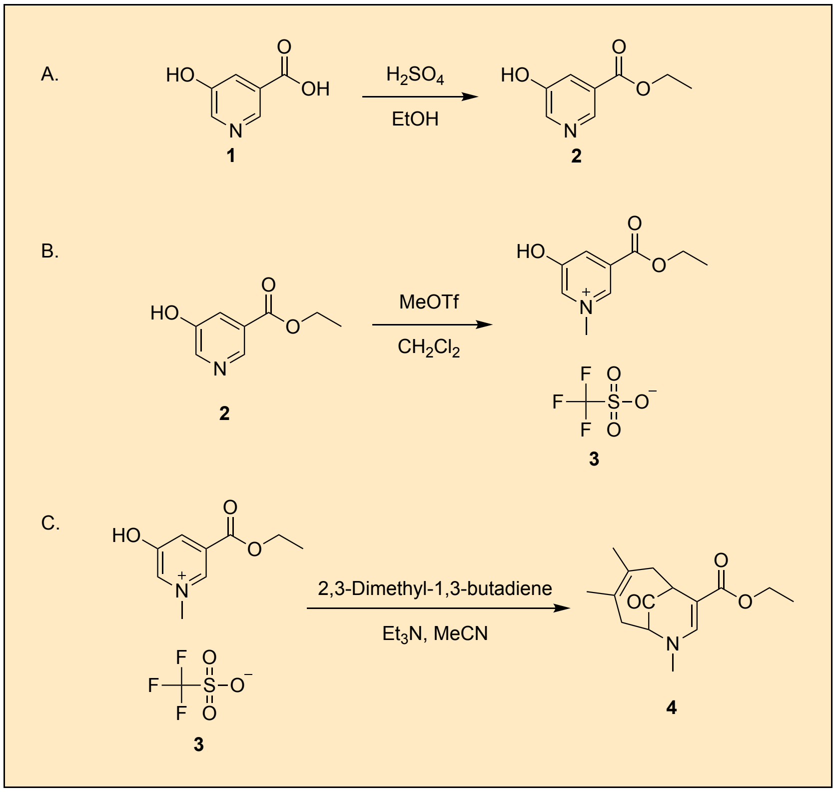
From 5-Hydroxynicotinic Acid to Nitrogenous (4+3)-Cycloadducts

Alexander S. Harmata and Michael Harmata*[1]

Department of Chemistry, University of Missouri-Columbia, MO 65211

Checked by Feng Peng and Kevin Campos



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Procedure (Note 1)

A. *Ethyl 5-hydroxynicotinate* (**2**). A 200 mL, single-necked recovery flask dried in a 120 °C oven and cooled in a desiccator is equipped with a Teflon-coated magnetic stir bar (20 x 6 mm, cylindrical). 5-Hydroxynicotinic acid (5.01 g, 36.0 mmol, 1.0 equiv) (Note 2) is added through a powder addition funnel, which is rinsed with absolute ethanol (20 mL, 343 mmol, 9.5 equiv) (Note 3). Upon stirring, this gives a white suspension. Sulfuric acid (2.0 mL, 37.5 mmol, 1.0 equiv) (Note 4) is carefully added in a two portions over 1 min via pipette (Note 5). The flask is immediately equipped with a condenser topped with a drying tube filled with Drierite (Note 6) and placed in an oil bath at 95–100 °C. Upon heating, most of the solids dissolve to produce a yellow solution. The mixture is refluxed with stirring for 18 h and monitored by TLC (Note 7). The solution is allowed to cool to 23 °C and is made basic by the careful addition over 10 min of saturated sodium bicarbonate solution (125 mL) (Note 8). A white solid precipitates during the addition. The mixture is transferred to a 500 mL separatory funnel and extracted with ethyl acetate (4 x 50 mL) (Note 9). The organic extracts are combined and dried over sodium sulfate (20 g) (Note 10) and vacuum-filtered into a pre-weighed 500 mL recovery flask through a fritted funnel. The sodium sulfate is washed with ethyl acetate (50 mL). The solvent is removed by rotary evaporation at 50 °C (150 to 75 mmHg) followed by evaporation at 23 °C under high vacuum (<1 mmHg) to give a white powder (4.42 g, 73%) (Notes 11, 12, and 13) (Figure 1).

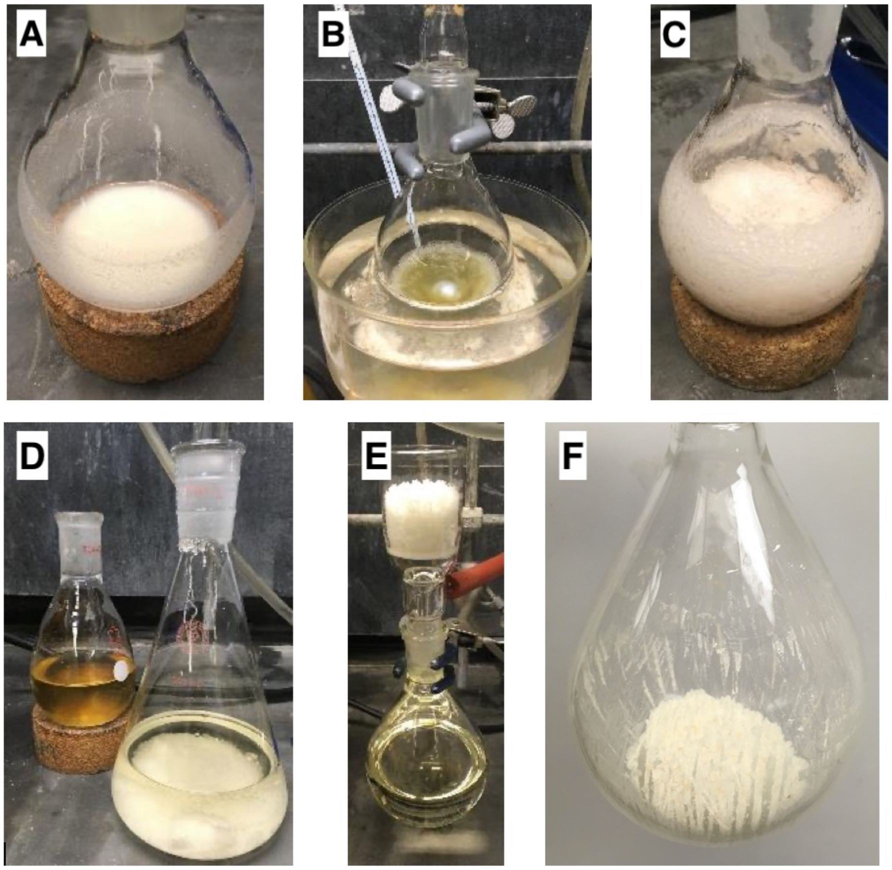


Figure 1. A) Suspension of 1 in ethanol; B) Refluxing reaction mixture; C) Precipitation during quenching with sodium bicarbonate solution; D) Aqueous phase (left) and organic phase (right) after extraction; E) Filtration of sodium sulfate from aqueous phase; F) Solid 2 after drying under high vacuum

B. *3-(Ethoxycarbonyl)-5-hydroxy-1-methylpyridin-1-ium trifluoromethanesulfonate (***3***)*. A 500 mL, single-necked recovery flask dried in a 120 °C oven and cooled in a desiccator is equipped with a Teflon-coated magnetic stir bar (20 x 6 mm, cylindrical) and **2** (4.44 g, 26.6 mmol, 1.0 equiv) is added via powder addition funnel. The flask is equipped with a rubber septum and put under argon (Note 14). Dichloromethane (100 mL) (Note 15) is added via syringe. Stirring of the solution at 500 rpm gives a white suspension. Methyl trifluoromethanesulfonate (3.00 mL, 26.5 mmol, 1.0 equiv) (Note 16) is added in one portion via syringe (*CAUTION*: Note 17), leading to the formation of a yellow solution within one minute of addition. A white solid precipitates from the solution within 10 min of addition and stirring becomes labored, but the stirring does not stop (Figure 2).

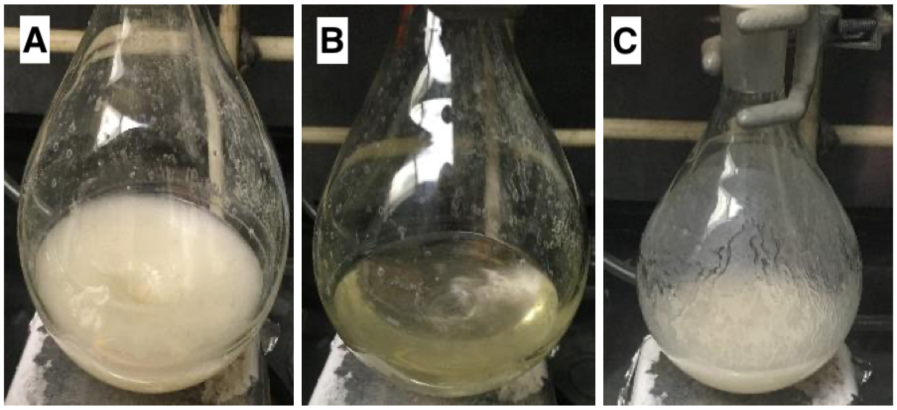


Figure 2. A) Suspension of 2 in dichloromethane; B) Homogeneous solution following addition of methyl trifluoromethanesulfonate; C) Precipitation of 3

The mixture is stirred for 4 h at 23 °C and monitored by TLC (Note 18). The septum is removed and pentane (50 mL) (Note 19) is added. The flask is placed in an ice bath and cooled for 30 min. The suspension is filtered within the same fume hood through a sintered glass funnel. The precipitate is washed once with pentane (50 mL) (Note 20). The filtered product is transferred to a pre-weighed 250 mL round-bottomed flask and further dried at 23 °C under high vacuum (<1 mmHg) to give a white solid (8.21 g, 95%) (Notes 21 and 22) (Figure 3).

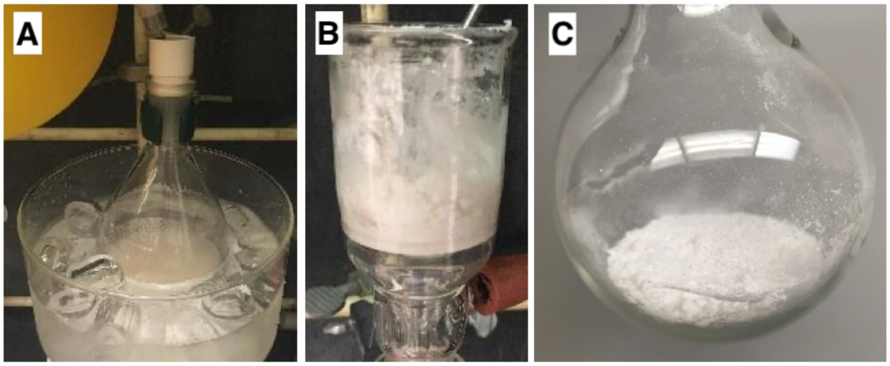


Figure 3. A) Cooling mixture in ice bath; B) Filtration of 2; C) Solid 2 after drying under high vacuum

C. *Ethyl 3,4,7-trimethyl-10-oxo-7-azabicyclo[4.3.1]deca-3,8-diene-9-carboxylate (**4**).* A 350 mL pressure tube (Note 23), dried in a 120 °C oven and cooled in a desiccator, is equipped with a Teflon-coated magnetic stir bar (20 x 6 mm, cylindrical). Using a powder addition funnel, **3** (6.66 g, 20.1 mmol, 1.0 equiv) is added to the tube and the funnel is rinsed with acetonitrile (100 mL) (Note 24). To the mixture is added 2,3-dimethyl-1,3-butadiene (11.4 mL, 100 mmol, 5.0 equiv) (Note 25) in one portion via syringe. Triethylamine (8.4 mL, 60 mmol, 3.0 equiv) (Note 26) is then added in one portion via syringe. Upon the addition of triethylamine, the solution becomes yellow. Immediately the tube is tightly sealed under air. The reaction vessel is placed behind a blast shield and placed in a silicone oil bath at 85–90 °C such that the level of the oil in the bath is the same as the level of solvent in the tube (Figure 4).

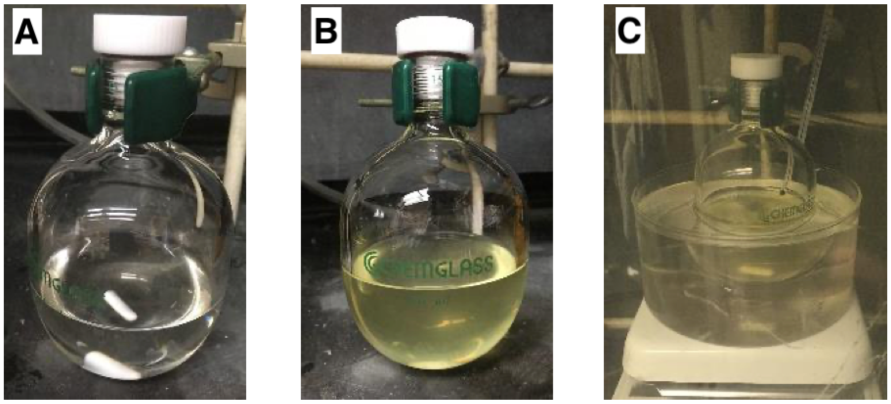


Figure 4. A) Solution of 3 and 2,3-dimethyl-1,3-butadiene in acetonitrile; B) Mixture after addition of triethylamine; C) Tube immediately after inserting into oil bath

The mixture is heated with stirring for 7 h and monitored by TLC (Note 27). The reaction mixture is allowed to cool to 23 °C and is transferred to a 500 mL separatory funnel and diluted with 0.5 M HCl (200 mL) (Note 28). The aqueous layer is extracted with dichloromethane (3 x 100 mL) and dried over sodium sulfate (40 g). The liquid is decanted from the sodium sulfate, which is rinsed with dichloromethane (50 mL), and the organic solvents are combined. A plug of silica gel (160 g, 18 cm x 5 cm) (Note 29) is equilibrated with dichloromethane (Note 30), and the dichloromethane solution is passed through the plug with positive pressure until the solvent level is at the height of the plug. The plug is rinsed with dichloromethane (700 mL). The combined filtrate is concentrated by rotary evaporation at 40 °C (400-200 mmHg) to remove the majority of the dichloromethane followed by rotary evaporation at 50 °C (200 to 75 mmHg). Further drying at 23 °C under high vacuum (<1 mmHg) gives a light yellow solid (3.94 g, 75%) (Notes 31, 32, and 33) (Figure 5).

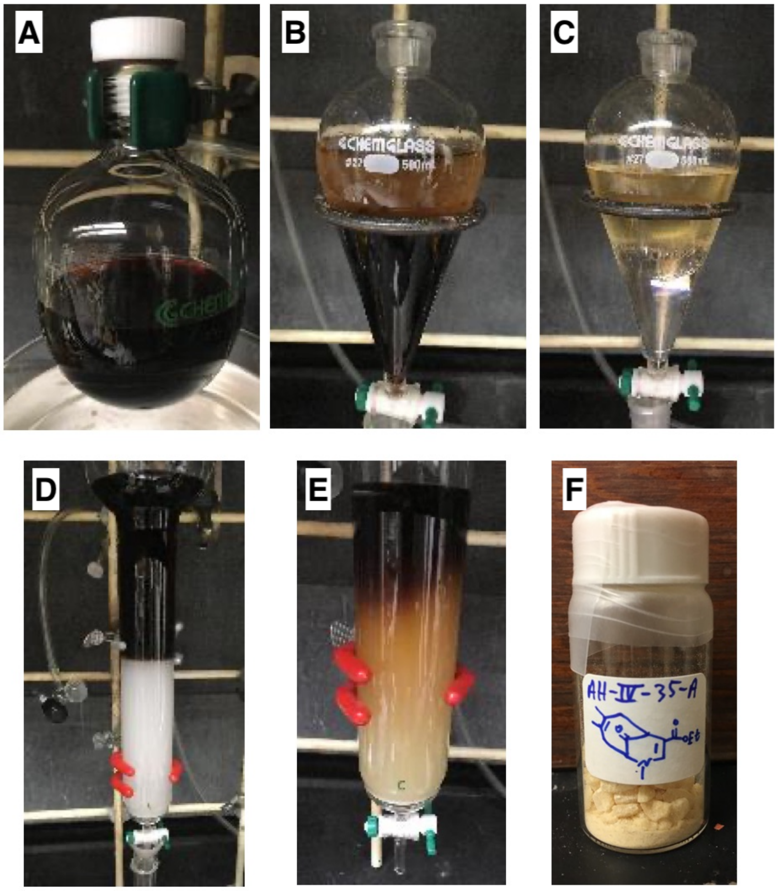


Figure 5. A) Reaction vessel after cooling; B) First extraction with dichloromethane; C) Third extraction with dichloromethane; D) Silica plug before elution; E) Silica plug after elution; F) Solid 3 after drying under high vacuum

Notes

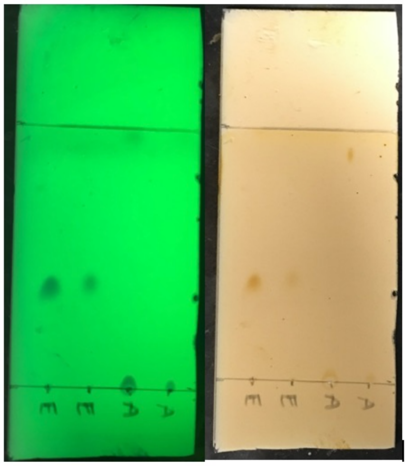
1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for

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 5-Hydroxynicotonic acid, ethanol, sulfuric acid, Drierite, sodium bicarbonate, ethyl acetate, sodium sulfate, dichloromethane, methyl trifluoromethanesulfonate, pentane, acetonitrile, 2,3-dimethyl-1,3-butadiene, triethylamine, hydrochloric acid, and silica gel. The cycloaddition is performed approximately 20 °C above boiling point of 2,3-dimethyl-1,3-butadiene, so the use of a pressure tube is advantageous. While the pressure in the tube is not expected to be dangerously high, the reaction should be performed behind a blast shield. Particular care must be taken with the handling of the volatile alkylating agent methyl trifluoromethanesulfonate, as it is suspected to be acutely toxic to humans by inhalation, absorption through skin, and other routes of exposure. The related compound methyl fluoromethanesulfonate ("Magic Methyl") has been blamed for at least one human fatality by pulmonary edema.[2] Methyl trifluoromethanesulfonate should only be handled in a functional fume hood and with all due caution. Syringes, needles, and filtrates contaminated with methyl trifluoromethanesulfonate should be quenched in the same hood in which they were used with a solution of diethylamine or triethylamine in dichloromethane.

2. 5-Hydroxynicotinic acid (97%) was purchased from Ambeed, Inc. and used as received.
3. Ethanol (200 proof) was purchased from Decon Labs, Inc. and used as received. KF < 500 ppm is recommended.
4. Sulfuric Acid (96.4% w/w) was purchased from Fisher Scientific and used as received.
5. Addition of sulfuric acid is exothermic, and the checkers noted an exotherm of 20 °C when adding the sulfuric acid over a period of

1 minute as described in Step A. If the reaction is performed on larger scales, addition over a 1 minute period may be inappropriate.

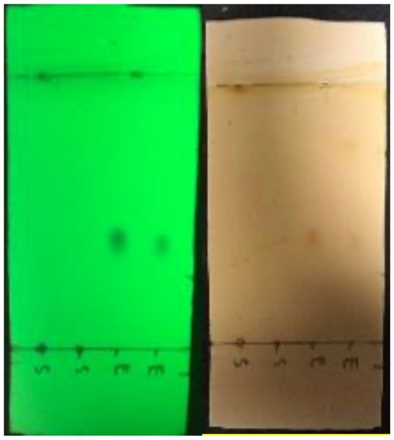
6. Drierite (10-20 mesh) was purchased from W.A. Hammond Drierite Company, Ltd. and used as received.
7. TLC was performed using 50% ethyl acetate in hexane as eluent. Starting material and product can be visualized under UV lamp and with an iodine stain. The starting material has R_f = 0.03 (pink under UV) and the product has R_f = 0.37 (pink under UV).



8. Sodium bicarbonate (100%) was purchased from Fischer Chemical and was shaken with less than 8 mL of deionized water per gram. After settling for several days, the supernatant was decanted to give a saturated solution of sodium bicarbonate.
9. Ethyl acetate (99.9%) was purchased from Fisher Chemical and used as received.
10. Sodium sulfate (99.32%) was purchased from Chem-Impex International and used as received.
11. The product has been characterized as follows: mp 135–136 °C; ^{1}H NMR (500 MHz, DMSO-*d6*) δ : 1.33 (t, *J* = 7.1 Hz, 3H); 4.33 (q, *J* = 7.1 Hz, 2H), 7.61 (dd, *J* = 2.7, 1.9 Hz, 1H), 8.36 (d, *J* = 2.7 Hz, 1H), 8.50 – 8.63 (m, 1H), 10.39 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d6) δ : 14.5, 61.6, 122.3, 126.8, 141.1, 142.8, 154.1, 165.3; FTIR (cm^{-1}) 3014, 2991, 2921, 1719, 1584, 1444, 1299, 1211, 1100, 1024; ESI [M + H] *m/z* calcd for $(C_8H_9NO_3)H^+$ 168.06552,

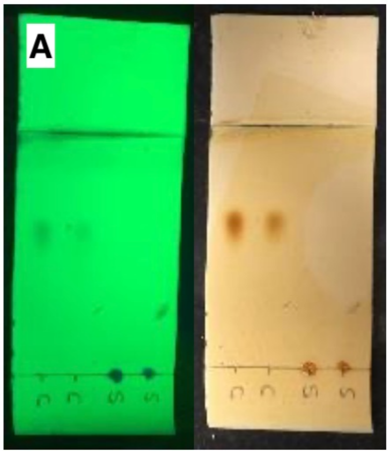
found 168.06555. A second run on scale gave 4.35 g (72%) of compound **2** as a white solid.

12. Compound **2** (25.7 mg) and 1,3,5-trimethoxybenzene (17.9 mg) (99%) were dissolved in 3 mL of DMSO-*d6*. An aliquot of 0.5 mL of this solution was analyzed. Quantitative ^{1}H NMR comparison of the peak from **2** at 1.33 ppm (3H) with the peak from 1,3,5-trimethoxybenzene at 6.21 ppm (3H) gave a 97.9 % purity by weight.
13. Commercially available ethyl 5-hydroxynicotinate works equally as well as freshly prepared ester in downstream chemistry.
14. Balloons containing a total of 5 liters of argon were used to displace the air in the flask and the flask was maintained under an argon atmosphere with a balloon.
15. Dichloromethane (99.9%) was purchased from Fisher Chemical and distilled from calcium hydride before use. The use of dry dichloromethane is recommended, KF < 200 ppm.
16. Methyl trifluoromethanesulfonate (98%) was purchased from CombiBlocks and used as received.
17. Addition of the volatile, toxic alkylating methyl trifluoromethanesulfonate is exothermic (checkers observed an exotherm of 10 °C) and addition in one portion may be inappropriate on larger scales than that described. Familiarity with the hazards of methyl trifluoromethanesulfonate is necessary. A thorough hazard analysis should be performed before using this reagent.
18. TLC was performed using 50% ethyl acetate in hexane as eluent. Starting material and product can be visualized under UV lamp and with an iodine stain. The starting material has $R_f = 0.37$ (pink under UV) and the product has $R_f = 0.00$ (pink under UV).

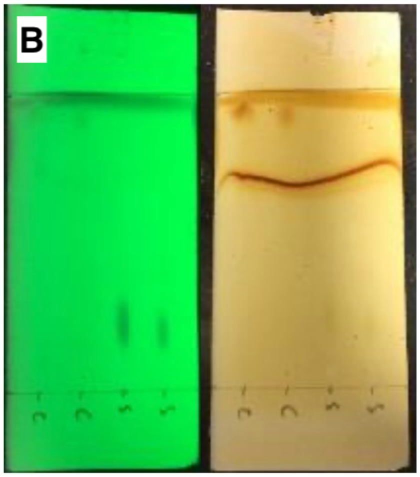


19. Pentane (98%) was purchased from Fisher Chemical and used as received.
20. The filtrate was treated with triethylamine (1 mL) to quench any unreacted methyl trifluoromethanesulfonate.
21. The product has been characterized as follows: mp 132–133 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ : 1.36 (t, *J* = 7.1 Hz, 3H); 4.34 (s, 3H), 4.42 (q, *J* = 7.1 Hz, 2H), 8.18 (s, 1H), 8.69 (s, 1H), 8.97 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ : 13.9, 48.2, 62.5, 116.8, 119.4, 121.9, 124.5, 130.2, 136.3, 137.5, 157.6, 161.8. FTIR (cm^{-1}) 3072, 1732, 1647, 1490, 1347, 1287, 1160.; HRMS [M +] *m/z* calcd for $C_9H_{12}NO_3$: 182.0817. Found: 182.0824. A second run gave 8.35 g (95%) of compound **3** as a white powder.
22. Compound **3** (53.6 mg) and 32.3 mg of 1,3,5-trimethoxybenzene (99%) were dissolved in 5 mL of DMSO-d_6. Quantitative ^{1}H NMR comparison of the peak from **3** at 4.34 ppm (3H) with the peak from 1,3,5-trimethoxybenzene at 6.21 ppm (3H) gave a 99.0% purity by weight.
23. The heavy wall pressure vessel was purchased from Chemglass (CG-1880-45).
24. Acetonitrile was purchased from Fisher Chemical and distilled from calcium hydride before use.
25. 2,3-Dimethyl-1,3-butadiene (98% containing 100 ppm BHT as stabilizer) was purchased form Alfa Aesar and used as received. It is used in significant excess to ensure complete consumption of the oxidopyridinium.
26. Triethylamine (99.5%) was purchased from Sigma-Aldrich and distilled under argon from calcium hydride before use.

27. TLC was performed using 50% ethyl acetate in hexane as eluent (Figure A). Starting material and product can be visualized under UV lamp and with an iodine stain. The starting material has R$_f$ = 0.00 (pink under UV) and the product has R$_f$ = 0.58 (pink under UV).



TLC was also performed using 15% methanol in dichloromethane as eluent (Figure B). Starting material and product can be visualized under UV lamp and with an iodine stain. The starting material has R$_f$ = 0.25 (pink under UV) and the product has R$_f$ = 0.95 (pink under UV).



28. Concentrated hydrochloric acid (36.5-38% w/w) was purchased from Fisher Chemical and added to deionized water to a concentration of 0.5 M.
29. Silica gel (40-63 micron) was purchased from Zeochem and used as received.
30. Dichloromethane (99.9%) was purchased from Fischer Chemical and used as received.
31. If evaporation provides a thick oil, scratching of the oil with a glass rod or cooling of the oil for several hours in a –20 °C freezer can lead to nucleation and the isolation of the product as a solid.
32. The product has been characterized as follows: mp 80–81 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ : 1.22 (t, *J* = 7.1 Hz, 2H), 1.79 (s, 3H), 1.62 (s, 3H), 2.14 (d, *J* = 14.6 Hz, 1H), 2.24 (d, *J* = 15.5 Hz, 1H), 2.64 (td, *J* = 15.2, 14.7, 7.2 Hz, 2H), 2.92 (s, 3H), 3.43 (d, *J* = 6.9 Hz, 1H), 3.57 (dd, *J* = 7.0, 2.1 Hz, 1H), 4.02 – 4.18 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ : 14.6, 23.2, 23.5, 36.8, 38.1, 40.2, 45.7, 59.0, 66.2, 92.6, 125.2, 132.3, 146.7, 167.1, 206.7; FTIR (cm^{-1}) 3025, 2939, 2854, 1721, 1671, 1620, 1604; ESI [M + H] *m/z* calcd for $C_8H_9NO_3$: 264.1599. Found: 264.1613 A second run on 6.66 g scale gave 3.83 g (73%) of compound **4** as a light yellow solid.
33. Compound **4** (37.1 mg) and 1,3,5-trimethoxybenzene (99%) (21.5 mg) were dissolved in 5 mL of $CDCl_3$. Quantitative ^{1}H NMR comparison of the peak from **4** at 2.94 ppm (3H) with the peak from 1,3,5-trimethoxybenzene at 6.17 ppm (3H) gave a 98.0% purity by weight.

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.

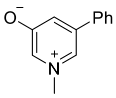
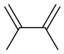
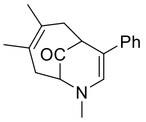
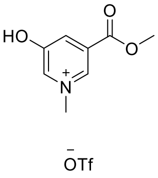
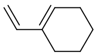
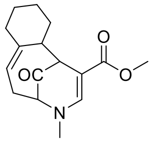
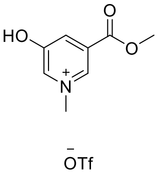
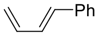
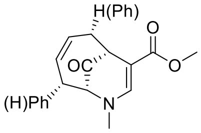
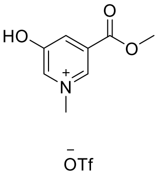
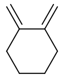
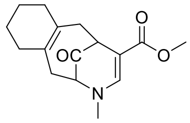
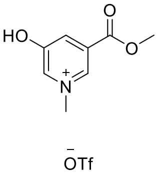
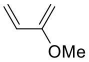
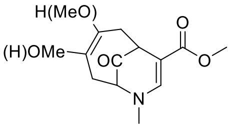
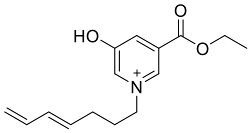
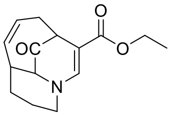
Discussion

Before our 2017 work,[3] the published (4+3) cycloaddition chemistry of oxidopyridinium ions with conjugated dienes was largely restricted to ions bearing aryl or alkenyl substitution on nitrogen.[4,5] These groups serve to further delocalize the lone pair of electrons that emerges on the nitrogen in the course of the reaction, helping to favor the (4+3) cycloaddition over competing pathways. However, a single example published by Katritzky[6] showed how an *N*-alkyl oxidopyridinium can show (4+3) reactivity enabled by delocalization not with nitrogen substitution, but with a vinylogous phenyl group (Table 1, Entry 1). We replaced the phenyl group from Katritzky's work with a superior electron withdrawing group, an ester, and observed a drastic improvement in (4+3) cycloaddition reactivity. The ester group also provides a functional handle that may prove useful in the synthesis of natural products or molecular libraries. The scope of the reaction with a variety of dienes was explored, in some cases demonstrating regioselectivity and/or diastereoselectivity (Table 1, Entries 2, 3, 5, and 6). We have also published an intramolecular example of this reaction, generating a particularly complex polycyclic structure (Table 1, Entry 6). The reversibility of the reaction is diene dependent, with 1-phenylbutadiene being readily displaced from its cycloaddition product by 2,3-dimethyl-1,3-butadiene under the reaction conditions. Symmetrical 2,3-disubstituted dienes show the best behavior, reacting in high yield to give a single product (Table 1, Entry 4).

In this work, we report a high-yielding and simple procedure for the preparation of **4**. Over three steps from cheap commercial materials, **4** can be synthesized in analytical quality with a single silica gel plug purification and without recrystallization, distillation, or sublimation. The excess of diene was reduced from our typical condition of ten equivalents to five equivalents to demonstrate the feasibility of this chemistry on larger scales where excesses can complicate separations and become cost prohibitive.

The (4+3) cycloaddition of ester-bearing *N*-alkyl oxidopyridinium salts is a robust, convergent method to generate the 7-azabicyclo[4.3.1]decane ring system found in several natural products, and this procedure should provide sufficient material for extensive elaboration. New functionalized oxidopyridinium salts and the chemistry of the cycloadducts are being explored in our laboratory and will be reported in due course.

Table 1. Selected examples demonstrating scope

Entry	Oxidopyridinium Salt/Betaine	Diene	Conditions	Product(s)	Yield
1			A		28%
2			B		99% (1:1.7)
3			B		86% (10:1)
4			B		90%
5			B		70% (1:1.5)
6		NA	C		84% (1:1.9)

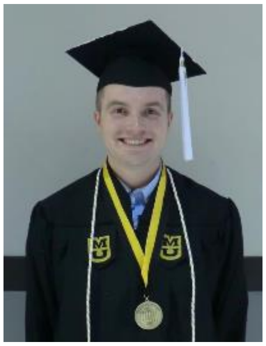
Conditions: A) 4 equiv diene, THF, 0.4 M, 40-45 °C B) 10 equiv diene, 3 equiv Et_3N, MeCN, 0.1 M, 80-85 °C
C) 3 equiv Et_3N, MeCN, 0.05 M, 80-85 °C

References

1. Michael Harmata: Department of Chemistry, University of Missouri-Columbia, 125 Chemistry Building, 601 S College Ave, Columbia, MO 65211. Email: HarmataM@missouri.edu. Alexander S. Harmata: Department of Chemistry, University of Michigan, Willard H. Dow Chemistry & Laboratory, 930 University Ave, Ann Arbor, MI 48109. Email: harmataa@umich.edu. This work was supported by the National Science Foundation.
2. van der Ham, D. M. W.; van der Meer, D. *Chem. Eng. News*, **1976**, 54, *36*, 5.
3. Fu, C.; Lora, N.; Kirchoefer, P. L.; Lee, D. R.; Altenhofer, E.; Barnes, C. L.; Hungerford, N. L.; Krenske, E. H.; Harmata, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 14682–14687.
4. Dennis, N.; Ibrahim, B.; Katritzky, A. R. *J. Chem. Soc. Chem. Commun.* **1975**, 425–427.
5. Dennis, N.; Ibrahim, B.; Katritzky, A. R. *J. Chem. Soc. Perkins Trans. 1*, **1976**, 2307–2328.
6. Dennis, N.; Katritzky, A. R.; Rittner, R. *J. Chem. Soc. Perkins Trans. 1*, **1976**, 2329–2334.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

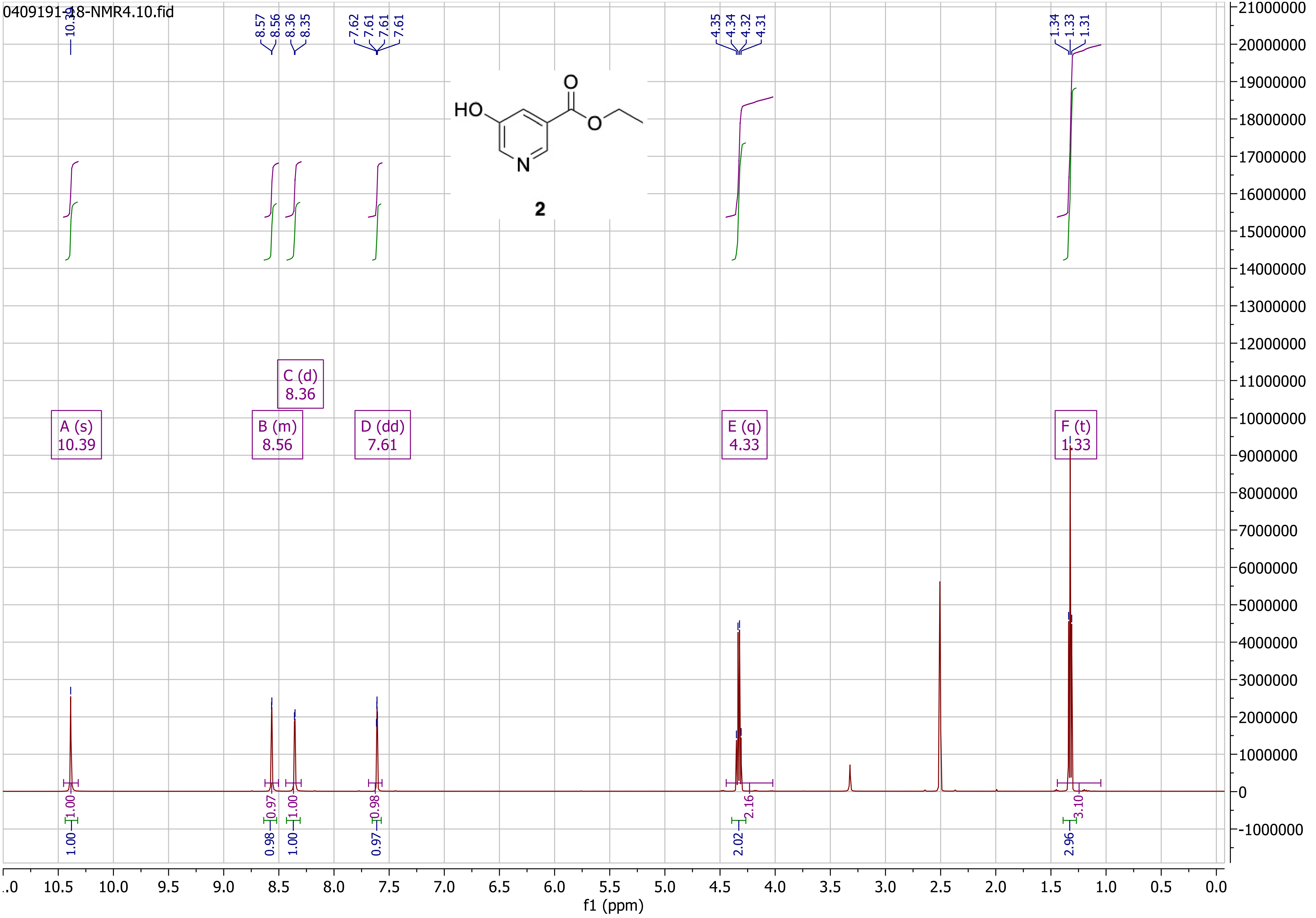
5-Hydroxynicotinic acid: 5-Hydroxypyridine-3-carboxylic acid; (27828-71-3)
Sulfuric acid: Sulfuric acid; (7664-93-9)
Drierite: Calcium sulfate; (7778-18-9)
Sodium bicarbonate: Sodium bicarbonate; (144-55-8)
Sodium sulfate: Sodium sulfate; (7757-82-6)
Methyl trifluoromethanesulfonate: Methyl trifluoromethanesulfonate; (333-27-7)
2,3-Dimethyl-1,3-butadiene: 2,3-Dimethyl-1,3-butadiene; (513-81-5)
Triethylamine: *N,N*-Diethylethanamine; (121-44-8)
Hydrochloric acid: Hydrochloric acid; (7647-01-0)



Alexander S. Harmata was born in Columbia, Missouri. He received his bachelor's degree in chemistry from the University of Missouri in the spring of 2019. He began graduate studies in chemistry at the University of Michigan in the fall of 2019 and is a researcher in the laboratory of Professor Corey Stephenson at the time of this publication.

Michael Harmata was born in Chicago, Illinois and lived on the south side of Chicago for the first 20 years of his life. He received a bachelor's degree from the University of Illinois-Chicago and earned his Ph.D. with Scott Denmark at UIUC. He then headed west to do an NIH postdoctoral fellowship with Paul Wender at Stanford University. He started doing his own thing in 1986 at the University of Missouri Columbia, where he is now the Norman Rabjohn Distinguished Professor of Chemistry.

Feng Peng joined the Process Research Department of Merck & Co., Inc. in 2012. His research focuses on using state-of-art organic chemistry to address critical problems in drug development. He received his B.S. degree from Beijing Normal University. He obtained his M.S. under the supervision of Professor Dennis Hall at University of Alberta with a research focus on Boron Chemistry. Feng then moved to New York City, where he obtained Ph.D. in the area of total synthesis (maoecrystal V) with Professor Samuel Danishefsky at Columbia University.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7.61
7.61
7.61
4.35
4.34
4.32
4.31
1.34
1.33
1.31
HO
O
O
N
A (s)
10.39
B (m)
8.56
C (d)
8.36
D (dd)
7.61
E (q)
4.33
F (t)
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1.00
0.97
0.98
1.00
1.00
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0.97
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2.02
3.10
2.96
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18000000
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16000000
15000000
14000000
13000000
12000000
11000000
10000000
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8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
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8.0
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5.5
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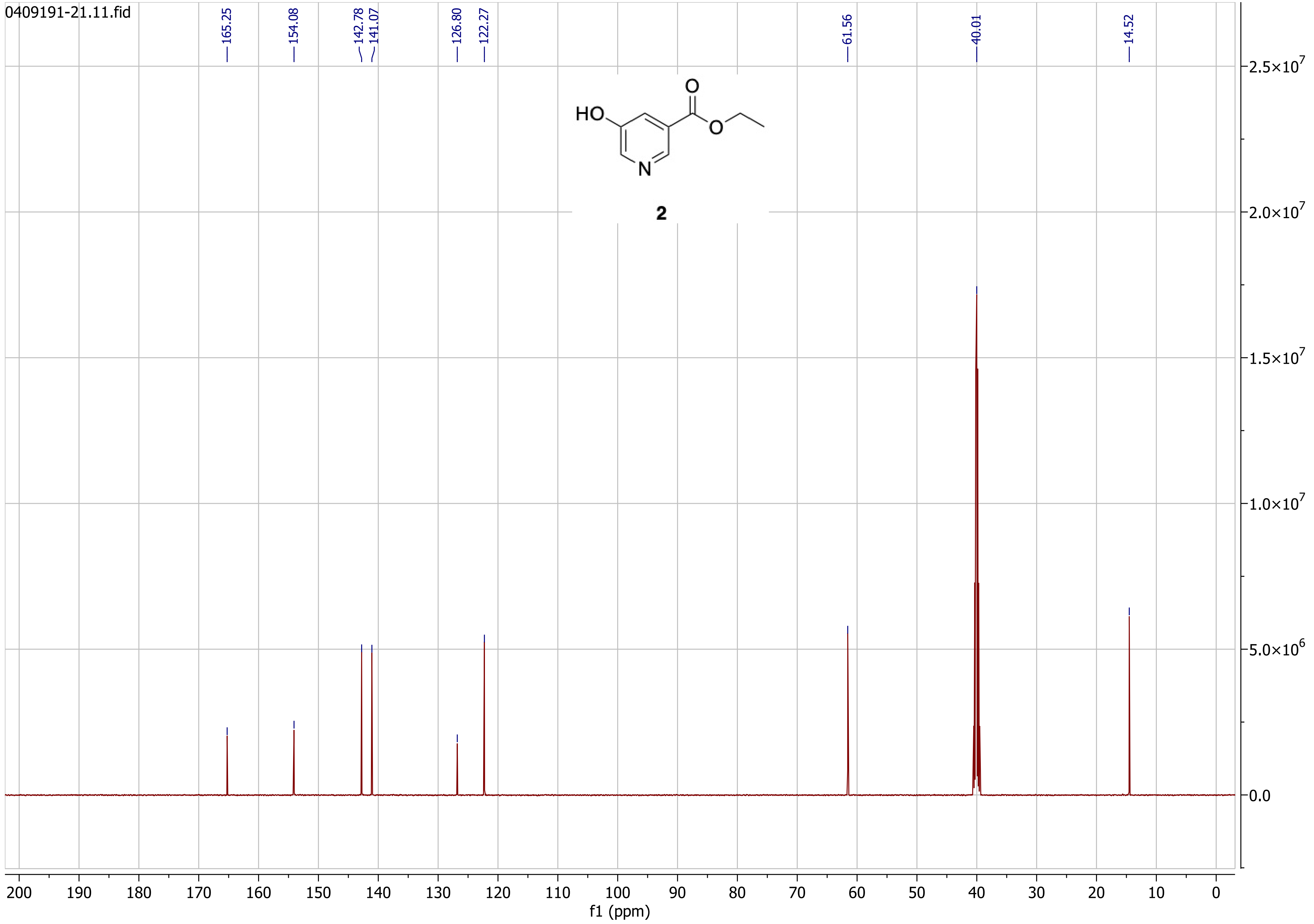
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O
N
2
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2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
200
190
180
170
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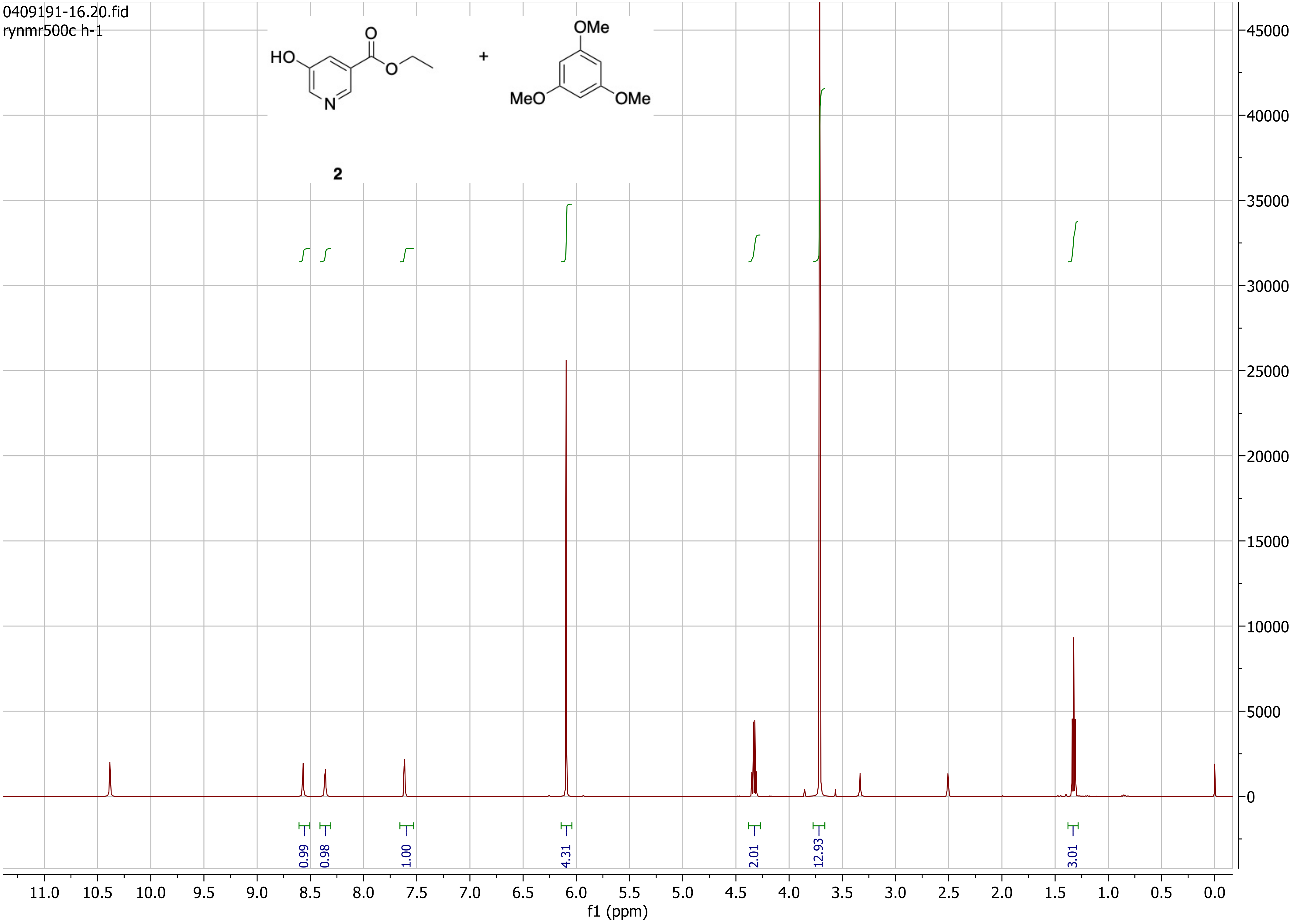
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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+
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9.0
8.5
8.0
7.5
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6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
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35000
30000
25000
20000
15000
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5000
0


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4.42
4.40
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1.38
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1.35
HO
O
O
N+
F
F
F
S
O
O
O−
3
A (s)
8.97
B (s)
8.69
C (s)
8.18
D (q)
4.42
E (s)
4.34
F (t)
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18000000
17000000
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12000000
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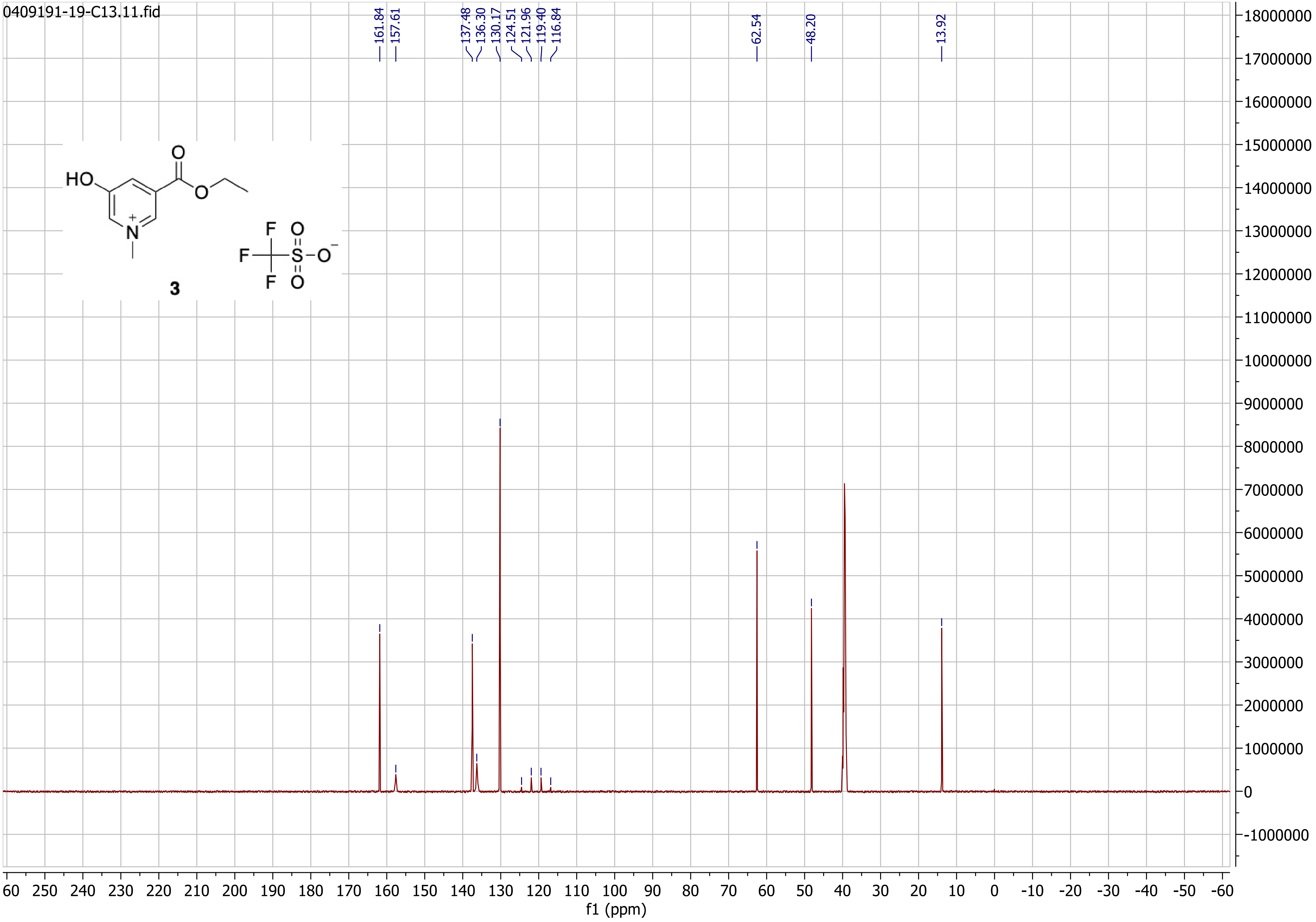
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O
N
+
F
F
F
S
O
O
O
−
3
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15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
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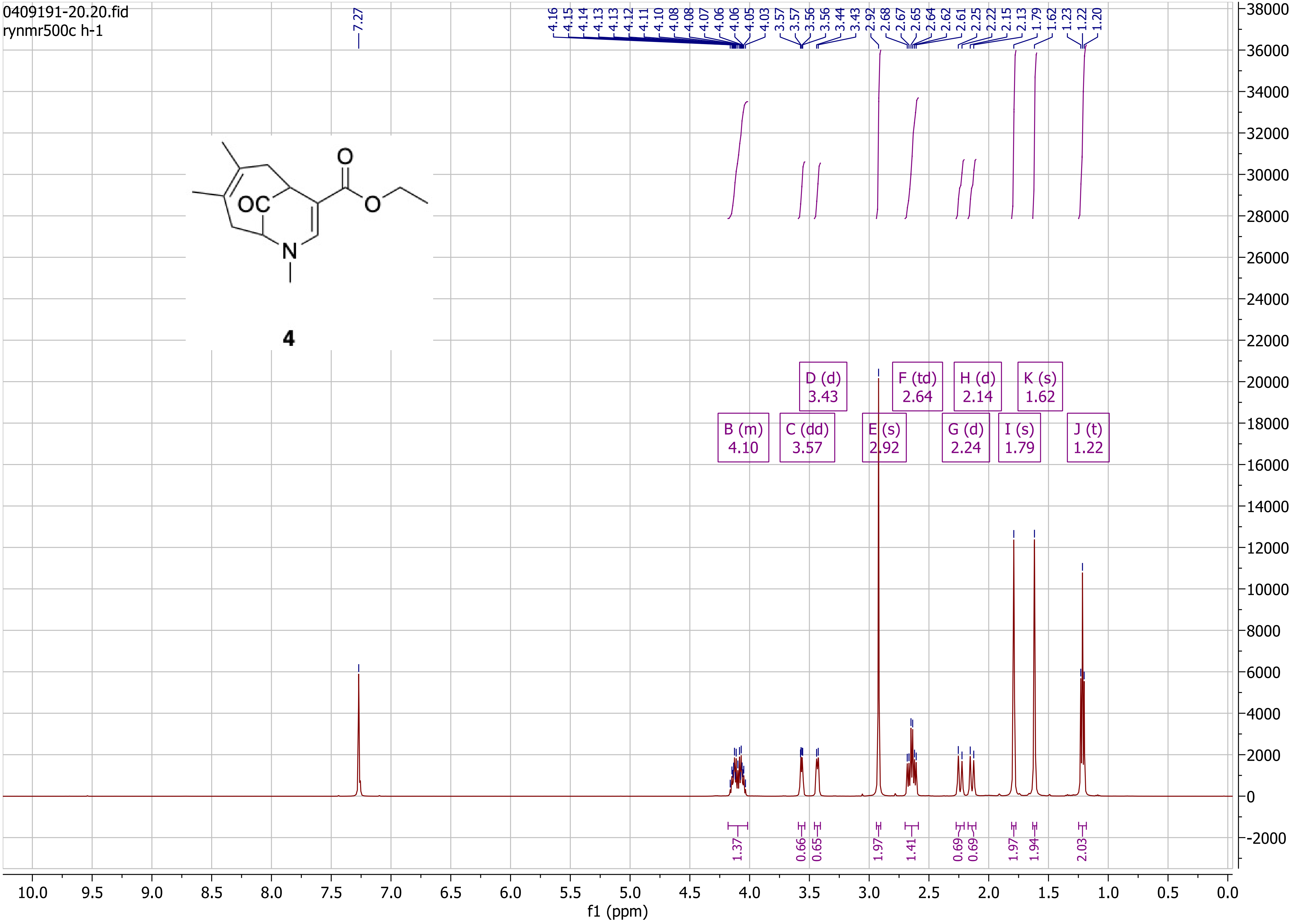
f1 (ppm)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4.13
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2.65
2.64
2.62
2.61
2.25
2.22
2.15
2.13
1.79
1.62
1.23
1.22
1.20
O
OC
O
N
4
B (m) 4.10
C (dd) 3.57
D (d) 3.43
E (s) 2.92
F (td) 2.64
G (d) 2.24
H (d) 2.14
I (s) 1.79
K (s) 1.62
J (t) 1.22
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0.65
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0.69
1.97
1.94
2.03
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9.5
9.0
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6.5
6.0
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
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34000
32000
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6000
4000
2000
0
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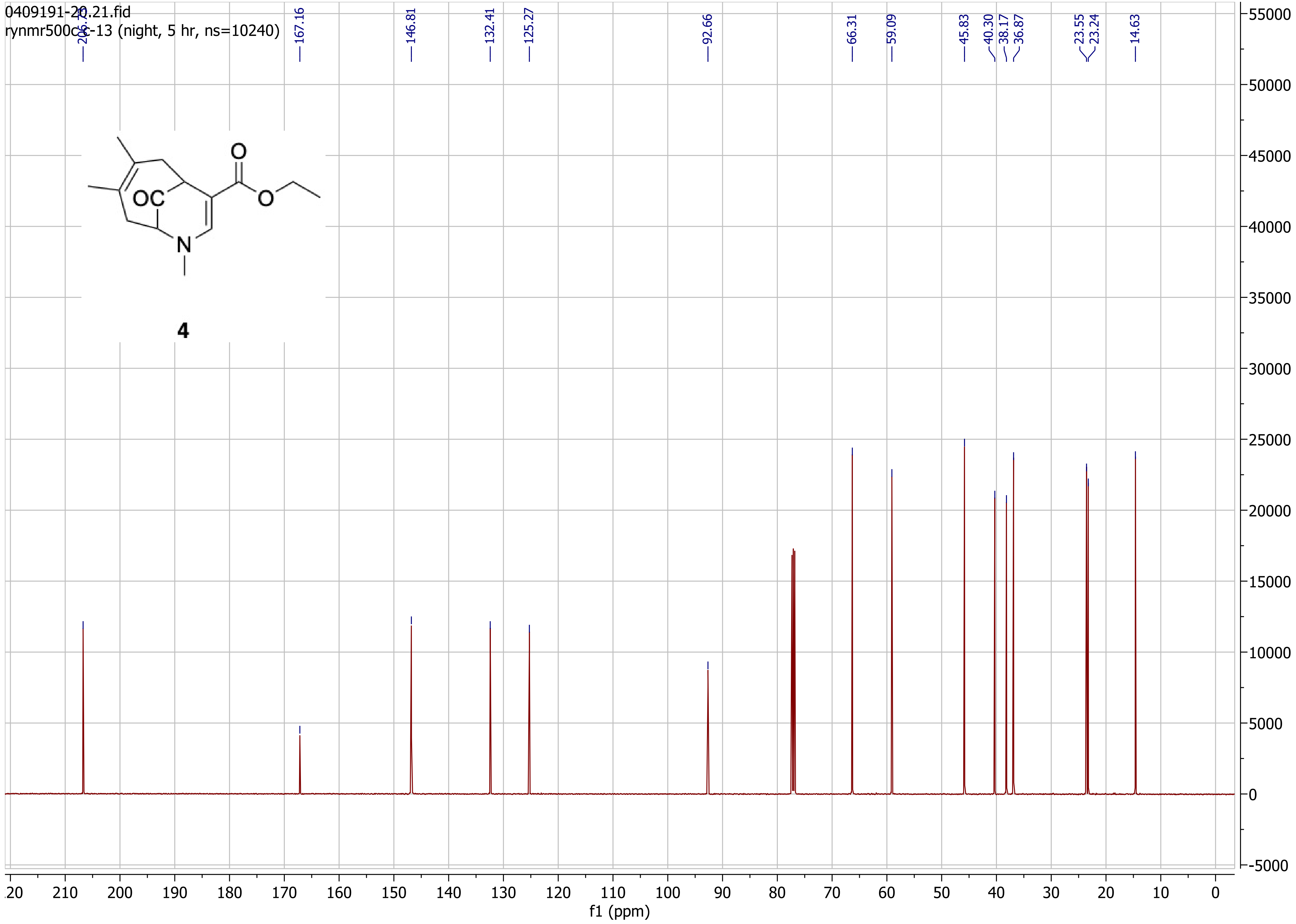
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146.81
132.41
125.27
92.66
66.31
59.09
45.83
40.30
38.17
36.87
23.55
23.24
14.63
O
OC
O
N
4
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
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210
200
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180
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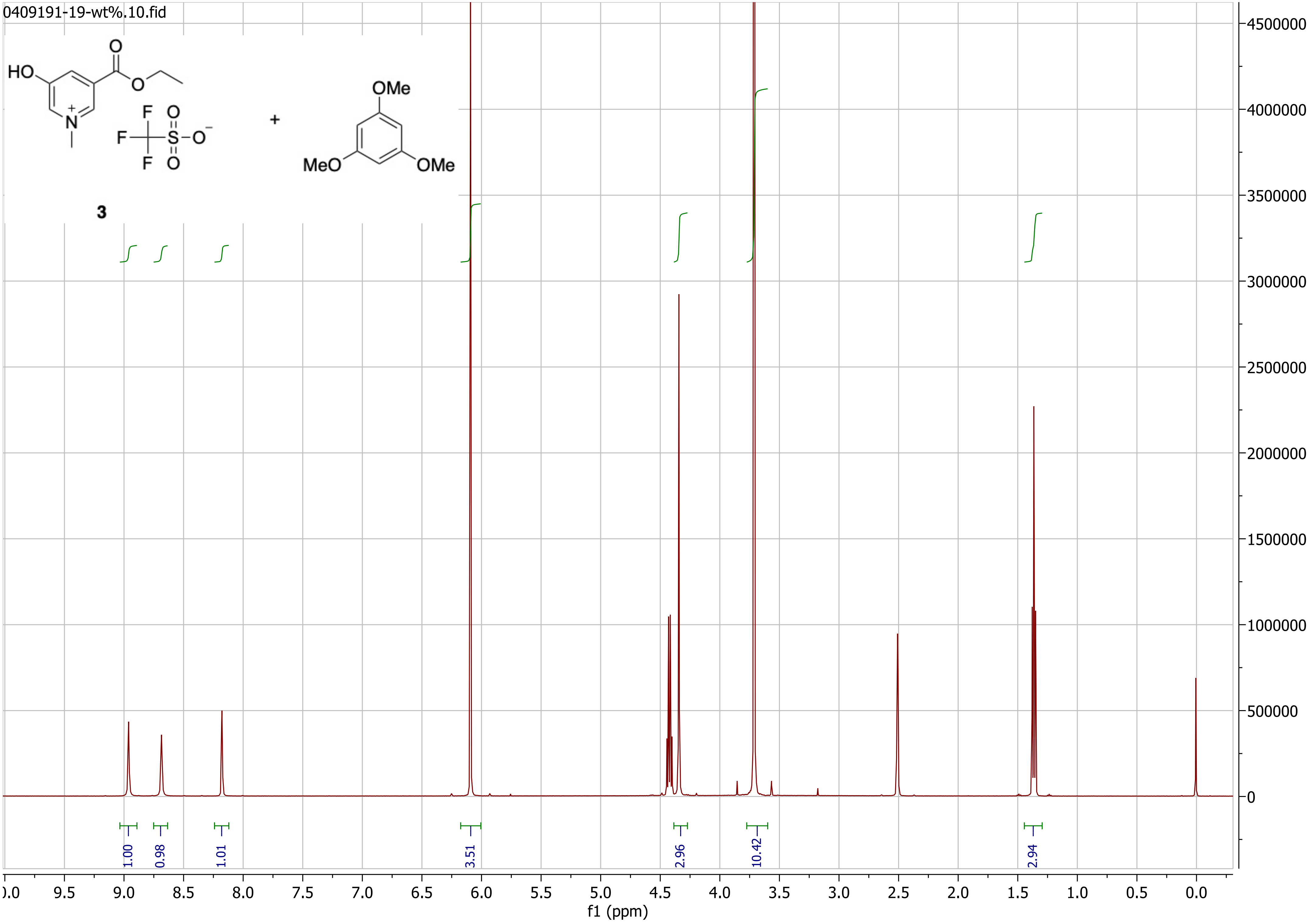
f1 (ppm)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+
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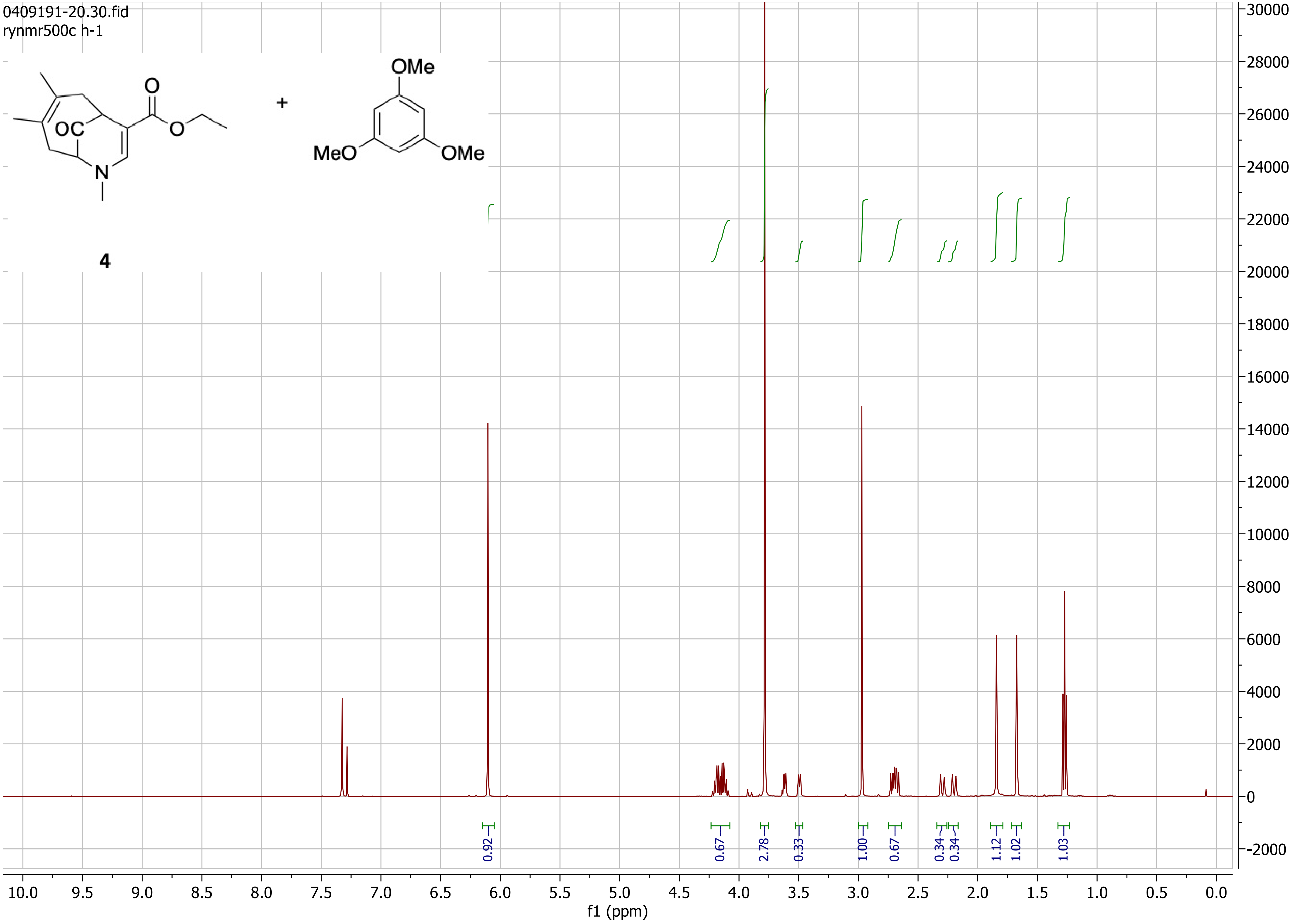
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OMe
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N
+
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1.00
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
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26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
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