Organic Syntheses

Synthesis of (((1*R*,3*S*,3'*S*)-3,3'-Diethyl-3*H*,3'*H*-1,1'-spirobi[isobenzofuran]-7,7'-diyl)bis(oxy))bis(diphenylphosphane)

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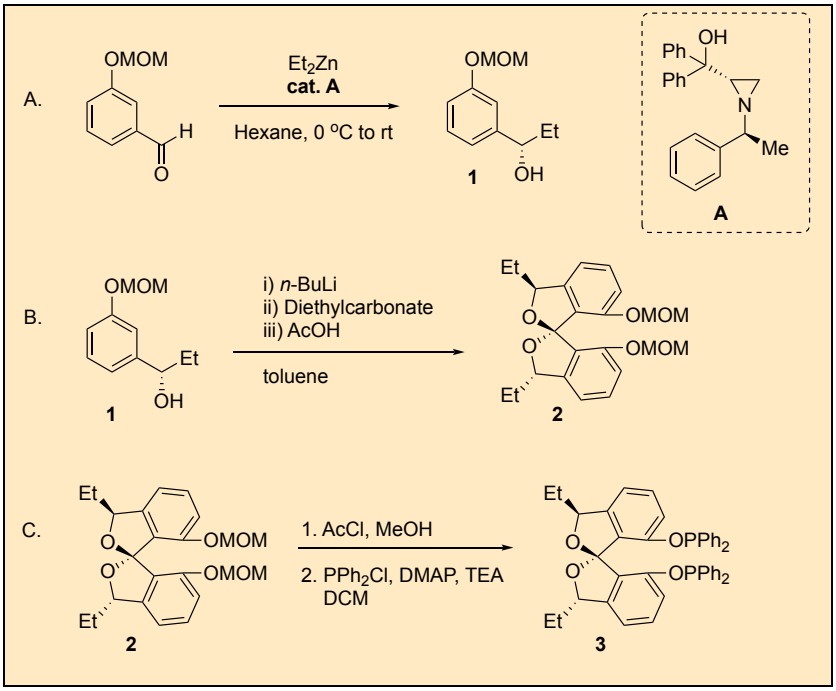
Checked by Renee Sifri and Kevin Campos



Published on the Web 07/08/2022

Procedure (Note 1)

A. *(S)-1-(3-(Methoxymethoxy)phenyl)propan-1-ol* (***1***). An oven-dried (Note 2) 1000-mL single-necked round-bottomed flask (24/40 joint) (Note 2) equipped with a Teflon coated magnetic stir bar (16 x 32 mm, egg-shape) is allowed to cool to 23 °C (Note 3) in a desiccator. Diphenyl((*S*)-1-((*S*)-1-phenylethyl) aziridin-2-yl)methanol (Note 4) (1.98 g, 6.00 mmol, 5.0 mol%) is added to the flask, and the flask is sealed with a rubber septum, connected to a Schlenk line with a needle adapter, and purged to a nitrogen atmosphere (Figure 1A). Hexane (265 mL) (Note 5) is then added to the flask using a syringe, and the solution is stirred (Note 6) and cooled to 0 °C (Note 7).

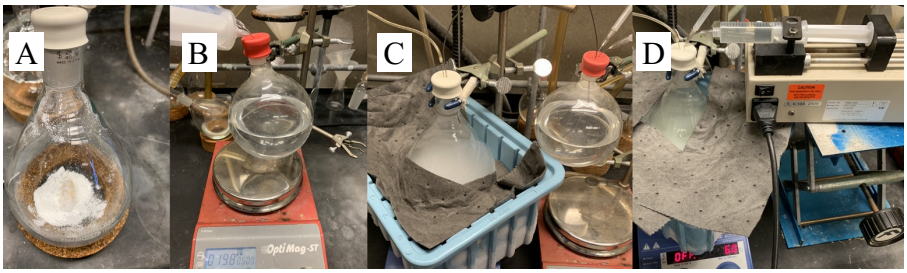


Figure 1. A) Reaction flask set-up after addition of catalyst (a); B) self-made Et_2Zn solution; C) reaction set-up for Et_2Zn transfer; D) reaction set-up for addition of 3-(methoxymethoxy)benzaldehyde (photos provided by submitters)

An oven-dried (Note 2) 500-mL single-necked, round-bottomed flask (14/20 joint) is sealed with a rubber septum, connected to a Schlenk line with a needle adapter, and subsequently cooled to 23 °C (Note 3). Hexane (265 mL) (Note 5) followed by diethylzinc (27.2 mL, 264.8 mmol, 2.20 equiv) (Note 8) are added to the flask using syringes under nitrogen atmosphere (Figure 1B). The solution is gently swirled to ensure mixing. The resulting clear solution is transferred to the 1000-mL flask dropwise over 60 min via cannula (Note 9) 0 °C (Note 7) (Figure 1C). The reaction mixture is stirred (Note 6) at 0 °C (Note 7) for 90 min. 3-(Methoxymethoxy)benzaldehyde (20.0 g, 120.4 mmol, 1.00 equiv) (Note 10) is added (Figure 1D) to the reaction dropwise over 60 min via syringe pump (Note 11) (Figure 2A). The reaction mixture is maintained at 0 °C (Note 7) for 10 h (Figure 2B), then the ice bath is removed, and the reaction mixture is allowed to warm to slowly warm to 23 °C (Note 3) and stirred for 20 h (Figure 2C) (Note 12).

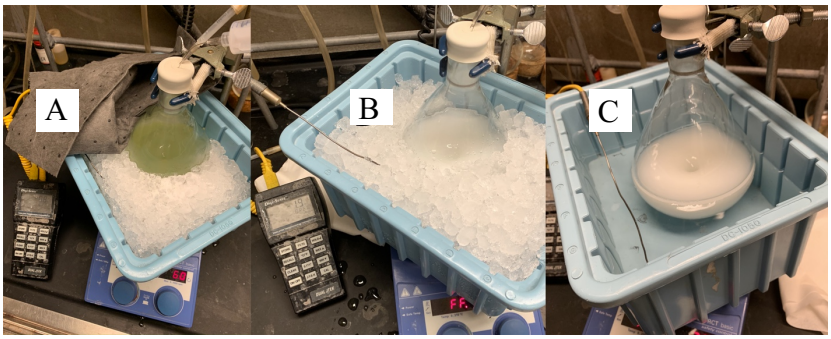


Figure 2. A) Reaction solution after addition of 3-(methoxymethoxy) benzaldehyde; B) reaction mixture after 10 hours at 0 °C; C) reaction mixture after 20 h at 23 °C (photo provided by submitter)

The reaction progress is stopped by the slow addition of 1N HCl solution (150 mL) (Note 13) at 0 °C (Note 7) and then filtered (Notes 14 and 15) into a 1000-mL round-bottomed flask (24/40 joint) with dichloromethane (DCM) washings (2 x 50 mL) (Notes 16). Deionized water (400 mL) (Notes 17) is added to the filtrate, and the biphasic mixture is transferred to a 2000-mL separatory funnel (Note 17). The organic layer is collected, and the aqueous layer is extracted with DCM (4 x 100 mL) (Notes 16). The combined organic phases are dried with $MgSO_4$ (100 g) (Note 18), filtered (Notes 14 and 15) into a 2000-mL single-necked, round-bottomed flask (24/40 joint) with DCM washings (3 x 50 mL) (Notes 16). The solution is concentrated by the aid of a rotary evaporator (Note 19) to afford a crude yellow oil. The crude product is purified by chromatography on silica (Note 20) to afford (*S*)-1-(3-(methoxymethoxy)phenyl)propan-1-ol **1** (21.4 g, 89%, 99% ee, 97% purity) (Note 21) as a pale yellow oil (Figure 3).

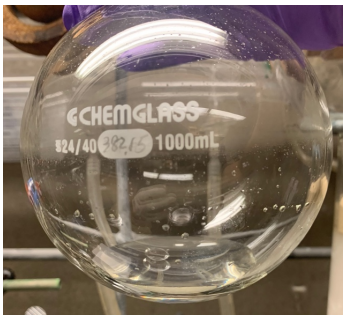


Figure 3. Product 1 (photo provided by submitter)

B. *(1R,3S,3'S)-3,3'-Diethyl-7,7'-bis(methoxymethoxy)-3H,3'H-1,1'-spirobi-[isobenzofuran]* (**2**). An oven-dried (Note 2) 1000-mL single-necked, round-bottomed flask (24/40 joint) is equipped with a Teflon-coated magnetic stir bar (16 x 32 mm, egg-shape). The flask is sealed with a rubber septum, connected to a Schlenk line via a needle adapter and subsequently cooled to 23 °C (Note 3). (*S*)-1-(3-(Methoxymethoxy)phenyl)propan-1-ol (**1**) (23.0 g, 117.1 mmol, 1.00 equiv) and toluene (330 mL) (Note 23) are added to the flask using syringes and the solution is cooled to 0 °C (Figure 4A) (Note 7). At this time, *n*-butyllithium solution (97.7 mL, 236.5 mmol, 2.02 equiv) (Note 23) is added dropwise (Figure 4B and 4C) to the solution over 90 min with the syringe pump (Note 24).

Figure 4. A) Reaction flask set-up after addition of starting material (1) and toluene; B) reaction solution before the *n*-BuLi addition; C) reaction solution during the *n*-BuLi addition (photo provided by submitter)

The reaction mixture is then allowed to slowly warm to 23 °C by removing the ice-bath (Note 3). After 3 h, THF (12 mL) (Note 25) is added to the resulting suspension (Note 26) and then cooled again to 0 °C (Note 7). Diethyl carbonate (7.52 mL, 62.1 mmol, 0.53 equiv) (Note 27) is incorporated over 2 h at 0 °C (Note 7) by syringe pump (Note 11) (Figure 5A and 5B). The reaction mixture is allowed to warm slowly to 23 °C (Note 3) overnight (Note 28) (Figure 5C). Glacial acetic acid (100 mL) (Note 29) is then added to the solution slowly over 30 min (Note 30). After 4 h (Note 31) deionized water (400 mL) (Notes 17) is added to the reaction mixture and the biphasic mixture is transferred to a 2000-mL wide-mouth Erlenmeyer flask (Note 32).

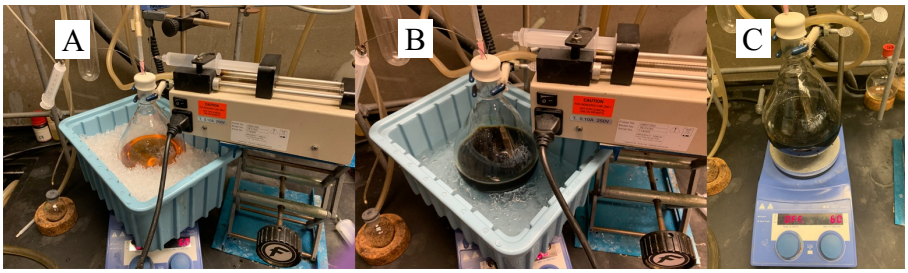


Figure 5. A) Reaction solution before addition of diethyl carbonate; B) reaction solution after addition of diethyl carbonate; C) reaction solution after overnight stirring at 23 °C (photo provided by submitter)

Sodium bicarbonate (100 g) (Note 33) is added to the solution in small portions (Note 34), and the flask is swirled between additions. The biphasic mixture is transferred to a 2000-mL separatory funnel (Note 17). The organic layer is collected, and the aqueous layer is extracted with DCM (4 x 100 mL) (Notes 16). The combined organic phases are dried with $MgSO_4$ (100 g) (Note 18), filtered (Notes 14 and 15) into a 2000-mL single-necked, round-bottomed flask (24/40 joint) with DCM washings (3 x 50 mL) (Notes 16). The solution is concentrated with the aid of a rotary evaporator (Note 19) to afford a crude yellow oil. The crude product is purified by chromatography on silica (Note 35) to afford (*1R,3S,3'S*)-3,3'-diethyl-7,7'-bis(methoxymethoxy)-3*H*,3'*H*-1,1'-spirobi-[isobenzofuran] **2** (14.9 g, 62%, 99% ee, 98% purity) (Note 36) as a bright yellow oil (Figure 6).

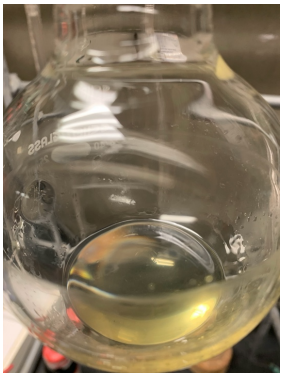


Figure 6. Product 2 (photo provided by submitters)

C. *(((1R,3S,3'S)-3,3'-Diethyl-3H,3'H-1,1'-spirobi[isobenzofuran]-7,7'-diyl)-bis(oxy))bis(diphenylphosphane)* (**3**). An oven-dried (Note 2) 50-mL single-necked round-bottomed flask (14/20 joint) is equipped with a Teflon coated magnetic stir bar (3.2 x 12.7 mm, round). The flask is sealed with a rubber septum, connected to a Schlenk line via a needle adapter and subsequently cooled to 23 °C (Note 3). (*1R,3S,3'S*)-3,3'-Diethyl-7,7'-bis (methoxymethoxy)-3*H*,3'*H*-1,1'-spirobi[isobenzofuran] (**2**) (1.88 g, 4.69 mmol, 1.00 equiv) (Figure 7A) and methanol (9.4 mL) (Note 37) are added to the flask under nitrogen, and the solution is sonicated (Note 38) for 1 min (Note 39) (Figure 7B). The solution is cooled to 0 °C (Note 7) while stirring (Note 6), and the acetyl chloride (667 µL, 9.39 mmol, 2.00 equiv) (Note 40) is added with a micro-syringe (Note 41) over 10 min at 0 °C (Note 7) (Figure 7C). The ice bath is removed and the reaction mixture is stirred at 23 °C (Note 3) for 130 min (Note 42) (Figure 7D). Saturated $NaHCO_3$ (Note 33) aqueous solution (10 mL) is added to the solution (Note 43), and the mixture is concentrated to about half of its original volume with the aid of a rotary evaporator (Note 19). The mixture is then transferred to a 60-mL separatory funnel (Note 17) and the flask is rinsed with DCM (5 mL) (Notes 16). The organic layer is collected, and the aqueous layer is extracted with DCM (4 x 10 mL) (Notes 16). The combined organic phases are dried with Na_2SO_4 (10 g) (Note 44), filtered (Notes 14 and 15) into a 100-mL single-necked pear-shaped flask (14/20 joint) with DCM washings (3 x 5 mL) (Notes 16). The solution is concentrated with the aid of a rotary evaporator (Note 19) to afford crude pale, yellow solids (Note 45).

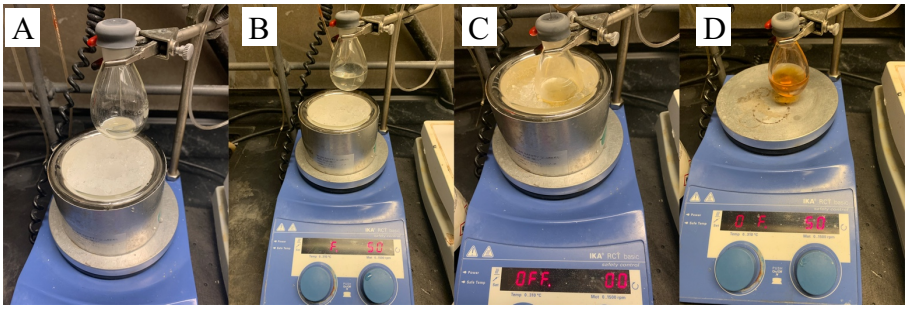


Figure 7. A) Starting material (2) in the reaction flask; B) reaction solution after sonication; C) reaction solution after AcCl addition; D) reaction solution after completion (photo provided by submitters)

An oven-dried (Note 2) 100-mL single-necked round-bottomed flask (24/40 joint) equipped with a Teflon coated magnetic stir bar (9 x 18 mm, egg-shape) is cooled to 23 °C (Note 3) in a desiccator. The crude solids (1.00 g, 3.20 mmol, 1.00 equiv) and DMAP (58 mg, 0.48 mmol, 15 mol%) (Note 46) are added to the flask (Figure 8A) and then sealed with a rubber septum, connected to a Schlenk line with a needle adapter, and purged to a nitrogen atmosphere. Dichloromethane (32 mL) (Notes 16) and triethylamine (1.78 mL, 12.80 mmol, 4.00 equiv) (Note 47) are added to the flask (Figure 8B), and the solution is cooled to 0 °C (Note 7) while stirring (Note 6). Chlorodiphenylphosphine (1.69 g, 7.68 mmol, 2.40 equiv) (Note 48) is added to the solution over 30 min at 0 °C (Note 7) (Figure 8C) with the syringe pump (Note 11). The reaction mixture is stirred at to 23 °C (Note 3) for 8 h (Note 49) (Figure 8D).

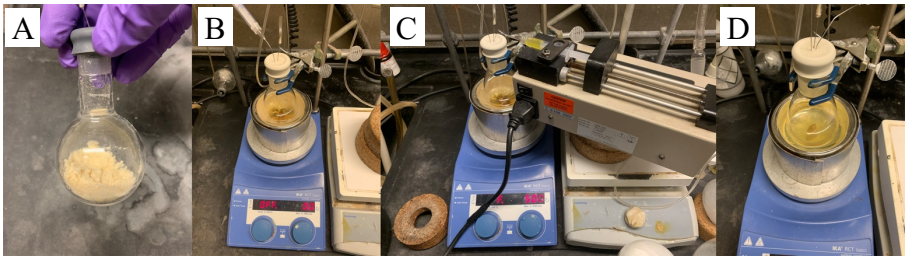


Figure 8. A) Starting material and DMAP in the reaction flask; B) reaction solution in DCM; C) addition of PPh_2Cl; D) reaction solution after 8 hours (photo provided by submitters)

The stir bar is removed, and the solution is concentrated with the aid of a rotary evaporator (Note 19). The crude product is purified by chromatography on deactivated silica (Note 50) to afford (((1*R*,3*S*,3'*S*)-3,3'-diethyl-3*H*,3'*H*-1,1'-spirobi[isobenzofuran]-7,7'-diyl)bis(oxy))bis(diphenyl-phosphane) **3** (1.68 g, 68.4%, 99% purity) as a white foam (Notes 51 and 52) (Figure 9).

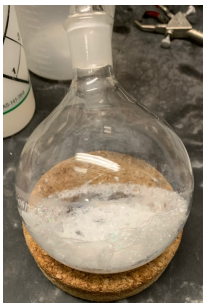


Figure 9. Product 3 (photo provided by submitters)

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to 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 1,3,5-trimethoxybenzene, 3-(methoxymethoxy)-benzaldehyde, 4-(dimethyl-amino)pyridine, acetic acid, acetyl chloride, ammonium chloride, benzene, chlorodiphenylphosphine, chloroform, dibromomethane, diethyl carbonate, diethylzinc, ethyl acetate, hexanes, hydrochloric acid, magnesium sulfate anhydrous, methylene chloride, *n*-butyllithium, silica, sodium bicarbonate, sodium chloride, sodium sulfate anhydrous, THF, toluene, triethylamine, as well as the proper procedures for working with dry ice and under an inert atmosphere. Diethylzinc (neat)

is highly pyrophoric, hygroscopic, heat sensitive and a highly water reactive chemical. It should be handled using inert atmosphere techniques and special waste treatment procedure should be followed.

2. Unless otherwise reported, all glassware was dried in a 120 °C oven prior to use and then brought down to 23 °C in a desiccator containing Drierite™. The checkers used three-necked flasks in lieu of the single-necked, round-bottomed flasks and equipped the flask with a temperature probe with no change in yield, provided the flask is oven dried in a similar manner and kept under nitrogen as described.
3. 23 °C was determined to be between 22 °C and 23 °C.
4. Diphenyl((*S*)-1-((*S*)-1-phenylethyl) aziridin-2-yl)methanol (**A**) was prepared following our procedure described in *Org. Synth.* **2021**, *98*, 446–462.
5. Hexane (mixture of isomers, anhydrous, ≥99%) was purchased from Sigma-Aldrich and used as received.
6. IKA RET basic hot plate stirrer (115V, 620W, 50-60 Hz) and Cole-Parmer IKA C-Mag hot plate stirrer (115V, 1000W, 50-60 Hz) were used. Unless indicated otherwise, 500 rpm was used for stirring.
7. The temperature of 0 °C was reached and maintained by mixing deionized water with ice.
8. Diethylzinc (≥52 wt. % Zn basis) was purchased from Sigma-Aldrich and used as received.
9. The checkers equipped the flask containing **A** with an oven-dried pressure equalizing addition funnel and transferred the diethylzinc solution by cannula to the addition funnel, which was used for the slow addition of the diethylzinc solution. Instead of addition via cannula, an oven-dried addition funnel can be used for the slow addition of diethylzinc. A three-necked round-bottomed flask should be used in this case (Note 2). Cannula (Chemglass Life Sciences Supplier Diversity Partner Cannula, Stainless Steel, 18 Gauge X 24" Length, Airfree, Schlenk) was purchased from Fisher Scientific.
10. 3-(Methoxymethoxy)benzaldehyde (≥95%) was purchased from Toronto Research Chemicals and used as received (CAS# 13709-05-2).
11. The Fisherbrand™ syringe pump was setup with a built-in syringe size table for Air-Tite™ All-Plastic Norm-Ject™ Syringes.
12. The reaction progress can be monitored by TLC (SiO_2, hexane/EtOAc (4/1), starting material: R_f 0.57, product **4**: R_f 0.41; UV-C 254 nm) to observe complete consumption of starting material (S refers to starting

material, C refers to co-spot of reaction mixture and starting materials, and R refers to the reaction mixture (Figure 10)).

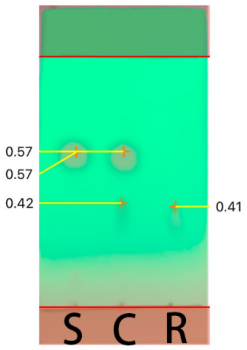


Figure 10. TLC monitoring of Step A (photo provided by submitters)

13. Hydrochloric acid (ACS reagent, 37%) was purchased from Sigma-Aldrich and diluted to 1N with deionized water.
14. Büchner filter funnels, 24/40 lower vacuum assembly, with coarse frit were purchased from Chemglass Life Sciences. For filtration, a vacuum pump supplied by Heidolph was used to establish reduced pressure.
15. To wash the filter cake effectively, vacuum was turned off between separate washing cycles, washing solvent was added and the resultant mixture was stirred thoroughly with a stainless-steel spatula before removal of the washing solvent by vacuum suction.
16. Dichloromethane (HPLC) was purchased from Fisher Scientific and purified by pressure filtration under nitrogen through activated alumina prior to use.
17. Deionized water was obtained and used directly from the university supply.
18. Magnesium sulfate anhydrous (Powder/Certified) was purchased from Fisher Scientific and used as received.
19. BUCHI™ Rotavapor™ Scholar with Dry Ice Cold Trap Condenser was connected to Heidolph™ Valve-Regulated Vacuum Pump. Unless specified differently, water bath remained at 30 °C and the vacuum was regulated to 20 mmHg.
20. The crude material was loaded onto a slurry-packed (hexane) column (ID 72 mm) containing SiO_2 (400 g, 40 - 63 µm, 60 Å silica gel purchased from SiliCycle Inc.), and the flask was then rinsed with DCM (20 mL) (Note 36) which was loaded afterwards. After loading, solvents were

eluted under positive nitrogen pressure and fractions were taken in 50-mL tubes. The solvent system was switched to 5000 mL of 4/1 hexane/EtOAc (ACS grade purchased from Fisher Scientific which was used as received). Product **1** (R_f 0.41, hexane/EtOAc 4/1, v/v) eluted, and fractions 31 through 98 were combined (Figure 11), concentrated on a rotary evaporator (30 °C, 780 to 20 mmHg), and dried in vacuo (1-2 mmHg) at ambient temperature for 12 h.

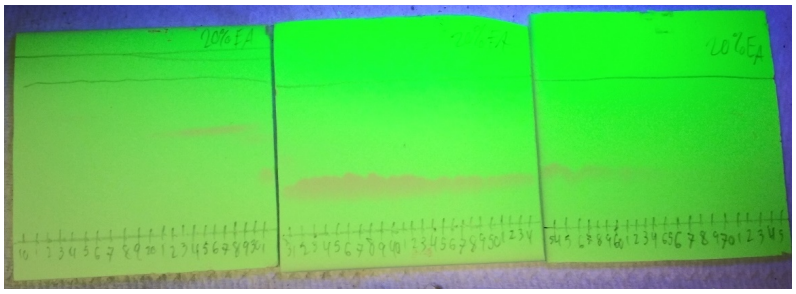


Figure 11. TLC analysis of fractions. (Visualization with UV-C 254 nm) (photo provided by submitters)

21. The product **(1)** exhibited the following properties: 99% ee (HPLC (Chiralpak IA column, 97:3 hexanes/isopropanol, 1.0 ml/min), tr = 15.4 min (*R*), 17.0 min (*S*)); $[\alpha]_D^{23}$ –27.35 (*c* 0.30, $CHCl_3$); R_f 0.41 (4/1, hexanes/EtOAc, v/v); bp 89.5 °C (8.5 mmHg); IR (film): 3360 (br), 2972, 2928, 1602, 1590, 1488, 1454, 1240, 1148, 1076,1014, 992, 924 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.28–7.24 (m, 1H), 7.07–7.03 (m,1H), 6.97 (ddd, *J* = 17.0, 7.5, 2.4 Hz, 2H), 5.18 (s, 2H), 4.57 (t, *J* = 6.6 Hz, 1H), 3.48 (s, 3H), 1.83–1.72 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d: 157.3, 146.6, 129.9, 119.6, 115.1, 114.0, 94.4, 75.7, 55.9, 31.8, 10.1. HRMS (ESI) *m/z* calcd for $C_{11}H_{17}O_3$ $[M+H]^+$ 197.1171, found 197.1175. Purity was determined by quantitative ^1H NMR spectroscopic analysis using biphenyl as an internal standard to be 97% by weight. The checkers also performed this reaction on half the reported scale, which resulted in a 91% yield of product. The ee was determined by HPLC analysis with a Waters Alliance e2695 Separations Module HPLC system equipped with a CHIRALPAK IA column (length 250 mm, I.D. 4.6 mm). Optical rotations were measured at 23 °C in a solvent of choice on a JASCO P-2000 digital polarimeter at 589 nm (D-line).

22. Toluene (Certified ACS) was purchased from Fisher Scientific and purified by pressure filtration under nitrogen through activated alumina prior to use.
23. *n*-Butyllithium solution (2.5 M in hexanes) was purchased from Sigma-Aldrich, titrated to be 2.42 M, and used after titration with diphenyl acetic acid.
24. The SyringeONE syringe pump was purchased from Fisher Scientific and was programmed based on specifications of Air-Tite™ All-Plastic Norm-Ject™ Syringes. The checkers recommend addition of the *n*-butyllithium solution in two portions using a 100-mL syringe.
25. THF (HPLC) was purchased from Fisher Scientific and purified by pressure filtration under nitrogen through activated alumina prior to use.
26. The reaction mixture was changed from an off-white thick mixture to orange solution (Figure 12).

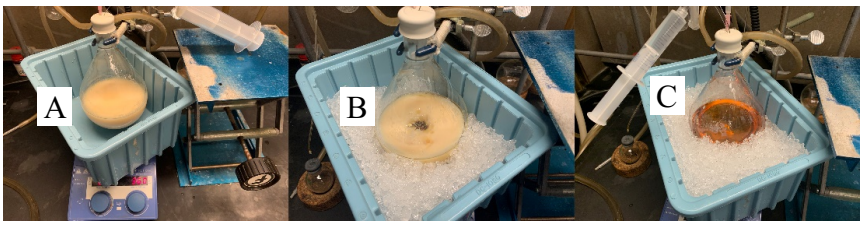


Figure 12. A) Reaction suspension at 3 hours after addition of nBuLi; B) reaction mixture during the addition of THF; C) reaction solution after addition of THF (photo provided by submitters)

27. Diethyl carbonate (99+%, Alfa Aesar) was purchased from Fisher Scientific and was dried with activated 4A molecular sieves prior to use.
28. Overnight throughout this manuscript refers to 14 h.
29. Acetic acid (Glacial (Certified ACS), Fisher Chemical) was purchased from Fisher Scientific and used as received.
30. The reaction mixture color changed from black to dark orange after the addition of acetic acid and turned to yellow after 4 h (Figure 13). The checkers observed an exotherm of 7 °C during the 30 min addition of acetic acid.

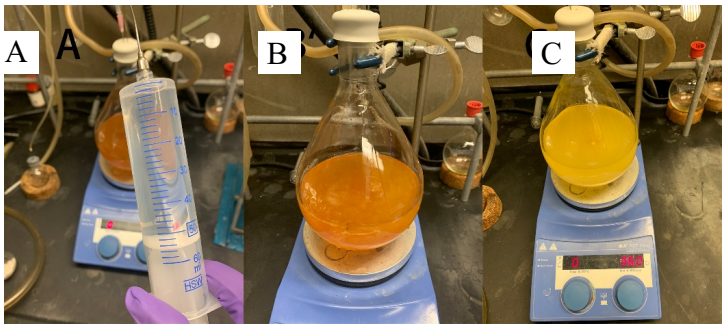


Figure 13. A) Reaction mixture during addition of AcOH; B) reaction mixture after addition of AcOH; C) reaction mixture after 4 h of stirring (photo provided by submitters)

31. The reaction progress can be monitored by TLC (SiO_2, Hexane/EtOAc 4/1, starting material **1**: R_f 0.39, product **2**: R_f 0.53; UV-C 254 nm) (S refers to starting material, C refers to co-spot of reaction mixture and starting materials, and R refers to the reaction mixture (Figure 14)).

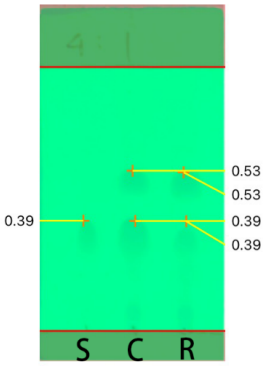
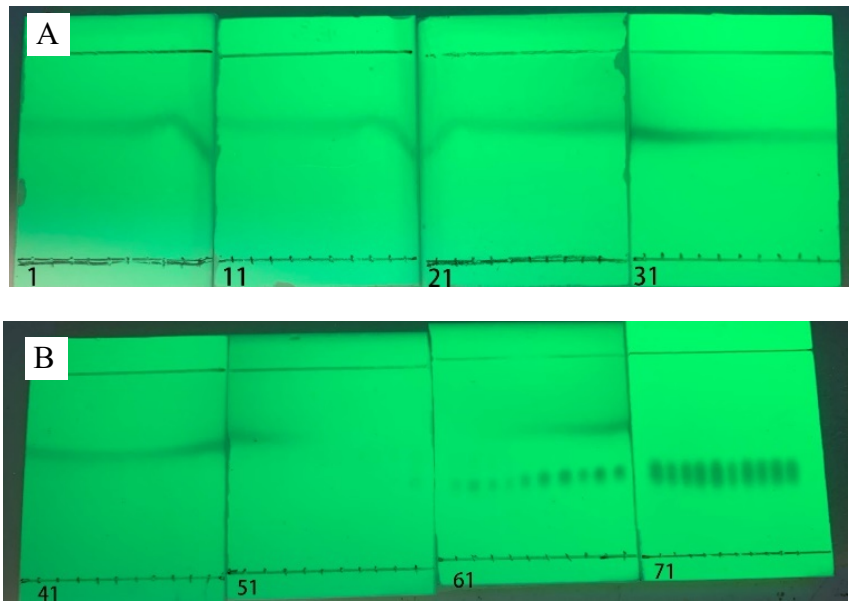


Figure 14. TLC monitoring of Step B (photo provided by submitters)

32. Fisherbrand™ reusable glass wide-mouth Erlenmeyer flasks were purchased from Fisher Scientific.
33. Sodium bicarbonate (Powder/Certified ACS, Fisher Chemical) was purchased from Fisher Scientific and used as received.
34. The first 50 g of $NaHCO_3$ was added in 1-g portions and the last 50 g were added in 2-g portions.
35. The crude material was loaded onto a slurry-packed (hexane) column (ID 72 mm) containing SiO_2 (500 g, 40 - 63 µm, 60 Å silica gel purchased from

SiliCycle Inc.), and the flask was then rinsed with 9/1 hexane/EtOAc (40 mL), which was loaded afterwards. After loading, solvents were eluted under positive nitrogen pressure and fractions were taken in 50-mL tubes. The solvent system was switched to 1000 mL of 9/1 hexane/EtOAc (ACS grade purchased from Fisher Scientific which was used as received), then 1800 mL of 8/1 hexane/EtOAc, followed by 800 mL of 7/1 hexane/EtOAc, and finished by 1500 mL of 6/1 hexane/EtOAc. Product **2** (R_f 0.53, hexane/EtOAc 4/1, v/v) eluted first and fractions 60 through 99 were combined (Figure 15), concentrated on a rotary evaporator (30 °C, 780 to 20 mmHg), and dried in vacuo (1-2 mmHg) at ambient temperature for 12 h. Starting material **1** (R_f 0.39, hexane/EtOAc 4/1, v/v) eluted later and fractions 111 through 130 were combined, concentrated on a rotary evaporator (30 °C, 780 to 20 mmHg), and dried in vacuo (1-2 mmHg) at ambient temperature for 12 h.



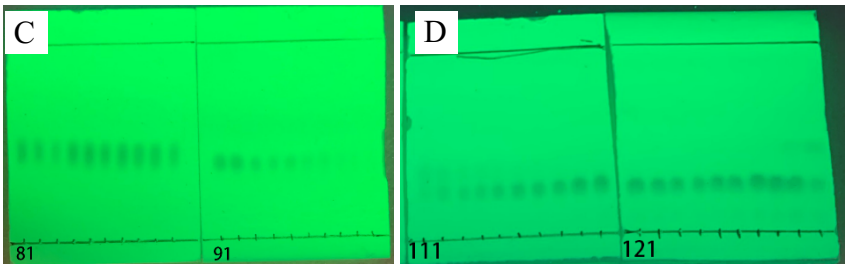


Figure 15. TLC analysis of the fractions. (Visualization with UV-C 254 nm) A) fractions 1 through 40; B) fractions 41 through 80; C) fractions 81 through 100; D) fractions 111 through 130 (photo provided by submitters)

36. The product **(2)** exhibited the following properties: 99% ee (HPLC (Chiralpak IA column, 99:1 hexanes/isopropanol, 1.0 ml/min), tr = 12.9 min (*R*), 15.2 min (*S*)); $[\alpha]_D^{23}$ +4.76 (*c* 2.30, $CHCl_3$); R_f 0.53 (4/1, hexanes/EtOAc, v/v); bp 161.4 °C; IR (film): 2968, 2942, 1616, 1599, 1478, 1258, 1154, 1008, 964, 926, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.28 (t, *J* = 7.7 Hz, 2H), 6.87 (dd, *J* = 8.3, 4.7 Hz, 4H), 5.40 (dd, *J* = 7.3, 3.9 Hz, 2H), 4.94 (d, *J* = 6.6 Hz, 2H), 4.82 (d, *J* = 6.6 Hz, 2H), 3.07 (s, 6H), 2.03–1.94 (m, 2H), 1.89–1.82 (m, 2H), 1.04 (t, *J* = 7.43 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) d: 152.6, 145.7, 130.7, 127.9, 115.9, 114.1, 112.3, 93.4, 83.2, 55.7, 53.5, 28.2, 9.8; Purity was determined by quantitative ^1H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard to be 97% by weight. The checkers also performed this reaction on half the described scale, which resulted in a 67% yield of product. The ee was determined by HPLC analysis with a Waters Alliance e2695 Separations Module HPLC system equipped with a CHIRALPAK IA column (length 250 mm, I.D. 4.6 mm). Optical rotations were measured at 23 °C in a solvent of choice on a JASCO P-2000 digital polarimeter at 589 nm (D-line).
37. Methanol (Certified ACS, Fisher Chemical) was purchased from Fisher Scientific and used as received.
38. Branson® Ultrasonic Bath (115 Vac, 60 Hz) was used with 2.8 L (0.75-gal) tank filled with water at 23 °C.
39. The solution should be homogeneous or more time would be needed in the ultrasonic machine.
40. Acetyl chloride (reagent grade, 98%) was purchased from Sigma Aldrich and used as received.

41. All micro-syringes (Chemglass Life Sciences, Gas-Tight, Fixed Needle, 22s Gauge) were purchased from Fisher Scientific. A 1 mL syringe may be substituted for a micro syringe if needed.
42. The reaction can be monitored by TLC (SiO_2, Hexane/EtOAc 5/1, starting material **2**: R_f 0.49, product: R_f 0.32; UV-C 254 nm) (S refers to starting material. C refers to co-spot of reaction mixture and starting materials. R refers to the reaction mixture (Figure 16)).

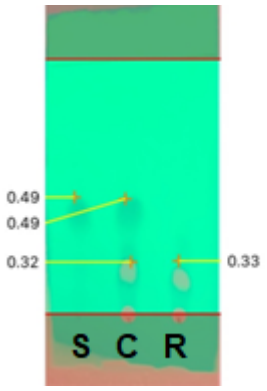


Figure 16. TLC monitoring of Step C, Part 1 (photo provided by submitters)

43. The resulting solution was shown slight basic (pH = 8) by the pH paper.
44. Sodium sulfate anhydrous (Granular/Certified ACS) was purchased from Fisher Scientific and used as received.
45. Only 1.00 g of crude product (Figure 17) was used for the remaining step of the ligand synthesis.

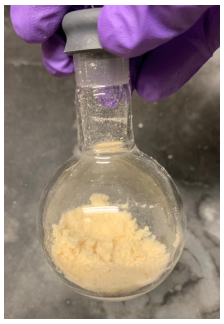


Figure 17. Crude material from the deprotection step (photo provided by submitters)

46. 4-(Dimethylamino)pyridine (≥99%) was purchased from Sigma Aldrich and used as received.
47. Triethylamine (99%) was purchased from Fisher Scientific and distilled under nitrogen from sodium hydride before the use. The use of dry triethylamine is recommended, KF < 200 ppm.
48. Chlorodiphenylphosphine (96%) was purchased from Sigma Aldrich, stored in the glovebox and used as received.
49. The reaction can be monitored by TLC (SiO_2, Hexane/EtOAc 5/1, starting materials: R_f 0.19, product **3**: R_f 0.53; UV-C 254 nm) (S refers to starting materials. C refers to co-spot of reaction mixture and starting materials. R refers to the reaction mixture (Figure 18)).

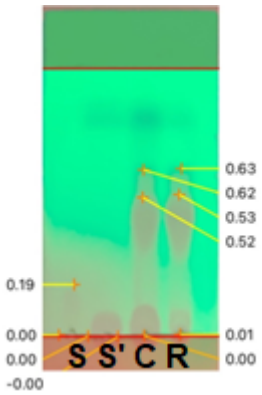


Figure 18. TLC monitoring of Step C, Part 2 (photo provided by submitters)

50. The crude was loaded onto a slurry-packed (hexane with 1% TEA) column (ID 42 mm) containing SiO_2 (120 g, 40 - 63 µm, 60 Å silica gel purchased from SiliCycle Inc.), and the flask was then rinsed with chloroform (3 mL) which was loaded afterwards. After loading, solvents were eluted under positive nitrogen pressure and fractions were taken in 25-mL tubes. The solvent system was switched to 1.1 L of 25/1 hexane (with 1% TEA)/EtOAc (ACS grade purchased from Fisher Scientific which were used as received), followed by 500 mL of 20/1 hexane (with 1% TEA)/EtOAc, and then 500 mL of 10/1 hexane (with 1% TEA)/EtOAc. Product **3** (R_f 0.52, hexane/EtOAc 5/1, v/v) eluted, fractions 56 through 96 were combined (Figure 19), concentrated on a

rotary evaporator (30 °C, 780 to 20 mmHg), and dried in vacuo (1-2 mmHg) at ambient temperature for 12 h.

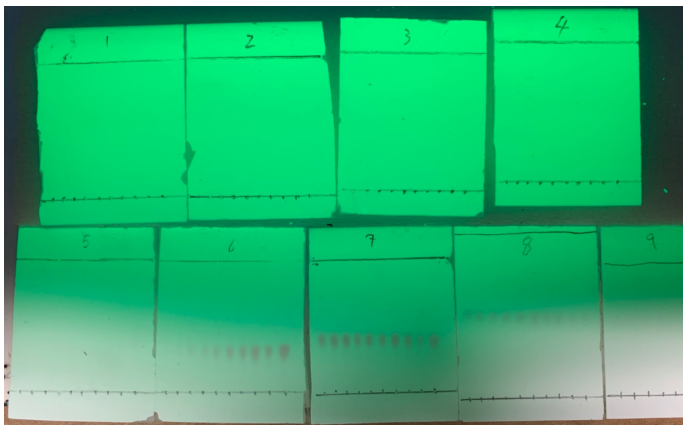


Figure 19. TLC analysis of fractions 1 to 96. (Visualization with UV-C 254 nm) (photo provided by submitters)

51. The product **(3)** exhibited the following properties: $[\alpha]_D^{23}$ –108.77 (*c* 0.20, toluene); R_f 0.52 (5/1, hexanes/EtOAc, v/v); mp 159.4–160.1 °C; IR (film, ATR): 3049, 2967, 2926, 2874, 1594, 1471, 1435, 1344, 1283, 1247, 1091, 1065, 1020, 1006, 994, 937, 831, 771, 730, 701, 652, 633 cm^{-1}; ^1H NMR (500 MHz, benzene-d6) d: 7.39–7.35 (m, 4H), 7.25 (dd, *J* = 5.2, 2.5 Hz, 2H), 7.16–7.11 (m, 4H), 7.02–6.96 (m, 8H), 6.95–6.92 (m, 6H), 6.57 (d, *J* = 7.5, 2H), 5.35 (dd, *J* = 8.8, 3.7 Hz, 2H), 1.57–1.43 (m, 4H), 0.93 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (126 MHz, benzene-d6) d: 153.0, 152.9, 147.4, 141.1, 141.0, 140.9, 140.8, 131.1, 131.0, 130.8, 130.7, 130.2, 130.0, 129.9, 129.8, 129.2, 128.8, 128.7, 128.7, 128.7, 128.5, 115.7, 115.6, 115.5, 115.0, 83.2, 28.6, 10.8; ^{31}P NMR (202 MHz, benzene-d6) d: 105.3. HRMS (ESI) *m/z* calcd for $C_{43}H_{39}O_4P_2^+$ 681.2317 $[M+H]^+$ found 681.2316. When the checkers performed the reaction a second time on full scale, 1.49 g (68%) of the product was isolated. Purity was determined by quantitative ^1H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard to be 97% by weight.
52. The compound **3** should be stored in the glove box after purification.

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.

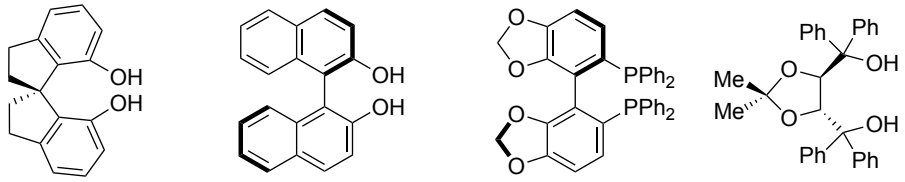
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Chiral organic ligands have been of great importance for the asymmetric transition-metal catalysis since the discovery of Noyori asymmetric hydrogenation.[2] After many decades of research, several generally well-performing privileged ligand scaffolds have been identified (Figure 20). The ligands containing these privileged scaffolds have been particularly effective in various types of asymmetric catalysis and have demonstrate excellent

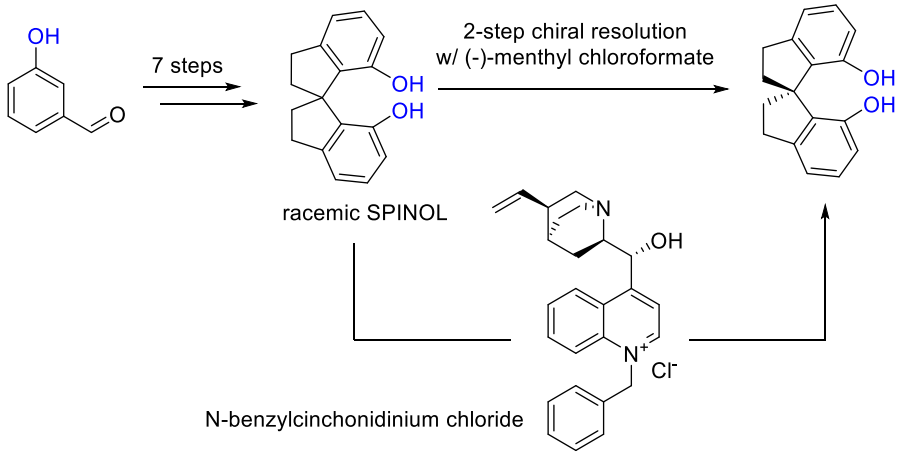
substrate scope and enantioselectivity profiles even for the most challenging transformations.[4]



(*R*)-SPINOL (*R*)-BINOL (*R*)-SEGPHOS (*R*,*R*)-TADDOL

Figure 20. Selected example of privileged chiral ligands and scaffolds

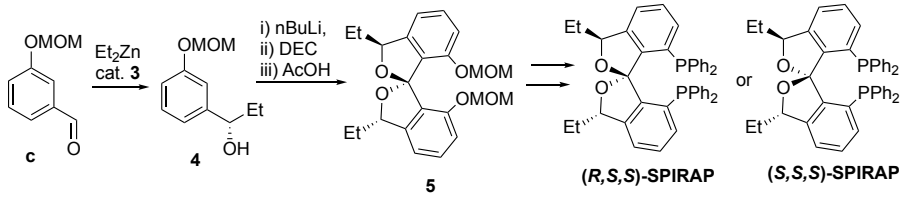
Among the various chiral scaffolds, the C_2-symmetric SPINOL scaffold has been of great importance to chiral ligand design. In particular, 7,7′-bis(diarylphosphino)-2,2′,3,3′-tetrahydro-1,1′-spiro-biindenes (SDPs) or SPINOL-derived diphosphine ligands have been used with great success in the past decades .[5] However, high prices and tedious preparation methods for chiral SPINOLs have become a limiting issue in the application of these ligands.



Scheme 1. Synthesis of SPINOL with racemic intermediate

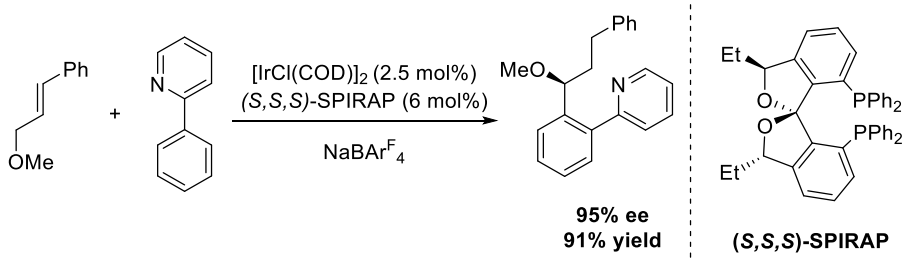
The first SPINOL synthesis[6] was reported by the Birman group in 1999 and included a 7-step synthesis towards the racemic SPINOL followed by a challenging and inefficient chiral resolution with (-)-menthyl chloroformate (Scheme 1). Zhou group subsequently reported another method for the resolution based on inclusion crystallization route with *N*-

benzylcinchonidium chloride (Scheme 12); however, this has not lead to the drastic improvement in availability of enantioenriched SPINOL.[7] A recent approach by Tan and coworkers provided improved access to enantioenriched SPINOL derivatives by eliminating the SPINOL resolution step through the use of an enantioselective catalytic cyclization; however, this method suffers from the obligatory use of SPINOL-derived phosphoric acid-based catalysts to achieve enantiocontrol.[8]



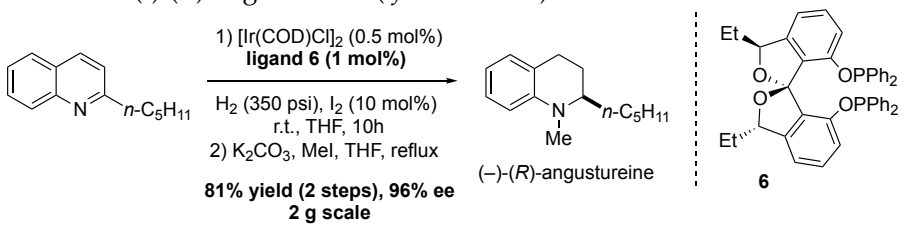
Scheme 2. Enantioselective synthesis of SPIROL

In 2018, our group reported a new, easily accessible, spiroketal-based C_2-symmetric chiral scaffold termed SPIROL for an array of stereoselective transformations.[9] The procedure reported was a three-step synthesis of C_2-symmetric MOM-protected spirocyclic **2** from commercially available starting material (Scheme 2). The asymmetric alkylation with diethyl zinc was achieved with readily available aziridine-based precatalyst.[10] Compound **1** was obtained in high yields and enantiopure, and the aziridine catalyst was recycled after column chromatography. The spirocyclization towards **2** could be easily performed on a decagram-scale with good yields and the optimized variant of this protocol is described above. Upon selective deprotection protocols, both (*S*,*S*,*S*)- and (*R*,*S*,*S*)-SPIROL diastereomers can be accessed from **2**. The (*S*,*S*,*S*)-SPIROL-derived ligands are structurally similar to (*S*)-SPINOL-based ligands and demonstrate excellent performance in various asymmetric transformations including the Ir(I)-catalyzed hydroarylation reaction depicted in Scheme 3.



Scheme 3. Iridium-catalyzed hydroarylations with (*S*,*S*,*S*)-SPIRAP

Pseudoenantiomeric (*R*,*S*,*S*)-SPIROL ligands not only provided reversed selectivity in comparison to (*S*,*S*,*S*)-SPIROL or (*S*)-SPINOL-based ligands, but also possessed unique backbone architecture with distinctly different structural parameters such as bite angle, etc.[9] In our recent studies, (*R*,*S*,*S*)-SPIROL-based phosphinite **3**, synthesis of which is described above, exhibits excellent performance in Ir(I)-catalyzed dearomatizative hydrogenations of nitrogen-containing heterocycles (Scheme 4).[11] Ligand **3** is readily available, and its use allowed an expansion in substrate scope and the performance of the hydrogenation under the milder reaction conditions. This, in turn, allowed to use of ligand **3** to achieve facile gram-scale asymmetric synthesis of alkaloid (-)-(*R*)-angustureine (*cf.* Scheme 15).



Scheme 4. Application to enantioselective synthesis of (-)-(*R*)-angustureine

References

1. Department of Chemistry, University of Michigan, Ann Arbor, MI 48109, USA, E-mail: nagorny@umich.edu; ORCID: 0000-0002-7043-984X. Financial support from National Science Foundation (grant CHE-1955069 to PN) is gratefully acknowledged.
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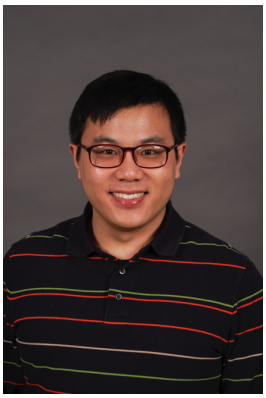
Appendix
Chemical Abstracts Nomenclature (Registry Number)

Diphenyl((*S*)-1-((*S*)-1-phenylethyl) aziridin-2-yl)methanol; (1315320-57-0))
Diethylzinc; (557-20-0)
3-(Methoxymethoxy)benzaldehyde; (13709-05-2)
n-Butyllithium solution; (109-72-8)
Diethyl carbonate; (105-58-8)
Glacial acetic acid: Acetic acid; (64-19-7)
Magnesium sulfate (anhydrous): Sulfuric acid magnesium salt (1:1); (7487-88-9)
Acetyl chloride; (75-36-5)
Sodium bicarbonate; (144-55-8)
Sodium sulfate (anhydrous); (7757-82-6)
N,N-Dimethylaminopyridine (DMAP): 4-(Dimethylamino)pyridine; (1122-58-3)
Triethylamine; (121-44-8)
Chlorodiphenylphosphine; (1079-66-9)



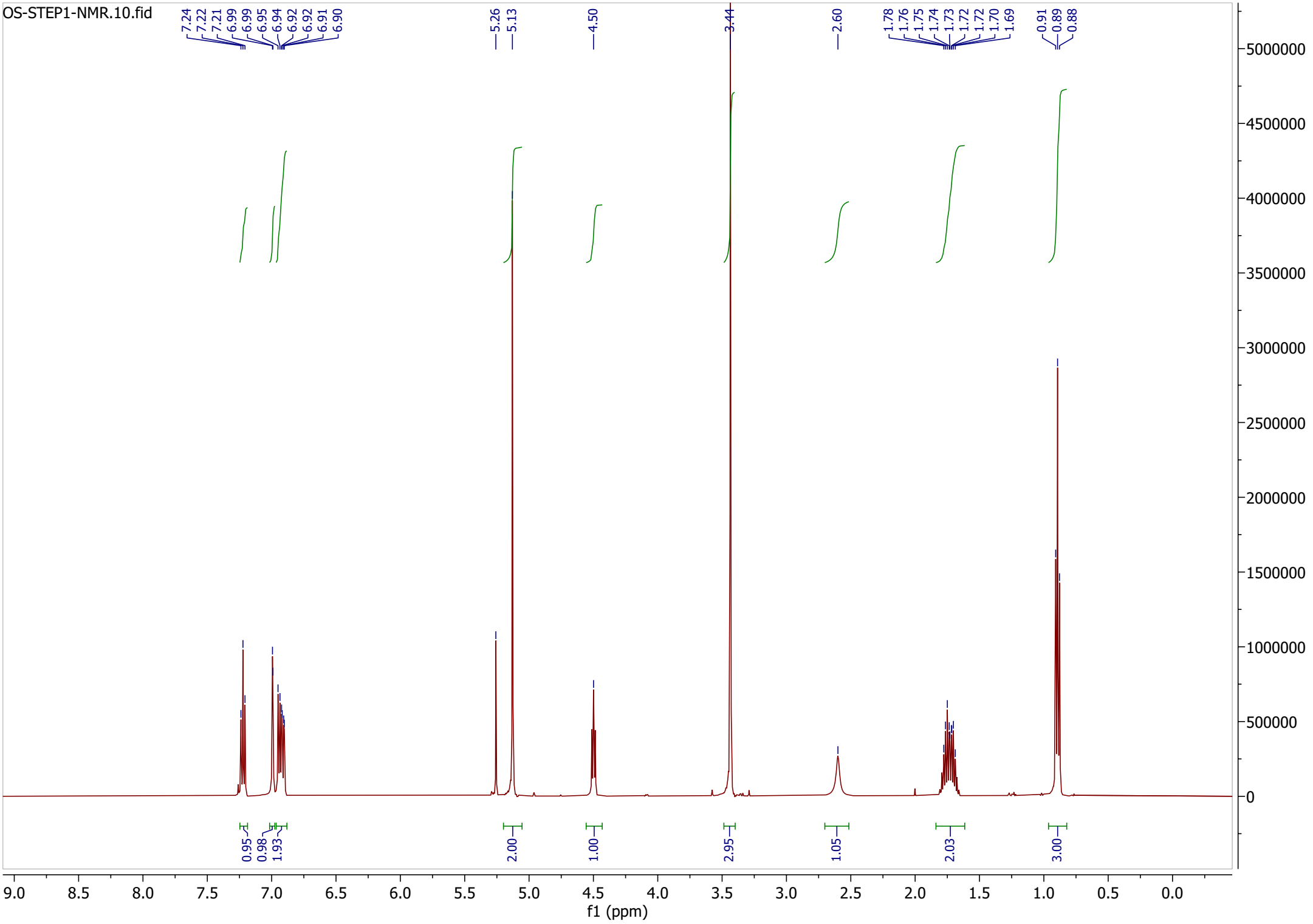
Siyuan Sun was born in Suzhou, China. He obtained a B.S. degree from the Purdue University, where he studied the monoterpene indole alkaloids synthesis under the direction of Prof. Mingji Dai. He is currently pursuing his Ph.D. in the laboratory of Prof. Pavel Nagorny at the University of Michigan, Ann Arbor where he studies the synthesis and catalysis of novel SPIROL-based ligands for asymmetric catalysis.

Zachary Fejedelem joined the Nagorny Group in May of 2017. Zack received his B.S. in Chemistry with Honors, from Kent State University in Kent, Ohio. While at Kent State, he was working with Drs. Paul Sampson and Alexander Seed to develop photo-labile HNO donors for quick and efficient production of HNO in situ. He currently is working towards the total synthesis of cardiotonic steroid natural products.

Solomon Song is currently an undergraduate at the University of Michigan studying biochemistry and computer science. Solomon has an interest in organic chemistry and continues to enjoy working in the lab.

Dr. Pavel Nagorny received his B.S. degree in chemistry in 2001 from the Oregon State University. After earning his Ph.D. degree in chemistry from Harvard University in 2007, he spent three years as a postdoctoral fellow with at the Memorial Sloan-Kettering Cancer Center. In 2010, Pavel joined the faculty of the University of Michigan. From 2014-2017 he was appointed as a William R. Roush Assistant Professor in Chemistry, and in 2017 he was promoted to the rank of Associate Professor with tenure, and in 2022 to the rank of Professor in Chemistry. Pavel's research group interests range from natural product synthesis to asymmetric catalysis, organocatalysis and carbohydrate chemistry.

Dr. Renee J. Sifri joined the Process Research and Development Department of Merck & Co., Inc. in 2021. Her work focuses on using state-of-the-art organic and organometallic chemistry to address critical problems in drug discovery and drug development. Renee received her B.S. degree in chemistry from U.C. Berkeley in 2016. She then moved to Ithaca, NY to obtain her Ph.D. in synthetic polymer chemistry at Cornell University under the supervision of Professor Brett Fors.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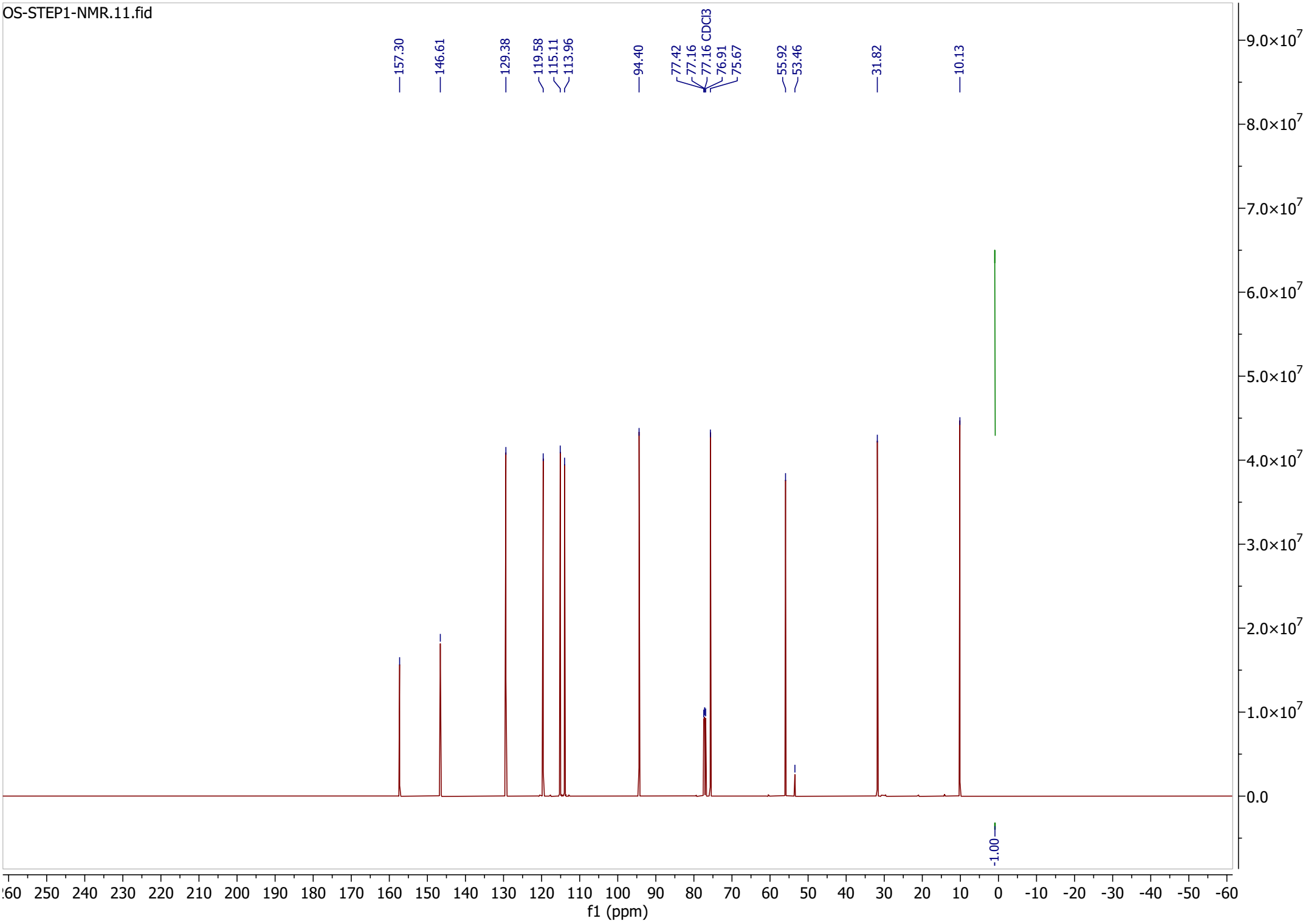
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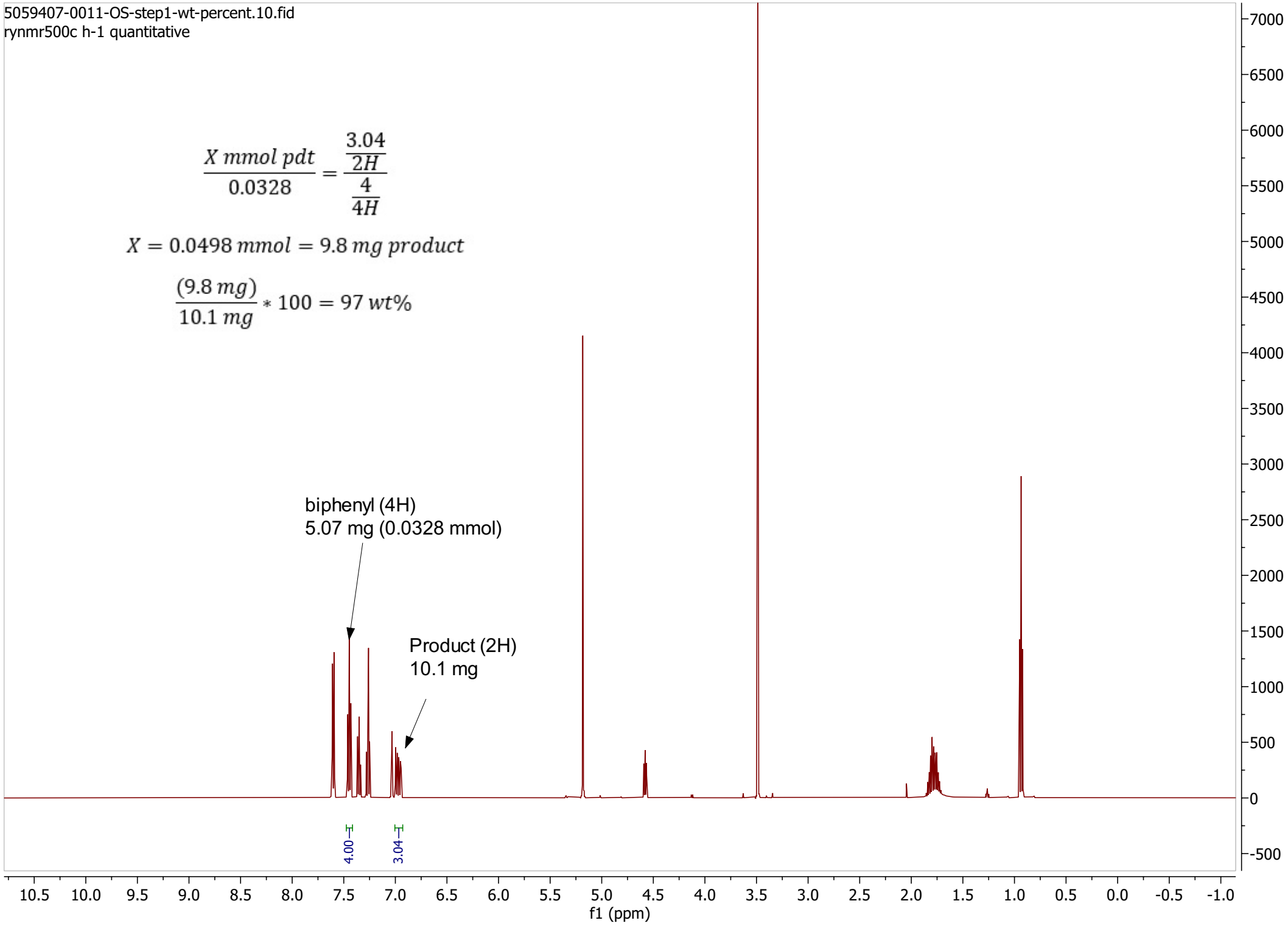
f1 (ppm)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$X = 0.0498\ mmol = 9.8\ mg\ product$
$\frac{(9.8\ mg)}{10.1\ mg} * 100 = 97\ wt\%$
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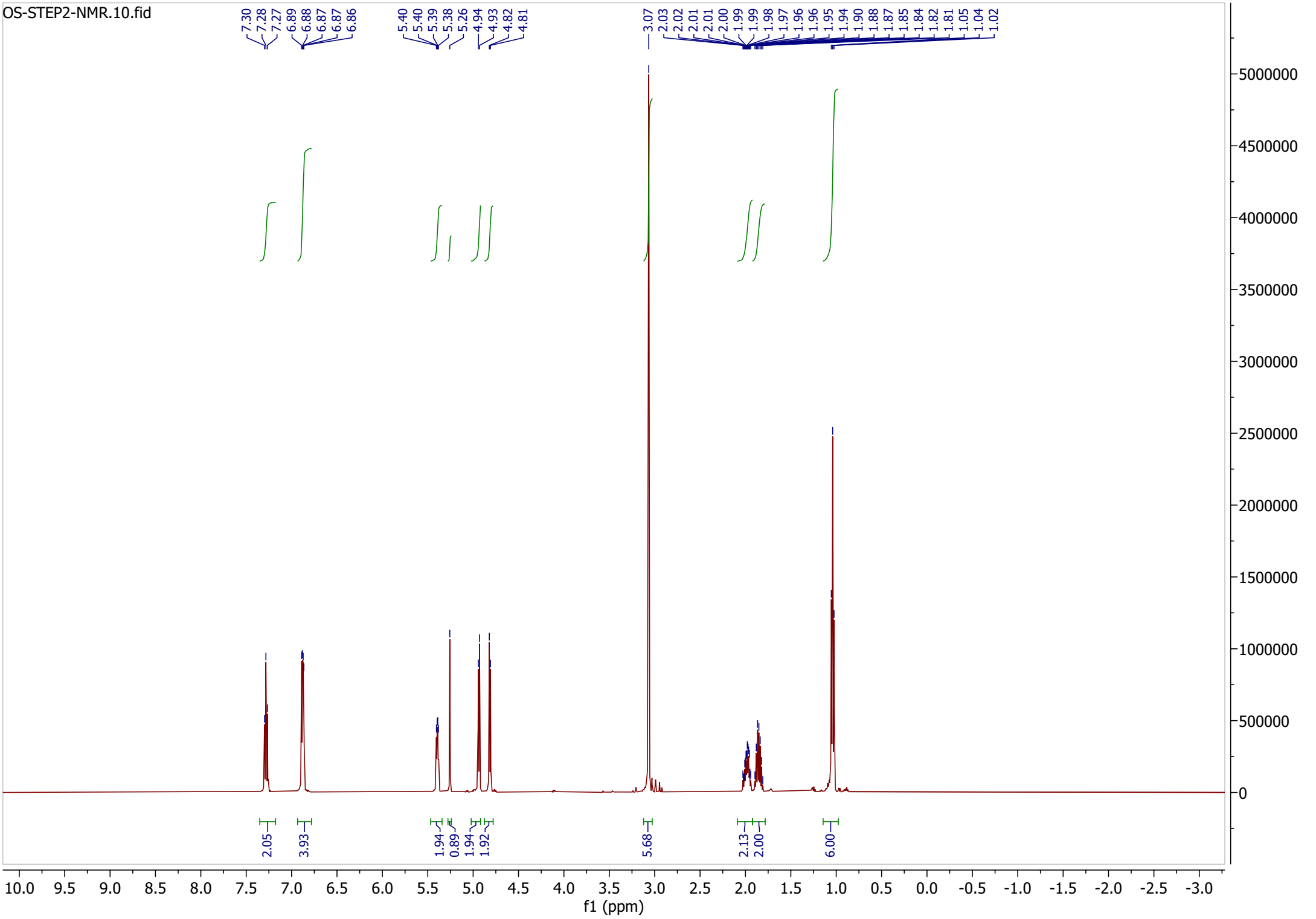
f1 (ppm)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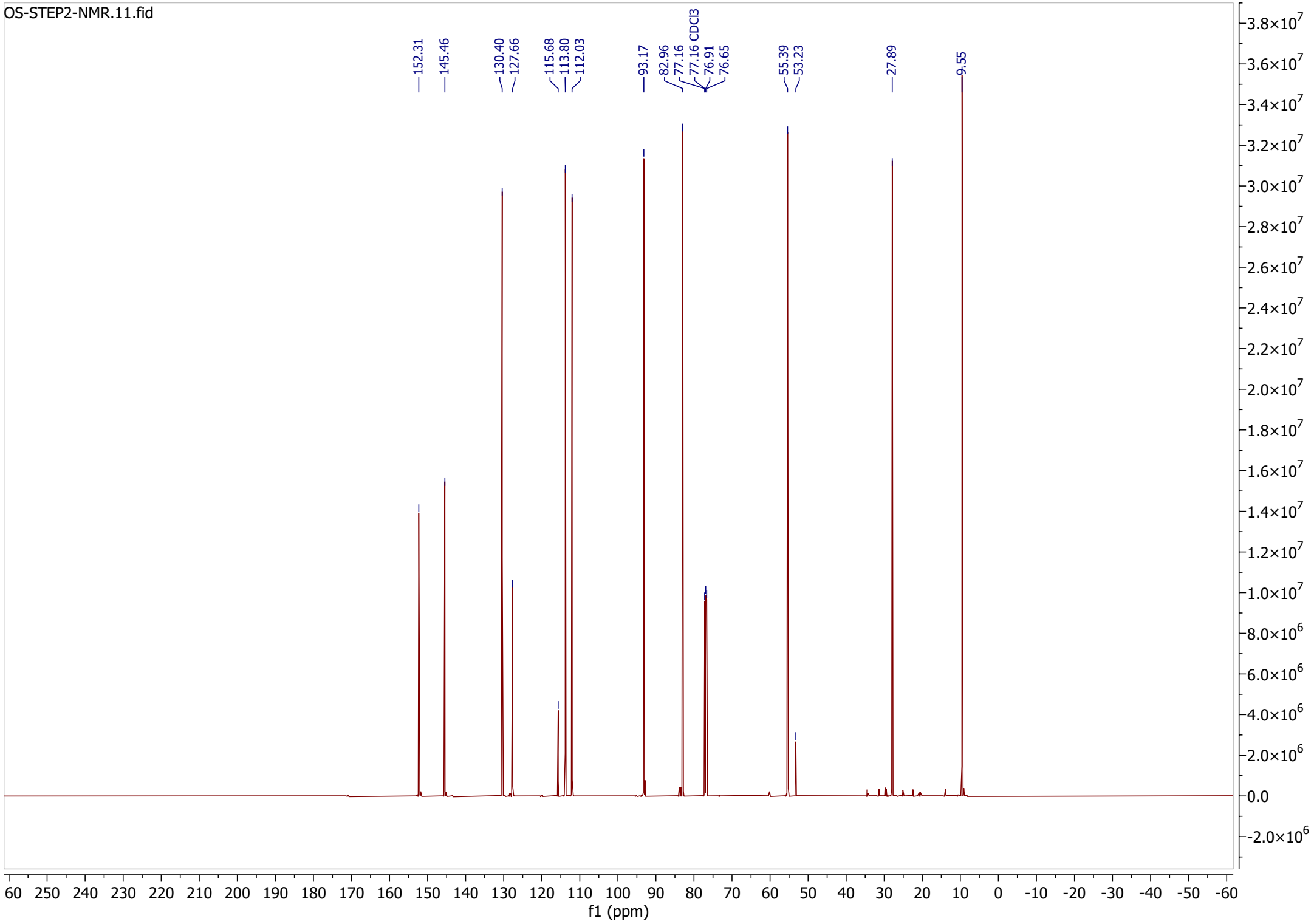
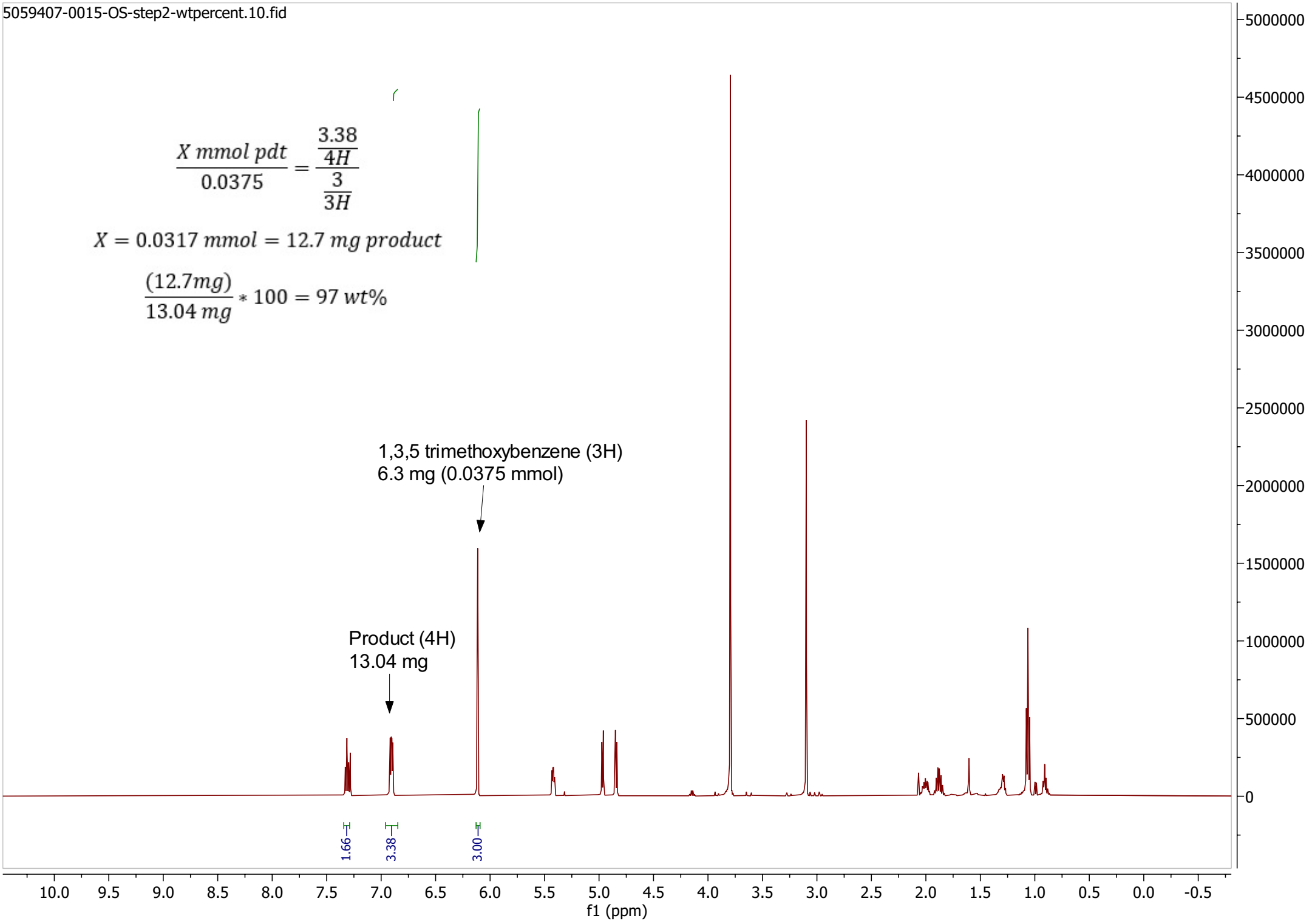
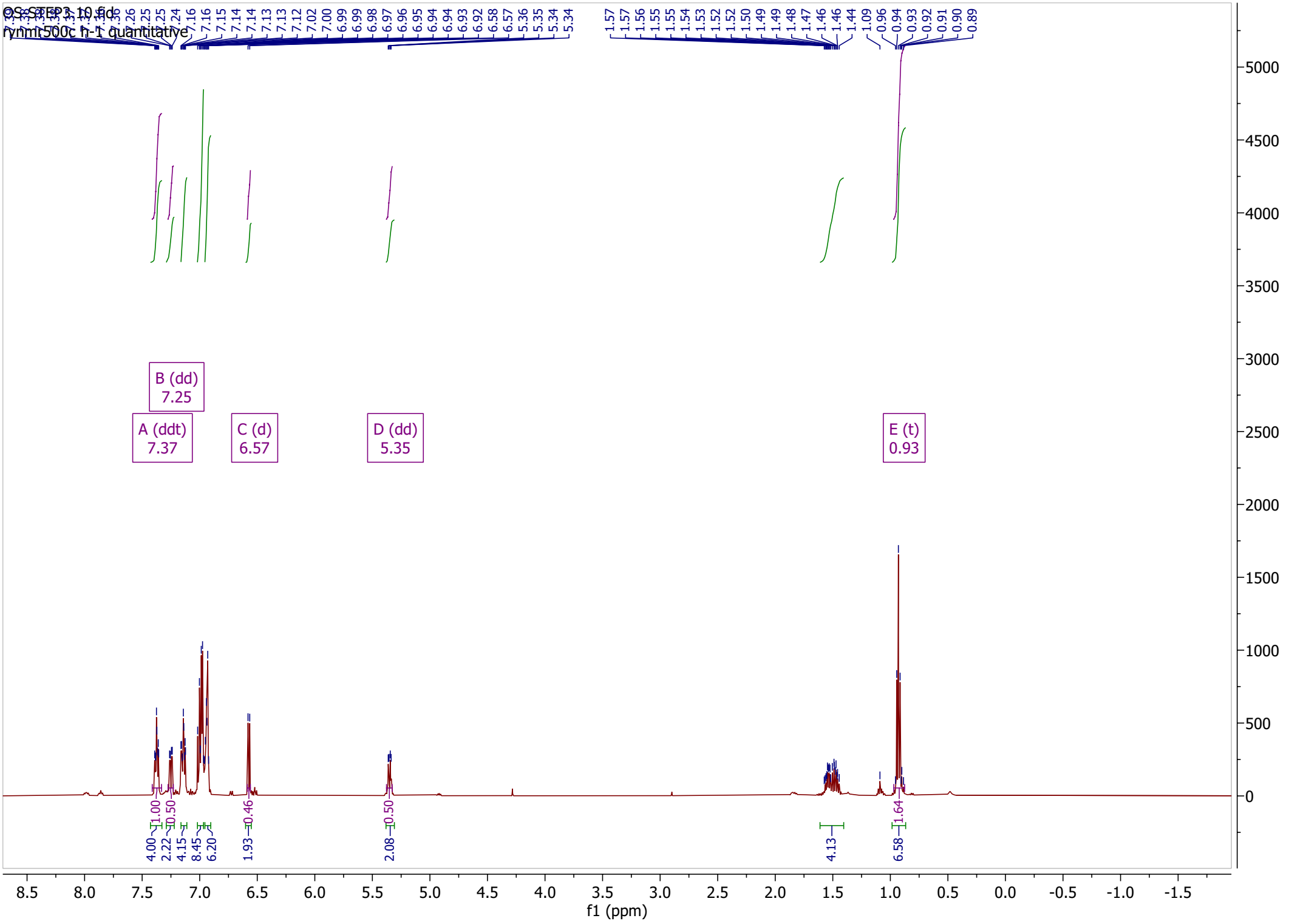
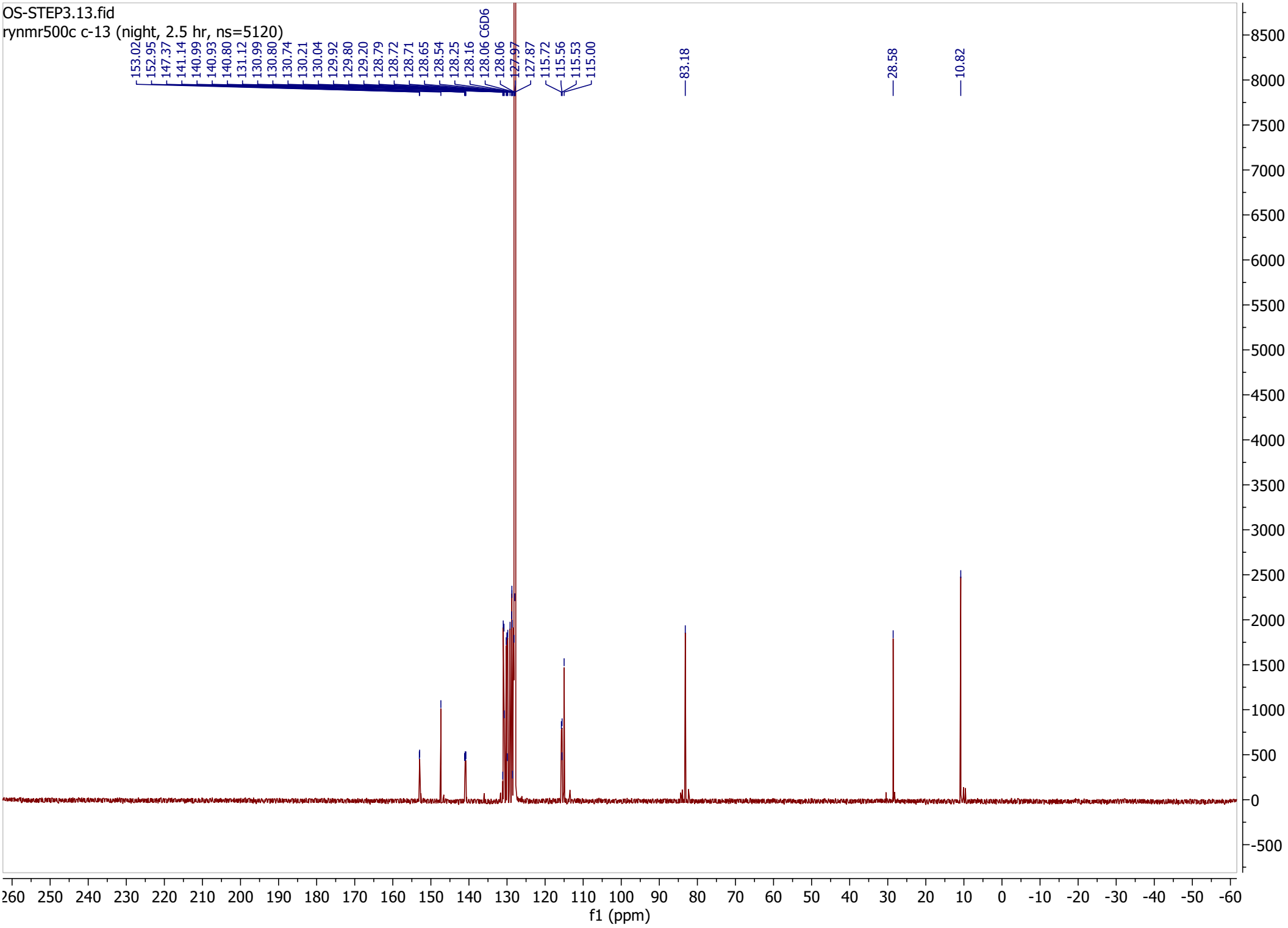
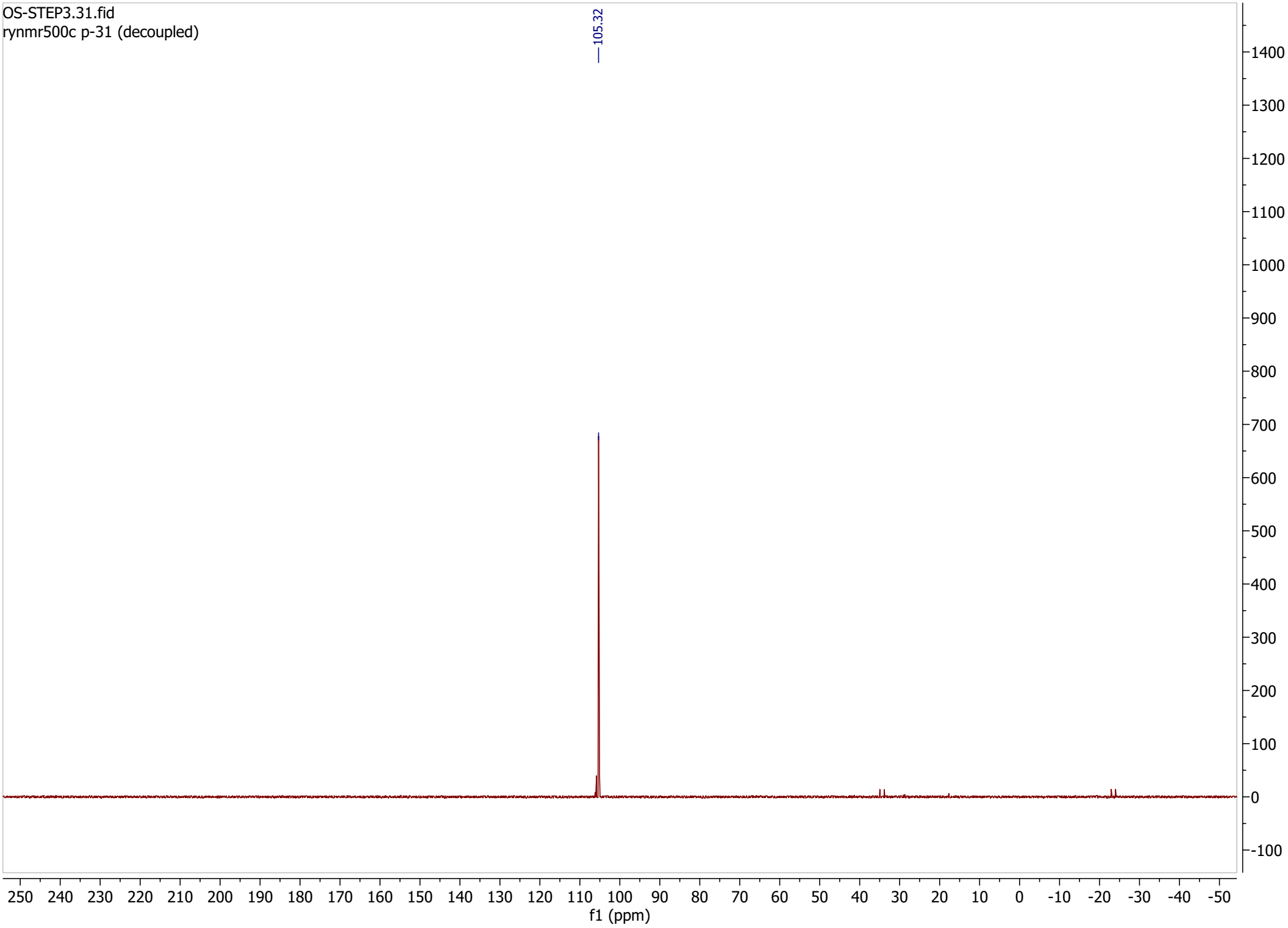
2.05 3.93 1.94 0.89 1.94 1.92 5.68 2.13 2.00 6.00
5000000 4500000 4000000 3500000 3000000 2500000 2000000 1500000 1000000 500000 0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0 -2.5 -3.0
f1 (ppm)

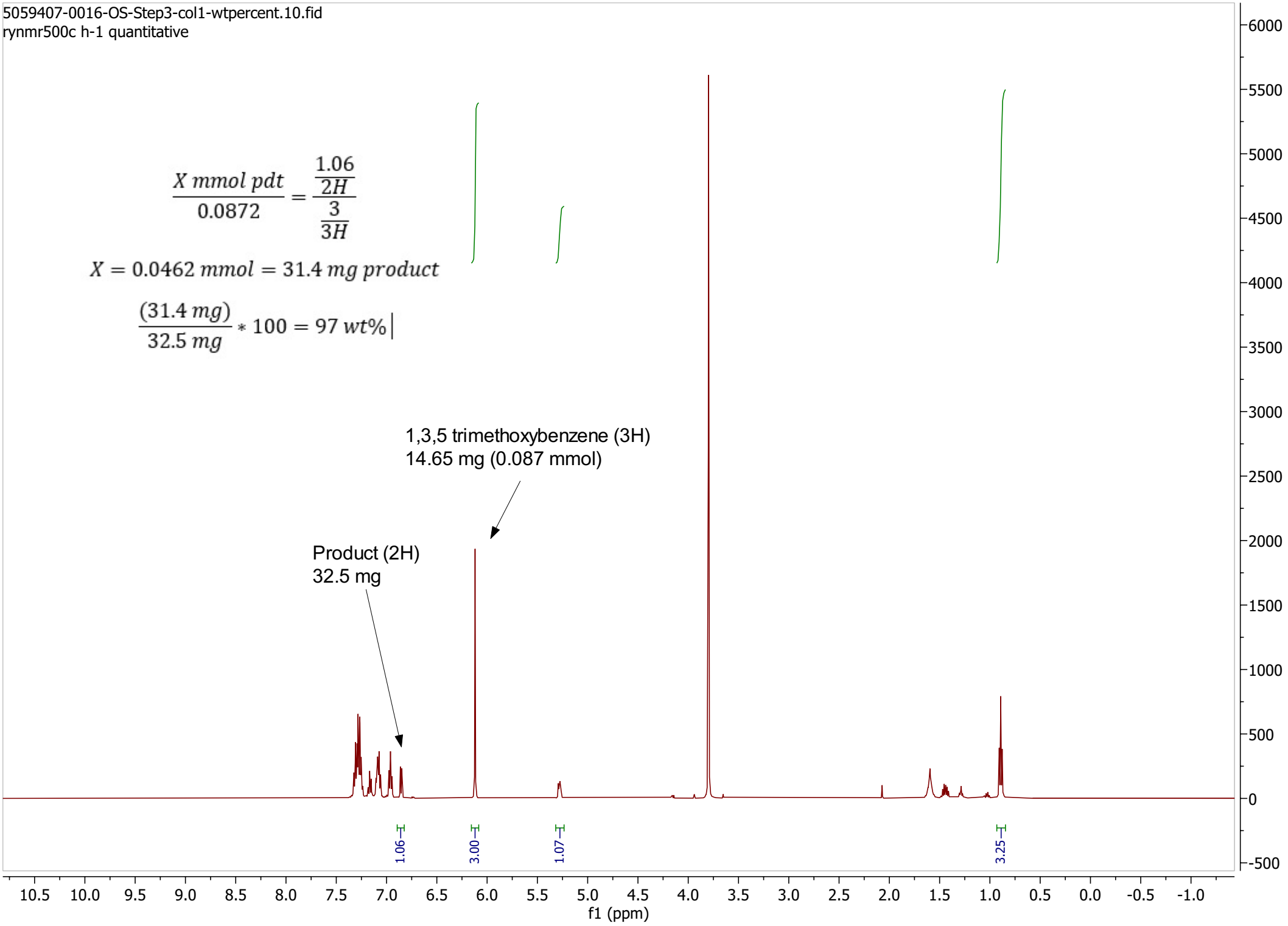

OS-STEP2-NMR.11.fid
152.31
145.46
130.40
127.66
115.68
113.80
112.03
93.17
82.96
77.16
77.16 CDCl3
76.91
76.65
55.39
53.23
27.89
9.55
3.8×10^7
3.6×10^7
3.4×10^7
3.2×10^7
3.0×10^7
2.8×10^7
2.6×10^7
2.4×10^7
2.2×10^7
2.0×10^7
1.8×10^7
1.6×10^7
1.4×10^7
1.2×10^7
1.0×10^7
8.0×10^6
6.0×10^6
4.0×10^6
2.0×10^6
0.0
-2.0×10^6
60 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60
f1 (ppm)


5059407-0015-OS-step2-wtpercent.10.fid
$\frac{X\ mmol\ pdt}{0.0375} = \frac{\frac{3.38}{4H}}{\frac{3}{3H}}$
$X = 0.0317\ mmol = 12.7\ mg\ product$
$\frac{(12.7mg)}{13.04\ mg} * 100 = 97\ wt\%$
1,3,5 trimethoxybenzene (3H)
6.3 mg (0.0375 mmol)
Product (4H)
13.04 mg
1.66
3.38
3.00
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


OS-STEP3-10.fid
rynmr500c h-1 quantitative
B (dd)
7.25
A (ddt)
7.37
C (d)
6.57
D (dd)
5.35
E (t)
0.93
4.00
1.00
2.22
0.50
4.15
8.45
6.20
1.93
0.46
2.08
0.50
4.13
6.58
1.64
f1 (ppm)


OS-STEP3.13.fid
rynmr500c c-13 (night, 2.5 hr, ns=5120)
153.02
152.95
147.37
141.14
140.99
140.93
140.80
131.12
130.99
130.80
130.74
130.21
130.04
129.92
129.80
129.20
128.79
128.72
128.71
128.65
128.54
128.25
128.16
128.06 C6D6
128.06
127.97
127.87
115.72
115.56
115.53
115.00
83.18
28.58
10.82
f1 (ppm)


OS-STEP3.31.fid
rynmr500c p-31 (decoupled)
105.32
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50
f1 (ppm)


5059407-0016-OS-Step3-col1-wtpercent.10.fid
rynmr500c h-1 quantitative
$\frac{X\ mmol\ pdt}{0.0872} = \frac{\frac{1.06}{2H}}{\frac{3}{3H}}$
$X = 0.0462\ mmol = 31.4\ mg\ product$
$\frac{(31.4\ mg)}{32.5\ mg} * 100 = 97\ wt\%$
1,3,5 trimethoxybenzene (3H)
14.65 mg (0.087 mmol)
Product (2H)
32.5 mg
1.06
3.00
1.07
3.25
f1 (ppm)