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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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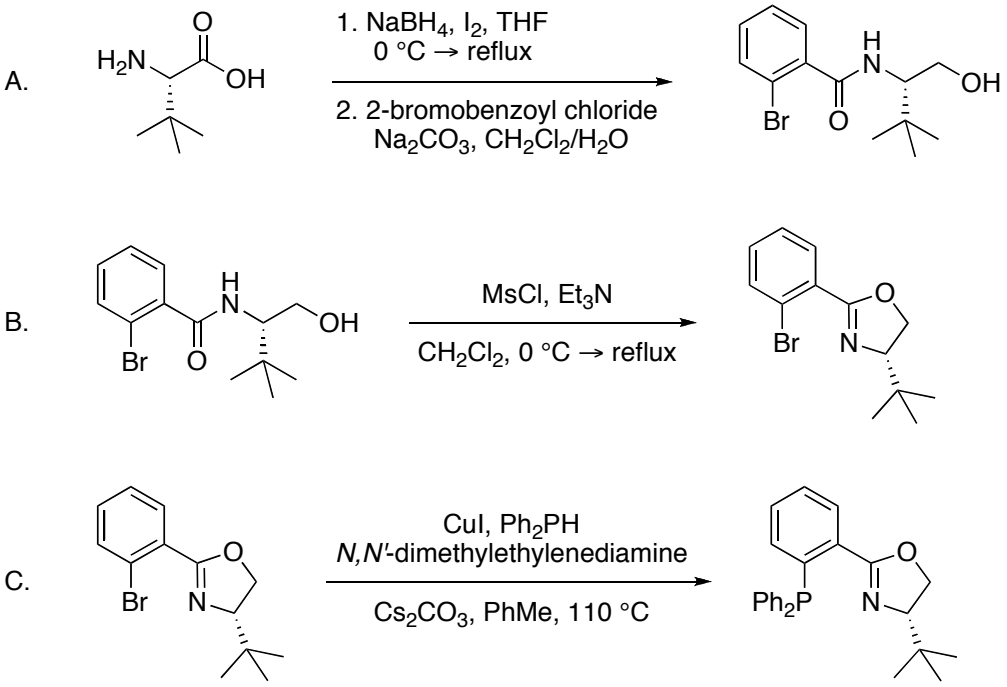
PREPARATION OF (*S*)-*tert*-ButylPHOX (Oxazole, 4-(1,1-dimethylethyl)-2-[2-(diphenylphosphino)phenyl]-4,5-dihydro- (4*S*)-)



Submitted by Michael R. Krout, Justin T. Mohr, and Brian M. Stoltz.*[1]
Checked by Andreas Schumacher and Andreas Pfaltz.
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1. Procedure

Caution! This procedure should be carried out in an efficient fume hood due to the evolution of hydrogen gas during the reaction.

A. 2-Bromo-N-[(1S)-1-(hydroxymethyl)-2,2-dimethylpropyl]-benzamide. An oven-dried, 500-mL, 3-neck flask equipped with a 3.0 cm × 1.4 cm, egg-shaped, teflon-coated magnetic stirring bar, pressure-equalizing addition funnel, an internal thermometer, and a reflux condenser (central neck) equipped with a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 1) is assembled hot and cooled under a stream of argon. The flask is charged with (L)-*tert*-leucine (5.00 g, 38.1 mmol, 1.00 equiv, 99% ee) (Note 2) and tetrahydrofuran (100 mL, 0.38 M) (Note 3) under a positive pressure of argon. The resulting suspension is cooled to approximately 4 °C in an ice-water bath and sodium borohydride

(3.46 g, 91.5 mmol, 2.40 equiv) (Note 2) is added in one portion (Note 4). The addition funnel is charged with a solution of iodine (9.67 g, 38.1 mmol, 1.00 equiv) (Note 2) in tetrahydrofuran (25 mL) (Note 3) via syringe and added dropwise to the suspension over 30 min. After complete addition, the bath is removed, the addition funnel and the thermometer are removed and replaced by glass stoppers and the reaction is warmed to reflux (80 °C oil bath temperature). After 18 h the reaction is allowed to cool to ambient temperature and methanol (50 mL) (Note 3) is added slowly resulting in an almost clear solution (Note 5). After stirring for 30 min the solution is quantitatively transferred to a 500-mL, 1-necked flask with methanol (ca. 50 mL) and concentrated on a rotary evaporator under reduced pressure (40 °C, ca. 53 mmHg) to a white semi-solid. The resulting material is dissolved in 20% aqueous potassium hydroxide (75 mL) and stirred for 5 h at ambient temperature with a 3.0 cm × 1.4 cm, egg shaped, teflon-coated magnetic stirring bar. The aqueous phase is extracted with dichloromethane (6 × 60 mL) and the combined organic extracts are dried over sodium sulfate (ca. 7 g), filtered, and concentrated on a rotary evaporator under reduced pressure (40 °C, 38 mmHg) and dried under vacuum (0.13 mmHg) to yield 4.42–4.45 g (37.7–37.9 mmol, 99% yield) of crude (*S*)-*tert*-leucinol as a colorless oil (Note 6). This material is used in the following step without purification.

A 500-mL flask containing a 3.0 cm × 1.4 cm, egg shaped, teflon-coated magnetic stirring bar is charged with crude (*S*)-*tert*-leucinol (4.42 g, 37.7 mmol, 1.00 equiv), dichloromethane (125 mL, 0.30 M) (Note 3) and then a solution of sodium carbonate (11.98 g, 113.1 mmol, 3.00 equiv) (Note 2) in distilled water (95 mL) (Note 3) is added at ambient temperature. The biphasic mixture is stirred vigorously to emulsify and neat 2-bromobenzoyl chloride (5.67 mL, 43.3 mmol, 1.15 equiv) (Note 2) is added dropwise via syringe over approximately 15 min. The reaction flask is capped with a two-tap Schlenk adapter connected to a bubbler (Note 1) and stirred for 10 h, after which time the layers are partitioned in a 500 mL separatory funnel and the aqueous phase is extracted with dichloromethane (4 × 50 mL). The combined organic extracts are stirred with 1 N potassium hydroxide solution in methanol (19 mL) in a 500 mL Erlenmeyer flask with a 3.0 cm × 1.4 cm, egg-shaped, teflon-coated magnetic stirring bar for 30 min at ambient temperature and then acidified to neutral pH with 1 N hydrochloric acid (ca. 16 mL). Water (25 mL) is added, the phases are partitioned in a 1-L separatory funnel, and the aqueous phase is extracted with dichloromethane (4 × 35 mL). The combined organic extracts are washed with saturated brine

(75 mL), dried over sodium sulfate (3.00 g), filtered, and concentrated on a rotary evaporator under reduced pressure (40 °C, ca. 11 mmHg) to an off-white solid. The crude white solid is dissolved in a minimal amount of hot acetone (ca. 10 mL) (Note 3) and hexanes (Note 3) are added until a cloudy solution is obtained (ca. 45 mL). The crystals formed upon cooling and aging for 3 hours at 0 °C are collected, washed with hexanes, and dried under vacuum to afford 2-bromo-*N*-[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]-benzamide (9.23–9.61 g, 30.8–32.0 mmol) as white blocks (Note 7). The filtrate is concentrated and recrystallized in a similar manner (with acetone (ca. 2 mL) and hexanes (10 mL)) to provide additional product (0.62–1.13 g, 2.1–3.76 mmol) as white blocks (Note 8), for a combined yield of 9.85–10.74 g (32.8–35.77 mmol, 86–94 % yield over two steps).

B. 2-(2-Bromophenyl)-4-(1,1-dimethylethyl)-4,5-dihydro-(4S)-oxazole. An oven-dried, 500-mL, 3-necked flask equipped with a 3.0 cm × 1.4 cm, egg-shaped, teflon-coated magnetic stirring bar, an internal thermometer, a glass stopper and a reflux condenser (central neck) equipped with a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 1) is assembled hot and cooled under a stream of argon. The flask is charged with 2-bromo-*N*-[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]-benzamide (9.85 g, 32.8 mmol, 1.00 equiv), dichloromethane (170 mL, 0.19 M) (Note 3), and triethylamine (11.0 mL, 78.6 mmol, 2.40 equiv) (Note 2) under a positive pressure of argon. The resulting colorless solution is cooled to approximately 4 °C in an ice-water bath and neat methanesulfonyl chloride (2.92 mL, 37.7 mmol, 1.15 equiv) (Note 2) is added dropwise via syringe over 3 min, at which point the solution turns slightly yellow. The reaction is warmed to reflux (50 °C oil bath temperature) while monitoring conversion by TLC (Note 9). Upon completed cyclization, the reaction is allowed to cool to ambient temperature and 60 mL of saturated aqueous sodium bicarbonate is added with vigorous stirring for 5 min. The layers are partitioned in a 1-L separatory funnel, the aqueous phase is extracted with dichloromethane (2 × 35 mL), the combined organic phases are washed with saturated brine (75 mL), dried over anhydrous magnesium sulfate (1.50 g), filtered, and concentrated on a rotary evaporator under reduced pressure (40 °C, 23 mmHg) to afford a red-brown semi-solid. The residue is dissolved in a minimal amount of dichloromethane (ca. 35 mL), dry-loaded onto silica gel (8 g), and purified by silica gel chromatography (Note 10) to afford 8.85–8.86 g (31.4 mmol, 96% yield) of 2-(2-bromophenyl)-4-(1,1-dimethyl-ethyl)-4,5-dihydro-(4*S*)-

oxazole as a pale yellow oil. This material solidifies when placed in a –20 °C freezer and is preferred in this state for the subsequent reaction (Note 11).

C. 4-(1,1-dimethylethyl)-2-[2-(diphenylphosphino)phenyl]-4,5-dihydro-(4S)-oxazole ((S)-tert-ButylPHOX). A 150-mL Schlenk flask equipped with a glass valve, a glass stopper, and a 1.7 cm × 0.7 cm, egg-shaped, teflon-coated magnetic stirring bar is dried with a heat gun under vacuum and cooled under argon atmosphere. The glass stopper is removed under a positive pressure of argon and the flask is charged with copper(I) iodide (19.0 mg, 0.10 mmol, 0.005 equiv) (Note 2), diphenylphosphine (4.35 mL, 25.0 mmol, 1.25 equiv) (Note 2), *N*,*N'*-dimethylethylenediamine (53 μL, 0.50 mmol, 0.025 equiv) (Note 2) and toluene (20 mL) (Note 3). The flask is sealed with the glass stopper and the colorless contents are stirred at ambient temperature for 20 min. The glass stopper is then removed under a positive pressure of argon and the flask is charged with 2-(2-bromophenyl)-4-(1,1-dimethylethyl)-4,5-dihydro-(4*S*)-oxazole (5.64 g, 20.0 mmol, 1.00 equiv), cesium carbonate (9.78 g, 30.0 mmol, 1.50 equiv) (Note 2), and toluene (20 mL, 0.50 M total) to wash the neck and walls of the flask. The flask is equipped with a reflux condenser with a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 1). The now yellow heterogeneous reaction is placed in a 110 °C oil bath and vigorously stirred under argon atmosphere (Note 12). Following consumption of starting material (Note 13), the reaction is allowed to cool to ambient temperature, filtered through a pad of celite, and the filter cake is washed with dichloromethane (2 × 40 mL) (Note 14). The filtrate is concentrated on a rotary evaporator under reduced pressure (40 °C, 15 mmHg) to a pale yellow semi-solid. The residue is dissolved in a minimal amount of dichloromethane (ca. 40 mL) (Note 15), dry-loaded onto silica gel (10 g), and purified by silica gel chromatography eluting with 24:1 hexanes/diethyl ether until excess Ph_2PH elutes, then with a 9:1 dichloromethane/diethyl ether mixture until the desired product elutes (Note 16). The combined fractions are concentrated on a rotary evaporator under reduced pressure (40 °C, 14 mmHg) to a viscous, pale yellow oil and layered with acetonitrile (ca. 5 mL) to facilitate crystallization (Notes 3 and 17). The flask is swirled while crystals form within seconds (Note 18). After approximately 15 minutes, the flask is placed under high vacuum to remove volatiles to afford 6.81 g (17.6 mmol, 88% yield) of (*S*)-*tert*-ButylPHOX as white blocks (Note 19).

2. Notes

1. A two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold is illustrated in Yu, J.; Truc, V.; Riebel, P.; Hierl, E. and Mudryk, B. *Org. Synth.* **2008**, *85*, 64–71.

2. Submitters and checkers purchased (L)-*tert*-leucine (99%, 99% ee), sodium borohydride (98%), cesium carbonate (99%), and *N*,*N*'-dimethylethylenediamine (99%) from Aldrich and used as received. (2)-Bromobenzoyl chloride (98%) and methanesulfonyl chloride (99.5%) were purchased from Acros and used as received. Copper iodide (98%) was purchased from Strem and used as received. Submitters and checkers purchased triethylamine (99.5%) from Aldrich and distilled it from calcium hydride prior to use. Submitters and checkers purchased diphenylphosphine (99%) from Strem and transferred it through a cannula to a dry Schlenk tube under nitrogen to prolong reagent life. The submitters purchased iodine (≥99%) and sodium carbonate (99%) from Aldrich and used as received. The checkers purchased iodine (puriss. p. a.) and potassium hydroxide (puriss. p. a.) from Riedel-de-Haën (puriss. p. a.) and sodium carbonate (99.5%) from Merck and used as received.

3. Submitters distilled tetrahydrofuran from sodium 9-fluorenone ketyl[2] prior to use. Submitters and checkers used methylene chloride, toluene, and acetonitrile purified by passage through an activated alumina column under argon.[3] The submitters purchased reagent grade acetone from EMD, and hexanes and methanol (both ACS grade) were purchased from Fisher and used as received. The submitters used distilled water purified with a Barnstead NANOpure Infinity UV/UF system. The checkers used tetrahydrofuran (VWR, HPLC-grade) dried using a Pure-Solve™ system. Reagent grade acetone was purchased from VWR, methanol (Baker analyzed) was purchased from J.T. Baker and hexanes were distilled.

4. The evolution of hydrogen gas during the addition of sodium borohydride is minor due to the adequate size of the reaction flask and the surface area of cooling. This is readily vented through the oil bubbler.

5. The initial reaction quench with methanol proceeds with vigorous gas evolution. Methanol should be added dropwise until the intensity of gas evolution abates.

6. The reduction product, (*S*)-*tert*-leucinol, can be purified by distillation,[4] but this was not necessary for this application. The material showed the following characterization data: ^{1}H NMR (400 MHz, $CDCl_3$) δ:

0.89 (s, 9 H), 2.49 (dd, *J* = 10.2, 3.9 Hz, 1 H), 3.19 (t, *J* = 10.2 Hz, 1 H), 3.70 (dd, *J* = 10.2, 3.9 Hz, 1 H). This material may also be purchased from commercial sources, but is less expensive in the amino acid form. Similar amino acid reductions have appeared in *Organic Syntheses*.[5]

7. 2-Bromo-*N*-[(1*S*)-1-(hydroxymethyl)-2,2-dimethylpropyl]-benzamide showed the following characterization data: mp 117–118 °C from acetone/hexanes; R_f = 0.14 (2:1 hexanes/acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.03 (s, 9 H), 2.40 (br dd, *J* = 5.0 Hz, 1 H), 3.64–3.70 (m, 1 H), 3.91-3.97 (m, 1 H), 4.04–4.08 (m, 1 H), 6.20 (br d, *J* = 8.4 Hz, 1 H), 7.27 (ddd, *J* = 7.9, 7.9, 1.6 Hz, 1 H), 7.35 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.55 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 27.1, 33.8, 60.3, 63.0, 119.0, 127.6, 129.7, 131.3, 133.3, 137.9, 168.6; IR (ATR) 3223, 3065, 2961, 1627, 1544 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{19}NO_2Br$ $[M+H]^+$: 300.0599, found 300.0590; MS (FAB) *m/z* (relative intensity): 300 (100%), 185 (49%), 77 (21%); $[\alpha]_D^{20}$ +17.3 (*c* 2.38, methanol); Anal. calc'd. for $C_{13}H_{18}NO_2Br$: C, 52.01; H, 6.04; N, 4.67. Found: C, 52.01; H, 5.95; N, 4.51.

8. In some cases the resulting filtrate was purified by silica gel flash chromatography, eluting with a 3:1 → 2:1 hexanes/acetone gradient to afford an additional 2–6% of an off-white amorphous solid that is spectroscopically identical to the crystalline material.

9. Reaction progress can be monitored by TLC analysis (the checkers used Polygram®SIL/UV_{254}-TLC-plates from Macherey-Nagel) using 2:1 ethyl acetate/hexanes as the eluent with UV visualization (R_f amide = 0.28, R_f mesylate = 0.43, R_f bromooxazoline = 0.64). Mesylate formation is typically complete upon final addition of methanesulfonyl chloride, whereas cyclization to the bromooxazoline typically requires ca. 5 h at 50 °C to complete.

10. Flash chromatography column dimensions: 3 cm diameter × 20 cm height of silica gel (checkers used "Silica Gel 60" (0.040-0.063 mm) from Merck), eluting with 200 mL of 9:1 hexanes/ethyl acetate, then 450 mL of 6:1 hexanes/ethyl acetate, collecting ca. 20–25 mL fractions. Fraction purity can be assayed by TLC (the checkers used Polygram®SIL/UV_{254}-TLC-plates from Macherey-Nagel) analysis using 4:1 hexanes/ethyl acetate with UV visualization. This method of purification removes color from the crude material and a minor impurity at R_f = 0.33.

11. 2-(2-Bromophenyl)-4-(1,1-dimethylethyl)-4,5-dihydro-(4*S*)-oxazole showed the following characterization data: mp 47–48 °C; R_f = 0.27

(4:1 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.00 (s, 9 H), 4.11 (dd, *J* = 10.2, 8.0 Hz, 1 H), 4.26 (dd, *J* = 8.3, 8.3 Hz, 1 H), 4.38 (dd, *J* = 10.2, 8.7 Hz, 1 H), 7.27 (ddd, *J* = 7.7, 7.6, 1.9 Hz, 1 H), 7.33 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1 H), 7.63 (dd, *J* = 8.0, 0.9 Hz, 1 H), 7.66 (dd, *J* = 7.6, 1.3 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 26.0, 34.1, 69.0, 76.8, 121.9, 127.1, 130.3, 131.3, 131.5, 133.7, 162.8; IR (ATR) 2958, 1660, 1476, 1358, 1095, 1022, 959 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{17}NOBr$ $[M+H]^+$: 282.0493, found 282.0488; MS (FAB) *m*/*z* (relative intensity): 282 (100%), 224 (10%), 183 (17%), 77 (12%); $[\alpha]_D^{20}$ –48.9 (c 3.77, hexane); Anal. calc'd. for $C_{13}H_{16}NOBr$: C, 55.33; H, 5.72; N, 4.96. Found: C, 55.37; H, 5.70; N, 4.84.

12. Submitters sealed the teflon valve and placed the sealed flask in a 110 °C oil bath protected with a blast shield. Reactions performed with minimal stirring or that cease to stir result in incomplete conversion. The preferred stirring rate of the coupling reaction is ca. 700 setting (ca. 700 rpm) on an IKAmag RET basic stir/hot plate (a range between 500–800 rpm is sufficient). Additionally, the color of the reaction becomes an intense yellow within 5–10 minutes of heating. The color of the inorganic base then dominates as it turns to light gray, and finally to a dark maroon/purple color after several hours.

13. The reaction typically requires 21 h to reach complete conversion. Reaction progress can be monitored by TLC analysis (the checkers used Polygram®SIL/UV_{254}-TLC-plates from Macherey-Nagel) using 4:1 hexanes/diethyl ether as the eluent (developed twice) with UV visualization (R_f bromooxazoline = 0.17, R_f reduced oxazoline = 0.27, R_f *tert*-ButylPHOX = 0.33, R_f Ph_2PH = 0.51).

14. Fritted glass funnel (Por. 3, pore size 15–40 μm), 4 cm diameter × 5 cm height) filled with 16 g of celite.

15. Submitters dissolved the pale yellow semi-solid in a minimal amount of dichloromethane (ca. 40 mL) and diethyl ether (ca. 50 mL).

16. Flash chromatography column dimensions: 5 cm diameter × 16 cm height of silica gel, (checkers used "Silica Gel 60" (0.040-0.063 mm) from Merck). Checkers eluted with 500 mL of 24:1 hexanes/diethyl ether, then 400 mL of 9:1 dichloromethane/diethyl ether, collecting ca. 50 mL fractions. Fraction purity can be assayed by TLC (the checkers used Polygram®SIL/UV_{254}-TLC-plates from Macherey-Nagel) analysis using 4:1 hexanes/diethyl ether with UV visualization. The mixture of products may

contain reduced arene, starting bromooxazoline, and desired (*S*)-*tert*-ButylPHOX, depending on the extent of reaction (Note 12).

17. As the percentage of desired (*S*)-*tert*-ButylPHOX in the crude mixture increases, the oil readily solidifies upon concentration under reduced pressure. To decrease the time required to induce crystallization, this oil can then be dissolved in diethyl ether and further concentrated. Additionally, acetonitrile efficiently promotes crystallization of (*S*)-*tert*-ButylPHOX in concentrated solutions.

18. If the reaction is pushed to completion, the material obtained from this simple purification is typically quite pure (no impurities were detected by ^{1}H NMR analysis of the crude oil). If the purity is unsatisfactory, this crystalline material can be recrystallized with hot acetonitrile. A typical recrystallization is performed as follows: in an experiment run on 20.0 mmol scale, 7.033 g (18.15 mmol) of crude product was dissolved in a minimal amount (ca. 8–10 mL) of boiling acetonitrile and allowed to cool slowly to ambient temperature. The crystals are then filtered and washed with ca. 15–25 mL of hexanes, then dried under high vacuum to yield 6.613 g (17.07 mmol, 85.3% yield) of white blocks. This material is analytically pure by ^{1}H NMR and all other spectroscopic data (see Note 19).

19. In a run carried out on half-scale, 3.49 g of (*S*)-*tert*-ButylPHOX was obtained (90% yield). (*S*)-*tert*-ButylPHOX showed the following characterization data; mp 113–114 °C from acetonitrile; R_f = 0.33 (4:1 hexanes/diethyl ether); ^{31}P NMR (162 MHz, $CDCl_3$) δ: –5.49 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.73 (s, 9 H), 3.88 (dd, *J* = 10.2, 8.2 Hz, 1 H), 4.01 (dd, *J* = 8.3 Hz, 8.3 Hz, 1 H), 4.08 (dd, *J* = 10.2, 8.5 Hz, 1 H), 6.87 (ddd, *J* = 7.7, 4.0, 0.8 Hz, 1 H), 7.33–7.21 (m, 11 H), 7.36 (apparent dt, *J* = 7.6, 1.3 Hz, 1 H), 7.94 (ddd, *J* = 7.7, 3.7, 0.9 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 25.8, 33.6, 68.3, 76.7 (overlaps with $CHCl_3$-rest-signal, detected in DEPT135-experiment), 128.0, 128.3 (d, J_{CP} = 5.9 Hz), 128.2 (2 lines), 128.5 (d, J_{CP} = 9.7 Hz), 129.8 (d, J_{CP} = 3.1 Hz), 130.3, 132.0 (d, J_{CP} = 19.7 Hz), 133.6 (d, J_{CP} = 20.2 Hz), 134.1, 134.3 (d, J_{CP} = 21.0 Hz), 138.3 (d, J_{CP} = 9.7 Hz), 138.5 (d, J_{CP} = 12.6 Hz), 138.8 (d, J_{CP} = 25.5 Hz), 162.7 (d, J_{CP} = 2.7 Hz); IR (ATR) 3069, 2955, 2897, 2866, 1653, 1583, 1475, 1433, 1354, 1090, 1024, 955, 742, 669, 580, 511 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{27}NOP$ $[M+H]^+$: 388.1830, found 388.1831; MS (EI) *m*/*z* (relative intensity): 388 (1%), 372 (9%), 330 (55%), 302 (100), 228 (6), 183 (12); $[\alpha]_D^{20}$ –75.2 (c 0.925, $CHCl_3$); Anal. calc'd. for $C_{25}H_{26}NOP$: C, 77.50; H, 6.76; N, 3.62. Found: C, 77.22; H, 6.82; N, 3.57. The enantiomeric excess of

(*S*)-*tert*-ButylPHOX can be determined by analytical supercritical fluid chromatography; this was performed using a Berger Analytix SFC (Thar Technologies) equipped with a Chiralcel® OJ-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. and a diode array detector. The assay conditions are 10% ethanol, 35 °C, 2 mL/min flow rate, with visualization at 210 nm (optimal), retention times: (*R*) enantiomer = 4.67 min, (*S*) enantiomer = 5.17 min. The minor (*R*) enantiomer can not be detected from SFC analyses of ligand prepared from the reported procedure, and is therefore >99% ee. This crystalline material is stable indefinitely at ambient temperatures in a closed container under an atmosphere of nitrogen or argon.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

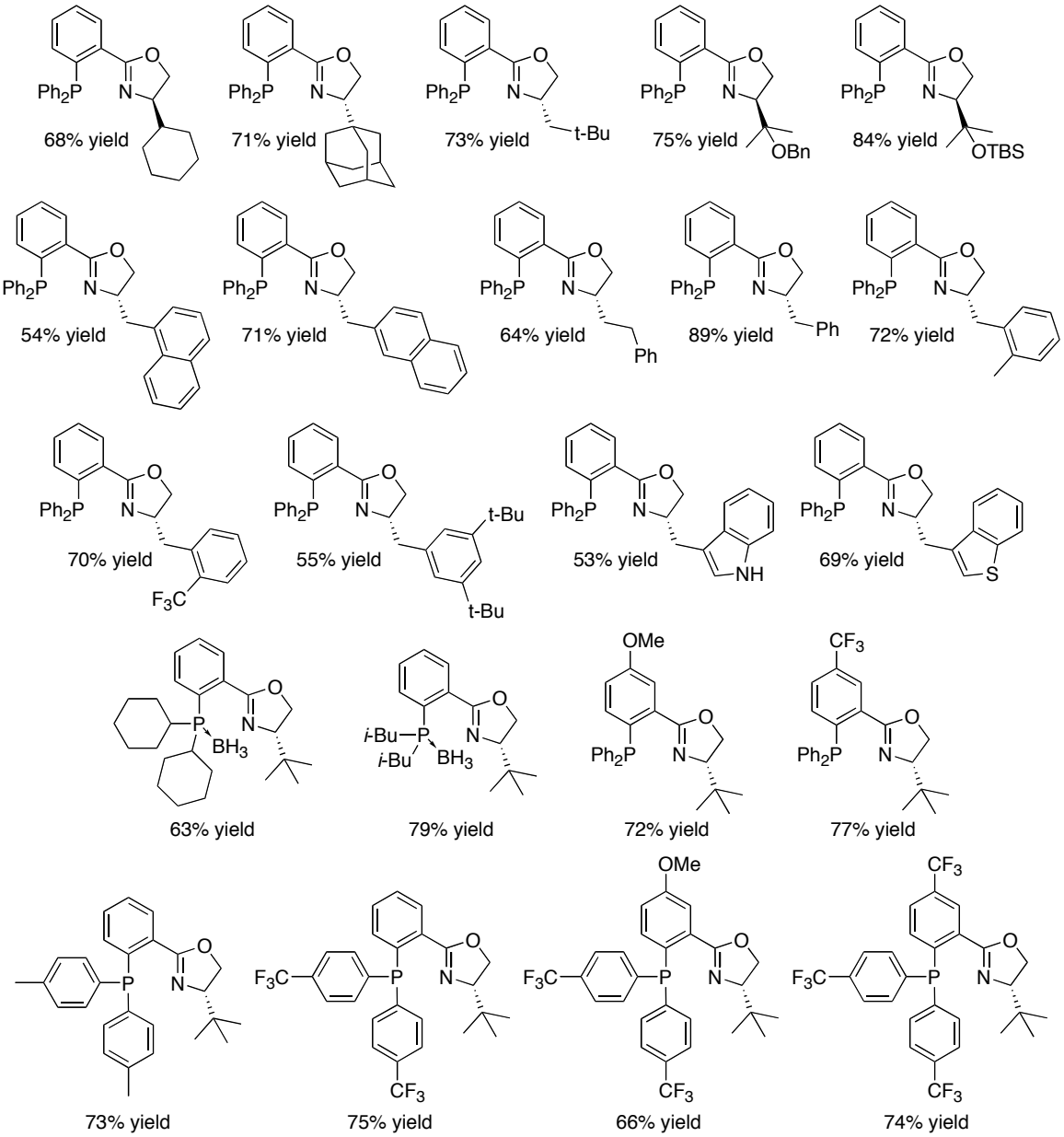
3. Discussion

This synthesis of (*S*)-*tert*-ButylPHOX (4-(1,1-dimethylethyl)-2-[2-(diphenylphosphino)phenyl]-4,5-dihydro-(4*S*)-oxazole) is a modification of our previously reported procedure.[6] Several improvements have been implemented that facilitate large-scale preparation of this ligand. Recrystallization of 2-bromo-*N*-[(1*S*)-1-(hydroxymethyl)-2,2-dimethyl-propyl]-benzamide obviates the previous need for flash column chromatography. Subsequent oxazoline formation is now accomplished via mesylate displacement with improved efficiency and yield. The use of methanesulfonyl chloride enables rapid mesylate formation at milder temperatures, and aqueous reaction workup is favored over the previous method, where incomplete hydrolysis of *p*-toluenesulfonyl chloride complicated purification. The copper(I) iodide-catalyzed phosphine coupling[7] has been optimized to maximize the efficiency of the reaction by minimizing the use of catalyst and diamine ligand, as well as reducing the quantities of phosphine, cesium carbonate, and solvent. Finally, a procedure to purify (*S*)-*tert*-ButylPHOX is described, using a simple silica gel plug, followed by crystallization with acetonitrile (or recrystallization when

necessary), to afford the ligand as a white crystalline solid in four steps from (L)-*tert*-leucine in excellent overall yield (71.9–80.4% over four steps).

The phosphinooxazoline[8] (*S*)-*tert*-ButylPHOX is a chiral P/N-ligand useful for an array of organometallic transformations, including alkylations,[8,9] desymmetrizations of *meso*-anhydrides,[10] Heck reactions,[11] hetero-Diels–Alder cycloadditions,[12] Meerwein–Eschenmoser Claisen rearrangements,[13] and hydrogenations.[14] Our laboratory has recently described its use as a uniquely effective ligand for the palladium-catalyzed

Table 1. PHOX derivatives prepared via this protocol.[6b]



asymmetric decarboxylative allylation[6,15] and protonation[16] of prochiral ketone enolates. This synthesis of (*S*)-*tert*-ButylPHOX highlights improvements of a general and efficient strategy to access PHOX ligands of varied structure and electronics in substantial quantities (Table 1).[6b]

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

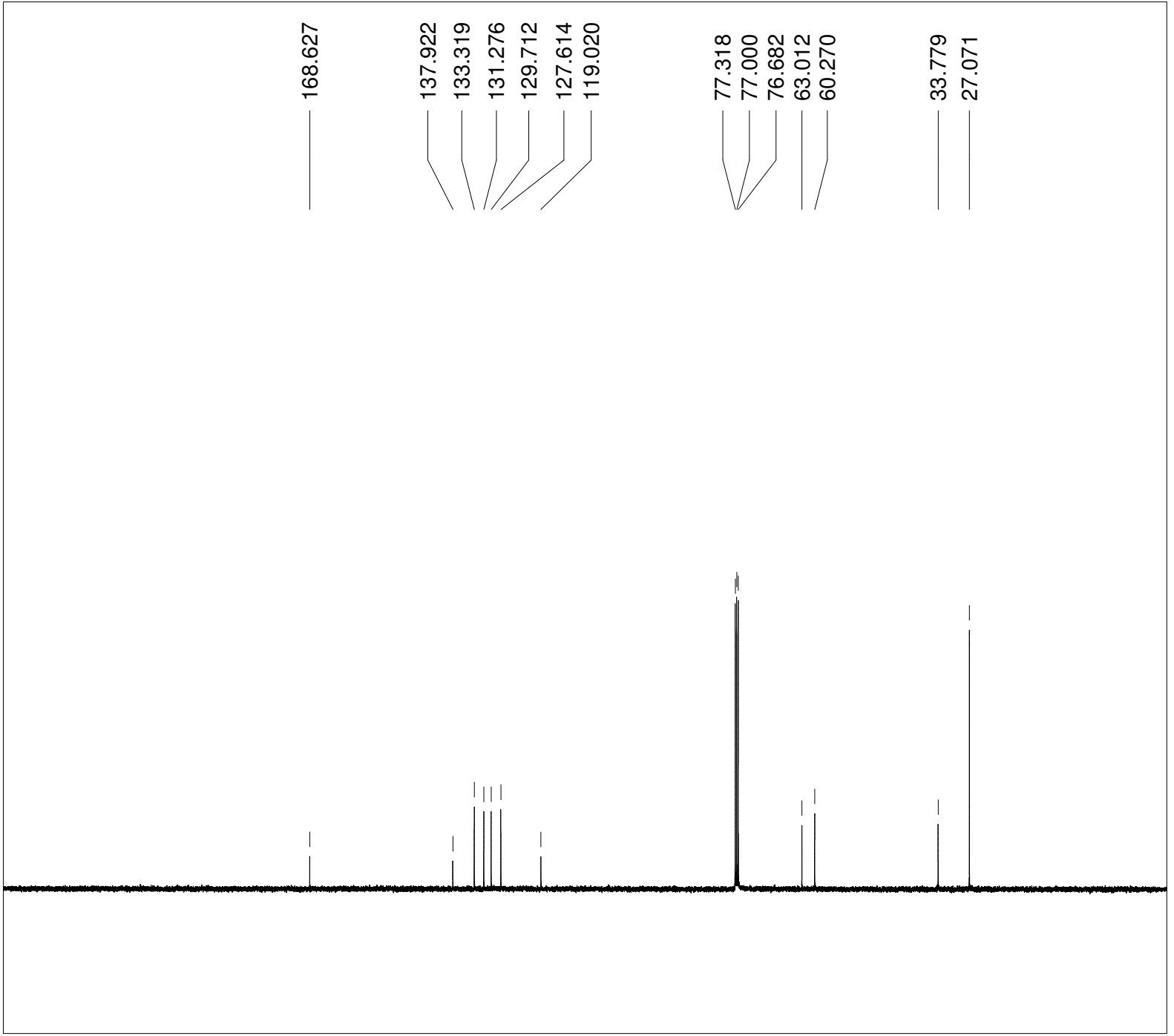
(L)-*tert*-Leucine: L-Valine, 3-methyl-; (20859-02-3)
(*S*)-*tert*-Leucinol: 1-Butanol, 2-amino-3,3-dimethyl-, (2*S*)-; (112245-13-3)
Sodium borohydride: Borate(1-), tetrahydro-, sodium (1:1); (16940-66-2)
2-Bromobenzoyl chloride: Benzoyl chloride, 2-bromo-; (7154-66-7)
Methansulfonyl chloride; (124-63-0)
Copper iodide; (1335-23-5)
Diphenylphosphine: Phosphine, diphenyl-; (829-85-6)
N,N'-dimethylethylenediamine: 1,2-Ethanediamine, N1,N2-dimethyl-; (110-70-3)
Cesium carbonate: Carbonic acid, cesium salt (1:2); (534-17-8)
(*S*)-*tert*-ButylPHOX: Oxazole, 4-(1,1-dimethylethyl)-2-[2-(diphenylphosphino)phenyl]-4,5-dihydro-, (4S)-; (148461-16-9)

Brian M. Stoltz was born in Philadelphia, PA in 1970 and obtained his B.S. degree from the Indiana University of Pennsylvania in Indiana, PA. After graduate work at Yale University in the labs of John L. Wood and an NIH postdoctoral fellowship at Harvard in the Corey labs he took a position at the California Institute of Technology. A member of the Caltech faculty since 2000, he currently is the Ethel Wilson Bowles and Robert Bowles Professor of Chemistry and a KAUST GRP Investigator. His research interests lie in the development of new methodology for general applications in synthetic chemistry.

Michael R. Krout received his B.S. degree in biochemistry from the Indiana University of Pennsylvania in 2002. He then worked in the medicinal chemistry department at Merck Research Laboratories in West Point, PA, where he was involved in the development of non-steroidal selective androgen receptor modulators aimed toward the treatment of osteoporosis. In the fall of 2003, he joined the lab of Professor Brian Stoltz at Caltech where he has worked toward his Ph.D. as a Lilly fellow. His research interests include the development of catalytic, asymmetric methods and their utility in natural product total synthesis.

Justin T. Mohr received his A.B. degree in chemistry in 2003 from Dartmouth College where he conducted research with Professor Gordon W. Gribble. He joined the laboratories of Professor Brian M. Stoltz at Caltech in 2003 where he has pursued Ph.D. studies as a Lilly fellow. His research interests include the development of enantioselective reactions and applications in natural product total synthesis.

Andreas Schumacher was born in Binningen (Switzerland) in 1983. He studied chemistry at the University of Basel (Switzerland) where he obtained his B.Sc. in Chemistry in 2006 and his M.Sc. in Chemistry in 2008. He started his Ph.D, studies in 2008 under the supervision of Prof. Andreas Pfaltz at the University of Basel and is currently working in the field of Ir-catalyzed enantioselective hydrogenation.



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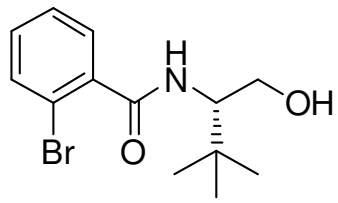

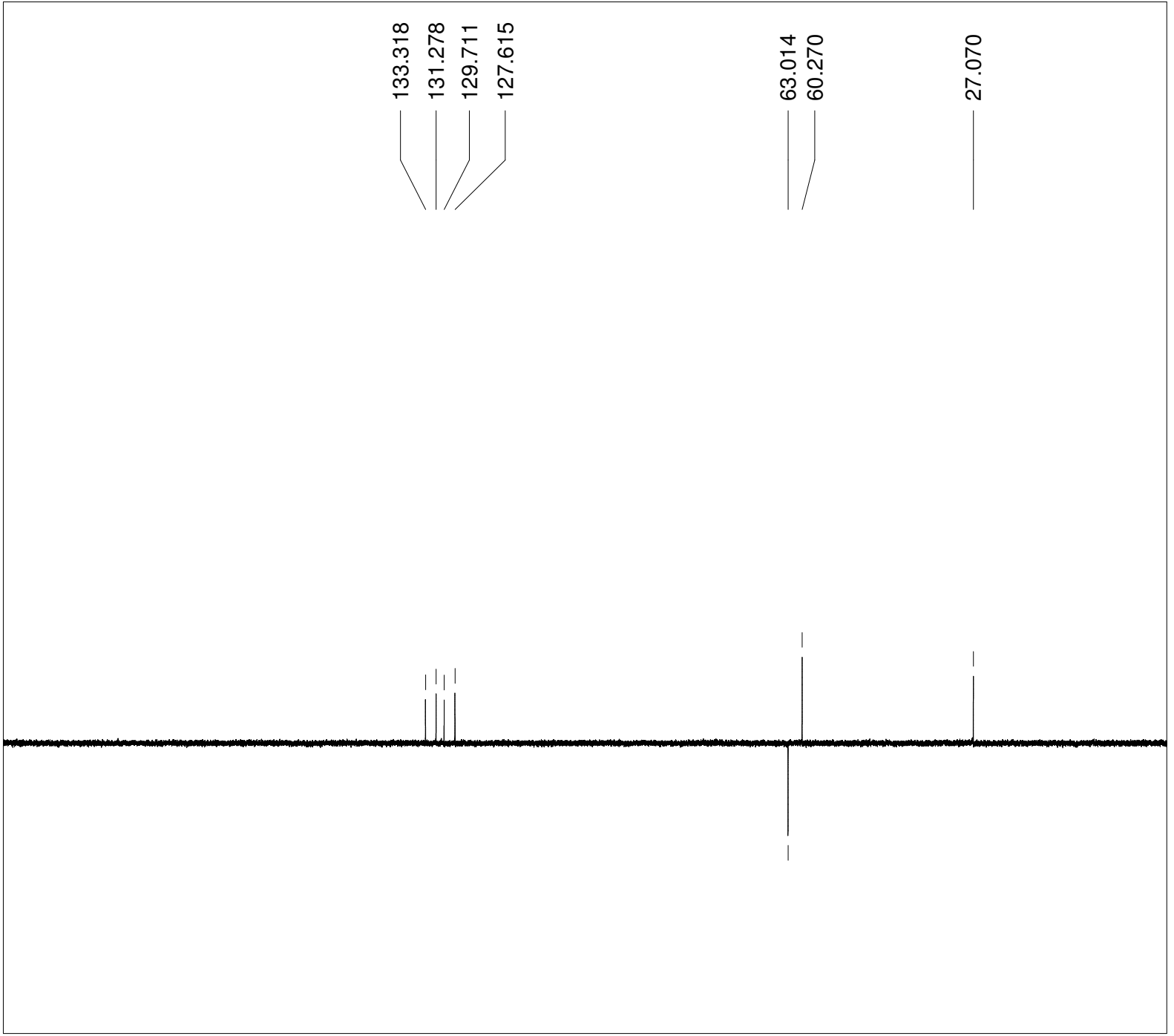

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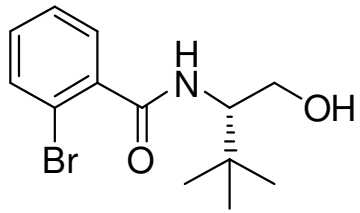

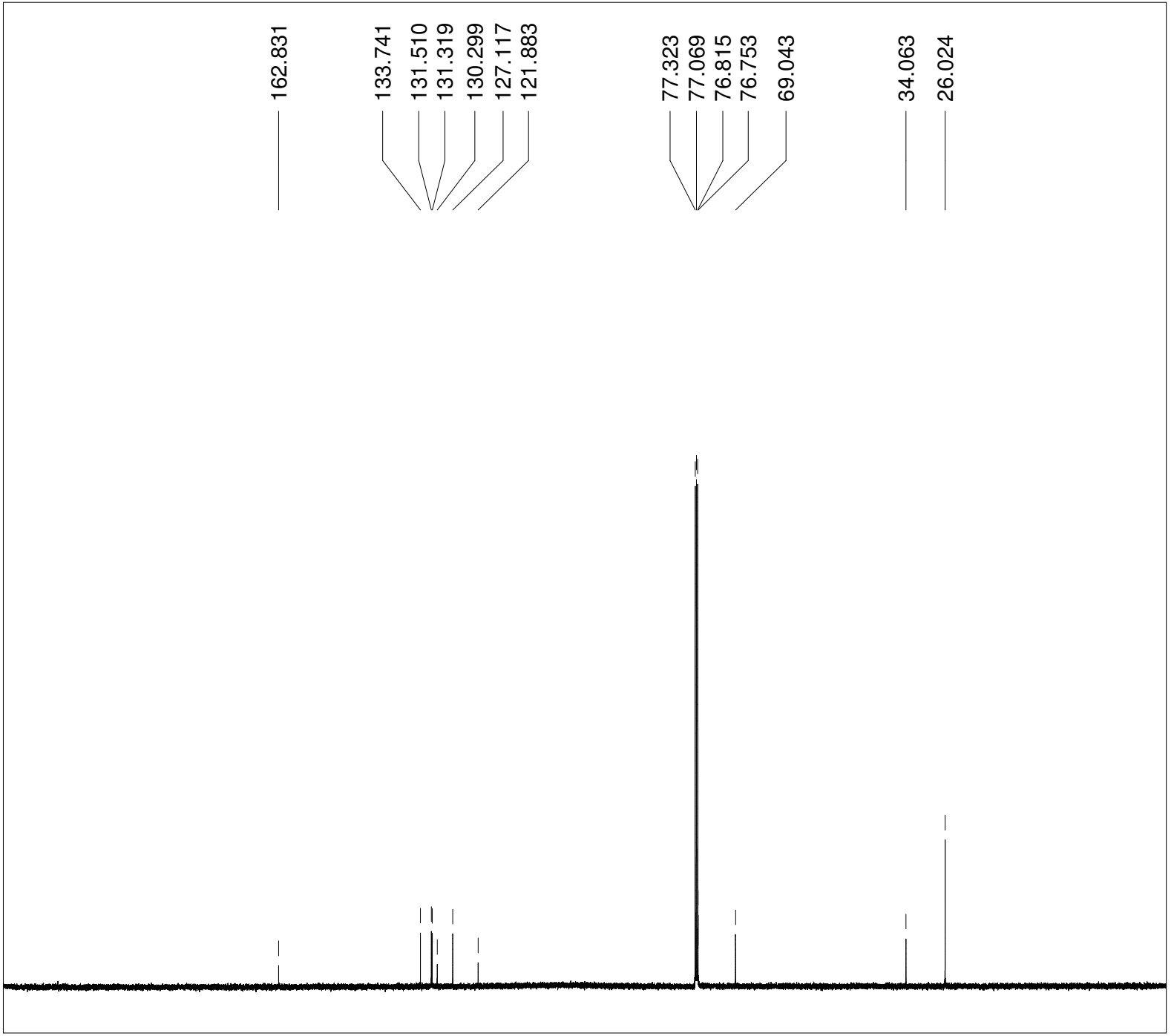

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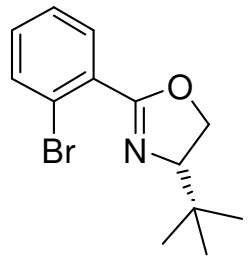

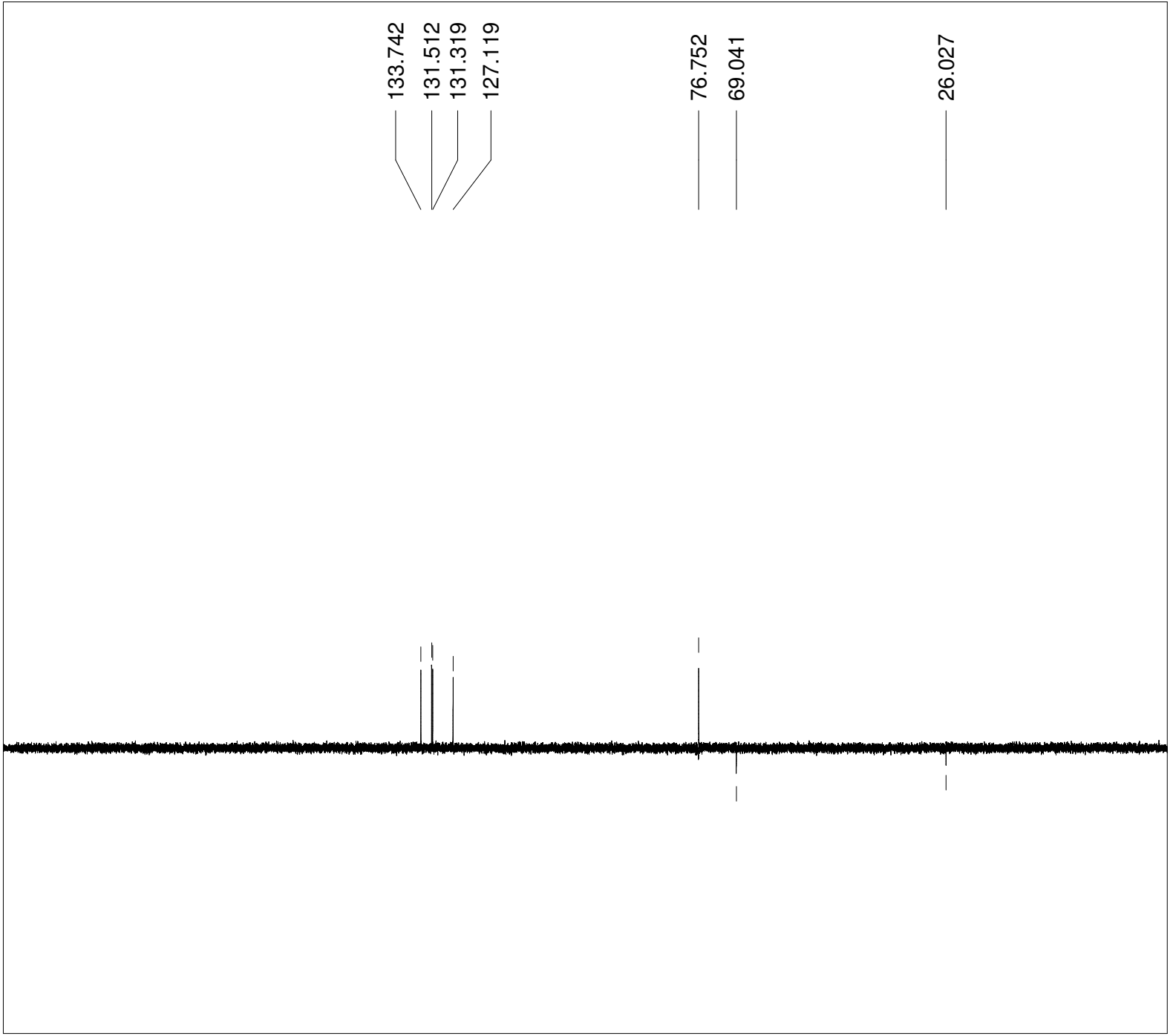

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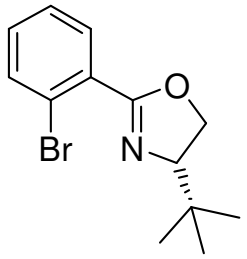

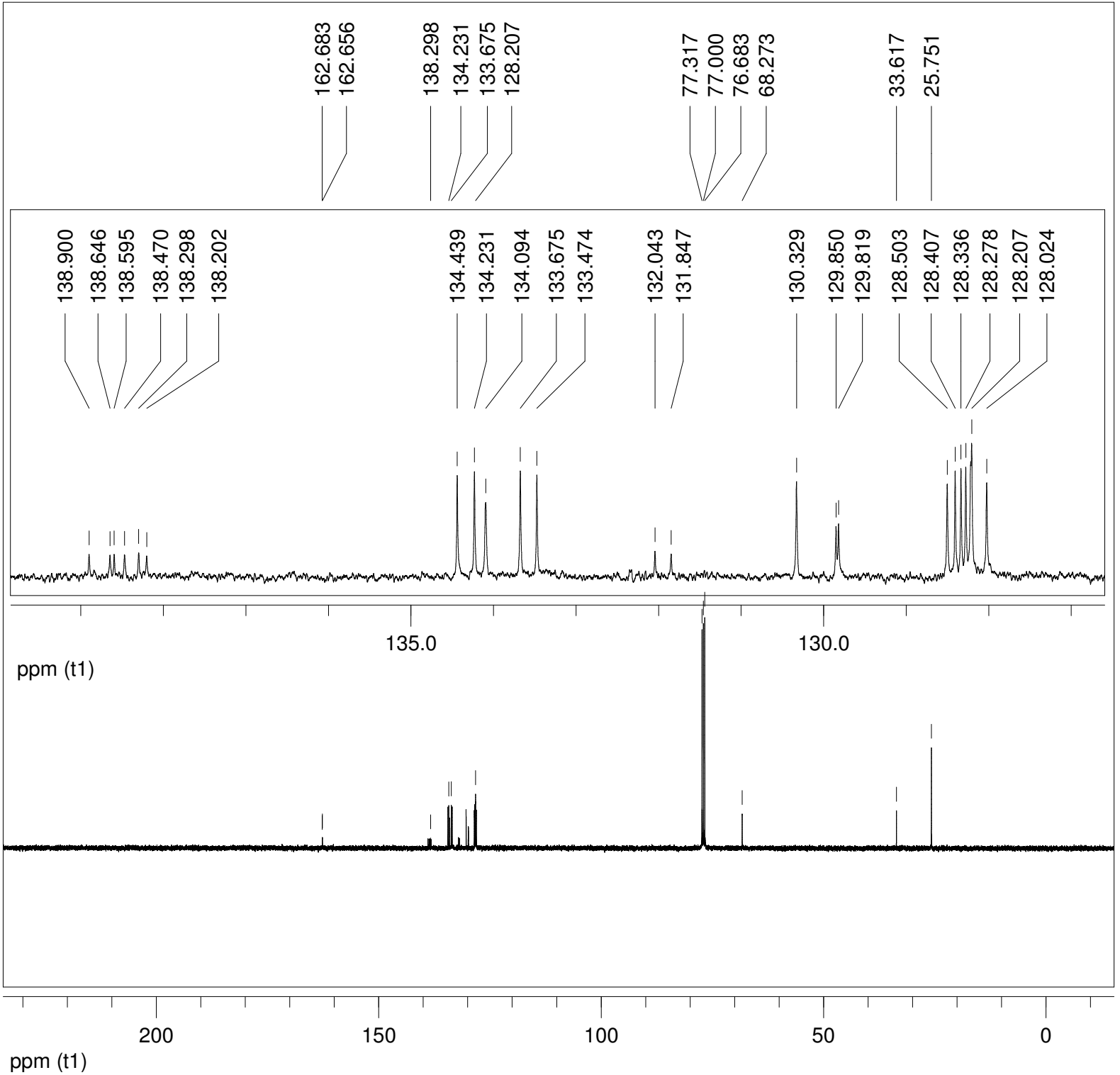

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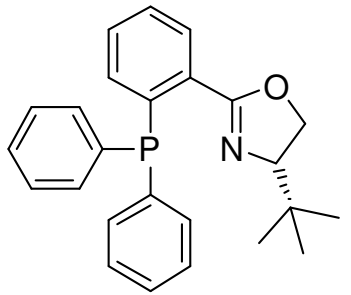

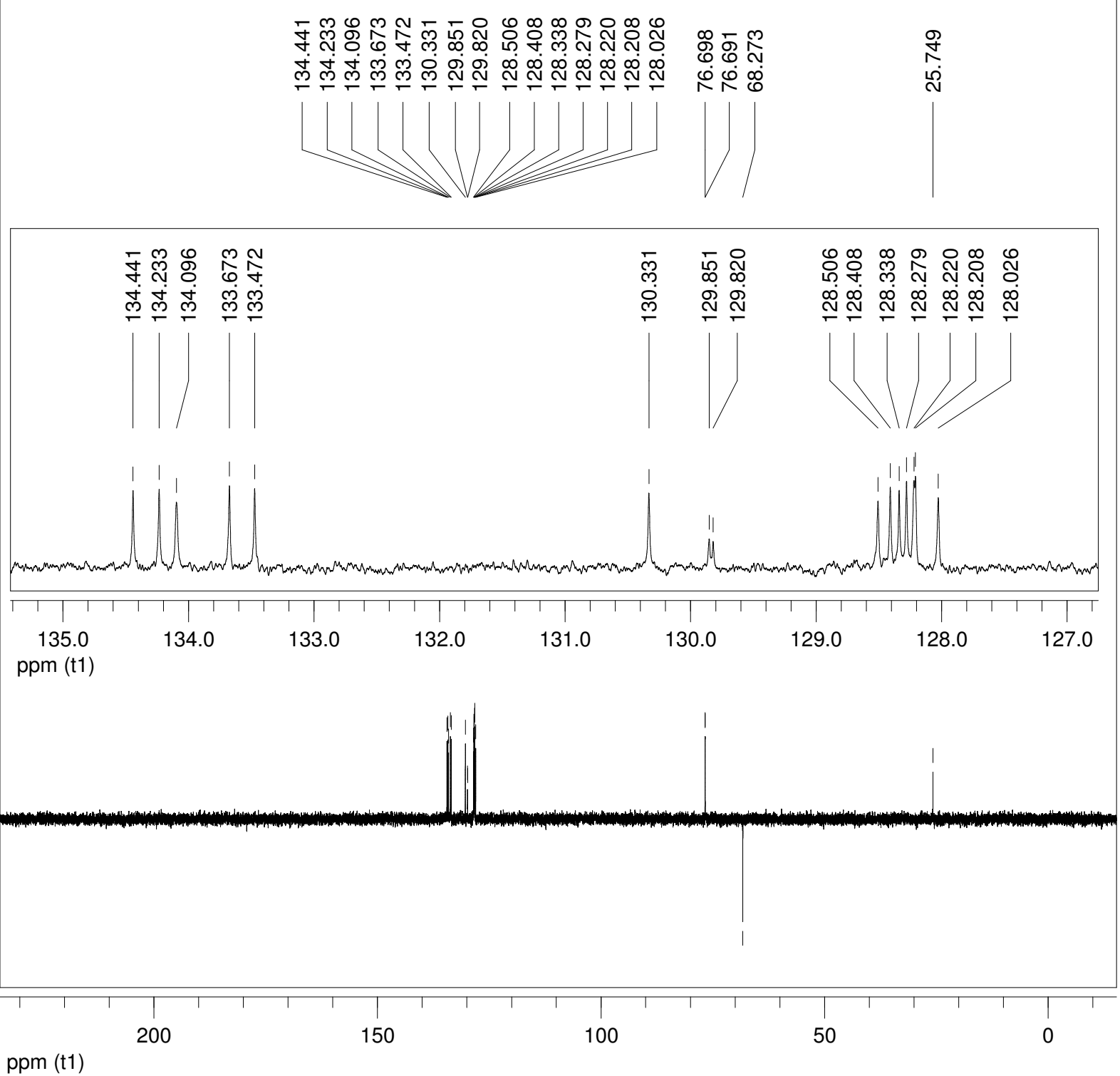

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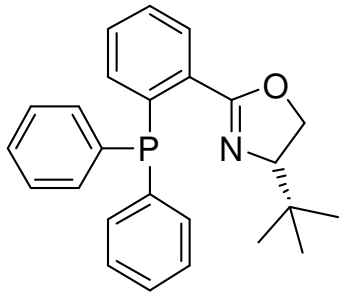

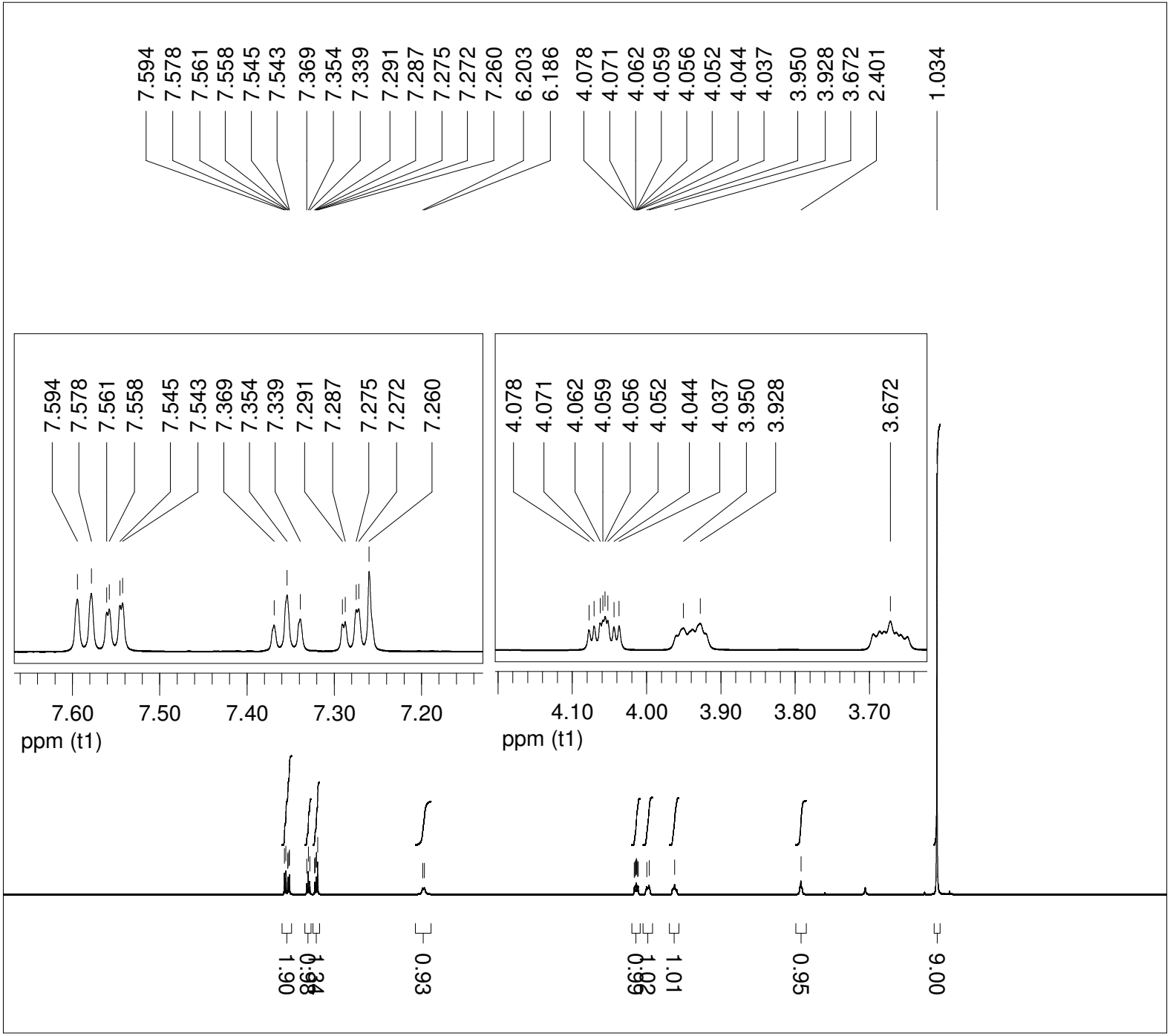

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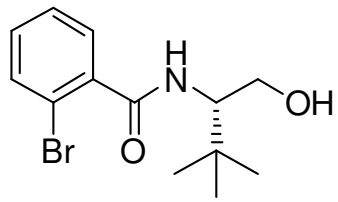

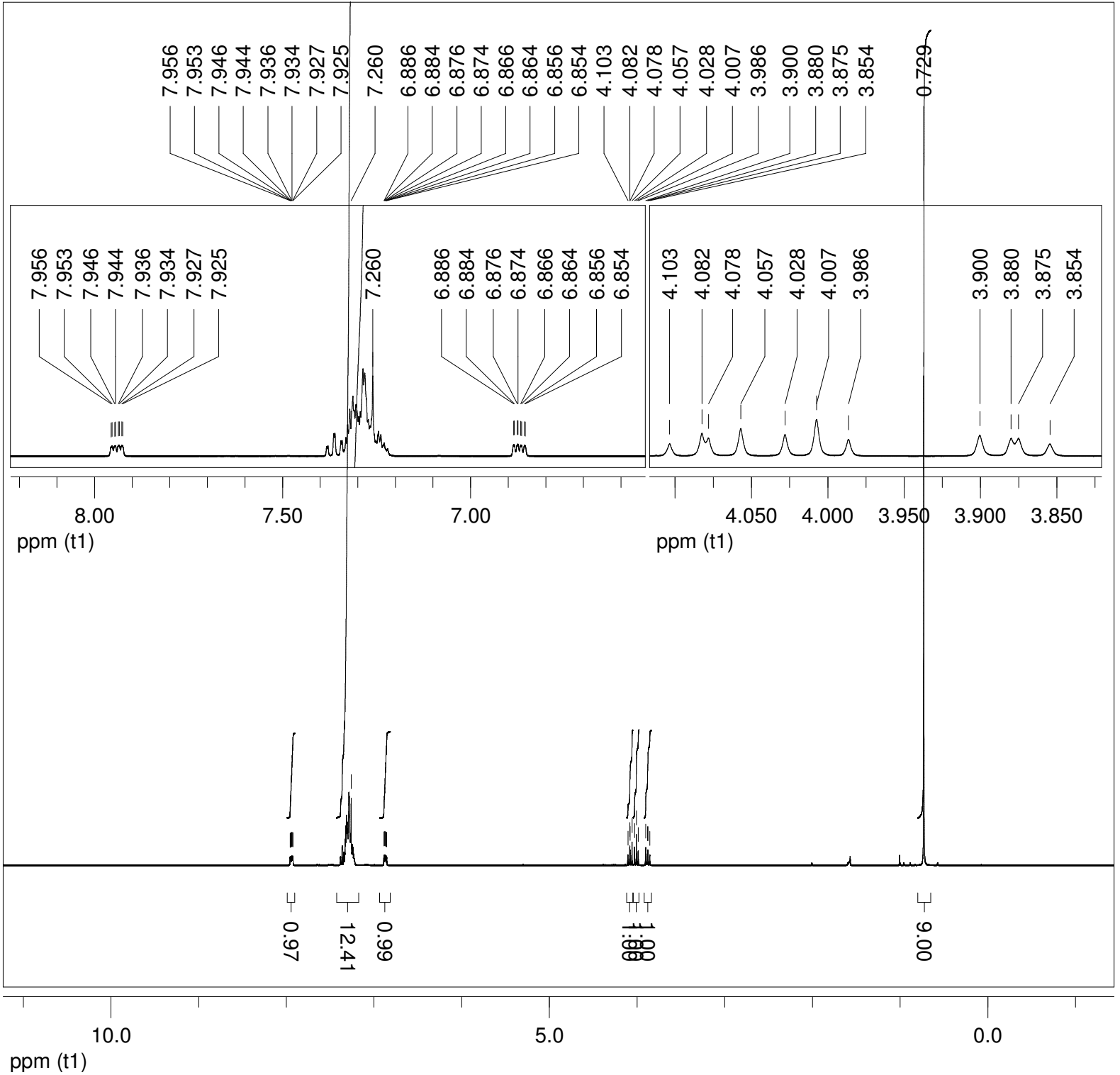

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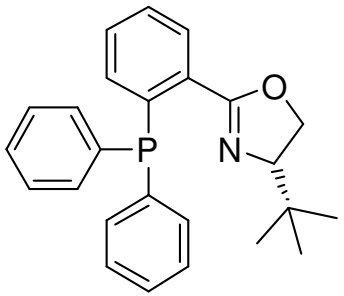

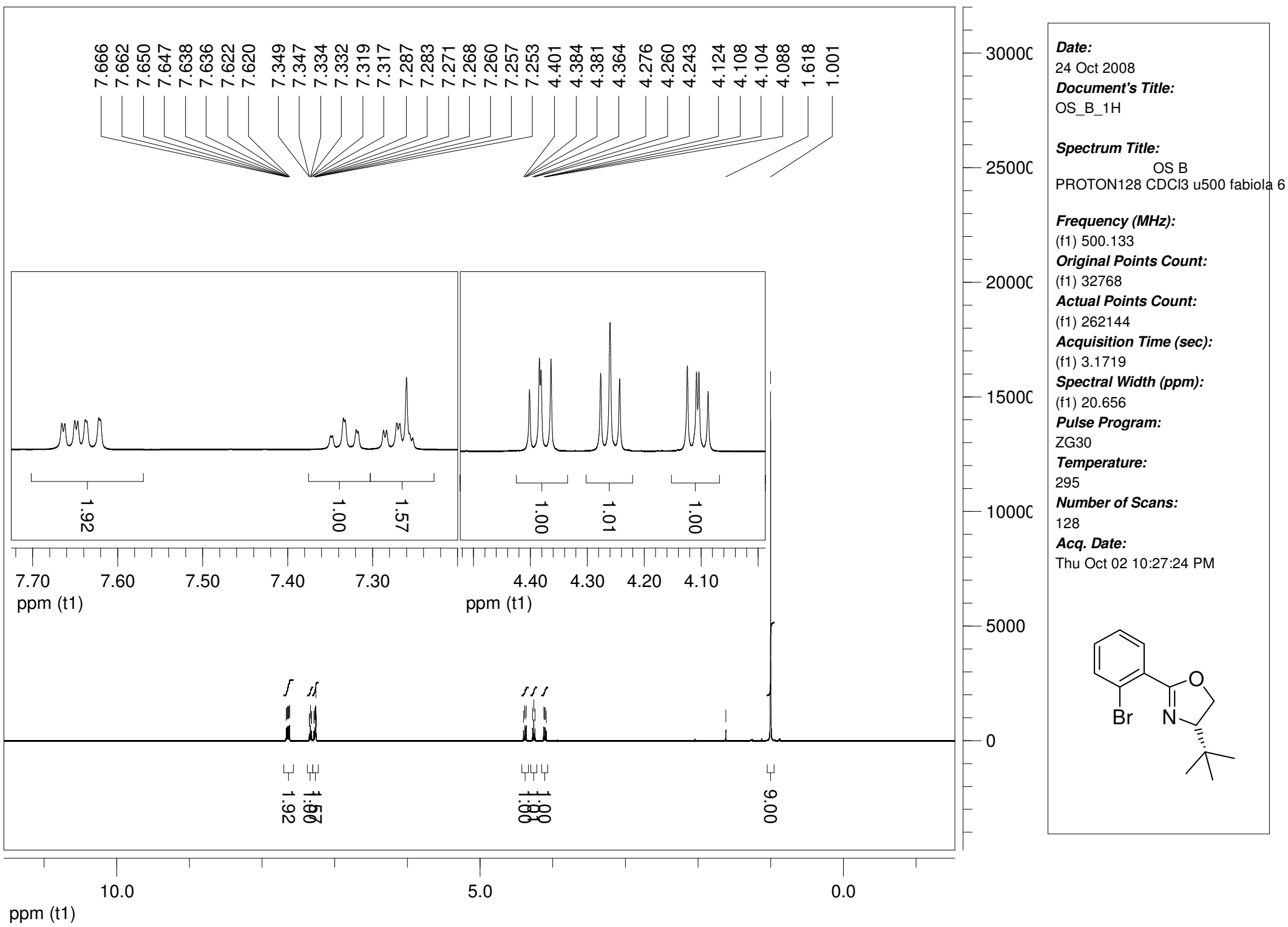

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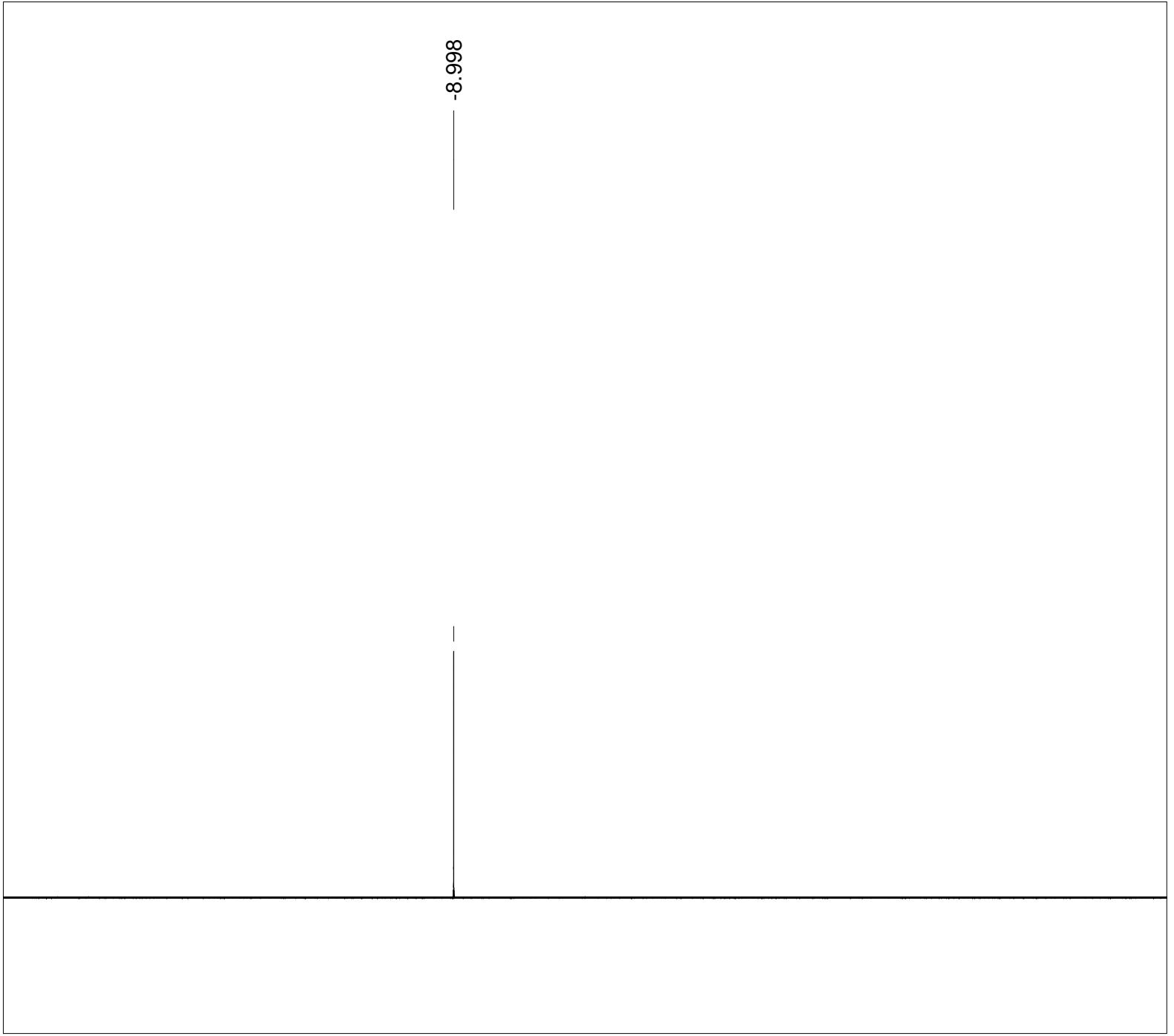

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