

A Concise Asymmetric Synthesis of Torcetrapib

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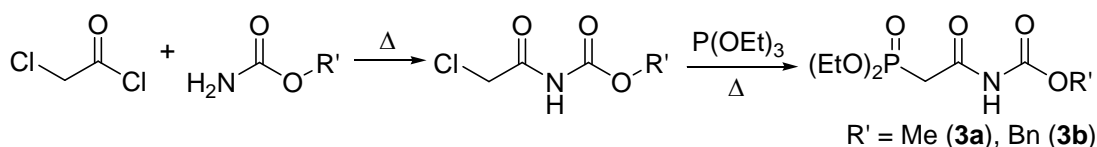
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General experimental

All reactions involving air and/or moisture sensitive compounds were conducted under an atmosphere of dry nitrogen, using oven-dried glassware and dry solvents. Nuclear magnetic resonance (NMR) spectra were recorded as solutions in CDCl₃. The peak positions are reported with shifts (δ) in ppm referenced to the residual undeuterated chloroform solvent peak (δ_{H} 7.26, δ_{C} 77.00). The coupling constants (J) are reported in Hertz (Hz). The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Assignment of resonance signals (where given) was confirmed by relevant correlation experiments. Melting points were uncorrected.

Experimental

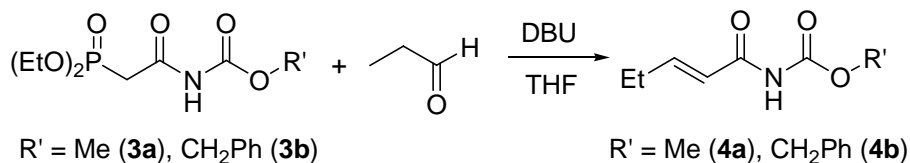


Preparation of the phosphonate esters 3a and 3b: Under a N₂ atmosphere, a mixture of alkyl carbamate (0.132 mol) and chloroacetyl chloride (10.8 mL, 0.136 mol) was heated at 110 °C for 30 minutes, whereupon the reaction mixture solidified. After cooling to room temperature, the residue was triturated with diethyl ether (25 mL) to yield a pale yellow solid, which was collected by filtration. The solid was then placed in a flask with triethylphosphite (44 mL, 0.259 mol), and heated at 80 °C under a N₂ atmosphere for 48 hours. After cooling to room temperature, the solid residue was washed with n-hexane to remove the excess phosphite reagent, and may be used in the next step without further purification.

Methyl carbamate phosphonate ester, 3a (R = Me, white solid, 87% yield, over 2 steps). mp 45-47 °C; δ_{H} (270 MHz, CDCl₃) 9.09 (1H, br s, NH), 4.20 - 4.10 (4H, m, 2 × OCH₂), 3.74 (3H, s, OCH₃), 3.30 (2H, d, J 24 Hz, CH₂), 1.36-1.21 (6H, m, 2 × CH₃). δ_{C} (67.5 MHz, CDCl₃) 164.7, 151.8, 63.5 (d, J 6.5 Hz), 52.8, 35.9 (d, J 131 Hz), 16.2 (d, J 6.5 Hz). m/z (EI) 253 (M⁺, 100%), 131 (99), 105 (100), 77 (58).

Benzyl carbamate phosphonate ester, 3b (R = Bn, off-white solid, 88% yield over 2 steps). mp 101-102 °C; δ_{H} (400 MHz, CDCl₃) 9.60 (1H, br. s, NH), 7.32 (5H, d, J 6.8 Hz, ArH), 5.13 (2H, s, CH₂Ph), 4.07 (4H, q, J 7.2 Hz, CH₂CH₃), 3.26 (2H, d, J = 22.0 Hz, CH₂P), 1.28 (6H, t, J 7.1 Hz, CH₂CH₃); δ_{C} (100.6 MHz, CDCl₃) 164.6, 151.2, 135.0, 128.6, 128.5, 128.4, 67.7, 62.9 (d, J 6.8

H_z), 35.9 (d, *J* 130 Hz), 16.2 (d, *J* 6.8 Hz); *m/z* (EI) 329 (M⁺, 30%), 222 (23), 195 (32), 179 (49), 152 (58), 91 (100).



The HWE reaction: DBU (6.6 mL, 43.5 mmol) and propionaldehyde (3.2 mL, 43.5 mmol) were added successively to a solution of the phosphonate imide **3a** (11 g, 43.5 mmol) in THF (50 mL), with cooling in a water bath. Upon completion (TLC, *ca.* 8-12 h), the reaction mixture was diluted with ethyl acetate (400 mL) and water (200 mL). The aqueous phase was extracted twice with ethyl acetate (2 × 200 mL) and the combined organic extracts were washed with brine (200 mL) and dried over MgSO₄. Concentration under vacuum gave **4a** as a pale yellow solid, which was recrystallised from EtOAc/hexane, giving the product as white crystals (6.5 g, 95% yield). mp 87-88°C; δ_H (270 MHz, CDCl₃) 7.84 (1H, s br, NH), 7.20 (1H, dt, *J* 6.5, 16 Hz, EtCH=CH), 6.82 (1H, dt, *J* 1.5, 16 Hz, CH=CHCO), 3.78 (3H, s, OCH₃), 2.30 (2H, m, CH₂), 1.08 (3H, t, *J* 7.5 Hz, CH₃); δ_C (100 MHz, CDCl₃) 166.2 (C=O), 152.9 (CH), 152.4 (C=O), 120.3 (CH), 53.0 (CH₃), 25.7 (CH₂), 12.1 (CH₃); *m/z* (EI) 157 (M⁺, 25%), 83 (65), 82 (100), 55 (35).

4b was similarly prepared similarly from **3b** as a white solid (88%). Recrystallised from EtOAc/hexane, or column chromatography (EtOAc/*n*-hexane, 1:1, *R_f* = 0.71); mp 96-97 °C; ν_{max}(KBr)/cm⁻¹ 3268, 1713, 1670, 1603 and 1420; δ_H (400 MHz, CDCl₃) 8.07 (1H, br. s, NH), 7.38 (5H, m, ArH), 7.26 (1H, dq, *J* 15.3 and 7.5, CH₂CH), 6.80 (1H, d, *J* 15.3, COCH), 5.20 (2H, CH₂Ph), 2.28-2.38 (2H, m, CH₃CH₂), 1.10 (3H, t, *J* 7.5, CH₃CH₂); δ_C (100.6 MHz, CDCl₃) 166.0 (C=O), 152.9 (C=O), 151.6 (1C, CH), 135.1 (1C, C), 128.7 (CH), 128.6 (1C, CH), 128.4 (2C, CH), 120.4 (1C, CH), 67.9 (CH₂), 25.7 (1C, CH₂), 12.1 (1C, CH₃); *m/z* (EI) 233 (M⁺, 40%), 179 (30), 152 (32), 132 (45), 127 (65), 91 (100).

Aza-Michael reaction (reaction optimization/catalyst screening): Reaction optimisation was performed in a Radley's 12-placed reaction carousel, equipped with magnetic stirring and temperature control. A reaction tube was charged with the corresponding ligand (1.1 equiv. wrt Pd) and Pd(OTf)₂·2H₂O (9.3 mg, 5 mol%, 0.02 mmol). The reaction tube was placed in the carousel and flushed with a nitrogen atmosphere, before the addition of anhydrous toluene (1 mL). The solution was allowed to stir for an hour at ambient temperature to generate the active catalyst. A solution of

the substrates – **4a** (100 mg, 0.636 mmol) and 4-(trifluoromethyl)aniline (53 μ L, 0.424 mmol) were then added, followed by the addition of toluene, to attain the desired dilution. The temperature was obtained and maintained by adjustment of the thermostat, whereupon the reaction mixture was left for 72 hours. It was then filtered through a short column of silica gel, and evaporation of the solvent furnished a viscous residue, which was analysed by ^1H NMR spectroscopy and chiral HPLC.

Table S1. Reaction optimisation 1: Dilution, reaction temperature and catalyst loading.

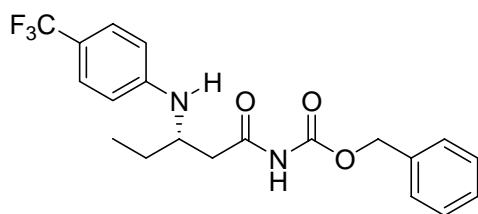
Entry	Ligand	[4a] / M	[Pd] /mol%	Temp/ $^{\circ}\text{C}$	Yield /% ^a	ee/% ^b
1	<i>R</i> -BINAP	0.3	5	rt	57	84
2	<i>R</i> -BINAP	0.2	5	rt	55	85
3	<i>R</i> -BINAP	0.16	5	rt	52	88
4	<i>R</i> -BINAP	0.6	2	rt	25	79
5	<i>R</i> -BINAP	0.4	2	rt	26	81
6	<i>R</i> -BINAP	0.3	2	rt	25	82
7	<i>R</i> -BINAP	0.16	5	50	75	85
8	<i>R</i> -BINAP	0.1	5	50	68	88
9	<i>R</i> -BINAP	0.08	5	50	64	91
10	<i>R</i> -BINAP	0.3	2	50	62	79
11	<i>R</i> -BINAP	0.2	2	50	62	81
12	<i>R</i> -BINAP	0.16	2	50	52	86
13	<i>R</i> -BINAP	0.1	2	50	48	88
14	<i>R</i> -BINAP	0.08	2	50	35	91
15	<i>R</i> -BINAP	0.06	2	50	33	89

Reaction conditions: 2-5 mol% catalyst, 3 days, 1.5 equiv. **4a** : 1 equiv. amine, alkene **4a** (100 mg, 0.63 mmol); ^a Calculated by ^1H NMR; ^b Determined by chiral HPLC, (-)-(*S*)-enantiomer predominates in all cases.

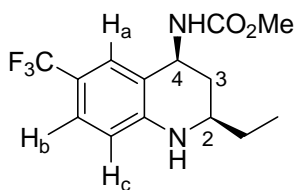
Table S2. Reaction optimisation 2: Solvent and substrate ratio.

Entries	Solvent	Substrate ratio ^a	% yield ^b	%ee ^c
1	Toluene	1.5 : 1	52	85
2	THF	1.5 : 1	14	-
3	DCM	1.5 : 1	30	69
4	MeOH	1.5 : 1	13	-
5	DME	1.5 : 1	17	-
6	Dioxane	1.5 : 1	12	-
7	Toluene	1 : 1	78	85
8	Toluene	1 : 1.5	55	87
9 ^d	Toluene	1 : 1.5	85	88

Reaction conditions: Unless otherwise stated, 5 mol% catalyst, [**4a**] = 0.2 M, RT, 3 days; ^a**4a** : aniline. ^bCalculated by ^1H NMR; ^cDetermined by chiral HPLC. (-)-(*S*)-Enantiomer predominates in all cases. ^dAt 50 $^{\circ}\text{C}$, with 0.08 M substrate.

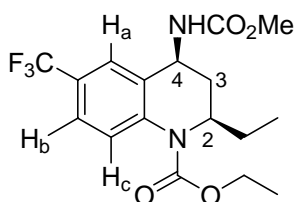


(S)-N-[3-(4-trifluoromethyl-phenylamino)-pentanoyl]benzyl carbamate, 2b. Obtained using (*R*)-BINAP as the chiral phosphine. White solid, 79% yield. $R_f = 0.23$ (Et₂O/*n*-pentane, 1:2); mp 99-100 °C (lit.² 100.6-101.4 °C). $[\alpha]_D^{25} -18.5^\circ$ ($c = 0.01$ g/mL in CHCl₃, 86% ee); Daicel Chiralpak AD, 10% IPA in *n*-hexane, flow rate: 1.0 mL/min, $t_R = 21.9$ (*R*-isomer) and 24.8 (*S*-isomer) min; $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3367, 3215, 1727, 1677, 1601, 1456, 819 and 704; δ_H (400 MHz, CDCl₃) 7.89 (1H, br. s, CONH), 7.39 (7H, m, ArH), 6.59 (2H, d, J 8.4, ArH), 5.19 (2H, s, CH₂Ph), 4.24 (1H, br. s, ArNH), 3.91-3.94 (1H, m, CH), 3.77 (3H, s, OCH₃), 3.12 (1H, dd, J 15.9 and 6.9 Hz, CH₂CO), 3.00 (1H, dd, J 15.9 and 5.4 Hz, CH₂CO), 1.62-1.75 (2H, m, CH₃CH₂), 0.99 (3H, t, J 6.9 Hz, CH₃CH₂); δ_C (100.6 MHz, CDCl₃) 173.0 (C=O), 151.8 (C=O), 149.9 (C), 134.8 (C), 129.0 (CH), 128.8 (CH), 128.4 (CH), 126.7 (CH), 125.0 (q, J 270 Hz, CF₃), 118.6 (1C, q, J 33 Hz, CH), 111.2 (CH), 68.1 (CH₂), 51.3 (CH), 40.0 (CH₂), 27.9 (CH₂), 10.5 (CH₃); m/z (EI) 394 (M^+ , 30%), 365 (22), 257 (18), 214 (25), 202 (75), 172 (29), 91 (100).



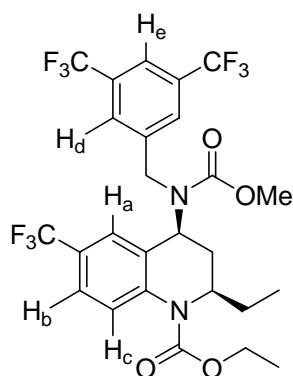
(2*R*,4*S*)-(2-Ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamic acid methyl ester, 5. The acyclic precursor (*R*)-**5** (190 mg, 0.60 mmol) was dissolved in 95% aq. EtOH (5 mL) with stirring. Sodium borohydride (17 mg, 0.45 mmol) was then added in one portion. At the cessation of effervescence, the solution was cooled to -10 °C, and a solution of MgCl₂·6H₂O (135 mg, 0.66 mmol) in water (0.5 mL) was added dropwise via syringe. The mixture was then warmed to 0 °C, and stirring was continued for 2 h. The reaction was quenched by the addition of CH₂Cl₂ (5 mL) and dilute HCl (1M, 5 mL) at 0 °C. The layers were separated at room temperature, and the aqueous layer was extracted with further portions of CH₂Cl₂ (2 x 5 mL). The combined organic extracts were washed with H₂O (5 mL), brine (10 mL) and dried over Na₂SO₄. Evaporation of the solvent yielded the cyclic product **5** as a white solid, which was dried under vacuum at 50 °C overnight (166 mg, 92%). The compound was of sufficient purity to be employed in the next step without further purification. For analytical purposes, a small sample was purified by column chromatography on flash silica gel (30% ethyl acetate in hexane). m.p. 124-125.5 °C (lit.² 139.0-140.5 °C, recryst. from CH₂Cl₂-hexane). δ_H (500 MHz, CDCl₃) 7.39 (1H, s, H_a), 7.24 (1H, d, J 8.2

Hz, H_b), 6.49 (1H, d, *J* 8.2 Hz, H_c), 5.02 (1H, td, *J* 6.0, 9.6 Hz, H₄), 4.81 (1H, d, *J* 9.6 Hz, NH), 4.10 (1H, br. s, NH), 3.77 (3H, s, OCH₃), 3.47-3.40 (1H, m, H₂), 2.34 (1H, ddd, *J* 2.4, 6.0, 12.3 Hz, H₃), 1.42-1.53 (3H, m, H₃' and CH₂CH₃), 1.01 (3H, t, *J* 7.5 Hz, CH₂CH₃). δ_C (100.6 MHz, CDCl₃) 157.0 (C=O), 147.4 (C), 125.5 (q, *J* 3 Hz, CH), 123.8 (q, *J* 3 Hz, CH), 124.8 (q, *J* 270 Hz, CF₃), 113.4 (CH), 52.3 (CH), 52.2 (OMe), 47.9 (CH), 35.2 (CH₂), 29.0 (CH₂), 9.6 (CH₃); *m/z* (ESI+) 303.1310 (MH⁺), C₁₄H₁₈N₂O₂F₃ requires 303.1320.



(2*R*,4*S*)-2-Ethyl-4-methoxycarbonylamino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-

carboxylic acid ethyl ester, 6. A 3-necked round-bottom flask equipped with a nitrogen inlet and a condenser was charged with a magnetic stirrer bar, the tetrahydroquinoline **7** (110 mg, 0.36 mmol), anhydrous pyridine (150 μL, 1.95 mmol.) and dry CH₂Cl₂ (5 mL). The mixture was cooled to 0 °C, before the addition of ethyl chloroformate (180 μL, 1.80 mmol), causing the the development of a red colour solution. Stirring was continued at 0 °C for 30 min, then at room temperature for a further 2 h, during which the colour of the solution slowly discharged to light yellow. Excess chloroformate was destroyed by the addition of 1M aq. NaOH (2 mL) at 0 °C. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (5 mL). The organic extracts were washed with dilute HCl (1M, 3 mL) and brine, dried over Na₂SO₄, and evaporated to dryness. Trituration of the residue furnished the required product as a white solid (111 mg, 82%). m.p. 153-155 °C (lit.² 157.3-157.6 °C). δ_H (500 MHz, CDCl₃, 55 °C) 7.58 (1H, d, *J* 8.0 Hz, H_b), 7.49 (1H, d, *J* 8.0 Hz, H_c), 7.49 (1H, s, H_a), 4.88 (1H, br. d, *J* 9.0 Hz, NH), 4.80 (1H, ddd, *J* 5.0, 9.0, 10.0 Hz, H₄), 4.48 (1H, m, H₂), 4.17-4.29 (2H, m, OCH₂CH₃), 2.54 (1H, ddd, *J* 5.0, 8.0, 13.0 Hz, H₃), 1.61-1.66 (1H, m, CH₂CH₃), 1.49-1.57 (1H, m, H₃'), 1.43-1.49 (1H, m, CH₂CH₃), 1.30 (3H, t, *J* 7.5 Hz, OCH₂CH₃), 0.86 (3H, t, *J* 7.5 Hz, CH₂CH₃). δ_C (125.7 MHz, CDCl₃) 156.4 (C=O), 154.4 (C=O), 139.4 (C), 134.12 (C), 126.26 (q, *J* 33 Hz, C), 126.2 (CH), 124.3 (q, *J* 4 Hz, CH), 124.0 (q, *J* 272 Hz, CF₃), 120.7 (q, *J* 4 Hz, CH), 62.2 (CH₂O), 53.4 (OMe), 52.6 (CH), 46.7 (CH), 37.9 (CH₂), 28.2 (CH₂), 14.4 (CH₃), 9.8 (CH₃); *m/z* (CI+) 392 (MNH₄⁺, 100%), *m/z* (ESI+) 397.1356 (MNa⁺), C₁₇H₂₁N₂O₄F₃Na requires 397.1351.



(2*R*,4*S*)-4-[(3,5-*Bis*(trifluoromethyl)benzyl)methoxycarbonylamino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid ethyl ester, **1** (**Torcetrapib**). A 2-neck round bottom flask was charged with a magnetic stirrer bar, compound **7** (108 mg, 0.29 mmol.) and potassium *tert*-butoxide (35 mg, 0.31 mmol.) under an N₂ atmosphere. Dry CH₂Cl₂ (1.5 mL) was added, and the solution was stirred at room temperature for 5 min to generate a yellow solution, before the addition of 3,5-*bis*(trifluoromethyl)benzyl bromide (54 μL, 0.29 mmol.). Stirring was continued for 4 h, whereupon a suspension was formed. CH₂Cl₂ (10 mL) and water (5 mL) were added, and the layers were separated. The aqueous layer was further extracted with CH₂Cl₂ (2 x 5 mL) and the combined organic extract was dried (MgSO₄) and evaporated. The product was initially obtained as a sticky residue after column chromatography, which turned into a foamy white solid after it was triturated with *n*-hexane and dried under vacuum (90 mg, 52%), *R*_f = 0.44 (EtOAc/hexane, 1: 4). m.p. 54-56 °C [lit. (monoethanolate):¹ mp 54-58 °C]. δ_H (500 MHz, CDCl₃, 55 °C) 7.80 (1H, s, H_e), 7.74 (2H, s, H_d), 7.59 (1H, d, *J* 8.0 Hz, H_b), 7.52 (1H, d, *J* 8.0 Hz, H_c), 7.14 (1H, s, H_a), 4.8-5.2 (2H, br., CH₂N and H₄), 4.32-4.38 (1H, m, H₂), 4.17-4.30 (3H, m, CH₂O and CH₂N), 3.81 (3H, br. s, OMe), 2.27 (1H, br. s, H₃), 1.63-1.72 (1H, m, CH₂CH₃), 1.40-1.49 (2H, m H₃' and CH₂CH₃), 1.30 (3H, t, *J* 7.5 Hz, CH₃CH₂O), 0.75 (3H, br. t, *J* 7.2 Hz, CH₃CH₂); δ_C (125.7 MHz, CDCl₃, 55 °C) 157.3 (br. s, C=O), 154.4 (C=O), 141.6 (br. s, C), 133.5 (br. s, C), 132.3 (q, *J* 34 Hz, C), 127.3 (CH, CH_d), 126.9 (CH, CH_b), 126.7 (br. q, *J* 33 Hz, C), 124.4 (CH, CH_c), 124.1 (q, *J* 273 Hz, CF₃), 123.2 (q, *J* 273 Hz, CF₃), 121.5 (CH, CH_e), 119.6 (CH, CH_a), 62.3 (CH₂O), 54.4 (CH, C₂), 53.5 (br. s, OMe), 47.0 (br. s, CH, C₄), 36.8 (br. s, CH₂, C₃), 29.1 (CH₃CH₂), 14.3 (OCH₂CH₃), 9.3 (CH₃CH₂). δ_F (376.5 MHz, CDCl₃, 55 °C) -61.3 (1F), -62.1 (2F). *m/z* (CI⁺) 618 (MNH₄⁺), *m/z* (ESI⁺) 601.1758 (MH⁺), C₂₆H₂₆N₂O₄F₉ requires 601.1749.

References

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2. Damon, D. B.; Dugger, R. W.; Hubbs, S. E.; Scott, J. M.; Scott, R. W. *Org. Process Res. & Dev.*

2006, *10*, 472-480.

Fig. S1. ^1H NMR spectrum of methyl carbamate phosphonate ester **3a**

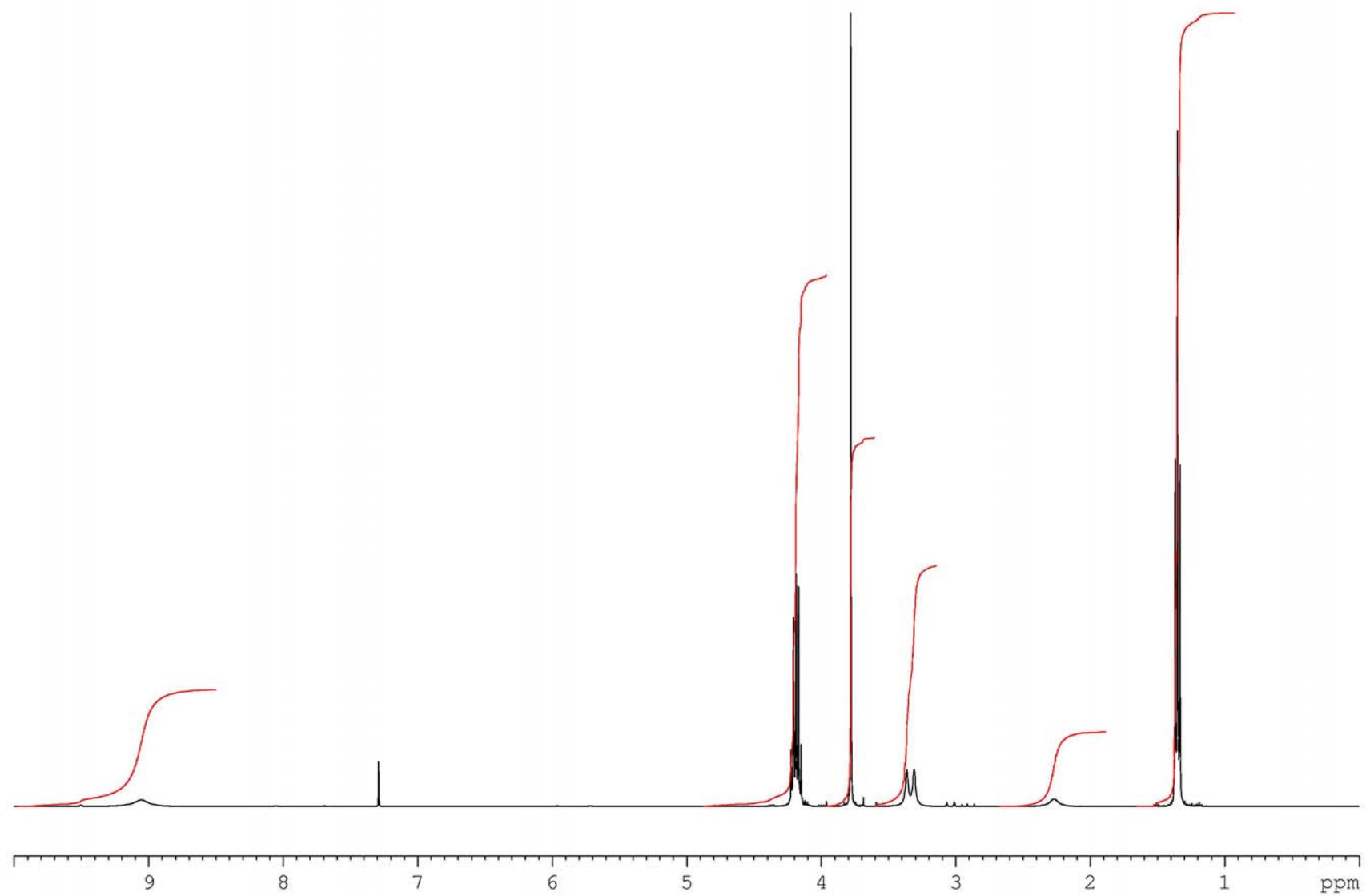


Fig. S2. ^{13}C NMR spectrum of methyl carbamate phosphonate ester **3a**

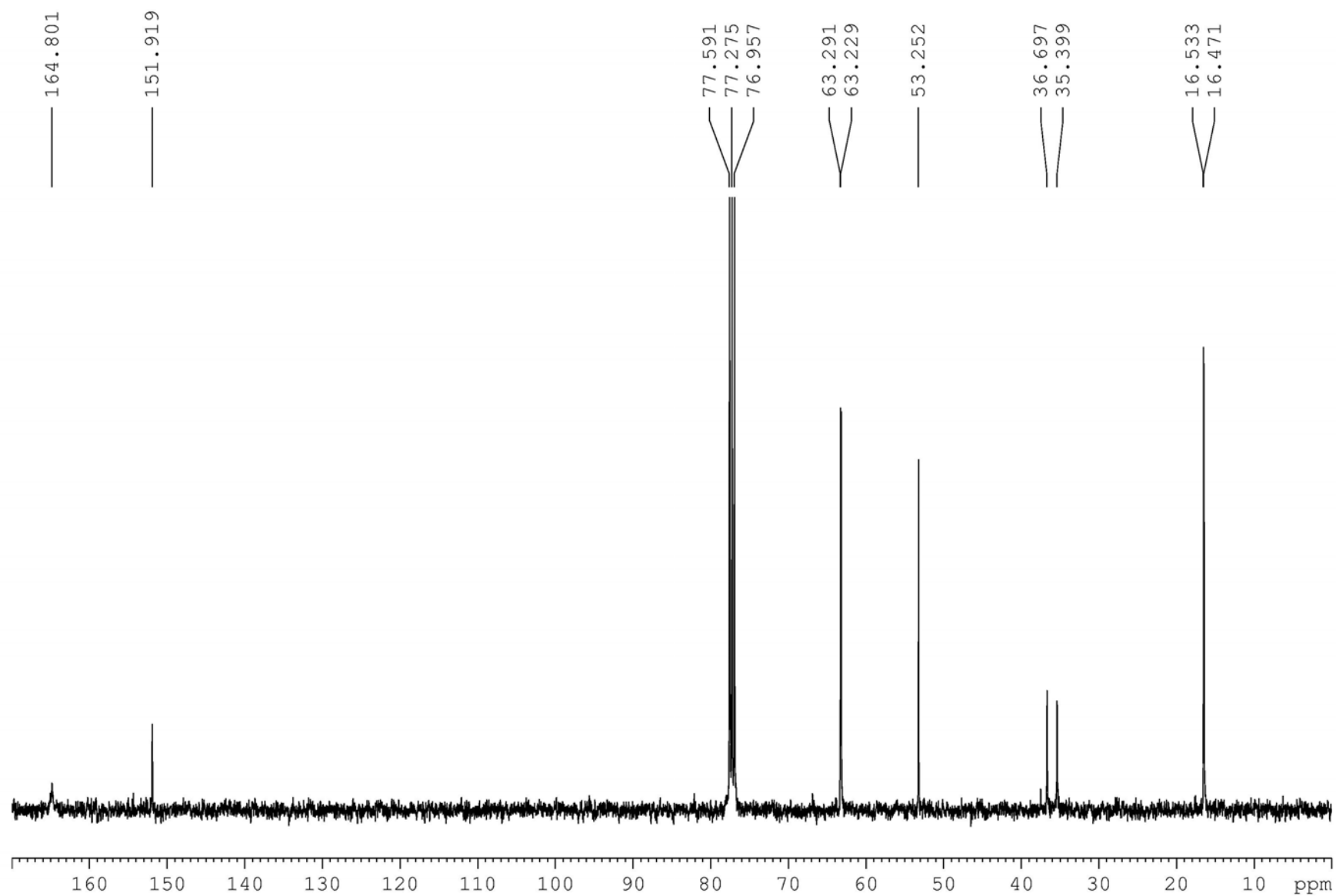


Fig. S3. ^1H NMR spectrum of benzyl carbamate phosphonate ester **3b**

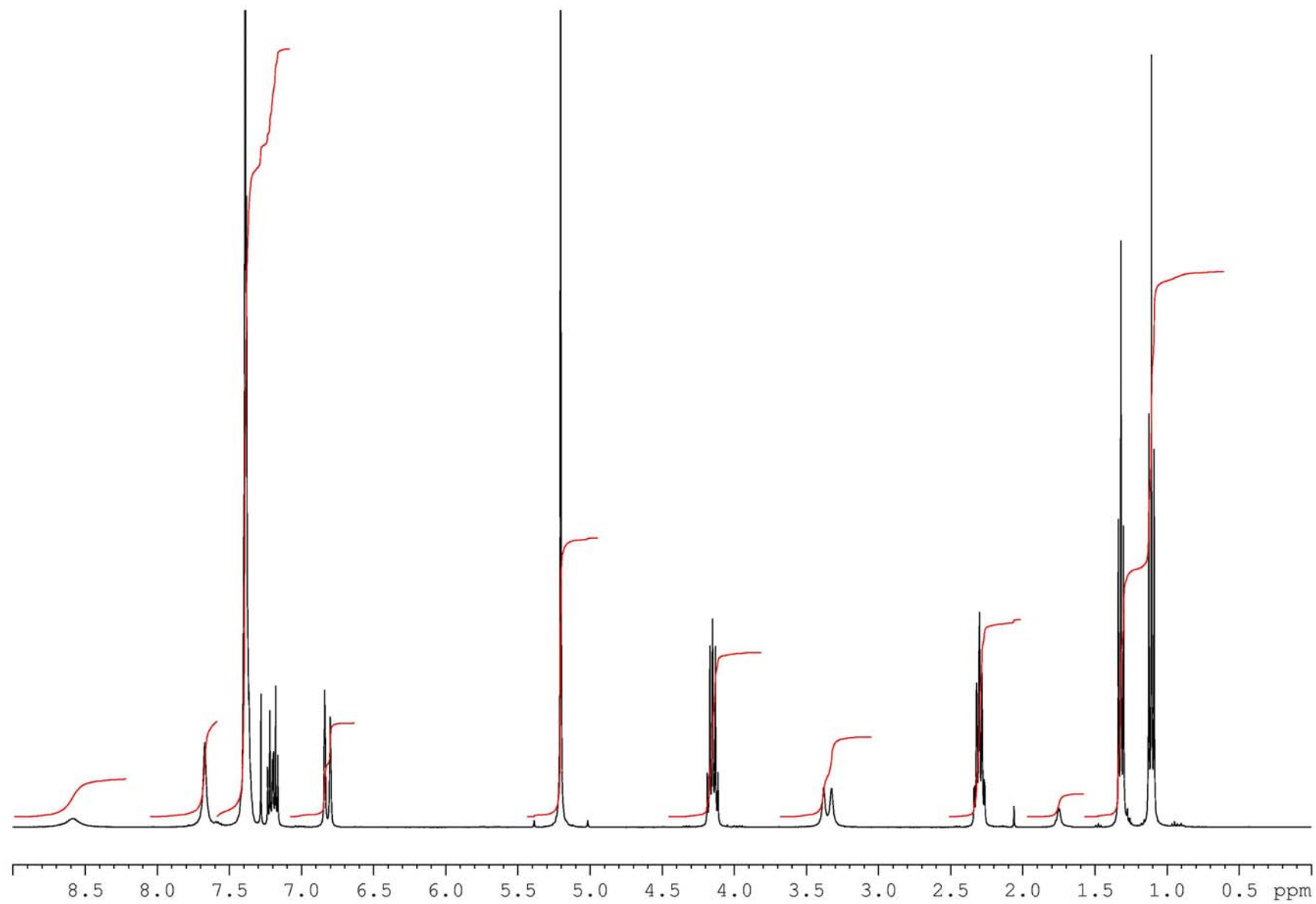


Fig. S4. ^{13}C NMR spectrum of benzyl carbamate phosphonate ester **3b**

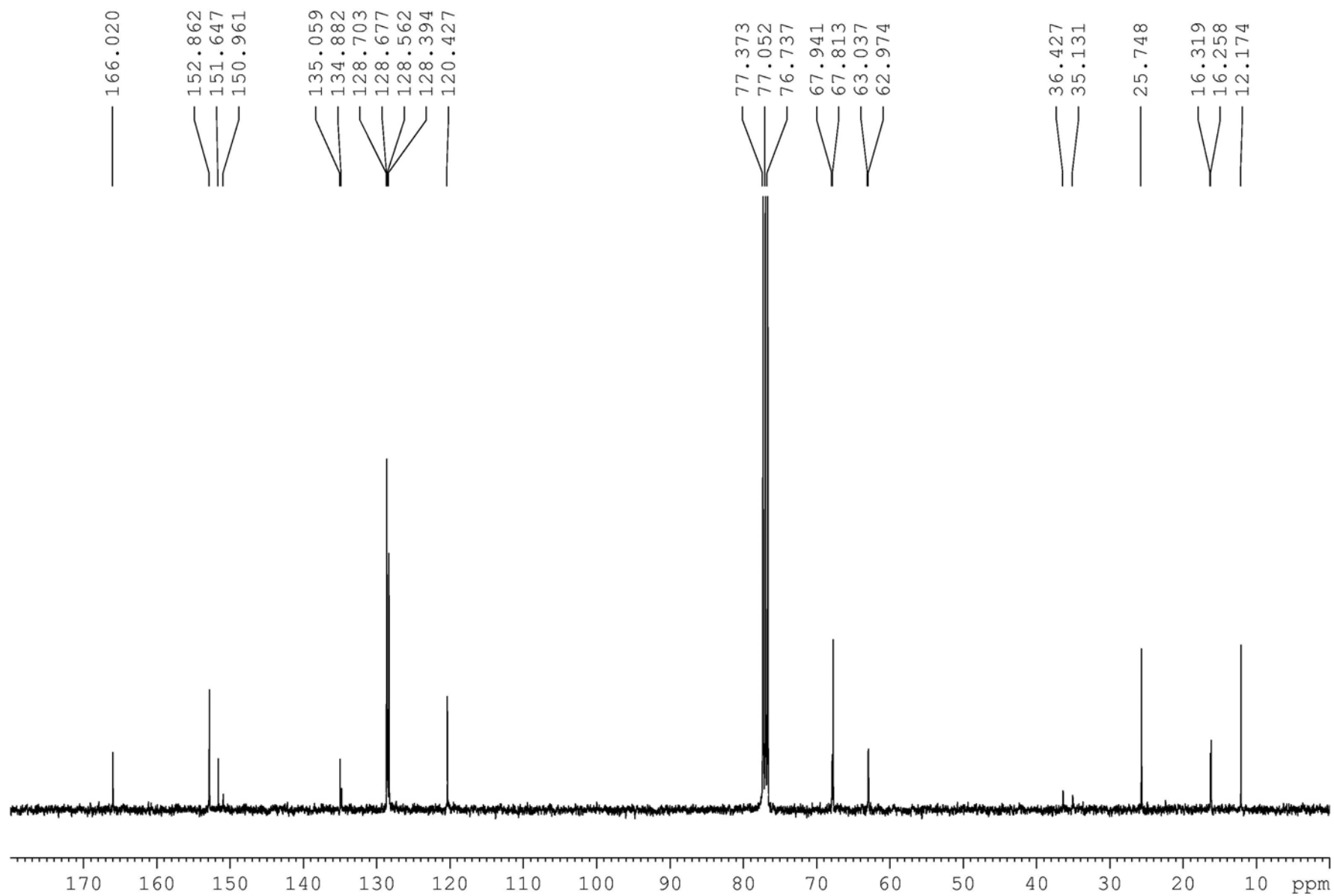


Fig. S5. ^1H NMR spectrum of *N*-(Pent-2-enoyl)methyl carbamate, **4a**

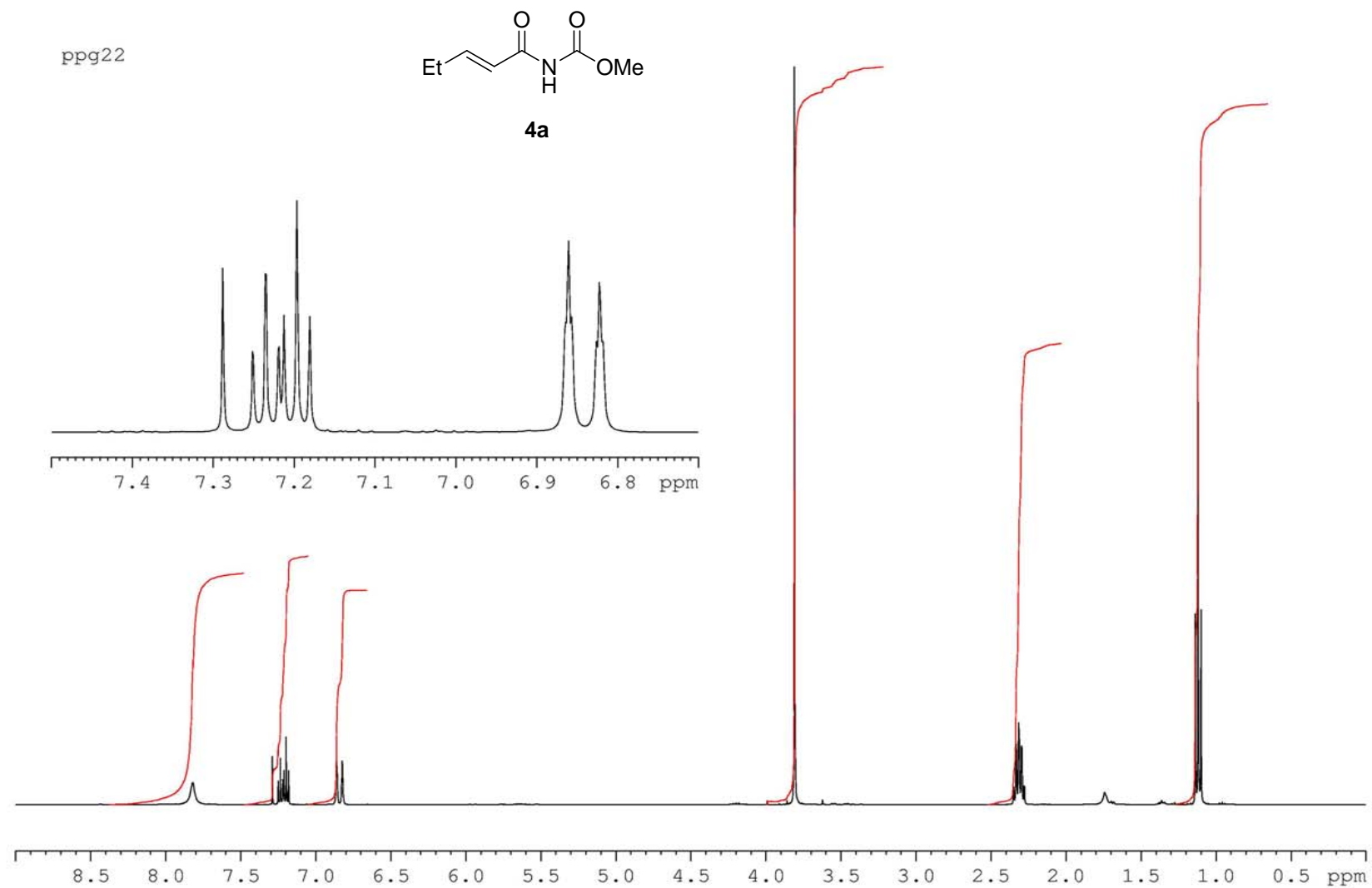


Fig. S6. ^{13}C NMR spectrum of *N*-(Pent-2-enoyl)methyl carbamate, 4a

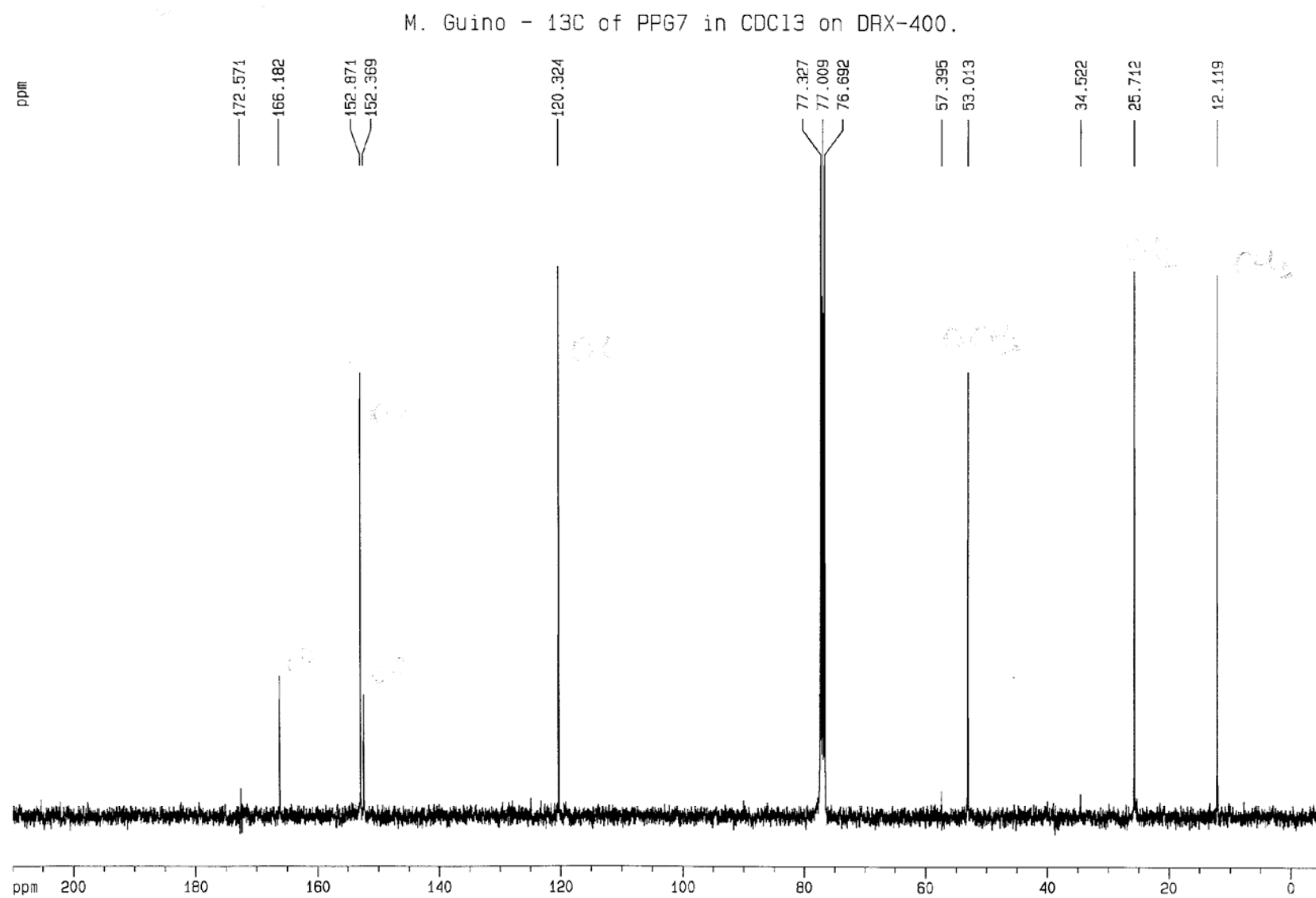


Fig. S7. ^1H NMR spectrum of *N*-(Pent-2-enoyl)benzyl carbamate, **4b**

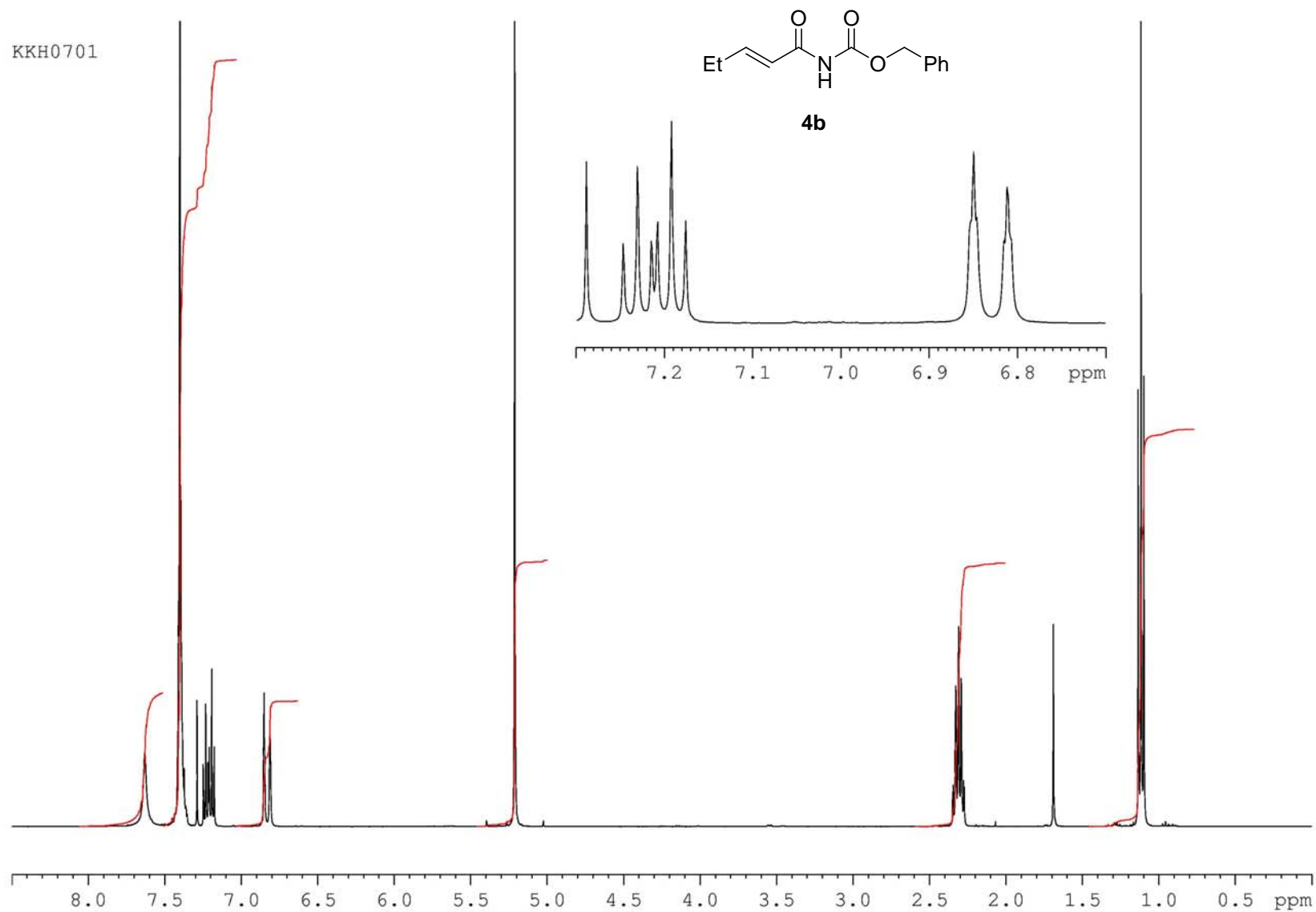


Fig. S8. ^{13}C NMR spectrum of *N*-(Pent-2-enoyl)benzyl carbamate, 4b

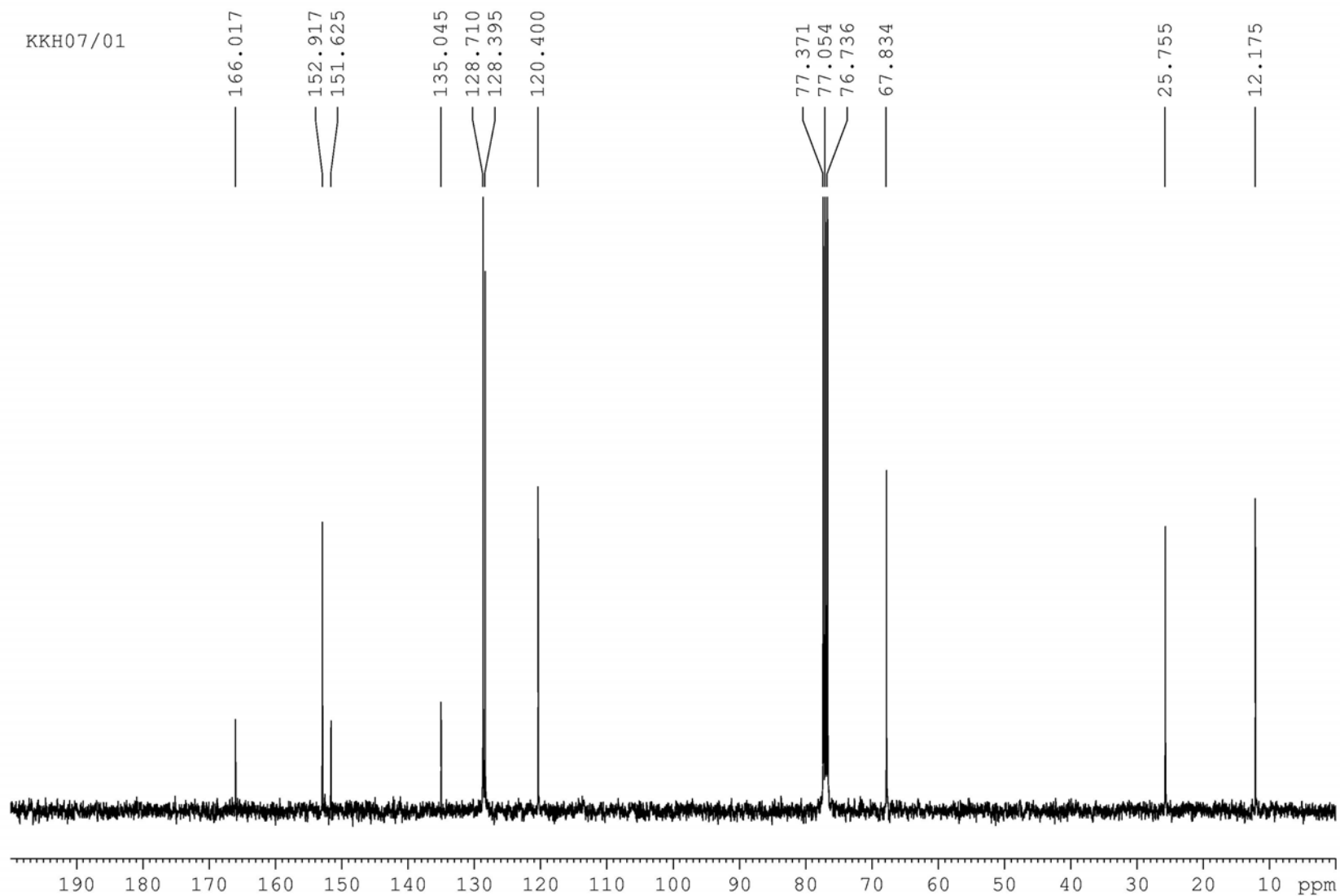


Fig. S9. ^1H NMR spectrum of *N*-[3-(4-trifluoromethyl-phenylamino)-pentanoyl]methyl carbamate, **2a**

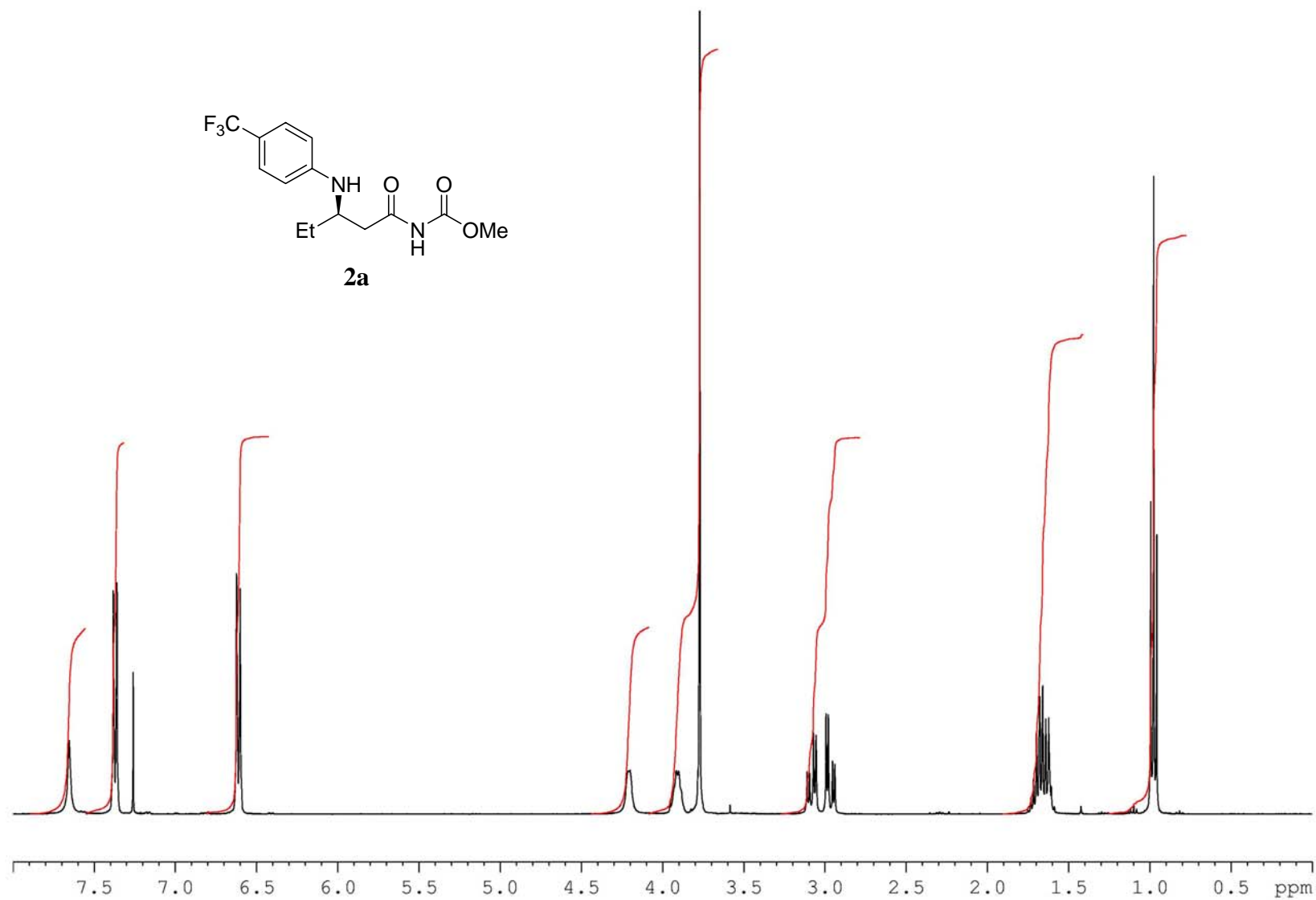


Fig. S10. ^{13}C NMR spectrum of *N*-[3-(4-trifluoromethyl-phenylamino)-pentanoyl]methyl carbamate, **2a**

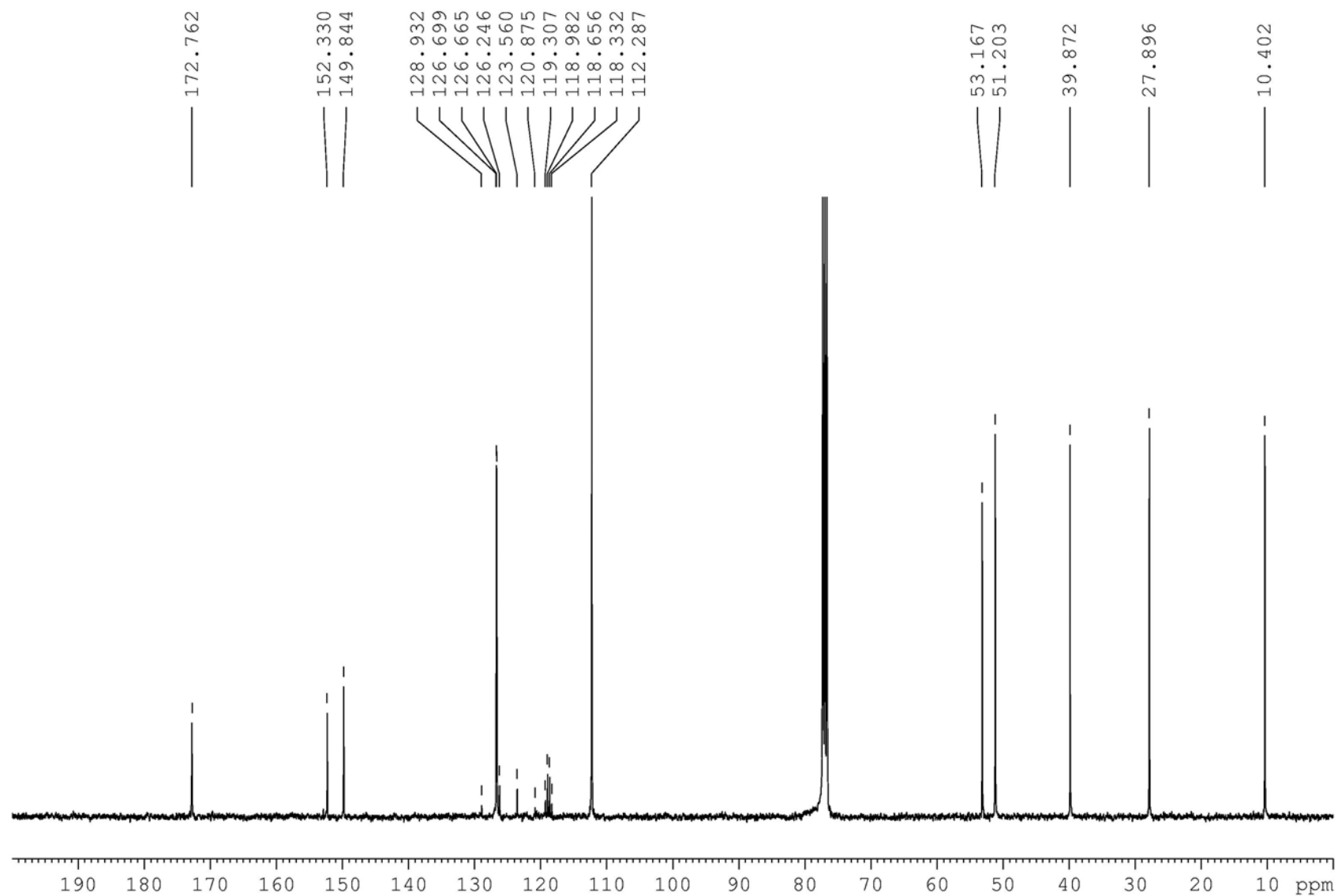


Fig. S11. ^1H NMR spectrum of *N*-[3-(4-trifluoromethyl-phenylamino)-pentanoyl]benzyl carbamate, **2b**

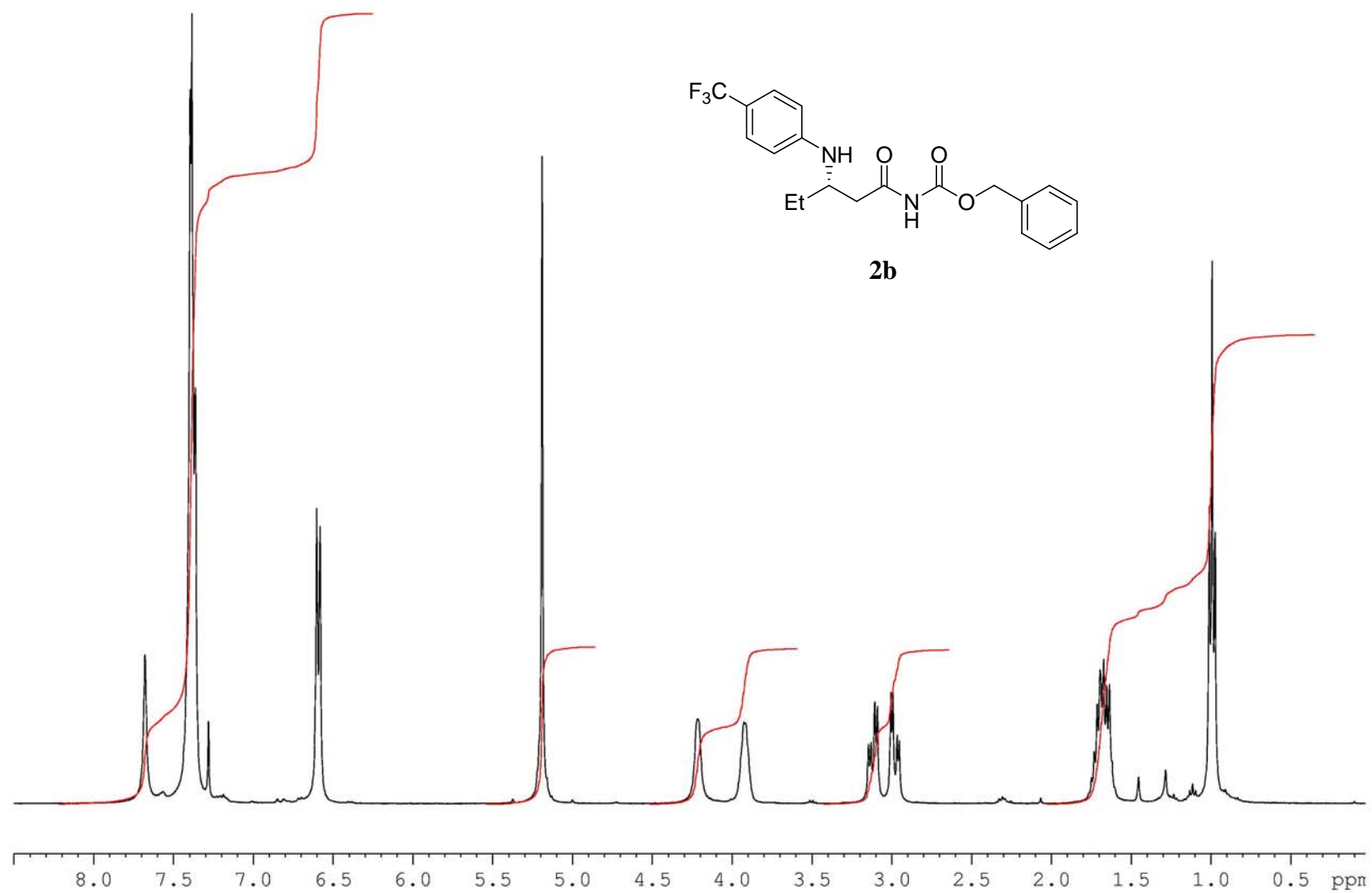


Fig. S12. ^{13}C NMR spectrum of *N*-[3-(4-trifluoromethyl-phenylamino)-pentanoyl]benzyl carbamate, 2b

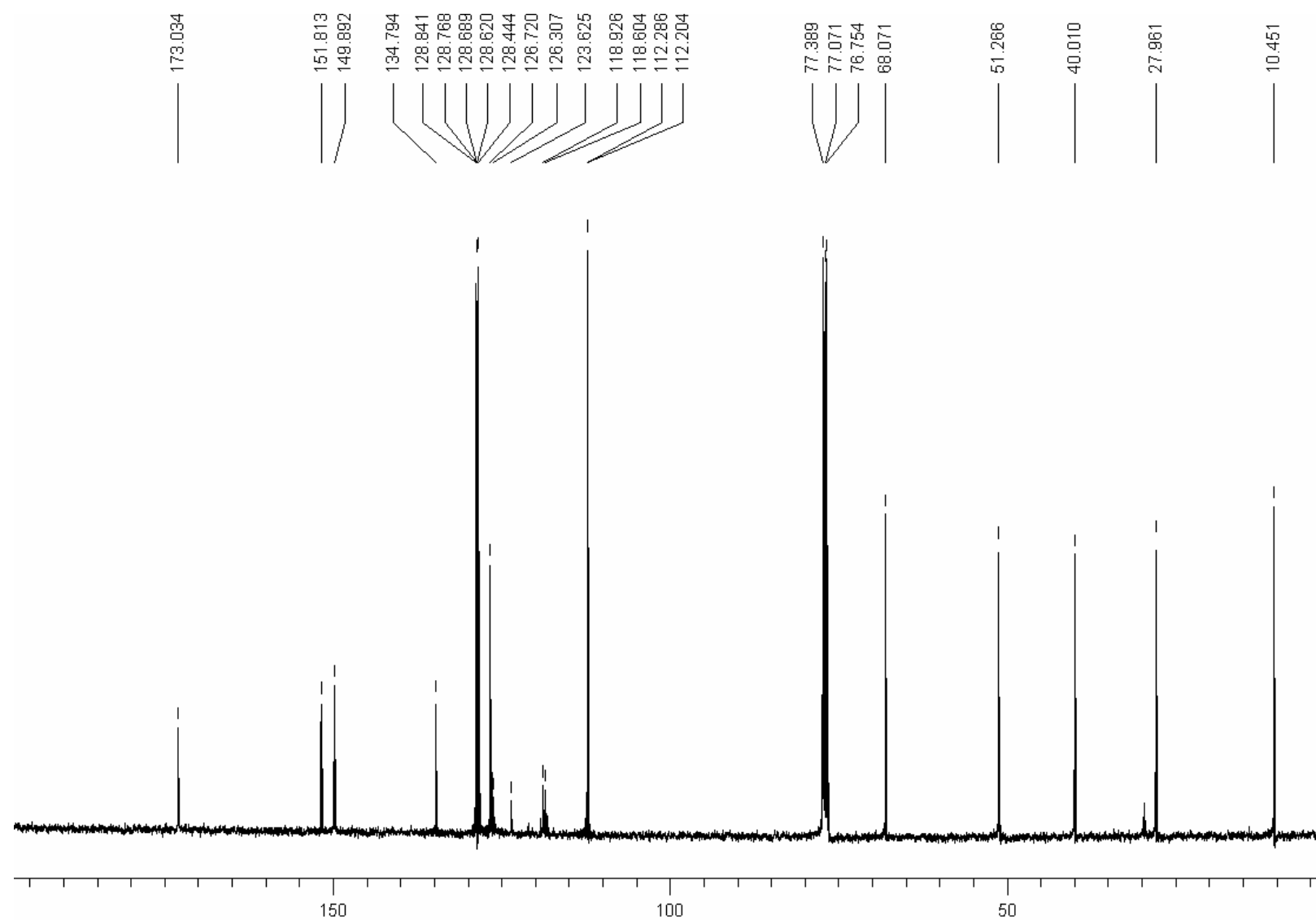


Fig. S13. HPLC chromatograph of *rac*-*N*-[3-(4-trifluoromethyl-phenylamino)-pentanoyl]benzyl carbamate, *rac*-2b

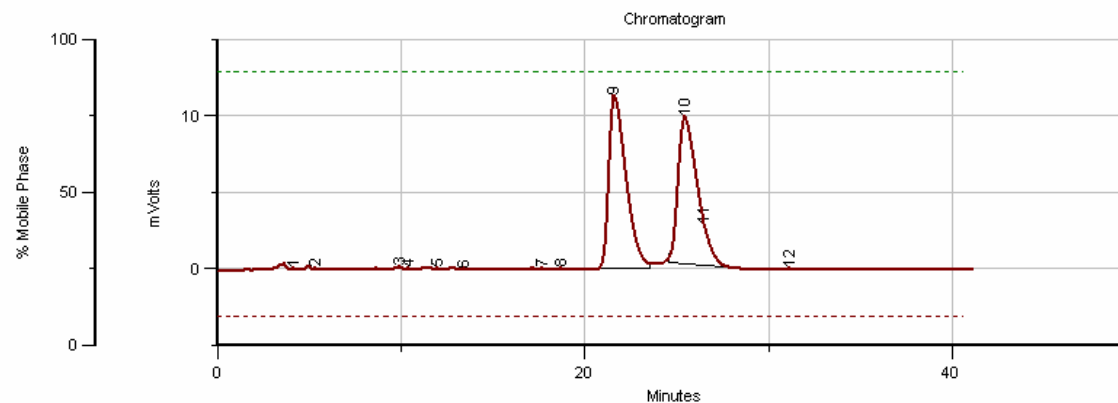


Fig. S14. HPLC chromatograph of (*S*)-*N*-[3-(4-trifluoromethyl-phenylamino)-pentanoyl]benzyl carbamate, *N*-[3-(4-trifluoromethyl-phenylamino)-pentanoyl]benzyl carbamate, (*S*)-2b (89% ee).

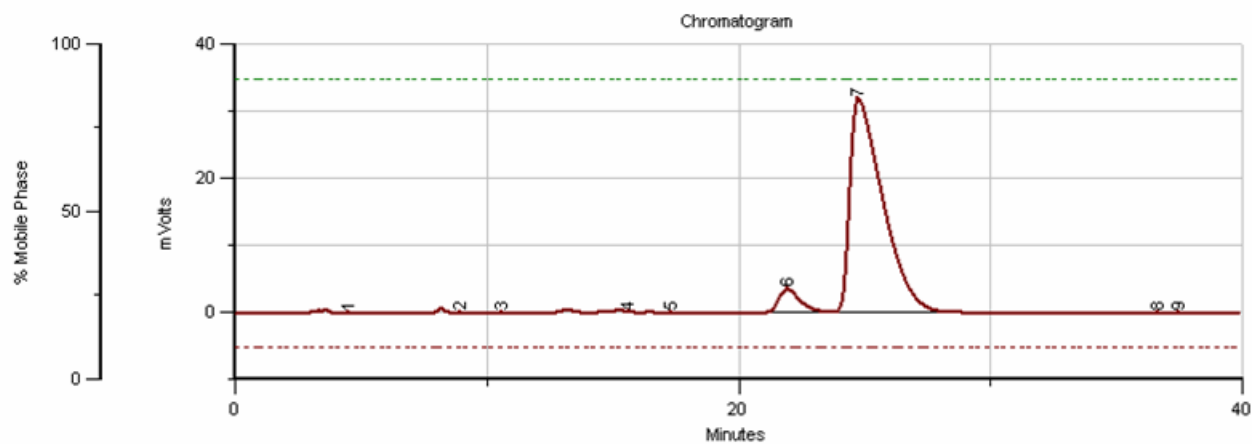


Fig. S15. ^1H NMR spectrum of (2*R*,4*S*)-(2-Ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamic acid methyl ester, **5**.

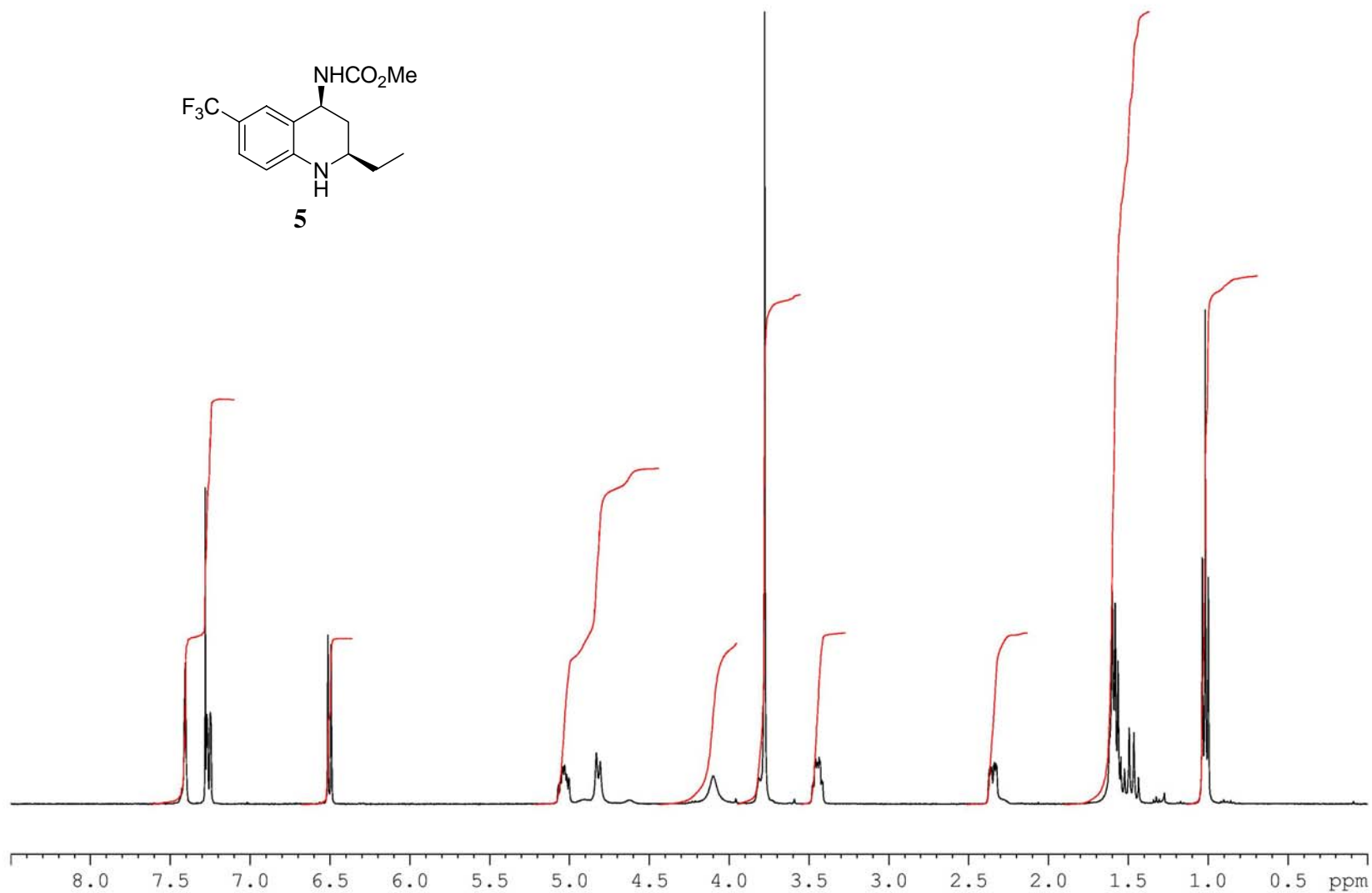


Fig. S16. ^{13}C NMR spectrum of (2*R*,4*S*)-(2-Ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroquinolin-4-yl)carbamic acid methyl ester, **5**.

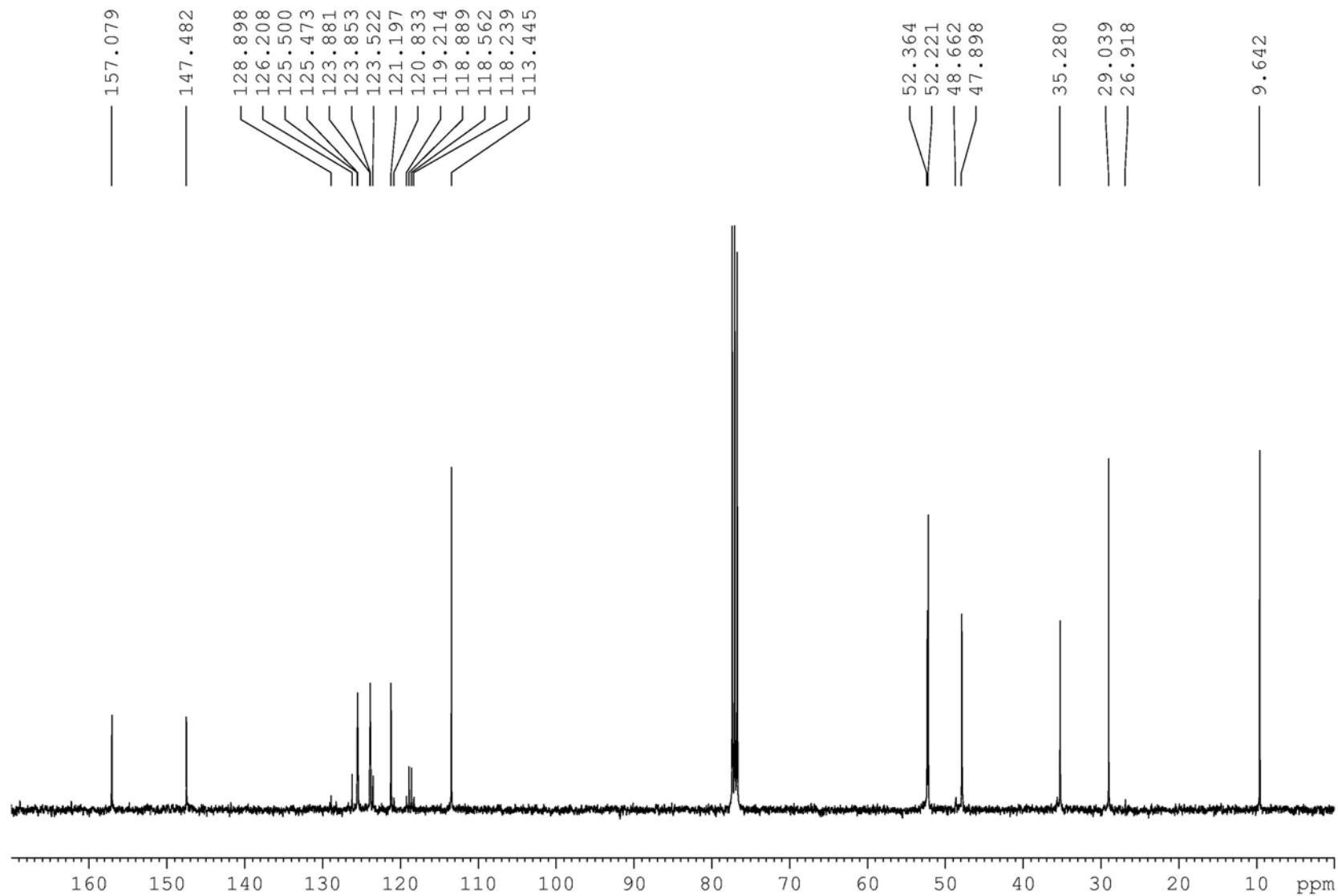
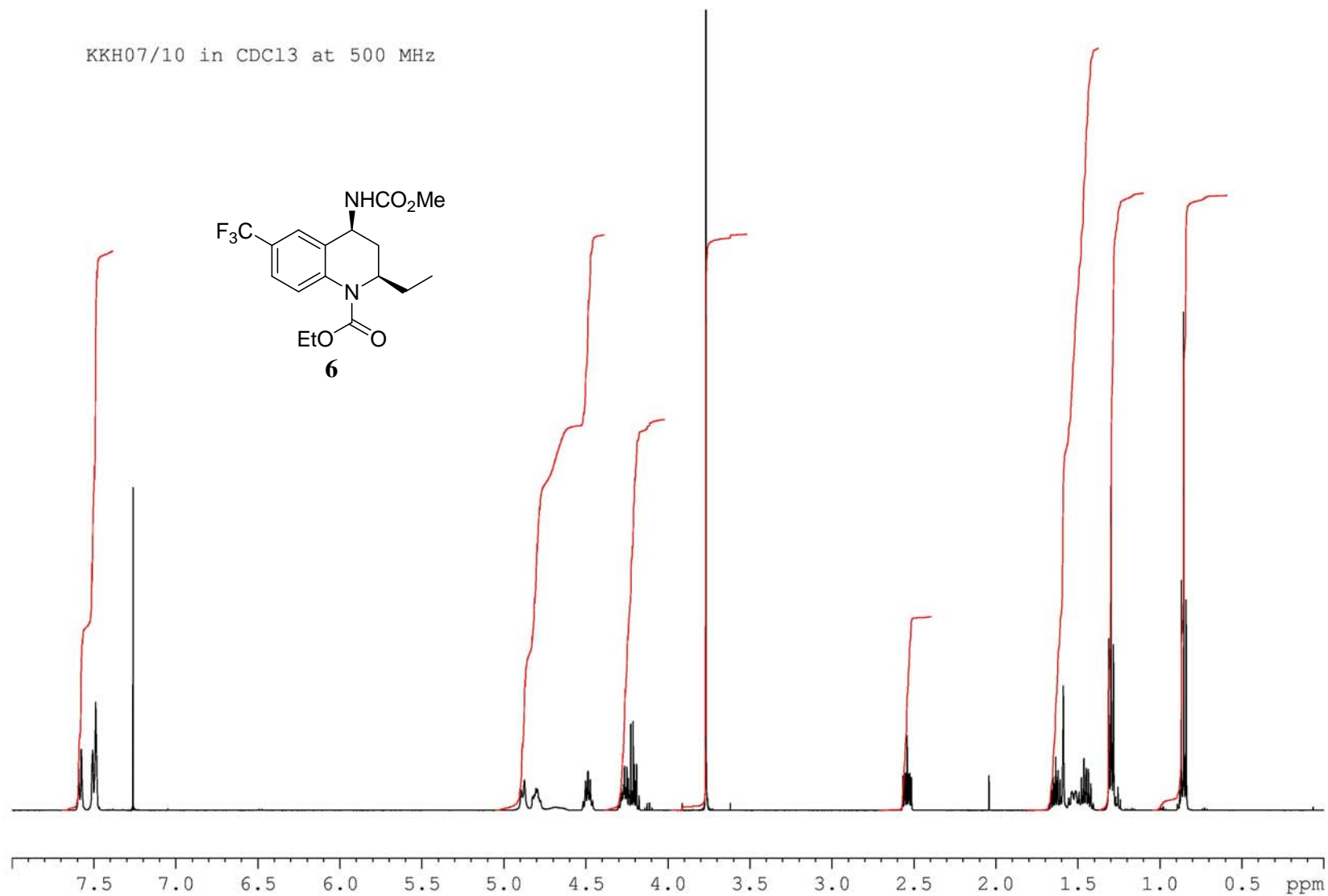


Fig. S17. ^1H NMR spectrum of (2*R*,4*S*)-2-Ethyl-4-methoxycarbonylamino-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic Acid Ethyl Ester, **6**.



S18. ^{13}C NMR spectrum of (2*R*,4*S*)-2-Ethyl-4-methoxycarbonylamino-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, **6**.

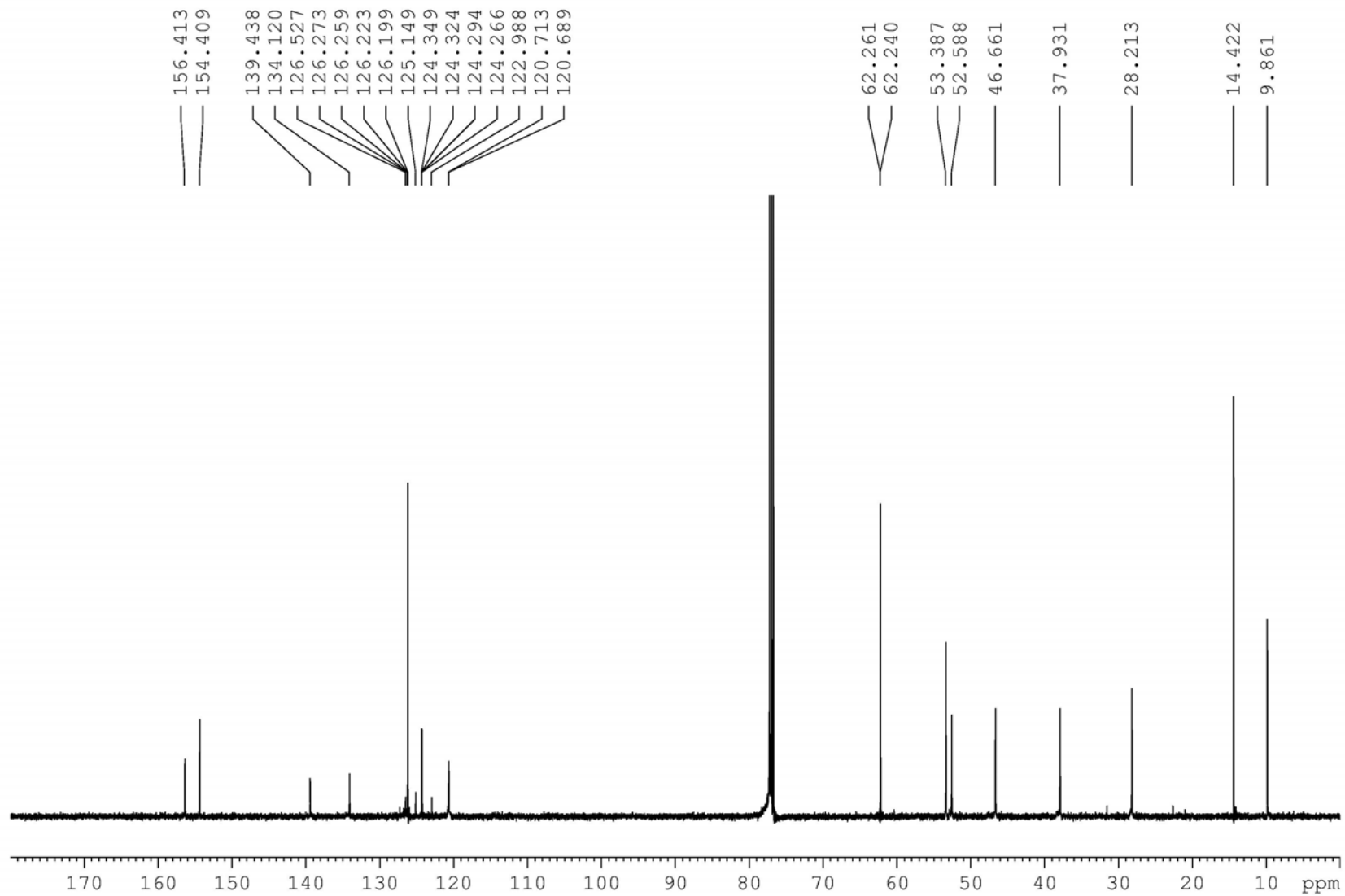


Fig. S19. ^1H NMR spectrum of Torcetrapib, **1** (at 55 °C).

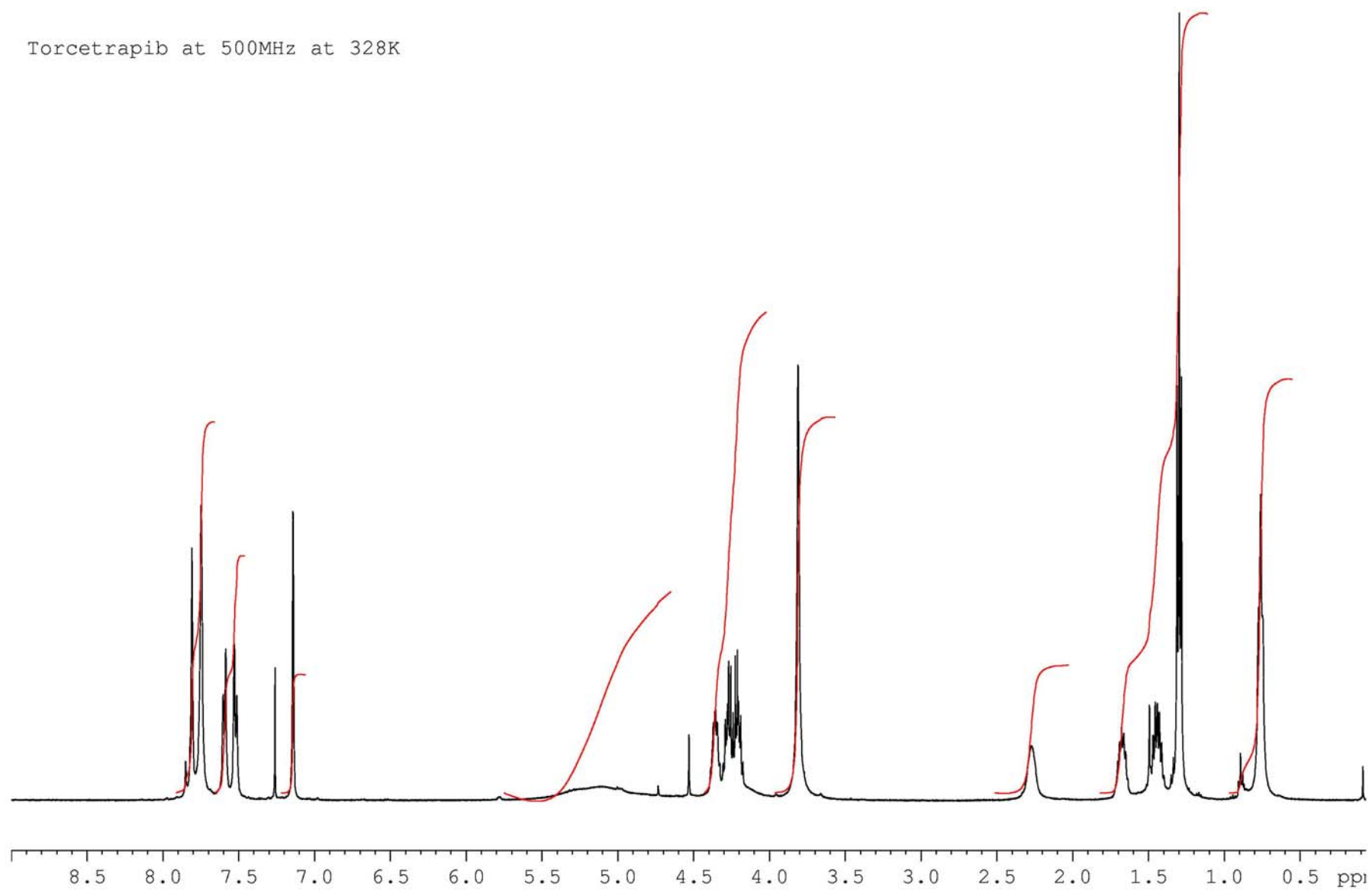


Fig. S20. ^{13}C NMR spectrum of Torcetrapib, **1** (at 55 $^{\circ}\text{C}$).

