Supplementary Material (ESI) for Chemical Communications

Supporting Information

A Biomimetic Approach to the Guanidinium Core of the Cylindrospermopsin Alkaloids

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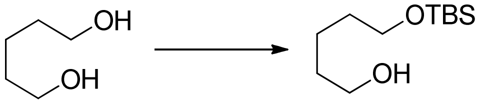
General Information

Unless otherwise noted, reactions were magnetically stirred and monitored by TLC. The chromatograms were visualized with iodine, phosphomolybdic acid, potassium permanganate or under UV light. All anhydrous reactions were performed under a static argon atmosphere using oven dried glassware, anhydrous solvents were dried and distilled before use using standard methods.[1] Flash column chromatography was performed on Davisil® silica gel (35-70 microns) with the eluent specified in each case, TLC was conducted on precoated E. Merck silica gel 60 F_{254} glass plates.

^{1}H and ^{13}C NMR spectra were recorded a Bruker Avance 500 spectrometer using an internal deuterium lock at ambient temperature at 500 MHz and 125MHz with internal references of δ_H 7.26, δ_C 77.00 and δ_H 3.31, δ_C 49.00 for $CDCl_3$ and CD_3OD. Melting temperatures were determined using a Gallenkamp instrument and are uncorrected. Low resolution Chemical Ionisation (CI) and Electrospray Ionisation (ESI) mass spectra were recorded on a Micromass Quattro II spectrometer and high resolution mass spectra were recorded on either a Finnigan MAT 900 XLT or a Finnigan MAT 95 XP at the EPSRC National Mass Spectrometry Service Centre based in Swansea.

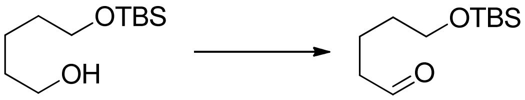
Experimental Procedures

Preparation of 5-(*tert*-butyl-dimethyl-silanyloxy)-pentan-1-ol (11)[2]



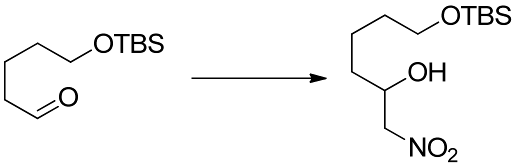
To a stirred suspension of sodium hydride (1.92 g, 50 mmol) in anhydrous THF (150 mL) was added pentane-1,5-diol (5.26 mL, 50 mmol), after one hour *tert*-butyldimethylsilyl chloride (7.54 g, 50 mmol) was added and vigorous stirring continued for a further hour. The reaction mixture was diluted with diethyl ether (300 mL) and washed with potassium carbonate (aq. 10%, 100 mL), brine (100 mL) and the organic layer dried over magnesium sulphate. After purification by flash column chromatography on silica gel using ethyl acetate/petroleum ether (10:90 to 40:60), **11** was obtained as a clear oil (6.66 g, 30.4 mmol, 61%). R_f = 0.36 (20% ethyl acetate in petrol); δ_H (500MHz; $CDCl_3$) -0.01 (s, 6H), 0.84 (s, 9H), 1.30-1.36 (m, 2H), 1.46-1.55 (m, 4H), 2.74 (s, 1H, OH) and 3.53-3.57 (m, 4H); δ_C(125 MHz; $CDCl_3$) -5.6 (2xCH_3), 18.0 (C), 21.7 (CH_2), 25.6 (3xCH_3), 32.1 (CH_2), 32.2 (CH_2), 62.2 (CH_2) and 62.9 (CH_2).

Preparation of 5-(*tert*-butyl-dimethyl-silanyloxy)-pentanal (12)



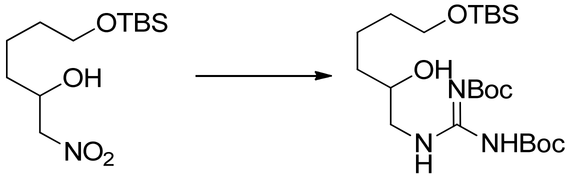
To a cooled (-78°C) and stirred solution of oxalyl chloride (3.98 mL, 46.4 mmol) in anhydrous dichloromethane (120 mL) was added anhydrous dimethyl sulfoxide (5.96 mL, 84.0 mmol). After 20 min a solution of alcohol **11** (6.34 g, 29.0 mmol) in anhydrous dichloromethane (50 mL) was added to the reaction mixture. After a further 20 min triethylamine (24.2 mL, 173.9 mmol) was also added. After 3 h TLC analysis indicated the complete consumption of **11** and the reaction was diluted with brine (100 mL) and warmed to rt. After separation the organic layer was washed with brine (2 x 100 mL), HCl (0.25M, 3 x 100 mL) and water (3 x 100 mL). After drying and evaporation the resulting yellow oil was dissolved in petroleum ether (50 mL) and passed through a plug of silica (ca. 1 cm) eluting with further petroleum ether (200 mL). After evaporation **12** was obtained as a pale yellow oil (5.57 g, 25.7 mmol, 89%) which was used without further purification. R_f = 0.62 (20% ethyl acetate in petrol); δ_H (500MHz; $CDCl_3$) 0.01 (s, 6H), 0.85 (s, 9H), 1.50-1.54 (m, 2H), 1.64-1.70 (m, 2H), 2.42 (td, 2H, J = 1.90, 1.55, 7.25, 7.60), 3.59 (t, 2H, J = 6.30, 6.00) and 9.73 (t, 1H, J = 1.60, 1.90); δ_C (125 MHz; $CDCl_3$) -5.4 (2 x CH_3), 18.2 (C), 18.6 (CH_2), 25.8 (3xCH_3), 32.0 (CH_2), 43.5 (CH_2), 64.5 (CH_2) and 202.4 (C=O).

Preparation 5-(*tert*-butyl-dimethyl-silanyloxy)-1-nitro-pentan-2-ol (13)



To a stirred solution of **12** (4.93 g, 22.7 mmol) in dichloromethane (80 mL) at rt was added nitromethane (73.7 mL, 1.36 mol) and the mixture cooled (0°C) and diisopropylethylamine (9.90 mL, 56.9 mmol) added. Reaction progress was monitored *via* TLC and after 5 days the reaction was quenched with ammonium chloride solution (sat., 200 mL), separated and the aqueous layer extracted with chloroform (3 x 100 mL). The combined organic extracts where washed with brine (100 mL), dried over anhydrous magnesium sulphate and purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether (10:90 to 30:70). Fractions eluting in 10:90 ethyl acetate/petroleum ether gave **13** as a pale yellow oil (5.11 g, 18.4 mmol, 81%). R_f = 0.29 (20% ethyl acetate in petrol); δ_H (500MHz; $CDCl_3$) 0.04 (s, 6H), 0.88 (s, 9H), 1.43-1.59 (m, 6H), 2.87 (s, 1H, OH), 3.62 (t, 2H, J = 5.70, 6.00), 4.30-4.33 (m, 1H), 4.36 (dd, 1H, J = 12.60, 12.90, 8.50, 8.20) and 4.41 (dd, 1H, J = 12.60, 3.15); δ_C (125 MHz; $CDCl_3$) -5.4 (2 x CH_3), 18.3 (C), 21.6 (CH_2), 25.9 (3 x CH_3), 32.1 (CH_2), 33.4 (CH_2), 62.8 (CH_2), 68.6 (CH) and 80.6 (CH_2); LRMS, CI, *m/z* 295.3 ($[M+NH_3]^+$, 3%), 278.3 ($[M+H]^+$, 9%), 235 (5), 234 (30), 219 (7), 218 (20), 217 (100), 176 (5), 159 (8), 132 (6), 102 (3), 91 (6) and 85 (6); HRMS, ESI, *m/z* $C_{12}H_{28}NO_4Si$, requires 287.1782, found 287.1784 $[M+H]^+$.

***N,N'-bis-*(*tert*-butyloxycarbonyl)-*N''*-(6-(*tert*-butyldimethylsilyloxy)-2-hydroxyhexyl)-guanidine (15)**

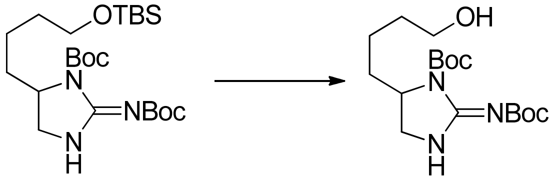


To a vigorously stirred, cooled (0°C) solution of nickel (II) chloride hexahydrate (8.67 g, 36.5 mmol) in methanol (50 mL) added sodium borohydride (4.10 g, 109.4 mmol) and stirring continued for 30 min. To the resultant black suspension was added **13** (3.38 g, 12.2 mmol) in methanol (20 mL), followed by the portion-wise addition of further sodium borohydride (9.23 g, 246.8 mmol). The reaction mixture was stirred for a further 2 hrs at rt after which time the reaction was filtered through a pad of Celite which was washed with further methanol (150 mL). Triethylamine (149.0 mL, 1.07 mol) was added and after stirring for 45 min, the guanylating agent time **14** (4.14 g, 13.4 mmol) dissolved in methanol (15 mL) was also added. After 48 hrs the reaction was diluted with water (400 mL) and extracted with ethyl acetate (3 x 250 mL). The combined organic extracts were dried over magnesium sulphate, evaporated and the resultant crude product purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether (5:95 to 25:75). Fractions eluting in 10:90 ethyl acetate/petroleum ether gave **15** as a clear oil (4.66 g, 9.5 mmol, 78%). R_f = 0.34 (40% ether in petrol); δ_H (500MHz; $CDCl_3$) 0.04 (s, 6H), 0.88 (s, 9H), 1.35-1.63 (m, 6H), 1.47 (s, 9H), 1.52 (s, 9H), 3.33-3.39 (m, 1H), 3.54 (ddd, 1H, *J* = 2.20, 6.30, 14.20), 3.62 (t, 2H, *J* = 6.00, 6.30), 3.74-3.76 (m, 1H), 4.59 (s, 1H, OH), 8.67 (t, 1H, *J* = 4.35, NH) and 11.47 (s, 1H, NH); δ_C (125 MHz; $CDCl_3$) -5.3 (2 x CH_3), 18.3 (C), 21.8 (CH_2), 26.0 (3 x CH_3), 28.0 (3 x CH_3), 28.2 (3 x CH_3), 32.7 (CH_2), 34.9 (CH_2), 47.6 (CH_2), 63.1 (CH_2), 71.8 (CH), 79.5 (C), 83.4 (C), 153.1 (C=N), 157.4 (C=O) and 162.9 (C=O); LRMS, CI, *m/z* 490.5 ($[M+H]^+$, 40%), 434 (4), 390 (3), 373 (4), 370 (1), 320 (2), 275 (3), 274 (9), 273 (14), 248 (6), 232 (11), 231 (44), 217 (100), 204 (11), 175 (4), 174 (5), 160 (15) 159 (21), 145 (20), 132 (16), 104 (18), 92 (18), 60 (30), 58 (49) and 45 (71); HRMS, ESI, *m/z* $C_{23}H_{48}N_3O_6Si$, requires 490.3307, found 490.3312 $[M+H]^+$.

tert-Butyl 2-(*tert*-butoxycarbonylimino)-5-(4-(tert-butyldimethylsilyloxy)butyl)imidazolidine-1-carboxylate (16)

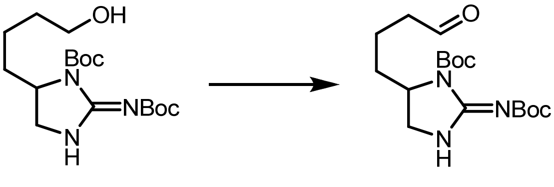
A stirred solution of **15** (628.3 mg, 1.28 mmol) in dichloromethane (13.5 mL) was cooled (-20°C) and triphenylphosphine (773.5 mg, 2.949 mmol), imidazole (340.5 mg, 5.001 mmol) and iodine (604.6 mg, 2.564 mmol) were added. Reaction progress was monitored by TLC and after stirring for 1 hr the reaction was diluted with chloroform (120 mL) which was then washed with ammonium chloride solution (sat, 120 mL) and brine (120 mL). After drying over magnesium sulphate and evaporation the crud product was purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether (10:90 to 40:60). Fractions eluting in 30:70 ethyl acetate/petroleum ether gave **16** as a pale yellow oil (576.8 mg, 1.23 mmol, 96%). R_f = 0.18 (40% ethyl acetate in petrol); δ_H (500MHz; $CDCl_3$) 0.02 (s, 6H), 0.87 (s, 9H), 1.30-1.67 (m, 6H), 1.47 (s, 9H), 1.51 (s, 9H), 3.38-3.52 (m, 1H), 3.59 (t, 2H, J = 6.30, 6.65, CH_2OTBS), 3.75-3.88 (m, 1H) and 4.08-4.16 (m, 1H); δ_C (125 MHz; $CDCl_3$) -5.3 (2 x CH_3), 18.3 (C), 20.7 (CH_2), 25.9 (3 x CH_3), 28.1 (3 x CH_3), 28.1 (3 x CH_3), 32.6 (CH_2), 33.6 (CH_2), 56.4 (CH), 56.4 (CH_2), 62.7 (CH_2) and 82.8 (C), four quaternary carbon signals were not detected; LRMS, CI, *m/z* 472.5 ($[M+H]^+$, 100%), 430 (2), 416 (20), 372 (76), 357 (35), 330 (2), 316 (16), 302 (12), 272 (18), 257 (31), 243 (7), 214 (8), 184 (15), 159 (6), 148 (13), 132 (29), 116 (11), 84 (57), 69 (37), 58 (96) and 45 (44); HRMS, ESI, *m/z* $C_{23}H_{46}N_3O_5Si$, requires 472.3201, found 472.3201 $[M+H]^+$.

Preparation of 2-*tert*-butoxycarbonylimido-4-(4-hydroxy-butyl)-imidazolidine-1-carboxylic acid *tert*-butyl ester



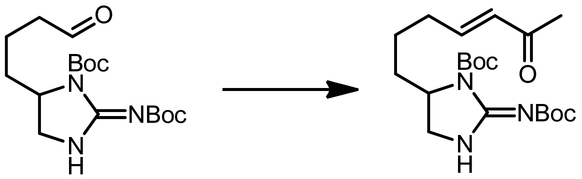
To a stirred solution of **16** (72.4 mg, 0.154 mmol) in THF (2 mL) at 0°C was added a solution of TBAF in THF (1M, 0.16 mL, 0.16 mmol). Reaction progress was monitored by TLC and after 24 hrs the reaction was quenched with saturated ammonium chloride solution (2 mL) and extracted with chloroform (3 x 5 mL). The combined organic extracts where washed with brine (5 mL) and dried over anhydrous magnesium sulphate. After evaporation, purification was achieved by flash column chromatography on silica gel using ethyl acetate/petroleum ether (80:20 to 100:0) and ethyl acetate/methanol (90:10). Fractions eluting in ethyl acetate gave the title compound as a clear oil (54.4 mg, 0.152 mmol, 99%). R_f = 0.03 (100% ethyl acetate); δ_H (500MHz; $CHCl_3$) 1.22-1.40 (m, 2H), 1.44 (s, 9H), 1.45 (s, 9H), 1.46-1.58 (m, 4H), 3.27-3.35 (m, 1H), 3.50 (t, 2H, J = 6.30), 3.66-3.72 (m, 1H) and 3.93-4.40 (m, 1H); δ_C (125 MHz; $CHCl_3$) 20.2 (CH_2), 27.8 (3 x CH_3), 27.8 (3 x CH_3), 32.0 (CH_2), 33.2 (CH_2), 56.0 (CH), 56.0 (CH_2), 61.8 (CH_2), 80.2 (C) and 82.6 (C), three quaternary carbon signals were not detected; LRMS, EI, *m/z* 358.4 ($[M+H]^+$, 55%), 319 (5), 302 (36), 279 (7), 258 (29), 243 (18), 211 (5), 202 (30), 186 (13), 156 (8), 133 (40), 116 (29), 98 (20), 79 (48), 69 (53), 58 (100) and 45 (54); HRMS, ESI, *m/z* $C_{17}H_{31}N_3O_5$, requires 358.2336, found 358.2335 $[M+H]^+$.

Preparation of *tert*-butyl 2-(*tert*-butoxycarbonylimino)-5-(4-oxobutyl)imidazolidine-1-carboxylate (17)



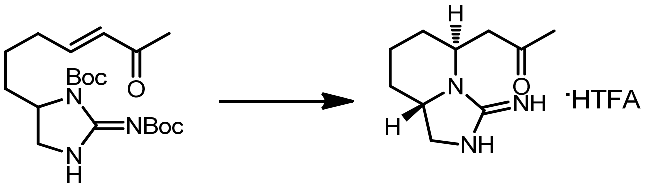
To a stirred solution of **16** (200.9 mg, 0.563 mmol) in DCM (2 mL) at rt was added Dess-Martin periodinane (716.0 mg, 1.69 mmol). Reaction progress was monitored by TLC and after 3.5 hrs the reaction was quenched with a saturated solution of sodium bicarbonate (20 mL) and the aqueous layer extracted with chloroform (3 x 20 mL). The combined organic extracts where washed with brine (20 mL) and dried over magnesium sulphate. After evaporation, trituration/filtration of the resultant material using diethyl ether (5 x 20 mL) followed by evaporation of the filtrate gave **17** as a clear oil (192.5 mg, 0.542 mmol, 96%) which was used immediately without further purification. R_f = 0.30 (1% methanol in ethyl acetate); δ_H (500MHz; $CDCl_3$) 1.41 (s, 9H), 1.46 (s, 9H), 1.50-1.62 (m, 4H), 2.44 (td, 2H, J = 0.95, 6.65), 3.43 (dd, 1H, J = 3.15, 12.65), 3.79 (dd, 1H, J = 9.15, 10.35, 12.30, 12.60), 4.05-4.09 (m, 1H) and 9.71 (s, 1H); δ_C (125 MHz; $CDCl_3$) 16.6 (CH_2), 27.9 (3 x CH_3), 28.0 (3 x CH_3), 33.0 (CH_2), 43.2 (CH_2), 55.9 (CH), 55.9 (CH_2), 80.5 (C), 83.1 (C) and 201.2 (C=O), three quaternary carbon signals were not detected. LRMS, ESI, m/z 356.2 ($[M+H]^+$, 100%), 332 (39), 316 (78), 300 (54), 260 (76), 214 (67), 182 (58) and 164 (29); HRMS, ESI, m/z $C_{17}H_{30}N_3O_5$, requires 356.2180, found 356.2186 $[M+H]^+$.

Preparation of *tert*-butyl 2-(*tert*-butoxycarbonylimino)-5-((*E*)-6-oxohept-4-enyl)imidazolidine-1-carboxylate (19)



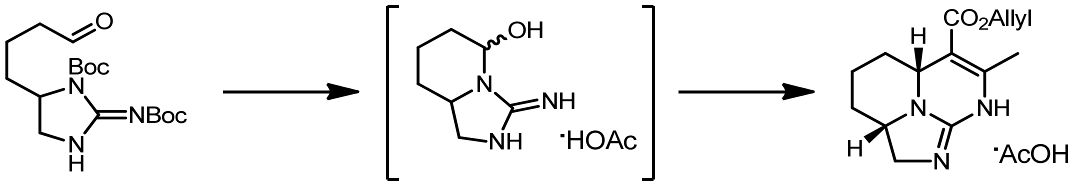
To a stirred suspension of lithium chloride (28.2 mg, 0.65 mmol) in dry acetonitrile (3 mL) was added phosphonate **18** (0.075 mL, 0.54 mmol). After 10 min, diisopropylethylamine (0.11 mL, 0.65 mmol) was added and the mixture stirred for a further 10 min. At this point **17** (192.4 mg, 0.54 mmol) dissolved in acetonitrile (2 mL) was added and the mixture stirred for 48 hrs. The reaction was diluted with water (15 mL) and extracted with diethyl ether (3 x 15 mL) and the combined organic extracts washed with brine (10 mL) and dried over anhydrous magnesium sulphate. After evaporation, compound **19** (183.3 mg, 0.464 mmol, 86%) was obtained as a pale yellow oil and was used without further purification. R_f = 0.22 (100% ethyl acetate); δ_H (500MHz; $CDCl_3$) 1.22–1.69 (m, 6H), 1.49 (s, 9H), 1.50 (s, 9H), 1.64-1.75 (m, 2H), 2.23 (s, 3H), 3.42–3.52 (m, 1H), 3.77–3.87 (m, 1H), 4.09–4.18 (m, 1H), 6.07 (d, 1H, J = 15.75) and 6.74 (dt, 1H, J = 6.95, 15.75); δ_C (125 MHz; $CDCl_3$) 22.7 (CH_2), 27.0 (CH_3), 28.1 (3 x CH_3), 28.1 (3 x CH_3), 32.1 (CH_2), 33.3 (CH_2), 56.1 (CH), 56.1 (CH_2), 80.8 (C), 83.1 (C), 131.7 (CH), 146.8 (CH) and 198.3 (C=O), three quaternary carbon signals were not detected; LRMS, ESI, *m/z* 791.5 ($[2M+H]^+$, 79%), 762 (7), 708 (3), 692 (6), 593 (7), 448 (12), 430 (17), 412 (49), 396 ($[M+H]^+$,100), 374 (2), 356 (13), 340 (27), 296 (10), 279 (19), 256 (6), 240 (23), 212 (3) and 196 (17); HRMS, ESI, *m/z* $C_{20}H_{34}N_3O_5$, requires 396.2493, found 396.2497 $[M+H]^+$.

Preparation of (5*S*,8a*S*)-5-(2-oxopropyl)hexahydroimidazo[1,5-*a*]pyridin-3(2*H*)-iminium trifluoroacetate (20)



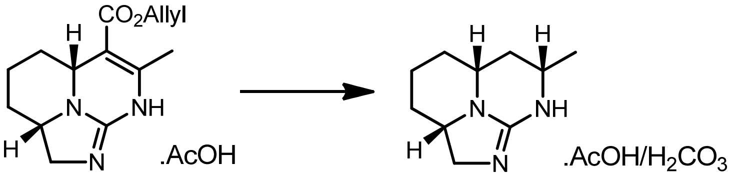
To a stirred solution of **19** (162.2 mg, 0.410 mmol) in dichloromethane (1.5 mL) was added trifluoroacetic acid (1.5 mL) and the mixture stirred at rt for 24 hrs. After evaporation under reduced pressure, residual trifluoroacetic acid was removed by azeotropic evaporation with chloroform (3 x 15 mL) and the residue dried under high vacuum for 4 hrs. The resultant guanidinium salt was dissolved in dichloromethane (4 mL) and triethylamine (0.07 mL, 0.45 mmol) was added and the mixture stirred at rt for 48 hrs. After evaporation, purification by flash column chromatography on silica gel using chloroform/methanol (100:0 to 86:14 in 0.5% increments) gave **20** (88.5 mg, 0.276 mmol, 70%) as a viscous oil. An analytical sample was obtained by slow crystallisation from ethyl acetate. R_f = 0.08 (10% methanol in chloroform); δ_H (500MHz; $CDCl_3$) 1.44 (td, 1H, *J* = 3.15, 13.55), 1.55 (qt, 1H, *J* = 2.85, 3.15, 3.50, 13.20, 13.25, 13.55, 16.40, 16.75), 1.63 (d, 1H, *J* = 13.55), 1.72 (ddd, 1H, *J* = 3.80, 3.75, 5.35, 5.40, 13.55) 1.80 (dt, 1H, *J* = 3.15, 3.35, 3.45, 13.55, 13.85), 1.92 (dd, 1H, *J* = 2.80, 3.15, 12.60, 12.95), 2.20 (s, 3H), 2.54 (dd, 1H, *J* = 3.15, 18.50), 3.04 (dd, 1H, *J* = 9.15, 9.45, 18.00, 18.30), 3.23 (dd, 1H, *J* = 7.25, 9.45), 3.77 (t, 1H, *J* = 9.45, 9.50), 3.85 (td, 1H, *J* = 3.45, 3.80, 11.35), 4.39 (t, 1H, *J* = 4.10, 5.05) and 9.75 (s, 1H, NH); δ_C (125 MHz; $CDCl_3$) 18.2 (CH_2), 28.9 (CH_2), 30.1 (CH_3), 31.0 (CH_2), 44.3 (CH_2), 45.4 (CH_2), 47.6 (CH), 53.7 (CH), 157.9 (C=N) and 206.7 (C=O); LRMS, Positive ESI, *m/z* 391.3 ($[2M+H]^+$, 22%), 196 ($[M+H]^+$, 100), 138 (5) and 130 (8); LRMS, Negative ESI *m/z* 227.0 ($[2M-H]^-$, 44%), and 113.0 (100); HRMS, ESI, *m/z* $C_{10}H_{18}N_3O$, requires 196.1444, found 196.1441 $[M+H]^+$.

Preparation of (5aR,8aS)-5-((allyloxy)carbonyl)-4-methyl-3,5a,6,7,8,8a-hexahydro-1*H*-2,2a^1,3-triazaacenaphthylen-2-ium acetate (23)



A solution of **17** (143.6 mg, 0.402 mmol) in glacial acetic acid (3 mL) was stirred at rt for 24 hrs. After evaporation under reduced pressure, residual acetic acid was removed by azeotropic evaporation with chloroform (3 x 15 mL) and the residue dried under high vacuum for 4 hrs. The resultant salt was dissolved in trifluoroethanol (1.5 mL), morpholine acetate (147.9 mg, 1.005 mmol), **22** (285.8 mg, 2.01 mmol) and anhydrous sodium sulphate (1 g) were added and the resultant mixture stirred at 70°C for 12 d. After cooling to rt and evaporation purification was achieved by flash column chromatography on silica gel using methanol/chloroform (stepwise gradient 0:100 to 96:4 on 0.5% increments) containing 1% acetic acid. The fractions eluting in 98:2 methanol chloroform gave **23** as a tan oil (55.8 mg, 0.174 mmol, 43%). R_f = 0.26 (10% methanol in chloroform); δ_H (500MHz; $CDCl_3$) 1.36 (qd, 1H, J = 2.50, 2.55, 2.80, 3.15, 12.30, 12.60, 12.90), 1.51-1.72 (m, 3H), 1.87 (dt, 1H, J = 2.80, 2.85, 3.15, 13.20, 13.25, 13.55), 1.96 (dd, 1H, J = 2.85, 3.15, 12.90, 13.20) 2.00 (s, 3H), 2.36 (s, 3H), 3.39 (dd, 1H, J = 1.85, 10.40), 3.75 (t, 1H, t, J = 9.15, 9.80), 3.91 (tt, 1H, J = 1.55, 2.20, 6.60, 7.25), 4.41 (dd, 1H, J = 2.80, 11.35), 4.63-4.65 (m, 2H), 5.32 (ddd, 2H, J = 0.95, 1.25, 15.5, 17.30, 33.40) and 5.89-5.97 (m, 1H); δ_C (125 MHz; $CDCl_3$) 18.6 (CH_3), 21.3 (CH_2), 24.0 (CH_3), 29.5 (CH_2) 31.3 (CH_2), 48.0 (CH_2), 52.7 (CH), 57.9 (CH), 65.0 (CH_2), 101.5 (C), 118.2 (CH_2), 132.2 (CH), 146.7 (C), 154.6 (C=N), 165.1 (C=O) and 179.5 (C=O); LRMS, Positive ESI, *m/z* 523.3 ($[2M+H]^+$, 5%), 402 (4), 314 (15), 304 (6), 262 ($[M+H]^+$, 100) and 222 (2); HRMS, ESI, *m/z* $C_{14}H_{20}N_3O_2$, requires 262.1550, found 262.1548 $[M+H]^+$.

Preparation of (4S,5aR,8aS)-4-methyl-3,4,5,5a,6,7,8,8a-octahydro-1*H*-2,2a1,3-triazaacenaphthylen-2-ium acetate (24)



To a stirred solution of **23** (21.5 mg, 0.067 mmol) in a mixture of anhydrous methanol (1 mL) and anhydrous THF (1 mL) was added tetrakis(triphenylphosphine)palladium(0) (1.6 mg, 0.0014 mmol) and pyrrolidine (5.6 mg, 0.079 mmol). The reaction was stirred at rt and progress monitored by TLC. After 1.5 hr the solvent was removed under reduced pressure and the residue dissolved in methanol (0.5 mL) and acetic acid (0.5 mL) and cooled (0°C), whereupon sodium cyanoborohydride (21.4 mg, 0.340 mmol) was added and the mixture stirred to rt over 16 hrs. After evaporation the crude product was purified by flash column chromatography on silica gel using methanol/chloroform (stepwise gradient of 0.5% increments 0:100 to 96:4) containing 1% acetic acid. The fractions eluting in 98:2 methanol chloroform gave **24** (7.0 mg, 0.034 mmol, 57%) as a pale yellow oil; on standing or in methanol solution the acetate counter-ion is slowly converted to the carbonate by atmospheric CO_2. R_f = 0.15 (10% methanol in chloroform); δ_H (500MHz; $CD_3OD/CDCl_3$) 1.16-1.22 (m, 1H), 1.27 (d, 3H, J = 6.65), 1.36-1.43 (m, 1H), 1.51-1.54 (m, 1H) 1.92-1.97 (m, 1H), 2.05-2.07 (m, 1H), 2.16 (s, 3H) 2.18 (dt, 1H, J = 3.44, 3.45, 3.80, 13.55), 3.16-3.20 (m, 1H), 3.34-3.39 (m, 1H), 3.56-3.60 (m, 1H) and 3.75-3.83 (m, 2H); δ_C (125 MHz; $CD_3OD/CDCl_3$) 20.7 (CH_2), 23.1 (CH_2), 30.6 (CH_2) 31.9 (CH_2), 37.8 (CH_2), 47.0 (CH), 51.6 (CH), 58.2 (CH), guanidine quaternary carbon signal not detected; LRMS, Positive ESI, *m/z* 395.3 (5), 239.2 (2) and 180.2 ($[M+H]^+$, 100%). HRMS, ESI, *m/z* $C_{10}H_{18}N_3$, requires 180.1495, found 180.1492 $[M+H]^+$.

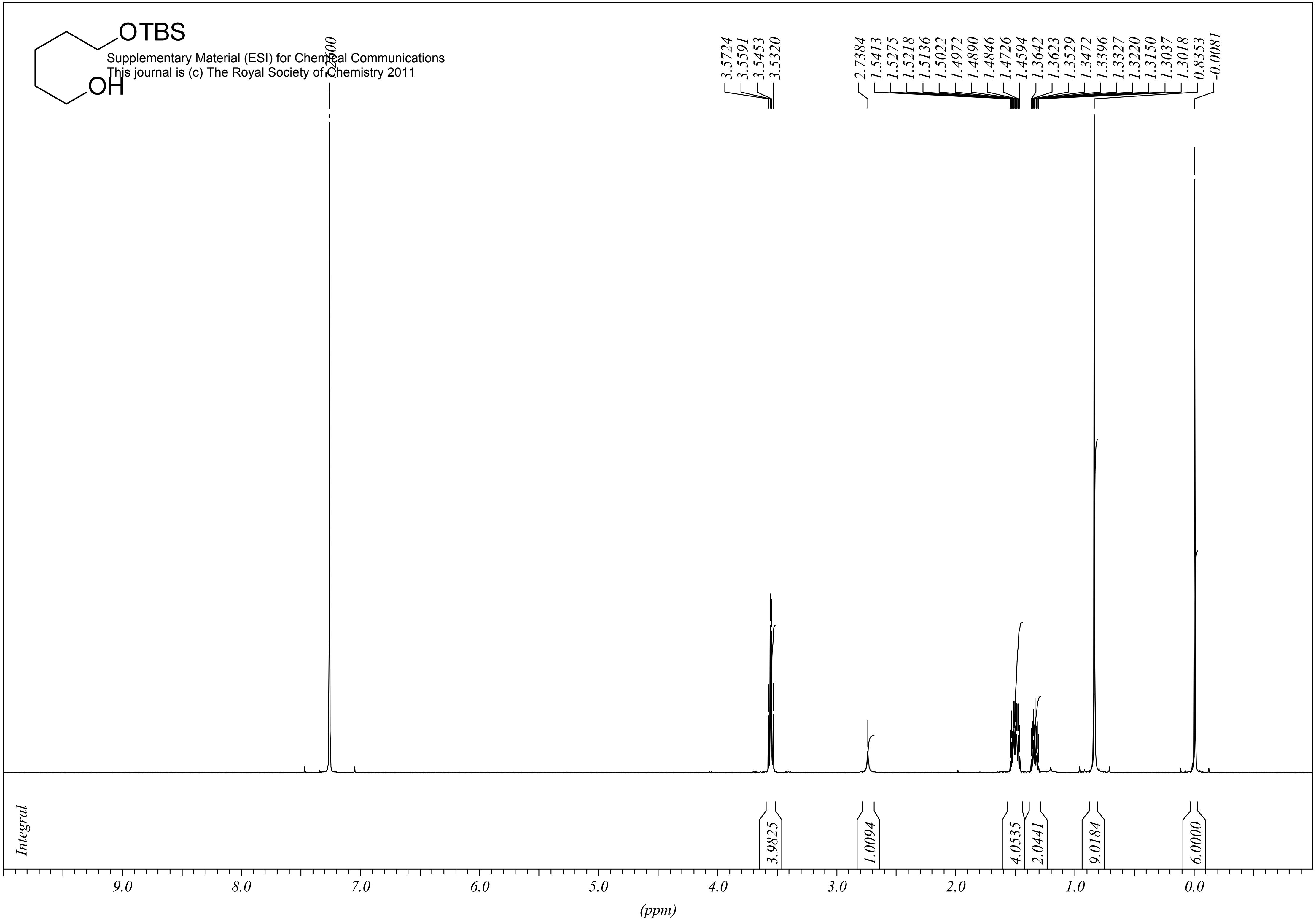
References

1. J. Leonard, B. Lygo, G. Procter, *Advanced Practical Organic Chemistry 2nd Edition.,* Chapman & Hall, New York, 1995

2. P. G. McDougal, J. G. Rico, Y. Oh, B. D. Condon, *J. Org. Chem.*, 1986, **51**, 3388

3. J. C. Gilbert, T. A. Kelly, *J. Org. Chem.*, 1988, **53**, 449

DML-07-10-15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1.3472
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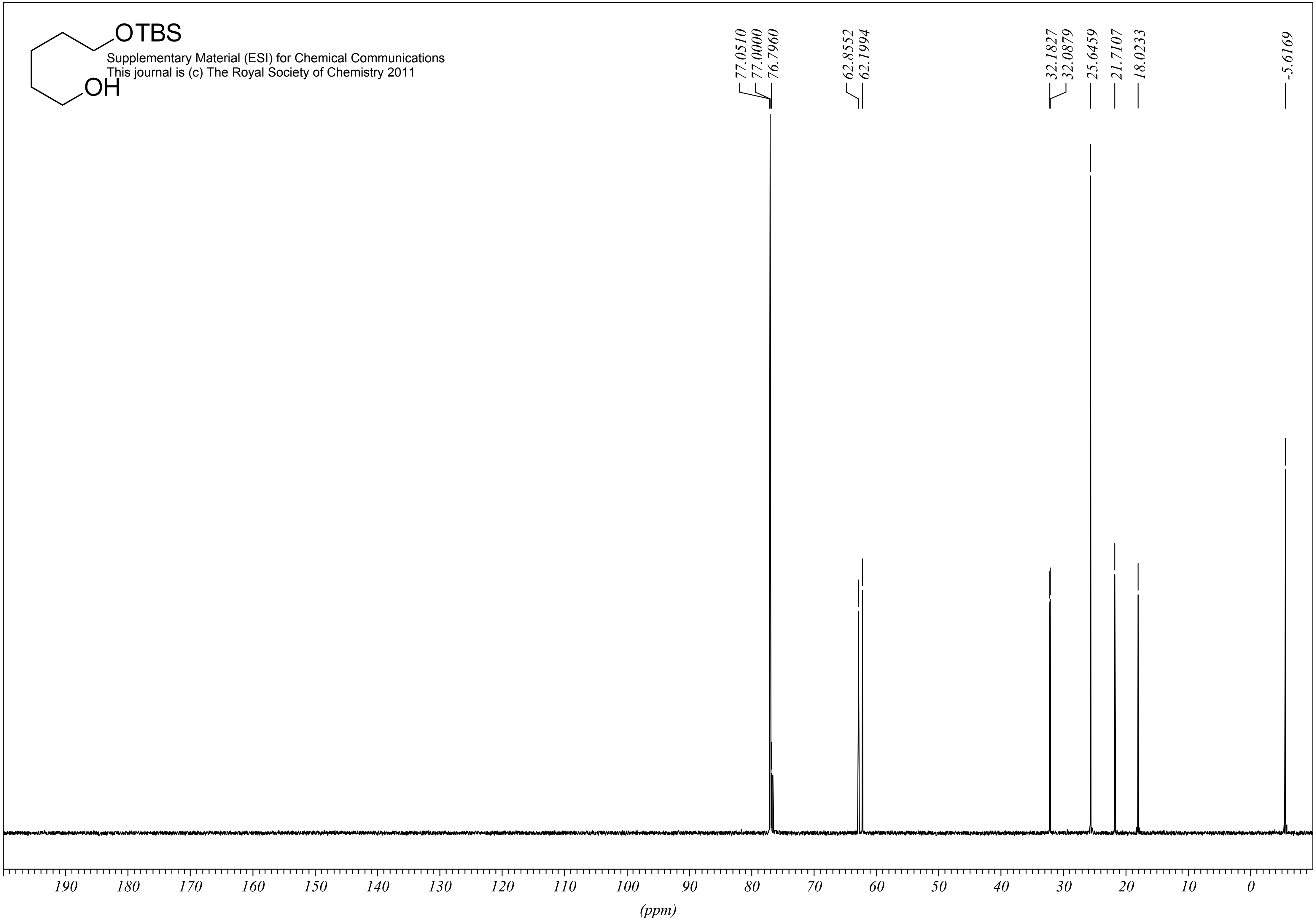
DML 07 10 15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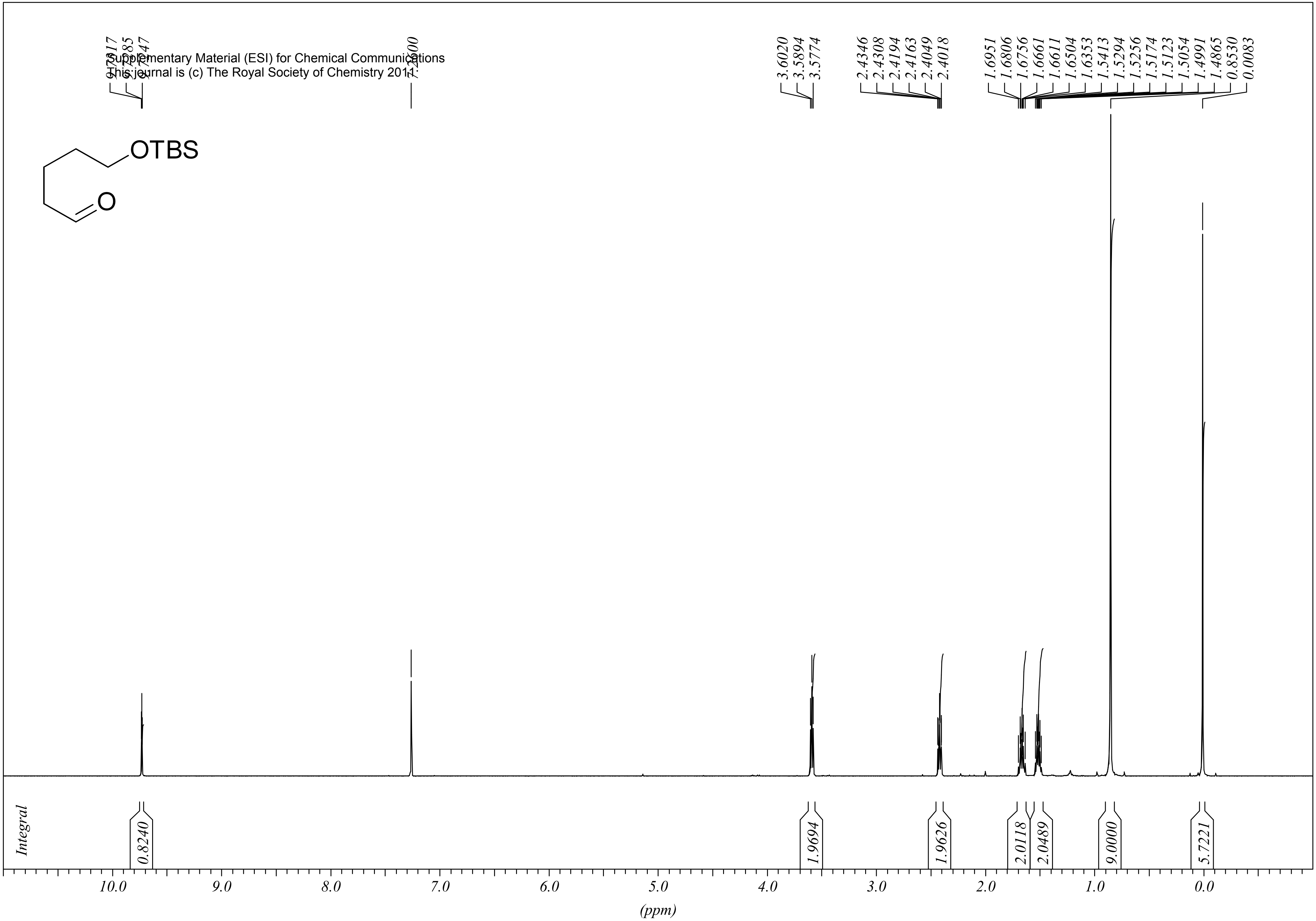
(ppm)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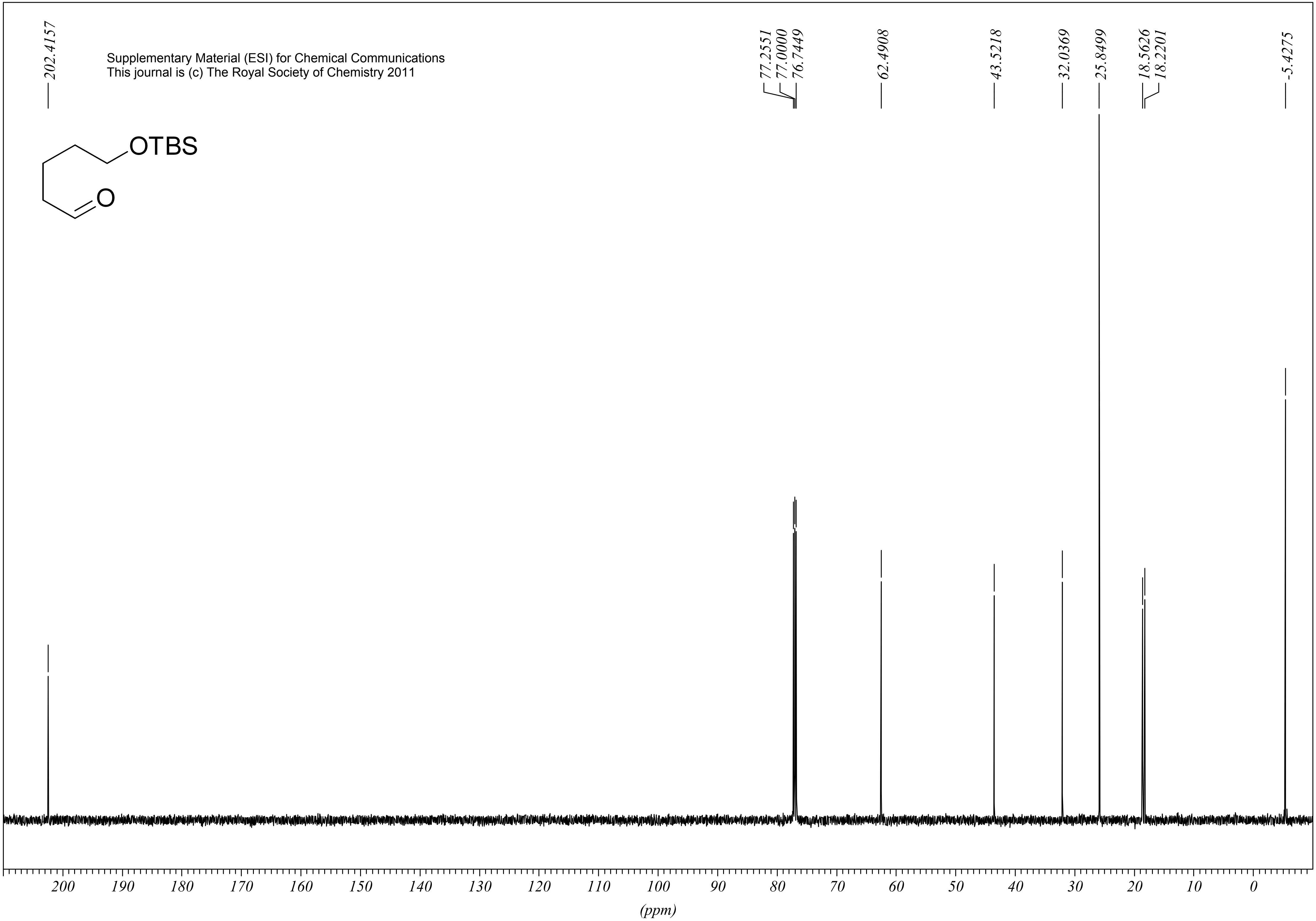
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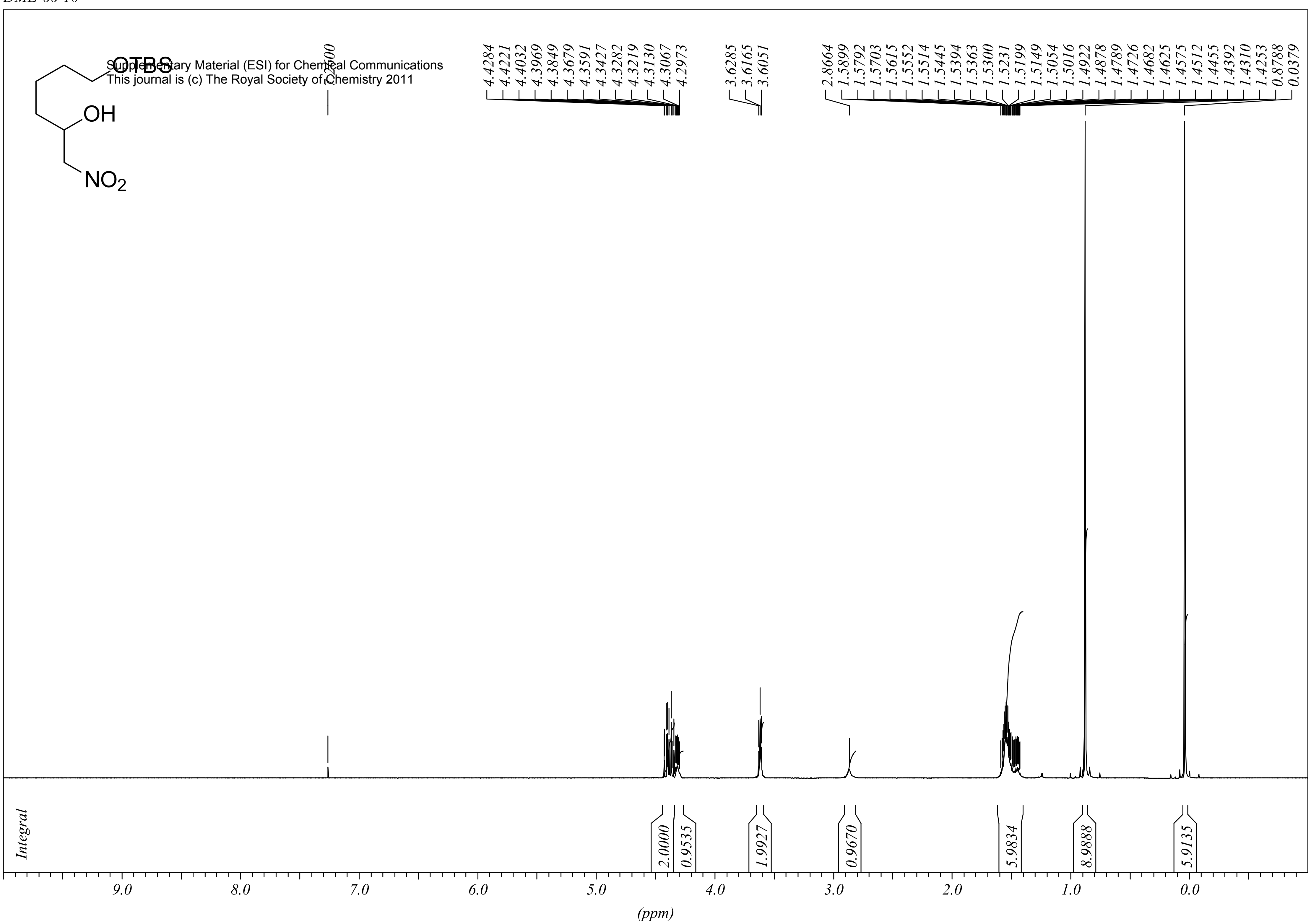
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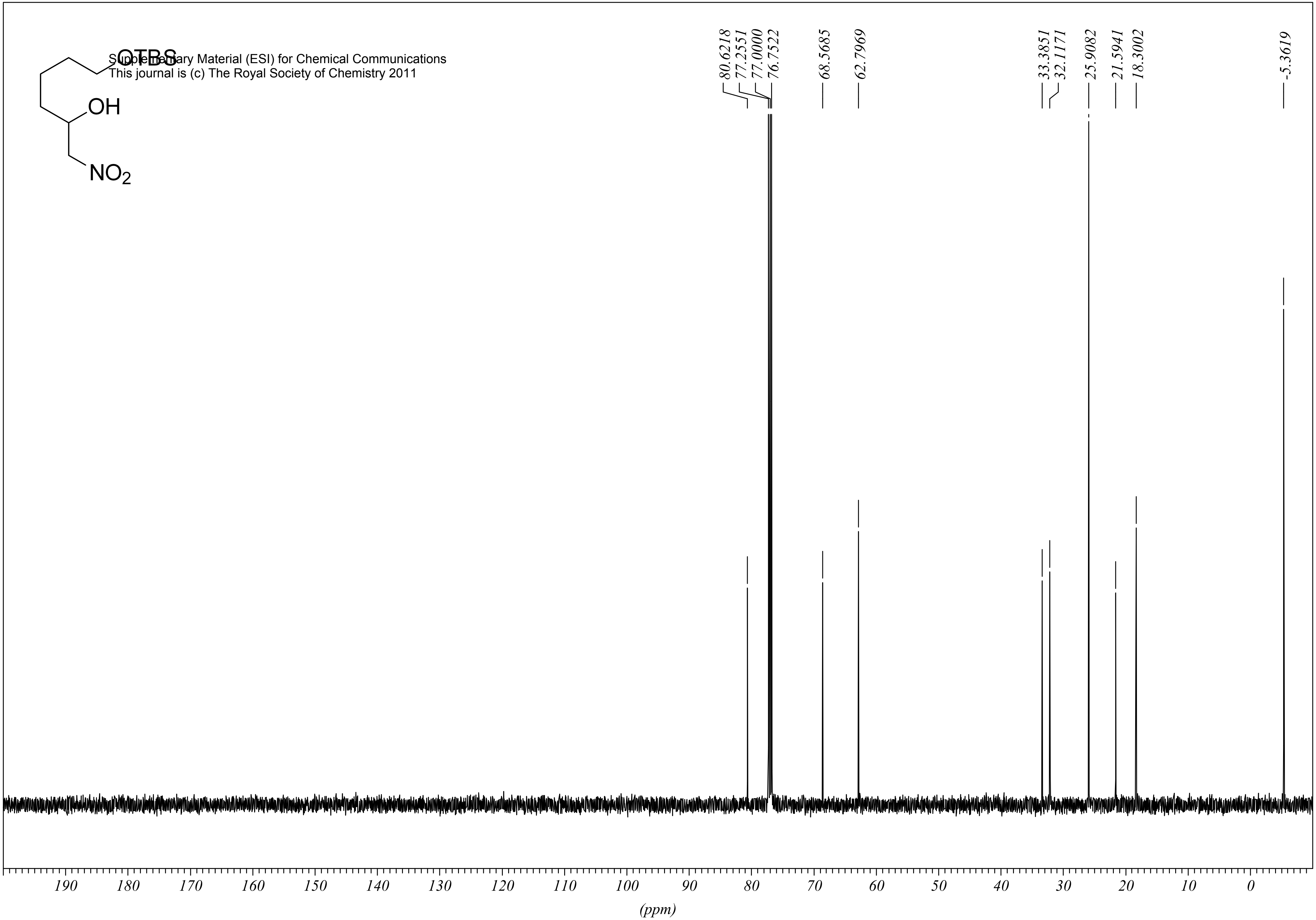
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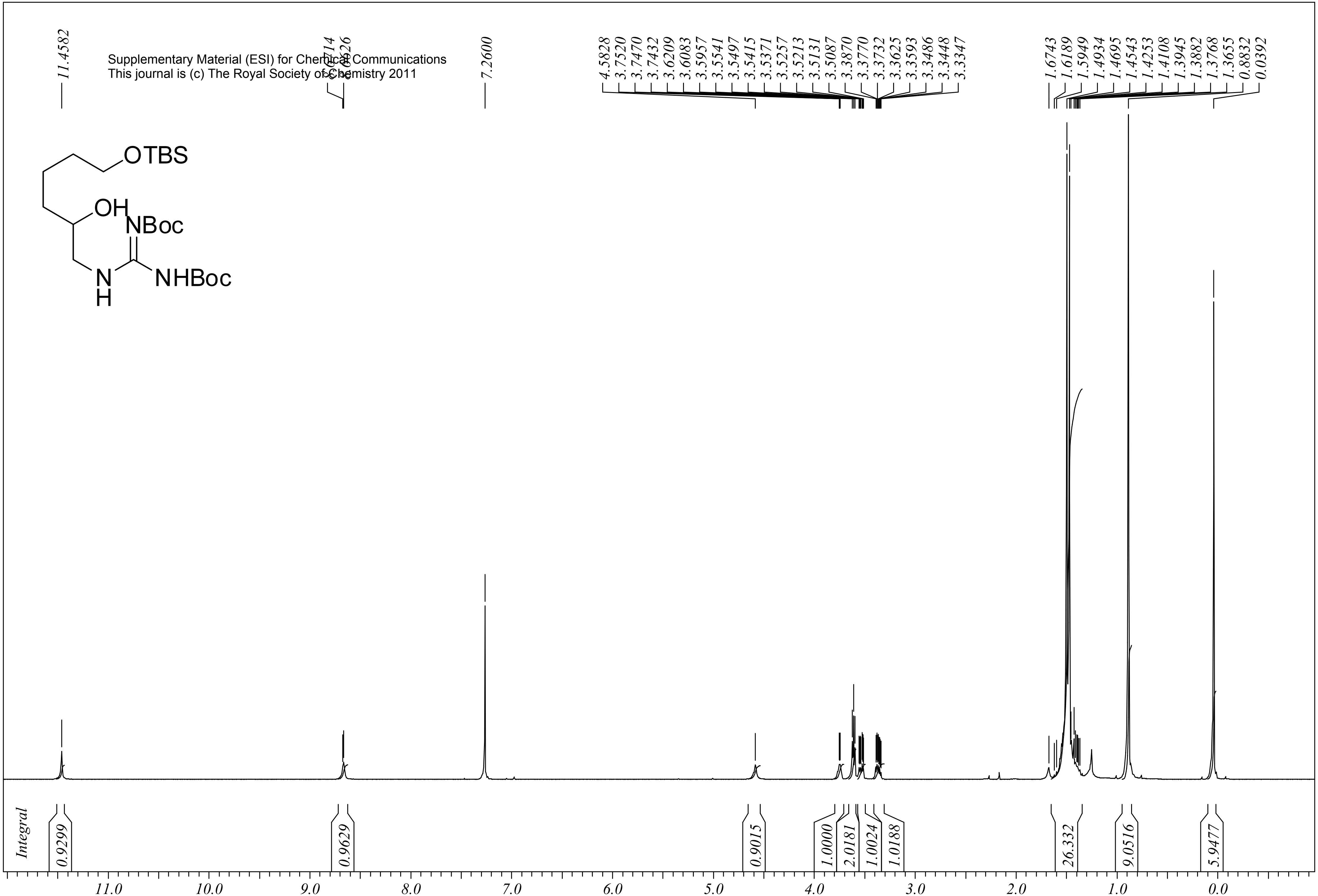
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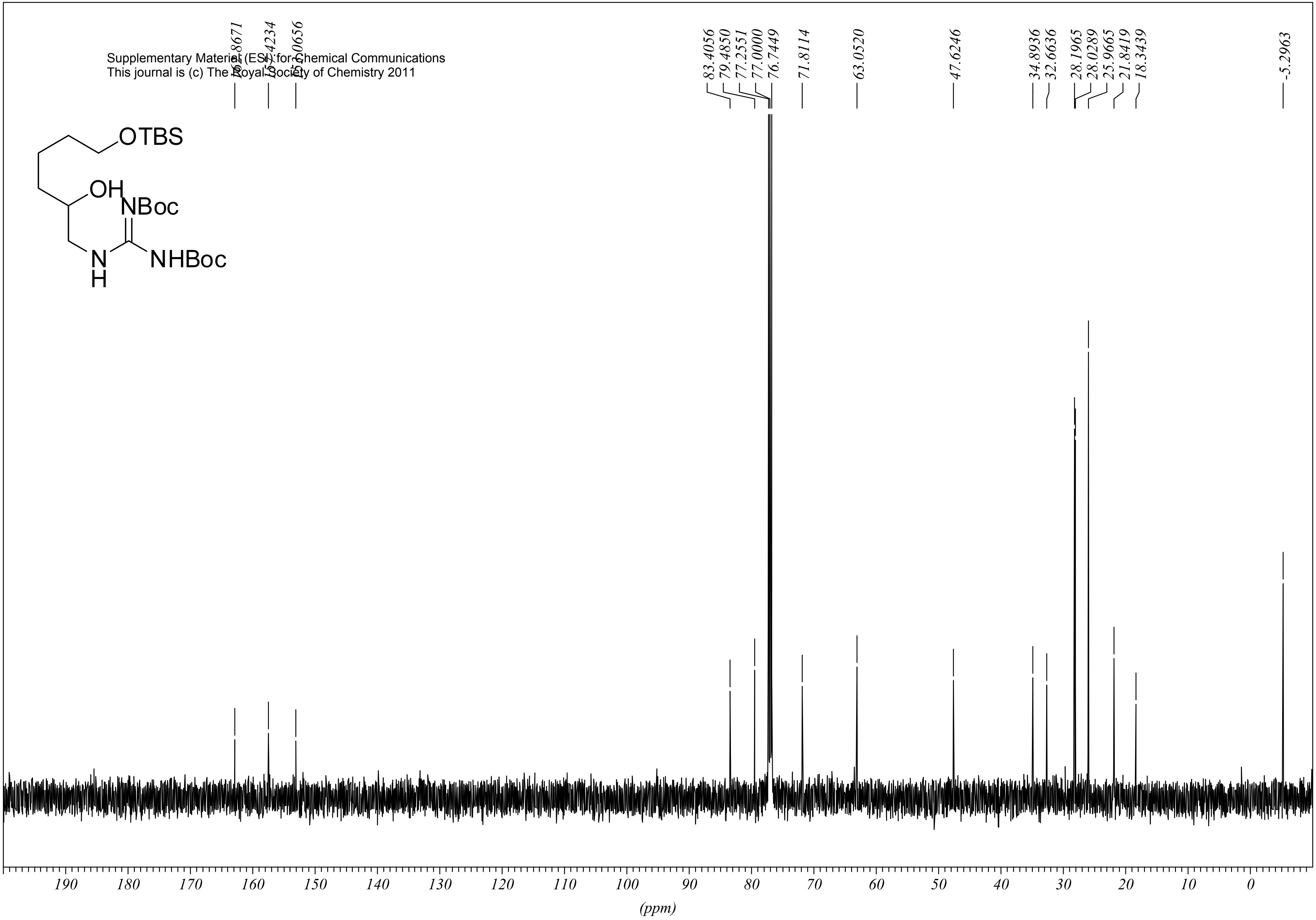
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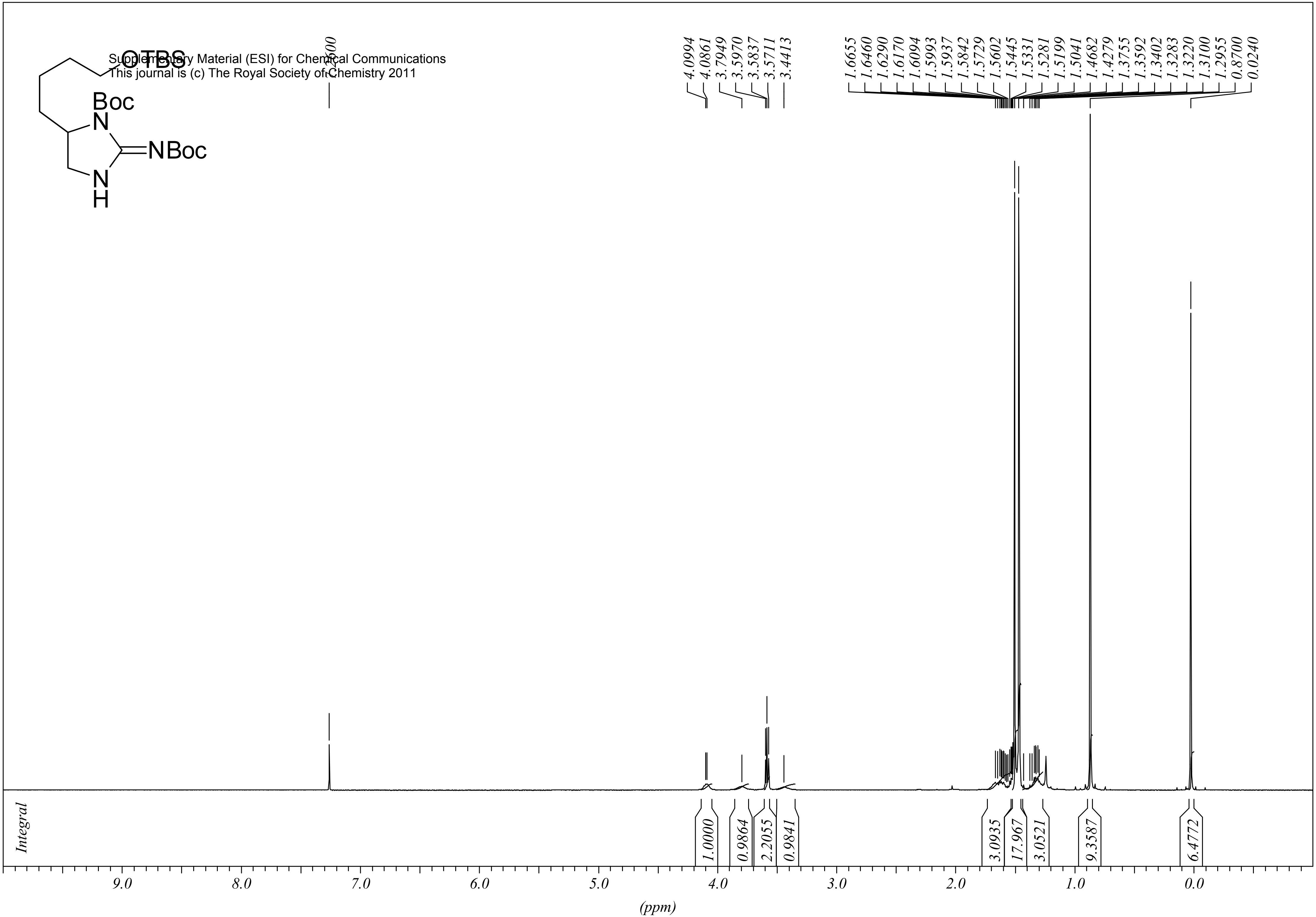
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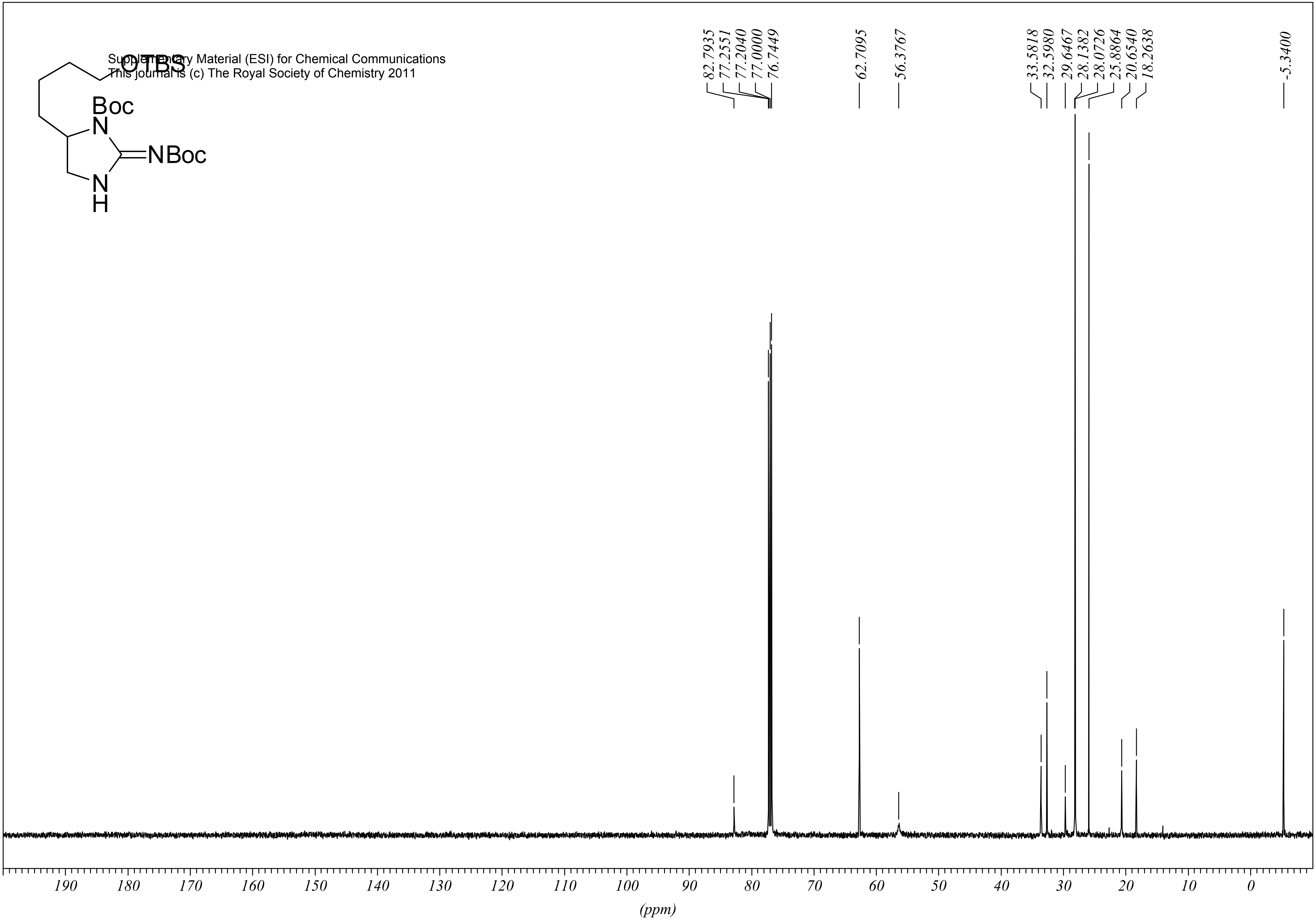
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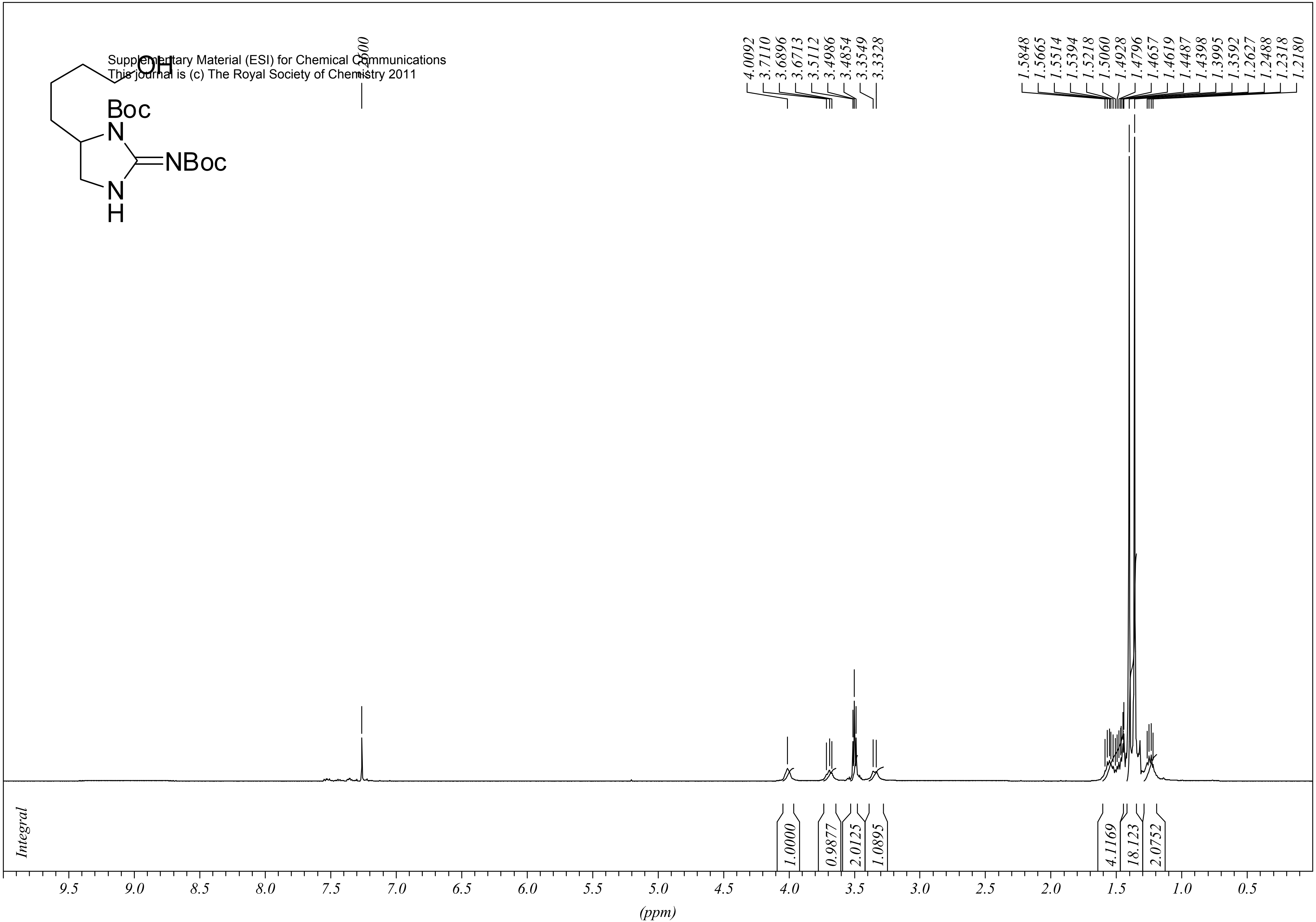
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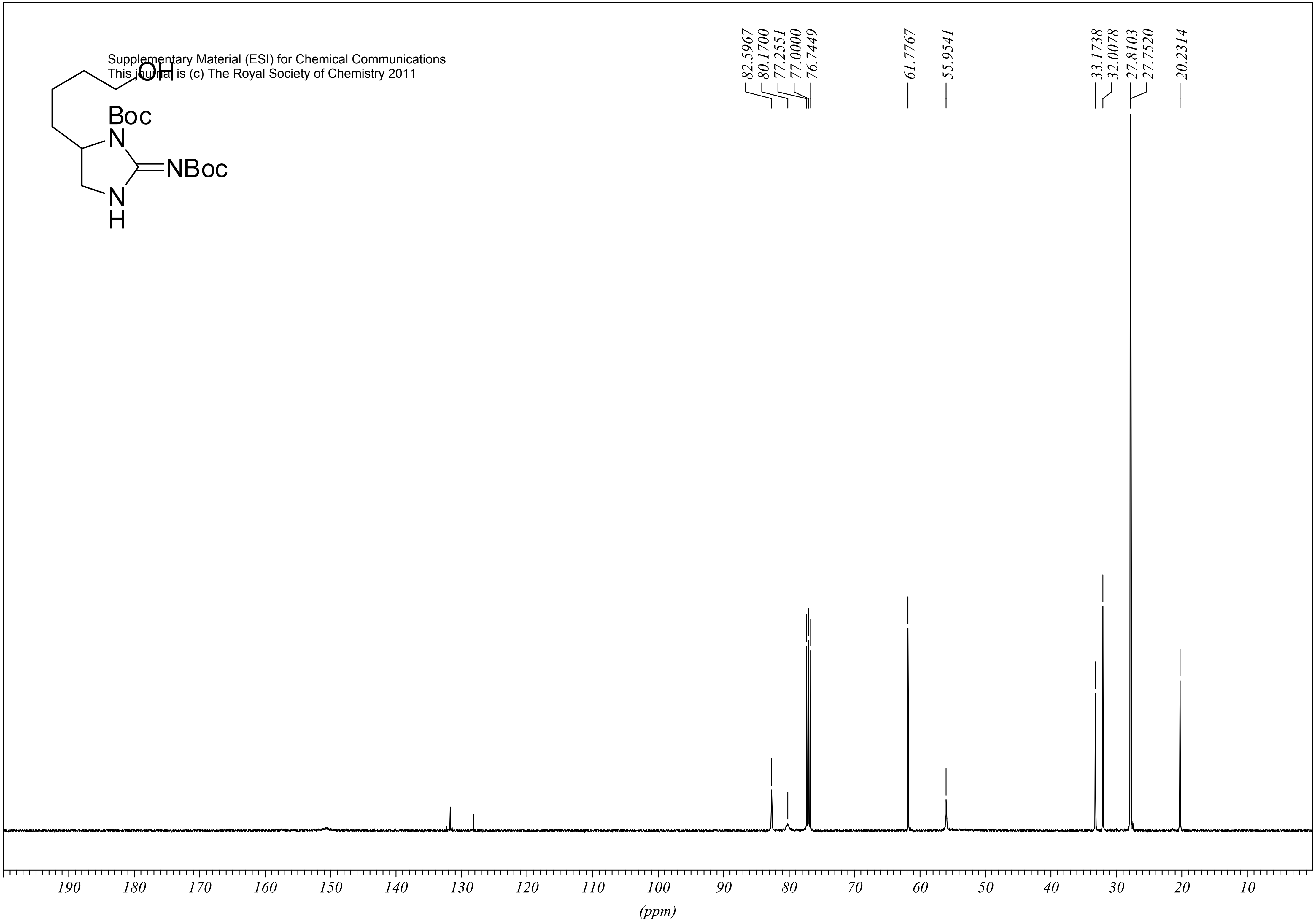
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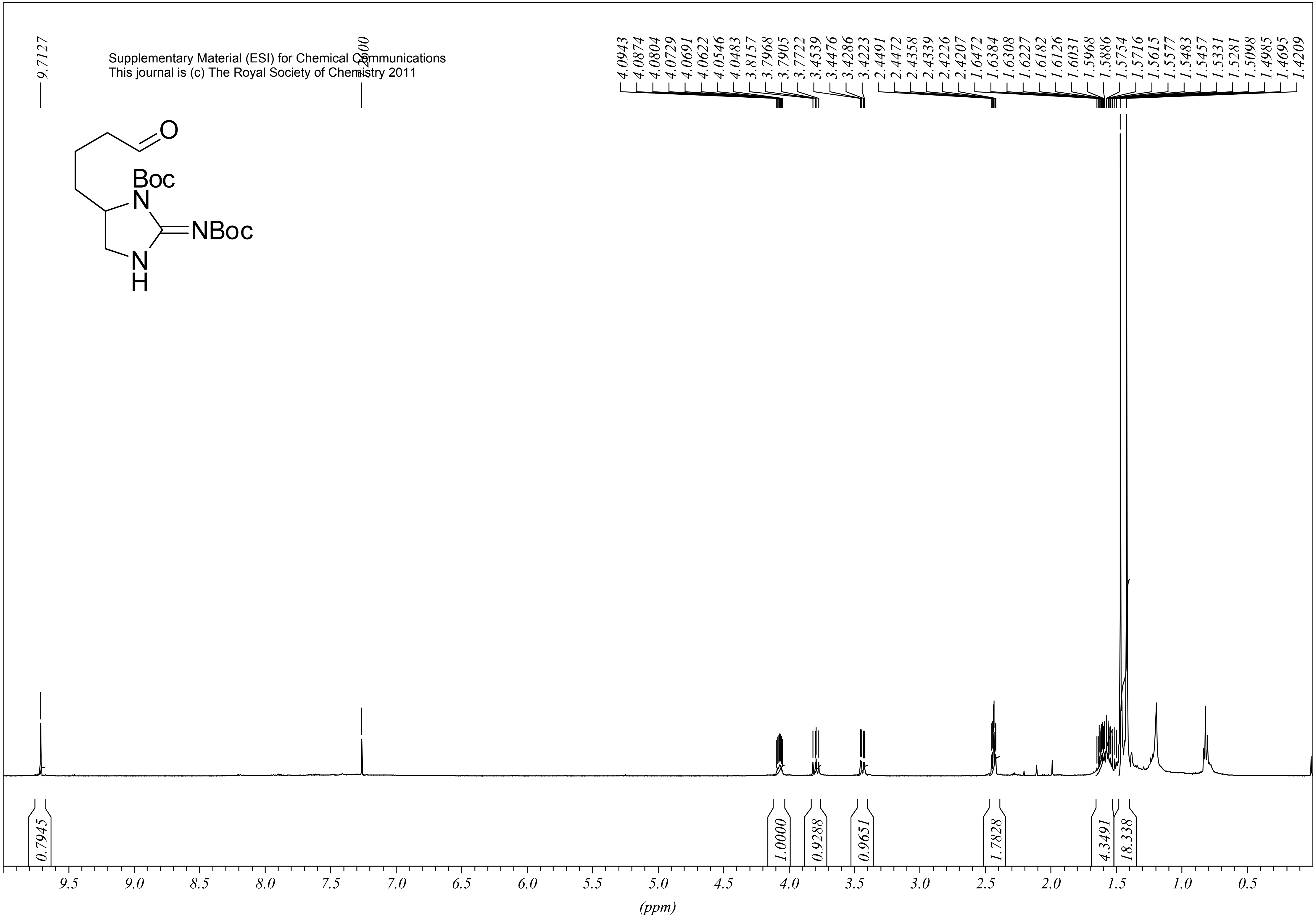
DML 200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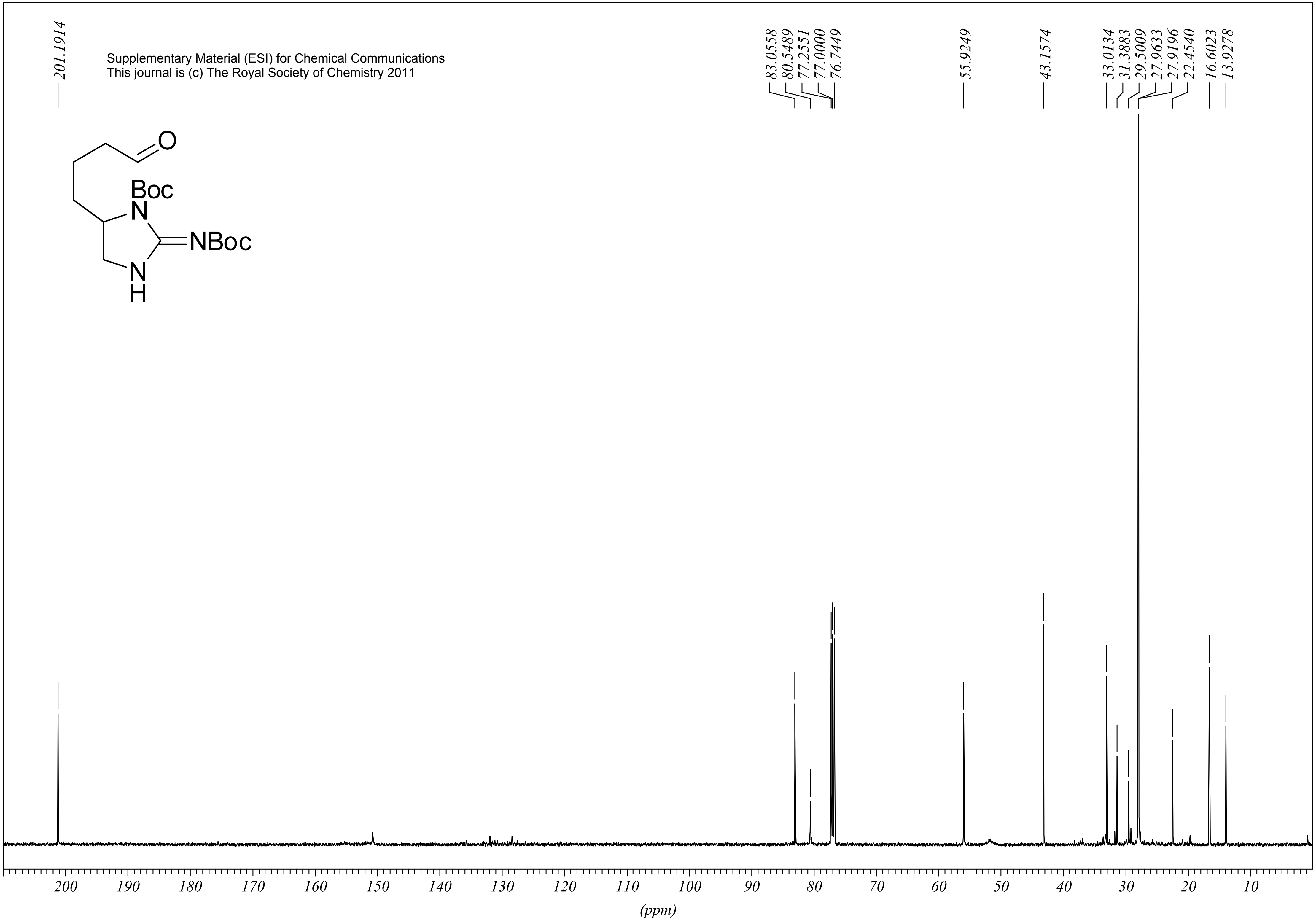
DML-200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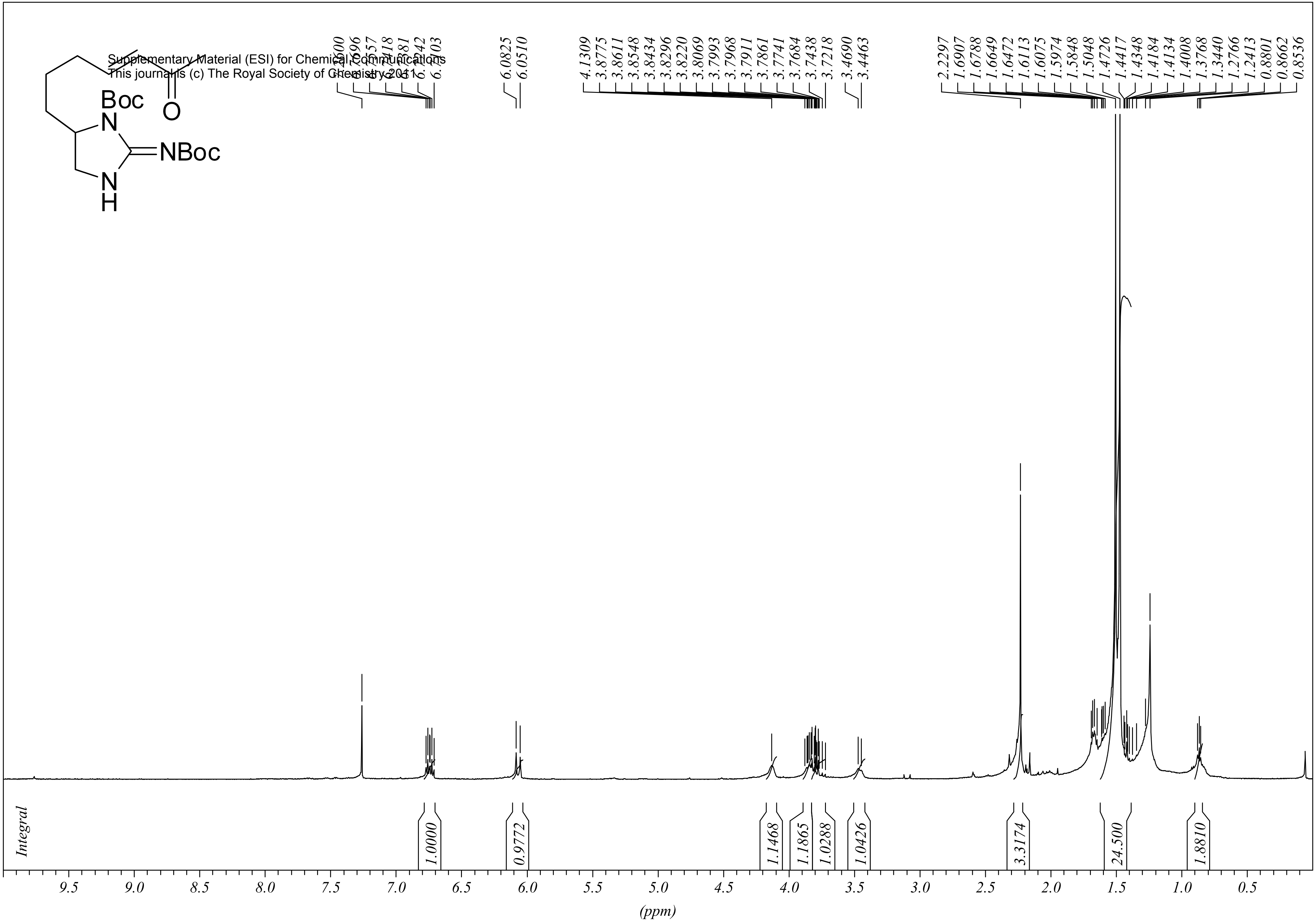
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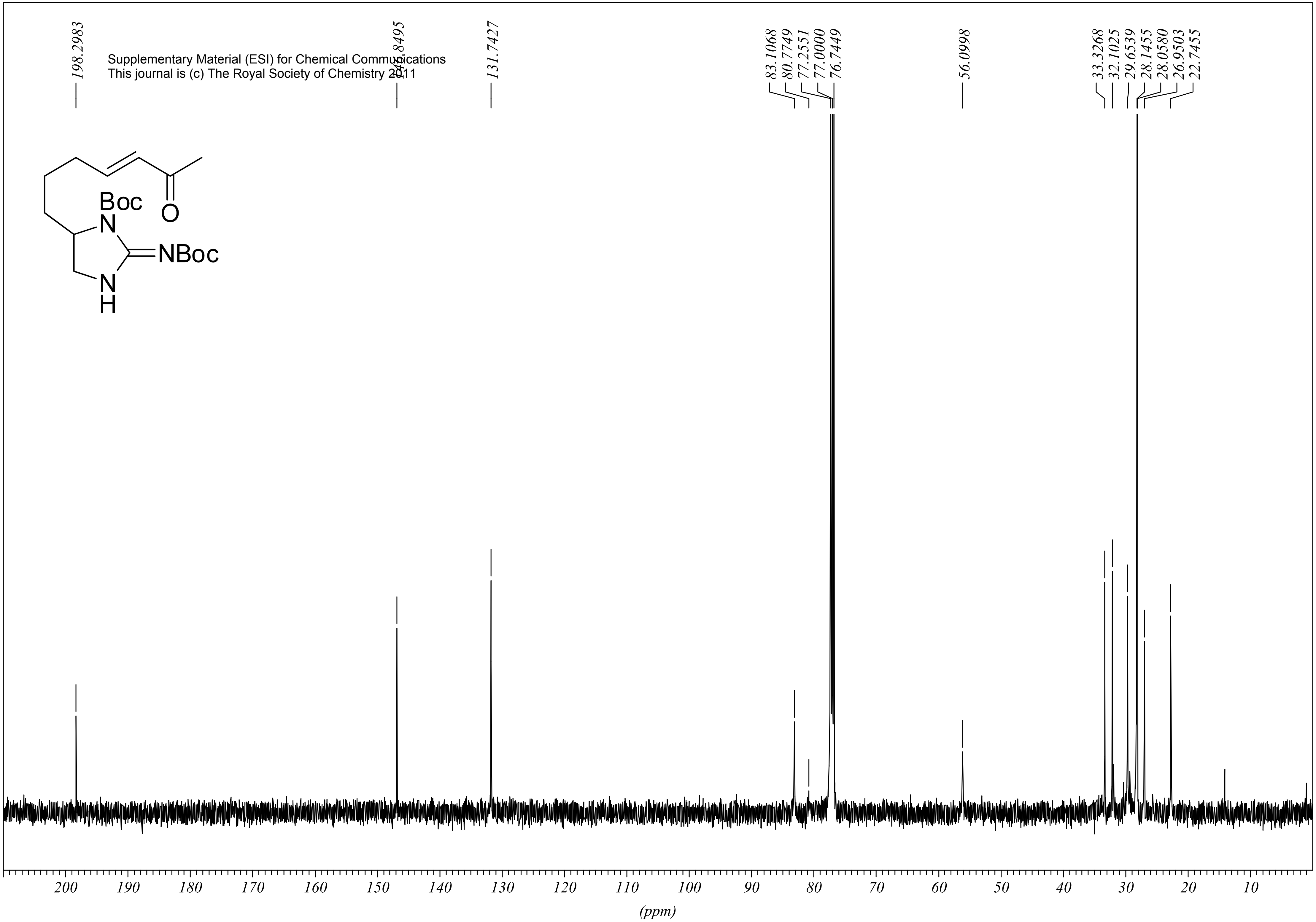
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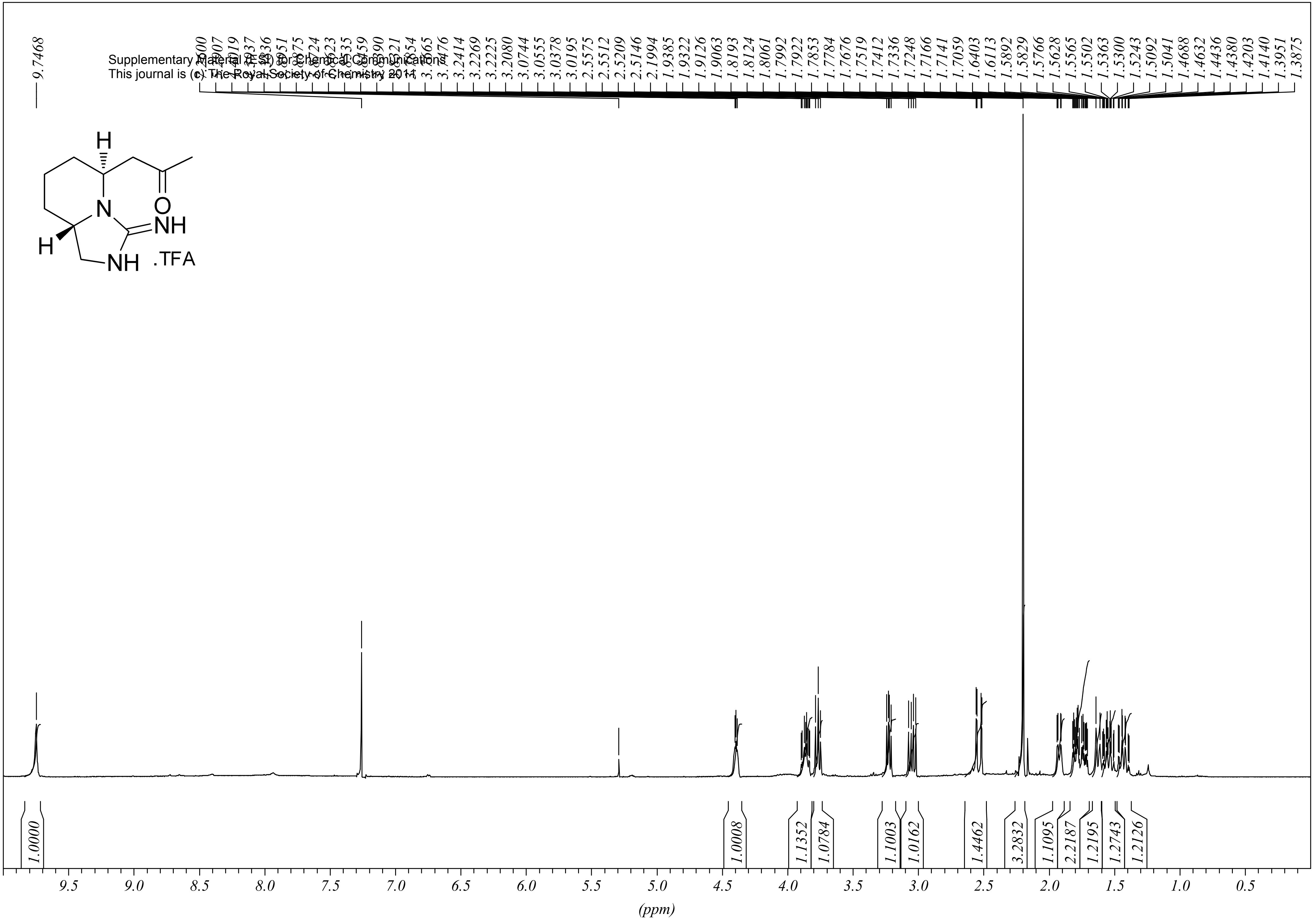
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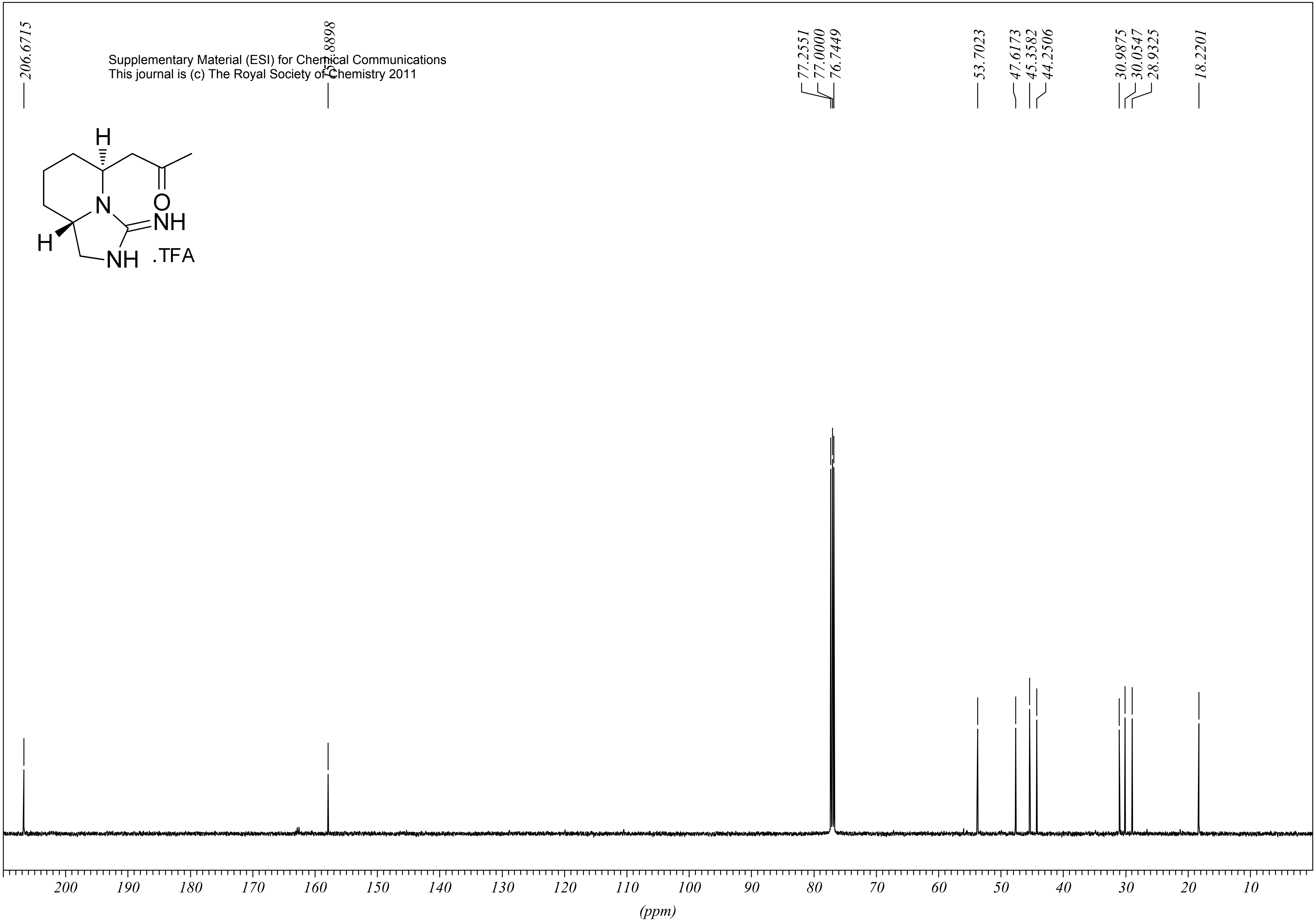
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200
190
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160
150
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120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

University of Southampton · School of Chemistry

EPSRC National Crystallography Service

Table 1. Crystal data and structure refinement.

Identification code	**2009src1065 / DME-176-8-10**	
Empirical formula	$C_{12}H_{18}F_3N_3O_3$	
Formula weight	309.29	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 7.9832(6) Å	α = 95.866(3)°
	b = 8.8773(7) Å	β = 107.215(4)°
	c = 12.1929(10) Å	γ = 114.500(4)°
Volume	725.49(10) $Å^3$	
Z	2	
Density (calculated)	1.416 Mg / m^3	
Absorption coefficient	0.127 mm^{-1}	
F(000)	324	
Crystal	Cut Blade; Colourless	
Crystal size	0.12 × 0.08 × 0.05 mm^3	
θ range for data collection	2.93 – 27.48°	
Index ranges	$-10 \le h \le 9$, $-11 \le k \le 11$, $-15 \le l \le 15$	
Reflections collected	12761	
Independent reflections	3301 [R_{int} = 0.0487]	
Completeness to θ = 27.48°	99.1 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9937 and 0.9849	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3301 / 124 / 222	
Goodness-of-fit on F^2	1.151	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0792, *wR2* = 0.1219	
R indices (all data)	*R1* = 0.1279, *wR2* = 0.1416	
Largest diff. peak and hole	0.319 and –0.254 e $Å^{-3}$	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** *ORTEP3 for Windows* (L. J. Farrugia, J. Appl. Crystallogr. 1997, 30, 565).

Special details:

All hydrogen atoms were fixed using a standard riding model.
The trifluoroacetate anion was partially disordered over 2 main sites.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	4244(4)	2482(3)	5322(2)	31(1)	1
C2	6691(4)	3793(4)	4599(3)	40(1)	1
C3	7655(4)	3769(4)	5891(3)	35(1)	1
C4	8778(5)	2735(5)	6039(3)	49(1)	1
C5	9250(5)	2444(5)	7283(3)	53(1)	1
C6	7341(5)	1520(4)	7504(3)	47(1)	1
C7	6139(4)	2501(4)	7370(3)	35(1)	1
C8	7074(4)	4085(4)	8405(3)	36(1)	1
C9	5787(5)	4930(4)	8424(3)	41(1)	1
C10	6677(5)	6527(5)	9402(3)	52(1)	1
N1	5920(3)	2964(3)	6237(2)	32(1)	1
N2	4575(4)	2911(3)	4366(2)	40(1)	1
N3	2431(3)	1646(3)	5322(2)	35(1)	1
O1	4109(3)	4335(3)	7697(2)	56(1)	1
C11	–525(4)	1369(4)	2489(3)	33(1)	1
O11	1134(3)	2274(3)	2477(2)	45(1)	1
O12	–974(3)	638(3)	3245(2)	48(1)	1
C12	–2358(17)	1175(16)	1479(10)	46(1)	0.441(10)
F11	–3441(14)	1720(16)	1852(5)	86(3)	0.441(10)
F12	–1907(10)	1943(14)	672(8)	83(3)	0.441(10)
F13	–3638(18)	–435(12)	938(10)	81(4)	0.441(10)
C212	–2217(14)	1185(13)	1387(8)	46(1)	0.559(10)
F211	–2359(11)	2600(8)	1443(8)	102(3)	0.559(10)
F212	–1949(10)	877(13)	386(5)	91(2)	0.559(10)
F213	–3920(11)	–103(12)	1200(8)	92(3)	0.559(10)

Table 3. Bond lengths [Å] and angles [°].

C1–N3	1.324(3)	C8–C9	1.506(4)
C1–N1	1.327(4)	C8–H8A	0.9900
C1–N2	1.328(4)	C8–H8B	0.9900
C2–N2	1.456(4)	C9–O1	1.214(4)
C2–C3	1.542(4)	C9–C10	1.502(5)
C2–H2A	0.9900	C10–H10A	0.9800
C2–H2B	0.9900	C10–H10B	0.9800
C3–N1	1.481(3)	C10–H10C	0.9800
C3–C4	1.517(4)	N2–H2	0.8800
C3–H3	1.0000	N3–H3A	0.8800
C4–C5	1.528(5)	N3–H3B	0.8800
C4–H4A	0.9900	C11–O12	1.234(3)
C4–H4B	0.9900	C11–O11	1.237(3)
C5–C6	1.523(5)	C11–C212	1.535(9)
C5–H5A	0.9900	C11–C12	1.540(11)
C5–H5B	0.9900	C12–F13	1.311(11)
C6–C7	1.529(4)	C12–F11	1.312(12)
C6–H6A	0.9900	C12–F12	1.305(11)
C6–H6B	0.9900	C212–F213	1.297(9)
C7–N1	1.463(3)	C212–F211	1.305(10)
C7–C8	1.528(4)	C212–F212	1.321(10)
C7–H7	1.0000		
N3–C1–N1	125.6(3)	N1–C7–H7	108.2
N3–C1–N2	122.4(3)	C8–C7–H7	108.2
N1–C1–N2	112.0(2)	C6–C7–H7	108.2
N2–C2–C3	103.3(2)	C9–C8–C7	114.7(2)
N2–C2–H2A	111.1	C9–C8–H8A	108.6
C3–C2–H2A	111.1	C7–C8–H8A	108.6
N2–C2–H2B	111.1	C9–C8–H8B	108.6
C3–C2–H2B	111.1	C7–C8–H8B	108.6
H2A–C2–H2B	109.1	H8A–C8–H8B	107.6
N1–C3–C4	109.7(2)	O1–C9–C10	121.9(3)
N1–C3–C2	102.5(2)	O1–C9–C8	121.7(3)
C4–C3–C2	114.9(3)	C10–C9–C8	116.4(3)
N1–C3–H3	109.8	C9–C10–H10A	109.5
C4–C3–H3	109.8	C9–C10–H10B	109.5
C2–C3–H3	109.8	H10A–C10–H10B	109.5
C3–C4–C5	110.5(3)	C9–C10–H10C	109.5
C3–C4–H4A	109.5	H10A–C10–H10C	109.5
C5–C4–H4A	109.5	H10B–C10–H10C	109.5
C3–C4–H4B	109.5	C1–N1–C7	127.3(2)
C5–C4–H4B	109.5	C1–N1–C3	110.6(2)
H4A–C4–H4B	108.1	C7–N1–C3	120.9(2)
C6–C5–C4	110.1(3)	C1–N2–C2	111.3(2)
C6–C5–H5A	109.6	C1–N2–H2	124.3
C4–C5–H5A	109.6	C2–N2–H2	124.3
C6–C5–H5B	109.6	C1–N3–H3A	120.0
C4–C5–H5B	109.6	C1–N3–H3B	120.0
H5A–C5–H5B	108.2	H3A–N3–H3B	120.0
C5–C6–C7	112.5(3)	O12–C11–O11	129.6(3)
C5–C6–H6A	109.1	O12–C11–C212	117.8(4)
C7–C6–H6A	109.1	O11–C11–C212	112.6(4)
C5–C6–H6B	109.1	O12–C11–C12	112.1(5)
C7–C6–H6B	109.1	O11–C11–C12	118.2(5)
H6A–C6–H6B	107.8	C212–C11–C12	6.7(8)
N1–C7–C8	111.1(2)	F13–C12–F11	101.7(9)
N1–C7–C6	108.4(2)	F13–C12–F12	107.6(11)
C8–C7–C6	112.6(2)	F11–C12–F12	108.4(10)

F13–C12–C11	112.2(10)	F211–C212–F212	105.6(8)
F11–C12–C11	113.4(8)	F213–C212–C11	113.9(8)
F12–C12–C11	112.8(8)	F211–C212–C11	110.7(7)
F213–C212–F211	110.3(9)	F212–C212–C11	113.1(7)
F213–C212–F212	102.8(8)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}\,]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	34(2)	27(2)	33(2)	9(1)	14(1)	14(1)
C2	38(2)	42(2)	45(2)	16(2)	23(2)	18(2)
C3	30(2)	33(2)	46(2)	13(1)	20(1)	14(1)
C4	49(2)	53(2)	61(2)	18(2)	29(2)	30(2)
C5	49(2)	65(2)	63(2)	25(2)	22(2)	40(2)
C6	52(2)	43(2)	51(2)	21(2)	17(2)	27(2)
C7	30(2)	37(2)	34(2)	16(1)	11(1)	11(1)
C8	32(2)	45(2)	32(2)	15(1)	12(1)	17(1)
C9	44(2)	51(2)	35(2)	17(2)	21(2)	24(2)
C10	58(2)	58(2)	47(2)	10(2)	26(2)	29(2)
N1	27(1)	36(1)	34(1)	14(1)	13(1)	13(1)
N2	33(1)	43(2)	32(1)	12(1)	11(1)	8(1)
N3	26(1)	39(1)	31(1)	13(1)	8(1)	9(1)
O1	44(1)	80(2)	45(1)	9(1)	12(1)	36(1)
C11	35(2)	29(2)	31(2)	9(1)	10(1)	12(1)
O11	33(1)	50(1)	41(1)	19(1)	12(1)	10(1)
O12	33(1)	58(2)	42(1)	28(1)	11(1)	10(1)
C12	42(2)	50(2)	40(2)	17(2)	12(2)	18(2)
F11	80(5)	132(6)	61(4)	6(4)	7(3)	80(5)
F12	51(3)	94(6)	56(5)	58(4)	−2(3)	−2(4)
F13	80(6)	49(4)	60(5)	−18(3)	−22(4)	22(4)
C212	42(2)	50(2)	40(2)	17(2)	12(2)	18(2)
F211	81(4)	73(4)	120(5)	10(4)	−24(4)	54(3)
F212	71(3)	128(6)	36(2)	11(3)	6(2)	23(4)
F213	31(3)	115(6)	68(4)	65(4)	−3(3)	−15(4)

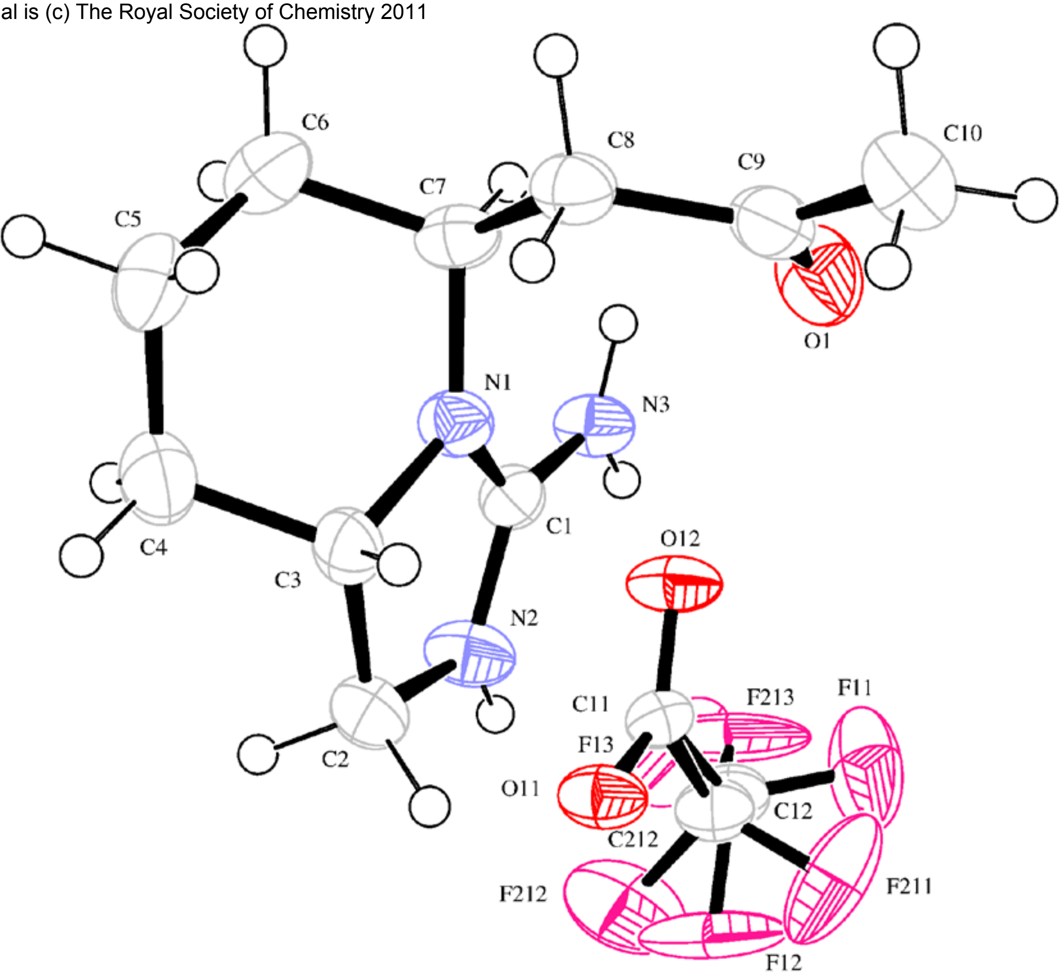
Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [Å^2 × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2A	7117	4982	4522	48	1
H2B	7032	3178	4048	48	1
H3	8549	4969	6398	42	1
H4A	10028	3353	5908	59	1
H4B	7968	1616	5438	59	1
H5A	9961	1751	7363	63	1
H5B	10123	3560	7884	63	1
H6A	7674	1354	8317	56	1
H6B	6518	373	6935	56	1
H7	4788	1718	7343	42	1
H8A	7408	3752	9159	43	1
H8B	8331	4935	8372	43	1
H10A	5684	6918	9363	79	1
H10B	7824	7423	9310	79	1
H10C	7103	6281	10173	79	1
H2	3635	2691	3680	48	1
H3A	2265	1364	5967	42	1
H3B	1392	1372	4676	42	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
N2–H2···O11	0.88	1.95	2.805(3)	162.4
N3–H3B···O12	0.88	1.96	2.836(3)	177.0
N3–H3A···O12^{i}	0.88	2.14	2.914(3)	147.1

Symmetry transformations used to generate equivalent atoms:
(i) –x,–y,–z+1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C10
C7
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N1
N3
C1
C4
C3
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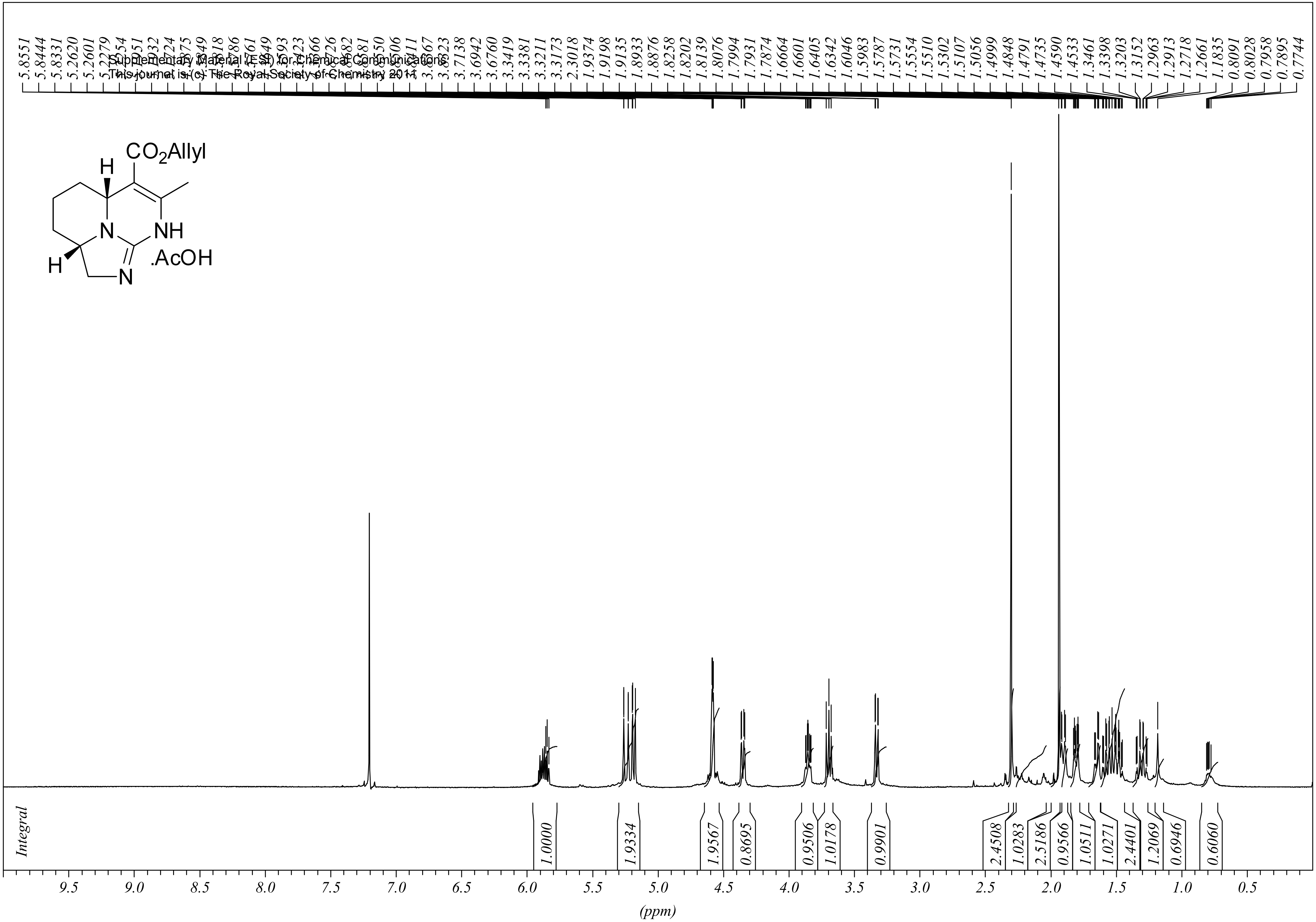
F11
F13
O11
C12
C2
C212
F212
F211
F12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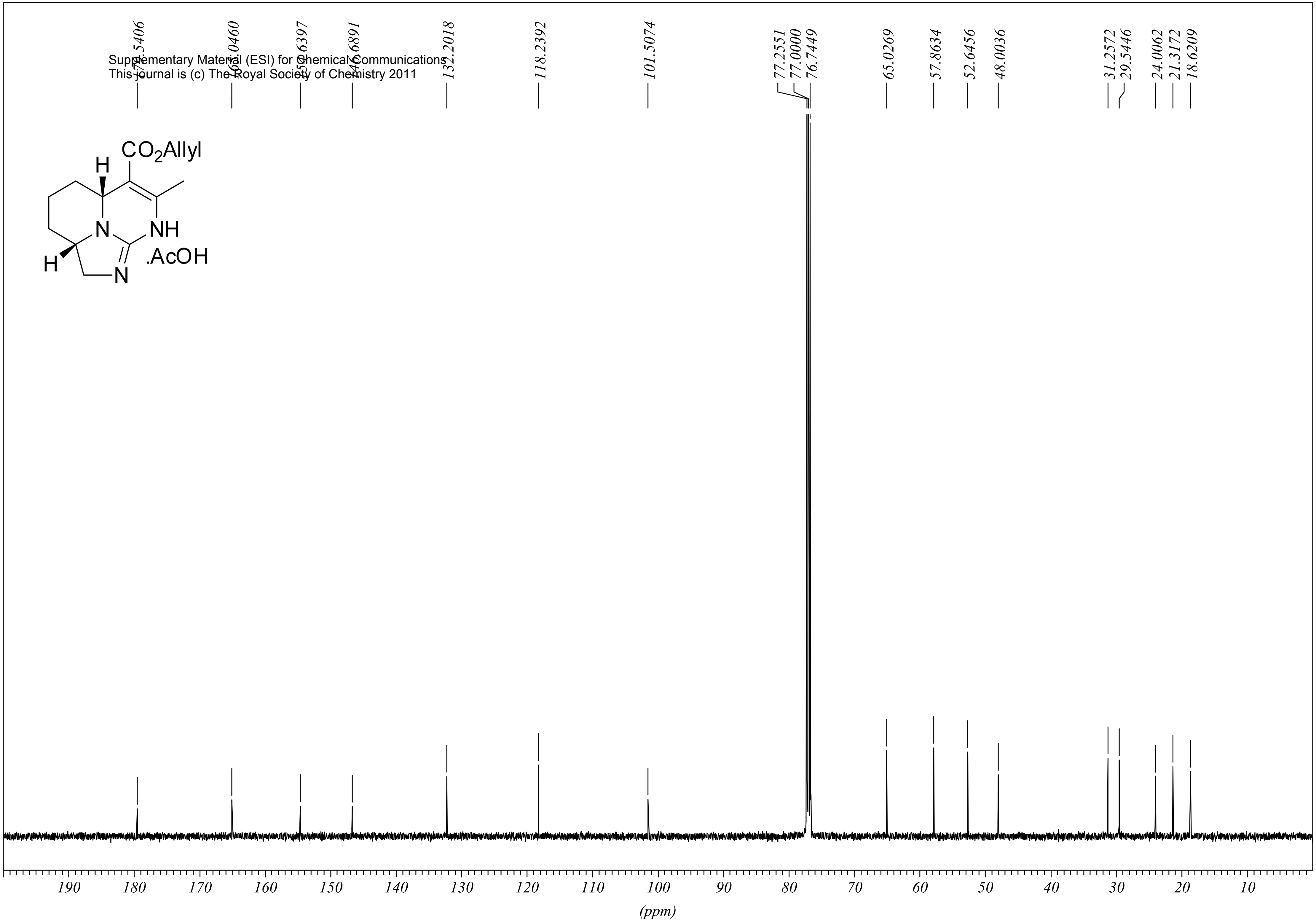
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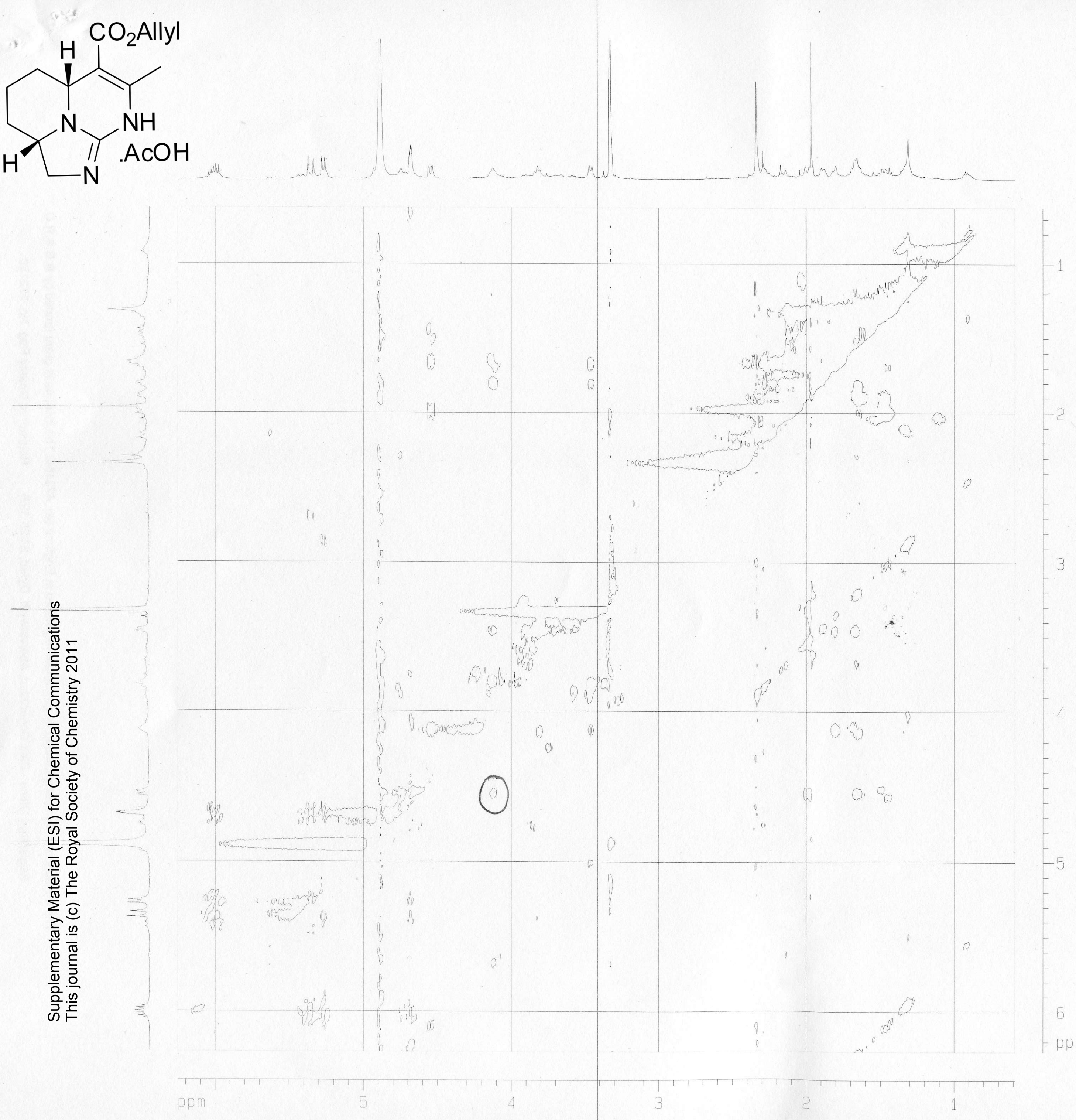

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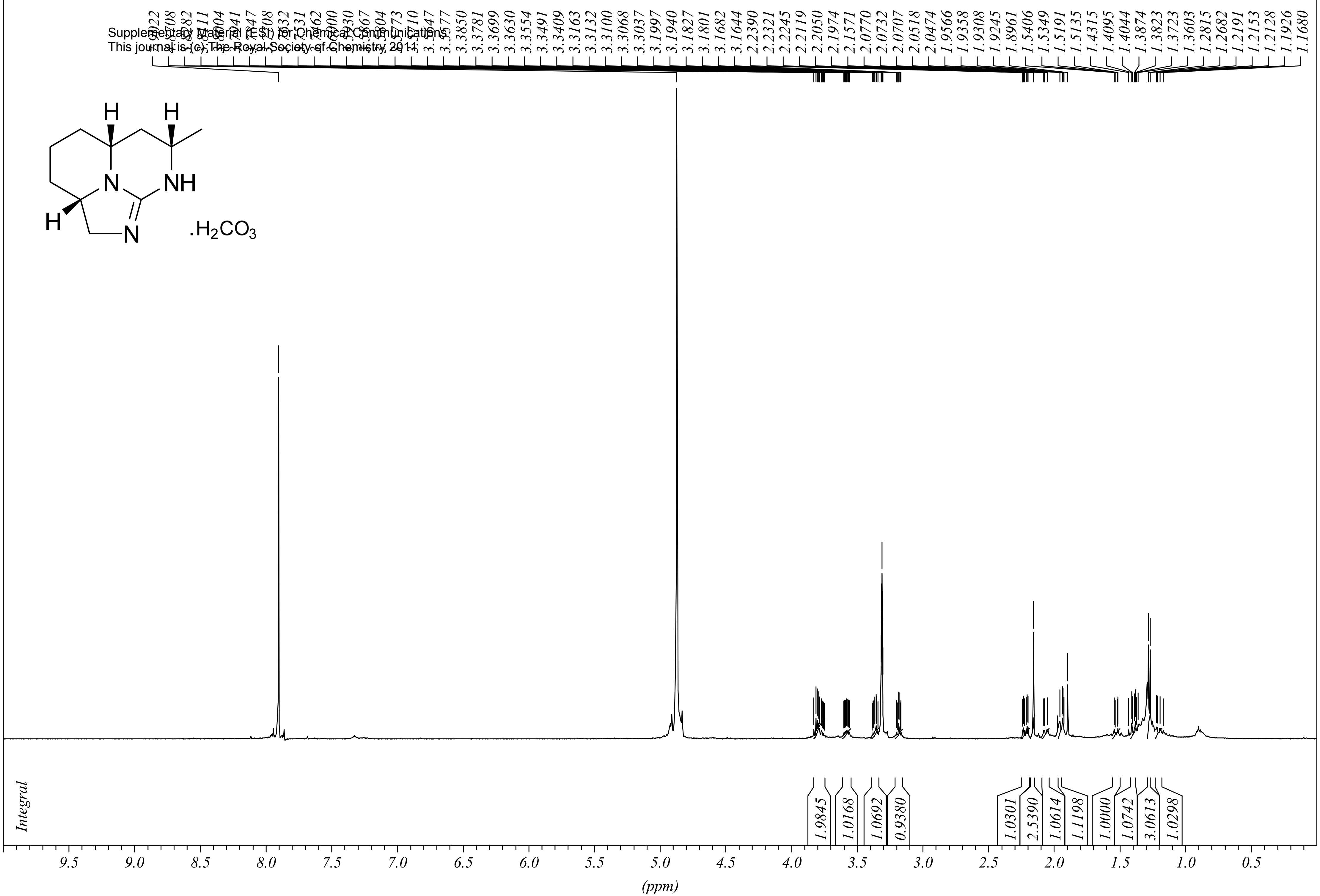
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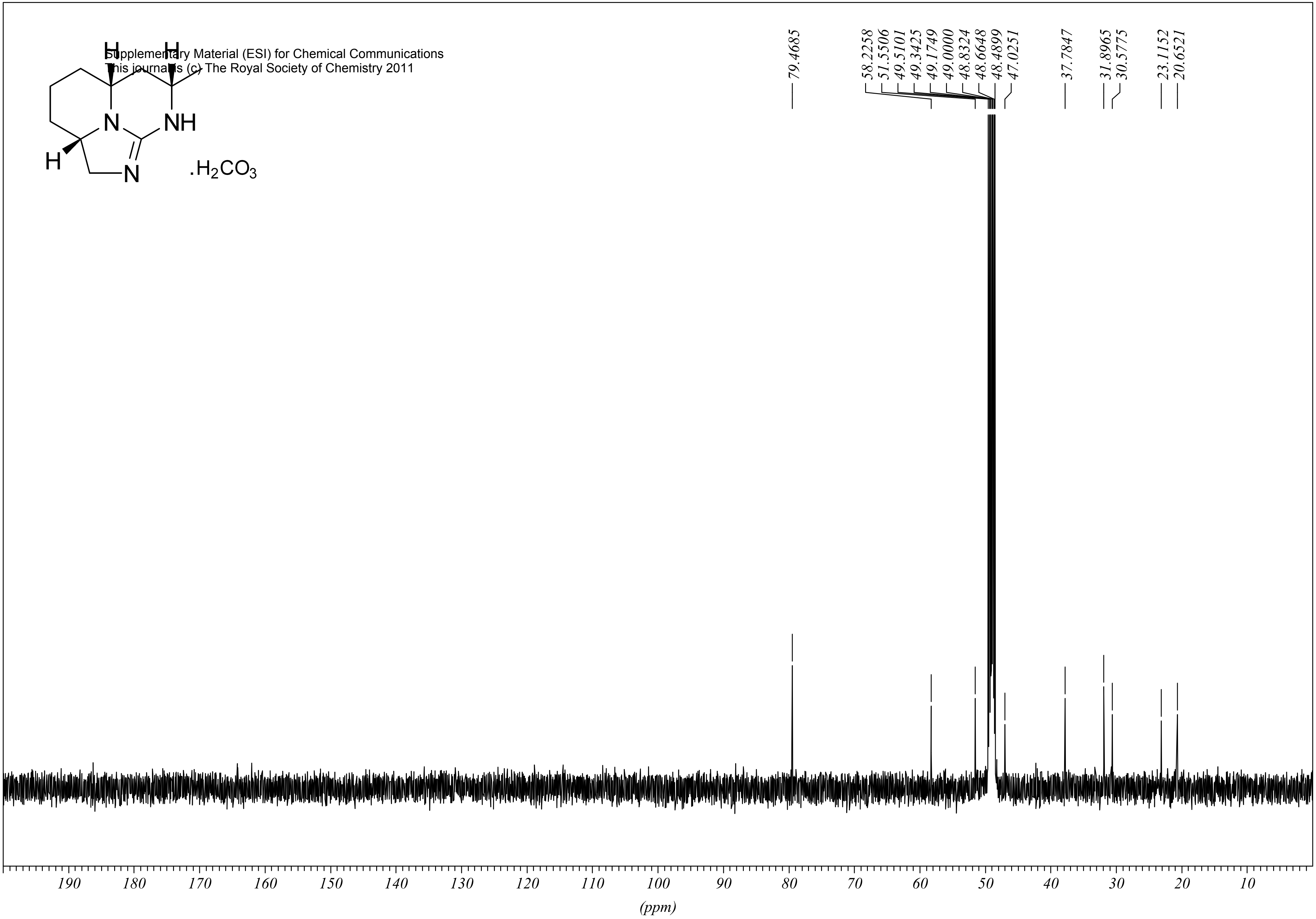
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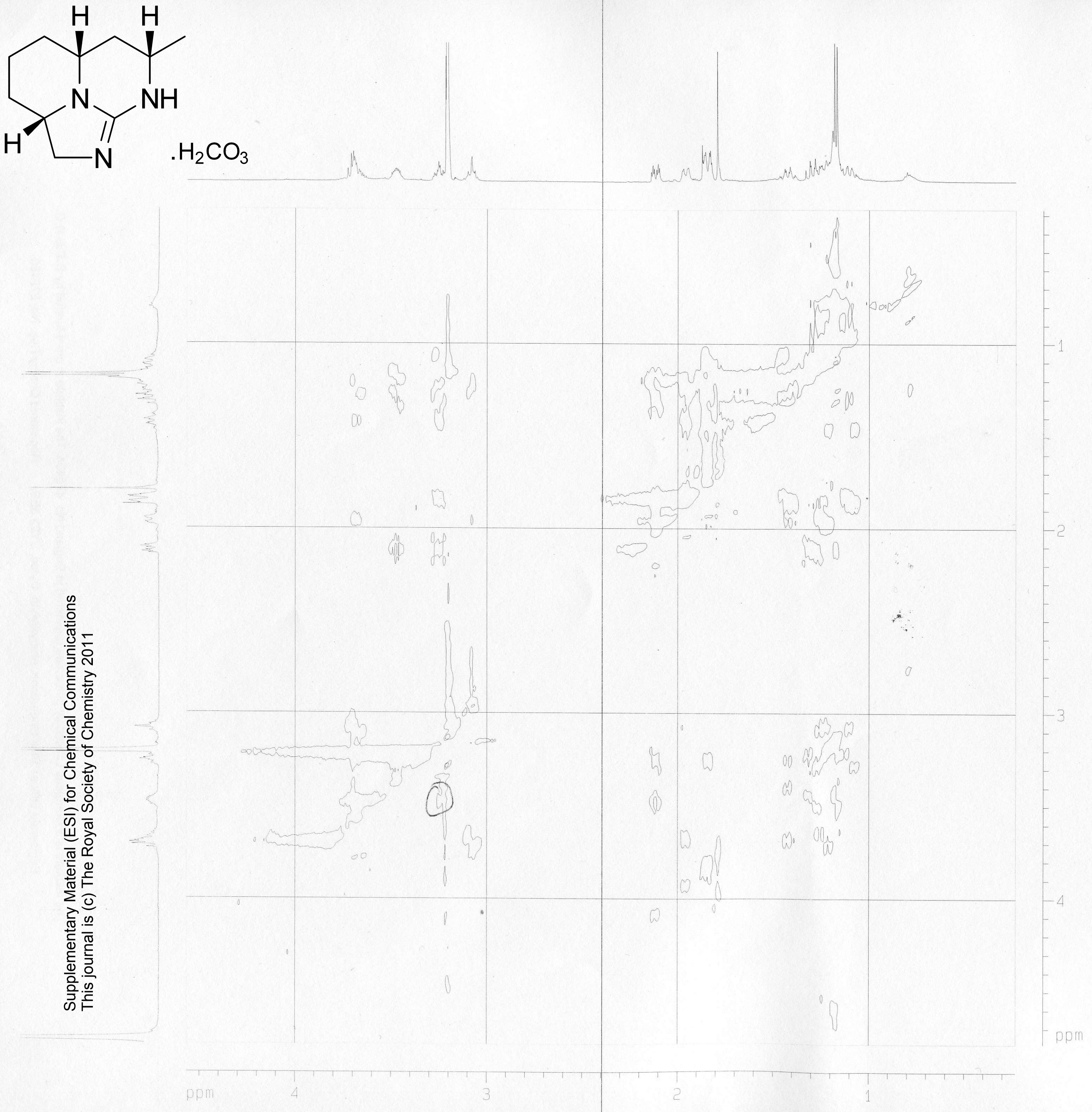

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Time                 17.58
INSTRUM              spect
PROBHD   5 mm DUL 1H-13
PULPROG            noesyph
TD                    2048
SOLVENT               MeOD
NS                      16
DS                       4
SWH               3930.818 Hz
FIDRES            1.919345 Hz
AQ               0.2606828 sec
RG                   203.2
DW                 127.200 usec
DE                    6.00 usec
TE                   297.0 K
d0              0.00011113 sec
D1              1.93978798 sec
D8              0.40000001 sec
IN0             0.00025440 sec
MCREST          0.00000000 sec
MCWRK           0.96989399 sec
ST1CNT                 128

    ======== CHANNEL f1 ========
NUC1                    1H
P1                   12.62 usec
PL1                   0.00 dB
SFO1           500.1319849 MHz

     F1 - Acquisition parameters
ND0                      1
TD                     256
SFO1               500.132 MHz
FIDRES           15.354756 Hz
SW                   7.860 ppm
FnMODE         States-TPPI

      F2 - Processing parameters
SI                    1024
SF             500.1300611 MHz
WDW                  QSINE
SSB                      2
LB                    0.00 Hz
GB                       0
PC                    1.00

      F1 - Processing parameters
SI                    1024
MC2            States-TPPI
SF             500.1300611 MHz
WDW                  QSINE
SSB                      2
LB                    0.00 Hz
GB                       0

         2D NMR plot parameters
CX2                  15.00 cm
CX1                  15.00 cm
F2PLO                4.568 ppm
F2LO               2284.60 Hz
F2PHI                0.231 ppm
F2HI                115.74 Hz
F1PLO                4.783 ppm
F1LO               2392.08 Hz
F1PHI                0.270 ppm
F1HI                134.93 Hz
F2PPMCM            0.28911 ppm/cm
F2HZCM           144.59062 Hz/cm
F1PPMCM            0.30087 ppm/cm
F1HZCM           150.47661 Hz/cm
```