Organic Syntheses

Synthesis of Methyl 2-Bromo-3-oxocyclopent-1-ene-1-carboxylate

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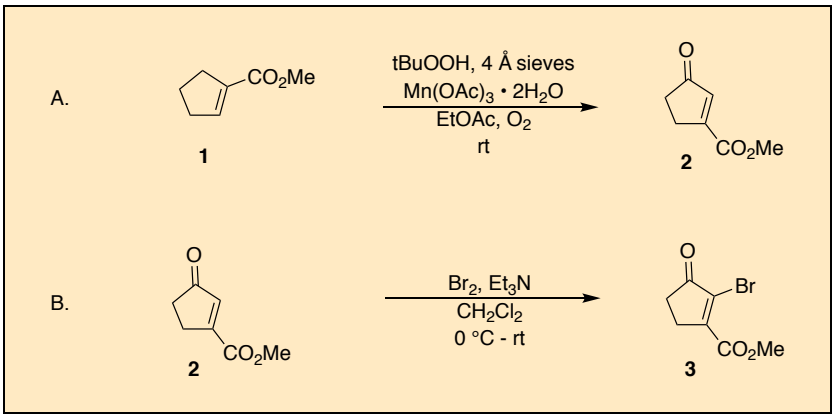
Checked by Leonardo J. Nannini and Erick M. Carreira



Procedure (Note 1)

A. *Methyl 3-oxocyclopent-1-ene-1-carboxylate* (**2**).[2] A 1000-mL, one-necked, oven-dried, round-bottomed flask equipped with a teflon-coated magnetic stir bar (25 mm x 10 mm) is fitted with a septum and an argon balloon, and then cooled to ambient temperature (21–23 °C). The flask is charged with methyl 1-cyclopentene-1-carboxylate (**1**) (Note 2) (7.0 g, 55 mmol, 1.0 equiv). Ethyl acetate (280 mL) (Note 3) is added, followed by 4 Å molecular sieves (7.0 g) (Note 4). The septum is replaced with a pressure-equalizing addition funnel that is capped with a septum. A *tert*-butylhydroperoxide solution in decane (5.5 M) (41 mL, 221 mmol, 4.0 equiv) is added via the addition funnel over 15 min (Figure 1) (Note 5). The

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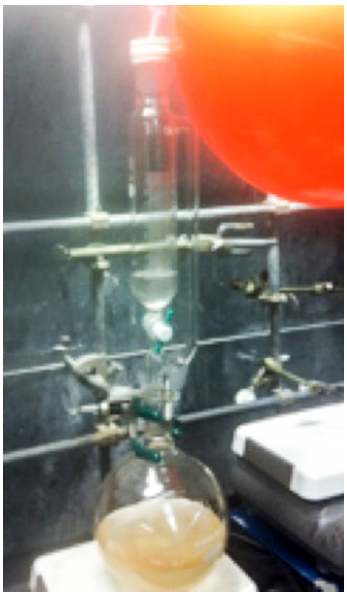

Figure 1. Addition of *t*-BuOOH

reaction mixture is stirred for 30 min. Manganese (III) acetate dihydrate (1.487 g, 5.5 mmol, 0.1 equiv) (Figure 2) (Note 6) is transferred to a vial in a glove bag under a nitrogen atmosphere and the solid is added quickly to the reaction mixture. The argon balloon is removed and the reaction flask is

Figure 2. Glove bag

flushed with oxygen using a balloon for 10 min (Figure 3). The reaction mixture is stirred under an oxygen atmosphere at 23 °C for 48 h using a balloon filled with oxygen (Figure 4) (Note 7). The reaction is monitored by TLC on silica using 30% EtOAc-hexane as the eluent (Note 8). After completion of the reaction, the reaction mixture is filtered through a Celite pad (Note 9) that is then washed with diethyl ether (40 mL). The filtrate is diluted with water (150 mL) and transferred to 1 L separatory funnel. The aqueous phase is separated and the organic layer is washed again with water (150 mL). The organic extract is tested for peroxides with KI starch paper and no color is observed (Note 10). The organic extract is dried over anhydrous sodium sulfate for 10 min and concentrated using a rotary evaporator (40 °C, 10 mmHg). A chromatography column (6.4 cm x 45 cm) is loaded with 150 g of silica gel (Note 11) and wetted with pentane (200 mL). Sand is placed on top of the silica gel. The crude compound is loaded on the column. Elution begins with 100% pentane (100 mL) and continues with diethyl ether in pentane 10% (100 mL), 20% (100 mL), and 30% (200 mL), which are collected in 250 mL Erlenmeyer flasks. The desired compound elutes with 40% diethyl ether/pentane (700 mL), which is collected in 10 mL test tubes. The collected fractions (5-75) are concentrated by rotary evaporation (40 °C, 10 mmHg). The compound is obtained as colorless oil (3.0 g, 40% yield) (Notes 12 and 13). The purity of the compound is determined to be 94.5 % by qNMR (Note 14).

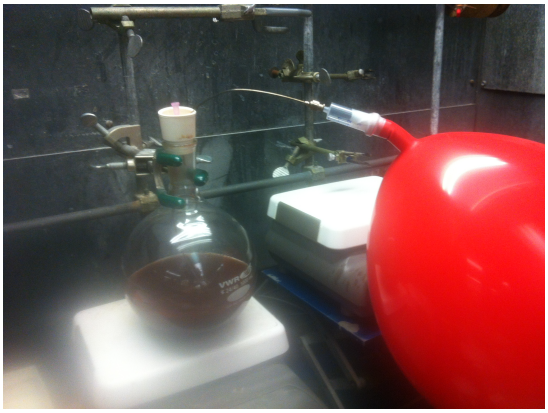

Fig 3. Purging with oxygen

Fig 4. Oxidation under oxygen

B. *Methyl 2-bromo-3-oxocyclopent-1-ene-1-carboxylate* (**3**).[3] A 1000-mL, three-necked, oven-dried, round-bottomed flask is equipped with a teflon-coated magnetic stir bar (25 mm x 10 mm). The middle neck is fitted with a pressure equalizing addition funnel (150 mL) equipped with a rubber septum and an argon balloon. One side neck is equipped with a septum pierced by a thermometer and the remaining neck is sealed with a rubber septum. The flask is charged with methyl 3-oxocyclopent-1-enecarboxylate (**2**) (3.0 g, 21.4 mmol, 1.0 equiv), followed by the addition of dichloromethane (214 mL, 0.1 M) by syringe. The reaction flask is cooled in an ice bath with stirring for 10 min (Note 15). A solution of bromine (1.62 mL, 32.1 mmol, 1.5 equiv) (Note 16) in dichloromethane (40 mL) is charged into the addition funnel and is added dropwise to the reaction mixture over 30 min. The addition funnel is rinsed with dichloromethane (4 mL). The initially colorless solution turned red over the course of this addition (Figure 5A). After complete addition of the bromine solution, the reaction mixture is warmed to 23 °C and stirred for 1 h (Figure 5B). The reaction mixture is again cooled in an ice bath and a solution of triethylamine (5.98 mL, 42.8 mmol, 2.0 equiv) (Note 17) in dichloromethane (40 mL) (Note 18) is carefully added dropwise through the addition funnel

to the reaction mixture over 30 min (Note 19). The red-colored solution turns yellow during the addition of triethylamine (Figure 6A) (Note 20). After complete addition, the reaction mixture is again warmed to 23 °C and stirred for 8 h, during which time the yellow color turns red (Figure 6B). The reaction is monitored by TLC on silica using 30% EtOAc-hexane as the eluent (Note 21). The reaction mixture is diluted with dichloromethane (200 mL) and washed with 1M HCl (2 x 250 mL) followed by saturated $Na_2S_2O_3$ solution (1 x 200 mL) in a 1 L separatory funnel. The organic extract is dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator (40 °C, 10 mmHg). Dry silica gel (100 g) (Note 11) is added to a chromatography column (6.4 cm x 45 cm) and pentane (200 mL) is used to wet the column. Sand is added on the top of the silica gel, and then the crude compound is loaded onto the sand at the top of the column. Elution is started with 100% pentane (100 mL) and continues with 5% diethyl ether in pentane (100 mL), 10% (100 mL), 20% (100 mL), 30% (100 mL), 40% (100 mL) and 50% (300 mL). Fractions are collected in 10 mL test tubes beginning with 40% diethyl ether in pentane. Fractions containing the desired compound (13-49) are concentrated by rotary evaporator (40 °C, 10 mmHg). The compound is obtained as a off-white solid (3.0 g, 64%) (Notes 22 and 23), and the purity of the product is 95% as determined by qNMR (Note 24).

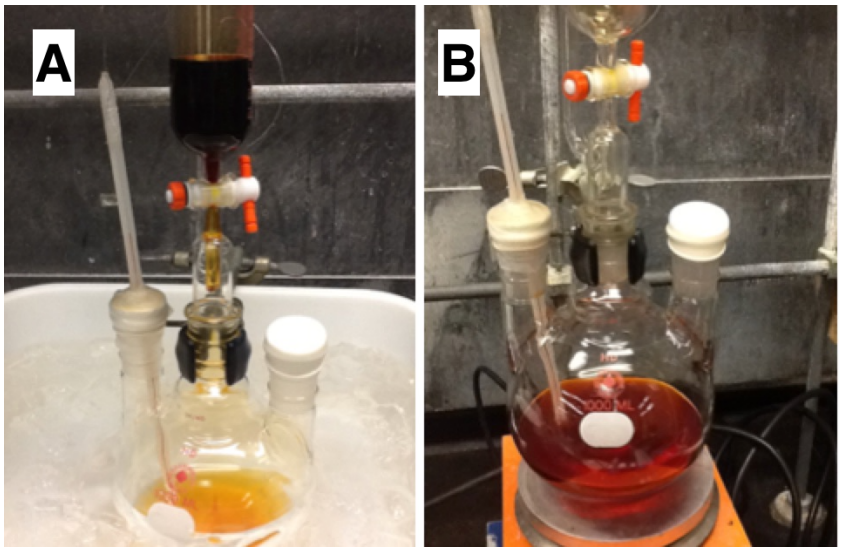

Figure 5. A) Addition of bromine; B) After addition of bromine

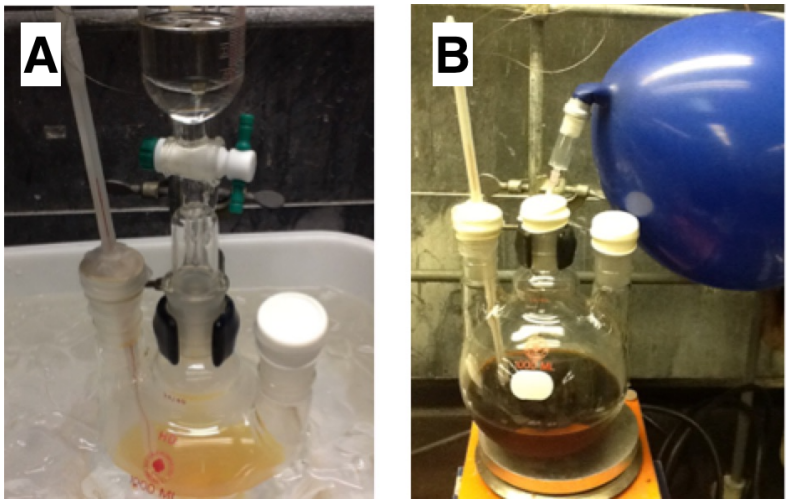

Figure 6. A) Addition of triethylamine; B) After addition of triethylamine

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 methyl 1-cyclopentene-1-carboxylate, molecular sieves, *tert*-butylhydroperoxide, decane, manganese (III) acetate dihydrate, oxygen, nitrogen, argon,

ethyl acetate, hexane, celite, sodium sulfate, silica gel, pentane, diethyl ether, dichloromethane, bromine, triethylamine, iodine, and sodium thiosulfate.

2. Methyl 1-cyclopentene-1-carboxylate was purchased from Ark Pharm and used as received.
3. Ethyl acetate was purchased from Fisher Scientific and distilled over CaH_2.
4. Molecular sieves (4Å) were activated in an oven at 100 °C heat for more than 2 weeks.
5. *tert*-Butyl hydroperoxide solution (5.5 M in decane) was purchased from Sigma Aldrich and used as received.
6. Manganese(III) acetate dihydrate (97%) was purchased from Sigma-Aldrich and used as received. This catalyst was weighed in a glove bag under nitrogen atmosphere. The checkers compared the reaction with and without glove bag, observing no change in the yield.
7. Two oxygen balloons are used over the course of the two days. One balloon is used each day.
8. TLC was performed using 30% EtOAc-hexane as eluent. Starting material and product can be visualized under UV lamp and with an iodine stain. The starting material has R_f = 0.6 (pink) and the product has R_f = 0.3 (pink).
9. Celite was purchased from Fisher and used as received.
10. Starch paper was purchased from Fisher Scientific.
11. Silica gel (F60, particle size 230-400 mesh) was purchased from Silicycle and used as received.
12. The product has been characterized as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.53–2.55 (m, 2H), 2.85–2.87 (m, 2H), 3.87 (s, 3H), 6.76 (dd, J = 3.0, 2.0 Hz, 1H); ^{13}C NMR (125 MHz) δ: 27.6, 35.7, 52.7, 138.4, 164.0, 164.9, 209.3.
13. Other reactions performed on half and full scale provided yields of 1.6 g (42%) and 2.7 g (36%), respectively.
14. Checkers determined the purity by qNMR using 8.8 mg of compound **2** and 3.3 mg of standard 1,2,4,5-tetrachlorobenzene (purity 88.1%). The purity was determined using the following equation.

$$Px = \frac{Ix}{Istd} \times \frac{Nstd}{Nx} \times \frac{mstd}{mx} \times \frac{Mx}{Mstd} \times Pstd$$

P = Purity, x = product, std = standard, Ix = Integration of the methyl peak, Istd = Integration of the standard, Nstd = Number of protons for the standard, Nx = Number of protons for methyl signal, m = Prepared weight, M = Molecular weight.

15. The internal temperature of the reaction mixture was measured to be between 1 °C and 3 °C during the reaction.
16. Reagent grade bromine was purchased from Sigma-Aldrich and used as received.
17. Triethylamine was purchased from Sigma-Aldrich and used as received.
18. Dichloromethane was purchased from Fisher and distilled over CaH_2.
19. White fumes were formed during the addition of triethylamine. Triethylamine was carefully added dropwise.
20. The internal temperature of the reaction mixture was measured to be between 1 °C and 3 °C during the reaction.
21. TLC was performed using 30% EtOAc-hexane as eluent. Starting material and product were visualized under a UV lamp. Both starting material and product have same $R_f = 0.3$ (pink).
22. The product has been characterized as follows: mp 66–68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.65 (m, 2H), 2.89 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz) δ: 28.4, 32.7, 52.8, 131.1, 157.7, 163.9, 201.6; FTIR (cm^{-1}) 2954, 1725, 1436, 1282, 1202, 1178; ESI [M + H] *m*/*z* calcd for $C_7H_8BrO_3$: 218.9651. Found: 218.9651.
23. A second run on half scale provided 0.9 g (41%) of compound **3** as an off-white solid.
24. Checkers determined the purity by qNMR using 4.3 mg of compound **3** and 4 mg of standard 1,2,4,5-tetrachlorobenzene (purity 99.8%). Purity was calculated using the equation in Note 13.

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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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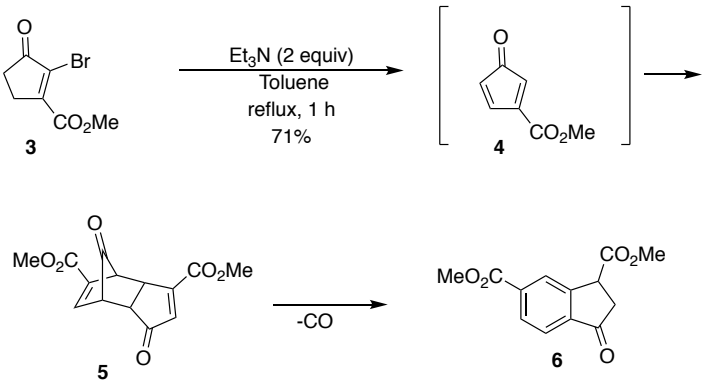
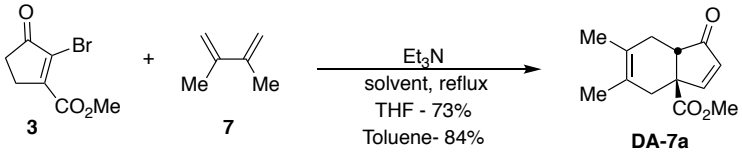
Discussion

Cyclopentadienones can be used as dienophiles in [4+2] cycloaddition reactions,[4,5] but they are highly reactive and dimerize rapidly.[4] Treatment of 2-bromocyclopentenone derivative **3** with triethylamine in refluxing toluene for 1 h affords the indanone **6** in 71% yield. The reaction presumably proceeds via formation of intermediate cyclopentadienone **4**, which undergoes dimerization and subsequent decarbonylation to generate the product **6** (Scheme 1).



Scheme 1. Generation of a cyclopentadienone 4 from 3

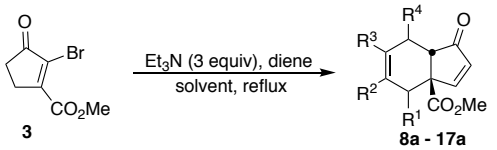
Recently, our group developed conditions suitable for [4+2] cycloadditions using **3.** To optimize the reaction conditions, we treated **3** and 2,3-dimethylbutadiene (**7**) with various bases and in various solvents. Toluene and tetrahydrofuran (THF) showed promising results. The starting material decomposed when treated with strong bases such as DBU, and the use of hindered base 2,2,6,6-tetramethylpiperidine (TMP) in THF solvent produced cycloadducts in only moderate yield. The reaction proceeded very well with triethylamine (Scheme 2).



Scheme 2. [4+2] Cycloaddition reaction of 3 with 7

With the optimized conditions in hand, several dienes were tested in the cycloaddition. The diene **8** produced the cycloaddition product **8a** in toluene in very good yield (82%). Cyclopentadiene (**9**) afforded the corresponding cycloadduct in THF in 89% yield. Cyclohexadiene (**10**) afforded **10a** in only 17% yield under these conditions. However, diene **10** gave a better yield (57%) using toluene as solvent. Interestingly, the diene **11** produced the corresponding cylcoadduct **11a** as single regio- and stereoisomer in 80% yield. The product **11a** has the carbocylic skeleton of a steroid, so this methodology could be used in various syntheses of steroid-like molecules.

Table 1. [4+2] Cycloaddition reactions of cyclopentadienone 6



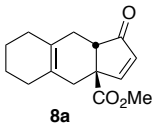
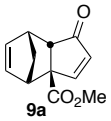
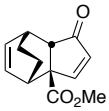
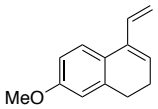
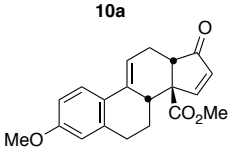
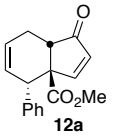
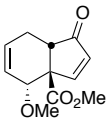
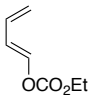
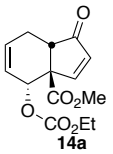
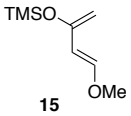
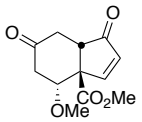
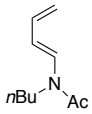
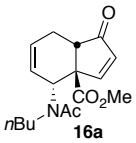
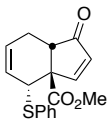
Substrate	Diene	Time	Solvent	Product	Yield (%)
1	 **8**	1.25	Toluene	 **8a**	82
2	 **9**	2.75	THF	 **9a**	89
3	 **10**	4 1.5	THF Toluene	 **10a**	17 57
4	 **11**	1.5	Toluene	 **11a**	80
5	 **12**	1.25	Toluene	 **12a**	66
6	 **13**	6	THF	 **13a**	52
7	 **14**	1.75	Toluene	 **14a**	72

Table 1 (cont.)

Substrate	Diene	Time	Solvent	Product	Yield (%)
8	 **15**	5	Benzene	 **15a**	53
9	 **16**	1.75	Toluene	 **16a**	84
10	 **17**	1.25	Toluene	 **17a**	69

To ascertain the electronic effects on the cycloaddition, various experiments were conducted with the 1-substituted dienes (Table 1, entries 5-7). The dienes 1-phenylbutadiene **12** and 1-methoxybutadiene **13** afforded the corresponding Diels-Alder adducts **12a** and **13a** in yields of 66% and 52%, respectively. However, under the same conditions the diene **14** (2 equiv) gave **14a** in only 30% yield. This might be due to the lower reactivity of diene **14**. Increasing the equivalents of diene to five increased the cycloadduct yield to 72%. Danishefsky's diene **15** produced the cycloadduct **15a** in 53% yield under standard conditions but benefited from the presence of 20 mol% triethylamine hydrobromide. The nitrogen and sulfur substituted dienes **16** and **17** also produced the corresponding cycloadducts in good yields.

In conclusion, we have developed an efficient generalized procedure for the synthesis of methyl 2-bromo-3-oxocyclopent-1-ene-1-carboxylate **3**. This substrate can be used in [4+2] cycloaddition reactions and these reactions proceed with excellent regioselectivity and diasteroselectivity.

References

1. Department of Chemistry, University of Missouri-Columbia, 125 Chemistry Building, Columbia, MO 65211. Email: HarmataM@missouri.edu. Eurofins Biopharm Product Testing, 7200 East ABC Lane, Columbia, MO 65202. This work was supported by the National Science Foundation.
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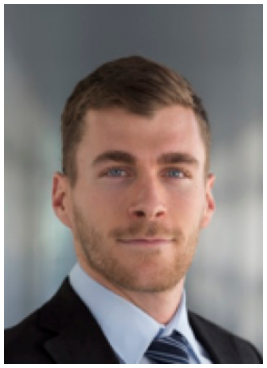
Appendix
Chemical Abstracts Nomenclature (Registry Number)

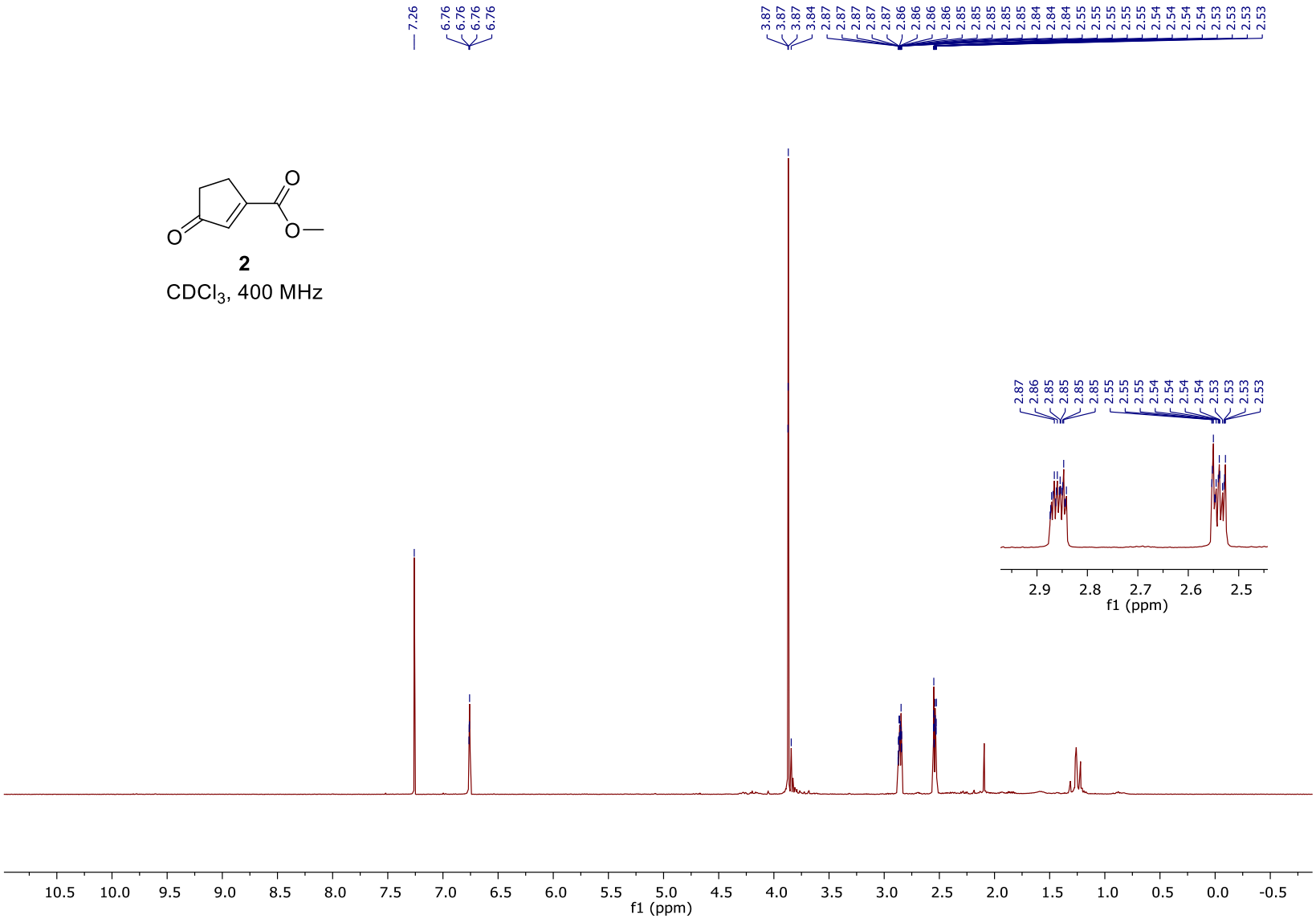
Methyl 1-cyclopentene-1-carboxylate (25662-28-6)
tert-Butyl hydroperoxide solution (75-91-2)
Manganese(III) acetate dihydrate (19513-05-4)
Bromine (7726-95-6)
Triethylamine (121-44-8)

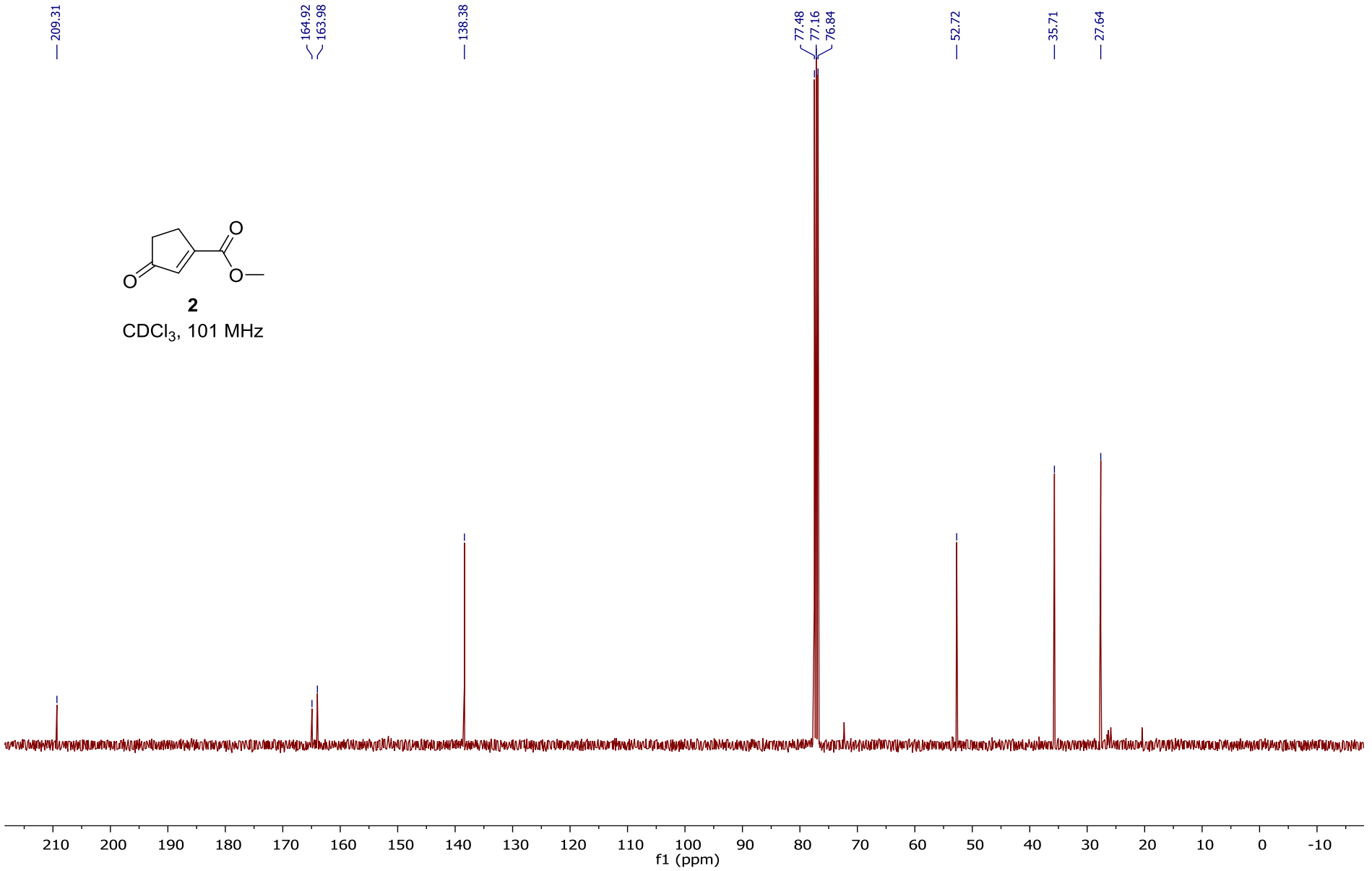
Rama Rao Tata was born in India. He received his Master degree in organic chemistry in 2007 from the Pondicherry University. He received his doctoral degree in 2015 from the University of Missouri-Columbia under the supervision of Prof. Michael Harmata. He performed his postdoctoral work in University of Missouri-Columbia under the supervision of Prof. Bret Ulery and worked on the synthesis of biodegradable polymers and their applications in bone and spinal cord regeneration. Currently, he is employed as a staff scientist II at Eurofina Biopharma Product Testing in Columbia, MO, working on radiolabeled pharmaceuti-cals and 14C-labeled pesticides.

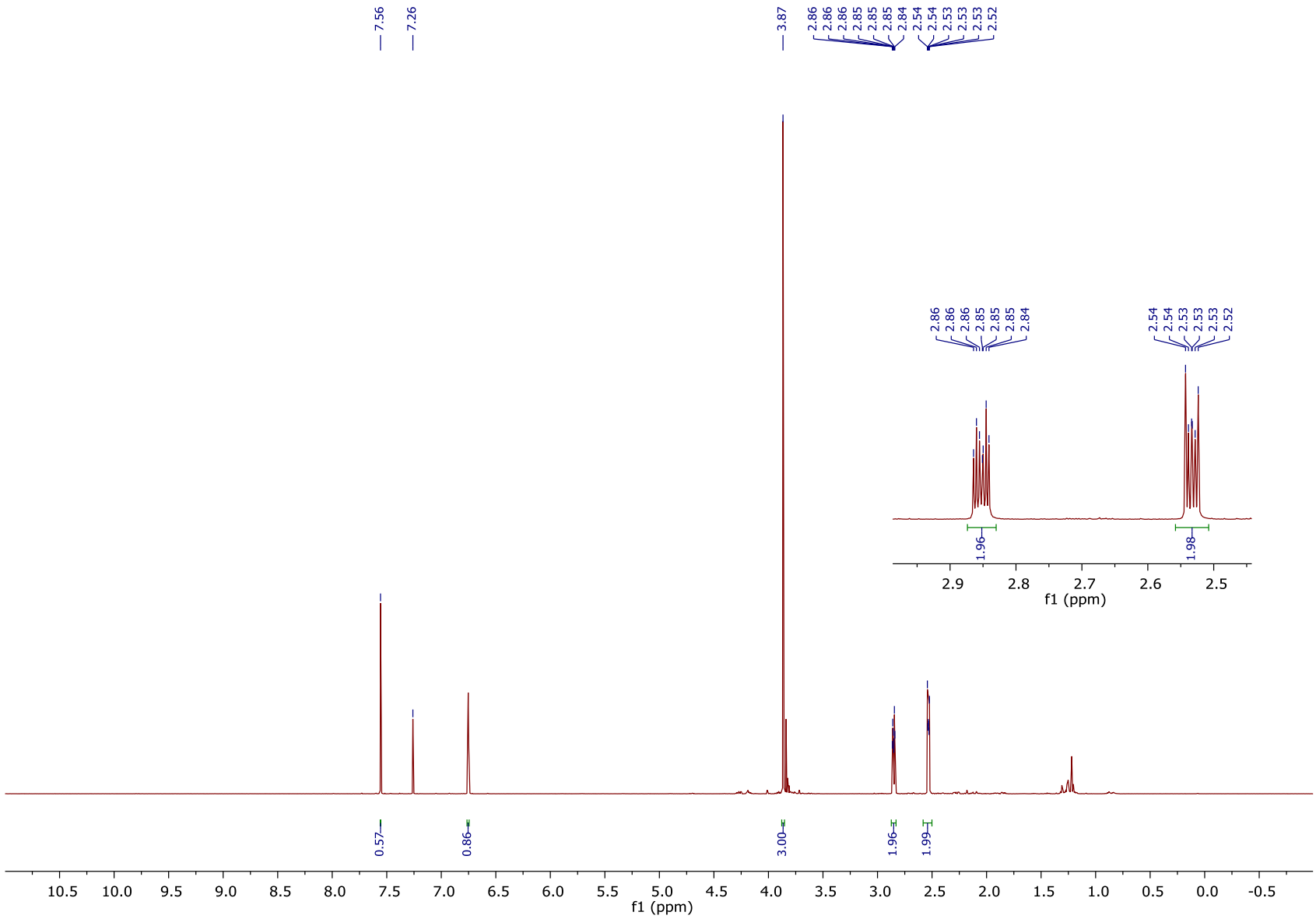
Michael Harmata was born in Chicago, Illinois and lived on the south side of Chicago for the first 20 years of his life. He received a bachelor's degree from the University of Illinois-Chicago and earned his Ph.D. with Scott Denmark at UIUC. He then headed west to do an NIH postdoctoral fellowship with 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.

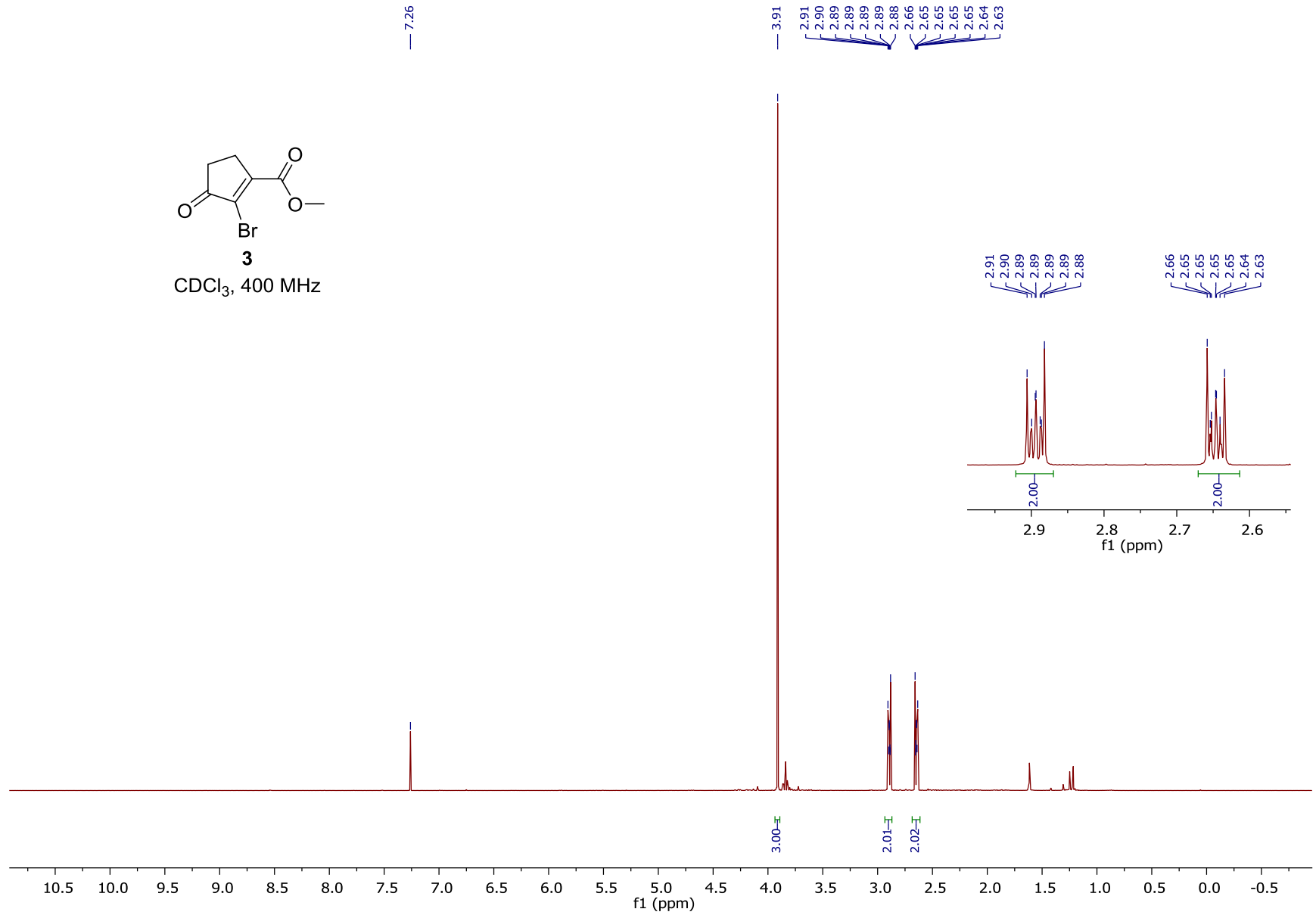


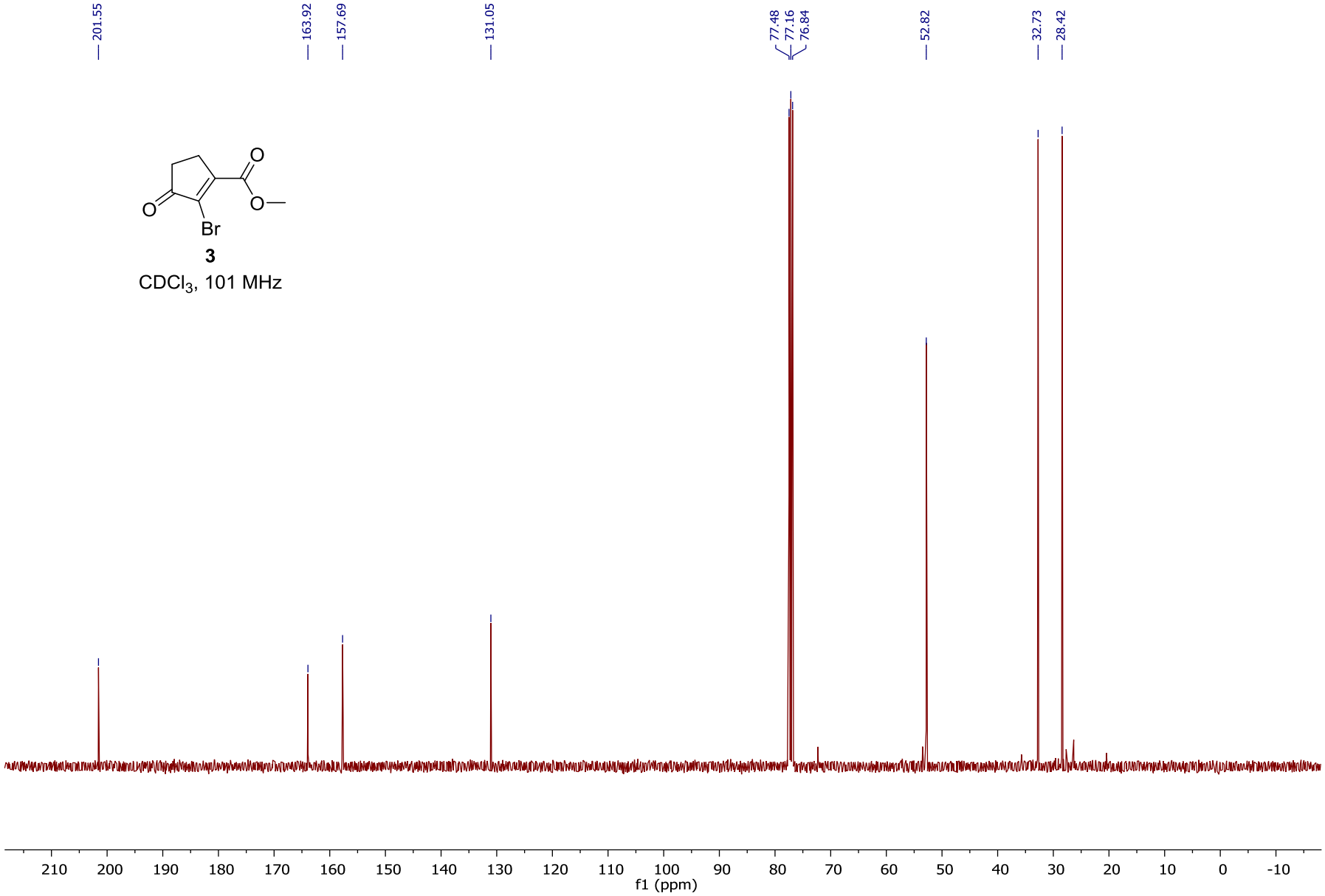
Leonardo J. Nannini was born in Bellinzona (Switzerland), where he lived for the first 20 years of his life. He then moved to Zurich, where he earned the bachelor's and master degree in interdisciplinary science at ETH. He has been a Ph.D. candidate under the supervision of Erick M. Carreira since 2014.

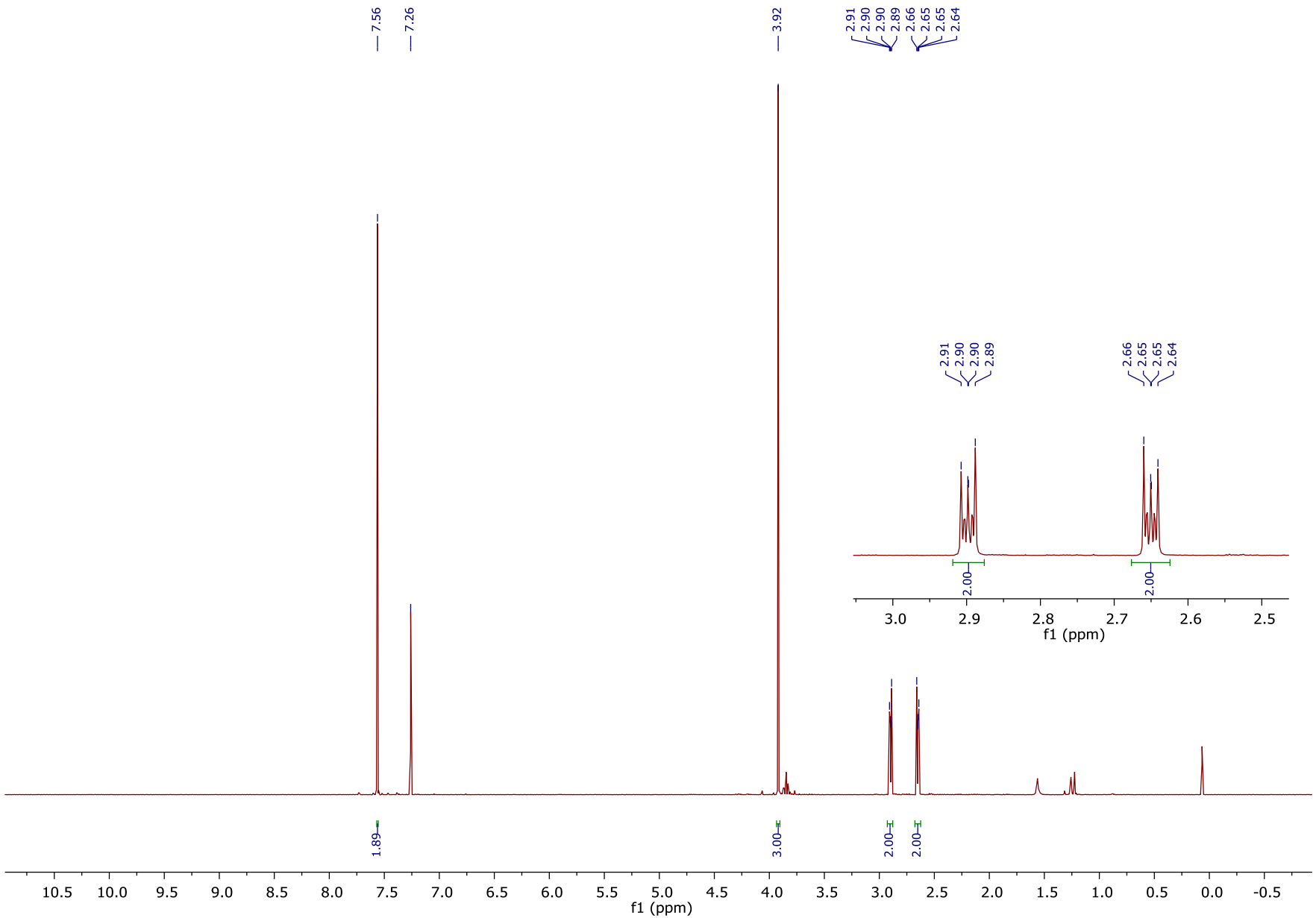

7.26
6.76
6.76
6.76
6.76
3.87
3.87
3.87
3.84
2.87
2.87
2.87
2.87
2.86
2.86
2.86
2.85
2.85
2.85
2.85
2.84
2.84
2.84
2.55
2.55
2.55
2.54
2.54
2.54
2.54
2.53
2.53
2.53
O
O
O
2
CDCl3, 400 MHz
2.87
2.86
2.85
2.85
2.85
2.85
2.55
2.55
2.55
2.54
2.54
2.54
2.54
2.53
2.53
2.53
2.53
2.9
2.8
2.7
2.6
2.5
f1 (ppm)
10.5
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)


209.31
164.92
163.98
138.38
77.48
77.16
76.84
52.72
35.71
27.64
O
O
O
2
CDCl3, 101 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.56
7.26
3.87
2.86
2.86
2.86
2.85
2.85
2.85
2.84
2.54
2.54
2.53
2.53
2.53
2.52
0.57
0.86
3.00
1.96
1.99
10.5 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)
1.96
1.98
2.9 2.8 2.7 2.6 2.5
f1 (ppm)


7.26
3.91
2.91
2.90
2.89
2.89
2.89
2.89
2.88
2.66
2.65
2.65
2.65
2.65
2.64
2.63
O
O
O
Br
3
CDCl3, 400 MHz
2.00
2.00
2.9
2.8
2.7
2.6
f1 (ppm)
3.00
2.01
2.02
10.5
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)


201.55
163.92
157.69
131.05
77.48
77.16
76.84
52.82
32.73
28.42
O
O
O
Br
3
CDCl3, 101 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.56
7.26
3.92
2.91
2.90
2.90
2.89
2.66
2.65
2.65
2.64
1.89
3.00
2.00
2.00
f1 (ppm)
2.00
2.00
f1 (ppm)