Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supplementary Information

A Viedma ripening route to an enantiopure building block for Levetiracetam and Brivaracetam

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General remarks:

^{1}H and ^{13}C NMR were recorded using Agilent VNMRS300 or Agilent MercuryPlus300 spectrometers (the NMR spectra were recorded in either $CDCl_3$, DMSO-d6 or CD_3OD solutions; NMR chemical shifts δ are given in parts per million (ppm); coupling constants *J* are in hertz (Hz)). Chiral HPLC analyses were performed using an Agilent Technologies Infinity 1260 HPLC system equipped with a Chiralpak IA (250 x 4.6 mm, 5 μm) column; eluent: *n*-heptane/isopropanol: 80/20 (*v/v*) or 95/5 (*v/v*) for **3-a** and **3-b**, respectively; flow rate: 0.7 mL/min; UV-light detector: 220 nm). Differential Scanning Calorimetry (DSC) measurements were performed on a TA Instruments Q20. Optical rotation was measured using a Krüss P3001 polarimeter. Second Harmonic Generation (SHG) measurements were performed according to the previously described procedure. X-Ray powder diffraction patterns were measured using a Bruker D2 Phaser with a Cu X-ray source (Cu K-α, λ = 1.5418 Å). (±)- and (*S*)-2-Aminobutanamide ((±)-**2** and (*S*)-**2**) are commercially available as hydrochloride salt, amongst others, from Aris Pharmaceuticals (USA) and TCI Europe (Belgium), respectively. Glass beads (borosilicate, diam. 2 mm) were purchased from sigma-aldrich. 20 mL vials used (WHEATON® 180 low potassium borosilicate glass) were purchased from VWR International.

Experimental Section:

(±)-2-((benzylidene)amino)butanamide (rac-3a). [*General procedure for all imines **3** preparation*]. Racemic 2-aminobutyramide HCl-salt (**2**•HCl, 5.0 g, 36 mmol) was dissolved in 40 mL MeOH/H2O 1:1 at room temperature. To this solution was added N-methylmorpholine (4.1 g, 40 mmol) followed by slow addition of a solution of benzaldehyde (3.72 g, 35 mmol) in 10 mL MeOH over 30 minutes. By the end of the addition slow crystallization started. After stirring for 30 minutes 20 mL of water was slowly added and the suspension was stirred for an additional hour. The solid was filtered, washed with 20 mL of MeOH/water 1:1 and dried under reduced pressure to afford 5.26 g (27.6 mmol, 79%) of (±)-2-((benzylidene)amino)butanamide (rac-**3a**) as white solid. ^{1}H NMR (DMSO-d6, δ, ppm): 8.34 (s, 1H), 7.84 (dd, 2H), 7.48 (m, 3H), 7.17 and 7.12 (2 x br s, 2H), 3.66 (dd, 1H), 1.85 (m, 1H), 1.70 (m, 1H) and 0.82 (t, 3H). ^{13}C NMR (DMSO-d6, δ, ppm): 174.38 (s), 162.30 (d), 136.26 (s), 131.40 (d), 129.08 (d), 128.75 (d), 75.07 (d), 27.50 (t), 10.65 (q).

(*S*)-2-((benzylidene)amino)butanamide ((*S*)-3a). According to the general procedure on 136 mmol scale: 22.15 g (116.4 mmol, 85%) of (*S*)-2-((benzylidene)amino)butanamide ((*S*)-**3a**) as a white solid. $[\alpha]^{21}_{D}$ +46.8 (c=1, MeCN).

(±)-2-((2-methylbenzylidene)amino)butanamide (rac-3b). According to the general procedure: 2.74 g (13.4 mmol, 76%) of (±)-2-((2-methylbenzylidene)amino)butanamide (rac-**3b**) was obtained as a white solid. ^{1}H NMR (DMSO-d6, δ, ppm): 8.59 (s, 1H), 7.93 (d, 1H), 7.38-7.24 (m, 3H), 7.18 (br s, 1H), 7.06 (br s, 1H), 3.69 (dd, 1H), 2.50 (s, 3H), 1.87 (m, 1H), 1.71 (m, 1H) and 0.82 (t, 3H). ^{13}C NMR (DMSO-d6, δ, ppm): 174.36 (s), 161.02 (d), 138.10 (s), 134.06 (s), 131.16 (d), 130.78 (d), 128.04 (d), 126.33 (d), 75.47 (d), 27.45 (t), 19.37 (q), 10.50 (q).

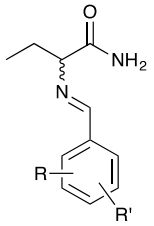
(*S*)-2-((2-methylbenzylidene)amino)butanamide ((*S*)-3b). According to the general procedure on 18 mmol scale: 6.37 g (31.2 mmol, 89%) of (*S*)-2-((2-methylbenzylidene)-amino)butanamide ((*S*)-**3b**) as a white solid.

(*S*)-(-)-2-aminobutanamide hydrochloride ((*S*)-2•HCl). Aqueous HCl (37% ww, 5.8 mmol, 0.57 mL) was added to a solution of imine (*S*)-**3a** (1.0 g, 5.26 mmol) in acetone (20 mL). The reaction mixture was stirred for 1 hour at ambient temperature. The white solid formed was collected by filtration, rinsed

with acetone (3 x 5.0 mL) and dried to afford a white solid (0.51 g, 94%). ^{1}H NMR (DMSO-d6, δ, ppm): 8.27 (br s, 3H), 8.00 (br s, 1H), 7.50 (br s, 1H), 3.67 (t, 1H), 1.78 (m, 2H) and 0.89 (t, 3H).

Second Harmonic Generation (SHG) measurements:

Table S1. Second harmonic generation (SHG) responses for imines **3**.



Compound	***Substituent(s)***	***SHG response***
3a	R = H; R' = H	large SHG effect
3b	R = 2-Me; R' = H	large SHG effect
3c	R = 2-Me; R' = H	small SHG effect
3d	R = 2-Cl; R' = H	no SHG effect
3e	R = 2-OMe; R' = 3-OMe	no SHG effect
3f	R = 2-OMe; R' = 4-OMe	no SHG effect

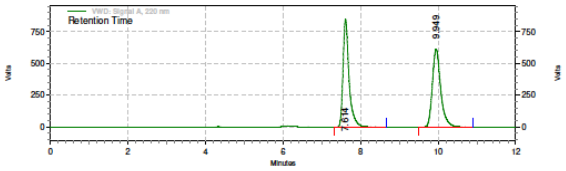
Differential Scanning Calorimetry (DSC) results of compounds (±) and (S)-3a,b:

Compound*	**melting point (°C)**	**ΔH_f (J/g)**
(*S*)-**3a**	137.2	176
(±)-**3a**	111.9	170
(*S*)-**3b**	133.5	211
(±)-**3b**	112.9	188

* Crystallization from methanol/water or acetonitrile

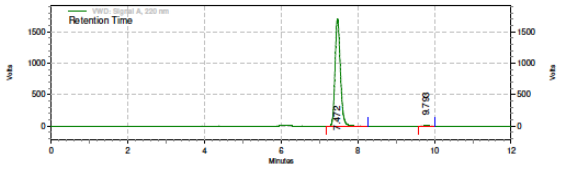
Deracemization experiments:

Deracemization of (±)-2-((benzylidene)amino)butanamide (3a). A screw cap vial (20 mL) was charged with 2 mm glass beads (10 g), imine (RS)-**3a** (2.0 g, 10.5 mmol), (S)-**3a** (0.1 g, 0.5 mmol) and PhMe (10 mL). The vial was placed in an ultrasonic bath, equipped with a thermostat (maintaining the temperature at 20 °C), and was sonicated for 30 min. Then, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.3 eq, 0.48 g, 3.16 mmol) was added, and the mixture was sonicated at 20 °C overnight. Chiral HPLC analysis of the isolated solid sample indicated complete deracemization overnight. The suspension was replaced into a P4 filter, using a Pasteur's pipet to separate the suspension and glass beads, and filtered. The isolated solid was rinsed with PhMe (2 x 3.0 mL) and dried to afford the desired (S)-**3a** as a white solid (1.52 g, 73%, ee > 99%).



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
7.614	154631497	49.84	14264392	58.06
9.949	155646759	50.16	10303622	41.94
Totals	310278256	100.00	24568014	100.00



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
7.472	275703925	99.53	28731802	99.63
9.793	1301794	0.47	105658	0.37
Totals	277005719	100.00	28837460	100.00

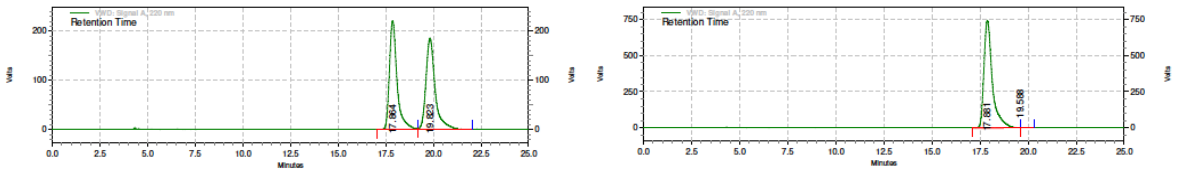
Figure S1. Chiral HPLC chromatograms of racemate ***(RS)-3a*** *(left)* and deracemized ***(S)-3a*** *(right).*

*[**Note:** The isolated mother liquor (corresponds to saturated (RS)-**3a** solution in PhMe + DBU) was recycled two times without significant influence on the deracemization rate.]*

Deracemization of (*RS*)-3a with recycled mother liquor:

A screw cap vial (20 mL) was charged with 2 mm glass beads (10 g), imine (RS)-**3a** (1.8 g, 9.47 mmol), (S)-**3a** (0.2 g, 1.0 mmol) and the mother liquor (10 mL) isolated from a previous deracemization of **3a** *[corresponds to a saturated solution of (RS)-**3a** in PhMe and DBU]* was added. The resulting mixture was sonicated at 20 °C overnight. The suspension was replaced into a P4 filter, using a Pasteur's pipet to separate the suspension and glass beads, and filtered. The collected solid was rinsed with *n*-heptane (2.0 mL) and dried to afford the desired (S)-**3a** as a white solid (1.98 g, ee > 99%).

Deracemization of (±)-2-((2-methylbenzylidene)amino)butanamide (3b). A screw cap vial (10 mL) was charged with 2 mm glass beads (5 g), imine (RS)-**3b** (1.0 g, 4.9 mmol), (S)-**3b** (0.1 g, 0.49 mmol) and PhMe (5 mL). The vial was placed in an ultrasonic bath, equipped with a thermostat (maintaining the temperature at 20 °C), and was sonicated for 30 min. Then, DBU (0.3 eq, 0.22 g, 1.47 mmol) was added, and the mixture was sonicated at 20 °C overnight. Chiral HPLC analysis of the isolated solid sample indicated complete deracemization overnight. The suspension was replaced into a P4 filter, using a Pasteur's pipet to separate the suspension and glass beads, and filtered. The isolated solid was rinsed with PhMe (2 x 2.0 mL) and dried to afford the desired (S)-**3b** as a white solid (0.68 g, 61.8%, ee > 99%).



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
17.864	102238693	49.82	3697018	54.35
19.823	102984188	50.18	3105102	45.65
Totals	205222881	100.00	6802120	100.00

VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
17.881	376726588	99.92	12459060	99.88
19.588	302131	0.08	14396	0.12
Totals	377028719	100.00	12473456	100.00

Figure S2. Chiral HPLC chromatograms of racemate ***(RS)-3b*** *(left)* and deracemized ***(S)-3b*** *(right).*

Racemization rate determination:

(*S*)-**3a** (10 mg) was dissolved in 20 mL of solvent (MeCN, PhMe, MTBE, Heptane). The stock solution (1.5 mL) was placed into a 2 mL HPLC vial followed by DBU (5.0 μL) addition. The vial was shaken for 30 seconds and placed into HPLC tray. Enantiomeric excess in the solution was monitored by chiral HPLC (by direct injection of 4 μL of the obtained reaction solution per analysis). Data collected are represented in Figure 2.

Deracemization rate determination:

Standard protocol:

A saturated solution of RS-**3a** in a solution of DBU (40 μL/mL) in a solvent was prepared by the following protocol:

A screw cap vial was charged with RS-**3a (*)**, solvent (12 mL) and DBU (0.48 mL):

Solvent	**Amount of RS-3a:**
MeCN	1.5 g
PhMe	0.5 g
MTBE	0.3 g
n-Heptane	0.2 g

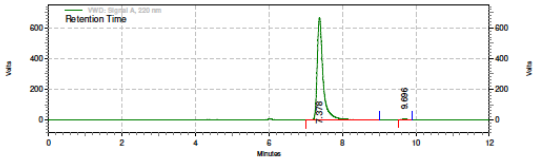
A 20 mL screw cap vial was charged with 2 mm glass beads (10 g), imine (RS)-**3a,** solvent (12 mL) and DBU (0.5 mL). The vial was sonicated for 30 minutes at 20 °C. The suspension was filtered through a P4 filter. The isolated mother liquor was used in the following experiments:

A 20 mL screw cap vial was charged with 2 mm glass beads (10 g), (RS)-**3a** (0.85 g), (S)-**3a** (0.15 g) and the corresponding mother liquor (10 mL). The vial was sonicated at 20°C while the solid phase *ee* was monitored by chiral HPLC of samples prepared by isolating small amounts of the solid by filtration. The data collected are represented in Figure 3.

After complete deracemization of the solid phase, the slurry was filtered. The solid collected was washed with the corresponding solvent (3 x 2.0 mL; MeCN, PhMe or MTBE) and dried to give (S)-**3a** as a white solid in nearly quantitative yield (corrected on sampling and washing the solid) in 97-99% *ee*.

Large Scale Deracemization of (±)-2-((benzylidene)amino)butanamide (3a):

A 100 mL flask was charged with 2 mm glass beads (50 g), imine (*RS*)-**3a** (13.2 g, 69.4 mmol), (*S*)-**3a** (1.8 g, 9.5 mmol) and PhMe (50 mL). The vial was placed in an ultrasonic bath, equipped with a thermostat (maintaining the temperature at 20 °C), and was sonicated for 30 min before DBU (24 mmol, 3.6 g, 0.3 eq) was added. The resulting mixture was sonicated at 20 °C for 60 hours. The slurry was replaced into a P4 filter, using a 10 mL pipet to separate the suspension from the glass beads, and filtered. The solid collected was washed with PhMe (3 x 20 mL) and dried to afford the desired (*S*)-**3a** a white solid (11.61 g; $ee_{(S)}$ = 98.9%; isolated yield: 77.4%). The mother liquor was washed with a phosphate buffer (pH = 7; 2 x 50 mL). The organic layer was concentrated under reduced pressure to give (*RS*)-**3a** as a white solid (2.3 g). Compound **3a** ((*S*)-**3a** + (*RS*)-**3a**) was isolated in amount of 13.91 g, which corresponds to isolated yield of 92.7%. During the experiment enantiomeric enrichment of the solid phase was monitored by chiral HPLC analysis of the isolated solid samples. As expected, the time evolution of the *ee* in the solid phase follows the exponential behavior (Figure S4).



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
7.378	123218083	99.43	11181987	99.47
9.696	703260	0.57	59285	0.53
Totals	123921343	100.00	11241272	100.00

Figure S3. Chiral HPLC chromatogram of the isolated solid ***(S)*-3a**.

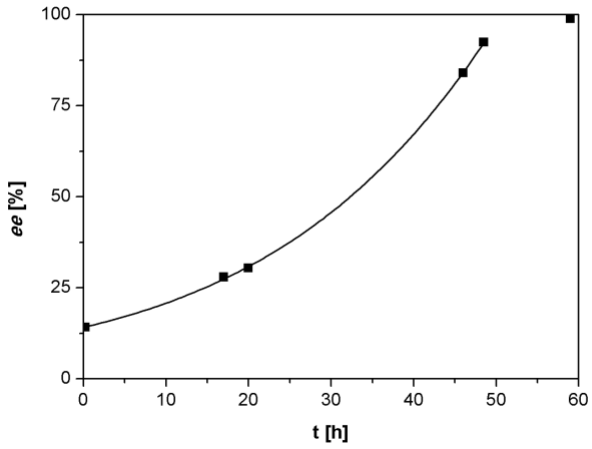


Figure S4. Enantiomeric enrichment of the solid phase during the large-scale experiment.

NMR spectra:

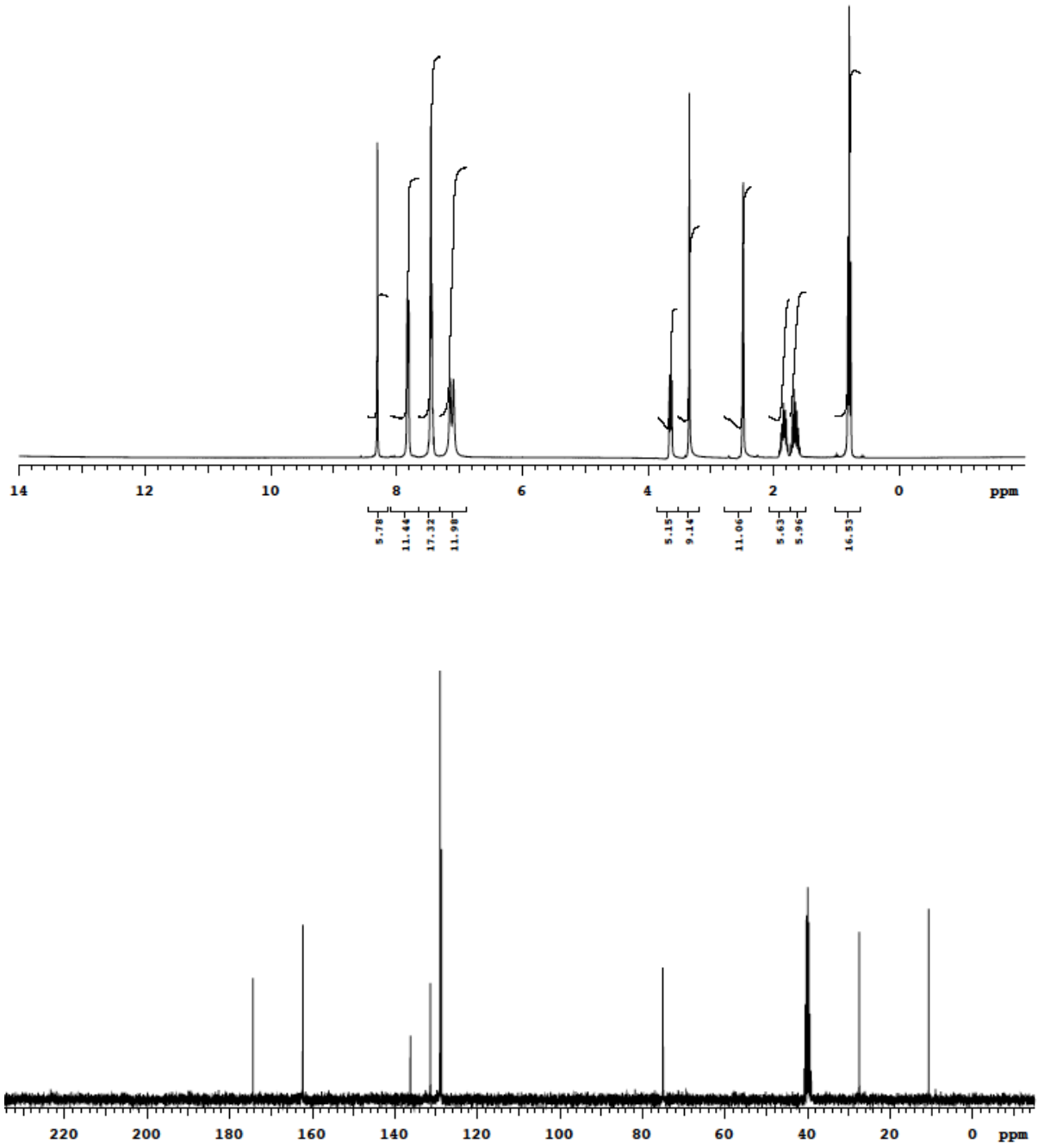


Figure S6. ^{1}H (*top*) and ^{13}C (*bottom*) NMR spectra of racemate **3a**.

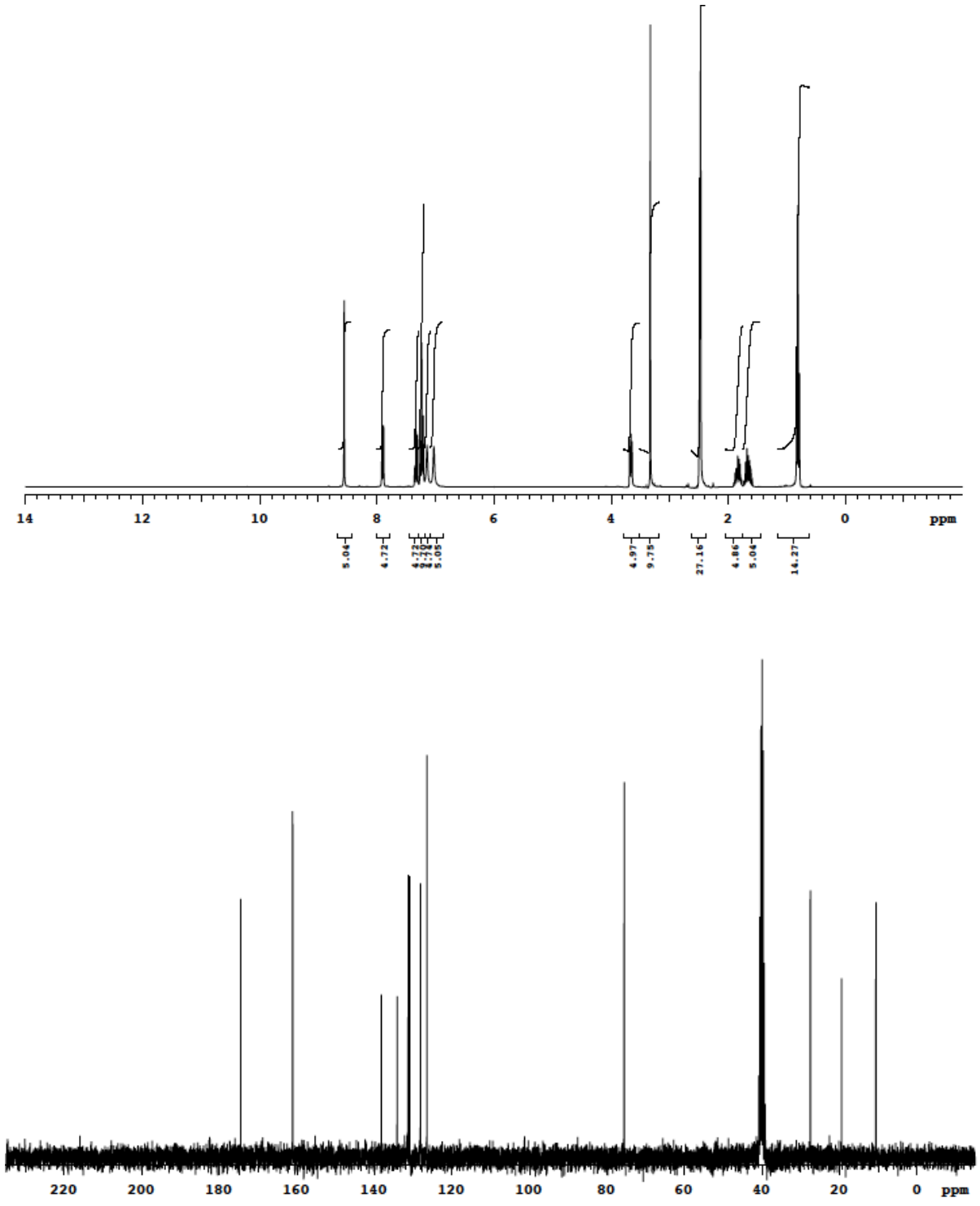


Figure S7. ^{1}H (*top*) and ^{13}C (*bottom*) NMR spectra of racemate **3b**.

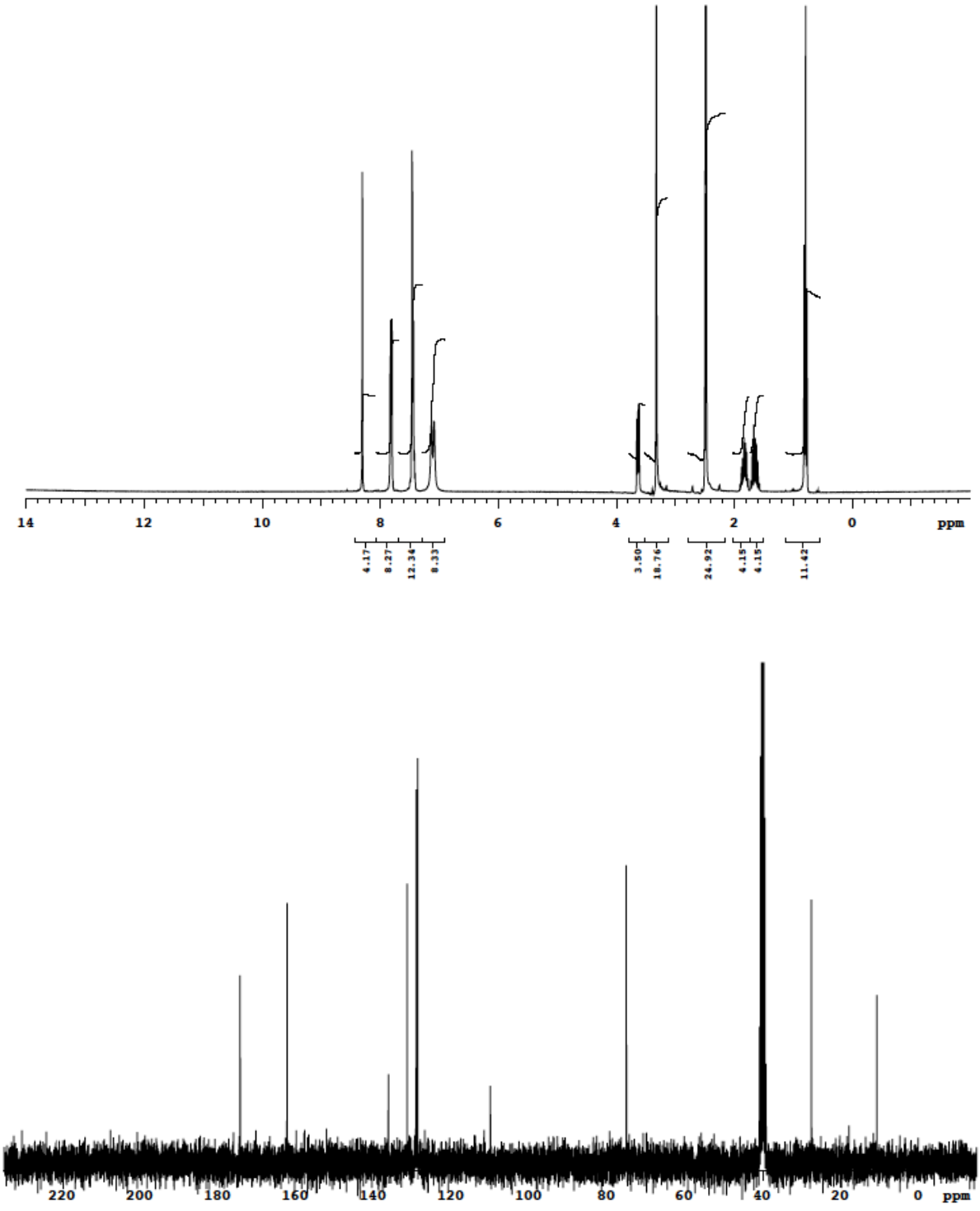


Figure S8. ^{1}H (*top*) and ^{13}C (*bottom*) NMR spectra of deracemized (S)-**3a**.

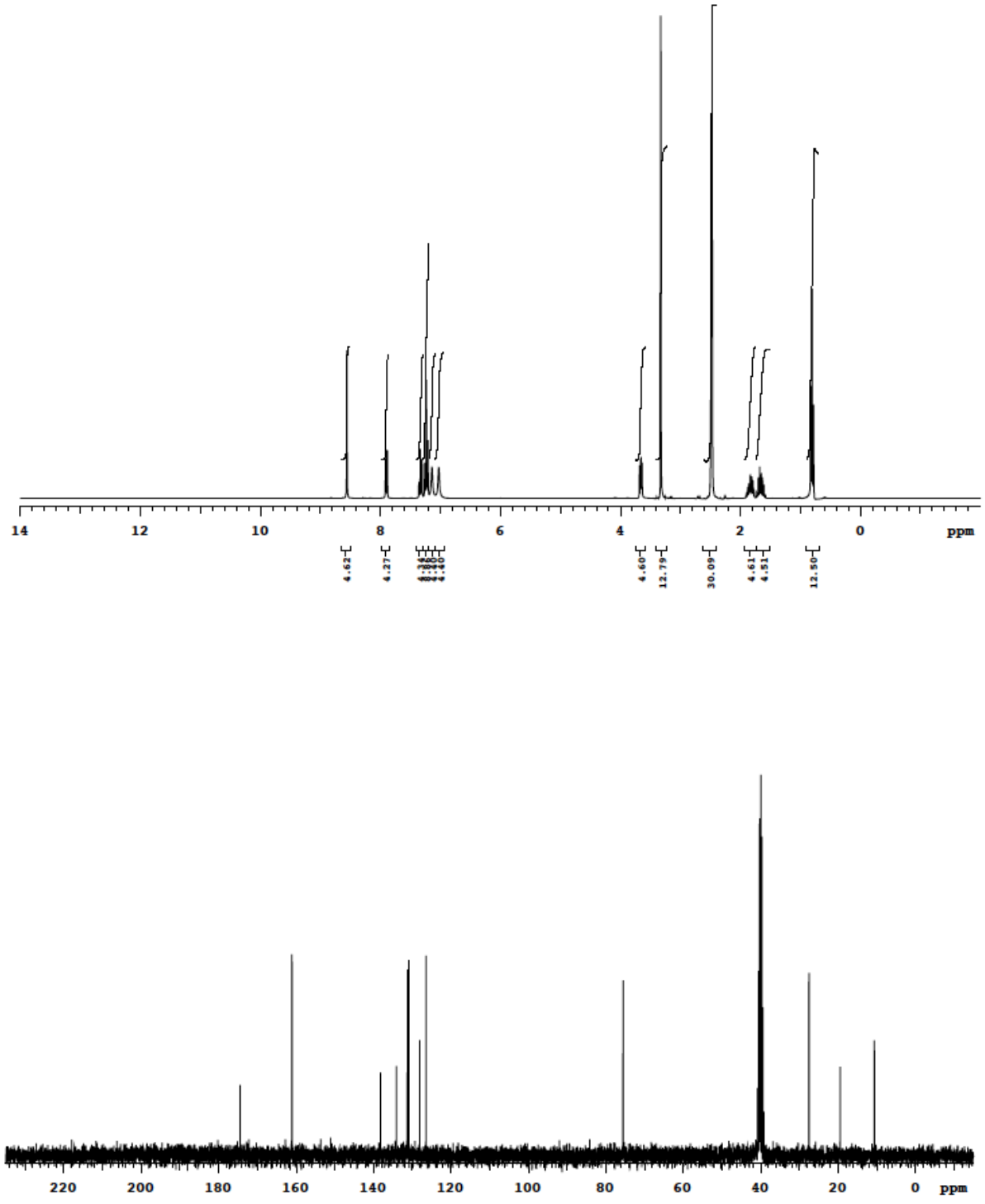


Figure S9. ^{1}H (*top*) and ^{13}C (*bottom*) NMR spectra of deracemized (S)-**3b**.

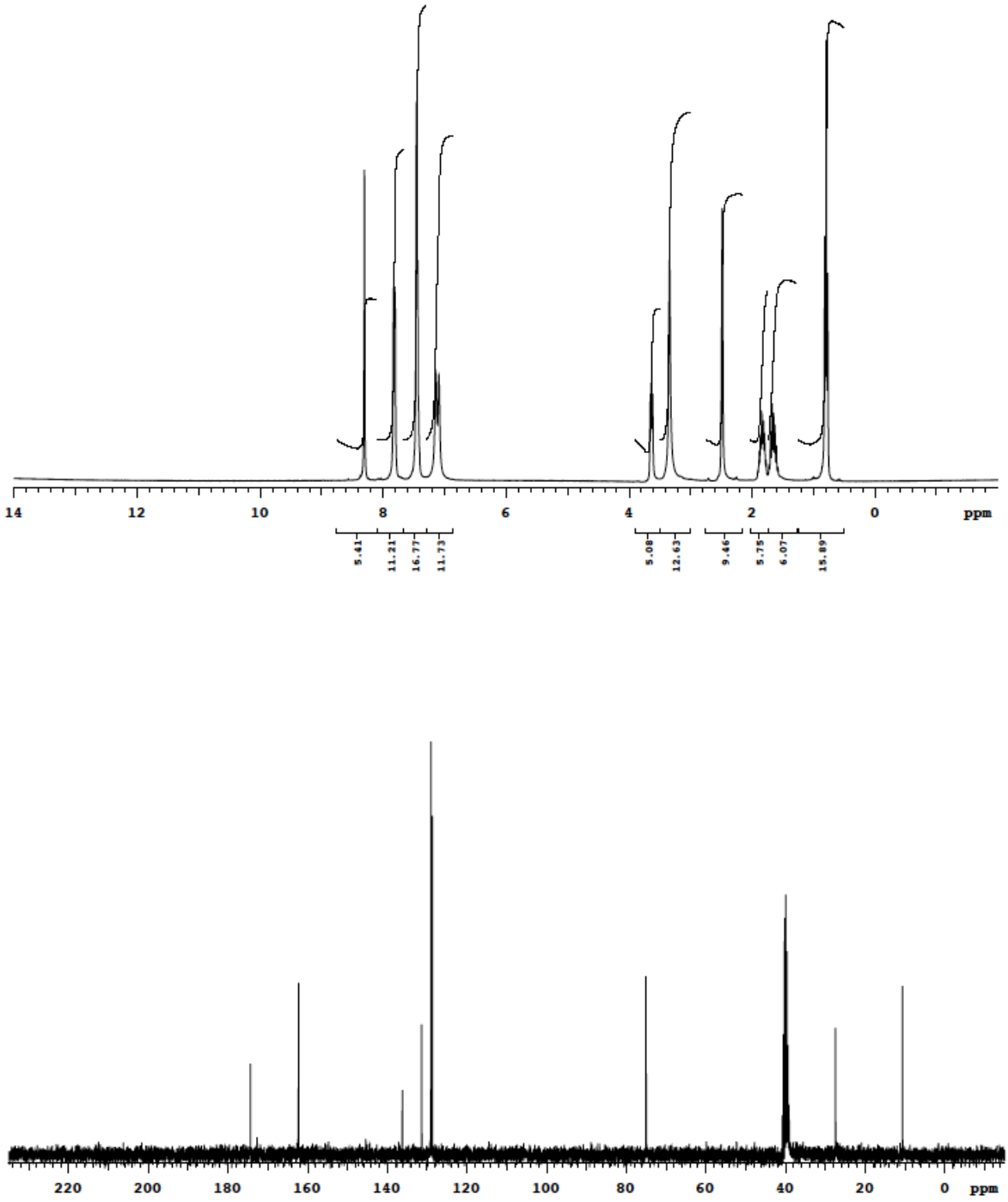


Figure S10. ^{1}H (*top*) and ^{13}C (*bottom*) NMR spectra of deracemized on a demo (15 g) scale (S)-**3a**.