Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting information

Stereospecific C-H activation as a key step for asymmetric synthesis of various biologically active cyclopropanes

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General considerations

Anhydrous conditions term denotes reactions conducted under argon in dry glassware using dry solvents. Tetrahydrofuran was distilled over Na/benzophenone. Anhydrous dichloromethane, diethyl ether, tetrahydrofuran and acetonitrile were purchased from Aldrich (Sure/Seal packaging, kept over 3Å molecular sieves). Molecular sieves were activated by heating at 250 °C under vacuum overnight. Palladium(II) acetate and silver(I) acetate were kept in a desiccator prior to use.

Purification on column chromatography either refers to manual column chromatography loaded with silica 60 (40-63 µm) or to flash chromatography using Armen Flash Instrument and Biotage SNAP Cartridge KP-Silica 60 µm.

NMR experiments were recorded on a Brucker 400 MHz, FID treated with NMR Notebook. The chemical shift δ is given relatively to the residual solvent. Broad = br s, singulet = s, doublet = d, triplet = t, quadruplet = q, multiplet = m.

Melting points were taken on a Buchi M-560 apparatus, with three measures per compound.

Infrared experiments were done on a PerkinElmer UATR Two FT-IR C92778 spectrometer, neat or in solution in dichloromethane. Broad = br s, weak = w, medium = m, strong = s.

Optical rotations were measured with an Anton Paar Polarimeter MCP 200.

Chiral HPLC measurements were performed on a Shimadzu system with a quaternary low-pressure LC-20AD pump, an automatic SIL-20A HT injector, a CTO-10 AS oven and a SPD-M20 A diode array detector (DAD). The injection volume was 1 µL, the temperature of the oven set to 35 °C and the concentration of the sample around 1 g/L.

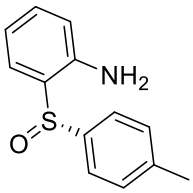
HMRS measurements were performed by the Service de Spectrométrie de Masse de l'Institut de Chimie at the University of Strasbourg.

X-Ray crystallographic measurements were performed by the Crystallography Service of the University of Strasbourg.

Chiral auxiliary and cyclopropane substrates syntheses

(*S*)-2-(*p*-tolylsulfinyl)aniline APS

The title compound was prepared according to the literature procedure.[1]



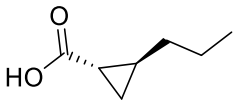
^{1}H NMR (400 MHz, $CDCl_3$): 7.40-7.48 (3H, m), 7.19-7.28 (3H, m), 6.76 (1H, t, J=7.4 Hz), 6.59 (1H, d, J=8 Hz), 4.91 (1H, br s, NH_2), 2.37 (1H, s, PhCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 147.54, 140.70, 140.09, 132.84, 129.66, 128.32, 124.79, 123.87, 117.59, 117.26, 21.35; $[\alpha]_D^{20} + 40.3°$ ($c = 1.0$, $CHCl_3$); R_t (min, IC, Hex/IPA 80/20, 0.5 mL/min): 64.58 (99%), 79.57 (1%); other data match the described ones.

General procedure for the preparation of trans-cyclopropanecarboxylic acids[2]

Sodium hydride (2 equiv.) and trimethylsulfoxonium iodide (2.2 equiv.) in anhydrous DMSO were stirred at room temperature for 2 h. Then, appropriate crotonate (1 equiv.) was added and the mixture was stirred overnight at room temperature. A 10M NaOH sol. was added and the mixture was stirred for 6 h at room temperature. Diethyl ether (50 mL) was added. The aqueous layer was extracted and acidified with conc. HCl (few drops). Diethyl ether (100 mL) was added. The organic layer was extracted, washed with water (3x 50 mL), brine (50 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to afford the desired cyclopropane.

***trans* 2-propylcyclopropane-1-carboxylic acid 5[3]**

General procedure for the preparation of trans-cyclopropanecarboxylic acids was applied using ethyl (*E*)-hex-2-enoate (7.7 mL, 50.6 mmol, 1 equiv.) as substrate. The title compound (3.15 g, 49%) was isolated as an orange oil.



^{1}H NMR (400 MHz, $CDCl_3$): 1.37-1.46 (2H, m), 1.32-1.36 (1H, m), 1.18-1.31 (3H, m), 0.92 (3H, t, J=7.2 Hz), 0.83-0.88 (1H, m), 0.77 (1H, dd, J=8.3, 6.0, 4.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 181.08, 35.10, 23.78, 22.22, 20.04, 16.31, 13.78; other data match the reported ones.

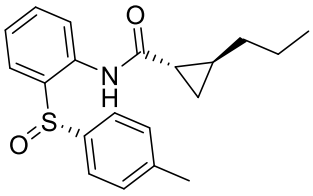
***trans*-2-propyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide 4**

5 (1.72 g, 13.4 mmol, 2 equiv.) and **APS** (1.55 g, 6.7 mmol, 1 equiv.) were dissolved in 5 mL of anhydrous DMF, followed by addition of pyridine (3.2 mL, 40.2 mmol, 6 equiv.) and propylphosphonic anhydride (8.7 mL, 14.74 mmol, 2.2 equiv., 50% weight solution in DMF). The resulting mixture was stirred 18h at room temperature. Brine (50 mL) and diethyl ether (50 mL) were added to the mixture and the phases were separated. The organic layer was washed with brine (2x 20 mL), sat. $NaHCO_3$ sol. (3x 30 mL), 1M HCl sol. (3x 30 mL), brine (2x 10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to give the title compound (2.17 g, 95%) as a brownish oil as an approximate 1:1 mixture of diastereomers.

[1] Jerhaoui S., Djukic J.-P., Wencel-Delord J., Colobert F., **2017**, *submitted.*

[2] Adapted from Merschaert et al., *Org. Process Res. & Dev.*, **2007**, *11*, 1104-1111

[3] Jerhaoui S., Chadoura F., Rose C., Djukic J.-P., Wencel-Delord J., Colobert F*., Chem. Eur. J.*, **2016**, *22*, 17393-17406

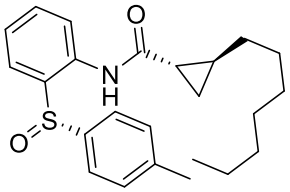


^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (1H, m, N*H*), 8.38 and 8.32 (1H, d, J=8.8 Hz), 7.51 (1H, dd, J=7.6, 1.2 Hz), 7.38- 7.48 (3H, m), 7.24 (2H, dd, J=8.4, 3.4 Hz), 7.12 (1H, t, J=7.4 Hz), 2.36 (3H, s, PhCH_3), 1.01- 1.50 (7H,m), 0.93 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$), 0.62- 0.73 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 171.98 and 171.95 (1C), 141.32 and 141.27 (1C), 140.54 and 140.45 (1C), 139.67 and 139.60 (1C), 132.96 and 132.90 (1C), 129.94, 127.66 and 127.59 (1C), 124.42 and 124.37 (1C), 122.99 and 122.89 (1C), 122.76 and 122.62 (1C), 117.81 and 117.63 (1C), 35.29 and 35.18 (1C), 23.61 and 23.48 (1C), 22.48 and 22.37 (1C), 22.35 and 22.31 (1C), 21.30, 15.49 and 15.13 (1C), 13.95 and 13.88 (1C); other data match the reported ones.

trans-2-heptyl-_N_-(2-((_S_)-_p_-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide 8

General procedure for the preparation of *trans*-cyclopropanecarboxylic acids was applied using ethyl (*E*)-dec-2-enoate (1 mL, 4.3 mmol, 1 equiv.) as substrate. The title compound (779 mg) was obtained as an orange oil and used as such without purification.

A solution of acid (779 mg, 4.23 mmol, 1.2 equiv.) and **APS** (800 mg, 3.46 mmol, 1 equiv.) were dissolved in 3 mL of anhydrous DMF, followed by addition of pyridine (750 µL, 9.32 mmol, 2.7 equiv.) and propylphosphonic anhydride (2.8 mL, 4.74 mmol, 1.4 equiv., 50% weight solution in DMF). The resulting mixture was stirred 18 h at room temperature. Brine (20 mL) and diethyl ether (20 mL) were added to the mixture and the phases were separated. The organic layer was washed with brine (2x 10 mL), sat. $NaHCO_3$ sol. (3x 10 mL), 1M HCl sol. (3x 10 mL), brine (2x 10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to give the title compound (1.35 g, 98%) as a brownish oil as an approximate 1:1 mixture of diastereomers.



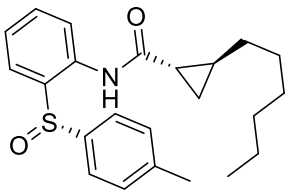
^{1}H NMR (400 MHz, $CDCl_3$): 10.22-10.46 (1H, m, N*H*), 8.35 and 8.29 (1H, d, J=8.4 Hz), 7.47-7.54 (1H, m), 7.37-7.46 (3H, m), 7.21 (2H, d, J=8.3 Hz), 7.07-7.13 (1H, m), 2.34 (3H, s, PhCH_3), 0.97-1.38 (15H, m), 0.82-0.92 (3H, m), 0.59-0.71 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 172.21 and 172.19 (1C), 141.52 and 141.49 (1C), 140.73 and 140.71 (1C), 140.63 and 140.61 (1C), 139.82 and 139.77 (1C), 133.13 and 133.10 (1C), 130.14, 127.80 and 127.79 (1C), 124.57, 123.24 and 123.10 (1C), 122.99 and 122.84 (1C), 33.47 and 33.32 (1C), 32.10 and 32.05 (1C), 29.63 and 29.54 (1C), 29.48, 29.41 and 29.39 (1C), 23.81 and 23.71 (1C), 22.94 and 22.92 (1C), 22.88 and 22.76 (1C), 21.50, 15.79 and 15.44 (1C), 14.32; FT-IR (cm^{-1}): 1691 (m, C=O), 1020 (m, S=O); HRMS (ESI-TOF): m/z calcd for $C_{24}H_{32}NO_2S^+$: 398.2148, found: 398.2131.

trans-2-hexyl-_N_-(2-((_S_)-_p_-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide 11

General procedure for the preparation of *trans*-cyclopropanecarboxylic acids was applied using methyl (*E*)-non-2-enoate (1 mL, 5.1 mmol, 1 equiv.) as substrate. The title compound (644 mg, 74%) was obtained as a yellow thick oil and used as such without purification.

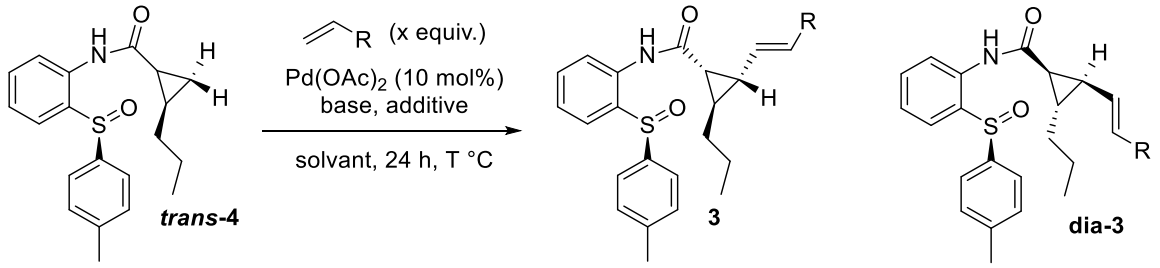
A solution of acid (644 mg, 3.78 mmol, 1.2 equiv.) and **APS** (729 mg, 3.15 mmol, 1 equiv.) were dissolved in 3 mL of anhydrous DMF, followed by addition of pyridine (700 µL, 8.66 mmol, 2.7 equiv.) and propylphosphonic anhydride (2.6 mL, 4.32 mmol, 1.4 equiv., 50% weight solution in DMF). The resulting mixture was stirred 18 h at room temperature. Brine (20 mL) and diethyl ether (20 mL) were added to the mixture and the phases were separated. The organic layer was washed with brine (2x 10

mL), sat. NaHCO3 sol. (3x 10 mL), 1M HCl sol. (3x 10 mL), brine (2x 10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to give the title compound (1.2 g, 99%, mixed with around 5% of impurity coming from the cyclopropane) as a yellowish oil as an approximate 1:1 mixture of diastereomers.

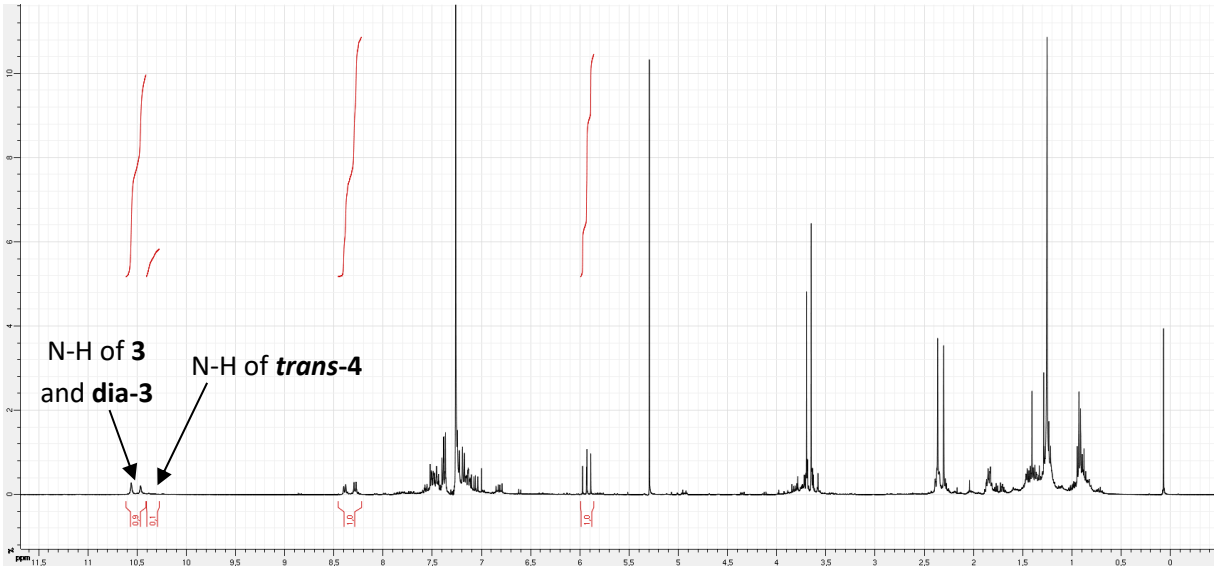


^{1}H NMR (400 MHz, $CDCl_3$): 10.20-10.45 (1H, m, N*H*), 8.35 and 8.29 (1H, d, J=8.4 Hz), 7.47-7.52 (1H, m), 7.36-7.45 (3H, m), 7.22 (2H, d, J=8.4 Hz), 7.08-7.13 (1H, m), 2.34 (3H, s, PhC*H*$_3$), 0.98-1.39 (13H, m), 0.82-0.92 (3H, m), 0.58-0.70 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 172.18 and 172.15 (1C), 141.49 and 141.45 (1C), 140.73 and 140.62 (1C), 139.81 and 139.76 (1C), 133.11 and 133.08 (1C), 130.13, 127.78, 124.55, 123.21 and 123.07 (1C), 122.95 and 122.80 (1C), 33.45 and 33.30 (1C), 32.07 and 32.00 (1C), 29.35 and 29.33 (1C), 29.31 and 29.22 (1C), 23.80 and 23.70 (1C), 22.91 and 22.87 (1C), 22.83 and 22.73 (1C), 21.48, 15.76 and 15.41 (1C), 14.32 and 14.29 (1C); FT-IR (cm^{-1}): 1694 (s, C=O), 1025 (m, S=O); HRMS (ESI-TOF): m/z calcd for $C_{23}H_{30}NO_2S^+$: 384.1992, found: 384.1979.

Optimization of the Heck-type reaction conditions



A reactor was charged with ***trans*-4** (20 mg, 0.059 mmol, 1 equiv.), base (1 to 4 equiv.), additive (0.1 to 1 equiv.), coupling partner (3 to 6 equiv.) and palladium(II) acetate (1.32 mg, 0.0059 mmol, 10 mol%). To the solids was added 500 µL of solvent. The vial was capped and the mixture was stirred at the appropriate temperature during 24h. After cooling down to room temperature, the mixture was filtered through PTFE 45 µm filter, washed with dichloromethane and evaporated under reduced pressure. Conversion was determined by crude ^{1}H NMR analysis, as shown below.



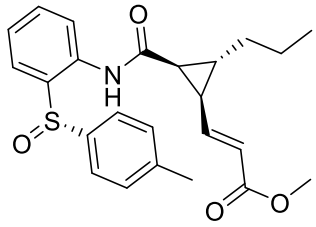
Entry	Base (equiv.)	Additive (equiv.)	R (x equiv.)	Solvant	Conversion (%)
1	AgOAc (4)	NaTFA (0.5)	CO_2Me (6)	HFIP/H_2O (4:1)	90
2	AgOAc (3)	NaTFA (0.5)	CO_2Me (3)	HFIP	60
3	AgOAc (3)	NaTFA (0.5)	CO_2Me (3)	HFIP/H_2O (4:1)	70
4	AgOAc (2.5)	NaTFA (0.5)	CO_2Me (2.5)	HFIP/H_2O (4:1)	60
5	AgOAc (4)	NaTFA (0.5)	$CO_2{}^tBu$ (5)	HFIP/H_2O (4:1)	0
6[4]	AgOAc (4)	NaTFA (0.5)	CO_2Me (6)	HFIP/H_2O (4:1)	88
7	AgOAc (4)	NaTFA (0.5)	CO_2Et (5)	HFIP/H_2O (4:1)	80
8	AgOAc (4)	NaTFA (0.5)	CO_2Et (4)	HFIP/H_2O (4:1)	80

[4] Reaction was performed on a 1.5 mmol scale.

9[5]	AgOAc (2)	NaTFA (0.5)	CO_2Et (4)	HFIP/H_2O (4:1)	75
10[5]	$Cu(OAc)_2$ (1)	NaTFA (0.5)	CO_2Et (4)	HFIP/H_2O (4:1)	10
11[5]	-	NaTFA (0.5)	CO_2Et (4)	HFIP/H_2O (4:1)	10
12[5]	AgOAc (1)	NaTFA (0.5)	CO_2Et (4)	HFIP/H_2O (4:1)	50
13[5]	1,4-BQ (1)	NaTFA (0.5)	CO_2Et (4)	HFIP/H_2O (4:1)	0
14[5,6]	AgOAc (2)	NaTFA (0.5)	CO_2Et (4)	HFIP/H_2O (4:1)	85
15[5,6,7]	AgOAc (2)	NaTFA (0.5)	CO_2Et (4)	HFIP/H_2O (4:1)	90
16	AgOAc (2)	NaTFA (0.5)	CN (4)	HFIP/H_2O (4:1)	0

methyl (*E*)-2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate 3

***trans*-4** (500 mg, 1.5 mmol, 1 equiv.), methyl acrylate (750 µL, 8.3 mmol, 5.6 equiv.), silver acetate (489 mg, 2.9 mmol, 2 equiv.), palladium(II) acetate (33 mg, 0.15 mmol, 10 mol%) and sodium trifluoroacetate (100 mg, 0.73 mmol, 50 mol%) were dissolved in 10 mL of HFIP/H_2O (4:1). The resulting mixture was flushed with oxygen and then stirred 24 h at 80 °C under oxygen atmosphere. After cooling down to room temperature, the mixture was diluted with DCM, filtered over celite and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel with CyHex/EtOAc (95:5 to 85:5) to afford the two diastereoisomers **3** (262 mg, 42%) as a clear oil and **dia-3** (300 mg, 48%) as a yellow solid, which afforded suitable mono crystals for X-Ray diffraction analysis in chloroform/benzene/pentane.

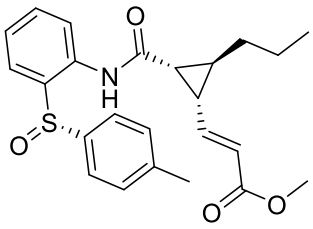


^{1}H NMR (400 MHz, $CDCl_3$): 10.56 (1H, s, N*H*), 8.28 (1H, d, J=8.4 Hz), 7.42-7.52 (2H, m), 7.37 (2H, d, J=8.4 Hz), 7.18 (2H,d, J=8.4 Hz), 7.13 (1H, td, J=7.6, 0.8 Hz), 6.82 (1H, dd, J=15.6, 9 Hz, C*H*=CH-CO_2Me), 5.90 (1H, d, J=15.6 Hz, CH=C*H*-CO_2Me), 3.64 (3H, s, C(O)OC*H*$_3$), 2.30 (3H, s, PhC*H*$_3$), 1.78-1.89 (3H, m), 1.23-1.53 (4H, m), 0.92 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 167.97, 166.49, 146.77, 141.66, 140.28, 139.35, 133.01, 130.16, 127.95, 127.61, 124.36, 123.34, 123.09, 120.98, 51.41, 34.60, 32.44, 31.64, 29.00, 22.10, 21.29, 13.90; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{27}NNaO_4S^+$: 448.1553, found: 448.1495; $[\alpha]_D^{20} - 16.5°$ ($c = 0.7$, $CHCl_3$); R_t (min, IC, Hex/IPA 80/20, 0.5 mL/min): 49.21 (99%), 63.37 (1%).

[5] Reaction was performed under oxygen atmosphere.

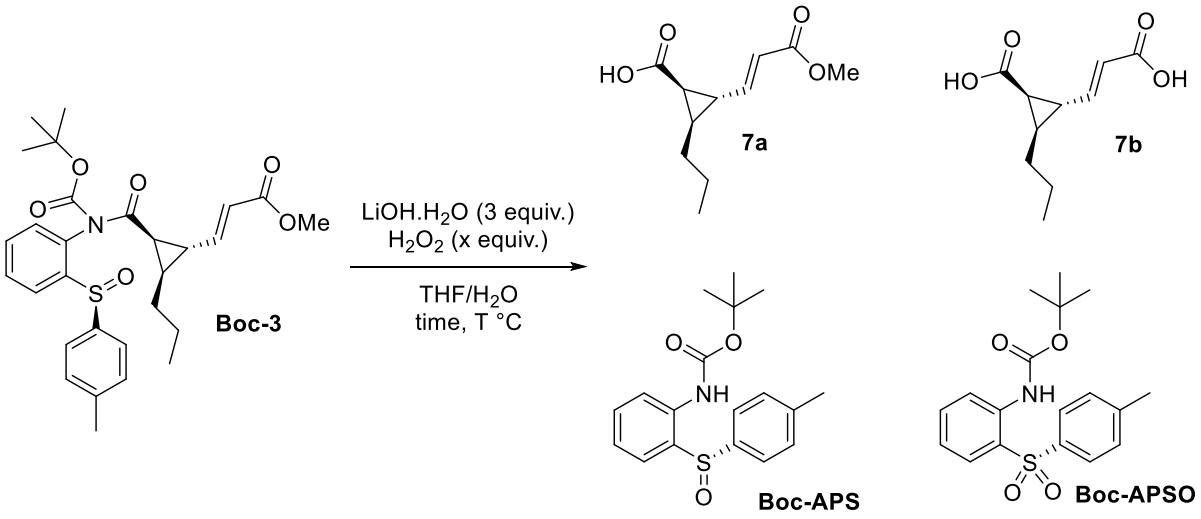
[6] Reaction was premixed during 20 min at room temperature before being heated at 80 °C.

[7] Reaction was heated during 30 h at 80 °C. On large scale, ie 6.4 mmol, same conversion was obtained while using 5 mol% $Pd(OAc)_2$ during 30 h. When using 5 mol% $Pd(OAc)_2$ on a smaller scale, only 30% conversion was observed.

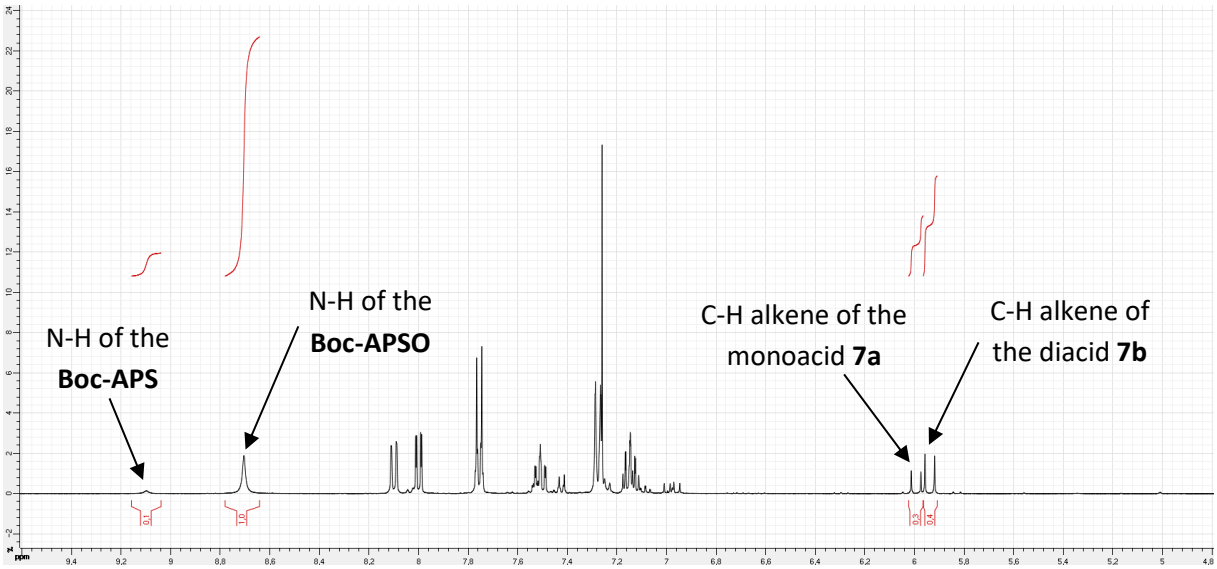


^{1}H NMR (400 MHz, $CDCl_3$): 10.46 (1H, s, N*H*), 8.39 (1H, d, J=8.8 Hz), 7.42-7.53 (2H, m), 7.39 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.4 Hz), 7.13 (1H, td, J=7.6, 1.2 Hz), 7.06 (1H, dd, J=16, 8.2 Hz, C*H*=CH-CO_2Me), 5.95 (1H, d, J=16 Hz, CH=C*H*-CO_2Me), 3.69 (3H, s, C(O)OC*H*$_3$), 2.36 (3H, s, PhC*H*$_3$), 1.66-1.90 (3H, m), 1.22-1.46 (4H, m), 0.91 (3H, t, J=7 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.08, 166.75, 146.70, 141.52, 140.34, 139.88, 133.10, 130.11, 127.75, 127.53, 124.51, 123.23, 123.11, 121.21, 51.47, 34.66, 32.65, 31.91, 29.04, 22.08, 21.41, 13.93; mp: 76 °C $[\alpha]_D^{20} + 23.3°$ ($c = 0.8$, $CHCl_3$); R_t (min, IA, Hex/IPA 80/20, 0.5 mL/min): 16.02 (99%), 31.72 (1%).

Optimization of the selective mild deprotection amide vs ester



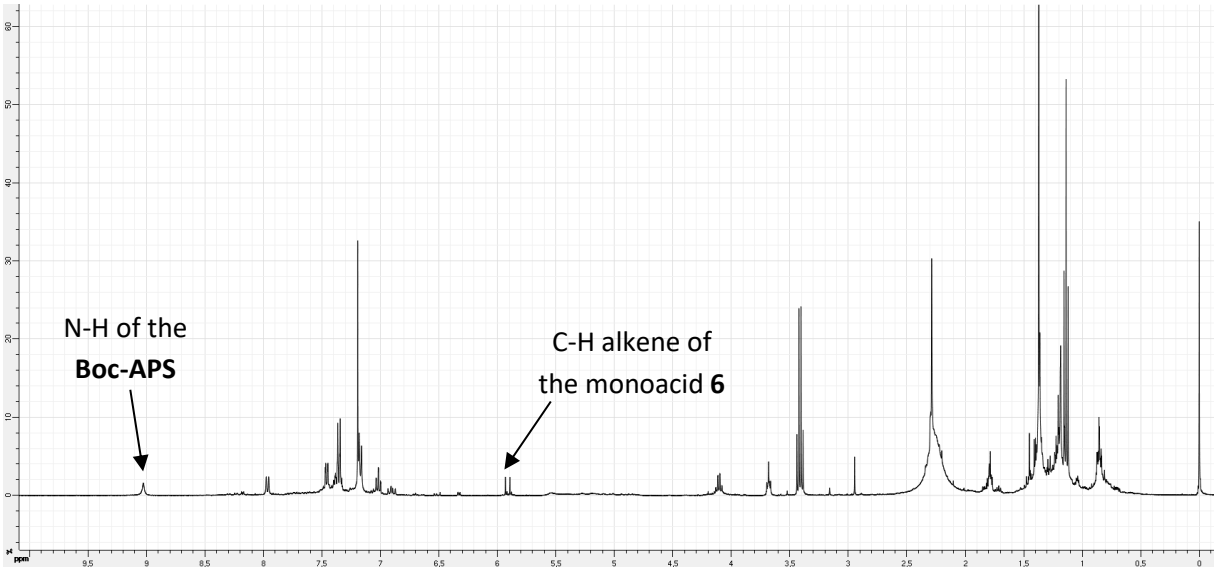
In a tube and at 0 °C were added **Boc-3** (20 mg, 0.038 mmol, 1 equiv.) and lithium hydroxide monohydrate (4.89 mg, 0.114 mmol, 3 equiv.) in 500 µL of a 4:1 mixture of THF and H_2O. H_2O_2 (1 to 5 equiv., 30% in water) was then added and the mixture was stirred at 0°C during the appropriate time. The mixture was then acidified with 1M HCl sol. (5 mL). Diethyl ether (5 mL) was added and phases were separated. The organic layer was evaporated under reduced pressure. Conversion was determined by crude ^{1}H NMR analysis of the aromatic region, as shown below.[8]



[8] Other deprotection methods, not involving prior Boc-protection, were tested without success. Usually the diacid was obtained.

Entry	H_2O_2 (x equiv.)	T °C	Time (h)	Conversion (%)	Ratio 7a/7b	Ratio Boc-APS/Boc-APSO
1	5	25	1,5	100	40/60	10/90
2	0	25	2	80	25/75	100/0
3	5	0	1,2	100	100/0	0/100
4	0	0	4,5	50	20/80	100/0
5[9]	0	0	1,5	85	80/20	70/30
6[10]	5	0	1,5	100	95/5	20/80
7[10,11]	0	0	1,5	90	>95/5	100/0

Particularly, the crude ^{1}H NMR for entry 7 showed clearly no **Boc-APSO** and almost full conversion to the desired mono-acid product **6**:

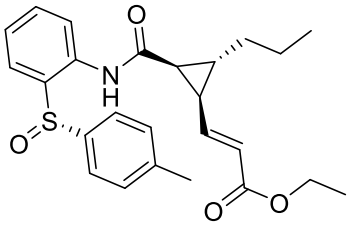


[9] In this case, commercially available lithium peroxide was used as deprotecting agent.
[10] In this case, ethyl acrylate ester derivative was used as substrate.
[11] In this case, only 2 equiv. of $LiOH.H_2O$ was used.

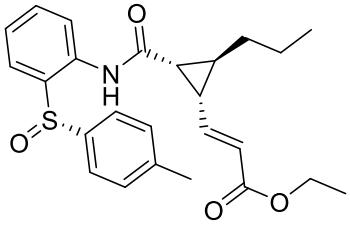
Hoshinolactame synthesis[12]

ethyl (*E*)-3-(2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate 3'

***trans*-4** (1 g, 2.9 mmol, 1 equiv.), ethyl acrylate (1 mL, 9.2 mmol, 3.1 equiv.), silver acetate (1 g, 6.0 mmol, 2 equiv.), palladium(II) acetate (35 mg, 0.16 mmol, 5 mol%) and sodium trifluoroacetate (200 mg, 1.47 mmol, 50 mol%) were dissolved in 20 mL of HFIP/H_2O (4:1). The resulting mixture was flushed with oxygen and then stirred 24 h at 80 °C under oxygen atmosphere. After cooling down to room temperature, the mixture was diluted with DCM, filtered over celite and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel with CyHex/EtOAc (95:5 to 85:5) to afford the two diastereoisomers **3'** (564 mg, 44%) and **dia-3'** (597 mg, 46%) as yellow oils.



^{1}H NMR (400 MHz, $CDCl_3$): 10.53 (1H, br s, N*H*), 8.28 (1H, d, J=8.4 Hz), 7.41-7.50 (2H, m), 7.36 (2H, d, J=8.2 Hz), 7.17 (2H, d, J=8.4 Hz), 7.11 (1H, td, J=7.6, 0.8 Hz), 6.80 (1H, dd, J=15.6, 9.4 Hz), 5.88 (1H, d, J=15.6 Hz), 4.03-4.16 (2H, m, C(O)OC*H*$_2$CH$_3$), 2.29 (3H, s, PhC*H*$_3$), 1.74-1.86 (3H, m), 1.29-1.49 (4H, m), 1.21 (3H, t, J=7.2 Hz, C(O)OCH$_2$C*H*$_3$), 0.91 (3H, t, J=7.1 Hz, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.07, 166.21, 146.51, 141.75, 140.37, 139.47, 133.09, 130.25, 127.99, 127.69, 124.48, 123.40, 123.15, 121.50, 60.26, 34.71, 32.54, 31.75, 29.07, 22.18, 21.40, 14.50, 13.98; FT-IR (cm^{-1}): 1716 (s, C=O ester), 1689 (s, C=O amide), 1021 (s, S=O); HRMS (ESI-TOF): m/z calcd for $C_{25}H_{30}NO_4S^+$: 440.1890, found: 440.1871; $[\alpha]_D^{20} - 18.6°$ $(c = 0.9,\ CHCl_3)$.



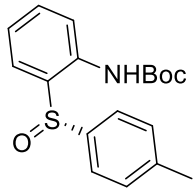
^{1}H NMR (400 MHz, $CDCl_3$): 10.43 (1H, br s, N*H*), 8.37 (1H, d, J=8.4 Hz), 7.48 (1H, dd, J=7.8, 1.1 Hz), 7.44 (1H, ddd, J=8.6, 7.3, 1.8 Hz), 7.37 (2H, d, J=8.2 Hz), 7.21 (2H, d, J=8.3 Hz), 7.12 (1H, td, J=7.5, 0.7 Hz), 7.04 (1H, dd, J=15.6, 10.2 Hz), 5.93 (1H, d, J=15.6 Hz), 4.07-4.19 (2H, m, C(O)OC*H*$_2$CH$_3$), 2.34 (3H, s, PhC*H*$_3$), 1.83 (1H, ddd, J=10.2, 8.3, 6.3 Hz), 1.72-1.79 (1H, m), 1.68 (1H, dd, J=8.2, 5.6 Hz), 1.27-1.39 (4H, m), 1.24 (3H, t, J=7.2 Hz, C(O)OCH$_2$C*H*$_3$), 0.89 (3H, t, J=7.1 Hz, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.17, 166.47, 146.46, 141.59, 140.43, 139.92, 133.21, 130.19, 127.85, 127.59, 124.58, 123.30, 123.21, 121.73, 60.30, 34.75, 32.69, 32.02, 29.05, 22.17, 21.50, 14.52, 14.02; FT-IR (cm^{-1}): 1711 (s, C=O ester), 1687 (s, C=O amide), 1025 (s, S=O); $[\alpha]_D^{20} + 36.5$ $(c = 1.1,\ CHCl_3)$.

***tert*-butyl (2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamate Boc-APS and (1*S*,2*R*,3*R*)-2-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)-3-propylcyclopropane-1-carboxylic acid 7a'**

To a stirred solution of **3'** (500 mg, 1.14 mmol, 1 equiv.) in 1 mL of anhydrous THF was added 4-(dimethylamino)-pyridine (12.5 mg, 0.102 mmol, 10 mol%), followed by di-tert-butyl dicarbonate (248 mg, 1.14 mmol, 1 equiv.). The resulting orange mixture was stirred 10 min at room temperature. The previous mixture was cooled to 0 °C with an ice-bath, followed by slow addition of a solution of lithium hydroxide monohydrate (100 mg, 2.391 mmol, 2.1 equiv.) in 1 mL of water. The resulting yellow mixture was stirred at 0 °C during 2 h.

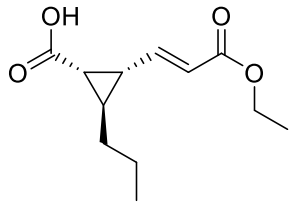
[12] Ogawa, H., Iwasaki, A., Sumimoto, S., Iwatsuki, M., Ishiyama, A., Hokari, R., Otoguro, K., Omura, S., Suenaga, K., *Org. Lett.*, **2017**, 19(4), pp. 890-893.

1M HCl sol. (10 mL) was added to reach pH 1-2, followed by diethyl ether (10 mL). The organic layer was extracted and washed with 1M HCl sol. (10 mL). Then, sat. $NaHCO_3$ solution (10 mL) was added to the organic layer, which was stirred 5 min at room temperature. It was extracted twice with sat. $NaHCO_3$ solution (5 mL). The organic layer was washed with water, dried (Na_2SO_4), filtered off and evaporated under reduced pressure to afford *tert*-butyl (2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamate (345 mg, 92 %) as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): 9.11 (1H, br s, N*H*), 8.02 (1H, d, J=8.4 Hz), 7.51 (1H, dd, J=7.6, 1.6 Hz), 7.37-7.44 (3H, m), 7.22 (2H, d, J=8.3 Hz), 7.06 (1H, td, J=7.6, 1.2 Hz), 2.34 (3H, s, PhC*H*$_3$), 1.42 (9H, s, NH*Boc*); ^{13}C NMR (100 MHz, $CDCl_3$): 152.76, 141.31, 140.66, 139.80, 133.05, 129.99, 128.92, 127.87, 124.65, 122.49, 122.09, 80.71, 28.50, 21.50; FT-IR (cm^{-1}): 1033 (m, S=O); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{22}NO_3S^+$: 332.1315, found: 332.1312; $[\alpha]_D^{20} + 74.2°$ ($c = 1.0$, $CHCl_3$); R_t (min, IA, Hex/iPrOH 98/2, 0.5 mL/min): 35.84 (99%), 38.34 (1%).

The combined aqueous layers were carefully acidified with 1M HCl sol. to pH *ca.* 1. Diethyl ether (20 mL) was added. The organic layer was extracted, and the aqueous layer back-extracted with diethyl ether (2 x 10mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to get the crude carboxylic acid (255 mg) as a yellow oil.



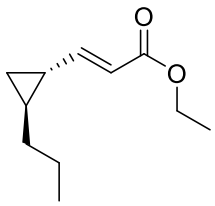
^{1}H NMR (400 MHz, $CDCl_3$): 9.10 (1H, br s, COO*H*), 6.95 (1H, dd, J=15.5, 9.9 Hz), 5.96 (1H, d, J=15.6 Hz), 4.15 (2H, qd, J=7.1, 0.6 Hz, C(O)OC*H*$_2$CH$_3$), 1.72-1.93 (3H, m), 1.31-1.48 (4H, m), 1.25 (3H, t, J=7.1 Hz, C(O)OCH$_2$C*H*$_3$), 0.90 (3H, t, J=7.1 Hz, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 177.58, 166.40, 145.78, 122.32, 60.47, 34.67, 32.13, 30.70, 29.02, 22.06, 14.46, 13.88; FT-IR (cm^{-1}): 3143 (br w, OH acid), 1694 (s, C=O); HRMS (ESI-TOF): m/z calcd for $C_{12}H_{19}O_4^+$: 227.1278, found: 227.1274; $[\alpha]_D^{20} + 41.0°$ ($c = 0.9$, $CHCl_3$).[13]

ethyl (*E*)-3-((1*S*,2*S*)-2-propylcyclopropyl)acrylate 2

Under dark, 2-mercaptopyridine-N-oxide (144 mg, 1.14 mmol, 1 equiv.) and DCC (234 mg, 1.14 mmol, 1 equiv.) were added to a solution of the crude acid **6'** (255 mg, 1.14 mmol, 1 equiv.) in 20 mL of anhydrous DCM. The resulting mixture was stirred under argon atmosphere at room temperature during 3 h. The previous mixture was then evaporated under reduced pressure under dark and then redissolved in 20 mL of benzene. 2-methyl-2-propanethiol (205 mg, 0.256 mL, 2.27 mmol, 2 equiv.) was added and the solution was degassed under dark, before being lightened with two sun lamps (distance around 20 - 30 cm) during 3 h.

The mixture was evaporated *in vacuo*. Diethyl ether (20 mL) and 1M HCl sol. (10 mL) were added. The organic layer was extracted, washed with 1M HCl sol. (2x 5 mL), sat. $NaHCO_3$ sol. (2x 5 mL), brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified by a short column chromatography on silica gel with CyHex/EtOAc (95:5) to afford the title compound (174 mg, 84% over four steps) as a clear oil.

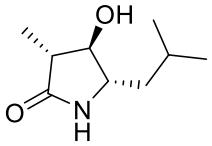
[13] For the other enantiomer, $[\alpha]_D^{20} - 40.8°$ ($c = 1.0$, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$): 6.45 (1H, dd, J=15.4, 10.1 Hz), 5.80 (1H, d, J=15.4 Hz), 4.14 (2H, q, J=7.2 Hz), 1.32-1.43 (2H, m), 1.21-1.30 (5H, m), 0.93-1.02 (1H, m), 0.89 (3H, t, J=7.3 Hz), 0.79 (1H, ddd, J=8.3, 4.6, 4.6 Hz), 0.73 (1H, ddd, J=8.1, 6.1, 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.13, 154.03, 117.68, 60.20, 35.87, 23.31, 22.57, 22.33, 16.19, 14.56, 14.08; $[\alpha]_D^{25} + 65.9°$ ($c = 1.0$, $CHCl_3$);[14] other data match the reported ones.

(3*R*,4*R*,5*S*)-4-hydroxy-5-isobutyl-3-methylpyrrolidin-2-one

This compound was synthesized according to the literature procedure.[12]

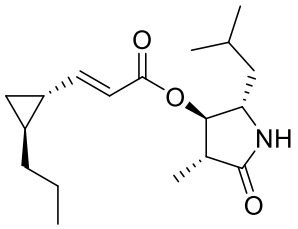


^{1}H NMR (400 MHz, MeOD): 3.50 (1H, dd, J=7.9, 6.1 Hz), 3.37 (1H, ddd, J=8.4, 6.1, 5.2 Hz), 2.30 (1H, dq, J=7.4, 7.3 Hz), 1.74-1.85 (1H, m), 1.50 (1H, ddd, J=13.7, 8.5, 5.1 Hz), 1.38 (1H, ddd, J=13.6, 8.3, 6.0 Hz), 1.19 (3H, d, J=7.2 Hz), 0.97 (3H, d, J=6.7 Hz), 0.95 (3H, d, J=6.6 Hz); ^{13}C NMR (100 MHz, MeOD): 179.68, 82.04, 59.89, 46.80, 45.19, 26.30, 23.88, 22.60, 13.88; $[\alpha]_D^{25} - 21.0°$ ($c = 0.9$, $CHCl_3$);[15] other data match the reported ones.

(2*S*,3*R*,4*R*)-2-isobutyl-4-methyl-5-oxopyrrolidin-3-yl (*E*)-3-((1*S*,2*S*)-2-propylcyclopropyl)acrylate 1

2 (10 mg, 54.9 µmol, 1 equiv.) was dissolved in 1 mL of a 1:1 mixture of 1,4-dioxane/H_2O. Lithium hydroxide monohydrate (10 mg, 238 µmol, 4.3 equiv.) was added and the mixture was stirred 3 h at 90 °C. After cooling to room temperature, the mixture was carefully acidified with 1M HCl sol. to reach pH *ca* 1-2. Ethyl acetate (10 mL) was added. The organic layer was extracted, washed with brine (2x 10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure.

The crude acid (8.4 mg, 54 µmol, 1 equiv.), **(3*R*,4*R*,5*S*)-4-hydroxy-5-isobutyl-3-methylpyrrolidin-2-one** (10 mg, 58.4 µmol, 1.1 equiv.) and 2-methyl-6-nitrobenzoic anhydride (60 mg, 174 µmol, 3.2 equiv.) were dissolved in 1 mL of anhydrous DCM. Triethylamine (50 µL, 360 µmol, 6.5 equiv.) and 4-(dimethylamino)-pyridine (1 mg, 8.2 µmol, 15 mol%) were added and the mixture was stirred 2 h at room temperature. Sat. $NaHCO_3$ sol. (5 mL) was added. The organic layer was extracted, washed with brine (5 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified by preparative thin layer chromatography with CyHex/EtOAc (1:1) to afford the title compound (11 mg, 67% over two steps) as a clear oil.



^{1}H NMR (500 MHz, C_6D_6): 6.60 (1H, dd, J=15.5, 10.2 Hz), 6.04 (1H, br s, N*H*), 5.88 (1H, d, J=15.5 Hz), 4.92 (1H, dd, J=5.3, 4.5 Hz), 3.34 (1H, ddd, J=9.3, 4.6, 4.5 Hz), 2.48 (1H, dq, J=7.5, 5.2 Hz), 1.39-1.45 (1H, m), 1.32 (3H, d, J=7.5 Hz), 1.25-1.42 (2H, m), 1.16-1.21 (2H, m), 0.93-1.01 (2H, m), 0.89-0.92 (1H, m), 0.78 (3H, t, J=J=7.3 Hz), 0.71 (3H, d, J= 6.3 Hz), 0.65 (3H, d, J=6.2 Hz), 0.55-0.61 (1H, m), 0.41 (1H, ddd, J=8.8, 4.4, 4.4 Hz), 0.35 (1H, ddd, J=8.5, 6.2, 4.4 Hz); ^{13}C NMR (125 MHz, C_6D_6): 176.07, 166.02, 155.11, 117.41,

[14] Litt. $[\alpha]_D^{29.6} + 64°$ ($c = 1.0, CHCl_3$).
[15] Litt. $[\alpha]_D^{27.9} - 21°$ ($c = 1.0$, $CHCl_3$).

80.79, 56.66, 44.43, 43.78, 35.68, 25.12, 23.22, 23.18, 22.58, 22.41, 21.71, 16.14, 14.94, 14.00; $[\alpha]_D^{25} + 63.7°$ ($c = 0.4$, $CHCl_3$);[16] other data match the reported ones.

Unit	Position	δ_C (Litt.)[17]	δ_C (Exp.)[17]	δ_H (Litt.), couplings[17]	δ_H (Exp.), couplings[17]
HIMP	1	177.8	176.1		
	2	44.1	43.8	2.51, dq (5.2, 7.6)	2.48, dq (5.2, 7.5)
	3	80.8	80.8	4.94, dd (4.6, 5.2)	4.92, dd (4.5, 5.3)
	4	57.3	56.7	3.49, ddd (4.6, 4.7, 9.4)	3.34, ddd (4.5, 4.6, 9.3)
	5a	44.6	44.4	1.21, m	1.34, m
	5b			1.36, m	
	6	25.0	25.1	1.61, m	1.41, m
	7	21.7	21.7	0.74, d (6.2)	0.65, d (6.2)
	8	23.2	23.2	0.76, d 6.3)	0.71, d (6.3)
	9	15.0	14.9	1.33, d (7.6)	1.32, d (7.5)
	NH			7.65, s	6.04, s[18]
PCPA	1	166.0	166.0		
	2	117.4	117.4	5.88, d (15.5)	5.88, d (15.5)
	3	155.0	155.1	6.59, dd (10.3, 15.5)	6.60, dd (15.5, 10.2)
	4	22.4	22.4	0.91, m	0.90, m
	5	23.3	23.2	0.59, m	0.59, m
	6	35.7	35.7	0.96, m	0.96, m
	7	22.5	22.6	1.20, tq (7.1, 7.3)	1.19, m
	8	14.0	14.0	0.78, t (7.3)	0.78, t (7.3)
	9a	16.1	16.1	0.35, ddd (4.5, 6.0, 8.2)	0.35, ddd (8.5, 6.2, 4.4)
	9b			0.42, ddd (4.5, 4.5, 8.8)	0.41, ddd (8.8, 4.4, 4.4)

[16] Litt. $[\alpha]_D^{27.5} + 66°$ ($c = 0.25$, $CHCl_3$)

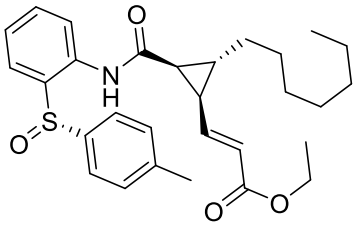
[17] Proton NMRs were recorded at 500 MHz, carbon NMRs at 125 MHz, in benzene-*d6*. The comparison is done with extracted hoshinolactame, recorded at 400 MHz for proton and 100 MHz for carbon.

[18] Water contained in benzene-*d6* may have affected NH shift and others.

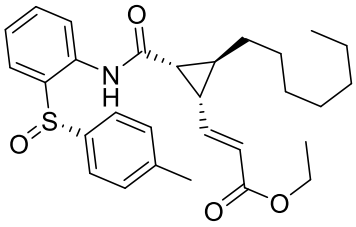
Grenadamide and cascarillic acid key intermediates synthesis

ethyl (*E*)-3-(2-heptyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate 9

***trans*-8** (100 mg, 0.25 mmol, 1 equiv.), ethyl acrylate (100 µL, 0.92 mmol, 3.6 equiv.), silver acetate (85 mg, 0.51 mmol, 2 equiv.), palladium(II) acetate (5.6 mg, 0.03 mmol, 10 mol%) and sodium trifluoroacetate (17 mg, 0.13 mmol, 50 mol%) were dissolved in 1 mL of HFIP/H_2O (4:1). The resulting mixture was flushed with oxygen and then stirred 24 h at 80 °C under oxygen atmosphere. After cooling down to room temperature, the mixture was diluted with DCM, filtered over celite and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel with CyHex/EtOAc (95:5 to 9:1) to afford **9** (57 mg, 46%) and the key diastereomer **dia-9** (52 mg, 43%) as clear oils.



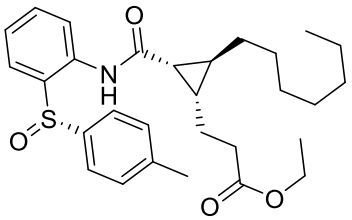
^{1}H NMR (400 MHz, $CDCl_3$): 10.52 (1H, br s, N*H*), 8.27 (1H, d, J=8.3 Hz), 7.40-7.49 (2H, m), 7.36 (2H, d, J=8.3 Hz), 7.16 (2H, d, J=8.2 Hz), 7.10 (1H, td, J=7.6, 1.0 Hz), 6.79 (1H, dd, J=15.6, 9.1 Hz), 5.88 (1H, d, J=15.6 Hz), 3.99-4.19 (2H, m, C(O)OC*H*$_2$CH$_3$), 2.28 (3H, s, PhC*H*$_3$), 1.76-1.87 (3H, m), 1.15-1.50 (15H, m), 0.85 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 168.06, 166.20, 146.53, 147.74, 140.34, 139.44, 133.08, 130.22, 128.01, 127.68, 124.46, 123.39, 123.16, 121.46, 60.24, 32.69, 32.59, 31.95, 31.78, 29.39, 29.37, 29.31, 28.96, 22.83, 21.38, 14.49, 14.28; FT-IR (cm^{-1}): 1722 (s, C=O ester), 1687 (s, C=O amide), 1027 (m, S=O); $[\alpha]_D^{20} - 5.4°$ ($c = 0.5$, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$): 10.45 (1H, br s, N*H*), 8.34 (1H, d, J=8.4 Hz), 7.46 (1H, dd, J=7.6, 1.3 Hz), 7.35-7.43 (3H, m), 7.20 (2H, d, J=8.1 Hz), 7.10 (1H, td, J=7.6, 1.1 Hz), 7.03 (1H, dd, J=15.6, 10.1 Hz), 5.92 (1H, d, J=15.6 Hz), 4.06-4.18 (2H, m, C(O)OC*H*$_2$CH$_3$), 2.33 (3H, s, PhC*H*$_3$), 1.83 (1H, ddd, J=8.3, 6.2, 2.4 Hz), 1.72-1.78 (1H, m), 1.65-1.71 (1H, m), 1.14-1.41 (14H, m), 0.85 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 168.13, 166.41, 146.45, 141.55, 140.39, 139.86, 133.12, 130.15, 127.71, 127.62, 124.54, 123.27, 123.14, 121.66, 60.25, 32.75, 32.68, 32.07, 31.97, 29.42, 29.41, 29.25, 28.93, 2.85, 21.47, 14.50, 14.27; FT-IR (cm^{-1}): 1717 (s, C=O ester), 1687 (m, C=O amide), 1021 (m, S=O); $[\alpha]_D^{20} + 51.5°$ ($c = 1.0$, $CHCl_3$).

ethyl 3-((1*S*,2*S*,3*R*)-2-heptyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)propanoate 10

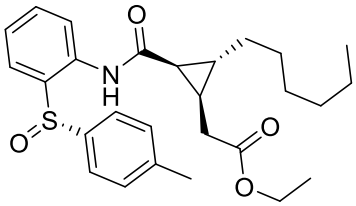
***trans*-9** (54 mg, 0.11 mmol, 1 equiv.) was dissolved in 5 mL of EtOH. The solution was flushed with argon and vacuum few times, before addition of Pd/C (10 wt. % loading, matrix activated carbon support, 20 mg). The resulting mixture was flushed with argon and vacuum before being put under hydrogen atmosphere and stirred 24 h at room temperature. The mixture was carefully filtered over celite, washed with EtOH and evaporated under reduced pressure to yield the title compound (54%, 99%) as a clear oil.



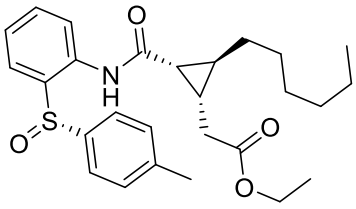
^{1}H NMR (400 MHz, $CDCl_3$): 10.35 (1H, br s, N*H*), 8.31 (1H, d, J=8.5 Hz), 7.51 (1H, dd, J=7.6, 1.6 Hz), 7.37-7.46 (3H, m), 7.26 (2H, d, J=8.2 Hz), 7.10 (1H, td, J=7.6, 1.1 Hz), 4.09 (2H, q, J=7.1 Hz), 2.34 (3H, s), 2.03-2.19 (2H, m), 1.50-1.72 (2H, m), 1.19-1.39 (17H, m), 1.03-1.13 (1H, m), 0.86 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 173.43, 170.15, 141.60, 140.62, 139.77, 133.18, 130.22, 127.96, 127.81, 124.52, 123.00, 122.83, 60.39, 34.25, 33.29, 32.02, 29.53, 29.46, 29.29, 29.17, 28.75, 27.46, 22.86, 22.07, 21.43, 14.51, 14.31; FT-IR (cm^{-1}): 1732 (C=O ester), 1690 (C=O amide), 1022 (S=O); HRMS (ESI-TOF): m/z calcd for $C_{29}H_{39}NNaO_4S^+$: 520.2492, found: 520.2510; $[\alpha]_D^{20} + 8.5°$ $(c = 0.5,\ CHCl_3)$.

ethyl 2-(2-hexyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acetate 12

***trans*-11** (200 mg, 0.52 mmol, 1 equiv.), ethyl iodoacetate (186 µL, 1.6 mmol, 3 equiv.), silver acetate (180 mg, 1.1 mmol, 2 equiv.), palladium(II) acetate (12 mg, 0.05 mmol, 10 mol%) and sodium trifluoroacetate (35 mg, 0.26 mmol, 50 mol%) were dissolved in 2 mL of HFIP/H_2O (4:1). The resulting mixture was stirred 24 h at 80 °C. After cooling down to room temperature, the mixture was diluted with DCM, filtered over celite and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel with CyHex/EtOAc (95:5 to 90:10) to afford **12** (116 mg, 47%) as a yellow oil and the key intermediate diastereoisomer **dia-12** (107 mg, 44%) as a clear oil.



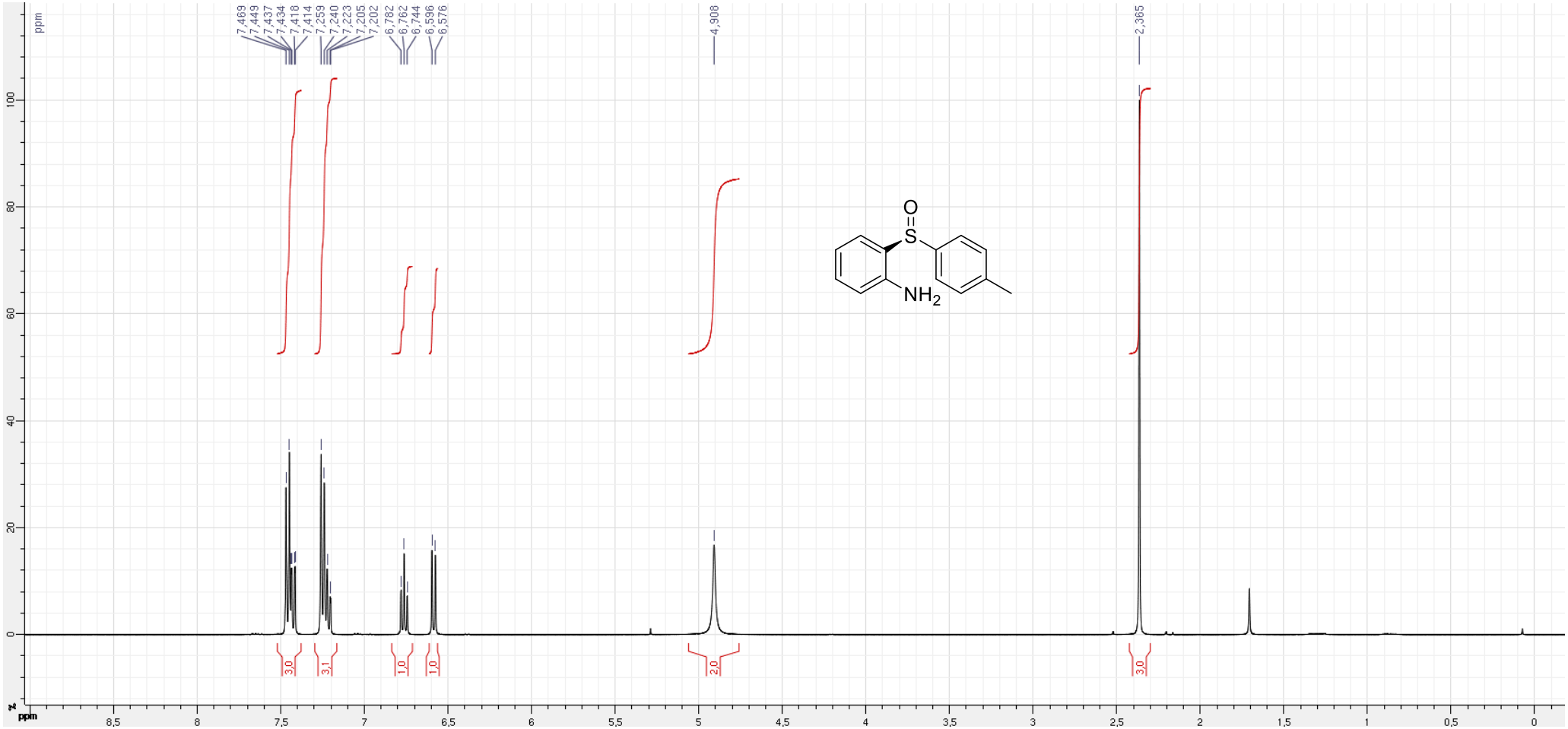
^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (1H, br s, N*H*), 8.27 (1H, d, J=8.5 Hz), 7.50 (1H, dd, J=7.7, 1.6 Hz), 7.37-7.45 (3H, m), 7.25 (2H, d, J=7.2 Hz), 7.11 (1H, td, J=7.6, 0.8 Hz), 4.04 (2H, qq, J=10.8, 7.2 Hz, C(O)OC*H*$_2$CH$_3$), 2.38 (1H, dd, J=16.5, 8.2 Hz), 2.33 (3H, s, PhC*H*$_3$), 2.15 (1H, dd, J=16.8, 5.1 Hz), 1.20-1.42 (13H, m), 1.16 (3H, t, J=7.2 Hz, C(O)OCH$_2$C*H*$_3$), 0.85 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 173.13, 170.04, 141.57, 140.43, 139.94, 133.10, 130.22, 130.17, 127.89, 124.69, 123.22, 123.07, 60.39, 33.12, 32.02, 31.99, 29.23, 29.02, 27.95, 27.56, 24.53, 22.83, 21.43, 14.42, 14.30; FT-IR (cm^{-1}): 1736 (s, C=O ester), 1688 (m, C=O amide), 1023 (m, S=O); $[\alpha]_D^{20} - 1.8°$ $(c = 0.7,\ CHCl_3)$.

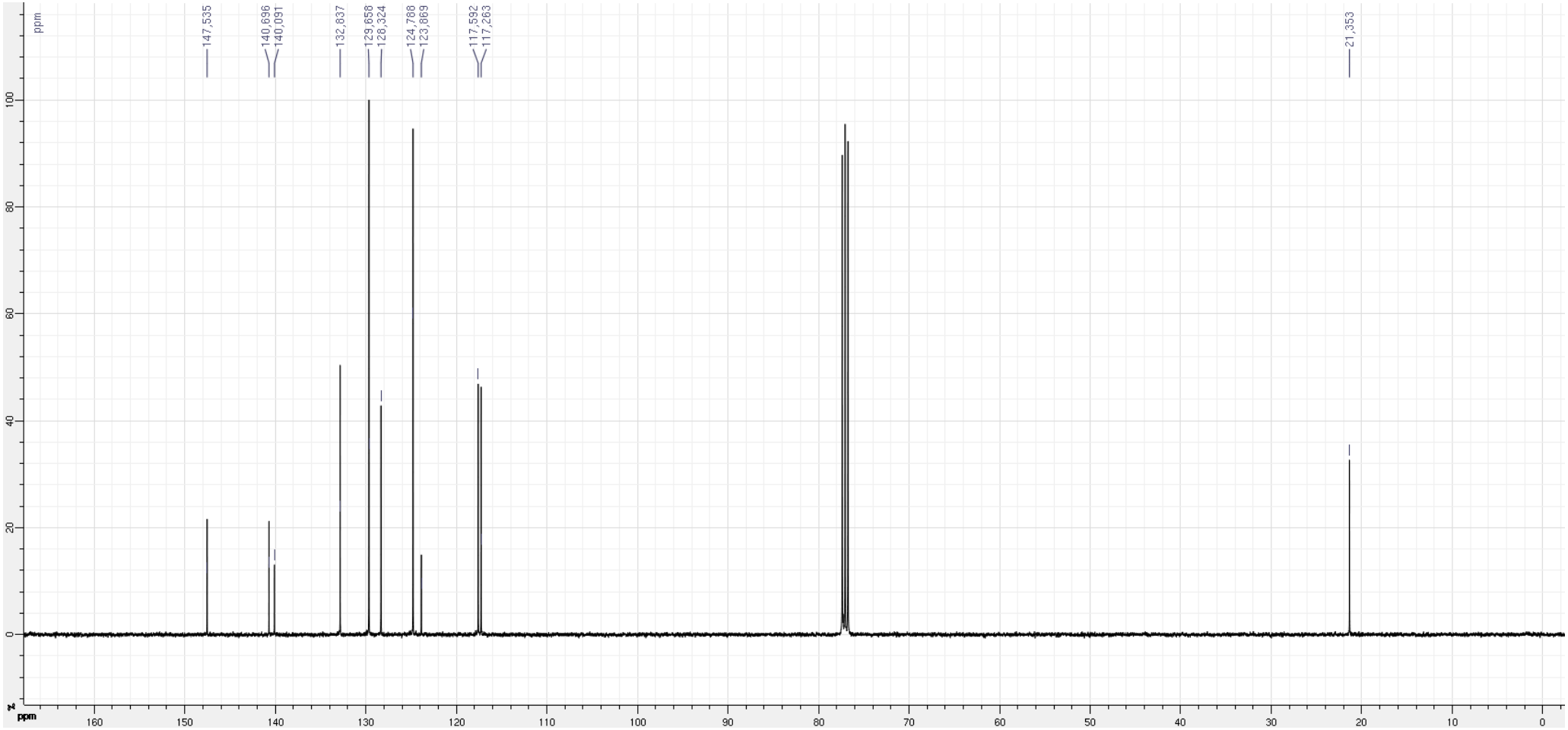


^{1}H NMR (400 MHz, $CDCl_3$): 10.32 (1H, br s, N*H*), 8.26 (1H, d, J=8.6 Hz), 7.45 (1H, dd, J=7.5, 1.3 Hz), 7.31-7.40 (3H, m), 7.17 (2H, d, J=8.1 Hz), 7.06 (1H, td, J=7.6, 1.1 Hz), 4.02 (2H, q, J=7.1 Hz, C(O)OC*H*$_2$CH$_3$), 2.51-2.70 (2H, m), 2.23-2.36 (4H, m), 1.16-1.37 (12H, m), 1.12 (3H, t, J=7.2 Hz, C(O)OCH$_2$C*H*$_3$), 0.83 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 172.93, 169.84, 141.27, 140.35, 139.65, 132.88, 129.94, 127.68, 127.63, 124.34, 122.87, 122.80, 60.34, 32.95, 31.92, 31.86, 29.07, 28.81, 27.98, 27.08, 24.91, 22.66, 21.30, 14.20, 14.13; FT-IR (cm^{-1}): 1736 (s, C=O ester), 1688 (m, C=O amide), 1023 (m, S=O); HRMS (ESI-TOF): m/z calcd for $C_{27}H_{36}NO_4S^+$: 470.2360, found: 470.2338; $[\alpha]_D^{20} + 35.0°$ $(c = 0.6,\ CHCl_3)$.

NMR Spectra

(*S*)-2-(*p*-tolylsulfinyl)aniline APS




ppm
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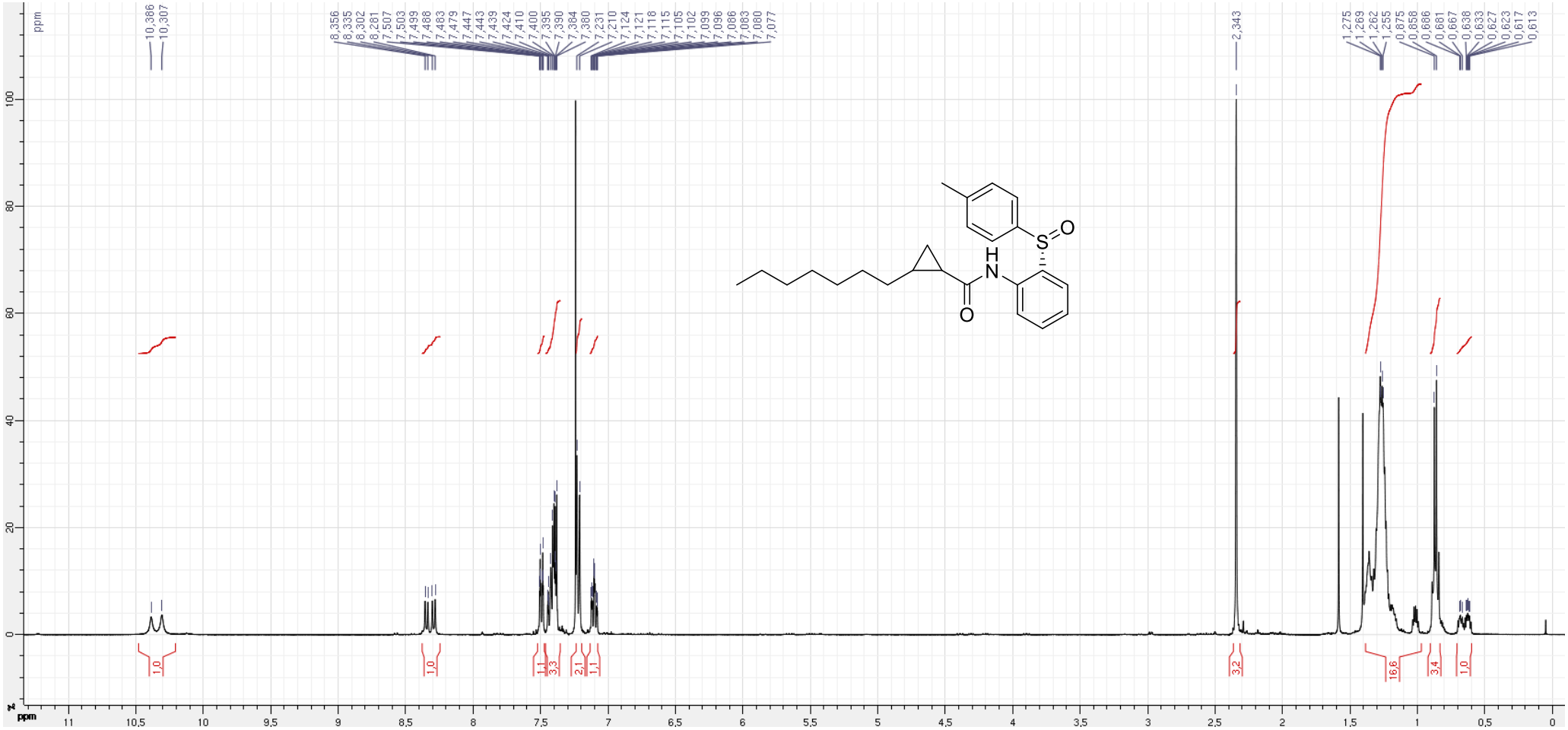
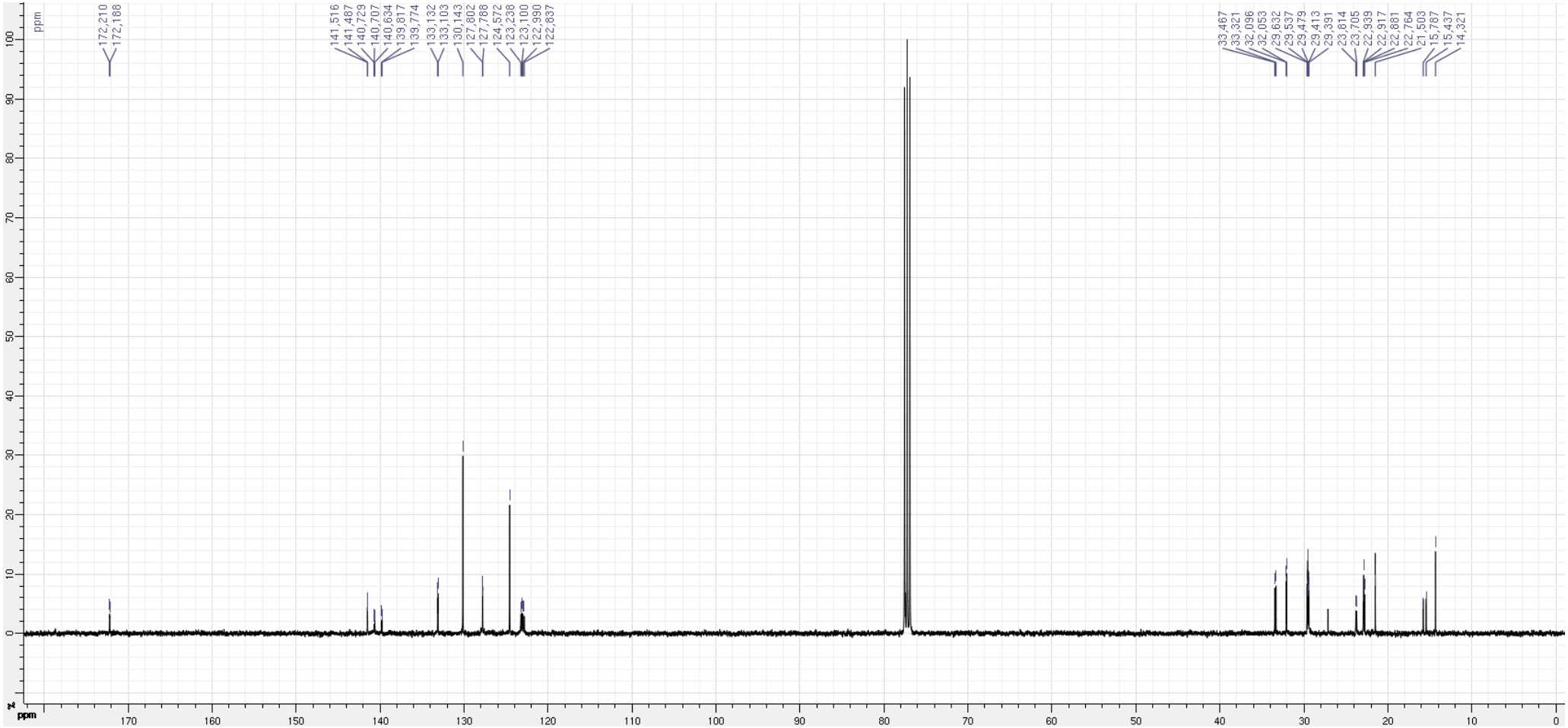
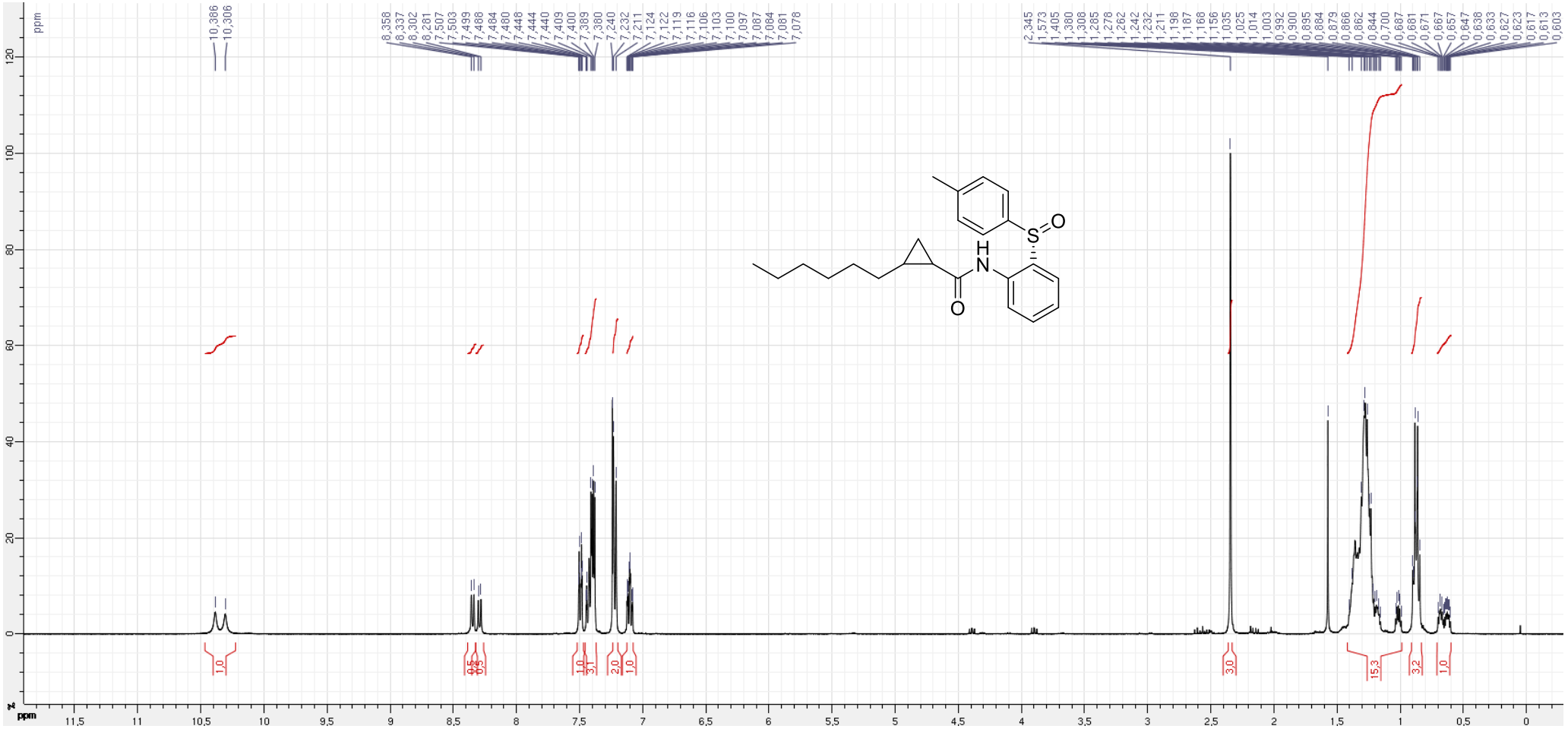
140,696
140,091
132,837
129,658
128,324
124,768
123,869
117,592
117,263
21,353
100
80
60
40
20
0
%
ppm
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

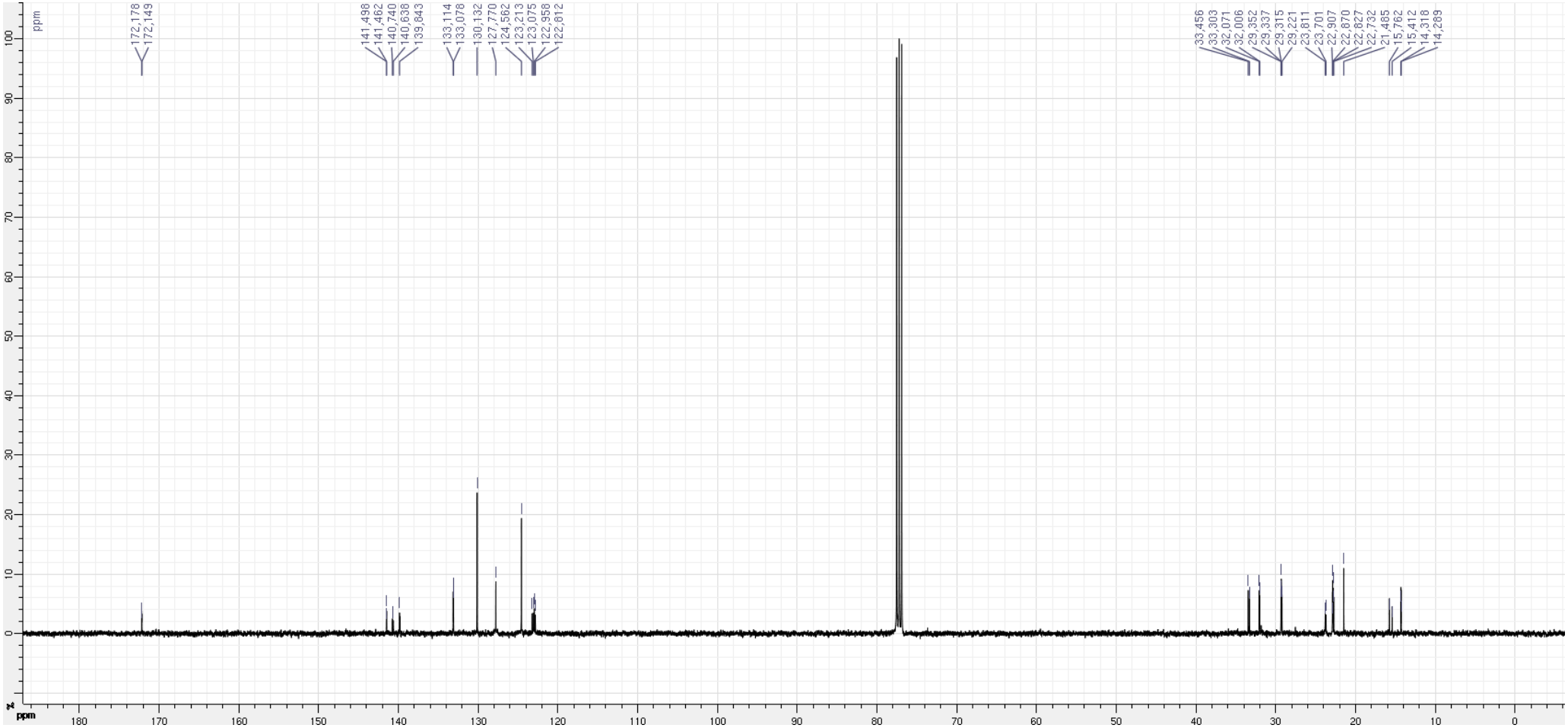
***trans*-2-heptyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide 8**



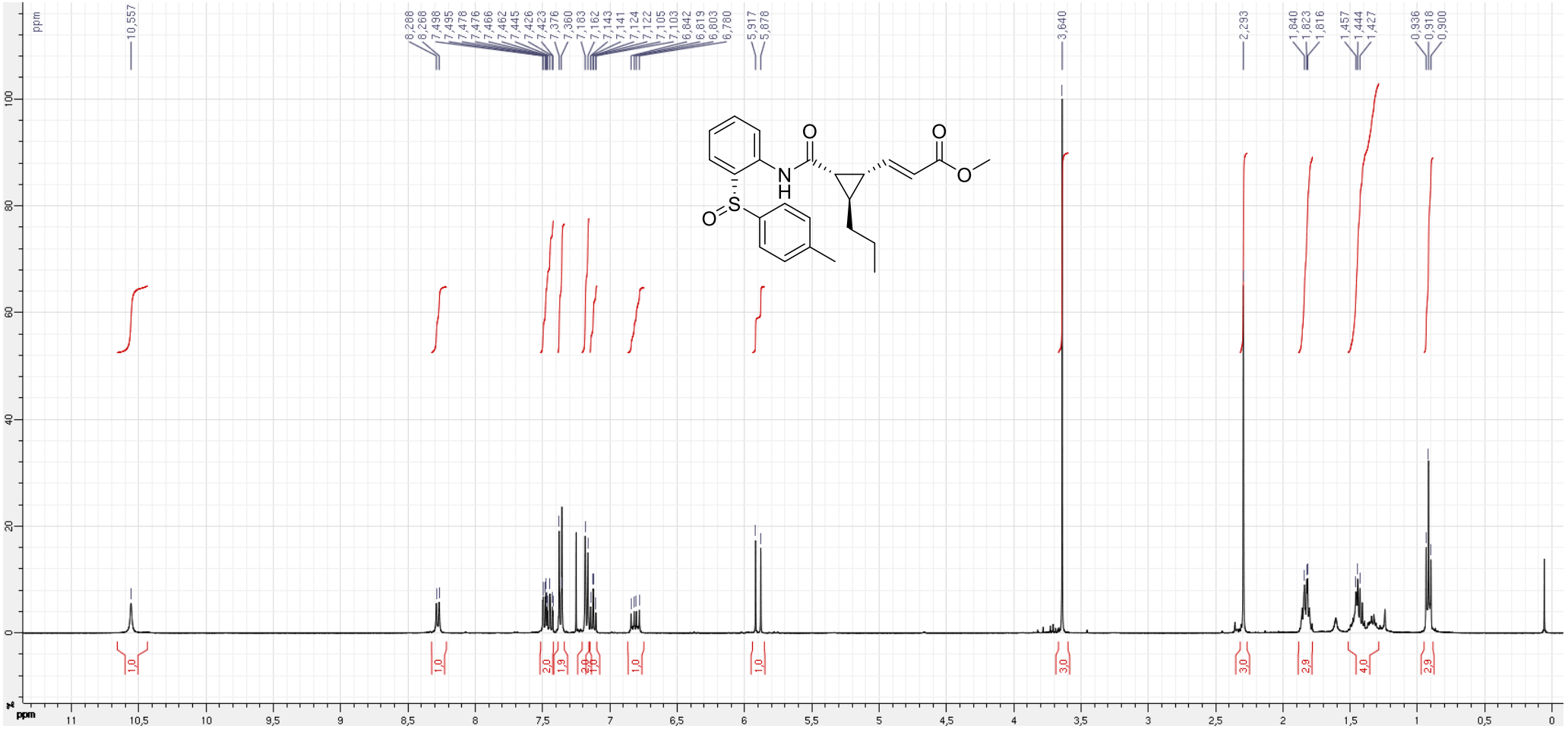

ppm
172,210
172,188
141,516
141,487
140,729
140,707
140,634
139,817
139,774
133,132
133,103
130,143
127,802
127,788
124,572
123,238
123,100
122,990
122,837
33,467
33,321
32,096
32,053
29,632
29,537
29,479
29,413
29,391
23,814
23,705
22,939
22,917
22,881
22,764
21,503
15,787
15,437
14,321
%
ppm

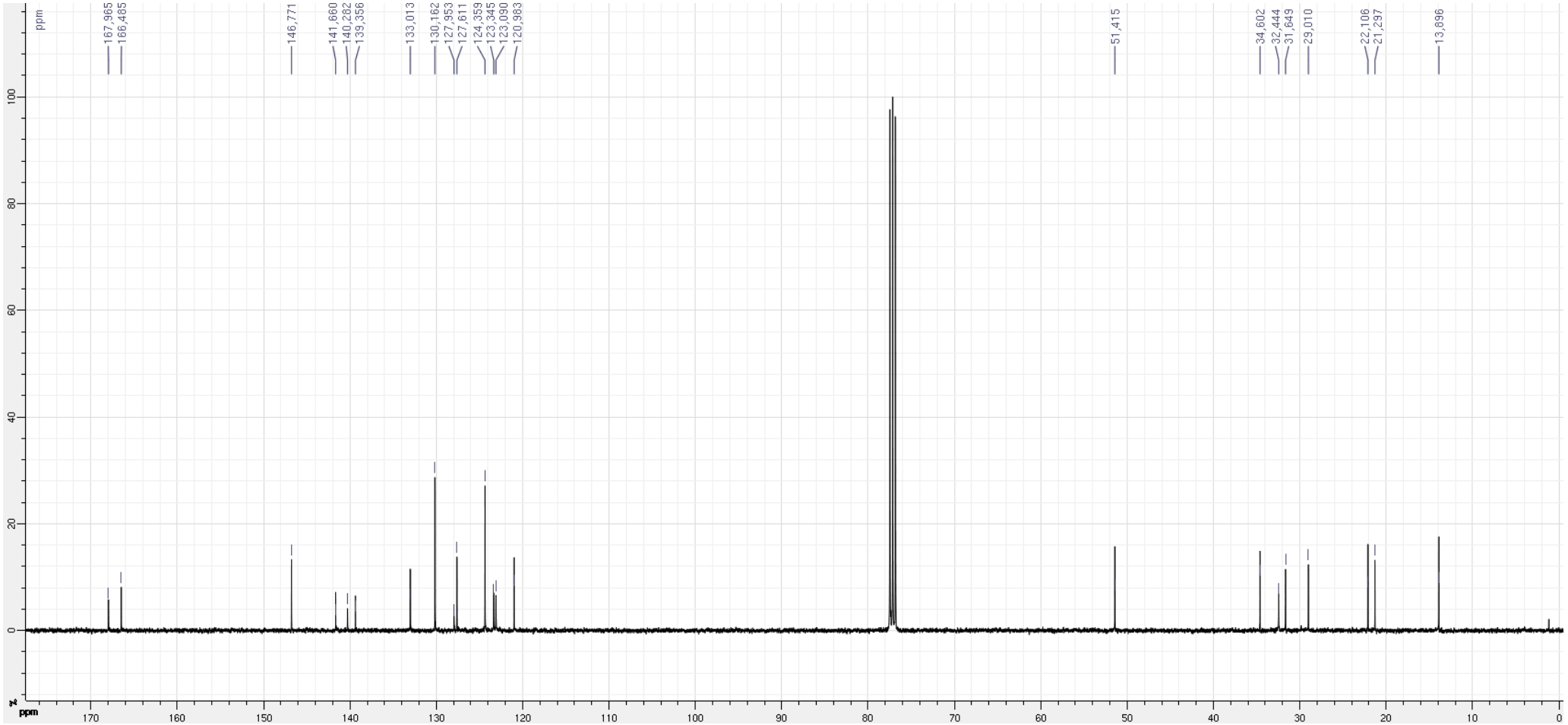
***trans*-2-hexyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide 11**



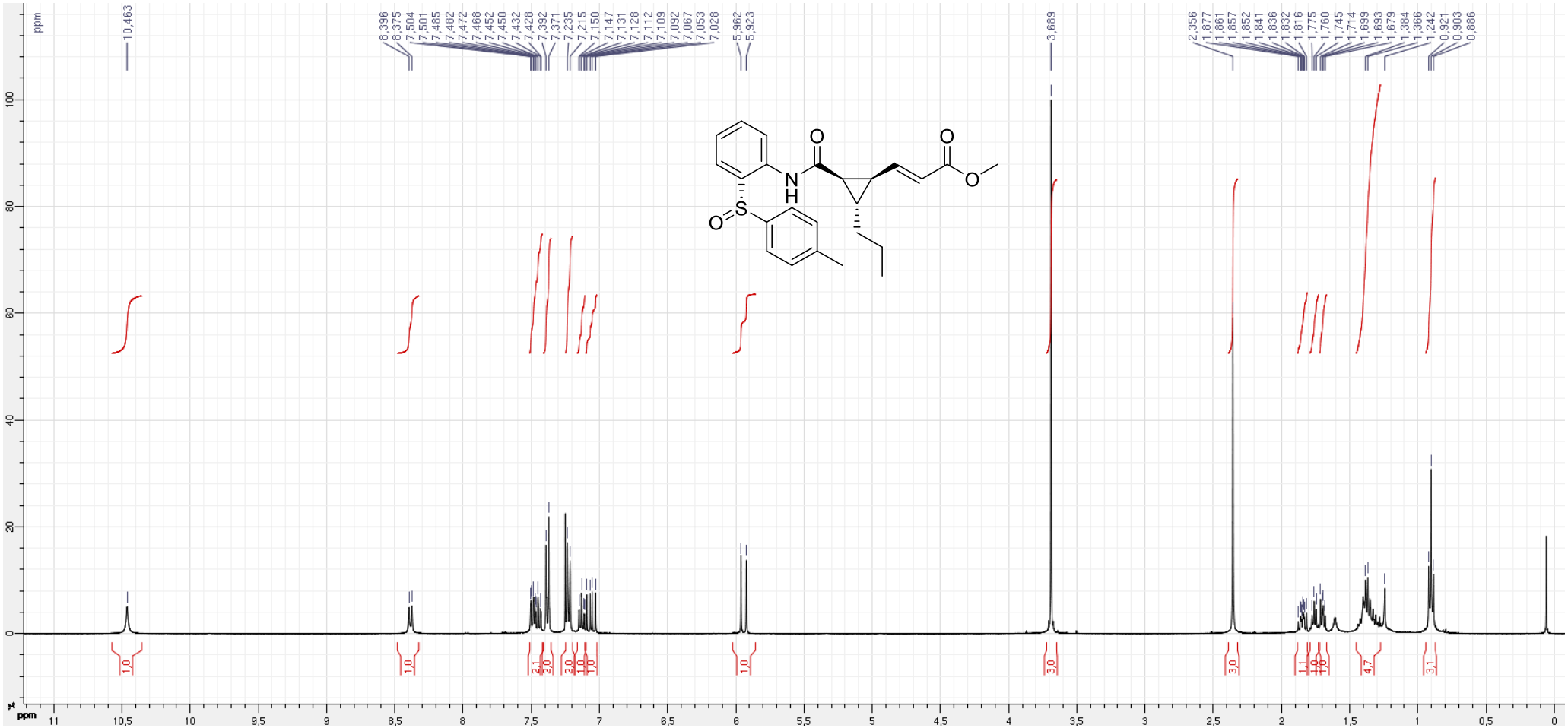

ppm
172,178
172,149
141,498
141,462
140,740
140,638
139,843
133,114
133,078
130,132
127,770
124,562
123,213
123,075
122,958
122,812
33,456
33,303
32,071
32,006
29,352
29,337
29,315
29,221
23,811
23,701
22,907
22,870
22,827
22,732
21,485
15,762
15,412
14,318
14,289
%
ppm

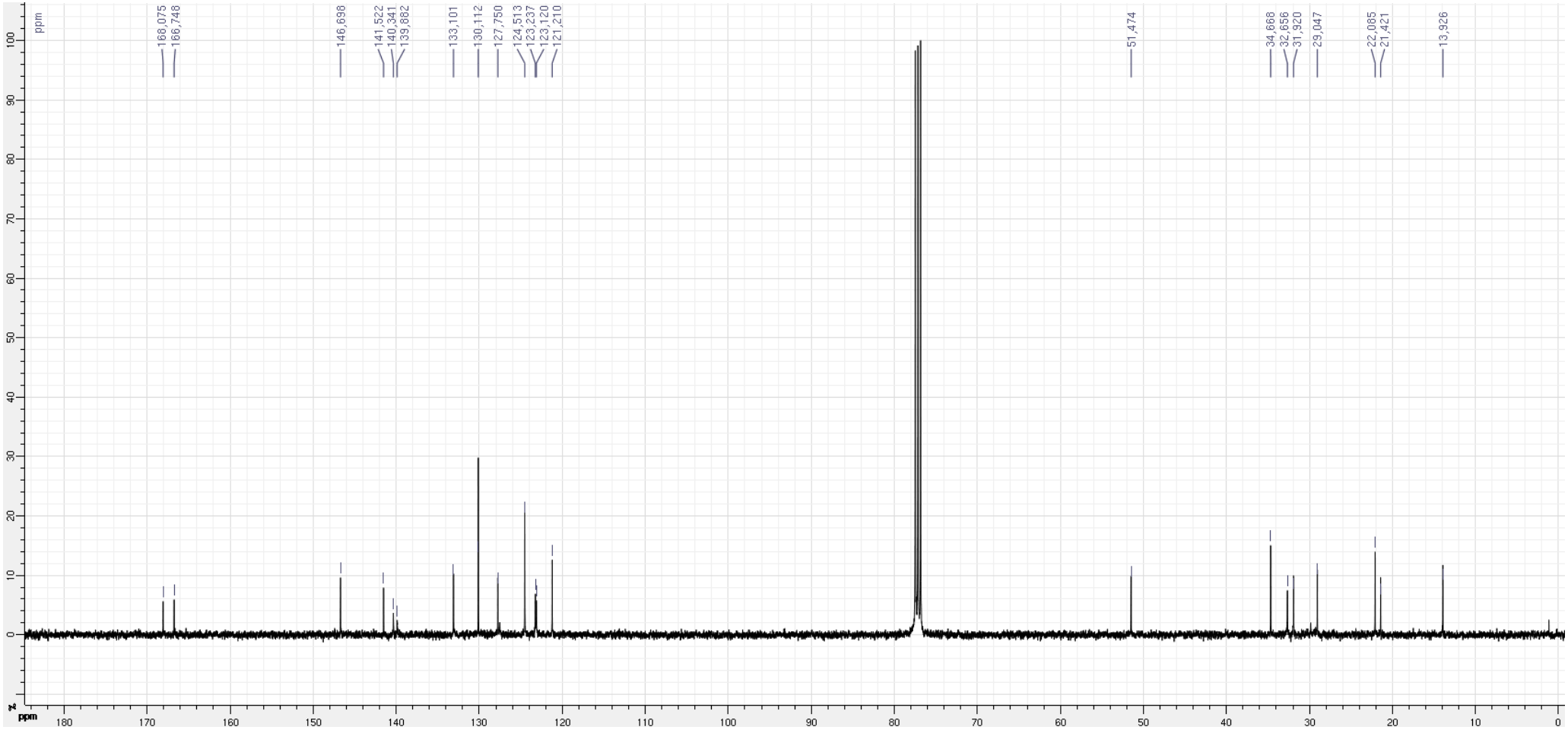
methyl (*E*)-3-((1*R*,2*R*,3*S*)-2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate 3




ppm
167,965
166,485
146,771
141,660
140,282
139,356
133,013
130,162
127,953
127,611
124,359
123,345
123,090
120,983
51,415
34,602
32,444
31,649
29,010
22,106
21,297
13,896
100
80
60
40
20
0
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

methyl (*E*)-3-((1*S*,2*S*,3*R*)-2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate dia-3




ppm
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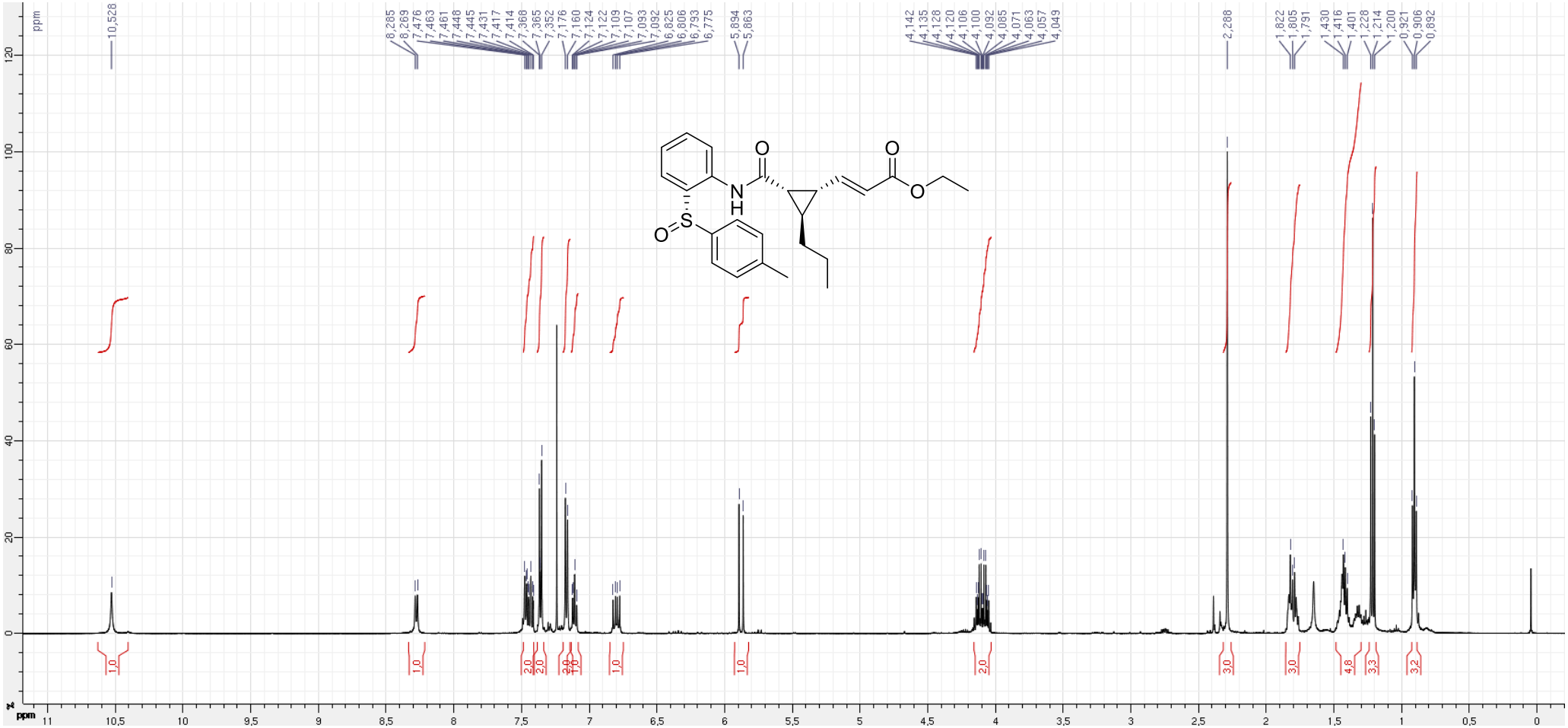
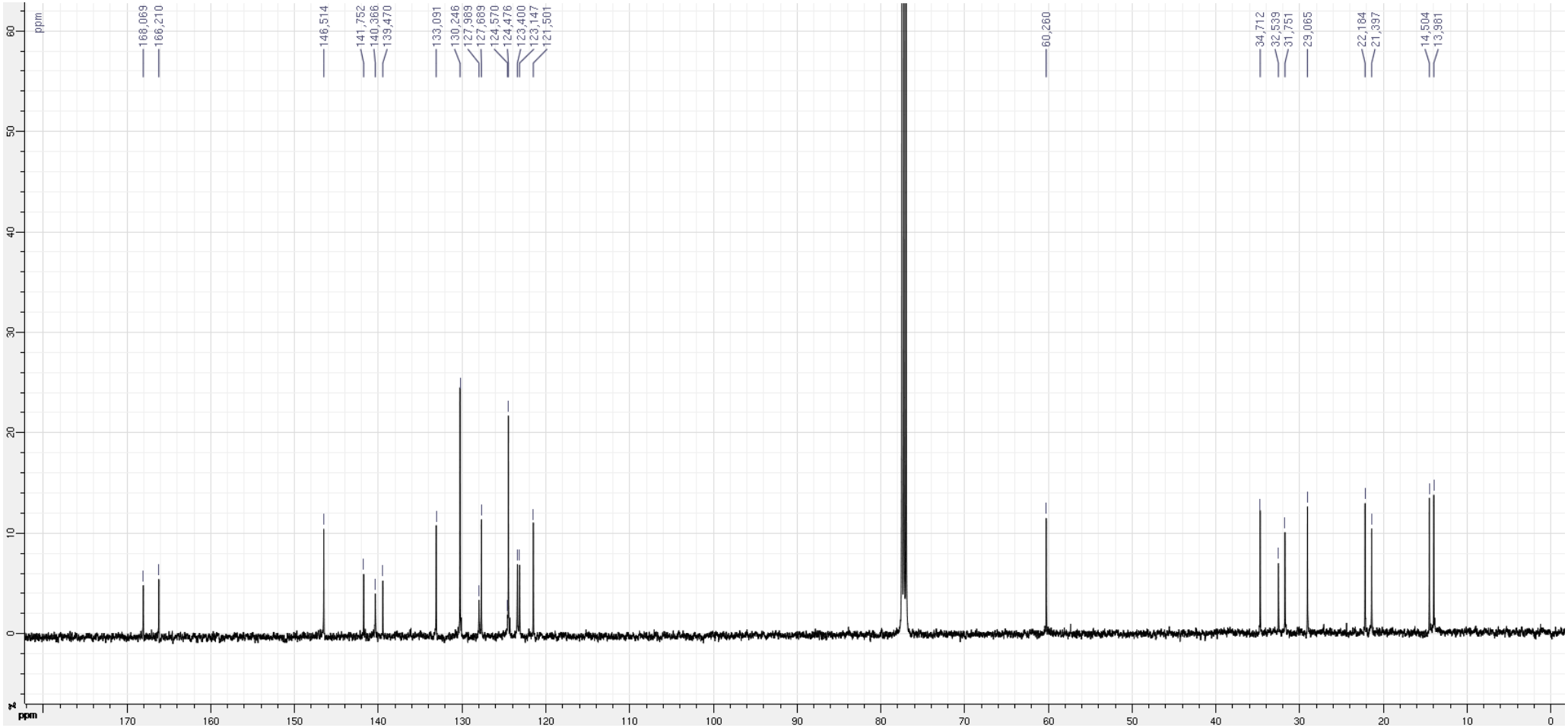
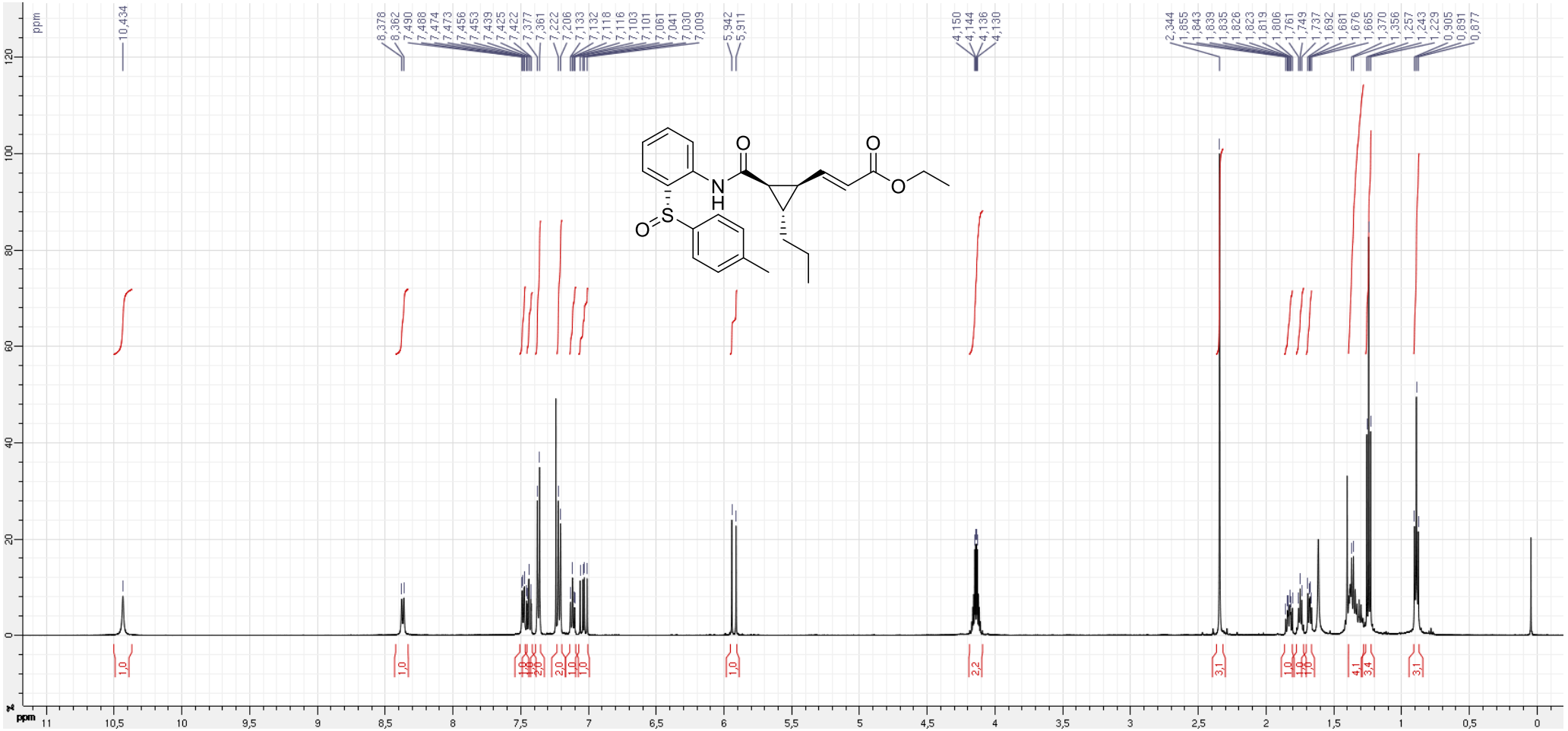
166,748
146,698
141,522
140,341
139,882
133,101
130,112
127,750
124,513
123,237
123,120
121,210
51,474
34,668
32,656
31,920
29,047
22,085
21,421
13,926

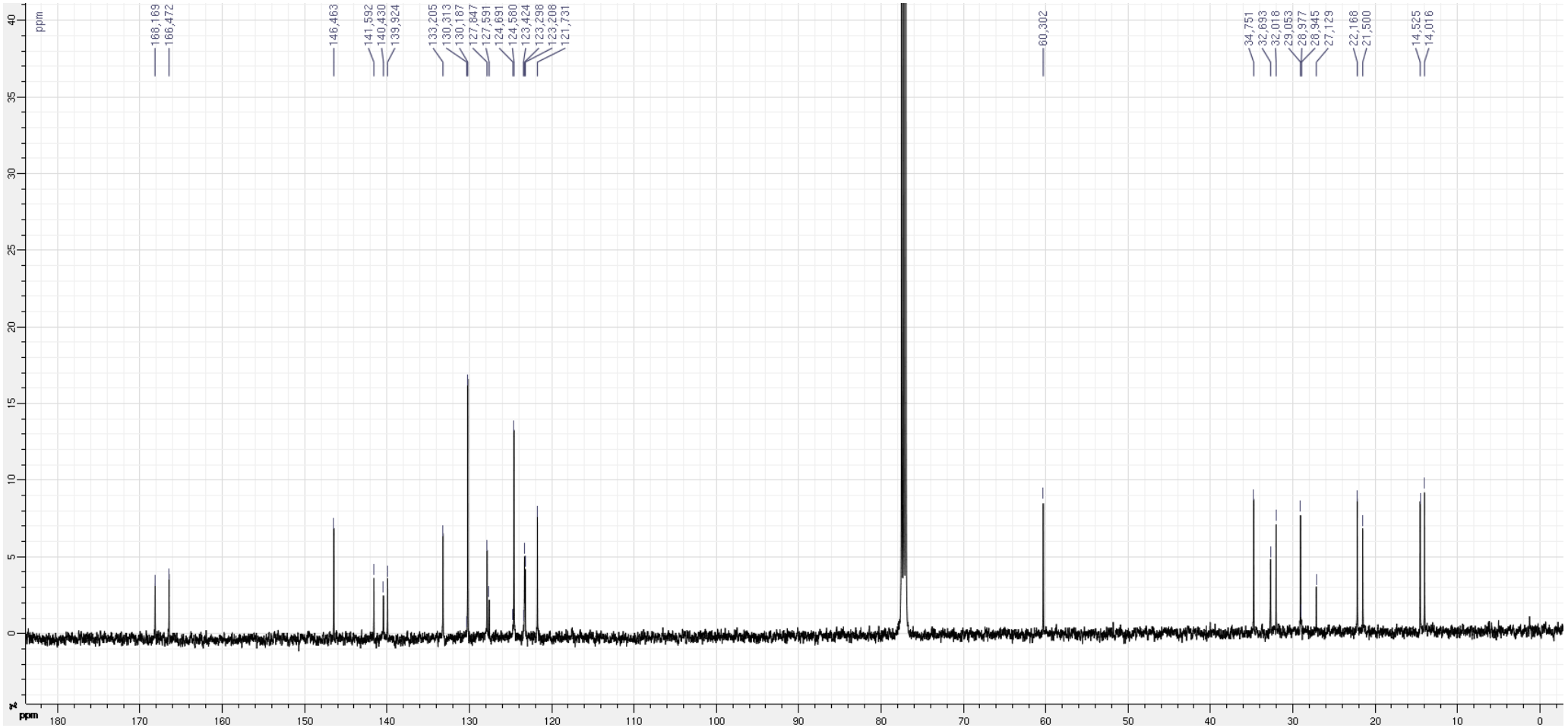
ethyl (*E*)-3-((1*R*,2*R*,3*S*)-2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate 3'




ppm
168,069
166,210
146,514
141,752
140,366
139,470
133,091
130,246
127,989
127,689
124,570
124,476
123,400
123,147
121,501
60,260
34,712
32,539
31,751
29,065
22,184
21,397
14,504
13,981

ethyl (*E*)-3-((1*S*,2*S*,3*R*)-2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate dia-3'




ppm
168,169
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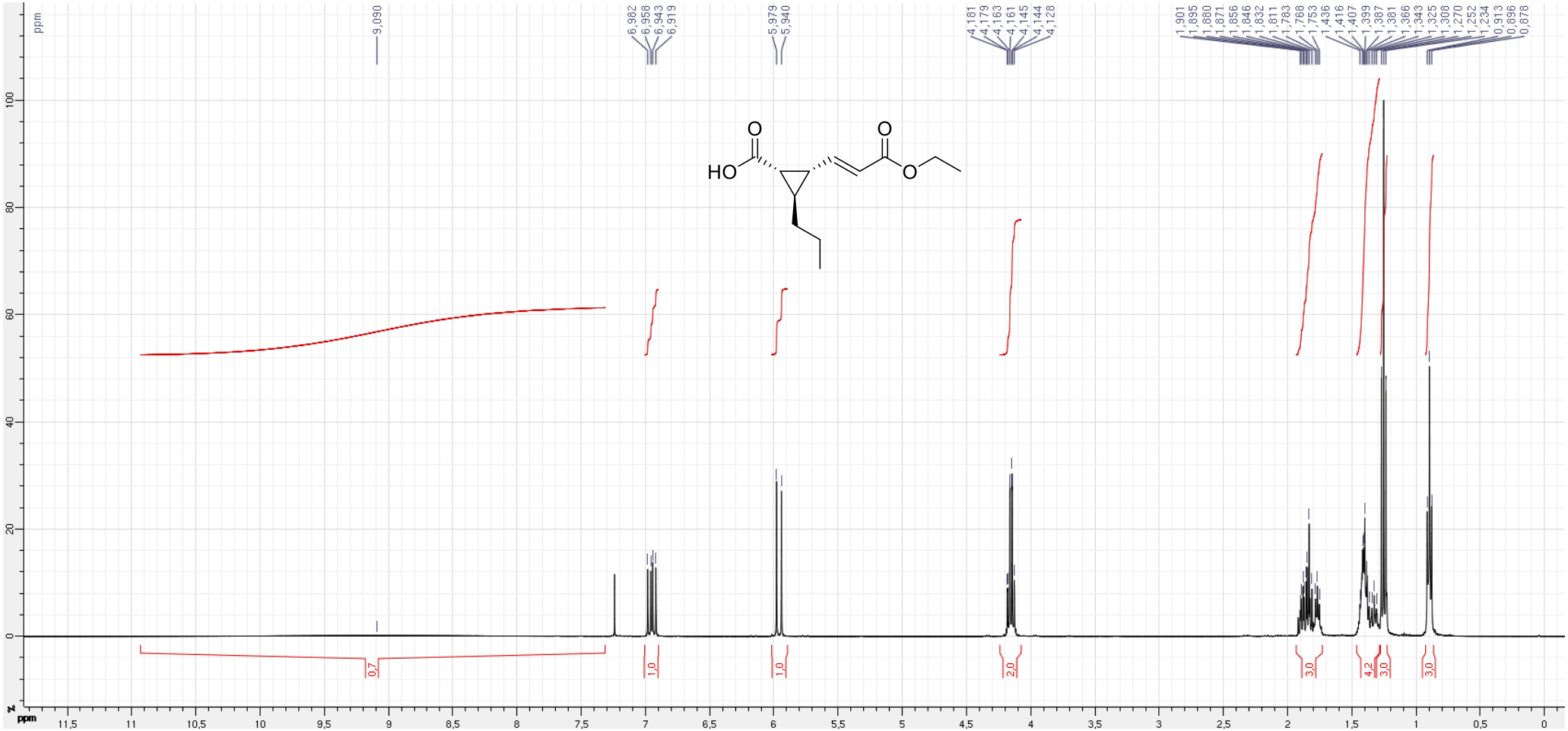
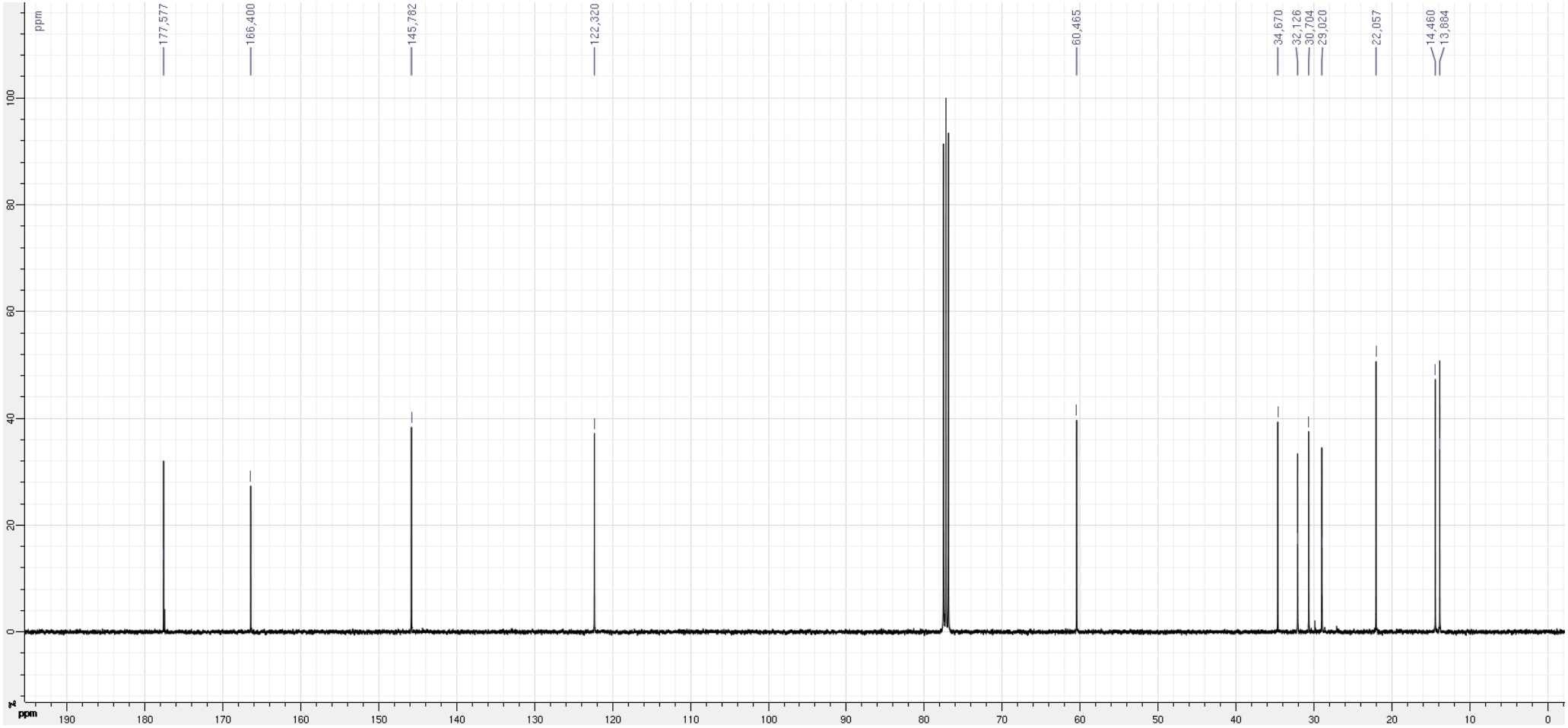
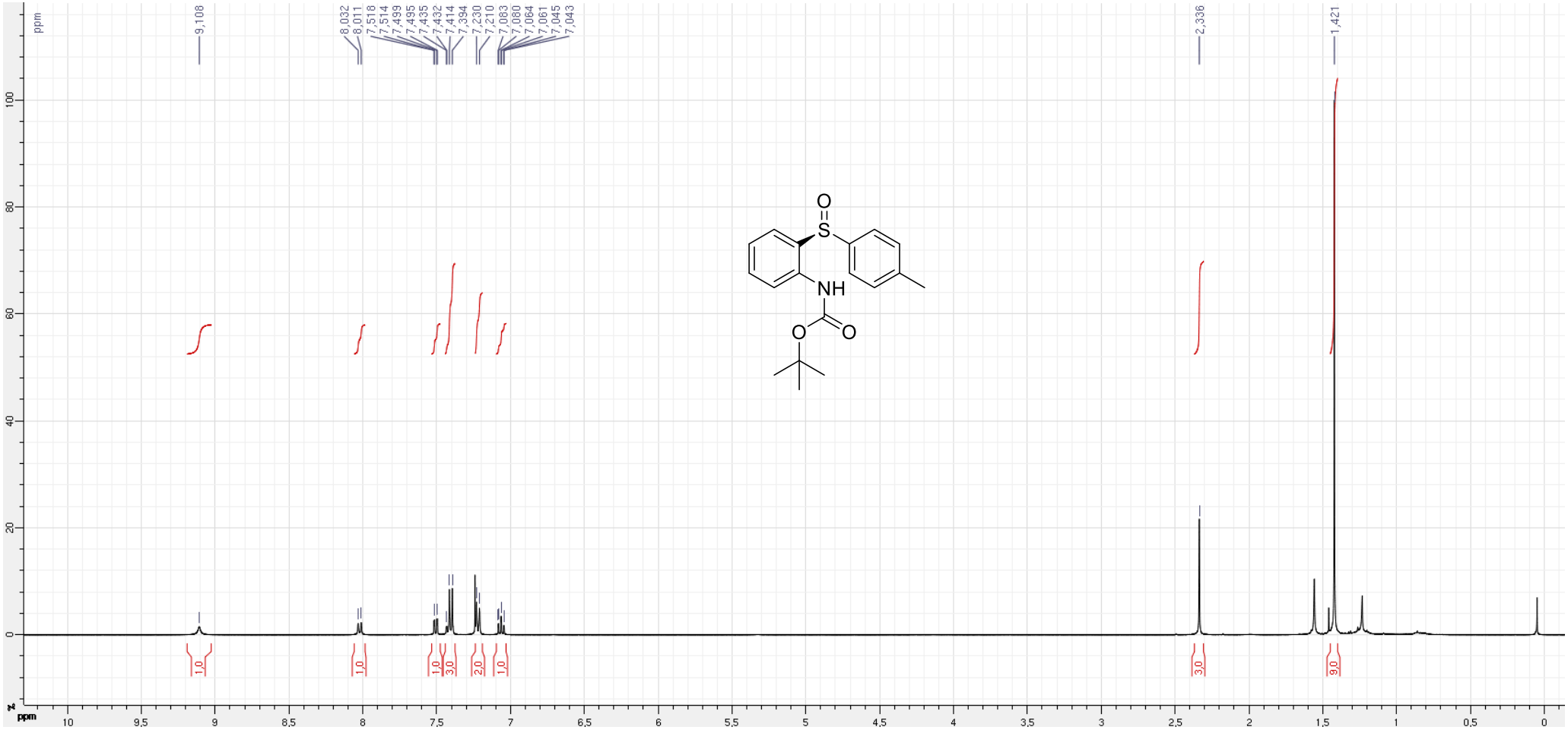
141,592
140,430
139,924
133,205
130,313
130,187
127,847
127,591
124,691
124,580
123,424
123,298
123,208
121,731
60,302
34,751
32,693
32,018
29,053
28,377
26,945
27,129
22,168
21,500
14,525
14,016

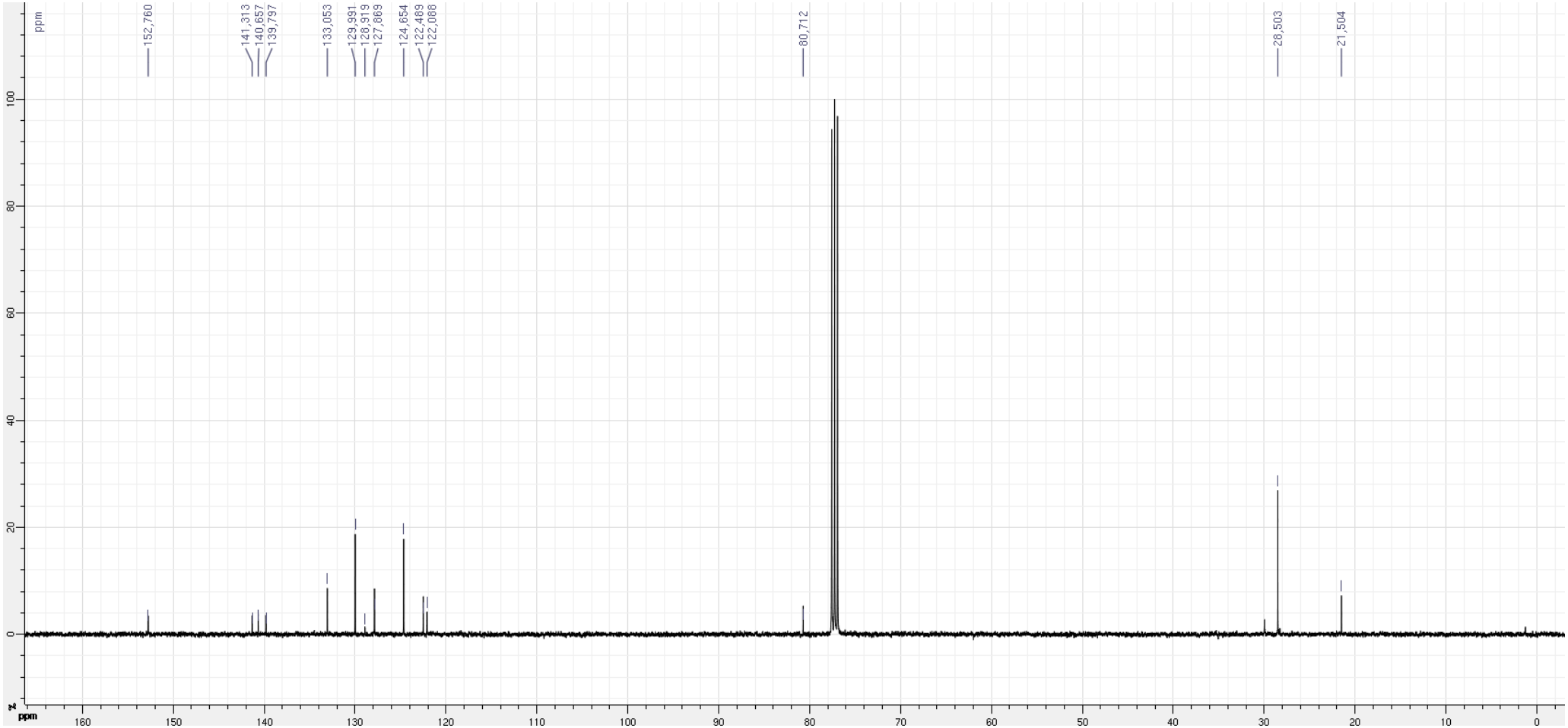
(1*S*,2*R*,3*R*)-2-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)-3-propylcyclopropane-1-carboxylic acid 7a'




ppm
177,577
166,400
145,782
122,320
60,465
34,670
32,126
30,704
29,020
22,057
14,460
13,884
100
80
60
40
20
0
%
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

***tert*-butyl (2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamate Boc-APS**




ppm
152,760
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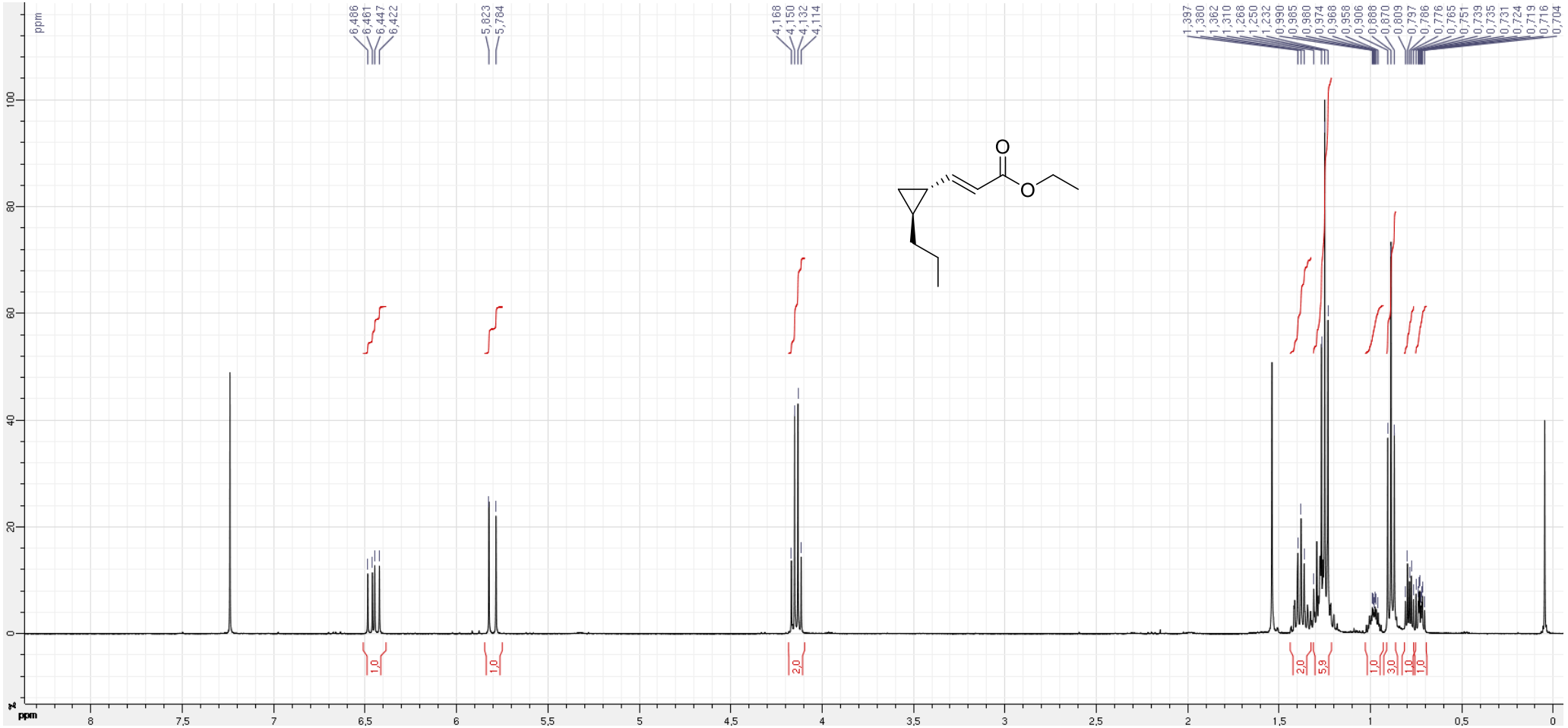
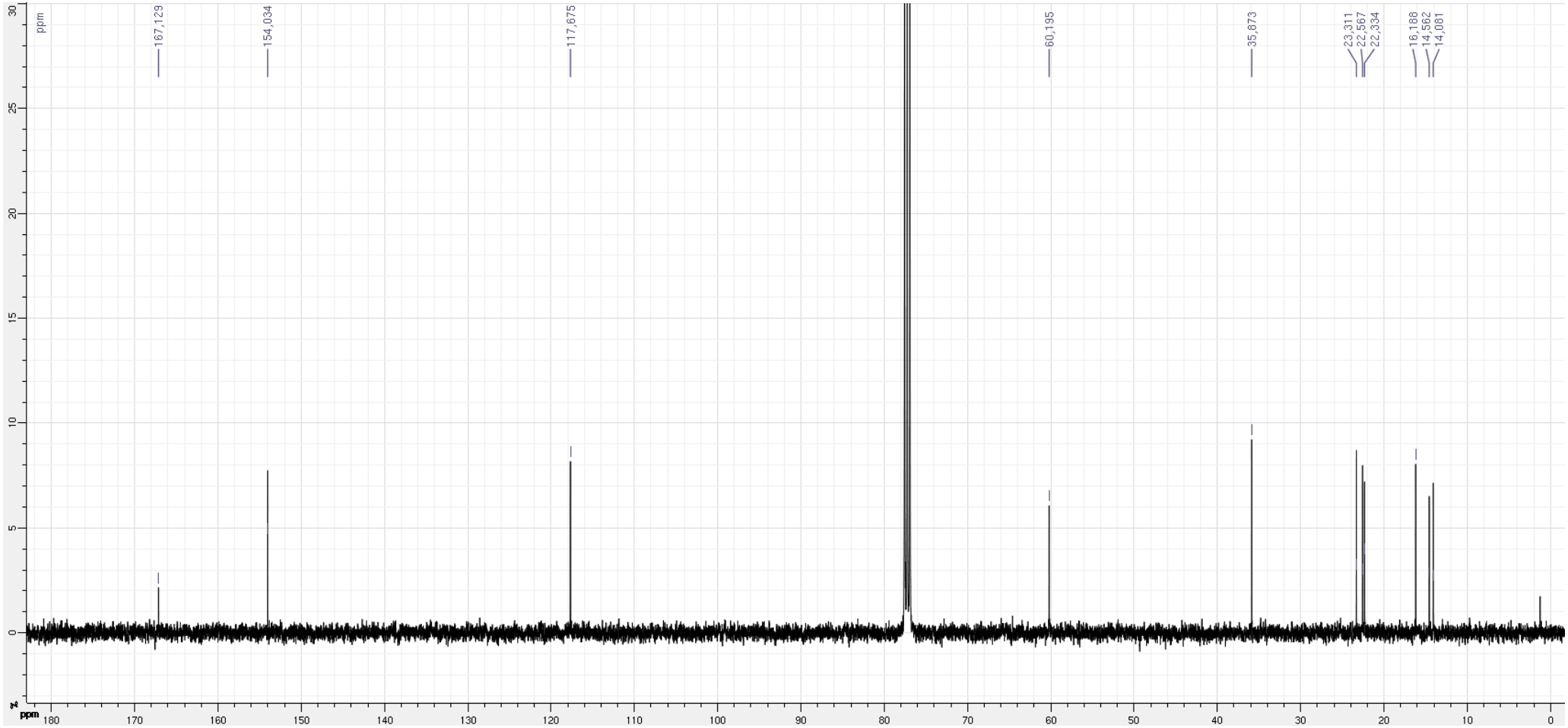
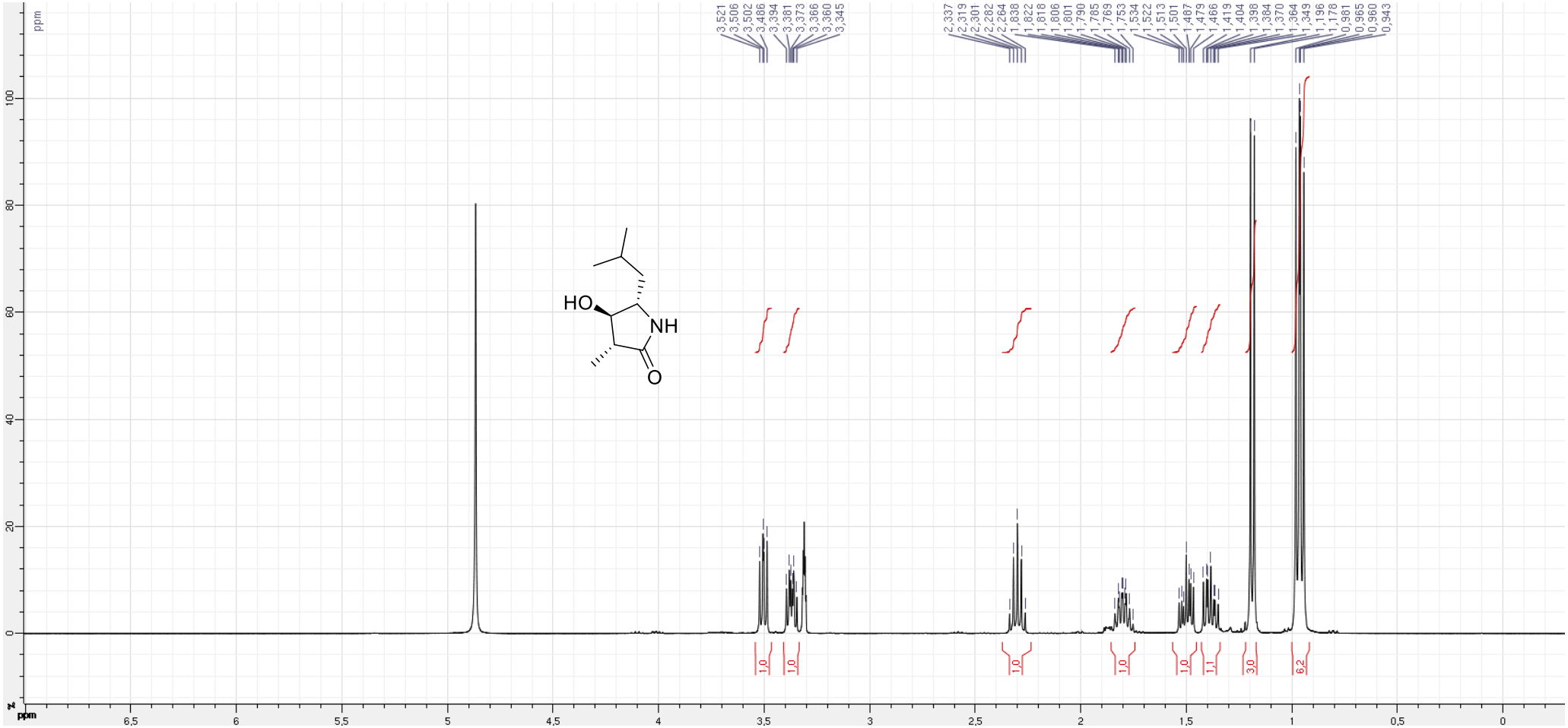
139,797
133,053
129,991
128,919
127,869
124,654
122,489
122,088
80,712
28,503
21,504
100
80
60
40
20
0
%
ppm
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

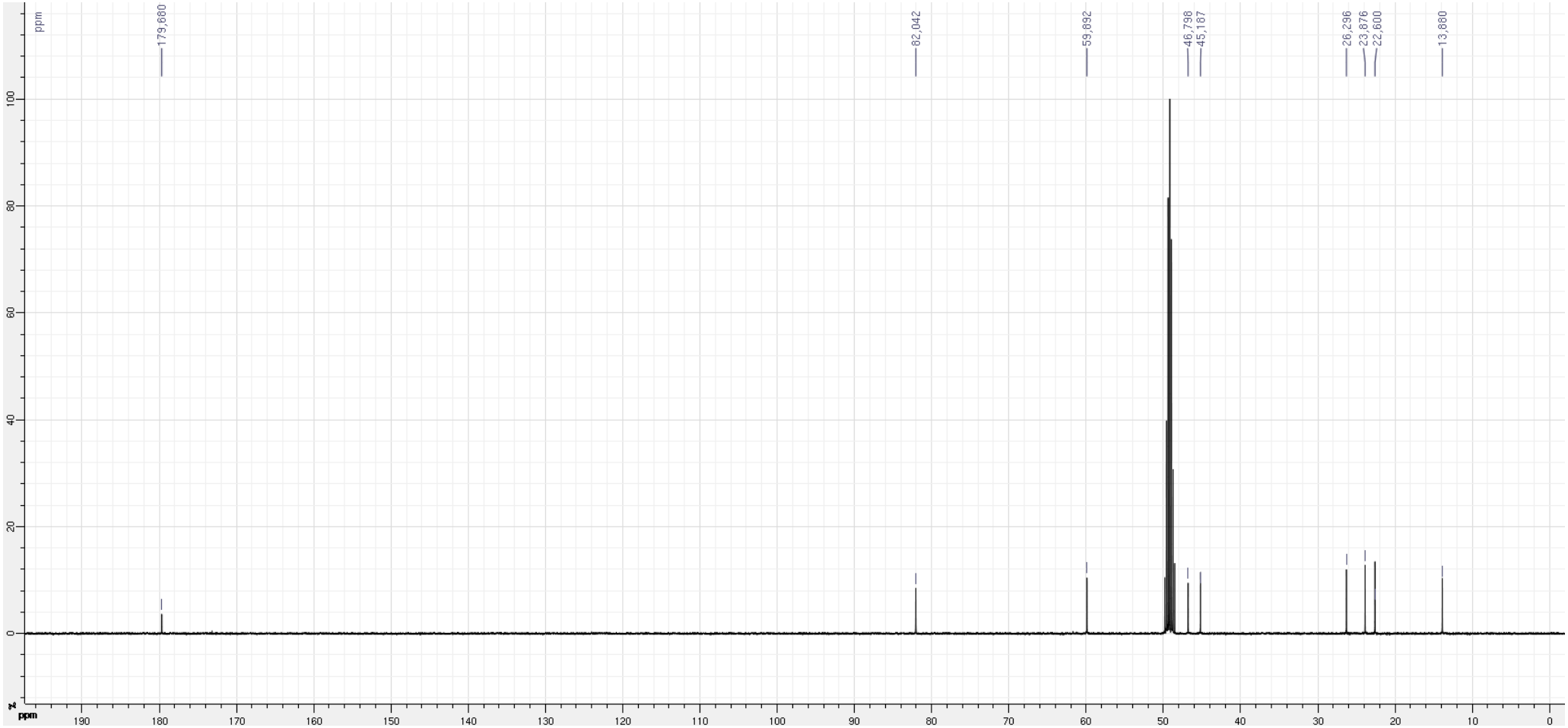
ethyl (*E*)-3-((1*S*,2*S*)-2-propylcyclopropyl)acrylate 2



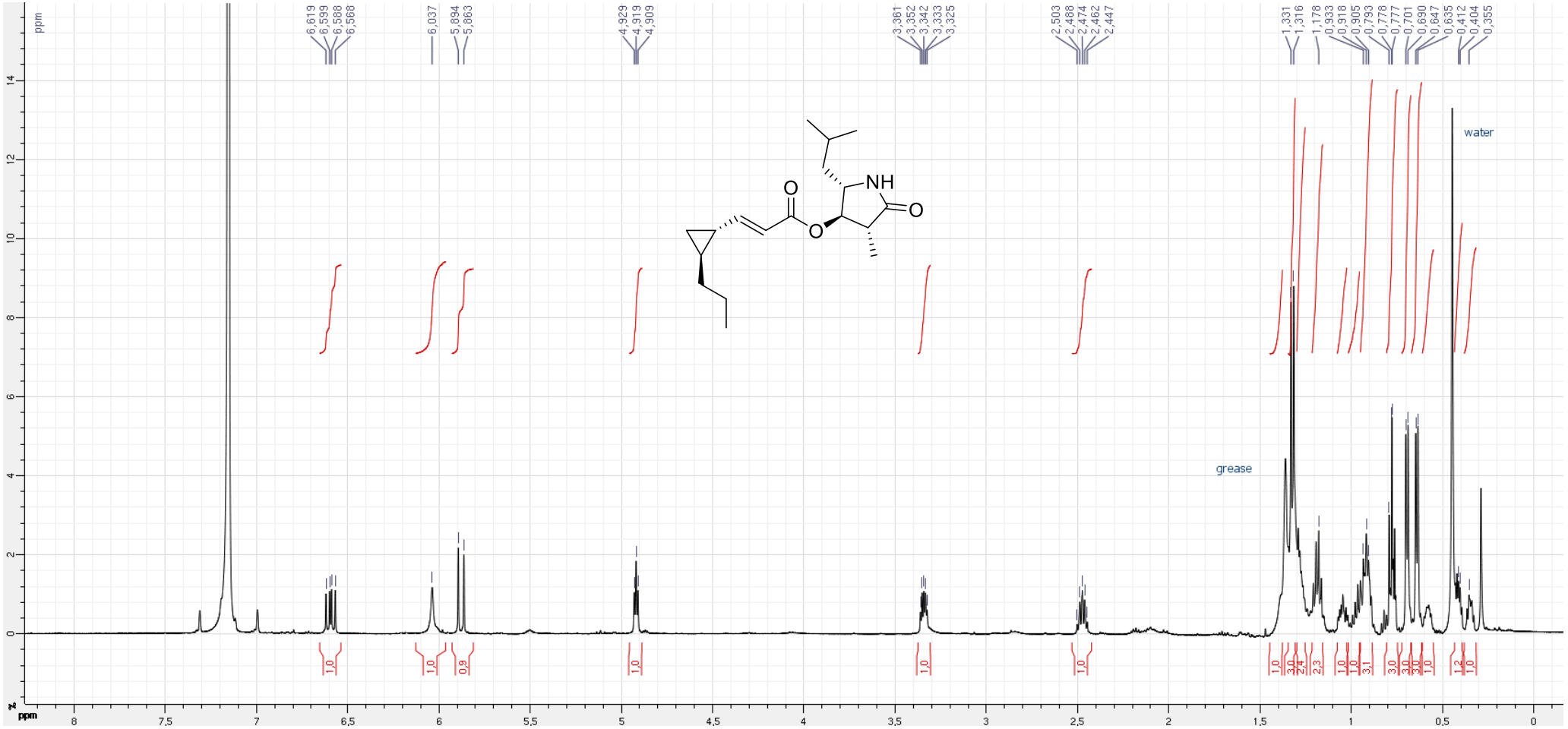

ppm
167,129
154,034
117,675
60,195
35,873
23,311
22,567
22,334
16,188
14,562
14,081
ppm

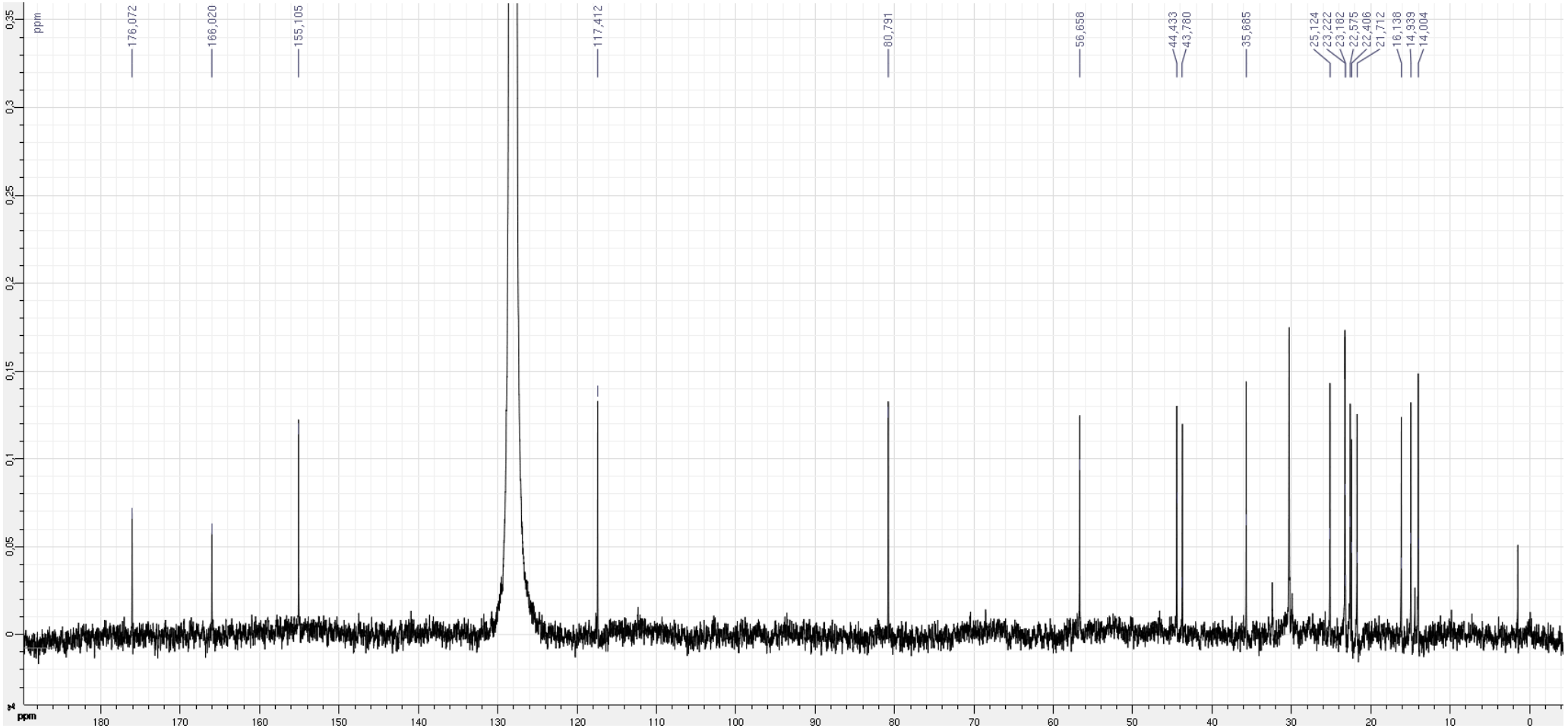
(3*R*,4*R*,5*S*)-4-hydroxy-5-isobutyl-3-methylpyrrolidin-2-one



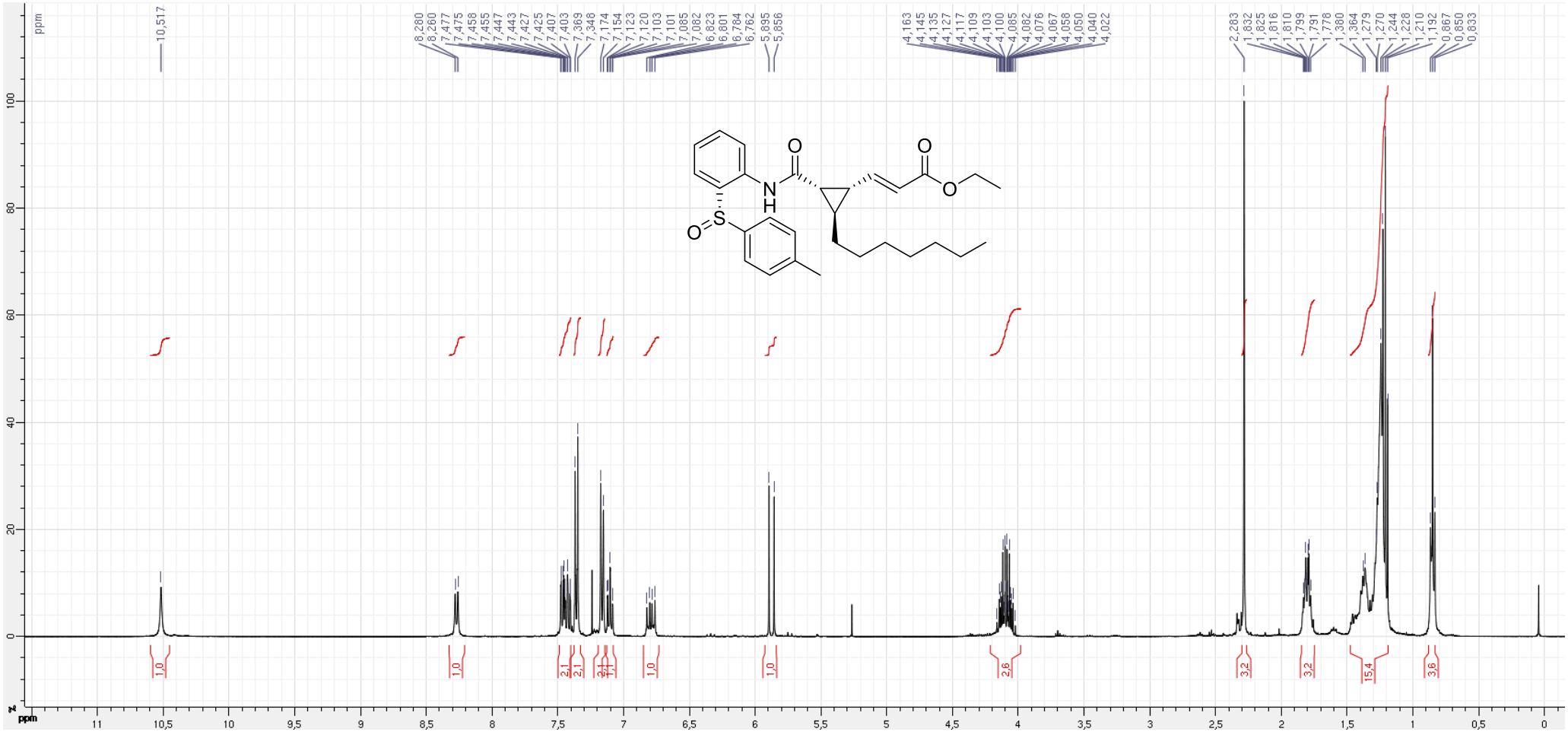

ppm
179,680
82,042
59,892
46,798
45,187
26,296
23,876
22,600
13,880
100
80
60
40
20
0
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

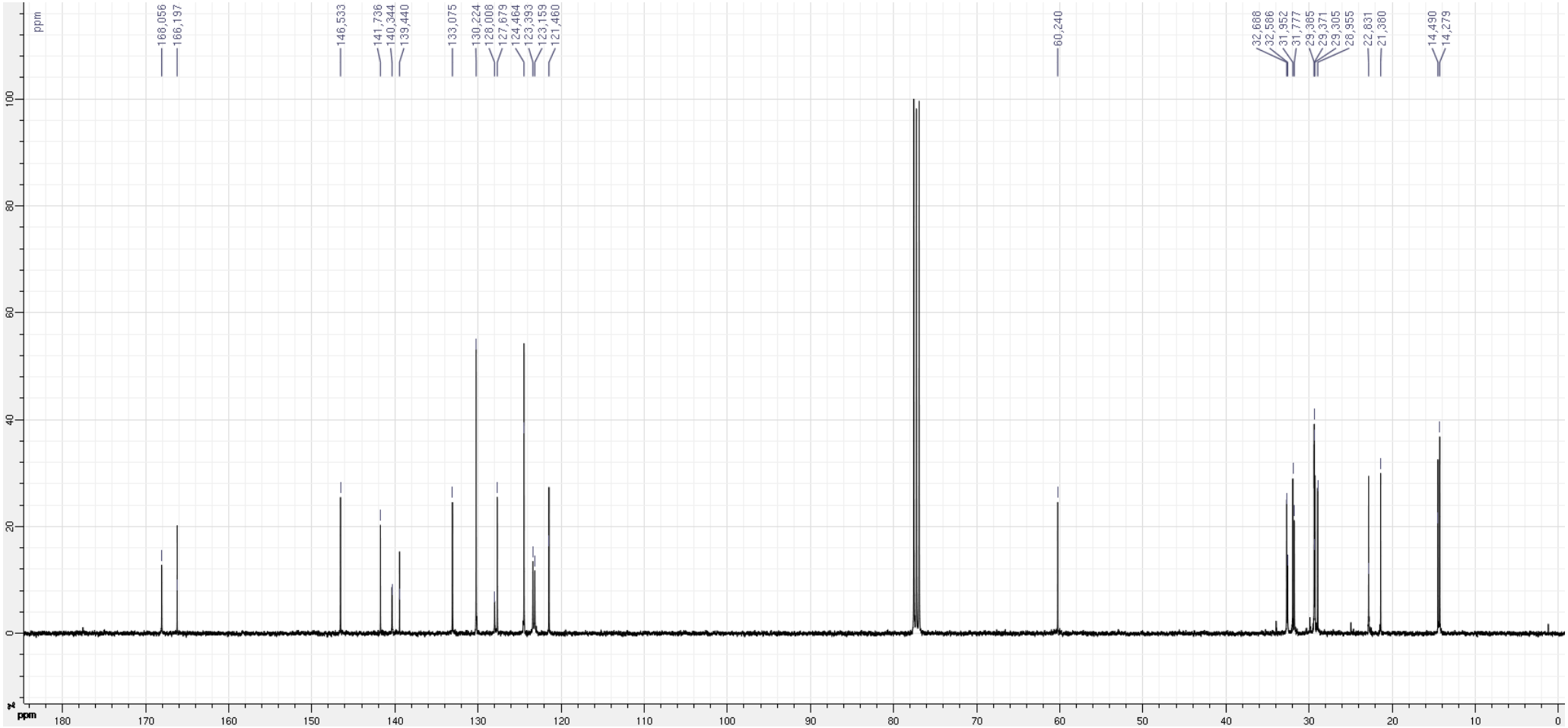
(2*S*,3*R*,4*R*)-2-isobutyl-4-methyl-5-oxopyrrolidin-3-yl (*E*)-3-((1*S*,2*S*)-2-propylcyclopropyl)acrylate 1



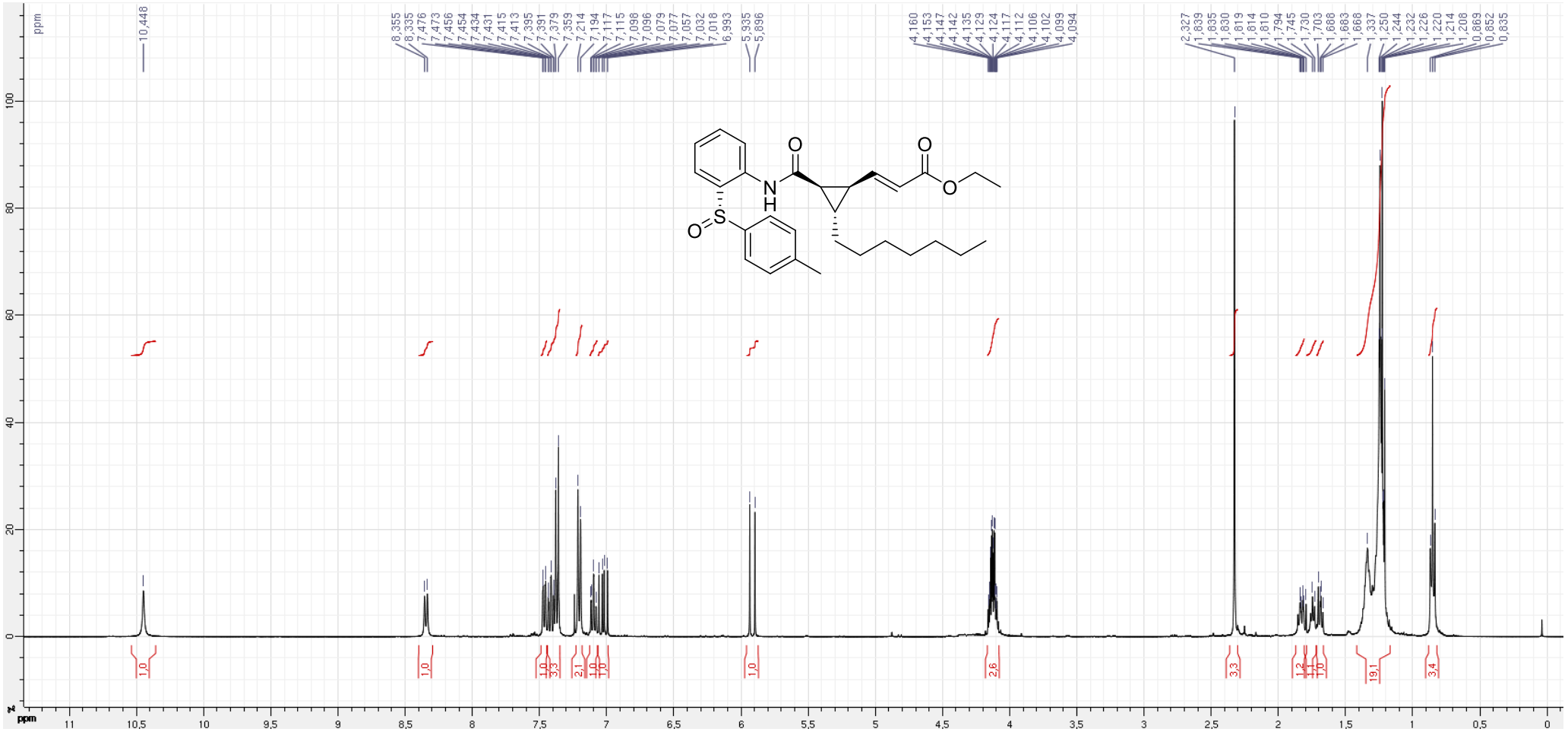

ppm
176,072
166,020
155,105
117,412
80,791
56,658
44,433
43,780
35,685
25,124
23,222
23,182
22,575
22,406
21,712
16,138
14,939
14,004
0,35
0,3
0,25
0,2
0,15
0,1
0,05
0
%
ppm
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

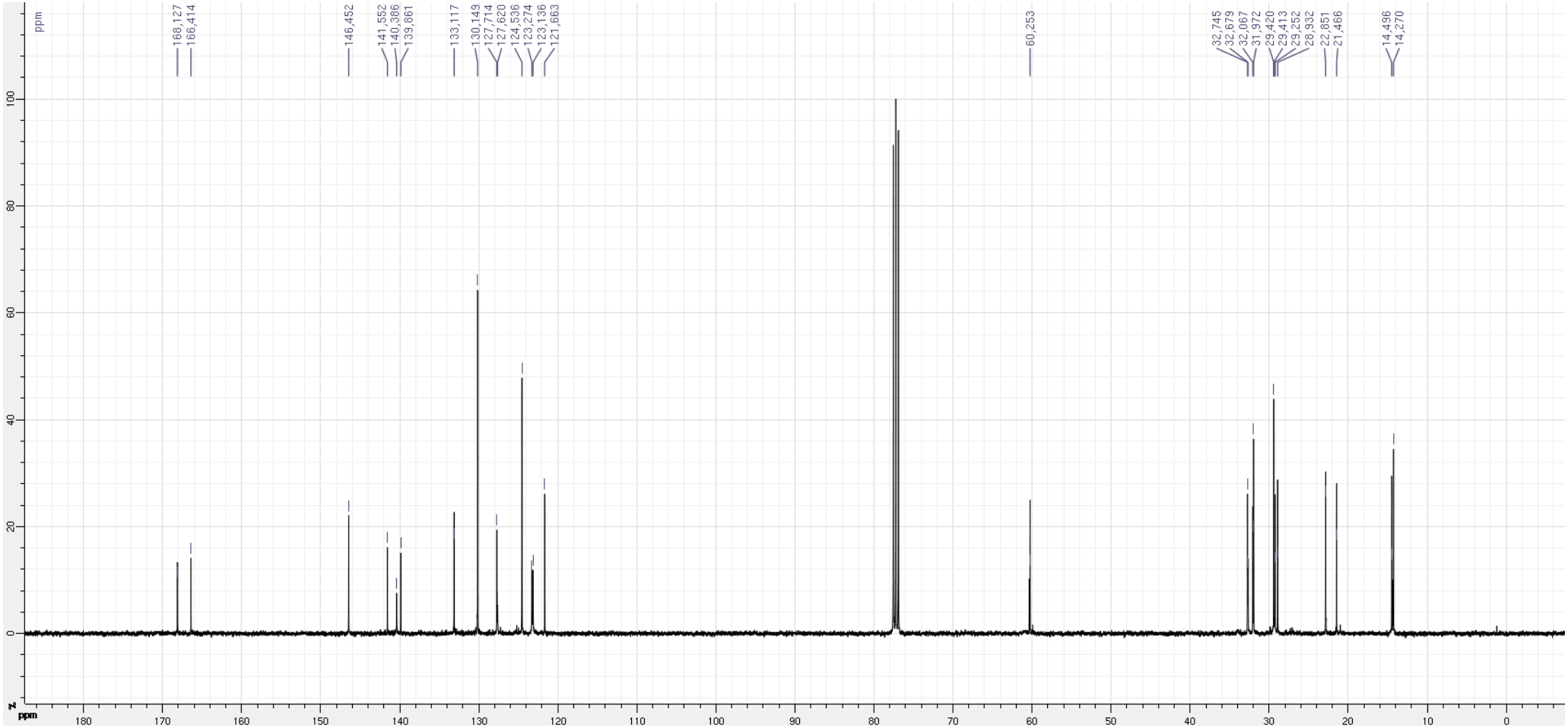
ethyl (*E*)-3-((1*R*,2*R*,3*S*)-2-heptyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate 9



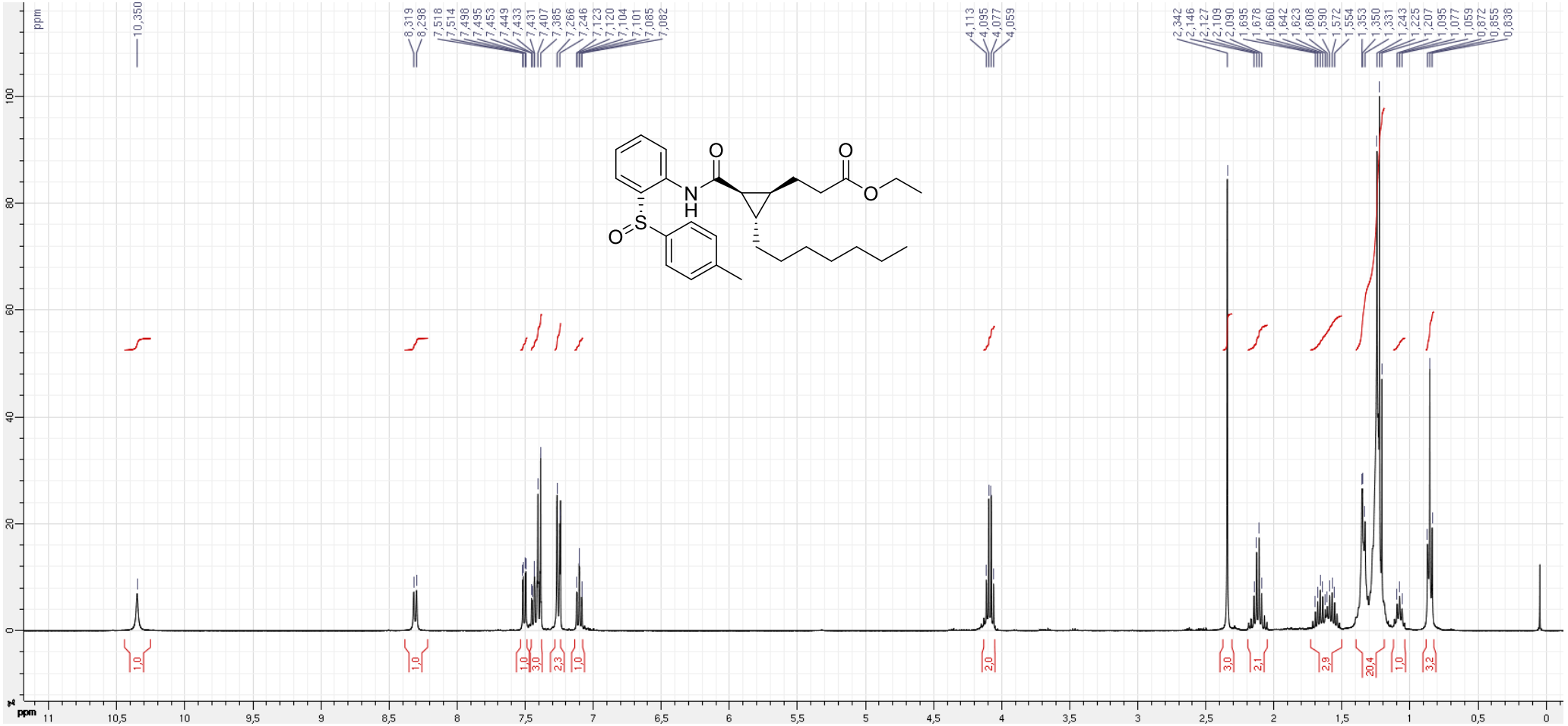

ppm
168,056
166,197
146,533
141,736
140,344
139,440
133,075
130,224
128,008
127,679
124,464
123,393
123,159
121,460
60,240
32,688
32,586
31,952
31,777
29,385
29,371
29,305
28,955
22,831
21,380
14,490
14,279
%
ppm

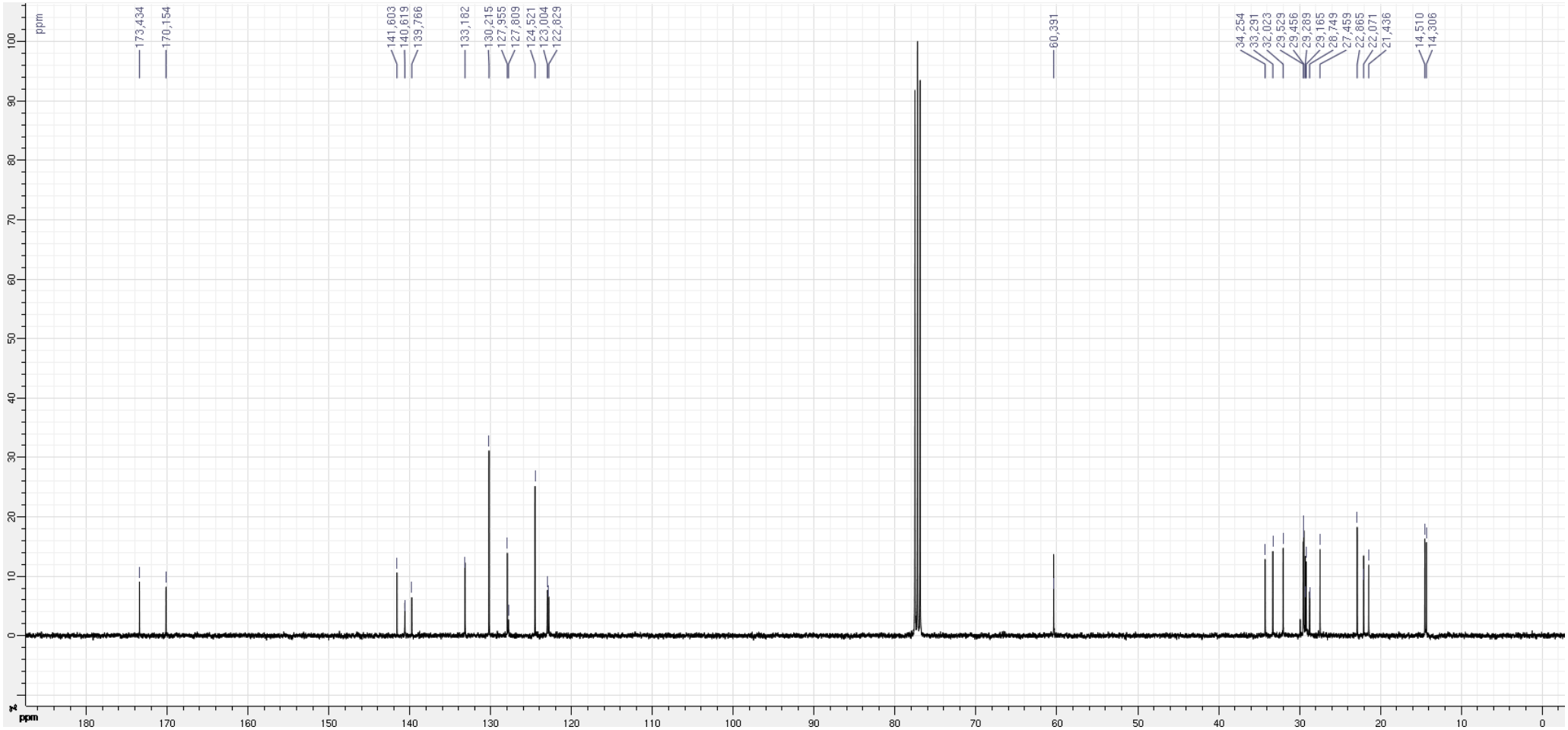
ethyl (*E*)-3-((1*S*,2*S*,3*R*)-2-heptyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate dia-9



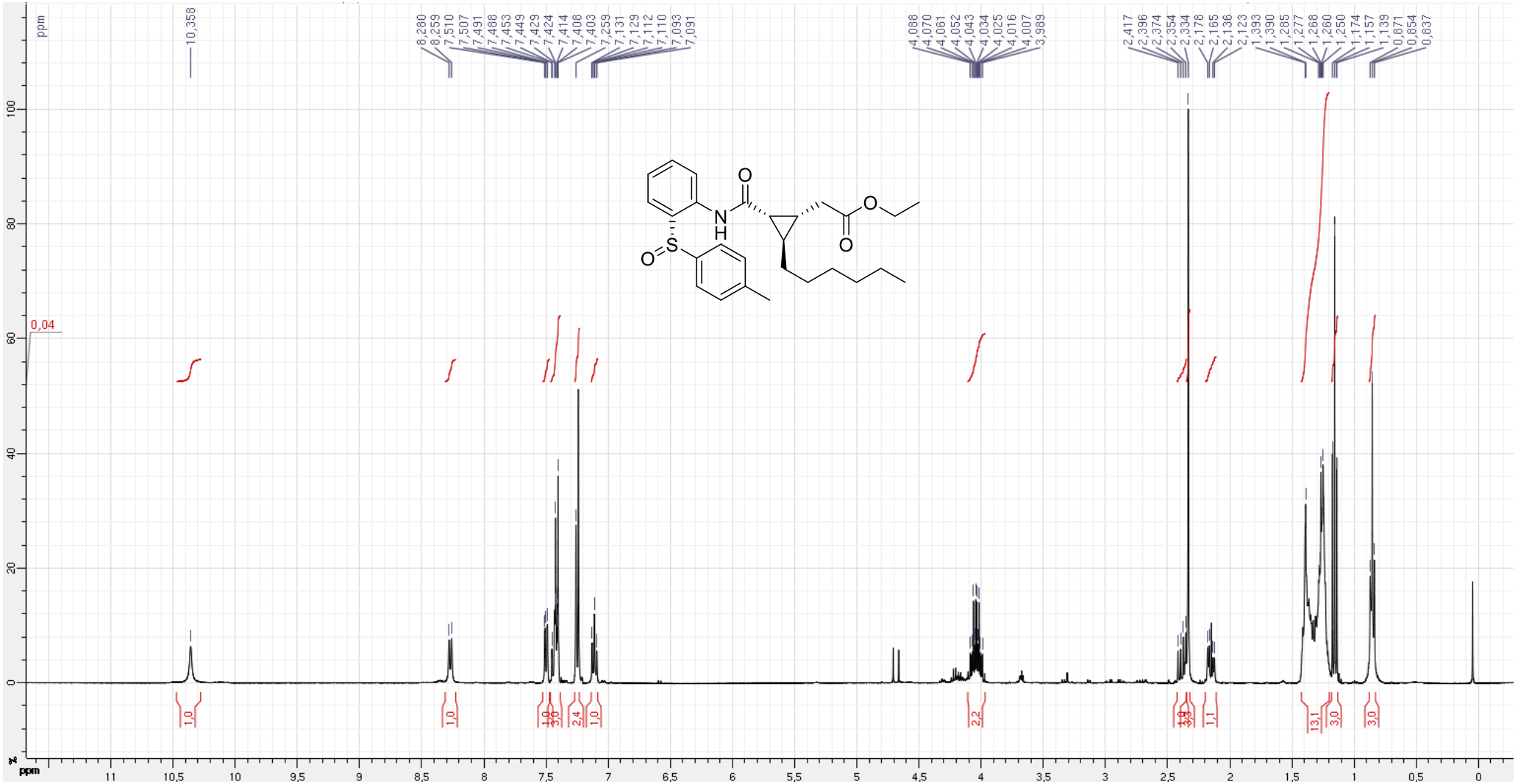

ppm
168,127
166,414
146,452
141,552
140,386
139,861
133,117
130,149
127,714
127,620
124,536
123,274
123,136
121,663
60,253
32,745
32,679
32,067
31,972
29,420
29,413
29,252
28,932
22,851
21,466
14,496
14,270

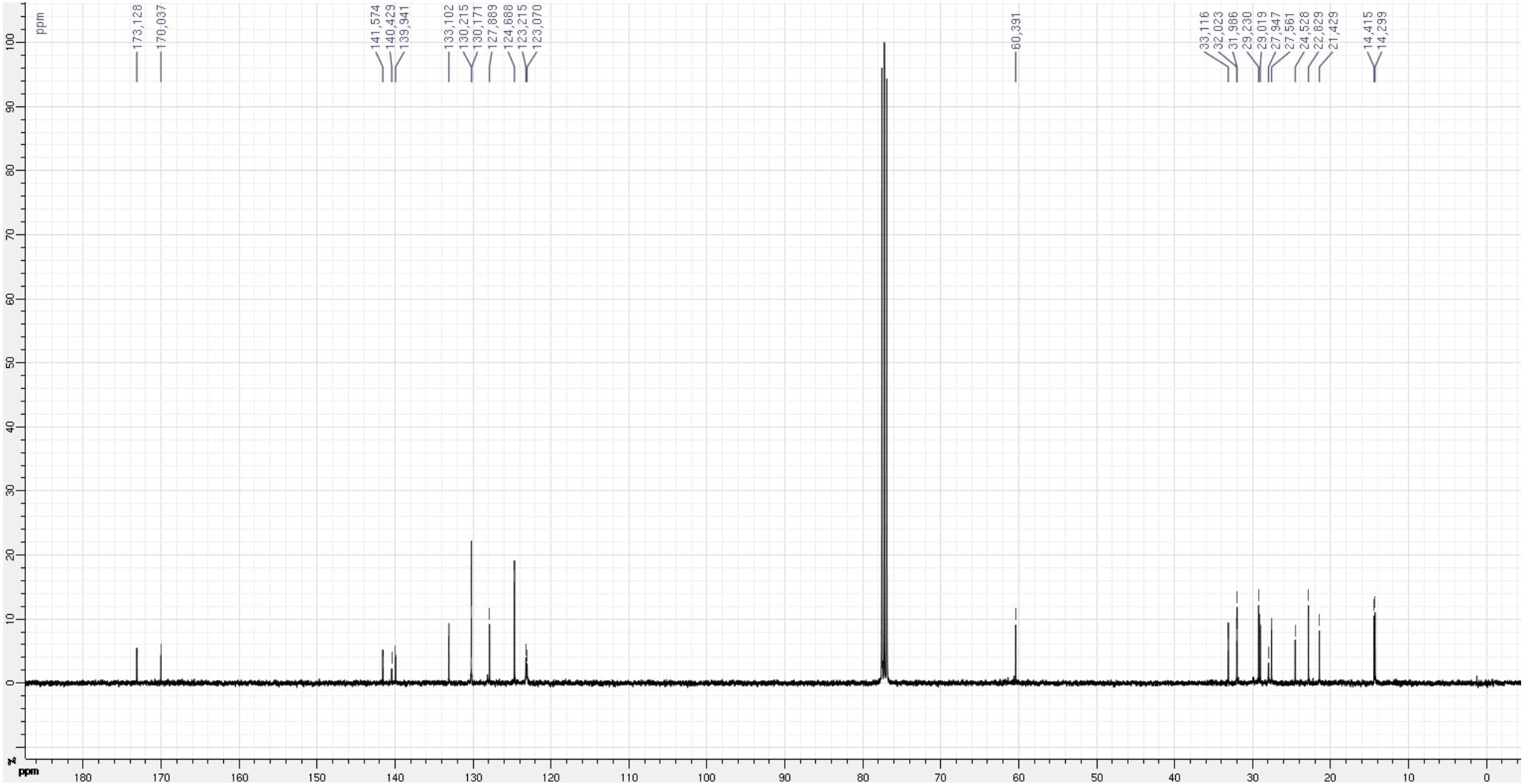
ethyl 3-((1*S*,2*S*,3*R*)-2-heptyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)propanoate 10



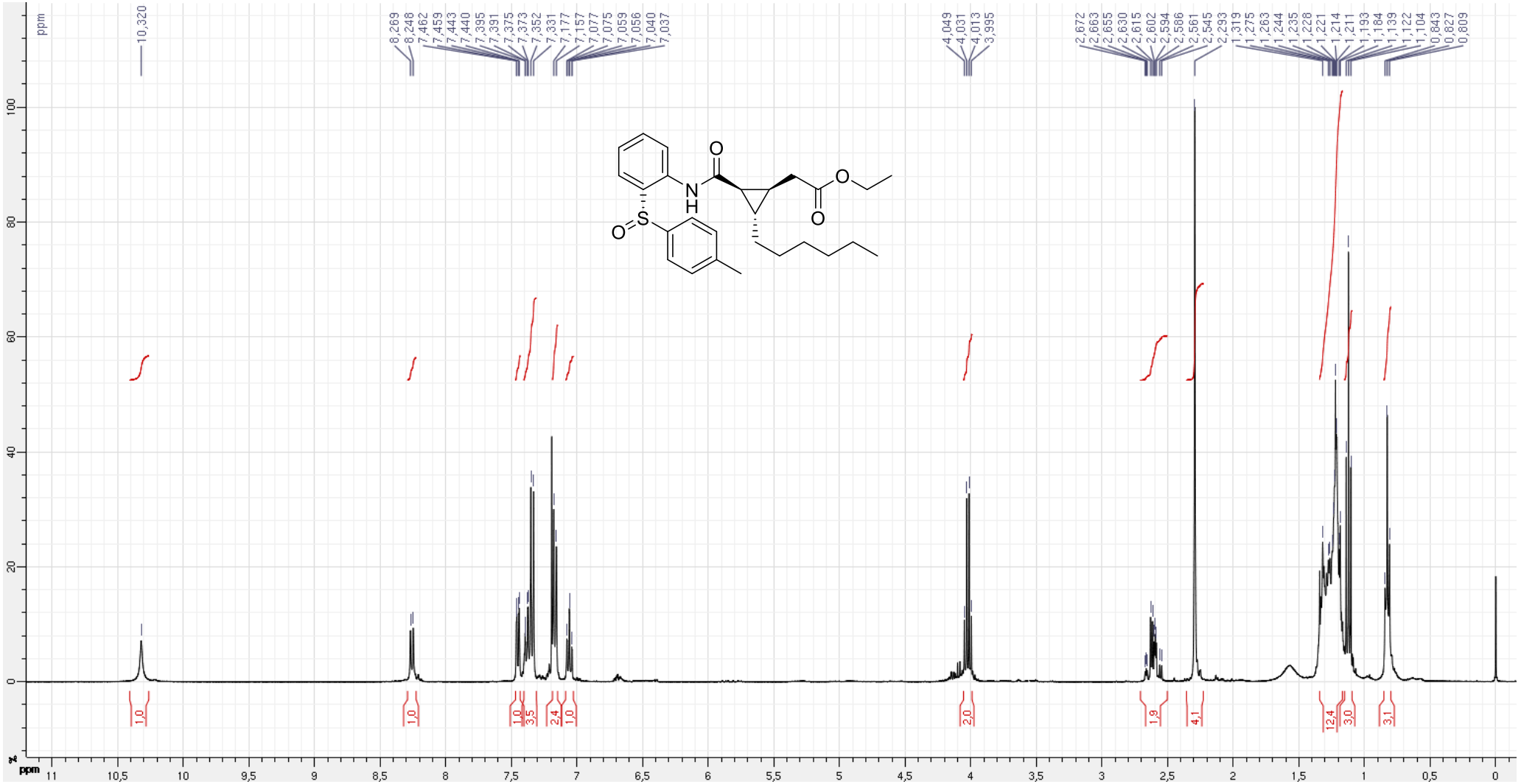

ppm
173,434
170,154
141,603
140,619
139,766
133,182
130,215
127,955
127,809
124,521
123,004
122,829
60,391
34,254
33,291
32,023
29,529
29,456
29,289
29,165
28,749
27,459
22,865
22,071
21,436
14,510
14,306

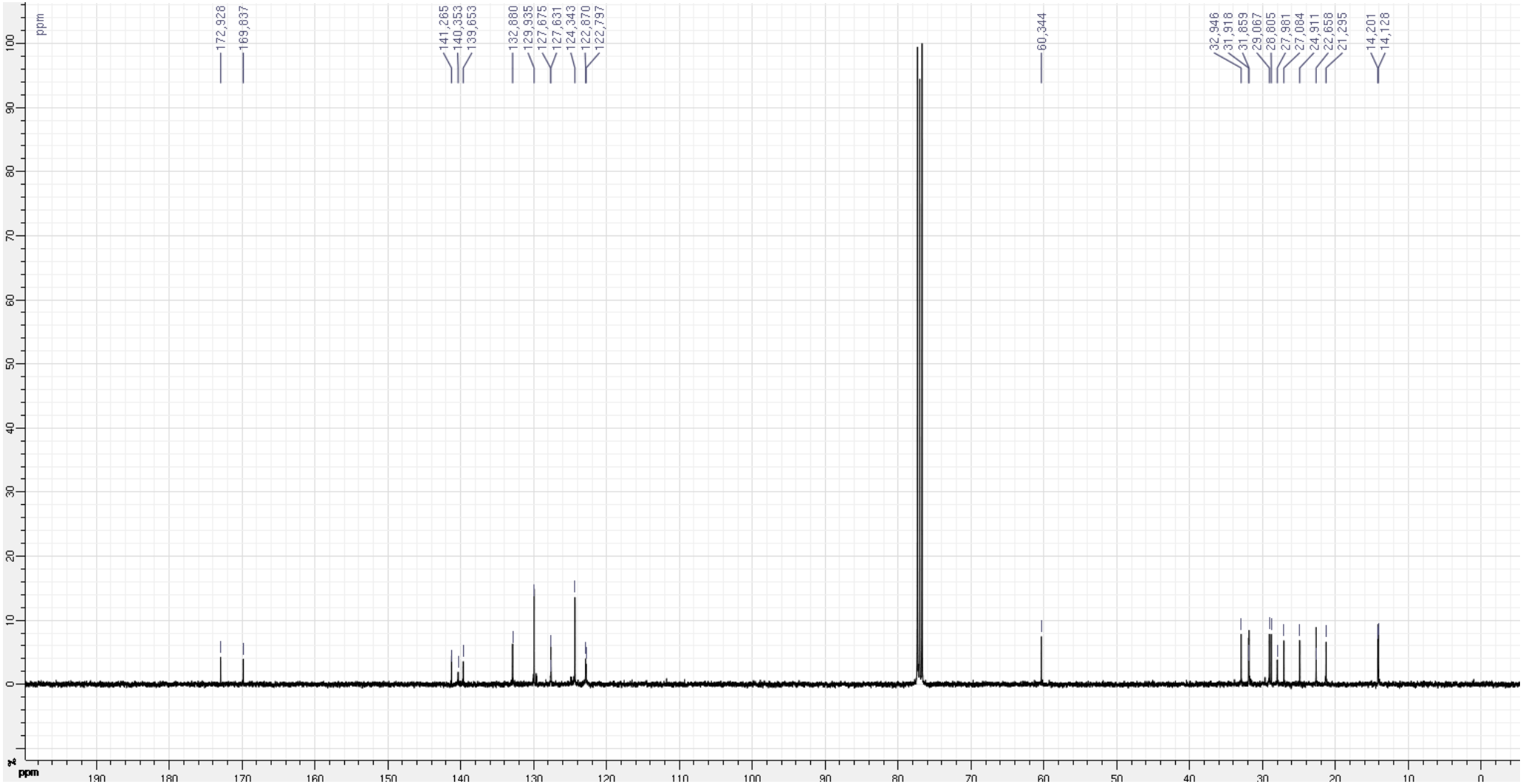
ethyl 2-((1*R*,2*R*,3*S*)-2-hexyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acetate 12




ppm
173,128
170,037
141,574
140,429
139,941
133,102
130,215
130,171
127,889
124,688
123,215
123,070
60,391
33,116
32,023
31,986
29,230
29,019
27,947
27,561
24,528
22,829
21,429
14,415
14,299
ppm

ethyl 2-((1*S*,2*S*,3*R*)-2-hexyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acetate dia-12




ppm
172,928
169,837
141,285
140,353
139,653
132,880
129,935
127,675
127,631
124,343
122,870
122,797
60,344
32,946
31,918
31,859
29,067
28,805
27,981
27,084
24,911
22,658
21,295
14,201
14,128

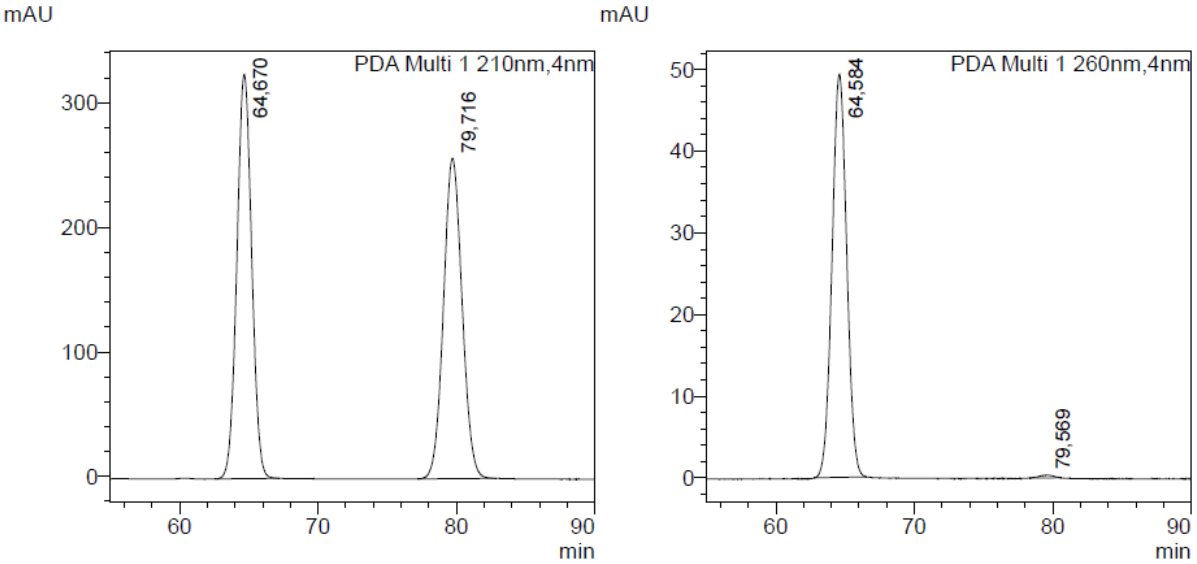
Chiral HPLC Data

(*S*)-2-(*p*-tolylsulfinyl)aniline APS

<Sample Information>

Sample Name	: PP002-F1-rac	Sample Name	: SJE603-en_01
Method Filename	: Hex_IPA_8020_0-5ml.lcm	Method Filename	: Hex_IPA_8020_0-5ml.lcm
Vial #	: 1-4	Vial #	: 1-1
Injection Volume	: 1 uL	Injection Volume	: 1 uL
Date Acquired	: 14/02/2017 10:40:56	Date Acquired	: 13/04/2017 20:29:42
Date Processed	: 14/02/2017 12:29:21	Date Processed	: 18/04/2017 07:37:22
Conditions	: IC Hex/IPA 80/20 0.5ml/min	Conditions	: IC Hex/IPA 80/20 0.5ml/min

<Chromatogram>



<Peak Table>

PDA Ch1 210nm

Peak#	Ret. Time	Area	Conc.
1	64,670	24064482	50,003
2	79,716	24061181	49,997
Total		48125663	

PDA Ch1 260nm

Peak#	Ret. Time	Area	Conc.
1	64,584	3626988	99,356
2	79,569	23512	0,644
Total		3650500	

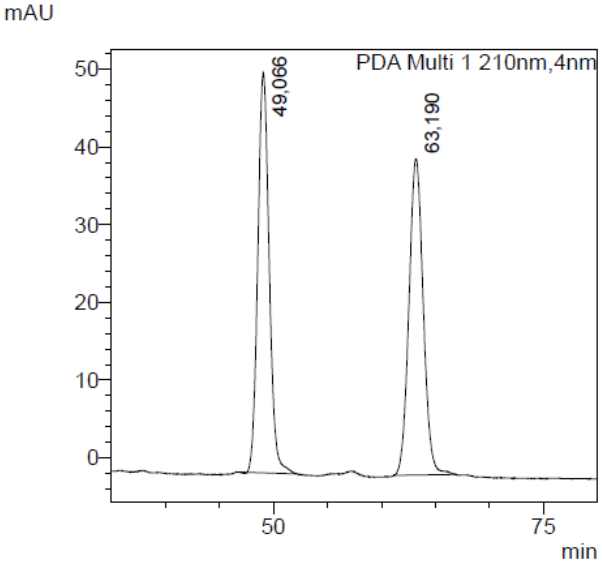
methyl (*E*)-3-((1*R*,2*R*,3*S*)-2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate 3

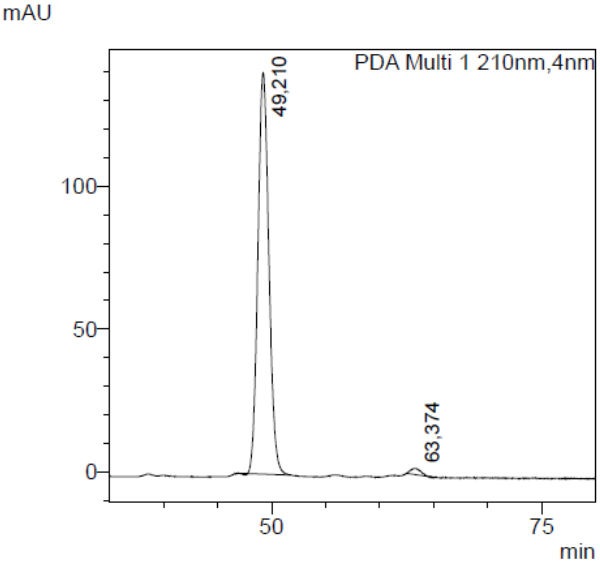
<Sample Information>

Sample Name	: PP038-1-rac_01
Method Filename	: Hex_IPA_8020_0-5ml.lcm
Vial #	: 1-2
Injection Volume	: 1 uL
Date Acquired	: 13/04/2017 22:00:11
Date Processed	: 18/04/2017 07:39:50
Conditions	: IC Hex/IPA 80/20 0.5ml/min

Sample Name	: SJE629-1_en_02
Method Filename	: Hex_IPA_8020_0-5ml.lcm
Vial #	: 1-1
Injection Volume	: 1 uL
Date Acquired	: 12/05/2017 08:27:49
Date Processed	: 15/05/2017 11:39:09
Conditions	: IC Hex/IPA 80/20 0.5ml/min

<Chromatogram>





<Peak Table>

PDA Ch1 210nm

Peak#	Ret. Time	Area	Conc.
1	49,066	3757563	50,143
2	63,190	3736132	49,857
Total		7493695	

PDA Ch1 210nm

Peak#	Ret. Time	Area	Conc.
1	49,210	9917506	98,561
2	63,374	144844	1,439
Total		10062350	

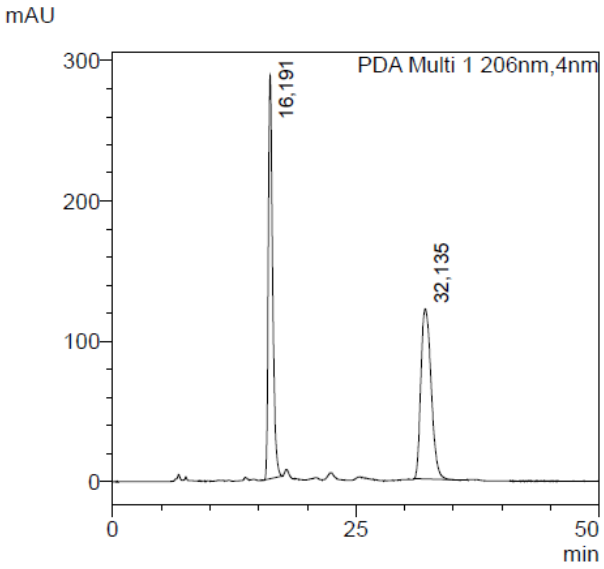
methyl (*E*)-3-((1*S*,2*S*,3*R*)-2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate dia-3

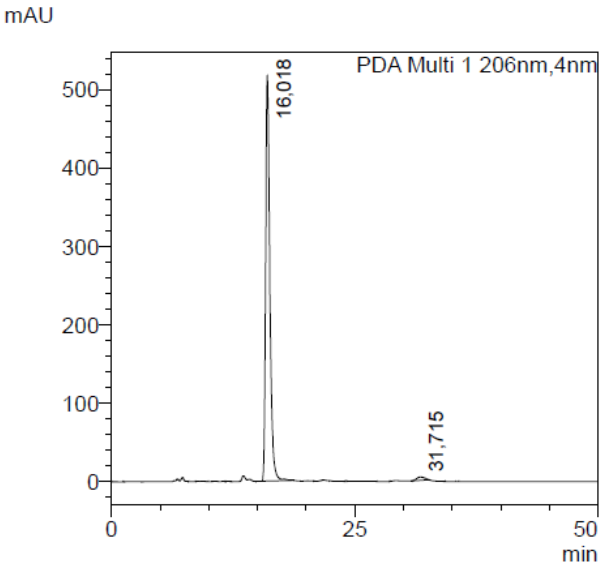
<Sample Information>

Sample Name	: PP038-2-rac_01
Method Filename	: Hex_IPA_8020_0-5ml.lcm
Vial #	: 1-2
Injection Volume	: 1 uL
Date Acquired	: 20/04/2017 19:15:05
Date Processed	: 21/04/2017 09:28:29
Conditions	: IA Hex/IPA 80/20 .5ml/min

Sample Name	: SJE629-2_en_01
Method Filename	: Hex_IPA_8020_0-5ml.lcm
Vial #	: 1-2
Injection Volume	: 1 uL
Date Acquired	: 11/05/2017 21:28:53
Date Processed	: 12/05/2017 07:10:37
Conditions	: IA Hex/IPA 80/20 0.5ml/min

<Chromatogram>





<Peak Table>

PDA Ch1 206nm

Peak#	Ret. Time	Area	Conc.
1	16,191	8821617	49,730
2	32,135	8917337	50,270
Total		17738954	

PDA Ch1 206nm

Peak#	Ret. Time	Area	Conc.
1	16,018	15576097	98,495
2	31,715	237972	1,505
Total		15814069	

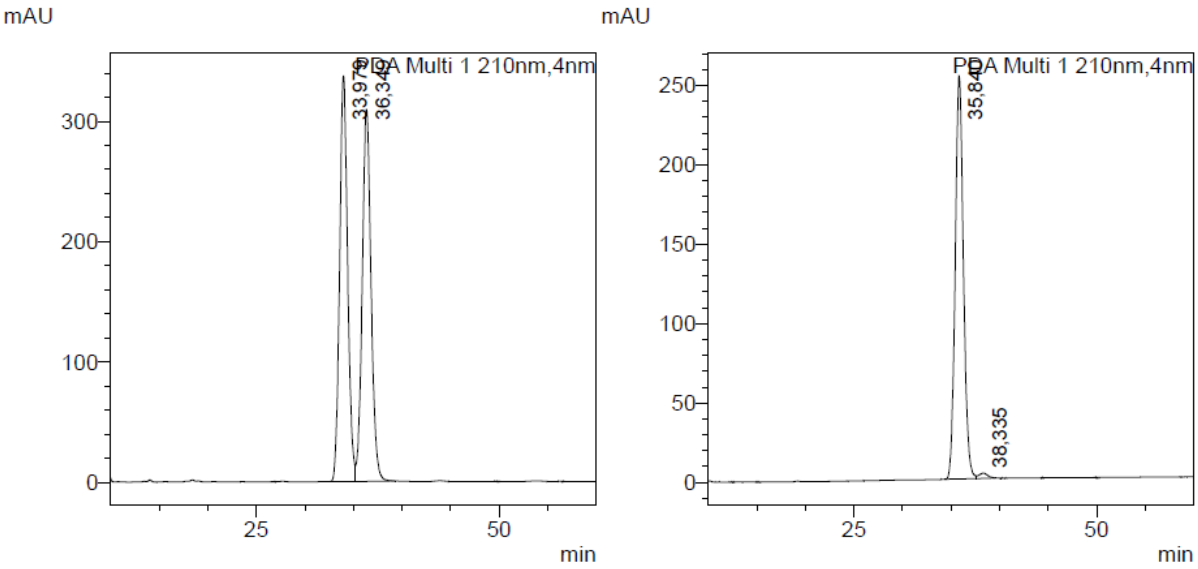
***tert*-butyl (2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamate Boc-APS**

<Sample Information>

Sample Name	: SJE650-rac_13
Method Filename	: Hex_IPA_9802_0-5ml.lcm
Vial #	: 1-2
Injection Volume	: 1 uL
Date Acquired	: 07/07/2017 12:36:58
Date Processed	: 10/07/2017 09:55:19
Conditions	: IA Hex/IPA 98/2 0.5ml/min

Sample Name	: SJE650-en_02
Method Filename	: Hex_IPA_9802_0-5ml.lcm
Vial #	: 1-1
Injection Volume	: 1 uL
Date Acquired	: 07/07/2017 11:06:29
Date Processed	: 10/07/2017 09:55:04
Conditions	: IA Hex/IPA 98/2 0.5ml/min

<Chromatogram>



<Peak Table>

PDA Ch1 210nm

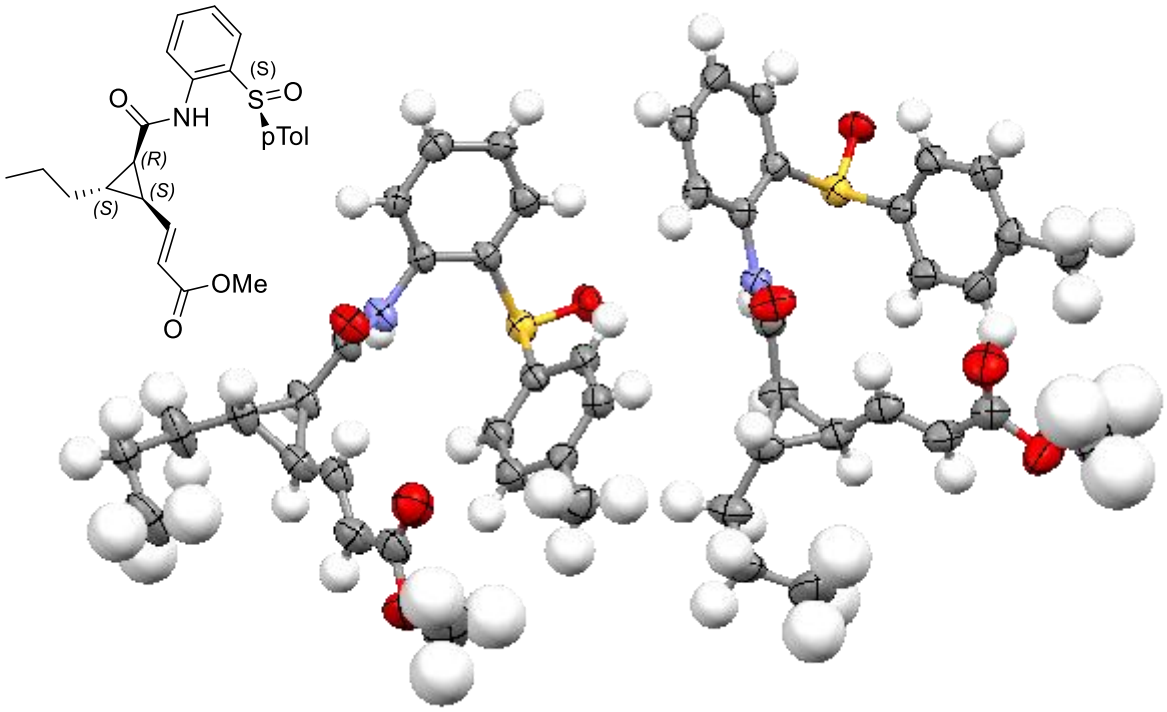
Peak#	Ret. Time	Area	Conc.
1	35,840	14914817	98,666
2	38,335	201715	1,334
Total		15116533	

PDA Ch1 210nm

Peak#	Ret. Time	Area	Conc.
1	35,840	14914817	98,666
2	38,335	201715	1,334
Total		15116533	

X-Ray Data

methyl (*E*)-3-((1*S*,2*S*,3*R*)-2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate dia-3



General data

Formula	$C_{24}H_{27}NO_4S$
Space group	P 2_1
Cell lengths	**a** 22.1340(6) **b** 4.95080(10) **c** 24.5460(6)
Cell angles	α 90 β 115.741(2) γ 90
Cell volume	2422.86
Z, Z'	**Z**: 4 **Z'**: 0
Symmetry cell setting	Monoclinic
R_1	5.79

Atomic coordinates

Label	x	y	z	Label	x	y	z
C1	0.6077	0.0167	0.4440	C28	0.7418	0.3211	0.1459
C2	0.6020	0.2237	0.4794	C29	0.7838	0.1243	0.1400
H2	0.6395	0.2723	0.5158	H29	0.7841	0.0963	0.1018
C3	0.5417	0.3605	0.4619	C30	0.8248	-0.0301	0.1889
H3	0.5382	0.5009	0.4868	H30	0.8532	-0.1624	0.1841
C4	0.4872	0.2949	0.4091	C31	0.6955	0.4839	0.0920
C5	0.4930	0.0902	0.3729	H31A	0.6802	0.3723	0.0555
H5	0.4554	0.0454	0.3362	H31B	0.7195	0.6421	0.0874
C6	0.5533	-0.0515	0.3897	H31C	0.6567	0.5434	0.0982
H6	0.5571	-0.1904	0.3646	C32	0.9335	0.0451	0.3514
C7	0.4209	0.4401	0.3913	C33	0.9284	0.1433	0.4015

H7A	0.4007	0.3821	0.4179
H7B	0.3906	0.3963	0.3493
H7C	0.4287	0.6355	0.3953
C8	0.7374	0.0739	0.4671
C9	0.7841	0.1799	0.5216
H9	0.7873	0.1105	0.5588
C10	0.8260	0.3876	0.5213
H10	0.8569	0.4648	0.5584
C11	0.8229	0.4835	0.4668
H11	0.8517	0.6257	0.4667
C12	0.7772	0.3695	0.4120
H12	0.7754	0.4323	0.3748
C13	0.7347	0.1648	0.4124
C14	0.6477	0.1982	0.3082
C15	0.6065	0.0275	0.2539
H15	0.6192	-0.1676	0.2568
C16	0.5821	0.1519	0.1921
H16	0.5929	0.3479	0.1920
C17	0.5320	0.0895	0.2171
H17	0.5038	-0.0736	0.1988
C18	0.4961	0.3086	0.2303
H18	0.5211	0.4569	0.2539
C19	0.4297	0.3084	0.2103
H19	0.4050	0.1579	0.1875
C20	0.3941	0.5257	0.2219
C21	0.2870	0.7010	0.2013
H21A	0.2800	0.6651	0.2374
H21B	0.2436	0.7073	0.1657
H21C	0.3101	0.8743	0.2059
C22	0.5825	-0.0075	0.1400
H22A	0.5700	-0.1970	0.1431
H22B	0.6285	-0.0079	0.1429
C23	0.5344	0.1060	0.0787
H23A	0.5462	0.2973	0.0768
H23B	0.5415	0.0069	0.0469
C24	0.4626	0.0920	0.0646
H24A	0.4513	-0.0928	0.0714
H24B	0.4356	0.1415	0.0222
H24C	0.4530	0.2168	0.0909
N1	0.6883	0.0493	0.3570
O1	0.7029	-0.2353	0.5357
O2	0.6455	0.4452	0.3082
O3	0.4176	0.7198	0.2526
O4	0.3274	0.4885	0.1938
S1	0.6818	-0.1838	0.4697
H1N	0.6870	-0.1440	0.3520
C25	0.8250	0.0055	0.2449
C26	0.7841	0.2013	0.2518
H26	0.7845	0.2297	0.2903
H33	0.8944	0.0775	0.4118
C34	0.9727	0.3378	0.4371
H34	0.9685	0.4080	0.4713
C35	1.0238	0.4319	0.4228
H35	1.0545	0.5646	0.4475
C36	1.0295	0.3315	0.3729
H36	1.0639	0.3962	0.3629
C37	0.9845	0.1336	0.3368
C38	0.9964	0.1850	0.2423
C39	1.0080	0.0274	0.1961
H39	1.0165	-0.1701	0.2045
C40	1.0461	0.1598	0.1656
H40	1.0584	0.3530	0.1768
C41	0.9724	0.1068	0.1288
H41	0.9628	-0.0499	0.1005
C42	0.9237	0.3243	0.1052
H42	0.9272	0.4722	0.1311
C43	0.8750	0.3267	0.0500
H43	0.8722	0.1816	0.0236
C44	0.8256	0.5410	0.0274
C45	0.7280	0.7020	-0.0544
H45A	0.7488	0.8812	-0.0432
H45B	0.6945	0.6803	-0.0387
H45C	0.7063	0.6852	-0.0986
C46	1.0968	-0.0038	0.1531
H46A	1.0753	-0.1700	0.1306
H46B	1.1345	-0.0575	0.1917
C47	1.1239	0.1700	0.1149
H47A	1.1396	0.3478	0.1343
H47B	1.1619	0.0765	0.1119
C48	1.0653	0.2060	0.0515
H48A	1.0528	0.0294	0.0315
H48B	1.0791	0.3262	0.0273
H48C	1.0267	0.2839	0.0554
N2	0.9906	0.0275	0.2856
O5	0.8327	-0.2603	0.3400
O6	0.9952	0.4331	0.2436
O7	0.8247	0.7425	0.0545
O8	0.7799	0.4927	-0.0285
S2	0.8742	-0.2066	0.3069
H2N	0.9890	-0.1370	0.2800
H46C	0.0908	0.8028	0.1598
H46D	0.1424	0.0491	0.1827
C47B	0.0921	0.0290	0.0885
H47C	0.1255	0.9094	0.0841
H47D	0.0470	0.9706	0.0586
C48B	0.1038	0.3130	0.0743
H48D	0.0676	0.4292	0.0735
H48E	0.1047	0.3177	0.0347

C27	0.7424	0.3563	0.2023	H48F	0.1468	0.3775	0.1054
H27	0.7139	0.4880	0.2072				

Bond lengths

Atom1	Atom2	Length	Atom1	Atom2	Length
C1	C2	1.384(8)	C25	C26	1.386(9)
C1	C6	1.395(6)	C25	C30	1.38(1)
C1	S1	1.782(6)	C25	S2	1.779(5)
C2	H2	0.949	C26	H26	0.952
C2	C3	1.388(9)	C26	C27	1.394(8)
C3	H3	0.951	C27	H27	0.950
C3	C4	1.372(7)	C27	C28	1.39(1)
C4	C5	1.39(1)	C28	C29	1.40(1)
C4	C7	1.52(1)	C28	C31	1.507(8)
C5	H5	0.950	C29	H29	0.951
C5	C6	1.402(9)	C29	C30	1.379(8)
C6	H6	0.951	C30	H30	0.950
C7	H7A	0.981	C31	H31A	0.979
C7	H7B	0.979	C31	H31B	0.980
C7	H7C	0.980	C31	H31C	0.98
C8	C9	1.390(6)	C32	C33	1.372(8)
C8	C13	1.393(8)	C32	C37	1.395(9)
C8	S1	1.792(6)	C32	S2	1.795(5)
C9	H9	0.949	C33	H33	0.950
C9	C10	1.387(9)	C33	C34	1.381(7)
C10	H10	0.950	C34	H34	0.950
C10	C11	1.39(1)	C34	C35	1.40(1)
C11	H11	0.950	C35	H35	0.950
C11	C12	1.403(8)	C35	C36	1.38(1)
C12	H12	0.949	C36	H36	0.951
C12	C13	1.386(8)	C36	C37	1.404(6)
C13	N1	1.420(5)	C37	N2	1.422(8)
C14	C15	1.505(7)	C38	C39	1.49(1)
C14	N1	1.361(6)	C38	N2	1.368(9)
C14	O2	1.224(7)	C38	O6	1.229(7)
C15	H15	1.000	C39	H39	1.000
C15	C16	1.503(7)	C39	C40	1.50(1)
C15	C17	1.528(8)	C39	C41	1.541(8)
C16	H16	1.000	C40	H40	1.000
C16	C17	1.51(1)	C40	C41	1.505(8)
C16	C22	1.51(1)	C40	C46	1.52(1)
C17	H17	1.000	C41	H41	1.001
C17	C18	1.46(1)	C41	C42	1.454(9)
C18	H18	0.950	C42	H42	0.951
C18	C19	1.332(9)	C42	C43	1.315(8)
C19	H19	0.949	C43	H43	0.951
C19	C20	1.43(1)	C43	C44	1.45(1)
C20	O3	1.192(9)	C44	O7	1.20(1)

C20	O4	1.343(8)	C44	O8	1.326(7)
C21	H21A	0.98	C45	H45A	0.98
C21	H21B	0.98	C45	H45B	0.98
C21	H21C	0.98	C45	H45C	0.981
C21	O4	1.44(2)	C45	O8	1.47(1)
C22	H22A	0.990	C46	H46A	0.990
C22	H22B	0.989	C46	H46B	0.989
C22	C23	1.524(9)	C46	C47	1.57(2)
C23	H23A	0.99	C47	H47A	0.99
C23	H23B	0.991	C47	H47B	0.99
C23	C24	1.47(1)	C47	C48	1.54(2)
C24	H24A	0.98	C48	H48A	0.98
C24	H24B	0.980	C48	H48B	0.98
C24	H24C	0.98	C48	H48C	0.98
N1	H1N	0.96(7)	N2	H2N	0.82(7)
O1	S1	1.502(4)	O5	S2	1.490(5)

Bond angles

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C2	C1	C6	120.2(5)	C26	C25	C30	119.3(5)
C2	C1	S1	120.7(4)	C26	C25	S2	119.8(4)
C6	C1	S1	118.9(4)	C30	C25	S2	120.8(5)
C1	C2	H2	119.8	C25	C26	H26	120.0
C1	C2	C3	120.3(5)	C25	C26	C27	119.9(6)
H2	C2	C3	119.9	H26	C26	C27	120.1
C2	C3	H3	119.6	C26	C27	H27	119.5
C2	C3	C4	120.6(6)	C26	C27	C28	121.0(6)
H3	C3	C4	119.8	H27	C27	C28	119.5
C3	C4	C5	119.3(6)	C27	C28	C29	118.2(6)
C3	C4	C7	120.2(6)	C27	C28	C31	121.1(6)
C5	C4	C7	120.5(6)	C29	C28	C31	120.7(6)
C4	C5	H5	119.4	C28	C29	H29	119.6
C4	C5	C6	121.1(6)	C28	C29	C30	120.8(6)
H5	C5	C6	119.5	H29	C29	C30	119.6
C1	C6	C5	118.4(6)	C25	C30	C29	120.7(6)
C1	C6	H6	120.8	C25	C30	H30	119.6
C5	C6	H6	120.8	C29	C30	H30	119.7
C4	C7	H7A	109.4	C28	C31	H31A	109.5
C4	C7	H7B	109.4	C28	C31	H31B	109.4
C4	C7	H7C	109.4	C28	C31	H31C	109.4
H7A	C7	H7B	109.5	H31A	C31	H31B	109.6
H7A	C7	H7C	109.5	H31A	C31	H31C	109.5
H7B	C7	H7C	109.5	H31B	C31	H31C	109.4
C9	C8	C13	120.6(5)	C33	C32	C37	120.6(5)
C9	C8	S1	118.0(4)	C33	C32	S2	117.9(4)
C13	C8	S1	121.4(4)	C37	C32	S2	121.4(4)
C8	C9	H9	120.2	C32	C33	H33	120.0
C8	C9	C10	119.6(6)	C32	C33	C34	120.1(5)

H9	C9	C10	120.2	H33	C33	C34	119.8
C9	C10	H10	119.9	C33	C34	H34	119.9
C9	C10	C11	120.2(6)	C33	C34	C35	120.1(6)
H10	C10	C11	119.9	H34	C34	C35	119.9
C10	C11	H11	120.1	C34	C35	H35	120.1
C10	C11	C12	119.9(6)	C34	C35	C36	119.9(6)
H11	C11	C12	120.0	H35	C35	C36	120.0
C11	C12	H12	120.1	C35	C36	H36	120.0
C11	C12	C13	119.8(6)	C35	C36	C37	120.0(5)
H12	C12	C13	120.1	H36	C36	C37	120.0
C8	C13	C12	119.9(5)	C32	C37	C36	119.2(5)
C8	C13	N1	120.2(5)	C32	C37	N2	120.6(4)
C12	C13	N1	119.9(5)	C36	C37	N2	120.1(4)
C15	C14	N1	113.0(5)	C39	C38	N2	113.5(5)
C15	C14	O2	123.5(5)	C39	C38	O6	123.9(6)
N1	C14	O2	123.5(5)	N2	C38	O6	122.6(6)
C14	C15	H15	115.8	C38	C39	H39	115.8
C14	C15	C16	118.5(5)	C38	C39	C40	118.2(5)
C14	C15	C17	119.6(5)	C38	C39	C41	120.4(5)
H15	C15	C16	115.7	H39	C39	C40	115.7
H15	C15	C17	115.7	H39	C39	C41	115.7
C16	C15	C17	59.9(4)	C40	C39	C41	59.3(4)
C15	C16	H16	114.7	C39	C40	H40	115.2
C15	C16	C17	60.9(4)	C39	C40	C41	61.7(4)
C15	C16	C22	120.7(6)	C39	C40	C46	119.5(6)
H16	C16	C17	114.6	H40	C40	C41	115.2
H16	C16	C22	114.6	H40	C40	C46	115.4
C17	C16	C22	120.8(6)	C41	C40	C46	119.3(6)
C15	C17	C16	59.2(4)	C39	C41	C40	59.0(4)
C15	C17	H17	114.0	C39	C41	H41	113.7
C15	C17	C18	124.7(5)	C39	C41	C42	124.2(6)
C16	C17	H17	114.0	C40	C41	H41	113.6
C16	C17	C18	120.2(5)	C40	C41	C42	122.2(6)
H17	C17	C18	113.9	H41	C41	C42	113.6
C17	C18	H18	118.7	C41	C42	H42	118.2
C17	C18	C19	122.5(6)	C41	C42	C43	123.5(7)
H18	C18	C19	118.9	H42	C42	C43	118.3
C18	C19	H19	118.6	C42	C43	H43	118.5
C18	C19	C20	122.7(7)	C42	C43	C44	123.0(7)
H19	C19	C20	118.7	H43	C43	C44	118.5
C19	C20	O3	127.2(7)	C43	C44	O7	125.8(7)
C19	C20	O4	111.8(7)	C43	C44	O8	111.9(6)
O3	C20	O4	121.0(7)	O7	C44	O8	122.2(7)
H21A	C21	H21B	109	H45A	C45	H45B	109
H21A	C21	H21C	110	H45A	C45	H45C	109
H21A	C21	O4	109	H45A	C45	O8	109
H21B	C21	H21C	110	H45B	C45	H45C	110
H21B	C21	O4	109	H45B	C45	O8	110
H21C	C21	O4	109	H45C	C45	O8	109

C16	C22	H22A	109.0	C40	C46	H46A	109.7
C16	C22	H22B	109.0	C40	C46	H46B	109.9
C16	C22	C23	112.7(6)	C40	C46	C47	109.6(8)
H22A	C22	H22B	107.8	H46A	C46	H46B	108.2
H22A	C22	C23	109.1	H46A	C46	C47	109.7
H22B	C22	C23	109.1	H46B	C46	C47	109.7
C22	C23	H23A	108.3	C46	C47	H47A	110
C22	C23	H23B	108.3	C46	C47	H47B	110
C22	C23	C24	115.7(8)	C46	C47	C48	107(1)
H23A	C23	H23B	107.6	H47A	C47	H47B	109
H23A	C23	C24	108.3	H47A	C47	C48	110
H23B	C23	C24	108.4	H47B	C47	C48	110
C23	C24	H24A	109	C47	C48	H48A	109
C23	C24	H24B	110	C47	C48	H48B	110
C23	C24	H24C	110	C47	C48	H48C	109
H24A	C24	H24B	109	H48A	C48	H48B	109
H24A	C24	H24C	109	H48A	C48	H48C	109
H24B	C24	H24C	110	H48B	C48	H48C	110
C13	N1	C14	123.5(5)	C37	N2	C38	123.6(5)
C13	N1	H1N	119(4)	C37	N2	H2N	120(4)
C14	N1	H1N	117(4)	C38	N2	H2N	116(4)
C20	O4	C21	116.0(8)	C44	O8	C45	115.0(7)
C1	S1	C8	97.6(3)	C25	S2	C32	97.2(3)
C1	S1	O1	106.4(3)	C25	S2	O5	106.2(3)
C8	S1	O1	105.2(3)	C32	S2	O5	104.7(3)