

SUPPORTING INFORMATION

for

Telescoped Continuous Flow Synthesis of Optically Active γ -Nitrobutyric Acids as Key Intermediates of Baclofen, Phenibut, and Fluorophenibut

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1. General information

All chemicals and solvents were purchased from commercial vendors (Sigma-Aldrich, TCI, Alfa Aesar, Fluorochem or VWR) and were used as received, without further purification.

Chromatographic purification was carried out by using a Biotage Isolera automated flash chromatography system with cartridges packed with KP-SIL, 60 Å (32–63 µm particle size). Analytical thin-layer chromatography (TLC) were performed on Merck silica gel 60 GF254 plates. Compounds were visualized by means of UV or KMnO₄.

¹H- and ¹³C-NMR spectra were recorded on a Bruker Avance III 300 MHz instrument at ambient temperature, in CDCl₃ as solvent, at 300 MHz and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm using TMS as internal standard. Coupling constants are given in Hz units.

The ee of the compounds was determined by using a Shimadzu HPLC system (DGU-14A degasser, SCL-10A VP system controller, SPD-10 UV-VIS detector, LC-20AT pumps) and Chiralpak IB or IC chiral columns with isocratic mixtures of hexane and *i*PrOH as eluent. Chromatographic conditions are represented in Section 8.

Optical rotation was measured in CHCl₃ (HPLC-grade) at 25 °C against the sodium D-line (λ = 589 nm) on a Perkin Elmer Polarimeter 341 using a 10-cm pathlength cell.

High resolution mass spectra of pure substances were recorded in negative mode on an Agilent 6230 TOF LC/MS (G6230B) by flow injections (0.5 µL) on an Agilent 1260 Infinity Series HPLC (HiP Degasser G4225A, Binary Pump G1312B, ALS Autosampler G1329B, TCC Column thermostat G1316A, DAD Detector G4212B). The solvent was 40% H₂O (+0.1% 5 M ammonium formate solution) and 60% CH₃CN/H₂O 5:1 (ammonium formate solution) at a flow rate of 0.3 mL·min⁻¹. A Dual AJS ESI source was used with the following settings: Gas temperature (N₂) 300 °C, drying gas (N₂): 5 L·min⁻¹; nebulizer: 15 psig; fragmentor voltage: 150 V; skimmer voltage: 65 V, OCT 1 RF Vpp: 750 V; Vcap: 1400 V; nozzle voltage: 2000 V; reference mass: 966.0007. The scan range was 100–1100 m/z and 1 spectra per second was recorded.

IR spectra were recorded on a Bruker Tensor 27 / Diamond ATR FT-IR spectrometer.

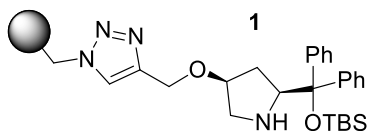
Elemental analyses of catalyst **1** were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid, Spain.

Equipment for the continuous flow reactions was assembled from commercially available components. Liquid streams were pumped by using a Syrris Asia syringe pump and/or a UNIQUISIS Binary Pump Module equipped with two high-pressure HPLC pumps, two injection valves and a pressure sensor to monitor system pressure. Flow systems were pressurized by applying an adjustable backpressure regulator (BPR) from Zaiput and/or by using a fixed-pressure BPR from IDEX. Column-type reactors were heated by using a Syrris Asia column heater, reaction coils by means of a conventional oil bath. Sample loops and reactor coils were prepared by using perfluoroalkoxy alkane (PFA) tubings (1/16" OD, 0.80 mm ID or 1/8" OD, 1.58 mm ID). In aerobic oxidation reactions, O₂ gas was introduced from a gas cylinder using a calibrated mass flow controller (MFC, Bronkhorst-EL). The inclusion of a check valve prevented any backflow of liquid towards the MFC. The gas flow rate was measured in units of mL_n min⁻¹ (n represents measurement under standard conditions: T_n = 0 °C, P_n = 1.01 bar). To determine residence time on packed-bed reactor columns, a solution of a dye was pumped. The elapsed time between the first contact of the dye with the column and the moment when the colored solution appeared at column the outlet was measured. Details of reaction set-ups as well as general procedures can be found in Sections 3–6

The E-factor was calculated by dividing the mass of waste generated by the mass of product formed. The mass of the waste did not include water, pre-swelling and carrier solvents.

CAUTION: Peracids are very unstable and, depending on the concentration, they are prone to explosive decompositions. Performic acid in concentrations >50% is highly reactive: it readily decomposes upon heating and explodes when rapidly heated to 80–85 °C. Extreme care must therefore be taken when handling peracids at higher temperatures! All equipment must be set up in a well-ventilated fume hood. A thorough safety assessment should be made before conducting any experiments.

2. Organocatalyst synthesis



Catalyst **1** was immobilized on a cross-linked polystyrene resin (100-200 mesh) through a 1,2,3-triazole linker. The monomer synthesis and the azide-alkyne cycloaddition-based immobilization was carried out according to our recently published procedure.^{1,2}

The level of functionalization of the polystyrene-supported catalyst f (mmol of monomeric catalyst / gram of resin) was calculated based on the results of nitrogen elemental analysis by the following formula:³

$$f \text{ (mmol g}^{-1}\text{)} = \%N \times 1000 \times (\text{number of N atoms})^{-1} \times M_w(N)^{-1} \times 100^{-1}$$

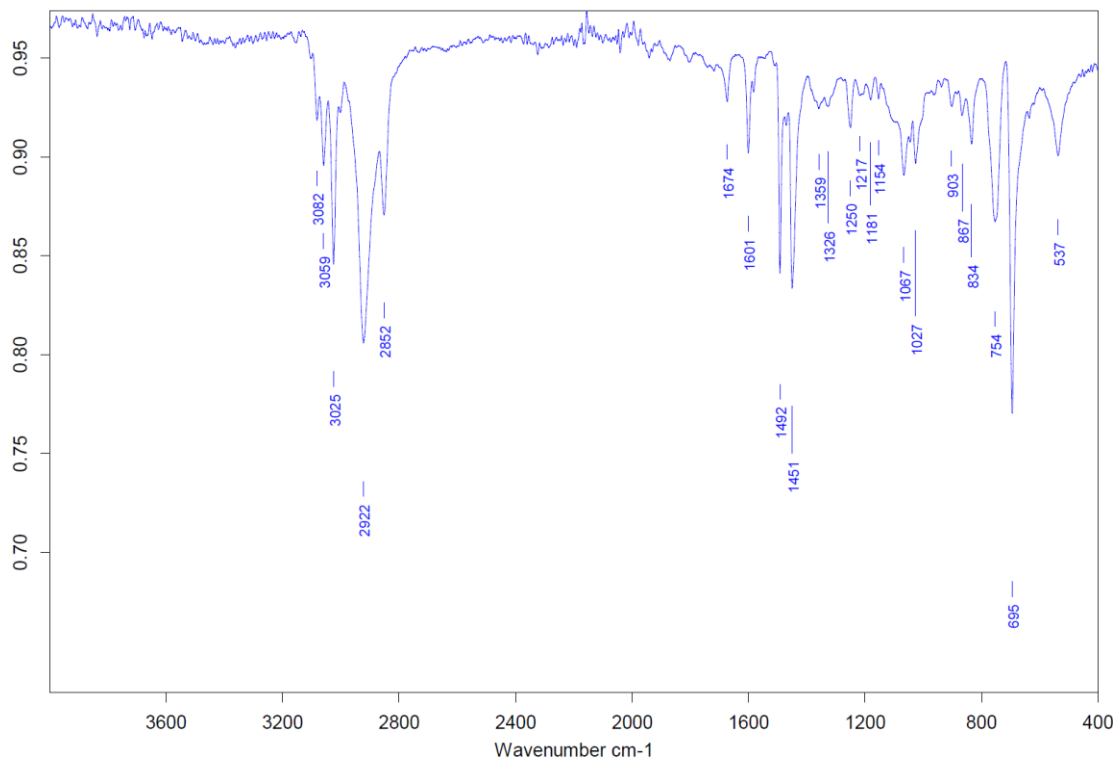
Elemental analysis: N 2.30, C 82.87, H 7.43

$f = 0.411$ mmol g⁻¹ (Complete functionalization.)

The supported material was checked by means of IR (ATR):

$\nu = 3059, 3025, 2922, 2852, 1601, 1492, 1451, 1250, 1067, 1027, 834, 754, 695, 537$ cm⁻¹

The characterization of the material matches the data reported in the literature.⁴



3. Flow synthesis of chiral γ -nitroaldehydes **2**, **3** and **4**

3.1. Optimization of the reaction conditions of the organocatalytic conjugate addition

A typical procedure for the continuous flow reactions is as follows.

1.5 g of catalyst **1** ($f = 0.411 \text{ mmol g}^{-1}$) was filled into an adjustable Omnifit glass column (6.6 mm ID) which was heated by a Syrris Asia column heater. Prior to the reactions, the catalyst was swollen by pumping EtOAc at $200 \mu\text{L min}^{-1}$ for 30 min. The system was pressurized at 5 bar by applying a Zaiput BPR. The reaction mixture consisting of *trans*-cinnamaldehyde (1 equiv), CH_3NO_2 and AcOH was streamed by using a Syrris Asia syringe pump equipped with an injection valve and a sample loop (3 mL; 1/16" OD, 0.80 mm ID), with EtOAc serving as carrier solvent. (Note: EtOAc was chosen as pre-swelling and carrier solvent due to its environmentally-benign nature and also because it swells the polystyrene catalyst carrier similarly to nitromethane.) In each run, the product stream was collected for 5 min after reaching steady state. The resulting material was concentrated under reduced pressure and analyzed by $^1\text{H-NMR}$ and chiral HPLC.

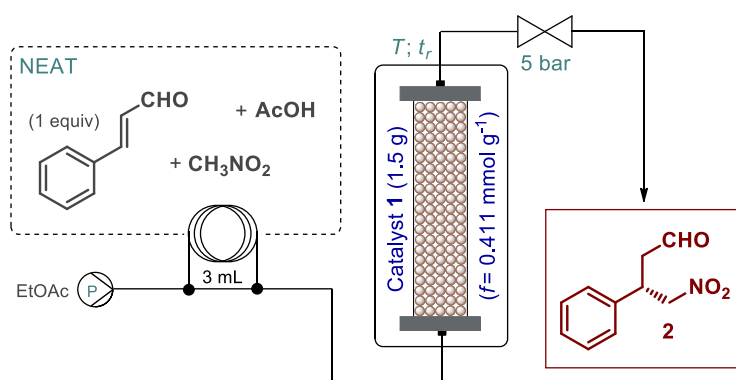


Table S1. Effects of reaction temperature.^a

# ^b	T (°C)	Conversion (%) ^c	ee (%) ^d
1	25	34	97
2	50	92	97
3	60	99	97
4	65	100	97
5	70	100	96

^a5 equiv CH_3NO_2 , 0.6 equiv AcOH, neat, $100 \mu\text{L min}^{-1}$ flow rate ($t_r = 14 \text{ min}$). ^bNo side product formation, chemoselectivity was 100% in all reactions. ^cDetermined by $^1\text{H-NMR}$ analysis of the crude product. ^dDetermined by chiral HPLC.

Table S2. Effects of flow rate and residence time.^a

# ^b	Flow rate ($\mu\text{L min}^{-1}$)	t_r (min)	Conversion (%) ^c	ee (%) ^d
1	100	14	92	97
2	75	19	98	97
3	50	28	100	96

^a5 equiv CH_3NO_2 , 0.6 equiv AcOH, neat, $T = 50 \text{ }^\circ\text{C}$. ^bNo side product formation, chemoselectivity was 100% in all reactions. ^cDetermined by $^1\text{H-NMR}$ analysis of the crude product. ^dDetermined by chiral HPLC.

Table S3. Effects of CH₃NO₂ excess.^a

# ^b	CH ₃ NO ₂ amount (equiv)	Conversion (%) ^c	ee (%) ^d
1	2	58	97
2	3	69	97
3	5	92	97
4	10	100	97

^a0.6 equiv AcOH, neat, 100 μL min⁻¹ flow rate (*t*_r = 14 min), *T* = 50 °C. ^bNo side product formation, chemoselectivity was 100% in all reactions. ^cDetermined by ¹H-NMR analysis of the crude product. ^dDetermined by chiral HPLC.

Table S4. Effects of additives.^a

# ^b	Additive		Conversion (%) ^c	ee (%) ^d
	Name	Amount (equiv)		
1	None	0	50	97
2	AcOH	0.2	89	97
3	AcOH	0.6	92	97
4	AcOH	1	90	97
5	AcOH H ₂ O	0.6 0.6	87	96
6	PhCOOH	0.2 ^e	88	97

^a5 equiv CH₃NO₂, neat, 100 μL min⁻¹ flow rate (*t*_r = 14 min), *T* = 50 °C. ^bNo side product formation, chemoselectivity was 100% in all reactions. ^cDetermined by ¹H-NMR analysis of the crude product. ^dDetermined by chiral HPLC. ^e0.6 equiv of PhCOOH could not be investigated due to solubility issues.

The conditions in Table S1, entry 4 were designated as optimal and were applied in the subsequent preparative scale syntheses.

3.2. Preparative-scale syntheses

The procedure for the large-scale asymmetric flow synthesis of chiral γ-nitroaldehydes **2**, **3** and **4** is as follows.

1.5 g of catalyst **1** (*f* = 0.411 mmol g⁻¹) was filled into an adjustable Omnifit glass column (6.6 mm ID) which was heated by a Syrris Asia column heater at 65 °C. Prior to the reactions, the catalyst was swollen by pumping EtOAc at 200 μL min⁻¹ for 30 min. The system was pressurized at 5 bar by applying a Zaiput BPR. The reaction mixture consisting of the corresponding cinnamaldehyde (1 equiv), CH₃NO₂ (5 equiv) and AcOH (0.6 equiv) was pumped directly by using a Syrris Asia syringe pump. In each substrate mixture, the concentration of the aldehyde component was 2.29 M as determined experimentally. The flow rate was set to 100 μL min⁻¹ which corresponded to 14 min residence time on the catalyst bed. In each experiment, the product stream was collected continuously for 2.5 h after reaching steady state. During this period, samples were taken at 50, 100 and 150 min, in which conversion and chemoselectivity was determined by means of ¹H-NMR. Between each experiment, the catalyst bed was washed carefully with AcOH (0.5 mL min⁻¹, 25 min) and then with AcOH/EtOAc 1:9 (0.5 mL min⁻¹, 25 min). After the reactions, excess CH₃NO₂ and residual AcOH was removed by simple evaporation to obtain the desired chiral intermediates without chromatographic purification. Isolated yield and ee were determined for each experiments. The results are summarized in Table S5.

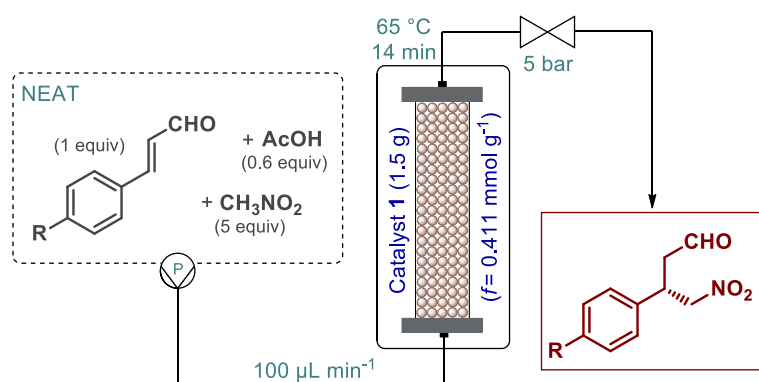


Table S5. Summarized results of the preparative-scale asymmetric flow synthesis of chiral γ -nitroaldehydes **2**, **3** and **4**.

R	H	F	Cl
Compound no.	2	3	4
Collection time	2.5 h	2.5 h	2.5 h
Conversion after 50 min ^{a, b}	100%	100%	99%
Conversion after 100 min ^{a, b}	99%	99%	97%
Conversion after 150 min ^{a, b}	96%	95%	92%
Amount of isolated product	6.29 g (32.56 mmol)	6.87 g (32.53 mmol)	7.22 g (31.72 mmol)
Isolated yield	95%	95%	92%
Productivity	2.52 g h ⁻¹ of pure product	2.75 g h ⁻¹ of pure product	2.89 g h ⁻¹ of pure product
Accumulated TON	53	53	52
ee ^b	97%	96%	96%

^aDetermined by ¹H-NMR analysis of the crude product. ^bNo side product formation, chemoselectivity was 100% in cases of all substrates. ^cDetermined by chiral HPLC.

4. Studies towards the aerobic oxidation of chiral γ -nitroaldehyde **2**

4.1. Catalyst-free aerobic aldehyde oxidation

A typical procedure for the continuous flow reactions is as follows.

A 0.5 M solution of **2** was streamed at $100 \mu\text{L min}^{-1}$ by using a Syrris Asia syringe pump which was equipped with an injection valve and a sample loop (2 mL; 1/16" OD, 0.80 mm ID). O_2 gas was introduced at 1.20 mL min^{-1} (1.07 equiv of O_2) using a calibrated MFC. The liquid and gaseous streams were combined in an Y-mixer at room temperature and the resulting stream was directed through a 4.5-mL reaction coil (1/16" OD, 0.80 mm ID) which was heated in an oil bath. The system was pressurized at 5 bar by applying a Zaiput BPR. In a typical experiment, the carrier solvent flow was started first. Then, when the pressure and temperature stabilized, the gas flow was initiated by setting the desired flow rate on the MFC. Once a stable segmented flow regime was observed, the system was ready for feed injection. In each run, the product stream was collected for 5 min after reaching steady state. The resulting material was concentrated under reduced pressure and analyzed by $^1\text{H-NMR}$.

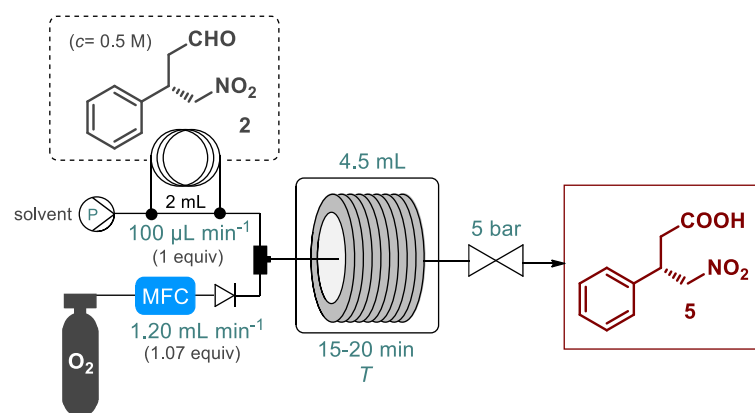


Table S6. Effects of various solvents and reaction temperatures.

#	Solvent	T ($^{\circ}\text{C}$)	Conversion (%) ^a	Chemoselectivity (%) ^a
1	CH_3NO_2	25	0	-
2	CH_3NO_2	60	0	-
3	CH_3NO_2	90	0	-
4	CH_3CN	90	trace	not determined
5	CH_2Cl_2	90	5	not determined
6	toluene	90	0	-

^aDetermined by $^1\text{H-NMR}$ analysis of the crude product.

4.2. Platinum-catalyzed aerobic aldehyde oxidation

A typical procedure for the continuous flow reactions is as follows.

A 0.5 M solution of **2** was streamed by using a Syrris Asia syringe pump which was equipped with an injection valve and a sample loop (2 mL; 1/16" OD, 0.80 mm ID). O_2 gas was introduced using a calibrated MFC. The liquid and gaseous streams were combined in an Y-mixer at room temperature and the resulting stream was directed through a 70 mm long 5% Pt/C or PtO_2 CatCart (purchased from ThalesNano) which was heated in a Syrris Asia column heater. The system was pressurized at 5 bar by applying a Zaiput BPR. In a typical experiment, the carrier solvent flow was started first. Then, when the pressure and the temperature stabilized, the gas flow was initiated by setting

the desired flow rate on the MFC. Once a stable segmented flow regime was observed, the system was ready for feed injection. In each run, the product stream was collected for 5 min after reaching steady state. The resulting material was concentrated under reduced pressure and analyzed by $^1\text{H-NMR}$.

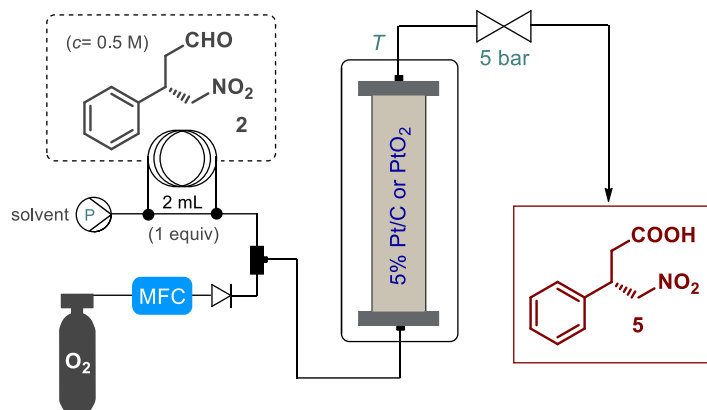


Table S7. Effects of various reaction conditions.

#	Substrate flow rate ($\mu\text{L min}^{-1}$)	O ₂ stream		T (°C)	Catalyst	Solvent	Conversion (%) ^a	Chemoselect. (%) ^a
		Flow rate (mL min^{-1})	Equiv					
1	100	0.62	0.55	90	5% Pt/C	toluene	15	approx. 30
2	100	0.62	0.55	90	PtO ₂	toluene	18	100
3	100	0	0	140	PtO ₂	toluene	0	-
4	100	0.62	0.55	140	PtO ₂	toluene	38	100
5	50	0.31	0.55	140	PtO ₂	toluene	49	100
6	100	0.62	0.55	140	PtO ₂	toluene/ <i>t</i> BuOH 1:1	49	100
7	100	0.62	0.55	140	PtO ₂	toluene/ <i>t</i> BuOH 2:1	57	100
8	100	0.62	0.55	140	PtO ₂	toluene/ <i>t</i> BuOH 3:1	65	100
9 ^b	100	0.62	0.55	140	PtO ₂	toluene/ <i>t</i> BuOH 3:1	57	100
10 ^b	100	0.62	0.55	140	PtO ₂	toluene/ <i>t</i> BuOH 3:1	39	100

^aDetermined by $^1\text{H-NMR}$ analysis of the crude product. ^bRepeated reaction with the same CatCart.

Due to fast catalyst deactivation (Table S7, entries 8–10), the PtO₂-catalyzed aerobic aldehyde oxidation was deemed impractical and was not investigated further.

4.3. NHPI-catalyzed aerobic aldehyde oxidation

A typical procedure for the continuous flow reactions is as follows.

Compound **2** and *N*-hydroxyphthalimide (NHPI) as homogeneous oxidation catalyst was dissolved in the appropriate solvent and the mixture was homogenized carefully. The starting material solution was streamed by using a Syrris Asia syringe pump which was equipped with an injection valve and a sample loop (2 mL; 1/16" OD, 0.80 mm ID). O₂ gas was introduced using a calibrated MFC. The flow rate of the feeds were adjusted in a manner to acquire 1 equiv of the substrate and 0.55 equiv of O₂. The liquid and gaseous streams were combined in an Y-mixer at room temperature and the resulting stream was directed through a 4.5-mL reaction coil (1/16" OD, 0.80 mm ID) which was

heated in an oil bath. The system was pressurized by applying a Zaiput BPR. In a typical experiment, the carrier solvent flow was started first. Then, when the pressure and temperature stabilized, the gas flow was initiated by setting the desired flow rate on the MFC. Once a stable segmented flow regime was observed, the system was ready for feed injection. In each run, the product stream was collected for 5 min after reaching steady state. The resulting material was concentrated under reduced pressure and analyzed by $^1\text{H-NMR}$.

On the basis of literature findings, the reaction was investigated initially using CH_3CN as solvent.⁵ With the aim to develop a methodology which is compatible upon telescoping with the organocatalytic conjugate addition, the reaction medium was exchanged later to CH_3NO_2 .

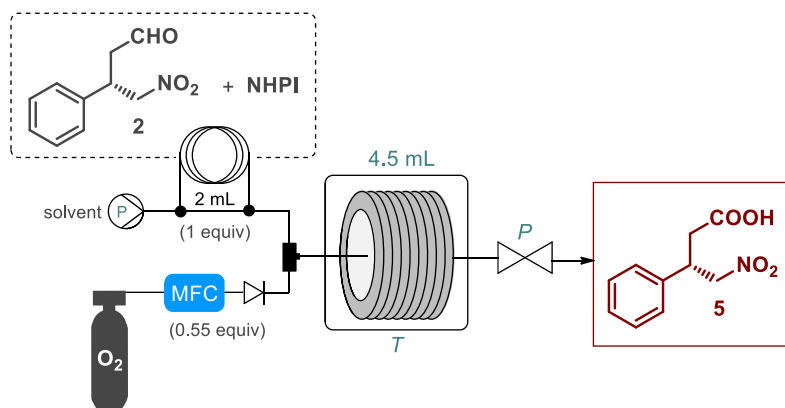


Table S8. Effects of various reaction conditions.

#	C_2 (M)	NHPI amount (equiv)	Liquid flow rate ($\mu\text{L min}^{-1}$)	O_2 flow rate ($\mu\text{L min}^{-1}$)	Solvent	T ($^\circ\text{C}$)	P (bar)	Conversion (%) ^a	Chemoselect. (%) ^a
1	0.5	0	100	0.62	CH_3CN	50	5	0	-
2	0.5	0.1	100	0.62	CH_3CN	25	5	19	>99 ^d
3	0.5	0.1	100	0.62	CH_3CN	50	5	98	>99 ^d
4	0.5	0.1	100	0.62	CH_3NO_2	50	5	74	>99 ^d
5	0.5	0.1	70	0.43	CH_3NO_2	50	5	88	100
6	0.5	0.1	100	0.62	CH_3NO_2	70	5	92	>99 ^d
7	0.5	0.1	100	0.62	CH_3NO_2	90	5	95	>99 ^d
8	0.5	0.1	100	0.62	CH_3NO_2	90	10	100	100
9	0.5	0.05	100	0.62	CH_3NO_2	90	10	100	>99 ^d
10 ^{b, c}	1	0.05	100	1.23	CH_3NO_2	90	10	100	>99 ^d

^aDetermined by $^1\text{H-NMR}$ analysis of the crude product. ^bSolubility limit of NHPI in CH_3NO_2 . ^cResidence time was measured experimentally as 33 min. ^dTraces of the corresponding peracid intermediate were detected in the $^1\text{H-NMR}$ spectrum of the crude product.

Due to the limited solubility of NHPI in CH_3NO_2 , the flow set-up had to be modified to reach higher concentrations. Solutions of **2** and NHPI were thus pumped as separate feeds by using a Syrris Asia syringe pump module which was equipped with two injection valves and two sample loops (2 mL; 1/16" OD, 0.80 mm ID, each). The flow rate of the substrate feed (P1) was set to $100 \mu\text{L min}^{-1}$ with NHPI flow rate (P2) adjusted appropriately to acquire 0.05 equiv. The liquid feeds were combined in a Y-mixer, and the resulting stream was mixed with O_2 (introduced using a calibrated MFC at 2.83 mL min^{-1} ; 0.55 equiv of O_2) via a second Y-mixer before being passed through a 10-mL reaction coil at 90°C and 10 bar. In each run, the product stream was collected for 5 min after reaching steady state. The resulting material was concentrated under reduced pressure and analyzed by $^1\text{H-NMR}$.

Compound **2** was employed at 2.3 M concentration in CH_3NO_2 , which corresponded to the aldehyde concentration determined experimentally in the appropriate organocatalytic conjugate addition (see section 3.2). Solubility of NHPI was found limited in most typical organic solvents suitable for oxidation reactions. Besides DMSO and DMF, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 8:1 was found reasonable as solvent.

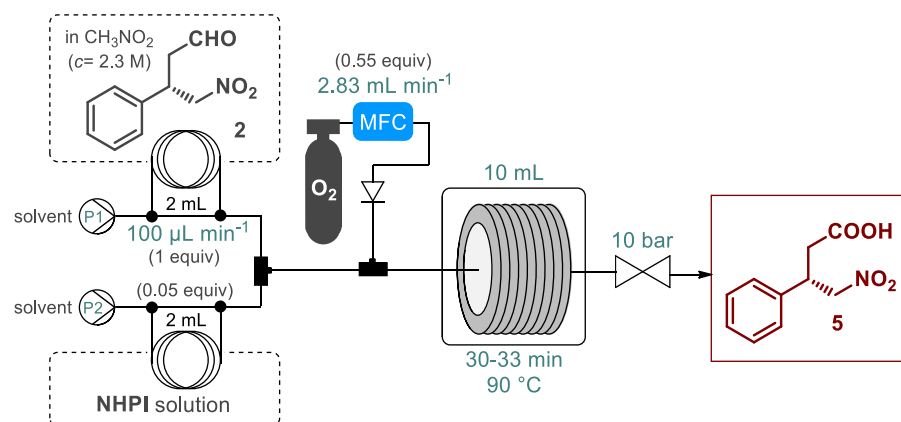
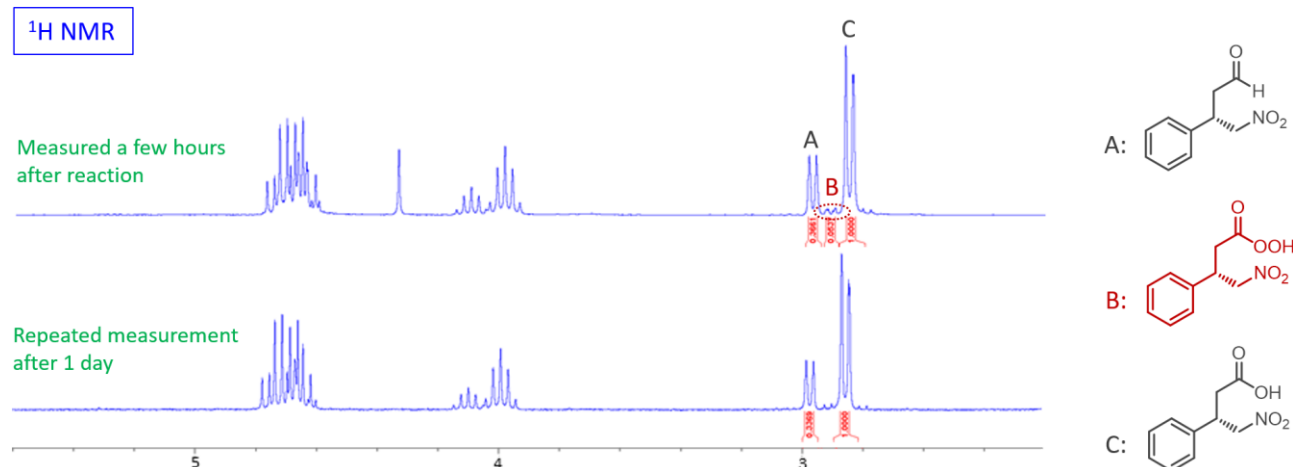


Table S9. Effects of various solvents for NHPI streaming.

#	NHPI stream (P2)			Conversion (%) ^a	Chemoselectivity (%) ^a
	Solvent	C_{NHPI} (M)	Flow rate ($\mu\text{L min}^{-1}$)		
1	DMSO	0.5	23	52	100
2	DMF	0.5	23	50	100
3	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 8:1	0.33 ^c	35	100	>99 ^e
4 ^b	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 8:1	0.33 ^c	35	100 (92) ^d	>99 ^e

^aDetermined by $^1\text{H-NMR}$ analysis of the crude product. ^b4.6 mmol scale experiment (4-fold scale-out). ^cSolubility limit. ^dIsolated yield shown in parentheses; amount isolated: 887 mg. ^eTraces of the corresponding peracid intermediate were detected in the $^1\text{H-NMR}$ spectrum of the crude product.

In most of the reactions shown in Tables S8 and S9, besides the carboxylic acid product, traces of the corresponding peracid were detected by means of $^1\text{H-NMR}$, which is in accordance with the literature suggesting peracids as labile intermediary products transforming into the desired carboxylic acid.⁶ It was verified that the peracid formed is not stable, it readily decomposes to give the corresponding carboxylic acid (see the repeated NMR measurement on the figure below).



5. Peroxy acid-mediated homogeneous oxidations

5.1. Oxidation with commercially available peracetic acid solution

A typical procedure for the continuous flow reactions is as follows.

A 0.5 M solution of compound **2** in AcOH and commercially available AcOOH solution (35 wt% in aq. AcOH) were pumped as separate feeds (P1 and P2; at $450 \mu\text{L min}^{-1}$ and $43.3 \mu\text{L min}^{-1}$, respectively; corresponds to 1 equiv of both reagents) by using a Syrris Asia syringe pump module which was equipped with two injection valves and two sample loops (8 mL and 0.8 mL; 1/16" OD, 0.80 mm ID, each). AcOH served as carrier solvent for the substrate stream, and H₂O for the peracid stream. The liquid feeds were combined in a Y-mixer, and the resulting stream was directed through a 10-mL reaction coil (1/16" OD, 0.80 mm ID) which was heated in an oil bath. The system was pressurized at 5 bar by applying a Zaiput BPR. In each run, the product stream was collected for 5 min after reaching steady state. The resulting material was concentrated under reduced pressure and analyzed by ¹H-NMR.

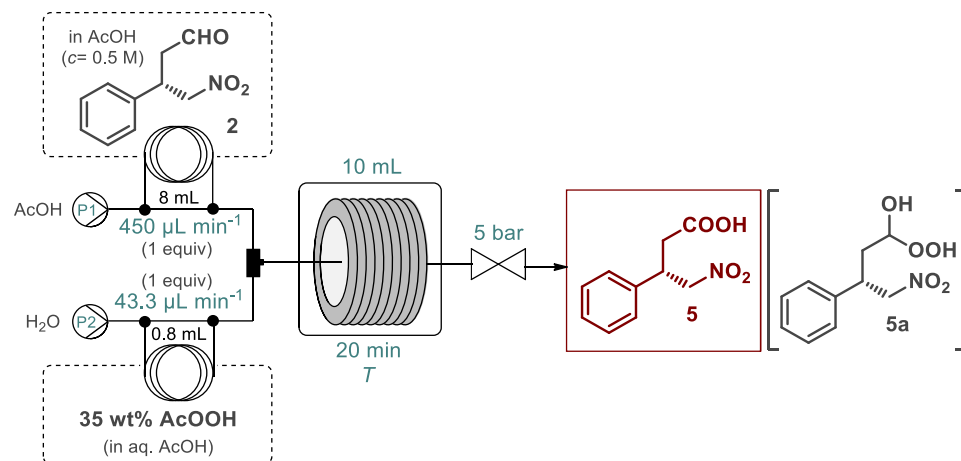


Table S10. Effects of reaction temperature.

#	<i>T</i> (°C)	Conversion (%) ^a	Chemoselectivity (%) ^a	
			5	5a
1	25	63	14	86
2	50	76	28	72
3	100	100	100	0

^aDetermined by ¹H-NMR analysis of the crude product.

5.2. Oxidation with *in situ* generated performic acid

A typical procedure for the continuous flow reactions is as follows.

A 0.5 M solution of compound **2** in HCOOH and commercially available 35 wt% aq. H₂O₂ solution were pumped as separate feeds (P1 and P2; at $475 \mu\text{L min}^{-1}$ and $20.3 \mu\text{L min}^{-1}$, respectively; corresponds to 1 equiv of both reagents) by using a Syrris Asia syringe pump module which was equipped with two injection valves and two sample loops (8 mL and 0.8 mL; 1/16" OD, 0.80 mm ID, each). HCOOH served as carrier solvent for the substrate stream, and H₂O for the H₂O₂ stream. The liquid feeds were combined in a Y-mixer, and the resulting stream was directed through a 10-mL reaction coil (1/16" OD, 0.80 mm ID) which was heated in an oil bath. The system was pressurized at 5 bar by applying a Zaiput BPR. In each run, the product stream was collected for 5 min after reaching steady state. The resulting material was concentrated under reduced pressure and analyzed by ¹H-NMR.

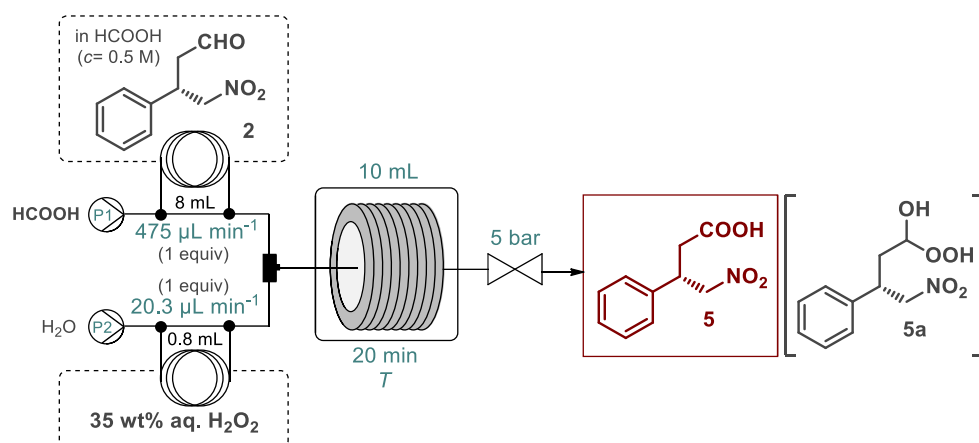


Table S11. Effects of reaction temperature.

#	T (°C)	Conversion (%) ^a	Chemoselectivity (%) ^a	
			5	5a
1	25	74	41	51
2	50	91	91	9
3	100	100	100	0

^aDetermined by ¹H-NMR analysis of the crude product.

After experiments with HCOOH serving as solvent for compound **2** and, simultaneously, also as a precursor for the corresponding peracid (Table S11), the flow setup was modified to become compatible during telescoping with the organocatalytic conjugate addition. 35 wt% aq. H₂O₂ solution and HCOOH were thus streamed as separate feeds (P2 and P3) by using a Syrris Asia syringe pump module, the former being injected *via* a sample loop (1.5 mL; 1/16" OD, 0.80 mm ID) and the latter being pumped directly. The solution of **2** was streamed (P1) *via* a sample loop (3 mL; 1/16" OD, 0.80 mm ID) using a built-in HPLC pump of a UNIQUISIS Binary Pump Module. Compound **2** was employed at 2.3 M concentration in CH₃NO₂, which corresponded to the aldehyde concentration determined experimentally in the appropriate organocatalytic conjugate addition (see section 3.2). The flow rates of the substrate and the peroxide feeds were adjusted in a manner to acquire 1 equiv of both reagents. The HCOOH, H₂O₂ and the substrate feeds were combined in two sequential Y-mixers, and the resulting stream was passed through a 5-mL reaction coil at 100 °C and 5 bar. In each run, the product stream was collected for 1–5 min after reaching steady state. The resulting material was concentrated under reduced pressure and analyzed by ¹H-NMR.

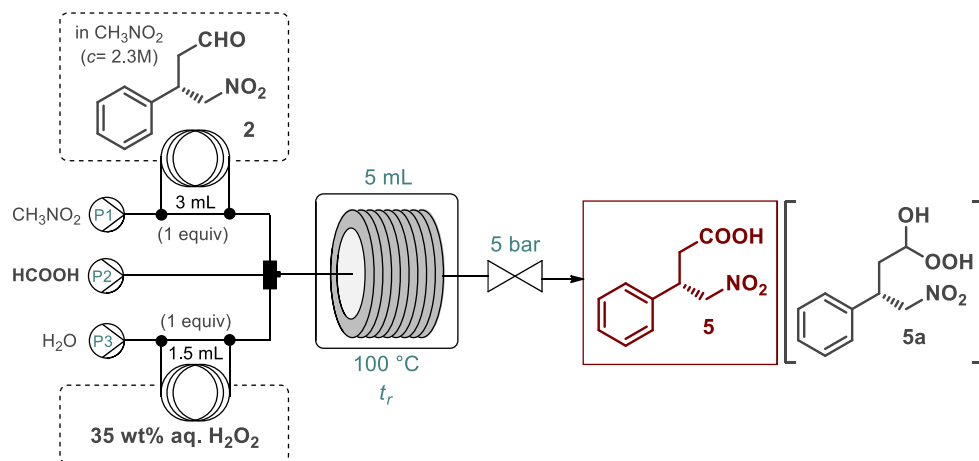
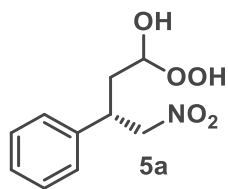


Table S12. Effects of reagent flow rates and residence time.

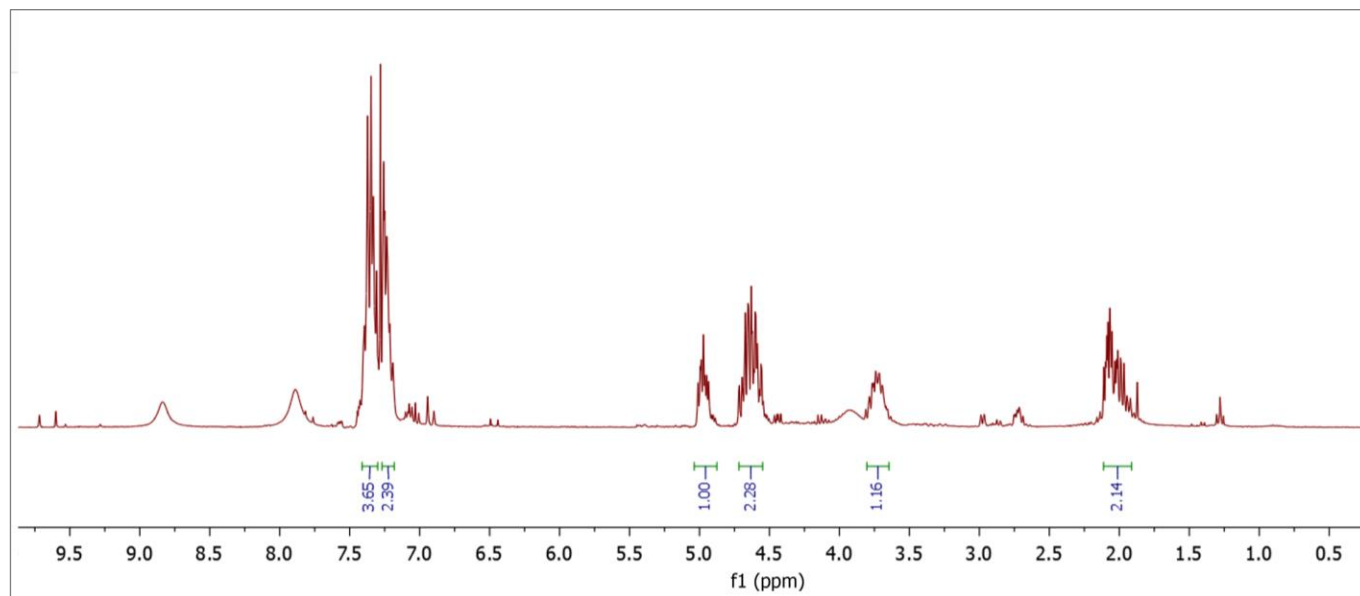
#	Flow rates ($\mu\text{L min}^{-1}$)			HCOOH amount (equiv)	t_r (min)	Conversion (%) ^a	Chemoselectivity (%) ^a	
	P1	P2	P3				5	5a
1	610	265	120	5	5	96	56	44
2	350	76	66	2.5	10	97	48	52
3	310	135	61	5	10	100	89	11
4	220	76	43	4	15	100	98	2
5	210	91	41	5	15	100	100	0
6	180	39	35	2.5	20	99	84	16
7	150	65	30	5	20	100	100	0
8	280	0	55	0	15	92	3	97

^aDetermined by ¹H-NMR analysis of the crude product.

In case of reaction temperatures ≤ 50 °C or inadequately short residence times (Table S10–12), the formation of perhydrate **5a** as side product occurred according to the NMR spectra of the crude materials.



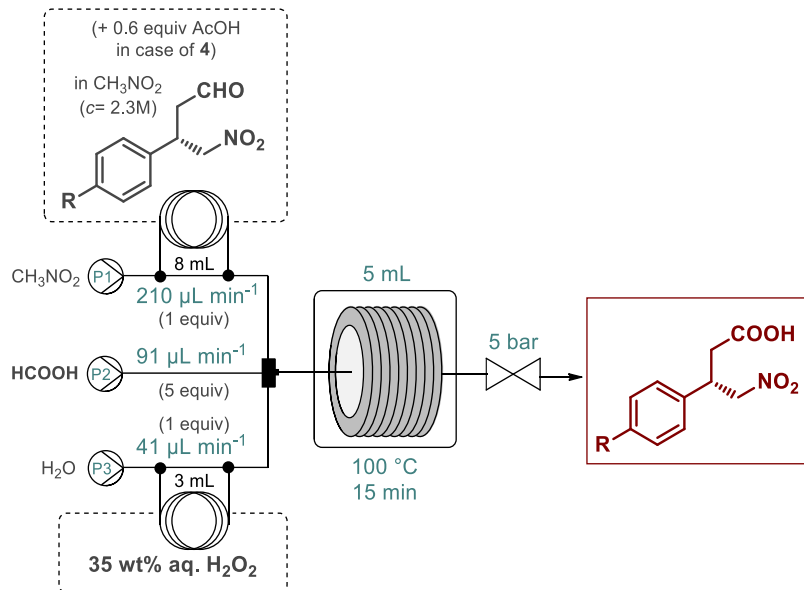
When no HCOOH was pumped but only H₂O₂ (see Table S12, entry 8), perhydrate **5a** became the main product and carboxylic acid **5** were formed only in very small quantities as corroborated by the ¹H-NMR spectrum taken after the corresponding experiment:



It cannot be excluded, however, that perhydrate **5a** may react further with unreacted aldehyde **2** to give small quantities of the corresponding bis(hydroxyalkyl) peroxide as a further side product.

The conditions in Table S12, entry 5 were designated as optimal and were employed for larger scale oxidations of chiral γ -nitroaldehydes **2**, **3** and **4**.

For the reactions, the procedure described on page S12 was followed. In case of dissolution of compound **4** in CH_3NO_2 , the addition of 0.6 equiv of AcOH was necessary to achieve a clear solution. In each experiment, the product stream was collected continuously for 20 min after reaching steady state. The resulting materials were concentrated under reduced pressure and analyzed by $^1\text{H-NMR}$.



The system proved stable during the scale-out experiments. In all reactions, sufficiently pure products were obtained after evaporation, no chromatographic purification were therefore needed. Isolated yield and ee were determined for each products. The results are summarized in Table S13.

Table S13. Summarized results of the preparative-scale oxidations of chiral aldehydes **2**, **3** and **4**.

R	H	F	Cl
Compound no.	5	6	7
Collection time	20 min	20 min	20 min
Conversion ^{a, b}	100%	100%	100%
Amount of isolated product ^b	1.99 g (9.51 mmol)	2.15 g (9.46 mmol)	2.31 g (9.48 mmol)
Isolated yield	99%	98%	98%
ee ^b	97%	96%	96%

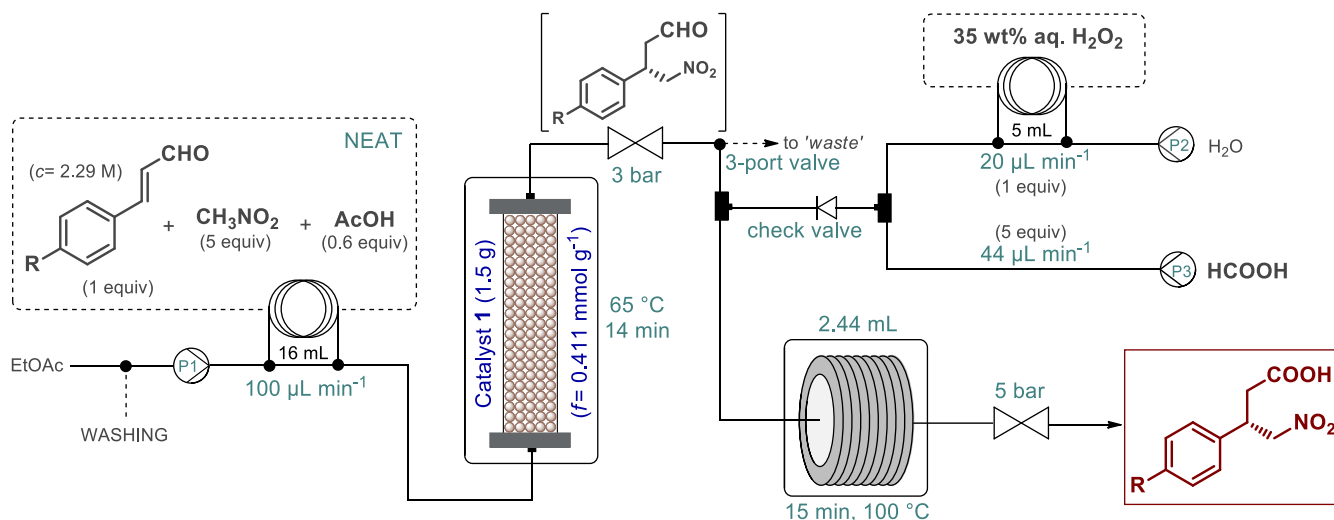
^aDetermined by $^1\text{H-NMR}$ analysis of the crude product. ^bNo side product formation, chemoselectivity was 100% in all reactions.

^cDetermined by chiral HPLC.

6. Telescoped flow synthesis of γ -nitrobutyric acids **5**, **6** and **7**

The optimal conditions determined during the step-by-step experiments (Table S1, entry 4 and Table S12, entry 5) served as basis in planning the telescoped organocatalytic conjugate addition–aldehyde oxidation sequence. A general procedure for the experiments is as follows.

For the organocatalytic conjugate addition, 1.5 g of catalyst **1** ($f = 0.411 \text{ mmol g}^{-1}$) was filled into an adjustable Omnifit glass column (6.6 mm ID) which was heated by a Syrris Asia column heater at $65 \text{ }^\circ\text{C}$. The continuous flow of the liquid stream was provided by a built-in HPLC pump of a UNIQUISIS Binary Pump Module (P1). A 3-bar fixed-pressure BPR (IDEX) was installed after the column outlet to ensure a stable flow. Prior to the reactions, the catalyst was swollen by pumping EtOAc at $200 \text{ } \mu\text{L min}^{-1}$ for 30 min. The reaction mixture consisting of the corresponding cinnamaldehyde (1 equiv), CH_3NO_2 (5 equiv) and AcOH (0.6 equiv) was streamed *via* a 16-mL sample loop (1/8" OD, 1.58 mm ID) using the built-in injection valve of the pump module and EtOAc as carrier solvent. In each substrate mixture, the concentration of the aldehyde component was 2.29 M as determined experimentally. The flow rate was set to $100 \text{ } \mu\text{L min}^{-1}$ which corresponded to 14 min residence time on the catalyst bed. 35 wt% aq. H_2O_2 solution and HCOOH were introduced as separate feeds (P2 and P3) by using a Syrris Asia syringe pump module at flow rates of $20 \text{ } \mu\text{L min}^{-1}$ and $44 \text{ } \mu\text{L min}^{-1}$, respectively, which corresponded to 1 equiv of H_2O_2 and 5 equiv of HCOOH with respect to the aldehyde stream. The peroxide solution was injected using a manual injection valve *via* a 5-mL sample loop (1/16" OD, 0.80 mm ID) with H_2O serving as carrier solvent, and HCOOH were pumped directly; the two feeds were combined in a Y-mixer. The reaction mixture exiting the chiral catalyst column was directed through a 3-port valve, and was next mixed up with the combined HCOOH/ H_2O_2 stream in a second Y-piece. The inclusion of a check valve prevented any incidental backflow of liquid towards the syringe pump module. The resulting solution was finally directed through a 2.44-mL reaction coil (1/16" OD, 0.80 mm ID) which was heated at $100 \text{ }^\circ\text{C}$ in an oil bath. The system was pressurized at 5-bar using a Zaiput BPR.



In a typical experiment, the carrier solvent flows (P1 and P2) and HCOOH (P3) were started first with the 3-port valve set to 'waste' direction. Once pressure and temperature were stabilized, the cinnamaldehyde/ CH_3NO_2 /AcOH feed were injected. After 30 min, when the stream exiting the chiral catalyst column reached steady state, the flow direction was switched by the 3-port valve, and, simultaneously, the H_2O_2 stream was initiated by injection. The product stream exiting the heated reaction coil was collected continuously for 1 h after reaching steady state (30 min after initiating the H_2O_2 stream). After this time, first H_2O_2 then substrate injection were stopped. Between each experiment, the catalyst bed was washed carefully with AcOH (0.5 mL min^{-1} , 25 min) and then with AcOH/EtOAc 1:9 (0.5 mL min^{-1} , 25 min) while the eluting liquid was directed to 'waste' direction. During this time, the 2.44-mL reaction coil was washed with MeOH ($200 \text{ } \mu\text{L min}^{-1}$).

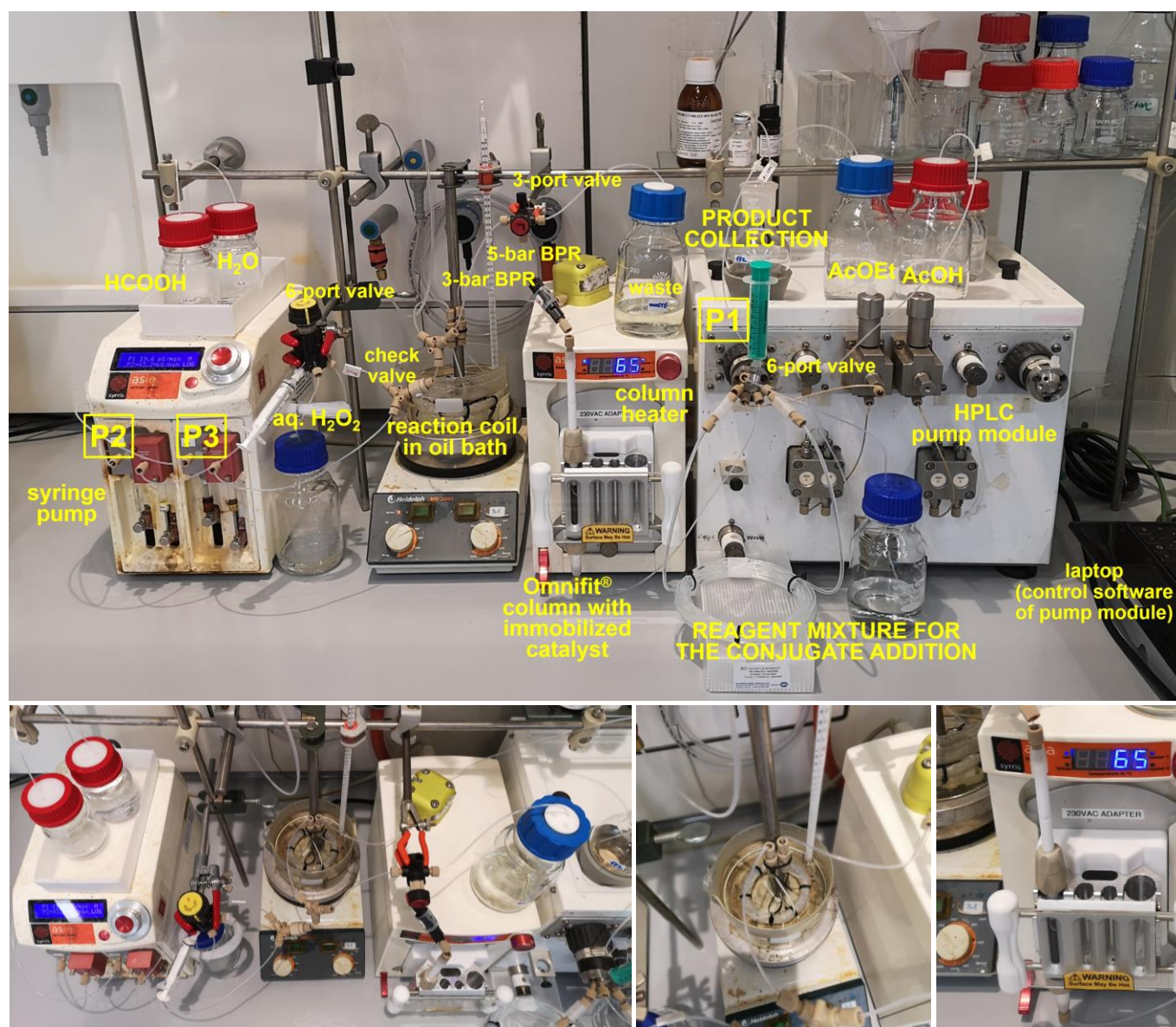
The resulting materials were concentrated under reduced pressure and analyzed by NMR. In all reactions, sufficiently pure products were obtained after evaporation, no chromatographic purification were therefore needed. Isolated yield and ee were determined for each products. The results of the telescoped syntheses are summarized in Table S14.

Table S14. Summarized results of the telescoped continuous flow synthesis of chiral γ -nitrobutyric acids **5**, **6** and **7**.

R	H	F	Cl
Compound no.	5	6	7
Collection time	1 h	1 h	1 h
Amount of isolated product	2.77 g (13.24 mmol)	2.94 g (12.94 mmol)	3.14 g (12.89 mmol)
Isolated yield	96%	94%	94%
Productivity	2.77 g h ⁻¹ of pure product	2.94 g h ⁻¹ of pure product	3.14 g h ⁻¹ of pure product
ee ^a	97%	96%	96%

^aDetermined by chiral HPLC.

Pictures of the telescoped continuous flow setup:



7. Synthetic protocols for enantiomeric excess determination

7.1. Preparation of racemic reference samples

Racemic reference samples of γ -nitroaldehydes **2**, **3** and **4** were prepared by using 1:1 mixtures of (*R*)- and (*S*)- α,α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether as organocatalyst according to the following procedure. A mixture containing the corresponding cinnamaldehyde derivative (3 mmol), nitromethane (9 mmol), AcOH (0.9 mmol) and 10 mol% of the racemic catalyst was stirred for 24 h at RT in MeOH (6 mL) as solvent. After then, the mixture was filtrated through a pad of celite, washed with CH₂Cl₂ and evaporated. In each cases, the crude product was purified by means of column chromatography using 10–70% gradient of ethyl acetate in 40-60 petroleum ether as eluent.

Racemic samples of γ -nitrobutyric acids **5**, **6** and **7** were prepared by oxidation of (*rac*)-**2**, (*rac*)-**3** and (*rac*)-**4** according to the general continuous flow procedure detailed in section 5.2. Sufficiently pure products were obtained after evaporation at reduced pressure.

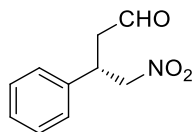
7.2. Product derivatization

Chiral γ -nitroaldehydes **2**, **3** and **4** as well as the racemic samples were reduced to the corresponding alcohols according to the following procedure. To a cooled solution ($-5\text{ }^{\circ}\text{C}$) of NaBH₄ (0.1 mmol) in EtOH (1 mL) the solution of the corresponding aldehyde (1 equiv, 0.2 mmol) in EtOH (2 mL) was added dropwise. The reaction was stirred at the same temperature for 20 min and was then quenched with H₂O (10 mL). The mixture was extracted with CH₂Cl₂ (3 x 10 mL), washed with brine, dried over MgSO₄ and evaporated at reduced pressure. The derivatized samples were used for enantiomeric excess determination without further purification.

Chiral γ -nitrobutyric acids **5**, **6** and **7** as well as the racemic samples were converted to the corresponding methyl esters according to the following procedure. The chiral acid (0.2 mmol) was dissolved in a mixture of CH₂Cl₂ and MeOH (2 mL and 0.4 mL, respectively), and cooled to 0 $^{\circ}\text{C}$. To this cooled solution, *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDC·HCl; 0.3 mmol) and 4-dimethylaminopyridine (DMAP; 0.02 mmol) were added. The reaction was stirred at the same temperature for 2 h and was then quenched with saturated NH₄Cl (8 mL). The mixture was extracted with diethyl ether (3 x 10 mL), dried over Na₂SO₄ and evaporated at reduced pressure. The derivatized samples were used for enantiomeric excess determination without further purification.

8. Characterization data

(S)-4-nitro-3-phenylbutanal (**2**):



Following the general continuous flow procedure (section 3.2) using nitromethane and *trans*-cinnamaldehyde, 6.29 g (32.56 mmol, 95%) of the title compound was obtained as a pale yellow oil.

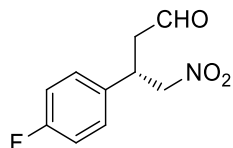
NMR data of the compound matches the reported literature.⁷

HRMS (ESI, negative mode) *m/z*: [M – H][–] Calcd for C₁₀H₁₀NO₃ 192.0666; Found 192.0667.

The product was converted to the corresponding alcohol and ee was determined by HPLC using a Chiralpak IB column (hexane-*i*PrOH 9/1, 1 mL min⁻¹, 210 nm, 25 °C): *t*_{minor}= 14.80 min, *t*_{major}= 16.88 min, ee= 97%.

[α]_D²⁵= –10.1 (c= 1.00, CHCl₃) {lit.⁸ [α]_D²⁴= –8.3 (c= 1.00, CHCl₃)}.

(S)-3-(4-fluorophenyl)-4-nitrobutanal (**3**):



Following the general continuous flow procedure (section 3.2) using nitromethane and 4-fluorocinnamaldehyde, 6.87 g (32.53 mmol, 95%) of the title compound was obtained as a pale yellow oil.

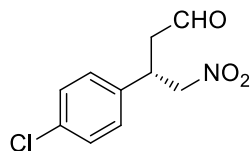
NMR data of the compound matches the reported literature.⁷

HRMS (ESI, negative mode) *m/z*: [M – H][–] Calcd for C₁₀H₉FNO₃ 210.0572; Found 210.0572.

The product was converted to the corresponding alcohol and ee was determined by HPLC using a Chiralpak IC column (hexane-*i*PrOH 9/1, 1 mL min⁻¹, 210 nm, 25 °C): *t*_{minor}= 15.60 min, *t*_{major}= 17.88 min, ee= 96%.

[α]_D²⁵= –3.3 (c= 1.00, CHCl₃) {lit.⁸ [α]_D²⁵= –2.4 (c= 1.00, CHCl₃)}.

(S)-3-(4-chlorophenyl)-4-nitrobutanal (**4**):



Following the general continuous flow procedure (section 3.2) using nitromethane and 4-chlorocinnamaldehyde, 7.22 g (31.72 mmol, 92%) of the title compound was obtained as a pale yellow oil.

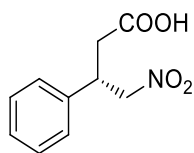
NMR data of the compound matches the reported literature.⁷

HRMS (ESI, negative mode) *m/z*: [M – H][–] Calcd for C₁₀H₉ClNO₃ 226.0276; Found 226.0276.

The product was converted to the corresponding alcohol and ee was determined by HPLC using a Chiralpak IC column (hexane-*i*PrOH 9/1, 1 mL min⁻¹, 210 nm, 25 °C): *t*_{minor}= 15.56 min, *t*_{major}= 17.34 min, ee= 96%.

[α]_D²⁵= –23.1 (c= 1.00, CHCl₃) {lit.⁸ [α]_D²⁶= –20.5 (c= 1.00, CHCl₃)}.

(S)-4-nitro-3-phenylbutanoic acid (**5**):



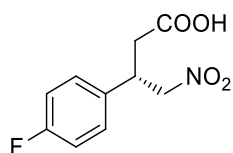
Following the general continuous flow procedure (section 6) using *trans*-cinnamaldehyde as substrate, 2.77 g (13.24 mmol, 96%) of the title compound was obtained as a pale yellow solid (mp: 86–90 °C).

NMR data of the compound matches the reported literature.⁸

HRMS (ESI, negative mode) m/z : $[M - H]^-$ Calcd for $C_{10}H_{10}NO_4$ 208.0615; Found 208.0615.

The product was converted to the corresponding methyl ester and ee was determined by HPLC using a Chiralpak IB column (hexane-*i*PrOH 95/5, 1 mL min⁻¹, 210 nm, 25 °C): t_{minor} = 15.73 min, t_{major} = 21.13 min, ee = 97%.

(S)-3-(4-fluorophenyl)-4-nitrobutanoic acid (**6**):



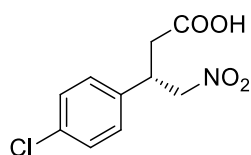
Following the general continuous flow procedure (section 6) using 4-fluorocinnamaldehyde as substrate, 2.94 g (12.94 mmol, 94%) of the title compound was obtained as a pale yellow oil.

NMR data of the compound matches the reported literature.⁹

HRMS (ESI, negative mode) m/z : $[M - H]^-$ Calcd for $C_{10}H_9FNO_4$ 226.0521; Found 226.0521.

The product was converted to the corresponding methyl ester and ee was determined by HPLC using a Chiralpak IC column (hexane-*i*PrOH 95/5, 1 mL min⁻¹, 210 nm, 25 °C): t_{minor} = 16.72 min, t_{major} = 17.44 min, ee = 96%.

(S)-3-(4-chlorophenyl)-4-nitrobutanoic acid (**7**):



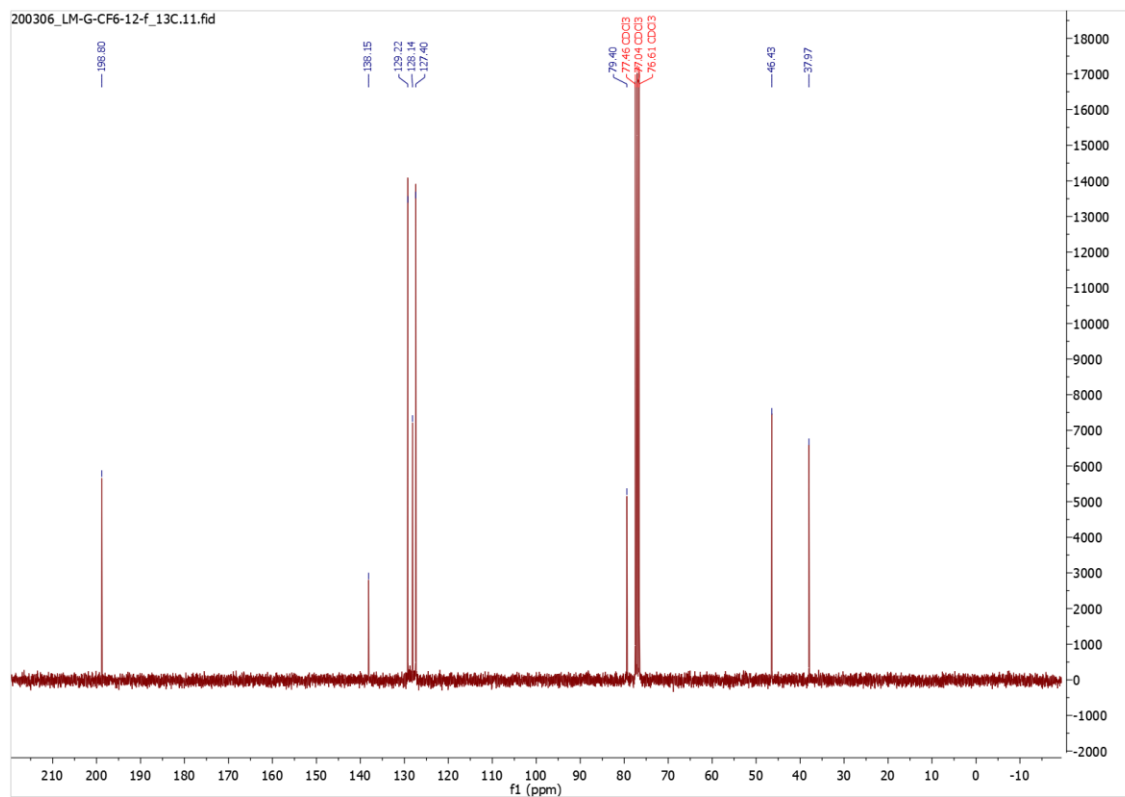
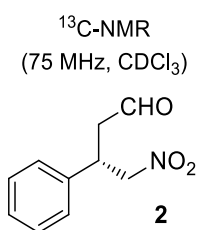
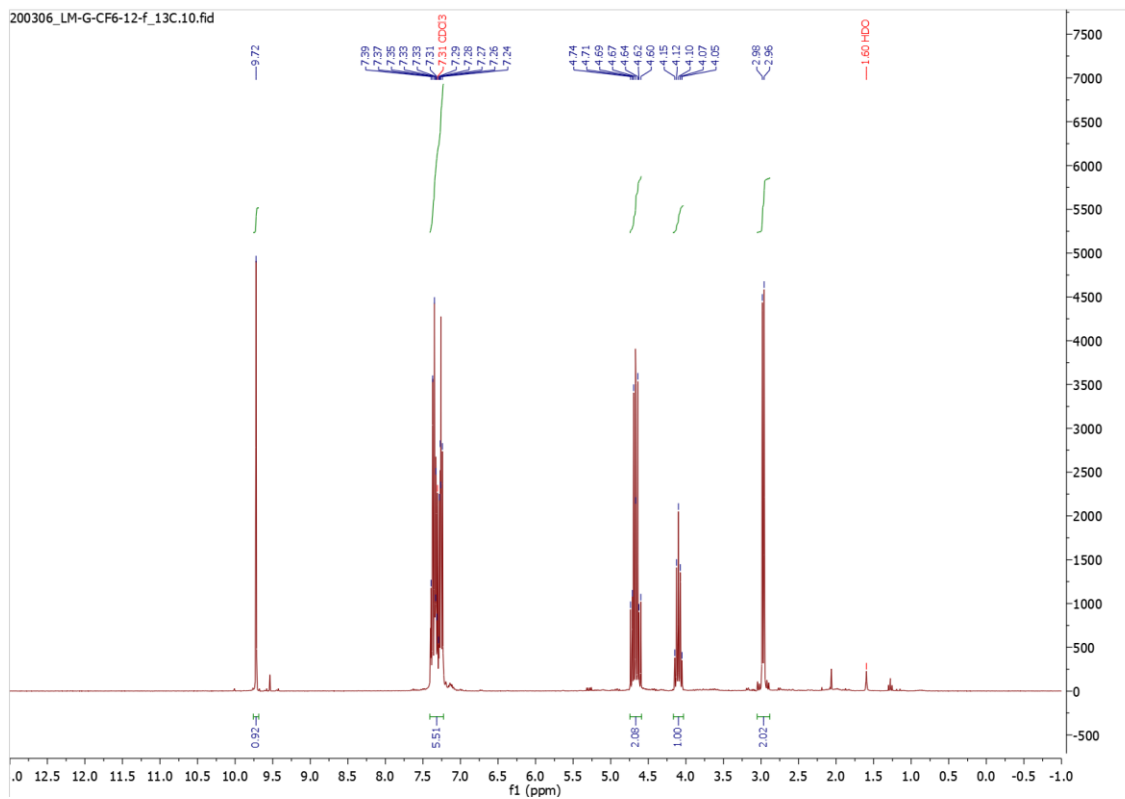
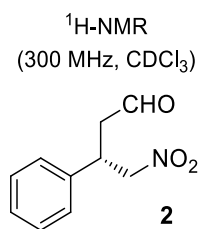
Following the general continuous flow procedure (section 6) using 4-chlorocinnamaldehyde as substrate, 3.14 g (12.89 mmol, 94%) of the title compound was obtained as a pale yellow solid (mp: 73–76 °C; lit.¹⁰ 78–79 °C).

NMR data of the compound matches the reported literature.¹¹

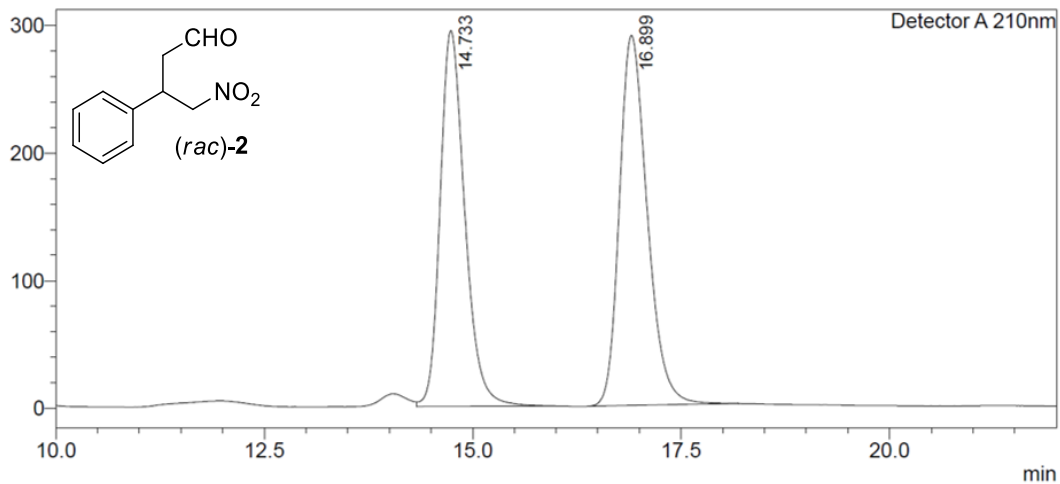
HRMS (ESI, negative mode) m/z : $[M - H]^-$ Calcd for $C_{10}H_9ClNO_4$ 242.0226; Found 242.0225.

The product was converted to the corresponding methyl ester and ee was determined by HPLC using a Chiralpak IB column (hexane-*i*PrOH 95/5, 1 mL min⁻¹, 210 nm, 25 °C): t_{minor} = 19.98 min, t_{major} = 23.10 min, ee = 96%.

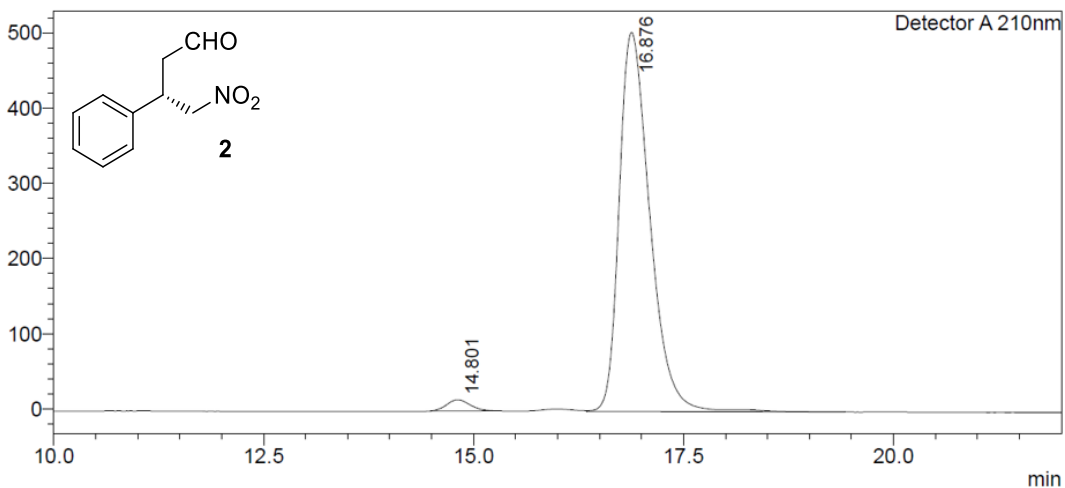
9. Collection of NMR spectra and HPLC chromatograms



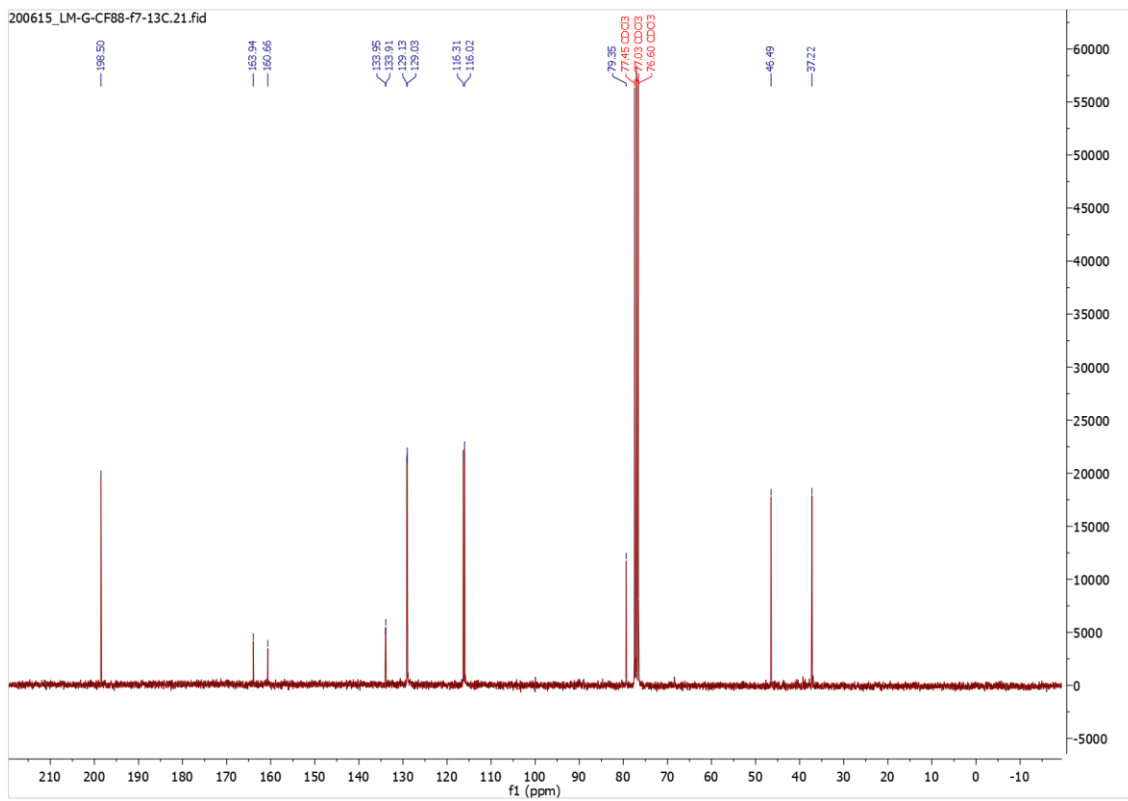
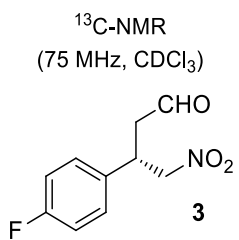
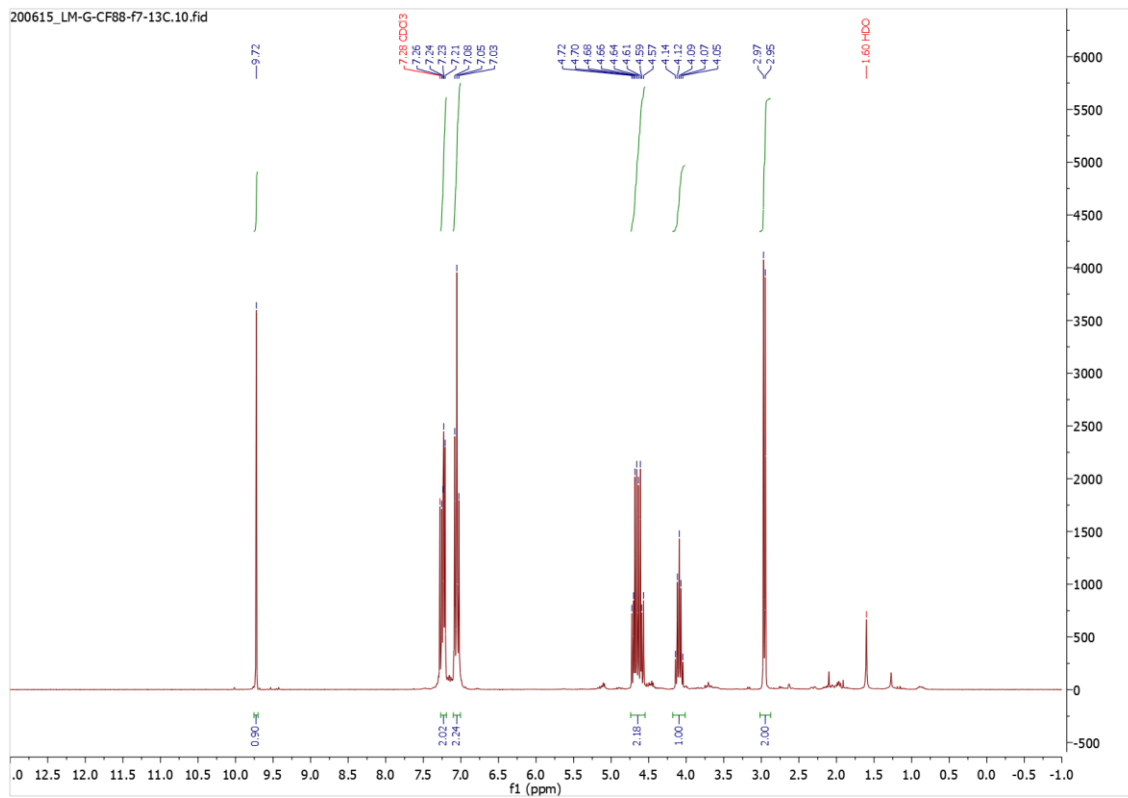
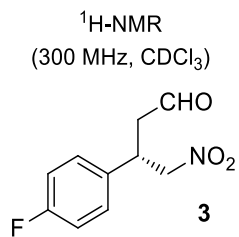
HPLC chromatograms



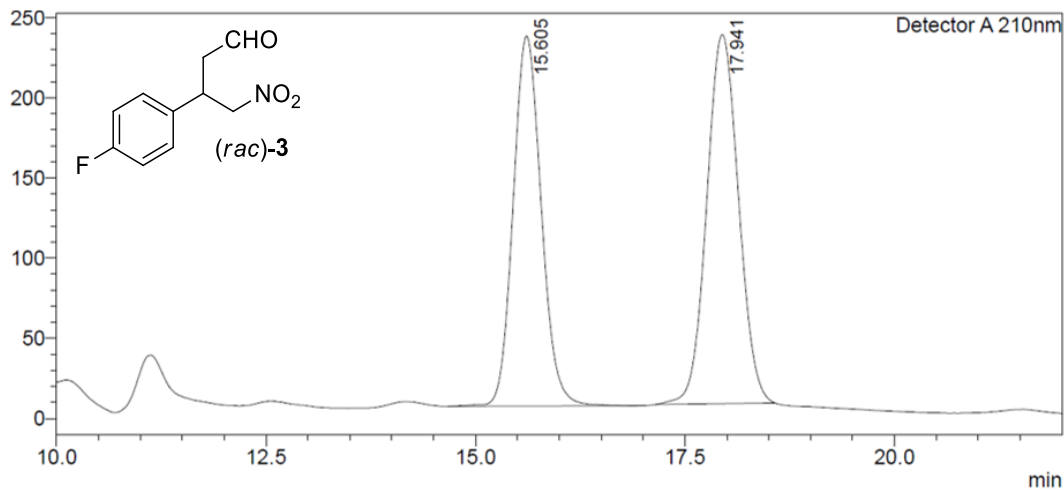
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2	16.899	6748273	290247	52.652
Total		12816834	584854	



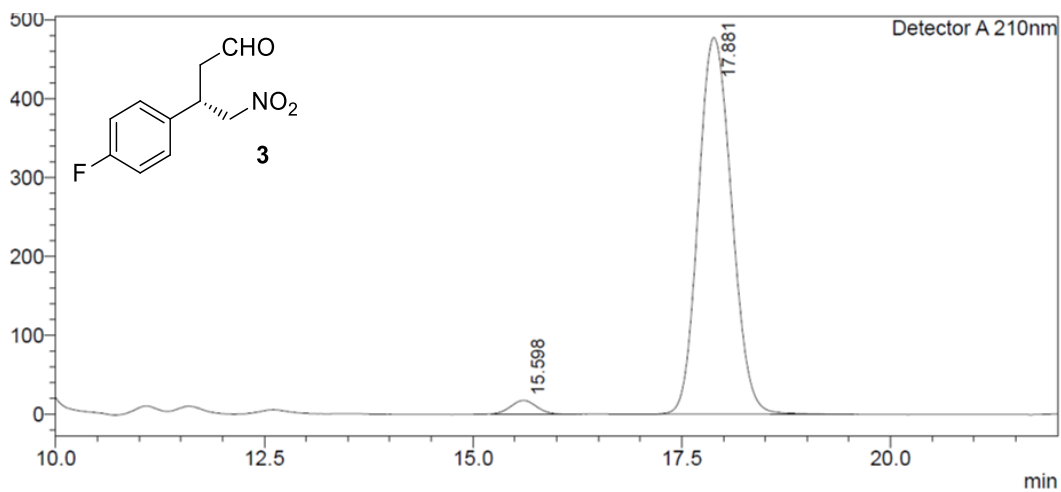
Peak#	Ret. Time	Area	Height	Conc.
1	14.801	223131	13066	1.714
2	16.876	12791596	503658	98.286
Total		13014727	516724	



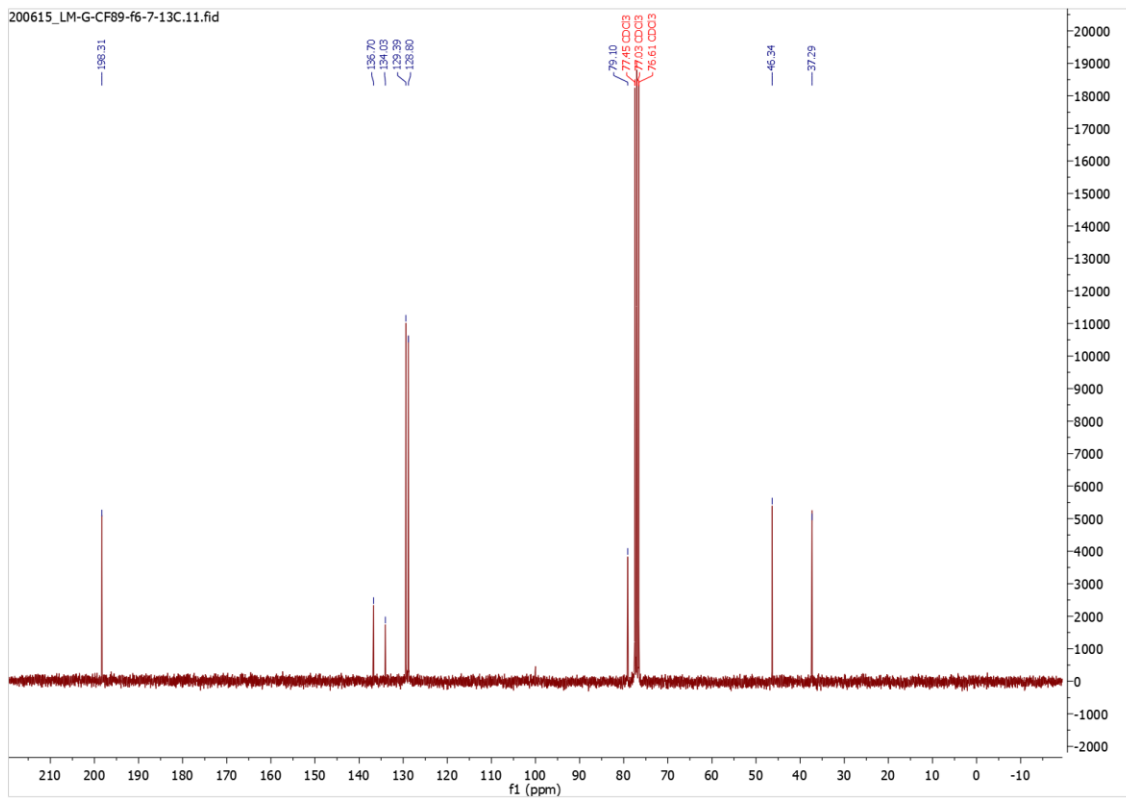
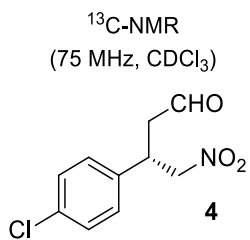
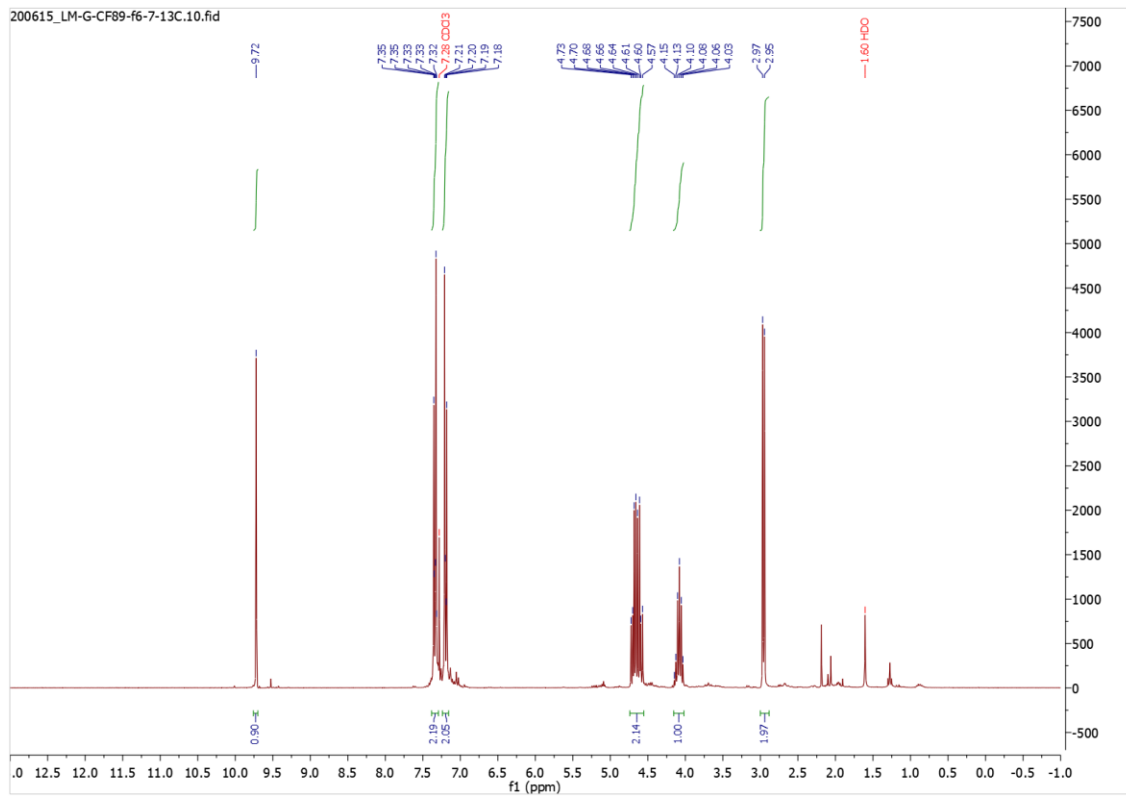
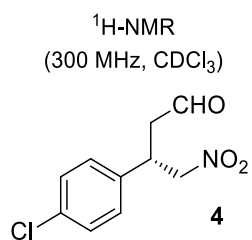
HPLC chromatograms



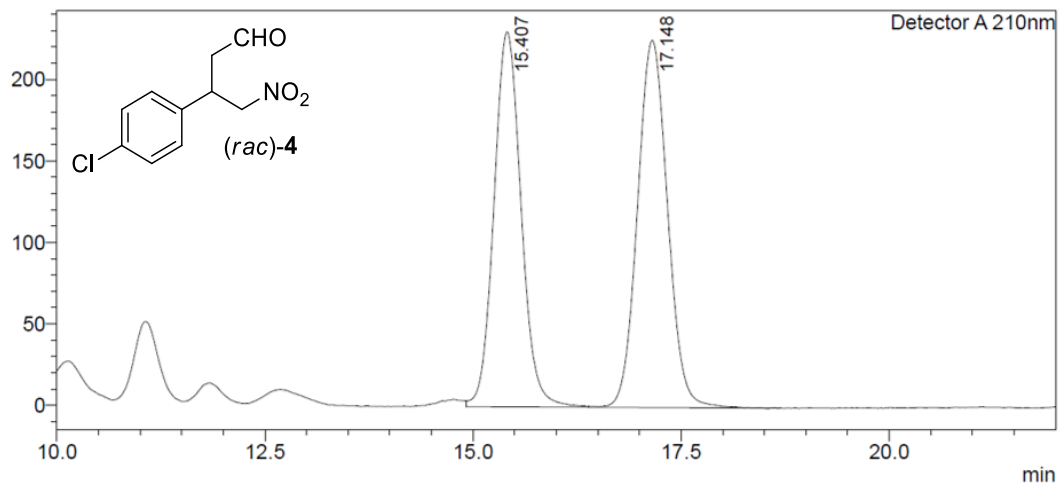
Peak#	Ret. Time	Area	Height	Conc.
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2	17.941	5546887	221808	51.107
Total		10853476	451719	



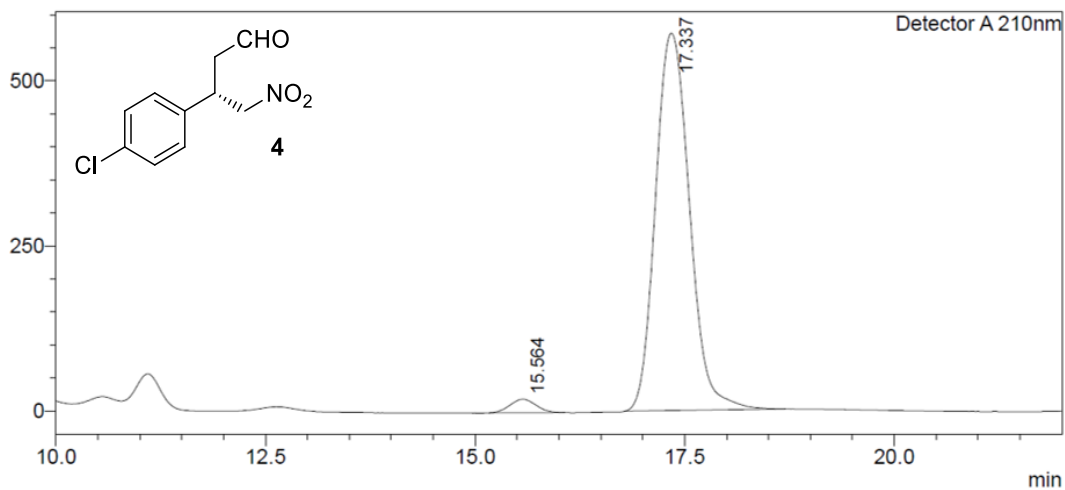
Peak#	Ret. Time	Area	Height	Conc.
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2	17.881	13223244	476924	97.790
Total		13522103	492540	



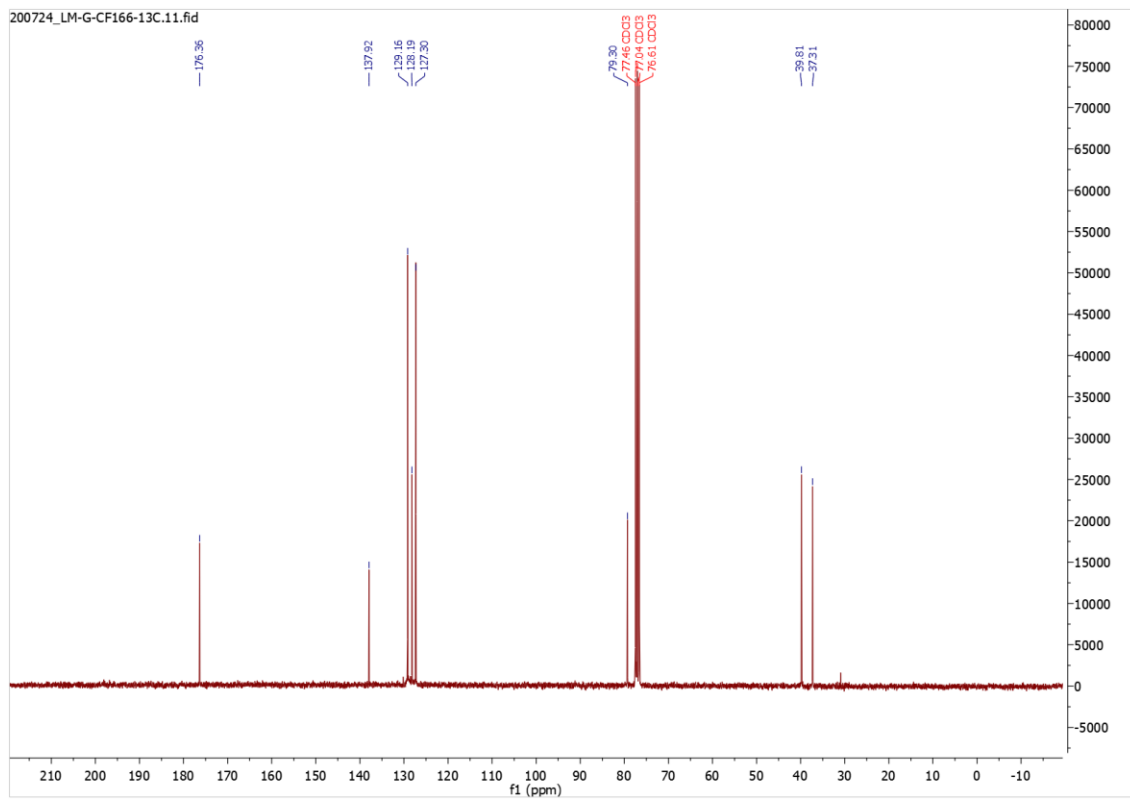
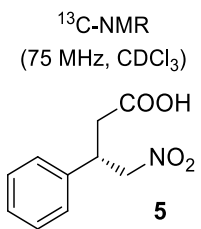
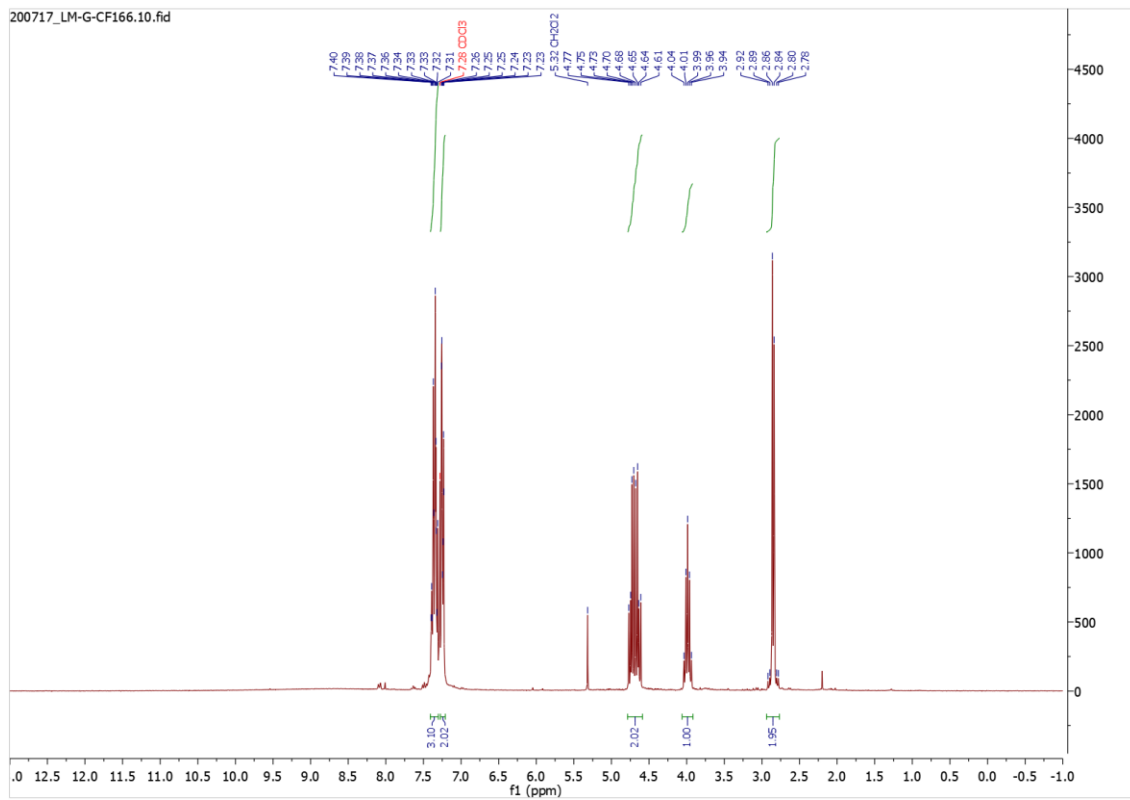
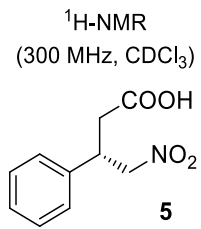
HPLC chromatograms



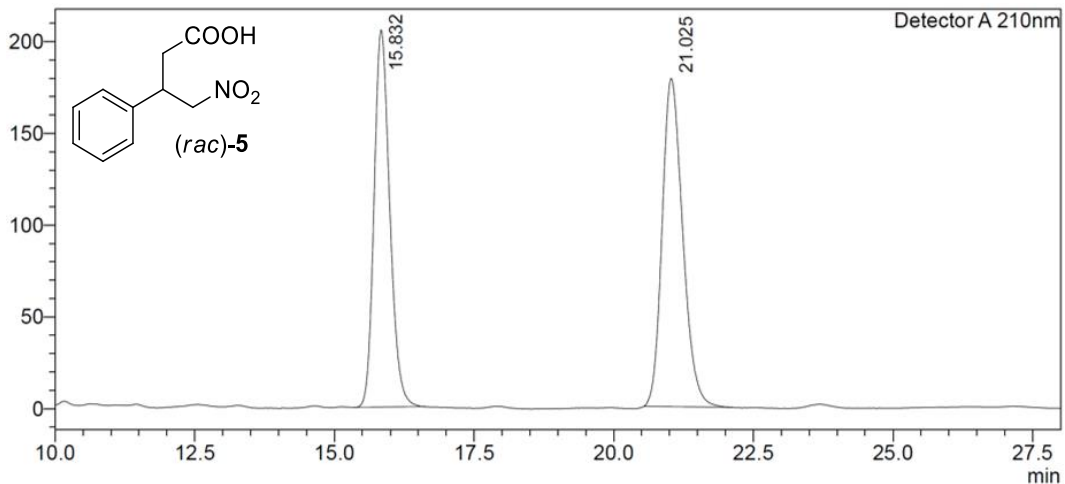
Peak#	Ret. Time	Area	Height	Conc.
1	15.407	5312080	230121	49.562
2	17.148	5405909	222056	50.438
Total		10717989	452177	



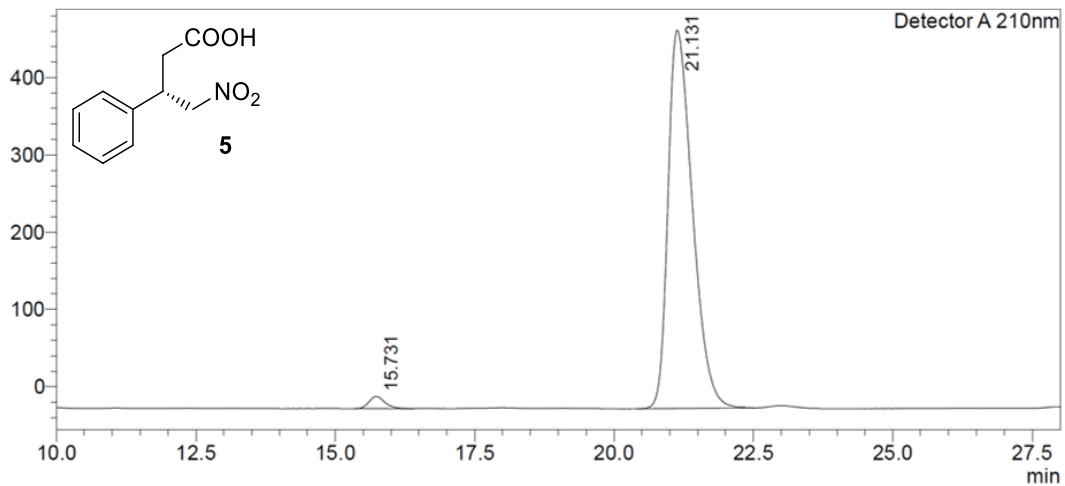
Peak#	Ret. Time	Area	Height	Conc.
1	15.564	353593	18413	2.146
2	17.337	16125273	571428	97.854
Total		16478866	589841	



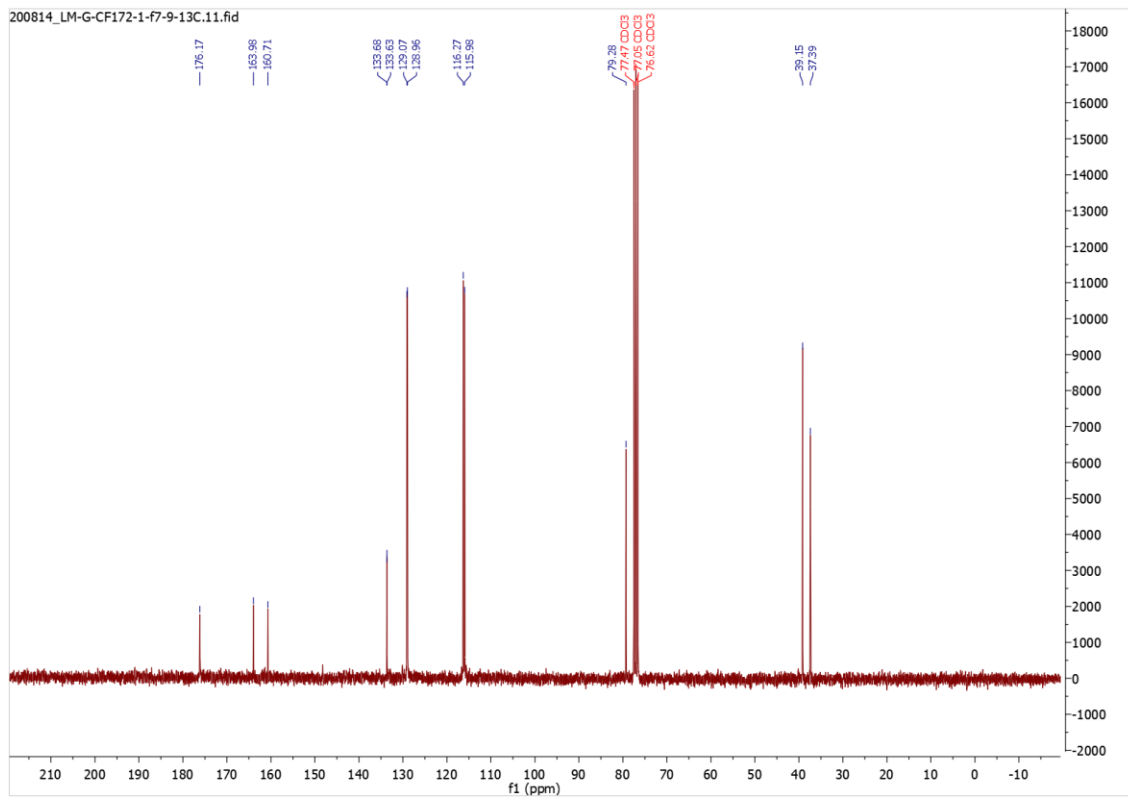
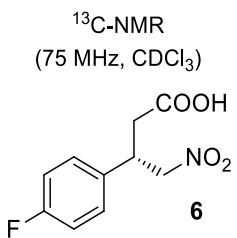
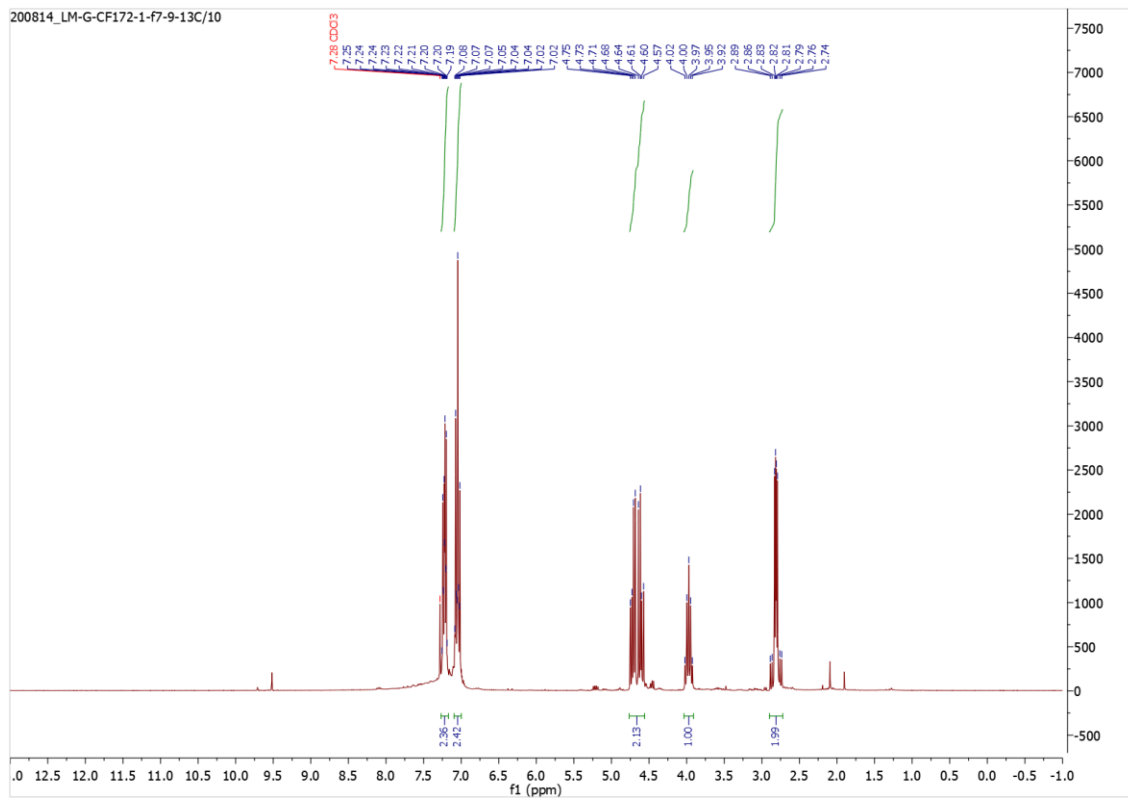
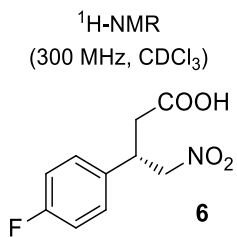
HPLC chromatograms



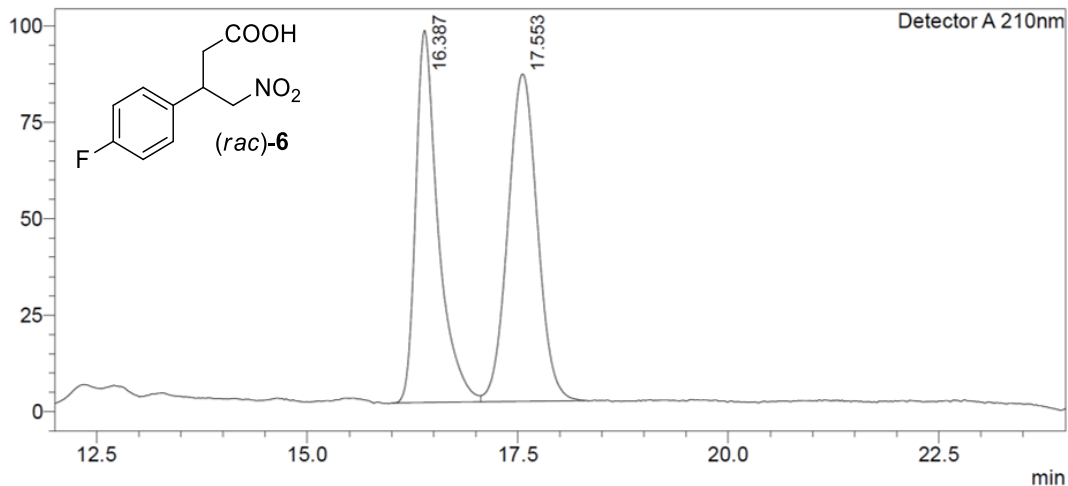
Peak#	Ret. Time	Area	Height	Conc.
1	15.832	4027899	205504	48.267
2	21.025	4317205	174987	51.733
Total		8345104	380491	



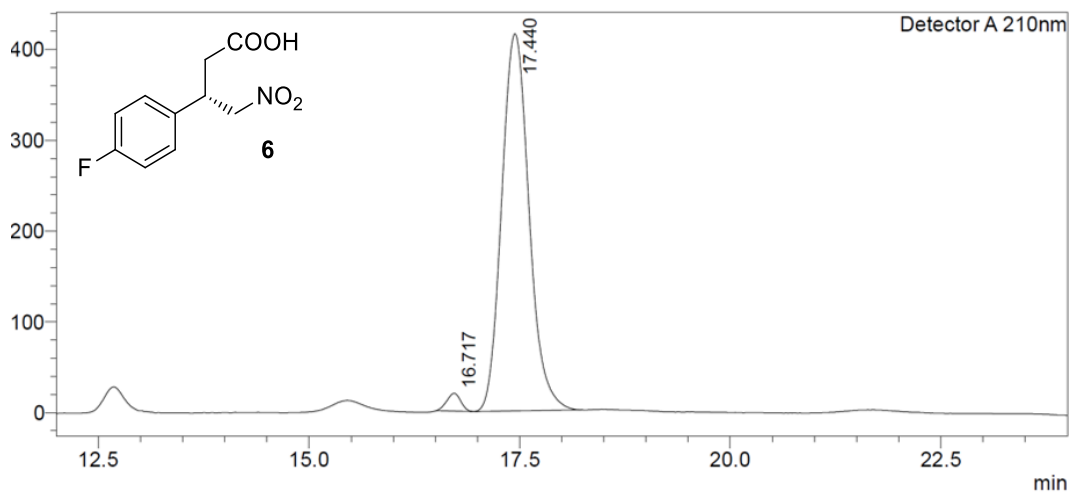
Peak#	Ret. Time	Area	Height	Conc.
1	15.731	267762	14854	1.763
2	21.131	14922716	489457	98.237
Total		15190477	504311	



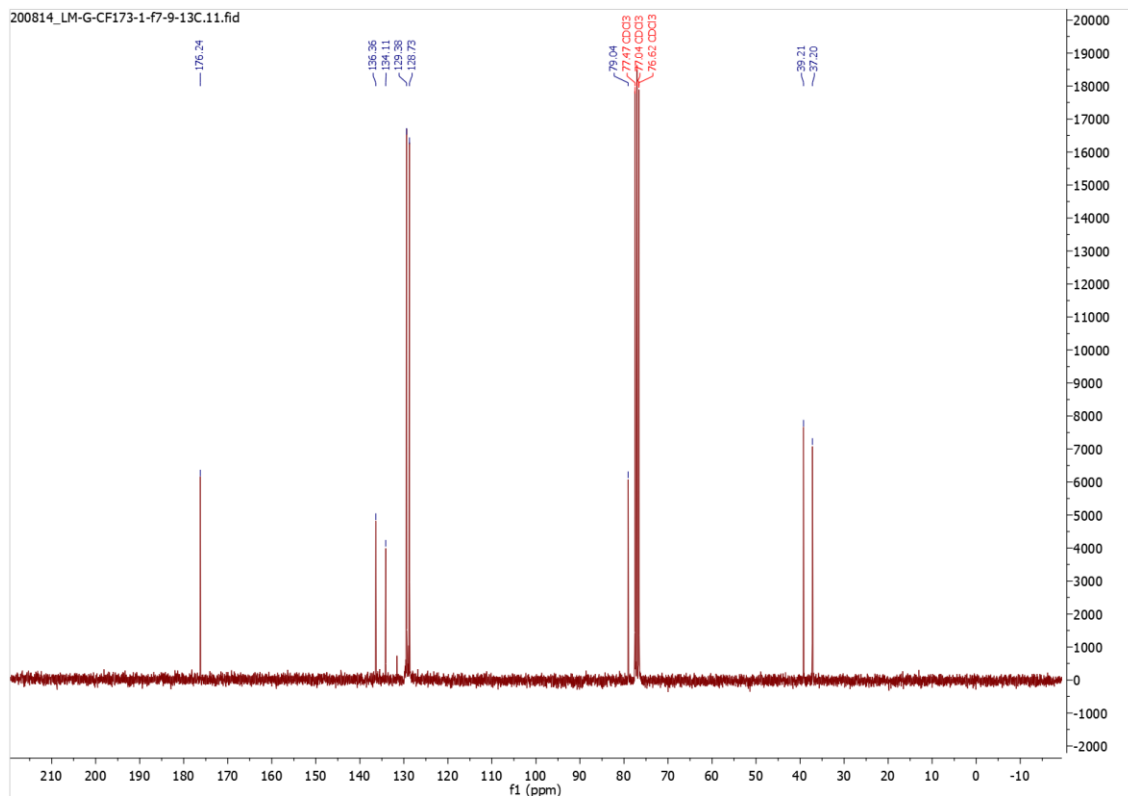
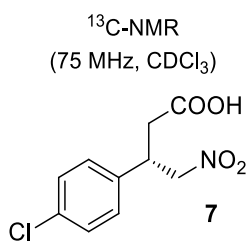
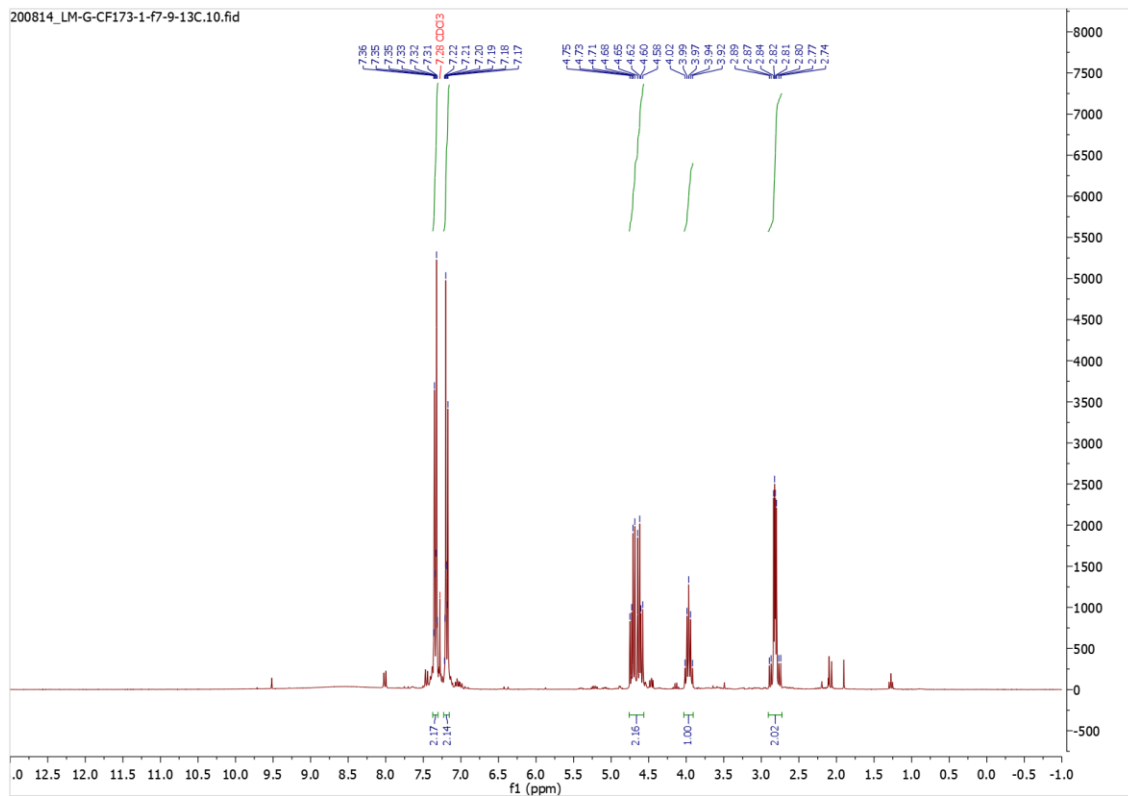
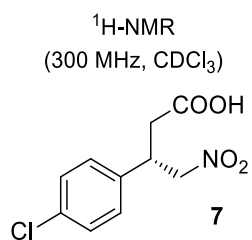
HPLC chromatograms



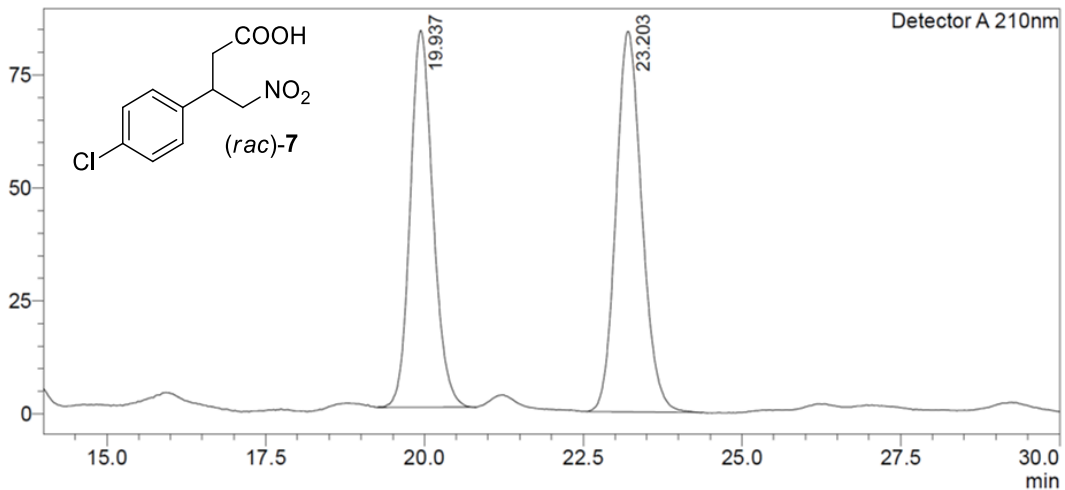
Peak#	Ret. Time	Area	Height	Conc.
1	16.387	1788960	96405	49.074
2	17.553	1856481	81192	50.926
Total		3645442	177597	



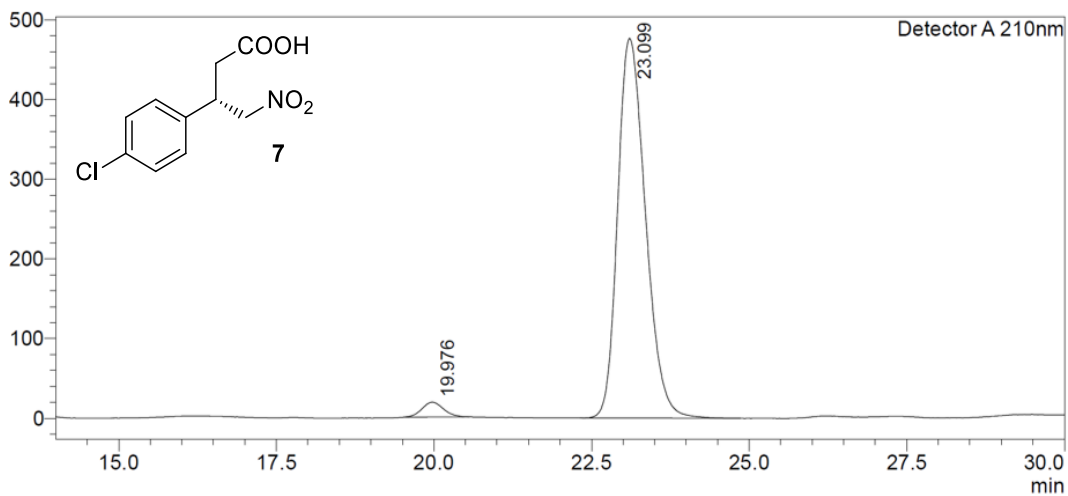
Peak#	Ret. Time	Area	Height	Conc.
1	16.717	207663	18851	2.161
2	17.440	9401914	415419	97.839
Total		9609577	434270	



HPLC chromatograms



Peak#	Ret. Time	Area	Height	Conc.
1	19.937	2088084	83438	48.174
2	23.203	2246379	82331	51.826
Total		4334463	165770	



Peak#	Ret. Time	Area	Height	Conc.
1	19.976	332671	16235	2.223
2	23.099	14631094	476833	97.777
Total		14963765	493068	

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