Preparation of 9-Azabicyclo[3.3.1]nonane-N-oxyl (ABNO)

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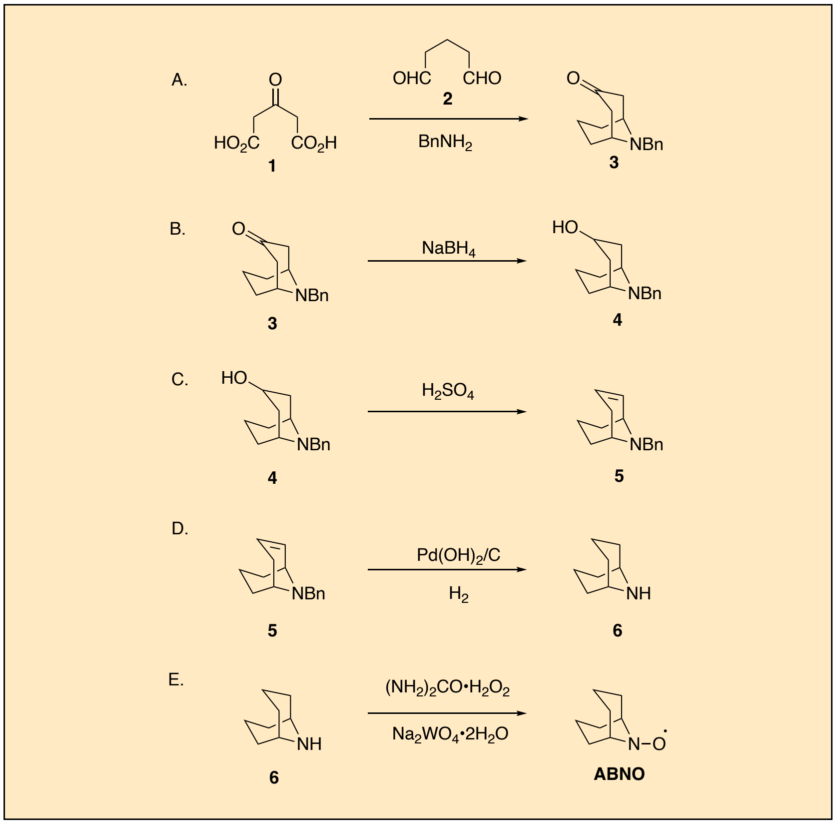

Procedure (Note 1)

A. *9-Benzyl-9-azabicyclo[3.3.1]nonan-3-one (**3**)*[2b] (Note 1) A 500 mL six-necked jacketed, round-bottomed flask is equipped with a mechanical stirrer (IKA:180 rpm), a PTFE-coated temperature probe, and a 250 mL addition funnel (Note 2). Water (50 g) and benzylamine (12.9 mL, 13.2 g, 0.123 mol, 0.9 equiv) are added (Note 3 and Note 4). The reactor jacket is cooled by a recirculating chiller to 0–10 °C (Figure 1) and then 18% sulfuric acid (43.2 mL, 0.089 mol, 0.65 equiv made from 98% sulfuric acid) is added over 1 h while maintaining the reaction mixture at 4–8 °C (Note 5). The reaction flask is protected from light with aluminum foil as a general precaution. Glutaraldehyde (50%) (**2**) (25.8 mL, 0.137 mol, 1.0 equiv) (Note 6) is added followed by acetone dicarboxylic acid (**1**, 20 g, 0.137 mol, 1.0 equiv) (Notes 7 and 8) while maintaining the reaction mixture at <5 °C to give a light-yellow solution. At this time 9% sodium acetate (47.8 mL, 0.055 mol, 0.4 equiv) solution is added over 1.5 h (Figure 2) (Note 9). The reaction mixture is aged at 5 °C for 20 h and then at 25 °C for 20 h. Slow gas evolution (CO_2) is observed during the reaction (Note 10). A sample analyzed by HPLC indicates complete consumption of acetone dicarboxylic acid and less than 10:90 ratio of benzylamine to product (Note 11). Additional 18% sulfuric acid (approximately 10 mL) is added at 20–30 °C to adjust the solution's pH to 2. The solution is transferred to a 0.5 L separation funnel and extracted with MTBE (3 x 80 mL). The organic layers are discarded. The aqueous layer (Figure 3) is charged into a 2 L round-bottomed flask and mixed with heptane (500 mL). Silica gel (20 g) (Note 12) is added to the aqueous layer followed by aqueous 20% Na_2CO_3 (80 mL) to adjust the pH to 8 (Figure 4) (Note 13). The batch is filtered, and the filter cake washed with heptane (320 mL) (Note 14). The layers of the combined filtrate are separated (Figure 5), and the organic layer is dried with Na_2SO_4 (100 g) (Note 15). After removal of the drying agent by filtration, the solution is concentrated using a rotovap in a 1 L round-bottomed flask (bath temperature: 40 °C, vacuum: 75 mmHg). The residue is diluted with methanol (100 mL) and concentrated by rotary evaporation again. The residue is diluted with methanol to give a solution of **3** (93.8 g of solution) which contains 17.9 g (57%) of compound **3**, as determined by quantitative ^{1}H NMR assay. The purity of compound **3** is determined by HPLC and qNMR analysis (Notes 11 and 16). The crude product solution is used in the next step directly.


Figure 1. Step A recirculating chiller assembly (Photos provided by checkers)


Figure 2. Step A reaction assembly (Photos provided by submitters)

Figure 3. The aqueous layer after reaction (Photo provided by submitters)

Figure 4. After addition of silica gel (Photo provided by submitters)

Figure 5. Separation after filtering (Photo provided by submitters)

B. *9-Benzyl-9-azabicyclo[3.3.1]nonan-3-ol (**4**).*[2b] A 500 mL three-necked round-bottomed flask is equipped with a mechanical stirrer (IKA:180 rpm), PTFE-coated temperature probe and a nitrogen line fitted to a glass bubbler. The one remaining neck is fitted loosely with a septum and is opened for addition of reagents (Figure 6) (Note 17). A solution of **3** (20.0 g in 190 g methanol, 0.087 mol, 1.0 equiv) is added and the reaction mixture is cooled to 0–10 °C using an ice bath. Sodium borohydride (6.6 g, 0.174 mol, 2.0 equiv) is charged in portions over 0.5 h while maintaining the batch temperature at 0–

Figure 6. Step B reaction assembly (Photo provided by submitters)

5 °C (Note 18). The batch is stirred at 25 °C for 0.5 h until HPLC analysis indicates completion of reaction (Note 19). The batch is then cooled to 5 °C and quenched by slow addition of 10% hydrochloric acid (40 mL) to adjust the batch pH to 5-6 (**Caution**: Initial addition of the HCl solution needs to be very slow to give enough time for decomposition of unreacted borohydride. Hydrogen gas evolution is dissipated by nitrogen flow. Addition of the HCl solution was performed over the course of 1 h) (Note 20). The flask is fitted with a distillation head assembly and is heated under vacuum to concentrate the solution (Figure 7) (bath temperature: 35 °C, vacuum: 75 mmHg) to about 50 mL, at which point the solution is cooled to 5 °C and mixed with MTBE (160 mL) (Note 21). At this time 20% NaOH solution (25 mL) is added at 5 °C to adjust the pH to 11–12 (Note 22). The two layers are separated, and the aqueous layer extracted with MTBE (160 mL). The combined organic layer is washed with 4% aqueous $NaHCO_3$ solution (80 mL) and concentrated under reduced pressure (bath temperature: 35 °C, pressure: 75 mmHg) to remove all solvents (Note 23). Crude compound **4** is obtained in 19.2 g as a light-yellow solid (Figure 8) (95.5% by HPLC analysis, 93.0% by quantitative ^{1}H NMR assay) containing 17.9 g product (89% yield), which is used directly in the next step (Note 24).

Figure 7. Distillation assembly (Photo provided by submitters)

Figure 8. Compound 4 solid (Photo provided by submitters)

C. *9-Benzyl-9-azabicyclo[3.3.1]non-3-ene* (**5**). A 500 mL three-necked round-bottomed flask is equipped with a reflux condenser, mechanical stirrer, a PTFE-coated temperature probe and a nitrogen line connected to a bubbler, and the one remaining neck is left open for the addition of reagents (Note 25). Crude **4** from the previous step (17.9 g based on assay amount, 77.4 mmol, 1.0 equiv) is dissolved in 70% aq. H_2SO_4 (111 mL, 1.28 mol, 17 equiv) (Note 26) and the batch is heated to 100 °C and stirred for 20 h (Figure 9) until >99% conversion is observed by HPLC (Note 27). The solution is poured into a 500 mL addition funnel and added dropwise into a solution of NaOH (500 mL of 20% NaOH) over 1.5 hours while maintaining the quench batch temperature at or below 30 °C using an ice bath (Note 28). The pH of the resulting solution is observed to be 8–9. The solution is then extracted in a 2 L separatory funnel with ethyl acetate (3 x 400 mL), and the combined organic layers are washed with water (120 mL). The organic layer is concentrated in vacuo (bath temperature: 40°C, pressure: 40 mmHg) to remove all solvents to give 17.1 g of an oily residue (Figure 10), which contained 14.3 g (17.1 g x 83.5 wt%) **5** by quantitative ^{1}H NMR analysis and 97% by HPLC analysis (Note 11) in 93% yield (Note 29).

Figure 9. Step C reaction assembly (Photo provided by submitters)

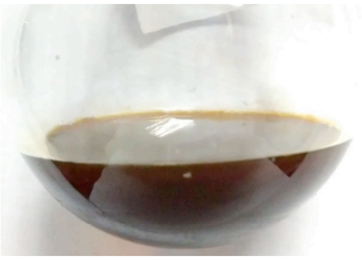

Figure 10. Product appearance (Photo provided by submitters)

D. *9-Azabicyclo[3.3.1]nonane* (**6**)[2b] In a 300 mL hydrogenation reactor (Note 30), a solution of **5** (24.5 g x 90.0 wt%, 95.32 mmol) in 100 mL isopropanol (Note 31) is purged with nitrogen three times and mixed with $Pd(OH)_2$ on carbon (20 wt%) (4.0 g). (Caution: See Note 32). The reactor is then purged with nitrogen and pressurized with hydrogen at 50 psi and stirred (300 rpm) at 50 °C for 48 h (Figure 11) until the reaction is judged to be complete by GC (Note 33). The catalyst is filtered off through Solka Floc (Note 34), and the cake washed with isopropyl alcohol (100 mL). (Caution: fire hazard! See Note 32) The filtrate is concentrated by rotary evaporation (bath temperature: 30 °C, pressure: 50 mmHg) to remove most of the solvents to give an oil residue which contained 11.6 g (29.1 g x 39.9 wt%) of product **6** as determined by quantitative ^{1}H NMR analysis (89.6% yield) (Note 35).

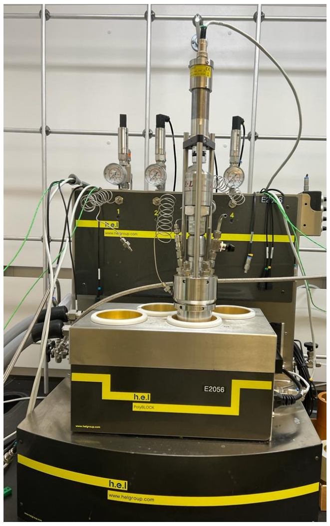

Figure 11. Step D reaction assembly (Photo provided by checkers)

E. *9-Azabicyclo[3.3.1]nonane-N-oxyl* (***ABNO***)^{2b} A 500 mL four-necked jacketed round-bottomed flask is equipped with a mechanical stirrer, a PTFE-coated temperature probe, and a nitrogen line connected to a bubbler. The one remaining neck is left open for addition of reagents (Note 24). The solution of compound **6** (29.1 g x 39.9 wt% = 11.6 g, 92.6 mmol) in isopropyl alcohol, H_2O (100 mL) and 3.05 g (9.26 mmol, 0.1 equiv) of $Na_2WO_4•2H_2O$ (Note 36) are added. The batch is cooled to 0–10 °C, and a pre-cooled aqueous solution (0–10 °C) of urea hydrogen peroxide (UHP, 29.6 g, 342 mmol, 3.4 equiv) (Notes 37 and 38) (93 mL) is added dropwise over 70 min through a peristaltic pump (Figure 12). A sample is taken after another 0.5 h, and GC analysis indicates about 97% conversion (Note 39). The batch is transferred to a separation funnel and extracted with dichloromethane (DCM) (3 x 110 mL). A sample is taken from the combined organic layer and HPLC analysis indicates residual urea is 0.15 wt% (Note 40). The combined organic layers are concentrated using a rotary evaporator until most solvents are removed and the residue weighs about 24 g. The residue is dissolved in DCM (200 mL), and extracted with water (2 x 100 mL). The residual urea in the organic layer is below 0.05%, as determined by HPLC (Note 40). The aqueous layer is extracted with dichloromethane (60 mL). The residual urea in this organic layer is below 0.05% as determined by HPLC (Note 40). The combined organic layer is concentrated under reduced pressure (bath temperature: 30°C, pressure: 75 mmHg) to ca. 110 mL. The solution is then

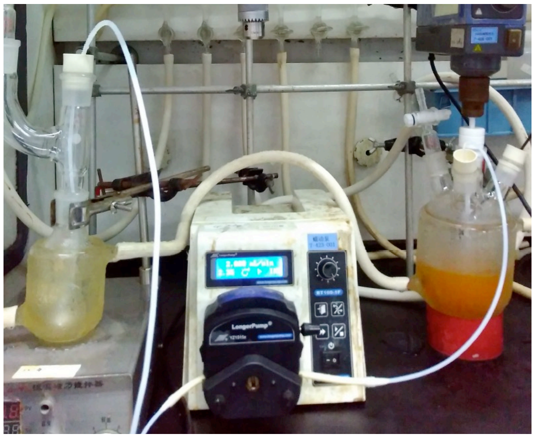

Figure 12. Addition of UHP solution under thermal insulation (Photos provided by submitters)

further azeotropically distilled at constant volume with *n*-heptane (220 mL) under reduced pressure (jacket temperature: 30 °C, batch temperature: 14 °C, vacuum: 75 mmHg) to a final volume of 110 mL. The batch is cooled to between –10 °C and –5 °C, and a red solid forms during cooling (Figure 13). The slurry is stirred at this temperature for 18 h. The mixture is filtered, and the cake dried under vacuum (vacuum: 40 mmhg) below 30 °C for 2 h (Note 41). ABNO is obtained as a red solid (8.79 g, 68%) (Note 42) (Figure 14) in 99% purity as determined by GC analysis (Note 43).

Figure 13. Red solid formation (Photo provided by checkers)

Figure 14. ABNO solid product (Photo provided by submitters)

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out about each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with benzylamine, sulfuric acid, glutaraldehyde, acetone dicarboxylic acid, sodium acetate, MTBE, silica gel, Na_2CO_3, heptane, Na_2SO_4, methanol, sodium borohydride, hydrochloric acid, NaOH, hexanes, $NaHCO_3$, ethyl acetate, isopropanol, $Pd(OH)_2$ on carbon, $Na_2WO_4{\bullet}2H_2O$, urea hydrogen peroxide, dichloromethane, H_3PO_4, $CDCl_3$, dimethylsulfone, dimethyl fumarate, and 1,3,5-trimethoxybenzene, as well as the proper procedures for running hydrogenations, running reactions that releases gas such as carbon dioxide, oxygen.
2. The reaction is stirred at 180-200 rpm with an IKA mechanical stirrer with a PTFE propeller with diameter of 65 mm. The reaction is run under a slow nitrogen flow of rate about 0.6 L/min. The reaction flask is protected from light with aluminum foil as a general precaution.
3. Reagents and raw materials are purchased from commercial suppliers and used as is. The purity is >98% unless noted otherwise.
4. The benzylamine (>99.0%) is purchased from TCI.
5. The 18% sulfuric acid is made from 98% sulfuric acid purchased from Oakwood Chemicals.
6. The glutaraldehyde (50% aqueous solution) is purchased from Sigma-Aldrich.

7. One of the major challenges we faced for this step is the facile decomposition of acetone dicarboxylic acid **1**. Even the process of NMR sample preparation and analysis led to partial decarboxylation. Similar decarboxylation is also observed when **1** is analyzed by reverse phase HPLC. Due to the lack of analytical standard of this compound, the weight percentage purity of the material is not confirmed but only estimated to be >90% by NMR. We suspect the different reported yields of this step are largely due to the variable quality of the raw materials used. Compound **1** refrigerated until needed for reaction.
8. Acetone dicarboxylic acid (technical) is purchased from Sigma-Aldrich.
9. The sodium acetate (≥99.0%, anhydrous) is purchased from Sigma-Aldrich.
10. Running this reaction at higher temperature (>30 °C) should be avoided due the potential for rapid release of gas.
11. The conversion is determined by HPLC using a Waters Atlantis T3 (150 mm × 4.6 mm × 3.0 μm) operating at 40 °C with a flow rate of 0.5 mL/min using a gradient of solvents A) 0.1% H_3PO_4 in water and B) acetonitrile. t=0 min, A:B (95:5); t=5 min, A:B (75:25); t=10 min, A:B (65:35); t=16 min, A:B (5:95); t=18 min, A:B (95:5); Retention times for the following compounds are as indicated **1**, 2.4 min; **3**, 7.2 min; **4**, 7.8 min; **5**, 9.3 min. The reaction is complete when **1** is fully consumed and the ratio of **3** to benzylamine is greater than 90:10.
12. *n*-Heptane is purchased from Oakwood Chemical. Silica gel (230-400 mesh) is purchased from Silicycle Inc.
13. The Na_2CO_3 (≥99.0%, anhydrous) is purchased from VWR Chemicals. A slight exotherm is observed during addition of 20% Na_2CO_3. The temperature is easily controlled by ice bath.
14. Use of heptane as a co-solvent in addition to MTBE minimizes the decomposition of **3** during the workup.
15. The Na_2SO_4 (99.0%, anhydrous) is purchased from Fisher chemical.
16. Purity is determined by HPLC (Note 11) to be 98.2%. Analysis of the solution by quantitative ^{1}H NMR, using dimethyl sulfone (99.6% purity) as an internal standard, indicated the solution was determined to contain 19.1 wt% **3** (17.9 g). A second run on full scale provided 17.2 g (55%) at 97% purity. About 0.8 g pure sample of **3** was obtained for characterization by silica gel column purification of about 1.1 g crude compound and 24 g silica gel using 1:4 ethyl acetate/hexanes as eluent (TLC: EA/hexanes=1/4, $R_f = 0.4$), which results in a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.46–7.40 (m, 2H), 7.38–7.33 (m, 2H), 7.31–7.27 (m,

1H), 3.93 (brs, 2H), 3.36–3.30 (m, 2H), 2.75 (dd, *J* = 6.4, 16.4 Hz, 2H), 2.27 (d, *J* = 16.5 Hz, 2H), 2.01–1.93 (m, 2H), 1.62–1.46 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 211.6, 139.4, 128.5, 128.4, 127.3, 57.2, 53.7, 43.0, 29.5, 16.7.

17. The reaction is stirred at 180-200 rpm with an IKA mechanical stirrer with a PTFE propeller with diameter of 65 mm. The rate of nitrogen is approximately 0.6 L / min.
18. Sodium borohydride (≥98%) is purchased from Sigma-Aldrich. Caution: hydrogen gas evolution! A slow flow of nitrogen is maintained during and after the addition of the $NaBH_4$ from the neck of the flask used for addition of reagents by a glass joint with an open valve.
19. Completion of the reaction is determined by HPLC (Note 11). The reaction is complete when **4** is consumed.
20. The 10% hydrochloric acid is made from 36.5-38% hydrochloric acid which is purchased from Oakwood Chemical.
21. The MTBE is purchased from Oakwood Chemical.
22. The NaOH (≥99.0%, anhydrous) is purchased from Oakwood Chemical.
23. The $NaHCO_3$ (≥99.0%, anhydrous) is purchased from Oakwood Chemical.
24. Purity is determined by quantitative ^{1}H NMR using dimethyl fumarate (99% purity) as an internal standard and by HPLC (Note 11). The crude product is determined to contain 93.0 wt% **4** by NMR with 95.5% purity by HPLC. A second reaction at full scale provided 17.4 g (86%) of compound **4** in 93% purity. For characterization purposes about 0.6 g pure sample of **4** is obtained from 1 g crude compound by silica gel column purification on 40 g silica gel with ethyl acetate as eluent (TLC: R_f = 0.5) as eluent which results in a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.29 (m, 4H), 7.27–7.21 (m, 1H), 4.34–4.25 (m, 1H), 3.81 (s, 2H), 3.09–3.03 (m, 2H), 2.45–2.36 (m, 2H), 2.29–2.15 (m, 1H), 2.01–1.90 (m, 3H), 1.58–1.51 (m, 1H), 1.41–1.33 (m, 2H), 1.18–1.10 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 140.5, 128.3, 128.2, 126.8, 64.1, 56.0, 49.8, 35.6, 25.2, 14.7.
25. The reaction is stirred at 180-200 rpm with an IKA mechanical stirrer with a PTFE propeller with diameter of 65 mm. The rate of nitrogen is approximately 0.6 L / min.
26. The 70% sulfuric acid is made from 98% sulfuric acid which is purchased from Oakwood Chemical.

27. Reaction completion is determined by HPLC (Figure 15). The reaction is complete when less than 1% of **4** remains.
28. The NaOH (≥99.0%, anhydrous) is purchased from Oakwood Chemical. The end pH is slightly basic, shown to be approximately 8-9 by pH paper.
29. A second reaction at full scale provided 14.5 g (17.2 g x 84.1 wt%) **5** by quantitative ^{1}H NMR analysis, using dimethylfumarate (99%) as an internal standard, and 95% purity by HPLC analysis. About 0.5 g sample of pure(>99%) **5** is obtained as a light-yellow oil via silica gel column purification from 1.0 g crude product on 100 g silica with ethyl acetate/heptane as eluent (TLC: EA/*n*-heptane = 1/3, R_f = 0.6–0.7). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.45–7.38 (m, 2H), 7.37–7.33 (m, 2H), 7.31–7.25 (m, 1H), 6.07 (td, *J* = 3.5, 10.1 Hz, 1H), 5.61–5.60 (m, 1H), 3.78–3.63 (m, 2H), 3.19 (br. s, 1H), 3.03–2.95 (m, 1H), 2.48 (ddd, *J* = 3.0, 4.3, 18.8 Hz, 1H), 1.93–1.68 (m, 4H), 1.56–1.38 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 140.4, 128.9, 128.3, 128.1, 127.4, 126.8, 58.0, 52.7, 50.8, 33.6, 28.6, 25.9, 16.3
30. The reaction is stirred using the overhead stirrer of the hydrogenation apparatus.
31. The isopropanol (≥99.7%) is purchased from Sigma-Aldrich.
32. Palladium hydroxide on carbon is purchased from Sigma-Aldrich and used as is. Caution: fire hazard! Proper precaution must be taken when charging palladium hydroxide on activated carbon to organic solvents/ Purging the solvent with and operating under an atmosphere of nitrogen or argon and cooling of the organic solvent prior to addition of palladium hydroxide is highly recommended. It is also recommended that palladium hydroxide be premixed with solvent before substrate is added. When filtering off the palladium hydroxide on carbon after reaction, an inverted funnel with a flow of nitrogen should be placed on top of the filter to create an inert atmosphere and the catalyst should be constantly submerged below the surface of solvent to avoid direct exposure to air. The catalyst should be wetted with water before properly disposed or collected for recovery.
33. Reaction conversion is determined by GC using a HP-5 (30.0 m × 0.25 mm I.D. × 0.25 μm) with nitrogen (400 mL/min) as the carrier gas. The temperature gradient involved starting temperature gradient of 50 °C/min to 30 °C, then 15 °C/min to 160 °C, 5 °C/min to 180 °C, 20 °C/min to 280 °C, hold at 280 °C for 7 min. Retention times for the following compounds are as indicated **6**, 8.8 min; ABNO, 11.5 min; *N*-

Benzyl-6, 16.0 min; **5**, 16.4 min, **3**, 16.5 min; The reaction is complete when less than 1% of **5** remains.

34. The Solka-Floc cellulose powder (grade SF-40) is purchased from General Filtration.
35. The internal standard for qNMR analysis was 1,3,5-trimethoxybenzene. The reported chemical shifts of compound **6** do not match perfectly with the ^{1}H NMR spectrum obtained in the checking process; however, the integral areas of signals match with compound **6** and ^{1}H NMR spectrum of the author. To confirm the assigned structure, a detailed 2D NMR analysis of compound **6** was performed. ^{1}H-^{1}H correlations were established using 2D COSY NMR and confirmed a spin system consistent with compound **6**. HSQC spectrum clearly indicates 3C's and associated protons for 2 CH_2 and 1 CH moieties. Isopropyl alcohol impurity is also detected in the sample containing compound **6**. HMBC correlations confirmed connectivity between carbons in compound **6**. Overall, NMR analysis confirms compound **6**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.57 (br. s, 2H), 2.41–2.18 (m, 2H), 2.05–1.88 (m, 4H), 1.80–1.59 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 46.39, 27.05, 18.65.
36. The $Na_2WO_4{\bullet}2H_2O$ (≥99.0%) is purchased from Sigma-Aldrich.
37. It is critical that a nitrogen flow is maintained during this reaction to prevent oxygen build up in the headspace of the reaction flask.
38. The UHP (≥98%) is purchased from Sigma-Aldrich. Incomplete conversion is observed when less UHP is used.
39. Reaction conversion is determined by GC (Note 33). The reaction is complete when less than 3% of **6** remains.
40. The residual quantity of urea is determined by HPLC using a Waters Atlantis T3 (150 mm × 4.6 mm × 3.0 μm) operating at 40 °C with a flow rate of 1.2 mL/min using a stepped gradient of solvents A) 0.1% H_3PO_4 in water and B) acetonitrile. t=0 min, A:B (100:0); t=9 min, A:B (5:95); t= 20 min (stop); Retention times for the following compounds are as indicated urea, 3.4 min; ABNO, 9.7 min. Residual urea is below 0.15% in the combined organic layers, and below 0.05% after washing with water (2 x 100 mL).
41. Prolonged heating and drying of ABNO is not recommended since it can sublime over time. It is recommended ABNO be stored refrigerated. Solid ABNO exhibits large exotherm of 960 J/g in the temperature range of 80-220 ºC. In fall-hammer tests, it gave 3 positive (explosion) out of 8 tests at impact energy level of 30 J, but 0 out of 8 at 20 J. Thus, ABNO is potentially shock sensitive and proper precaution should be exercised

when handling solids as to avoid compression and shock (for DSC data see Appendix).

42. DSC showed two melting endotherms, 53 °C and 70 °C, indicating crystal form conversions. ^{1}H NMR (600 MHz, CD_3CN) δ: 166.7 (br. s, 2H), 96.7 (br. s, 2H), 74.7 (br. s, 4H), 26.2 (br. s, 2H), -45.5 (br. s, 4H). More details on the peak assignments are described in the discussion section.
43. Purity is determined by GC (Note 33).

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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Discussion

ABNO (9-azabicyclo[3.3.1]nonane-N-oxyl) is an effective catalyst for aerobic oxidation of alcohols to ketones and aldehydes. This type of oxidation is particularly attractive for large scale preparations because of the potential to reduce cost and minimize waste. Typically, 1-10 mol% of the catalyst is employed, which would represent significant quantities on scale.[2,3] The current procedure is developed to address the rather limited commercial availability and high cost of ABNO on large quantities.[4] Compared to prior syntheses, the current route starts with the same acetone-1,3-dicarboxylic acid (**1**) and glutaraldehyde (**2**) and forms compound **6** which is oxidized to the N-O radical. The key feature of the current route is that the benzylated compound **3** is prepared readily from compound **1** and **2** and it can be easily extracted into organic solvents. The crude **3** is reduced to alcohol **4** which is through processed by treatment with sulfuric acid to form the olefin **5**. Upon hydrogenation, crude **5** is converted to **6**. Crude **6** is again through processed into the oxidation step with urea hydrogen peroxide catalyzed with sodium tungstate to give ABNO which is purified by crystallization. This process does not require any chromatographic purification, and the final product (ABNO) is purified by crystallization.[4]

The purity analysis of ABNO poses unique challenges. Because of the paramagnetic property of ABNO, its NMR spectra cannot be obtained under normal conditions. However, proton NMR as shown in Figure 15 can be obtained under special instrument settings.[5] It can otherwise be analyzed with GC. The GCMS or LCMS under standard electron spray ionization conditions exhibited the expected *m*/*z* = 140 but higher than expected *m+1*/*z* = 141 peak.[4]

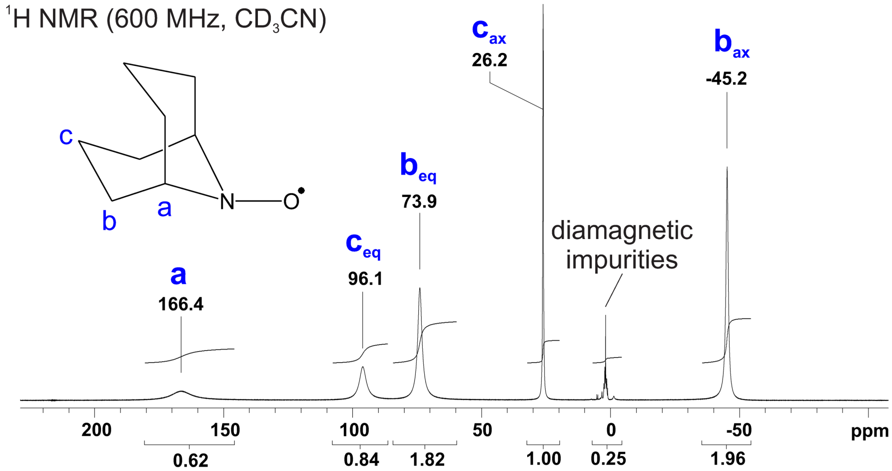


Figure 15. NMR spectrum of a typical batch of ABNO. Note that diamagnetic impurities include the HDO and residual acetonitrile-d_2 peaks as the largest signals

References

1. Zhiguo Jake Song, Process R & D, Merck & Co., Inc., 2000 Galloping Hill Road, Kenilworth, NJ 07033, USA (MSD). Email: zhiguo_song@merck.com
2. Synthesis of ABNO: (a) Shibuya, M.; Tomizawa, M.; Sasano, Y.; Iwabuchi, Y. *J. Org. Chem.* **2009**, *74*, 4619–4622. (b) Lauber, M. B.; Stahl S. S. *ACS Catal.* **2013**, *3*, 2612–2616.
3. ABNO catalyzed oxidations: (a) Steves, J. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 15742–15745. (b) TEMPO/ABNO: McCann, S. D.; Stahl, S. S. *Acc. Chem. Res.* **2015**, *48*, 1756–1766. (c) Steves, J. E.; Preger, J.; Martinelli, J. R.; Welch, C. J.; Root, T. W.; Hawkins, J. M.; Stahl, S. S. *Org. Process Res. Dev.* **2015**, 19, 1548-1553. (d) Greene, J. F.; Preger, J.; Stahl, S. S.; Root, T.W. *Org. Process Res. Dev.* **2015,** *19*, 858–864. (e) Kim, J.; Stahl, S. S. *ACS Catal.* **2013**, 3, 1652–1656. (f) Cao, Q.; Dornan, L. M.; Rogan, L.; Hughes, N. L.; Muldoon, M. J. *Chem. Commun.* **2014,** 50, 4524. (g) Rogan, L.; Hughes, N. L.; Cao, Q.; Dornan, L. M.; Muldoon, M. J. *Catal. Sci. Technol.*, **2014**, 4, 1720–1725. (h) Zultanski, S. L.; Zhao, J.; Stahl, S. S. *J. Am. Chem. Soc.* **2016**, *138*, 6416–6419.

4. This procedure is first published in: Song, Z. J.; Zhou, G.; Cohen, R.; Tan, L. *Org. Process Res. Dev*. **2018**, *22*, 1257–1261 and references cited therein.
5. Proton NMR spectrum of ABNO is recorded on a Bruker AVANCE III HD 600 MHz spectrometer equipped with a triple resonance (HCN) helium cryoprobe. Sample is dissolved in CD_3CN at 200 mg/ml concentration because a high concentration resulted in markedly narrower line widths due to the process of intermolecular spin exchange. Proton NMR spectra are acquired using a 30° flip angle, 256 scans, 0.7 s acquisition time, 0.1 s recovery delay, spectral width from –120 to 240 ppm and transmitter frequency set to 70 ppm. Spectra are processed in Mnova, ver. 12.0 using backward linear prediction (20 points predicted using the Toeplitz method with 262119 basis points and 24 coefficients), which corrected the baseline distortion.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

Benzylamine; (100-46-9)
Sulfuric acid; (7664-93-9)
Acetone-1,3-dicarboxylic acid (**1**); (542-05-2)
Glutaraldehyde (**2**); (111-30-8)
Sodium borohydride; (10940-66-2)
Hydrochloric acid; (7647-01-0)
Sodium hydroxide; (1310-73-2)
Palladium hydroxide (20% on activated carbon) (12135-22-7)
Sodium tungstate dihydrate (10213-22-7)
Urea-hydrogen peroxide (UHP) (124-43-6)
9-Benzyl-9-azabicyclo[3.3.1]nonan-3-one (**3**) (2291-58-9)
9-Benzyl-9-azabicyclo[3.3.1]nonan-3-ol (**4**) (289487-86-1)
9-Benzyl-9-azabicyclo[3.3.1]non-3-ene (**5**) (55286-17-4)
9-Azabicyclo[3.3.1]nonane (**6**) (280-97-7)
9-Azabicyclo[3.3.1]nonane-*N*-oxyl (**ABNO**) (31785-68-9)

Zhiguo Jake Song is currently a Principal Scientist in Process R & D at MSD. He got his BS degree in chemistry from Nankai University in Tianjin China and his PhD in organic chemistry from University of Illinois at Urbana-Champaign in the research group of Prof. Peter Beak. He joined the MSD Process R&D in 1990 after his PhD work where he has been focusing on development of economical, safe and environmentally benign synthetic processes for drug candidates.

Guoyue Zhou obtained his B.S. in pharmaceutical engineering in 2006 from Zhejiang University of Technology under the supervision of Professor Jiehua Shi. He then joined in STA Pharmaceutical Co., Ltd. (a WuXi AppTec Company) as a process chemist after graduation. In 2007, he joined the STA-MSD collaboration team. He leads a team with more than 15 members to do process research and development work and has finished a large variety of MSD projects.

Honglin Ye was born in Jiangxi province, China. He received his Master degree at Beijing Technology and Business University in 2011. In the summer of 2011 he began working as a process chemist in the Process Research and Development group at STA Pharmaceutical Co., Ltd. (a WuXi AppTec Company). He is currently a senior scientist at STA.

Ryan Cohen is currently an Associate Principal Scientist at MSD with expertise in a variety of structure elucidation techniques. He received his B.A. in chemistry from Rutgers in 2001 and his M.S. in pharmaceutical engineering from New Jersey Institute of Technology in 2011. He joined Schering-Plough as an analytical scientist in 2005, working on chromatographic method development. After the MSD merger in 2009, he moved to the Rahway site where he began training on mass spectrometry, followed by NMR and EPR spectroscopy. In his spare time, he enjoys rock climbing and downhill skiing.

Lushi Tan is an alumnus of Hunan Normal University (B.S.) and Nanjing University (M.S.). He received his Ph.D. from the University of Minnesota in 1995 and then joined MSD Process R&D in New Jersey as a senior chemist. He is now a Distinguished Scientist and External Capability Lead at MSD. He supervises a team of senior scientists working to improve the capability of MSD strategic partners around the world, with responsibility for the process development and manufacturing of all MSD development compounds. Lushi's research interests range from asymmetric synthesis, catalysis, and biocatalysis to mechanistic investigations of new reactions.

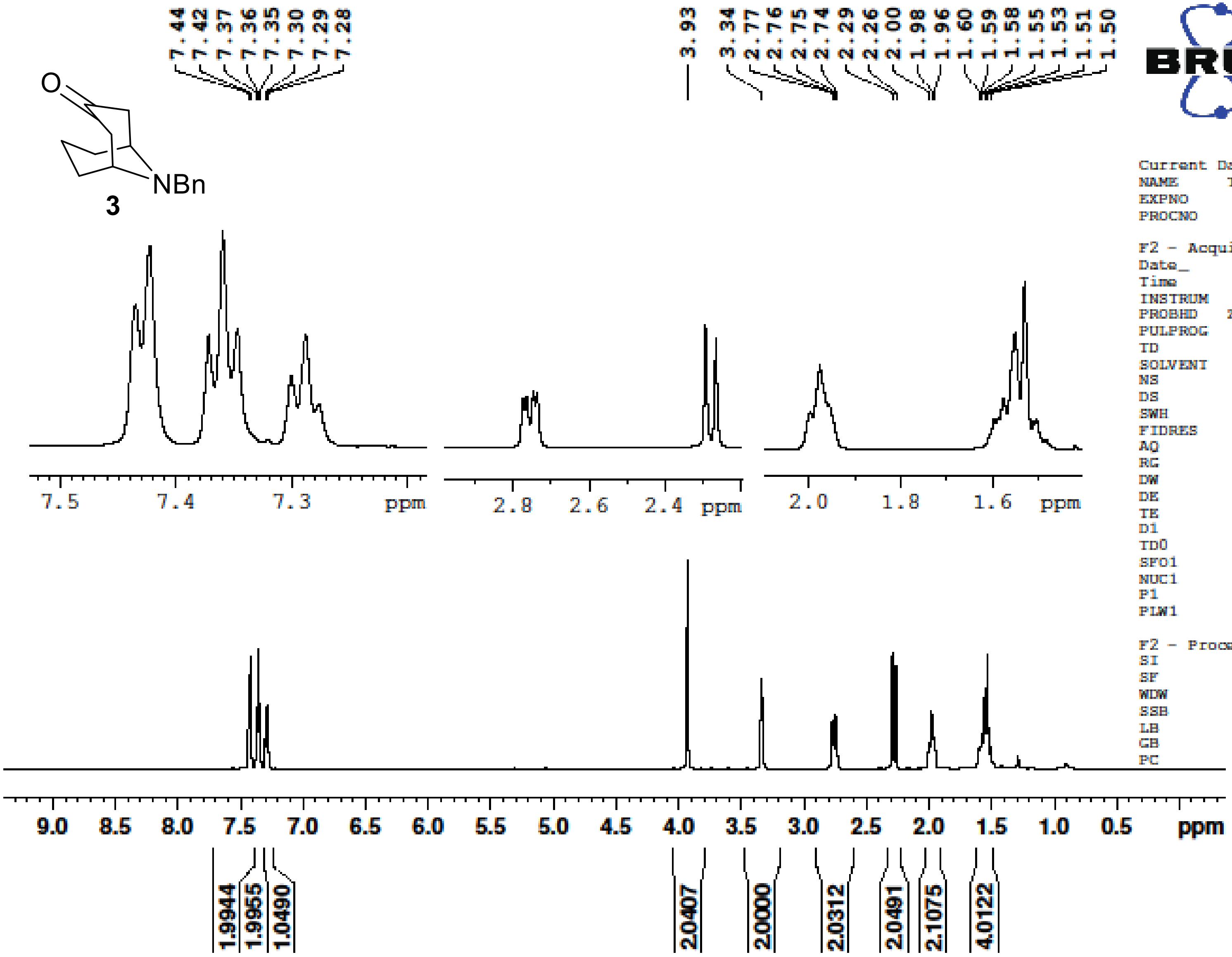
Rohit Mahar is a Senior Scientist in Analytical Chemistry Division of TCG GreenChem Inc., Ewing, NJ. He received his Ph.D. in chemistry from CSIR-Central Drug Research Institute/Jawaharlal Nehru University, India (March 2017). He started his first postdoctoral research in the field of Microscopic MRI at Oakland University, MI, USA. In March 2018, he moved to University of Florida for his second postdoctoral research, where he worked on measuring metabolic fluxes in the *in vitro* and *in vivo* systems, employing Nuclear Magnetic Resonance (NMR/MRI) and Mass Spectrometry (MS).

Dr. Vasudevan Natarajan is a Senior Scientist at TCG GreenChem Inc., Ewing, NJ. He completed his doctoral research (Ph.D.) in 2017 under the guidance of Dr. D. Srinivasa Reddy at CSIR-National Chemical Laboratory, Pune, India. He moved as post-doctoral research associate in Prof. François-Xavier Felpin's research group at University of Nantes, France where he focused on asymmetric synthesis, carbon-carbon bond formation using algorithm directed self-optimizing continuous flow platform. In December 2019, he joined Prof. Gupton's research group, and worked on developing new the synthetic routes to access active pharmaceutical ingredients (APIs) through process intensification and continuous flow operations.

Nathaniel Kaetzel is a scientist at TCG GreenChem, Inc. Process R&D Center, Ewing, NJ. He joined the TCG GreenChem, Inc. Innovation Center in Richmond, VA in 2020, after studying under the guidance of Dr. Joshua Sieber and Dr. Christopher Kelly at Virginia Commonwealth University's Medicines for All institute (M4ALL).

Dr. Gopal Sirasani received his Bachelor's and Master's degrees in Hyderabad, India. He obtained his Ph.D. in synthetic organic chemistry in 2011 from Temple University, Philadelphia under the guidance of Prof. Rodrigo B. Andrade. His doctoral research was focused on developing novel methodologies, total syntheses of natural products and their analogs thereof. He got his post-doctoral training in the laboratory of Prof. Emily Balskus at Harvard University, where he developed biocompatible organic reactions utilizing microbially generated reagents to realize transition metal catalysis in the presence of microbes. In 2013, Gopal began his industrial career at Melinta Therapeutics, New Haven, CT. He currently works as a Director at TCG GreenChem, Inc.

9-Benzyl-9-azabicyclo[3.3.1]nonan-3-one



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PROCNO                      1

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FIDRES             0.366798 Hz
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DE                     6.50 usec
TE                    296.6 K
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TD0                       1
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P1                    15.50 usec
PLW1            13.23200035 W

F2 - Processing parameters
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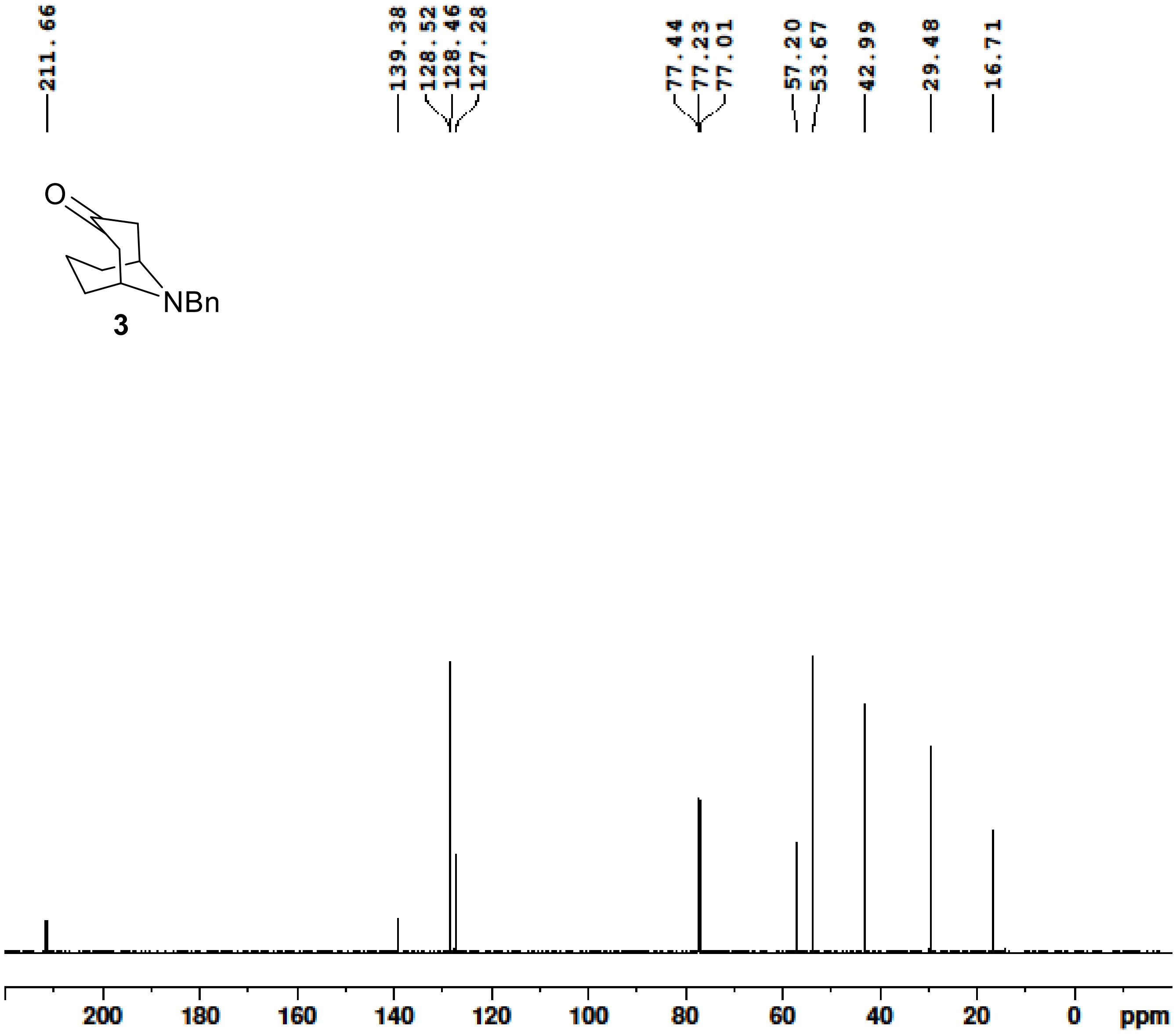
9-Benzyl-9-azabicyclo[3.3.1]nonan-3-one



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TD                65536
SOLVENT           CDCl3
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FIDRES         1.105709 Hz
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RG               199.73
DW               13.800 usec
DE                 6.50 usec
TE                298.4 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1
SFO1        150.8864644 MHz
NUC1                13C
P1                12.00 usec
PLW1        77.65699768 W
SFO2        600.0074000 MHz
NUC2                 1H
CPDPRG[2        waltz16
PCPD2             70.00 usec
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PLW12        0.64876997 W
PLW13        0.32633001 W

F2 - Processing parameters
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WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
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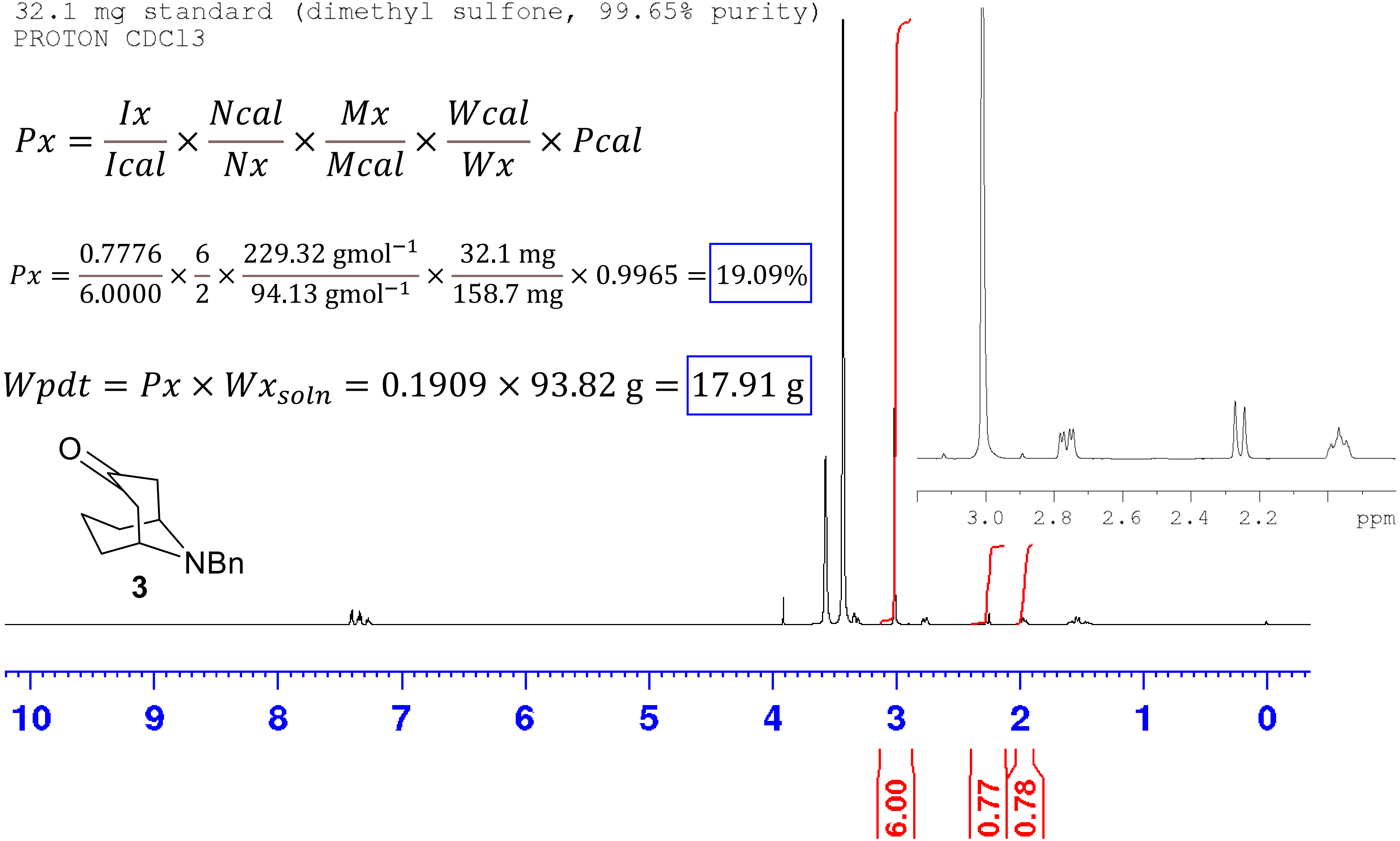
158.7 mg crude solution (93.82 g total)
32.1 mg standard (dimethyl sulfone, 99.65% purity)
PROTON CDCl3

$$Px = \frac{Ix}{Ical} \times \frac{Ncal}{Nx} \times \frac{Mx}{Mcal} \times \frac{Wcal}{Wx} \times Pcal$$

$$Px = \frac{0.7776}{6.0000} \times \frac{6}{2} \times \frac{229.32\ \mathrm{gmol^{-1}}}{94.13\ \mathrm{gmol^{-1}}} \times \frac{32.1\ \mathrm{mg}}{158.7\ \mathrm{mg}} \times 0.9965 = \boxed{19.09\%}$$

$$Wpdt = Px \times Wx_{soln} = 0.1909 \times 93.82\ \mathrm{g} = \boxed{17.91\ \mathrm{g}}$$



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FIDRES            0.366798 Hz
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RG                     18.2
DW                   41.600 usec
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TE                    296.3 K
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TD0                       1
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NUC1                     1H
P1                    15.50 usec
PLW1            13.23200035 W

F2 - Processing parameters
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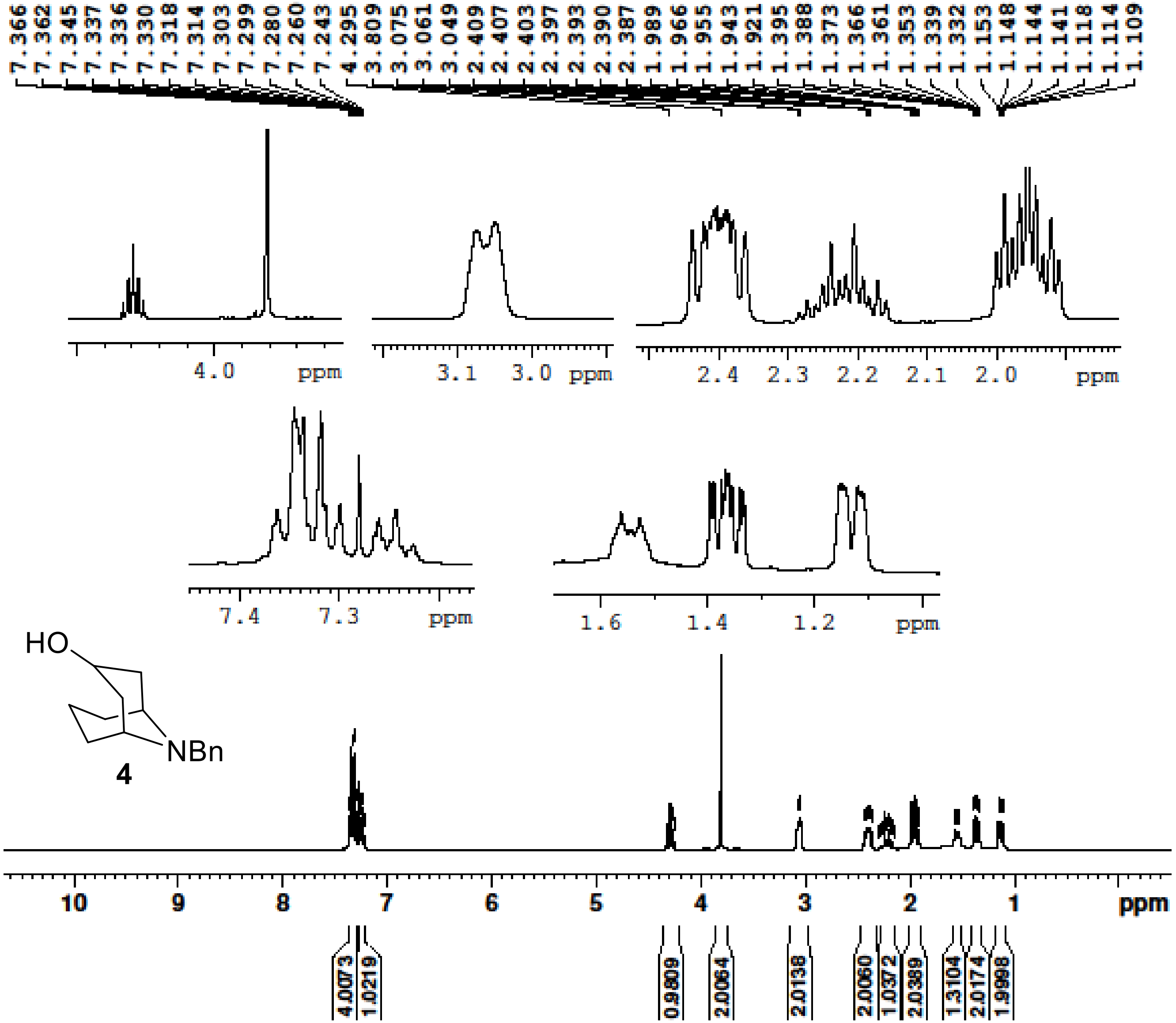
9-Benzyl-9-azabicyclo[3.3.1]nonan-3-ol



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TD                   65536
SOLVENT              CDCl3
NS                      32
DS                       2
SWH            8196.722 Hz
FIDRES         0.250144 Hz
AQ            3.9976959 sec
RG                 90.4281
DW              61.000 usec
DE               13.95 usec
TE                 298.0 K
D1           4.00000000 sec
TD0                      1
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NUC1                    1H
P0                2.54 usec
P1                7.61 usec
PLW1         23.42000008 W

F2 - Processing parameters
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SF          400.1300022 MHz
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SSB                      0
LB                 0.30 Hz
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PC                    1.00
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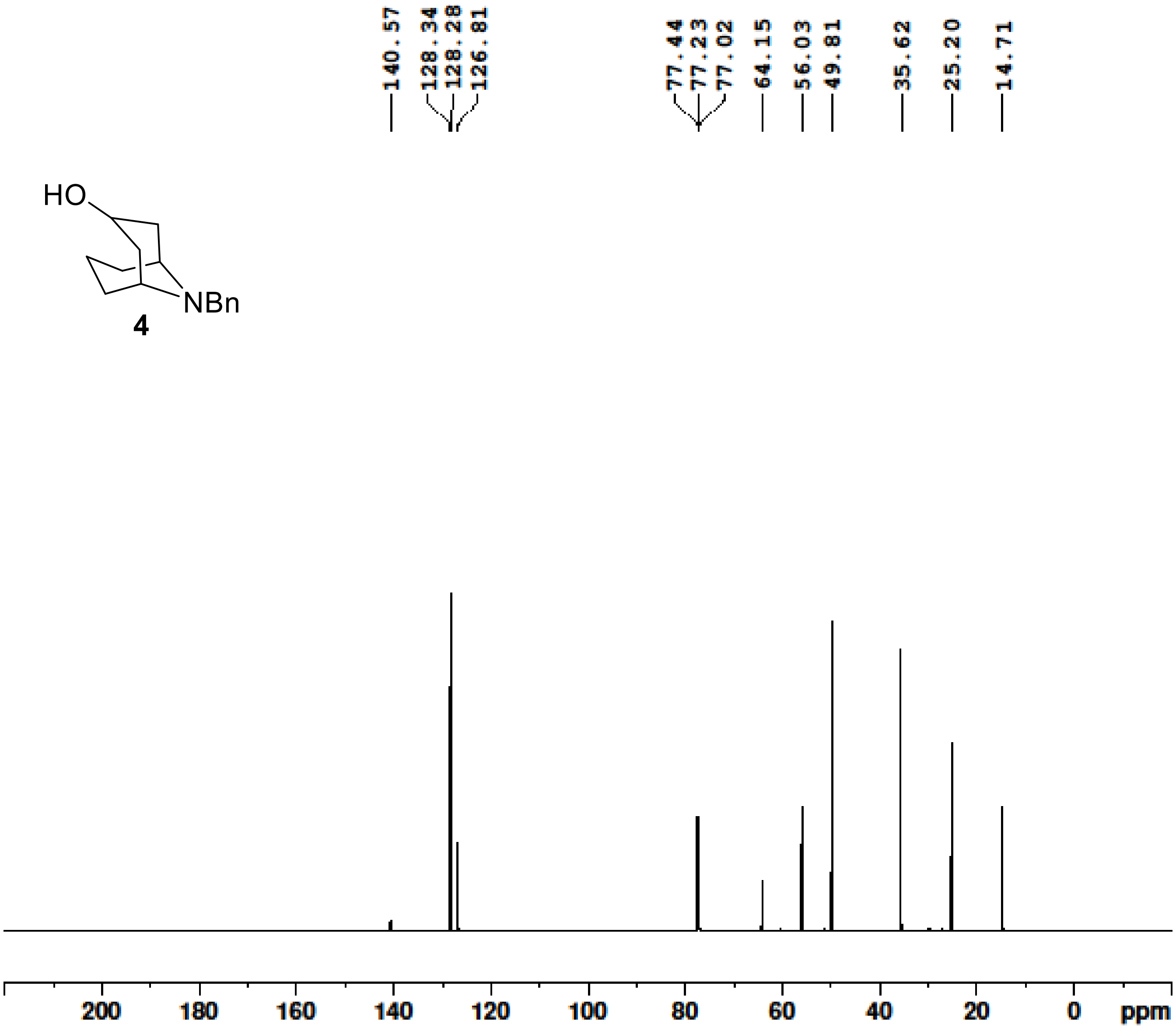
9-Benzyl-9-azabicyclo[3.3.1]nonan-3-ol



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SWH              36231.883 Hz
FIDRES            1.105709 Hz
AQ               0.9043968 sec
RG                  199.73
DW                  13.800 usec
DE                    6.50 usec
TE                   298.3 K
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D11             0.03000000 sec
TD0                      1
SFO1          150.8864644 MHz
NUC1                   13C
P1                   12.00 usec
PLW1           77.65699768 W
SFO2          600.0074000 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                70.00 usec
PLW2           13.23200035 W
PLW12           0.64876997 W
PLW13           0.32633001 W

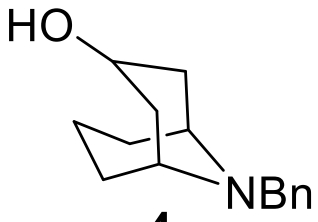
F2 - Processing parameters
SI                   32768
SF            150.8713683 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

23.4 mg product (19.2 g total)
18.0 mg standard (dimethyl fumarate, 99.0% purity)
PROTON CDCl3

$$Px = \frac{Ix}{Ical} \times \frac{Ncal}{Nx} \times \frac{Mx}{Mcal} \times \frac{Wcal}{Wx} \times Pcal$$

$$Px = \frac{1.5218}{2.0000} \times \frac{2}{2} \times \frac{231.34\ \mathrm{gmol^{-1}}}{144.13\ \mathrm{gmol^{-1}}} \times \frac{18.0\ \mathrm{mg}}{23.4\ \mathrm{mg}} \times 0.990 = \boxed{93.0\%}$$

$$Wpdt = Px \times Wx_{crude} = 0.930 \times 19.2\ \mathrm{g} = \boxed{17.9\ \mathrm{g}}$$



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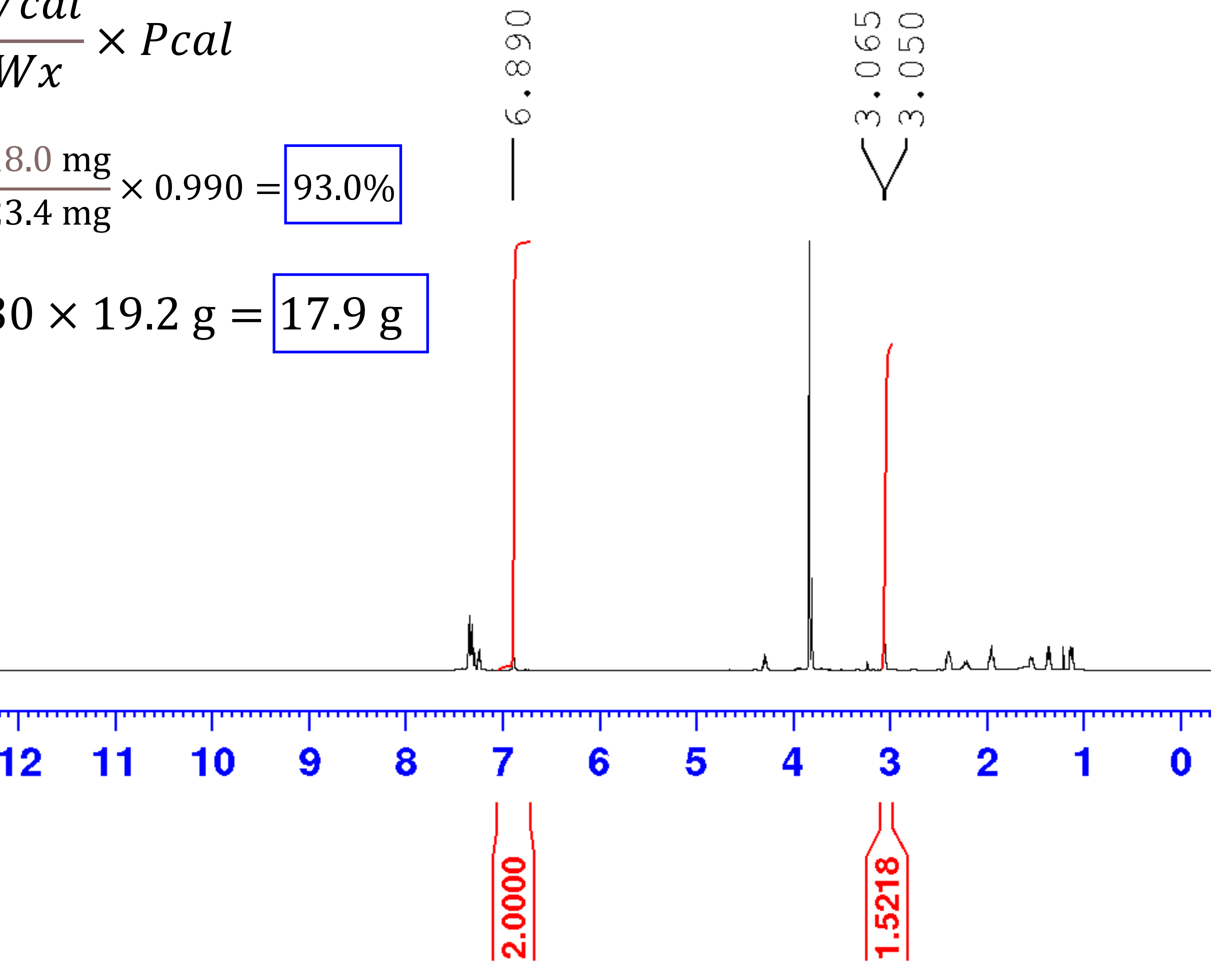

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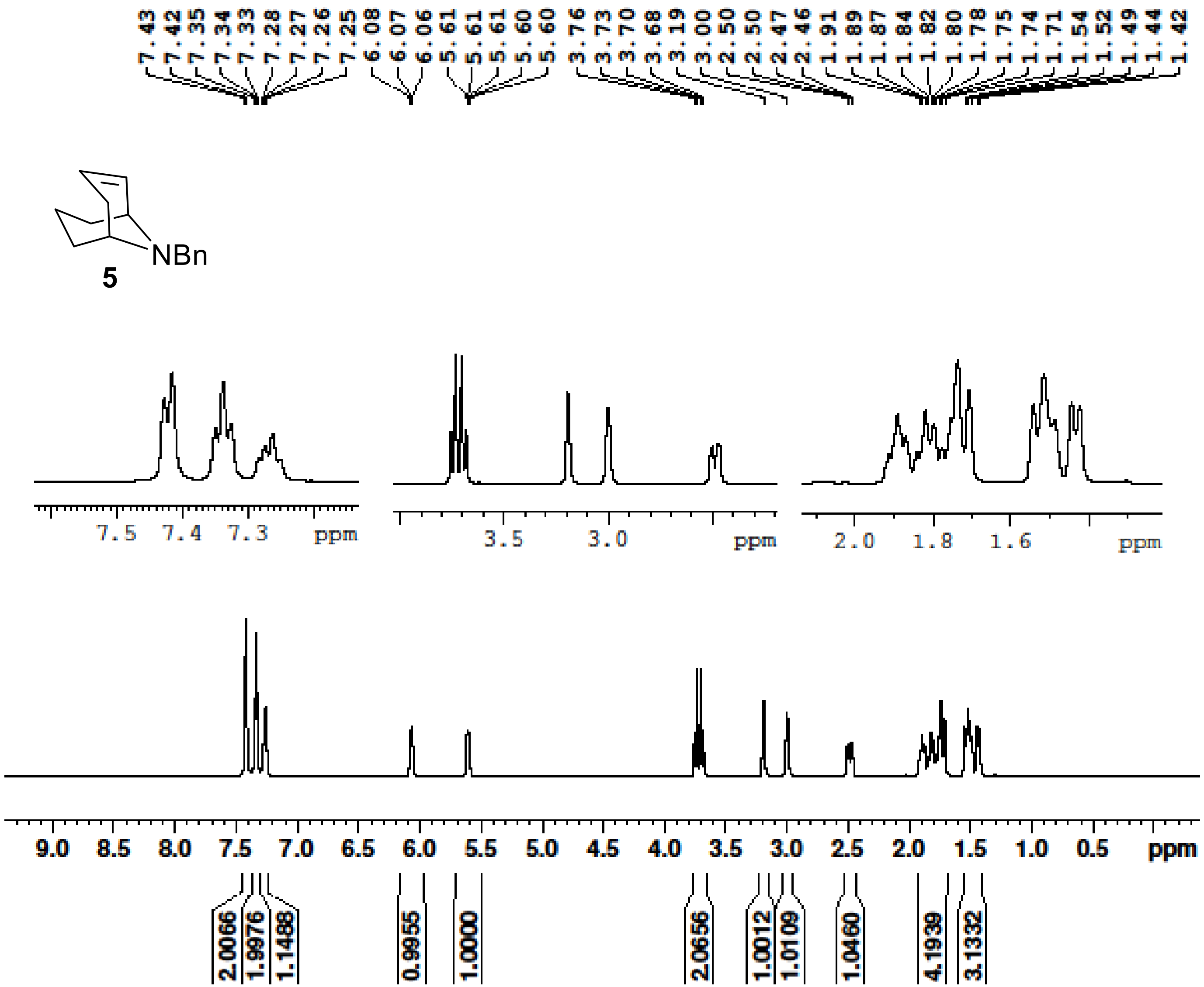
FIDRES	0.366798 Hz
AQ	2.7262976 sec
RG	78.64
DW	41.600 usec
DE	6.50 usec
TE	296.3 K
D1	4.00000000 sec
TD0	1
SFO1	600.0087050 MHz
NUC1	1H
P1	15.50 usec
PLW1	13.23200035 W

F2 - Processing parameters

SI	65536
SF	600.0050000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

9-Benzyl-9-azabicyclo[3.3.1]non-3-ene



5

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PROCNO                  1

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PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     32
DS                      2
SWH             12019.230 Hz
FIDRES           0.366798 Hz
AQ              2.7262976 sec
RG                  30.85
DW                 41.600 usec
DE                   6.50 usec
TE                  298.0 K
D1             1.00000000 sec
TD0                     1
SFO1          599.9587047 MHz
NUC1                   1H
P1                   7.75 usec
PLW1          11.99499989 W

F2 - Processing parameters
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SF            599.9550019 MHz
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PC                   1.00
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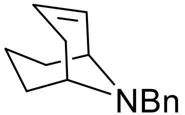
9-Benzyl-9-azabicyclo[3.3.1]non-3-ene



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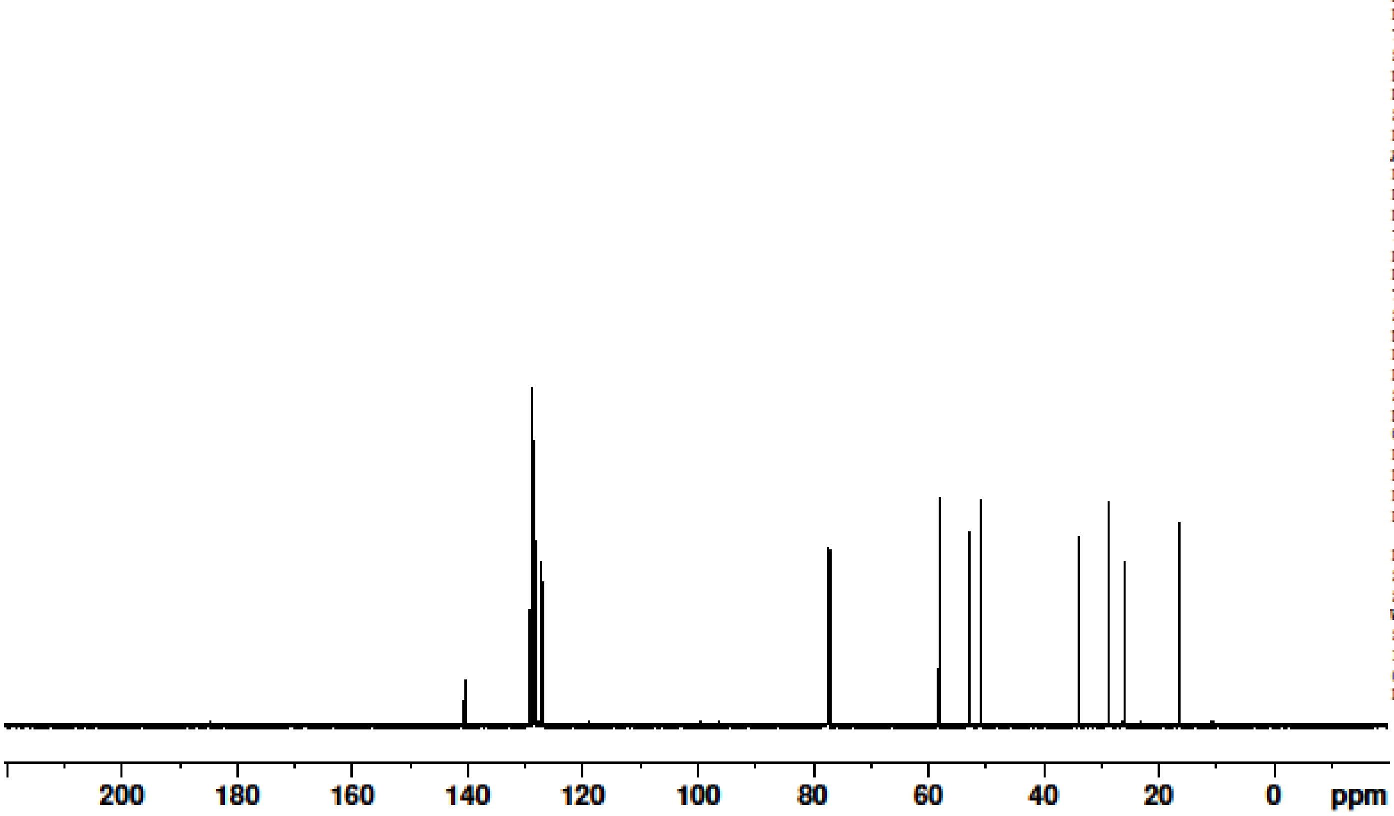

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NS	500
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SWH	36231.883 Hz
FIDRES	1.105709 Hz
AQ	0.9043968 sec
RG	194.75
DW	13.800 usec
DE	6.50 usec
TE	298.0 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
SFO1	150.8738906 MHz
NUC1	13C
P1	11.40 usec
PLW1	176.19999695 W
SFO2	599.9573998 MHz
NUC2	1H
CPDPRG[2	waltz16
PCPD2	70.00 usec
PLW2	11.99499989 W
PLW12	0.14703000 W
PLW13	0.07395500 W

F2 - Processing parameters

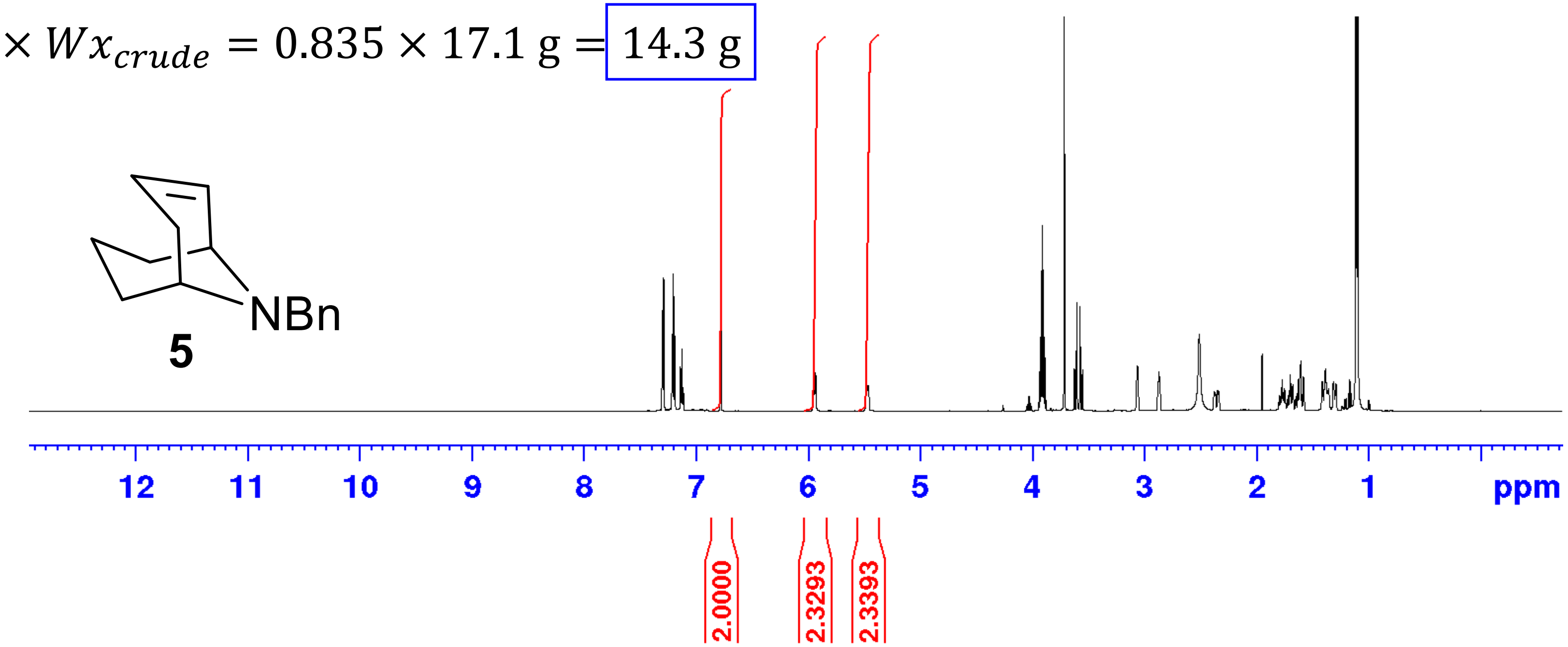
SI	32768
SF	150.8587778 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

82.5 mg product (crude, 17.1 g total)
20.1 mg standard (dimethyl fumarate, 99.0% purity)
PROTON CDCl3

$$Px = \frac{Ix}{Ical} \times \frac{Ncal}{Nx} \times \frac{Mx}{Mcal} \times \frac{Wcal}{Wx} \times Pcal$$

$$Px = \frac{2.3293}{2.0000} \times \frac{2}{1} \times \frac{213.32\ \mathrm{gmol^{-1}}}{144.13\ \mathrm{gmol^{-1}}} \times \frac{20.1\ \mathrm{mg}}{82.5\ \mathrm{mg}} \times 0.990 = \boxed{83.5\%}$$

$$Wpdt = Px \times Wx_{crude} = 0.835 \times 17.1\ \mathrm{g} = \boxed{14.3\ \mathrm{g}}$$



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SWH	12019.230 Hz
FIDRES	0.366798 Hz
AQ	2.7262976 sec
RG	15.88
DW	41.600 usec
DE	10.33 usec
TE	296.6 K
D1	8.00000000 sec
TD0	1
SFO1	600.0087050 MHz
NUC1	1H
P0	5.17 usec
P1	15.50 usec
PLW1	13.23200035 W

F2 - Processing parameters

SI	65536
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WDW	EM
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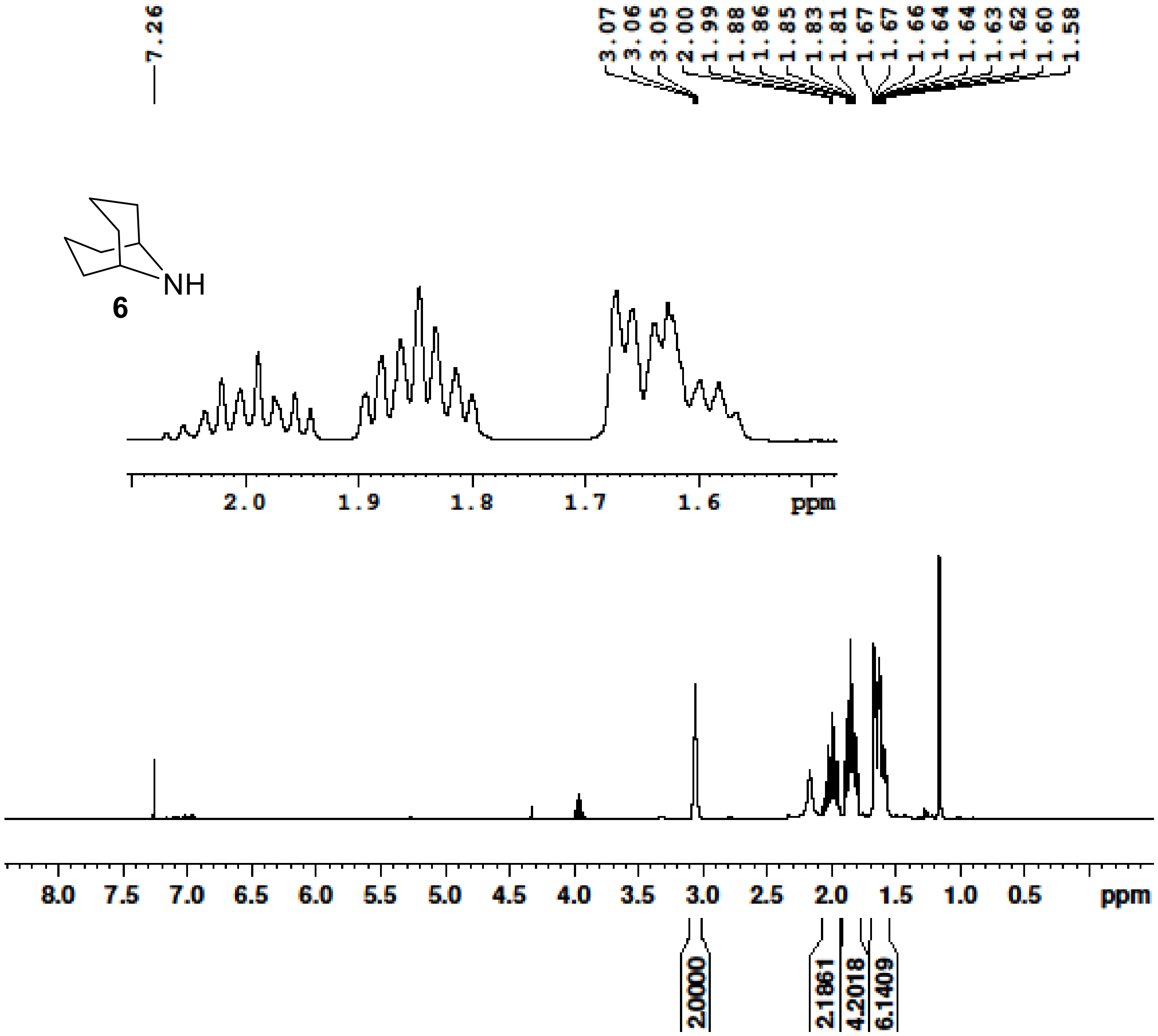
PC	1.00

9-Azabicyclo[3.3.1]nonane



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TD                 50000
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             6250.000 Hz
FIDRES          0.250000 Hz
AQ             4.0000000 sec
RG               50.7317
DW                80.000 usec
DE                  8.72 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                    1
SFO1         400.1324008 MHz
NUC1                  1H
P0                  2.50 usec
P1                  7.51 usec
PLW1         23.42000008 W

F2 - Processing parameters
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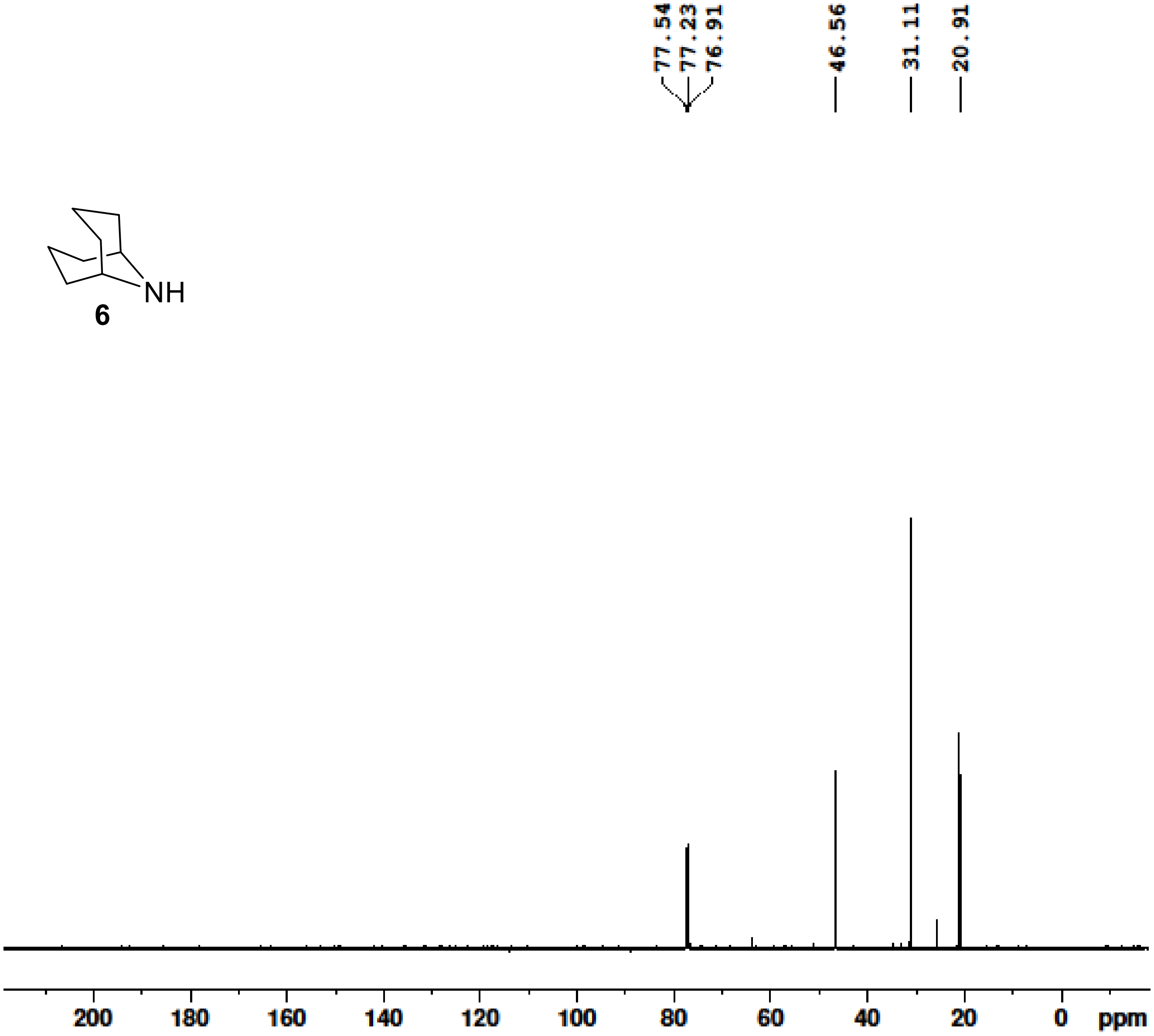
9-Azabicyclo[3.3.1]nonane



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TD                  71428
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NS                     71
DS                      4
SWH             23809.523 Hz
FIDRES           0.666672 Hz
AQ              1.4999880 sec
RG                    101
DW                 21.000 usec
DE                   6.50 usec
TE                  298.1 K
D1             1.50000000 sec
D11            0.03000000 sec
TD0                     1
SFO1          100.6228298 MHz
NUC1                  13C
P0                   2.67 usec
P1                   8.00 usec
PLW1          98.97000122 W
SFO2          400.1316005 MHz
NUC2                   1H
CPDPRG[2          waltz65
PCPD2               90.00 usec
PLW2          23.42000008 W
PLW12          0.16306999 W
PLW13          0.08202400 W

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LB                   1.00 Hz
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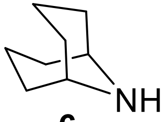
9-Azabicyclo[3.3.1]nonane



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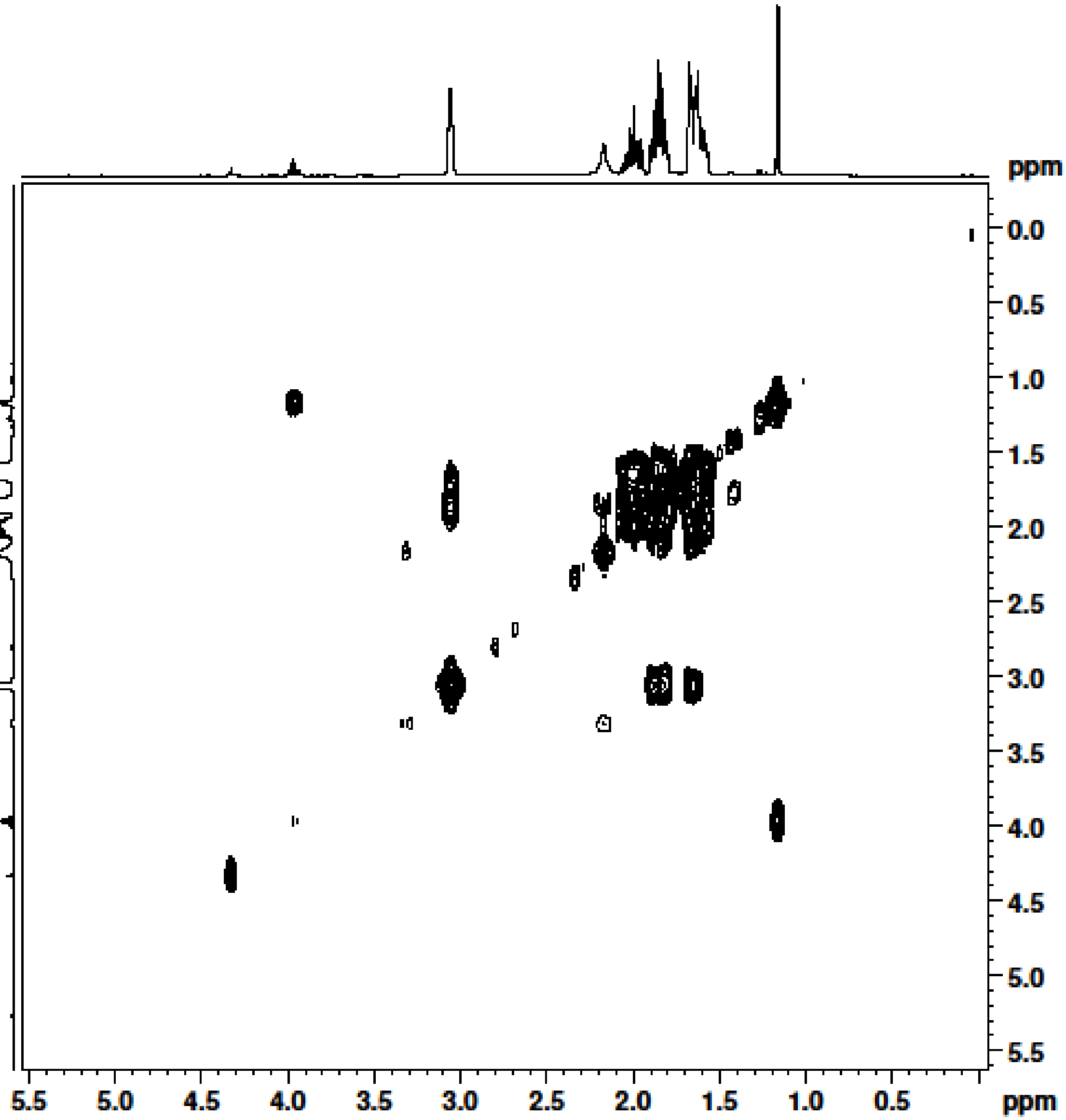


```
Current Data Parameters
NAME               NVD-67
EXPNO                  15
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220608
Time                15.28 h
INSTRUM            Avance
PROBHD    Z163739_0288 (
PULPROG        cosygpppqf
TD                   2048
SOLVENT             CDCl3
NS                      4
DS                     16
SWH              6250.000 Hz
FIDRES           6.103516 Hz
AQ              0.1638400 sec
RG                90.4348
DW                 80.000 usec
DE                   6.50 usec
TE                  298.0 K
D0            0.00000300 sec
D1            2.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
D13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00015620 sec
TDav                    1
SFO1        400.1324008 MHz
NUC1                   1H
P0                   7.51 usec
P1                   7.51 usec
P17               2500.00 usec
PLW1          23.42000008 W
PLW10          1.46770000 W
GPNAM[1]       SMSQ10.100
GPZ1                10.00 %
P16               1000.00 usec

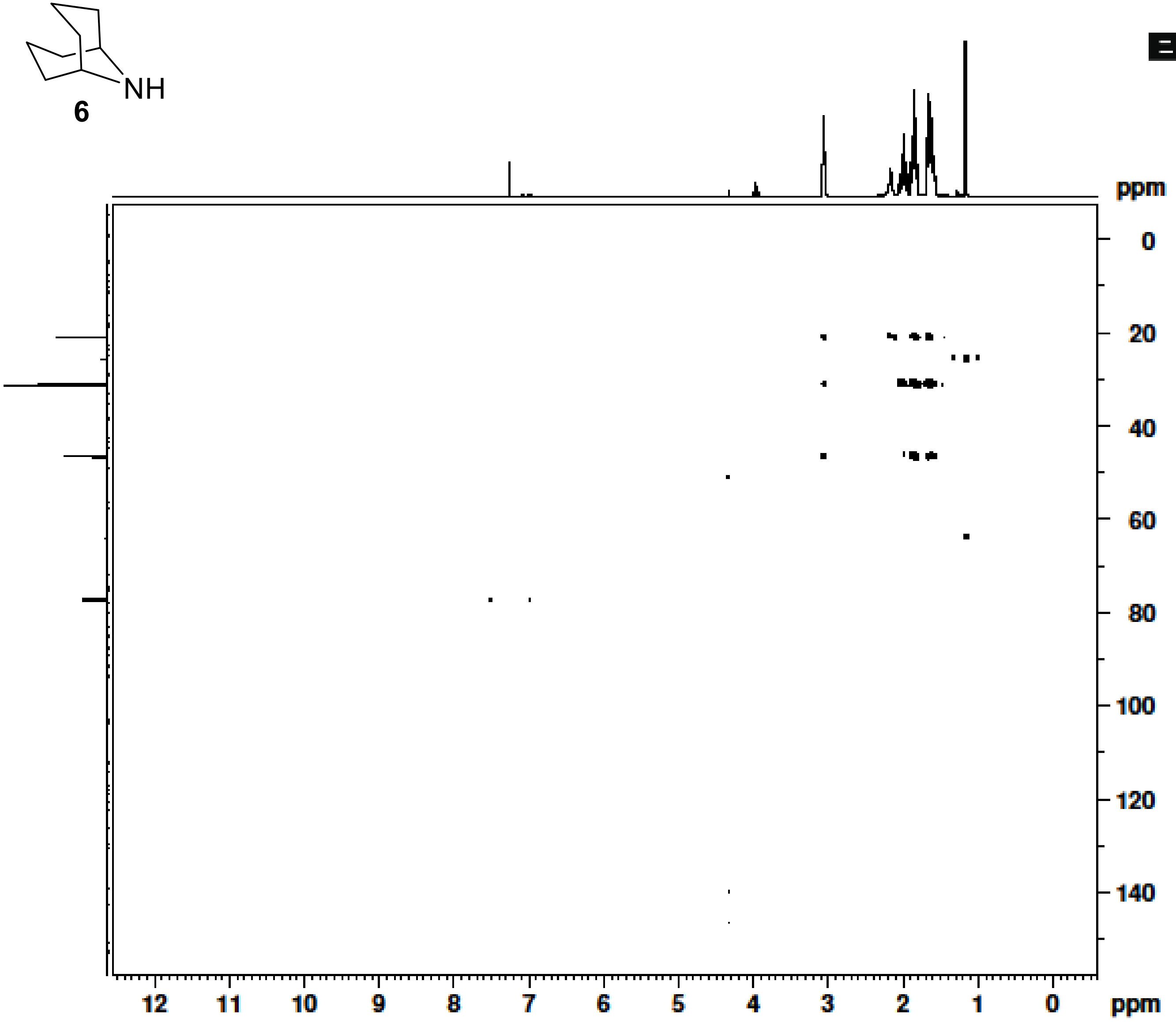
======== F1 INDIRECT DIMENSION ========
td1       128
sw_F1     16.000000

F1 - Acquisition parameters
TD                    128
SFO1             400.1324 MHz
FIDRES         100.032013 Hz
SW                 16.000 ppm
FnMODE                 QF

F2 - Processing parameters
SI                   4096
SF            400.1300105 MHz
WDW                 QSINE
SSB                     0
LB                      0 Hz
GB                      0
PC                   1.40

F1 - Processing parameters
SI                    512
MC2                    QF
SF            400.1300109 MHz
WDW                 QSINE
SSB                     0
LB                      0 Hz
GB                      0
```

9-Azabicyclo[3.3.1]nonane



6

```
Current Data Parameters
NAME               NVD-67
EXPNO                  19
PROCNO                  1

F2 - Acquisition Parameters
Date_            20220608
Time                16.11 h
INSTRUM             Avance
PROBHD   X163739_0288 (
PULPROG     hmbcgplpndqf
TD                   4096
SOLVENT             CDCl3
NS                      2
DS                     16
SWH              5263.158 Hz
FIDRES           2.569901 Hz
AQ              0.3891200 sec
RG                    101
DW                 95.000 usec
DE                   6.50 usec
TE                  298.0 K
CNST2         145.0000000
CNST13         10.0000000
D0             0.00000300 sec
D1             1.50000000 sec
D2             0.00344828 sec
D6             0.05000000 sec
D16            0.00020000 sec
IN0            0.00003011 sec
TDav                    1
SFO1          400.1324008 MHz
NUC1                   1H
P1                   7.51 usec
P2                  15.02 usec
PLW1          23.42000008 W
SFO2          100.6203145 MHz
NUC2                  13C
P3                   8.00 usec
PLW2          98.97299957 W
GPNAM[1]       SMSQ10.100
GPZ1                50.00 %
GPNAM[2]       SMSQ10.100
GPZ2                30.00 %
GPNAM[3]       SMSQ10.100
GPZ3                40.10 %
P16               1000.00 usec

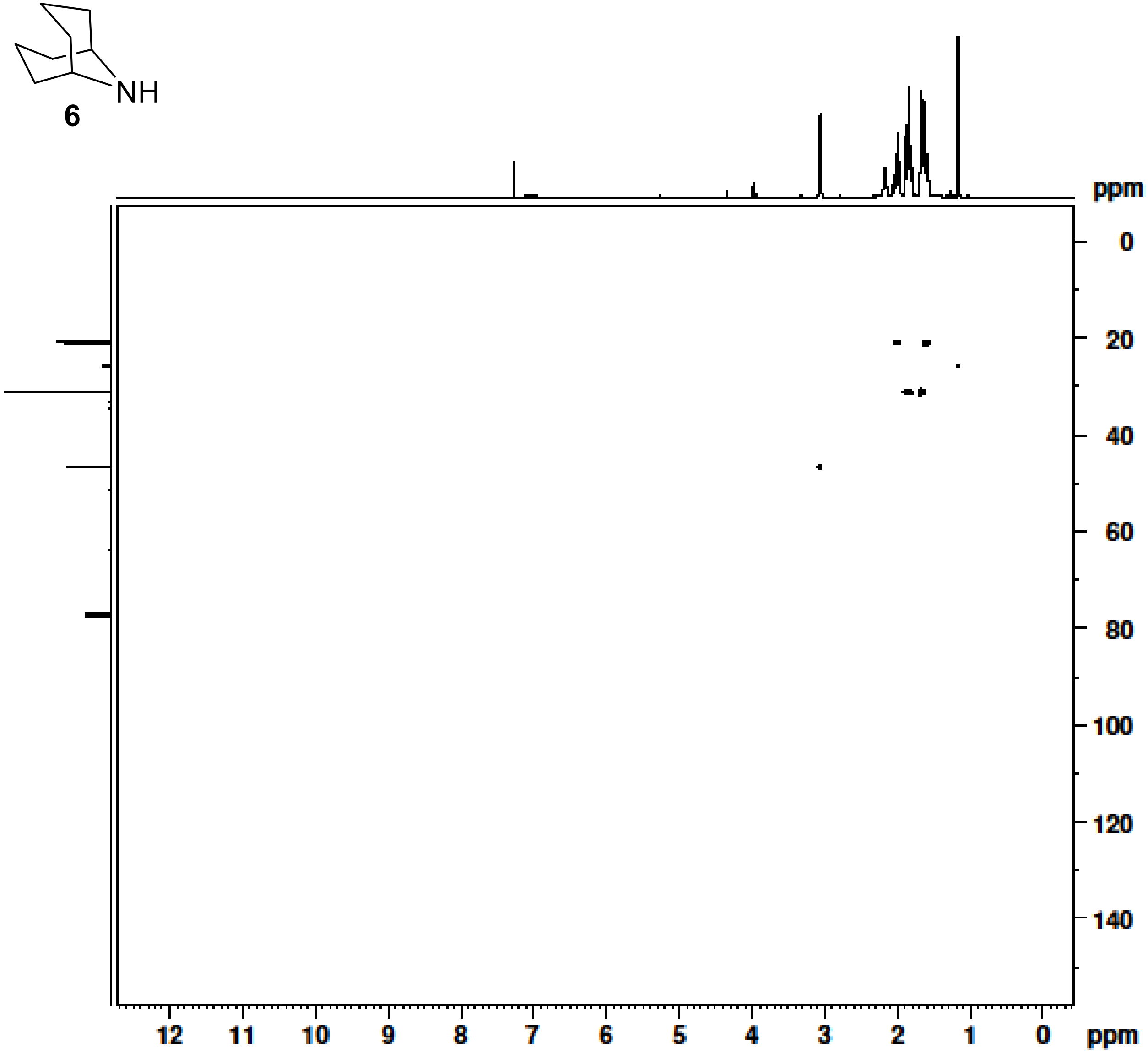
======== F1 INDIRECT DIMENSION ========
td1        256
sw_F1      165.004120

F1 - Acquisition parameters
TD                    256
SFO1             100.6203 MHz
FIDRES         129.721878 Hz
SW                165.030 ppm
FnMODE                 QF

F2 - Processing parameters
SI                   4096
SF            400.1300117 MHz
WDW                 QSINE
SSB                     0
LB                      0 Hz
GB                      0
PC                   1.40

F1 - Processing parameters
SI                    512
MC2                    QF
SF            100.6127617 MHz
WDW                 QSINE
SSB                     0
LB                      0 Hz
GB                      0
```

9-Azabicyclo[3.3.1]nonane



6

```
Current Data Parameters
NAME                  WVD-67
EXPNO                     16
PROCNO                     1

F2 - Acquisition Parameters
Date_               20220608
Time                   15.45 h
INSTRUM               Avance
PROBHD     Z163739_0288 (
PULPROG          hsqcedetgp
TD                      2048
SOLVENT                CDCl3
NS                         2
DS                        16
SWH                 5263.158 Hz
FIDRES              5.139802 Hz
AQ                 0.1945600 sec
RG                       101
DW                    95.000 usec
DE                      6.50 usec
TE                     298.1 K
CNST2            145.0000000
D0                0.00000300 sec
D1                1.50000000 sec
D4                0.00172414 sec
D11               0.03000000 sec
D16               0.00020000 sec
D21               0.00345000 sec
IN0               0.00003013 sec
TDav                       1
SGOPTNS
SFO1             400.1324708 MHz
NUC1                      1H
P1                      7.51 usec
P2                     15.02 usec
PLW1             23.42000008 W
SFO2             100.6203145 MHz
NUC2                     13C
CPDPRG[2                garp
P3                      8.00 usec
P4                     16.00 usec
PCPD2                  80.00 usec
PLW2             98.97299957 W
PLW12             0.98973000 W
GPNAM[1]          SMSQ10.100
GPZ1                   80.00 %
GPNAM[2]          SMSQ10.100
GPZ2                   20.10 %
P16                  1000.00 usec

-------- F1 INDIRECT DIMENSION --------
td1          256
sw_F1        165.000000

F1 - Acquisition parameters
TD                       256
SFO1                100.6203 MHz
FIDRES            129.694962 Hz
SW                   164.986 ppm
FnMODE          Echo-Antiecho

F2 - Processing parameters
SI                      1024
SF               400.1300096 MHz
WDW                    QSINE
SSB                        2
LB                         0 Hz
GB                         0
PC                      1.40

F1 - Processing parameters
SI                      1024
MC2             echo-antiecho
SF               100.6127503 MHz
WDW                    QSINE
SSB                        2
LB                         0 Hz
GB                         0
```

44.41 mg product (29.1 g total, solution)
12.74 mg standard (trimethoxybenzene, 99.0% purity)
PROTON CDCl3

$$Px = \frac{Ix}{Ical} \times \frac{Ncal}{Nx} \times \frac{Mx}{Mcal} \times \frac{Wcal}{Wx} \times Pcal$$

$$Px = \frac{3.7732}{9.0000} \times \frac{9}{2} \times \frac{125.22\ \mathrm{gmol^{-1}}}{168.19\ \mathrm{gmol^{-1}}} \times \frac{12.74\ \mathrm{mg}}{44.41\ \mathrm{mg}} \times 0.990 = \boxed{39.9\%}$$

$$Px = \frac{7.5429}{9.0000} \times \frac{9}{4} \times \frac{125.22\ \mathrm{gmol^{-1}}}{168.19\ \mathrm{gmol^{-1}}} \times \frac{12.74\ \mathrm{mg}}{44.41\ \mathrm{mg}} \times 0.990 = \boxed{39.9\%}$$

$$Wpdt = Px \times Wx_{crude} = 0.399 \times 29.1\ \mathrm{g} = \boxed{11.6\ \mathrm{g}}$$

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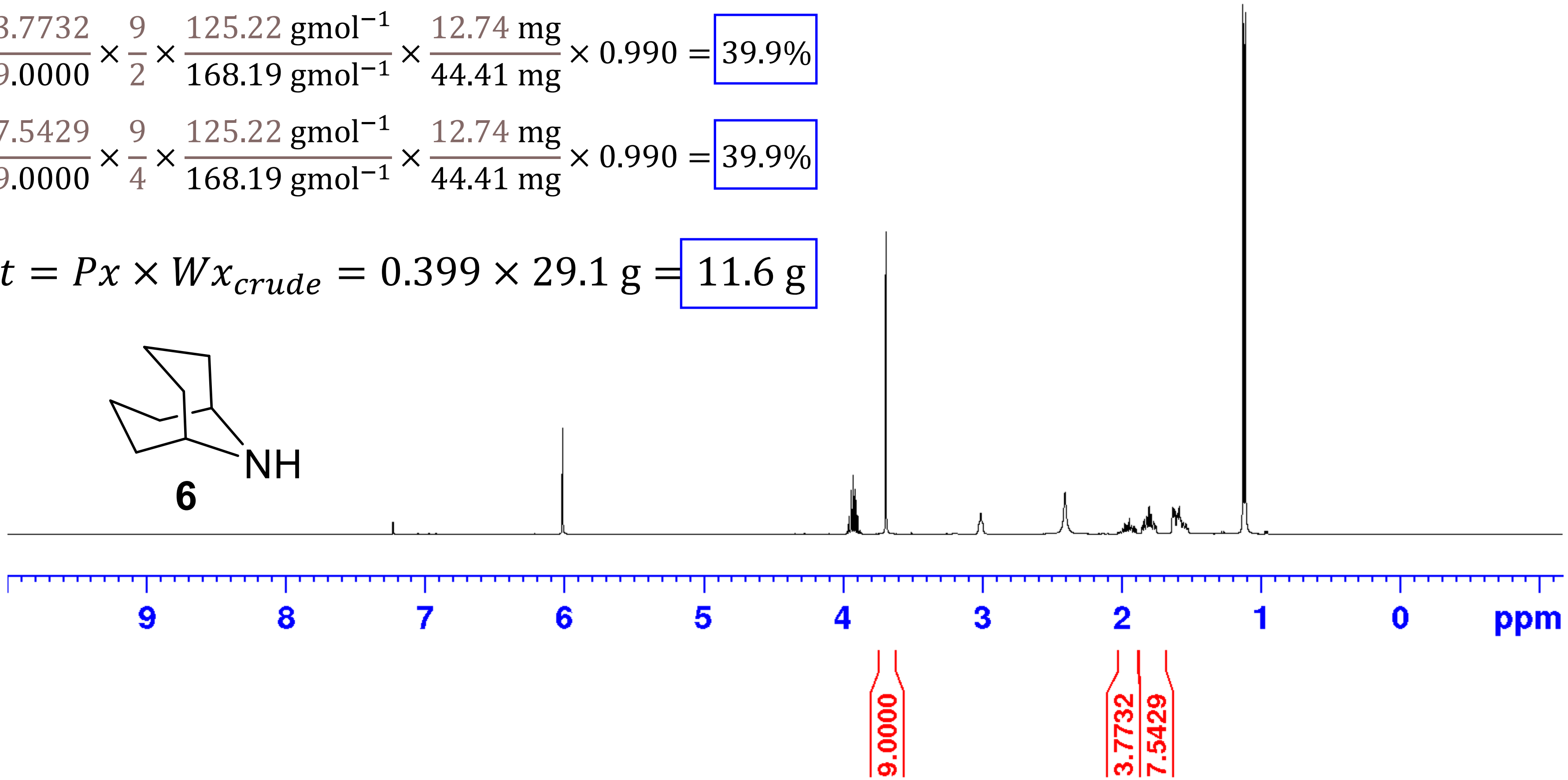


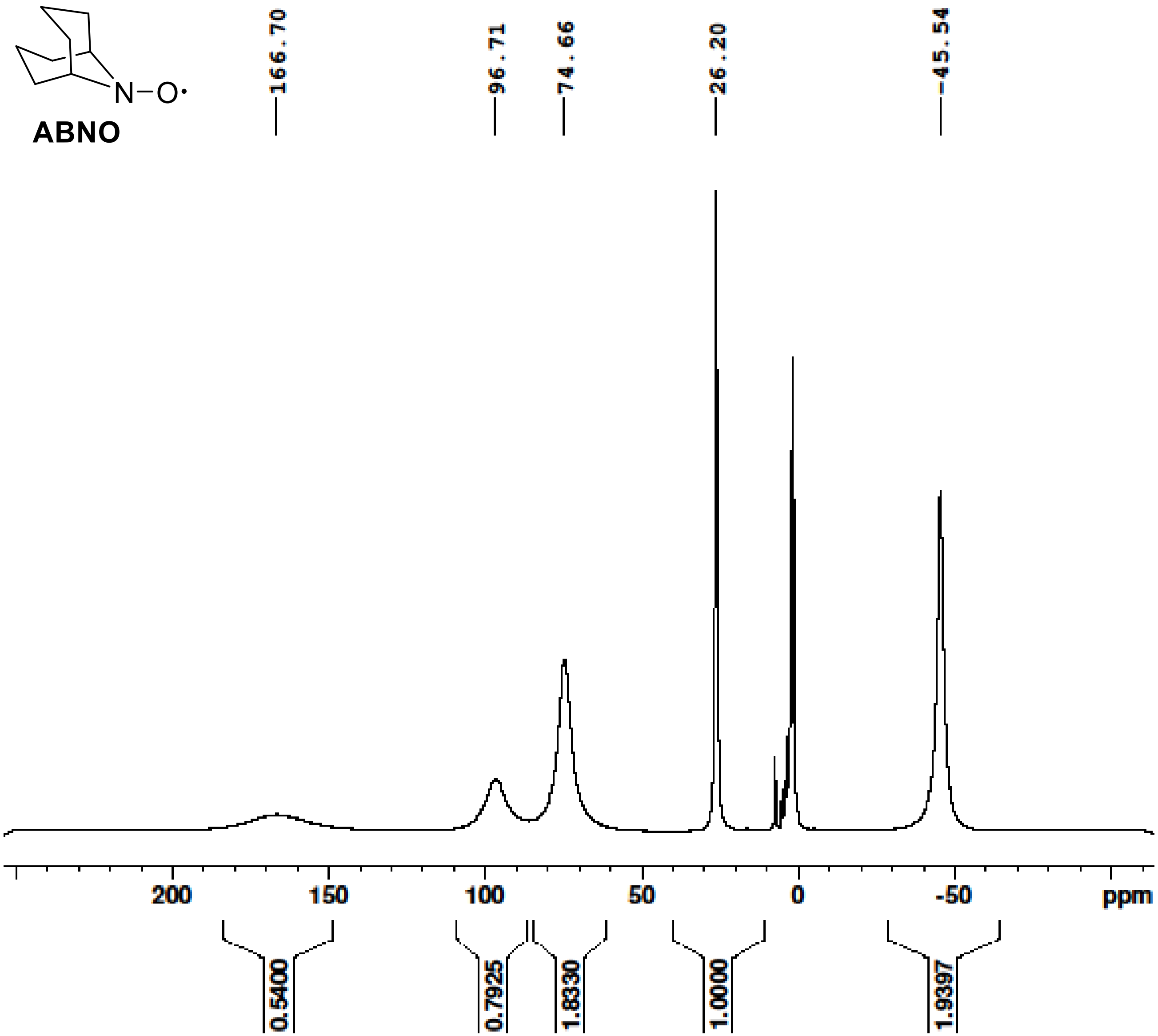
F2 - Acquisition Parameters

Date_	20220729
Time	13.01 h
INSTRUM	Avance
PROBHD	Z163739_0288 (
PULPROG	zg
TD	65536
SOLVENT	CDCl3
NS	10
DS	0
SWH	7812.500 Hz
FIDRES	0.238419 Hz
AQ	4.1943040 sec
RG	13.9716
DW	64.000 usec
DE	11.40 usec
TE	298.0 K
D1	30.00000000 sec
TD0	1
SFO1	400.1318006 MHz
NUC1	1H
P1	7.23 usec
PLW1	23.42000008 W

F2 - Processing parameters

SI	65536
SF	400.1300204 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

9-Azabicyclo[3.3.1]nonane



```
Current Data Parameters
NAME                ABNO
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20220802
Time               16.25 h
INSTRUM           Avance
PROBHD    Z163739_0288 (
PULPROG             zg30
TD                205882
SOLVENT            CD3CN
NS                   256
DS                     2
SWH           147058.828 Hz
FIDRES          1.428574 Hz
AQ             0.6999988 sec
RG                    32
DW                 3.400 usec
DE                  6.78 usec
TE                 298.0 K
D1            0.10000000 sec
TD0                    1
SFO1         400.1580091 MHz
NUC1                  1H
P0                  2.54 usec
P1                  7.61 usec
PLW1         23.42000008 W

F2 - Processing parameters
SI                 65536
SF           400.1299638 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```