Supplementary Information

One-Sequence Mechanochemical Synthesis–Deracemisation of a Levetiracetam Intermediate.

Guillaume Wery[a] and Tom Leyssens *[a]

*Corresponding author: tom.leyssens@uclouvain.be

[a] G. Wery, Prof. Dr. T. Leyssens,; Department of Molecular Chemistry, Materials and Catalysis; Institute of Condensed Matter and Nanosciences; Université Catholique de Louvain; Place Louis Pasteur, 1 bte L4.01.06, 1348 Louvain-La-Neuve (Belgium)

Table of Contents

1. Tables of experiments 3
1.1. Mechanochemical synthesis of **1a** 3
1.2. One-pot deracemisation 4
1.2.1. Compound **1a** 4
1.2.2. Compound **1b** 5
2. Experimental Section 6
2.1. General Information 6
2.1.1. Materials 6
2.1.2. Devices 6
2.2. Experimental Protocols 7
3. Characterization 9
3.1. ^{1}H-NMR-Spectra 9
3.2. cHPLC Analysis 18

1. Tables of experiments

1.1. Mechanochemical synthesis of 1a

Table S1 : List of the mechanochemical syntheses performed on **1a**. The mixture was milled 90 min at 30 Hz.

N°	Base	$m_{I(RS)\text{-}2}$ [mg]	Bulk	V_{Bulk} [mL]	Additives	Balls Ø [mm]	# of balls
S1	NMM	280	NaCl	5.0	/	10	3
S2	NMM	280	Na_2SO_4	5.0	/	10	3
S3	DBU	280	NaCl	5.0	/	10	3
S4	DBU	280	Na_2SO_4	5.0	/	10	3
S5	NaOH	280	NaCl	5.0	/	10	3
S6	NaOH	280	Na_2SO_4	5.0	/	10	3

1.2. One-pot deracemisation

1.2.1. Compound 1a

Table S2: List of one-pot syntheses of enantioenriched **1a**. The mixture was milled 24 h at 30 Hz. [a] 0.3 equiv. of DBU + 1.0 equiv. of NaOH.

N°	Base	Jar	$m_{I(RS)\text{-}2}$ [mg]	Bulk	V_{Bulk} [mL]	Additives	Balls Ø [mm]	# of balls	Final *ee*	Yield
A1	NMM	PTFE	280	NaCl	5.0	/	10	3	0%	/
A2	NMM	PTFE	204	NaCl	5.0	/	10	3	2%	/
A3	NMM	PTFE	280	Na_2SO_4	5.0	/	10	3	0%	/
A4	NMM	PTFE	204	Na_2SO_4	5.0	/	10	3	5%	/
A5	DBU	PTFE	280	NaCl	5.0	/	10	3	38%	/
A6	DBU	PTFE	204	NaCl	5.0	/	10	3	27%	/
A7	DBU	PTFE	280	Na_2SO_4	5.0	/	10	3	37%	/
A8	DBU	PTFE	204	Na_2SO_4	5.0	/	10	3	67%	/
A9	DBU + NaOH[a]	PTFE	204	NaCl	5.0	/	10	3	17%	/
A10	DBU + NaOH[a]	PTFE	204	Na_2SO_4	5.0	/	10	3	4%	/
A11	DBU	PTFE	280	Sand	5.0	/	10	3	54%	47%
A12	DBU	PTFE	204	Sand	5.0	/	10	3	7%	55%
A13	DBU	PTFE	280	NaCl	5.0	Na_2SO_4	10	3	73%	/
A14	DBU	PTFE	204	NaCl	5.0	Na_2SO_4	10	3	36%	/
A15	DBU	PTFE	280	Sand	5.0	Na_2SO_4	10	3	47%	89%
A16-1	DBU	PTFE	204	Sand	5.0	Na_2SO_4	10	3	87%	80%
A16-2	DBU	PTFE	204	Sand	5.0	Na_2SO_4	10	3	66%	64%
A16-3	DBU	PTFE	204	Sand	5.0	Na_2SO_4	10	3	81%	72%
A16-4	DBU	PTFE	204	Sand	5.0	Na_2SO_4	10	3	73%	77%
A17	DBU	PTFE	175	Sand	5.0	Na_2SO_4	10	3	55%	50%
A18	DBU	PTFE	150	Sand	5.0	Na_2SO_4	10	3	59%	34%
A19-1	DBU	PTFE	204	Sand	6.0	Na_2SO_4	10	3	94%	46%
A19-2	DBU	PTFE	204	Sand	6.0	Na_2SO_4	10	3	70%	49%
A19-3	DBU	PTFE	204	Sand	6.0	Na_2SO_4	10	3	62%	68%
A20	DBU	PTFE	204	Sand	5.0	Na_2SO_4	3	111	60%	54%
A21	DBU	PTFE	204	Sand	5.0	Na_2SO_4	5	24	72%	96%
A22	DBU	PTFE	204	Sand	5.0	Na_2SO_4	12	1	63%	57%
A23	DBU	PTFE	204	Sand	5.0	Na_2SO_4	12	2	20%	49%
A24	DBU	PTFE	204	Sand	6.0	Na_2SO_4	5	24	30%	70%
A25	DBU	PTFE	204	Sand	6.0	Na_2SO_4	10	4	36%	52%
A26	DBU	PTFE	204	Sand	6.0	Na_2SO_4	12	1	11%	81%
A27-1	DBU	ZrO_2	146	Sand	3.6	Na_2SO_4	10	1	86%	57%
A27-2	DBU	ZrO_2	146	Sand	3.6	Na_2SO_4	10	1	96%	44%
A27-3	DBU	ZrO_2	146	Sand	3.6	Na_2SO_4	10	1	68%	77%

1.2.2. Compound 1b

Table S3: List of one-pot syntheses of enantioenriched **1b**. The mixture was milled 24 h at 30 Hz.

N°	Base	Jar	$m_{I(RS)\text{-}2}$ [mg]	Bulk	V_{Bulk} [mL]	Additives	Balls Ø [mm]	# of balls	Final *ee*	Yield
B1	DBU	PTFE	204	Sand	5.0	Na_2SO_4	10	3	80%	55%
B2-1	DBU	PTFE	190	Sand	5.0	Na_2SO_4	10	3	92%	86%
B2-2	DBU	PTFE	190	Sand	5.0	Na_2SO_4	10	3	89%	62%
B2-3	DBU	PTFE	190	Sand	5.0	Na_2SO_4	10	3	62%	/
B2-4	DBU	PTFE	190	Sand	5.0	Na_2SO_4	10	3	17%	72%
B3-1	DBU	ZrO_2	136	Sand	3.6	Na_2SO_4	10	1	40%	66%
B3-2	DBU	ZrO_2	136	Sand	3.6	Na_2SO_4	10	1	73%	53%
B3-3	DBU	ZrO_2	136	Sand	3.6	Na_2SO_4	10	1	59%	77%

2. Experimental Section

2.1. General Information

2.1.1. Materials

All chemicals were obtained from commercial sources and used without further purification. Benzaldehyde (>98%) and N-Methylmorpholine (>99%) were purchased from TCI Chemicals (Tokyo, Japan). (*RS*)-2-Aminobutyramide hydrochloride (95%)[1] and o-Tolualdehyde (99.47%) were obtained from BLDPharm (Shanghai, China), while additional (*RS*)-2-Aminobutyramide hydrochloride[2] was supplied by Fluorochem Ltd (Glossop, United Kingdoms). Sodium chloride (>99.8%) and sodium sulphate (>99%)[3] were purchased from Carl Roth (Karlsruhe, Germany), whereas sodium sulphate (99%)[4] was also obtained from Thermo Scientific (Waltham, United States of America). Sodium hydroxide (98.4%) was purchased from Fisher (Pittsburgh, United States of America). DBU (98%) was obtained from Sigma-Aldrich (Burlington, United States of America). Methanol and Fontainebleau sand (technical grade) were supplied by VWR (Radnor, United States of America).

All chemicals were obtained from commercial sources and used without further purification.

2.1.2. Devices

^{1}H-Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded on a JEOL (Tokyo, Japan) JNM-ECZL400 R series spectrometer operating at 400 MHz. All spectra were acquired in DMSO-d_6, with residual solvent signals used as internal standards. Chemical shifts (δ) and signal multiplicities are reported as follows: s = singlet, t = triplet, dd = doublet of doublets and m = multiplet.

Chiral High-Performance Liquid Chromatography (cHPLC) analyses were carried out on a Waters (Milford, United States of America) ARC HPLC system equipped with a Waters PDA 2998 detector set at 230 nm. Separations were performed on Daicel (Osaka, Japan) Chiralpak IA (5 µm, 4.6 × 250 mm) whose has a stationary phase consisting of an amylose derivative, 3,5-dimethylphenylcarbamate, immobilised on silica. The mobile phase consisted of mixtures of isohexane (A) and 2-propanol (B), with solvent ratios optimized for each analyte. The chromatographic conditions applied to each compound are detailed below:

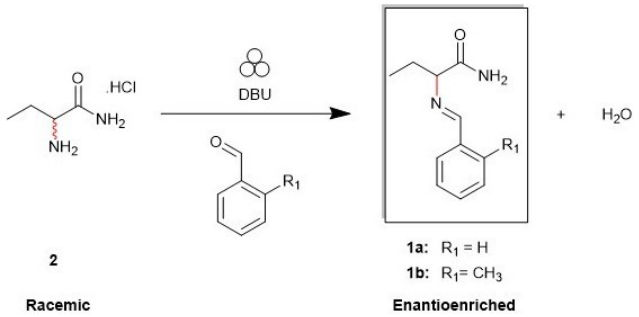
- Compound **1a**: elution with 90% A / 10% B for 15 min; flow rate 1.0 mL.min^{-1}; injection volume 5 µL.
- Compound **1b**: elution with 95% A / 5% B for 15 min; flow rate 1.0 mL.min^{-1}; injection volume 5 µL.

The samples were prepared by dissolving 10 mg of sample in 4 ml of a mixture 90% A / 10% B. Subsequently, 1 ml of this sample was filtered into the appropriate cHPLC vial.

Ball-milling experiments were performed using a MM400 mixer mill provided by Retsch (Haan, Germany) either in ZrO_2 jars (Retsch, 10 mL ; 18 mm ID x 50.5 mm IL) or in PTFE jars (InSolido Technologies (Zagreb, Croatia), 14 mL, 19 mm ID x 57.2 mm IL). The ZrO_2 vessels were cleaned between each use, first by grinding them half-filled with sand and technical ethanol for 3 minutes at 30 Hz, then by washing them with water and subsequently with acetone. The PTFE vessels were cleaned between each use by washing them with water and subsequently with acetone.

[1] For the synthesis part
[2] For the one-pot deracemisation
[3] For compound **1b**
[4] For compound **1a**

2.2. Experimental Protocols



Scheme S1: One-pot synthesis of enantioenriched imines. The absolute configuration of **1a**/**1b** cannot be predicted but is determined by cHPLC. Complete details of experimental conditions and the final *ee* are reported in **Tables S1**-**5**

A 14 mL PTFE or a 10 mL ZrO_2 milling jar was sequentially charged with (RS)-2 (1.0 equiv.), bulk material, the corresponding additive (2.0 equiv., when applicable), ZrO_2 milling balls, the base (1.1 equiv. for the synthesis study or 1.3 equiv. for MCDR experiments), and the aldehyde (1.0 equiv.). The mixture was milled at 30 Hz for 1.5 h (synthesis study) or 24 h (MCDR). Upon completion of milling, the resulting solid was suspended in approximately 25 mL of water and filtered to remove inorganic salts, excess base, and any unreacted starting materials. The crude product was subsequently dissolved in MeOH to maximize recovery of the imine and to separate it from the sand. After filtration, the solvent was removed under reduced pressure. The product was obtained as a white powder and is characterized by ^{1}H-NMR spectroscopy and cHPLC to determine the final *ee*. cHPLC conditions are described in section 2.1.2.

For the synthesis study, ^{1}H-NMR analysis was also performed directly after milling, prior to suspension in water, in order to confirm that the reaction occurred during the milling process and that no side reactions took place during the subsequent work-up.

The mass/volume of reactants/bulk change in function of the conditions (initial $m_{(RS)\text{-}2}$, nature/equiv. of base, bulk, …). **Tables S4-5** indicate the calculated mass/volume.

^{1}H-NMR results

- Compound **1a** (exp A16-1)**:** ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.84 (dd, 2H), 7.54 – 7.41 (m, 3H), 7.16 (s, 1H), 7.11 (s, 1H), 3.64 (dd, 1H), 1.93 – 1.77 (m, 1H), 1.74 – 1.58 (m, 1H), 0.81 (t, 3H). (**Figure S13**)
- Compound **1b** (exp B2-2)**:** ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.92 (dd, 1H), 7.40 – 7.31 (m, 1H), 7.30 – 7.21 (m, 2H), 7.16 (s, 1H), 7.05 (s, 1H), 3.67 (dd, 1H), 2.50 (s, 3H), 1.93 – 1.76 (m, 1H), 1.74 – 1.59 (m, 1H), 0.82 (t, 3H). (**Figure S16**)

cHPLC results

N.B. One different chiral column "Daicel Chiralpak IA (5 µm, 4.6 × 250 mm)" were used, leading to two different pairs of retention time (RT) for each molecule.

- Compound **1a**:
  - Exp S1, S3, A1-4, A12, A16-26: cHPLC (RT, min.) 7.8; 10.7 (**Figures S22**, **S24**, **S28**-**S31**, **S39**, **S43**-**S58**)
  - Exp S2, S4-6, A5-11, A13-15, A27: cHPLC (RT, min.) 7.4; 10.1 (**Figures S23**, **S25**-**S27**, **S32**-**S38**, **S40**-**S42**, **S59**-**S61**)
- Compound **1b**:
  - Exp B1, B2: cHPLC (RT, min.) 11.5; 12.5 (**Figures S62**-**S66**)
  - Exp B3: cHPLC (RT, min.) 11.2; 12.2 (**Figures S67**-**S69**)

Table S4: Mass of the bulk material, depending on their volume

Bulk	m_{Bulk}
NaCl	5.0 mL → 6.3 g
Na_2SO_4	5.0 mL → 7.0 g
Sand	3.6 mL → 5.4 g 5.0 mL → 7.6 g 6.0 mL → 9.3 g

Table S5: Calculate volume/mass of reactants, depending on the conditions.

$m_{(RS)\text{-}2}$	Additive	Base	Aldehyde
0.280 g; 2.02 mmol	4.04 mmol: - *Na_2SO_4*: 0.574 g	1.1 equiv. → 2.22 mmol: - *NMM*: 244.4 µL - *DBU*: 332.4 µL - *NaOH*: 0.089 g 1.3 equiv. → 2.63 mmol: - *NMM*: 288.8 µL - *DBU*: 392.8 µL	2.02 mmol: - *Benzaldehyde*: 204.2 µL
0.204 g; 1.47 mmol	2.94 mmol: - *Na_2SO_4*: 0.418 g	1.3 equiv. → 1.91 mmol: - *NMM*: 210.4 µL - *DBU*: 286.2 µL - *NaOH* (1.0 equiv.): 0.059 g + *DBU* (0.3 equiv.): 66.0 µL	1.47 mmol: - *Benzaldehyde*: 148.8 µL - *o-Tolualdehyde*: 170.0 µL
0.190 g; 1.37 mmol	2.74 mmol: - *Na_2SO_4*: 0.389 g	1.3 equiv. → 1.78 mmol: - *DBU*: 266.6 µL	1.37 mmol: - *o-Tolualdehyde*: 158.4 µL
0.175 g; 1.26 mmol	2.52 mmol: - *Na_2SO_4*: 0.359 g	1.3 equiv. → 1.64 mmol: - *DBU*: 245.4 µL	1.26 mmol: - *Benzaldehyde*: 127.6 µL
0.150 g; 1.08 mmol	2.17 mmol: - *Na_2SO_4*: 0.307 g	1.3 equiv. → 1.41 mmol: - *DBU*: 210.4 µL	1.08 mmol: - *Benzaldehyde*: 109.4 µL
0.146 g; 1.05 mmol	2.10mmol: - *Na_2SO_4*: 0.299 g	1.3 equiv. → 1.37 mmol: - *DBU*: 204.8 µL	1.05 mmol: - *Benzaldehyde*: 106.4 µL
0.146 g; 0,98 mmol	1.96 mmol: - *Na_2SO_4*: 0.279 g	1.3 equiv. → 1.27 mmol: - *DBU*: 190.8 µL	0.98 mmol: - *Benzaldehyde*: 113.4 µL

3. Characterization

3.1. ^{1}H-NMR-Spectra

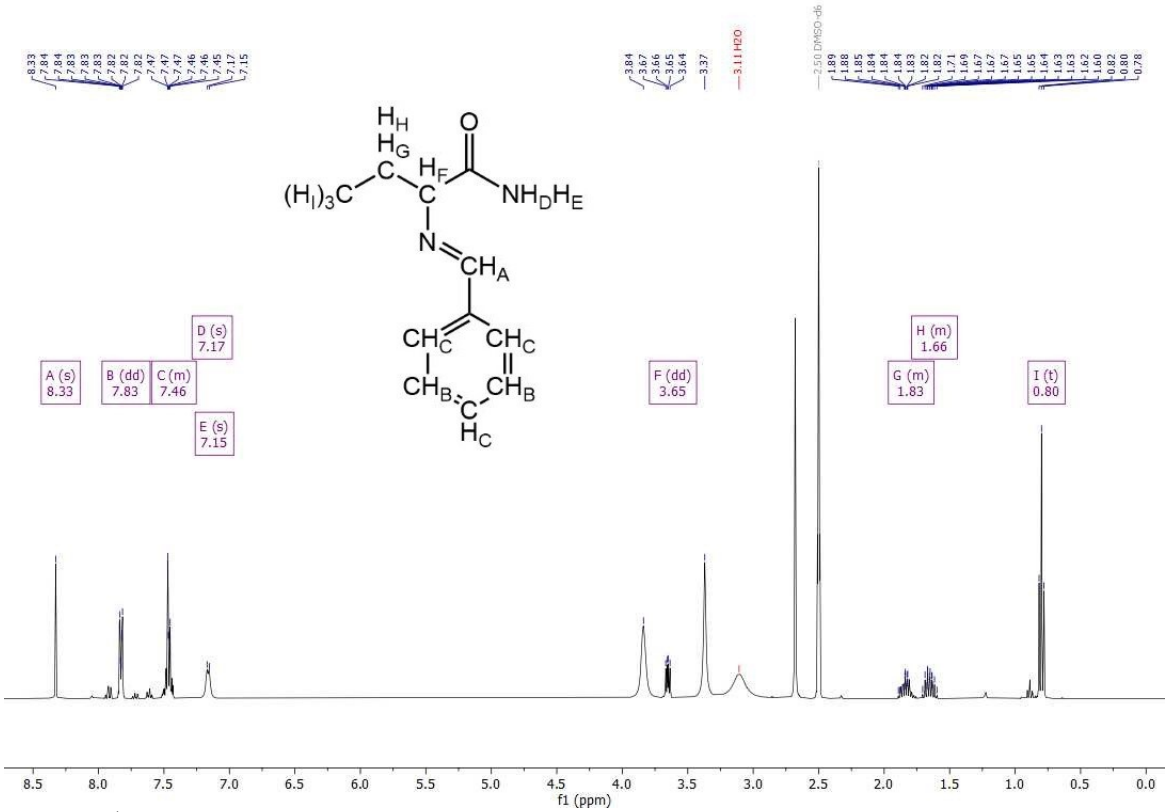


Figure S1: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of crude **1a** obtained under S1 condition, recorded directly after milling. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.11 ppm) corresponds to residual traces of water.

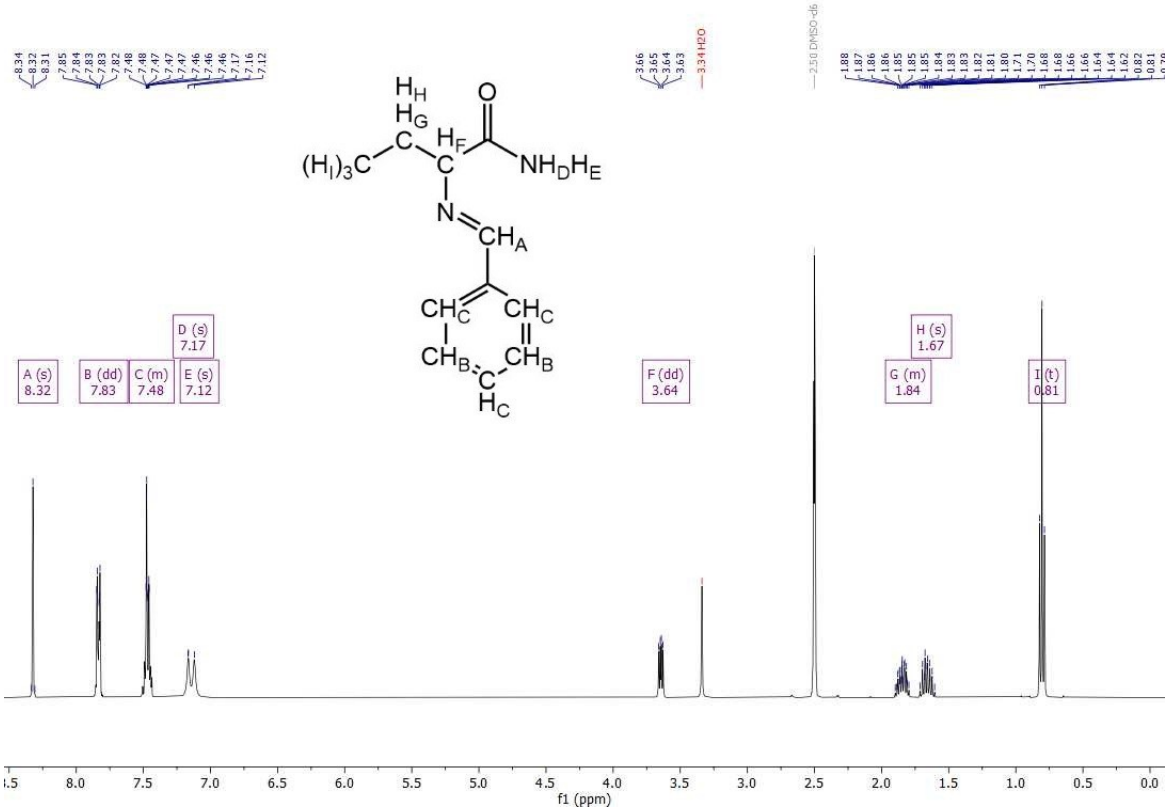


Figure S2: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of **1a** obtained under S1 condition, recorded after work-up. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.34 ppm) corresponds to residual traces of water.

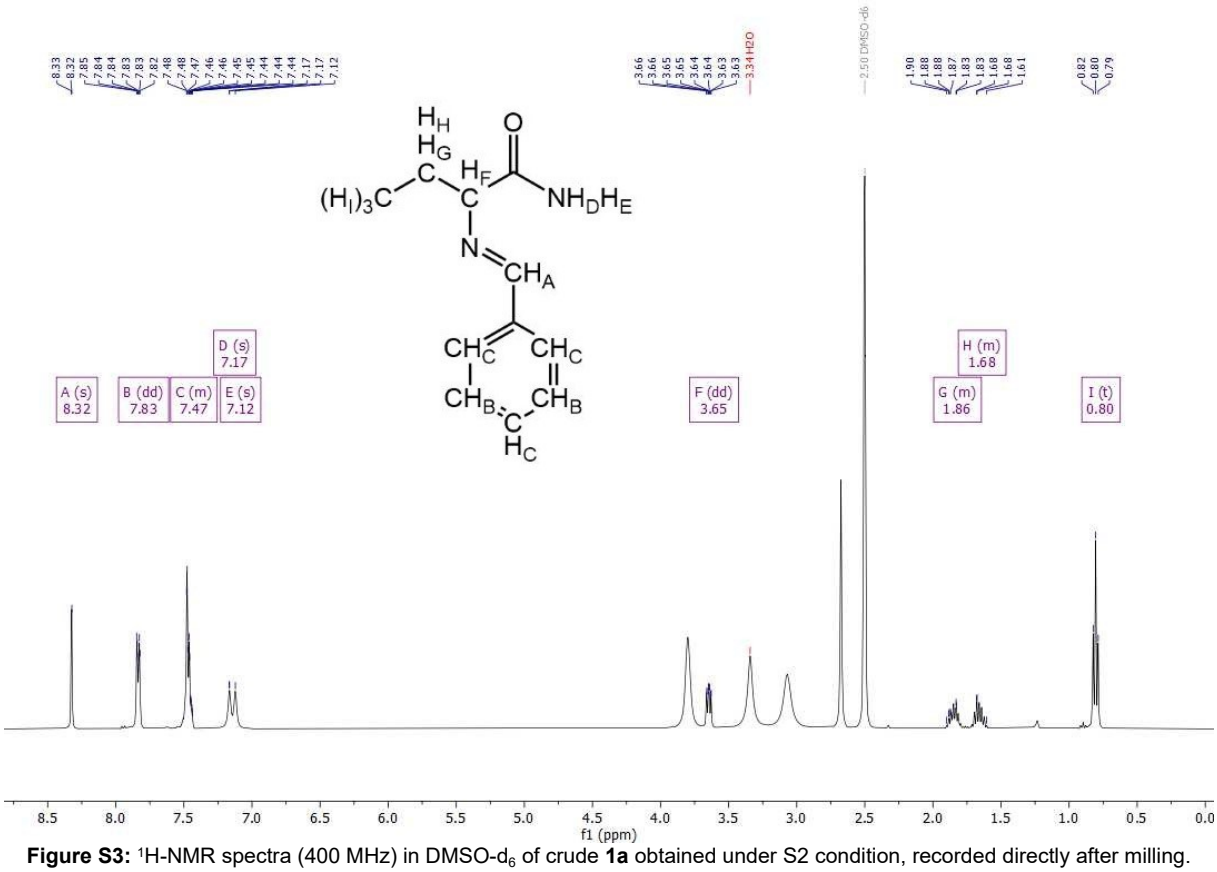


Figure S3: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of crude **1a** obtained under S2 condition, recorded directly after milling. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.34 ppm) corresponds to residual traces of water.

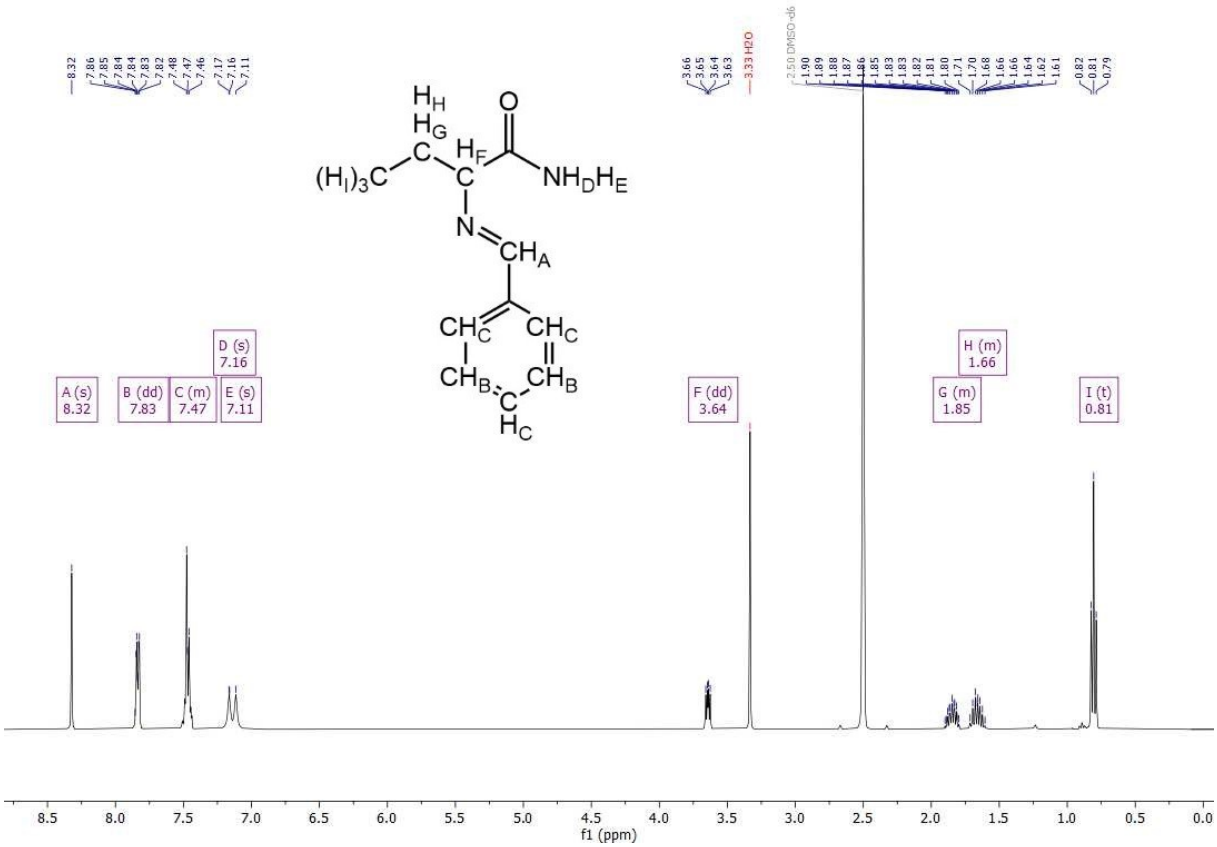


Figure S4: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of **1a** obtained under S2 condition, recorded after work-up. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.33 ppm) corresponds to residual traces of water.

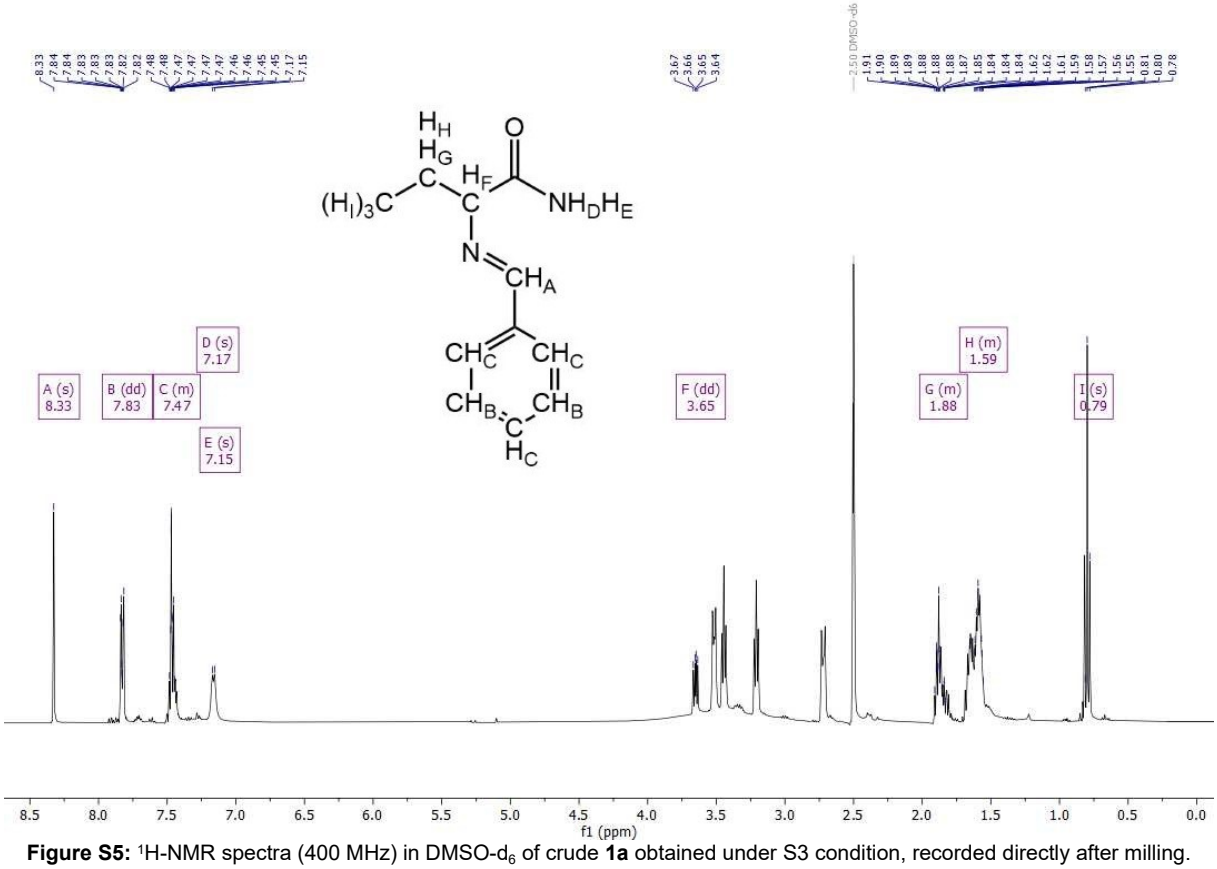


Figure S5: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of crude **1a** obtained under S3 condition, recorded directly after milling. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO.

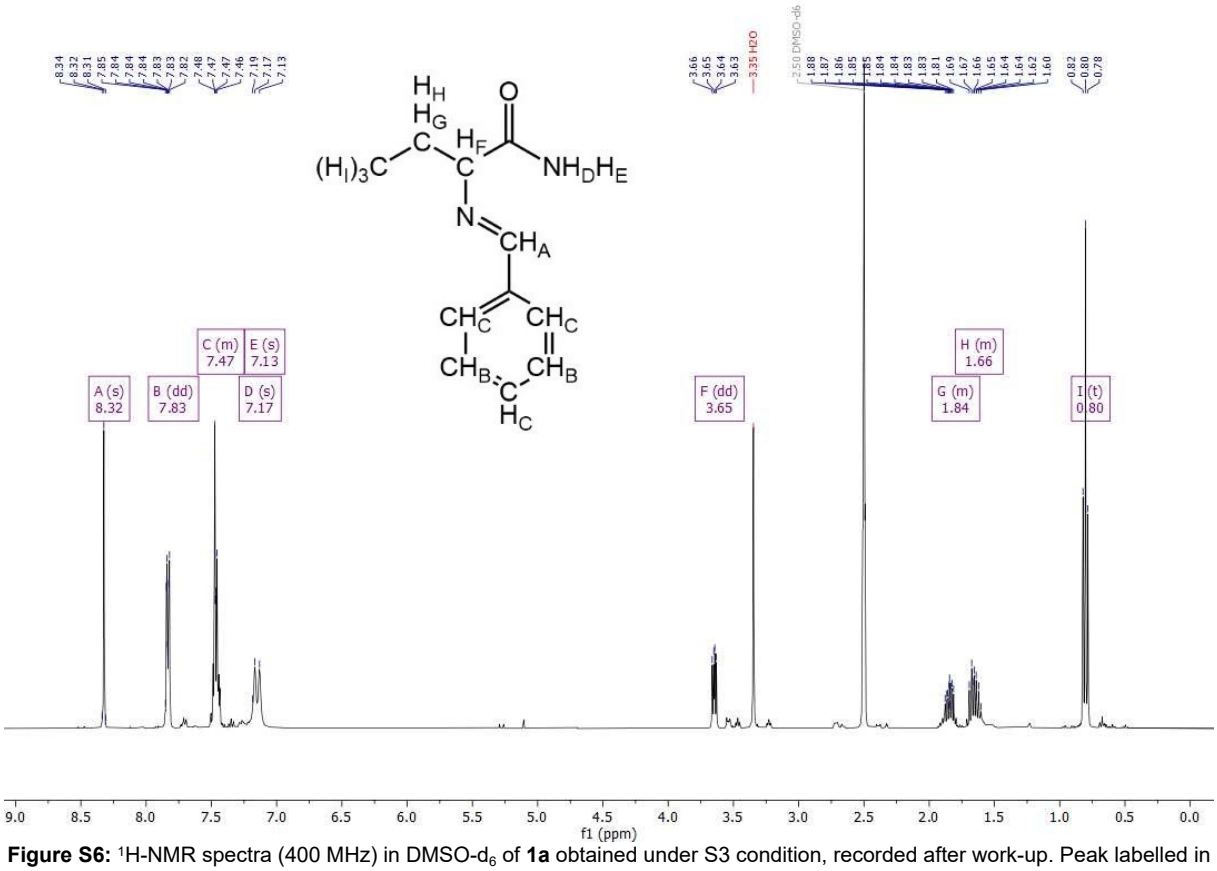


Figure S6: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of **1a** obtained under S3 condition, recorded after work-up. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.35 ppm) corresponds to residual traces of water.

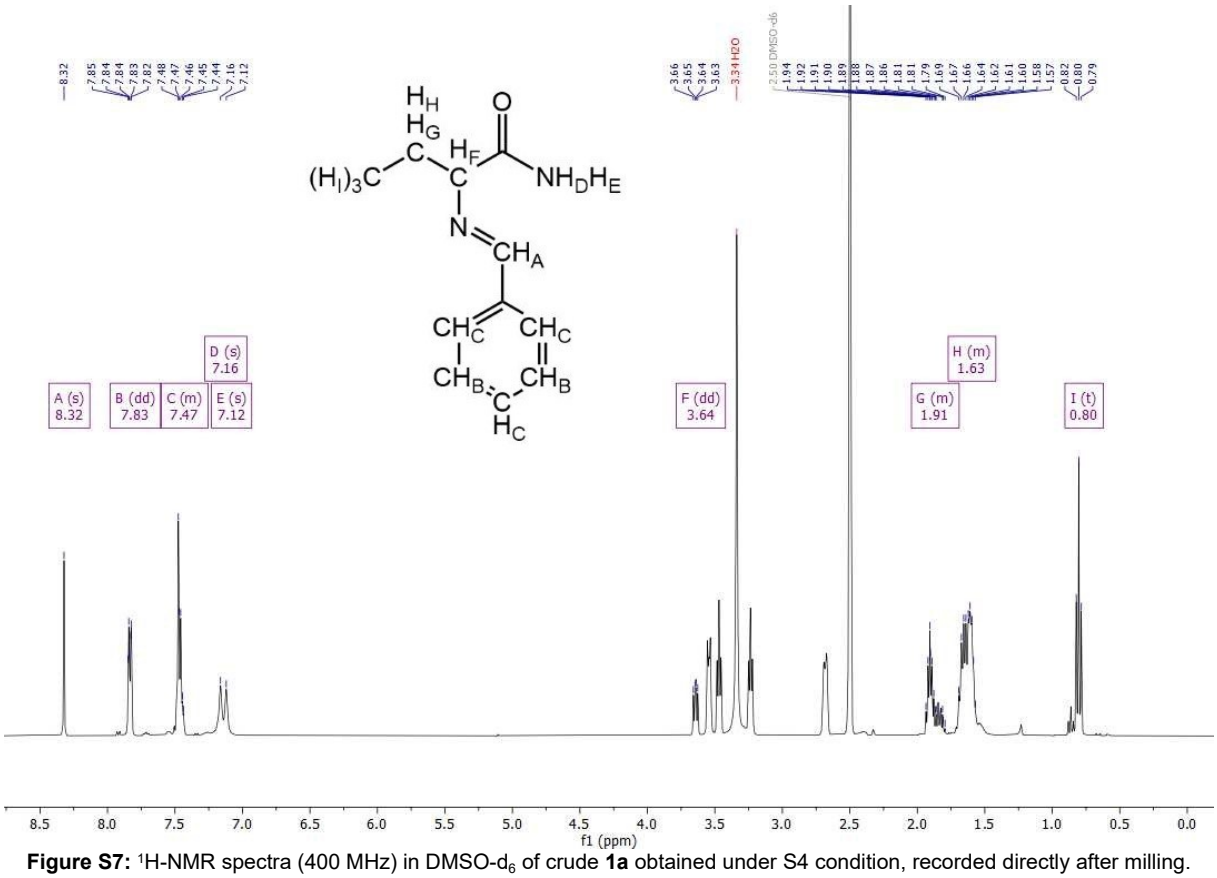


Figure S7: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of crude **1a** obtained under S4 condition, recorded directly after milling. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.34 ppm) corresponds to residual traces of water.

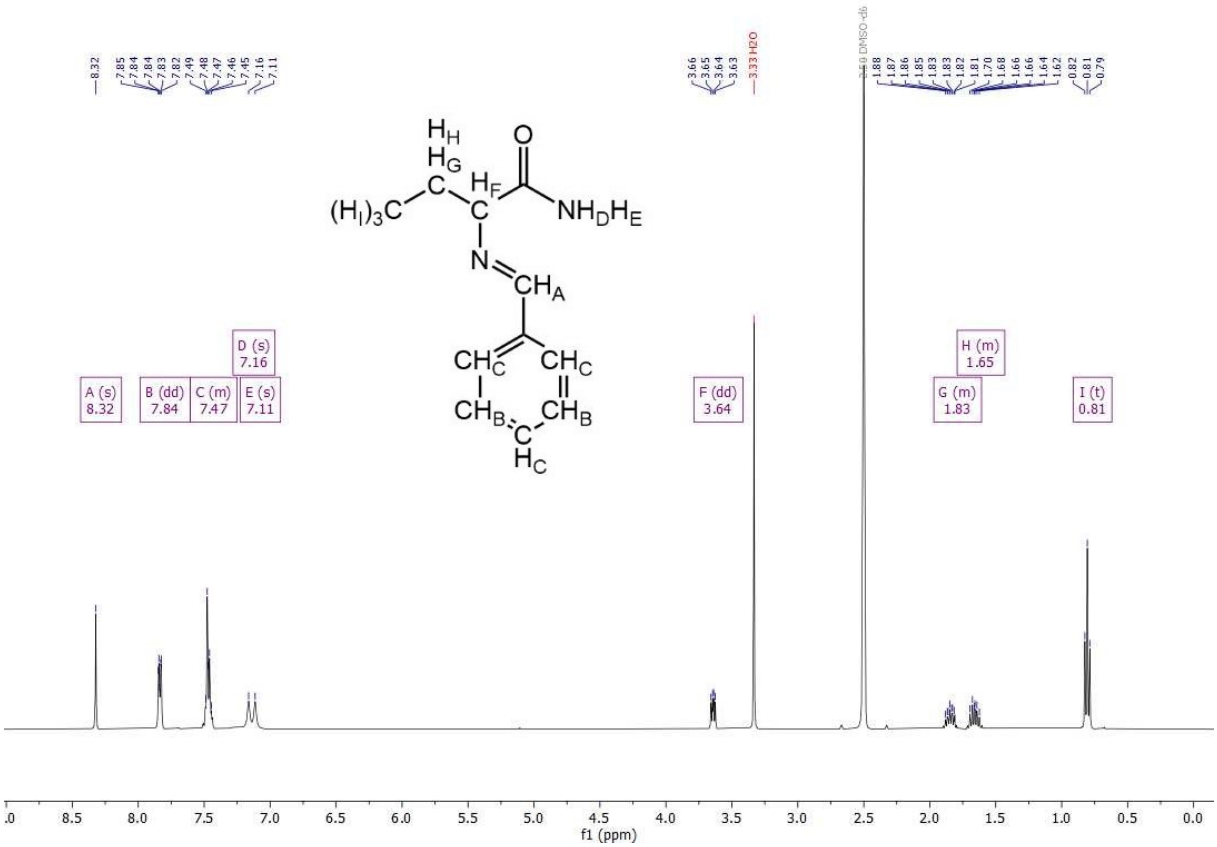


Figure S8: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of **1a** obtained under S4 condition, recorded after work-up. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.33 ppm) corresponds to residual traces of water.

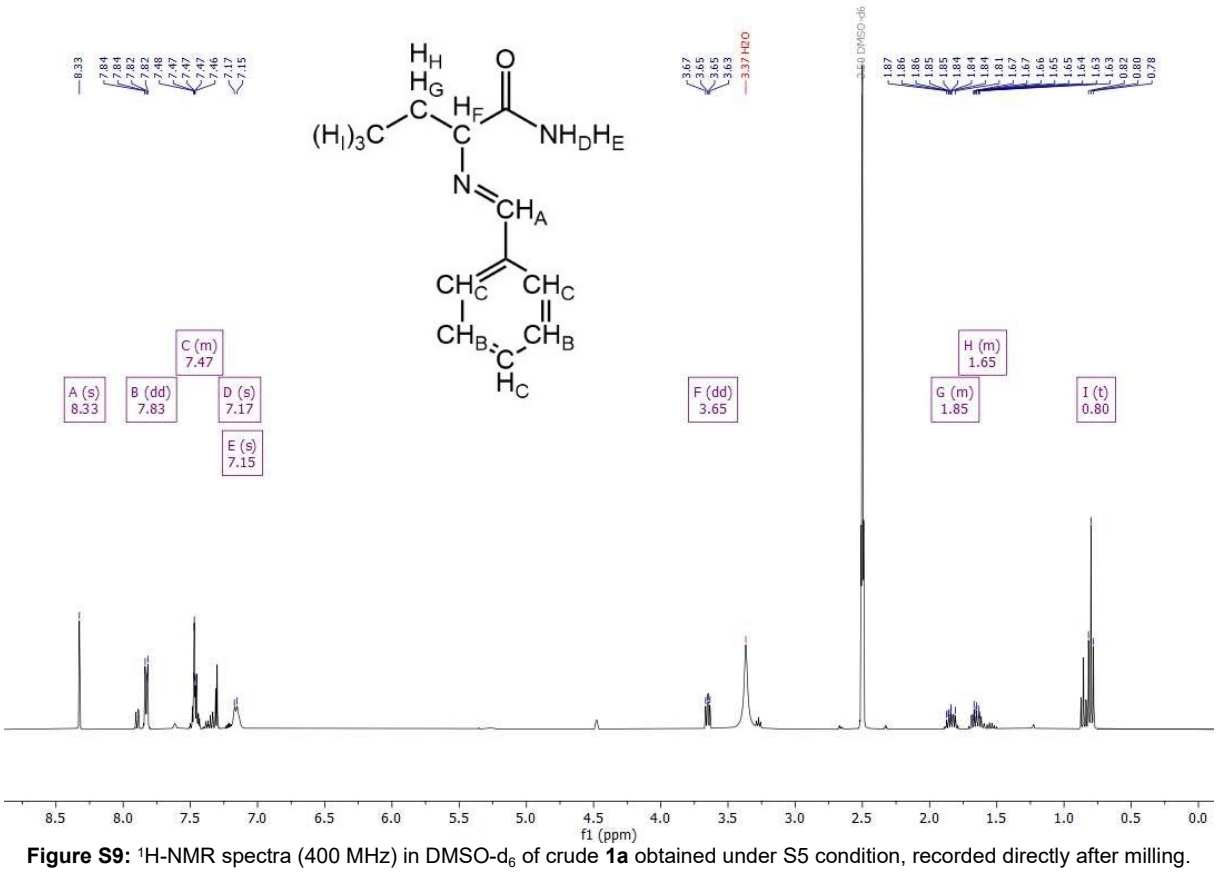


Figure S9: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of crude **1a** obtained under S5 condition, recorded directly after milling. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.37 ppm) corresponds to residual traces of water.

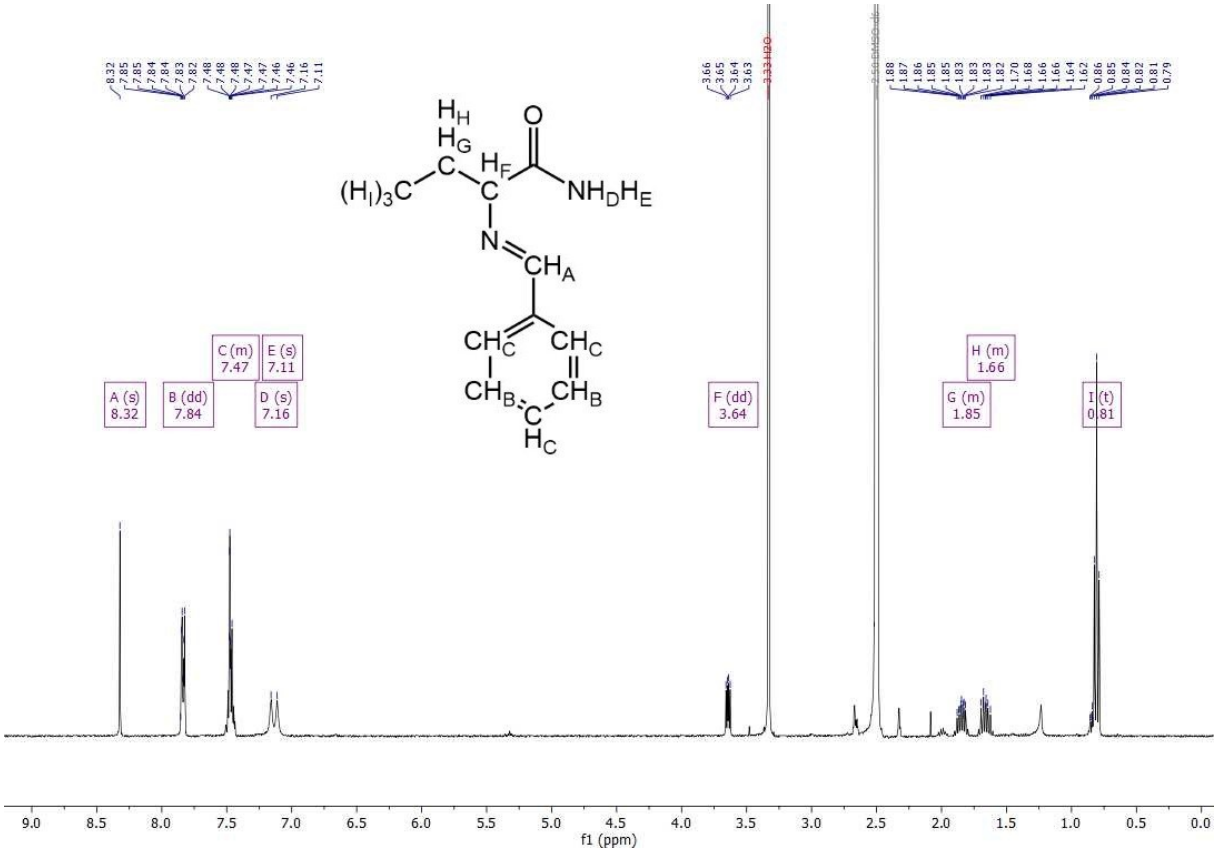


Figure S10: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of **1a** obtained under S5 condition, recorded after work-up. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.33 ppm) corresponds to residual traces of water.

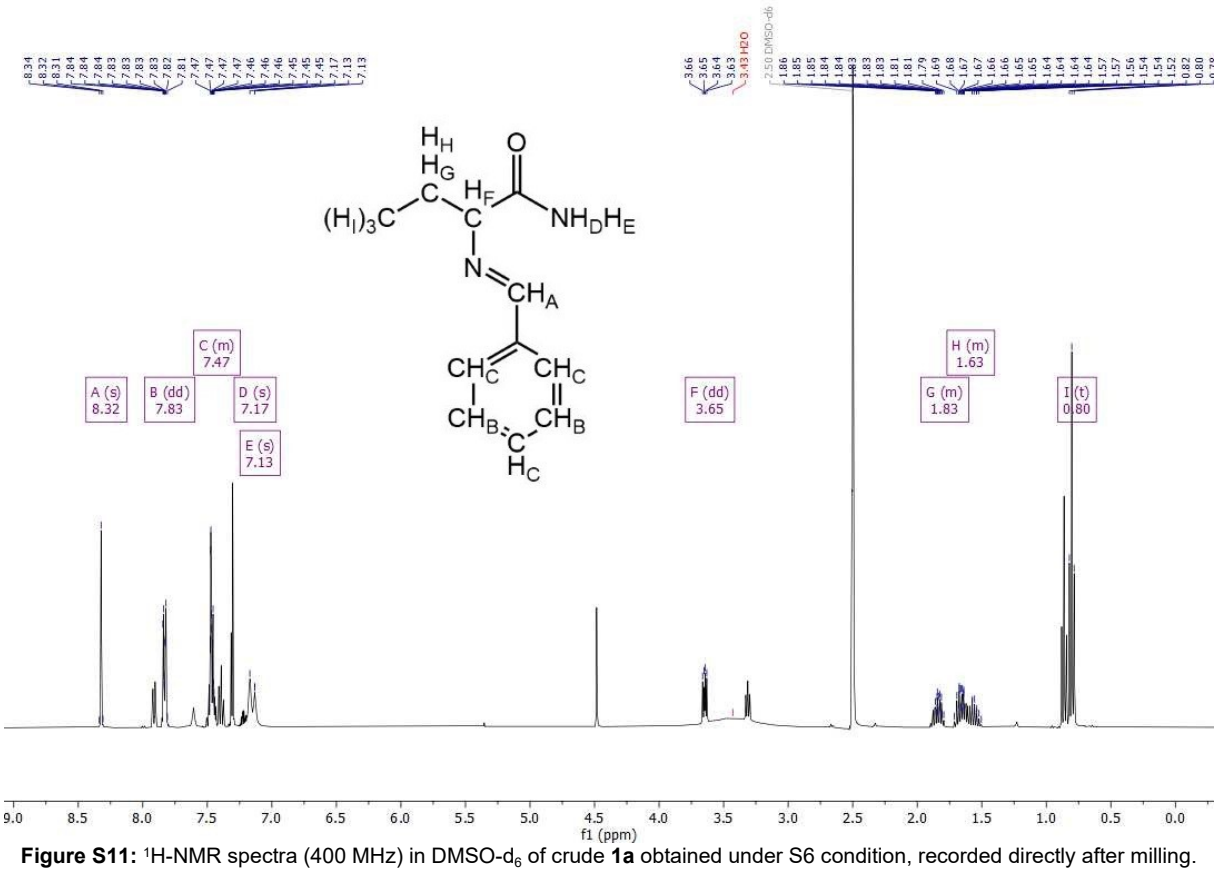


Figure S11: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of crude **1a** obtained under S6 condition, recorded directly after milling. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.43 ppm) corresponds to residual traces of water.

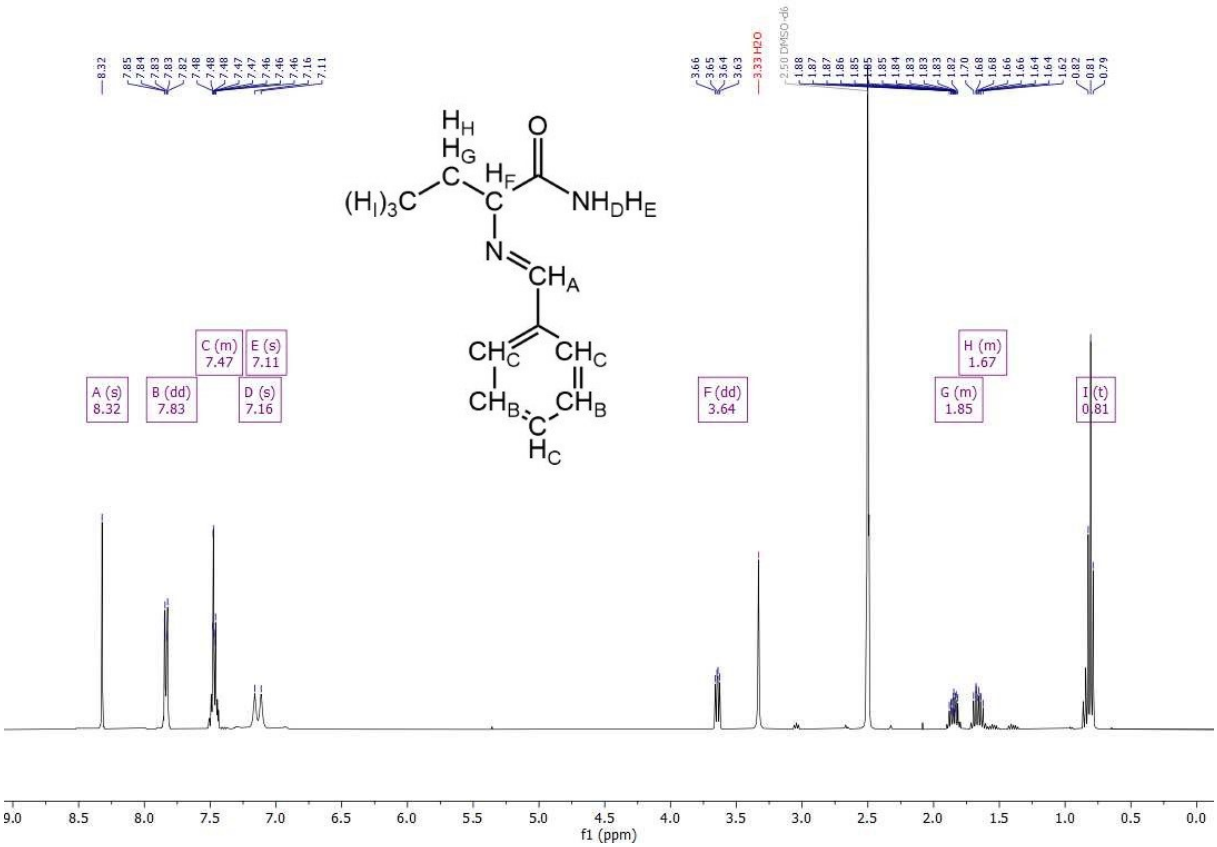


Figure S12: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of **1a** obtained under S6 condition, recorded after work-up. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.33 ppm) corresponds to residual traces of water.

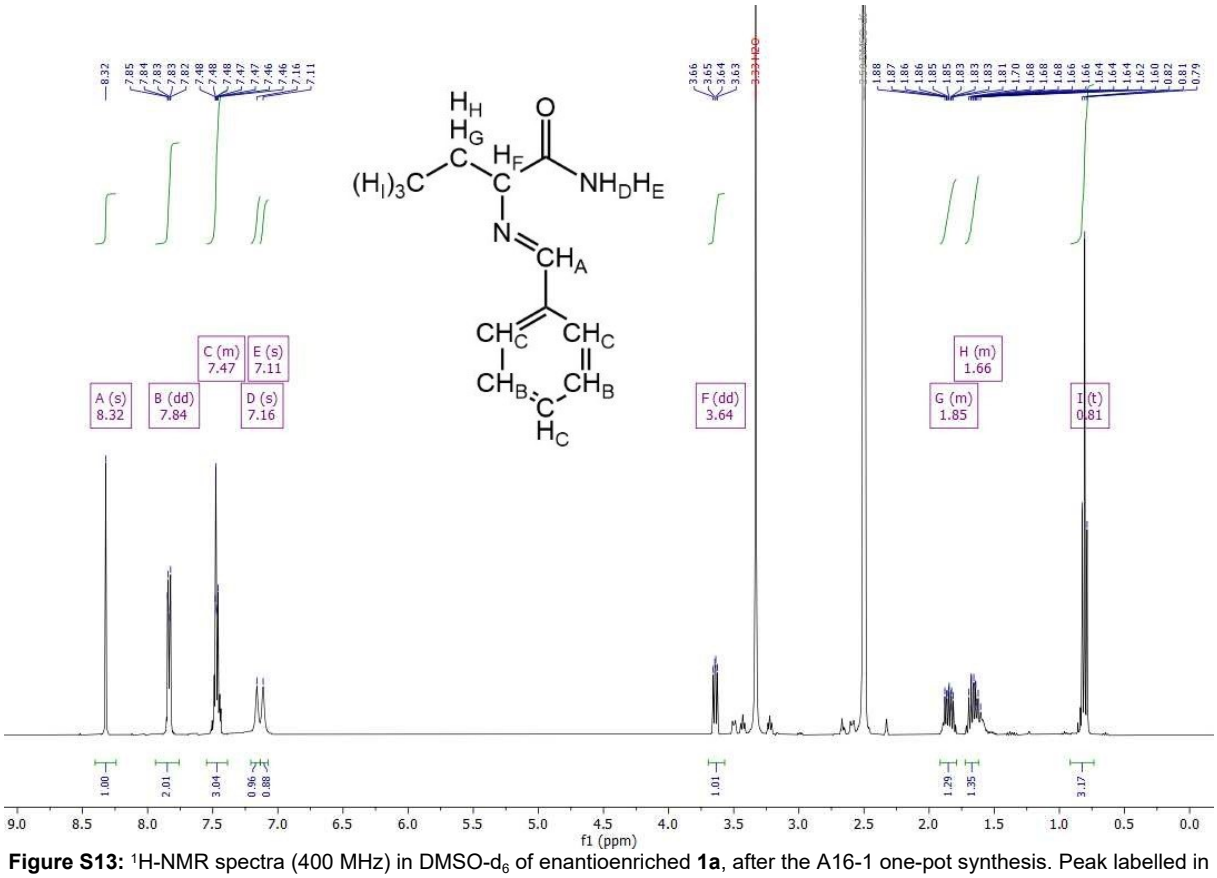


Figure S13: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of enantioenriched **1a**, after the A16-1 one-pot synthesis. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.33 ppm) corresponds to residual traces of water.

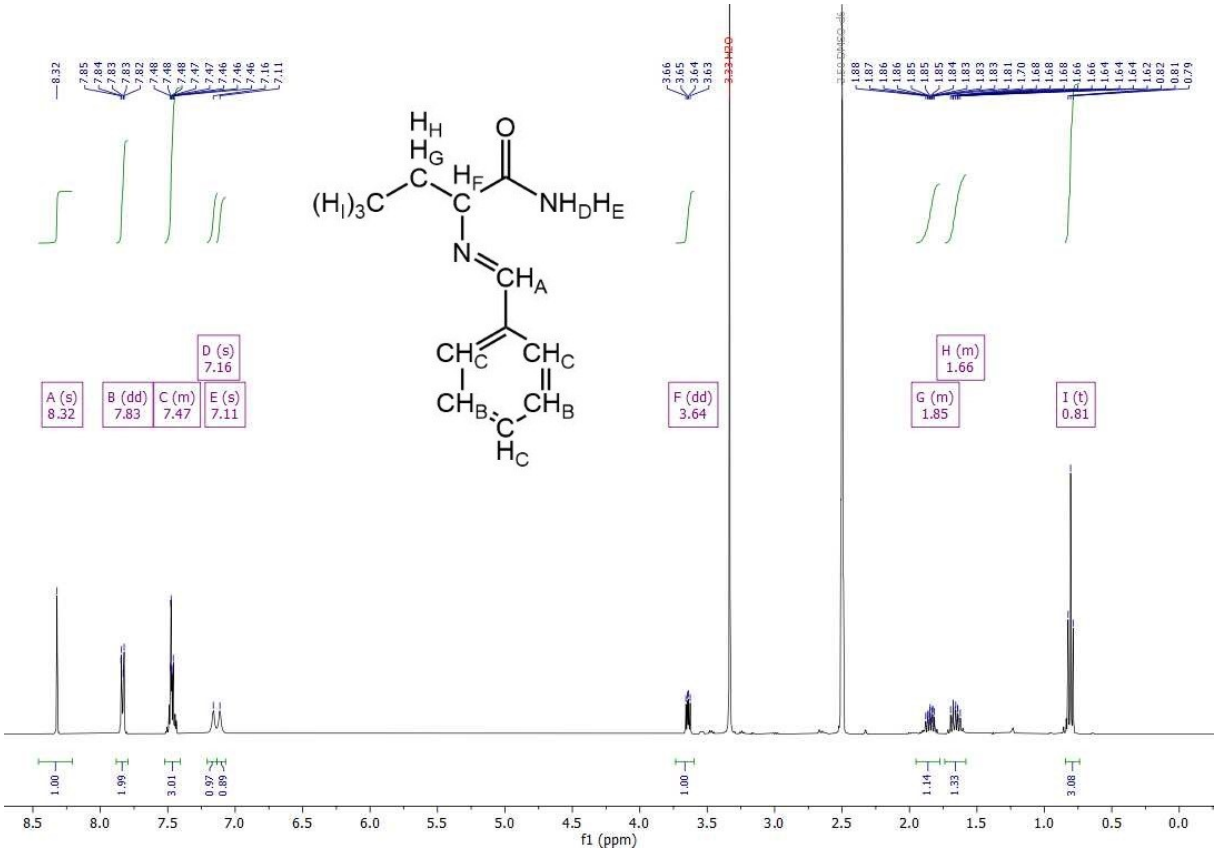


Figure S14: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of enantioenriched **1a**, after the A19-1 one-pot synthesis. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.33 ppm) corresponds to residual traces of water.

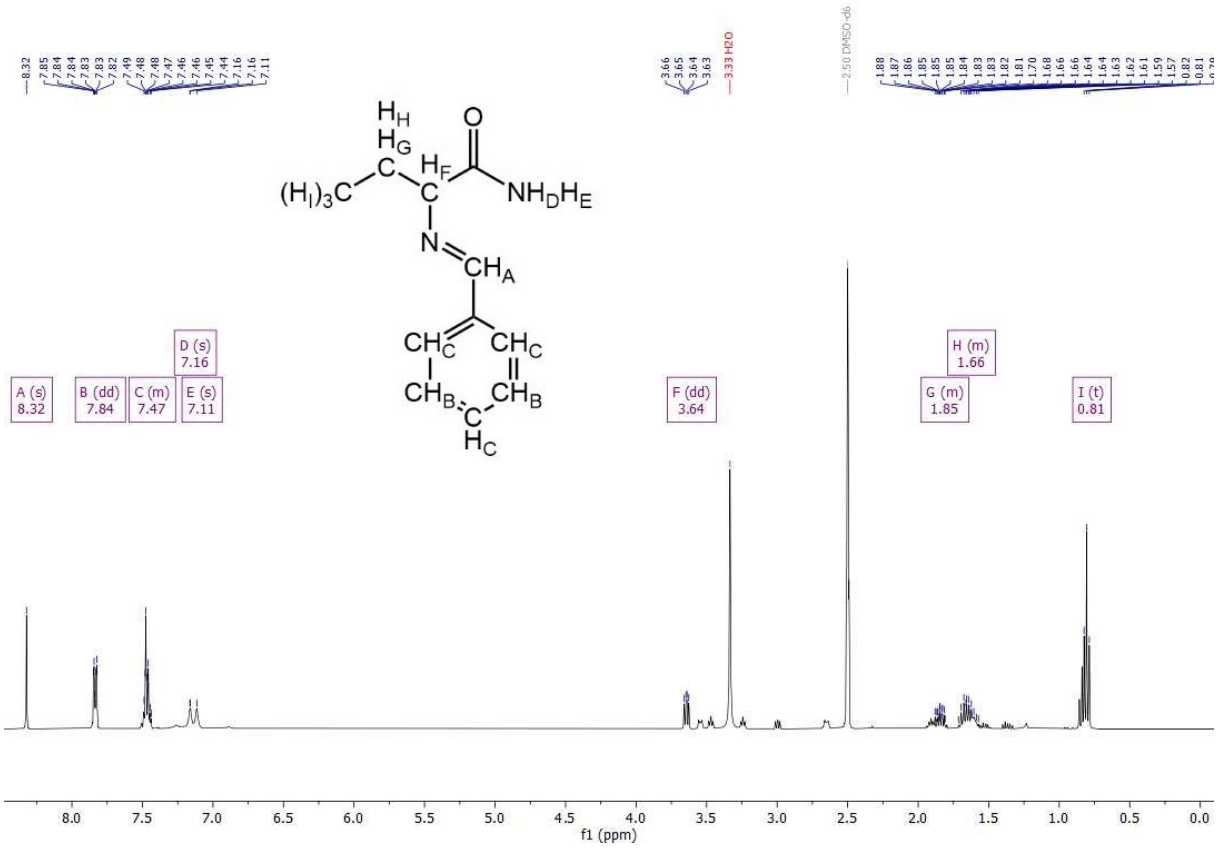


Figure S15: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of enantioenriched **1a**, after the A27-2 one-pot synthesis. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.33 ppm) corresponds to residual traces of water.

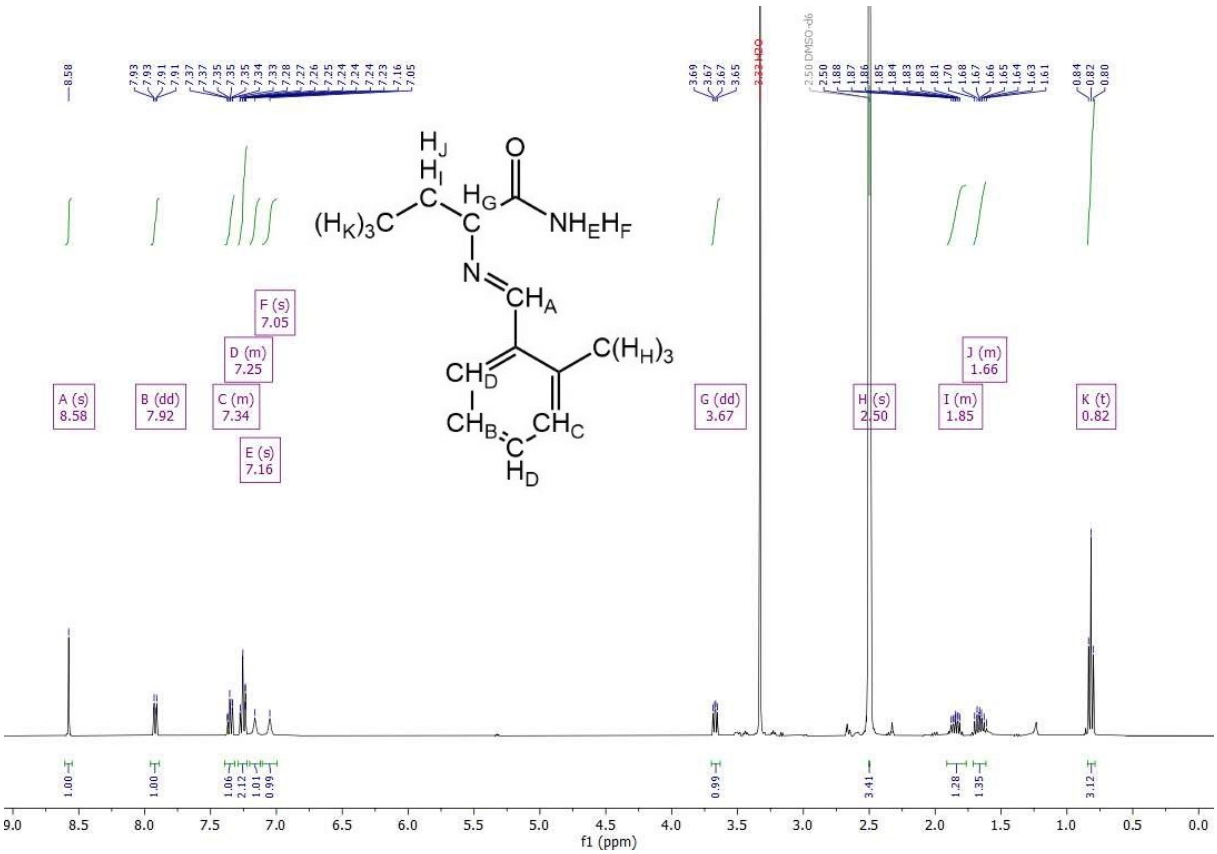


Figure S16: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of enantioenriched **1b**, after the B2-2 one-pot synthesis. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.33 ppm) corresponds to residual traces of water.

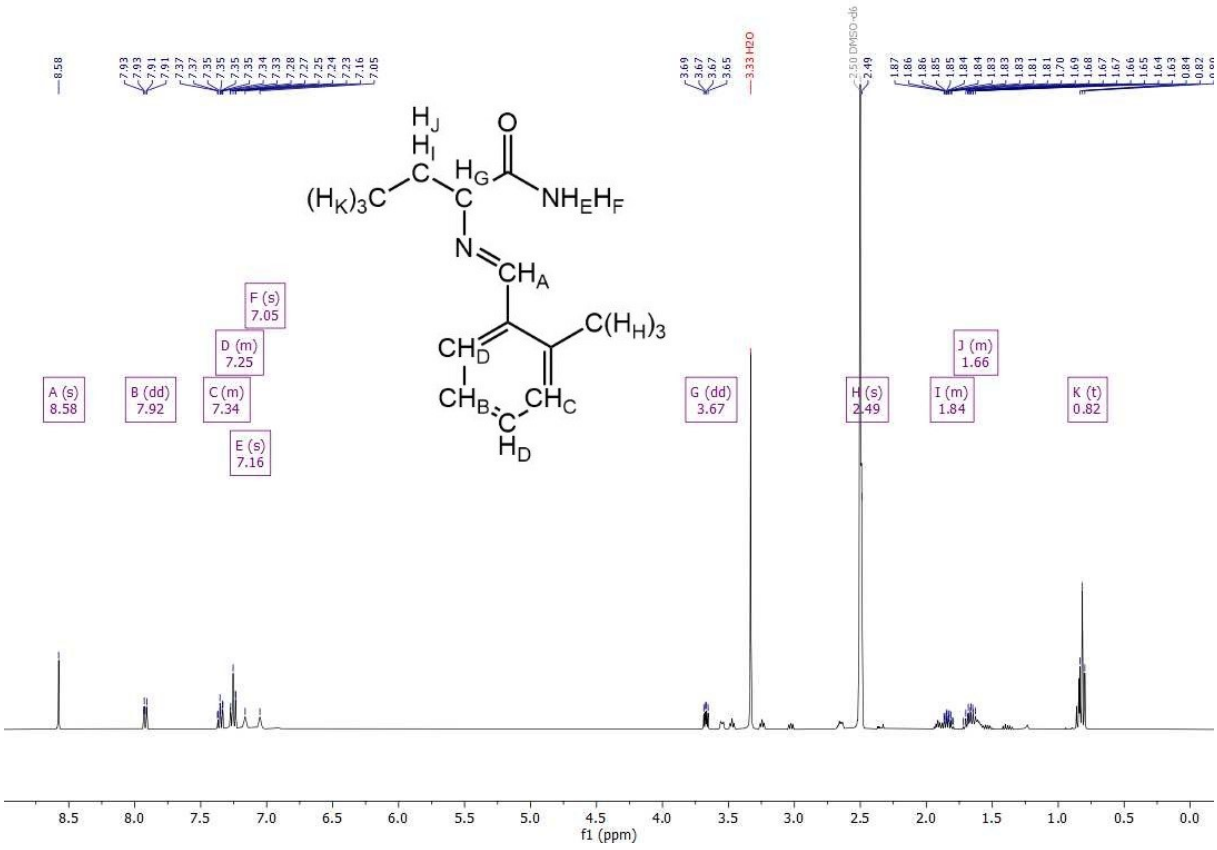
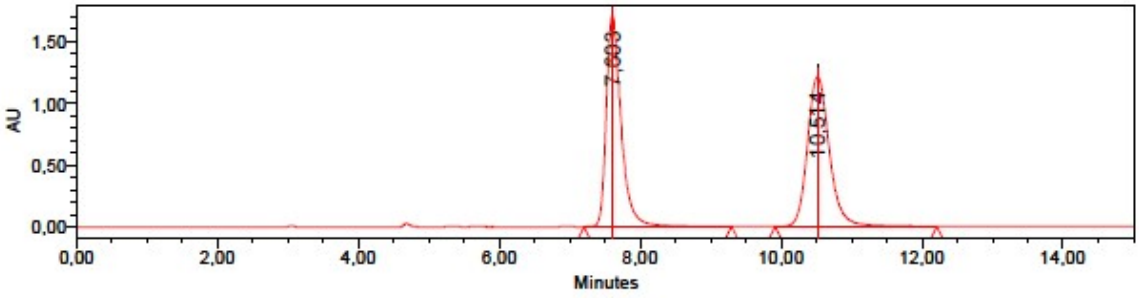


Figure S17: ^{1}H-NMR spectra (400 MHz) in DMSO-d_6 of enantioenriched **1b**, after the B3-1 one-pot synthesis. Peak labelled in grey (2.50 ppm) corresponds to residual DMSO and peak labelled in red (3.33 ppm) corresponds to residual traces of water.

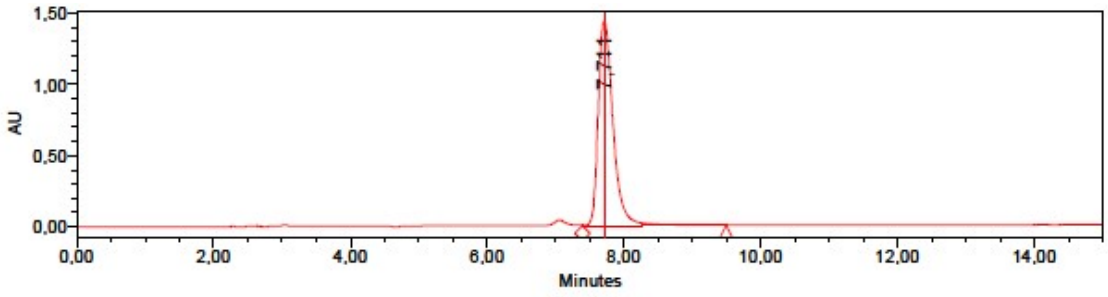
3.2. cHPLC Analysis



Peak Results

	Name	RT	Area	% Area
1		7,603	24725666	48,51
2		10,514	26239612	51,49

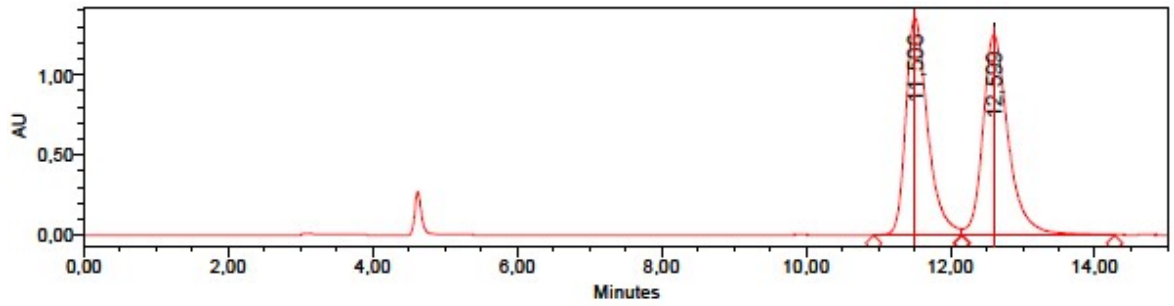
Figure S18: cHPLC analysis of (*RS*)-**1a** reference. Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.60 min; 48.51%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.51 min; 51.49%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,711	21581527	100,00

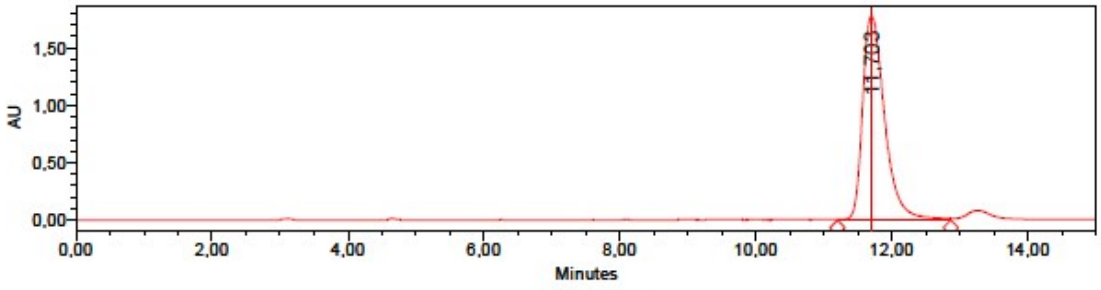
Figure S19: cHPLC analysis of (S)-**1a** reference (RT: 7.71 min; 100%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		11,506	28670932	48,41
2		12,599	30555095	51,59

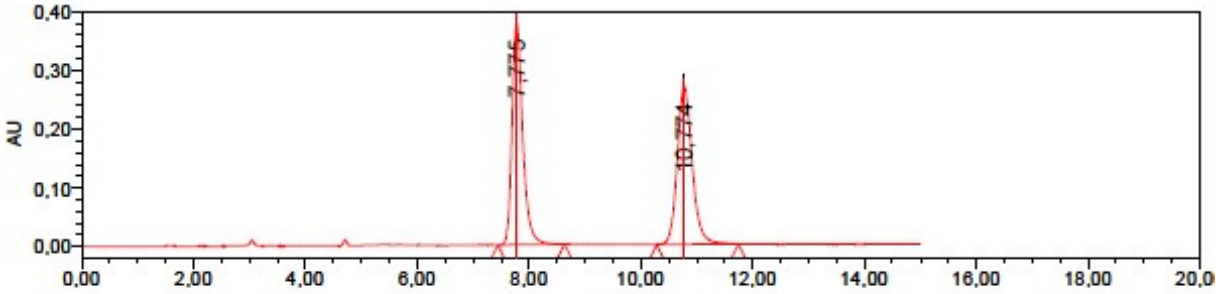
Figure S20: cHPLC analysis of (RS)-**1b** reference. Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 11.51 min; 48.41%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 12.60 min; 51.59%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 95% of isohexane and 5% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		11,703	39754137	100,00

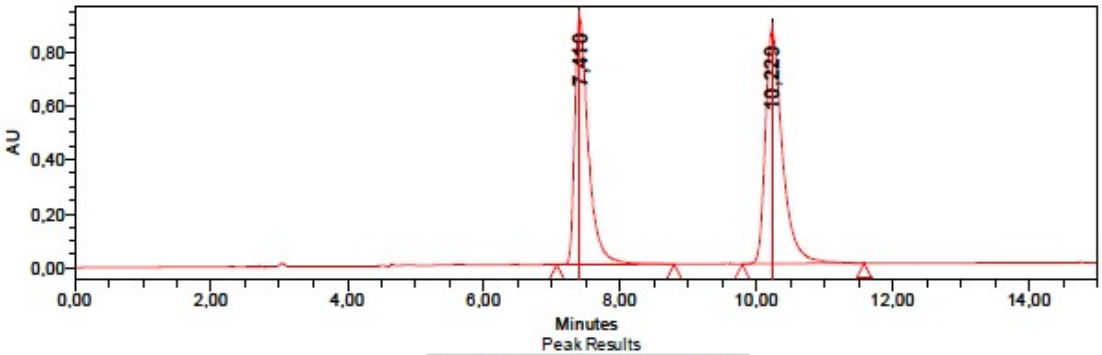
Figure S21: cHPLC analysis of (S)-**1b** reference (RT: 11.70 min; 100%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 95% of isohexane and 5% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,775	5057683	50,05
2		10,774	5047369	49,95

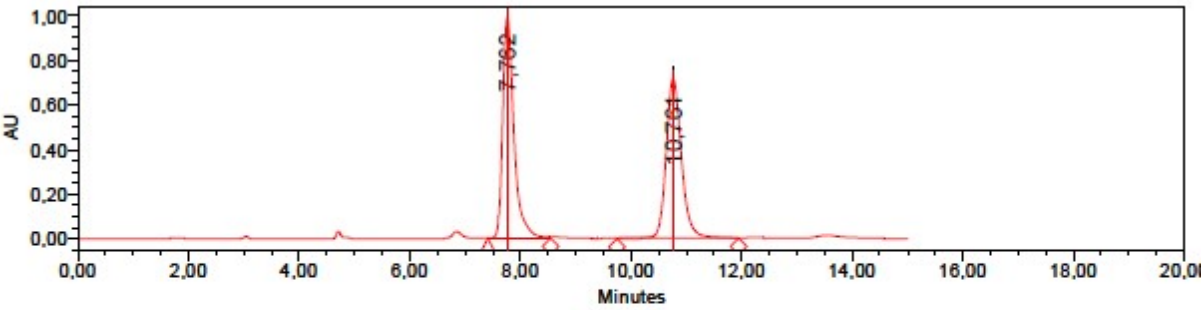
Figure S22: cHPLC analysis of **1a** synthesised by milling for 90 min at 30 Hz (Table S1, Method S1). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.78 min; 50.05%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.77 min; 49.95%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,410	12778795	45,62
2		10,229	15232120	54,38

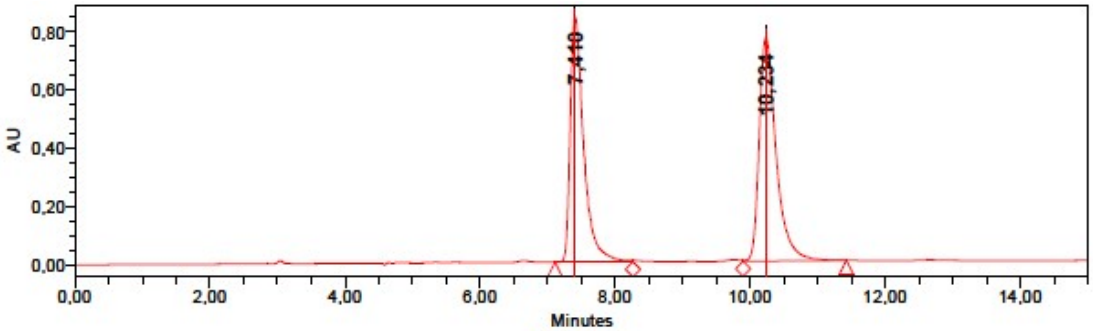
Figure S23: cHPLC analysis of **1a** synthesised by milling for 90 min at 30 Hz (Table S1, Method S2). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.41 min; 45.62%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.23 min; 54.38%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,762	14050599	50,28
2		10,761	13893662	49,72

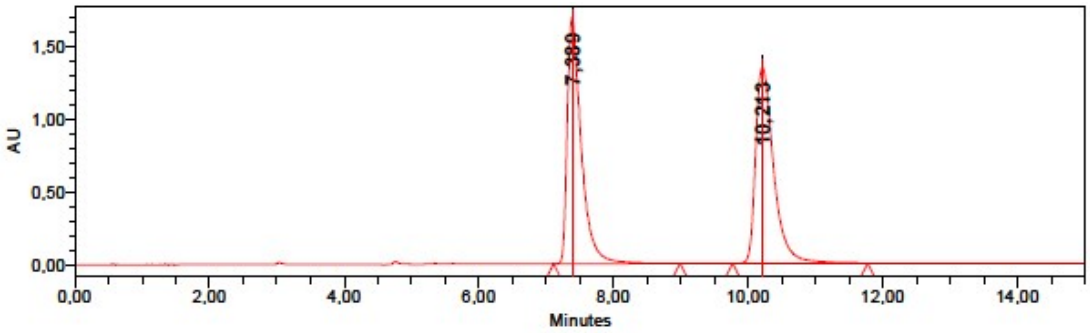
Figure S24: cHPLC analysis of **1a** synthesised by milling for 90 min at 30 Hz (Table S1, Method S3). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.76 min; 50.28%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.76 min; 49.72%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,410	11691772	46,53
2		10,234	13437670	53,47

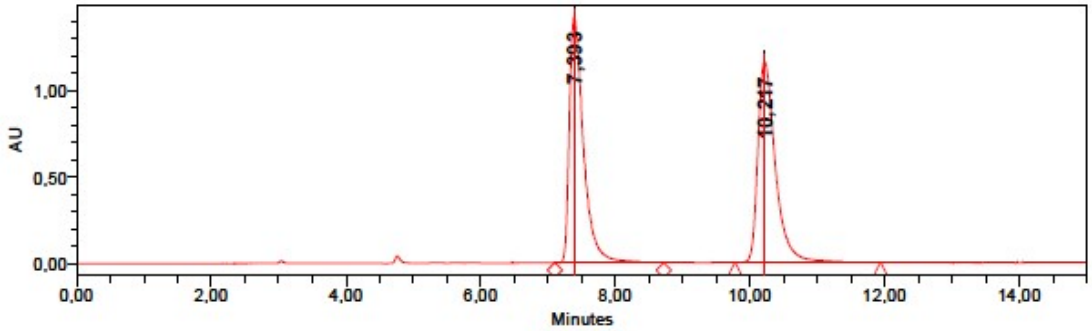
Figure S25: cHPLC analysis of **1a** synthesised by milling for 90 min at 30 Hz (Table S1, Method S4). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.41 min; 46.53%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.23 min; 53.47%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,389	24307800	49,06
2		10,213	25238518	50,94

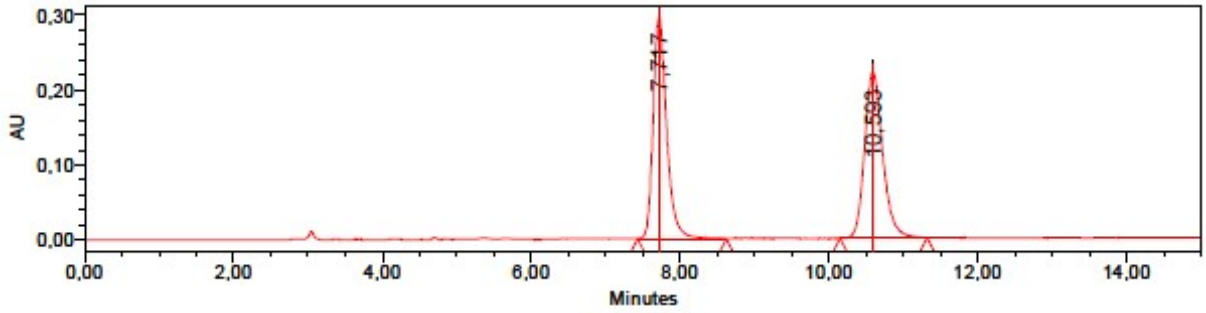
Figure S26: cHPLC analysis of **1a** synthesised by milling for 90 min at 30 Hz (Table S1, Method S5). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.39 min; 49.06%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.21 min; 50.94%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,393	20633239	49,55
2		10,217	21010257	50,45

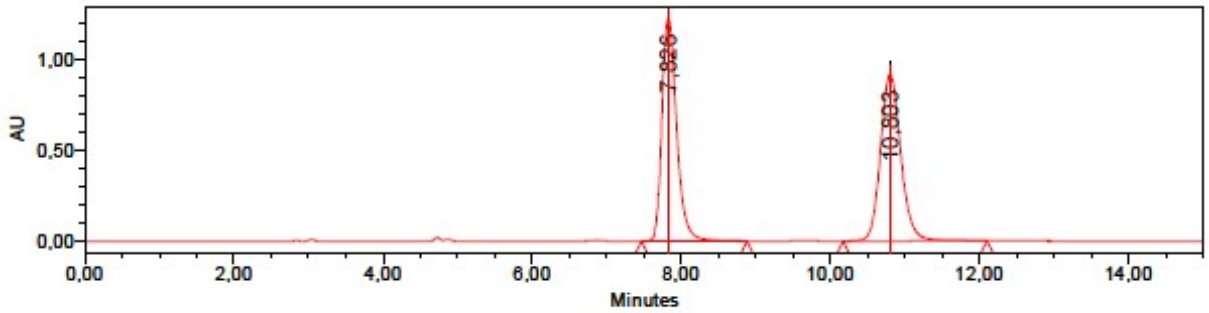
Figure S27: cHPLC analysis of **1a** synthesised by milling for 90 min at 30 Hz (Table S1, Method S6). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.39 min; 49.55%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.22 min; 50.45%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,717	3688512	49,76
2		10,593	3724711	50,24

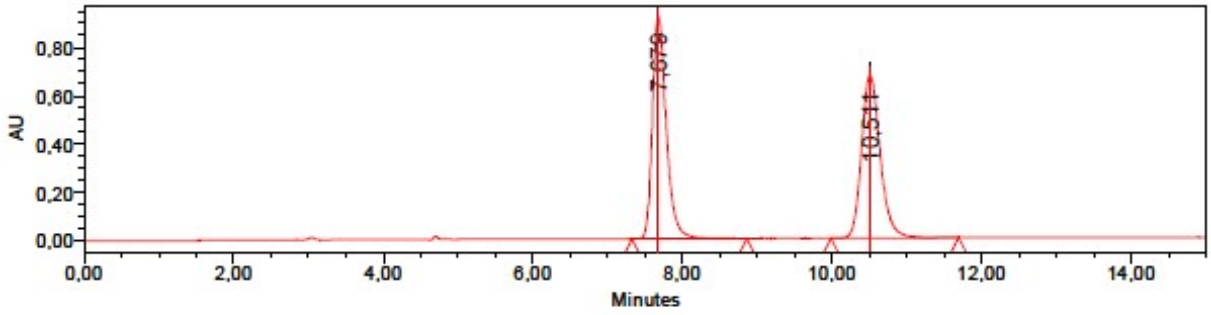
Figure S28: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A1). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.71 min; 49.76%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.59 min; 50.24%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,826	16705311	49,16
2		10,803	17272822	50,84

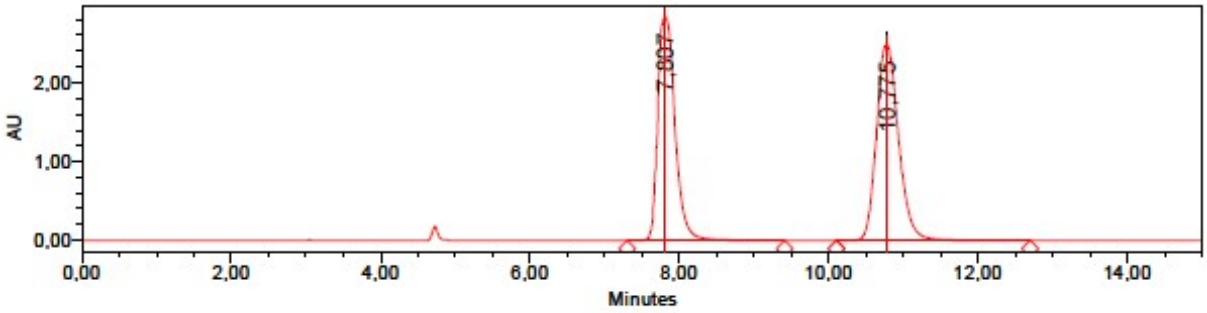
Figure S29: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A2). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.83 min; 49.16%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.80 min; 50.84%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,679	11737460	50,15
2		10,511	11668614	49,85

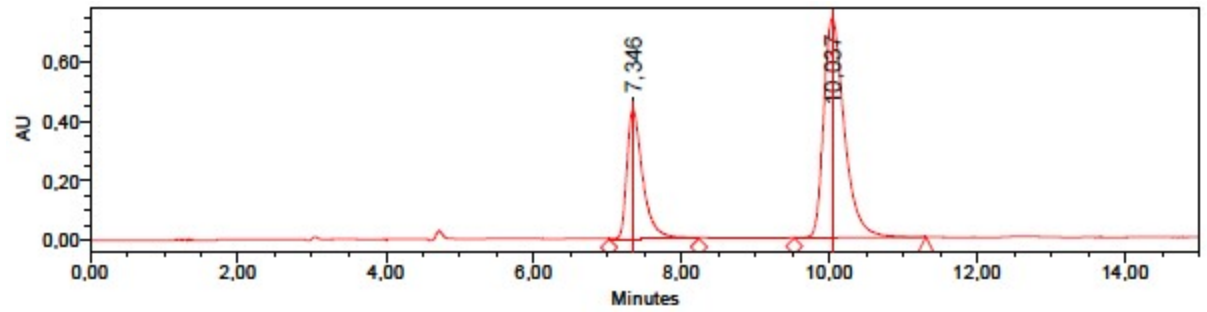
Figure S30: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A3). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.70 min; 50.15%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.51 min; 49.85%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,807	45354475	47,26
2		10,775	50613335	52,74

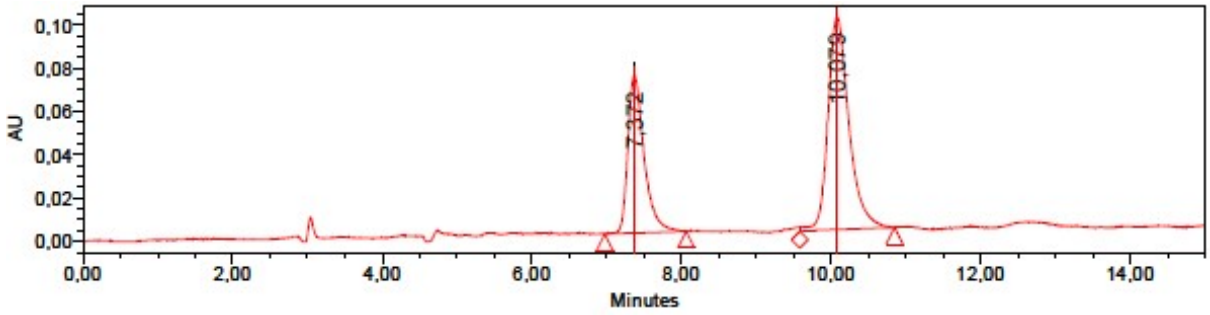
Figure S31: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A4). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.81 min; 47.26%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.78 min; 52.74%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,346	6525971	31,24
2		10,037	14366531	68,76

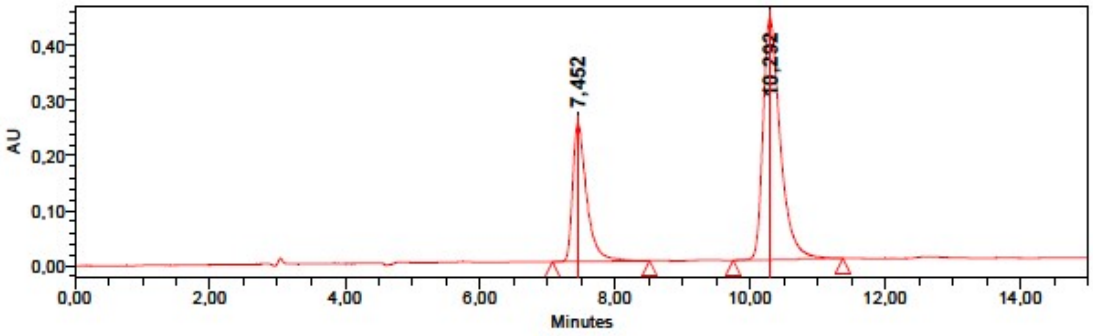
Figure S32: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A5). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.35 min; 31.24%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.04 min; 68.76%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,372	1101416	36,39
2		10,079	1924918	63,61

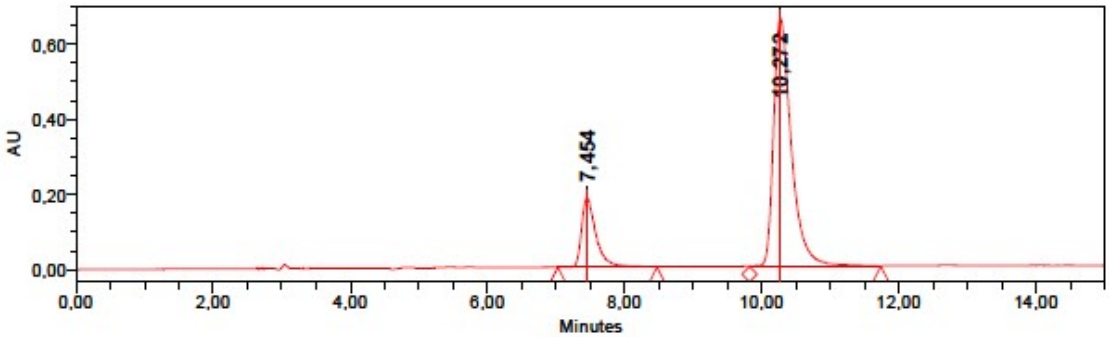
Figure S33: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A6). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.37 min; 36.39%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.08 min; 63.61%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,452	3601279	31,51
2		10,292	7828505	68,49

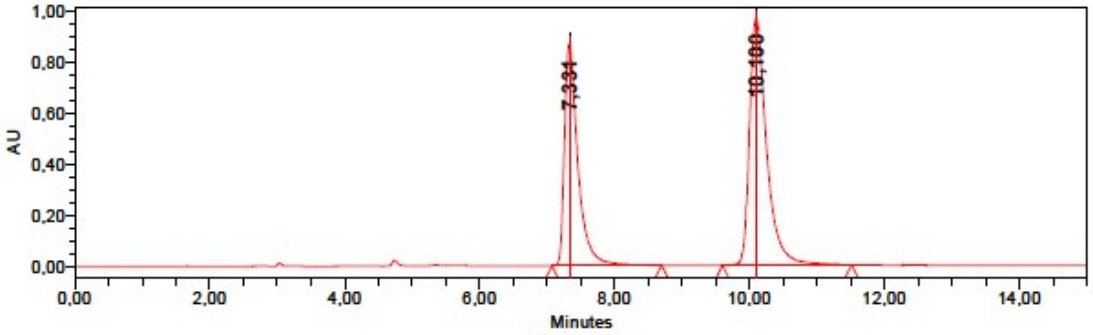
Figure S34: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A7). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.45 min; 31.51%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.29 min; 68.49%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,454	2704281	18,44
2		10,272	11964137	81,56

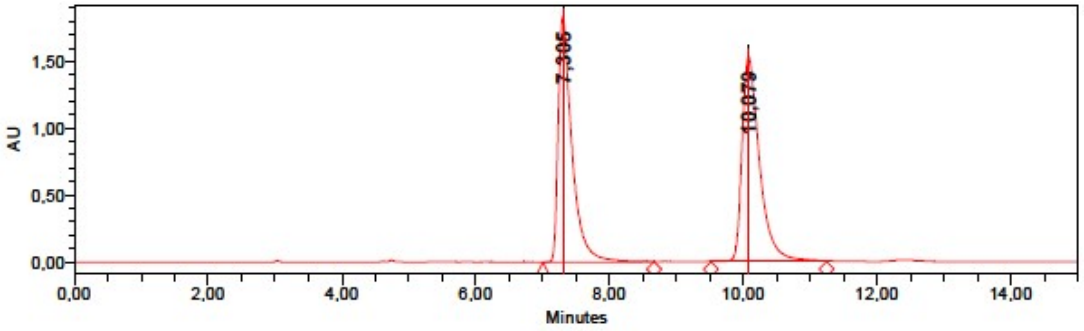
Figure S35: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A8). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.45 min; 18.44%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.27 min; 81.56%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,331	11997674	41,28
2		10,100	17064366	58,72

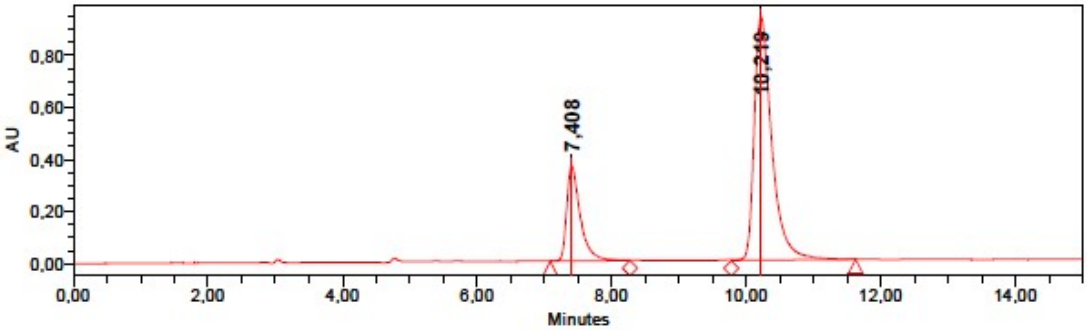
Figure S36: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A9). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.33 min; 41.28%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.10 min; 58.72%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,305	26186072	48,19
2		10,079	28156028	51,81

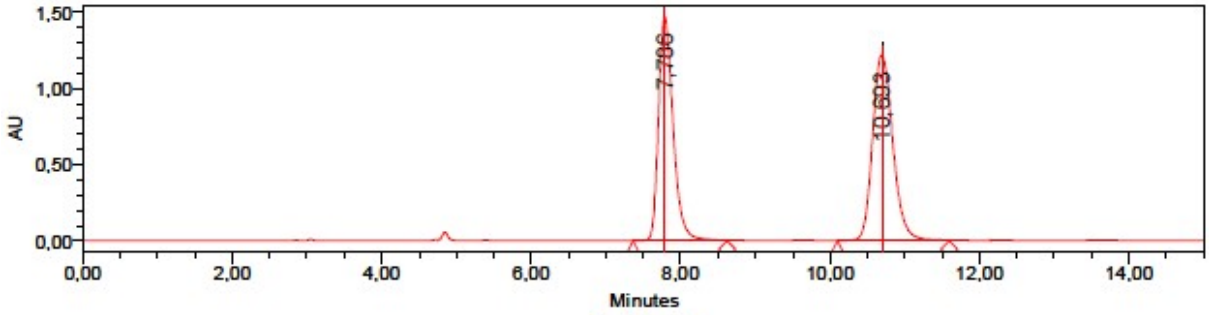
Figure S37: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A10). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.31 min; 48.19%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.08 min; 51.81%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,408	5165902	23,22
2		10,219	17076981	76,78

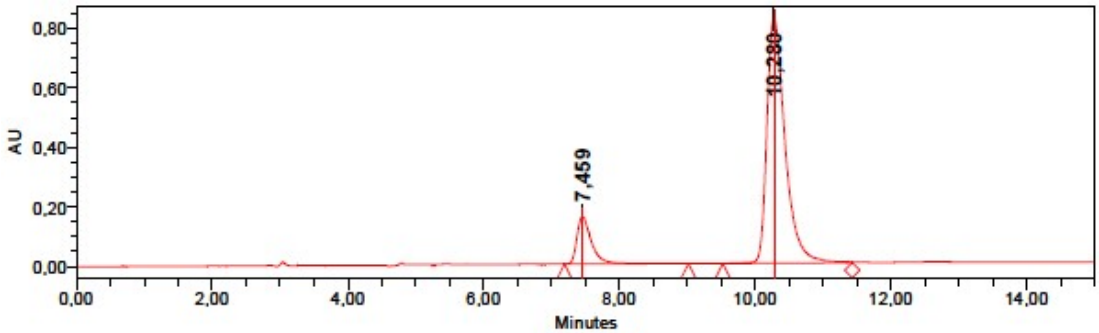
Figure S38: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A11). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.41 min; 23.22%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.22 min; 76.78%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,786	19898908	46,56
2		10,693	22841997	53,44

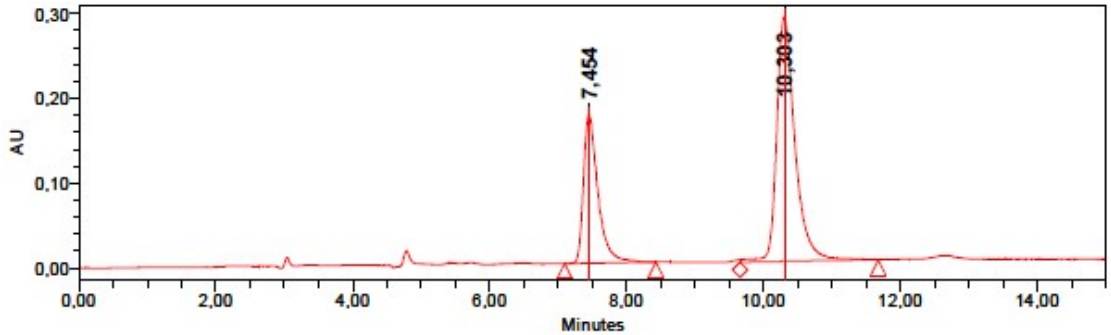
Figure S39: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A12). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.79 min; 46.56%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.69 min; 53.44%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,459	2418543	13,54
2		10,280	15450119	86,46

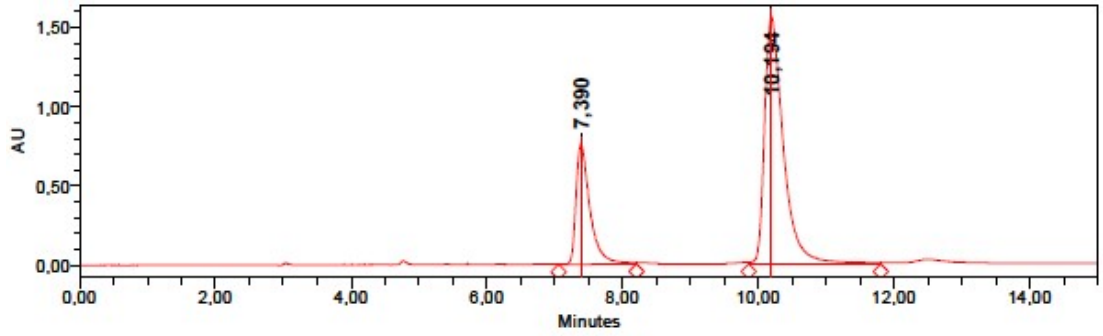
Figure S40: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A13). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.46 min; 13.54%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.28 min; 86.46%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,454	2554279	32,17
2		10,303	5385232	67,83

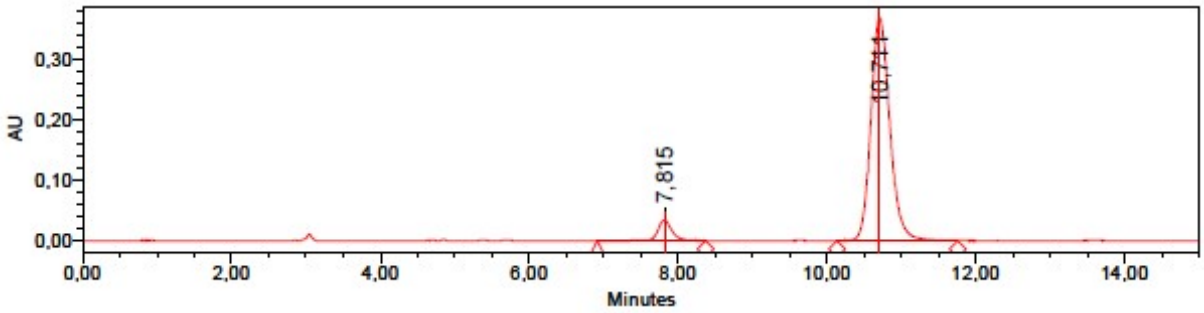
Figure S41: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A14). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.45 min; 32.17%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.30 min; 67.83%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,390	10791775	26,39
2		10,194	30107498	73,61

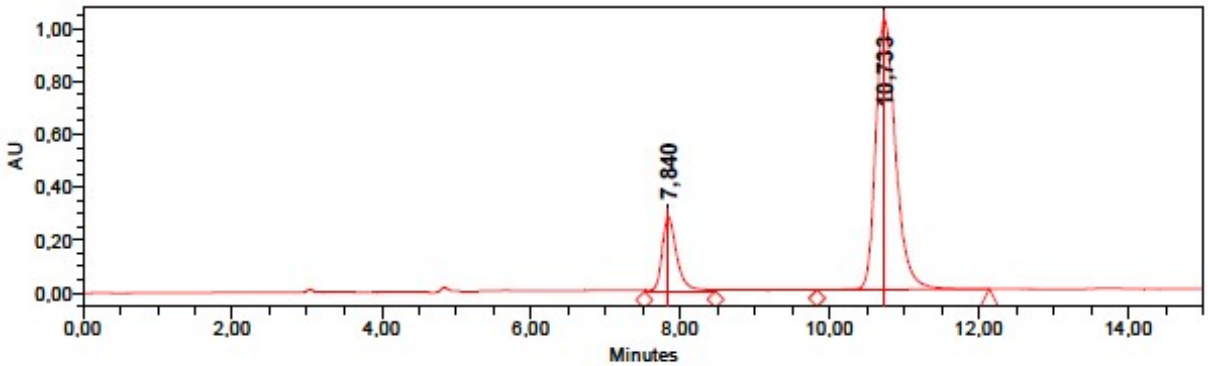
Figure S42: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A15). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.39 min; 26.39%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.19 min; 73.61%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,815	449504	6,51
2		10,711	6458093	93,49

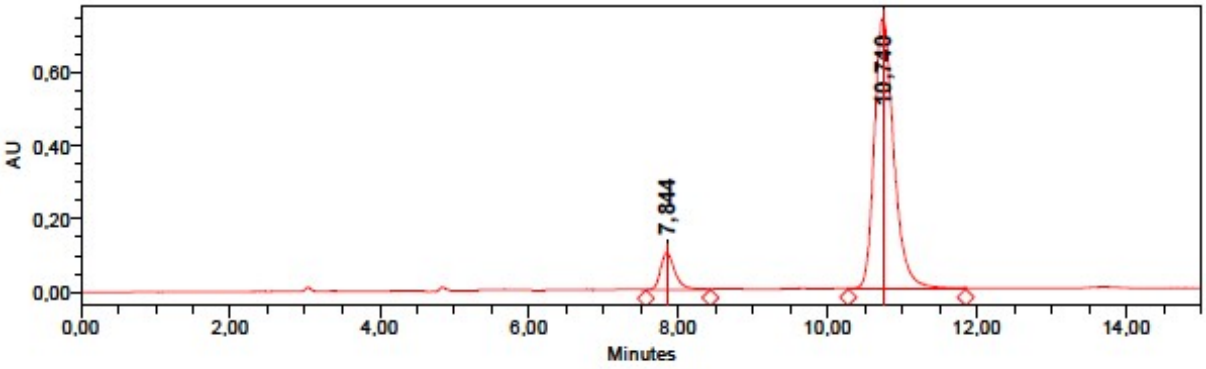
Figure S43: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A16-1). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.81 min; 6.51%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.71 min; 93.49%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,840	3831192	16,85
2		10,733	18908491	83,15

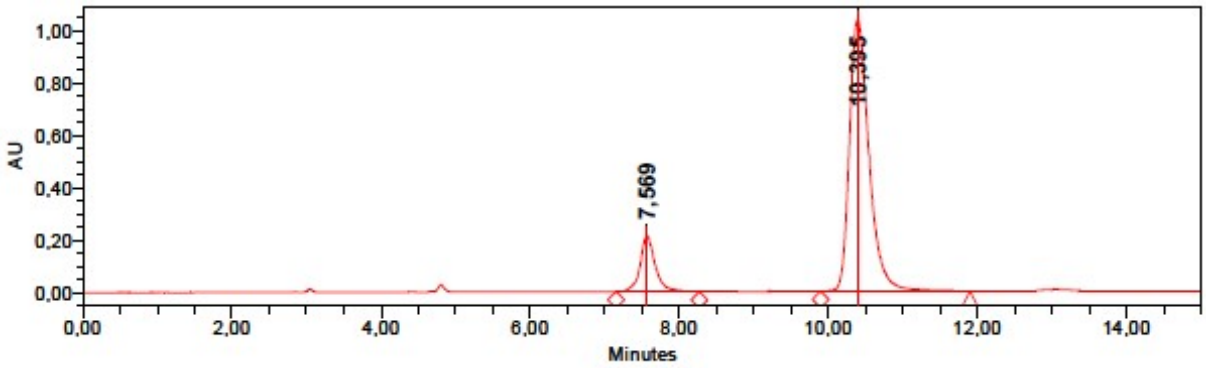
Figure S44: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A16-2). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.84 min; 16.85%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.73 min; 83.15%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,844	1371115	9,26
2		10,740	13443485	90,74

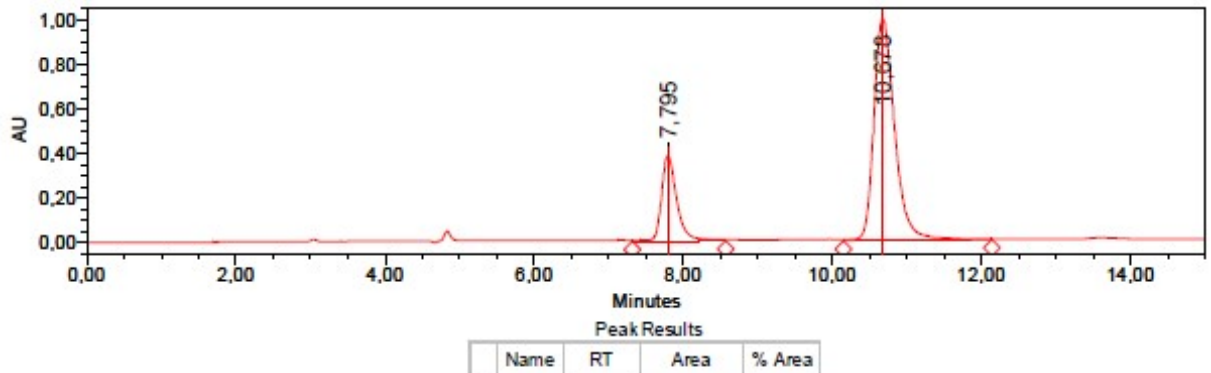
Figure S45: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A16-3). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.84 min; 9.26%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.74 min; 90.74%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,569	2988607	13,63
2		10,395	18943187	86,37

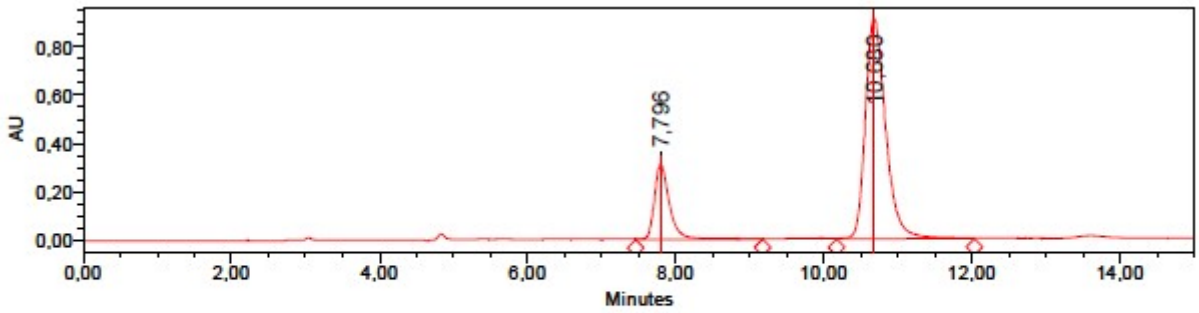
Figure S46: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A16-4). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.60 min; 13.63%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.40 min; 86.37%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,795	5525649	22,27
2		10,678	19287939	77,73

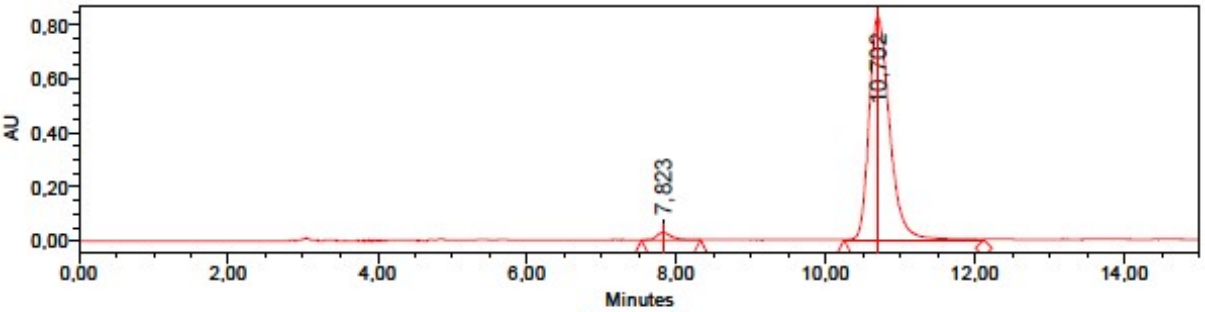
Figure S47: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A17). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.80 min; 22.27%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.68 min; 77.73%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,796	4480540	20,61
2		10,680	17256467	79,39

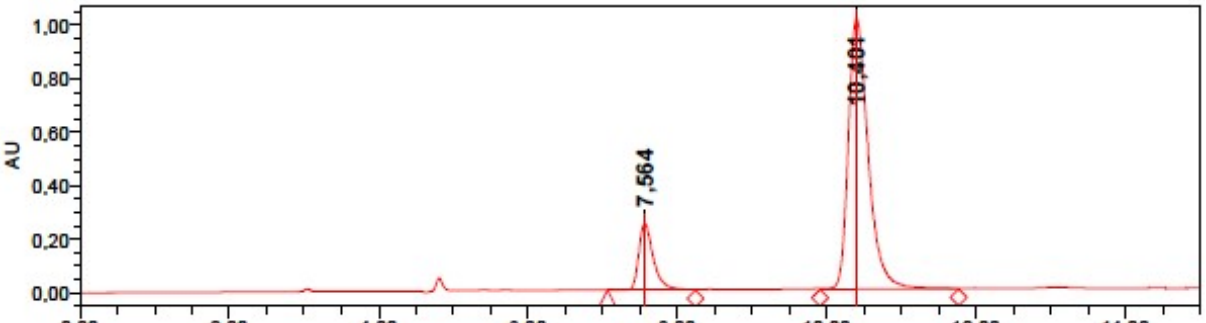
Figure S48: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A18). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.80 min; 20.61%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.68 min; 579.39%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,823	374942	2,35
2		10,702	15605599	97,65

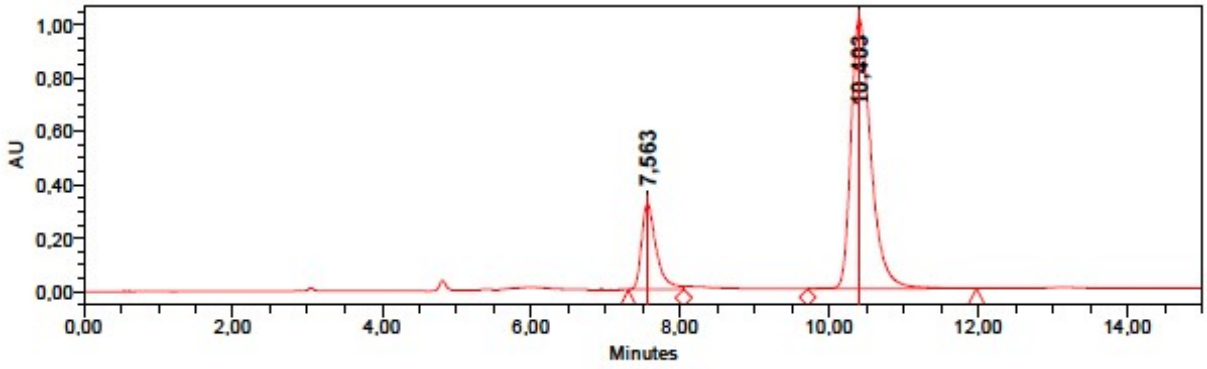
Figure S49: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A19-1). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.82 min; 2.35%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.70 min; 97.65%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,564	3371901	15,15
2		10,401	18889467	84,85

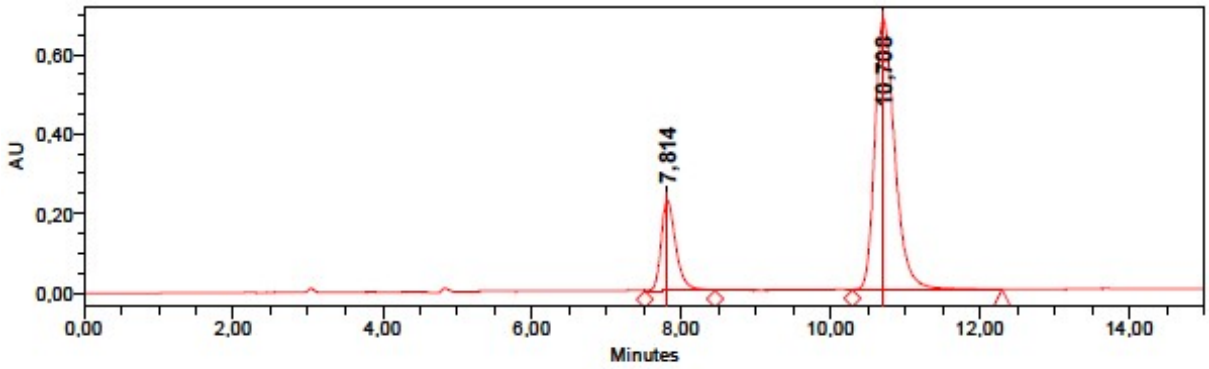
Figure S50: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A19-2). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.56 min; 15.15%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.40 min; 84.85%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,563	4415573	18,90
2		10,403	18948872	81,10

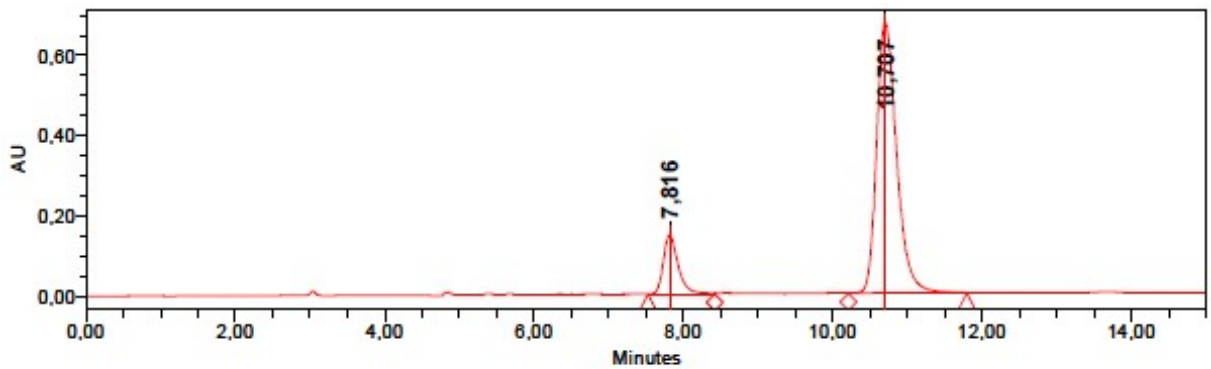
Figure S51: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A19-3). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.56 min; 18.90%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.40 min; 81.10%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,814	3116458	19,77
2		10,708	12648748	80,23

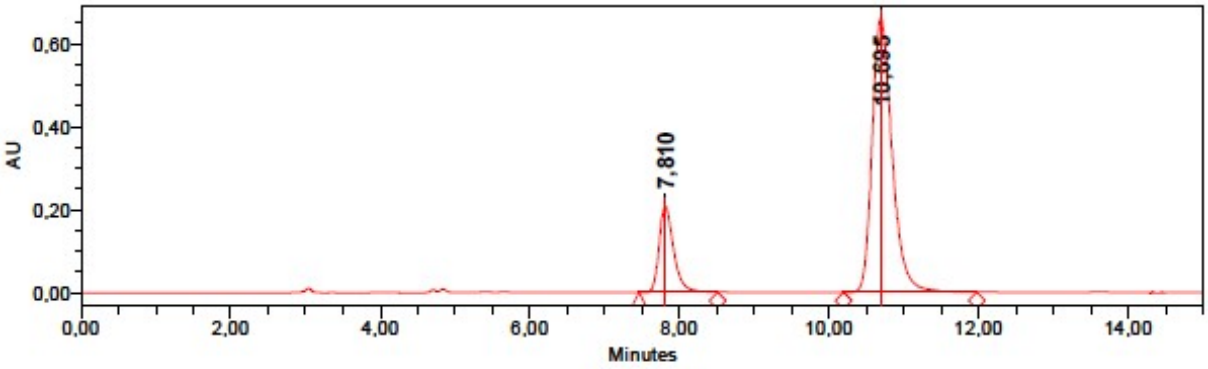
Figure S52: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A20). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.81 min; 19.77%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.71 min; 80.23%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,816	2014992	13,90
2		10,707	12479536	86,10

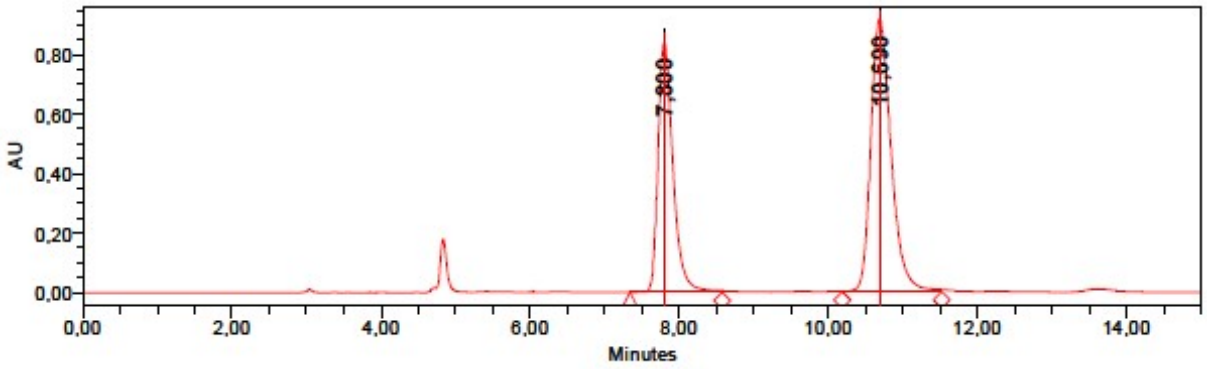
Figure S53: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A21). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.82 min; 13.90%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.71 min; 86.10%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,810	2800068	18,72
2		10,695	12157940	81,28

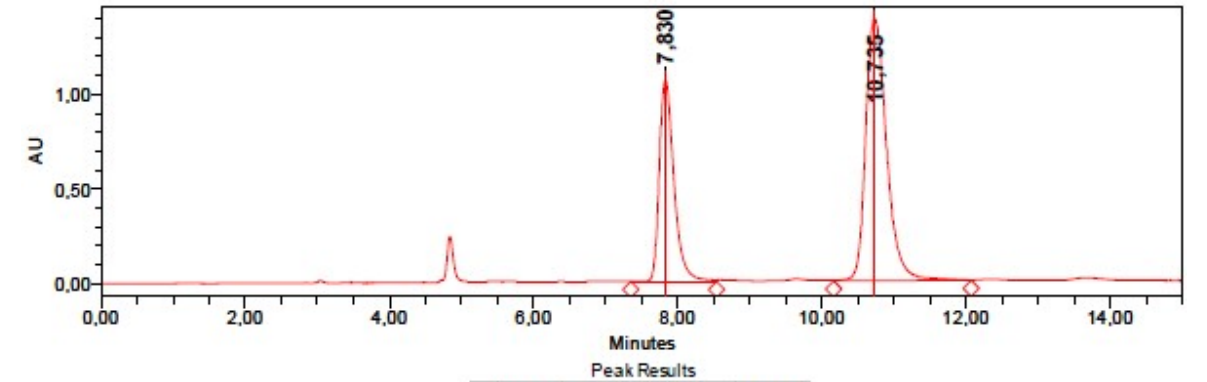
Figure S54: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A22). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.81 min; 18.72%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.70 min; 81.28%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,800	11629107	40,20
2		10,690	17298795	59,80

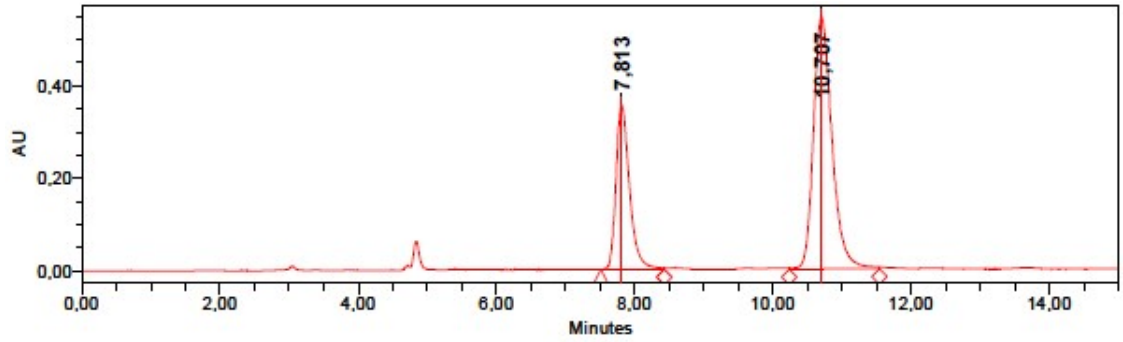
Figure S55: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A23). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.80 min; 40.20%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.69 min; 59.80%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,830	15037114	34,96
2		10,735	27973707	65,04

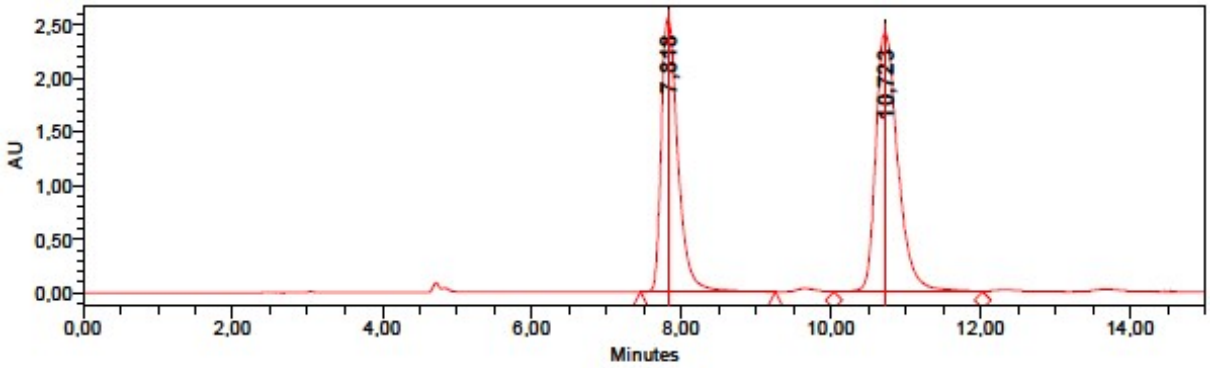
Figure S56: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A24). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.83 min; 34.96%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.73 min; 65.04%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,813	4807596	32,17
2		10,707	10137502	67,83

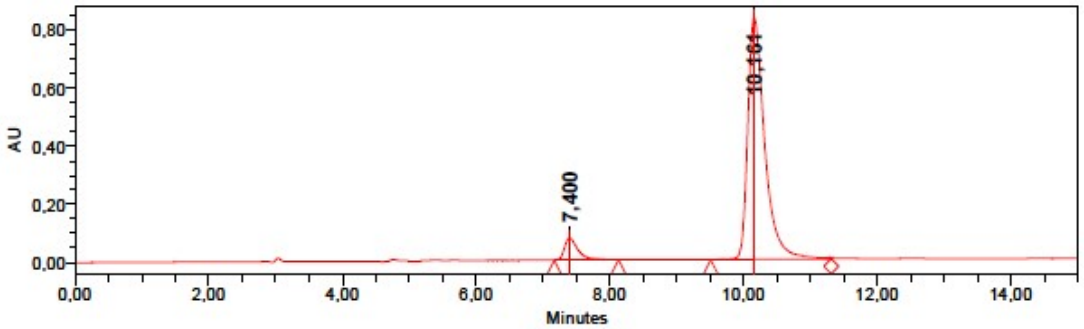
Figure S57: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A25). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.81 min; 32.17%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.71 min; 67.83%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,818	39339293	44,33
2		10,723	49407271	55,67

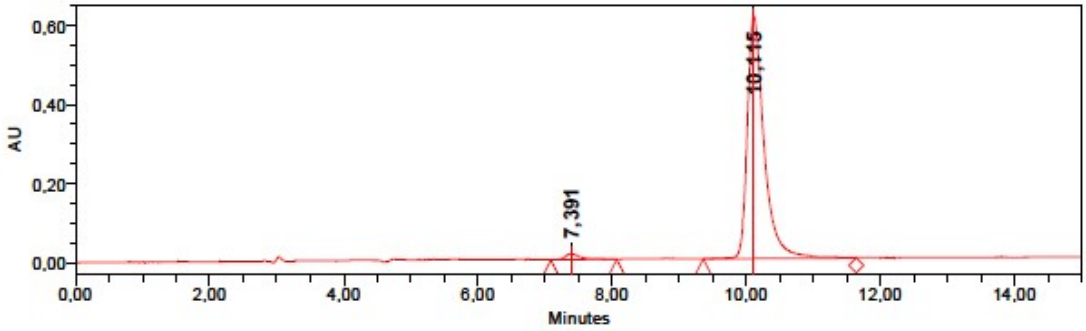
Figure S58: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A26). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.82 min; 44.33%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.72 min; 55.67%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,400	1074147	6,77
2		10,161	14784892	93,23

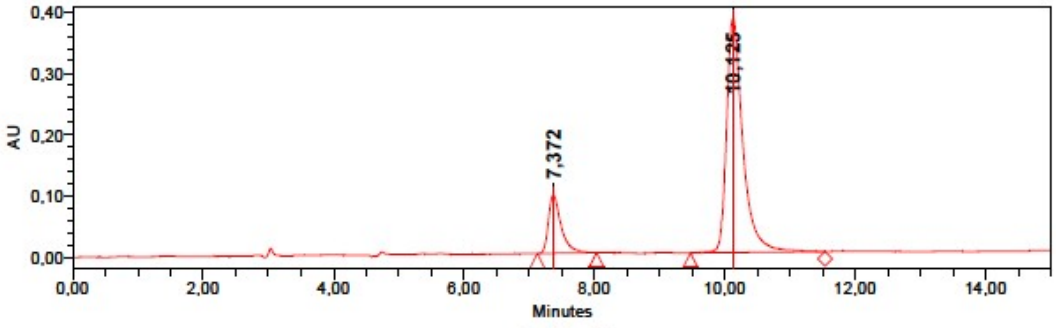
Figure S59: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A27-1). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.40 min; 6.77%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.16 min; 93.23%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,391	225377	2,06
2		10,115	10714153	97,94

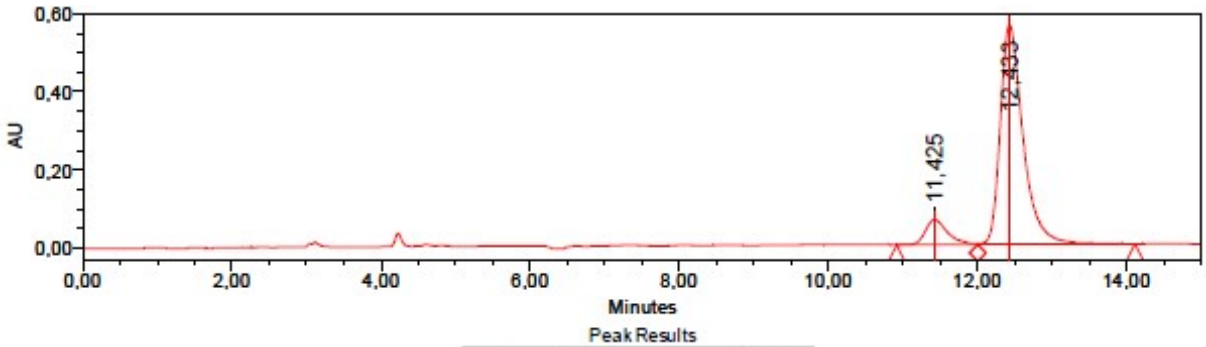
Figure S60: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A27-2). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.39 min; 2.06%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.11 min; 97.94%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		7,372	1286264	16,20
2		10,125	6651656	83,80

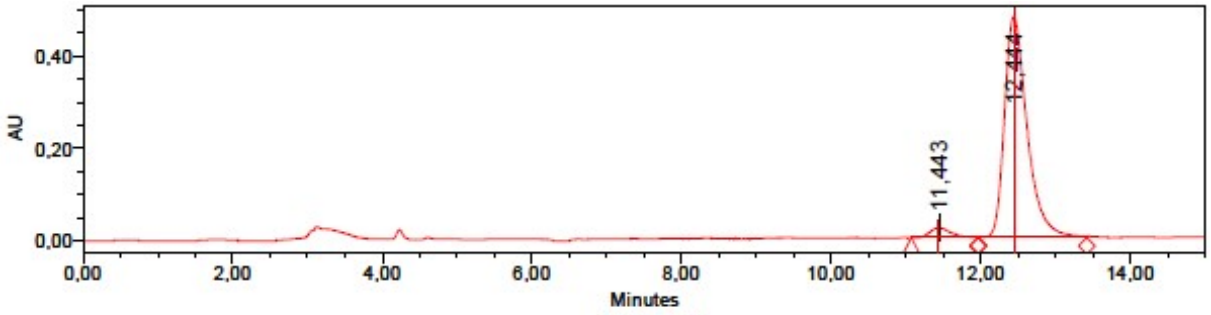
Figure S61: cHPLC analysis of **1a** from one-pot synthesis after 24 h milling at 30 Hz (Table S2, Method A27-3). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 7.37 min; 16.20%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 10.13 min; 83.80%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 90% of isohexane and 10% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		11,425	1311780	9,88
2		12,433	11967759	90,12

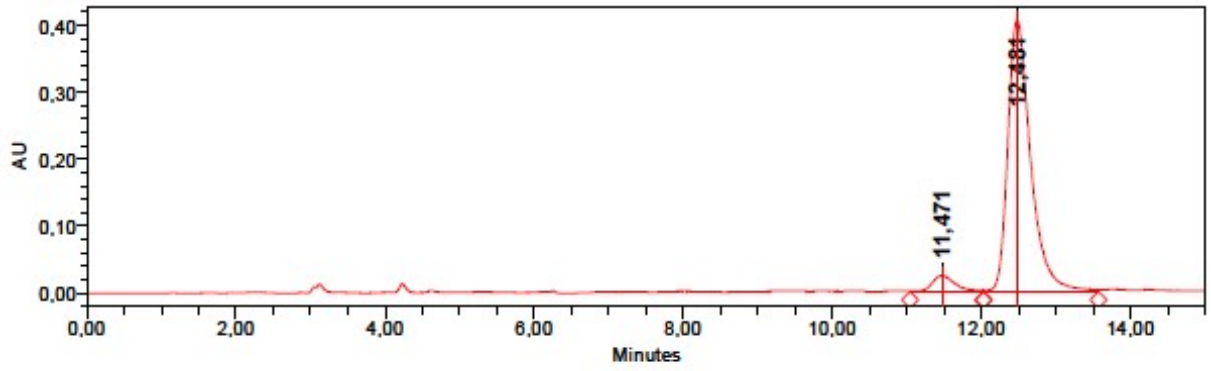
Figure S62: cHPLC analysis of **1b** from one-pot synthesis after 24 h milling at 30 Hz (Table S3, Method B1). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 11.43 min; 9.88%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 12.43 min; 90.12%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 95% of isohexane and 5% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		11,443	437443	4,15
2		12,444	10112719	95,85

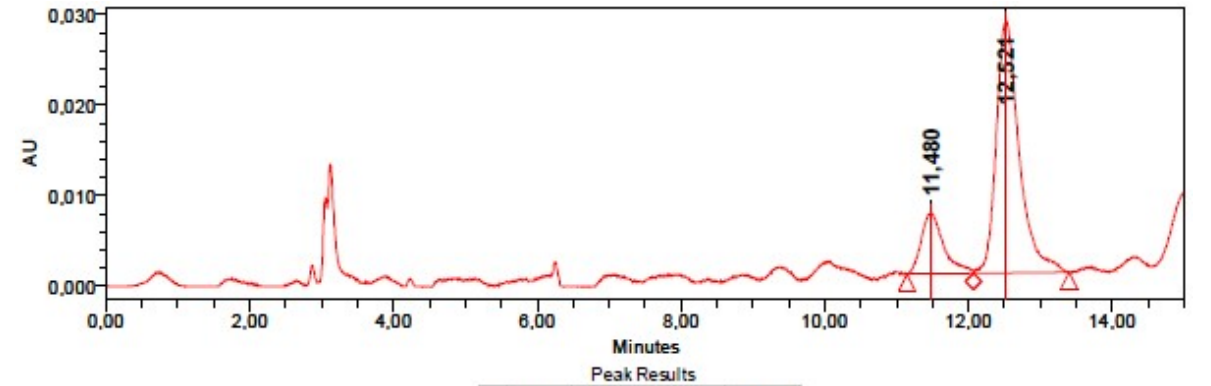
Figure S63: cHPLC analysis of **1b** from one-pot synthesis after 24 h milling at 30 Hz (Table S3, Method B2-1). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 11.44 min; 4.15%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 12.44 min; 95.85%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 95% of isohexane and 5% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		11,471	511833	5,60
2		12,481	8633101	94,40

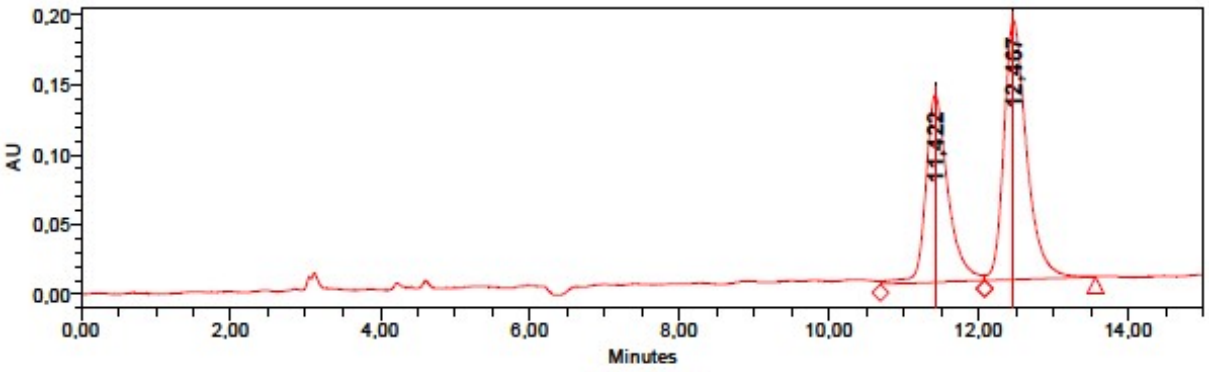
Figure S64: cHPLC analysis of **1b** from one-pot synthesis after 24 h milling at 30 Hz (Table S3, Method B2-2). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 11.47 min; 5.60%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 12.48 min; 94.40%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 95% of isohexane and 5% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		11,480	145959	19,09
2		12,521	618694	80,91

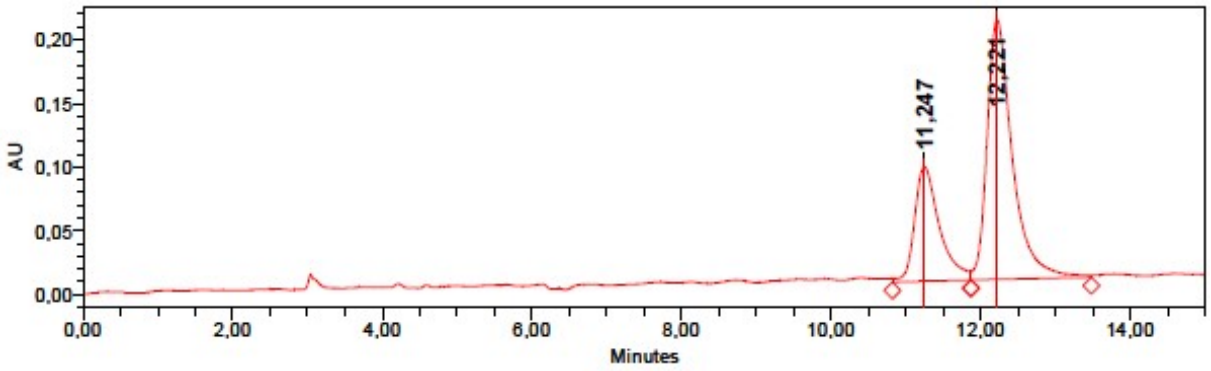
Figure S65: cHPLC analysis of **1b** from one-pot synthesis after 24 h milling at 30 Hz (Table S3, Method B2-3). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 11.48 min; 19.09%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 12.52 min; 80.91%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 95% of isohexane and 5% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		11,422	2787207	41,51
2		12,467	3928131	58,49

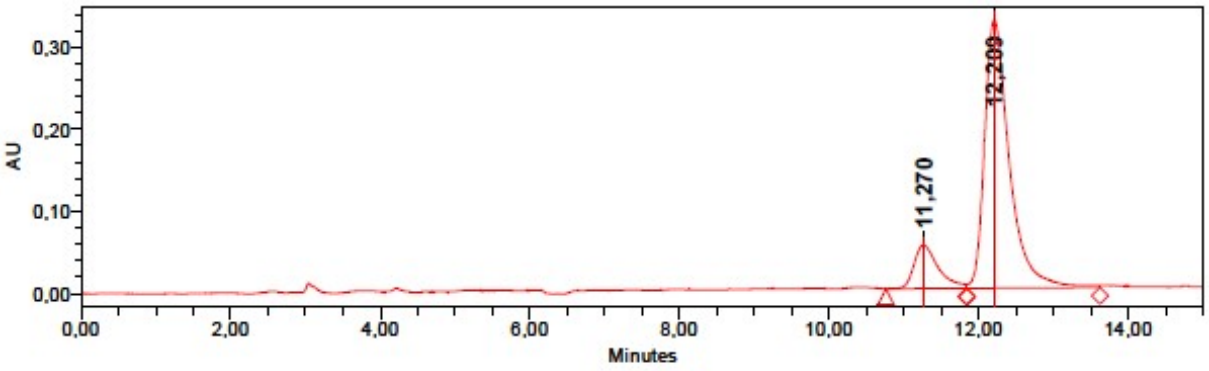
Figure S66: cHPLC analysis of **1b** from one-pot synthesis after 24 h milling at 30 Hz (Table S3, Method B2-4). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 11.42 min; 41.51%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 12.47 min; 58.49%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 95% of isohexane and 5% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		11,247	2086195	30,22
2		12,221	4817985	69,78

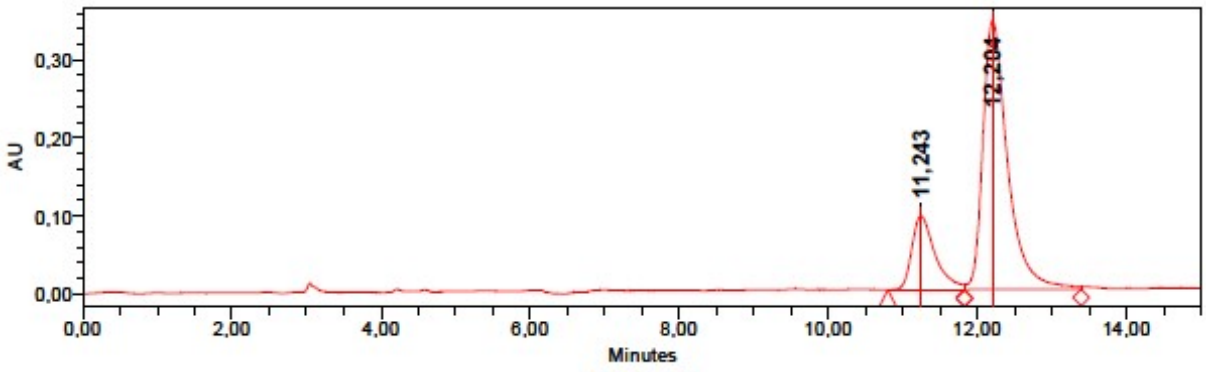
Figure S67: cHPLC analysis of **1b** from one-pot synthesis after 24 h milling at 30 Hz (Table S3, Method B3-1). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 11.24 min; 30.22%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 12.22 min; 69.78%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 95% of isohexane and 5% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		11,270	1192166	13,67
2		12,209	7528867	86,33

Figure S68: cHPLC analysis of **1b** from one-pot synthesis after 24 h milling at 30 Hz (Table S3, Method B3-2). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 11.27 min; 13.67%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 12.21 min; 86.33%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 95% of isohexane and 5% of ethanol.



Peak Results

	Name	RT	Area	% Area
1		11,243	2063056	20,52
2		12,204	7992522	79,48

Figure S69: cHPLC analysis of **1b** from one-pot synthesis after 24 h milling at 30 Hz (Table S3, Method B3-3). Left peak (n°1 in the table below the chromatogram) represents the (*S*)-enantiomer (RT: 11.24 min; 20.52%). Right peak (n°2 in the table below the chromatogram) represents the (*R*)-enantiomer (RT: 12.20 min; 79.48%). The stationary phase is the Chiralpak IA column and the mobile phase is composed of 95% of isohexane and 5% of ethanol.