAMP/RAMP Hydrazones

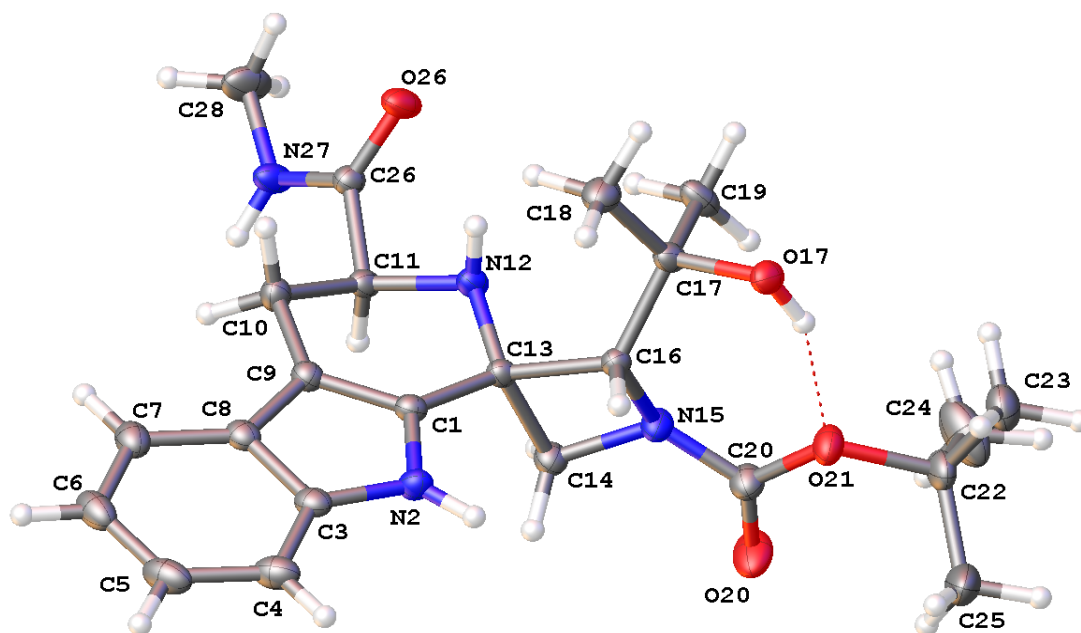
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Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, UK.

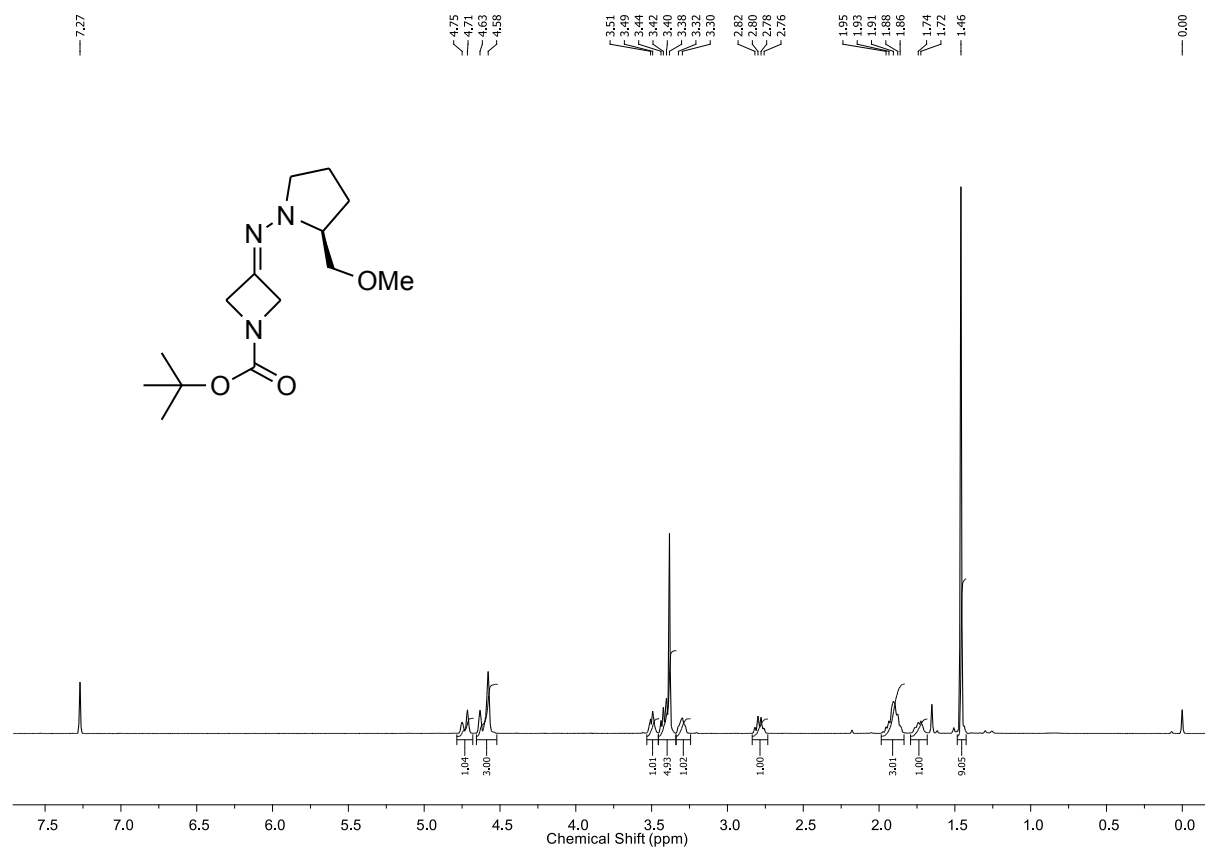
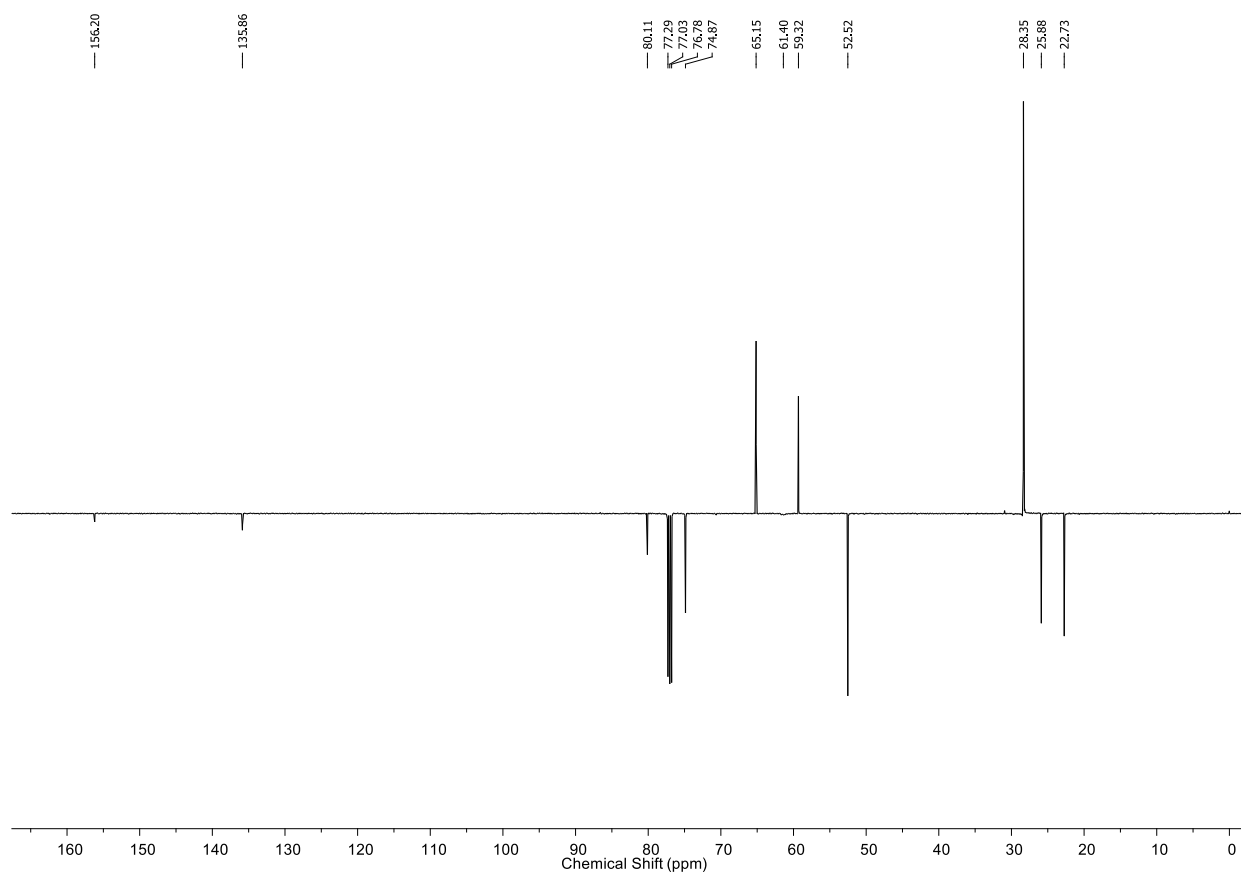
SUPPORTING INFORMATION

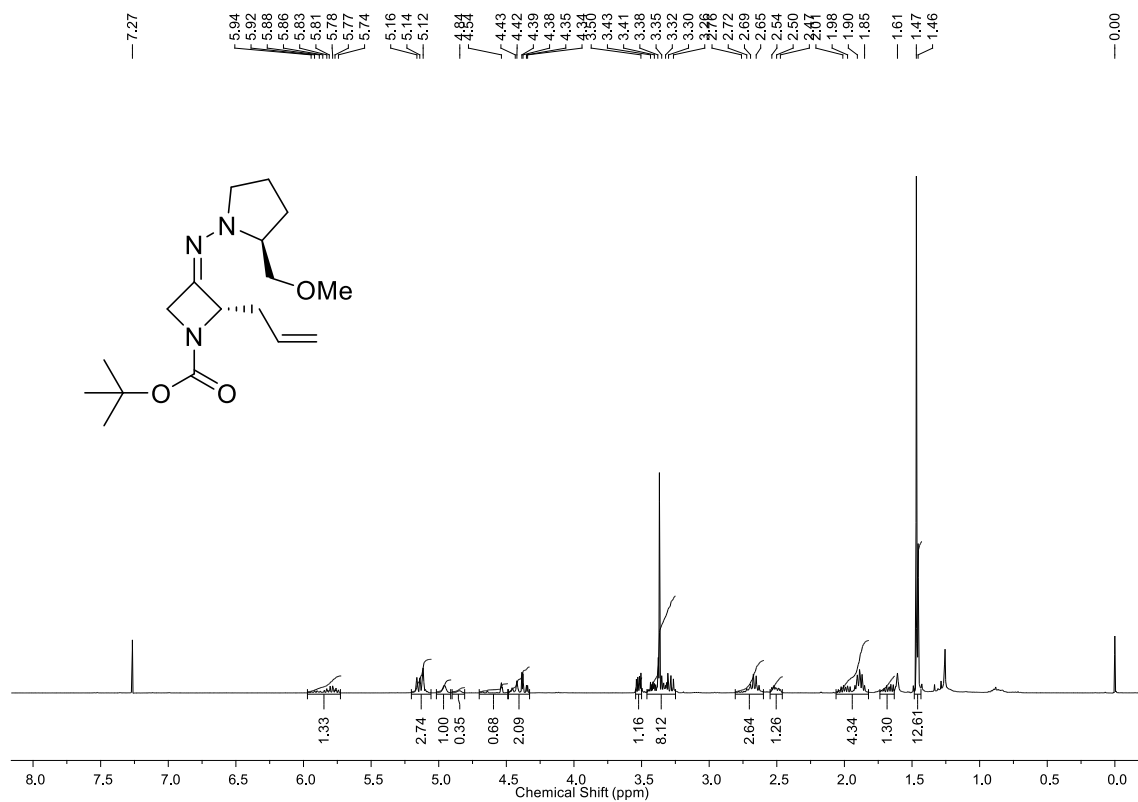
Depiction of X-ray structure of 16	S2
Copies of ¹ H and ¹³ C NMR spectra of compounds 1 and 3-16	S3-S17
Copies of chiral GC and HPLC chromatograms for determination of <i>ee</i> values	S18-S27
References	S28

X-ray crystal structure of 16 with thermal ellipsoids are drawn at 50% probability level:

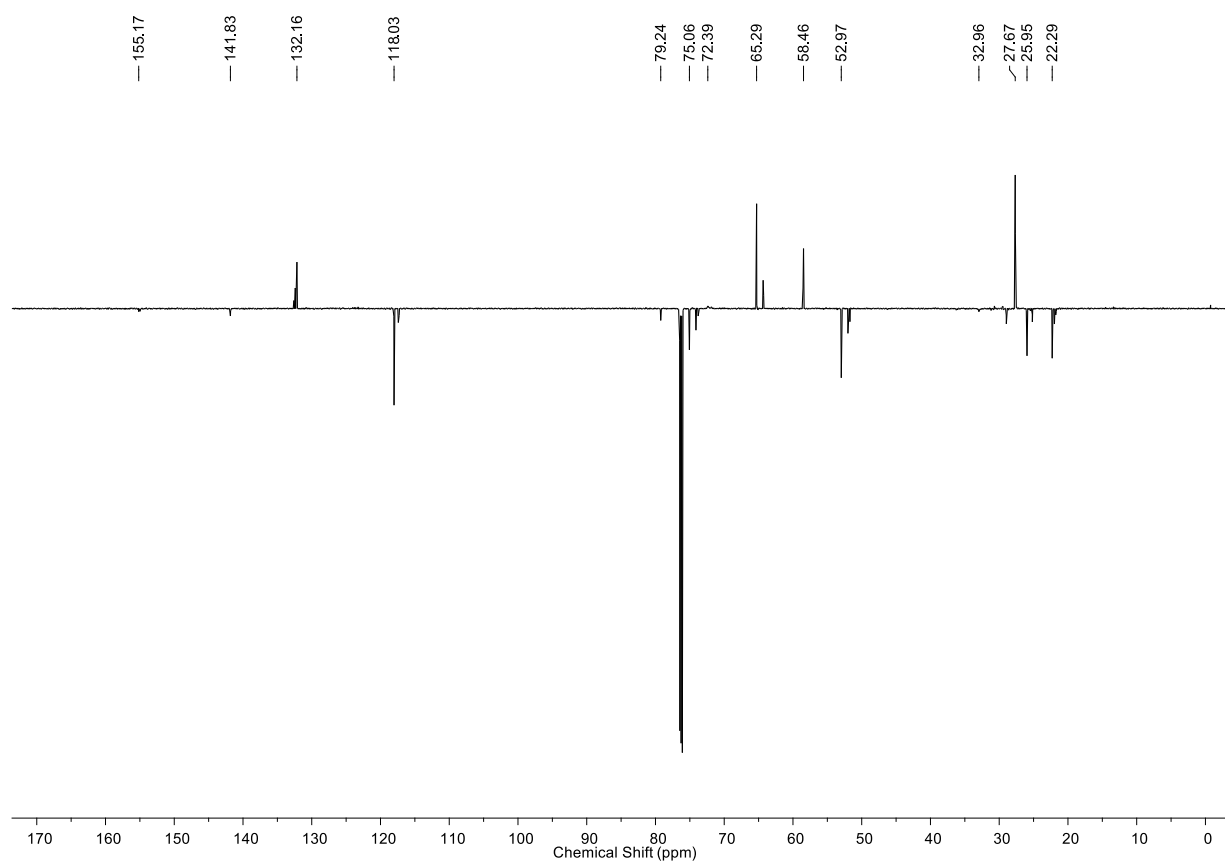


Single crystals of $C_{23}H_{32}N_4O_4$ (**16**) were grown from methanol. A suitable crystal was selected and mounted on a glass fibre with Fromblin oil and placed on a Rigaku SuperNova diffractometer (Dual source with Cu at zero), with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2¹, the structure was solved with the ShelXT² structure solution program using Direct Methods and refined with the ShelXL³ refinement package using Least Squares minimisation. The NHs and OH were located in a difference map but refined at calculated positions except the hydrogen on amine N12 which was allowed to refine freely but given thermal parameters Uiso 1.5 time Ueqiv of the parent atom. The Flack parameter of the crystal chosen was Flack x: 0.017(37) (ShelXL 2014) and is also confirmed by the known stereochemistry of the L-tryptophan starting material. This structure has been deposited in the Cambridge Crystallographic Data Centre (<http://www.ccdc.cam.ac.uk/>) as CCDC 1481935. **Crystal Data** for $C_{23}H_{32}N_4O_4$ ($M=428.52$ g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 9.24482(4)$ Å, $b = 13.77957(5)$ Å, $c = 18.20928(9)$ Å, $V = 2319.672(17)$ Å³, $Z = 4$, $T = 150(2)$ K, $\mu(\text{CuK}\alpha) = 0.689$ mm⁻¹, $D_{\text{calc}} = 1.227$ g/cm³, 108912 reflections measured ($8.046^\circ \leq 2\theta \leq 147.448^\circ$), 4697 unique ($R_{\text{int}} = 0.0497$, $R_{\text{sigma}} = 0.0129$) which were used in all calculations. The final R_1 was 0.0283 ($I > 2\sigma(I)$) and wR_2 was 0.0727 (all data).

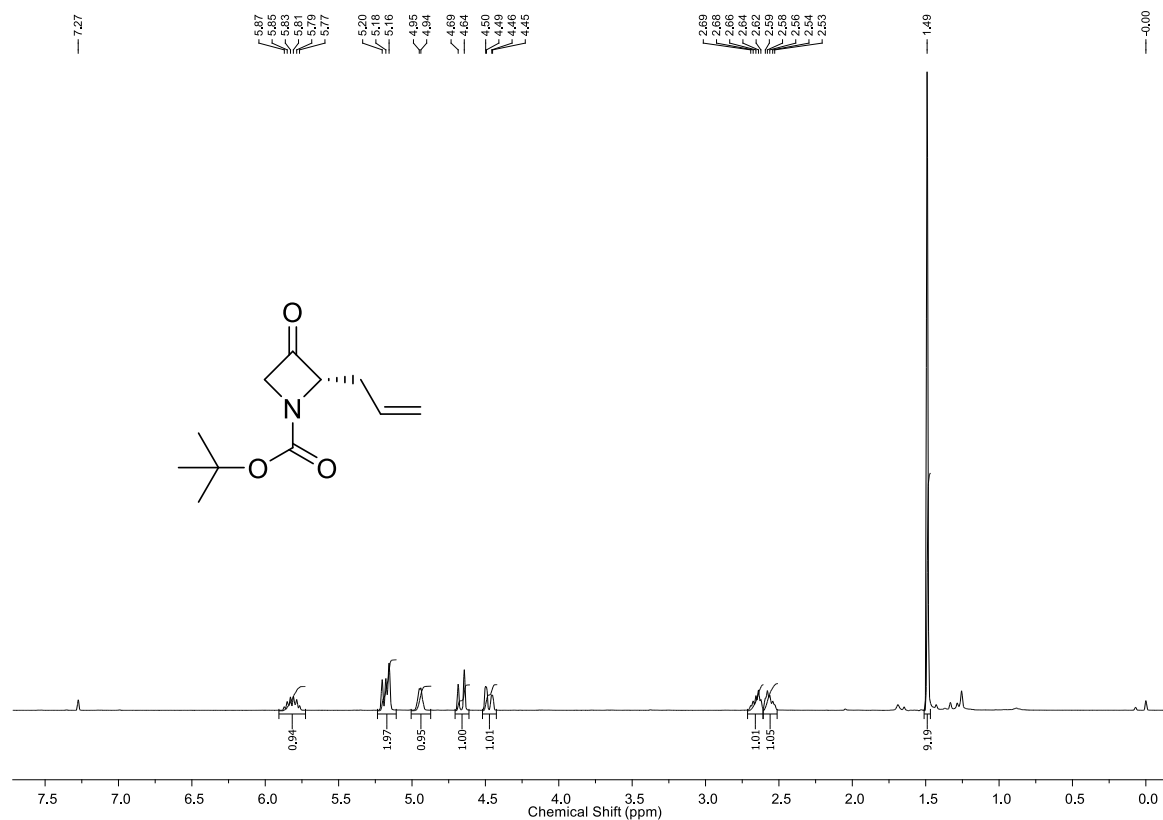
**1** ¹H NMR (400 MHz, CDCl₃)**1** ¹³C NMR (100 MHz, CDCl₃)



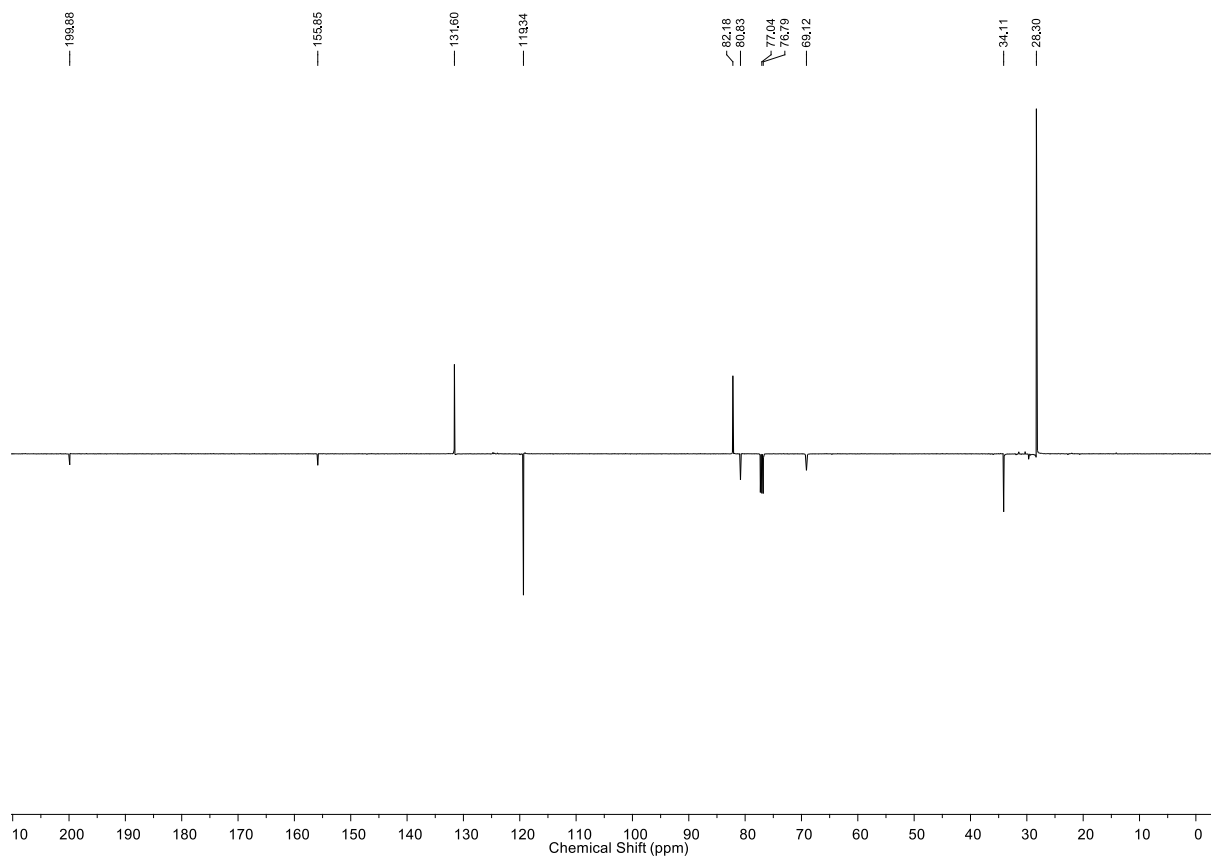
3 ^1H NMR (400 MHz, CDCl_3)



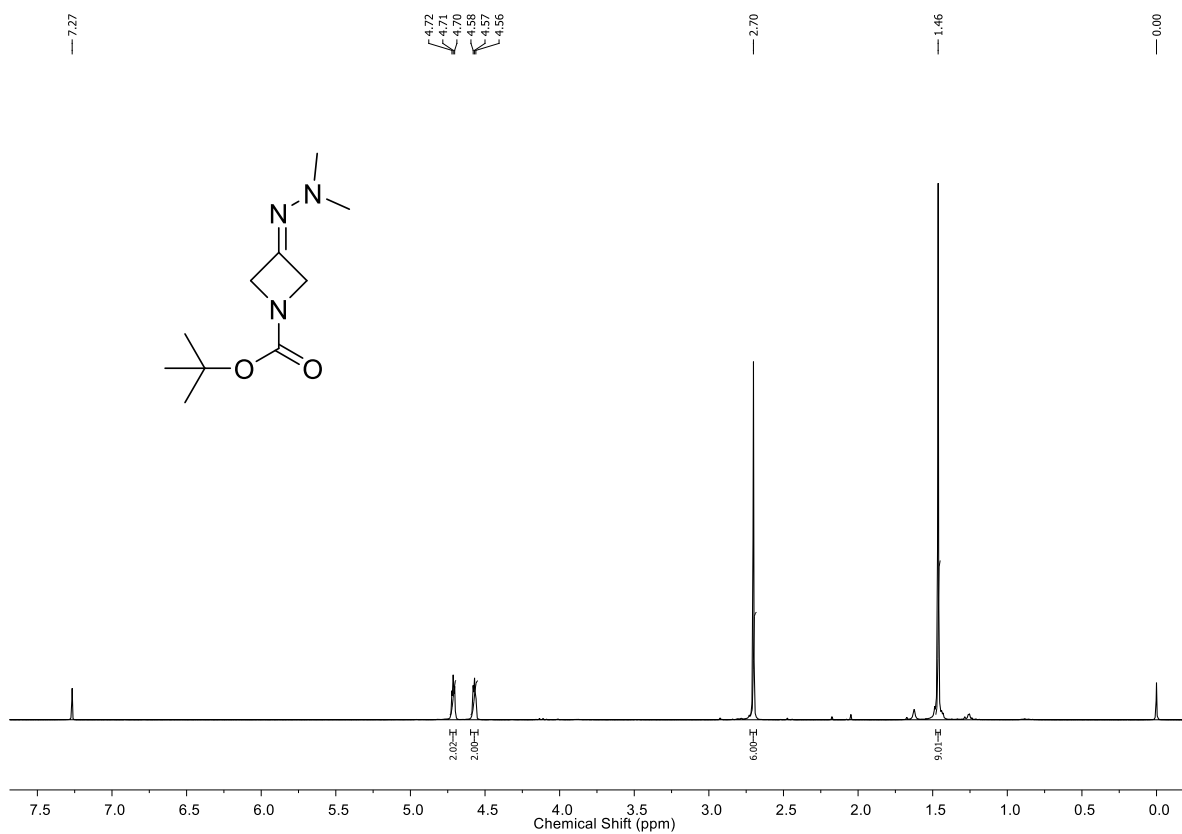
3 ^{13}C NMR (176 MHz, CDCl_3)



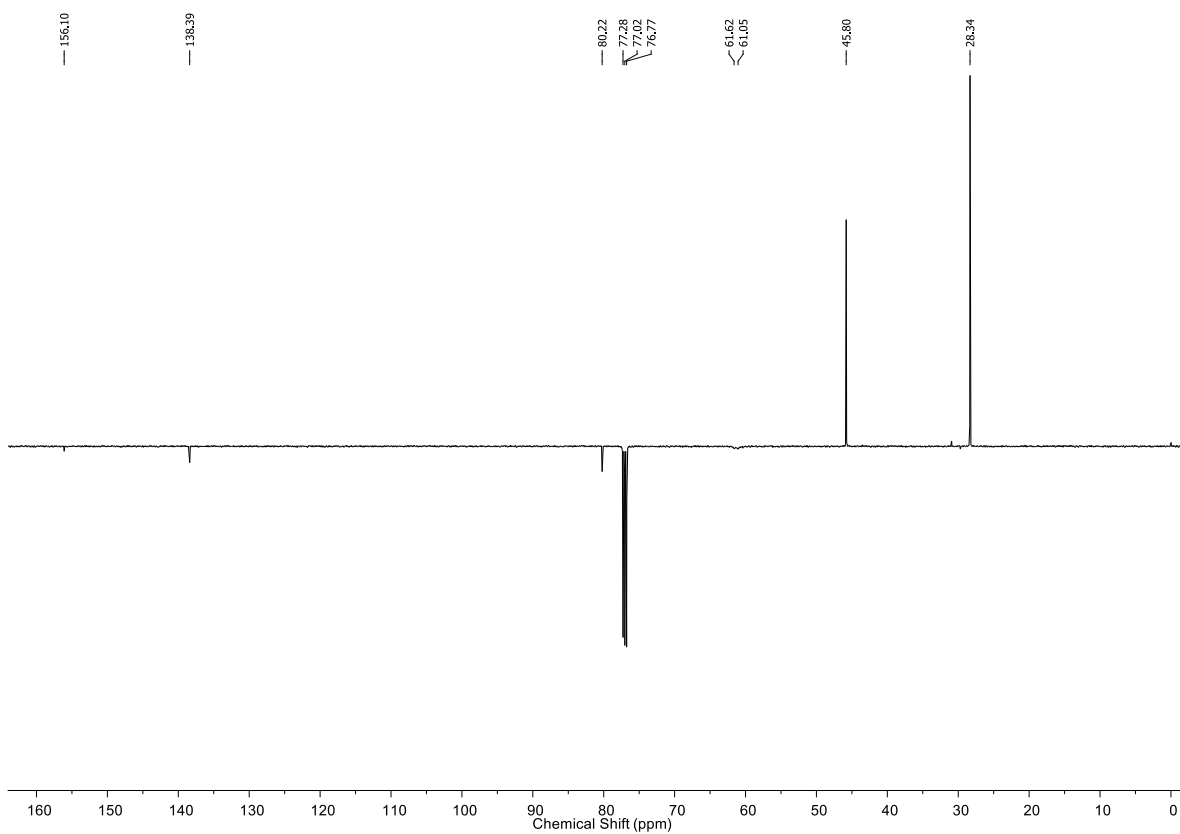
4 ¹H NMR (400 MHz, CDCl₃)



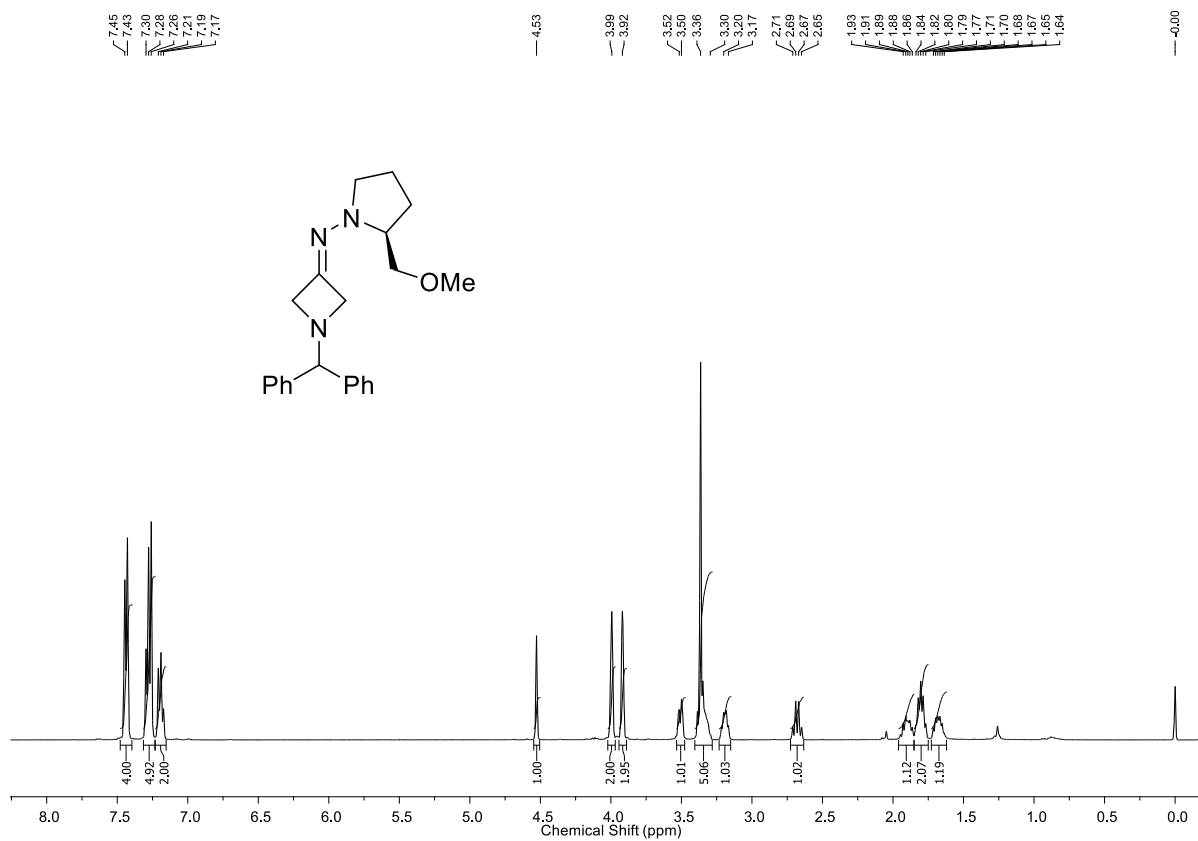
4 ¹³C NMR (125 MHz, CDCl₃)



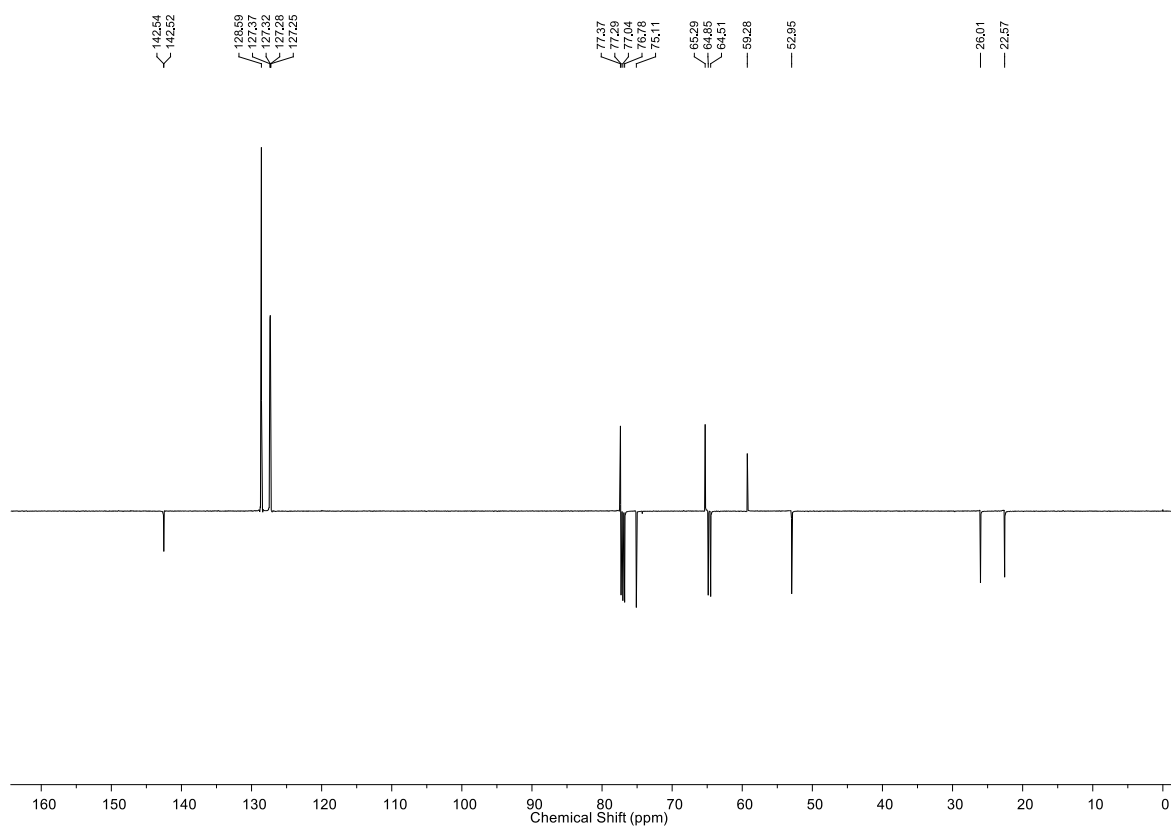
5 ¹H NMR (400 MHz, CDCl₃)



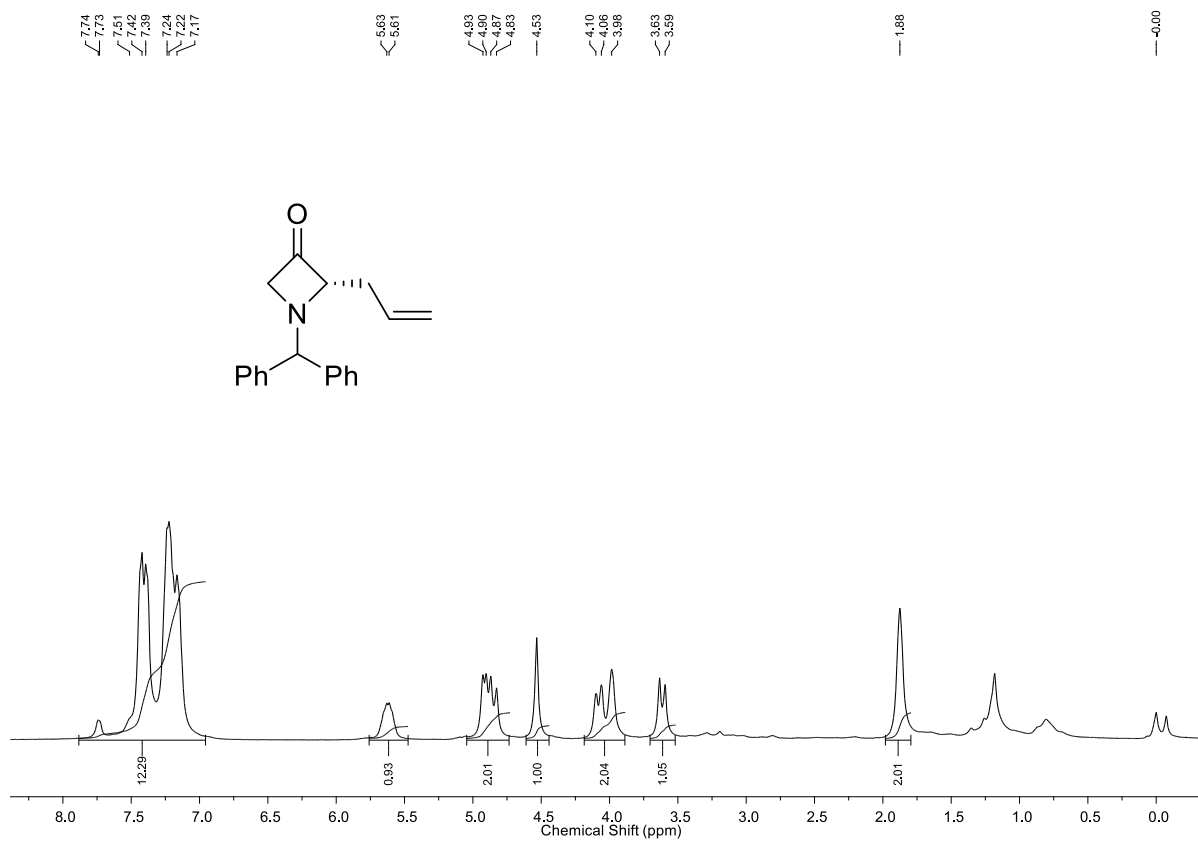
5 ¹³C NMR (125 MHz, CDCl₃)



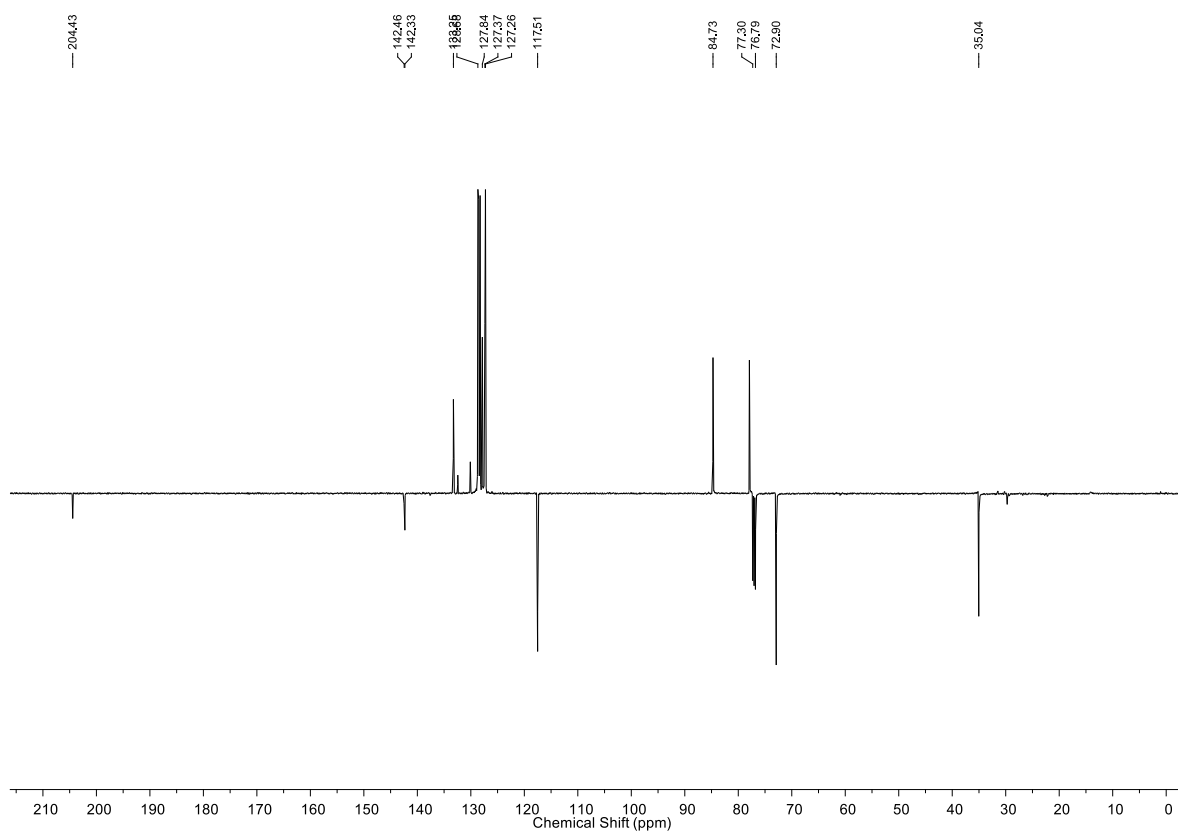
6 ^1H NMR (400 MHz, CDCl_3)



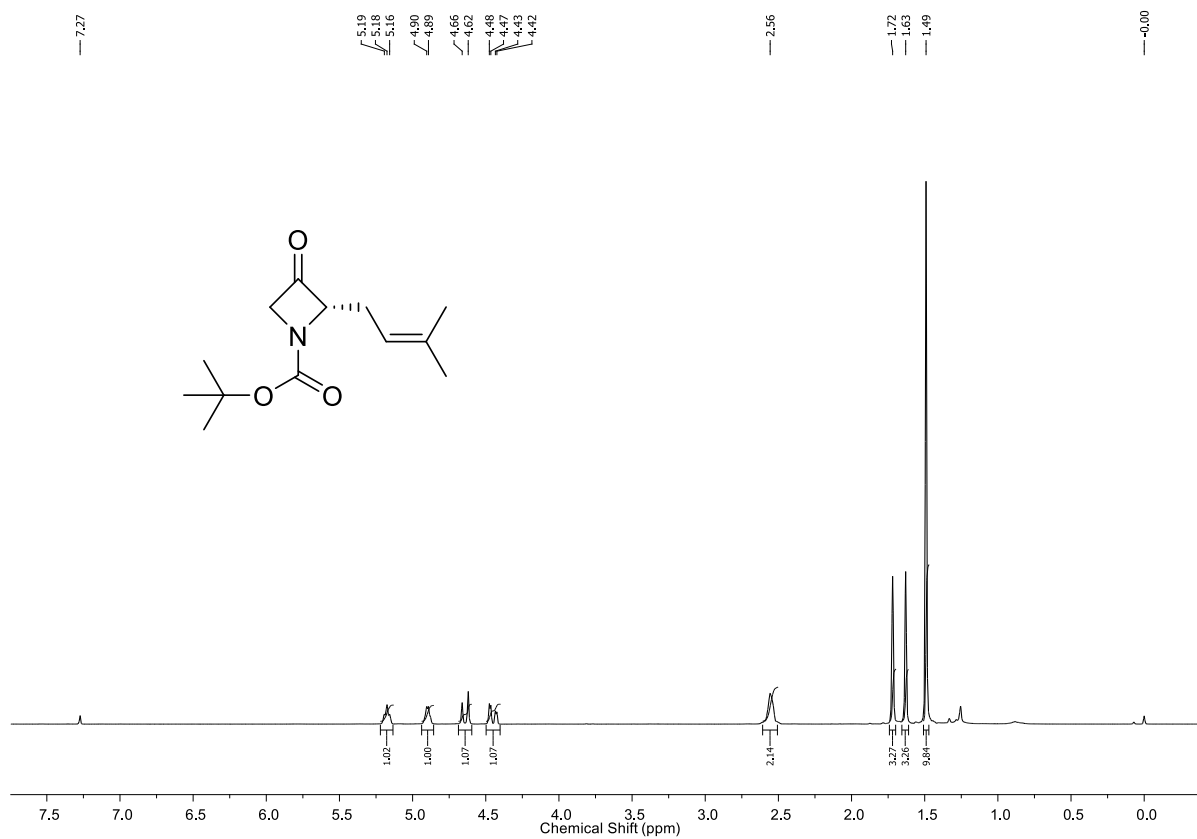
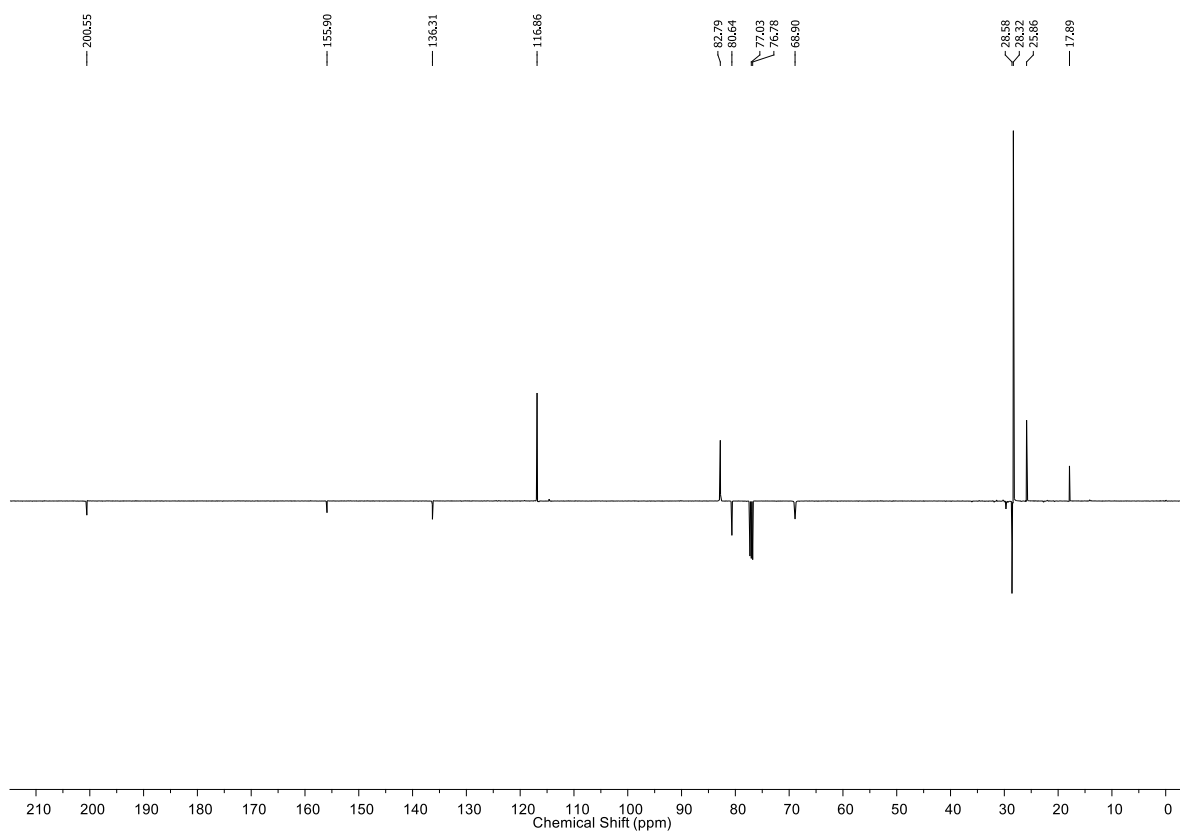
6 ^{13}C NMR (125 MHz, CDCl_3)

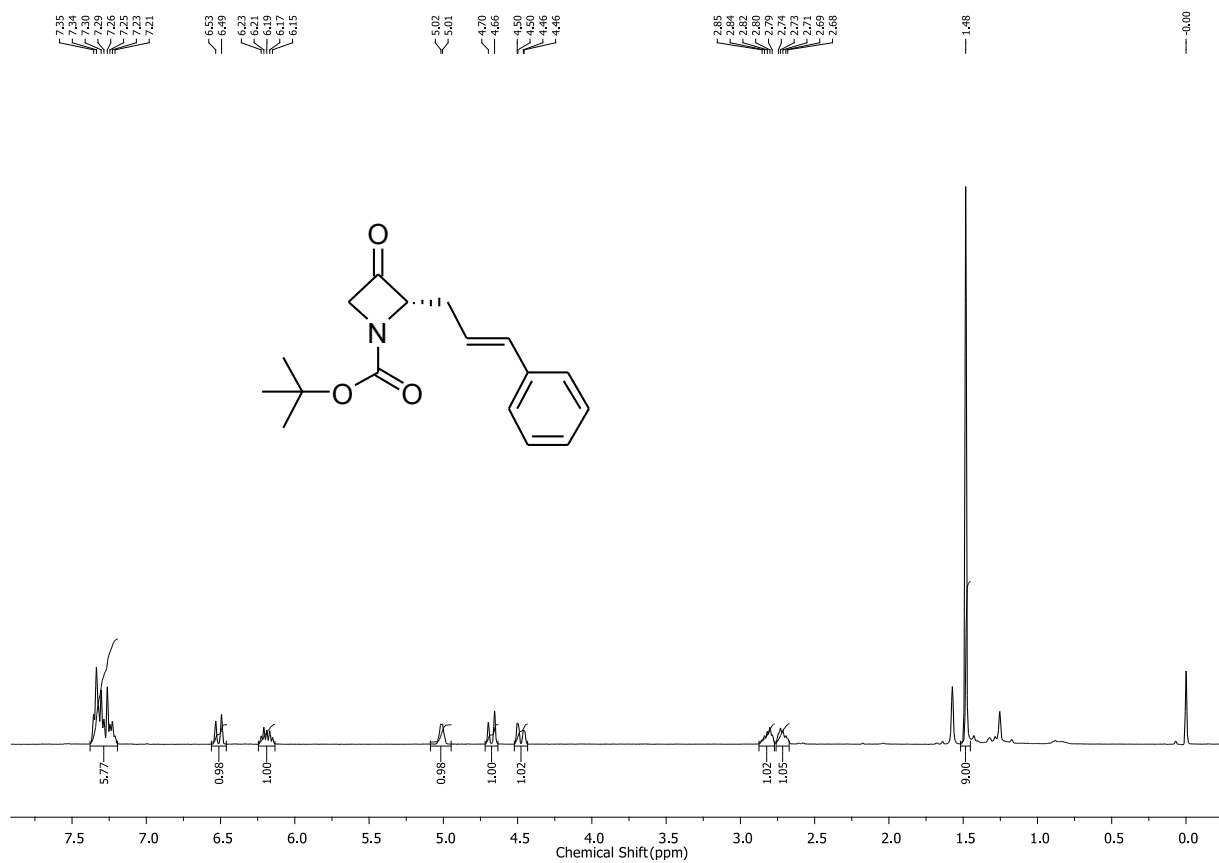


7 ¹H NMR (400 MHz, CDCl₃)

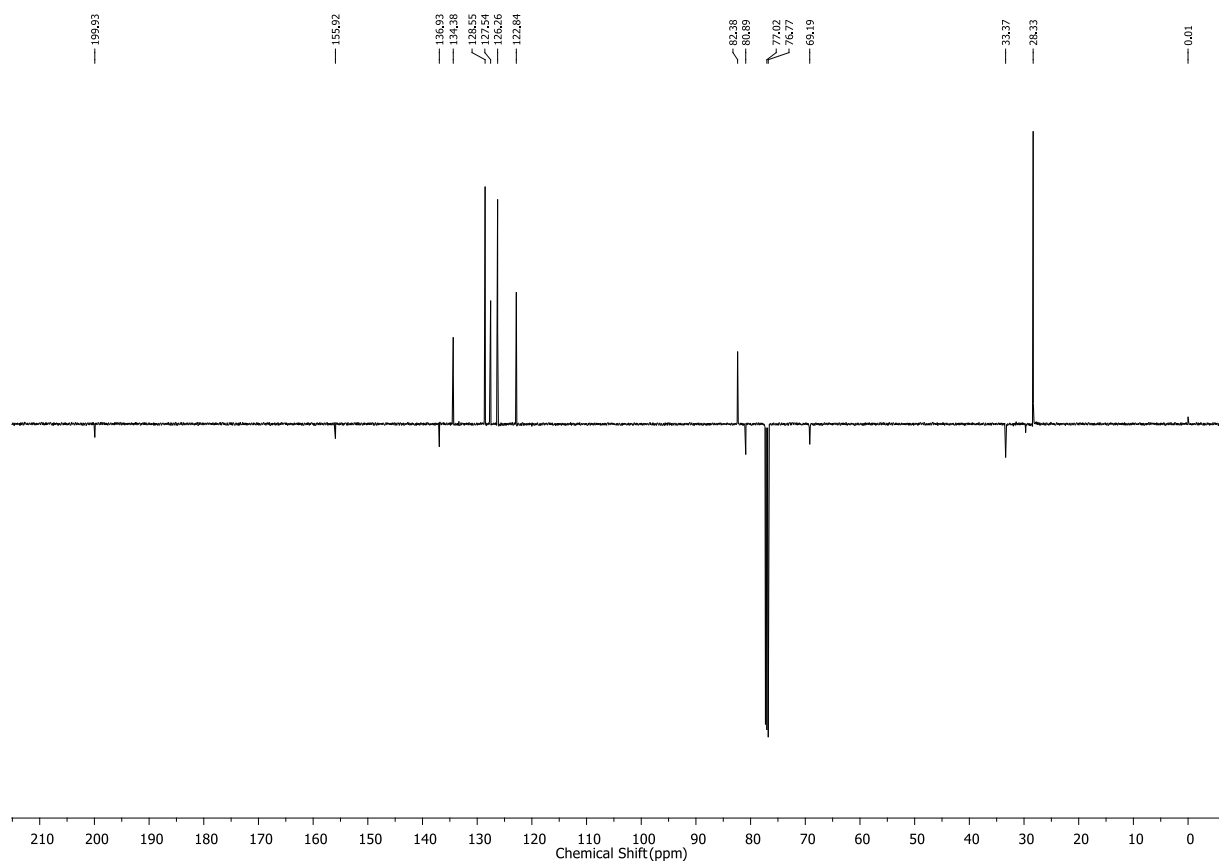


7 ¹³C NMR (125 MHz, CDCl₃)

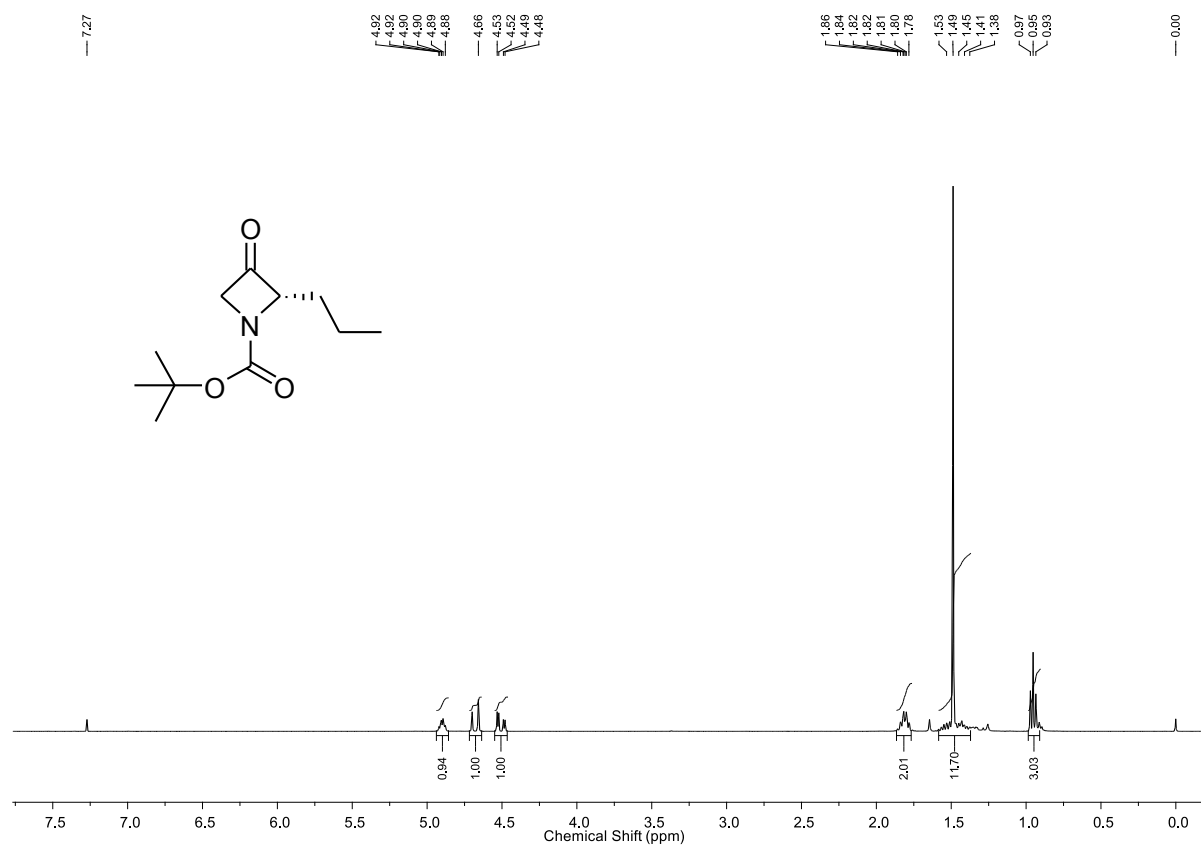
**8** ¹H NMR (400 MHz, CDCl₃)**8** ¹³C NMR (125 MHz, CDCl₃)



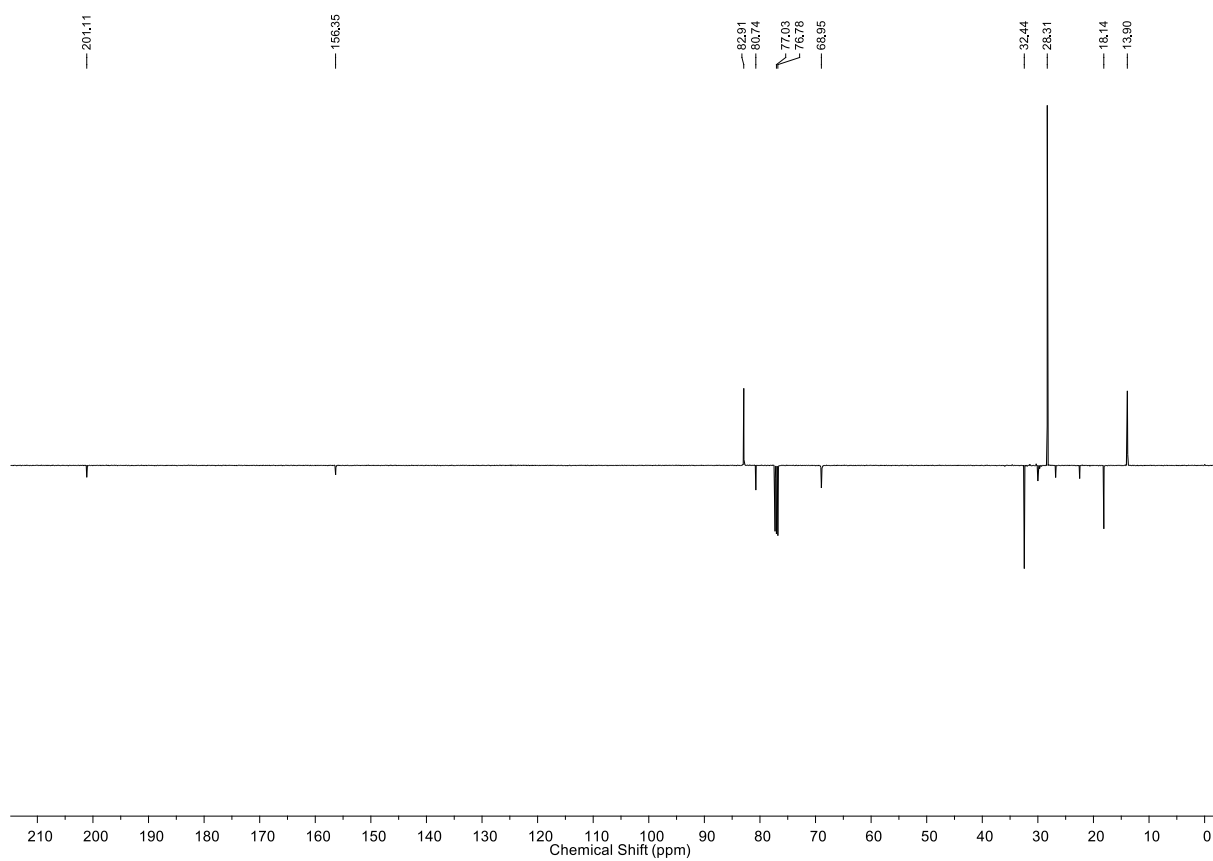
9 ¹H NMR (400 MHz, CDCl₃)



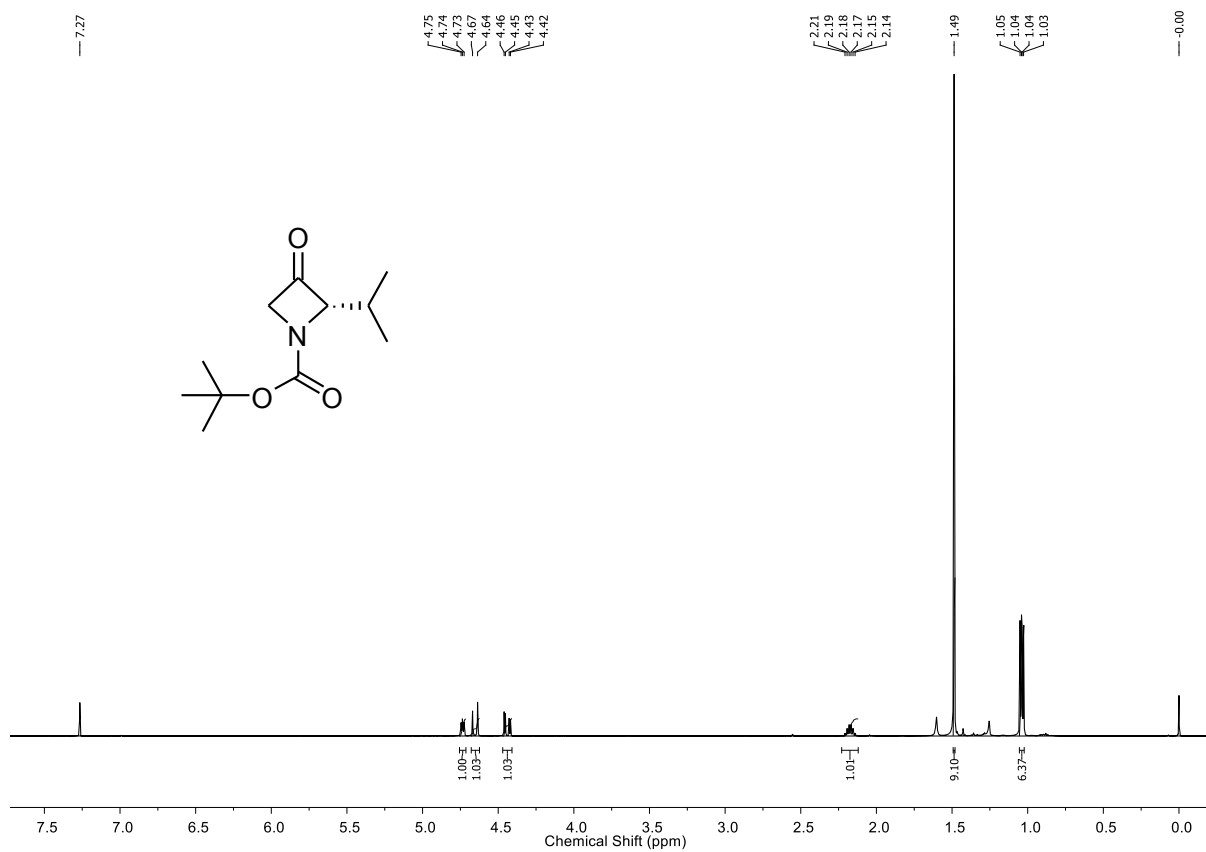
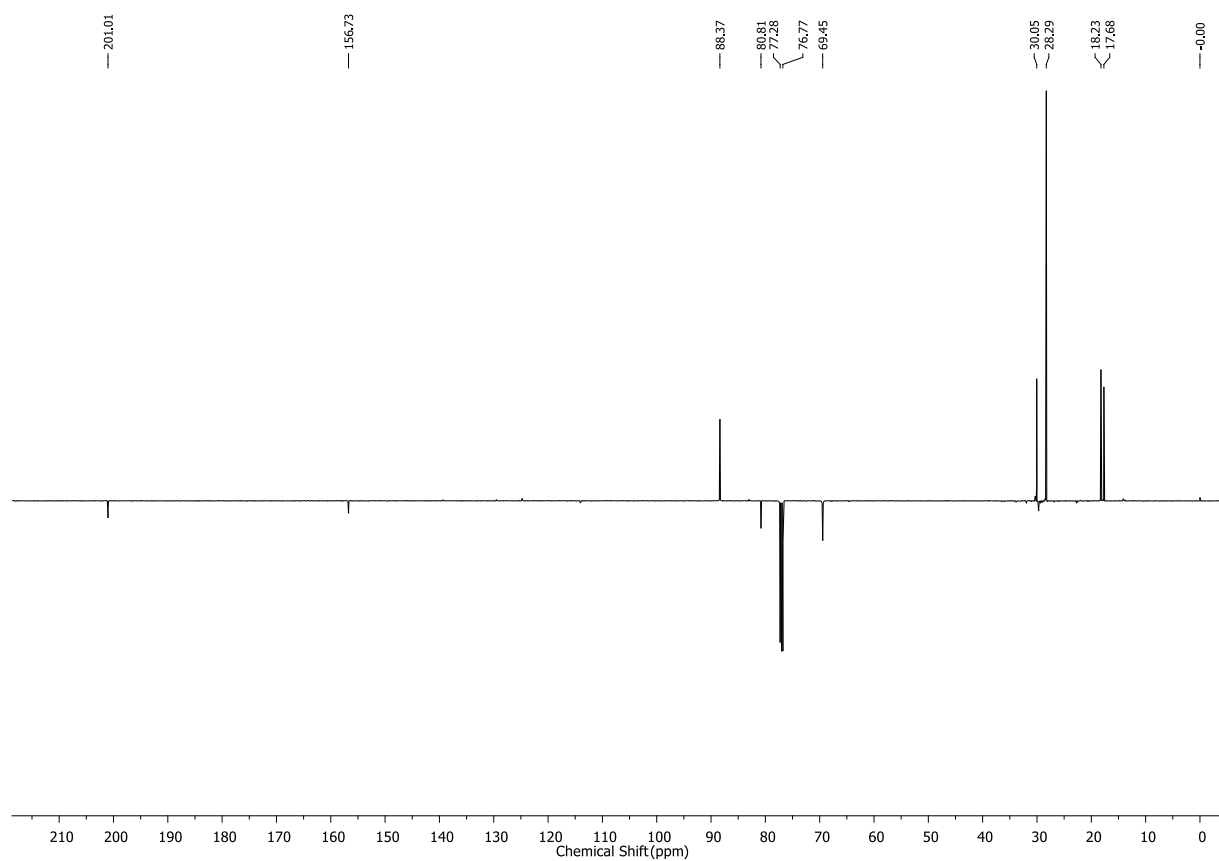
9 ¹³C NMR (125 MHz, CDCl₃)



10 ^1H NMR (400 MHz, CDCl_3)

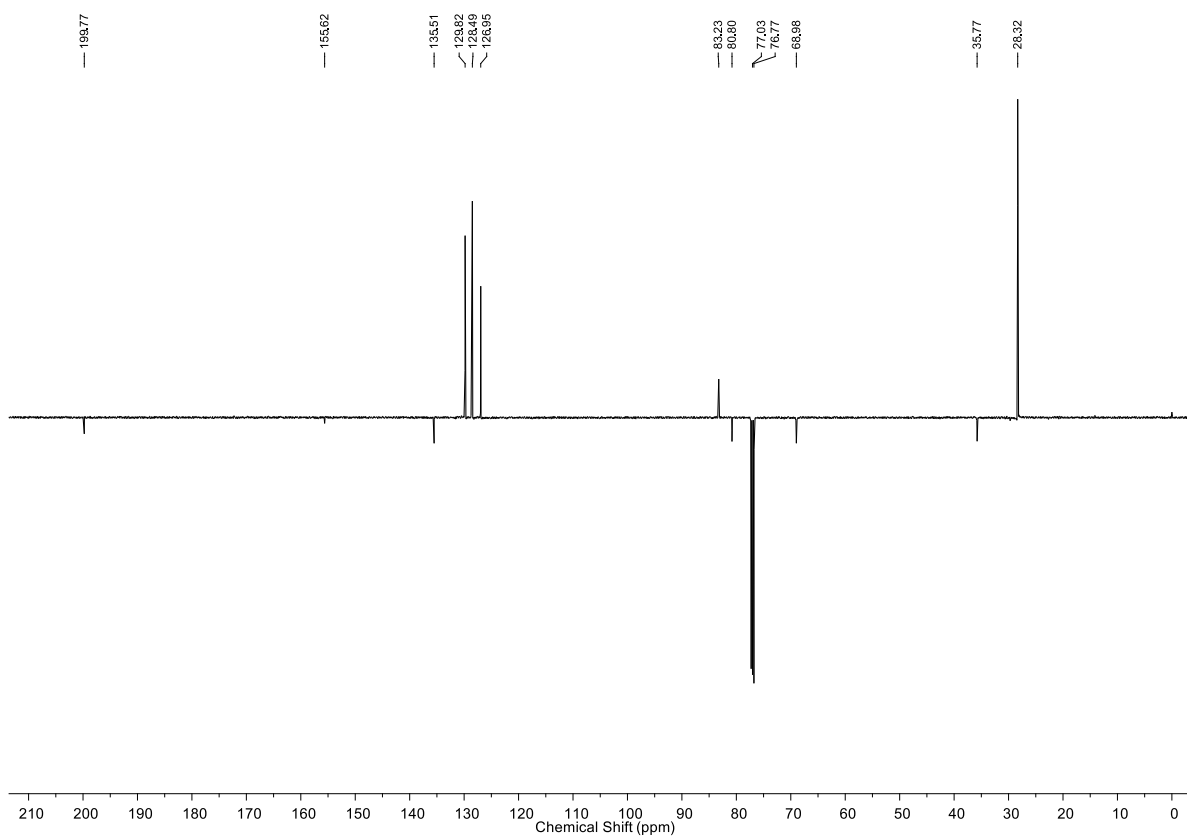


10 ^{13}C NMR (125 MHz, CDCl_3)

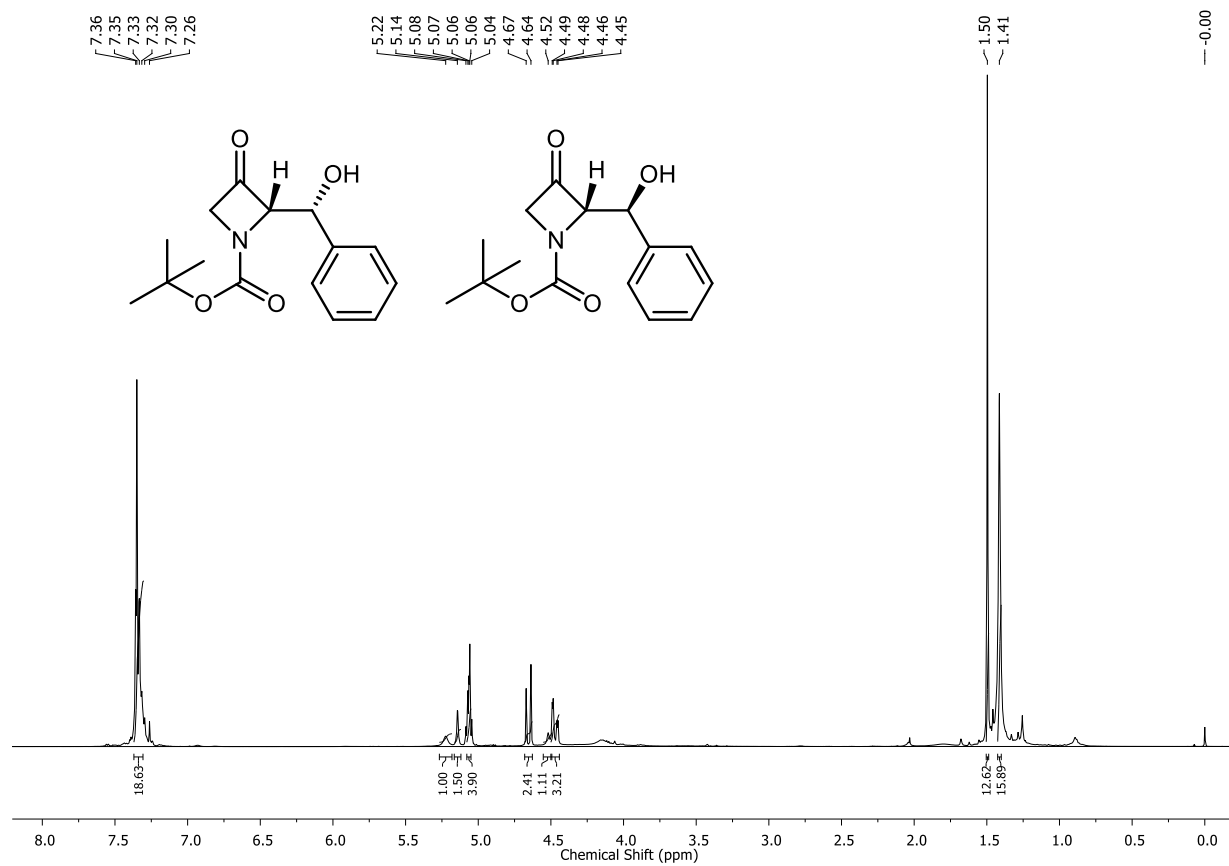
**11** ¹H NMR (500 MHz, CDCl₃)**11** ¹³C NMR (125 MHz, CDCl₃)



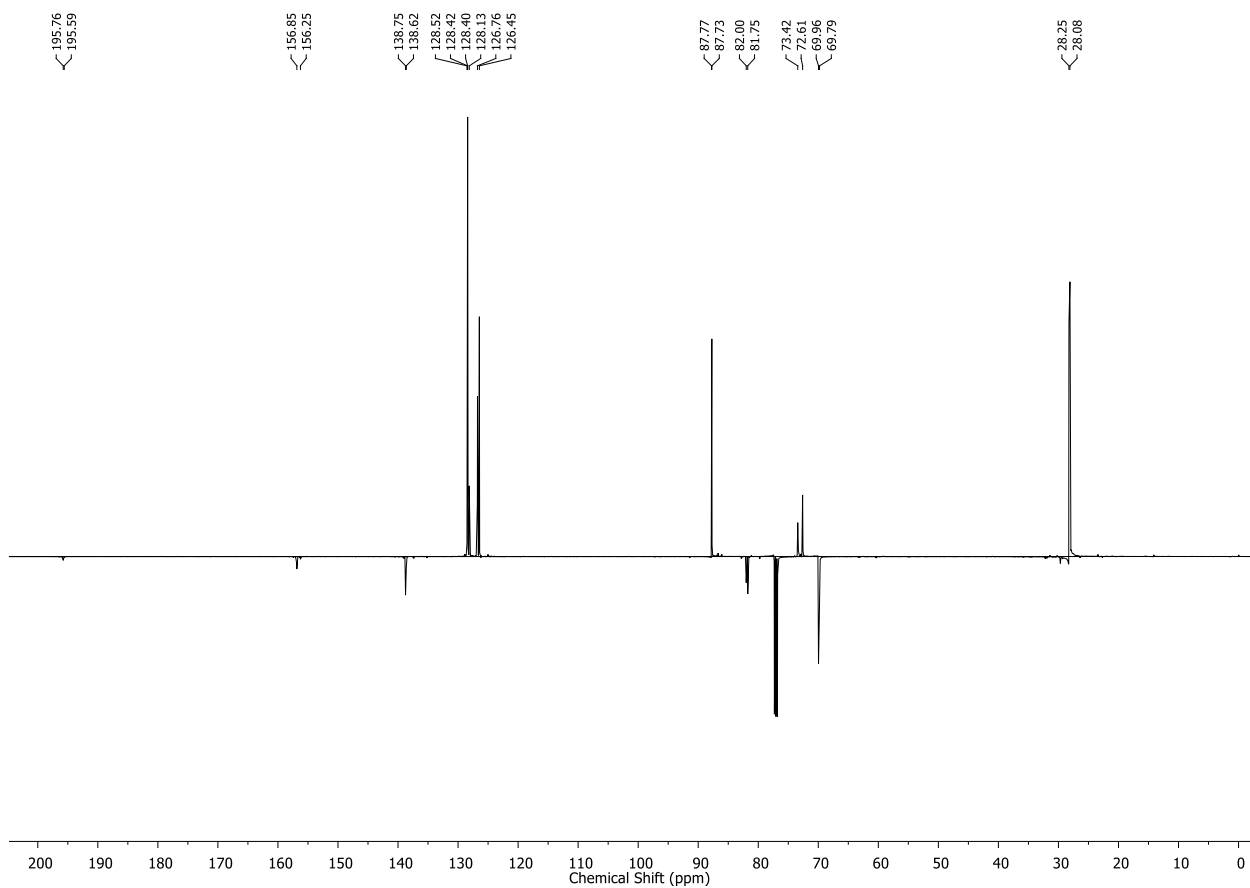
12 ^1H NMR (400 MHz, CDCl_3)



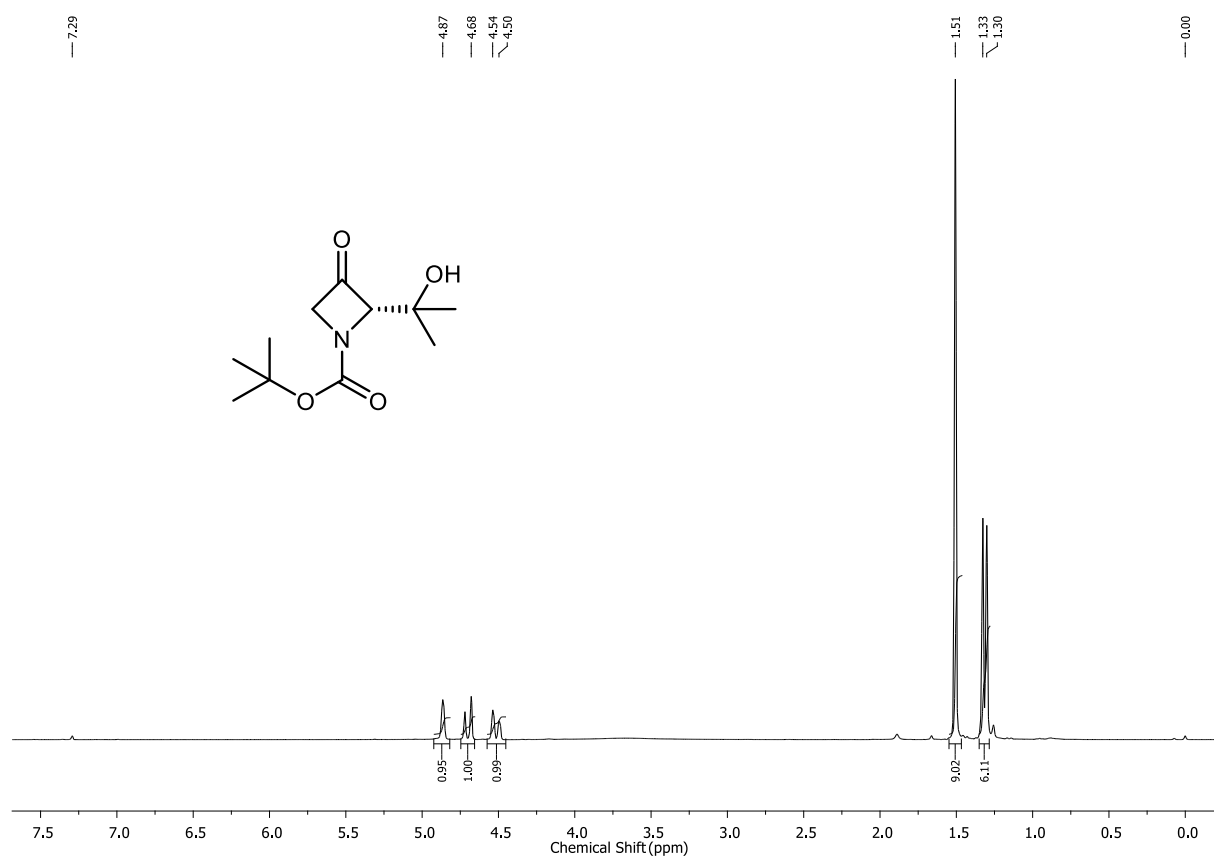
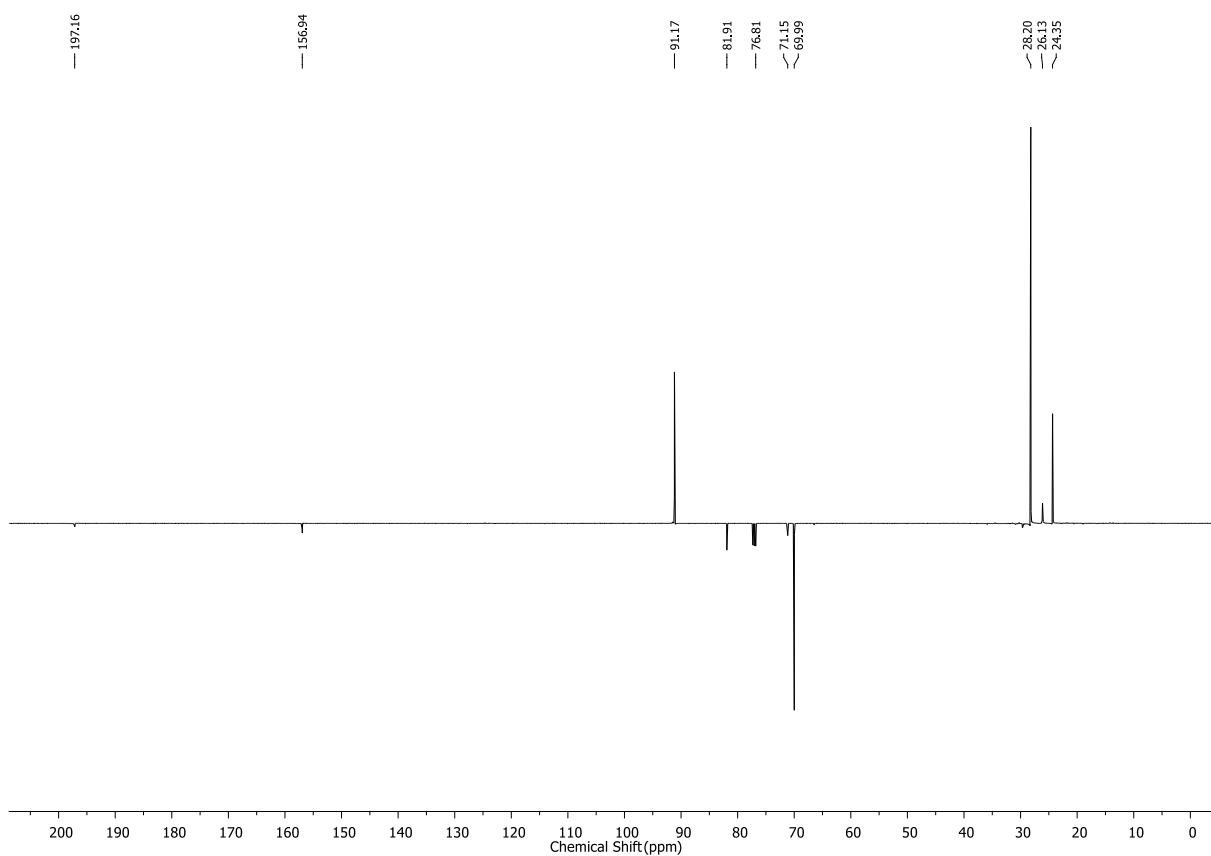
12 ^{13}C NMR (125 MHz, CDCl_3)

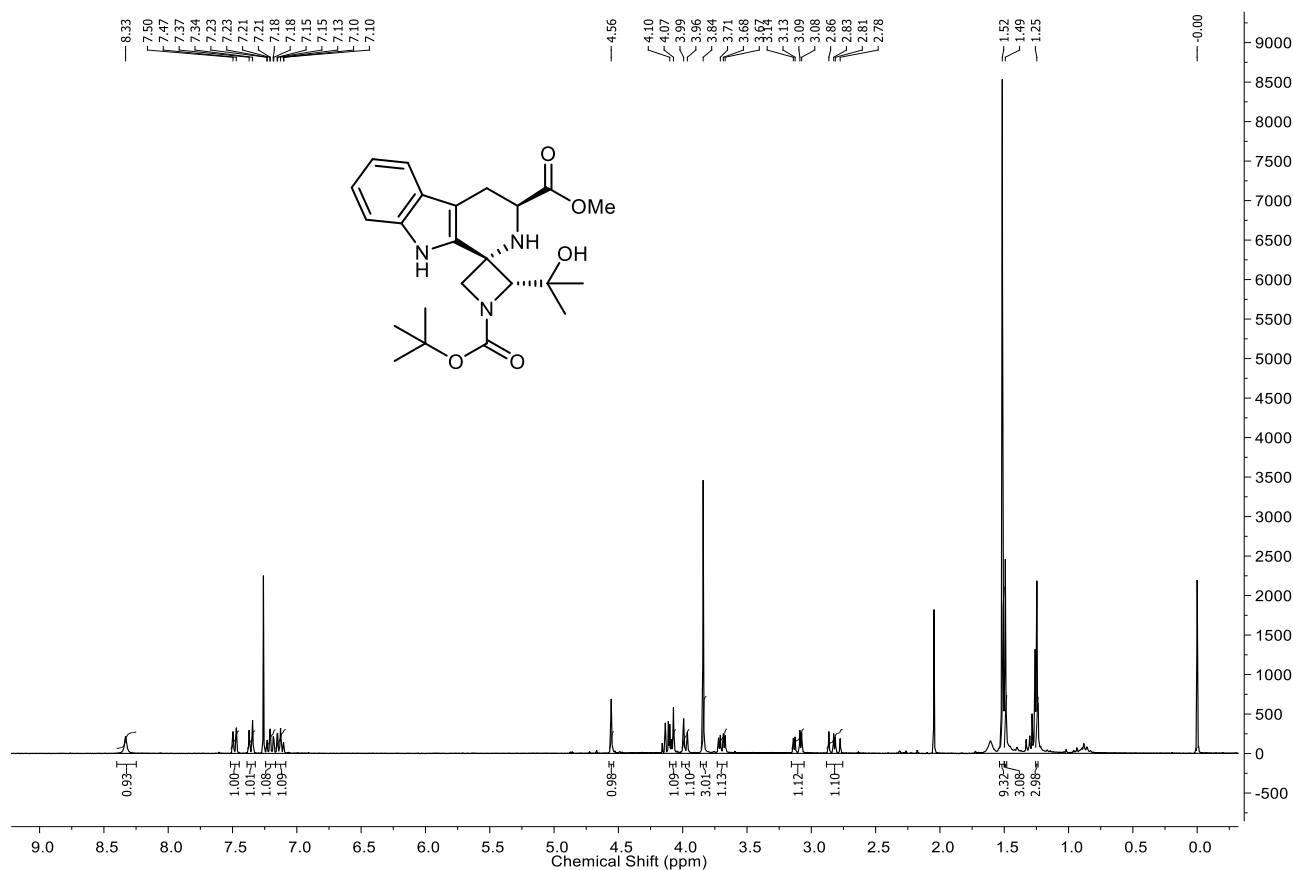


¹³C NMR (125 MHz, CDCl₃)

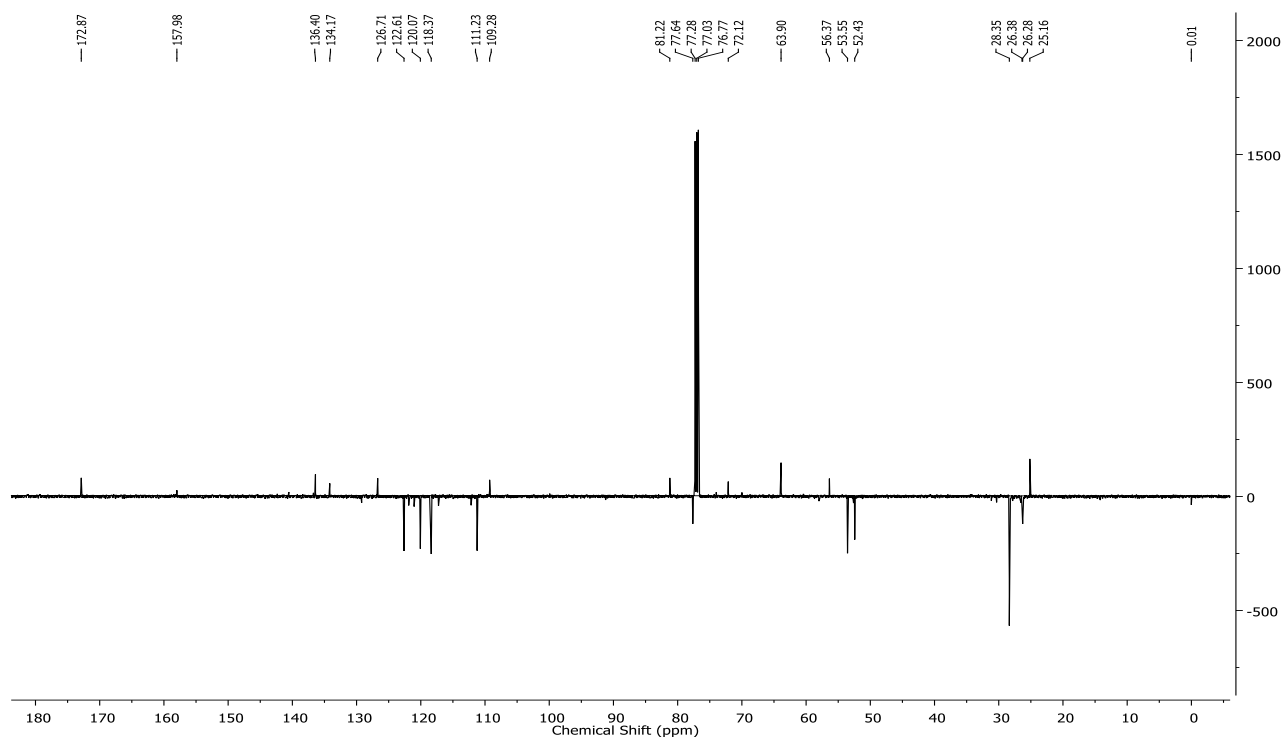


¹³C NMR (125 MHz, CDCl₃)

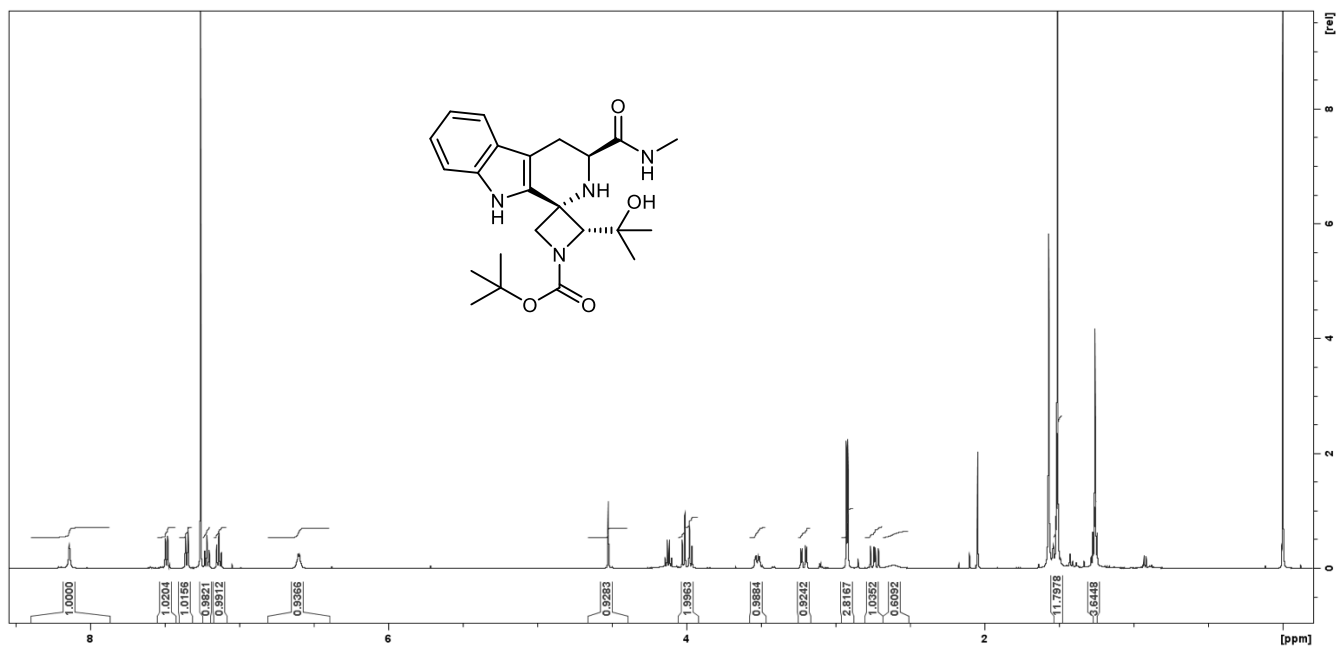
**14** ^1H NMR (400 MHz, CDCl_3)**14** ^{13}C NMR (125 MHz, CDCl_3)



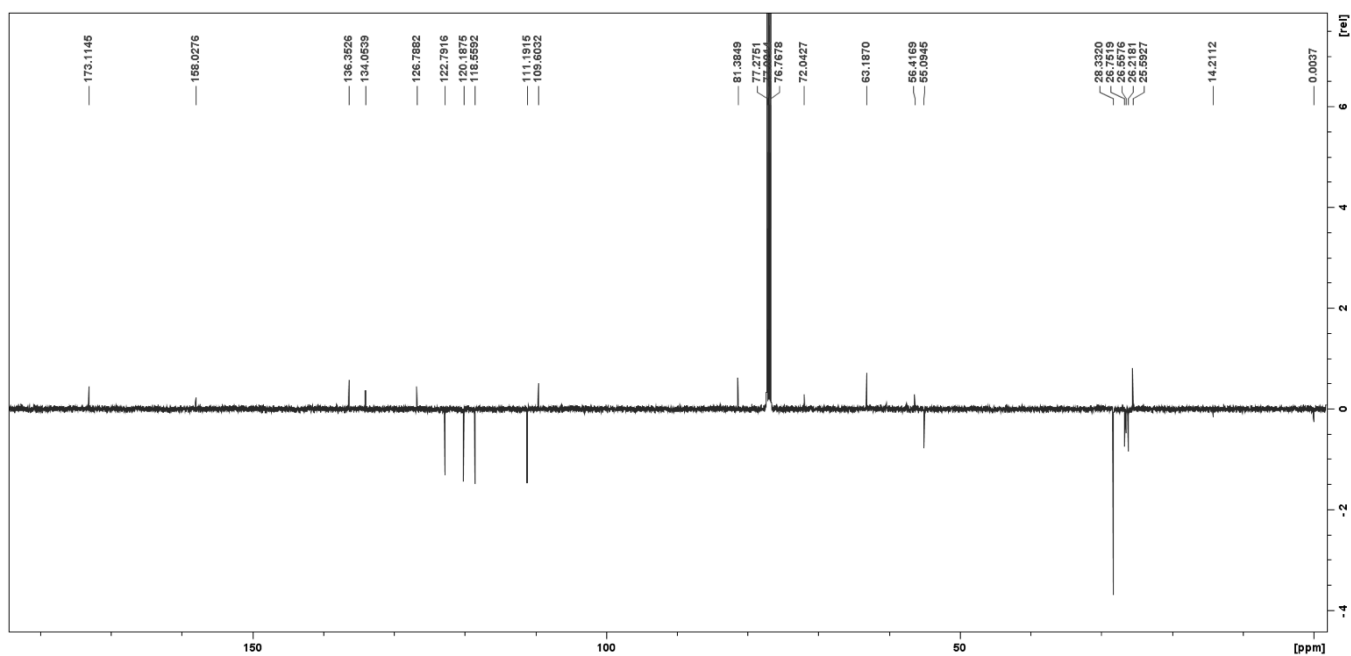
15 ¹H NMR (300 MHz, CDCl₃)



15 ¹³C NMR (125 MHz, CDCl₃)



16 ^1H NMR (500 MHz, CDCl_3)

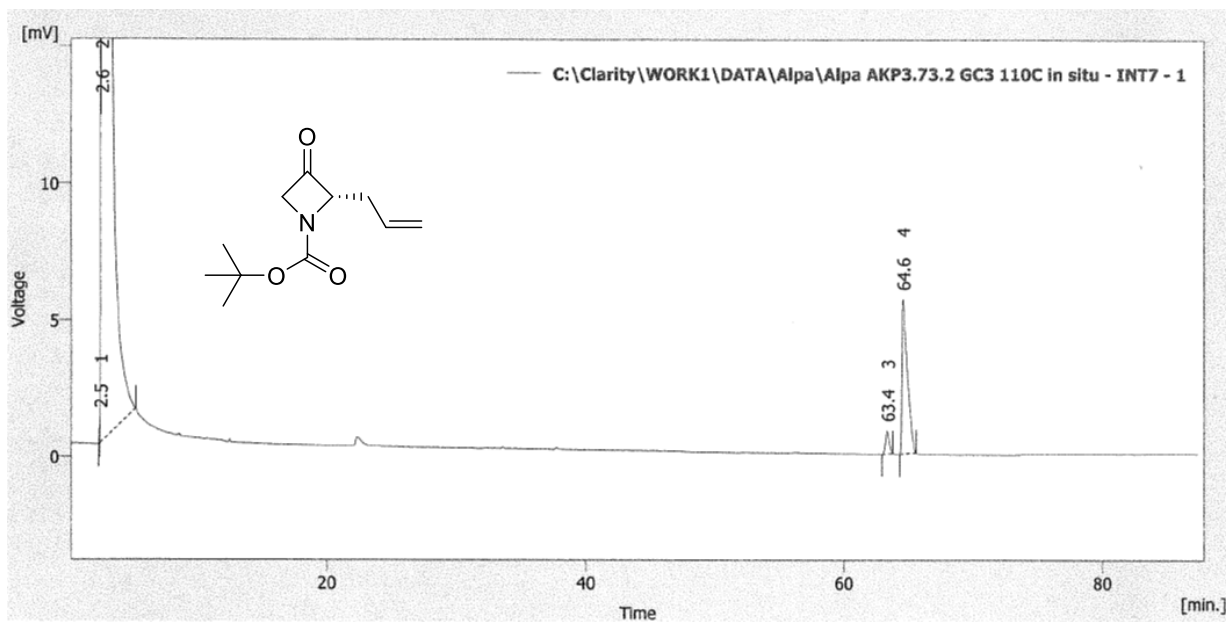


16 ^{13}C NMR (125 MHz, CDCl_3)

Chiral GC Chromatograms for 4

Chromopac cyclodextrin- β -236M-19 50m x 0.25mm x 0.25 μ m column, T = 110°C, P = 15 psi, H₂ carrier gas

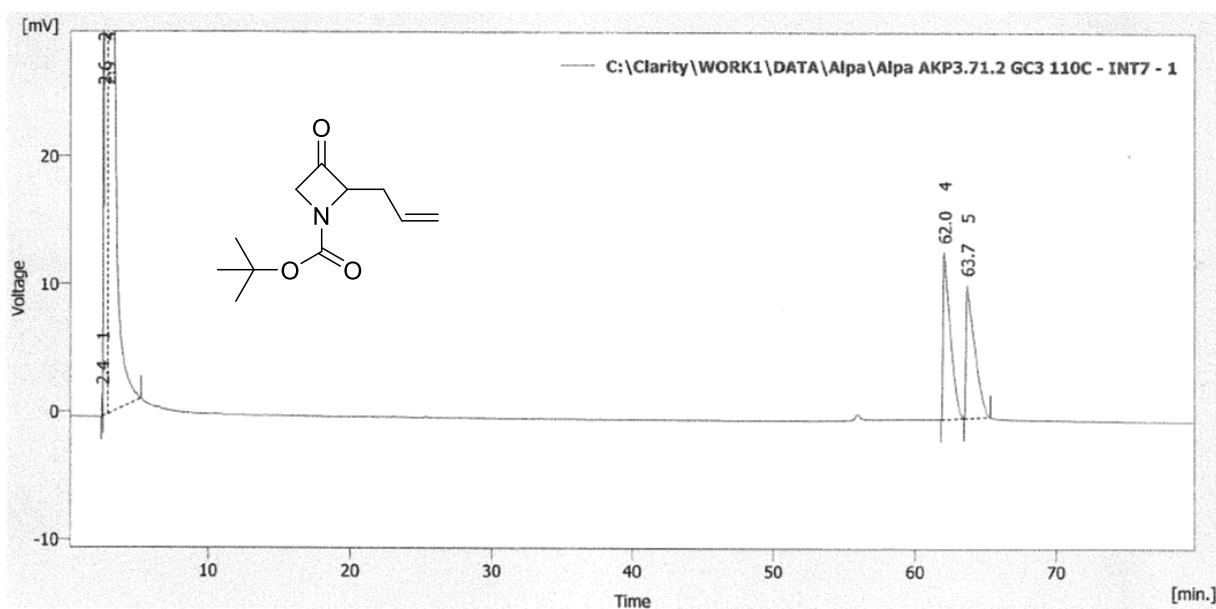
Prepared from SAMP Hydrazone (*S*)-1 (*ee* = 81%):



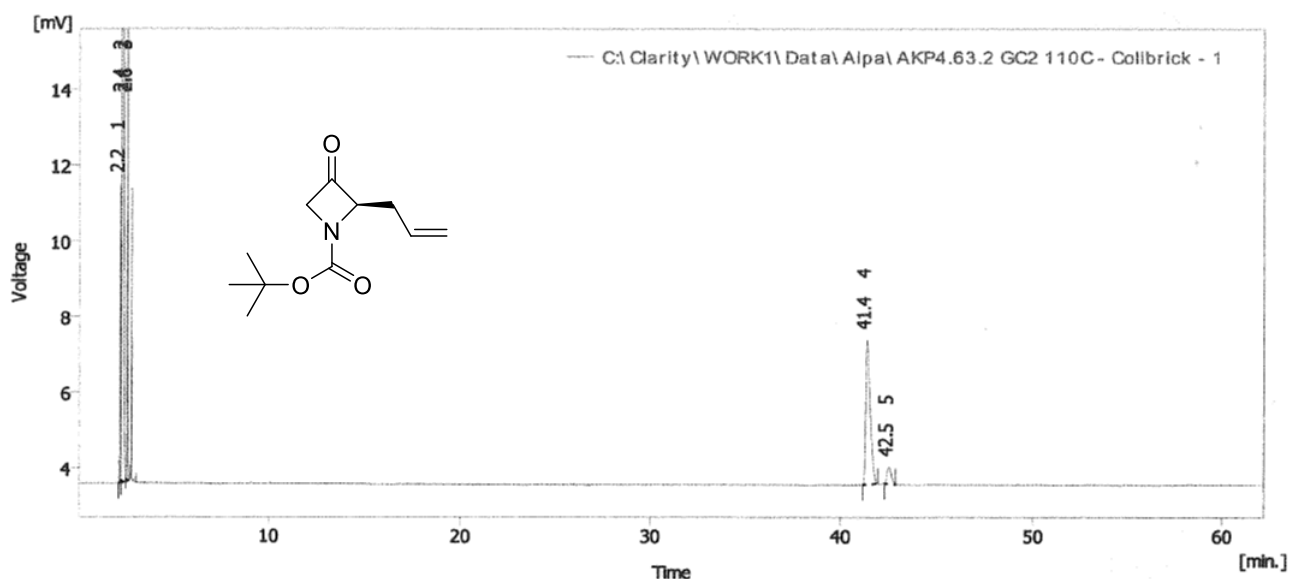
Result Table (Uncal - C:\Clarity\WORK1\DATA\Alpa\Alpa AKP3.73.2 GC3 110C in situ - INT7 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	2.460	4.400	0.959	0.0	0.1	0.09	
2	2.593	31199.835	1249.448	99.4	99.4	0.39	
3	63.353	17.239	0.853	0.1	0.1	0.32	
4	64.553	166.146	5.661	0.5	0.5	0.47	
Total		31387.619	1256.922	100.0	100.0		

Prepared from dimethyl hydrazone 5 (racemic):



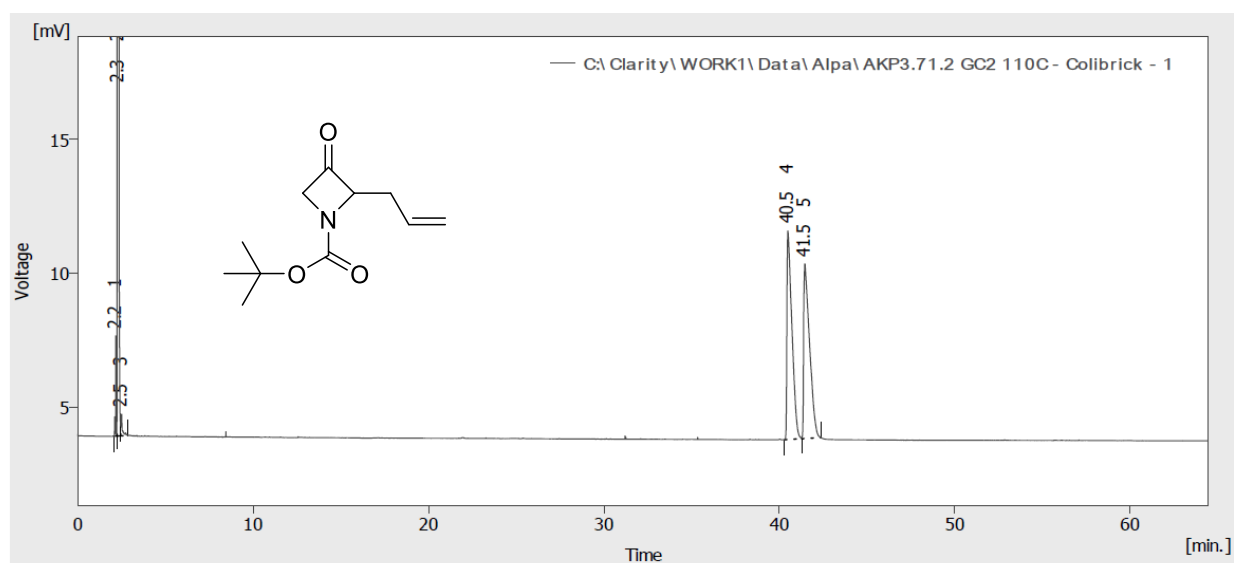
Prepared from RAMP Hydrazone (*R*)-**1** (*ee* = 81%):



Result Table (Uncal - C:\Clarity\WORK1\Data\Alpa\AKP4.63.2 GC2 110C - Colibrick - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	2.228	15.945	7.904	0.3	0.8	0.02	
2	2.368	4935.699	979.956	97.8	97.3	0.09	
3	2.600	27.271	14.861	0.5	1.5	0.02	
4	41.372	63.504	3.810	1.3	0.4	0.26	
5	42.524	6.572	0.433	0.1	0.0	0.24	
	Total	5048.990	1006.964	100.0	100.0		

Prepared from dimethyl hydrazone **5** (racemic):

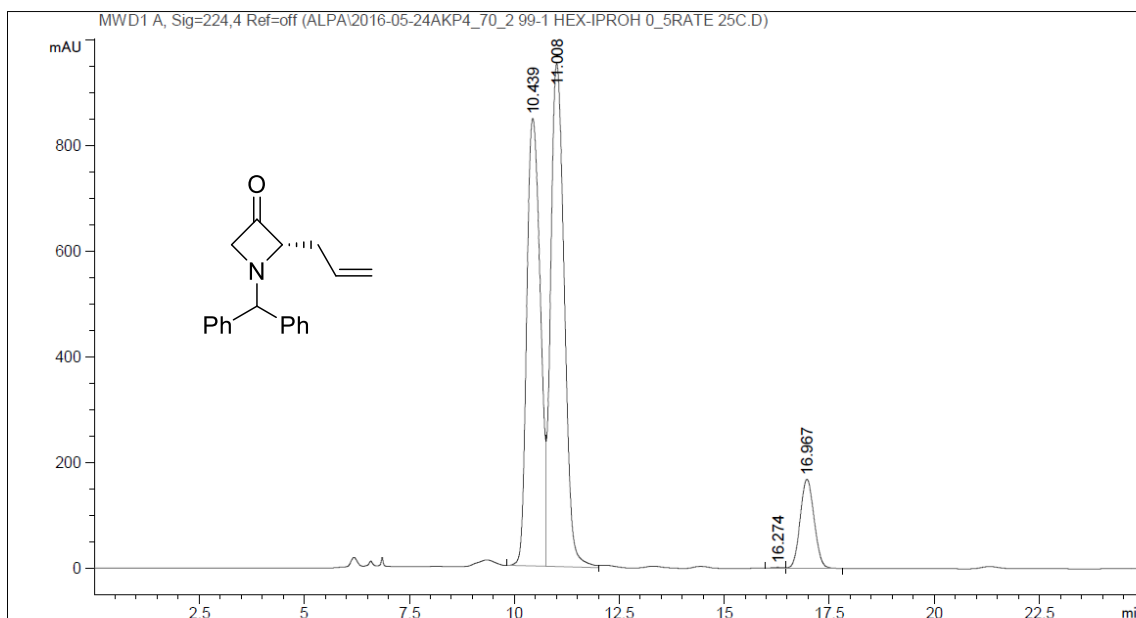


Different GC set ups and columns were used for analysis of the two enantiomers leading to different retention times in the (*R*)- and (*S*)-series. However, in each case the integrity of the analysis was confirmed by splitting of the racemic material.

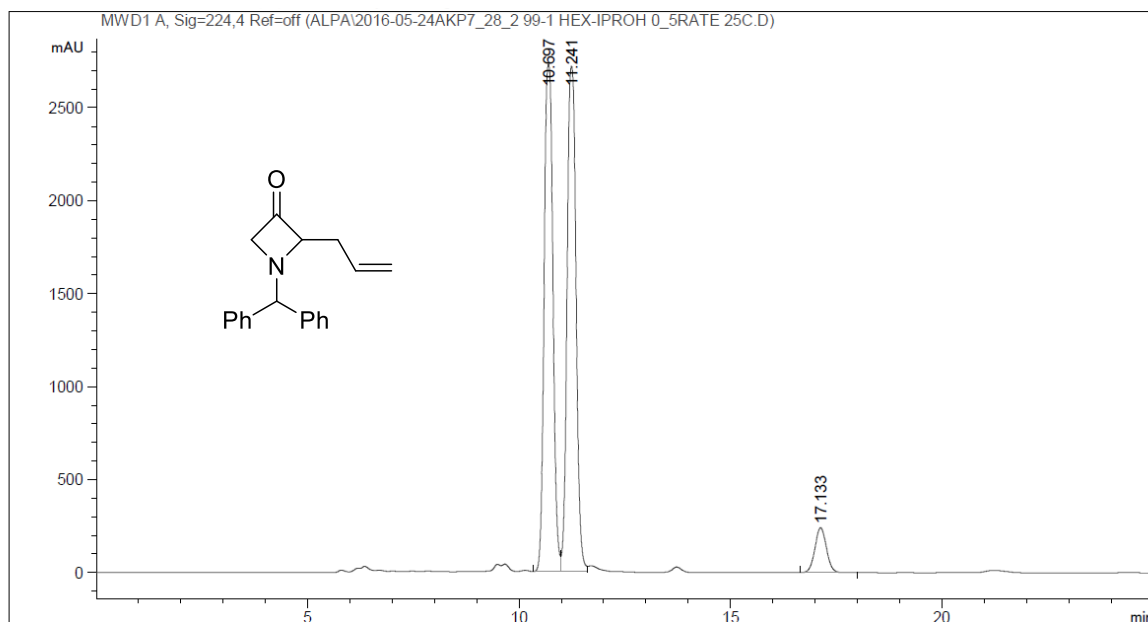
Chiral HPLC Chromatogram for 7

Chiralpak AD-H column (0.46cm ø x 25 cm), 99:1 hexane: propan-2-ol, T = 25°C, flow rate = 0.5 mL/min, λ = 224 nm.

Prepared from SAMP Hydrazone (*S*)-6 (*ee* = 7%):



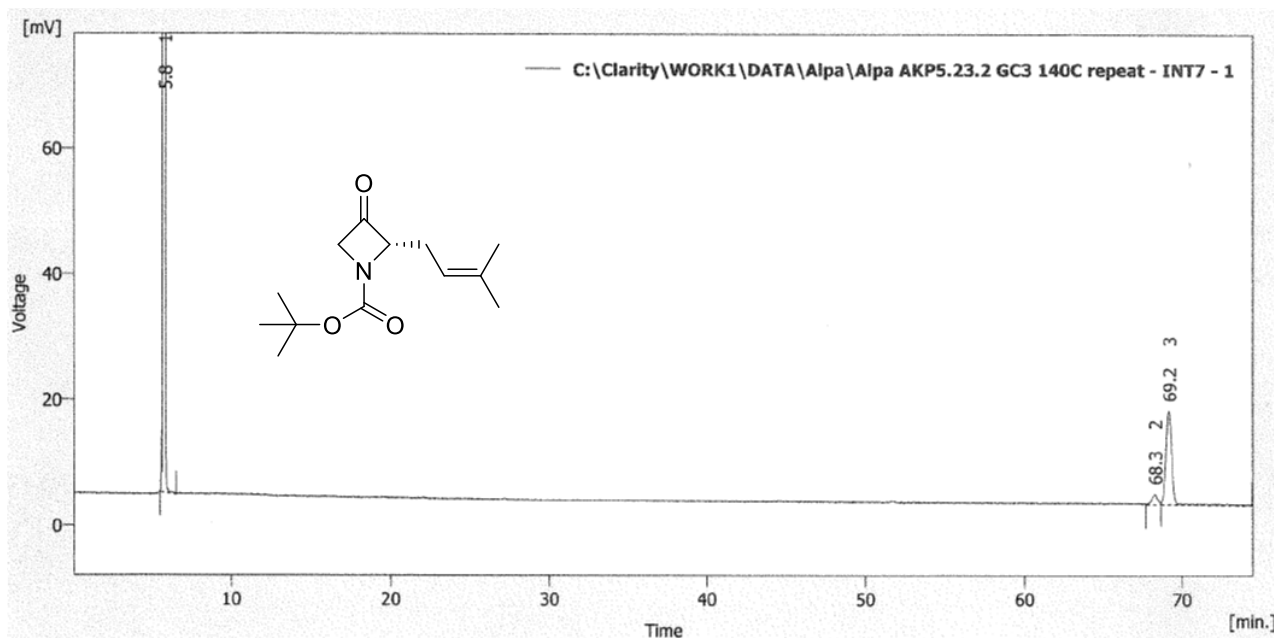
Prepared from racemic 6:



Chiral GC Chromatograms for 8

Chrompac cyclodextrin- β -236M-19 50m x 0.25mm x 0.25 μ m column, T = 140°C, P = 15 psi, He carrier gas

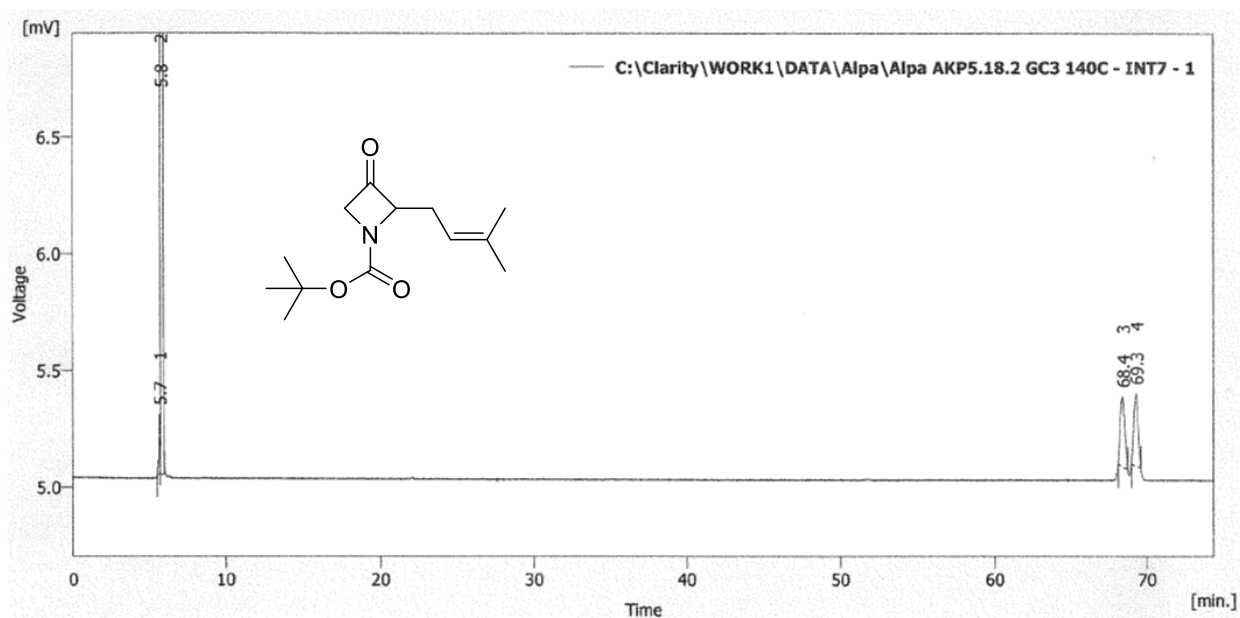
Prepared from SAMP Hydrazone (*S*)-**1** (*ee* = 81%):



Result Table (Uncal - C:\Clarity\WORK1\DATA\Alpa\Alpa AKP5.23.2 GC3 140C repeat - INT7 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	5.787	8845.573	995.046	95.0	98.4	0.16	
2	68.267	43.767	1.657	0.5	0.2	0.41	
3	69.173	420.547	14.961	4.5	1.5	0.40	
Total		9309.887	1011.664	100.0	100.0		

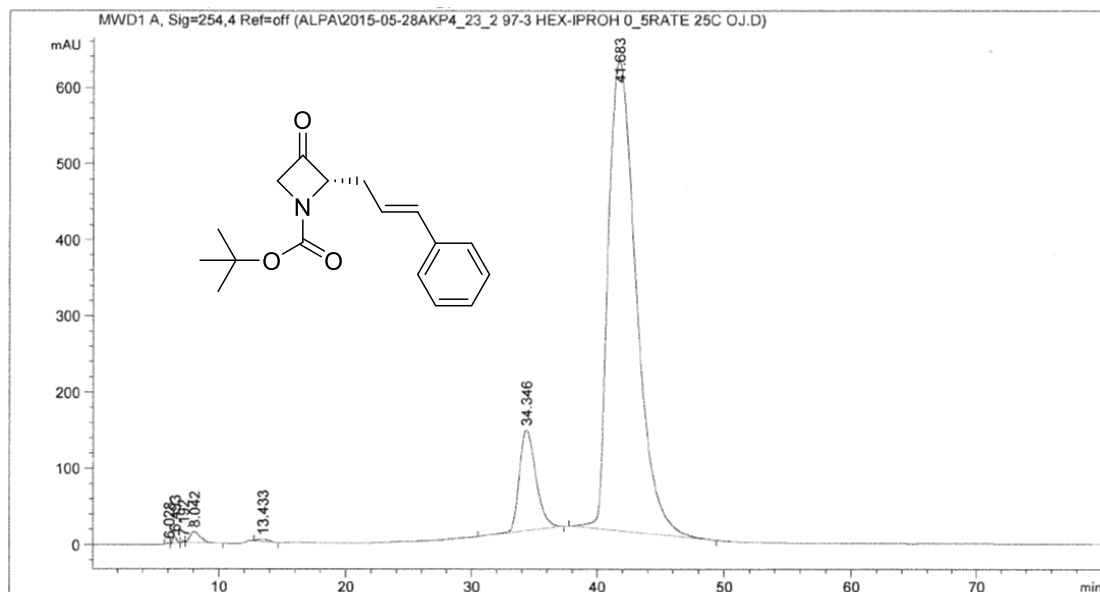
Prepared from dimethyl hydrazone **5** (racemic):



Chiral HPLC Chromatograms for 9

Chiralcel OJ column (0.46cm ø x 25 cm), 97:3 hexane: propan-2-ol, T = 25°C, flow rate = 0.5 mL/min, λ = 254 nm.

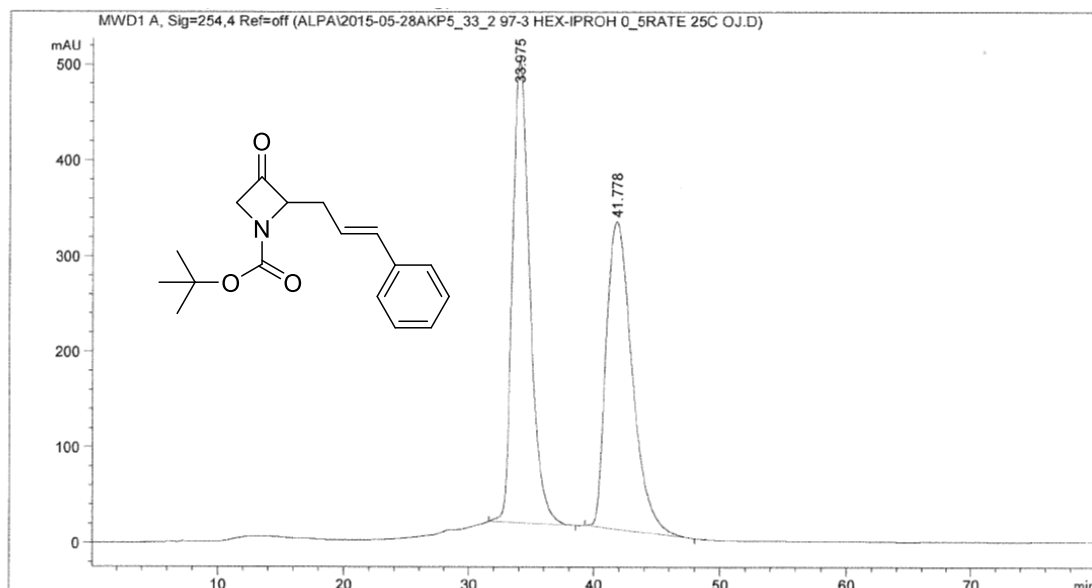
Prepared from SAMP Hydrazone (*S*)-**1** (*ee* = 77%):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.028	BV	0.1974	29.61179	1.78173	0.0273
2	6.493	VB	0.2751	204.86739	9.87397	0.1889
3	7.192	BV	0.1922	44.49460	3.25113	0.0410
4	8.042	VB	0.7209	919.04889	14.95653	0.8474
5	13.433	BB	0.6974	164.05620	2.75431	0.1513
6	34.346	BB	1.0880	1.22208e4	132.02003	11.2681
7	41.683	BB	1.8039	9.48725e4	615.98022	87.4760

Totals : 1.08455e5 780.61792

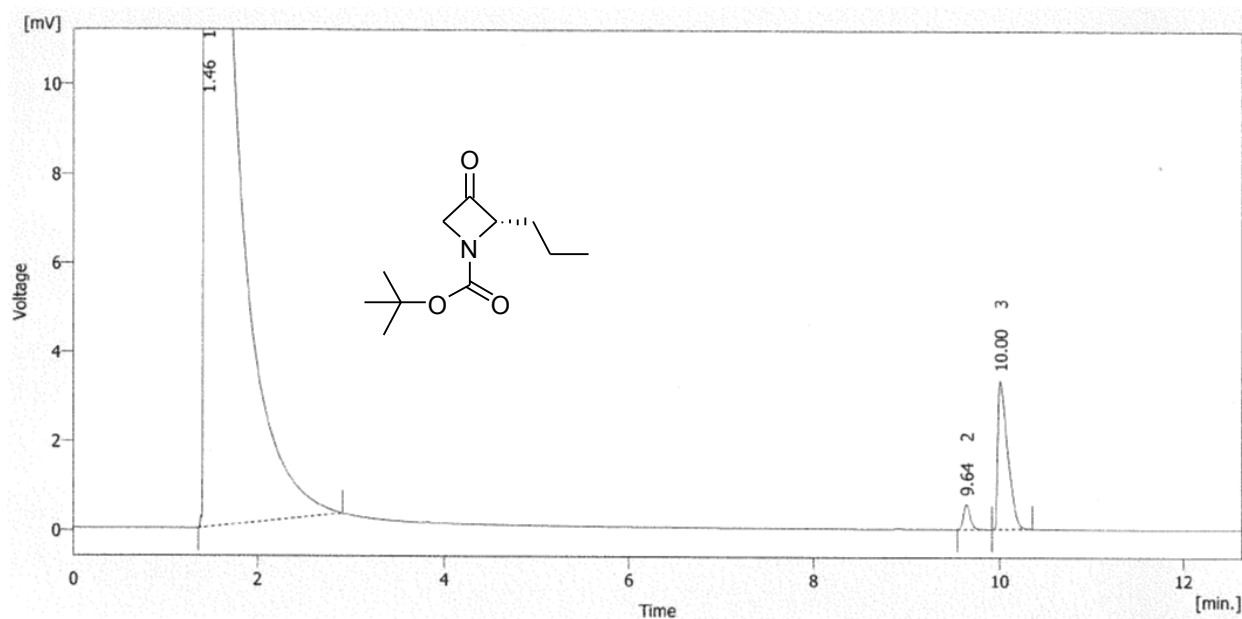
Prepared from dimethyl hydrazone **5** (racemic):



Chiral GC Chromatograms for 10

CP-ChiraSil-DEX CB 25m x 0.25mm x 0.25 μ m column, T = 130°C, P = 18 psi, He carrier gas.

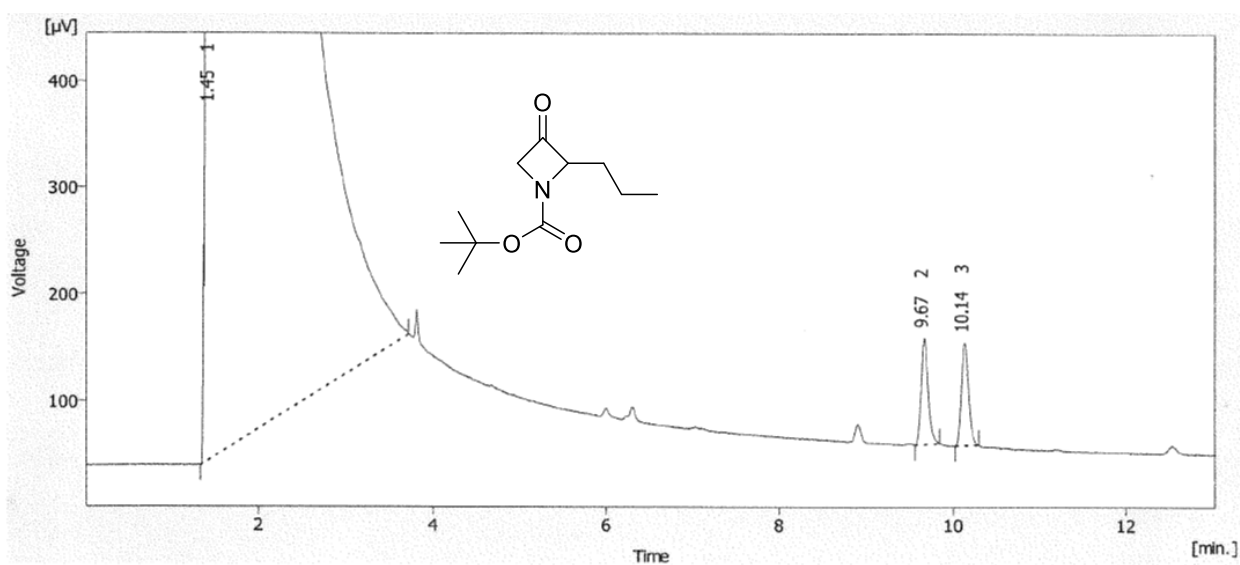
Prepared from SAMP Hydrazone (*S*)-**1** (*ee* = 79%):



Result Table (Uncal - C:\Clarity\WORK1\DATA\Alpa\Alpa AKP4.30.2 130C final zoom - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	1.460	5815.508	1094.093	99.5	99.6	0.08	
2	9.640	2.790	0.547	0.0	0.0	0.08	
3	10.004	23.949	3.329	0.4	0.3	0.12	
	Total	5842.247	1097.969	100.0	100.0		

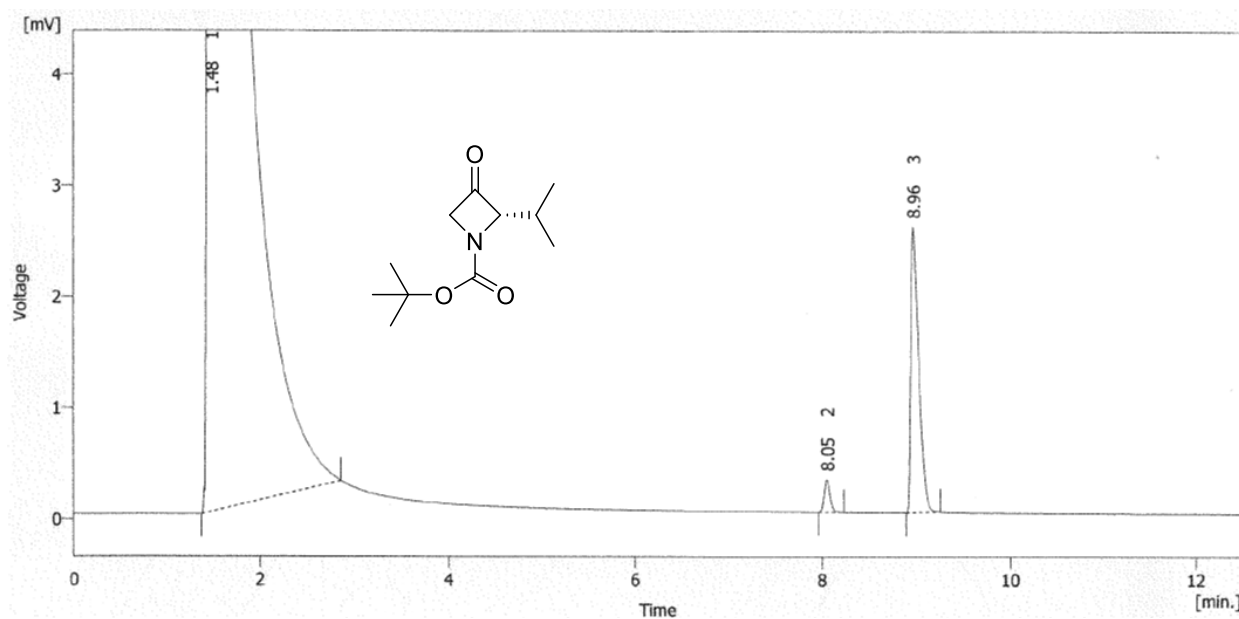
Prepared from dimethyl hydrazone **5** (racemic):



Chiral GC Chromatograms for 11

CP-ChiraSil-DEX CB 25m x 0.25mm x 0.25µm column, T = 130°C, P = 18 psi, He carrier gas.

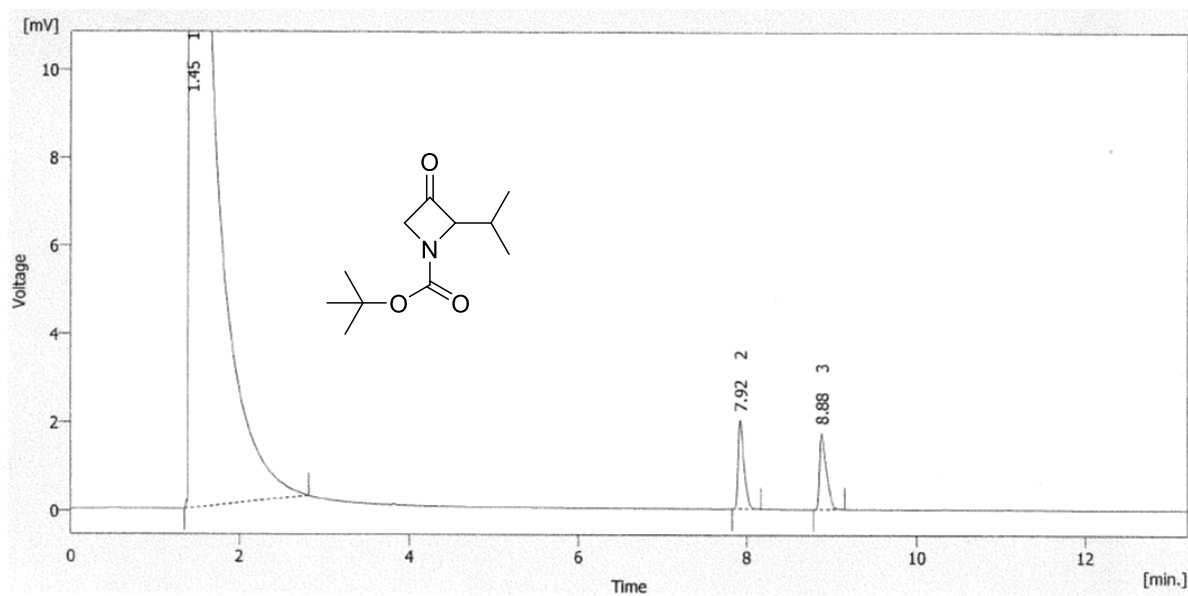
Prepared from SAMP Hydrazone (*S*)-**1** (*ee* = 85%):



Result Table (Uncal - C:\Clarity\WORK1\DATA\Alpa\Alpa AKP4.36.2 130C - U-PAD2 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	1.476	5195.910	1094.038	99.7	99.7	0.07	
2	8.052	1.254	0.290	0.0	0.0	0.07	
3	8.964	15.128	2.566	0.3	0.2	0.10	
Total		5212.292	1096.894	100.0	100.0		

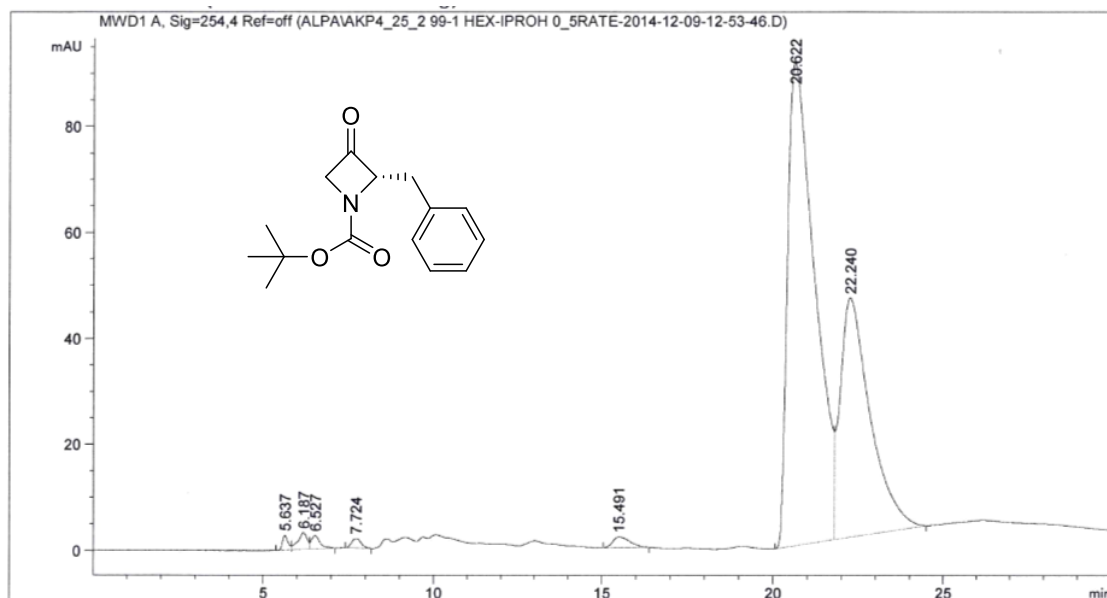
Prepared from dimethyl hydrazone **5** (racemic):



Chiral HPLC Chromatograms for 12

Chiralcel OD column (0.46cm ø x 25 cm), 99:1 hexane: propan-2-ol, T = 23°C, flow rate = 0.5 mL/min, λ = 254 nm.

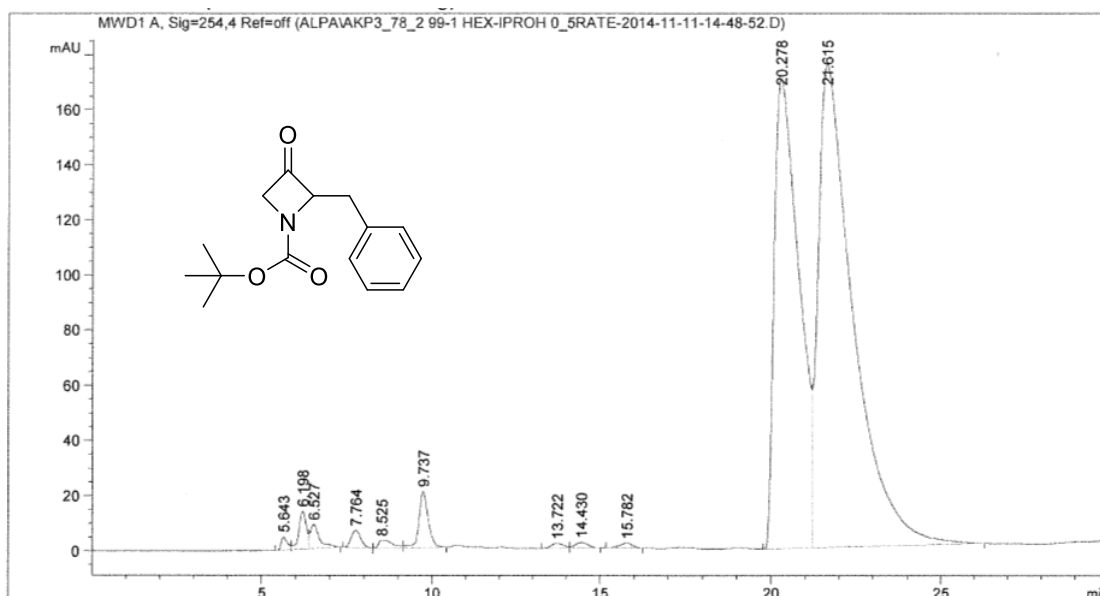
Prepared from SAMP Hydrazone (*S*)-**1** (*ee* = 33%):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.637	BV	0.1673	31.57697	2.78368	0.3938
2	6.187	VV	0.2370	59.39250	3.17820	0.7406
3	6.527	VB	0.2107	44.57138	2.50346	0.5558
4	7.724	BB	0.2237	33.44839	1.76827	0.4171
5	15.491	VB	0.4103	70.99445	2.03346	0.8853
6	20.622	BV	0.7427	5002.23389	91.16113	62.3763
7	22.240	VB	0.7446	2777.23462	45.21692	34.6312

Totals : 8019.45220 148.64511

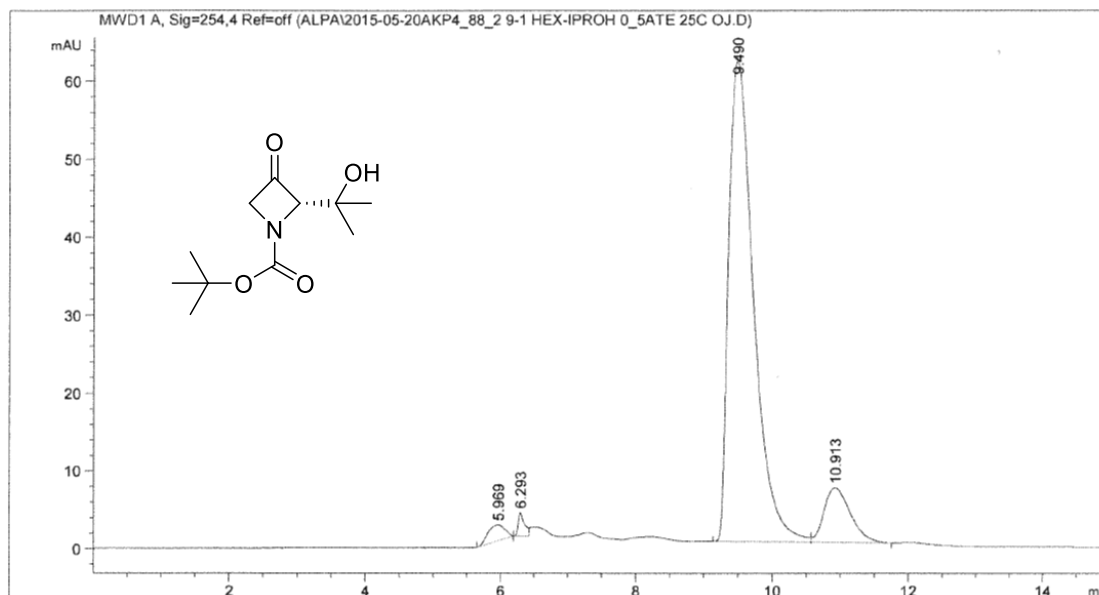
Prepared from dimethyl hydrazone **5** (racemic):



Chiral HPLC Chromatograms for 13

Chiralcel OJ column (0.46cm ø x 25 cm), 9:1 hexane: propan-2-ol, T = 25°C, flow rate = 0.5 mL/min, λ = 254 nm.

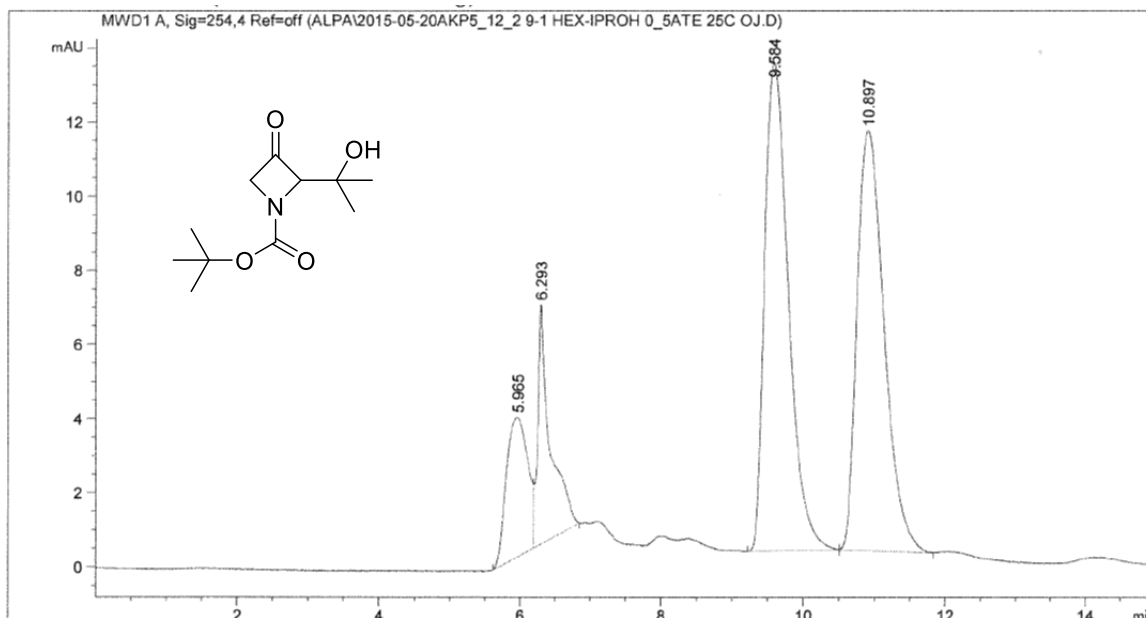
Prepared from SAMP Hydrazone (*S*)-1 (*ee* = 78%):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.969	BB	0.2158	36.22143	2.00001	2.0080
2	6.293	BV	0.0883	19.41742	3.00964	1.0765
3	9.490	BV	0.3895	1557.19141	61.58243	86.3277
4	10.913	VB	0.3383	190.98471	7.05560	10.5878

Totals : 1803.81496 73.64767

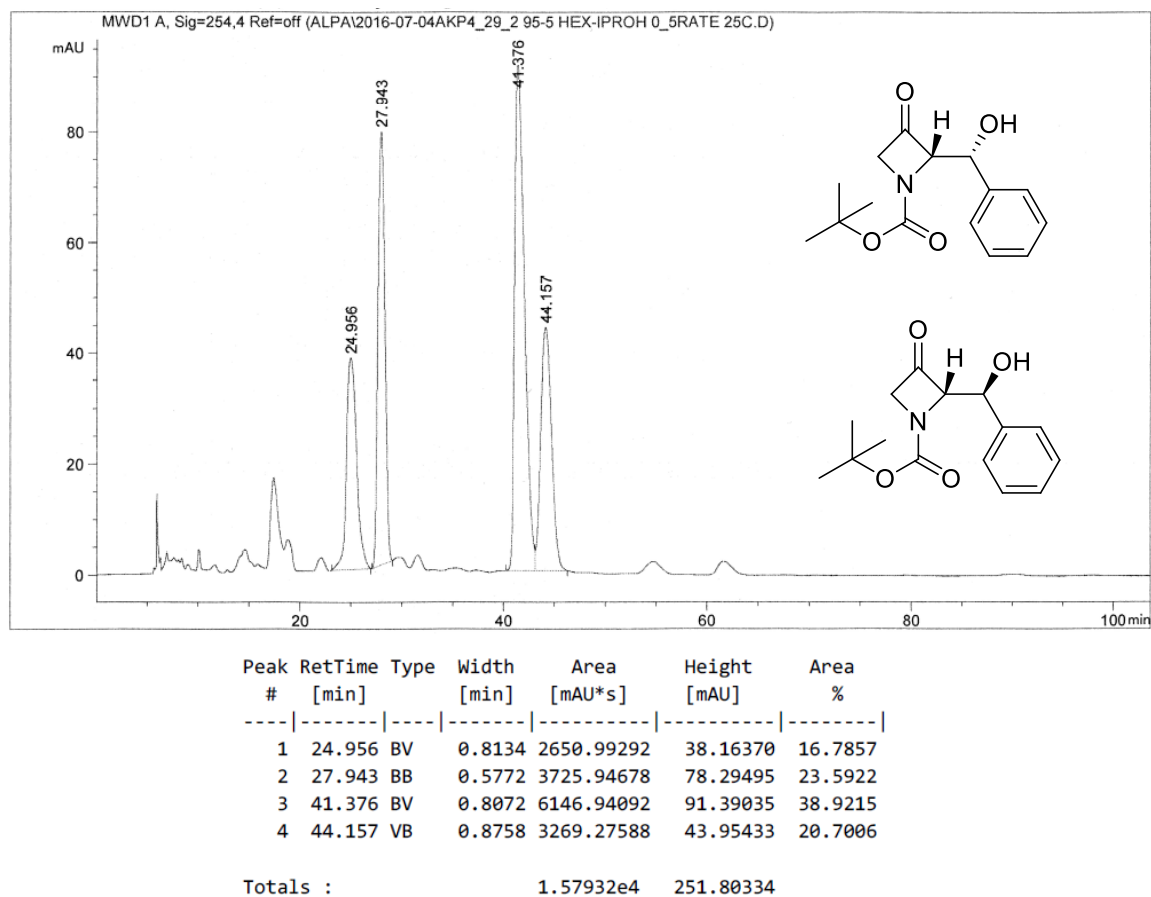
Prepared from dimethyl hydrazone **5** (racemic):



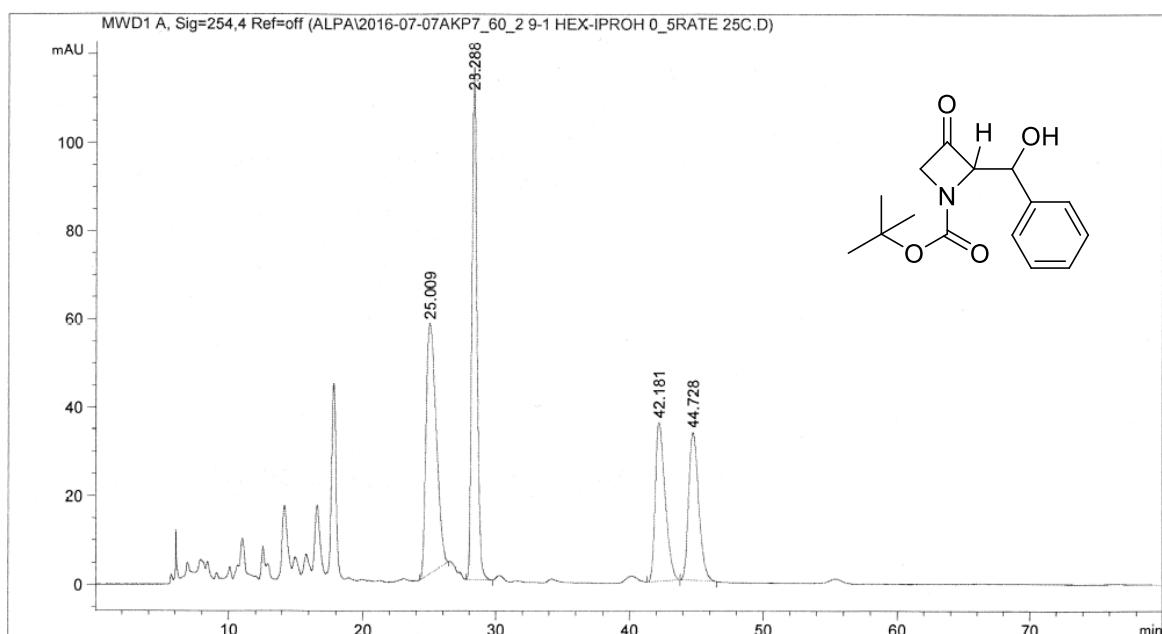
Chiral HPLC Chromatograms for 14

Chiralpak IA column (0.46cm ø x 25 cm), 95:5 hexane: propan-2-ol, T = 25°C, flow rate = 0.5 mL/min, λ = 254 nm.

Prepared from SAMP Hydrazone (*S*)-1 (*ee* = 31%, 17%):



Prepared from dimethyl hydrazone **5** (racemic):



References

- 1 Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339-341.
- 2 Sheldrick, G. M. *Acta Cryst.* **2015**, *A71*, 3-8.
- 3 Sheldrick, G. M. *Acta Cryst.* **2015**, *C71*, 3-8.