Supporting Information: Experimental Part

# Expedient Synthesis of *syn*-β-Hydroxy-α-amino acid derivatives: Phenylalanine, Tyrosine, Histidine and Tryptophan.

David Crich* and Abhisek Banerjee

*Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061*

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**General.** Unless otherwise stated $^{1}H$ and $^{13}C$ NMR were recorded in $CDCl_3$ solution. Optical rotations were recorded in $CHCl_3$ solutions, unless otherwise stated. All organic extracts were dried over sodium sulfate, and concentrated under aspirator vaccum. Chromatographic purifications were carried out over silica gel.

**1. General procedure for the synthesis of di-*N*-*tert*-butoxycarbonyl α-amino acids.**[1,2]

To a suspension of α-amino acid methyl ester hydrochloride in THF: water (2: 1), $Na_2CO_3$ was added portion wise. At 0 $^{o}C$, $(Boc)_2O$ (2 equiv.) was added and the reaction mixture was stirred at room temperature for 2 h. The organic layer was extracted with ethyl acetate and washed with saturated $NH_4Cl$ solution, water and brine. Then the organic layer was dried and concentrated. A solution of the concentrate and DMAP (1 equiv.) in $CH_3CN$ was treated with $(Boc)_2O$ (3 equiv.) and stirred at room temperature for

12 h. Then the reaction mixture was concentrated. The concentrate was diluted with ethyl acetate and washed with saturated $NH_4Cl$ solution, water and brine. The organic layer was dried and concentrated. Chromatographic purification afforded the di-*N*-*tert*-butoxycarbonyl α-amino acid methyl esters.

***N,N*-di-*tert*-Butoxycarbonyl-L-phenylalanine methyl ester (2).**[3] Following the general procedure 1, and eluting with 8% ethyl acetate in hexane, **2** was obtained in quantitative yield. $[\alpha]^{22}_D$ -90.3 (*c* 0.7); $^1$H NMR (400 MHz) δ: 7.27-7.15 (m, 5H), 5.16-5.12 (dd, *J* = 5.6, 10.4 Hz, 1H), 3.73 (s, 3H), 3.44-3.39 (dd, *J* = 4.4, 14.0 Hz, 1H), 3.23-3.17 (dd, *J* = 10.8, 13.6 Hz), 1.37 (s, 18H); $^{13}$C NMR (100 MHz) δ: 170.9, 151.6, 137.6, 129.6, 128.4, 126.5, 82.9, 59.4, 52.3, 36.2, 27.8.

**(2*R*,3*R*)-3-Bromo-*N,N*-di-*tert*-butoxycarbonyl-L-phenylalanine methyl ester (3).** Following the general procedure 2 with silver carbonate or silver oxide, and eluting with 8% ethyl acetate in hexane, **3** was obtained in 45% yield along with **4** in 48% yield. $[\alpha]^{22}_D$ -165.4 (*c* 1.1); $^1$H NMR (500 MHz) δ: 7.54-7.53 (d, *J* = 7.0 Hz, 2H), 7.36-7.33 (t, *J* = 8.0 Hz, 2H), 7.29-7.26 (t, *J* = 7.0 Hz, 1H), 5.77-5.75 (d, *J* = 10.0 Hz, 1H), 5.69-5.67 (d, *J* = 10.5 Hz, 1H), 3.58 (s, 3H), 1.58 (s, 18H); $^{13}$C NMR (125 MHz) δ: 168.1, 151.7, 141.1, 128.6, 128.5, 128.3, 83.8, 61.6, 53.8, 52.4, 28.1; ESI-HRMS Calcd for $C_{20}H_{28}BrNO_6$ $[M + Na]^+$ : 480.0998. Found 480.0987.

***N*-*tert*-Butoxycarbonyl-(2*S*,3*R*)-β-hydroxy-L-phenylalanine methyl-$D_3$ ester (7).** Following the general procedure of oxazolidinone hydrolysis in MeOH-$D_4$, and eluting with 20% ethyl acetate in hexane, **7** was obtained in 76% yield. $[\alpha]^{25}_D$ -15.4 (*c* 0.7); $^1$H NMR (400 MHz) δ: 7.36-7.26 (m, 5H), 5.27 (bs, 1H), 5.21 (bs, 1H), 4.53-4.51 (d, *J* = 7.2

Hz, 1H), 3.11 (bs, 1H), 1.31 (s, 9H); $^{13}$C NMR (100 MHz) δ: 171.5, 155.6, 139.8, 128.3, 128.0, 126.0, 80.1, 73.84, 73.78, 59.4, 28.2.

***N-tert*-Butoxycarbonyl-(2*S*,3*S*)-β-hydroxy-L-phenylalanine methyl ester (8).**[4] Following the general procedure of oxazolidinone hydrolysis at 0 $^{o}$C, and eluting with 20% ethyl acetate in hexane, **8** was obtained in 79% yield. $[\alpha]^{25}_{D}$ +83.0 (*c* 0.8); $^{1}$H NMR (400 MHz) δ:7.35-7.24 (m, 5H), 5.30-5.29 (d, , *J* = 6.8 Hz, 1H), 5.17 (bs, 1H), 4.72-4.70 (dd, *J* = 3.6, 7.6 Hz, 1H), 4.00-3.99 (d, *J* = 5.6 Hz, 1H), 3.69 (s, 3H), 1.43 (s, 9H); $^{13}$C NMR (100 MHz) δ: 170.3, 156.4, 139.2, 128.3, 128.1, 126.0, 80.7, 75.1, 59.7, 52.4, 28.2.

**Methyl (4*S*,5*R*)-5-phenyl-1,3-oxazolidin-2-oxo-4-carboxylate (9)** and **Methyl (4*S*,5*S*)-5-phenyl-1,3-oxazolidin-2-oxo-4-carboxylate (10).**[5] Following the general procedure of oxazolidinone formation with silver trifluoromethanesulfonate and eluting with 40-44% ethyl acetate in hexane **9** and **10** were obtained in 10: 1 ratio and 55% yield. **9**: $[\alpha]^{22}_{D}$ +46.4 (*c* 1.4); $^{1}$H NMR (400 MHz) δ:7.41-7.36 (m, 5H), 6.87 (bs, 1H), 5.64-5.63 (d, *J* = 5.2 Hz, 1H), 4.31-4.30 (d, *J* = 4.8 Hz, 1H), 3.84 (s, 3H); $^{13}$C NMR (100 MHz) δ:170.2, 158.6, 138.1, 129.2, 129.0, 125.4, 79.4, 61.4, 53.2. **10**: $[\alpha]^{24}_{D}$ +119.3 (*c* 1.0); $^{1}$H NMR (500 MHz) δ:7.38-7.35 (m, 3H), 7.32-7.26 (dd, *J* = 2.5, 7.5 Hz, 2H), 6.68 (bs, 1H), 5.87-5.85 (d, *J* = 9.0 Hz, 1H), 4.73-4.71 (d, *J* = 9.5 Hz, 1H), 3.22 (s, 3H); $^{13}$C NMR (125 MHz) δ:169.0, 160.0, 133.7, 129.4, 128.5, 128.3, 126.2, 79.6, 60.1, 52.2.

**General procedure for the preparation of 4 and 5 from 9 and 10.**

A solution of the **9** or **10** and DMAP (1 equiv.) in $CH_2Cl_2$ was treated with $(Boc)_2O$ (1.5 equiv.) and stirred at room temperature for 30 mins. Then the reaction mixture was concentrated. The concentrate was diluted with ethyl acetate and washed with saturated

$NH_4Cl$ solution, water and brine. The organic layer was dried and concentrated. Chromatographic purification afforded the **4** or **5** in quantitative yield.

***N,N*-di-*tert*-Butoxycarbonyl-*O-tert*-butoxycarbonyl-L-tyrosine methyl ester (12).** Following the general procedure 1, and eluting with 10% ethyl acetate in hexane, **12** was obtained in quantitative yield. $[\alpha]^{22}_D$ -79.4 (*c* 1.0); $^1$H NMR (500 MHz) δ:7.17-7.15 (d, *J* = 8.5 Hz, 2H), 7.06-7.04 (d, *J* = 8.5 Hz, 2H), 5.13-5.10 (dd, *J* = 5.0, 10.0 Hz, 1H), 3.72 (s, 3H), 3.42-3.38 (dd, *J* = 5.0, 14.0 Hz, 1H), 3.20-3.15 (dd, *J* = 10.0, 14.5 Hz, 1H), 1.52 (s, 9H), 1.37 (s, 18H); $^{13}$C NMR (125 MHz) δ: 170.7, 151.7, 151.6, 149.8, 135.1, 130.4, 121.1, 83.3, 83.1, 59.2, 52.3, 35.6, 27.8, 27.7; ESI-HRMS Calcd for $C_{25}H_{37}NO_9$ $[M + Na]^+$ : 518.2366. Found 518.2355.

***N,N*-di-*tert*-Butoxycarbonyl-4-$N^{im}$-*tert*-butoxycarbonyl-L-hystidine methyl ester (18).**[2] To a solution of the **17**[1] (1.85 g, 5 mmol) and DMAP (0.61 g, 5 mmol)) in $CH_3CN$ (10 mL) was treated with $(Boc)_2O$ (3.38 g, 15 mmol) and stirred at room temperature for 12 h. Then the reaction mixture was concentrated. The concentrate was diluted with ethyl acetate and washed with saturated $NH_4Cl$ solution, water and brine. The organic layer was dried and concentrated. Chromatographic purification using 24% ethyl acetate in hexane afforded **18** (2.35 g, quant.). $[\alpha]^{22}_D$ -60.3 (*c* 0.7); $^1$H NMR (400 MHz) δ: 7.96 (s, 1H), 7.10 (s, 1H), 5.30-5.27 (dd, *J* = 5.2, 9.6 Hz, 1H), 3.73 (s, 3H), 3.43-3.39 (dd, *J* = 4.8, 14.8 Hz, 1H), 3.16-3.10 (dd, *J* = 5.2, 14.4 Hz, 1H), 1.58 (s, 9H), 1.44 (s, 18H); $^{13}$C NMR (100 MHz) δ: 170.8, 151.7, 147.0, 139.8, 136.6, 114.4, 85.3, 83.0, 57.5, 52.3, 29.2, 27.9; ESI-HRMS Calcd for $C_{22}H_{35}N_3O_8$ $[M + Na]^+$ : 492.2322. Found 492.2311.

**Preparation of 21 from 20.** A solution of **20** (0.21 g, 0.51 mmol) in methanol (5 mL) at 0 $^oC$ was treated with $Cs_2CO_3$ (0.01 g, 0.03 mmol) and stirred at the same temperature for

1 h. Then the reaction mixture was concentrated and the concentrate was diluted with ethyl acetate and washed with saturated $NH_4Cl$ solution, water and brine. The organic layer was dried and concentrated. Chromatographic purification using 4% MeOH in $CHCl_3$ afforded **21** (0.15 g, 72%).

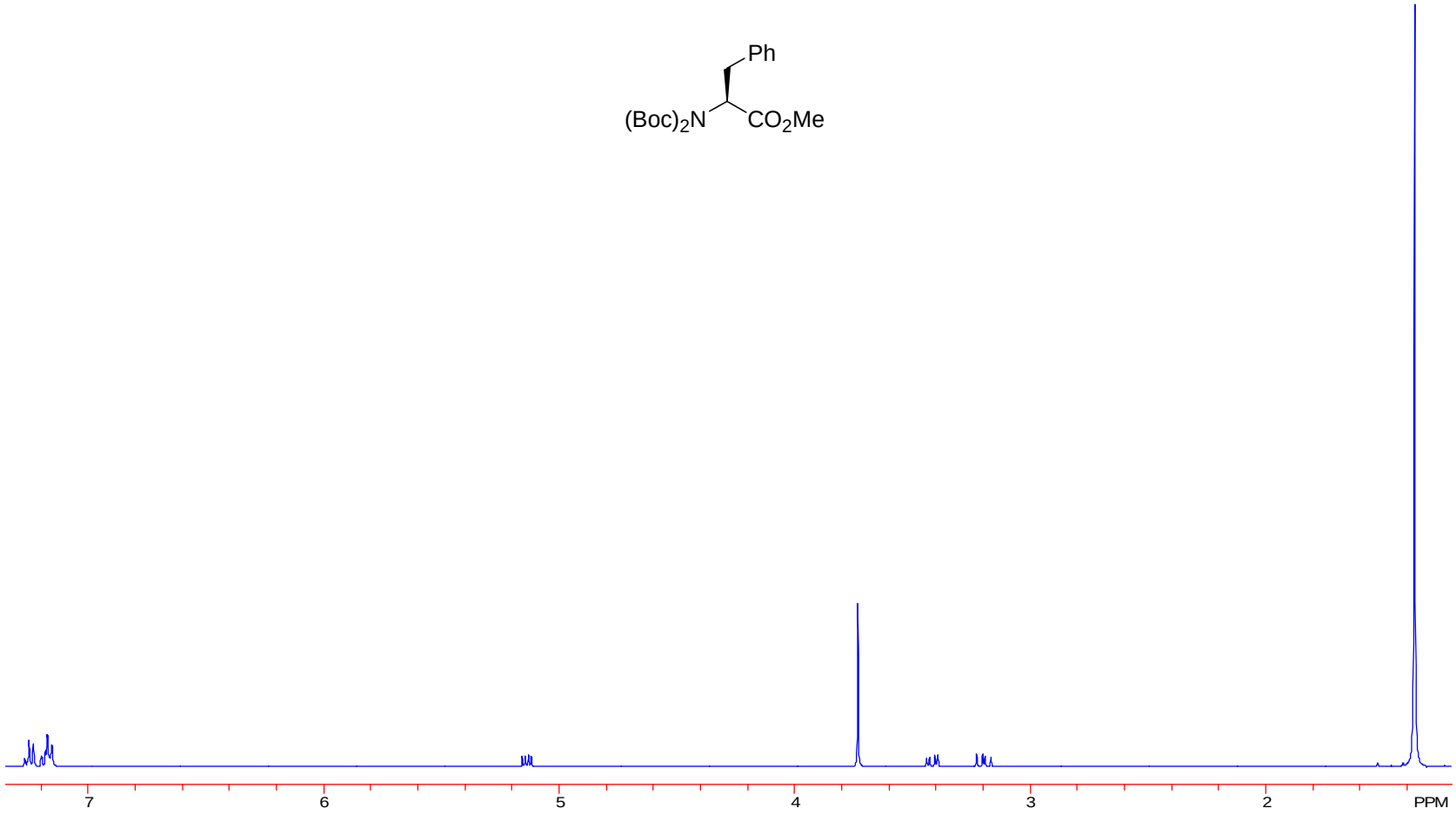
***N-tert*-Butoxycarbonyl-2,3-didehydro-L-hystidine methyl ester (22).** $^1$H NMR (400 MHz) δ: 7.66 (s, 1H), 7.16 (s, 1H), 6.66 (bs, 1H), 3.80 (s, 3H), 1.44 (s, 9H); $^{13}$C NMR (100 MHz) δ:166.4, 154.0, 135.8, 126.0, 114.1, 113.9, 81.0, 52.3, 28.2; ESI-HRMS Calcd for $C_{12}H_{17}N_3O_4$ $[M + Na]^+$ : 290.1117. Found 290.1115.

***N,N*-di-*tert*-Butoxycarbonyl-$N^{in}$-*tert*-butoxycarbonyl-L-tryptophan methyl ester (25).**[3] Following the general procedure 1, and eluting with 8% ethyl acetate in hexane, **25** was obtained in quantitative yield. $[\alpha]^{22}_D$ -75.5 (*c* 0.9); $^1$H NMR (400 MHz) δ:8.11-8.09 (d, *J* = 7.2 Hz, 1H), 7.52-7.50 (d, *J* = 8.0 Hz, 1H), 7.38 (s, 1H), 7.29-7.26 (t, *J* = 7.6 Hz, 1H), 7.22-7.18 (t, *J* = 7.2 Hz, 1H), 5.22-5.18 (dd, *J* = 4.8, 9.6 Hz, 1H), 3.75 (s, 3H), 3.53-3.49 (dd, *J* = 4.8, 14.4 Hz, 1H), 3.39-3.32 (dd, *J* = 9.6, 14.0 Hz, 1H), 1.63 (s, 9H), 1.31 (s, 18H); $^{13}$C NMR (100 MHz) δ:170.8, 151.7, 149.5, 135.4, 130.5, 124.3, 124.2, 122.5, 118.9, 116.4, 115.2, 83.4, 82.9, 58.2, 52.3, 28.1, 27.7, 25.6.

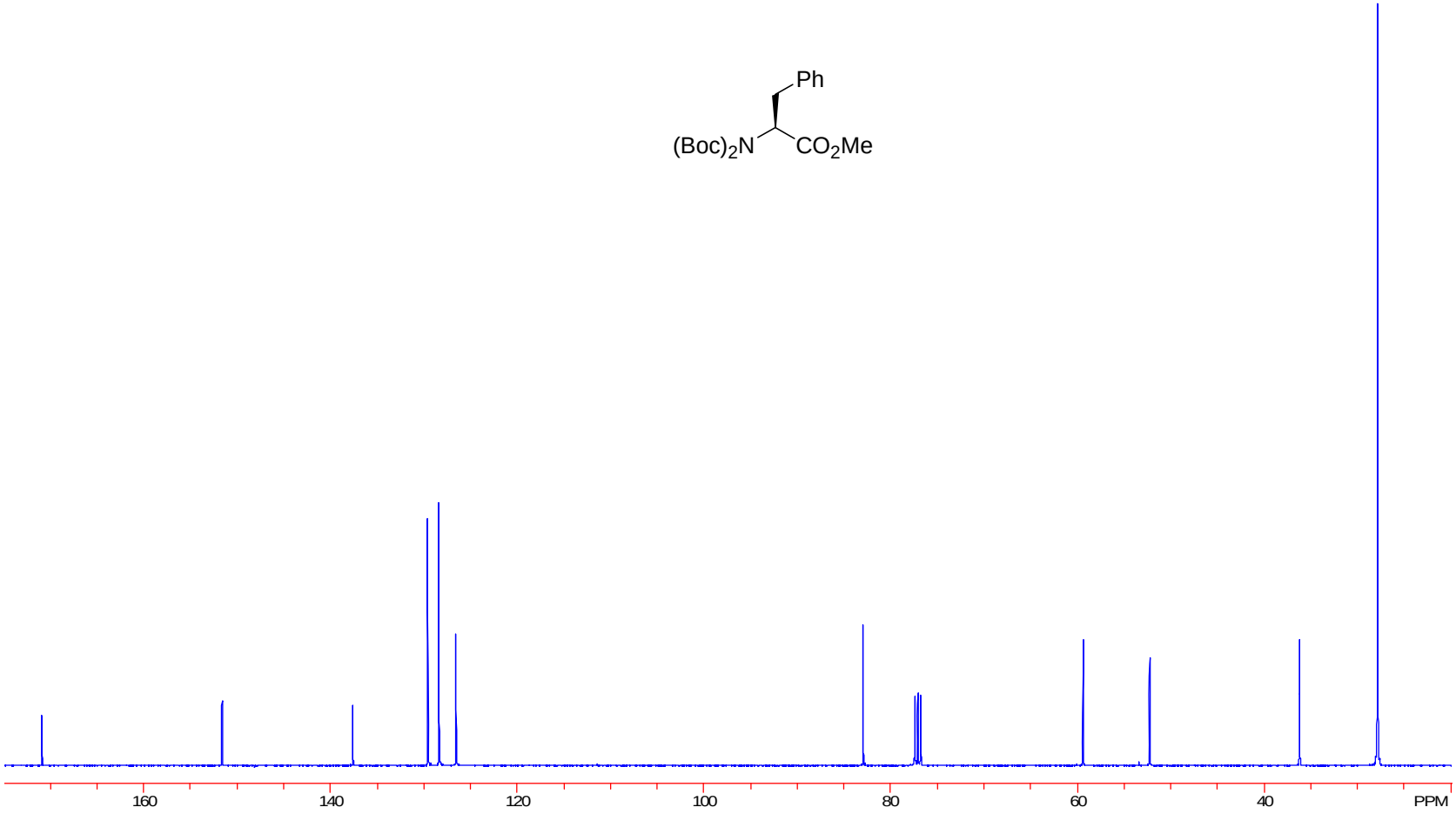
**References.**


1. Xu, J.; Yadan, J. C. *J. Org. Chem.* **1995**, *60*, 6296.
2. (a) Kokotos, G.; Padron, J. M.; Martin, T.; Gibbons, W. A.; Martin, V. S. *J. Org. Chem.* **1998**, *63*, 3741. (b) Padron, J. M.; Kokotos, G.; Martin, T.; Markidis, T.; Gibbons, W. A.; Martin, V. S. *Tetrahedron: Asymmetry* **1998**, *9*, 3381.
3. Mohapatra, D. K.; Durugkar, K. A. *ARKIVOC* **2005**, *xiv*, 20.
4. Miyata, O.; Asai, H.; Naito, T. *Chem. Pharm. Bull.* **2005**, *53*, 355.
5. (a) Hamersak, Z.; Sepac, D.; Ziher, D.; Sunjic, V. Synthesis **2003**, 375. (b) Tomashini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153.

**_N,N_-di-_tert_-Butoxycarbonyl-L-phenylalanine methyl ester (2)**



**_N,N_-di-_tert_-Butoxycarbonyl-L-phenylalanine methyl ester (2)**



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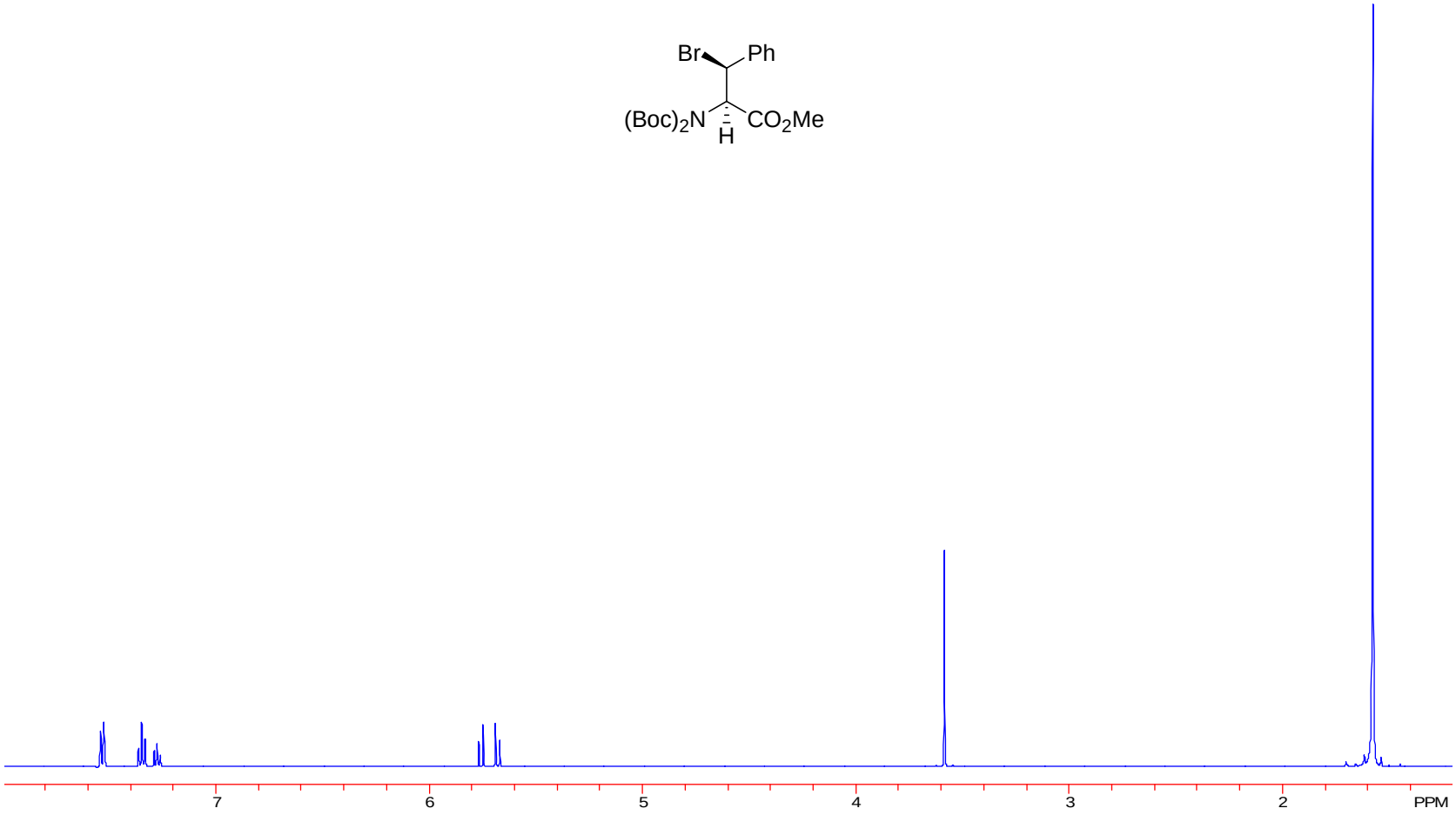

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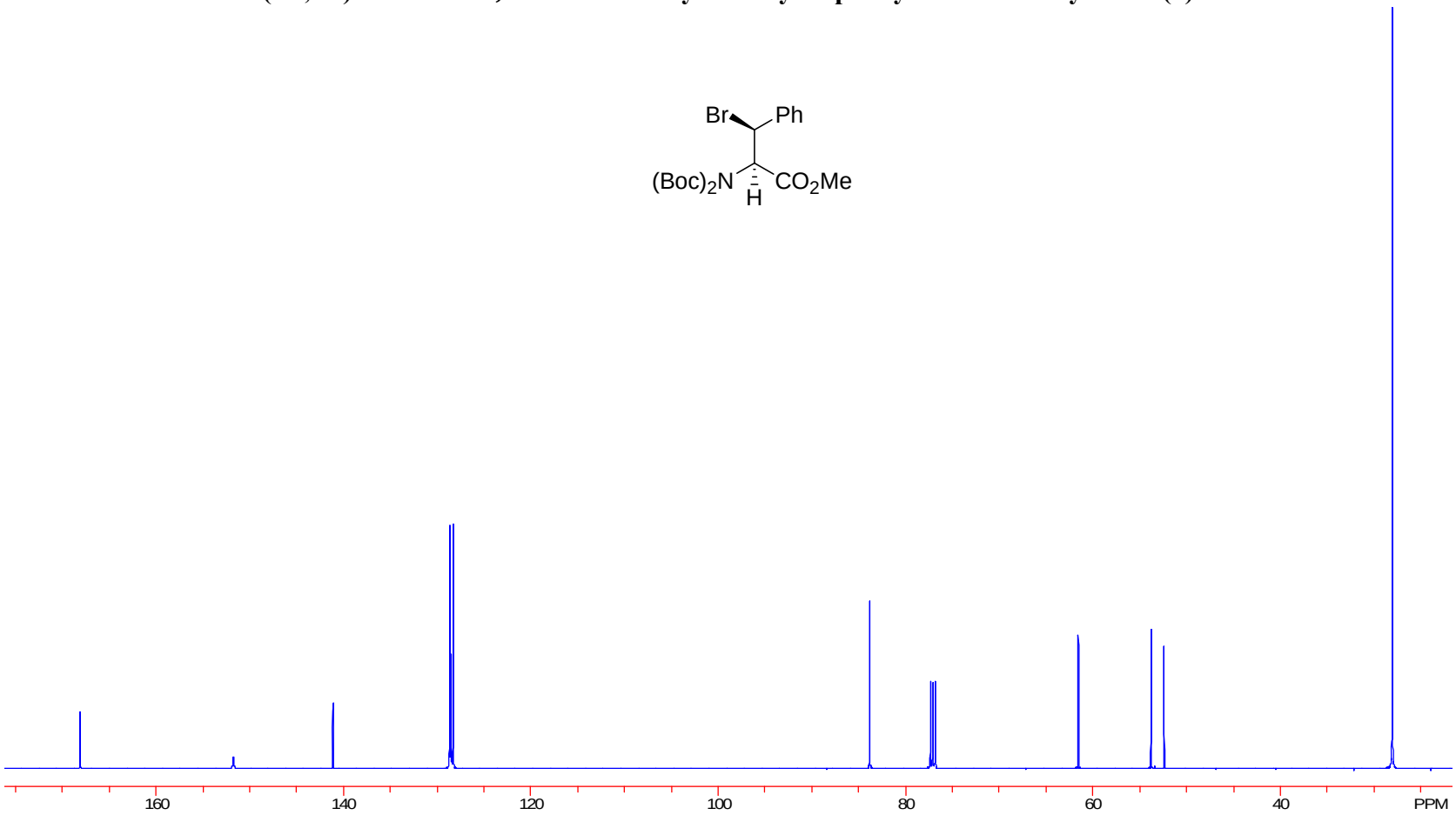
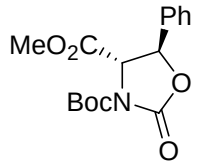


**Methyl (4*S*,5*R*)-3-*N*-*tert*-butoxycarbonyl-5-phenyl-1,3-oxazolidin-2-oxo-4-carboxylate (4)**



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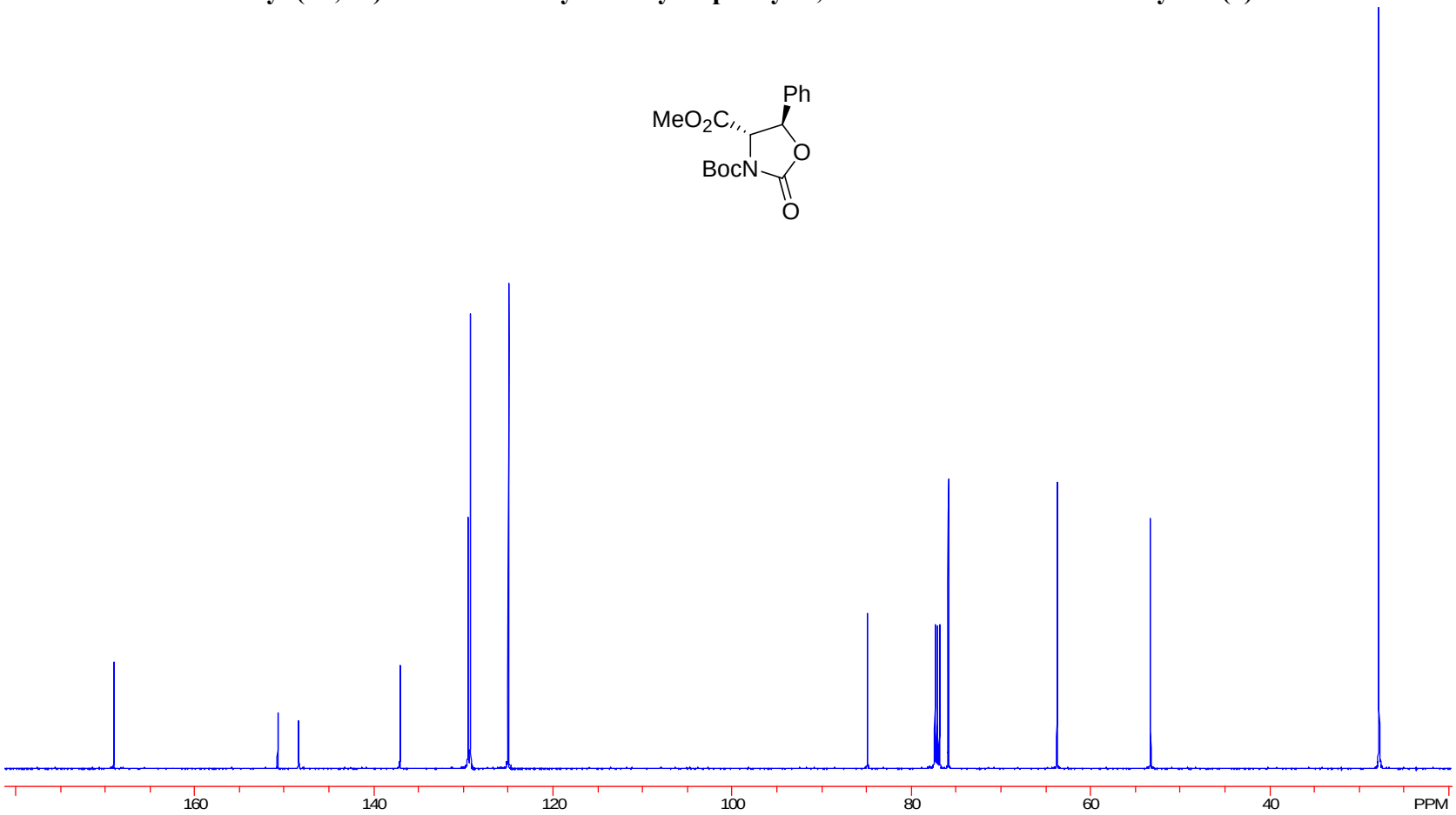

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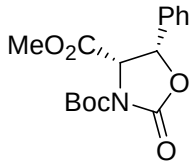

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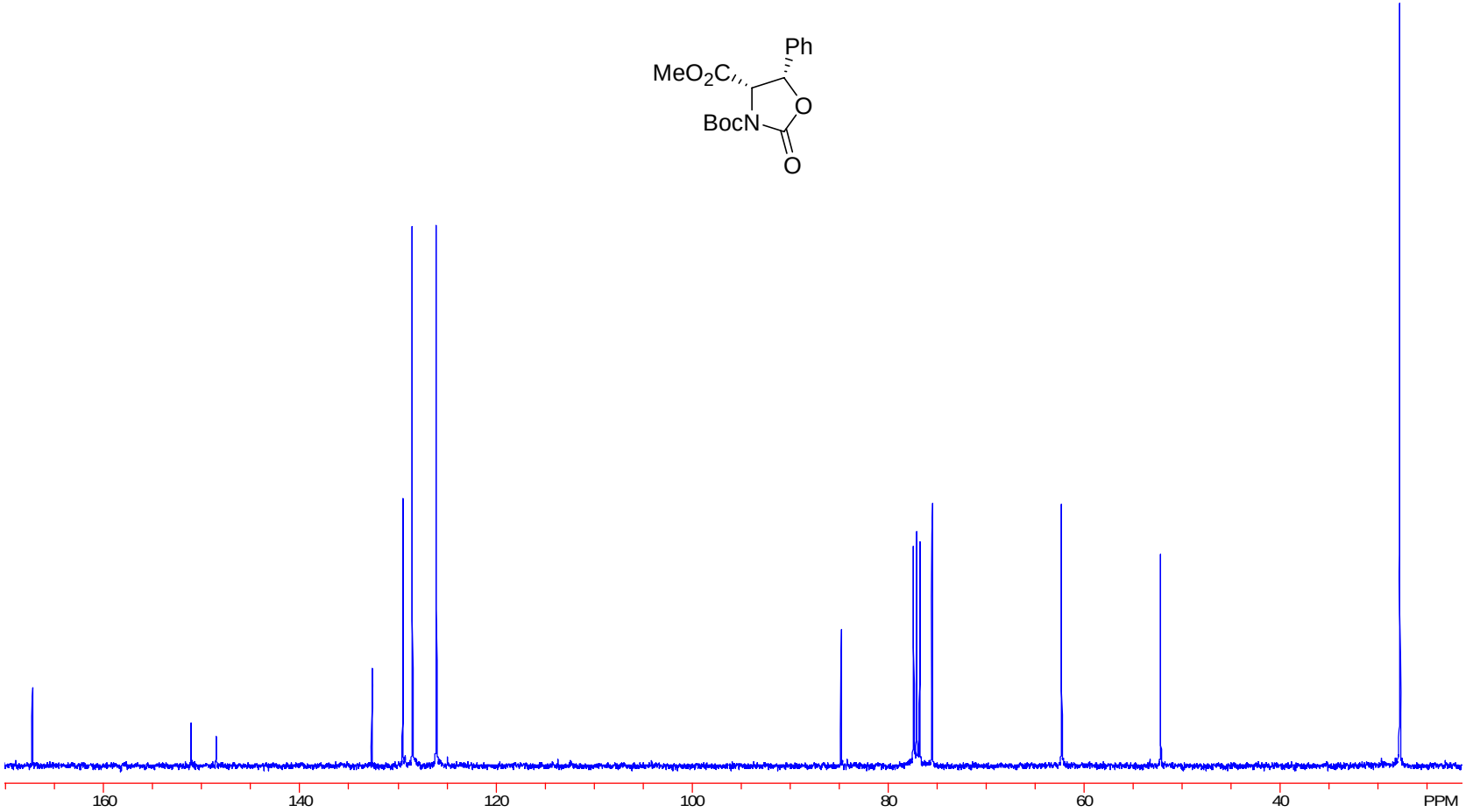

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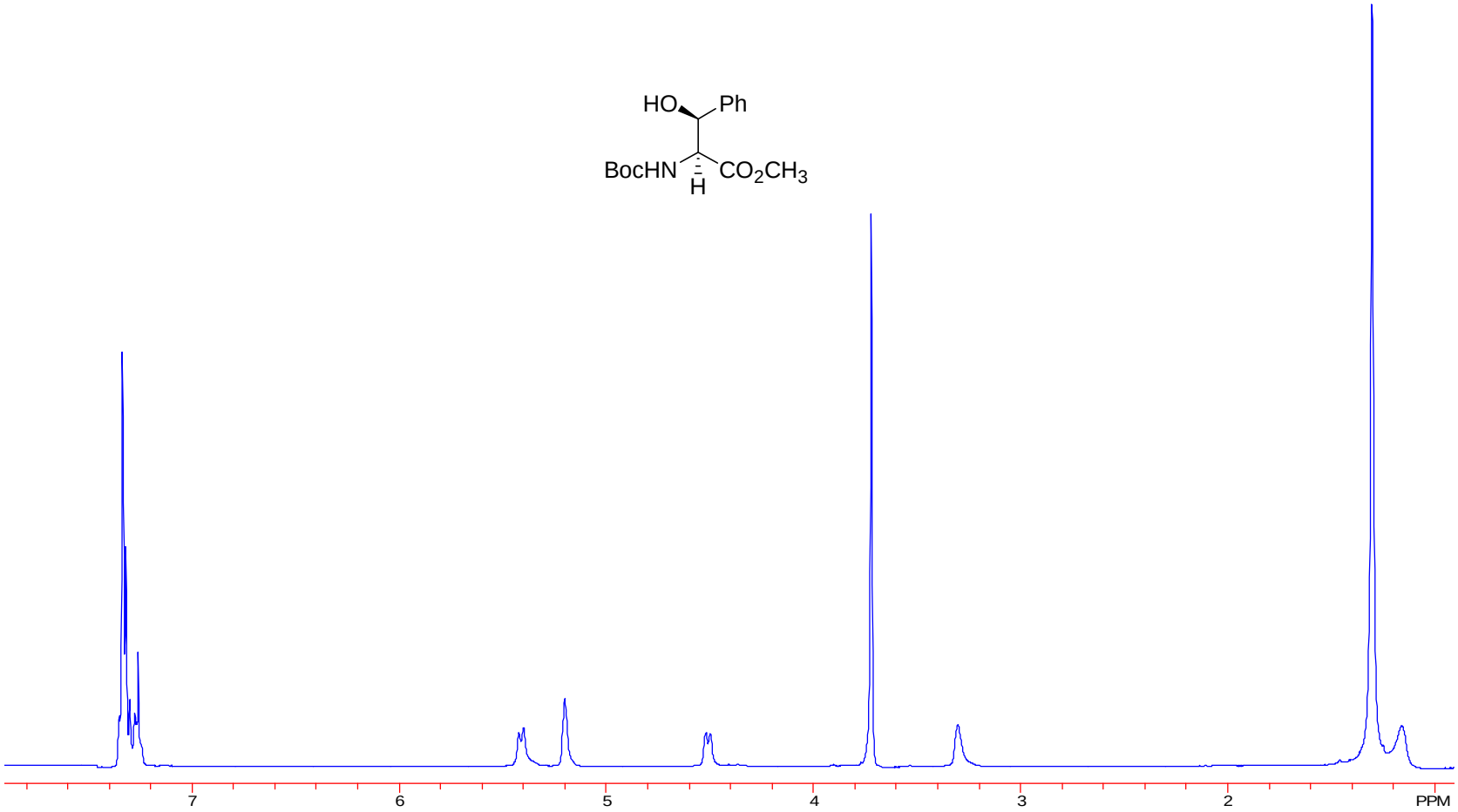

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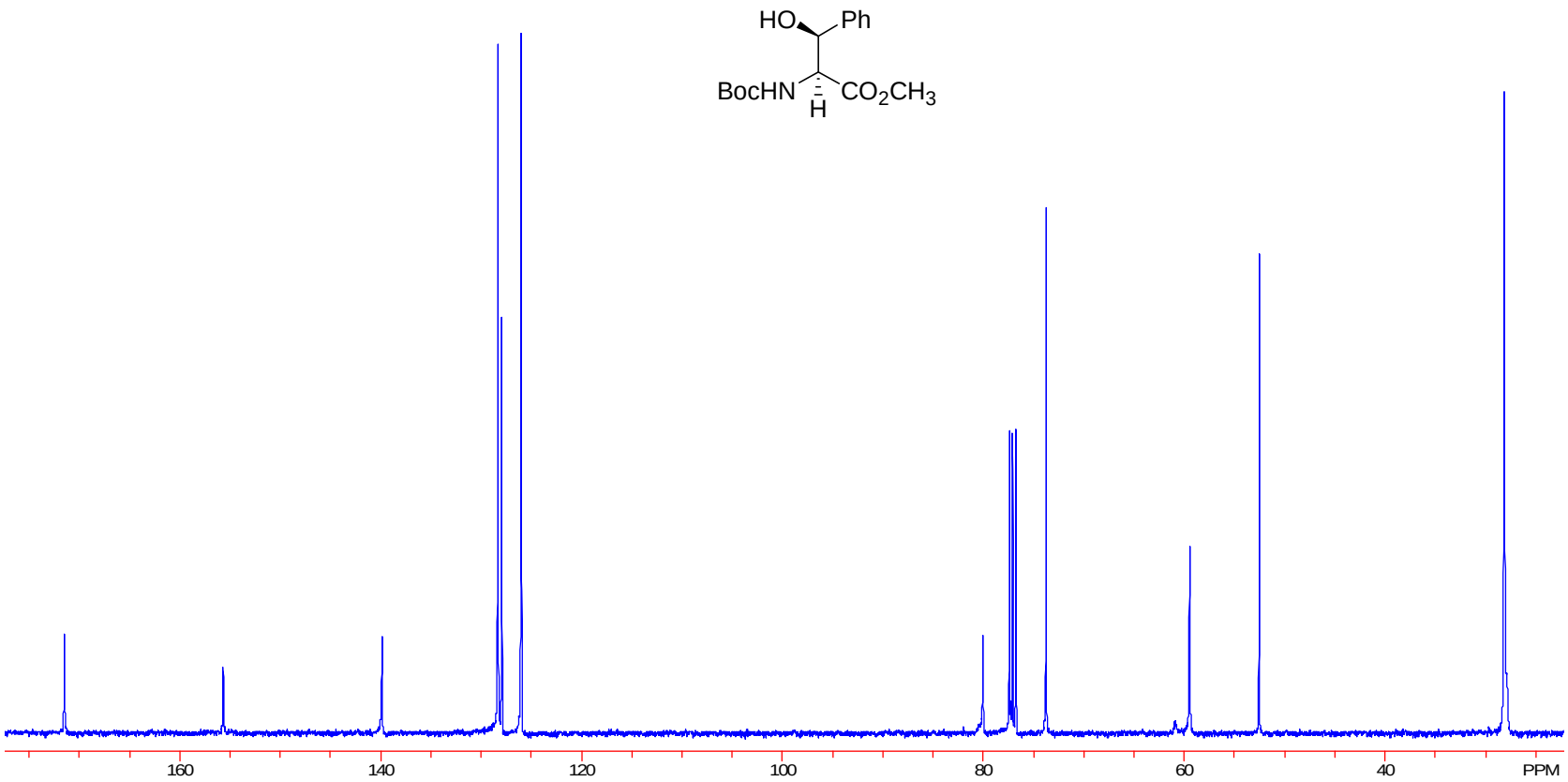

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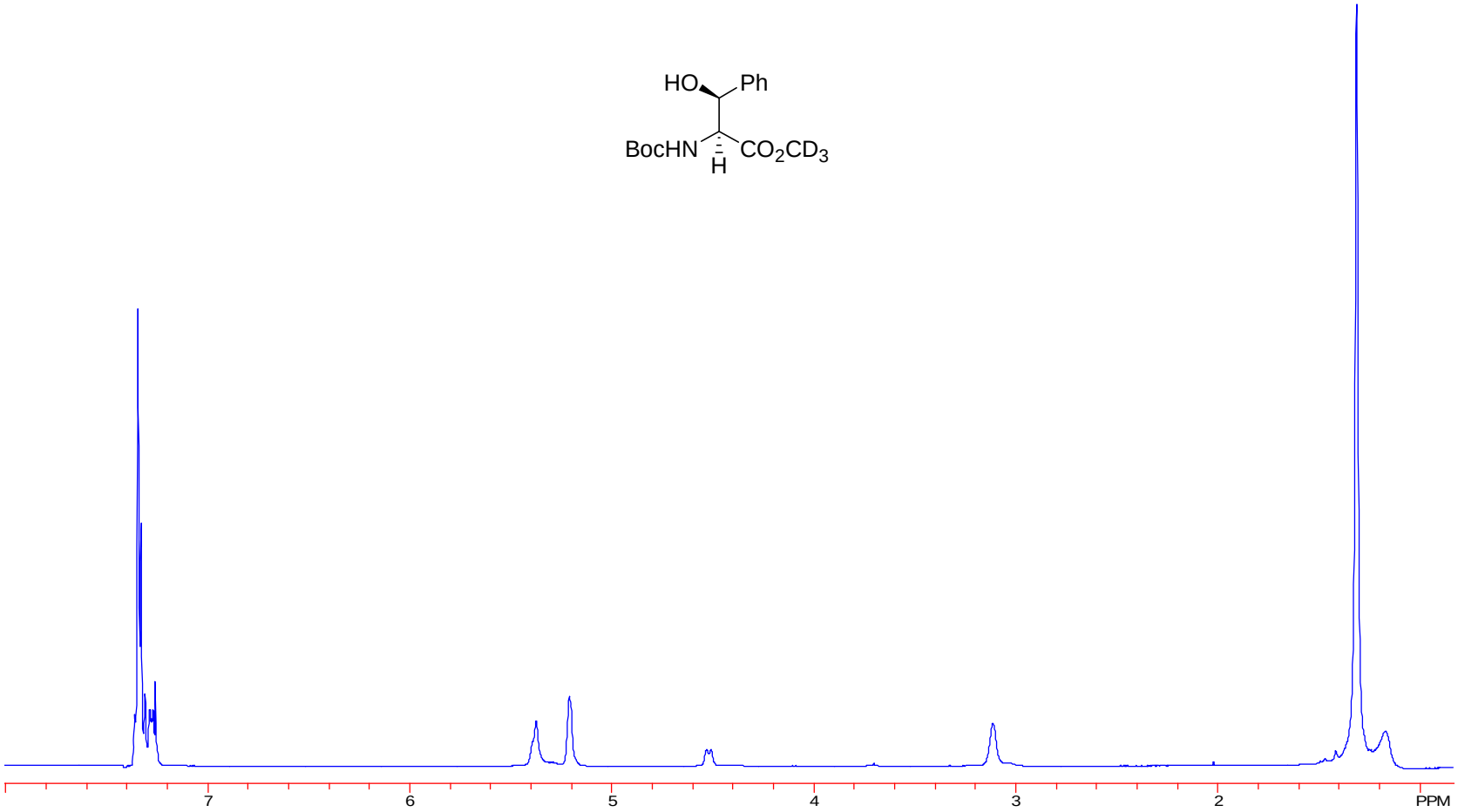

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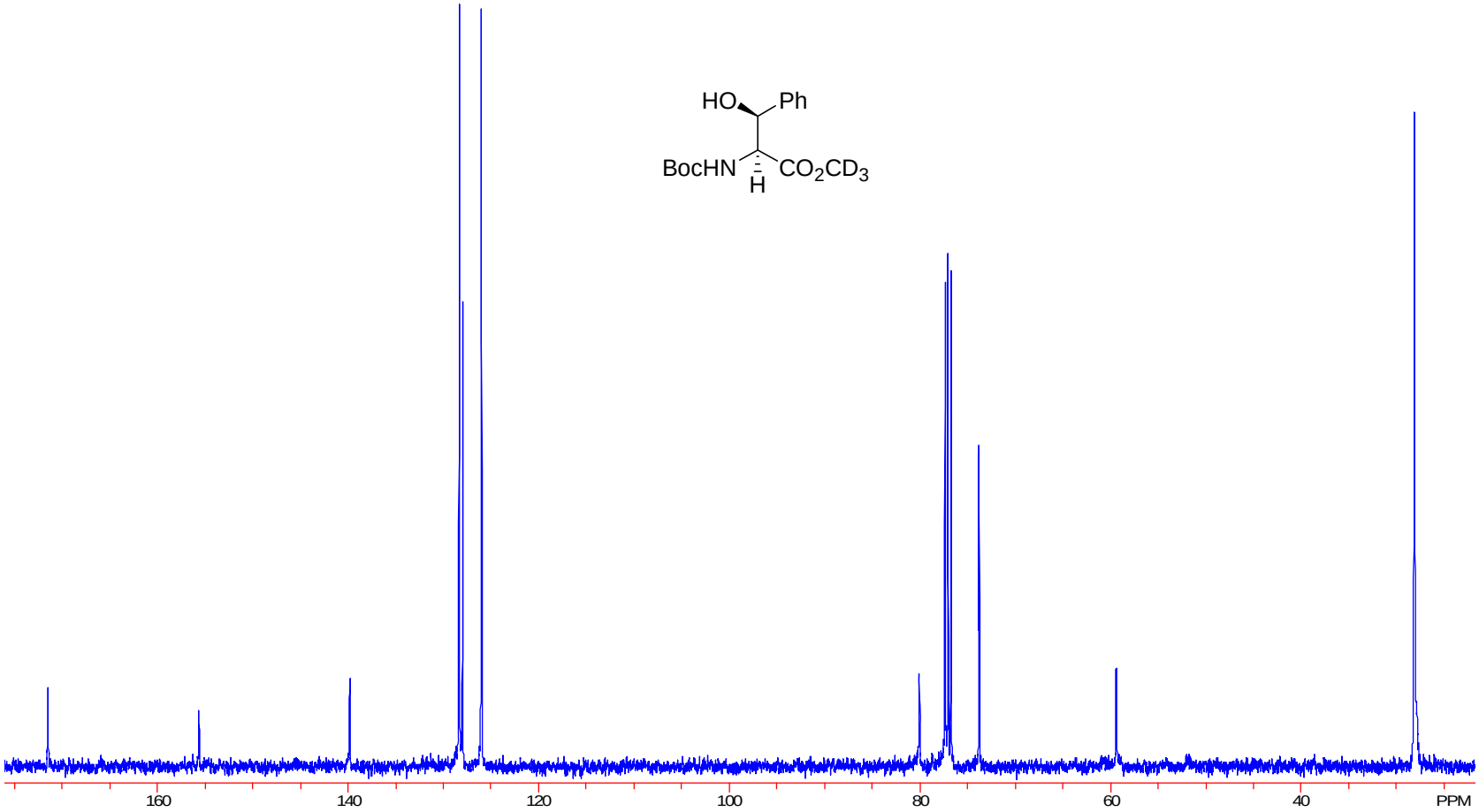

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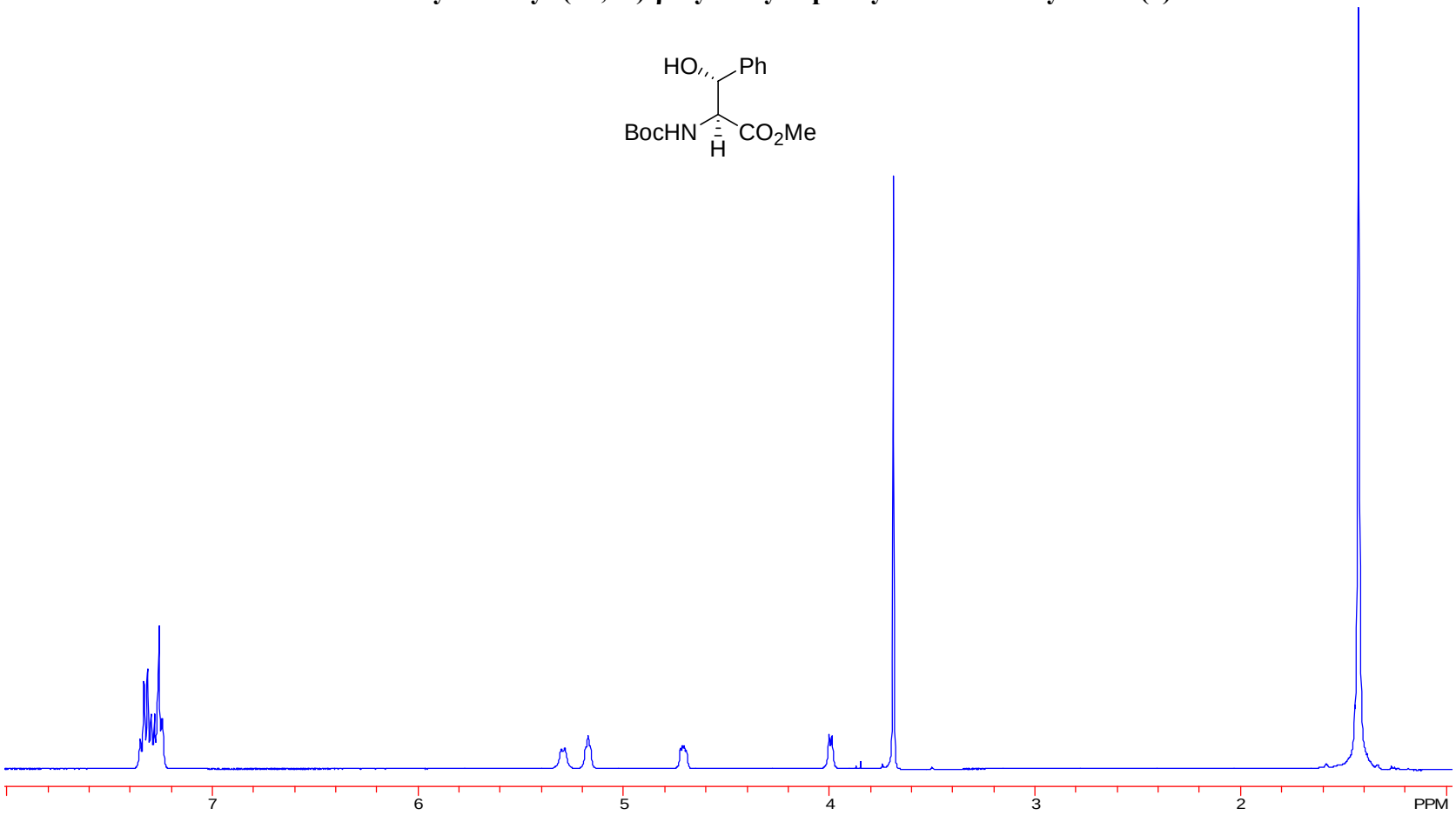

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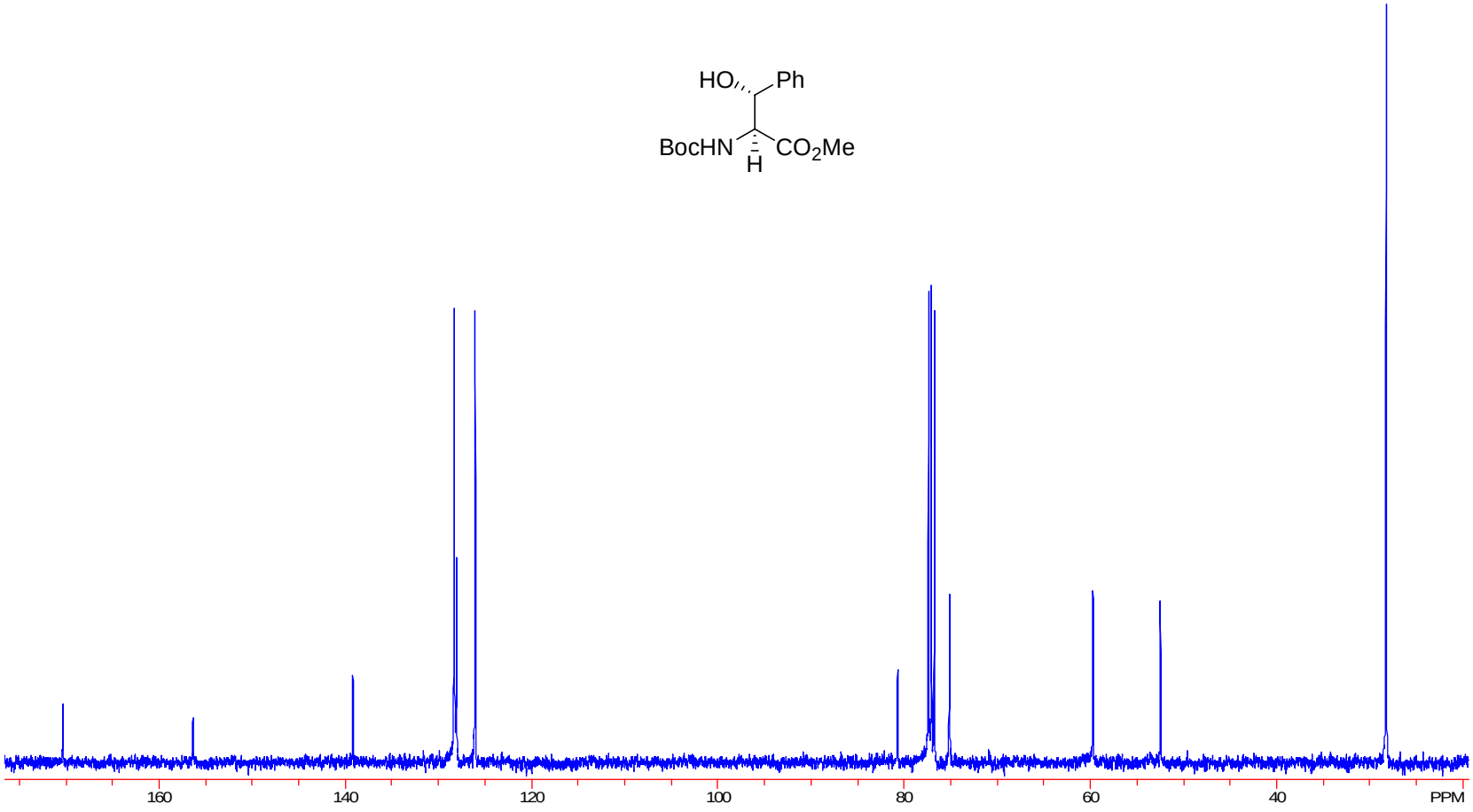
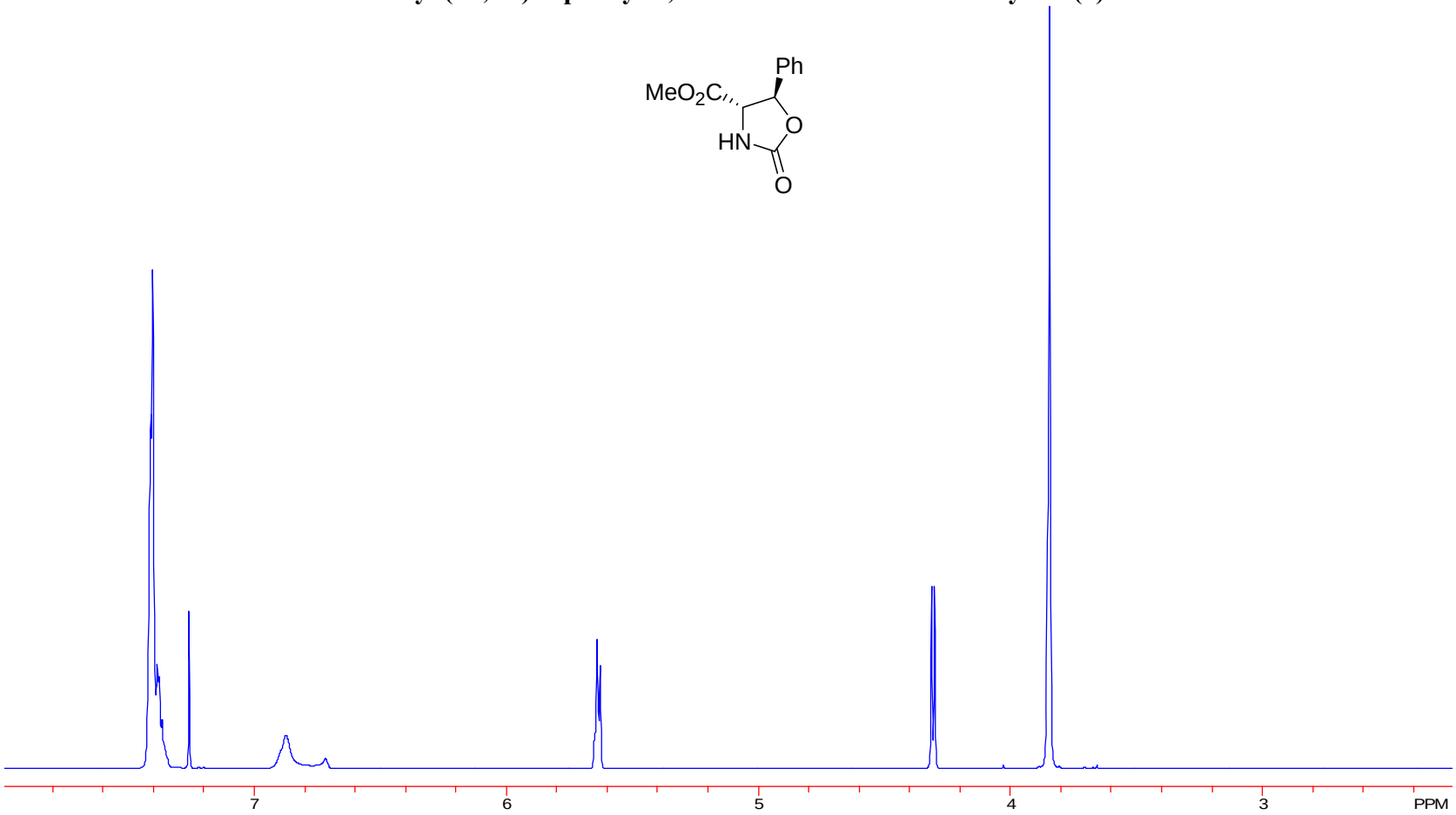


**Methyl (4*S*,5*R*)-5-phenyl-1,3-oxazolidin-2-oxo-4-carboxylate (9)**



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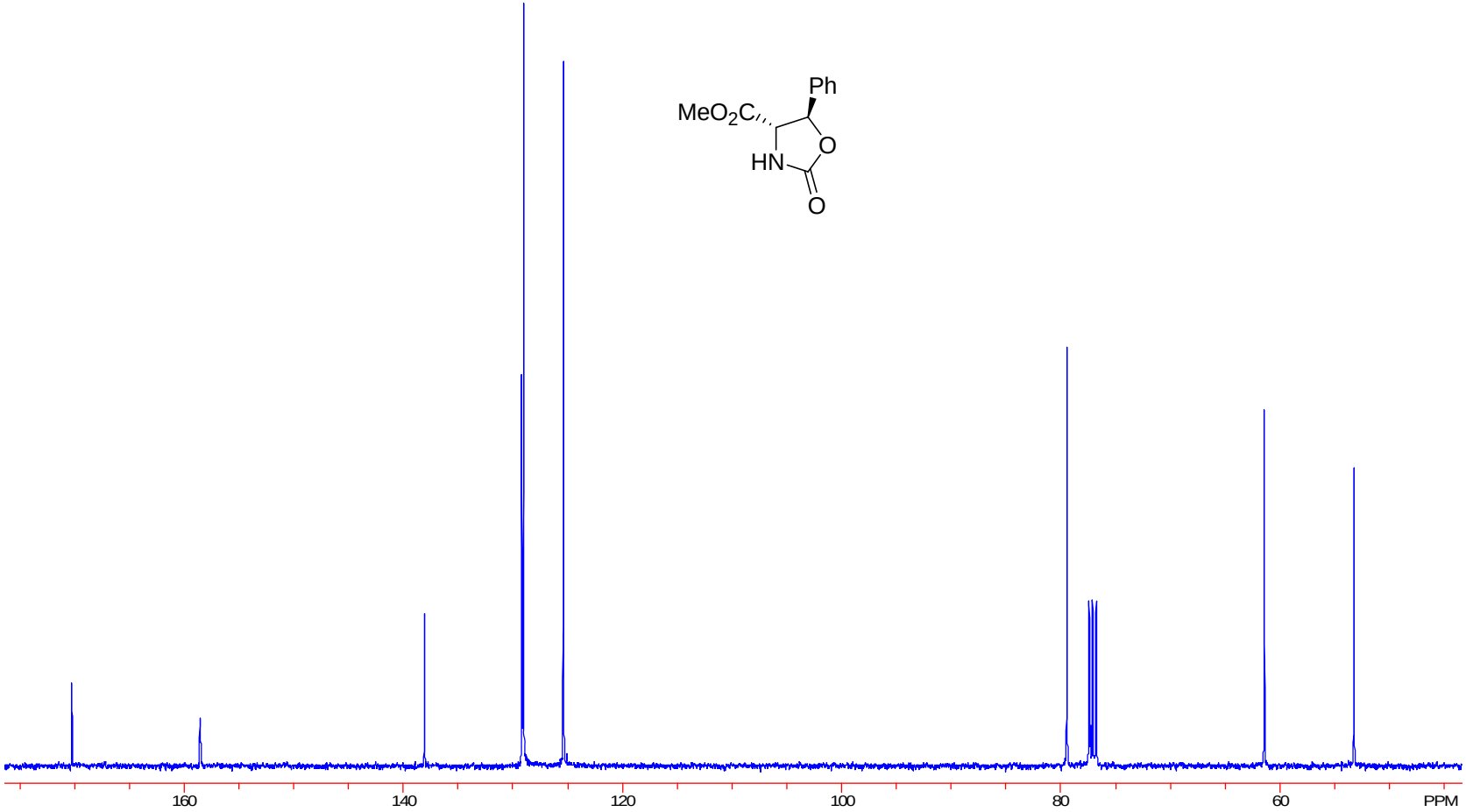

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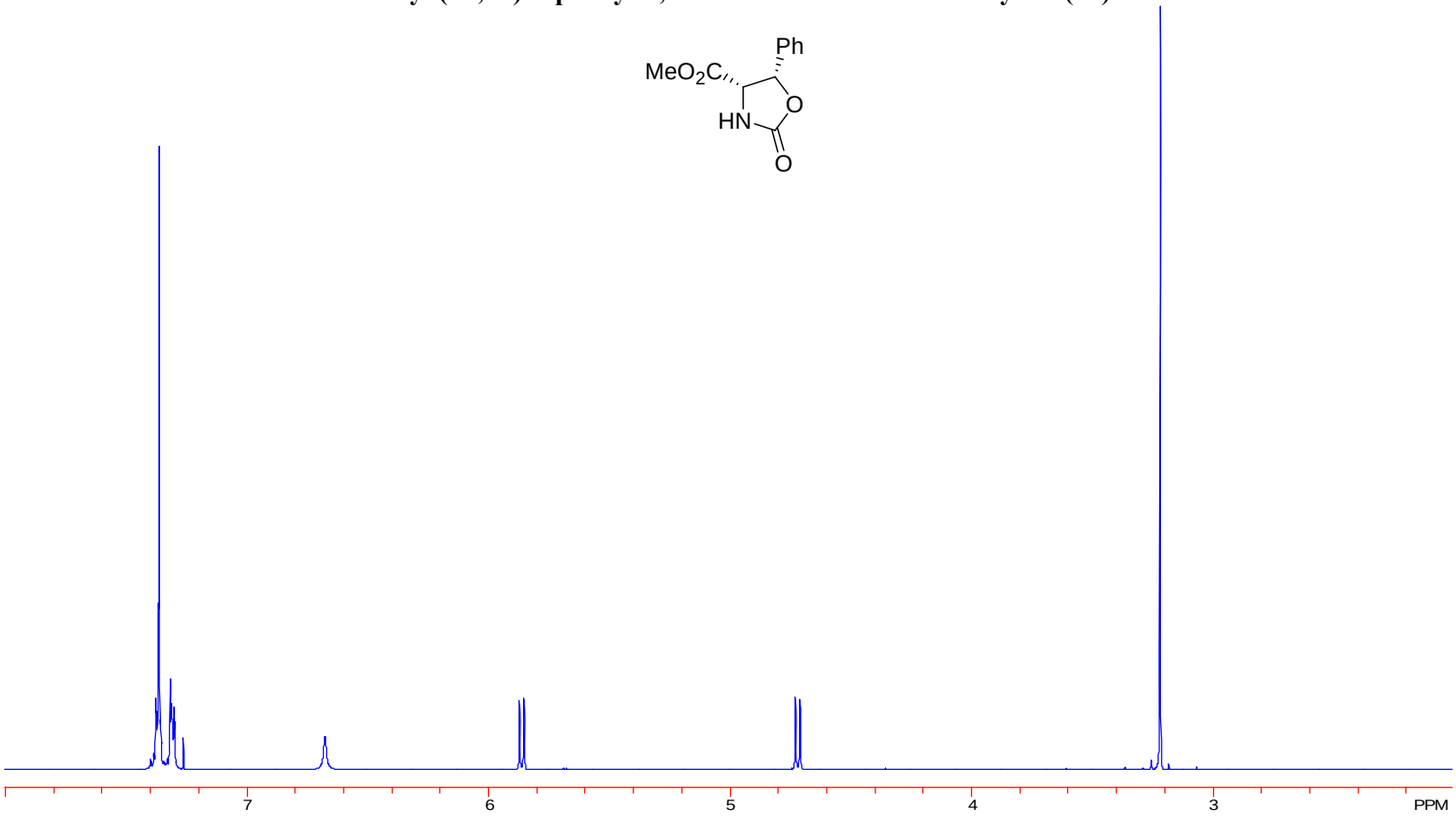

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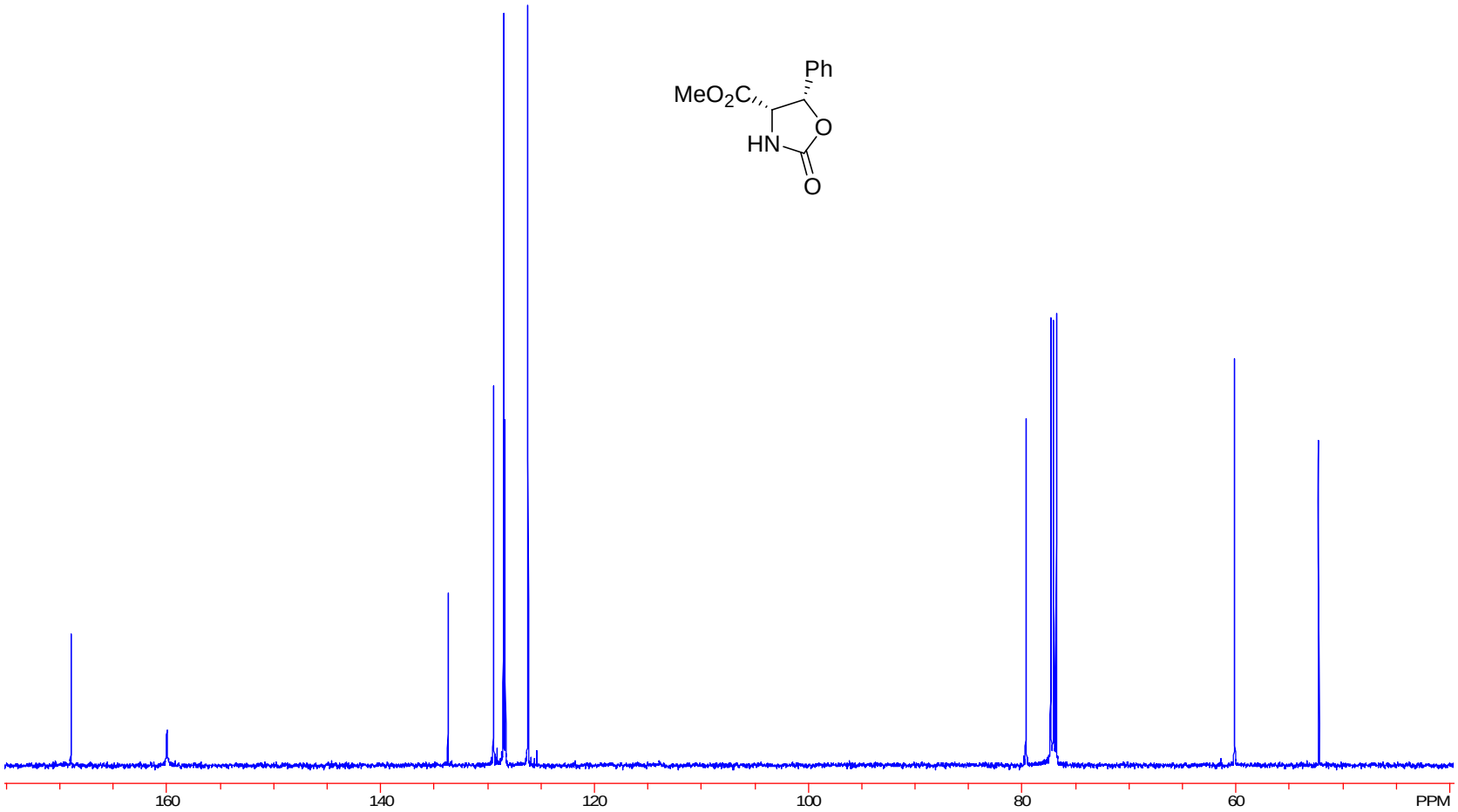

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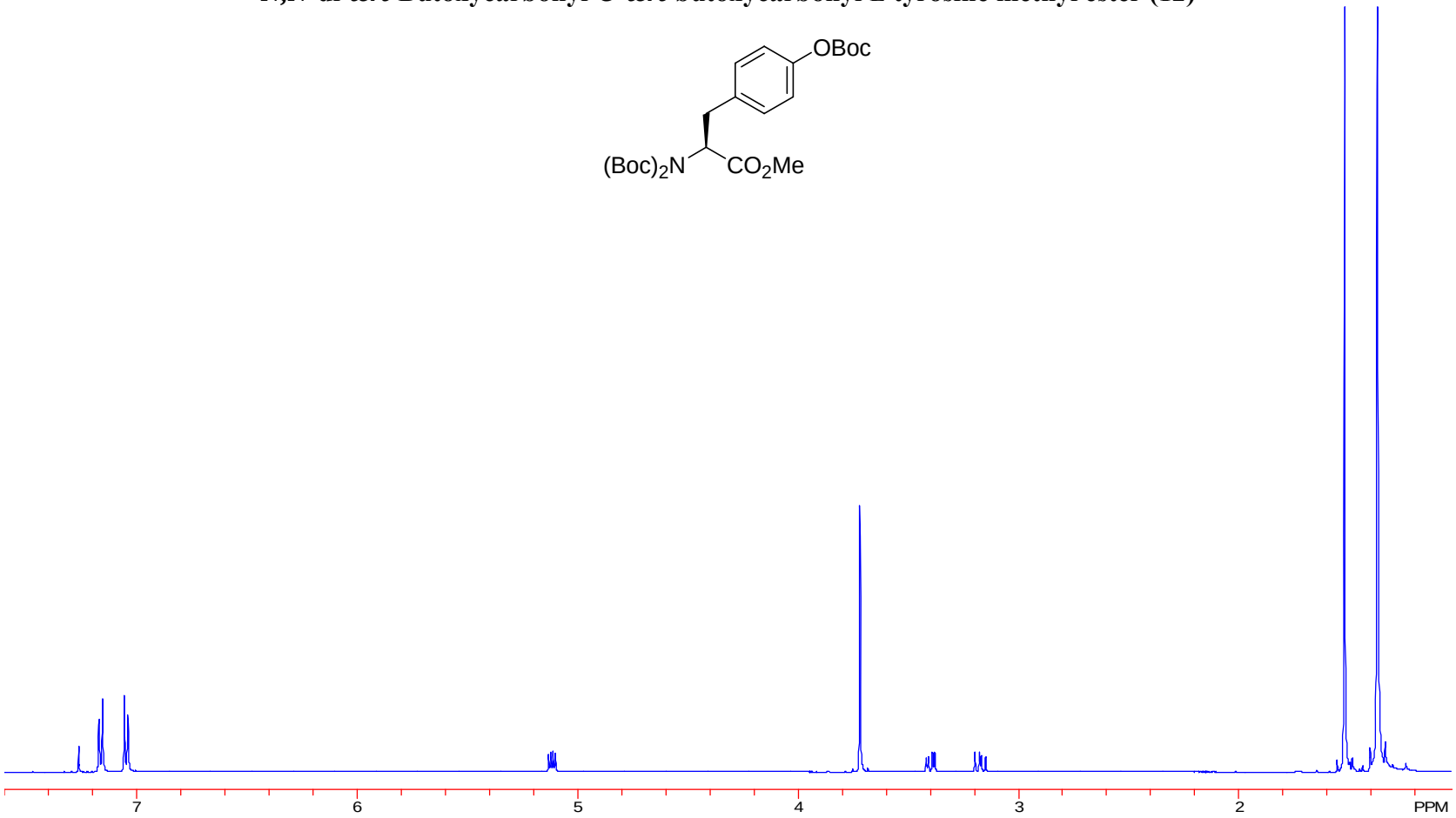

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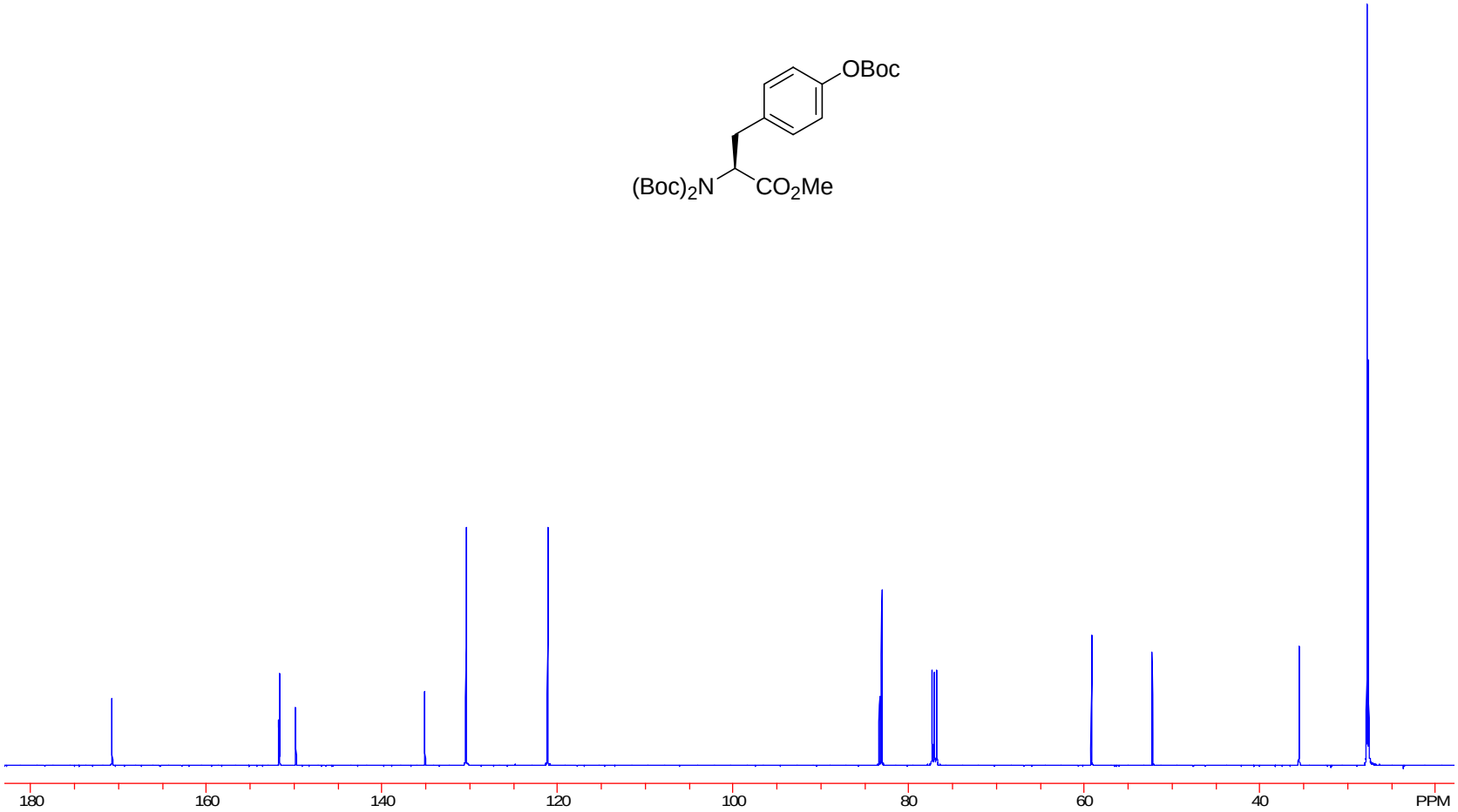
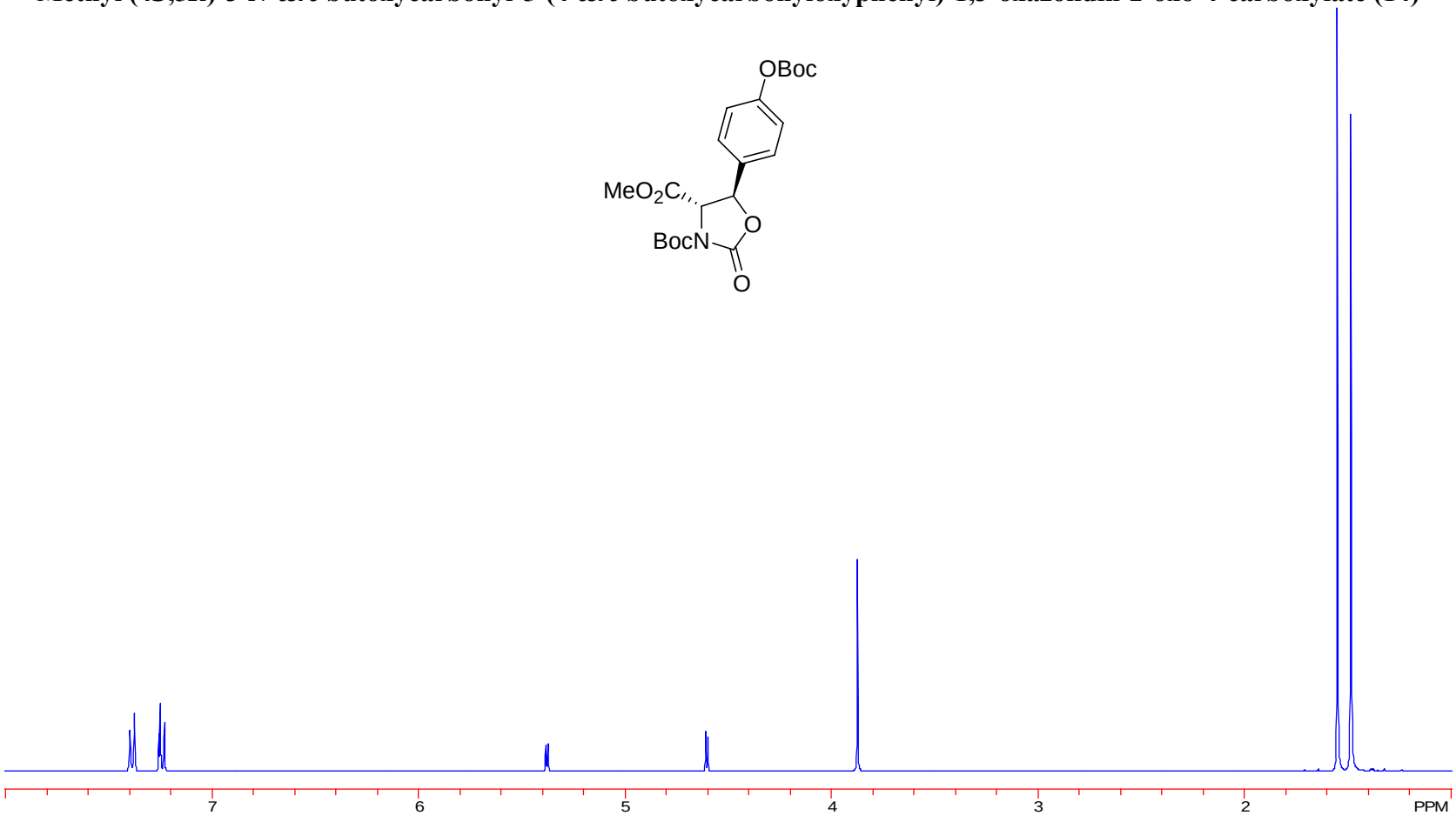
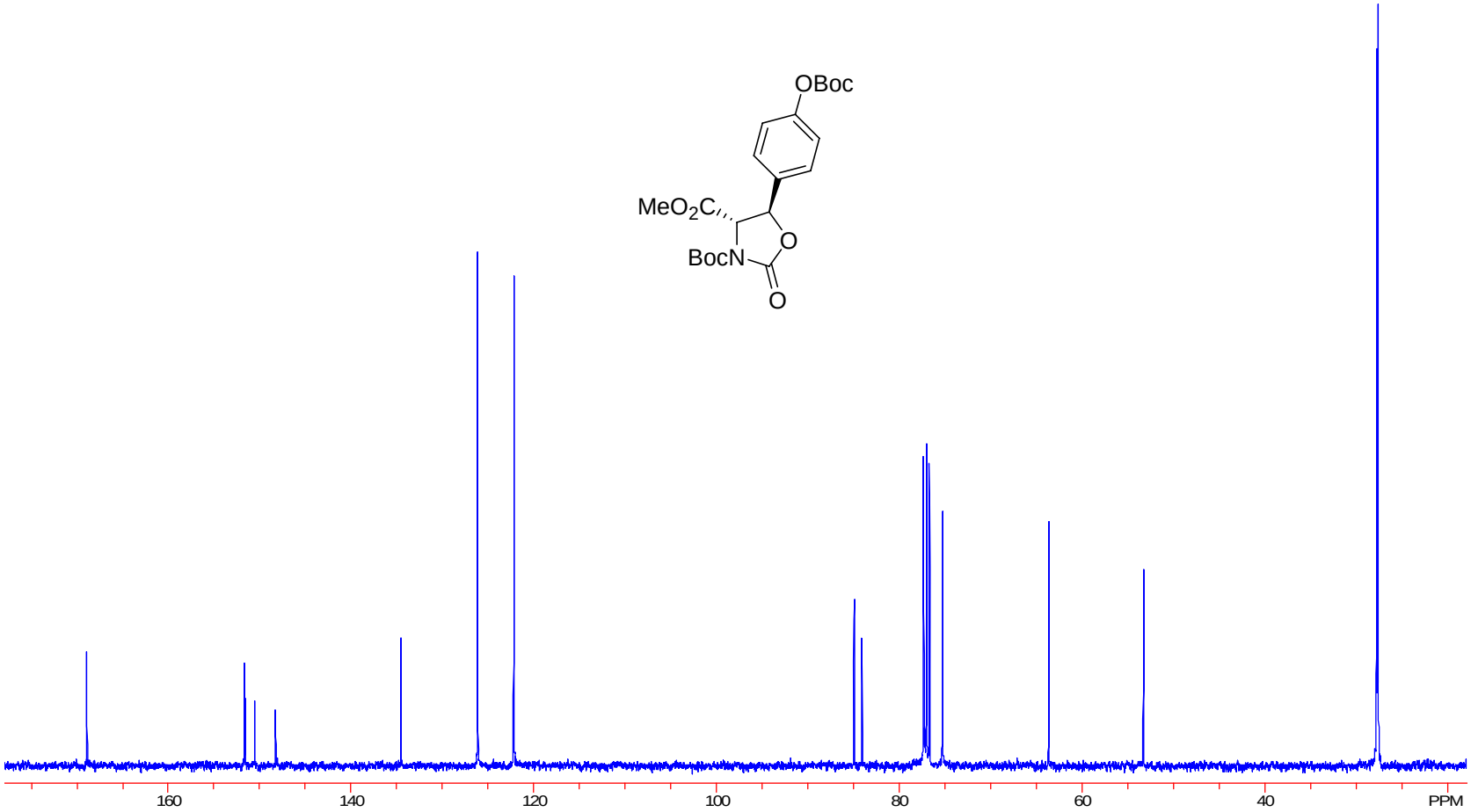


**Methyl (4*S*,5*R*)-3-*N*-*tert*-butoxycarbonyl-5-(4-*tert*-butoxycarbonyloxyphenyl)-1,3-oxazolidin-2-oxo-4-carboxylate (14)**



**Methyl (4*S*,5*R*)-3-*N*-*tert*-butoxycarbonyl-5-(4-*tert*-butoxycarbonyloxyphenyl)-1,3-oxazolidin-2-oxo-4-carboxylate (14)**



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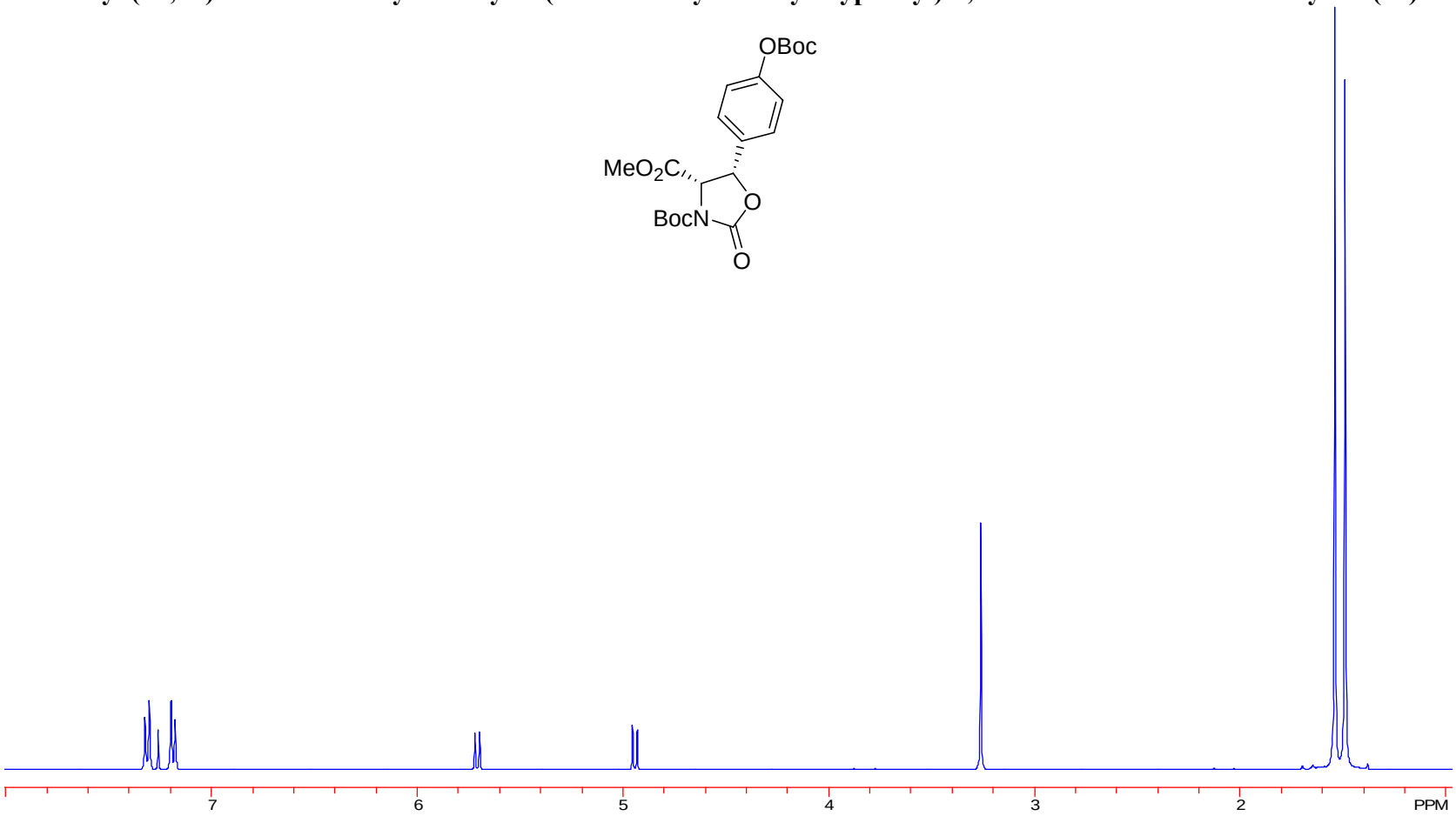
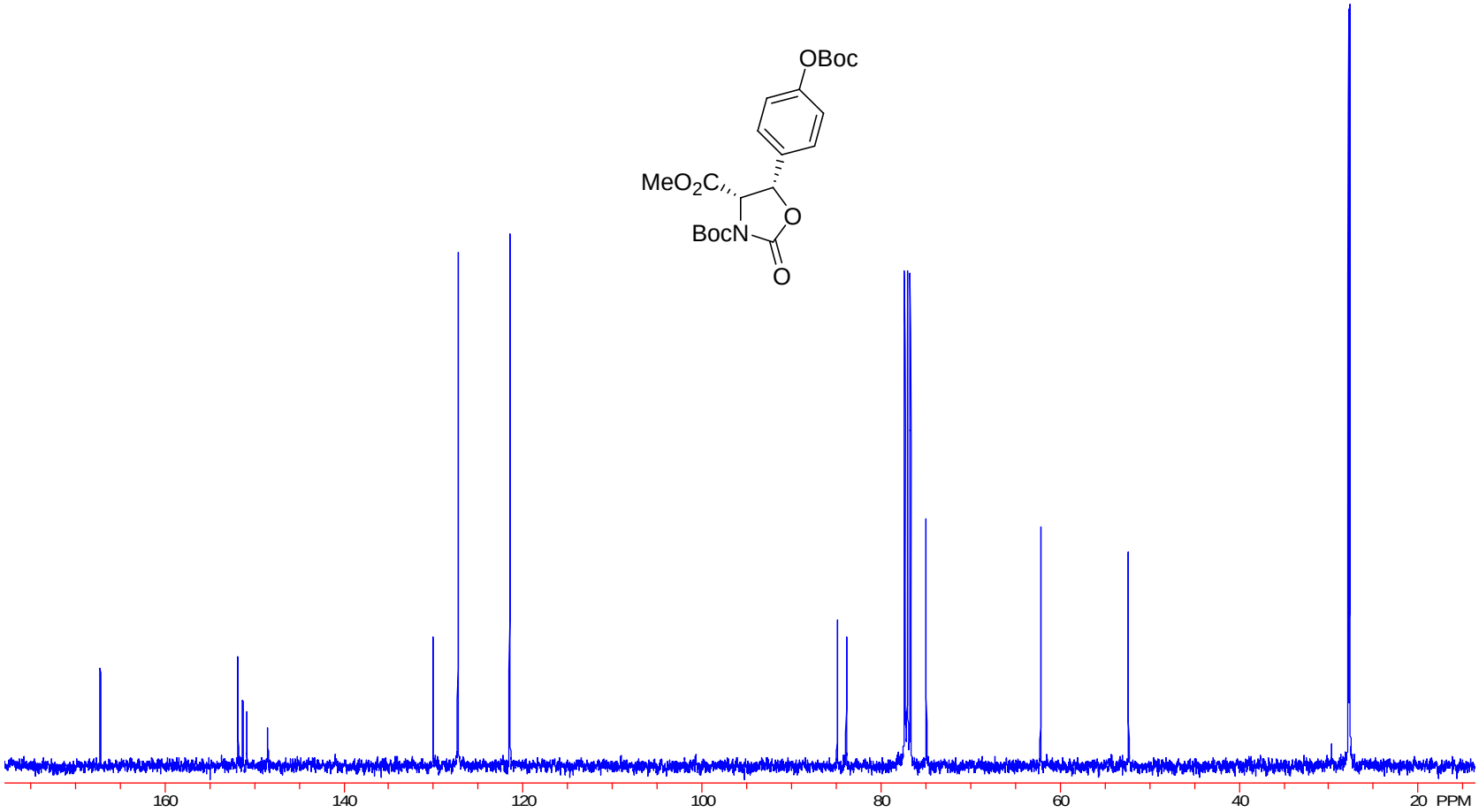


**Methyl (4*S*,5*S*)-3-*N*-*tert*-butoxycarbonyl-5-(4-*tert*-butoxycarbonyloxyphenyl)-1,3-oxazolidin-2-oxo-4-carboxylate (15)**



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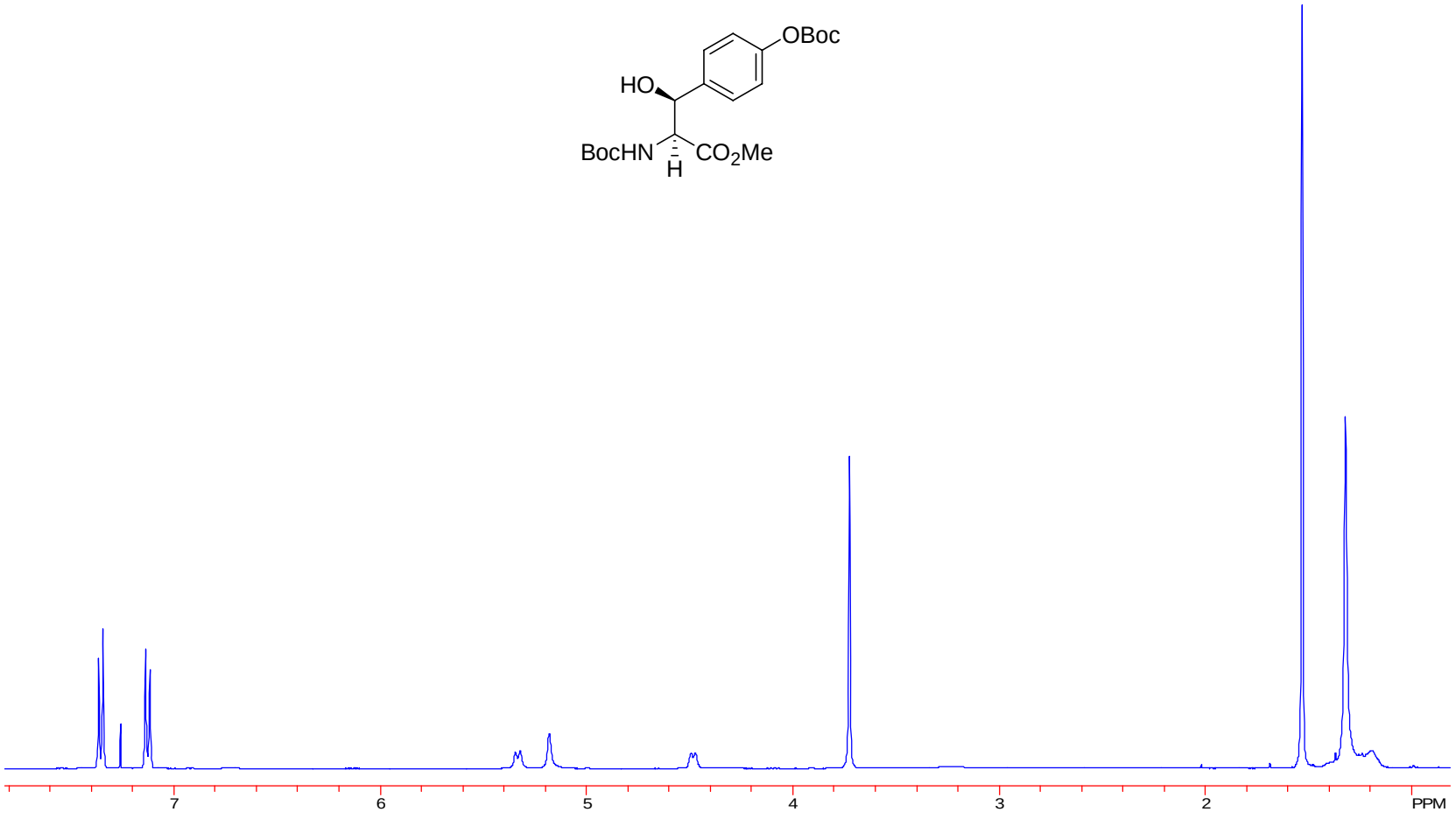
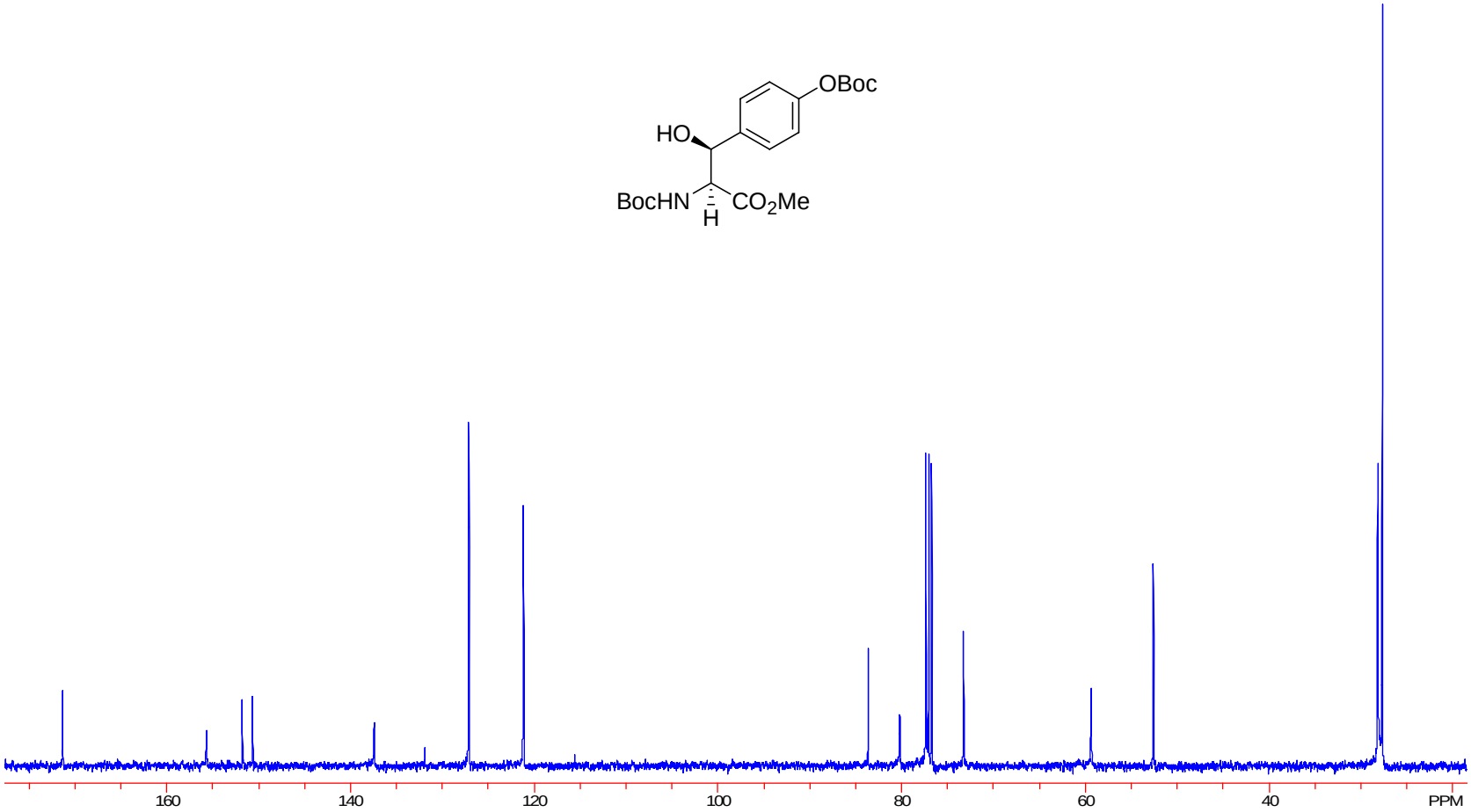
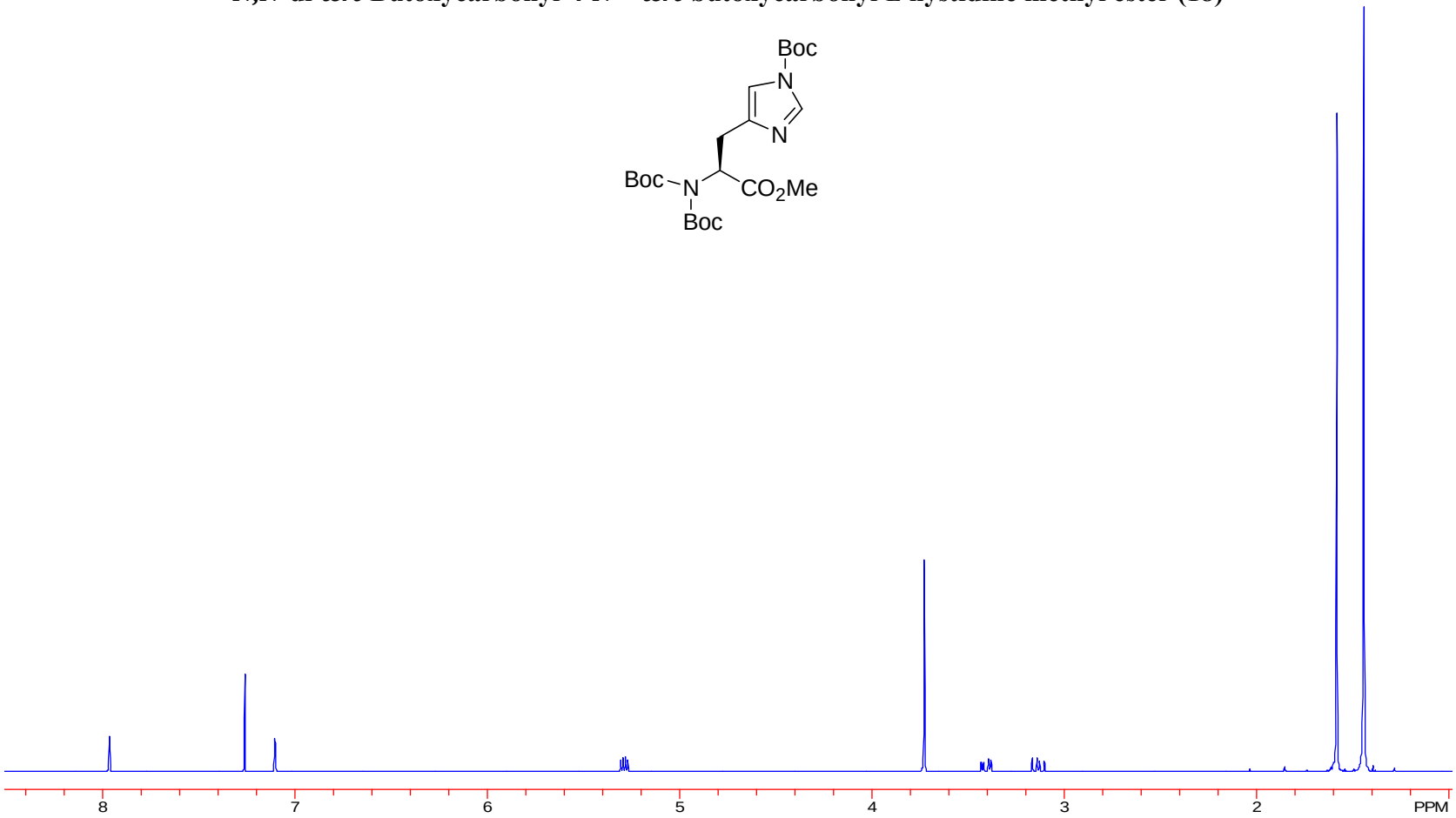


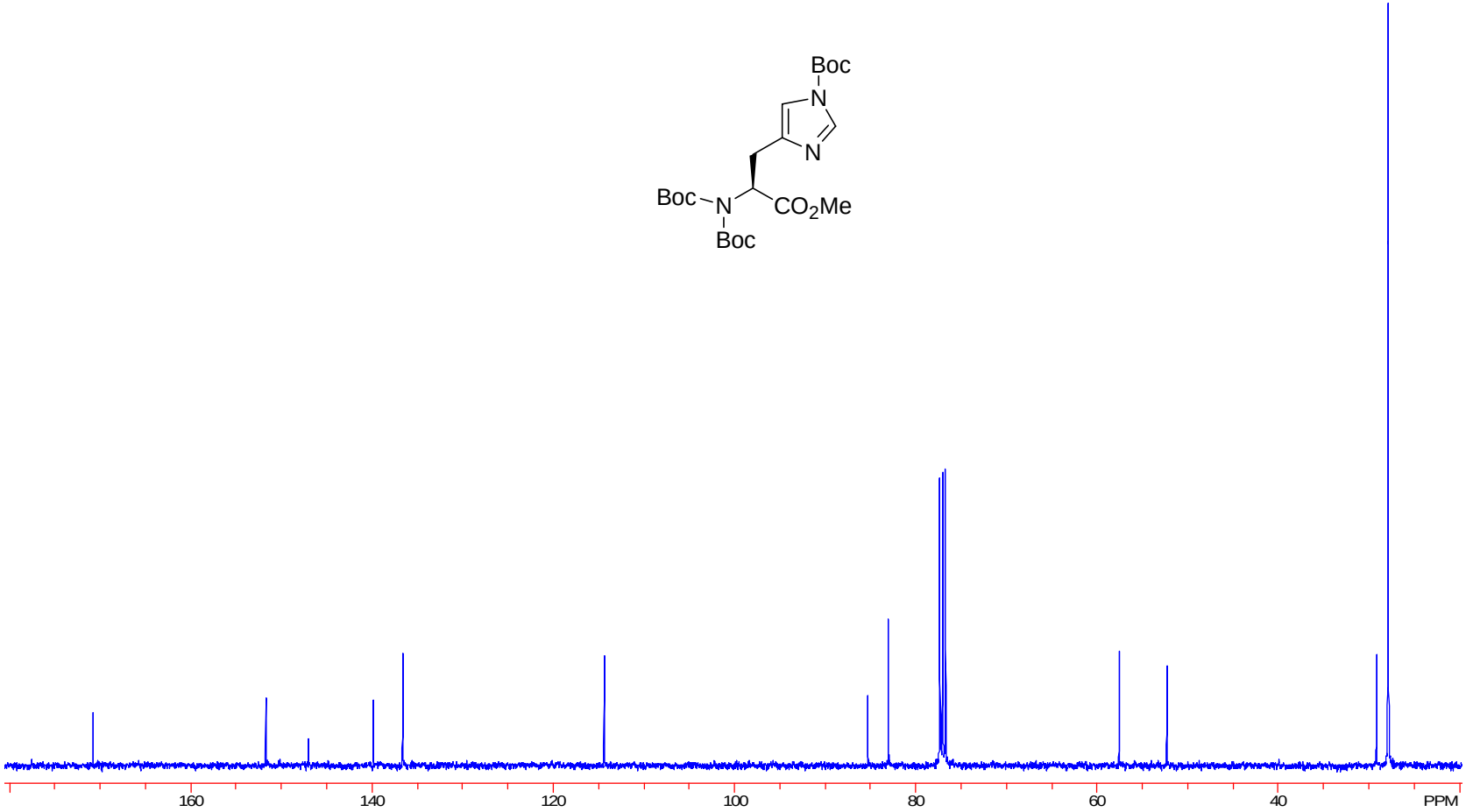
**_N_-*tert*-Butoxycarbonyl-_O_-*tert*-butoxycarbonyl-(2_S_,3_R_)-β-hydroxy-L-tyrosine methyl ester (16)**



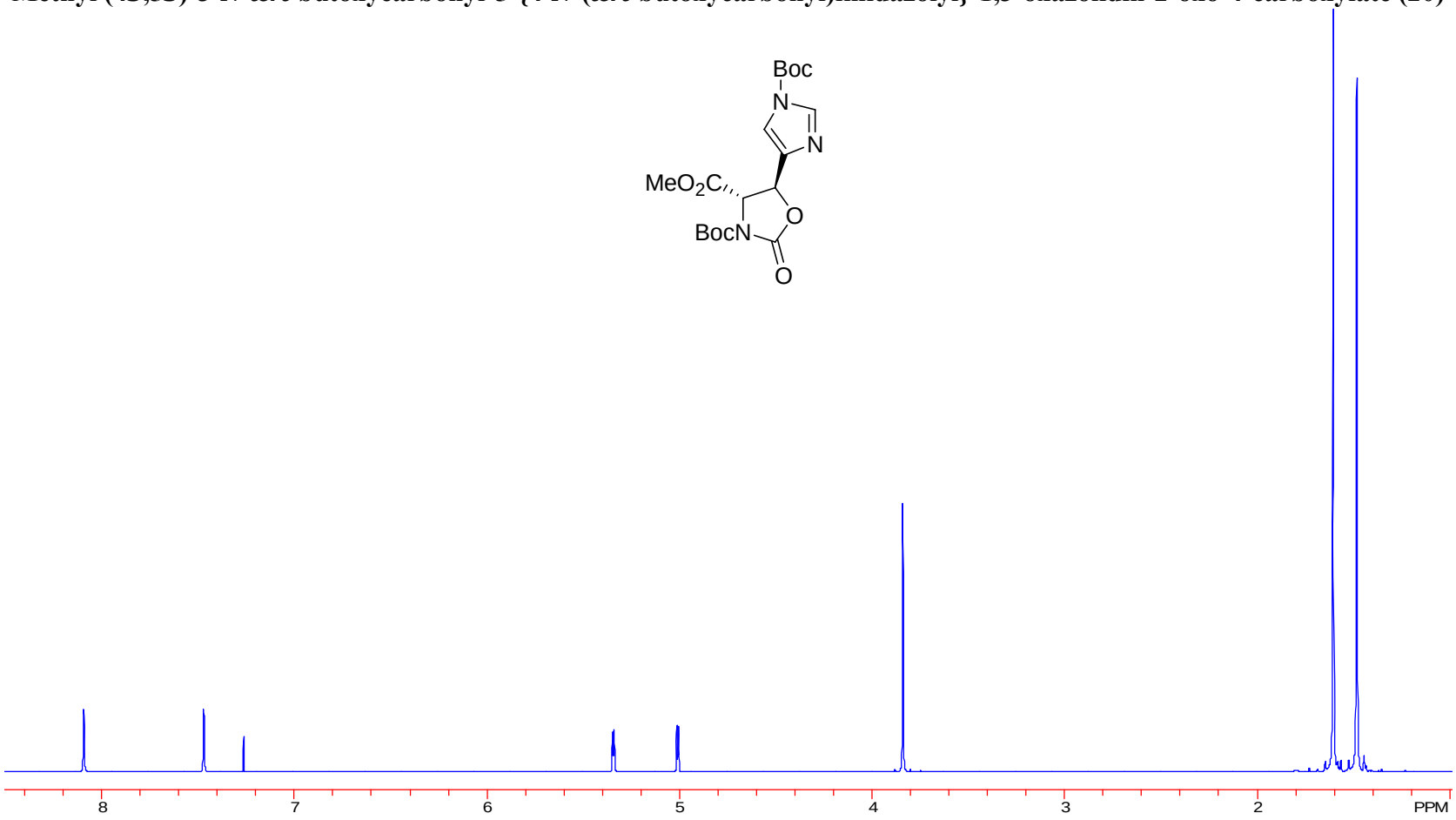
**_N,N_-di-_tert_-Butoxycarbonyl-4-$N^{im}$-_tert_-butoxycarbonyl-L-hystidine methyl ester (18)**



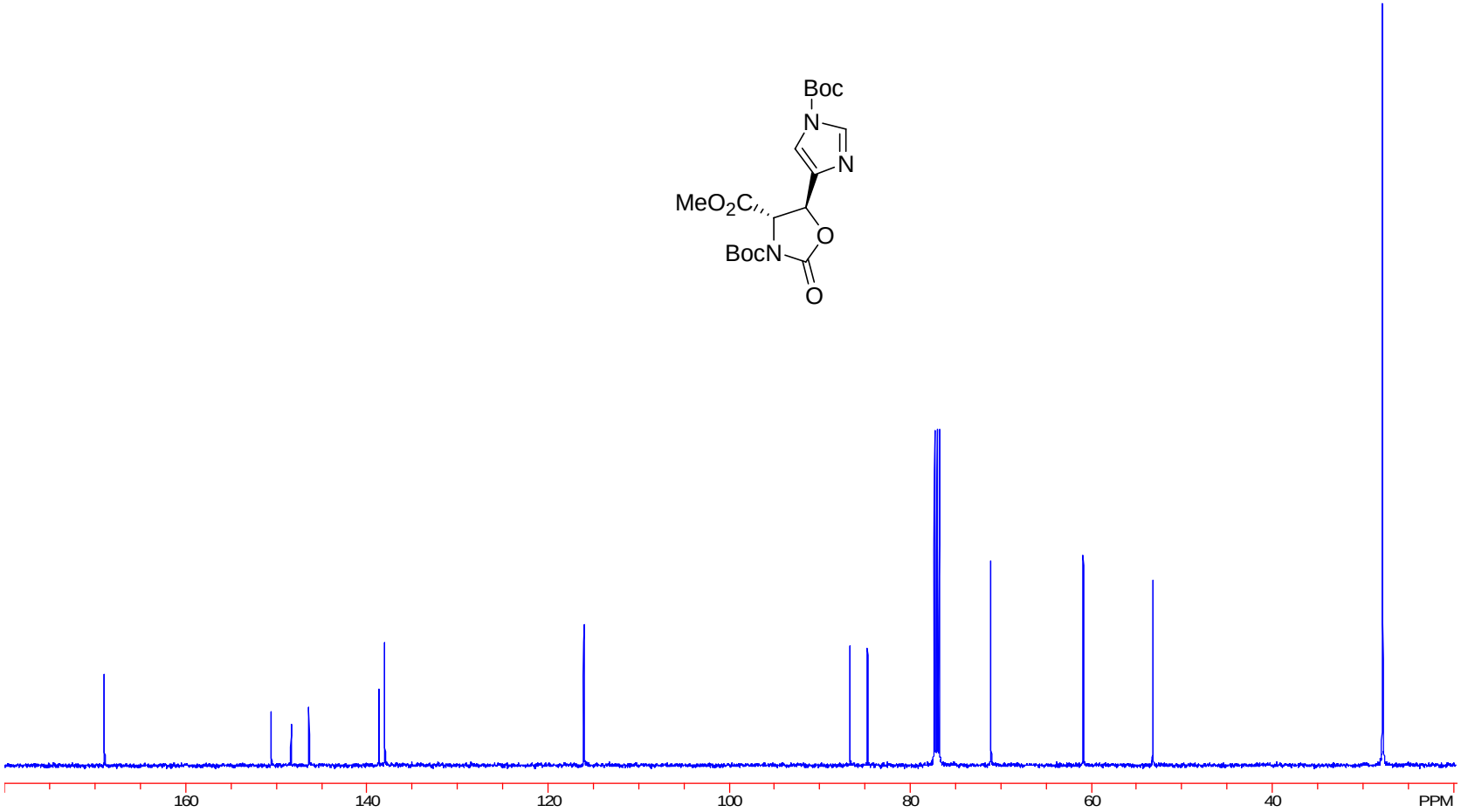
**_N,N_-di-_tert_-Butoxycarbonyl-4-$N^{im}$-_tert_-butoxycarbonyl-L-hystidine methyl ester (18)**



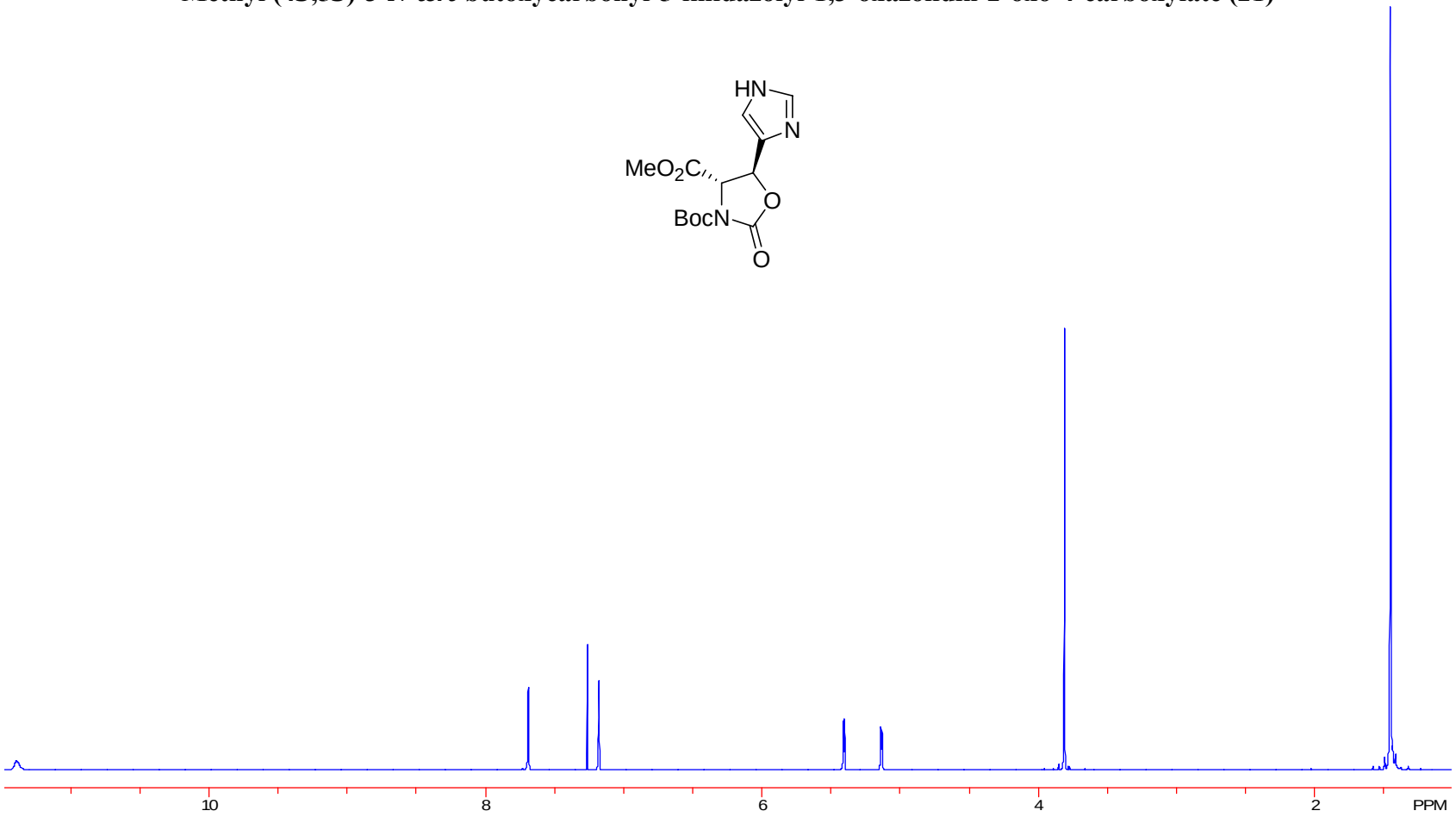
**Methyl (4*S*,5*S*)-3-*N*-*tert*-butoxycarbonyl-5-{4-*N*-(*tert*-butoxycarbonyl)imidazolyl}-1,3-oxazolidin-2-oxo-4-carboxylate (20)**



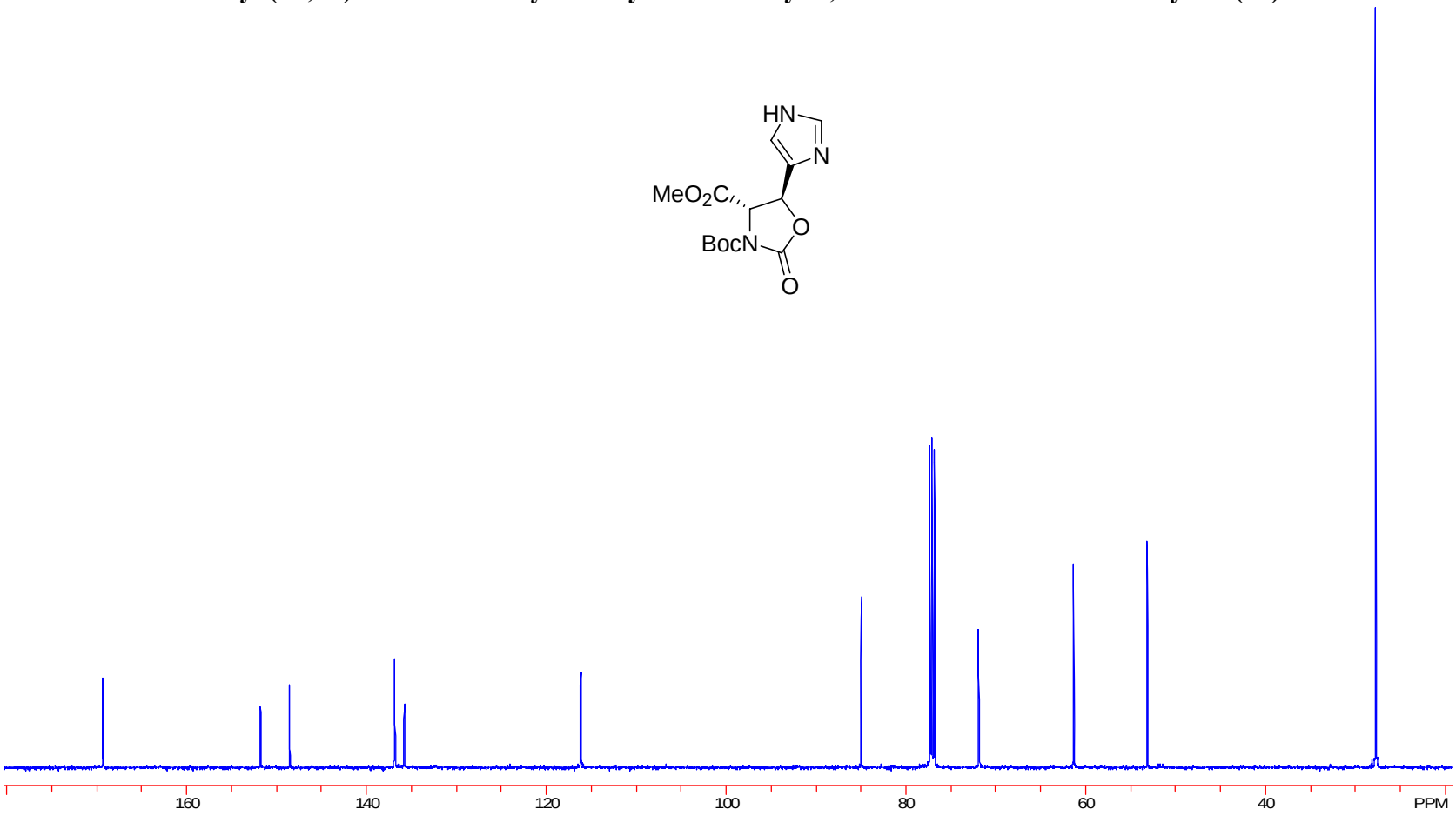
**Methyl (4*S*,5*S*)-3-*N*-*tert*-butoxycarbonyl-5-{4-*N*-(*tert*-butoxycarbonyl)imidazolyl}-1,3-oxazolidin-2-oxo-4-carboxylate (20)**



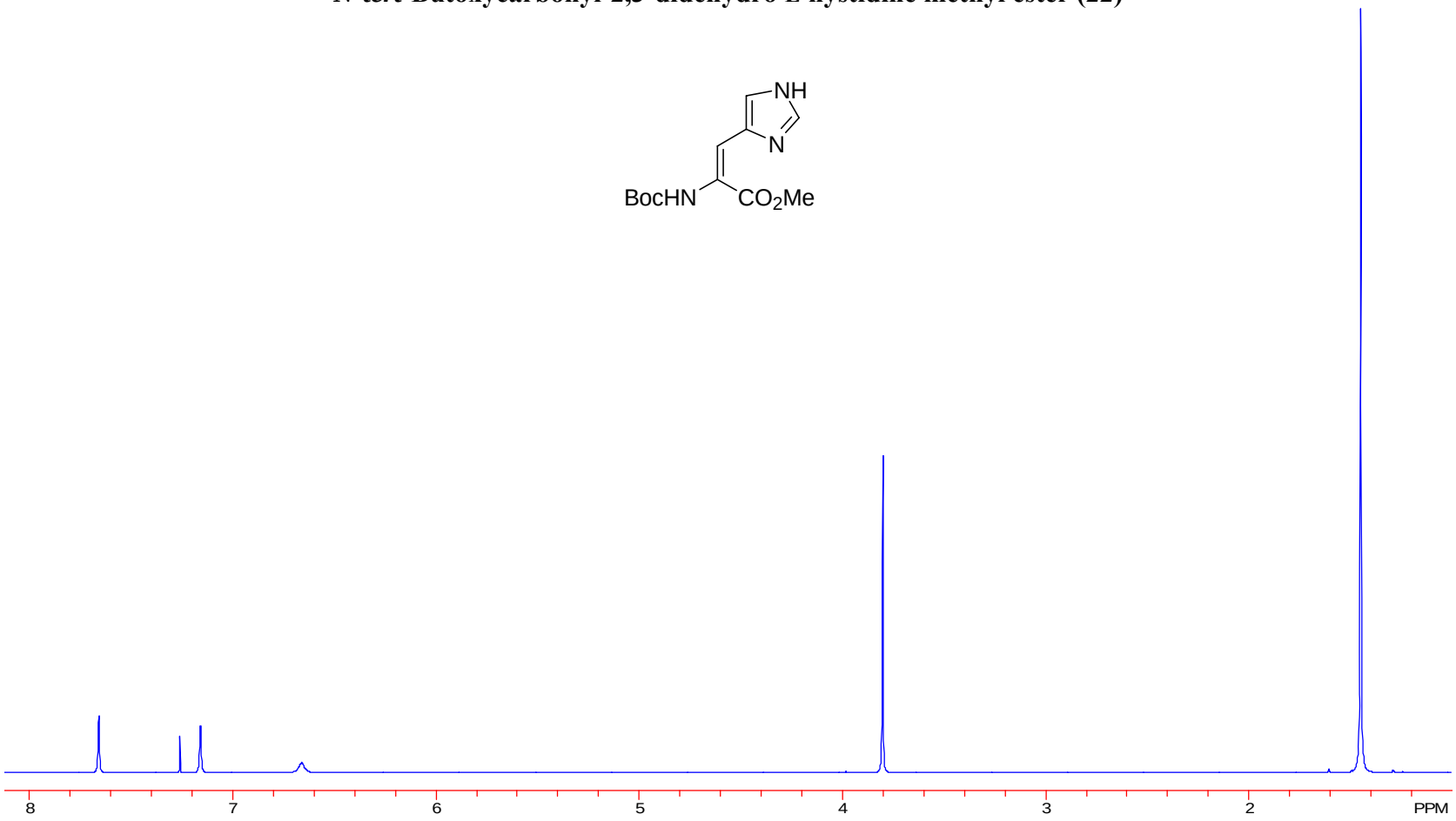
**Methyl (4*S*,5*S*)-3-*N*-*tert*-butoxycarbonyl-5-imidazolyl-1,3-oxazolidin-2-oxo-4-carboxylate (21)**



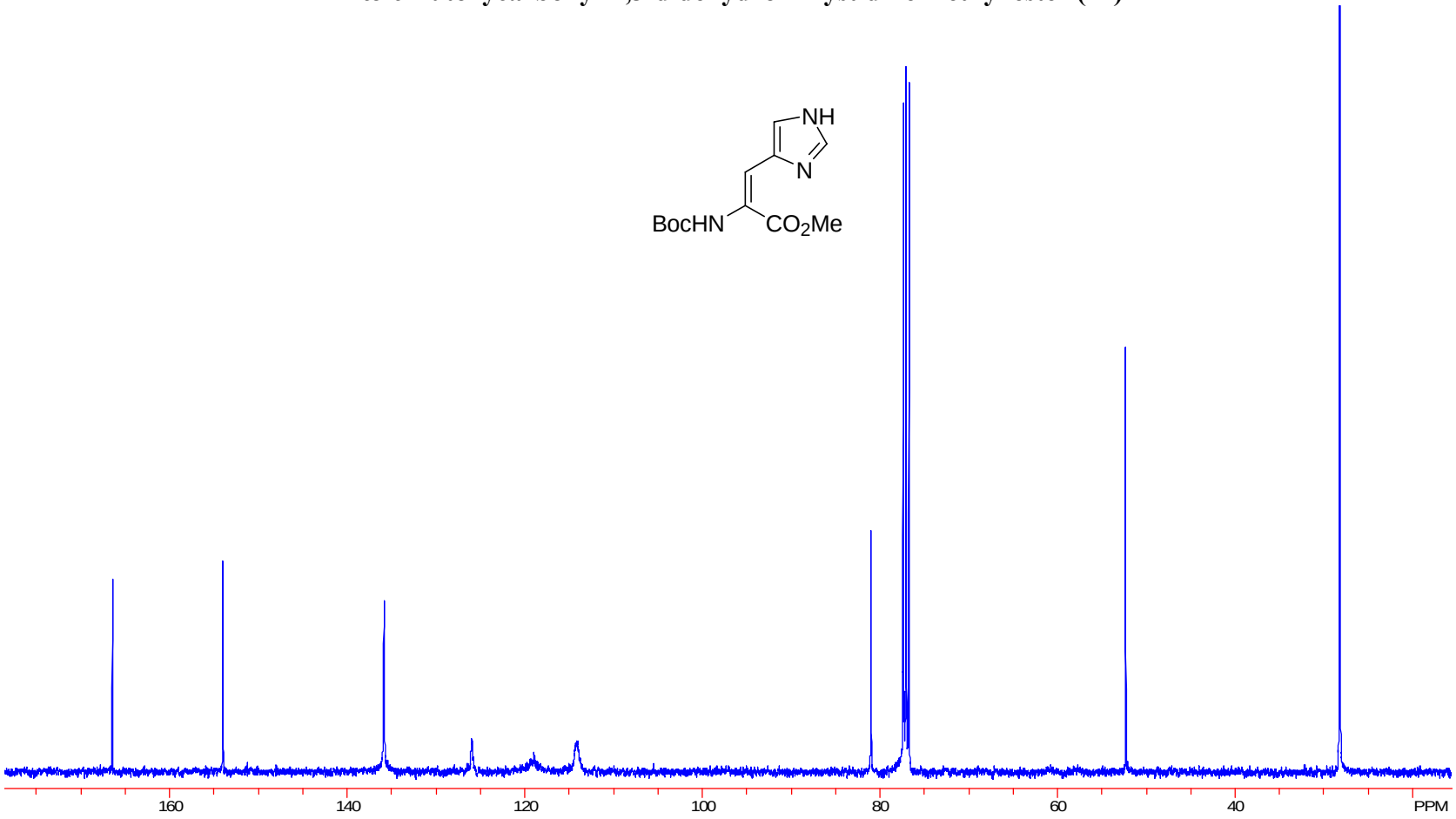
**Methyl (4*S*,5*S*)-3-*N*-*tert*-butoxycarbonyl-5-imidazolyl-1,3-oxazolidin-2-oxo-4-carboxylate (21)**



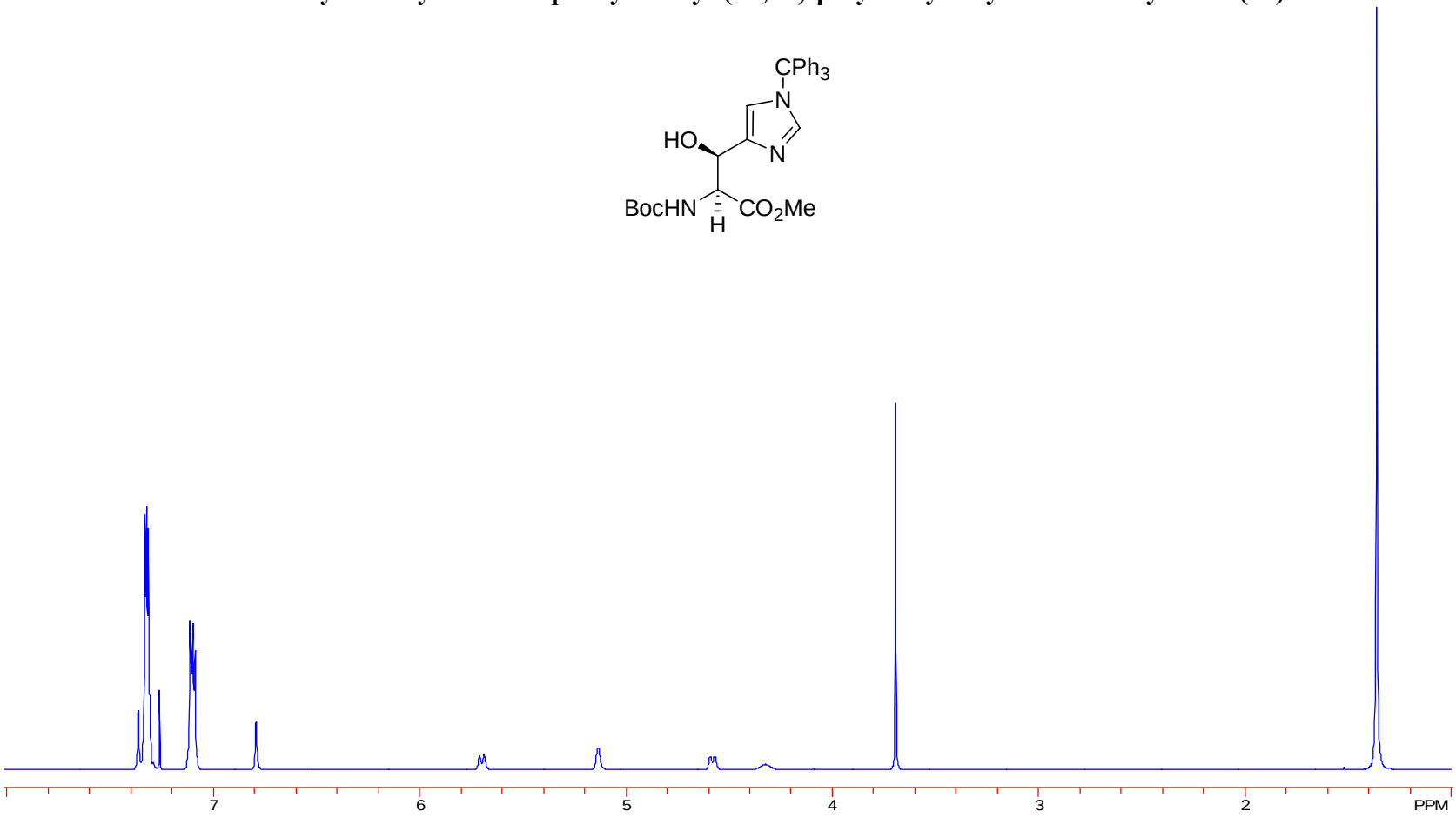
**_N_-_tert_-Butoxycarbonyl-2,3-didehydro-L-hystidine methyl ester (22)**



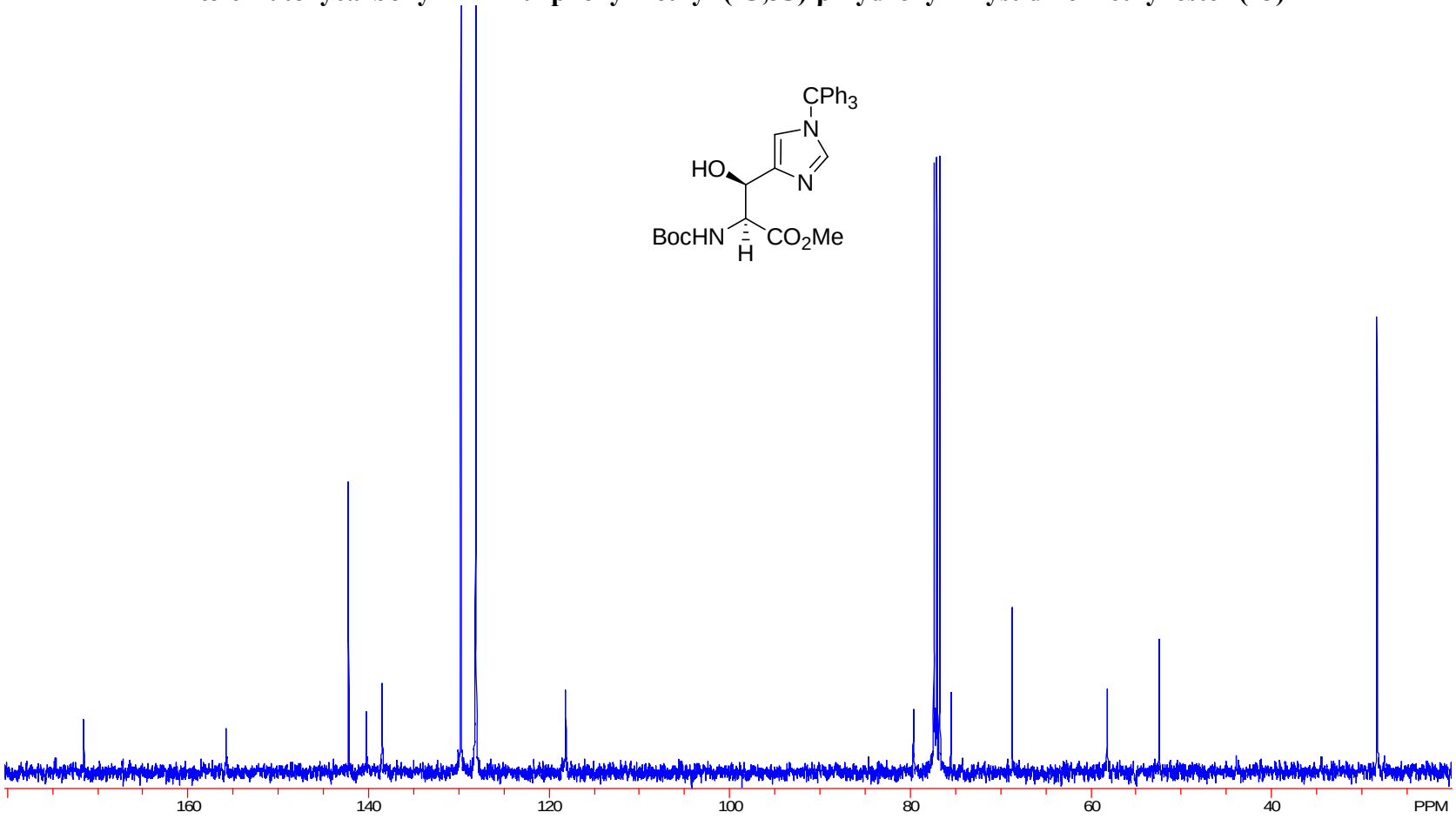
**_N-tert_-Butoxycarbonyl-2,3-didehydro-L-hystidine methyl ester (22)**



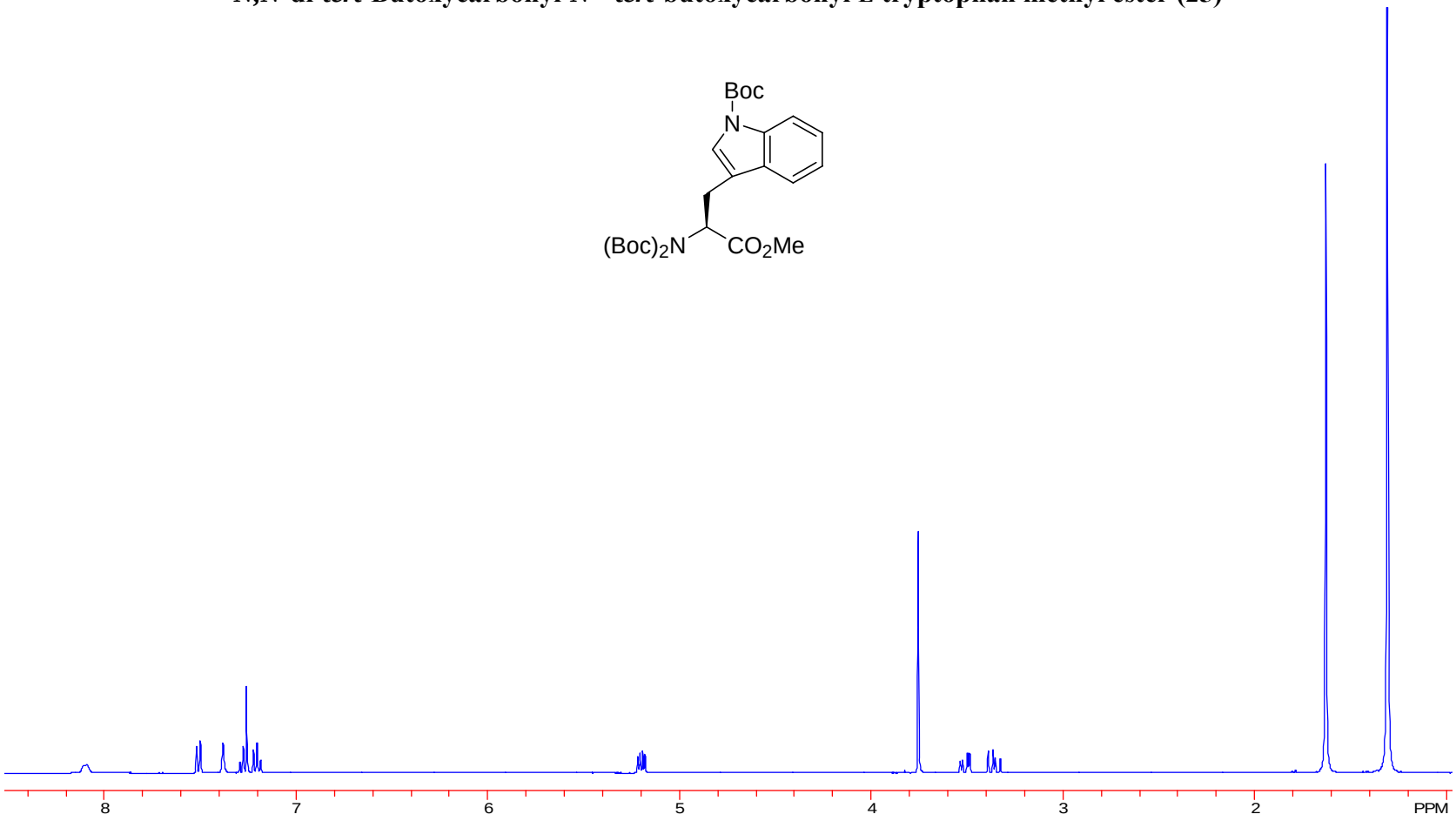
**_N_-*tert*-Butoxycarbonyl-4-$N^{im}$-triphenylmethyl-(2*S*,3*S*)-β-hydroxy-L-hystidine methyl ester (23)**



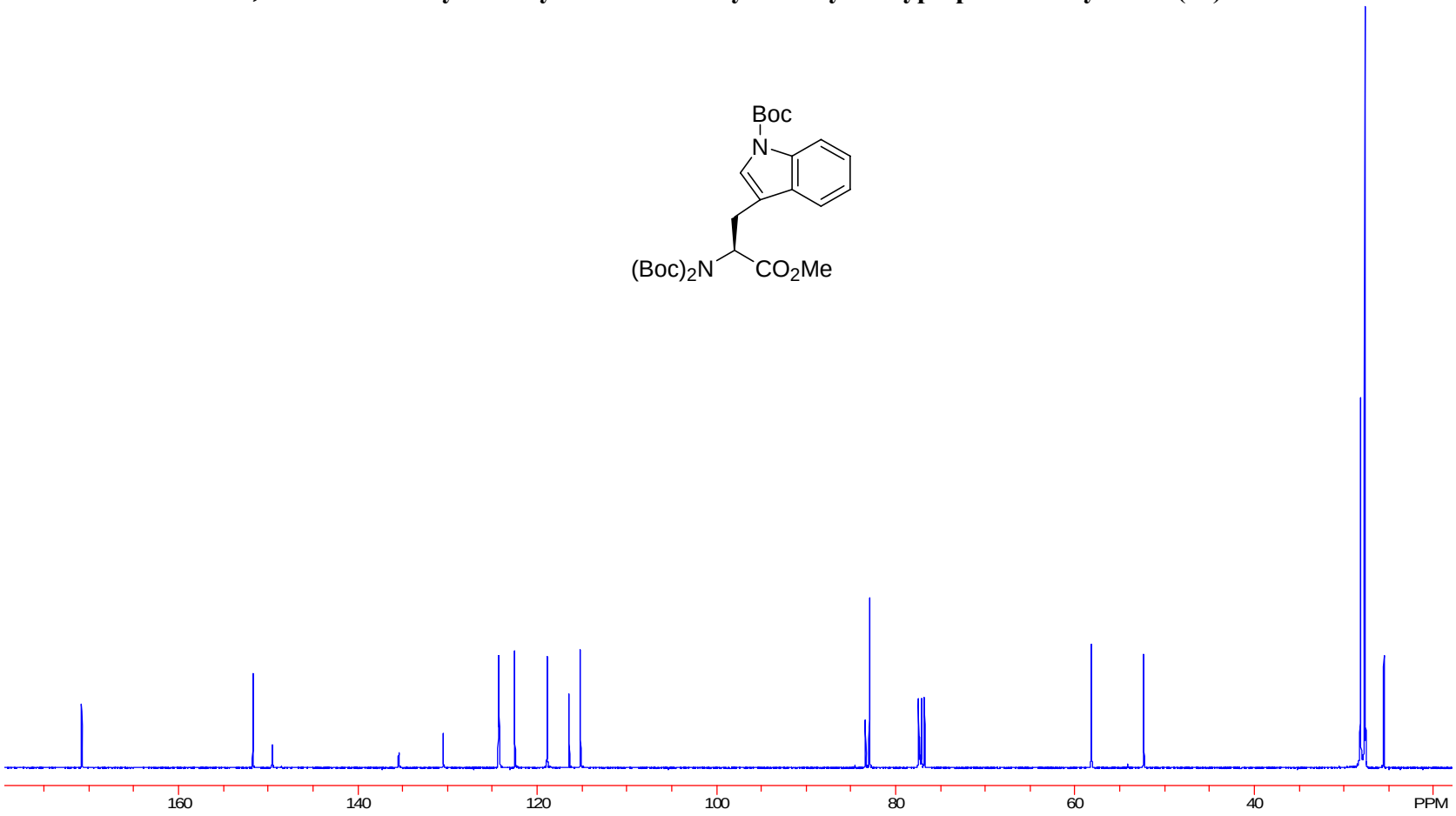
**_N_-*tert*-Butoxycarbonyl-4-$N^{im}$-triphenylmethyl-(2*S*,3*S*)-β-hydroxy-L-hystidine methyl ester (23)**



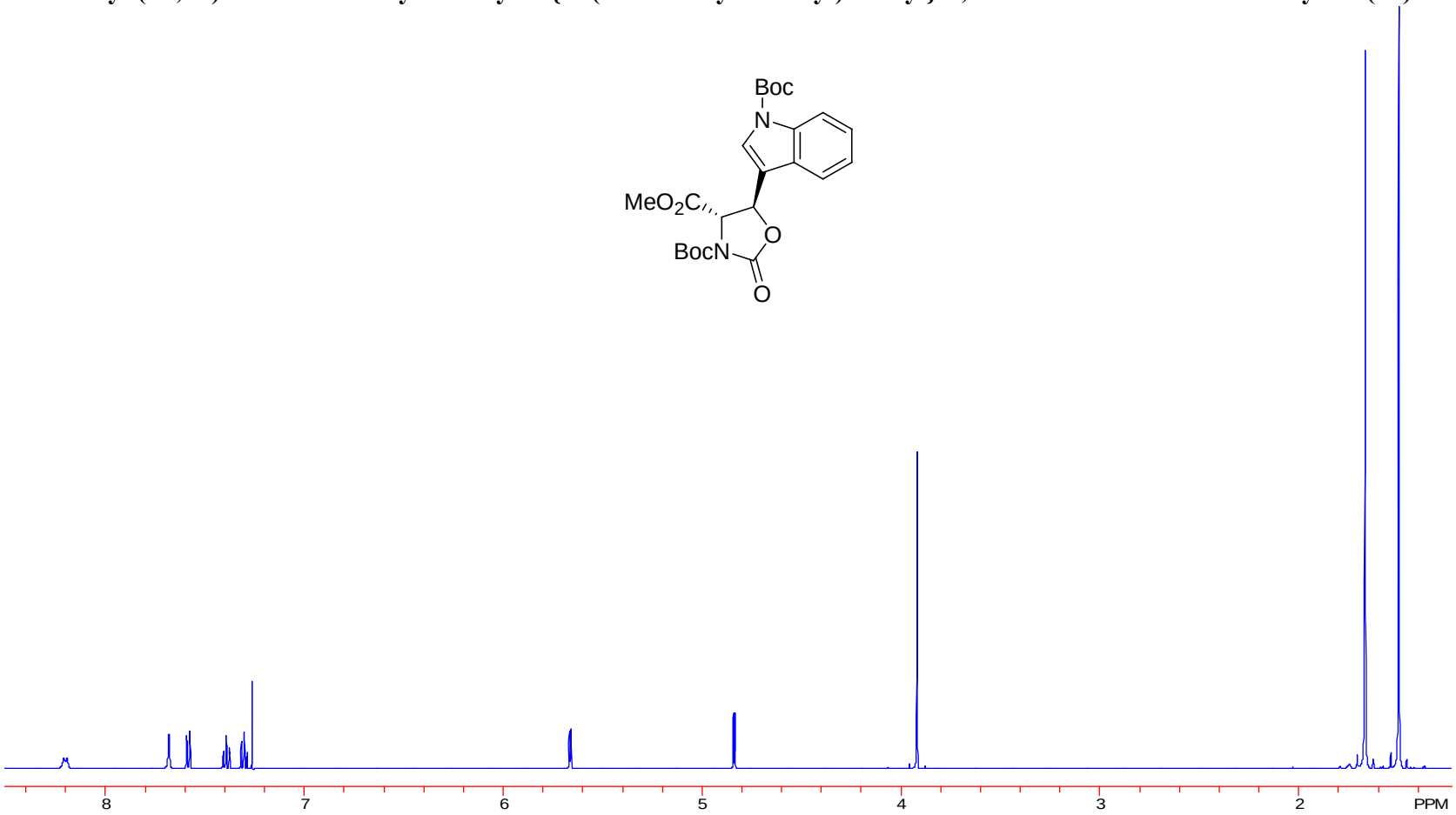
**_N,N_-di-_tert_-Butoxycarbonyl-$N^{in}$-_tert_-butoxycarbonyl-L-tryptophan methyl ester (25)**



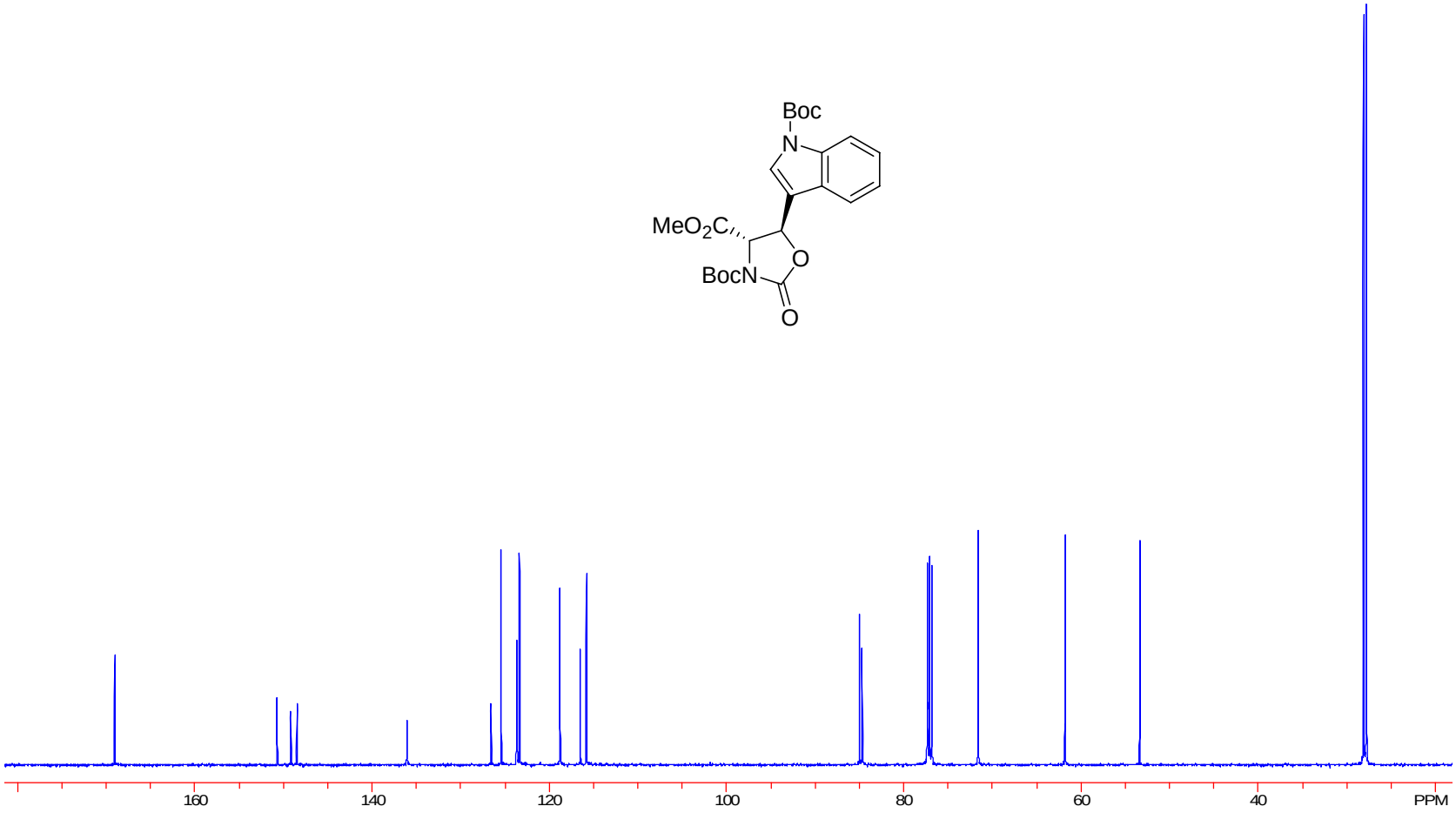
**$N,N$-di-*tert*-Butoxycarbonyl-$N^{in}$-*tert*-butoxycarbonyl-L-tryptophan methyl ester (25)**



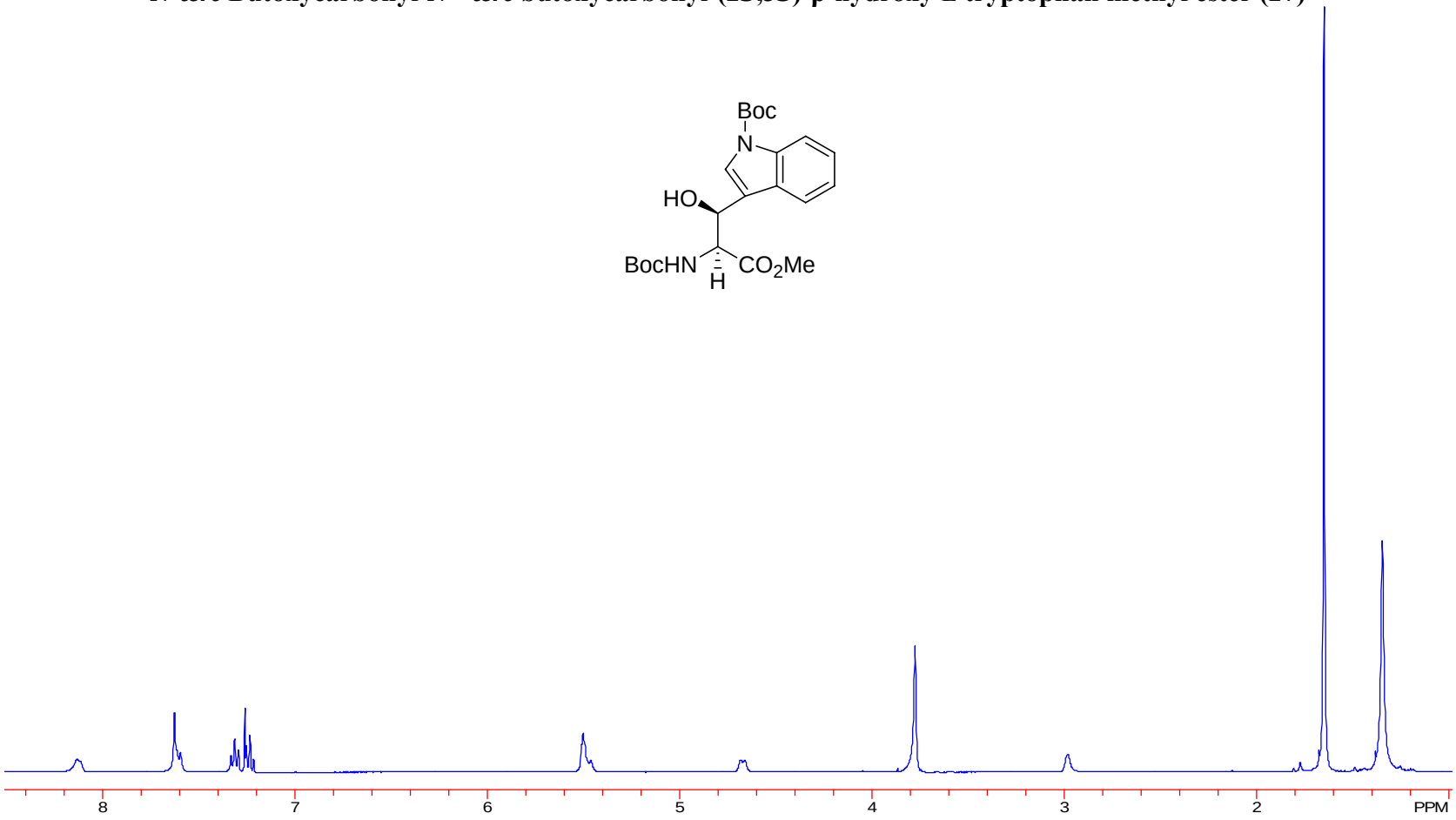
**Methyl (4*S*,5*S*)-3-*N*-*tert*-butoxycarbonyl-5-{*N*-(*tert*-butoxycarbonyl)indolyl}-1,3-oxazolidin-2-oxo-4-carboxylate (26)**



**Methyl (4*S*,5*S*)-3-*N*-*tert*-butoxycarbonyl-5-{*N*-(*tert*-butoxycarbonyl)indolyl}-1,3-oxazolidin-2-oxo-4-carboxylate (26)**



**_N_-*tert*-Butoxycarbonyl-$N^{in}$-*tert*-butoxycarbonyl-(2*S*,3*S*)-β-hydroxy-L-tryptophan methyl ester (27)**



**_N_-_tert_-Butoxycarbonyl-$N^{in}$-_tert_-butoxycarbonyl-(2_S_,3_S_)-β-hydroxy-L-tryptophan methyl ester (27)**