

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

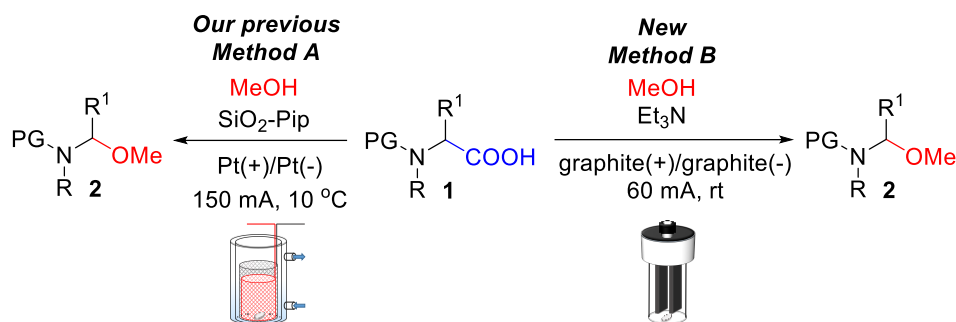


Table S1 Decarboxylative α -methoxylation of *N*-protected α -amino acids **1** to *N*-protected (1-methoxyalkyl)amines **2**

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

^a Conditions: Substrate **1** (3 mmol), SiO₂-Pip (200 mg, 0.22 mmol), MeOH (10 mL), at 10 °C, constant current (150 mA), and charge 3.0-3.75 F/mol. Alkoxylation was 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.

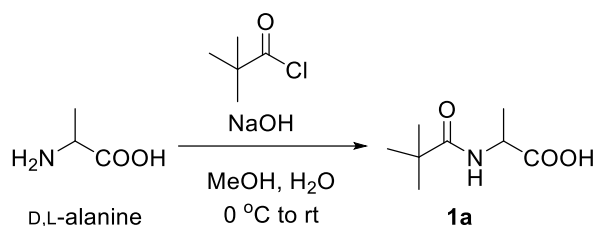
^b Conditions: Substrate **1** (0.4 mmol), Et₃N (4.2 μ L, 0.03 mmol), MeOH (4 mL) in a 5 mL vial, at room temperature, constant current (60 mA), graphite SK-50 electrodes (anode and cathode), and charge 2.1 F/mol. Methoxylation was carried out using commercially available, compact setup –IKA®ElectraSyn 2.0

^c Isolated yield. ^d A complex reaction mixture.

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

² A. Wałęcka-Kurczyk, K. Walczak, A. Kuźnik, S. Stecko, A. Październiak-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 Na₂SO₄, 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.

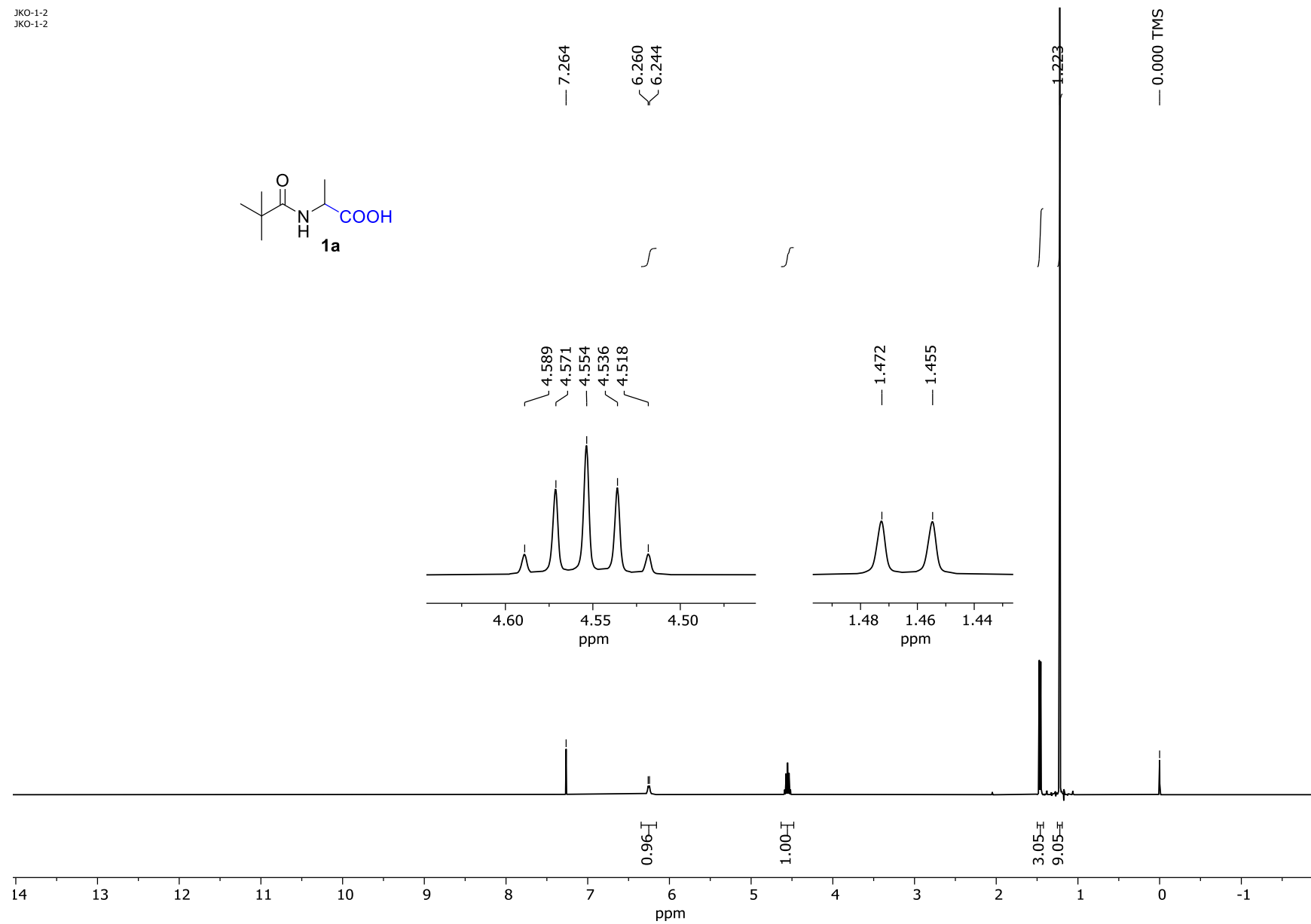
N-Pivaloyl-D,L-alanine (**1a**)

White solid (7.27 g, 70% yield): mp = 137.0-139.0 °C (lit.³ mp = 122.0-126.0 °C). ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (100 MHz, CDCl₃) 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.

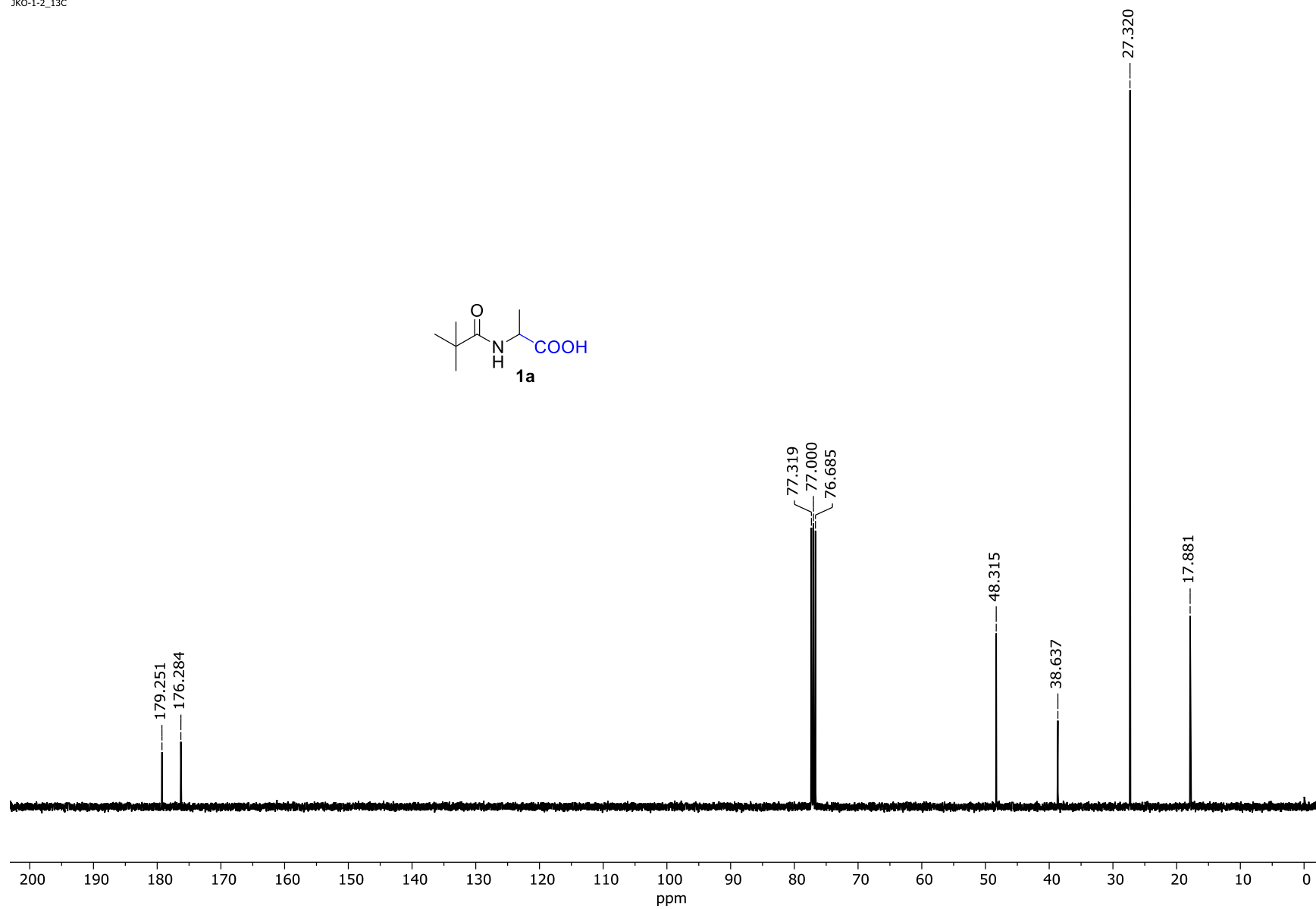
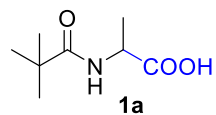
***N*-Pivaloyl-D,L-alanine (1a): ¹H NMR [400 MHz/CDCl₃/TMS]**

JKO-1-2
JKO-1-2



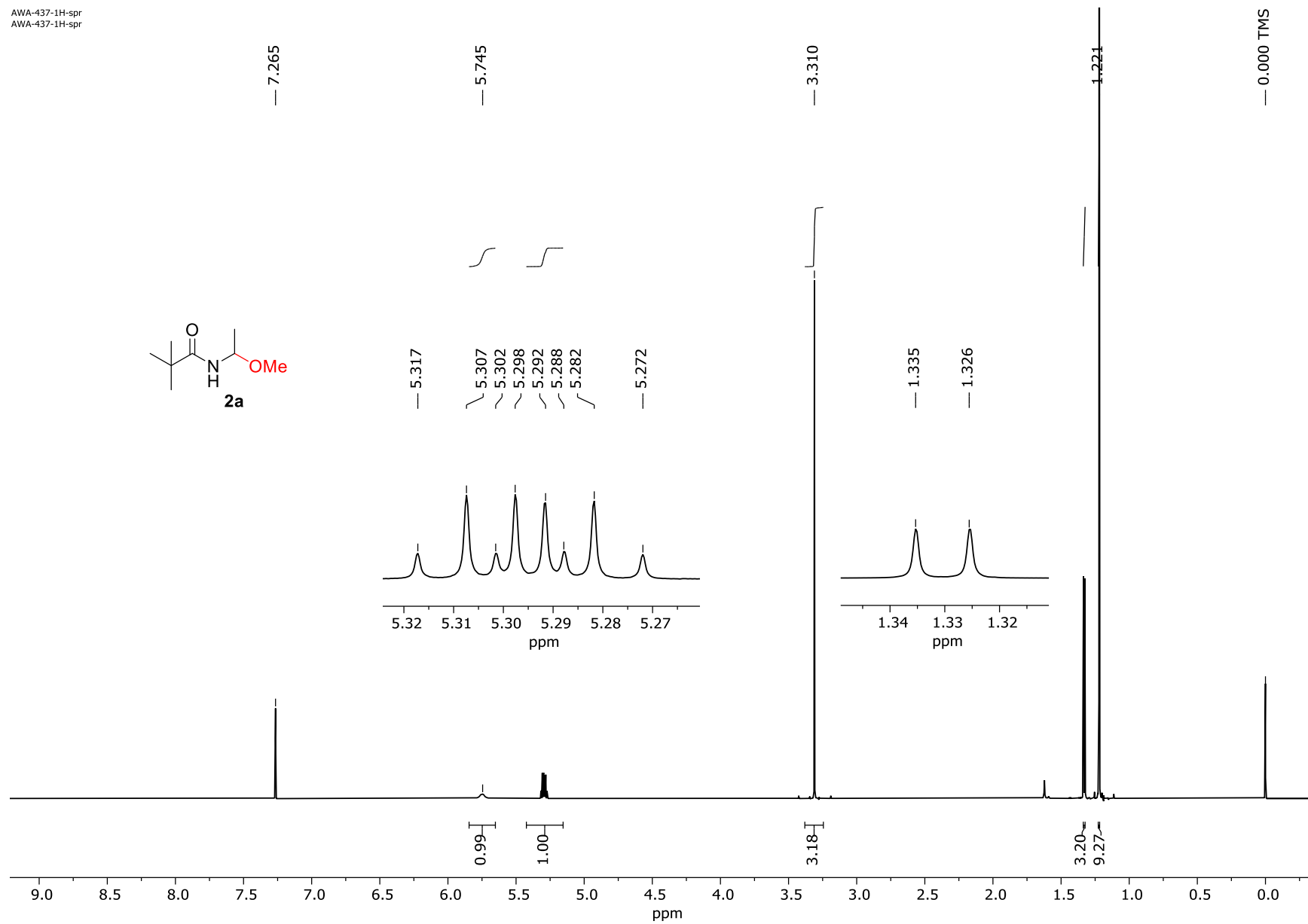
***N*-Pivaloyl-D,L-alanine (1a):** ^{13}C NMR [100 MHz/ CDCl_3]

JKO-1-2-13c
JKO-1-2_13C



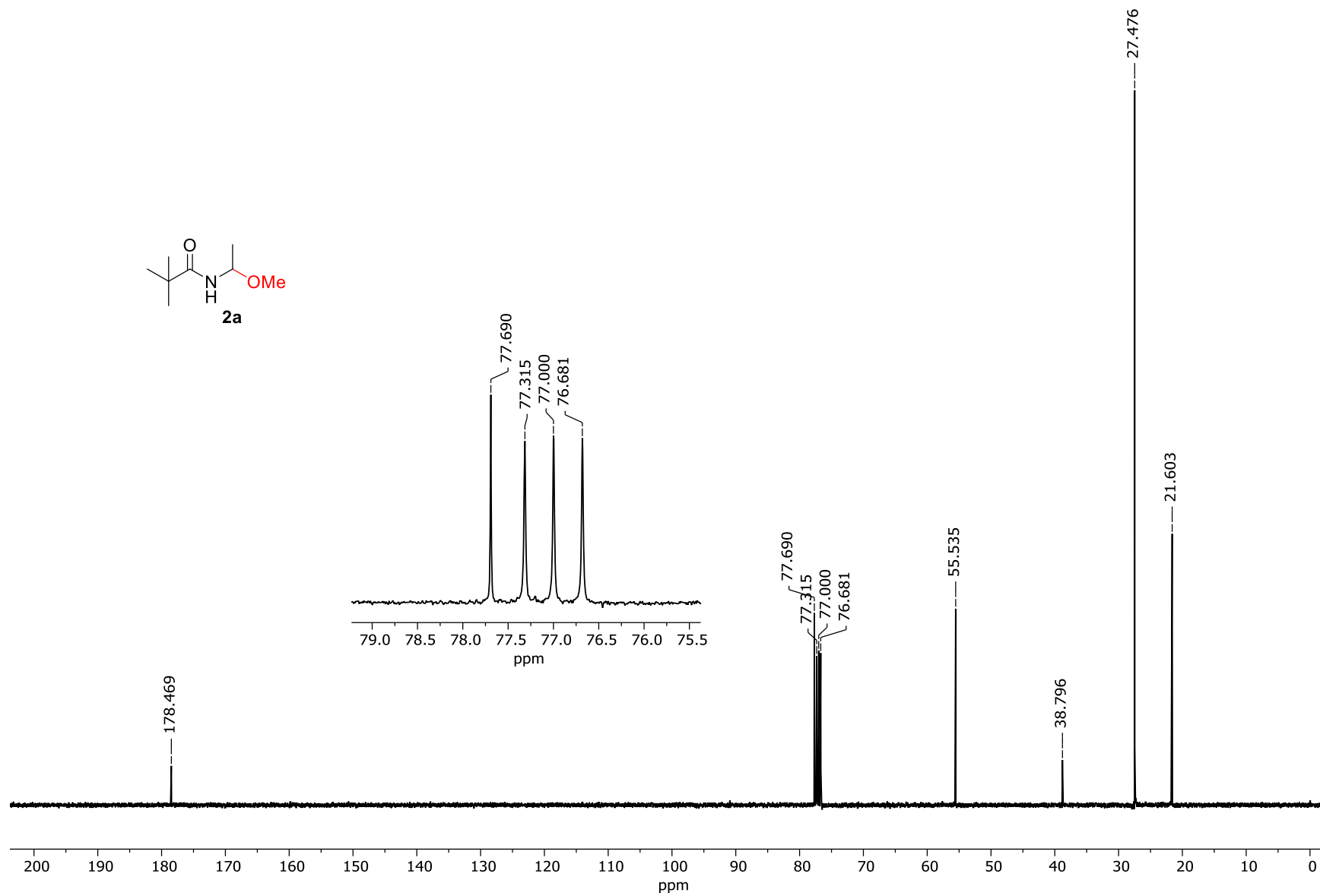
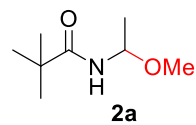
***N*-(1-methoxyethyl)pivaloylamide (2a): ¹H NMR [600 MHz/¹³CDCl₃/TMS]**

AWA-437-1H-spr
AWA-437-1H-spr



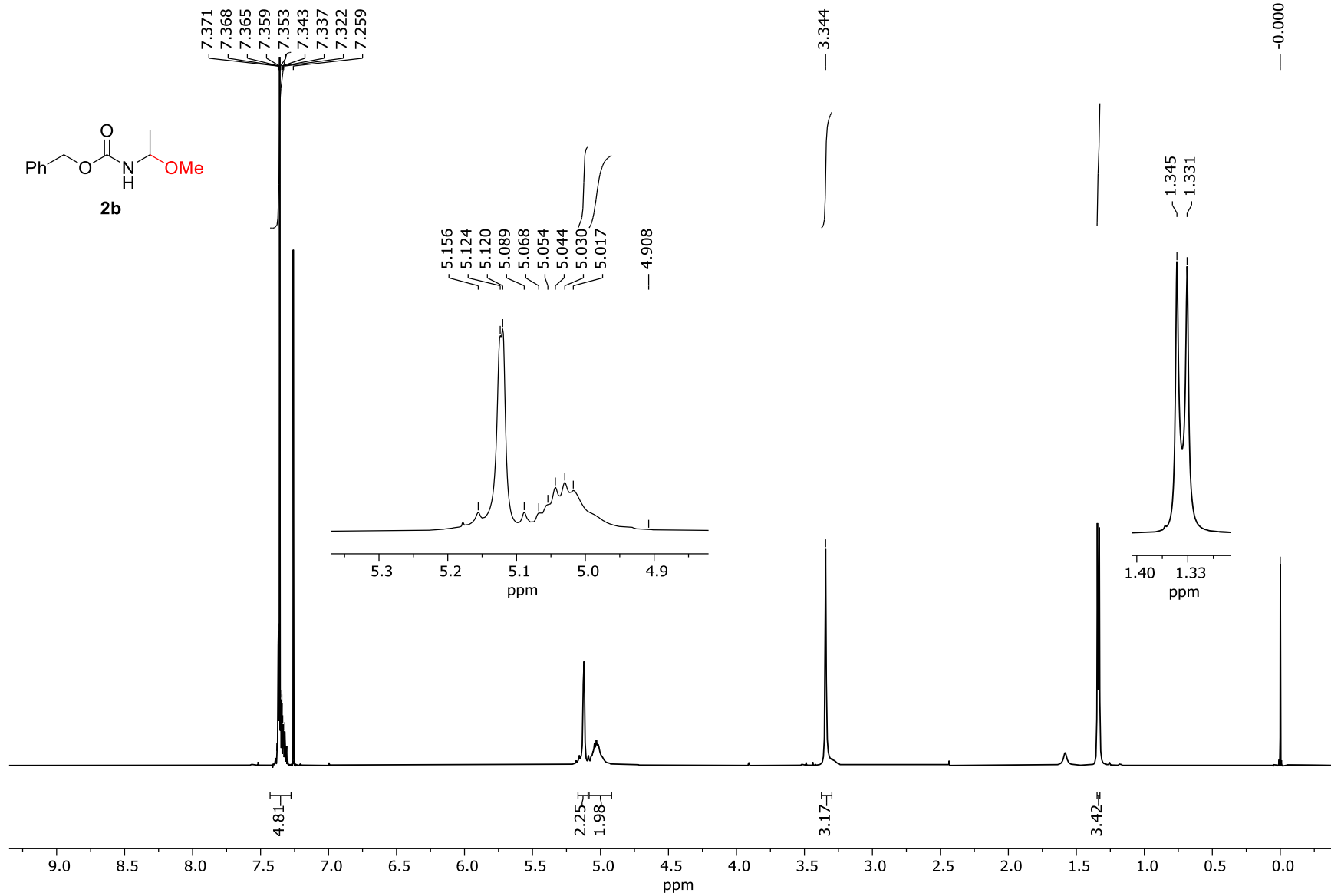
***N*-(1-methoxyethyl)pivaloylamide (2a): ^{13}C NMR [100 MHz/ CDCl_3]**

AWA-431-13C
AWA-431-13C



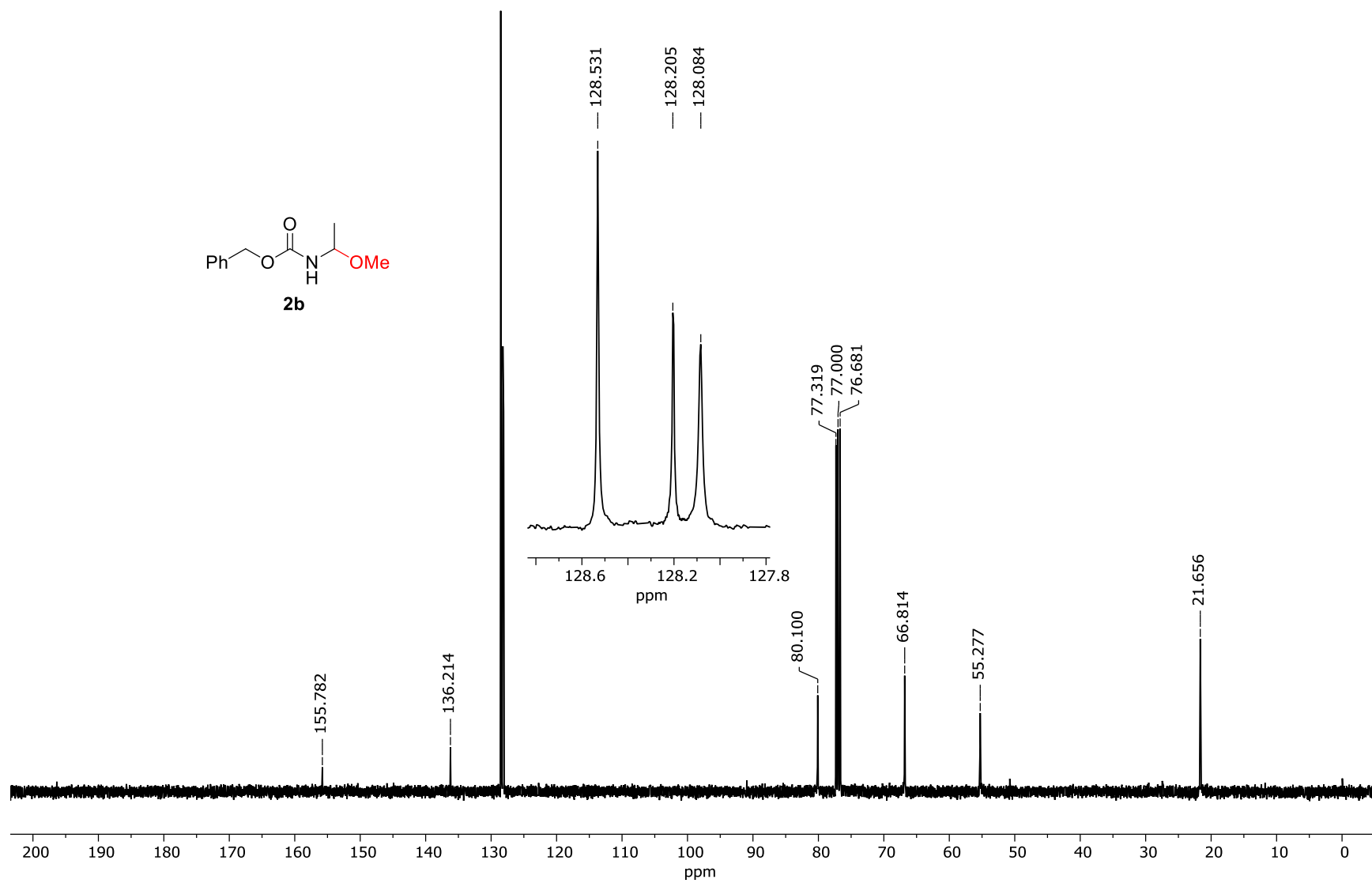
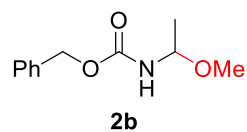
Benzyl *N*-(1-methoxyethyl)carbamate (2b): ¹H NMR [400 MHz/CDCl₃/TMS]

AWA-359-1
AWA-359-1



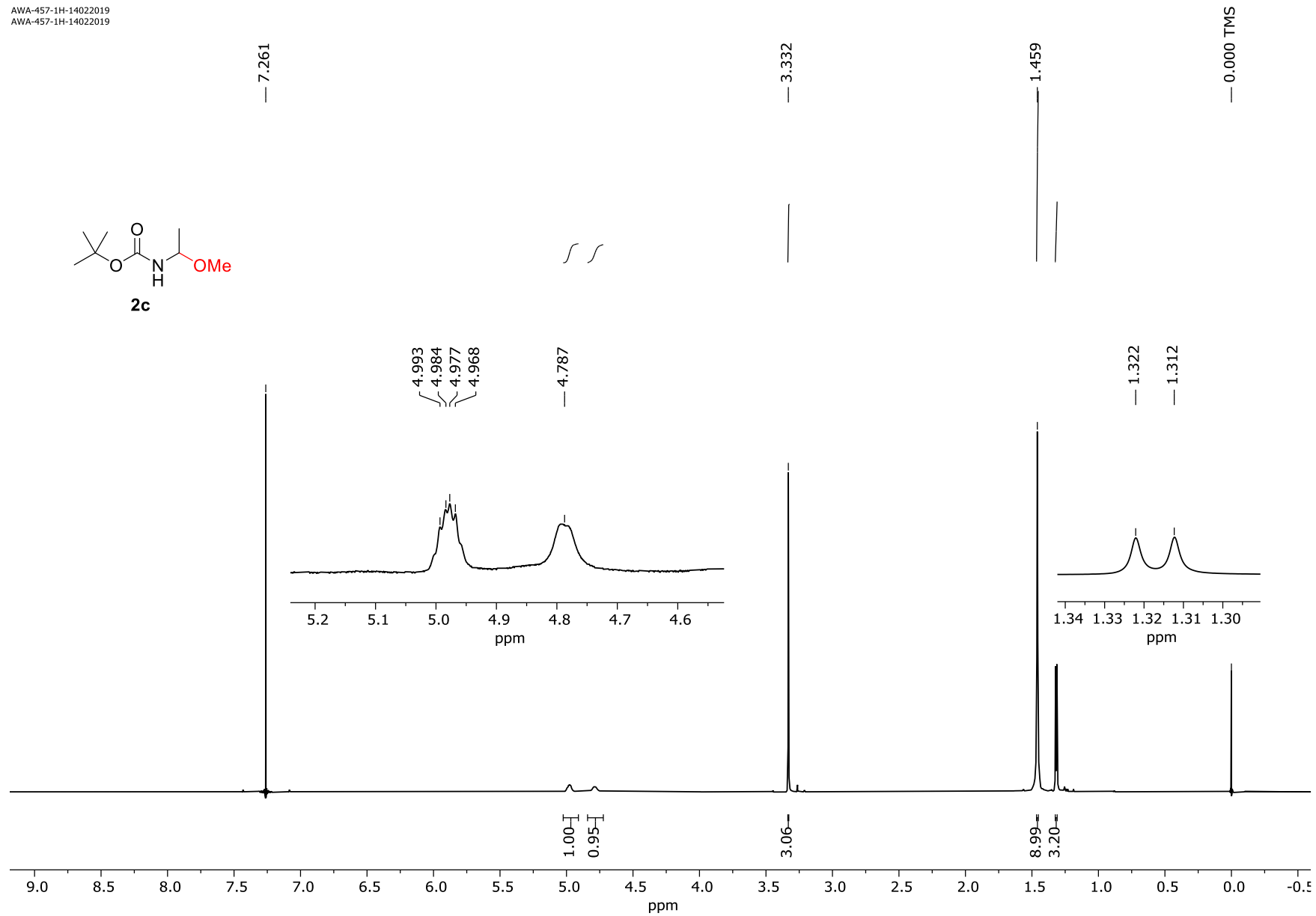
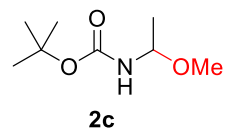
Benzyl N-(1-methoxyethyl)carbamate (2b): ^{13}C NMR [100 MHz/ CDCl_3]

AWA-439-13C
AWA-439-13C



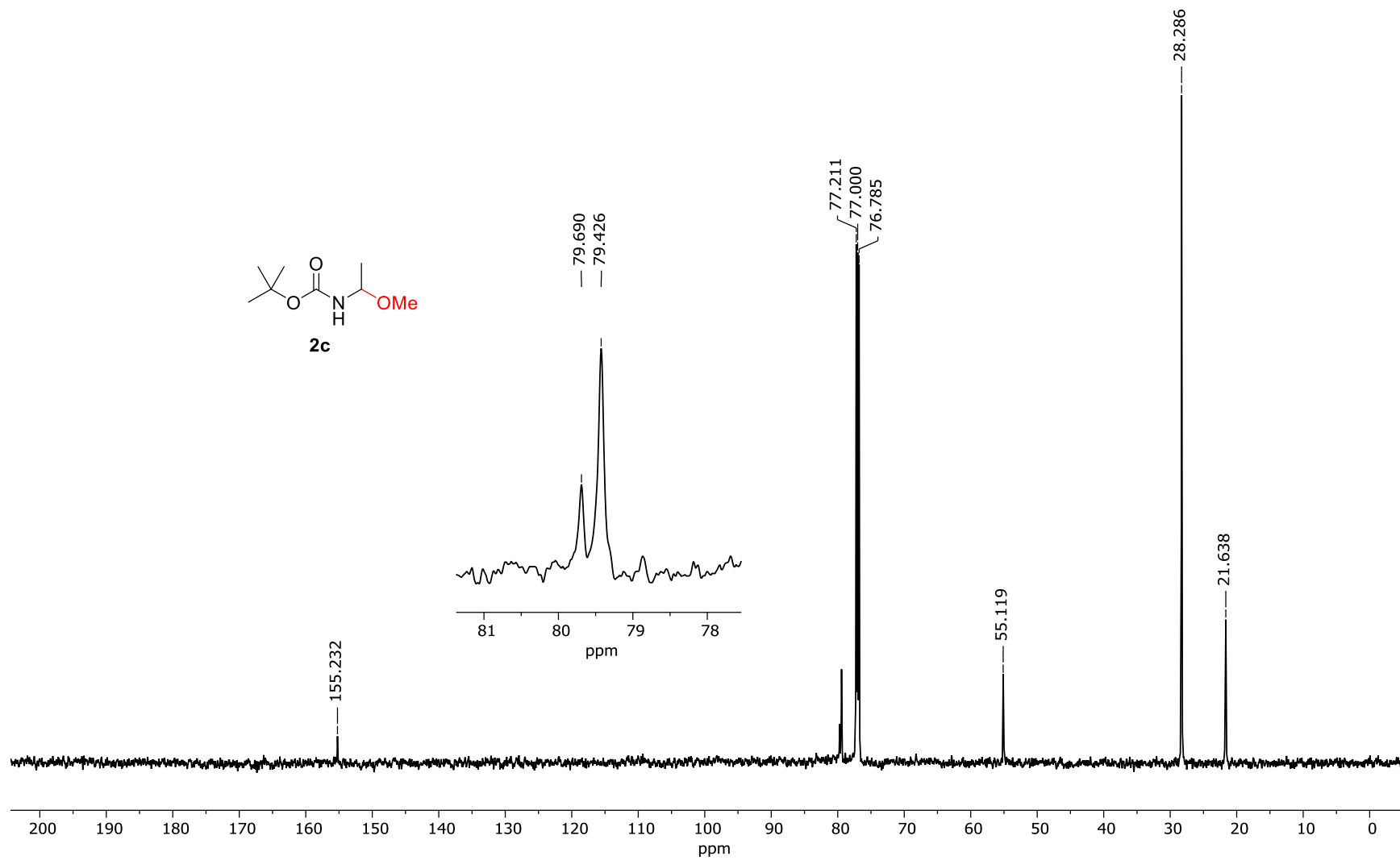
Tert-butyl N-(1-methoxyethyl)carbamate (2c): ^1H NMR [600 MHz/ CDCl_3 /TMS]

AWA-457-1H-14022019
AWA-457-1H-14022019



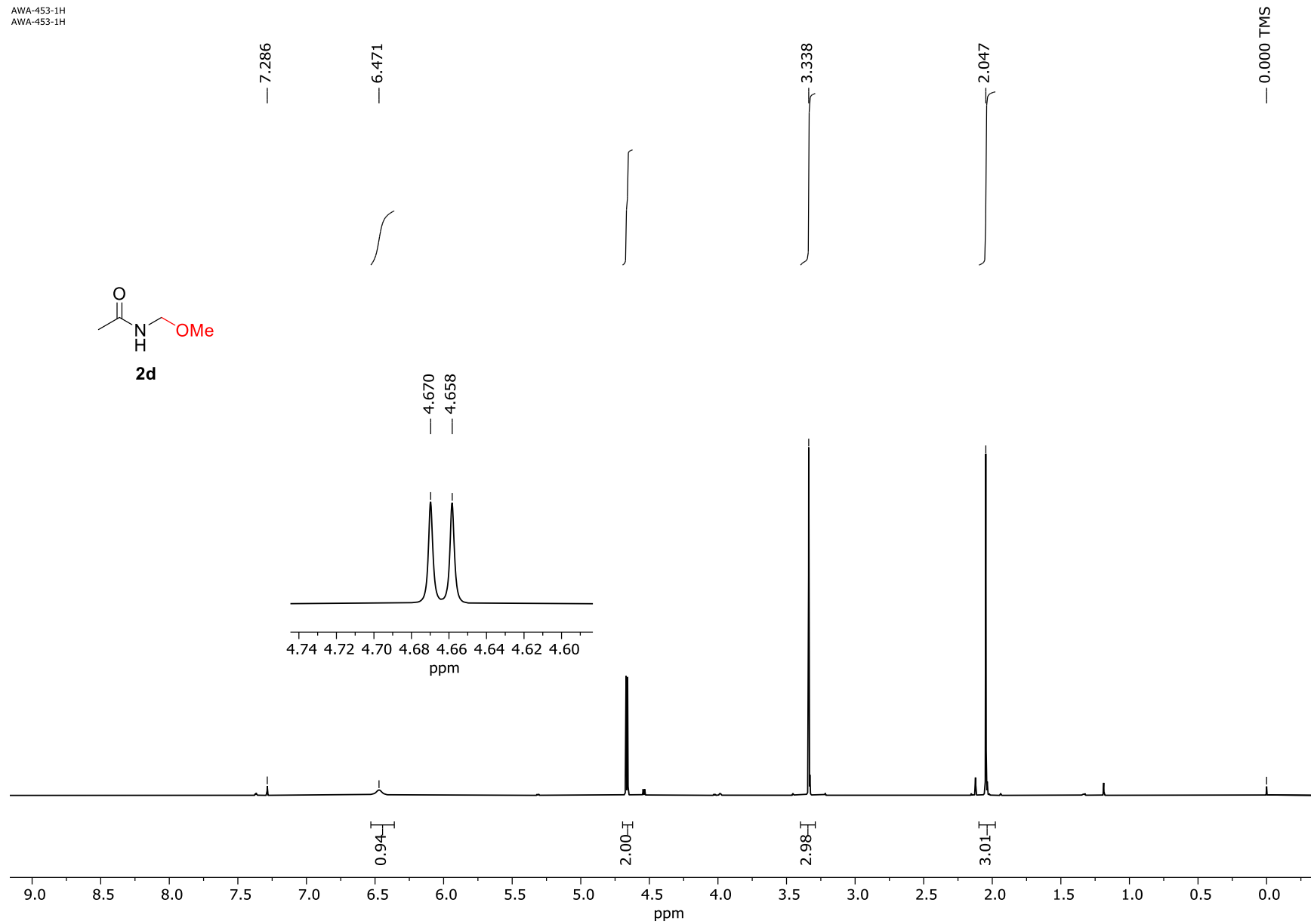
***Tert*-butyl *N*-(1-methoxyethyl)carbamate (**2c**): ^{13}C NMR [150 MHz/ CDCl_3]**

AWA-457-13C
AWA-453-13C



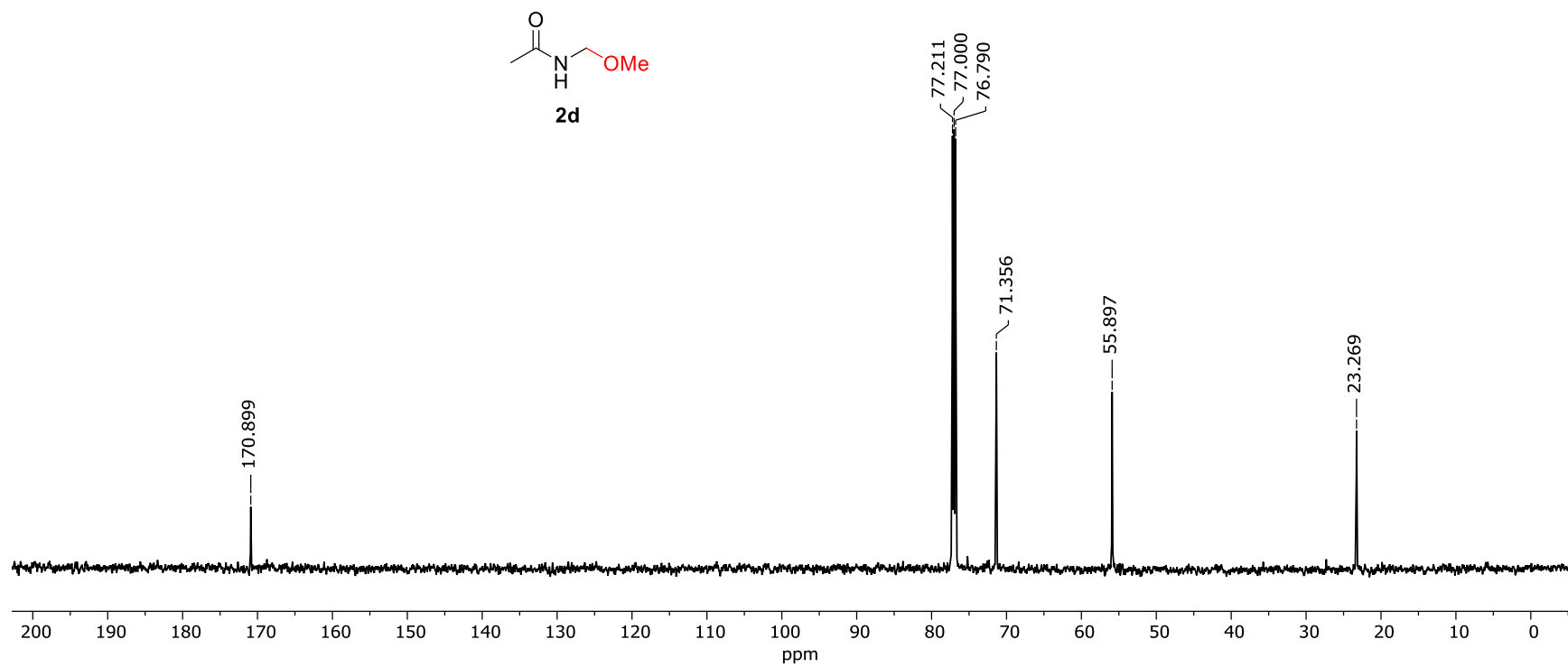
***N*-(methoxymethyl)acetamide (2d): ^1H NMR [600 MHz/ CDCl_3/TMS]**

AWA-453-1H
AWA-453-1H



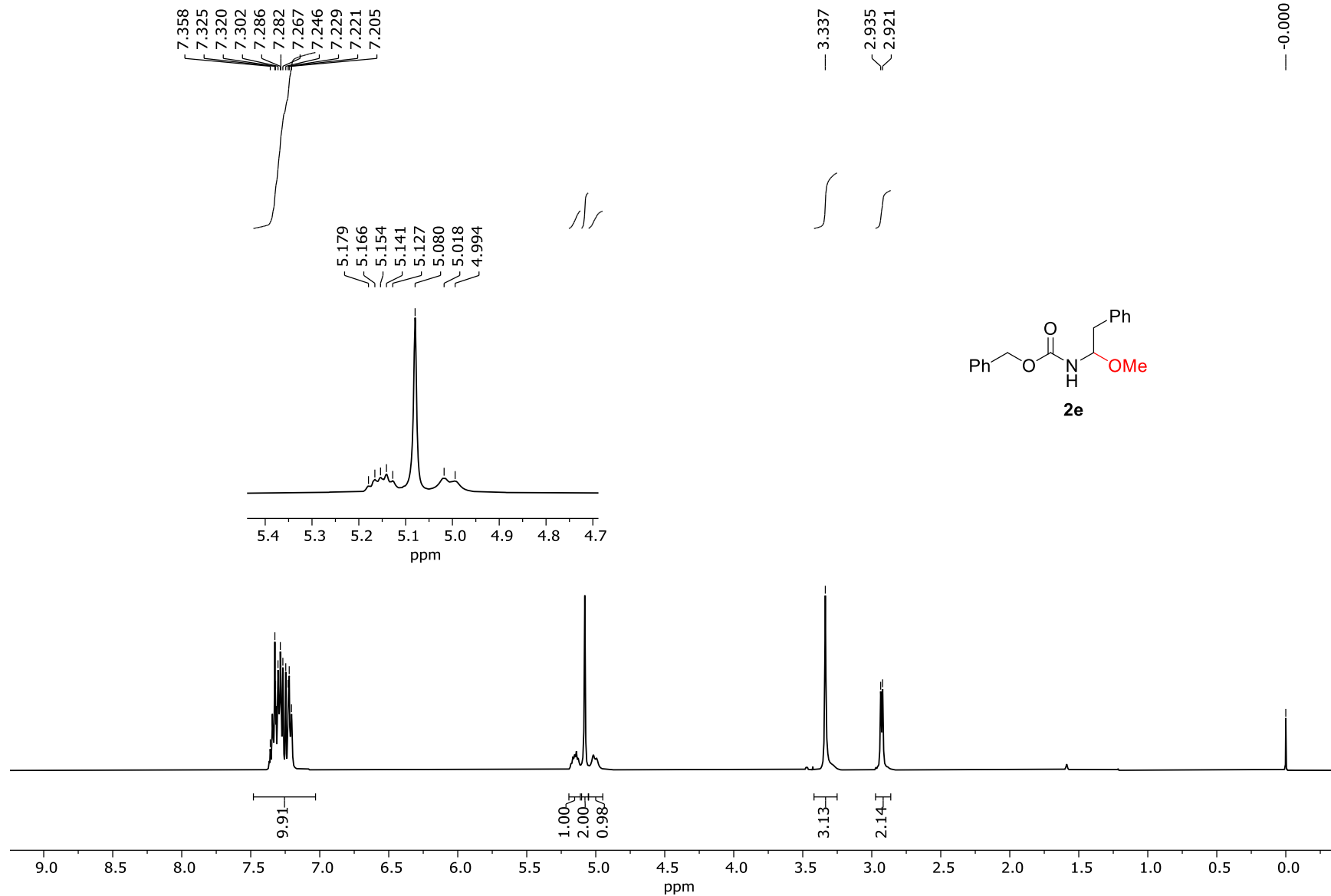
***N*-(methoxymethyl)acetamide (2d):** ^{13}C NMR [150 MHz/ CDCl_3]

AWA-453-13C
AWA-453-13C



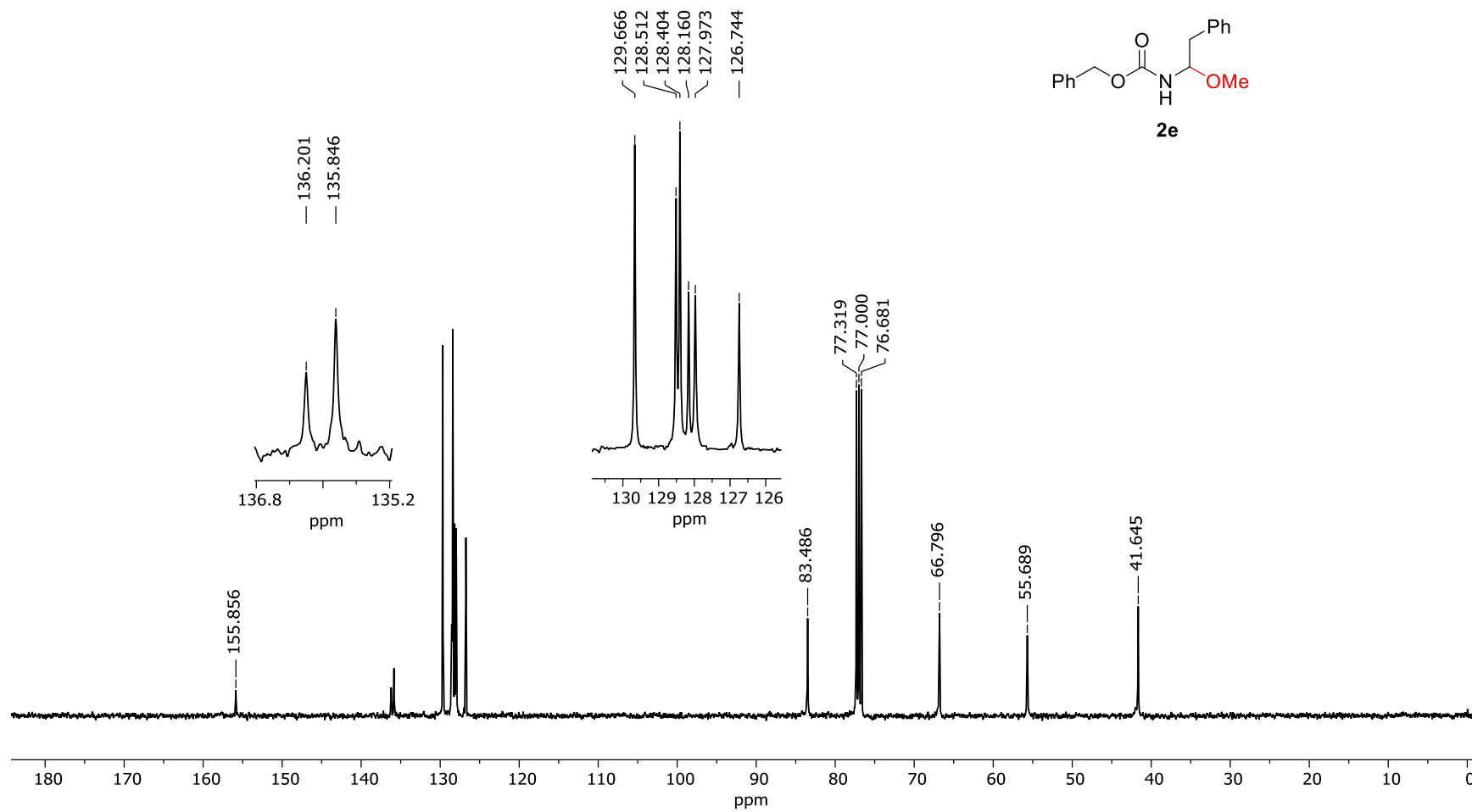
Benzyl N-(1-methoxy-2-phenylethyl)carbamate (2e): ^1H NMR [400 MHz/ CDCl_3 /TMS]

AWA-440-1H
AWA-440-1H



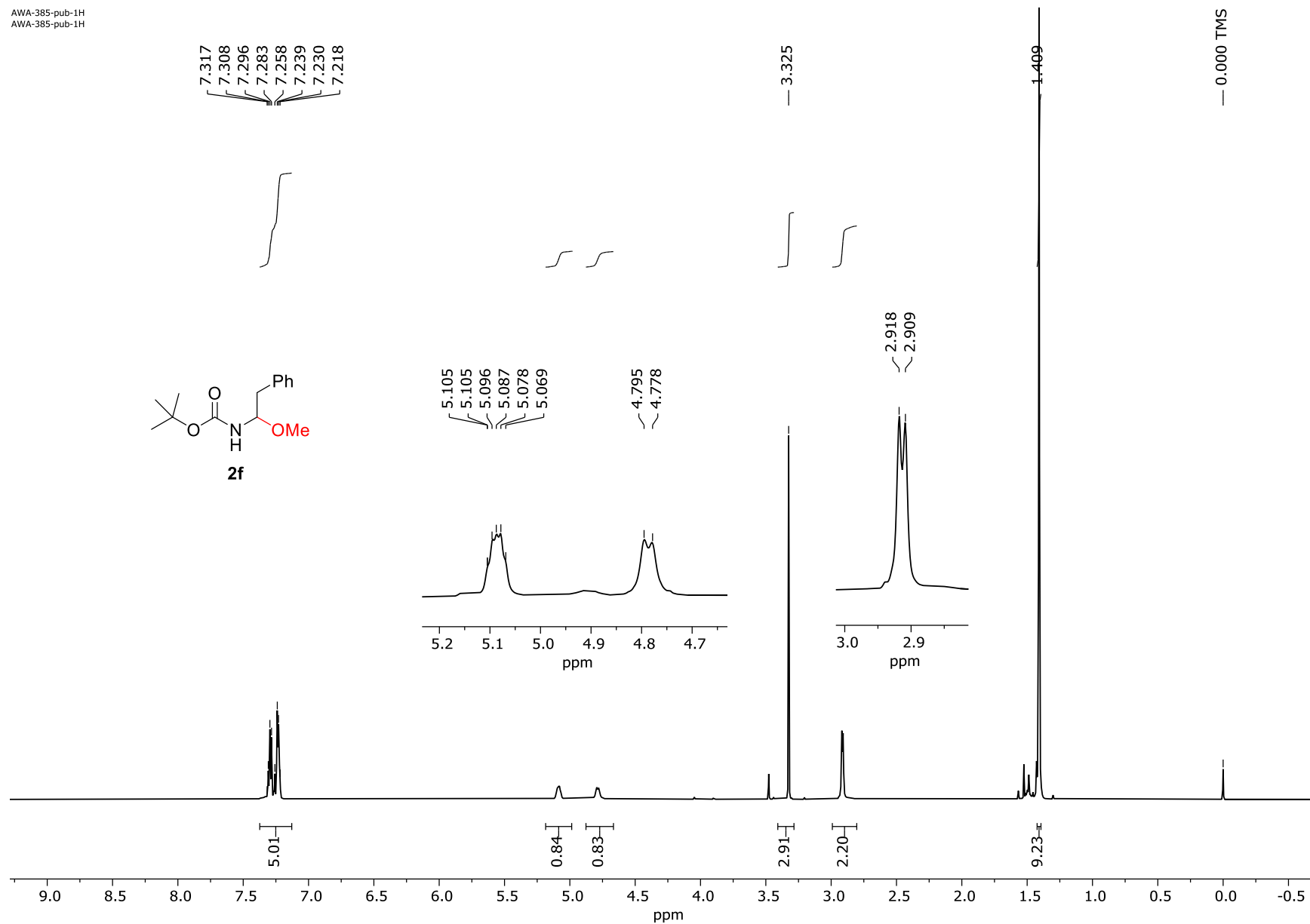
Benzyl *N*-(1-methoxy-2-phenylethyl)carbamate (**2e**): ^{13}C NMR [100 MHz/ CDCl_3]

AWA-440-13c
AWA-440-13C



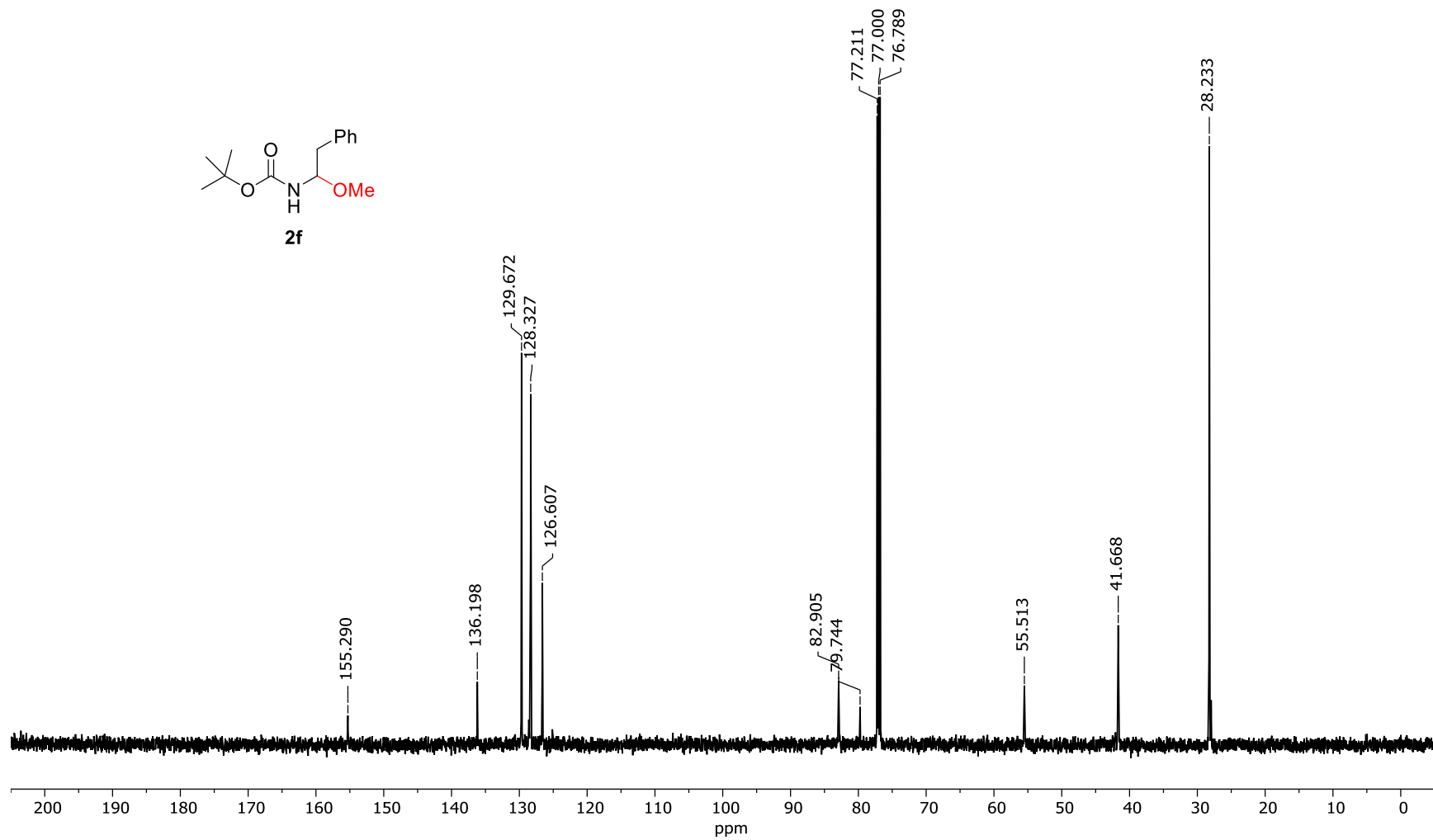
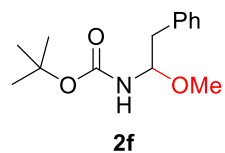
Tert-butyl *N*-(1-methoxy-2-phenylethyl)carbamate (**2f**): ¹H NMR [600 MHz/¹³CDCl₃/TMS]

AWA-385-pub-1H
AWA-385-pub-1H



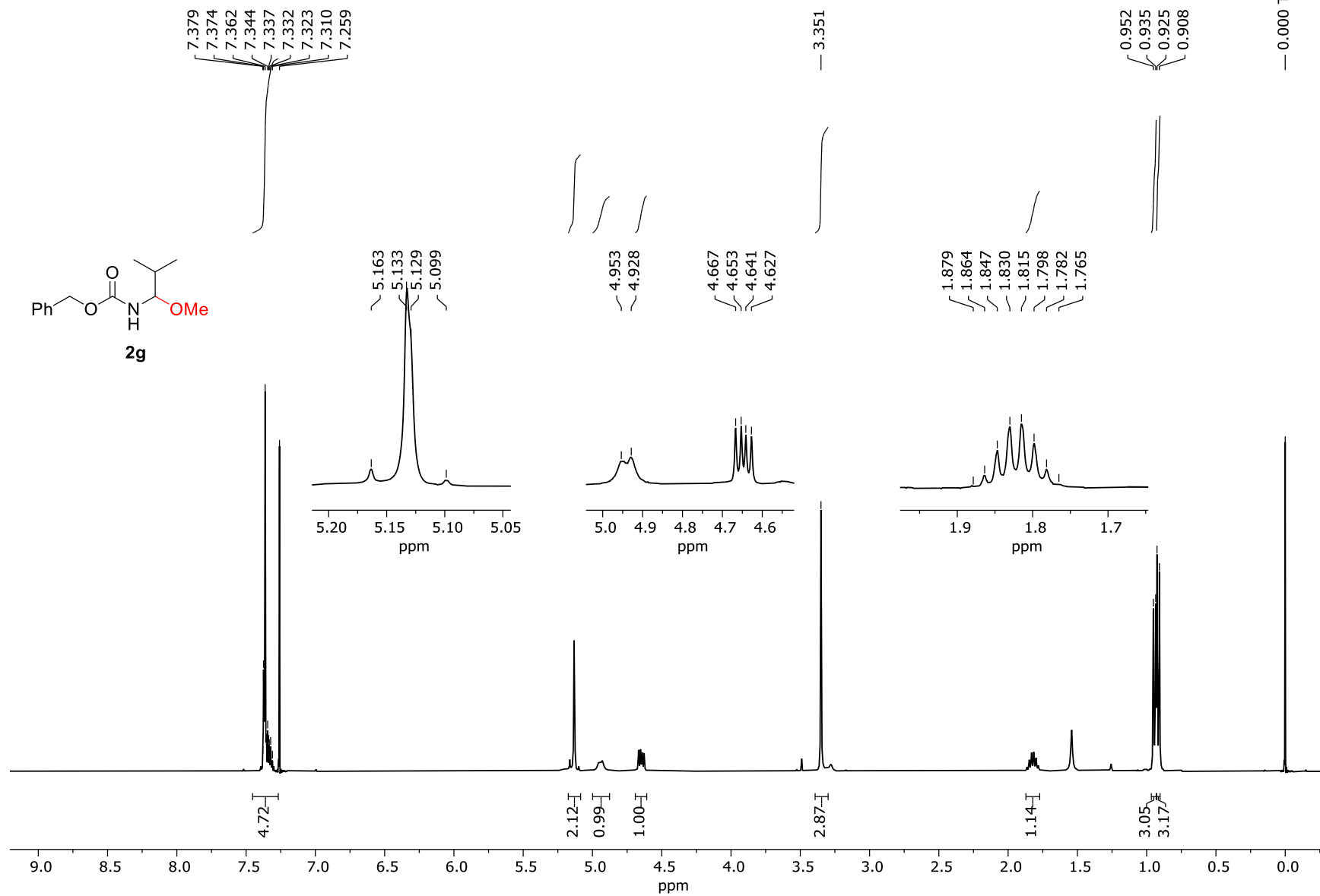
***Tert*-butyl *N*-(1-methoxy-2-phenylethyl)carbamate (**2f**): ^{13}C NMR [150 MHz/ CDCl_3]**

AWA-385-pub-13C
AWA-385-pub-13C



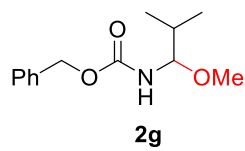
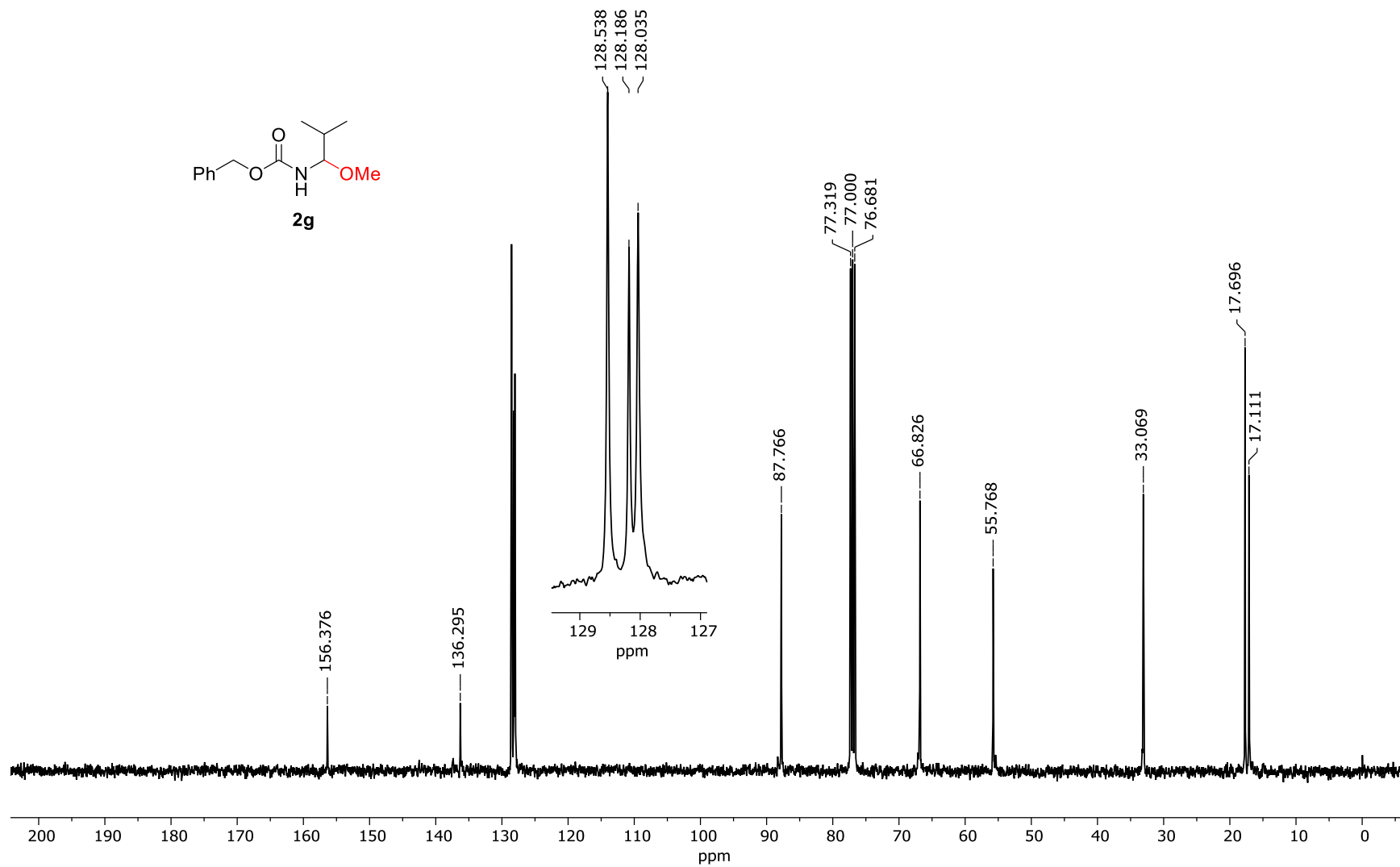
Benzyl *N*-(1-methoxy-2-methylpropyl)carbamate (2g): ¹H NMR [400 MHz/CDC₁₃/TMS]

AWA-451-1H
AWA-451-1H



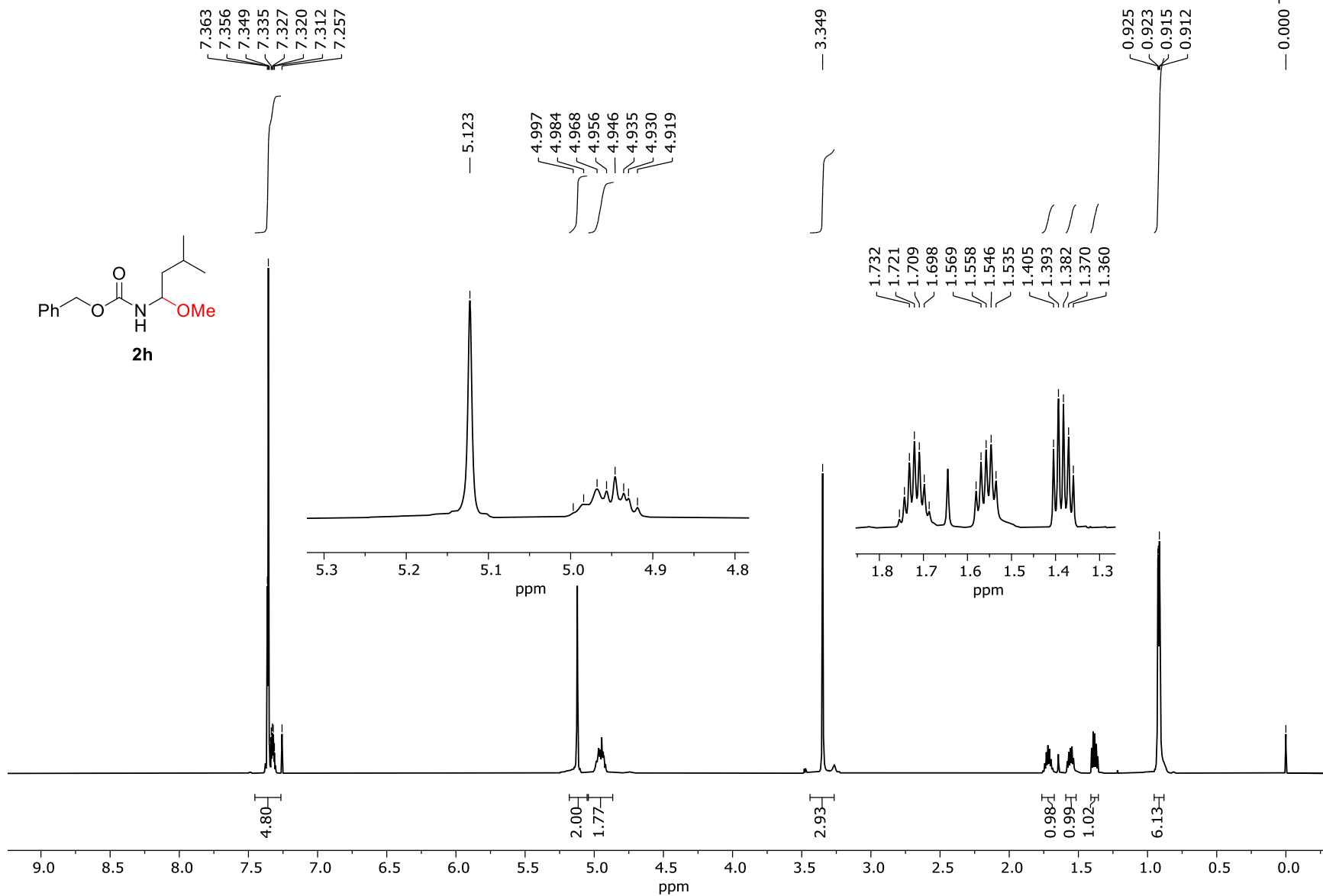
Benzyl *N*-(1-methoxy-2-methylpropyl)carbamate (2g): ^{13}C NMR [100 MHz/ CDCl_3]

AWA-442-13C
AWA-442-13C



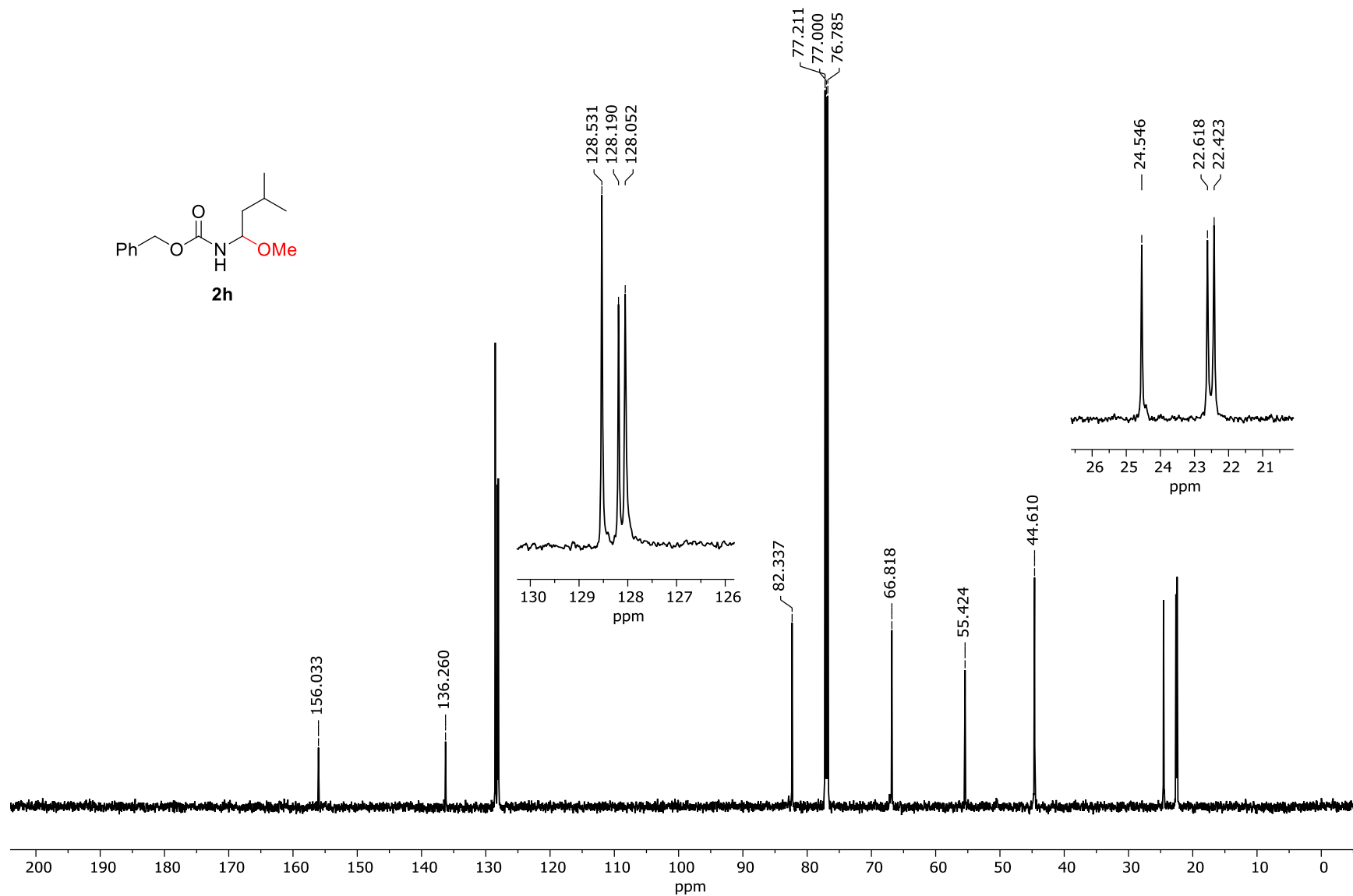
Benzyl *N*-(1-methoxy-3-methylbutyl)carbamate (**2h**): ¹H NMR [400 MHz/CDCl₃/TMS]

AWA-443-1H
AWA-443-1H



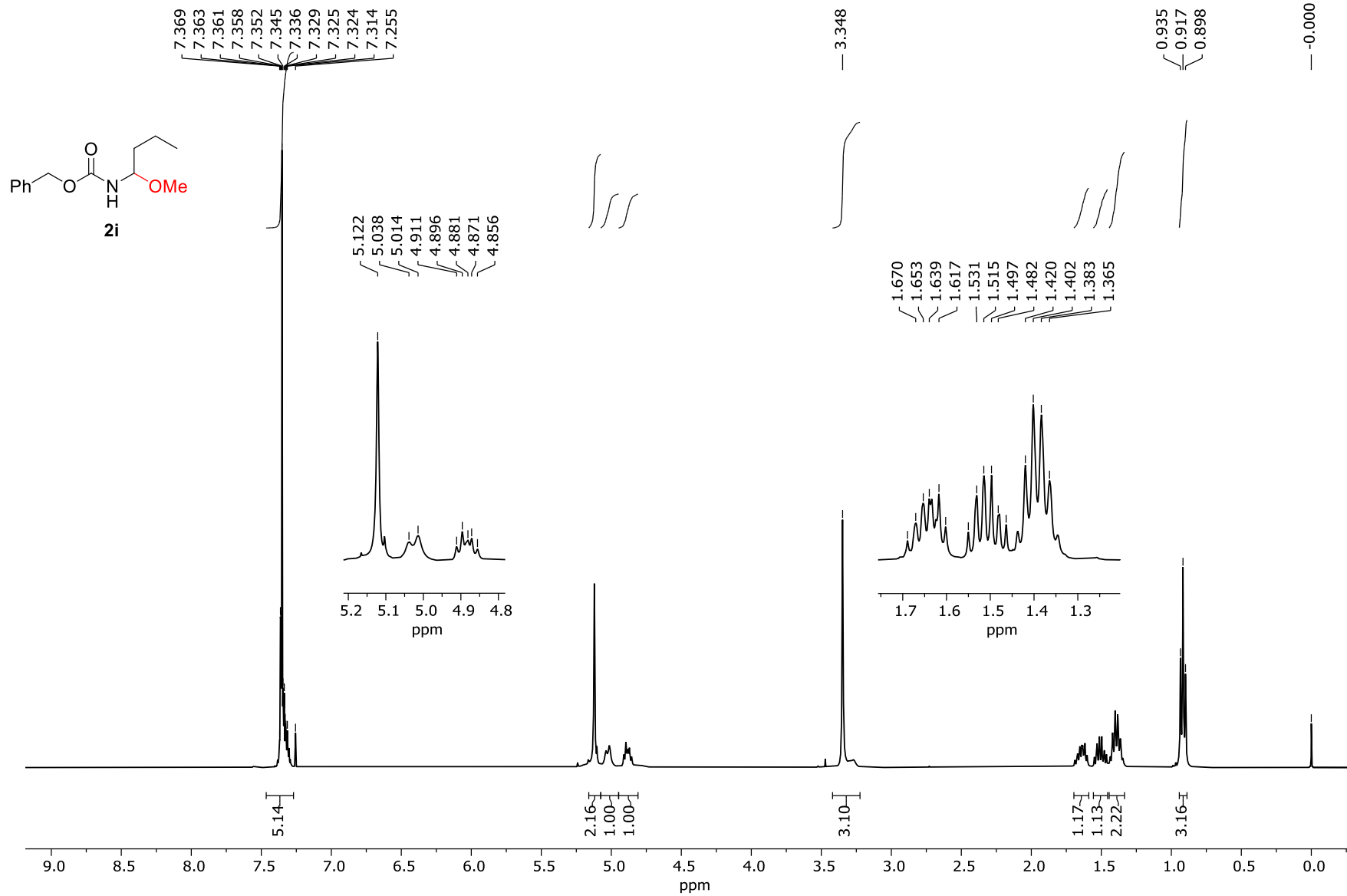
Benzyl *N*-(1-methoxy-3-methylbutyl)carbamate (2h): ^{13}C NMR [100 MHz/ CDCl_3]

AWA-443-13C
AWA-443-13C



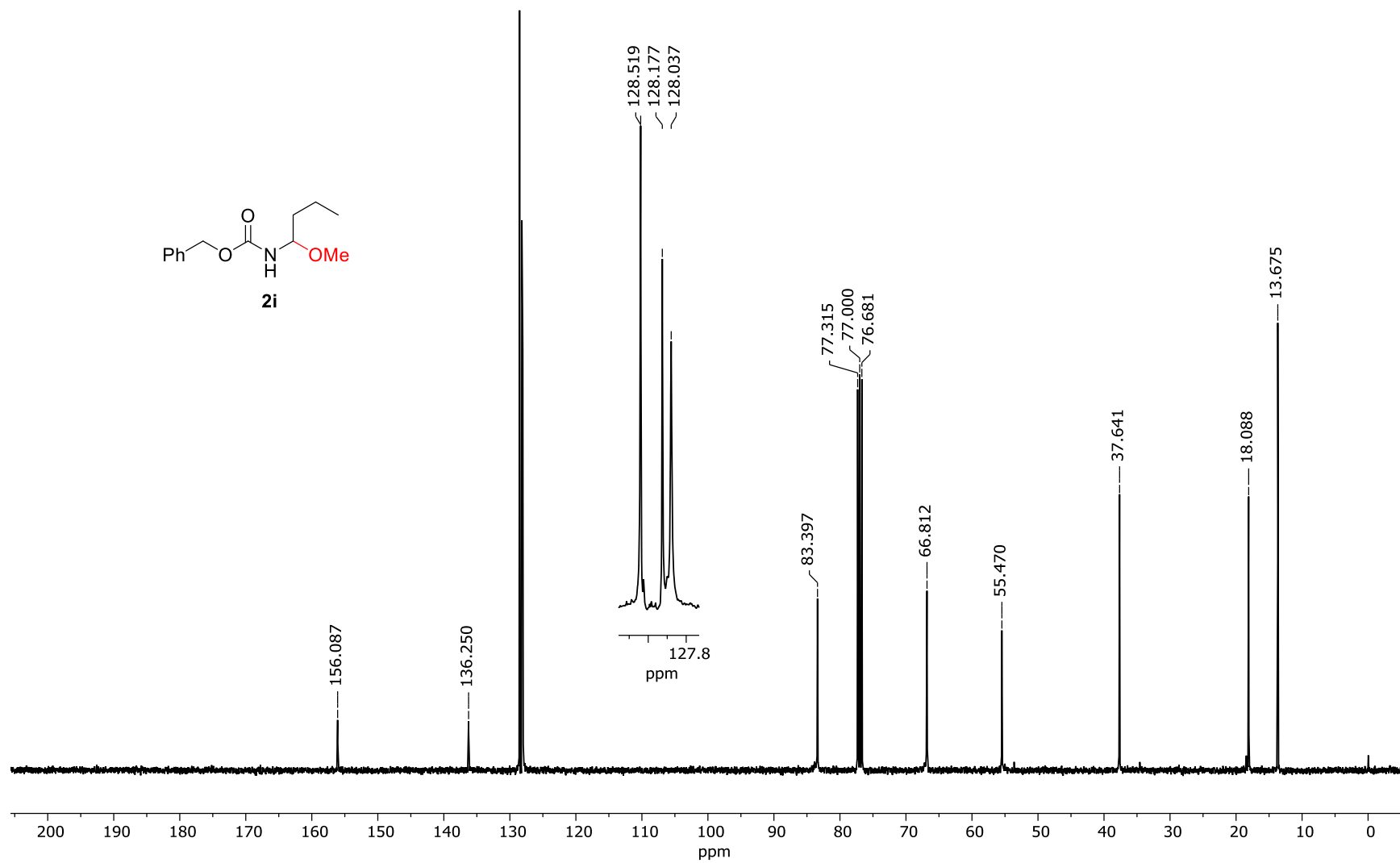
Benzyl N-(1-methoxybutyl)carbamate (2i): ¹H NMR [400 MHz/CDCl₃/TMS]

AWA-196-pub
AWA-196-pub



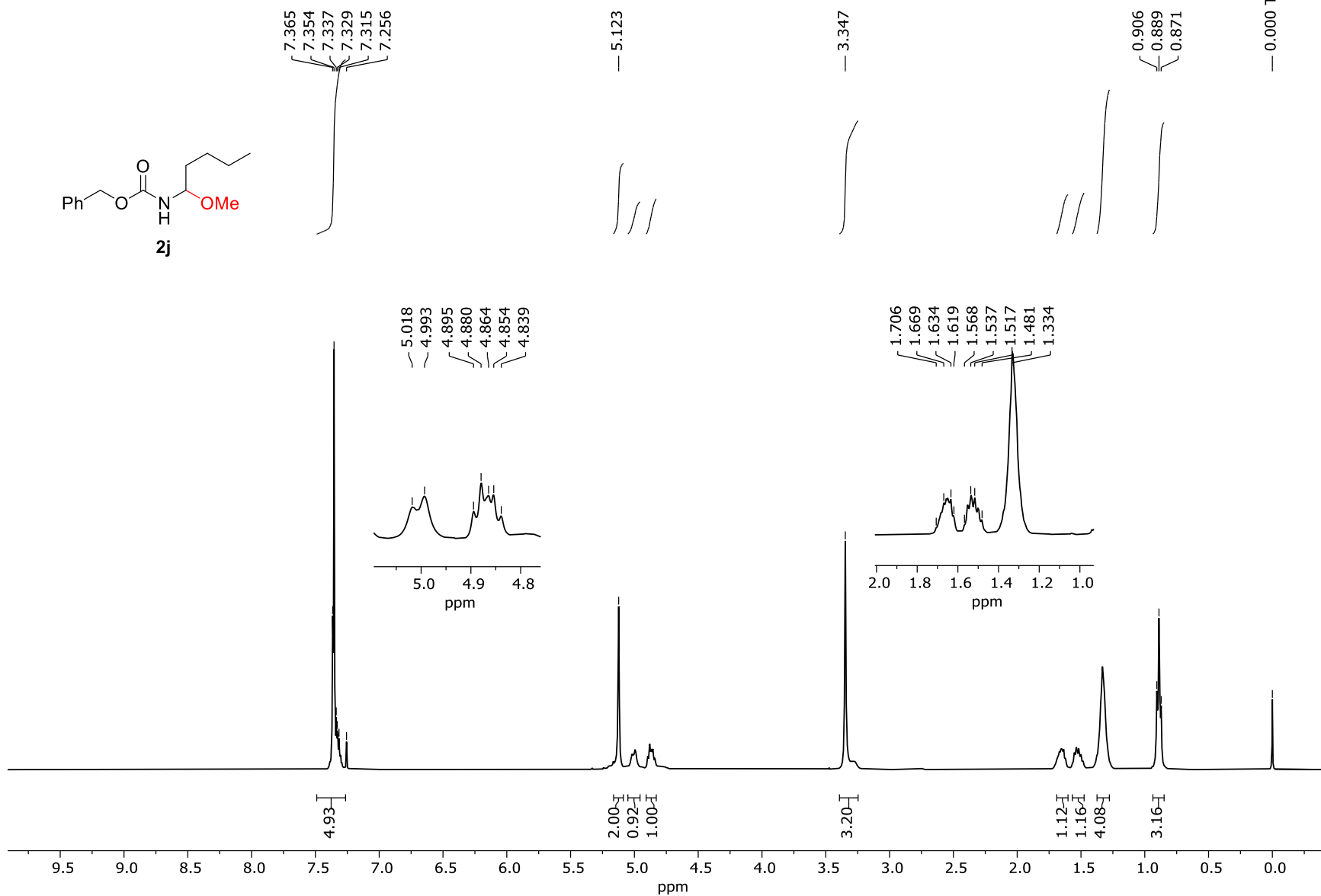
Benzyl N-(1-methoxybutyl)carbamate (2i): ^{13}C NMR [100 MHz/ CDCl_3]

AWA-196-pub-13C-2
AWA-196-pub-13C



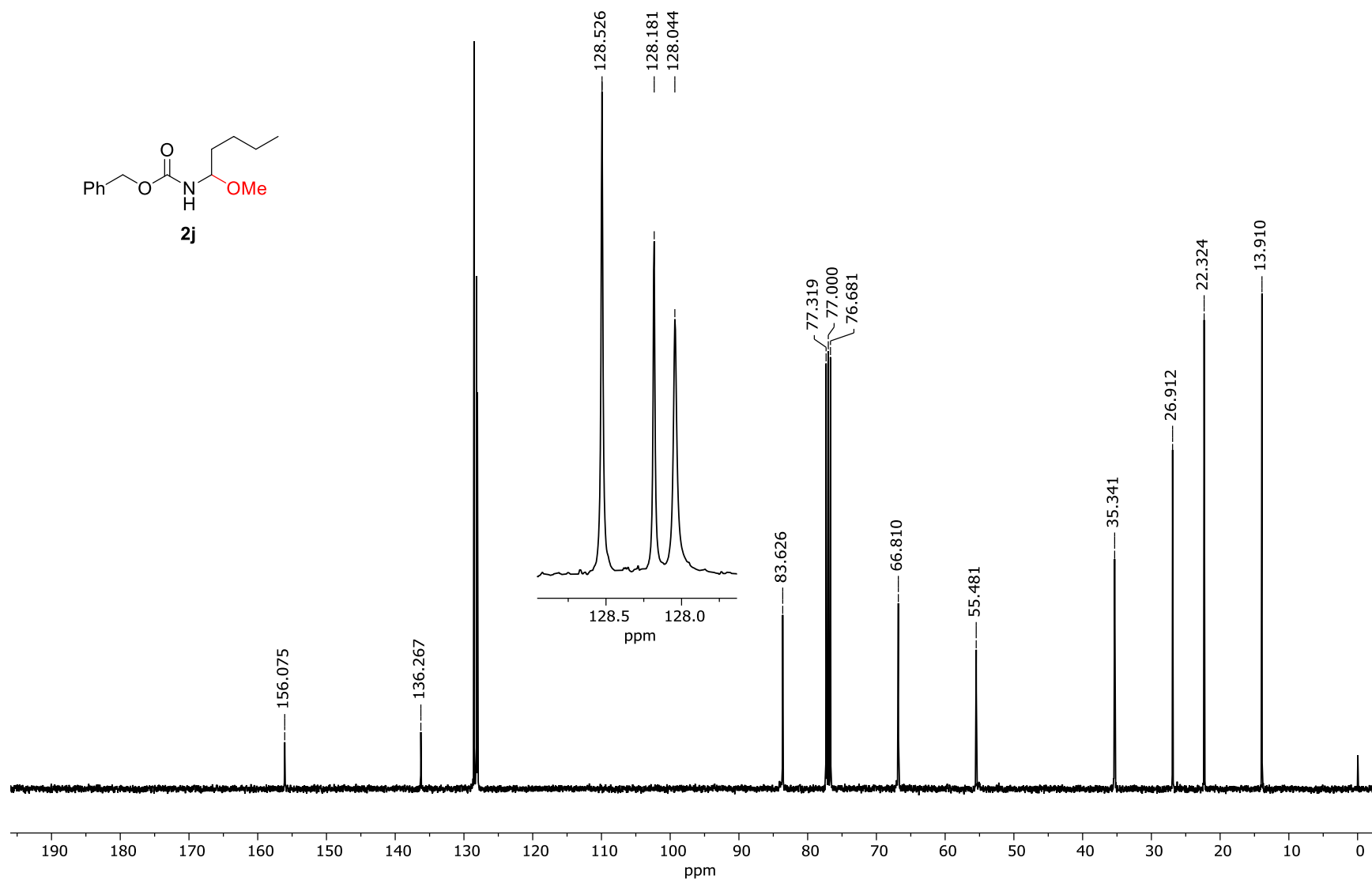
Benzyl N-(1-methoxypentyl)carbamate (2j): ¹H NMR [400 MHz/CDCl₃/TMS]

AWA-176-pub-1H
AWA-176-pub



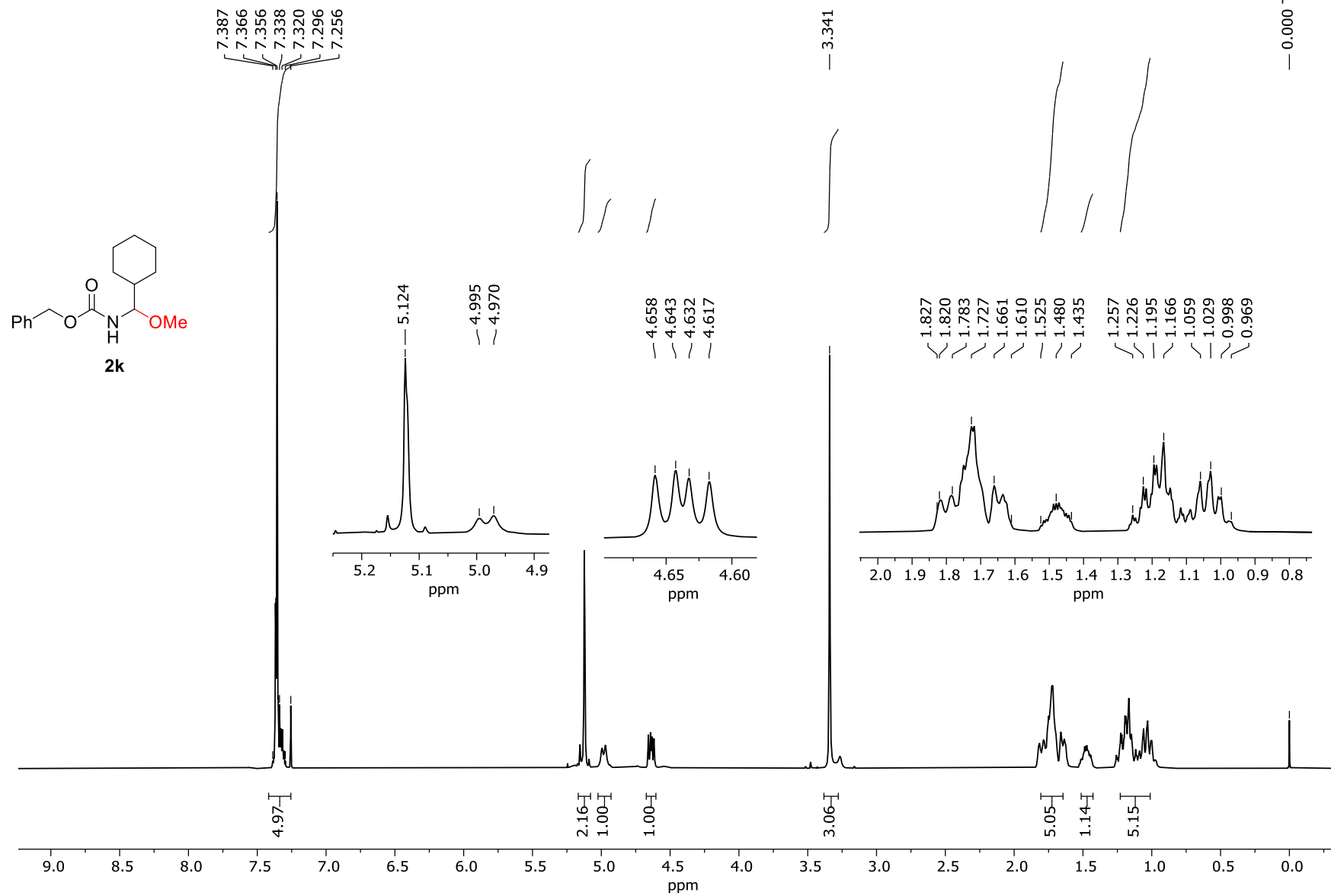
Benzyl *N*-(1-methoxypentyl)carbamate (2j): ^{13}C NMR [100 MHz/ CDCl_3]

AWA-176-pub-13C
AWA-176-pub-13C



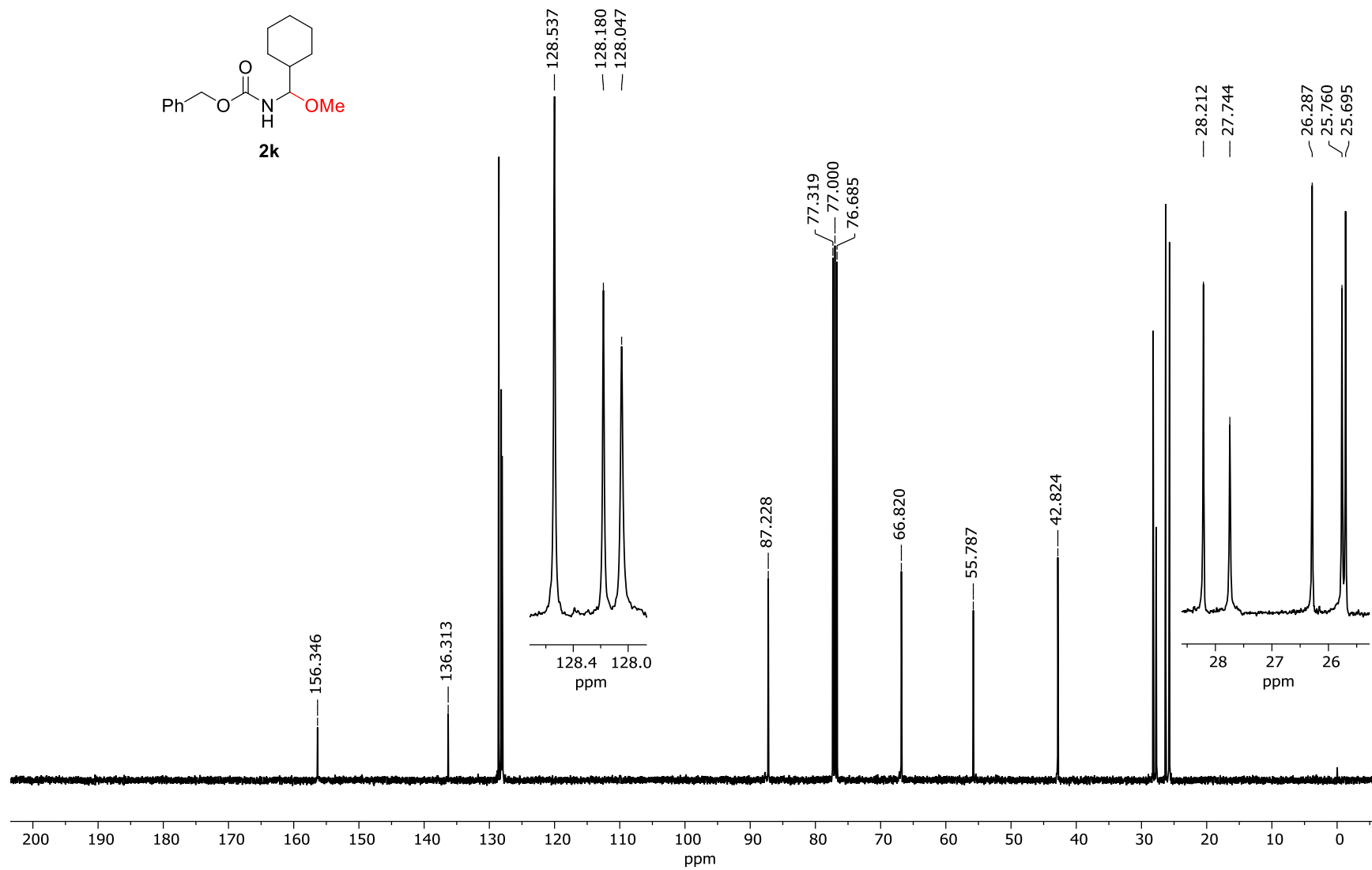
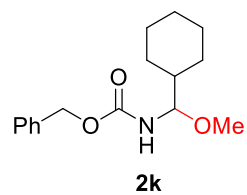
Benzyl N-[cyclohexyl(methoxy)methyl]carbamate (2k) ¹H NMR [400 MHz/CDCl₃/TMS]

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AWA-269-pub



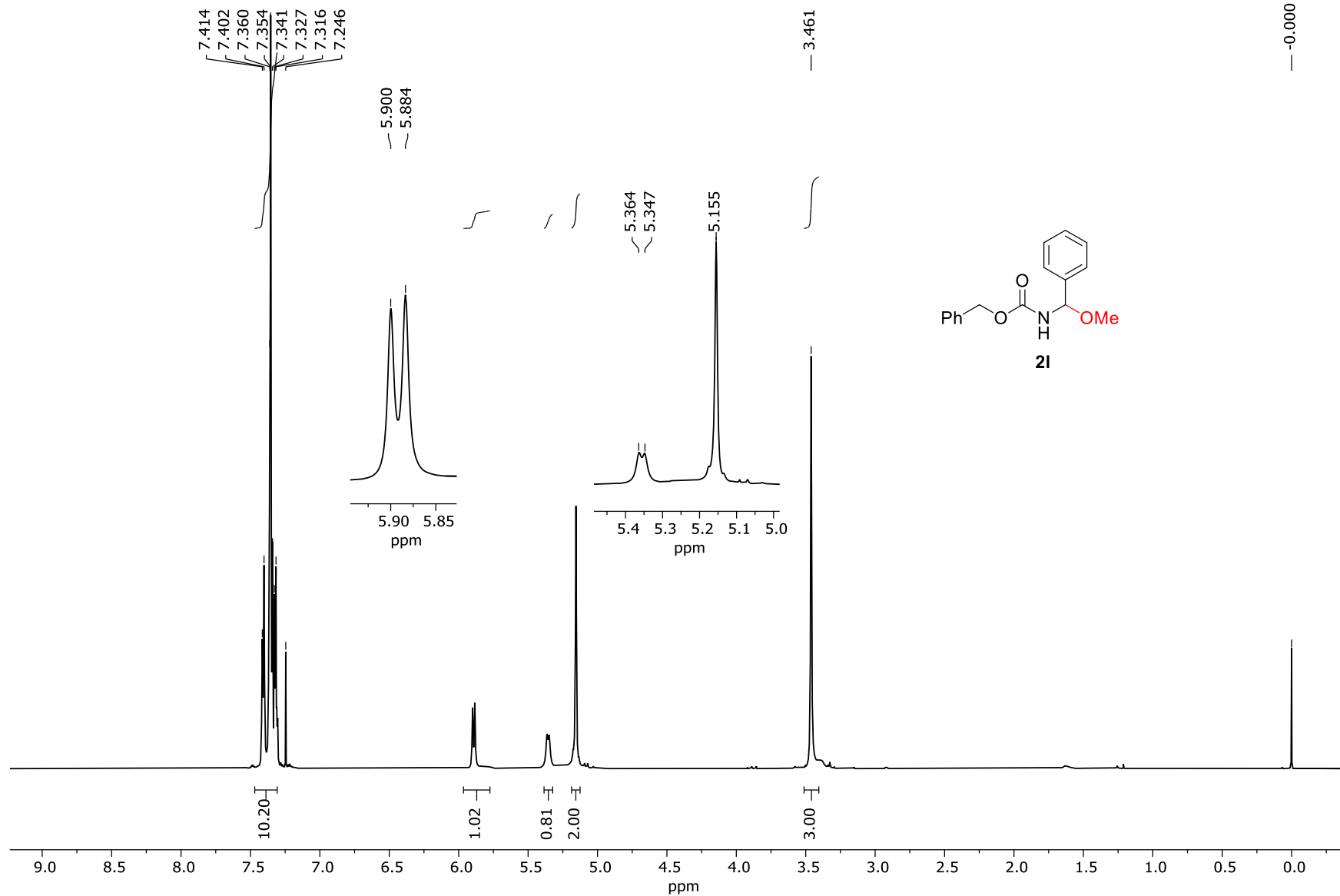
Benzyl *N*-[cyclohexyl(methoxy)methyl]carbamate (**2k**) ^{13}C NMR [100 MHz/ CDCl_3]

AWA-269-pub-13C
AWA-269-pub-13C



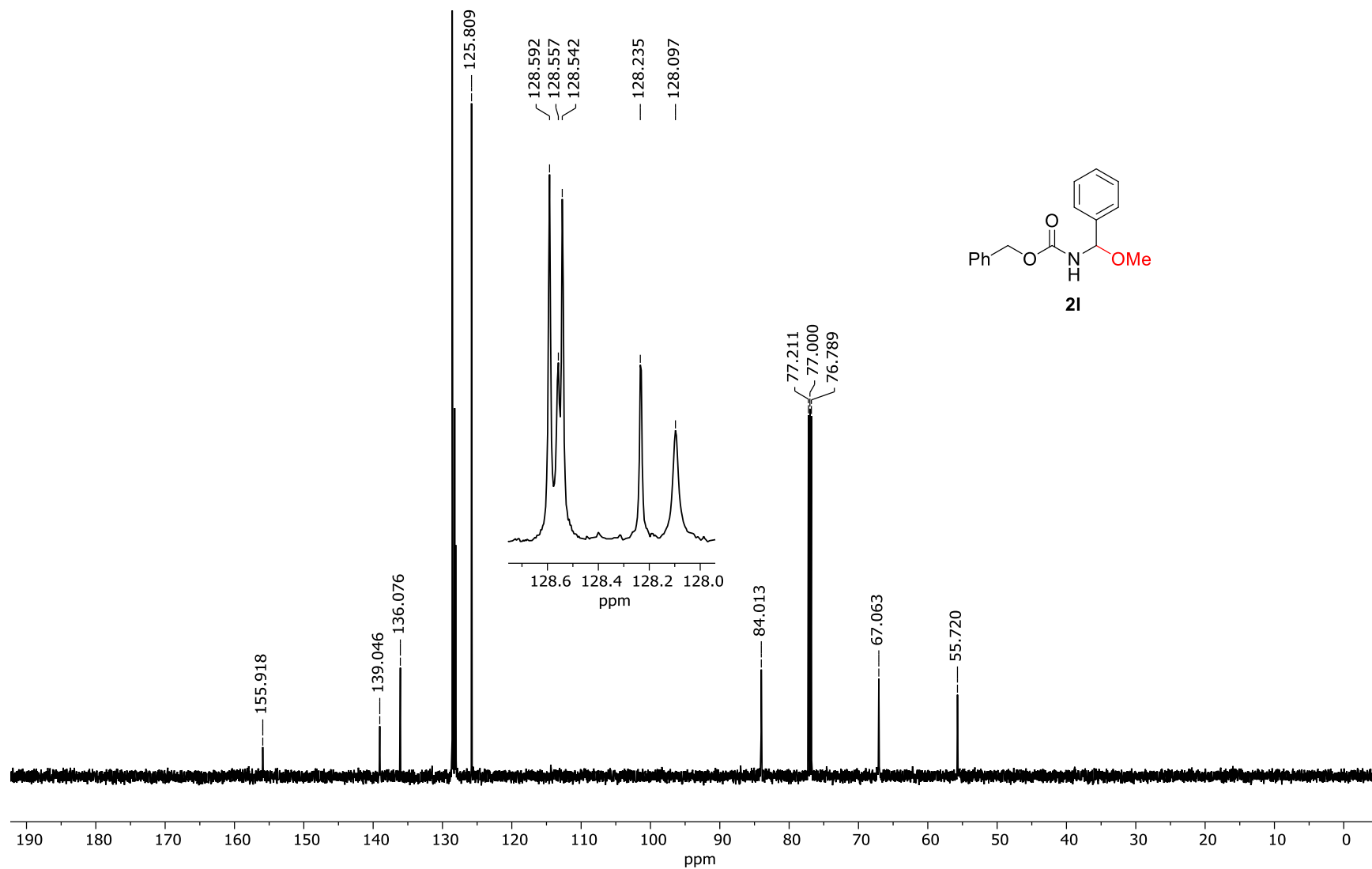
Benzyl N-(1-methoxy-1-phenylmethyl)carbamate (21): ¹H NMR [600 MHz/CDCl₃/TMS]

AWA-441-1-600-1H
AWA-441-1-600-1H



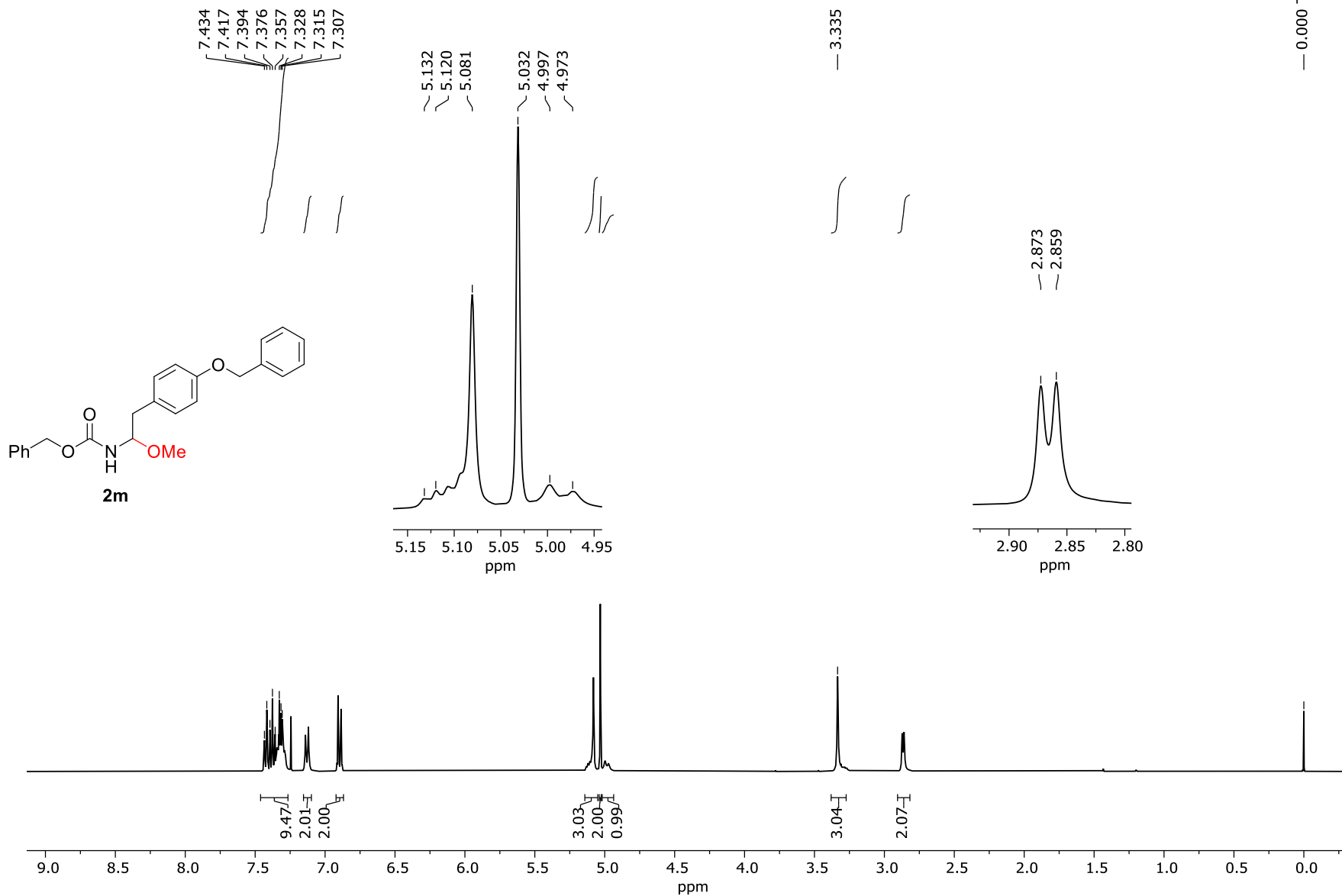
Benzyl *N*-(1-methoxy-1-phenylmethyl)carbamate (2I): ^{13}C NMR [150 MHz/ CDCl_3]

AWA-441-1-600-13C
AWA-441-1-600-13C



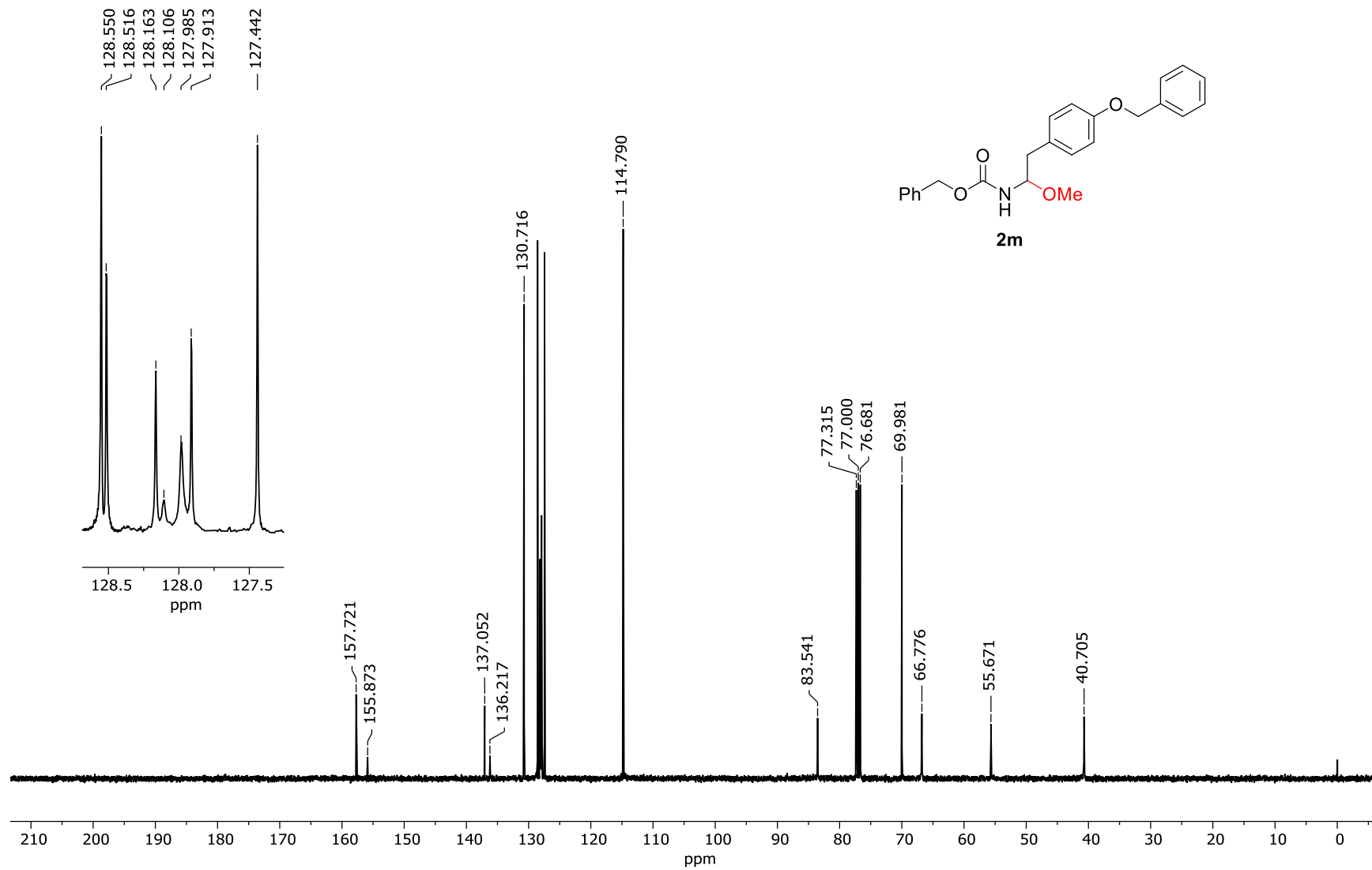
Benzyl N-[1-methoxy-2-(4-benzyloxyphenyl)ethyl]carbamate (2m): ¹H NMR [400 MHz/CDCl₃/TMS]

APH-158-2-Tyr_OBn_OMe
APH-158-2-Tyr(OBn)_OMe



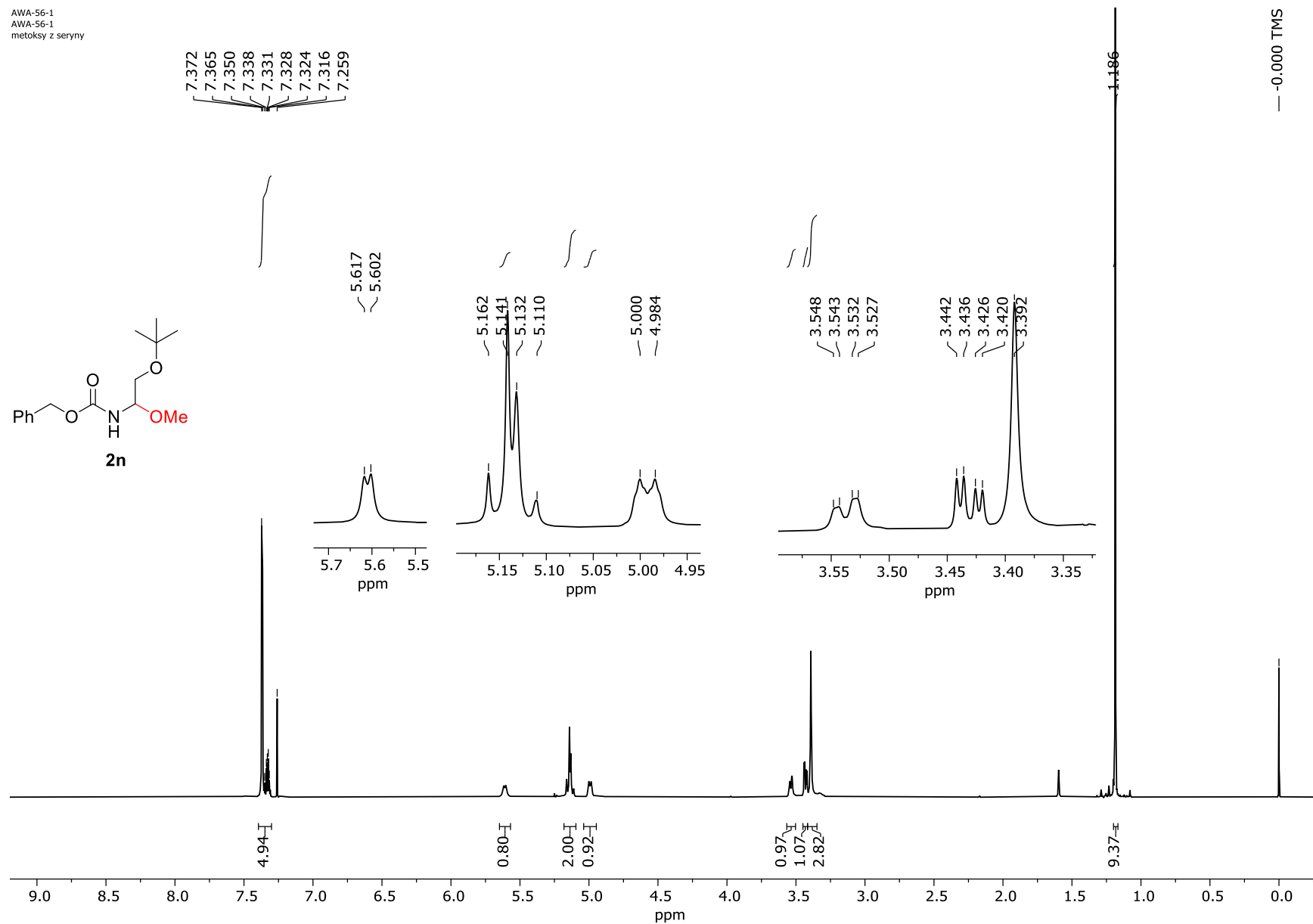
Benzyl N-[1-methoxy-2-(4-benzyloxyphenyl)ethyl]carbamate (2m): ^{13}C NMR [100 MHz/ CDCl_3]

APH-158-2-Tyr_OBn_OMe-13Cpub
APH-158-2-Tyr_OBn_OMe-13C



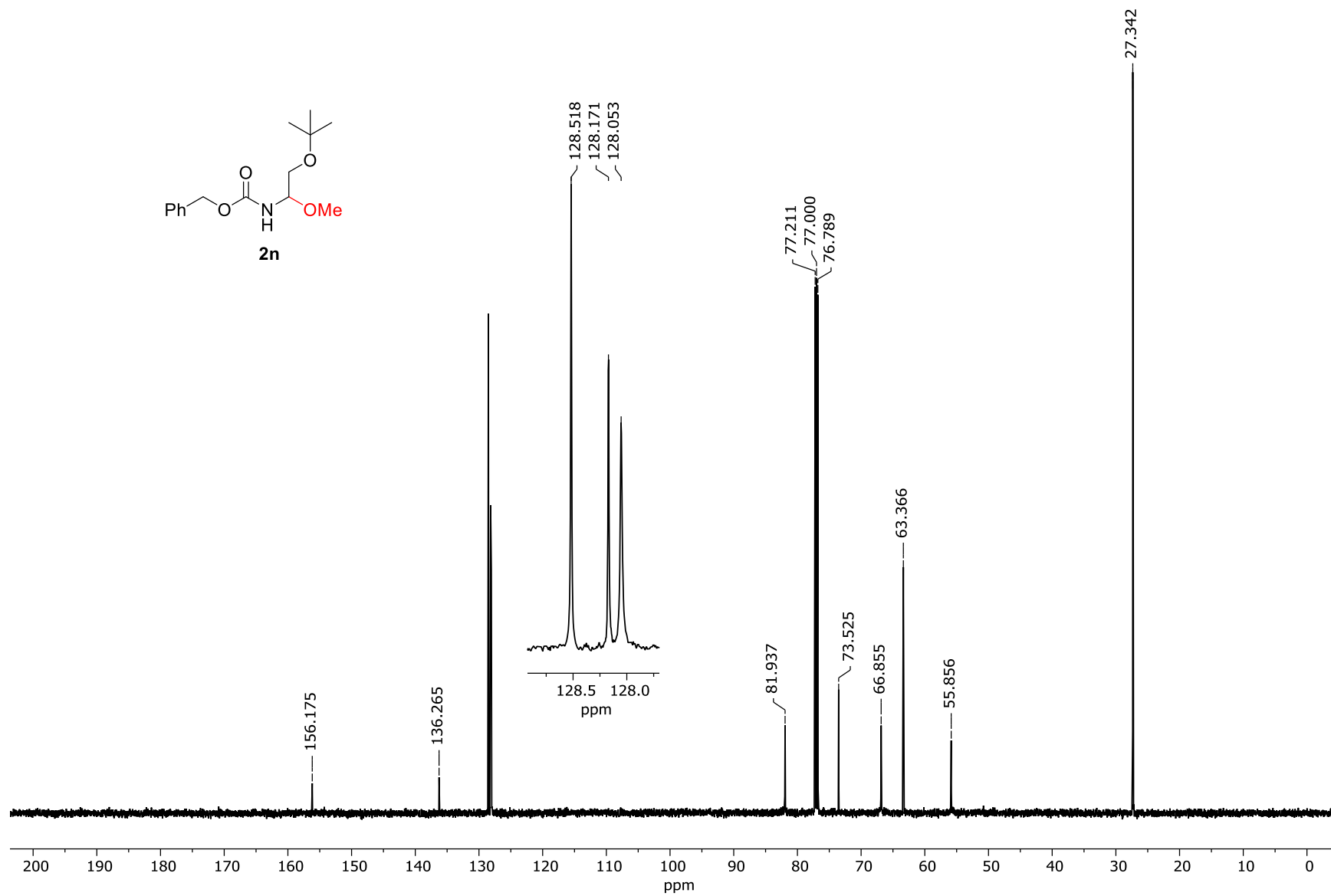
Benzyl *N*-(2-*tert*-butoxy-1-methoxyethyl)carbamate (2n): ¹H NMR [600 MHz/CDC₁₃/TMS]

AWA-56-1
AWA-56-1
metoksy z seryny



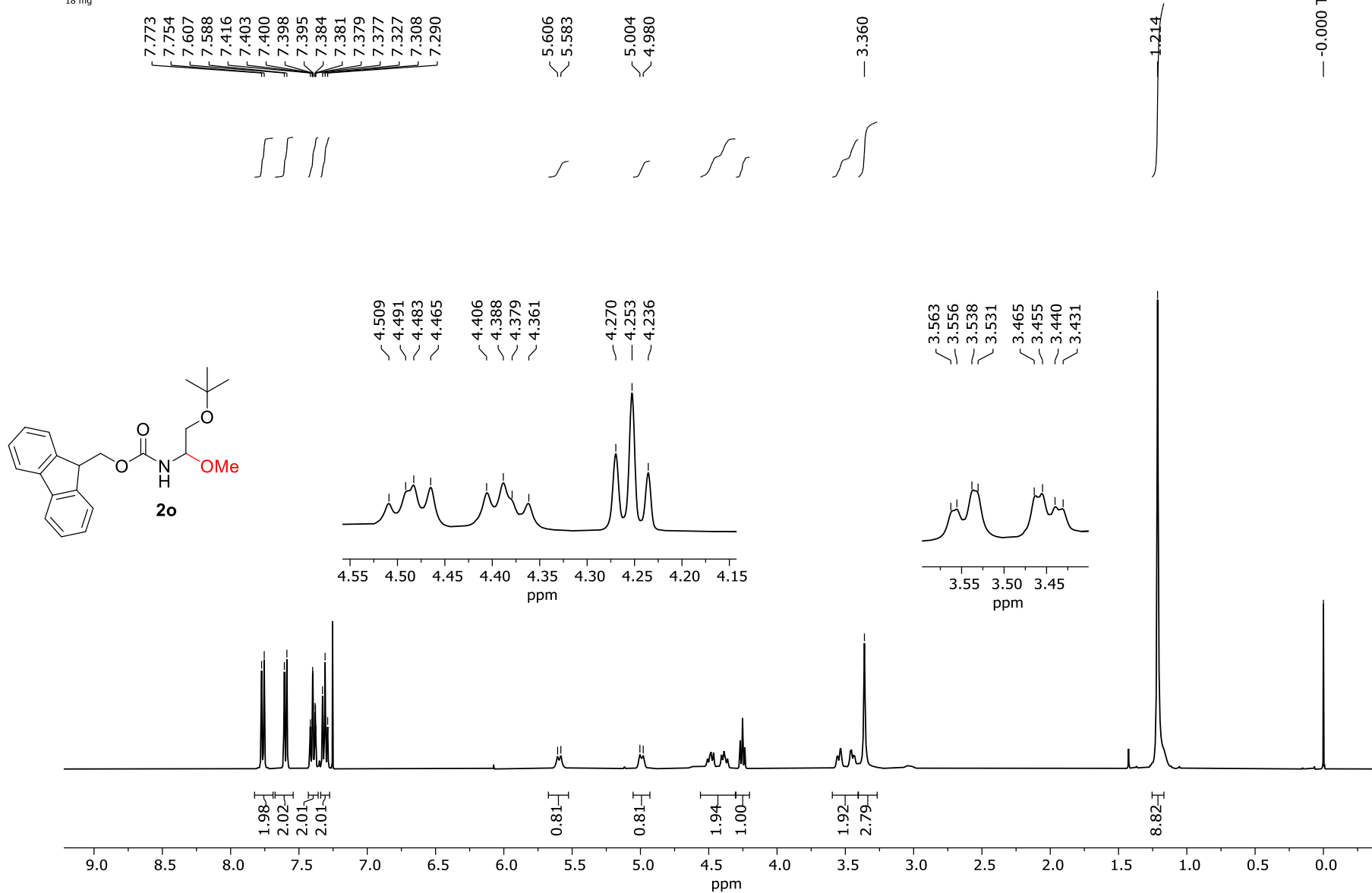
Benzyl *N*-(2-*tert*-butoxy-1-methoxyethyl)carbamate (**2n**): ^{13}C NMR [150 MHz/ CDCl_3]

AWA-452-13C
AWA-452-13C



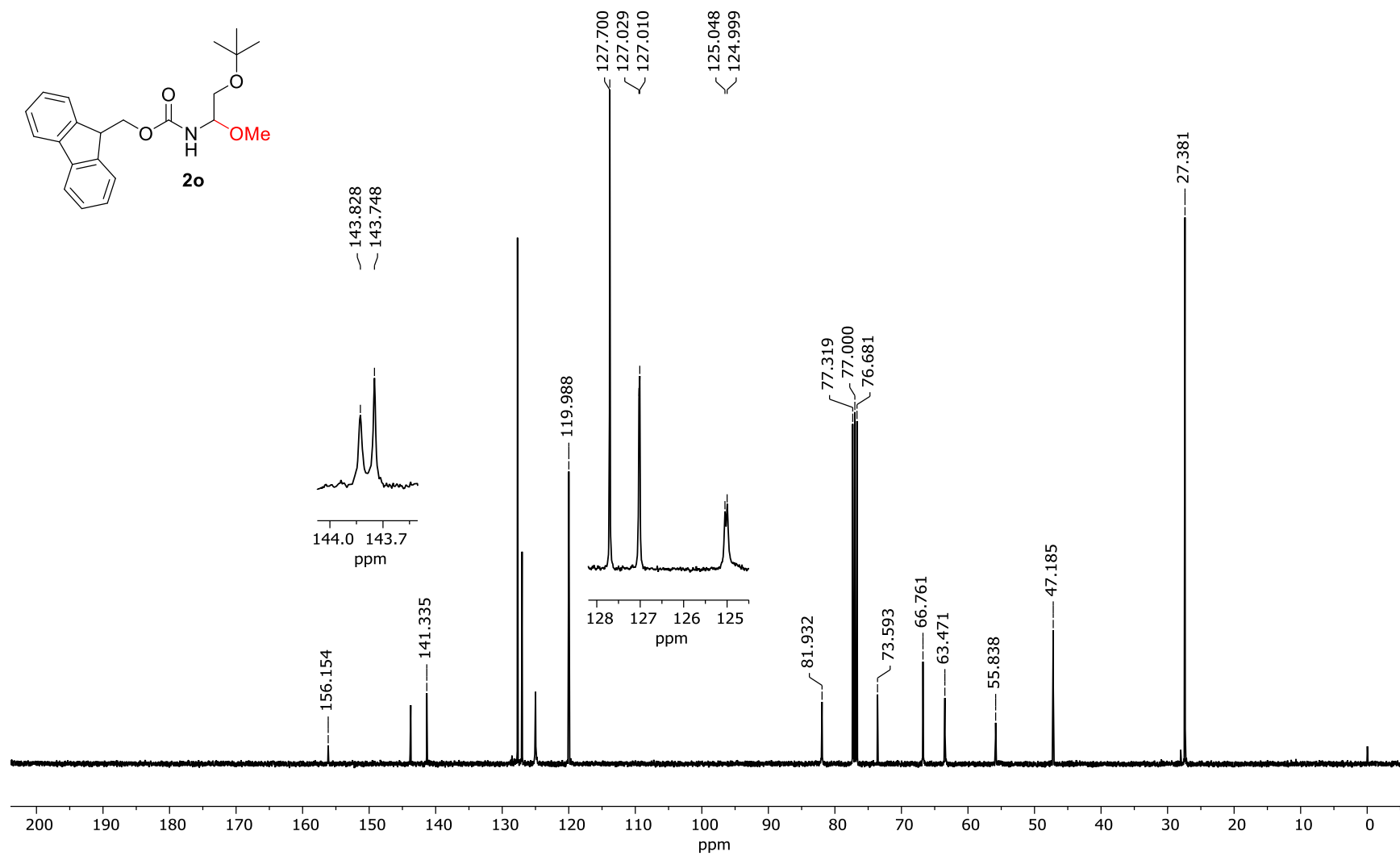
Fluorenylmethyl *N*-(2-*tert*-butoxy-1-methoxyethyl)carbamate (2o): ¹H NMR [400 MHz/CDCl₃/TMS]

APH-150-Fmoc-Ser_OtBu_OMe-pub
 APH-150-Fmoc-Ser_OtBu_OMe-pub
 18 mg

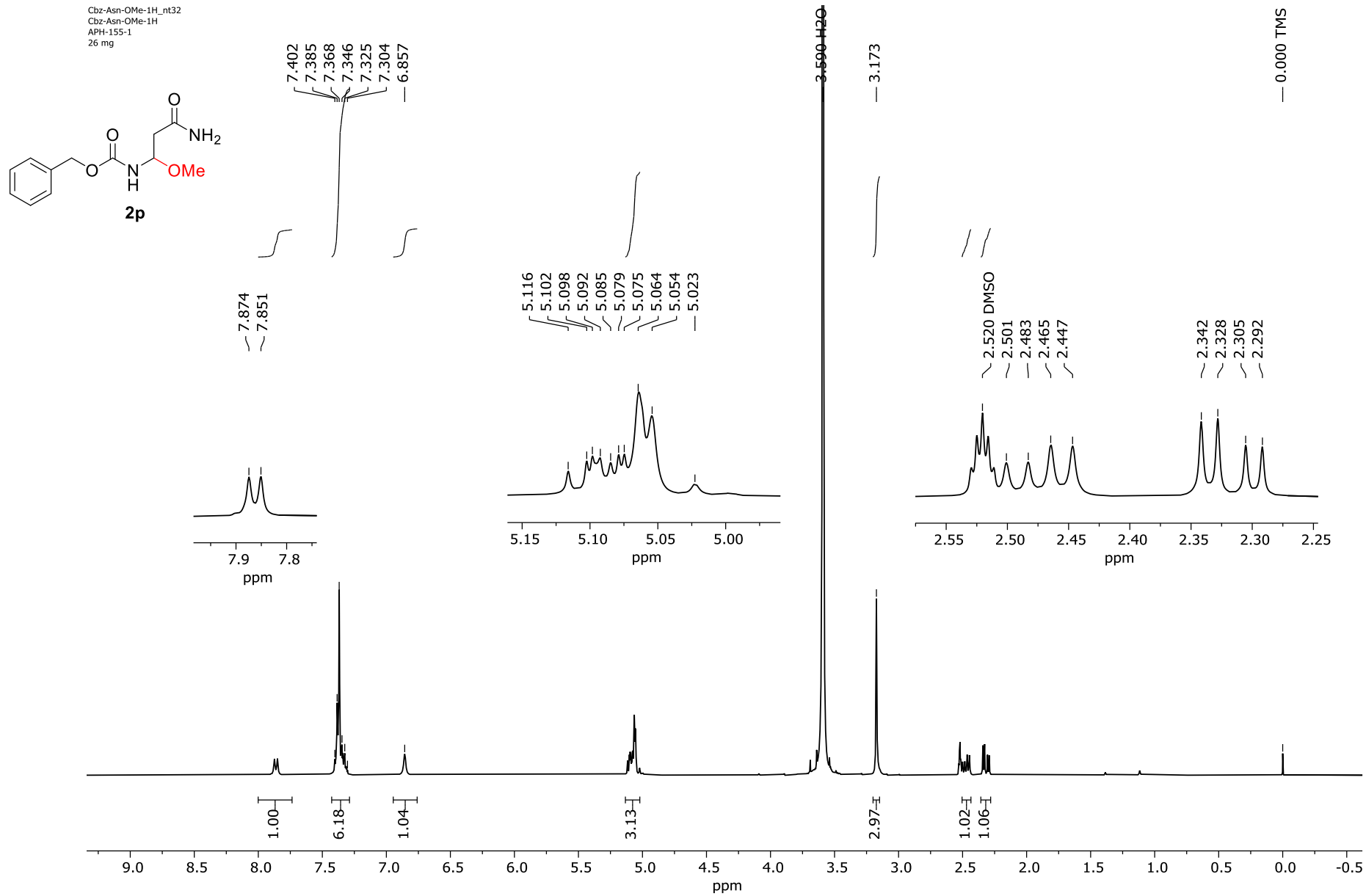


Fluorenylmethyl *N*-(2-*tert*-butoxy-1-methoxyethyl)carbamate (**2o**): ^{13}C NMR [100 MHz/ CDCl_3]

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APH-150-Fmoc-Ser_OtBu_OMe-13C-pub

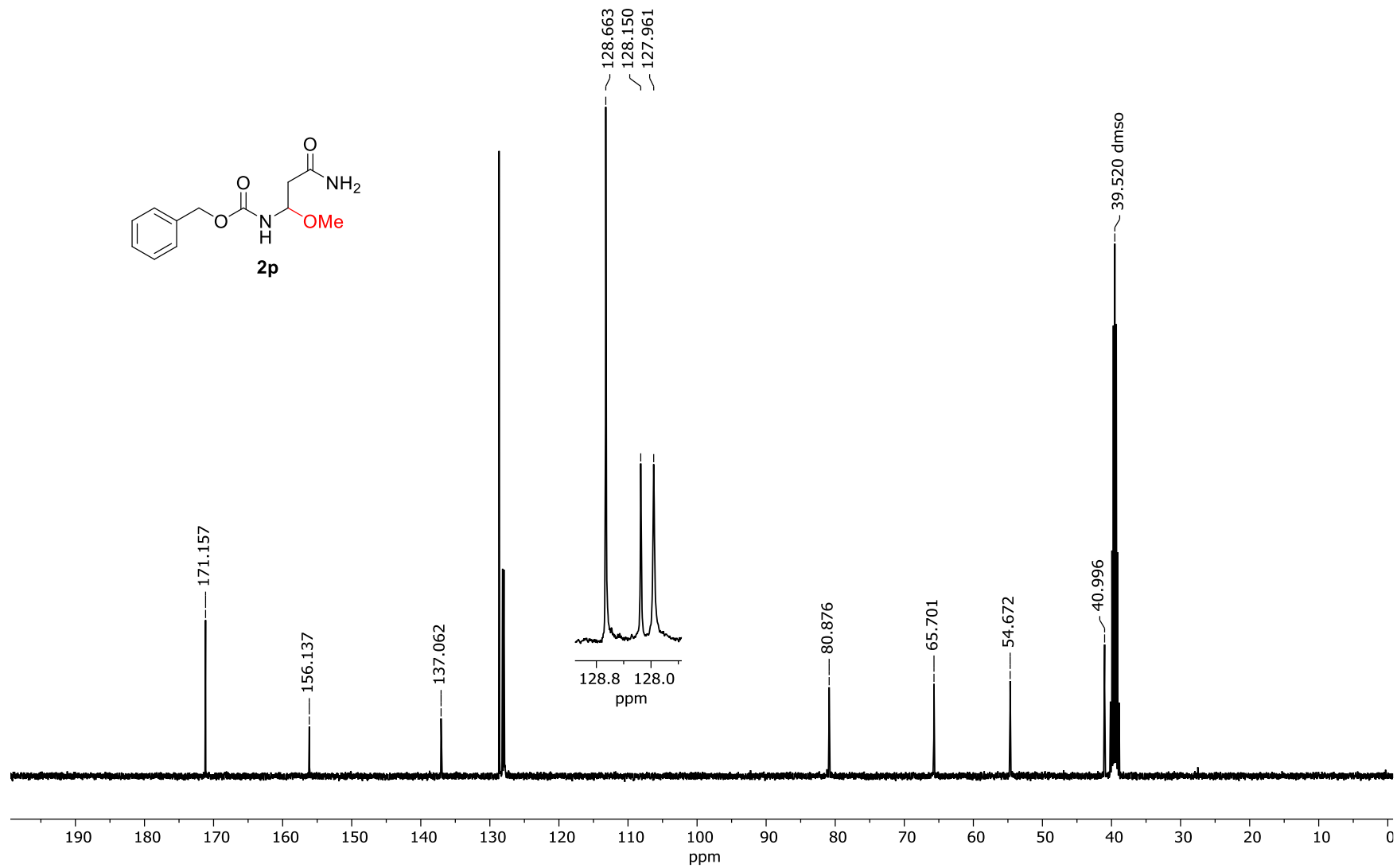
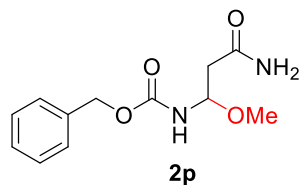


Benzyl N-(2-carbamoyl-1-methoxyethyl)carbamate (2p): ¹H NMR [400 MHz/DMSO/TMS]



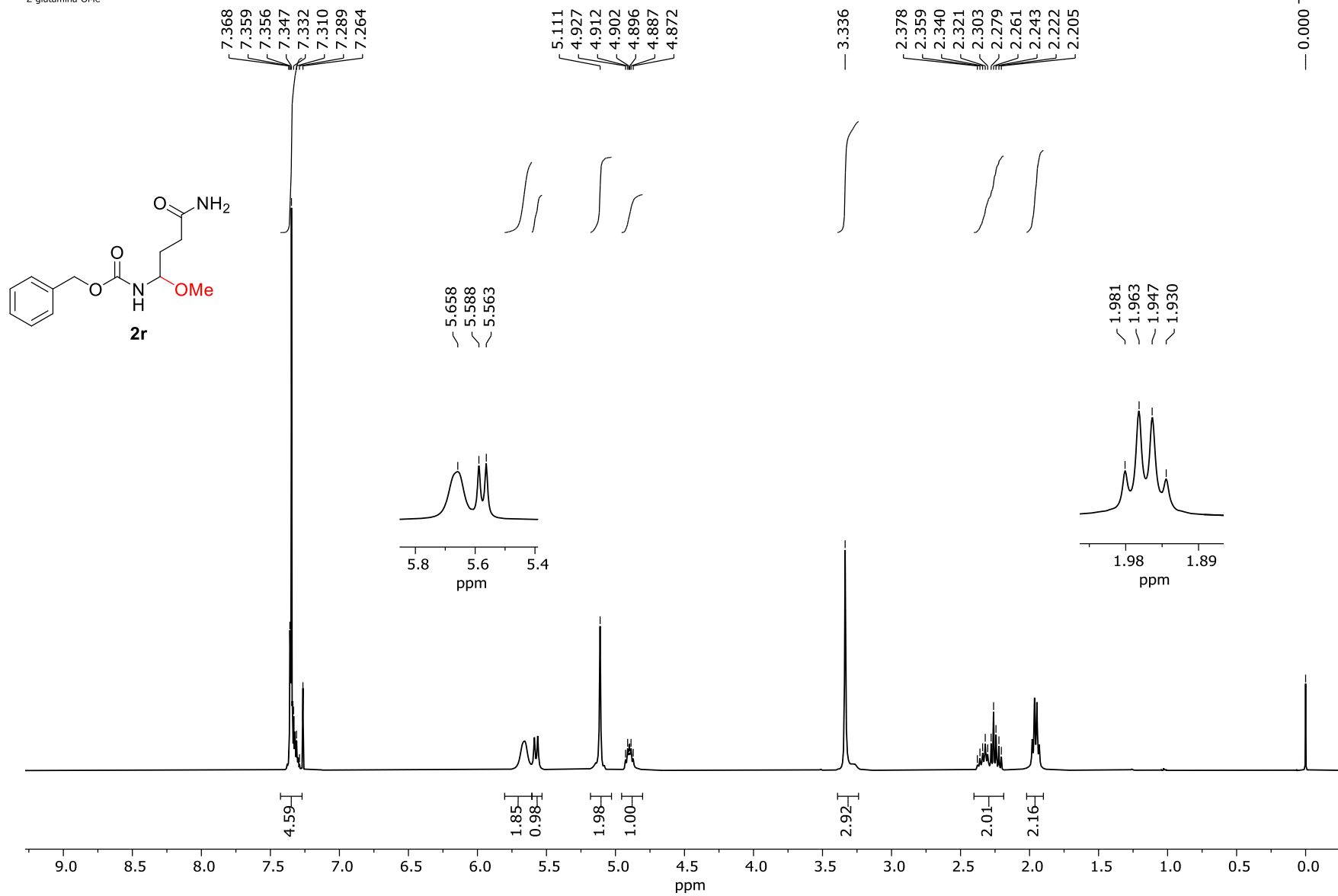
Benzyl N-(2-carbamoyl-1-methoxyethyl)carbamate (2p): ^{13}C NMR [100 MHz/DMSO]

Cbz-Asn-OMe-13C
Cbz-Asn-OMe-13C



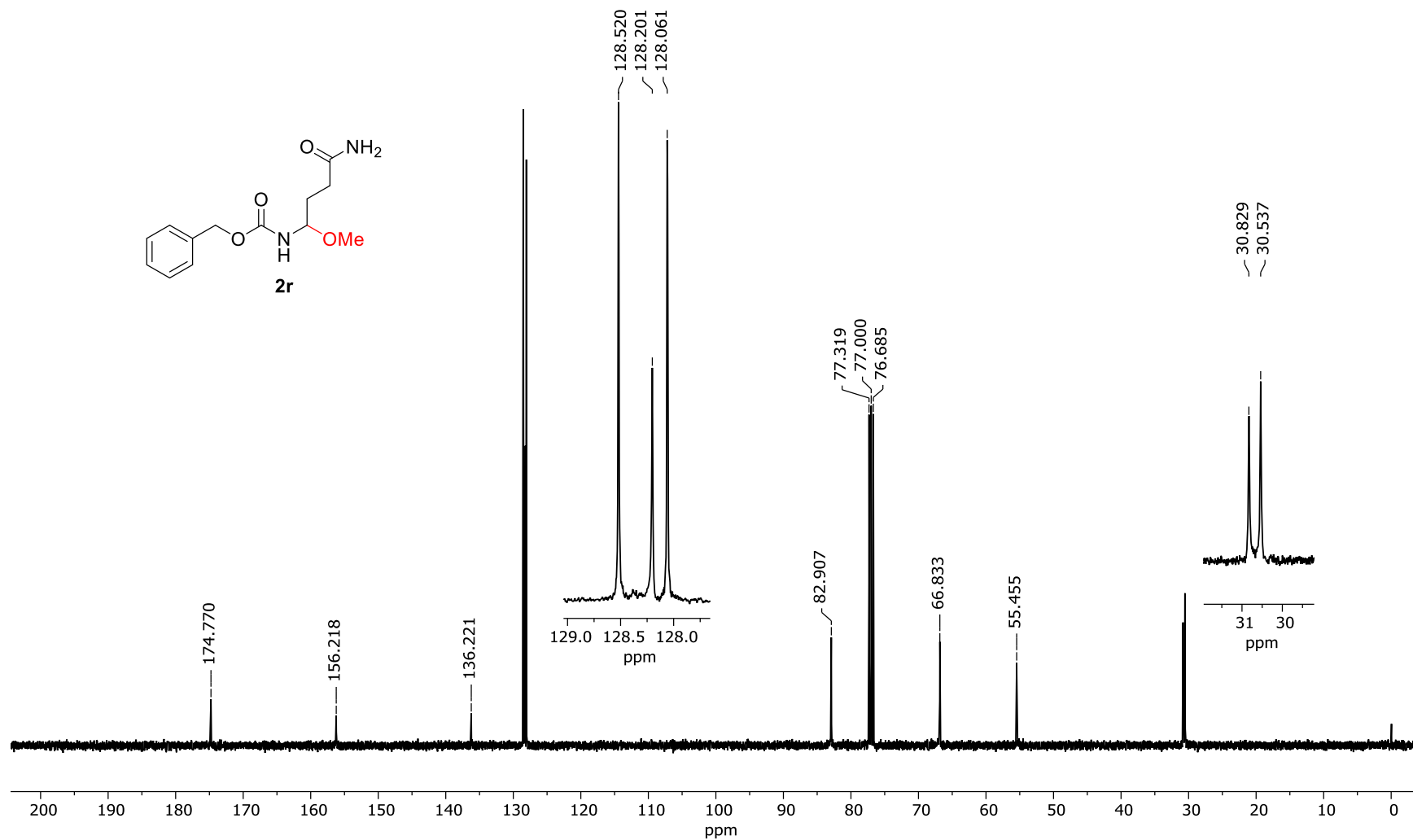
Benzyl N-(2-carbamoyl-1-methoxyethyl)carbamate (2r): ¹H NMR [400 MHz/CDCl₃/TMS]

APH-153-Z-Glu-OMe-1H_nt16
APH-153-Z-Glu-OMe-1H
Z-glutamina-OMe



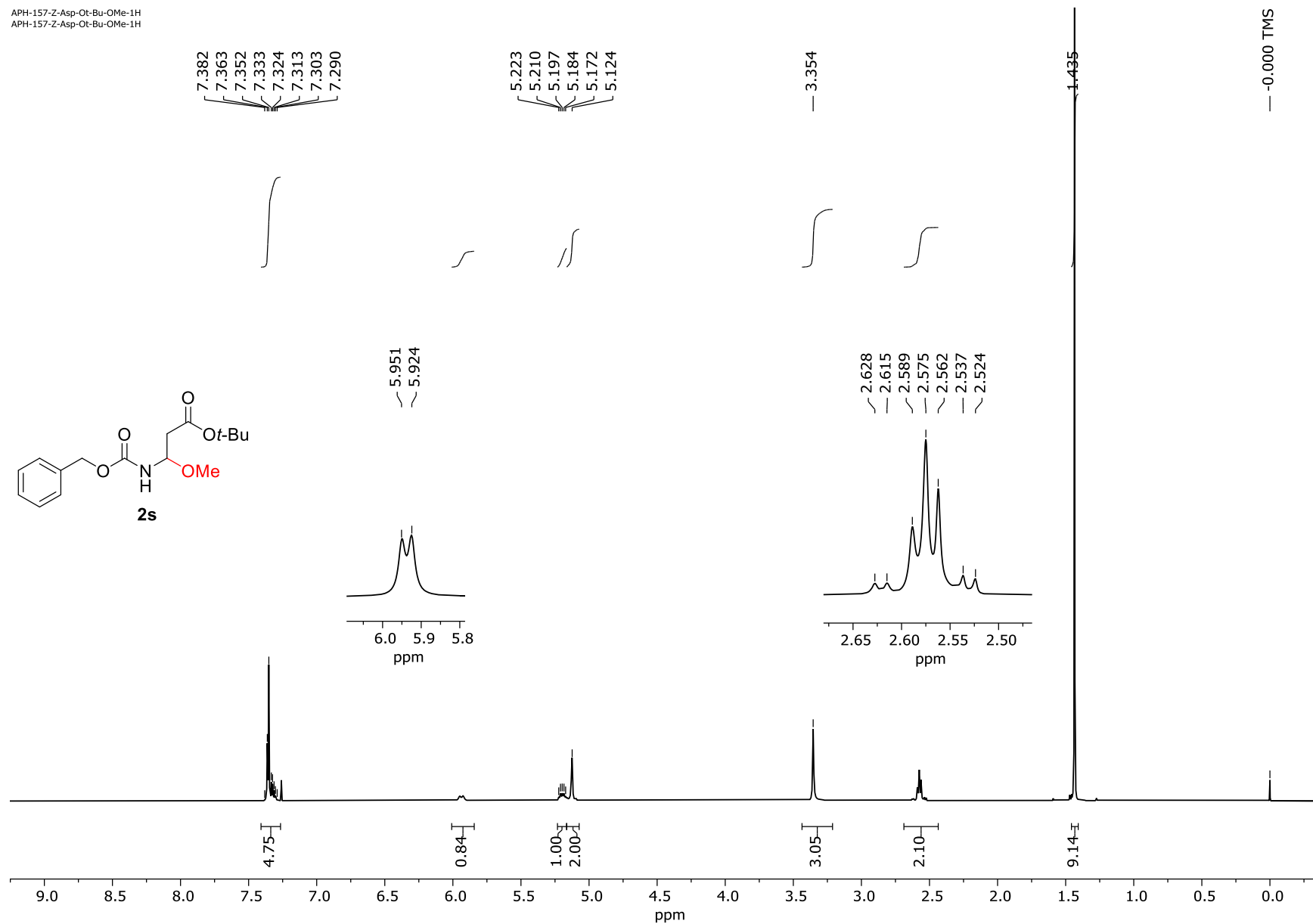
Benzyl *N*-(2-carbamoyl-1-methoxyethyl)carbamate (2r): ^{13}C NMR [100 MHz/ CDCl_3]

APH-153-Z-Glu-OMe-13C
APH-153-Z-Glu-OMe-13C
Z-glutamina-OMe



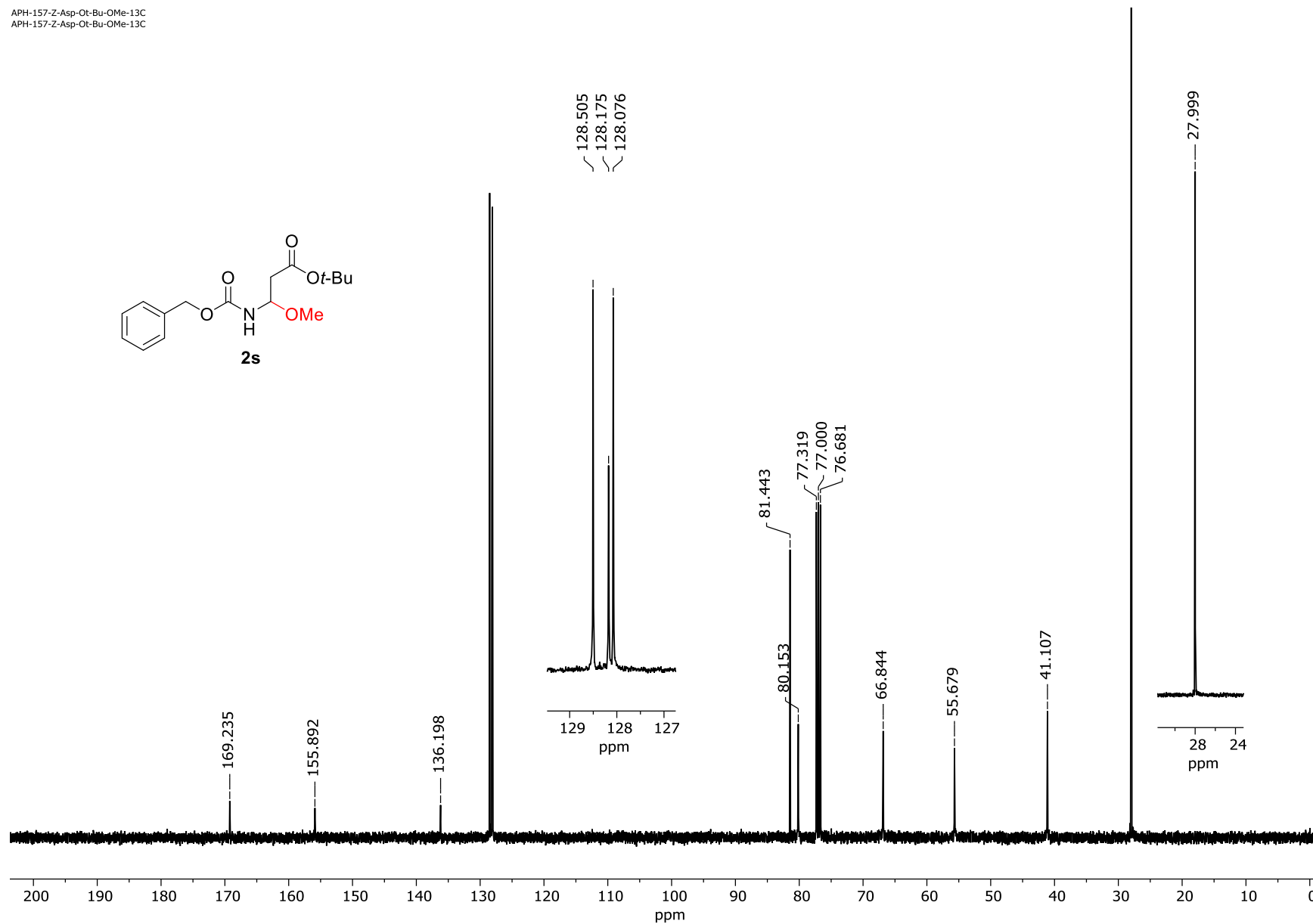
Benzyl N-(2-*tert*-butoxycarbonyl-1-methoxyethyl)carbamate (2s): ¹H NMR [400MHz/CDCl₃/TMS]

APH-157-Z-Asp-Ot-Bu-OMe-1H
APH-157-Z-Asp-Ot-Bu-OMe-1H



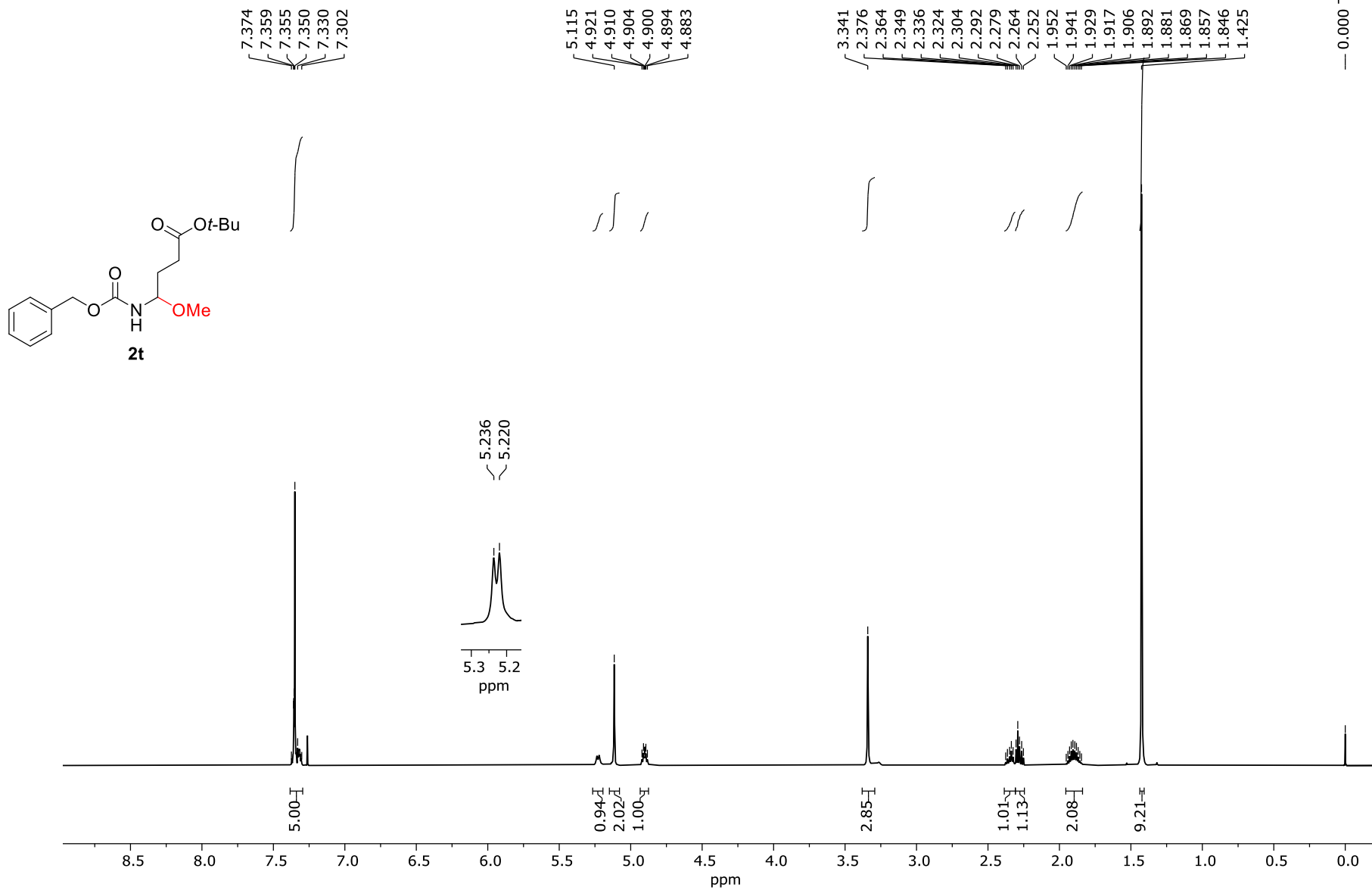
Benzyl *N*-(2-*tert*-butoxycarbonyl-1-methoxyethyl)carbamate (**2s**): ^{13}C NMR [100 MHz/ CDCl_3]

APH-157-Z-Asp-Ot-Bu-OMe-13C
APH-157-Z-Asp-Ot-Bu-OMe-13C

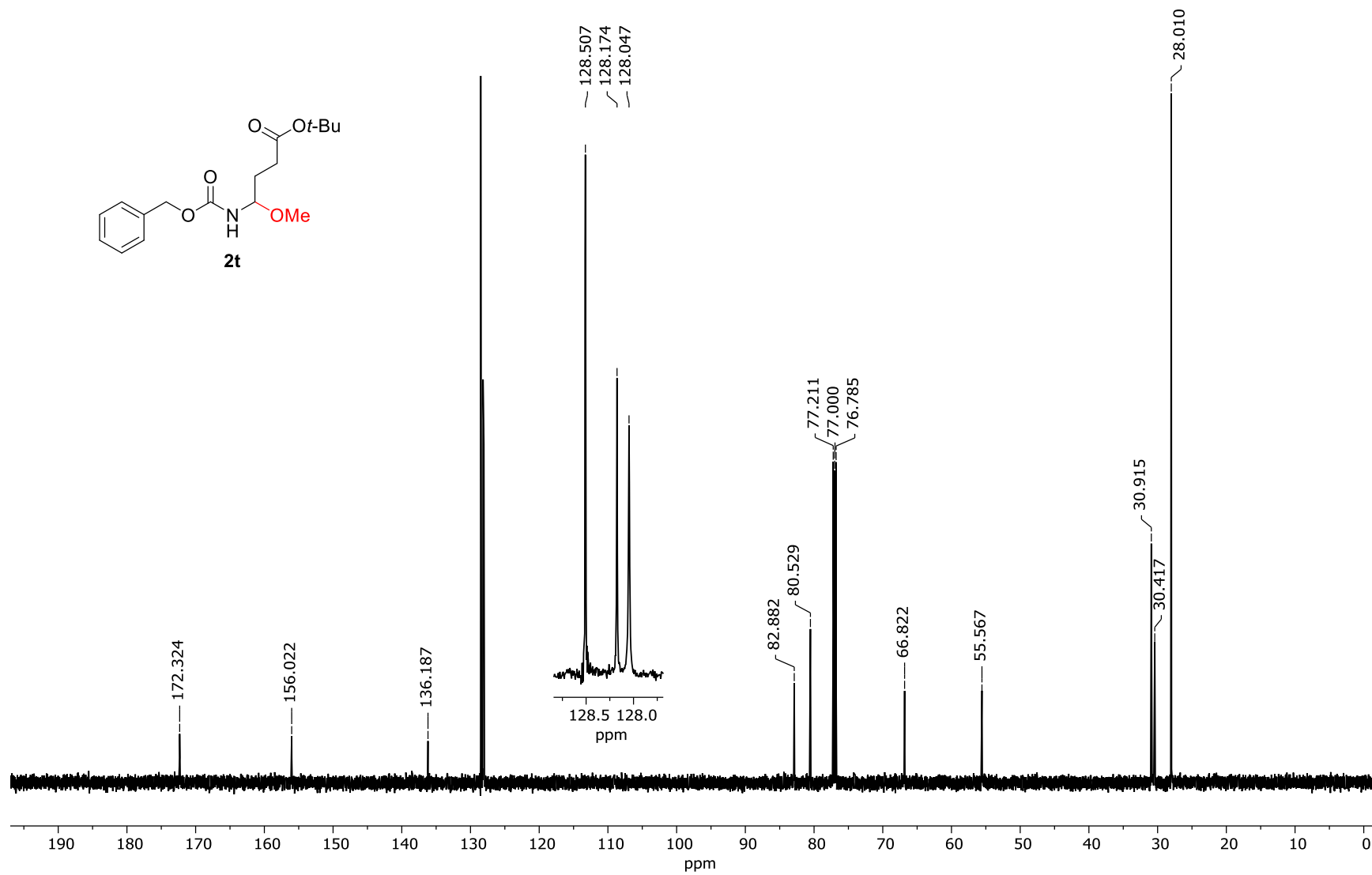


Benzyl *N*-(3-*tert*-butoxycarbonyl-1-methoxypropyl)carbamate (2t): ¹H NMR [600 MHz/CDCl₃/TMS]

APH-154-1-600-1H-D1-5
APH-154-1-600-1H

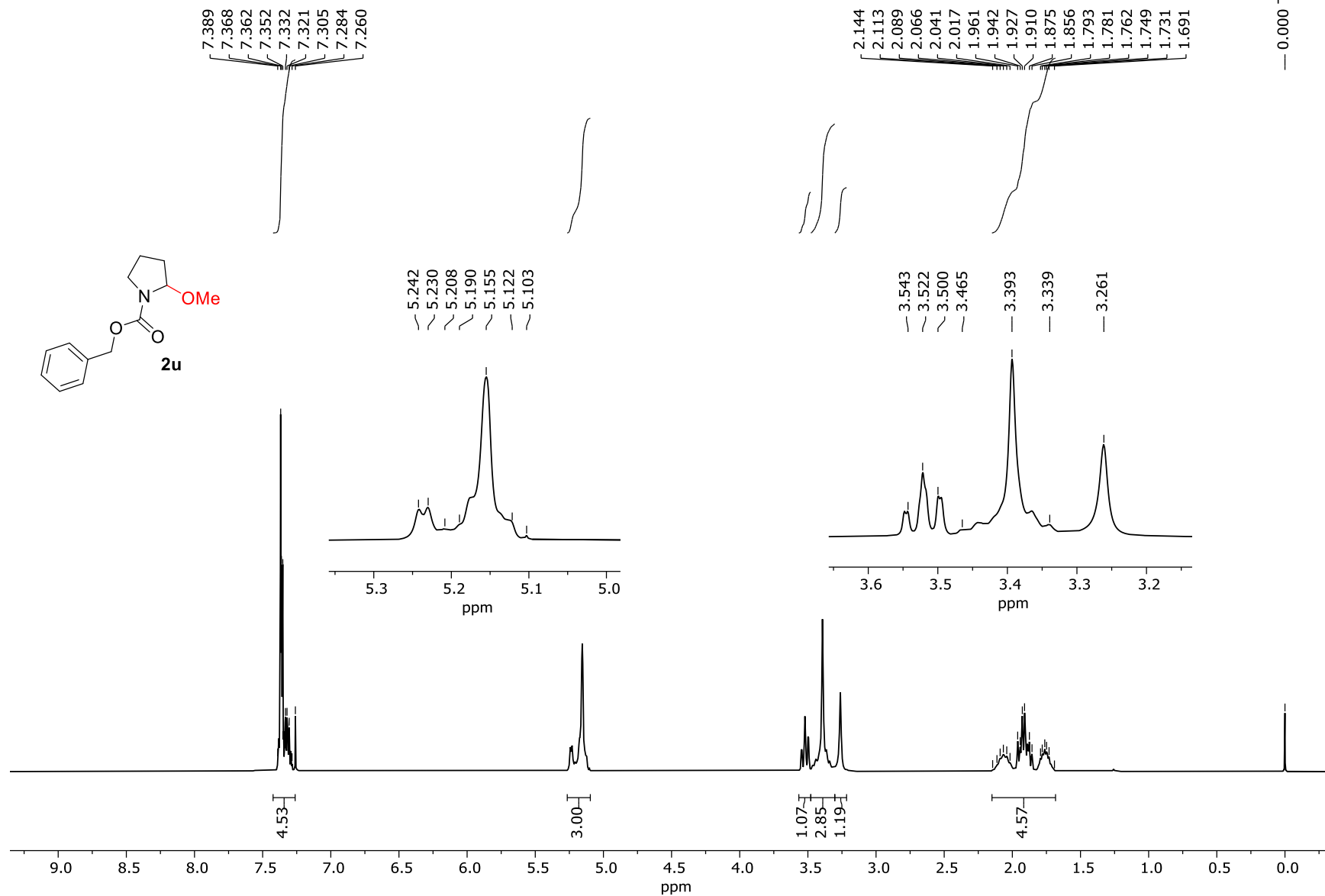


Benzyl *N*-(3-*tert*-butoxycarbonyl-1-methoxypropyl)carbamate (**2t**): ^{13}C NMR [150 MHz/ CDCl_3]



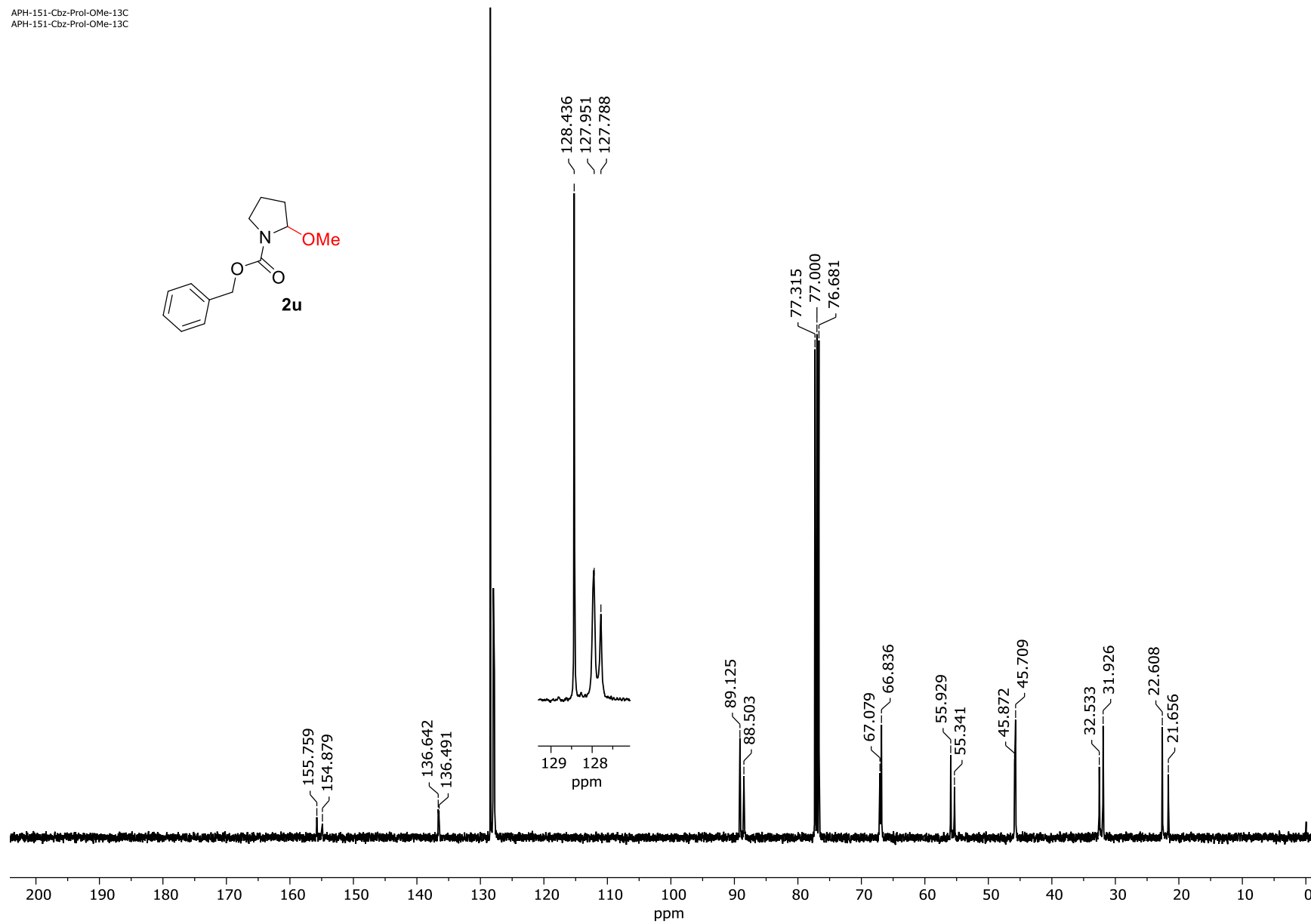
***N*-(Benzyloxycarbonyl)-2-methoxyproline (**2u**): ¹H NMR [400 MHz/CDCl₃/TMS]**

APH-151-Cbz-Prol-OMe
APH-151-Cbz-Prol-OMe

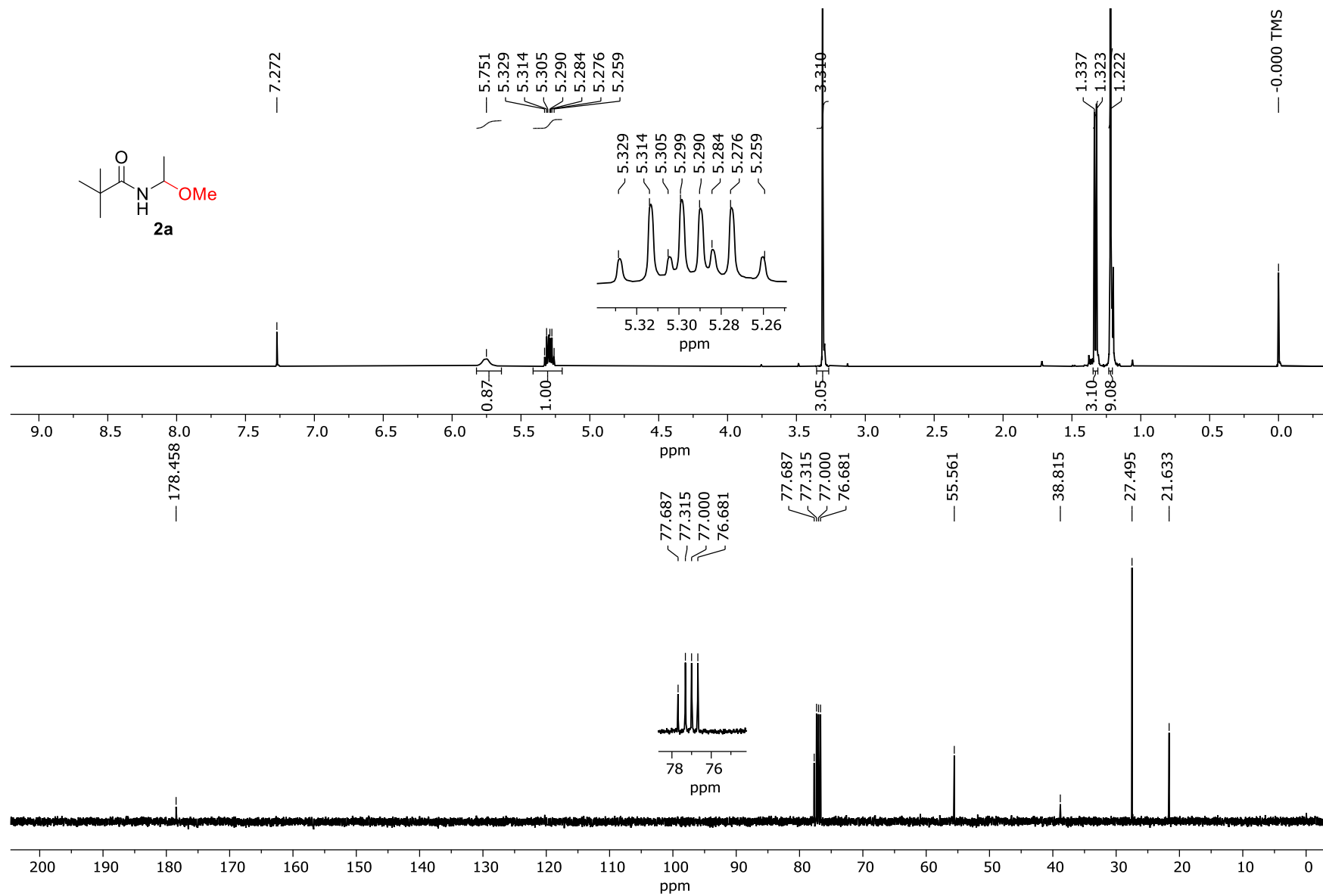


***N*-(Benzyloxycarbonyl)-2-methoxyproline (**2u**): ^{13}C NMR [100 MHz/ CDCl_3]**

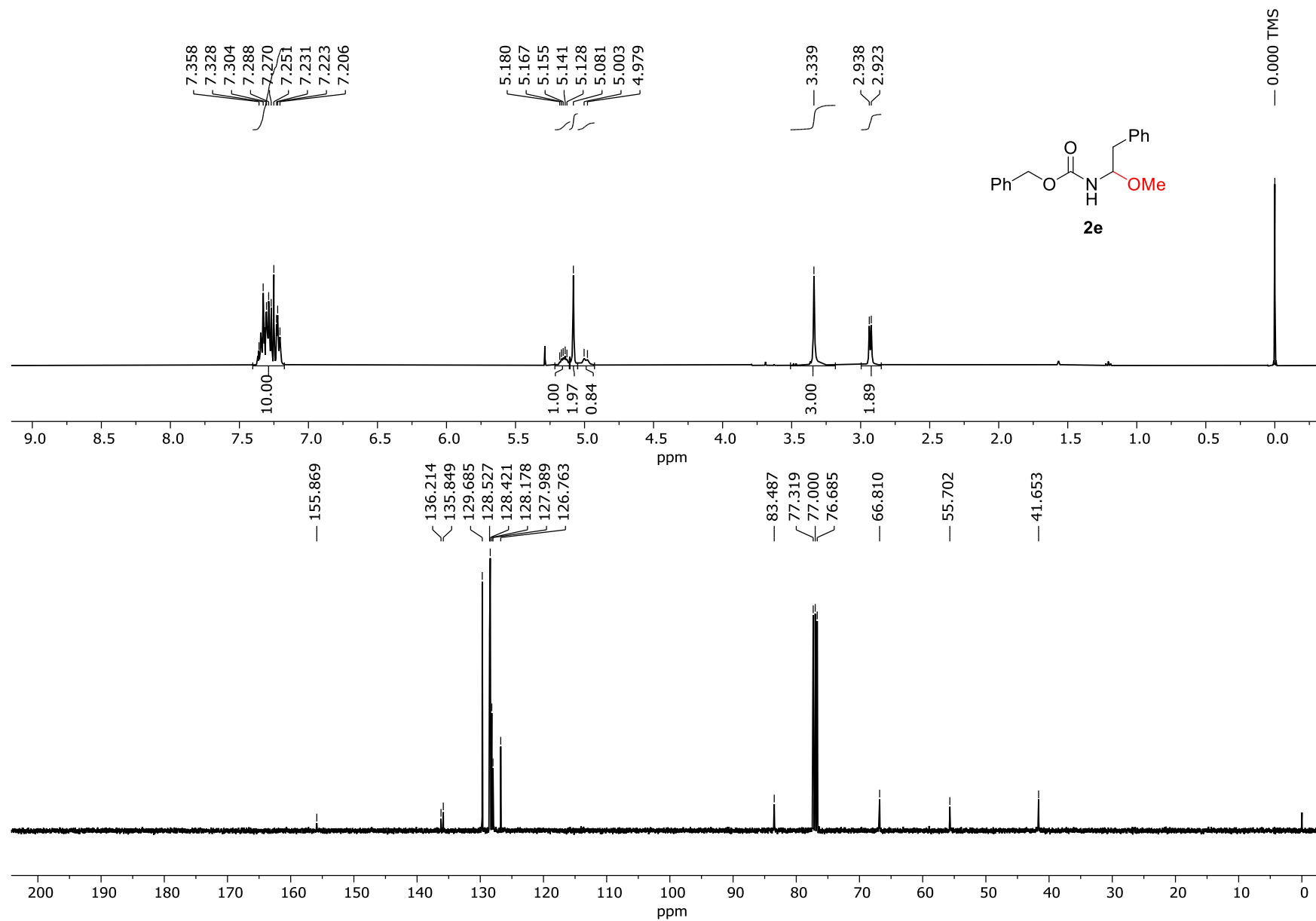
APH-151-Cbz-Prol-OMe-13C
APH-151-Cbz-Prol-OMe-13C



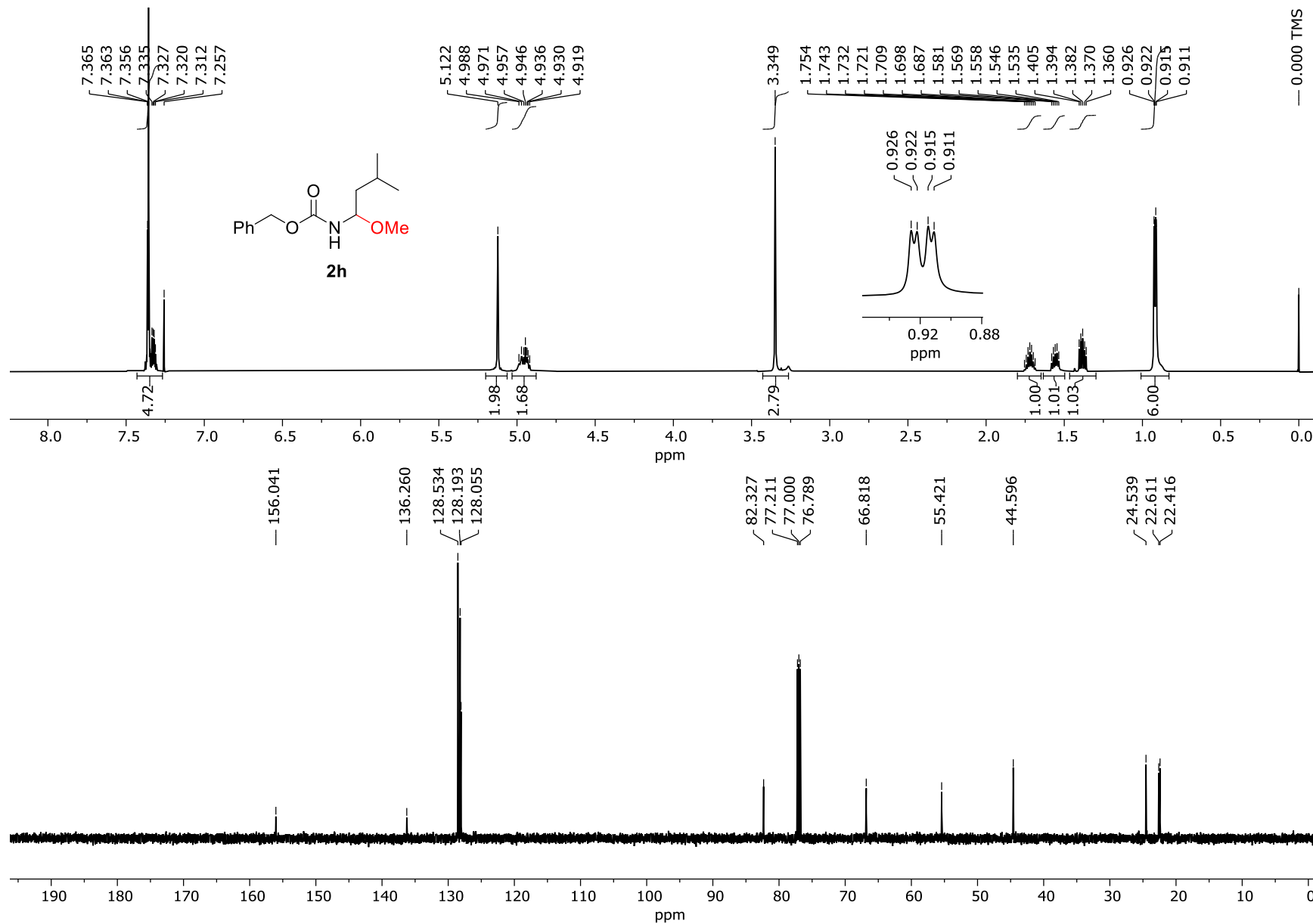
***N*-(1-methoxyethyl)pivaloylamide (2a):** ^1H NMR [400 MHz/ CDCl_3/TMS] and ^{13}C NMR [100 MHz/ CDCl_3]



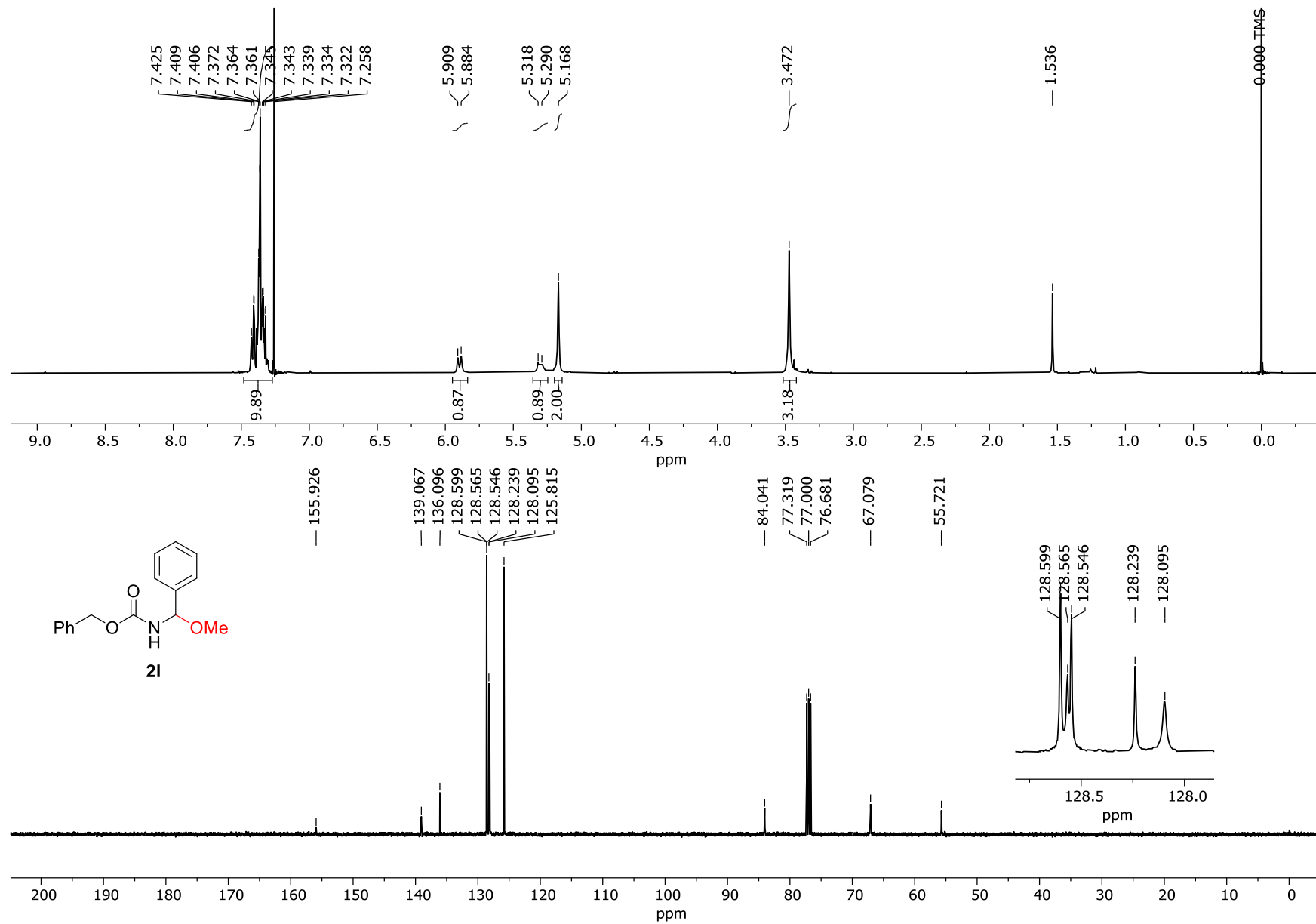
Benzyl *N*-(1-methoxy-2-phenylethyl)carbamate (2e): ^1H NMR [400 MHz/ CDCl_3 /TMS] and ^{13}C NMR [100 MHz/ CDCl_3]



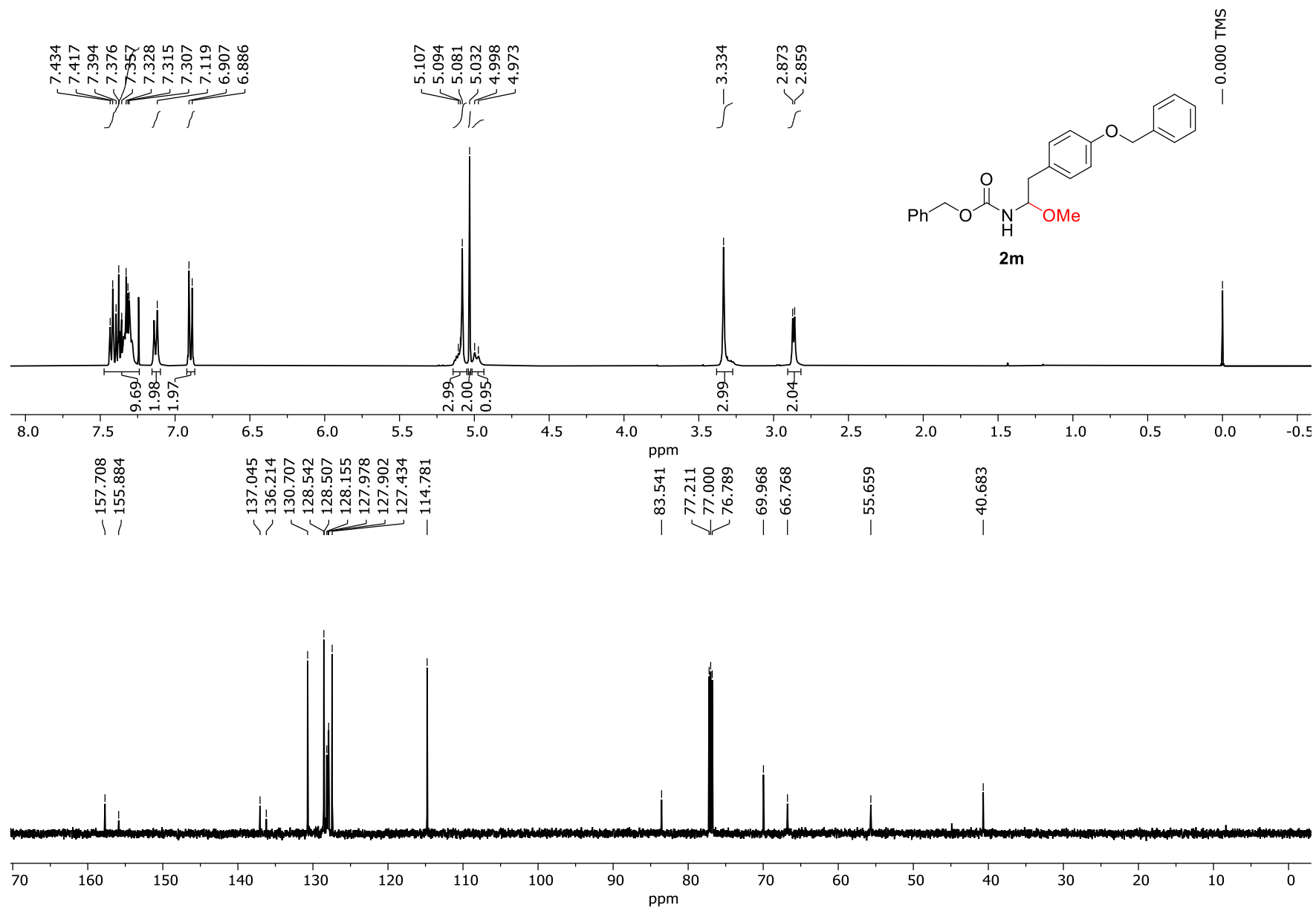
Benzyl N-(1-methoxy-3-methylbutyl)carbamate (2h): ^1H NMR [600 MHz/ CDCl_3 /TMS] and ^{13}C NMR [150 MHz/ CDCl_3]



Benzyl N-(1-methoxy-1-phenylmethyl)carbamate (2l): ¹H NMR [400 MHz/CDCl₃/TMS] and ¹³C NMR [100 MHz/CDCl₃]



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



Benzyl *N*-(3-*tert*-butoxycarbonyl-1-methoxypropyl)carbamate (2t): ¹H NMR [400 MHz/CDCl₃/TMS] and ¹³C NMR [100 MHz/CDCl₃]

