Supplementary Material

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Experimental Section

Experimental Material and Methods

All chemicals used were obtained commercially (Aldrich) and used without further purification. Melting points were measured in open capillary tubes using a Melt-temp electrothermal apparatus and are uncorrected. Reactions were monitored by TLC on Merck Al plates coated with silica gel of 0.25 mm with fluorescent indicator (60F-254) using ultraviolet light, iodine, and potassium permanganate as relay agents as appropriate. The [2+2] cycloaddition reactions were carried out in a 110 Volt RPR 100 Reactor Rayonet equipped with model RPR-2537A lamps with a wavelength of 254 nm.

Analytical Methods

NMR spectra: Varian Gemini 200 MHz (^{1}H) and 50 MHz (^{13}C), Bruker AVANCE III HD 500 MHz (^{1}H) and 125 MHz (^{13}C), Jeol ECZ 600 MHz (^{1}H) and 150 MHz (^{13}C). Spectra were obtained in DMSO-d_6 (D, 99.9 %), chloroform-D (D, 99.8 %) +0.03 % V/V TMS of Cambridge Isotope Laboratories, Inc. The residual protic solvent signal acted as an internal reference for ^{1}H NMR ($CHCl_3$ = 7.26 ppm) and the deuterated solvent carbon signal acted as an internal reference for ^{13}C NMR; (^{13}C NMR = 77.16 ppm).

*Synthesis of (E)-3-(4-nitrophenyl)propenoic acid **1***. In a flask of 100 mL provided with a magnetic stirrer 2 g (13.3 mmol) of 4-nitrobenzaldehyde, 4.15 g (3 equiv, 39.9 mmol) of malonic acid and 30 mL of pyridine. Subsequently, the flask was placed in a hot oil bath at 75 °C and a condenser was installed. It was reacted for two hours and monitored by thin layer chromatography using a 7:3 hexane:EtOAc system, the presence of 4-nitrobenzaldehyde was no longer observed, the same plate was eluted in a 1:1 EtOAc:MeOH system to appreciate the α,β-unsaturated acid **1**. To finish the reaction the flask was allowed to cool and once cooled it was placed in a container with ice in frost. It was added drop by drop HCl 37 % until reaching a pH = 2 maintaining the agitation (approximately 30 mL). Once a pH of 2 was reached, it was filtered with a Buchner funnel under vacuum, the flask was rinsed with cold water and the product was allowed to dry. The acid was obtained as a white solid (2.28 g, 11.8 mmol, **89 %**).

White solid, mp 294-296 °C (H_2O), descomposition; [lit. 292-293 °C].
R_f = 0.34 (7:3 EtOAc:MeOH).
Data were consistent with that reported [1].

^{1}H NMR (600 MHz, DMSO-d_6) δ 6.75 (d, *J* = 16.0 Hz, 1H), 7.57 (d, *J* = 16.0 Hz, 1H), 7.89 (d, *J* = 8.9 Hz, 2H), 8.20 (d, *J* = 8.8 Hz, 2H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 124.0, 126.8, 129.0, 139.2, 141.6, 147.6, 168.3.

*Synthesis of methyl (E)-3-(4-nitrophenyl)propenoate **2***. In a flask of 100 mL provided with a magnetic stirrer, 2.28 g (11.8 mmol) of (*E*)-3-(4-nitrophenyl)propenoic acid **1** was weighed, suspended with 30 mL of methanol and purged with molecular nitrogen. The flask was placed in a frost ice bath and left in agitation for five minutes. With the help of a syringe 1.28 mL (1.5 equiv, 17.7 mmol) of thionyl chloride was added dropwise and allowed to react under stirring until room temperature was reached. It was monitored by thin layer chromatography 64 hours of reaction using a 7:3 hexane:EtOAc system

and the formation of the esterified compound **2** was observed. That same plate was eluted with a 1:1 EtOAc:MeOH system and traces of the α,β-unsaturated acid were observed. To terminate the reaction the methanol was first concentrated, then 30 mL of distilled water was added and the pH was adjusted to 7 with potassium bicarbonate. Extractions (3 x 30 mL) were carried out with dichloromethane in a separating funnel, the organic phase was dried with sodium chloride and filtered with a funnel and absorbent cotton. The organic phase was concentrated, and the esterified product was recovered as a white solid (2.3 g, 11.2 mmol, **95 %**).

White solid, mp 161-164 °C [lit. 161 °C]
R_f = 0.62 (7:3 hexane:EtOAc).
Data were consistent with that reported [2].

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.84 (s, 3H), 6.57 (d, *J* = 16.1 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 15.7 Hz, 1H), 8.26 (d, *J* = 8.9 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 52.2, 122.3, 124.3, 128.8, 140.6, 142.0, 166.6.

*Synthesis of dimethyl 3,4-bis(4-nitrophenyl)cyclobutane-1,2-dicarboxylate rctt-**3a***. In a Petri plate without cover 220 mg (1.06 mmol) of methyl (*E*)-3-(4-nitrophenyl)propenoate **2** (previously finely crushed with a mortar and pestle and without any previous recrystallization) was extended over the whole Petri plate and placed inside the Rayonet UV equipment. It was allowed to react without solvent for ten hours, homogenizing with a spatula every 20 minutes. It was monitored by thin layer chromatography using a 7:3 hexane:EtOAc mobile phase, observing still the presence of ester α,β-unsaturated and the formation of a single [2+2] cycloaddition product with a stereochemistry corresponding to a β-truxinate derivative. Purification was carried out by column chromatography employing a 7:3 CH_2Cl_2:hexane mobile phase recovering α,β-unsaturated ester **2** (94 mg, 0.45 mmol, 42.4 %) and obtaining the cycloaddition product as a slightly yellow solid (112 mg, 0.27 mmol, **51 %**).

Slightly yellow solid, mp 128-130 °C
R_f = 0.32 (6:4 hexano:EtOAc)
Data were consistent with that reported [3].

^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.78 (s, 6H), 3.89 (d, *J* = 6 Hz, 2H), 4.58 (d, *J* = 6 Hz, 2H), 7.11 (d, *J* = 6 Hz, 4H), 8.01 (d, *J* = 6 Hz, 4H). **^{13}C NMR** ($CDCl_3$, 150 MHz): δ 43.1, 44.9, 52.7, 123.8, 128.5, 145.5, 146.9, 172.0.

*Synthesis of dimethyl 3,4-bis(4-nitrophenyl)cyclobutane-1,2-dicarboxylate rcct-rac-**3b***. In a vial of 1 mL provided with a magnetic stirrer, 20 mg ($4.8x10^{-2}$ mmol) of *dimethyl 3,4-bis(4-nitrophenyl)cyclobutane-1,2-dicarboxylate rctt-3a* was weighed. Later, 20.8 μL of a 0.46 M solution of TMG in acetonitrile were added. The vial was placed in an oil bath at 55°C during 90 min. The reaction was stopped performing a column chromatography in silica using a 7:3 hexane:EtOAc system. Cycloadduct *rcct-rac*-**3b** was recovered as a white solid (18 mg, $4.3x10^{-2}$ mmol, **90 %**).

White solid, mp 167-170 °C

R_f = 0.40 (6:4 hexane:EtOAc)
Data were consistent with that reported [4].

^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.39 (s, 3H), 3.43 (dd, *J* = 10.2, 8.6 Hz, 1H), 3.76 (s, 3H), 3.99 (ddd, *J* = 9.5, 8.5, 1.0 Hz, 1H), 4.09 (dd, *J* = 11.0, 9.4 Hz, 1H), 4.82 (t, *J* = 10.5 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 8.19 (d, *J* = 8.4 Hz, 2H), 8.19 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 150 MHz): δ 43.5, 43.8, 44.4, 46.6, 52.1, 52.4, 124.0, 124.2, 127.6, 128.3, 145.0, 147.3, 147.4, 148.5, 171.1, 171.7.

*Synthesis of dimethyl 3,4-bis(4-nitrophenyl)cyclobutane-1,2-dicarboxylate rtct-rac-**3c***. In a vial of 1 mL provided with a magnetic stirrer, 20 mg ($4.8x10^{-2}$ mmol) of *dimethyl 3,4-bis(4-nitrophenyl)cyclobutane-1,2-dicarboxylate rctt-3a* was weighed. Then, 25.2 μL of a 0.38 M solution of DBU in acetonitrile were added. The vial was placed in an oil bath at 55°C during 45 min. The reaction was stopped performing a column chromatography in silica using a 7:3 hexane:EtOAc system. Cycloadduct *rtct-rac*-3c was recovered as a slightly yellow solid (12 mg, $2.8x10^{-2}$ mmol, **60 %**).

Slightly yellow solid, mp 94-96 °C
R_f = 0.48 (6:4 hexane:EtOAc)
Data were consistent with that reported [3].

^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.55 (d, *J* = 9.6 Hz, 2H), 3.78 (s, 6H), 3.84 (d, *J* = 9.6 Hz, 2H), 7.45 (d, *J* = 9 Hz, 4H), 8.20 (d, *J* = 8.4 Hz, 4H). **^{13}C NMR** ($CDCl_3$, 150 MHz): δ 44.3, 46.7, 52.8, 124.3, 127.8, 147.4, 147.4, 172.1.

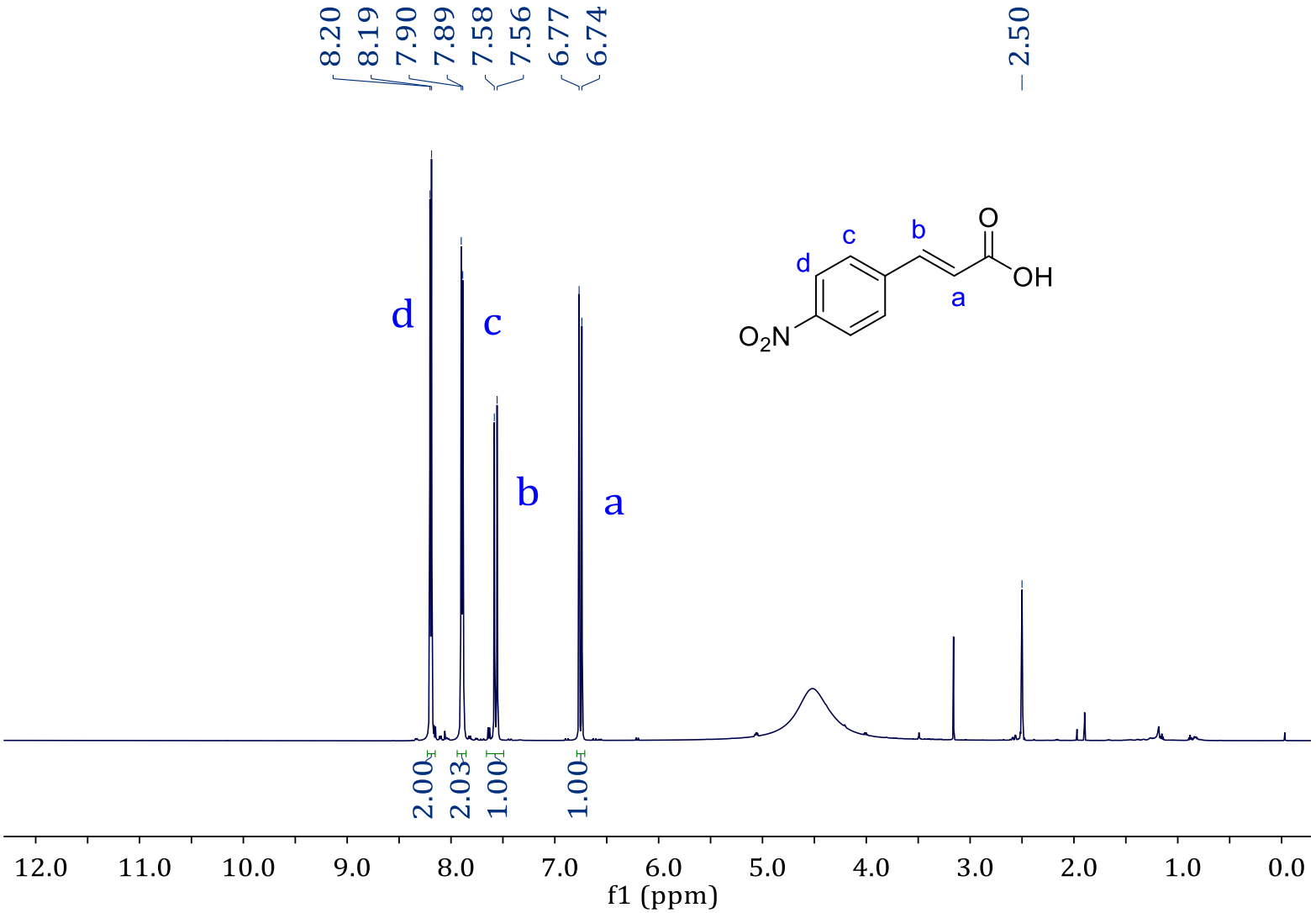

Figure S1 ^{1}H NMR (600 MHz, DMSO-d_6) of (*E*)-3-(4-nitrophenyl)propenoic acid **1**

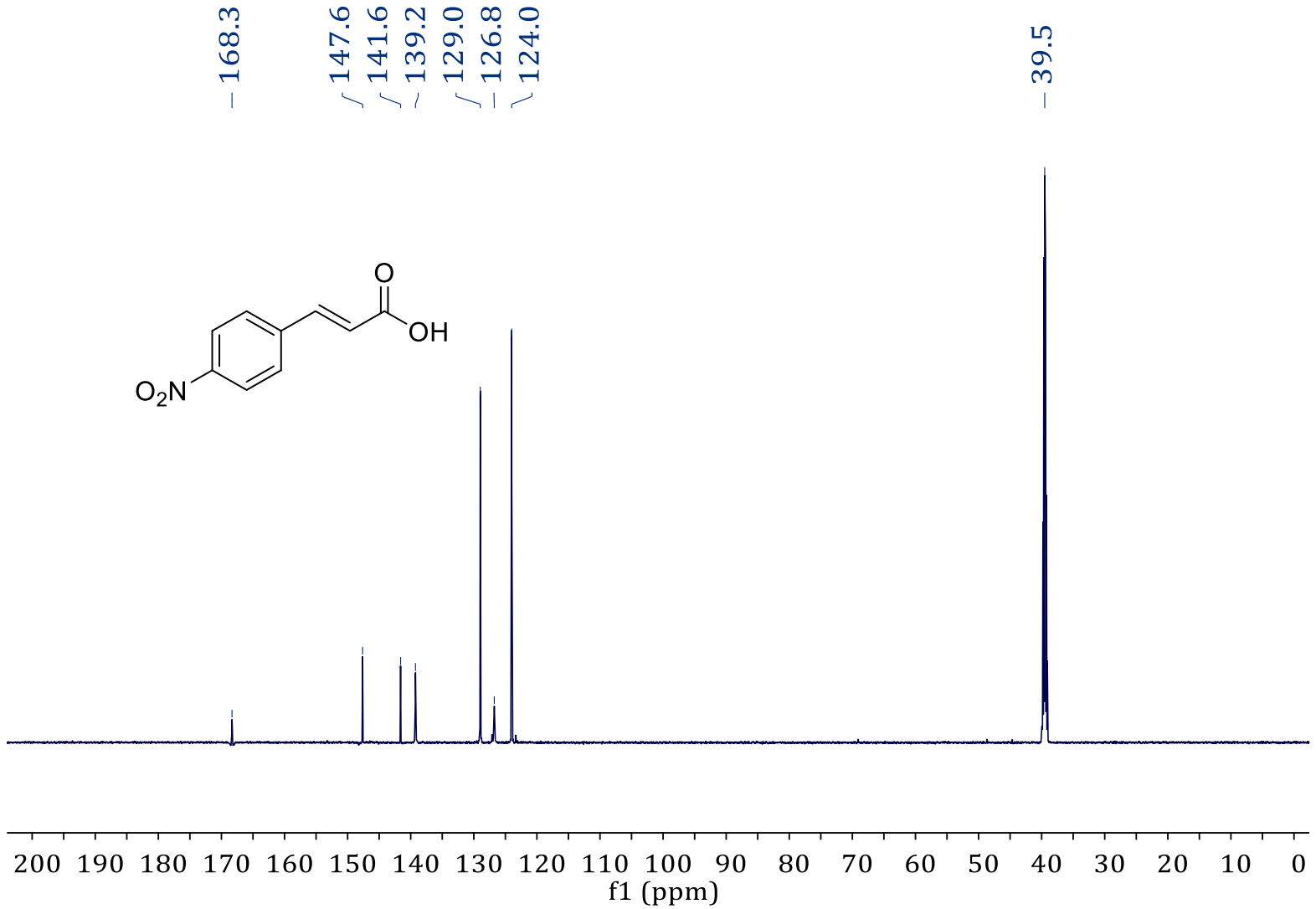

Figure S2 ^{13}C NMR (150 MHz, DMSO-d_6) of (*E*)-3-(4-nitrophenyl)propenoic acid **1**

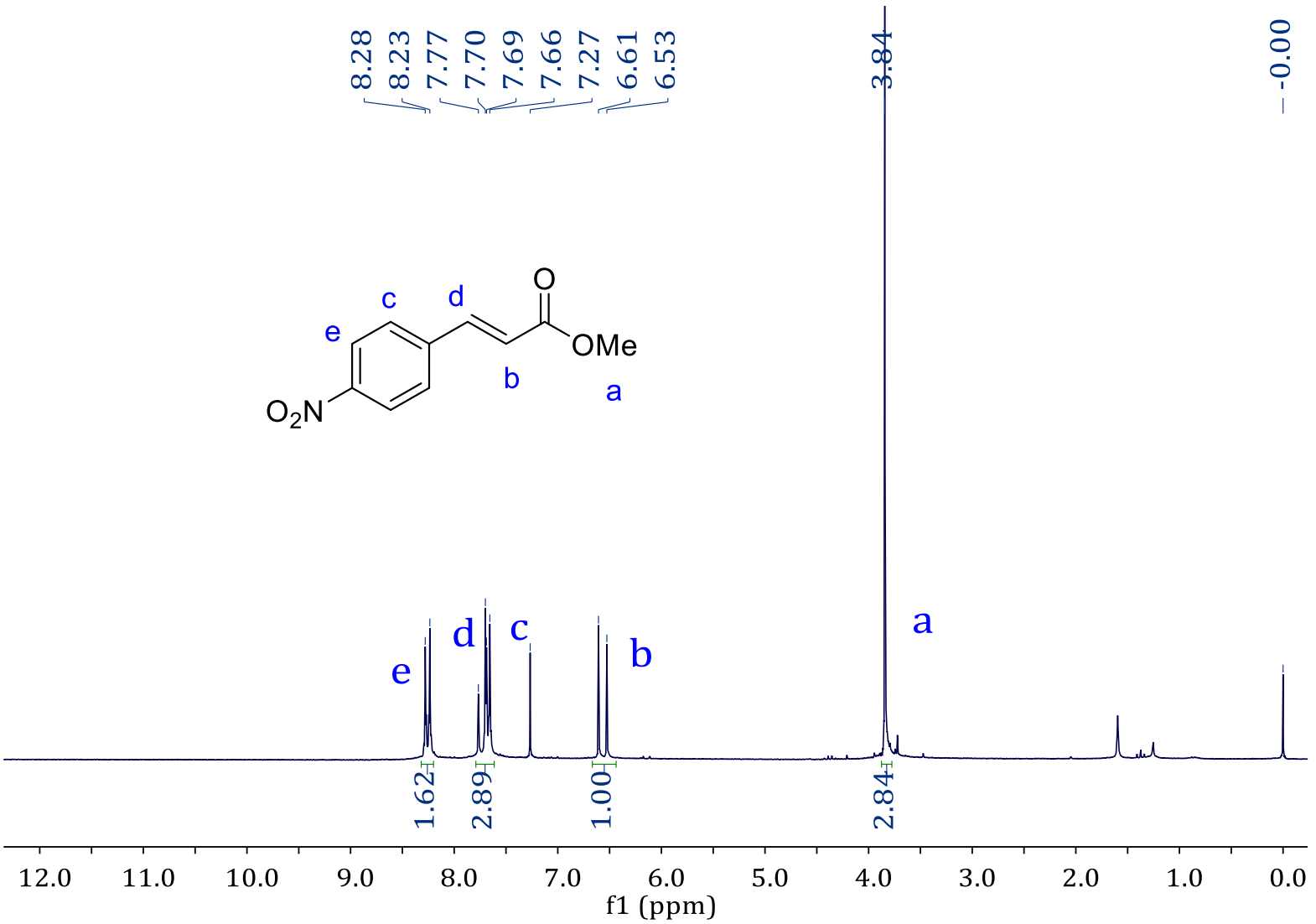

Figure S3 ^{1}H NMR (200 MHz, $CDCl_3$) methyl (*E*)-3-(4-nitrophenyl)propenoate **2**

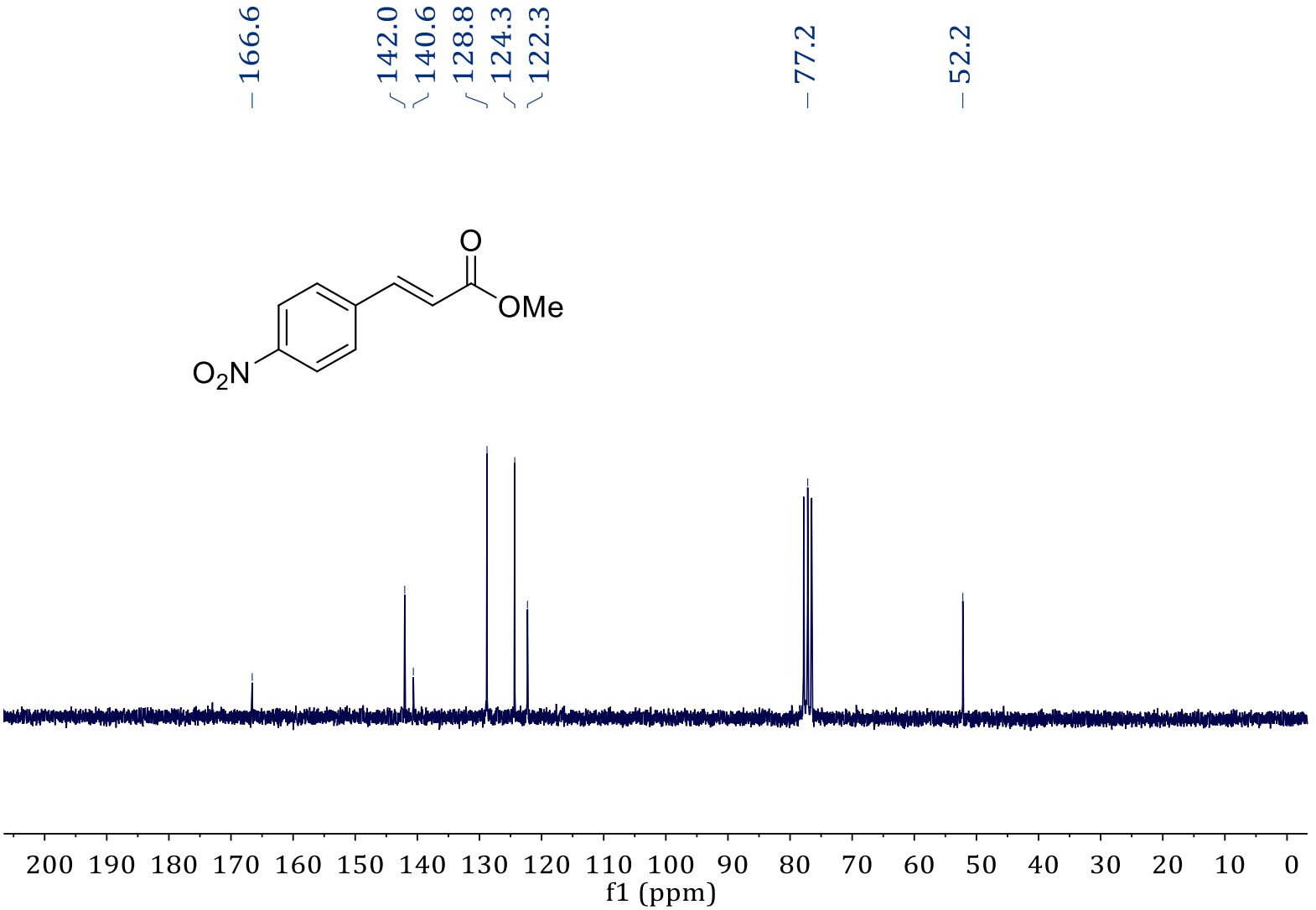

Figure S4 ^{13}C NMR (50 MHz, $CDCl_3$) methyl (*E*)-3-(4-nitrophenyl)propenoate **2**

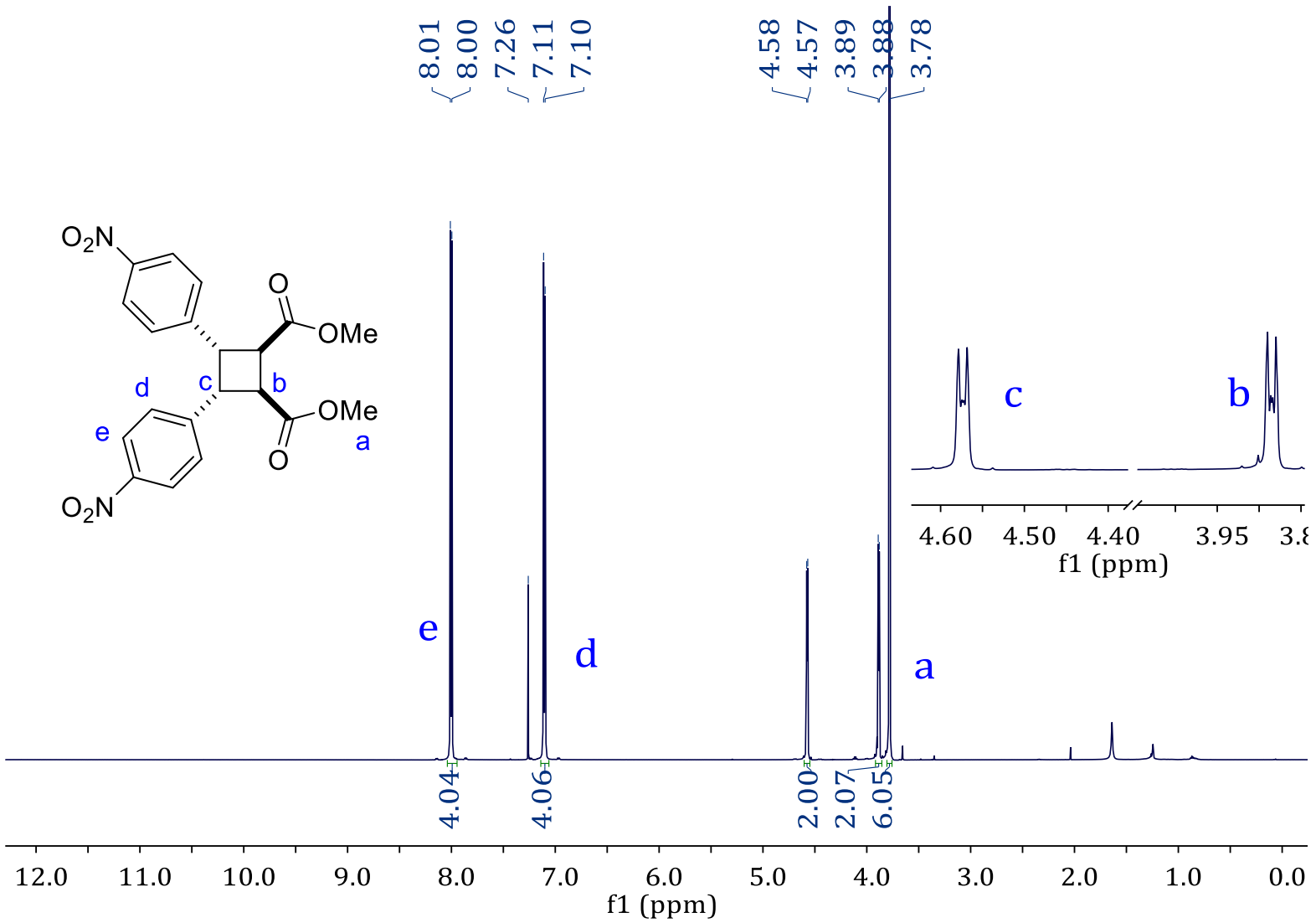

Figure S5 ^{1}H NMR (600 MHz, $CDCl_3$) of dimethyl 3,4-bis(4-nitrophenyl)cyclobutane-1,2-dicarboxylate *rctt*-**3a**

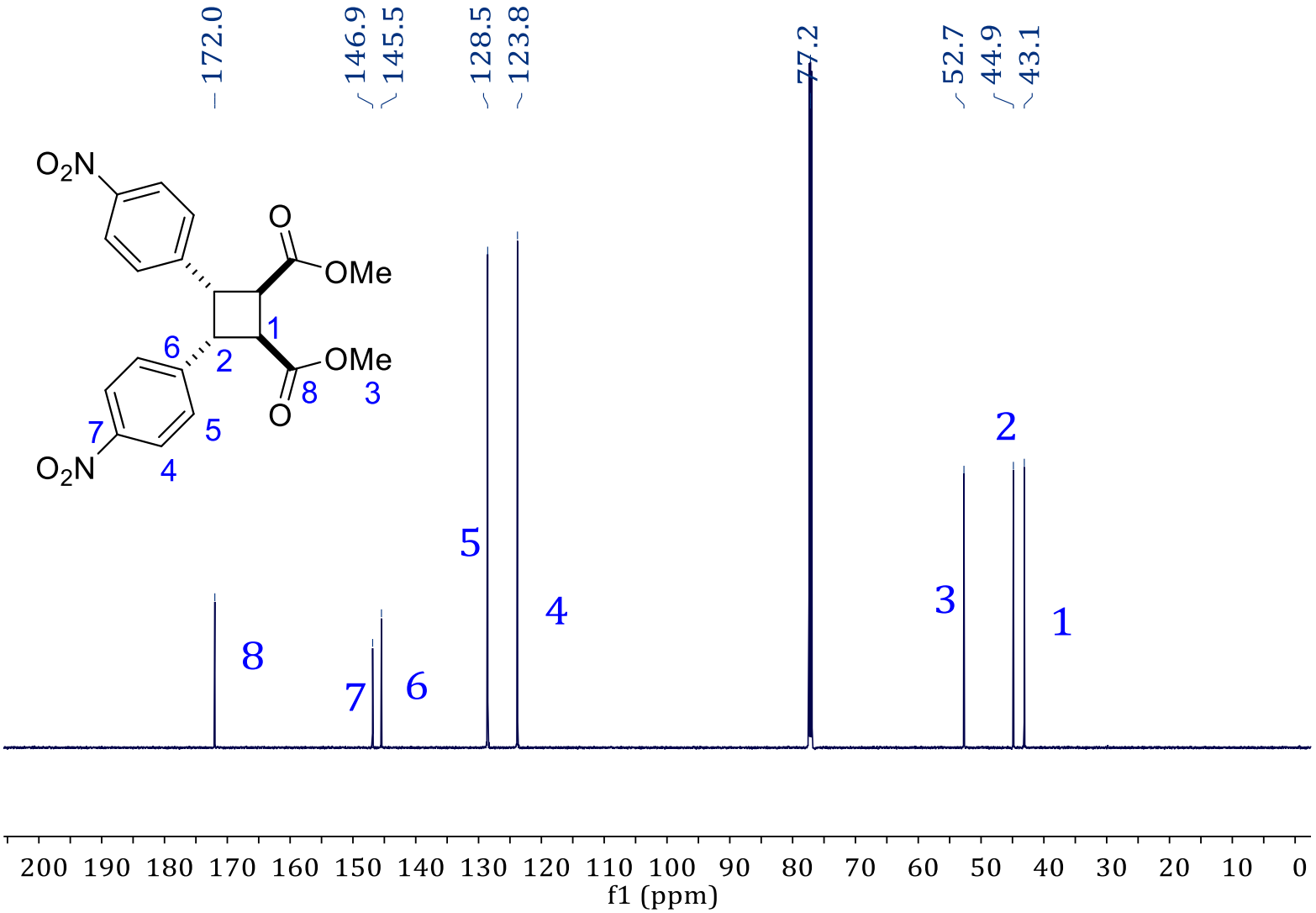

Figure S6 ^{13}C NMR (150 MHz, $CDCl_3$) of dimethyl 3,4-bis(4-nitrophenyl)cyclobutane-1,2-dicarboxylate *rctt*-**3a**

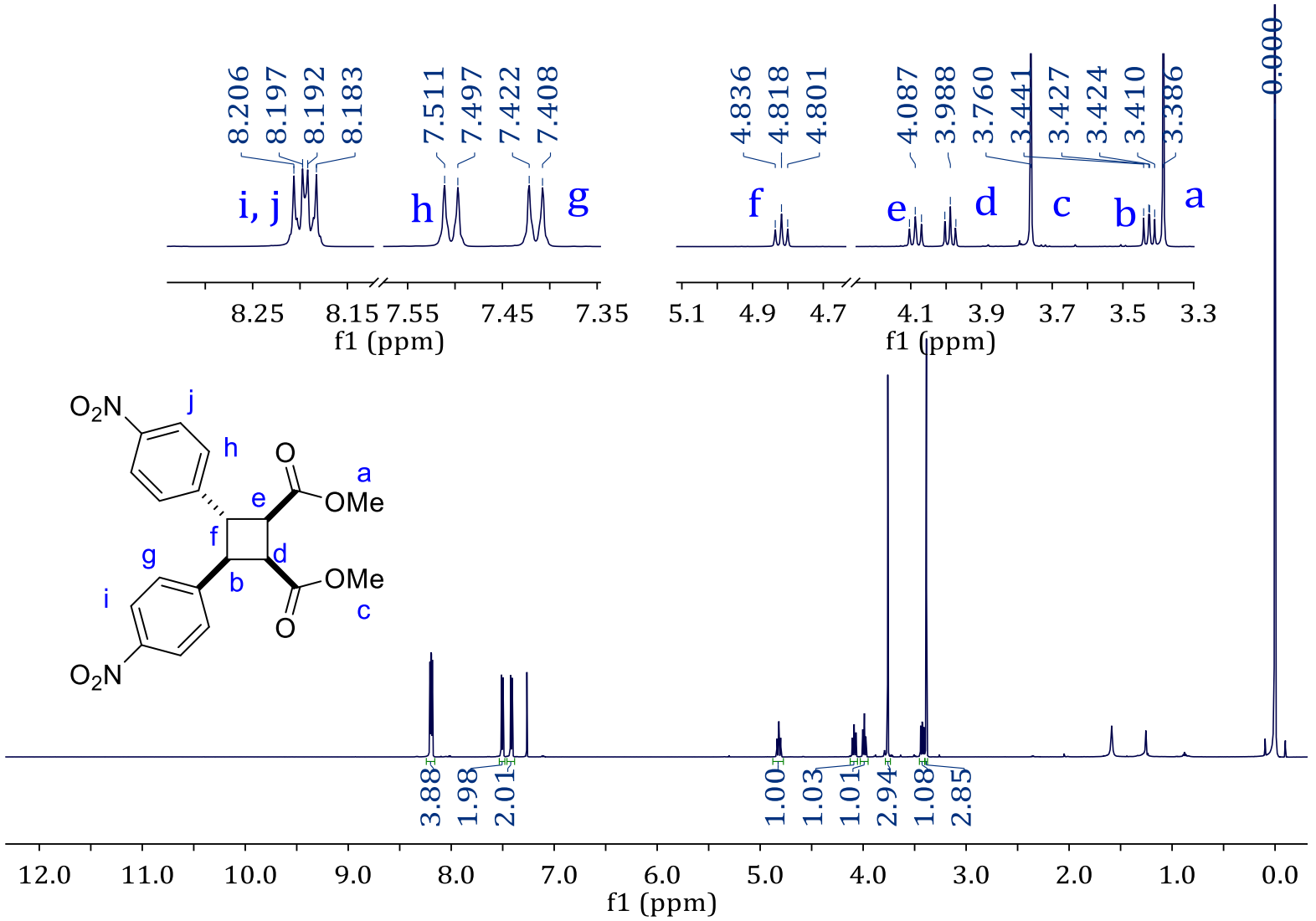

Figure S7 ^{1}H NMR (600 MHz, $CDCl_3$) of dimethyl 3,4-bis(4-nitrophenyl)cyclobutane-1,2-dicarboxylate *rcct-rac*-**3b**

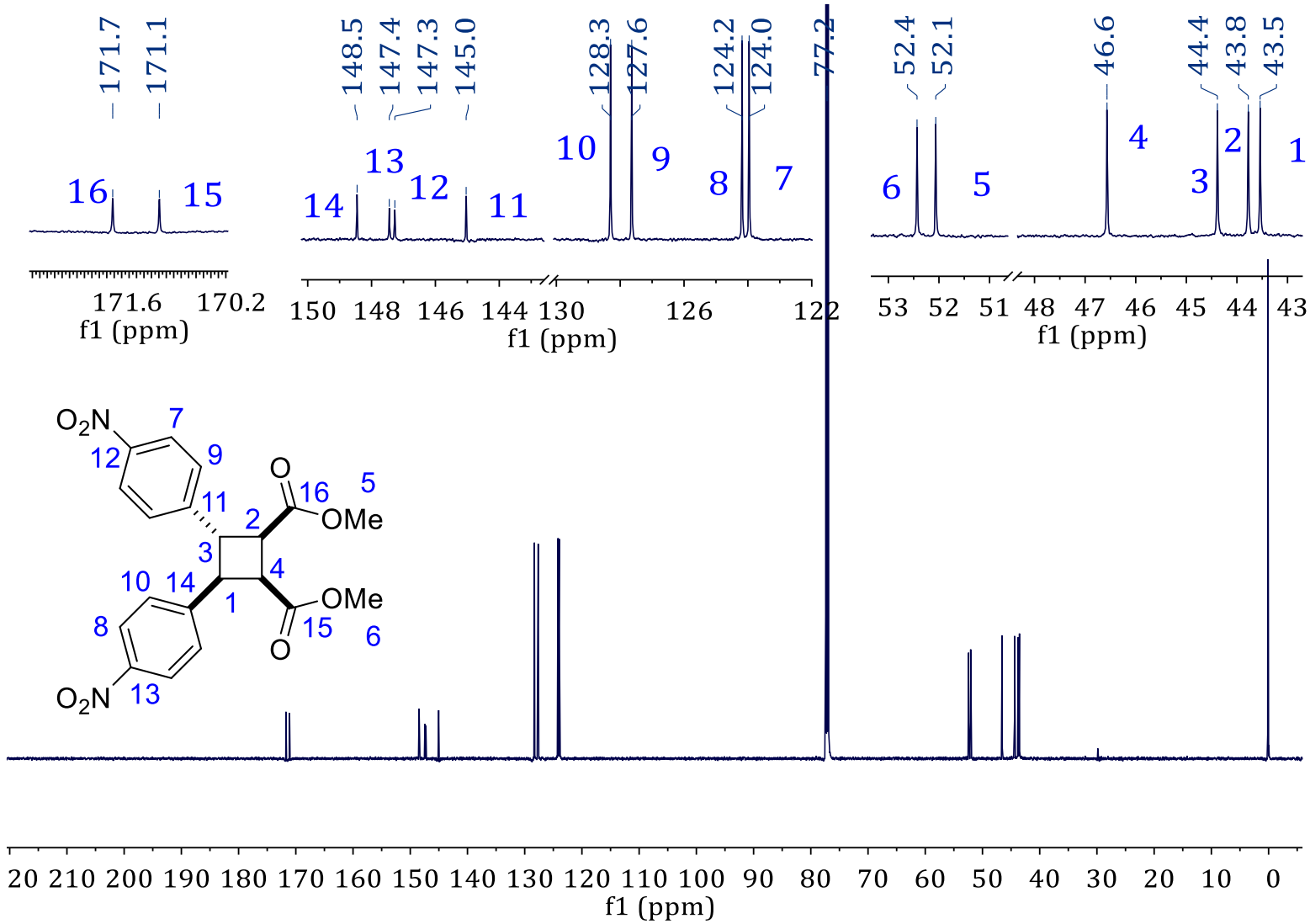

Figure S8 ^{13}C NMR (150 MHz, $CDCl_3$) of dimethyl 3,4-bis(4-nitrophenyl)cyclobutane-1,2-dicarboxylate *rcct-rac*-**3b**

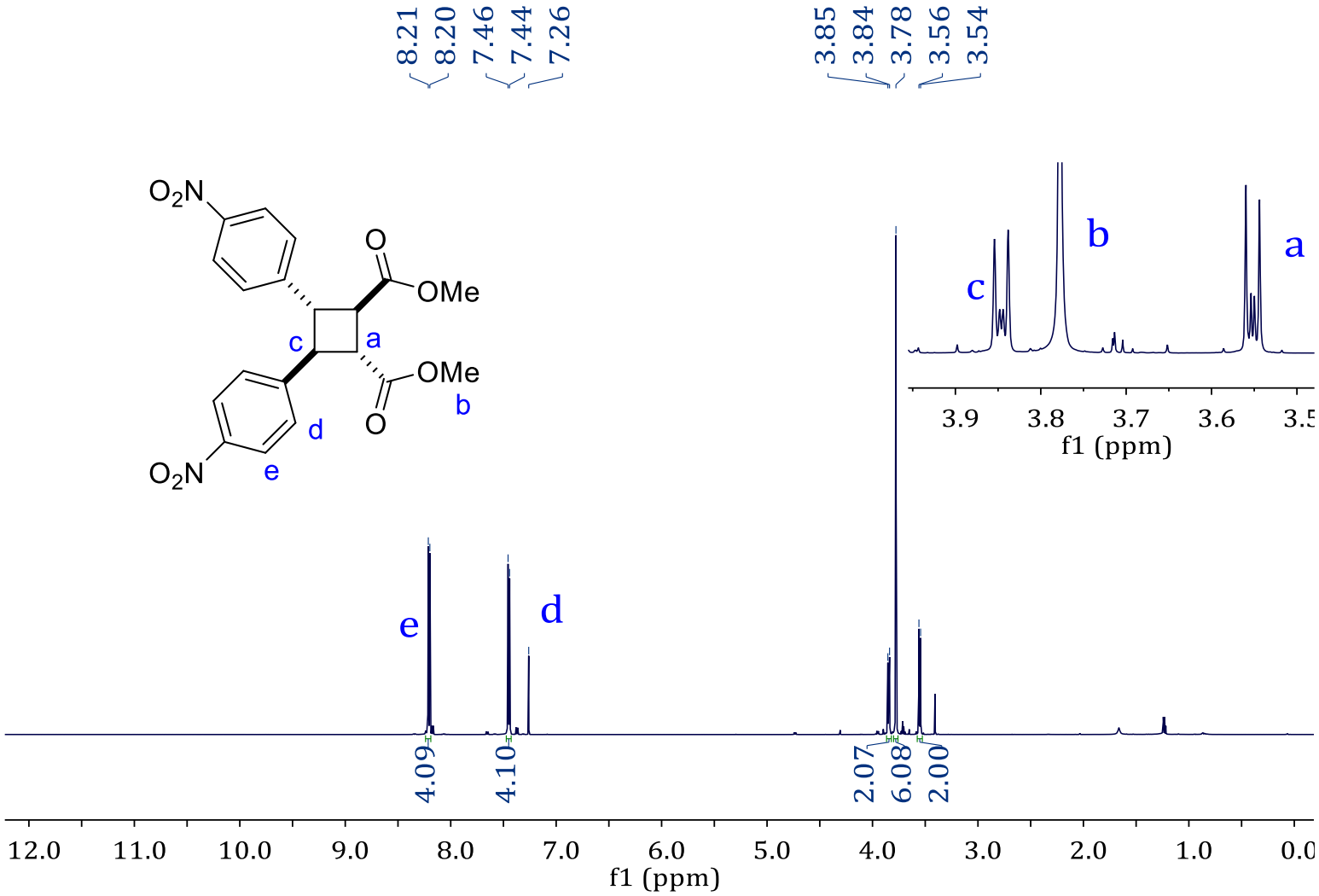

Figure S9 ^{1}H NMR (600 MHz, $CDCl_3$) of dimethyl 3,4-bis(4-nitrophenyl)cyclobutane-1,2-dicarboxylate *rtct-rac*-**3c**

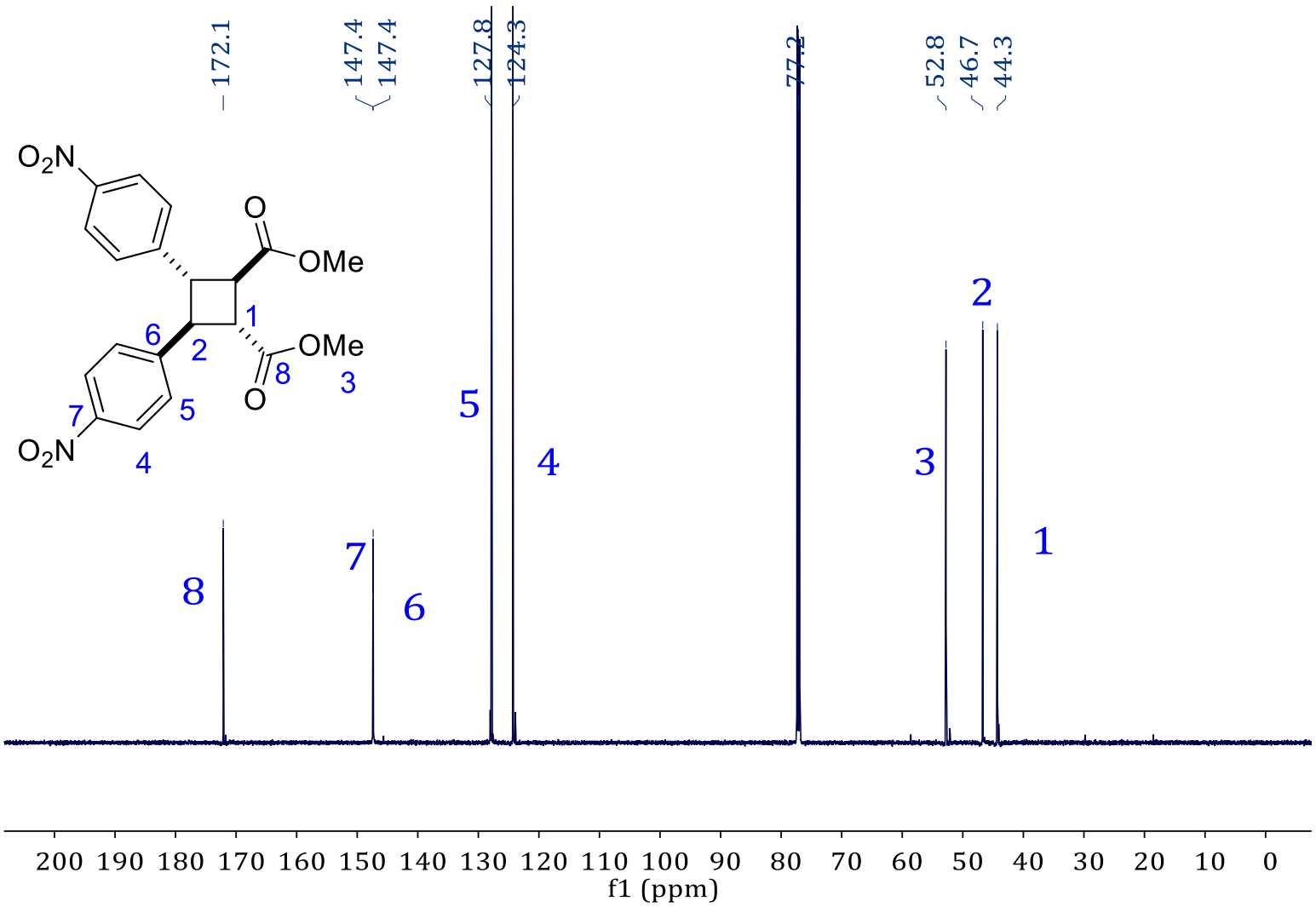

Figure S10 ^{13}C NMR (150 MHz, $CDCl_3$) of dimethyl 3,4-bis(4-nitrophenyl)cyclobutane-1,2-dicarboxylate *rtct-rac*-**3c**

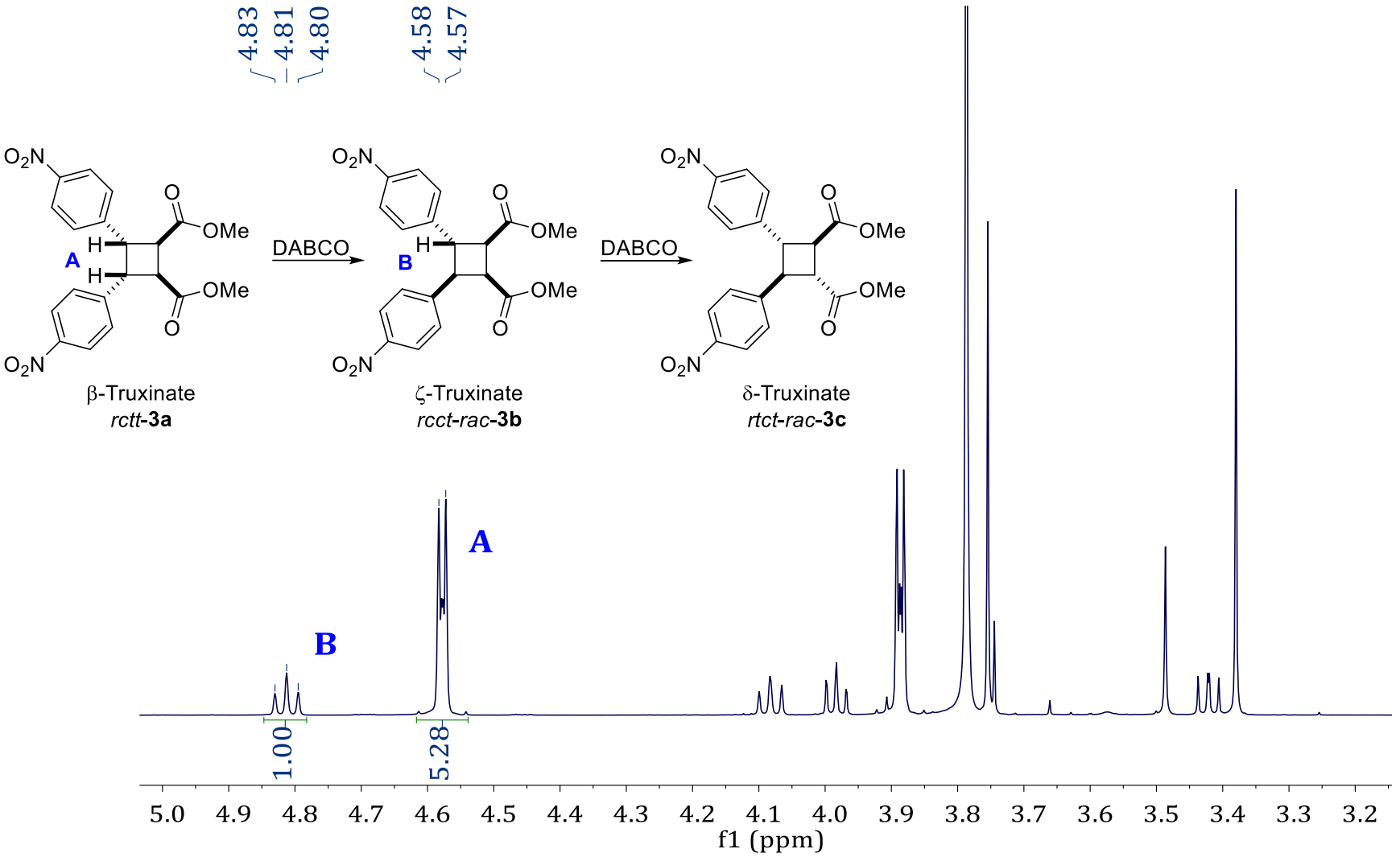

Figure S11 ^{1}H NMR (600 MHz, $CDCl_3$) of the reaction crude of β- → ζ- → δ-truxinate process using DABCO (0.2 equiv), 55 °C, 48 h

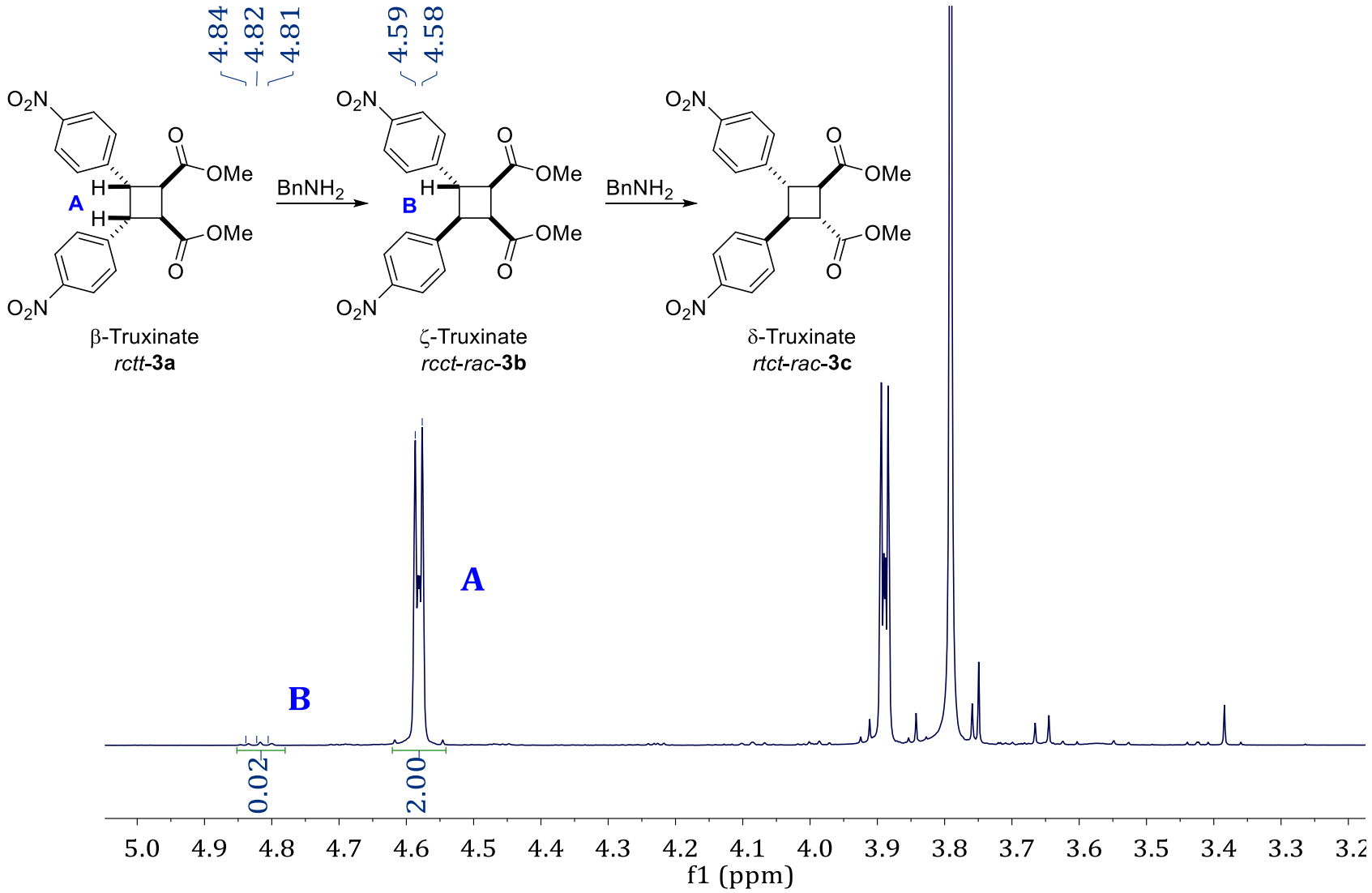

Figure S12 ^{1}H NMR (600 MHz, $CDCl_3$) of the reaction crude of β- → ζ- → δ-truxinate process using $BnNH_2$ (0.2 equiv), 55 °C, 48 h

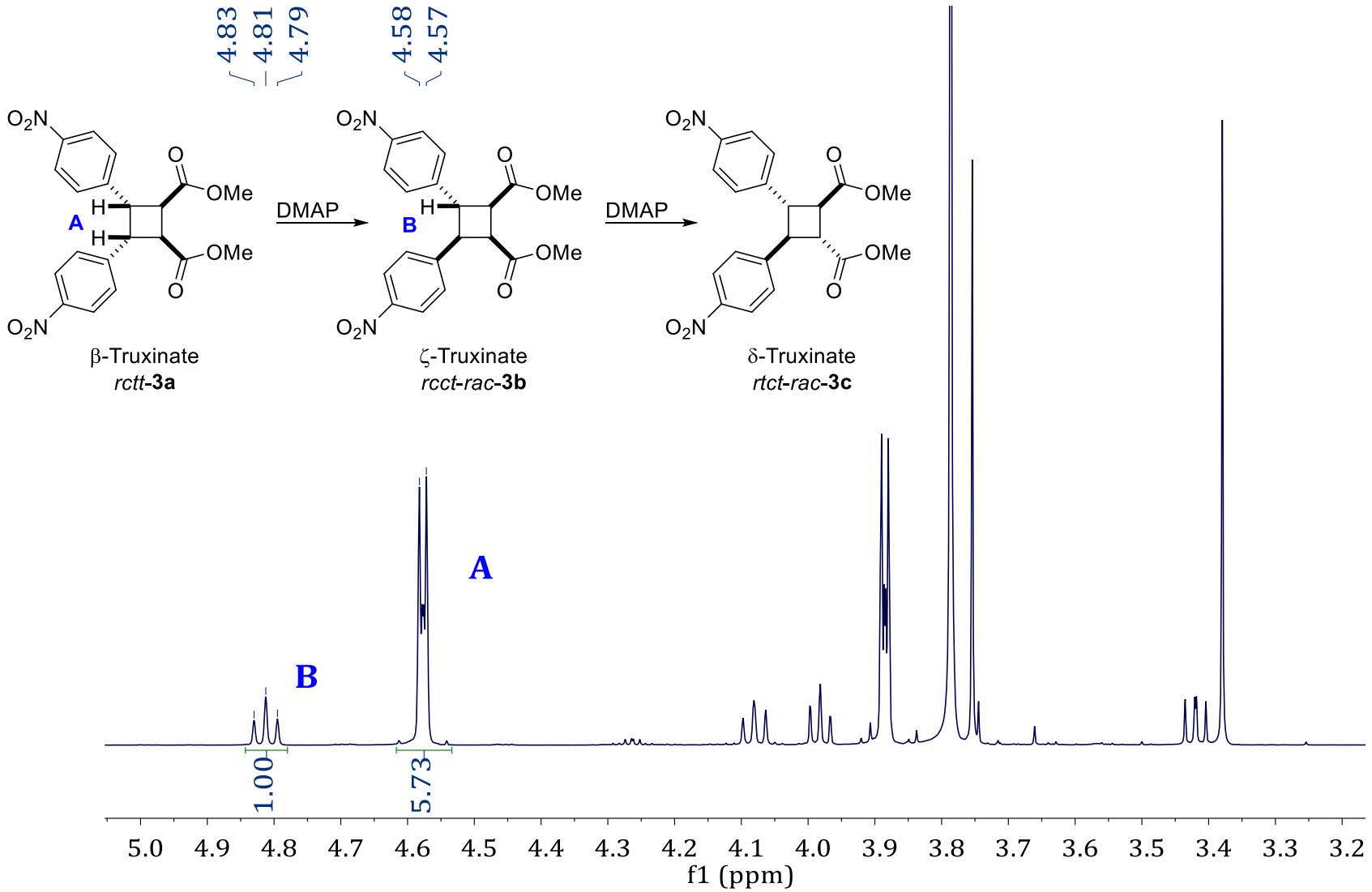

Figure S13 ^{1}H NMR (600 MHz, $CDCl_3$) of the reaction crude of β- → ζ- → δ-truxinate process using DMAP (0.2 equiv), 55 °C, 48 h

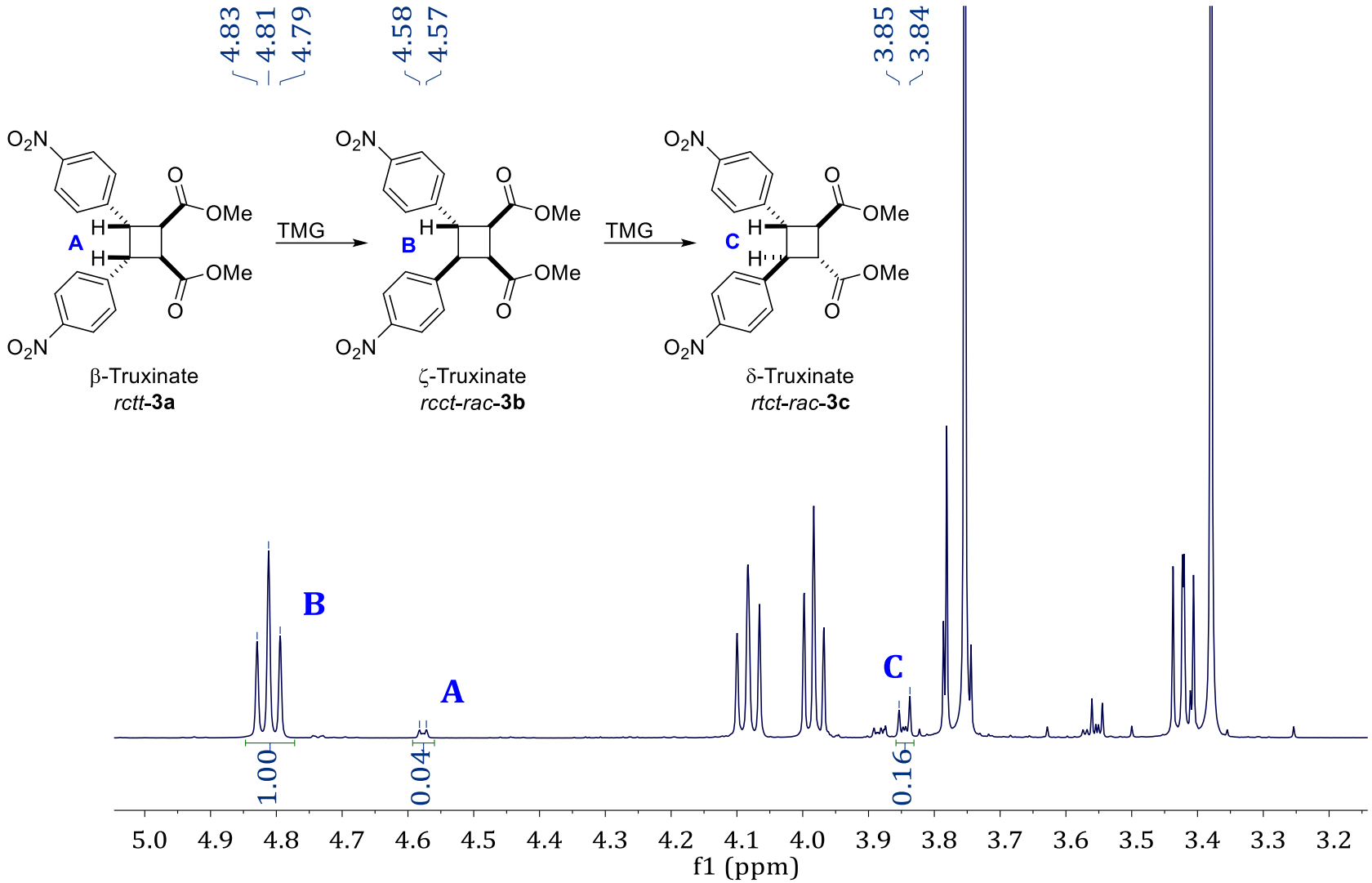

Figure S14 ^{1}H NMR (600 MHz, $CDCl_3$) of the reaction crude of β- → ζ- → δ-truxinate process using TMG (0.2 equiv), 55 °C, 90 min

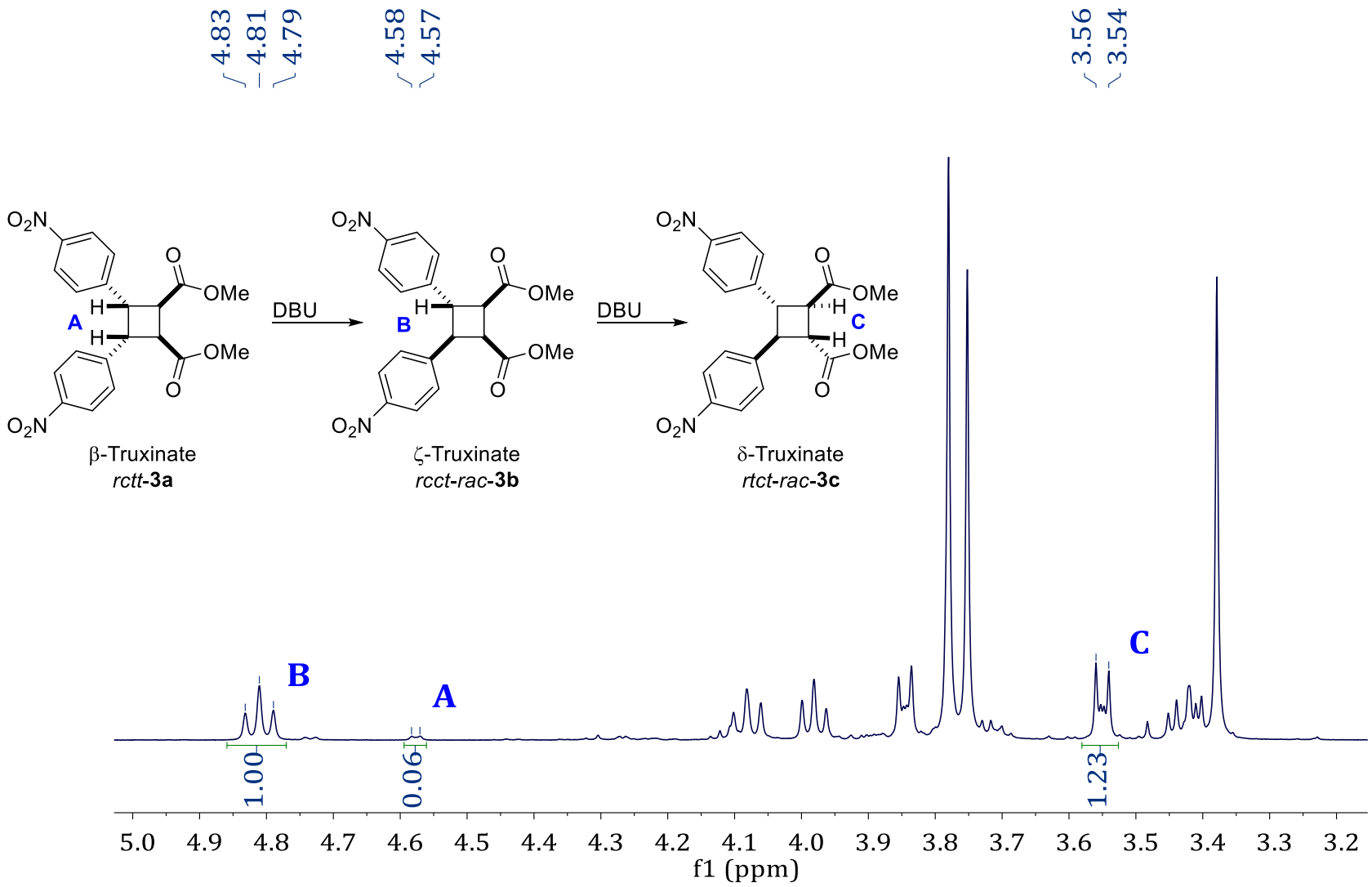

Figure S15 ^{1}H NMR (500 MHz, $CDCl_3$) of the reaction crude of β- → ζ- → δ-truxinate process using DBU (0.2 equiv), 55 °C, 20 min

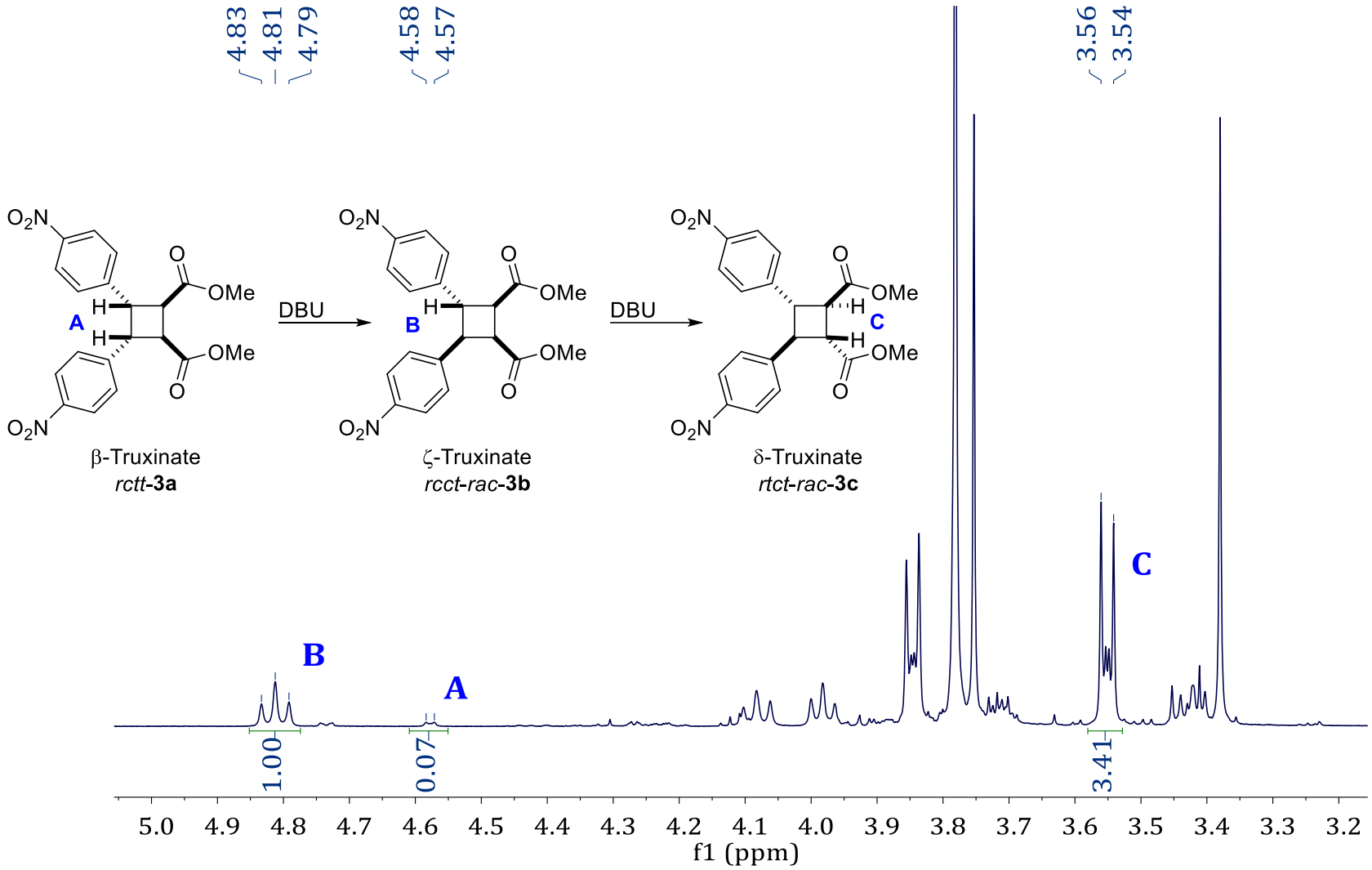

Figure S16 ^{1}H NMR (500 MHz, $CDCl_3$) of the reaction crude of β- → ζ- → δ-truxinate process using DBU (0.2 equiv), 55 °C, 45 min

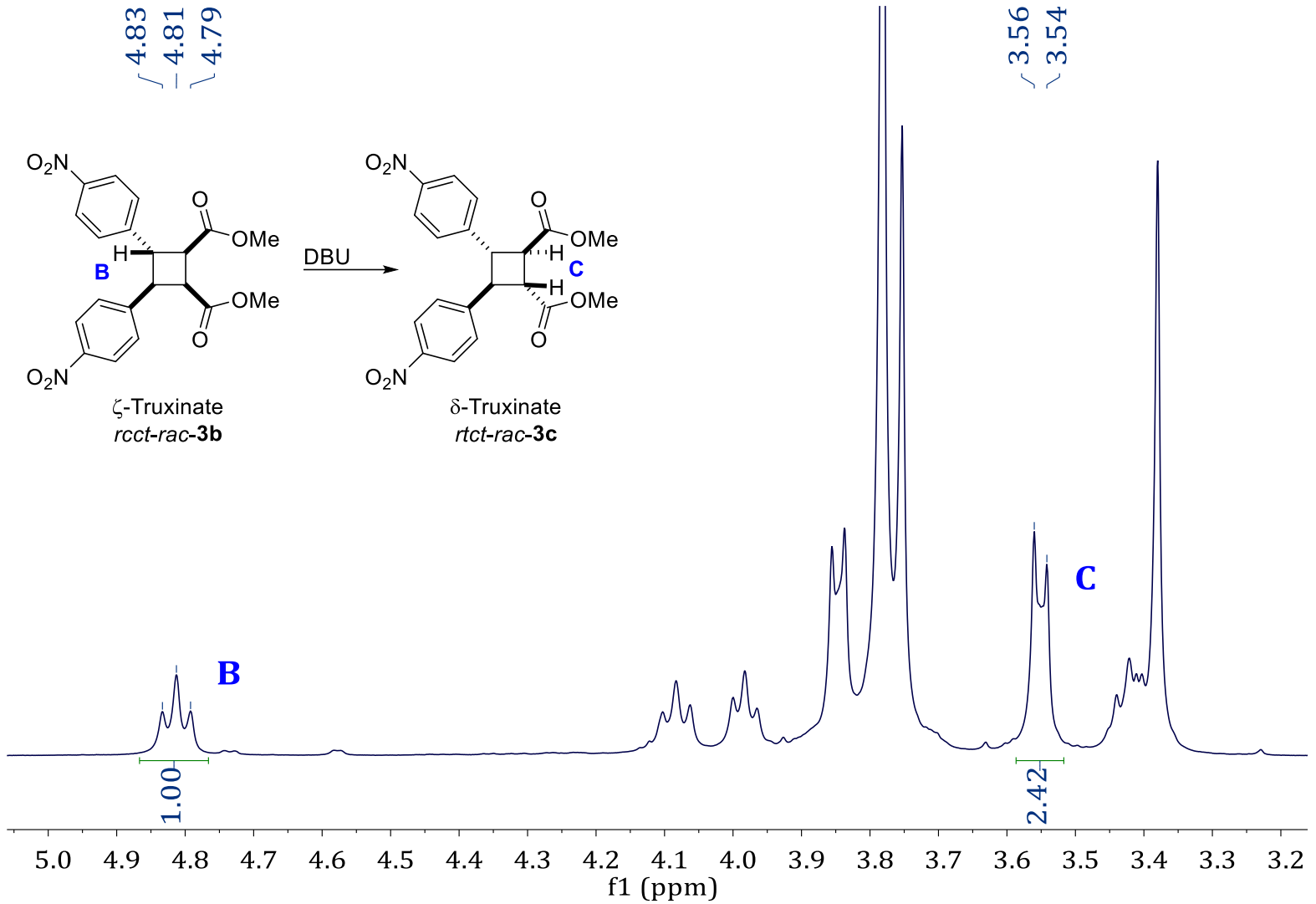

Figure S17 ^{1}H NMR (500 MHz, $CDCl_3$) of the reaction crude of ζ- → δ-truxinate process using DBU (0.2 equiv), 55 °C, 4.5 h

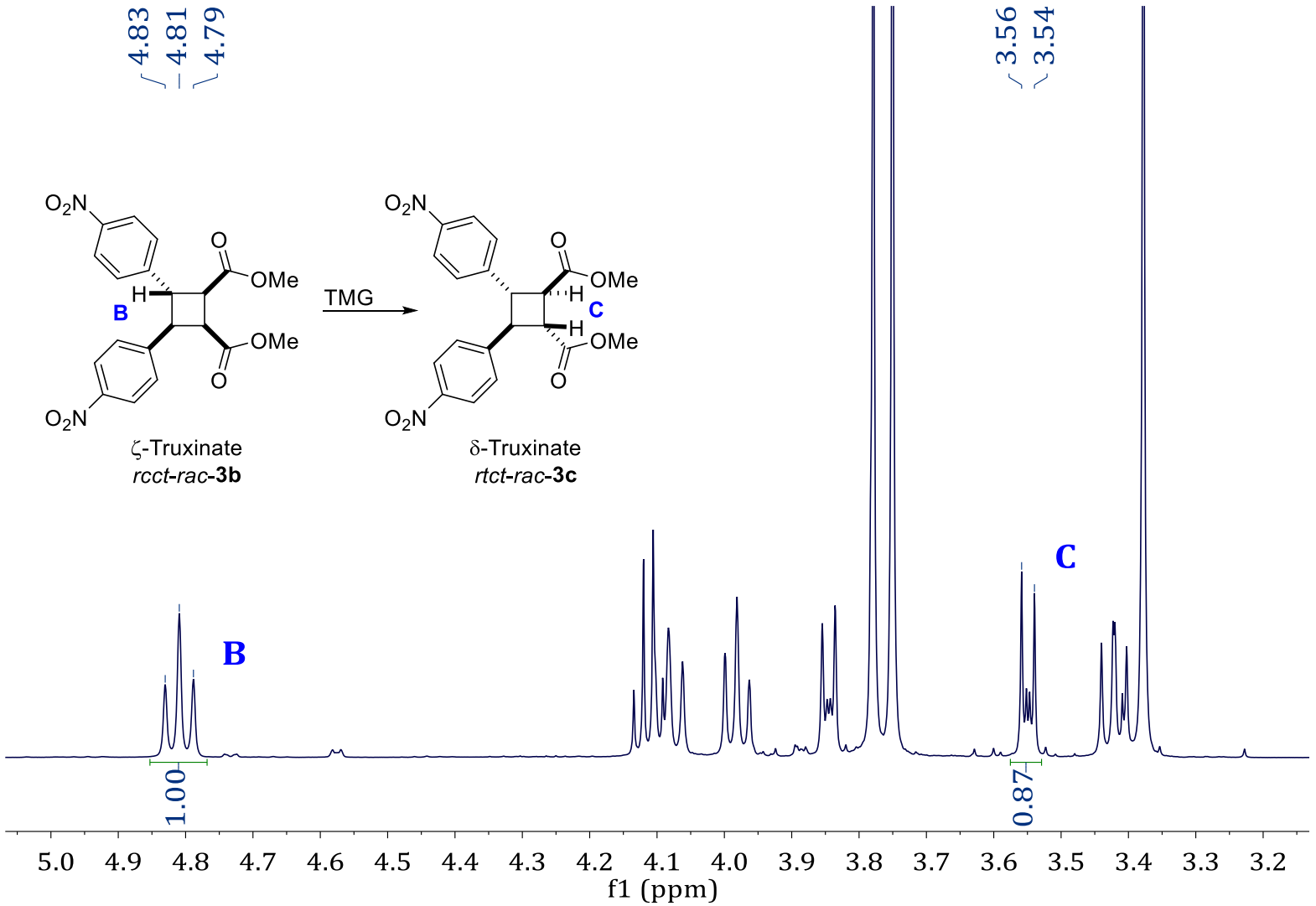

Figure S18 ^{1}H NMR (500 MHz, $CDCl_3$) of the reaction crude of ζ- → δ-truxinate process using TMG (0.2 equiv), 55 °C, 4.5 h

References

(1) Szymanski, W.; Wu, B.; Weiner, B.; De Wildeman, S.; Feringa, B. L.; Janssen, D. B. Phenylalanine Aminomutase-Catalyzed Addition of Ammonia to Substituted Cinnamic Acids: A Route to Enantiopure α- and β-Amino Acids. *J. Org. Chem.* **2009**, *74* (23), 9152–9157. https://doi.org/10.1021/jo901833y.

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