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Supplementary Information for:

Non-Kolbe electrolysis of *N*-protected-α-amino acids: A standardized method for the synthesis of *N*-protected (1-methoxyalkyl)amines

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Comparison of the yields for both (previous and current) experimental procedures

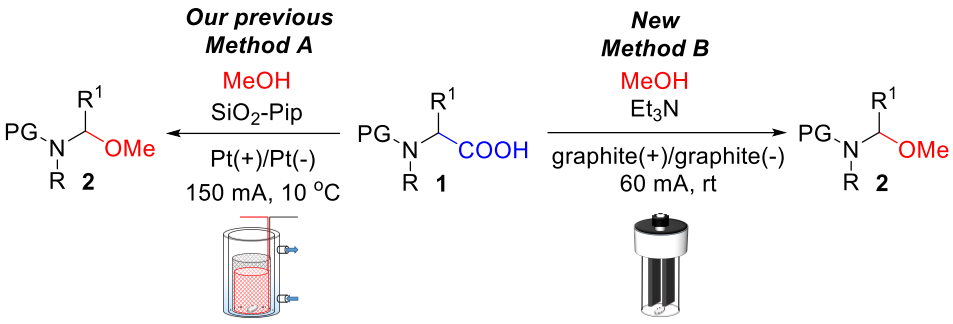


Table S1 Decarboxylative α-methoxylation of *N*-protected α-amino acids **1** to *N*-protected (1-methoxyalkyl)amines **2**

Entry	*N*-protected α-amino acid **1**	Product 2	Method A[a]	Mathod B[b]
			Yield[c] [%][1,2]	Yield[c] [%]
1	*N*-Piv-D,L-Ala-OH	**2a**	94	95
2	*N*-Cbz-L-Ala-OH	**2b**	94	99
3	*N*-Ac-Gly-OH	**2d**	96	99
4	*N*-Cbz-L-Phe-OH	**2e**	94	99
5	*N*-Boc-L-Phe-OH	**2f**	91	98
6	*N*-Cbz-L-Val-OH	**2g**	97	99
7	*N*-Cbz-D,L-Leu-OH	**2h**	91	97
8	*N*-Cbz-D,L-Nval-OH	**2i**	95	99
9	*N*-Cbz-D,L-Nleu-OH	**2j**	92	99
10	*N*-Cbz-L-Chg-OH	**2k**	91	98
11	*N*-Cbz-Phg-OH	**2l**	98	99
12	*N*-Cbz-L-Tyr(*O*-Bn)-OH	**2m**	80	98
13	*N*-Cbz-L-Ser(*O*-*t*-Bu)-OH	**2n**	94	98
14	*N*-Cbz-L-Asn-OH	**2p**	93	99
15	*N*-Cbz-L-Gln-OH	**2r**	95	94
16	*N*-Cbz-L-Asp(*O*-*t*-Bu)-OH	**2s**	79	92
17	*N*-Cbz-L-Glu(*O*-*t*-Bu)-OH	**2t**	88	97
18	*N*-Cbz-L-Pro-OH	**2u**	93	99
19	*N*-Cbz-D,L-Met-OH	**2w**	–[d]	–[d]
20	*N*-Boc-L-Cys(*S*-Bn)-OH	**2x**	–[d]	–[d]
21	*N*-Ac-D,L-Trp-OH	**2y**	–[d]	–[d]

[a] Conditions: Substrate **1** (3 mmol), SiO_2-Pip (200 mg, 0.22 mmol), MeOH (10 mL), at 10 °C, constant current (150 mA), and charge 3.0-3.75 F/mol. Alkoxylations were conducted in an undivided cylindrical glass electrolyzer with a thermostatic jacket, equipped with a magnetic stirrer, and using a DC power supply. A cylindrical mesh anode (Pt) and cathode (Pt) were arranged concentrically 2.5 ± 0.5 mm from each other.

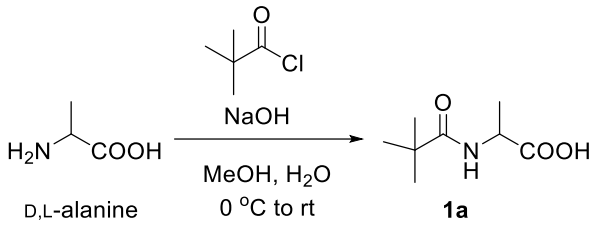
[b] Conditions: Substrate **1** (0.4 mmol), Et_3N (4.2 µL, 0.03 mmol), MeOH (4 mL) in a 5 mL vial, at room temperature, constant current (60 mA), graphite SK-50 electrodes (anode and cathode), and charge 2.1 F/mol. Methoxylations were carried out using commercially available, compact setup –IKA®ElectraSyn 2.0

[c] Isolated yield. [d] A complex reaction mixture.

[1] R. Mazurkiewicz, J. Adamek, A. Październiok-Holewa, K. Zielińska, W. Simka, A. Gajos and K. Szymura, *J. Org. Chem.*, 2012, **77**, 1952-1960.

[2] A. Walęcka-Kurczyk, K. Walczak, A. Kuźnik, S. Stecko, A. Październiok-Holewa, *Molecules*, 2020, **25**, 405.

Procedure for the synthesis of *N*-pivaloyl-D,L-alanine 1a and characterization data



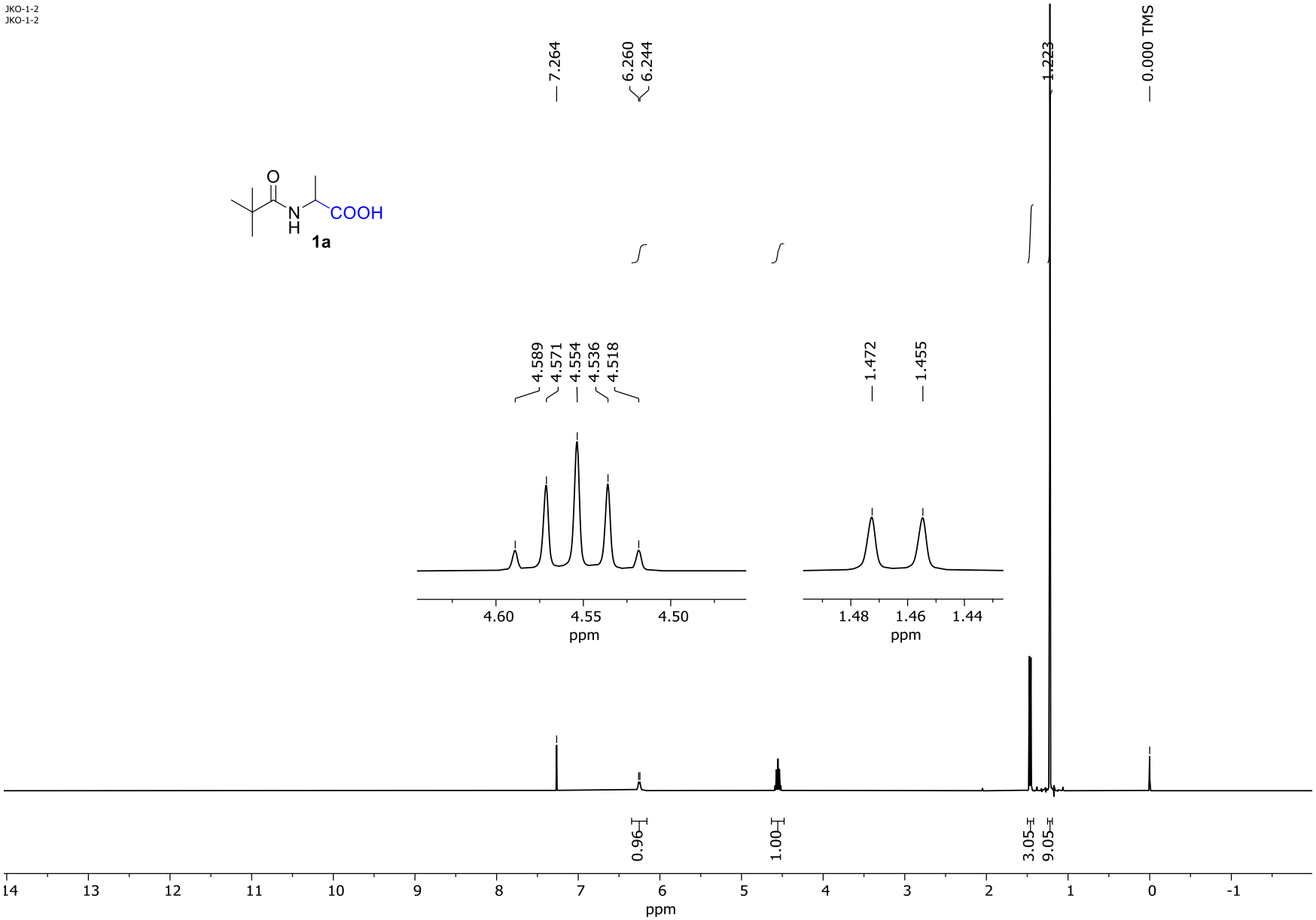
To a 250 mL round bottom flask, D,L-alanine (5.34 g, 0.06 mol), MeOH (60 mL) and 1M NaOH (60 mL) were added. After the mixture was cooled to 0 °C, pivaloyl chloride (7.23 g, 7.39 mL, 0.06 mol) was added dropwise. The reaction mixture was vigorously stirred at room temperature overnight. Next, MeOH was evaporated in vacuo and the aqueous solution was acidified with 1M HCl to pH 2-3. The white precipitate was filtered off and washed with water. The aqueous filtrate was extracted with ethyl acetate (3 × 20 mL). The ethyl acetate extracts were pooled, washed with water, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was combined with the previously separated precipitate and dried under reduced pressure to give the expected product **1a** with 70% yield.

***N*-Pivaloyl-D,L-alanine (1a)**

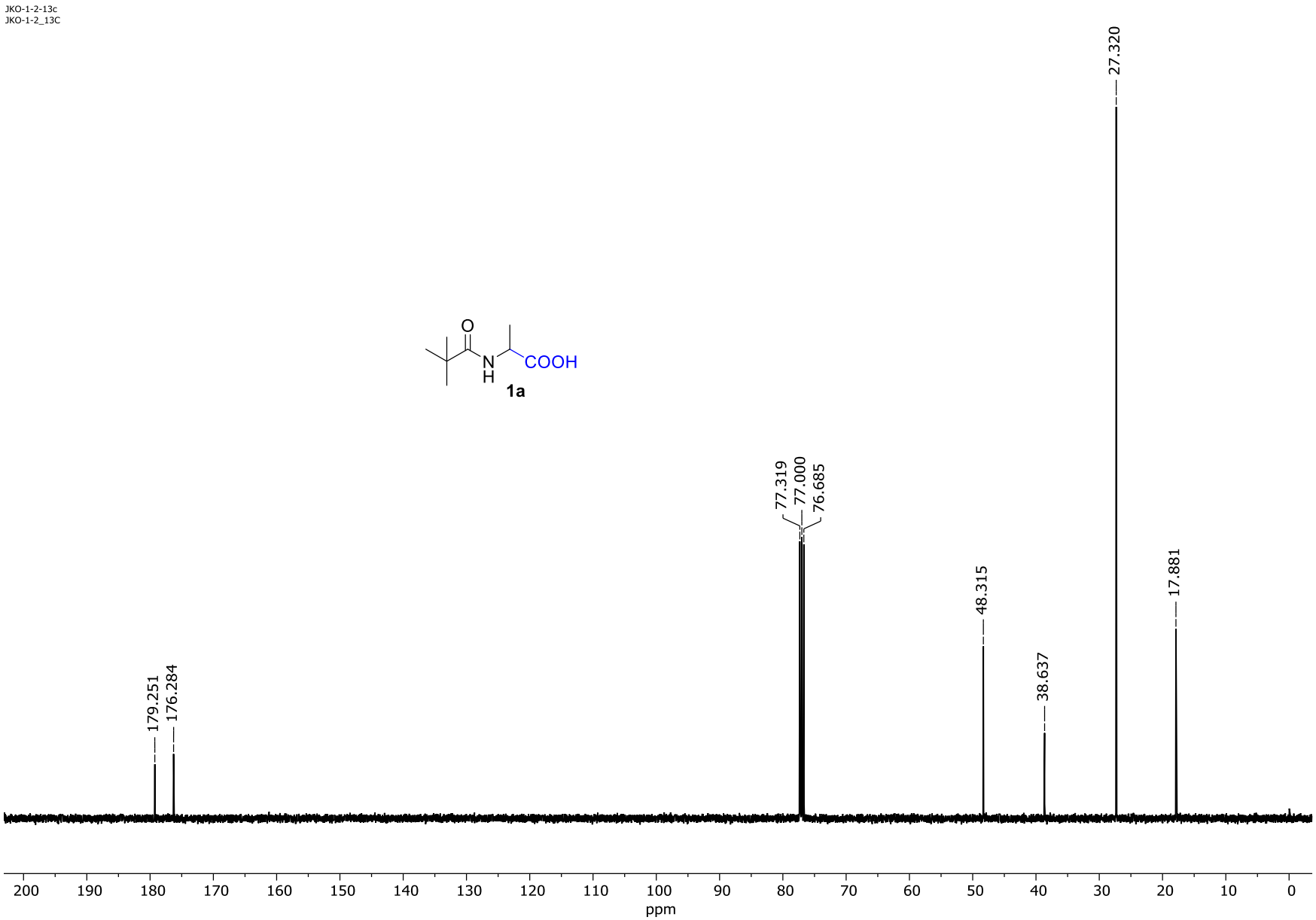
White solid (7.27 g, 70% yield): mp = 137.0-139.0 °C (lit.[3] mp = 122.0-126.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (br d, J = 6.4 Hz, 1H), 4.55 (qu, , J = 7.2 Hz 1H), 1.46 (d, J = 6.8 Hz, 3H), 1.22 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 176.3, 48.3, 38.6, 27.3, 17.9.

[3] A. K. Das, P. P. Bose, M. G. B. Drew, A. Banerjee, *Tetrahedron*, 2007, **63**, 7432-7442.

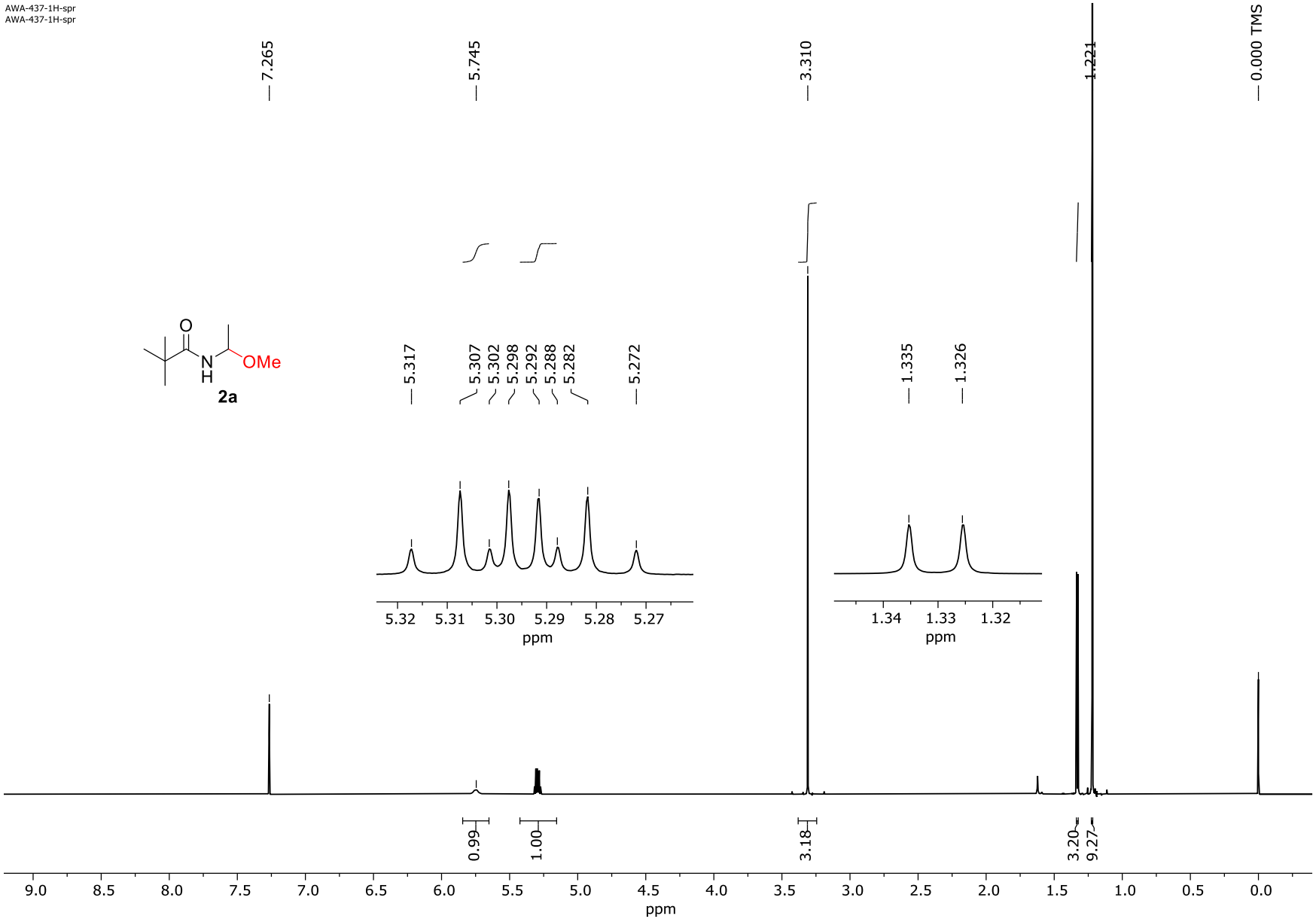
_N_-Pivaloyl-D,L-alanine (1a): ^{1}H NMR [400 MHz/$CDCl_3$/TMS]



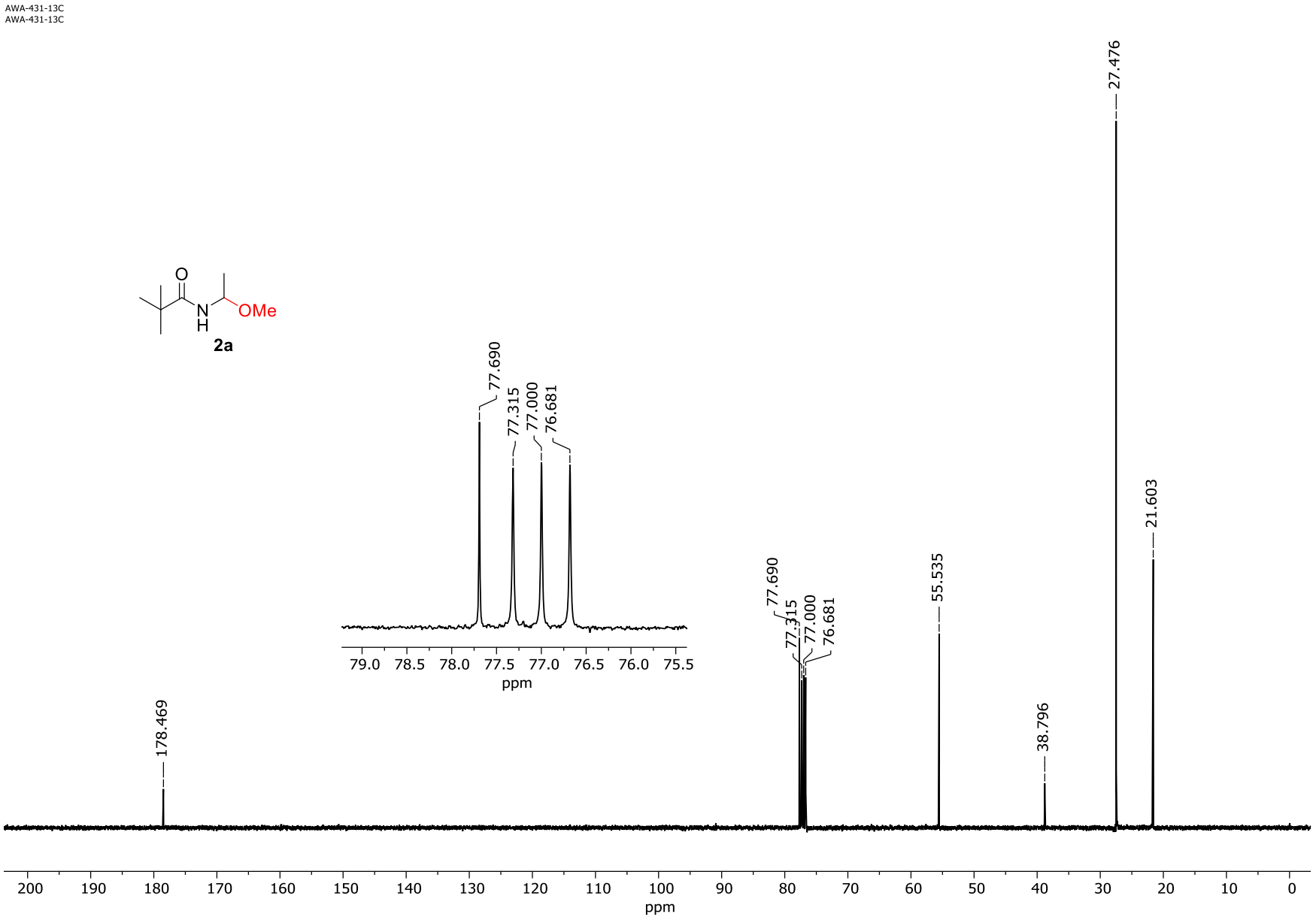
_N_-Pivaloyl-D,L-alanine (1a): ^{13}C NMR [100 MHz/$CDCl_3$]



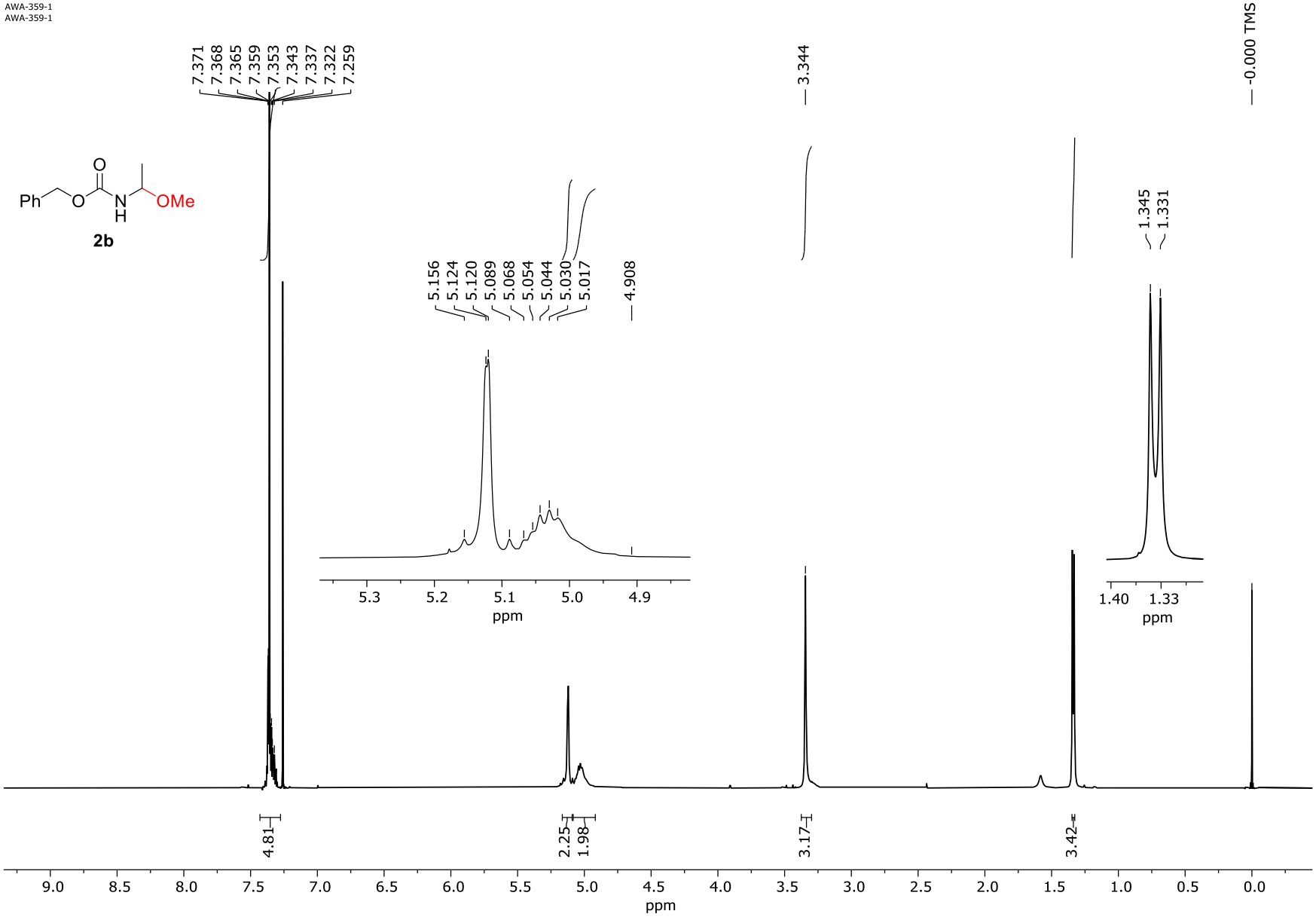
***N*-(1-methoxyethyl)pivaloylamide (2a):** ^{1}H NMR [600 MHz/$CDCl_3$/TMS]



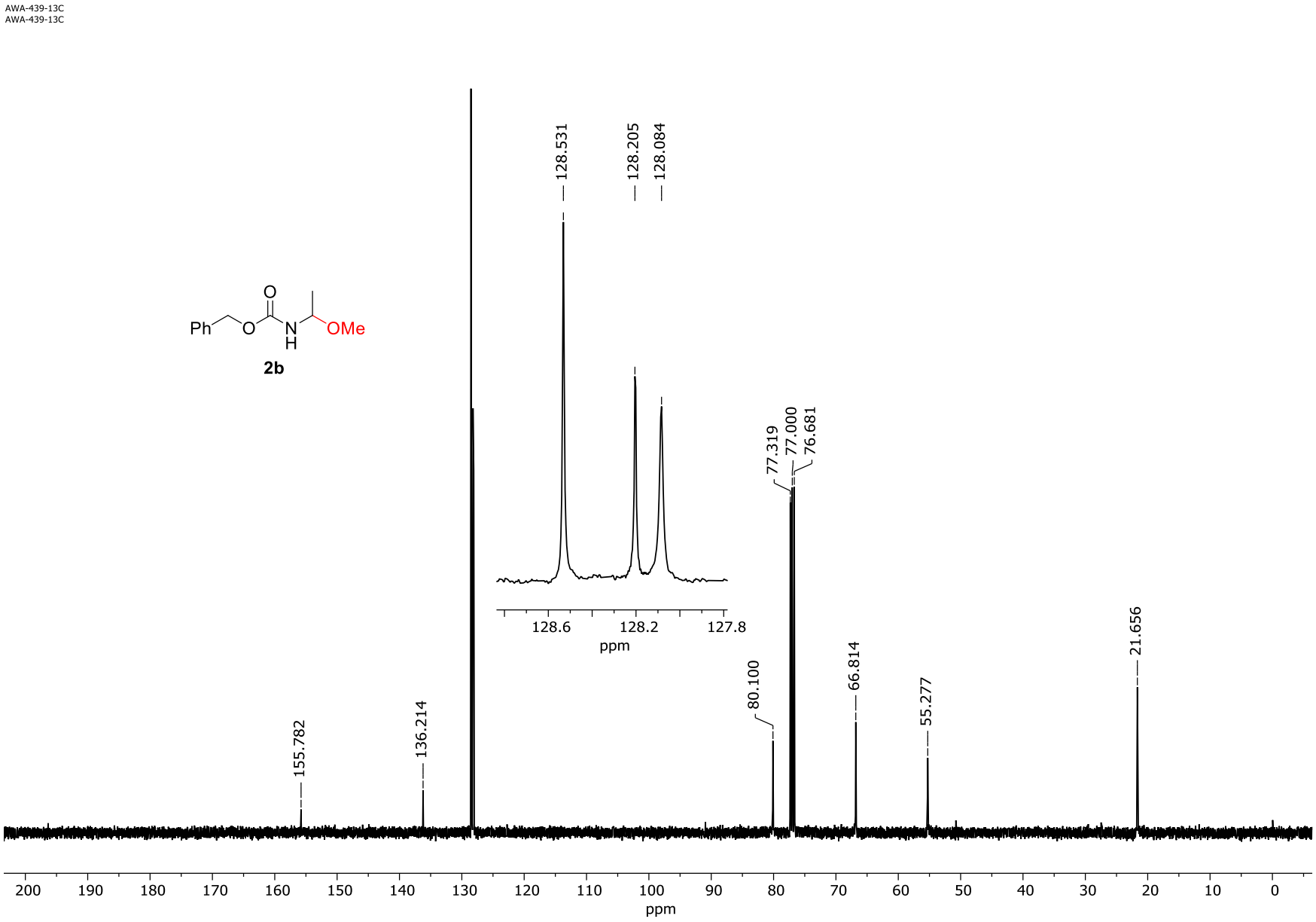
_N_-(1-methoxyethyl)pivaloylamide (2a): ^{13}C NMR [100 MHz/$CDCl_3$]



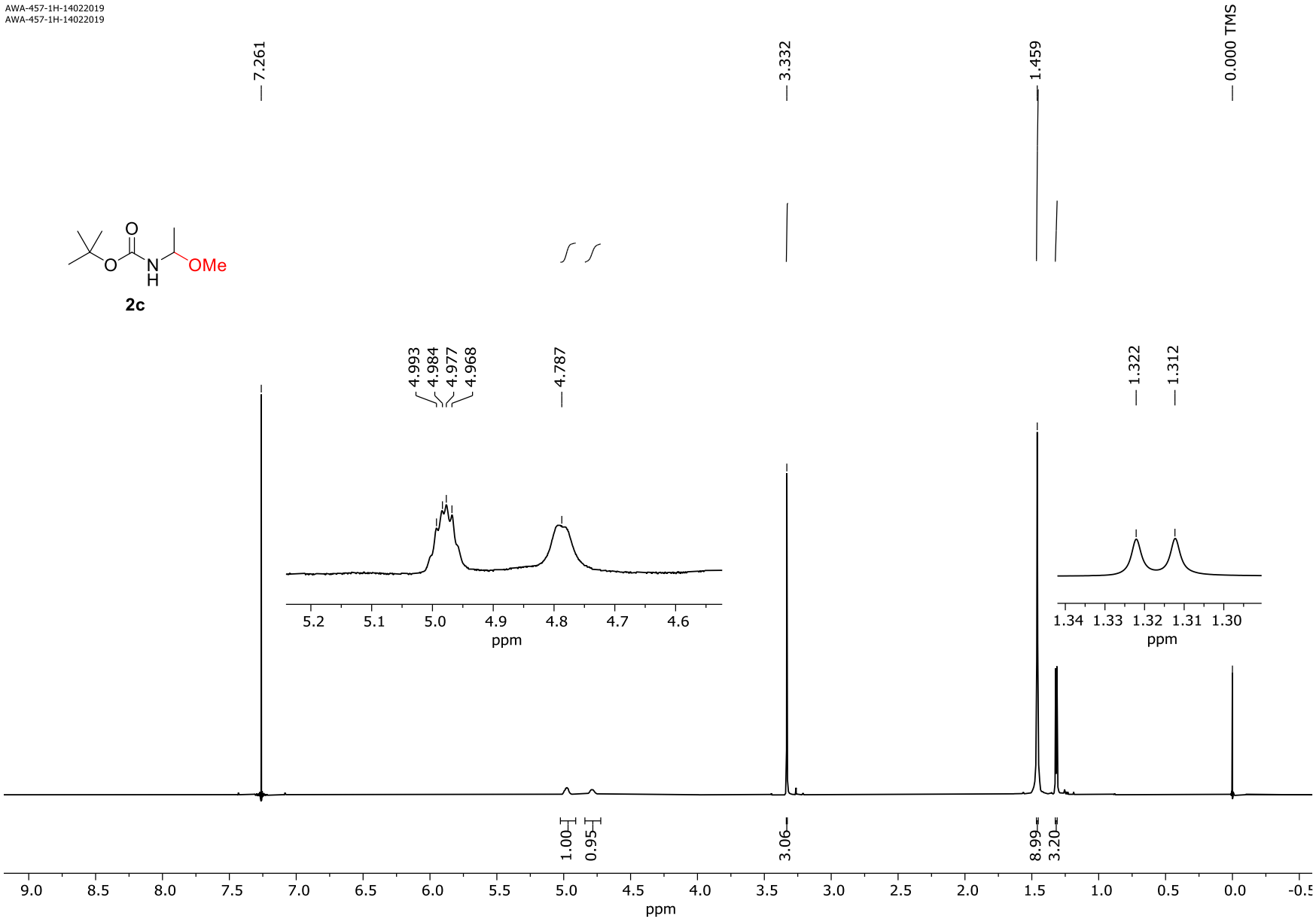
Benzyl *N*-(1-methoxyethyl)carbamate (2b): ^{1}H NMR [400 MHz/$CDCl_3$/TMS]



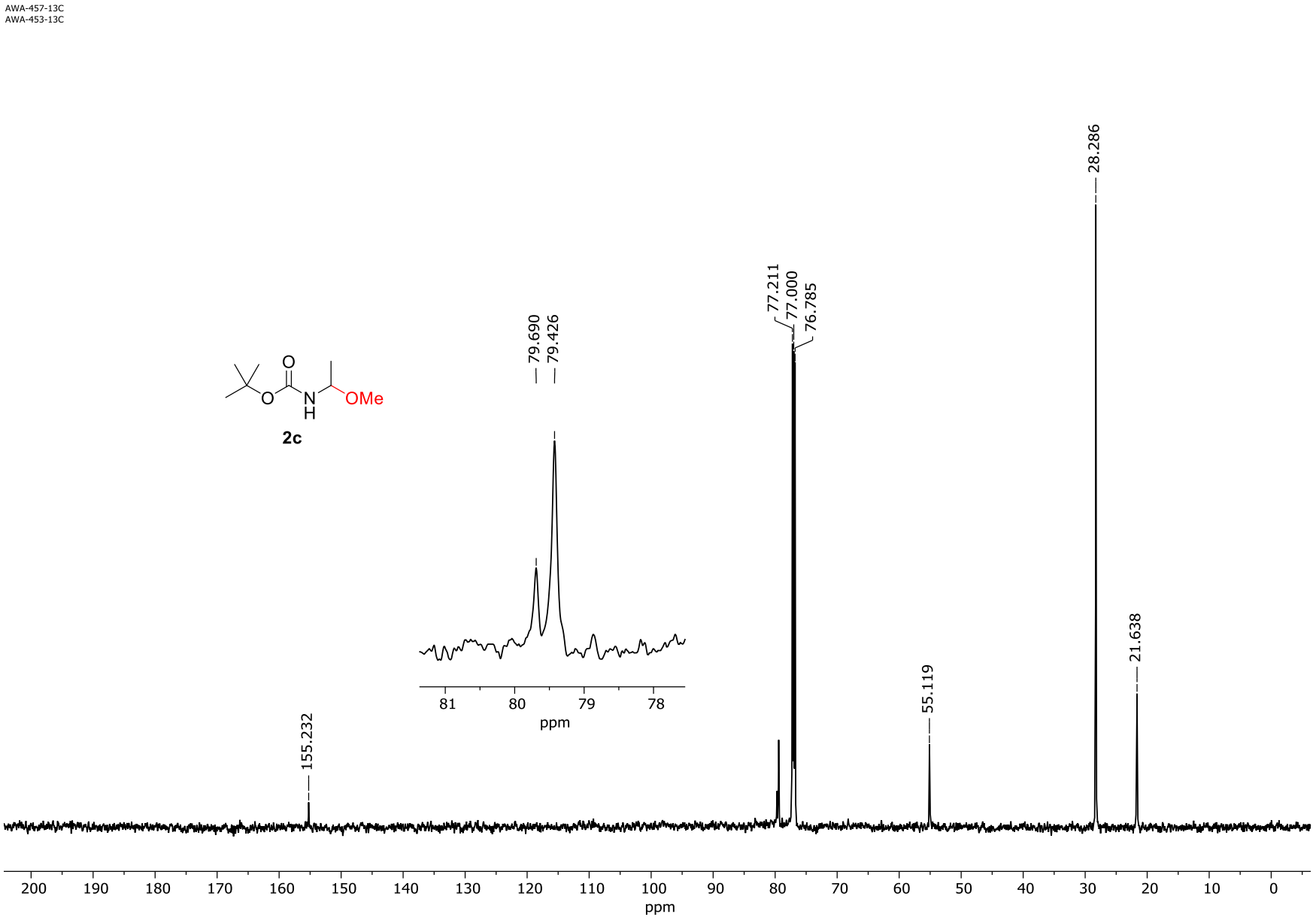
Benzyl *N*-(1-methoxyethyl)carbamate (2b): ^{13}C NMR [100 MHz/$CDCl_3$]



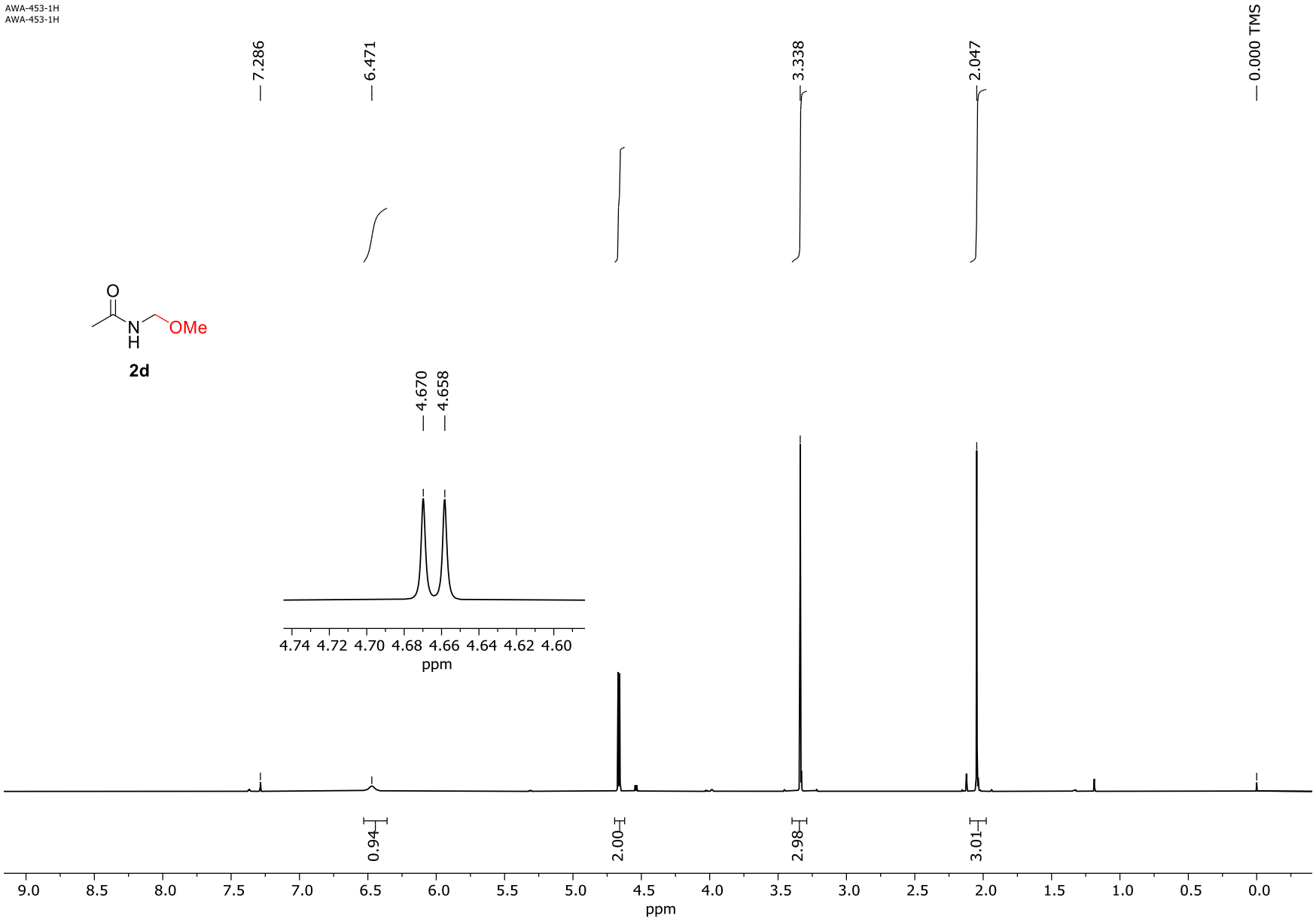
***Tert*-butyl *N*-(1-methoxyethyl)carbamate (2c)**: ^{1}H NMR [600 MHz/$CDCl_3$/TMS]



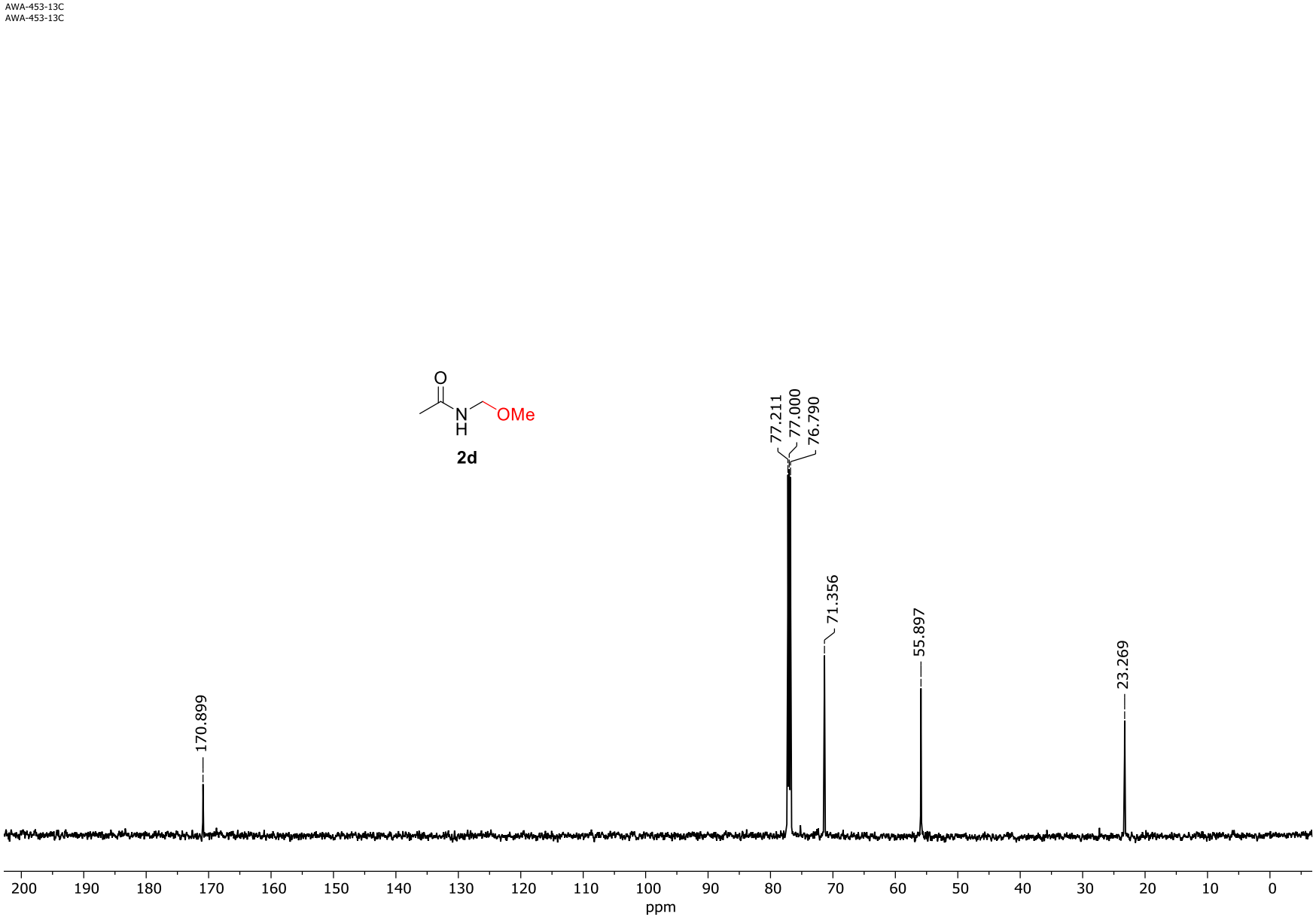
***Tert*-butyl *N*-(1-methoxyethyl)carbamate (2c)**: ^{13}C NMR [150 MHz/$CDCl_3$]



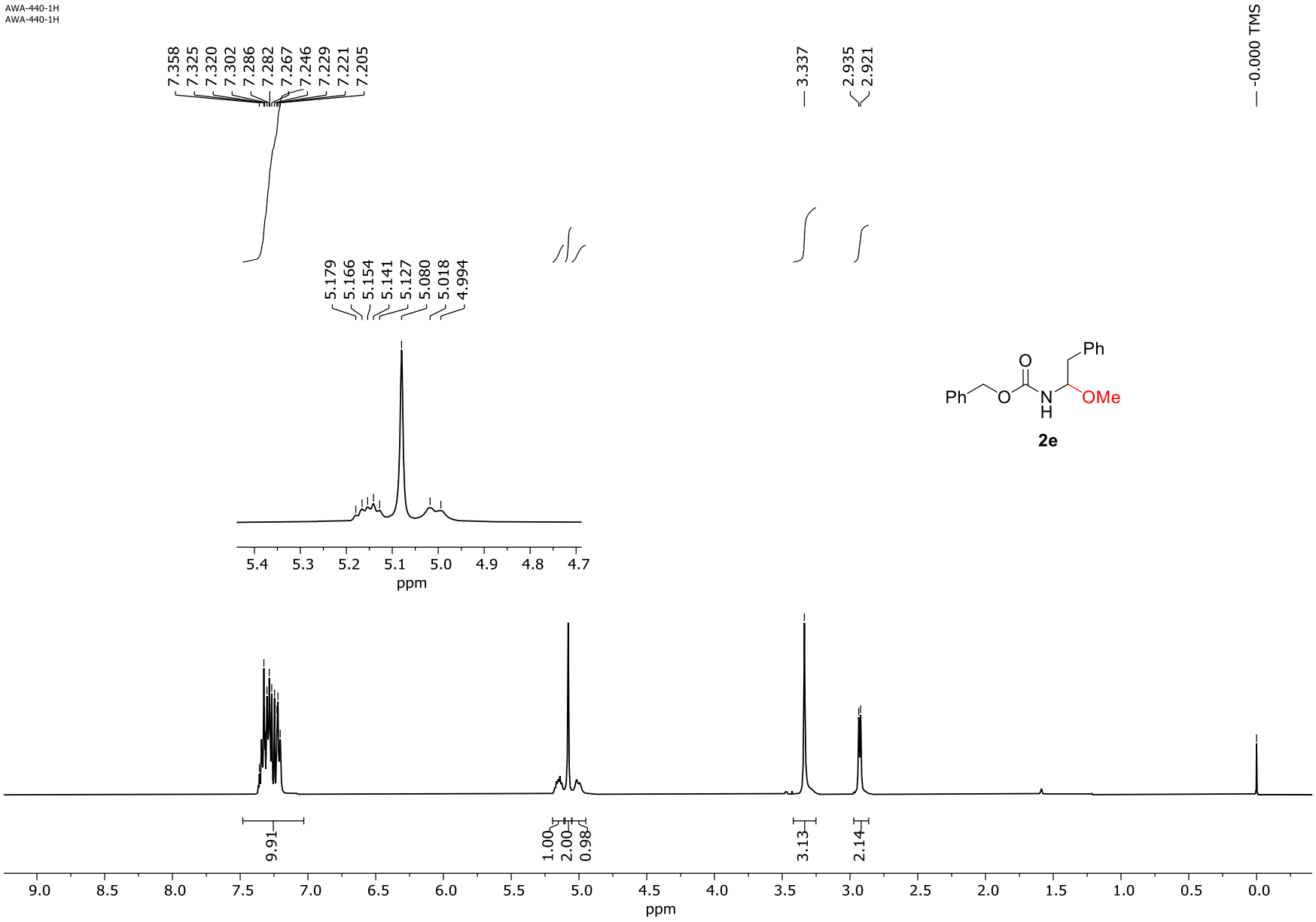
***N*-(methoxymethyl)acetamide (2d)**: ^{1}H NMR [600 MHz/$CDCl_3$/TMS]



***N*-(methoxymethyl)acetamide (2d):** ^{13}C NMR [150 MHz/$CDCl_3$]



Benzyl *N*-(1-methoxy-2-phenylethyl)carbamate (2e): ^{1}H NMR [400 MHz/$CDCl_3$/TMS]



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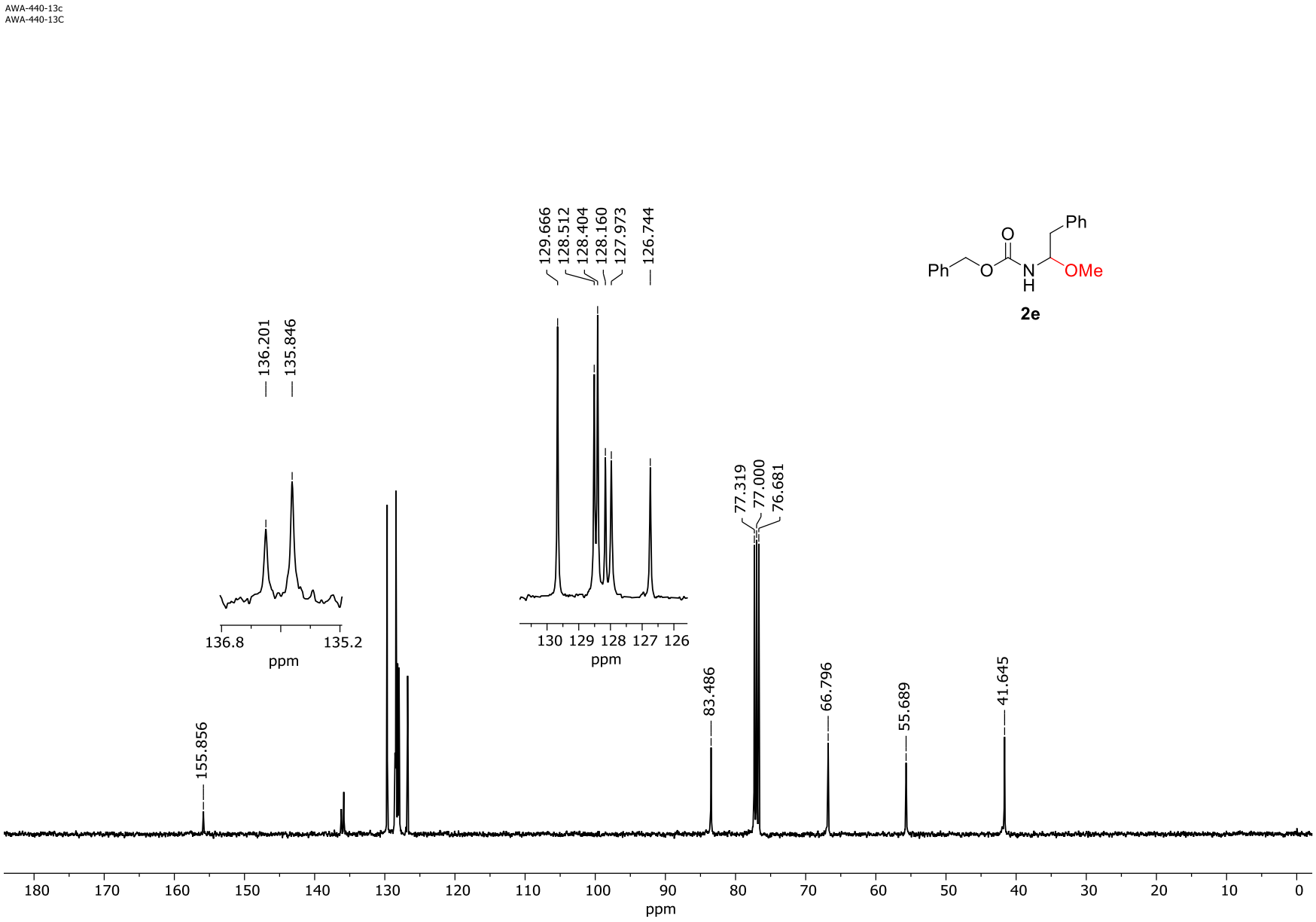
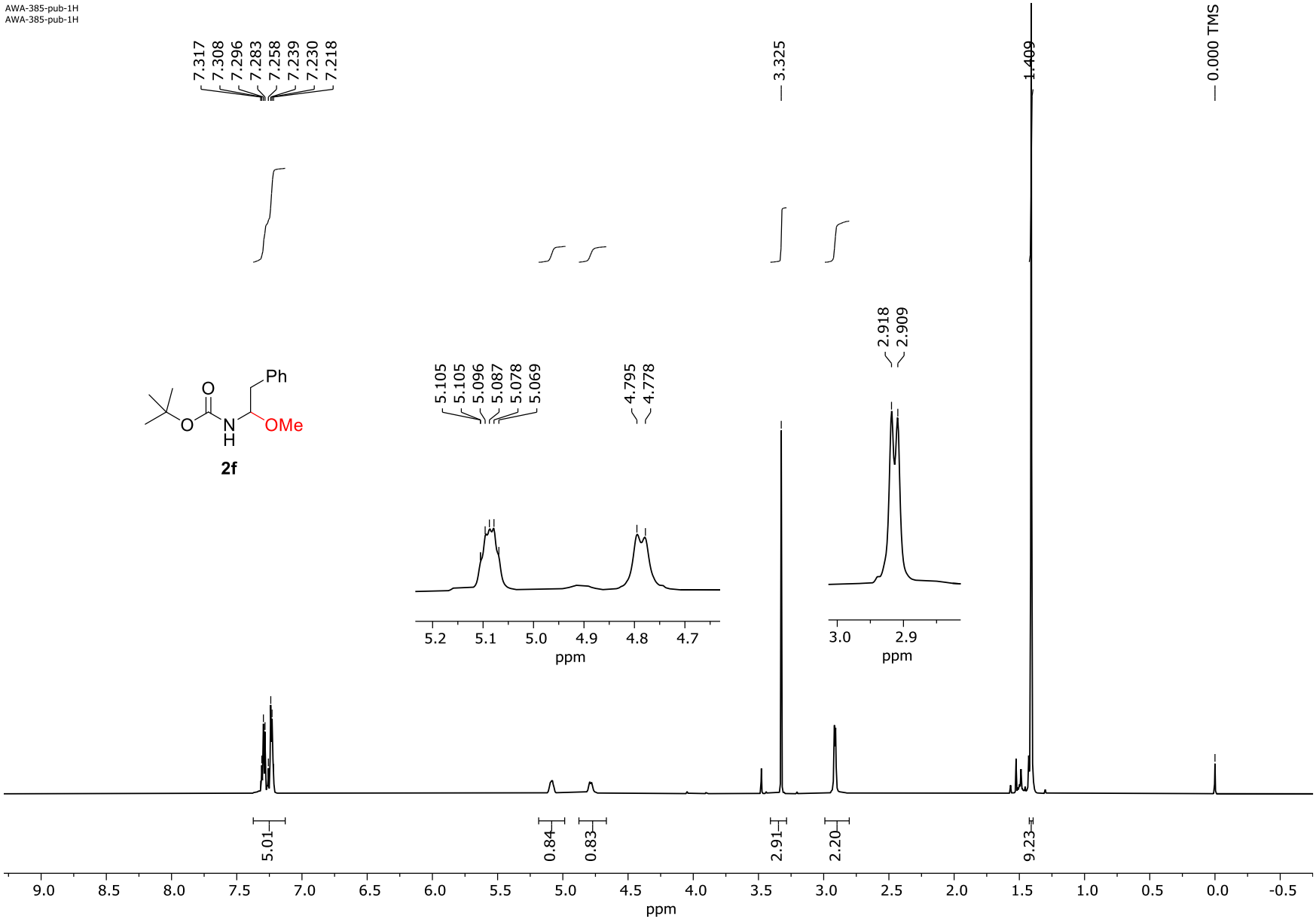
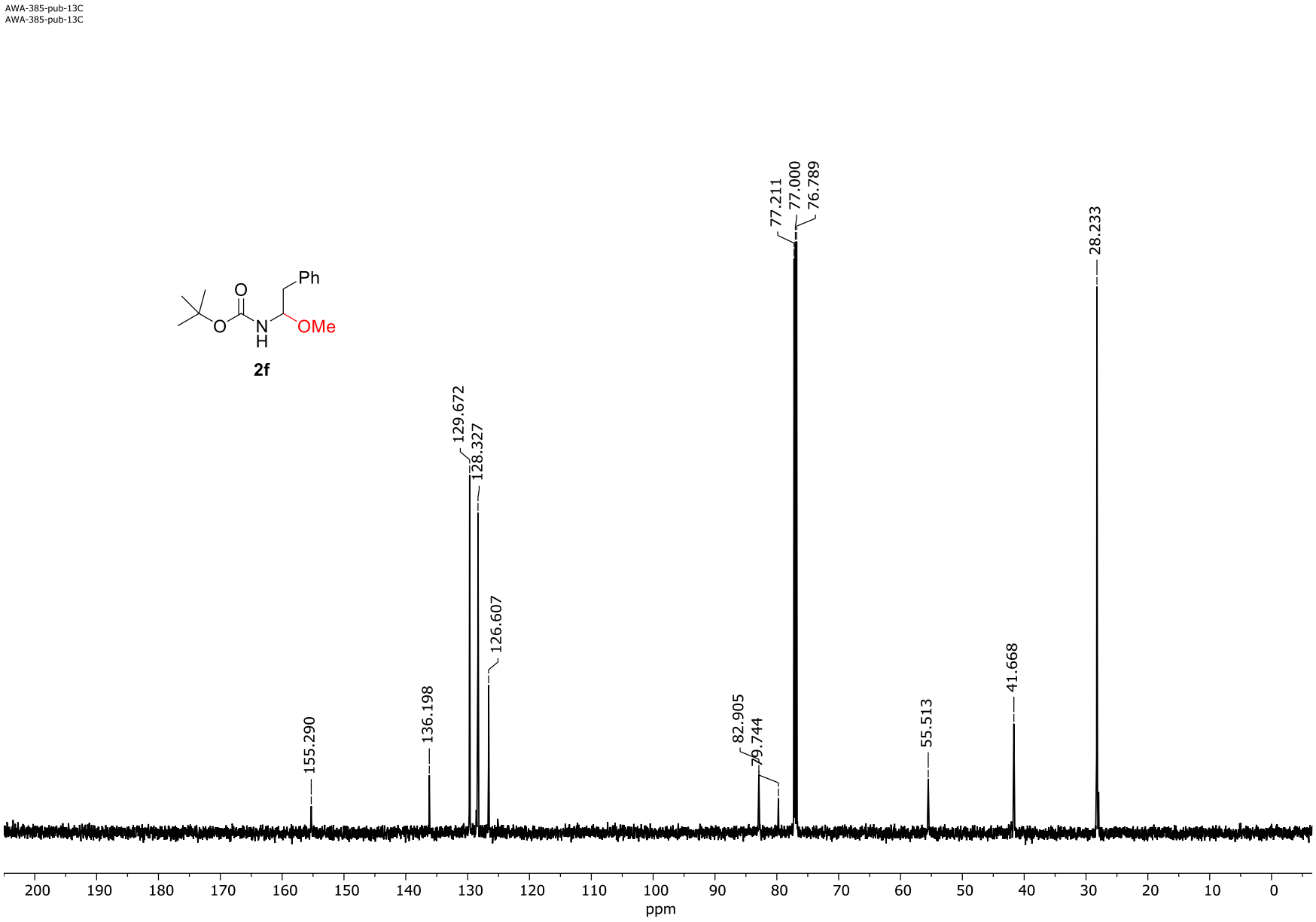


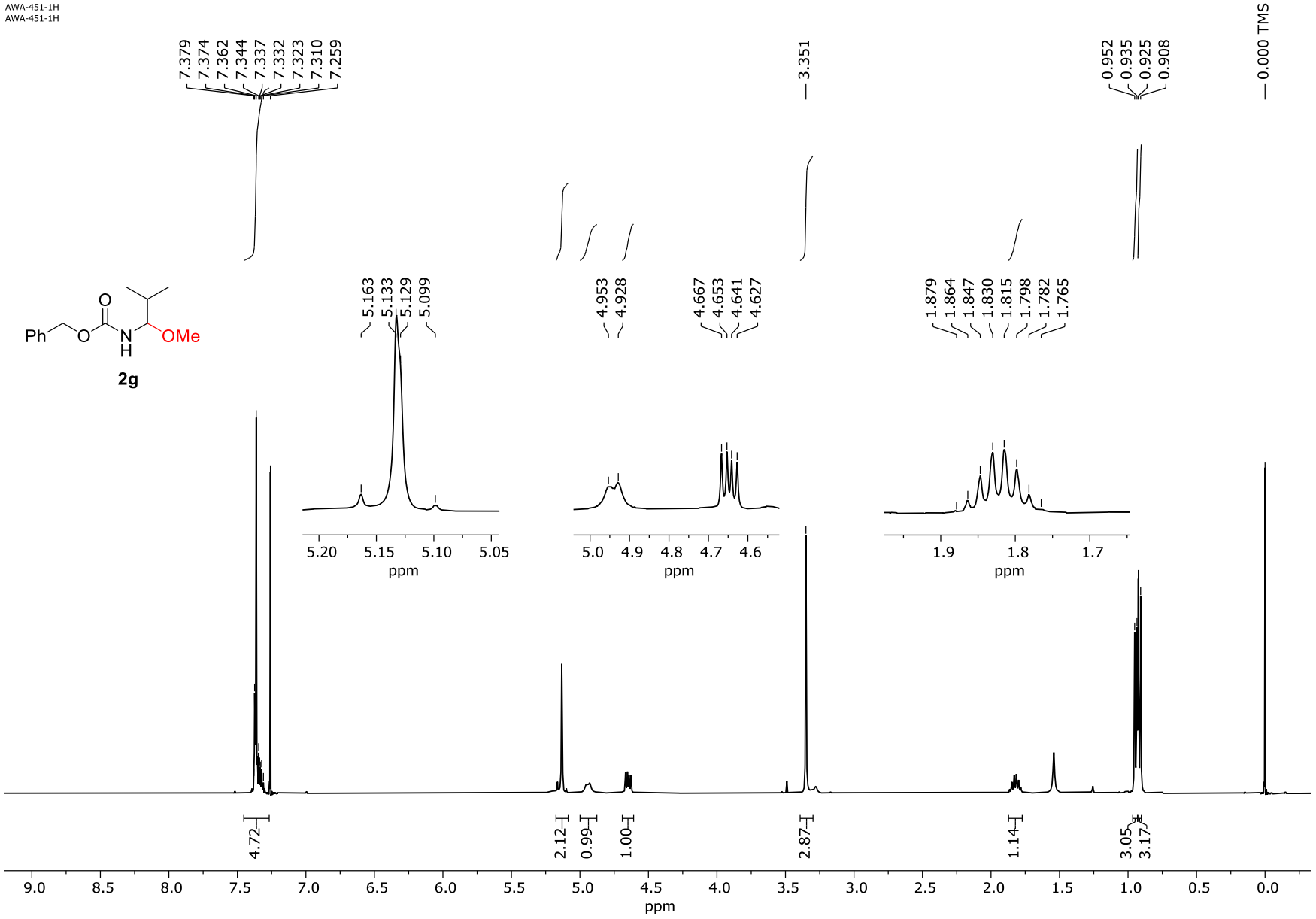
***Tert*-butyl *N*-(1-methoxy-2-phenylethyl)carbamate (2f)**: ^{1}H NMR [600 MHz/$CDCl_3$/TMS]



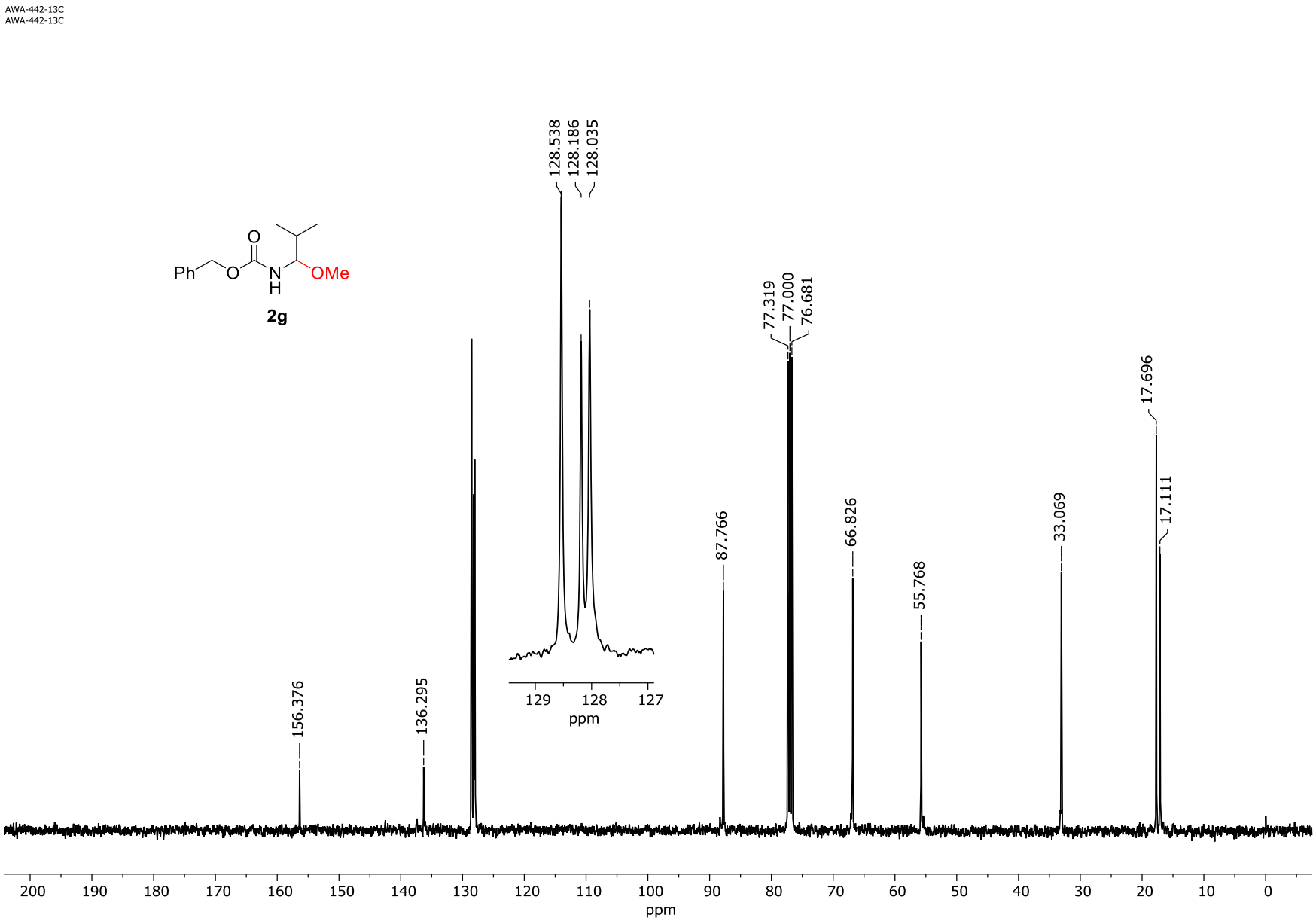
***Tert*-butyl *N*-(1-methoxy-2-phenylethyl)carbamate (2f)**: ^{13}C NMR [150 MHz/$CDCl_3$]



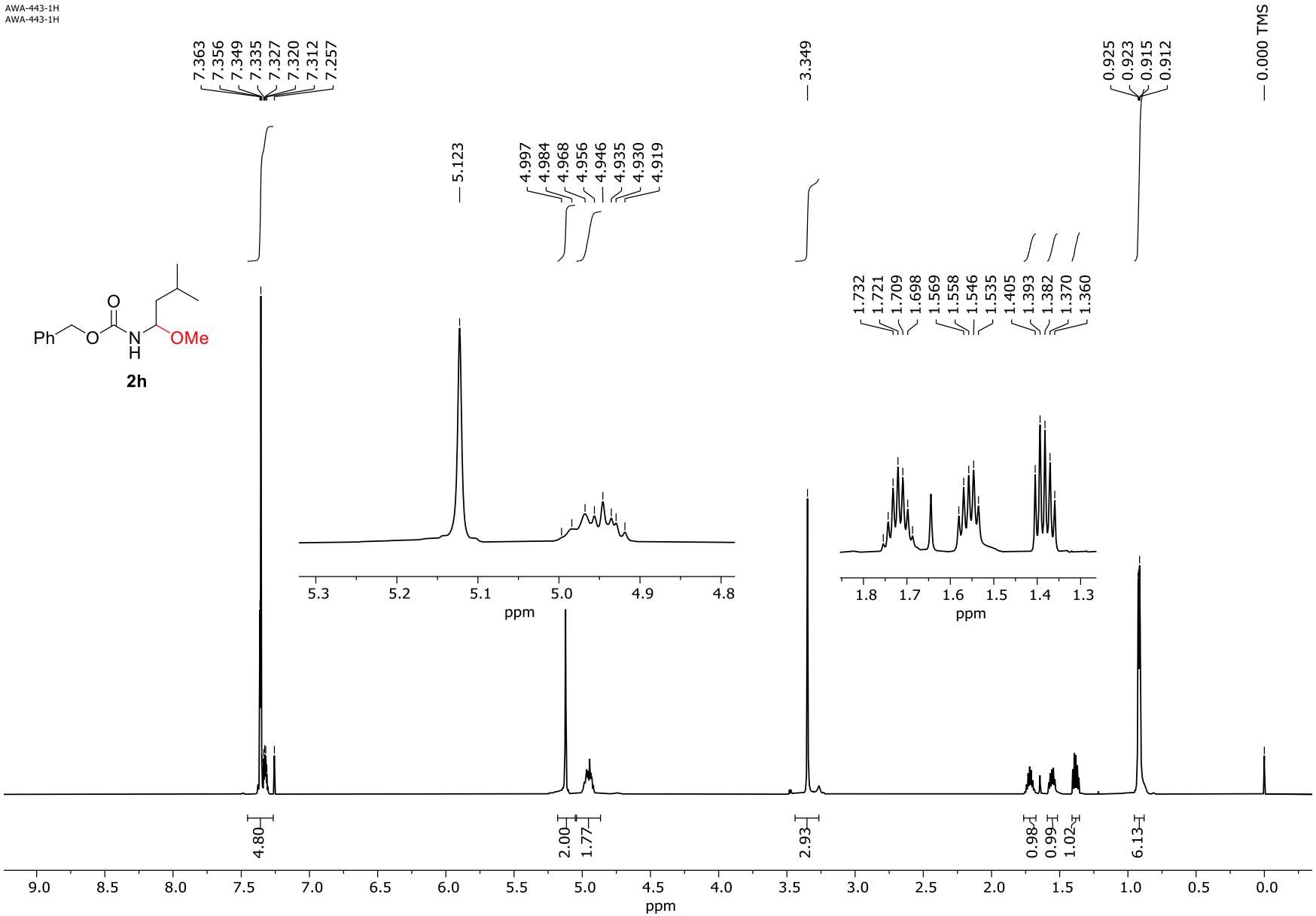
Benzyl *N*-(1-methoxy-2-methylpropyl)carbamate (2g): ^{1}H NMR [400 MHz/$CDCl_3$/TMS]



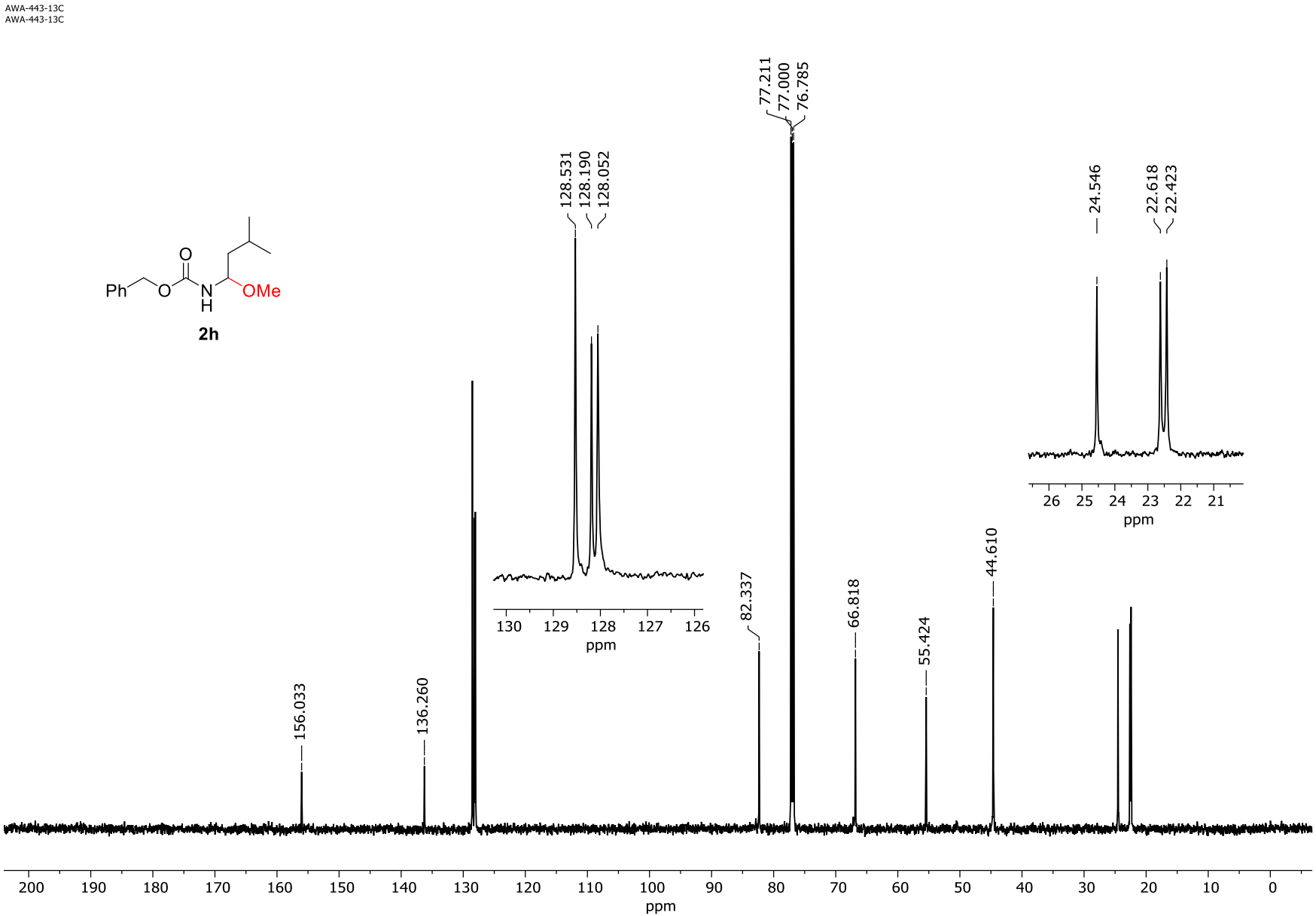
Benzyl *N*-(1-methoxy-2-methylpropyl)carbamate (2g): ^{13}C NMR [100 MHz/$CDCl_3$]



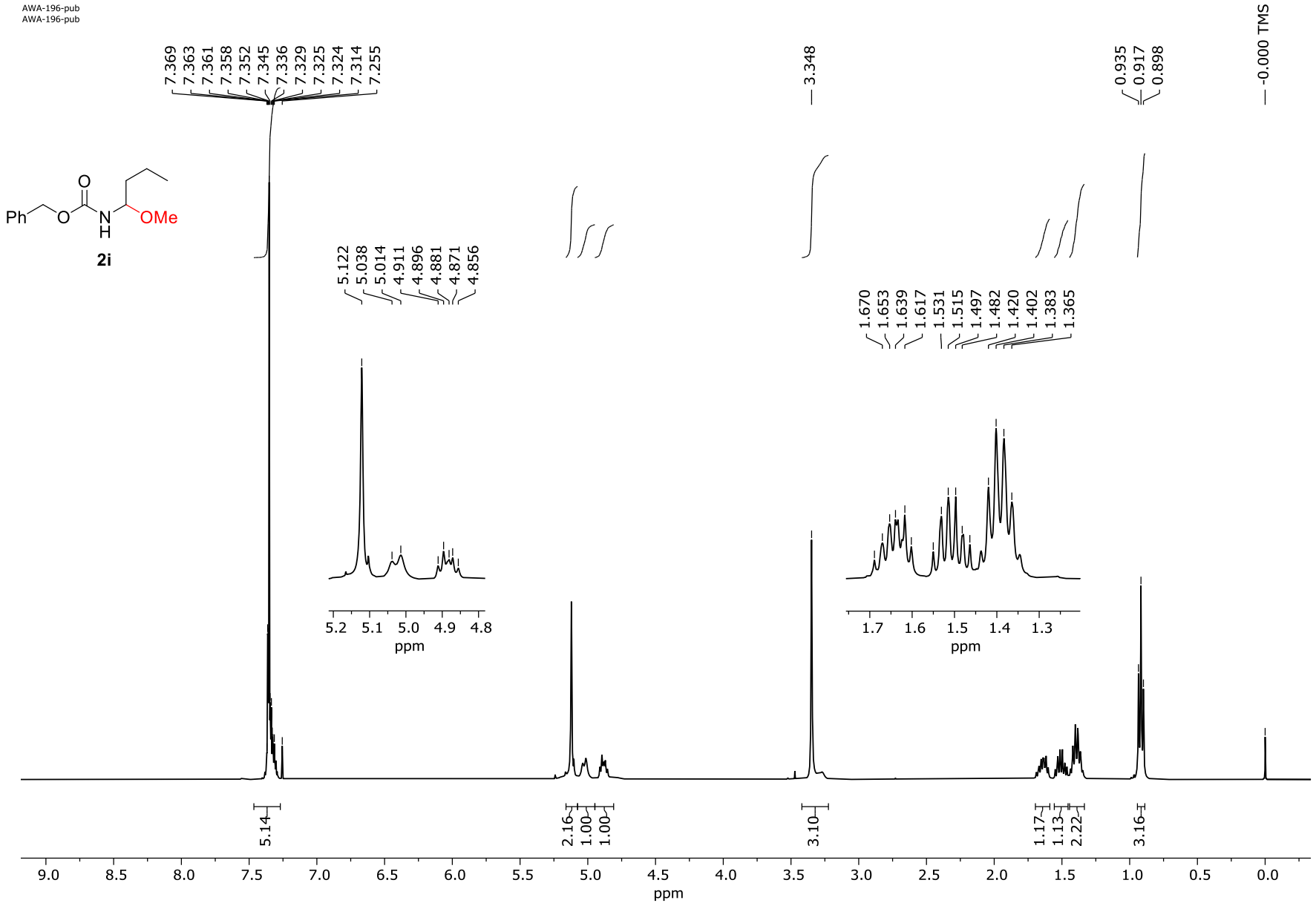
Benzyl *N*-(1-metoxy-3-methylbutyl)carbamate (2h): ^{1}H NMR [400 MHz/$CDCl_3$/TMS]



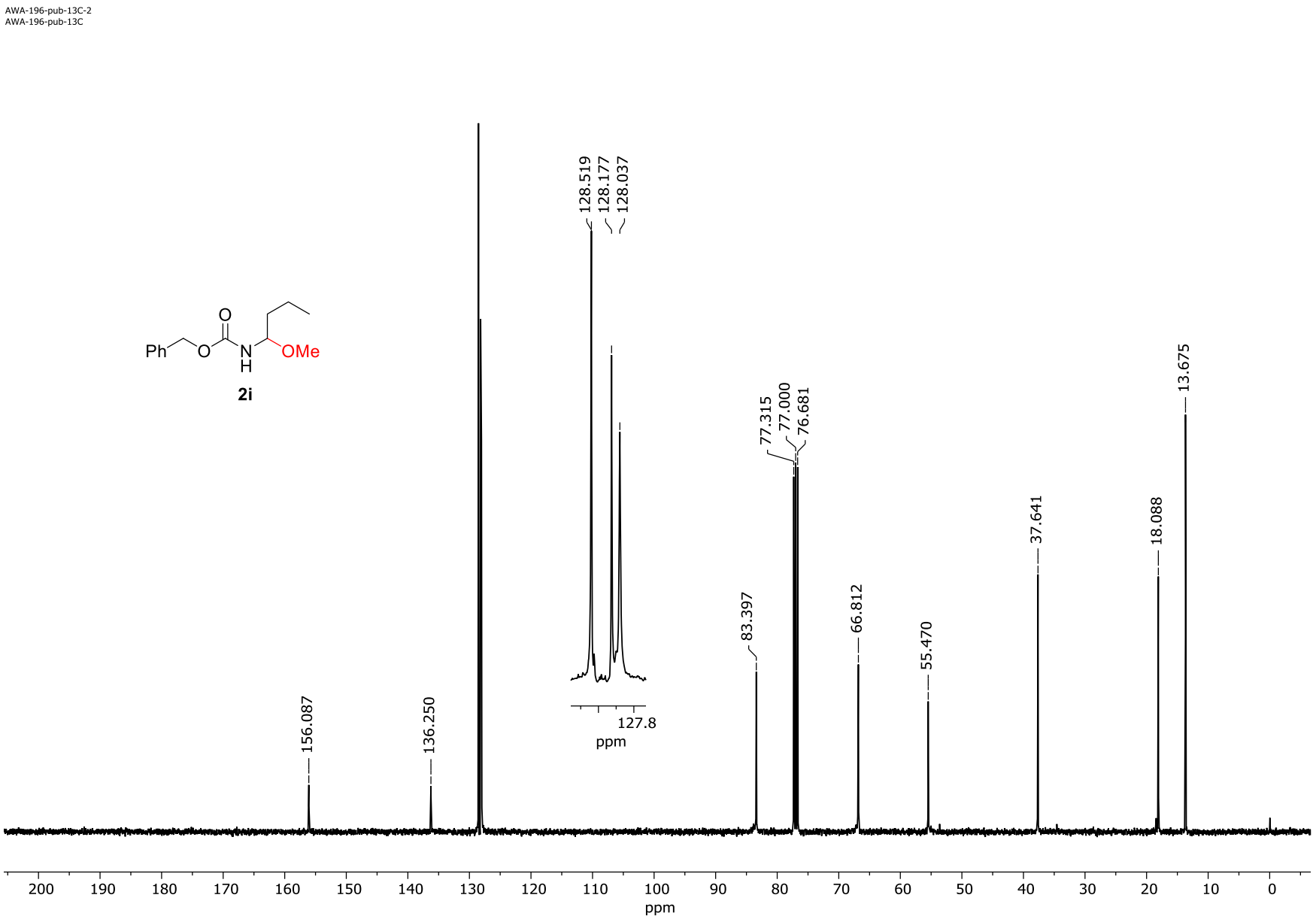
Benzyl *N*-(1-metoxy-3-methylbutyl)carbamate (2h): ^{13}C NMR [100 MHz/$CDCl_3$]



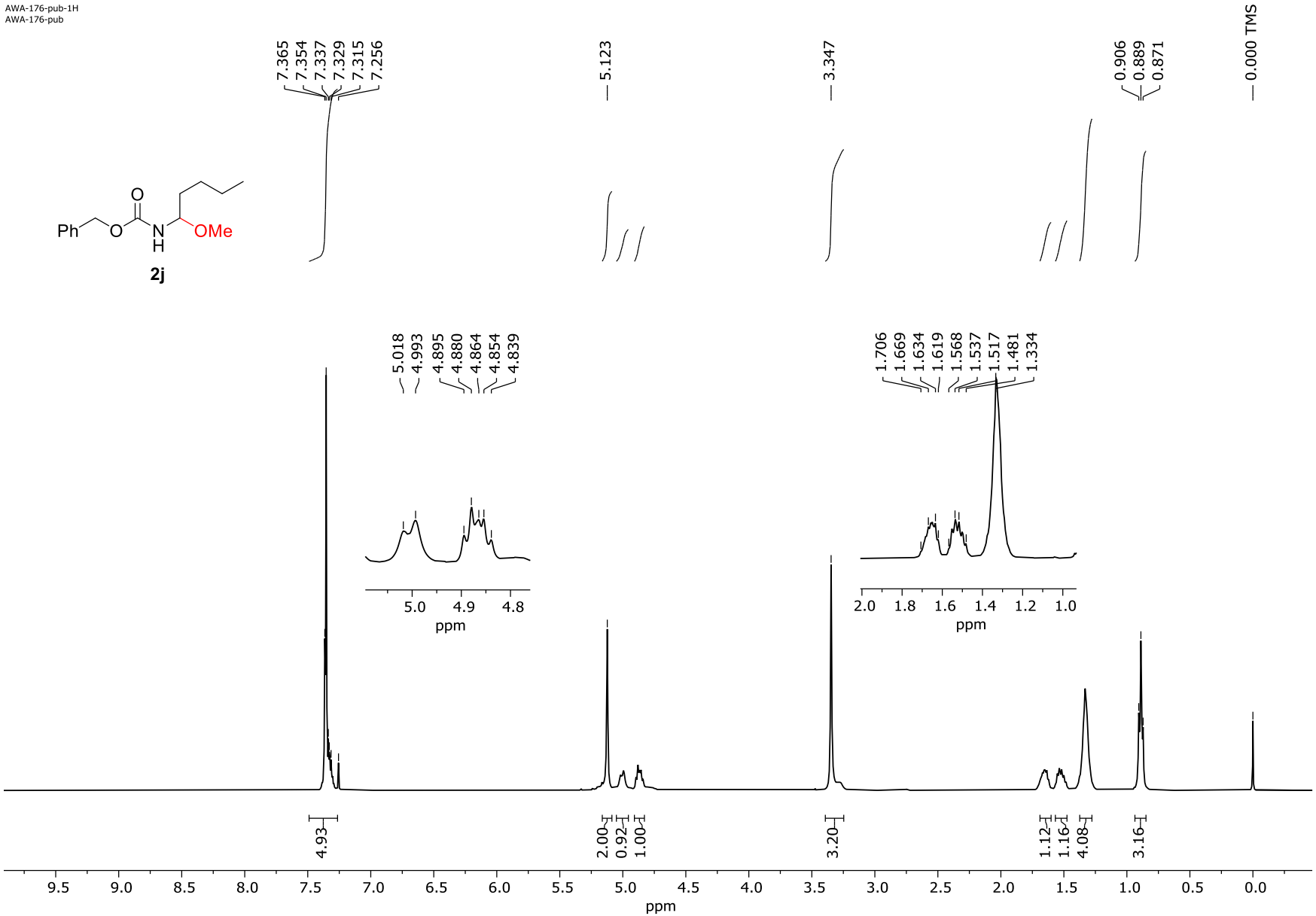
Benzyl *N*-(1-methoxybutyl)carbamate (2i): ^{1}H NMR [400 MHz/$CDCl_3$/TMS]



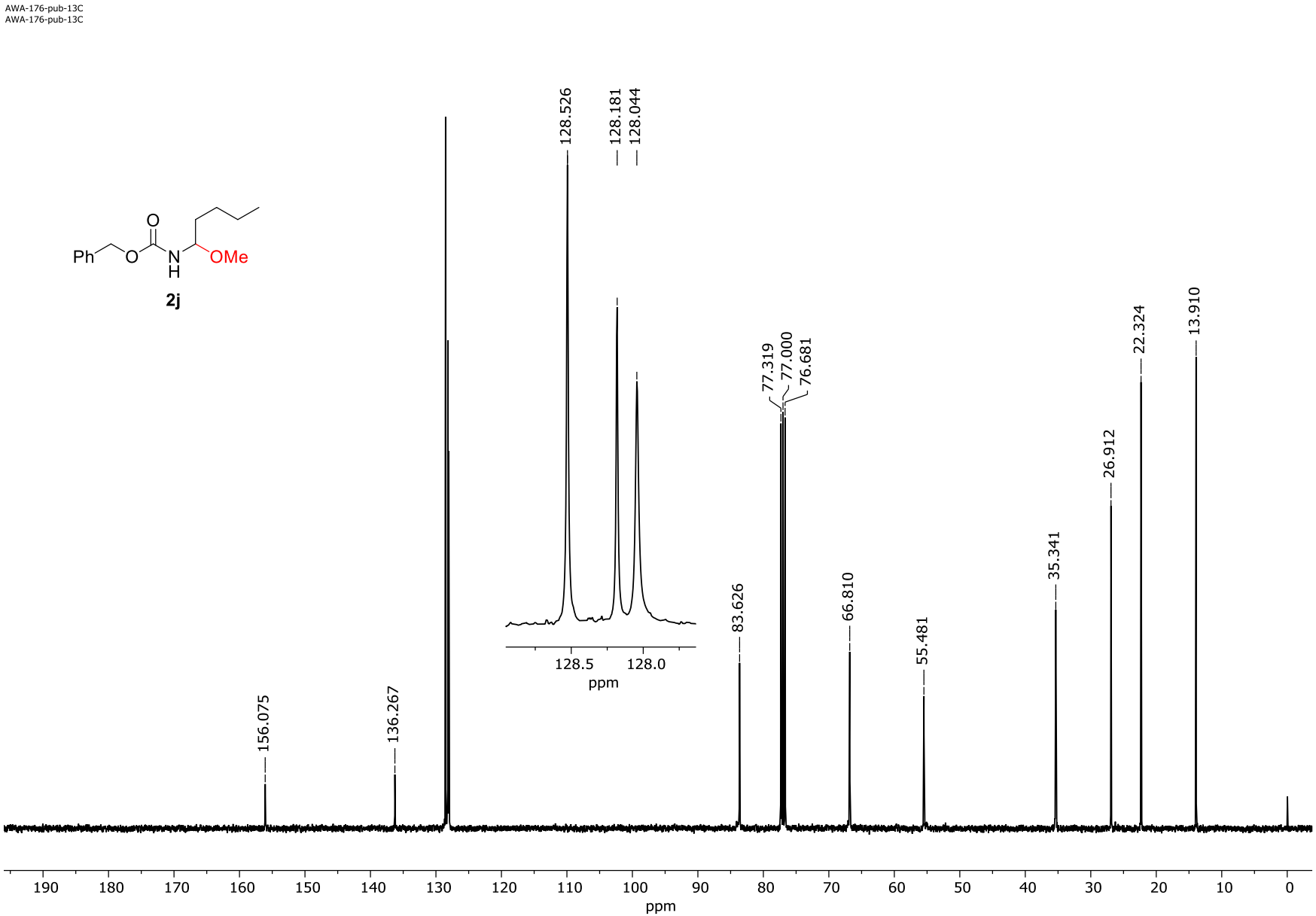
Benzyl *N*-(1-methoxybutyl)carbamate (2i): ^{13}C NMR [100 MHz/$CDCl_3$]



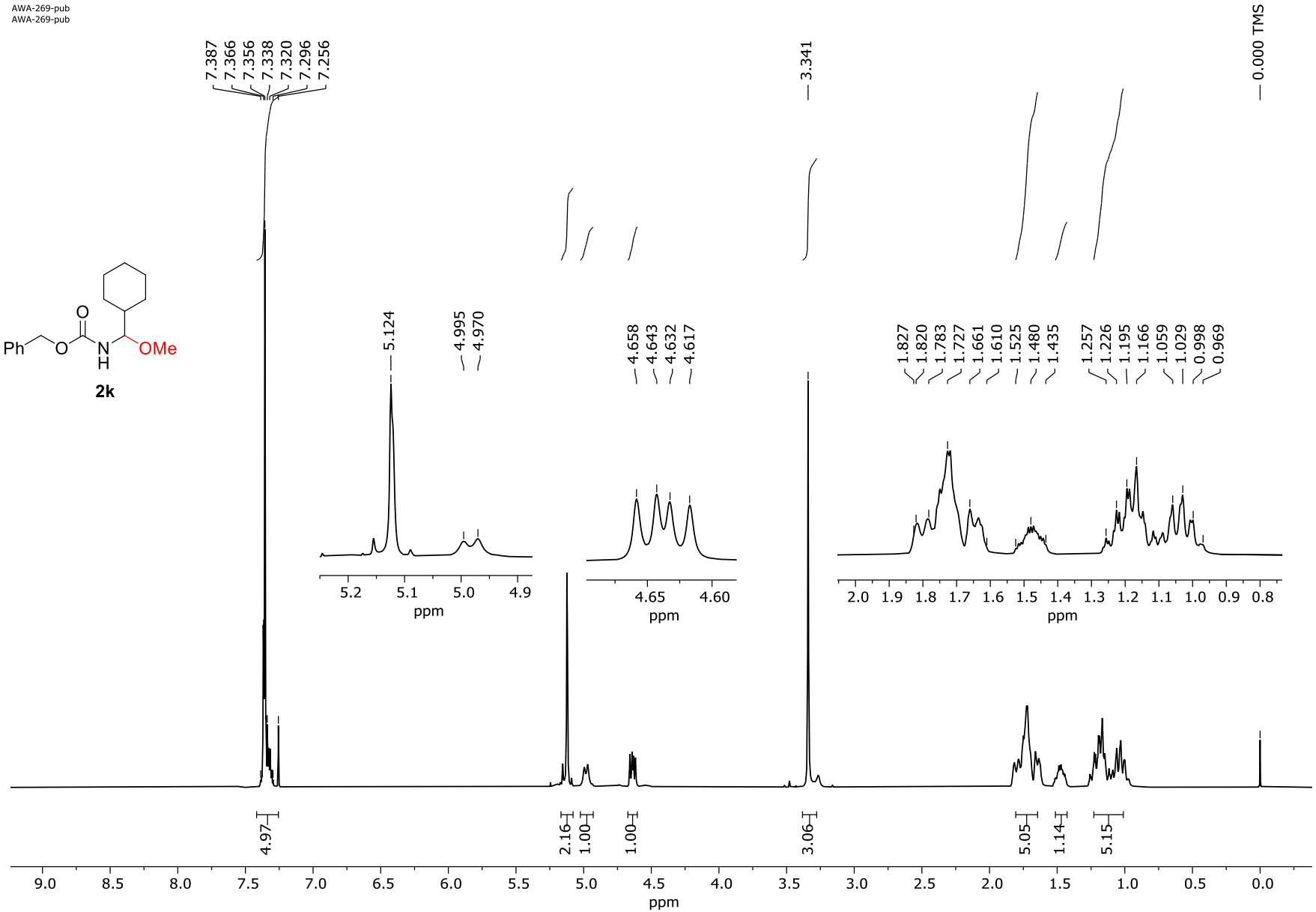
Benzyl *N*-(1-methoxypentyl)carbamate (2j): ^{1}H NMR [400 MHz/$CDCl_3$/TMS]



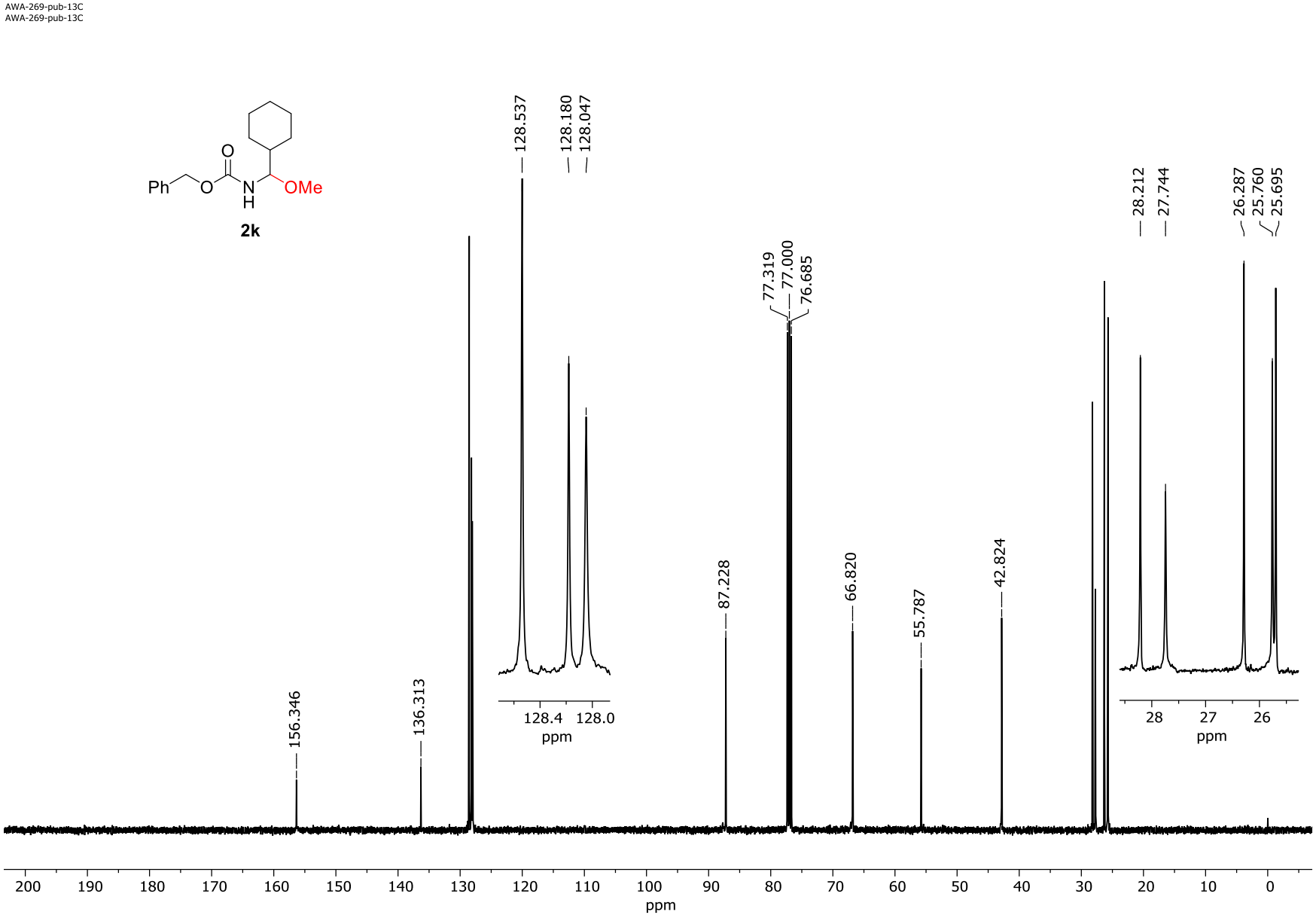
Benzyl *N*-(1-methoxypentyl)carbamate (2j): ^{13}C NMR [100 MHz/$CDCl_3$]



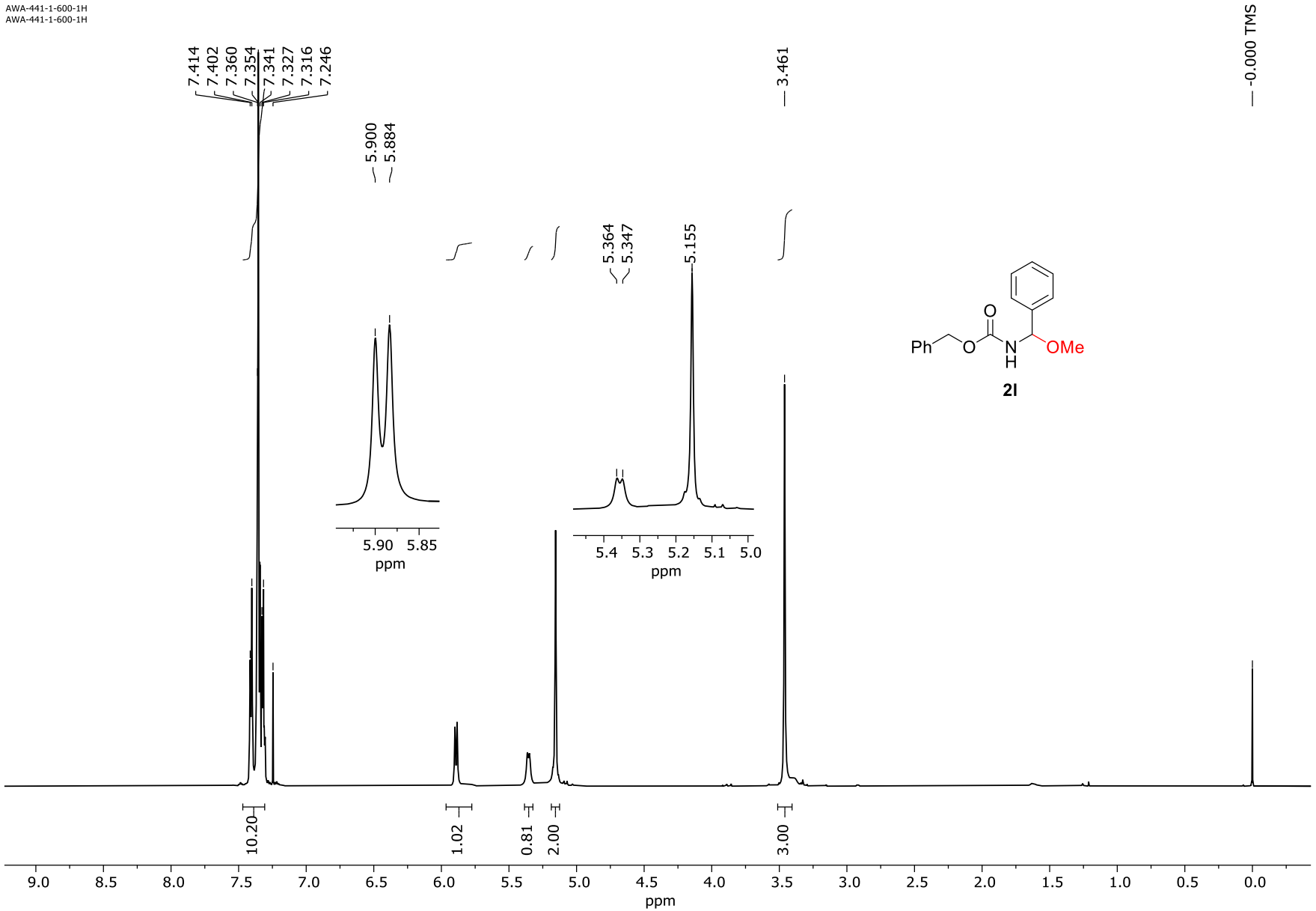
Benzyl *N*-[cyclohexyl(methoxy)methyl]carbamate (2k) ^{1}H NMR [400 MHz/$CDCl_3$/TMS]



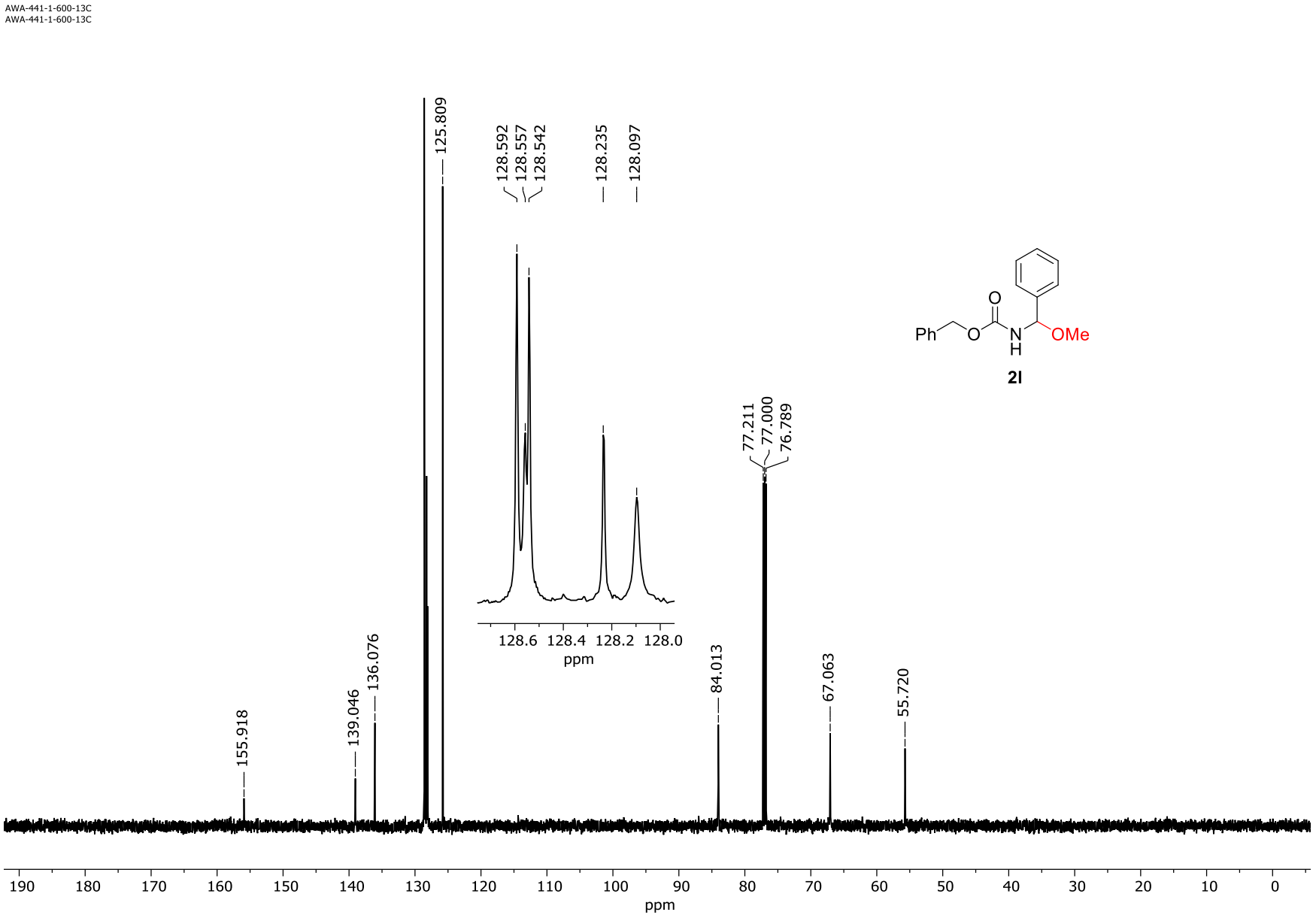
Benzyl *N*-[cyclohexyl(methoxy)methyl]carbamate (2k) ^{13}C NMR [100 MHz/$CDCl_3$]



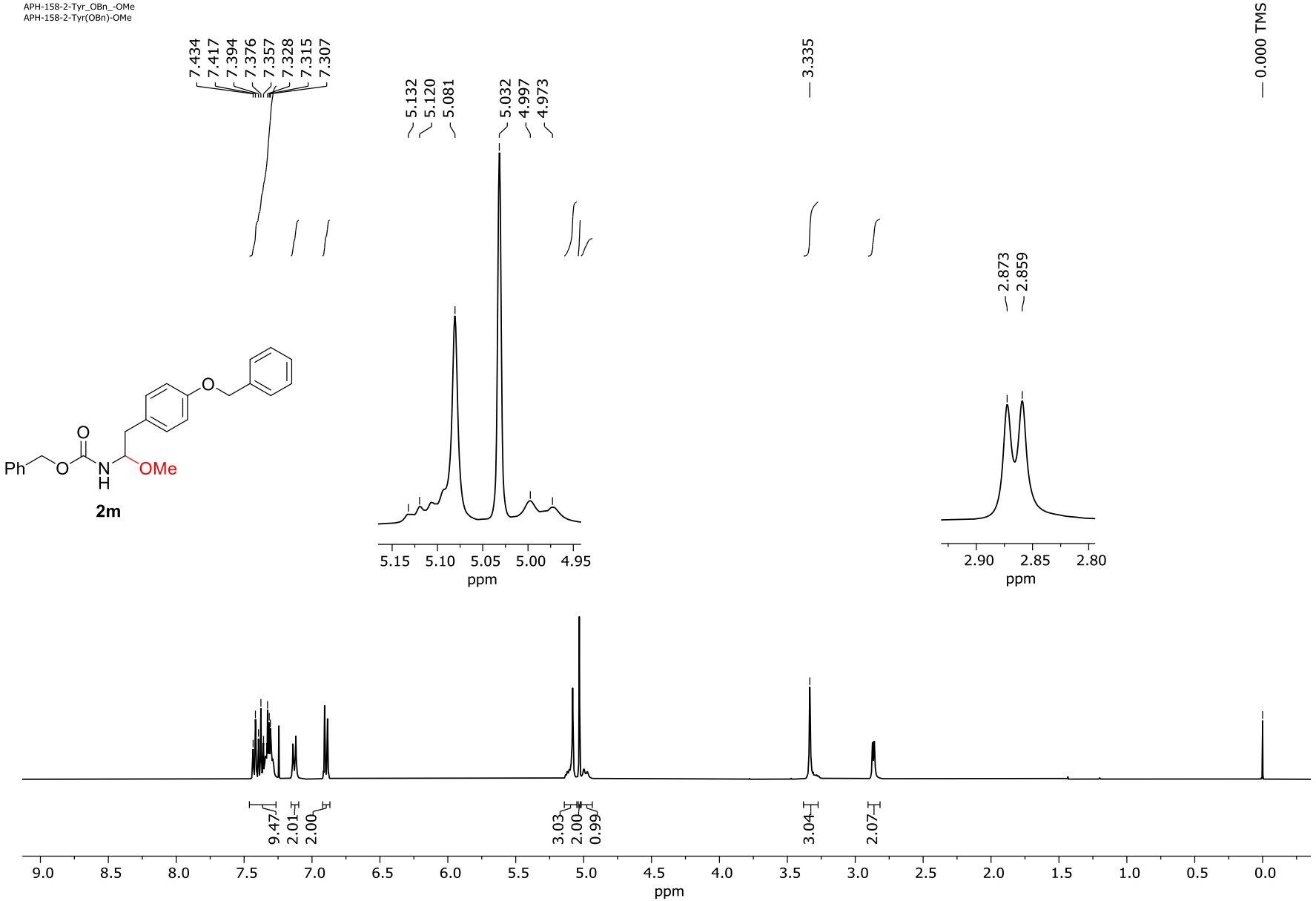
Benzyl *N*-(1-methoxy-1-phenylmethyl)carbamate (2l): ^{1}H NMR [600 MHz/$CDCl_3$/TMS]



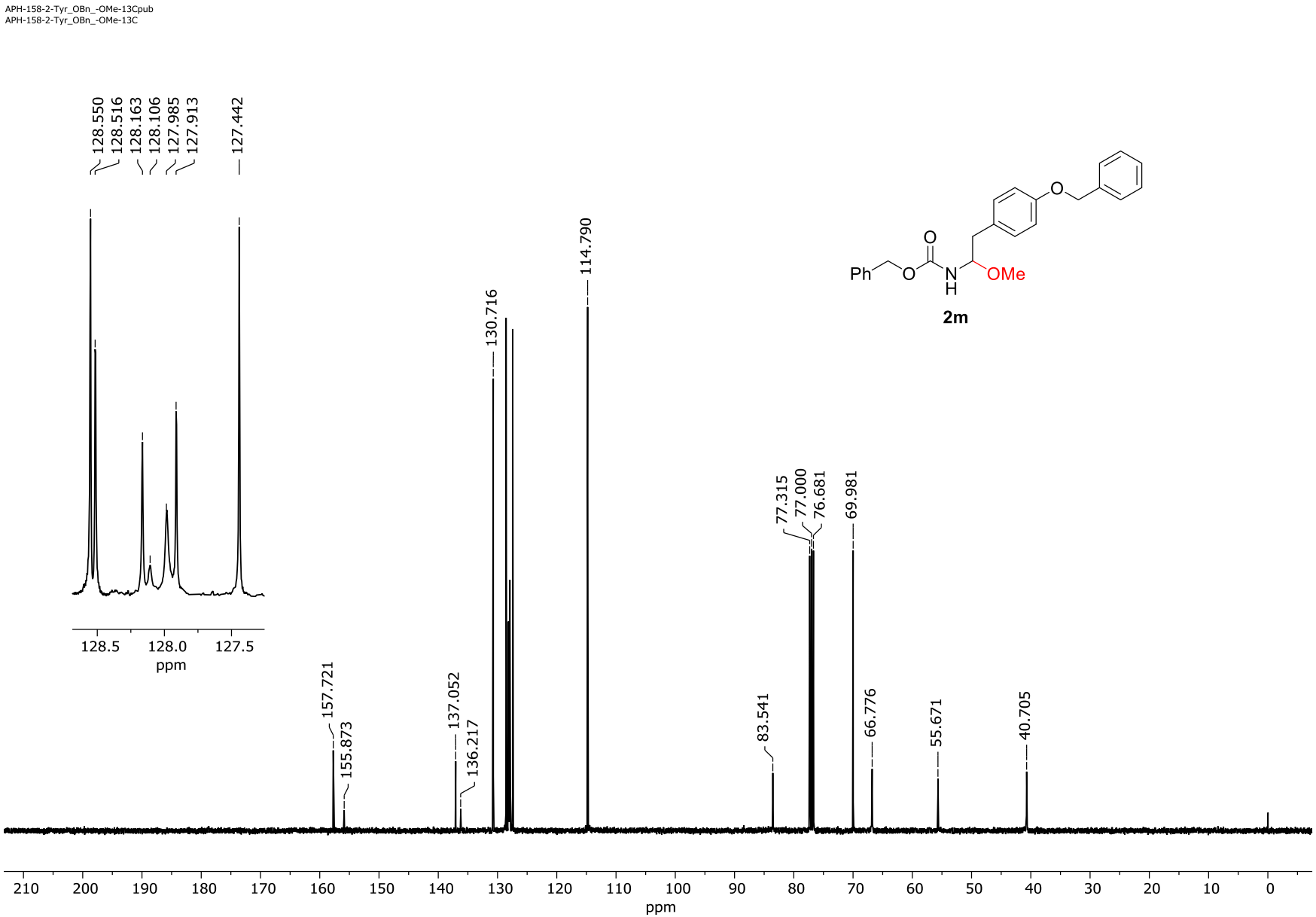
Benzyl *N*-(1-methoxy-1-phenylmethyl)carbamate (2l): ^{13}C NMR [150 MHz/$CDCl_3$]



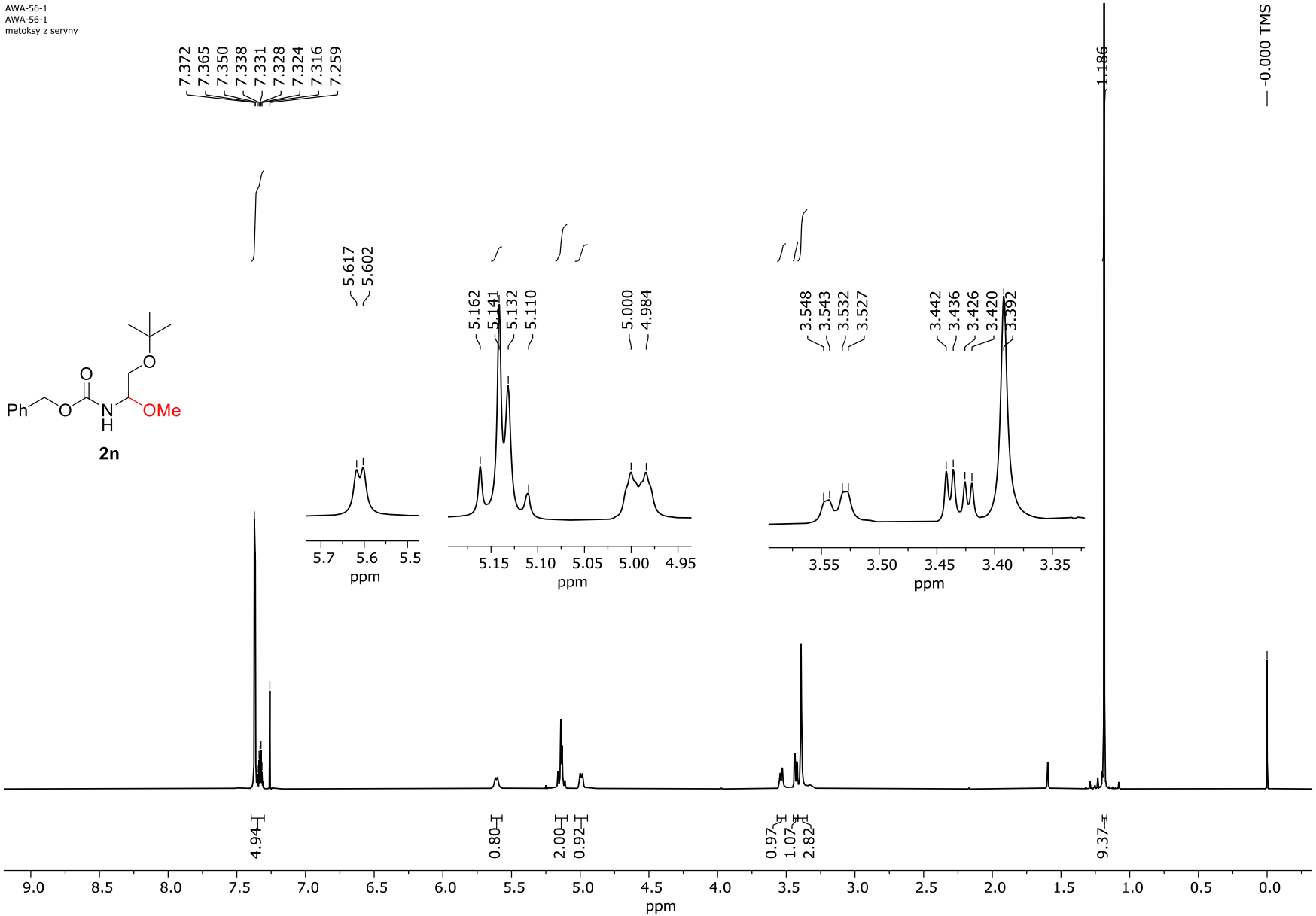
Benzyl *N*-[1-methoxy-2-(4-benzyloxyphenyl)ethyl]carbamate (2m): ^{1}H NMR [400 MHz/$CDCl_3$/TMS]



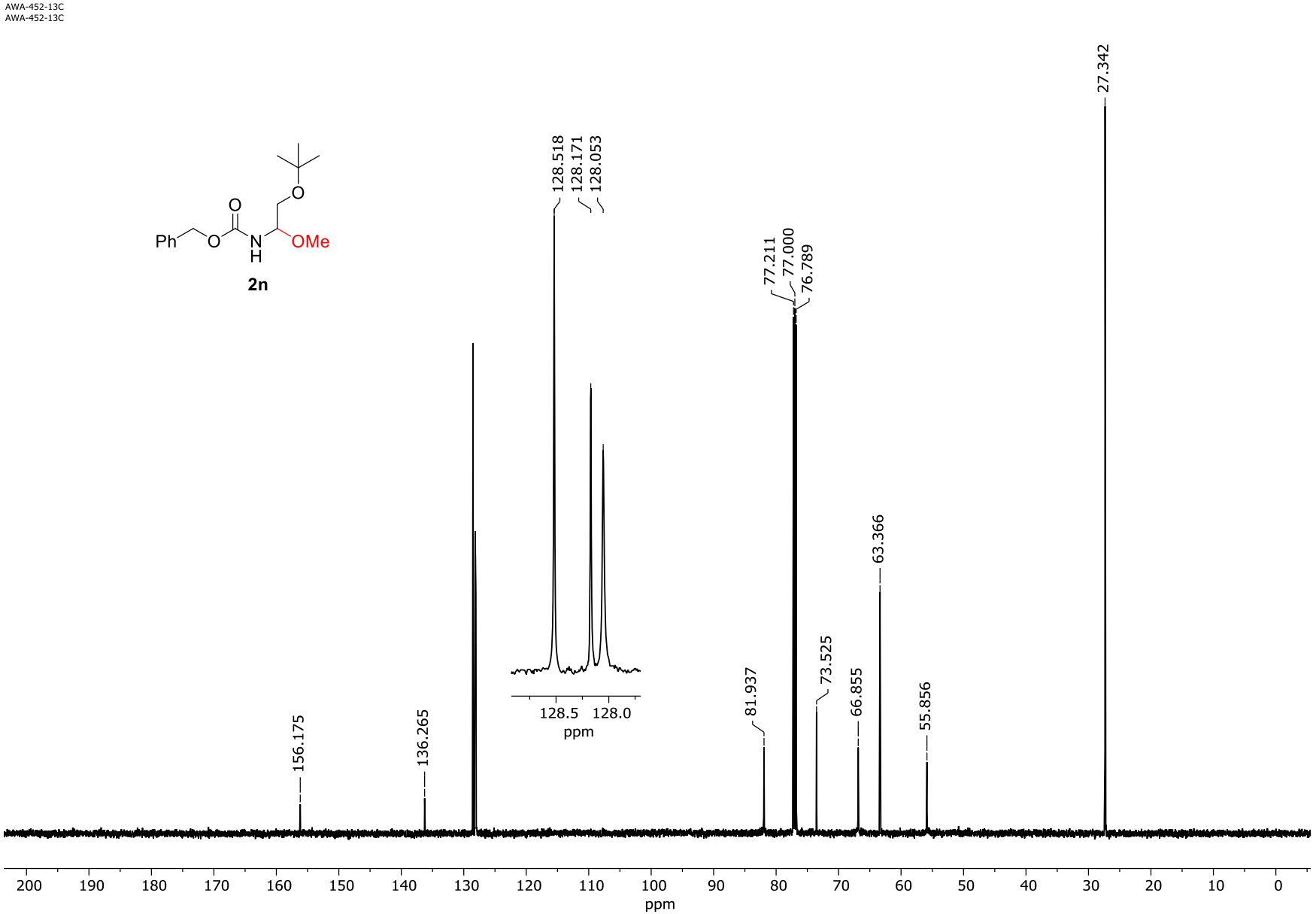
Benzyl *N*-[1-methoxy-2-(4-benzyloxyphenyl)ethyl]carbamate (2m): ^{13}C NMR [100 MHz/$CDCl_3$]



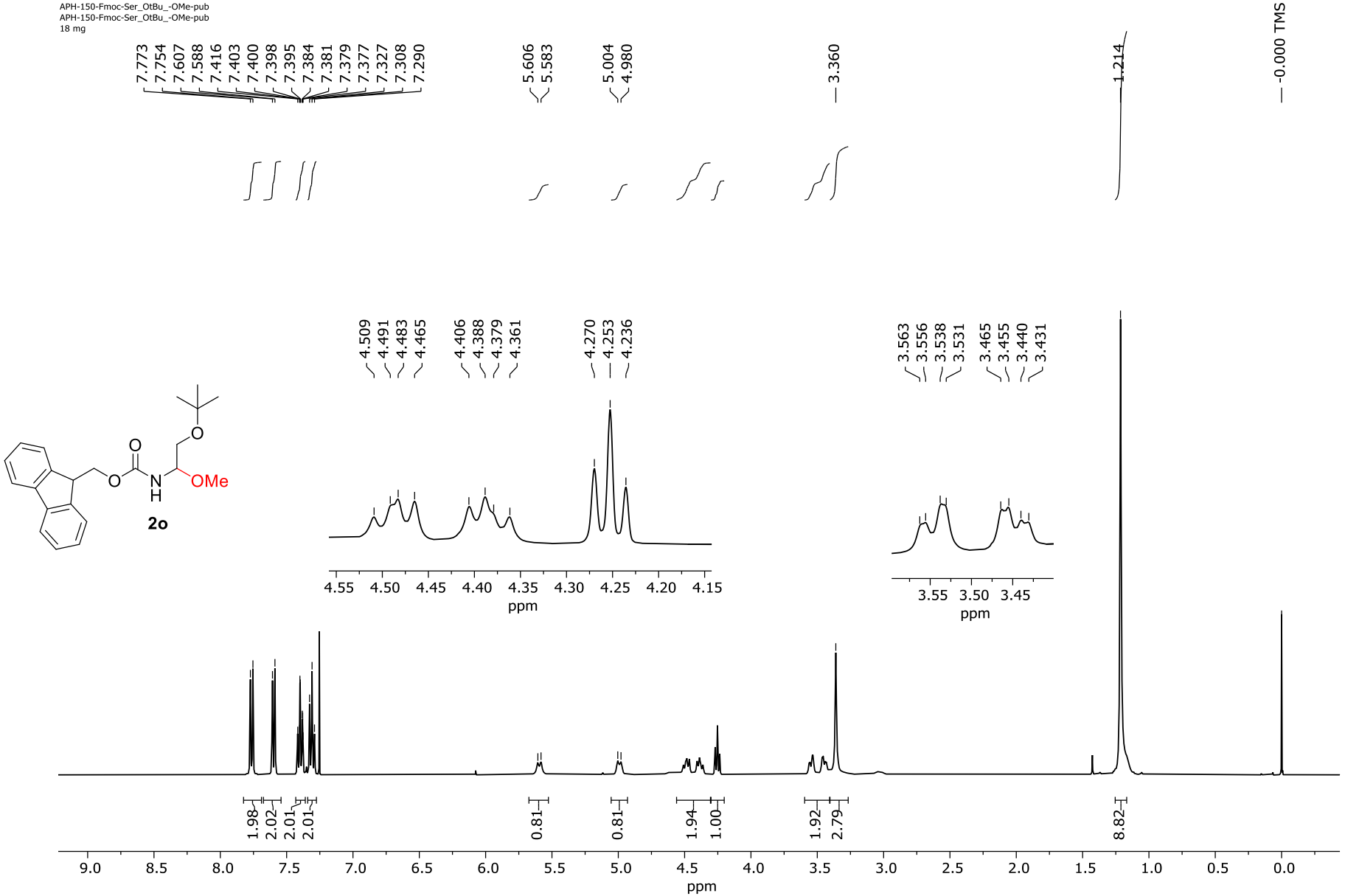
Benzyl *N*-(2-tert-butoxy-1-methoxyethyl)carbamate (2n): ^{1}H NMR [600 MHz/$CDCl_3$/TMS]



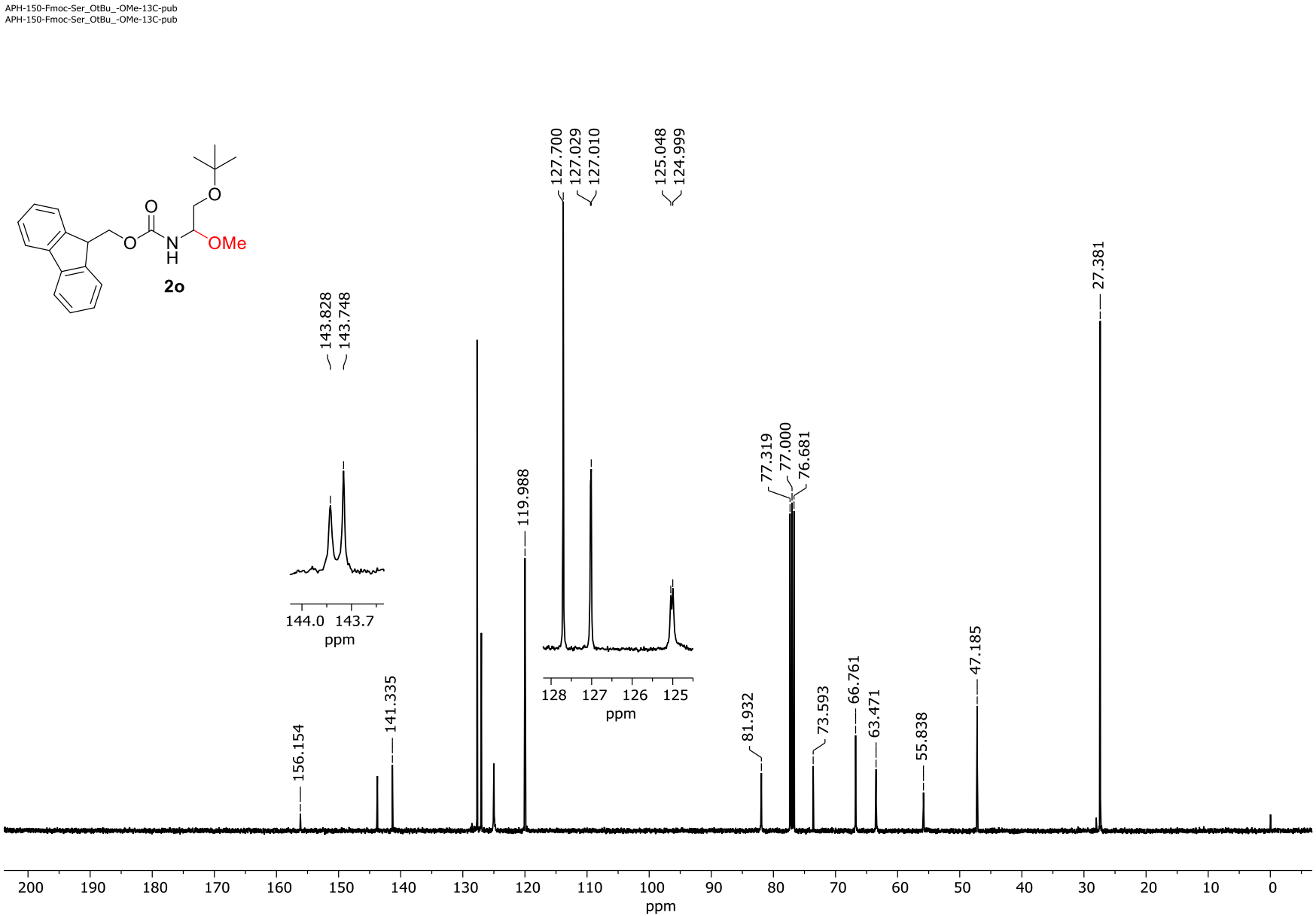
Benzyl *N*-(2-tert-butoxy-1-methoxyethyl)carbamate (2n): ^{13}C NMR [150 MHz/$CDCl_3$]



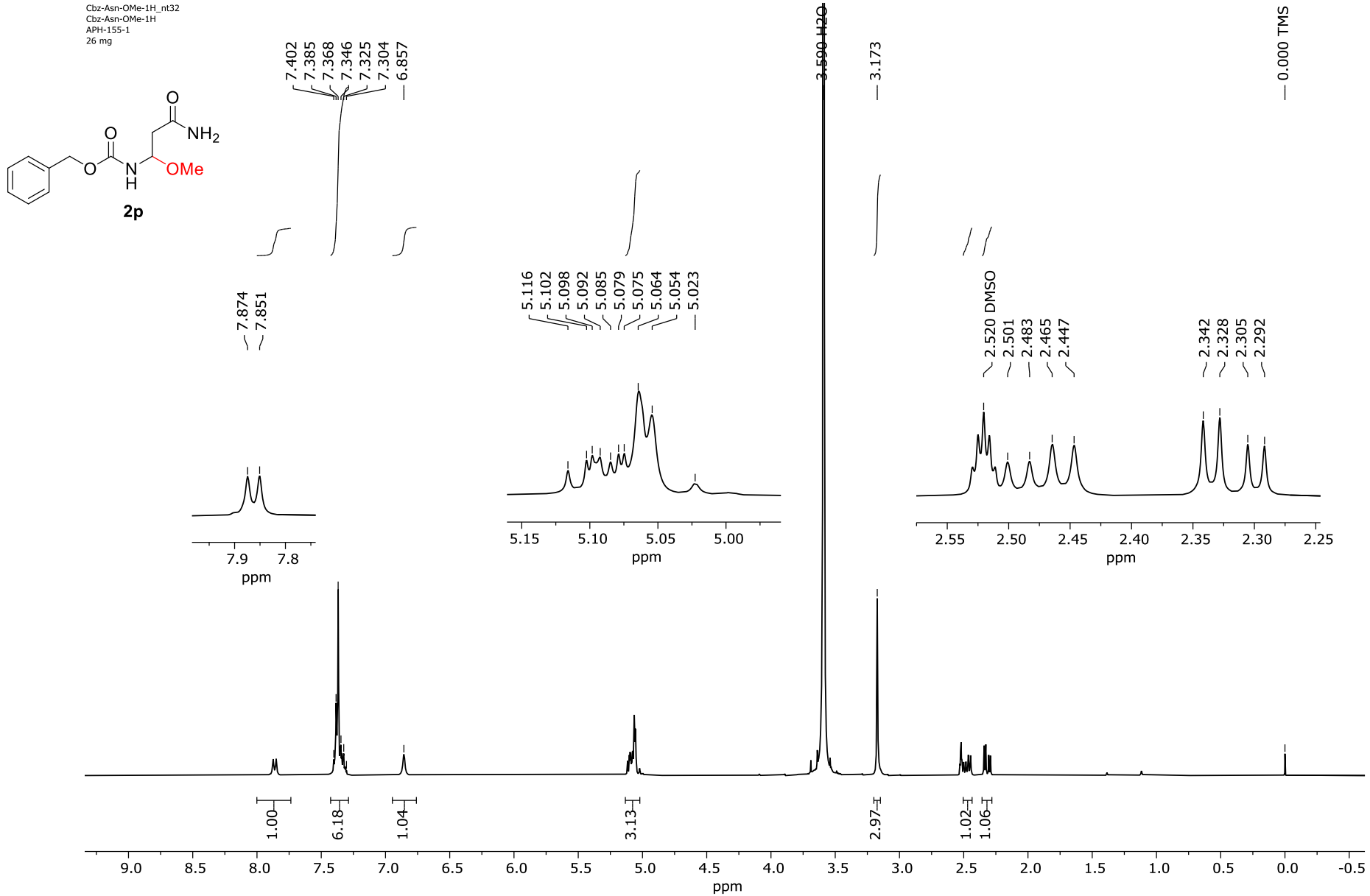
Fluorenylmethyl *N*-(2-tert-butoxy-1-methoxyethyl)carbamate (2o): ^{1}H NMR [400 MHz/$CDCl_3$/TMS]



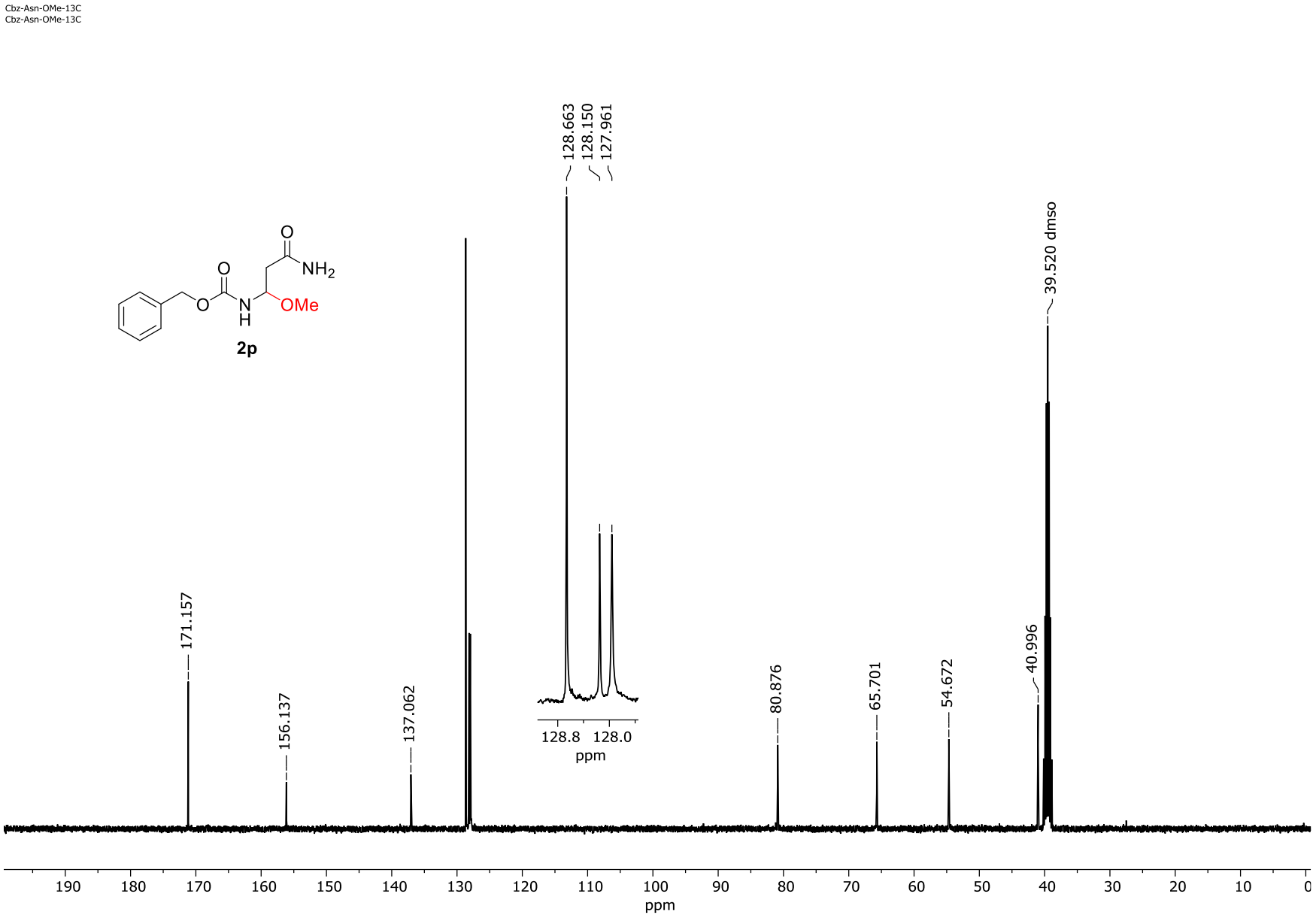
Fluorenylmethyl *N*-(2-tert-butoxy-1-methoxyethyl)carbamate (2o): ^{13}C NMR [100 MHz/$CDCl_3$]



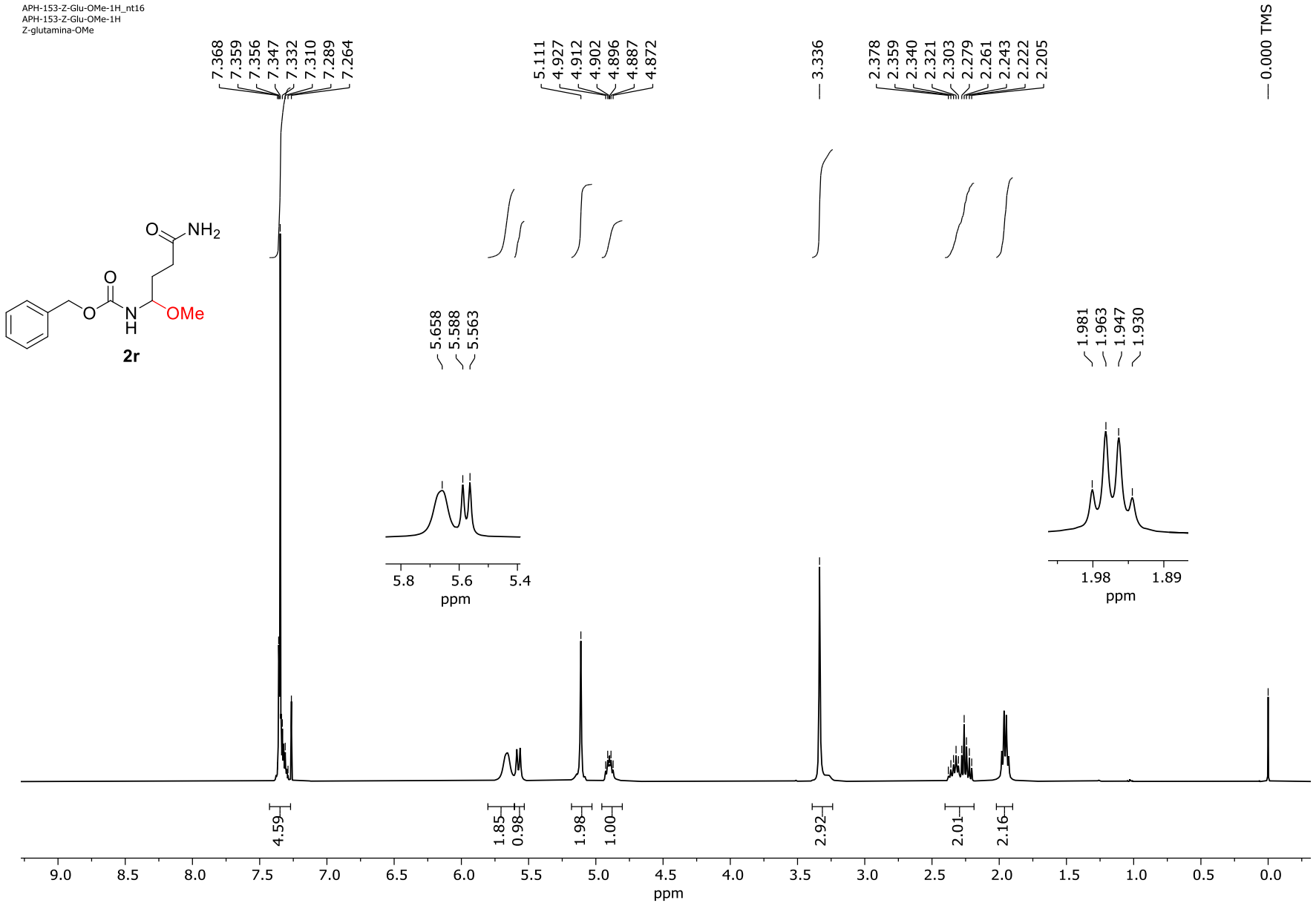
Benzyl *N*-(2-carbamoyl-1-methoxyethyl)carbamate (2p): ^{1}H NMR [400 MHz/DMSO/TMS]



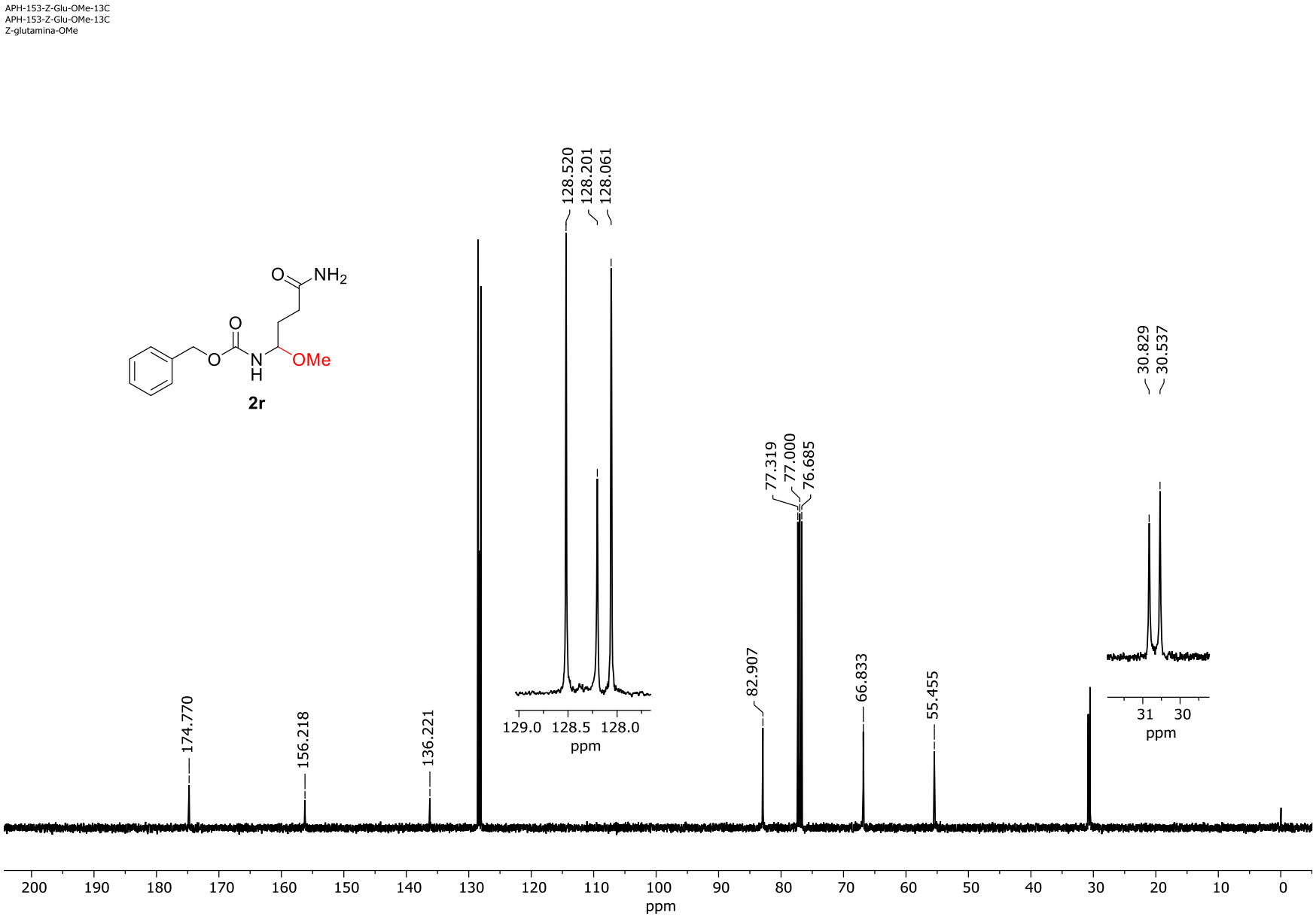
Benzyl *N*-(2-carbamoyl-1-methoxyethyl)carbamate (2p): ^{13}C NMR [100 MHz/DMSO]



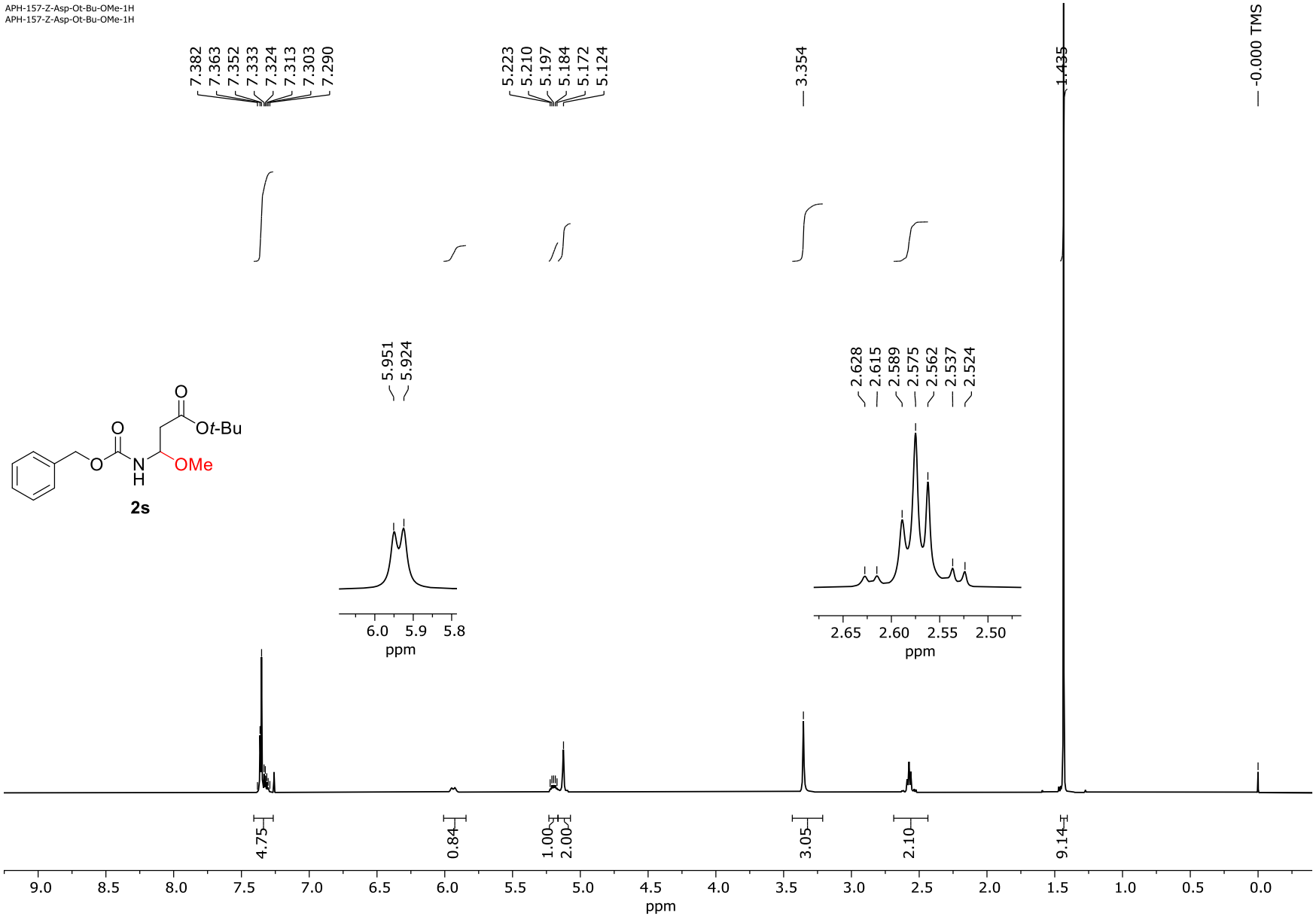
Benzyl *N*-(2-carbamoyl-1-methoxyethyl)carbamate (2r): ^{1}H NMR [400 MHz/$CDCl_3$/TMS]



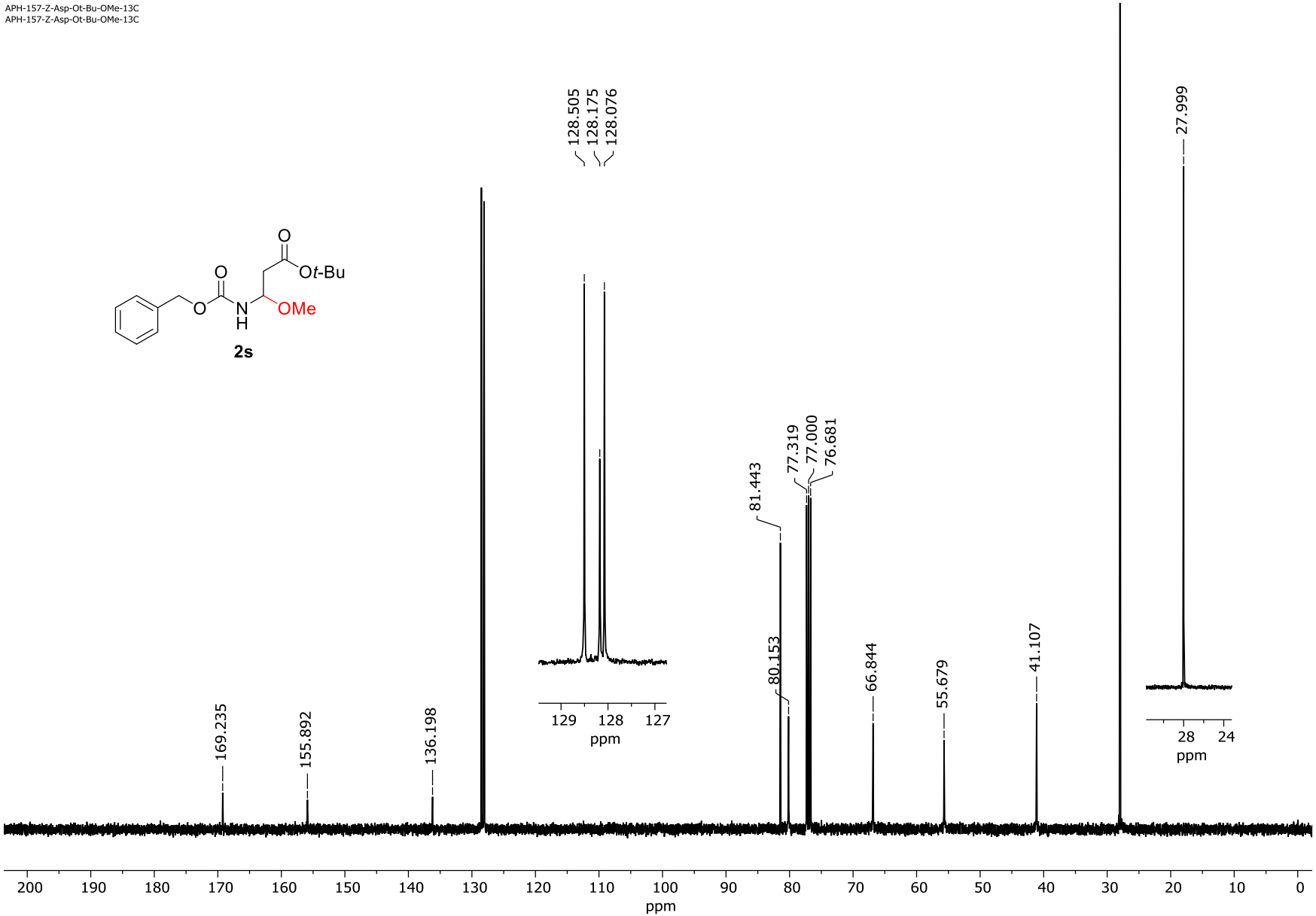
Benzyl *N*-(2-carbamoyl-1-methoxyethyl)carbamate (2r): ^{13}C NMR [100 MHz/$CDCl_3$]



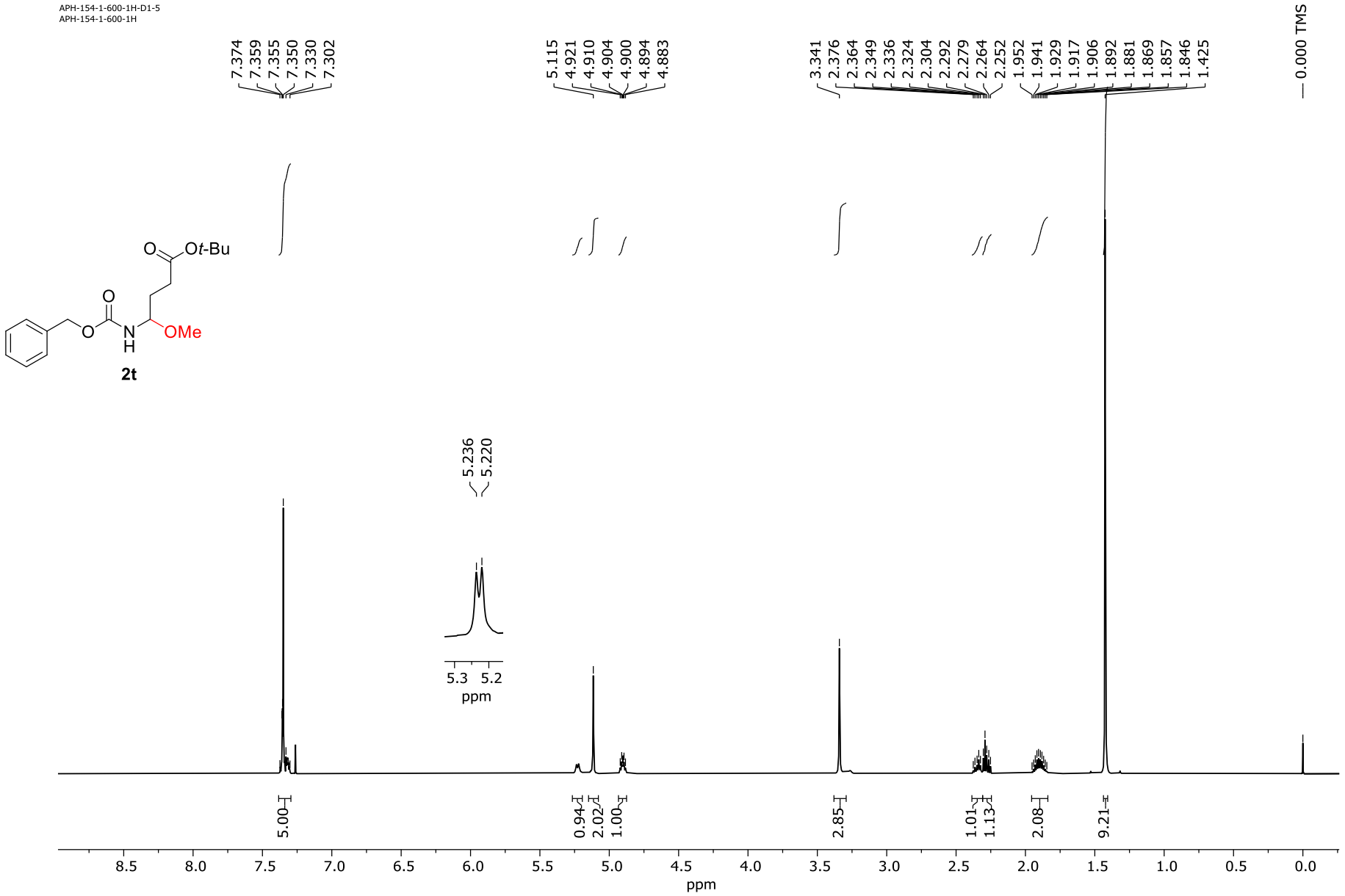
Benzyl *N*-(2-*tert*-butoxycarbonyl-1-methoxyethyl)carbamate (2s): ^{1}H NMR [400MHz/$CDCl_3$/TMS]



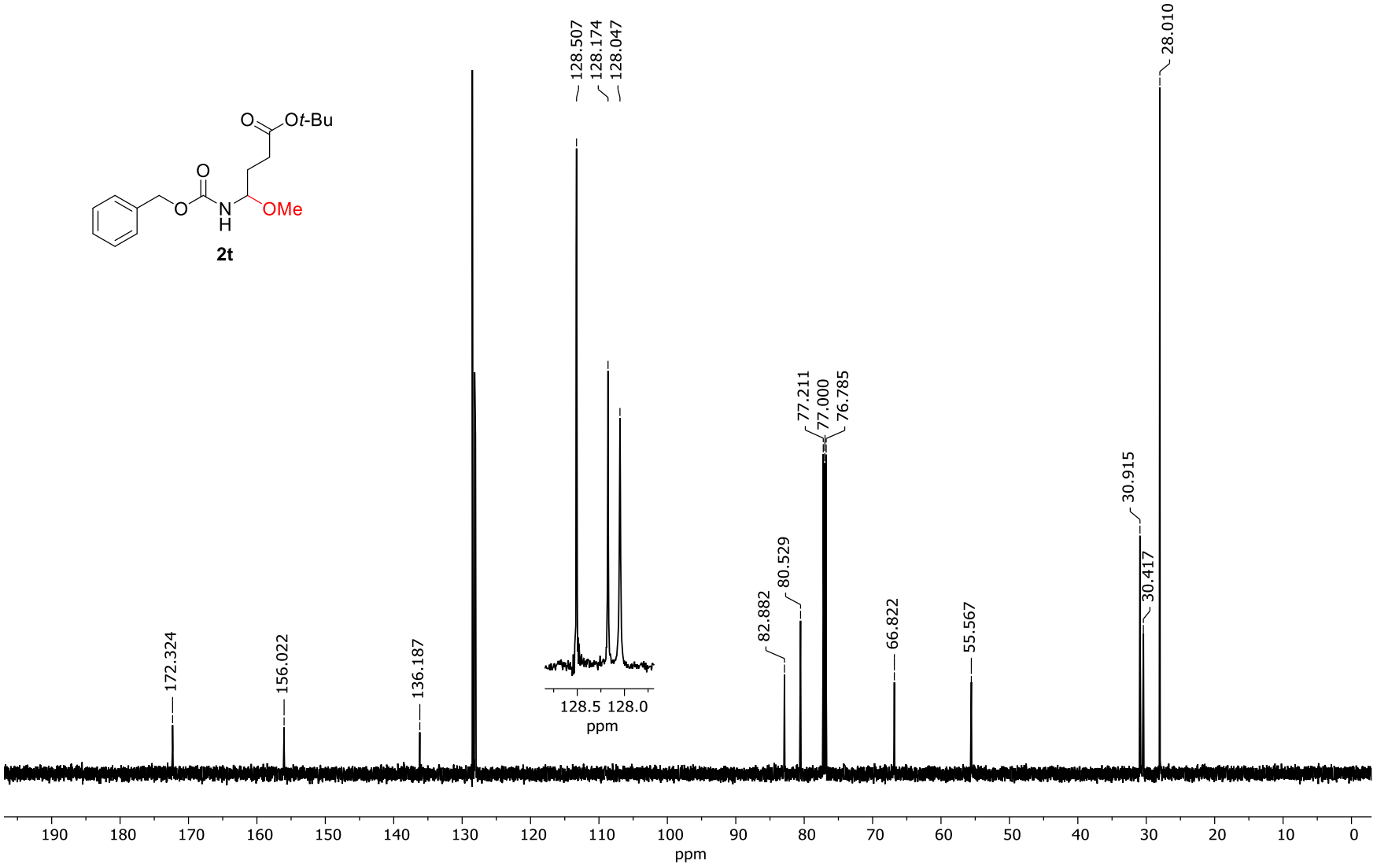
Benzyl *N*-(2-*tert*-butoxycarbonyl-1-methoxyethyl)carbamate (2s): ^{13}C NMR [100 MHz/$CDCl_3$]



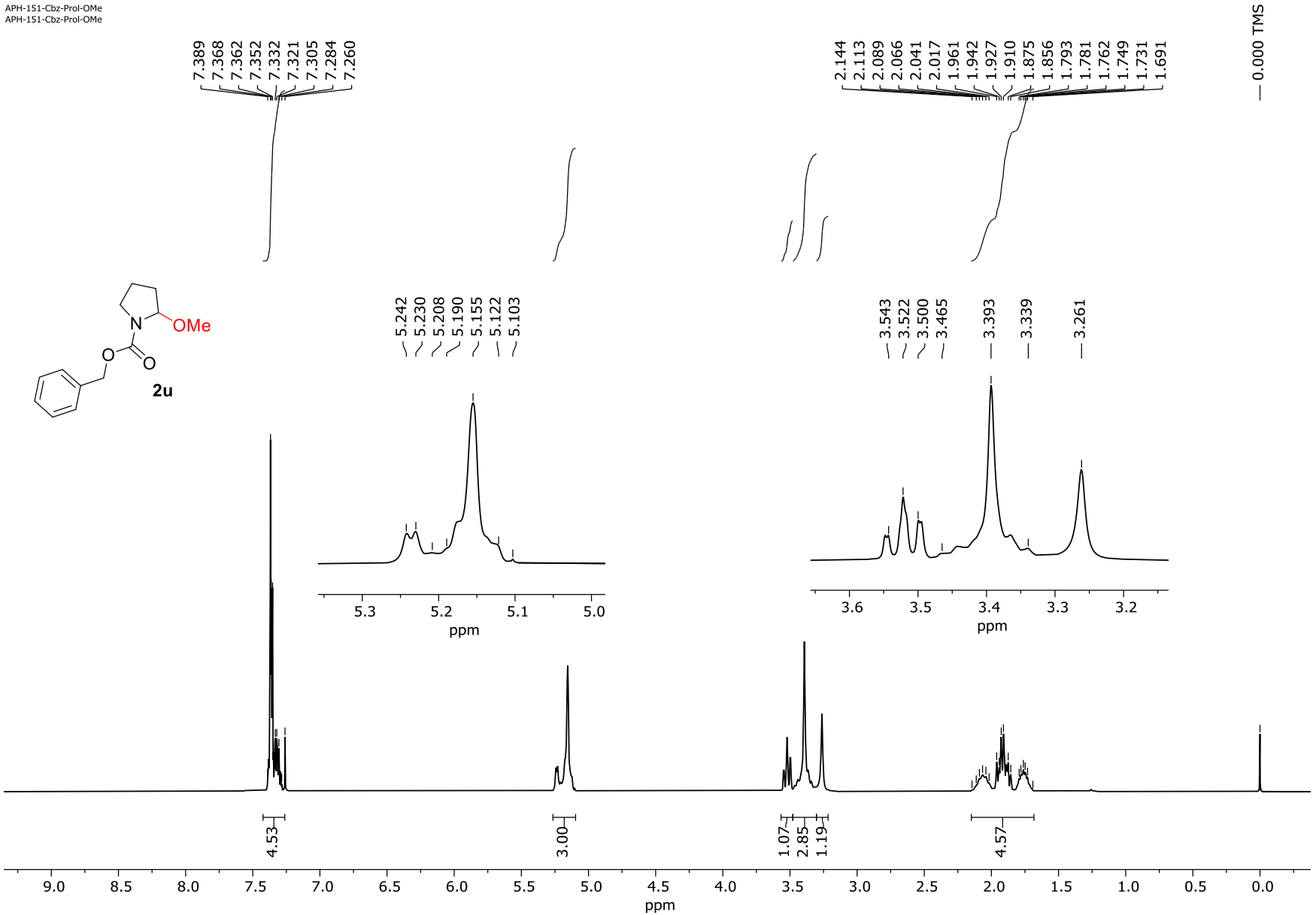
Benzyl *N*-(3-*tert*-butoxycarbonyl-1-methoxypropyl)carbamate (2t): ^{1}H NMR [600 MHz/$CDCl_3$/TMS]



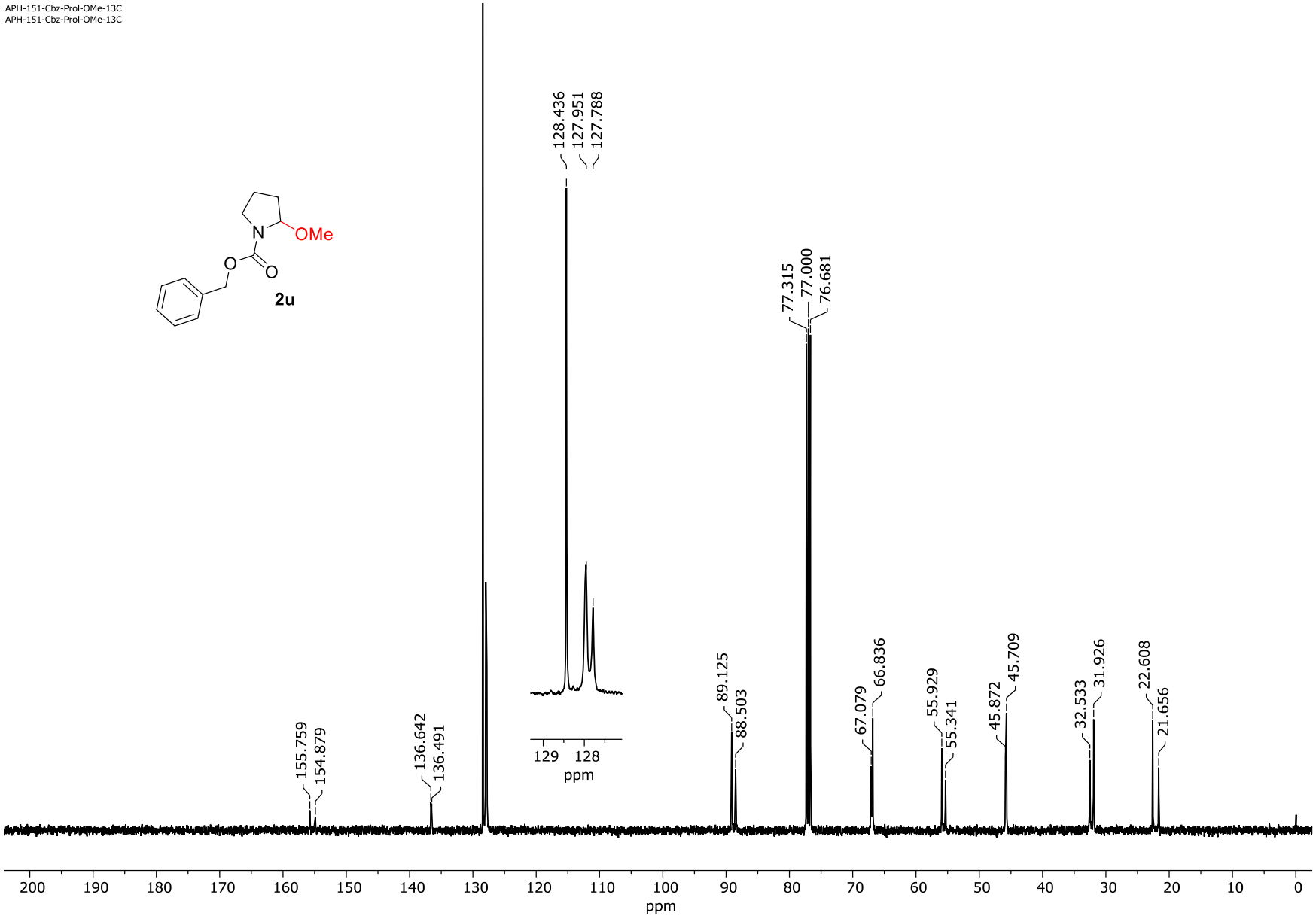
Benzyl *N*-(3-*tert*-butoxycarbonyl-1-methoxypropyl)carbamate (2t): ^{13}C NMR [150 MHz/$CDCl_3$]



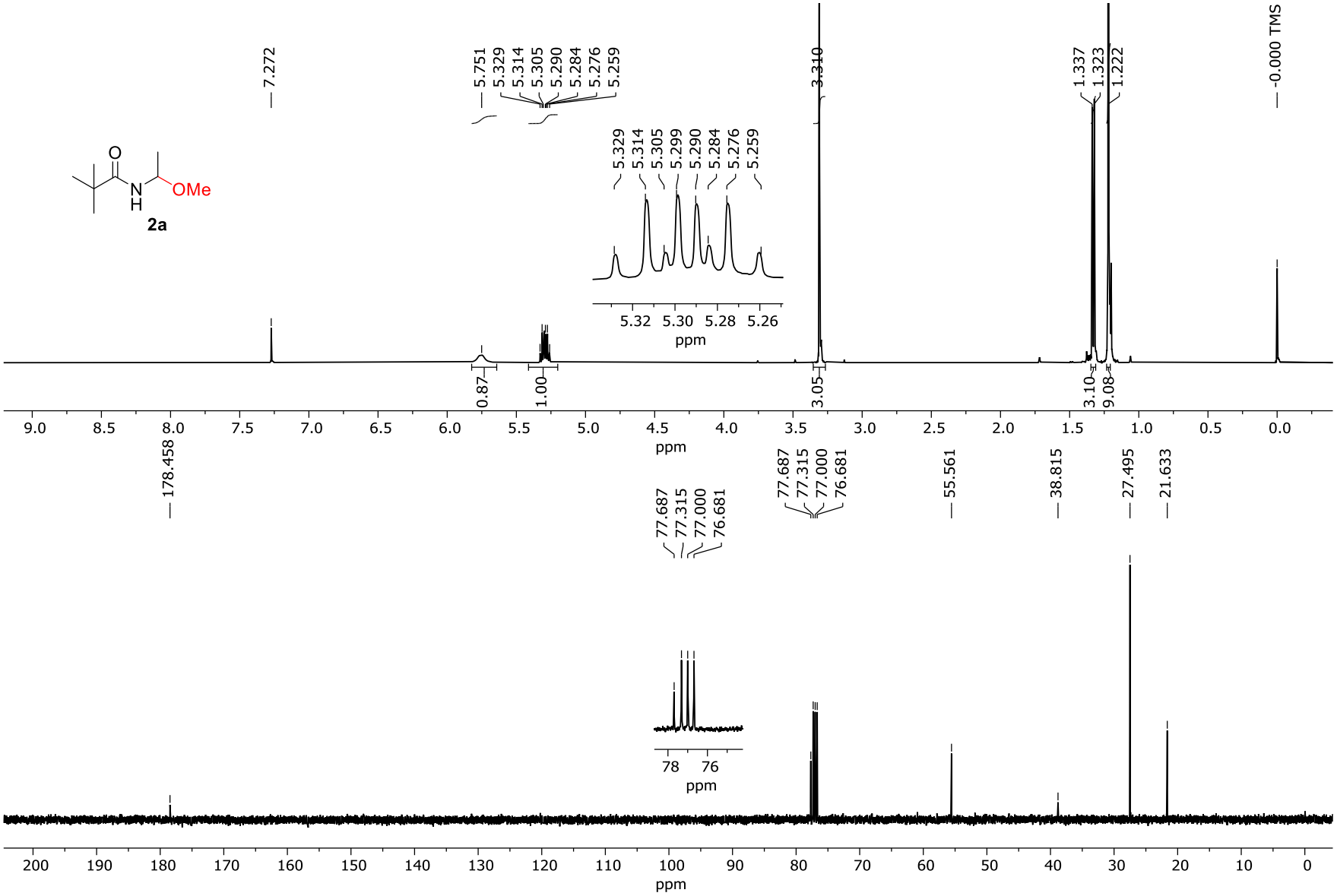
***N*-(Benzyloxycarbonyl)-2-methoxypyrolidine (2u):** ^{1}H NMR [400 MHz/$CDCl_3$/TMS]



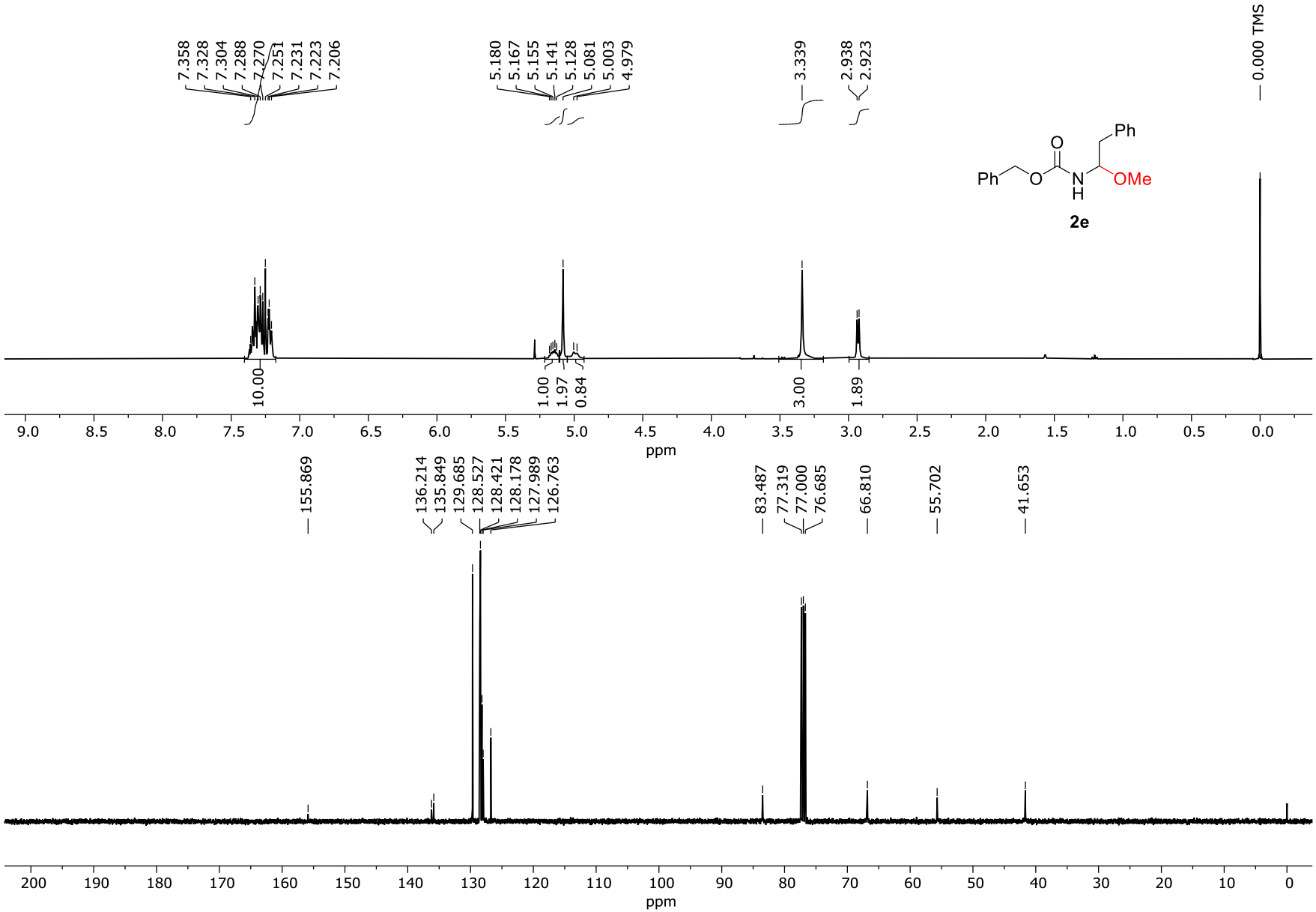
_N_-(Benzyloxycarbonyl)-2-methoxypyrolidine (2u): ^{13}C NMR [100 MHz/$CDCl_3$]



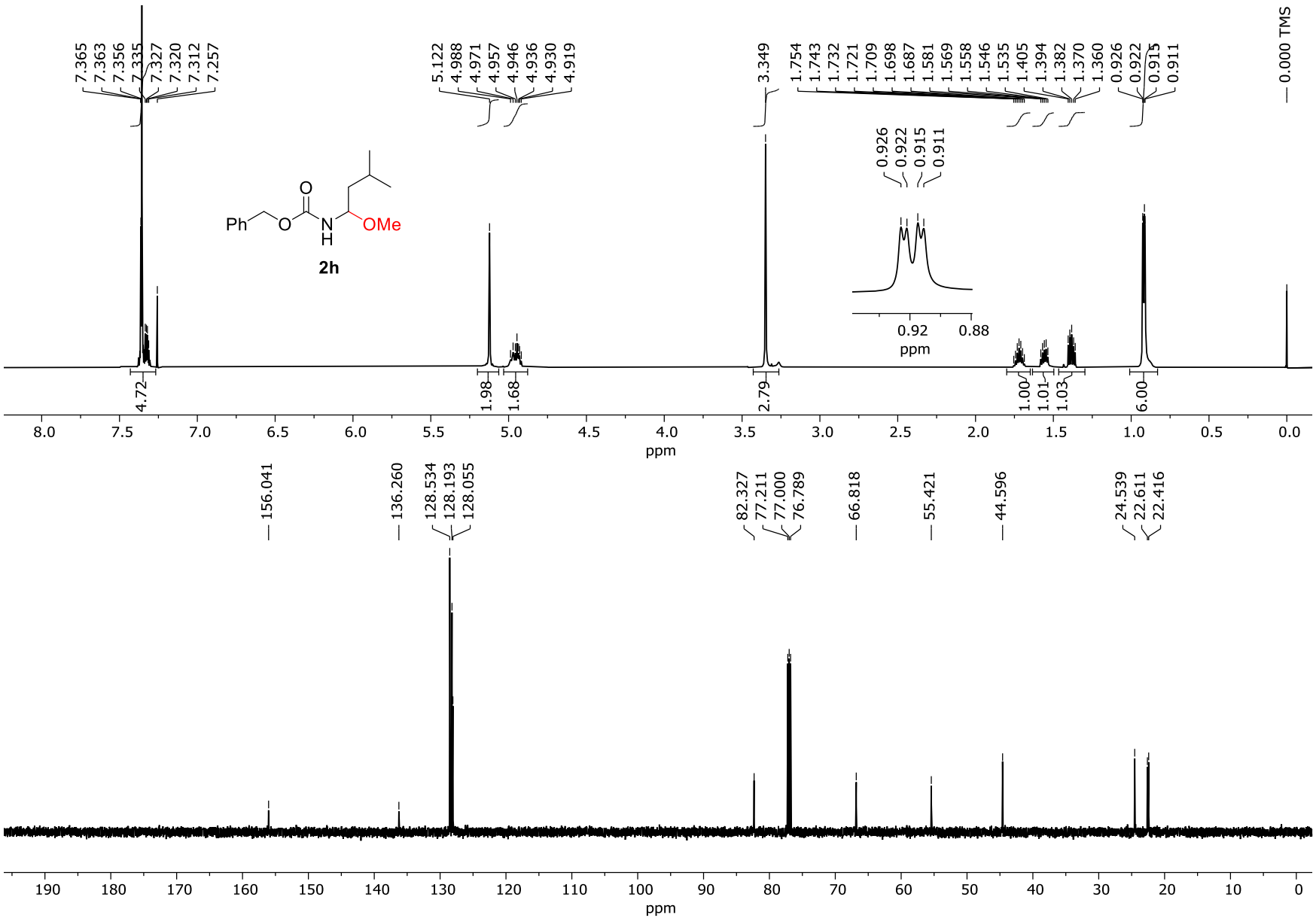
***N*-(1-methoxyethyl)pivaloylamide (2a):** ^{1}H NMR [400 MHz/$CDCl_3$/TMS] and ^{13}C NMR [100 MHz/$CDCl_3$]



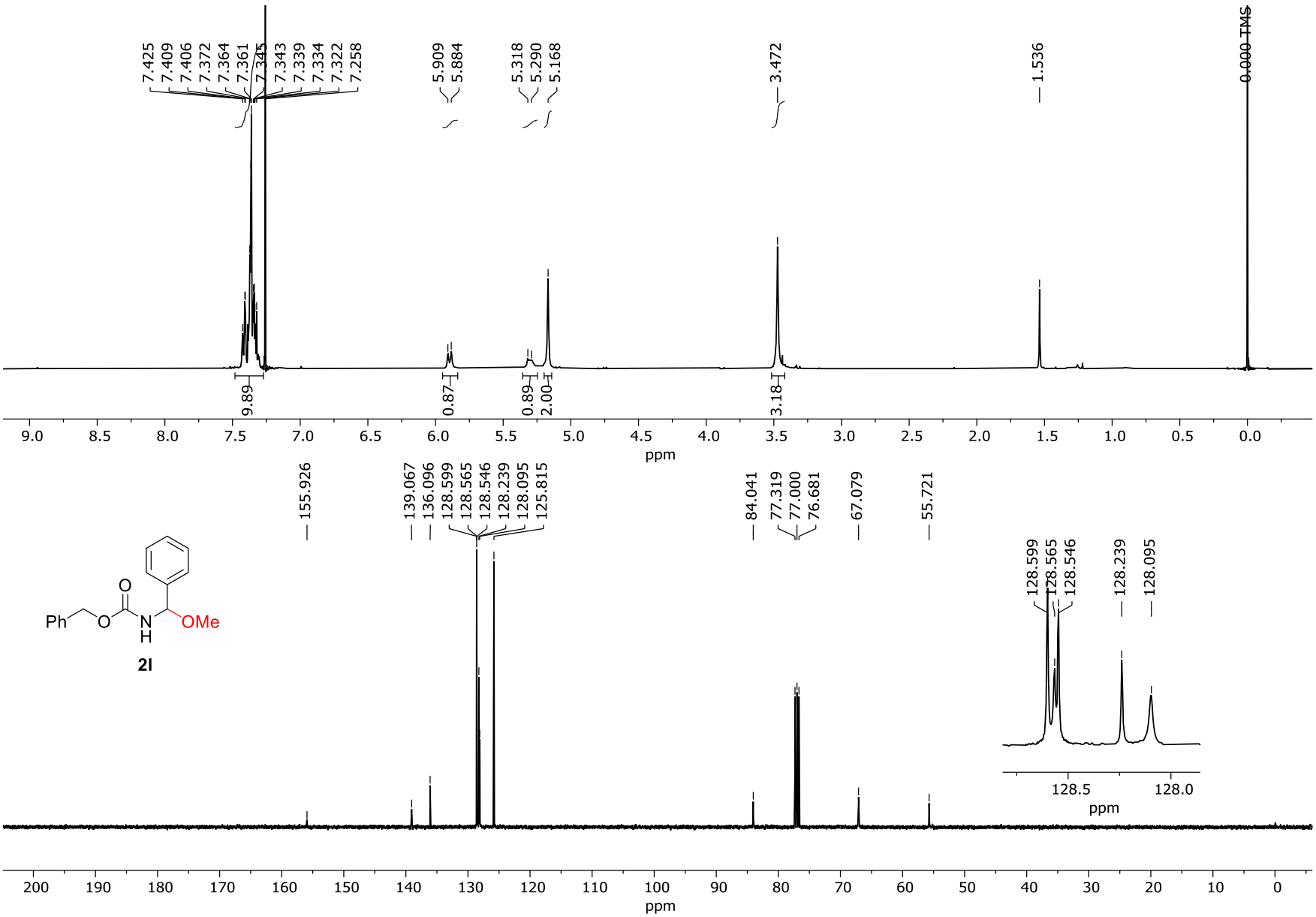
Benzyl *N*-(1-methoxy-2-phenylethyl)carbamate (2e): ^{1}H NMR [400 MHz/$CDCl_3$/TMS] and ^{13}C NMR [100 MHz/$CDCl_3$]



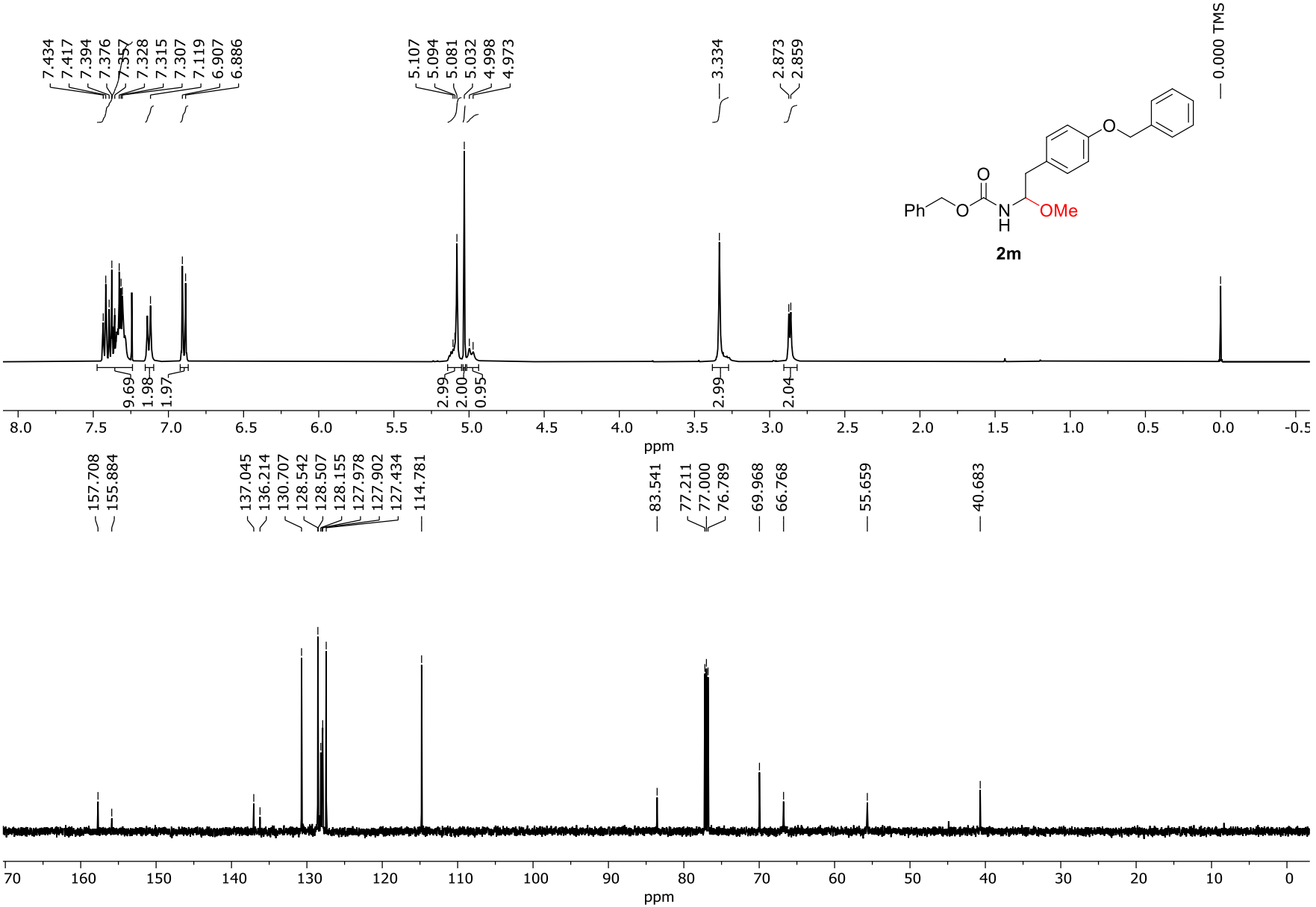
Benzyl *N*-(1-metoxy-3-methylbutyl)carbamate (2h): ^{1}H NMR [600 MHz/$CDCl_3$/TMS] and ^{13}C NMR [150 MHz/$CDCl_3$]



Benzyl *N*-(1-methoxy-1-phenylmethyl)carbamate (2l): ^{1}H NMR [400 MHz/$CDCl_3$/TMS] and ^{13}C NMR [100 MHz/$CDCl_3$]



Benzyl *N*-[1-methoxy-2-(4-benzyloxyphenyl)ethyl]carbamate (2m): ^{1}H NMR [400 MHz/$CDCl_3$/TMS] and ^{13}C NMR [150 MHz/$CDCl_3$]



Benzyl *N*-(3-*tert*-butoxycarbonyl-1-methoxypropyl)carbamate (2t): ^{1}H NMR [400 MHz/$CDCl_3$/TMS] and ^{13}C NMR [100 MHz/$CDCl_3$]