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for the Preparation
of Organic Compounds

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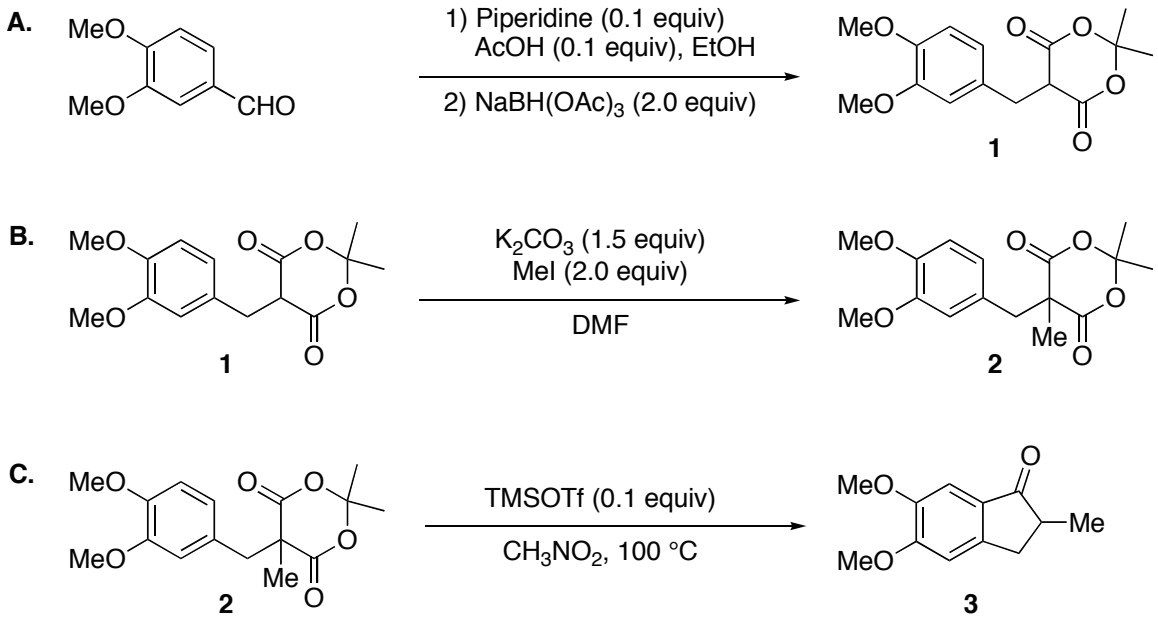
*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

# Catalytic Intramolecular Friedel-Crafts Reaction of Benzyl Meldrum's Acid Derivatives: Preparation of 5,6-Dimethoxy-2-Methyl-1-Indanone




Submitted by Tiantong Lou, E-Ting Liao, Ashraf Wilsily, and Eric Fillion.[1]
Checked by Maurizio Bernasconi and Andreas Pfaltz.

## 1. Procedure

A. *5-(3,4-Dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**1**).* An oven-dried 1-L, two-necked, round-bottomed flask equipped with an oval (Note 1) magnetic stir bar, a rubber septum and a two-tap Schlenk adaptor connected to a bubbler and an nitrogen/vacuum manifold (Note 2) is charged with 3,4-dimethoxybenzaldehyde (20.0 g, 120 mmol, 1.0 equiv) (Note 3), 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (17.7 g, 123 mmol, 1.0 equiv) (Note 4) and ethanol (250 mL) (Notes 5 and 6) by temporary removal of the septum. After complete dissolution of the reactants, piperidine (1.2 mL, 12.3 mmol, 0.1 equiv) (Note 7) and acetic acid (0.7 mL, 12.3 mmol, 0.1 equiv) (Note 7) are added sequentially by syringe (Note 8) and the solution is stirred at room temperature for 30 min. Sodium triacetoxyborohydride (52.1 g, 246 mmol, 2.0 equiv) (Note 9) is then added in four equal portions, one after the other on a 30 min interval by temporarily removing the septum. The reaction mixture is stirred for another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60 min at room temperature (Note 10), after which it is cooled using an ice bath and quenched by the addition of saturated ammonium chloride solution (60 mL).

The reaction mixture is then transferred into a 1-L separatory funnel using dichloromethane (3 x 80 mL) and saturated ammonium chloride (3 x 80 mL). Deionized water (50 mL) is added to facilitate the separation of the two layers. The layers are separated and the organic phase is collected into a 2-L Erlenmeyer flask. The aqueous phase is extracted with dichloromethane (2 x 150 mL) and the combined organic layers are dried over $MgSO_4$ (20 g), filtered through a coarse glass frit (Note 11) into a 1-L round-bottomed flask, concentrated by rotary evaporation (35 °C, approximately 2 mmHg) and dried under reduced pressure (room temperature, 0.15 mmHg) over 30 min. The crude product is transferred into a 500-mL round-bottomed flask equipped with an oval (Note 1) stir bar, suspended in methanol (80 mL) (Notes 6 and 12) and warmed at 55 °C for 20 min (Note 13). After allowing the suspension to cool to room temperature (~20 min), the reaction vessel is stored in a freezer at –25 ºC for 17 h. The yellow solid is collected by suction filtration (room temperature, approximately 10 mmHg), through a coarse frit (Note 11), washed with methanol (10 mL, –25 °C), dried for 30 min under reduced pressure (0.15 mmHg, room temperature, 1 h) to yield 29.9 g (85 % yield) of product **1** as pale yellow crystals (Notes 14 and 15).

B. *5-(3,4-Dimethoxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (**2**).* An oven-dried 500-mL, three-necked, round-bottomed flask equipped with an oval (Note 1) magnetic stir bar, a 50-mL addition funnel, a two-tap Schlenk adaptor connected to a bubbler and an nitrogen/vacuum manifold (Note 2) and a rubber septum is charged with **1** (21.9 g, 74.5 mmol, 1.0 equiv) and potassium carbonate (15.4 g, 112 mmol, 1.5 equiv) (Note 16) by temporary removal of the septum. Freshly distilled *N,N*-dimethylformamide (74 mL) (Note 17) is added into the reaction flask (Note 18). After complete dissolution of the reactants, iodomethane (9.3 mL, 149 mmol, 2.0 equiv) (Note 19) is added via syringe to the addition funnel, and added dropwise to the reaction mixture (Note 20).

After 3.5 h (Note 21), the reaction mixture is transferred with deionized water (2 x 30 mL) and dichloromethane (2 x 30 mL) into a 1-L Erlenmeyer flask equipped with an oval (Note 1) stir bar, filled with deionized water (100 mL) and cooled using an ice bath. After stirring for 5 min, the solution is transferred into a 1-L separatory funnel using deionized water (30 mL) and dichloromethane (30 mL). The layers are partitioned and the organic

phase is collected into a 1-L Erlenmeyer flask. The aqueous phase is further extracted with 10% dichloromethane in hexanes (3 x 150 mL). The combined organic layers are washed with water (200 mL) and brine (200 mL), dried over $MgSO_4$ (20 g), filtered through a coarse glass frit (Note 11) into a 1-L round bottom flask, and concentrated by rotary evaporation (40 ºC, approximately 10 mmHg). The crude product is dried under reduced pressure (room temperature, 0.2 mmHg) for 30 min prior being transferred to a 250-mL round-bottomed flask, dissolved in methanol (30 mL) (Notes 6 and 12) and warmed at 55 °C for 20 min (Note 13). After allowing the solution to cool to room temperature (~20 min), it is stored in the freezer at –25 ºC for 17 h. The crystals are collected by suction filtration through a coarse frit (Note 11) under vacuum (room temperature, approximately 10 mmHg) and washed with methanol (10 mL, –25 °C). Product **2** is then collected into a 250-mL round-bottom flask and dried under reduced pressure (room temperature, 0.15 mmHg) for 30 min to give 20.21 g (88 % yield) of pale yellow crystals (Note 22).

C. *5,6-Dimethoxy-2-methyl-1-indanone (**3**)*. An oven-dried 1-L, three-necked, round-bottomed flask equipped with an oval (Note 1) magnetic stir bar, a 500-mL addition funnel, a reflux condenser with a two-tap Schlenk adaptor connected to a bubbler and an nitrogen/vacuum manifold (Note 2) on the top, and a glass stopper is charged with **2** (12.0 g, 38.9 mmol, 1.0 equiv) by temporary removal of the glass stopper. Freshly distilled nitromethane (390 mL) (Notes 23 and 24) is added into the reaction flask (Note 25) via the addition funnel. When the reaction mixture begins to reflux at 100 °C (Note 13), TMSOTf (0.7 mL, 0.1 equiv) (Note 26) is added via the addition funnel, which is rinsed with nitromethane (approximately 5 mL). After 60 min (Note 27) the reaction mixture is allowed to cool for 15 min before it is placed in an ice bath. After stirring for 5 min, saturated ammonium chloride solution (10 mL) is added.

After 15 min of stirring, the reaction mixture is then transferred into a 1-L round-bottom flask with dichloromethane (100 mL) before it is concentrated by rotary evaporation (45 ºC, approximately 4 mmHg). The resulting crude product is transferred into a 2-L separatory funnel using deionized water (2 x 50 mL) and ethyl acetate (3 x 100 mL). The layers are separated and the organic phase is collected into a 2-L Erlenmeyer flask. The aqueous phase is then extracted with ethyl acetate (2 x 200 mL) and the combined organic phases are washed with brine (200 mL), dried over $MgSO_4$ (20 g), filtered through a coarse glass frit (Note 11) into a 2-L round-

bottomed flask and concentrated by rotary evaporation (40 ºC, approximately 4 mmHg). The crude product is transferred using dichloromethane (2 x 50 mL) into a 250-mL round-bottomed flask equipped with an oval (Note 1) magnetic stir bar, then concentrated by rotary evaporation (40 °C, approximately 4 mmHg) and dried under reduced pressure (room temperature, 0.2 mmHg) for 30 min to yield a slightly purple powder. To the solid crude product is added ethanol (30 mL) (Notes 5 and 6) and the suspension is heated to 90 °C for 20 min (Note 13). The solution is allowed to cool to room temperature for 40 min. The precipitated colorless crystals are filtered off through a coarse frit (Note 11), washed with cold ethanol (5 °C, 10 mL) (Note 5 and 6) collected into a 250-mL round-bottomed flask and dried under reduced pressure overnight (room temperature, 0.08 mmHg), to give 5.36 g (67 % yield) of white crystals (Notes 28, 29 and 30).

## 2. Notes

1. Length: 4 cm, diameter: 2 cm
2. A picture of this adaptor can be found in: *Org. Synth.* **2008**, *85*, 64–71.
3. 3,4-Dimethoxybenzaldehyde (99%) was purchased from Aldrich Chemical Company, Inc. and was ground to a fine powder before use.
4. 2,2-Dimethyl-1,3-dioxane-4,6-dione (98%) was purchased from Aldrich Chemical Company and was used as received.
5. Ethanol (ACS reagent) was obtained from Fluka and was used as received.
6. The graduated cylinder was oven-dried.
7. Piperidine (99%, ReagentPlus) and acetic acid (≥ 99.7%, ACS reagent) were obtained from Aldrich Chemical Company, Inc. and both reagents were used as received. The rate of addition of those compounds does not influence the outcome of the reaction.
8. During the condensation, the reaction changed from a clear yellow mixture to a cloudy yellow mixture.
9. Sodium triacetoxyborohydride (95%) was purchased from Aldrich Chemical Company, Inc. and was used as received. **Caution**: After the addition of each portion of the reducing agent (mainly after the first two portions) strong hydrogen gas evolution is observed and the internal temperature of the reaction increases (from 25 °C to 36 °C). The checkers

observed in some cases that upon the first addition of the reducing agent the reaction could not be stirred properly due to the increased viscosity of the reaction mixture. In this case an additional 80 mL of ethanol were added.

10. The reaction was monitored via TLC with 3:1 *n*-hexane/ethyl acetate as eluent ($R_f$ value of 0.31). The color of the reaction mixture changed from cloudy yellow to cloudy white as sodium triacetoxyborohydride was added.

11. A 125-mL filter funnel with a coarse frit, porosity 3, was used.

12. Methanol (Exceeds ACS Specifications) was obtained from J.T. Baker and used as received.

13. A silicon oil bath was used.

14. The product displays the following physicochemical properties: pale yellow crystals; mp 136 °C. Lit. 142–144 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.48 (s, 3 H), 1.72 (s, 3 H), 3.45 (d, $J$ = 4.8 Hz, 2 H), 3.72 (t, $J$ = 4.8 Hz, 1 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 6.77 (m, 1 H), 6.85–6.87 (m, 2 H); $^{13}$C NMR ($CDCl_3$, 400 MHz) δ: 27.6, 28.6, 32.1, 48.5, 56.0 (2 C), 105.4, 111.3, 113.3, 122.2, 129.6, 148.3, 149.0, 165.6 (2 C); IR (ATM): 2993, 2943, 2860, 1782, 1747, 1516, 1447, 1259, 1155, 1020, 862 cm$^{-1}$; Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.20; H, 6.16, found: C, 61.07; H, 6.39.

15. In some cases the product contained 5–8% of a side product. This side product was identified as the alkylidene Meldrum's acid (Knoevenagel condensation intermediate). This product has the following analytical data: $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.79 (s, 6 H), 3.96 (s, 3 H), 3.99 (s, 3 H), 6.96 (d, $J$ = 8.5 Hz, 1 H), 7.65 (dd, $J$ = 8.5, 2.0 Hz, 1 H), 8.31 (d, $J$ = 2.1 Hz, 1H), 8.37 (s, 1 H). The side product does not influence the outcome of the subsequent reactions, and it is removed in the recrystallization in Step B.

16. Potassium carbonate (≥ 99.0%, ACS reagent) was purchased from Aldrich Chemical Company, Inc. and used as received.

17. *N,N*-Dimethylformamide (certified ACS) was purchased from Aldrich Chemical Company and was freshly distilled over calcium hydride.

18. The solvent was added using a syringe.

19. Iodomethane (99%, stabilized with copper, ReagentPlus) was purchased from Aldrich Chemical Company, Inc. and used as received.

20. Iodomethane was added over a period of 9 min (1 mL/minute). The internal temperature raised from 28 °C to 33 °C.

21. The reaction was monitored via TLC with 3:1 *n*-hexane/ethyl acetate as eluent ($R_f$ value of 0.30). The reaction mixture was a cloudy white solution.

22. The product displays the following physicochemical properties: pale yellow crystals; mp 88–89 °C. $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 0.99 (s, 3 H), 1.61 (s, 3 H), 1.73 (s, 3 H), 3.28 (s, 2 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 6.69–6.77 (m, 3 H); $^{13}$C NMR ($CDCl_3$, 400 MHz) δ: 26.1, 28.7, 29.5, 44.7, 52.6, 56.0 (2 C), 105.4, 111.3, 113.2, 122.5, 128.0, 148.7, 149.1, 170.2 (2 C); IR (ATM): 3006, 2937, 2840, 1774, 1738, 1512, 1379, 1261, 1238, 1201, 1145, 1022, 980, 825, 680 $cm^{-1}$. Anal. Calcd for $C_{16}H_{20}O_6$: C,62.33; H, 6.54. Found: C, 62.33; H, 6.42.

23. Nitromethane (96%, Reagent Grade) was purchased from Aldrich Chemical Company, Inc. and was freshly distilled under nitrogen over calcium hydride behind a safety shield.

24. The use of nitromethane gave optimal selectivity, yielding product **3** over its regioisomer, 6,7-dimethoxy-2-methyl-1-indanone (**4**)**,** in a >20:1 ratio. Since regioisomer **4** is an oil at room temperature, it was easily separated from product **3** through a simple recrystallization. The Friedel-Crafts acylation was also carried out at reflux in acetonitrile (**3**:**4** ratio of 9:1), toluene (**3**:**4** ratio of 8:1), and chlorobenzene (**3**:**4** ratio of 7:1).

25. The addition funnel was charged with the solvent using a cannula.

26. TMSOTf (99%) was purchased from Aldrich Chemical Company, Inc. and distilled under vacuum at approximately 10 mmHg and stored in a Schlenk tube protected from light. TMSOTf was added over a period of 2 min (0.35 mL/min).

27. The reaction was monitored via TLC with 2:1 *n*-hexane/ethyl acetate as eluent ($R_f$ value of 0.31). The reaction mixture changed from yellow to dark purple over the course of one hour.

28. The product displays the following physicochemical properties: white crystals; mp 133 °C. Lit. 132–133 °C; $^{1}$H NMR ($CDCl_3$, 500 MHz) δ: 1.29 (d, $J$ = 7.4 Hz, 3 H), 2.63 (dd, $J$ = 16.8, 3.4 Hz, 1 H), 2.69 (ddq, $J$ = 7.4, 7.4 , 3.6 Hz, 1 H), 3.30 (dd, $J$ = 16.8, 7.4 Hz, 1 H), 3.90 (s, 3 H), 3.96 (s, 3 H), 6.86 (s, 1 H), 7.17 (s, 1 H); $^{13}$C NMR ($CDCl_3$, 500 MHz) δ 16.8, 34.9, 42.3, 56.2, 56.3, 104.6, 107.5, 129.1, 148.9, 149.5, 155.6, 208.4; IR (ATM): 2963, 2925, 2838, 1679, 1588, 1496, 1461, 1427, 1364, 1318, 1239, 998, 834 $cm^{-1}$; Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84, found: C, 69.83; H, 6.89.

29. To isolate the regioisomer, the reaction was performed in toluene and regioisomer **4** was purified using flash silica gel chromatography eluting with 2:1 *n*-hexane/ethyl acetate.

30. The regioisomer, 6,7-dimethoxy-2-methyl-1-indanone, displays the following physicochemical properties: light yellow oil; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ: 1.27 (d, *J* = 7.2 Hz, 3 H), 2.57–2.72 (m, 2 H), 3.27 (dd, *J* = 16.3, 7.7 Hz, 1 H), 3.86 (s, 3 H), 3.99 (s, 3 H), 7.04 (d, *J* = 8.2 Hz, 1 H), 7.15 (d, *J* = 8.2 Hz, 1 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 16.1, 33.6, 43.0, 58.8, 61.5, 119.9, 120.8, 128.4, 145.9, 146.9, 150.9, 206.6; IR ($CH_2Cl_2$): 1708 $cm^{-1}$; HRMS *m/z* calcd for $C_{12}H_{14}O_3$ ($M^+$): 206.0943. Found: 206.0945.

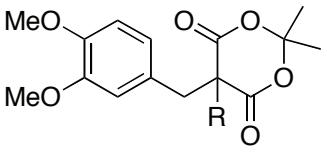
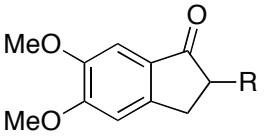
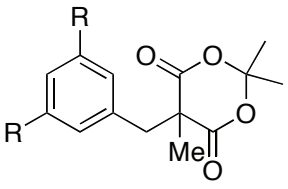
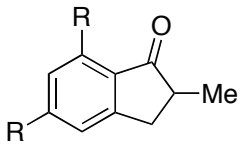
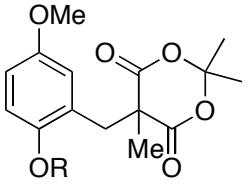
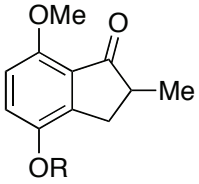
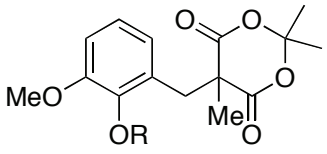
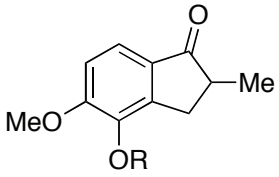
## Waste Disposal Information

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

## 3. Discussion

1-Indanones have proven synthetic utility in numerous biologically active natural products and play a major role in medicinal chemistry and the development of pharmaceuticals.[2] Although the intramolecular Friedel-Crafts acylation is the most powerful means of preparing 1-indanones, it suffers from significant drawbacks.[3] Typical procedures rely on the reaction of carboxylic acids or acid chlorides with stoichiometric amounts of Brønsted or Lewis acids, which poses problems for cyclization precursor preparation, product isolation, and functional group compatibility. Our group has reported that the use of Meldrum's acid as acylating agent provides a solution that overcomes the problems associated with the carbocyclization of carboxylic acids or acid chlorides. Furthermore, the cyclization of Meldrum's acid derivatives provides an expedient and efficient entry into 2-substituted 1-indanones.[4] Enolizable benzyl Meldrum's acid derivatives are readily functionalized under mild reactions conditions. Such facile α-alkylations are significantly more difficult for carboxylic acids and acid chlorides, and therefore synthesis of 2-substituted 1-indanones is typically performed after Friedel-Crafts acylation, where the standard difficulties of mono-alkylating ketones present themselves. In addition, compared to traditional acylation procedures, the generation of volatile and inert side products, acetone and $CO_2$, simplified product isolation.[5,6,7]

**Table 1.** Preparation of 2-substituted 1-indanones

| Entry | Quaternized Meldrum's acid | $Sc(OTf)_3$ (mol%) | Time (min) | Indanone | Yield (%) |
|---|---|---|---|---|---|
| |  | | |  | |
| 1 | R = Me | 10 | 45 | R = Me | 77 |
| 2 | R = Ph | 10 | 60 | R = Ph | 67 |
| 3 | R = Bn | 10 | 45 | R = Bn | 80 |
| 4 | R = $CHCH=CH_2$ | 10 | 45 | R = $CHCH=CH_2$ | 76 |
| 5 | R = $CH_2CCH$ | 10 | 45 | R = $CH_2CCH$ | 80 |
| 6 | R = $CH_2C_6H_4$ (4-CN) | 10 | 320 | R = $CH_2C_6H_4$ (4-CN) | 78 |
| 7 | R = $CH_2C_6H_4$ (4-$NO_2$) | 10 | 250 | R = $CH_2C_6H_4$ (4-$NO_2$) | 81 |
| 8 | R = $CH_2C_6H_5$ | 7 | 85 | R = $CH_2C_6H_5$ | 80 |
| |  | | |  | |
| 9 | R = OMe | 10 | 45 | R = OMe | 80 |
| 10 | R = Me | 11 | 30 | R = Me | 87 |
| |  | | |  | |
| 11 | R = Me | 10 | 20 | R = Me | 69 |
| 12 | R = TBDPS | 12 | 20 | R = TBDPS | 94 |
| |  | | |  | |
| 13 | R = Me | 9 | 20 | R = Me | 75 |
| 14 | R = TBDPS | 9 | 30 | R = TBDPS | 86 |
| 15 | R = TIPS | 10 | 40 | R = TIPS | 77 |

As shown in Table 1, reactions of quaternized benzyl Meldrum's acids gave 2-substituted 1-indanones in excellent yields. A variety of groups could be added to C(5) of the starting materials, leading to diverse 2-substituents in the products while demonstrating further functional group compatibility (alkenes, alkynes, nitro and cyano groups).

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**7.** Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. *J. Org. Chem*. **2005**, *70*, 1316–1327.

## Appendix
## Chemical Abstracts Nomenclature; (Registry Number)

3,4-Dimethoxybenzaldehyde; (120-14-9)
2,2-Dimethyl-1,3-dioxane-4,6-dione; (2033-24-1)
Piperidine; (110-89-4)
Sodium Triacetoxyborohydride; (56553-60-7)
Iodomethane; (74-88-4)
Trimethylsilyl Trifluoromethanesulfonate; (27607-77-8)

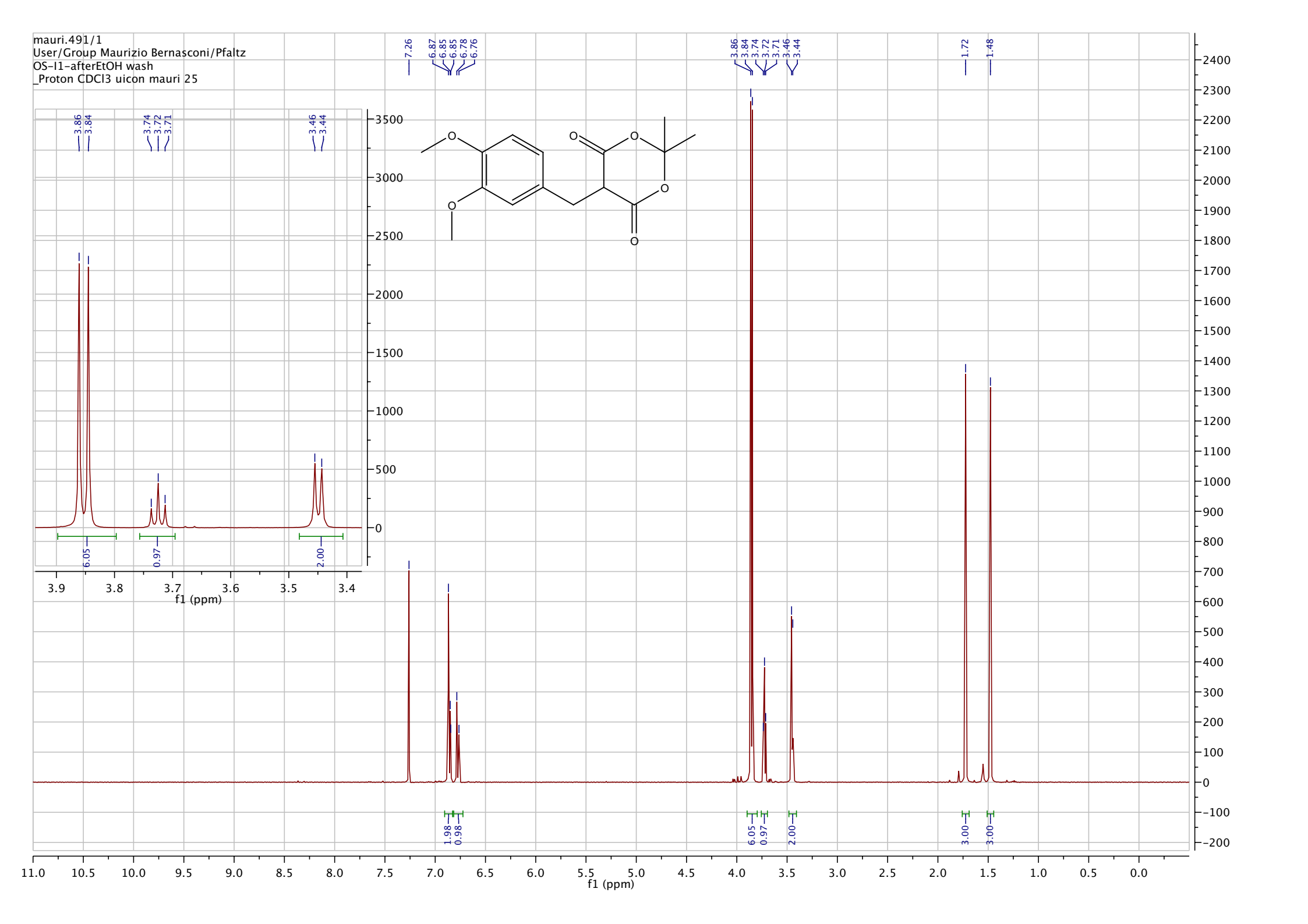
Eric Fillion received his undergraduate degree in biochemistry at the Universite de Sherbrooke. After completing his M. Sc. in medicinal chemistry at the Université de Montreal with Professor Denis Gravel, he began his doctoral studies at the University of Toronto under the direction of Professor Mark Lautens. From 1998-2000, he was an NSERC post-doctoral fellow in the laboratories of Professor Larry E. Overman at the University of California, Irvine. In August 2000, he joined the Department of Chemistry at the University of Waterloo, where he is currently a Professor of Chemistry.

Tiantong (Tim) Lou was born in 1987 in Nanjing, China and moved with his family to Canada in 1997. Starting in the summer of 2008, he joined the Fillion group as an NSERC USRA and worked on the asymmetric methylation of alkylidene Meldrum's acids.

E-Ting Liao was born in 1985 in Taiwan. She graduated with a Bachelor's degree in Biomedical Sciences in 2008 from the University of Waterloo. She is now in the university's School of Pharmacy. As an NSERC USRA student, E-Ting has worked with Professor Eric Fillion's group for three summers, dealing with Meldrum's Acid derivatives. Her projects involved 1,6-conjugate addition of dialkylzinc reagents to 5-(3-aryl-2-propenylidene) Meldrum's Acids, as well as Friedel-Crafts acylation.

Ashraf Wilsily (born 1982) received a B.Sc. (Hons.) in Chemistry (2004) from the University of Waterloo. In 2005, he pursued a doctoral studies with Professor Eric Fillion in the area of asymmetric conjugate addition reactions and persistent intramolecular C–H•••X (X = O, S, Br, Cl, F) hydrogen bonds involving benzyl Meldrum acid derivatives. In January 2010, he joined the group of Professor Gregory C. Fu at MIT to pursue his postdoctoral studies.

Maurizio Bernasconi was born in 1985 in Mendrisio, Switzerland. He studied chemistry at the ETH Zürich where he received his M.Sc degree in 2009 after completing his Master thesis under the direction of F. D. Toste at the University of California, Berkeley. In 2009 he joined the lab of Andreas Pfaltz at the University of Basel, where he is currently carrying out his Ph.D. thesis working on Iridium catalyzed asymmetric hydrogenation.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3.84
3.74
3.72
3.71
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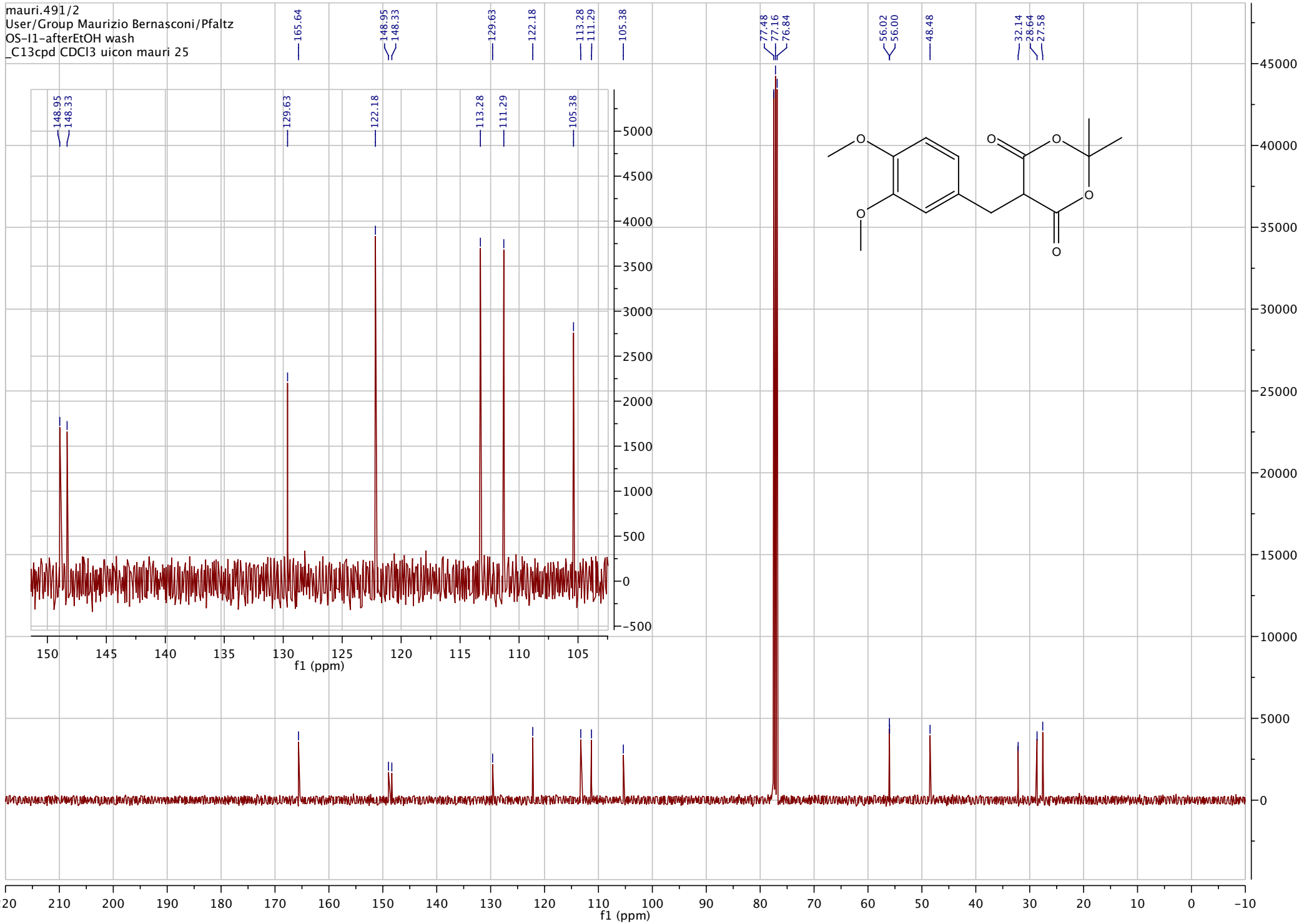
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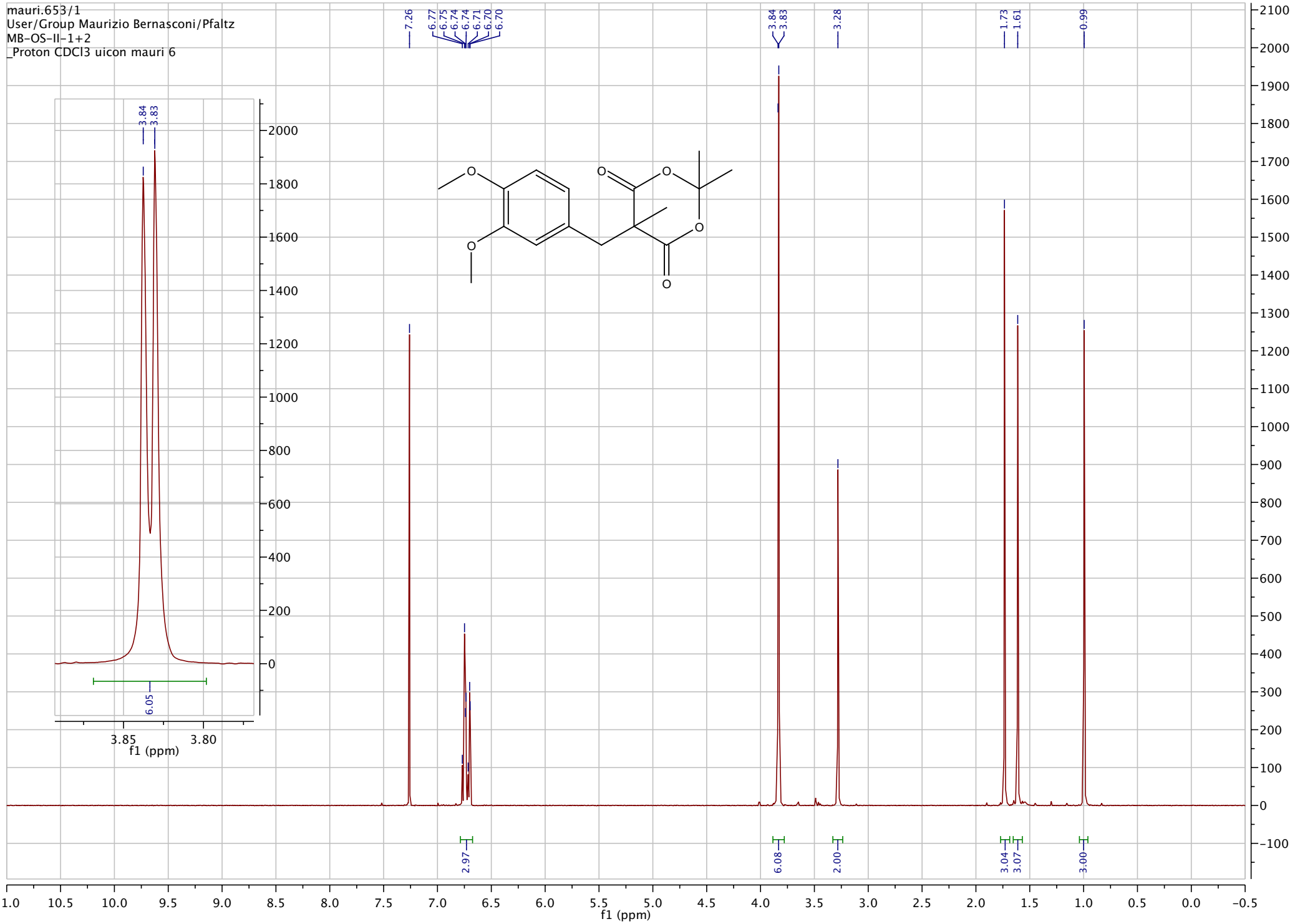
f1 (ppm)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6.70
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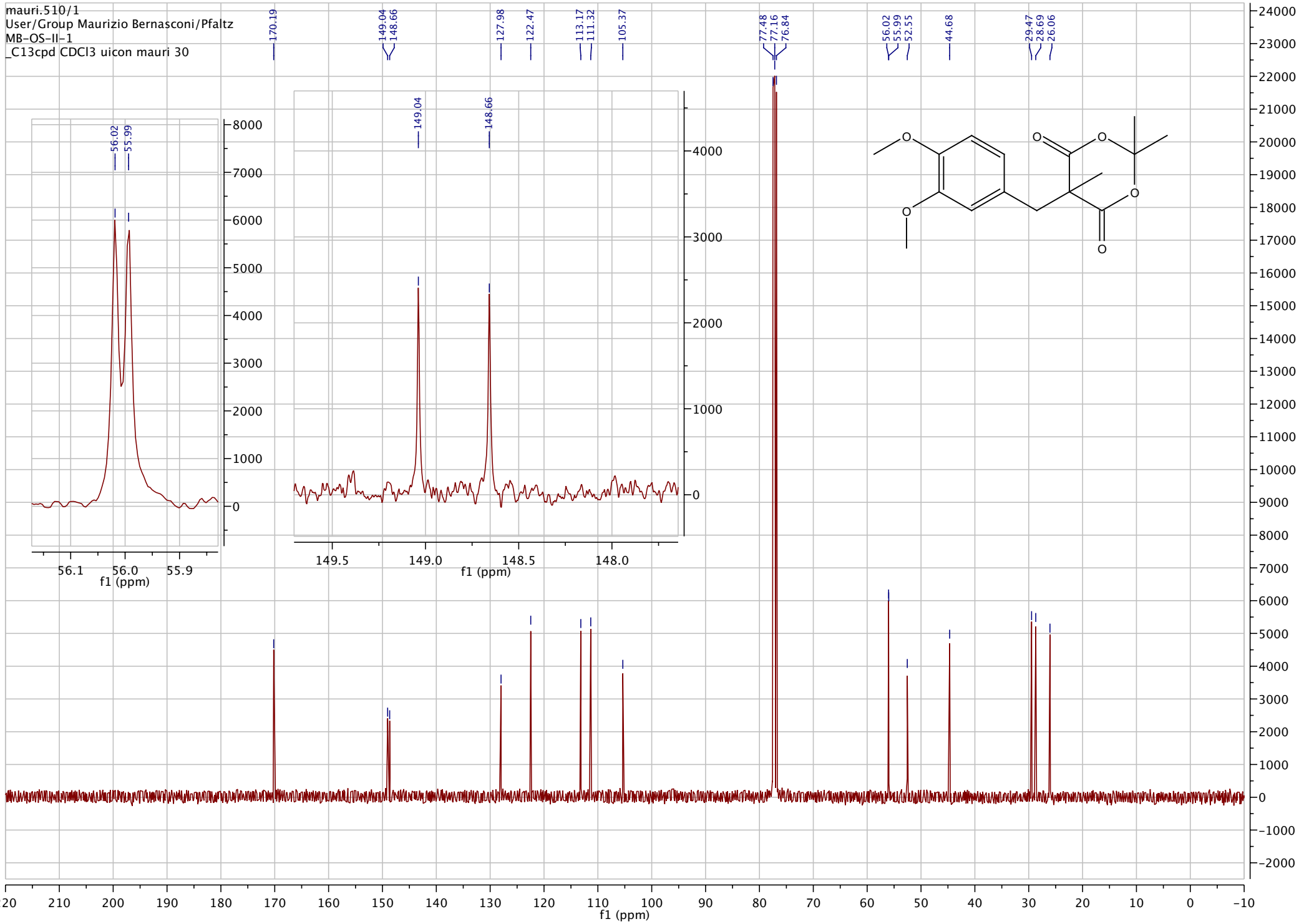
f1 (ppm)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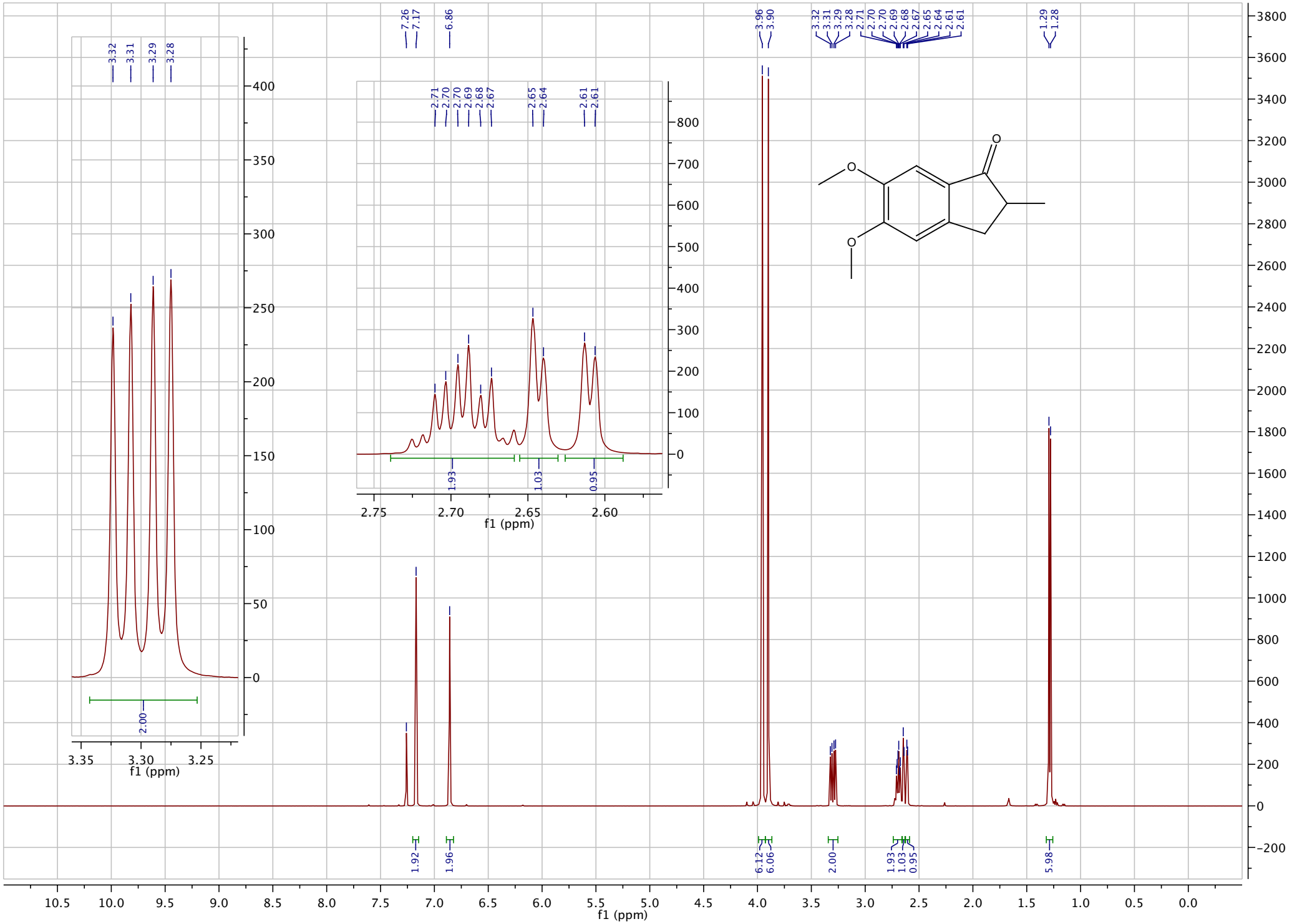
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2.68
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2.65
2.64
2.61
2.61
1.29
1.28
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6.06
2.00
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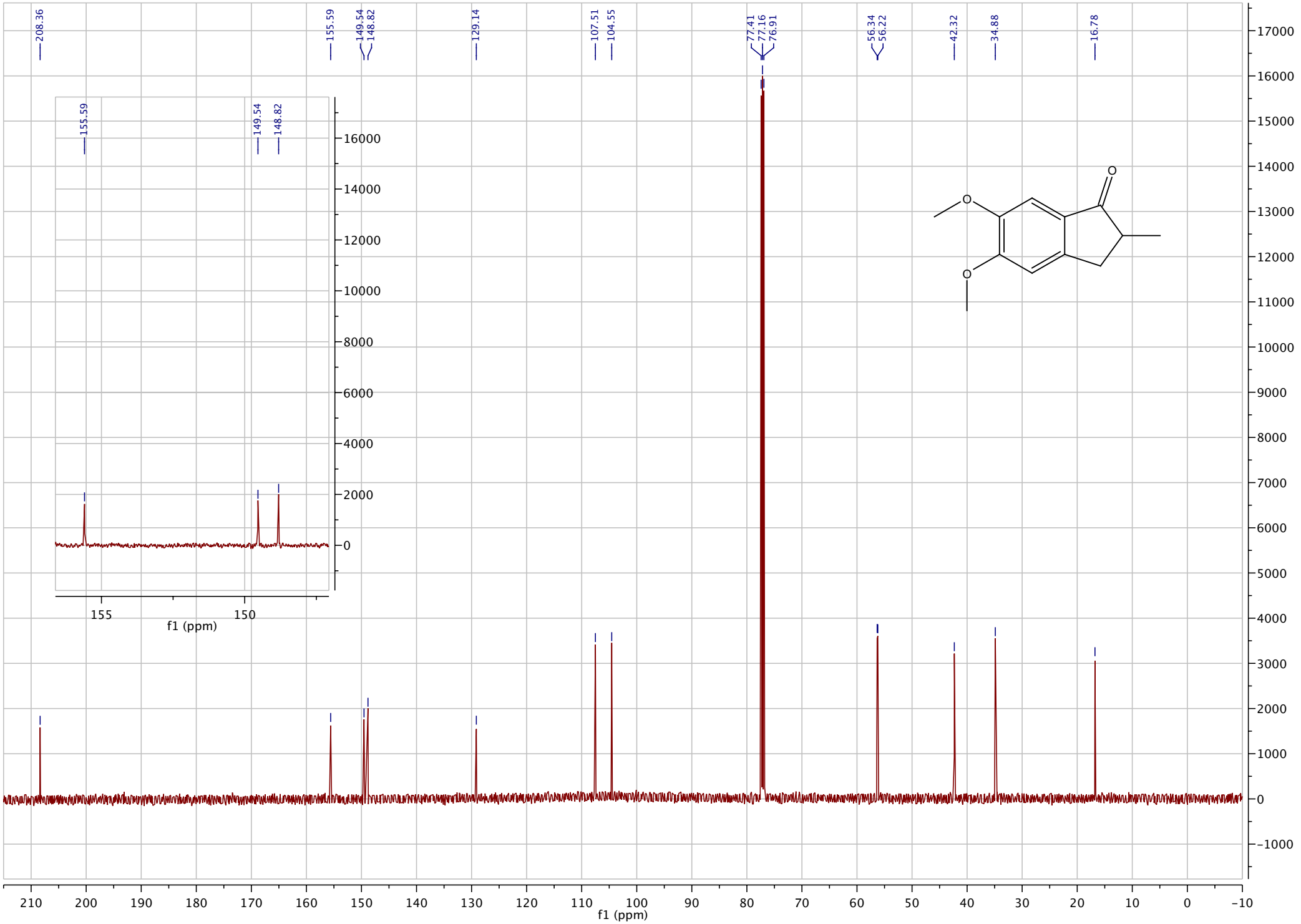
1.03
0.95
5.98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56.34
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34.88
16.78
f1 (ppm)