A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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

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

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.

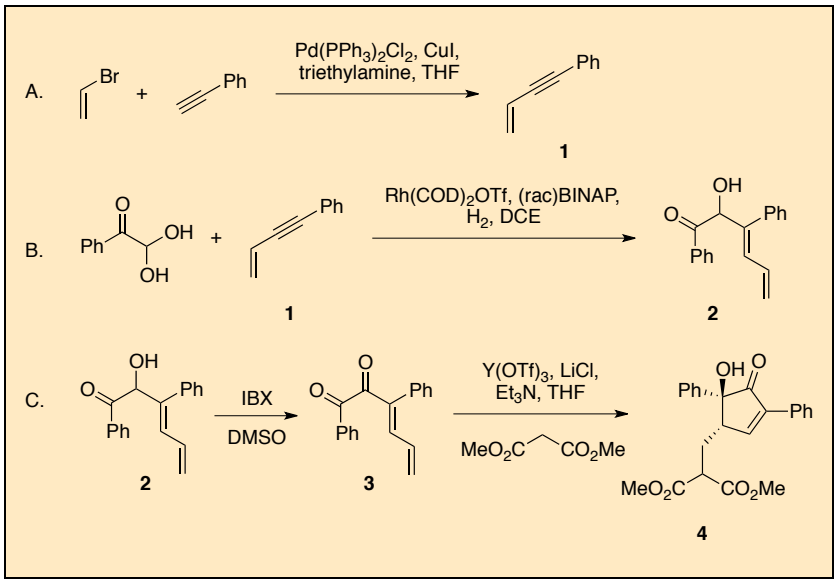
Organic Syntheses

Preparation of 5-Hydroxycyclopentenones Via Conjugate Addition-Initiated Nazarov Cyclization

Joshua L. Brooks, Yu-Wen Huang, and Alison J. Frontier*[1]

Department of Chemistry, University of Rochester, Rochester, NY 14627

Checked by Raffael Vorberg and Erick M. Carreira



Procedure

Caution: IBX is heat- and shock-sensitive compound, showing exothermic behavior at temperatures exceeding 130 °C. All operations should be conducted behind an explosion shield.

A. *3-Buten-1-yn-1-yl-benzene (**1**).* An oven-dried 1-L, three-necked (2 x 29/32 and 1 x 14.5/23 joint) round-bottomed flask containing a Teflon-

DOI: 10.15227/orgsyn.091.0093

coated magnetic stir bar (55 x 8 mm), equipped with three rubber septa and a contact thermometer inserted through the rubber septa in the center neck, is charged with bis(triphenylphosphine)palladium(II) dichloride (2.81 g, 4.00 mmol, 0.02 equiv) (Note 1) and copper(I) iodide (0.38 g, 2.00 mmol, 0.01 equiv.). The flask is then purged with argon, followed by the addition of anhydrous tetrahydrofuran (200 mL) (Note 2) and vinyl bromide (1 M solution in tetrahydrofuran, 200 mL, 200 mmol). The solution is then cooled to 0 ºC with an ice bath. Triethylamine (70.0 mL, 500 mmol, 2.5 equiv) is added over the course of 90 sec, which is followed by the addition of phenylacetylene (23.0 mL, 210 mmol, 1.05 equiv) over the course of 30 sec, at which time the solution turns black (Note 3). The solution stirs for 1 h at 0 ºC, after which the ice bath is removed and the solution is stirred at room temperature for an additional 12 h (Note 4).

The reaction is diluted with saturated aqueous NH_4Cl solution (300 mL), and the resulting solution is transferred to a 1-L separatory funnel. The aqueous phase is separated and extracted with diethyl ether (3 x 100 mL). The combined organic layers are washed sequentially with 10% aqueous HCl solution (200 mL) and saturated NaCl solution (200 mL). The organic layer is then dried over $MgSO_4$ (20 g), filtered through a 250-mL coarse porosity sintered glass funnel, and concentrated by rotary evaporation (25 ºC, 20 mmHg). The resulting oil is transferred to a 100-mL round-bottomed flask equipped with Teflon-coated magnetic stir bar (25 x 6 mm). The product is distilled under vacuum through a 12 cm Vigreux column equipped with a short path distilling head with Vigreux indentations connected to a spider (3 x 14.5/23 joint). The sample is placed under vacuum (3.7 mmHg) and the temperature is slowly increased until distillation commences. A forerun (ca. 1 mL) is collected and discarded, and the desired product is then obtained, distilling at 63–65 ºC (3.7 mmHg) to yield pure **1** as a colorless oil (19.4-22.2 g, 151-173 mmol, 75-86%) (Notes 5 and 6).

B. *(±)-(E)-2-Hydroxy-1,3-diphenylhexa-3,5-dien-1-one (**2**)*.[2] An oven-dried, 100-mL one-necked (29/32 joint) round-bottomed flask containing a Teflon-coated magnetic stir bar (14 x 6 mm) is purged with argon, and bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (0.80 g, 1.70 mmol, 0.020 equiv), (±)-BINAP (1.17 g, 1.88 mmol, 0.022 equiv), and anhydrous 1,2-dichloroethane (50 mL) (Note 7) are added. The solution is purged with argon for 15 min. A separate oven-dried 500-mL, one-necked (29/32 joint) round-bottomed flask containing a Teflon-coated magnetic stir bar (38 x 7 mm) is purged with argon, and phenylglyoxal monohydrate (13.0 g,

85.4 mmol) (Note 7), **1** (16.3 g, 127.0 mmol, 1.50 equiv), and anhydrous 1,2-dichloroethane (200 mL) (Note 8) are added. This suspension is purged with argon for 15 min, and the solution containing the rhodium catalyst is transferred to this flask via cannula over the course of 20 min (Note 9). The resulting mixture is then purged with hydrogen gas for 30 min, during which time the cloudy suspension dissolves (Notes 10 and 11). The reaction is then stirred under a hydrogen atmosphere for 40 h (Note 12), until TLC analysis indicates complete consumption of phenylglyoxal.

The solution is then purged with nitrogen for 20 min and concentrated by rotary evaporation (35 °C, 40 mmHg). The residue is purified by column chromatography (20% ethyl acetate/hexanes) to yield (±)-(*E*)-2-hydroxy-1,3-diphenylhexa-3,5-dien-1-one (**2**) (19.6 g, 74.3 mmol, 87%) as a thick orange oil (Notes 13, 14 and 15).

C. *(±)-Dimethyl-2-((5-hydroxy-4-oxo-3,5-diphenylcyclopent-2-en-1-yl)methyl) malonate (**4**)*. To an oven-dried, 100-mL one-necked (29/32 joint) round-bottomed flask containing a Teflon-coated magnetic stir bar (27 x 5 mm) is added **2** (9.0 g, 34.1 mmol) as a solution in DMSO (27 mL), followed by 2-iodoxybenzoic acid (14.3 g, 51.1 mmol, 1.5 equiv) in one portion (Notes 16 and 17). The cloudy suspension is allowed to stir while open to air. The suspension is stirred until TLC analysis indicates complete consumption of alcohol **2** (usually 15 min) (Note 18). The solution is then diluted with water (200 mL), transferred to a 500-mL separatory funnel, and extracted with diethyl ether (5 x 150 mL) (Note 19). The combined ether extracts are transferred to a 1-L separatory funnel and washed with saturated aqueous $NaHCO_3$ solution (150 mL), dried over $MgSO_4$ (30 g), filtered through a 250 mL coarse porosity sintered glass funnel, and concentrated by rotary evaporation (25 °C, 15 mmHg). (*E*)-1,3-Diphenylhexa-3,5-diene-1,2-dione (**3**) is obtained as a yellow oil, which is used in the next step without further purification (Note 20).

An oven-dried 250-mL, one-necked (29/32 joint) round-bottomed flask containing a Teflon-coated magnetic stir bar (27 x 5 mm) is charged with yttrium (III) triflate (0.18 g, 0.34 mmol, 0.01 equiv) and lithium chloride (2.89 g, 68.2 mmol, 2 equiv), after which tetrahydrofuran (68 mL), triethylamine (4.75 mL, 34.1 mmol, 1 equiv), and dimethyl malonate (4.87 mL, 42.6 mmol, 1.25 equiv) are added. The suspension is stirred at room temperature and left open to air. Diketone **3**, as a solution in 10 mL of tetrahydrofuran, is added rapidly over 10 sec (Note 21). The reaction turns from yellow to dark red and is stirred until TLC analysis indicates complete consumption of diketone (**3**), which typically requires 5 min (Note 22).

The reaction is then quenched by the addition of 1M aqueous HCl solution (50 mL) over 5 min and the resulting solution is transferred to a 250-mL separatory funnel. The aqueous phase is separated and extracted with diethyl ether (3 x 40 mL). The combined ether extracts are washed with 50 mL of saturated NaCl solution, dried over 20 g of $MgSO_4$, filtered through a 250-mL coarse porosity sintered glass funnel, and concentrated by rotary evaporation (25 ºC, 20 mmHg). Purification by column chromatography (33.3% ethyl acetate/hexanes) yields **4** (9.93 g, 25.2 mmol, 74%) as a pale yellow solid (Notes 23 and 24).

Notes

1. All glassware was dried overnight at 120 °C prior to use. All reactions were run under 1 atm of argon, unless otherwise noted. The checkers purchased bis(triphenylphosphine)palladium (II) dichloride (98%) from Combi-Blocks Inc. and used as received. Vinyl bromide (1 M) was purchased from Sigma-Aldrich. Phenylacetylene (98%) and copper iodide (99+%) were purchased from abcr and were used as received. Triethylamine (99+%) was purchased from Sigma-Aldrich and distilled from CaH_2 prior to use. The submitters purchased bis(triphenylphosphine)palladium(II) dichloride from Strem Chemical Inc. and used it as received. All other chemicals were purchased from Sigma-Aldrich and used as received unless another vendor is specified.
2. The checkers purchased THF (>95.5%) from Sigma-Aldrich and passed it through a column of alumina before use. The submitters purchased anhydrous 99.9%, inhibitor free tetrahydrofuran from Fisher Scientific and purified it using the Glass Contour solvent purification system directly before use.
3. The checkers purged the reaction mixture with argon for 20 min while the reaction was stirring at 0 °C. This process increased the yield by 11% compared to the reactions that were not purged with argon.
4. TLC analysis was performed on Merck glass plates coated with 0.25 mm 230-400 mesh silica gel containing a fluorescent indicator. The plate was eluted with hexane/EtOAc (95/5) and visualized by ultraviolet lamp at 254 nm. The product and phenylacetylene possess similar R_f values of approximately 0.7. The product stains well with cerium-ammonium-

molybdate (CAM) while phenylacetylene does not react. Vinyl bromide could not be detected by UV or CAM staining.

5. The submitters reported a yield of 79% (20.3 g, 159 mmol).
6. Compound **1** exhibits the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.55 (dd, *J* = 11.1, 2.1 Hz, 1 H), 5.74 (dd, *J* = 17.5, 2.1 Hz, 1 H), 6.03 (dd, *J* = 17.5, 11.1 Hz, 1 H), 7.29–7.35 (m, 3 H), 7.42–7.48 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 88.22, 90.10, 117.34, 123.28, 127.04, 128.42, 128.45, 131.71. IR ($CDCl_3$) (cm^{-1}) 3081-3011, 2925, 2856, 1606, 1489, 1442, 1069, 1026, 969, 916, 754, 689. HRMS (EI) *m*/*z* calc. for $C_{10}H_8$ (M^+) 128.0626, found 128.0621. Anal. Calcd. for $C_{10}H_8$: C, 93.71; H, 6.29. Found: C, 93.55; H, 6.43.
7. The checkers purchased bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (99%) from Strem Chemical Inc. and used it as received. (rac)-BINAP (98%) was obtained from abcr and used as received. Phenylglyoxal monohydrate (97%) was purchased from Alfa Aesar and recrystallized twice from water prior to use. The submitters purchased bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate and (rac)-BINAP from Strem Chemical Inc. and used them as received. Phenylglyoxal monohydrate was prepared by the reaction of selenium (IV) oxide and acetophenone followed by recrystallization in water.[3]
8. The checkers purchased anhydrous 1,2-dichloroethane (99.8%) from Sigma Aldrich and used it as received. The submitters purchased anhydrous 99.9%, inhibitor free 1,2-dichloroethane from Fisher Scientific and the solvent was purified using the Glass Contour solvent purification system directly before use.
9. The solution with catalyst contained small amounts of white crystals, some of which were left behind after cannula transfer. The remaining crystals were partially dissolved with additional 1,2-dichloroethane and added to the reaction mixture. A small amount of white crystals were discarded.
10. While purging the suspension with argon, the needle got clogged and was rinsed with small amounts of 1,2-dichloroethane several times. The suspension was cleared after 20 min.
11. The needle used for purging was kept in the solution for the entire reaction time while an additional balloon filled with hydrogen and outfitted with a needle was used to provide positive pressure of H_2. Without keeping the needle in the solution yields dropped by 15 %.
12. The reaction was purged again with hydrogen gas for 30 min after 4 h, 19 h and 26 h.

13. In 20% ethyl acetate/hexane, enyne **1**, R_f= 0.94; phenylglyoxal R_f= 0.16; alcohol **2** R_f= 0.58.
14. The product was isolated by the checkers in 73% when the reaction was performed on a 63 mmol scale, and in 71% when the reaction was performed on a 47 mmol scale. The purging needle was not immersed in solvent for the duration of these smaller scale reactions (Note 11).
15. Alcohol **2** is purified on a column (5.5 x 33 cm) packed with 280 g of silica (high purity grade from Fluka, 60 Å pore size, 230-400 mesh) in 10% ethyl acetate/hexane, 1000 mL of 10% ethyl acetate/hexane is first flushed through the column. At this point the solvent is switched to 20% ethyl acetate/hexane and fraction collection is begun (30 mL fractions). Tubes 16-22 are pooled and contain unreacted enyne **1**. Fractions 24-46 are pooled and contain the desired product. The product has an R_f= 0.58 in 20% ethyl acetate/hexane, is UV active and stains strongly with potassium permanganate. The checkers were not able to completely separate the product. Small amounts of enyne (<2%) are contained in the product. For a better separation adding more silica is recommended. Alcohol **2** exhibits the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.32 (d, *J* = 6.1 Hz, 1 H), 5.12 (dd, *J* = 10.1, 1.4 Hz, 1 H), 5.35 (dd, *J* = 16.9, 1.4 Hz, 1 H), 5.68 (d, *J* = 6.1 Hz, 1 H), 6.15–6.29 (m, 1 H), 6.47 (d, *J* = 10.9 Hz, 1 H), 7.01–7.08 (m, 2 H), 7.24–7.29 (m, 3 H), 7.38–7.43 (m, 2 H), 7.56 (t, *J* = 7.4 Hz, 1 H), 7.82–7.87 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 78.83, 120.46, 127.85, 128.26, 128.44, 128.72, 129.00, 129.36, 133.36, 133.63, 134.03, 136.86, 140.84, 198.65. IR (neat) (cm^{-1}) 3451, 3058, 1679, 1597, 1492, 1448, 1260, 1087, 1001, 972, 951, 916, 774, 755, 699, 688, 670, 617. HRMS (EI) *m*/*z* calc for $C_{18}H_{16}O$ (M^+) 264.1150, found 264.1145. Anal. calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.31; H, 5.86.
16. 2-Iodoyxbenzoic acid (>95%) was prepared from 2-iodobenzoic acid by the procedure of Santagostino.[4a] DMSO (>99%) was purchased from Sigma Aldrich and used as received. The submitters prepared 2-iodoxybenzoic acid (>90%) from 2-iodobenzoic acid by the procedure of Boeckman.[4b]
17. The submitters report that other oxidation procedures were attempted (see Discussion), but they all led to formation of byproducts that could not be separated using typical purification techniques, and led to diminished yields in the subsequent (Nazarov cyclization) step.
18. The submitters report that the suspension dissolves to leave a yellow solution. The reaction was extremely exothermic, but no cooling was

provided. The submitters do, however, recommend the use of an ice bath to control the exotherm. In 20% ethyl acetate/hexane, diketone **3**, R_f = 0.65.

19. During the first extraction with ether, an emulsion is formed and the organic layer is slow to separate from the aqueous layer. The mixture is swirled gently and allowed to stand for 20 min. Any remaining emulsion is removed with the ether layer, and extraction of the homogeneous aqueous layer is continued as described.
20. Aqueous workup typically yielded the product (**3**) in high purity (< 95% as determined by NMR analysis). If diketone of higher purity is required, the product can be purified by column chromatography with 10% ethyl acetate/hexane; however, the product does show signs of decomposition on the column. Diketone **3** exhibits the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.56 (d, *J* = 10.1 Hz, 1 H), 5.71 (d, *J* = 16.9 Hz, 1 H), 6.48–6.61 (m, 1 H), 7.16 (d, *J* = 11.0 Hz, 1 H), 7.26–7.31 (m, 2 H), 7.36–7.46 (m, 3 H), 7.52 (t, *J* = 7.7 Hz, 2 H), 7.65 (t, *J* = 10.6 Hz, 1 H), 7.95 (d, *J* = 7.2 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 128.46, 128.60, 129.13, 129.23, 129.92, 130.31, 132.78, 133.21, 133.31, 134.89, 138.45, 146.99, 195.10, 196.08. IR (neat) (cm^{-1}) 3059, 1735, 1677, 1658, 1612, 1450, 1222, 1141, 698. HRMS (ESI) *m*/*z* calc. for $C_{18}H_{15}O_2$ (M+H) 263.1072, found 263.1072.
21. The checkers purchased yttrium(III) triflate (98%) from Strem Chemicals Inc. and used it as received. Lithium chloride (99%) and THF (>95.5%) were purchased from Sigma Aldrich and both were used as received. Triethylamine (99+%) was purchased from Sigma-Aldrich and distilled from CaH_2 prior to use. Dimethyl malonate (>99%) was purchased from Acros Organics and used as received.
22. In 20% ethyl acetate/hexane, cyclopentenone **4**, R_f=0.14 .
23. The column (5 x 28 cm) is packed with 200 g of silica in hexane, 400 mL of 12.5% ethyl acetate/hexane are first eluted, followed of 33.3% ethyl acetate/hexane. Fractions are collected using 30 mL test tubes. Fractions 70-104 are pooled and contain the desired product. The product has an R_f = 0.14 in 20% ethyl acetate/hexane, is UV active and stains strongly with potassium permanganate. Cyclopentenone **4** exhibits the following characteristics: mp = 114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.80 (ddd, *J* = 14.3, 9.2, 5.5 Hz, 1 H), 1.98 (ddd, *J* = 14.3, 9.2, 6.5 Hz, 1 H), 3.20 (ddd, *J* = 9.2, 6.5, 2.5 Hz, 1 H), 3.26 (s, 1 H), 3.41 (dd, *J* = 9.2, 5.5 Hz, 1 Hz), 3.62 (s, 3 H), 3.76 (s, 3 H), 7.26–7.47 (m, 8 H), 7.78 (dd, *J* = 8.0, 1.7 Hz, 2 H), 7.80 (d, *J* = 2.5 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 28.66, 49.31,

49.84, 52.75, 52.92, 84.11, 125.57, 127.09, 128.26, 128.71, 128.90, 129.40, 130.49, 139.46, 142.09, 158.40, 169.20, 169.57, 206.66. IR (neat) (cm^{-1}) 3463, 3059, 3027, 1716, 1493, 1436, 1306, 1236, 1155, 1051, 909, 832, 788, 765, 698. HRMS (ESI) *m*/*z* calc. for $C_{23}H_{23}O_6$ (M+H) 395.1489, found 395.1483. Anal. calcd for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62 . Found: C, 69.75; H, 5.53.

24. The product was isolated by the checkers in 75% when the reaction was performed on a half scale.

Handling and Disposal of Hazardous Chemicals

The procedures in this article are intended for use only by persons with prior 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 www.nap.edu). 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.

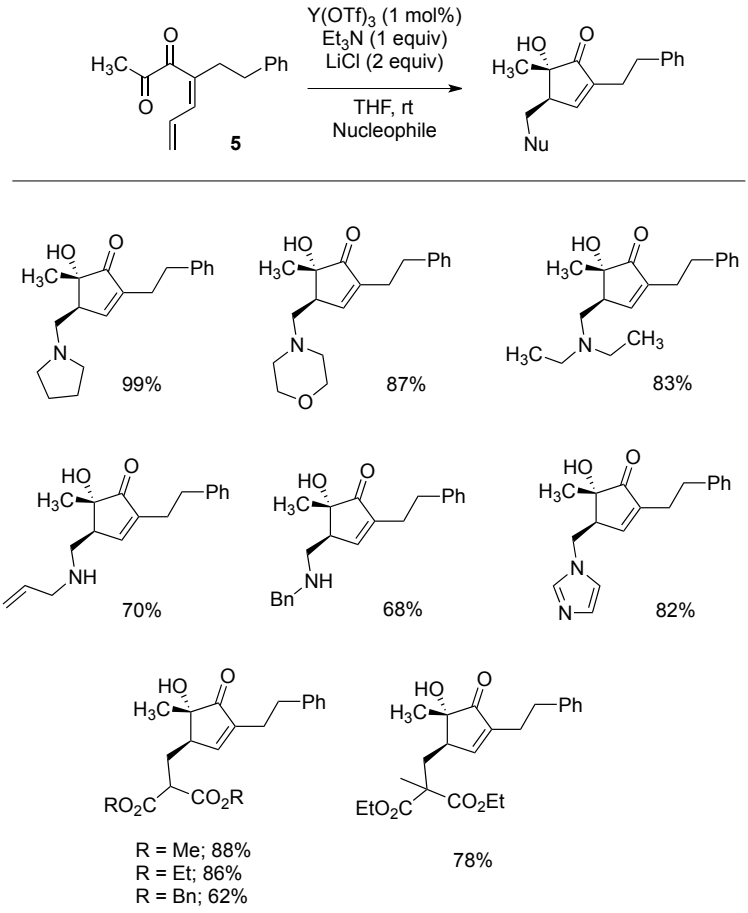
These procedures must be conducted at one's own risk. *Organic Syntheses, Inc*., its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related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

Discussion

The Nazarov electrocyclization has become a versatile method for the synthesis of cyclopentenones with a broad range of substitution patterns, with excellent potential as building blocks for complex molecule synthesis.[5] While the classical Nazarov cyclization requires stoichiometric or super amounts of Bronsted or Lewis Acid, recent advances in substrate design, Lewis acid catalysts, and methods for the synthesis of reactive intermediates have increased the utility of the reaction. Herein, we describe the synthesis and use of dienyl diketones as substrates in Nazarov cyclizations, initiated by 1,6-conjugate addition of an amine or malonate nucleophile.[6] A three-step protocol is employed to prepare the dienyl

diketones, and the cyclization produces 5-hydroxycyclopentenones in high yields.

Table 1. Nucleophile Scope for Nazarov Cyclization Initiated by 1,6-Addition to Dienyl Diketones

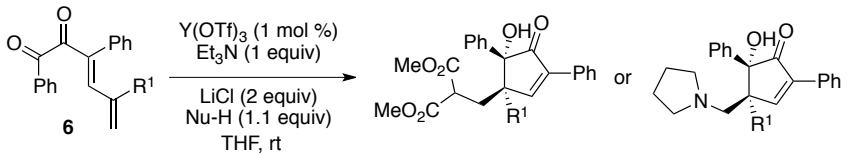


The Nazarov cyclization of dienyl diketone **5** can be initiated with various nucleophiles, proceeding in good to excellent yield with primary, cyclic, and acyclic secondary amines (Table 1). Malonate derivatives are also effective nucleophiles, allowing the creation of a new carbon-carbon bond in the first step of the cascade. In all cases only one diastereoisomer was

detected, and the *syn* relationship was confirmed by either nOe analysis or single X-ray crystallographic data.[6]

The conjugate addition-initiated cyclization is efficient for both dienyl diketone **5** and a number of dienyl diketones of type **3** (Table 2). The cyclization can be used to install a quaternary stereogenic center at the 4-position of the cyclopentenone, using either pyrrolidine or malonate to initiate the reaction (Table 2).[7] The cyclization cascade is remarkably convenient and robust: the reaction is not air- or moisture sensitive, and the reactions are complete in less than 30 minutes at ambient temperature.

Table 2. Scope of the Conjugate Addition-Initiated Nazarov Cyclization



entry	R_1	nucleophile	yield (%)
1	-H	pyrrolidine	87
2	-H	dimethylmalonate	83
3	$-CH_3$	pyrrolidine	85
4	$-CH_3$	dimethylmalonate	78
5	$-(CH_2)_2OAc$	dimethylmalonate	89
6	$-(CH_2)_3OAc$	dimethylmalonate	87

The synthesis of dienyl diketones of type **3** relies upon the Rh-catalyzed reductive coupling of enynes with glyoxals, using a protocol developed by Krische and coworkers.[2] The reaction is regioselective and delivers the target dienyl alcohols of type **2** in good to excellent yield.[8] After extensive experimentation, we found that the optimal method for oxidizing the dienyl alcohols to dienyl diketones of type **3** was the use of 2-iodoxybenzoic acid (IBX) in DMSO. The target substrates were obtained in excellent yields, and they could be cyclized without the need for additional purification. A number of alternative oxidants and oxidation methods were screened, including the Dess-Martin reagent, the Jones reagent, MnO_2, TEMPO, TPAP- NMO, and $Bi(NO_3)_3$, but in all cases, the oxidation led to byproduct formation resulting in reduced yields and requiring purification of the dienyl diketones by column chromatography.[9]

References

1. Department of Chemistry, University of Rochester, Rochester, NY 14627, email frontier@chem.rochester.edu. This project has been supported by the NIGMS (R01 GM079364).
2. (a) Huddleston, R. R.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488–11489. (b) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4664–4668.
3. Riley , H. A.; Gray, A. R. *Org. Synth.* **1935**, *15*, 67.
4. (a) Boeckman, R. K.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141. (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
5. (a) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517. (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577–7606. (c) Tius, M. A. *Eur. J. Org. Chem.* **2005**, *2005*, 2193–2206. (d) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676–5688. (e) Nakanishi, W.; West, F. G. *Curr. Opin. Drug Discov. Devel.* **2009**, *12*, 732–751. (f) Vaidya, T.; Eisenberg, R.; Frontier, A. J. *Chem Cat Chem* **2011**, *3*, 1531–1548.
6. Brooks, J. L.; Caruana, P. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 12454–12457.
7. Brooks, J. L.; Frontier, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 16551–16553.
8. The Krische protocol can only be employed in couplings with aryl glyoxals or non-enolizable aliphatic glyoxals, because alphatic glyoxals with α-protons polymerize rapidly (Riley, H. L.; Morley, J. F.; Friend, N. A. C. *J. Chem. Soc.* **1932**, 1875–1883). Therefore, a different synthetic strategy must be used to prepare dienyl diketones like **5** (see reference 6).
9. Byproducts resulting from oxidative cleavage were observed in oxidation experiments using the Dess-Martin reagent, Jones reagent and MnO_2, while decomposition was observed when TEMPO, TPAP-NMO, and $Bi(NO_3)_3$ were tested.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

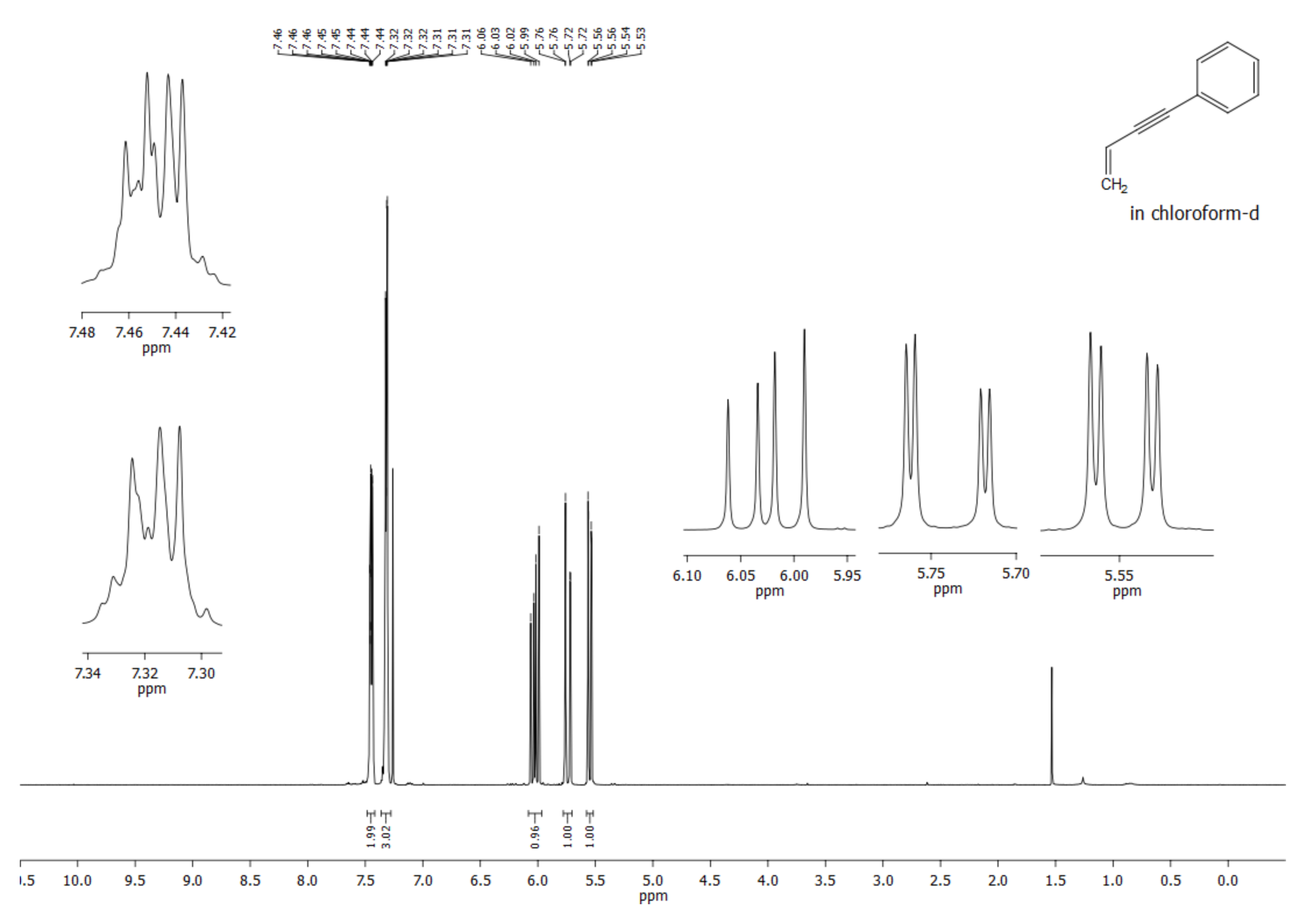
Bis(triphenylphosphine)palladium(II) dichloride; (13965-03-2)
Copper(I) iodide; (7681-65-4)
Vinyl bromide solution; (593-60-2)
Triethylamine; (121-44-8)
Phenylacetylene; (536-74-3)
3-Buten-1-yn-1-yl-Benzene; (13633-26-6)
Bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate; (99326-34-8)
(±)-BINAP; 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (98327-87-8)
Phenylglyoxal monohydrate; (1074-12-0)
(±)-(E)-2-Hydroxy-1,3-diphenylhexa-3,5-dien-1-one; (690211-20-2)
2-Iodylbenzoic acid; (64297-64-9)
(*E*)-1,3-Diphenylhexa-3,5-diene-1,2-dione; (1401539-00-1)
Yttrium (III) triflate; Yttrium(III) trifluoromethanesulfonate (52093-30-8)
Lithium chloride; (7447-41-8)
Dimethyl malonate; (108-59-8)
(±)-Dimethyl 2-((-5-hydroxy-4-oxo-3,5-diphenylcyclopent-2-en-1-yl)methyl) malonate; (1401539-14-7)

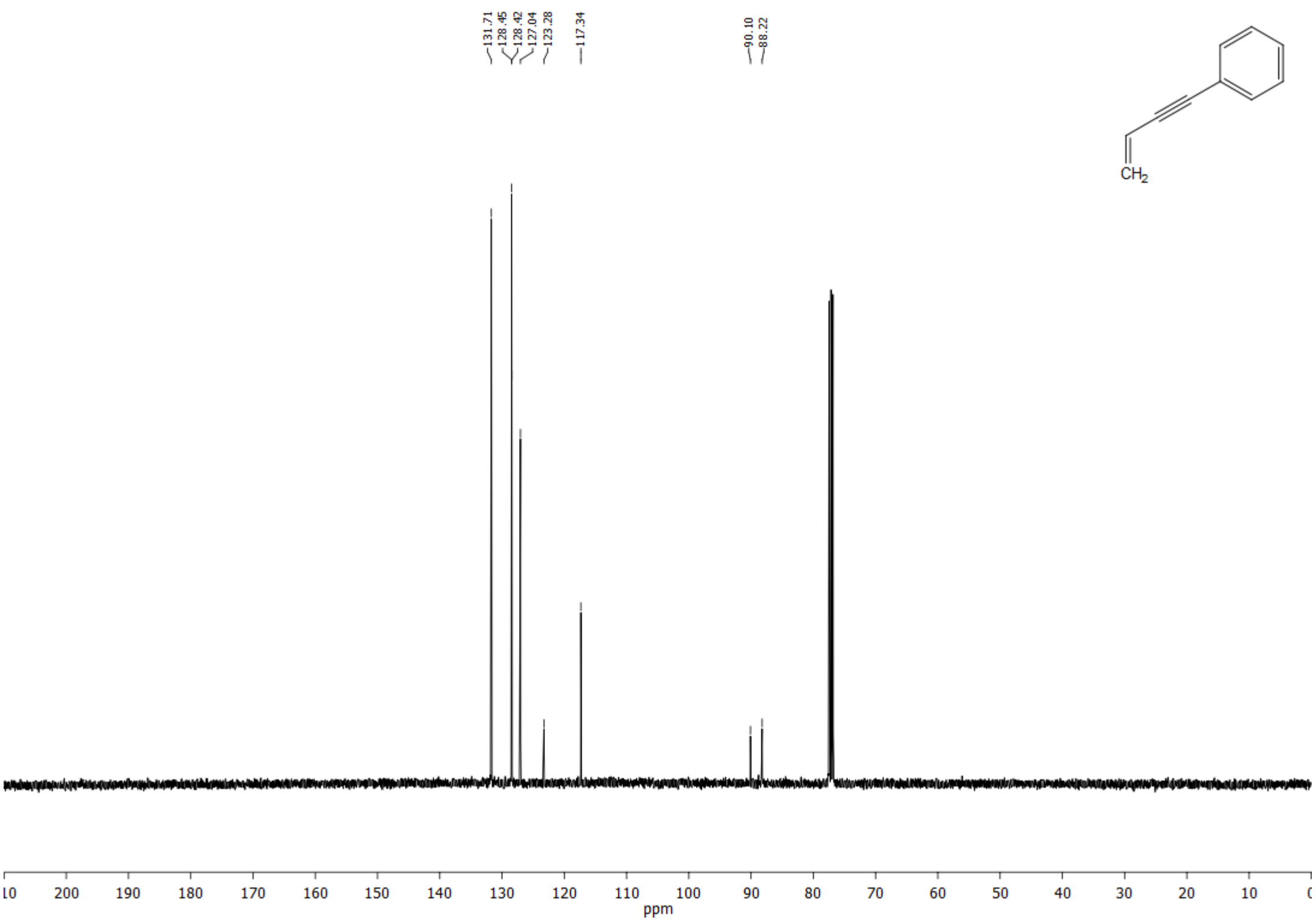
Joshua L. Brooks received his B.S. The State University of New York, College of Environmental Science and Forestry (SUNY-ESF) in 2005. He continued at SUNY-ESF until 2008 where he studied under Professor José-L. Giner completing a Masters Degree. He earned his Ph.D. in 2012 from the University of Rochester where he studied with Alison J. Frontier, and is currently undertaking postdoctoral work with Derek S. Tan at Memorial Sloan-Kettering Cancer Center

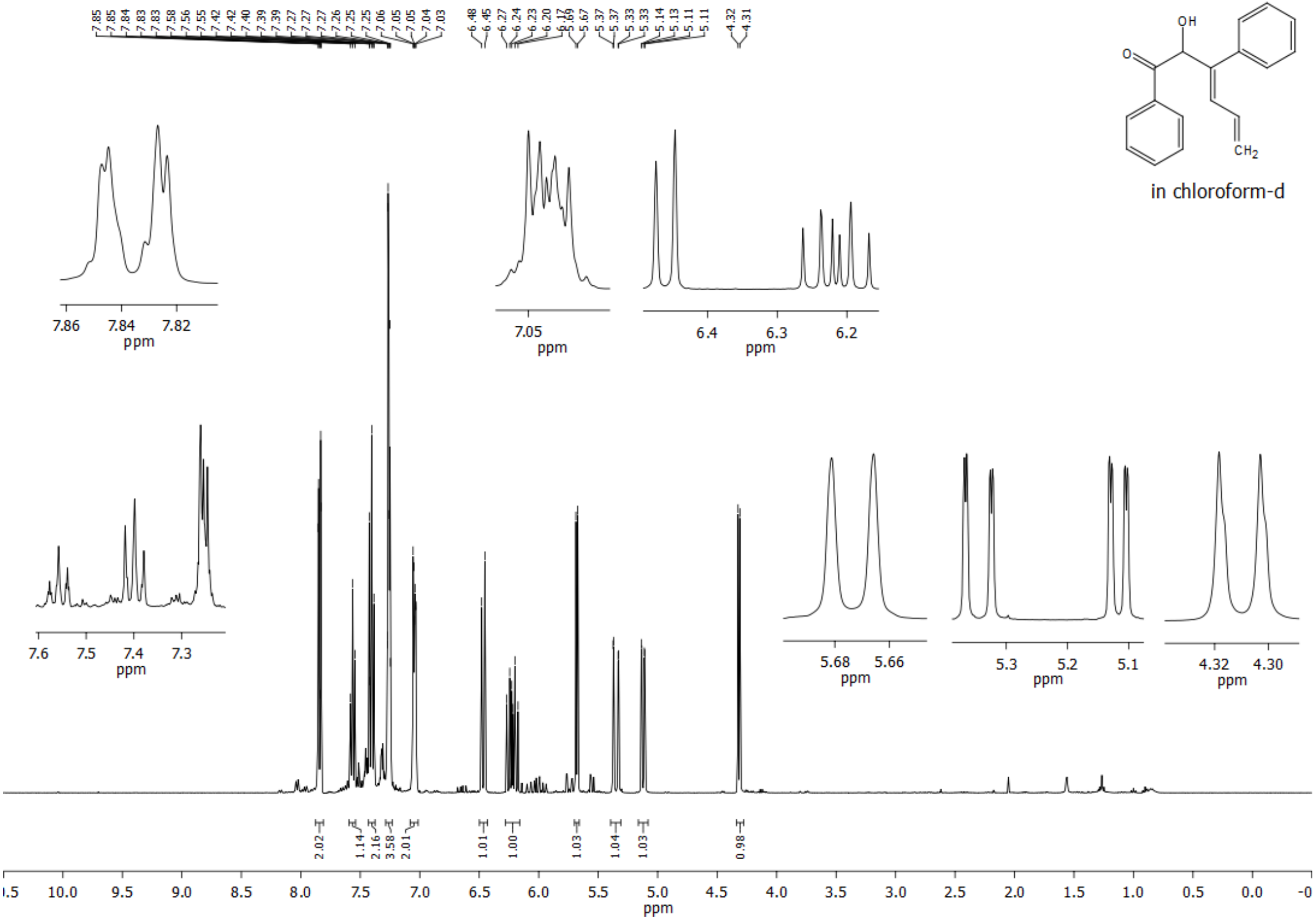
Yu-Wen Huang was born in Hsinchu, Taiwan (R.O.C.) in 1982. He received his bachelor's degree from National Cheng Kung University in 2005. He then joined M.S. program at National Tsing Hua University, whereas he obtained his master degree under the supervision of Professor Shang-Cheng Huang in carbohydrate synthesis. He is currently a Ph.D. student in University of Rochester with Professor Alison J. Frontier. His research focuses on the new methodology development and its application toward total synthesis.

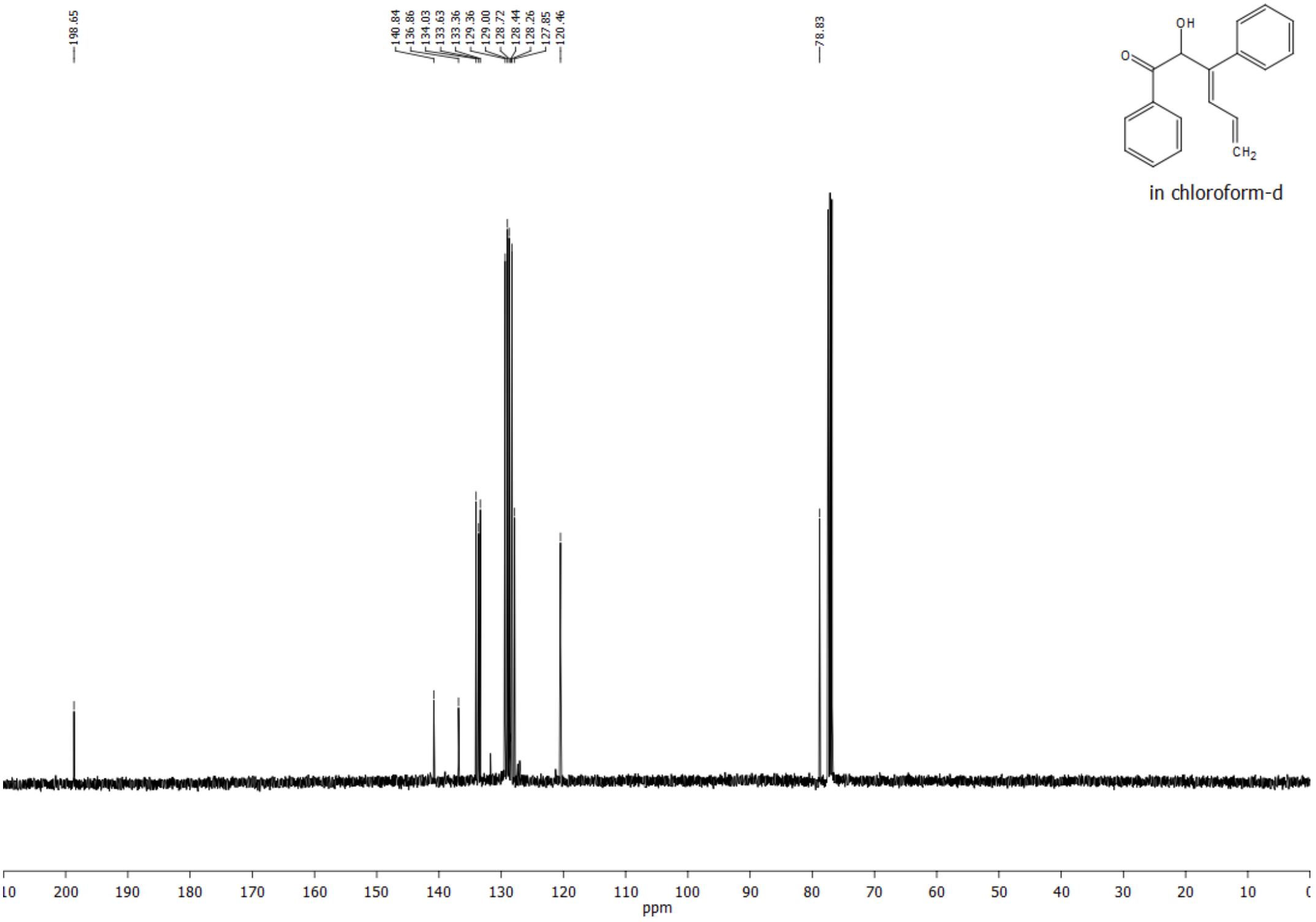
Alison J. Frontier received her AB from Harvard in 1992, and then took a two-year position as an Associate Chemist at the Merck Research Laboratories in Rahway, NJ. She earned her PhD in 1999 from Columbia University, where she studied with Samuel Danishefsky, and then she did postdoctoral work with Barry Trost at Stanford University. She has been on the faculty at the University of Rochester since 2002. Her research interests focus on target molecule synthesis and reaction development using novel catalytic methods, cationic and neutral pericyclic reactions and multistep cyclization cascades.

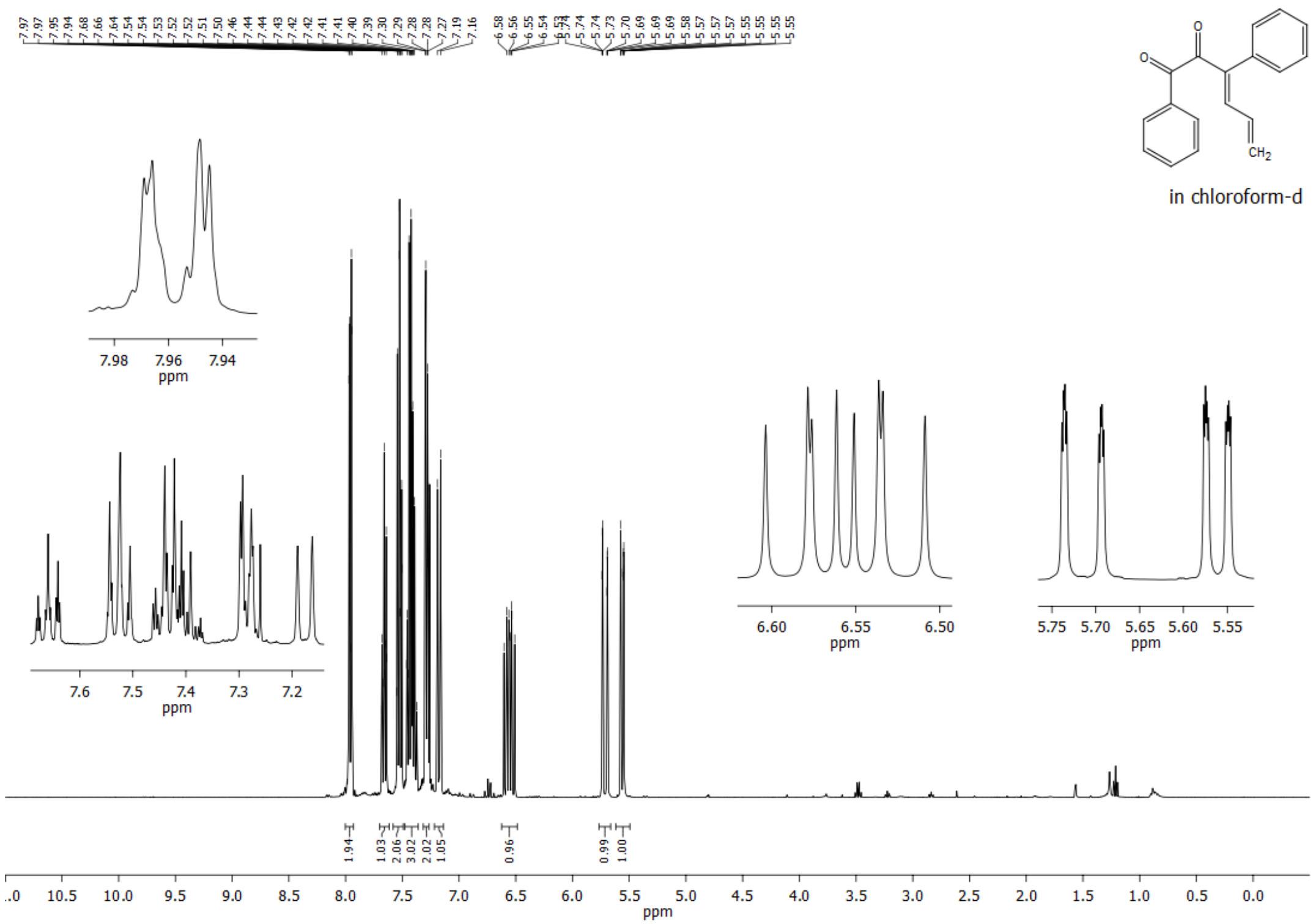
Raffael Vorberg received his B.S. and M.S degrees at the ETH Zürich, Switzerland in 2011. He then carried out an 8 month internship at Roche in Basel, Switzerland. In 2012 he joined the research group of Prof. Carreira at ETH Zürich to pursue his Ph. D. degree. His research is focused on the synthesis of small fluorinated building blocks for applications in drug design.

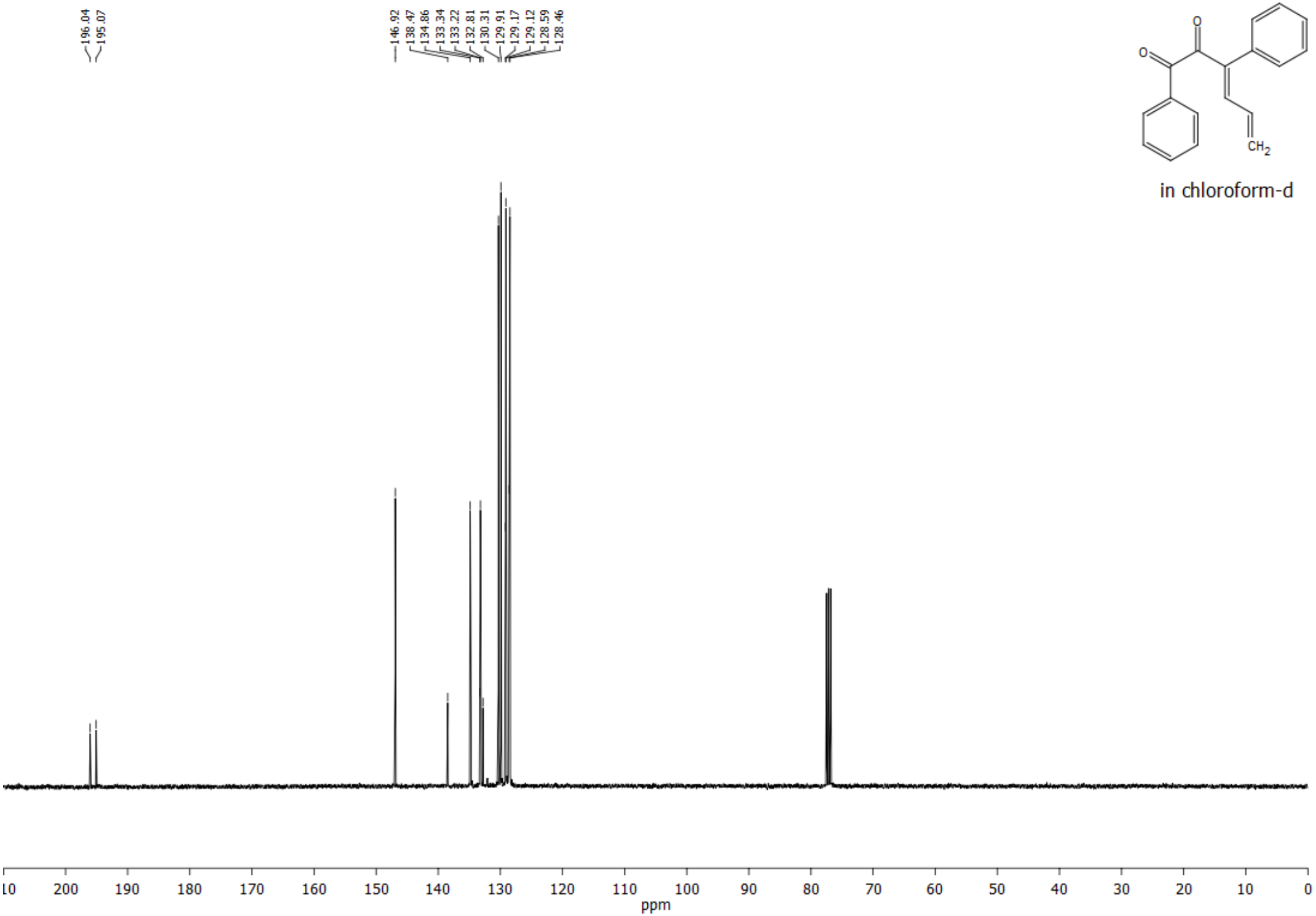

7.46 7.46 7.46 7.45 7.45 7.44 7.44 7.44 7.32 7.32 7.32 7.31 7.31 7.31 6.06 6.03 6.02 5.99 5.76 5.76 5.72 5.72 5.56 5.56 5.54 5.53
CH2
in chloroform-d
7.48 7.46 7.44 7.42
ppm
7.34 7.32 7.30
ppm
6.10 6.05 6.00 5.95
ppm
5.75 5.70
ppm
5.55
ppm
1.99
3.02
0.96
1.00
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

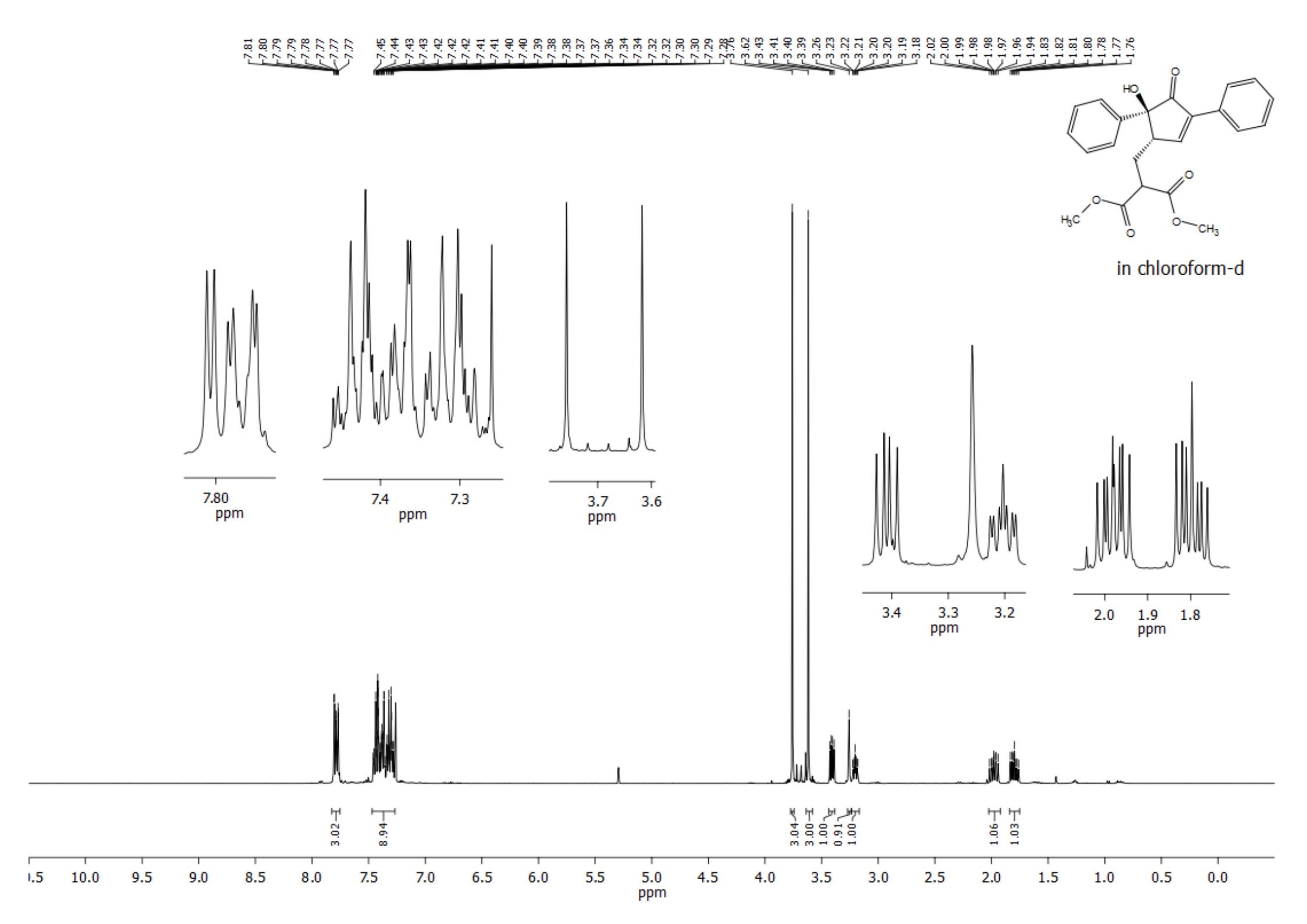

131.71
128.45
128.42
127.04
123.28
117.34
90.10
88.22
CH2
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

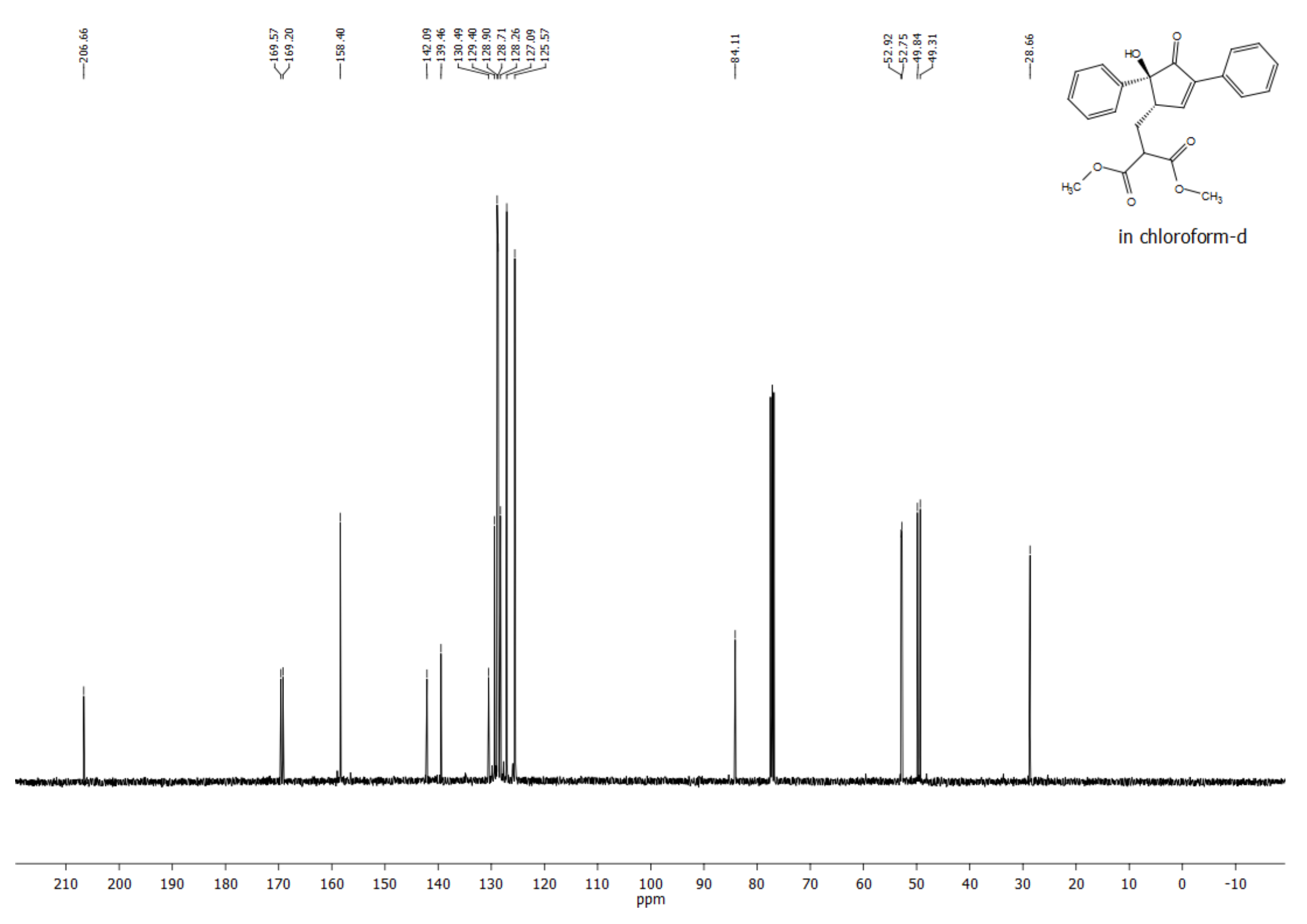

7.85 7.85 7.84 7.83 7.83 7.58 7.56 7.55 7.42 7.42 7.40 7.39 7.39 7.27 7.27 7.27 7.26 7.25 7.25 7.06 7.05 7.05 7.04 7.03
6.48 6.45 6.27 6.24 6.23 6.20 6.17 6.09 5.67 5.37 5.37 5.33 5.33 5.14 5.13 5.11 5.11 4.32 4.31
OH
O
CH2
in chloroform-d
7.86 7.84 7.82 ppm
7.05 ppm
6.4 6.3 6.2 ppm
7.6 7.5 7.4 7.3 ppm
5.68 5.66 ppm
5.3 5.2 5.1 ppm
4.32 4.30 ppm
2.02 1.14 2.16 3.58 2.01 1.01 1.00 1.03 1.04 1.03 0.98
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
ppm


198.65
140.84
136.86
134.03
133.63
133.36
129.36
129.00
128.72
128.44
128.26
127.85
120.46
78.83
OH
O
CH2
in chloroform-d
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


7.97 7.97 7.95 7.94 7.68 7.66 7.64 7.54 7.54 7.53 7.52 7.52 7.51 7.50 7.46 7.44 7.44 7.43 7.42 7.42 7.41 7.41 7.40 7.39 7.30 7.29 7.28 7.28 7.27 7.19 7.16
6.58 6.56 6.55 6.54 5.74 5.74 5.73 5.70 5.69 5.69 5.69 5.58 5.57 5.57 5.57 5.55 5.55 5.55 5.55
O
O
CH2
in chloroform-d
7.98 7.96 7.94
ppm
7.6 7.5 7.4 7.3 7.2
ppm
6.60 6.55 6.50
ppm
5.75 5.70 5.65 5.60 5.55
ppm
1.94 1.03 2.06 3.02 2.02 1.05 0.96 0.99 1.00
.0 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
ppm


196.04
195.07
146.92
138.47
134.86
133.34
133.22
132.81
130.31
129.91
129.17
129.12
128.59
128.46
O
O
CH2
in chloroform-d
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


HO
O
O
O
O
O
O
CH3
in chloroform-d
7.80
ppm
7.4
7.3
ppm
3.7
3.6
ppm
3.4
3.3
3.2
ppm
2.0
1.9
1.8
ppm
3.02
8.94
3.04
3.00
1.00
0.91
1.00
1.06
1.03
ppm


206.66
169.57
169.20
158.40
142.09
139.46
130.49
129.40
128.90
128.71
128.26
127.09
125.57
84.11
52.92
52.75
49.84
49.31
28.66
HO
O
O
O
O
O
H3C
CH3
in chloroform-d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm