Supporting Information

Easy Access to Drug Building-Blocks through Benzylic C-H Functionalization of Phenolic Ethers by Photoredox Catalysis

Content

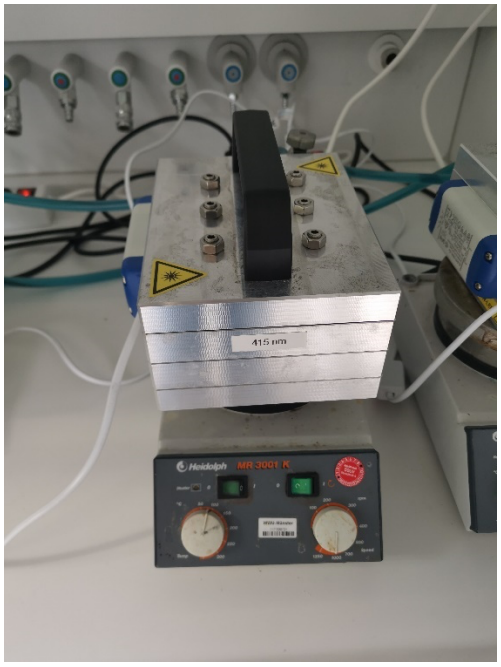
1. General Information and Materials

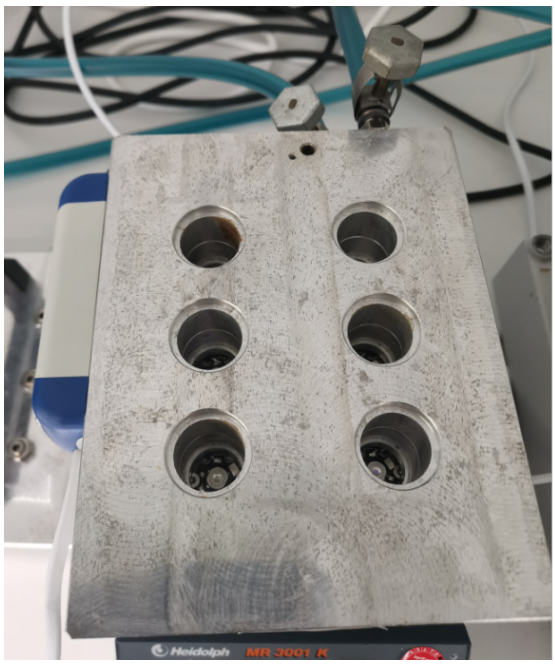
^{1}H and ^{13}C and spectra were recorded in $CDCl_3$ (reference signals: ^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm, $CDCl_3$) or in d^6-DMSO (reference signals: ^{1}H = 2.50 ppm, ^{13}C = 39.52 ppm, d^6-DMSO) on a Bruker Avance II 300, Bruker Avance II 400 or Agilent DD2 600. Chemical shifts (δ) are given in ppm and spin-spin coupling constants (*J*) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F254 and $KMnO_4$ served as staining agent. Column chromatography was performed on silica gel 60 (0.040-0.063 mm). Exact masses (HRMS) were recorded on a Bruker MicroTof ESI spectrometer or on Thermo Fisher Scientific Orbitrap LTQ XL spectrometer using electrospray ionization (ESI) techniques or on a Bruker Daltonic Autoflex Speed MALDI-TOF using matrix-assisted laser ionization (MALDI) technique with DHB as matrix. The LC-MS analysis for the optimization were performed on an Agilent 1260 Infinity II with a YMC J´sphere H80 (2.1x20 mm, 4µm) column using an acetonitrile/water (+0.05% TFA) mixture as eluent. Preparative RP-HPLC separations and RP-HPLC analysis were performed in a Waters HPLC with a SunFire™ Prep C18 OBD (50x100 mm, 5µm) column and in a HPLC-Agilent 1200 series with an Poroshell 120 EC C18 (5x50 mm, 2.7µm) column, respectively, using an acetonitrile/water (+0.1% TFA) mixture as eluent. Reaction monitoring was carried out using an SFC-MS Agilent 1260 Infinity II with a Chiralpak IG (4.6x250 mm, 5µm) column using a CO_2/MeOH mixture as eluent. Electrochemical measurements were performed on a Metrohm Autolab PGSTAT204 potentiostate. UV/VIS spectra were recorded on a Jasco 750 spectrometer. Fluorescence quenching experiments were performed on a Jasco FP-8500 spectrofluorometer. Dry solvents were purchased from Sigma Aldrich or dried over molecular sieves. Unless otherwise noted, other solvents and commercially available reagents were used without any further purification. ImideAcr-Ph^+ were prepared according to a literature procedure.[1] Unless otherwise noted, the peptides were provided by Sanofi Aventis Gmbh and used as received.

2. Photoreaction Set-up

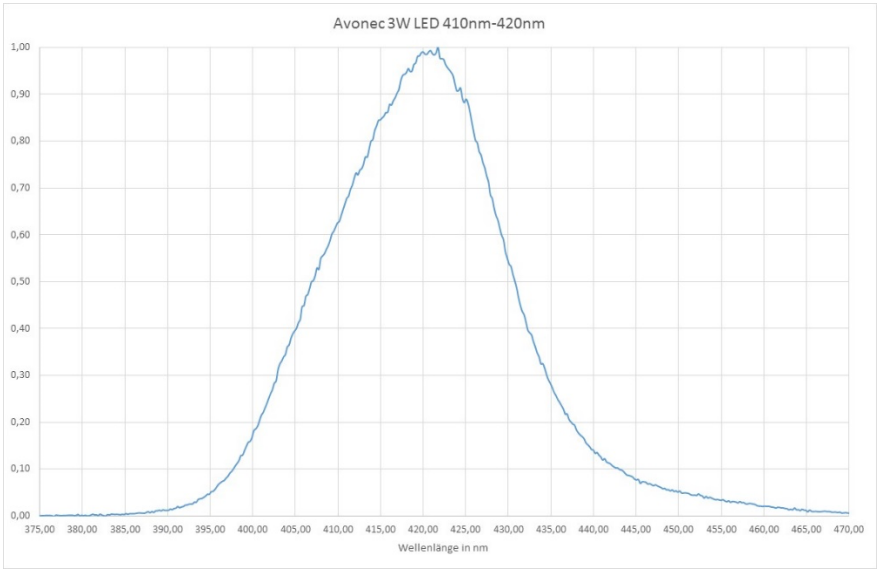
All reactions were degassed by bubbling argon for several minutes. The optimization reactions were performed in a Hepatochem PhotoRedOx Box with a blue light source (product number HCK1006-01-016) in screw-cap vials purchased from Chemglass (product nr. CG-4912-01). The reactions for the scope and the mechanistic studies were performed in a custom-build photoreactor, manufactured by the precision engineering workshop of the organic chemistry institute of the WWU Münster (see pictures below). The screw-cap vials (VWR headspace bottles product nr. 548-0133, screw-caps from VWR product nr. 548-0062) were irradiated from the bottom by a 3W LED 410-420 nm (purchased from Avonec; product nr. 3W410420s) under defined temperature (20 °C) adjusted by a Huber Minichiller 280. The results obtained from both photoreactors were comparable.

Photoreactor with six integrated 3W LED sources:



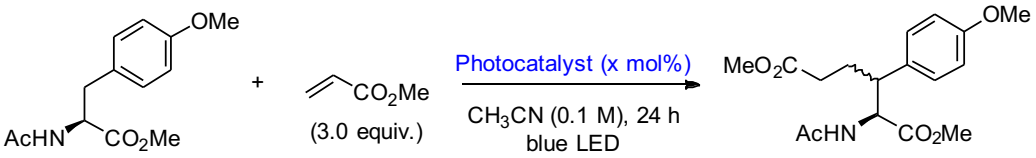


Emission spectra of the used 3W LED (Source: https://avonec.de/images/410nm-420nm_ohne_star.jpg ; opened 19.03.2020).

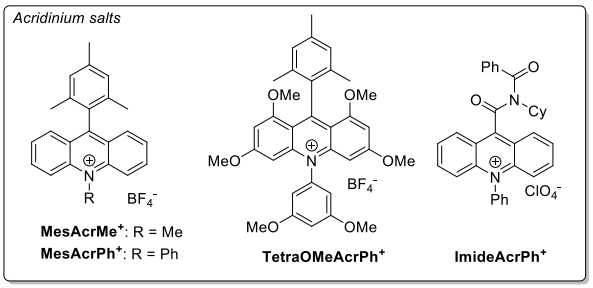


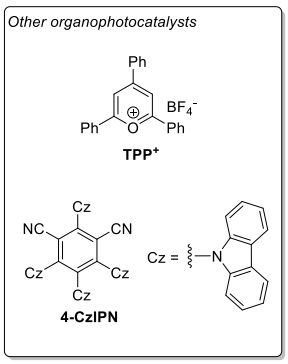
3. Optimization

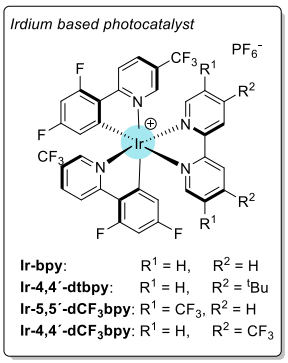
Screening of photocatalysts:



Entry	Photocatalyst (mol%)	Conversion [a] [%]
1	MesAcrMe$^+$ (5)	0
2	MesAcrPh$^+$ (5)	0
3	TetraOMeAcr$^+$ (5)	5
4	ImideAcrPh$^+$ (5)	0
5	TPP$^+$ (5)	0
6	4-CzIPN (5)	0
7	Ir-bpy (2)	0
8	Ir-4,4´-dtbpy (2)	0
9	Ir-4,4´-dCF$_3$bpy (2)	30
10	Ir-5,5´-dCF$_3$bpy (2)	19
11	Ir-4,4´-dCF$_3$bpy (1)	16
12[b]	Ir-4,4´-dCF$_3$bpy (2)	0
13	-	0

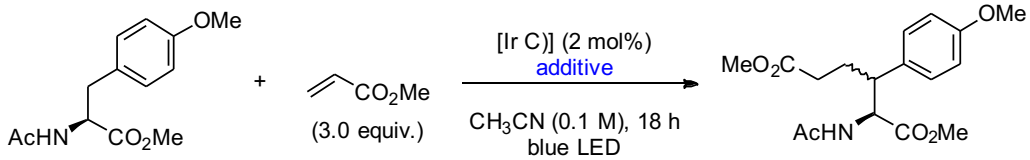






[a] The reactions were performed on a 0.05 mmol scale. Conversions were determined by using the peak AUC of the UV 220 nm in LC-MS spectra of the reaction mixture; [b] no light.

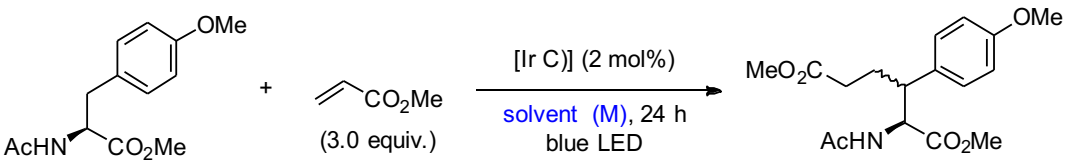
Screening of additives:



Entry	Additive (equiv.)	Conversion [%][a]
1	-	30
2	$(PhS)_2$ (0.2)	0
3	PhSH (0.4)	0
4	$(TripS)_2$ (0.2)	0
5	$(^iPr)_3SiSH$ (0.2)	15
6	K_2HPO_4 (3)	12
7	K_3PO_4 (3)	21
8	K_2CO_3 (3)	9
9	2 M aq. K_2HPO_4 (3)	8
10	2,6-Lutidine (1.2)	10
11	H_2O (25)	25
12	MeOH (25)	26
13	$Cu(OTf)_2$ (0.3)	20
14	$Cu(BF_4)_2$ (0.3)	15
15	$BF_3{*}Et_2O$ (0.3)	4

[a] The reactions were performed on a 0.05 mmol scale using Ir-4,4´-dCF$_3$bpy. Conversions and yields were determined by using the peak AUC of the UV 220 nm in LC-MS spectra of the reaction mixture.

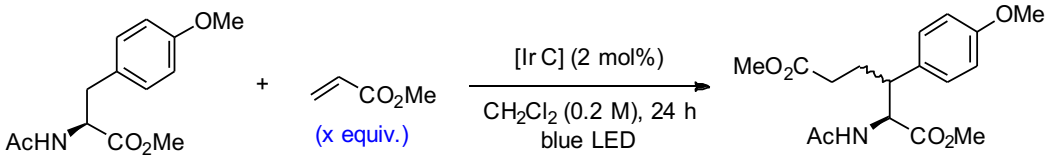
Screening of solvents and concentration



Entry	Solvent (M)	Conversion [%][a]
1	CH_3CN (0.1)	30
2	CH_2Cl_2 (0.1)	36
3	$CHCl_3$ (0.1)	28
4	DCE (0.1)	<5
5	DMF (0.1)	9
6	Dioxane (0.1)	28
7	HFIP (0.1)	22
8	CH_2Cl_2 (0.05)	16
9	CH_2Cl_2 (0.2)	41
10	CH_2Cl_2 (0.4)	52[b]

[a] The reactions were performed on a 0.05 mmol scale using Ir-4,4´-dCF$_3$bpy. Conversions were determined by using the peak AUC of the UV 220 nm in LC-MS spectra of the reaction mixture; [b] oligomerization as the major product.

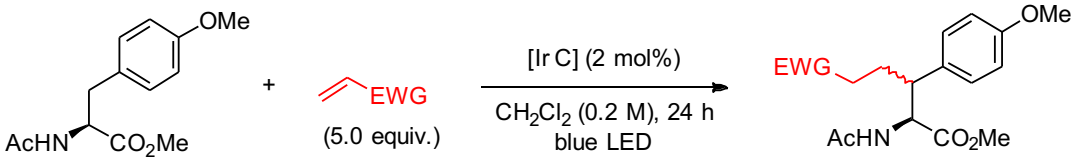
Screening of the methyl acrylate equivalents

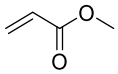
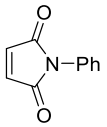
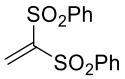
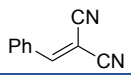


Entry	Methyl acrylate [equiv.]	Conversion [%][a]
1	1.5	24
2	3.0	41
3	5.0	48
4	10.0	52[b]

[a] The reactions were performed on a 0.05 mmol scale using Ir-4,4´-dCF$_3$bpy. Conversions were determined by using the peak AUC of the UV 220 nm in LC-MS spectra of the reaction mixture; [b] oligomerization as the major product.

Screening of alkenes

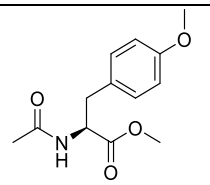
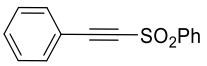
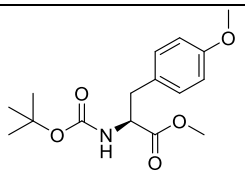
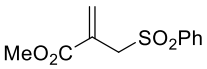
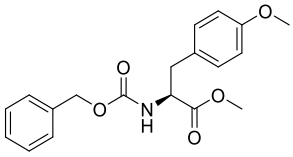
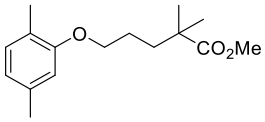
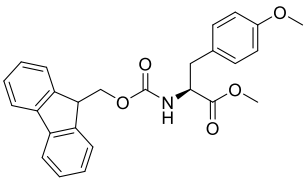
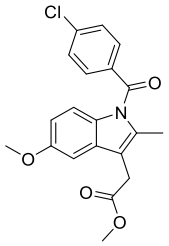
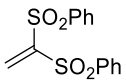
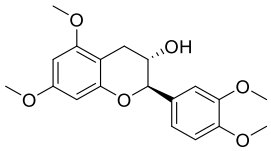


Entry	alkene	Conversion [%][a]	Side Products
1		48	Oligomerization
2		54	Oligomerization
3		100 (96[b])	No detected
4		100 (81[b])	No detected

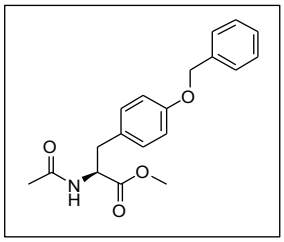
[a] The reactions were performed on a 0.1 mmol scale using Ir-4,4´-dCF$_3$bpy. Conversions were determined by using the peak AUC of the UV 220 nm in LC-MS spectra of the reaction mixture; [b] isolated yield.

4. Synthesis of the Starting Material

Literature known synthesis with references:

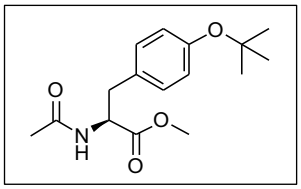
Compound	Reference	Compound	Reference
	Commercially available (CAS 17355-24-7) Synthesis: See also below		Ref. 6: D. Qi, W. Dong, Z. Peng, Y. Zhang, D. An, *Tetrahedron* **2019**, *75*, 130427-130435.
	Ref. 2: D. Reich, A. Trowbridge, M. Gaunt, J. *Angew. Chem. Int. Ed. 2020*, *59*,2256–2261.		Ref. 7: H. Liu, L. Ge, D.-X. Wang, N. Chen, C. Feng, *Angew. Chem. Int. Ed.* **2019**, *58*, 3918-3922.
	Ref. 3: T. C. Roberts, P. A. Smith, R. T. Cirz, F. E. Romesberg, *J. Am. Chem. Soc.* **2007**, *129*, 15830-15838.		Ref. 8: L.-Y. Liu, K.-S. Yeung, J.-Q. Yu, *Chem. Eur. J.* **2019**, *25*, 2199–2202.
	Ref. 4: M. Berthet, F. Davanier, G. Dujardin, J. Martinez, I. Parrot, *Chem. Eur. J.* **2015**, *21*, 11014–11016.		Ref. 9: D. Zhao, P. Xu, T. Ritter, *Chem.* **2019**, *5*, *97*-107.
	Commercially available (CAS 39082-53-6) Synthesis: Ref. 5: S. Sulzer-Mossé, A. Alexakis, J. Mareda, G. Bollot, G. Bernardinelli, Y. Filinchuk, *Chem. Eur. J.* **2009**, *15*, 3204-3220.		Ref. 10: R. Bernini, F. Crisante, P. Gentili, F. Morana, M. Pierini, M. Piras, *J. Org. Chem.* **2011**, *76*, 820–832.

Methyl (S)-2-acetamido-3-(4-methoxyphenyl)propanoate



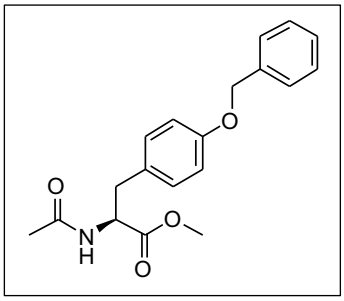
Ac-*L*-Tyr(OH)-OMe hydrate (1.19 g, 5 mmol, 1.0 equiv.) and potassium carbonate (2.07 g, 15 mmol, 3 equiv.) was suspended in 30 mL DMF. Then, iodomethane (1.24 mL, 20 mmol, 4.0 equiv.) was added and the mixture was stirred at room temperature for 16 h. The solvent was removed under vacuum and 30 mL CH_2Cl_2 and 30 mL water was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. After drying under vacuum, the product (1.24 g, 4.99 mmol, 99 %) was obtained as a white solid. Spectroscopic data are in accordance with the commercially available compound. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.99 (d, *J* = 7.9 Hz, 1H), 4.83 (dt, *J* = 7.7, 5.8 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.08 (dd, *J* = 14.0, 5.9 Hz, 1H), 3.03 (dd, *J* = 14.0, 5.6 Hz, 1H), 1.98 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 172.3, 169.8, 158.8, 130.3, 127.8, 114.1, 55.3, 53.4, 52.4, 37.1, 23.2. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{13}H_{17}NO_4$ + Na: 274.1055; found 274.1051.

Methyl (S)-2-acetamido-3-(4-(tert-butoxy)phenyl)propanoate



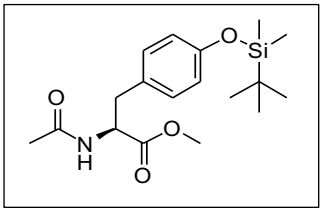
To a mixture of Ac-*L*-Tyr(^{t}Bu)-OH (309 mg, 1.5 mmol, 1.0 equiv.) and potassium carbonate (311 mg, 2.25 mmol, 1.5 equiv.) in 10 mL DMF was added iodomethane (280 µL, 4.5 mmol, 3 equiv.) and the mixture was stirred at room temperature for 18 h. The solvent was removed under vacuum and 30 mL EtOAc and 30 mL water was added. The phases were separated and the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic phases were washed with aq. $NaHCO_3$ (sat.), brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. After drying under vacuum, the product (434 mg, 1.49 mmol, 99%) was obtained as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.89 (d, *J* = 7.9 Hz, 1H), 4.85 (dt, *J* = 7.8, 5.8 Hz, 1H), 3.70 (s, 3H), 3.14 – 2.99 (m, 2H), 1.98 (s, 3H), 1.33 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.29, 169.67, 154.63, 130.69, 129.80, 124.35, 78.60, 53.30, 52.41, 37.41, 28.97, 23.31. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{23}NO_4$ + Na: 316.1519; found 316.1512.

Methyl (S)-2-acetamido-3-(4-(benzyloxy)phenyl)propanoate



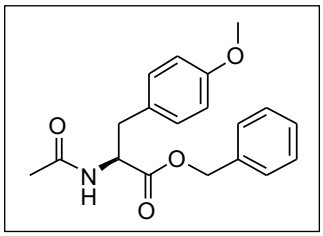
Ac-*L*-Tyr(OH)-OMe (712 mg, 3.0 mmol, 1.0 equiv.) and potassium carbonate (1.24 g, 9.0 mmol, 3.0 equiv.) was dissolved in 10 mL DMF and benzyl bromide (535µL, 4.5 mmol, 1.5 equiv.) was added and the mixture was stirred at room temperature for 18 h. The 10 mL water was added to induce precipitation. The white solid was filtered off and washed with water (2x10 mL). The remaining water was removed by azeotropic distillation with toluene (5x10 mL) and dried under vacuum. The product (980 mg, 2.99 mmol, 98%) was obtained as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 5H), 7.04 – 6.98 (m, 2H), 6.92 – 6.89 (m, 2H), 5.94 (d, *J* = 7.9 Hz, 1H), 5.03 (s, 2H), 4.85 (dt, *J* = 7.8, 5.7 Hz, 1H), 3.72 (s, 3H), 3.12 – 3.01 (m, 2H), 1.99 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3, 169.7, 158.1, 137.0, 130.4, 128.7, 128.2, 128.1, 127.6, 115.1, 70.1, 53.3, 52.4, 37.1, 23.3. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{19}H_{21}NO_4$ + Na: 350.1368; found 350.1363.

Methyl (S)-2-acetamido-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate



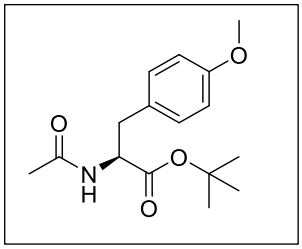
Under argon, to a mixture of Ac-*L*-Tyr(OH)-OMe (0.5 g, 1.83 mmol, 1.0 equiv.) and 4-(dimethylamino)-pyridine (44.7 mg, 0.37 mmol, 0.2 equiv.) in 15 mL CH_2Cl_2 was added triethylamine (0.77 mL, 5.49 mmol, 3.0 equiv.) and was stirred for 10 min. Then, *tert*-butyldimethylsilyl chloride (552 mg, 3.7 mmol, 2.0 equiv.) was added and the solution was stirred at room temperature for 72 h. Then, 15 mL aq. NH_4Cl (sat.) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were washed with $NaHCO_3$ (sat.) and brine, dried over $MgSO_4$ and the solvent was removed under vacuum. The crude was purified by flash column chromatography (70% EtOAc/pentane), obtaining the product (561 mg, 1.61 mmol, 88%) as a colorless oil, which solidified after several days. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 – 6.92 (m, 2H), 6.78 – 6.74 (m, 2H), 5.86 (d, *J* = 7.9 Hz, 1H), 4.83 (dt, *J* = 7.9, 5.7 Hz, 1H), 3.71 (s, 3H), 3.10 – 3.00 (m, 2H), 1.98 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3, 169.7, 154.9, 130.4, 128.5, 120.3, 77.4, 53.4, 52.4, 37.3, 25.8, 23.31, 18.3. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{18}H_{29}NO_4Si$ + Na: 374.1764; found 374.1762.

Benzyl (S)-2-acetamido-3-(4-methoxyphenyl) propanoate



L-Tyrosine benzyl ester *p*-toluenesulfonate (2.22 g, 5 mmol, 1.0 equiv.) was suspended in 15 mL CH_2Cl_2, triethylamine (1.39 mL, 10 mmol, 2.0 equiv.) was added and the mixture was stirred at room temperature for 20 min. Acetyl chloride (714 µL, 10 mmol, 2.0 equiv.) was slowly added at 0°C and the reaction mixture was stirred at room temperature for 18 h. Then, 10 mL water was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were washed with 1M HCl, brine and the solvent was removed under reduced pressure. The residue was dissolved in 15 mL DMF. K_2CO_3 (1.04 g, 7.5 mmol, 1.5 equiv.) and iodomethane (1.56 mL, 25 mmol, 5 equiv.) was added and the mixture was stirred at room temperature for 18 h. The solvent was removed under vacuum and 30 mL CH_2Cl_2 and 30 mL water was added. The phases were separated and the aqueous phases was extracted with CH_2Cl_2 (3x15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (70% EtOAc/pentane), obtaining the product (1.11 g, 3.40 mmol, 68%) as a colorless oil, which solidified over several days. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (qd, *J* = 2.8, 2.0 Hz, 3H), 7.31 (dd, *J* = 7.2, 2.5 Hz, 2H), 6.91 – 6.88 (m, 2H), 6.77 – 6.72 (m, 2H), 5.92 (d, *J* = 7.9 Hz, 1H), 5.18 (d, *J* = 12.1 Hz, 1H), 5.12 (d, *J* = 12.1 Hz, 1H), 4.89 (dt, *J* = 7.9, 5.7 Hz, 1H), 3.77 (s, 3H), 3.06 (d, *J* = 1.9 Hz, 1H), 3.05 (d, *J* = 1.6 Hz, 1H), 1.98 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.7, 169.7, 158.8, 135.2, 130.4, 128.8, 128.7, 127.7, 121.7, 114.1, 67.4, 55.3, 53.4, 37.1, 23.3. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{19}H_{21}NO_4$ + Na: 350.1359; found 350.3363.

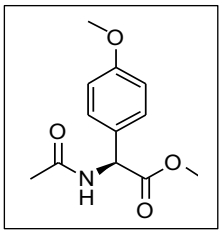
tert-Butyl (S)-2-acetamido-3-(4-methoxyphenyl) propanoate



L-Tyrosine *tert*butyl ester hydrochloride (0.5 g, 2.1 mmol, 1.0 equiv.) was suspended in 10 mL CH_2Cl_2, triethylamine (438 µL, 3.15 mmol, 1.5 equiv.) was added and the mixture was stirred at room temperature for 20 min. Acetyl chloride (165 µL, 2.31 mmol, 1.1 equiv.) was slowly added at 0°C and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure. 10 mL water and 10 mL EtOAc was added, the phases were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine and the solvent was removed under reduced pressure. The residue was dissolved in 10 mL DMF. K_2CO_3 (435 mg, 3.15 mmol, 1.5 equiv.) and iodomethane (654 µL, 10.5 mmol, 5 equiv.) was added and the mixture was stirred at room temperature for 18 h. The solvent was removed under vacuum and 30 mL CH_2Cl_2 and 30 mL water was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (70% EtOAc/pentane), obtaining the product (456 mg, 1.55 mmol, 74%) as a colorless oil, which solidified over several days. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.08 – 7.03 (m, 2H), 6.84 – 6.79 (m, 2H), 5.90 (d, *J* = 7.8 Hz, 1H), 4.72 (dt, *J* = 7.8, 5.7 Hz, 1H), 3.78 (s, 3H), 3.05 – 3.01 (m, 2H), 1.98 (s, 3H), 1.42 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.9, 169.4, 158.6, 130.5, 128.1, 121.5, 113.8, 82.3, 55.2, 53.6, 37.1, 28.0, 23.3. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{23}NO_4$ + Na: 316.1519; found 316.1517.

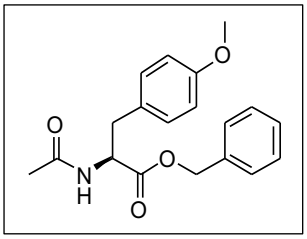
Methyl (S)-2-acetamido-2-(4-methoxyphenyl)acetate

(S)-2-Amino-2-(4-hydroxyphenyl) acetic acid (3.34 g, 20 mmol, 1.0 equiv.) was dissolved in 100 mL methanol and thionylchloride (2.18 ml, 30 mmol, 1.5 equiv.) was added and the mixture was stirred for 18 h. The solvent was removed under reduced pressure and washed with methanol and diethyl ether. After drying under vacuum, the methyl ester hydrochloride salt was obtained as a white solid. The solid was suspended



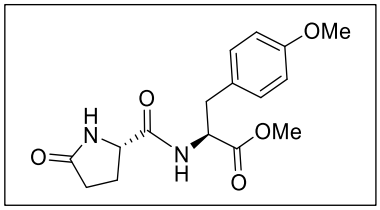
in 30 mL CH_2Cl_2, triethylamine (8.36 mL, 60 mmol, 3 equiv.) was added and the mixture was stirred for 20 min. Then, acetic anhydride (5.67 mL, 60 mmol, 3.0 equiv.) was slowly added and the mixture was stirred at ambient temperature for 4 h. The solution was diluted with 30 mL CH_2Cl_2 and washed with water (3x50 mL), 1M HCl (1x50 mL), $NaHCO_3$ (sat.) (1x50 mL) and brine (1x50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. 50 mL methanol and 50 mL $NaHCO_3$ (sat.) was added to the crude and stirred for 12 h. The mixture was acidified to pH 3 with 4 M HCl, diluted with 100 mL CH_2Cl_2 and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2x 30 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. After drying under vacuum, methyl (S)-2-acetamido-2-(4-hydroxyphenyl) acetate was obtained as a white solid. The solid was dissolved in 40 mL DMF and K_2CO_3 (4.15 mmol, 30 mmol, 1.5 equiv.) and iodomethane (3.74 mL, 60 mmol, 3.0 equiv.) was added and the mixture was stirred for 18 h. The solvent was removed under reduced pressure and 60 mL CH_2Cl_2 and 50 mL water was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x30 mL). The combined organic phases were washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. After drying under vacuum, the product (3.37 g, 14.2 mmol, 71%) was obtained as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.43 (d, *J* = 7.1 Hz, 1H), 5.45 (d, *J* = 7.1 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 1.95 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.9, 169.5, 159.8, 128.7, 128.6, 114.5, 55.9, 55.4, 52.9, 23.2. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{12}H_{15}NO_4$ + Na: 260.0893; found 260.0888.

Methyl (S)-2-acetamido-3-(3,4-dimethoxyphenyl)propanoate



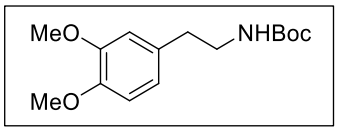
3-Hydroxy-L-tyrosine (0.99g, 5 mmol, 1.0 equiv.) was dissolved in 30 mL methanol and thionyl chloride (0.55 ml, 7.5 mmol, 1.5 equiv.) was added and the mixture was stirred for 18 h. The solvent was removed under reduced pressure and washed with methanol and diethyl ether. After drying under vacuum, the methyl ester hydrochloride salt was obtained as a white solid. The solid was suspended in 10 mL CH_2Cl_2, triethylamine (2.8 mL, 20 mmol, 4 equiv.) was added and the mixture was stirred for 20 min. Then, acetic anhydride (1.89 mL, 20 mmol, 4.0 equiv.) was slowly added and the mixture was stirred at ambient temperature for 4 h. The solution was diluted with 10 mL CH_2Cl_2 and washed with water (3x20 mL), 1M HCl (1x20 mL), $NaHCO_3$ (sat.) (1x20 mL) and brine (1x20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. 20 mL methanol and 20 mL $NaHCO_3$ (sat.) was added to the crude and stirred for 12 h. The mixture was acidified to pH 3 with 4 M HCl, diluted with 100 mL CH_2Cl_2 and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2x30 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained solid was dissolved in 15 mL DMF and K_2CO_3 (2.08 g, 15 mmol, 3 equiv.) and iodomethane (1.56 mL, 25 mmol, 5.0 equiv.) was added and the mixture was stirred for 18 h. The solvent was removed under reduced pressure and 10 mL CH_2Cl_2 and 10 mL water was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (60→70% EtOAc/pentane), obtaining the product (758 mg, 2.70, 54%) as a yellow solid. Spectroscopic data are in accordance with the literature.[11] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.75 (d, *J* = 7.9 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 2H), 6.06 (d, *J* = 7.8 Hz, 1H), 4.81 (dt, *J* = 7.8, 5.8 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.69 (s, 3H), 3.05 (dd, *J* = 14.0, 5.9 Hz, 1H), 2.99 (dd, *J* = 13.9, 5.8 Hz, 1H), 1.95 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3, 169.7, 148.9, 148.2, 128.3, 121.3, 112.4, 111.2, 55.9, 55.8, 53.3, 52.3, 37.5, 23.1. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{14}H_{19}NO_5$ + Na: 304.1161; found 304.1158.

Methyl (S)-3-(4-methoxyphenyl)-2-((S)-5-oxopyrrolidine-2-carboxamido)propanoate



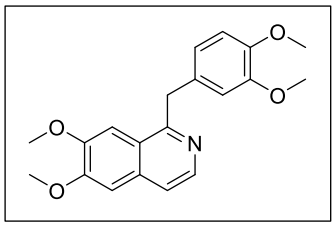
Under argon, L-pyroglutamic acid (129 mg, 1.0 mmol, 1.0 equiv.) and H-*L*-Tyr(Me)-OMe•HCl (240 mg, 1.0 mmol, 1.0 equiv.) were dissolved in 10 mL dry DMF and N-methyl morpholine (0.69 mL, 5.0 mmol, 5.0 equiv.) and EDC•HCl (232 mg, 1.0 mmol, 1.0 equiv.) and HOBt hydrate (164 mg, 1.0 mmol, 1.0 equiv.) was added. The mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure. The residue was re-dissolved in 30 mL EtOAc and 30 mL water was added. The phases were separated and the aqueous phase was extracted three times with 20 mL EtOAc. The combined organic phases were washed with 2x 1 M HCl (aq.), 2x aq. $NaHCO_3$ (sat.) and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. After drying under vacuum, the product (145 mg, 0.45 mmol, 45%) was obtained as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.6 Hz, 1H), 7.10 – 7.05 (m, 3H), 6.81 – 6.77 (m, 2H), 4.86 (td, *J* = 8.5, 5.3 Hz, 1H), 4.08 (dd, *J* = 8.8, 4.3 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.13 (dd, *J* = 13.9, 5.3 Hz, 1H), 2.40 – 2.30 (m, 1H), 2.29 – 2.19 (m, 2H), 1.92 – 1.82 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.6, 172.7, 172.4, 158.7, 130.3, 128.1, 113.9, 57.2, 55.3, 53.2, 52.6, 36.9, 29.2, 25.7. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{20}N_2O_5$+ Na: 343.1270; found 343.1268.

tert-Butyl (3,4-dimethoxyphenethyl) carbamate



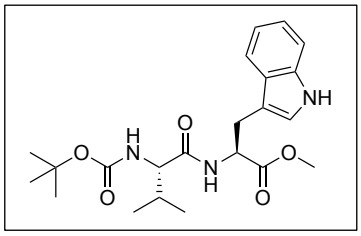
Dopamine hydrochloride (306.4 mg, 2 mmol, 1.0 equiv.) was suspended in 10 mL CH_2Cl_2. Triethylamine (555 µL, 4 mmol, 2.0 equiv.) and di-*tert*-butyldicarbonate (458.3 mg, 2.1 mmol, 1.05 equiv.) was added and the mixture was stirred at room temperature for 18 h. Then, 10 mL water was added, the phases were separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were washed with 1M HCl and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained white solid was dissolved in 10 mL DMF. Potassium carbonate (1.11 g, 8 mmol, 4 equiv.) and iodomethane (1.25 mL, 20 mmol, 10 equiv.) was added and the mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and 10 mL CH_2Cl_2 and 10 mL water was added, the phases were separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were washed with $NaHCO_3$ (sat.) and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (25% EtOAc/pentane), obtaining the product (495.0 mg, 1.76 mmol, 88%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.81 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 2.0 Hz, 1H), 6.71 (s, 1H), 4.54 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.35 (q, *J* = 6.8 Hz, 2H), 2.74 (t, *J* = 7.0 Hz, 2H), 1.44 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.0, 149.1, 147.8, 131.7, 120.8, 112.1, 111.5, 79.4, 56.1, 56.0, 42.0, 35.9, 28.6. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{15}H_{23}NO_4$ + Na: 304.1515; found 304.1519.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline (Papaverine)



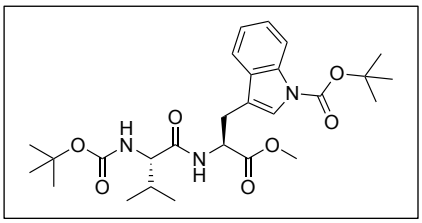
Papaverine hydrochloride (752 mg, 2.0 mmol, 1.0 equiv.) was suspended in 10 mL CH_2Cl_2. Triethylamine (282 µL, 2.0 mmol, 1.0 equiv.) was added and stirred at room temperature for 30 min. The solution was washed with water and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. After drying under vacuum, the product (665 mg, 1.96 mmol, 98%) was obtained as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 5.7 Hz, 1H), 7.41 (dd, *J* = 5.7, 0.8 Hz, 1H), 7.33 (s, 1H), 7.03 (s, 1H), 6.82 – 6.79 (m, 2H), 6.77 – 6.73 (m, 1H), 4.52 (s, 2H), 3.98 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.9, 152.5, 149.9, 149.1, 147.6, 141.1, 133.5, 132.3, 123.0, 120.6, 118.8, 111.9, 111.3, 105.4, 104.3, 56.1, 56.0, 55.9, 55.8, 42.3. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{20}H_{21}NO_4$ + Na: 362.1363; found 362.1360.

Methyl (tert-butoxycarbonyl)-L-valyl-L-tryptophanate



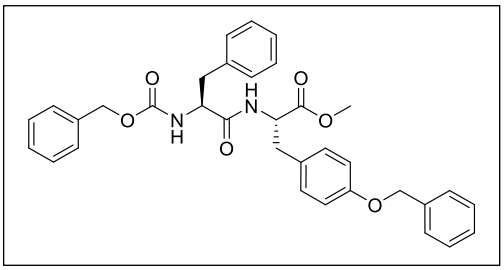
Under argon, *N*-(*tert*-butoxycarbonyl)-*L*-valin (434.5 mg, 2.0 mmol, 1.0 equiv.) and H-*L*-Trp(H)-OMe•HCl (509.4 mg, 2.0 mmol, 1.0 equiv.) were dissolved in 20 mL dry DMF and *N*-methyl morpholine (606.9 mg mL, 6.0 mmol, 3.0 equiv.) and EDC•HCl (460.1 mg, 2.4 mmol, 1.2 equiv.) and HOBt hydrate (324.3 mg, 2.4 mmol, 1.2 equiv.) was added. The mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure. The residue was re-dissolved in 40 mL EtOAc and 40 mL water was added. The phases were separated and the aqueous phase was extracted three times with 30 mL EtOAc. The combined organic phases were washed with 2x 1 M HCl (aq.), 2x aq. $NaHCO_3$ (sat.) and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (50% EtOAc/pentane), obtaining the product (631.1 mg, 1.5 mmol, 75%) as a pale-yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.53 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.35 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.19 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.35 (d, *J* = 7.8 Hz, 1H), 5.04 (d, *J* = 9.0 Hz, 1H), 4.92 (dt, *J* = 7.9, 5.5 Hz, 1H), 3.94 – 3.88 (m, 1H), 3.66 (s, 3H), 3.40 – 3.23 (m, 2H), 2.06 (dq, *J* = 13.1, 6.4 Hz, 2H), 1.43 (s, 9H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H). The analytic data is in accordance with the literature.[12]

tert-Butyl 3-((S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate



A round bottom flask was charged with *N*-Boc-Val-Trp(H)-OMe (200.0 mg, 0.48 mmol, 1.0 equiv.) dissolved in DCM (2 mL). Triehtylamine (109.7 mg, 0.96 mmol, 2.0 equiv.) was added and the mixture was stirred for 30 min. Boc_2O (135.9 mg, 0.62 mmol, 1.3 equiv.) was added and the mixture was stirred at room temperature for 18 h. Water was added, the phases were separated and the aqueous phase was extracted three times with 10 mL DCM. The combined organic phases were washed with 1 M HCl (aq.) and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (20% EtOAc/pentane), obtaining the product (108.5 mg, 0.21 mmol, 44%) as a pale-yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.49 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.41 (s, 1H), 7.31 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.27 – 7.22 (m, 2H), 6.42 (d, *J* = 7.7 Hz, 1H), 4.97 (d, *J* = 7.8 Hz, 0H), 4.93 (dt, *J* = 7.5, 5.8 Hz, 1H), 3.96 – 3.89 (m, 1H), 3.68 (s, 3H), 3.24 (d, *J* = 5.8 Hz, 2H), 2.18 – 2.07 (m, 1H), 1.67 (s, 9H), 1.42 (s, 9H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.9, 171.4, 155.8, 149.7, 135.5, 130.5, 124.8, 124.2, 122.8, 118.9, 115.5, 114.9, 83.9, 80.1, 60.0, 52.6, 52.5, 31.0, 28.4, 28.3, 27.8, 19.3, 17.7. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{27}H_{39}N_3O_7$ + Na: 540.2685; found 540.2680.

Methyl (S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-3-(4-(benzyloxy) phenyl) propanoate



Under argon, Z-*L*-Ph-OH (987 mg, 3.30 mmol, 1.0 equiv.) and H-*L*-Tyr(Bn)-OMe•HCl (1.06 g, 3.30 mmol, 1.0 equiv.) was dissolved in 25 mL dry DMF and N-methyl morpholine (1.09 mL, 9.90 mmol, 3.0 equiv.) and EDC•HCl (759 mg, 3.96 mmol, 1.2 equiv.) and HOBt hydrate (535 mg, 3.96 mmol, 1.2 equiv.) was added. The mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure. The residue was re-dissolved in 60 mL EtOAc and 60 mL water. The phases were separated and the aqueous phase was extracted three times with 40 mL EtOAc. The combined organic phases were washed with 2x 1 M HCl (aq.),

2x aq. $NaHCO_3$ (sat.) and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. After drying under vacuum, the product (1.77 g, 3.14 mmol, 95%) was obtained as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 5H), 7.27 – 7.23 (m, 5H), 7.18 (q, *J* = 3.1 Hz, 3H), 7.09 (d, *J* = 7.2 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.09 (d, *J* = 7.6 Hz, 1H), 5.15 (d, *J* = 7.7 Hz, 1H), 5.01 (s, 2H), 4.92 (s, 2H), 4.66 (dt, *J* = 7.7, 5.8 Hz, 1H), 4.33 (d, *J* = 7.7 Hz, 1H), 3.60 (s, 3H), 2.97 (q, *J* = 6.2 Hz, 2H), 2.93 – 2.84 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5, 170.4, 158.1, 156.0, 137.1, 136.4, 136.3, 130.4, 129.5, 128.9, 128.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.6, 127.2, 115.1, 70.1, 67.3, 56.2, 53.6, 52.5, 38.4, 37.2. **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{34}H_{34}N_2O_6$+ Na: 589.2309; found 589.2311.

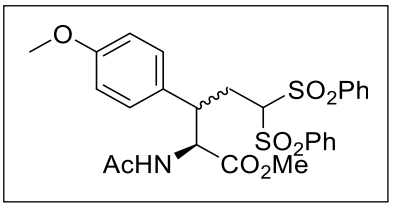
5. General Procedure

In an oven-dried screw-cap vial, $[Ir(dF(CF_3)ppy)(4,4´\text{-}dCF_3bpy)]PF_6$ (2.3 mg, 0.002 mmol, 2 mol%), the substrate (0.1 mmol, 1.0 equiv.) and the radical acceptor (1.1 - 5.0 equiv.) were dissolved in 0.5 mL dry CH_2Cl_2 (0.2 M). The mixture was degassed by bubbling argon for several minutes and the vial was sealed. The reaction mixture was irradiated by blue LEDs for 18-72 h (The reaction progress was monitored by LC-MS or TLC). The crude was purified by flash column chromatography.

Note: If the substrate was not completely dissolved in 0.2 M CH_2Cl_2, a lower solvent concentration was used as noted for the indicated reactions.

6. Characterization of Products

*Methyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (**3b**)*



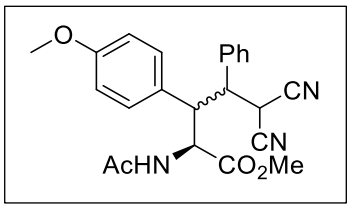
Following the general procedure, Ac-*L*-Tyr(Me)-OMe (**1**) (25.1 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (**2b**) (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (50→60 % EtOAc/pentane), obtaining the product (53.7 mg, 0.096 mmol, 96%, 3:1 d.r.) as a colorless solid. *Note*: The product could be further purified by recrystallization in CH_2Cl_2 (minimum amount)/heptane, if there was still unreacted tyrosine starting material. *Major isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (dt, *J* = 7.2, 1.3 Hz, 2H), 7.72 (dd, *J* = 7.2, 1.6 Hz, 2H), 7.58 (tt, *J* = 8.0, 2.3 Hz, 3H), 7.54 – 7.46 (m, 3H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.14 (d, *J* = 8.5 Hz, 1H), 4.67 (dd, *J* = 8.7, 7.1 Hz, 1H), 4.33 – 4.28 (dd, *J* = 8.5, 3.1, 1H), 3.79 (s, 3H), 3.48 – 3.42 (m, 4H), 2.68 – 2.61 (m, 2H), 2.03 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.1, 169.9, 159.4, 138.0, 137.5, 134.8, 134.6, 129.9, 129.7, 129.6, 129.3, 129.2, 128.0, 114.4, 80.6, 56.9, 55.4, 52.3, 46.3, 28.3, 23.3. *Minor isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.90 (m, 2H), 7.80 – 7.78 (m, 2H), 7.68 – 7.64 (m, 6H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 2H), 5.79 (d, *J* = 9.0 Hz, 1H), 4.92 (dd, *J* = 9.0, 4.8 Hz, 1H), 4.52 – 4.49 (m, 1H), 4.22 (t, *J* = 6.2 Hz, 1H), 3.87 – 3.84 (m, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 2.57 (dd, *J* = 8.9, 6.0 Hz, 2H), 2.01 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.3, 170.4, 159.5, 138.1, 137.5, 134.7, 134.6, 129.8, 129.7, 129.6, 129.2, 129.1, 128.0, 114.6, 80.7, 55.3, 53.6, 52.6, 44.4, 27.8, 23.3. **HRMS** (ESI): *m/z* $[M+Na^+]$ cacld. for $C_{27}H_{29}N_2O_8S_2$ + Na: 582.1227; found 582.1225.

➔ 1 mmol Upscaling Reaction:

In an oven-dried screw-cap vial, $[Ir(dF(CF_3)ppy)(4,4´\text{-}dCF_3bpy)]PF_6$ (23.4 mg, 0.02 mmol, 2 mol%), Ac-*L*-Tyr(Me)-OMe (**1**) (251 mg, 1.0 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (**2b**) (463 mg, 1.5 mmol, 1.5 equiv.) were dissolved in 5 mL dry CH_2Cl_2 (0.2 M). The mixture was degassed by bubbling argon for several minutes and the vial was sealed. The reaction mixture was irradiated by three 3W blue LEDs (max 415 nm) for 48 h (the reaction progress was monitored by TLC), The crude was purified by flash column chromatography (50→70% EtOAc/pentane). It was further purified by recrystallization in CH_2Cl_2 (minimum

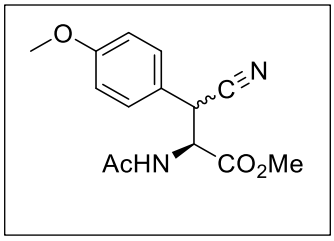
amount)/heptane, obtaining the product (431 mg, 0.74 mmol, 74%, d.r. 3:1) as a colorless solid. The spectroscopic data were in accordance with above. *Note:* 1,1-Bis(phenylsulfonyl)ethylene (138 mg, 0.45 mmol) could be recovered by further recrystallization in CH_2Cl_2 (minimum amount)/heptane.

*Methyl (2S)-2-acetamido-5,5-dicyano-3-(4-methoxyphenyl)-4-phenylpentanoate (**3c**)*



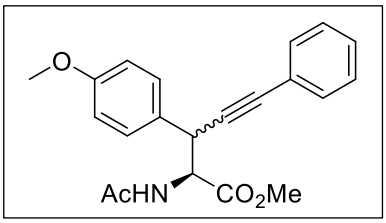
Following the general procedure, Ac-*L*-Tyr(Me)-OMe (**1**) (25.1 mg, 0.1 mmol, 1.0 equiv.) and benzylidenemalononitrile (**2c**) (77.1 mg, 0.5 mmol, 5.0 equiv.) were reacted in 0.5 mL CH_2Cl_2 for 32 h. The crude was purified by flash column chromatography (60% EtOAc/pentane), obtaining the product as a colorless oil (32.9 mg, 0.08 mmol, 81%, d.r. 6:2:1:0.5). *Major Isomer* (20.7 mg, 0.051 mmol, 51%, colorless oil): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 5H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 6.05 (d, *J* = 8.5 Hz, 1H), 5.85 (d, *J* = 4.6 Hz, 1H), 4.99 (dd, *J* = 8.4, 2.9 Hz, 1H), 4.05 (dd, *J* = 12.2, 2.9 Hz, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 3.48 (dd, *J* = 12.1, 4.6 Hz, 1H), 2.19 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.9, 170.4, 159.1, 135.3, 129.7, 128.9, 128.7, 126.9, 114.2, 112.2, 112.0, 55.2, 53.8, 53.2, 48.9, 46.2, 28.4, 23.5. Representative signals of the other isomers: *2nd isomer:* **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.74 (d, *J* = 7.7 Hz, 1H), 4.72 (dd, *J* = 7.7, 4.1 Hz, 1H), 3.06 (t, *J* = 5.1 Hz, 1H), 1.90 (s, 3H). 3rd isomer: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.90 (d, *J* = 7.8 Hz, 1H), 4.85 (dt, *J* = 7.7, 5.6 Hz, 1H), 1.99 (s, 3H). 4th isomer: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.86 (d, *J* = 4.6 Hz, 1H), 4.77 (dd, *J* = 7.9, 2.8 Hz, 1H), 2.19 (s, 3H). **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{23}H_{23}N_3O_4$ + Na: 428.1581; found 428.1578.

*Methyl (2S)-2-acetamido-3-cyano-3-(4-methoxyphenyl) propanoate (**3d**)*



Following the general procedure, Ac-*L*-Tyr(Me)-OMe (**1**) (25.1 mg, 0.1 mmol, 1.0 equiv.) and *p*-toluenesulfonyl cyanide (**2d**) (90.6 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (60% EtOAc/pentane), obtaining the product mixture (24.7 mg, 0.09 mmol, 90%, d.r. 3:1) as a yellow oil. *Major isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.17 (m, 2H), 6.90 – 6.87 (m, 2H), 6.11 (d, *J* = 8.3 Hz, 1H), 5.10 (dd, *J* = 8.3, 4.5 Hz, 1H), 4.47 (d, *J* = 4.5 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 2.01 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.8, 169.1, 160.2, 129.3, 122.6, 118.0, 114.6, 55.5, 55.2, 53.4, 39.1, 23.1. *Minor isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 2H), 6.93 – 6.90 (m, 2H), 6.23 (d, *J* = 8.1 Hz, 1H), 5.04 (dd, *J* = 8.2, 4.5 Hz, 1H), 4.53 (d, *J* = 4.4 Hz, 1H), 3.82 (s, 3H), 3.69 (s, 3H), 2.09 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.1, 168.9, 158.5, 129.2, 121.6, 117.9, 114.7, 55.7, 55.5, 53.0, 40.1, 23.3. **HRMS** (ESI): *m/z* $[M+Na^+]$ cacld. for $C_{14}H_{16}N_2O_4$ + Na: 299.1008; found 299.1007.

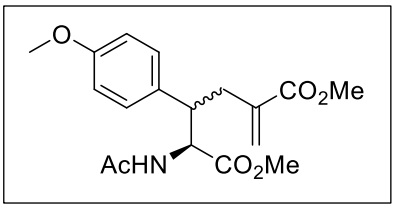
*Methyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5-phenylpent-4-ynoate (**3e**)*



Following the general procedure, Ac-*L*-Tyr(Me)-OMe (**1**) (25.1 mg, 0.1 mmol, 1.0 equiv.) and ((phenylethynyl)sulfonyl)benzene (**2e**) (121.1 mg, 0.5 mmol, 5.0 equiv.) were reacted for 48 h. The crude was purified by flash column chromatography (60% EtOAc/pentane), obtaining the product (30.6 mg, 0.087 mmol, 87%, 6:1) as a colorless solid. *Major isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.44 (m, 2H), 7.37 – 7.32 (m, 5H), 6.89 – 6.86 (m, 2H), 6.07 (d, *J* = 9.3 Hz, 1H), 5.05 (dd, *J* = 9.3, 4.4 Hz, 1H), 4.56 (d, *J* = 4.4 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 1.95 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.8, 169.9, 159.3, 131.9, 129.1, 128.7, 128.5, 128.4, 122.7, 114.1, 86.4, 85.8, 57.0, 55.4, 52.8, 40.5, 23.2. *Minor isomer*: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.35 (m, 2H), 7.25 – 7.23 (m, 3H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 5.52 (d, *J* = 7.8 Hz, 1H),

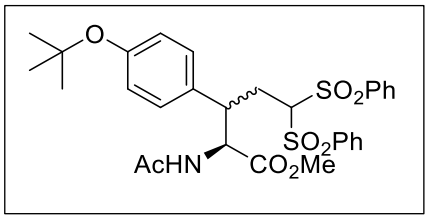
4.81 – 4.74 (m, 1H), 4.43 – 4.36 (m, 1H), 3.74 (s, 3H), 3.66 (s, 3H), 1.95 – 1.90 (m, 3H). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{21}H_{21}NO_4$ + Na: 374.1368; found 374.1363.

*Dimethyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5-methylenehexanedioate (**3f**)*



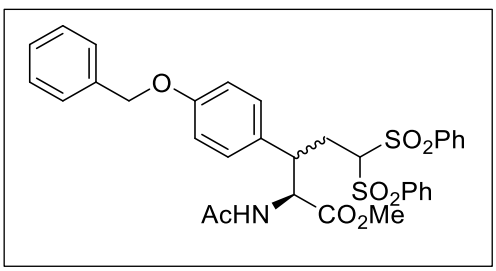
Following the general procedure, Ac-*L*-Tyr(Me)-OMe (**1**) (25.1 mg, 0.1 mmol, 1.0 equiv.) and methyl 3-(phenylsulfonyl)but-3-enoate (**2f**) (120.1 mg, 0.5 mmol, 5.0 equiv.) were reacted for 72 h. The crude was purified by flash column chromatography (50→60% EtOAc/pentane), obtaining the product (combined yield, 30 mg, 0.083 mmol, 83%, 3:1 d.r.). *Major isomer* (21.6 mg, 0.062 mmol, 62%, colorless oil): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.02 – 7.00 (m, 2H), 6.81 – 6.79 (m, 2H), 6.24 (d, *J* = 8.4 Hz, 1H), 6.05 (d, *J* = 1.3 Hz, 1H), 5.37 (q, *J* = 1.2 Hz, 1H), 4.77 (dd, *J* = 8.4, 7.9 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.48 (s, 3H), 3.13 (ddd, *J* = 9.8, 7.9, 4.8 Hz, 1H), 2.97 (ddd, *J* = 14.2, 4.9, 1.3 Hz, 1H), 2.59 (ddd, *J* = 14.3, 9.8, 0.9 Hz, 1H), 2.03 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.8, 169.8, 167.5, 158.8, 137.2, 130.6, 129.4, 127.6, 113.8, 56.8, 55.1, 52.0 and 51.9, 47.0, 34.9, 29.7, 23.2. *Minor isomer* (7.4 mg, 0.021 mmol, 21%, colorless oil): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.01 – 6.98 (m, 2H), 6.85 – 6.82 (m, 2H), 6.16 (d, *J* = 1.2 Hz, 1H), 5.63 (d, *J* = 9.1 Hz, 1H), 5.55 (d, *J* = 1.2 Hz, 1H), 4.94 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.49 (td, *J* = 7.5, 4.3 Hz, 1H), 2.78 (dd, *J* = 14.4, 6.8 Hz, 1H), 2.67 (ddd, *J* = 14.4, 8.2, 1.0 Hz, 1H), 2.00 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.9, 170.1, 167.3, 158.9, 137.2, 130.2, 129.1, 128.0, 114.0, 55.2 and 55.1, 52.3, 51.9, 45.4, 34.1, 29.7, 23.3. **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{18}H_{23}NO_6$ + Na: 372.1418; found 372.1414.

*Methyl (2S)-2-acetamido-3-(4-(tert-butoxy)phenyl)-5,5-bis(phenylsulfonyl)pentanoate (**4**)*



Following the general procedure, Ac-*L*-Tyr(^{t}Bu)-OMe (29.3 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (60 % EtOAc/pentane), obtaining the product (54.2 mg, 0.09 mmol, 90 %, 3.5:1 d.r.) as a colorless solid. *Major isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 2H), 7.72 – 7.70 (m, 2H), 7.59 – 7.54 (m, 3H), 7.50 (t, *J* = 7.9 Hz, 3H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.17 (d, *J* = 8.6 Hz, 1H), 4.66 (t, *J* = 8.1 Hz, 1H), 4.34 – 4.28 (m, 1H), 3.49 (dt, *J* = 10.2, 7.3 Hz, 1H), 3.40 (s, 3H), 2.67 (dt, *J* = 8.4, 4.5 Hz, 2H), 2.04 (s, 3H), 1.34 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.2, 160.0, 155.4, 138.0, 137.6, 134.8, 134.6, 131.0, 129.8, 129.6, 129.3, 129.2, 129.1, 124.5, 80.6, 78.9, 57.0, 52.2, 46.6, 29.0, 28.1, 23.3. *Minor isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.4, 1.3 Hz, 2H), 7.79 – 7.76 (m, 2H), 7.68 – 7.64 (m, 6H), 6.90 (s, 2H), 6.88 (s, 2H), 5.79 (d, *J* = 9.0 Hz, 1H), 4.93 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.52 (dd, *J* = 7.2, 5.5 Hz, 1H), 3.91 – 3.85 (m, 1H), 3.65 (s, 3H), 2.58 (dd, *J* = 9.3, 5.8 Hz, 2H), 2.00 (s, 3H), 1.35 (s, 9H). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{30}H_{35}NO_8S_2$ + Na: 624.1702; found 624.1698.

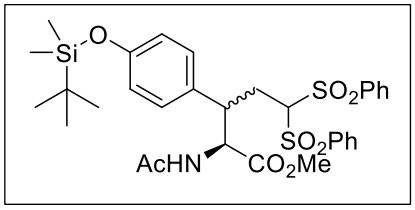
*Methyl (2S)-2-acetamido-3-(4-(benzyloxy)phenyl)-5,5-bis(phenylsulfonyl)pentanoate (**5**)*



Following the general procedure, Ac-*L*-Tyr(Bn)-OMe (32.7 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (60 % EtOAc/pentane), obtaining the product (56.4 mg, 0.89 mmol, 89%, 3:1 d.r.) as a colorless solid. Note: The product could be further purified by recrystallization in CH_2Cl_2 (minimum amount)/heptane. *Major isomer*: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 – 7.95 (m, 2H), 7.75 – 7.68 (m, 3H), 7.63

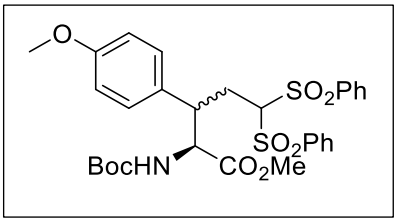
– 7.55 (m, 3H), 7.47 – 7.38 (m, 7H), 6.86 – 6.79 (m, 4H), 6.10 (d, *J* = 8.5 Hz, 1H), 5.05 (bs, 2H), 4.66 (dd, *J* = 8.5, 7.4 Hz, 1H), 4.32 – 4.25 (m, 1H), 3.76 – 3.68 (m, 1H), 3.45 (s, 3H), 2.68 – 2.60 (m, 2H), 2.04 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.0, 169.8, 155.4, 137.9, 137.4, 136.8, 134.7, 134.5, 129.8, 129.5, 129.5, 129.2, 129.1, 128.7, 128.2, 128.2, 127.5, 115.3, 80.5, 70.0, 56.8, 52.2, 46.2, 28.1, 23.2. *Minor isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.91 (m, 2H), 7.81 – 7.76 (m, 2H), 7.66 – 7.60 (m, 2H), 7.52 – 7.49 (m, 2H), 7.40 – 7.39 (m, 2H), 7.39 – 7.34 (m, 5H), 6.92 – 6.88 (m, 4H), 5.76 (d, *J* = 8.9 Hz, 1H), 5.03 (d, *J* = 8.1 Hz, 2H), 4.92 (dd, *J* = 8.9, 4.8 Hz, 1H), 4.53 – 4.48 (m, 1H), 3.91 – 3.84 (m, 1H), 3.68 (s, 3H), 2.60 – 2.54 (m, 2H), 2.01 (s, 3H). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{33}H_{33}NO_8S_2$+ Na: 658.1545; found 658.1542.

*Methyl (2S)-2-acetamido-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)-5,5-bis(phenylsulfonyl) pentanoate (**6**)*



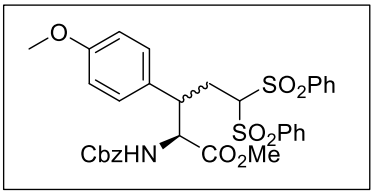
Following the general procedure, Ac-*L*-Tyr(TBS)-OMe (35.2 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenyl-sulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) was reacted for 48 h. The crude was purified by flash column chromatography (50→60 % EtOAc/pentane), obtaining the product (40.3 mg, 0.061 mmol, 61%, 3:1 d.r.) as a colorless solid. *Major isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.94 (m, 2H), 7.74 – 7.71 (m, 2H), 7.58 (t, *J* = 7.8 Hz, 3H), 7.51 (d, *J* = 7.7 Hz, 3H), 6.79 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.09 (d, *J* = 8.5 Hz, 1H), 4.65 (t, *J* = 8.1 Hz, 1H), 4.31 (dd, *J* = 8.9, 2.8 Hz, 1H), 3.47 (t, *J* = 6.6 Hz, 1H), 3.43 (s, 3H), 2.72 – 2.62 (m, 2H), 2.04 (s, 3H), 0.99 (s, 9H), 0.20 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.2, 169.9, 155.7, 138.0, 137.6, 134.8, 134.6, 129.9, 129.6, 129.3, 129.2, 128.8, 120.7, 80.6, 57.0, 52.2, 46.5, 28.18, 25.8 (b), 23.4, 18.3, -4.3, -4.2. *Minor isomer*: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.90 (m, 2H), 7.80 – 7.78 (m, 2H), 7.68 – 7.64 (m, 6H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.75 (d, *J* = 9.0 Hz, 1H), 4.91 (dd, *J* = 9.0, 4.8 Hz, 1H), 4.51 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.87 – 3.83 (m, 1H), 3.66 (s, 3H), 2.60 – 2.54 (m, 2H), 2.01 (s, 3H), 0.99 (s, 9H), 0.22 (s, 6H). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{32}H_{41}NO_8S_2Si$ + Na: 682.1946; found 682.1935.

*Methyl (2S)-2-((tert-butoxycarbonyl)amino)-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl) pentanoate (**7**)*



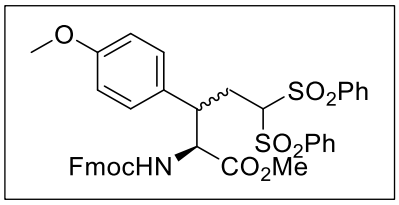
Following the general procedure, Boc-*L*-Tyr(Me)-OMe (30.9 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (2→5% EtOAc/CH_2Cl_2), obtaining the product (58.6 mg, 0.095 mmol, 95%, 4:1 d.r.) as a colorless oil. *Major isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 2H), 7.75 – 7.71 (m, 2H), 7.70 – 7.64 (m, 2H), 7.58 (t, *J* = 7.8 Hz, 2H), 7.53 – 7.47 (m, 2H), 6.86 – 6.83 (m, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 5.13 (d, *J* = 9.1 Hz, 1H), 4.36 (t, *J* = 8.3 Hz, 1H), 4.27 (d, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.47 (s, 3H), 3.43 – 3.38 (m, 1H), 2.63 (dd, *J* = 10.3, 3.4 Hz, 2H), 1.44 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.4, 159.3, 155.3, 137.7, 134.8, 134.6, 129.9, 129.7, 129.6, 129.3, 129.2, 114.4, 80.8, 77.4, 58.4, 55.4, 52.2, 46.5, 29.8, 28.5. *Minor isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 – 7.89 (m, 2H), 7.84 – 7.79 (m, 2H), 7.66 – 7.60 (m, 4H), 7.58 – 7.53 (m, 2H), 6.94 (d, *J* = 7.4 Hz, 2H), 6.83 – 6.78 (m, 2H), 5.41 – 5.32 (m, 1H), 4.93 (dd, *J* = 12.8, 9.4 Hz, 1H), 4.57 (d, *J* = 9.4 Hz, 1H), 4.19 – 4.11 (m, 1H), 3.83-3.76 (s, 3H), 3.66 (s, 3H), 2.59 – 2.51 (m, 2H), 1.46 (s, 9H). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{30}H_{35}NO_9S_2$ + Na: 640.1656; found 640.1643.

*Methyl (2S)-2-(((benzyloxy)carbonyl)amino)-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl) pentanoate (**8**)*



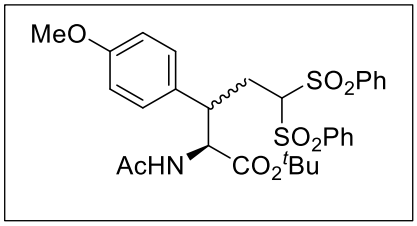
Following the general procedure, Cbz-*L*-Tyr(Me)-OMe (34.3 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (2→4% EtOAc/CH_2Cl_2), obtaining the product (37.8 mg, 0.058 mmol, 58%, 4:1 *d.r.*) as a yellow oil. *Major isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (dt, *J* = 8.1, 1.8 Hz, 2H), 7.73 – 7.69 (m, 2H), 7.55 (q, *J* = 7.8 Hz, 4H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 12.1 Hz, 5H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.75 – 6.70 (m, 2H), 5.36 (d, *J* = 9.2 Hz, 1H), 5.12 (d, *J* = 2.9 Hz, 2H), 4.44 (t, *J* = 8.2 Hz, 1H), 4.23 (d, *J* = 9.4 Hz, 1H), 3.79 (s, 3H), 3.77 – 3.71 (m, 1H), 3.49 (s, 3H), 2.69 – 2.57 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.3, 159.3, 157.9, 137.7, 134.7, 134.4, 129.8, 129.6, 129.4, 129.2, 129.1, 129.0, 128.6, 128.3, 128.2, 114.7, 80.6, 67.3, 58.7, 55.3, 52.2, 46.2, 29.7. *Minor isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.99 (m, 2H), 7.78 – 7.72 (m, 2H), 7.63 – 7.60 (m, 2H), 7.48 – 7.41 (m, 4H), 7.19 – 7.14 (m, 5H), 6.88 – 6.84 (m, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 5.59 – 5.56 (m, 1H), 4.95 (d, *J* = 9.0 Hz, 2H), 4.84 – 4.79 (m, 1H), 4.36 (d, *J* = 3.4 Hz, 1H), 4.32 (d, *J* = 3.3 Hz, 1H), 3.79 (s, 3H), 3.26 (s, 3H), 2.58 – 2.55 (m, 2H). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{33}H_{33}NO_9S_2$ + Na: 674.1489; found 674.1489.

*Methyl (2S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl) pentanoate (**9**)*



Following the general procedure, Fmoc-*L*-Tyr(Me)-OMe (43.1 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (1→2% EtOAc/CH_2Cl_2), obtaining the product (52.3 mg, 0.07 mmol, 71%, 4:1 d.r.) as a yellowish solid. *Major isomer*: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.96 (ddd, *J* = 8.7, 2.0, 1.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.73 (s, 2H), 7.69 – 7.65 (m, 2H), 7.61 (d, *J* = 5.1 Hz, 2H), 7.57 – 7.52 (m, 2H), 7.49 – 7.45 (m, 2H), 7.44 – 7.41 (m, 2H), 7.36 – 7.33 (m, 2H), 6.86 – 6.83 (m, 2H), 6.76 – 6.73 (m, 2H), 5.42 (d, *J* = 9.0 Hz, 1H), 4.44 (dd, *J* = 10.6, 7.3 Hz, 2H), 4.41 – 4.38 (m, 1H), 4.27 (d, *J* = 9.4 Hz, 1H), 4.24 – 4.21 (m, 1H), 3.80 (d, *J* = 0.9 Hz, 3H), 3.51 (s, 3H), 3.49 – 3.45 (m, 1H), 2.71 (t, *J* = 13.4 Hz, 1H), 2.66 – 2.62 (m, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.0, 159.4, 155.8, 143.9, 143.8, 141.5, 141.4, 137.9, 137.7, 134.8, 134.6, 129.9, 129.8, 129.6, 129.3, 129.2, 129.1, 128.0, 127.9, 127.3, 127.3, 127.2, 125.2, 120.2, 120.1, 114.5, 80.8, 67.5, 58.8, 55.4, 52.4, 47.3, 46.4, 28.1. *Minor isomer:* **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.94 – 7.92 (m, 2H), 7.77 – 7.74 (m, 4H), 7.70 – 7.68 (m, 4H), 7.59 – 7.56 (m, 2H), 7.53 – 7.49 (m, 2H), 7.33 – 7.30 (m, 4H), 6.82 (d, *J* = 8.2 Hz, 2H), 6.65 – 6.62 (m, 2H), 5.17 (d, *J* = 9.3 Hz, 1H), 4.83 (t, *J* = 5.6 Hz, 1H), 4.66 (dt, *J* = 10.7, 5.4 Hz, 1H), 4.62 (t, *J* = 4.9 Hz, 1H), 4.48 – 4.45 (m, 2H), 4.19 – 4.14 (m, 1H), 3.80 (s, 3H), 3.58 (s, 3H), 2.58 – 2.54 (m, 2H). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{40}H_{37}NO_9S_2$+ Na: 762.1802; found 762.1802.

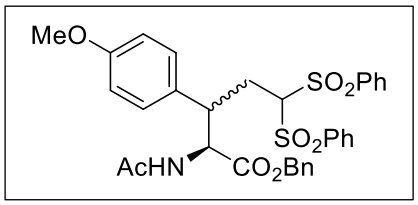
*tert-Butyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (**10**)*



Following the general procedure, Ac-*L*-Tyr(Me)-O^{t}Bu (29.3 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (50→60 % EtOAc/pentane), obtaining the product (54.7 mg, 0.091 mmol, 91%, 3.5:1 d.r.) as a colorless solid. *Major isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 2H), 7.72 – 7.70 (m, 2H), 7.59 – 7.54 (m, 3H), 7.50 (t, *J* = 7.9 Hz, 3H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.17 (d, *J* = 8.6 Hz, 1H), 4.66 (t, *J* = 8.1 Hz, 1H), 4.34 – 4.28 (m, 1H), 3.49 (dt, *J* = 10.2, 7.3 Hz, 1H), 3.40 (s, 3H), 2.67 (dt, *J* = 8.4, 4.5 Hz, 2H), 2.04 (s, 3H), 1.34 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.2, 170.0, 155.4, 138.0,

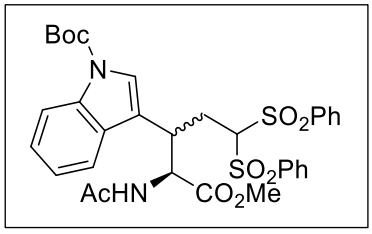
137.6, 134.8, 134.6, 131.0, 129.8, 129.6, 129.3, 129.2, 129.1, 124.5, 80.6, 78.9, 57.0, 52.2, 46.6, 29.0, 29.1, 23.3. *Minor isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.4, 1.3 Hz, 2H), 7.79 – 7.76 (m, 2H), 7.68 – 7.64 (m, 6H), 6.90 (s, 2H), 6.88 (s, 2H), 5.79 (d, *J* = 9.0 Hz, 1H), 4.93 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.52 (dd, *J* = 7.2, 5.5 Hz, 1H), 3.91 – 3.85 (m, 1H), 3.65 (s, 3H), 2.58 (dd, *J* = 9.3, 5.8 Hz, 2H), 2.00 (s, 3H), 1.35 (s, 9H). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{30}H_{35}NO_8S_2$ + Na: 624.1702; found 624.1696.

*Benzyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (**11**)*



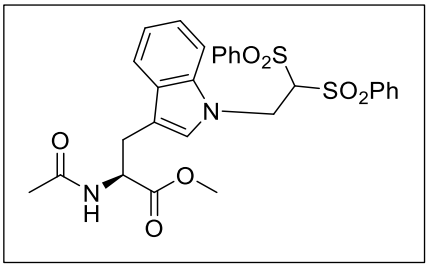
Following the general procedure, Ac-*L*-Tyr(Me)-OBn (32.7 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (50→60 % EtOAc/pentane), obtaining the product (55.2 mg, 0.087 mmol, 87%, 3:1 d.r.) as a colorless solid. *Major Iosmer:* **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96 – 7.91 (m, 2H), 7.70 – 7.64 (m, 4H), 7.59 – 7.55 (m, 2H), 7.52 – 7.43 (m, 4H), 7.32 – 7.29 (m, 3H), 7.12 – 7.07 (m, 2H), 6.81 – 6.77 (m, 2H), 6.67 – 6.63 (m, 2H), 6.17 (d, *J* = 8.6 Hz, 1H), 4.91 – 4.81 (m, 2H), 4.72 (t, *J* = 8.2 Hz, 1H), 4.27 (dd, *J* = 6.8, 5.0 Hz, 1H), 3.77 (s, 3H), 3.46 (q, *J* = 7.9 Hz, 1H), 2.64 (dd, *J* = 8.5, 5.4 Hz, 2H), 2.04 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.6, 169.8, 159.2, 137.9, 137.4, 134.7, 134.6, 134.4, 129.7, 129.6, 129.5, 129.2, 129.1, 128.6, 128.5, 128.5, 127.8, 114.3, 80.5, 67.4, 56.9, 55.2, 46.3, 29.7, 28.4, 23.3. *Minor Isomer*: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 1.6 Hz, 2H), 7.78 (dd, *J* = 7.2, 1.4 Hz, 2H), 7.65 – 7.62 (m, 4H), 7.53 – 7.51 (m, 2H), 7.40 – 7.35 (m, 5H), 6.97 – 6.90 (m, 2H), 6.74 (d, *J* = 7.7 Hz, 2H), 5.78 (d, *J* = 9.0 Hz, 1H), 5.15 (bs, 1H), 4.96 – 4.90 (m, 2H), 4.47 (t, *J* = 6.4 Hz, 1H), 3.79 (s, 2H), 3.11 (dd, *J* = 5.7, 2.2 Hz, 1H), 2.61 – 2.53 (m, 2H), 2.02 (s, 3H). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{33}H_{33}NO_8S_2$+ Na: 658.1545; found 658.1539.

*tert-Butyl 3-((2S)-2-acetamido-1-methoxy-1-oxo-5,5-bis(phenylsulfonyl)pentan-3-yl)-1H-indole-1-carboxylate (**15**)*



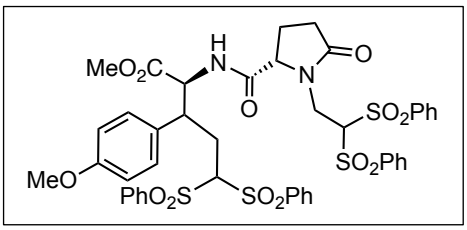
Following the general procedure, Ac-*L*-Trp(NBoc)-OMe (36.0 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (92.5 mg, 0.3 mmol, 3.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (70% EtOAc/pentane), obtaining the product (60.1 mg, 0.09 mmol, 90%, 3.5:1 *d.r.*) as a yellow oil. *Major isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 – 7.96 (m, 2H), 7.72 – 7.65 (m, 4H), 7.59 – 7.54 (m, 4H), 7.42 – 7.36 (m, 4H), 7.22 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H), 6.26 (d, *J* = 8.2 Hz, 1H), 4.87 (dd, *J* = 8.3, 6.3 Hz, 1H), 4.57 (t, *J* = 5.6 Hz, 1H), 3.81 (q, *J* = 7.3 Hz, 1H), 3.51 (s, 3H), 2.81 – 2.76 (m, 2H), 2.04 (s, 3H), 1.69 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.1, 170.0, 149.4, 137.8, 137.5, 134.9, 134.6, 129.9, 129.3, 129.2, 129.1, 125.1, 124.2, 123.0, 119.2, 116.6, 115.5, 84.4, 81.0, 56.3, 52.5, 38.3, 28.4, 28.0, 23.3. *Minor isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 3H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.84 – 7.81 (m, 2H), 7.66 – 7.64 (m, 1H), 7.48 (dd, *J* = 9.2, 1.6 Hz, 5H), 7.27 (d, *J* = 1.1 Hz, 1H), 7.25 (d, *J* = 0.9 Hz, 1H), 6.06 (d, *J* = 9.0 Hz, 1H), 5.09 (dd, *J* = 8.9, 3.9 Hz, 1H), 4.81 (dd, *J* = 7.5, 5.3 Hz, 1H), 4.36 – 4.28 (m, 1H), 3.56 (s, 3H), 2.58 (ddd, *J* = 15.1, 9.5, 5.3 Hz, 2H), 2.08 (s, 3H), 1.70 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.1, 170.7, 149.5, 138.2, 137.4, 135.4, 134.7, 134.6, 129.8, 129.7, 129.2, 129.1, 125.2, 124.1, 123.0, 119.3, 116.3, 115.6, 84.6, 80.8, 54.1, 52.7, 36.7, 29.8, 27.8, 23.5. **HRMS** (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{33}H_{36}N_2O_9S_2$+ Na: 691.1754; found 691.1754.

Methyl N-acetyl-1-(2,2-bis(phenylsulfonyl)ethyl)-L-tryptophanate[#]



Following the general procedure, Ac-*L*-Trp-OMe (26.0 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (92.5 mg, 0.3 mmol, 3.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (70% EtOAc/pentane), obtaining the product (55.0 mg, 0.097 mmol, 97%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.81 (m, 2H), 7.79 – 7.75 (m, 2H), 7.71 – 7.64 (m, 2H), 7.56 – 7.46 (m, 6H), 7.13 (dd, *J* = 6.2, 1.8 Hz, 2H), 7.09 (s, 1H), 6.18 (d, *J* = 8.0 Hz, 1H), 5.09 – 4.96 (m, 2H), 4.93 (dt, *J* = 8.0, 4.8 Hz, 1H), 4.85 (t, *J* = 5.1 Hz, 1H), 3.70 (s, 3H), 3.33 – 3.21 (m, 2H), 1.94 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.2, 170.0, 137.7, 137.5, 135.4, 135.0, 134.9, 129.4, 129.4, 129.3, 129.3, 128.9, 128.5, 122.6, 120.3, 119.2, 109.6, 109.1, 82.3, 52.6, 52.5, 42.1, 27.3, 23.2. **HRMS** (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{28}H_{28}N_2O_7S_2$+ Na: 591.1236; found 591.1226.

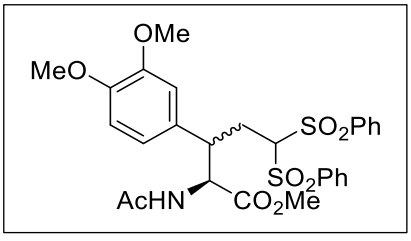
*Methyl (2S)-2-((S)-1-(2,2-bis(phenylsulfonyl)ethyl)-5-oxopyrrolidine-2-carboxamido)-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (**16**)*



Following the general procedure Glp-Tyr(Me)-OMe (32.0 mg, 0.1 mmol, 1.0 equiv.) and ,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (50→80% EtOAc/pentane). After evaporation of the solvent under reduced pressure, the residue was re-dissolved in minimum amount of CH_2Cl_2 and precipitate with heptane, obtaining the product (54.1 mg, 0.058 mmol, 58%, d.r. 3:1) as a colorless solid. *Major isomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 – 7.96 (m, 4H), 7.88 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.74 – 7.72 (m, 2H), 7.69 – 7.63 (m, 4H), 7.60 – 7.57 (m, 4H), 7.53 – 7.49 (m, 4H), 6.86 – 6.82 (m, 2H), 6.80 – 6.76 (m, 2H), 6.53 (d, *J* = 8.4 Hz, 1H), 5.32 (dd, *J* = 8.4, 3.3 Hz, 1H), 4.71 (dd, *J* = 8.4, 5.6 Hz, 1H), 4.51 (dd, *J* = 8.7, 3.5 Hz, 1H), 4.36 (dd, *J* = 8.5, 2.9 Hz, 1H), 4.22 (dd, *J* = 15.4, 3.3 Hz, 1H), 3.80 (s, 3H), 3.75 – 3.68 (m, 1H), 3.61 (s, 3H), 3.55 – 3.50 (m, 1H), 2.74 – 2.67 (m, 2H), 2.38 – 2.33 (m, 1H), 2.26 – 2.21 (m, 1H), 2.21 – 2.16 (m, 1H), 1.98 – 1.92 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.6, 171.2, 170.7, 159.6, 138.8, 138.1, 137.9, 137.5, 135.0, 134.9, 129.8, 129.7, 129.6, 129.5, 129.5, 129.5, 129.4, 129.4, 129.3, 129.3, 129.2, 127.8, 114.7, 80.8, 79.0, 62.3, 57.0, 55.4, 52.7, 45.7, 39.9, 29.3, 27.9, 23.9. *Minor isomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 – 7.45 (m, 20H*), 6.98 (d, *J* = 8.6 Hz, 1H), 6.86 – 6.76 (m, 4H*), 5.27 (dd, *J* = 8.5, 3.1 Hz, 1H), 4.87 (dd, *J* = 9.1, 5.6 Hz, 1H), 4.57 (dd, *J* = 8.2, 4.3 Hz, 1H), 4.48 – 4.42 (m, 1H), 4.20 – 4.13 (dd, *J* = 15.4, 3.2, 1H), 3.80 (s, 3H*), 3.75 – 3.68 (m, 1H*), 3.61 (s, 3H*), 3.55 – 3.50 (m, 1H*), 2.74 – 2.67 (m, 2H*), 2.38 – 2.33 (m, 1H*), 2.30 – 2.13 (m, 2H*), 1.98 – 1.92 (m, 1H*). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{44}H_{44}N_2O_{13}S_4$+ Na: 959.1624; found 959.1620.

Note: * overlapping signals with the major isomer given as multiplet. Due to signal overlapping, only the representative signals of the minor isomer are assigned.

*Methyl (2S)-2-acetamido-3-(3,4-dimethoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (**17**)*

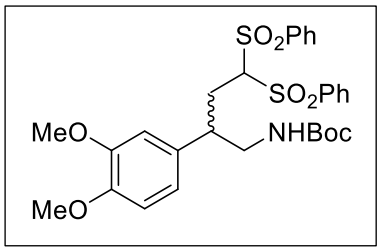


Following the general procedure, methyl (*S*)-2-acetamido-3-(3,4-dimethoxyphenyl)propanoate (28.1 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (92.5 mg, 0.3 mmol, 3.0 equiv.) were reacted for 18 h. The crude was purified by flash column chromatography (50→60% EtOAc/pentane), obtaining the product (54.1 mg, 0.092 mmol, 92 %, *3:1 d.r.*) as a white solid. *Major isomer:* **^{1}H**

[#] Surprisingly, tryptophan (+ 1.03 V), which has an easier oxidizable benzylic position than **1**, was selectively alkylated at the NH group. However, upon prolonged reaction times, the benzylic functionalization could be also detected.

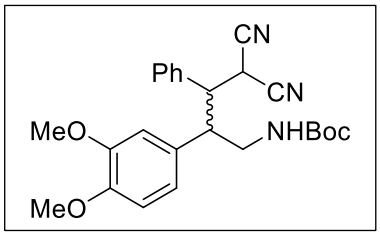
NMR (600 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 2H), 7.72 – 7.67 (m, 4H), 7.59 – 7.57 (m, 2H), 7.49 – 7.45 (m, 2H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 2.1 Hz, 1H), 6.53 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.15 (d, *J* = 8.6 Hz, 1H), 4.73 (t, *J* = 8.2 Hz, 1H), 4.31 (dd, *J* = 9.7, 1.9 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.48 (s, 3H), 3.45 (ddd, *J* = 11.8, 7.7, 4.4 Hz, 1H), 2.71 (ddd, *J* = 15.6, 11.5, 1.9 Hz, 1H), 2.59 (ddd, *J* = 20.4, 9.7, 4.9 Hz, 1H), 2.04 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.2, 169.9, 149.4, 149.0, 138.0, 137.5, 134.8, 134.6, 129.8, 129.6, 129.3, 129.2, 121.4, 111.3, 111.1, 80.7, 56.9, 56.1, 56.0, 52.3, 46.8, 28.2, 23.4. *Minor isomer:* **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.91 – 7.88 (m, 2H), 7.79 – 7.76 (m, 2H), 7.66 – 7.63 (m, 3H), 7.53 – 7.50 (m, 3H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 2.0 Hz, 1H), 6.59 – 6.57 (m, 1H), 5.79 (d, *J* = 9.0 Hz, 1H), 4.91 (dd, *J* = 8.9, 5.1 Hz, 1H), 4.47 (dd, *J* = 9.0, 3.4 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.75 – 3.71 (m, 1H), 3.70 (s, 3H), 2.52 (ddd, *J* = 15.2, 8.9, 5.8 Hz, 2H), 2.00 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.3, 170.3, 149.4, 149.1, 138.0, 137.5, 134.7, 134.7, 129.8, 129.7, 129.2, 128.6, 120.9, 111.5, 111.5, 80.8, 56.1, 56.0, 55.5, 52.6, 45.0, 29.8, 27.8. **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{28}H_{31}NO_9S_2$ + Na: 612.1332; found 612.1333.

*tert-Butyl (2-(3,4-dimethoxyphenyl)-4-methylpentyl)carbamate (**18**)*



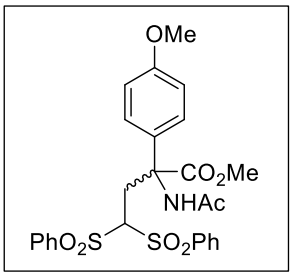
Following the general procedure, *tert*-butyl (3,4-dimethoxyphenethyl) carbamate (28.4 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (92.5 mg, 0.3 mmol, 3.0 equiv.) were reacted for 18 h. The crude was purified by flash column chromatography (40→50% EtOAc/pentane), obtaining the product (55.3 mg, 0.094 mmol, 94%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.69 – 7.61 (m, 4H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.48 – 7.43 (m, 2H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.58 (s, 1H), 6.56 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.51 (br, 1H), 4.31 (d, *J* = 6.3 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.37 (bs, 1H), 3.18 (q, *J* = 6.3, 4.8 Hz, 2H), 2.45 (tt, *J* = 6.7, 4.0 Hz, 2H), 1.42 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.9, 149.5, 148.5, 138.0, 137.7, 134.7, 134.5, 131.5, 129.8, 129.4, 129.2, 129.1, 120.6, 111.5, 110.7, 80.8, 79.6, 56.1, 56.0, 46.2, 43.7, 28.9, 28.5. **HRMS** (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{29}H_{35}NO_8S_2$ + Na: 612.1694; found 612.1696.

*tert-Butyl (4,4-dicyano-2-(3,4-dimethoxyphenyl)-3-phenylbutyl) carbamate (**19**)*



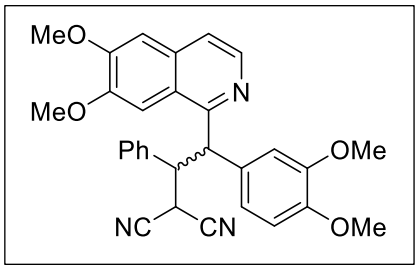
Following the general procedure, *tert*-butyl (3,4-dimethoxyphenethyl) carbamate (28.4 mg, 0.1 mmol, 1.0 equiv.) and benzylidenemalononitrile (46.3 mg, 0.3 mmol, 3.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (30% EtOAc/pentane), obtaining the product (41.4 mg combined yield, 0.095 mmol, 95%, 4:1 d.r.) as a colorless oil. *Major isomer* (33.1 mg, 0.076 mmol, 76%, colorless oil): **^{1}H NMR** δ 7.27 (d, *J* = 6.7 Hz, 3H), 7.04 (s, 2H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.58 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.32 (s, 1H), 4.75 (d, *J* = 7.8 Hz, 1H), 4.51 (t, *J* = 5.7 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 3.60 (t, *J* = 7.8 Hz, 1H), 3.56 – 3.47 (m, 2H), 3.43 (ddd, *J* = 13.3, 6.2, 4.5 Hz, 1H), 1.46 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 148.9, 148.6, 134.3, 129.2, 128.9, 128.8, 121.3, 112.7, 112.1, 112.0, 111.3, 80.5, 55.9, 55.8, 47.8, 47.1, 43.7, 28.5, 27.8. (Note: Not every carbon is observed due to signal overlapping). *Minor isomer*: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.1 Hz, 2H), 7.38 (t, *J* = 6.9 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.84 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.76 (s, 1H), 4.05 (d, *J* = 11.1 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.60 (d, *J* = 4.2 Hz, 1H), 3.46 – 3.37 (m, 1H), 3.30 (ddd, *J* = 12.5, 7.4, 4.6 Hz, 1H), 3.14 (dd, *J* = 11.8, 4.1 Hz, 1H), 2.98 – 2.88 (m, 1H), 1.26 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.5, 150.1, 149.4, 134.7, 130.3, 129.7, 129.7, 128.5, 120.0, 112.4, 112.0, 111.5, 77.4, 56.3, 56.2, 51.1, 47.3, 44.0, 29.0, 28.4. **HRMS** (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{25}H_{29}N_3O_4$ + Na: 458.2050; found 458.2045.

*Methyl 2-acetamido-2-(4-methoxyphenyl)-4,4-bis(phenylsulfonyl)butanoate (**20**)*



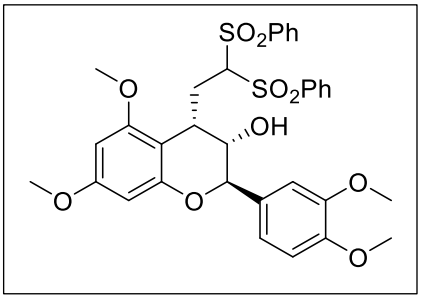
Following the general procedure, methyl (*S*)-2-acetamido-2-(4-methoxyphenyl)acetate (23.7 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (92.5 mg, 0.3 mmol, 3.0 equiv.) were reacted for 72 h. The crude was purified by flash column chromatography (60-70% EtOAc/pentane), obtaining the product (37.7 mg, 0.069 mmol, 69%) as a colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.85 (m, 2H), 7.76 – 7.71 (m, 2H), 7.64 – 7.56 (m, 2H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.26 (s, 1H), 7.20 (dd, *J* = 8.4, 1.6 Hz, 2H), 6.82 – 6.77 (m, 2H), 4.88 (dd, *J* = 5.6, 3.3 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.24 (dd, *J* = 16.3, 5.6 Hz, 1H), 3.16 (dd, *J* = 16.2, 3.3 Hz, 1H), 2.05 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.1, 170.2, 159.2, 137.9, 136.3, 134.8, 134.6, 130.3, 129.9, 129.8, 129.1, 127.6, 113.9, 79.7, 63.1, 55.3, 53.6, 31.2, 23.6. **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{26}H_{27}NO_8S_2$ + Na: 568.1070; found 568.1069.

*2-(2-(6,7-Dimethoxyisoquinolin-1-yl)-2-(3,4-dimethoxyphenyl)-1-phenylethyl)malononitrile (**21**)*



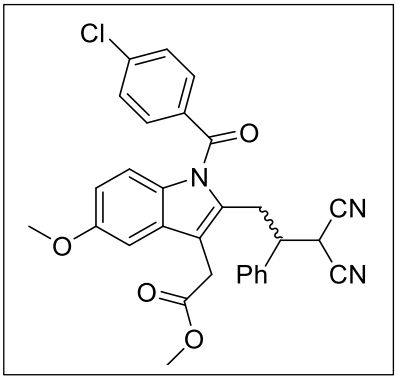
Following the general procedure, Papaverine (33.9 mg, 0.1 mmol, 1.0 equiv.) and benzylidenemalononitrile (46.3 mg, 0.3 mmol, 3.0 equiv.) were reacted for 18 h. The crude was purified by flash column chromatography (50% EtOAc/pentane + 0.1 % NEt_3), obtaining the product mixture (41.7 mg, 0.085 mmol, 85%, 1:1 d.r.) as a brown solid. *Diastereomeric mixture:* **^{1}H NMR** (400 MHz,$CDCl_3$) δ 8.38 (d, *J* = 5.5 Hz, 1H), 8.15 (d, *J* = 5.6 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.43 (d, *J* = 5.6 Hz, 1H), 7.39 – 7.36 (m, 2H), 7.35 (s, 1H), 7.31 (s, 1H), 7.26 – 7.19 (m, 3H), 7.18 (d, *J* = 1.7 Hz, 1H), 7.16 (q, *J* = 3.0, 2.1 Hz, 3H), 7.14 – 7.07 (m, 3H), 6.98 (s, 1H), 6.85 (s, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.50 (d, *J* = 6.6 Hz, 2H), 6.42 (d, *J* = 8.9 Hz, 1H), 5.28 (d, *J* = 11.4 Hz, 1H), 5.15 – 5.10 (m, 2H), 4.74 (dd, *J* = 11.4, 3.9 Hz, 1H), 4.46 (dd, *J* = 11.2, 5.1 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.77 (s, 6H), 3.61 (s, 3H), 3.54 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.6, 155.4, 153.0, 152.6, 150.5, 150.4, 150.0, 149.2, 148.8, 147.9, 140.5, 140.4, 136.4, 136.3, 134.0, 133.4, 132.2, 131.2, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 123.2, 122.8, 121.1, 119.8, 118.8, 112.7, 112.5, 112.4, 112.3, 111.7, 111.6, 110.8, 110.6, 105.5, 103.0, 102.3, 56.2, 56.1, 56.1 (br), 56.0 (br), 55.9, 55.7, 50.8, 50.3, 49.6, 49.5, 29.9, 27.5. **HRMS** (ESI): [M + Na]$^+$ calcd. for $C_{30}H_{27}N_3O_4$ + Na: 516.1899; found 516.1894.

*(2R,3S,4R)-4-(2,2-Bis(phenylsulfonyl)ethyl)-2-(3,4-dimethoxyphenyl)-5,7-dimethoxychroman-3-ol (**22**)*



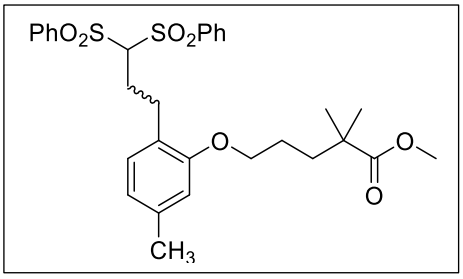
Following the general procedure, (+)-Catechine methyl ether (34.6 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (92.5 mg, 0.3 mmol, 3.0 equiv.) were reacted for 48 h. The crude was purified by flash column chromatography (40% EtOAc/pentane), obtaining the product as single diastereoisomer (37.8 mg, 0.058 mmol, 58%) and as a yellowish solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.85 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.74 – 7.67 (m, 2H), 7.62 – 7.55 (m, 3H), 7.47 – 7.44 (m, 2H), 6.97 – 6.95 (m, 2H), 6.92 – 6.89 (m, 1H), 6.02 (d, *J* = 2.3 Hz, 1H), 5.99 (d, *J* = 2.3 Hz, 1H), 5.76 (t, *J* = 5.3 Hz, 1H), 4.85 (d, *J* = 10.0 Hz, 1H), 4.07 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.83 – 3.79 (m, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.92 (dt, *J* = 15.8, 6.1 Hz, 1H), 2.42 (ddd, *J* = 15.8, 6.6, 5.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.5, 158.0, 154.8, 149.7, 149.5, 138.5, 138.0, 134.5, 134.4, 130.2, 129.8, 129.5, 129.1, 129.0, 120.5, 111.2, 110.2, 104.9, 93.6, 92.2, 81.2, 71.6, 56.1, 56.1, 55.7, 55.5, 33.4, 27.4. **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{33}H_{34}O_{10}S_2$+ Na: 677.1491; found 677.1486.

*Methyl 2-(1-(4-chlorobenzoyl)-2-(3,3-dicyano-2-phenylpropyl)-5-methoxy-1H-indol-3-yl) acetate (**23**)*



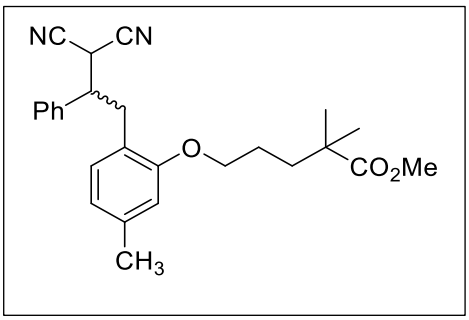
Following the general procedure, indomethacin methyl ester (37.2 mg, 0.1 mmol, 1.0 equiv.) and benzylidenemalononitrile (46.3 mg, 0.3 mmol, 3.0 equiv.) were reacted for 48 h. The crude was purified by flash column chromatography (10-20% EtOAc/pentane), obtaining the product (37.7 mg, 0.72 mmol, 72 %) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.3 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.40 – 7.31 (m, 5H), 6.89 (d, *J* = 2.5 Hz, 1H), 6.62 (dd, *J* = 9.1, 2.5 Hz, 1H), 6.37 (d, *J* = 9.0 Hz, 1H), 4.42 (d, *J* = 5.7 Hz, 1H), 3.85 (dt, *J* = 12.8, 5.7 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.74 – 3.69 (m, 1H), 3.63 – 3.54 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.3, 168.7, 156.3, 139.9, 136.7, 135.5, 133.1, 131.4, 130.9, 130.2, 129.4, 129.3, 129.2, 128.2, 115.7, 115.4, 112.9, 112.3, 112.2, 101.8, 55.8, 52.7, 46.9, 30.2, 28.9. **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{30}H_{24}N_3O_4Cl$ + Na: 548.1348; found 548.1350.

*Methyl 5-(2-(3,3-bis(phenylsulfonyl)propyl)-5-methylphenoxy)-2,2-dimethylpentanoate (**24**)*



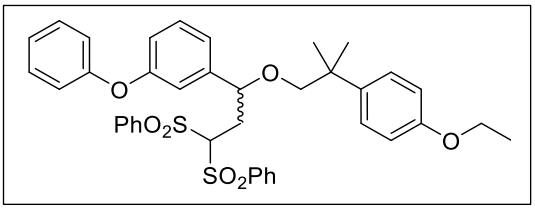
Following the general procedure, Gemifibrozil methyl ester (26.4 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl) ethylene (34.0 mg, 0.11 mmol, 1.1 equiv.) were reacted for 48 h. The crude was purified by flash column chromatography (20-30% EtOAc/pentane), obtaining the product (38.5 mg, 0.67 mmol, 67%, r.r. 18:1; 20% SM reisolated) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 – 7.83 (m, 4H), 7.65 (ddt, *J* = 7.8, 7.1, 1.2 Hz, 2H), 7.53 – 7.49 (m, 4H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 7.4 Hz, 1H), 6.48 (s, 1H), 4.43 (t, *J* = 5.6 Hz, 1H), 3.79 (q, *J* = 4.4, 3.6 Hz, 2H), 3.65 (s, 3H), 2.90 (t, *J* = 6.9 Hz, 2H), 2.45 (q, *J* = 6.8 Hz, 2H), 2.30 (s, 3H), 1.69 (d, *J* = 3.0 Hz, 4H), 1.22 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 178.3, 156.7, 138.1, 137.9, 134.2, 130.5, 129.4, 128.9, 123.8, 120.8, 112.3, 81.8, 67.8, 51.7, 42.1, 37.0, 28.5, 25.3, 25.2, 25.1, 21.5. **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{30}H_{36}O_7S_2$+ Na: 596.1827; found 596.1823.

*Methyl 5-(2-(3,3-dicyano-2-phenylpropyl)-5-methylphenoxy)-2,2-dimethylpentanoate (**25**)*



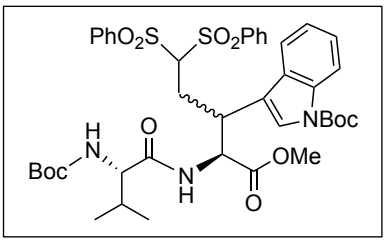
Following the general procedure, Gemifibrozil methyl ester (26.4 mg, 0.1 mmol, 1.0 equiv.) and benzylidenemalononitrile (23.1 mg, 0.15 mmol, 1.5 equiv.) were reacted for 48 h. The crude was purified by flash column chromatography (10% EtOAc/pentane), obtaining the product (39.0 mg, 0.093 mmol, 93%) as a yellow liquid. *Rotameric structure*: **^{1}H NMR** (400 MHz, $CDcl_3$) δ 7.43 – 7.40 (m, 5H), 7.09 – 7.06 (m, 1H), 6.69 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.57 (d, *J* = 1.7 Hz, 1H), 3.90 – 3.85 (m, 3H), 3.67 (s, 3H), 3.46 – 3.39 (m, 1H), 3.20 (d, *J* = 8.8 Hz, 2H), 2.19 (s, 3H), 1.75 – 1.71 (m, 4H), 1.23 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.3, 160.1, 156.8, 139.1, 137.3, 134.8, 130.9, 130.8, 129.8, 129.1, 128.9, 128.2, 122.1, 121.4, 112.7, 112.5 111.9, 68.1, 51.9, 46.2, 42.2, 37.3, 33.9, 28.7, 25.3, 25.3, 25.2, 21.7. **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{33}H_{30}N_2O_3$ + Na: 441.2149; found 441.2144.

*(3-(2-(4-Ethoxyphenyl)-2-methylpropoxy)-3-(3-phenoxyphenyl)propane-1,1-diyldisulfonyl)dibenzene (**26**)*



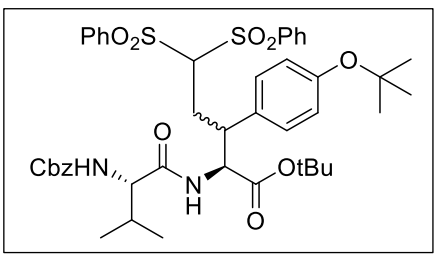
Following the general procedure, Etofenprox (37.7 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl) ethylene (92.5 mg, 0.3 mmol, 3.0 equiv.) were reacted for 48 h. The crude was purified by flash column chromatography (30% EtOAc/pentane), obtaining the product (57.5 mg, 0.084 mmol, 84%) as a colorless solid. *Rotameric structure:* **^{1}H NMR** (600MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.5, 1.1 Hz, 2H), 7.90 – 7.87 (m, 2H), 7.73 (ddt, *J* = 8.7, 7.3, 1.2 Hz, 1H), 7.66 (ddt, *J* = 8.7, 7.3, 1.2 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.54 – 7.50 (m, 2H), 7.40 – 7.36 (m, 2H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.15 (tt, *J* = 7.5, 1.1 Hz, 1H), 7.05 (tdd, *J* = 6.5, 1.8, 1.0 Hz, 3H), 7.00 (t, *J* = 2.0 Hz, 1H), 6.95 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.75 – 6.72 (m, 2H), 4.85 (dd, *J* = 9.0, 2.3 Hz, 1H), 4.80 (ddp, *J* = 9.5, 6.1, 3.1 Hz, 1H), 4.51 (bs, 2H), 3.47 (s, 2H), 2.58 (ddd, *J* = 15.5, 10.0, 2.3 Hz, 1H), 2.48 (ddd, *J* = 15.4, 9.0, 3.2 Hz, 1H), 1.36 (s, 6H), 1.30 - 1.28 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.5, 157.2, 155.5, 141.0, 140.6, 138.4, 137.7, 134.7, 134.6, 129.9, 129.7, 129.5, 129.3, 129.2, 127.4, 123.4, 122.1, 119.1, 117.8, 117.6, 115.6, 80.23, 79.9, 72.9, 70.9, 38.7, 33.4, 26.4, 26.3, 20.0. **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{39}H_{40}O_7S_2$ + Na: 707.2108; found 707.2109.

*tert-Butyl 3-((2S)-2-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido)-1-methoxy-1-oxo-5,5-bis(phenylsulfonyl)pentan-3-yl)-1H-indole-1-carboxylate (**27**)*



Following the general procedure, Boc-Val-Trp(Boc)-OMe (51.8 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (92.5 mg, 0.3 mmol, 3.0 equiv.) were reacted for 48 h. The crude was purified by flash column chromatography (DCM → 10% EA/DCM), obtaining the product (49.8 mg, 0.060 mmol, 60%, 3:1 d.r.) as pale-yellow oil. *Major isomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 1H), 8.01 – 7.93 (m, 2H), 7.73 – 7.67 (m, 3H), 7.59 – 7.53 (m, 3H), 7.41 – 7.29 (m, 5H), 7.22 (td, *J* = 7.5, 1.0 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 5.04 (bs, 1H), 4.86 (t, *J* = 7.1 Hz, 1H), 4.62 (bs, 1H), 4.01 (bs, 1H), 3.74 (q, *J* = 7.3 Hz, 1H), 3.50 (s, 3H), 2.81 – 2.75 (m, 2H), 2.21 – 2.14 (m, 1H), 1.69 (s, 9H), 1.46 (s, 9H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.8, 170.8, 155.8, 149.4, 137.9, 137.5, 135.5, 134.9, 134.6, 130.0, 129.5, 129.4, 129.3, 129.0, 125.1, 124.3, 123.1, 119.3, 116.6, 115.5, 84.3, 81.1, 60.0, 56.2, 52.5, 38.5, 31.0, 29.8, 28.5, 28.4, 19.3, 17.7. *Minor isomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.0 Hz, 1H), 7.96 – 7.94 (m, 1H), 7.89 (d, *J* = 7.9 Hz, 2H), 7.81 – 7.76 (m, 2H), 7.69 – 7.61 (m, 3H), 7.51 (t, *J* = 7.9 Hz, 3H), 7.48 – 7.42 (m, 3H), 6.54 (d, *J* = 9.4 Hz, 1H), 5.04 – 4.95 (m, 2H), 4.69 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.31 (bs, 2H), 3.57 (s, 3H), 2.81 – 2.67 (m, 2H), 2.36 – 2.29 (m, 1H), 1.70 (s, 9H), 1.42 (s, 9H), 0.97 (d, *J* = 8.1 Hz, 3H), 0.91 (d, *J* = 8.4 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.5, 170.8, 155.8, 149.4, 138.3, 137.3, 135.2, 134.8, 134.6, 129.9, 129.7, 129.6, 129.2, 129.1, 129.0, 125.2, 124.5, 123.0, 119.3, 115.8, 115.6, 84.4, 80.2, 58.6, 54.6, 52.7, 36.9, 30.9, 29.5, 28.4, 28.1, 22.8, 21.9. **HRMS** (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{41}H_{51}N_3O_{11}$ + Na: 848. 2862; found 848.2857.

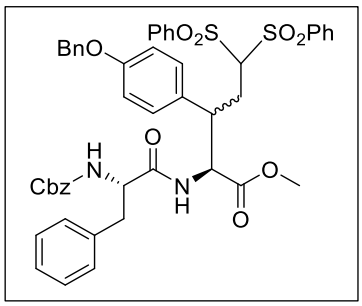
*tert-Butyl (2S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-methylbutanamido)-3-(4-(tert-butoxy)phenyl)-5,5-bis(phenylsulfonyl)pentanoate (**28**)*



Following the general procedure, Cbz-Val-Tyr(^{t}Bu)-O^{t}Bu (52.7 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (2→10% EtOAc/CH_2Cl_2). After evaporation of the solvent under reduced pressure, the residue was re-dissolved in minimum amount of CH_2Cl_2 and precipitate with heptane, obtaining the product (74.2 mg, 0.089 mmol, 89%, d.r. 3.5:1) as a colorless solid. *Major isomer:* **^{1}H**

NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 2H), 7.68 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.41 – 7.37 (m, 3H), 7.35 (d, *J* = 7.3 Hz, 2H), 7.33 – 7.29 (m, 2H), 6.89 – 6.86 (m, 2H), 6.85 – 6.82 (m, 2H), 6.52 (d, *J* = 8.5 Hz, 1H), 5.36 (d, *J* = 8.8 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.15 (d, *J* = 11.9 Hz, 1H), 4.55 (t, *J* = 8.4 Hz, 1H), 4.27 – 4.24 (m, 1H), 4.08 (t, *J* = 7.3 Hz, 1H), 3.38 (q, *J* = 8.1 Hz, 1H), 2.62 (dd, *J* = 8.6, 5.3 Hz, 2H), 2.16 (td, *J* = 12.8, 12.3, 6.2 Hz, 1H), 1.34 (s, 9H), 1.18 (s, 9H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.1, 169.2, 155.3, 134.6, 134.3, 134.2, 130.2, 129.7, 129.6, 129.4, 129.1, 128.9, 128.6, 128.3, 128.2, 124.2, 82.6, 80.6, 78.7, 67.2, 60.3, 57.2, 46.3, 31.1, 28.9, 27.6, 19.1, 17.7. *Minor isomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 3H), 7.74 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.66 – 7.63 (m, 3H), 7.61 (t, *J* = 7.6 Hz, 4H), 7.40 – 7. 30 (m, 4H), 6.93 – 6.90 (m, 2H), 6.82 – 6.79 (m, 2H), 5.55 – 5.49 (m, 1H), 5.14 – 5.07 (m, 2H), 4.76 (bs, 1H), 4.40 (dd, *J* = 9.0, 4.1 Hz, 1H), 4.00 – 3.95 (m, 1H), 3.89 (bs, 1H), 2.58 (d, *J* = 4.0 Hz, 1H), 2.35 (bd, *J* = 13.1 Hz, 2H), 1.34 (s, 9H), 1.18 (s, 9H), 0.94 (d, *J* = 8.5 Hz, 3H), 0.89 (d, *J* = 7.5 Hz, 3H). **HRMS** (ESI): *m/z* [M+Na^+] cacld. for $C_{44}H_{54}N_2O_{10}S_2$+ Na: 857.3118; found 857.3112.

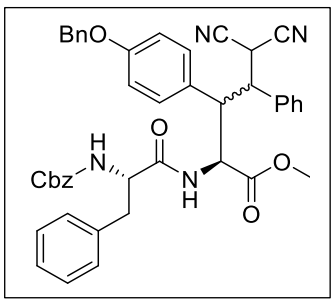
*Methyl (2S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-3-(4-(benzyloxy)phenyl)-5,5-bis(phenylsulfonyl)pentanoate (**29**)*



Following the general procedure, Cbz-Phe-Tyr(Bn)-OMe (56.7 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (2→10% EtOAc/CH_2Cl_2). After evaporation of the solvent under reduced pressure, the residue was re-dissolved in minimum amount of CH_2Cl_2 and precipitate with heptane, obtaining the product (54.1 mg, 0.062 mmol, 62%, d.r. 2:1) as a colorless solid. *Major isomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 – 7.97 (m, 2H), 7.95 – 7.91 (m, 2H), 7.84 (ddd, *J* = 7.1, 3.8, 2.0 Hz, 2H), 7.76 – 7.72 (m, 2H), 7.70 – 7.66 (m, 2H), 7.64 – 7.62 (m, 2H), 7.55 – 7.51 (m, 4H), 7.36 – 7.31 (m, 9H), 6.62 – 6.53 (m, 4H), 5.58 (dd, *J* = 10.1, 5.2 Hz, 1H), 5.26 (bs, 1H), 5.13 (s, 1H), 4.78 – 4.74 (m, 1H), 4.55 – 4.51 (m, 1H), 4.43 (bs, 1H), 4.29 – 4.23 (m, 1H), 3.37 (dd, *J* = 11.7, 6.4 Hz, 1H), 3.33 (s, 3H), 3.11 (d, *J* = 8.0 Hz, 1H), 3.05 (d, *J* = 6.7 Hz, 1H), 2.86 – 2.81 (m, 1H), 2.54 (ddd, *J* = 22.4, 10.3, 5.6 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.7, 170.6, 157.0, 151.7, 137.7, 134.8, 134.7, 134.6, 129.9, 129.8, 129.7, 129.7, 129.6, 129.5, 129.4, 129.3, 129.3, 129.2, 129.1, 129.0, 129.0, 128.9, 128.6, 128.3, 128.1, 127.5, 126.1, 126.0, 120.6, 116.3, 116.2, 80.6, 79.9, 67.3, 56.9, 56.8, 52.1, 46.1, 34.6, 11.9. *Minor isomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 – 7.10 (m, 20H*), 6.75 – 6.70 (m, 1H), 6.68 – 6.63 (m, 2H), 6.44 (bs, 2H), 5.21 (bs, 1H), 5.11 – 5.05 (m, 1H), 5.05 – 5.00 (m, 1H), 4.83 – 4-78 (m, 1H), 4.60 (dd, *J* = 8.2, 6.6, Hz, 1H), 4.35 – 4.32 (m, 1H), 3.44 (bs, 1H), 3.33 (s, 3H), 3.16 – 3.11 (m, 1H), 3.04 – 3.00 (m, 1H), 2.88 – 2.83 (m, 1H), 2.68 – 2.60 (m, 3H). **HRMS** (ESI): *m/z* [M+Na^+] cacld. for $C_{48}H_{46}N_2NaO_{10}S_2$+ Na: 897.2492; found 897.2491.

Note: * overlapping signals with the major isomer given as multiplet. Due to signal overlapping, only the representative signals of the minor isomer are assigned.

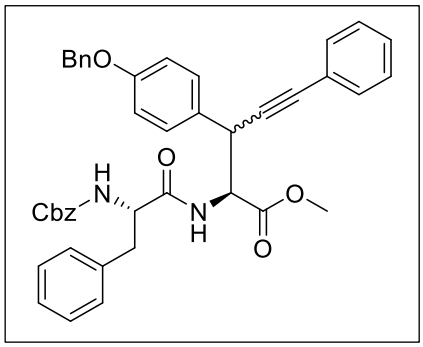
Methyl (2S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-3-(4-(benzyloxy)phenyl)-5,5-dicyano-4-phenylpentanoate (**30**)



Following the general procedure, Cbz-Phe-Tyr(Bn)-OMe (56.7 mg, 0.1 mmol, 1.0 equiv.) and benzylidenemalononitrile (77.1 mg, 0.5 mmol, 5.0 equiv.) were reacted for 48 h. The crude was purified by flash preparative HPLC, obtaining a major fraction (30.1 mg, 0.04 mmol, 42%) with two diastereomers (d.r. 1.5:1) as a colorless solid. *Diastereomeric mixture:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 3H), 7.34 – 7.29 (m, 6H), 7.27 (t, *J* = 1.8 Hz, 1H), 7.25 – 7.23 (m, 2H), 7.22 – 7.19 (m, 3H), 7.14 (dp, *J* = 5.1, 1.9, 1.5

Hz, 3H), 7.09 – 7.05 (m, 2H), 6.83 – 6.75 (m, 3H), 6.70 – 6.66 (m, 1H), 6.27 (dd, *J* = 20.3, 13.4 Hz, 1H), 5.67 (dd, *J* = 5.0, 1.6 Hz, 0.5H) and 5.47 (dd, *J* = 9.9, 3.4 Hz, 0.5H), 5.26 (t, *J* = 13.0 Hz, 1H), 5.06 (dq, *J* = 7.7, 4.1 Hz, 2H), 4.74 – 4.64 (m, 2H), 4.42 – 4.33 (m, 1H), 4.30 (d, *J* = 9.1 Hz, 0.5H) and 3.65 – 3.62 (m, 0.5H), 3.61 and 3.60 (s, 3H), 3.00 – 2.98 (m, 1H), 2.98 – 2.95 (m, 1H), 2.93 (d, *J* = 5.6 Hz, 1H), 2.89 – 2.84 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.6, 171.5, 171.4, 171.3, 171.2, 170.6, 158.1, 156.2, 156.1, 156.0, 155.9, 137.2, 137.1, 137.0, 136.9, 136.3, 133.7 133.6, 132.89 132.8, 130.5, 130.4, 130.3, 129.6, 129.5, 129.4, 129.4, 129.4, 129.3, 129.3, 129.28, 129.2, 129.1, 129.1, 128.9 128.9, 128.9, 128.8, 128.8, 128.8, 128.7, 128.7, 128.7, 128.6 128.5, 128.4, 128.4, 128.4, 128.4, 128.2, 128.1, 128.1, 128.1, 128.1, 127.7, 127.6, 127.2, 127.1, 127.0, 126.6, 126.5, 116.7, 116.6, 116.2, 116.2, 115.1, 112.2, 112.2, 112.1, 112.1, 112.0, 111.8, 111.8, 80.1, 80.7, 79.36, 79.3, 70.1, 67.3, 56.1, 56.1, 53.6, 53.5, 53.5, 53.4, 53.4, 53.2, 52.4, 52.3, 38.3, 38.2, 37.3, 37.2, 37.2, 37.1, 26.9, 26.8, 26.7, 26.6. **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{44}H_{40}N_4O_6$ + Na: 743.2840; found 743.2840.

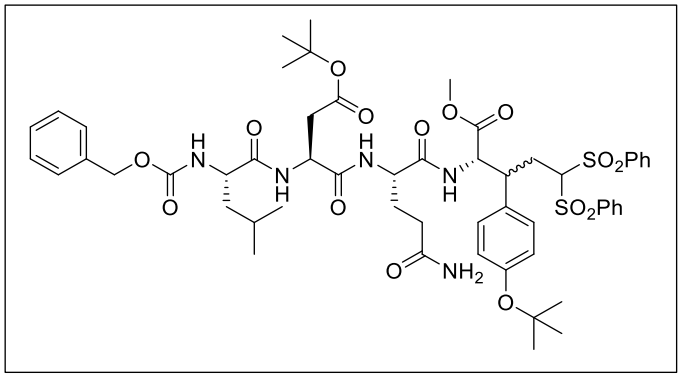
*Methyl (2S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-3-(4-(benzyloxy)phenyl)-5-phenylpent-4-ynoate (**31**)*



Following the general procedure, Cbz-Phe-Tyr(Bn)-OMe (56.7 mg, 0.1 mmol, 1.0 equiv.) and (phenylethynyl)sulfonyl)benzene (121.1 mg, 0.5 mmol, 5.0 equiv.) were reacted for 72 h. The crude was purified by preparative HPLC, obtaining the product (10.2 mg, 0.016 mmol, 16%, d.r. 6:1) as a colorless solid. *Major isomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 6.9 Hz, 2H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.39 (dd, *J* = 3.6, 1.2 Hz, 2H), 7.37 – 7.35 (m, 2H), 7.33 – 7.32 (m, 1H), 7.32 – 7.31 (m, 2H), 7.30 (d, *J* = 2.9 Hz, 2H), 7.29 (d, *J* = 3.5 Hz, 1H), 7.25 – 7.23 (m, 3H), 7.22 – 7.20 (m, 2H), 7.19 – 7.16 (m, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.60 (s, 1H), 5.05 (d, *J* = 11.4 Hz, 2H), 5.01 (d, *J* = 7.3 Hz, 3H), 4.98 – 4.95 (m, 1H), 4.51 (d, *J* = 4.4 Hz, 1H), 4.42 (d, *J* = 7.7 Hz, 1H), 3.74 (s, 3H), 3.03 (dd, *J* = 14.2, 6.9 Hz, 1H), 2.94 (dd, *J* = 12.1, 5.5 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.6, 169.7, 158.3, 149.4, 143.0, 136.9, 136.0, 131.9, 129.3, 129.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.5, 126.9, 114.9, 86.4, 85.3, 70.0, 67.1, 57.1, 52.7, 42.6, 40.4, 37.8. *Minor isomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 – 7.10 (m, 19H*), 6.92 (d, *J* = 8.7 Hz, 1H), 6.60 (bs, 1H*), 6.44 (d, *J* = 8.2 Hz, 1H), 5.07 – 4.94 (m, 6H*), 4.44 – 4.39 (m, 1H*), 4.39 (d, *J* = 4.9 Hz, 1H), 3.62 (s, 3H), 3.07 – 2.90 (m, 2H*). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{42}H_{38}N_2O_6$ + Na: 689.2628; found 689.2629.

Note: * overlapping signals with the major isomer given as multiplet. Due to signal overlapping, only the representative signals of the minor isomer are assigned.

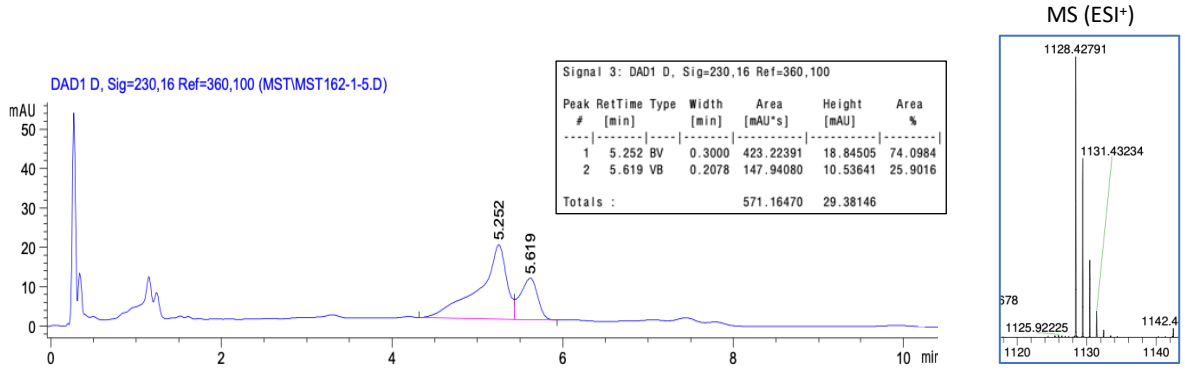
*Methyl (5S,8S,11S,14S)-11-(3-amino-3-oxopropyl)-8-(2-(tert-butoxy)-2-oxoethyl)-14-(1-(4-(tert-butoxy) phenyl)-3,3-bis(phenylsulfonyl)propyl)-5-isobutyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-4,7,10,13-tetraazapentadecan-15-oate (**32**)*



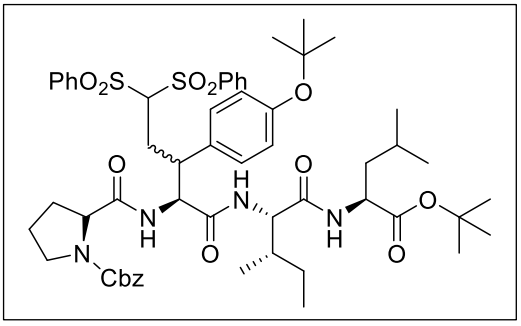
Following the general procedure, Cbz-Leu-Glu(^{t}Bu)-Asn(Mbh)-Tyr(^{t}Bu)-OMe (102.4 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (2→20 % EtOAc/CH_2Cl_2). After evaporation of the solvent under reduced pressure, the residue was re-dissolved in minimum amount of CH_2Cl_2 and precipitate with heptane, obtaining the product mixture (75.1 mg, 0.068 mmol, 68%, d.r. 3:1) as a slightly yellowish solid. *Major isomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.8 Hz, 2H), 7.76 – 7.72 (m, 2H), 7.68 – 7.64 (m, 2H), 7.63 – 7.61 (m, 2H), 7.48 (tdd, *J* = 7.5, 3.2, 1.2 Hz, 5H), 7.37

– 7.33 (m, 4H), 6.75 (s, 4H), 6.32 (bs, 1H), 6.12 (bs, 1H), 5.58 (d, *J* = 6.6 Hz, 1H), 5.18 – 5.13 (m, 1H), 5.11 – 5.04 (m, 2H), 4.87 – 4.80 (m, 1H), 4.66 (t, *J* = 9.0 Hz, 1H), 4.31 (dt, *J* = 9.6, 5.6 Hz, 2H), 4.08 (d, *J* = 10.3 Hz, 1H), 3.68 – 3.61 (m, 1H), 3.36 (s, 3H), 2.82 (dd, *J* = 14.5, 6.0 Hz, 2H), 2.72 (dd, *J* = 15.0, 5.6 Hz, 1H), 2.52 – 2.40 (m, 1H), 2.38 – 2.28 (m, 2H), 2.16 (d, *J* = 15.8 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.67 (d, *J* = 6.9 Hz, 3H), 1.44 (s, 9H), 1.31 (s, 9H), 0.93 – 0.90 (m, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.8, 173.7, 171.5, 171.1, 171.0, 170.4, 170.2, 155.2, 137.5, 136.6, 134.7, 129.7, 129.5, 129.3, 128.8, 128.7, 128.3, 128.2, 124.7, 81.8, 80.6, 79.0, 67.4, 58.0, 54.6, 52.2, 50.5, 45.9, 44.6, 41.3, 37.3, 32.2, 29.1, 29.0, 28.3, 25.1, 23.2, 21.8. *Minor isomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.96 – 7.90 (m, 2H), 7.83 (d, *J* = 9.1 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.58 – 7.51 (m, 3H), 7.32 – 7.28 (m, 4H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.23 (s, 1H), 5.95 (s, 1H), 5.42 (d, *J* = 7.2 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 5.06 (d, *J* = 12.3 Hz, 1H), 4.82 (dd, *J* = 8.8, 5.8 Hz, 1H), 4.71 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.40 (dd, *J* = 8.9, 3.5 Hz, 1H), 4.38 – 4.32 (m, 1H), 4.20 (bs, 1H), 3.84 (dt, *J* = 11.2, 5.8 Hz, 1H), 3.59 (s, 3H), 2.89 – 2.82 (m, 2H), 2.66 – 2.56 (m, 2H), 2.36 – 2.26 (m, 2H), 2.02 – 1.88 (m, 2H), 1.42 (s, 9H), 1.34 (s, 9H), 0.94 (s, 3H), 0.93 (s, 3H). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{55}H_{71}N_5O_{15}S_2$+ Na: 1128.4280 found 1128.4279.

RP-HPLC Analysis: Poroshell 120 EC C18, acetonitrile/water (+0.1% TFA): 45:55, F = 1 mL/min, λ = 230 nm, tr (major): 5.25 min, tr (minor): 5.62 min).



*Benzyl (2S)-2-(((2S)-1-(((2S,3R)-1-(((S)-1-(tert-butoxy)-4-methyl-1-oxopentan-2-yl)amino)-3,4-dimethyl-1-oxopentan-2-yl)amino)-3-(4-(tert-butoxy)phenyl)-1-oxo-5,5-bis(phenylsulfonyl)pentan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (**33**)*

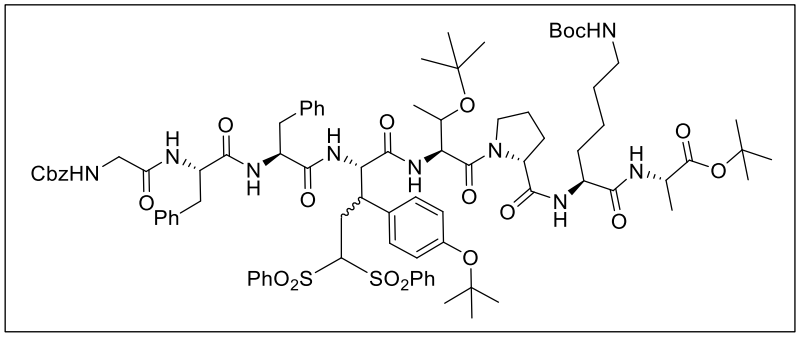


Following the general procedure, Z-Pro-Tyr(^{t}Bu)-Ile-Leu-O^{t}Bu (75.1 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenyl sulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted for 24 h. The crude was purified by flash column chromatography (50% EtOAc/pentane), obtaining the product (179.7 mg, 0.17 mmol, 85%, 2.3:1 d.r.) as a colorless solid. *Major isomer:* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 7.8 Hz, 2H), 7.70 – 7.67 (m, 2H), 7.66 – 7.63 (m, 2H), 7.56 (d, *J* = 6.5 Hz, 2H), 7.52 – 7.49 (m, 3H), 7.36 (m, 2H), 7.34 – 7.30 (m, 3H), 6.86 – 6.70 (m, 4H), 6.30 (bs, 1H), 6.24 (d, *J* = 7.9 Hz, 1H), 5.86 (bs, 1H), 5.73 – 5.65 (m, 1H), 5.34 (bs, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.01 – 4.96 (m, 1H), 4.61 (dd, *J* = 8.0, 6.0 Hz, 1H), 4.50 – 4.42 (m, 1H), 4.40 (d, *J* = 7.6 Hz, 1H), 4.31 (bs, 1H), 4.19 (d, *J* = 6.2 Hz, 1H), 3.91 – 3.85 (m, 1H), 3.54 (bs, 1H), 3.42 (d, *J* = 8.4 Hz, 1H), 2.74 (bs, 1H), 2.36 (bs, 2H), 2.16 (d, *J* = 7.4 Hz, 1H), 1.94 – 1.89 (m, 2H), 1.65 (d, *J* = 6.5 Hz, 1H), 1.60 (d, *J* = 5.8 Hz, 1H), 1.57 (d, *J* = 6.9 Hz, 1H), 1.45 (s, 9H), 1.32 (s, 9H), 0.95 – 0.90 (m, 6H), 0.87 – 0.81 (m, 6H), 0.80 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.9, 171.8, 155.5, 137.7, 134.8, 134.5, 130.0, 129.7, 129.3, 129.2, 129.2, 129.1, 129.1, 128.8, 128.7, 128.6, 128.2, 124.3, 81.2, 78.7, 77.4, 67.8, 61.2, 60.9, 58.1, 51.8, 51.7, 47.2, 42.2, 37.0,

31.6, 29.1, 29.0, 28.1, 25.0, 24.8, 22.9, 22.8, 22.1, 15.6, 11.6. **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{56}H_{74}N_4O_{12}S_2$+ Na: 1081.4642; found 1081.4637.

Note: Only the major isomer could be isolated pure by preparative RP-HPLC. Partial ^{t}Bu deprotection was observed during both preparative and analytic RP-HPLC separation and analysis, respectively. Signals for the rotamers of the major isomer are not assigned.

*tert-Butyl N2-(((2S)-2-((2S)-2-((S)-2-((S)-2-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-phenylpropanamido)-3-phenylpropanamido)-3-(4-(tert-butoxy)phenyl)-5,5-bis(phenylsulfonyl)pentanamido)-3-(tert-butoxy)butanoyl)-D-prolyl)-N6-(tert-butoxycarbonyl)-L-lysyl-L-alaninate (**34**)*

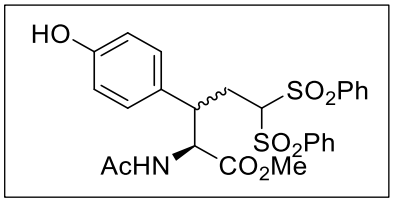


Following the general procedure, *Z*-Gly-Phe-Phe-Tyr(^{t}Bu)-Thr(^{t}Bu)-Pro-Lys(Boc)-Ala-O^{t}Bu (133.2 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.) were reacted in 1.2 mL CH_2Cl_2 (0.08 M) for 24 h. The crude was purified by flash column chromatography (50% EtOAc/pentane→ 5% MeOH/EtOAc). After evaporation of the solvent under reduced pressure, the residue was re-dissolved in minimum amount of CH_2Cl_2 and precipitate with heptane, obtaining the product (121.4 mg, 0.074 mmol, 74%, 2:1 d.r.) as a slightly brownish solid. *Diastereomeric mixture:* **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.22 (d, *J* = 8.6 Hz, 2H), 8.16 (d, *J* = 7.0 Hz, 1H), 8.13 (d, *J* = 6.6 Hz, 2H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.89 – 7.82 (m, 2H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 6.9 Hz, 5H), 7.32 – 7.28 (m, 2H), 7.23 (s, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 6.3 Hz, 5H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.82 (dd, *J* = 11.2, 8.2 Hz, 3H), 6.70 (t, *J* = 5.4 Hz, 1H), 5.01 (s, 2H), 4.96 (d, *J* = 10.6 Hz, 1H), 4.65 – 4.60 (m, 1H), 4.53 – 4.50 (m, 2H), 4.40 – 4.37 (m, 1H), 4.32 (d, *J* = 7.6 Hz, 1H), 4.23 – 4.19 (m, 1H), 4.08 (dd, *J* = 7.1, 2.2 Hz, 1H), 3.80 (d, *J* = 6.0 Hz, 1H), 3.73 (bs, 1H), 3.62 – 3.53 (m, 4H), 3.50 (d, *J* = 6.0 Hz, 1H), 3.47 (d, *J* = 5.9 Hz, 1H), 3.04 -2.93 (m, 4H), 2.92 (d, *J* = 9.1 Hz, 2H), 2.88 (t, *J* = 6.5 Hz, 2H), 2.80 – 2.76 (m, 2H), 2.69 (bs, 1H), 2.63 (bs, 1H), 2.15 (bs, 1H), 2.04 – 1.90 (m, 2H), 1.89 – 1.82 (m, 1H), 1.81 – 1.75 (m, 1H), 1.65 (bs, 2H), 1.51 – 1.45 (m, 2H), 1.39 and 1.38 (s, 9H), 1.37 and 1.36 (s, 9H), 1.33 (s, 3H), 1.23 and 1.22 (s, 9H), 1.14 (s, 9H), 1.08 – 1.01 (m, 5H). **HRMS** (ESI): *m/z* [M+H$^+$] cacld. for $C_{86}H_{113}N_9O_{19}S_2$ + H: 1640.7667; found 1640.7682; [M+2H^{2+}] cacld. for $C_{86}H_{113}N_9O_{19}S_2$+ 2H: 820.8873; found 820.8891.

Note: A separation of the two diastereomers was attempted by preparative RP-HPLC, but only decomposition and/or partially deprotected products were obtained.

7. Derivatization

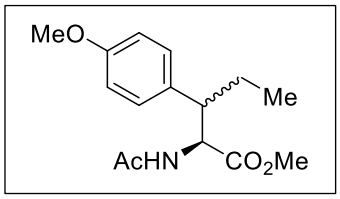
*Methyl (2S)-2-acetamido-3-(4-hydroxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (**35**)*



Methyl (2*S*)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl) pentanoate (**3b**) (22.3 mg, 0.04 mmol, 1.0 equiv.) was dissolved in 1 mL CH_2Cl_2. Trimethylsilyl iodide (27.3 µL, 0.2 mmol, 5.0 equiv.) was added and stirred at room temperature for 24 h. Then, the reaction was quenched with methanol (18 µL, 0.4 mmol, 10 equiv.) and the solid by-products was filtered off. After removing the solvent under vacuum, the product (18.7 mg, 0.036 mmol, 93%, d.r. 3:1) was obtained as a colorless solid. *Major isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.4 Hz, 2H), 7.72 – 7.70 (m, 2H), 7.70 – 7.64 (m, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 2H), 6.79 (d, *J* = 8.1 Hz, 2H), 6.67 (d, *J* = 8.1 Hz, 2H), 6.23 (d, *J* = 8.4 Hz, 1H), 4.68 (t, *J* = 7.8 Hz, 1H), 4.31 (dd, *J* = 8.5, 2.9 Hz,

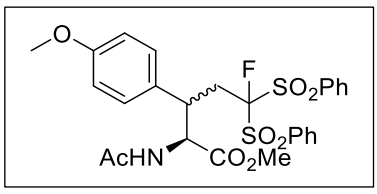
1H), 3.88 – 3.79 (m, 1H), 3.50 (s, 3H), 2.68 – 2.61 (m, 2H), 2.05 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.1, 170.4, 155.8, 136.1, 134.9, 129.81, 129.8, 129.7, 129.6, 129.3, 129.2, 127.9, 116.1, 80.6, 57.0, 52.5, 46.2, 29.9, 23.4, 22.9. *Minor isomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.87 (m, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.68 – 7.64 (m, 2H), 7.57 – 7.50 (m, 4H), 6.85 (d, *J* = 8.3 Hz, 2H), 6.72 (d, *J* = 8.2 Hz, 2H), 5.88 (d, *J* = 9.0 Hz, 1H), 4.92 (dd, *J* = 9.1, 5.0 Hz, 1H), 4.48 (t, *J* = 6.3 Hz, 1H), 3.69 (s, 3H), 2.60 – 2.52 (m, 2H), 2.01 (s, 3H). **HRMS** (ESI): *m/z* [M+Na$^+$] cacld. for $C_{26}H_{27}N_2O_8S_2$ + Na: 568.1081; found 568.1078.

*Methyl (2S)-2-acetamido-3-(4-methoxyphenyl)pentanoate (**36**)*



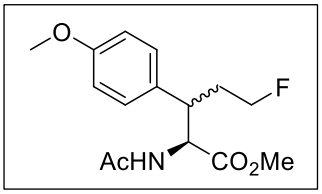
Methyl (2*S*)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl) pentanoate (**3b**) (28.0 mg, 0.05 mmol, 3.1 d.r. 1.0 equiv.) was dissolved in 2 mL dry methanol. Then, activated Mg (60.8 mg, 2.5 mmol, 50 equiv.) and catalytic amount of iodine (~ 2 mg) was added and the mixture was stirred at room temperature for 2 h (if no hydrogen evolution was observed after 5 min, an additional amount of I_2 was added). The reaction was quenched with 20 mL 1M HCl and 20 mL CH_2Cl_2 was added. The phases were separated and the aqueous phase was extracted two times with 15 mL CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (60% EtOAc/pentane), obtaining the product (11.8 mg, 0.042 mmol, 84%, 3:1 d.r.) as a colorless oil. *Major isomer*: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.03 – 6.99 (m, 2H), 6.85 – 6.81 (m, 2H), 5.89 (d, *J* = 8.8 Hz, 1H), 4.79 (dd, *J* = 8.9, 6.8 Hz, 1H), 3.79 (s, 3H), 3.56 (s, 3H), 2.80 (ddd, *J* = 11.1, 6.9, 4.6 Hz, 1H), 2.00 (s, 3H), 1.79 – 1.69 (m, 2H), 0.79 (d, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.0, 169.5, 158.7, 131.0, 129.3, 113.8, 56.9, 55.2, 52.0, 50.2, 29.7, 24.7, 23.3, 12.1. *Minor isomer*: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 2.8 Hz, 2H), 6.86 (d, *J* = 2.3 Hz, 2H), 5.60 (d, *J* = 8.9 Hz, 1H), 4.91 (dd, *J* = 8.9, 5.0 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.10 – 3.01 (m, 1H), 1.97 (s, 3H), 1.91 – 1.86 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H). **HRMS** (ESI): [M + Na]$^+$ calcd. for $C_{15}H_{21}NO_3$ + Na: 302.1363; found 302.1359.

*Methyl (2S)-2-acetamido-5-fluoro-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (**40**)*



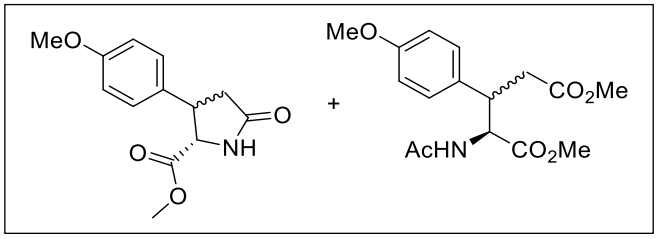
Methyl (2*S*)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl) pentanoate (**3b**) (56.0 mg, 0.1 mmol, 3:1 d.r., 1.0 equiv.) and potassium carbonate (41.4 mg, 0.3 mmol, 3.0 equiv.) was dissolved in 4 mL DMF. Selectfluor (39.0 mg, 0.11 mmol, 1.1 equiv.) was added and the mixture was stirred at 80 °C for 18 h. 10 mL CH_2Cl_2 and 10 mL water was added, the phases were separated and the aqueous phase was extracted two times with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (70% EtOAc/pentane), obtaining the product (53.7 mg, 0.093 mmol, 93%, 3:1 d.r.) as a colorless solid. *Major isomer*: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 – 7.99 (m, 2H), 7.61 (dtt, *J* = 16.2, 7.5, 1.3 Hz, 6H), 7.40 (ddt, *J* = 7.4, 6.4, 1.3 Hz, 2H), 6.70 (d, *J* = 4.0 Hz, 2H), 6.60 – 6.56 (m, 2H), 6.34 (d, *J* = 8.8 Hz, 1H), 4.60 (dd, *J* = 9.8, 8.7 Hz, 1H), 3.74 (s, 3H), 3.53 (td, *J* = 9.7, 9.3, 1.8 Hz, 1H), 3.34 (s, 3H), 3.30 – 3.18 (m, 1H), 2.67 (ddd, *J* = 16.4, 9.6, 4.8 Hz, 1H), 2.07 (s, 3H).**^{19}F NMR** (564 MHz, $CDCl_3$) δ -146.86 (dd, *J* = 24.6, 9.5 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.3, 170.4, 158.7, 135.6, 135.3, 135.1, 133.7, 131.3, 130.7, 130.7, 129.3, 129.1, 128.9, 115.3 (d, *J* = 271.5 Hz), 113.9, 57.3, 55.3, 52.1, 43.0 (d, *J* = 5.2 Hz), 32.4 (d, *J* = 16.7 Hz), 29.8, 23.3. Minor Isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 – 7.93 (m, 2H), 7.80 – 7.77 (m, 3H), 7.75 – 7.73 (m, 3H), 7.52 – 7.48 (m, 2H), 6.75 – 6.70 (m, 4H), 5.68 (d, *J* = 9.0 Hz, 1H), 4.82 (dd, *J* = 8.9, 4.6 Hz, 1H), 3.87 (d, *J* = 4.2 Hz, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 2.80 – 2.73 (m, 2H), 1.94 (s, 3H). **^{19}F NMR** (564 MHz, $CDCl_3$) δ -146.48 (dd, *J* = 24.4, 9.5 Hz). **HRMS** (ESI): [M + Na]$^+$ calcd. for $C_{27}H_{28}FNO_8S_2$ + Na: 600.1133; found 600.1131.

*Methyl (2S)-2-acetamido-5-fluoro-3-(4-methoxyphenyl) pentanoate (**37**)*



Methyl (2*S*)-2-acetamido-5-fluoro-3-(4-methoxyphenyl)-5,5-bis(phenyl sulfonyl)pentanoate (**3b**) (53.7 mg, 0.093 mmol, 3:1 d.r., 1.0 equiv.) was dissolved in 4 mL dry methanol. Then, activated Mg (113.0 mg, 4.65 mmol, 50 equiv.) and catalytic amount of iodine (~ 2 mg) was added and the mixture was stirred at room temperature for 2 h (if no hydrogen evolution was observed after 5 min, an additional amount of I_2 was added). The reaction was quenched with 20 mL 1M HCl and 20 mL CH_2Cl_2 was added. The phases were separated and the aqueous phase was extracted two times with 15 mL CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (60% EtOAc/pentane), obtaining the product (19.8 mg, 0.067 mmol, 72%, 3:1 d.r.) as a colorless oil. *Major isomer:* **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.05 – 7.03 (m, 2H), 6.85 – 6.84 (m, 2H), 5.92 (d, *J* = 8.9 Hz, 1H), 4.82 (dd, *J* = 8.9, 7.4 Hz, 1H), 4.23 (td, *J* = 9.3, 4.5 Hz, 1H), 4.15 (td, *J* = 9.3, 4.5 Hz, 1H), 3.79 (s, 3H), 3.54 (s, 3H), 3.11 (ddd, *J* = 11.4, 7.5, 4.1 Hz, 1H), 2.34 (dddt, *J* = 20.0, 14.8, 9.7, 4.9 Hz, 2H), 2.02 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.8, 169.7, 159.2, 130.0, 129.5, 114.3, 81.7 (d, *J* = 165.1 Hz), 56.9, 55.4, 52.2, 44.5 (d, *J* = 5.0 Hz), 32.9 (d, *J* = 19.9 Hz), 23.4. **^{19}F NMR** (564 MHz, $CDCl_3$) δ -220.91 (tdd, *J* = 47.1, 33.1, 16.0 Hz). *Minor isomer:* **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.02 – 6.98 (m, 2H), 6.85 (d, *J* = 3.3 Hz, 2H), 5.69 (d, *J* = 8.8 Hz, 1H), 4.95 (dd, *J* = 8.9, 4.6 Hz, 1H), 4.45 – 4.41 (m, 1H), 4.35 (ddd, *J* = 9.7, 5.8, 4.1 Hz, 1H), 3.79 (s, 3H), 3.71 and 3.55 (s, 3H), 3.47 – 3.43 (m, 1H), 2.10 – 2.02 (m, 2H), 1.99 (s, 3H). **^{19}F NMR** (564 MHz, $CDCl_3$) δ -221.28 (tdd, *J* = 46.9, 29.6, 20.9 Hz). **HRMS** (ESI): $[M + Na]^+$ calcd. for $C_{15}H_{20}FNO_4$ + Na: 320.1269; found 320.1265.

*Methyl (2S)-3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate (**39**) and dimethyl (2S)-2-acetamido-3-(4-methoxyphenyl)pentanedioate (**38**)*



Methyl (2*S*)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (**3b**) (56.0 mg, 0.1 mmol, 3:1 d.r., 1.0 equiv.) and potassium carbonate (138.2 mg, 1 mmol, 10 equiv.) were dissolved in 4 mL dry methanol. At 0 °C, *m*CBPA (77%) (100.8 mg, 0.45 mmol, 4.5 equiv.) was added and the mixture was stirred at 0 °C until full conversion of the starting material was observed (ca 1.5 h). The reaction was quenched with NaS_2O_3 (sat.) and 20 mL CH_2Cl_2 was added. The phases were separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were washed with $NaHCO_3$ (sat.) and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (60→70% EtOAc/pentane), obtaining the product mixture (19.8 mg) as a colorless oil.

Methyl (2*S*)-3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate (**39**) (14.0 mg, 0.056 mmol, 56%, 3:1 d.r.). *Major isomer*: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 – 7.11 (m, 2H), 6.85 – 6.82 (m, 2H), 5.90 (s, 1H), 4.53 (dd, *J* = 8.0, 0.7 Hz, 1H), 3.94 (q, *J* = 7.9 Hz, 1H), 3.79 (s, 3H), 3.35 (s, 3H), 2.73 (dd, *J* = 7.9, 3.6 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.3, 170.7, 159.3, 128.8, 128.1, 114.0, 61.2, 55.4, 52.1, 42.9, 36.2, 29.9. *Minor isomer*: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 – 7.19 (m, 2H), 6.82 (s, 2H), 5.95 (s, 1H), 4.20 (d, *J* = 5.3 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.70 – 3.66 (m, 1H), 2.66 (dd, *J* = 16.2, 7.7 Hz, 1H), 2.50 (dd, *J* = 17.3, 6.7 Hz, 1H). **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{13}H_{15}NO_4$ + Na: 272.0893; found 272.0892.

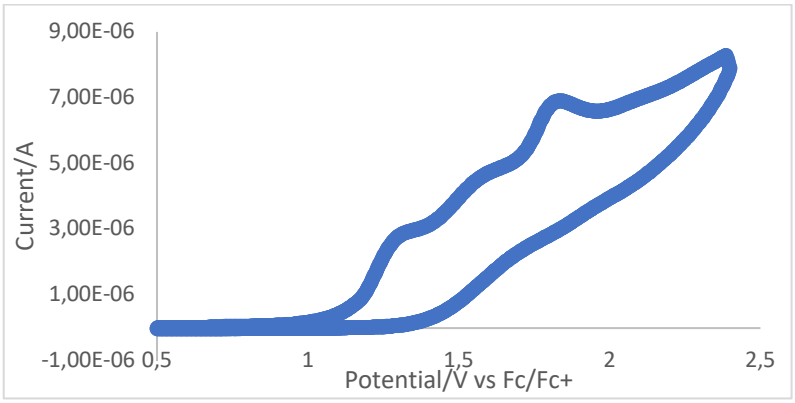
Dimethyl (2*S*)-2-acetamido-3-(4-methoxyphenyl) pentanedioate (**38**) (5.8 mg, 0.018 mmol, 18%, 3:1 d.r.). *Major isomer*: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.08 – 7.05 (m, 2H), 6.91 – 6.87 (m, 2H), 6.09 (d, *J* = 8.8 Hz, 1H), 4.81 (dd, *J* = 8.9, 7.8 Hz, 1H), 4.53 (dd, *J* = 8.0, 0.7 Hz, 3H), 3.78 (s, 3H), 3.59 (s, 3H), 3.53 (s, 3H), 3.51 – 3.46

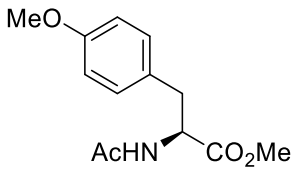
(m, 1H), 2.92 – 2.82 (m, 2H), 2.01 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.6, 171.7, 169.8, 158.2, 130.0, 129.1, 114.2, 63.1, 55.3, 52.3, 44.2, 37.6, 32.1, 23.3. *Minor isomer*: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.7 Hz, 2H), 6.87 – 6.84 (m, 2H), 5.76 (d, *J* = 8.6 Hz, 1H), 5.38 – 5.30 (m, 1H), 5.03 (dd, *J* = 8.9, 4.1 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.62 (s, 3H), 2.81 – 2.76 (m, 2H), 2.02 (s, 3H). **HRMS** (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{21}NO_6$ + Na: 346.1261; found 346.1258.

Note: Products **37** and **38** could not be separated from each other by flash column chromatography.

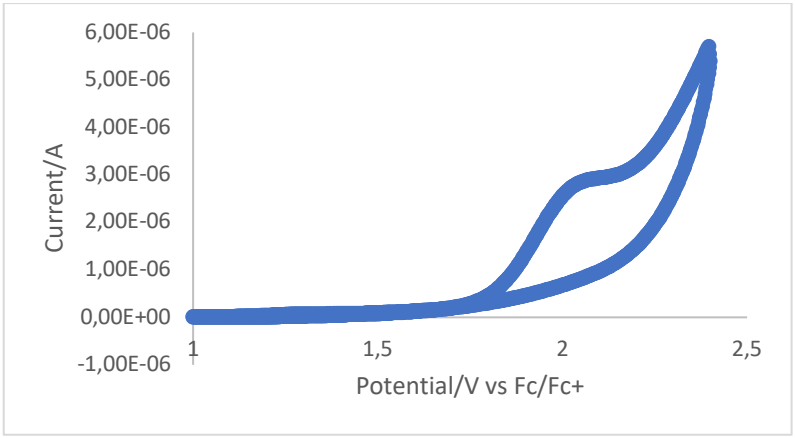
8. Cyclic Voltammetry

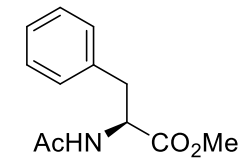
The cyclic voltammogram of the model tyrosine derivative **1** was taken on a Metrohm Autolab PGSTAT204 potentiostat using a platinum wire working electrode, a platinum mesh counter electrode and a silver reference electrode, which was referenced externally against the Fc/Fc+ couple. The pH was not adjusted and the voltammogram was taken at room temperature in a 0.1 M CH_3CN solution of tetrabutylammonium hexafluorophosphate containing 1 mM of the designated substrate. The scan rate was 50 mV/s. Ferrocene was added as internal standard. It is known that the Fc/Fc+ couple is 0.38 V more positive as the SCE. This value may be subtracted from the obtained difference to determine the potential against SCE.



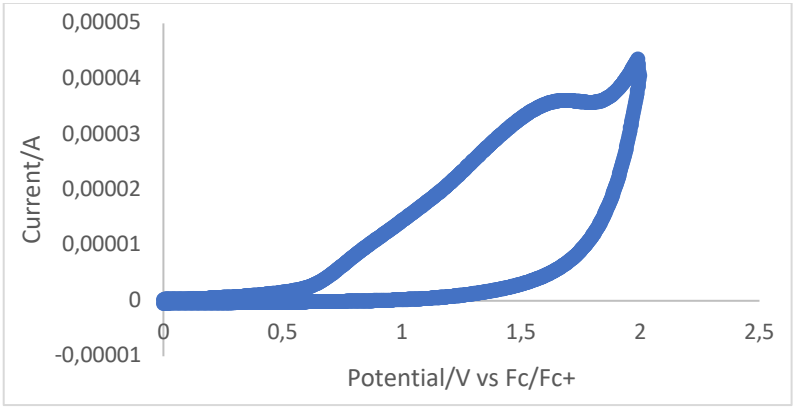


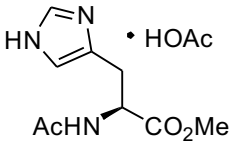
$E_{1/2}$ = + 1.20 V vs Fc/Fc+
$E_{1/2}$ = + 1.58 V vs SCE



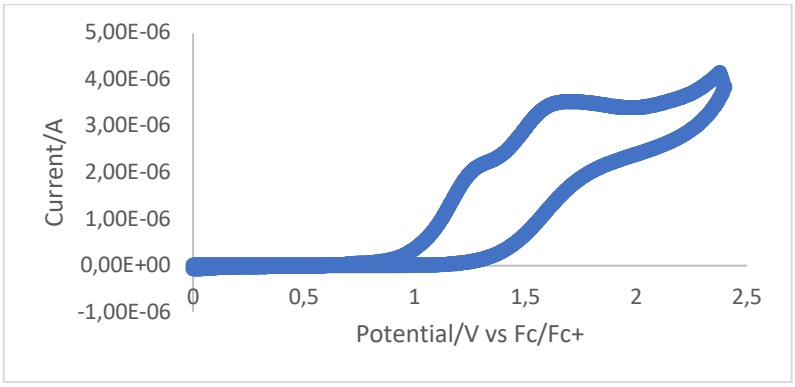


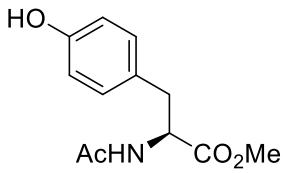
$E_{1/2}$ = + 1.90 V vs Fc/Fc+
$E_{1/2}$ = + 2.28 V vs SCE



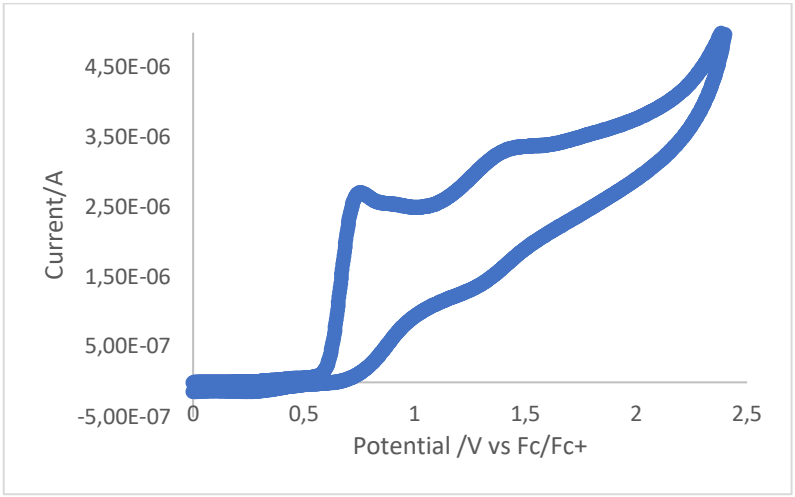


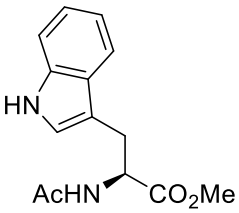
$E_{1/2}$ = + 1.33 V vs Fc/Fc+
$E_{1/2}$ = + 1.71 V vs SCE





$E_{1/2}$ = + 1.18 V vs Fc/Fc+
$E_{1/2}$ = + 1.56 V vs SCE



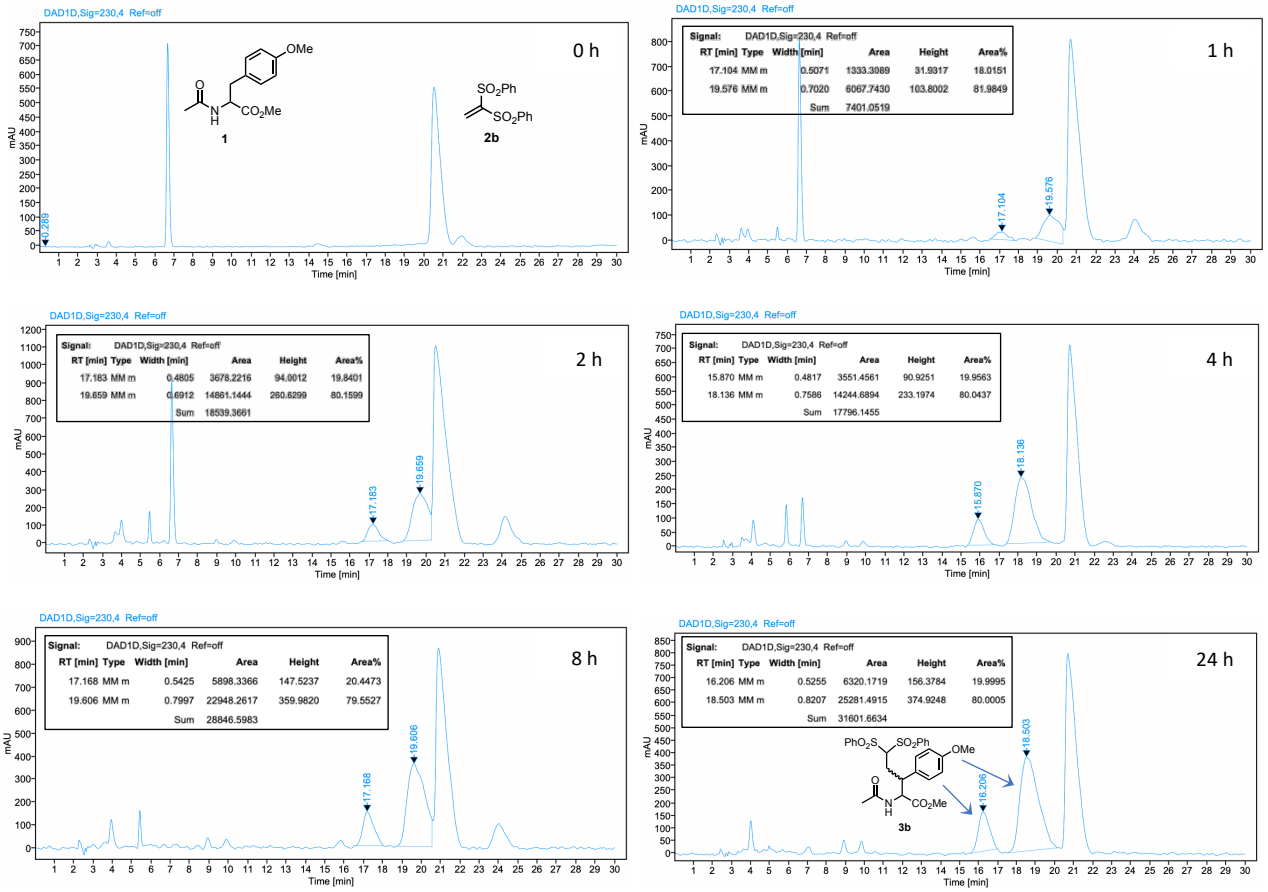


$E_{1/2}$ = + 0.65 V vs Fc/Fc+
$E_{1/2}$ = + 1.03 V vs SCE

9. Monitoring of the Model Reaction of 1 by SFC:

The photocatalytic reaction of **1** with **2b** was monitored by SFC-MS and the regioisomeric ratio was determined along the reaction from 0 to 24 h. We could observe a constant ~ 80:20 ratio (almost consistent with the isolated mixture), even at lower conversions. Moreover, the further treatment of the isolated product **3b** (3:1 d.r. mixture) under the reaction conditions did not alter the ratio. However, it cannot be ruled out a fast epimerization at the benzylic position under the catalytic conditions to deliver the observed d.r. as the equilibrated isomeric ratio.

SFC Analysis: Chiralpak IG, CO_2/MeOH: 70:30, F = 1 mL/min, λ = 230 nm, *tr* (major): 5.25 min, *tr* (minor): 5.62 min).



10. Mechanistic Studies

Determination of the photon flux at 415 nm via ferrioxalate actinometry:

According to the procedure of Yoon,[13] the photon flux of the LEDs (λ_{max} = 415 nm) was determined by standard ferrioxalate actinometry. A 0.15 M solution of ferrioxalate was prepared by dissolving potassium ferrioxalate trihydrate (0.737 g) in H_2SO_4 (10 mL, 0.05 M). A buffered solution of 1,10-phenanthroline was prepared by dissolving 1,10-phenanthroline (25 mg) and sodium acetate (5.63 g) in H_2SO_4 (25 mL of a 0.5M solution). Both solutions were stored in the dark. To determine the photon flux of the LED, the ferrioxalate solution (1.0 mL) was placed in a cuvette and irradiated for 30 min at λ_{max} = 415 nm. After irradiation, the phenanthroline solution (0.175 mL) was added to the cuvette and the mixture was allowed to stir in the dark for 1 h to allow the ferrous ions to completely coordinate to the phenanthroline. The absorbance of the solution was measured at 510 nm. A non-irradiated sample was also prepared and the absorbance at 510 nm was measured. Conversion was calculated according to the following formula:

$$molFe^{2+} = \frac{V \cdot \Delta A(510nm)}{l \cdot \varepsilon}$$

where V is the total volume (0.001175 L) of the solution after addition of phenanthroline, ΔA is the difference in absorbance at 510 nm between the irradiated and non-irradiated solutions, l is the path length (1.00 cm), and ε is the molar absorptivity of the ferrioxalate actinometer at 510 nm (11.100 $Lmol^{-1}cm^{-1}$). The photon flux can be calculated with the following equation:

$$Photon\ flux = \frac{molFe^{2+}}{\Phi \cdot t \cdot f}$$

where Φ is the quantum yield for the ferrioxalate actinometer, t is the irradiation time (1800 s), and f is the fraction of light absorbed at λ_{ex} = 415 nm by the ferrioxalate actinometer. This value is calculated using the following equation, where A (415 nm) is the absorbance of the ferrioxalate solution at 415 nm.

$$f = 1 - 10^{-A(415nm)}$$

A good agreement of the quantum yield Φ of ferrioxalate at 415 nm is 0.98, with known values of 0.997 at 405 nm and 0.962 at 436 nm.[14] The photon flux was thus calculated (average of two experiments) to be $5.14 \cdot 10^{-8}$ Einstein s^{-1}.

Determination of the reaction quantum yield:

In an oven-dried screw-cap vial, [Ir(dF(CF_3)ppy)(4,4´-dCF_3bpy)]PF_6 (2.3 mg, 0.002 mmol, 2 mol%), Ac-*L*-Tyr(Me)-OMe (25.1 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.), was dissolved in 0.5 mL dry CH_2Cl_2. The mixture was degassed by bubbling argon for several minutes and the vial was sealed. The reaction mixture was irradiated by blue LEDs for 1h. After removing the solvent under reduced pressure, the reaction yield was determined by ^{1}H-NMR (CH_2Br_2 (6.98 µL, 0.1 mmol) as internal standard), which gave the desired product in a yield of 6%. The reaction quantum yield could be calculated with the following formula:

$$\phi = \frac{mol\ of\ formed\ product}{Photon\ flux \cdot t \cdot f}$$

with a photon flux of $5.14 \cdot 10^{-8}$ Einsteins s^{-1}, t = 3600 s and f > 0.999.

The reaction quantum yield (Φ) was determined as 0.03.

Stern-Volmer quenching

Stern-Volmer experiments tracking the quenching of the phosphorescence of [Ir(dF(CF_3)ppy)$_2$(4,4'-dCF_3bpy)]PF_6 were conducted on an Jasco FP-8500 spectrofluorometer. In a typical procedure, the sample was dissolved in a cuvette (1 cm) in 1 mL of a degassed stock solution of the photocatalyst in CH_2Cl_2 (concentration of [Ir] 5.12×10^{-5} M). Samples were irradiated with 410 nm and the emission was detected at 560 nm. The data are graphically represented by Microsoft Excel.

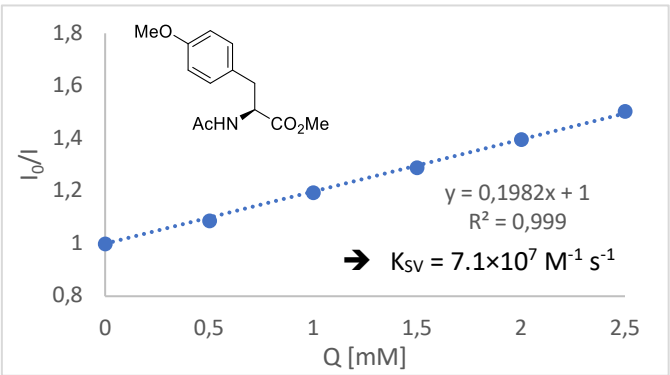
The Stern-Volmer quenching constant K_{SV} was calculated according the Stern-Volmer equation:

$$\frac{I_0}{I} = 1 + K_{SV}\tau_0[Q]$$

where I_0 is the luminescence without the quencher, I is the intensity with the quencher, τ_0 is the lifetime of the excited photocatalyst (279 ns for [Ir(dFCF_3ppy)$_2$(dCF_3bpy)]PF_6)[15] and [Q] is the concentration of the quencher.

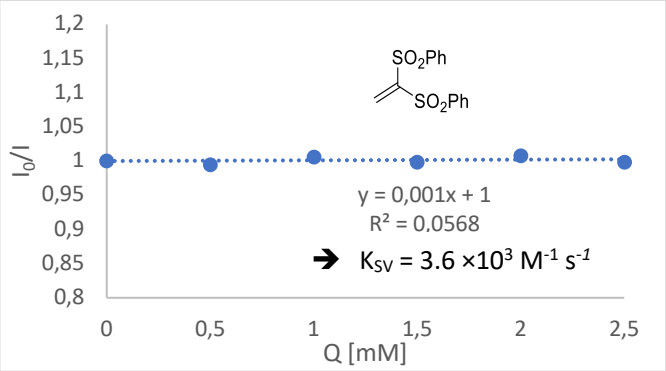
Quenching experiments with Ac-L-Tyr(Me)-OMe ***1a***

Quencher (mM)	*Emission (560 nm)*	*I_0/I*
0	6250	1
0.5	5748	1.087
1.0	5236	1.194
1.5	4844	1.290
2.0	4478	1.396
2.5	4154	1.504



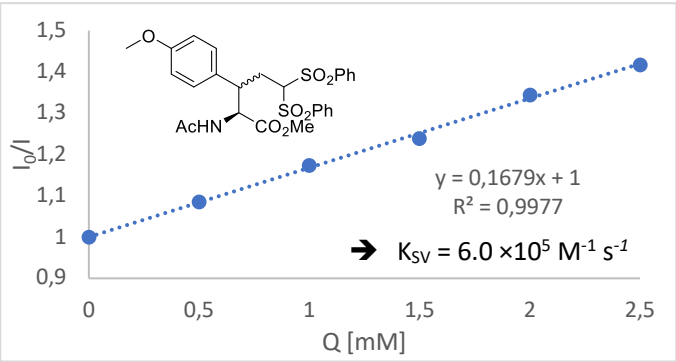
Quenching experiments with 1,1-Bis(phenylsulfonyl)ethylene ***2b***

Quencher (mM)	*Emission (560 nm)*	*I_0/I*
0	6250	1
0.5	6280	0.995
1.0	6210	1.006
1.5	6260	0.998
2.0	6200	1.008
2.5	6260	0.999



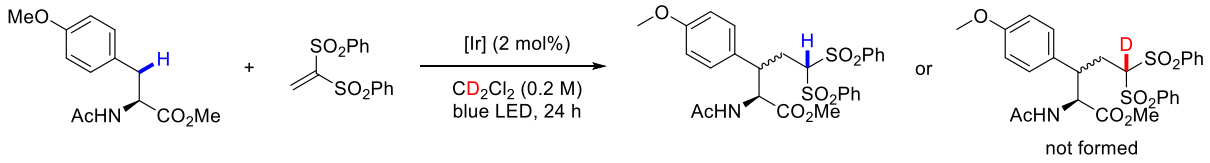
Quenching experiments with methyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis (phenylsulfonyl) pentanoate ***3b***

Quencher (mM)	*Emission (560 nm)*	*I_0/I*
0	6250	1
0.5	5753	1.086
1.0	5324	1.174
1.5	5042	1.240
2.0	4647	1.345
2.5	4411	1.417



Although the product **3b** is also a quencher, no difunctionalized products could be detected under the standard conditions, presumably due to steric effects.

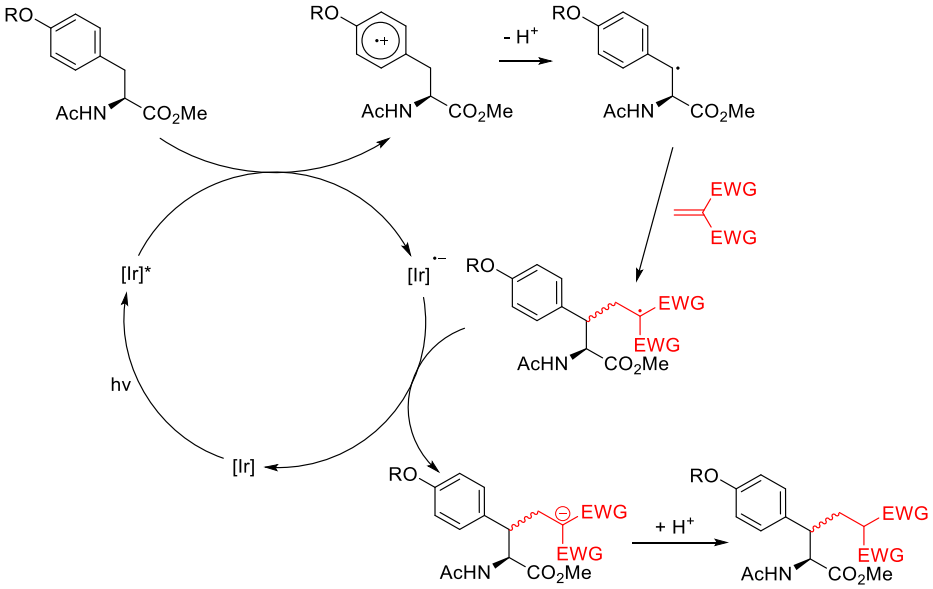
Reaction in deuterated CD_2Cl_2



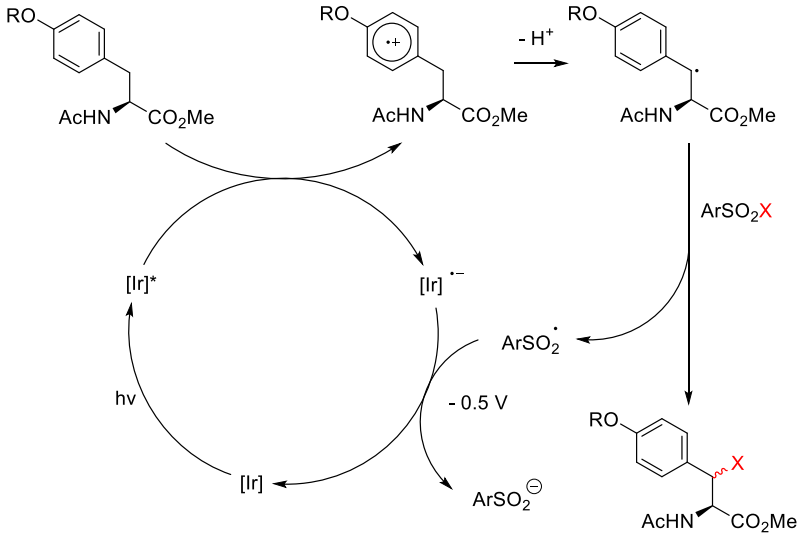
In an oven-dried screw-cap vial, [Ir(dF(CF_3)ppy)(4,4´-dCF_3bpy)]PF_6 (2.3 mg, 0.002 mmol, 2 mol%), Ac-*L*-Tyr(Me)-OMe (25.1 mg, 0.1 mmol, 1.0 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (154.2 mg, 0.5 mmol, 5.0 equiv.), was dissolved in 0.5 mL CD_2Cl_2. The mixture was degassed by bubbling argon for several minutes and the vial was sealed. The reaction mixture was irradiated by blue LEDs for 24 h. The crude was purified by flash column chromatography (50→60% EtOAc/pentane), obtaining the product (51.9 mg, 0.093 mmol, 93%, 3:1 d.r.) as a colorless solid. The ^{1}H-NMR spectrum showed no deuterium incorporation in the product.

11. Proposed Mechanisms

For alkenes as radical acceptors:



For aryl sulfonyl compounds as radical acceptors:



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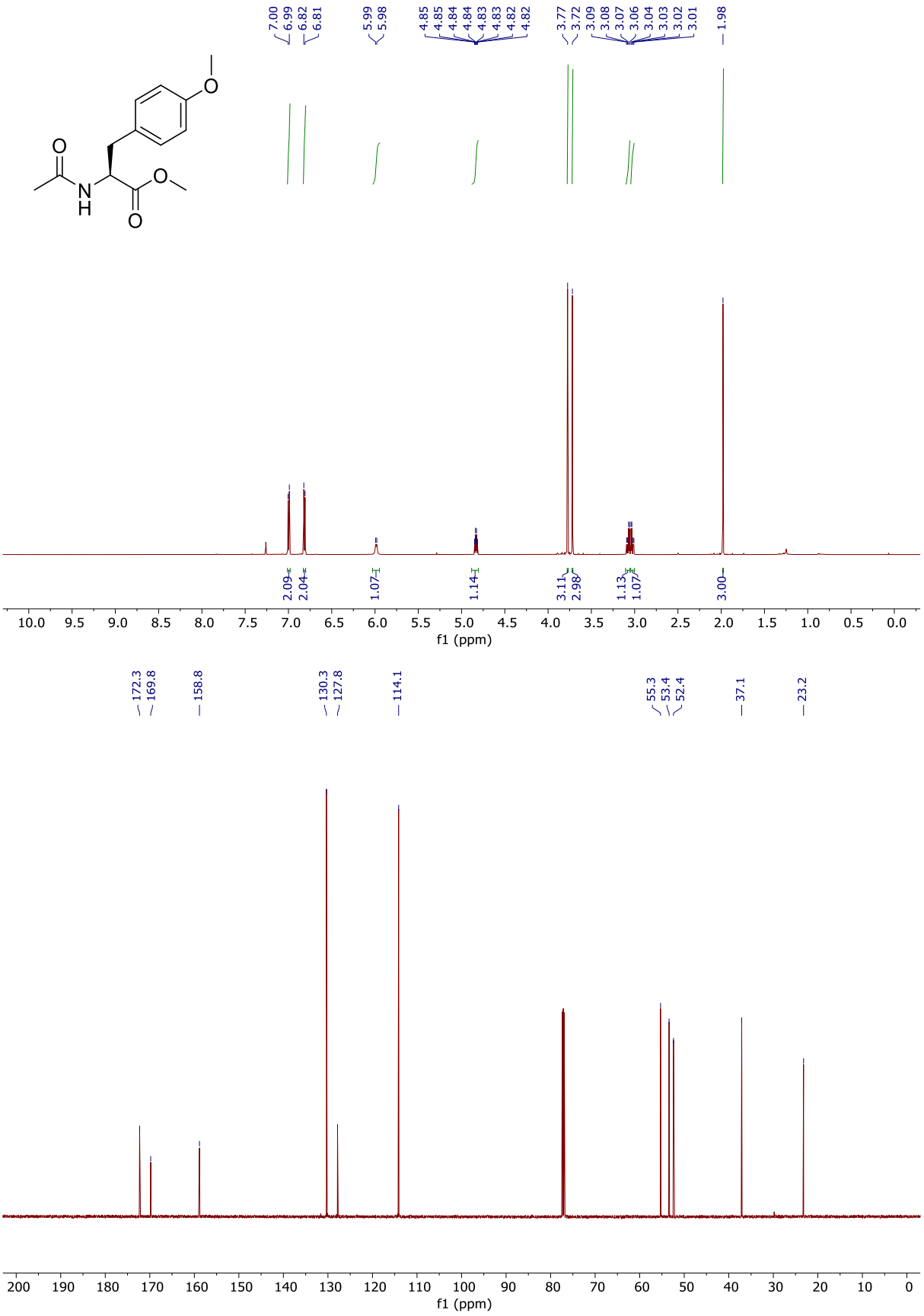
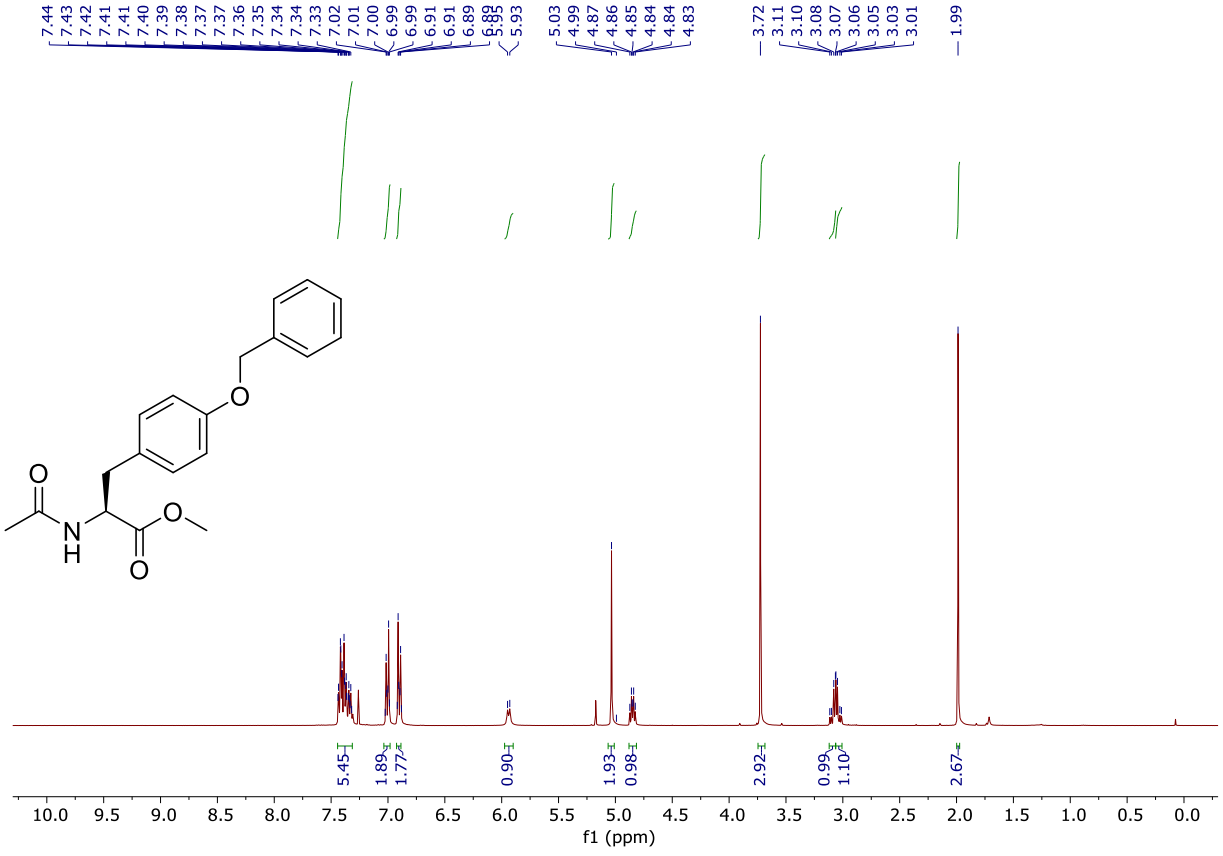
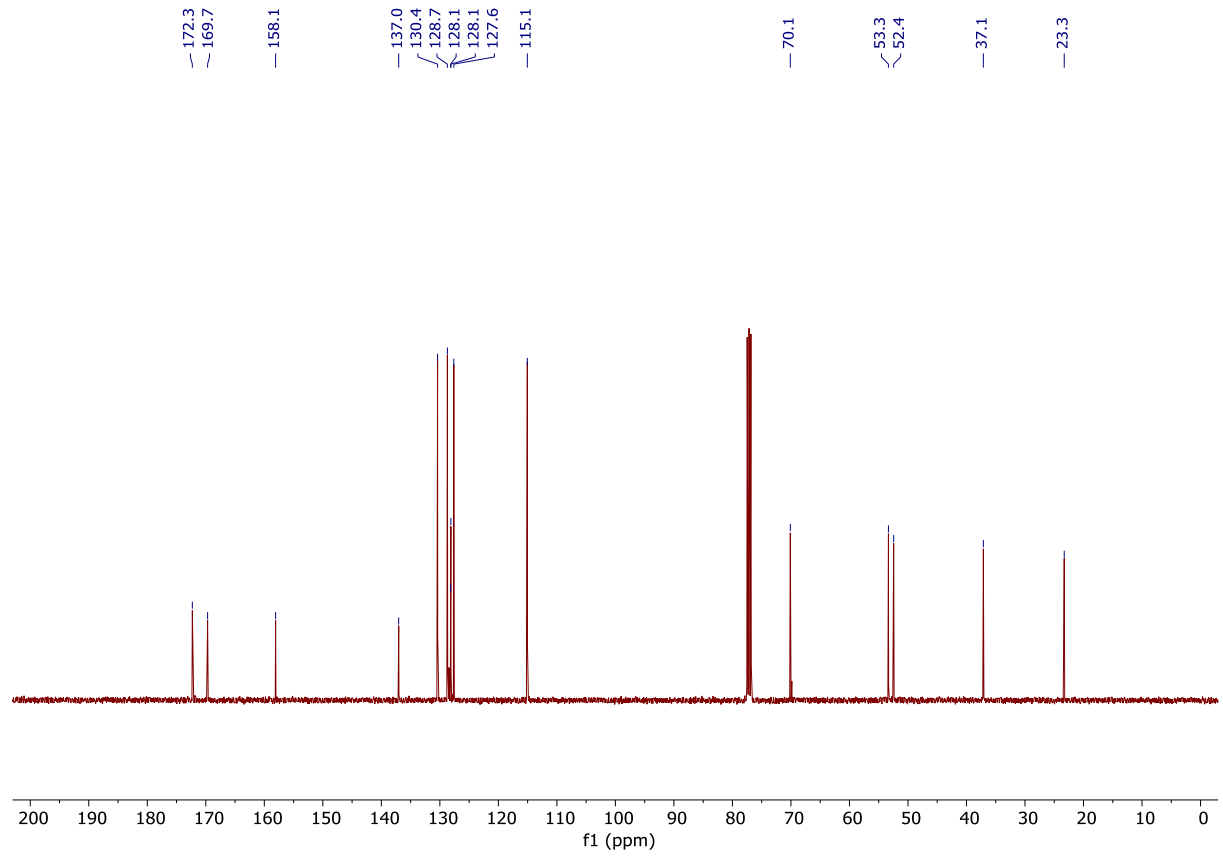
13. NMR Collection

*Methyl (S)-2-acetamido-3-(4-methoxyphenyl)propanoate (**1**)*

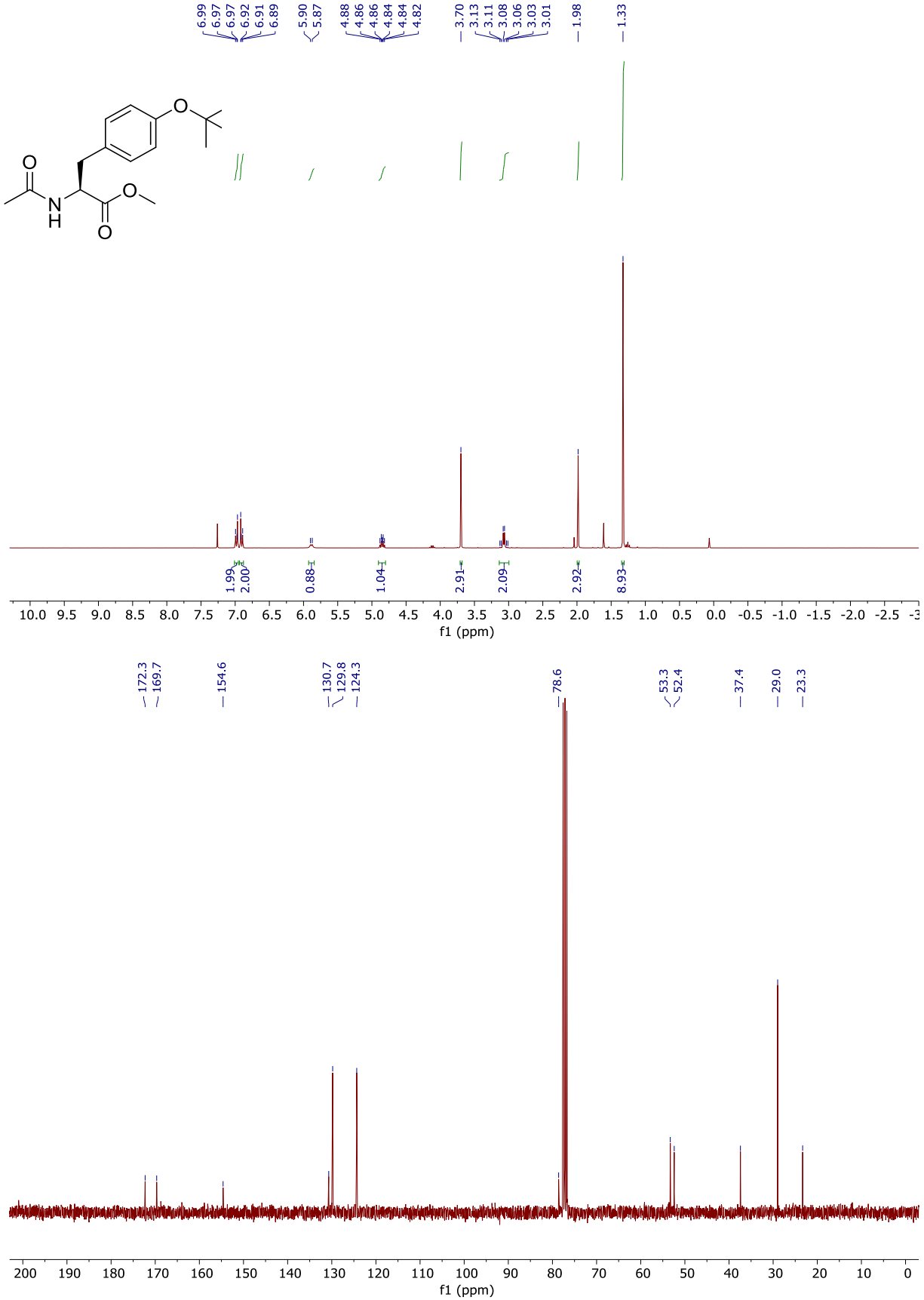


Methyl (S)-2-acetamido-3-(4-(benzyloxy)phenyl)propanoate

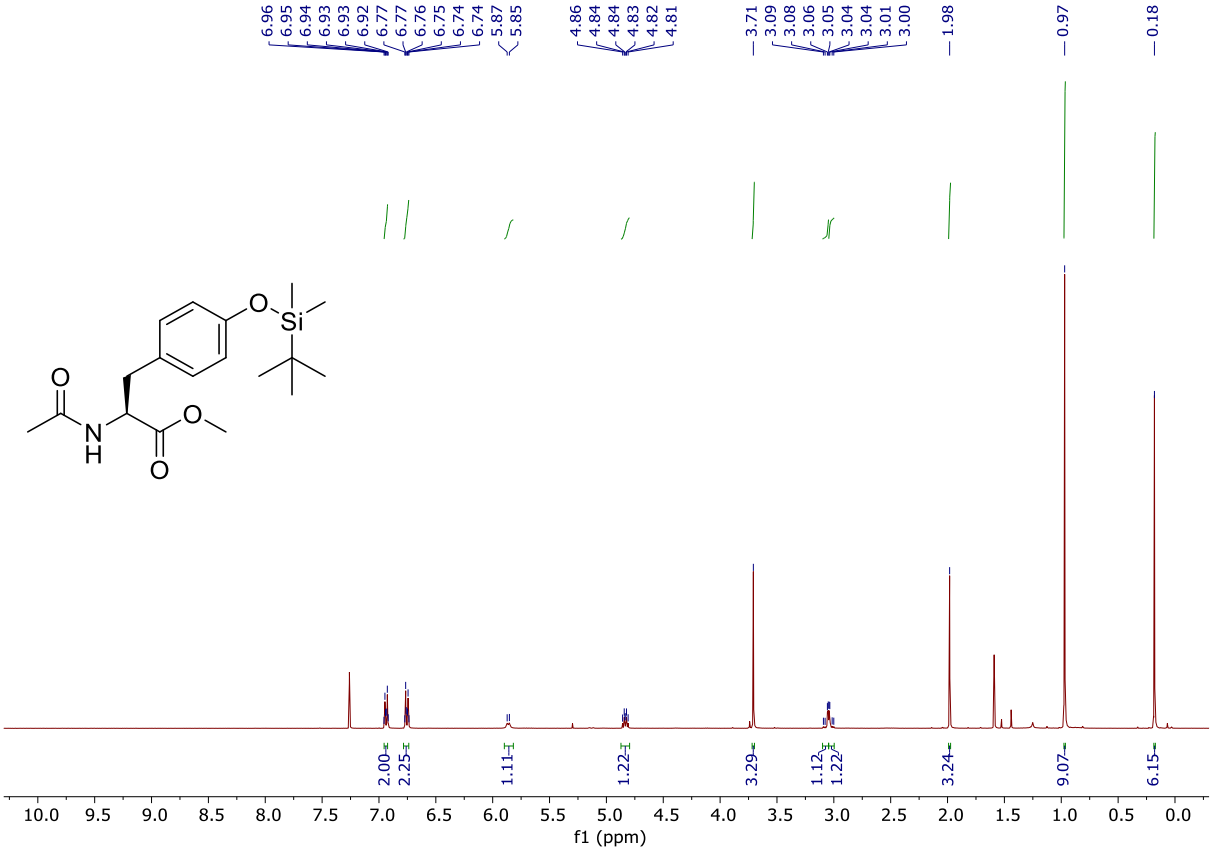


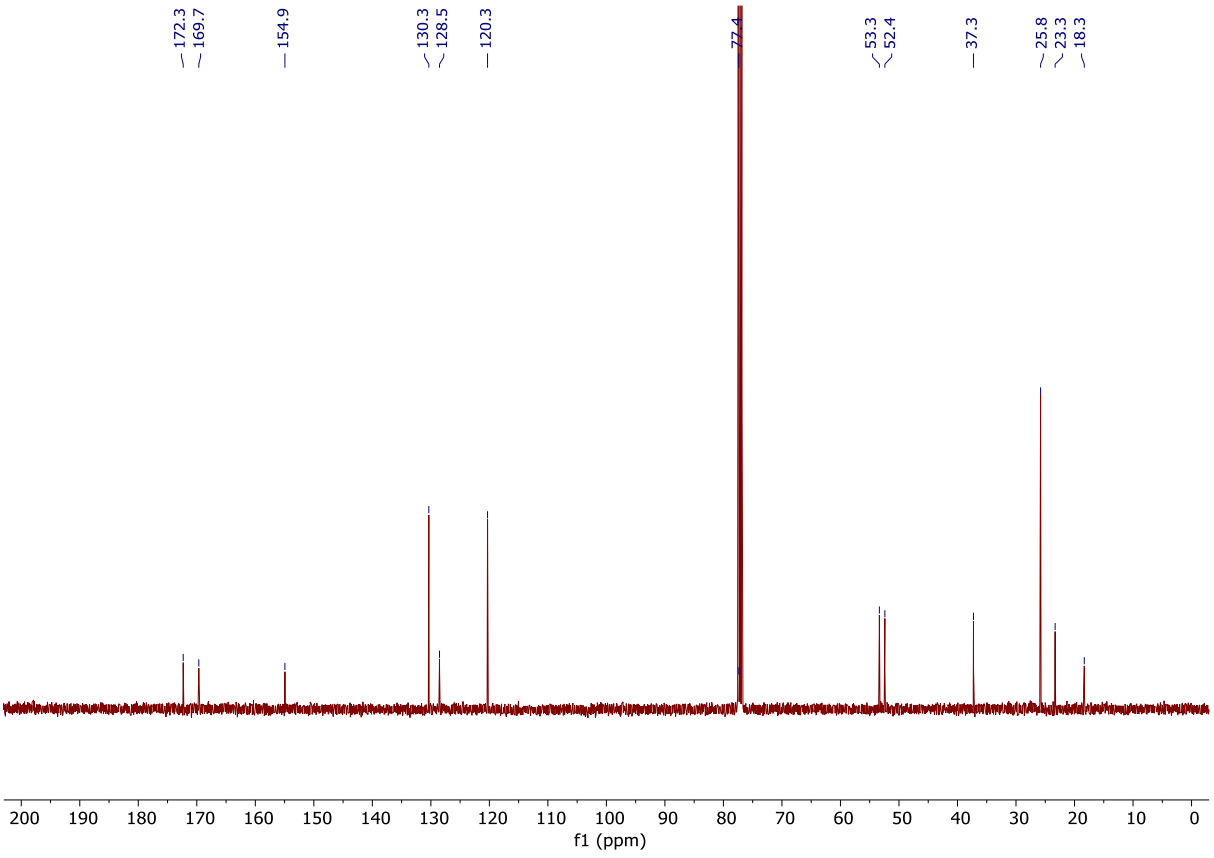


Methyl (S)-2-acetamido-3-(4-(tert-butoxy)phenyl)propanoate

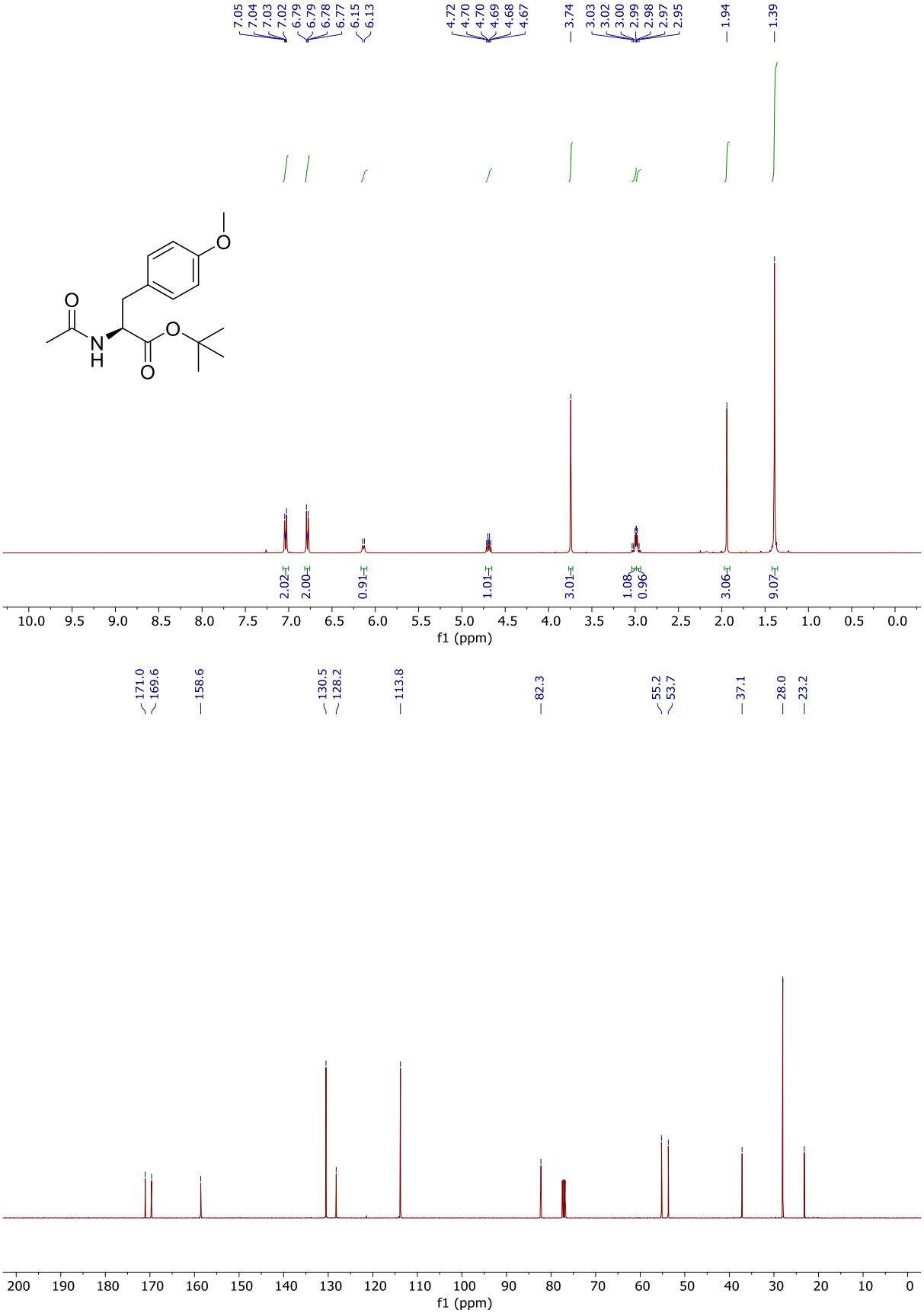


Methyl (S)-2-acetamido-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate

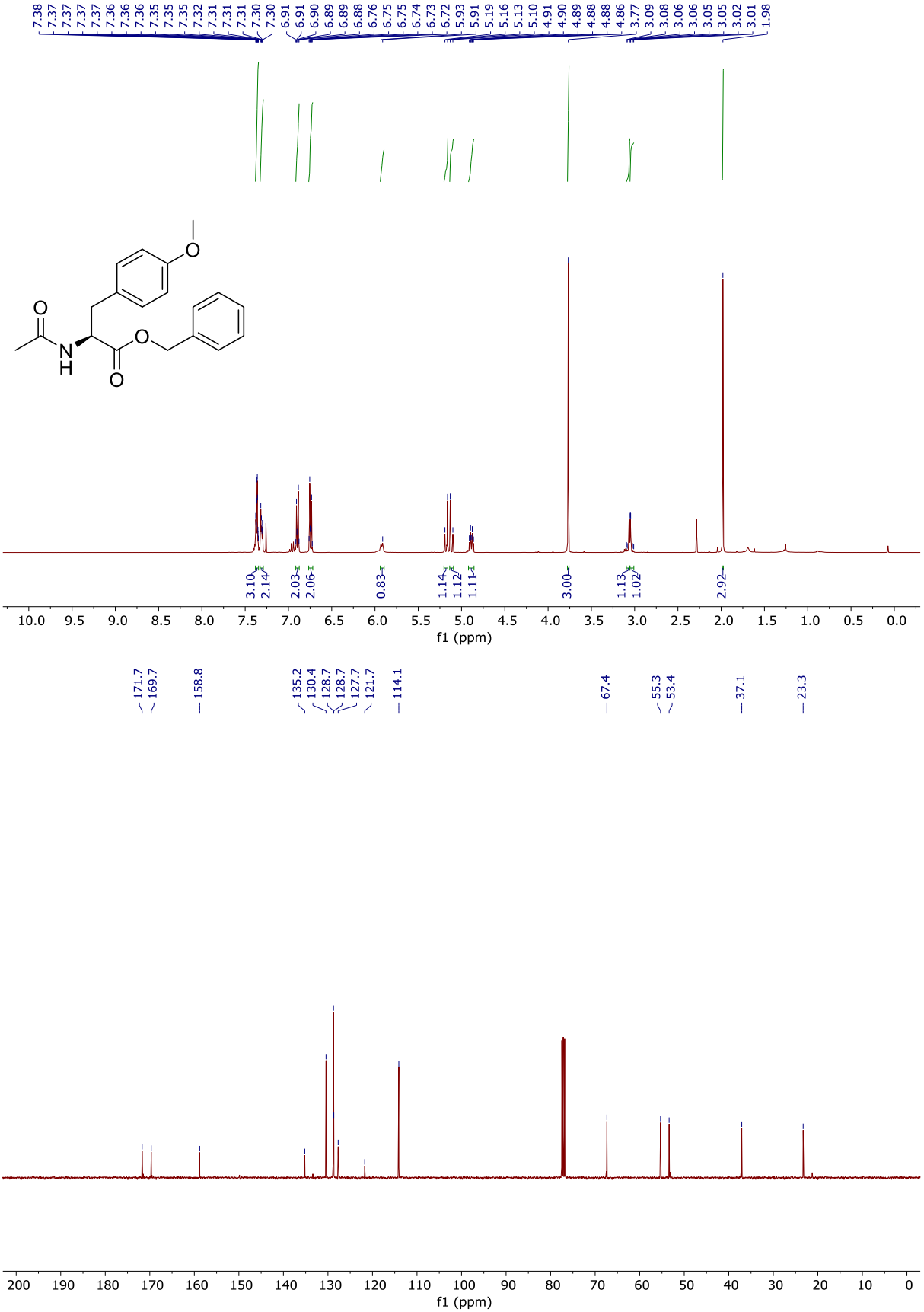




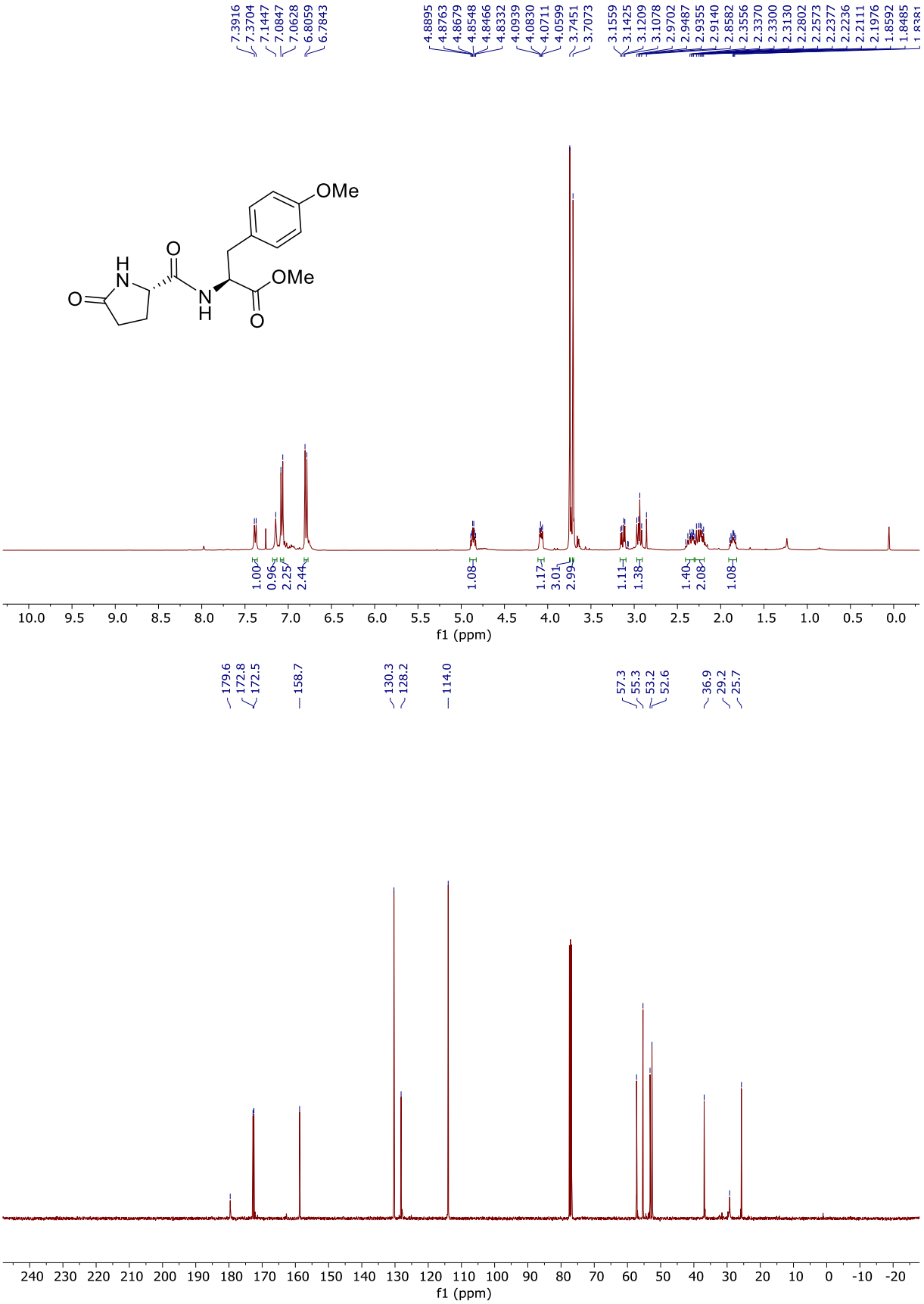
tert-Butyl (S)-2-acetamido-3-(4-methoxyphenyl) propanoate



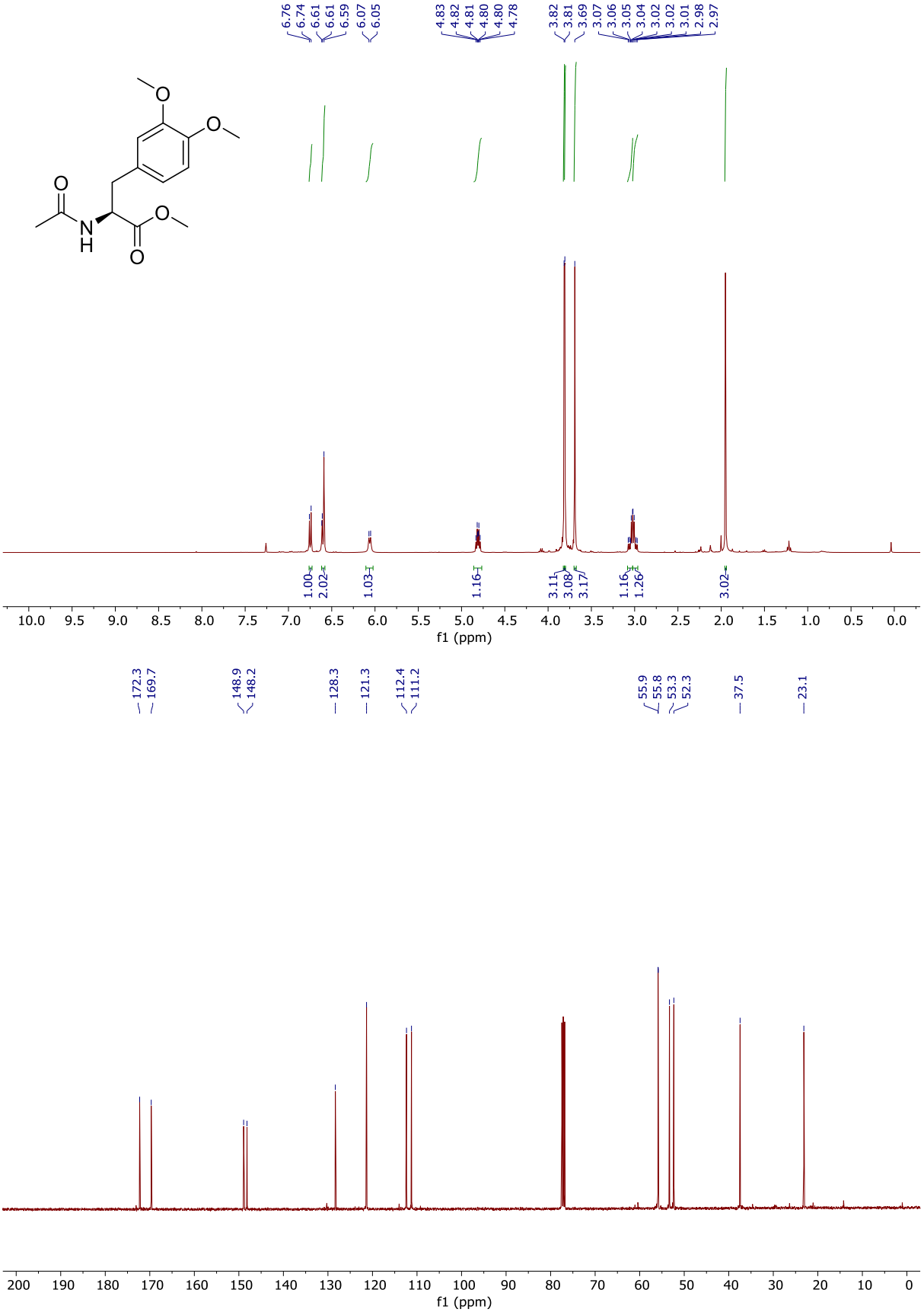
Benzyl (S)-2-acetamido-3-(4-methoxyphenyl)propanoate



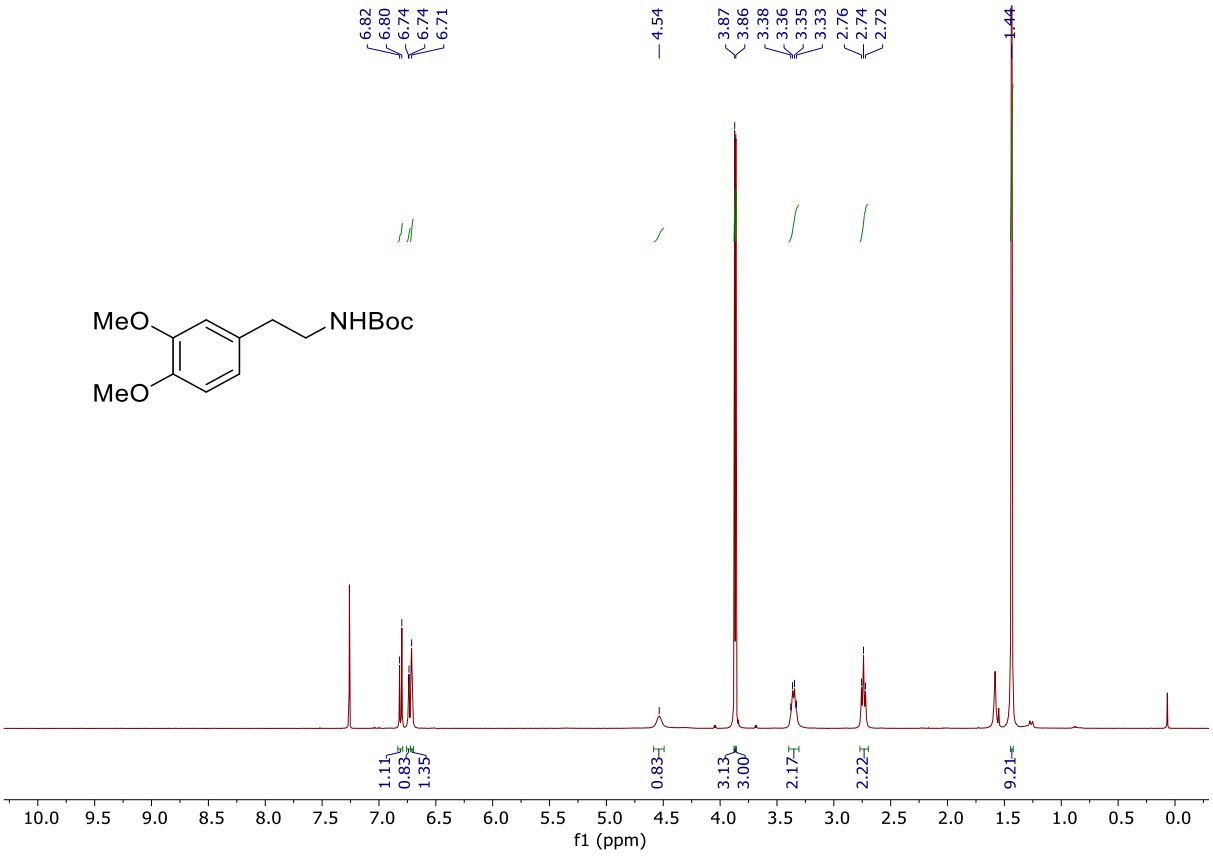
Methyl (S)-3-(4-methoxyphenyl)-2-((S)-5-oxopyrrolidine-2-carboxamido)propanoate

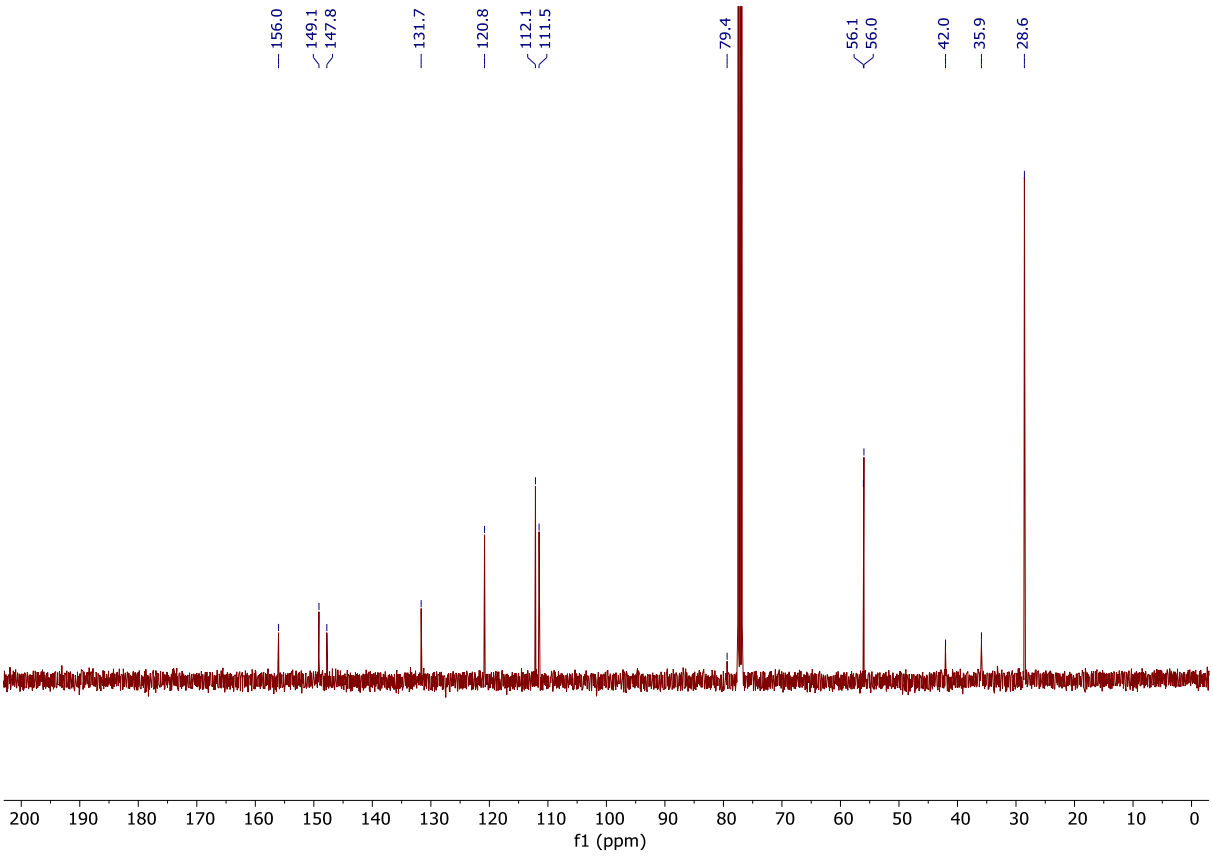


Methyl (S)-2-acetamido-3-(3,4-dimethoxyphenyl)propanoate

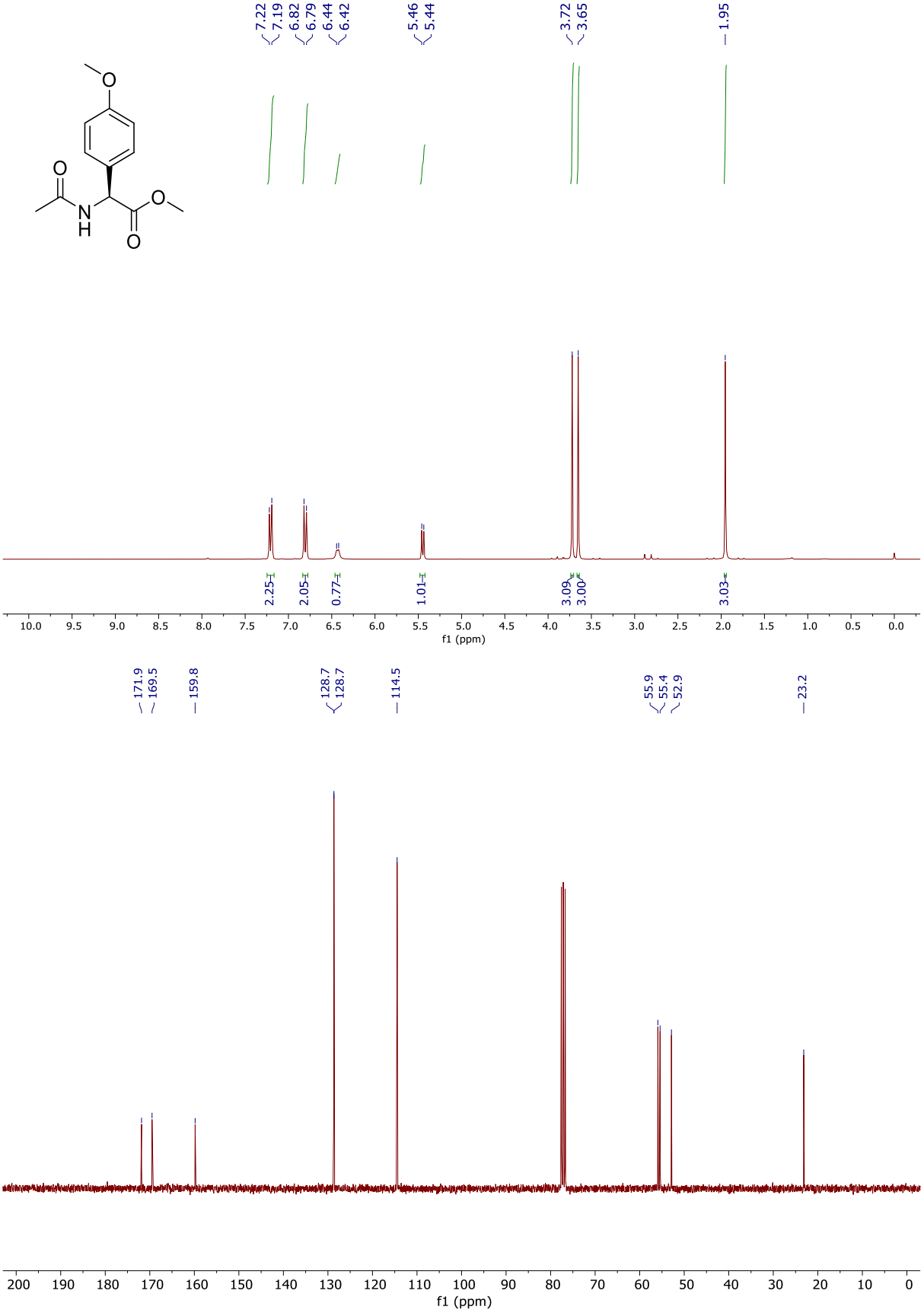


tert-Butyl (3,4-dimethoxyphenethyl) carbamate

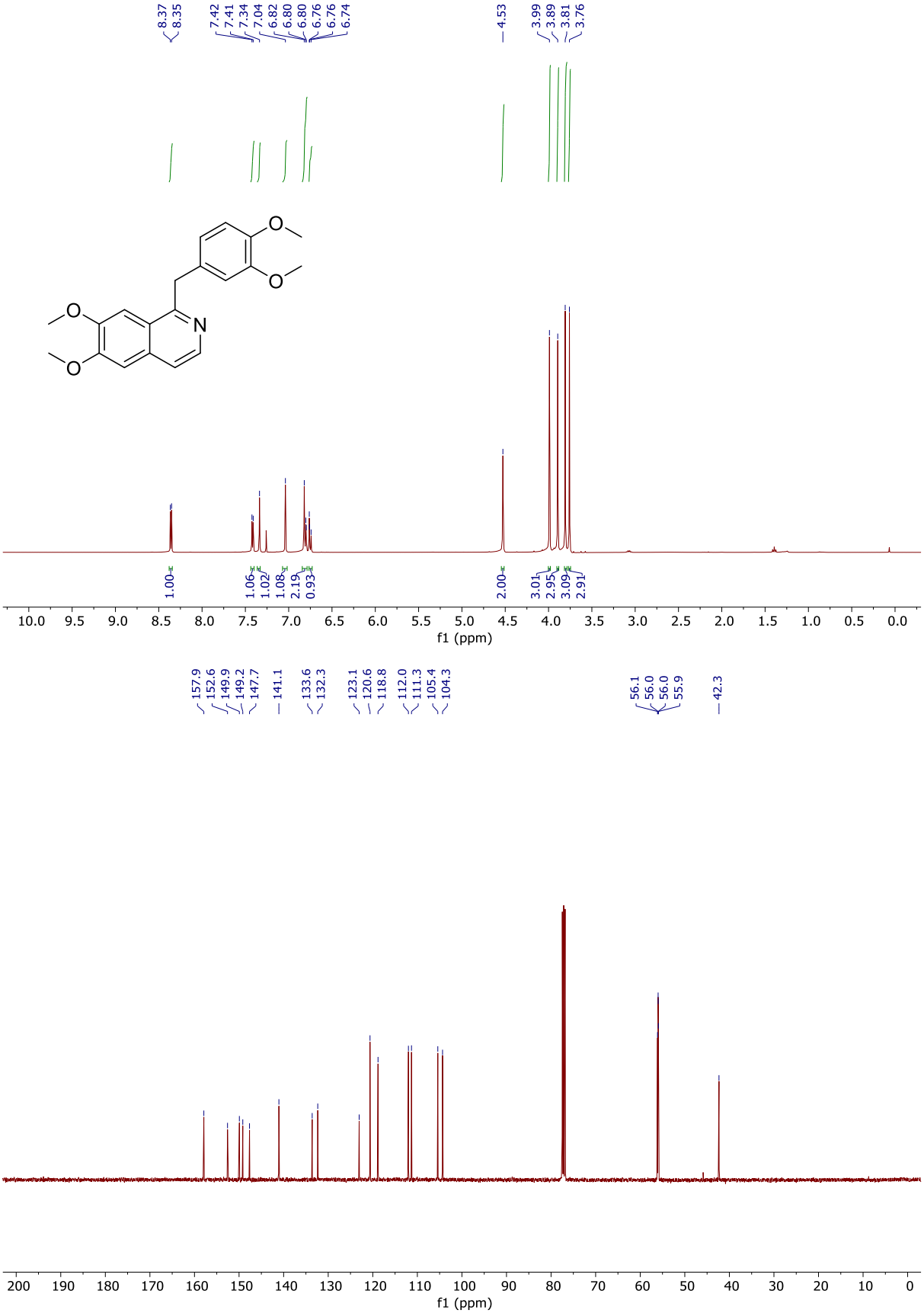




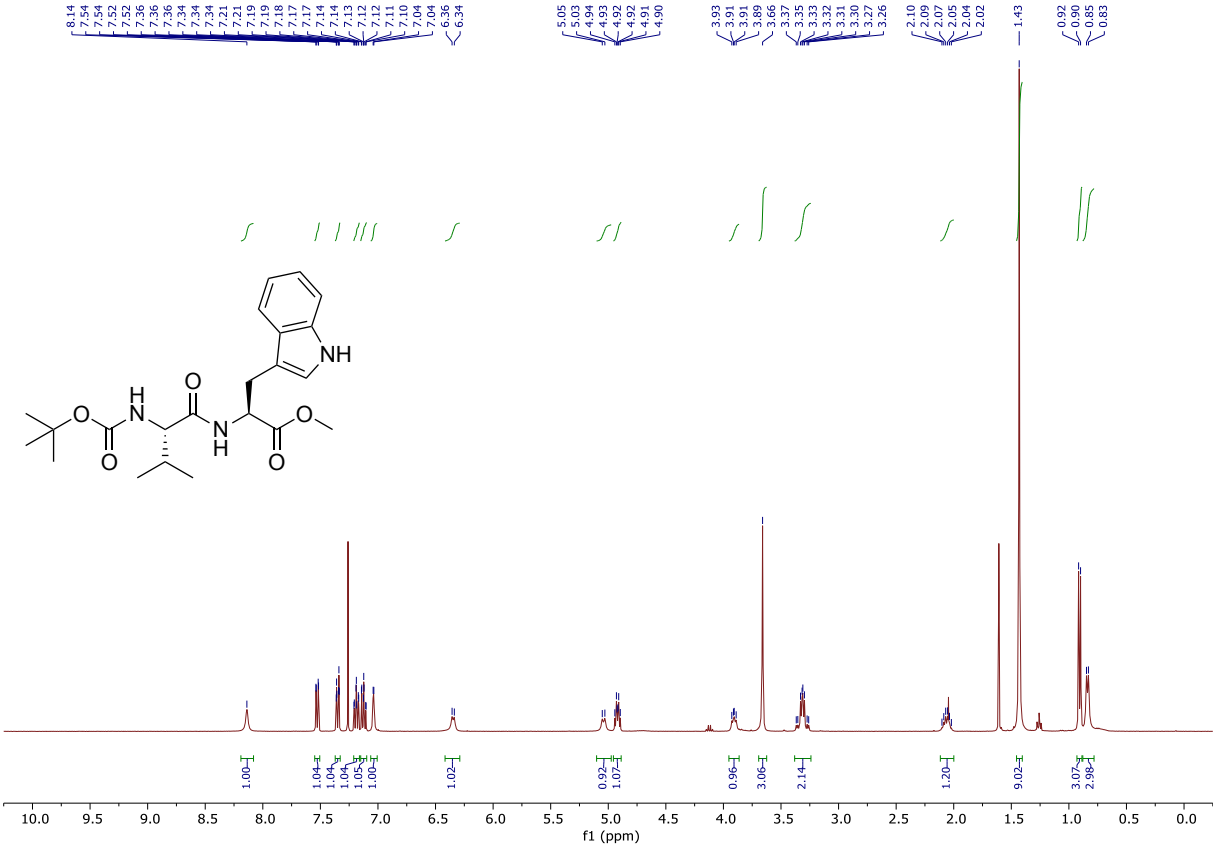
Methyl (S)-2-acetamido-2-(4-methoxyphenyl)acetate



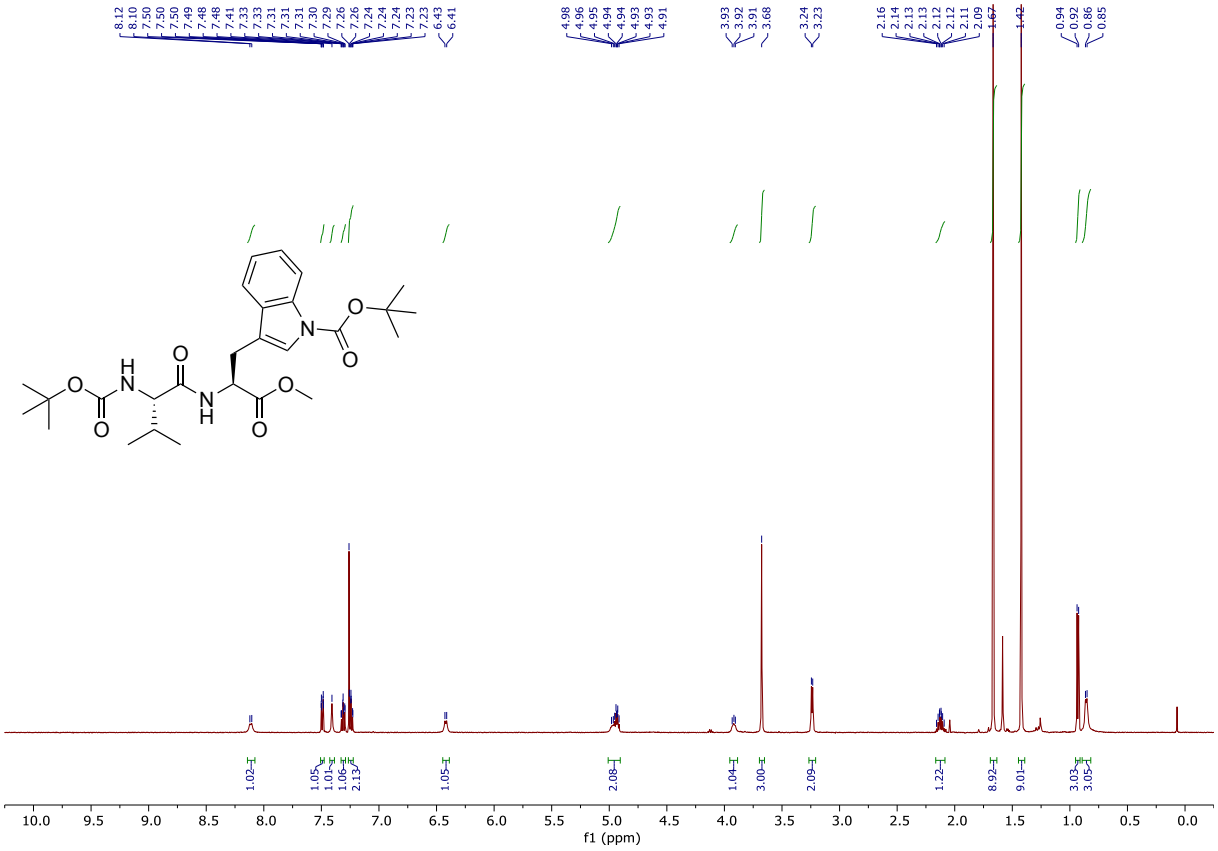
1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline (Papaverine)

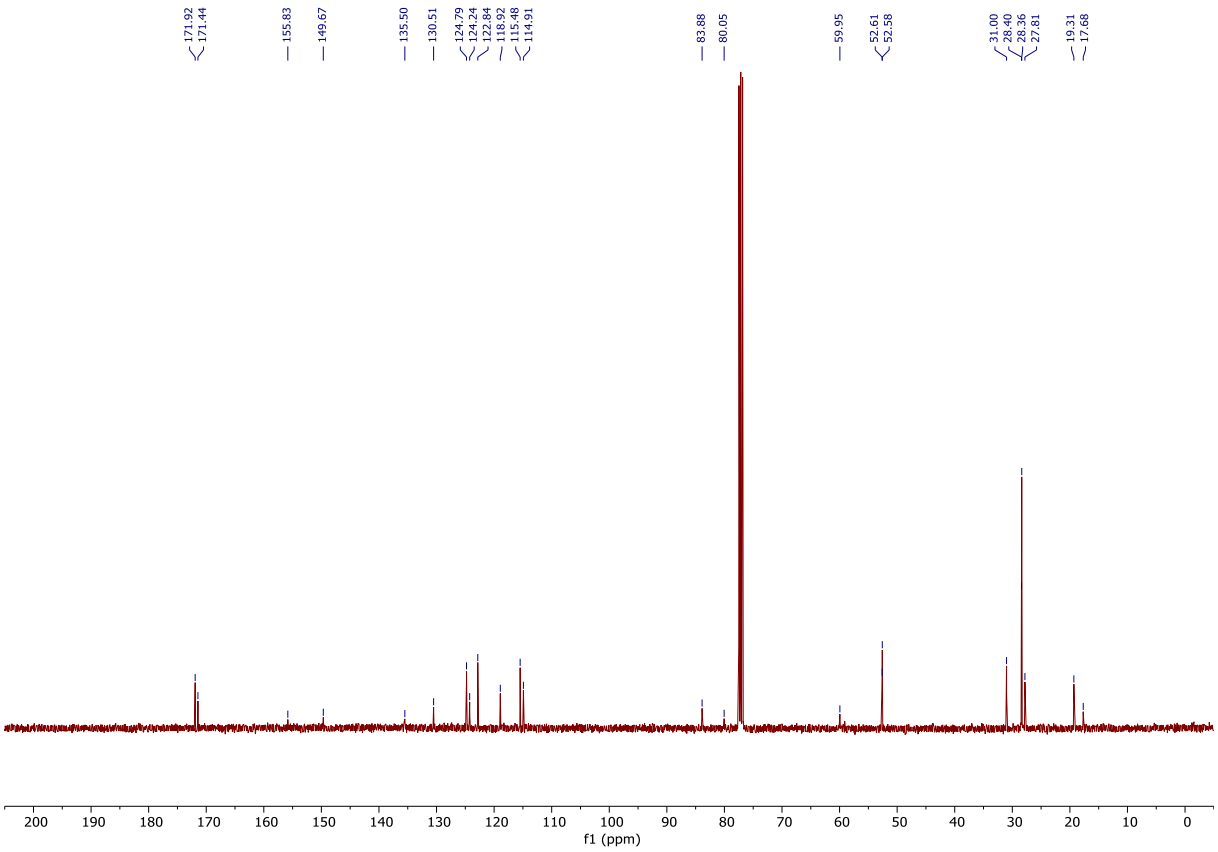


Methyl (tert-butoxycarbonyl)-L-valyl-L-tryptophanate

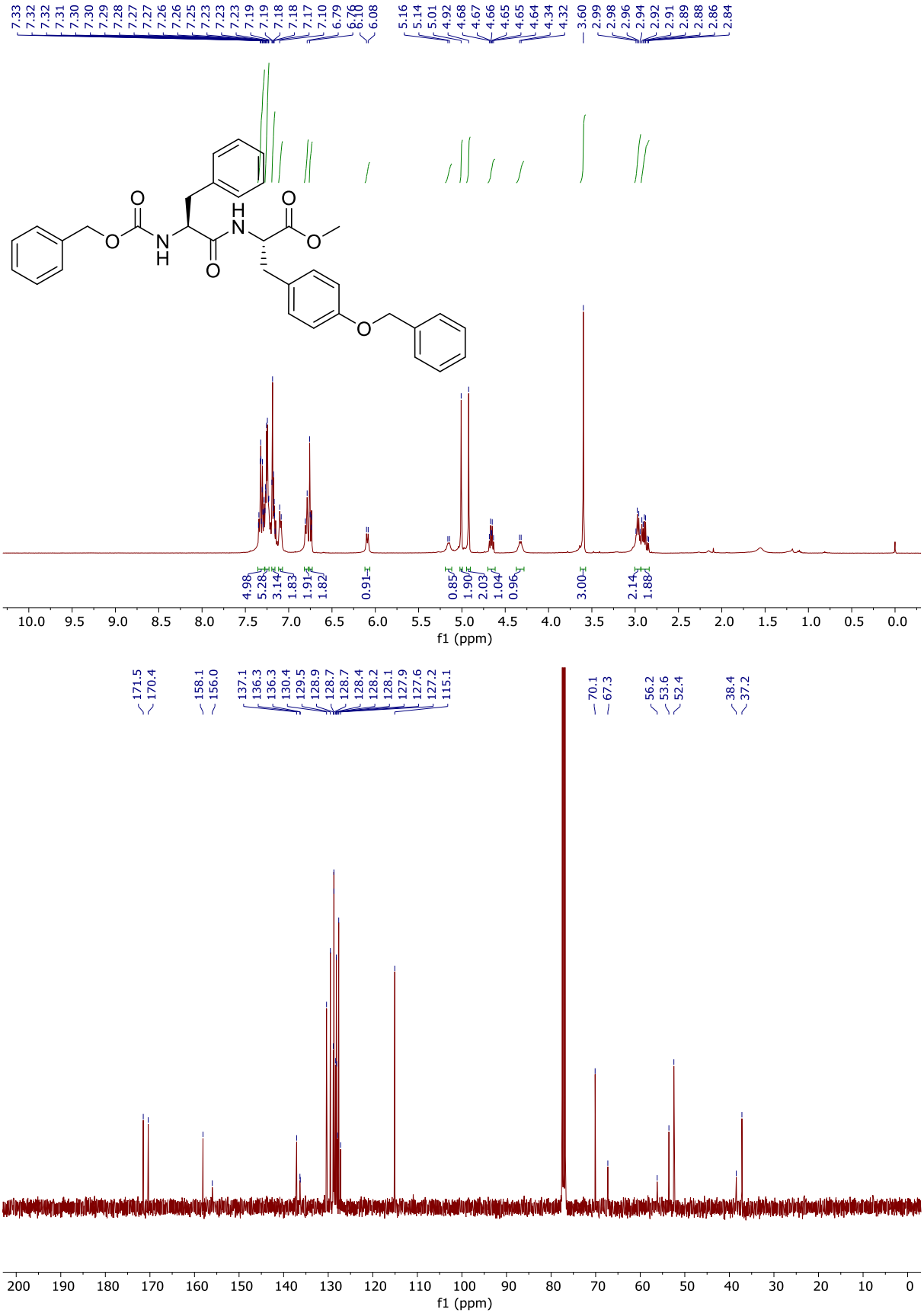


tert-Butyl 3-((S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate

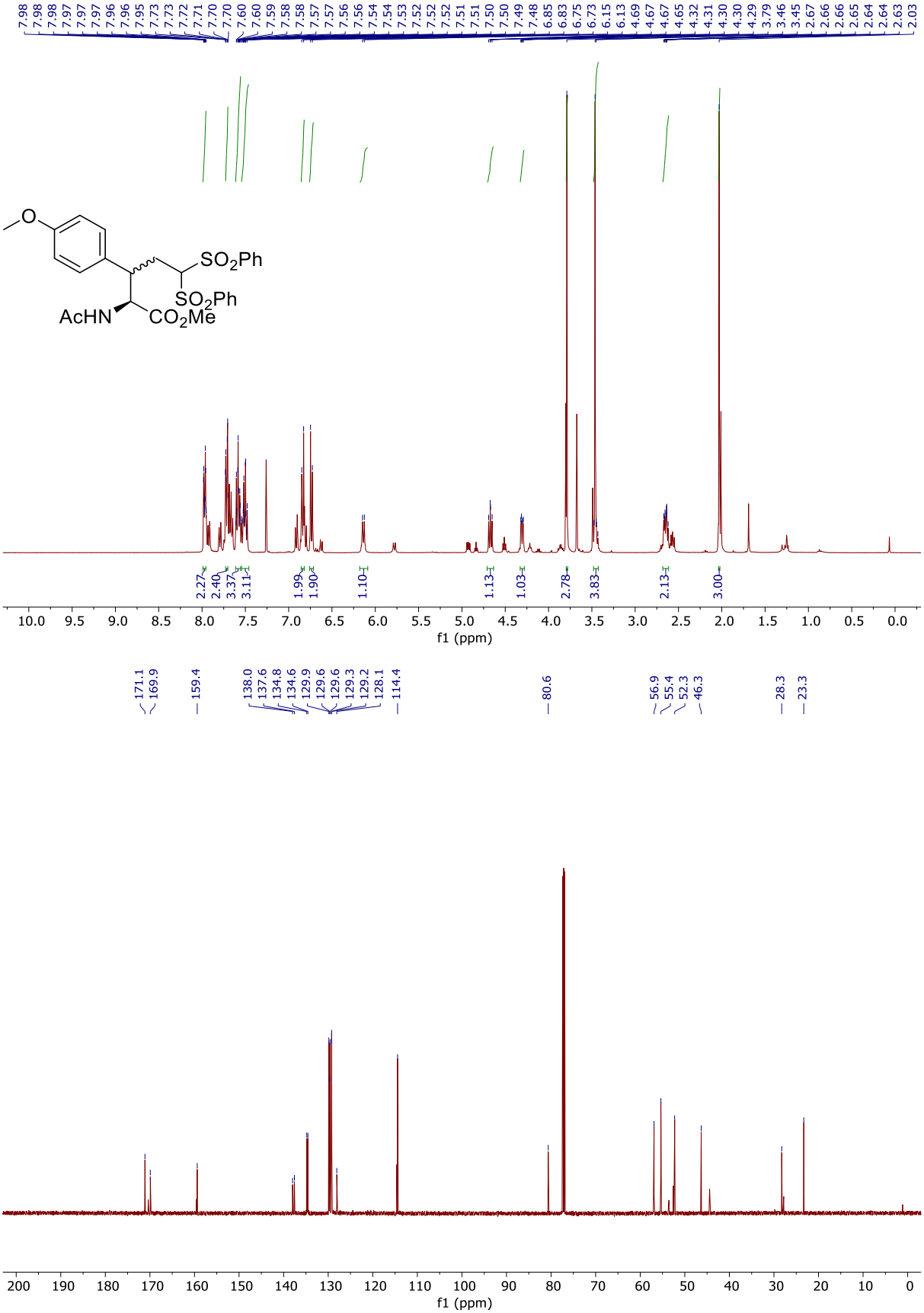




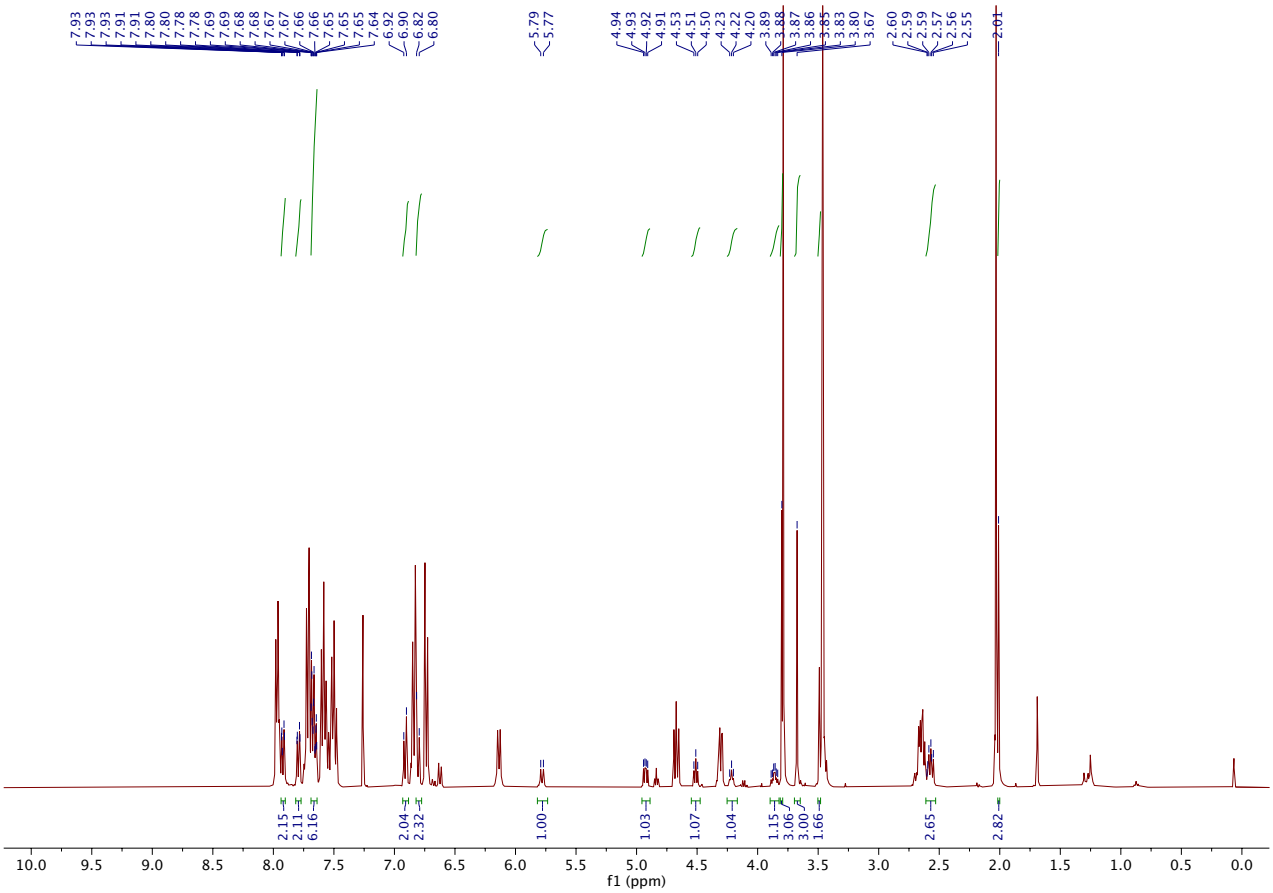
Methyl (S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-3-(4-(benzyloxy)phenyl) propanoate

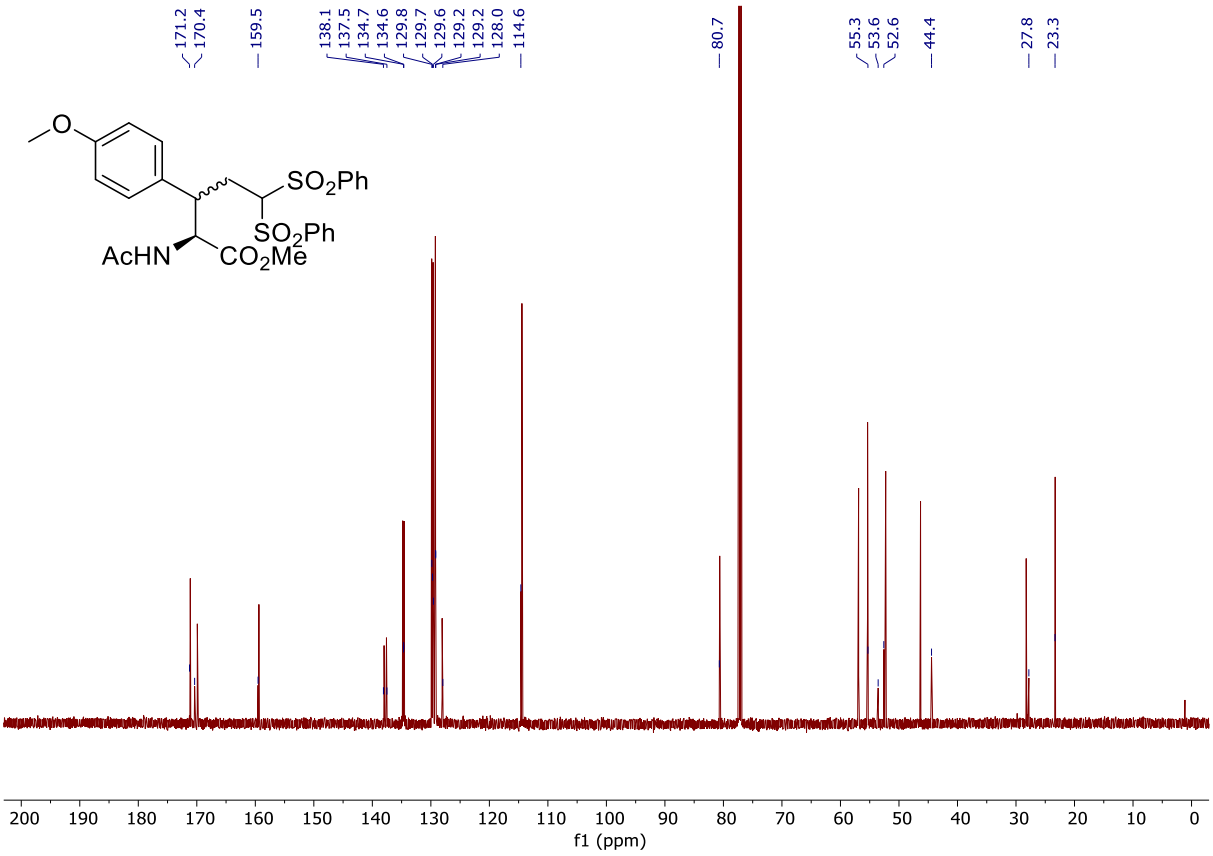


*Methyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (major **3b**)*

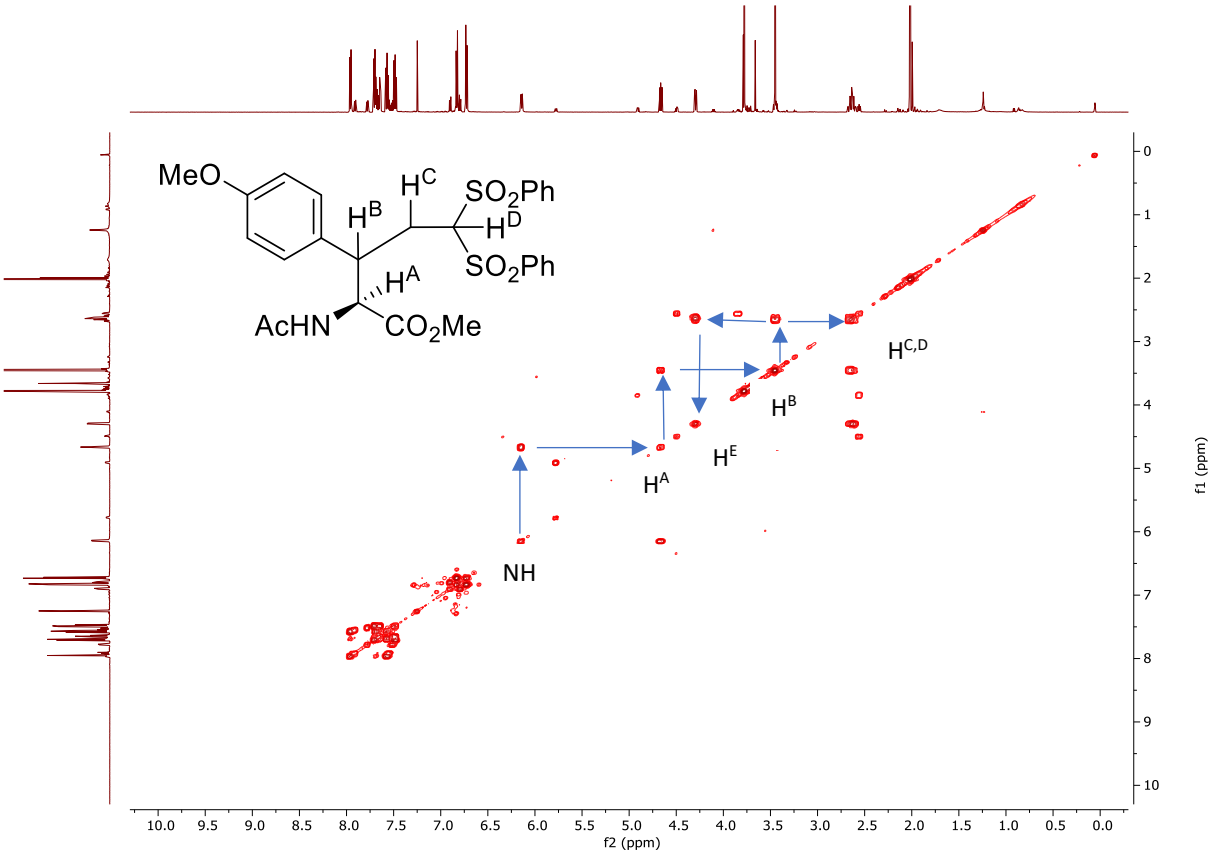


*Methyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (minor **3b**)*

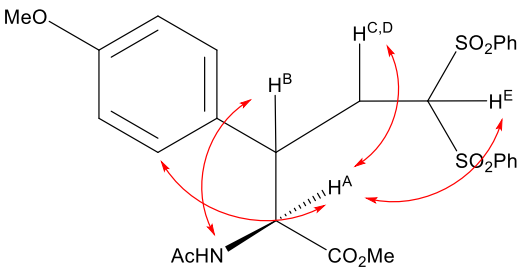




*COSY-Spectrum of **3b**:*



*Determination of the configuration of the major **3b**:*



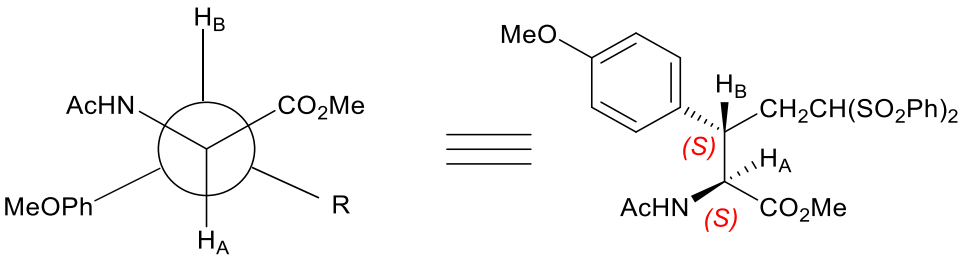
NH: 6.14 ppm (d, *J* = 8.5 Hz, 1H),

H^A: 4.67 ppm (dd, *J* = 8.7, 7.1 Hz, 1H),

H^B: 3.42 ppm (m, 1H)

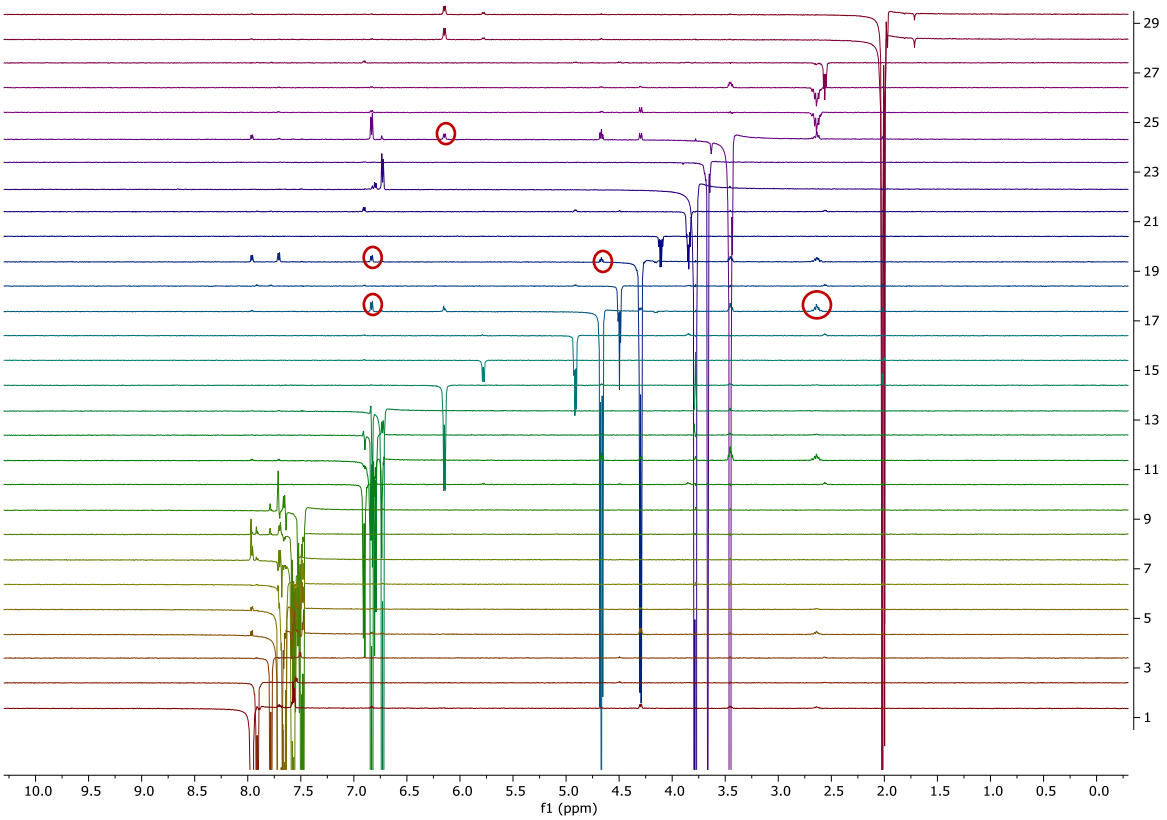
$H^{C,D}$: 2.68 – 2.61 ppm (m, 2H),

H^E: 4.33 – 4.28 ppm (dd, *J* = 8.5, 3.1, 1H)

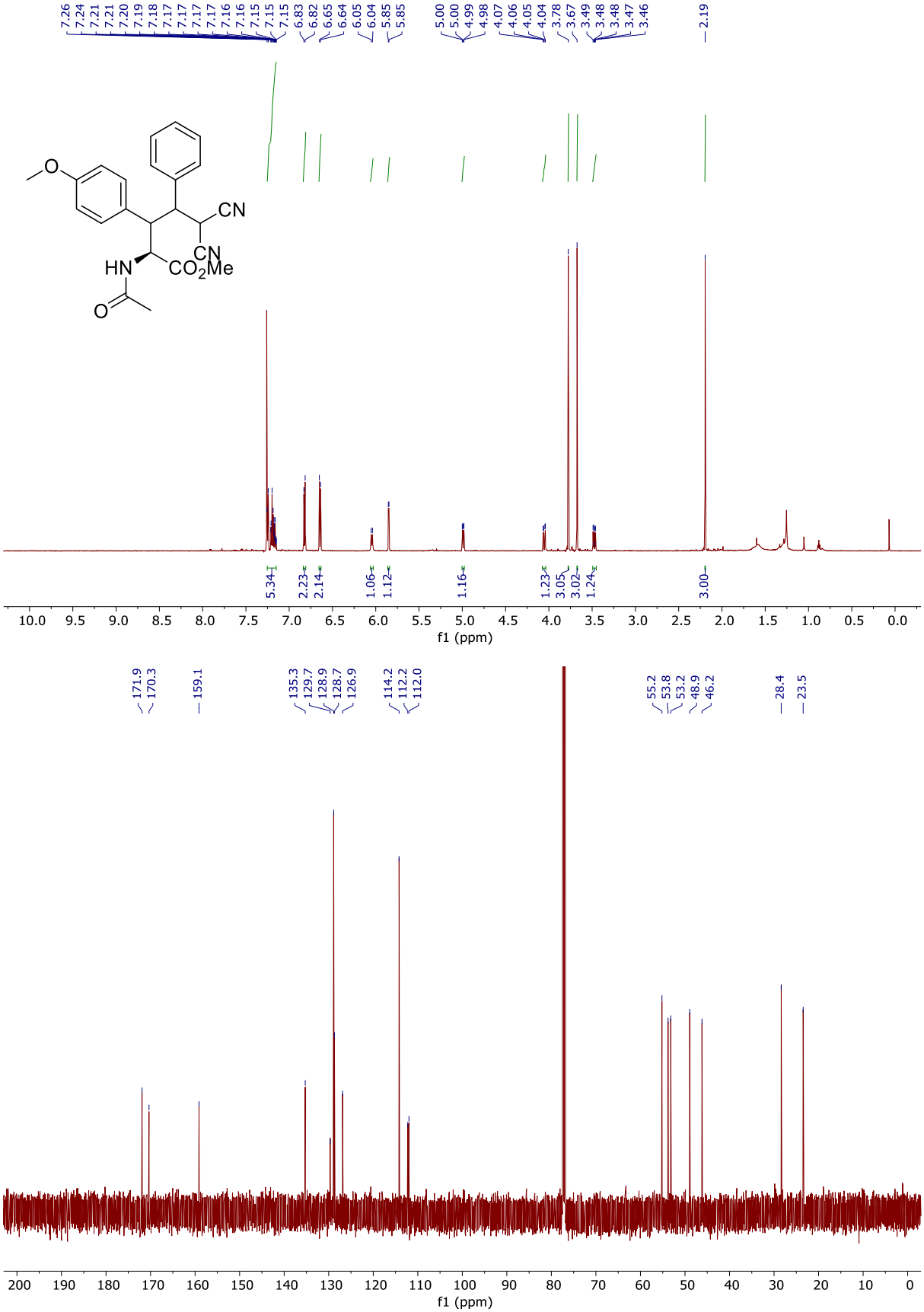


The coupling constant of the two methylene protons of the major isomer is *J* (H^A, H^B) is 7.1 Hz, which suggests a predominant *anti*-conformation as shown on Newman projection above. In the 1D-NOESY spectra, strong NOE interactions between H^A and H^C and also H^E with no NOE between NH and H^C, H^D or H^E were consistent with gauche conformation of these groups and a (*S*) configuration at Tyr β-carbon center.

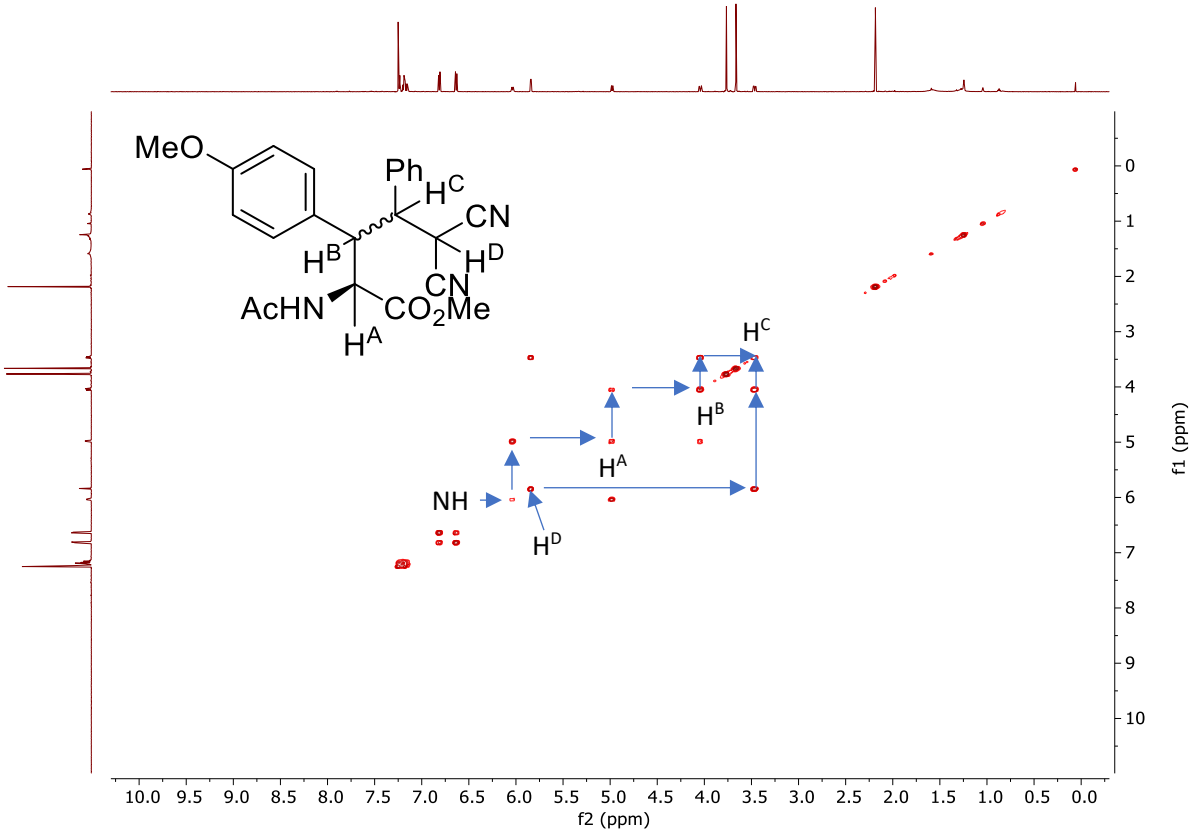
1D-NOESY-spectra of ***3b:***



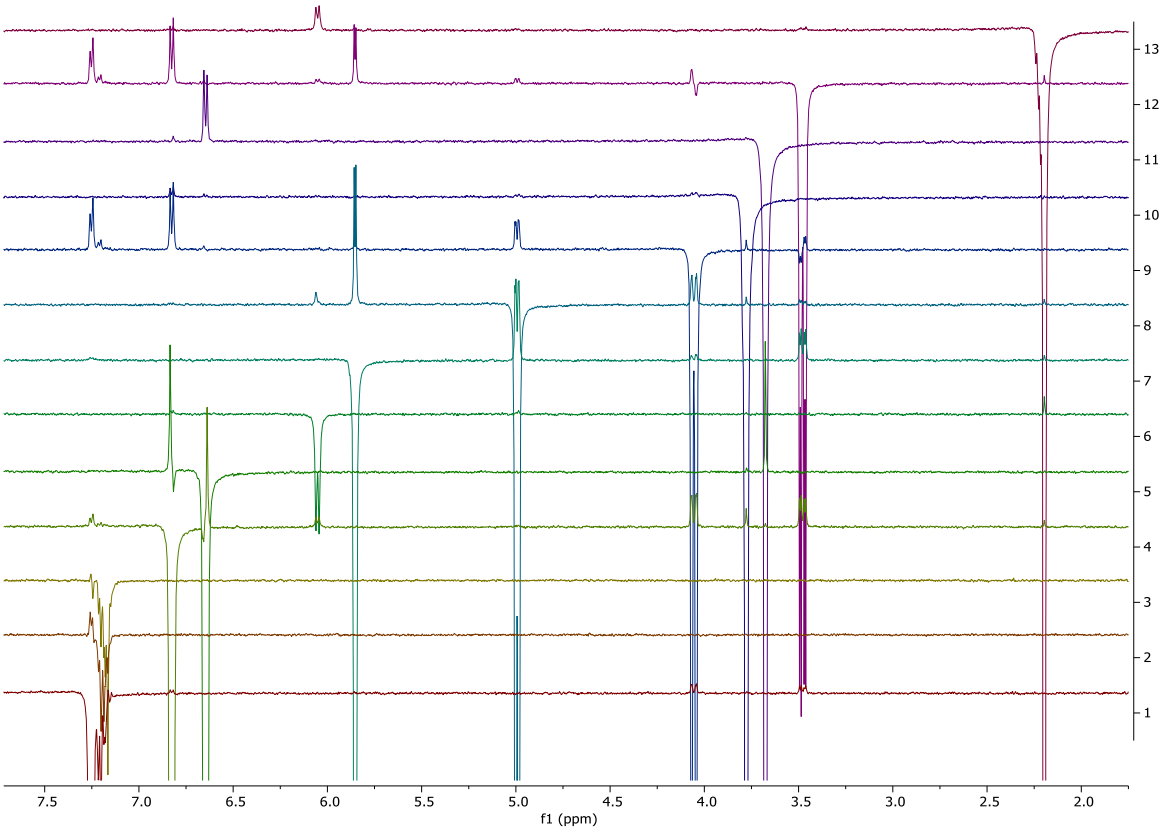
*Methyl (2S)-2-acetamido-5,5-dicyano-3-(4-methoxyphenyl)-4-phenylpentanoate (major **3c**)*



*COSY-spectrum of **3c**:*



*1D-NOESY spectra of **3c**:*



*Determination of the configuration of the major **3c**:*

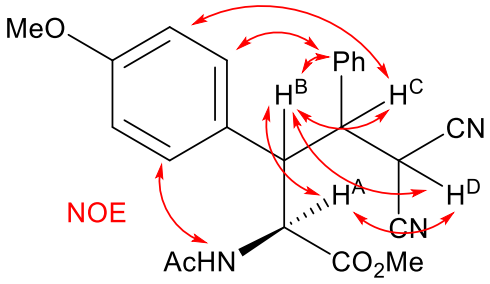
H_A: 4.99 ppm (dd, *J* = 8.4, 2.9 Hz, 1H)

H_B: 4.05 ppm (dd, *J* = 12.2, 2.9 Hz, 1H)

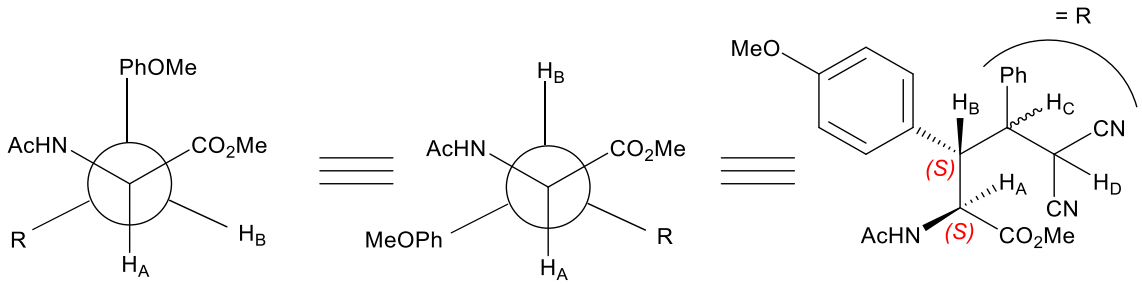
H_C: 3.48 ppm (dd, *J* = 12.1, 4.6 Hz, 1H)

H_D: 5.85 ppm (d, *J* = 4.6 Hz, 1H)

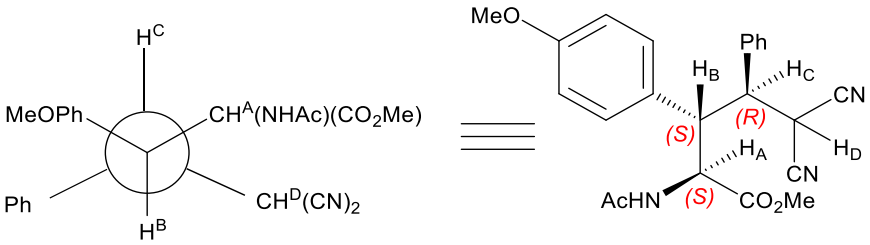
NH: 6.05 ppm (d, *J* = 8.5 Hz, 1H)



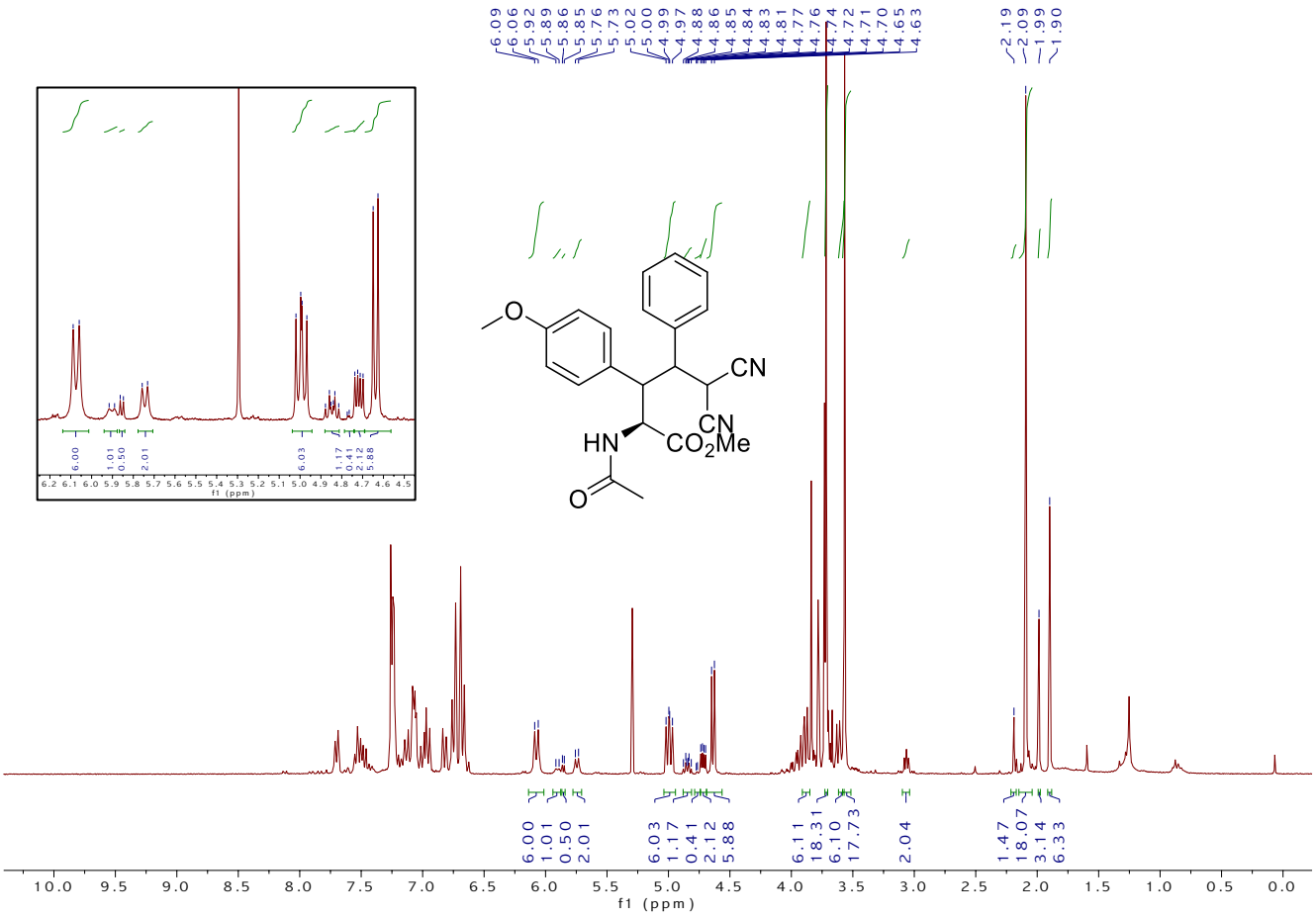
The coupling constant between H^A and H^B is 2.9 Hz, which suggests according to the Karplus equation an angle of around 50° and a predominant gauche conformation as shown in the Newman projection. A strong NOE interaction between NH and the methoxyaryl group and also between H^A and $H^{C,D}$ is consistent with a (*S*) configuration at the Tyr-β-carbon center.



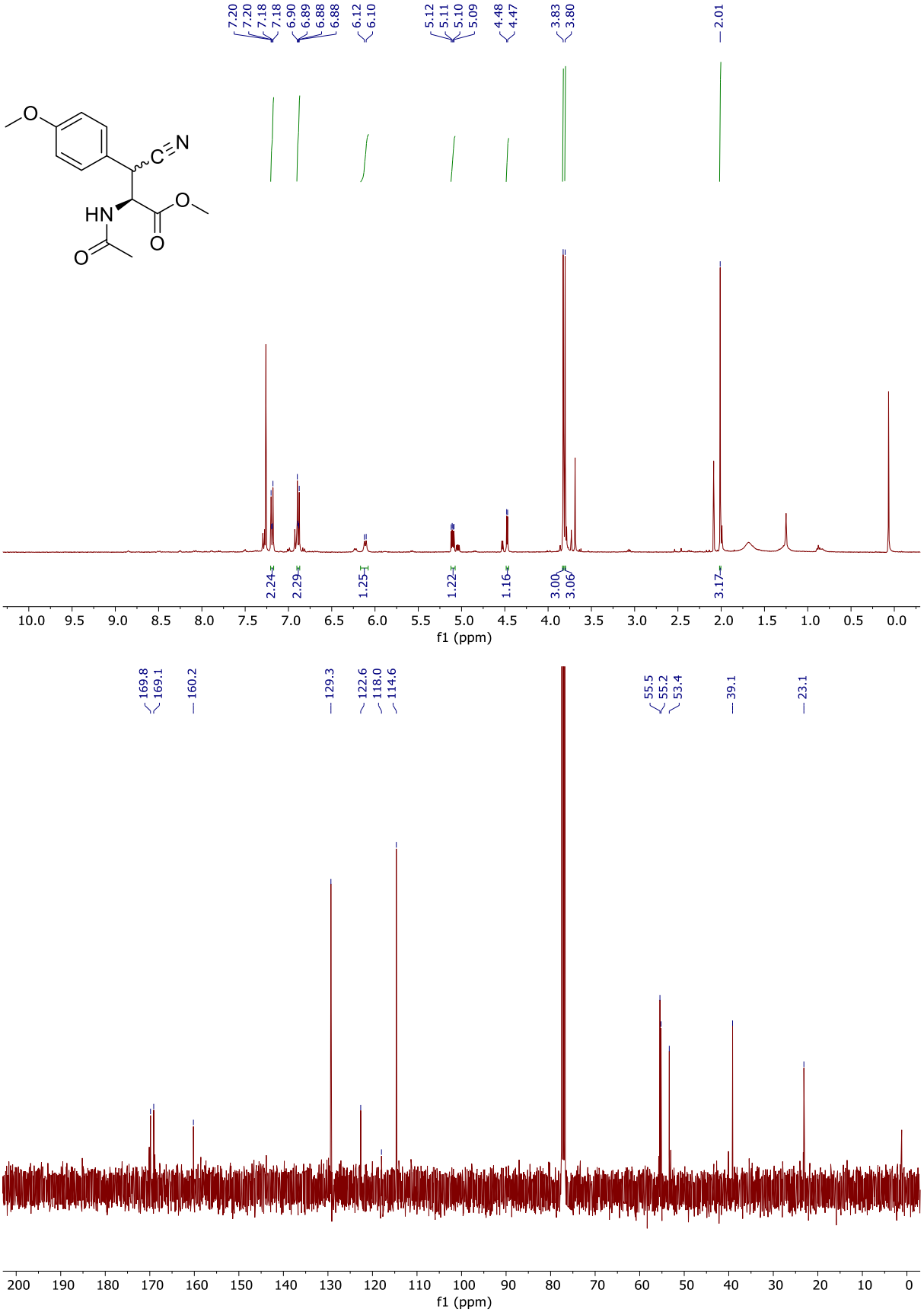
The relatively large coupling constant between H^B and H^C of 12.2 Hz suggests a predominant anti conformation. NOE interactions of the two aromatic scaffolds, H^C with the methoxyaryl group, H^B with H^D and H^B with the phenyl ring is consistent with a R configuration at the Tyr-γ-carbon center.



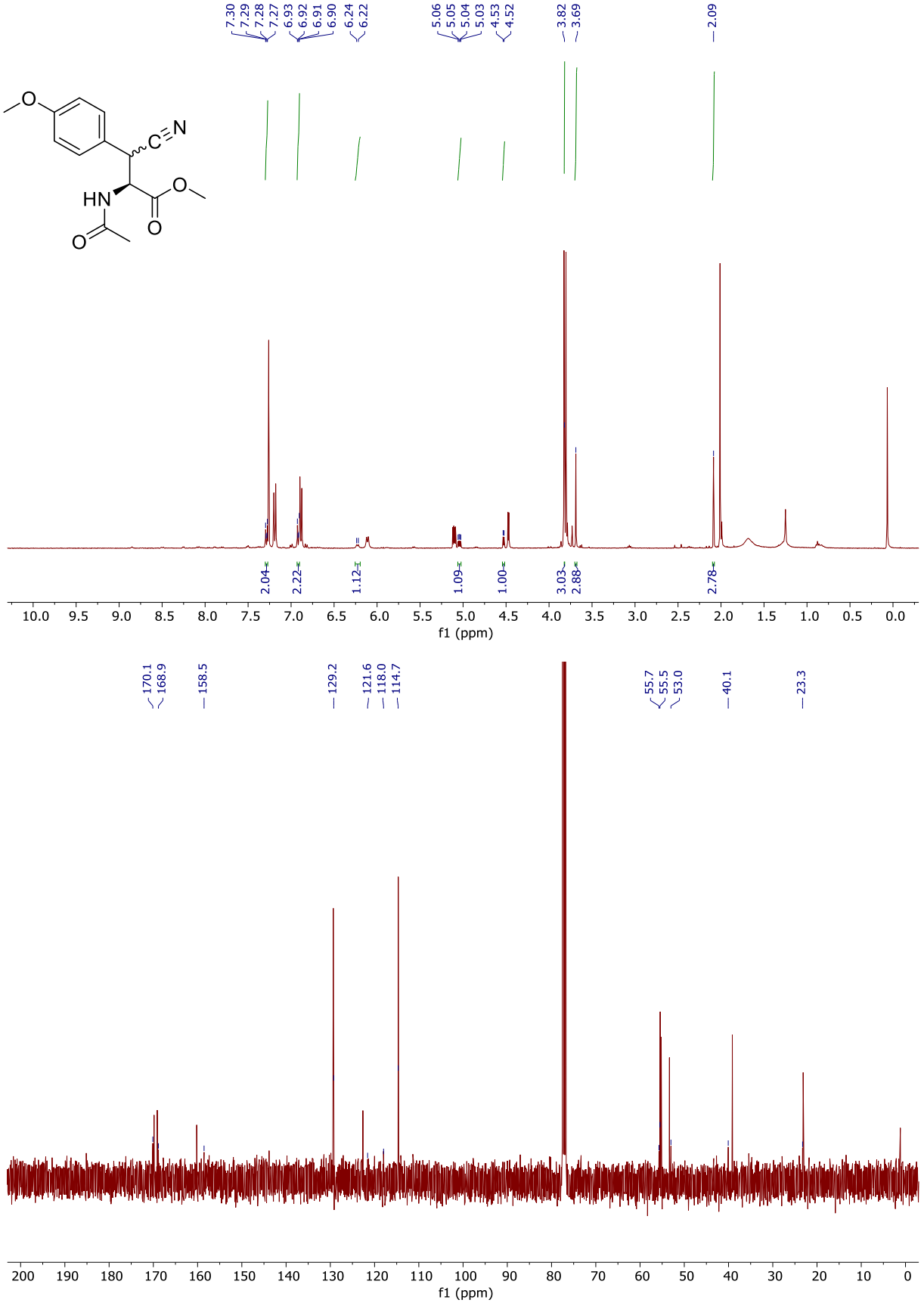
Methyl (2S)-2-acetamido-5,5-dicyano-3-(4-methoxyphenyl)-4-phenylpentanoate (crude reaction mixture ***3c:3c':3c'':3c'''****; 6:2:1:0.5 d.r.)*



*Methyl (2S)-2-acetamido-3-cyano-3-(4-methoxyphenyl)propanoate (major **3d**)*



*Methyl (2S)-2-acetamido-3-cyano-3-(4-methoxyphenyl)propanoate (minor **3d**)*

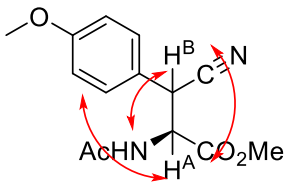


*Determination of the configuration of the major **3d**:*

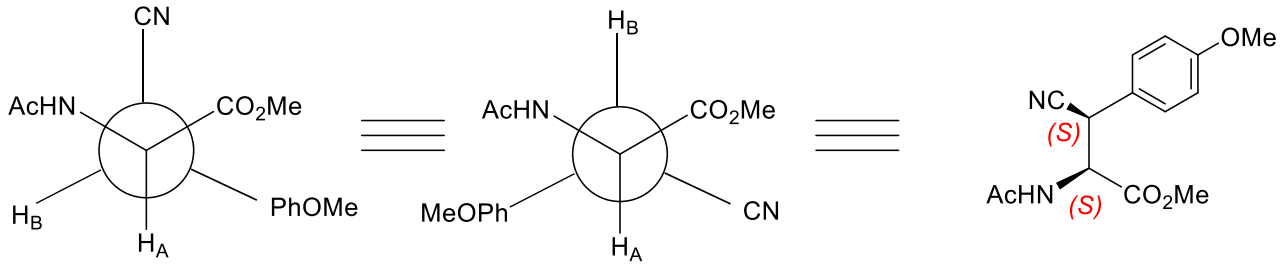
NH: 6.11 ppm (d, *J* = 8.3 Hz, 1H)

H^A: 5.10 ppm (dd, *J* = 8.3, 4.5 Hz, 1H)

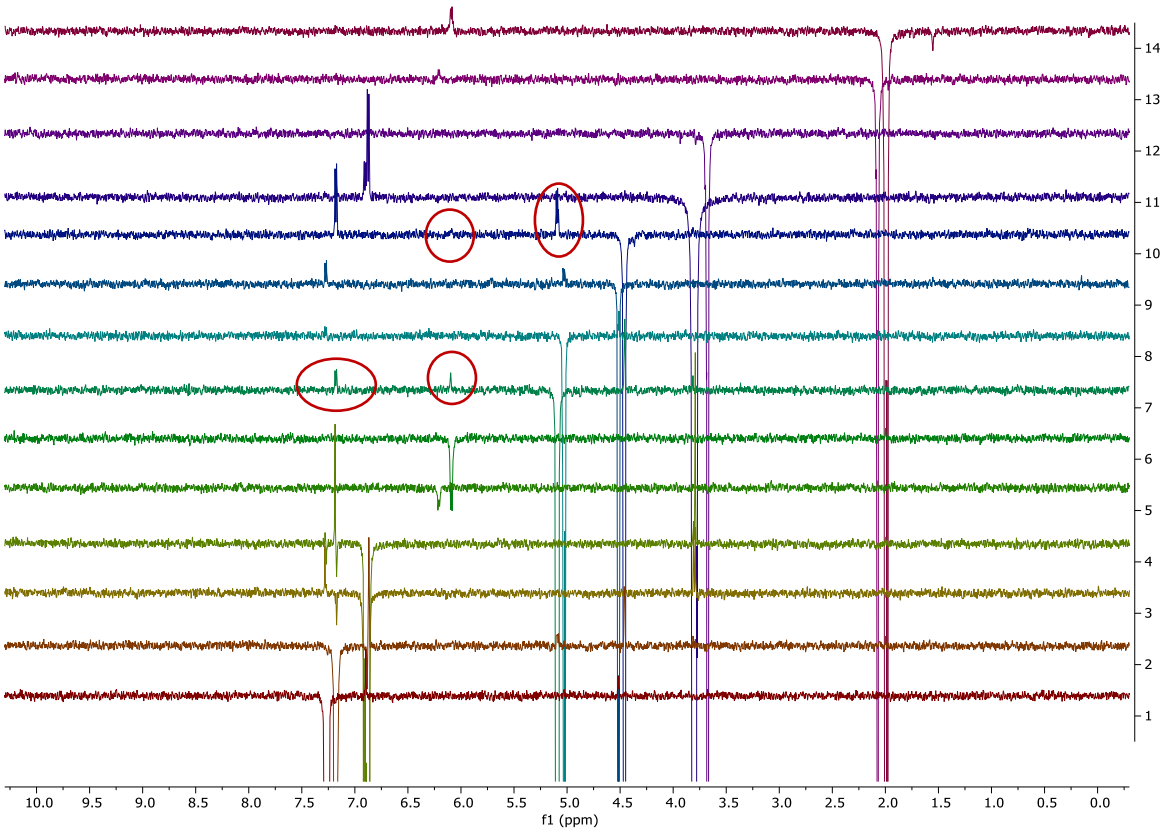
H^B: 4.47 (d, *J* = 4.5 Hz, 1H)



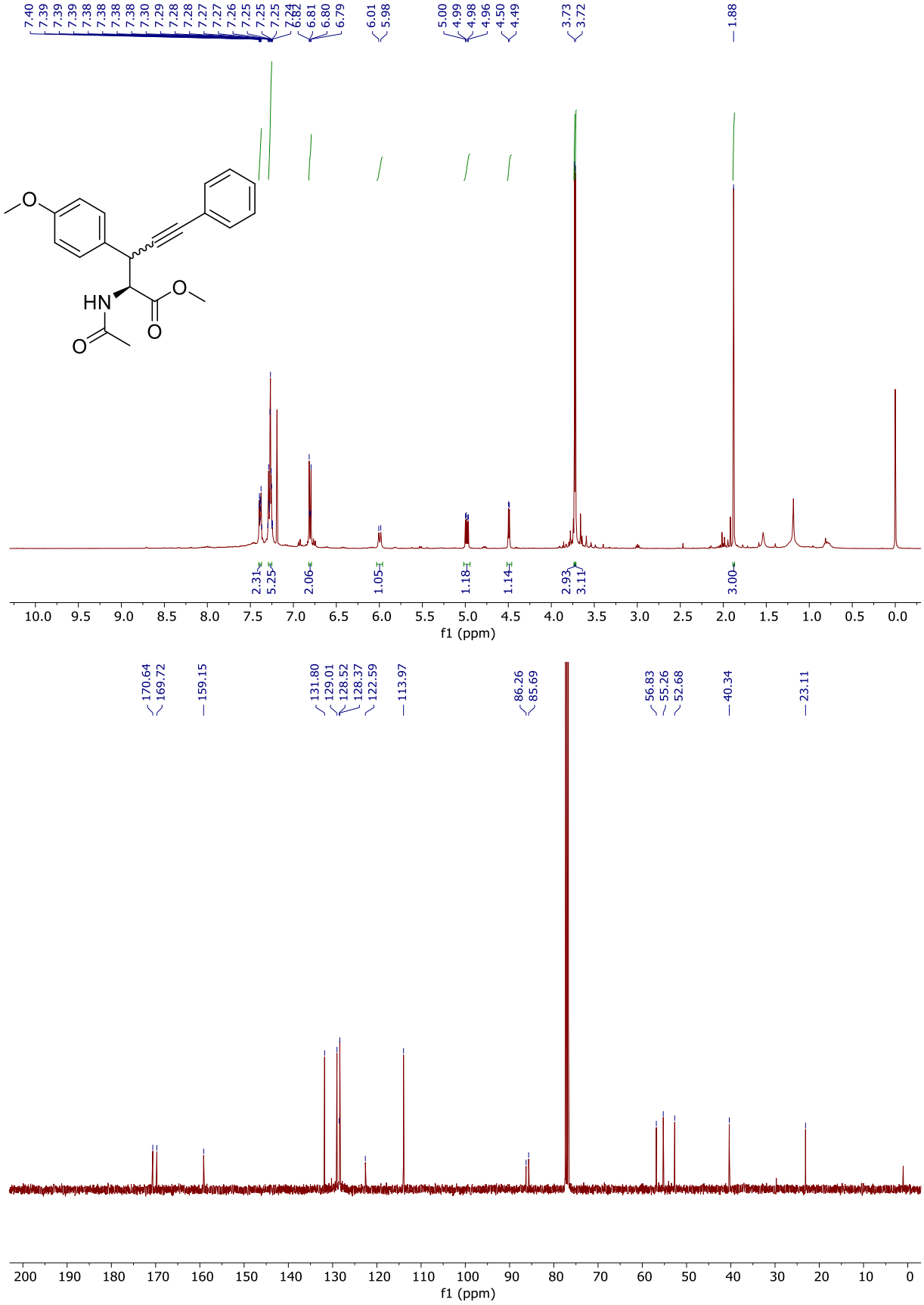
The relatively small coupling constant *J* (H^A, H^B) of 4.5 Hz suggests a predominant *gauche* conformation as shown in the Newman projection. In the 1D-NOESY spectra, NOE interactions between NH and H^B and between H^A and H^B or also with the methoxyphenyl group is consistent with gauche conformations between these groups and a S configuration at the Tyr β-carbon center.



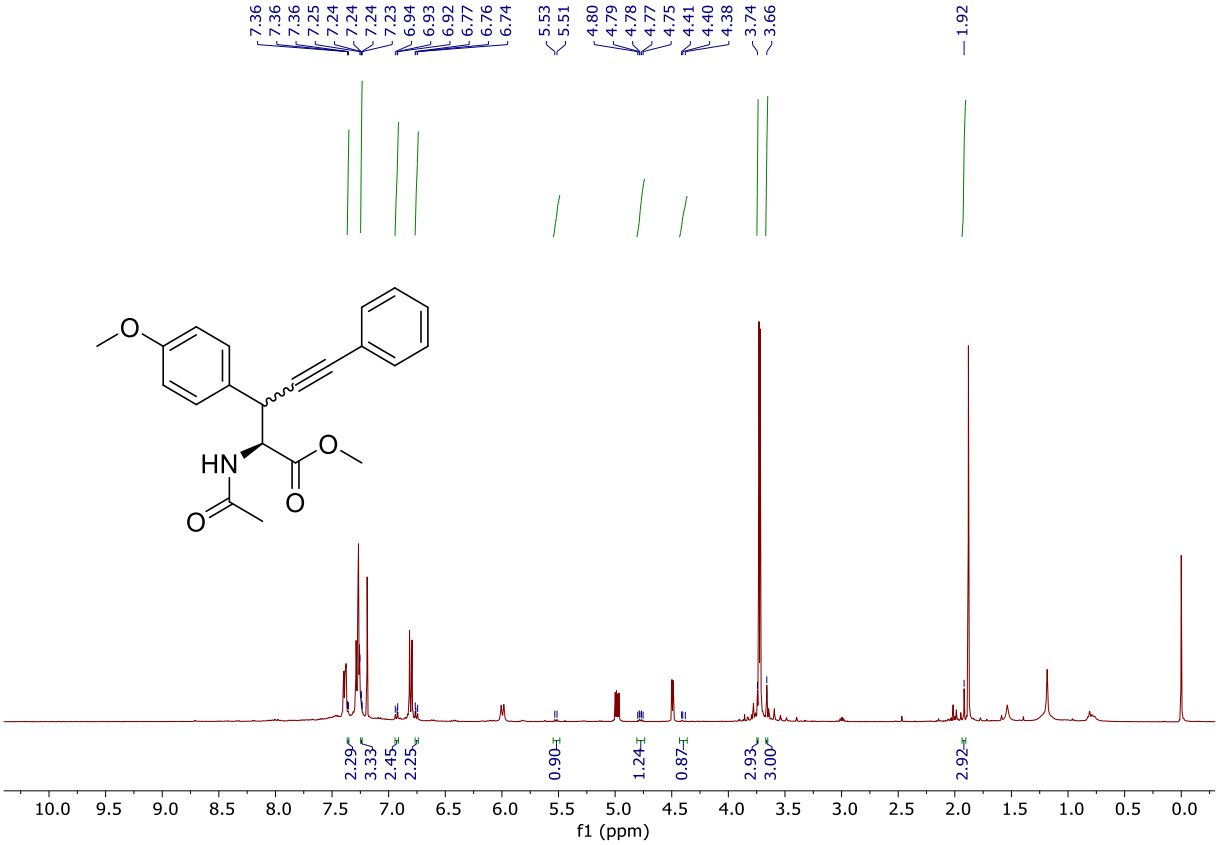
*1D-NOESY spectra of **3d**:*



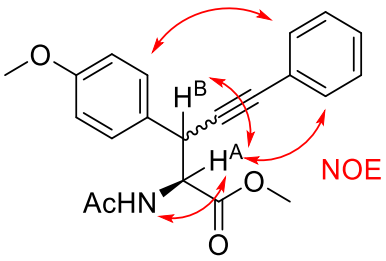
*Methyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5-phenylpent-4-ynoate (major **3e**)*



*Methyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5-phenylpent-4-ynoate (minor **3e**)*



*Determination of the configuration of the major **3e**:*



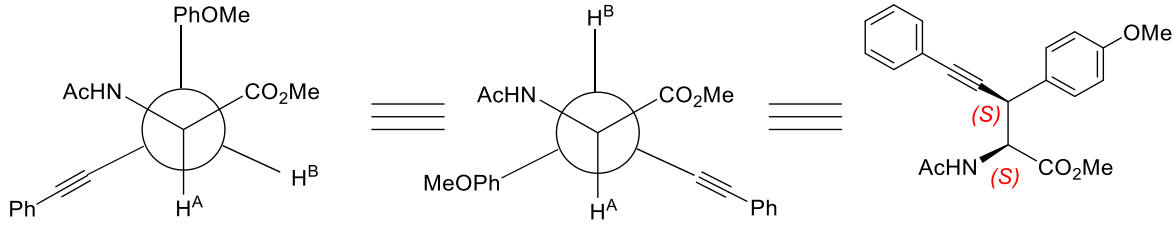
NH: 6.07 ppm (d, *J* = 9.3 Hz, 1H)

H^A: 5.05 ppm (dd, *J* = 9.3, 4.4 Hz, 1H)

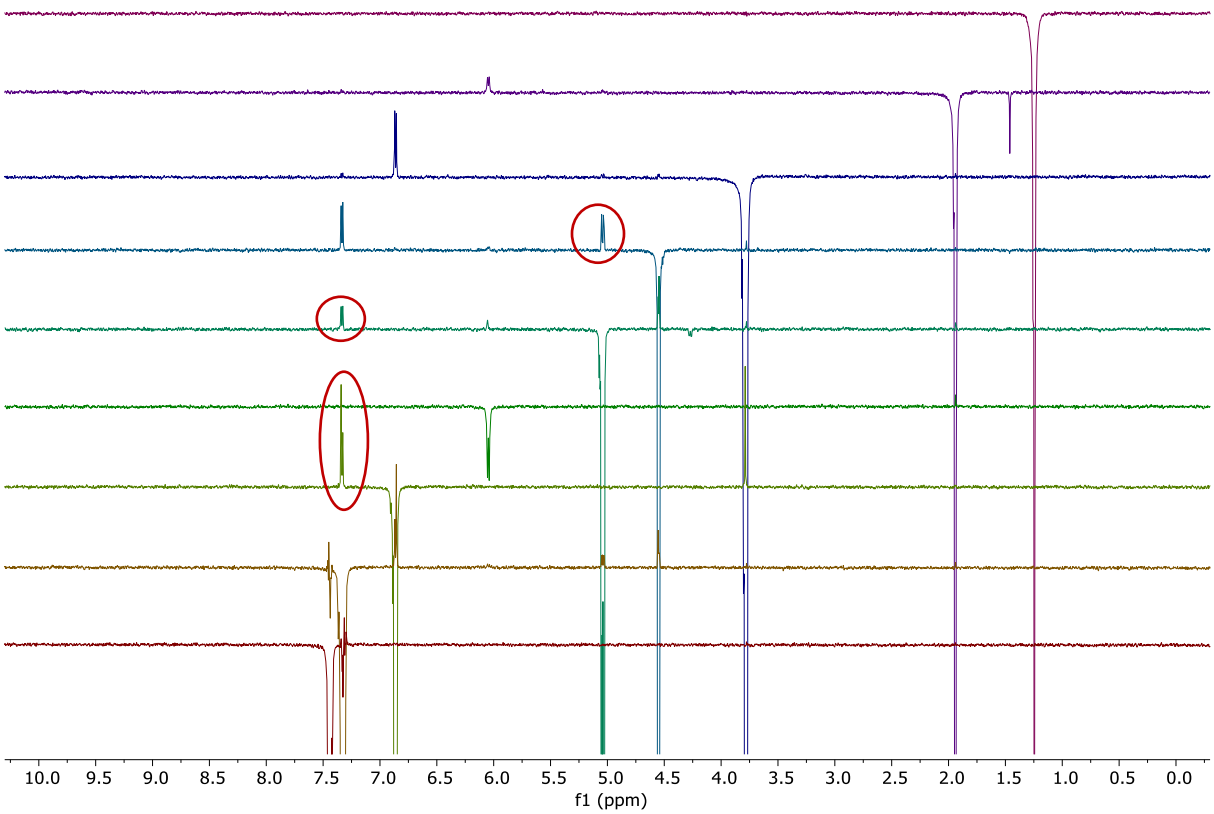
HB: 4.56 ppm (d, *J* = 4.

4 Hz, 1H)

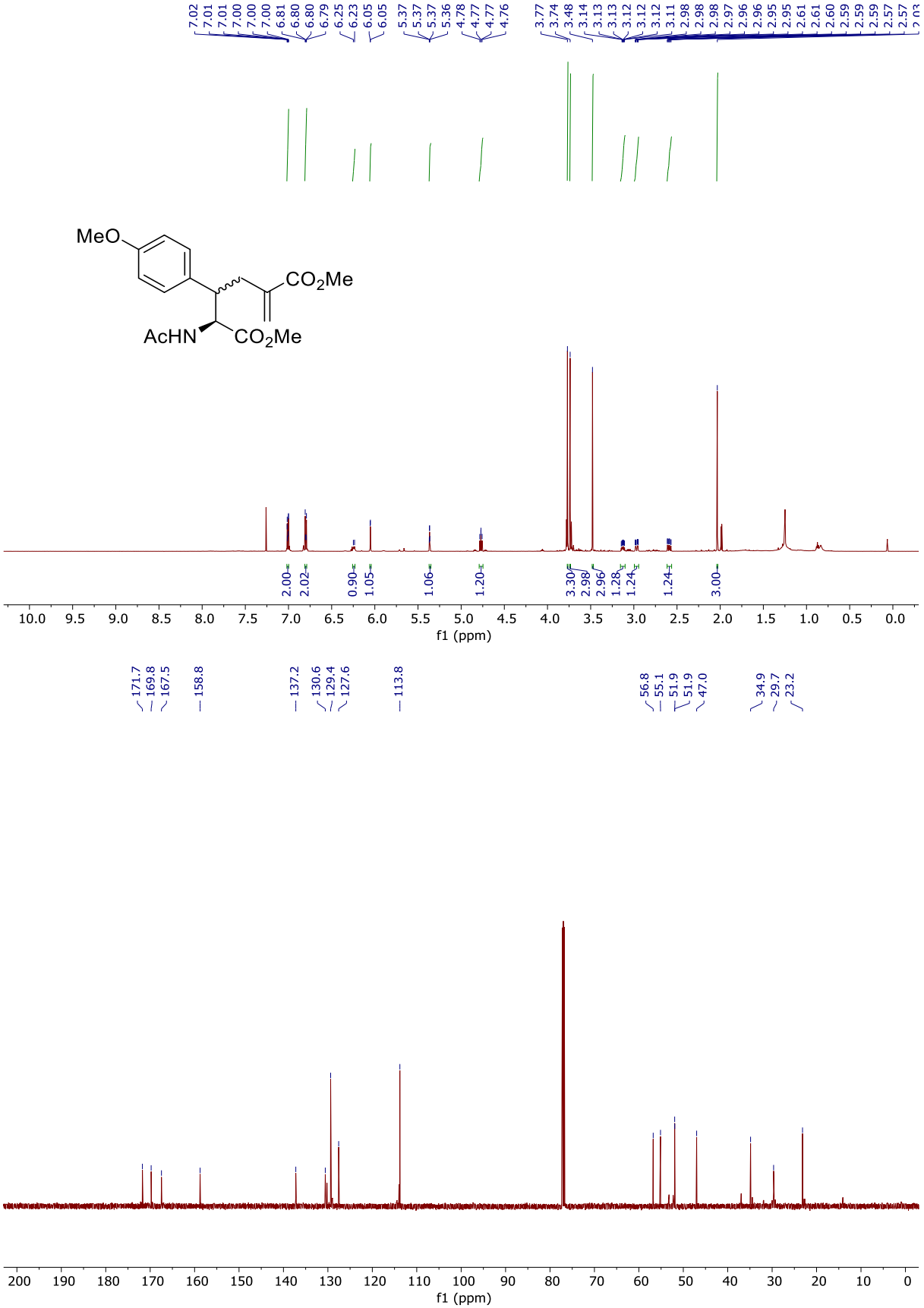
The relative low coupling constant of *J* (H^A, H^B) of 4.3 Hz suggests a predominant gauche conformation as shown in the Newman projection. In the 1D-NOESY spectra, strong NOE interaction between H^A with the phenyl group, H^A with H^B and no interaction between NH and H^B is consistent with a (*S*) configuration at the Tyr-β-carbon center.



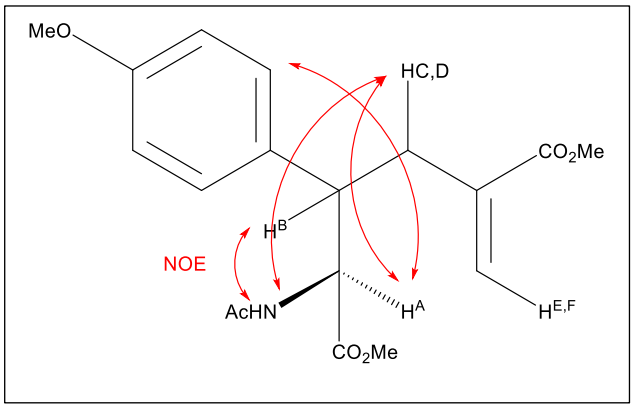
1D-NOESY spectra of major **3e**:



*Dimethyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5-methylenehexanedioate (major **3f**)*



*Determination of the configuration of the major **3f**:*



NH: 6.24 (d, *J* = 8.4 Hz, 1H),

H^E: 6.05 (d, *J* = 1.3 Hz, 1H)

H^F: 5.37 (q, *J* = 1.2 Hz, 1H)

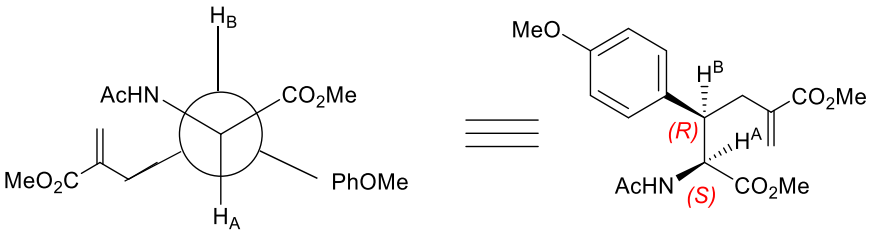
H^A: 4.77 (dd, *J* = 8.4, 7.9 Hz, 1H)

H^B: 3.13 (ddd, *J* = 9.8, 7.9, 4.8 Hz, 1H)

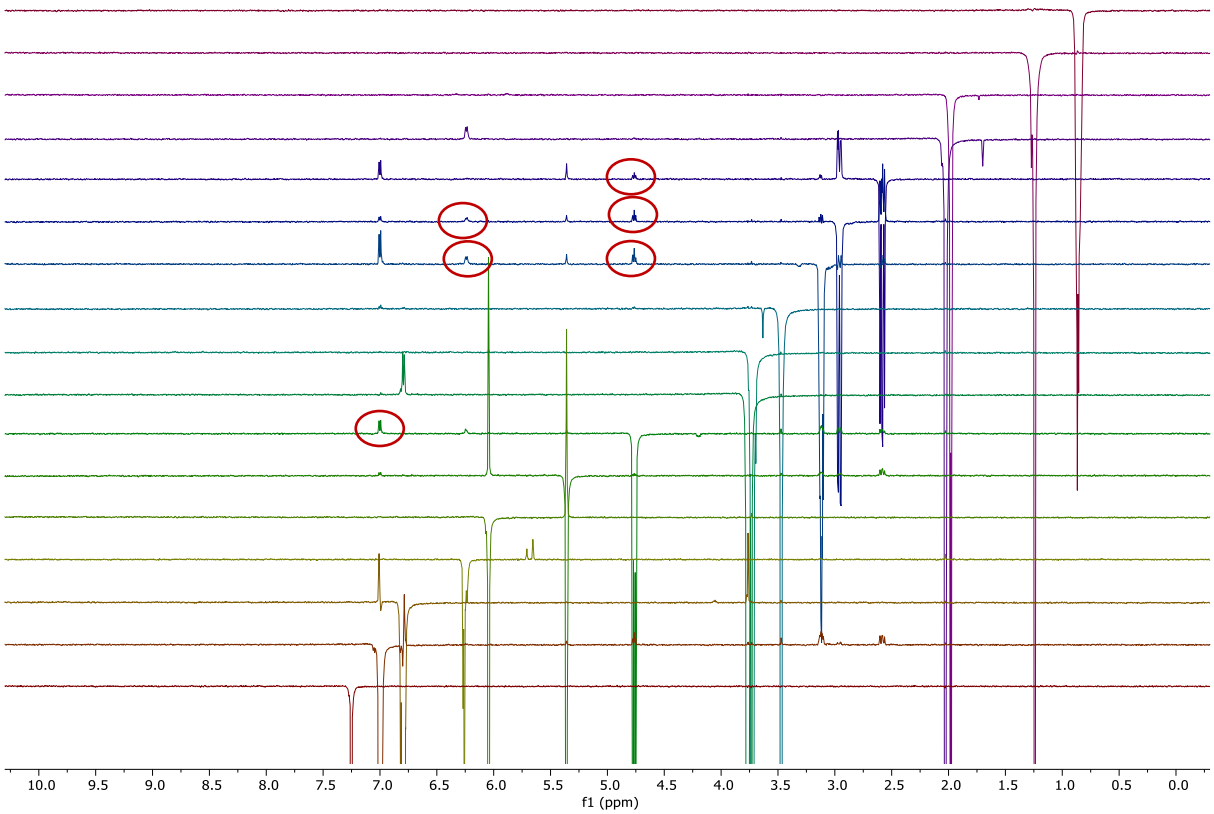
H^C: 2.97 (ddd, *J* = 14.2, 4.9, 1.3 Hz, 1H)

H^D: 2.59 (ddd, *J* = 14.3, 9.8, 0.9 Hz, 1H)

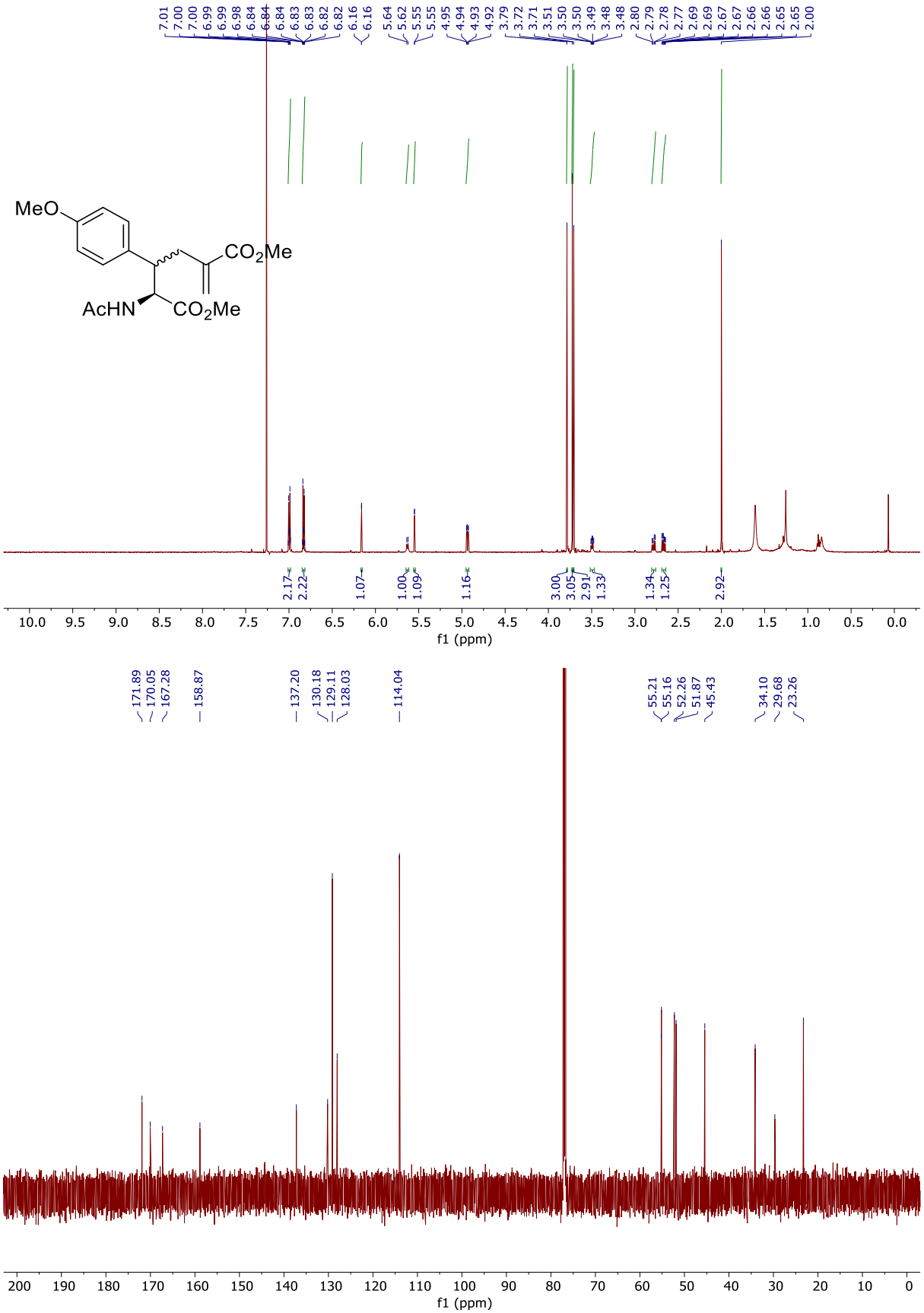
The relatively large coupling constant between H^A and H^B of 7.9 Hz suggests a predominant anti conformation as shown in the Newman projection. A strong NOE interaction between H^C and H^A and H^C and NH were consistent with a gauche conformation and a (*R*)-configuration at the β-carbon center.



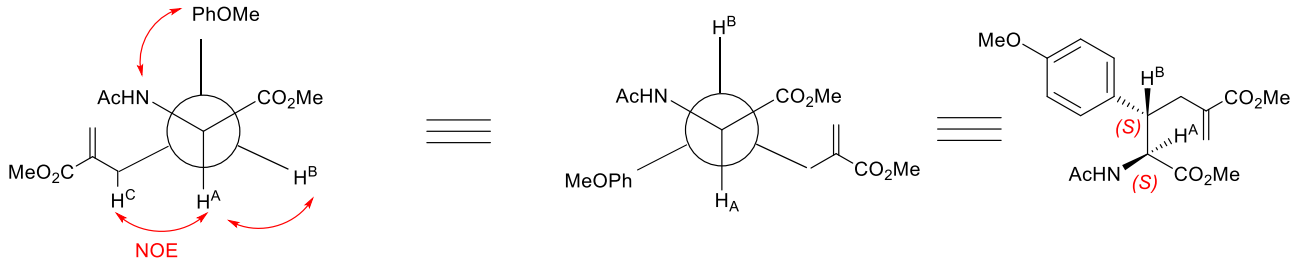
1D-NOESY spectra of major **3f**:



*Dimethyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5-methylenehexanedioate (minor **3f**)*

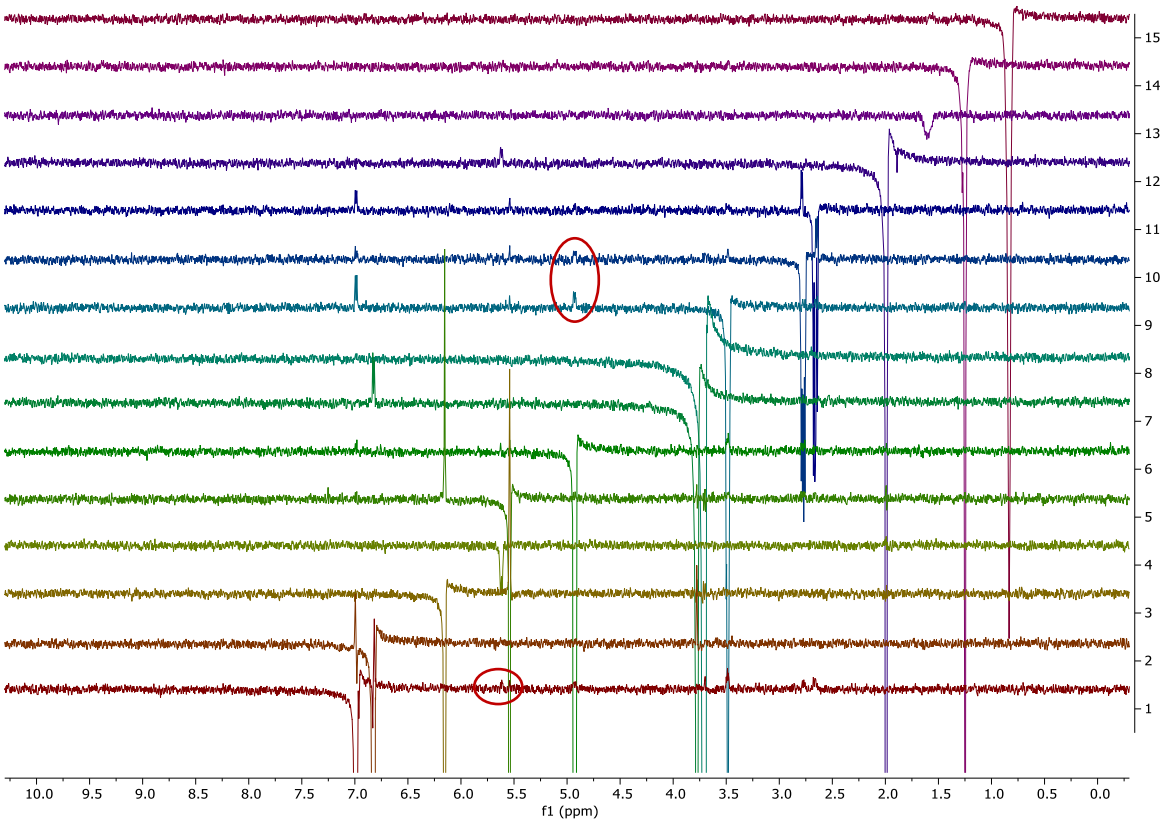


*Determination of the configuration of minor **3f**:*

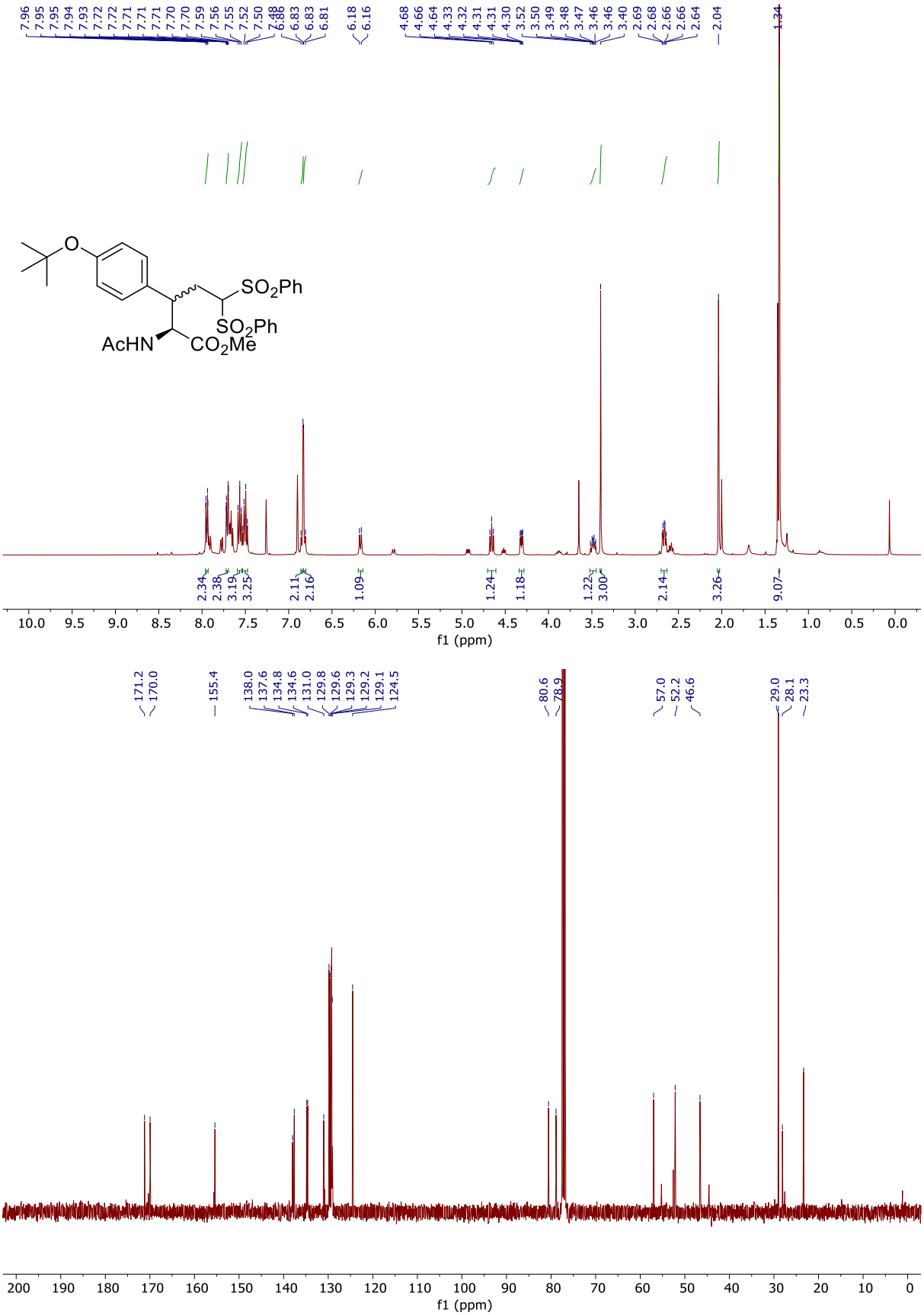


The relatively large coupling constant between H^A and H^B of 4.4 Hz suggests a predominant gauche conformation as shown in the Newman projection. A NOE interaction between NH and PhOMe, H^B and H^A or H^A and H^C were consistent with a *S*-configuration at the β-carbon center.

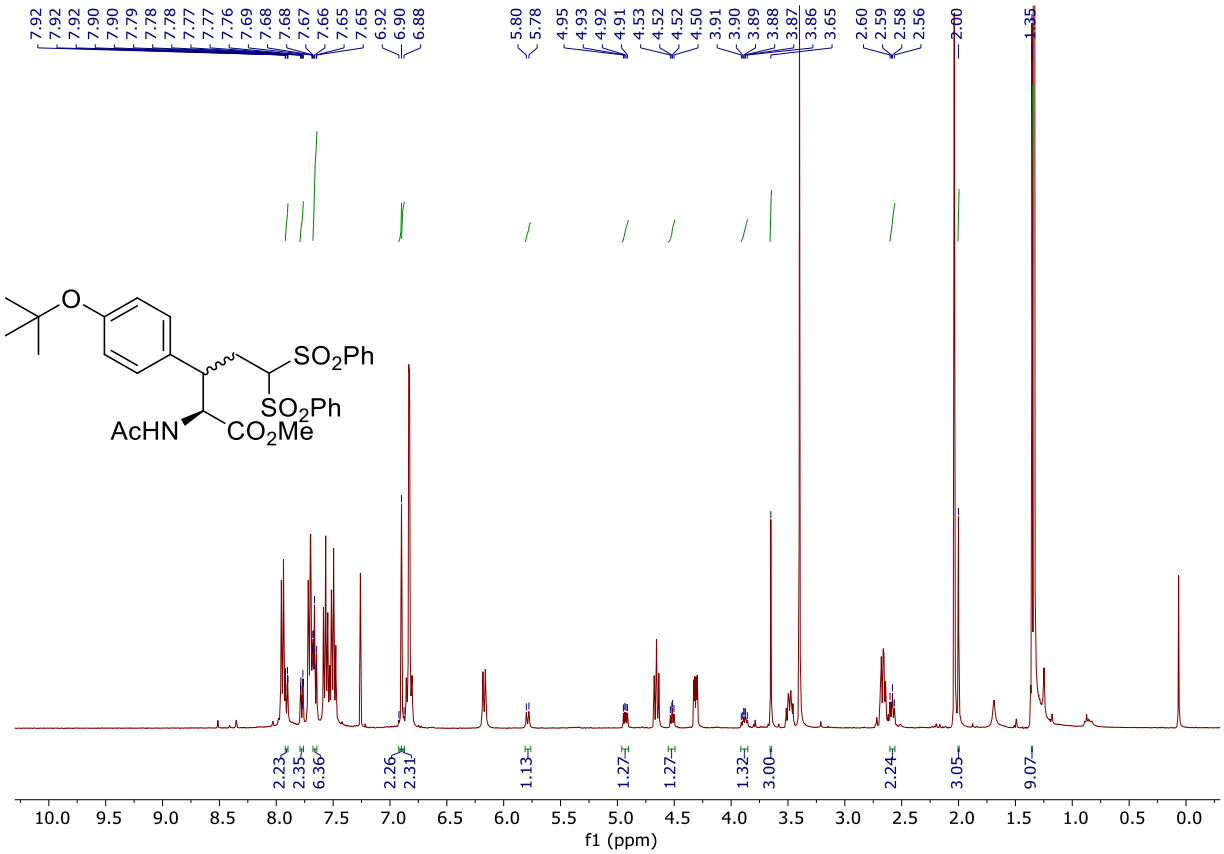
*1D-NOESY spectra of minor **3f**:*



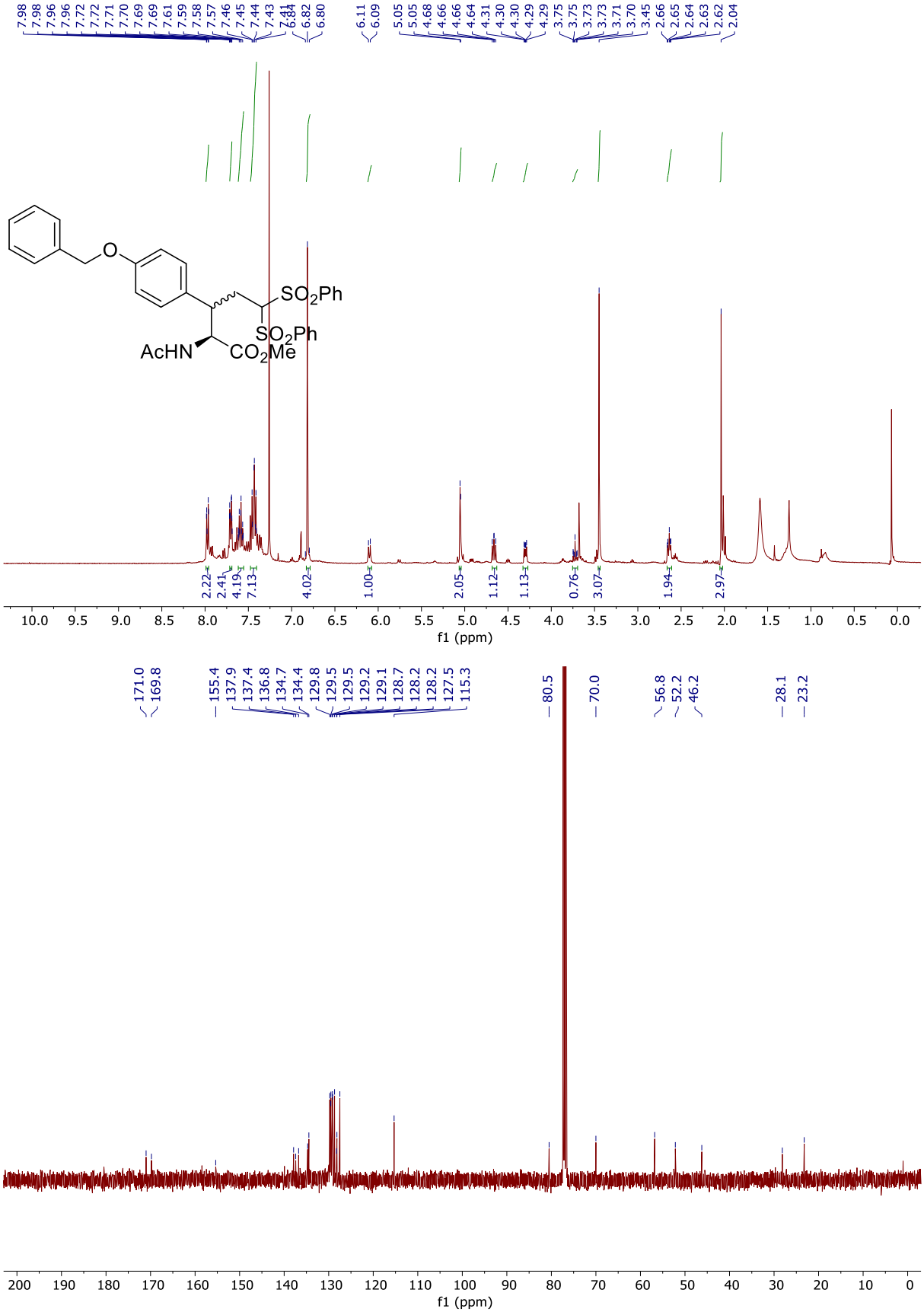
*Methyl (2S)-2-acetamido-3-(4-(tert-butoxy)phenyl)-5,5-bis(phenylsulfonyl)pentanoate (major **4**)*



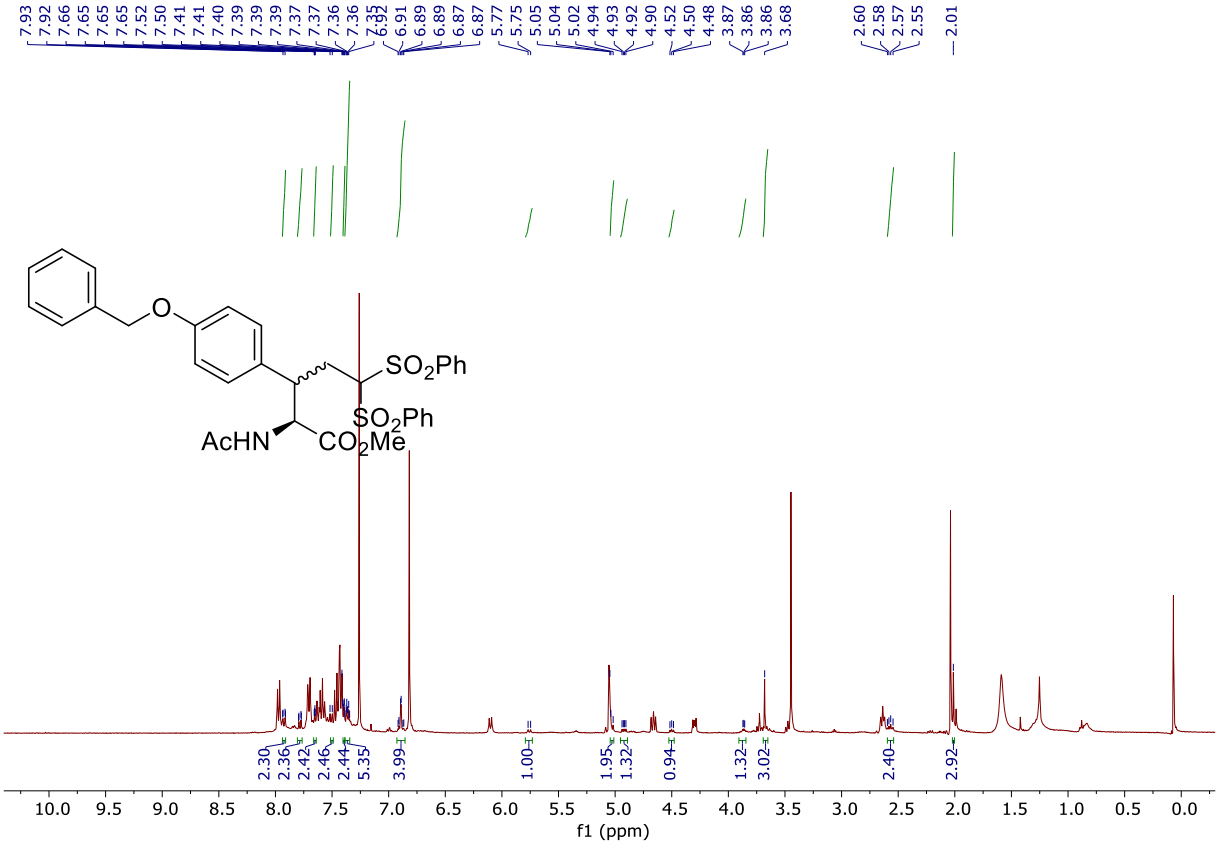
*Methyl (2S)-2-acetamido-3-(4-(tert-butoxy)phenyl)-5,5-bis(phenylsulfonyl)pentanoate (minor **4**)*



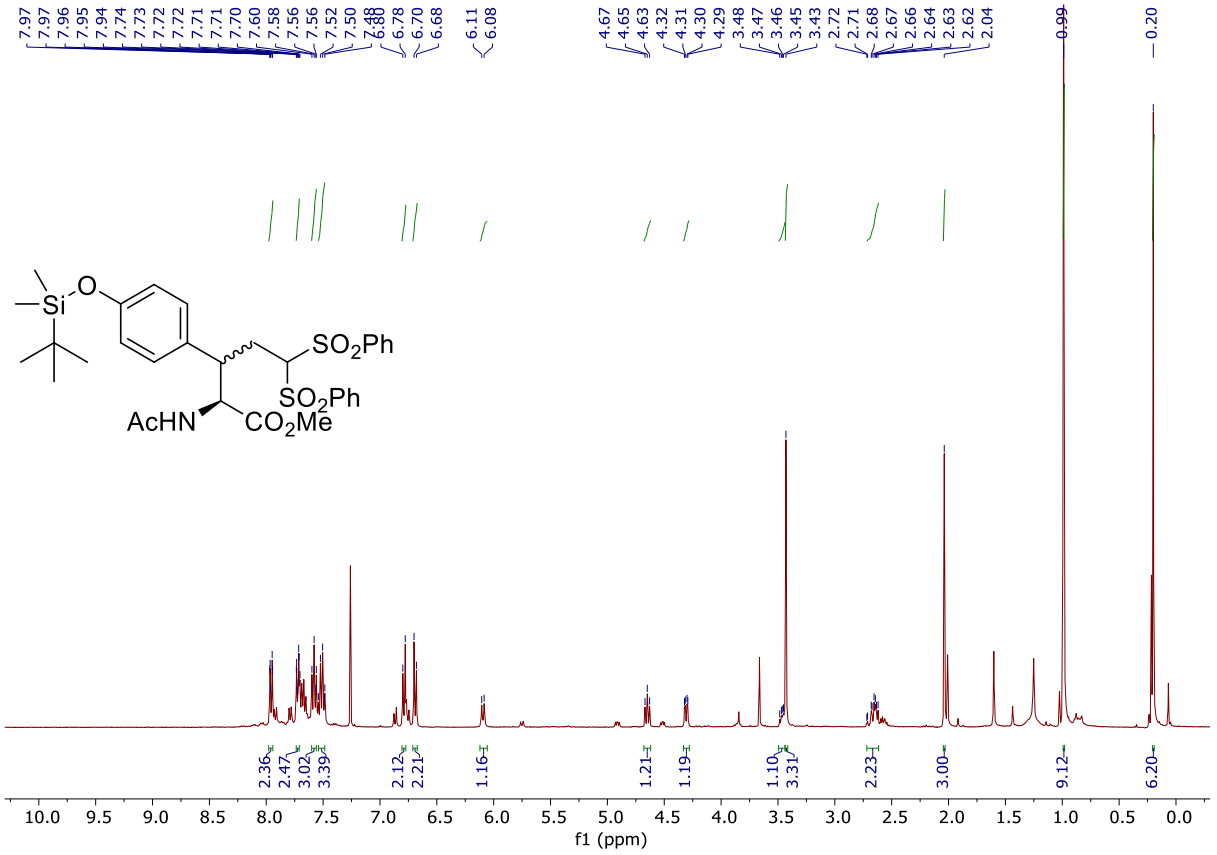
*Methyl (2S)-2-acetamido-3-(4-(benzyloxy)phenyl)-5,5-bis(phenylsulfonyl)pentanoate (major **5**)*

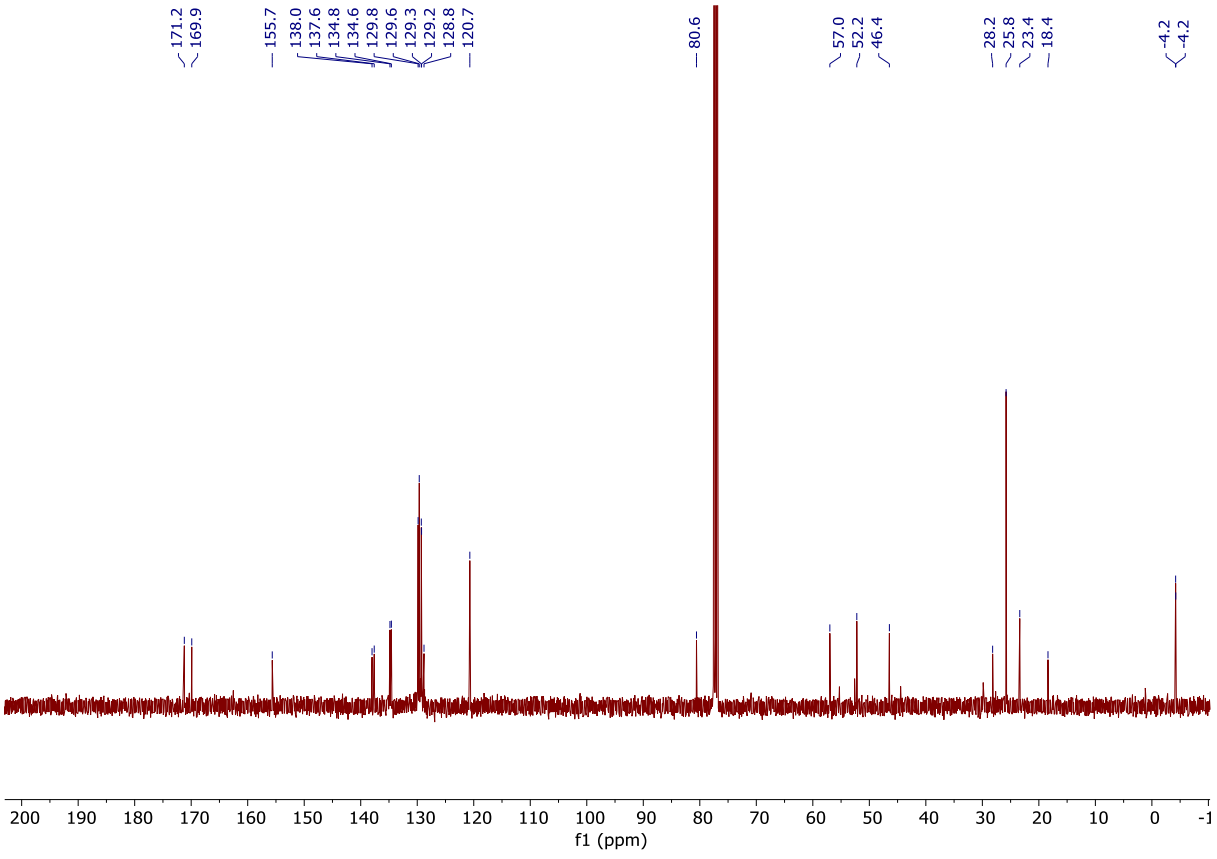


*Methyl (2S)-2-acetamido-3-(4-(benzyloxy)phenyl)-5,5-bis(phenylsulfonyl)pentanoate (minor **5**)*

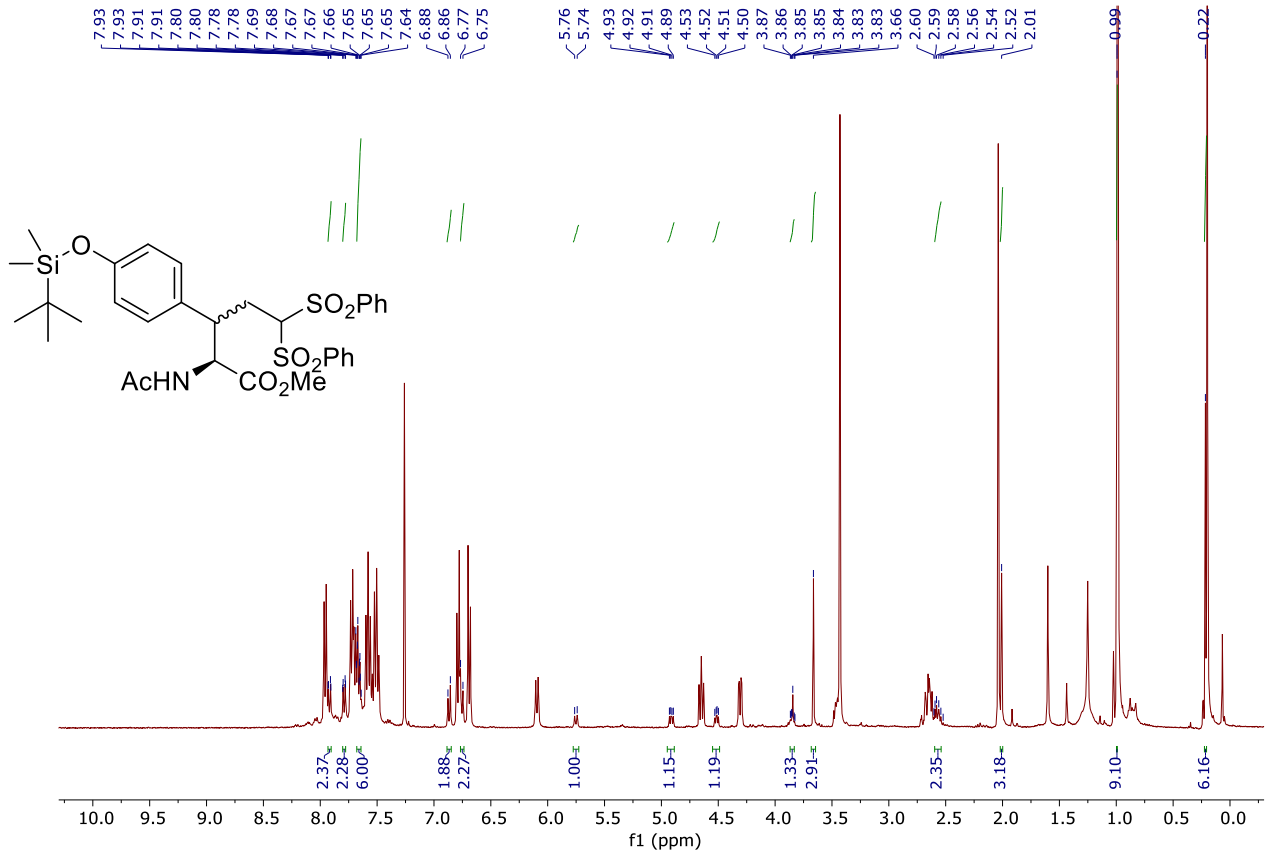


*Methyl-(2S)-2-acetamido-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)-5,5-bis(phenylsulfonyl) pentanoate (major **6**)*

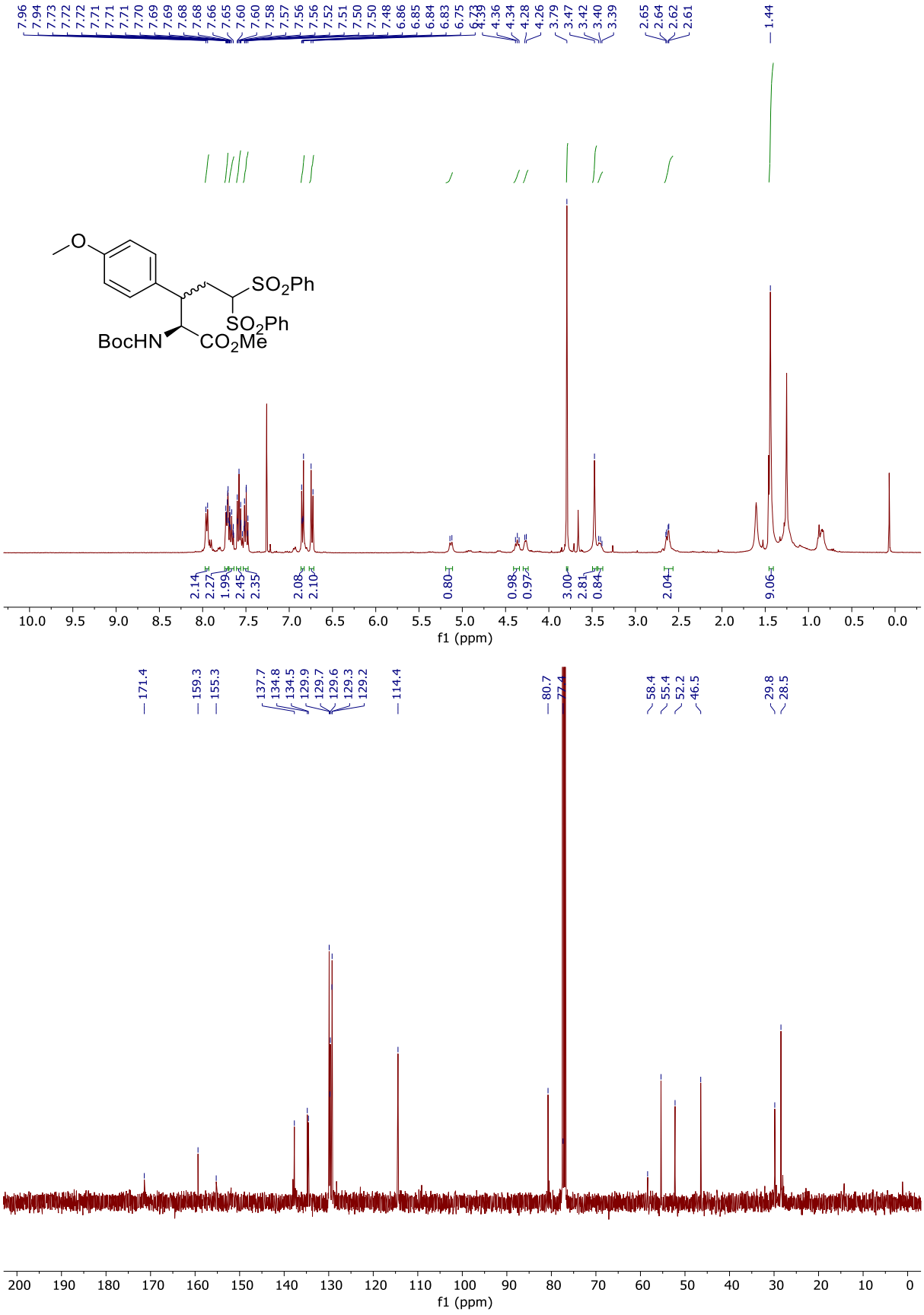




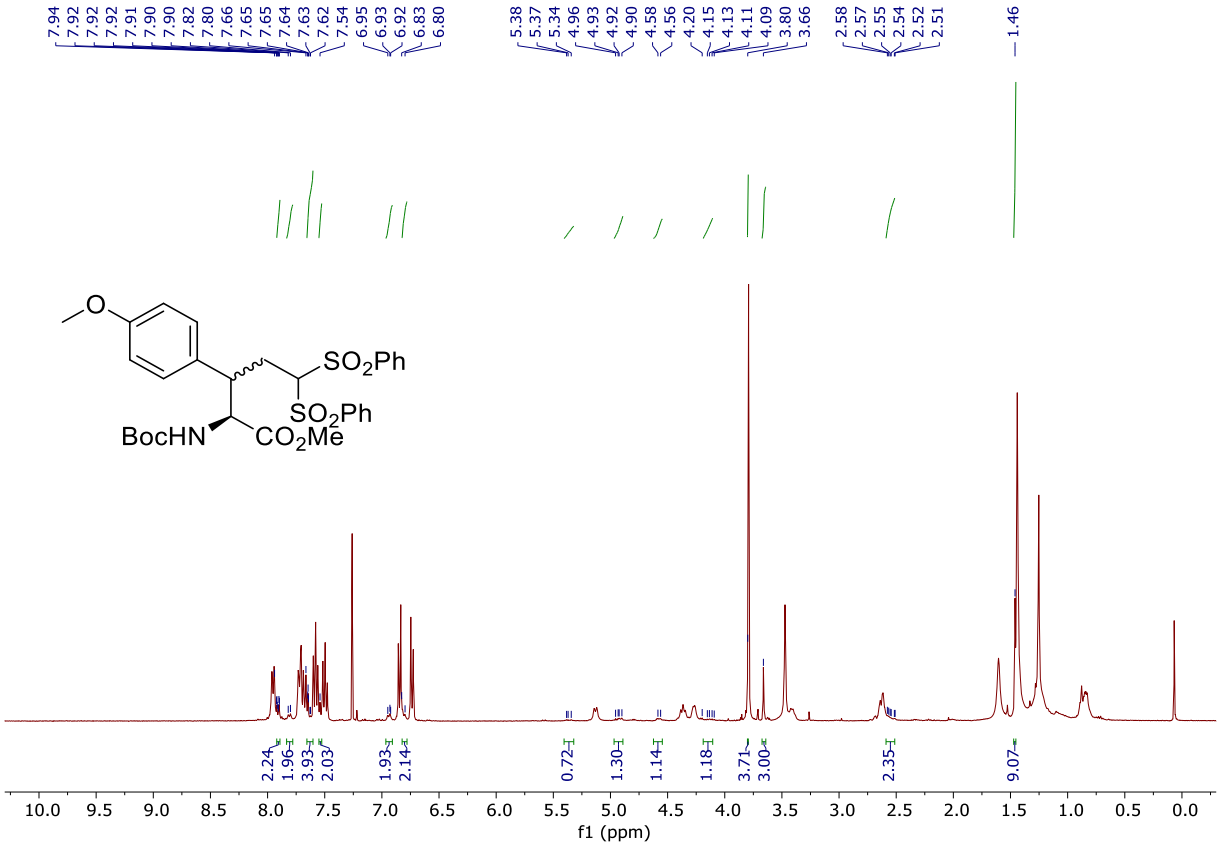
*Methyl-(2S)-2-acetamido-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)-5,5-bis(phenylsulfonyl) pentanoate (minor **6**)*



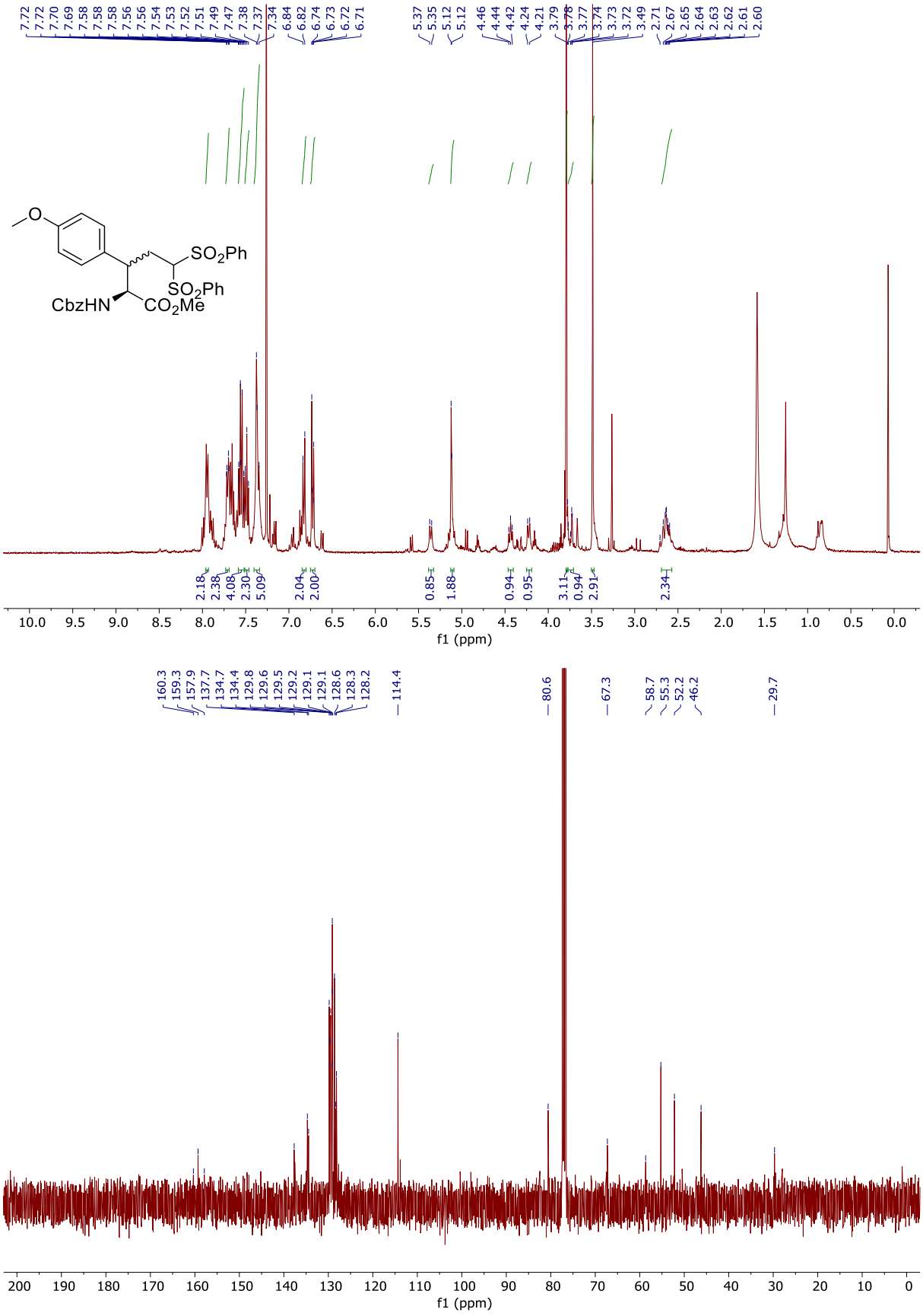
*Methyl (2S)-2-((tert-butoxycarbonyl)amino)-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl) pentanoate (major **7**)*



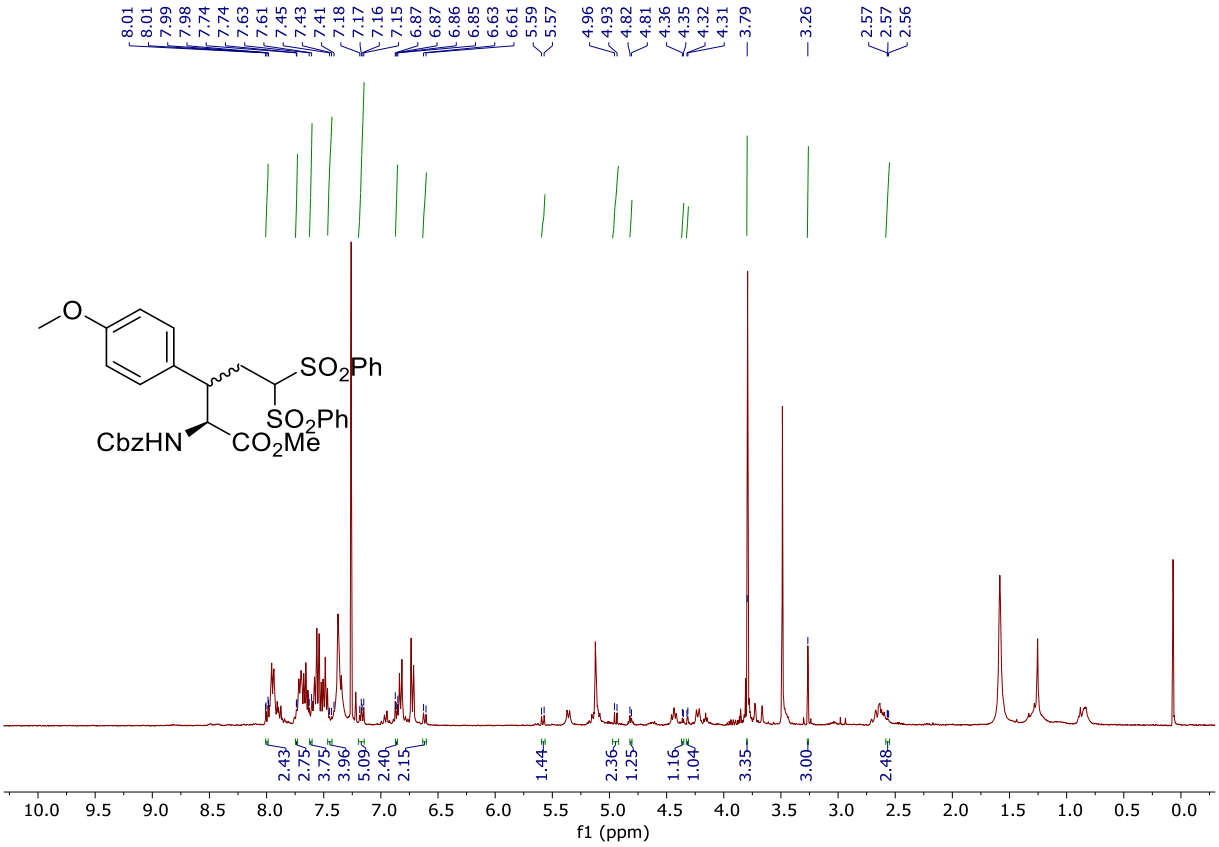
*Methyl (2S)-2-((tert-butoxycarbonyl)amino)-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl) pentanoate (minor **7**)*



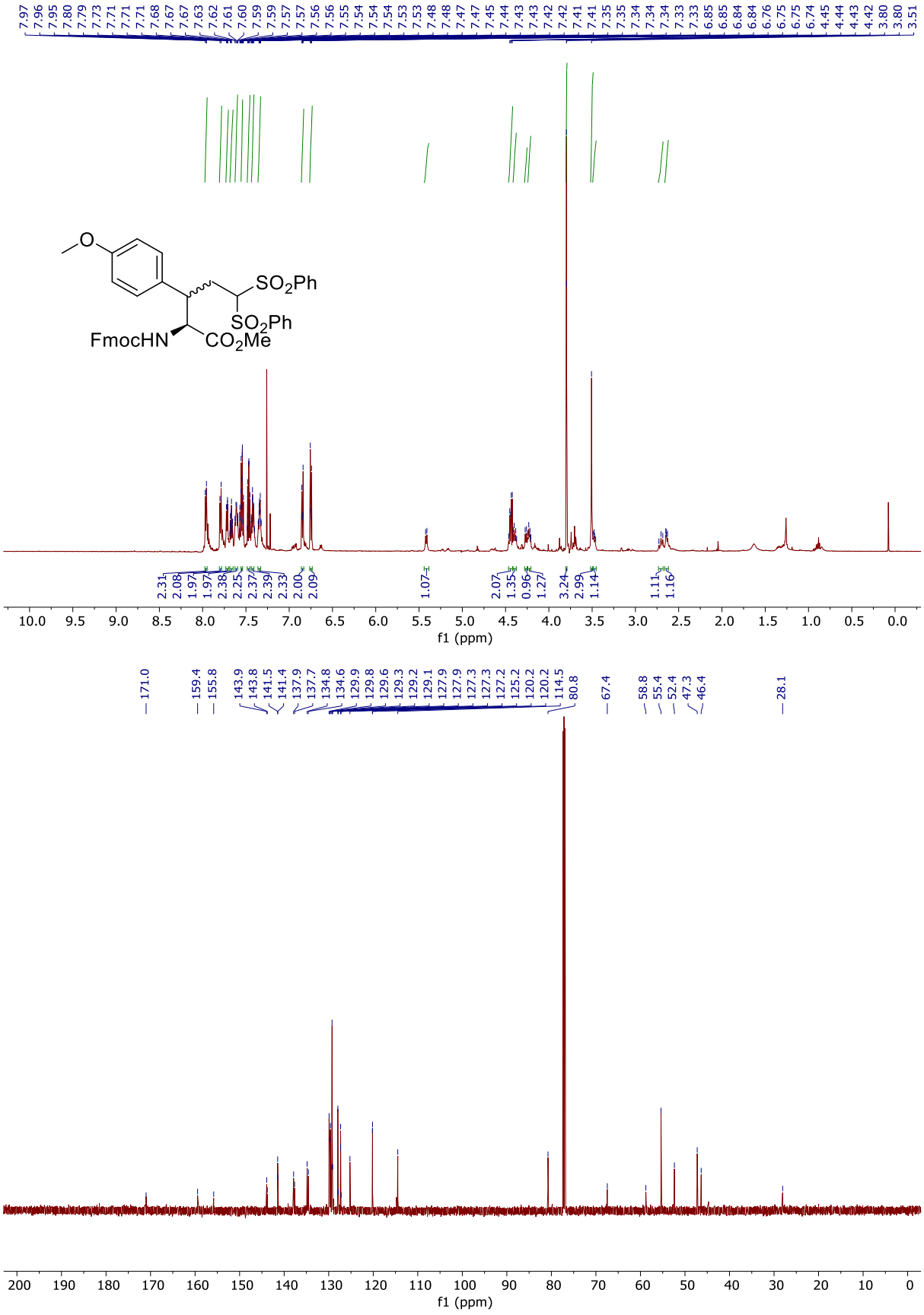
*Methyl (2S)-2-(((benzyloxy)carbonyl)amino)-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl) pentanoate (major **8**)*



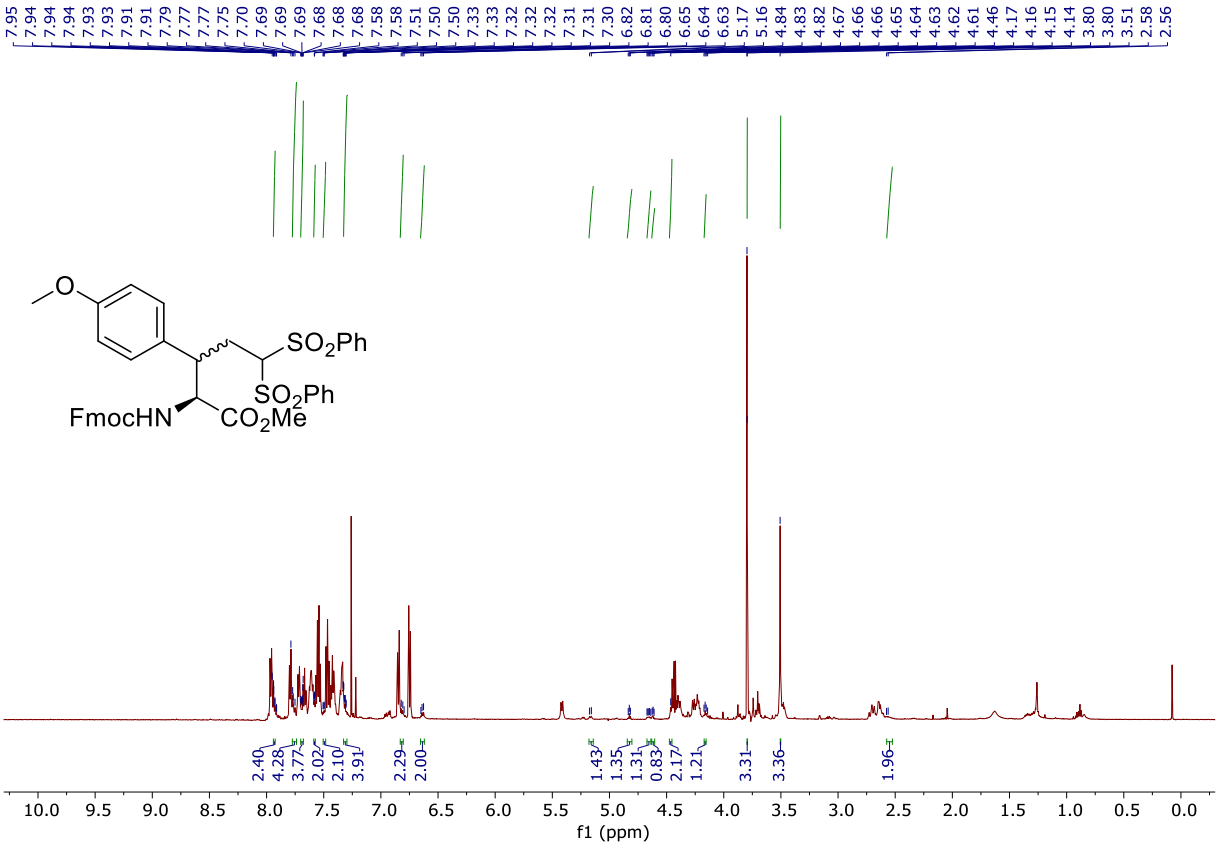
*Methyl (2S)-2-(((benzyloxy)carbonyl)amino)-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl) pentanoate (minor **8**)*



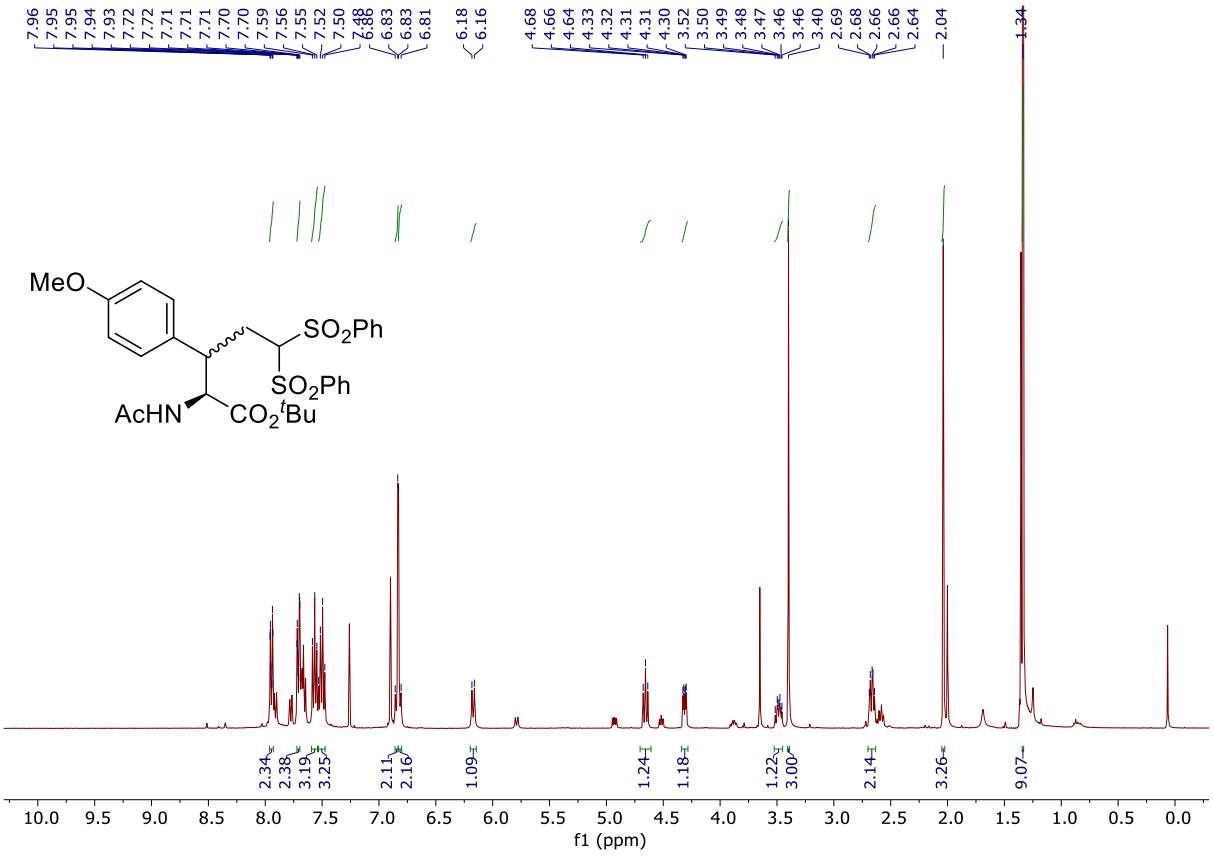
*Methyl (2S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl) pentanoate (major **9**)*

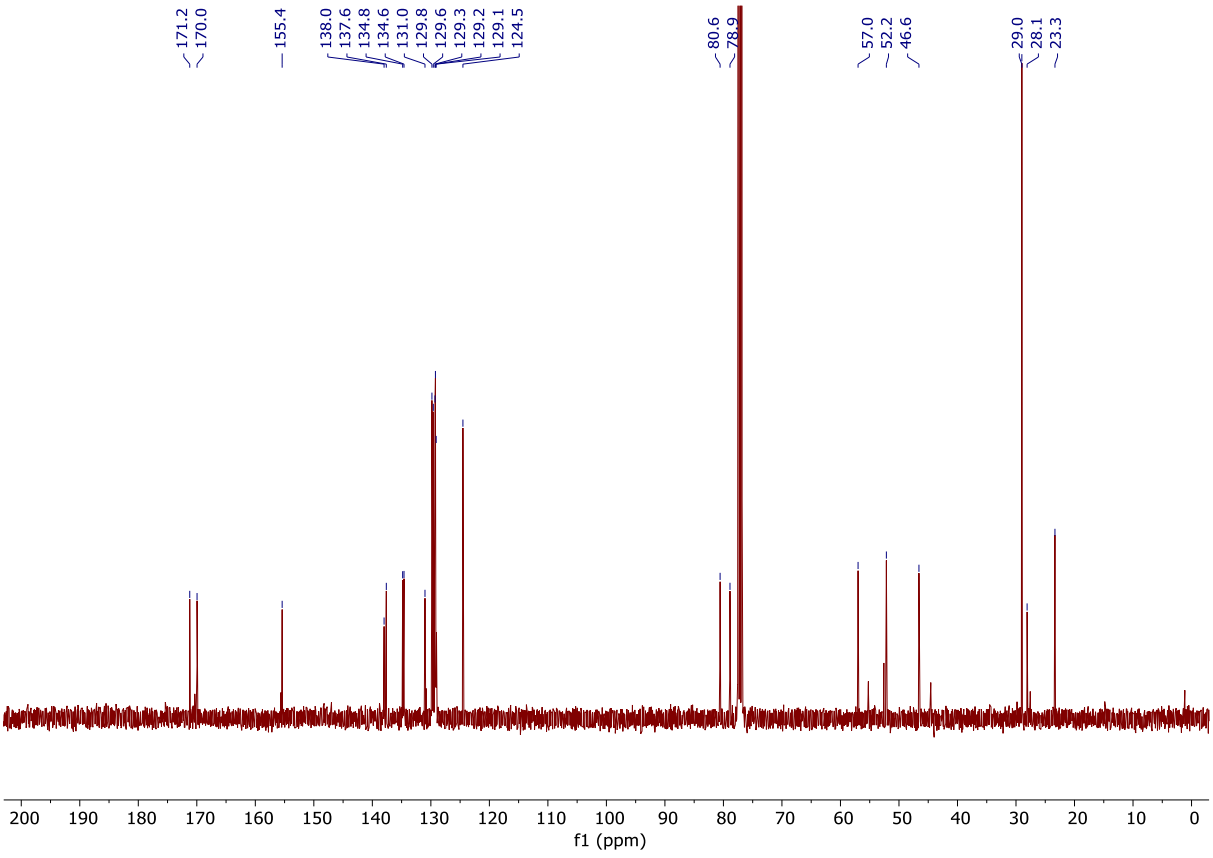


*Methyl (2S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl) pentanoate (minor **9**)*

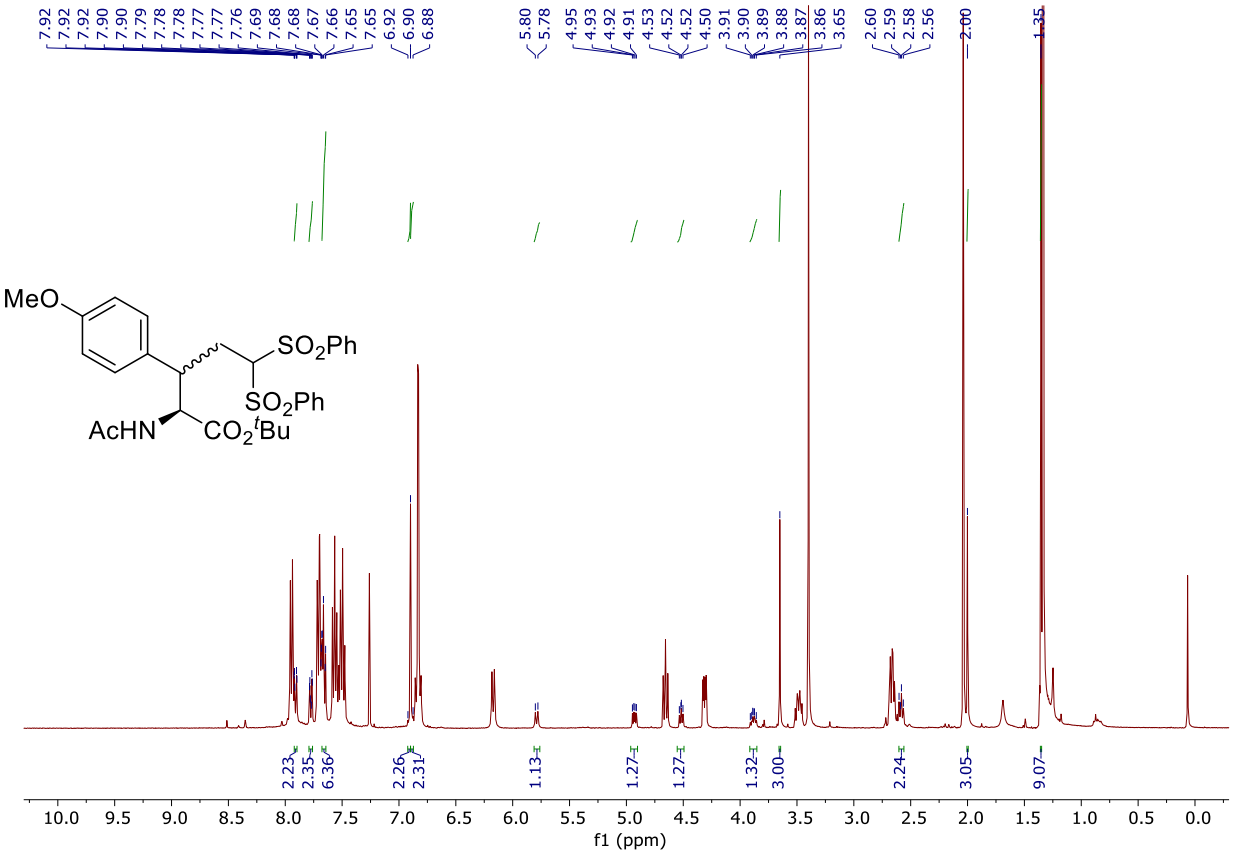


*tert-Butyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (major **10**)*

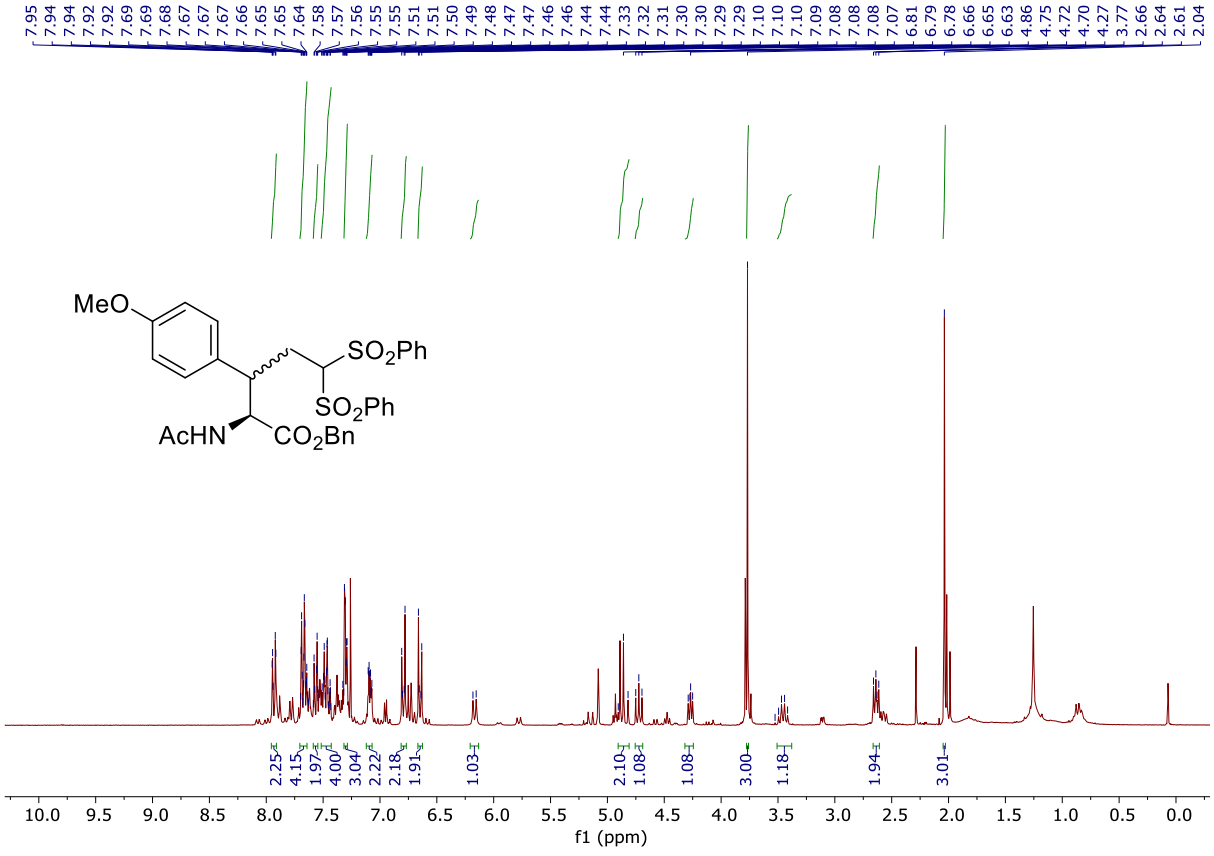


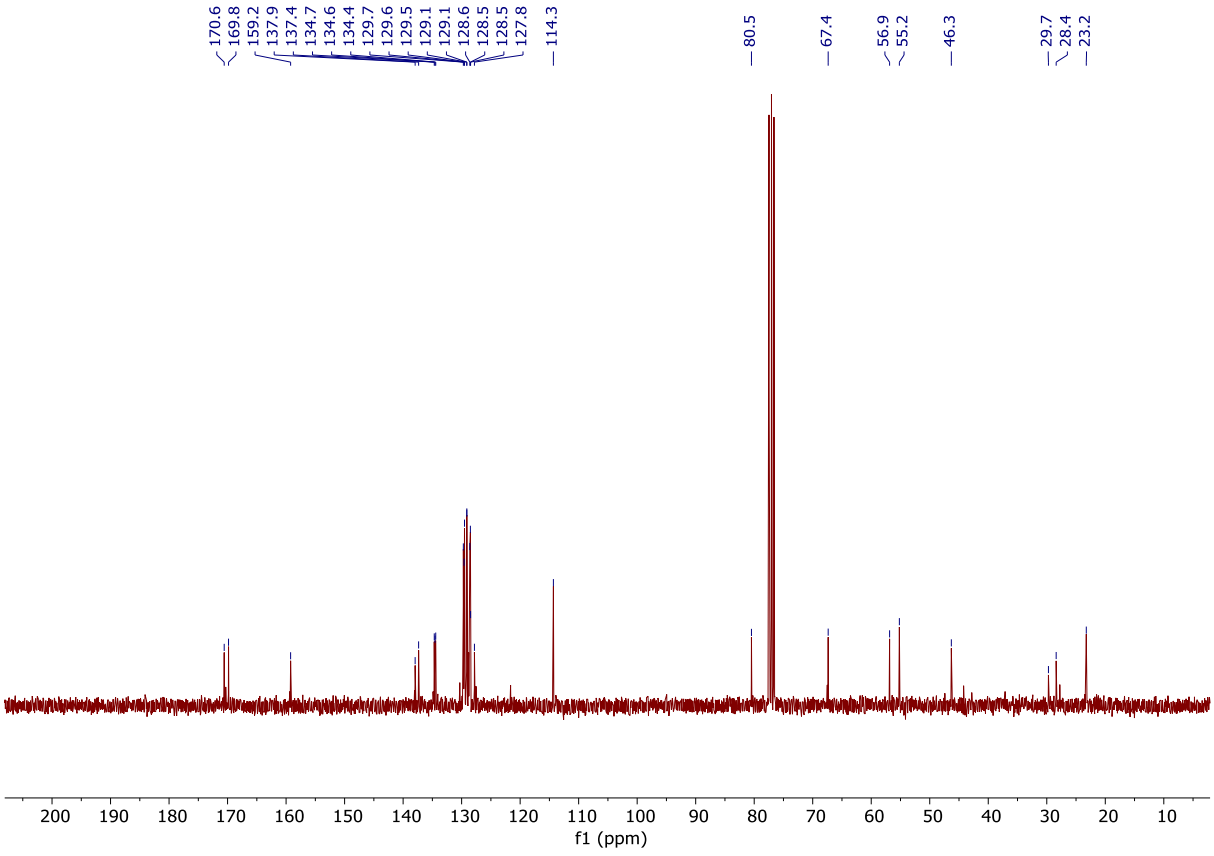


*tert-Butyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (minor **10**)*

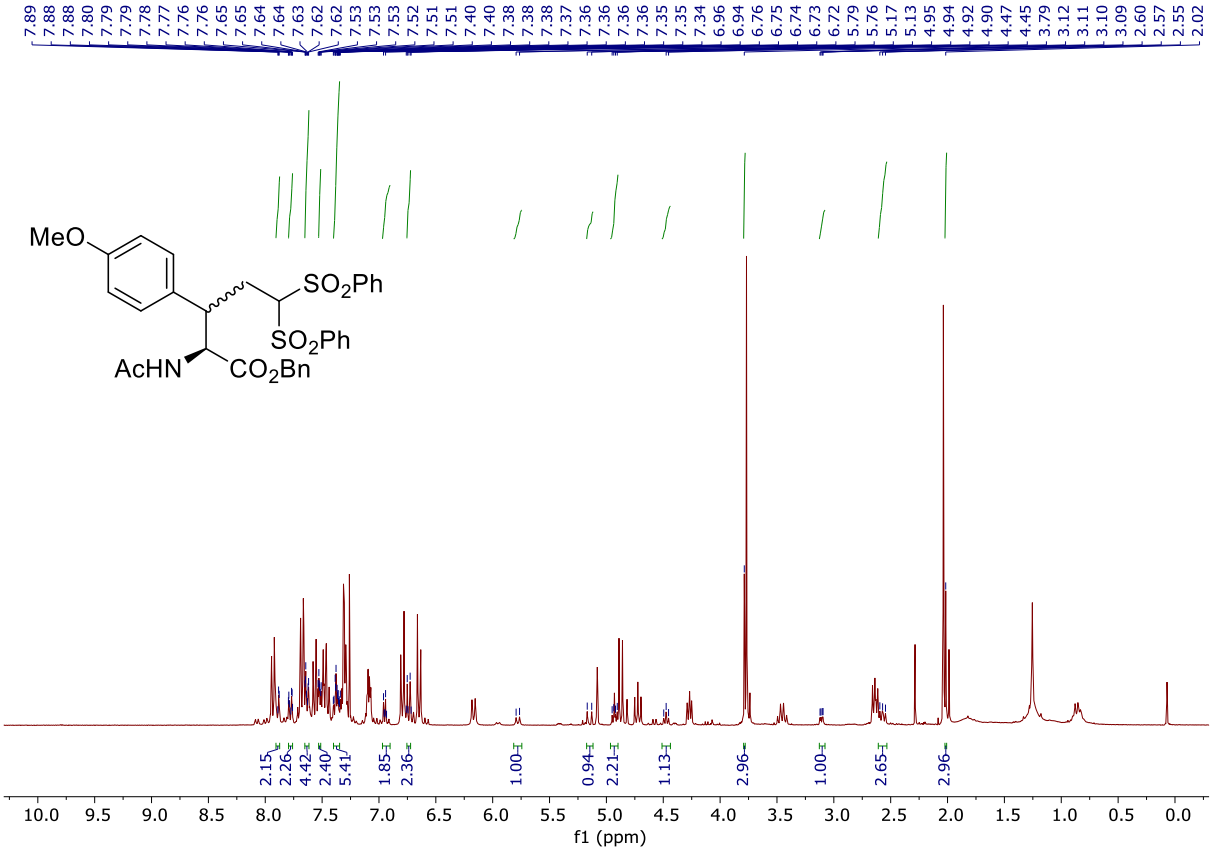


*Benzyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (major **11**)*

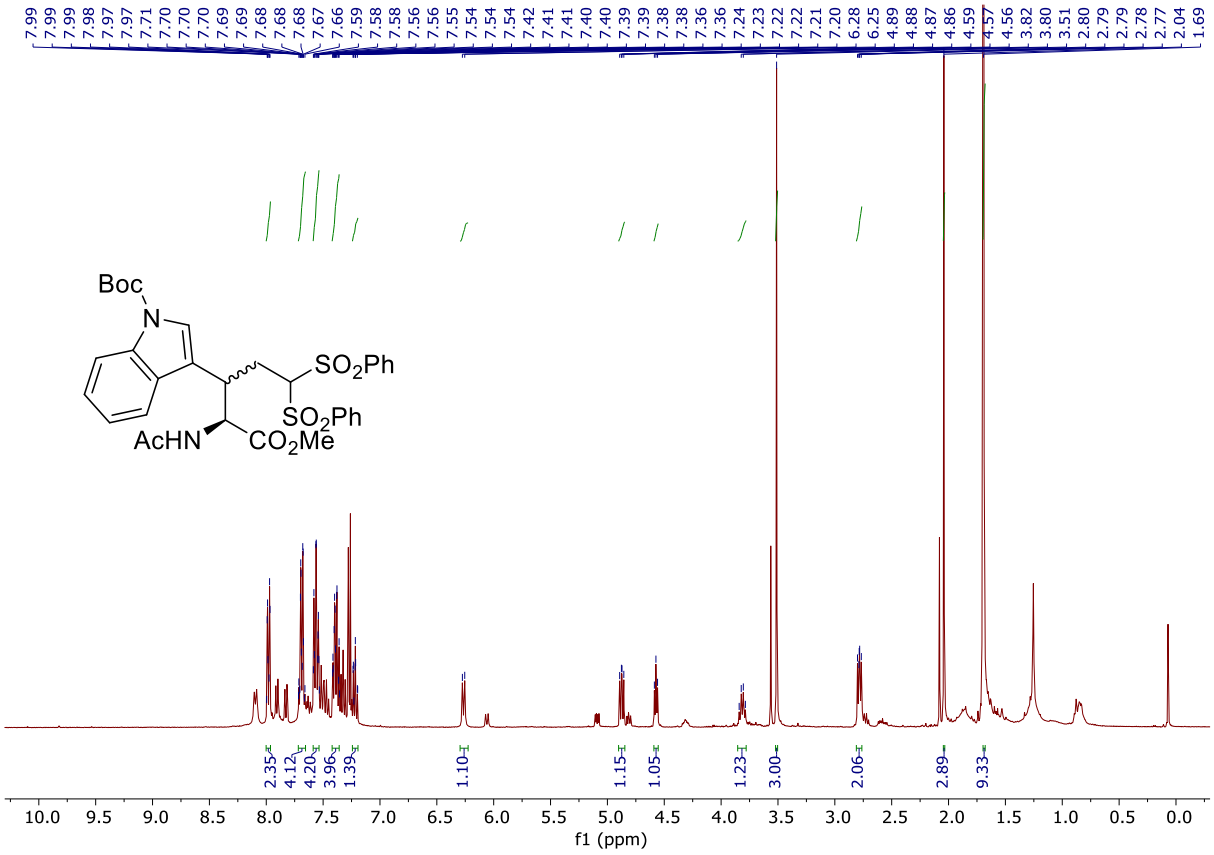


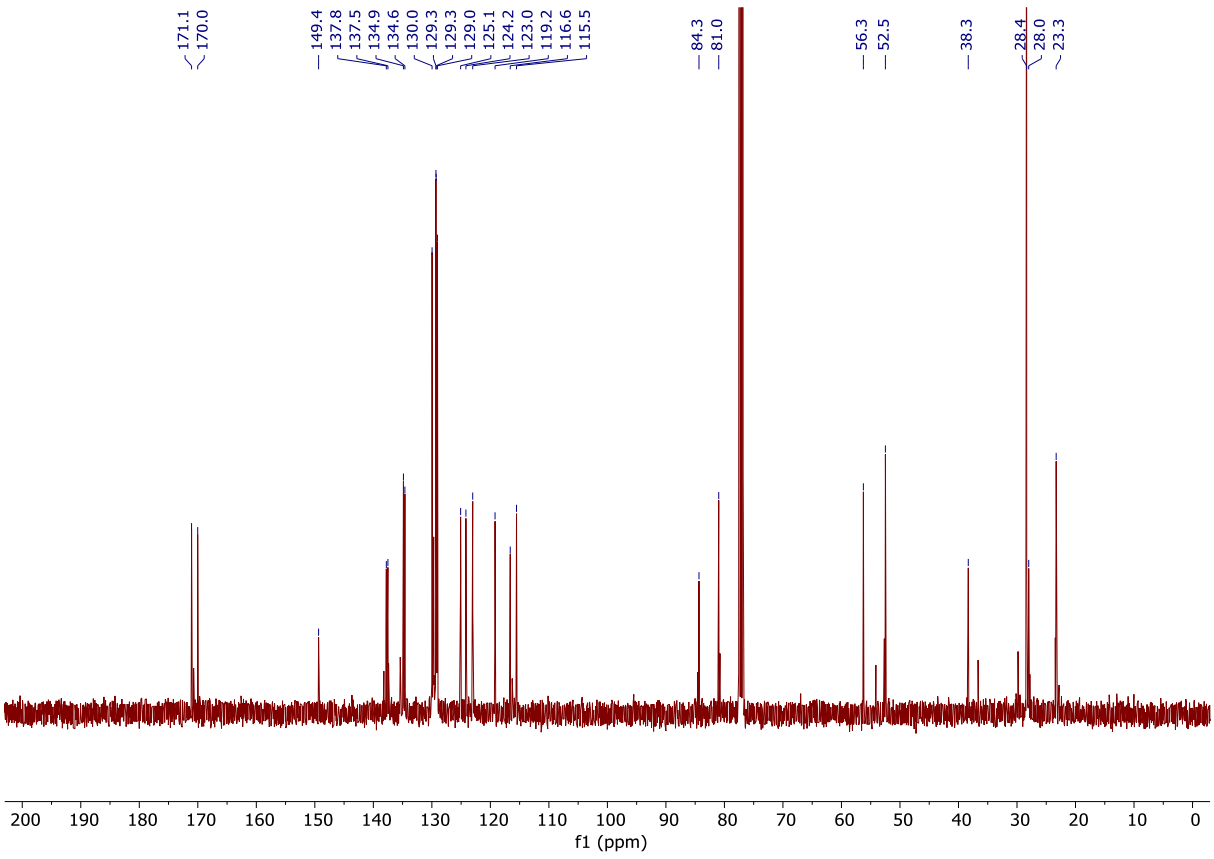


*Benzyl (2S)-2-acetamido-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (minor **11**)*

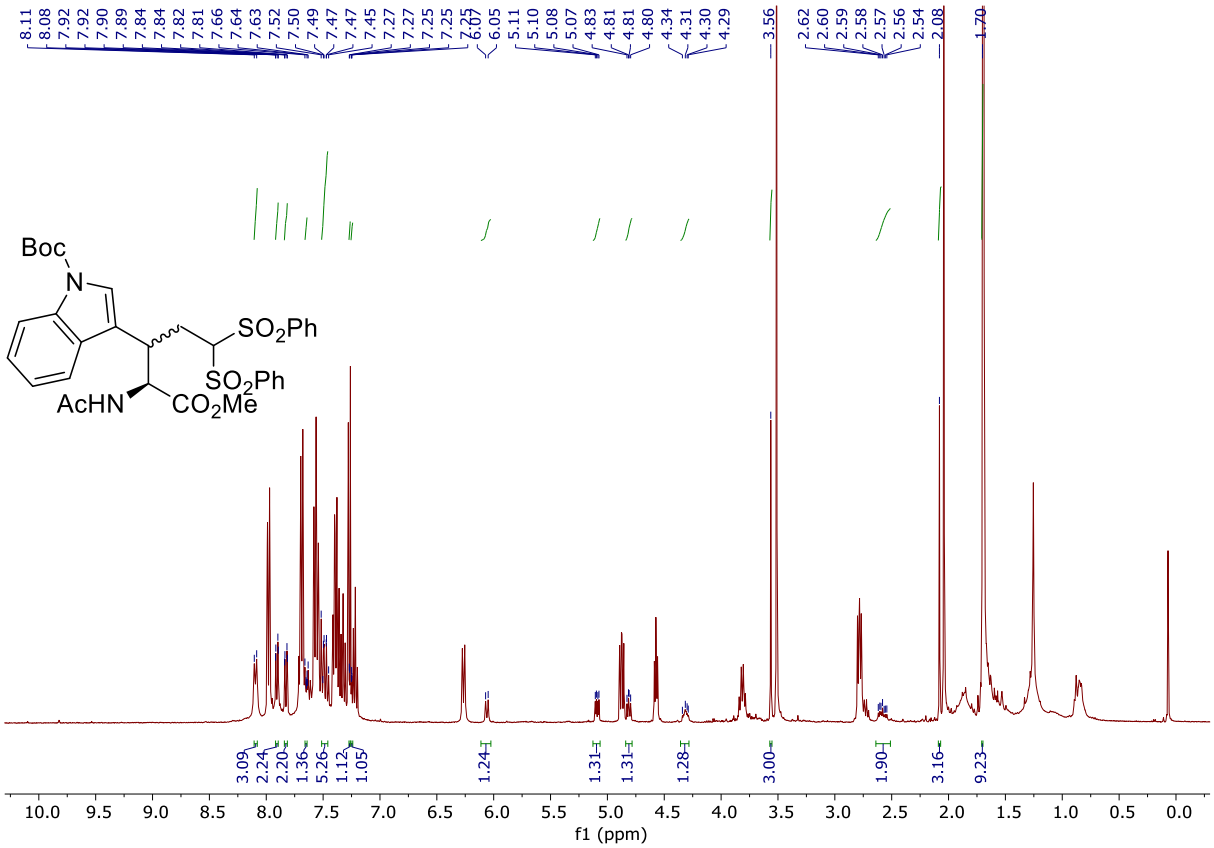


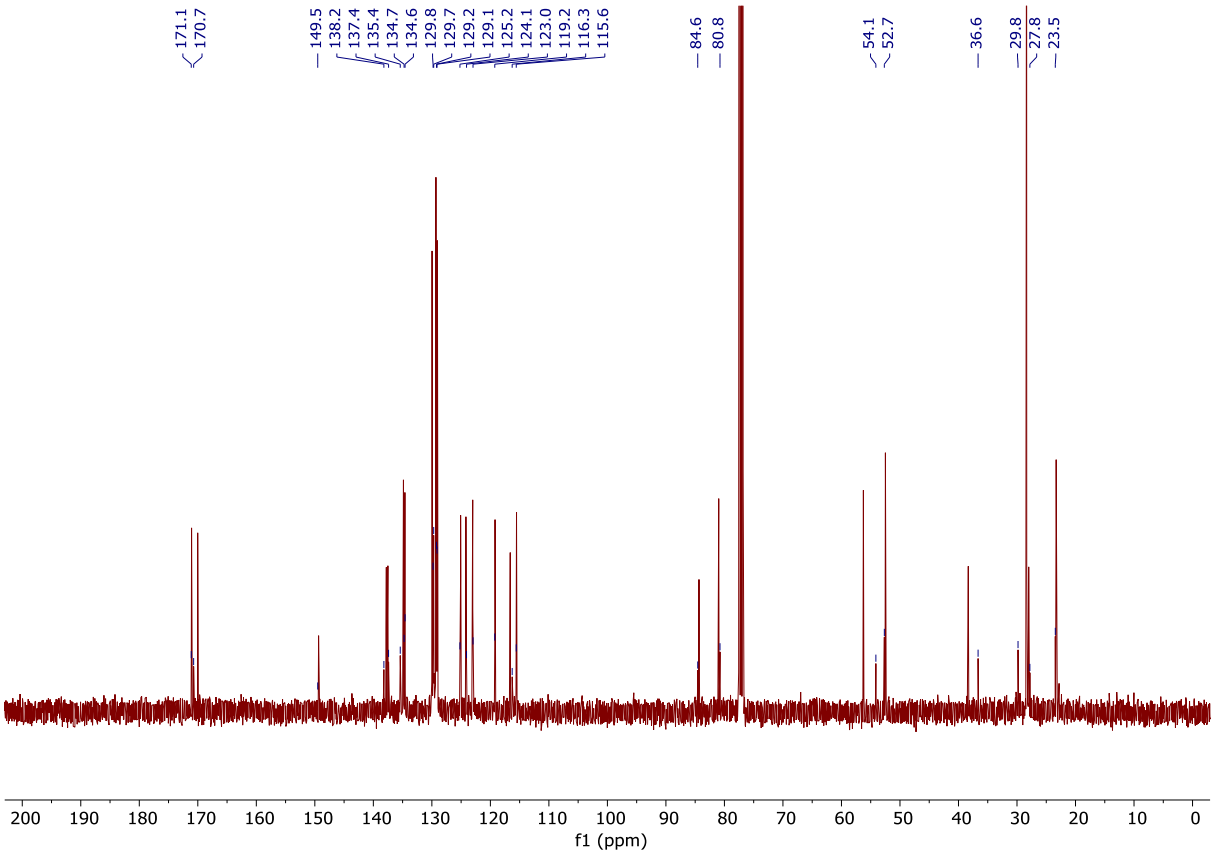
*tert-Butyl 3-((2S)-2-acetamido-1-methoxy-1-oxo-5,5-bis(phenylsulfonyl)pentan-3-yl)-1H-indole-1-carboxylate (major **15**)*



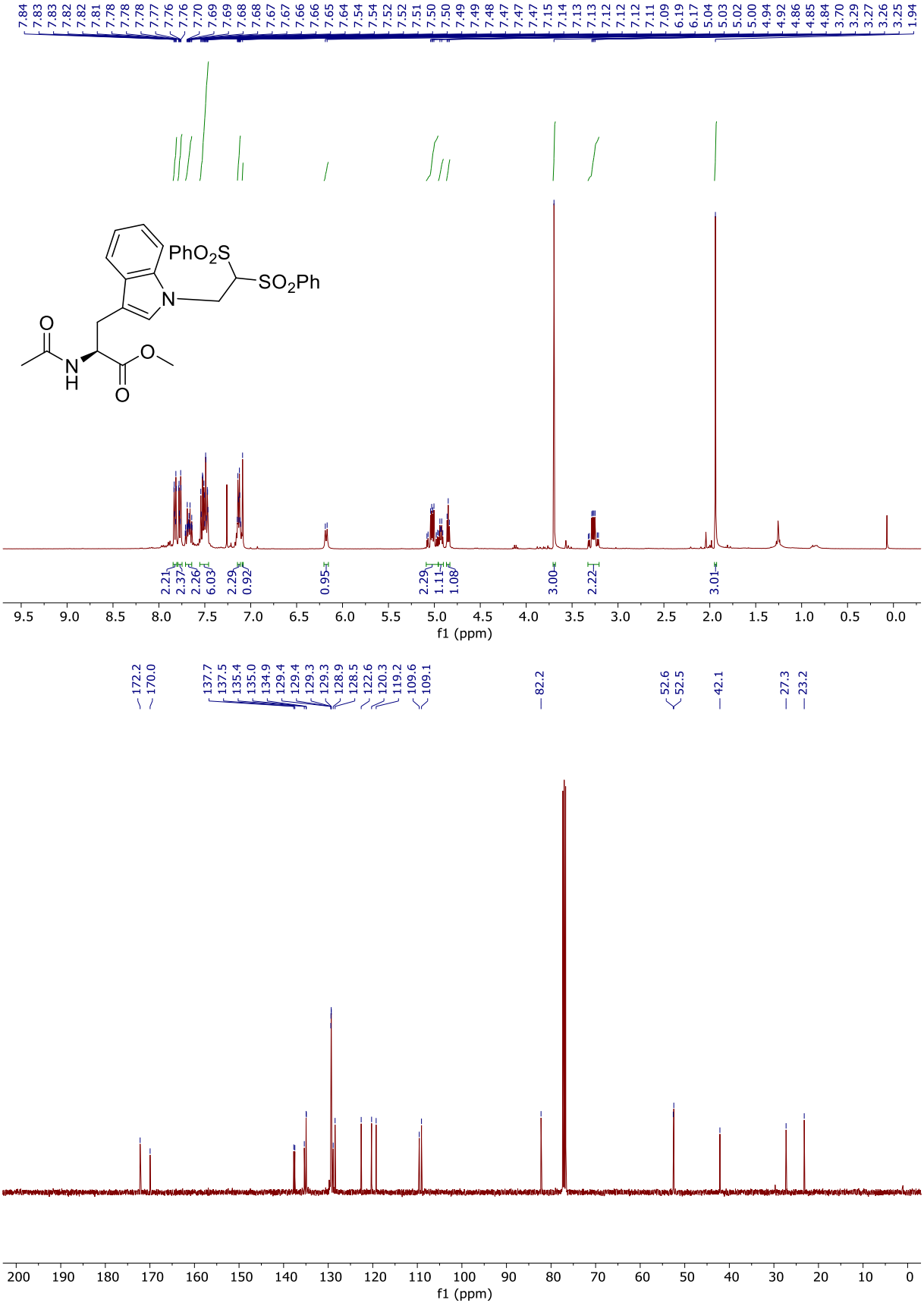


*tert-Butyl 3-((2S)-2-acetamido-1-methoxy-1-oxo-5,5-bis(phenylsulfonyl)pentan-3-yl)-1H-indole-1-carboxylate (minor **15**)*

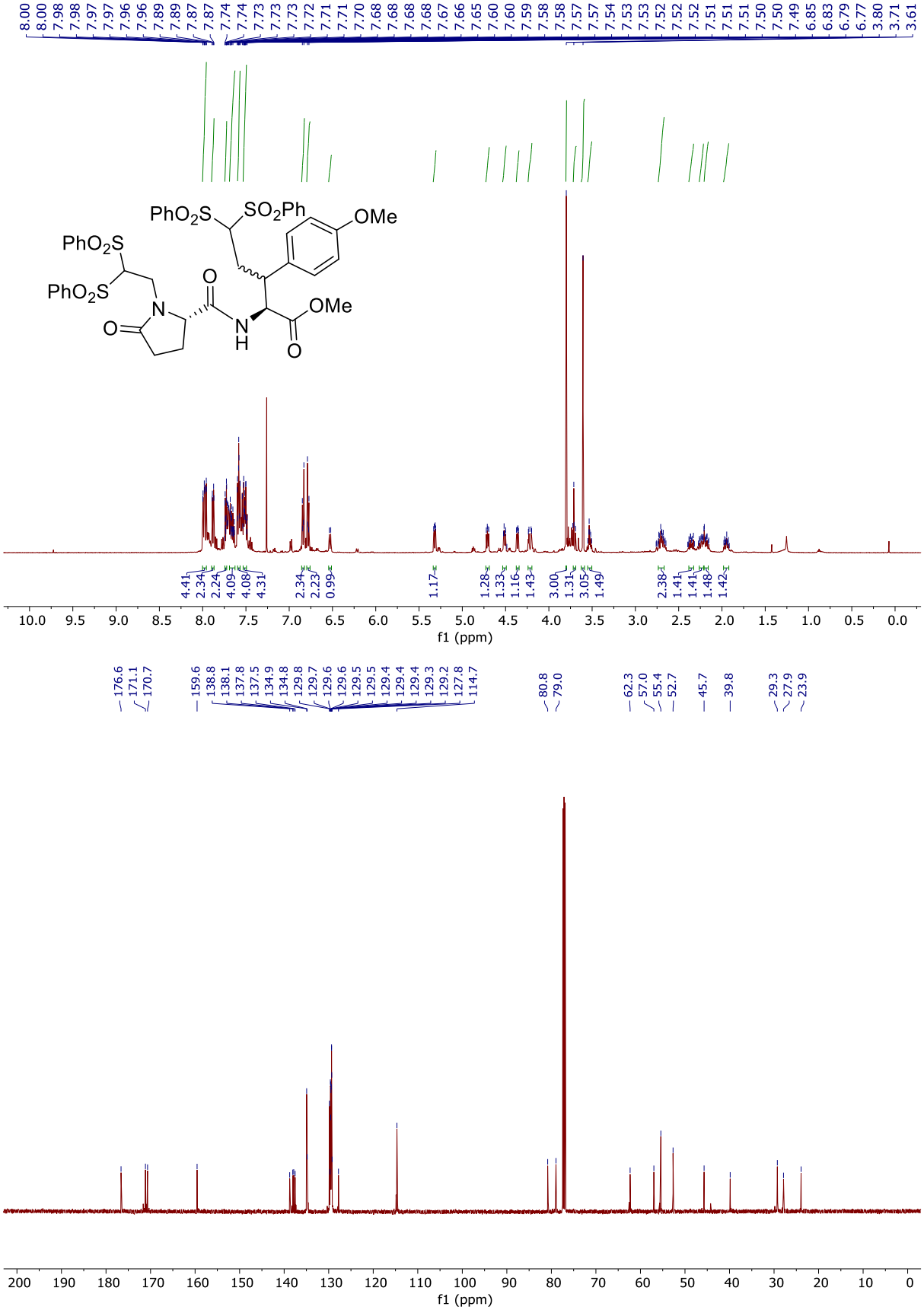




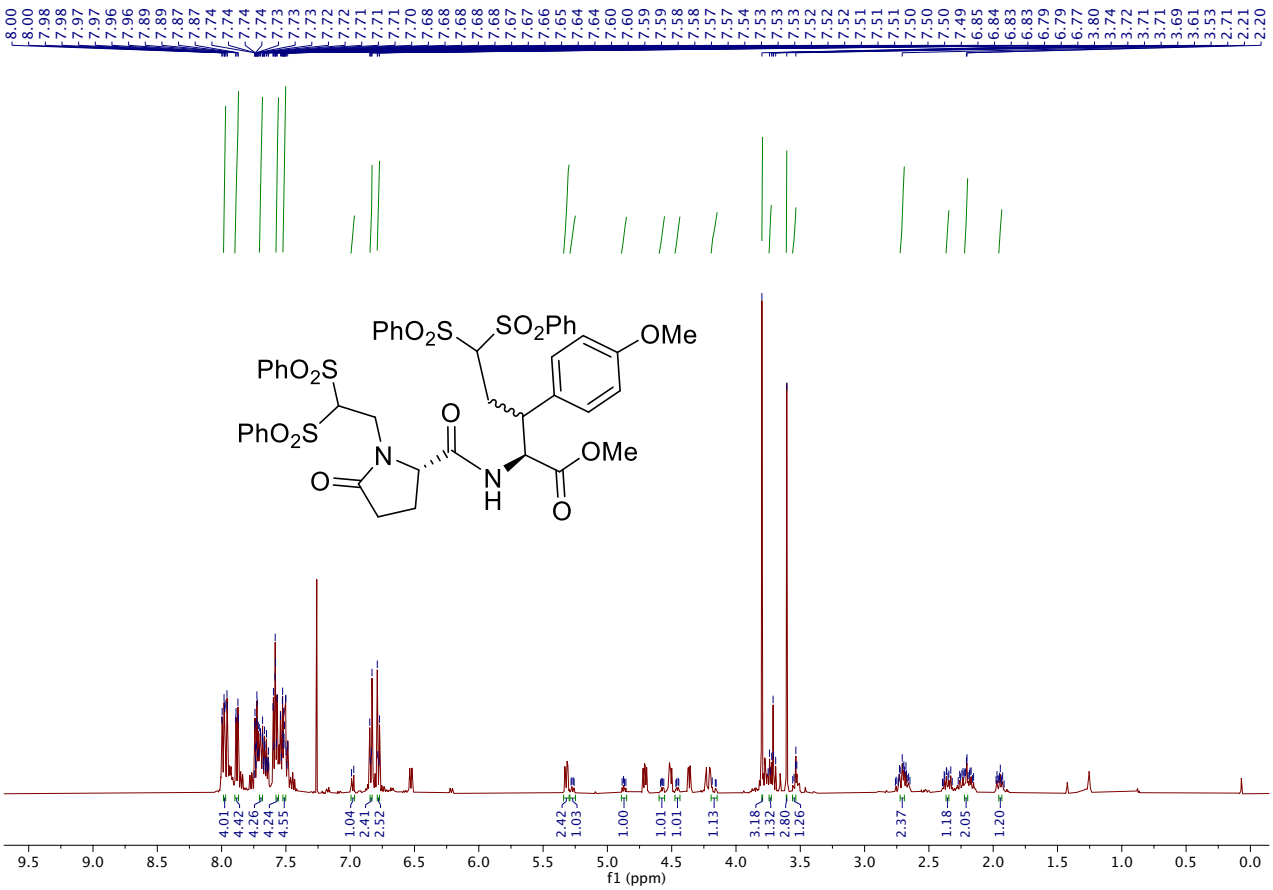
Methyl N-acetyl-1-(2,2-bis(phenylsulfonyl)ethyl)-L-tryptophanate



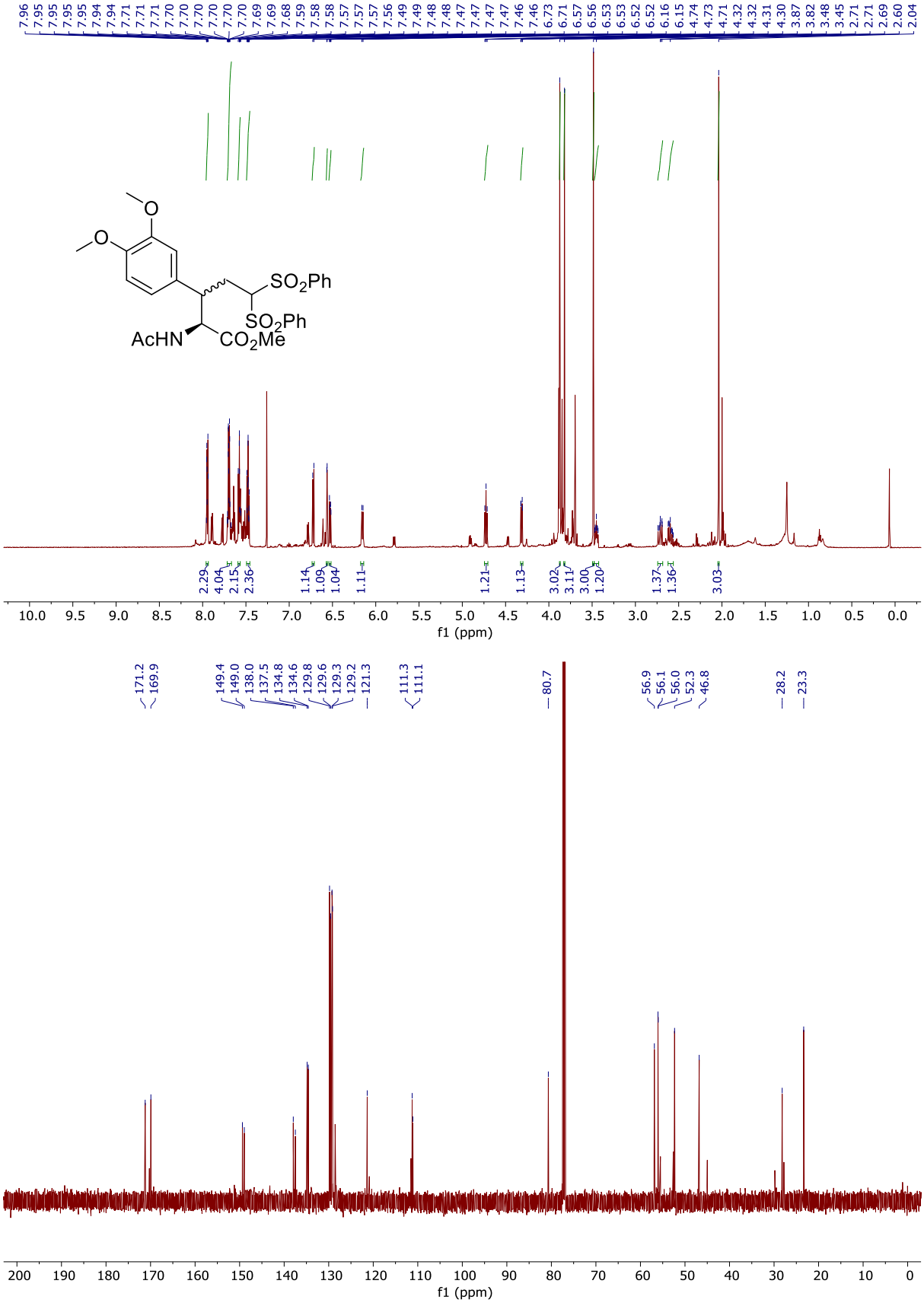
*Methyl (2S)-2-((S)-1-(2,2-bis(phenylsulfonyl)ethyl)-5-oxopyrrolidine-2-carboxamido)-3-(4-methoxypenyl)-5,5-bis(phenylsulfonyl)pentanoate (major **16**)*



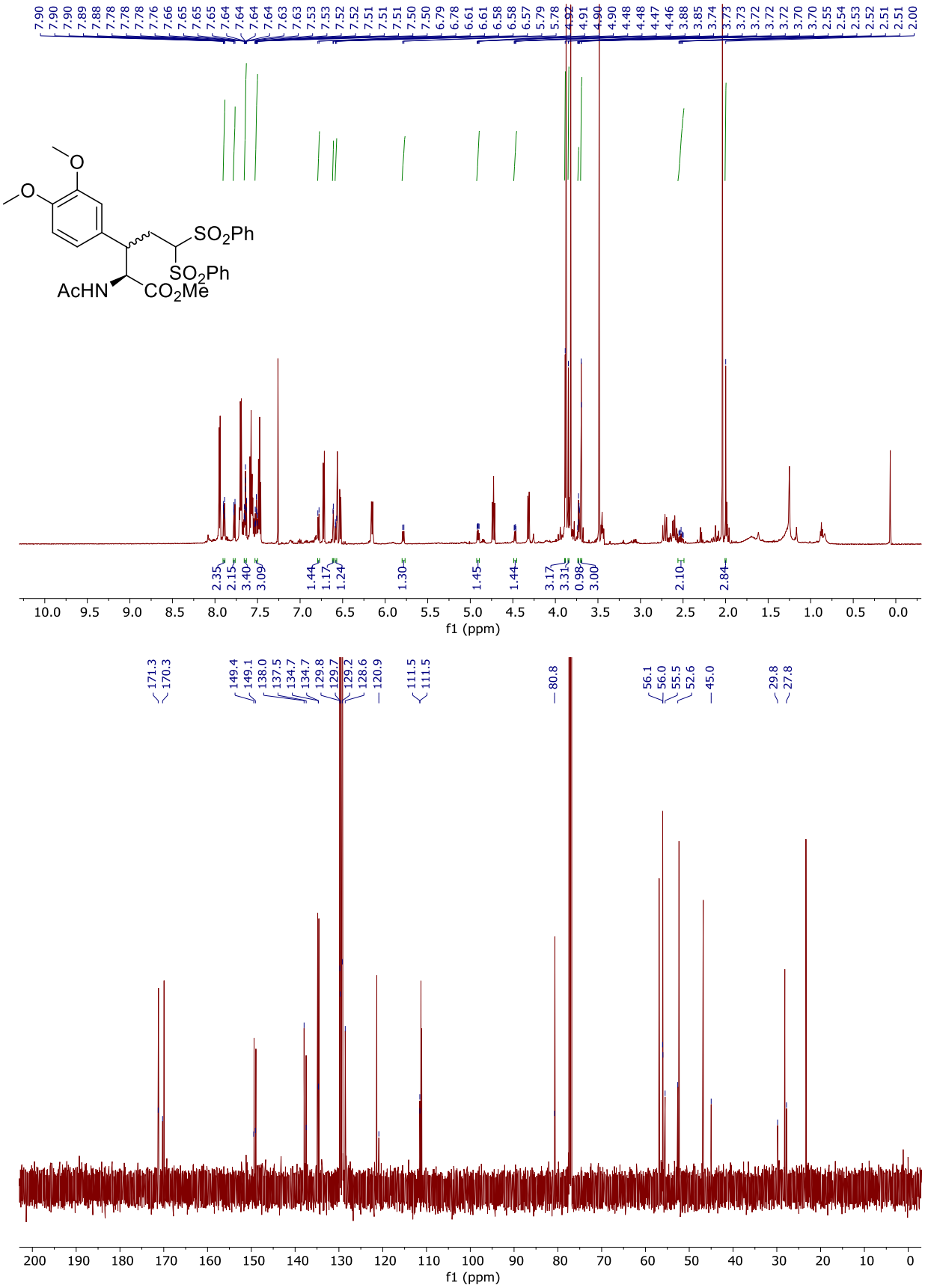
*Methyl (2S)-2-((S)-1-(2,2-bis(phenylsulfonyl)ethyl)-5-oxopyrrolidine-2-carboxamido)-3-(4-methoxypenyl)-5,5-bis(phenylsulfonyl)pentanoate (minor **16**)*



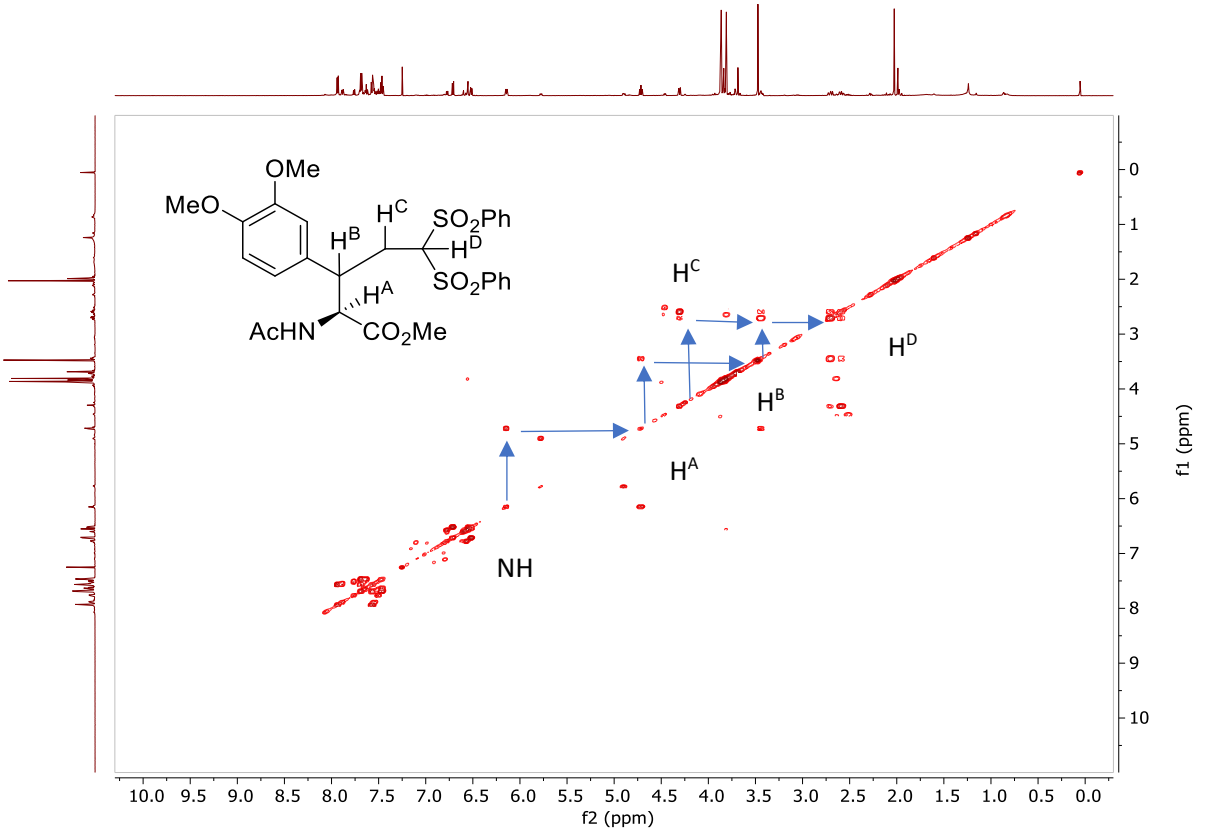
*Methyl (2S)-2-acetamido-3-(3,4-dimethoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (major **17**)*



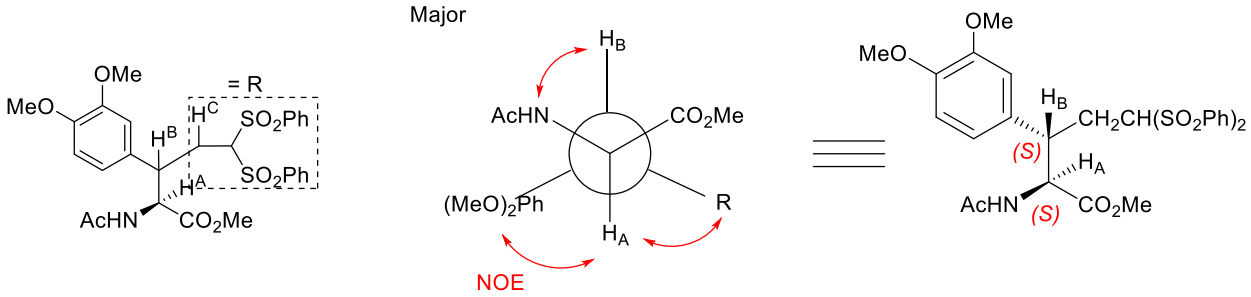
*Methyl (2S)-2-acetamido-3-(3,4-dimethoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (minor **17**)*



*COSY-spectrum of **17**:*

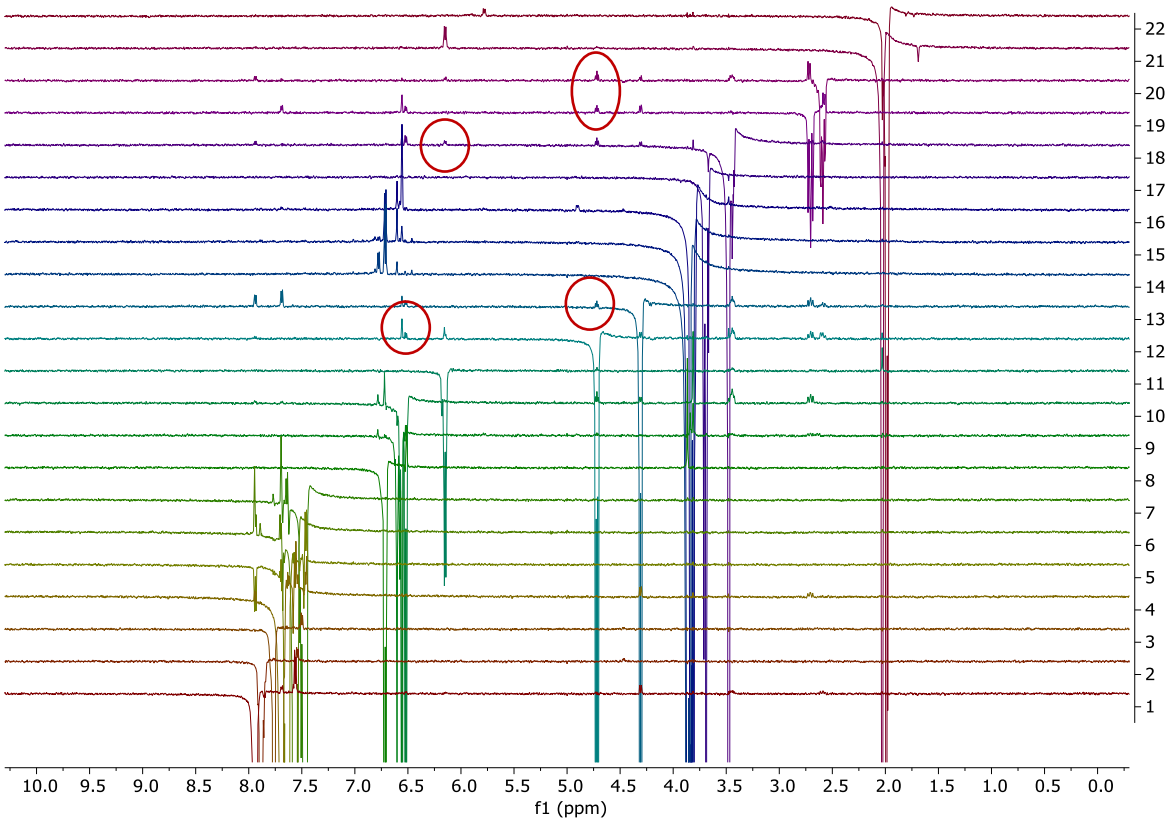


*Determination of the configuration of the major **17**:*

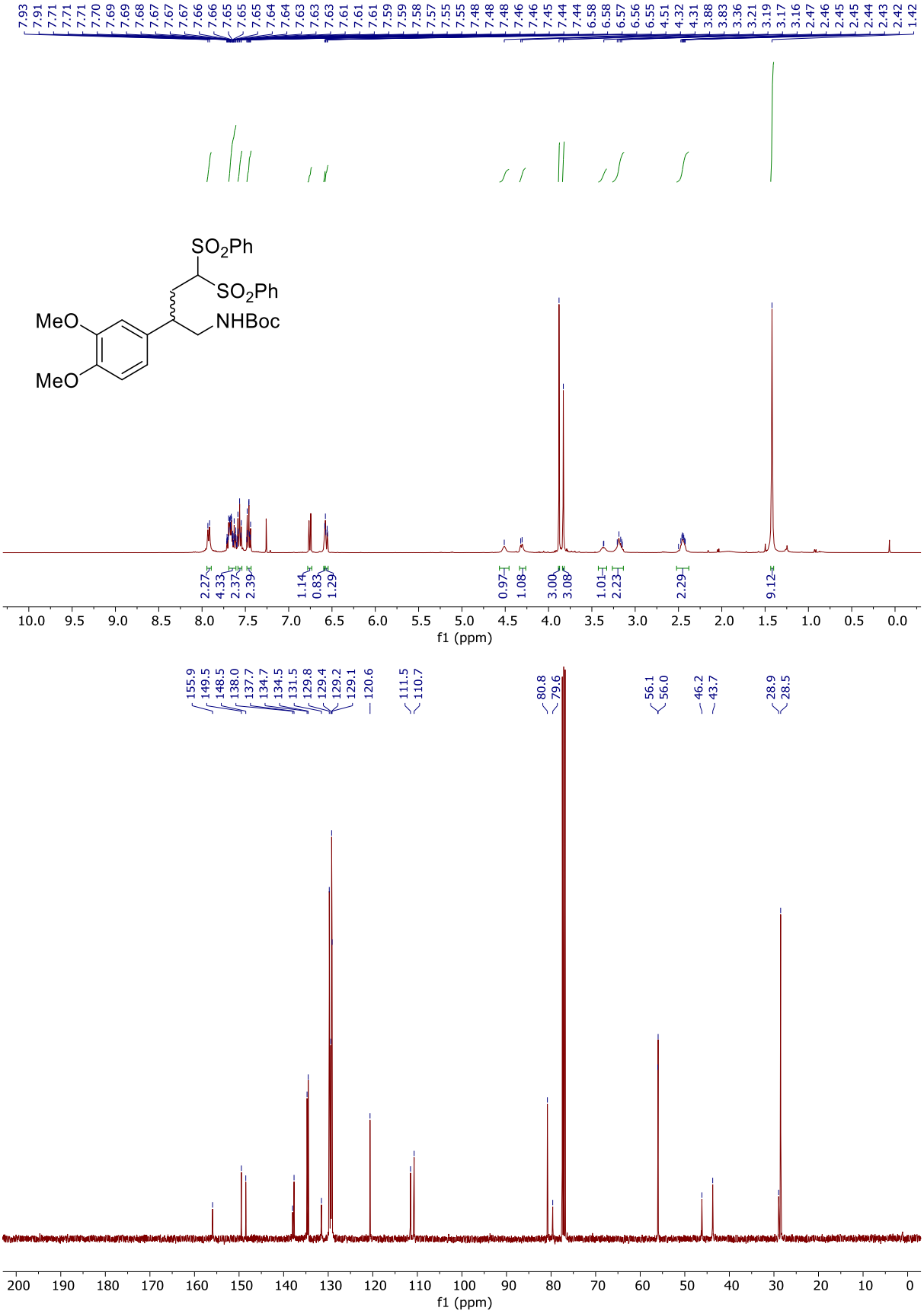


The coupling constant of the two methylene protons of the major isomer is $J(H^A, H^B)$ is 8.6 Hz, which suggests a predominant *anti*-conformation as shown on Newman projection above. In the 1D-NOESY spectra, strong interactions of NH↔H^B, H^A↔$Ph(OMe)_2$, H^A ↔H^C and H^A↔H^B were consistent with gauche conformation of these groups and (*S*) configuration at Tyr β-carbon.

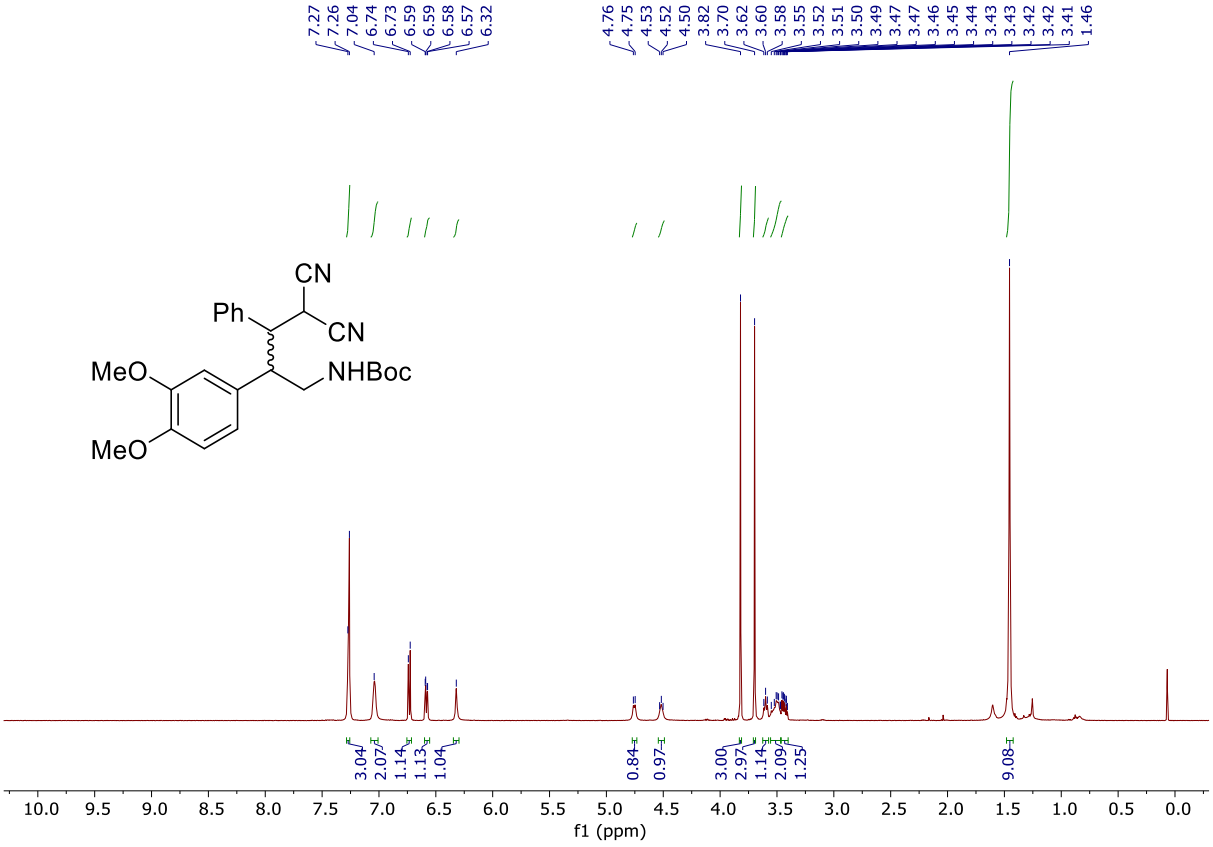
*1D-NOESY spectra of **17**:*

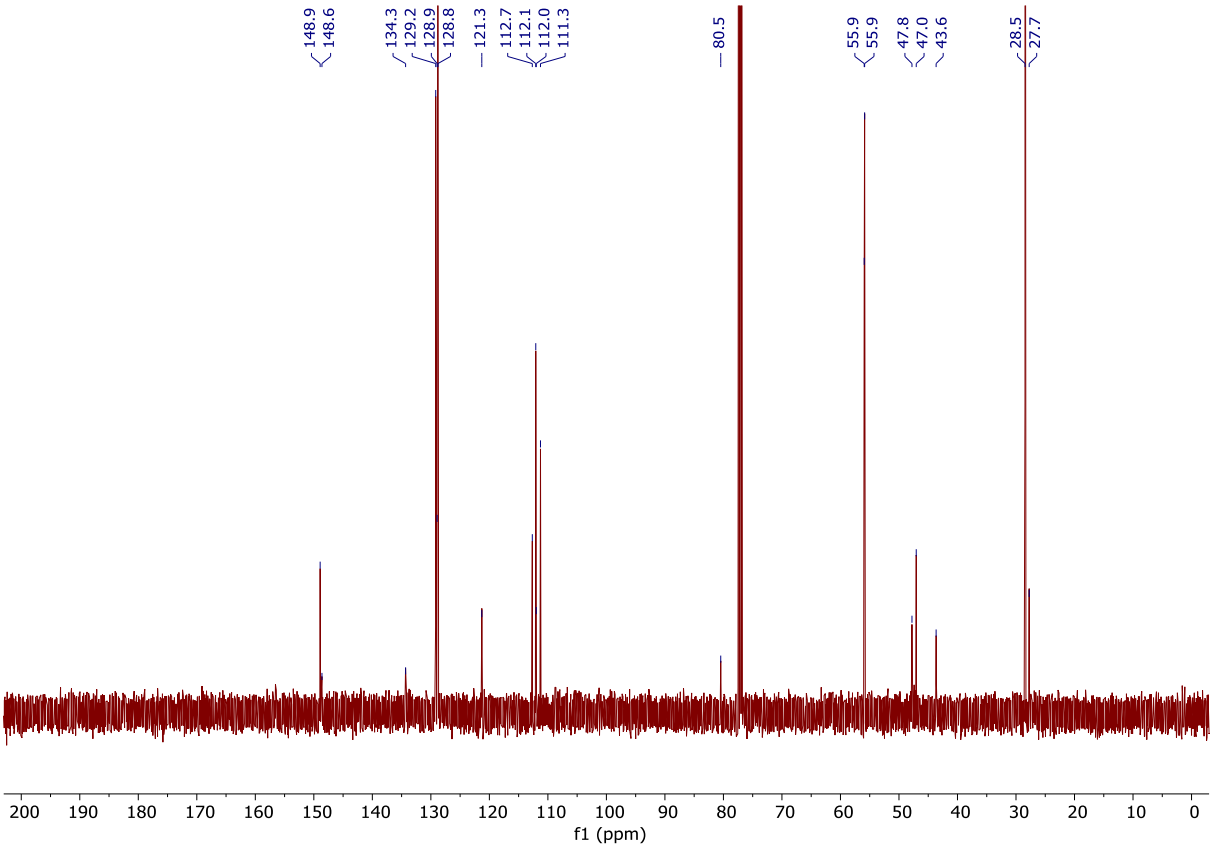


*tert-Butyl (2-(3,4-dimethoxyphenyl)-4-methylpentyl)carbamate (**18**)*

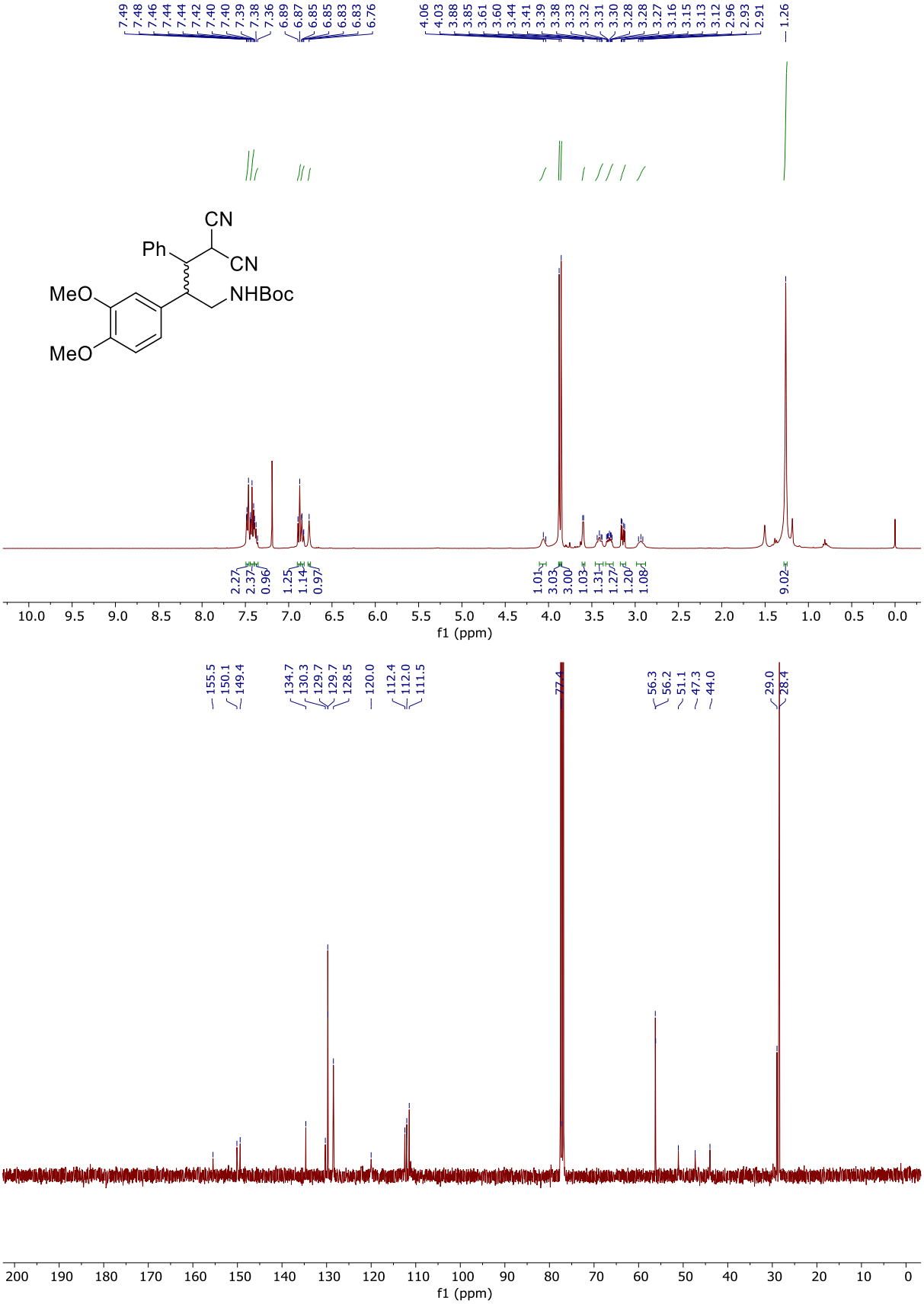


*tert-Butyl (4,4-dicyano-2-(3,4-dimethoxyphenyl)-3-phenylbutyl) carbamate (major **19**)*

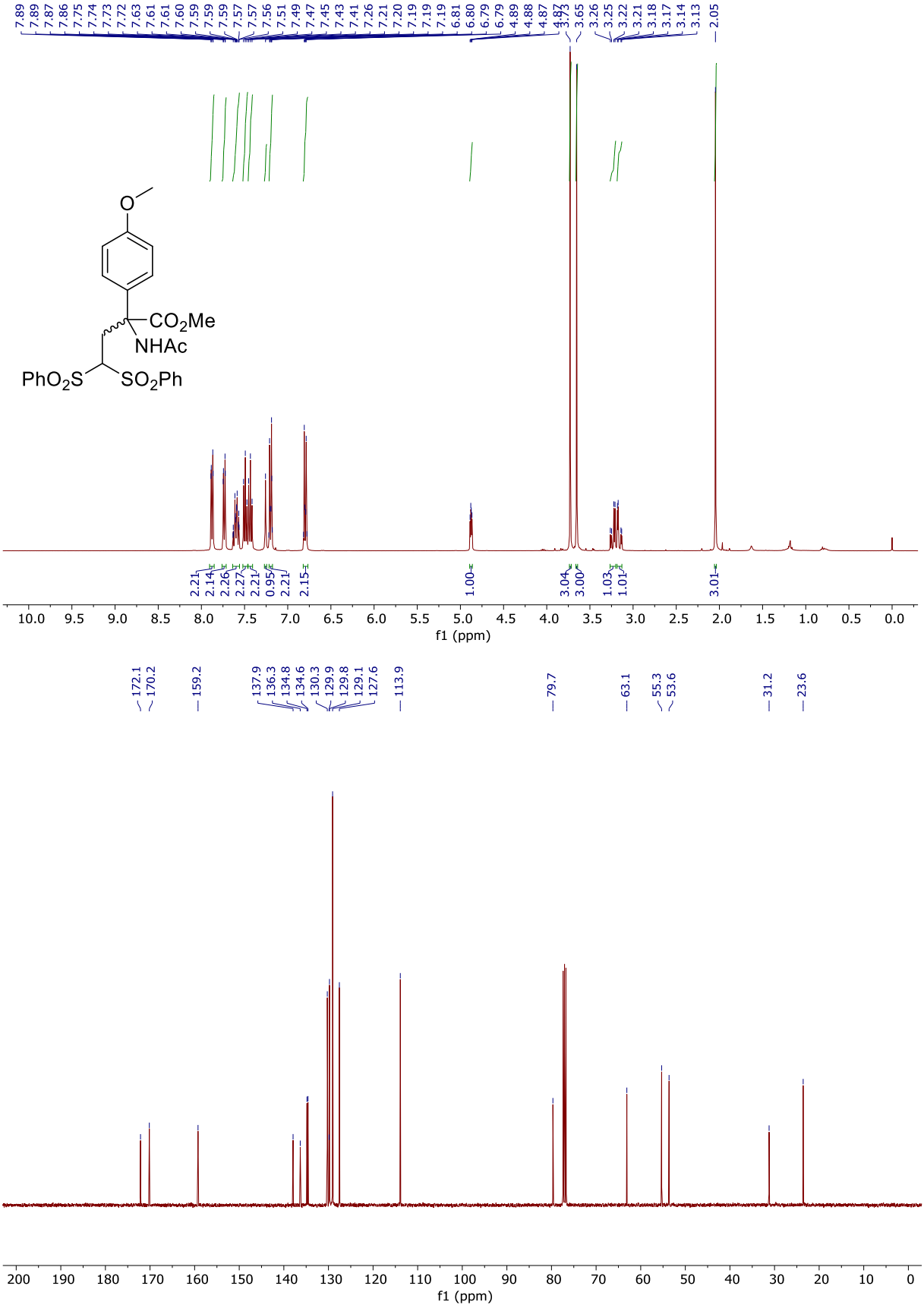




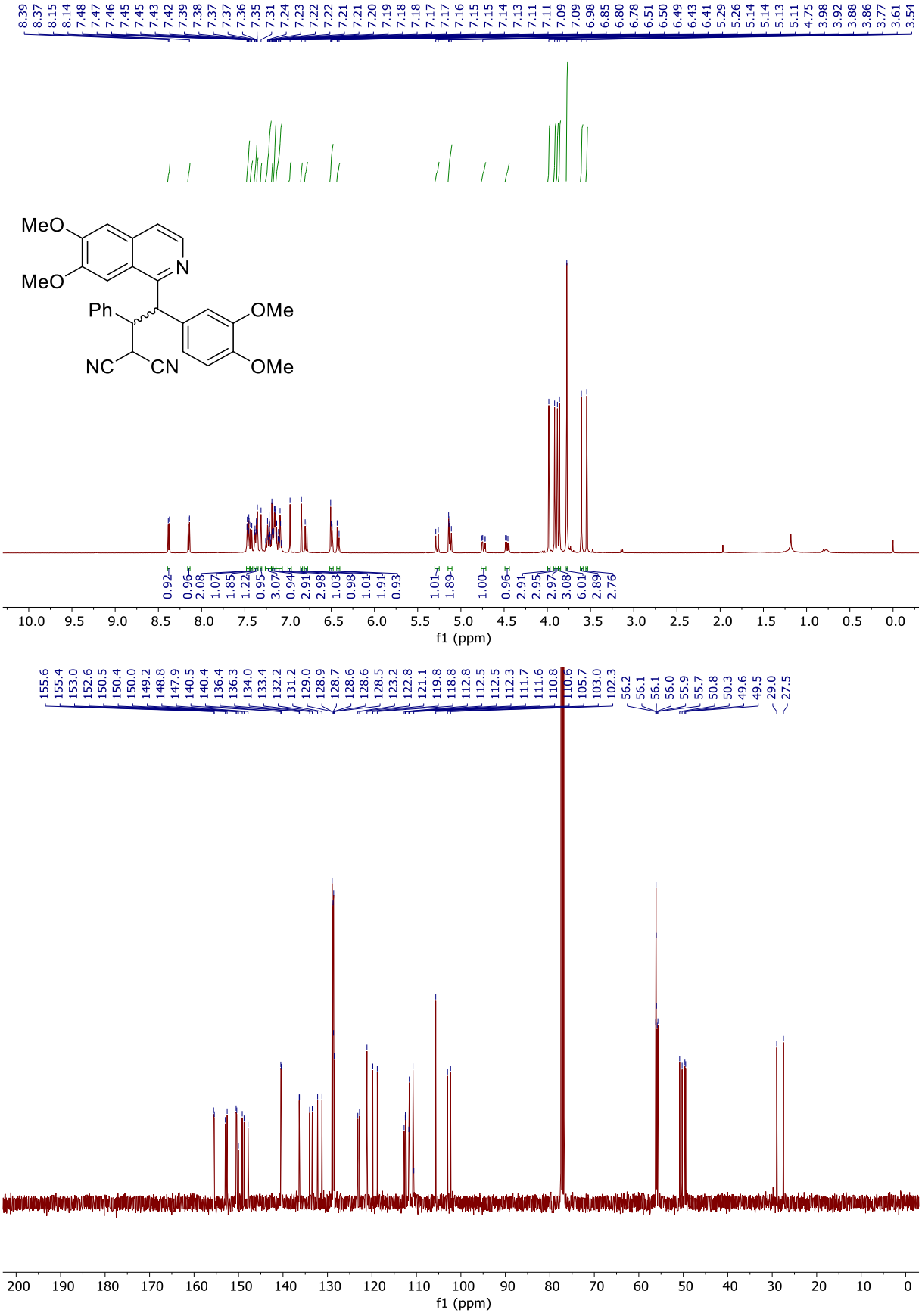
*tert-Butyl (4,4-dicyano-2-(3,4-dimethoxyphenyl)-3-phenylbutyl) carbamate (minor **19**)*



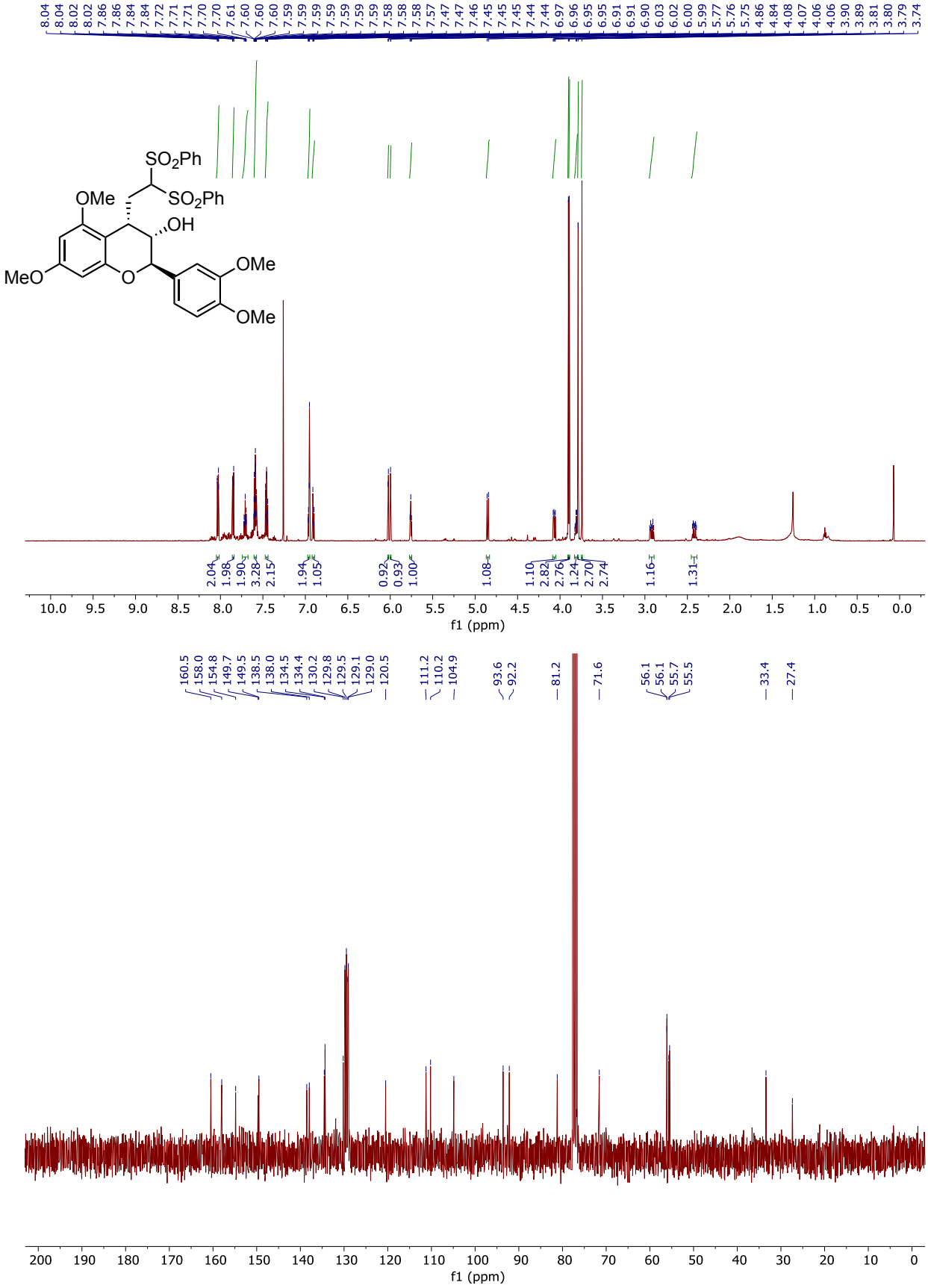
*Methyl 2-acetamido-2-(4-methoxyphenyl)-4,4-bis(phenylsulfonyl)butanoate (**20**)*



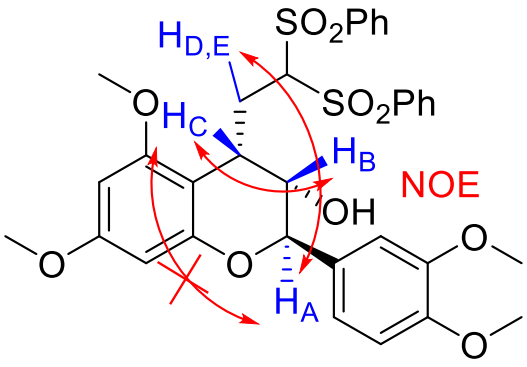
*2-(2-(6,7-Dimethoxyisoquinolin-1-yl)-2-(3,4-dimethoxyphenyl)-1-phenylethyl)malononitrile (**21**)*



*(2R,3S,4R)-4-(2,2-Bis(phenylsulfonyl)ethyl)-2-(3,4-dimethoxyphenyl)-5,7-dimethoxychroman-3-ol (**22**)*



*Determination of the configuration of **22**:*



H_A: 4.85 ppm (d, *J* = 10.0 Hz, 1H)

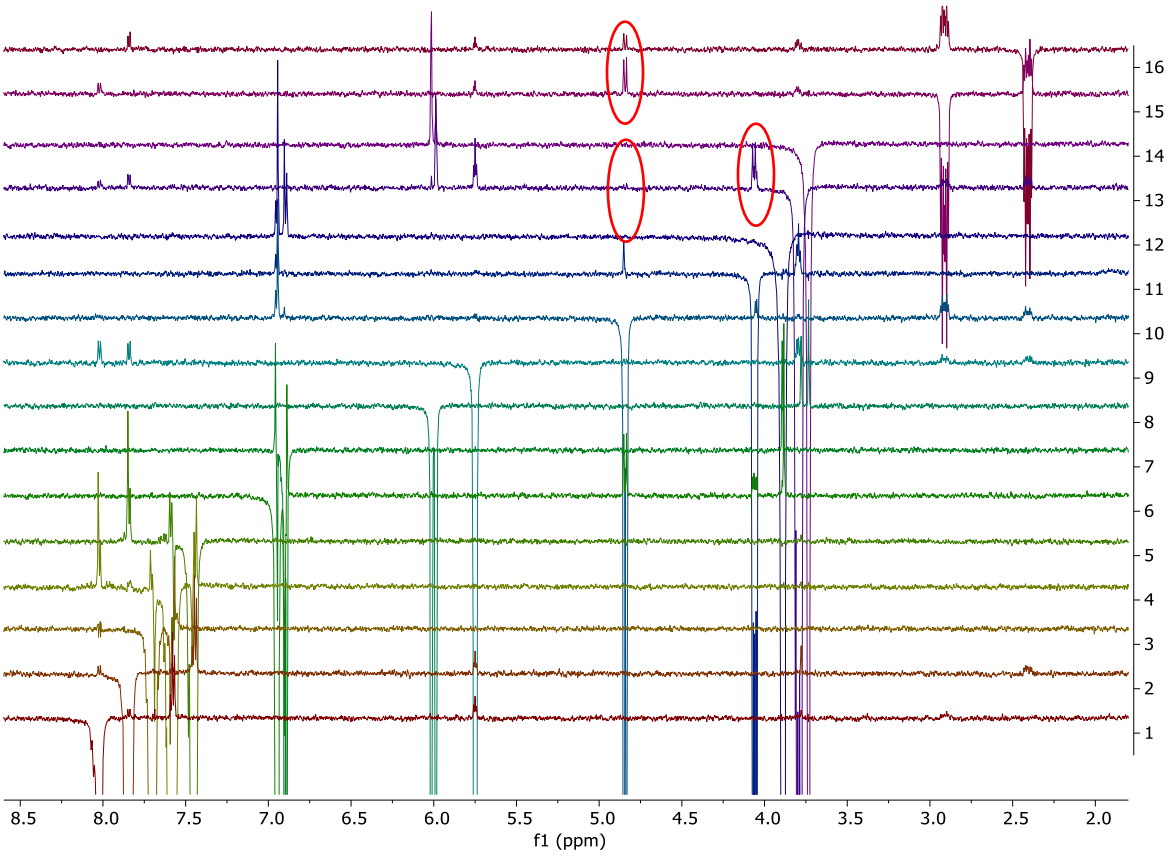
H_B: 4.07 ppm (dd, *J* = 10.0, 5.0 Hz, 1H)

H_C: 3.83-3.79 ppm (m, 1H)

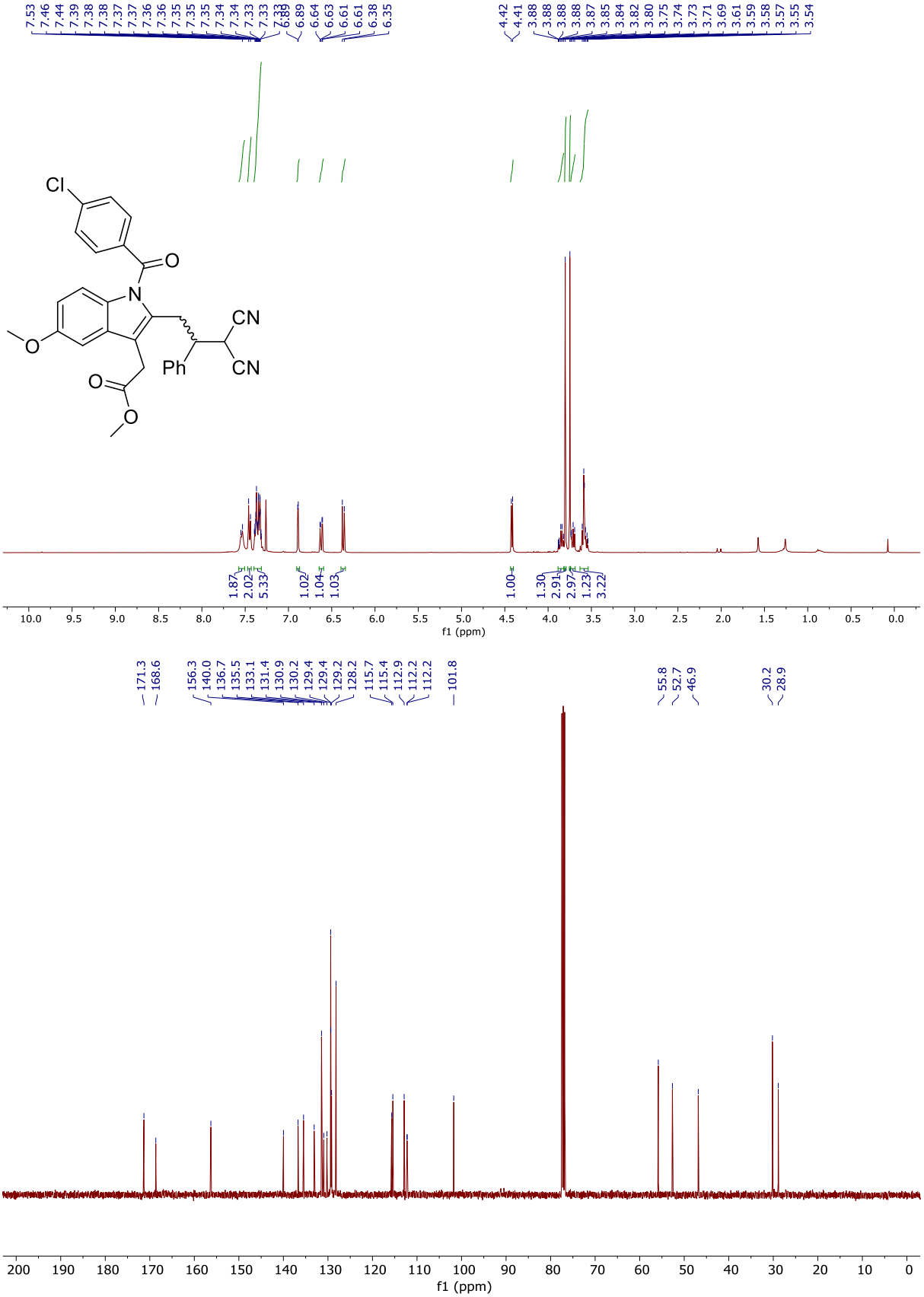
H_D: 2.92 ppm (dt, *J* = 15.8, 6.1 Hz, 1H)

H_E: 2.42ppm (ddd, *J* = 15.8, 6.6, 5.1 Hz, 1H)

*1D-NOESY spectra of **22**:*



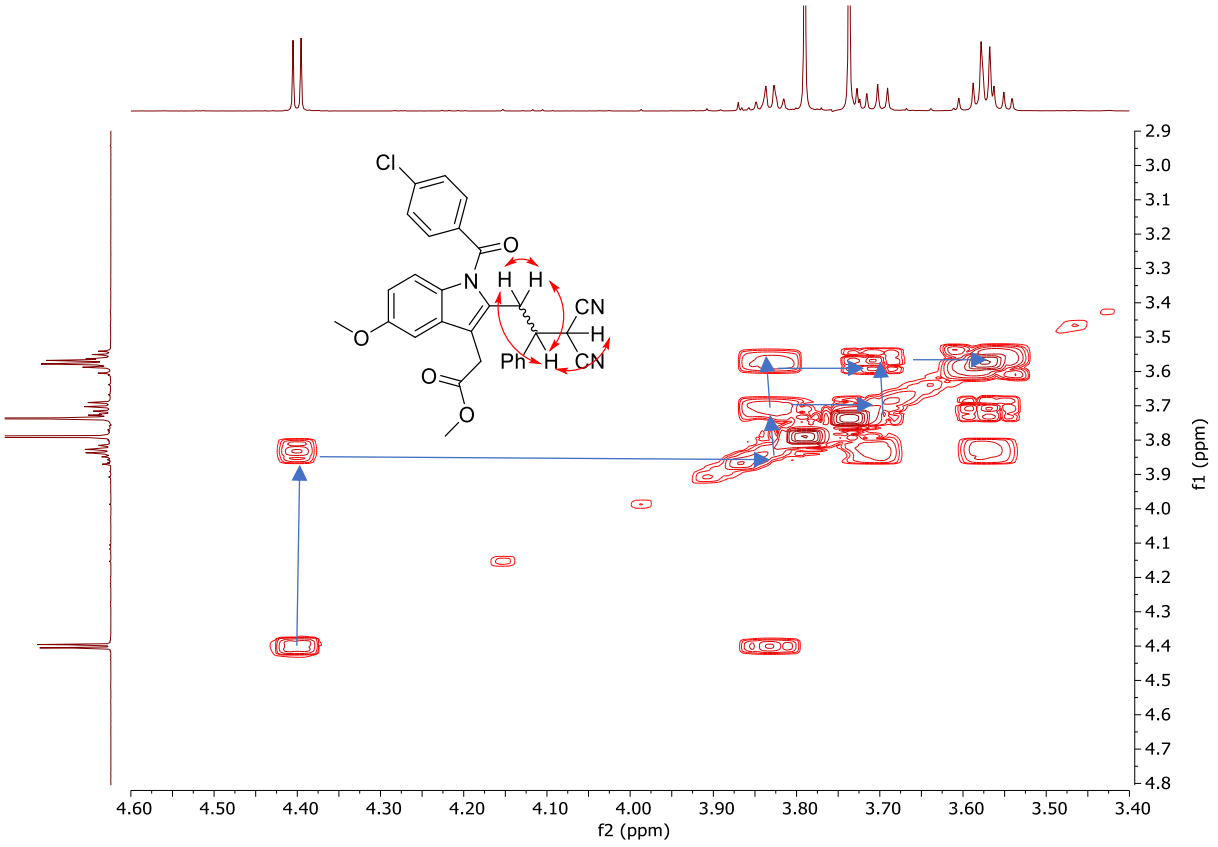
*Methyl 2-(1-(4-chlorobenzoyl)-2-(3,3-dicyano-2-phenylpropyl)-5-methoxy-1H-indol-3-yl) acetate (**23**)*



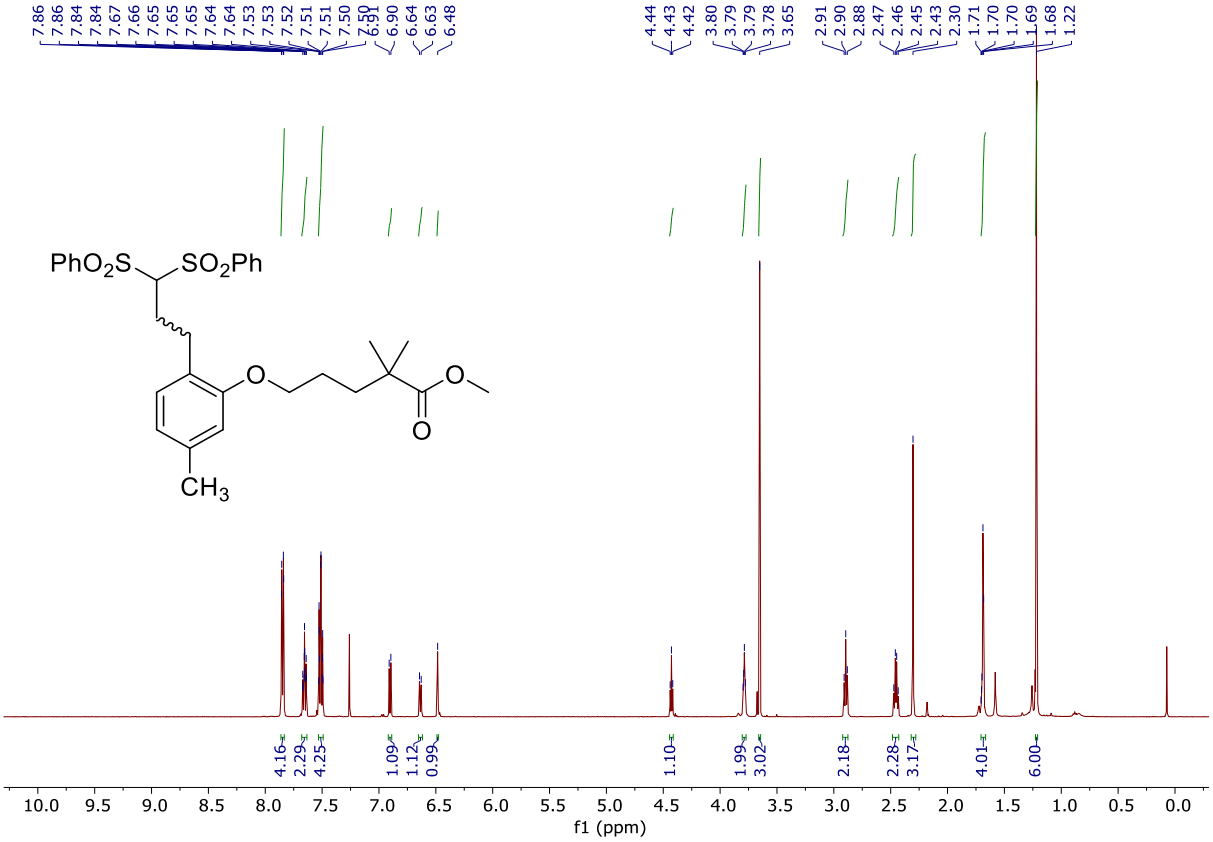
*Determination of the regioisomer of **23**:*

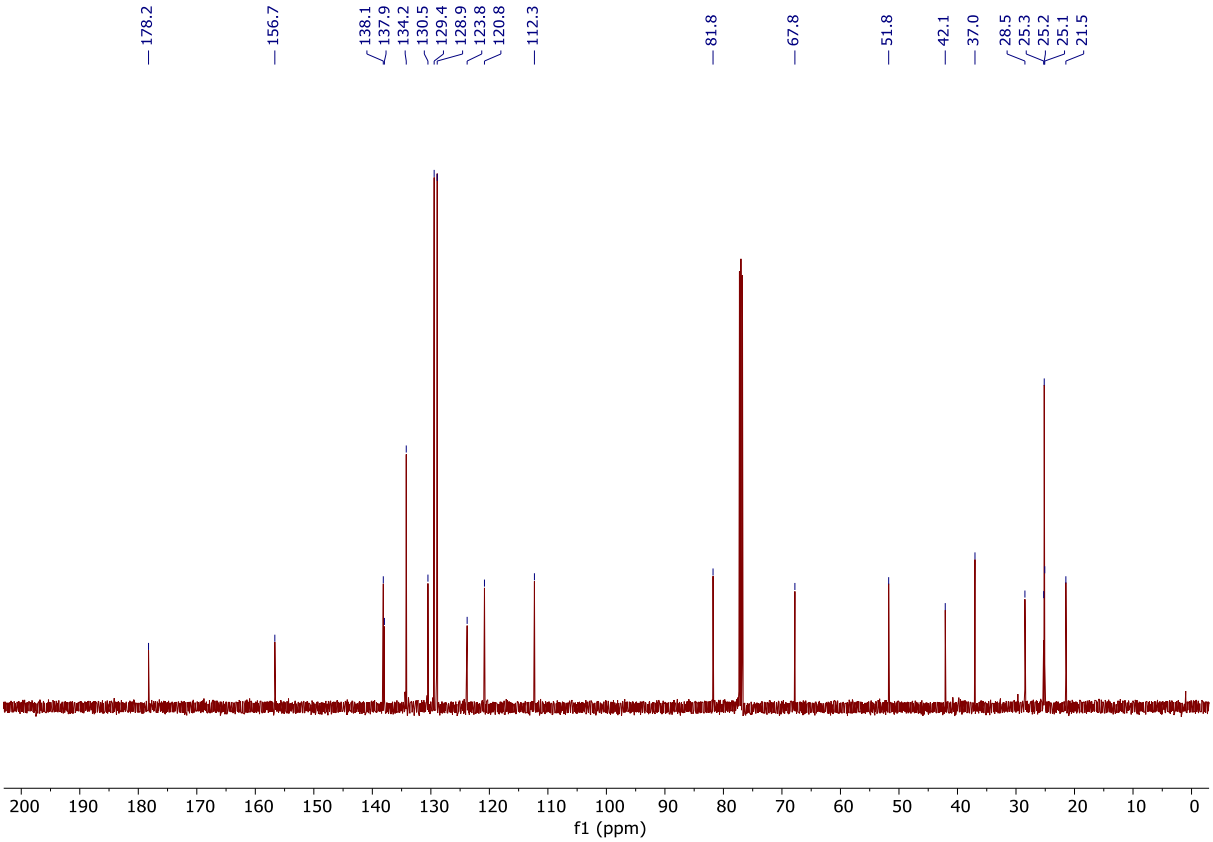
In the COSY spectrum, an alkylic spin-system consisting of 4 protons could be observed. This is consistent of the functionalization of the primary methyl group of indomethacin. Compared The functionalization of the secondary methylene group should deliver a spin-system of 3 protons.

*Section of the COSY spectrum of **23**:*

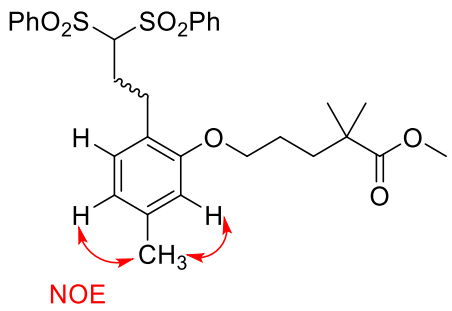


*Methyl 5-(2-(3,3-bis(phenylsulfonyl)propyl)-5-methylphenoxy)-2,2-dimethylpentanoate (**24**)*



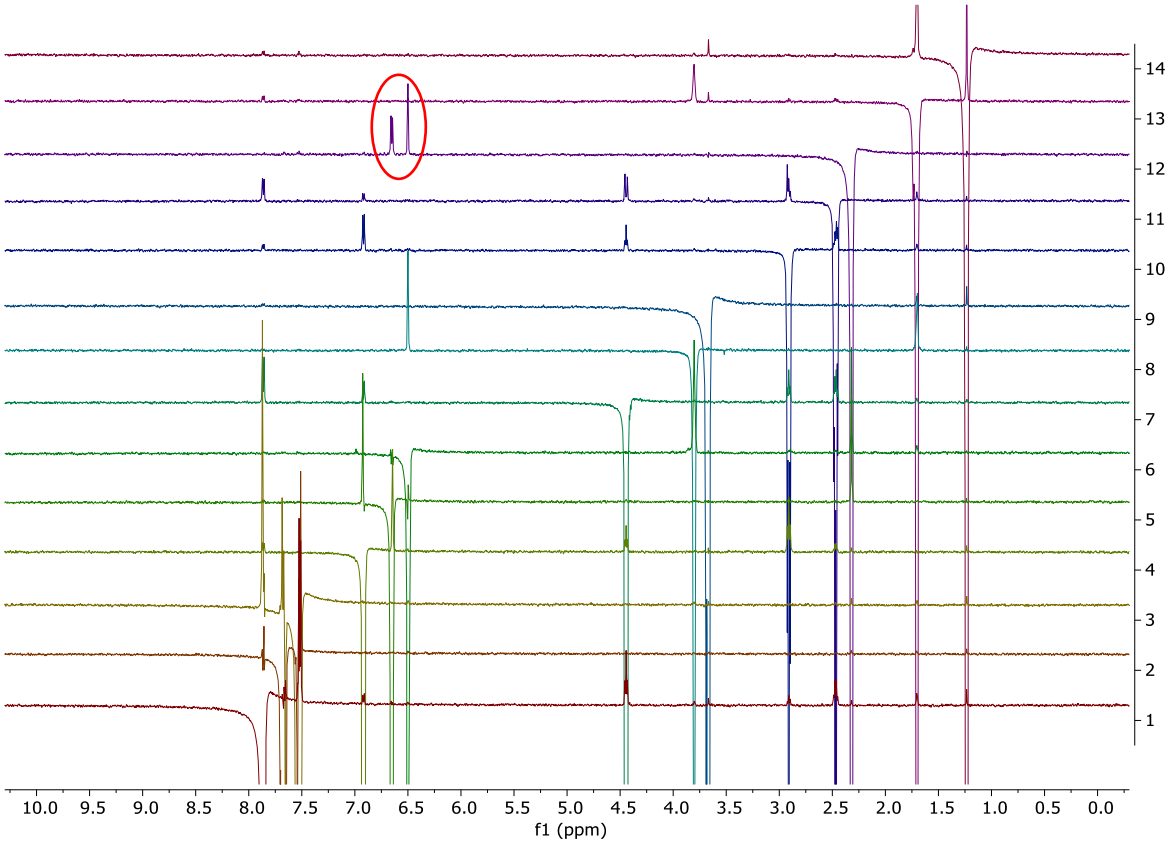


*Determination of the major regioisomer of **24**:*

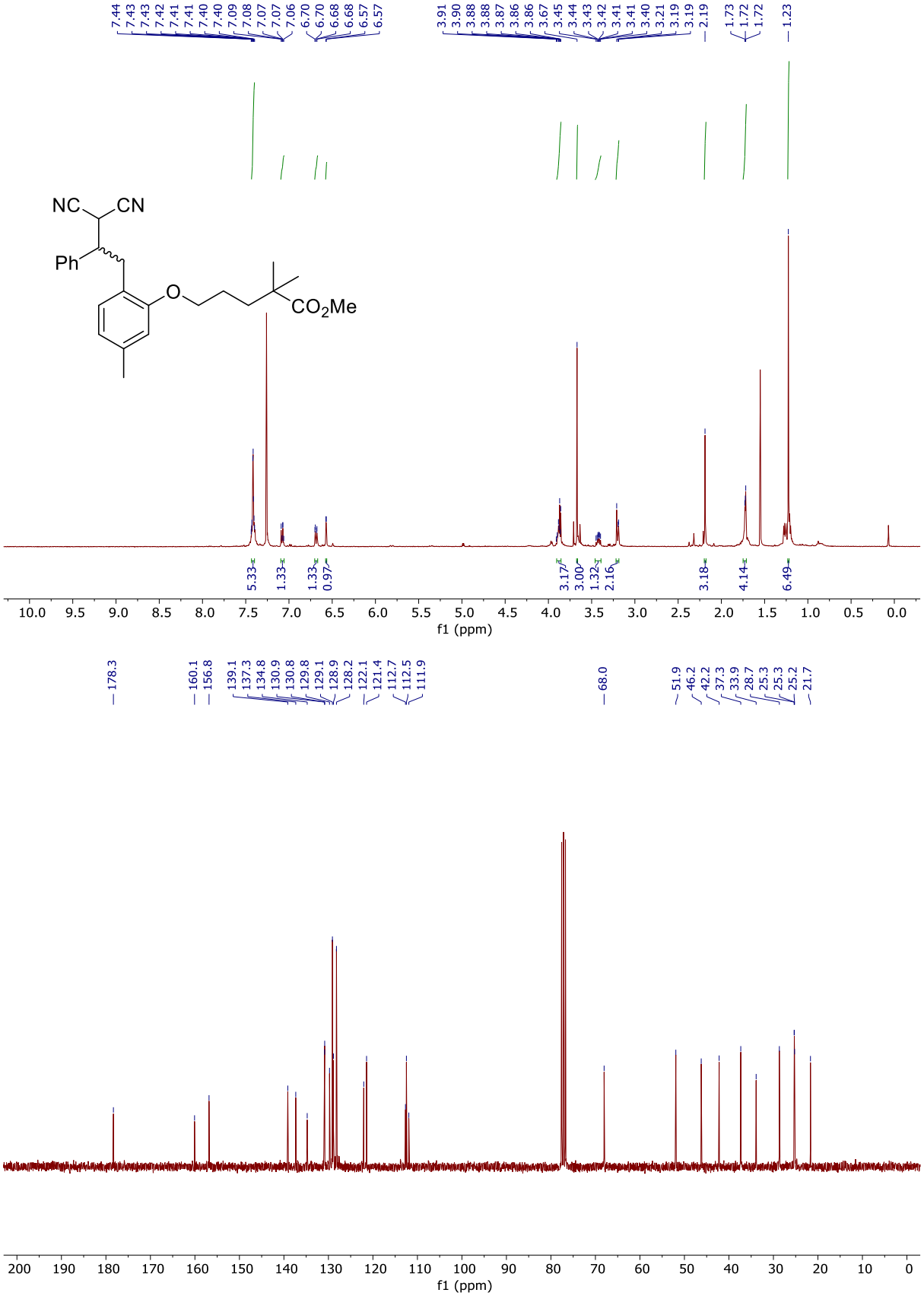


In the 1D-NOESY spectra, a strong NOE interaction of the CH_3-goup with two aromatic C-H groups of the core-scaffold. This is consistent with the *ortho*-functionalization.

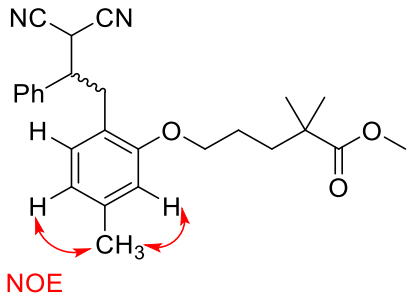
*1D-NOESY spectra of **24**:*



*Methyl 5-(2-(3,3-dicyano-2-phenylpropyl)-5-methylphenoxy)-2,2-dimethylpentanoate (**25**)*

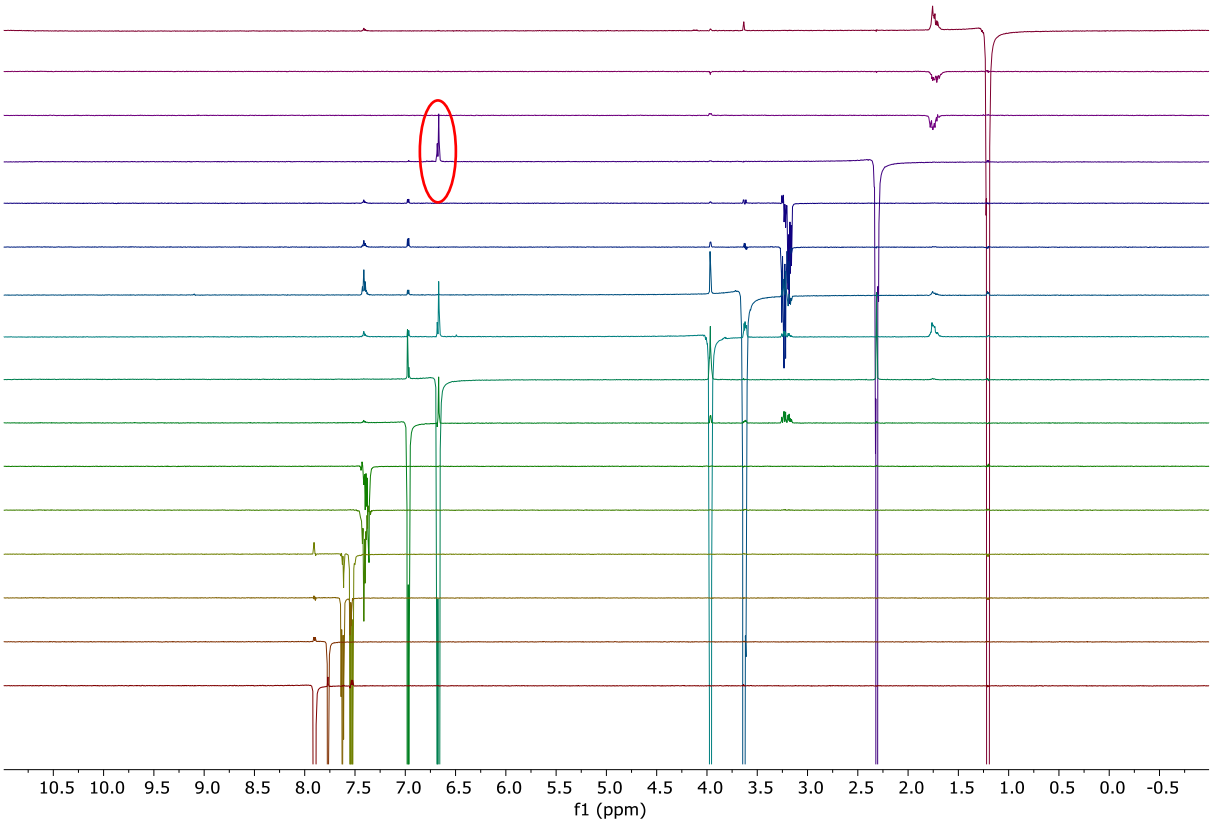


*Determination of the regioisomer of **25**:*

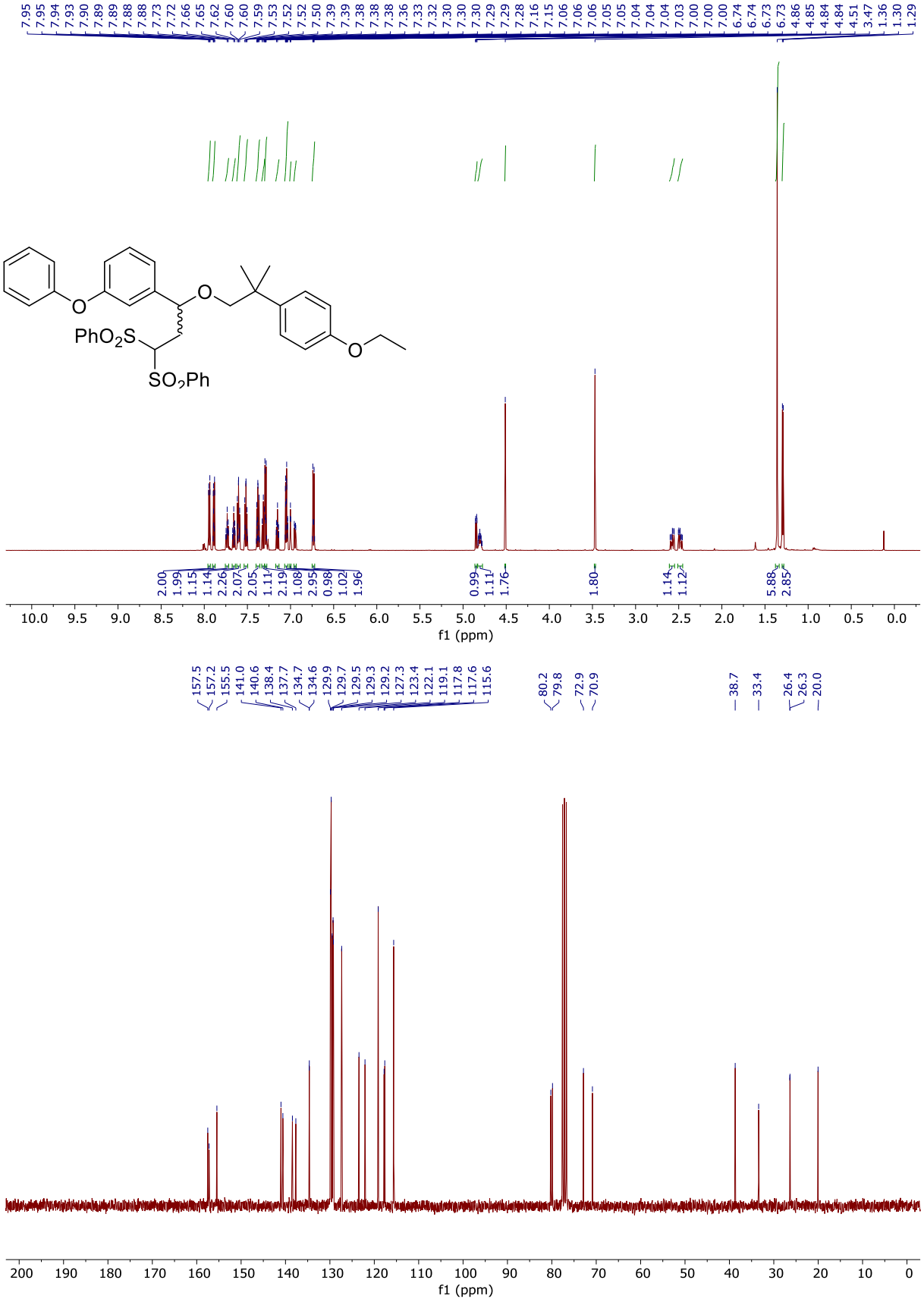


In the 1D-NOESY spectra, a strong NOE interaction of the CH_3-goup with two aromatic C-H groups of the core-scaffold. This is consistent with the *ortho*-functionalization.

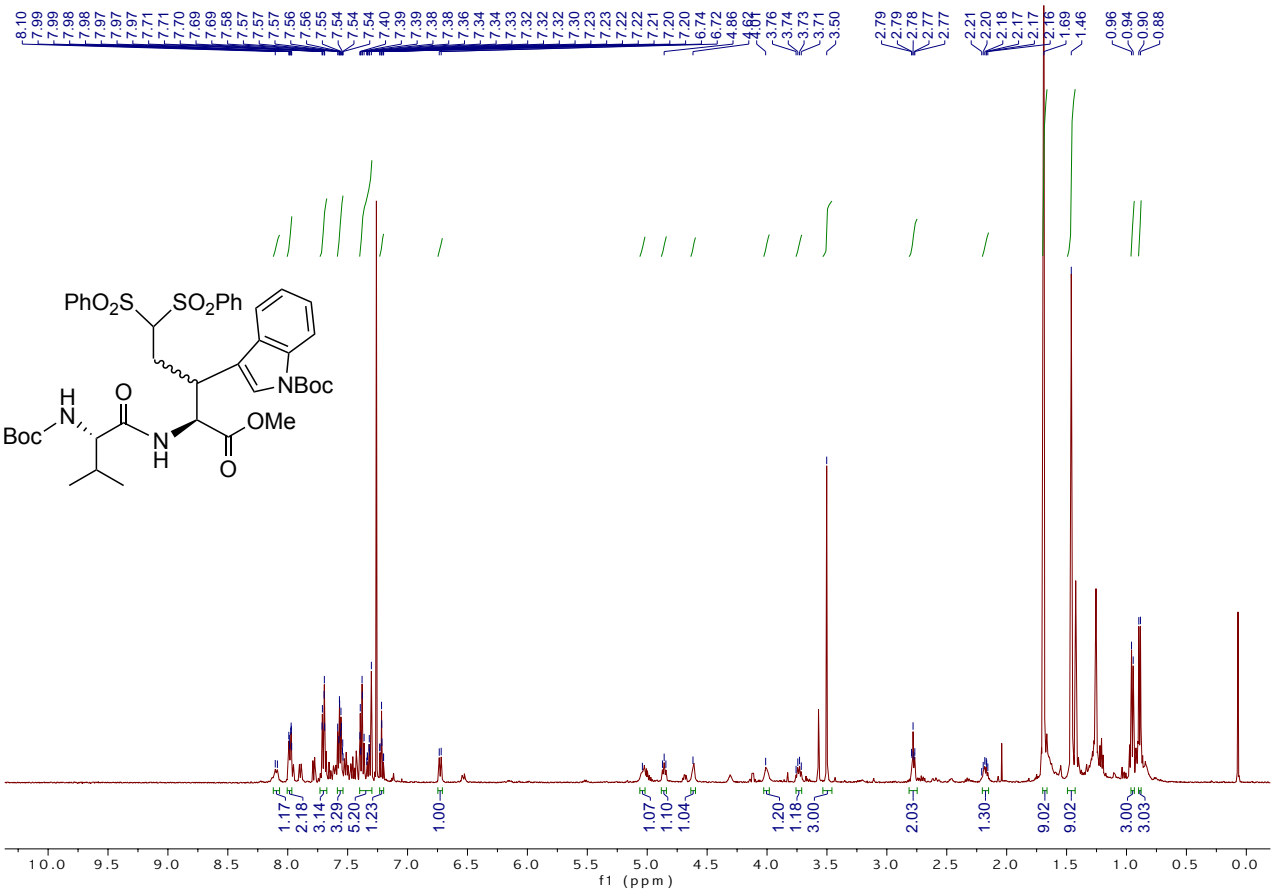
1D-NOESY spectra of **25**:

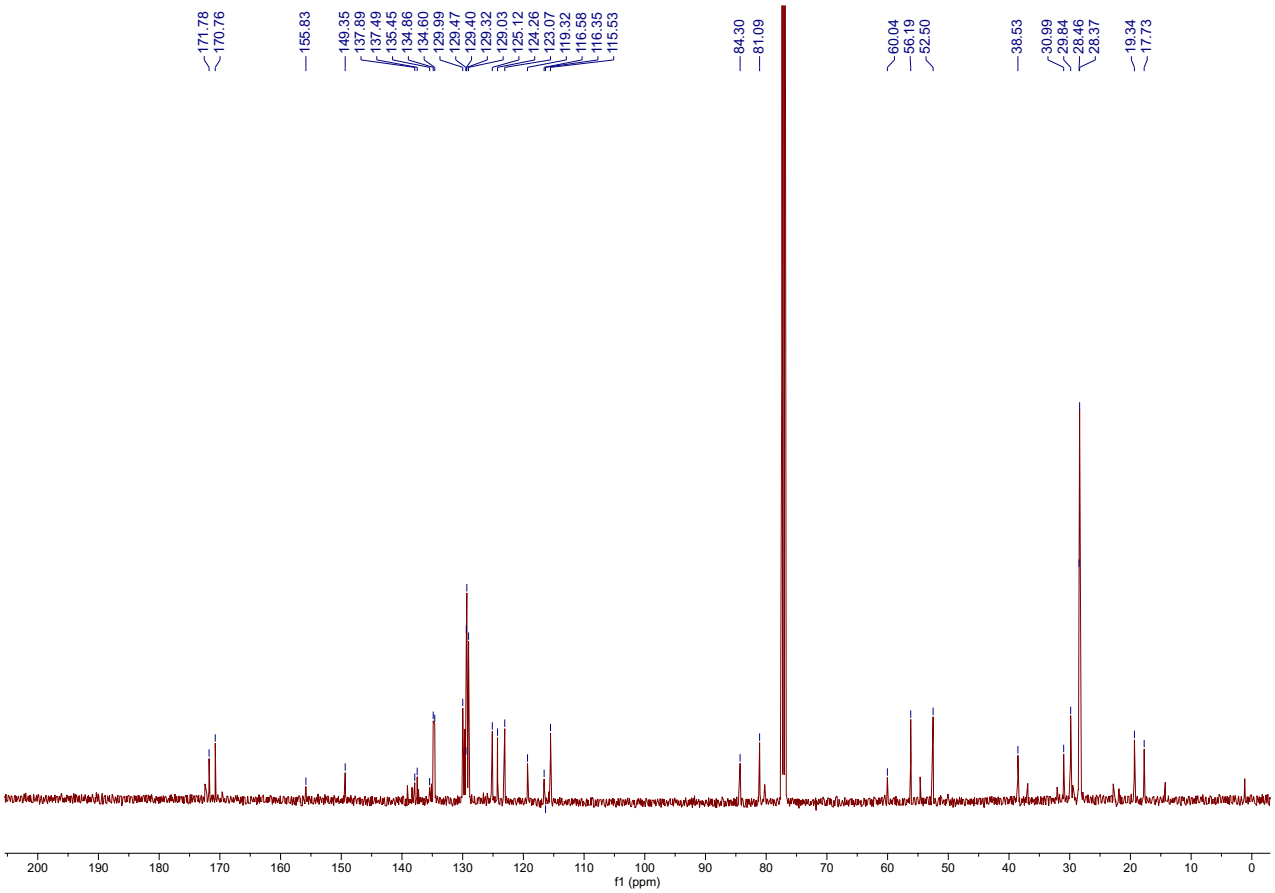


*(3-(2-(4-Ethoxyphenyl)-2-methylpropoxy)-3-(3-phenoxyphenyl)propane-1,1-diyldisulfonyl)dibenzene (**26**)*

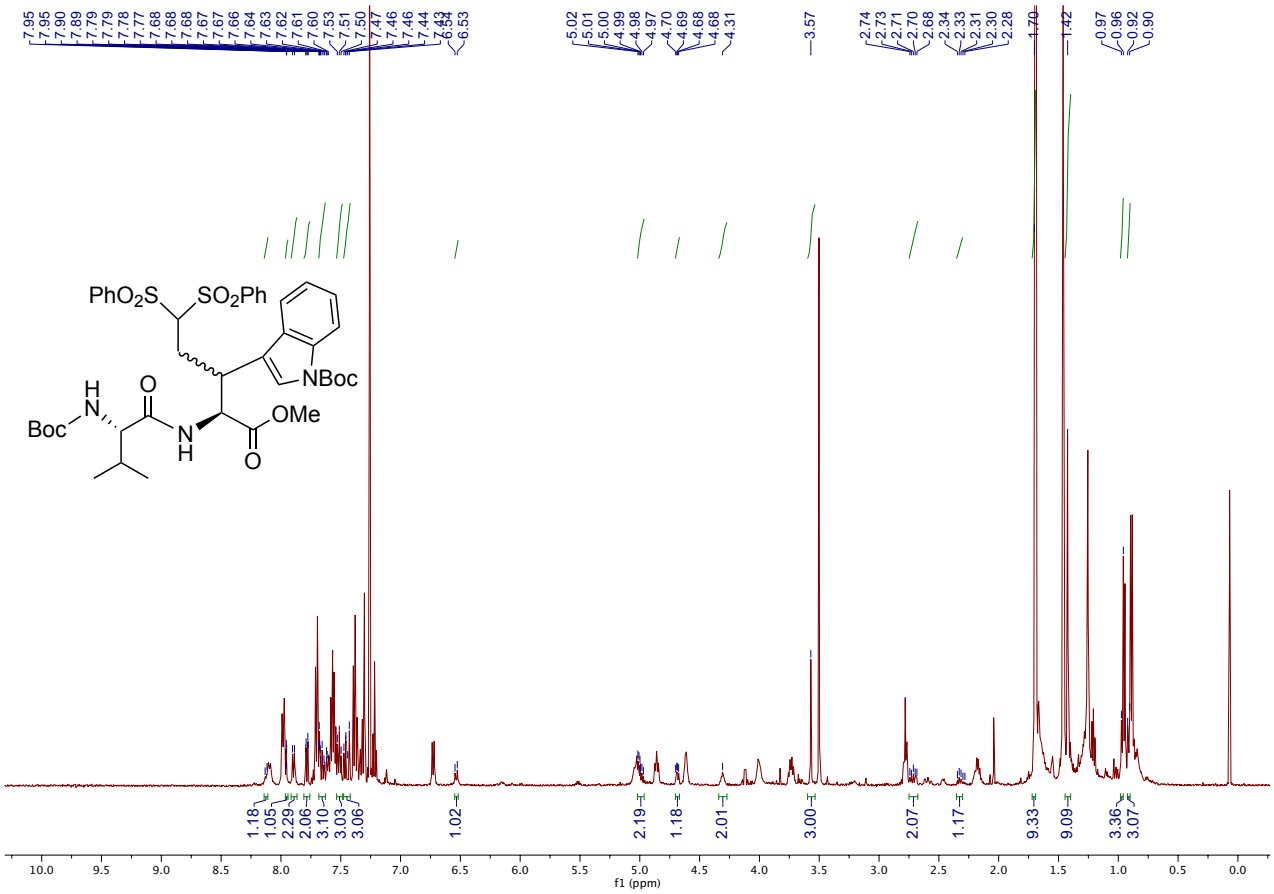


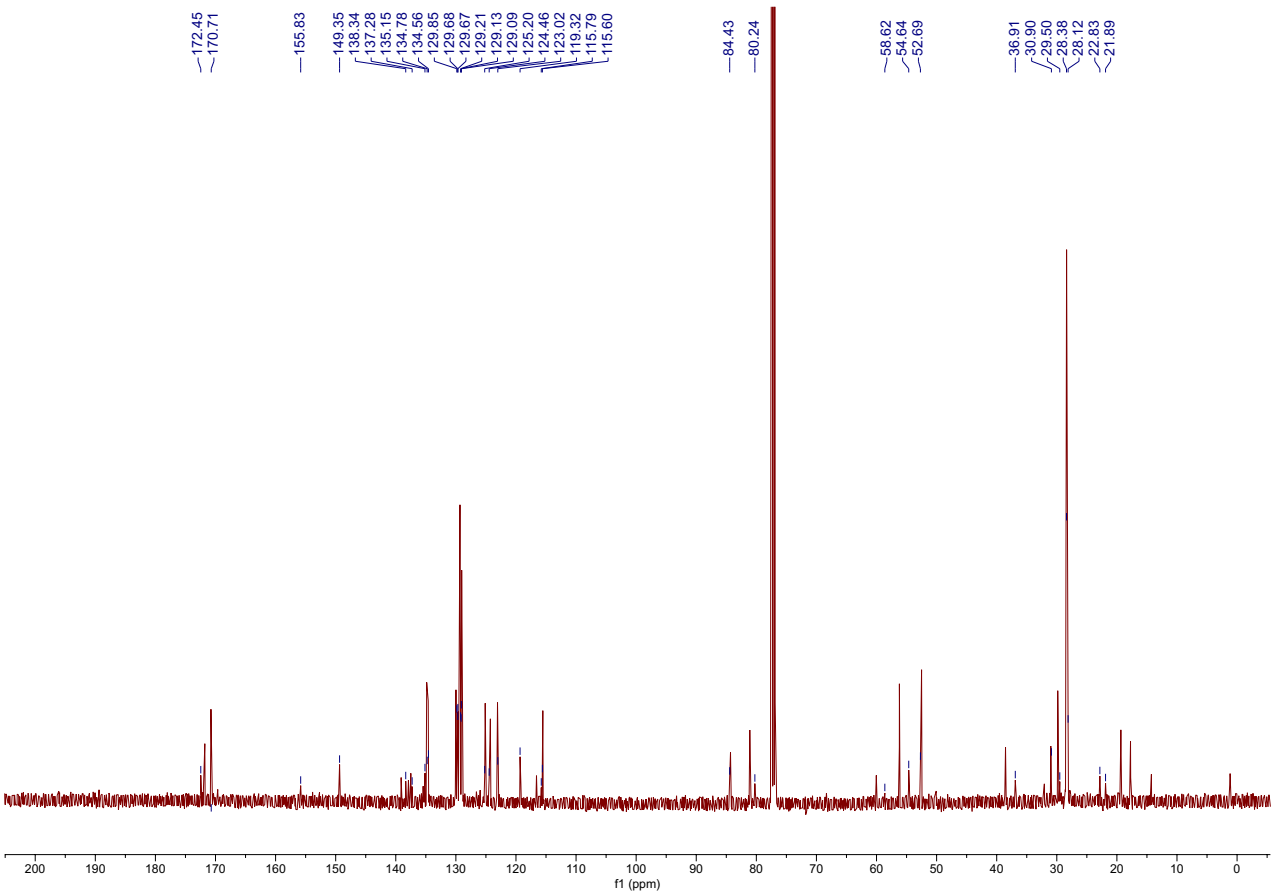
*tert-Butyl 3-((2S)-2-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido)-1-methoxy-1-oxo-5,5-bis(phenylsulfonyl)pentan-3-yl)-1H-indole-1-carboxylate (major, **27**)*



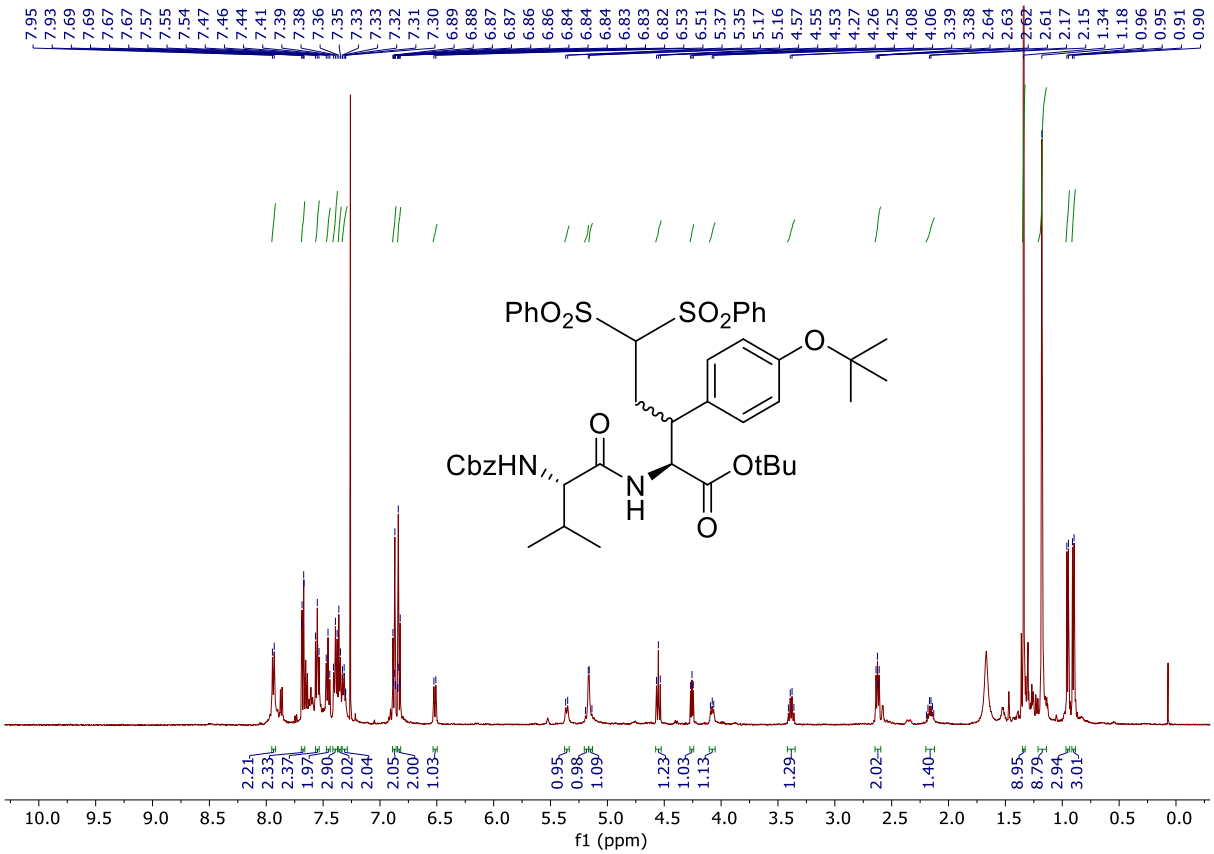


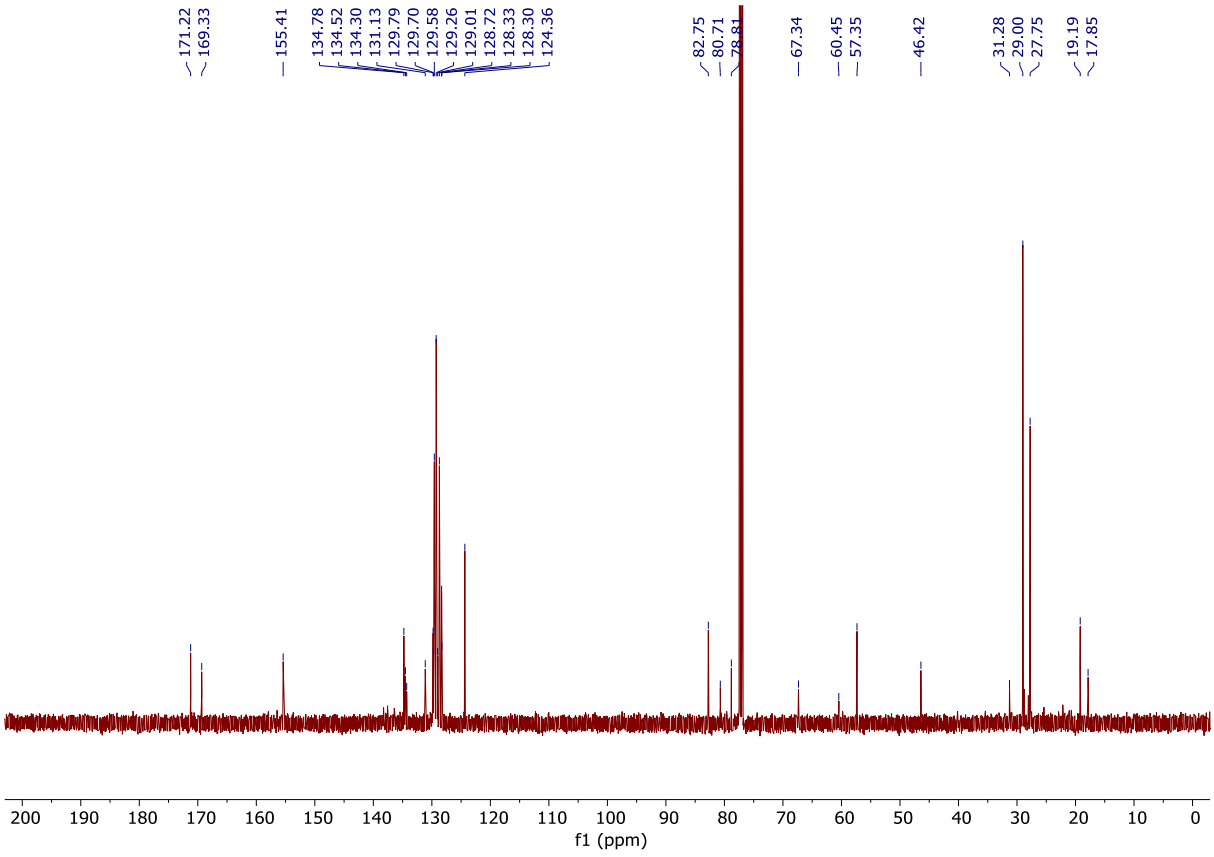
*tert-Butyl 3-((2S)-2-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido)-1-methoxy-1-oxo-5,5-bis(phenylsulfonyl)pentan-3-yl)-1H-indole-1-carboxylate (minor, **27**)*



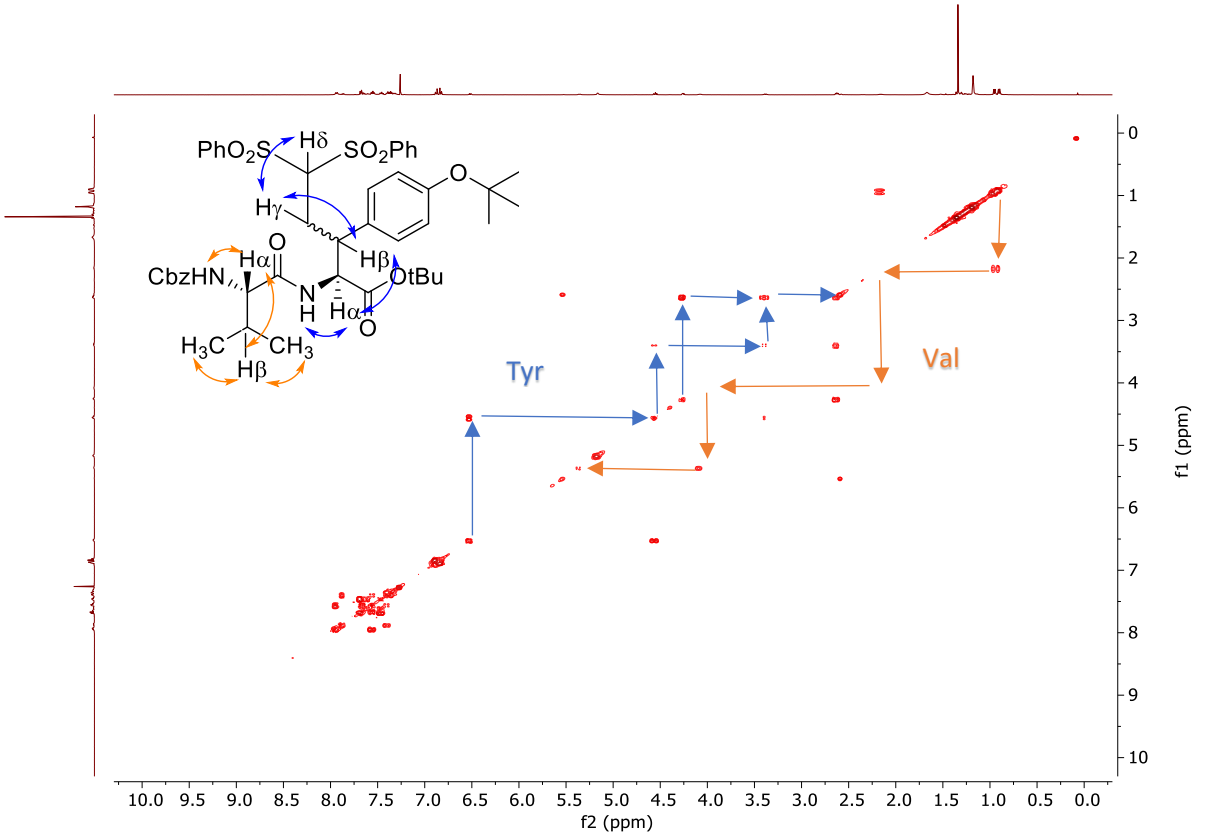


*tert-Butyl (2S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-methylbutanamido)-3-(4-(tert-butoxy)phenyl)-5,5-bis(phenylsulfonyl)pentanoate (major **28**)*





COSY Spectrum of ***28***



Determination of the configuration of the major ***28****:*

6.89 – 6.86 (m, 2H), Tyr Aromatic

6.85 – 6.82 (m, 2H), Tyr Aromatic

6.52 (d, *J* = 8.5 Hz, 1H), Tyr NH

5.36 (d, *J* = 8.8 Hz, 1H), Val NH

5.18 (d, *J* = 12.2 Hz, 1H), 5.15 (d, *J* = 11.9 Hz, 1H), Cbz

4.55 (t, *J* = 8.4 Hz, 1H), Tyr α-C-H

4.27 – 4.24 (m, 1H), Tyr-δ-C-H

4.08 (t, *J* = 7.3 Hz, 1H), Val α-C-H

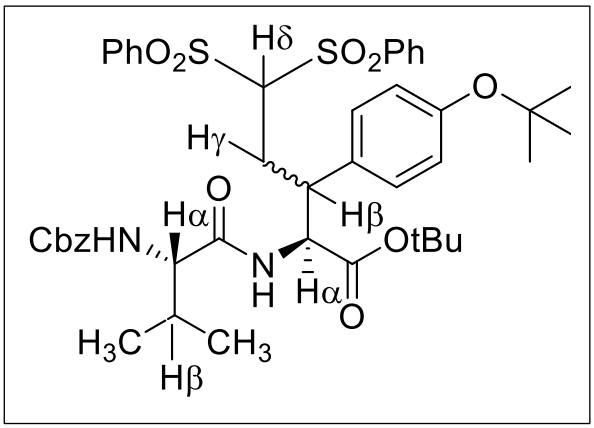
3.38 (q, *J* = 8.1 Hz, 1H),Tyr β-C-H

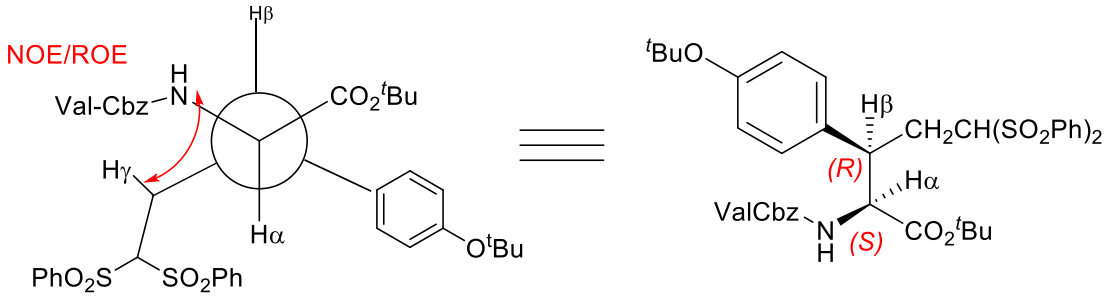
2.62 (dd, *J* = 8.6, 5.3 Hz, 2H),Tyr γ-C-H

2.16 (td, *J* = 12.8, 12.3, 6.2 Hz, 1H), Val β-C-H

1.34 (s, 9H), 1.18 (s, 9H),

0.95 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H). Val-γ-CH_3

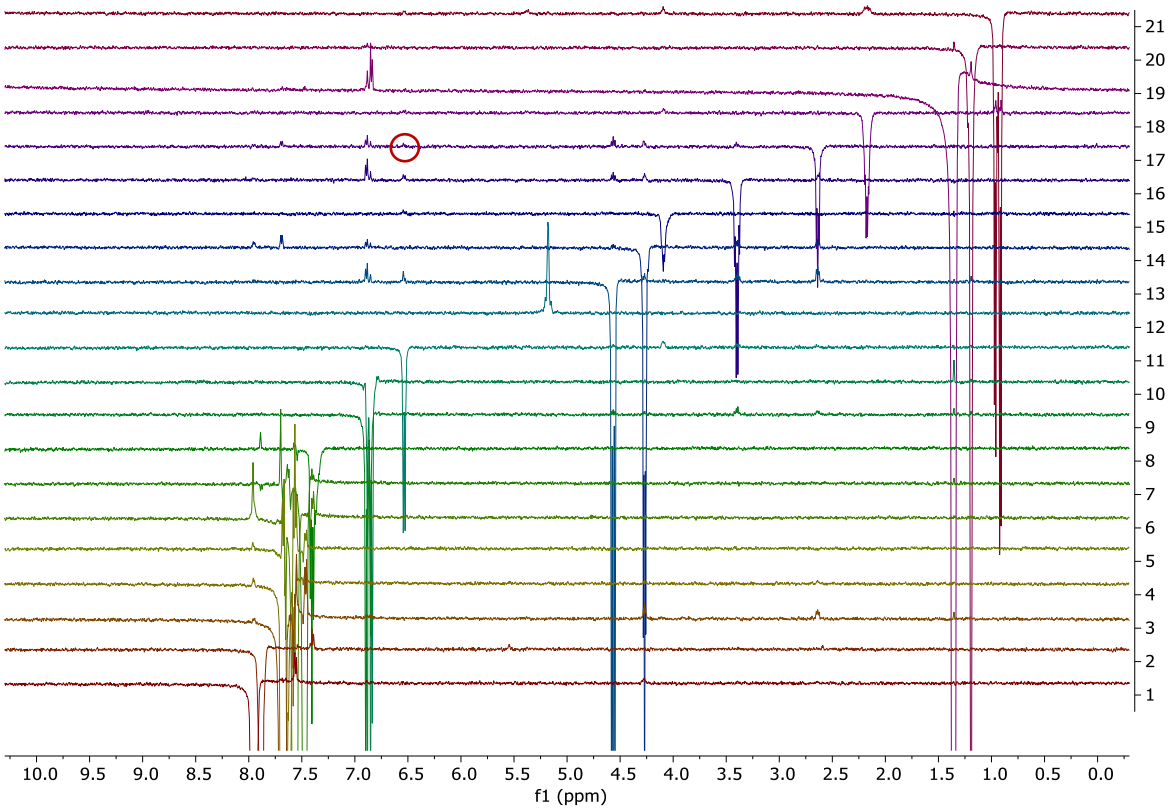




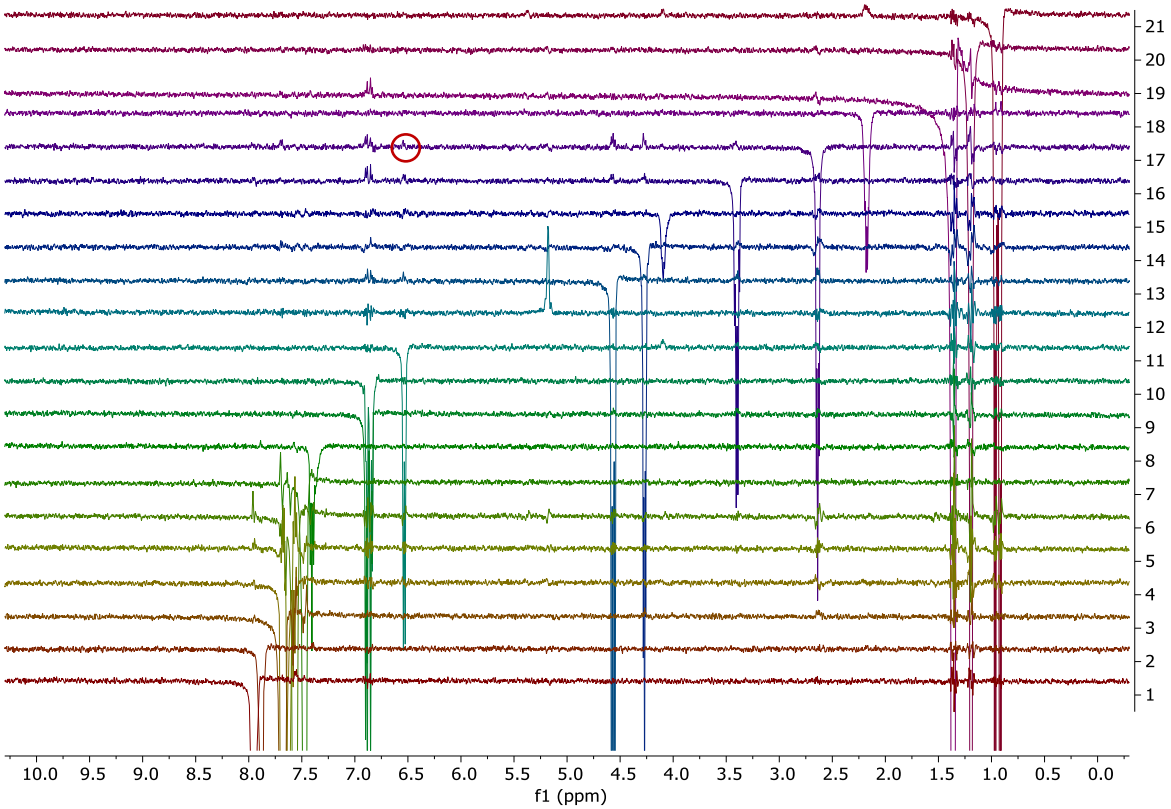
J (Hα, Hβ) = 8.4 Hz

The configuration of the major isomer was determined based on vicinal proton coupling and NOE/ROE. A coupling constant of *J* (Tyr-Hα, Tyr-Hβ) = 8.4 Hz suggests a predominant-*anti* conformation as shown in the Newman projection above. An observed NOE/ROE interaction between tyrosine´s NH and Tyr-Hγ is consistent with a (*R*)-configuration at the β-carbon center of tyrosine.

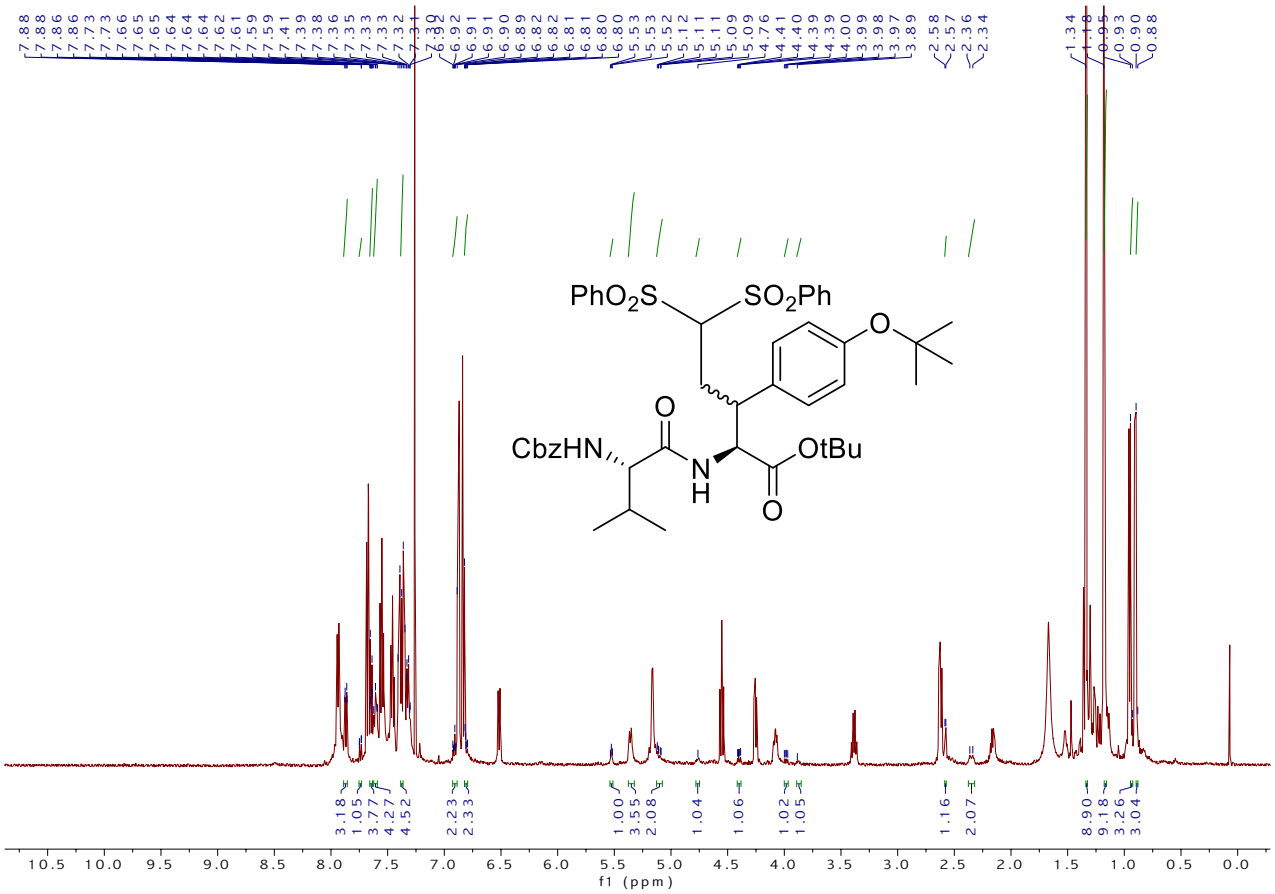
1D-NOESY spectra of ***28****:*



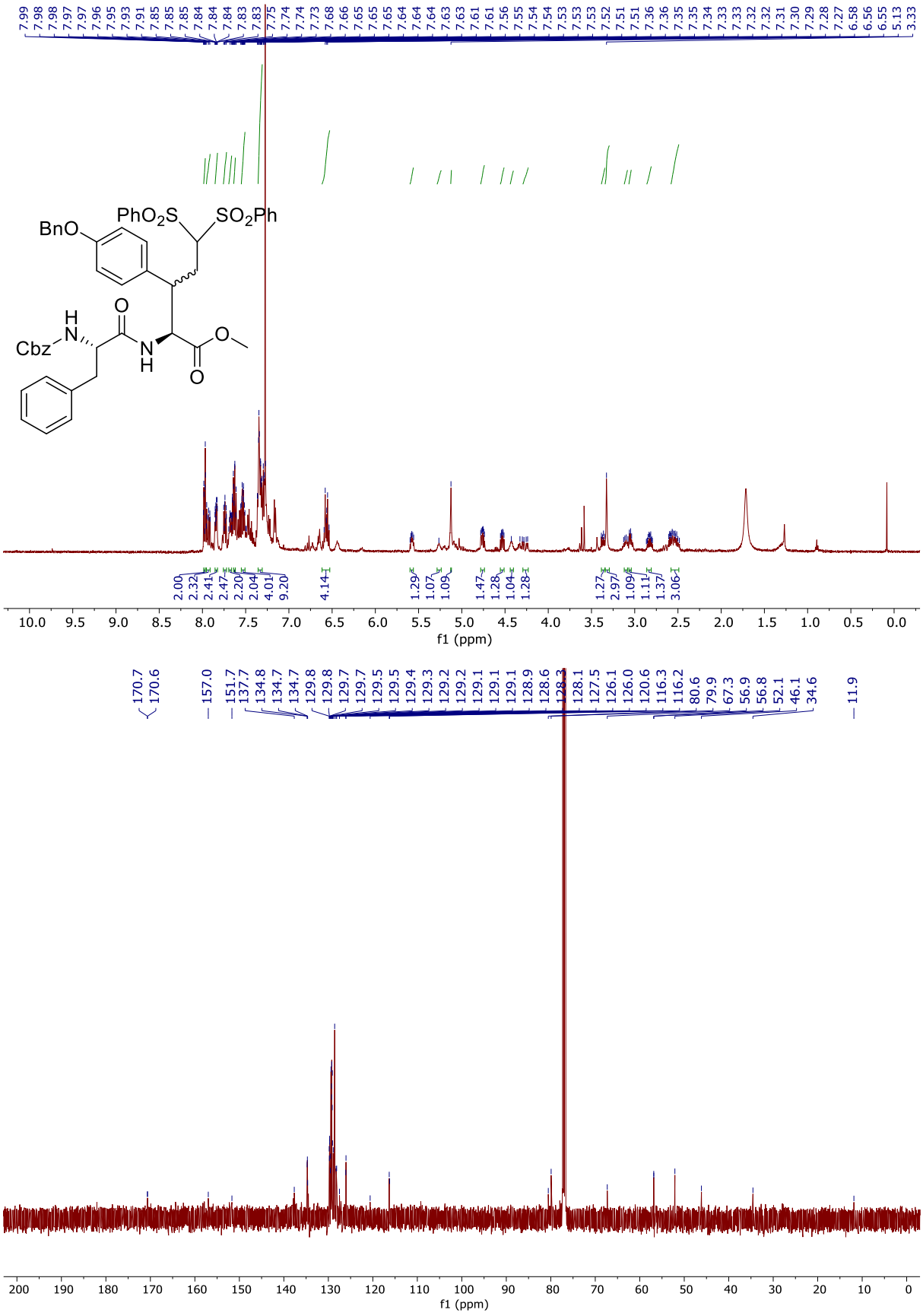
*1D-ROESY spectra of **28**:*



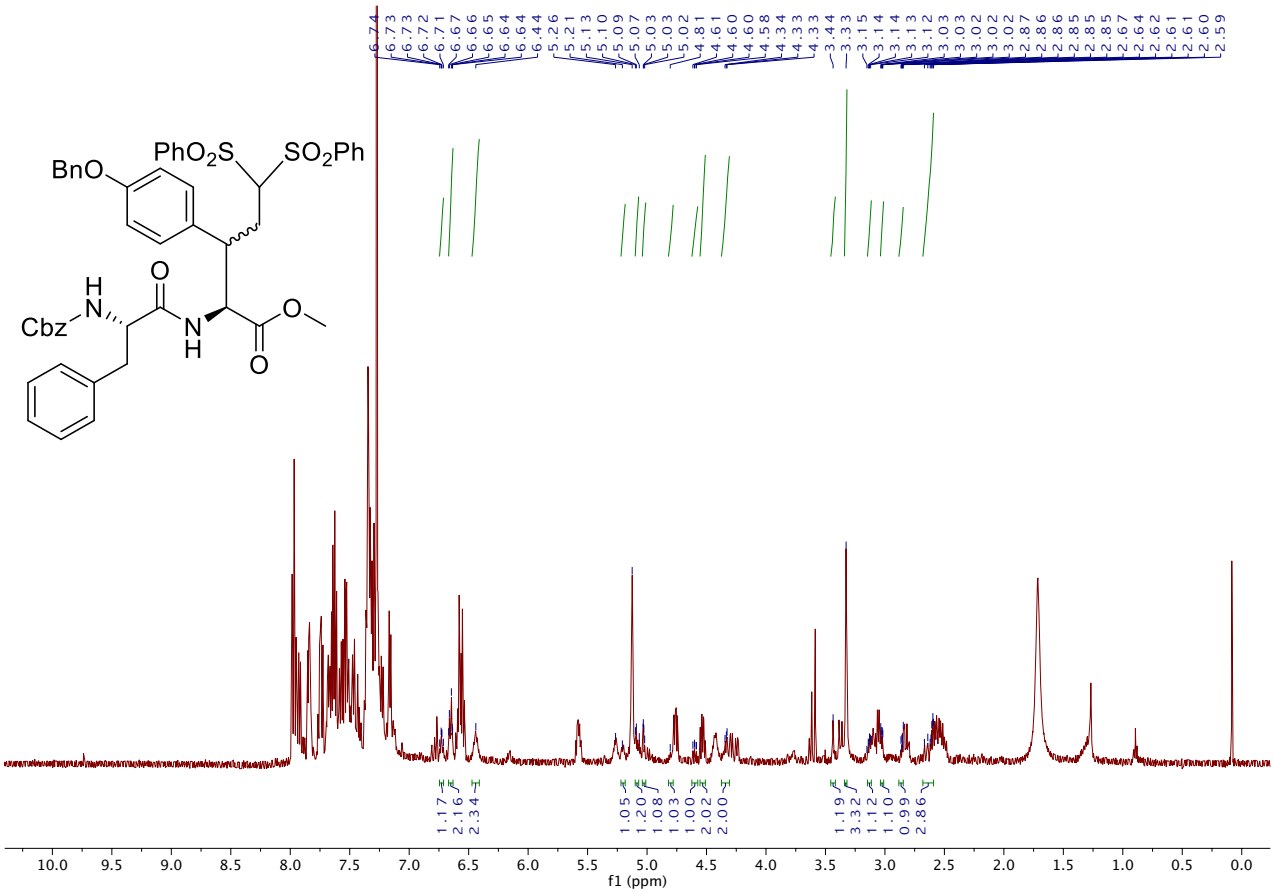
*tert-Butyl (2S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-methylbutanamido)-3-(4-(tert-butoxy)phenyl)-5,5-bis(phenylsulfonyl)pentanoate (minor **28**)*



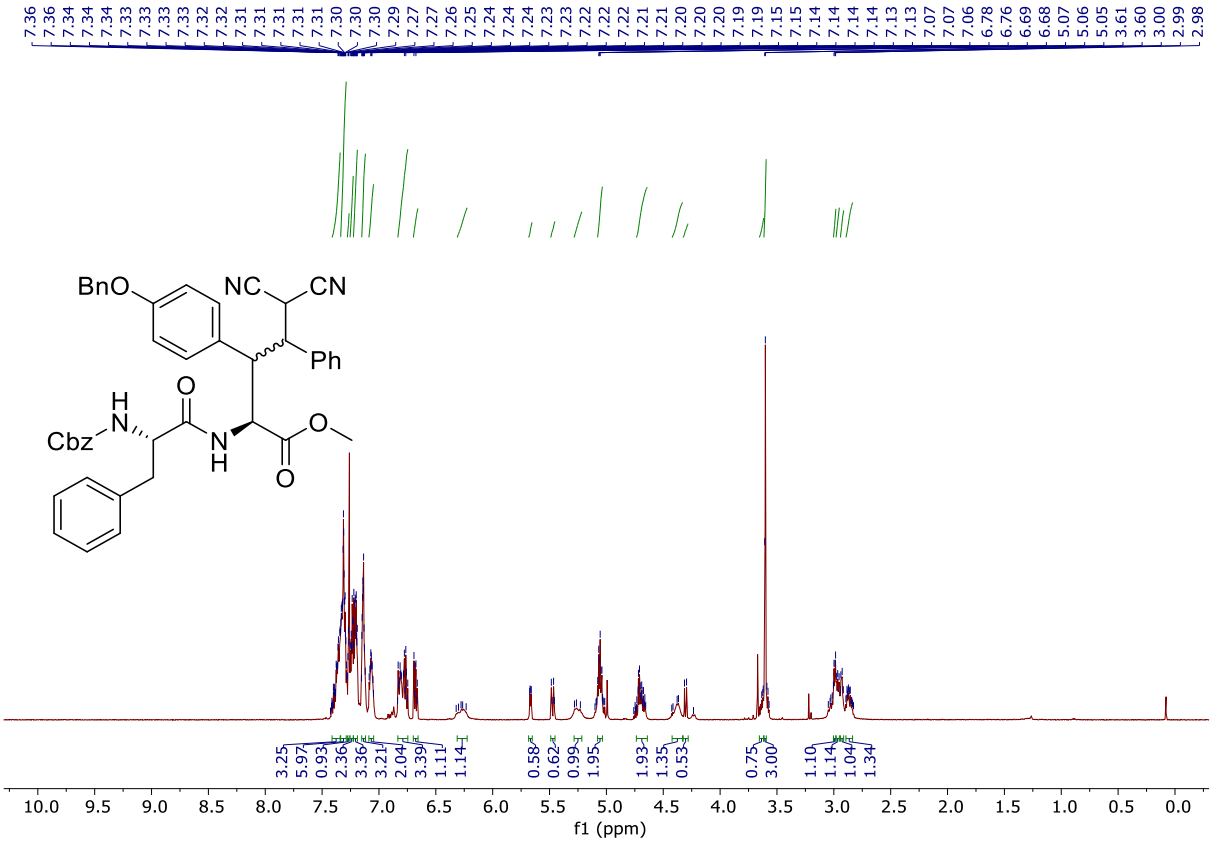
*Methyl (2S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-3-(4-(benzyloxy)phenyl)-5,5-bis(phenylsulfonyl)pentanoate (major **29**)*

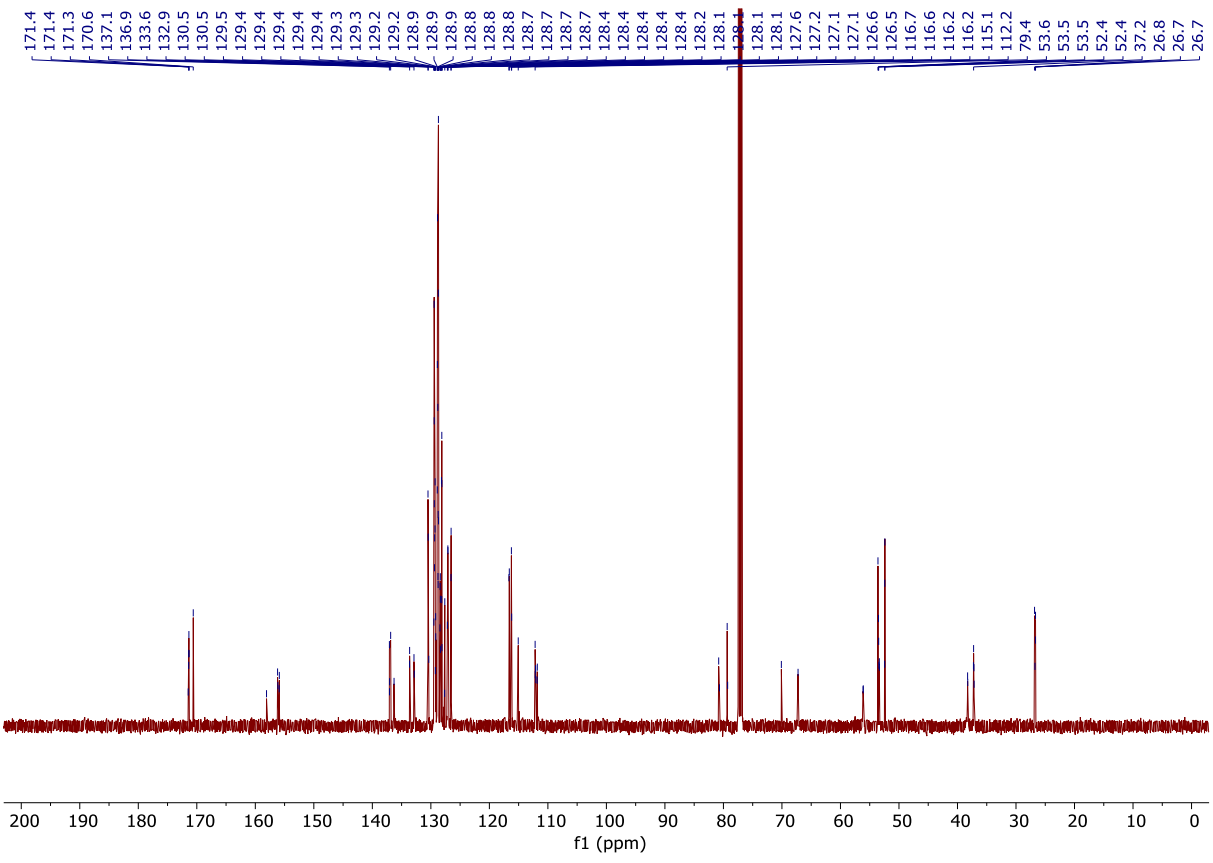


*Methyl (2S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-3-(4-(benzyloxy)phenyl)-5,5-bis(phenylsulfonyl)pentanoate (minor **29**)*

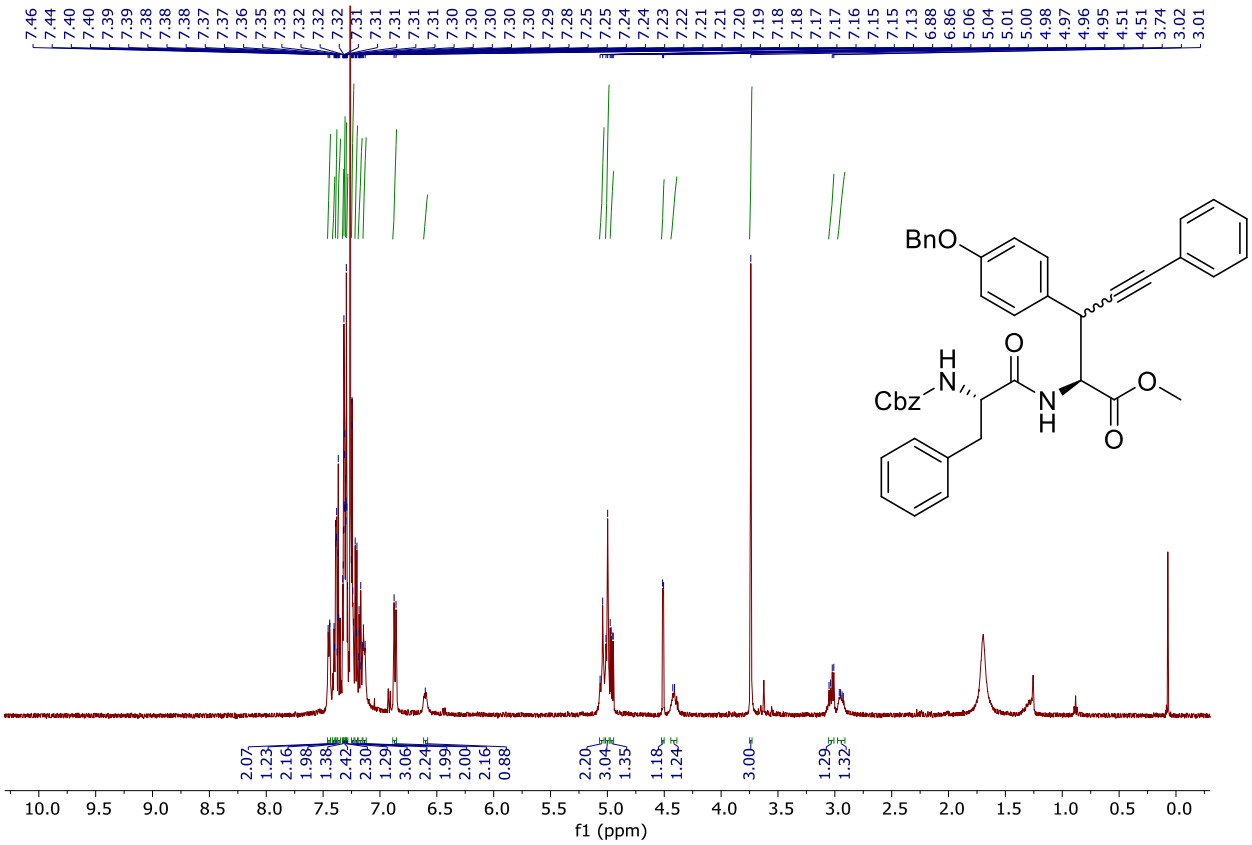


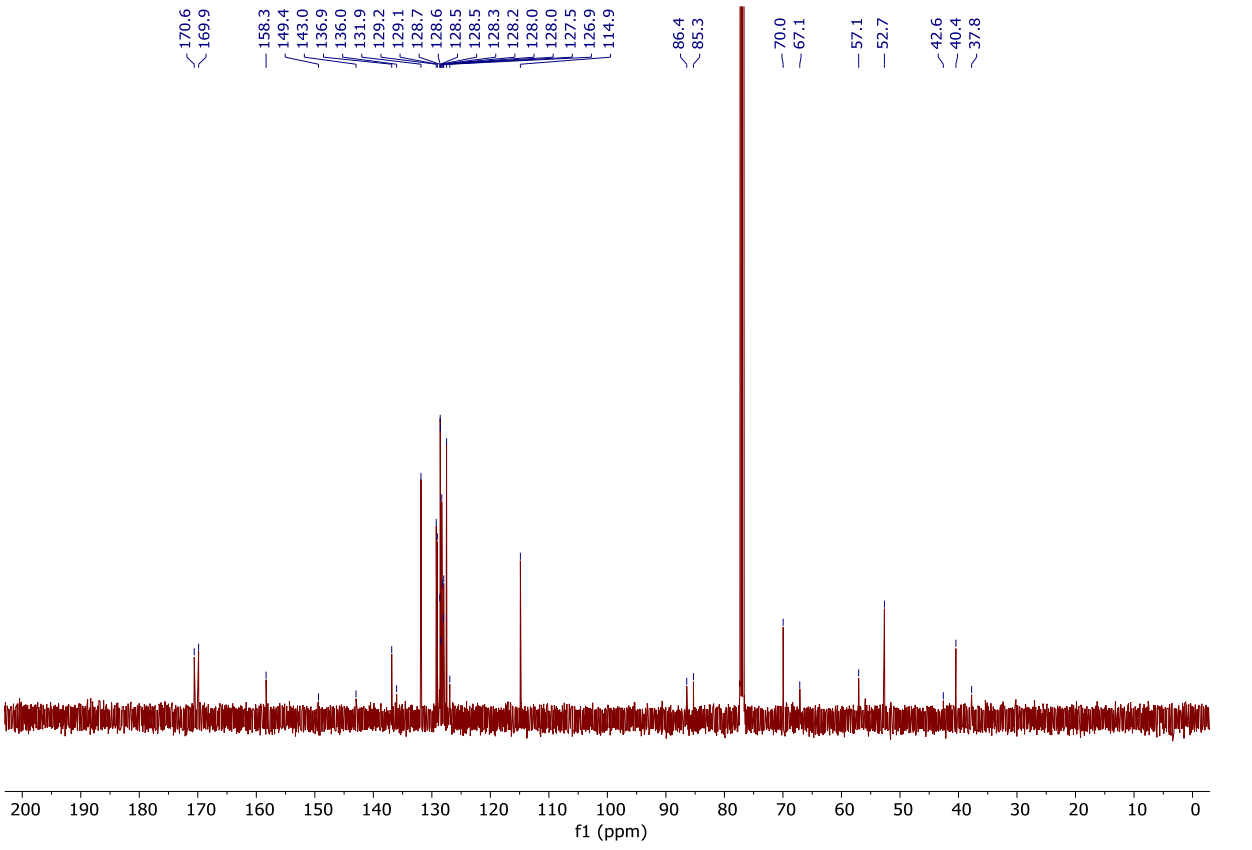
Methyl (2*S*)-2-((*S*)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-3-(4-(benzyloxy)phenyl)-5,5-dicyano-4-phenylpentanoate (**30**, 2 Diastereomers)



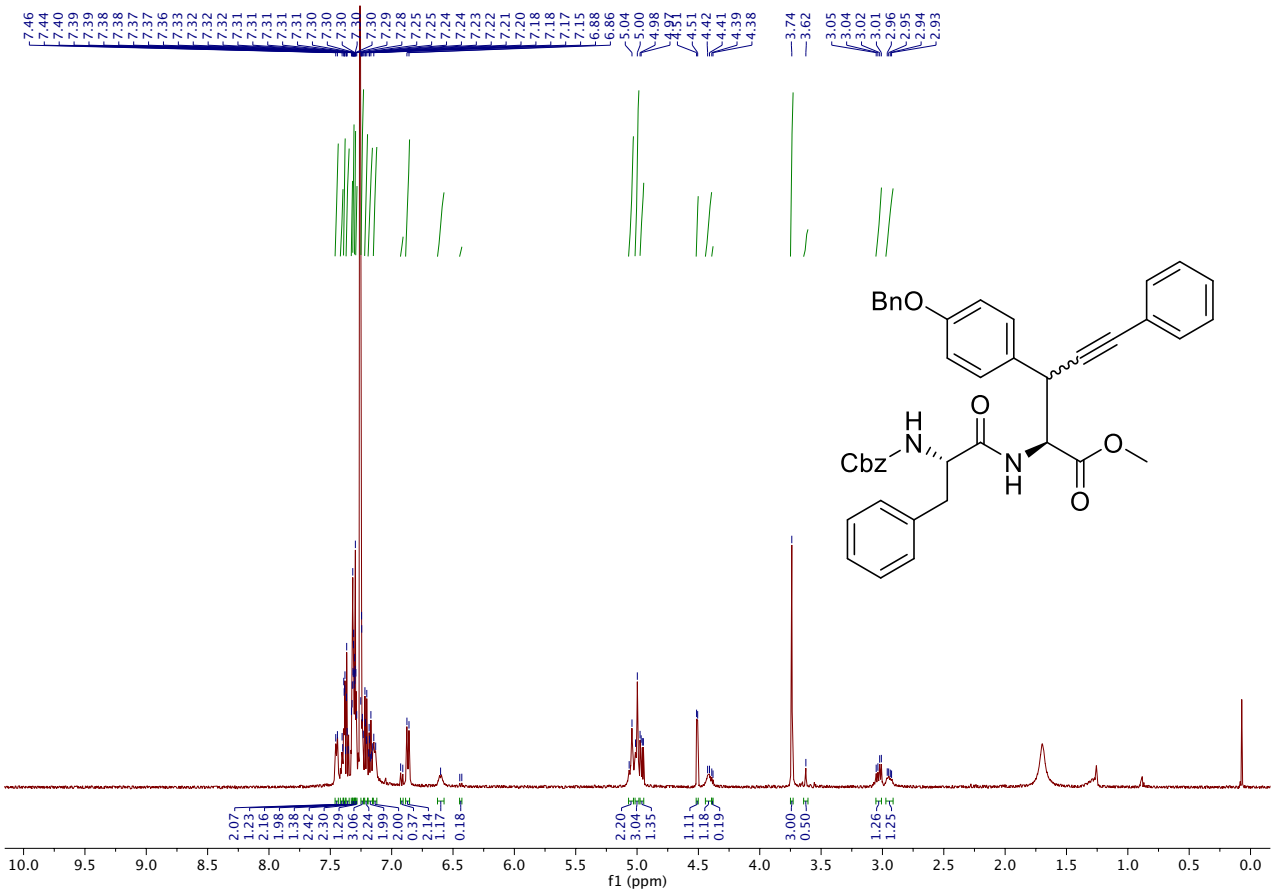


*Methyl (2S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-3-(4-(benzyloxy)phenyl)-5-phenylpent-4-ynoate (major **31**)*

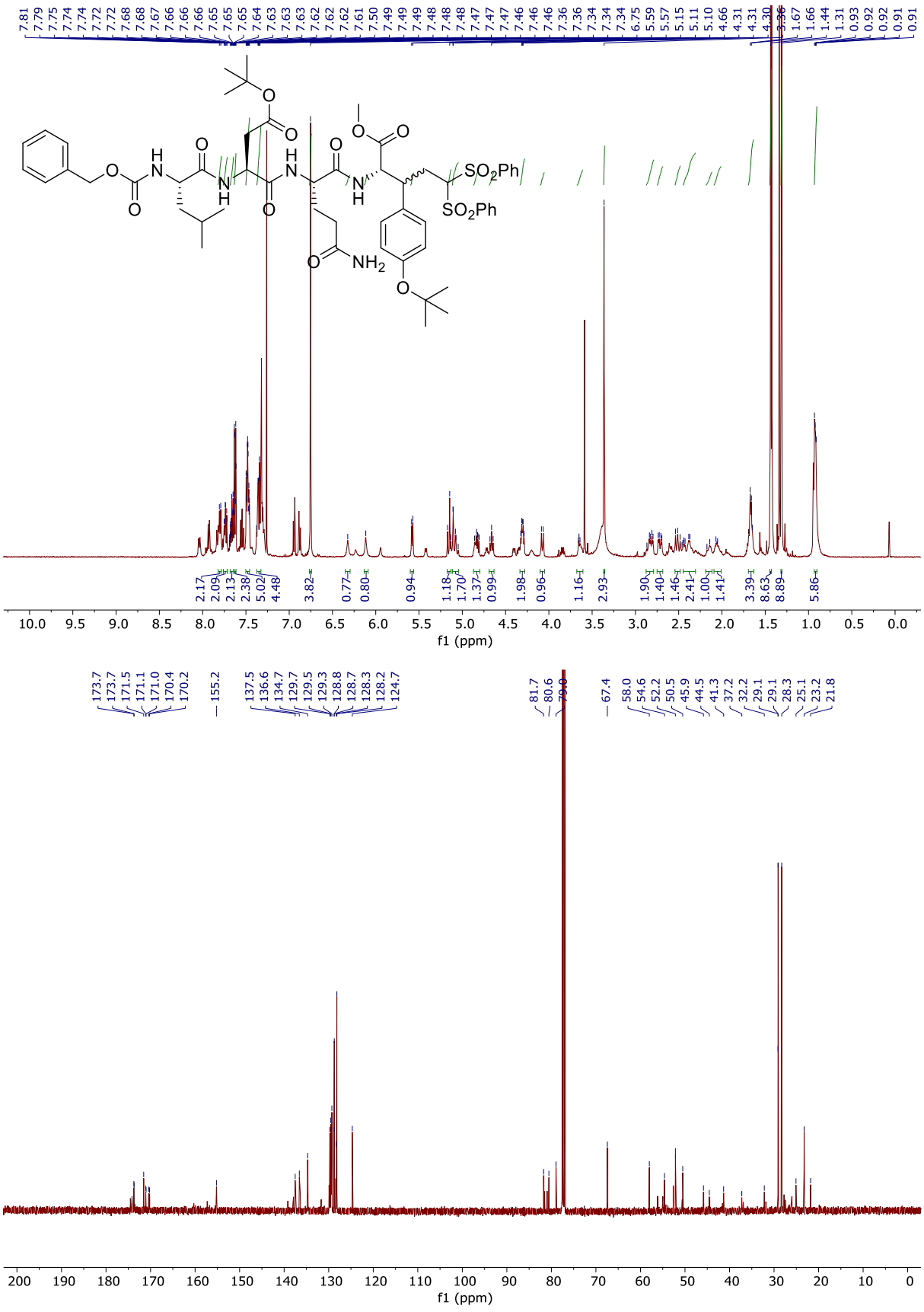




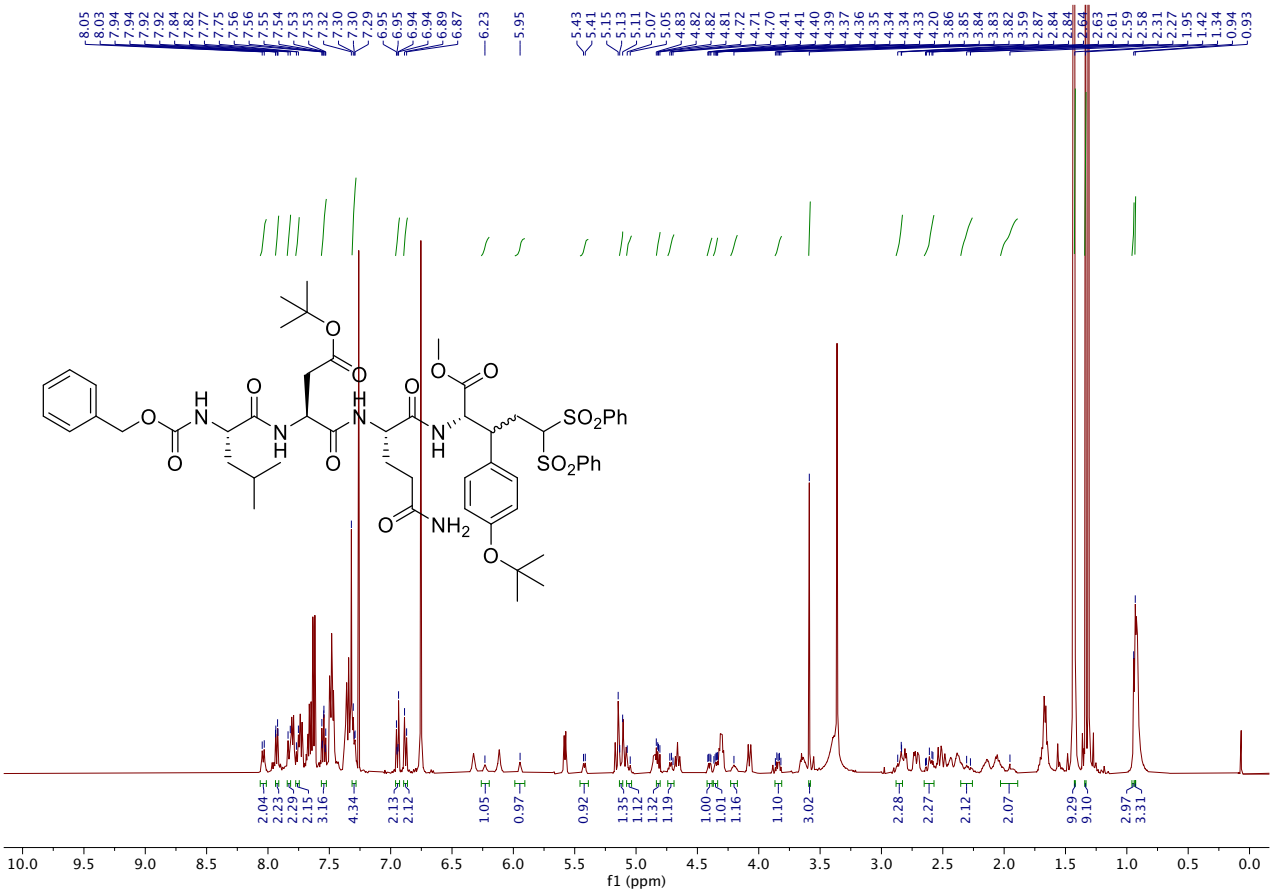
*Methyl (2S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanamido)-3-(4-(benzyloxy)phenyl)-5-phenylpent-4-ynoate (integration of both major + minor **31**)*



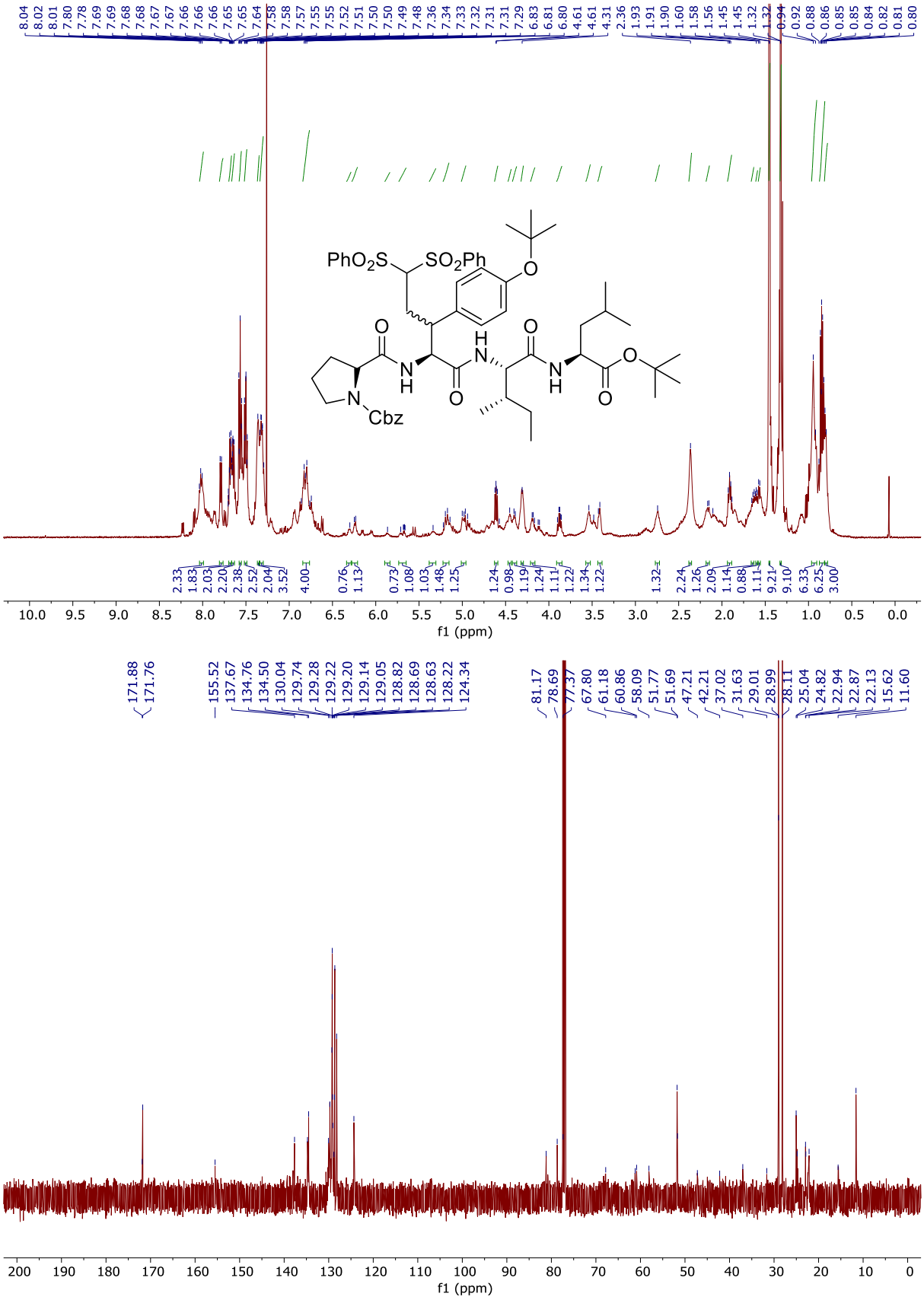
*Methyl (5S,8S,11S,14S)-11-(3-amino-3-oxopropyl)-8-(2-(tert-butoxy)-2-oxoethyl)-14-(1-(4-(tert-butoxy)phenyl)-3,3-bis(phenylsulfonyl)propyl)-5-isobutyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-4,7,10,13-tetraazapentadecan-15-oate (major **32**)*



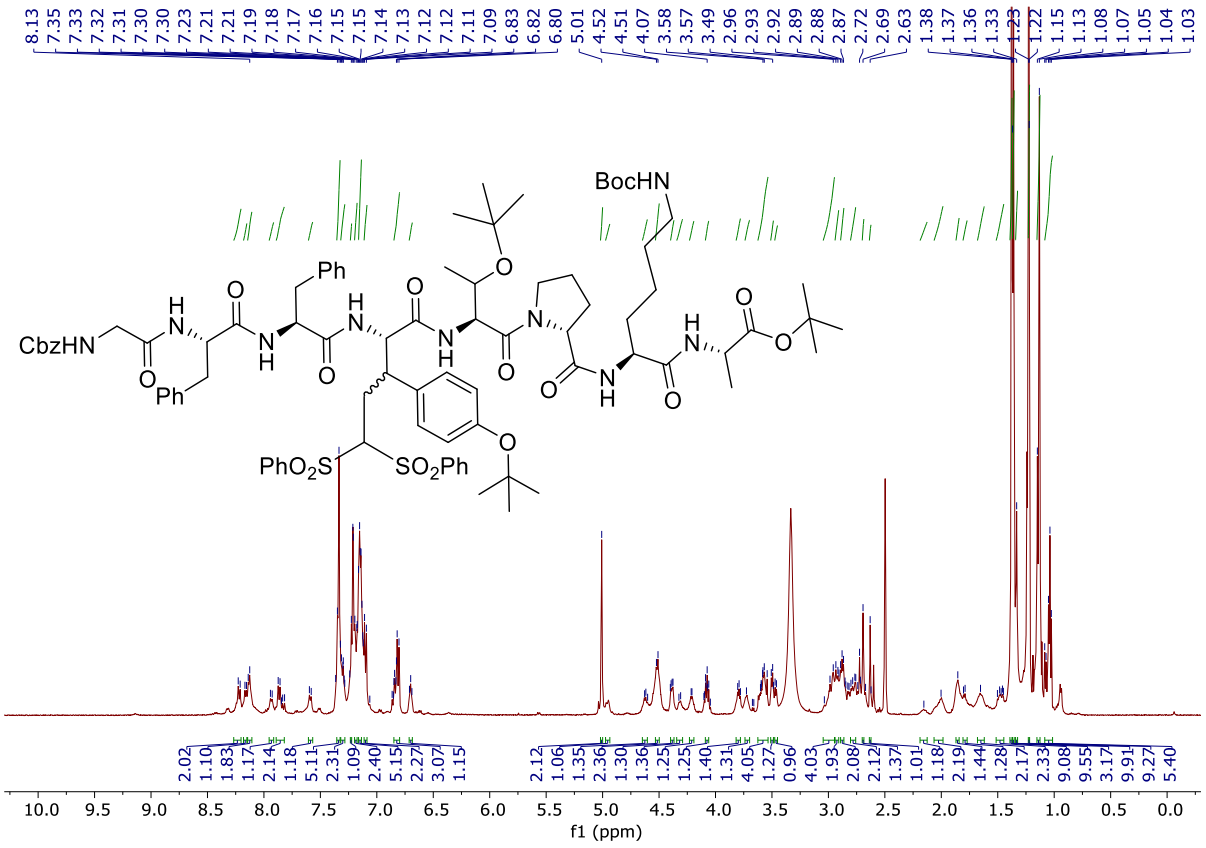
*Methyl (5S,8S,11S,14S)-11-(3-amino-3-oxopropyl)-8-(2-(tert-butoxy)-2-oxoethyl)-14-(1-(4-(tert-butoxy)phenyl)-3,3-bis(phenylsulfonyl)propyl)-5-isobutyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-4,7,10,13-tetraazapentadecan-15-oate (minor **32**)*



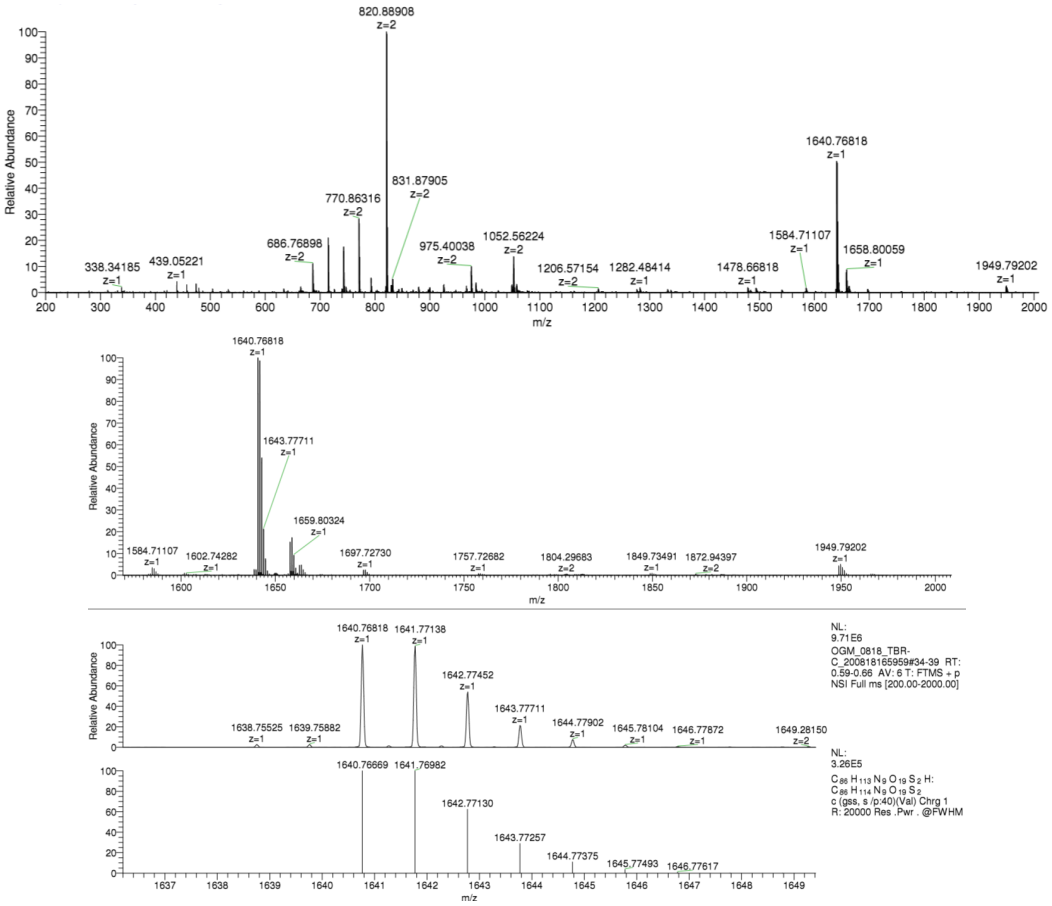
*Benzyl (2S)-2-(((2S)-1-(((2S,3R)-1-(((S)-1-(tert-butoxy)-4-methyl-1-oxopentan-2-yl)amino)-3,4-dimethyl-1-oxopentan-2-yl)amino)-3-(4-(tert-butoxy)phenyl)-1-oxo-5,5-bis(phenylsulfonyl)pentan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (major **33**)*



*tert-Butyl N2-(((2S)-2-((2S)-2-((S)-2-((S)-2-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-phenylpropanamido)-3-phenylpropanamido)-3-(4-(tert-butoxy)phenyl)-5,5-bis(phenylsulfonyl)pentanamido)-3-(tert-butoxy)butanoyl)-D-prolyl)-N6-(tert-butoxycarbonyl)-L-lysyl-L-alaninate (**34**)*

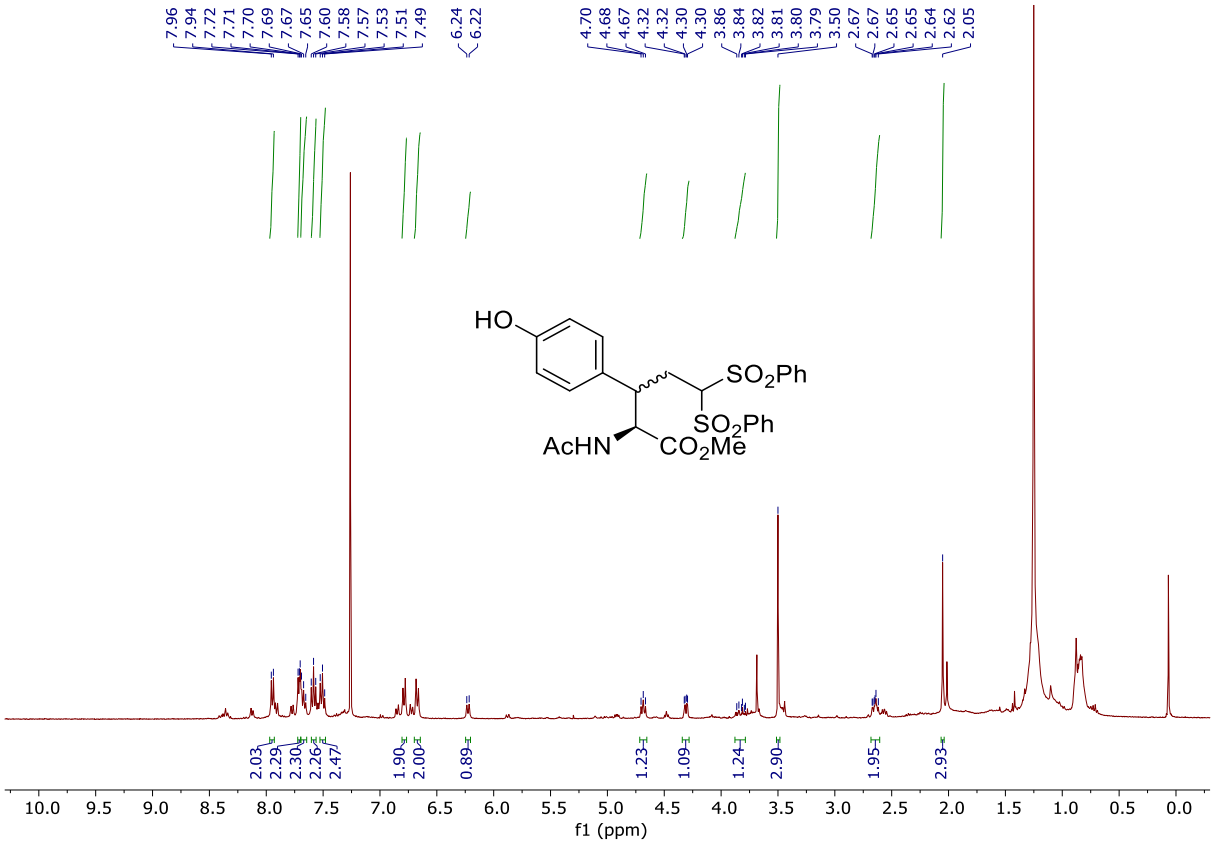


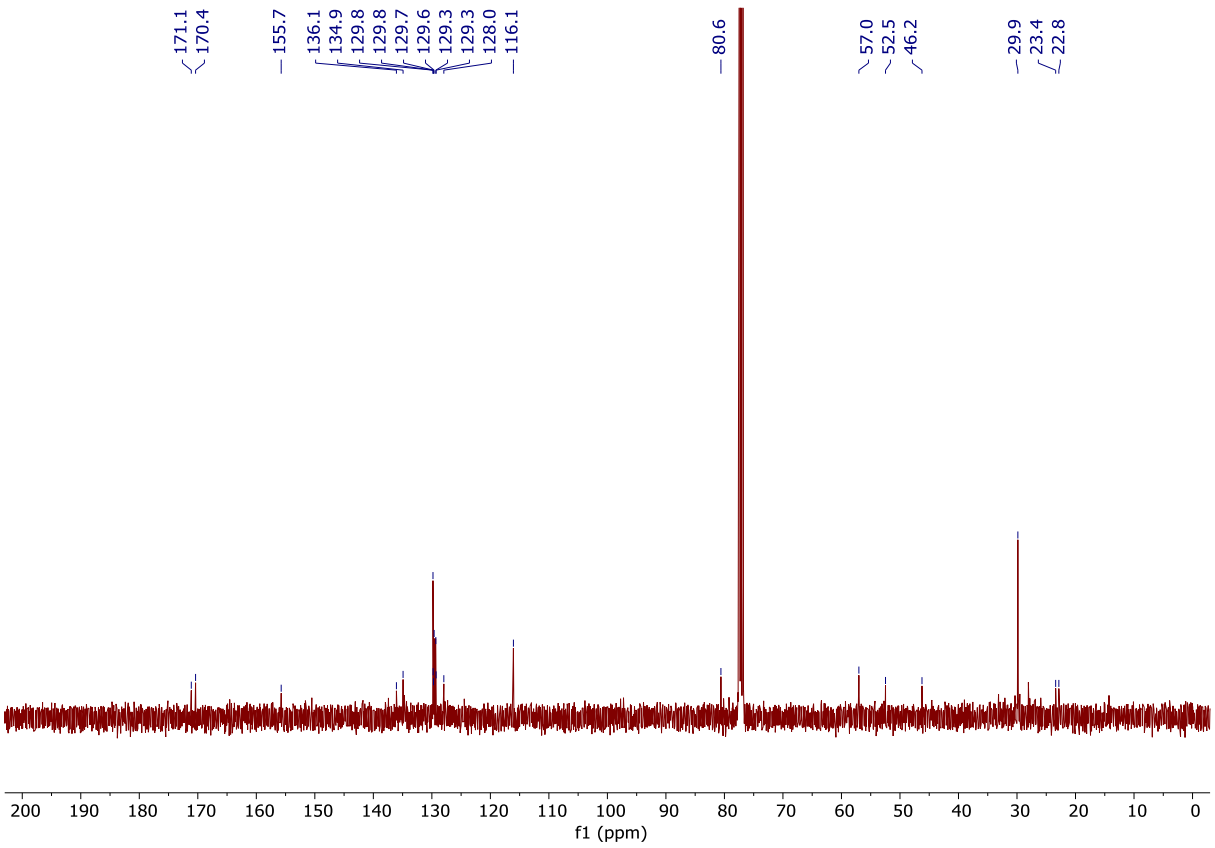
*ESI-HRMS Analysis of peptide **33**:*



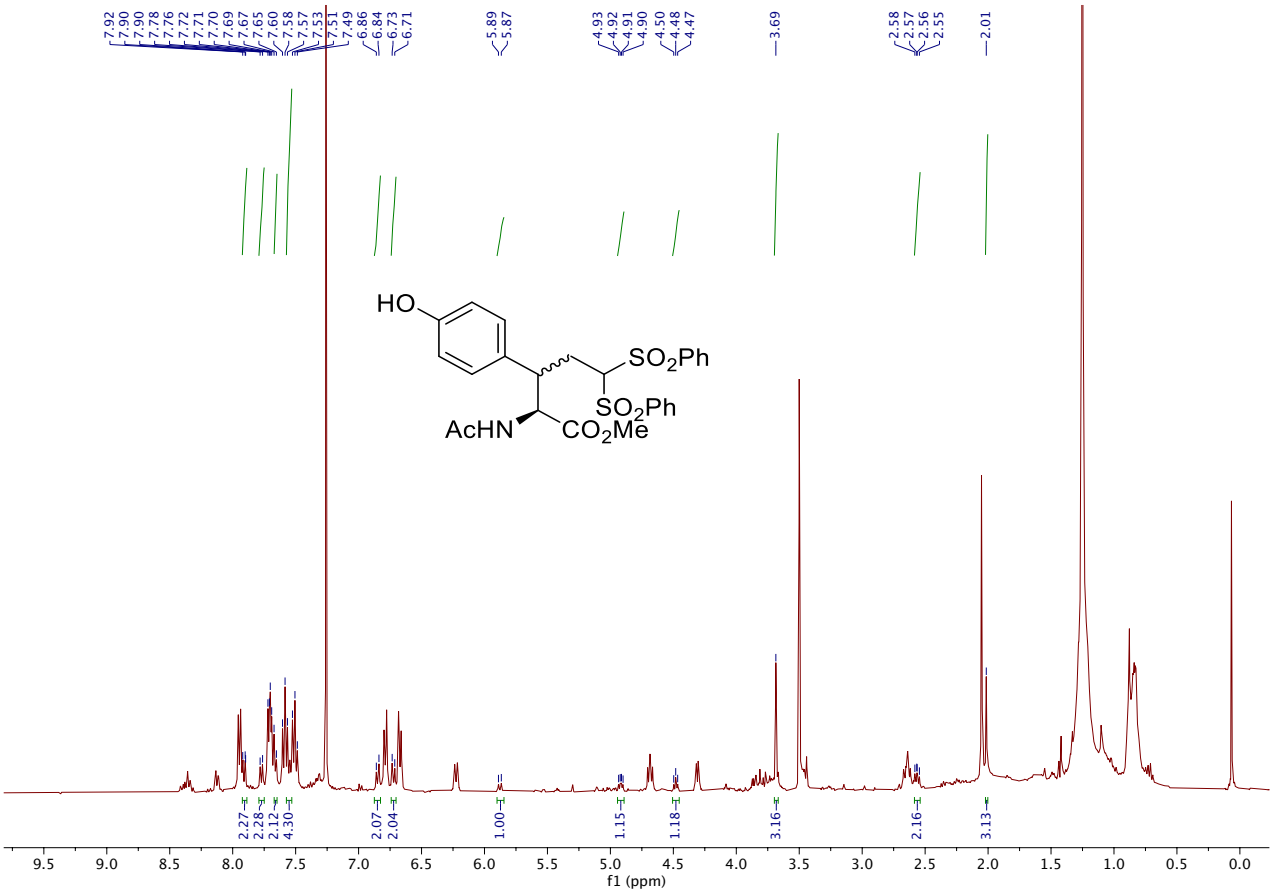
***Derivatization of Product 3b**:*

*Methyl (2S)-2-acetamido-3-(4-hydroxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (major **35**)*

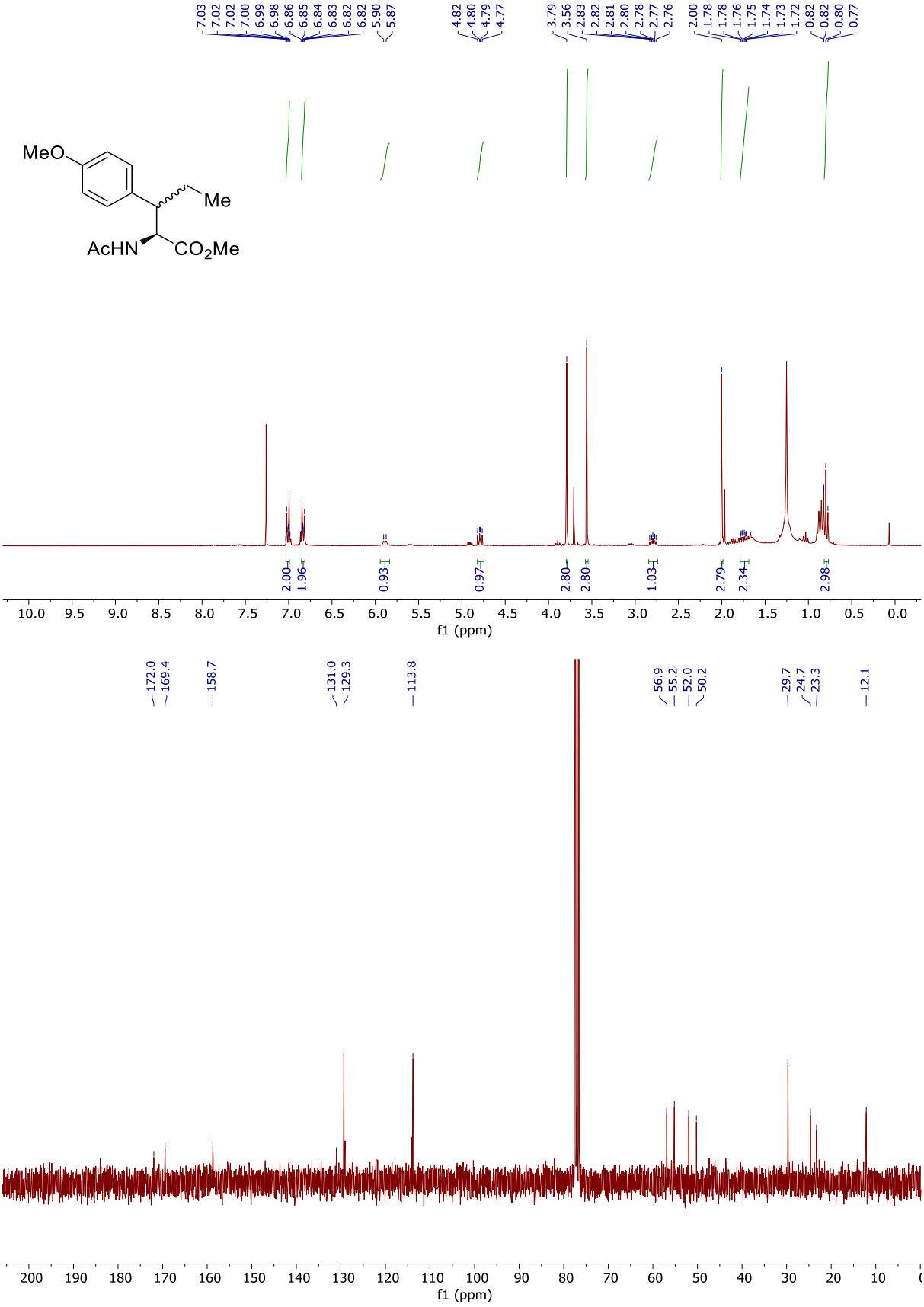




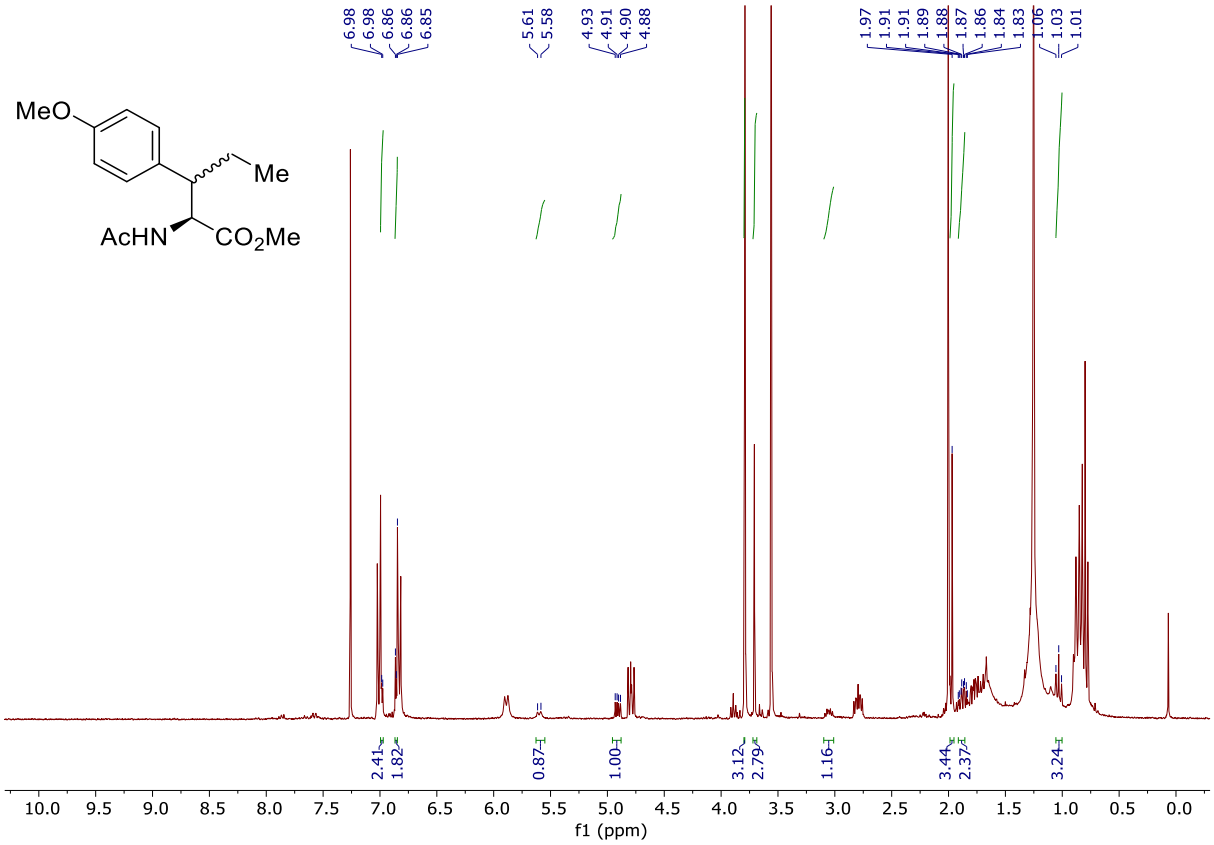
*Methyl (2S)-2-acetamido-3-(4-hydroxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (minor **35**)*



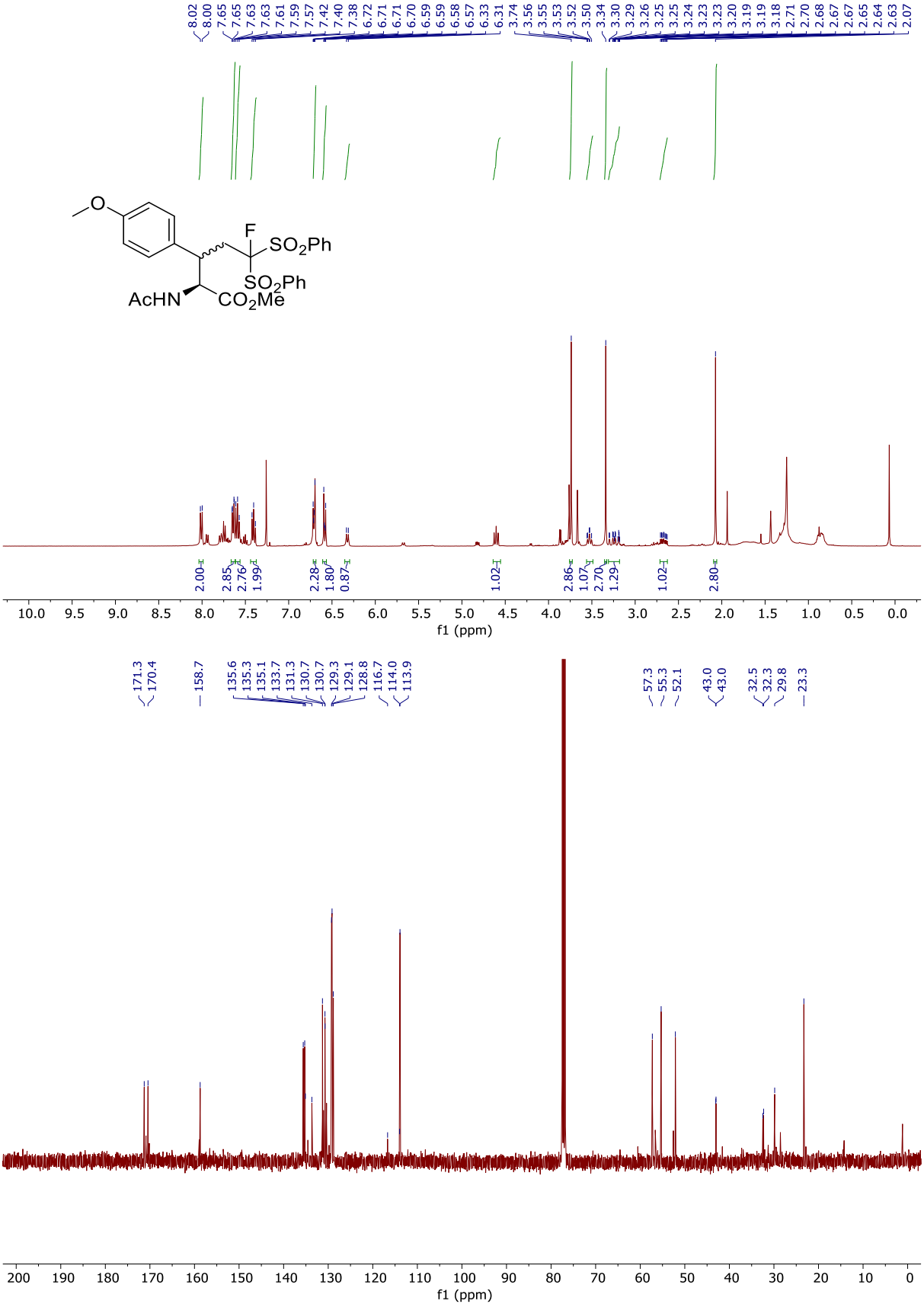
*Methyl (2S)-2-acetamido-3-(4-methoxyphenyl)pentanoate (*major **36***)*

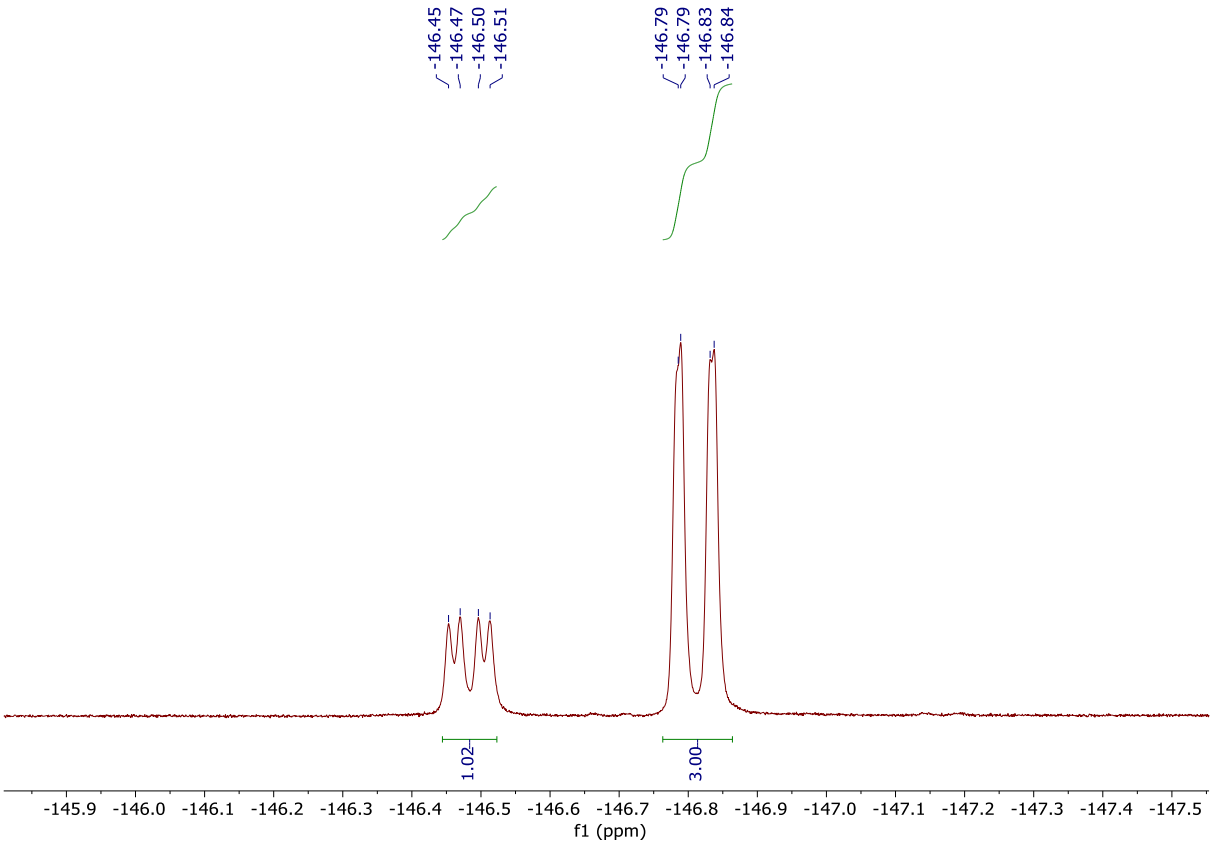


*Methyl (2S)-2-acetamido-3-(4-methoxyphenyl)pentanoate (*minor **36**)

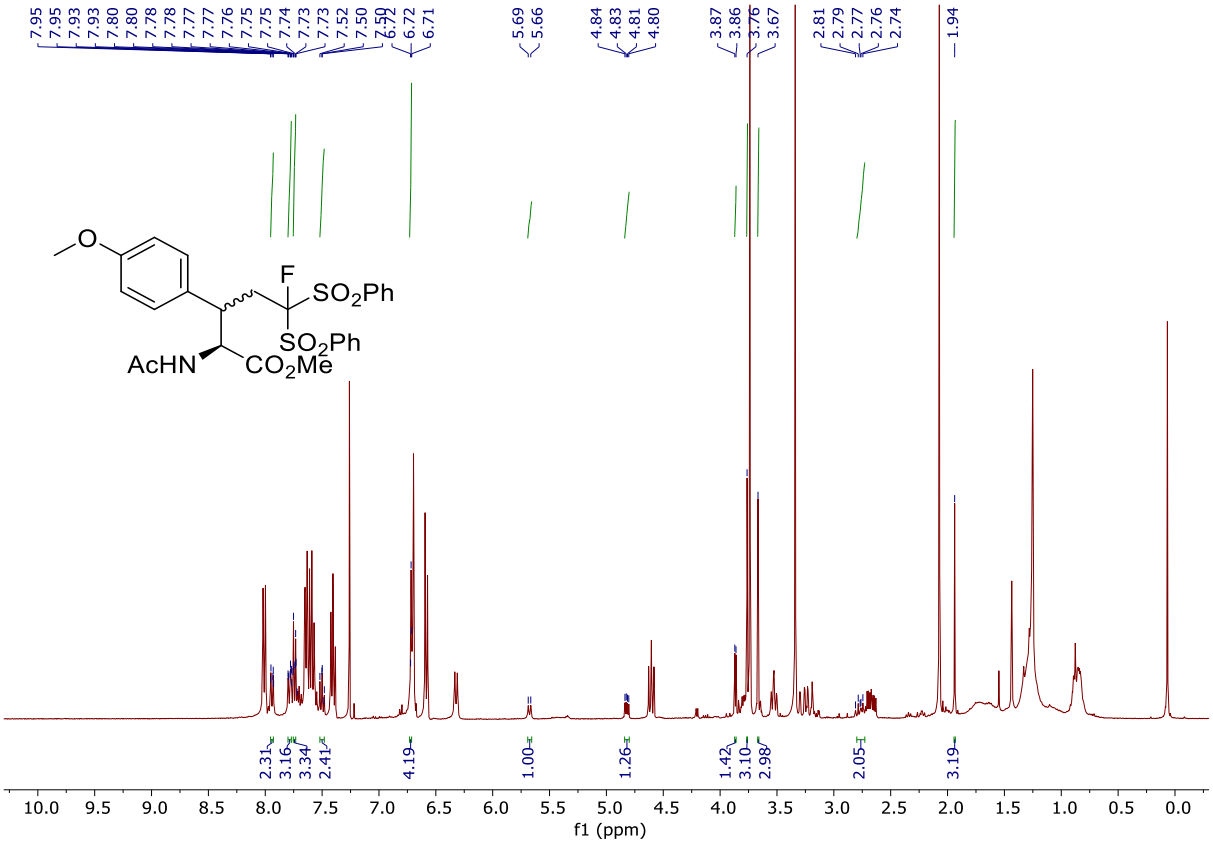


*Methyl (2S)-2-acetamido-5-fluoro-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (major **40**)*

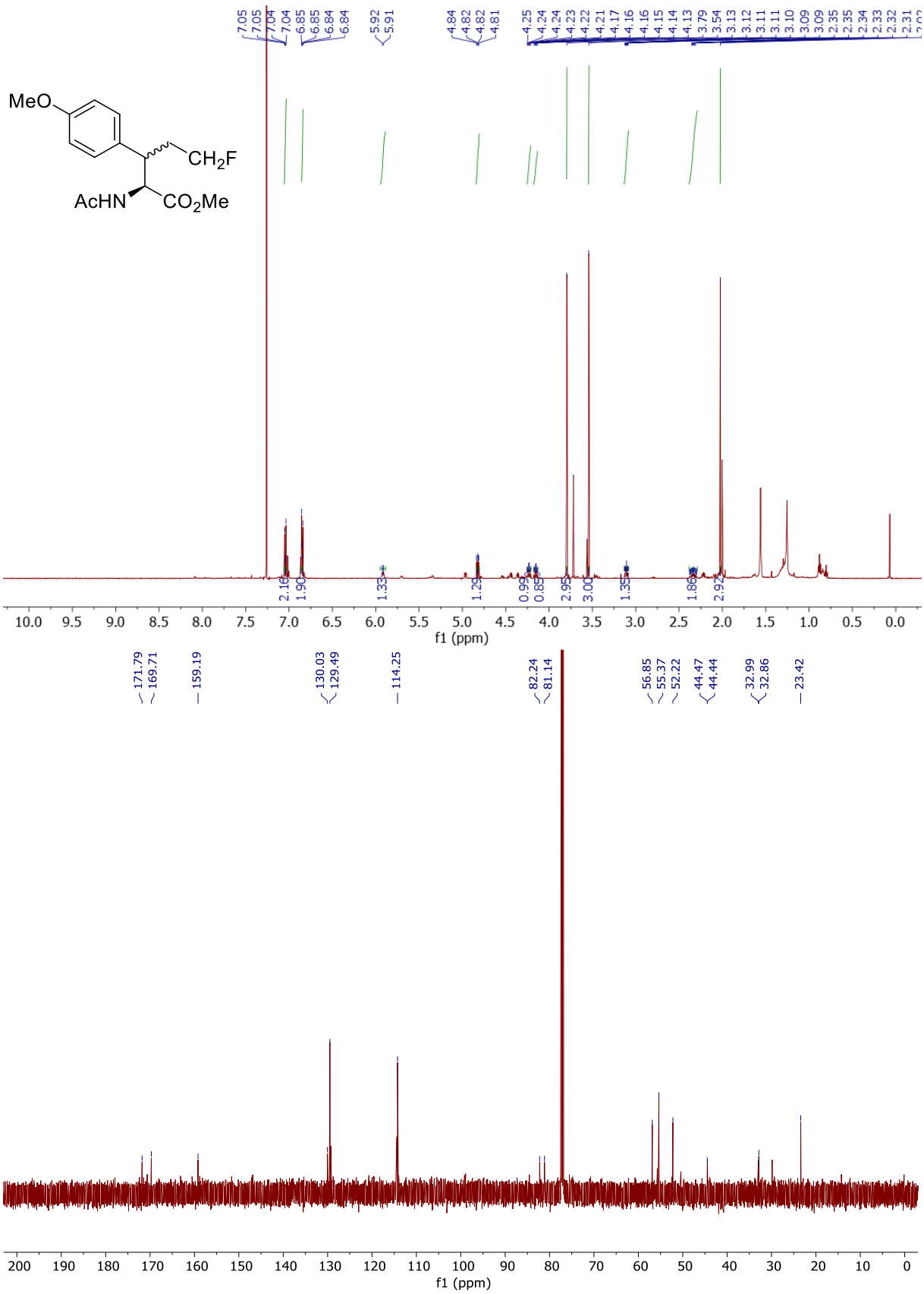


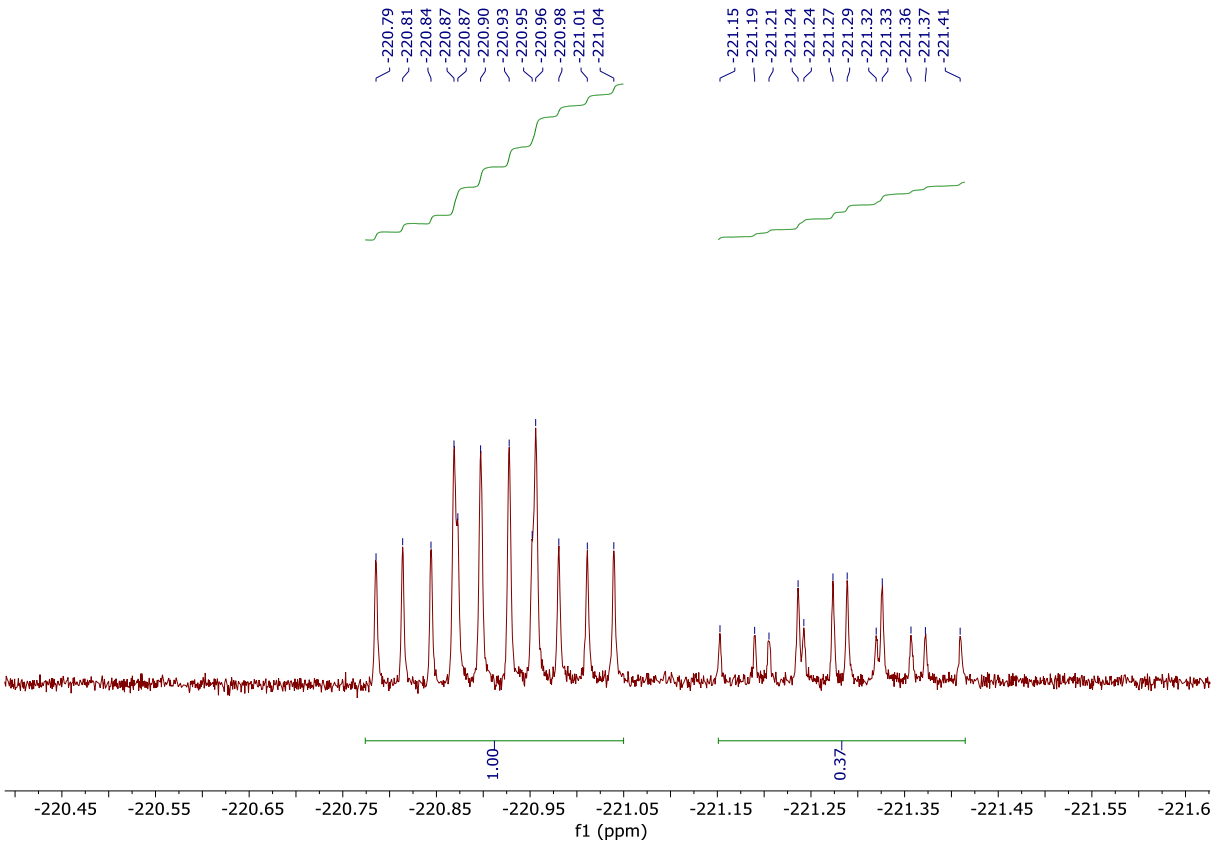


*Methyl (2S)-2-acetamido-5-fluoro-3-(4-methoxyphenyl)-5,5-bis(phenylsulfonyl)pentanoate (minor **40**)*

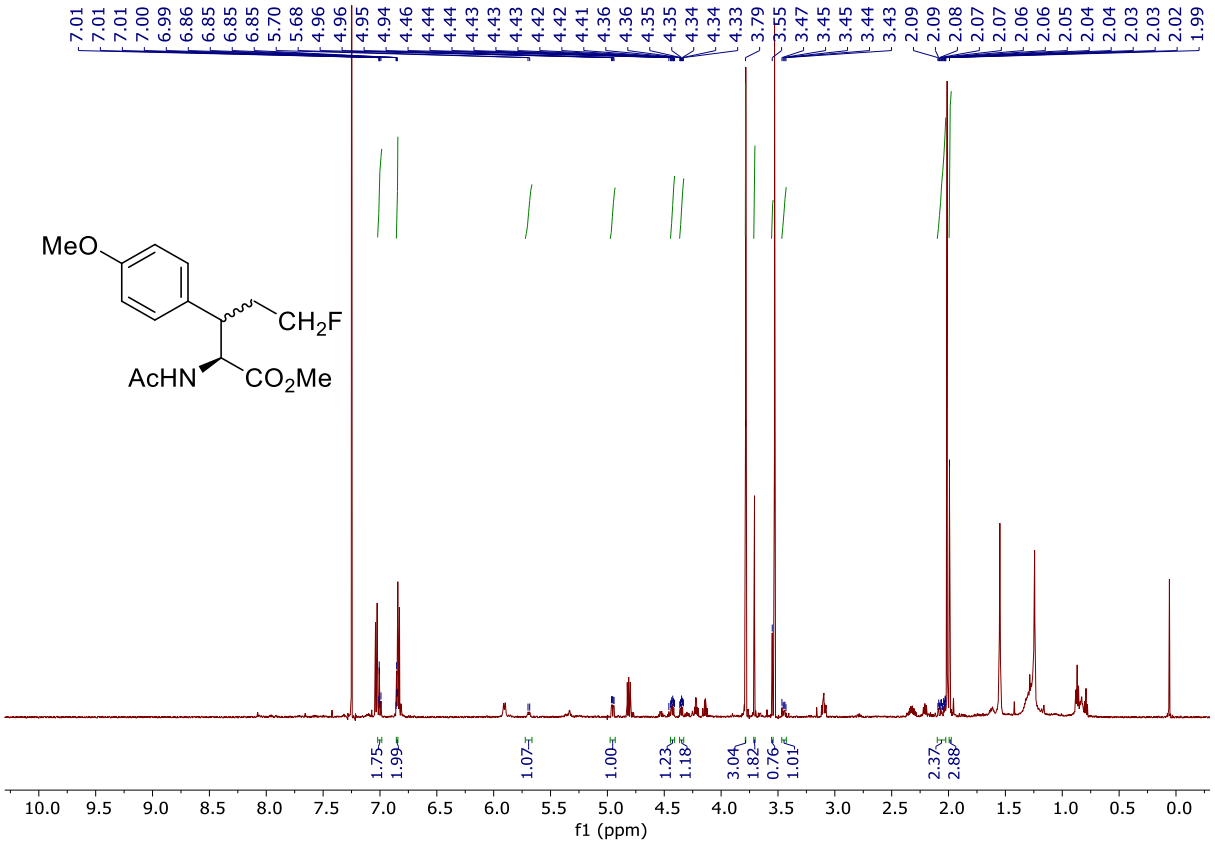


*Methyl (2S)-2-acetamido-5-fluoro-3-(4-methoxyphenyl)pentanoate (major **37**)*

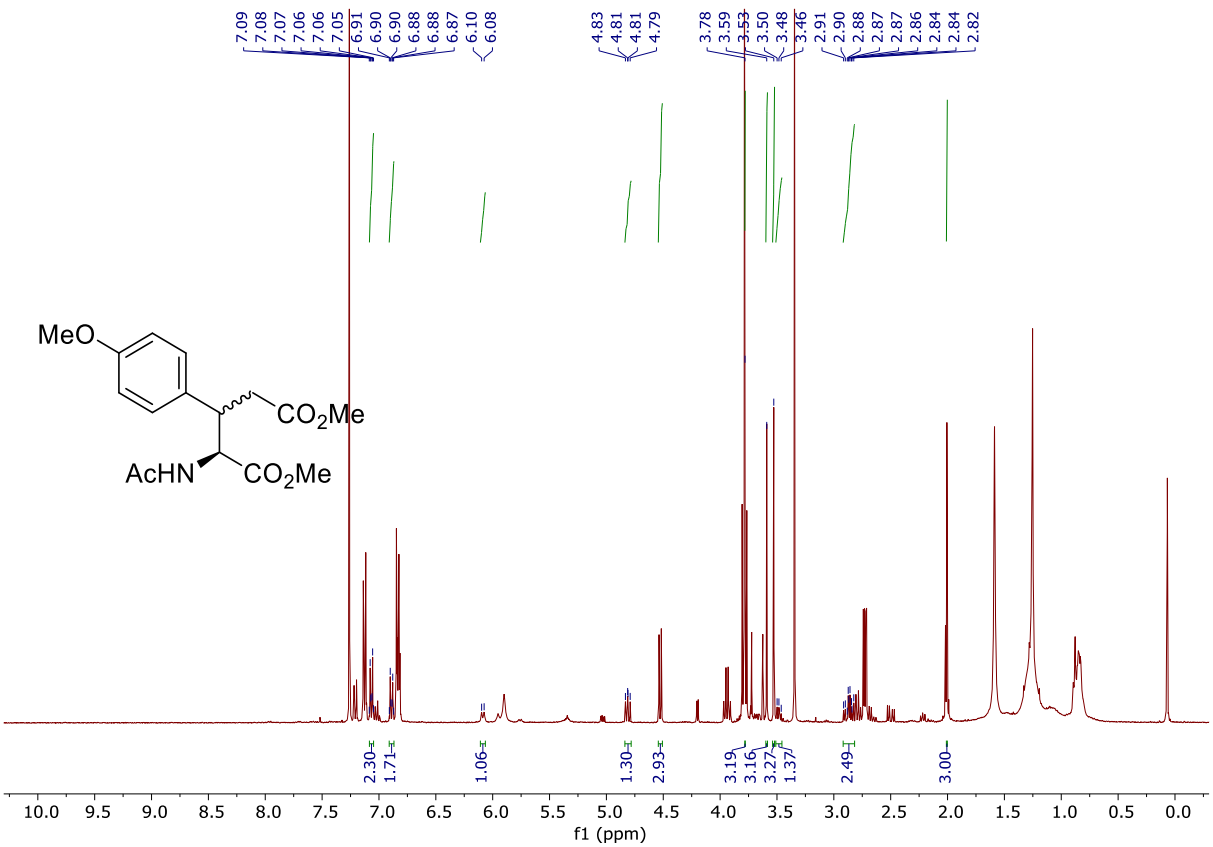


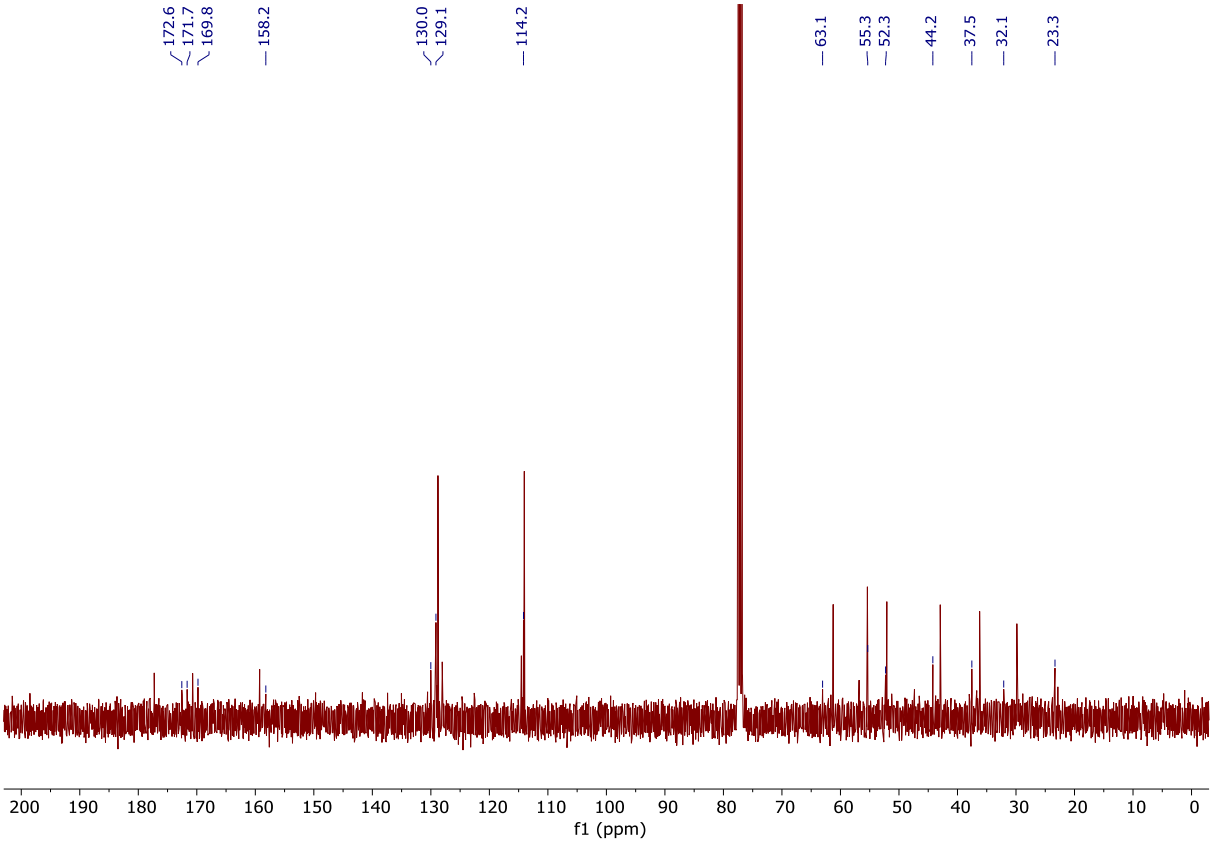


*Methyl (2S)-2-acetamido-5-fluoro-3-(4-methoxyphenyl)pentanoate (minor **37**)*

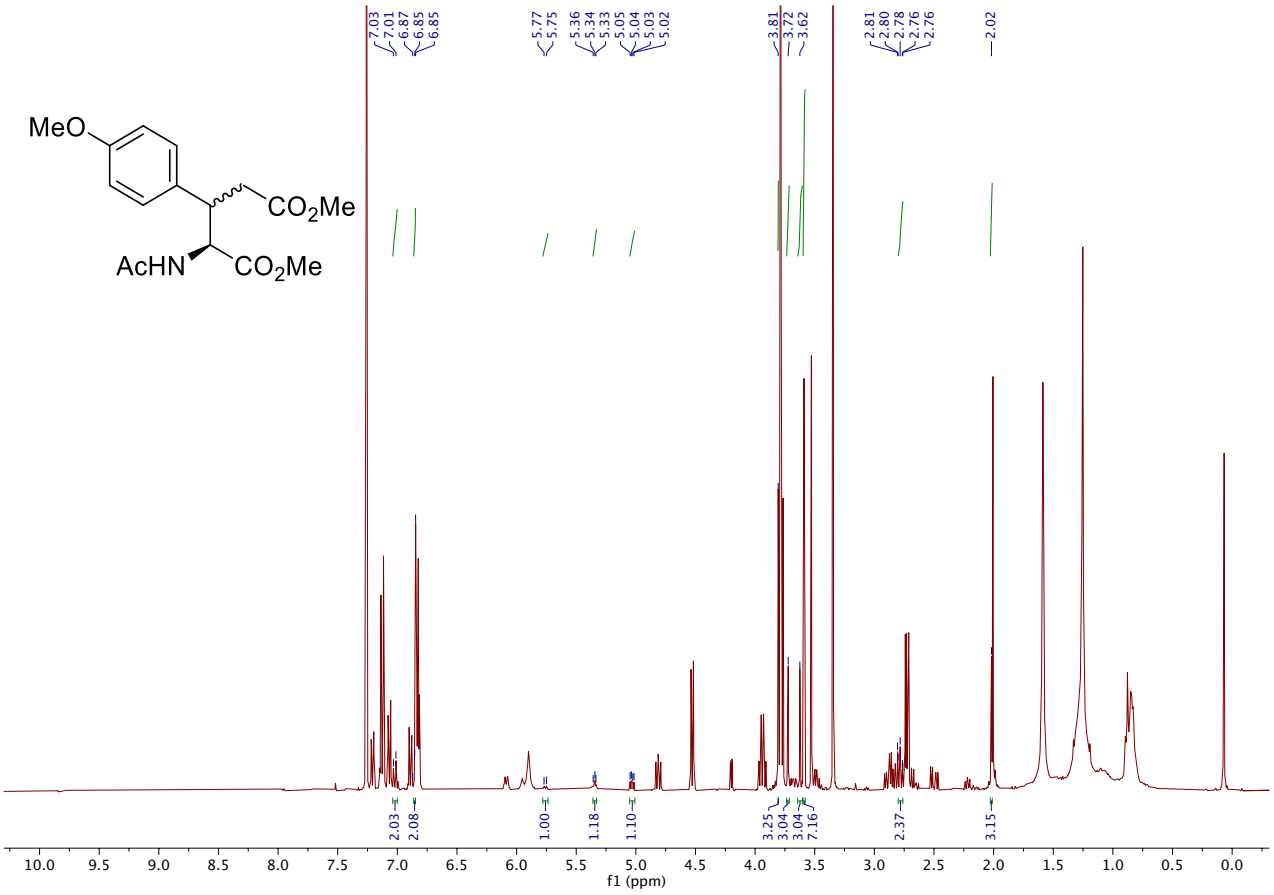


*Dimethyl (2S)-2-acetamido-3-(4-methoxyphenyl) pentanedioate (major **38**)*

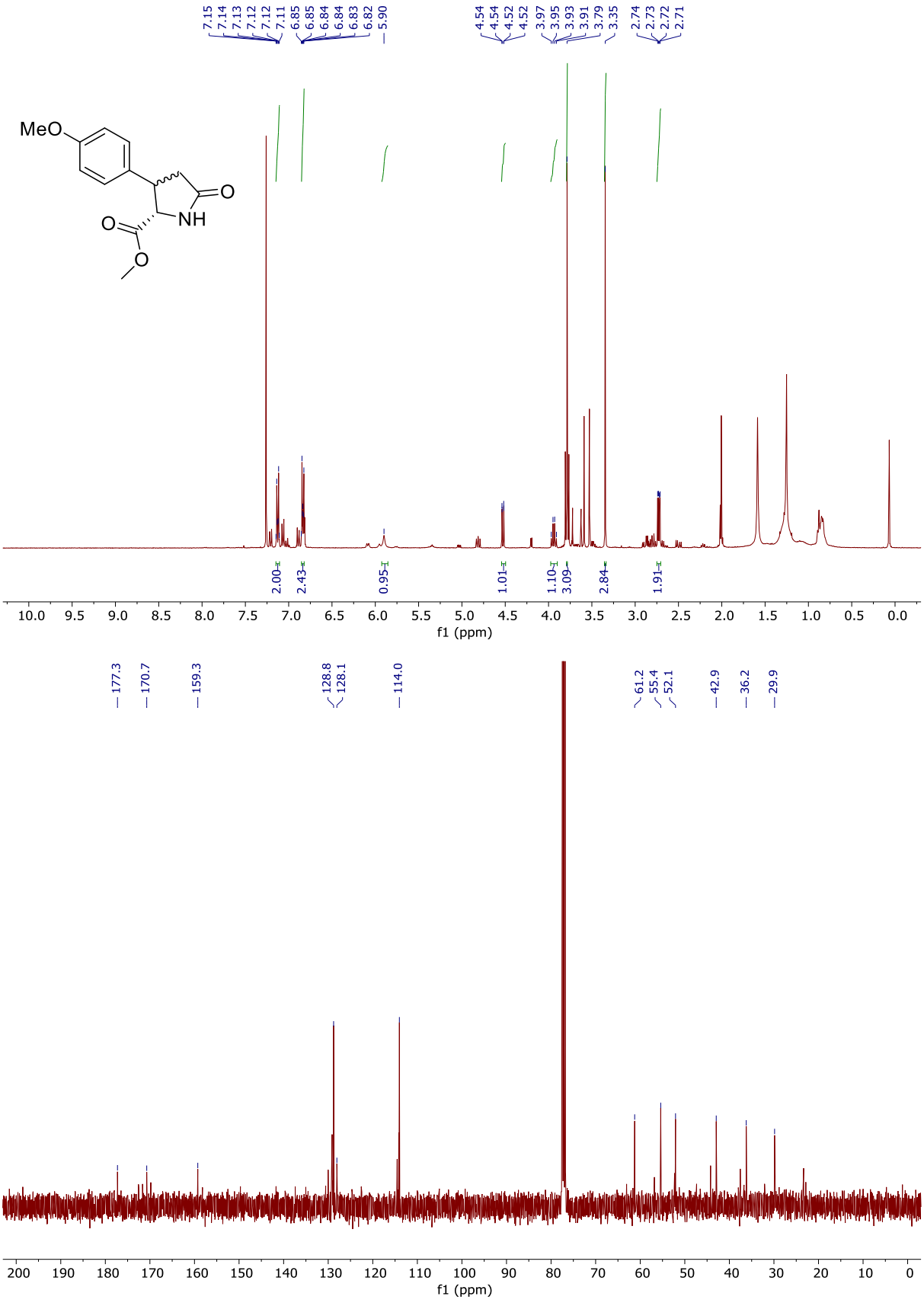




*Dimethyl (2S)-2-acetamido-3-(4-methoxyphenyl) pentanedioate (minor **38**)*



*Methyl (2S)-3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate (major **39**)*



*Methyl (2S)-3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate (minor **39**)*