Organic Syntheses

Hexafluoro-2-propanol-promoted Intramolecular Friedel-Crafts Acylation

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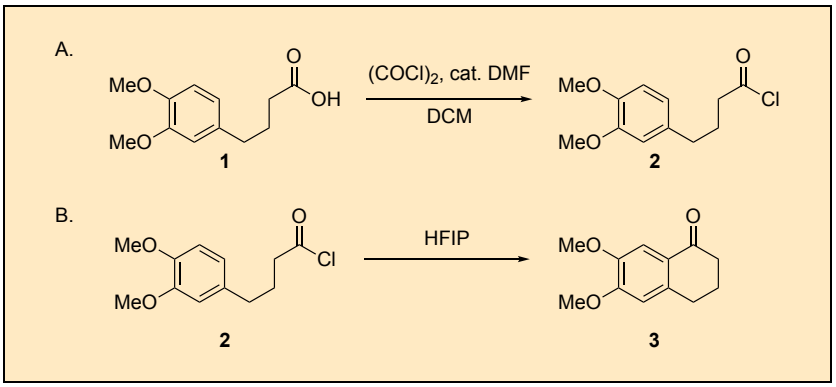
Checked and modified by Feng Peng and Kevin Campos



Procedure (Note 1)

A. *4-(3,4-Dimethoxyphenyl)butanoyl chloride* (**2**). An oven-dried, 250-mL, three-necked, 14/20 round-bottomed flask is equipped with an egg-shaped magnetic stir bar (2 cm), a pressure-equalizing addition funnel (25 mL), a rubber septum, and an argon inlet (Figure 1). The flask is charged with 4-(3,4-dimethoxyphenyl)butanoic acid (**1**) (7.25 g, 32.3 mmol, 1.0 equiv) (Note 2), anhydrous DCM (40 mL) (Note 3) and DMF (50. μL, 0.65 mmol, 0.02 equiv) (Note 4). Oxalyl chloride (5.5 mL, 64 mmol, 2.0 equiv) (Note 5) is added via syringe to the addition funnel, and the stopcock is opened such that the oxalyl chloride is added over 4 min, resulting in effervescence. The reaction mixture is stirred at 23 °C for 30 min from the start of the addition

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of oxalyl chloride (Note 6). The argon inlet is replaced with a rubber septum, the addition funnel is removed, and the flask placed on a rotary evaporator. Concentration under reduced pressure (35 °C, 30 mm Hg) afforded 8.35 g of crude acid chloride (**2**) as a yellow oil (Note 7 and 8), which is used in the next step without purification.

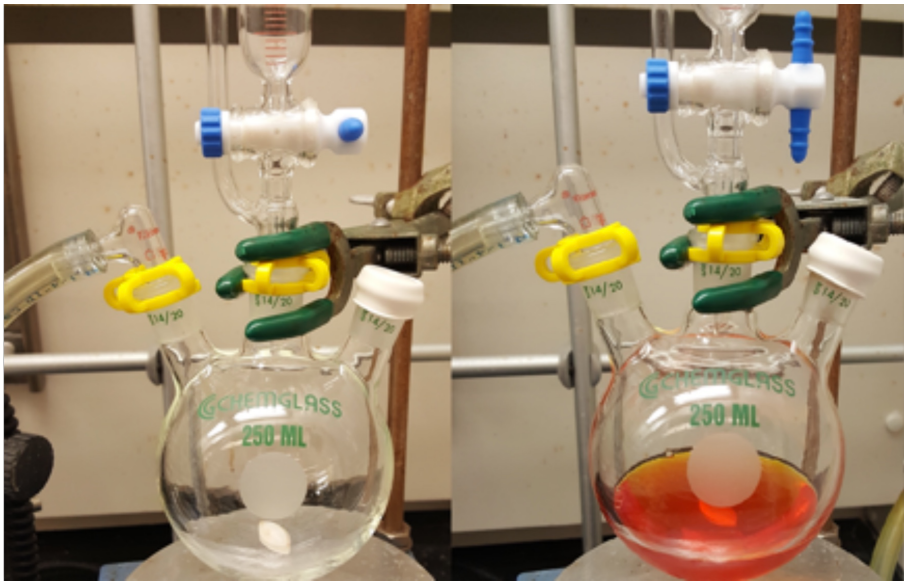

Figure 1. Left to right: reaction assembly for Step A, reaction appearance for Step A (photos provided by submitters)

B. *6,7-Dimethoxy-3,4-dihydronaphthalen-1(2H)-one* (***3***). An oven-dried, 100-mL, three-necked, 14/20 round-bottomed flask is equipped with an egg-shaped magnetic stir bar (2 cm), a water condenser, a thermocouple, and an argon inlet. Hexafluoroisopropanol (HFIP) (17 mL, 162 mmol, 5.0 equiv) (Note 9) is added. To this three-necked flask is charged a solution of acid chloride (**2**) in 3 mL of dichloroethane (Note 10) via plastic syringe at a rate that maintains the internal temperature below 35 °C. The reaction is allowed to cool and stirred at 23 °C for 2 h (Note 11). The stir bar is removed and rinsed with HFIP (1.0 mL) and the mixture is concentrated using a rotary evaporator (45 °C, 30 mmHg) to afford a dark brown oil (Figure 2), which is further dried for 15 min at 0.5 mmHg. The crude product is dissolved in DCM (50 mL) (Note 12), transferred to a 250-mL

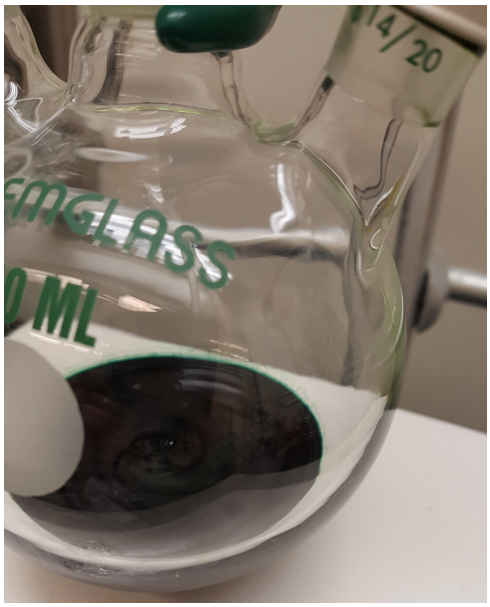

Figure 2. Reaction appearance following Step B

separatory funnel, and washed with saturated, aqueous sodium bicarbonate (2 × 50 mL) and brine (50 mL). The combined aqueous layers are extracted with DCM (75 mL) and the combined organic layers dried over 31 g of Na_2SO_4 (20 min) and gravity-filtered through a 185 mm Whatman qualitative circle into a 500 mL, single-necked, 24/40 round-bottomed flask. The flask and the Na_2SO_4 are washed with additional DCM (3 × 20 mL). Celite (13.6 g) (Note 13) is added to the flask and the mixture is concentrated (40 °C, 160 mmHg). In a 150-mL, coarse-fritted Büchner funnel with a 24/40 lower vacuum assembly with an attached 250-mL round-bottomed flask, 28 g of sand is layered over the frit followed by a slurry of 25 g of silica gel (Note 14) and hexanes (50 mL). Additional hexanes (50 mL) is used to rinse leftover silica gel into the funnel. After allowing the slurry to settle (2 min), the dry-loaded product is added. At this stage, the 250-mL flask is switched with a 500-mL flask and 150 mL of hexanes followed by 100 mL of 9:1 hexanes:EtOAc (Note 15) are added and pulled through with house vacuum (Note 16) such that the solvent level does not fall below the top of the Celite. The 500-mL flask is switched with a 1-L round-bottomed flask and 200 mL of 4:1 hexanes:EtOAc followed by 500 mL of 7:3 hexanes:EtOAc are run through the silica in the same fashion as before.

The filtrate from the 500-mL flask is discarded and the filtrate from the 1-L round bottom flask is concentrated by rotary evaporator (40 °C, 30 mmHg). The resulting white solid is scraped out of this flask and transferred to a 250-mL round-bottomed flask. The 1-L flask is rinsed with EtOAc (3 × 30 mL) into the 250-mL flask and the solution concentrated (40 °C, 80 mmHg) resulting in 6.4 g of pink solid (Note 17). The flask is allowed to stand overnight (17 h), at which time isopropanol (22 mL) (Note 18) is added to the flask. The mixture is heated and swirled every 25 sec (Note 19) to dissolve the solid. Once the solvent vapor condensate reaches the opening of the flask (2 min), the flask is removed from heat and covered with a laboratory wipe secured with a rubber band. After cooling to 23 °C and sitting overnight (24 h), the supernatant is decanted, and the crystals washed with –20 °C isopropanol (6 mL) (Note 20) and dried overnight under vacuum (0.5 mm Hg) to afford the product as light pink crystals (5.23 g, 78%) (Notes 21, 22, and 23) (Figure 3).

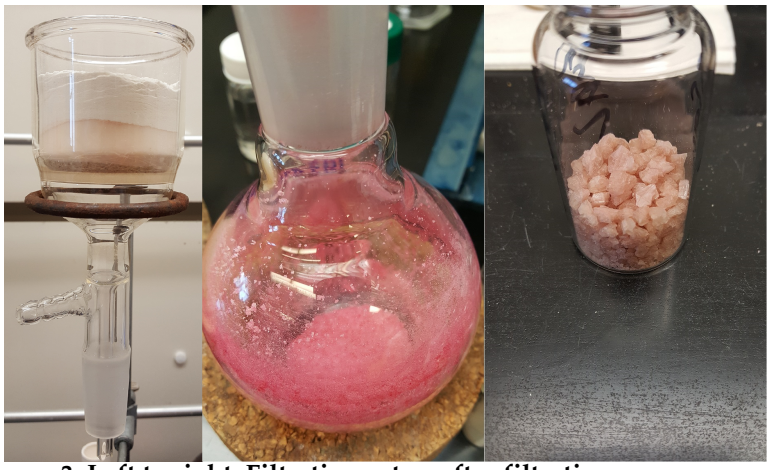

Figure 3. Left to right: Filtration setup after filtration, appearance of product before recrystallization, and appearance of product after recrystallization (photos provided by Submitters)

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 4-(3,4-dimethoxyphenyl)butanoic acid, dichloromethane, oxalyl chloride, dimethylformamide, HFIP, celite, silica gel, hexanes, EtOAc, and isopropanol.

2. 4-(3,4-Dimethoxyphenyl)butanoic acid (**1**) (99%) was purchased from Sigma–Aldrich and used as received.
3. Anhydrous DCM was purchased from Alfa Aesar (99.7+ %, packaged under argon in resealable ChemSeal bottles, stabilized with amylene) and used as received.
4. *N*,*N*-Dimethylformamide (99.8%) was purchased from Sigma–Aldrich and used as received.
5. Oxalyl chloride (98%) was purchased from Beantown Chemical and is used as received. CAUTION: Oxalyl chloride is irritating, toxic, and prone to release gas when used in a chemical reaction.
6. TLC analysis is performed with silica gel plates (10 × 20 cm, glass backed, purchased from Miles Scientific) with EtOAc–hexanes (1:1) and visualized using a 254 nm UV lamp. The acid chloride (**2**) is converted to the corresponding methyl ester for analysis purposes by dissolving a small aliquot in methanol prior to TLC. 4-(3,4-Dimethoxyphenyl)butanoic acid (**1**) R_f = 0.29, methyl 4-(3,4-dimethoxyphenyl)butanoate (from acid chloride) R_f = 0.57. In the latter case, the acid chloride hydrolyzes on the TLC plate to yield acid.
7. A second reaction on identical scale provided 8.67 g of the same product. The excess mass over the theoretical yield is attributed to leftover DCM not removed by rotary evaporation.

8. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.04 (m, 2H), 2.66 (t, J = 7.5 Hz, 2H), 2.91 (t, J = 7.2 Hz, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 6.70 (d, J = 2.0 Hz, 1H), 6.73 (br d, J = 7.9 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.7, 33.9, 46.2, 55.8, 55.9, 111.4, 111.7, 120.3, 132.9, 147.6, 149.1, 173.7.
9. Hexafluoroisopropanol was purchased from Oakwood Products, Inc. (>99%) and used as received (bp = 59 °C).
10. Dichloroethane was purchased from Sigma–Aldrich (99%) and used as received.
11. TLC analysis was performed with silica gel plates (10 × 20 cm, glass backed, purchased from Miles Scientific) with EtOAc–hexanes (1:1) and visualized with a 254 nm UV lamp. Ketone (**3**) R_f = 0.43.
12. DCM was purchased as a 19-L drum from BDH and used as received.
13. Celite (545) was purchased from Sigma–Aldrich and used as received.
14. Silica gel was purchased from SiliCycle (P60, 230–400 mesh) and used as received.
15. Hexanes and EtOAc were purchased in 19-L drums from BDH and used as received.
16. The vacuum measured 260 mmHg; care was taken to ensure solvent level remained above the Celite.
17. The solid is initially white after concentration, but during the time it takes to transfer the solid and measure its mass, the solid turns pink. The melting point of this solid was 98–100 °C.
18. Isopropanol was purchased in a 19-L drum from BDH and used as received.
19. Appropriate PPE was worn (insulated glove) when handling hot glassware. The solution was heated either by a heat gun or by an aluminum block set to 160 °C. Care was taken to avoid spilling isopropanol.
20. Isopropanol was placed in a –20 °C freezer in a covered Erlenmeyer flask for at least 1 h to chill before being used in this step.
21. A second run performed on the same scale yielded 5.15 g.
22. Physical properties and spectroscopic analysis of **3**: mp 99–101 °C (lit.[2] mp 98–100 °C). IR (powder) 2029, 1660, 1597, 1505, 1255, 1220 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ : 2.14 (m, 2H), 2.62 (t, J = 6.5 Hz, 2H), 2.91 (t, J = 6.1 Hz, 2H), 3.93 (s, 3H), 3.95 (s, 3H), 6.69 (s, 1H), 7.54 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 23.5, 29.3, 38.4, 55.8, 55.9, 108.4, 110.1, 125.7, 139.2, 147.8, 153.4, 197.1; HRMS (ESI) m/z calcd. for $C_{12}H_{15}O_3$ $[M+H]^+$ 207.1021, found 207.1017.

23. Purity was measured at 99% by quantitative NMR using or trimethoxybenzene as the standard. The compound is bench stable in open air.

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.

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Discussion

The Friedel–Crafts acylation is a storied and often-used procedure for preparing aromatic ketones; accordingly, a very extensive bibliography and review literature is available for this reaction.[3] Classically, the reaction is

promoted by acids such as $AlCl_3$, $FeCl_3$, $SnCl_4$ or H_2SO_4, generally requiring a stoichiometric amount of catalyst for full conversion due to complex formation between ketone products and Lewis acid catalysts, resulting in product inhibition. In such cases, the reactions entail an aqueous workup and produce metal-containing acidic waste streams. More recent methods use sub-stoichiometric, including heterogenous, catalysts.[3f,4] An important early example was Kobayashi's conditions of $Hf(OTf)_4$ in $LiClO_4$–nitromethane;[5] indeed, numerous examples employ ionic liquids and other unconventional media.[6] Another general approach is to modify the substrate, with a great deal of effort devoted to the study of highly electrophilic acylating agents as reaction partners.[7]

Here, we provide a detailed procedure for an intramolecular Friedel–Crafts acylation reaction that is notable for its simplicity: the substrate is merely dissolved in HFIP solvent at room temperature or below.[8] Following reaction, the workup consists of an aqueous wash to remove residual acid followed by removal of solvent under reduced pressure and purification of the product by appropriate means. This differs from the traditional reaction insofar as no aqueous metal waste streams are generated. Other workers have also reported the use of HFIP under similar conditions for Friedel–Crafts alkylation reactions.[9]

The mechanism of this variant of the Friedel–Crafts reaction is not known, but preliminary experiments have ruled out the possible intermediacy of an HFIP ester derived from the acyl chloride.[8] HFIP chemistry is often dominated by its strong hydrogen bonding potential[10] and any reasonable mechanism likely involves HFIP H-bonding to the acyl chloride. This could lead to formation of an acylium ion in a process reminiscent of the textbook mechanism for $AlCl_3$-promoted Friedel–Crafts reaction but direct addition of the arene is not out of the question. It has not been possible to distinguish between these possibilities, but it is worth mentioning that we have not been able to identify any reaction intermediates using *in situ* infrared spectroscopy.

Electron-rich arenes and heteroarenes worked well under these conditions (Table 1). In general, six- and seven-membered cyclic ketones were obtained in good yields but five-membered cyclic ketones proved more challenging (entries 18-20). Substrates without electron-donating groups on them resulted in lower yields (entries 8 and 12), and these reaction conditions do not succeed on electron-poor substrates. In cases where multiples isomers are possible, only one is formed (entries 1, 11, 12, and 17). Despite these constraints, this variation of the Friedel–Crafts

reaction provides easy and efficient access to a good range of attractive carbo- and heterocyclic ketones, and for many of these substrates, will be a method of choice.

Table 1. Substrate scope

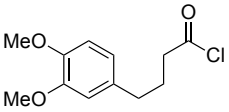
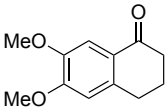
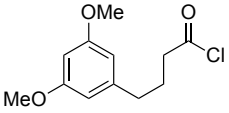
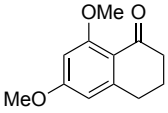
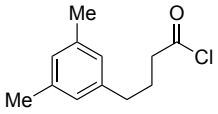
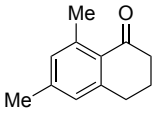
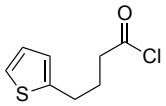
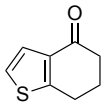
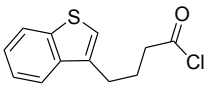
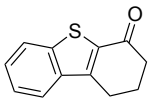
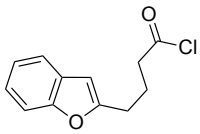
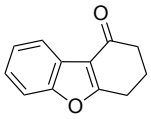
entry	acid chloride	product	yield (%)
1			97[a] 78[b]
2			86
3			73
4			81
5			99
6			90

Table 1. (cont.)

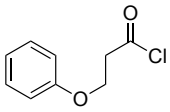
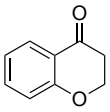
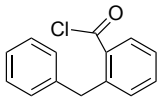
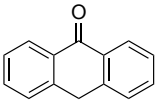
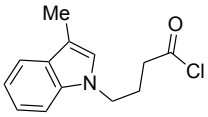
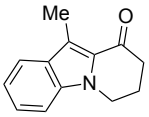
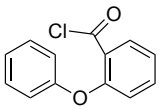
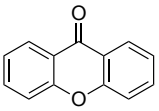
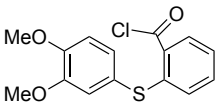
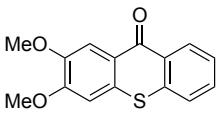
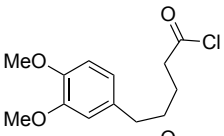
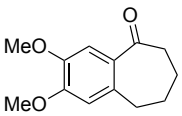
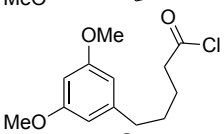
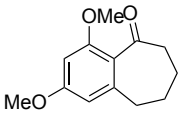
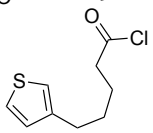
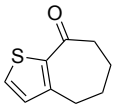
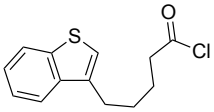
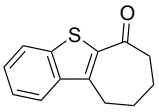
entry	acid chloride	product	yield (%)
7			70
8			77
9			72
10			77
11			93
12			56
13			61
14			72
15			68

Table 1. (cont.)

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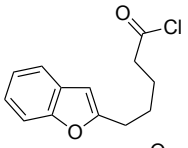
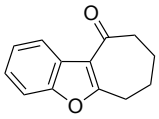
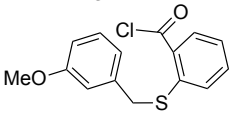
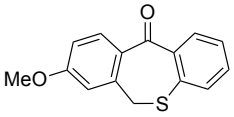
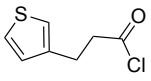
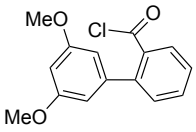
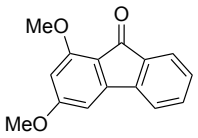
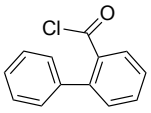
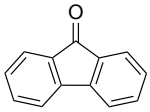
16			72
17			81
18			14
19			99
20			12

[a]Reaction was performed on 0.30 mmol scale with a full column and no recrystallization. [b]Yield from this work.

References

1. Rakesh H. Vekariya, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS, 66045, USA; Matthew C. Horton, Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599-7363, USA; Jeffrey Aubé, Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy, 125 Mason Farm Road, CB 7363, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599-7363, USA. Email: jaube@unc.edu. JA and MH thank the UNC Eshelman School of Pharmacy for financial support, Alexander Li for early experimental assistance, and the checkers for a useful modification of Step B.

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

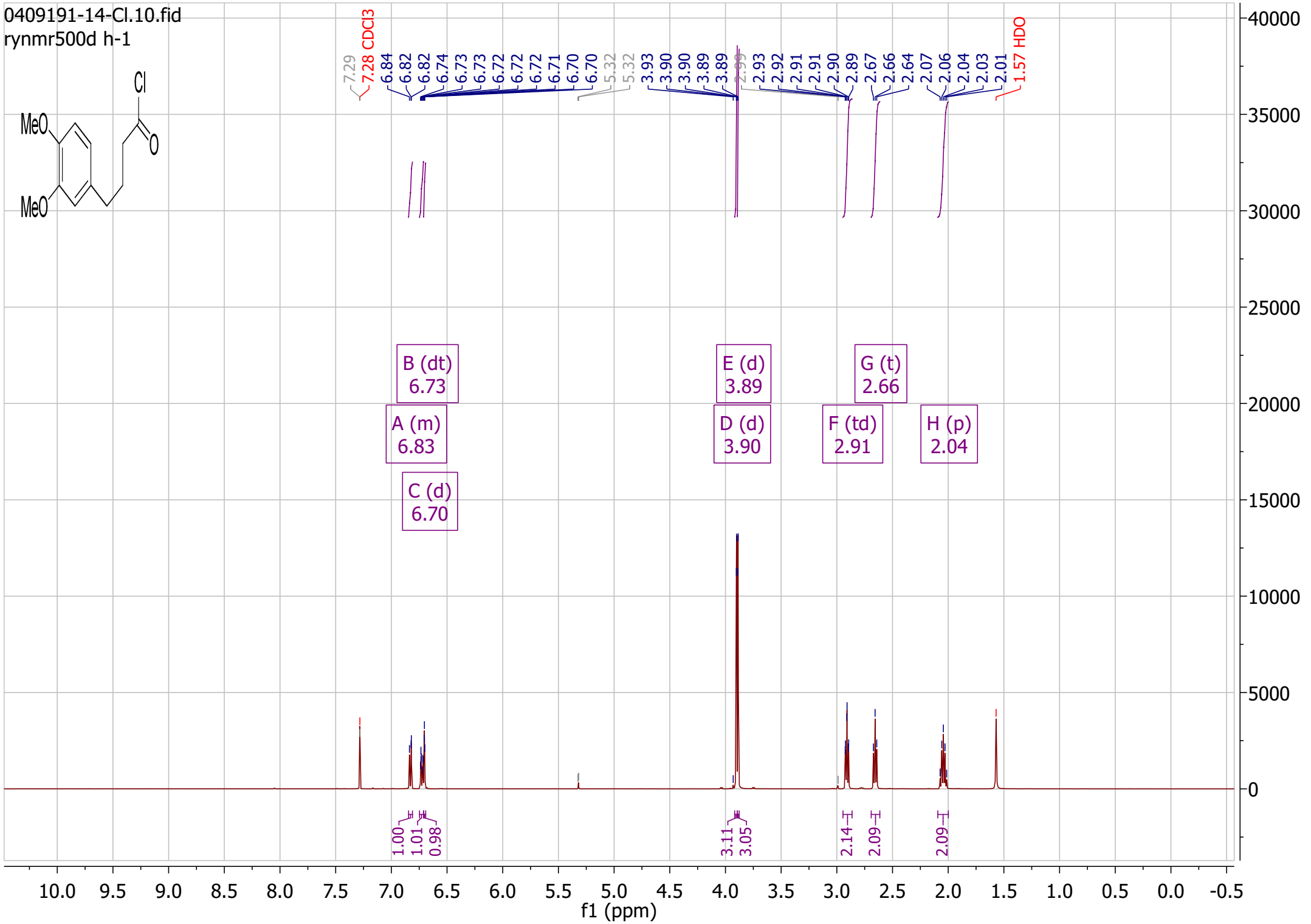
4-(3,4-Dimethoxyphenyl)butanoic acid; (13575-74-1)
4-(3,4-Dimethoxyphenyl)butanoyl chloride; (348143-75-9)
6,7-Dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one; (13575-75-2)
Oxalyl chloride, (79-37-8)
Hexafluoroisopropanol: 1,1,1,3,3,3-Hexafluoro-2-propanol; (920-66-1)

Rakesh Vekariya was born in Gujarat, India. He received a B.S. degree in Pharmacy in 2008 from JSS College of Pharmacy, India. He received M.S. degree in medicinal chemistry at Virginia Commonwealth University working in the research group of Professor Richard A. Glennon. He received his Ph.D. from the University of Kansas, working on synthetic method development and medicinal chemistry projects in the laboratory of Professor Jeffrey Aubé.

Matthew C. Horton grew up in Sugar Land, TX and received a B.S. degree in Chemistry from Louisiana State University in Baton Rouge, LA. He joined the lab of Professor Jeffrey Aubé at UNC in 2015 and is now a doctoral student. He has been working on the total synthesis of a virulence factor.

Jeffrey Aubé attended the University of Miami, where he did undergraduate research with Professor Robert Gawley and earned a B.S. degree in 1980. He received his Ph.D. in chemistry in 1984 from Duke University, working with Professor Steven Baldwin, and was an NIH postdoctoral fellow at Yale University with Professor Samuel Danishefsky. In 1986, he moved to the University of Kansas, where he worked until his retirement from that institution in 2015. He is currently an Eshelman Distinguished Professor at the University of North Carolina at Chapel Hill.

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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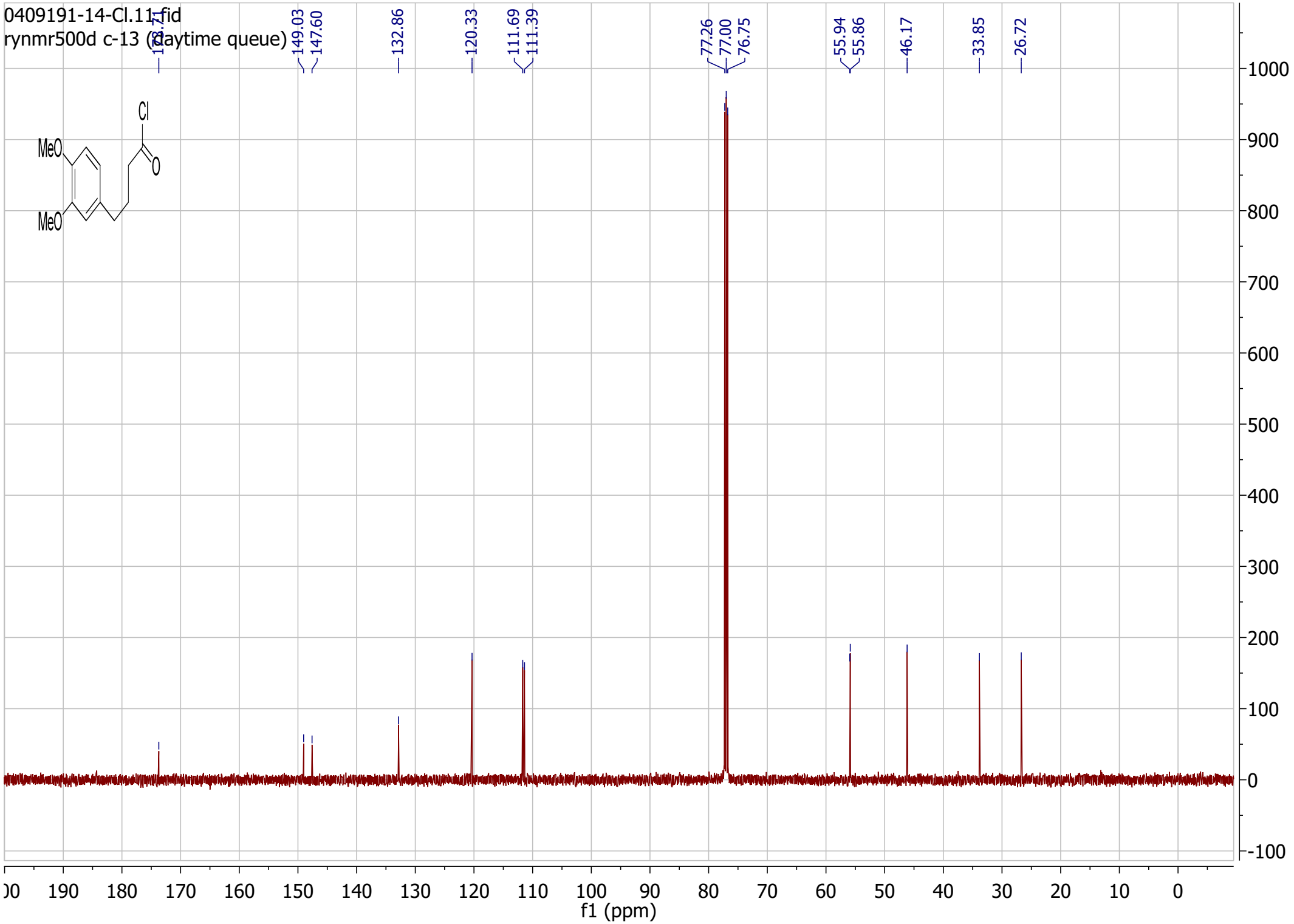
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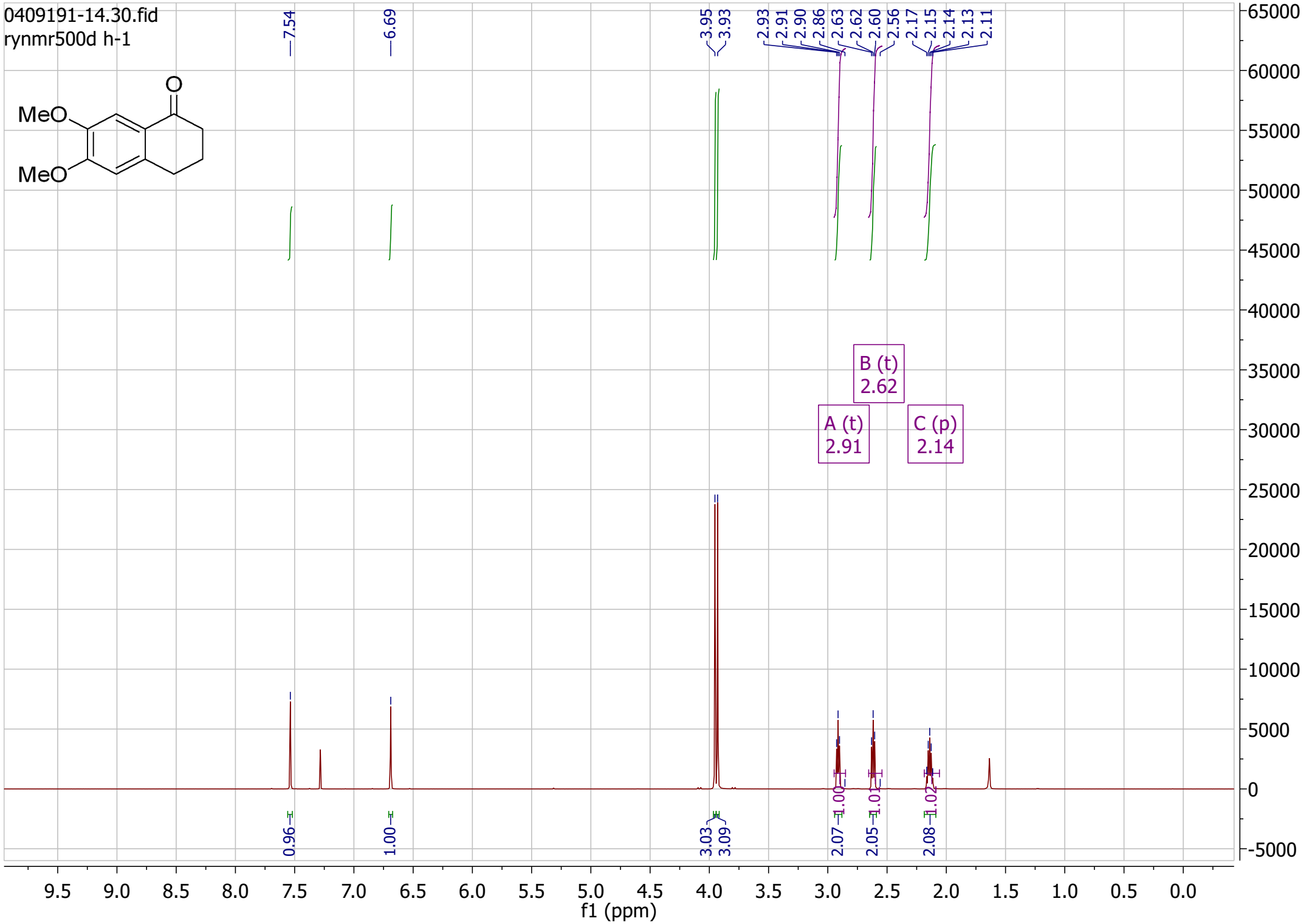
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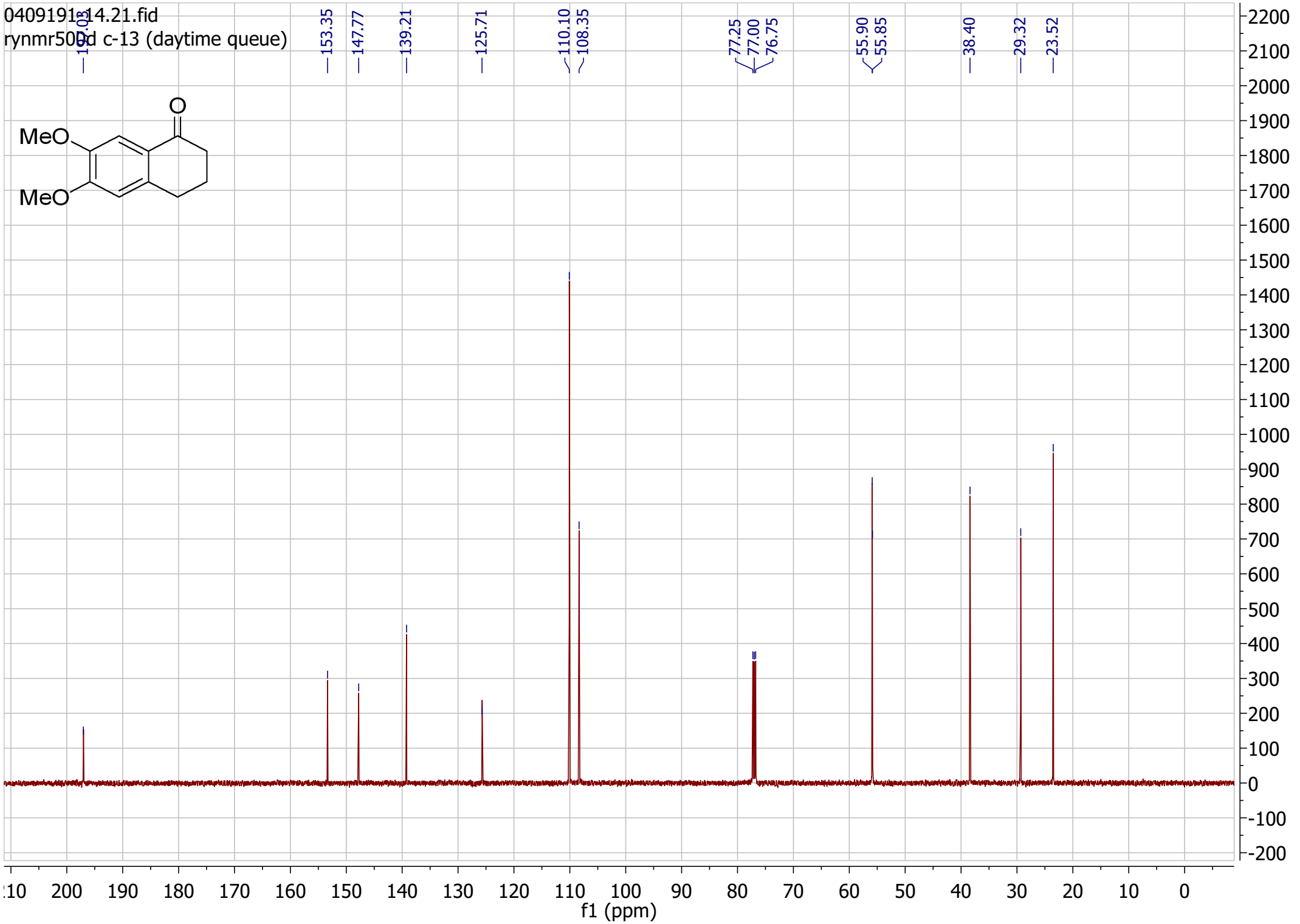
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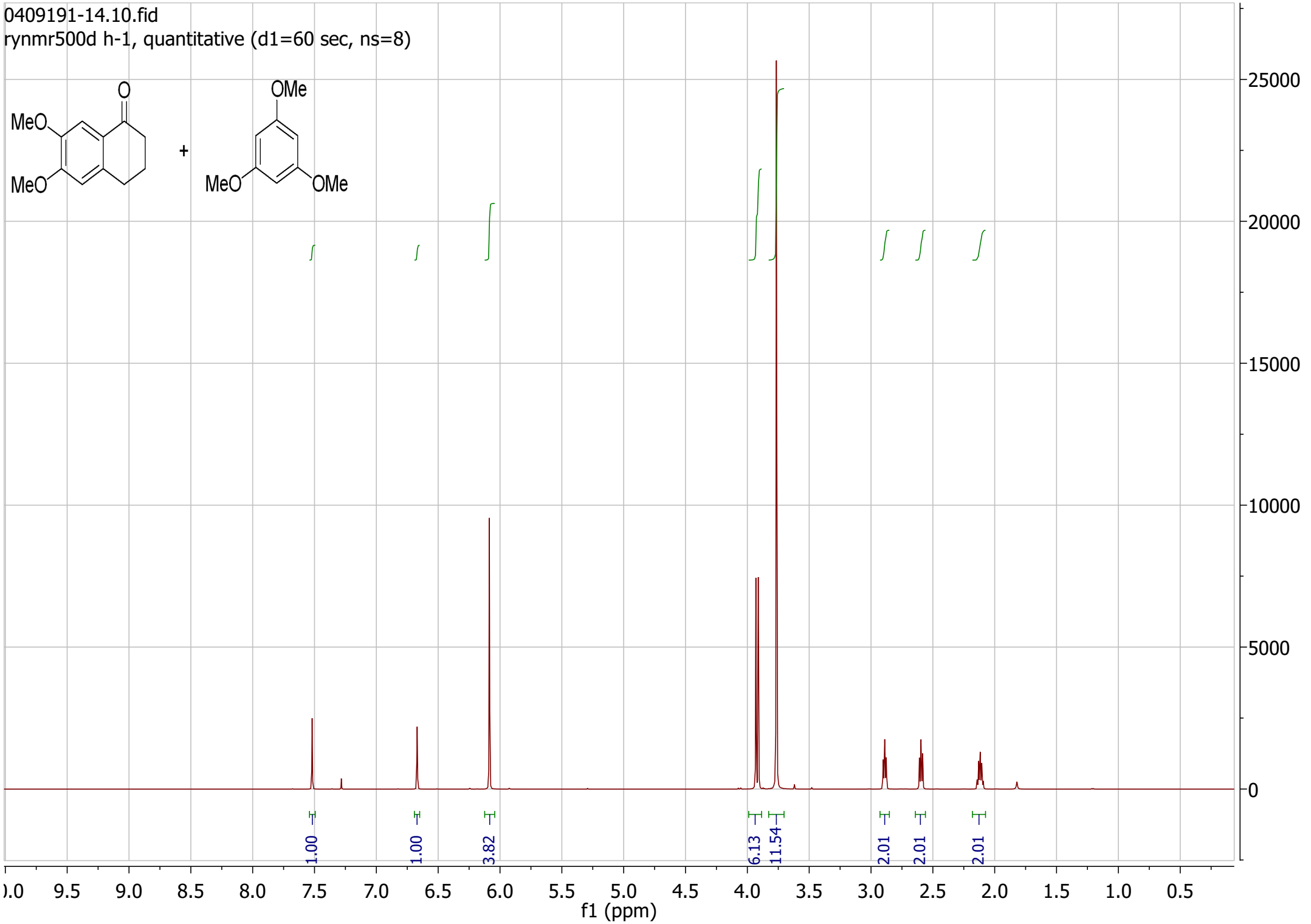
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