

Supporting Information

Enantioselective Synthesis of Levomilnacipran

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General

Unless otherwise specified, chemicals were purchased from Aldrich and used without further purification. Reactions were carried out under nitrogen using dry solvents, unless otherwise stated. THF was distilled from sodium/benzophenone before use. 1,4-Dioxane and toluene were distilled from sodium and stored under argon over 4Å molecular sieve. Flash chromatography was carried out on Kieselgel 60 (230–240 mesh, Merck) and analytical TLC was performed on Merck precoated silica gel plates (60 F₂₅₄); visualization was carried out with UV and/or heating with a solution of KMnO₄ in water. HRMS were recorded at the “Service de Spectrométrie de Masse de l’Institut de Chimie des Substances Naturelles” in Gif-sur-Yvette (France). ¹H and ¹³C NMR spectra were recorded on a Bruker Avance DPX 400 spectrometer at 400 and 100 MHz respectively. Chemical shifts (δ) are given in ppm and coupling constants (J) in hertz. IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR. Optical rotations were determined using the sodium D line (589 nm) on a Perkin Elmer 341 polarimeter.

***N*¹-*N*²-bis((*R*)-1-phenyl-2-(piperidin-1-yl)ethyl)propane-1,3-diamine (Koga's amine)¹**

Under N₂, (*R*)-styrene oxide (2 g, 16.6 mmol, 1 equiv) was diluted in EtOH (10 mL) before piperidine (2 mL, 1.2 equiv) was added. The solution was heated to reflux for 5 h. Volatiles were removed under vacuum by azeotropic distillation with toluene (2 × 6 mL). The mixture was then diluted in MTBE (18 mL) before NEt₃ (8.7 mL, 3.8 equiv) was added. After 10 min at rt, the reaction mixture was cooled down to -15 °C and stirred for additional 10 min. Methane sulfonyl chloride (1.54 mL, 1.2 equiv) was then added dropwise over 25 min and under vigorous stirring. After 40 min at -15 °C, 1,3-diaminopropane (0.7 mL, 0.5 equiv) was added, followed by H₂O (8.2 mL). The reaction mixture was warmed to rt over 1 h during which time the precipitate dissolved. The organic phase was collected and the aqueous layer was extracted with MTBE (2 × 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue (3.1 g) was first purified by flash chromatography (CH₂Cl₂/MeOH/NH₄OH 99:0.5:0.5 → 85:14.5:0.5). The product was then recrystallized from *i*-PrOH/H₂O at 0 °C, collected and dried under vacuum for 72 h. The title compound was recovered as a white solid (2.3 g, 62%).

¹H NMR (CDCl₃): δ 1.33–1.68 (14H, m), 2.21–2.53 (18H, m), 3.71 (2H, dd, *J* = 10.8 Hz, *J* = 3.5 Hz), 7.21–7.36 (10H, m).

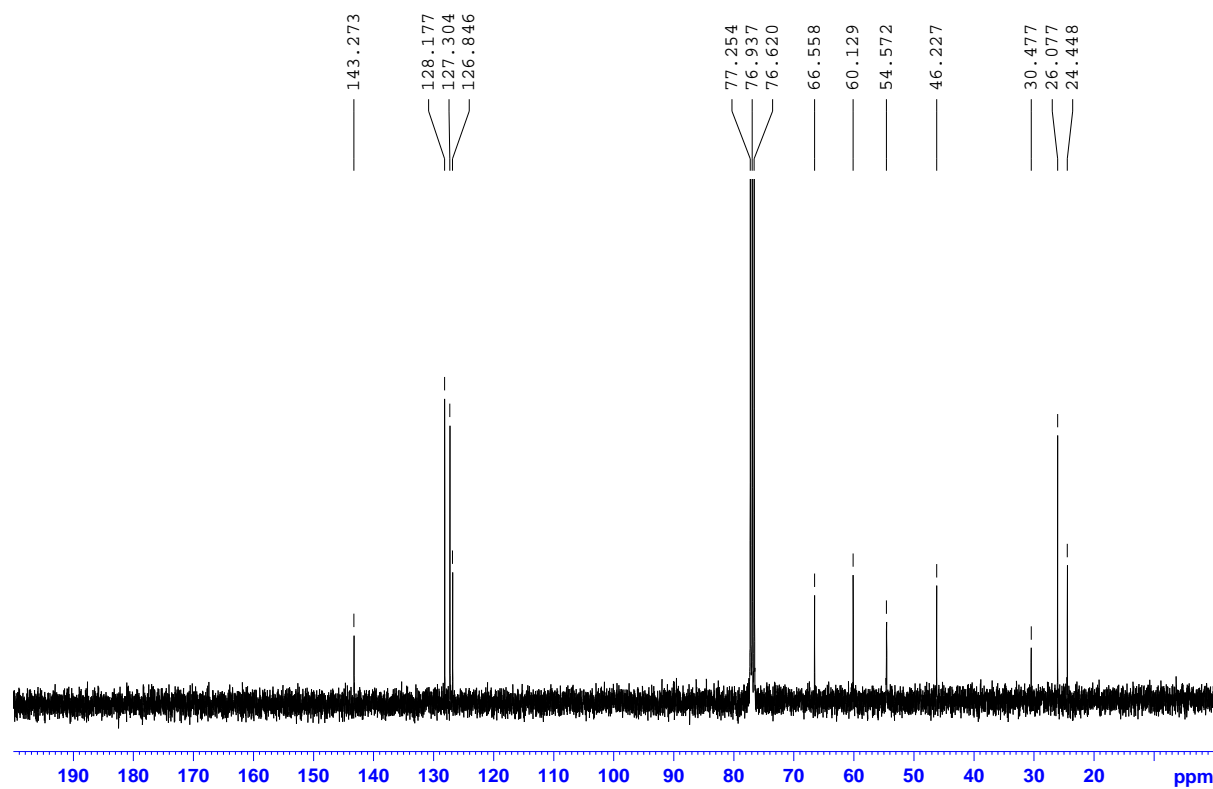
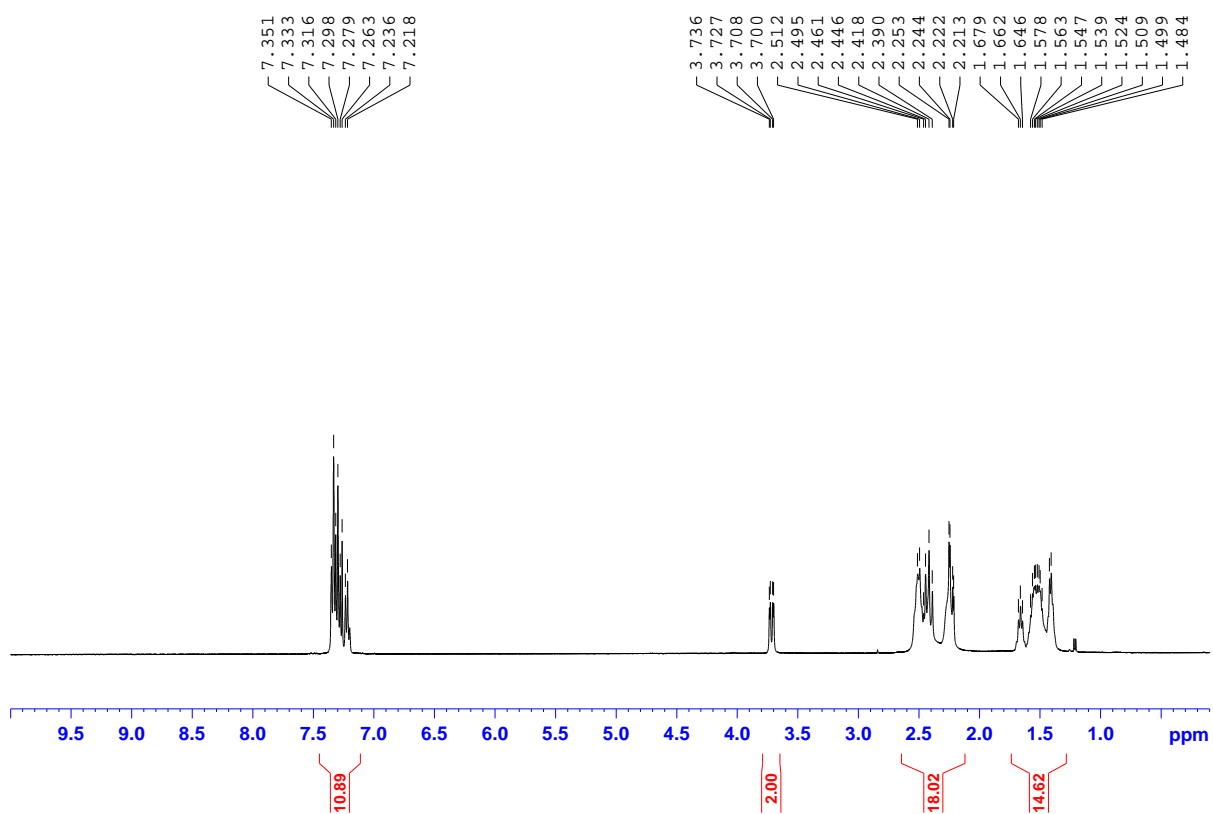
¹³C NMR (CDCl₃): δ 24.5, 26.1, 31.5, 46.2, 54.6, 60.1, 66.6, 126.8, 127.3, 128.2, 143.3.

IR (neat): 3301, 2934, 2801, 1452 cm⁻¹.

[α]_D²⁰ -111.6 (*c* 0.56, CHCl₃); (lit.,¹ [α]_D²⁰ -112 (*c* 5.45, CHCl₃), 99.9% ee).

MS (ES⁺): 449 [M+H]⁺.

¹ *Org. Process Res. Dev.* **2007**, *11*, 215.



(2*S*)-phenylpent-4-enoic acid (**3**)²

Under N₂ and at 0 °C, to a solution of phenylacetic acid (200 mg, 1.47 mmol, 1 equiv) and (*R*)-Koga's amine (686 mg, 1.04 equiv) in dry THF (10 mL), *n*-BuLi (2.35 mL of a 2.5 M soln in hexane, 4 equiv) was added over 5 min. The reaction mixture was stirred at 0 °C for 15 min, cooled down to -78 °C, and allyl bromide (509 μL, 4 equiv) was added over 10 min. After the addition, the reaction was immediately quenched with MeOH/THF 1:3 (1.9 mL) and stirred for 5 min. 1 M HCl (10 mL) and EtOAc (10 mL) were added. The organic phase was collected and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with 1 M HCl (5 mL), brine (5 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give compound **3** (214 mg, 83%) as a yellowish oil. No further purification was needed for this product.

R_f 0.40 (MeOH/CH₂Cl₂ 4:96).

¹H NMR (CDCl₃): δ 2.49–2.57 (1H, m), 2.79–2.87 (1H, m), 3.65 (1H, dd, *J* = 8.0 Hz, *J* = 7.6 Hz), 5.02 (1H, dd, *J* = 10.0 Hz, *J* = 1.6 Hz), 5.09 (1H, dd, *J* = 17.2 Hz, *J* = 1.6 Hz), 5.67–5.78 (1H, m), 7.25–7.37 (5H, m).

¹³C NMR (CDCl₃): δ 36.9, 51.2, 117.1, 127.5, 127.9 (2C), 128.6, (2C), 134.8, 137.7, 179.0.

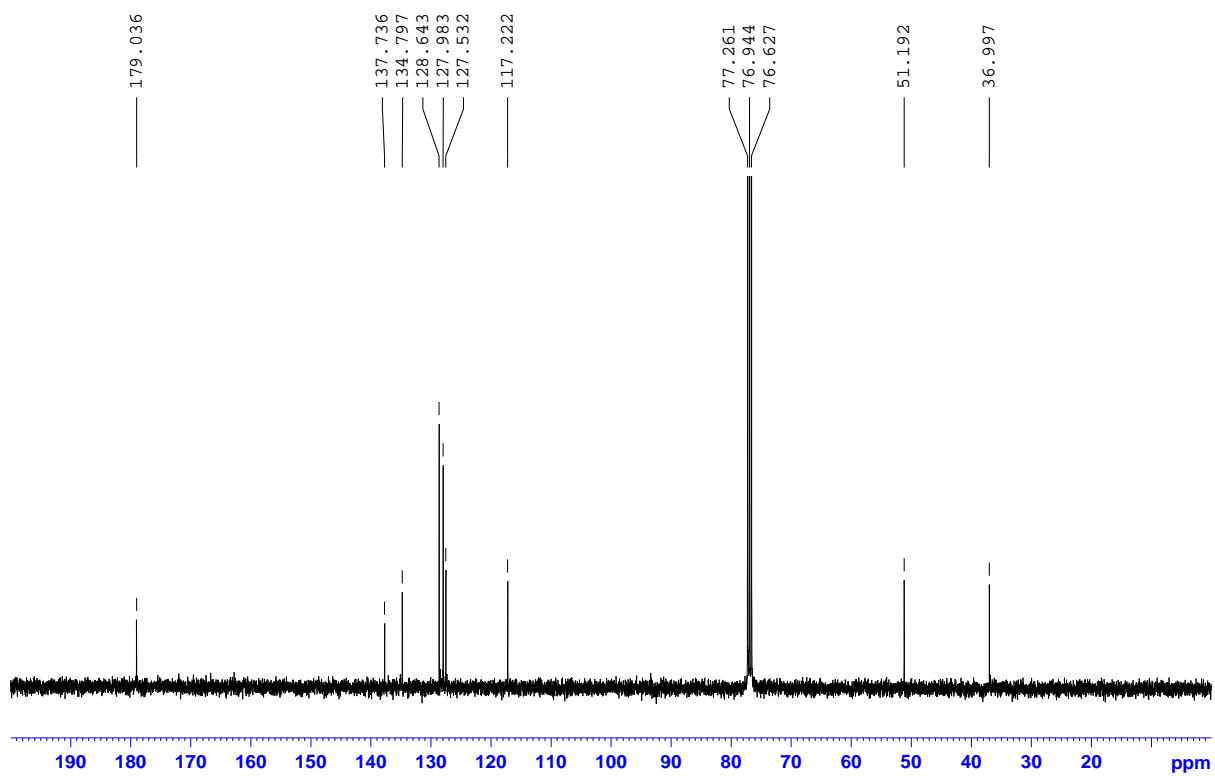
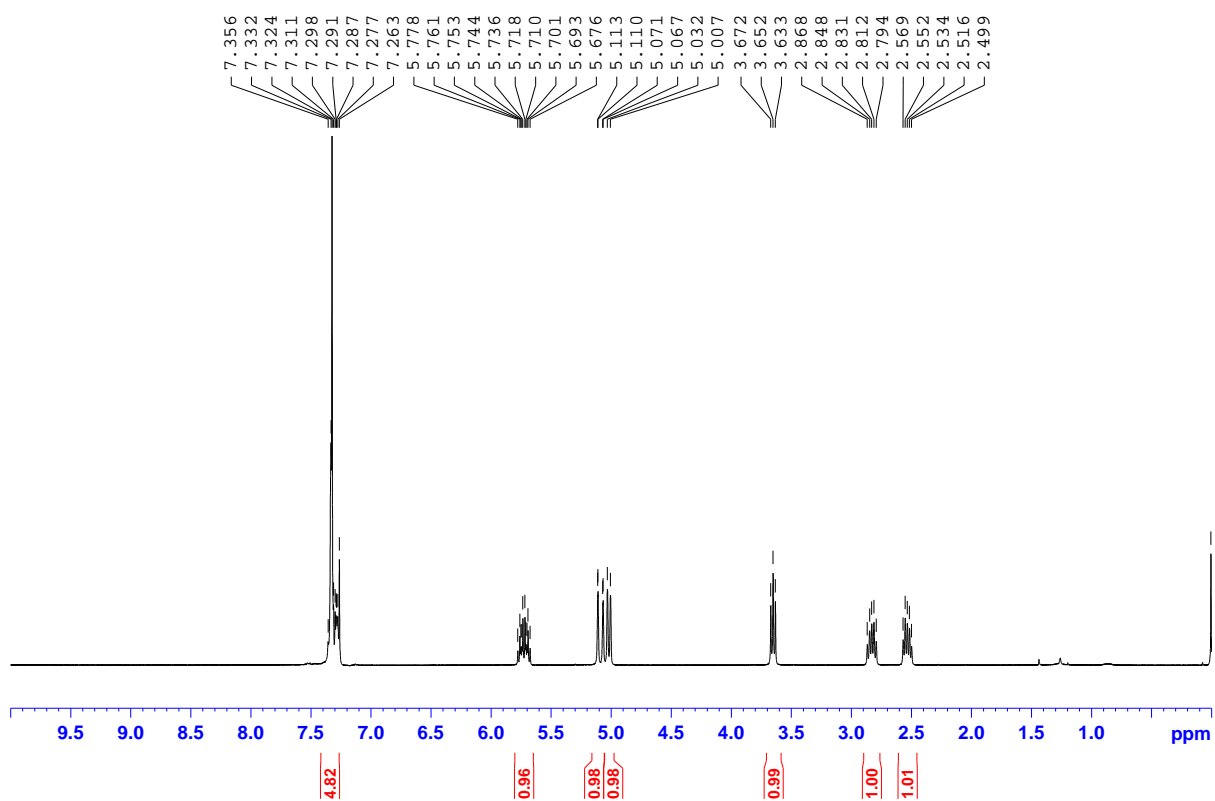
IR (neat): 3067, 1706, 1415, 918, 697 cm⁻¹.

Chiral HPLC: Chiralcel OJ 250 × 4.6 mm, *n*-hexane/*i*-PrOH 9:1, flow rate: 1 mL min⁻¹, detection at 220 nm, *t*_{major} = 9.6 min, *t*_{minor} = 11.5 min, 88% ee.

[α]_D²⁰ +77.6 (*c* 0.85, CHCl₃); (lit.,² [α]_D²⁰ +77.2 (*c* 1.00, CHCl₃), 93% ee).

MS (ES⁺): 177 [M+H]⁺.

² *J. Am. Chem. Soc.* **2011**, *133*, 11936.



(3*S*,5*R*)-5-(iodomethyl)-3-phenyldihydrofuran-2(3*H*)-one (4)

Under N₂ and at 0 °C, to a solution of acid **3** (330 mg, 1.87 mmol, 1 equiv) in Et₂O (12 mL), K₂CO₃ (310 mg, 1.2 equiv) was added, followed by I₂ (522 mg, 1.1 equiv) portionwise over 20 min. The dark mixture was stirred at 0 °C for 1 h and 5 h at rt. Iodide in excess was neutralized with sat Na₂S₂O₃ (5 mL). The organic phase was collected and the aqueous layer was extracted with Et₂O (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (EtOAc/*n*-hexane 2:8) to give *cis*-isomer **4** as a white solid (365 mg, 65%).

Spectral data obtained for **4** are in agreement with those previously reported in the literature for the racemic iodolactone.³

R_f 0.40 (EtOAc/*c*-hexane 3:7).

¹H NMR (CDCl₃): δ 2.10–2.19 (1H, m), 2.92–2.99 (1H, m), 3.37 (1H, dd, *J* = 10.6 Hz, *J* = 7.2 Hz), 3.53 (1H, dd, *J* = 10.6 Hz, *J* = 4.4 Hz), 3.95 (1H, dd, *J* = 12.4 Hz, *J* = 8.8 Hz), 4.48–4.55 (1H, m), 7.25–7.40 (5H, m).

¹³C NMR (CDCl₃): δ 6.4, 38.3, 47.3, 76.1, 127.8, 128.0 (2C), 128.8 (2C), 135.9, 175.7.

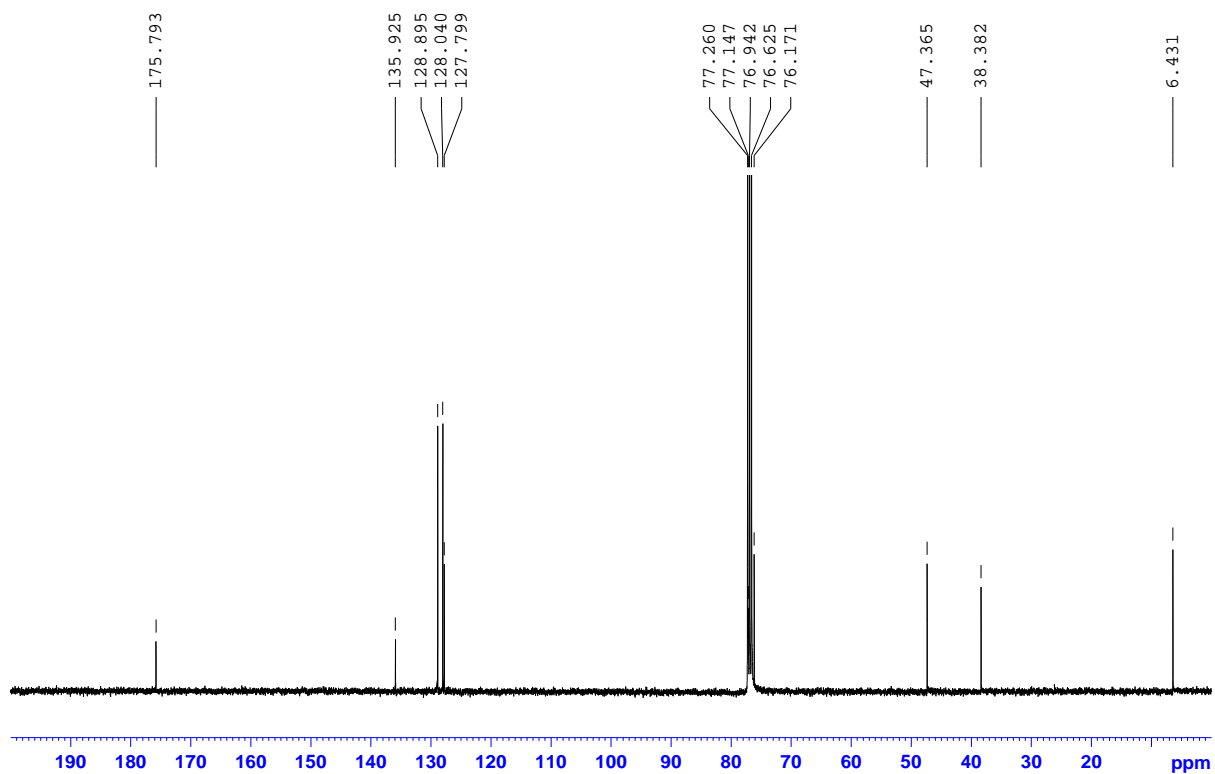
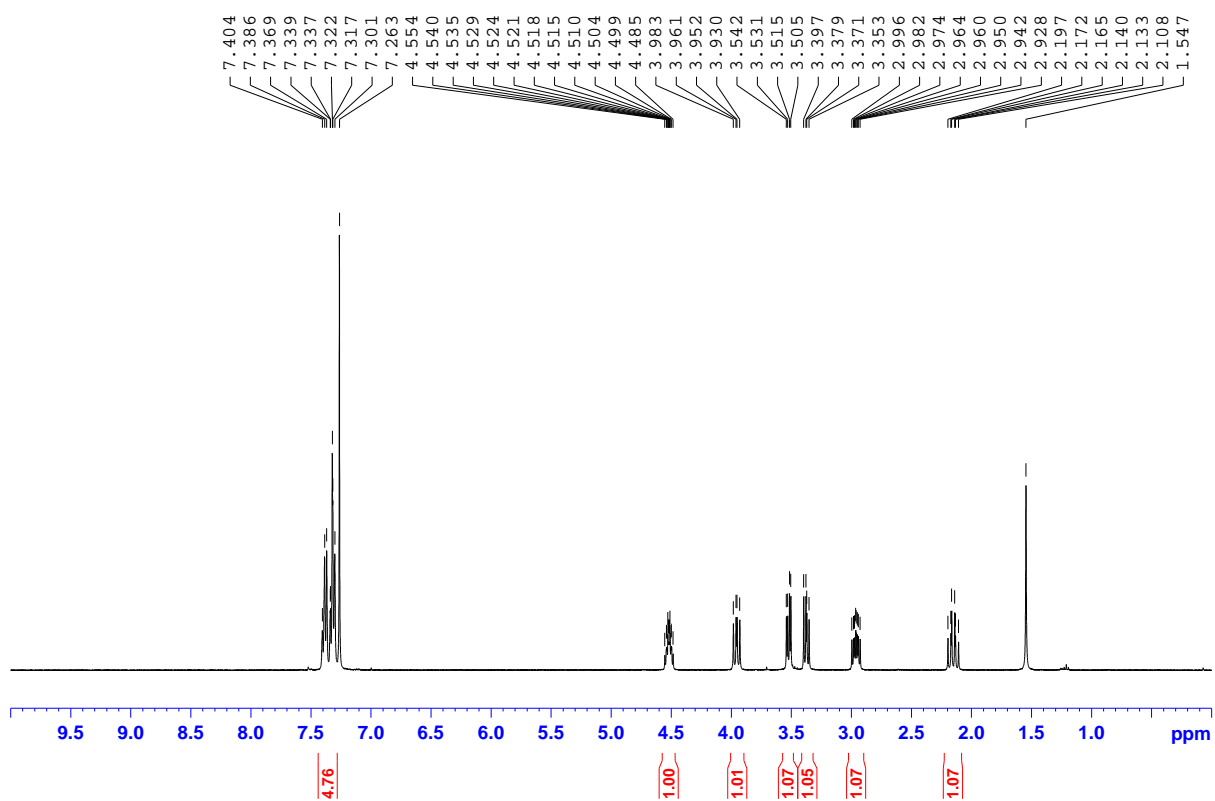
IR (KBr): 1771, 1154, 1005, 698 cm⁻¹.

Chiral HPLC: Daicel OJ-R 150 × 4.6 mm, H₂O/MeOH 1:9, flow rate: 1 mL min⁻¹, detection at 254 nm, *t*_{minor} = 4.1 min, *t*_{major} = 5.0 min, 88% ee.

[α]_D²⁰ +30.9 (*c* 0.50, CHCl₃).

MS (ES⁺): 303 [M+H]⁺.

³ *J. Med. Chem.* **1992**, *35*, 885.



Methyl 3-((*S*)-oxiran-2-yl)-2-phenylpropanoate (**5**)

To a solution of lactone **4** (264 mg, 0.87 mmol, 1 equiv) in MeOH (8.7 mL) K_2CO_3 (241 mg, 2 equiv) was added. The mixture was stirred for 2 h at rt, and the solvent was removed in vacuo. The solid was suspended in Et_2O , filtered, and washed twice with Et_2O (2×4 mL). Volatiles were evaporated under vacuum to give compound **5** as a colorless oil (175 mg, 98%).

R_f 0.35 ($EtOAc/c$ -hexane 3:7).

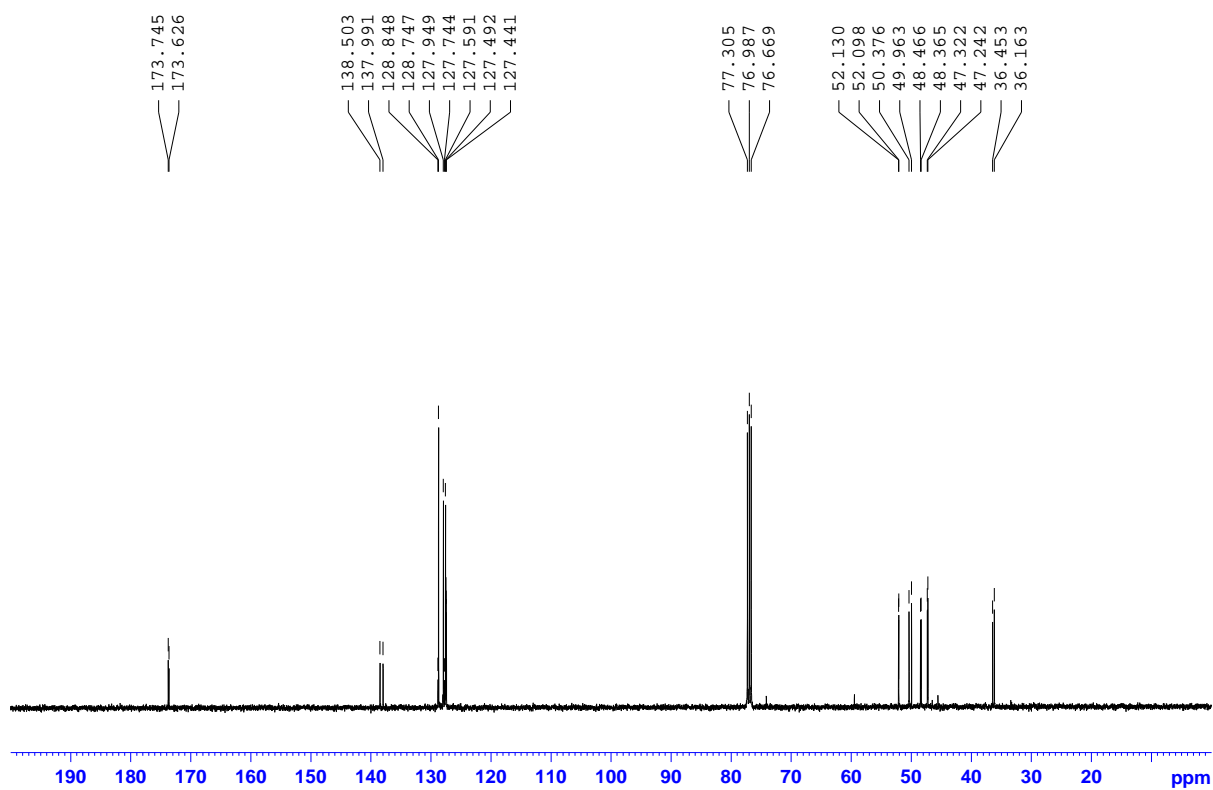
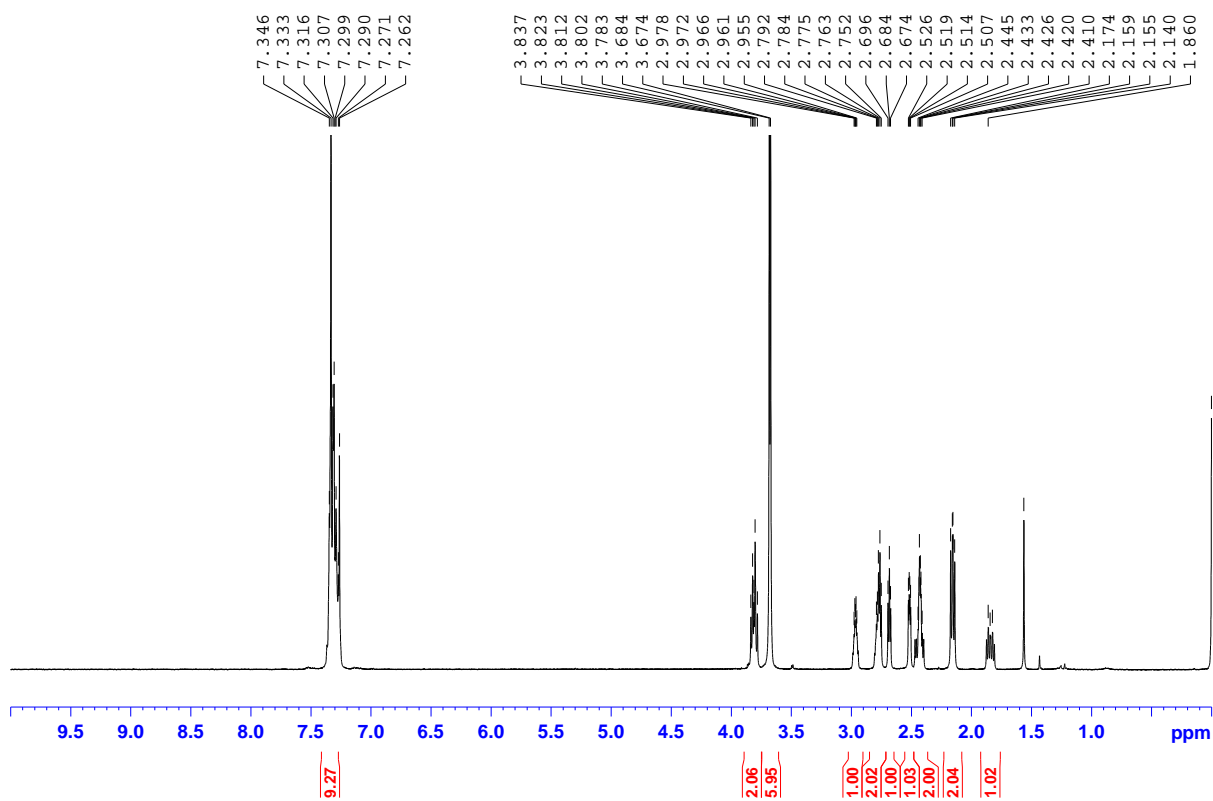
1H NMR ($CDCl_3$): δ 1.80–1.87 (1H, m), 2.11–2.17 (2H, m), 2.40–2.47 (2H, m), 2.51–2.53 (1H, m), 2.67–2.70 (1H, m), 2.75–2.80 (2H, m), 2.95–2.98 (1H, m), 3.67 (3H, s), 3.68 (3H, s), 3.78–3.84 (2H, m), 7.27–7.37 (10H, m).

^{13}C NMR ($CDCl_3$): δ 36.1, 36.4, 47.2, 47.3, 48.3, 48.4, 49.9, 50.3, 52.0, 52.1, 127.4, 127.5 (2C), 127.6, 127.7 (2C), 127.9 (2C), 128.7 (2C), 137.9, 138.5, 173.6, 173.7.

IR (neat): 1734, 1260, 1167 cm^{-1} .

MS (ES^+): 207 $[M+H]^+$.

HRMS: calcd for $C_{12}H_{15}O_3$ $[M+H]^+$ 207.1017, found 207.1023.



(1*S*,5*R*)-1-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (2)

LDA (2 mL of a 0.6 M soln in THF, 1.2 equiv) was added to a refluxing solution of epoxy ester **5** (202 mg, 0.98 mmol, 1 equiv) in anhydrous 1,4-dioxane (9 mL) and HMPA (1.2 mL). After 2 min, the reaction was cooled down to rt and HCl was bubbled until pH < 1. Et₂O (10 mL) and H₂O (10 mL) were added. The organic phase was collected and the aqueous layer was extracted with Et₂O (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The cyclopropyl lactone was separated from the *trans*-cyclopropane by column chromatography (EtOAc/*c*-hexane 2:8) to afford compound **2** as a colorless liquid (94 mg, 55%).

Spectral data obtained for **2** are in agreement with those previously reported in the literature.⁴

R_f 0.40 (EtOAc/*c*-hexane 3:7).

¹H NMR (CDCl₃): δ 1.37 (1H, t, *J* = 4.8 Hz), 1.65 (1H, dd, *J* = 7.6 Hz, *J* = 4.8 Hz), 2.54–2.58 (1H, m), 4.29 (1H, d, *J* = 9.4 Hz), 4.47 (1H, dd, *J* = 9.4 Hz, *J* = 4.8 Hz), 7.28–7.45 ppm (5H, m).

¹³C NMR (CDCl₃): δ 20.0, 25.0, 31.6, 67.9, 127.6, 128.2 (2C), 128.5 (2C), 134.0, 175.9 ppm.

IR (neat): 1760, 1249 cm⁻¹.

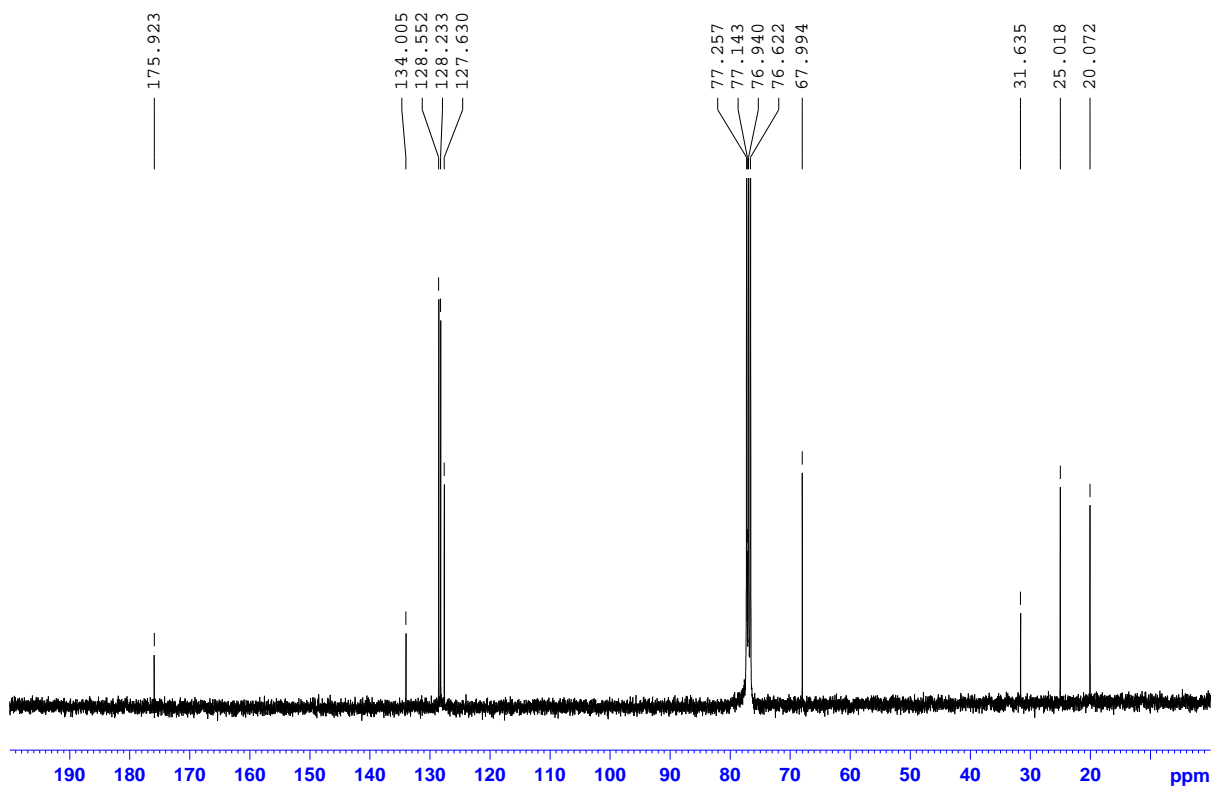
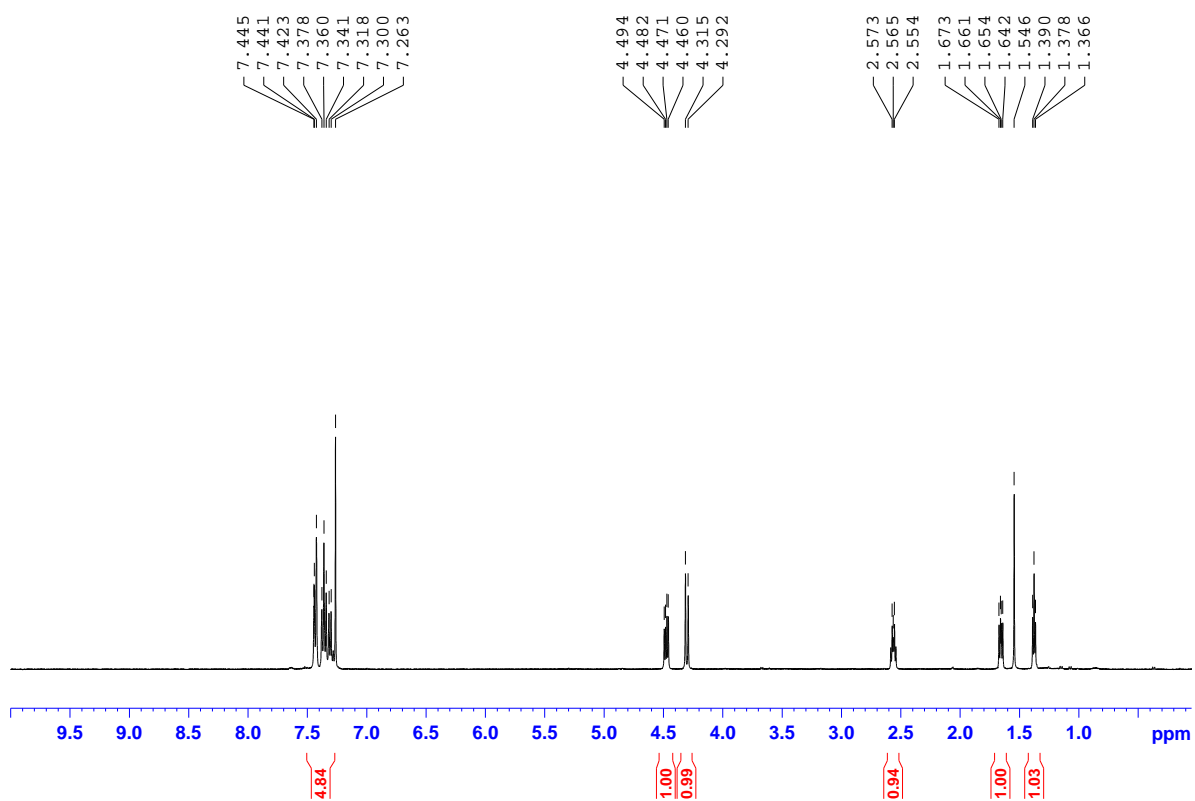
Chiral HPLC: Daicel OJ-R 150 × 4.6 mm, H₂O/MeOH 4:6, flow rate: 1 mL min⁻¹, detection at 254 nm, *t*_{major} = 15.4 min, *t*_{minor} = 17.7 min, 88% ee.

[α]_D²⁰ -62.4 (*c* 0.48, MeOH); (lit.,⁵ [α]_D²⁰ -78.5 (*c* 1.42, MeOH), 96% ee).

MS (ES⁺): 175 [M+H]⁺.

⁴ *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2834.

⁵ *J. Org. Chem.* **1996**, *61*, 915.



(1*S*,2*R*)-*N,N*-diethyl-2-(hydroxymethyl)-1-phenylcyclopropanecarboxamide (7)

Under N₂, diethylamine (210 μL, 2.6 equiv) was added to a suspension of AlCl₃ (137 mg, 1.3 equiv) in anhydrous toluene (1.5 mL). After 10 min, lactone **2** (138 mg, 0.79 mmol, 1 equiv) diluted in toluene (2 mL) was added dropwise. The suspension was stirred for 2 h and quenched with 0.1 N HCl (3 mL). The organic phase was collected and the aqueous layer extracted with toluene (2 × 3 mL). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by filtration over silica (CH₂Cl₂/EtOAc 99:1 → 80:20) to give compound **7** as a colorless oil (176 mg, 90%).

Spectral data obtained for **7** are in agreement with those previously reported in the literature.⁶

R_f 0.10 (EtOAc/*c*-hexane 3:7).

¹H NMR (CDCl₃): δ 0.91 (3H, t, *J* = 7.0 Hz), 1.09 (1H, t, *J* = 5.6 Hz), 1.13 (3H, t, *J* = 8.4 Hz), 1.54–1.60 (1H, m), 1.66 (1H, dd, *J* = 8.4 Hz, *J* = 5.6 Hz), 2.35 (1H, brs), 3.18 (1H, dd, *J* = 12.0 Hz, *J* = 10.4 Hz), 3.35–3.43 (3H, m), 3.47–3.55 (1H, m), 4.05 (1H, dd, *J* = 12.4 Hz, *J* = 4.8 Hz), 7.19–7.32 (5H, m).

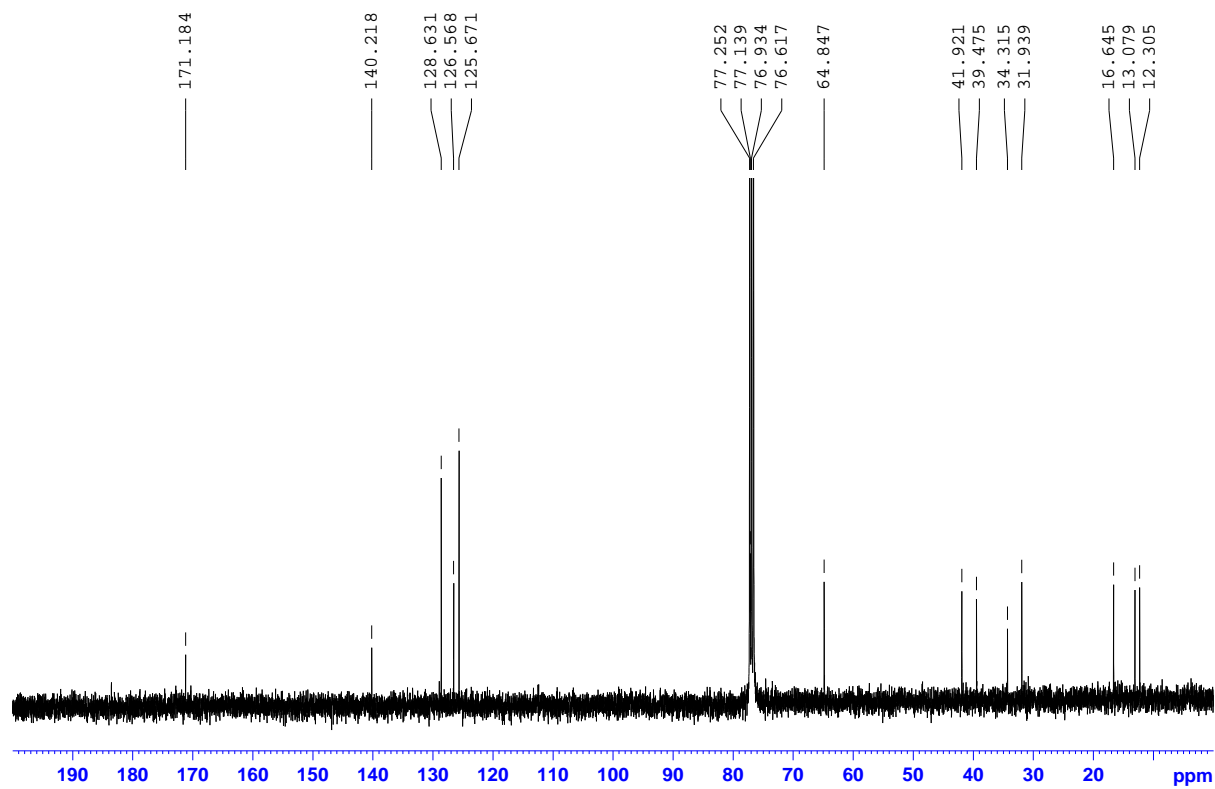
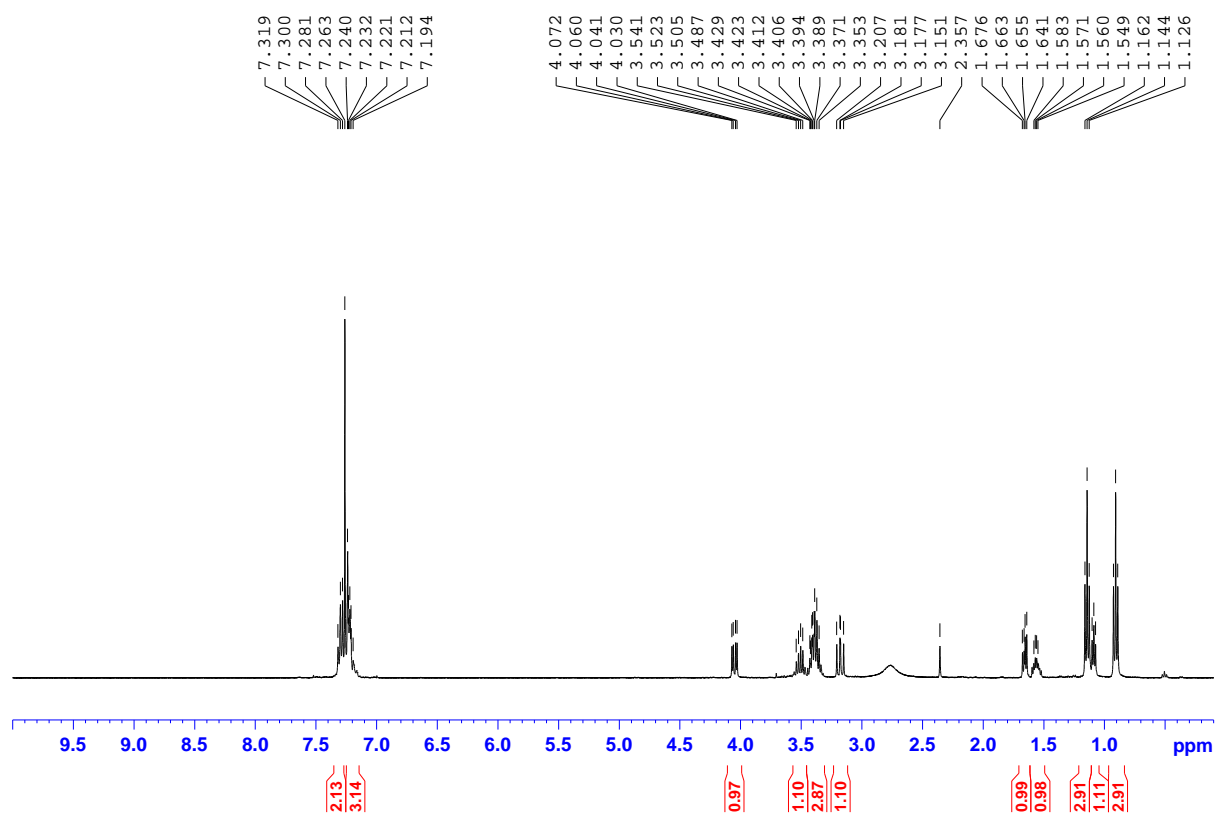
¹³C NMR (CDCl₃): δ 12.3, 13.0, 16.6, 31.9, 34.3, 39.4, 41.9, 64.8, 125.6, 126.5, 128.6, 140.2, 171.1.

IR (neat): 3418, 1616, 1431, 699 cm⁻¹.

[α]_D²⁰ +50.8 (*c* 0.51, CHCl₃).

MS (ES⁺): 248 [M+H]⁺.

⁶ *Adv. Synth. Catal.* **2001**, 343, 299.



(1*S*,2*R*)-2-(chloromethyl)-*N,N*-diethyl-1-phenylcyclopropanecarboxamide (8)

Under N₂, SOCl₂ (77 μL, 1.6 equiv) was added dropwise to a solution of alcohol **7** (164 mg, 0.66 mmol, 1 equiv) in anhydrous toluene (4 mL).

After 2 h, volatiles were removed in vacuo. The crude residue was purified by filtration over silica gel (CH₂Cl₂/EtOAc 99:1 → 80:20) to give compound **8** as a white solid (168 mg, 96%).

R_f 0.60 (EtOAc/*c*-hexane 3:7).

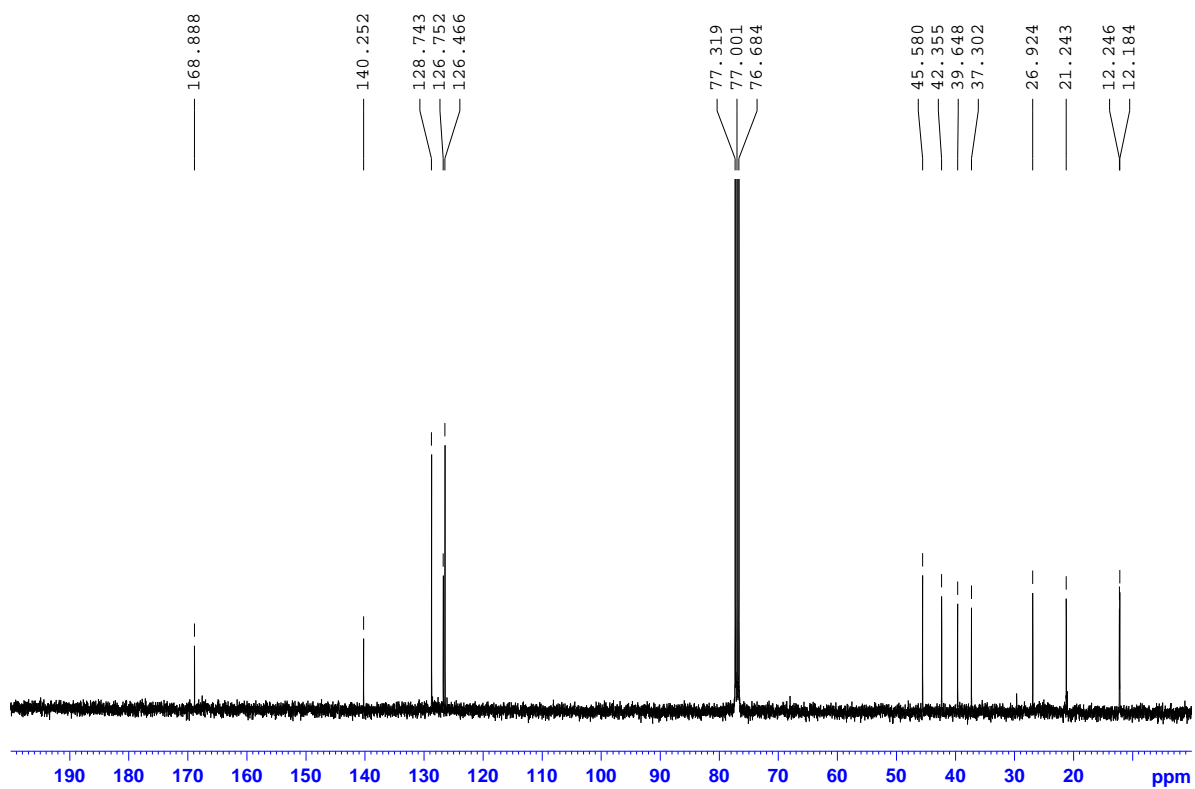
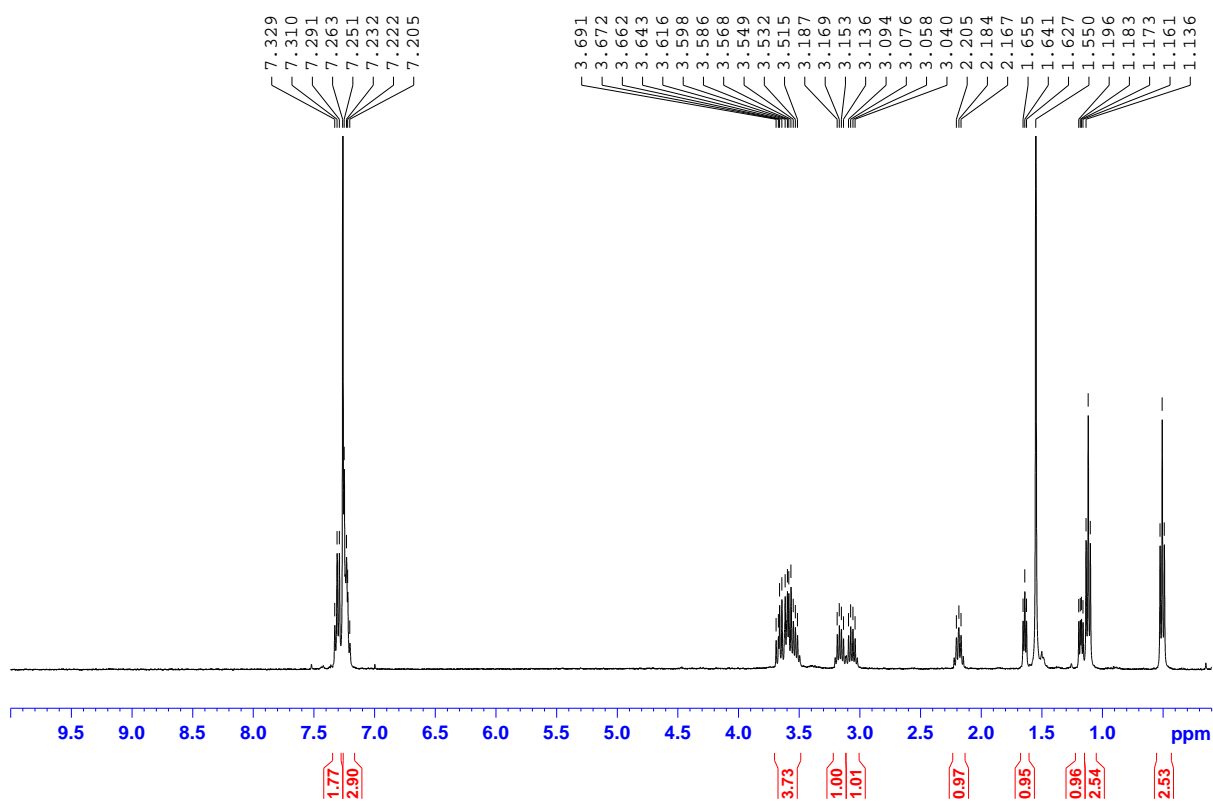
¹H NMR (CDCl₃): δ 0.55 (3H, t, *J* = 7.1 Hz), 1.12 (3H, t, *J* = 7.4 Hz), 1.18 (1H, dd, *J* = 9.2 Hz, *J* = 5.2 Hz), 1.61–1.66 (1H, m), 2.16–2.21 (1H, m), 3.04–3.10 (1H, m), 3.12–3.19 (1H, m), 3.50–3.70 (4H, m), 7.20–7.33 (5H, m).

¹³C NMR (CDCl₃): δ 12.2, 12.3, 21.2, 26.9, 37.3, 39.6, 42.3, 45.6, 126.5 (2C), 126.8, 128.7 (2C), 140.2, 168.9.

IR (KBr): 1630, 1427, 1141, 699 cm⁻¹.

[α]_D²⁰ +146 (*c* 0.62, CHCl₃).

MS (ES⁺): 266 [M+H]⁺.



(1*S*,2*R*)-2-((1,3-dioxisoindolin-2-yl)methyl)-*N,N*-diethyl-1-phenylcyclopropanecarboxamide (9)

Under N₂, cyclopropane **8** (120 mg, 0.45 mmol, 1 equiv) was diluted in anhydrous toluene (2 mL) and potassium phthalimide (167 mg, 2 equiv) was added. The reaction mixture was heated to reflux for 3 h, cooled down to rt, and quenched with H₂O (3 mL). The organic phase was collected and the aqueous layer was extracted with toluene (2 × 3 mL). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give **9** as a white solid (148 mg, 88%).

Spectral data obtained for **9** are in agreement with those previously reported in the literature.⁷

R_f 0.30 (EtOAc/cyclohexane 3:7).

¹H NMR (CDCl₃): δ 0.65 (3H, t, *J* = 7.0 Hz), 1.08–2.19 (4H, m), 1.65 (1H, t, *J* = 5.8 Hz), 1.99–2.05 (1H, m), 3.10–3.17 (1H, m), 3.29–3.35 (1H, m), 3.41–3.49 (2H, m), 3.53–3.59 (1H, m), 4.16 (1H, dd, *J* = 14.0 Hz, *J* = 4.0 Hz), 7.10–7.35 (5H, m), 7.68–7.73 (2H, m), 7.81–7.85 (2H, m).

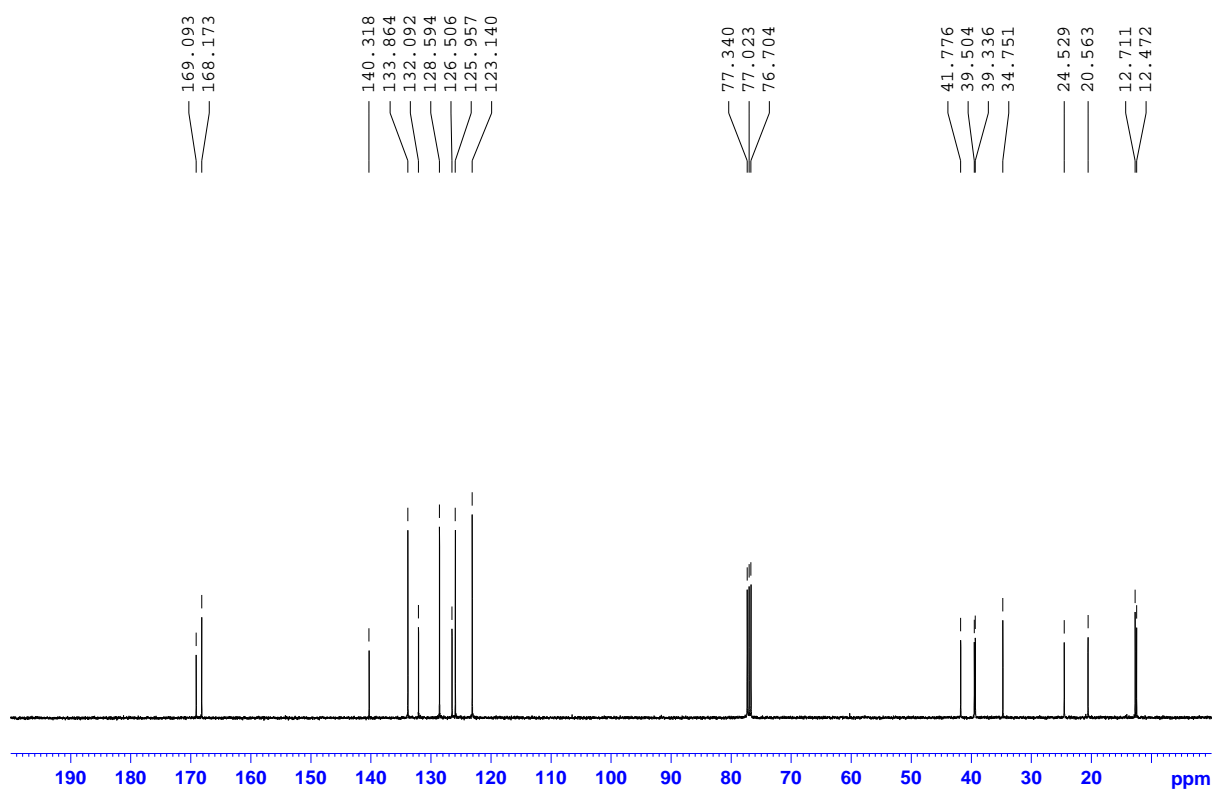
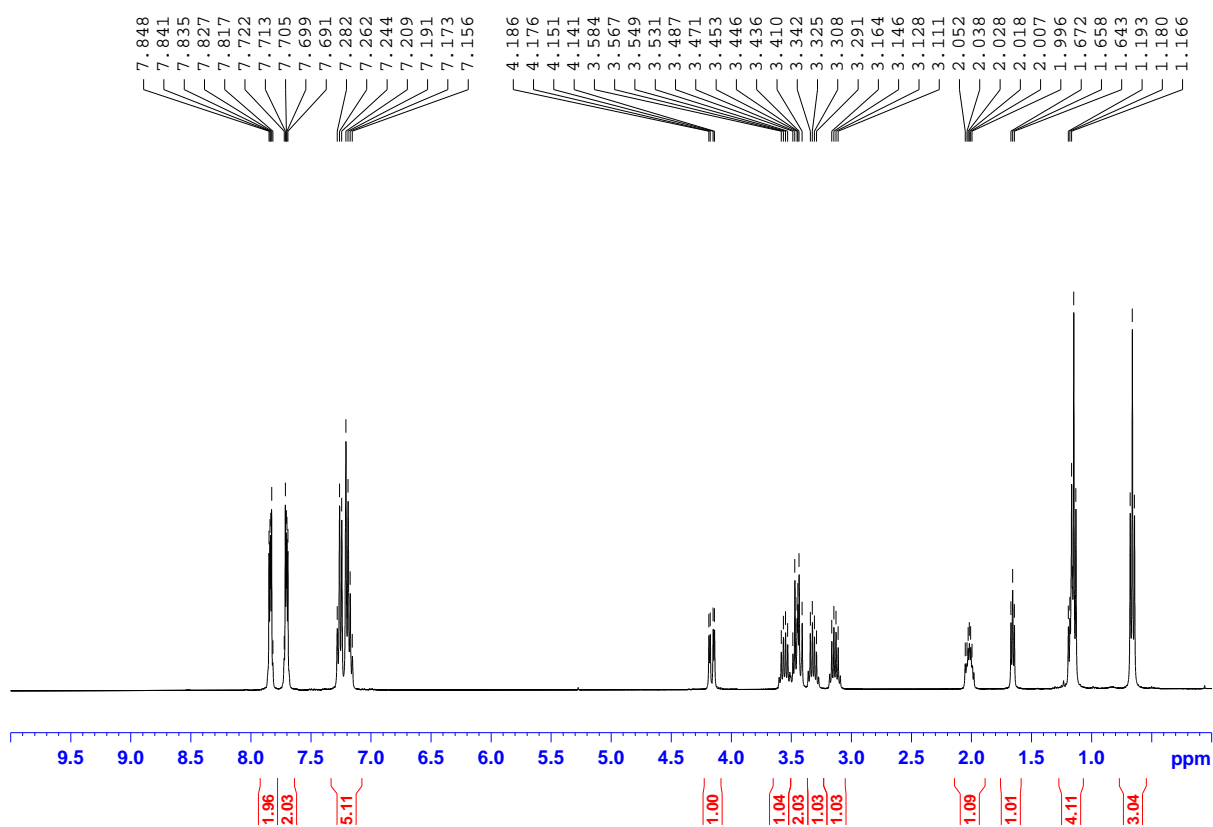
¹³C NMR (CDCl₃): δ 12.5, 12.7, 20.6, 24.5, 34.8, 39.3, 39.5, 41.8, 128.1 (2C), 126.0 (2C), 126.5, 128.6 (2C), 132.1 (2C), 133.9 (2C), 140.3, 168.2 (2C), 169.1.

IR (KBr): 1771, 1714, 1632, 1426, 1386, 722 cm⁻¹.

[α]_D²⁰ -64.6 (*c* 0.46, CHCl₃).

MS (ES⁺): 377 [M+H]⁺.

⁷ *J. Med. Chem.* **1987**, *30*, 318.



(1*S*,2*R*)-2-(aminomethyl)-*N,N*-diethyl-1-phenylcyclopropanecarboxamide (1)

Under N₂, phthalimide **9** (61 mg, 0.16 mmol, 1 equiv) was diluted in anhydrous toluene (2 mL) and ethanolamine (98 μL, 10 equiv) was added. The reaction mixture was heated to 100 °C for 3 h, cooled down to rt, and quenched with 20% NaCl (3 mL). The aqueous layer was extracted with toluene (2 × 3 mL). The combined organic layers were washed with 20% NaCl (2 × 3 mL) and extracted with 1 M HCl (2 × 3 mL). The organic phase was discarded. The combined aqueous layers were basified with 20% NaOH and extracted with toluene (3 × 3 mL). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give compound **1** as an oil (36 mg, 89%).

Spectral data obtained for **1** are in agreement with those previously reported in the literature.⁸

R_f 0.10 (CH₂Cl₂/MeOH 9:1).

¹H NMR (CDCl₃): δ 0.66 (3H, t, *J* = 7.3 Hz), 1.09 (3H, t, *J* = 7.6 Hz), 1.15 (1H, dd, *J* = 8.3 Hz, *J* = 5.2 Hz), 1.30–1.34 (1H, m), 1.56 (2H, brs), 1.72–1.77 (1H, m), 2.65 (1H, dd, *J* = 13.0 Hz, *J* = 7.2 Hz), 2.78 (1H, dd, *J* = 13.0 Hz, *J* = 7.2 Hz), 3.11–3.25 (2H, m), 3.44–3.55 (2H, m), 7.10–7.30 (5H, m).

¹³C NMR (CDCl₃): δ 12.3, 12.7, 19.4, 29.5, 34.7, 39.2, 41.6, 43.6, 125.9 (2C), 126.3, 128.6 (2C), 141.1, 170.1.

IR (neat): 3421, 3364, 1626, 1429 cm⁻¹.

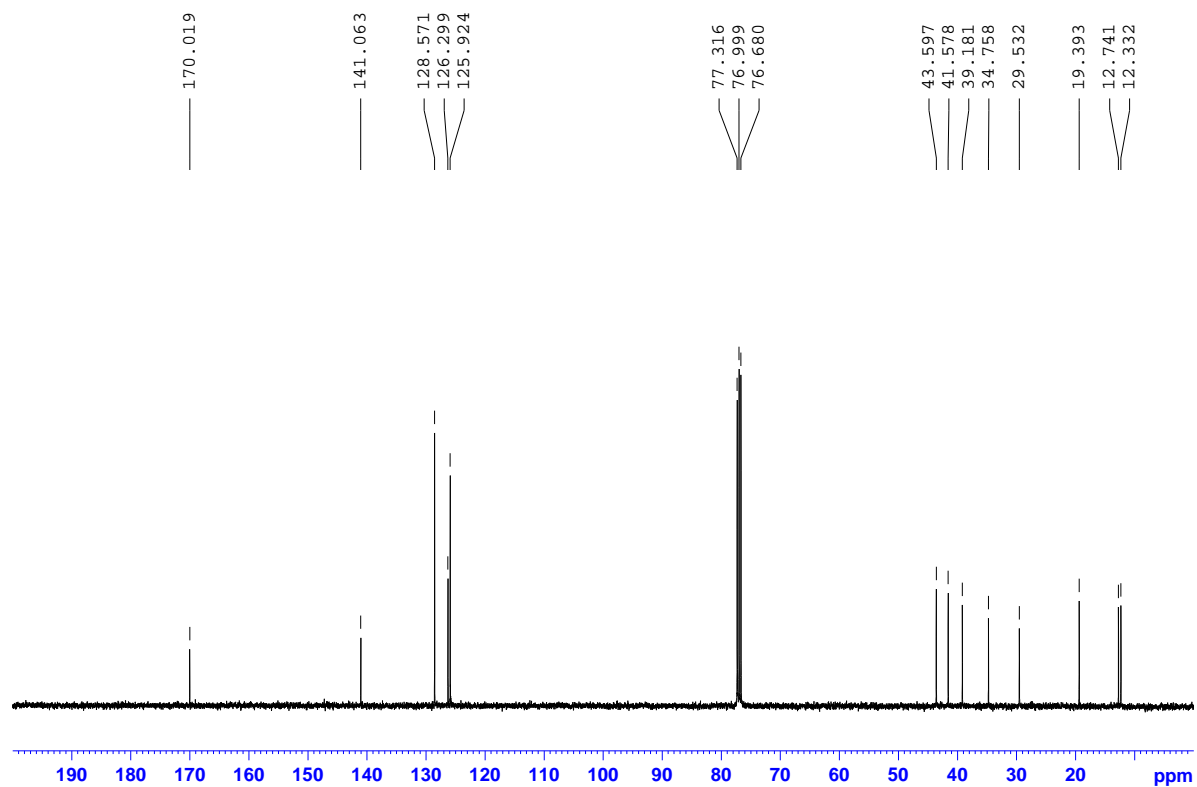
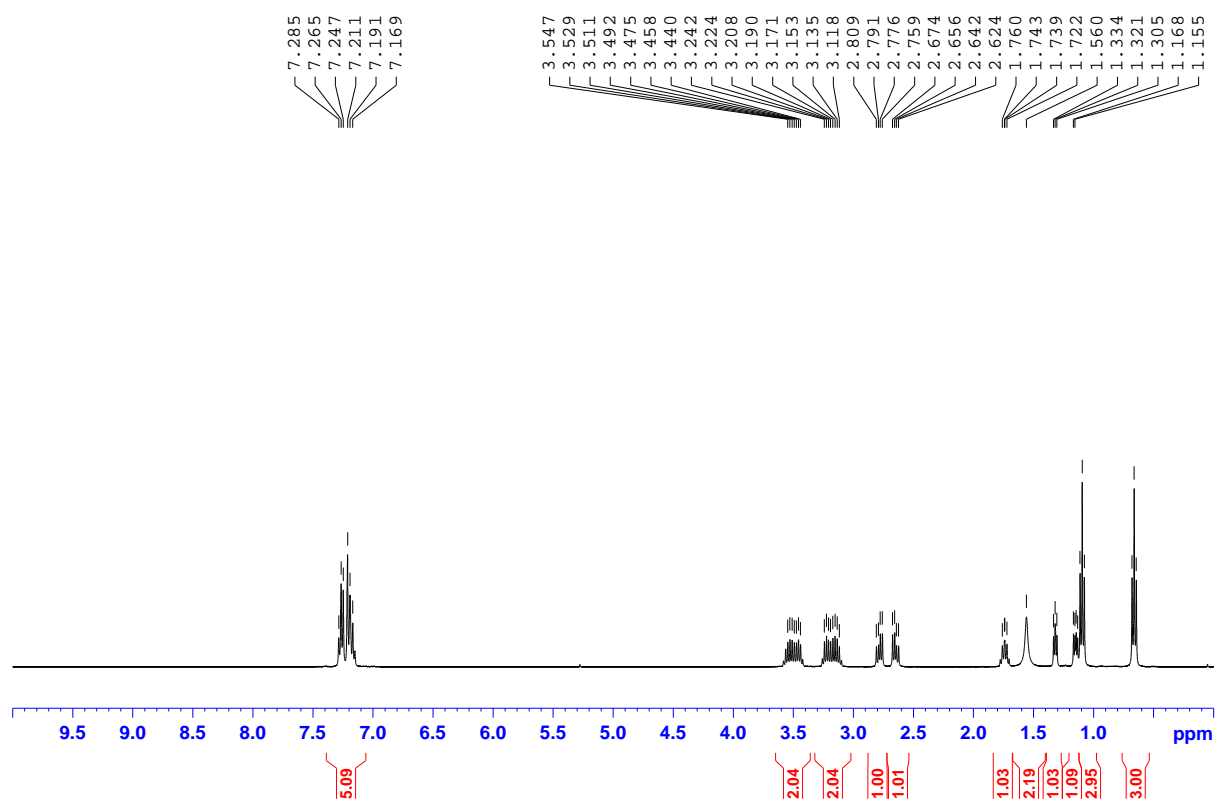
Chiral HPLC:

Enantiomeric excess was measured on *N*-acetyl-levomilnacipran which was obtained by acetylation of levomilnacipran **1**. Daicel OJ-R 150 × 4.6 mm, H₂O/MeOH 5:5, flow rate: 1 mL min⁻¹, detection at 200 nm, *t*_{major} = 7.0 min, *t*_{minor} = 8.9 min, 88% ee.

[α]_D²⁰ -88.3 (*c* 1.0, CHCl₃).

MS (ES⁺): 247 [M+H]⁺.

⁸ *Adv. Synth. Catal.* **2001**, 343, 299.



**(1*S*,2*R*)-2-(aminomethyl)-*N,N*-diethyl-1-phenylcyclopropanecarboxamide
hydrochloride (1·HCl)**

To a solution of **1** (18 mg, 0.073 mmol) in Et₂O (2 mL), was added a saturated solution of HCl in Et₂O (0.5 mL). The hydrochloride of **1** precipitated out spontaneously. The reaction mixture was further stirred for 15 min, decanted, and the supernatant was discarded. The solid was suspended in Et₂O (2 mL), stirred for 15 min, decanted, and the supernatant was discarded. The washing step was repeated twice. Finally, the solid was collected and dried under vacuum overnight to give compound **1·HCl** as a white solid (20 mg, 97 %).

Analytical data obtained for **1·HCl** are in agreement with those previously reported in the literature.⁹

¹H NMR (CDCl₃): δ 0.90 (3H, t, *J* = 7.0 Hz), 1.09–1.31 (4H, m), 1.62–1.80 (1H, m), 1.82–1.87 (1H, m), 2.35–2.53 (1H, m), 3.27–3.47 (4H, m), 3.72–3.84 (1H, m), 7.15–7.30 (5H, m), 8.83 (3H, brs).

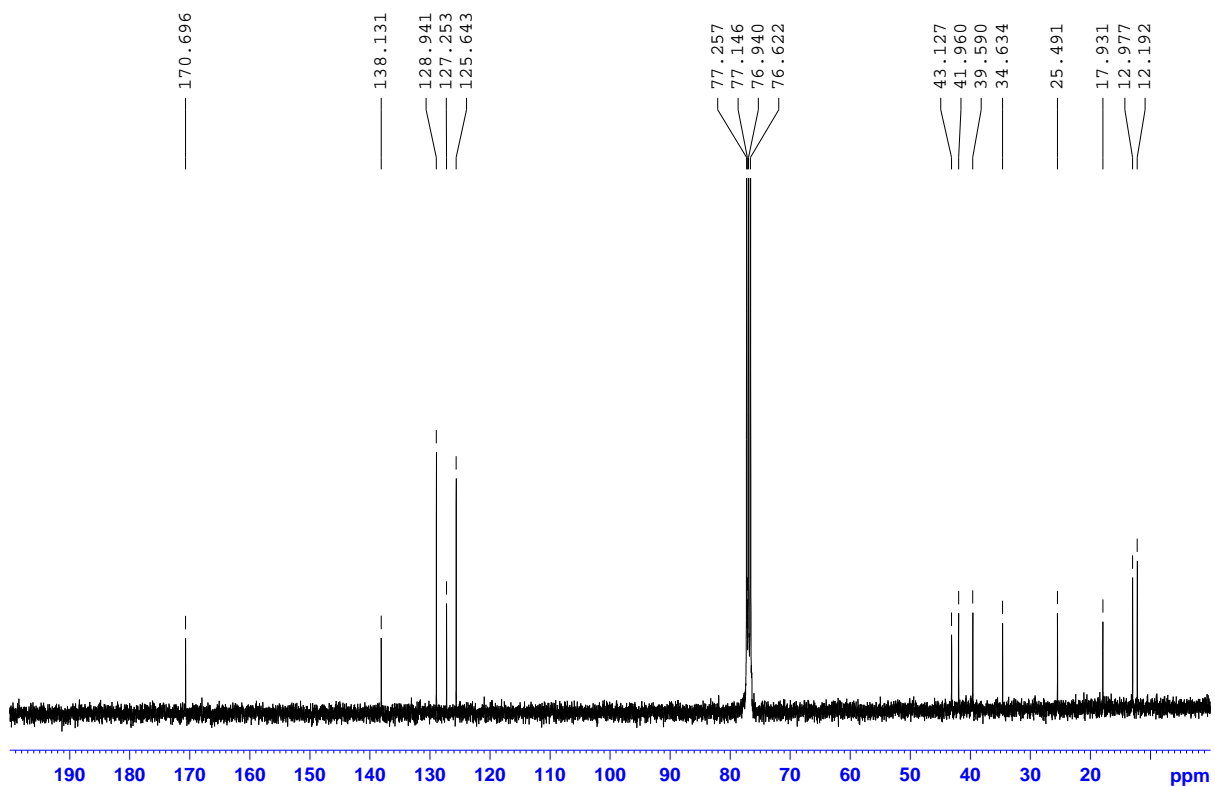
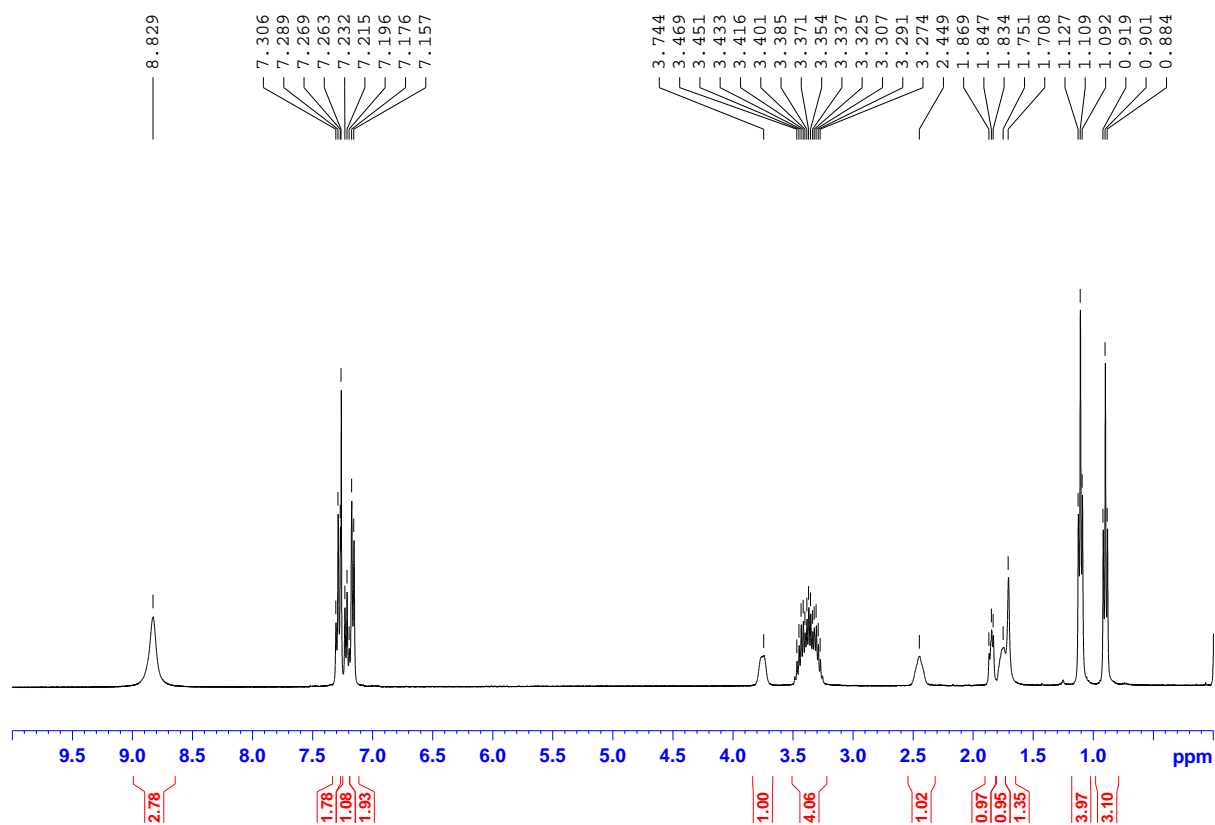
¹³C NMR (CDCl₃): δ 12.2, 13.0, 17.9, 25.5, 34.6, 39.6, 42.0, 43.1, 125.6 (2C), 127.3, 128.9 (2C), 138.1, 170.7.

IR (KBr): 3409, 1615, 1467 cm⁻¹.

[α]_D²⁰ +72.5 (*c* 0.70, CHCl₃); (lit.,¹⁰ [α]_D²⁰ +72.8 (*c* 0.95, CHCl₃), 96% ee).

⁹ *J. Med. Chem.* **1995**, *38*, 2967.

¹⁰ *Tetrahedron Lett.* **1996**, *37*, 641.



Model for the selective deprotonation of epoxy-ester 5¹¹

Figure S1

¹¹ *J. Org. Chem.* **1980**, *45*, 1066.