Organocatalytic Access to a cis-Cyclopentyl-γ-amino Acid: An Intriguing Model of Selectivity and Formation of a Stable 10/12-Helix from the Corresponding γ/α-Peptide.

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Optimisation of the 5-*exo-trig* cyclization for the final synthesis of the *cis*-nitroalcohol 11

Preliminary optimisation for the synthesis of the *trans*-γ-amino acid precursor 15.

The investigation was carried out at room temperature without any further reduction as a provisional study. This method led to the synthesis of the diastereomer *trans*-**15** as main product of the reaction.

Several amino based catalysts were tested (Figure S1).

Diastereoselectivity and enantioselectivity were not reported where yields were considerably low and the obtained results were not significant for the optimisation of the reaction. Bifunctional catalysts **XII**, **XIII** and **XIV** were synthesised according to literature procedures.[1,2] A preliminary catalytic screen was performed with the reaction catalysed by the Hayashi-Jørgensen catalyst **III** reaching completion in 20 minutes, in 62% yield, with a 1:4 *cis/trans* diastereoselectivity and a –59% *ee* of the major diastereomer.

The same reaction was performed in the presence of an acid co-catalyst (3-nitro benzoic acid) at rt and at 0 °C. In both cases, yields, diastereoselectivity and enantioselectivity improved to 94% and 98% yield with a 1:9 and 1:13 *dr* and –62% and –71% *ee* respectively (Entry 2 and 3, Table S1). The yield was improved further with the use of bifunctional catalyst **VI** and this is probably due to a lower amount of impurities forming (Table S1). As with catalyst **III**, repeating the reaction at 0 °C with tetrazole catalyst **VI** the *dr* improved to 1:7, which suggests that at lower temperature the diastereomer *cis* is more likely to be isolated. Several other secondary amine catalysts and bifunctional catalysts were tested (Table S1), however all with limited success in terms of *ee* and *dr*. Interestingly, Hayashi-Jørgensen-CF_3 catalyst **VIII** produced a 1:2 *dr* in favour of the *trans* product with mismatched enantioselectivity between the *cis* and *trans* diastereomers. Primary amine catalyst **IX** was screened

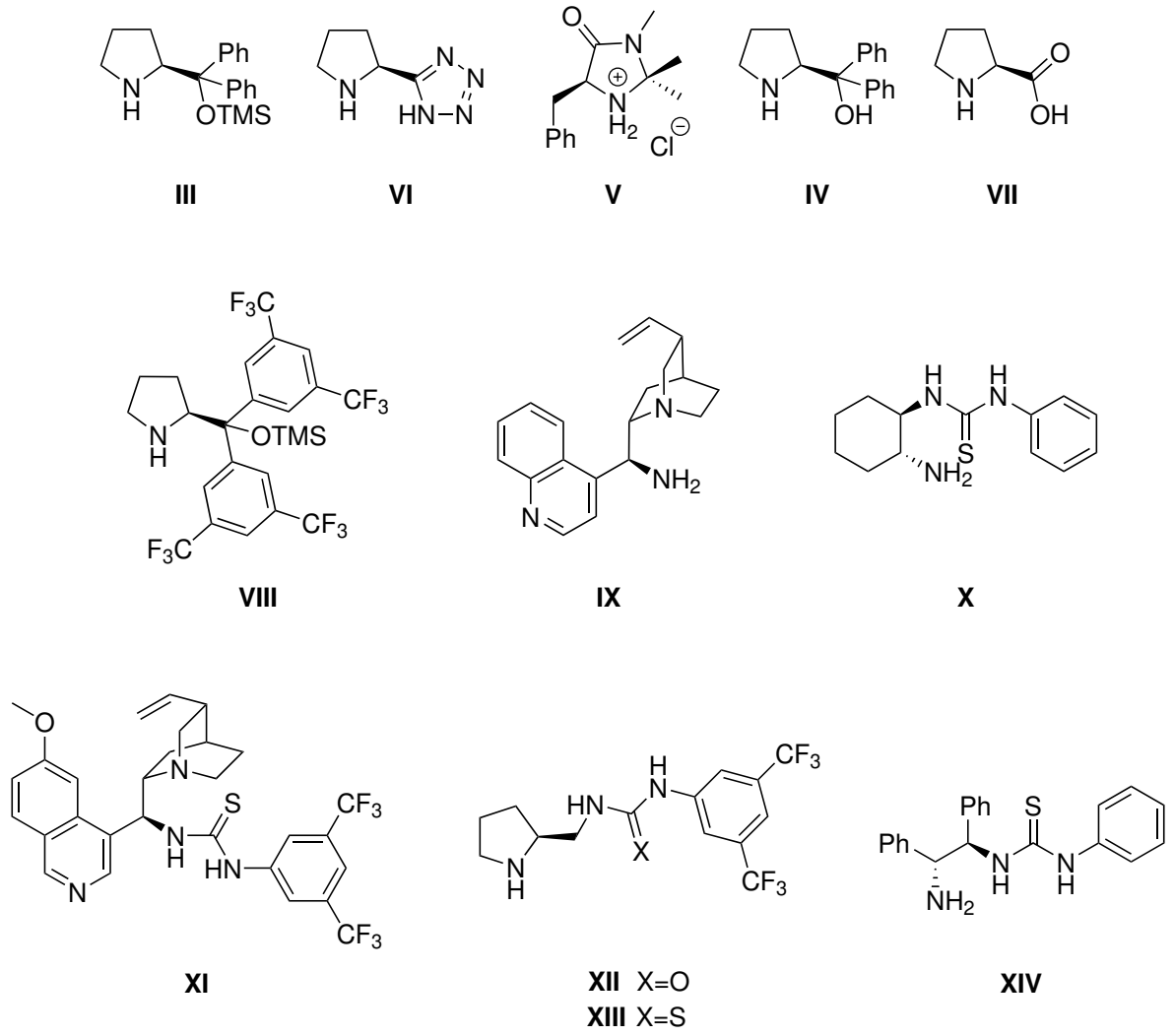
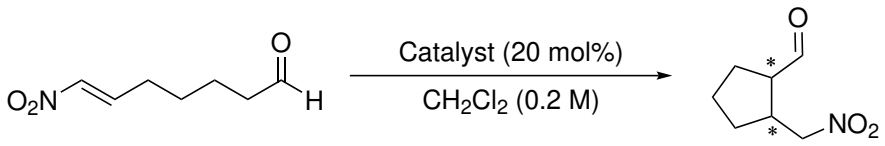


Figure S1: Selected catalysts to perform a preliminary screen at rt.

Table S1: Preliminary catalyst screen.



10 **15**

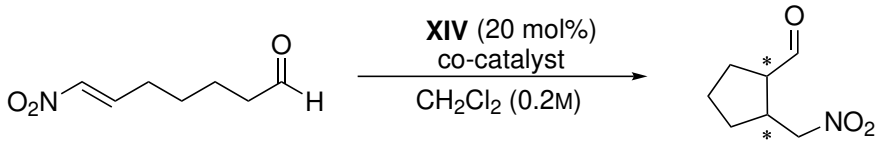
Entry	Cat.	Time [h]	T [°C]	Yield[i] [%]	dr^{ii} (*cis*/*trans*)	ee^{iii} [%] (*trans*)
1	**III**	0.3	rt	62	1:4	-59
2	**III**^{iv}	0.5	rt	94	1:9	-62
3	**III**^{iv}	0.5	0	98	1:13	-71
4	**VI**	1.5	rt	91	1:8	72
5	**VI**	9.5	0	74	1:7	79
6	**IV**	2.5	rt	67	1:2	6
7	**VII**	0.7	rt	67	1:9	-7
8	**VIII**	120	rt	67	1:2	15^{v}
9	**V**	2.5	rt	54	1:7	-59
10	**XI**	72	rt	26	1:1	ND
11	**IX**^{vi}	144	rt	11	1:2	-22
12	**X**	18	rt	51	1:5	85
13	**XII**	16	rt	50	1:3	63
14	**XIII**	19	rt	70	1:3	61
15	**XIV**	96	rt	41^{vii}	1:6	88

(i) Combinatorial isolated yield of separable diastereomers. (ii) Determined by crude ^{1}H NMR. (iii) Determined by HPLC analysis on a chiral stationary phase. (iv) In the presence of 3-nitrobenzoic acid (10 mol%) as co-catalyst. (v) -70% *ee* for diastereomer *cis*. (vi) In the presence of benzoic acid (10 mol%) as co-catalyst. (vii) Yield of single diastereomer *trans*.

alongside benzoic acid as co-catalyst to aid the enamine formation and hydrolysis as reported in literature (Table S1).[3] However, the reaction presented 1:2 *dr* and –22% *ee* of *trans*-**15** and only 11% yield after 6 days, which is probably due to the slow rate of hydrolysis of the iminium intermediate impeding the catalytic cycle to complete (Entry 11, Table S1). Catalysts **XII** and **XIII** gave moderate to good yields, moderate enantioselectivities (entry 13 and 14, Table S1) and 1:3 *dr*. The inclusion of a primary amine and thiourea moiety within the same catalyst (**X** and **XIV**) led to high enantioselectivity (entries 13 and 16, Table S1). The reaction catalysed by **XIV** achieved the best results from the catalyst screen and was used for further optimisation studies.

Mild and strong acids were tested as additives to the reaction, however all led to a reduction in diastereoselectivity and enantioselectivity (Table S2). A different strategy was

Table S2: Co-catalyst screen for the synthesis of the 5-membered ring *trans*-**15**.



10 **15**

Entry	Co-cat. (20 mol%)	Time [d]	Yield[i] [%]	*dr*[ii] (*cis*/*trans*)	*ee*[iii] (*trans*)[%]
1	-	96	41[iv]	1:6	88
2	Benzoic acid[v]	7	47[vi]	1:4	57
3	4-NBA	7	42	1:3	39
4	*p*-Toluene-sulfonic acid monohy-drate	7	15	1:1	-
5	*o*-Fluoro benzoic acid	5	43[vi]	1:2	45
6	TFA	7	23[vii]	1:1.5	40
7	3-NBA	6	44	1:1.5	37

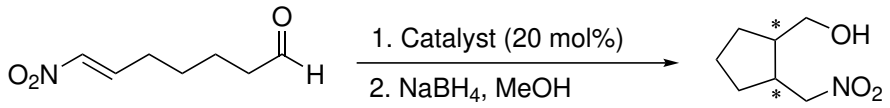
(i) Combinatorial isolated yield of separable diastereomers. (ii) Determined by crude ^{1}H NMR. (iii) Determined by HPLC analysis on a chiral stationary phase. (iv)) Yield of single diastereomer *trans*. (v) Co-catalyst loading of 10 mol%. (vi) Yield of single diastereomer *trans* because product *cis* was obtained together with not easily separable impurities. (vii) The reaction did not go to completion.

therefore outlined to optimise the enantioselective synthesis of the 5-membered ring **15**. This initial study was valuable to deepen our understanding of the targeted reaction and to select the best catalysts for further investigations. The enantioselectivity of *cis*-**15** was not recorded during this first preliminary study apart from entry 9 of Table S1 because it was obtained as minor diastereomer (*cis*-**15**) with poor yields. Having focused on the synthesis of the *trans* diastereomer in the first part of the study, the project moved on to target the synthesis of the *cis* diastereomer.

Asymmetric synthesis of *cis*-γ-amino acid precursor 11.

The study of the 5-*exo-trig* cyclisation at rt led to the identification of the best catalysts for further optimisation of the *cis*-nitroalcohol **11** synthesis. Five catalysts out of the catalyst screen performed at rt were selected to test at lower temperature followed by an *in situ* reduction in order to isolate *cis*-**11** (Table S3). The reactions were carried out at 0 °C except from the reaction catalysed by **XIV**, which was performed at rt due to slow reactivity (Table S3). Catalyst **XIV** gave the highest *ee* for *cis*-**11** albeit with a long reaction time, low yield and *dr*. Catalyst **III** and **VI** produced the best results in terms of yields, diastereoselectivity and enantioselectivity and therefore were selected for further investigation.

Table S3: Catalyst screen at 0 °C.



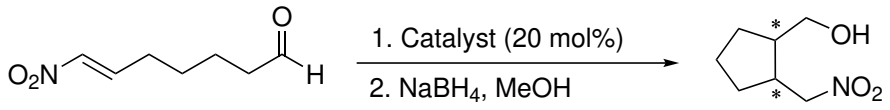
10 **11**

Entry	Catalyst	Time [h]	Yield[i] [%]	*dr*[ii] (*cis/trans*)	*ee*[iii] [%] (*cis,trans*)
1	**III**	1	57	1:1	87[iv], -27
2	**VI**	14	62	2:1	-83[iv], 71
3	**IV**	96	5[v]	1:1	ND, ND
4	**V**	72	42	1:6	-68, -74
5	**XIV**[vi]	104	6	1:1.5	-95, ND

(i) Combinatorial isolated yield of separable diastereomers. (ii) Determined by crude ^{1}H NMR. (iii) Determined by HPLC analysis on a chiral stationary phase. (iv) Determined by AD-H HPLC chiral column. (v) The reaction did not go to completion.(vi) The reaction was carried out at rt.

Temperature control of the reaction was unsurprisingly an important aspect of diastereoselecitivity. Temperature plays an important role as *cis*-**11** is the kinetic product and can only be isolated at low temperature after *in situ* reduction to the corresponding alcohol, since the diastereomer *cis* tends to convert to the more stable thermodynamic product *trans* in the presence of the secondary amine catalyst. The organocatalytic reaction was tested at 0, -10 and -20°C with catalysts **III** and **VI** (Table S4). The use of tetrazole catalyst **VI** at -20°C achieved the highest *dr*, a solvent screen was therefore performed with this catalyst.

Table S4: Temperature screen for the optimisation of the 5-*exo-trig* cyclisation.



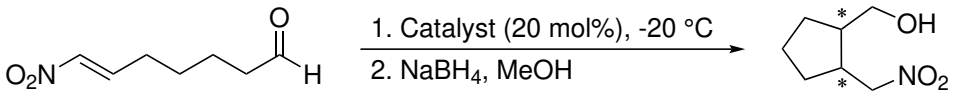
10 **11**

Entry	Catalyst	T [°C]	t [h]	Yield[i] [%]	*dr*[ii] (*cis/trans*)	*ee*[iii] [%] (*cis,trans*)
1	**III**	-20	5	20[iv]	1:1	36, 53
2	**III**	-10	3	64	1:1	-86, -26
3	**VI**	-20	22	62	3:1	82, 22
4	**VI**	-10	22	68	1:1	83, 67

(i) Combinatorial isolated yield of separable diastereomers. (ii) Determined by crude ^{1}H NMR. (iii) Determined by HPLC analysis on a chiral stationary phase. (iv) The reaction did not go to completion.

The intramolecular Michael addition was tested with different solvents, but only chlorinated solvents led to good diastereoselectivity and excellent enantioselectivity (Table S5). Protic and polar solvents such as methanol and THF (entry 4 and 6, Table S5) were found to have a detrimental effect on yield and enantioselectivity of the reaction and this can be associated to the coordination of the solvent to the tetrazole moiety interfering with the protonation step which might be crucial for the reactivity and the selectivity of the reaction. Interestingly, performing the reaction in dichloroethane gave the best results in terms of *dr* and *ee* (entry 7, Table S5).

Table S5: Solvent screen of the 5-*exo-trig* cyclisation.



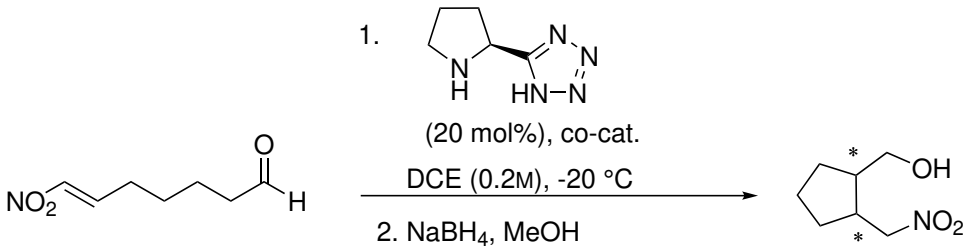
10 **11**

Entry	Solvent (0.2 M)	t [h]	Yield[i] [%]	dr^{ii} (*cis/trans*)	ee^{iii} [%] (*cis,trans*)
1	CH_2Cl_2	22	62	3:1	82, 22
2	Toluene	24	57	3:1	70, 32
3	CH_3CN	25	54	1:1	65, 56
4	THF	24	52	1:1	50, 38
5	$CHCl_3$	20	68	3:1	79, 48
6	MeOH	26	11	1.5:1	-10, ND
7	DCE	50	53	7:1	85, 54

(i) Combinatorial isolated yield of separable diastereomers. (ii) Determined by crude ^{1}H NMR. (iii) Determined by HPLC analysis on a chiral stationary phase.

The solvent screen was then followed by another co-catalyst screen. In the presence of an acidic co-catalyst, such as entry 1 and entry 2 of Table S6, the diastereoselectivity shifted towards the synthesis of *trans*-**11** as the main diastereomer. Basic co-catalysts on the other hand favoured the production of *cis*-**11** albeit in low yields (Table S6). This type of co-catalyst might promote the formation of side products, reducing the efficiency of the reaction. The next step for the optimisation of the 5-*exo-trig* intramolecular Michael addition was the concentration screen. As expected, yield improved considerably from 58% to 78% when diluting the reaction from 0.2M to 0.05M and this is possibly due to the suppression of side reactions, like nitroolefin polymerisation, which might occur at higher concentrations.[4,5]

Table S6: Co-catalyst screen of 5-*exo-trig* cyclisation for the synthesis of *cis*-**11**.



10 **11**

Entry	Co-catalyst (20 mol%)	Time [h]	Yield[i] [%]	dr^{ii} (*cis/trans*)	ee^{iii} [%] (*cis,trans*)
1	Benzoic acid	48	53	1:2	78, 80
2	3-NBA	48	68	1:5	70, 82
3	Acetic acid	77	54	2:1	86, 62
4	Catechol	48	47	N.A.[v]	74, 41
5	TEA	20	25	4:1	-26, ND
6	Dimethyl-piperazine	48	18	2.5:1	7, 5

(i) Combinatorial isolated yield of separable diastereomers. (ii) Determined by crude ^{1}H NMR. (iii) Determined by HPLC analysis on a chiral stationary phase. (iv) The reaction did not go to completion.(v) The *dr* cannot be calculated *via* NMR.

Table S7: Concentration screen of the 5-*exo-trig* cyclisation.

Entry	Conc. [M]	Time [h]	Yield[i] [%]	dr^{ii} (*cis/trans*)	ee^{iii} [%] (*cis,trans*)
1	0.2[iv]	42	58	6:1	83, -
2	0.05	168	74	8.5:1	93, -
3	0.1	48	66	6:1	89, -
4	0.2	50	60	5.5:1	88, -
5[v]	0.1	72	60	5.5:1	91, -
6[vi]	0.05	168	51	4:1	85, 45

(i) Combinatorial isolated yield of separable diastereomers. (ii) Determined by crude ^{1}H NMR. (iii) Determined by HPLC analysis on a chiral stationary phase. (iv) The reaction was carried out with anhydrous solvents. (v) The reaction was reduced with DIBAL-H. (vi) Cold addition of a solution of substrate (2M in DCE) to the reaction mixture.

A catalyst loading screen was performed to complete the reaction optimisation and it was found that the reaction maintains comparable results when using catalyst loading as low as 5 mol% (Table S8). Low catalyst loading is an important achievement for organocatalysis and it is likely that the reaction catalysed by 2 mol% catalyst would give higher yield if the reaction was carried out in larger scale due to encountered solubility issues (entry 5, Table S8).

Table S8: Catalyst loading screen for the optimisation of the 5-*exo-trig* cyclisation.

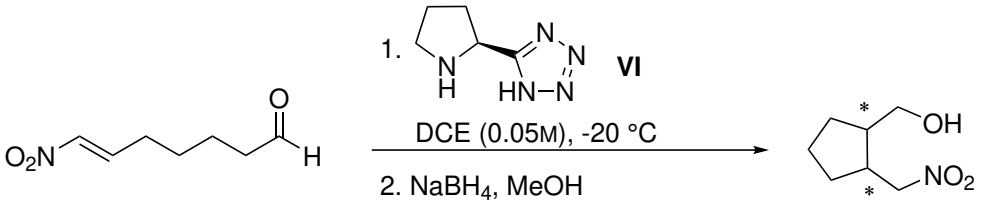
Entry	Conc. [M]	Catalyst loading [mol%]	Time [h]	Yield[i] [%]	dr^{ii} (*cis/trans*)	ee^{iii} [%] (*cis,trans*)
1	0.1	10	70	64	7:1	89, 26
2	0.1	5	168	52	11.5:1	88, 0
3	0.05	10	24	74	9:1	92, 34
4	**0.05**	**5**	**168**	**75**	**10:1**	**89, -56**
5	0.05	2	168	43	10:1	92, -11

(i) Combinatorial isolated yield of separable diastereomers. (ii) Determined by crude ^{1}H NMR. (iii) Determined by HPLC analysis on a chiral stationary phase.

Scale up of the reaction

The optimisation of the 5-*exo-trig* cyclisation assisted by the bifunctional tetrazole catalyst **VI** produced the desired *cis*-nitroalcohol **11** in high yield, good diastereoselectivity and excellent enantioselectivity. The reaction was then successfully scaled up to 7 mmol and it was stopped after 99 hours instead of 168 hours producing analogous results (Table S9). It is believed that the amount of starting material left in solution is not reacting as fast as in the first 4 days and this might be due to the high concentration of the competing product **15** formed that tends to condense again with the catalyst in order to convert to the more stable *trans*-**15**.

Table S9: Scale up of the 5-*exo-trig* cyclisation.



10 **11**

Entry	Reaction scale [mmol]	Catalyst loading [mol%]	Time [h]	Yield[i] [%]	*dr*[ii] (*cis/trans*)	*ee*[iii] (*cis*) [%]
1	0.64	20	168	74	8:1	93
2	0.64	5	168	75	10:1	89
3	**7.0**	**5**	**99**	**74**	**9:1**	**92**

(i) Combinatorial isolated yield of separable diastereomers. (ii) Determined by crude ^{1}H NMR. (iii) Determined by HPLC analysis on a chiral stationary phase.

General

All reactions were carried out at room temperature and magnetically stirred unless otherwise stated. Anhydrous CH_2Cl_2, THF, MeOH, DMF and toluene solvents were obtained from a dry solvent system all other solvents were supplied as Sureseal® bottles by Sigma Aldrich. All reagents were supplied by Sigma Aldrich, Alfa-Aesar, Fisher and VWR unless otherwise stated.

NMR data: Nuclear Magnetic Resonance (NMR) spectra were recorded using a Bruker Ascend 400 (400 MHz) or a Bruker NEO 600 (600 MHz) spectrometer using TMS as internal standard. Chemical shifts (δ) are quoted in parts per million (ppm) using the abbreviations: s, singlet; d, doublet; dd, double of dublets; t, triplet; dt, doublet of triplets; ddt, doublet of doublet of triplets; td, triplet of doublets; q, quartet. Resonances that could not be easily interpreted were designated multiplets (m) or broad (br). Coupling constants J are quoted in Hz. ^{13}C NMR spectra were recorded at 100 MHz on a Bruker Ascend 400 (400 MHz) or a Bruker NEO 600 (600 MHz) spectrometer. Two-dimensional spectroscopy (COSY, HSQC, HMBC, TOCSY, ROESY) was used to confirm the assignments where necessary. NMRs taken on the Bruker NEO 600 (600 MHz) were carried out at the NMR facility of the Centre for Biomolecular Spectroscopy at King's College London . Crosspeaks were integrated manually within Topspin 3.5. The average of the intensities of AMCP Hγ_1-Hγ_2 cross peaks was used as a reference, I_0, set to correspond to a distance, r_0, of 1.763 Å. All other upper limits for distance restraints were calculated using: $r_1 = [(I_0/I_1)(r_0^6)]^{1/6}$. Lower limits for all distance restraints were set to 1.8 Å.

IR data: IR spectra were recorded on a Shimadzu IRAffinity-1S FTIR Spectrophotometer as a thin film. The selected absorptions are quoted in wavenumbers (cm^{-1}). MS data: High-resolution mass spectra were recorded on either Waters LCT Premier (Es-Tof), Thermo Scientific Q-Exactive (APCI) and Micromass Autospec Premier (EI) by Imperial College London, Department of Chemistry Mass Spectrometry Service. Optical Rotation: Optical rotation readings were recorded using an Anton Parr MCP100 Polarimeter. Specific

rotations ($[\alpha]^{20}_D$) were recorded at the sodium D line (589 nm) in methanol or CH_2Cl_2 and are quoted in: deg cm^2 g^{-1}. Solution concentrations (c) are given in units of 10^{-2} g mL^{-1}. Temperatures are in degrees Celsius (°C). The prefixes (+) and (-) indicate the sign of the optical rotation. Correct units: deg cm^2 g^{-1}

Melting point: Melting points were determined on a Stuart SMP30 melting point apparatus and are uncorrected.

HPLC Profiles: HPLC analysis was determined on Agilent Technologies 1200 Series HPLC, using a ratio of HPLC grade hexanes and propan-1-ol as the eluent, using a Chiralpak AD-H, OD or AS column (0.46 cm x 25 cm) and detection by UV at 210 nm. Peaks were assigned spiking the enantioselective sample with the racemic.

Chromatography: Reactions were monitored by thin layer chromatography on silica gel precoated aluminium sheets (TLC Silica Gel 60 F254, Merck). Visualisation was accomplished by irradiation by UV light at 254 nm and/or ninhydrin stain, potassium permanganate stain, *p*-anisaldehyde, dinitrophenylhydrazine or vanilline. Column chromatography was performed on Merck silica gel (60 Å, 230 - 400 mesh, 40 - 63 μm) or on a CombiflashRF+ system.

Single Crystal X-ray: X-ray data was collected on an Oxford Gemini S-ultra diffractometer using Kalpha (lambda = 1.54180 Å) radiation.

Circular Dichroism: All CD spectra were measured in an Aviv Circular Dichroism Spectrophotometer, Model 410 (Biomedical Inc., Lakewood, NJ, USA), with specially adapted sample detection to eliminate scattering artefacts, or at the Karlsruhe synchrotron. A final oligomer concentration 1.6 mgml^{-1} for **18**, 1.2 mgml^{-1} for **20** and 1.6 mgml^{-1} for **21** was used in quartz rectangular Suprasil demountable cells of pathlength 0.2 mm (Hellma or 0.5 mm Analytics). Each sample was scanned two to four times from 270 to 185 nm, at 1-nm intervals with an averaging time of 0.5 s. The same cell containing buffer only was also measured for background subtraction during data analysis. All CD spectra were processed using CDTool.[6] First, the multiple scans were averaged and the buffer background was sub-

tracted. These subtracted spectra were zeroed and smoothed, which set the baseline at zero between 255 and 270 nm.

Synthesis of the *endo*-nitroolefin 10

Method A for the synthesis of 10

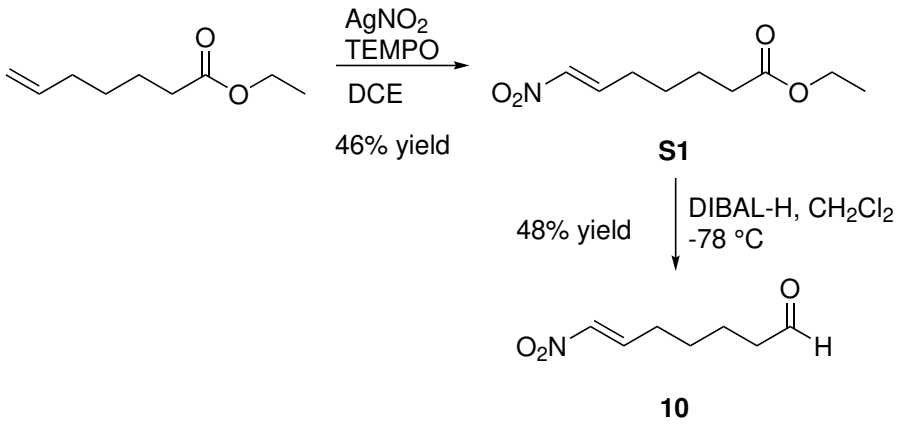
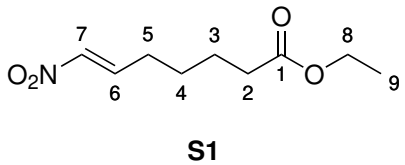


Figure S2: Synthesis of substrate **10** according to the synthetic procedure described in method A.

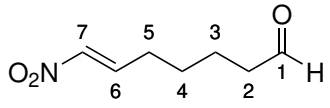
Ethyl (*E*)-7-nitrohept-6-enoate S1



To an oven-dried quick-fit cap test tube charged with magnetic stir-bar was added activated 4Åmolecular sieves (1.5 g), $AgNO_2$ (21.743g, 128 mmol) and TEMPO (2.0 g, 12.8 mmol). Ethyl-6-heptenoate (5.6 mL, 32.0 mmol) and anhydrous DCE (100 mL) were added. The tube was then placed in a preheated oil bath at 70 °C and the reaction mixture was left stirring vigorously for 18 hours. The progress of the reaction was monitored by TLC and then the reaction mixture was left to cool down to rt. The reaction mixture was then filtered through a short pad of celite washed with ethyl acetate (500 mL) and concentrated *in vacuum*. The crude product was then purified *via* combiflash using silica gel columns and a gradient solution of ethyl acetate and hexane up to 20% ethyl acetate in hexane to afford

the titled compound **S1** as a colourless oil (2.955 g, 14.7 mmol, 46%). IR (neat, cm^{-1}) 2936, 1728, 1650, 1522, 1462, 1349, 1179, 1152, 1097, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (1H, m, H-7), 7.01 (1H, dt, J = 13.4, 1.6 Hz, H-6), 4.15 (2H, q, J = 7.1 Hz, H-8), 2.43 – 2.23 (4H, m, H-2 and H-5), 1.74 – 1.56 (2H, m, H-4), 1.64 – 1.50 (2H, m, H-3), 1.28 (3H, t, J = 7.1 Hz, H-9). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.1 (C-1), 141.9 (C-6), 139.8 (C-7), 60.4 (C-8), 33.8 (C-2), 28.1 (C-5), 27.2 (C-3), 24.3 (C-4), 14.2 (C-9); HRMS required for $C_9H_{14}NO_4$ $[M-H]^+$ is 200.0923, found 200.0931.

(E)-7-nitrohept-6-enal 10



10

To a solution of ethyl **S1** (2.945g, 14.7 mmol) and anhydrous CH_2Cl_2 (80 mL) at -78 °C was added DIBAL-H (1M in hexane, 16.9 mL, 16.9 mmol) dropwise in 15 minutes. The progress of the reaction was monitored by TLC and the reaction went to completion in 4 hours. An aqueous solution of HCl (1M, 50 mL) was added and the reaction mixture was left to stir overnight at rt. Then, H_2O (80 mL) was added and the organic phase was extracted with CH_2Cl_2 (3 x 80 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by combiflash (silica gel, gradient up to 40% diethyl ether in hexane) afforded the titled compound **10** as a colourless oil (0.864 g, 5.5 mmol, 37% yield). IR (neat, cm^{-1}) 2937, 1719, 1648, 1517, 1347; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (1H, t, J = 1.4 Hz, H-1), 7.33 - 7.13 (1H, m, H-6), 6.99 (1H, dt, J = 13.4, 1.6 Hz, H-7), 2.50 (2H, td, J = 7.1, 1.4 Hz, H-2), 2.30 (2H, td, J = 7.4, 1.6 Hz, H-5), 1.92 - 1.60 (2H, m, H-3), 1.62 - 1.37 (2H, m, H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.6 (C-1), 141.78 (C-6), 139.90 (C-7), 43.41 (C-2), 28.26 (C-5), 27.19 (C-4), 21.42(C-3). HRMS required for $C_7H_{12}NO_3$ $[M+H]^+$ is 158.0817, found 158.0821.

Method B for the synthesis of the *endo*-nitroolefin 10.

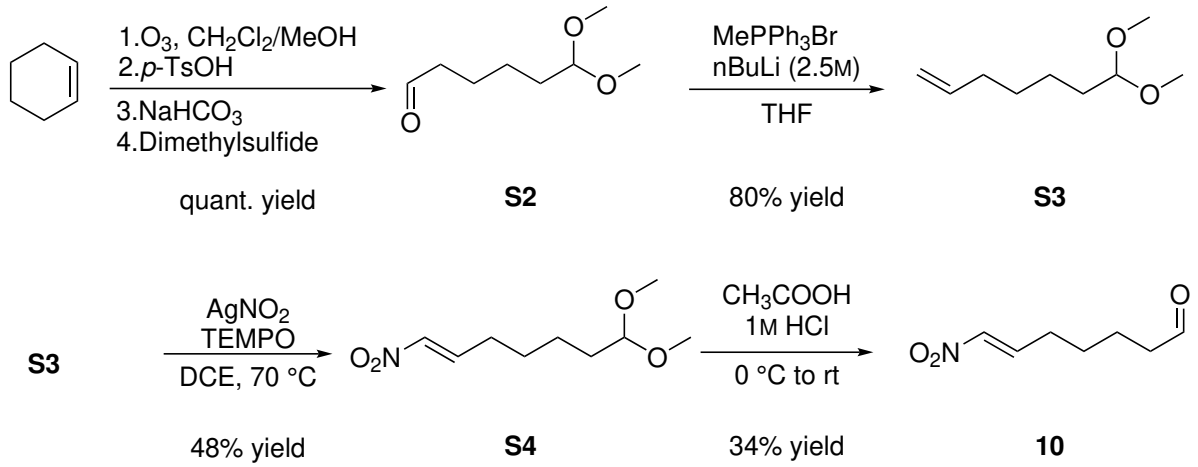
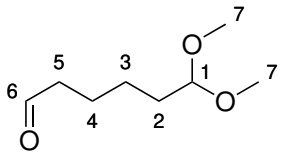


Figure S3: Synthesis of substrate **10** according to the synthetic procedure described in method B.

6,6-dimethoxyhexanal S2[7]

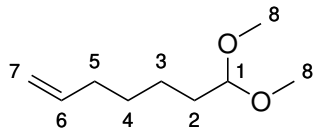


S2

A three neck round bottom flask was heat dried and each neck was respectively occupied by a drying tube loaded with CaCl as outlet, a glass stopper and the ozoniser inlet. Cyclohexene (7.6 mL, 75 mmol) was dissolved in a solution of CH_2Cl_2 (250 mL) and MeOH (50 mL) and it was then cooled to -78 °C. O_3 was then bubbled through the solution until a light blue colour developed. Excess of O_3 was removed by bubbling through the reaction mixture N_2 until the blue colour was discharged. The reaction mixture was then left to warm up to rt and the drying tube and the ozone inlet were replaced with rubber septums. p-tosylic acid monohydride (10% *w/w*, 1.215 g) was added to the solution and then it was left stirring at rt under N_2 for 90 min. $NaHCO_3$ (4mol-eq, 2.147g) was added followed by dimethyl sulphide

(12 mL, 163.4 mmol) after 15 minutes. The reaction mixture was left stirring overnight and then concentrated up to 50 mL of solution. Then, it was diluted with CH_2Cl_2 (100 mL) and washed with H_2O (75 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with H_2O (100 mL) and the aqueous phase was extracted with a final portion of CH_2Cl_2 (100 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product **S2** was obtained as a colourless oil (12.6 g, 12 mmol, quantitative yield) and it was used for the following reaction without further purification. IR (neat, cm^{-1}) 2946, 2830, 1724, 1460, 1387, 1191, 1126, 1071, 1050; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (1 H, s, H-6), 4.34 (1 H, t, J 5.7, H-1), 3.30 (6 H, s, H-7), 2.43 (2 H, td, J 7.3, 1.7, H-5), 1.82 – 1.51 (4 H, m, H-4, H-2), 1.45 – 1.31 (2 H, m, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.5 (C-6), 104.3 (C-1), 52.8 (C-7), 43.8 (C-5), 32.3 (C-2), 24.2 (C-3), 21.9 (C-4); HRMS required for $C_8H_{17}O_3$ $[M+H]^+$ is 161.1178, found 161.1180.

7,7-dimethoxyhept-1-ene S3[8]

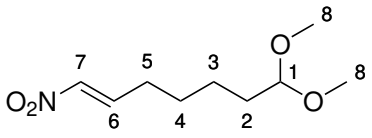


S3

To a suspension solution of $MePPh_3Br$ (53.6 g, 150 mmol) in THF (180 mL) at 0 °C was added *n*BuLi (2.5M in hexane, 60 mL, 150 mmol) dropwise and the reaction mixture was left stirring at 0 °C for 30 minutes. A solution of **S2** in THF (48 mL) was then added dropwise in 15 minutes. The reaction mixture was then left stirring at rt for 46 hours. A saturated aqueous solution of NH_4Cl (420 mL) was added. The organic phase was extracted with diethyl ether (3 x 300 mL) and then washed with brine (250 mL). The combined organic phases were dried over Na_2SO_4, filtered and then concentrated *in vacuo* keeping the water bath at a max temperature of 30 °C and a pressure of 100 mbar to avoid any evaporation of the targeted product. The concentrated organic phase was then filtered through a short pad

of silica and washed with a mixture of diethyl ether and pentane (1:1, 1.2 L). The organic solvent was concentrated again *in vacuo* to afford a colourless oil as pure product **S3** (9.5 g, 60.0 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (1 H, ddt, J = 16.9, 10.2, 6.7, H-6), 5.05 – 4.87 (1 H, m, H-7), 4.36 (1 H, t, J = 5.8, H-1), 3.31 (6 H, s, H-8), 2.19 – 1.94 (2 H, m, H-5), 1.73 – 1.47 (2 H, m, H-2), 1.49 – 1.25 (4 H, m, H-4, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8 (C-6), 114.4 (C-7), 104.5 (C-1), 52.6 (C-8), 33.7 (C-5), 32.3 (C-2), 28.8 (C-4), 24.1 (C-3).

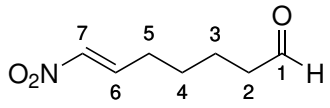
(*E*)-7,7-dimethoxy-1-nitrohept-1-ene S4



S4

To a heat dried two-neck round bottomed flask charged with magnetic stir-bar was added activated 4$\mathring{A}$ molecular sieves (2 g), $AgNO_2$ (40.4 g, 238 mmol) and TEMPO (3.7 g, 23.8 mmol). Olefin **S3** (9.4 g, 59.6 mmol) and anhydrous DCE (186 mL) were added. The round bottomed flask was then placed in a preheated oil bath at 70 °C and the reaction mixture was left stirring vigorously. The progress of the reaction was monitored by TLC and after 17 hours the reaction mixture was left to cool down to rt. The reaction mixture was then filtered through a short pad of celite washed with ethyl acetate (1 L) and concentrated *in vacuum*. The crude product was then purified *via* combiflash using silica gel columns and a gradient solution of ethyl acetate and hexane up to 30% diethyl ether in hexane to afford the titled compound **S4** as a colourless oil (5.8, 28.5 mmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.12 (1 H, m, H-6), 6.89 (1 H, dt, J = 13.4, 1.5, H-7), 4.47 – 4.03 (1 H, m, H-1), 3.22 (6 H, d, J = 3.8, H-8), 2.19 (2 H, qd, J = 7.4, 1.6, H-5), 1.72 – 1.39 (4 H, m, H-2, H-4), 1.39 – 1.22 (2 H, m, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3 (C-6), 139.7 (C-7), 104.3 (C-1), 52.9 (C-8), 32.2(C-2), 28.4(C-5), 27.6 (C-4), 24.1 (C-3).

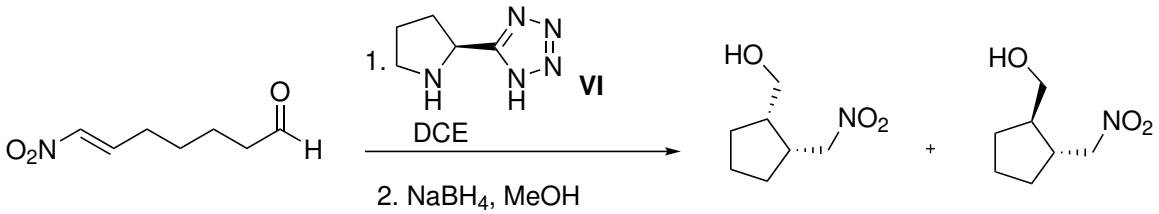
(*E*)-7-nitrohept-6-enal 10



10

To neat acetal **S4** (2.940 g, 14.5 mmol), glacial acetic acid (14.5 mL) was added at 0 °C and, as soon as frozen, HCl (1N, 4.8 mL) was added. The reaction mixture was left stirring at rt. The progress of the reaction was monitored by TLC and ^{1}H NMR and after 20 hours CH_2Cl_2 (30 mL) was added to the reaction mixture and washed with H_2O (2 x 50 mL) and a saturated aqueous solution of $NaHCO_3$ (50mL). The organic phase was back extracted with CH_2Cl_2 (3 x 50 mL) and then the organic phases were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* with a 30 °C water bath temperature at a max pressure of 100 mbar. Purification by combiflash (silica gel, gradient up to 55% diethyl ether in pentane) afforded the titled compound as a colourless oil (0.760 g, 4.8 mmol, 34% yield). The characterisation of compound **10** was described in method A.

Optimised synthesis of the nitroalcohol *cis*-11

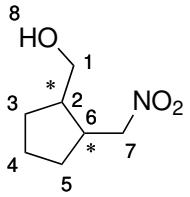


10 *cis*-**11** *trans*-**11**

Figure S4: Synthetic procedure for the synthesis of *cis*-**11**

((1*S*,2*R*)-2-(nitromethyl)cyclopentyl)methanol 11

To a solution of (*S*)-(-)-5-(2-pyrrolidinyl)-1H-tetrazole (5 mol%, 0.35 mmol, 0.051 g) and DCE (130 mL) previously sonicated for 30 min was added the nitroolefin **10** (1.104 g, 7.0



11

mmol) at -20 °C dropwise in 3 min followed by DCE (5 mL) to wash the syringe used and the sides of the reaction flask. The reaction mixture was left stirring at -20 °C for 99 hours. The progress of the reaction was monitored by TLC and ^{1}H NMR. Once the reaction went to completion the reaction was reduced *in situ*. $NaBH_4$ (0.397 g, 10.5 mmol) was added at -20 °C followed by MeOH (10.9 mL). The reaction went to completion in 1 hour. A saturated aqueous solution of NH_4Cl (15 mL) was added, followed by brine (50 mL) and H_2O (20 mL). The organic phase was extracted first with a mixture of chloroform and isopropanol (3:1, 80 mL x 5), then with diethyl ether (3 x 150 mL) and finally with ethyl acetate (3 x 100 mL) because of the high affinity of the product with the aqueous phase. The organic phase was then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel (25% ethyl acetate in hexane) to afford separately both diastereomers, *cis* and *trans*, as a colourless oil (0.820 g, 9:1 *cis/trans* ratio, 74%). *Cis*-**11**: 92% *ee*; $[\alpha]^{20}{}_D$ -14 (c = 0.1, CH_2Cl_2). IR (neat, cm^{-1}) 3376, 2958, 2877, 1543, 1383, 1022; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (2H, ABX, J_{AX} = 6.6 Hz, J_{BX} = 9.1 Hz, J_{AB} = 12.7, ν_{AB} = 138.5, H-7), 3.67 – 3.50 (2H, m, H-1), 2.87 – 2.71 (1H, m, H-6), 2.38 – 2.25 (1H, m, H-2), 1.91 – 1.79 (2H, m, H-5'and H-3'), 1.79 – 1.69 (1H, m, H-4'), 1.71 – 1.56 (1H, m, H-4''), 1.57 – 1.32 (2H, m, H-5'', H3''). ^{13}C NMR (101 MHz, $CDCl_3$) δ C 77.2 (C-7), 63.2 (C-1), 43.1 (C-2), 40.3 (C-6), 29.3 (C-5), 28.0 (C-3), 23.1 (C-4); HRMS required for $C_7H_{43}NO_3$ $[M+H]^+$ is 160.0974, found 160.0980. HPLC analysis: Chiralpack OD, 2% isopropanol in hexane, flow rate = 0.8 mL/min, λ = 210 nm. *Trans*-**11**: 45% *ee*; $[\alpha]^{20}{}_D$ - 8 (c = 0.1, CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (2 H, ABX, J_{AX} = 5.7 Hz, J_{BX} = 8.8 Hz,J_{AB} = 11.8 Hz, ν_{AB} = 110.5, H-7), 3.77 - 3.50 (2 H, m, H-1), 2.54 - 2.38 (1 H, m, H-6),

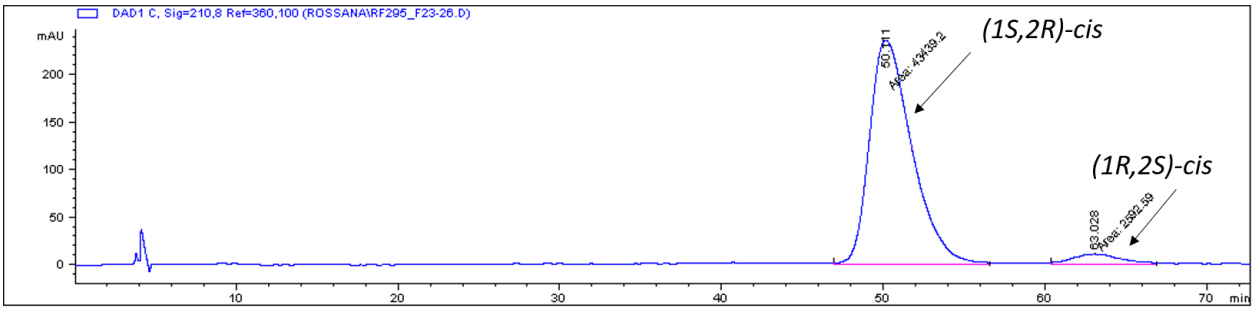


Figure S5: HPLC trace of *cis*-**11**.

2.01 - 1.88 (1 H, m, H-5'), 1.88 - 1.75 (2 H, m, H-2 and H-3'), 1.71 - 1.53 (2 H, m, H-4), 1.53 - 1.33 (1 H, m, H-5''and H-3'').^{13}C NMR ($CDCl_3$, 101 MHz) δ 79.1 (C-7), 64.9 (C-1), 44.1 (C-2), 40.6 (C-6), 29.8 (C-5), 27.9 (C-3), 23.1 (C-4). HPLC analysis: Chiralpack AS, 1% isopropanol in hexane, flow rate = 1 mL/min, λ = 230 nm.

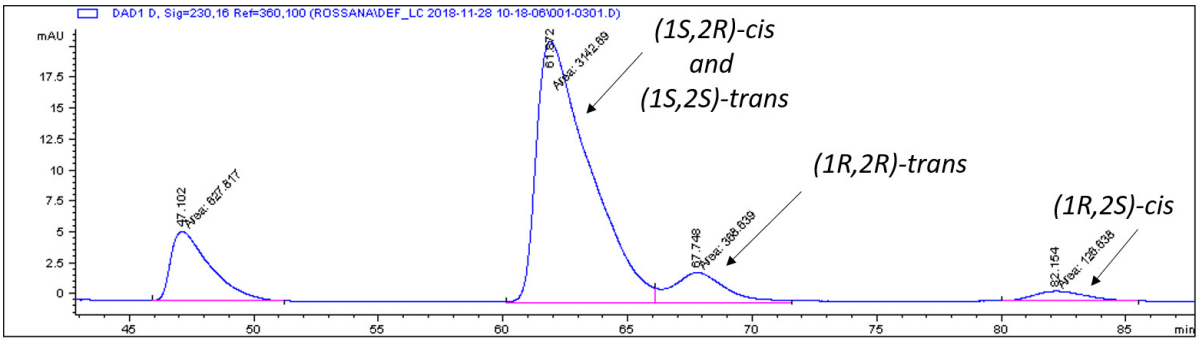
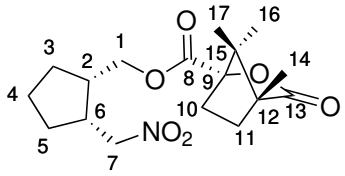


Figure S6: HPLC trace of *trans*-**11**. Separation of *Trans*-**11** from the *cis*-diastereomer was not possible, therefore the *ee* was calculated subtracting the area corresponding to the *cis*-peak overlapping with the *trans*. This was possible because one of the two *cis*-enantiomer peaks was separate and the area for the other enantiomer was calculated knowing the *ee* of the *cis* diastereomer that was independently obtained.

Synthesis of nitroalcohol derivative 12

((1*S*,2*R*)-2-(nitromethyl)cyclopentyl)methyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo [2.2.1]heptane-1-carboxylate 12



12

To a solution of compound *cis*-**11** (0.040 g, 0.25 mmol) and imidazole (17 μl, 0.30 mmol) in anhydrous THF (2.5 mL), (*S*)-(-)-camphanic chloride was added at 0 °C. The reaction mixture was refluxed for 4 hours and then left stirring at rt for 20 more hours as the reaction was not gone to completion yet. Then, H_2O (5 mL) was added and the organic phase was extracted with diethyl ether (3 x 10 mL), then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was then recrystallised to obtain the X-ray crystal of the titled compound **12**. mp = 71.5 - 73.6 °C; $[\alpha]^{20}{}_D$ - 12.0 (c = 0.1, CH_2Cl_2); IR (neat, cm^{-1}) 2969, 1778, 1743, 1546, 1449, 1398, 1381, 1315, 1266, 1225, 1173, 1154, 1113, 1063, 1034, 1020; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (2H, ABX, $J_{AX} = 6.7$ Hz, $J_{BX} = 8.9$ Hz, $J_{AB} = 12.6$ Hz, $\nu_{AB} = 96{,}4$ Hz, H-7), 4.10 (2H, qd, $J = 11.5, 6.7$, H-1), 2.85 - 2.70 (1H, m, H-6), 2.51 - 2.42 (1H, m, H-2), 2.42 - 2.29 (1H, m, H-10'), 2.06 - 1.92 (1H, m, H-10''), 1.92 - 1.77 (3H, m, H-5'and H-4', H-11'), 1.72 (2H, m, H-3), 1.68 - 1.51 (1H, m, H-11''), 1.51 - 1.31 (3H, m, H-4''and H-5'') 1.05 (3H, s, H-14), 1.00 (3H, s, H-16), 0.90 (3H, s, H-17). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0 (C-13), 167.5 (C-8), 91.0 (C-9), 76.5 (C-7), 65.3 (C-1), 54.8 (C-12), 54.3 (C-15), 40.2 (C-6), 39.9 (C-2), 30.7 (C-10), 29.0 (C-11), 28.9 (C-5), 28.1 (C-4), 22.6 (C-3), 16.8 (C-16), 16.8 (C-17), 9.7 (C-14). HRMS required for $C_{17}H_{26}NO_6$ $[M+H]^+$ is 340.1760, found 340.1762.

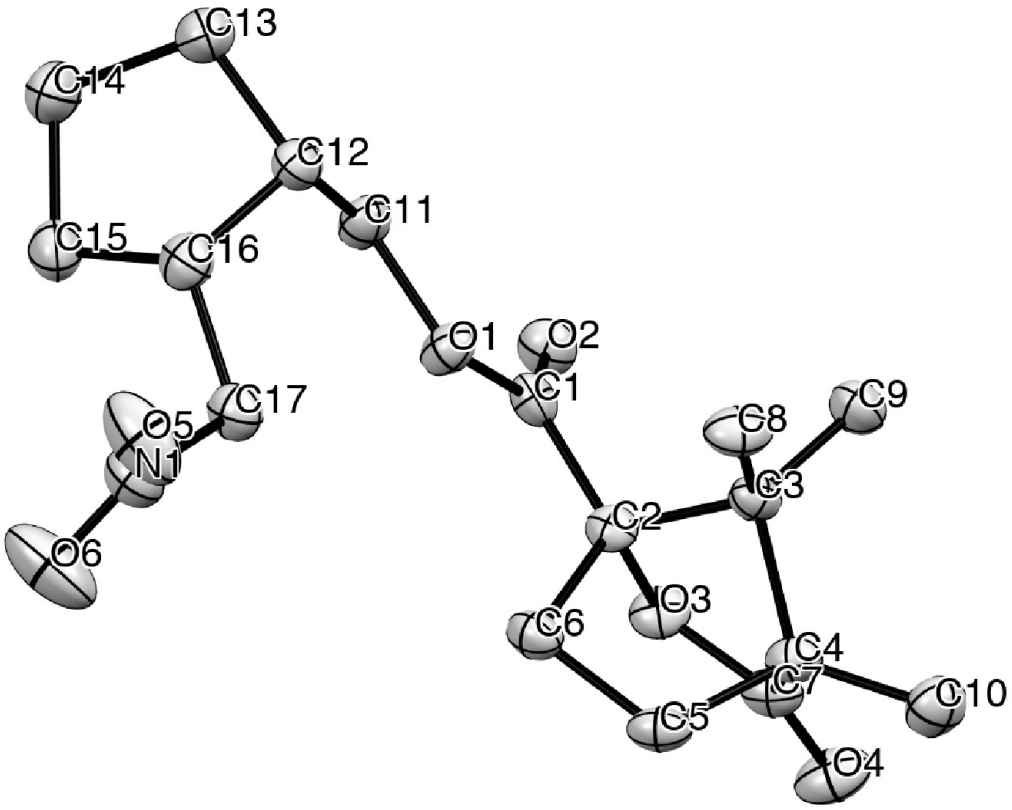
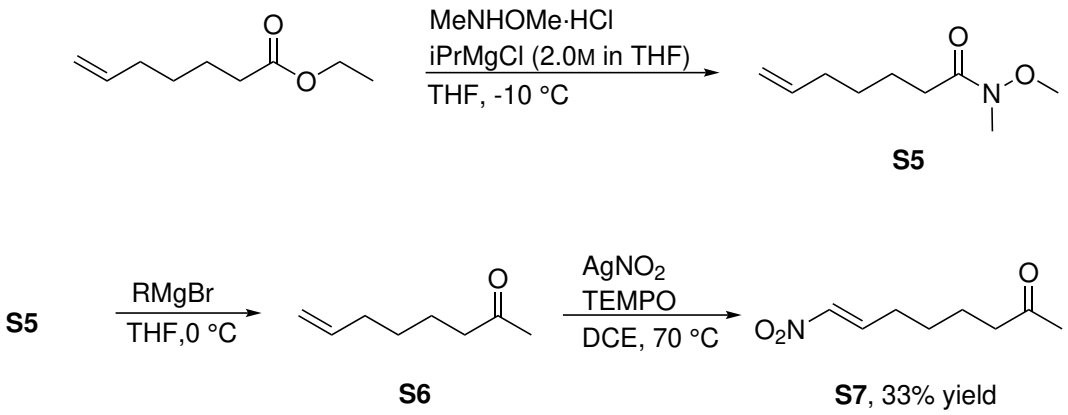


Figure S7: X-ray crystal structure of the nitro alcohol derivative **12**

Table S10: Crystal data and structure refinement for RF266A.

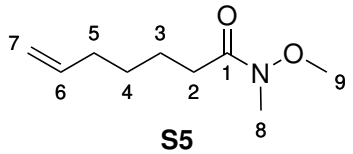
Identification code	RF266A
Empirical formula	$C_{17}H_{25}NO_6$
Formula weight	339.38
Temperature/K	153(5)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	6.4204(2)
b/Å	11.9299(4)
c/Å	11.1764(4)
α/°	90
β/°	95.772(3)
γ/°	90
Volume/Å^3	851.71(5)
Z	2
ρ_{calc}g/cm^3	1.323
μ/mm^{-1}	0.832
F(000)	364.0
Crystal size/mm^3	0.09 × 0.07 × 0.05
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.95 to 119.994
Index ranges	-7 ≤ h ≤ 6, -13 ≤ k ≤ 13, -12 ≤ l ≤ 12
Reflections collected	6574
Independent reflections	2431 [R_{int} = 0.0266, R_{sigma} = 0.0283]
Data/restraints/parameters	2431/1/220
Goodness-of-fit on F^2	1.097
Final R indexes [I¿=2σ (I)]	R_1 = 0.0292, wR_2 = 0.0719
Final R indexes [all data]	R_1 = 0.0310, wR_2 = 0.0737
Largest diff. peak/hole / e Å^{-3}	0.15/-0.17
Flack parameter	-0.10(9)

Synthetic procedure for the synthesis of ketones S7



Scheme S1: Synthesis of ketones

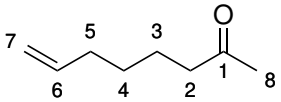
N-methoxy-N-methylhept-6-enamide S5



S5

To a solution of N,O-dimethylhydroxylamine hydrochloride (4.84 g, 49.6 mmol) in anhydrous THF (50 mL) was added a solution of ethyl-6-heptenoate in anhydrous THF (14 mL). The reaction mixture was then cooled to -15 °C and *iPr*MgCl (2.0Min THF, 48 mL) was added steadily dropwise in 30 min. The reaction mixture was stirred at -10° for 2 h and then a saturated aqueous solution of NH_4Cl (50 mL). The organic phase was extracted with diethyl ether (3 x 50 mL) and then washed with brine (50 mL). The combined organic layers were then dried ($MgSO_4$), filtered and concentrated *in vacuo* . The crude product was purified *via* flash chromatography on silica gel (30% EtOAc in Hex) to afford the titled product in quantitative yield as a colourless oil. IR (neat, cm^{-1}) 2938, 1664, 1652, 1414, 1384, 1177, 993, 909; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74 (1H, ddt, J = 16.9, 10.2, 6.7 Hz, H-6), 5.02 – 4.75 (2H, m, H-7), 3.61 (3H, s, H-9), 3.11 (3H, s, H-8), 2.36 (2H, t, J = 7.6 Hz, H-2), 2.13 – 1.93 (2H, m, H-5), 1.68 – 1.51 (2H, m, H-3), 1.46 – 1.27 (2H, m, H-4). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 138.7 (C-6), 114.6 (C-7), 61.2 (C-9), 33.6 (C-5), 32.2 (C-8), 31.7 (C-2) 28.7 (C-4), 24.2 (C-3). HRMS required for $C_9H_{17}NO_2$ $[M+H]^+$ 172.1332, found 172.1333.

Oct-7-en-2-one S6

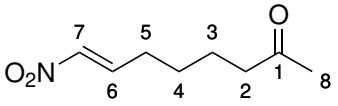


S6

To a solution of **S5** (1.37 g, 8.0 mmol) in anhydrous THF (80 mL) at 0 °C, methylmagnesium bromide (3.0Min THF, 10.7 mL) was added dropwise in 15 min. The reaction was left stirring at 0 °C for 30 min and then a saturated aqueous solution of NH_4Cl (50 mL)

was slowly added. The organic phase was extracted with diethyl ether and then washed with brine. The combined organic layers were dried ($MgSO_4$), filtered and concentrated at a maximum pressure of 100 mbar keeping the water bath at 25 °C to avoid any evaporation of the volatile product to finally achieve the desired product **S6** as a colourless oil (0.90 g, 89% yield). IR (neat, cm^{-1}) 2933, 1715, 1642, 1413, 1359, 1164, 995, 910; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.72 (1H, ddt, J = 16.9, 10.2, 6.7 Hz, H-6), 5.06 – 4.82 (2H, m, H-7), 2.38 (1H, d, J = 7.4 Hz, H-2), 2.07 (3H, s, H-8), 2.04 – 1.92 (2H, m, H-5), 1.64 – 1.49 (1H, m, H-3), 1.45 – 1.25 (2H, m, H-4). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 209.2 (C-1), 138.5 (C-6), 114.7 (C-7), 43.6 (C-2), 33.5 (C-5), 29.9 (C-8), 28.4 (C-4), 23.3 (C-3). HRMS required for $C_8H_{15}O$ $[M+H]^+$ 127.1120, found 127.1117.

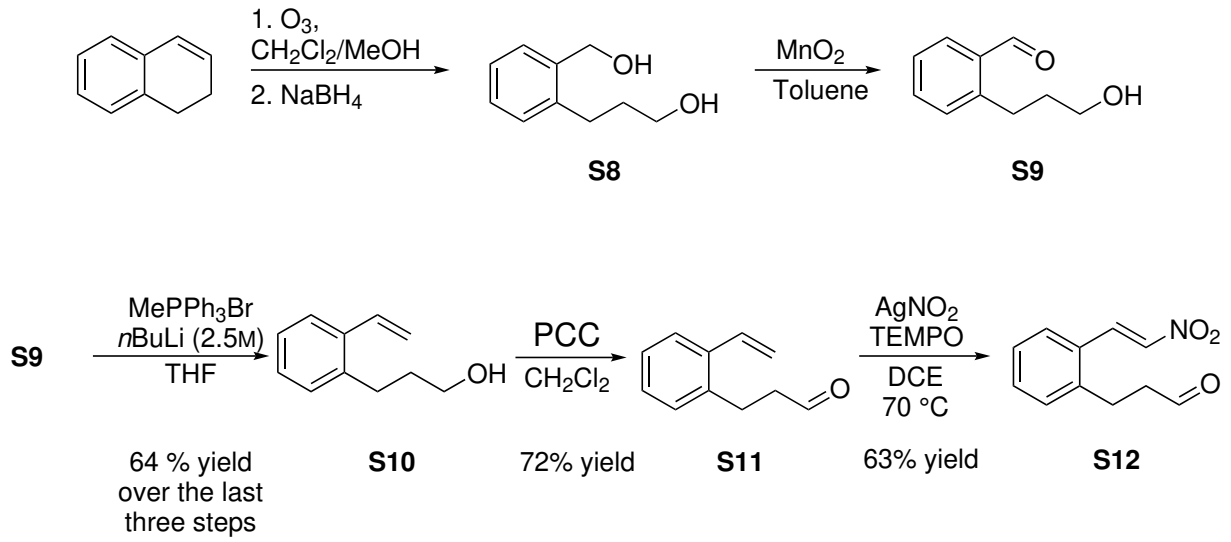
(*E*)-8-nitrooct-7-en-2-one S7



S7

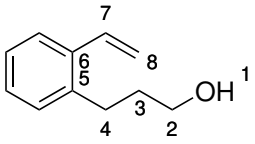
To a solution of $AgNO_2$ (4.49 g, 26.4 mmol), TEMPO (0.625 g, 4.0 mmol), 4$\mathring{A}$ molecular sieves (2 g) in anhydrous DCE (32 mL), **S6** (1.05 g, 8 mmol) was added and the reaction mixture was left stirring in a close reaction tube at 70 °C for 16 hours. The reaction mixture was then left to cool down to rt and then filtered over a short pad of celite and washed with EtOAc. The crude product was then purified *via* combiflash on silica gel (gradient 0-20% ethyl acetate in hexane) to afford the titled product as a colourless oil (0.45 g, 33% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 – 7.12 (1H, m, H-6), 6.93 (1H. dt, J = 13.5, 1.6 Hz, H-7), 2.41 (2H, t, J = 7.0 Hz, H-2), 2.23 (2H, qd, J = 7.3, 1.6 Hz, H-5), 2.08 (3H, s, H-8), 1.65 – 1.52 (2H, m, H-3), 1.52 – 1.40 (2H, m, H-4). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 208.2 (C-1), 142.1 (C-6), 139.8 (C-7), 43.0 (C-2), 30.0 (C-8), 28.4 (C-5), 27.2 (C-4), 23.0 (C-3). HRMS required for $C_8H_{13}NO_3$ $[M+H]^+$ 172.0974, found 172.0980.

Synthesis of nitroolefin S12



Scheme S2: Synthesis of the indane derivative precursor

3-(2-vinylphenyl)propan-1-ol S10[9]

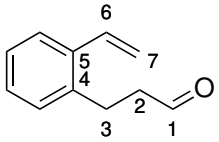


S10

1,2-dihydronaphtalene (3.0 g, 23 mmol) was dissolved in a mixture of CH_2Cl_2 and MeOH (*V*/*V* 1:1, 120 mL) and the mixture was cooled to -78°C. O_3 was then bubbled through until a blue colour developed. Excess of O_3 was removed bubbling through N_2 until the blue colour was discharged. $NaBH_4$ (1.74 g, 46.0 mmol) was added slowly and then the reaction mixture was stirred at rt for 1 h. The reaction was quenched with saturated aq. NH_4Cl solution (100 mL) and then the organic phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford compound **S8** as a dense colourless liquid. The obtained product did not require any further purification before the following step. To a solution of **S8** (3.30 g, 19.9 mmol) in

toluene (81 mL) was added activated MnO_2 powder (8.63 g, 99.3 mmol) every hour for the first three hours for a total of 15 eq. added. The reaction mixture was left stirring at rt for further 18 h. MnO_2 was filtered through a short pad of celite, washed with ethyl acetate (250 mL) and concentrated *in vacuo*. Compound **S9** was used for Wittig olefination without further purification. To a suspension of $MePPh_3Br$ (10.7 g, 30.0 mmol) in THF (36 mL) was added *n***b**uLi (2.5Min hexane, 12 mL) dropwise at 0°C. The reaction mixture was stirred at 0°C for 30 min and then a solution of **S9** (2.46 g, 15.0 mmol) in THF (9.5 mL) was added dropwise. The reaction mixture was left stirring at rt for 20 hours and then it was quenched with a saturated aq. solution of NH_4Cl (85 mL) at 0°C. The organic phase was extracted with diethyl ether (3 x 90 mL) and then combined organic layers were then dried over Na_2SO_4, filtered and concentrated *in vacuo* . The residue was purified *via* combiflash on silica gel (gradient from 20 to 30% ethyl acetate in hexane) to afford the titled product **S10** as a colourless oil (2.03 g, 64% yield for three steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 – 7.44 (1H, m, Ar-H), 7.26 – 7.14 (3H, m, Ar-H), 7.04 (1H, dd, J = 17.3, 10.9 Hz, H-7), 5.68 (1H, dd, J = 17.3, 1.4 Hz, H-8), 5.33 (1H, dd, J = 11.0, 1.4 Hz, H-8), 3.70 (2H, t, J = 6.3 Hz, H-2), 2.91 – 2.74 (2H, m, H-4), 1.97 – 1.79 (2H, m, H-3), 1.45 (1H, s, H-1). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 139.2 (C-6), 136.5 (C-5), 134.6 (C-7), 129.5 (Ar-C), 127.9 (Ar-C), 126.4 (Ar-C), 125.9 (Ar-C), 115.6 (C-8), 62.3 (C-2), 33.8 (C-3), 29.4 (C-4).

3-(2-vinylphenyl)propanal S11[9]

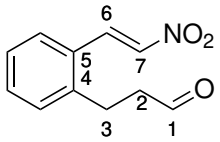


S11

To a solution of **S10** (0.487 g, 3.0 mmol) in CH_2Cl_2 (17 mL) was added a solution of PCC (1.29 g, 6.0 mmol) in CH_2Cl_2 (3 mL) and the reaction mixture was left stirring at rt for 3 h. Silica gel was added and the crude product was purified *via* combiflash on silica

gel (gradient up to 10% ethyl acetate in hexane) to afford compound **S11** as a colourless oil (0.346 g, 72% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.84 (1H, t, J = 1.4 Hz, H-1), 7.64 – 7.47 (1H, m, Ar-H), 7.40 – 7.12 (3H, m, Ar-H), 6.97 (1H, dd, J = 17.3, 11.0 Hz, H-6), 5.68 (1H, dd, J = 17.3, 1.4 Hz, H-7), 5.36 (1H, dd, J = 11.0, 1.4 Hz, H-7), 3.04 (2H, dd, J = 8.4, 7.1 Hz, H-3), 2.76 (2H, ddd, J = 8.7, 7.1, 1.4 Hz, H-2). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 201.4 (C-1), 137.6 (C-5), 136.6 (C-4), 134.2 (C-6), 129.3 (Ar-C), 128.0 (Ar-C), 126.8 (Ar-C), 126.2 (Ar-C), 116.3 (C-7), 44.8 (C-2), 25.6 (C-3). HRMS required for $C_{11}H_{13}O$ $[M+H]^+$ 161.0966, found 161.0970.

(*E*)-3-(2-(2-nitrovinyl)phenyl)propanal S12



S12

To an oven-dried quick-fit cap test tube charged with magnetic stir-bar was added activated 4$\mathring{A}$ molecular sieves (0.15 g), $AgNO_2$ (1.00 g, 5.9 mmol) and TEMPO (0.125 g, 0.8 mmol). Compound **S11** (0.314 g, 2.0 mmol) and anhydrous DCE (8 mL) were added. The tube was then placed in a preheated oil bath at 70 °C and the reaction mixture was left stirring vigorously for 17 hours. The progress of the reaction was monitored by TLC and then the reaction mixture was left to cool down to rt. The reaction mixture was then filtered through a short pad of celite washed with ethyl acetate (250 mL) and concentrated *in vacuum*. The crude product was then purified *via* combiflash using silica gel columns (gradient up to 20% ethyl acetate in hexane) to afford the titled compound **S12** as a yellow solid (0.257 g, 63% yield). mp = 63.0 - 64.8 °C IR (neat, cm^{-1})2841, 1713, 1700, 1627, 1597, 1500, 1331, 1299, 1270, 1211, 966, 957, 774, 750, 606; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.85 (1H, t, J = 1.1 Hz, H-1), 8.35 (1H, d, J = 13.5 Hz, H-7), 7.62 – 7.51 (2H, m, H-6 and Ar-H), 7.50 – 7.39 (1H, m, Ar-H), 7.33 (1H, d, J = 7,6 Hz, Ar-H), 7.32 - 7.29 (1H, m, Ar-H) 3.15

(2H, t, J = 7.4 Hz, H-3), 2.82 (2H, td, J = 7.5, 1.1 Hz, H-2). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 200.0 (C-1), 141.5 (C-5), 138.3 (C-6), 136.0 (C-7), 132.1 (Ar-C), 130.4 (Ar-C), 128.6 (C-4), 127.6 (Ar-C), 127.4 (Ar-C), 44.9 (C-2), 25.3 (C-3). HRMS required for $C_{11}H_{10}NO_3$ $[M\text{-}H]^-$ 204.0661, found 204.0665.

Organocatalytic products S7 and 14

General procedure C for the organocatalytic reactions

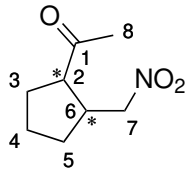
To a solution of (*S*)-(-)-5-(2-pyrrolidinyl)-1H-tetrazole (5 mol%) and DCE (0.05M) previously sonicated for 30 min was added the nitroolefin (1 eq.) at -20 °C dropwise in 3 min followed by DCE to wash the syringe used and the sides of the reaction flask. The reaction mixture was left stirring at -20 °C until completion of the reaction. $NaBH_4$ (1.5 eq.) was added at -20 °C followed by MeOH. The reaction went to completion in 1 hour. A saturated aqueous solution of NH_4Cl was added, followed by brine and H_2O. The organic phase was extracted first with a mixture of chloroform and isopropanol (*V/V*, 3:1), then with diethyl ether and finally with ethyl acetate because of the high affinity of the product with the aqueous phase. The organic phase was then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to afford the target product.

General procedure D for the organocatalytic racemic reactions

To a solution of the nitroolefin in DCE (0.2M), L-Proline (10 mol%) and D-Proline (10 mol%) were added at -20 °. The reaction was monitored by TLC and once gone to completion, $NaBH_4$ (1.5 eq.) and MeOH were added. The reaction mixture was left stirring at -20 ° until the reduction was completed. Then, a saturated aqueous solution of NH_4Cl was added, followed by brine and H_2O. The organic phase was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product

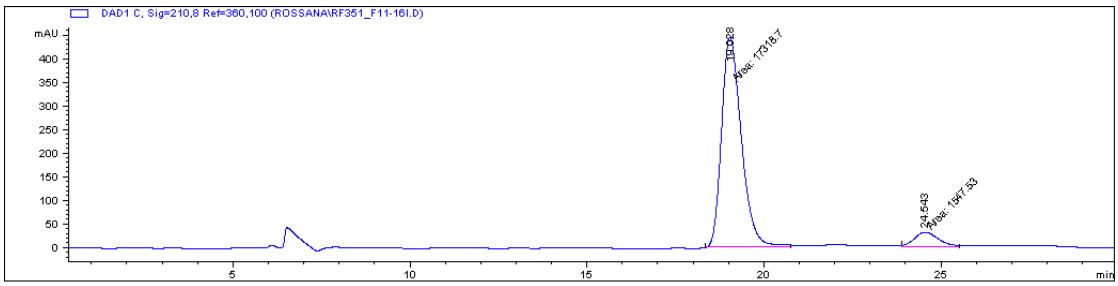
was then purified by flash chromatography on silica gel (gradient 10-20% ethyl acetate in hexane).

1-(2-(nitromethyl)-1l3,2l3-cyclopentyl)ethan-1-one 13

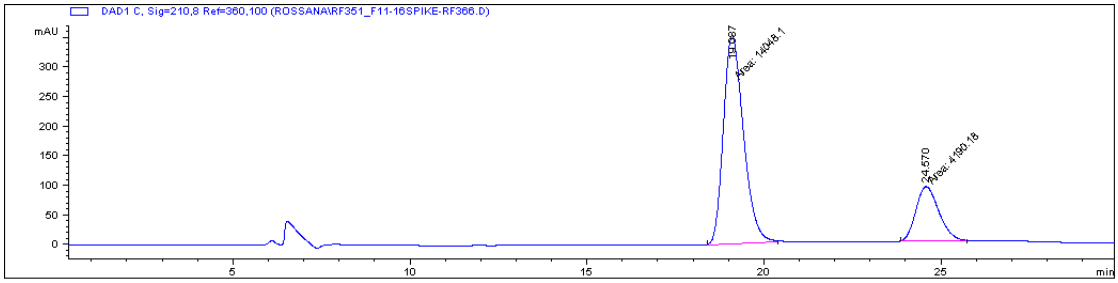


13

Following general procedure C, the nitroolefin **S6** (0.100 g, 0.58 mmol) was added to a mixture of catalyst **VI** (0.017 g, 0.12 mmol) in DCE (10.6 mL) at 0 °C. After 5 hours, the reaction did not show any formation of the product, therefore the reaction mixture was left stirring at rt. After 48 hours, the reaction was monitored by ^{1}H NMR, showing only partial formation of the product. Acetic acid (20 mol%, 7μL) was added as co-catalyst. After 8 days from start of the reaction, the reaction mixture was concentrated *in vacuo*. The crude product was purified *via* flash chromatography on silica gel (20% ethyl acetate in hexane) to afford separately *cis*- and *trans*-**13** as colourless oils (0.56 g, 56% yield of both diastereomers combined). *cis*-**13**: 84% *ee*; $[\alpha]^{20}{}_D$ + 24.0 (c = 0.1, CH_2Cl_2); IR (neat, cm^{-1}) 2960, 1699, 1545, 1422, 1382, 1355, 1178; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.59 (2H, ABX, J_{AX} = 8.5 Hz, J_{BX} = 6.9 Hz, J_{AB} = 12.9 Hz, ν_{AB} = 92.1 Hz, H-7), 3.23 (1H, ddd, J = 8.4, 7.1, 4.8 Hz, H-2), 2.77 (1H, tq, J = 8.9, 7.3 Hz, H-6), 2.22 (3H, s, H-8), 2.11 – 1.96 (1H, m, H-3), 1.96 – 1.76 (3H, m, H-5, H-3 and H-4), 1.76 – 1.62 (2H, m, H-5 and H-4). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 210.6 (C-1), 75.9 (C-7), 52.1 (C-2), 40.9 (C-6), 30.7 (C-8), 29.4 (C-3), 29.2 (C-5), 23.2 (C-4). HRMS required for $C_8H_{14}NO_3$ $[M+H]^+$ 172.0968, found 172.0972. HPLC analysis: Chiralpack OD, 2% isopropanol in hexane, flow rate = 0.8 mL/min, λ = 210 nm. *trans*-**13**: 38% *ee*; $[\alpha]^{20}{}_D$ + 2.0 (c = 0.1, CH_2Cl_2); IR (neat, cm^{-1}) 2960, 1705, 1545, 1431, 1371, 1356, 1174; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.31 (2H, ABX, J_{AX} = 6.8 Hz, J_{BX} = 7.2 Hz, J_{AB} = 12.1 Hz, ν_{AB} = 30.2 Hz, H-7), 2.94 (1H, m, H-2), 2.79 – 2.61 (1H, m, H-6), 2.13 (3H, s, H-8),



(a)



(b)

Figure S8: (a) chiral HPLC trace of cis-**13**. (b) Spike of cis-**13** with the racemic cis-**13**.

2.10 – 1.97 (1H, m, H-5), 1.97 – 1.85 (1H, m, H-3), 1.79 – 1.61 (3H, m, H-4 and H-5), 1.49 – 1.26 (2H, m, H-3). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 208.8 (C-1), 78.9 (c-7), 55.2 (C-6), 39.2 (C-2), 30.0 (C-8), 30.0 (C-5), 29.1 (C-3), 24.4 (C-4). HRMS required for $C_8H_{14}NO_3$ $[M+H]^+$ 172.0968, found 172.0972. HPLC analysis: Chiralpack AD-H, 0.5% isopropanol in hexane, flow rate = 0.5 mL/min, λ = 210 nm.

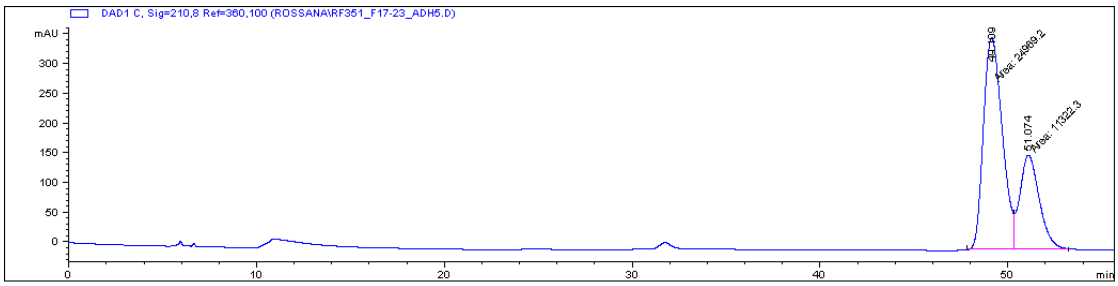
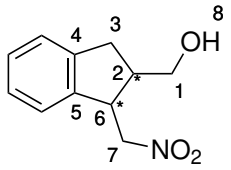


Figure S9: HPLC trace of *trans*-**13**.

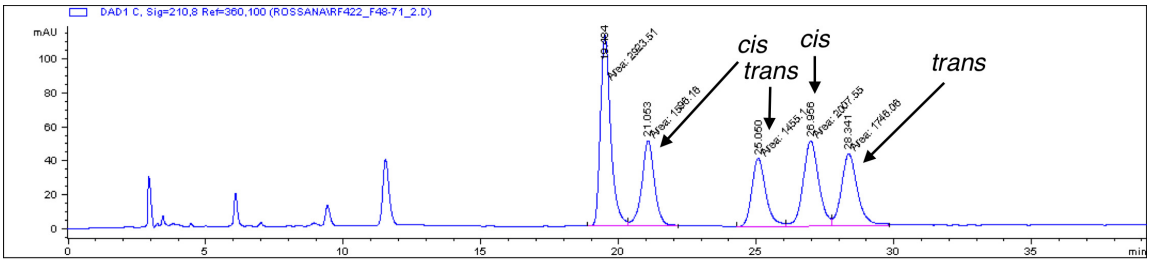
(1-(nitromethyl)-1,3-dihydro-2H-1l3,2l3-inden-2-yl)methanol 14



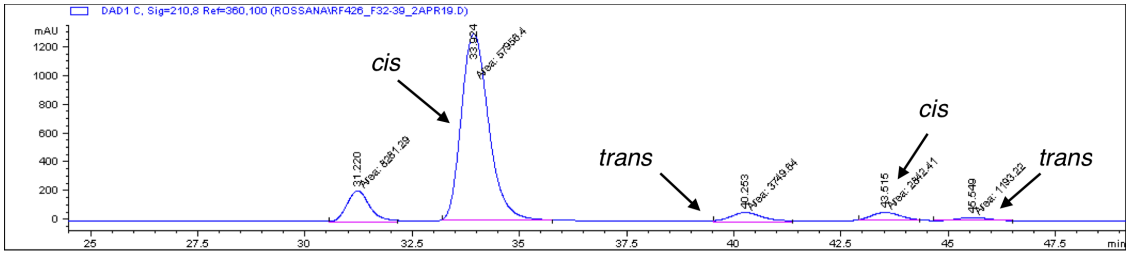
14

Following general procedure C, the nitroolefin **S12** (0.131 g, 0.64 mmol) was added to a solution of catalyst **VI** (0.019 g, 0.13 mmol) in DCE (12.8 mL). After 24 hours the reaction went to completion and it was reduced to the alcohol. The crude product was purified by flash chromatography on silica gel (25% ethyl acetate in hexane) to obtain a combination of *cis*- and *trans*-**14** as a colourless oil (0.97 g, 1:1 *cis/trans* ratio, 73% yield).

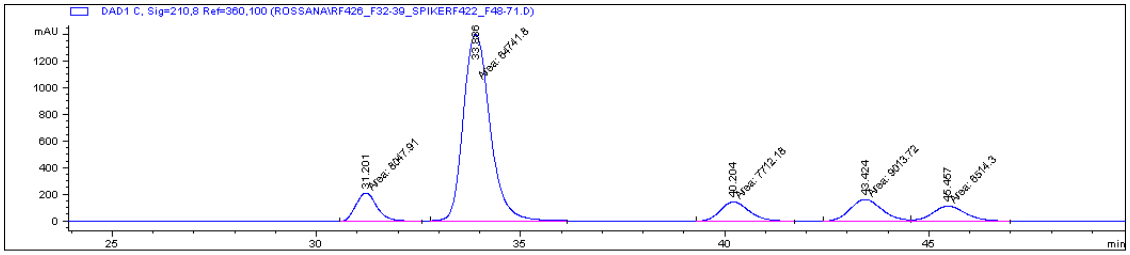
Mixture of diastereomers: $[\alpha]^{20}{}_D$ - 16.0 (c = 0.1, CH_2Cl_2) IR (neat, cm^{-1}) 3569, 3366, 2922, 1543, 1479, 1459, 1430, 1377, 1198, 1020, 752, 668; *cis*-**14**: 90% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 – 7.09 (4H, m, Ar-H), 4.71 (2H, ABX, J_{AX} = 7.5 Hz, J_{BX} = 7.8 Hz, J_{AB} = 13.2 Hz, ν_{AB} = 128.3 Hz, H-7), 4.14 (1H, q, J = 7.5 Hz, H-6), 3.94 – 3.73 (2H, m, H-1), 3.10 – 2.90 (2H, m, H-2 and H-3), 2.83 (1H, dd, J = 14.8, 7.2 Hz, H-3). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 142.3 (C-5), 141.4 (C-4), 128.0 (Ar-C), 127.0 (Ar-C), 125.0 (Ar-C), 124.0 (Ar-C), 76.0 (C-7), 62.6 (C-1), 44.5 (C-6), 44.3 (C-2), 33.9 (C-3). HPLC analysis: Chiralpack AD-H, 5% isopropanol in hexane, flow rate = 0.6 mL/min, λ = 210 nm. *trans*-**14**: 52% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 – 7.04 (4H, m, Ar-H), 4.65 – 4.42 (2H, m, H-7), 3.80 (1H, td, J = 7.0, 4.7 Hz, H-6), 3.70 – 3.49 (2H, m, H-1), 2.91 (2H, ABX, J_AX = 8.4 Hz, J_BX = 5.0 Hz, J_AB = 16.5 Hz, ν_{AB} = 19.4 Hz, H-3), 2.57 – 2.38 (1H, m, H-2). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 142.3 (C-5), 140.4 (C-4), 128.2 (Ar-C), 127.1 (Ar-C), 125.3 (Ar-C), 124.3 (Ar-C), 79.2 (C-7), 65.3 (C-1), 46.3 (C-6), 45.0 (C-2), 34.0 (C-3). HRMS required for $C_{11}H_{12}NO_3$ $[M-H]^-$ 206.0812, 206.0816. HPLC analysis: Chiralpack AD-H, 5% isopropanol in hexane, flow rate = 0.6 mL/min, λ = 210 nm.



(a)



(b)



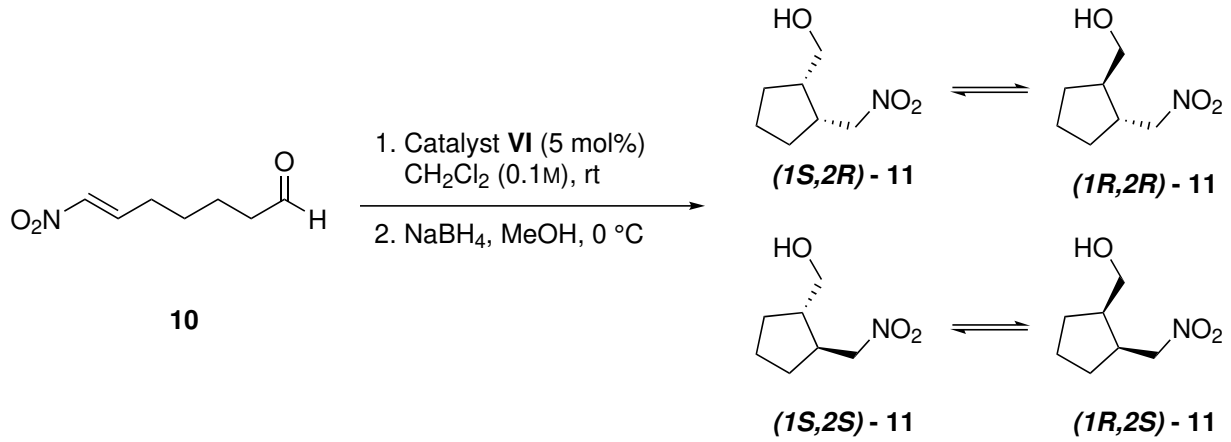
(c)

Figure S10: (a) Chiral HPLC trace of a racemic mixture of both diastereomers cis and trans **14**. (b) Chiral HPLC trace of **14**. (c) Chiral HPLC trace of spike of enantioselective **14** with racemic **14**.

Enantioselective study

In order to gain a better understanding of the mechanism of the reaction, an enantioselective study was performed (Table S11). The reaction was carried out under the same reaction

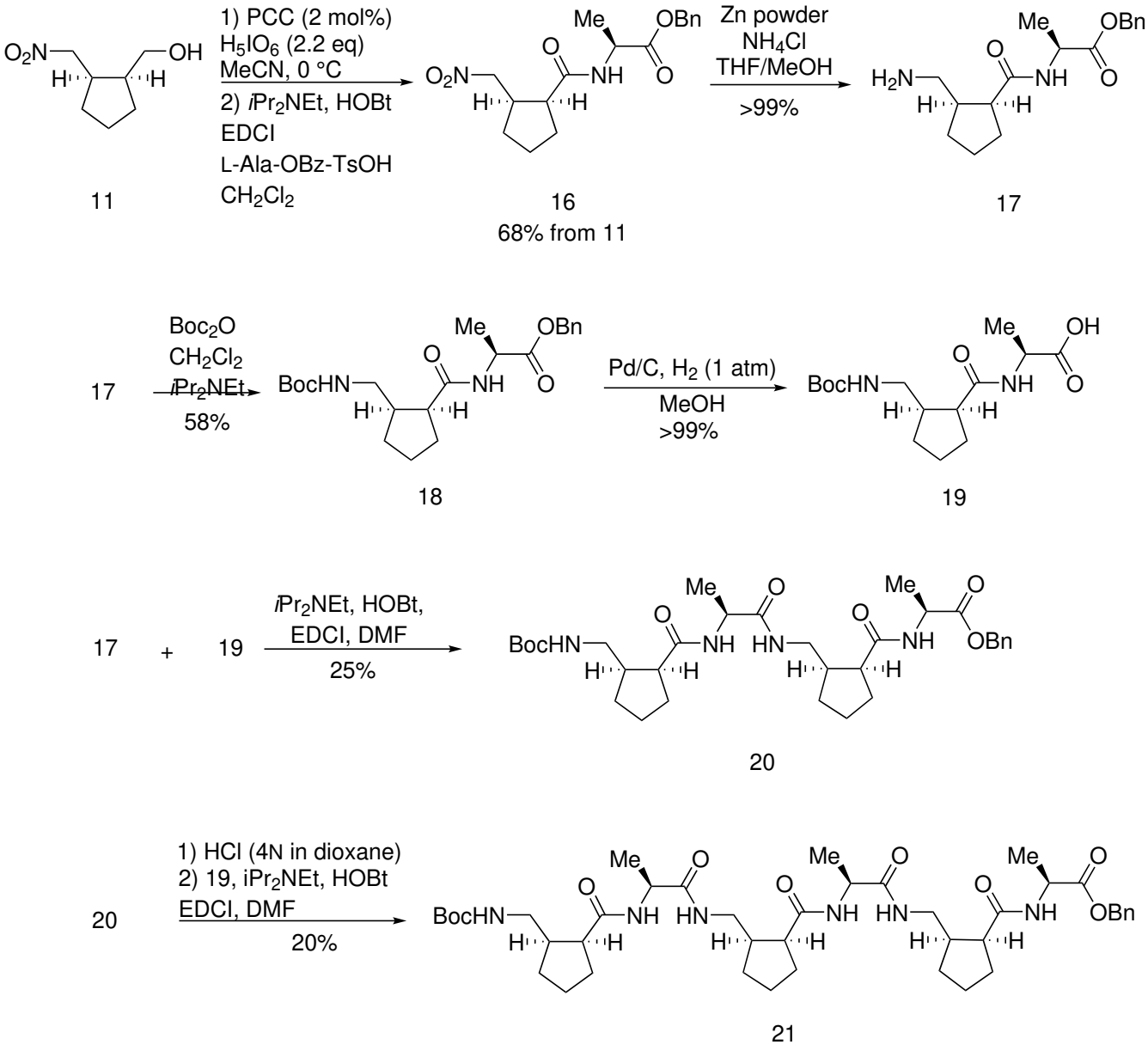
Table S11: Enantioselective study of 5-*exo-trig* cyclisation.



Entry	Time [h]	Yield [%]	*dr* (*cis*/*trans*)	*ee* – *cis*[%]	*ee* – *trans*[%]
1	2	62[i]	55:45	80	43
2	23	64	11:89	70	66

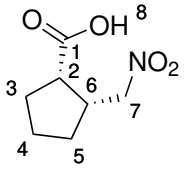
conditions used for the NMR kinetic study at rt in CH_2Cl_2 (0.1M) and in the presence of 5 mol% of the catalyst (Table S11). After 2 hours, 14 mL out of 28.7 mL of the reaction mixture were transferred in a separate flask and the reaction was reduced *in situ* with $NaBH_4$ at 0 °C to afford **11** in 62% yield, 1:1 *dr*, 80% *ee* for the diastereomer *cis* and 44% *ee* for the diastereomer *trans*. The rest of the reaction mixture was left stirring at rt for 23 hours and then reduced *in situ* to achieve **11** in 64% yield. Diastereoselectivity degradation to 1:9 *dr* in favour of the *trans* was then observed. Enantioselectivity diminished to 70% *ee* for the *cis*-**11** and raised to 66% *ee* for the *trans*-**11**.

Synthesis of γ/α-peptides



Scheme S3: Synthetic procedure for the synthesis of γ/α-peptides **18**, **20** and **21**.

(1*S*,2*R*)-2-(nitromethyl)cyclopentane-1-carboxylic acid S13

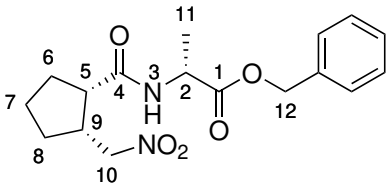


S13

To a solution of H_5IO_6 (2.198 g, 9.7 mmol) in anhydrous acetonitrile (19 mL) stirred vigorously for 15 minutes at room temperature was added ***cis*-11** (0.699 g, 4.4 mmol) at 0 °C in anhydrous acetonitrile (2 mL) followed by PCC (0.019 g, 0.09 mmol) in acetonitrile (4 mL). The reaction mixture was stirred at 0 °C for 45 minutes until the reaction went to completion. The reaction was monitored by TLC. Ethyl acetate (50 mL) was then added and the organic phase was washed first with brine (50 mL), then with a saturated aqueous solution of $NaHSO_3$ (70 mL) and brine (50 mL) again. The organic layers were then combined and dried on Na_2SO_4, filtered and concentrated *in vacuo*. The product obtained was a colourless oil (0.674 g, 3.9 mmol, 88%) and it was pure enough to carry on with the next step. $[\alpha]^{20}{}_D$ +21.0 (c = 0.1, CH_2Cl_2); IR (neat, cm^{-1}) 2963, 1701, 1547, 1383; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (2H, ABX, J_{AX} = 7.2 Hz, J_{BX} = 8.1 Hz, J_{AB} = 13.2 Hz, ν_{AB} = 99.0 Hz, H-7), 3.07 (1 H, td, *J* 7.4, 6.1, H-2), 2.90 (1 H, dt, *J* 9.3, 7.5, H-6), 2.12 – 1.99 (2 H, m, H-3), 2.00 – 1.84 (2 H, m, H-4', H-5'), 1.82 – 1.67 (1 H, m, H-4''), 1.67 – 1.50 (1 H, m, H-5''). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6 (C-1), 76.1 (C-7), 45.2 (C-2), 40.4 (C-6), 29.1 (C-3), 28.9 (C-5), 23.0 (C-4); HRMS required for $C_7H_{10}NO_4$ $[M\text{-}H]^-$ is 172.0610, found 172.0612.

Benzyl((1*S*,2*R*)-2-(nitromethyl)cyclopentane-1-carbonyl)-d-alaninate S14

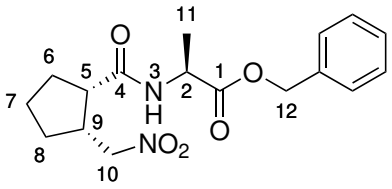
To a solution of the carboxylic acid **S13** (0.087 g, 0.5 mmol) in CH_2Cl_2 (3.4 mL), DIPEA (0.1 mL, 0.6 mmol), HOBt· H_2O (0.081 g, 0.6 mmol) and EDCI (0.115 g, 0.6 mmol) were added and the reaction mixture was stirred for 15 minutes at rt. D-Ala benzyl ester (0.090 g, 0.5 mmol) was then added and the reaction mixture was left stirring at rt for 16 hours.



S14

The reaction was monitored by TLC and after 24 hours ethyl acetate (50 mL) was added. The organic phase was washed first with an aqueous 1N solution of aqueous HCl (75 mL), then with an aqueous saturated solution of $NaHCO_3$ (25 mL) and finally with brine (25 mL). The acidic aqueous phase was then extracted again with CH_2Cl_2 (2 x 25 mL) and the same procedure was carried out for the basic phase ($NaHCO_3$ and brine phases combined) too. The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* combiflash on 80g silica gel columns (gradient ethyl acetate in hexane). The product was obtained as a white solid (0.056 g, 34%). mp = 48.8 - 50.4 °C; IR (neat, cm^{-1}) 3315, 2932, 1733, 1638, 1538, 1450, 1385, 1334, 1316, 1207, 1144, 958, 757, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (5 H, m, Ar-H), 6.10 (1 H, d, J = 7.4 Hz, H-3), 5.10 (2 H, ABq, J_{AB} = 12.3 Hz, H-12), 4.58 – 4.31 (3 H, ABX unresolved, m, H-10 and H-2), 2.84 – 2.66 (2 H, m, H-5 and H-9), 1.94 - 1.78 (2 H, m, H-8 and H-7'), 1.81 - 1.70 (1 H, m, H-6'), 1.62 – 1.48 (2 H, m, H-7''and H-6''), 1.32 (3 H, d, J = 7.2 Hz, H-11); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (C-4), 172.8 (C-1), 135.3 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.2 (Ar-C), 76.3 (C-10), 67.2 (C-12), 48.1 (C-2), 46.7 (C-5), 41.1 (C-9), 29.9 (C-8), 29.7 (C-6), 24.0 (C-7), 18.2 (C-11). HRMS required for $C_{17}H_{23}N_2O_5$ $[M+H]^+$ is 335.1607, found 335.1600.

Benzyl ((1*S*,2*R*)-2-(nitromethyl)cyclopentane-1-carbonyl)- l-alaninate 16



16

To a solution of the carboxylic acid **S13** (0.660 g, 3.8 mmol) in CH_2Cl_2 (27 mL), DIPEA (0.80 mL, 4.6 mmol), HOBt· H_2O (0.622 g, 4.6 mmol) and EDCI (0.882 g, 4.6 mmol) were added and the reaction mixture was stirred for 15 minutes at rt. L-Ala benzyl ester *p*-toluene sulfonate salt was then added and the reaction mixture was left stirring at rt for 16 hours. The reaction was monitored by TLC and once gone to completion ethyl acetate (150 mL) was added. The organic phase was washed first with an aqueous 1N solution of $NaHSO_4$ (75 mL), then with an aqueous saturated solution of $NaHCO_3$ (75 mL) and finally with brine (75 mL). The acidic aqueous phase was then extracted again with CH_2Cl_2 (2 x 75 mL) and the same procedure was carried out for the basic phase ($NaHCO_3$ and brine phases combined) too. The organic phase was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* combiflash on 80g silica gel columns (gradient ethyl acetate in hexane). The product was obtained as a white solid (0.399 g, 1.2 mmol, 31%). mp = 94.2 - 97.1 °C; $[\alpha]^{20}{}_D$ +15.0 (c = 0.1, CH_2Cl_2); IR (neat, cm^{-1}) 3316, 2959, 1744, 1640, 1550, 1527, 1456, 1389, 1376, 1188, 1168, 1153; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.32 (3 H, m, Ar-H), 6.14 (1 H, d, *J* 7.3, H-3), 5.19 (2H, AB, J_{AB} = 12.2 Hz, ν_{AB} = 27.9 Hz, H-12), 4.55 (2H, ABX, J_{AX} = 8.2 Hz, J_{BX} = 6.6 Hz, J_{AB} = 13.5 Hz, ν_{AB} = 119.4 Hz, H-10), 4.56 (1 H, p, *J* 7.2, H-2), 2.91 (1 H, td, *J* 7.7, 4.8, H-5), 2.87 – 2.71 (1 H, m, H-9), 2.10 – 1.89 (3 H, m, H-6, H-7'), 1.91 – 1.74 (1 H, m, H-8'), 1.74 – 1.58 (2 H, m, H-8'', H-7''), 1.43 (3 H, d, *J* 7.2, H-11). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C-4), 172.8 (C-1), 135.4 (Ar-C), 128.8 (Ar-C), 128.6 (Ar-C), 128.4 (Ar-C), 76.5 (C-10), 67.4 (C-12), 48.3 (C-2), 46.9 (C-5), 41.9 (C-9), 29.7 (C-8), 29.5 (C-6), 23.8 (C-7), 18.0 (C-11); HRMS required for $C_{17}H_{23}N_2O_5$

$[M+H]^+$ is 335.1607, found 335.1596.

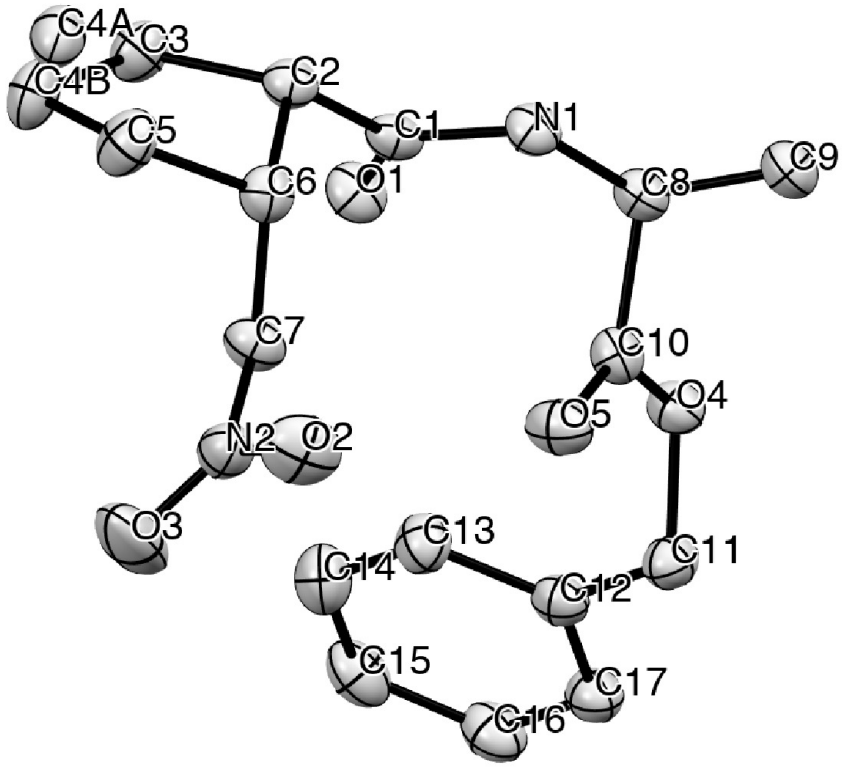
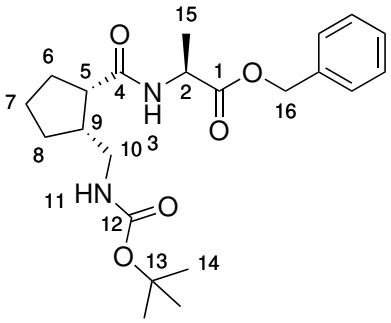


Figure S11: Crystal structure of the nitrodimer **16**.

Table S12: Crystal data and structure refinement for the nitrodimer **16**

Identification code	RF435-F32-34
Empirical formula	$C_{17}H_{22}N_2O_5$
Formula weight	334.36
Temperature/K	149.95(10)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.4637(2)
b/Å	9.36340(10)
c/Å	9.9797(2)
α/°	90
β/°	109.791(2)
γ/°	90
Volume/Å^3	832.09(3)
Z	2
ρ_{calc}g/cm^3	1.335
μ/mm^{-1}	0.819
F(000)	356.0
Crystal size/mm^3	0.26 × 0.05 × 0.02
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.418 to 140.84
Index ranges	-11 ≤ h ≤ 11, -11 ≤ k ≤ 11, -12 ≤ l ≤ 12
Reflections collected	15121
Independent reflections	3114 [R_{int} = 0.0432, R_{sigma} = 0.0291]
Data/restraints/parameters	3114/1/232
Goodness-of-fit on F2	1.046
Final R indexes [I¿=2σ (I)]	R_1 = 0.0327, wR_2 = 0.0838
Final R indexes [all data]	R_1 = 0.0342, wR_2 = 0.0856
Largest diff. peak/hole / e Å^{-3}	0.17/-0.18
Flack parameter	0.03(10)

Benzyl ((1*S*,2*R*)-2-(((tert-butoxycarbonyl)amino)methyl)cyclopentane-1-carbonyl)-l-alaninate 18



18

To a solution of compound **16** (0.556 g, 1.7 mmol) in anhydrous MeOH (33 mL) and anhydrous THF (33 mL), Zn powder (1.637 g, 24.9 mmol) and NH_4Cl (1.332 g, 24.9 mmol) were added. The reaction mixture was stirred at rt for 1 hour and it was worked up after monitoring it *via* TLC. Ehtyl acetate (500 mL) was added and it was then filtered through a short pad of celite. The white solid obtained was then dissolved in CH_2Cl_2 and filtered through cotton wool to remove any NH_4Cl left in solution. The product **17** obtained was a pale yellow paste (0.572 g, 1.8 mmol, quantitative yield) and it was pure enough to carry on the next step without any further purifcation. To a solution of the free amine **17** (0.552 g, 1.81 mmol) in anhydrous CH_2Cl_2 (14 mL), isopropyl amine (0.63 mL, 3.6 mmol) and Boc_2O (0.64 mol, 2.7 mmol) were added and the reaction mixture was stirred at rt. The reaction was monitored by TLC and it went to completion in 45 minutes. The reaction mixture was diluted with ethyl acetate (45 mL) and washed with an aqueous solution of 1M $NaHSO_4$ (30 mL) followed by brine (30 mL). The organic layers were then combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified *via* flash chromatography on silica gel (30% ethyl acetate in hexane). The titled product was obtained as a white solid (0.270 g, 0.7 mmol, 36%). mp = 131.3 - 133.9 °C; $[\alpha]^{20}{}_D$ +103.8 (c = 0.08, MeOH); IR (neat, cm^{-1}) 3350, 3322, 2958, 1739, 1676, 1640, 1533, 1454, 1370, 1281, 1152, 1058; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (5 H, m, Ar-H), 6.16 (1 H, d,

J 6.7, H-3), 5.39 (1 H, t J 6.2, H-11)), 5.19 (1 H, ABq, J_AB = 12.3 Hz, ν_{AB} = 30.5, H-16), 4.60 (1 H, p, J 7.3, H-2), 3.19 (1 H, dt, J 13.9, 5.9, H-10'), 3.11 - 2.91 (1 H, m, H-10''), 2.73 – 2.60 (1 H, m, H-5), 2.48 - 2.29 (1 H, m, H-9), 2.00 - 1.79 (3 H, m, H-6, H-7'), 1.79 - 1.69 (1 H, m, H-8'), 1.60 – 1.48 (2H, m H-7''and H-8''), 1.44 (9H, s, H-14), 1.41 (3H, m, H-15); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (C-4), 173.4 (C-1), 156.4 (C-12), 135.3 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 128.3 (Ar-C), 67.3 (C-16), 48.0 (C-2), 47.4 (C-5), 44.2 (C-9), 41.8 (C-10), 29.7 (C-8), 29.2 (C-6), 28.5 (C-14), 24.1(C-7), 18.0 (C-15); HRMS required for $C_{22}H_{33}N_2O_5$ $[M+H]^+$ is 405.2389, found 405.2399.

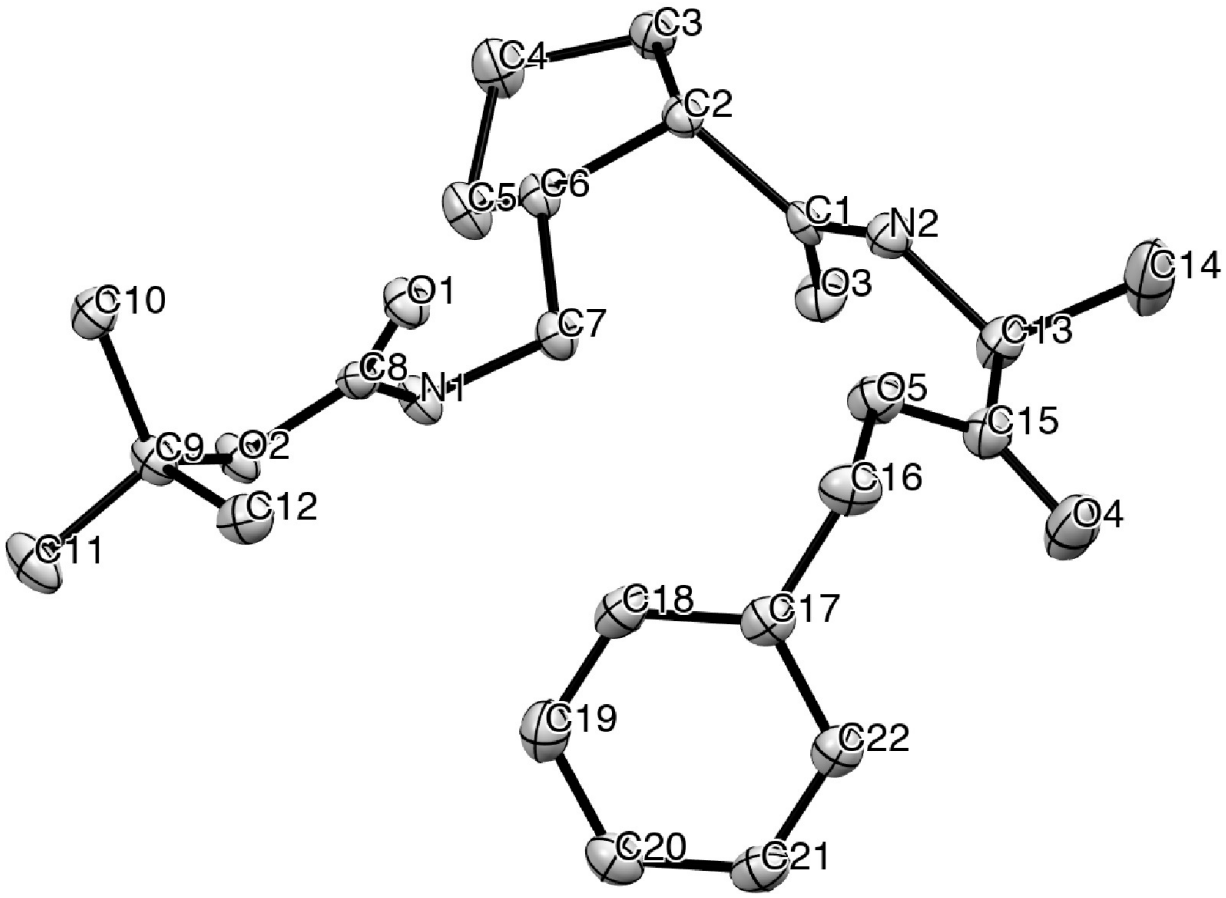


Figure S12: X-Ray crystal structure of the dimer **18**.

Table S13: Crystal data and structure refinement for exp13.

Identification code	exp_{13}
Empirical formula	$C_{22}H_{32}N_2O_5$
Formula weight	404.49
Temperature/K	100.00(10)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	5.03210(10)
b/Å	18.5414(4)
c/Å	11.6101(2)
$\alpha/^\circ$	90
$\beta/^\circ$	94.440(2)
$\gamma/^\circ$	90
Volume/Å^3	1080.00(4)
Z	2
ρ_{calc}g/cm^3	1.244
μ/mm^{-1}	0.716
F(000)	436.0
Crystal size/mm^3	0.14 × 0.03 × 0.03
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/$^\circ$	7.638 to 134.094
Index ranges	-5 ≤ h ≤ 4, -22 ≤ k ≤ 22, -13 ≤ l ≤ 13
Reflections collected	16639
Independent reflections	3822 [R_{int} = 0.0575, R_{sigma} = 0.0462]
Data/restraints/parameters	3822/1/266
Goodness-of-fit on F_2	1.068
Final R indexes [I>= 2σ (I)]	R_1 = 0.0343, wR_2 = 0.0828
Final R indexes [all data]	R_1 = 0.0383, wR_2 = 0.0848
Largest diff. peak/hole / e Å^{-3}	0.20/ − 0.17
Flack parameter	0.02(11)

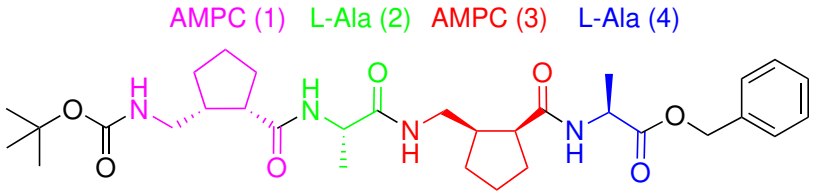
General procedure E for deprotection of the acid moiety

To a solution of benzyl ester in MeOH (20 mL/mmol), a spatula tip of Pd/C (10 %w/w) is added followed by 3 H_2 balloons that were emptied in the reaction mixture. The reaction is monitored by ^{1}H NMR and TLC. The reaction mixture was then filtered through a short pad of celite with a short pad of silica on top and it was washed with MeOH (50 mL). The organic phase was then concentrated *in vacuo*. The titled product is obtained pure and did not need any further purification.

General procedure F for deprotection of the amine moiety

To a solution of protected amine dissolved in a minimal amount of 1,4-dioxane, a solution of 4N HCl in 1,4-dioxane (5 mL/0.5 mmol) was added. The reaction flask is then sealed with a septum and stirred at rt. The reaction is monitored by ^{1}H NMR and TLC and after 4.5 hours the reaction mixture is then concentrated *in vacuo* to give pure free amine ready to be used for the following step.

γ/α-peptide BocNH(AMCP-l-Ala)$_2$-OBn 20



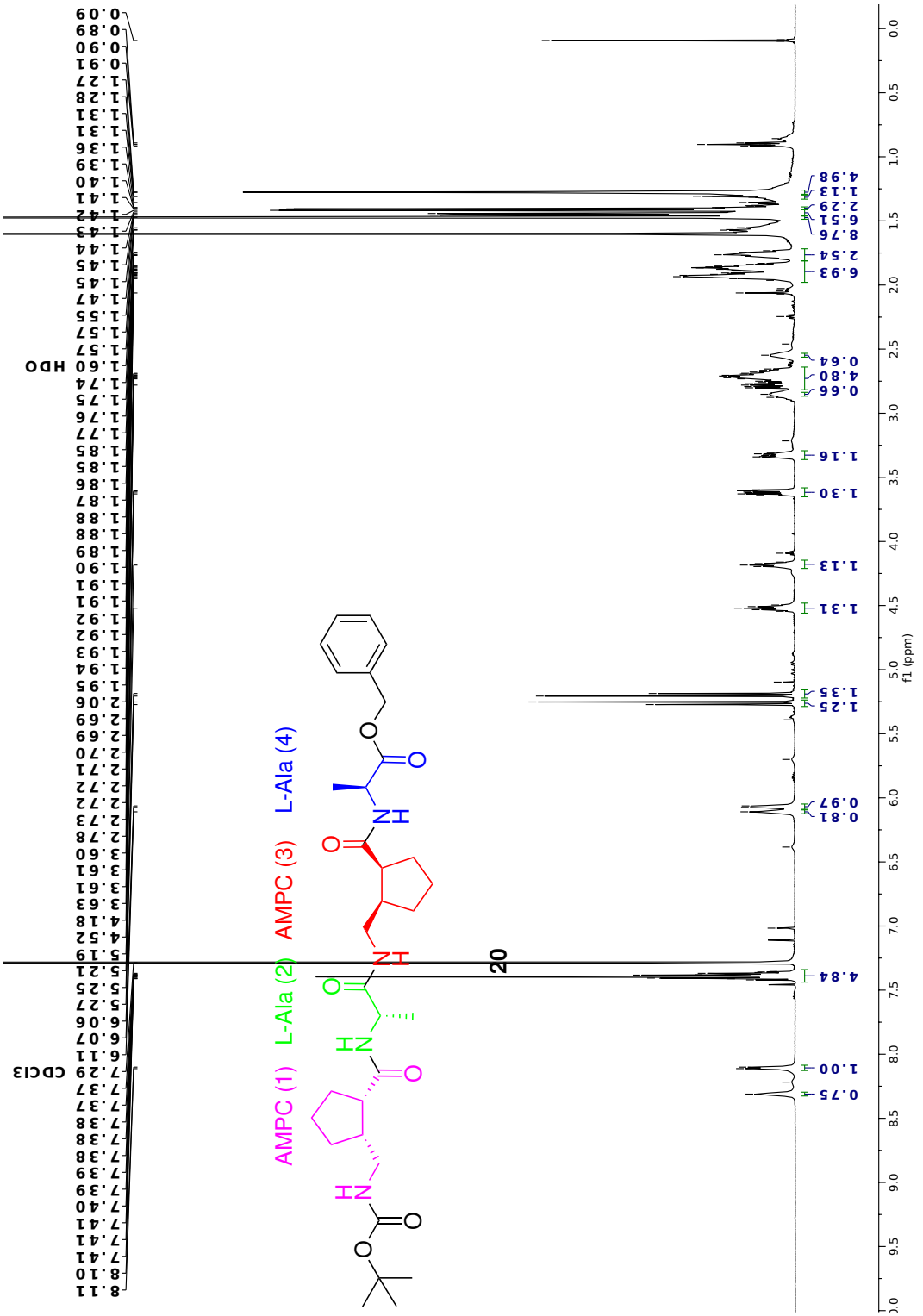
20

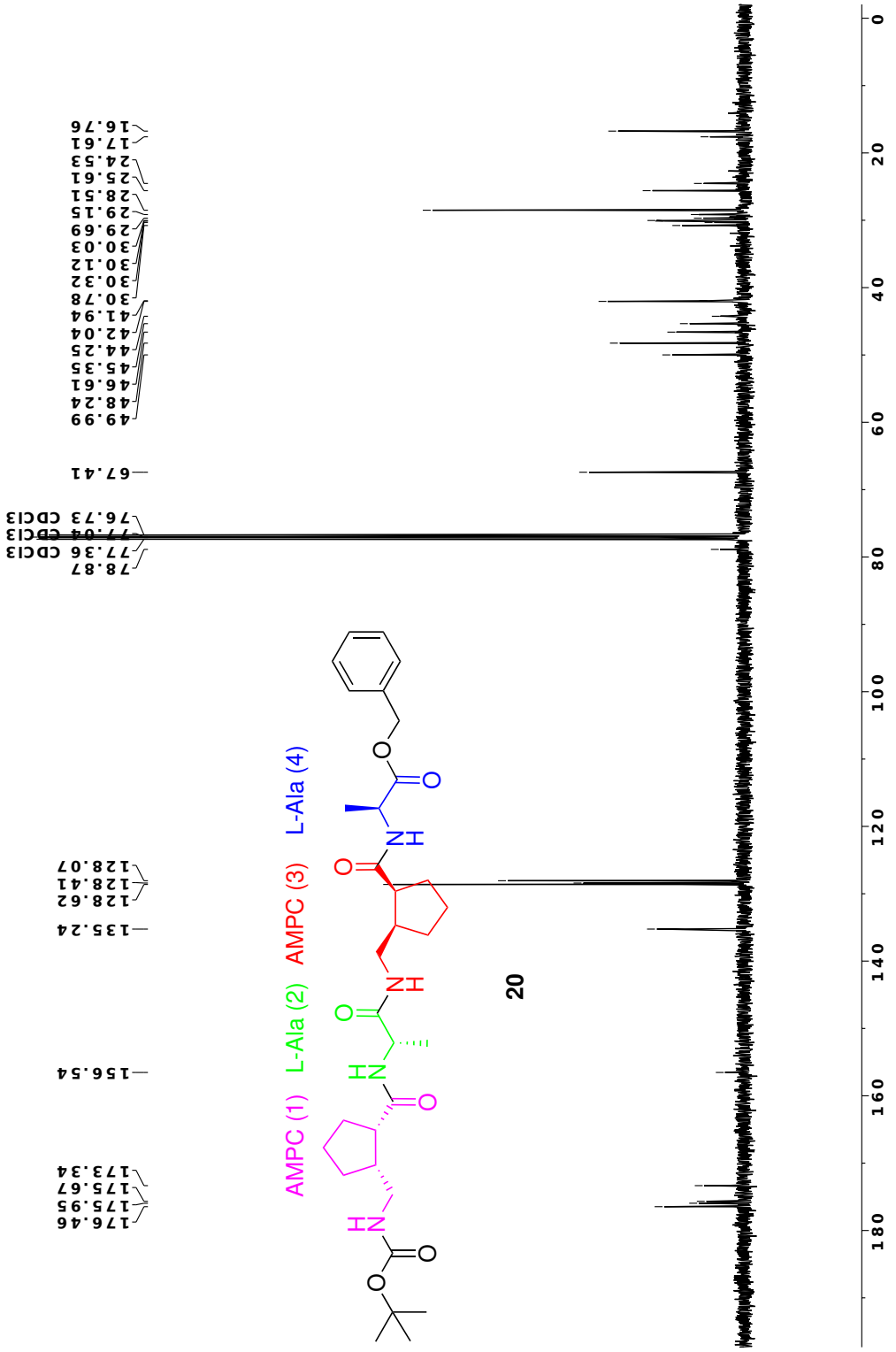
To a solution of compound **19** (0.063 g, 0.2 mmol) in DMF (0.5 mL), DIPEA (0.2 mL, 1.2 mmol), HOBt· H_2O (0.032 g, 0.24 mmol) and EDCI (0.046 g, 0.24 mmol) were added. The solution was stirred at rt for 15 minutes and then a solution of compound **17** (0.061 g, 0.2 mmol) in DMF (0.5 mL) was added. The reaction mixture was stirred at rt for 24 hours. Ethyl acetate (10 mL) was then added and the organic phase was washed with a 1M aqueous

solution of $NaHSO_4$ (2 x 5 mL), a saturated aqueous solution of $NaHCO_3$ (2 x 5 mL) and then brine (2 x 5 mL). Acid and basic aqueous layers were then extracted twice with CH_2Cl_2. All organic layers were combined, dried over Na_2SO_4, filtered and concentrate *in vacuo*. The crude product was then purified by flash chromatography on silica gel (gradient hexane/ethyl acetate/methanol) to obtain the titled product **20** as a white solid (0.031 g, 0.05 mmol, 26%). $[\alpha]^{20}{}_D$ +69.2 (c = 0.12, MeOH). IR (neat, cm^{-1}) 3300, 2931, 1741, 1636, 1534, 1449, 1366, 1278, 1247, 1169, 1114, 1034 . ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (1 H, m), 8.11 (1 H, d, *J* 7.0), 7.44 – 7.27 (5 H, m), 6.11 (1 H, d, *J* 4.9), 6.08 (1 H, d, *J* 6.7), 5.26 (1 H, d, *J* 12.3), 5.20 (1 H, dd, *J* 39.7, 12.3), 4.52 (1 H, t, *J* 7.3), 4.18 (1 H, q, *J* 6.9), 3.62 (1 H, ddd, *J* 13.4, 6.1, 4.7), 3.33 (1 H, dd, *J* 13.1, 6.3), 2.91 – 2.81 (2 H, m), 2.82 – 2.65 (3 H, m), 2.59 – 2.49 (1 H, m), 1.99 – 1.80 (6 H, m), 1.81 – 1.72 (2 H, m), 1.60 (9 H, s), 1.60-1.54 (2H, m) 1.47 - 1.43 (4 H, m), 1.42 (m, 1H), 1.41 (3 H, d, *J* 7.0). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5 (CO AMCP(3)), 176.0 (CO L-Ala(4)), 175.7 (CO L-Ala(2)), 173.3 (CO AMCP(1)), 156.5 (CO-Boc), 135.2 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 128.1 (C-Ar), 67.4 (CH_2-Bn), 50.0 (HCα L-Ala(2)), 48.2 (HCα L-Ala(4)), 46.6 (HCα AMCP(1)), 45.3(HCα AMCP(3)), 44.3 (HCβ AMCP(1)), 42.0 (H2Cγ AMCP(1)), 41.9 (HCγ AMCP(1), 30.8 (C1 AMCP(3)), 30.3, 30.1 (C1-AMCP(1)), 30.0 (C3-AMCP(3)), 29.7 (C3-AMCP(1)), 25.6 (C2 AMCP(3)), 24.5 (C2 AMCP(1)), 17.6 (HCβ L-Ala(2)), 16.8 (HCβ L-Ala(4)). HRMS required for $C_{32}H_{49}N_4O_7$ $[M+H]^+$ is 601.3601, found 601.3604.

Table S14: ^{1}H NMR assignments for the γ/α-peptide **20**.

Residue	Hα	Hβ	Hγ1	Hγ2	NH	H1	H2	H3
L-Ala(2)	4.19	1.41	-	-	6.08	-	-	-
AMCP (3)	2.71	2.87	3.62	2.79	8.31	1.75 and 1.42	1.88 and 1.58	1.93 and 1.86
L-Ala(4)	4.52	1.45	-	-	8.11	-	-	-
AMCP (1)	2.73	2.54	3.33	2.69	6.10	1.77 and 1.40	1.88 and 1.57	1.93 and 1.86


AMPC (1)
L-Ala (2)
AMPC (3)
L-Ala (4)
HDO
CDCl3
f1 (ppm)


AMPC (1)
L-Ala (2)
AMPC (3)
L-Ala (4)
20
176.46
175.95
175.67
173.34
156.54
135.24
128.62
128.41
128.07
78.87
77.36 CDCl3
77.04 CDCl3
76.73 CDCl3
67.41
49.99
48.24
46.61
45.35
44.25
42.04
41.94
30.78
30.32
30.12
30.03
29.69
29.15
28.51
25.61
24.53
17.61
16.76
0
20
40
60
80
100
120
140
160
180

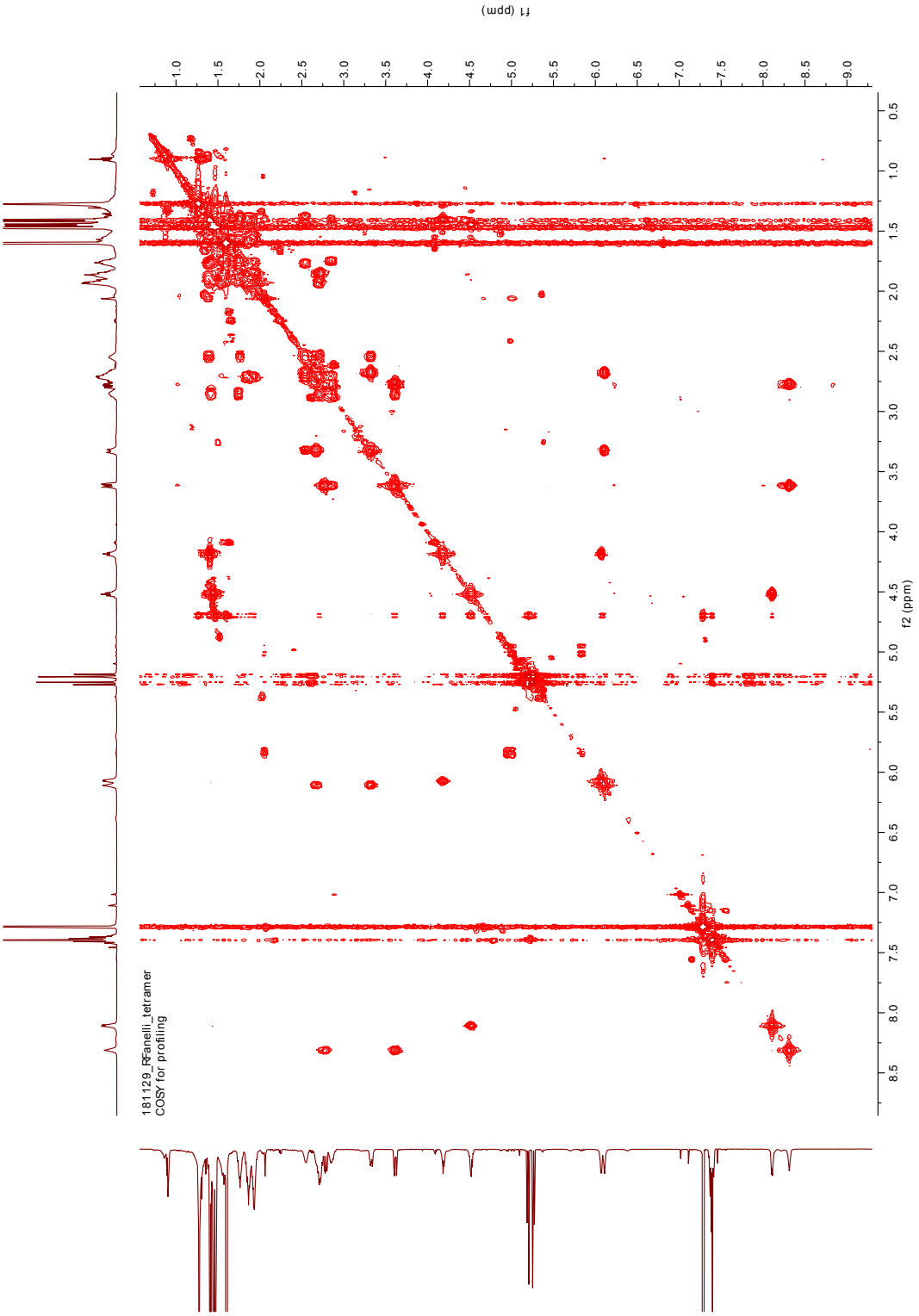


Figure S13: COSY NMR spectrum of **20**.

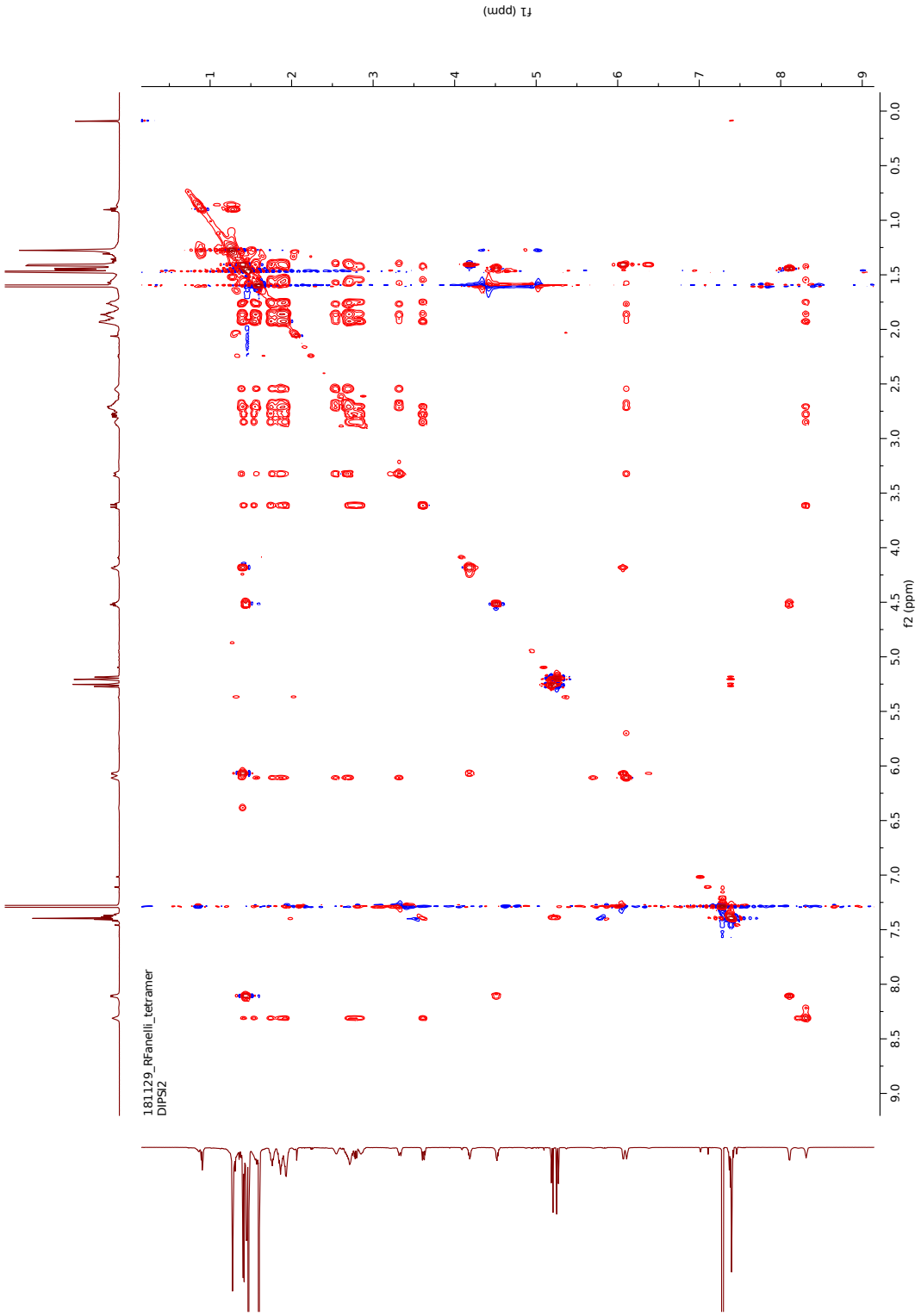


Figure S14: TOCSY NMR spectrum of **20**.

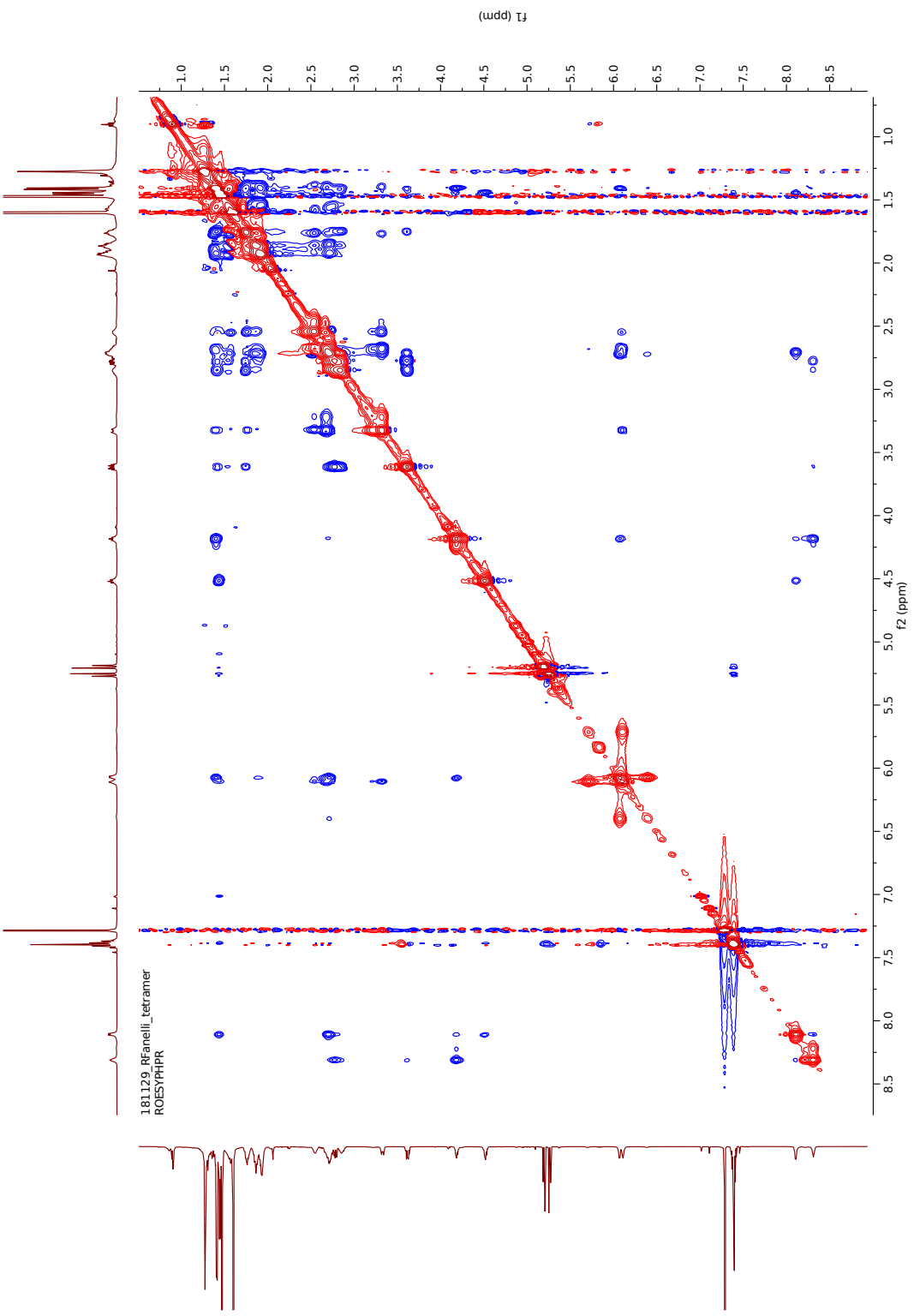


Figure S15: NOESY NMR spectrum of **20**.

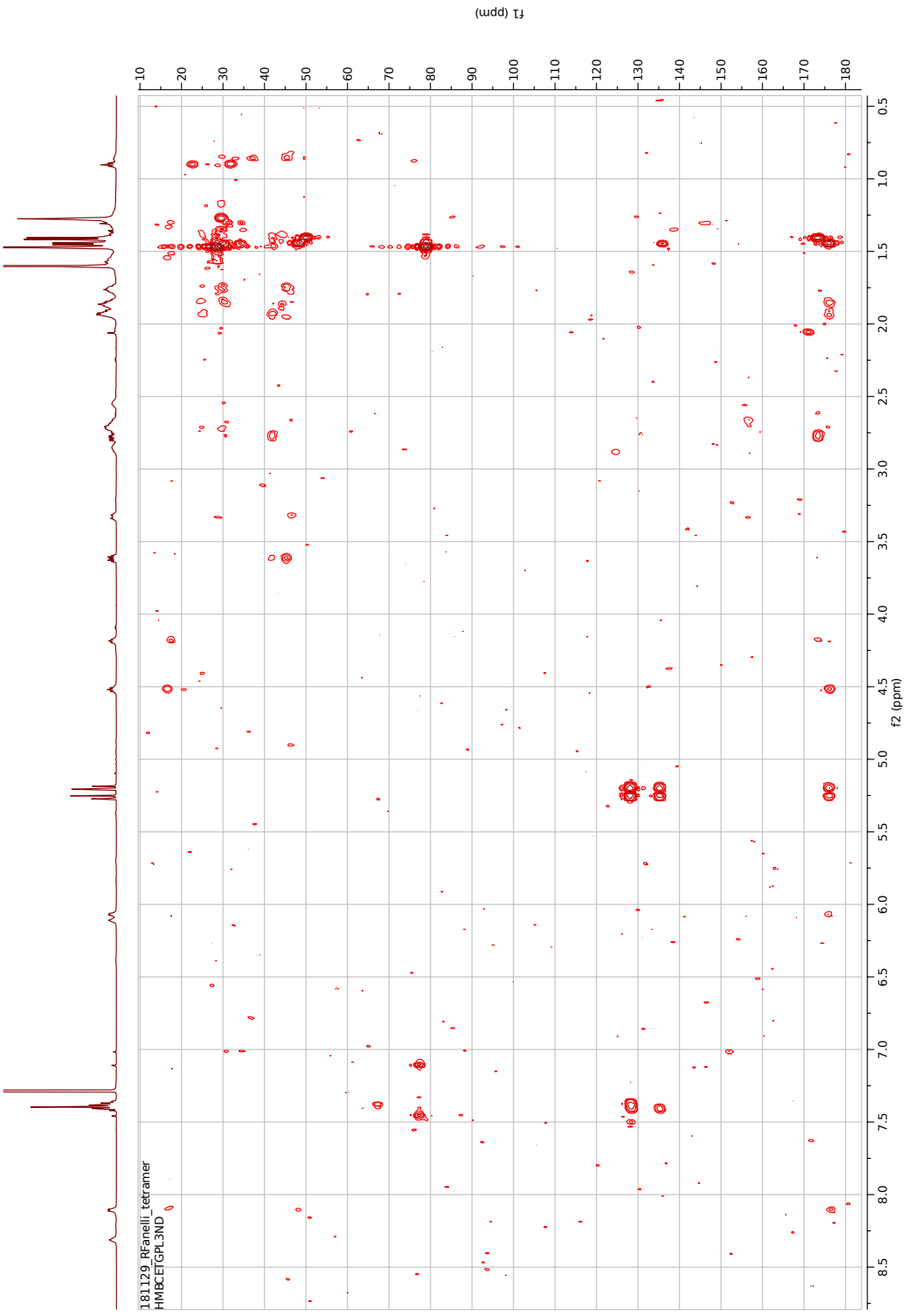
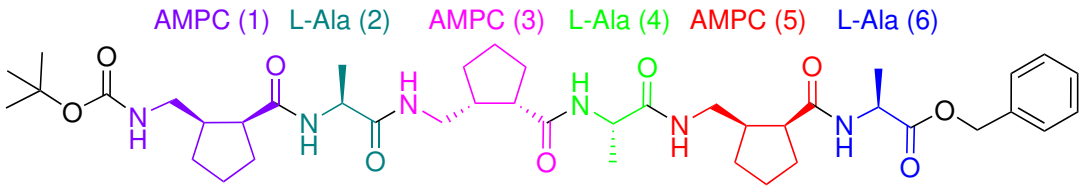


Figure S16: HMBC NMR spectra of **20**.

γ/α-peptide Boc(AMCP-l-Ala)$_3$OBn 21



21

To a solution of **19** (0.036 g, 0.1 mmol) in DMF (1 mL), DIPEA (0.1 mL, 0.6 mmol), HOBt· H_2O (0.018 g, 0.12 mmol), EDCI (0.023 g, 0.12 mmol) were added. The reaction mixture was stirred at rt for 15 minutes and then a solution of the amine deprotected **20** (0.054 g, 0.1 mmol) in DMF (1 mL) was added. The reaction mixture was sealed with a septum and it was left stirring at rt for 24 hours. Ethyl acetate (10 mL) was then added and the organic phase was washed with a 1M**a**queous solution of $NaHSO_4$ (2 x 5 mL), a saturated aqueous solution of $NaHCO_3$ (2 x 5 mL) and then brine (2 x 5 mL). Acid and basic aqueous layers were then extracted twice with CH_2Cl_2. All organic layers were combined, dried over Na_2SO_4, filtered and concentrate *in vacuo*. The crude product was then purified by flash chromatography on silica gel (gradient hexane/ethyl acetate/methanol) to obtain the titled product **21** as a white solid (0.016 g, 0.02 mmol, 20%).

$[\alpha]^{20}{}_D$ +106.0 (c = 0.05, CH_2Cl_2); IR (neat, cm^{-1}) 3288, 2927, 1739, 1701, 1635, 1529, 1449, 1366, 1247, 1225, 1169; HRMS required for $C_{42}H_{65}N_6O_9$ $[M+H]^+$ is 797.4813, found 797.4832. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.90 (1 H, s), 8.64 (1 H, d, *J* 6.8), 8.60 – 8.40 (2 H, m), 7.50 – 7.33 (5 H, m), 6.38 (1 H, s), 6.01 (1 H, d, *J* 6.2), 5.27 (1H, d, *J* = 12.3 Hz), 5.19 (1H, d, *J* = 12.3 Hz), 4.48 (1 H, p, *J* 7.3), 4.29 (1 H, q, *J* 6.7), 4.03 (1 H, p, *J* 6.8), 3.66 - 3,54 (2 H, m), 3.45 – 3.31 (1 H, m), 3.04 - 2.89 (2 H, m), 2.88 – 2.77 (2 H, m), 2.77 - 2.68 (2 H, m), 2.68 – 2.55 (2 H, m), 2.54 – 2.42 (1 H, m), 2.02 - 1.92 (2 H, m), 1.94 - 1.83 (4 H, m), 1.83 – 1.70 (3 H, m), 1.48 (10 H, s), 1.46 – 1.43 (5 H, m), 1.41 (3 H, d, *J* 7.5), 1.39 (3 H, d, *J* 7.1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 176.7, 176.3, 176.0, 175.4, 173.5, 156.6, 139.3,

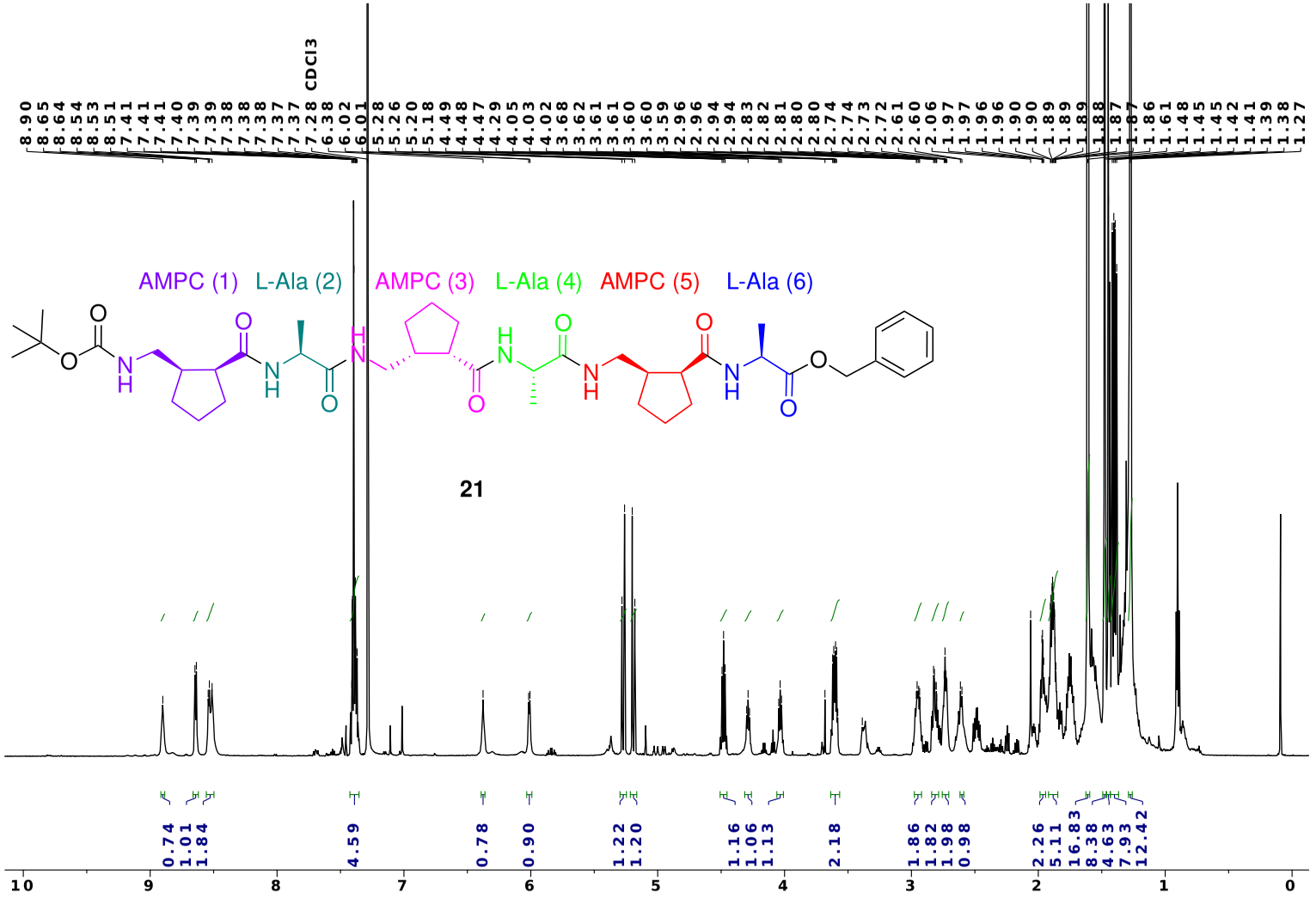
135.2, 128.6, 128.4, 128.1, 124.8, 114.1, 78.7, 67.4, 53.4, 50.7, 50.3, 48.3, 46.3, 45.1, 44.8, 44.4, 42.5, 42.3, 41.8, 41.7, 36.5, 34.3, 33.8, 31.9, 31.0, 30.9, 30.3, 30.2, 30.1, 29.7, 29.5, 29.4, 29.2, 29.0, 28.5, 25.7, 25.7, 24.7, 22.7, 17.6, 16.9, 16.6, 14.1.

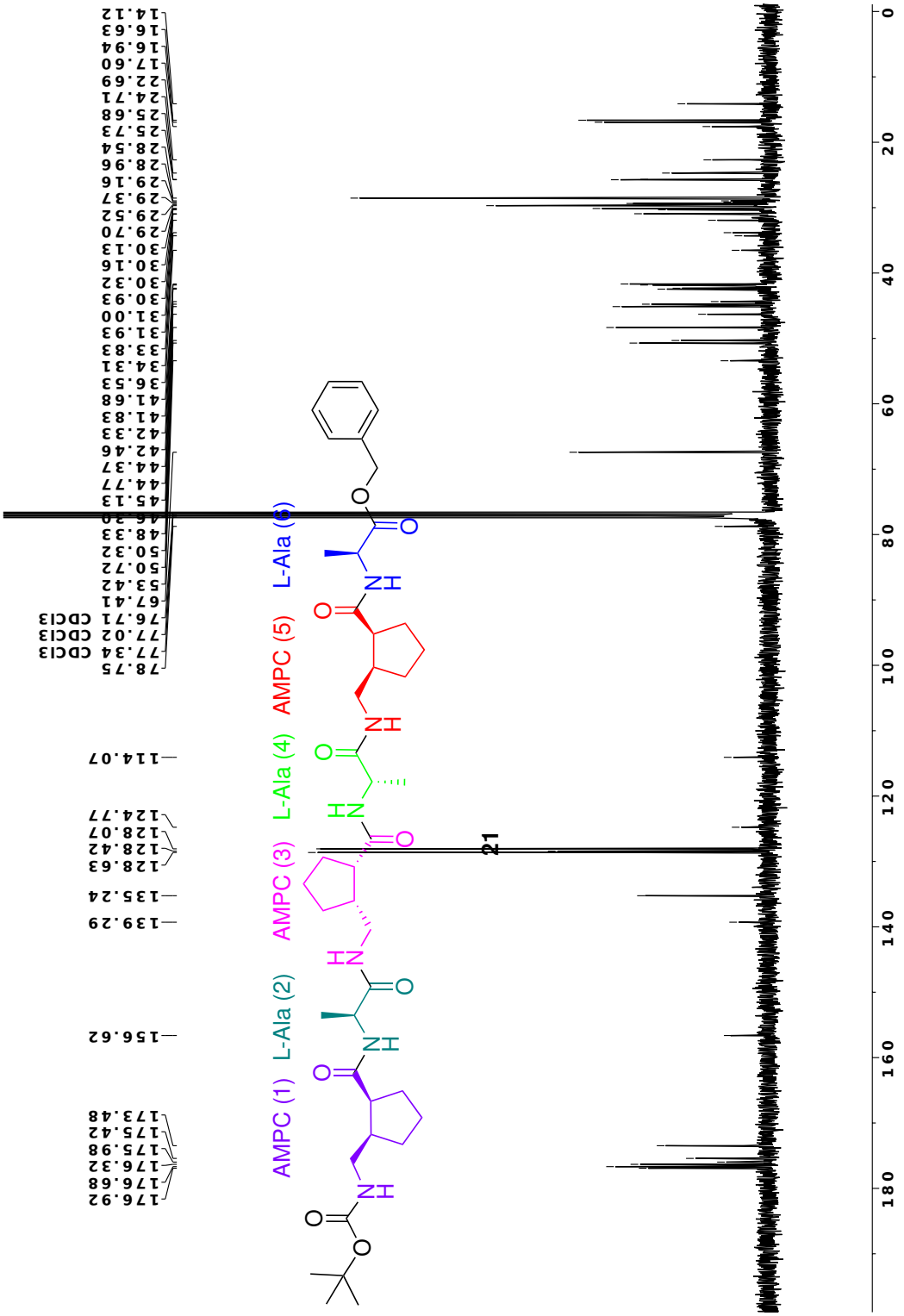
Table S15: ^{1}H NMR assignment for the γ/α-peptide **21**.

Residue	Hα	Hβ	Hγ1	Hγ2	NH	CH2	H-Ar
L-Ala(2)	4.287	1.438	-	-	6.005	-	-
AMCP(5)	2.821	2.952	3.611	2.8	8.513	-	
L-Ala(4)	4.033	1.387	-	-	8.537	-	-
AMCP(3)	2.739	2.954	3.6	2.483	8.901	-	-
L-Ala(6)	4.483	1.412	-	-	8.642	-	-
AMCP(1)	2.726	2.6	3.377	2.614	6.377	-	-
Benzyl	-	-	-	-	-	5.236	7.33 - 7.44

Table S16: ^{13}C NMR assignment for the γ/α-peptide **21**.

Residue	Cα	Cβ	Cγ	CH2	HAr	CO
L-Ala(2)	50.33	17.65	-	-	-	173.38
AMCP(5)	45.1	41.77	42.45	-	-	176.72
L-Ala(4)	50.71	16.98	-	-	-	175.51
AMCP(3)	44.71	41.77	42.33	-	-	176.9
L-Ala(6)	48.32	16.64	-	-	-	176.38
AMCP(1)	46.26	44.42	42	-	-	176.03
Benzyl	-	-	-	67.41	135.22, 128.6, 128.4, 128.1	-


AMPC (1) L-Ala (2) AMPC (3) L-Ala (4) AMPC (5) L-Ala (6)
21


AMPC (1)
L-Ala (2)
AMPC (3)
L-Ala (4)
AMPC (5)
L-Ala (6)
21
14.12
16.63
16.94
17.60
22.69
24.71
25.68
25.73
28.54
28.96
29.16
29.37
29.52
29.70
30.13
30.16
30.32
30.93
31.00
31.93
33.83
34.31
36.53
41.68
41.83
42.33
42.46
44.37
44.77
45.13
48.33
50.32
50.72
53.42
67.41
76.71 CDCl3
77.02 CDCl3
77.34 CDCl3
78.75
114.07
124.77
128.07
128.42
128.63
135.24
139.29
156.62
173.48
175.42
175.98
176.32
176.68
176.92
0
20
40
60
80
100
120
140
160
180

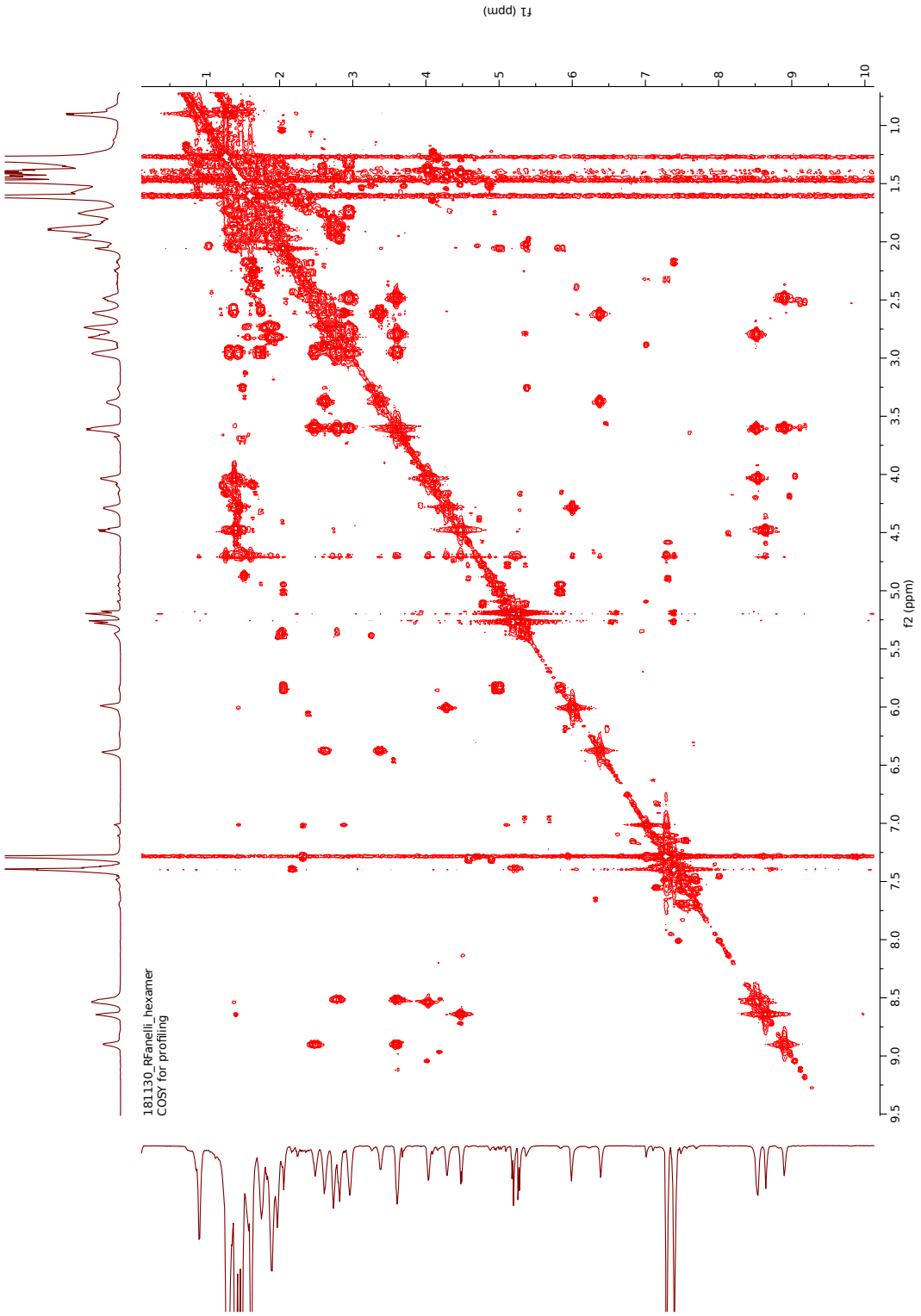


Figure S17: COSY NMR spectra of **21**.

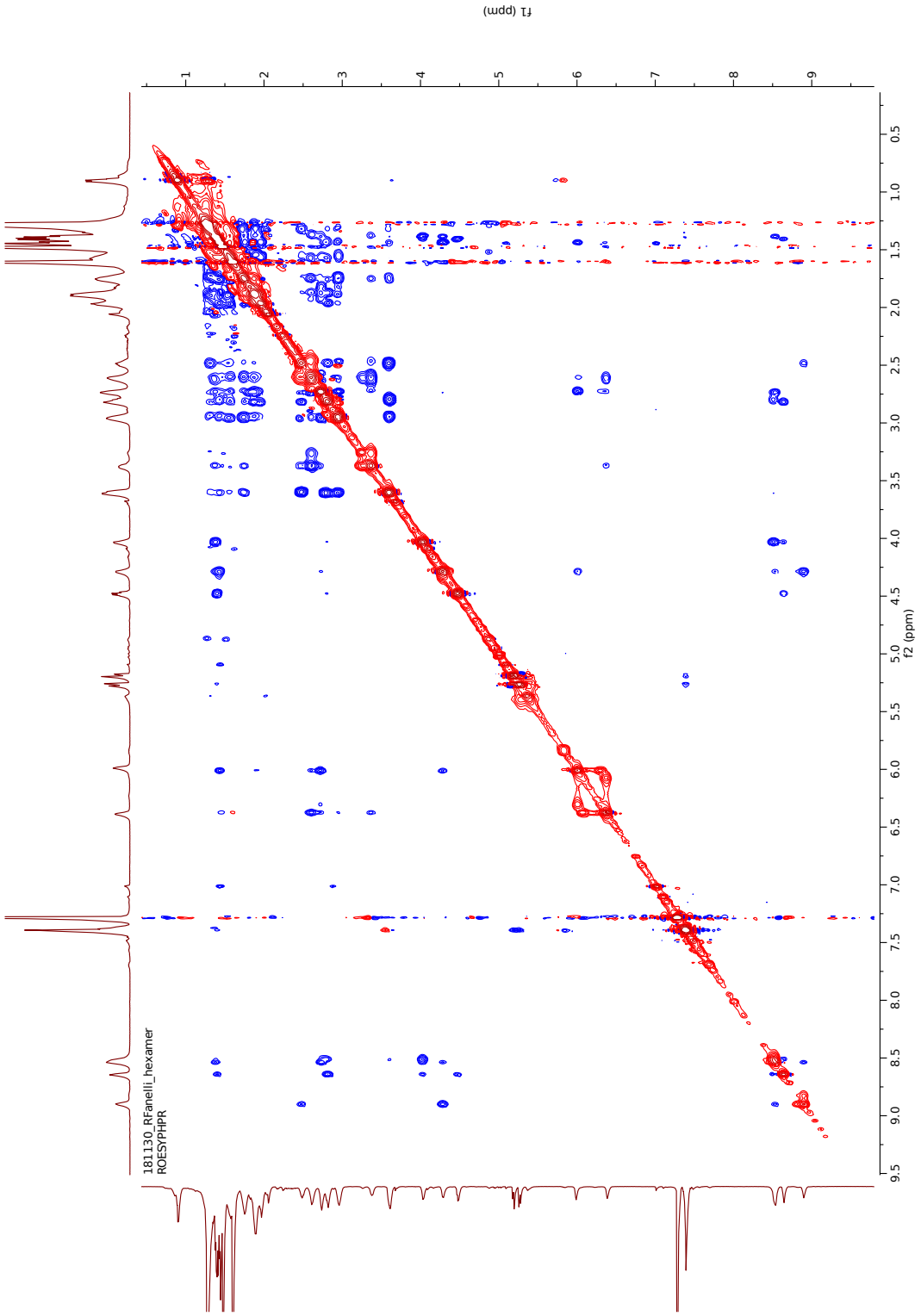


Figure S18: ROESY NMR spectra of **21**.

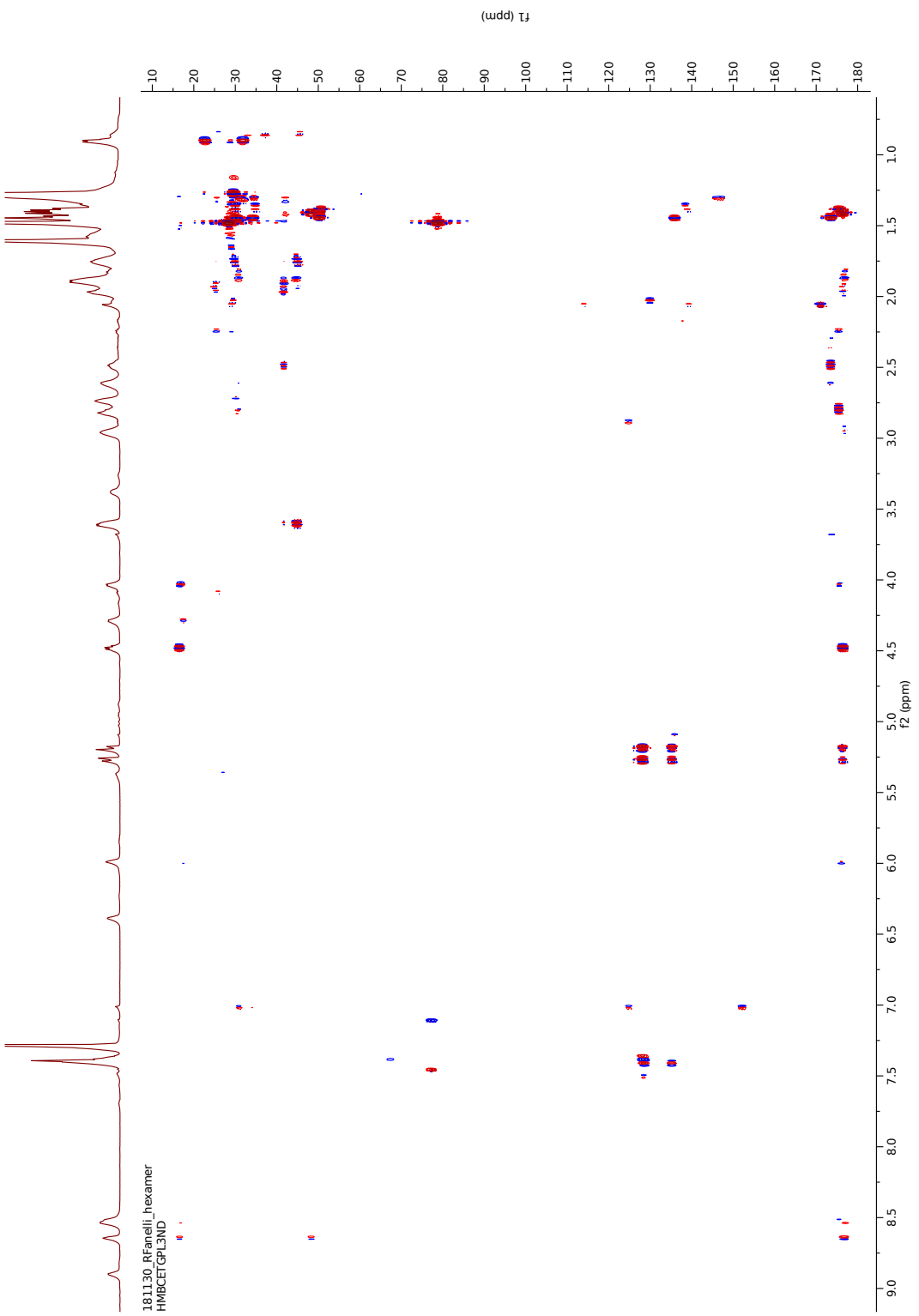


Figure S19: HMBC NMR spectra of **21**.

Circular Dichroism

A preliminary study of the secondary structure of peptides **18**, **20** and **21** was conducted with circular dichroism (CD, Figure S20). In contrast with dimer **18**, both tetramer **20** and hexamer **21** present a characteristic pattern associated with helical conformations (Figure S20).[10]

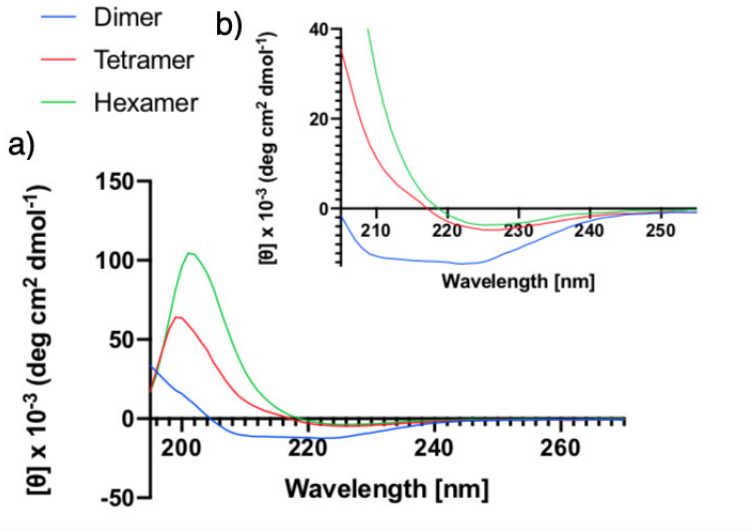


Figure S20: (a) circular dichroism of the α/γ-peptides **18**, **20** and **21** at 2mM concentration in methanol; (b) graph zoomed in 200-250 nm.

Aggregation control experiment and observed NOE cross peaks

An aggregation control experiment was conducted on hexamer **21** to prove there is no self-association and confirm that the downfield detected amide peaks are due to intramolecular interactions rather than intermolecular interactions. ^{1}H NMR of γ/α-peptide **21** was measured in $CDCl_3$ at different concentrations (0.04mM – 4 mM). This experiment displays the amide peaks at the same chemical shifts for all different concentrations, which confirms the fact that the downfield NH peaks are due to intramolecular H-bonds, rather than intermolecular H-bonds (Figure S21).[11,12] The experiment was conducted on the longest oligomer that was synthesised (**21**), which is also the one that presents a more defined secondary structure.

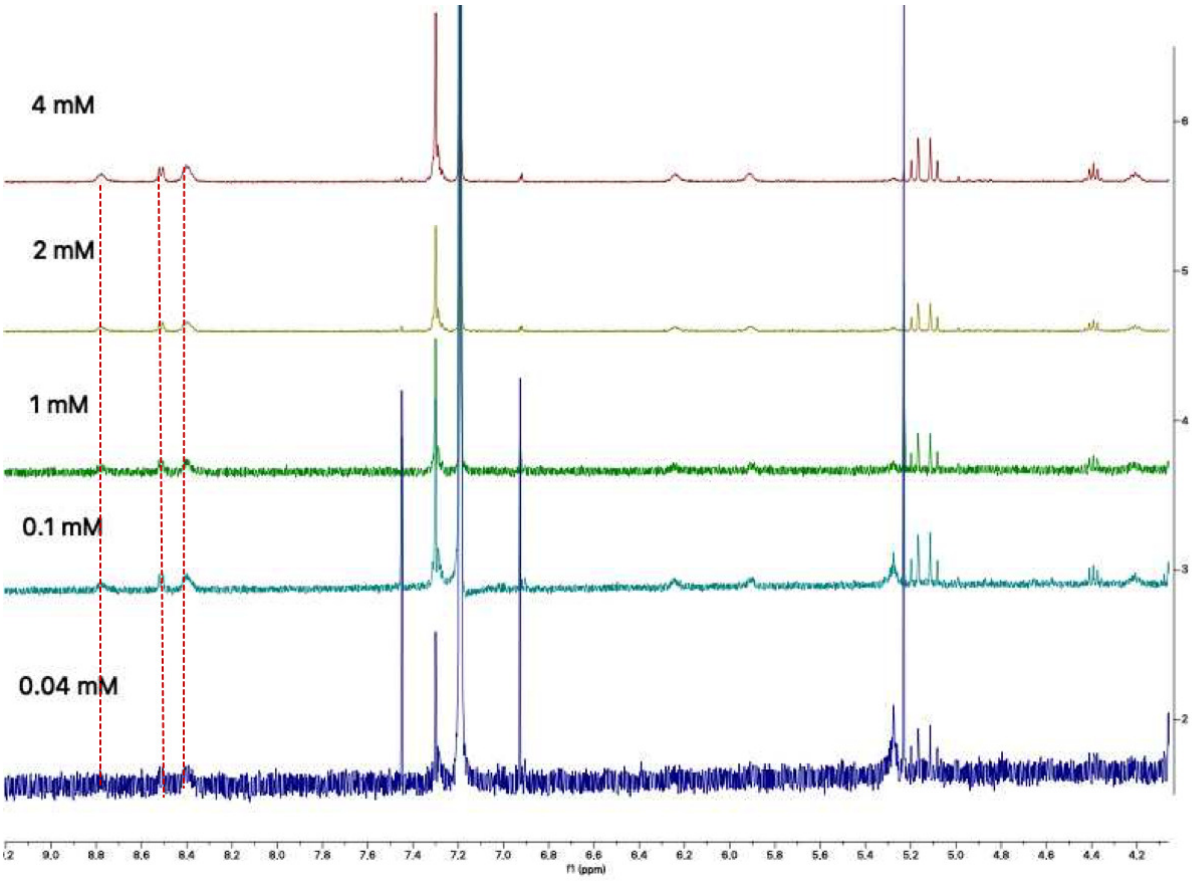
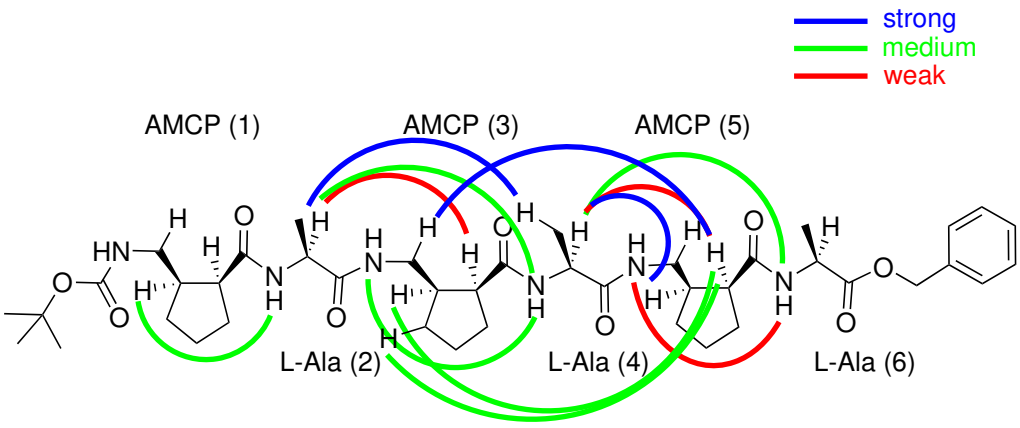


Figure S21: ^{1}NMR spectra in $CDCl_3$ of the γ/α-peptide **21** at 0.4, 0.1, 1, 2 and 4mM concentration for an aggregation control experiment.

Table S17: Unambiguous Observed NOE cross peaks for hexamer **21**.



21

NOE cross peak	NMR distance Å	Designation
NH (1) - HCα (2)	4.95	weak
HCα (1) - HCα (2)	4.28	weak
HCβ (1) - NH (2)	3.42	medium
HCβ (1) - HCα (2)	4.68	weak
NH (1) - Hβ (3)	3.90	weak
NH (1) - Hγ''(3)	4.20	weak
HC$_1$'(1) - HCγ''(3)	3.91	weak
HCα (2) - HCα (3)	**4.28**	**weak**
HCα (2) - HCβ (3)	4.27	weak
HCα (2) - HCγ''(3)	5.33	weak
HCα (2) - NH (4)	**3.47**	**medium**
HCα (2) - HCβ (4)	2.99	strong
HCβ (3) - NH (3)	4.09	weak
NH (3) - NH (4)	**3.46**	**medium**
HCα (3) - NH (4)	2.68	strong
HCα (3) - HCα (4)	4.30	weak
HCγ'(3) - HCα (4)	5.1	weak
HC$_1$'(3) - HCα (4)	5.03	weak
HCβ (3) - HCα (5)	3.27	medium
HCγ''(3) - HCα (5)	2.62	strong
HC$_3$''(3) - HCα (5)	3.25	medium
HCα (4) - NH (5)	2.48	strong
HCα (4) - HCβ (5)	2.96	strong
HCβ (4) - HCγ'(5)	4.27	weak
HCα (4) - NH (6)	**3.47**	**medium**
HCα (4) - HCα (5)	**3.96**	**weak**
NH (5) - NH (6)	**3.79**	**weak**
HCα (5) - NH (6)	2.58	strong
HCβ (5) - NH (6)	4.40	weak
HCα (5) - HCα (6)	4.73	weak
HC$_1$'(5) - HCα (6)	4.73	weak

Computations

Methods

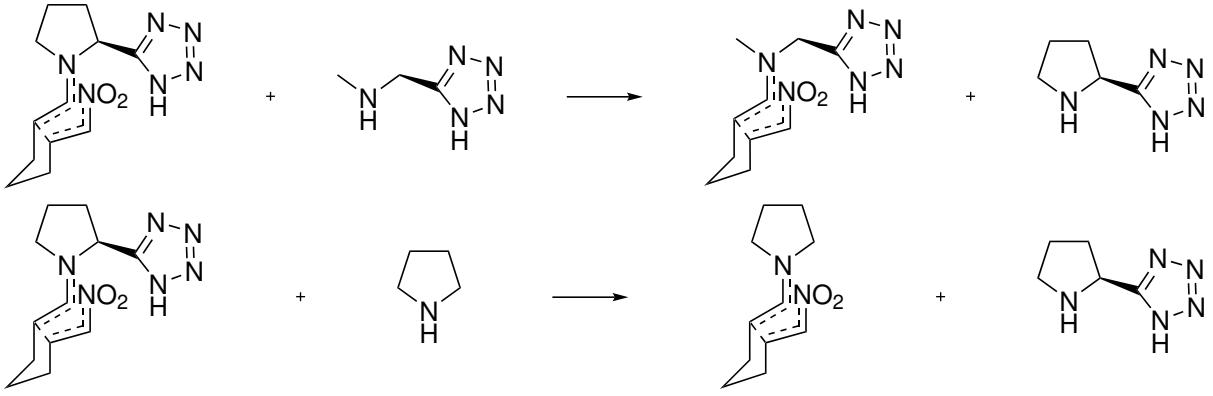
Conformational sampling was carried out using mixed low-mode Monte-Carlo search[13–15] as implemented in Schrodinger 2017-1[16] based on the OPLS 2005 all atom force field,[17–19] followed by conformational clustering.

Kohn-Sham DFT calculations were done for the mechanistic studies using Gaussian09 Rev.E.[20] The presented result were obtained employing the ωB97XD range separated hybrid functional,[21] with the basis 6-311G(d,p) for optimization, frequency and solvent calculations and the 6-311++G(3df,3pd) basis for electronic energies.[22–24] Thermochemical corrections were calculated according to Grimme's quasi-RRHO[25] approximation as implemented in goodvibes.[26] Solvent corrections are determined for DCE using PCM solvent model with Truhlar's SMD parametrization.[27,28]

Calculated Energies

Induction of Selectivity

The following hypothetical reactions have been constructed to understand the effect of the tetrazole unit and the pyrrolidine ring's conformation.



Scheme S4: Imaginary reaction to study the origin of selectivity. Notice the difference between the two sides is the interaction of the removed moiety with the rest of the structure.

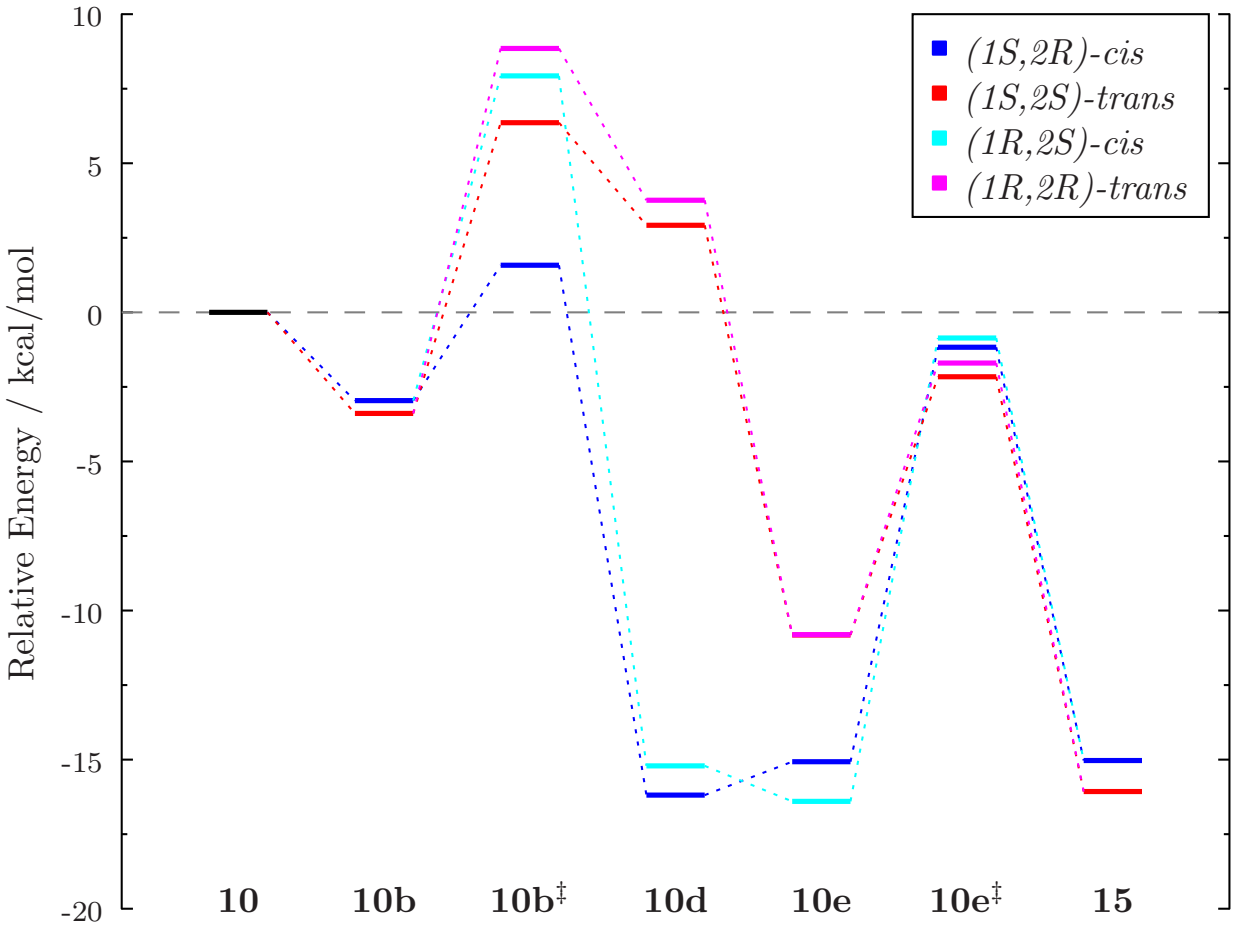


Figure S22: Solvent corrected electronic energy along the reaction coordinate. It is clearly shown that the protonation step's transition states lay lower than the CC bond forming step's without the entropy correction.

Table S18: Calculated energies and Gibbs free energies as presented in Figure 5 in the main text. Values were obtained at the ωB97XD/6-311G(d,p) level of theory, unless basis specified and are in hartree. G_{therm} is given at 298 K and 1 atm, qRRHO data is calculated at the concentration of 0.04 M

	E_{SP}	G_{therm}	$G_{qRRHO(253)}$	$G_{qRRHO(298)}$	$G_{solv=DCE}$	E(6-311++G(3df,3pd))
V	-469.621079737	-469.495528	-469.488611	-469.494561	-469.621079737	-469.665243816
1	-553.635288342	-553.496528	-553.486999	-553.494122	-553.635288342	-553.687704343
water	-76.423353397	-76.416192	-76.416192	-76.41622	-76.423353397	-76.4383130367
1b (pre-*cis*)	-946.836877190	-946.568887	-946.556856	-946.565660	-946.836877190	-946.922377559
1b (pre-*trans*)	-946.838583781	-946.572888	-946.559697	-946.568646	-946.838583781	-946.924128500
(*1S,2S*)-**1b**‡	-946.814746140	-946.543569	-946.532832	-946.541237	-946.814746140	-946.900771093
(*1R,2R*)-**1b**‡	-946.809430513	-946.537152	-946.526685	-946.535044	-946.809430513	-946.894996939
(*1S,2R*)-**1b**‡	-946.826248358	-946.552554	-946.542915	-946.551166	-946.826248358	-946.910825548
(*1R,2S*)-**1b**‡	-946.815806039	-946.543154	-946.533140	-946.541487	-946.815806039	-946.901350324
(*1S,2S*)-**1d**	-946.827251799	-946.554637	-946.542746	-946.551180	-946.827251799	-946.911608405
(*1R,2R*)-**1d**	-946.826485766	-946.554625	-946.542557	-946.551036	-946.826485766	-946.910800024
(*1S,2R*)-**1d**	-946.858429165	-946.585606	-946.573633	-946.581965	-946.858429165	-946.941568527
(*1R,2S*)-**1d**	-946.856453377	-946.585550	-946.572697	-946.581216	-946.856453377	-946.940468880
(*1S,2S*)-**1e**	-946.844975318	-946.571869	-946.560276	-946.568667	-946.844975318	-946.931214192
(*1R,2R*)-**1e**	-946.843954863	-946.570881	-946.559302	-946.567673	-946.843954863	-946.930217381
(*1S,2R*)-**1e**	-946.855548328	-946.581345	-946.570058	-946.578347	-946.855548328	-946.939941142
(*1R,2S*)-**1e**	-946.852894447	-946.578434	-946.567200	-946.575474	-946.852894447	-946.938840908
(*1S,2S*)-**1e**‡	-1023.26458131	-1022.974427	-1022.961950	-1022.970903	-1023.26458131	-1023.35749357
(*1R,2R*)-**1e**‡	-1023.26086660	-1022.969795	-1022.957859	-1022.966749	-1023.26086660	-1023.35273521
(*1S,2R*)-**1e**‡	-1023.25970289	-1022.967407	-1022.955583	-1022.964426	-1023.25970289	-1023.35113506
(*1R,2S*)-**1e**‡	-1023.26125226	-1022.968186	-1022.956924	-1022.965711	-1023.26125226	-1023.35272650
trans-**2**	-553.667031153	-553.520748	-553.512493	-553.519080	-553.667031153	-553.71648698
cis-**2**	-553.663855226	-553.518404	-553.510002	-553.516670	-553.663855226	-553.713705105

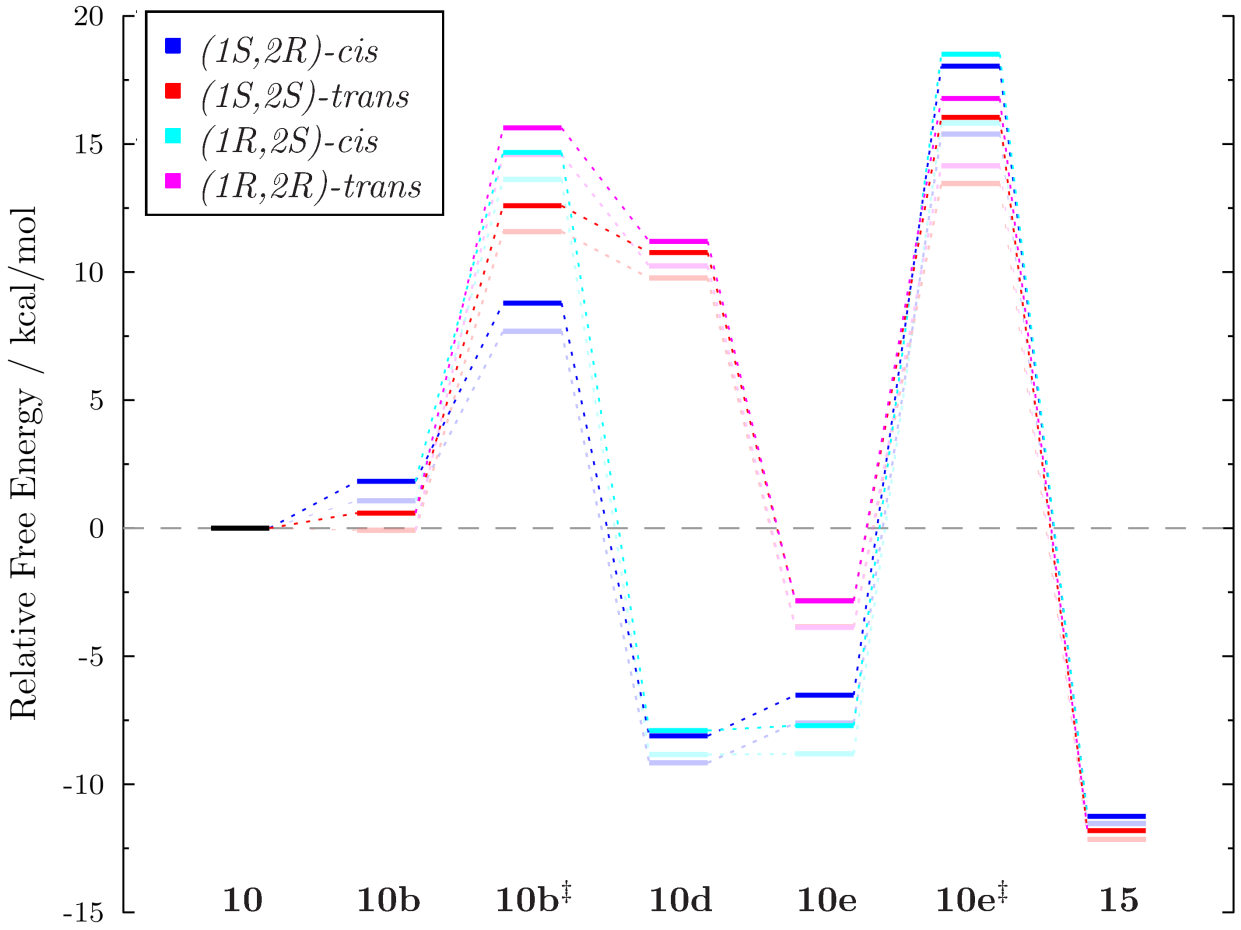


Figure S23: Temperature dependence of the Free Energy Profile, data for 253 K is shown hallow, while 298 K is opaque. While the first TSs increase with 1 kcal/mol, the protonation TSs lay higher by 2.6 kcal/mol.

Table S19: Energy values corresponding to the reactions presented in Scheme S4 and are in kcal/mol. ΔG(253K) is for the sake of comparing the paths as shown in Figure 5 in the manuscript. ΔE and ΔE_{opt} are the electronic energy before and after optimization, respectively, while ΔG is the Gibbs free energy after optimization. The more positive a value is, the more favourable the original interaction is.

tetrazole	ΔG(253K)	ΔE	ΔE_{opt}	ΔG
(1*S*,2*R*) (*cis* major)	9.3	7.2	6.3	-2.8
(1*S*,2*S*) (*trans* major)	13.2	5.2	4.0	-4.6
(1*R*,2*S*) (*cis* minor)	15.2	-1.0	-0.6	-8.3
(1*R*,2*R*) (*trans* minor)	16.2	6.5	1.2	-2.7
pyrrolidine	ΔG(253K)	ΔE	ΔE_{opt}	ΔG
(1*S*,2*R*) (*cis* major)	9.3	11.0	6.1	4.1
(1*S*,2*S*) (*trans* major)	13.2	9.3	4.3	2.5
(1*R*,2*S*) (*cis* minor)	15.2	7.7	-0.5	-1.6
(1*R*,2*R*) (*trans* minor)	16.2	8.5	0.5	1.9

The data presented in Table S19 underlines the strong H-bonding in the structures (seen in electronic energy), which is the most advanced in the (1*S*,2*R*) path. The pyrrolidine ring's conformation also favours the major product's structure.

Intermediates

As depicted in Figure 4b in the main text, we envisioned three intermediates between the two investigated steps. Even in polar medium, the zwitterionic intermediate **1c** is hard to localize as a stationary structure, the most stable geometry corresponded to 5.5 kcal/mol in the same reference as shown in Figure 4c in the main text, therefore intermediate **1c** is ignored in further discussion.

The 4-membered ring formation leads to intermediate **1d** also dubbed as CB intermediate. The *cis*-**1d** structures are quite stable, the serve as the resting state of the catalyst in the studied cycle. On the contrary, the *trans*-**1d** intermediate is rather unstable due to extreme ring strain (Figure S24).

Intermediate **1e** or OO, forms a six-membered ring bridging by the nitro group to the formed iminium. This intermediate is available for all diastereomers and provides basis for

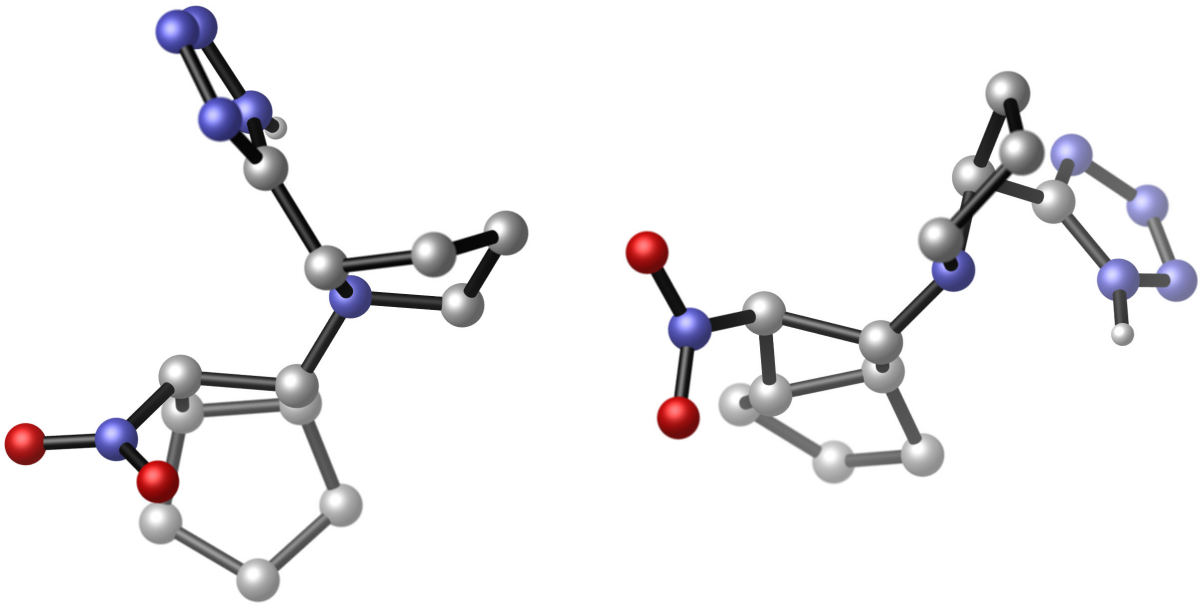


Figure S24: **left**: geometry of the most stable intermediate (*1S,2R*)-**1d**. **right**: twisted four-membered ring in (*1S,2S*)-**1d**, resulting in an unstable structure.

the subsequent protonation step.

Foldamer Conformers

The identified 55 conformers have been processed with DFT as detailed above, apart from the electronic energy calculations with larger basis set. Apart from conformer 23 and 27, all have been optimised to a local minimum according to the vibrational frequencies.

Table S20: DFT data for the foldamer conformers, energies shown in hartree, relative free energies (ΔG) are in kcal/mol.

conf	E	G_{therm}	G_{CDCl_3}	ΔG	$Pop\%$
2	-2644.68699609	-2643.728544	-2644.73530155	0.0	40.4
1	-2644.69218238	-2643.731061	-2644.73791821	0.0	38.3
3	-2644.69273043	-2643.726661	-2644.74126282	1.0	7.5
13	-2644.69179647	-2643.727440	-2644.73921455	1.2	5.3
15	-2644.68722408	-2643.725307	-2644.73569671	1.9	1.8
6	-2644.68830318	-2643.723753	-2644.73826996	2.0	1.7
4	-2644.69067077	-2643.726560	-2644.73765846	2.1	1.4
36	-2644.68999239	-2643.728052	-2644.73515110	2.3	1.0
7c	-2644.68664102	-2643.726629	-2644.73320216	2.3	1.0
21	-2644.68281779	-2643.723289	-2644.73226715	2.6	0.6
5	-2644.68624683	-2643.723673	-2644.73469509	3.0	0.3
48c	-2644.68554976	-2643.725689	-2644.73185672	3.0	0.3
19	-2644.68489999	-2643.724086	-2644.73242209	3.3	0.2
9	-2644.68641137	-2643.723480	-2644.73370708	3.8	0.1
29	-2644.68556255	-2643.723266	-2644.73281774	4.0	0.1
17	-2644.68664154	-2643.722931	-2644.73372975	4.3	0.0
12	-2644.68599286	-2643.724920	-2644.73098164	4.4	0.0
42	-2644.68342883	-2643.720420	-2644.73258366	4.6	0.0
8	-2644.68747109	-2643.721151	-2644.73589490	4.6	0.0
18	-2644.68213438	-2643.719856	-2644.73092248	5.1	0.0
44	-2644.68197103	-2643.716164	-2644.73423200	5.3	0.0
30	-2644.68058863	-2643.717996	-2644.73095954	5.3	0.0
16	-2644.68318582	-2643.720860	-2644.73042529	5.5	0.0
11	-2644.68317107	-2643.717081	-2644.73394925	5.6	0.0
23	-2644.68047735	-2643.719414	-2644.72891948	5.6	0.0
49	-2644.67786248	-2643.714263	-2644.73106703	5.9	0.0
33c	-2644.68181786	-2643.720704	-2644.72821781	6.1	0.0
10	-2644.68840009	-2643.721717	-2644.73344859	6.3	0.0
14	-2644.6871915	-2643.721810	-2644.73188780	6.5	0.0
55	-2644.67456623	-2643.714100	-2644.72646804	6.8	0.0
38	-2644.67866302	-2643.716416	-2644.72806146	6.9	0.0
45	-2644.68465842	-2643.720296	-2644.73015004	6.9	0.0
39	-2644.67931606	-2643.718411	-2644.72658773	7.0	0.0
34	-2644.67954929	-2643.716430	-2644.72874308	7.0	0.0
51	-2644.68007288	-2643.716644	-2644.72876918	7.2	0.0
41	-2644.67989286	-2643.715497	-2644.72957564	7.3	0.0
47	-2644.66677457	-2643.708734	-2644.72214856	8.0	0.0
20	-2644.68387582	-2643.715650	-2644.73180148	8.3	0.0
22c	-2644.68603818	-2643.719605	-2644.72995857	8.4	0.0
25	-2644.68093092	-2643.717417	-2644.72703656	8.4	0.0

31	-2644.6822678	-2643.717565	-2644.72820256	8.4	0.0
53	-2644.66985637	-2643.709825	-2644.72308257	8.7	0.0
26	-2644.6848354	-2643.718215	-2644.72934691	8.9	0.0
35c	-2644.67599832	-2643.715935	-2644.72274123	8.9	0.0
54	-2644.67203954	-2643.711219	-2644.72328760	9.0	0.0
40	-2644.6704656	-2643.711772	-2644.72102136	9.1	0.0
27	-2644.67571738	-2643.711273	-2644.72530966	10.0	0.0
37	-2644.67493904	-2643.710936	-2644.72473439	10.1	0.0
24	-2644.67310522	-2643.708253	-2644.72551838	10.2	0.0
43	-2644.67452023	-2643.711053	-2644.72389976	10.3	0.0
28	-2644.67252849	-2643.709870	-2644.72160322	11.2	0.0
46	-2644.66888856	-2643.706041	-2644.72114960	11.6	0.0
32	-2644.67932466	-2643.713084	-2644.72421571	11.8	0.0
50	-2644.67477119	-2643.709797	-2644.72271710	12.0	0.0
52	-2644.66830324	-2643.703964	-2644.71972771	13.5	0.0

In order to show that the computational ensemble conforms the NMR data, the distances originally obtained from the NOESY data are plotted against the original constrains. Note that while in the original Monte-Carlo conformational search, these constrains were in place, but there **were not** during DFT optimization.

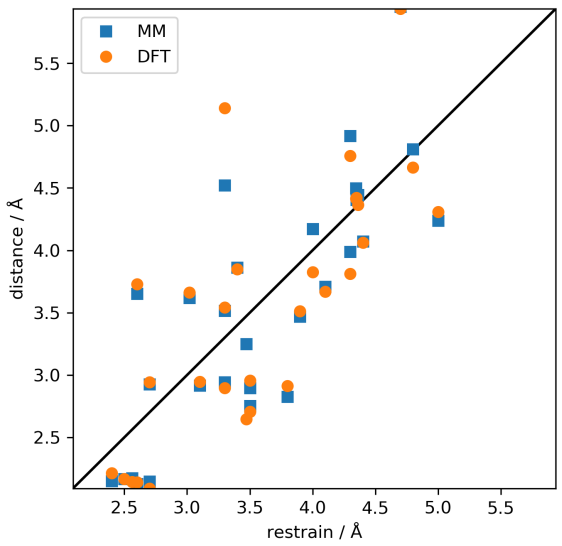


Figure S25: Distances for conformer 2.

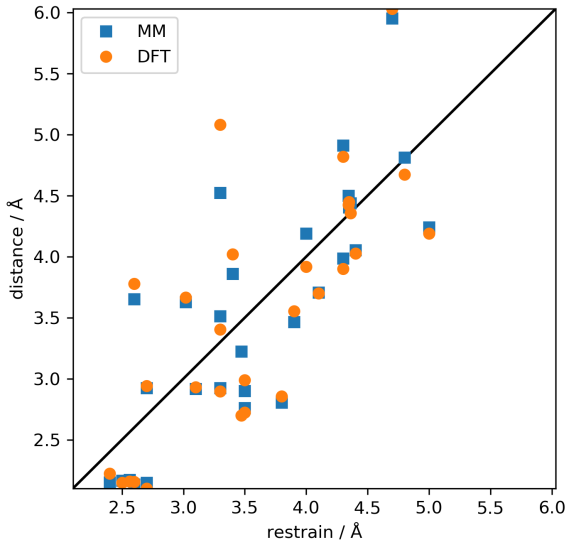


Figure S26: Distances for conformer 1.

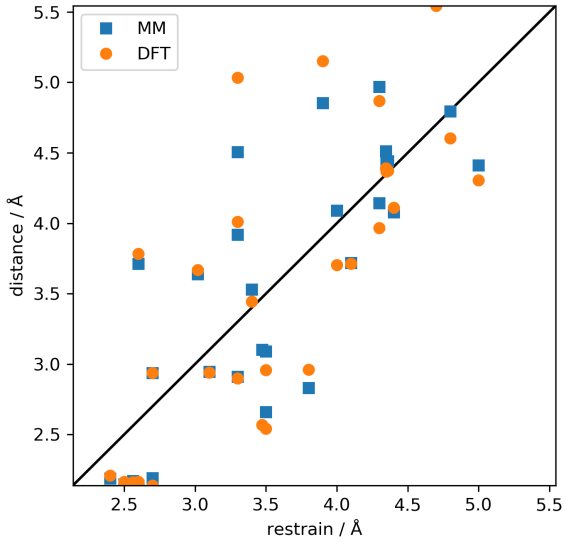


Figure S27: Distances for conformer 3.

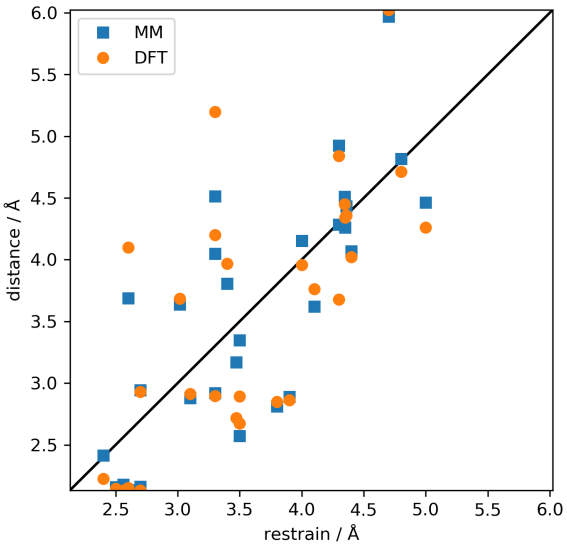


Figure S28: Distances for conformer 13.

Table S21: Weighted average diehedral angles for the 9 lowest energy foldamer conformers of **21**.

conf:	**conf1**	**conf1 x pop.**	**conf2**	**conf2 x pop.**	**conf3**	**conf3 x pop.**	**conf4**	**conf4 x pop.**
Residue 1								
phi	44	16.97	69	28.04	-139	-10.48	133	1.88
theta	38	14.75	52	21.03	-63	-4.70	54	0.77
zeta	46	17.58	41	16.58	-17	-1.29	36	0.50
psi	-108	-41.57	-100	-40.83	-108	-8.12	-142	-2.00
Residue 2		0.00		0.00		0.00		0.00
phi	-68	-26.03	-76	-30.73	-83	-6.25	-78	-1.09
psi	134	51.72	130	52.73	131	9.87	154	2.17
Residue 3		0.00		0.00		0.00		0.00
phi	61	23.46	64	26.16	57	4.26	55	0.78
theta	44	17.10	45	18.26	45	3.41	36	0.50
zeta	42	16.22	42	17.07	45	3.40	42	0.59
psi	-120	-46.24	-121	-49.24	-112	-8.41	-129	-1.82
Residue 4		0.00		0.00		0.00		0.00
phi	-72	-27.76	-75	-30.31	-81	-6.11	-68	-0.96
psi	142	54.60	145	58.80	144	10.85	144	2.03
Residue 5		0.00		0.00		0.00		0.00
phi	59	22.90	60	24.53	58	4.38	58	0.82
theta	48	18.53	45	18.44	46	3.45	47	0.67
zeta	29	11.09	28	11.54	30	2.24	29	0.42
psi	-118	-45.61	-124	-50.25	-124	-9.30	-118	-1.67
Residue 6		0.00		0.00		0.00		0.00
phi	-65	-24.86	-65	-26.28	-65	-4.88	-64	-0.91
psi*	133	51.33	152	61.93	134	10.07	133	1.87
Population	38.52%		40.64%		7.52%		1.41%	

Table S22: Weighted average diehedral angles for the 9 lowest energy foldamer conformers of **21**.

conf:	**conf6**	**conf6 x pop.**	**conf7c**	**conf7c x pop.**	**conf13**	**conf13 x pop.**	**conf15**	**conf15 x pop.**
Residue 1								
phi	-138	-2.32	44	0.43	-98	-5.23	-122	-2.17
theta	-62	-1.05	35	0.34	-88	-4.70	-60	-1.08
zeta	-18	-0.30	46	0.45	51	2.71	-25	-0.45
psi	-108	-1.81	-110	-1.08	-100	-5.34	-95	-1.69
Residue 2		0.00		0.00		0.00		0.00
phi	-82	-1.38	-65	-0.64	-76	-4.04	-77	-1.37
psi	131	2.20	142	1.39	145	7.77	149	2.66
Residue 3		0.00		0.00		0.00		0.00
phi	56	0.94	59	0.57	61	3.28	57	1.02
theta	46	0.77	41	0.40	36	1.93	37	0.67
zeta	46	0.77	42	0.41	43	2.29	42	0.75
psi	-110	-1.84	-122	-1.20	-127	-6.81	-128	-2.27
Residue 4		0.00		0.00		0.00		0.00
phi	-84	-1.42	-71	-0.70	-69	-3.67	-70	-1.25
psi	143	2.41	143	1.41	143	7.65	145	2.58
Residue 5		0.00		0.00		0.00		0.00
phi	60	1.01	59	0.58	58	3.13	58	1.03
theta	45	0.75	47	0.46	48	2.55	47	0.84
zeta	30	0.50	29	0.28	29	1.57	29	0.52
psi	-128	-2.15	-120	-1.17	-118	-6.31	-118	-2.11
Residue 6		0.00		0.00		0.00		0.00
phi	-66	-1.11	-60	-0.59	-64	-3.45	-64	-1.14
psi*	154	2.58	131	1.28	133	7.11	133	2.37
Population	1.68%		0.98%		5.35%		1.78%	

Table S23: Weighted average diehedral angles for the 9 lowest energy foldamer conformers of **21**.

conf:	**conf36**	**conf36 x pop.**	**weighted average**
Residue 1			
phi	-115	-1.15	**25.96**
theta	62	0.62	**9.65**
zeta	-53	-0.53	**35.25**
psi	-60	-0.60	**-103.04**
Residue 2		0.00	
phi	-128	-1.28	**-72.81**
psi	-179	-1.79	**128.71**
Residue 3		0.00	
phi	64	0.64	**61.11**
theta	46	0.46	**43.49**
zeta	38	0.38	**41.88**
psi	-119	-1.19	**-119.01**
Residue 4		0.00	
phi	-67	-0.67	**-72.83**
psi	142	1.42	**141.74**
Residue 5		0.00	**0.00**
phi	59	0.59	**58.97**
theta	48	0.48	**46.17**
zeta	29	0.29	**28.44**
psi	-117	-1.17	**-119.73**
Residue 6		0.00	**0.00**
phi	-65	-0.65	**-63.87**
psi*	132	1.32	**139.87**
Population	1.00%		

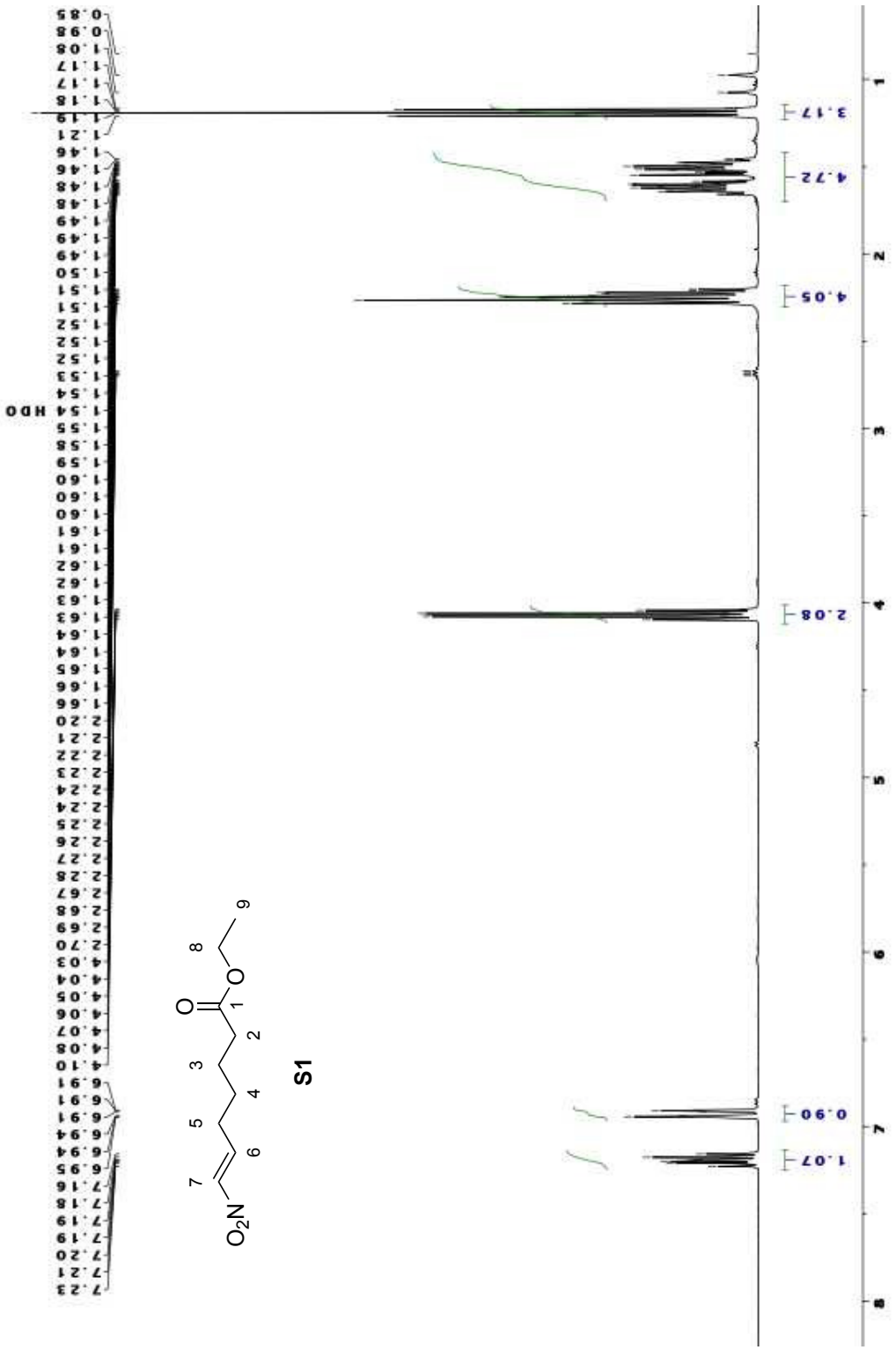
Cyclopentane ring molecular simulation

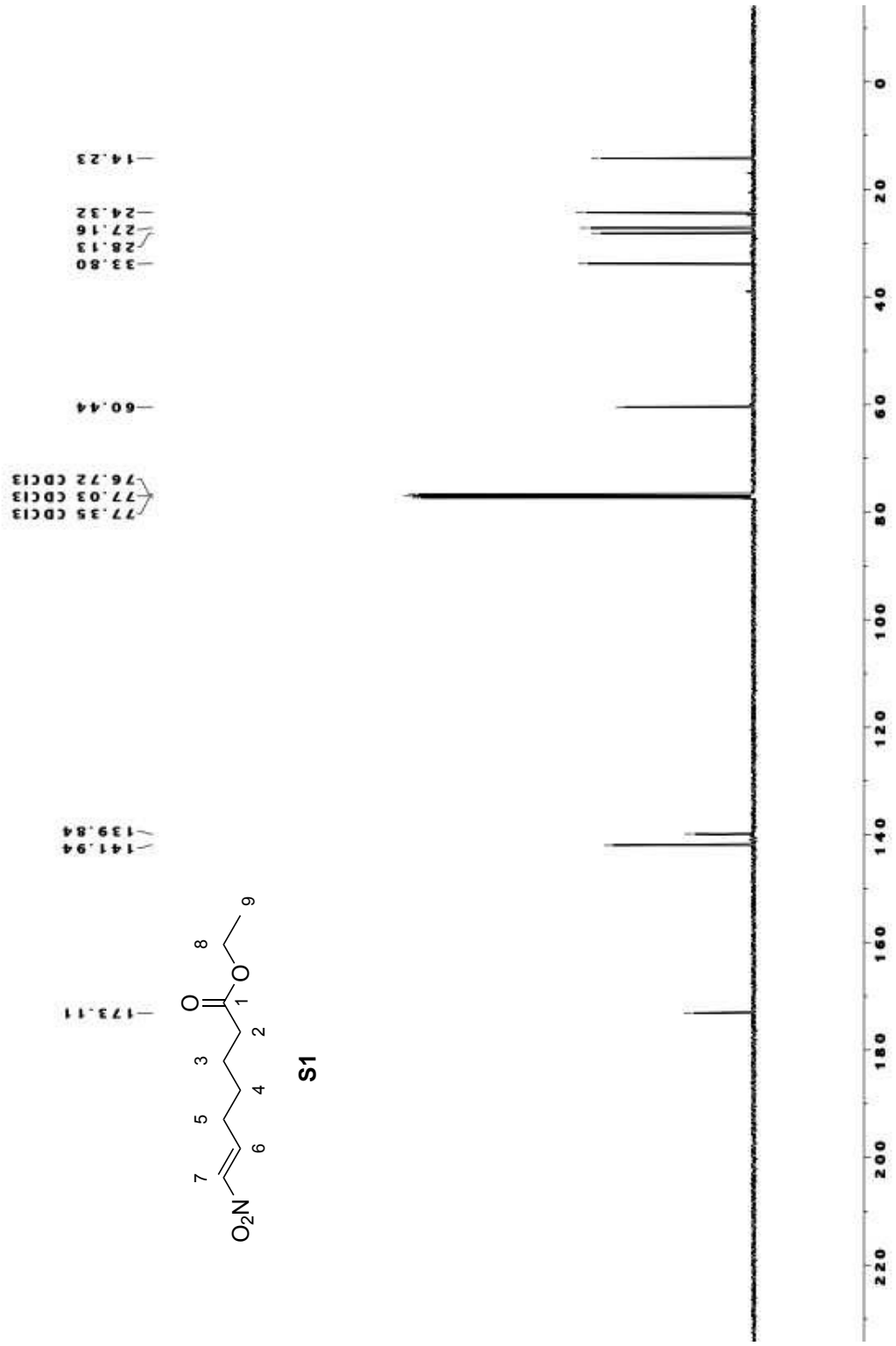
To understand why this might be the case, we performed molecular simulations at the ωB97XD/6-311G** level on the cyclopentane ring. In these calculations, it was shown that as expected, this will form an envelope conformation - i.e. one of the five ring carbons is always above or below the plane of the other four atoms. The values for ζ vary dependent on which bond of the ring is part of the sequence. In other words, it is different for all five pseudorotation states and the cyclopentane system must therefore select one of these (Table S24).

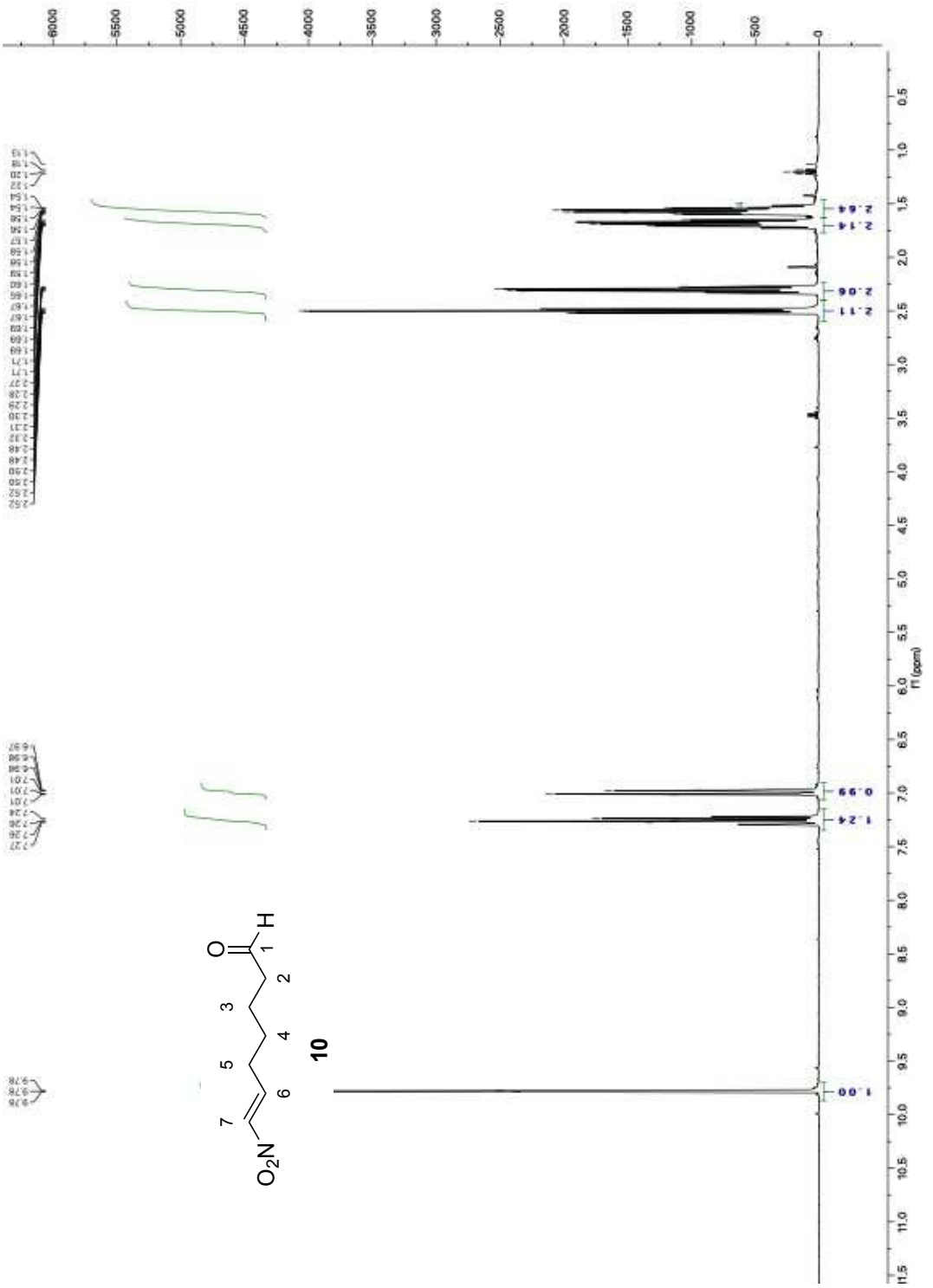
Table S24: ζ-Angles for the internal ring torsions of the five-membered ring envelope.

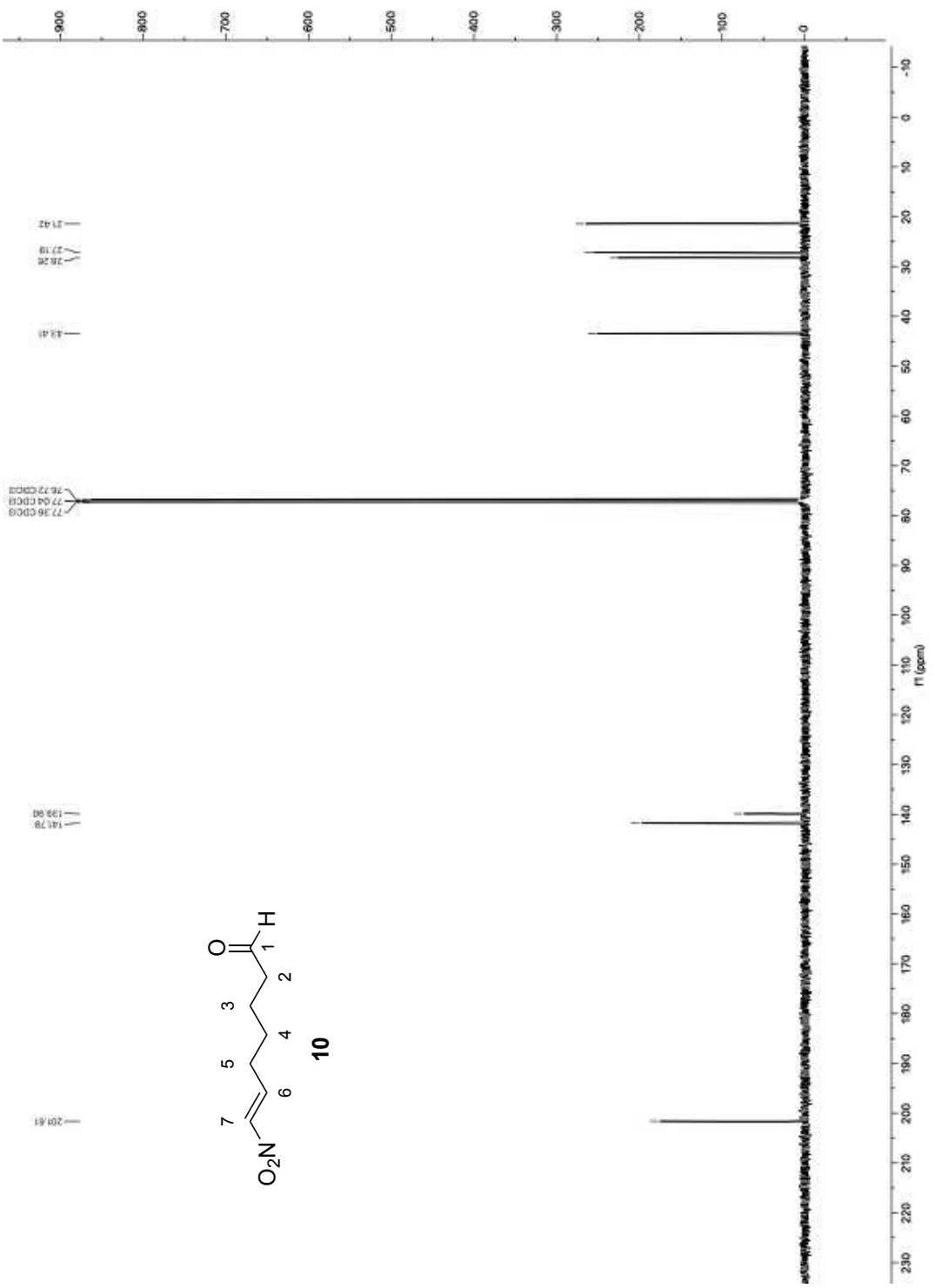
Internal Ring Torsions	*cis*		*trans*	
	(1S,2R)	*(1R,2S)*	*(1S,2S)*	*(1R,2R)*
0	0	0	118.8	-118.8
-24.5	-30.0	-28.6	89.8	-148.3
39.9	44.7	45.7	165.1	-74.7
-39.9	-44.8	-45.7	74.7	-165.2
24.6	30.0	28.8	148.6	-89.7

Spectra



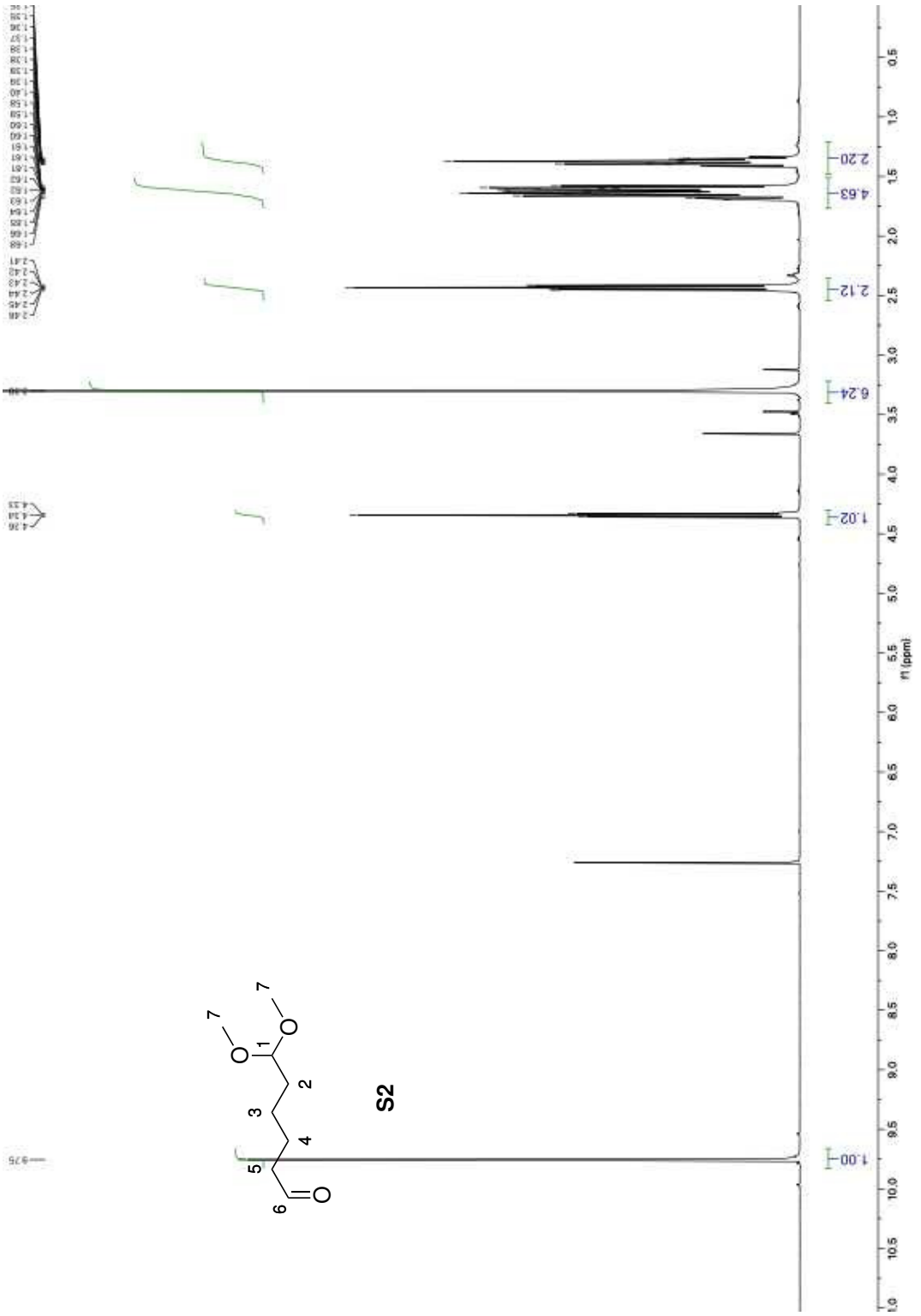

173.11
141.94
139.84
77.35 CDCl3
77.03 CDCl3
76.72 CDCl3
60.44
33.80
28.13
27.16
24.32
14.23
S1

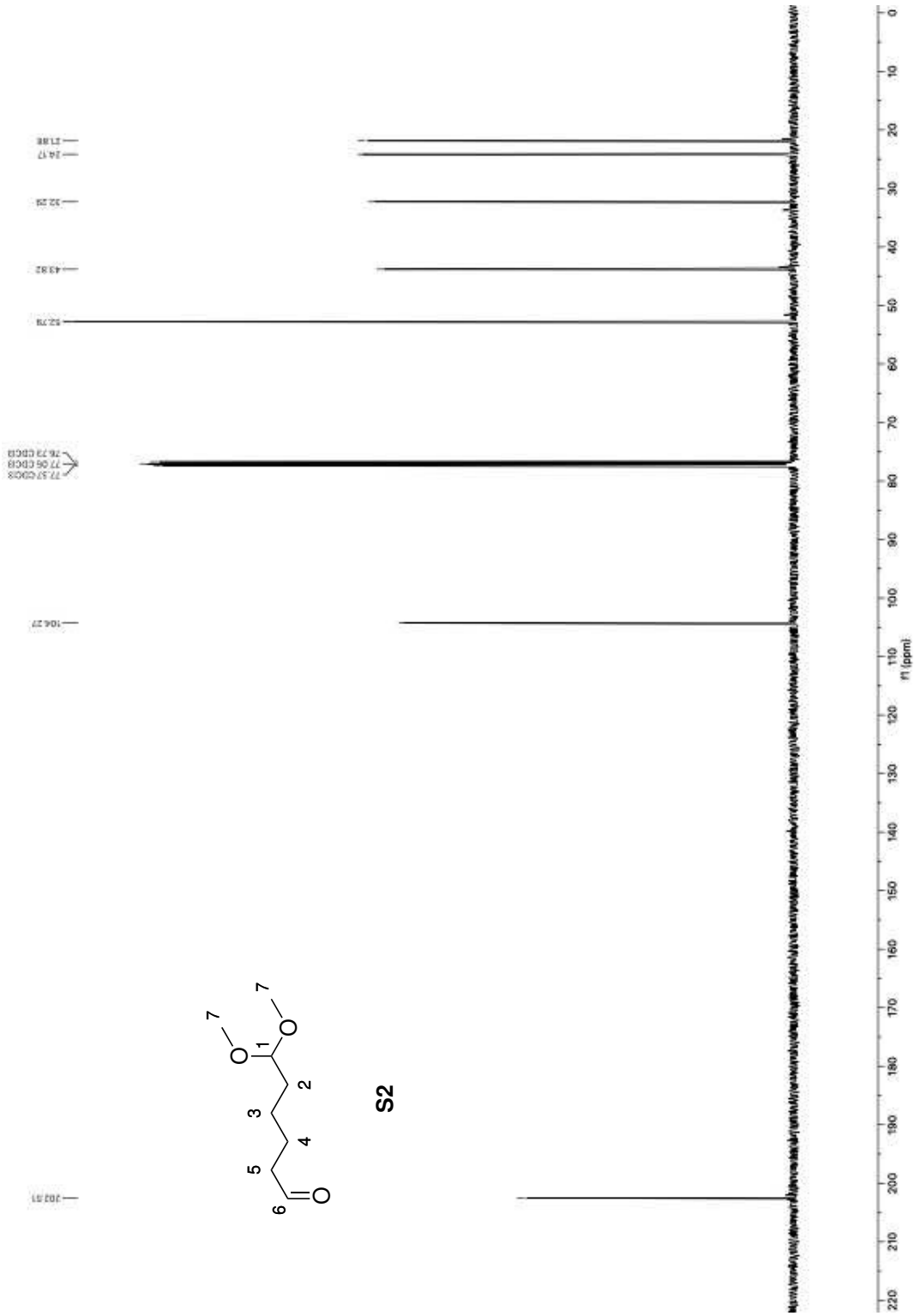

O
H
1
2
3
4
5
6
7
O_2N
10
2.64
2.14
2.06
2.11
0.99
1.24
1.00
f1 (ppm)

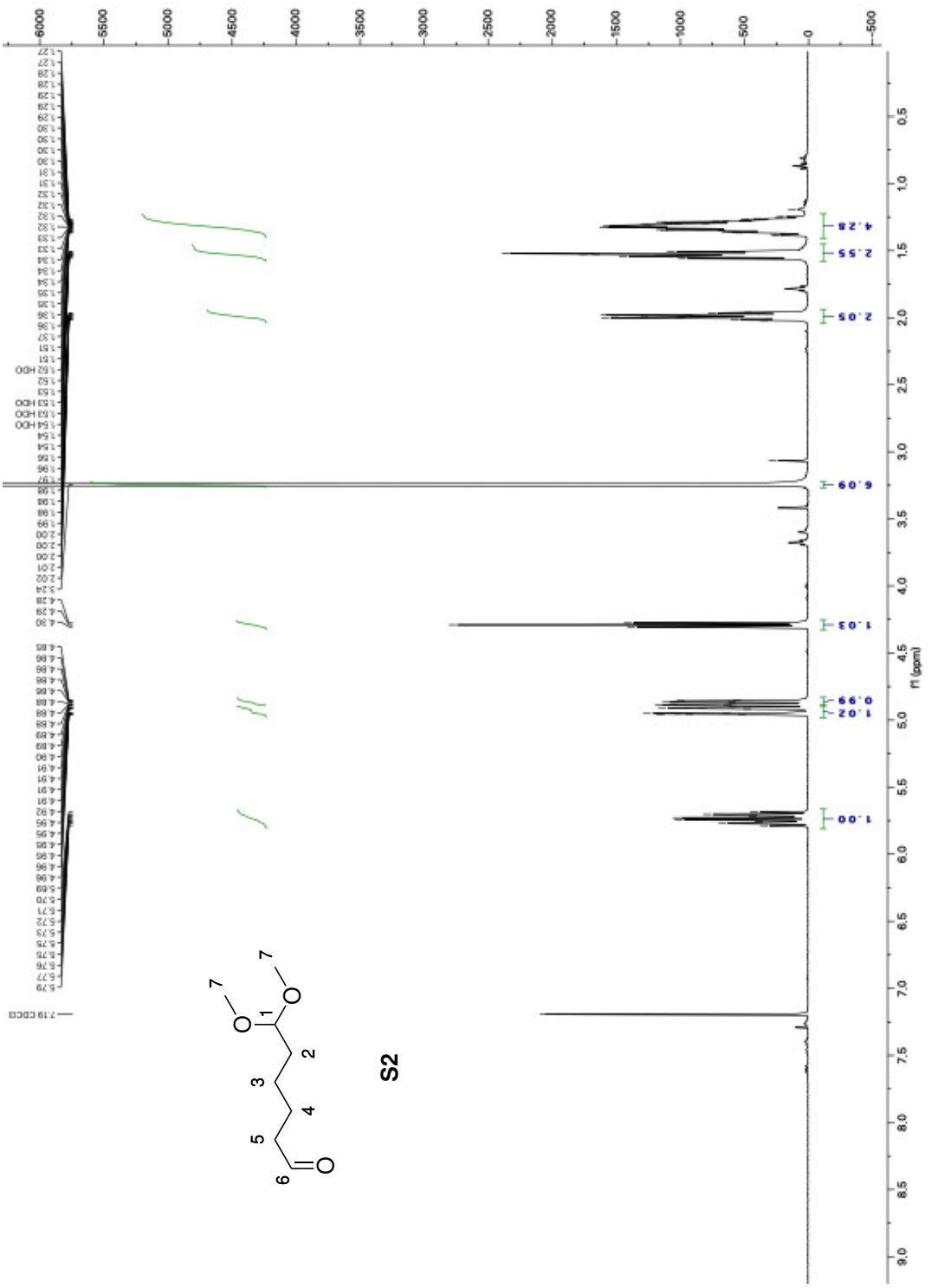

21.42
27.19
28.26
43.41
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
139.80
141.78
209.61
f1 (ppm)

O
H
1
2
3
4
5
6
7
O2N

10


S2
2.20
4.63
2.12
6.24
1.02
1.00
f1 (ppm)


S2
f1 (ppm)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f1 (ppm)
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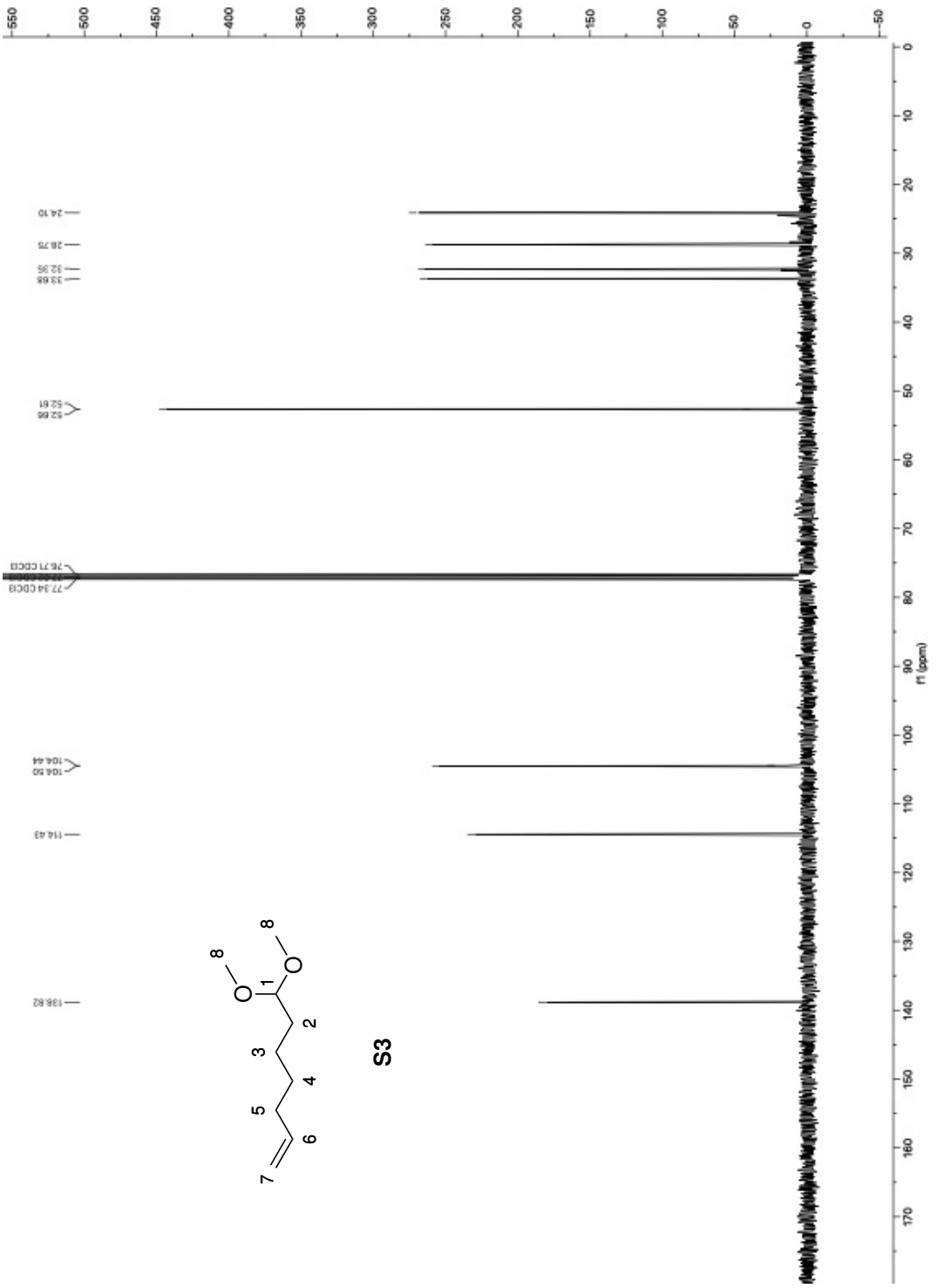
2.55
2.05
6.09
1.03
0.99
1.02
1.00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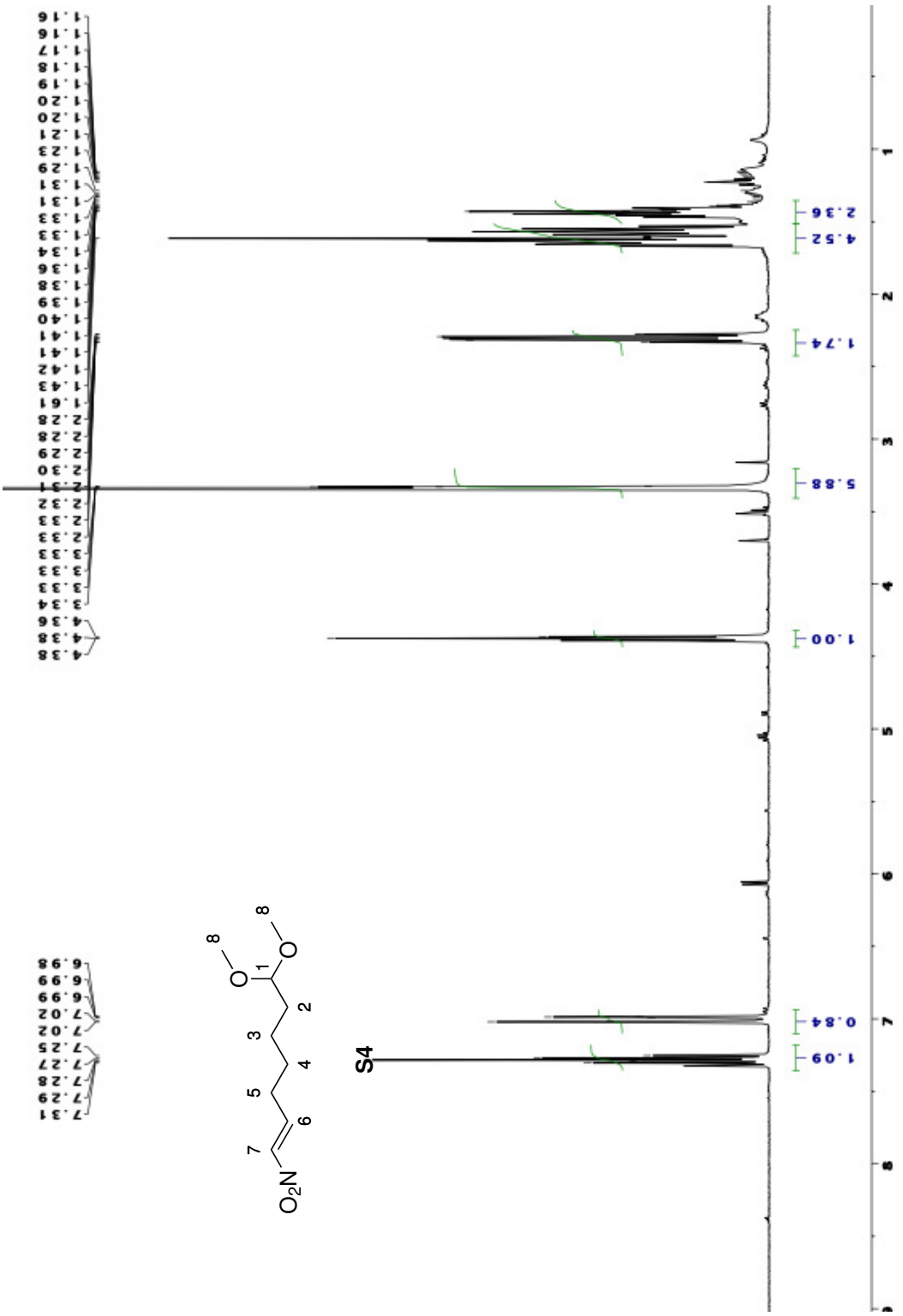
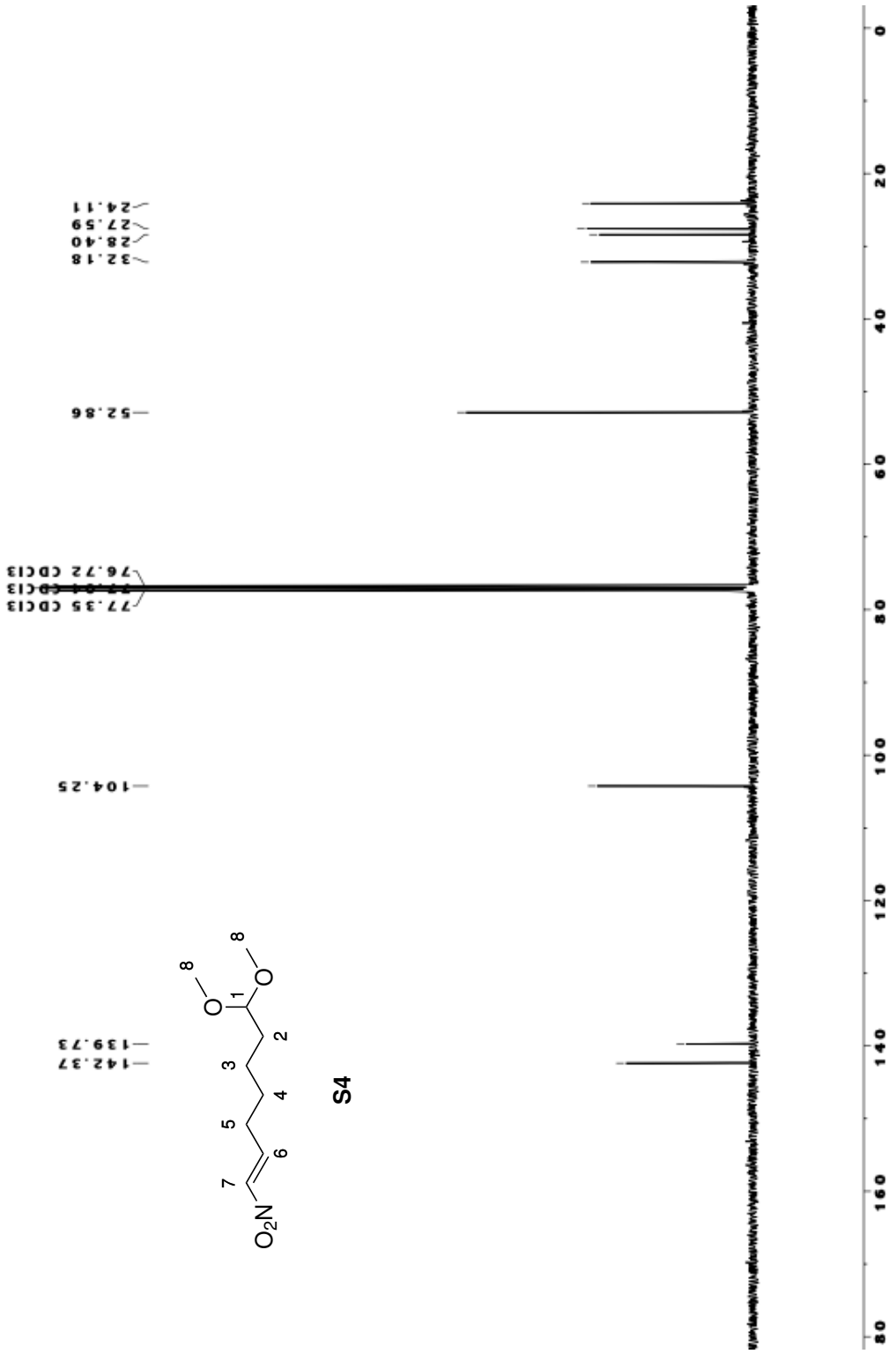
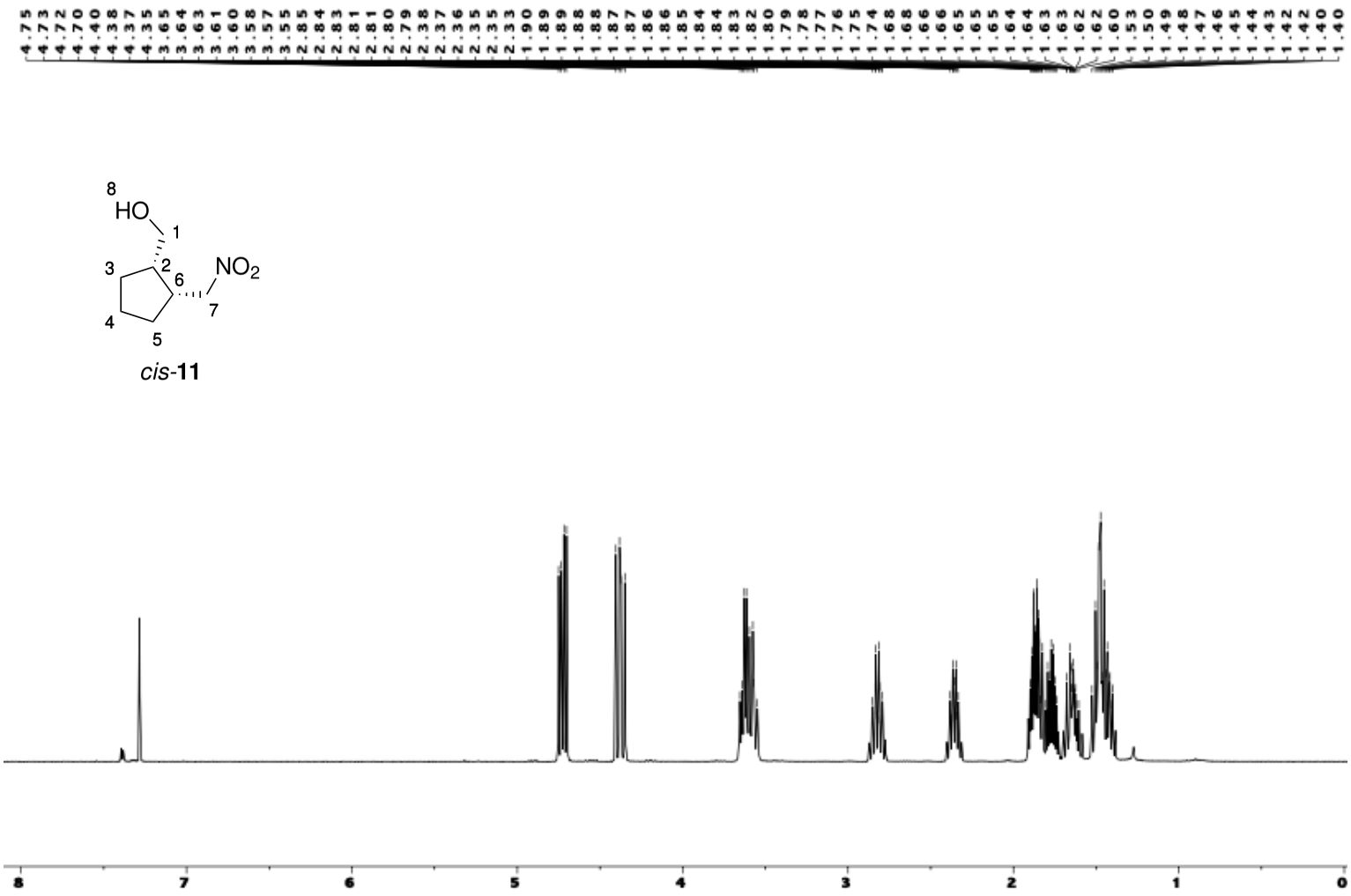
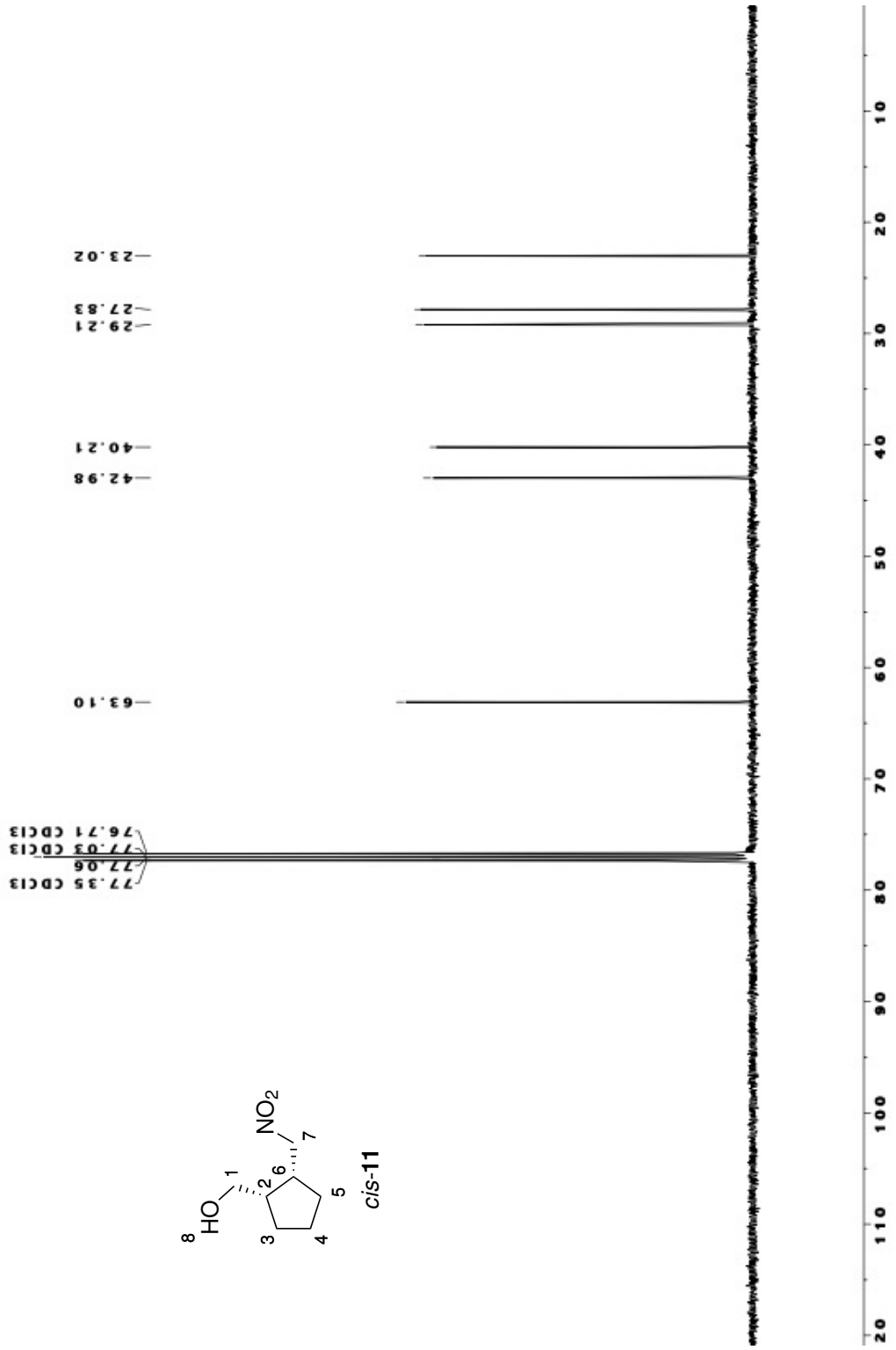
28.75
32.85
33.68
52.66
52.81
76.71 CDCl3
77.34 CDCl3
78.00 CDCl3
104.50
104.44
114.43
138.82
f1 (ppm)
S3

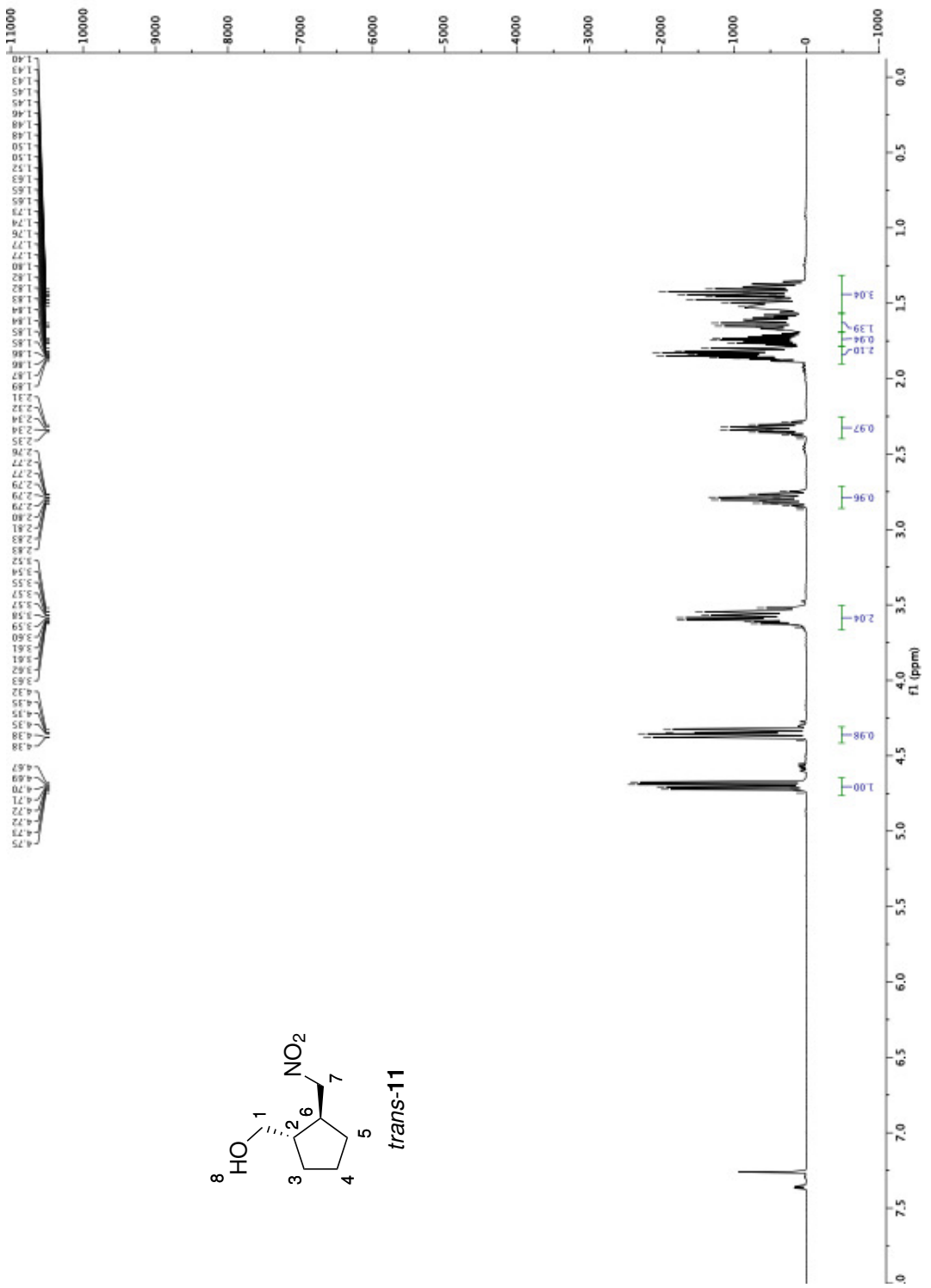

S4
O
O
O2N
1
2
3
4
5
6
7
8
8
2.36
4.52
1.74
5.88
1.00
0.84
1.09


142.37
139.73
104.25
77.35 CDCl3
76.72 CDCl3
52.86
32.18
28.40
27.59
24.11
S4

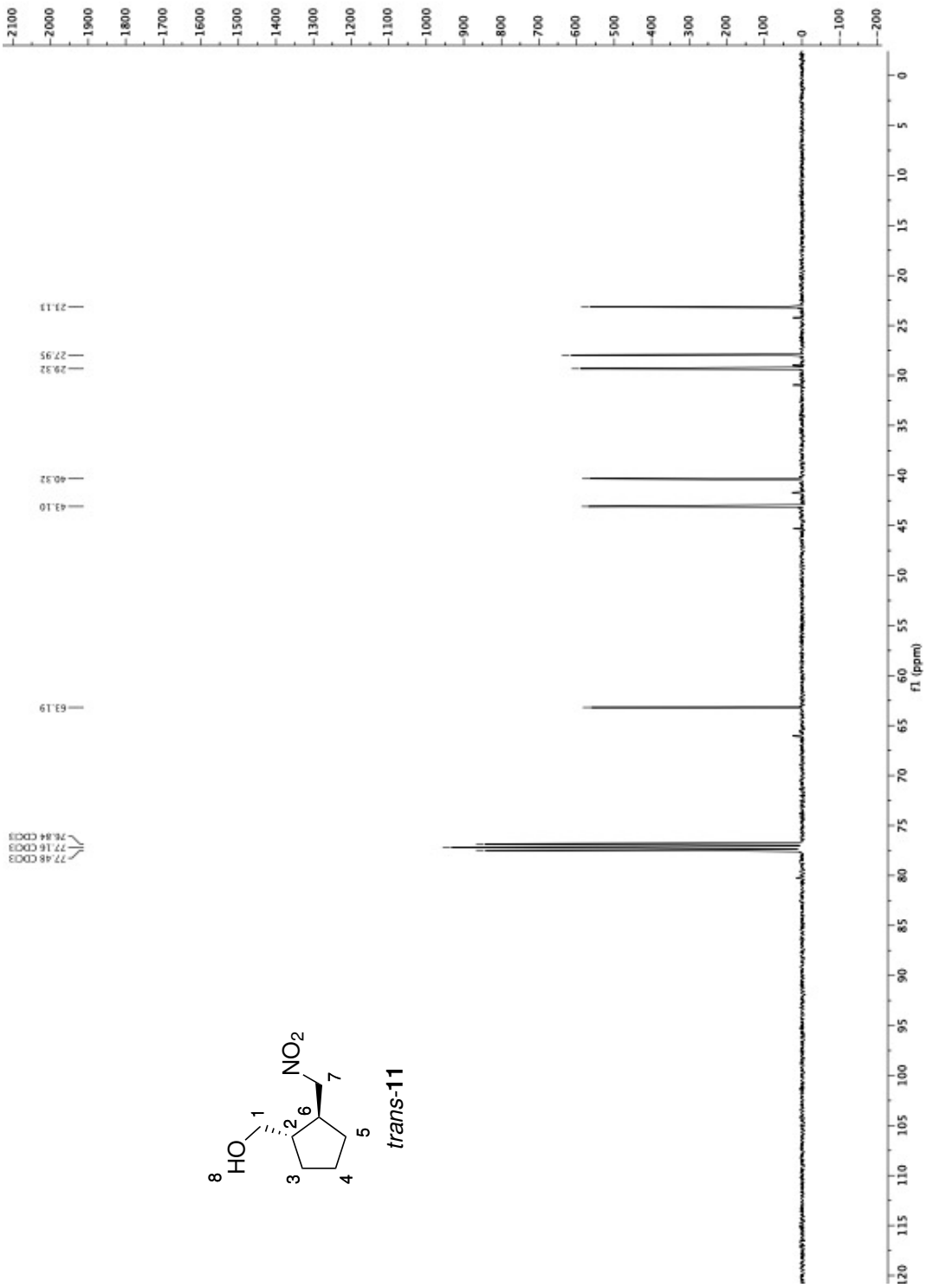

4.75 4.73 4.72 4.70 4.40 4.38 4.37 4.35 3.65 3.64 3.63 3.61 3.60 3.58 3.57 3.55 2.85 2.84 2.83 2.81 2.80 2.79 2.38 2.37 2.36 2.35 2.33 1.90 1.89 1.89 1.88 1.88 1.87 1.87 1.86 1.86 1.85 1.84 1.84 1.83 1.82 1.80 1.79 1.78 1.77 1.76 1.75 1.74 1.68 1.68 1.66 1.66 1.65 1.65 1.65 1.64 1.64 1.63 1.63 1.62 1.62 1.60 1.53 1.50 1.49 1.48 1.47 1.46 1.45 1.44 1.43 1.42 1.42 1.40 1.40
HO
NO2
8
1
2
3
4
5
6
7
8 7 6 5 4 3 2 1 0

cis-**11**


23.02
27.83
29.21
40.21
42.98
63.10
76.71 CDCl3
77.03 CDCl3
77.06
77.35 CDCl3
HO
NO2
cis-11



trans-**11**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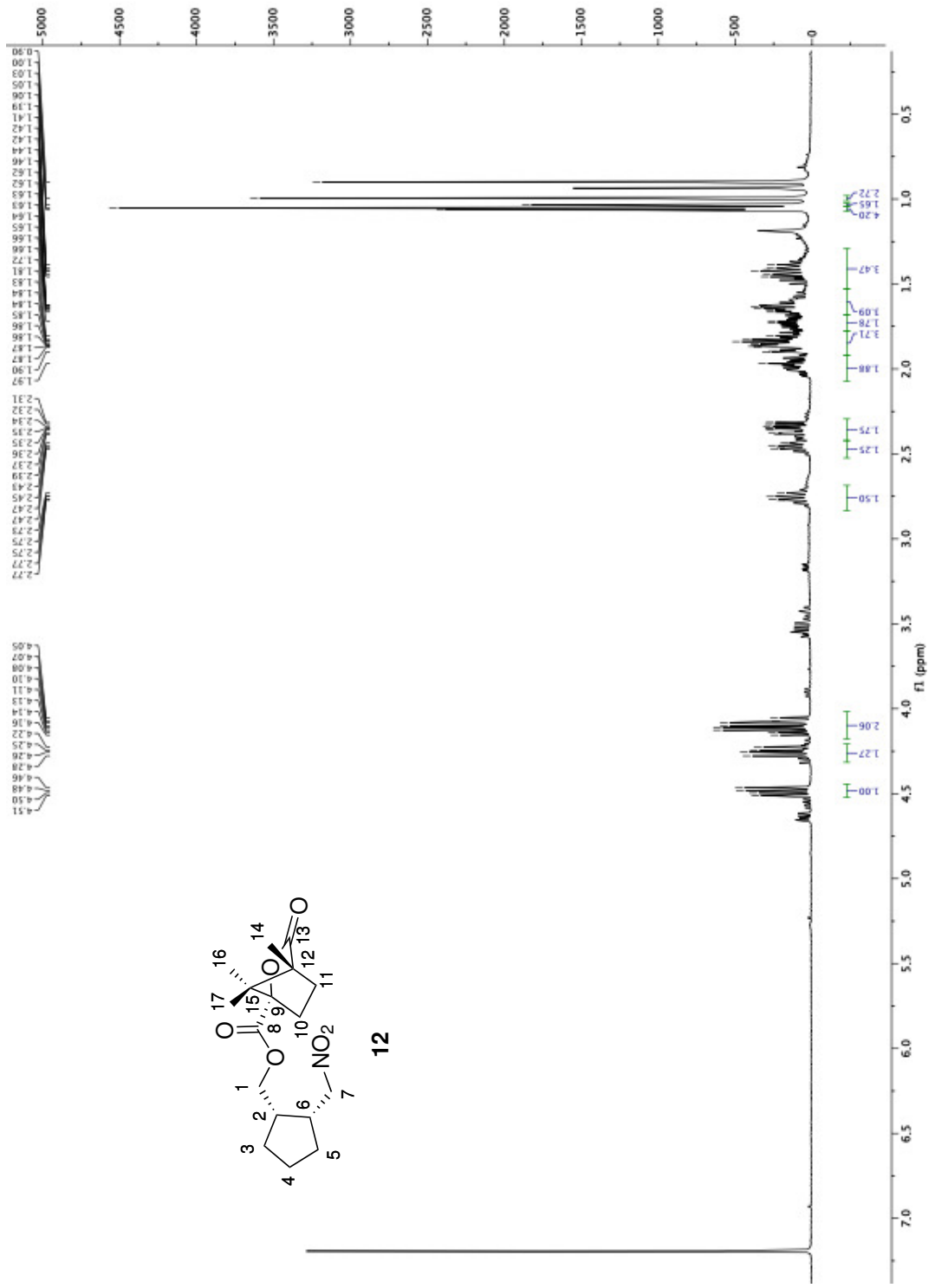
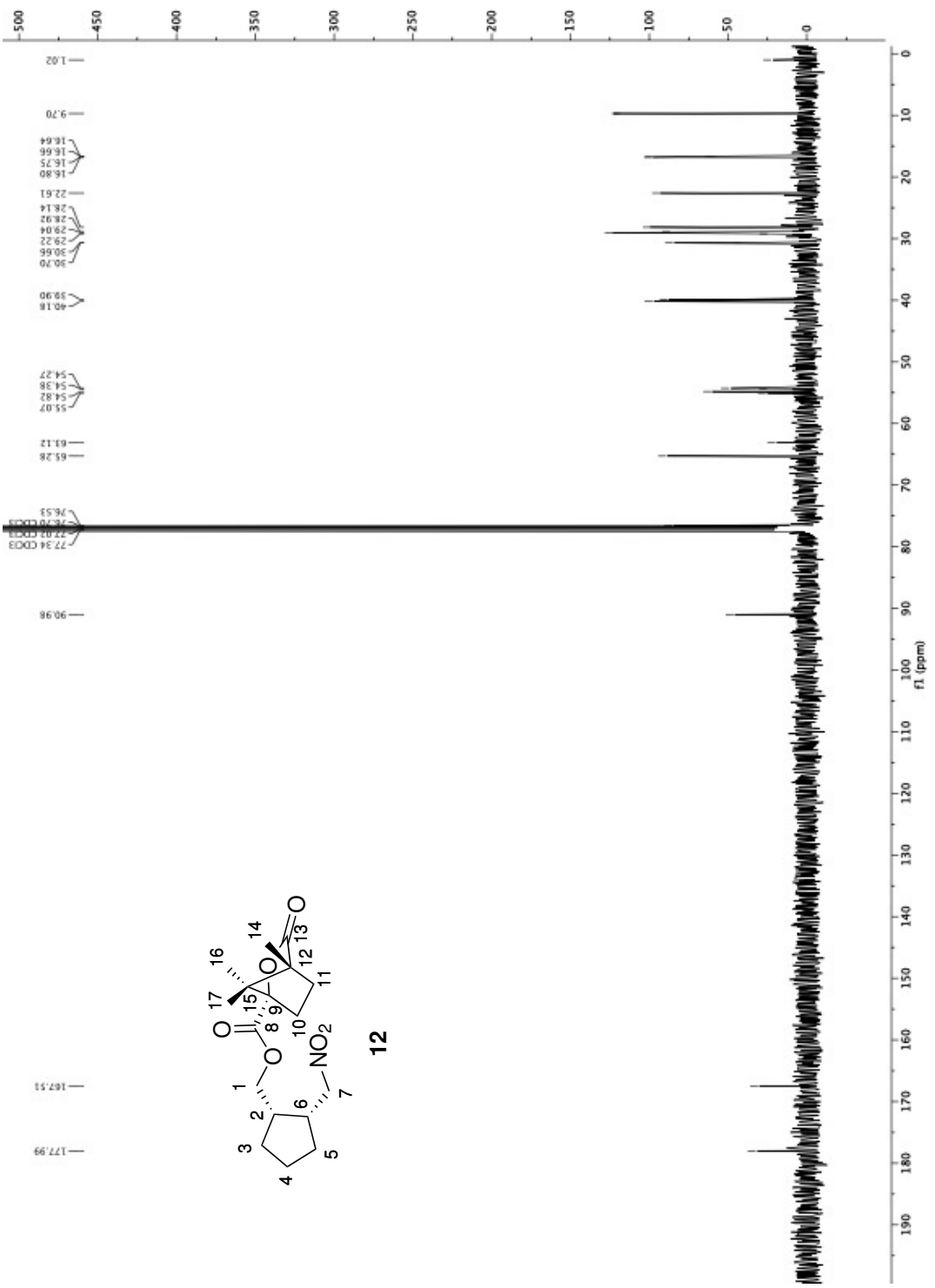
trans-11



12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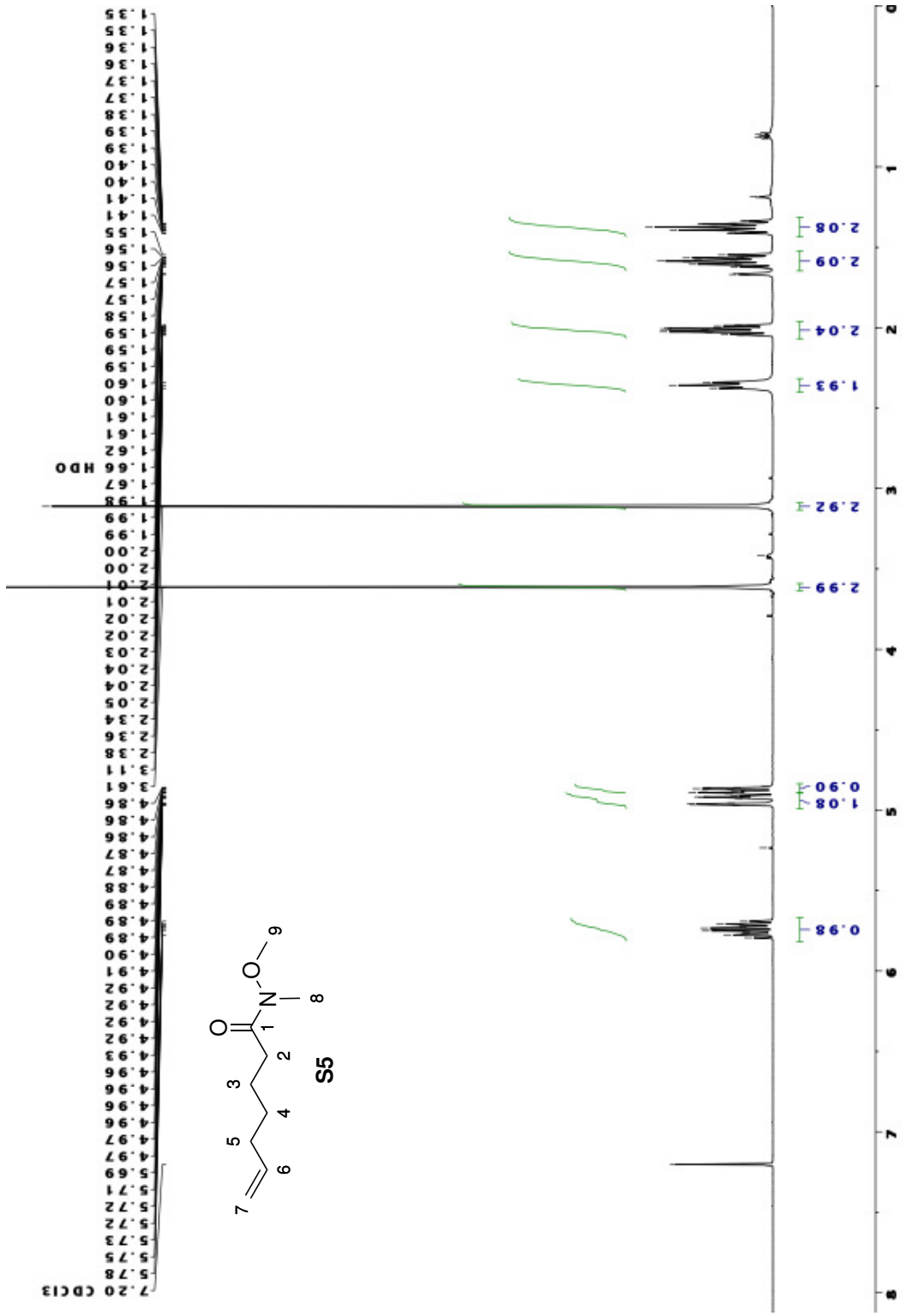
12


CDCl3
HDO
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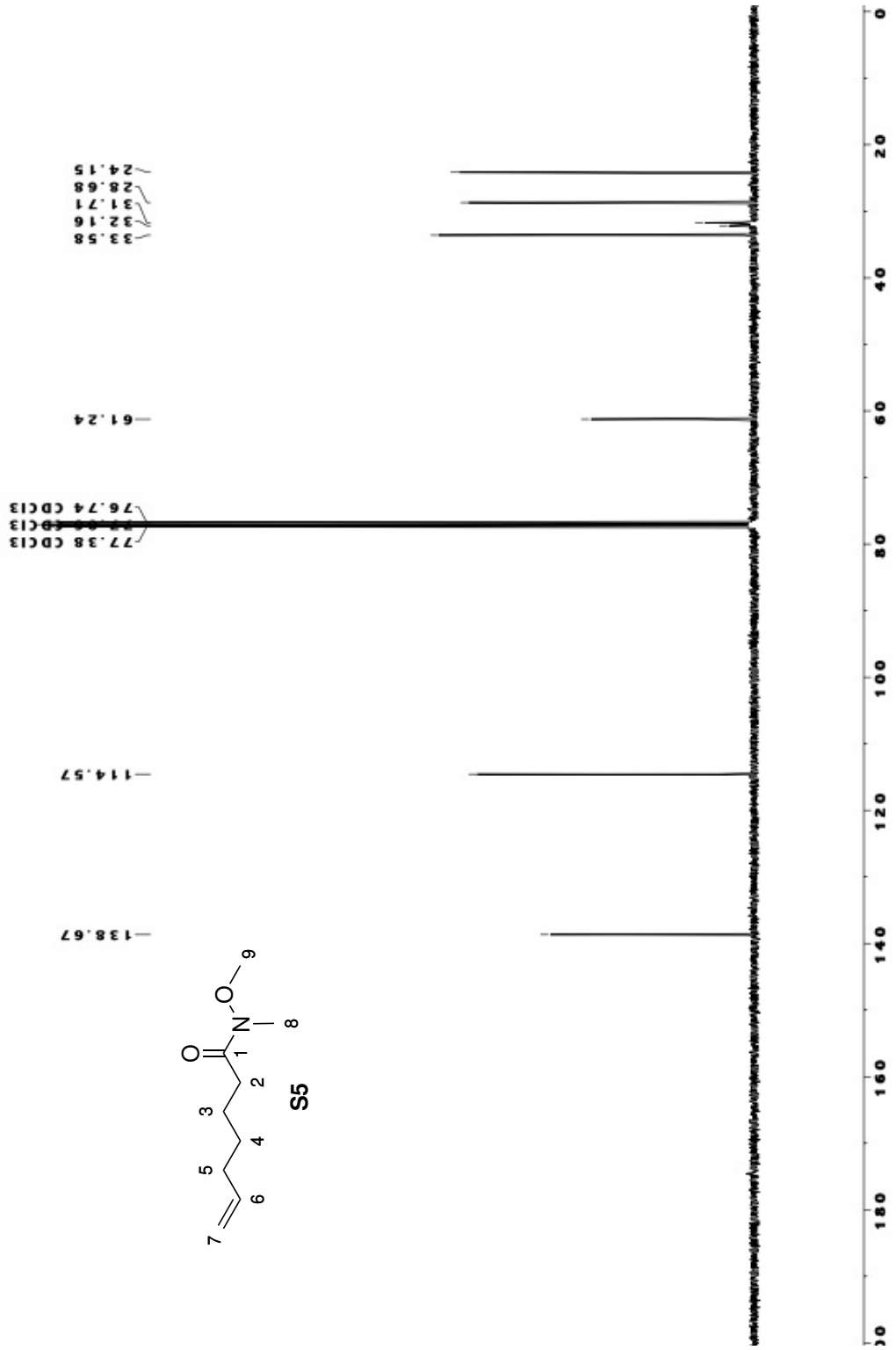
2.09
2.04
1.93
2.92
2.99
1.08
0.90
0.98
S5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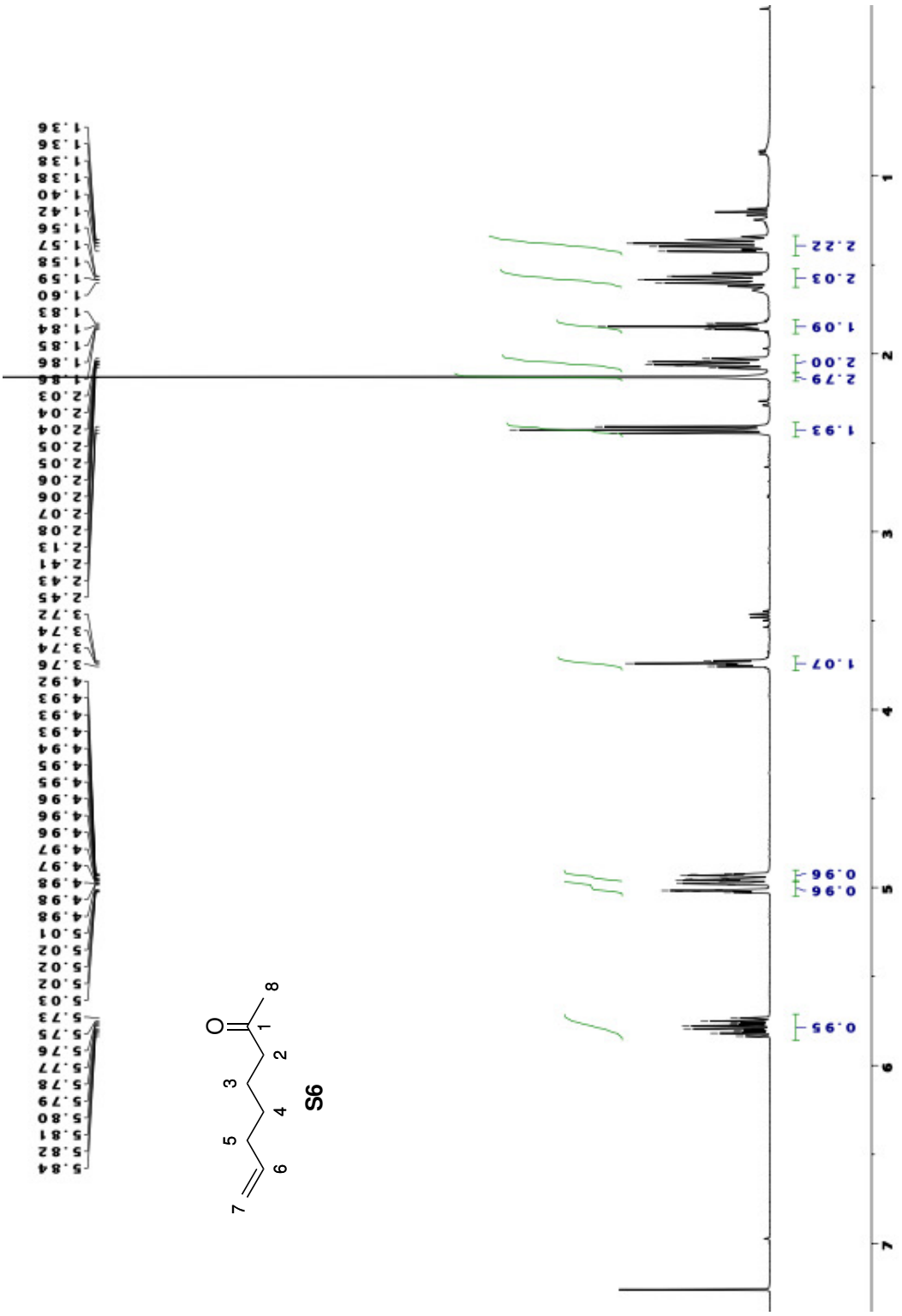
76.74 CDCl3
61.24
33.58
32.16
31.71
28.68
24.15
S5


S6
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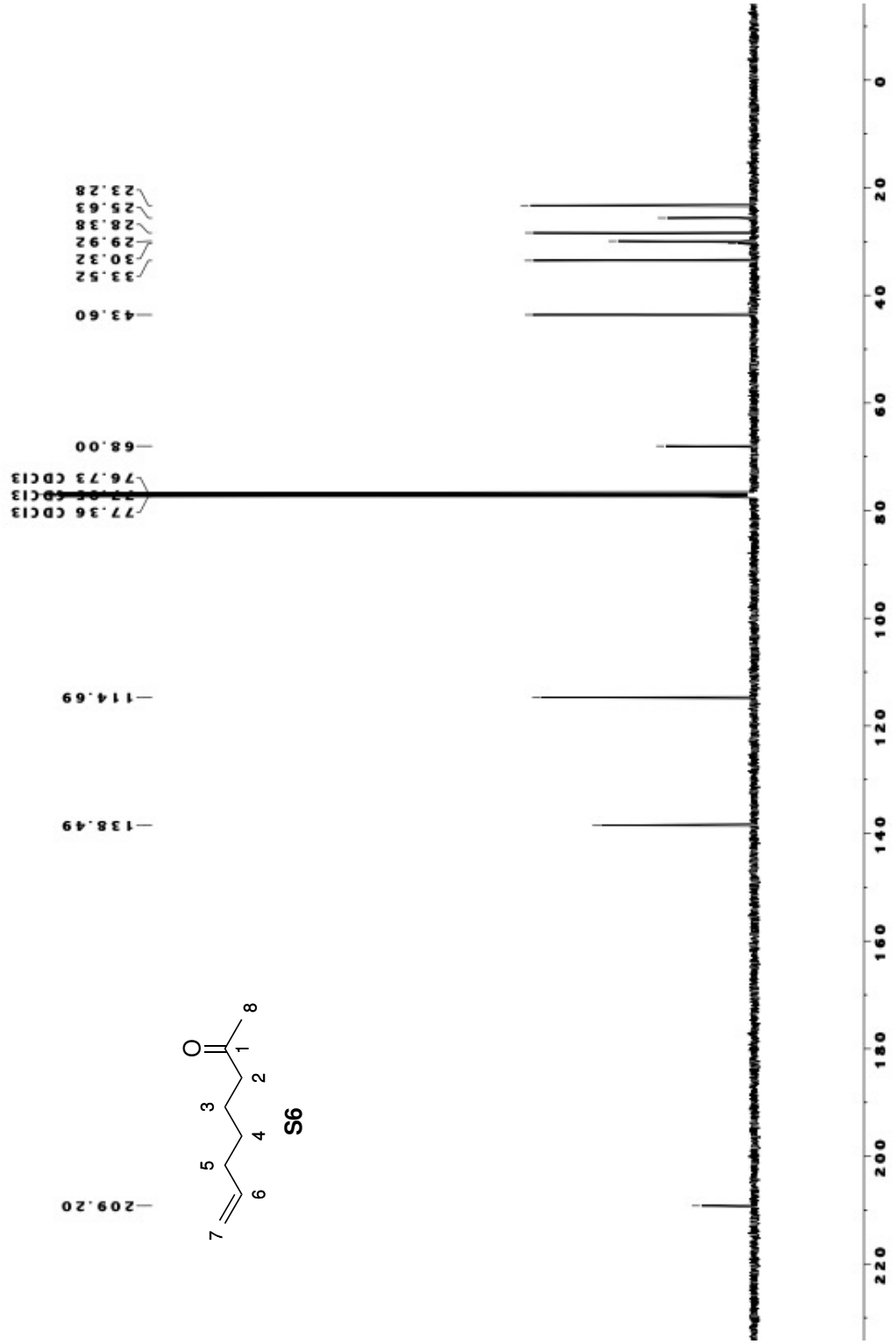
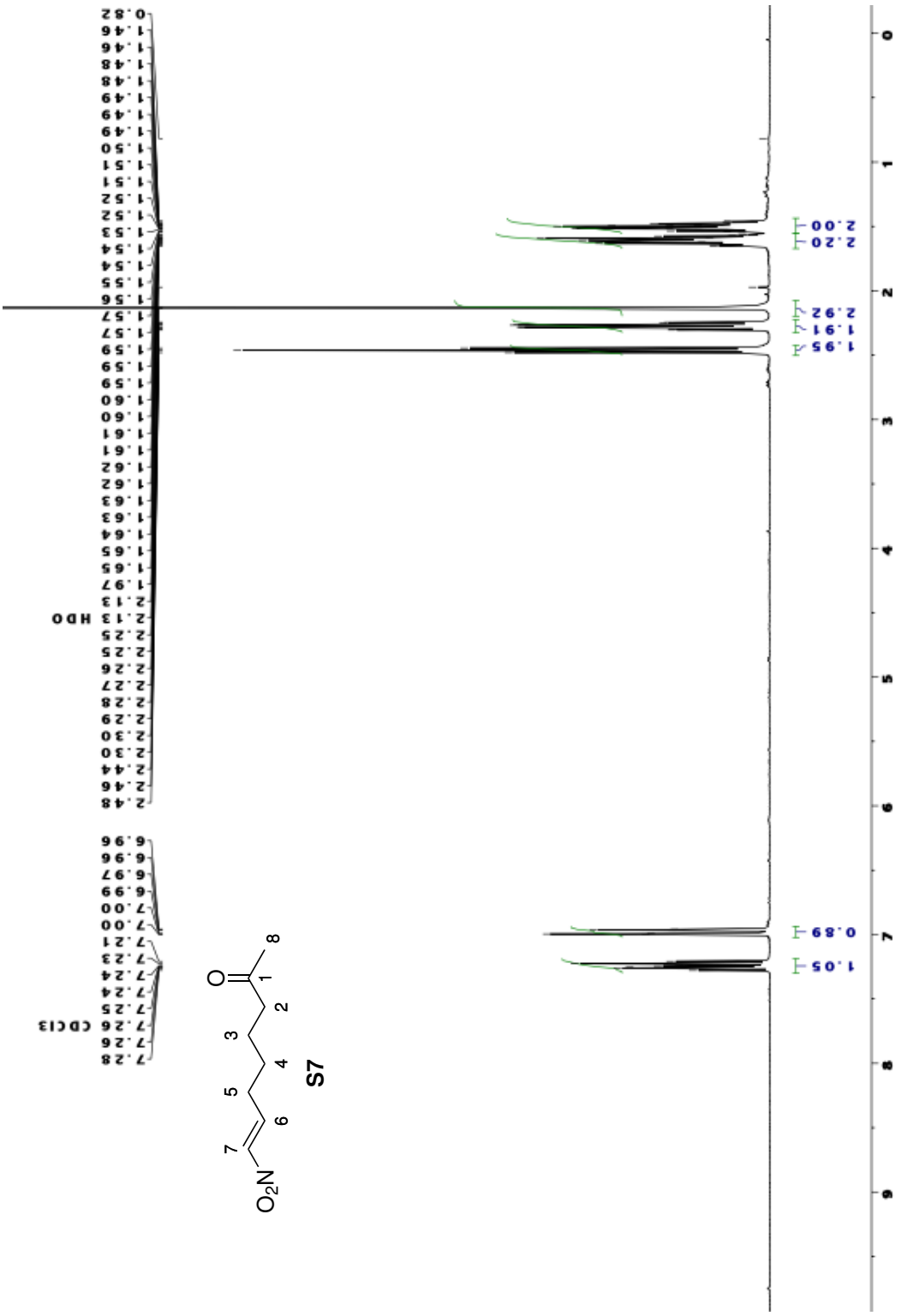
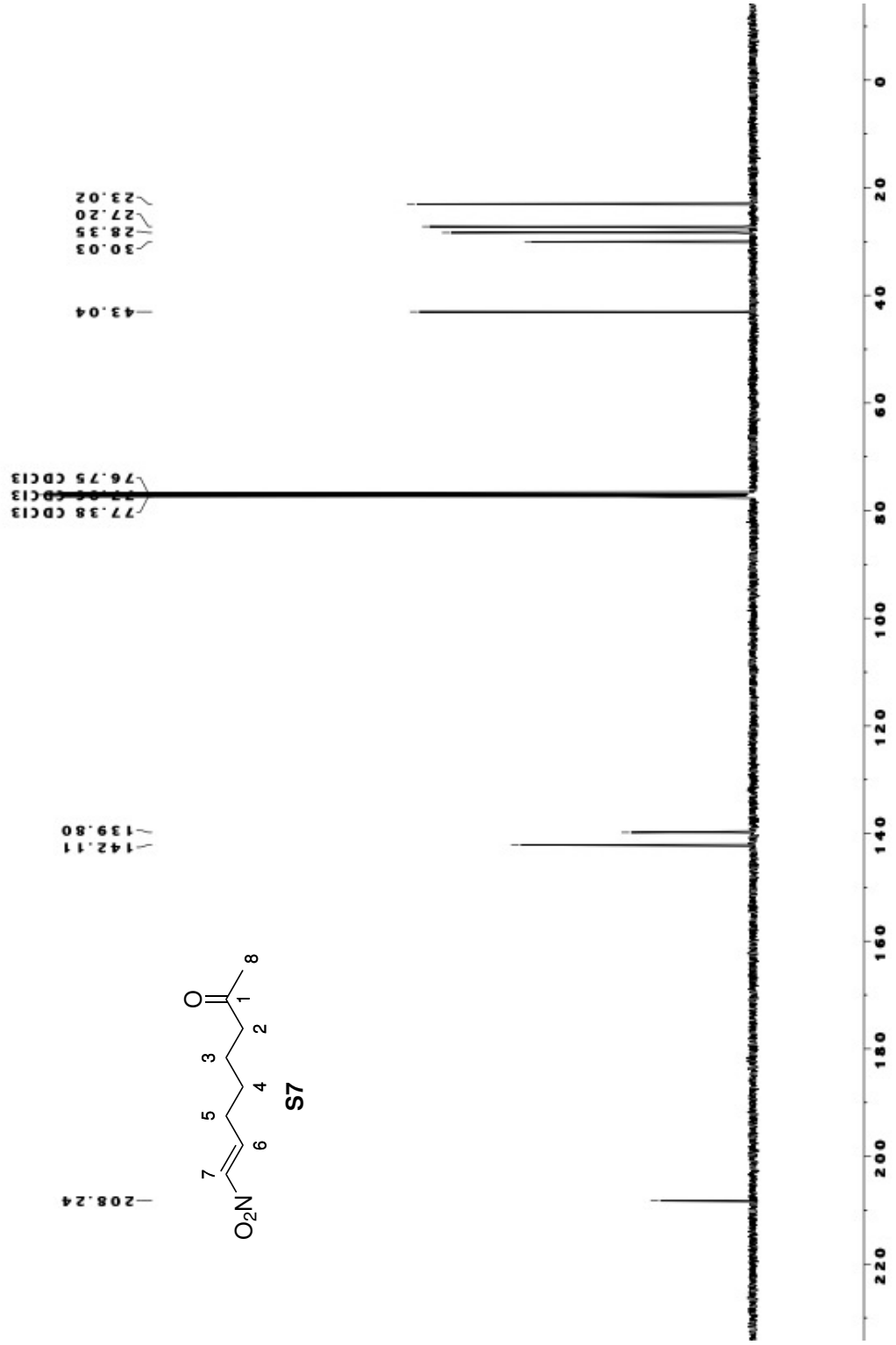
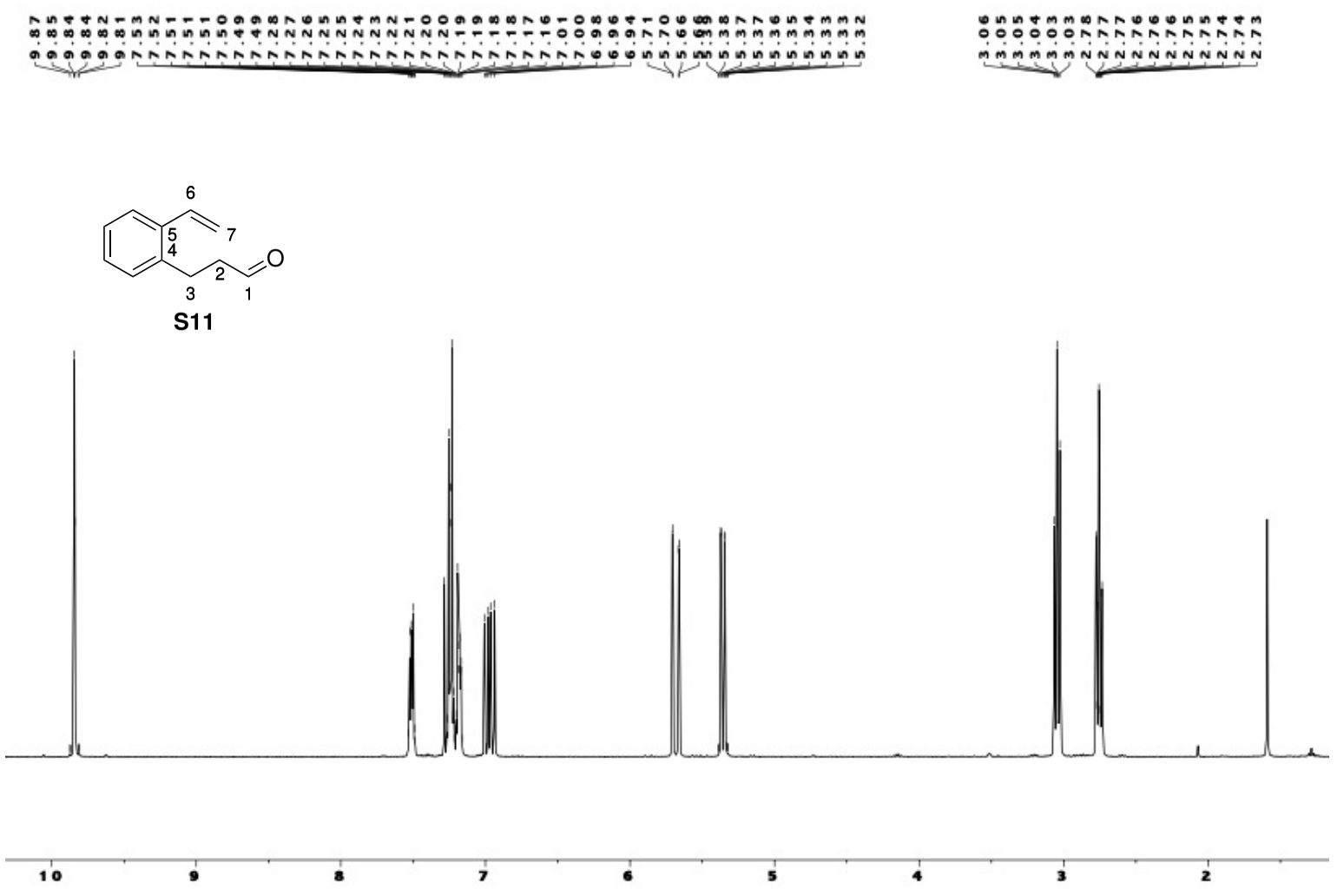
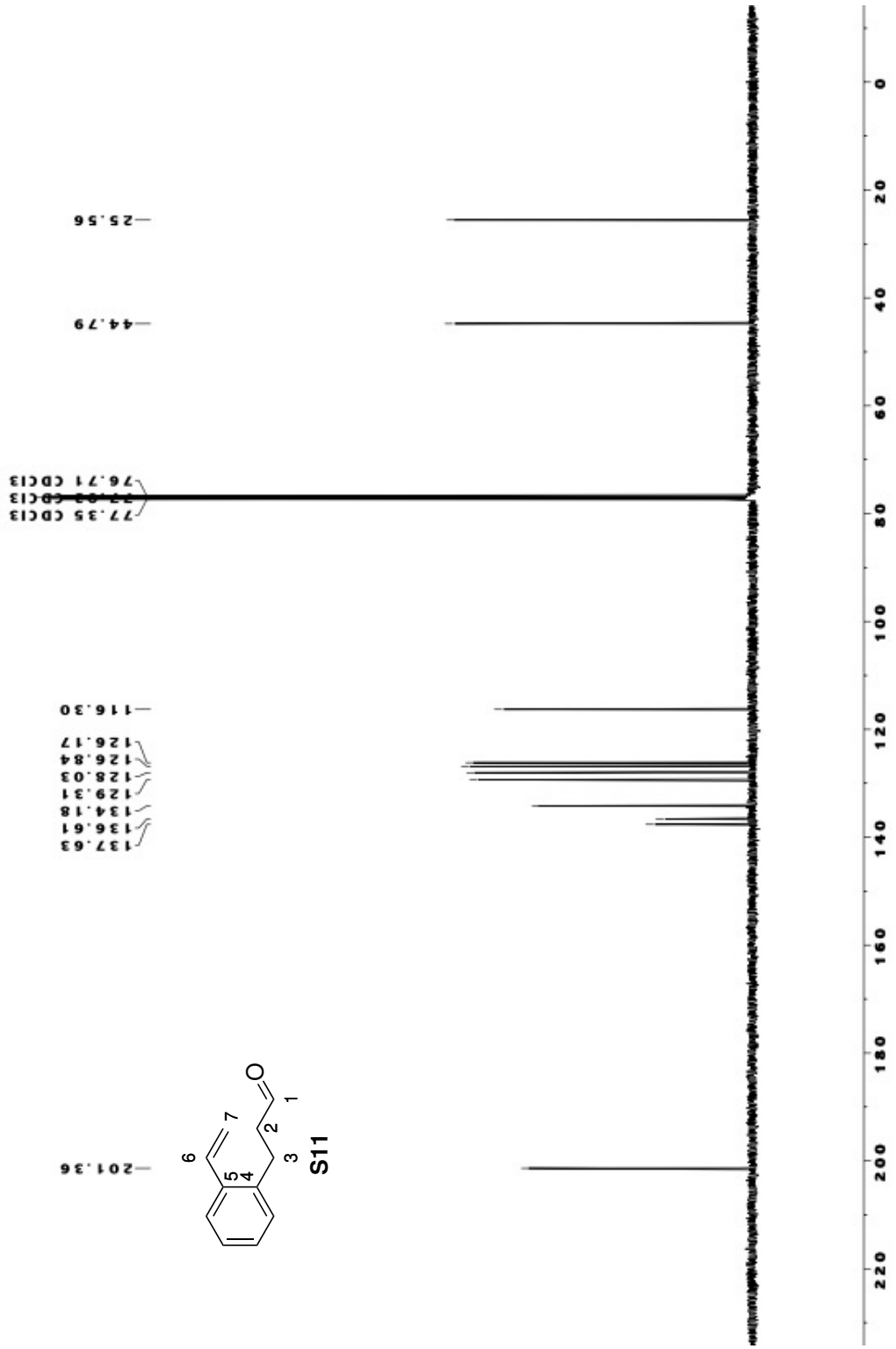
0.96
0.96
1.07
1.93
2.79
2.00
1.09
2.03
2.22

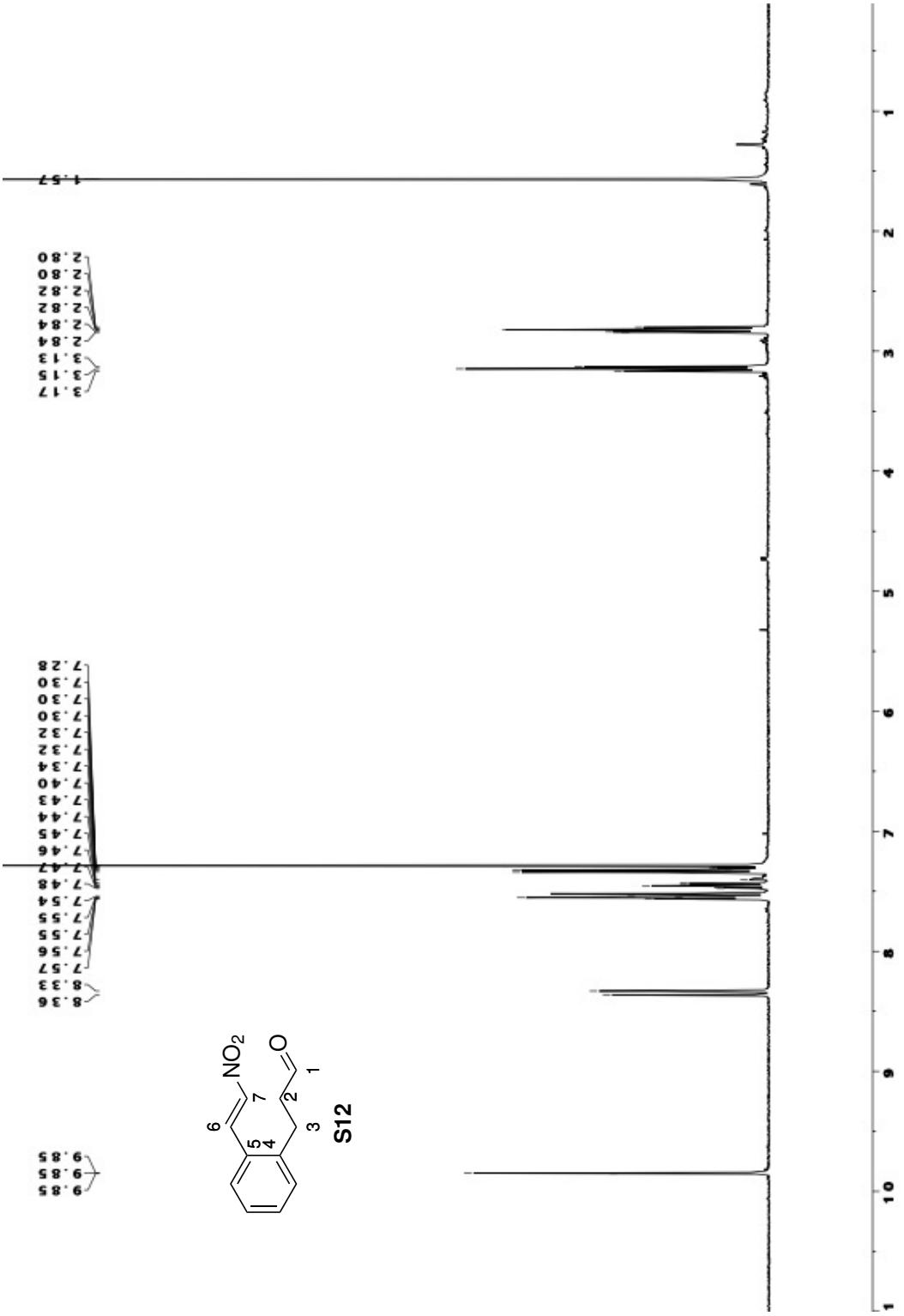

209.20
138.49
114.69
77.36 CDCl3
76.73 CDCl3
68.00
43.60
33.52
30.32
29.92
28.38
25.63
23.28
O
1
2
3
4
5
6
7
8
S6
0
20
40
60
80
100
120
140
160
180
200
220

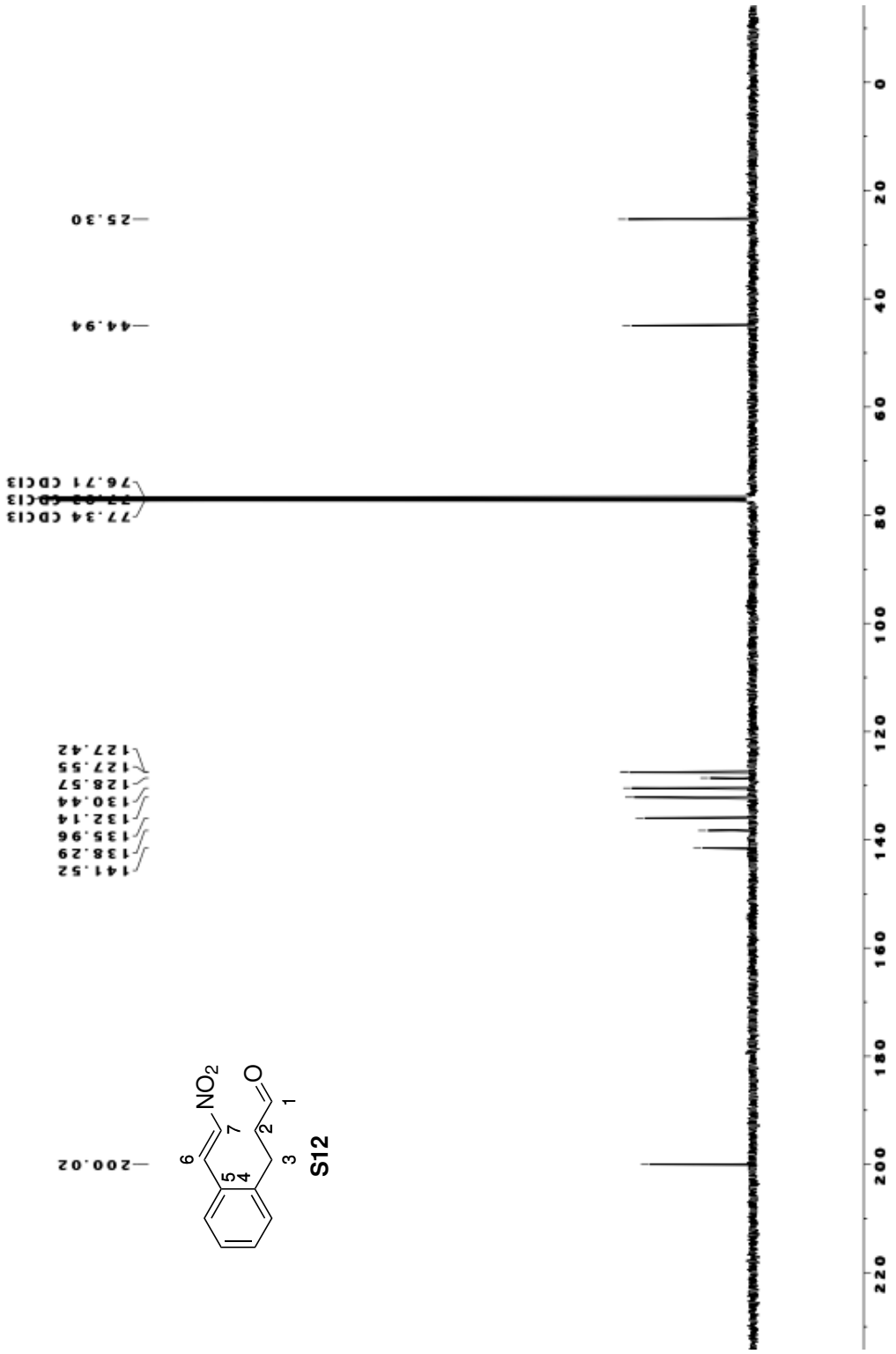

S7
O
O2N
1
2
3
4
5
6
7
8
CDCl3
HDO
0.89
1.05
1.91
1.95
2.00
2.20
2.92

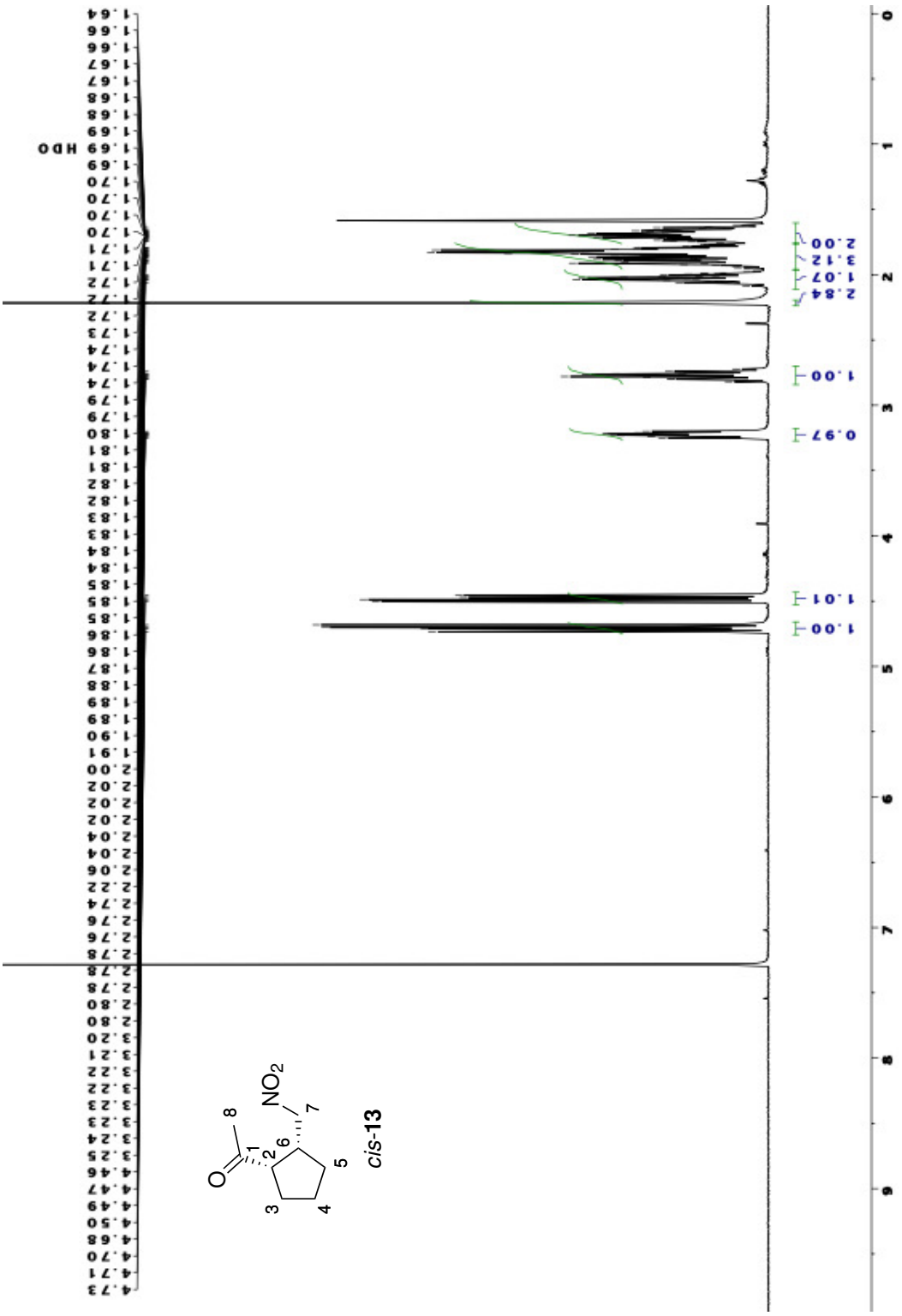

208.24
139.80
142.11
77.38 CDCl3
76.75 CDCl3
43.04
30.03
28.35
27.20
23.02
O
O2N
1
2
3
4
5
6
7
8
S7

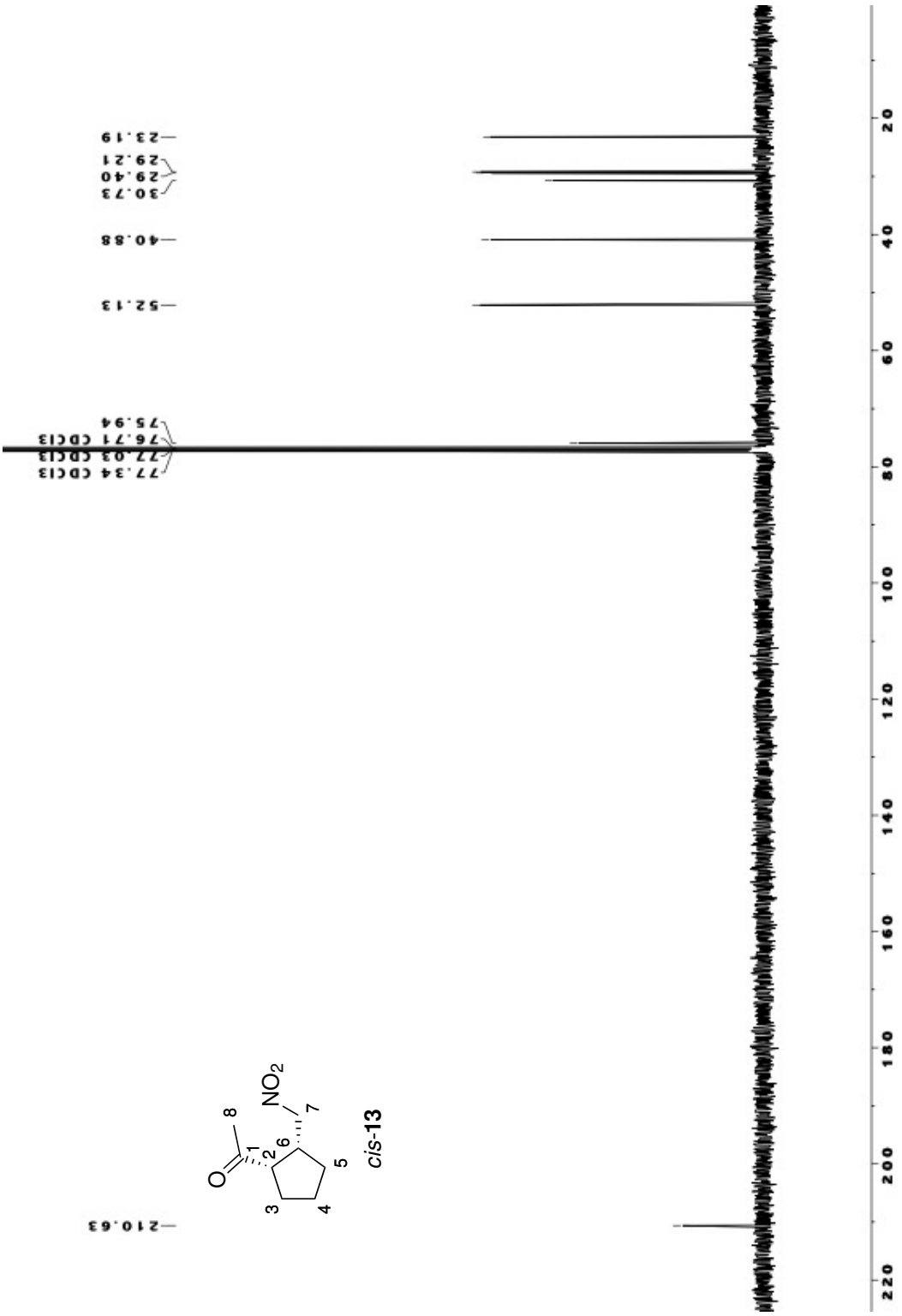

9.87 9.85 9.84 9.84 9.82 9.81 7.53 7.52 7.51 7.51 7.51 7.50 7.49 7.49 7.28 7.27 7.26 7.25 7.24 7.23 7.22 7.21 7.20 7.20 7.19 7.19 7.18 7.18 7.17 7.16 7.01 7.00 6.98 6.96 6.94 5.71 5.70 5.66 5.38 5.37 5.37 5.36 5.35 5.34 5.33 5.33 5.32
3.06 3.05 3.05 3.04 3.03 3.03 2.78 2.77 2.77 2.76 2.76 2.76 2.75 2.75 2.74 2.74 2.73
6
5
4
7
2
O
3
1
S11
10
9
8
7
6
5
4
3
2

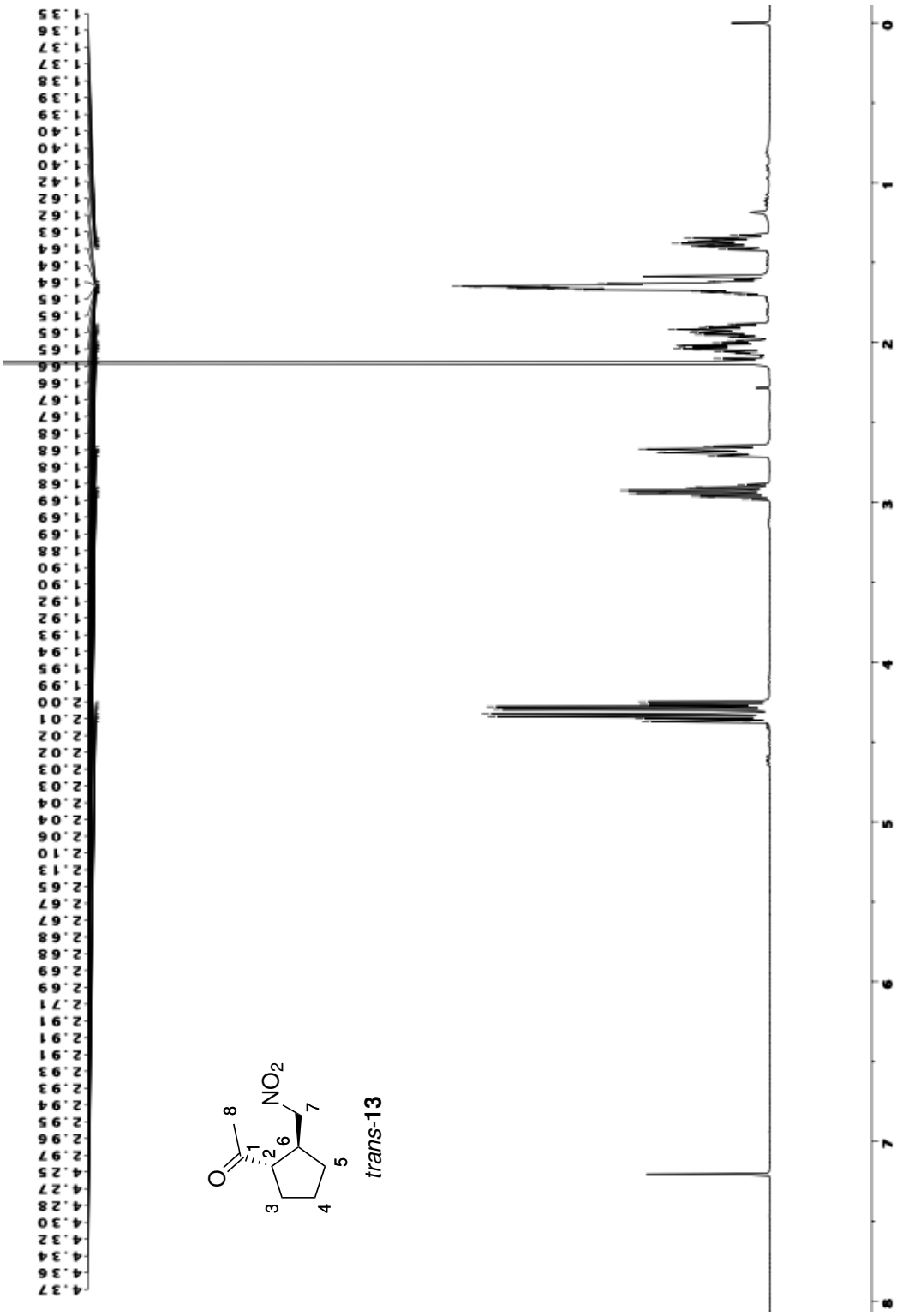

201.36
137.63
136.61
134.18
129.31
128.03
126.84
126.17
116.30
77.35 CDCl3
76.71 CDCl3
44.79
25.56
S11


9.85
9.85
9.85
8.33
8.36
7.54
7.55
7.55
7.56
7.57
7.44
7.45
7.46
7.47
7.48
7.28
7.30
7.30
7.30
7.32
7.32
7.34
7.40
7.43
7.44
7.45
3.13
3.15
3.17
2.80
2.80
2.82
2.82
2.84
2.84
1.57
O
NO2
1
2
3
4
5
6
7
S12

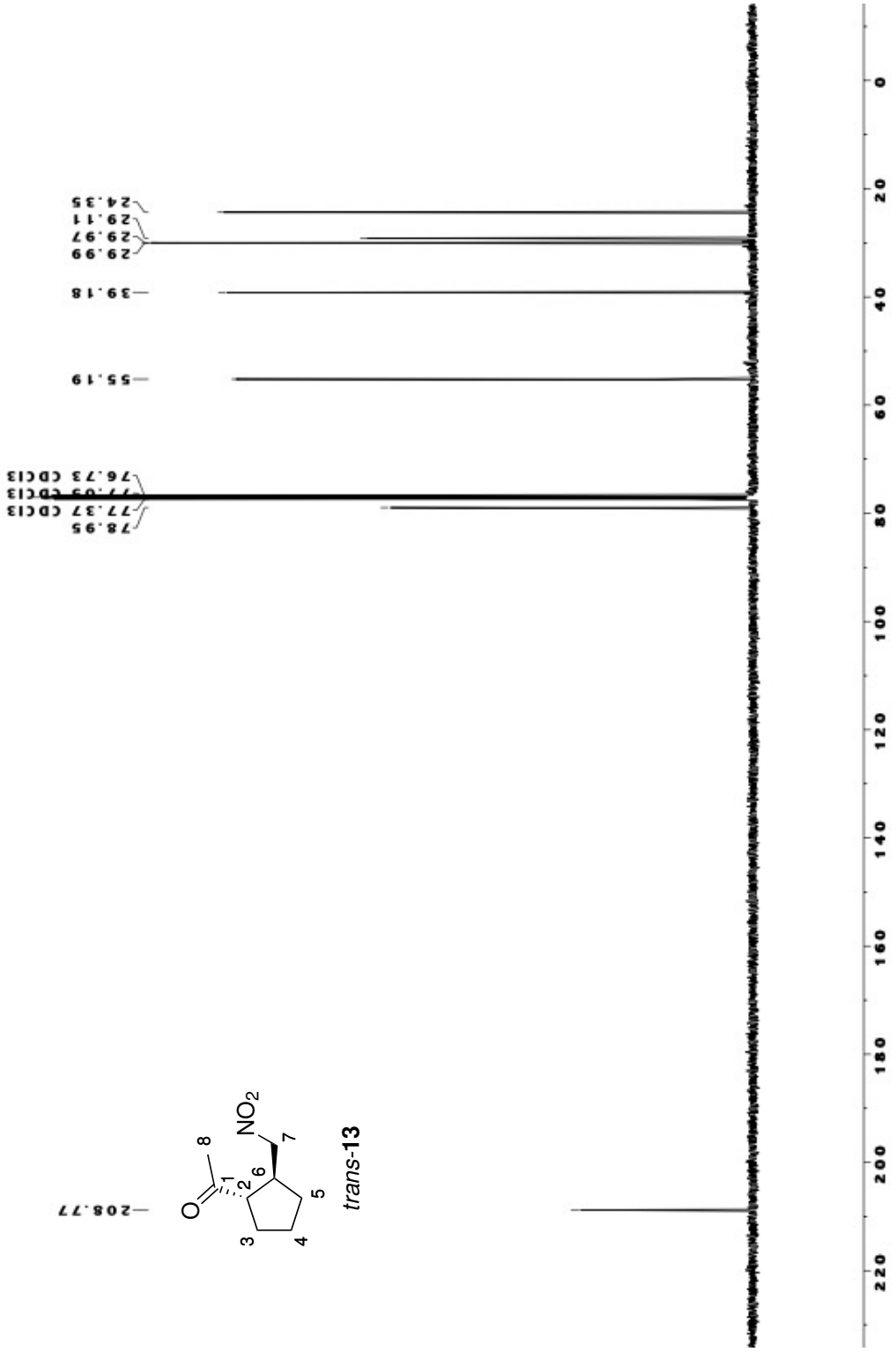

200.02
141.52
138.29
135.96
132.14
130.44
128.57
127.55
127.42
77.34 CDCl3
76.71 CDCl3
44.94
25.30
S12

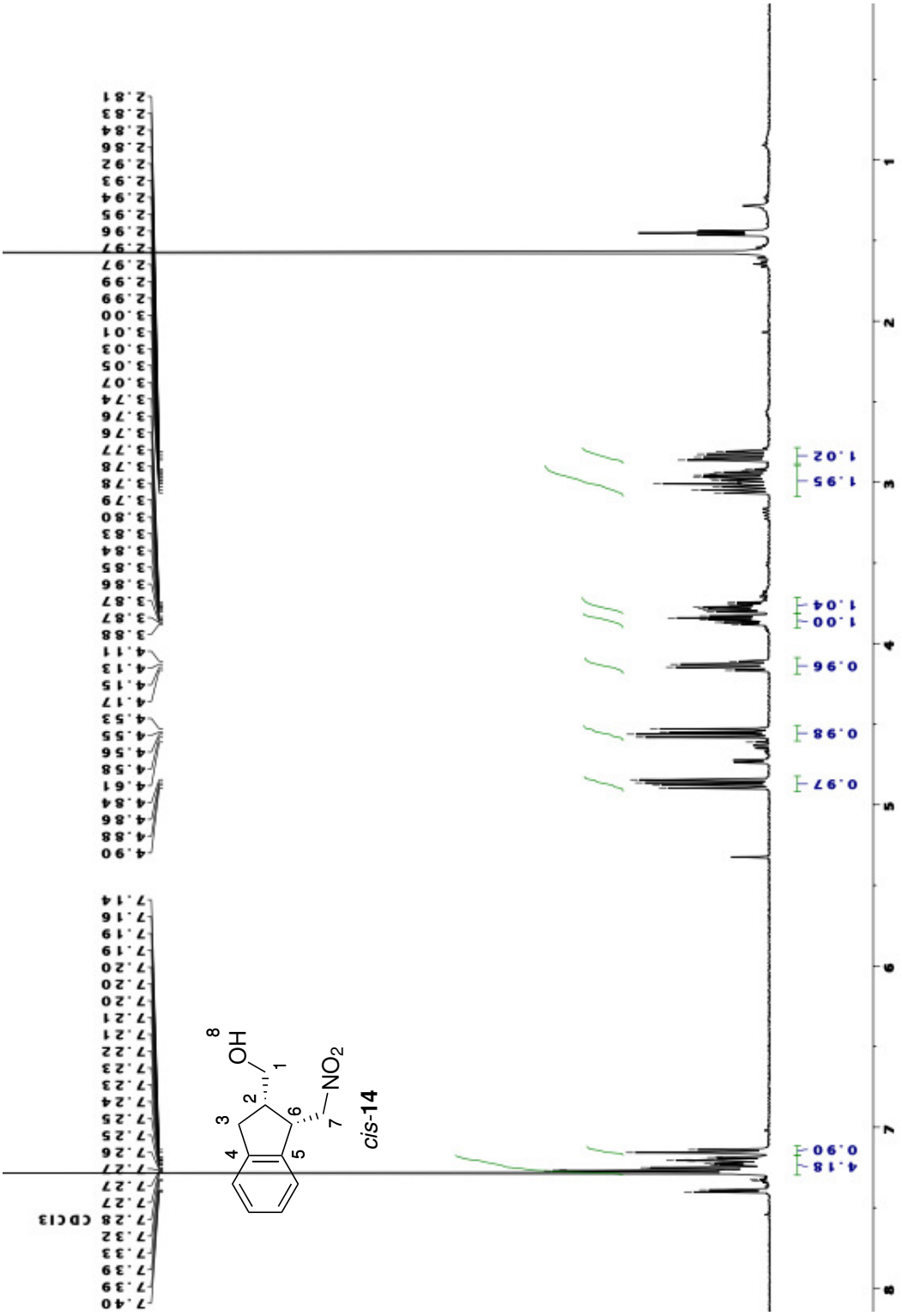

HDO
2.84
3.12
1.07
2.00
1.00
0.97
1.01
1.00
O
NO2
1
2
3
4
5
6
7
8
cis-13

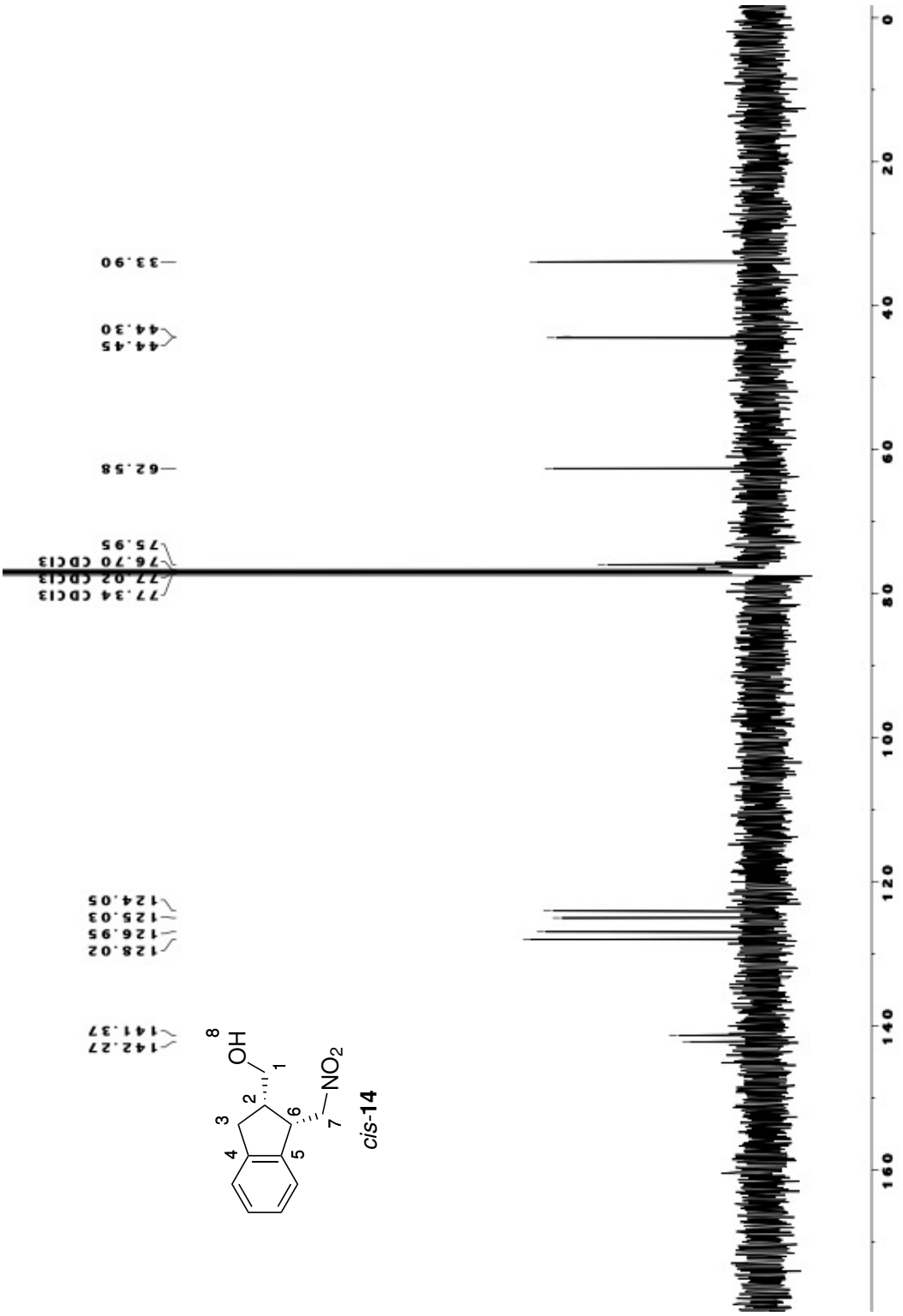

210.63
77.34 CDCl3
77.03 CDCl3
76.71 CDCl3
75.94
52.13
40.88
30.73
29.40
29.21
23.19
O
NO2
1
2
3
4
5
6
7
8
cis-13

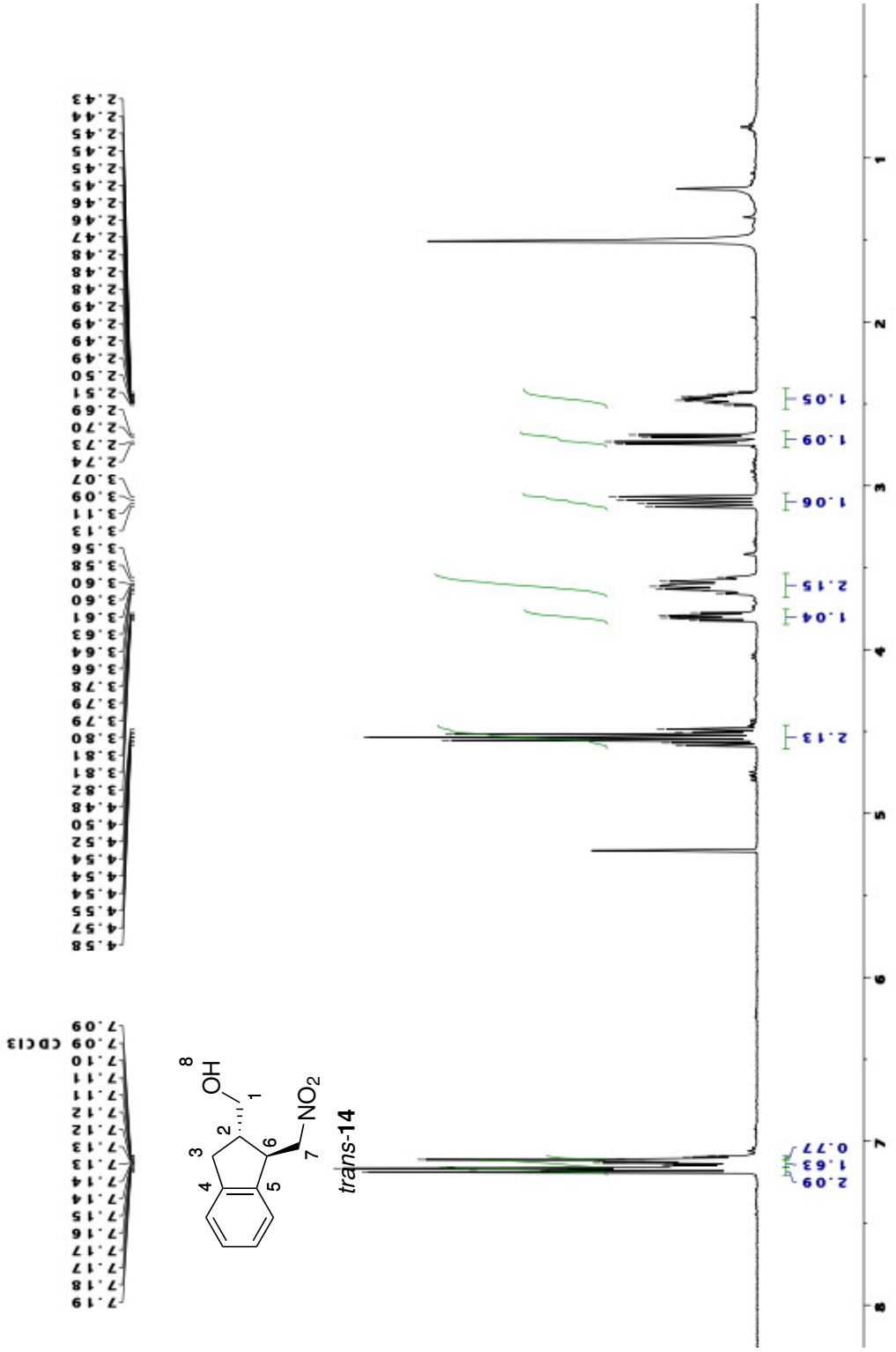


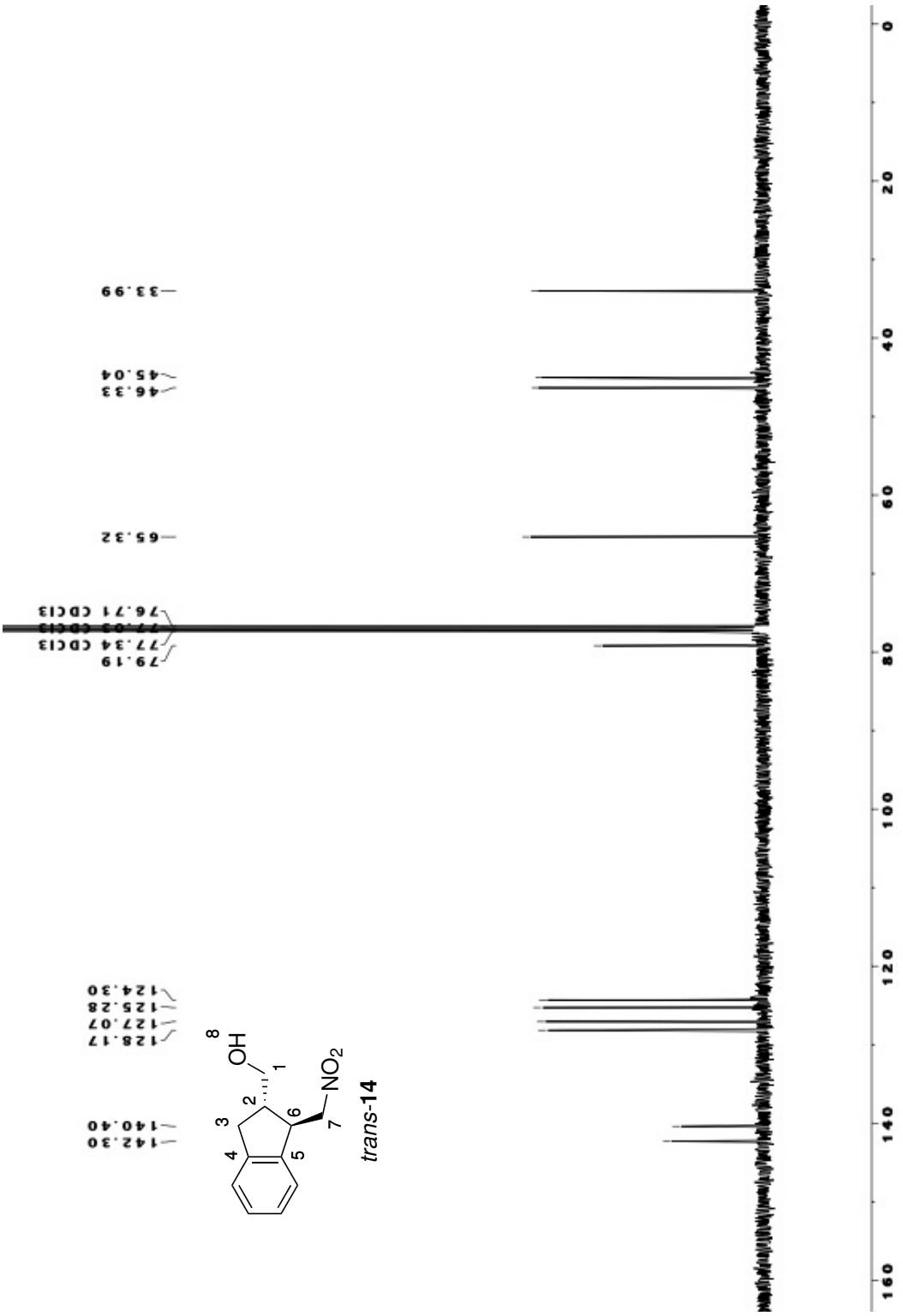
trans-**13**

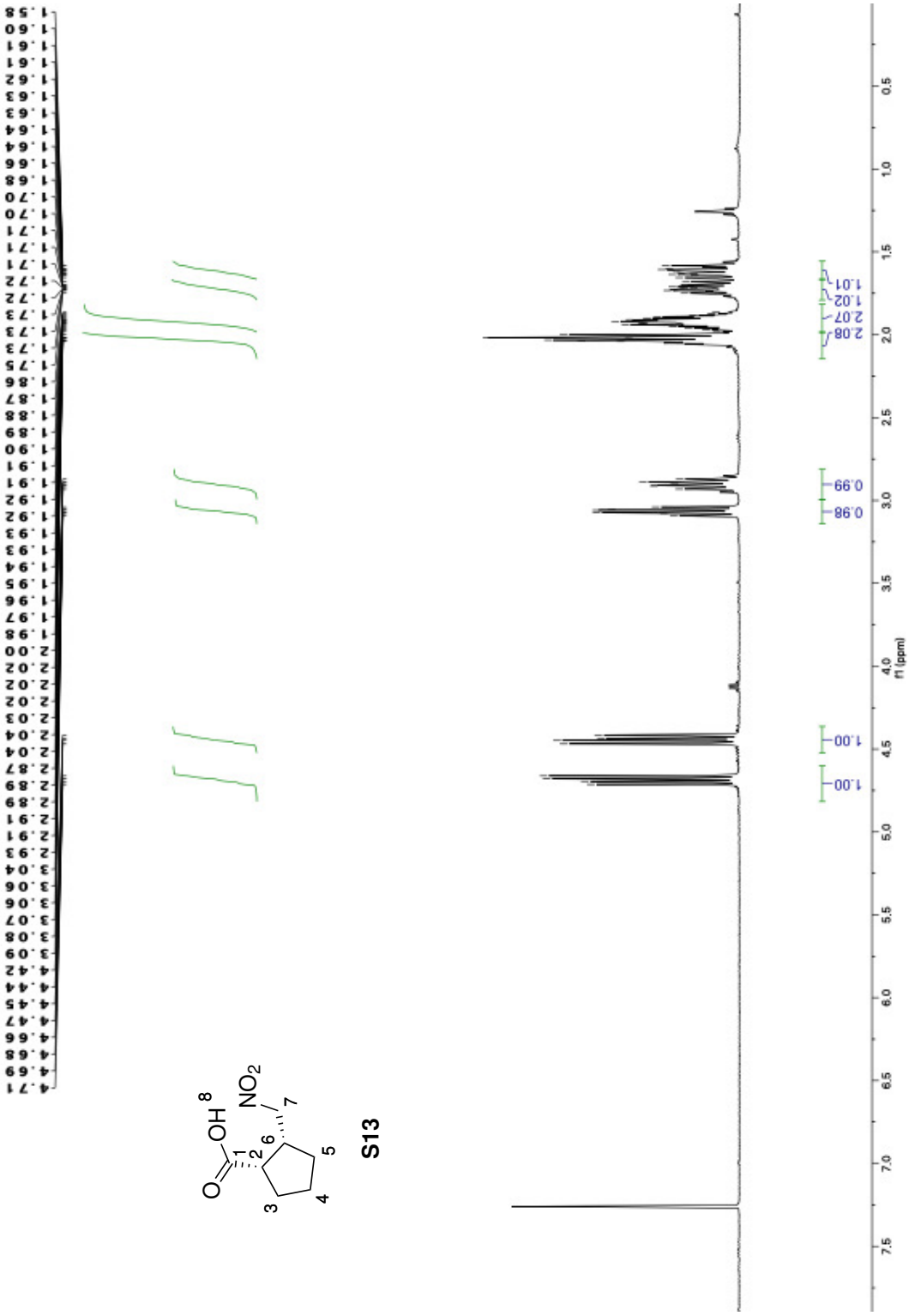

208.77
78.95
77.37 CDCl3
77.09 CDCl3
76.73 CDCl3
55.19
39.18
29.99
29.97
29.11
24.35
O
NO2
1
2
3
4
5
6
7
8
trans-13


OH
NO2
cis-14
CDCl3


142.27
141.37
128.02
126.95
125.03
124.05
77.34 CDCl3
77.02 CDCl3
76.70 CDCl3
75.95
62.58
44.45
44.30
33.90
OH
NO2
cis-14


OH
NO2
trans-14
CDCl3


33.99
45.04
46.33
65.32
76.71 CDCl3
77.03 CDCl3
77.34 CDCl3
79.19
124.30
125.28
127.07
128.17
140.40
142.30
OH
NO2
trans-14


1.58
1.60
1.61
1.61
1.62
1.63
1.63
1.64
1.64
1.66
1.68
1.70
1.70
1.71
1.71
1.72
1.72
1.73
1.73
1.75
1.86
1.87
1.88
1.89
1.90
1.91
1.91
1.92
1.92
1.93
1.93
1.94
1.95
1.96
1.97
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2.00
2.02
2.02
2.02
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2.04
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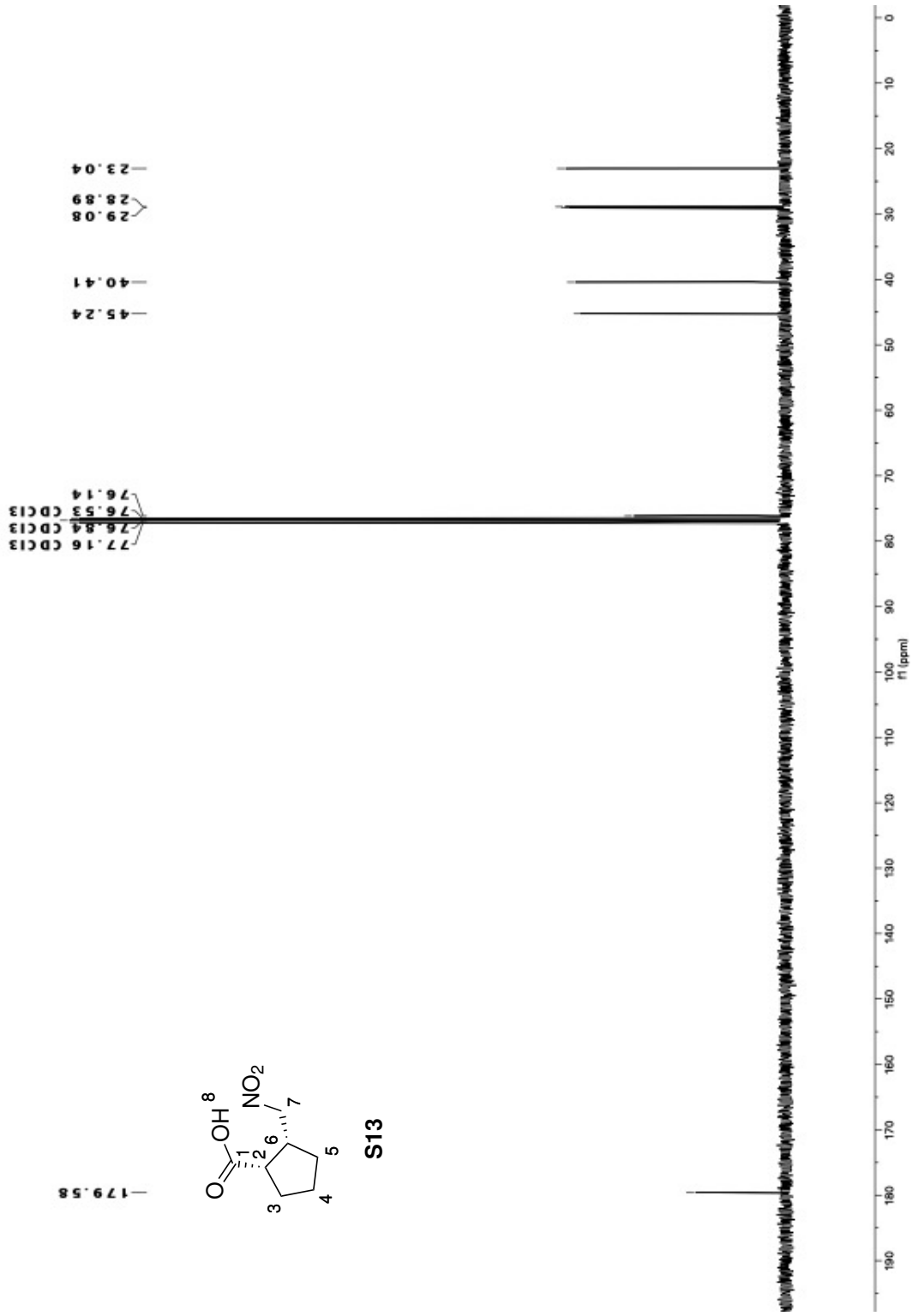
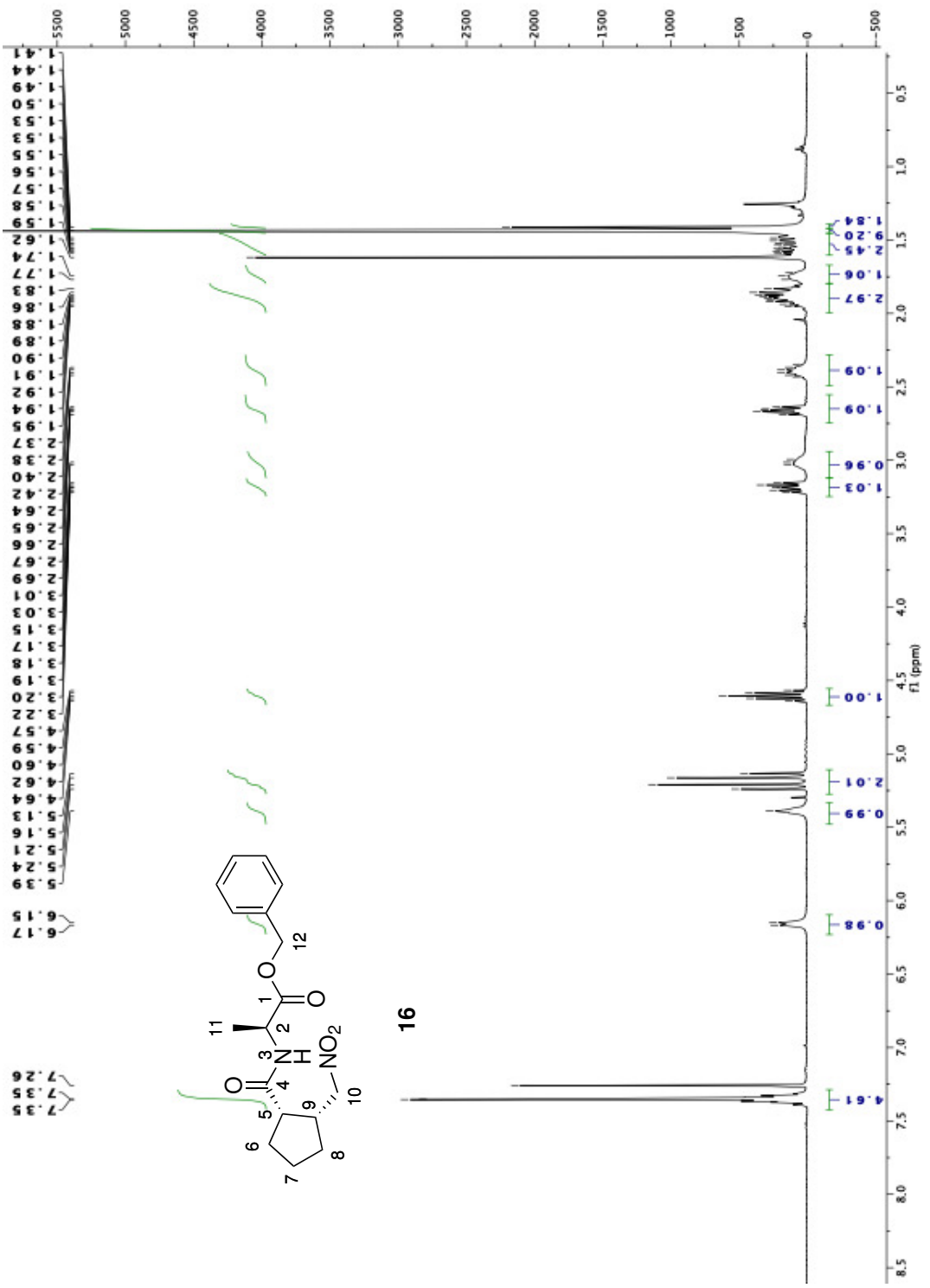
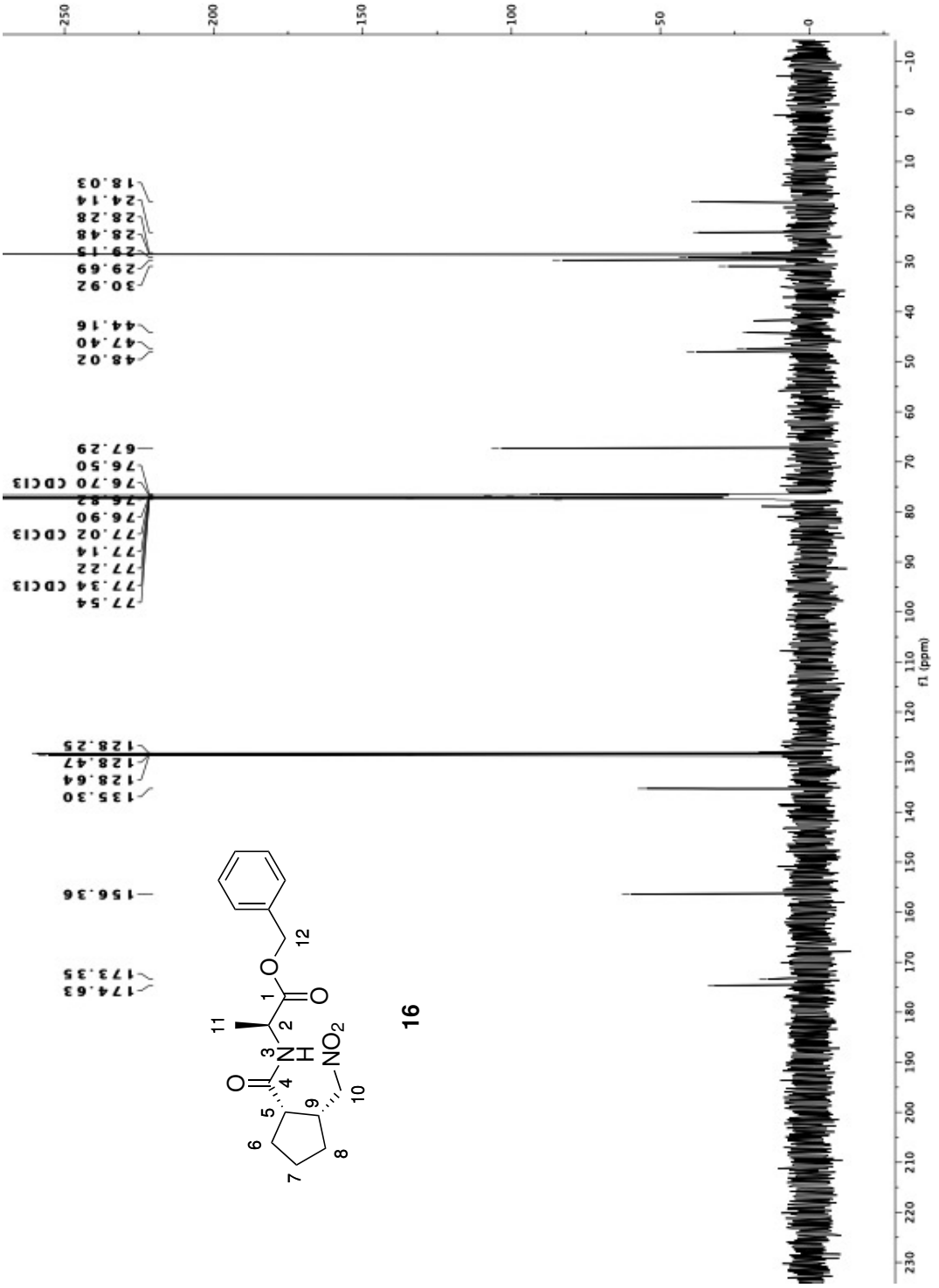
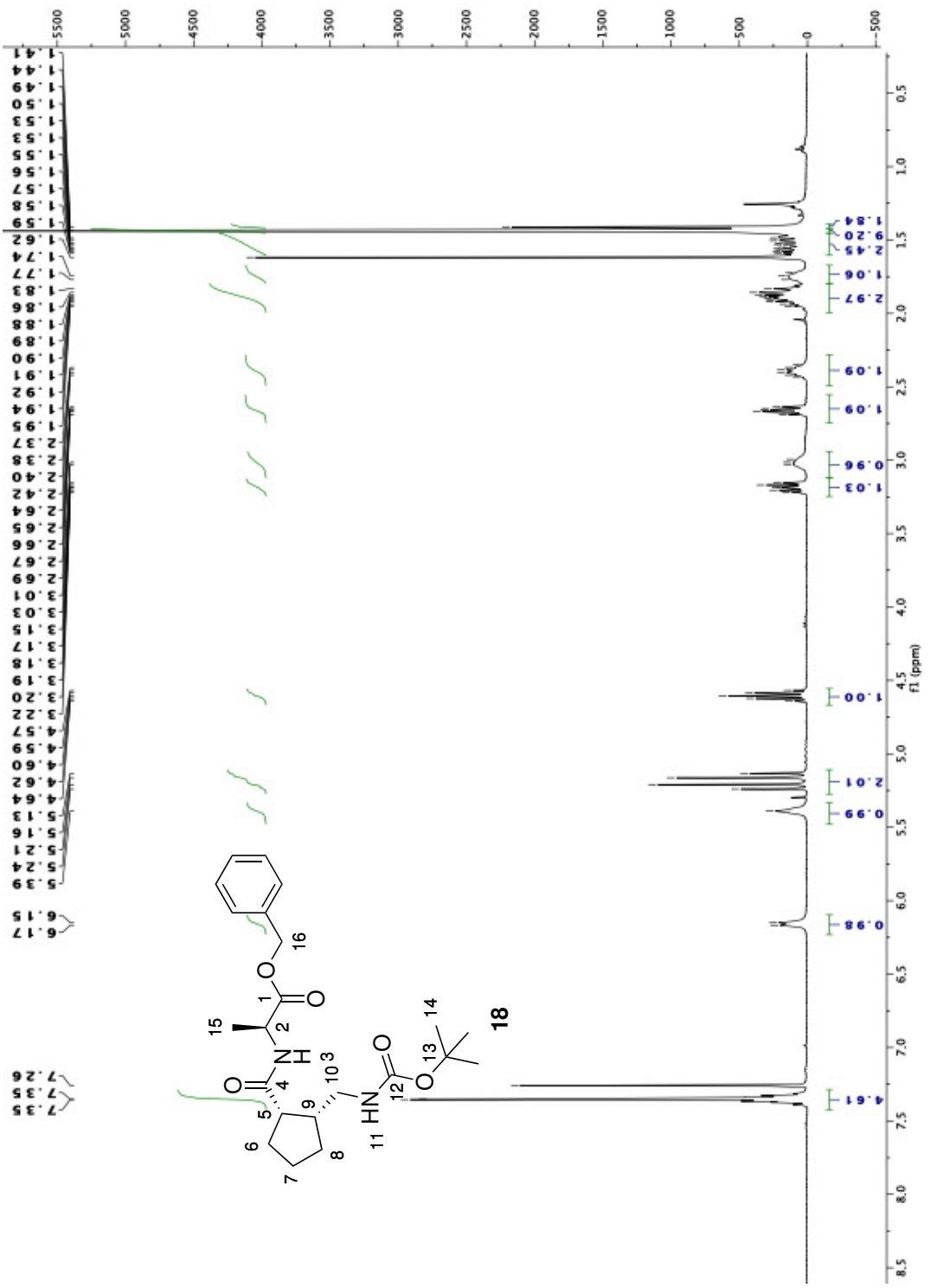
3.06
3.06
3.07
3.08
3.09
4.42
4.44
4.45
4.47
4.66
4.68
4.69
4.71
OH
8
O
NO2
1
2
3
4
5
6
7
S13
2.08
2.07
1.02
1.01
0.98
0.99
1.00
1.00
f1 (ppm)

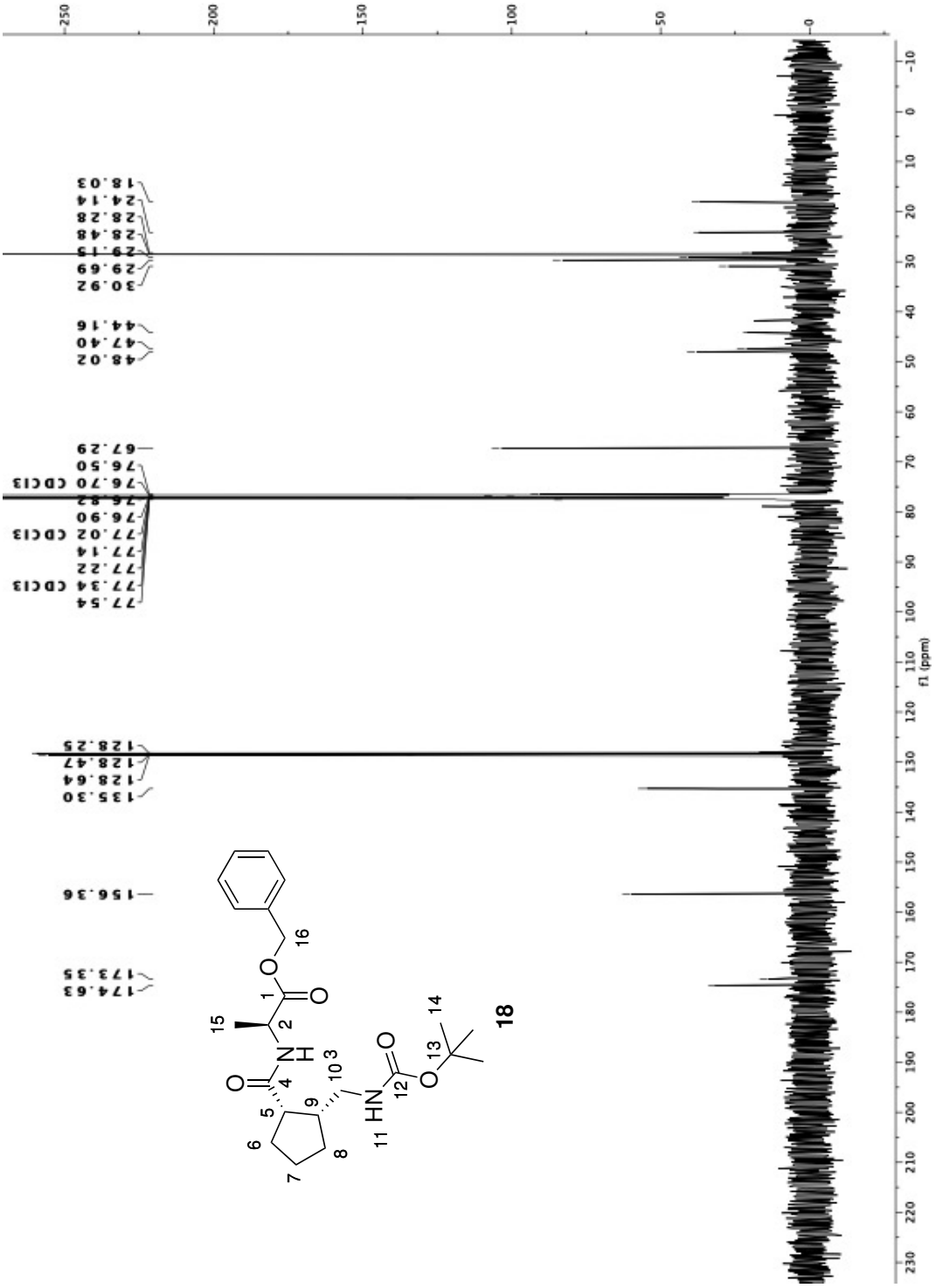

179.58
77.16 CDCl3
76.84 CDCl3
76.53 CDCl3
76.14
45.24
40.41
29.08
28.89
23.04
f1 (ppm)
S13

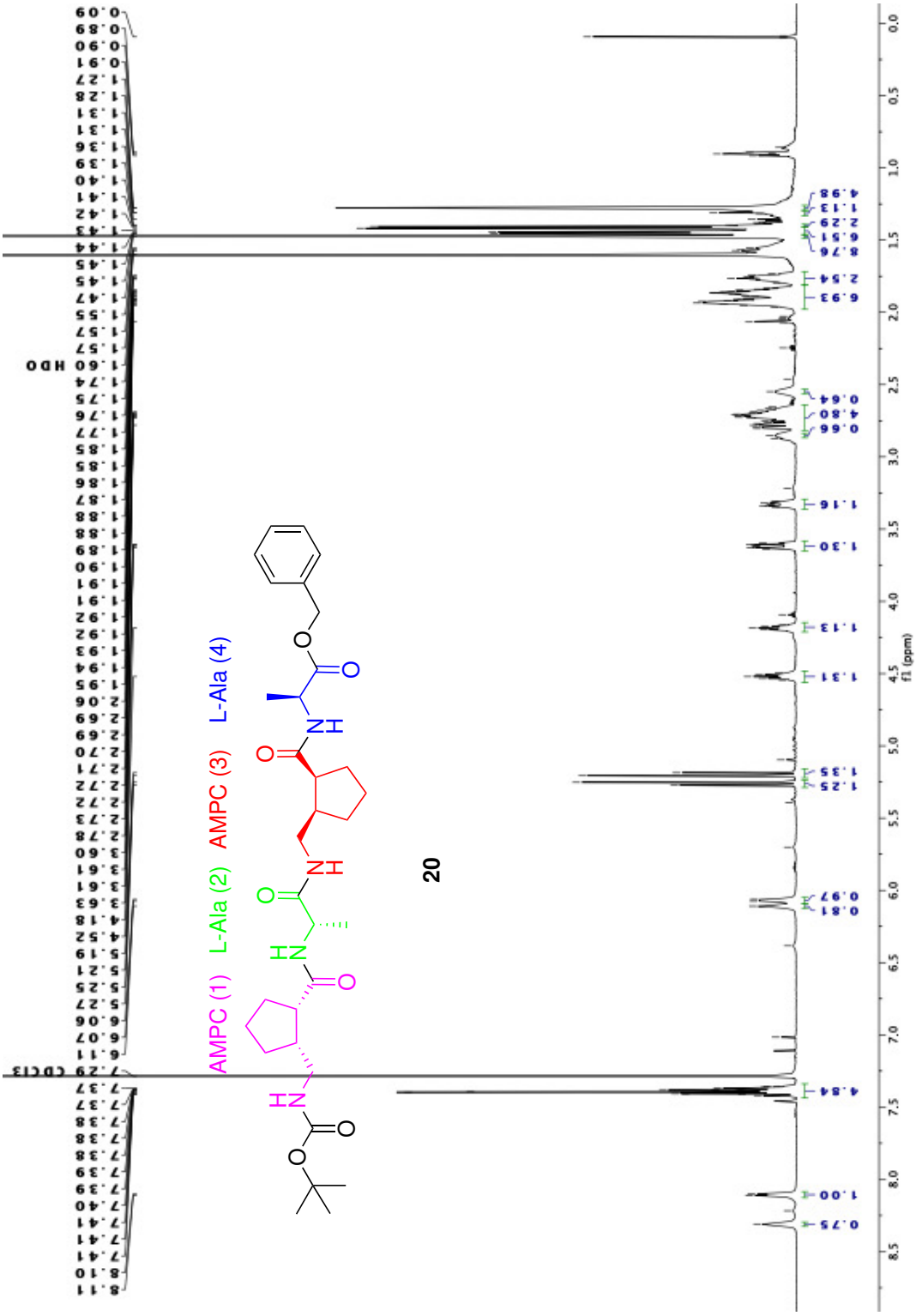

16
f1 (ppm)

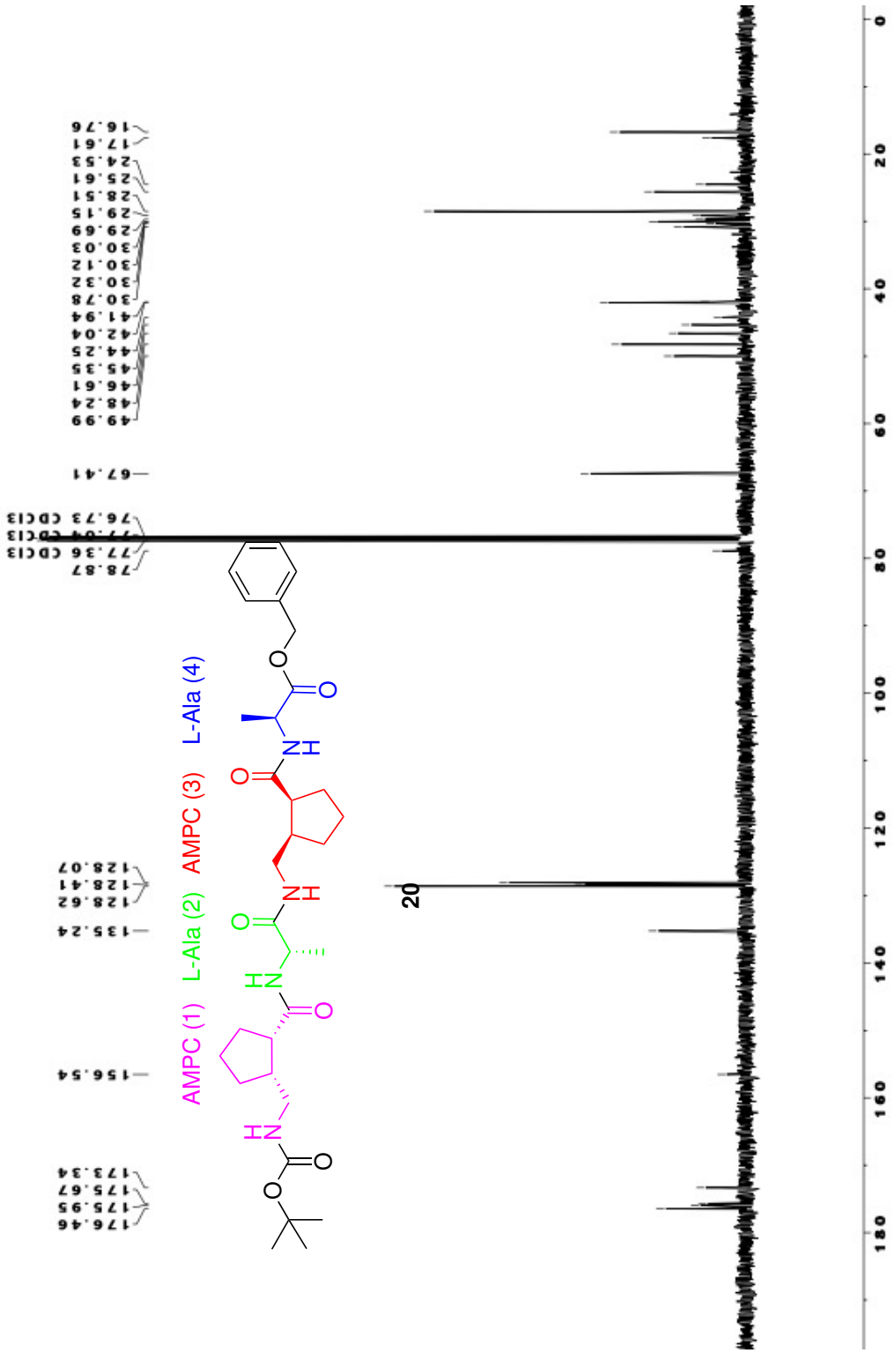

174.63
173.35
156.36
135.30
128.64
128.47
128.25
77.54
77.34 CDCl3
77.22
77.14
77.02 CDCl3
76.90
76.82
76.70 CDCl3
76.50
67.29
48.02
47.40
44.16
30.92
29.69
29.15
28.48
28.28
24.14
18.03
f1 (ppm)

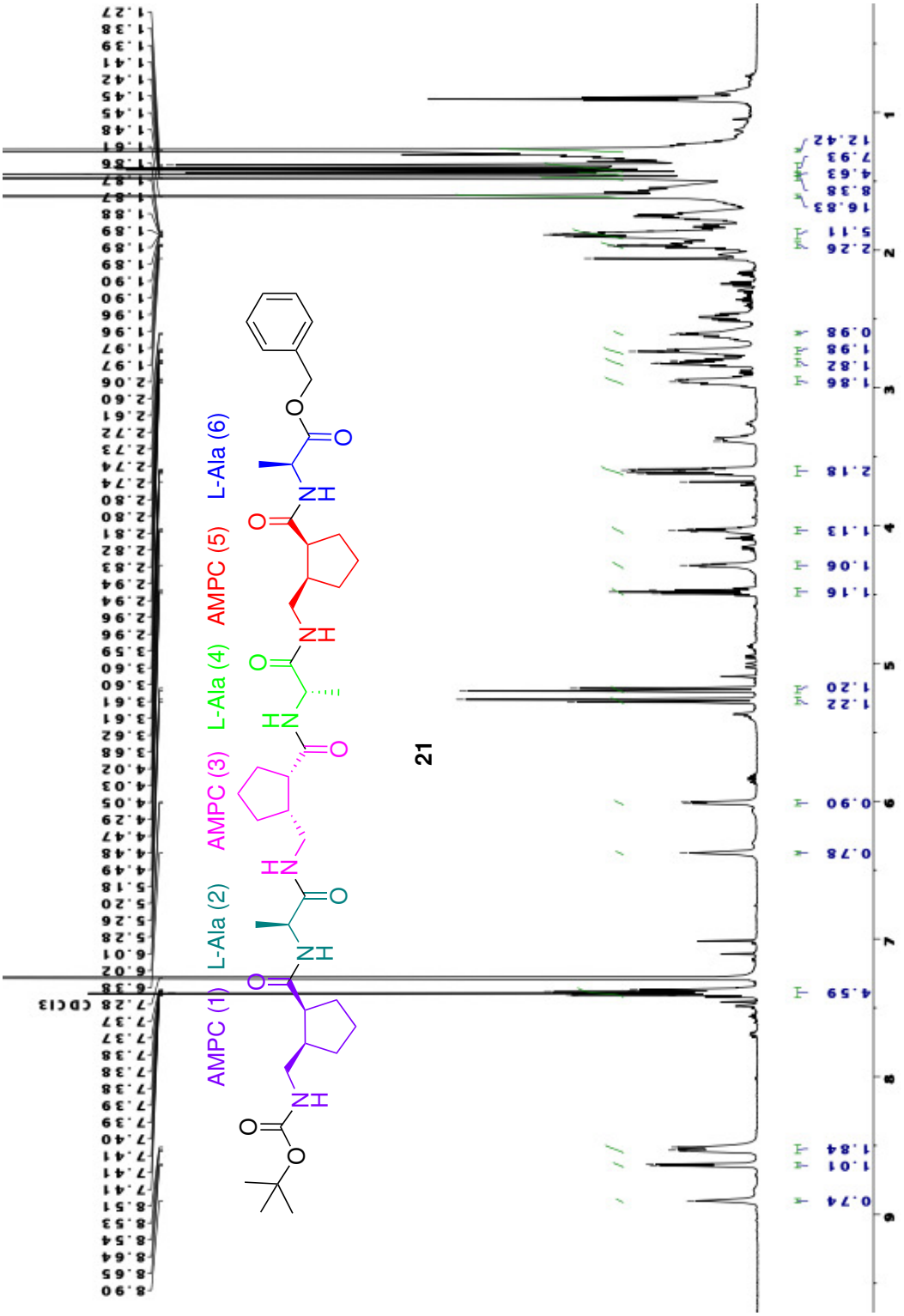
16

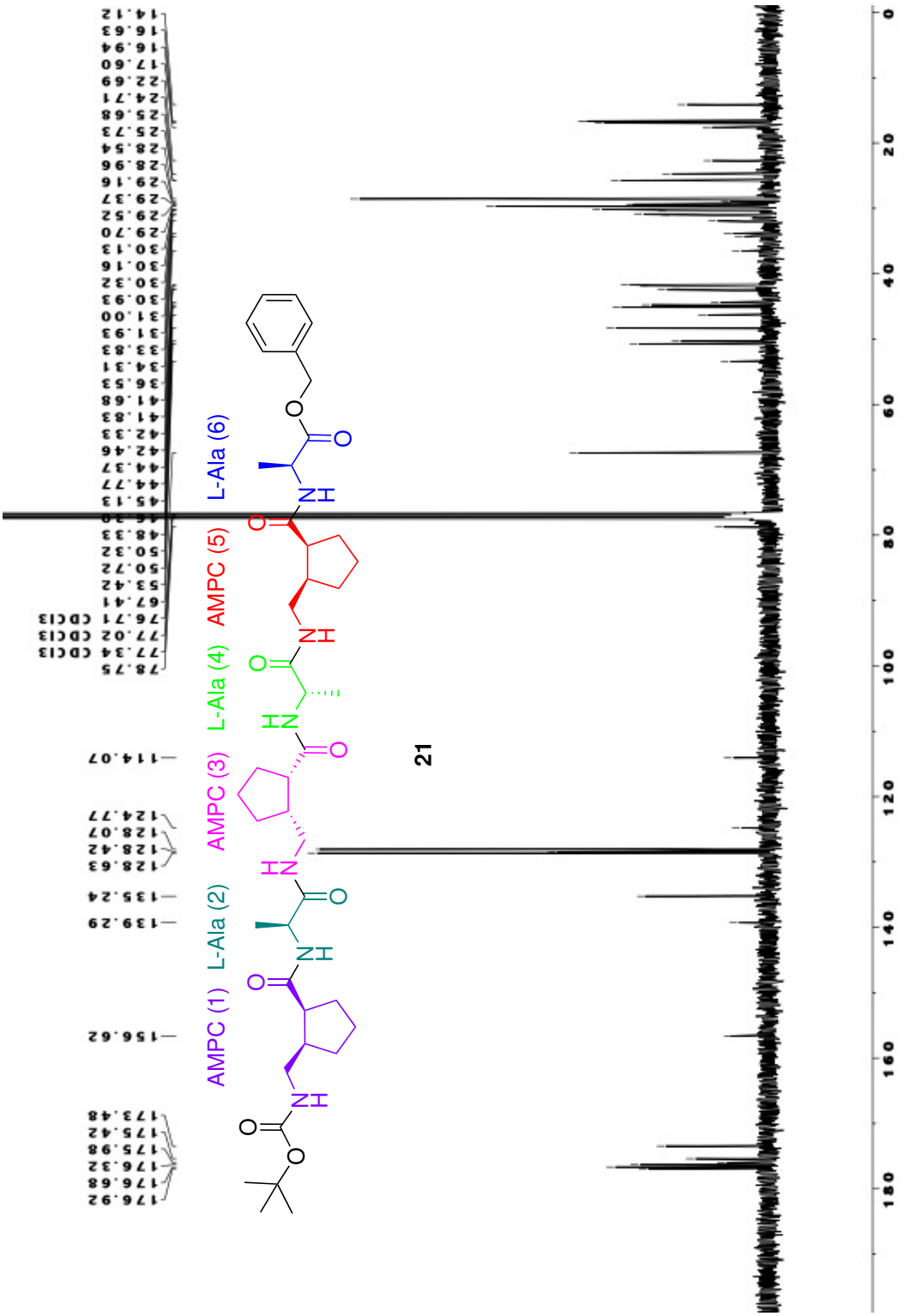

18
f1 (ppm)


18.03
24.14
28.28
28.48
29.15
29.69
30.92
44.16
47.40
48.02
67.29
76.50
76.70 CDCl3
76.82
76.90
77.02 CDCl3
77.14
77.22
77.34 CDCl3
77.54
128.25
128.47
128.64
135.30
156.36
173.35
174.63
f1 (ppm)
18


AMPC (1)
L-Ala (2)
AMPC (3)
L-Ala (4)
20
HDO
(CDCl3)
f1 (ppm)


AMPC (1)
L-Ala (2)
AMPC (3)
L-Ala (4)


AMPC (1)
L-Ala (2)
AMPC (3)
L-Ala (4)
AMPC (5)
L-Ala (6)
21


AMPC (1)
L-Ala (2)
AMPC (3)
L-Ala (4)
AMPC (5)
L-Ala (6)
21

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