Supporting Information

A Short and Flexible Route to Tetrahydropyran-4-ones via Conjugated Nitrile Oxides Cycloaddition and Oxa-Michael Cyclization: A Concise Diastereoselective Total Synthesis of (±)-Diospongin A

Hongliang Yao, Jingyun Ren and Rongbiao Tong*

Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China.

rtong@ust.hk

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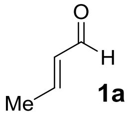
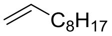
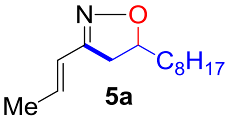
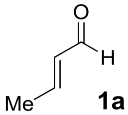
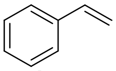
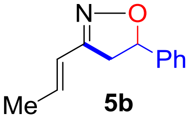
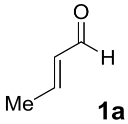
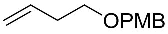
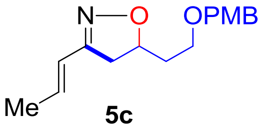
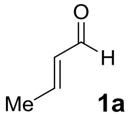
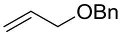
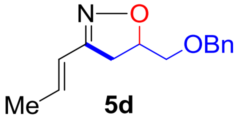
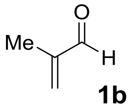
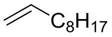
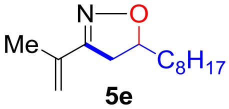
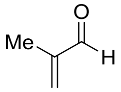
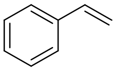
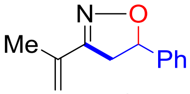
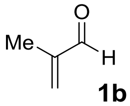
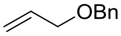
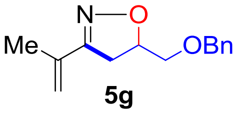
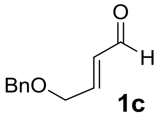
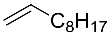
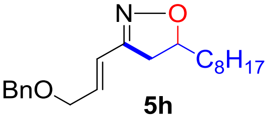
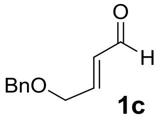
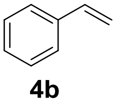
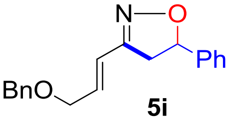
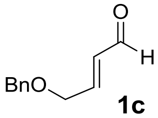
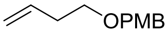
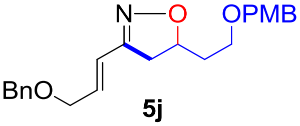
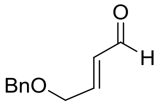
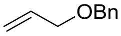
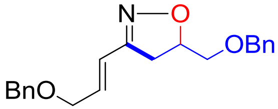
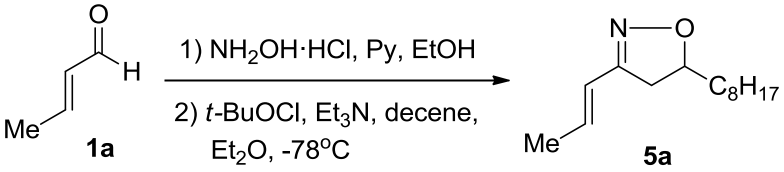
General Information

Reactions were carried out in oven or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. Tetrahydrofuran (THF) was freshly distilled before use from sodium using benzophenone as indicator. Dichloromethane (CH_2Cl_2) was freshly distilled before use from calcium hydride (CaH_2). All other anhydrous solvents were dried over 3Å or 4Å molecular sieves. Solvents used in workup, extraction and column chromatography were used as received from commercial suppliers without prior purification. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC, 0.25 mm) on Merck pre-coated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040-0.062 mm) supplied by Grace. Infrared spectra were collected on a Bruker model TENSOR27 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C). Chemical shifts are reported in parts per million (ppm) as values relative to the internal chloroform (7.27 ppm for ^{1}H and 77.23 ppm for ^{13}C). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High resolution mass spectra were measured at the Hong Kong University of Science and Technology Mass Spectrometry Service Center on either an Agilent GC/MS 5975C system or an API QSTAR XL System. Melting point was recorded on a Laboratory Devices model MEL-TEMP II melting point apparatus.

Table 1.1 Two-steps Synthesis of Isoxazolines (5a-5k)

Entry	Aldehyde	Olefin	Method	Product	Yield (%)
1	 **1a**	 **4a**	A	 **5a**	81
2	 **1a**	 **4b**	A	 **5b**	93
3	 **1a**	 **4c**	A	 **5c**	96
4	 **1a**	 **4d**	B	 **5d**	77
5	 **1b**	 **4a**	B	 **5e**	88
6	 **1b**	 **4b**	B	 **5f**	79
7	 **1b**	 **4d**	B	 **5g**	84
8	 **1c**	 **4a**	A	 **5h**	62
9	 **1c**	 **4b**	A	 **5i**	90
10	 **1c**	 **4c**	A	 **5j**	76
11	 **1c**	 **4d**	A	 **5k**	75

Synthesis of Isoxazolines (5a-5k, Table 1)



General Procedure A (5a-5c, 5h-5k)[1,2] To a solution of crotonaldehyde **1a** (160 mg, 2.29 mmol) in EtOH (95%, 17.6 mL) at room temperature was added $NH_2OH{\cdot}HCl$ (159 mg, 2.29 mmol) in pyridine (2.86 mL). The mixture was stirred at room temperature for 6 hrs and subsequently concentrated under reduced pressure. To the resulting residue were added EtOAc (12 mL) and H_2O (4 mL), and the organic layer was collected. The organic fractions were washed with H_2O (2 x 4 mL), brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. To the crude oximes in Et_2O (20 mL), Et_3N (0.65 mL) and decene **4a** (660 mg, 4.7 mmol) at -78 ^{o}C was added *t*-BuOCl (0.5 mL, 4.70 mmol) dropwise under a nitrogen atmosphere. The resulting reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (2 mL). The organic layer was collected and aqueous phase was extracted with Et_2O (3 x 2 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (Hexane/EtOAc=20:1) to afford the desired isoxazoline **5a** as a light yellow solid (425 mg, 81% yield). m.p: 36-37 ^{o}C. **IR** (neat, cm^{-1}): 2953, 2925, 2849, 1653, 1524, 1466, 1436, 960, 893. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 6.39 (dm, *J*=15.6 Hz, 1H), 5.95 (dq, *J*=15.6, 6.8 Hz, 1H), 4.61-4.53 (m, 1H), 3.09 (dd, *J*=16.4, 10.4 Hz, 1H), 2.66 (dd, *J*=16.4, 8.4 Hz, 1H), 1.88 (dd, *J*=6.8, 1.6 Hz, 3H), 1.72-1.67 (m, 2H), 1.56-1.51 (m, 1H), 1.32-1.22 (m, 11H), 0.88 (t, *J*=6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.5, 134.7, 121.9, 81.2, 39.0, 35.5, 32.0, 29.7, 29.6, 29.4, 25.7, 22.8, 18.7, 14.3. **HRMS** (CI^+) *m*/*z* calculated for $C_{14}H_{26}NO$ $[M+H]^+$ 224.2014, found 224.2015.

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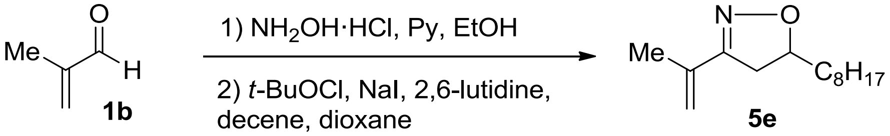
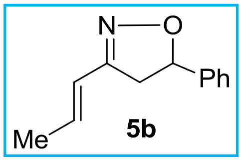
[1] D. Muri and E. M. Carreira, *J. Org. Chem.,* 2009, **74**, 8695.
[2] D. P. Curran, *J. Am. Chem. Soc.*, 1983, **105**, 5826.



General Procedure B (5d-5g)[3,4] To a solution of methacrolein **1b** (41.3 mg, 0.59 mmol) in EtOH (95%, 5.2 mL) at room temperature was added $NH_2OH\cdot HCl$ (41.0 mg, 0.59 mmol) in pyridine (0.65 mL). The reaction mixture was stirred at room temperature for 6 hrs and subsequently concentrated under reduced pressure. The resulting residue was distilled under reduced pressure (b.p. 46-47°C, 9.5 mmHg) to give methacrolein oxime. To the mixture of methacrolein oxime, decene **4a** (413 mg, 2.95 mmol), NaI (88.5 mg, 0.59 mmol) and 2,6-lutidine (0.07 mL, 0.59 mmol) in dioxane (5 mL) at room temperature was added *t*-BuOCl (0.14 mL, 1.18 mmol) dropwise. The resulting mixture was stirred under a nitrogen atmosphere for 24 hrs at rt and then quenched with addition of water (2 mL). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The residue was purified by flash column chromatography on silica gel (Hexane/EtOAc=25:1) to afford a yellow oil **5e** (116 mg, 88% yield). **IR** (neat, cm^{-1}): 2927, 2855, 1627, 1459, 1372, 1260, 909. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.30 (s, 1H), 5.17 (s, 1H), 4.67-4.59 (m, 1H), 3.15 (dd, *J*=16.0, 10.4 Hz, 1H), 2.73 (dd, *J*=16.0, 8.0 Hz, 1H), 2.05 (s, 3H), 1.76-1.69 (m, 1H), 1.60-1.51 (m, 1H), 1.46-1.28 (m,12H), 0.89 (t, *J*=7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 158.7, 136.2, 119.1, 82.1, 39.5, 35.5, 32.1, 29.7, 29.6, 29.4, 25.7, 22.9, 19.1, 14.3. **HRMS** (CI^+) *m*/*z* calculated for $C_{14}H_{26}NO$ $[M+H]^+$ 224.2014, found 224.2014.



5b

(Table 1, entry 2) Following the General Procedure A, compound **5b** was obtained from crotonaldehyde **1a** (42 mg, 0.6 mmol) and styrene **4b** (122 mg, 1.17 mmol) as an orange oil (103 mg, 93% yield) after flash column chromatography on silica gel (Hexane/EtOAc=10:1). **IR** (neat, cm-1): 3062, 3033, 2936, 2914, 1746, 1650, 1451, 1363, 1140, 962, 889, 760. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.40-7.29 (m, 5H), 6.45 (dm, *J*=15.6 Hz, 1H), 5.98 (dq, *J*=15.6, 6.8 Hz, 1H), 5.59 (dd, *J*=10.8, 8.0 Hz, 1H), 3.50 (dd, *J*=16.4, 10.8 Hz, 1H), 3.05 (dd, *J*=16.4, 8.0 Hz, 1H), 1.89 (dd, *J*=6.8, 1.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.1, 141.2, 135.5, 128.9, 128.3, 126.0, 121.5, 82.2, 42.2, 18.8. **HRMS** (CI^+) *m*/*z* calculated for $C_{12}H_{13}NO$ $[M]^+$ 187.0997, found 187.0993.

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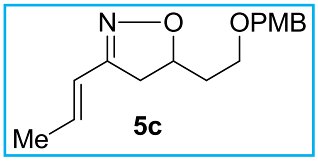
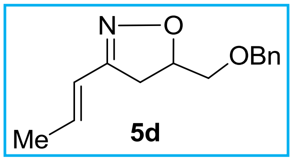
[3] S. Minakata, S. Okumura, T. Nagamachi and Y. Takeda, *Org. Lett.*, 2011, **13**, 2966.
[4] D. T. Mowry and R. R. Morner, *J. Am. Chem. Soc.*, 1947, **69**, 1831.



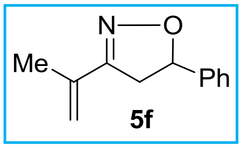
5c

(Table 1, entry 3) Following the General Procedure A, compound **5c** was obtained from crotonaldehyde **1a** (183 mg, 2.6 mmol) and olefin **4c**[5] (1 g, 5.6 mmol) as an orange oil (686 mg, 96% yield) after flash column chromatography on silica gel (Hexane/EtOAc=10:1). **IR** (neat, cm^{-1}): 3034, 2937, 2860, 1612, 1513, 1442, 1247, 1095, 965, 893, 820. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.26 (d, *J*=8.4 Hz, 2H), 6.89 (d, *J*=8.4 Hz, 2H), 6.39 (d, *J*=16.0 Hz, 1H), 5.98 (dq, *J*=16.0, 6.8 Hz, 1H), 4.79-4.72 (m, 1H), 4.47-4.41 (m, 2H), 3.81 (s, 3H), 3.64-3.57 (m, 2H), 3.11 (dd, *J*=16.4, 10.4 Hz, 1H), 2.77 (dd, *J*=16.4, 8.0 Hz, 1H), 2.00-1.82 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.2, 157.5, 134.9, 130.4, 129.3, 121.6, 113.8, 78.3, 72.8, 66.5, 55.3, 39.1, 35.4, 18.6. **HRMS** (CI^+) *m*/*z* calculated for $C_{16}H_{22}NO_3$ $[M+H]^+$ 276.1600, found 276.1593.



5d

(Table 1, entry 4) Following the General Procedure B, compound **5d** was obtained from crotonaldehyde **1a** (42 mg, 0.6 mmol) and olefin **4d**[6] (237mg, 1.8 mmol) as an orange oil (104 mg, 77% yield) after flash column chromatography on silica gel (Hexane/EtOAc=8:1). **IR** (neat, cm^{-1}): 3089, 2932, 2868, 1719, 1453, 1272, 1119, 932, 743, 715, 700. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.38-7.30 (m, 5H), 6.40 (dm, *J*=15.6 Hz, 1H), 5.98 (dq, *J*=15.6, 6.8 Hz, 1H), 4.82-4.75 (m, 1H), 4.60 (s, 2H), 3.62 (dd, *J*=10.8, 5.2 Hz, 1H), 3.54 (dd, *J*=10.8, 5.2 Hz, 1H), 3.10 (dd, *J*=16.0, 10.4 Hz, 1H), 2.96 (dd, *J*=16.0, 7.2 Hz, 1H), 1.89 (dd, *J*=6.8, 1.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.4, 138.1, 135.3, 128.6, 127.9, 121.6, 79.5, 73.8, 71.1, 36.4, 18.8. **HRMS** (CI^+) *m*/*z* calculated for $C_{14}H_{18}NO_2$ $[M+H]^+$ 232.1338, found 232.1330.



5f

(Table 1, entry 6) Following the General Procedure B, compound **5f** was obtained from methacrolein **1b** (42 mg, 0.6 mmol) and olefin **4b** (307mg, 2.95 mmol) as a yellow oil (87 mg, 79% yield) after flash column chromatography on silica gel (Hexane/EtOAc=20:1). **IR** (neat, cm^{-1}): 3091, 3032, 2979, 2925, 1626, 1566, 1453, 1370, 1226, 904, 758, 699. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.40-7.33 (m, 5H), 5.65 (dd, *J*=11.2, 8.4 Hz, 1H), 5.34 (s, 1H), 5.19 (s, 1H), 3.56 (dd, *J*=16.4, 10.8 Hz, 1H), 3.12 (dd, *J*=16.4, 8.0 Hz, 1H), 2.11 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 158.4, 142.1, 135.9, 128.9, 128.4, 126.1, 119.7, 83.2, 42.8, 19.2. **HRMS** (CI^+) *m*/*z* calculated for $C_{12}H_{14}NO$ $[M+H]^+$ 188.1070, found 188.1075.

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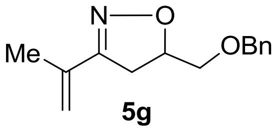
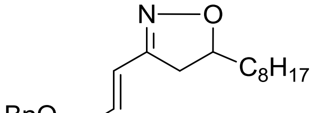
[5] M. Barbazanges, C. Meyer and J. Cossy, *Org. Lett.*, 2008, **10**, 4489.
[6] D. M. Heinrich, J. J. Youte, W. A. Denny and M. Tercel, *Tetrahedron Lett.*, 2011, **52**, 7000.



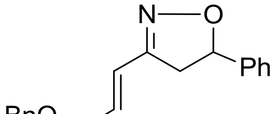
5g

(Table 1, entry 7) Following the General Procedure B, compound **5g** was obtained from methacrolein **1b** (42 mg, 0.6 mmol) and olefin **4d** (395mg, 2.95 mmol) as a yellow oil (114 mg, 84% yield) after flash column chromatography on silica gel (Hexane/EtOAc=10:1). **IR** (neat, cm^{-1}): 3089, 3030, 2858, 1626, 1558, 1454, 1369, 1263, 1117, 902, 738, 698. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.38-7.30 (m, 5H), 5.33 (s, 1H), 5.21 (s, 1H), 4.88-4.80 (m, 1H), 4.61 (s, 2H), 3.63 (dd, *J*=10.4, 5.2 Hz, 1H), 3.54 (dd, *J*=10.4, 5.2 Hz, 1H), 3.17 (dd, *J*=16.4, 10.8 Hz, 1H), 3.02 (dd, *J*=16.4, 7.6 Hz, 1H), 2.06 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 158.7, 138.1, 135.8, 128.6, 128.0, 127.9, 119.6, 80.4, 73.8, 71.2, 36.9, 19.2. **HRMS** (CI^+) *m/z* calculated for $C_{14}H_{18}NO_2$ $[M+H]^+$ 232.1338, found 232.1338.



5h

(Table 1, entry 8) Following the General Procedure A, compound **5h** was obtained from aldehyde **1c**[7] (92 mg, 0.53 mmol) and olefin **4a** (371 mg, 2.7 mmol) as a yellow oil (204 mg, 62% yield) after flash column chromatography on silica gel (Hexane/EtOAc=20:1). **IR** (neat, cm^{-1}): 3063, 2926, 2856, 1729, 1648, 1495, 1453, 1361, 1260, 1114, 739, 698. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.39-7.33 (m, 5H), 6.64 (d, *J*=16.0 Hz, 1H), 6.00 (dt, *J*=16.0, 5.6 Hz, 1H), 4.66-4.60 (m, 1H), 4.56 (s, 2H), 4.17 (dd, *J*=5.6, 1.6 Hz, 2H), 3.10 (dd, *J*=16.4, 10.4 Hz, 1H), 2.69 (dd, *J*=16.4, 8.4 Hz, 1H), 1.76-1.71 (m, 1H), 1.56-1.52 (m, 1H), 1.33-1.23 (m, 12H), 0.91-0.87 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.0, 138.1, 134.6, 128.7, 128.0, 127.9, 122.4, 81.7, 72.8, 70.1, 38.7, 35.5, 32.0, 29.7, 29.6, 29.4, 25.7, 22.9, 14.3. **HRMS** (CI^+) *m/z* calculated for $C_{21}H_{32}NO_2$ $[M+H]^+$ 330.2433, found 330.2431.



5i

(Table 1, entry 9) Following the General Procedure A, compound **5i** was obtained from aldehyde **1c** (46 mg, 0.26 mmol) and olefin **4b** (135 mg, 1.3 mmol) as a yellow oil (65 mg, 90% yield) after flash column chromatography on silica gel (Hexane/EtOAc=10:1). **IR** (neat, cm^{-1}): 3063, 3032, 2928, 2866, 1718, 1495, 1453, 1366, 1116, 968, 912, 750, 699. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.40-7.30 (m, 10H), 6.71 (d, *J*=16.0 Hz, 1H), 6.04 (dt, *J*=16.0, 5.6 Hz, 1H), 5.64 (dd, *J*=11.2, 8.0 Hz, 1H), 4.57 (s, 2H), 4.18 (dd, *J*=5.6, 1.6 Hz, 2H), 3.52 (dd, *J*=16.4, 11.2 Hz, 1H), 3.08 (dd, *J*=16.4, 8.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.6, 140.9, 137.9, 135.3, 128.9, 128.7, 128.4, 128.0, 127.9, 126.0, 121.7, 82.7, 72.9, 69.9, 41.9. **HRMS** (CI^+) *m/z* calculated for $C_{19}H_{20}NO_2$ $[M+H]^+$ 294.1494, found 294.1494.

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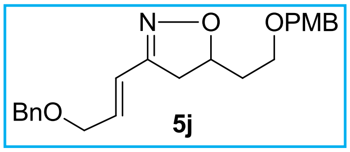
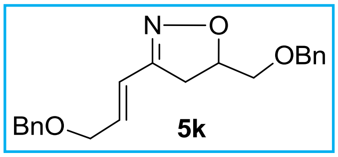
[7] P. A. Clarkea, G. A. Rolla, A. P. Cridland and A. A. Gill, *Tetrahedron*, 2007, **63**, 9124.



5j

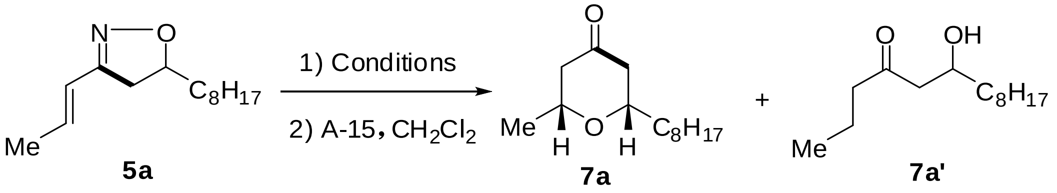
(Table 1, entry 10) Following the General Procedure A, compound **5j** was obtained from aldehyde **1c** (177 mg, 1.0 mmol) and olefin **4c** (384 mg, 2.0 mmol) as a yellow oil (288 mg, 76% yield) after flash column chromatography on silica gel (Hexane/EtOAc=5:1). **IR** (neat, cm^{-1}): 3031, 2930, 2858, 1612, 1513, 1455, 1248, 1097, 967, 905, 821, 743, 699. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.30-7.16 (m, 7H), 6.81-6.79 (m, 2H), 6.56 (d, *J*=16.0 Hz, 1H), 5.92 (dt, *J*=16.0, 5.6 Hz, 1H), 4.75-4.67 (m, 1H), 4.47 (s, 2H), 4.39-4.32 (m, 2H), 4.07 (dd, *J*=5.6, 1.2 Hz, 2H), 3.71 (s, 3H), 3.54-3.47 (m, 2H), 3.04 (dd, *J*=16.4, 10.4 Hz, 1H), 2.70 (dd, *J*=16.4, 8.0 Hz, 1H), 1.93-1.86 (m, 1H), 1.83-1.74 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.3, 157.2, 137.9, 134.9, 130.4, 129.4, 128.6, 127.9, 127.8, 121.8, 113.9, 78.8, 72.9, 72.7, 69.8, 66.5, 55.4, 38.9, 35.5. **HRMS** (CI^{+}) *m/z* calculated for $C_{23}H_{28}NO_4$ $[M+H]^+$ 382.2018, found 382.2025.



5k

(Table 1, entry 11) Following the General Procedure A, compound **5k** was obtained from aldehyde **1c** (46 mg, 0.26 mmol) and olefin **4d** (175mg, 1.3 mmol) as a yellow oil (63 mg, 75% yield) after flash column chromatography on silica gel (Hexane/EtOAc=5:1). **IR** (neat, cm^{-1}): 3064, 3031, 2928, 2861, 1717, 1364, 1270, 1117, 927, 739, 698. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.40-7.30 (m, 10H), 6.67 (d, *J*=16.0 Hz, 1H), 6.05 (dt, *J*=16.0, 5.6 Hz, 1H), 4.87-4.80 (m, 1H), 4.59 (d, *J*=12.8 Hz, 4H), 4.18 (dd, *J*=5.6, 1.6 Hz, 2H), 3.63 (dd, *J*=10.4, 4.8 Hz, 1H), 3.57 (dd, *J*=10.4, 4.8 Hz, 1H), 3.12 (dd, *J*=16.4, 10.8 Hz, 1H), 3.00 (dd, *J*=16.4, 7.2 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.9, 137.9, 135.2, 128.6, 128.5, 128.0, 127.9, 127.8, 121.7, 79.9, 73.7, 72.7, 70.9, 69.9, 36.0. **HRMS** (CI^{+}) *m/z* calculated for $C_{21}H_{24}NO_3$ $[M+H]^+$ 338.1756, found 338.1760.

Other Conditions for Reductive Cleavage of N-O and Oxa-Michael Cyclization



Entry	Reductant	Solvent	Temperature (°C)	Time	Conversion (%)[a]	**7a** (%)[b]	**7a’** (%)[b]
1	Cp_2TiCl_2/ Zn	THF	25	48h	< 5	< 5	0
2	Cp_2TiCl_2/ Zn	MeOH	25	48h	> 95	< 5	90
3	Cp_2TiCl_2/ Superhydride	THF	-78 → 25	2h	> 95	43	28
4	Cp_2TiCl_2/ EtMgBr	THF	0	10 min	100	0	50
5	Fe/NH_4Cl	EtOH/H_2O	80	24h	80	10	0
6	Zn/NH_4Cl	EtOH/H_2O	80	24h	0	0	0
7	Mg/NH_4Cl	EtOH/H_2O	80	24h	0	0	0
8	Mn/NH_4Cl	EtOH/H_2O	80	24h	0	0	0
9	SmI_2	THF	0	20 min	100	63	0

a: Reaction progress was monitored by TLC. b: Isolated yields over two steps.

Here we summarized some results from other conditions screened for reductive ring opening of isoxazoline **5a**, a model compound for this investigation. Single electron transfer reagents such as Cp_2TiCl_2 and Zn[8,9] in THF afforded trace amount of *β*-hydroxylenone due to the low conversions. Zn/MeOH could result in high conversion of **5a**, but only overreduction was observed. EtMgBr/Cp_2TiCl_2 gave the similar results to Zn/MeOH (entry 4) system. When Ti(III) was prepared *in situ* by reduction of Cp_2TiCl_2 with superhydride, a moderate yield (43%) of THPO was obtained after oxa-Michael cyclization (entry 3). Other elemental metal[10] (e.g. Fe, Zn, Mg, Mn) did not indicate promising reactivity towards the reductive cleavage of N-O bond of isoxazoline **5a**. Only about 10% yield of THPO **7a** was obtained in Fe/NH_4Cl system (entry 5), a condition developed by Chen.[10] Surprisingly, no reaction occurred with other better single electron transfer metals (Zn, Mg and Mn) in entries 6, 7 and 8.

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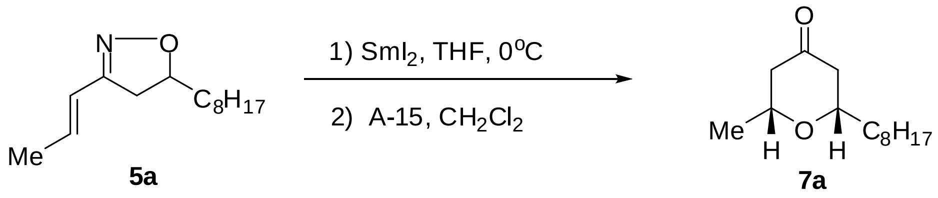
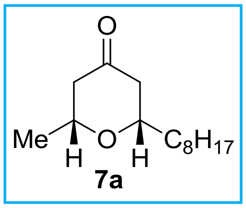
[8] A. Gansäuer and B. Rinker, *Tetrahedron*, 2002, **58**, 7017.
[9] M. Reiter, H. Turner and V. Gouverneur, *Eur. J. Org. Chem*., 2006, **12**, 7190.
[10] D. H. Jiang and Y. W. Chen, *J. Org. Chem.*, 2008, **73**, 9181.

Synthesis of Tetrahydropyran-4-ones (THPOs) (7a-7k)



General Procedure for Reductive Ring Opening of Isoxazolines[9,11] To the isoxazoline **5a** (223 mg, 1 mmol) in anhydrous and deoxygenated THF (36 mL) at 0 °C was added SmI_2 (36 mL, 0.1 M in THF, 3.6 mmol) slowly, maintaining a dark blue color throughout the reaction. The reaction mixture was stirred for additional 20 min at 0 °C after completion of addition of SmI_2. The reaction was quenched by bubbling with a stream of oxygen to give a bright yellow solution, which was poured into $B(OH)_3$ (900 mg) solution in H_2O (50 mL), and the mixture was stirred for 30 min at room temperature. Et_2O (20 mL) was added and careful separation was performed to avoid an emulsion. The organic layer was collected and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude *β*-hydroxylenone, which was subjected to intramolecular Michael cyclization directly. To the solution of *β*-hydroxylenone in dry CH_2Cl_2 (4 mL) was added Amberlyst-15 (452 mg, 2.0 equiv. w/w) under a nitrogen atmosphere. The reaction mixture was stirred vigorously at room temperature for 24 hrs and the Amberlyst-15 was removed by filtration. The solvent was evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (Hexane/EtOAc=10:1) to afford a light yellow oil **7a** (142 mg, 63% yield). The relative stereochemistry of **7a** was established based on the nOe experiment.



7a

(Table 1, entry 1) IR (neat, cm^{-1}): 2957, 2927, 2856, 1725, 1558, 1457, 1272, 1160. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.74-3.66 (m, 1H), 3.58-3.52 (m, 1H), 2.37-2.33 (m, 2H), 2.24-2.16 (m, 2H), 1.71-1.61 (m, 1H), 1.54-1.40 (m, 2H), 1.32-1.27 (m, 14H), 0.87 (d, *J*=7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 207.9, 77.2, 73.3, 49.6, 47.7, 36.6, 31.9, 29.6(2C), 29.4, 25.4, 22.8, 22.2, 14.2. **HRMS** (CI^+) *m/z* calculated for $C_{14}H_{27}O_2$ $[M+H]^+$ 227.2011, found 227.2013.

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[11] J. W. Bode and E. M. Carreira, *Org. Lett.*, 2001, **3**, 1587.

Relative Stereochemistry Substantiation of *syn*-7a via nOe

The strong nOe signal 2.81 clearly indicated the relative stereochemistry of the corresponding protons H_a and H_b (as shown in the Figure S-1) to be *syn*-configuration.

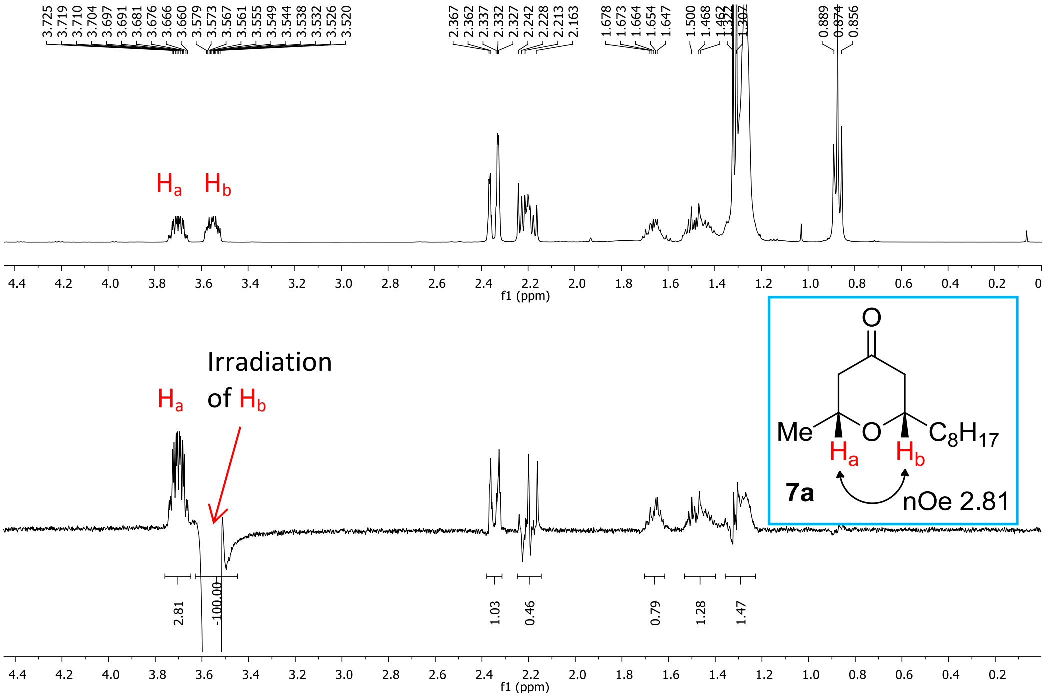
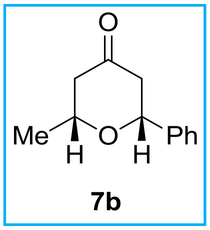
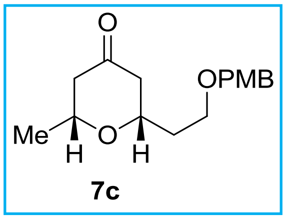


Figure S-1



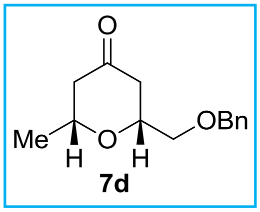
7b

(Table 1, entry 2) Following the General Procedure for synthesis of **7a**, THPO **7b** was obtained from isoxazoline **5b** (50 mg, 0.26 mmol) as a yellow oil (37 mg, 74% yield) after flash column chromatography on silica gel (Hexane/EtOAc=10:1). **IR** (neat, cm^{-1}): 2922, 2853, 1720, 1454, 1274, 1059, 756, 667. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ: 7.40-7.30 (m, 5H), 4.66 (dd, *J*=10.4, 3.2 Hz, 1H), 3.96-3.91 (m, 1H), 2.64-2.53 (m, 2H), 2.51-2.35 (m, 2H), 1.42 (d, *J*=6.0 Hz, 3H). ^{13}**C NMR** (100 MHz, $CDCl_3$) δ: 207.3, 140.9, 128.9, 128.3, 125.9, 79.0, 73.9, 49.6, 49.5, 22.4. **HRMS** (CI^+) *m*/*z* calculated for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.0994.



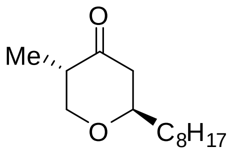
7c

(Table 1, entry 3) Following the General Procedure for synthesis of **7a**, THPO **7c** was obtained from isoxazoline **5c** (50 mg, 0.18 mmol) as an orange oil (39 mg, 77% yield) after flash column chromatography on silica gel (Hexane/EtOAc=5:1). **IR** (neat, cm^{-1}): 2971, 2933, 2861, 1720, 1613, 1514, 1248, 1089, 1034, 820, 669. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.25 (d, *J*=8.4 Hz, 2H), 6.88 (d, *J*=8.4 Hz, 2H), 4.47-4.40 (m, 2H), 3.81 (s, 3H), 3.79-3.67 (m, 2H), 3.63-3.52 (m, 2H), 2.39-2.34 (m, 2H), 2.26-2.17 (m, 2H), 1.95-1.90 (m, 1H), 1.85-1.77 (m, 1H), 1.29 (d, *J*=6.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 207.6, 159.4, 130.6, 129.4, 114.0, 74.2, 73.3, 72.9, 66.0, 55.5, 49.5, 47.7, 36.7, 22.2. **HRMS** (CI^+) *m/z* calculated for $C_{16}H_{22}O_4$ $[M]^+$ 278.1518, found 278.1519.



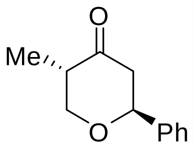
7d

(Table 1, entry 4) Following the General Procedure for synthesis of **7a**, THPO **7d** was obtained from isoxazoline **5d** (23 mg, 0.1 mmol) as a colorless oil (11 mg, 48% yield) after flash column chromatography on silica gel (Hexane/EtOAc=5:1). **IR** (neat, cm^{-1}): 2973, 2926, 2859, 1719, 1568, 1557, 1274, 1115, 715, 700. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.38-7.29 (m, 5H), 4.62 (s, 2H), 3.88-3.82 (m, 1H), 3.80-3.75 (m, 1H), 3.58 (d, *J*=4.8 Hz, 2H), 2.43-2.23 (m, 4H), 1.36 (d, *J*=6.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 207.4, 138.2, 128.7, 128.0, 127.9, 76.3, 73.7, 73.6, 72.6, 49.5, 44.1, 22.2. **HRMS** (CI^+) *m/z* calculated for $C_{14}H_{19}O_3$ $[M+H]^+$ 235.1334, found 235.1336.



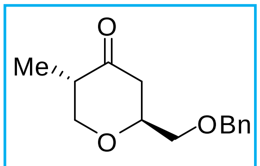
7e

(Table 1, entry 5) Following the General Procedure for synthesis of **7a**, THPO **7e** was obtained from isoxazoline **5e** (80 mg, 0.35 mmol) as a yellow oil (64 mg, 79% yield) after flash column chromatography on silica gel (Hexane/EtOAc=10:1). **IR** (neat, cm^{-1}): 2957, 2926, 2855, 1718, 1558, 1541, 1457, 1154. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 4.20 (dd, *J*=11.2, 6.8 Hz, 1H), 3.60-3.54 (m, 1H), 3.26 (t, *J*=11.2 Hz, 1H), 2.66-2.60 (m, 1H), 2.43-2.30 (m, 2H), 1.70-1.62 (m, 1H), 1.56-1.40 (m, 2H), 1.34-1.28 (m, 11H), 0.96 (d, *J*=6.8 Hz, 3H), 0.86 (t, *J*=6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 209.1, 79.5, 73.4, 48.5, 45.7, 36.7, 32.1, 29.7(2C), 29.4, 25.4, 22.9, 14.4, 9.2. **HRMS** (CI^+) *m/z* calculated for $C_{14}H_{27}O_2$ $[M+H]^+$ 227.2011, found 227.2005.



7f

(Table 1, entry 6) Following the General Procedure for synthesis of **7a**, THPO **7f** was obtained from isoxazoline **5f** (30 mg, 0.16 mmol) as a yellow oil (20 mg, 67% yield) after flash column chromatography on silica gel (Hexane/EtOAc=10:1). **IR** (neat, cm^{-1}): 2966, 2930, 2850, 1718, 1454, 1382, 1240, 1077, 759. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.42-7.31 (m, 5H), 4.67-4.63 (m, 1H), 4.38 (dd, *J*=11.2, 7.2 Hz, 1H), 3.47 (t, *J*=11.2 Hz, 1H), 2.83-2.76 (m, 1H), 2.68-2.66 (m, 2H), 1.04 (d, *J*=6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 208.2, 140.8, 128.9, 128.4, 125.8, 81.1, 73.6, 50.2, 45.6, 9.2. **HRMS** (CI$^+$) *m*/*z* calculated for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.0997.

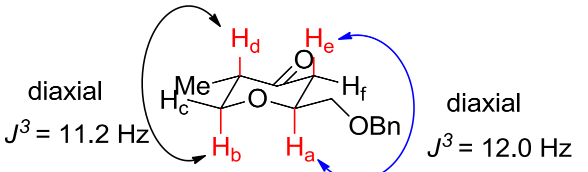


7g

(Table 1, entry 7) Following the General Procedure for synthesis of **7a**, THPO **7g** was obtained from isoxazoline **5g** (50 mg, 0.21 mmol) as a colorless oil (37 mg, 75% yield) after flash column chromatography on silica gel (Hexane/EtOAc=8:1). **IR** (neat, cm^{-1}): 2965, 2929, 2860, 1715, 1496, 1381, 1358, 1102, 740, 699. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.38-7.29 (m, 5H), 4.64-4.58 (m, 2H), 4.26 (dd, *J*=11.2, 6.8 Hz, 1H), 3.84 (ddt, *J*=12.0, 4.4, 2.4 Hz, 1H), 3.56 (d, *J*=4.4 Hz, 2H), 3.32 (t, *J*=11.2 Hz, 1H), 2.66 (dqd, *J*=11.2, 6.8, 1.2 Hz, 1H), 2.53 (ddd, *J*=14.0, 12.0, 1.2 Hz, 1H), 2.36 (dd, *J*=14.0 ,2.4 Hz, 1H), 0.97 (d, *J*=6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 208.5, 138.0, 128.7, 128.0, 127.8, 78.3, 73.8, 73.4, 72.5, 45.5, 44.6, 9.1. **HRMS** (CI$^+$) *m*/*z* calculated for $C_{14}H_{19}O_3$ $[M+H]^+$ 235.1334, found 235.1338. The relative stereochemistry of **7g** was established by nOe experiments and analysis of J^3 coupling constants of the most stable conformation.

Relative Stereochemistry Substantiation of *anti*-7g via nOe and J^3 Coupling Constant

The large coupling constants between H_a and H_e (*J*= 12.0 Hz) and between H_b and H_d (*J*= 11.2 Hz) indicated they sit on axial positions, which were further supported by the nOe experiments.



7g

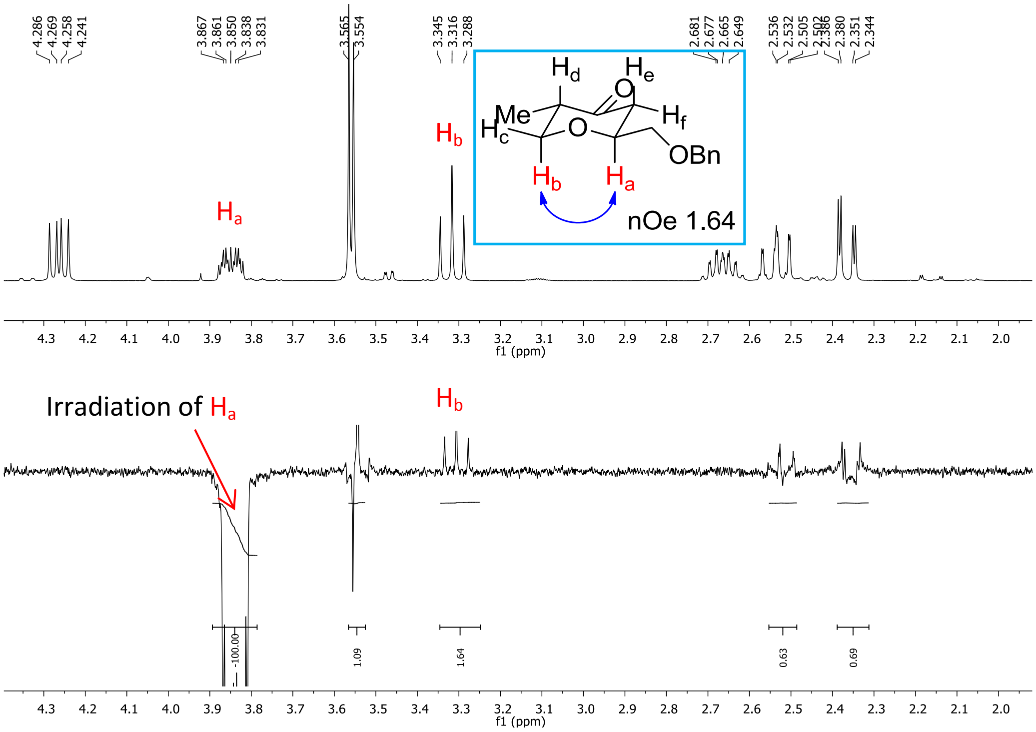


Figure S-2

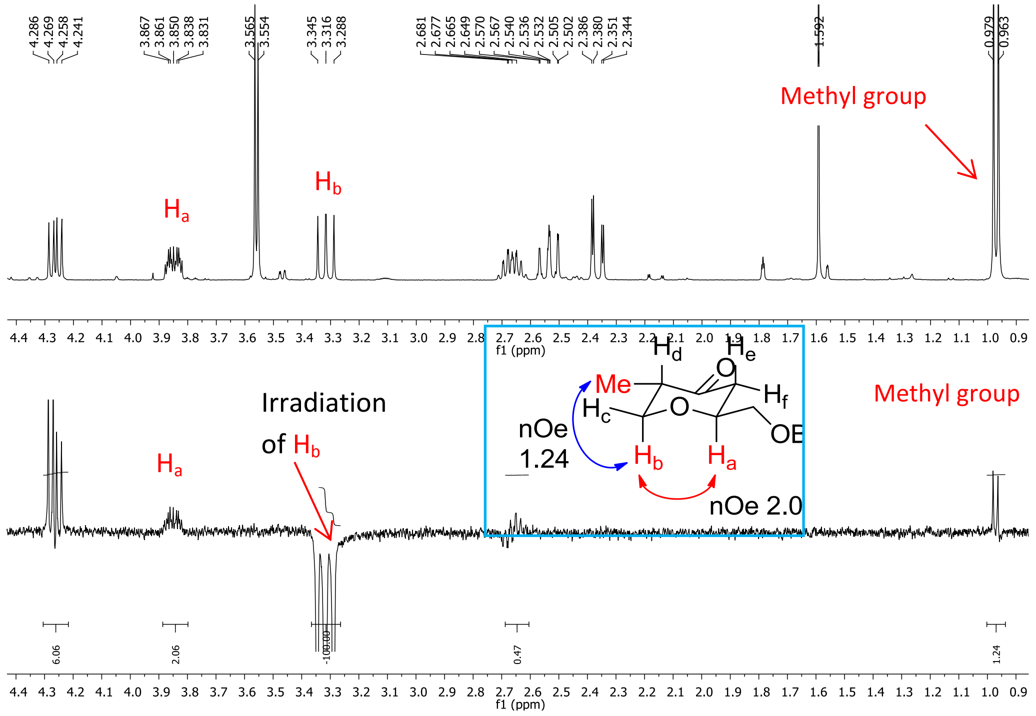


Figure S-3

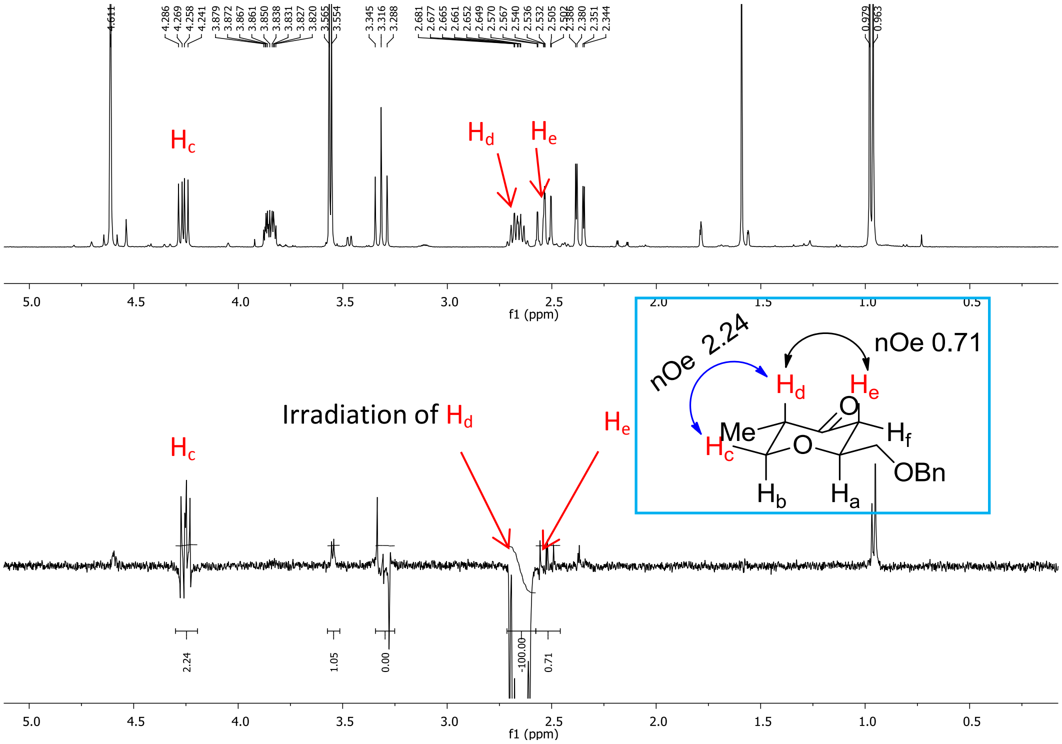
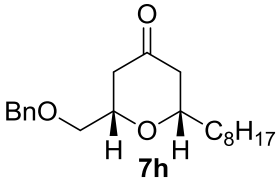
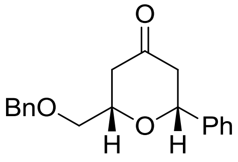


Figure S-4



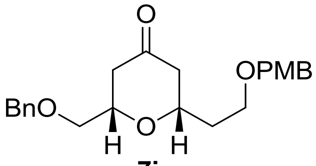
7h

(Table 1, entry 8) Following the General Procedure for synthesis of **7a**, THPO **7h** was obtained from isoxazoline **5h** (90 mg, 0.27 mmol) as a colorless oil (76 mg, 74% yield) after flash column chromatography on silica gel (Hexane/EtOAc=10:1). **IR** (neat, cm^{-1}): 3031, 2926, 2856, 1722, 1456, 1281, 1098, 738, 698. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 7.38-7.20 (m, 5H), 4.62 (s, 2H), 3.85-3.80 (m, 1H), 3.61-3.57 (m, 3H), 2.47-2.20 (m, 4H), 1.77-1.70 (m, 1H), 1.55-1.46 (m, 2H), 1.37-1.22 (m, 11H), 0.89 (t, *J*=4.4 Hz, 3H). **^{13}C NMR** (100 MHz, CDCl$_3$) δ: 207.6, 138.2, 128.6, 127.9, 127.8, 76.4, 73.7(2C), 72.5, 47.9, 44.5, 36.5, 32.0, 29.7(2C), 29.4, 25.4, 22.8, 14.3. **HRMS** (CI$^+$) *m*/*z* calculated for $C_{21}H_{33}O_3$ [M+H]$^+$ 333.2430, found 333.2432.



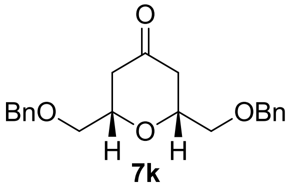
7i

(Table 1, entry 9) Following the General Procedure for synthesis of **7a**, THPO **7i** was obtained from isoxazoline **5i** (25 mg, 0.09 mmol) as a colorless oil (18 mg, 72% yield) after flash column chromatography on silica gel (Hexane/EtOAc=8:1). **IR** (neat, cm^{-1}): 3031, 2921, 2861, 1719, 1496, 1453, 1246, 1101, 752, 699. **^{1}H NMR** (400 MHz, CDCl$_3$) δ: 7.40-7.30 (m, 10H), 4.71-4.68 (m, 1H), 4.65-4.58 (m, 2H), 4.05-4.00 (m, 1H), 3.73-3.66 (m, 2H), 2.68-2.47 (m, 4H). **^{13}C NMR** (100 MHz, CDCl$_3$) δ: 206.7, 140.8, 138.2, 128.9, 128.7, 128.3, 128.0, 127.9, 125.9, 79.1, 76.8, 73.8, 72.5, 49.8, 44.4. **HRMS** (CI$^+$) *m*/*z* calculated for $C_{19}H_{21}O_3$ $[M+H]^+$ 297.1491, found 297.1492.



7j

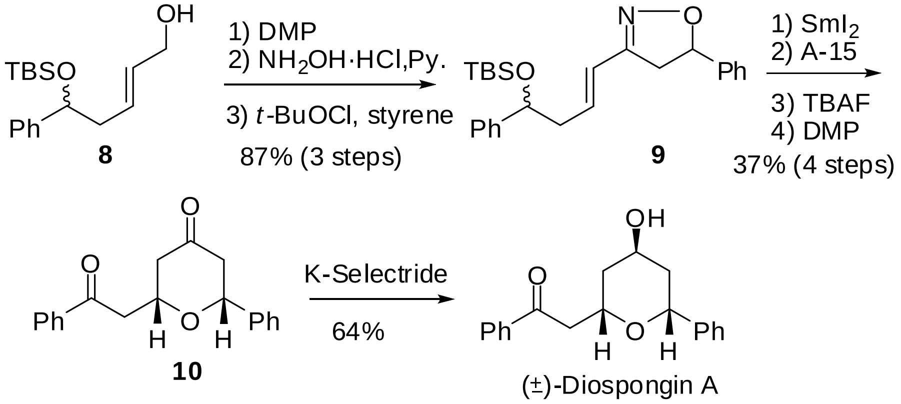
(Table 1, entry 10) Following the General Procedure for synthesis of **7a**, THPO **7j** was obtained from isoxazoline **5j** (120 mg, 0.32 mmol) as a colorless oil (116 mg, 78% yield) after flash column chromatography on silica gel (Hexane/EtOAc=2:1). **IR** (neat, cm^{-1}): 3031, 2919, 2861, 1718, 1612, 1512, 1247, 1095, 1033, 820, 742, 699. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.38-7.30 (m, 5H), 7.24 (d, *J*=8.8 Hz, 2H), 6.87 (d, *J*=8.8 Hz, 2H), 4.64-4.57 (m, 2H), 4.46-4.40 (m, 2H), 3.82-3.78 (m, 5H), 3.64-3.52 (m, 4H), 2.49-2.25 (m, 4H), 2.02-1.94 (m, 1H), 1.88-1.80 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 207.4, 159.4, 138.2, 130.6, 129.5, 128.7, 128.0, 127.9, 114.0, 76.3, 74.5, 73.7, 72.9, 72.4, 66.0, 55.5, 47.9, 44.4, 36.6. **HRMS** (CI$^+$) *m*/*z* calculated for $C_{23}H_{28}O_5$ $[M]^+$ 384.1937, found 384.1933.



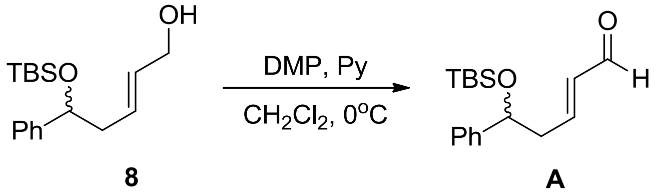
7k

(Table 1, entry 11) Following the General Procedure for synthesis of **7a**, THPO **7k** was obtained from isoxazoline **5k** (30 mg, 0.09 mmol) as a colorless oil (19 mg, 63% yield) after flash column chromatography on silica gel (Hexane/EtOAc=1:1). **IR** (neat, cm^{-1}): 3030, 2901, 2862, 1719, 1453, 1361, 1111, 739, 699. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.37-7.28 (m, 10H), 4.65-4.58 (m, 4H), 3.91-3.85 (m, 2H), 3.65-3.58 (m, 4H), 2.50-2.36 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 206.9, 138.2, 128.7, 128.0, 127.9, 76.6, 73.8, 72.5, 44.4. **HRMS** (CI$^+$) *m*/*z* calculated for $C_{21}H_{28}NO_4$ $[M+NH_4]^+$ 358.2018, found 358.2018.

Total Synthesis of (±)-Diospongin A



Synthesis of α,β-Unsaturated Aldehyde A



Dess-Martin Oxidation of Alcohol 8[12] To a solution of alcohol **8**[13] (2.1 g, 7.19 mmol) in dry CH_2Cl_2 (35 mL) at 0 °C was added pyridine (2.03 mL, 25.2 mmol) and Dess-Martin periodinane (3.6 g, 8.4 mmol). After vigorous stirring for 15 minutes at 0 °C, the cold bath was removed and the reaction mixture was stirred at room temperature for 1 hr until TLC indicated the complete consumption of the starting material. The reaction mixture was diluted with Et_2O (10 mL) and poured into a *sat.* aqueous $NaHCO_3$ solution containing excess $Na_2S_2O_3$. The mixture was stirred until the solid was completely dissolved. The organic phase was collected, washed sequentially with *sat.* aqueous $NaHCO_3$ solution, H_2O and brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (Hexane/EtOAc=15:1) to afford the aldehyde **A** (1.87 g, 92% yield) as a colorless oil. **IR** (neat, cm^{-1}): 2955, 2890, 2858, 1696, 1468, 1420, 1363, 1225, 1090, 837. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.43 (d, *J*=8.0 Hz, 1H), 7.31-7.20 (m, 5H), 6.77 (dt, *J*=15.6, 7.2 Hz, 1H), 6.05 (dd, *J*=15.6, 8.0 Hz, 1H), 4.80 (dd, *J*=6.8, 4.8 Hz, 1H), 2.73-2.60 (m, 2H), 0.85 (s, 9H), -0.01 (s, 3H), -0.17 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 194.1, 154.9, 144.1, 135.1, 128.5, 127.7, 125.8,

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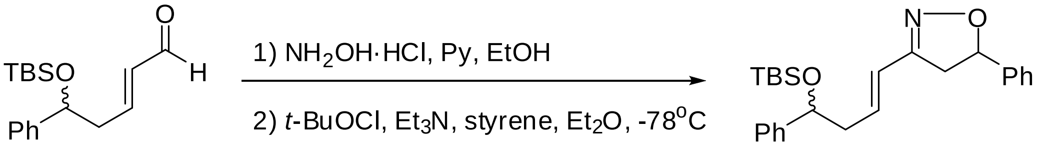
[12] D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155.

[13] G. Sirasani, T. Paul and R. B. Andrade, *Tetrahedron*, 2011, **67**, 2197.

73.9, 44.2, 25.9, 18.4, -4.5, -4.8. **HRMS** (CI$^+$) *m/z* calculated for $C_{17}H_{30}NO_2Si$ $[M+NH_4]^+$ 308.2046, found 308.2052.

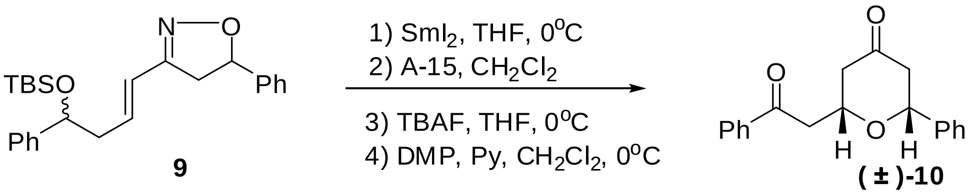
Synthesis of Isoxazoline 9 through 1,3-Dipolar Cycloaddition [1,2]



A **9**

To a solution of aldehyde **A** (305 mg, 1.05 mmol) in EtOH (95%, 8.75 mL) at room temperature was added $NH_2OH{\cdot}HCl$ (110 mg, 1.58 mmol) in pyridine (0.34 mL). The mixture was stirred at room temperature for 6 hrs and subsequently concentrated under reduced pressure. To the resulting residue were added EtOAc (6 mL) and H_2O (2 mL), and the organic phase was collected and washed with water (2 x 2 mL), brine, dried over anhydrous Na_2SO_4, evaporated under reduced pressure to give the crude oximes residue. To the crude oximes in Et_2O (15 mL) at -78 ^oC were added Et_3N (0.29 mL, 2.1 mmol), styrene (218 mg, 2.1 mmol) and then *t*-BuOCl (0.23 mL, 2.1 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (2 mL). The organic layer was collected and the aqueous phase was extracted by Et_2O (3 x 5 mL). The combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (Hexane/EtOAc=10:1) to afford the isoxazoline **9** as a yellow oil (401 mg, 94% yield). **IR** (neat, cm^{-1}): 3032, 2930, 2890, 2856, 1650, 1493, 1456, 1365, 1254, 1088, 898, 836, 777, 671. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.41-7.24 (m, 10H), 6.46 (dd, *J*=16.0, 4.4 Hz, 1H), 5.97 (dt, *J*=16.0, 7.2 Hz, 1H), 5.67-5.58 (m, 1H), 4.77-4.73 (m, 1H), 3.51-3.43 (m, 1H), 3.07-3.00 (m, 1H), 2.66-2.51 (m, 2H), 0.91-0.87 (m, 9H), 0.01 (s, 3H), -0.12 (d, *J*=2.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.0(2C), 144.7(2C), 141.2, 136.9, 128.9, 128.4(2C), 127.5, 126.1, 125.9, 122.3(2C), 82.4, 74.8(2C), 44.7, 44.6, 42.2, 42.1, 26.0, 18.4, -4.4, -4.8. **HRMS** (CI$^+$) *m/z* calculated for $C_{25}H_{34}NO_2Si$ $[M+H]^+$ 408.2359, found 408.2361.

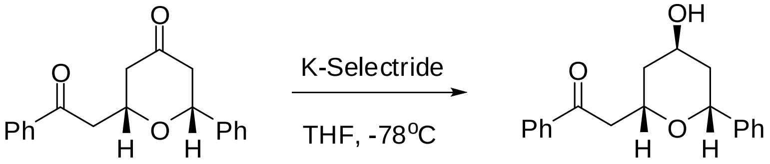
Synthesis of Diketone 10 [9,11,12]



To the isoxazoline **9** (100 mg, 0.25 mmol) in anhydrous and deoxygenated THF (8.8 mL) at 0 °C was added SmI_2 (8.8 mL, 0.1 M in THF, 0.88 mmol) slowly, maintaining a dark blue color throughout the reaction. The reaction mixture was stirred for additional 20 min at 0 °C and then was quenched by bubbling a stream of oxygen to give a yellow solution, which was poured into $B(OH)_3$ (360 mg) solution in H_2O (20 mL). The mixture was stirred for 30 min at room temperature and diluted with Et_2O (20 mL). The organic layer was collected and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give yellow β-hydroxylenone, which was subjected to intramolecular Michael cyclization directly. To the solution of β-hydroxylenone in dry CH_2Cl_2 (1 mL) was added Amberlyst-15 (200 mg, 2.0 equiv. w/w) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 18 hrs and Amberlyst-15 was removed by filtration. The volatile solvents were removed under reduced pressure to give the crude product without further purification. To the solution of crude tetrahydropyran-4-one obtained in dry THF (1.5 mL) at 0 °C was added tetrabutylammonium fluoride (TBAF, 0.288 ml, 1.0 M in THF, 0.288 mmol). After 1 hr, the reaction was quenched with *sat.* aqueous NH_4Cl solution. The organic layer was collected and the aqueous layer was extracted with Et_2O (3 x 1 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, evaporated under reduced pressure to give an alcohol product for next step without purification. To the solution of the second alcohol in dry CH_2Cl_2 (1 mL) at 0 °C was added pyridine (38 µL, 0.47 mmol) and Dess-Martin periodinane (100.3 mg, 0.24 mmol). After vigorous stirring for 15 minutes at 0 °C, the cold bath was removed and the reaction mixture was stirred at room temperature for 1 hr until the complete conversion of the starting material. The reaction mixture was diluted with Et_2O (1 mL) and poured into a *sat.* aqueous $NaHCO_3$ solution containing excess $Na_2S_2O_3$. The mixture was stirred until the solid was completely dissolved. The organic phase was collected, washed sequentially with *sat.* aqueous $NaHCO_3$, water and brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel

(Hexane/EtOAc=5:1) to afford the diketone **(±)-10** (26 mg, 37% yield over four steps) as a white solid. m.p. 76-77 °C. **IR** (neat, cm^{-1}): 2956, 2924, 2854, 1721, 1686, 1598, 1450, 1258, 1066, 695. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.99 (d, *J*=7.2 Hz, 2H), 7.60 (t, *J*=7.2 Hz, 1H), 7.49 (t, *J*=7.2 Hz, 2H), 7.38-7.30 (m, 5H), 4.75 (dd, *J*=11.6, 2.8 Hz, 1H), 4.50 (dtd, *J*=11.6, 6.4, 2.8 Hz, 1H), 3.60 (dd, *J*=16.4, 6.4 Hz, 1H), 3.19 (dd, *J*=16.4, 6.4 Hz, 1H), 2.73-2.67 (m, 2H), 2.62-2.46 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 206.0, 197.0, 140.7, 137.2, 133.6, 128.9, 128.8, 128.5, 128.3, 125.8, 78.8, 73.8, 49.3, 47.5, 45.1. **HRMS** (CI^+) *m*/*z* calculated for $C_{19}H_{18}O_3$ $[M]^+$ 294.1256, found 294.1256.

Synthesis of (±)-Diospongin A[14]



(±)-10

(±)-Diospongin A

To a solution of diketone **(±)-10** (10 mg, 0.034 mmol) in THF (0.34 mL) was added a solution of K-Selectride (0.034 mL, 1.0 M in THF, 0.034 mmol) at –78 °C. After stirring at –78 °C for 30 min, the reaction was quenched by addition of *sat.* aqueous $NaHCO_3$ (0.02 mL), EtOAc (2 mL) and H_2O (0.5 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc (2 x 2 mL). The combined organic fractions were washed with water (0.5 mL), brine (2 x 0.2 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (Hexane/EtOAc=2:1) to afford **(±)-Diospongin A** as a colorless amorphous solid (6.4 mg, 64% yield). **IR** (neat, cm^{-1}): 3445, 1683, 1597, 1507, 1449, 1058. **^{1}H NMR** (400 MHz, $CDCl_3$, 7.26 ppm) δ: 7.98-7.80 (m, 2H), 7.56 (t, *J*= 7.6 Hz, 1H), 7.46 (t, *J*= 7.6 Hz, 2H), 7.32-7.26 (m, 5H), 4.93 (dd, *J*= 11.6, 2.0 Hz, 1H), 4.68-4.62 (m, 1H), 4.38 (quint, *J*=2.8 Hz, 1H), 3.42 (dd, *J*= 16.0, 6.0 Hz, 1H), 3.07 (dd, *J*= 16.0, 6.8 Hz, 1H), 1.97-1.94 (m, 2H), 1.76 (ddd, *J*= 14.4, 11.6, 2.8 Hz, 1H), 1.69 (ddd, *J*= 14.0, 12.0, 2.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$, 77.0 ppm) δ: 198.3, 142.7, 137.3, 133.1, 128.5, 128.3, 128.2, 127.3, 125.8, 73.8, 69.1, 64.7, 45.1, 40.0, 38.5. **HRMS** (CI^+) *m*/*z* calculated for $C_{19}H_{21}O_3$ $[M+H]^+$ 297.1491, found 297.1492.

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[14] M. Anada, T. Washio, Y. Watanabe, K. Takeda and S. Hashimoto, *Eur. J. Org. Chem.*, 2010, **2010**, 6850.

Spectroscopic Data Comparison of Synthetic and Natural Diospongin A[15]

No.	^{1}H NMR ($CDCl_3$)		^{13}C NMR ($CDCl_3$)	
	Natural Diospongin A	Synthetic Diospongin A [a]	Natural Diospongin A	Synthetic Diospongin A [b]
1			198.4	198.3
2	3.41 (dd, *J*= 16.0, 6.0 Hz)	3.42 (dd, *J*= 16.0, 6.0 Hz)	45.1	45.1
	3.07 (dd, *J*= 16.0, 6.8 Hz)	3.07 (dd, *J*= 16.0, 6.8 Hz)		
3	4.65 (dddd, *J*= 11.2, 6.8, 6.0, 1.7 Hz)	4.65 (m)	69.0	69.1
4	1.97 (ddd, *J*= 14.0, 3.0, 1.7 Hz)	1.97 (m)	40.0	40.0
	1.67 (ddd, *J*= 14.0, 11.2, 3.0 Hz)	1.69 (ddd, *J*= 14.0, 12.0, 2.8 Hz)		
5	4.35 (quintet, *J*= 3.0 Hz)	4.38 (quintet, *J*= 2.8 Hz)	64.6	64.7
6	1.94 (ddd, *J*= 14.0, 3.0, 1.7 Hz)	1.94 (m)		
	1.75 (ddd, *J*= 14.0, 12.0, 3.0 Hz)	1.76 (ddd, *J*= 14.4, 11.6, 2.8 Hz)	38.4	38.5
7	4.95 (dd, *J*= 12.0, 1.7 Hz)	4.93 (dd, *J*= 11.6, 2.0 Hz)	73.8	73.8
1’			137.3	137.3
2’,6’	7.97 (dd, *J*= 7.8, 1.0 Hz)	7.99 (m)	128.3	128.3
3’,5’	7.44 (t, *J*= 7.8 Hz)	7.46 (t, *J*= 7.6 Hz)	128.5	128.5
4’	7.55 (t, *J*= 7.8 Hz)	7.56 (t, *J*= 7.6 Hz)	132.5	133.1
1’’			142.7	142.7
2’’,6’’	7.30 (m)	7.31 (m)	125.8	125.8
3’’,5’’	7.30 (m)	7.31 (m)	128.2	128.2
4’’	7.28 (m)	7.29 (m)	127.2	127.3

[a] Measured with 400 MHz, (7.26 ppm). [b] Measured with 100 MHz, (77.0 ppm).

Other Physical Properties Comparison

	Natural Diospongin A	Synthetic Diospongin A
Morphology	colorless amorphous solid	colorless amorphous solid
IR	3450, 1690, 1610, 1495, 1450, 1055 cm^{-1}	3445, 1683, 1597, 1507, 1449, 1058 cm^{-1}
HRMS: $[M+H]^+$ $C_{19}H_{21}O_3$ =297.1491	(FAB) 297.1523	(CI) 297.1492

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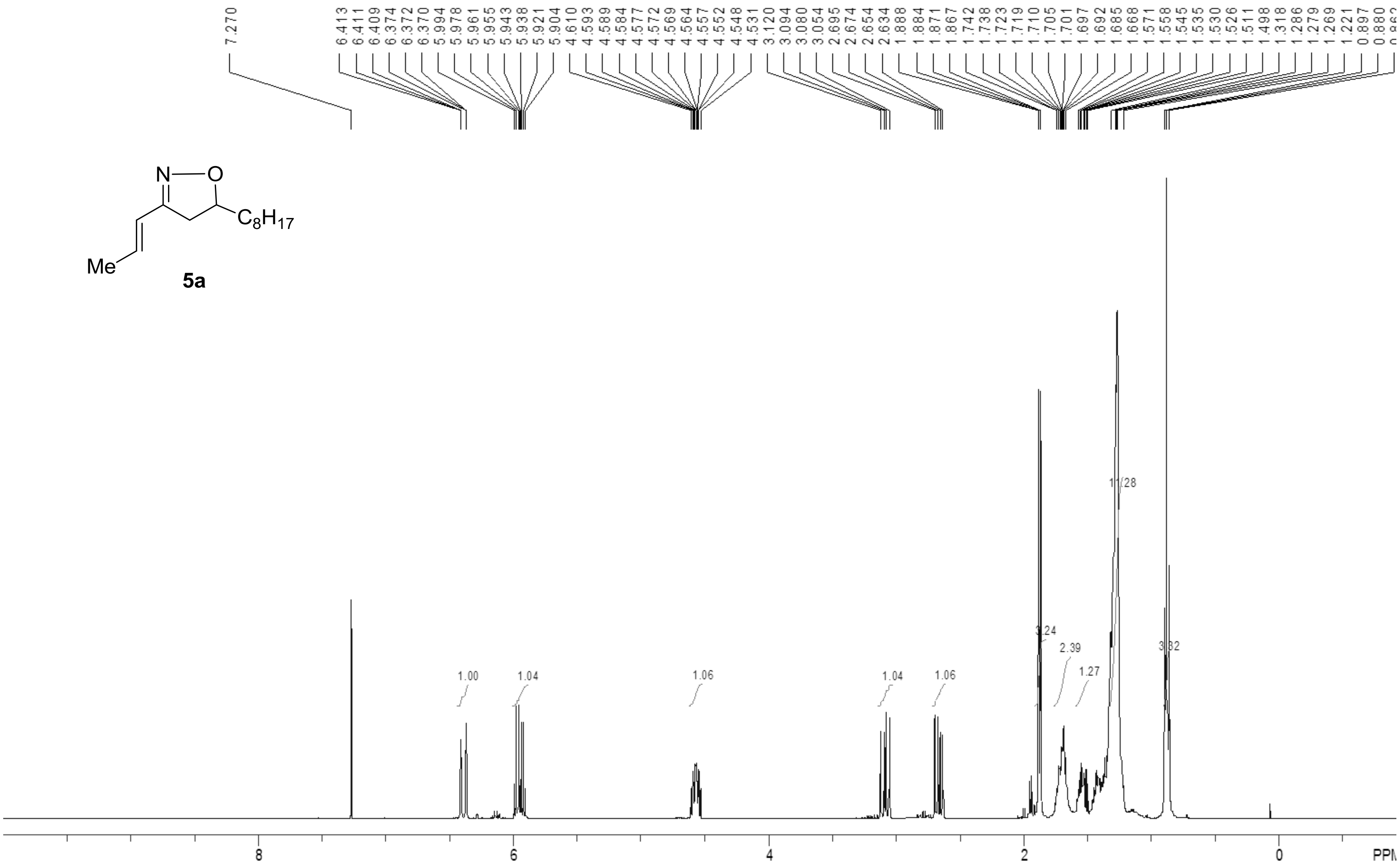
[15] J. Yin, K. Kouda, Y. Tezuka, Q. L. Tran, T. Miyahara, Y. Chen and S. Kadota, *Planta Med.*, 2004, **70**, 54.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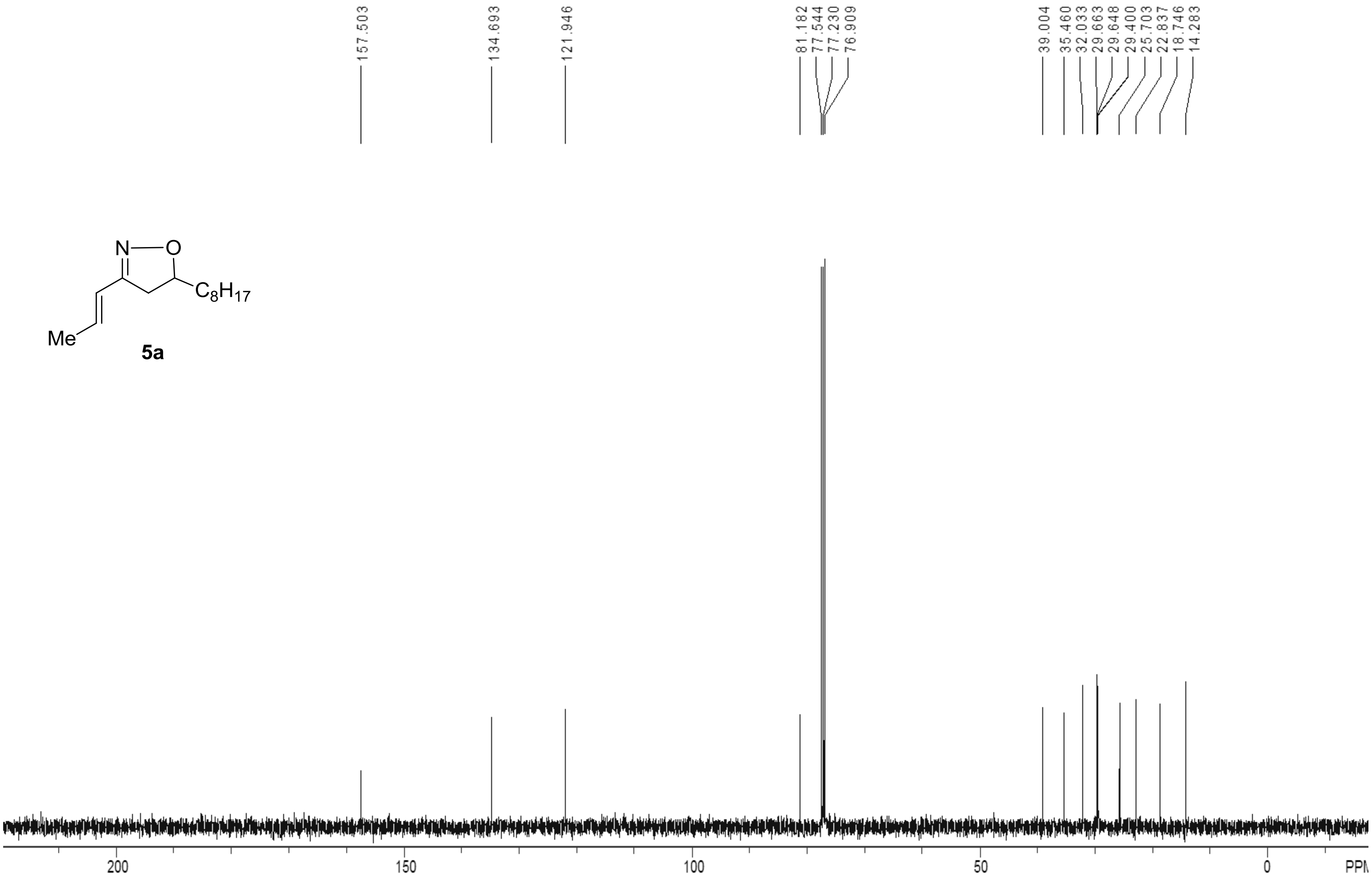
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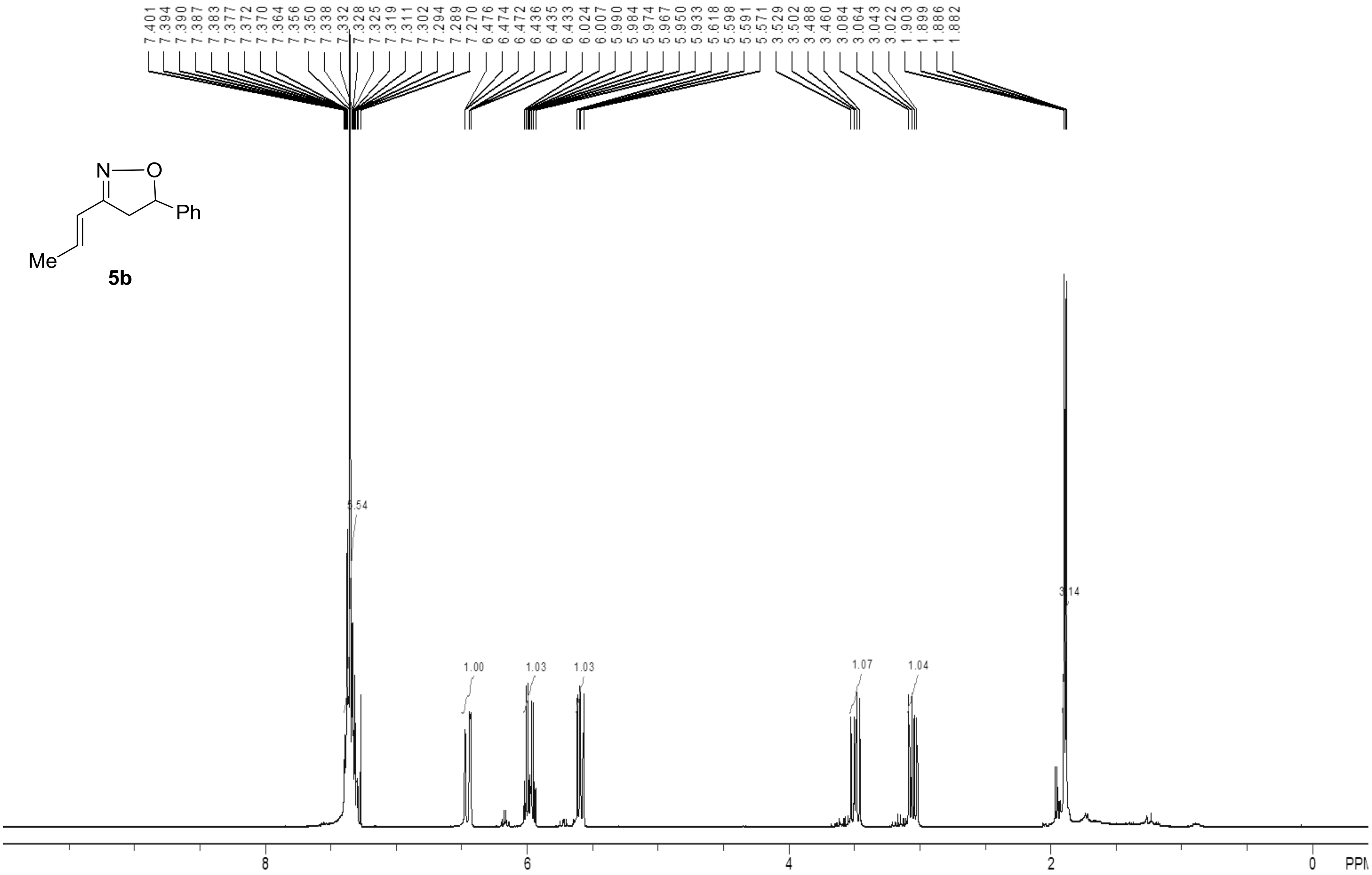
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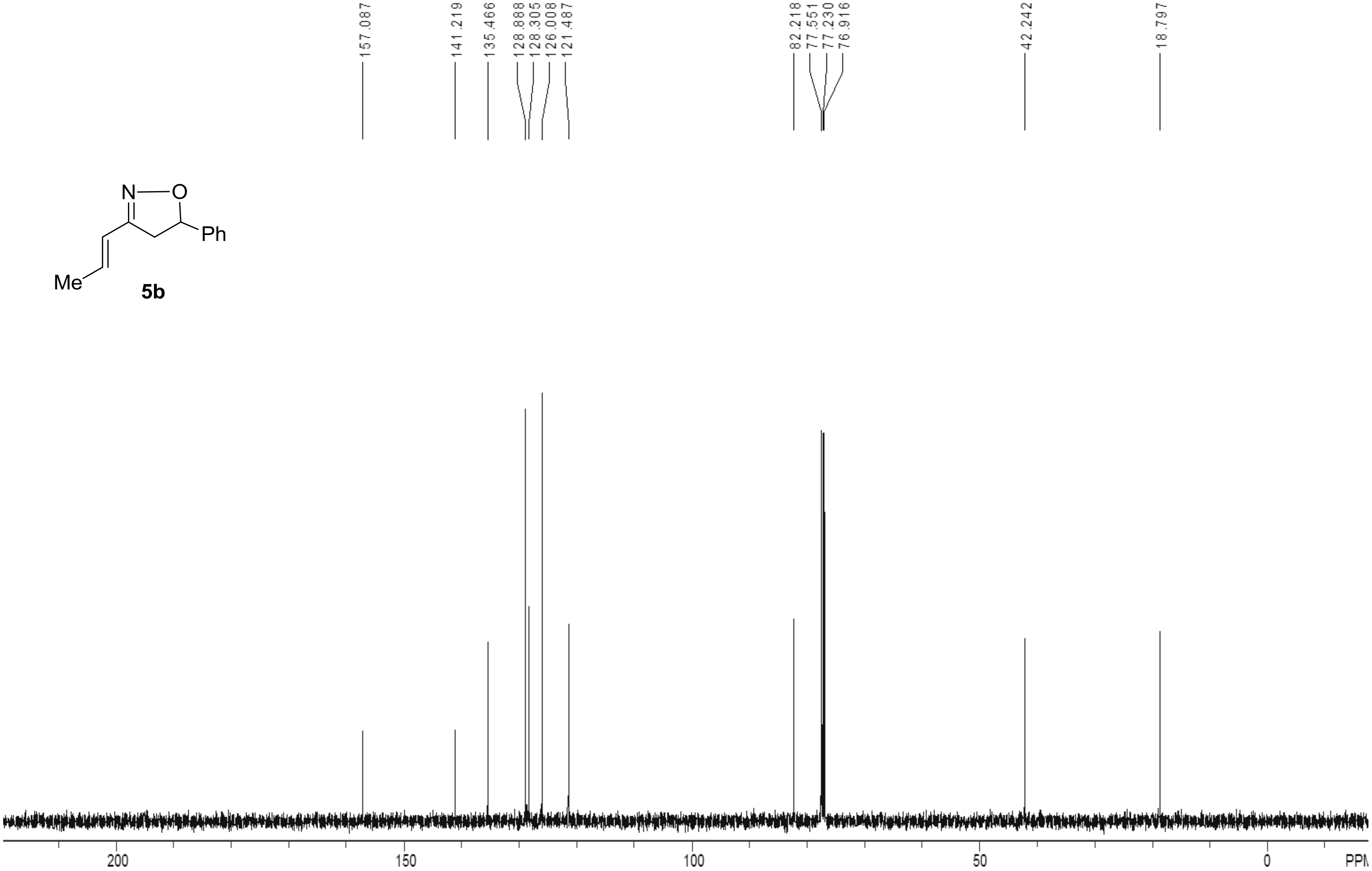
5b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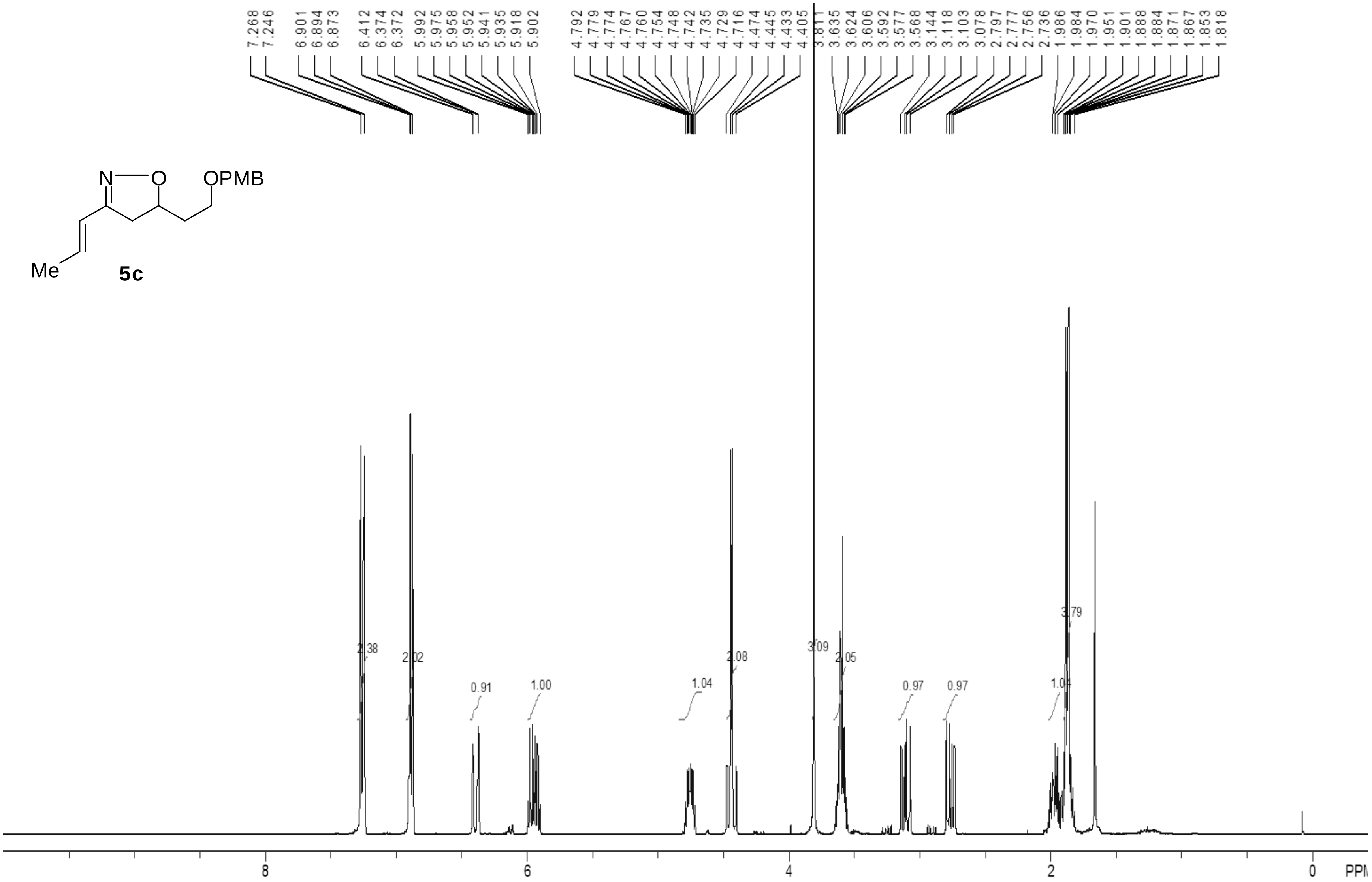
0
PPM

N
O
OPMB
Me

5c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1.888
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1.871
1.867
1.853
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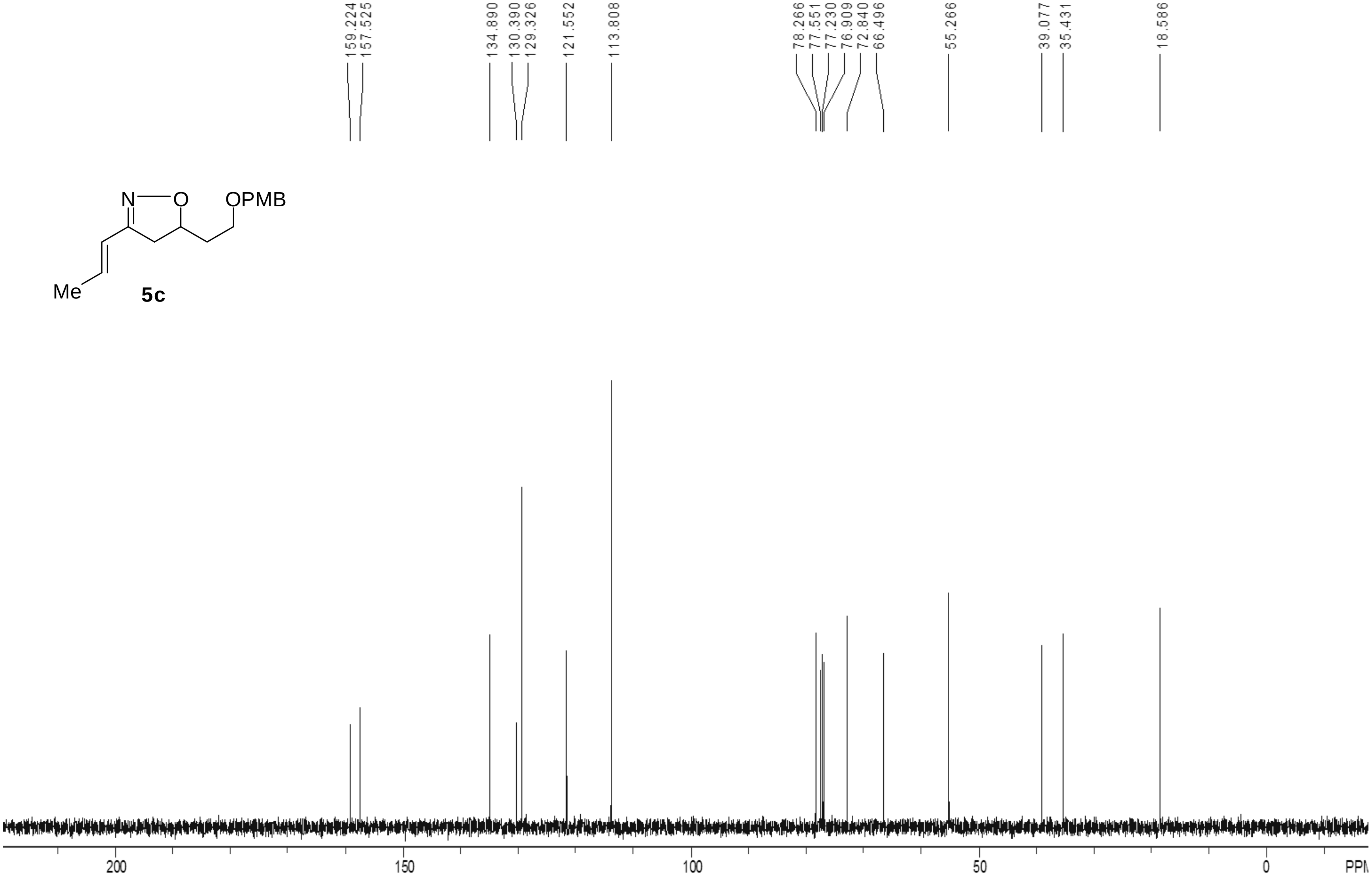
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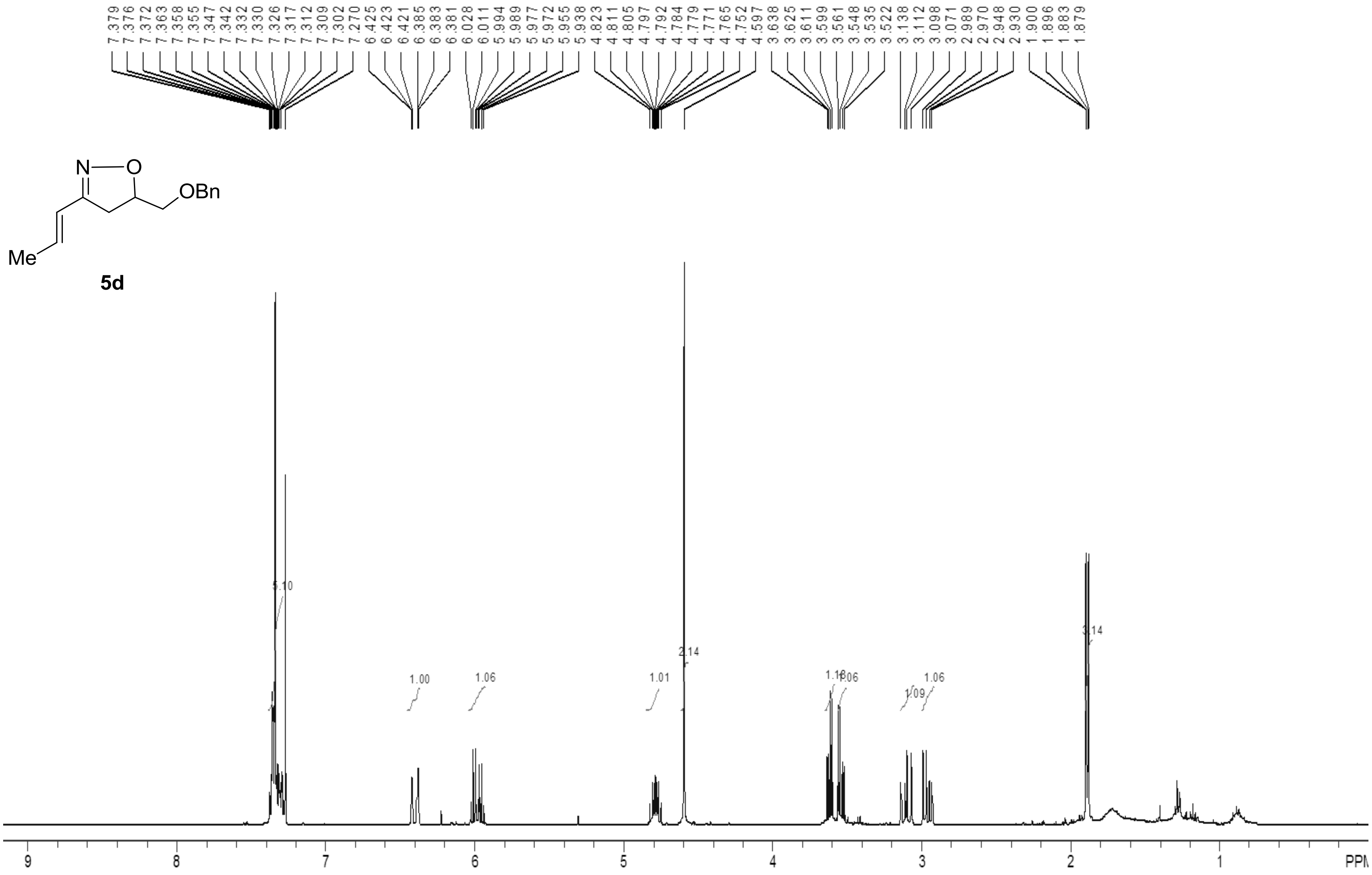
PP

5c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7.309
7.302
7.270
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6.423
6.421
6.385
6.383
6.381
6.028
6.011
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5.989
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3.098
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2.930
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1.896
1.883
1.879
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O
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Me
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1.01
2.14
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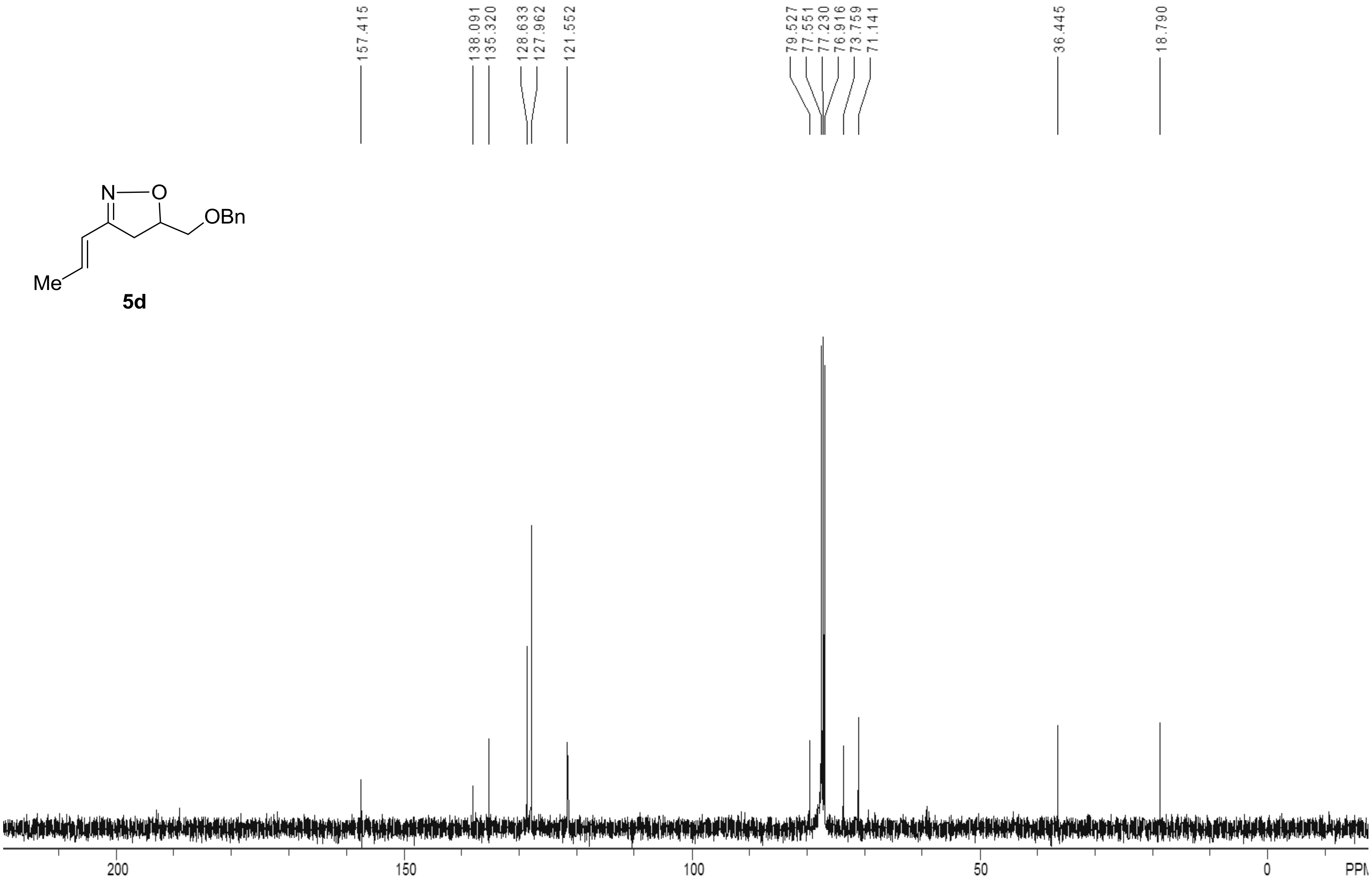
5d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OBn
Me

5d

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18.790
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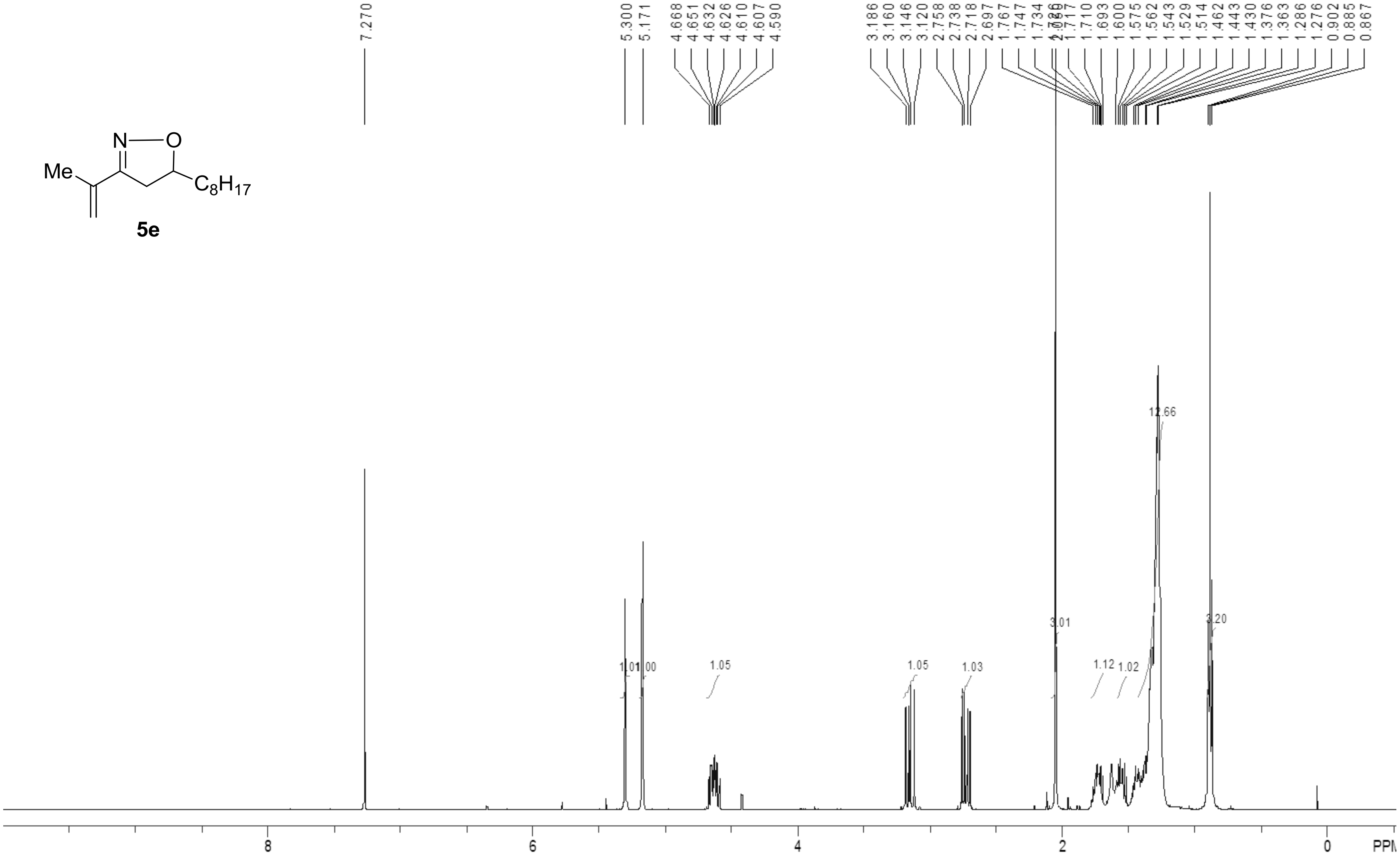
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4.626
4.610
4.607
4.590
3.186
3.160
3.146
3.120
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2.718
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1.767
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1.734
1.717
1.710
1.693
1.600
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1.562
1.543
1.529
1.514
1.462
1.443
1.430
1.376
1.363
1.286
1.276
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0.885
0.867
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1.00
1.05
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1.02
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8
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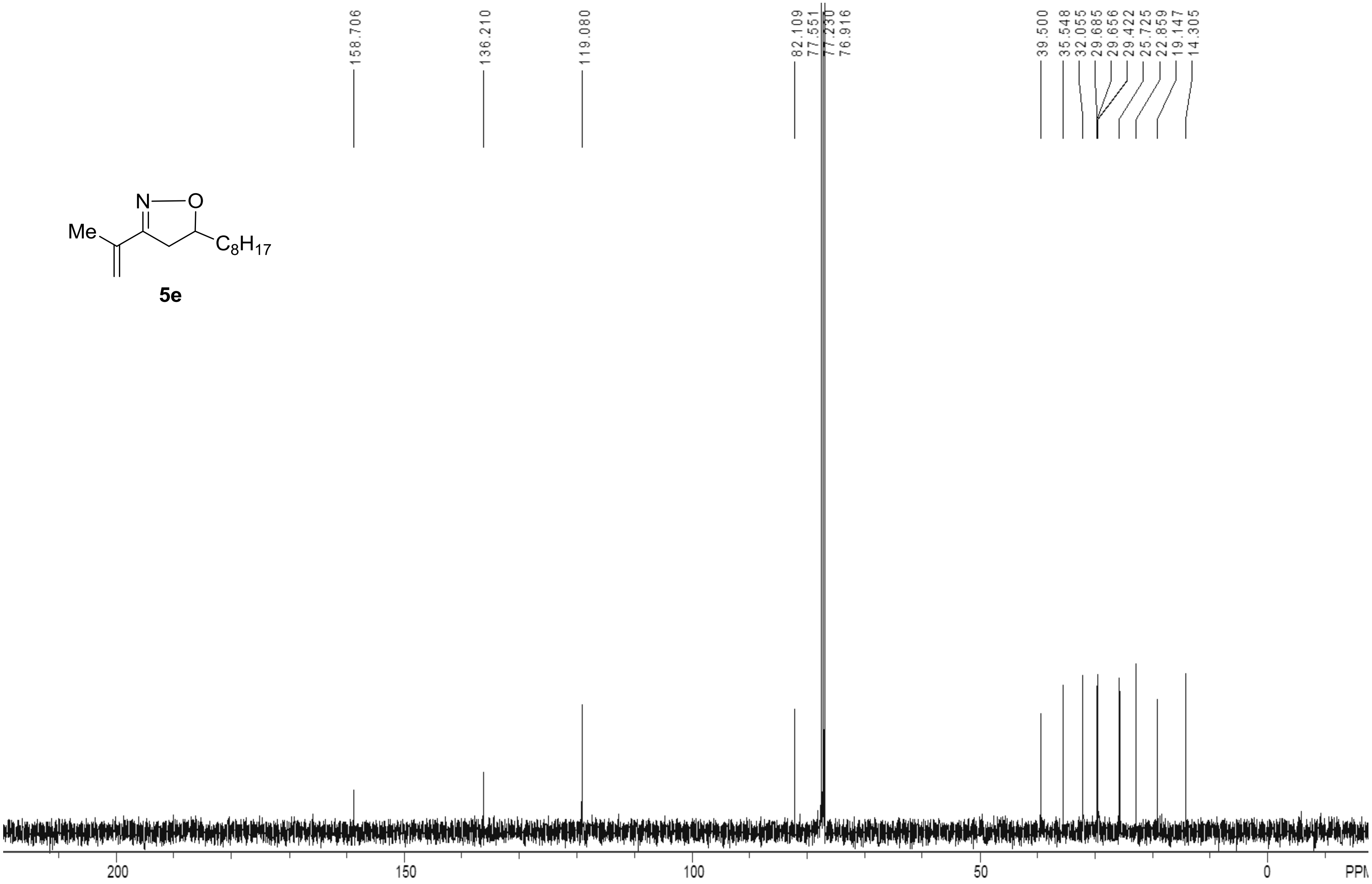
PPM

5e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32.055
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29.656
29.422
25.725
22.859
19.147
14.305
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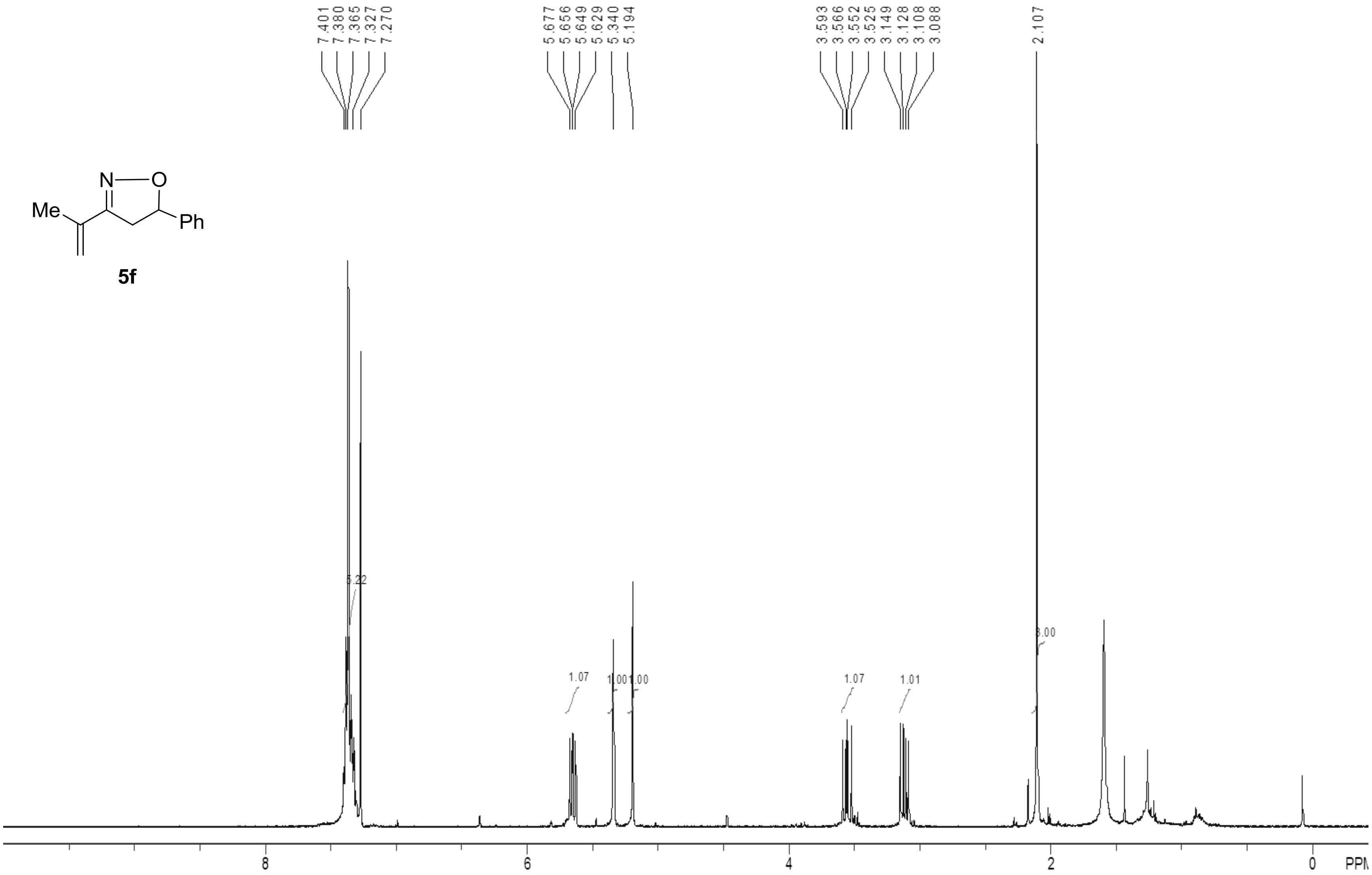
C_8H_{17}
200
150
100
50
0
PPM

5e

N
O
Me
Ph

5f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5.656
5.649
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5.340
5.194
3.593
3.566
3.552
3.525
3.149
3.128
3.108
3.088
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5.22
1.07
1.00
1.00
1.07
1.01
3.00
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4
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0
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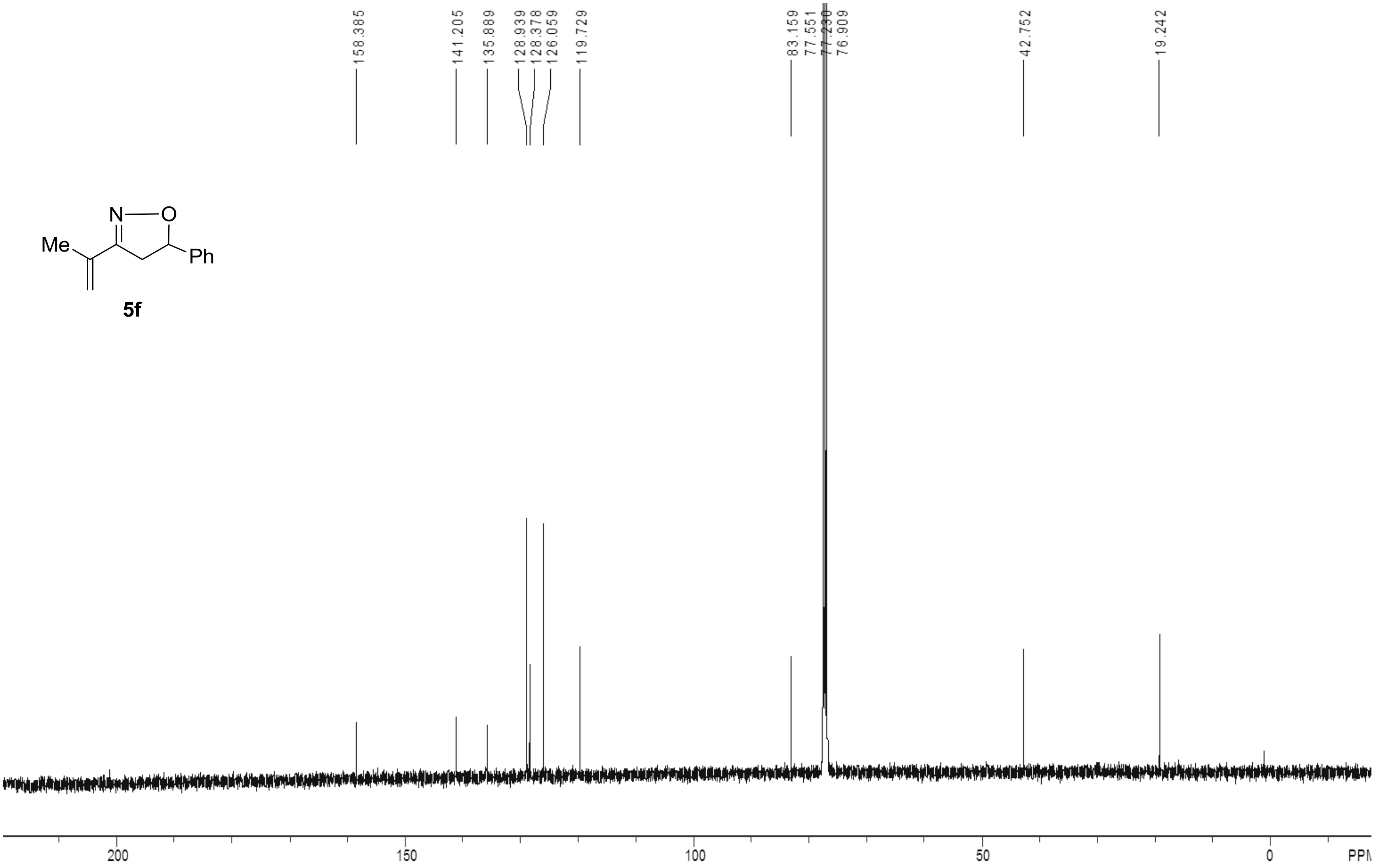
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77.230
76.909
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19.242
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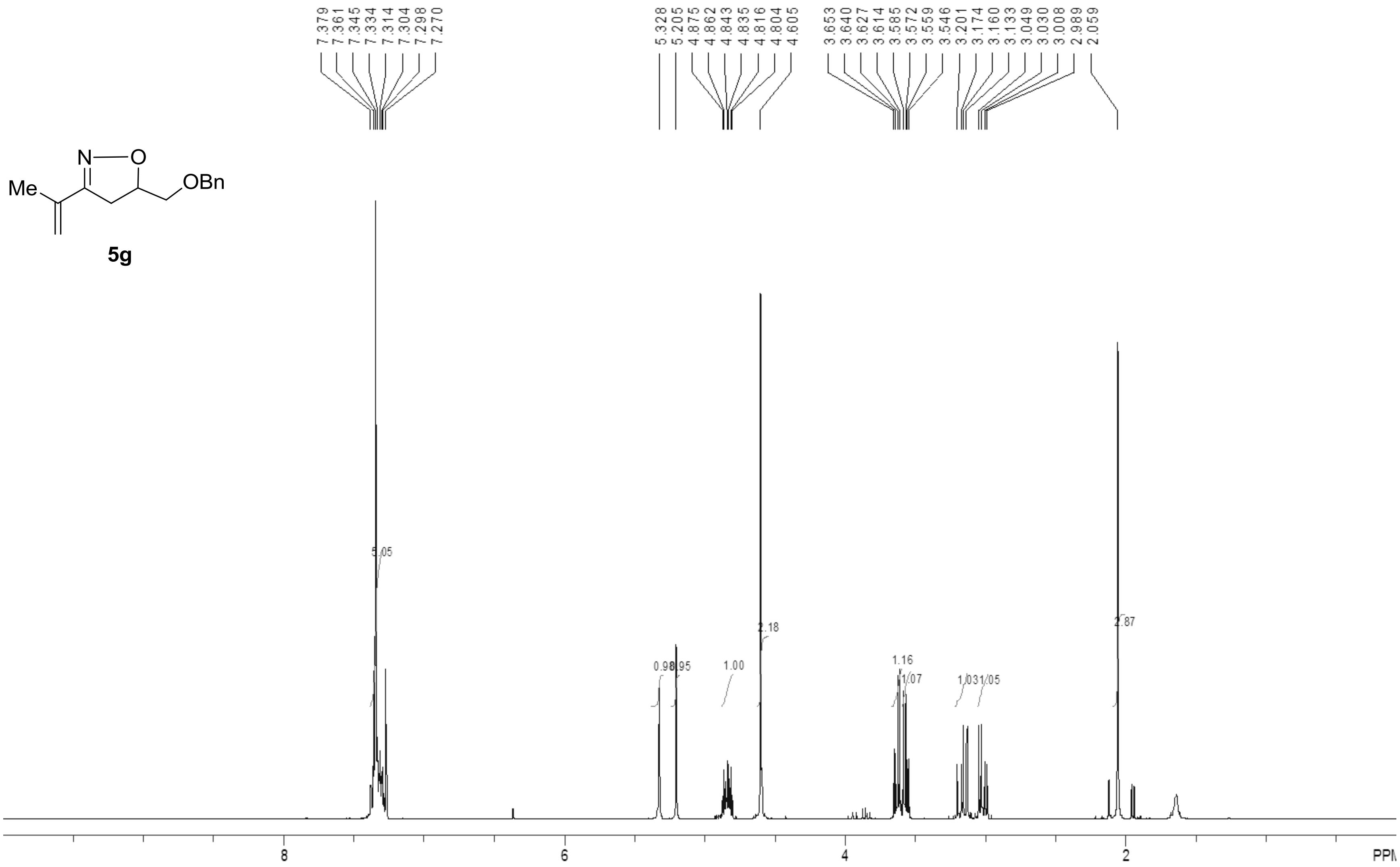
O
Me
Ph
5f
200
150
100
50
0
PPM

N
O
Me
OBn

5g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7.270
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4.843
4.835
4.816
4.804
4.605
3.653
3.640
3.627
3.614
3.585
3.572
3.559
3.546
3.201
3.174
3.160
3.133
3.049
3.030
3.008
2.989
2.059
5.05
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0.95
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2.18
1.16
1.07
1.03
1.05
2.87
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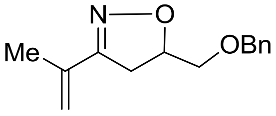
4
2
PPM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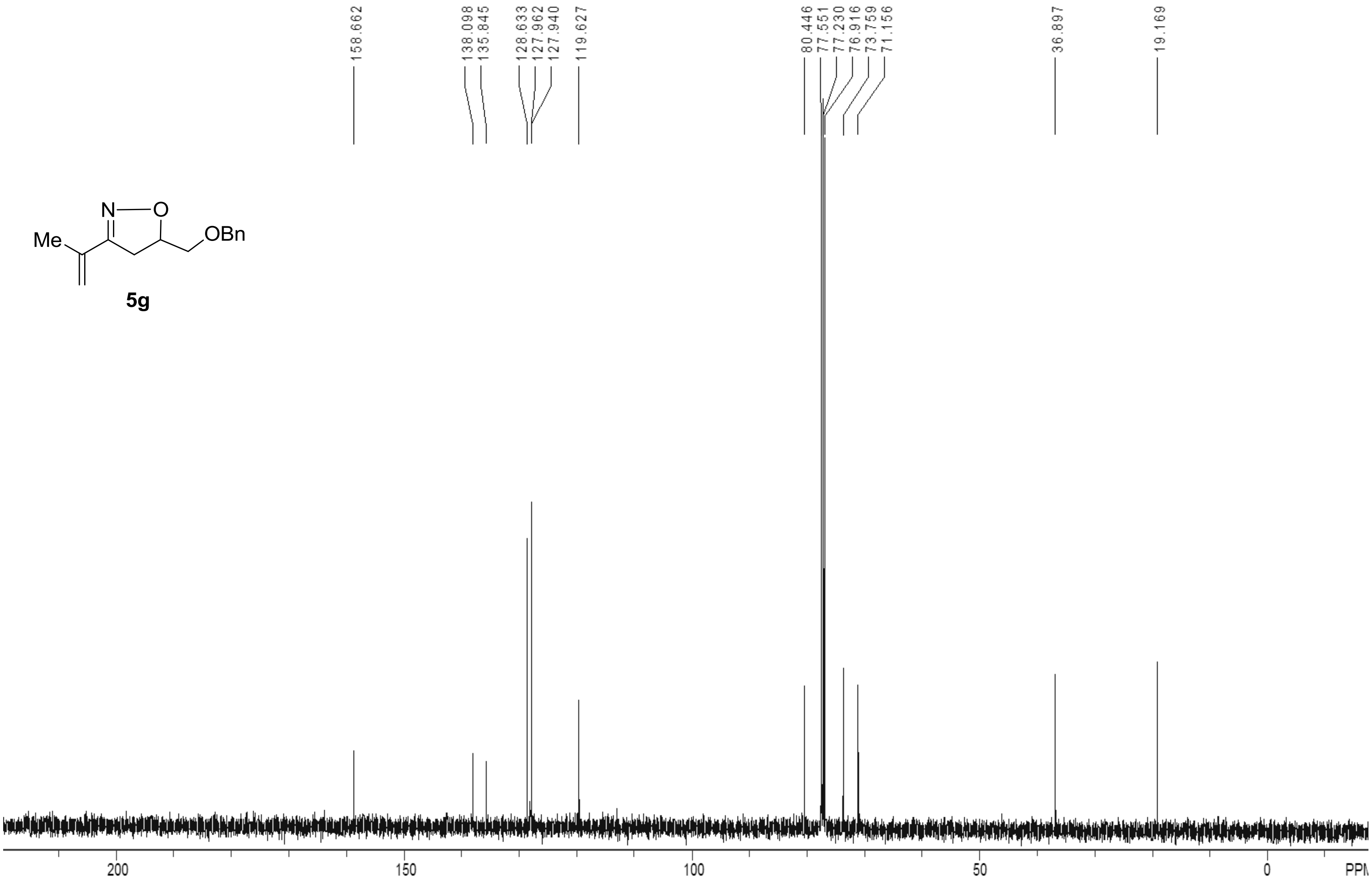
Me
OBn

5g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76.916
73.759
71.156
36.897
19.169
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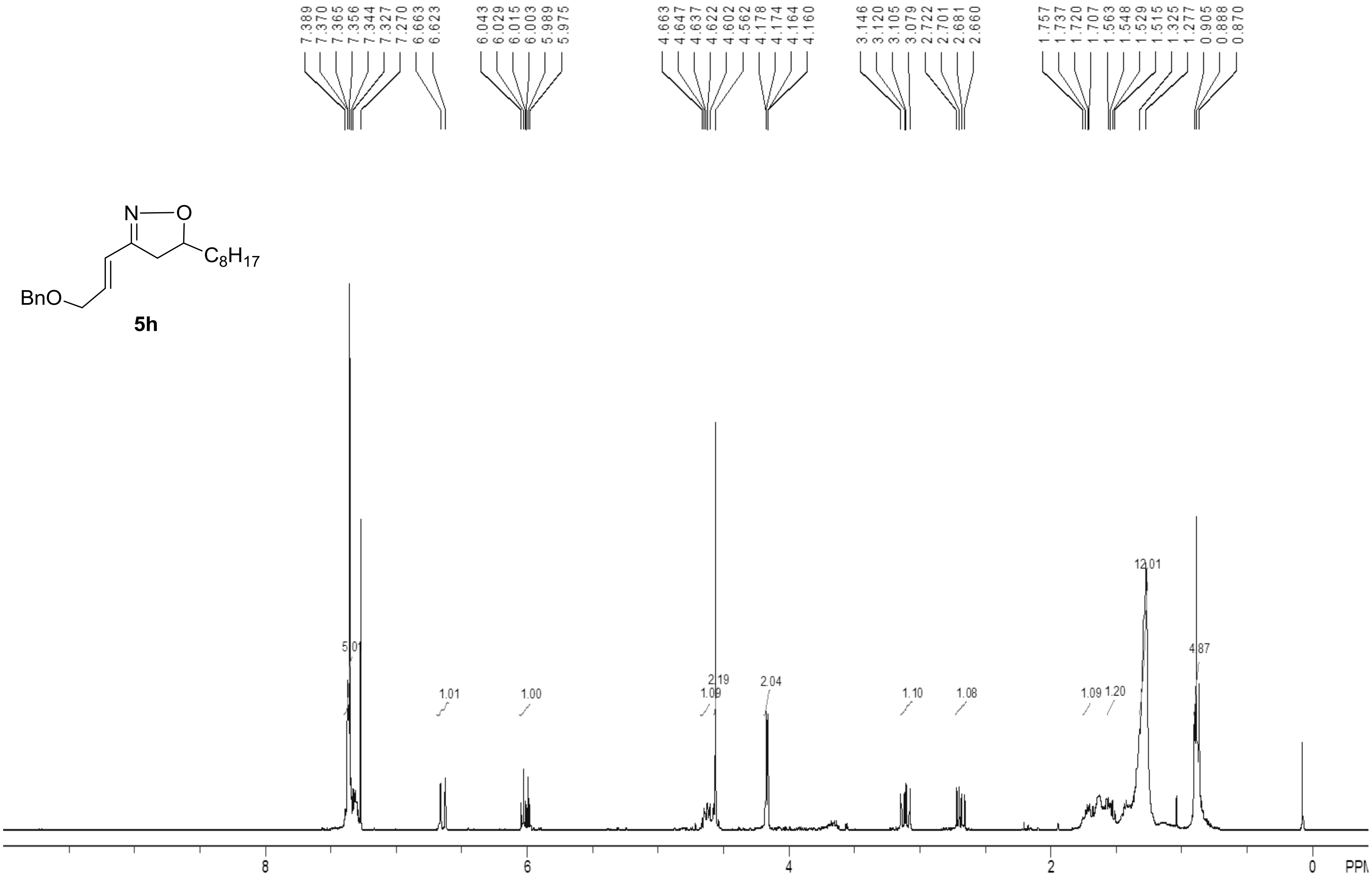
150
100
50
0
PPM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6.043
6.029
6.015
6.003
5.989
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4.622
4.602
4.562
4.178
4.174
4.164
4.160
3.146
3.120
3.105
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1.737
1.720
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1.515
1.325
1.277
0.905
0.888
0.870
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O
C8H17
BnO
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1.01
1.00
2.19
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1.08
1.09
1.20
12.01
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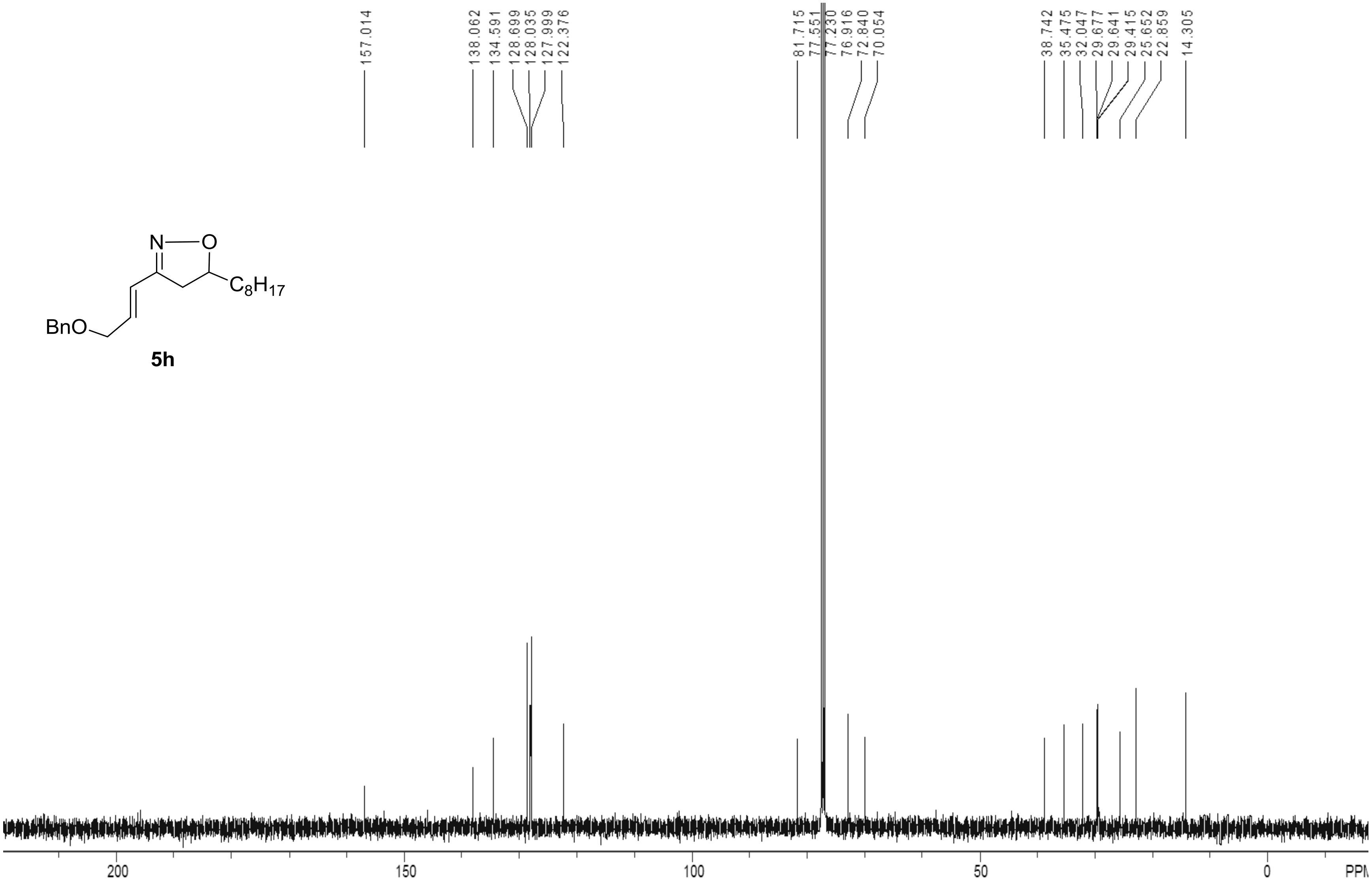
0
PPM

5h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77.230
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38.742
35.475
32.047
29.677
29.641
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14.305
N
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C_8H_{17}
BnO
5h
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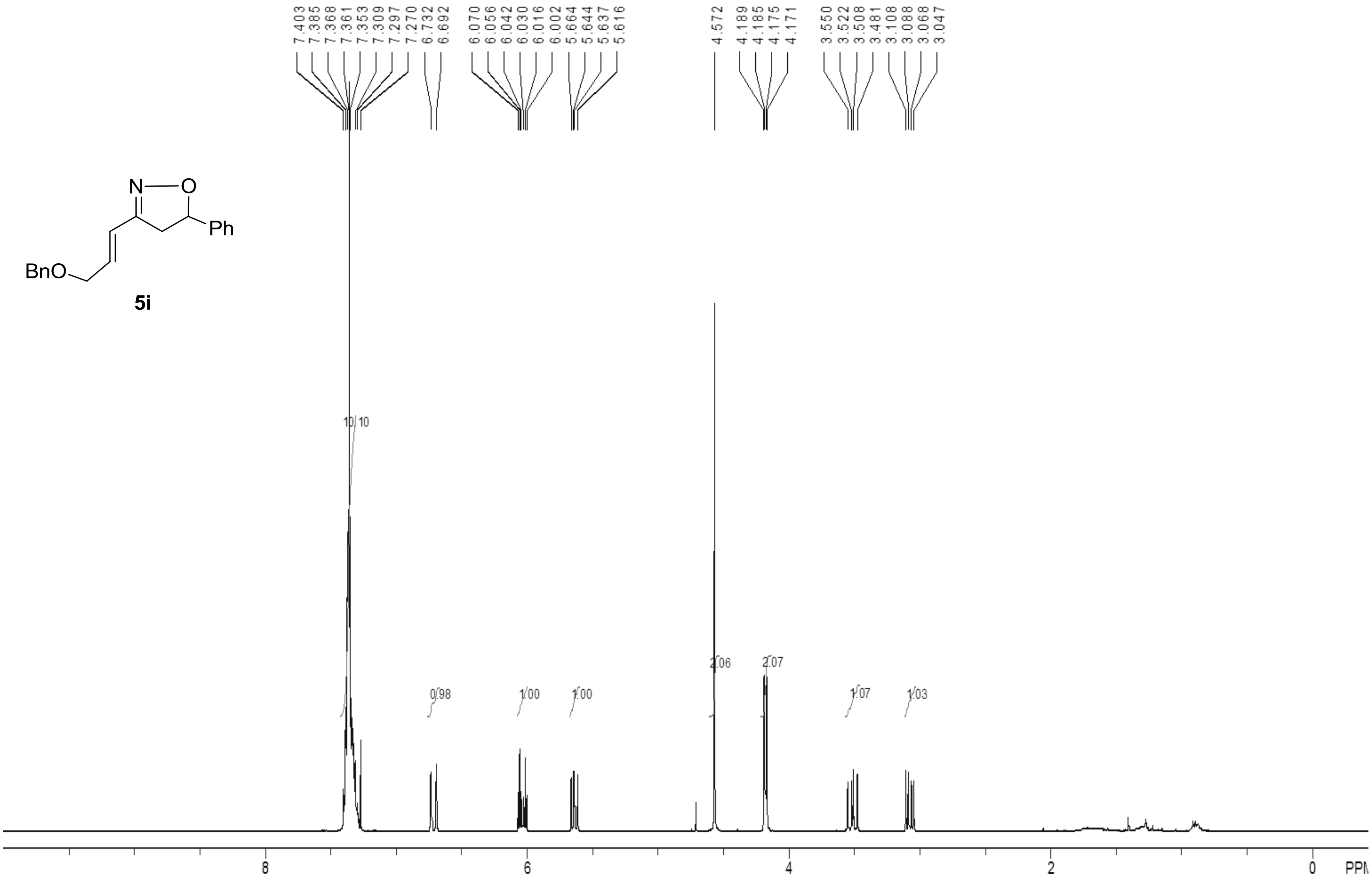
150
100
50
0
PP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6.042
6.030
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4.572
4.189
4.185
4.175
4.171
3.550
3.522
3.508
3.481
3.108
3.088
3.068
3.047
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O
Ph
BnO
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8
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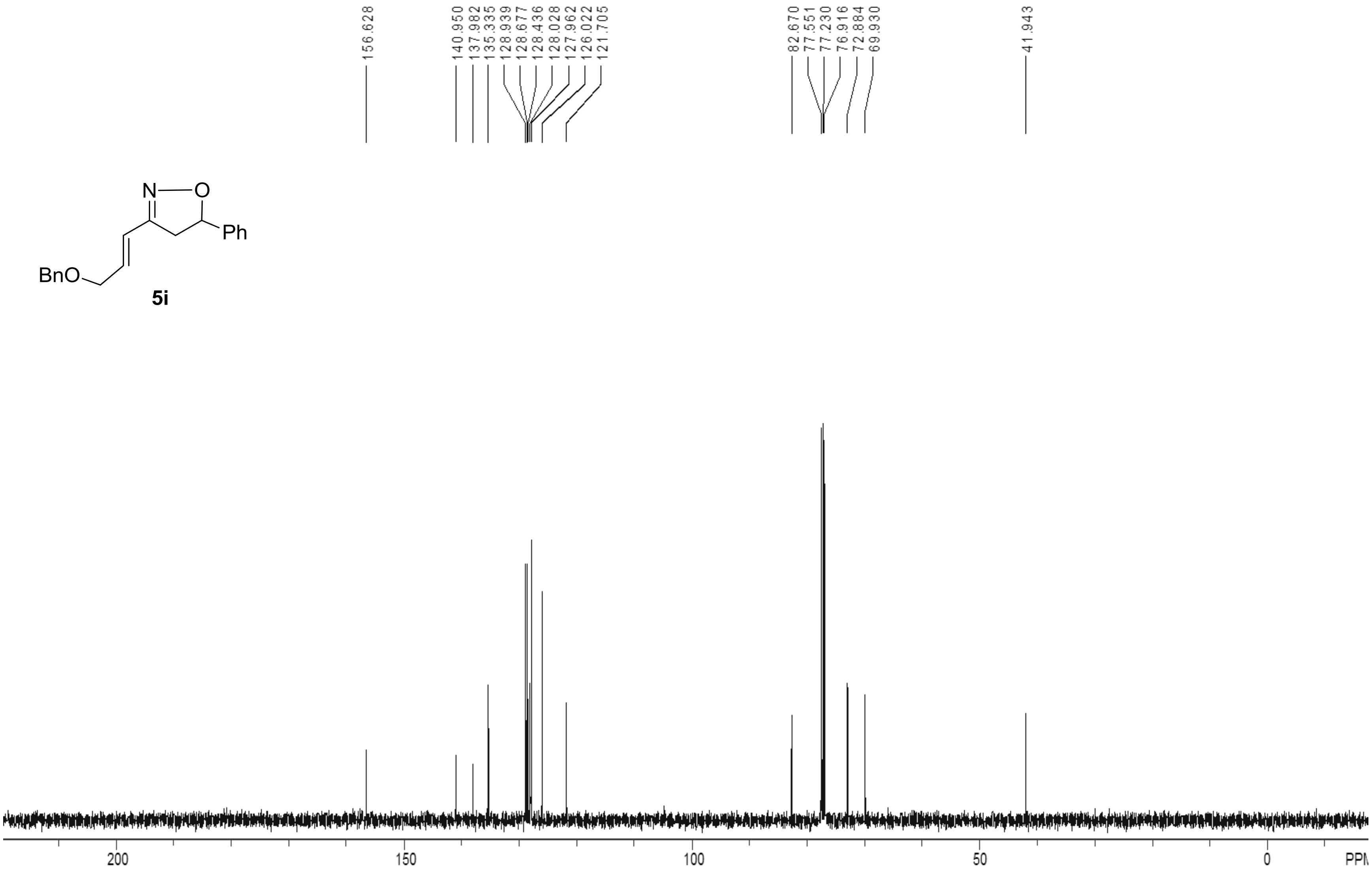
5i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O
Ph
BnO

5i

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126.022
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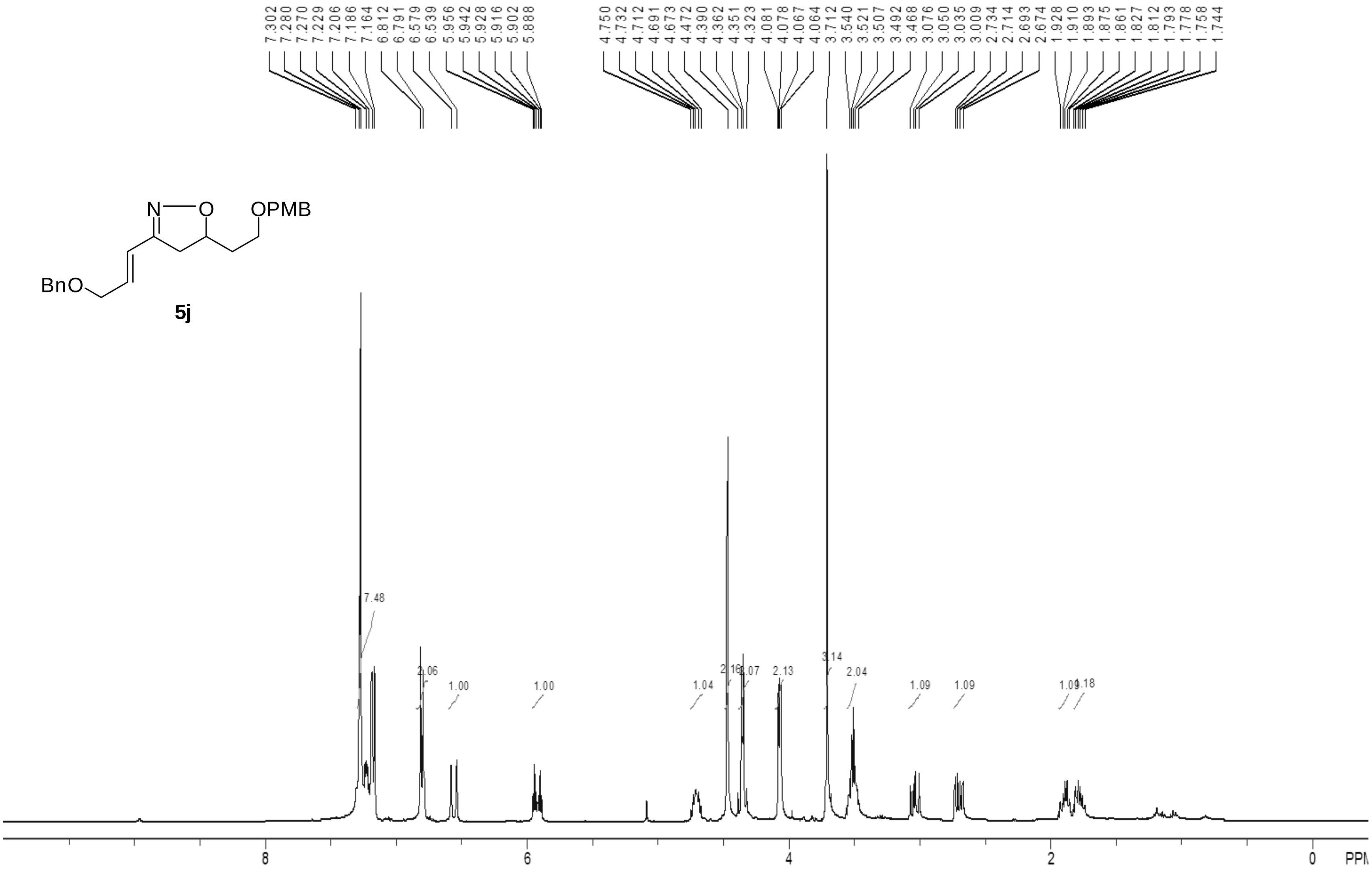
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5.916
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4.732
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1.744
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OPMB
BnO
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1.00
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2.16
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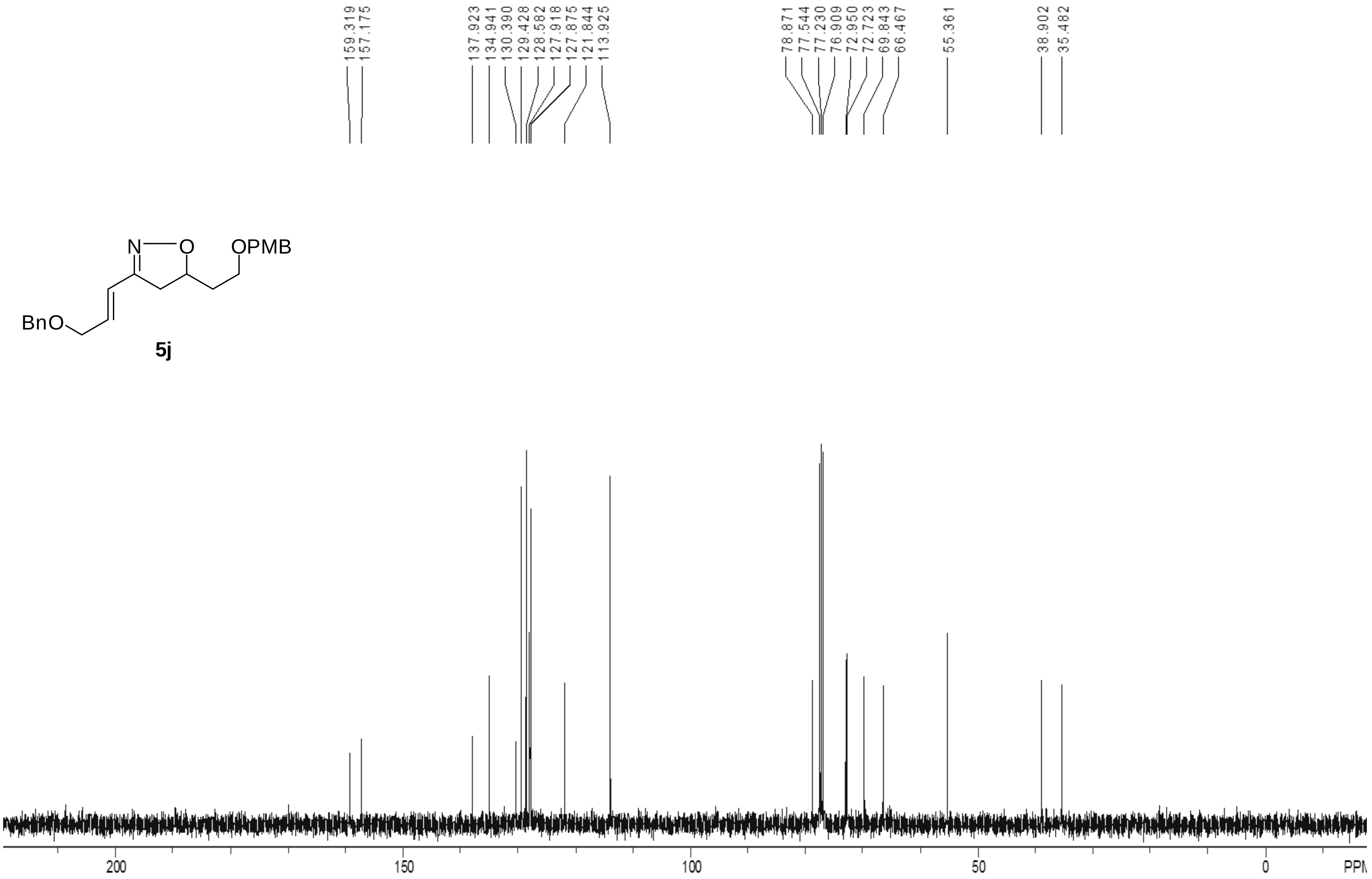
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OPMB
BnO

5j

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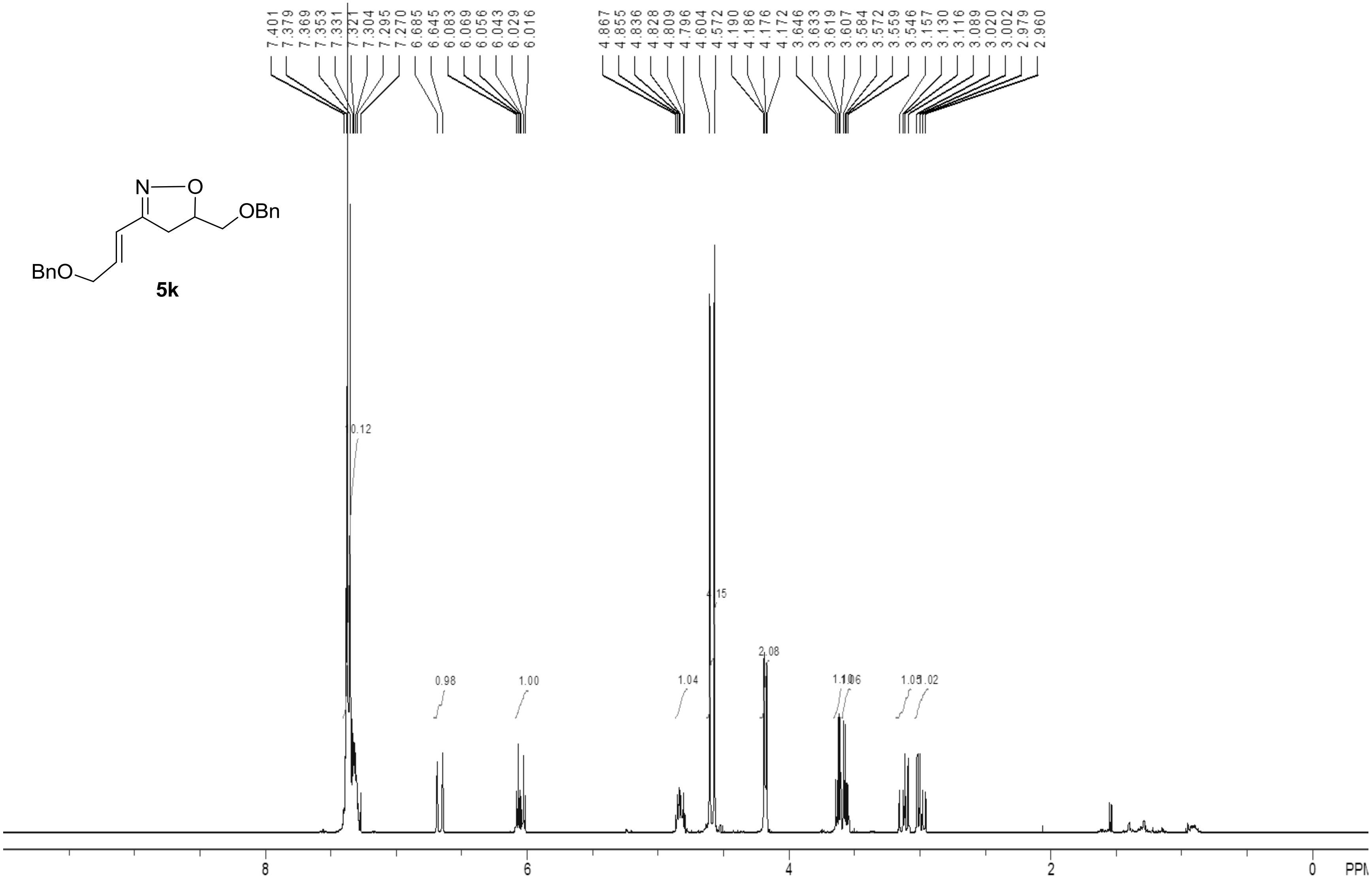
PPM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BnO
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7.331
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7.295
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6.685
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6.083
6.069
6.056
6.043
6.029
6.016
4.867
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4.809
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4.572
4.190
4.186
4.176
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3.607
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3.572
3.559
3.546
3.157
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3.020
3.002
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2.960
10.12
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1.10
1.06
1.05
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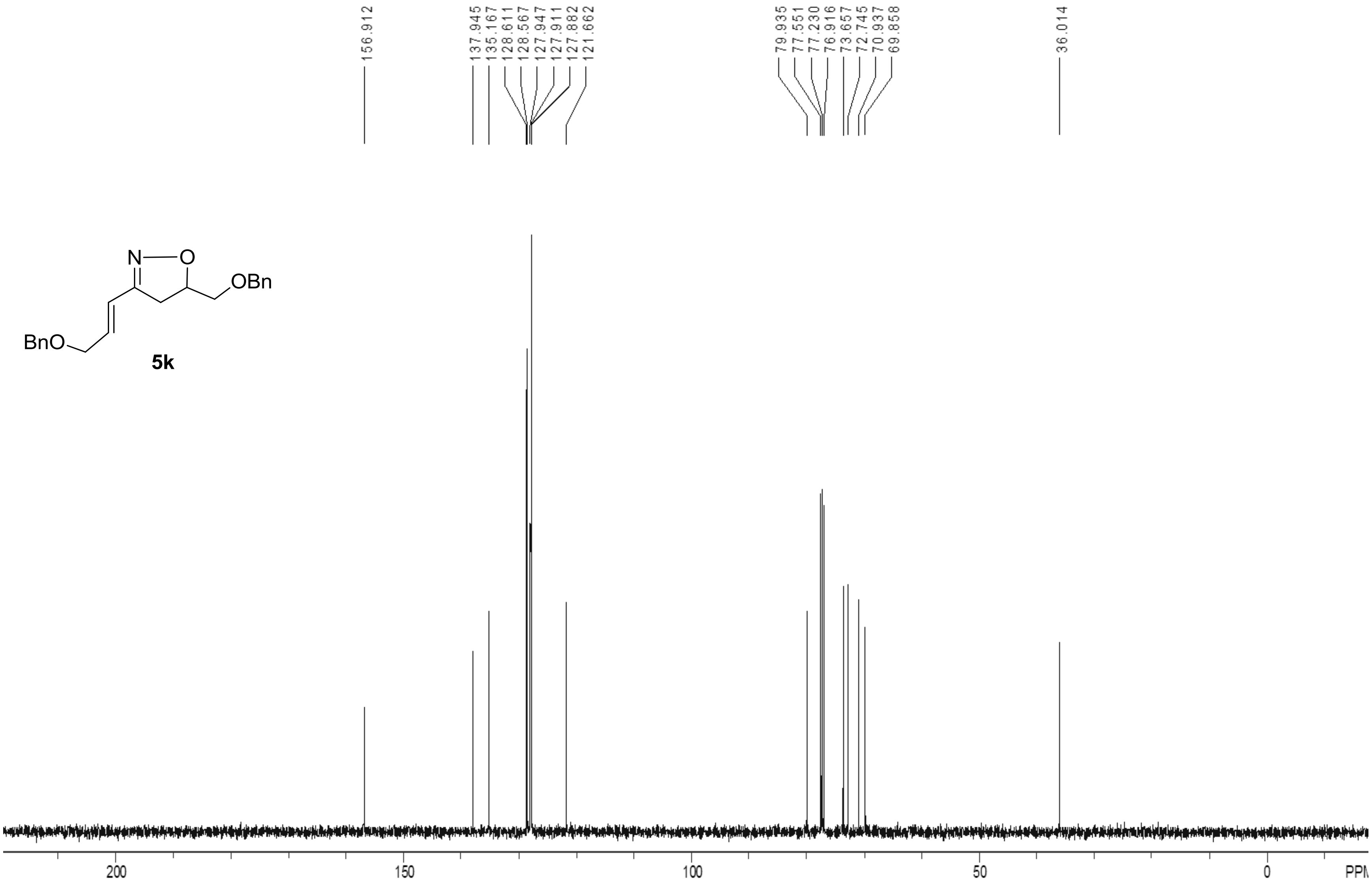
8
6
4
2
0
PPI

5k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77.551
77.230
76.916
73.657
72.745
70.937
69.858
36.014
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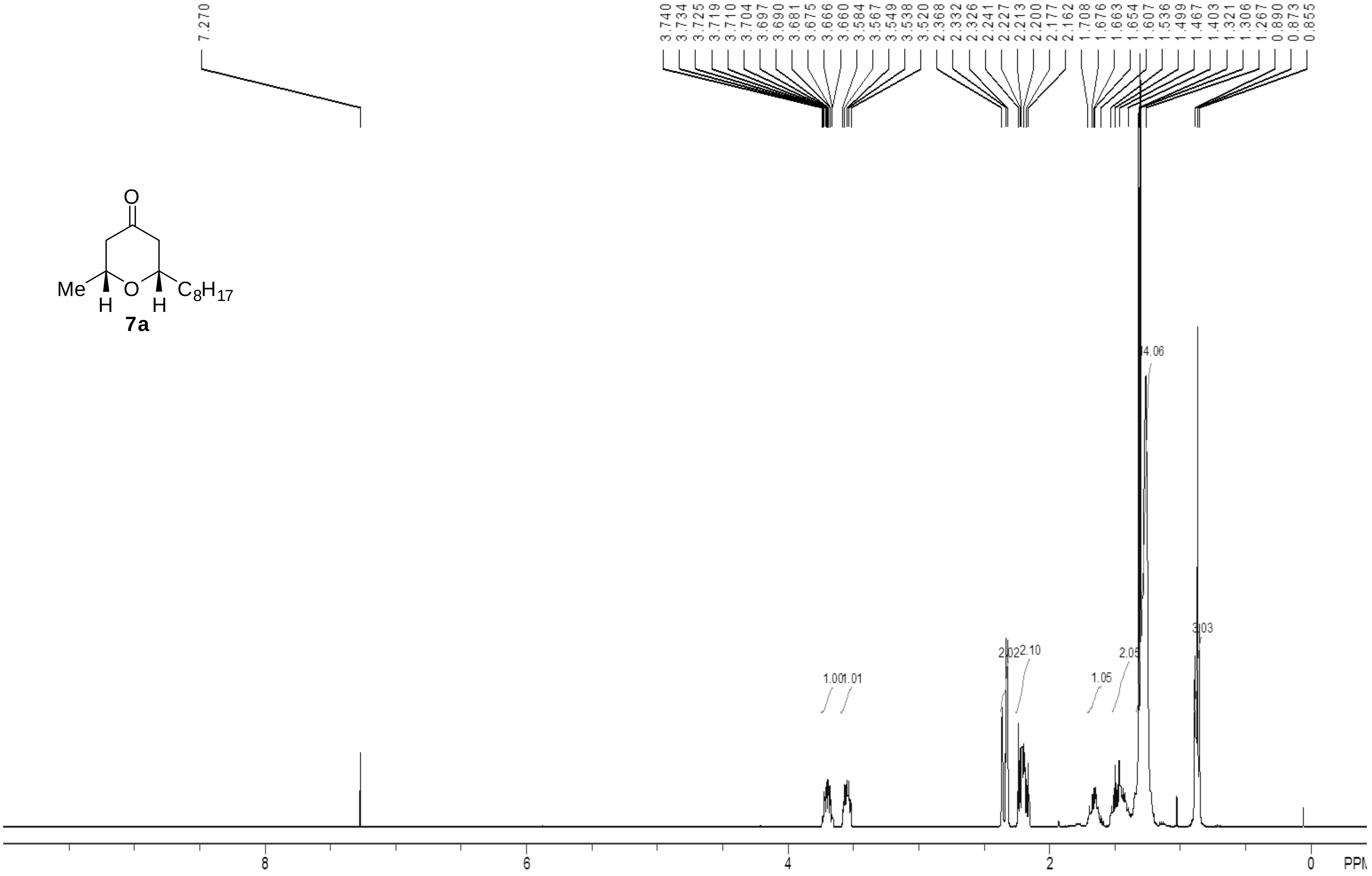
OBn
BnO
200
150
100
50
0
PPM

5k

O
Me
O
C8H17
H
H

7a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3.681
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3.660
3.584
3.567
3.549
3.538
3.520
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2.326
2.241
2.227
2.213
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2.177
2.162
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1.306
1.267
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3.03
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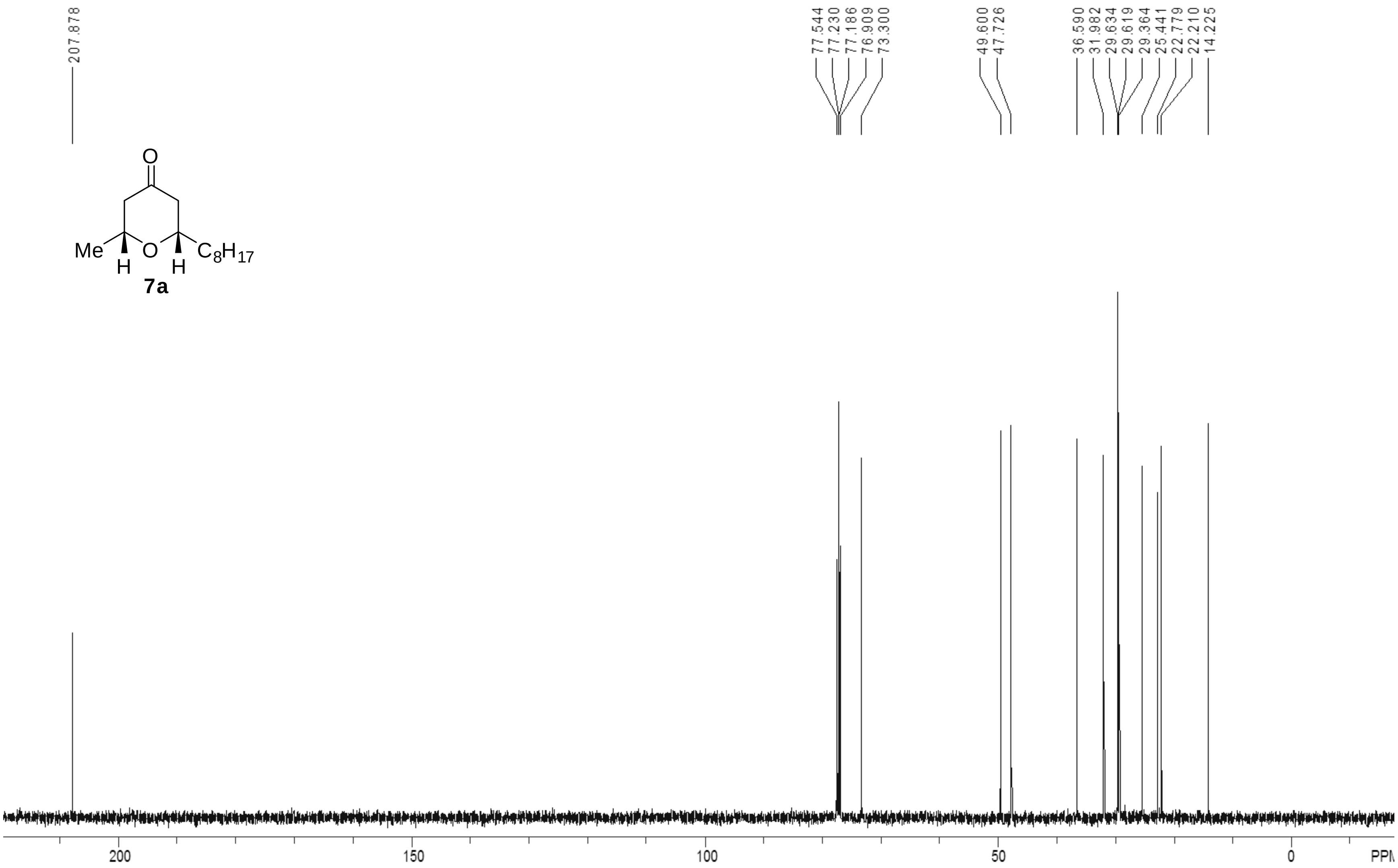
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29.364
25.441
22.779
22.210
14.225
O
Me
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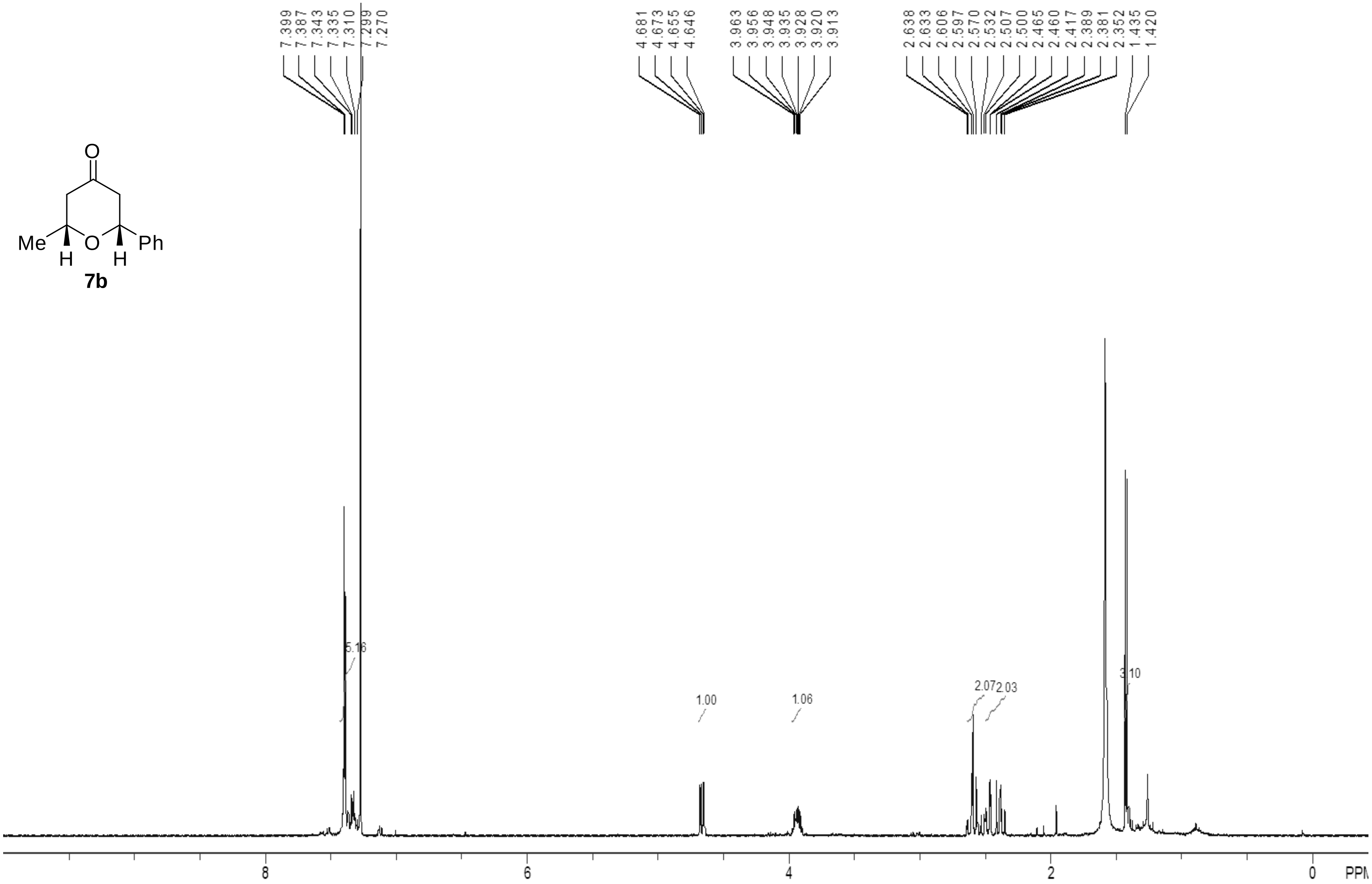
O
H
C_8H_{17}
200
150
100
50
0
PPM

7a

O
Me
H
O
H
Ph

7b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4.646
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3.956
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3.913
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2.633
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2.597
2.570
2.532
2.507
2.500
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2.460
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2.381
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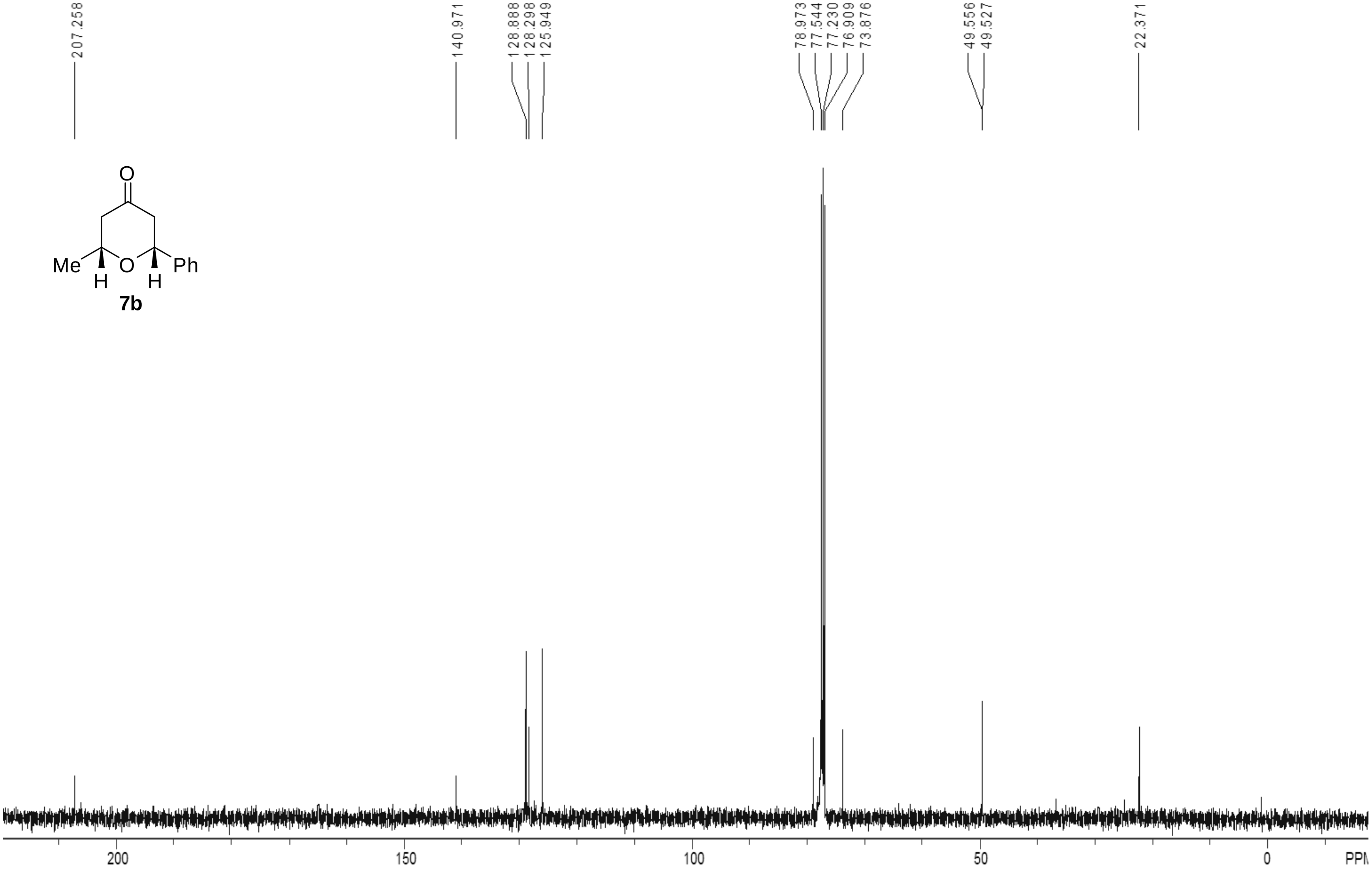
PP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O
Ph
H
H
7b
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150
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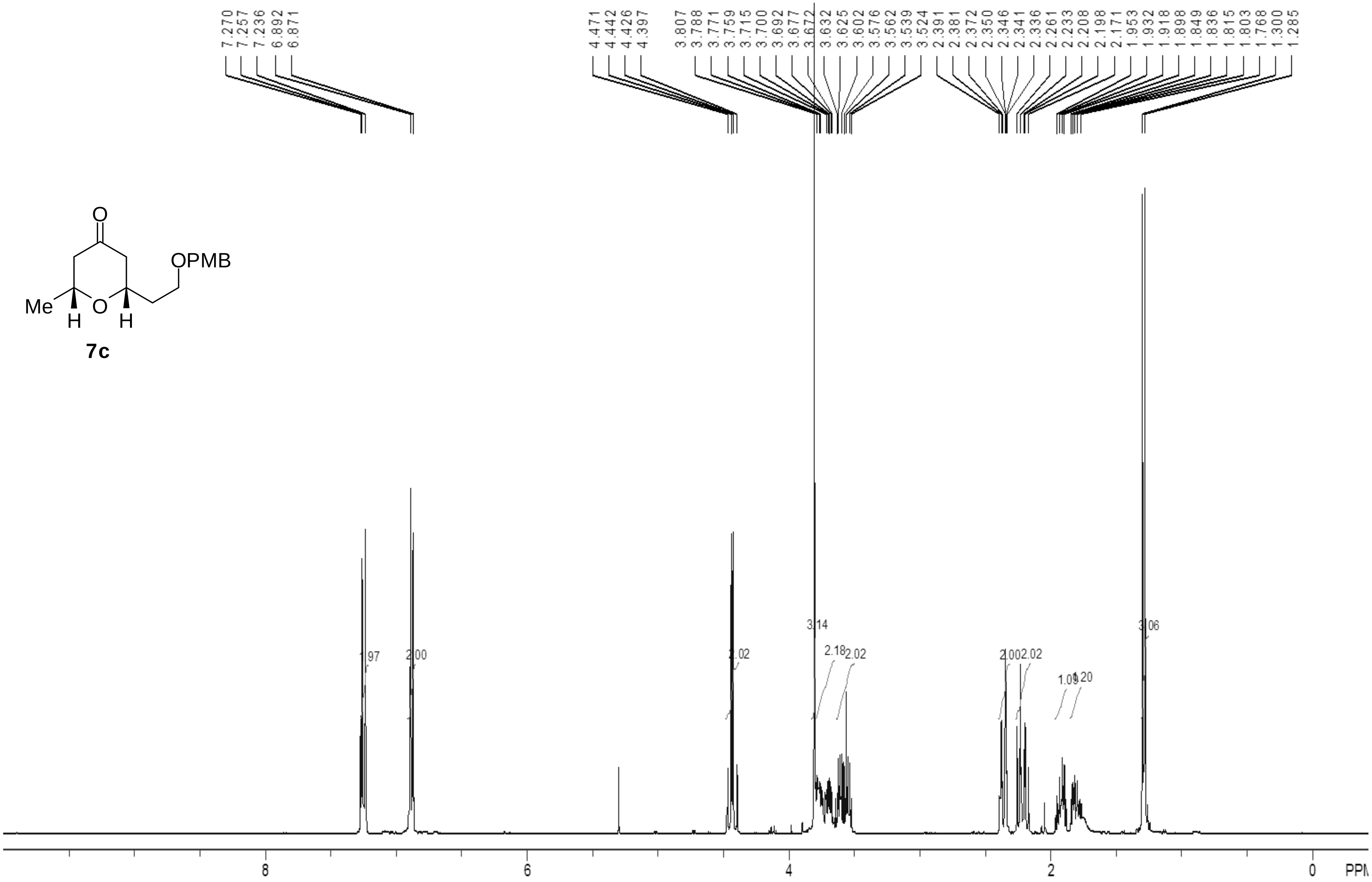
0
PPM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OPMB
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3.06
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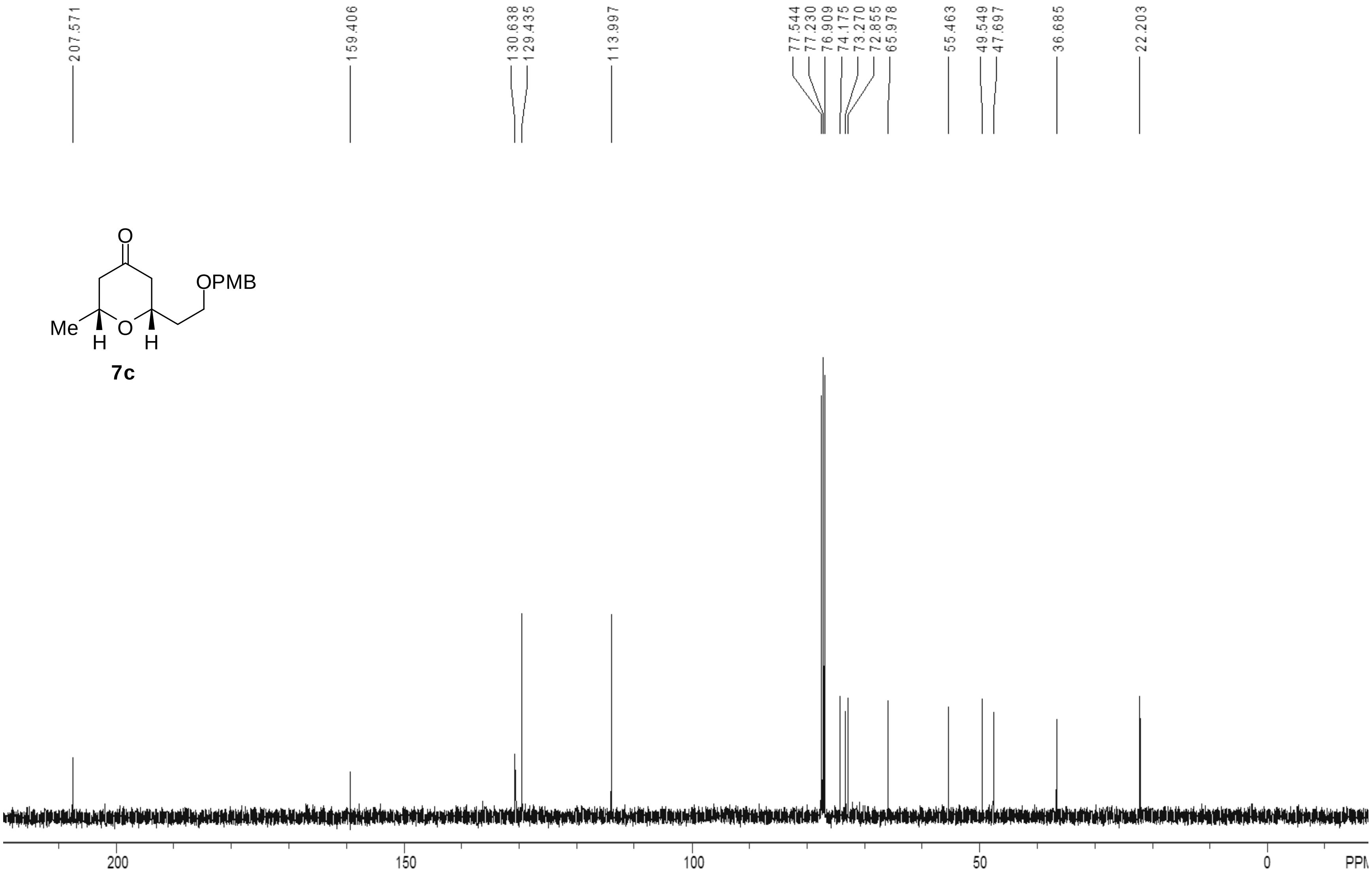
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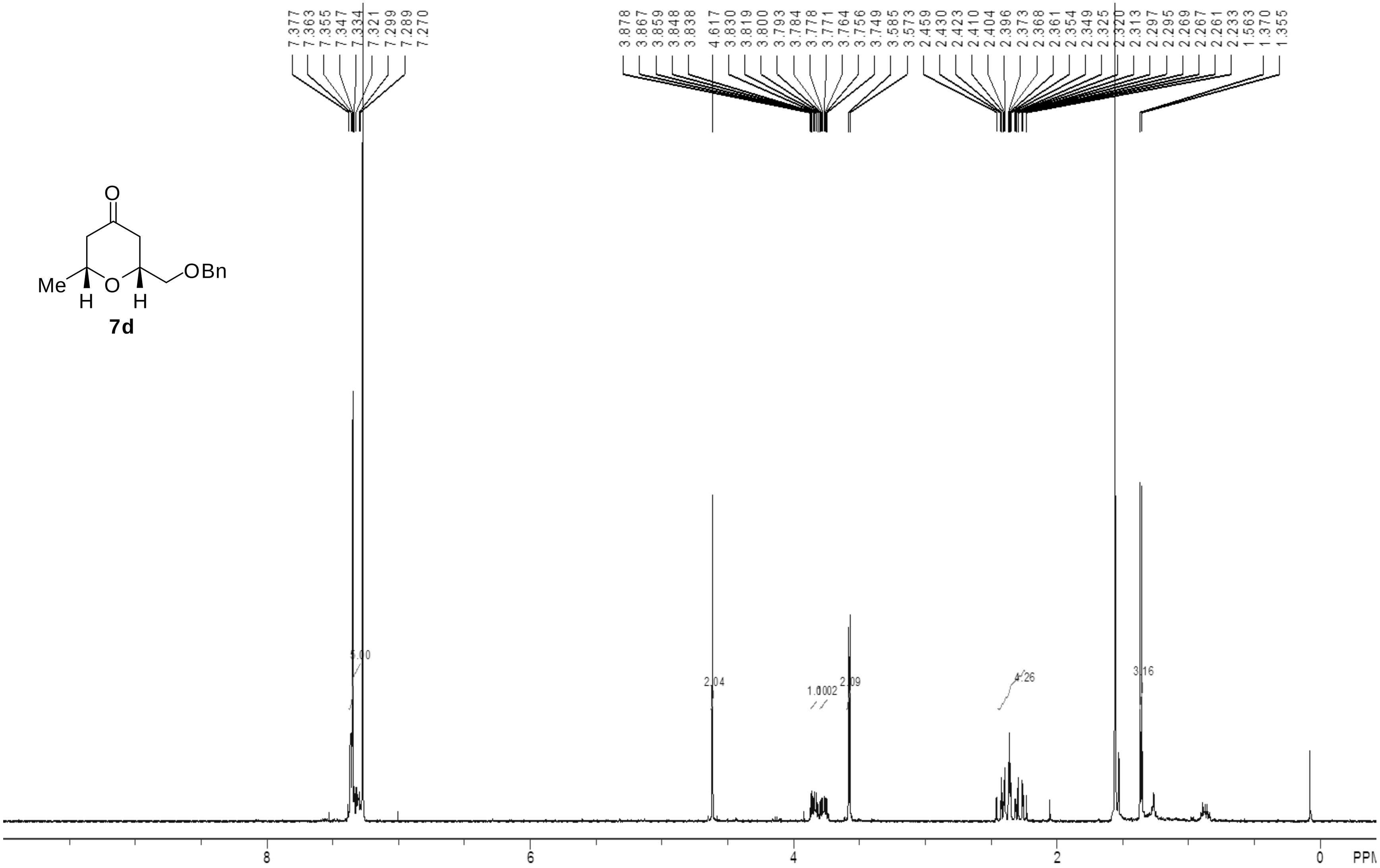
PPM

7c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Me
O
OBn
H
H

7d

7.377
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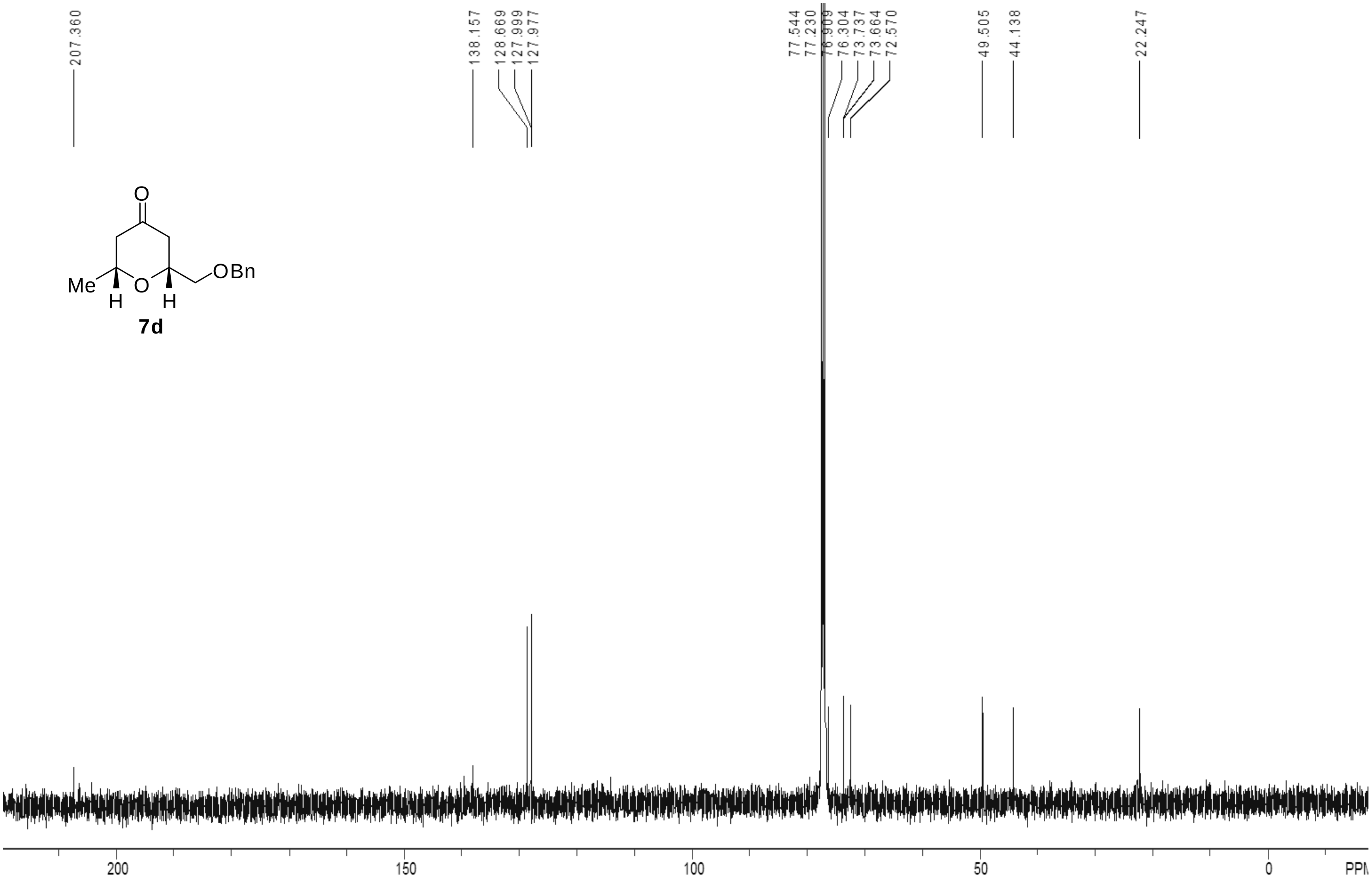
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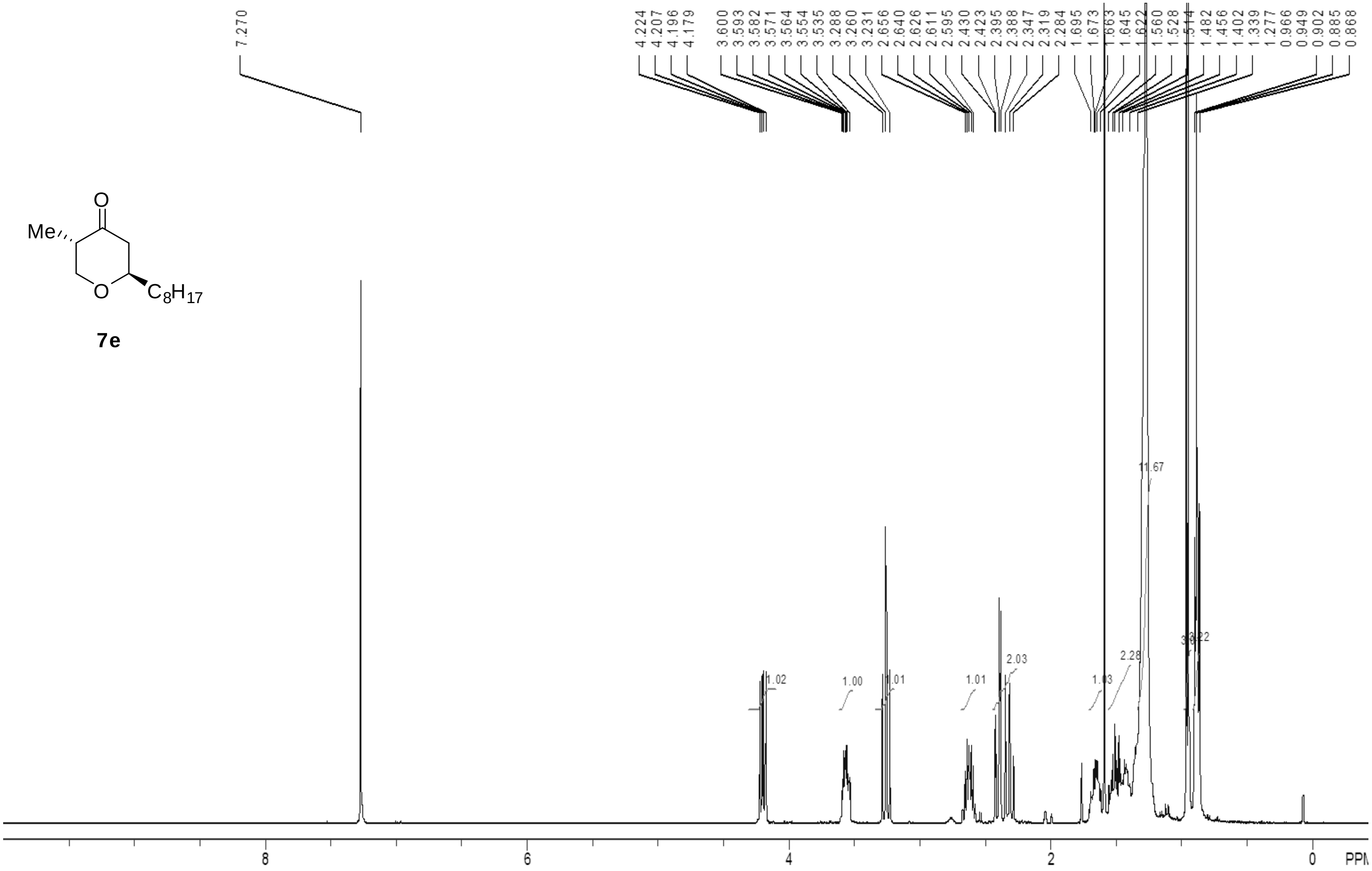
7d

O
Me
O
C_8H_{17}

7e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3.288
3.260
3.231
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1.456
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1.339
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0.949
0.902
0.885
0.868
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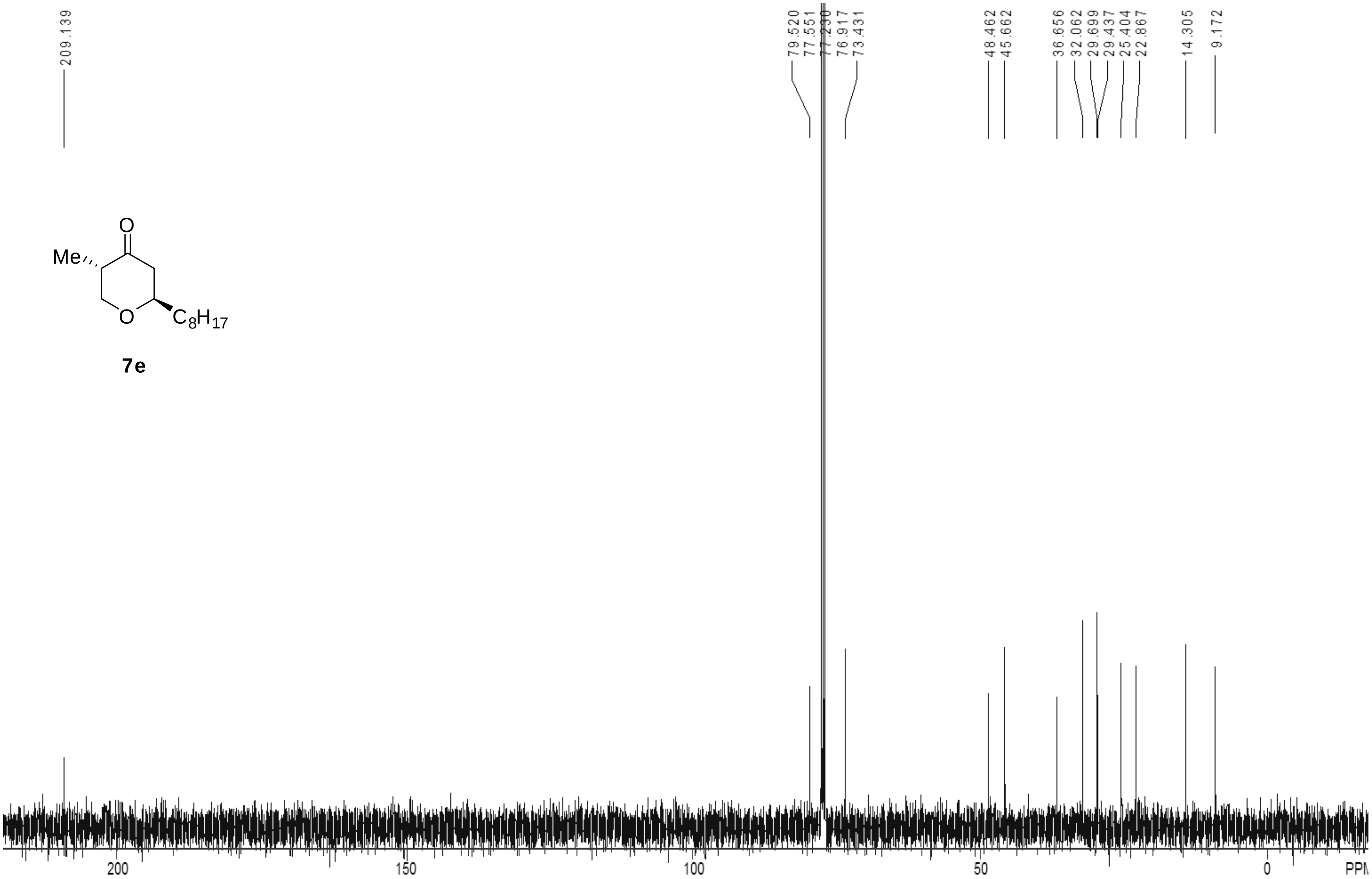
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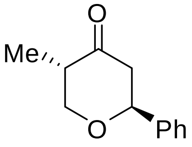
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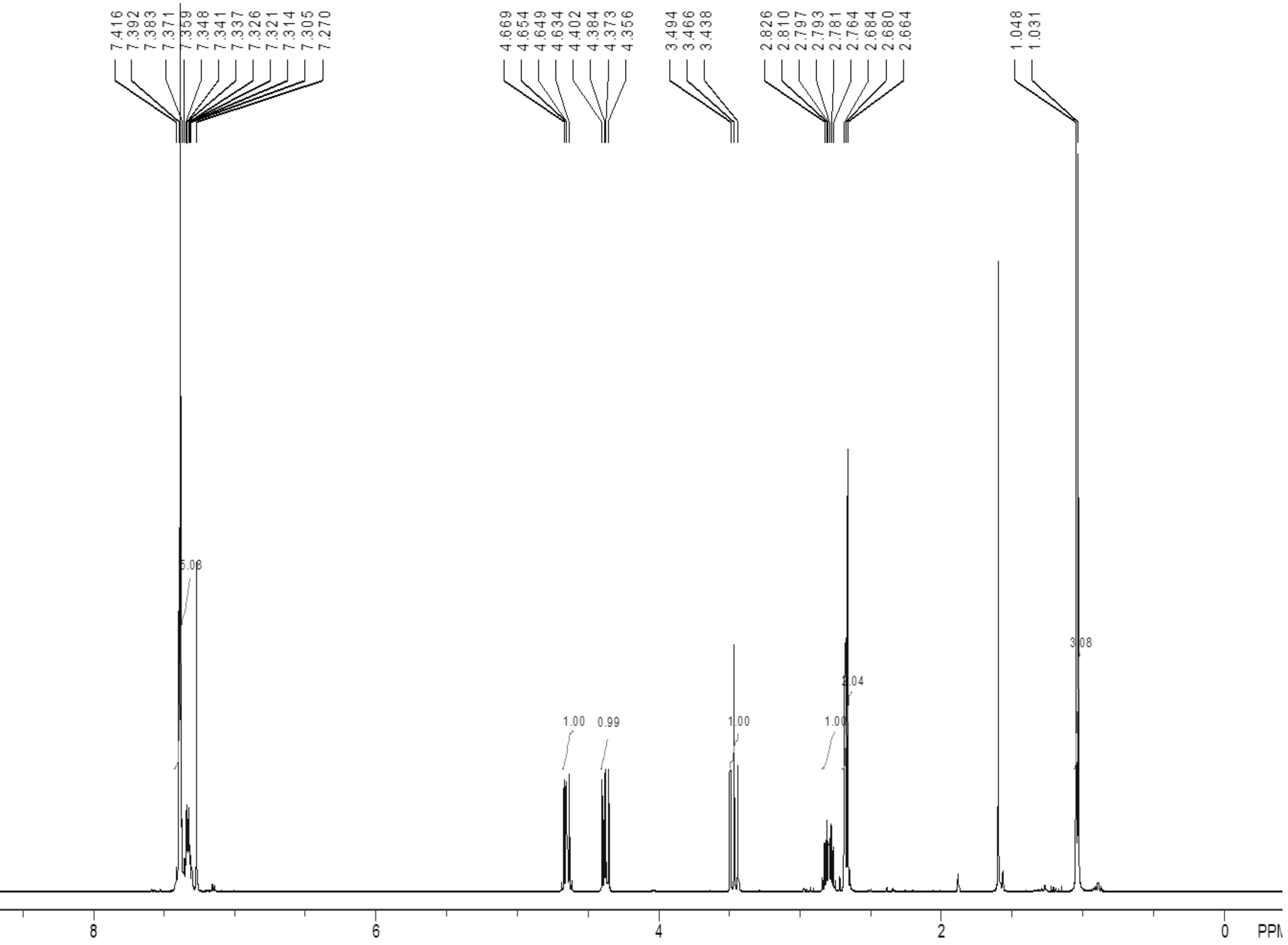
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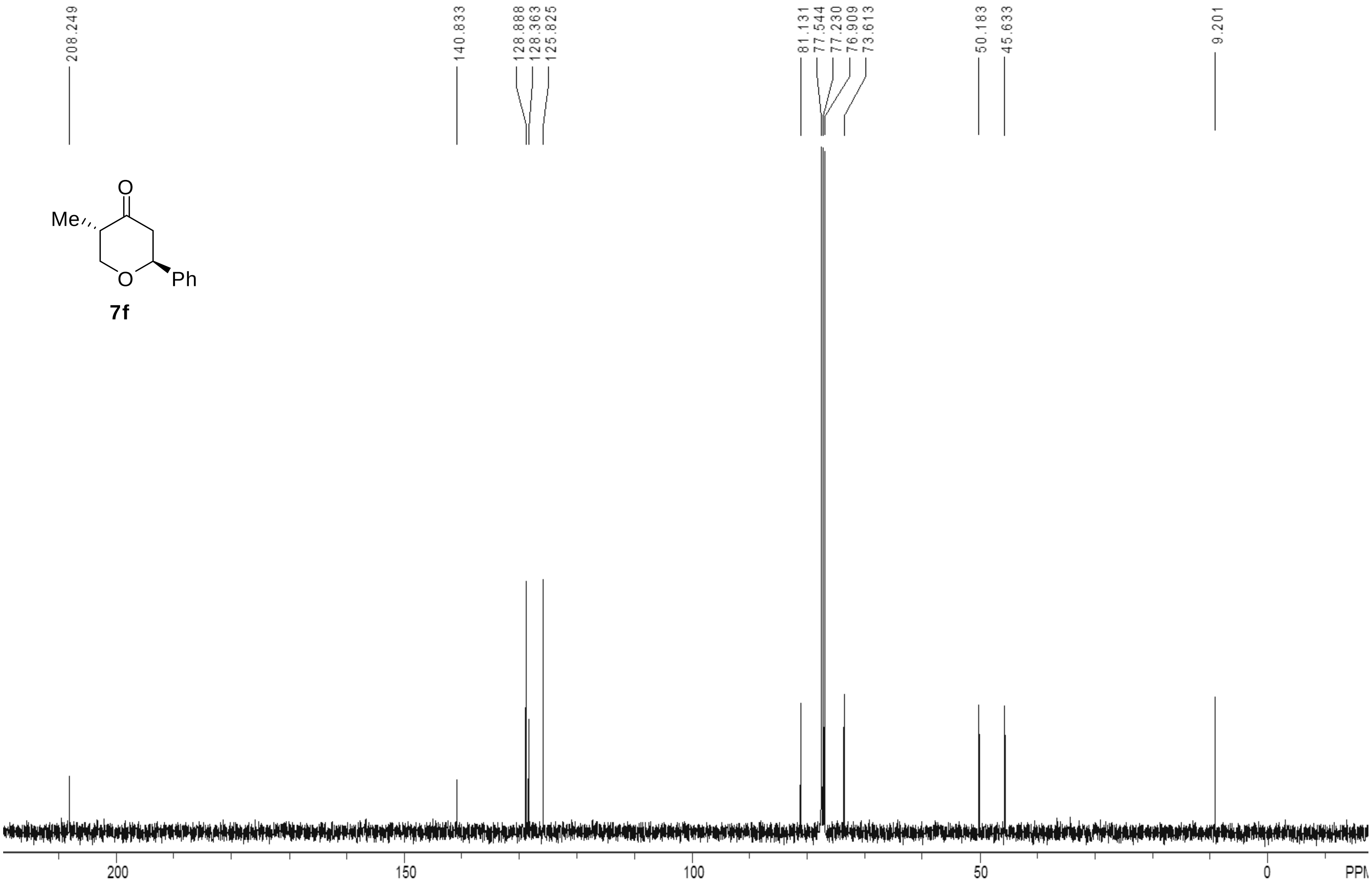
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O
Ph
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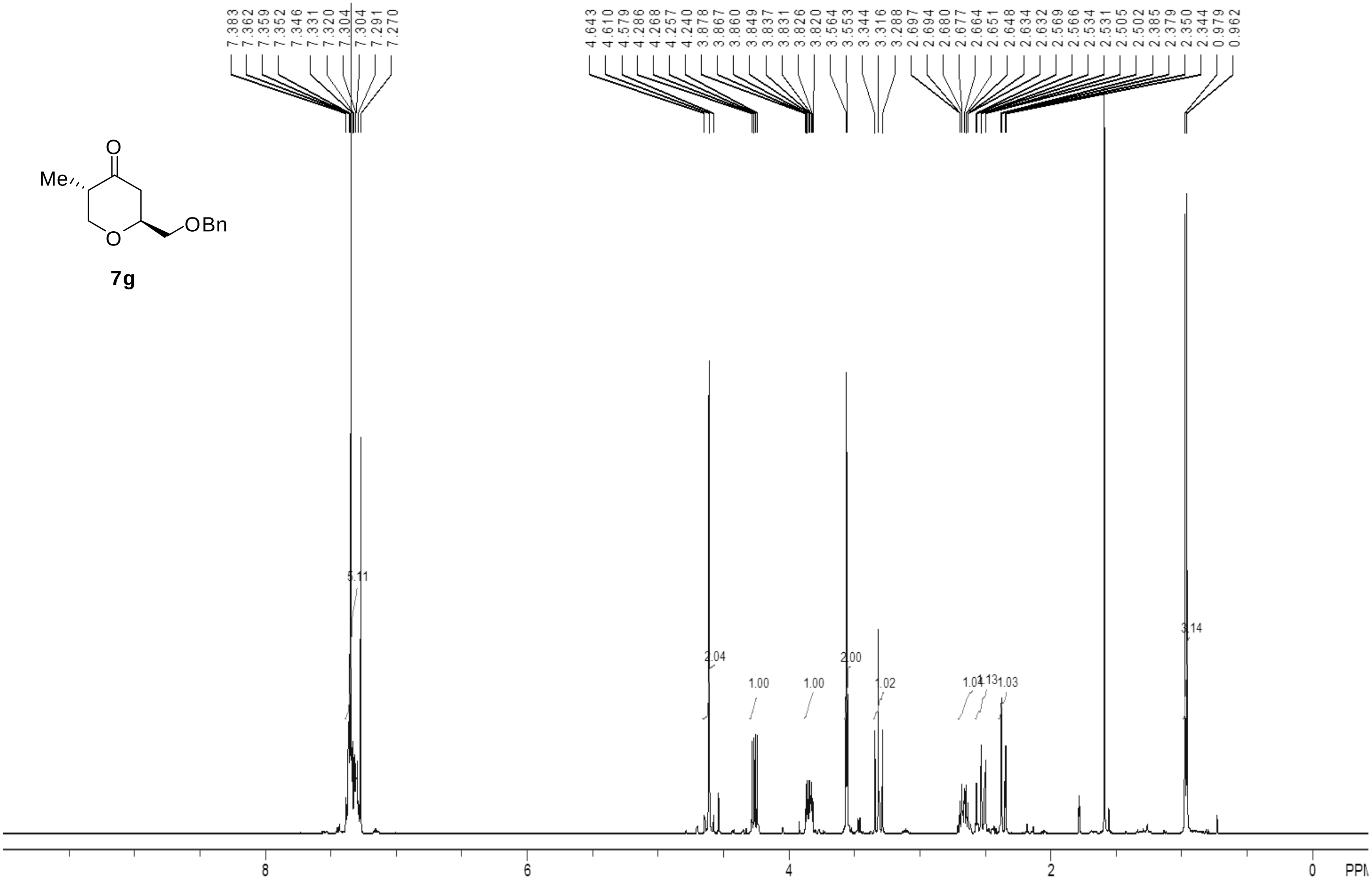
PPM

7f

O
Me
O
OBn

7g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3.867
3.860
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3.826
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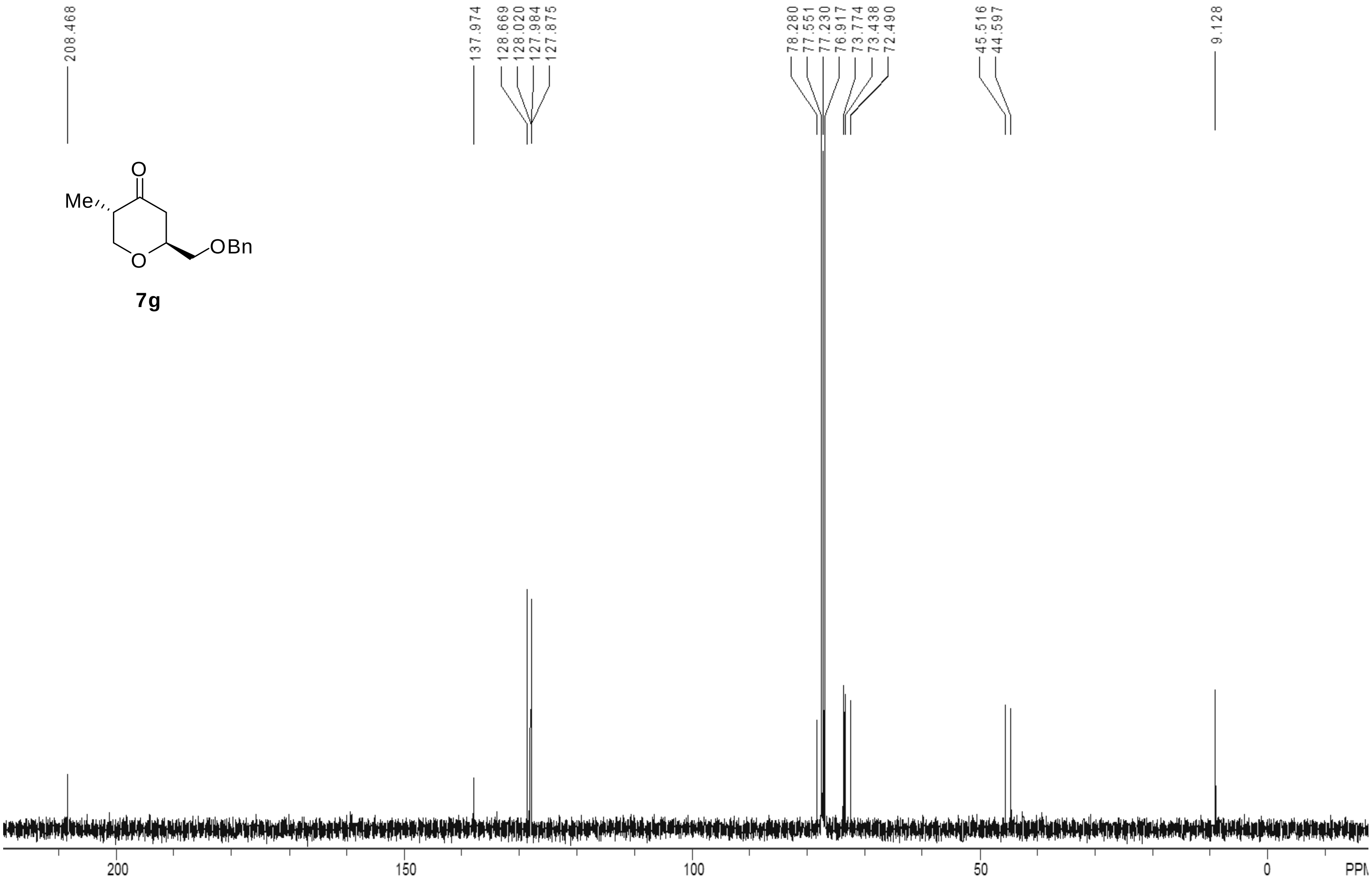
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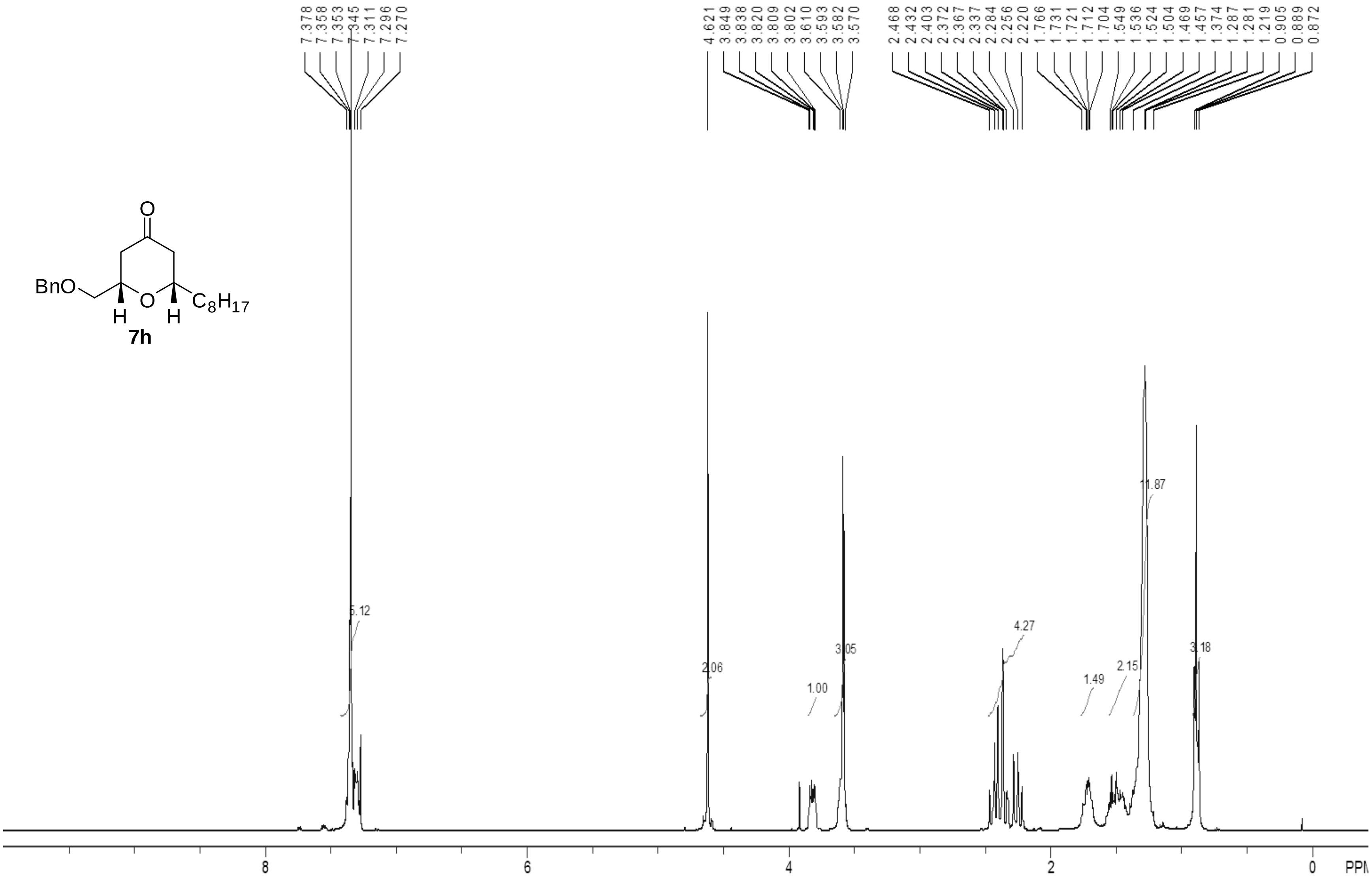
PPM

7g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3.802
3.610
3.593
3.582
3.570
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2.337
2.284
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1.731
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1.374
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BnO
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O
H
H
C8H17
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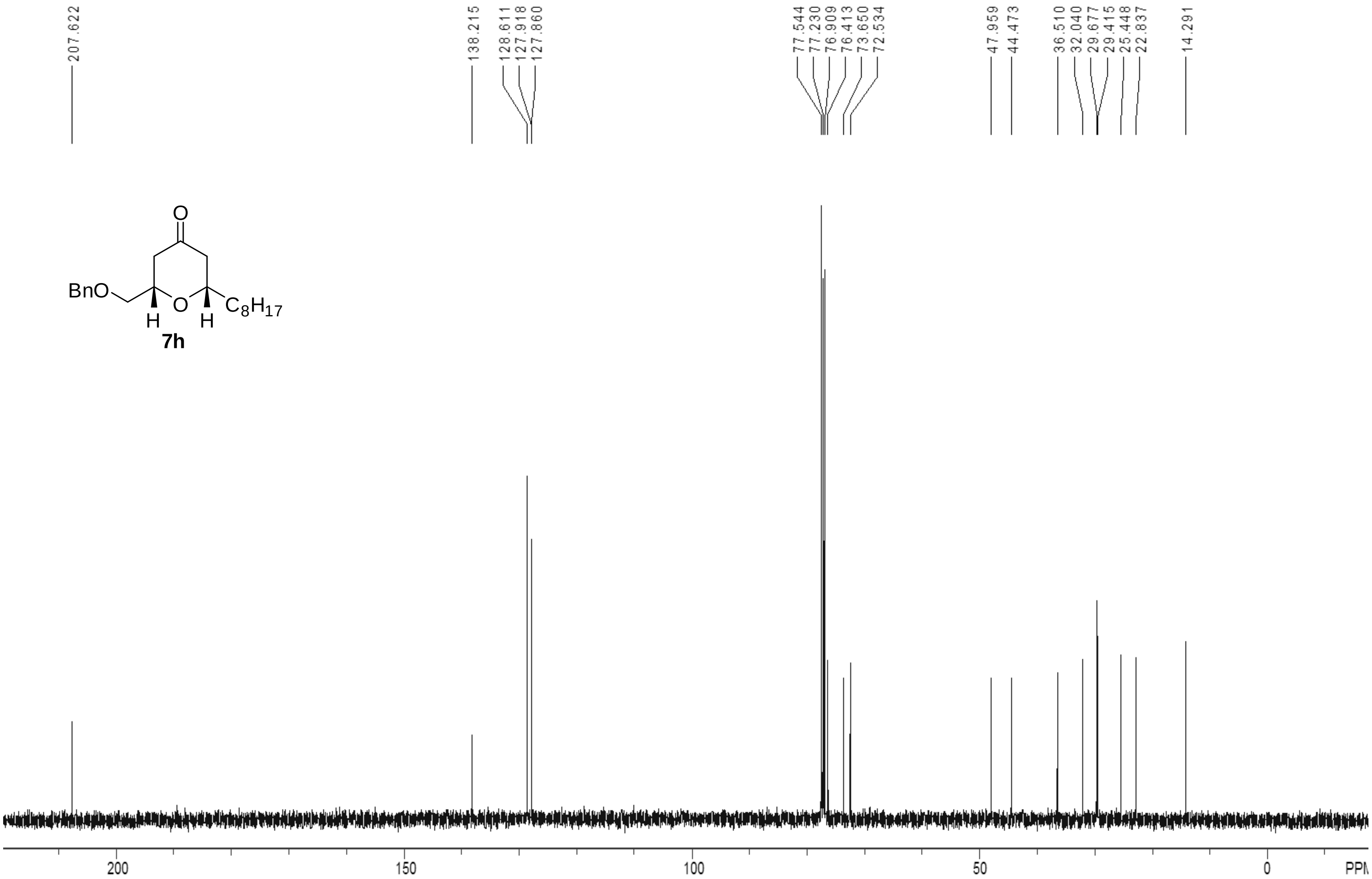
PPM

7h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44.473
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BnO
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C_8H_{17}
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H
7h
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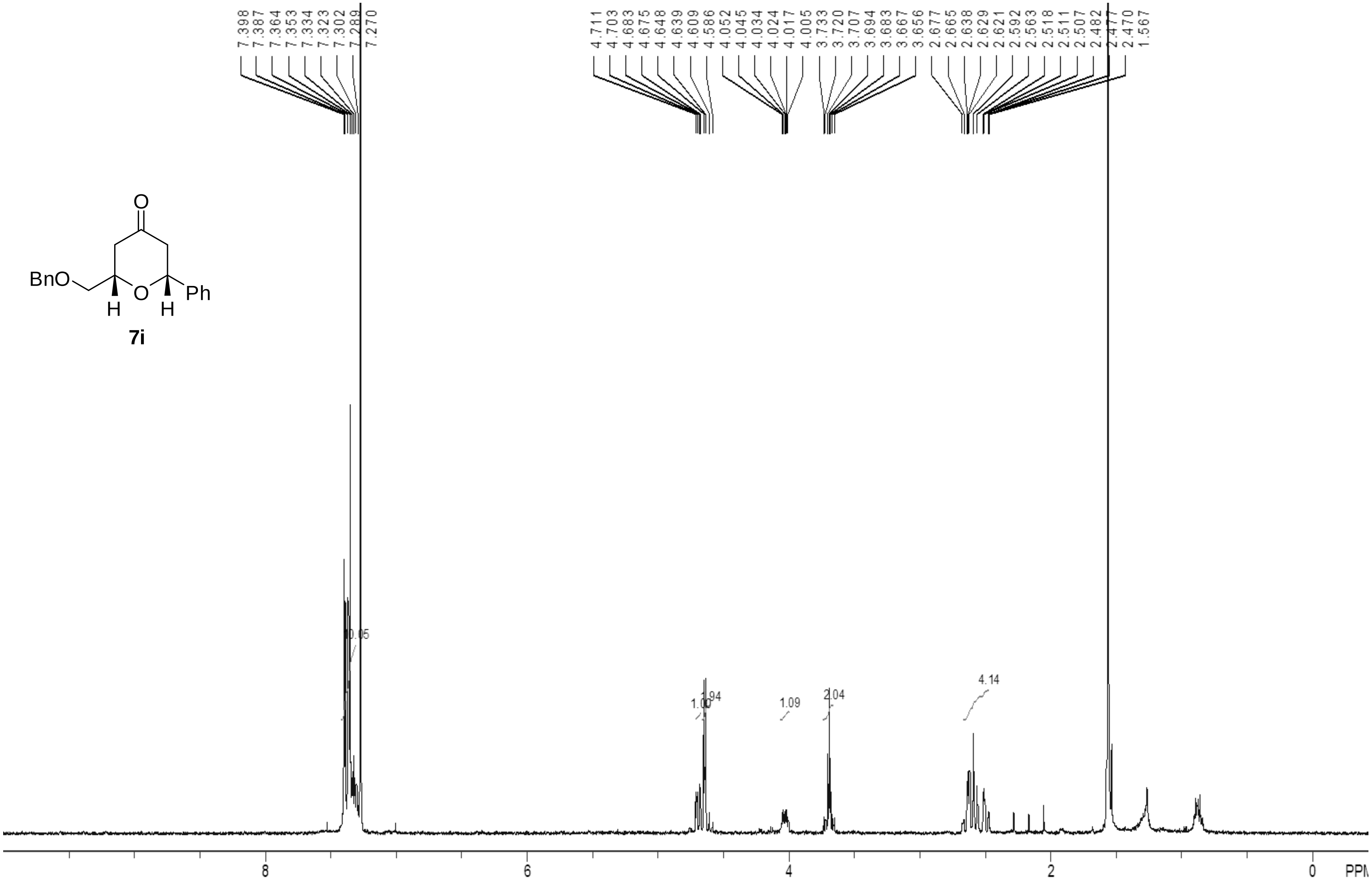
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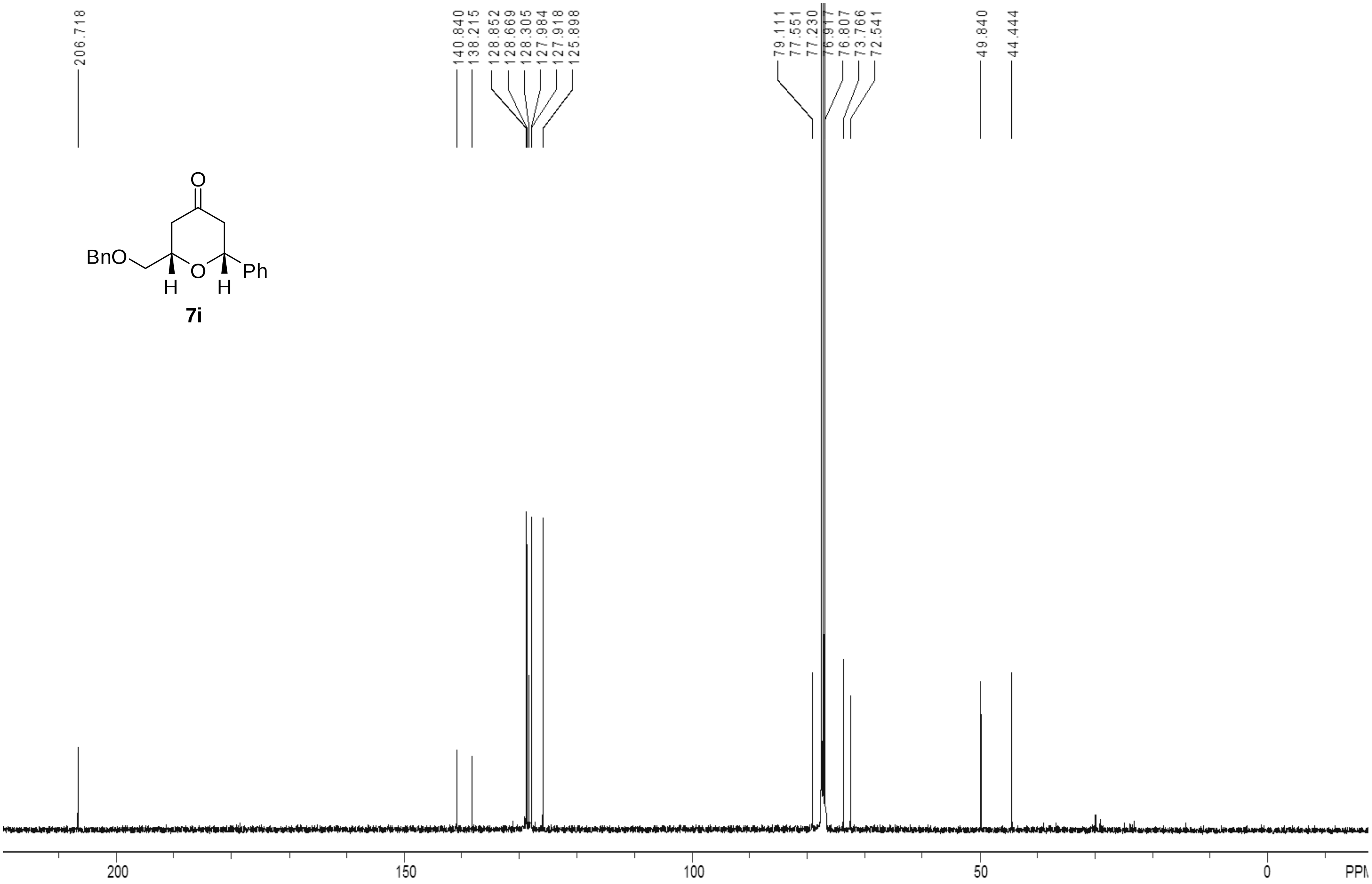
7i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76.917
76.807
73.766
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Ph
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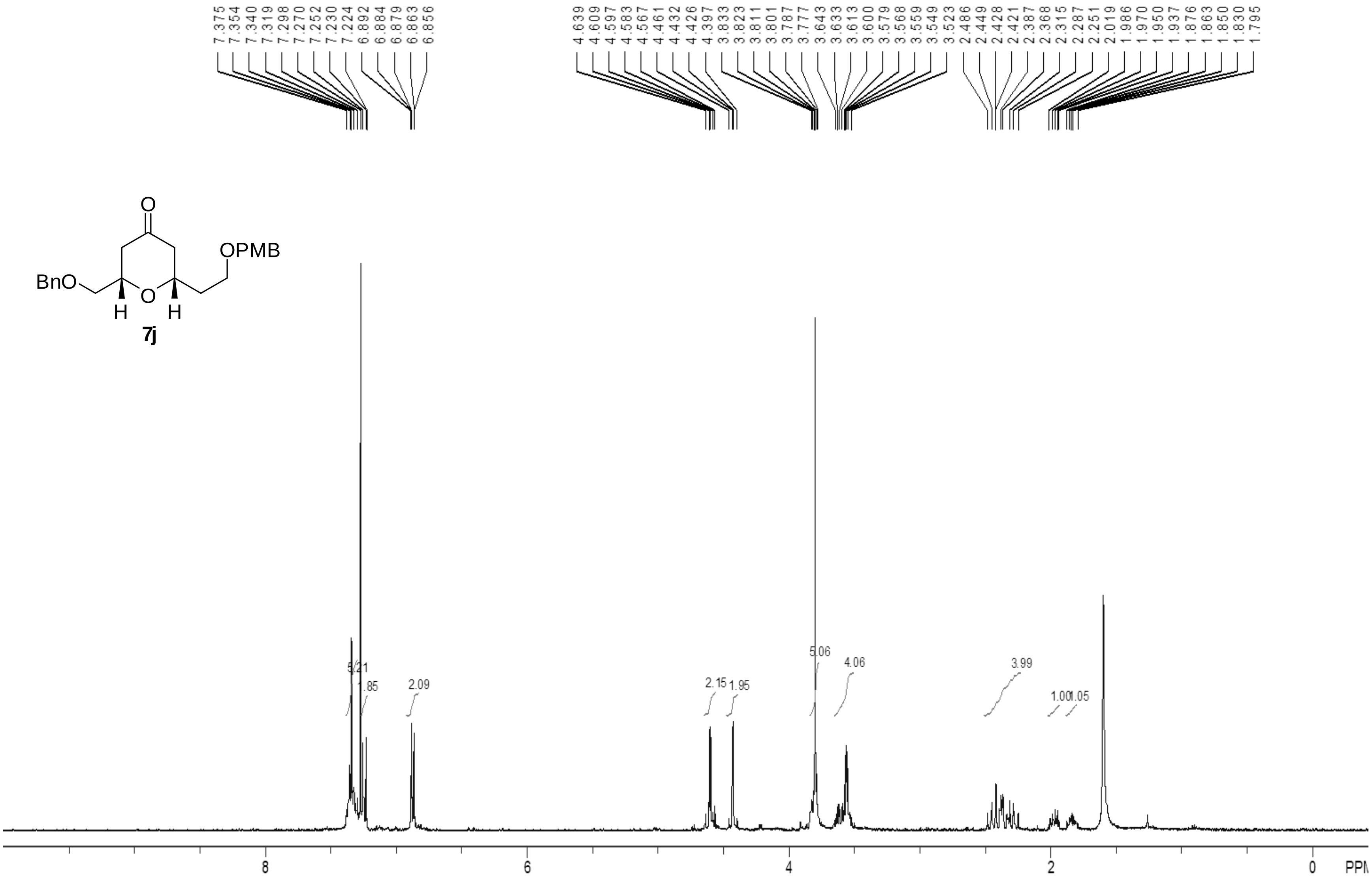
PPM

7i


O
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7j

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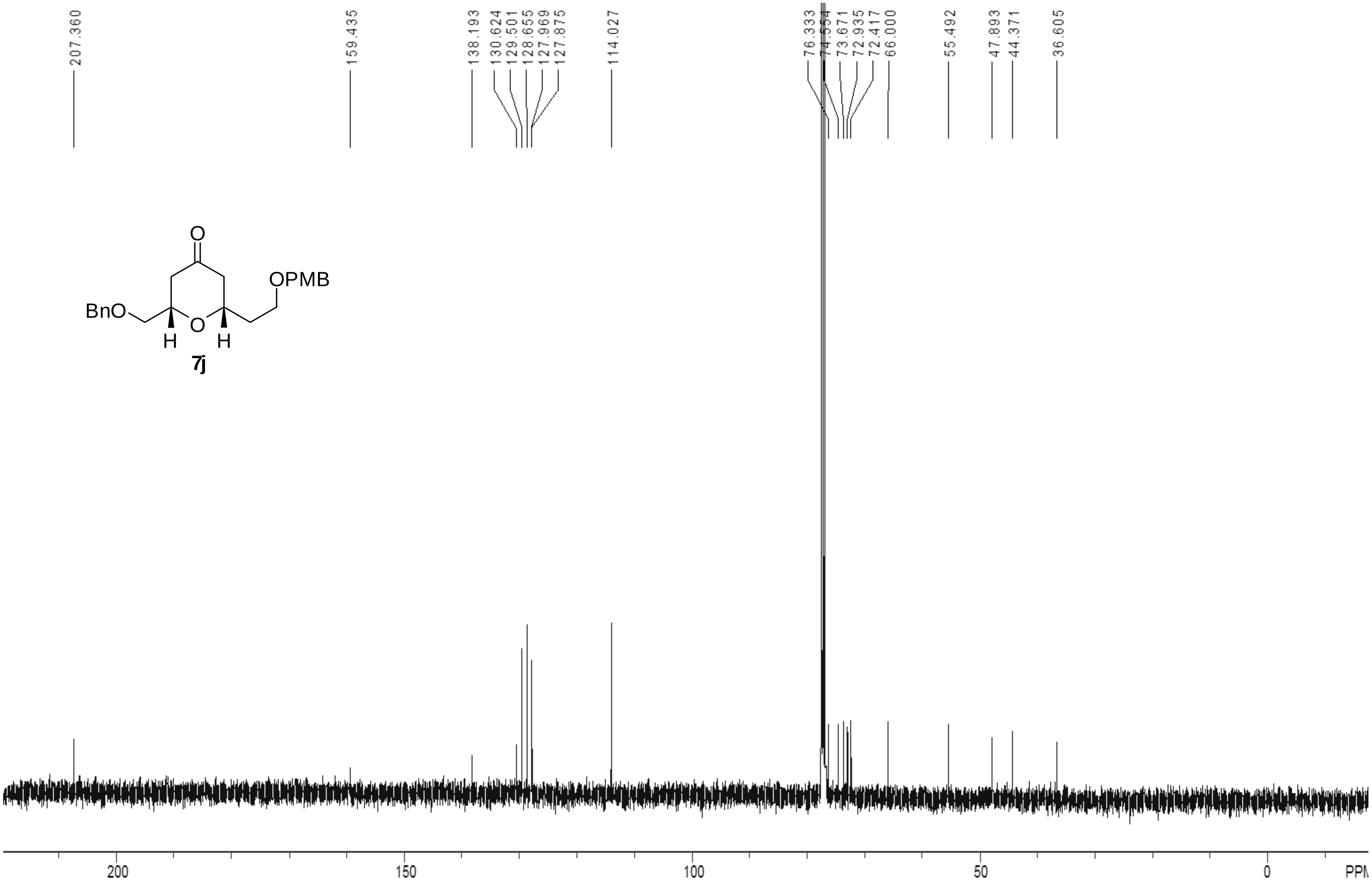
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72.417
66.000
55.492
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36.605
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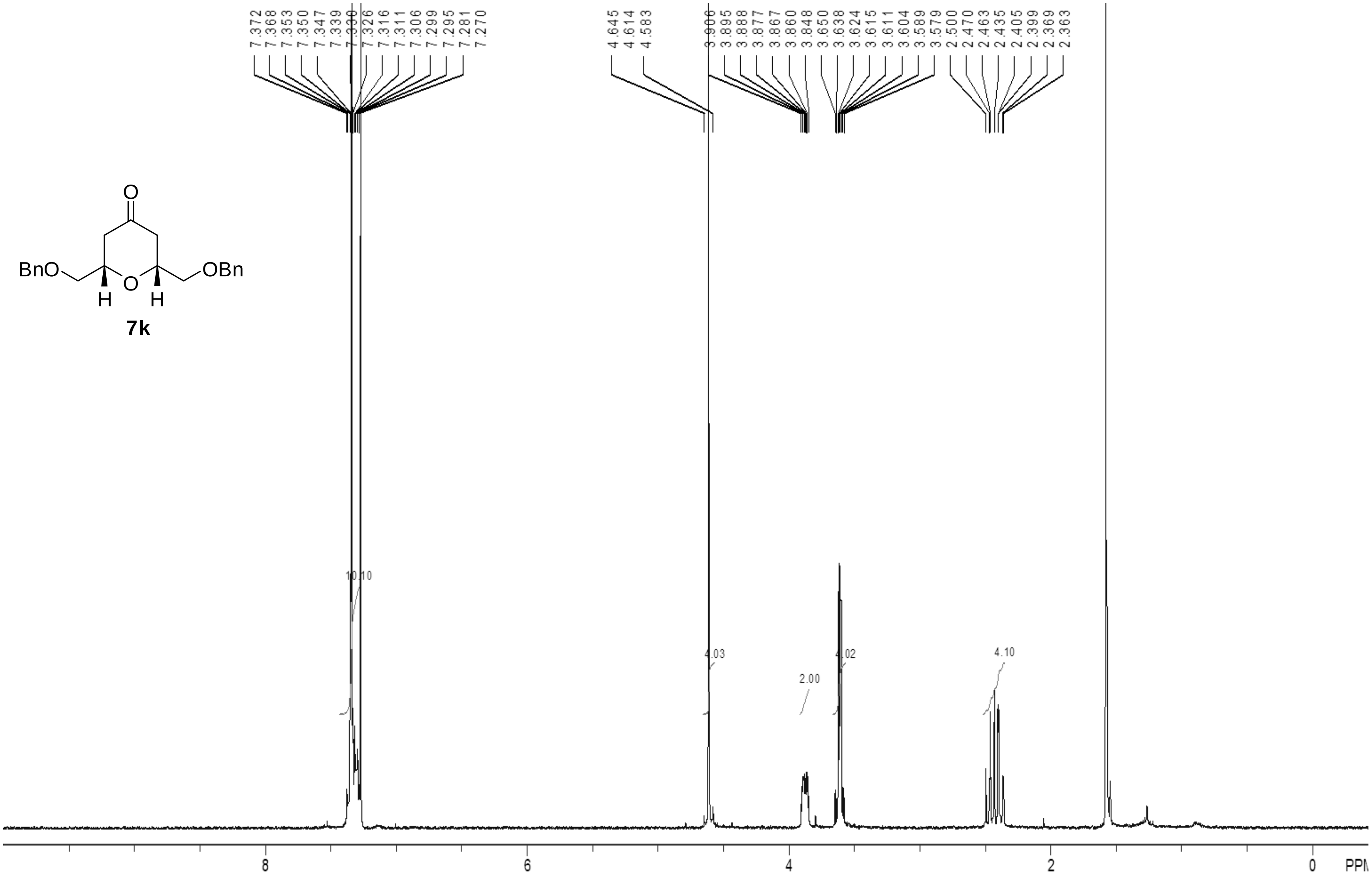
PPM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BnO
OBn
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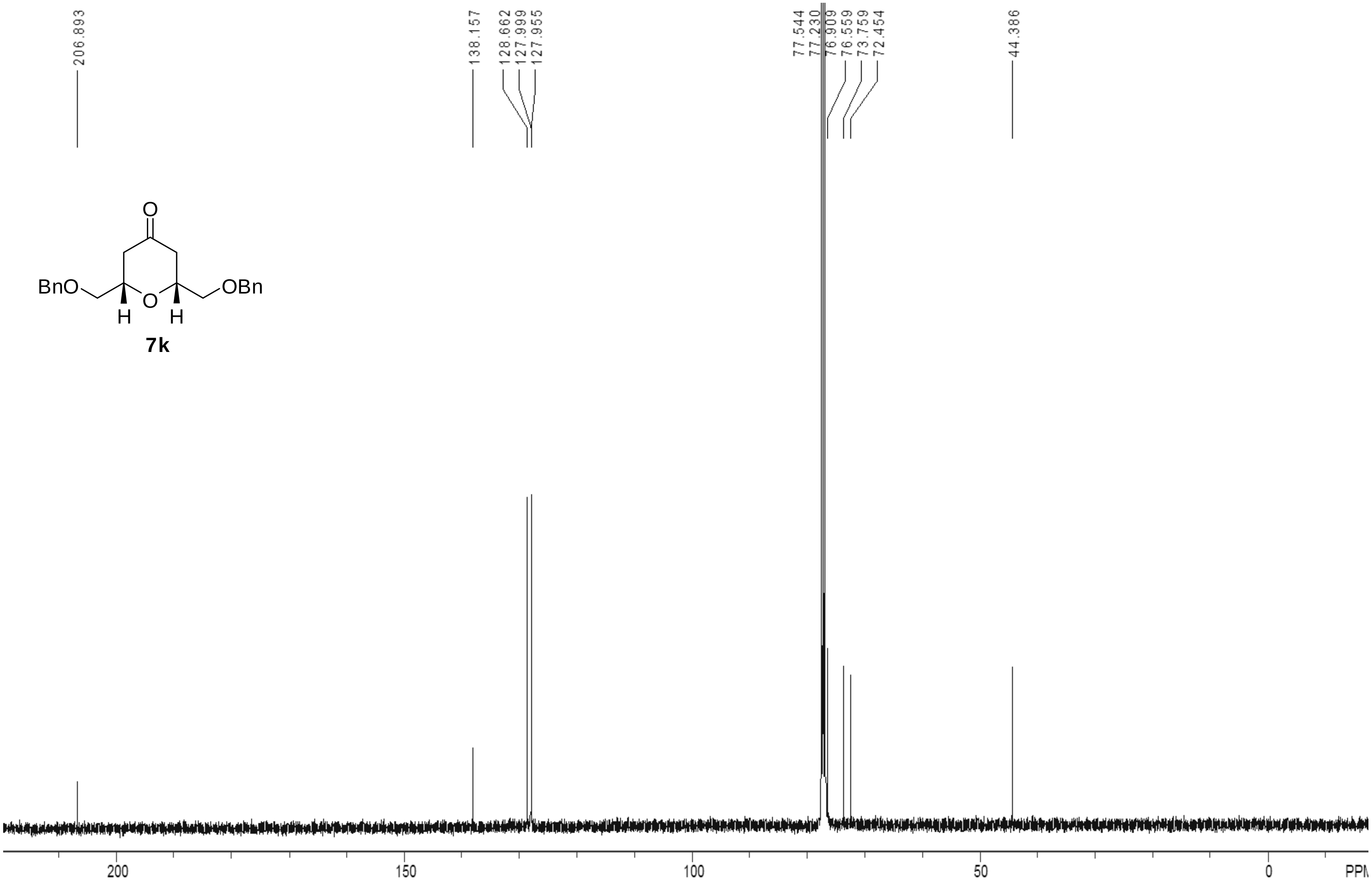
7k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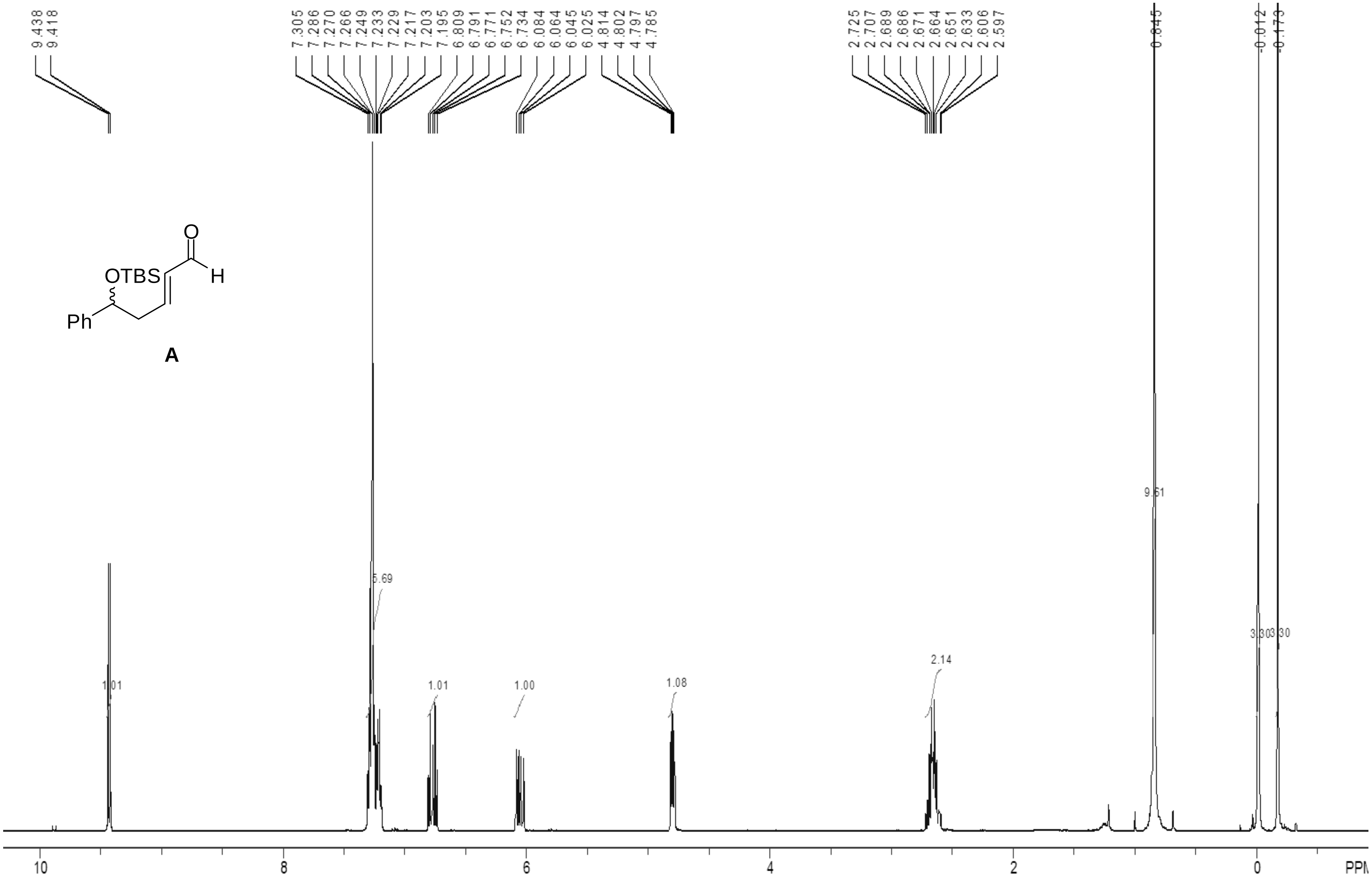
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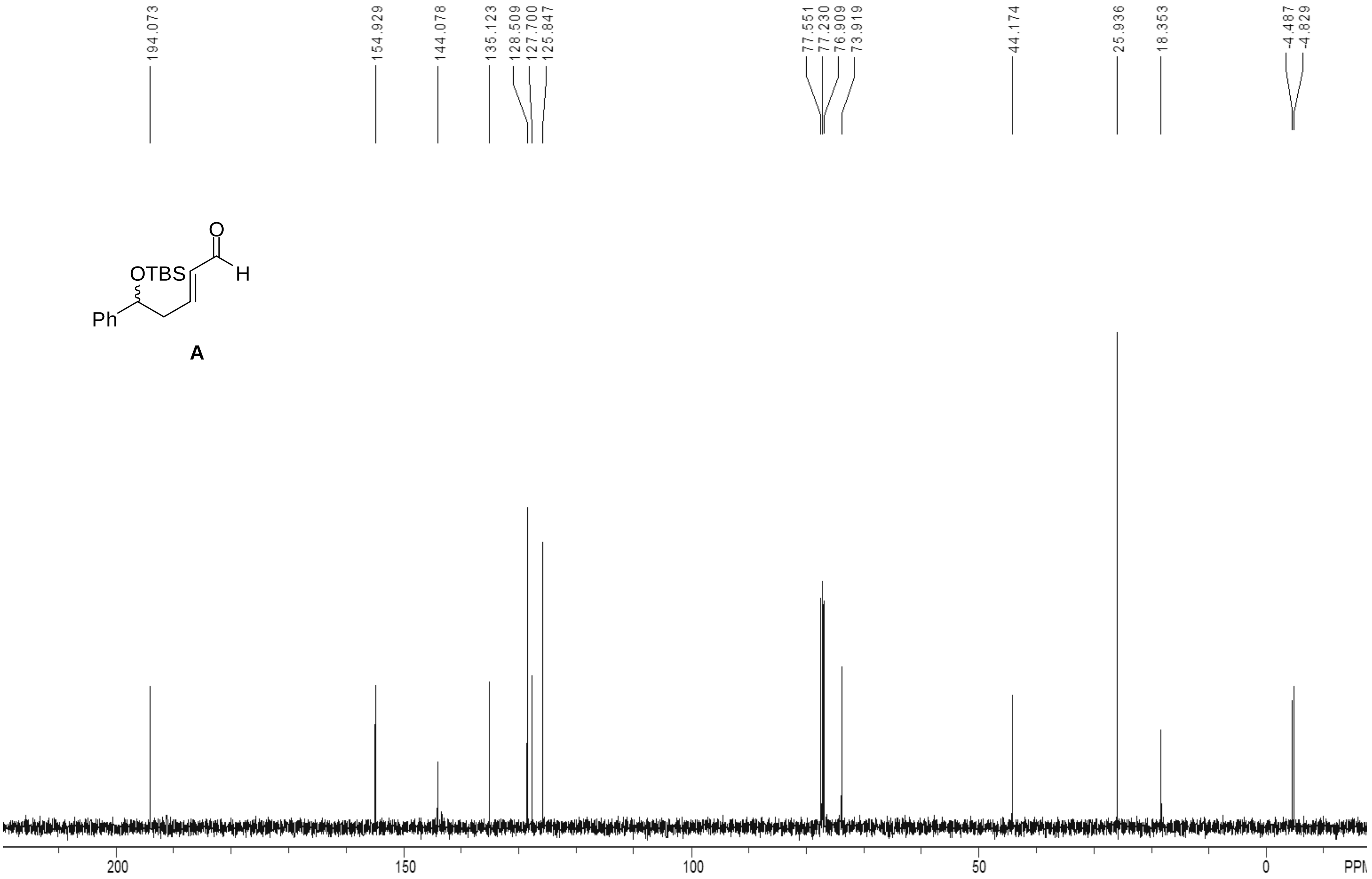
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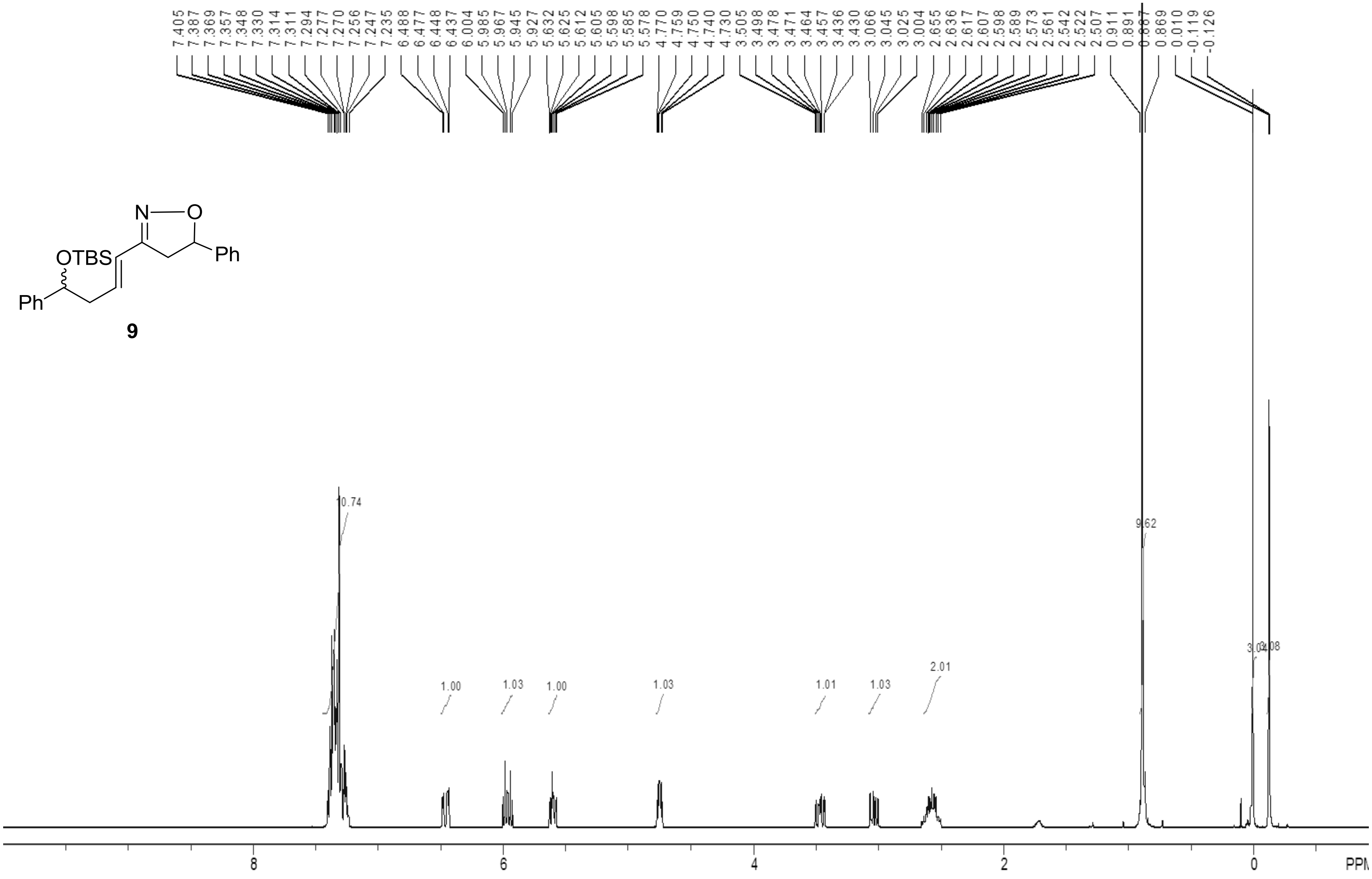
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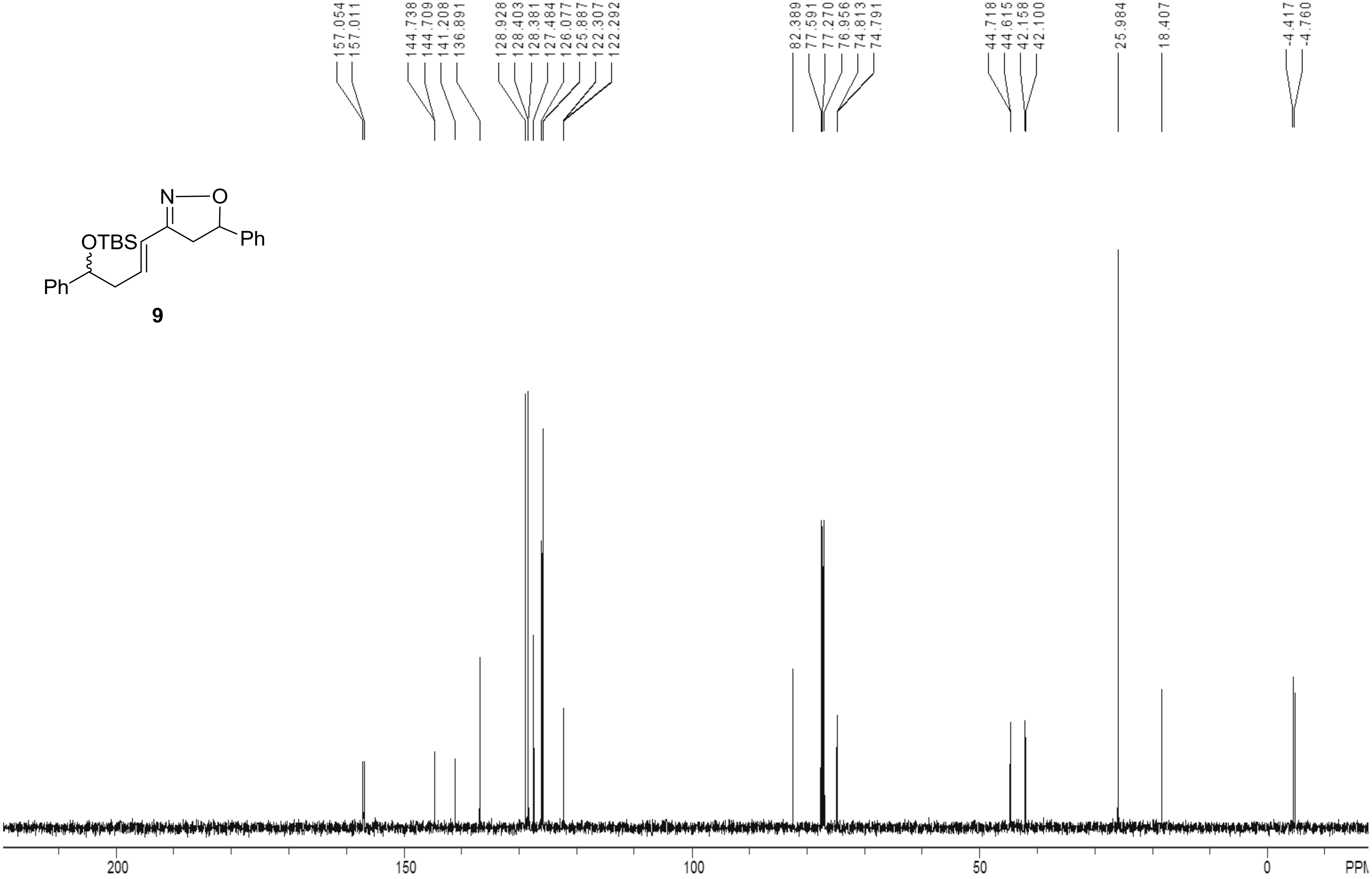
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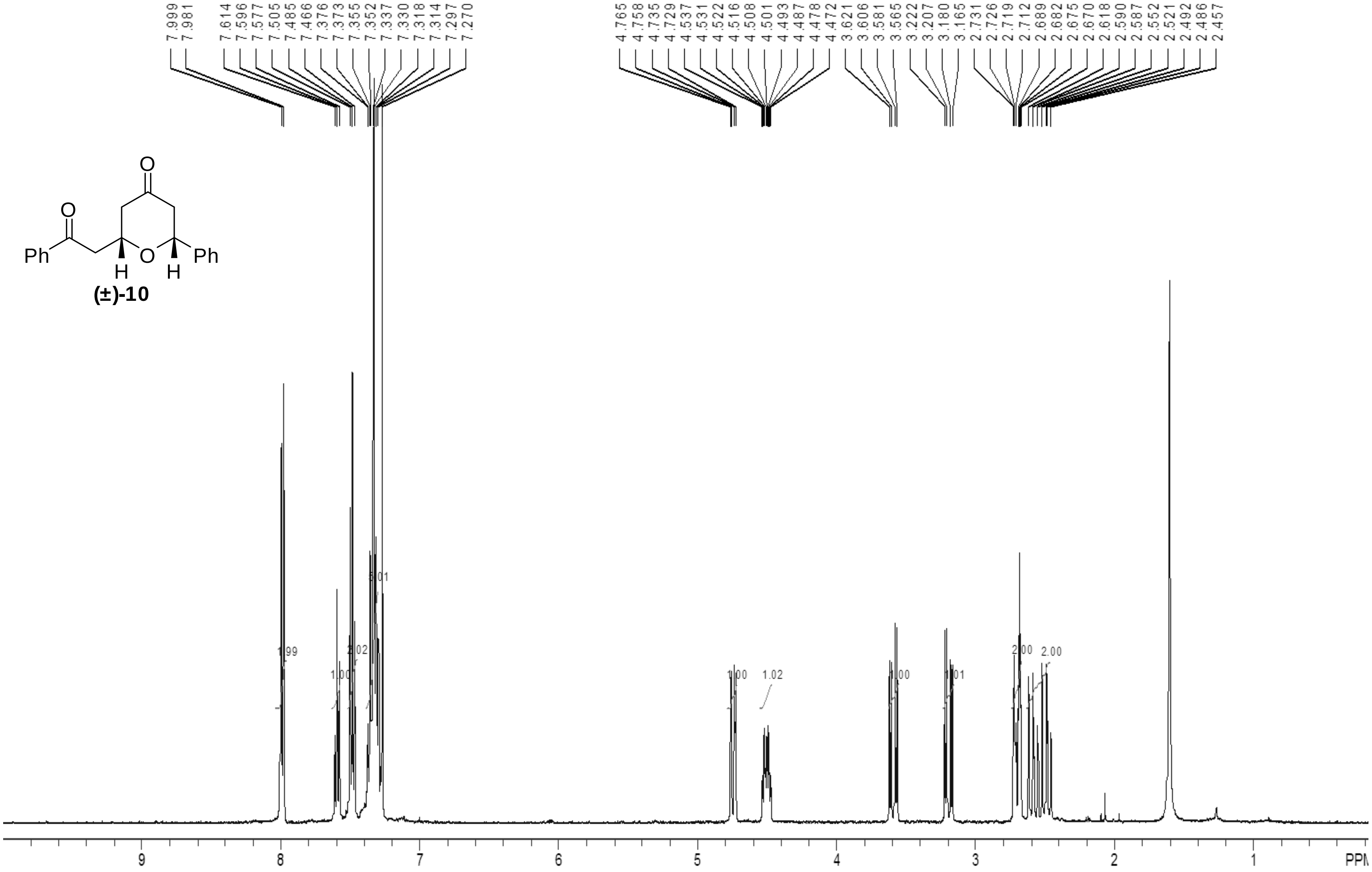
O
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(±)-10

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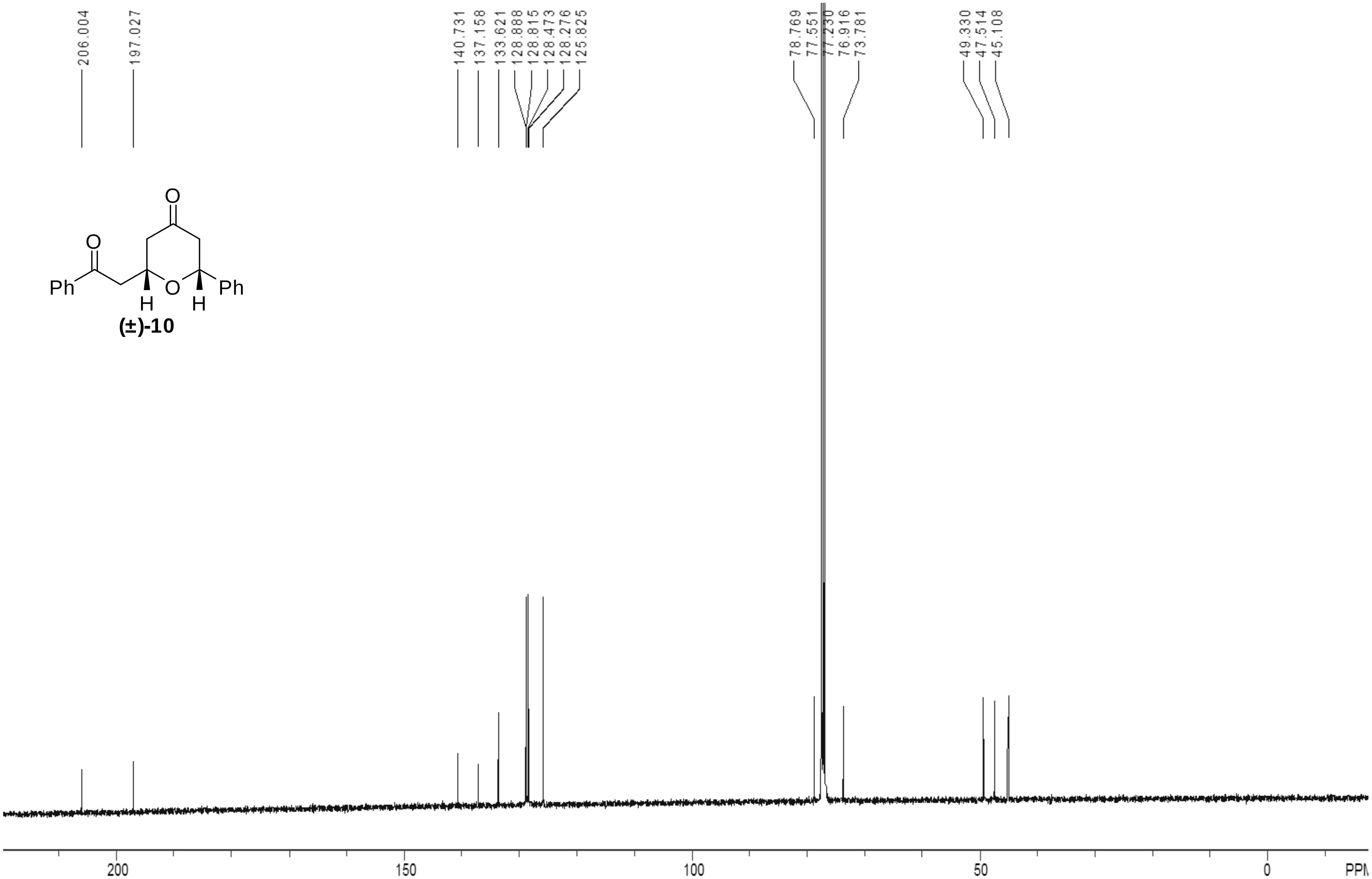
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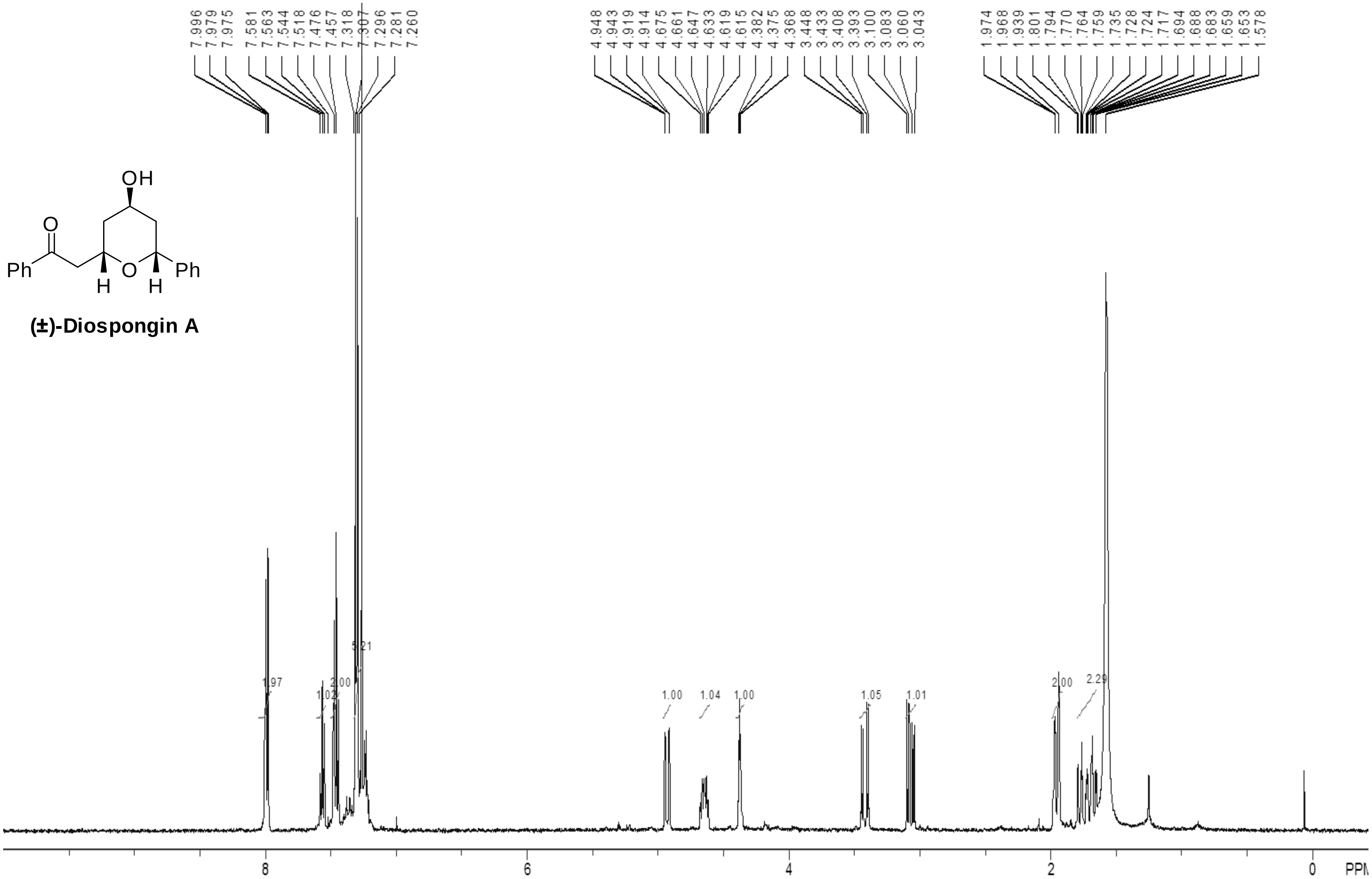
(±)-10



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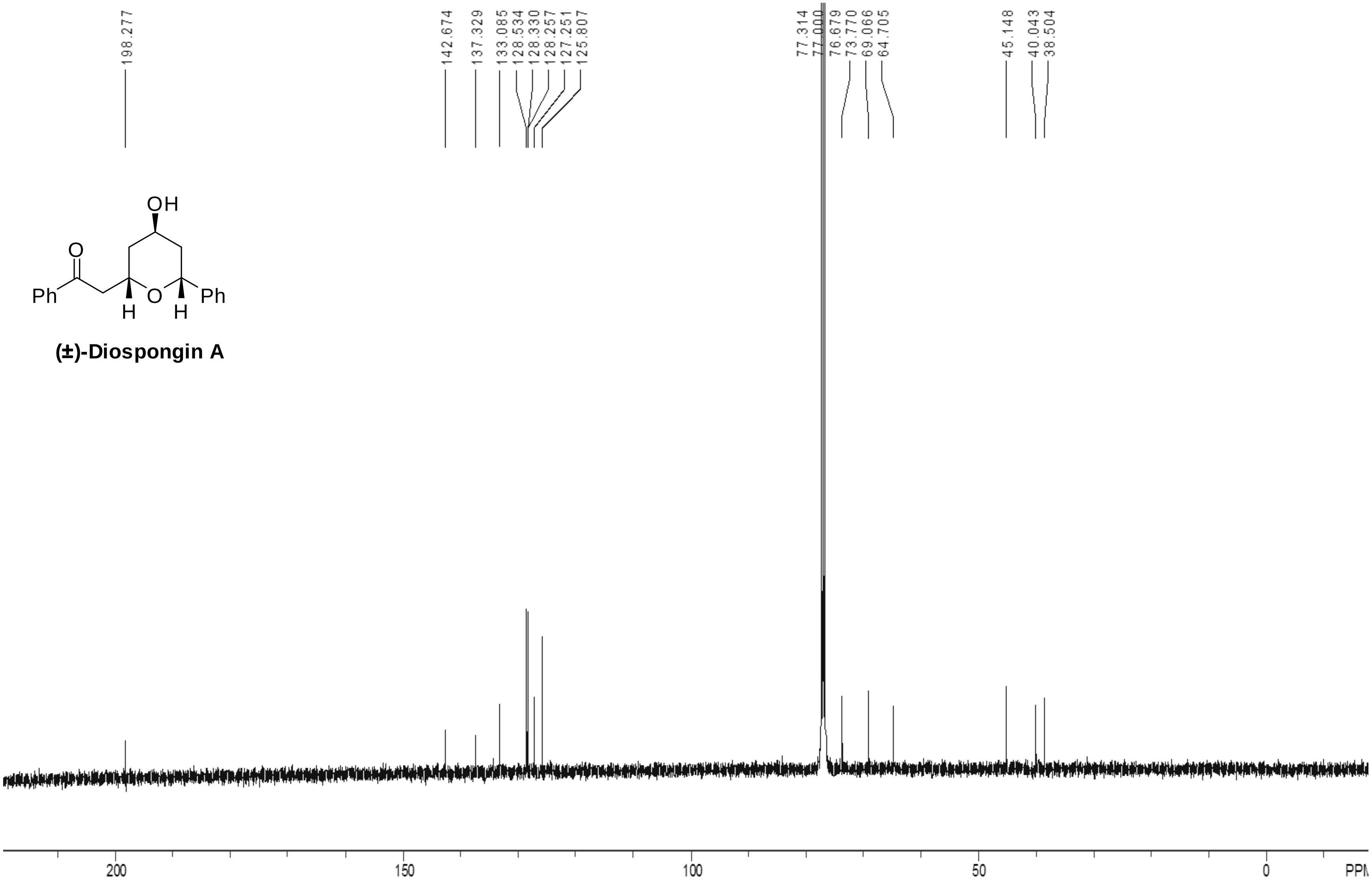

(±)-Diospongin A