A Guided-Inquiry Approach to Ring-Closing Metathesis
Supplementary Material

SOU Student Profile and Organic Chemistry Training

SOU is a four-year public liberal arts university. Many of our students are non-traditional or first-generation college students. The academic profile of the middle 50% of students accepted to SOU in 2008 is noted below:

GPA: 2.91 – 3.57
SAT: 910 - 1120
ACT: 19 - 25

SOU chemistry department provides an American Chemical Society-certified program. SOU is on the quarter system so students enrolled in organic chemistry take 3 terms of lecture and laboratory courses. The emphasis of the laboratory component for each of those terms is noted below:

Fall Term: Isolation and purification techniques
Winter Term: Organic Spectroscopy (FT-IR, FT-NMR, and GC-MS) theory, data acquisition and analysis.
By the end of this term, students can independently acquire and analyze IR, NMR, GC, and MS spectra.
Note: Students acquire their NMR data using the department's 400 MHz spectrometer but process their data in the department's computer lab using MestRe-C software.
Spring Term: Synthesis, purification, and analysis

Online References

Available free-of-charge

http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2005/popular-chemistryprize2005.pdf

http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2005/advanced-chemistryprize2005.pdf

http://pubs.acs.org/cen/coverstory/8051/8051olefin.html

Supplies Needed for Experiment

Chemicals

Distilled dichloromethane stored under N_2 and over 4A molecular sieves
Diethyl diallylmalonate
Grubbs Second Generation Catalyst
Dimethyl sulfoxide (DMSO)
$KMnO_4$ stain: 1 g $KMnO_4$, 2 g Na_2CO_3, 5 mL 5% NaOH, 100 mL dH_2O
    Store at RT in wide mouth container
Silica gel, 60-200 mesh
Activated Carbon, Darco® G-60, -100 mesh, powder

Common Lab Supplies

TLC Plates: ANALTECH UNIPLATE™ Silica Gel F with 10% silver nitrate, 250 μm
TLC chambers
Cotton/glass wool
8 inch glass TLC spotters
foil-covered hot plates
fritted glass filters
Hirsch funnel and 1cm filter paper disks
14/20 *threaded* septa
Rotary Evaporators
Nitrogen Tank
Syringe balloons
    3 mL disposable syringes with end cut off
    1.5-inch segments of PVC tubing (ID 3/8, OD ½, wall 1/16)
    parafilm
    9 inch latex balloons

Supplies For Each Student

2 50 mL (14/20) round-bottomed flasks
1 50 mL side arm Erlenmeyer flask
1 100 μL glass microsyringe
2 stir bars
2 20 gauge needles
2 18 gauge needles
1 glass funnel

Implementation

The laboratory was carried out in two phases over a three-week period. Prior to the first recitation, students were assigned background literature reading on olefin metathesis. In the first recitation, students reviewed the process of scientific investigation and were introduced to the concept of guided-inquiry experiments (Figure SM.9.3.1.1).

Pose a question → Review the literature → Develop a hypothesis →
Design and carry out an experiment → Analyze the results →
Refine the hypothesis → Design and carry out a modified experiment →
Analyze the results → Communicate the findings

Figure SM.9.3.1.1. General Process of Scientific Investigation

Afterwards, the RCM reaction was discussed and a general protocol was provided. In week one, each student worked with a partner to carry out the synthesis, purification, and analyses (^{1}H, COSY, ^{13}C, and DEPT-135 NMR and GC-MS) of their product. The following week's recitation included a discussion of the RCM reaction mechanism. Additionally, each group selected an experimental question and was asked to design a procedure that would attempt to answer the question selected.

Students were required to develop a detailed protocol and review it with their instructor prior to beginning their experiments. During weeks two and three, students had the opportunity to assess their reaction outcomes and optimize their experimental design and technique. As for implementation of the guided-inquiry component of the experiment, several factors were key to the success of this lab. First, having a partner helped ease student stress and provided a sounding board for their ideas. Second, allowing students to repeat their experiments increased their confidence and resulted in a deeper learning experience. Finally, in order for groups to compare their results to the initial protocol and to one another, it was

necessary to ensure that students alter *only* the experimental step having to do with their assigned variable and that *only one change be made per experiment*.

After completing their experiments, the students submitted a formal written report to their instructor. In addition, an oral presentation session was held wherein each group presented their findings to their peers. The class assessed each group's methods and results and then discussed optimal reaction conditions, purification techniques, and analysis methods.

Experiment Notes, Pictures and Results

The catalyst is air-sensitive, be sure to re-seal immediately after use. When not in use, the catalyst was stored under a blanket of nitrogen. Fresh catalyst was purchased every two years.

During synthesis, be sure to minimize the reaction's exposure to air.

Use gloves whenever handling Ag-TLC plates, the silver will stain hands brown.

Since the organic laboratory did not contain Schlenk lines, nitrogen-filled balloons fitted to plastic syringes were used to provide an inert atmosphere. Pictures of this setup are included below (Figure SM.9.3.1.2).

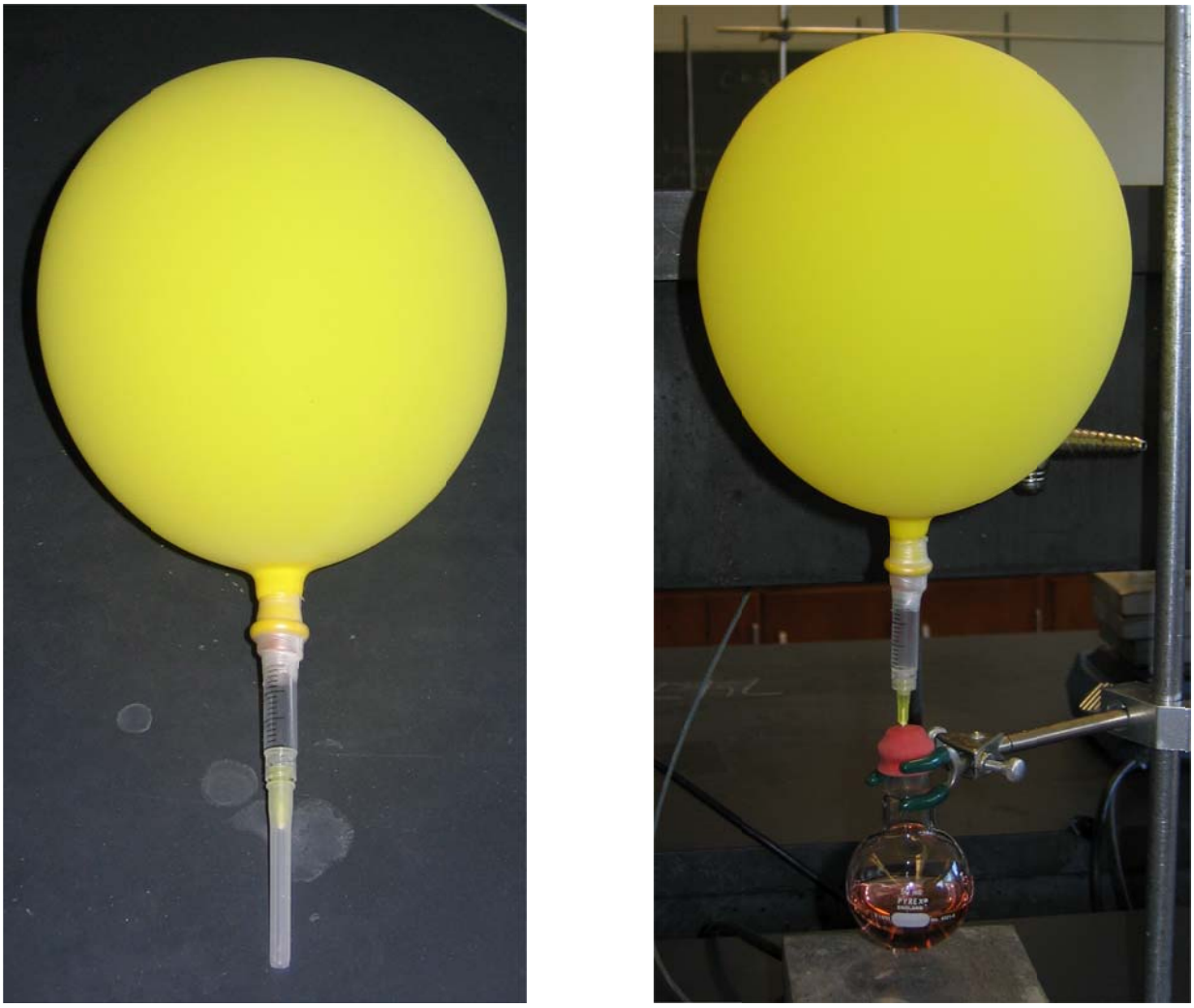


Figure SM.9.3.1.2. Nitrogen-filled balloon apparatus and reaction setup.

Supplementary information for *Comprehensive Organic Chemistry Experiments for the Laboratory Classroom*

Table SM.9.3.1.**1. Results of Experimental Questions**

Experimental Question	**General Trends**
Degree of catalyst's sensitivity to water	Exposure to moisture decreased product purity and yield
Minimum amount of catalyst required	Decreased catalyst quantities increased reaction time but made little impact on product yield
Minimum amount of solvent required	Excessively low solvent quantities increased reaction time and decreased yield
Optimal amount of activated carbon required to purify crude reaction	Addition of activated carbon improved product purity
Optimal amount of DMSO required to purify crude reaction	Addition of DMSO improved product purity
Optimal amount of silica gel required to purify reaction product	Excessive silica gel quantities improved purity but significantly decreased yield
Optimal GC Method to analyze progress of reaction	Increasing GC oven temperature and column pressure significantly decreased GC run times

Student Protocol for GC Method Development

Agilent 6890N Network GC
Phenyl Methyl Siloxane Column: 19091J-413
Length 30 m; Diameter 320 μm; Nominal Thickness 0.25 μm

Overall Goal: Use GC, instead of TLC, to monitor progress of reaction

Experiment Goals:
1. Develop a GC method to *completely* separate (i.e. baseline separation) your starting material from your product.

2. Minimize the total run time while maintaining baseline separation of your starting material and your product

Notes:
1. Choose a solvent for your samples.

2. Determine the appropriate concentration of your samples.

3. **Method Parameters:**
Inlet Temperature: **150 °C**
Column Pressure: **6.08 psi**
Initial Oven Setting: **100 °C held for 1 minute**
Oven Ramp: **40 °C/minute**
Final Oven Setting: **250 °C for 4 minutes**
Total Run Time: **8.75 minutes**

Retention Time:
Diethyl diallylmalonate: 6.09 minutes
Diethyl cyclopent-3-ene-1,1-dicarboxylate: 5.83 minutes

Parameters that you may vary:
Oven Temperature: **MAXIMUM 250 °C**
Time at a given Oven Temperature: No limits
Column Pressure: **MAXIMUM 25 psi** (Initial setting: 6 psi)

GC-MS Instrument and Method Information

6890N Network GC System/Agilent 5973 Network Mass Selective Detector

Front Inlet
- Pressure: 8.70 psi
- Mode: Split
- Split Ratio: 100:1
- Split Flow: 52.5 mL/min
- Total Flow: 55.8 mL/min
- Initial Temperature: 200 °C

Oven
- Initial Temperature: 100 °C
- Ramp: 30 °C/minute
- Final Temperature: 240 °C

Column
- Agilent 19091S-433 Capillary Column
- HP-5MS, 0.25 mm × 30 m × 0.25 μm
- Pressure: 8.70 psi

Retention Time
- Diethyl diallylmalonate: 4.20 minutes
- Diethyl cyclopent-3-ene-1,1-dicarboxylate: 3.94 minutes

GC TIC Data

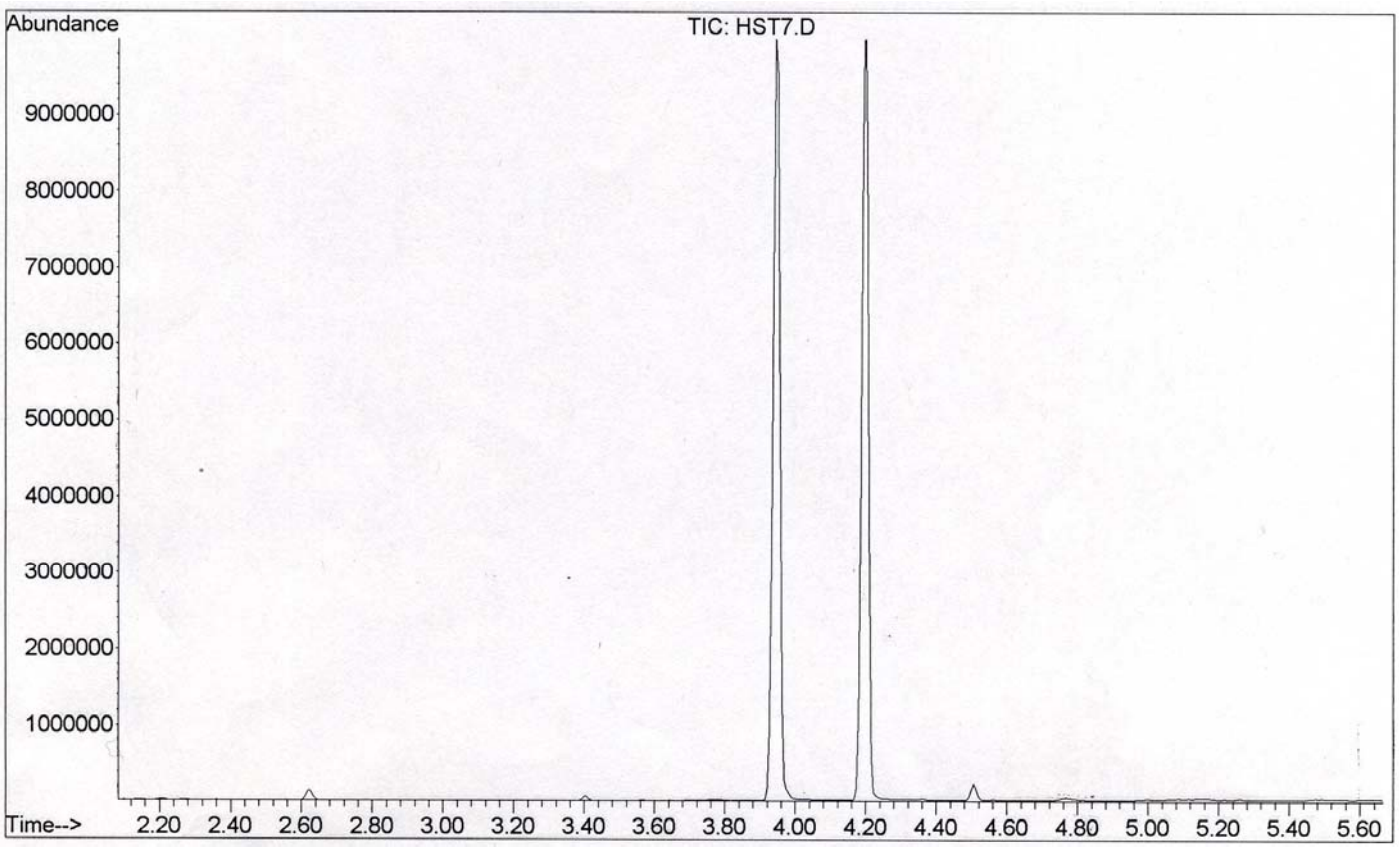


Figure SM.9.3.1.3. Mixture of diethyl diallylmalonate and diethyl cyclopent-3-ene-1,1-dicarboxylate.

MS Data

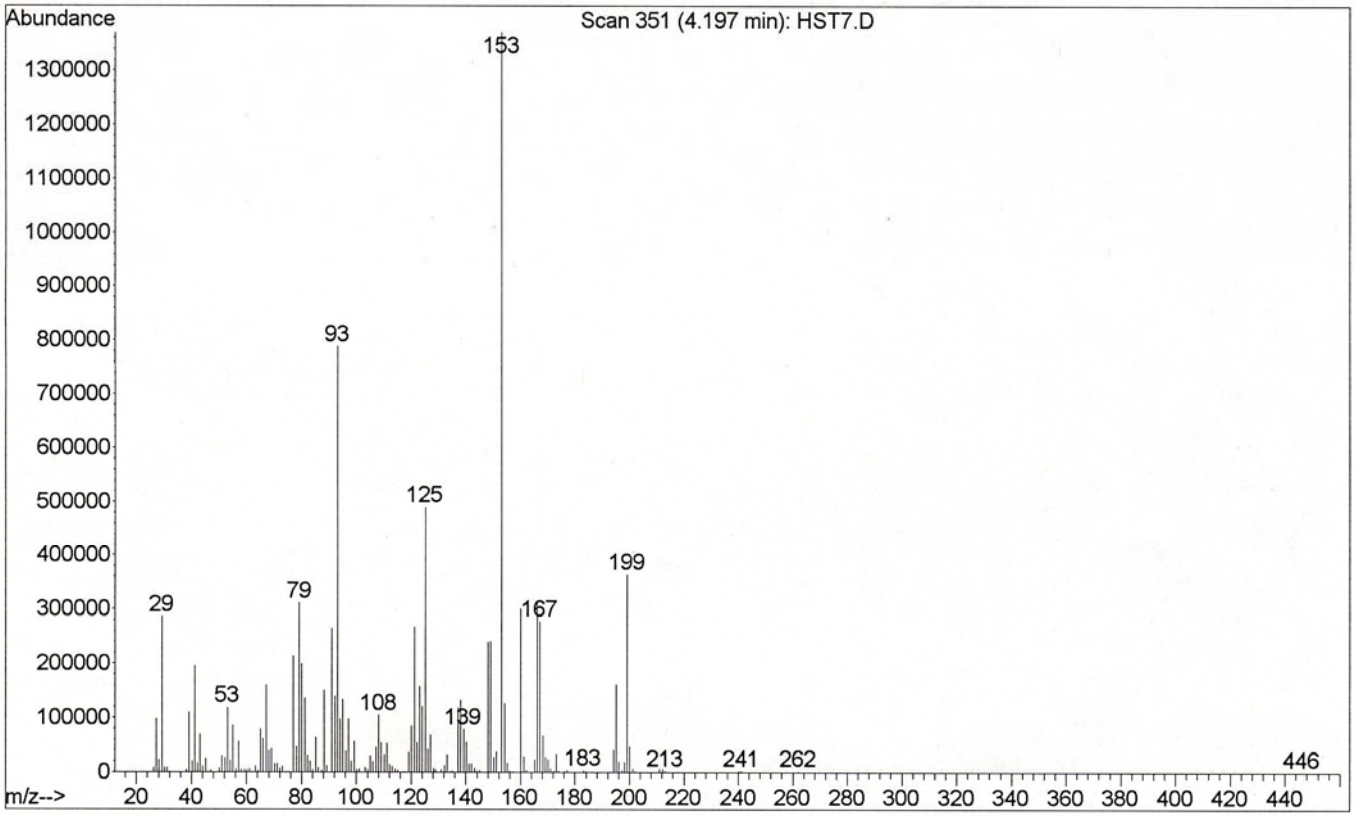


Figure SM.9.3.1.4. Diethyl diallylmalonate.

MS Data

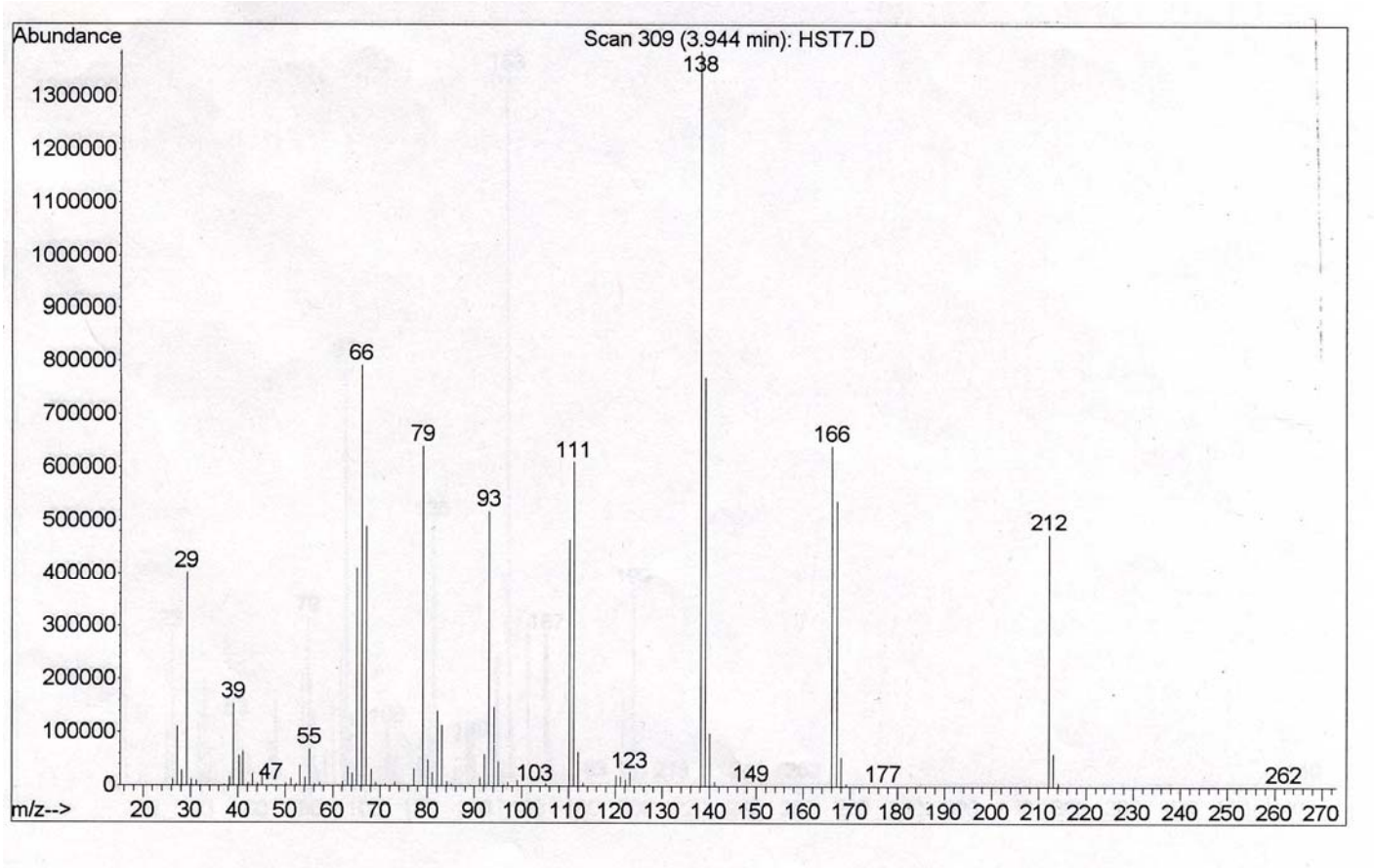


Figure SM.9.3.1.5. Diethyl cyclopent-3-ene-1,1-dicarboxylate.

NMR Data

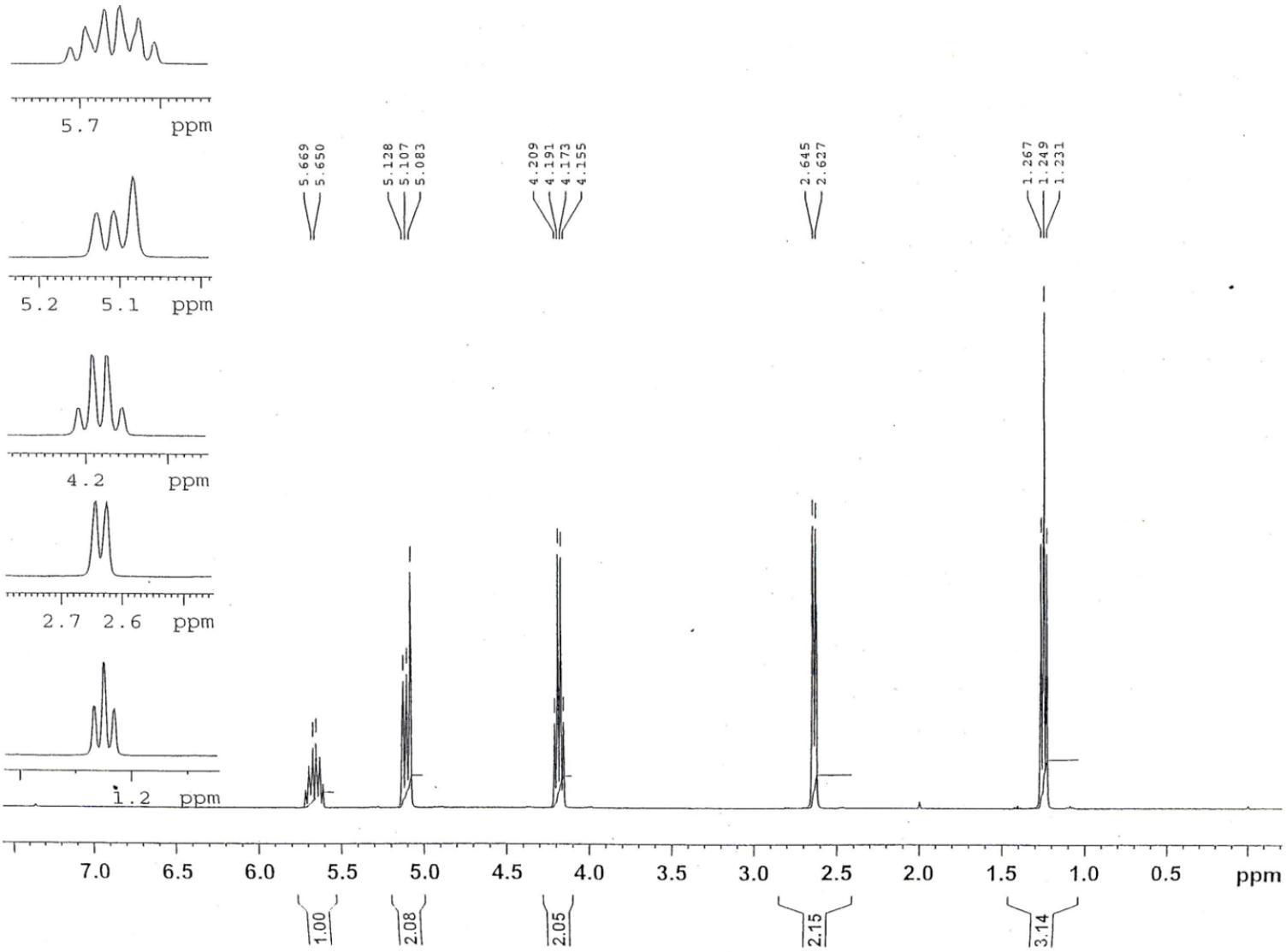


Figure SM.9.3.1.6. Diethyl diallylmalonate ^{1}H NMR, 400 MHz, $CDCl_3$.

NMR Data

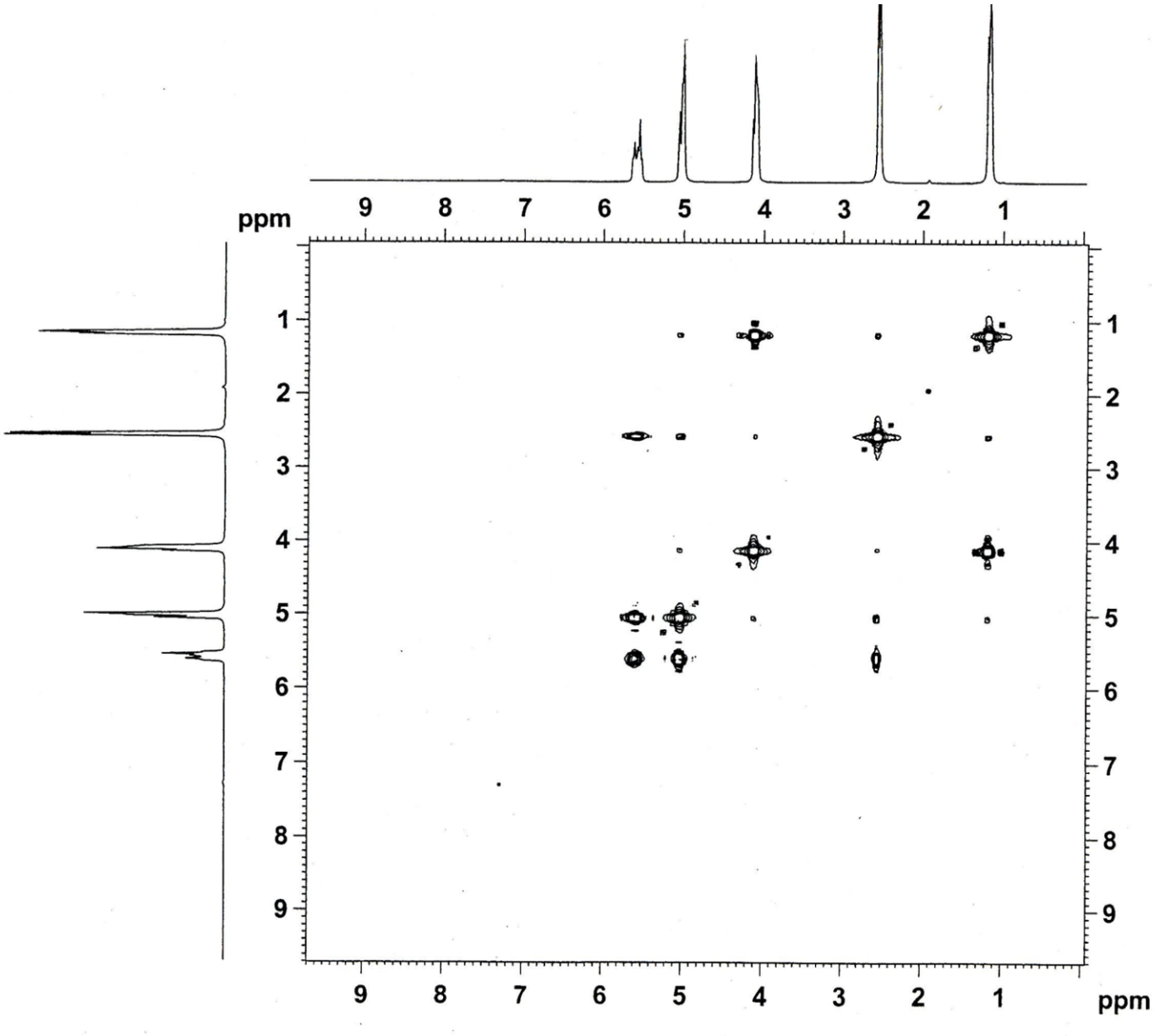


Figure SM.9.3.1.7. Diethyl diallylmalonate COSY NMR, 400 MHz, $CDCl_3$.

NMR Data

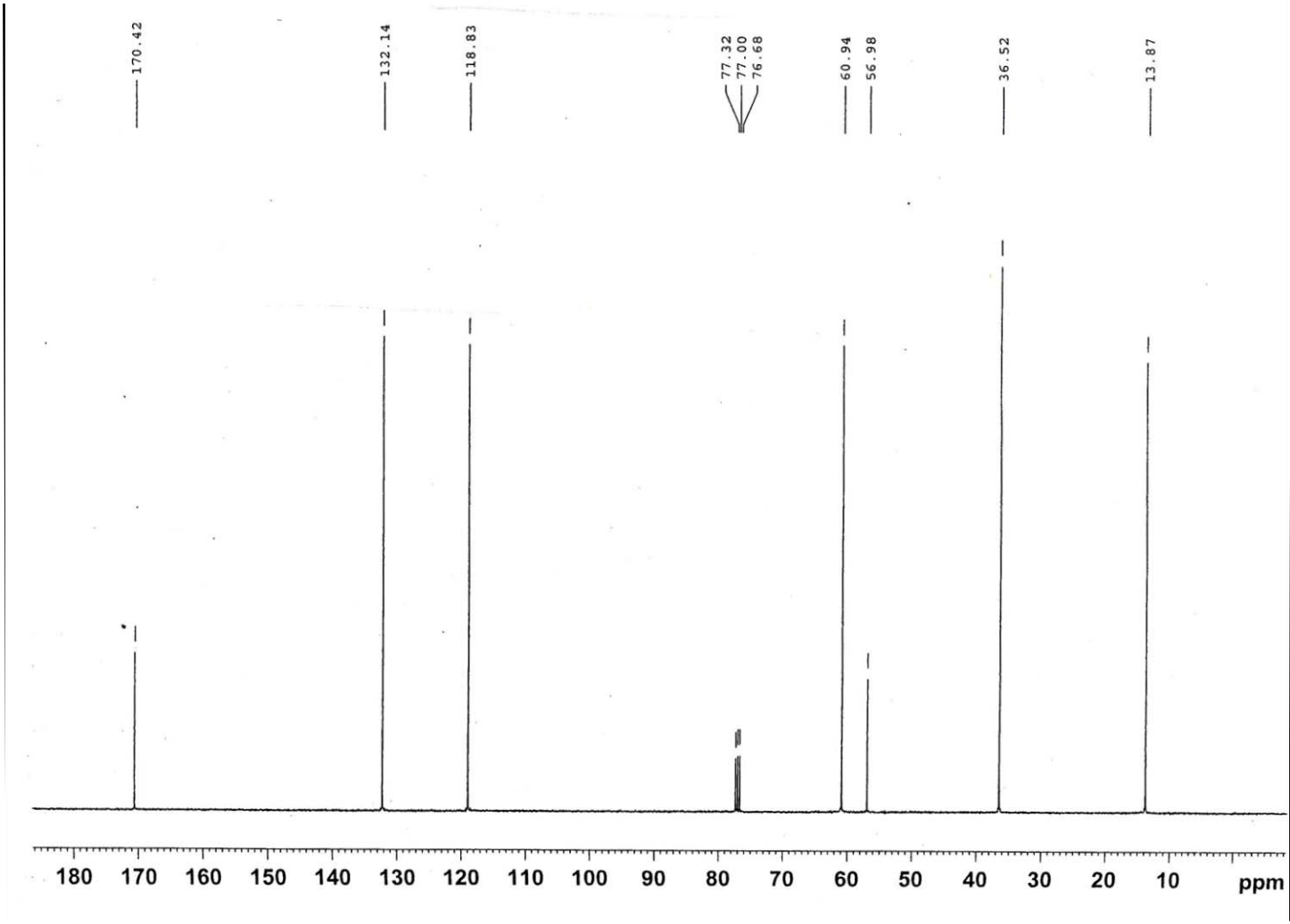


Figure SM.9.3.1.8. Diethyl diallylmalonate ^{13}C NMR, 400 MHz, $CDCl_3$.

NMR Data

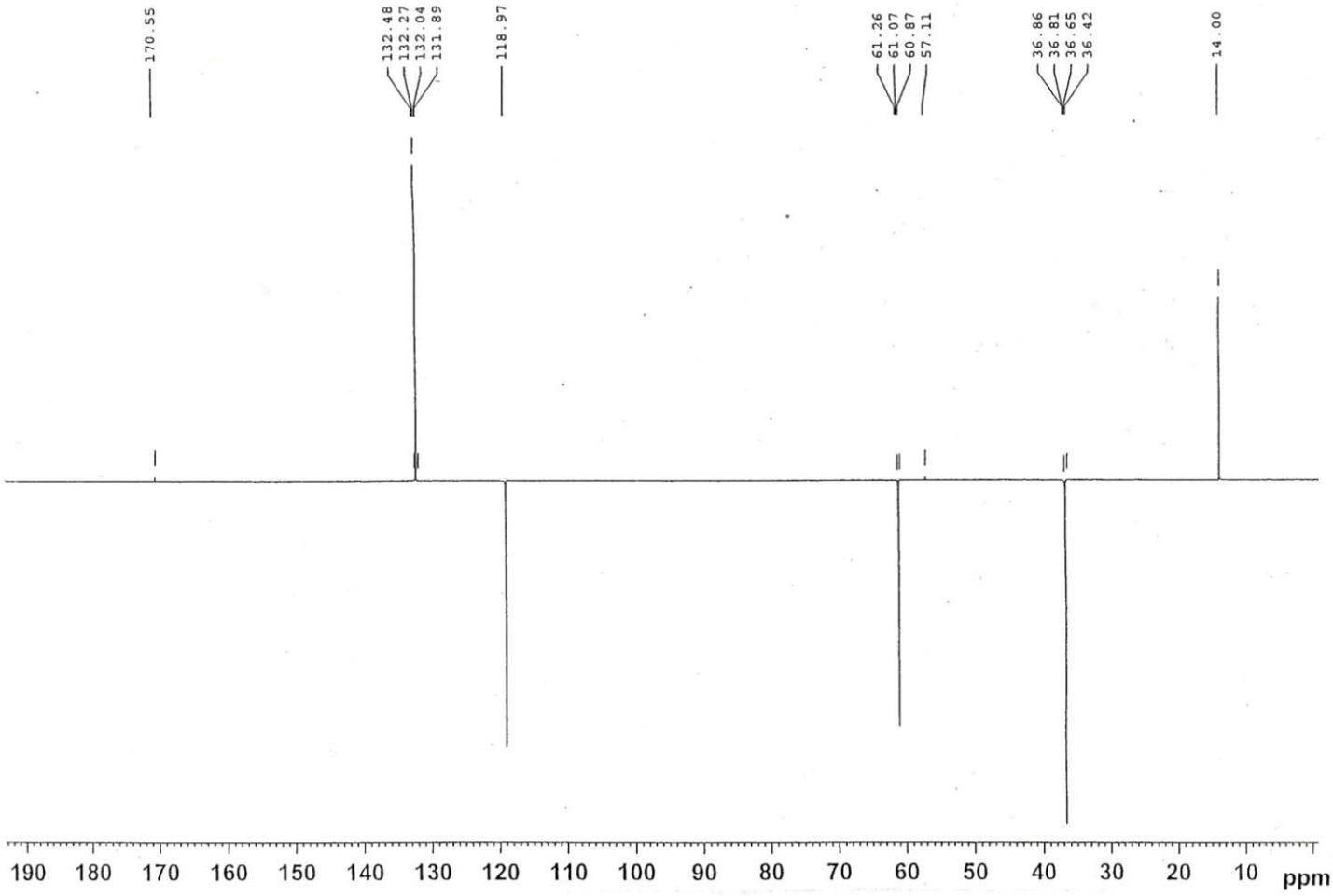


Figure SM.9.3.1.9. Diethyl diallylmalonate DEPT-135 NMR, 400 MHz, $CDCl_3$.

NMR Data

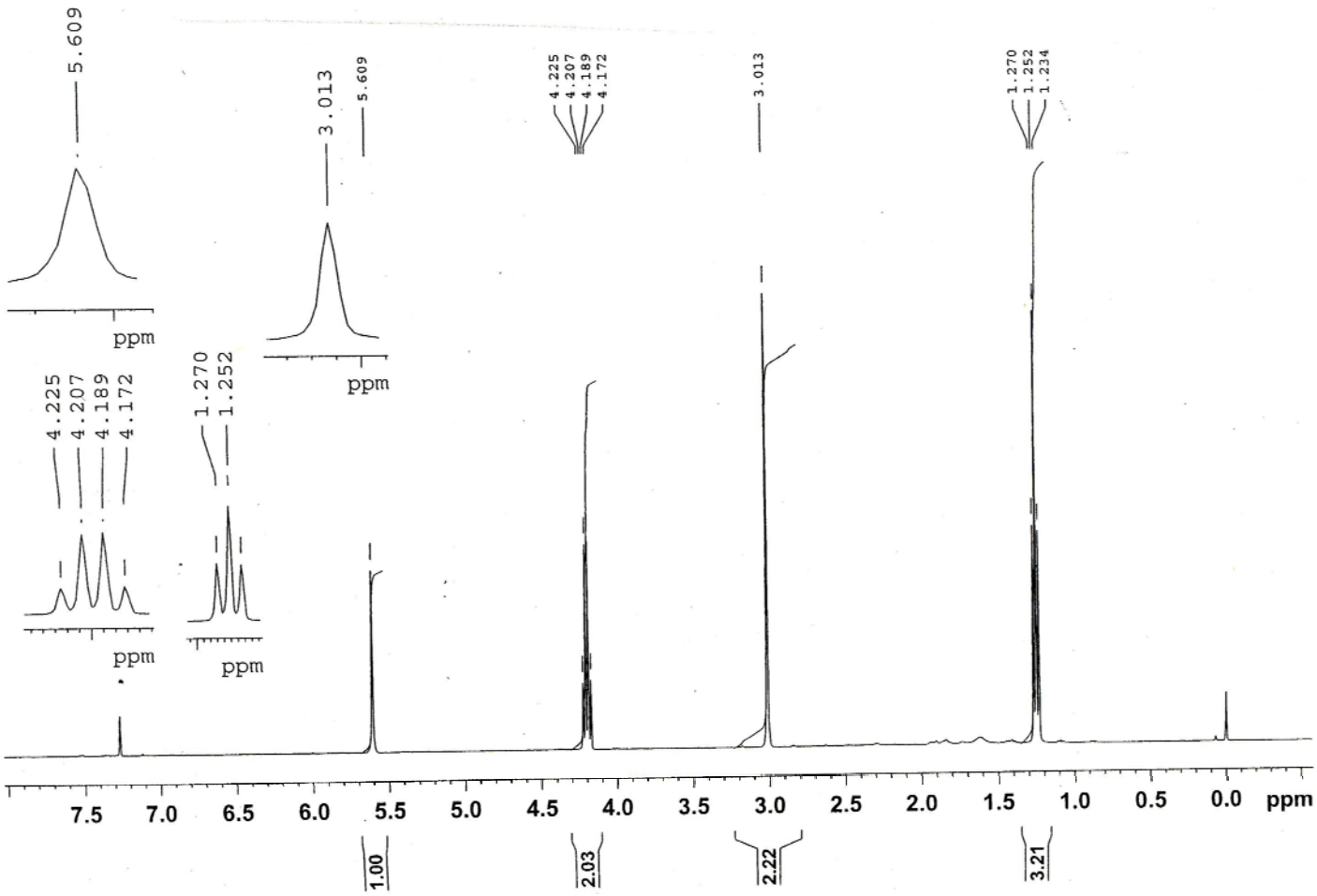


Figure SM.9.3.1.10. Diethyl cyclopent-3-ene-1,1-dicarboxylate ^{1}H NMR, 400 MHz, $CDCl_3$.

NMR Data

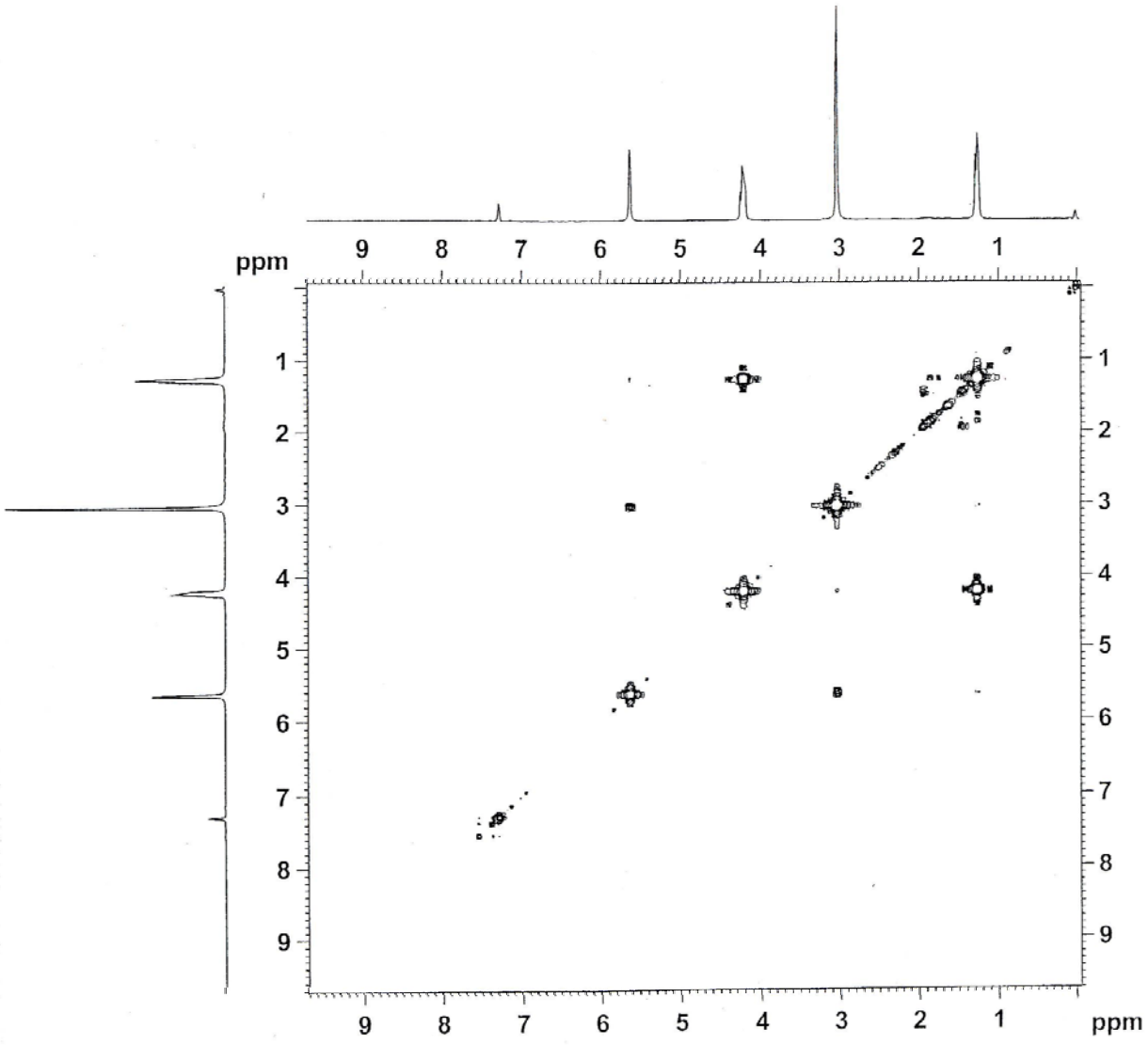


Figure SM.9.3.1.11. Diethyl cyclopent-3-ene-1,1-dicarboxylate COSY NMR, 400 MHz, $CDCl_3$.

NMR Data

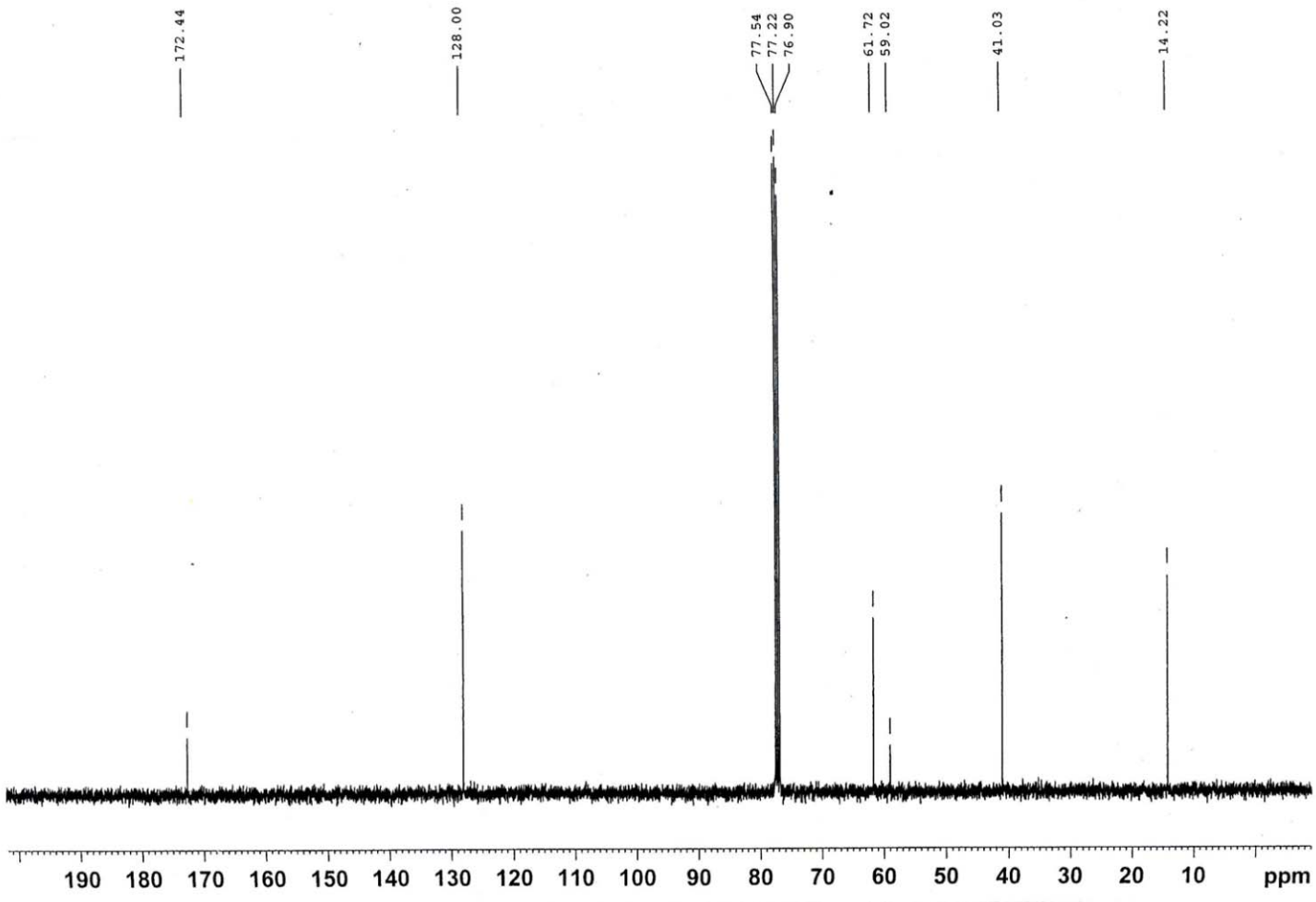


Figure SM.9.3.1.12. Diethyl cyclopent-3-ene-1,1-dicarboxylate ^{13}C NMR, 400 MHz, $CDCl_3$.

NMR Data

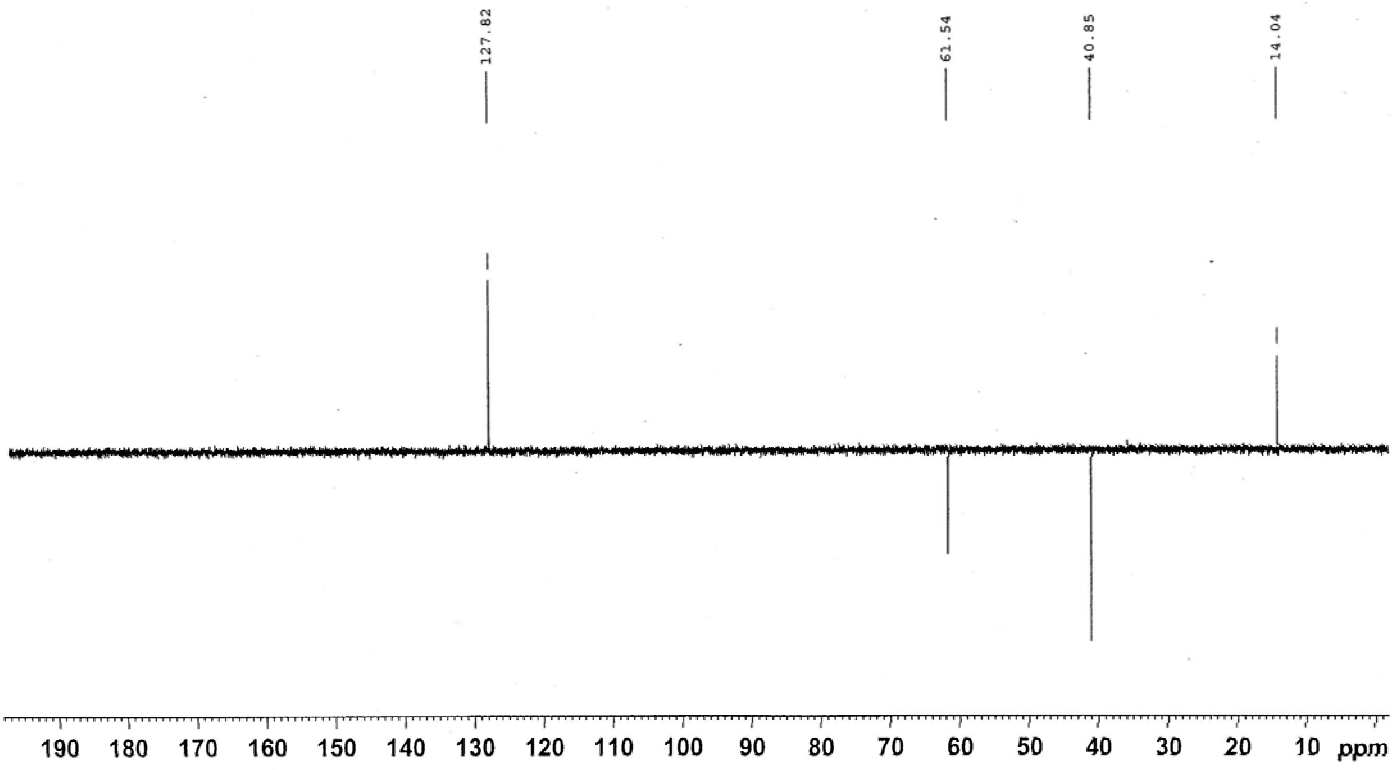


Figure SM.9.3.1.13. Diethyl cyclopent-3-ene-1,1-dicarboxylate DEPT-135 NMR, 400 MHz, $CDCl_3$.

Student Evaluation Form

Name:_____

Variable Tested:_____

Please respond to the following statements according to the rating system shown below and provide COMMENTS in the space next to each statement.

1=Low 3=Moderate 5=High

1. Level of comfort conducting first olefin metathesis experiment

1 2 3 4 5

2. Level of comfort conducting subsequent olefin metathesis experiments

1 2 3 4 5

3. Level of comfort designing olefin metathesis experiments

1 2 3 4 5

4. Degree of experience gained with respect to new laboratory techniques

1 2 3 4 5

5. Level of preparation for first olefin metathesis experiment in comparison to standard labs

1 2 3 4 5

6. Level of preparation for subsequent olefin metathesis experiments

1 2 3 4 5

7. Preference for Guided-Inquiry Lab over Standard Lab Format

1 2 3 4 5

8. Most enjoyable aspect of Olefin Metathesis Lab? Please explain

9. Most challenging aspect of Olefin Metathesis Lab (NOT the write up!)? Please explain

Supplementary information for *Comprehensive Organic Chemistry Experiments for the Laboratory Classroom*

Summary of Student Evaluations

Students completed a survey regarding the RCM experiment immediately following the oral presentation session. Students responded to a series of questions by rating them from one to five (1 = low, 3 = moderate, and 5 = high) and commenting on their responses. The rated questions focused on students' comfort level designing and conducting each experiment and their degree of preparation for each experiment. In addition, students were asked to comment on the most enjoyable and most challenging aspects of the laboratory. Over a three-year period, a total of 55 students completed the survey. The responses were averaged and the percentage of students responding with a three (moderate), four (moderately high) or five (high) was calculated.

Relative to the first RCM experiment, students noted an increased comfort level conducting subsequent RCM experiments (average: 3.7 vs. 4.3; percentage of moderately high to high responses: 60% vs. 84%). Correspondingly, there was a slight decrease in the number of students indicating a low to moderately low level of preparation (6 vs. 5) and degree of comfort conducting (5 vs. 3) the subsequent RCM experiments. This was also reflected in students' level of comfort designing the RCM experiments with 72% indicating a moderately high to high comfort level (3.8 average). Interestingly, students reported an increased level of preparation for the subsequent RCM experiments (average: 3.7 vs. 4.1; percentage of moderately high to high responses: 56% vs. 74%). When asked to rate their preference for the guided-inquiry lab format relative to the standard lab format, 90% indicated a moderate to high preference for the guided-inquiry format (3.8 average).

When queried about the most enjoyable aspect of the RCM lab, the two most common responses centered on the freedom allotted to students and the opportunity for independent

thinking. Students appreciated the freedom to design, modify, and repeat their experiments, indicating that it allowed them to build on their knowledge and skills and provided an opportunity for independent thinking. They noted that they had a good understanding of the experiment's theory and procedures because they had to think deeply about and plan more for the RCM lab. Several students reported they enjoyed reading the literature to determine the reaction mechanism and product. Finally, many individuals wrote that they had learned considerably more from the guided-inquiry lab relative to previous experiments.

The selection of a "Nobel" reaction increased student interest and involvement. Students reported they felt like they were "real scientists doing actual research" and that their experiment was important and worthwhile. Several groups used recent reports from the chemical literature to guide their experimental design. They indicated that being able to compare their results to published results made their work "seem more substantive and conclusive."

Students enjoyed learning new skills and indicated a very high degree of experience gained with respect to new laboratory techniques (average: 4.3; percentage of moderately high to high responses: 89%). They appreciated having a variable different from their classmates and suggested that future students be given the opportunity to come up with their own variable. A highlight for students was acquiring and analyzing their spectral data, especially as a means of "answering" their experimental question. In addition, numerous students were excited to present their work to their peers and to hear about experiments different from their own.

As for the most challenging aspect of the RCM lab, student responses centered on the increased effort required to carry out the lab. Interestingly, the majority of respondents also

mentioned the benefits they experienced of having put forth that extra effort. The uncertainty of not knowing the "expected" results or if the designed experiment would "work" proved to be disconcerting for some students yet highly enjoyable for others. Along those lines, a few students noted that their greatest challenge was analyzing their data; and that they would have liked to carry out additional trials in order to draw more definitive conclusions.

Sequential Pd-catalyzed allylic alkylation / Ru-catalyzed ring-closing metathesis

Supplementary Material[1]

Tetrakis(triphenylphosphine)palladium(0) is a tetrahedral 18-VE bright yellow crystalline solid that turns brown and deactivates with oxygen of air. Its manipulation under inert atmosphere is strongly suggested. The Grubbs II catalyst has a slightly distorted square pyramidal geometry (τ = 0.057) with the alkylidene moiety in the apical position. It is a 16-VE pinkish brown solid, stable toward moisture and air. Thus, it is easier to handle (Figure **SM 9.3.2.**1).

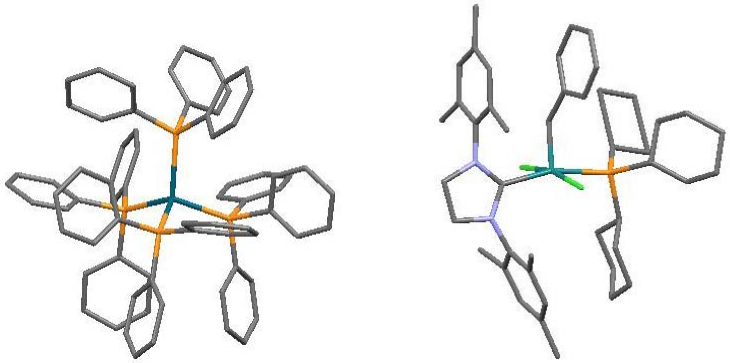


Figure SM 9.3.2.1. X-ray crystal structures. Left: tetrakis(triphenylphosphine)palladium(0);[2] right: Grubbs II catalyst.[3]

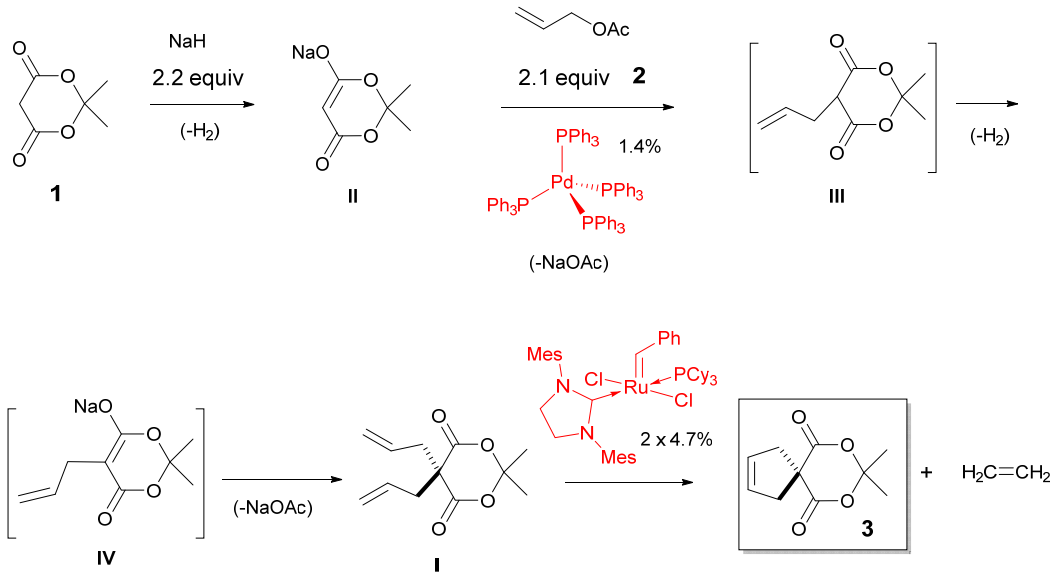
The experiment is performed on a rather small scale for several reasons. The catalysts (especially the Ru catalyst) are quite expensive. Furthermore, a column chromatography is needed to purify the product. This experiment will train the student to get acquainted with expensive materials and to work on a small scale. The scale used in this experiment gave 115 mg (0.59 mmol, 84 %) of 8,8-dimethyl-7,9-dioxaspiro[4.5]dec-2-ene-6,10-dione (**3**) as a white solid (mp 85 °C).

The complete sequence, with the involved intermediates, is shown in scheme **SM 9.3.2.**1. The amounts of materials engaged in the experiment are described in Table **SM 9.3.2.**1.

[1] The experiment has been run by five students in different trials and different periods, obtaining similar and reproducible results, (range 64-91%; average: 84%).

[2] V. G. Andrianov, I. S. Akhrem, N. M. Chistovalova, Y. T. Struchkov, *Zh.Strukt.Khim.(Russ.)(J.Struct.Chem.),* 1976**, 17,** 135.

[3] S. E. Lehman Junior, K. B. Wagener, *Organometallics* 2005, **24**, 1477.



Scheme SM 9.3.2.1. Complete sequence for the preparation of spirocyclic compound **3**.

Table SM 9.3.2.1. Material engaged in the experiment.[a]

	molar ratio	**MW** (g.mol^{-1})	**n (mmol)**	**weight** (mg)	**vol** (ml)	**d** (g.ml^{-1})
1	1	144.13	0.694	**100**		
2	2.1	100.12	1.458	145.97	**0.157**	0.928
NaH (60%)	2.2	24	1.527	36.65 -> **61**		
Pd cat	0.014	1155.56	0.010	**12**		
Ru cat	0.047 x 2	848.97	0.033 x 2	**28 x2**		
CH_2Cl_2					12 (**3** + **6** + **3**)	
3	1	196.20	0.694	136.16[a]		

a) Theoretical amount of product

The experiment

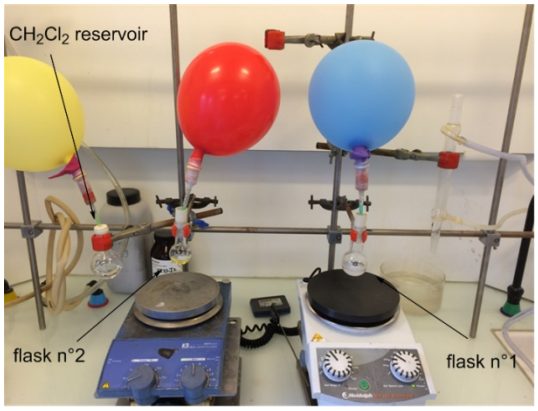


Figure SM 9.3.2.2. Flasks n° 1 and 2 charged with the substrates.

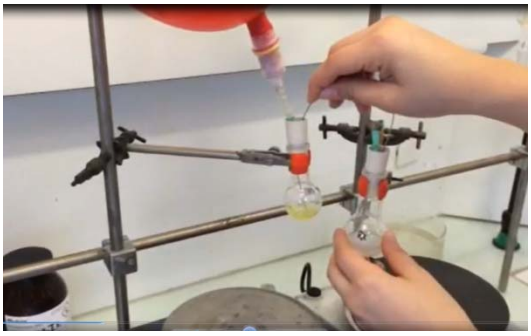


Figure SM 9.3.2.3. Transfer via cannula from flask n° 1 to flask n° 2.[4]

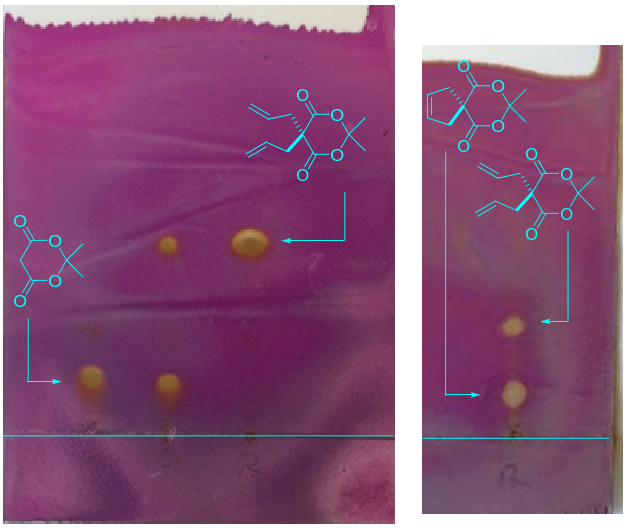


Figure SM 9.3.2.4. TLC analyses. Left: 1st step, after 1 hour reflux (eluent: cyclohexane/AcOEt 80/20; detection: $KMnO_4$). Left lane: starting material; middle lane: starting material + reaction mixture; right lane: reaction mixture. Right: 2nd step: 1 hour after the 1st addition of the ruthenium catalyst, (still incomplete conversion is apparent). (eluent: cyclohexane/AcOEt 95/5; detection: $KMnO_4$).

[4] The movie of the cannulation is provided as a supplementary file. It can be downloaded and run on a standard media player.

Spectra

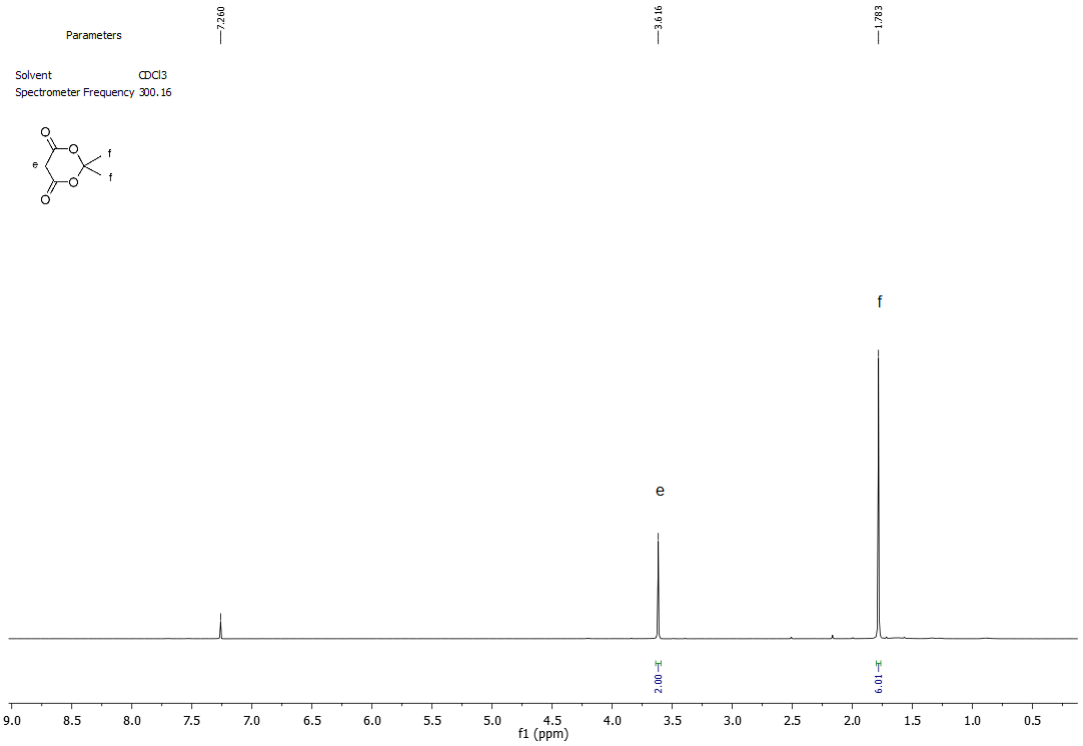


Figure SM 9.3.2.5. ^{1}H NMR spectrum of Meldrum's acid **1**.

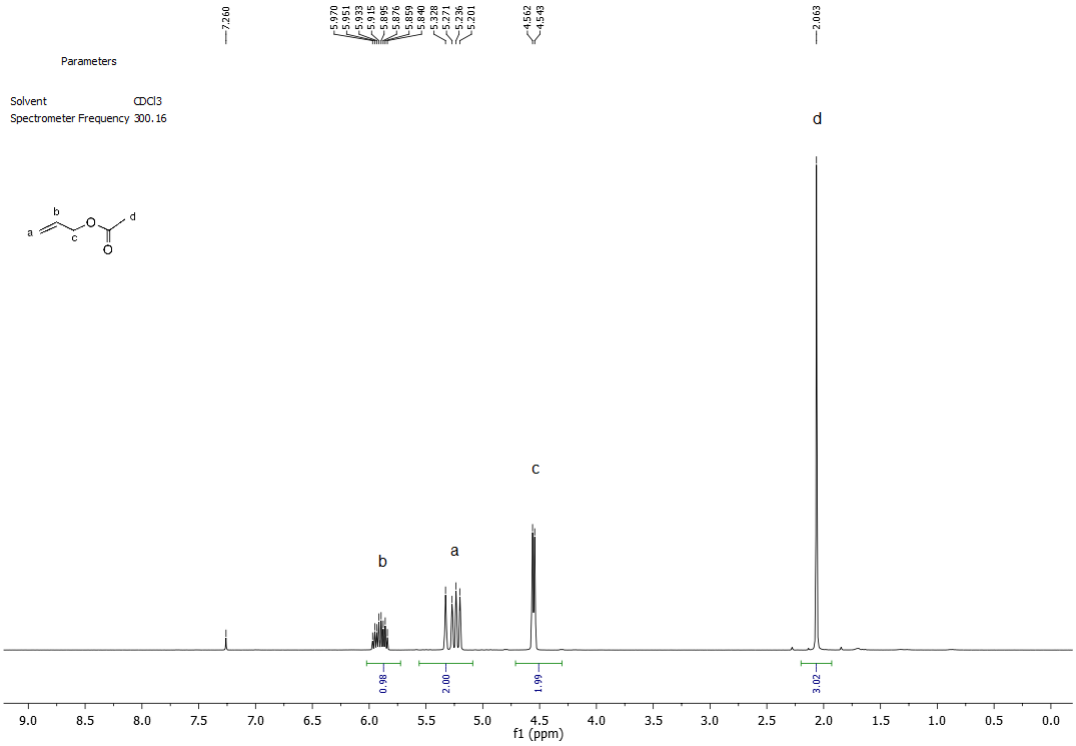


Figure SM 9.3.2.6. ^{1}H NMR spectrum of allyl acetate **2**.

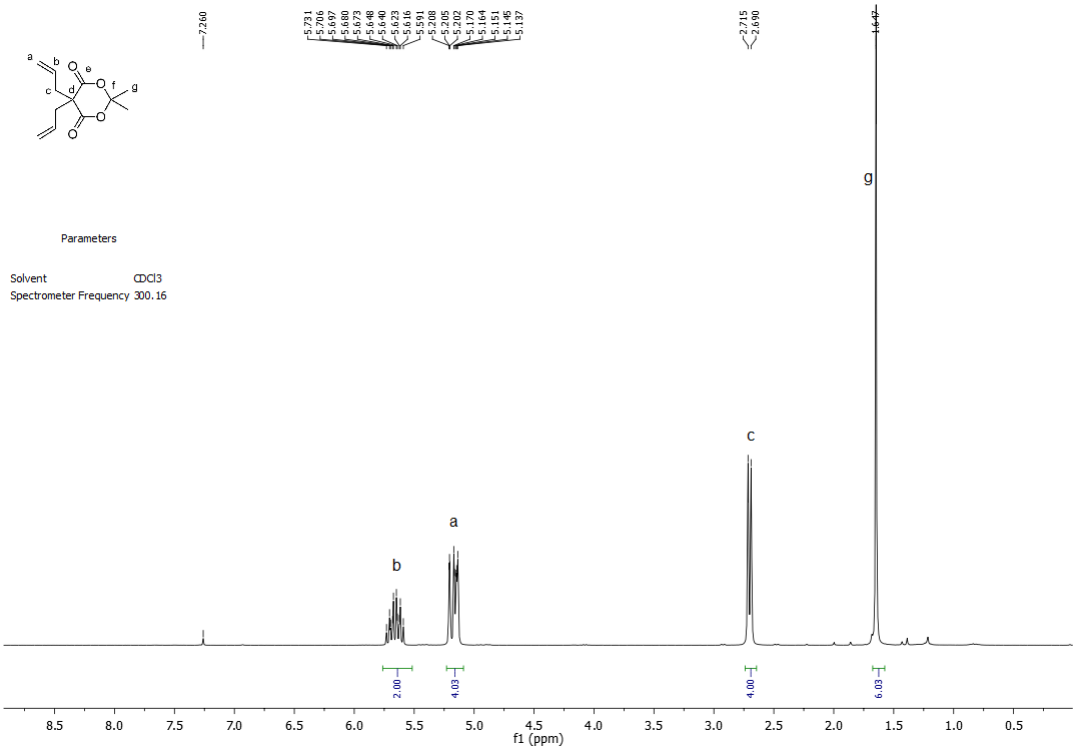


Figure SM 9.3.2.7. ^{1}H NMR spectrum of Intermediate **I**.

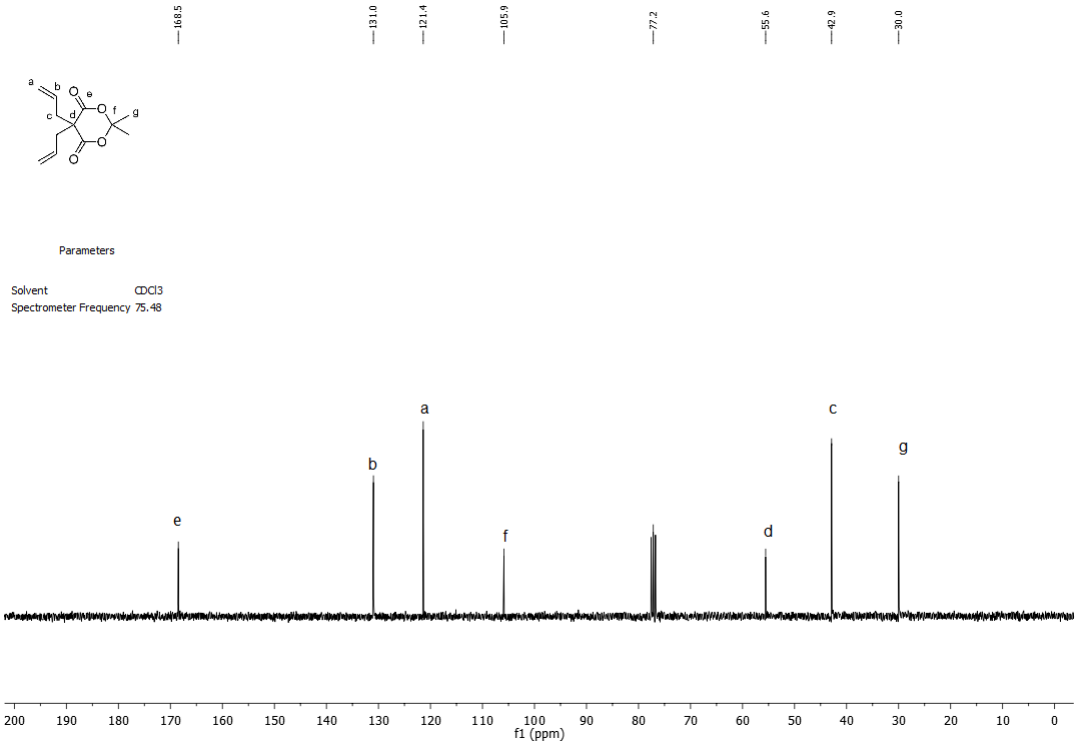


Figure **SM 9.3.2.**8. ^{13}C NMR spectrum of Intermediate I.

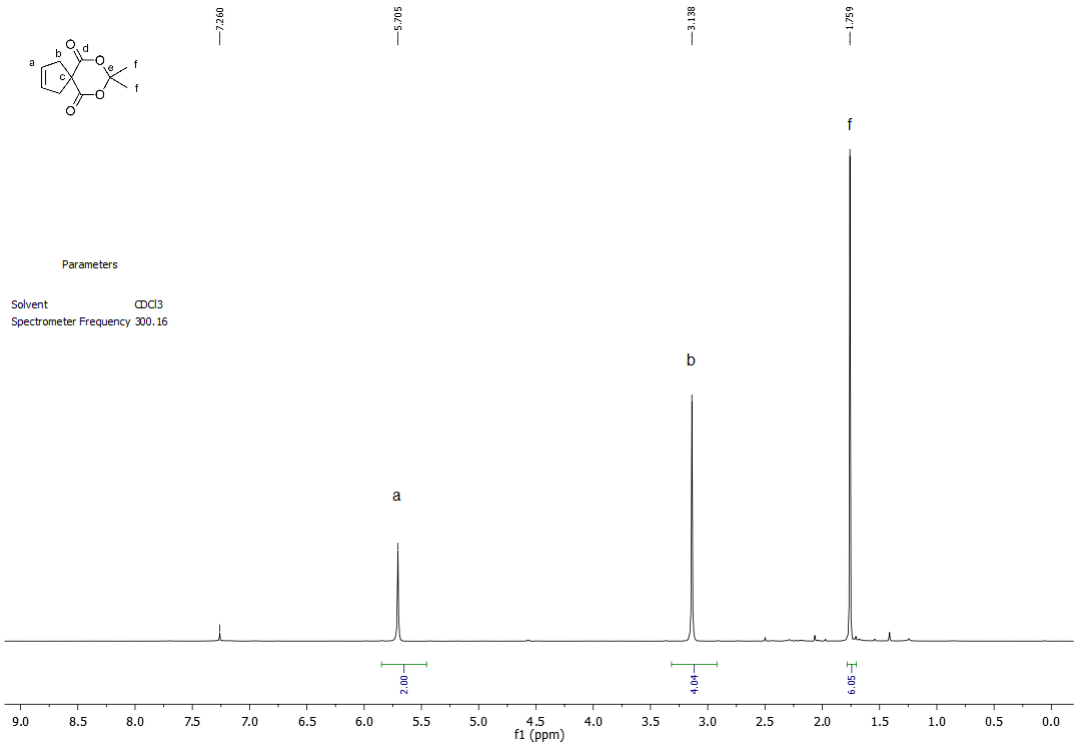


Figure SM 9.3.2.9. ^{1}H NMR spectrum of **3**. ^{1}H NMR (CDCl3, 300 MHz) : δ = 1.76 (s, 6H); 3.14 (s, 4H); 5.71 (s, 2H).

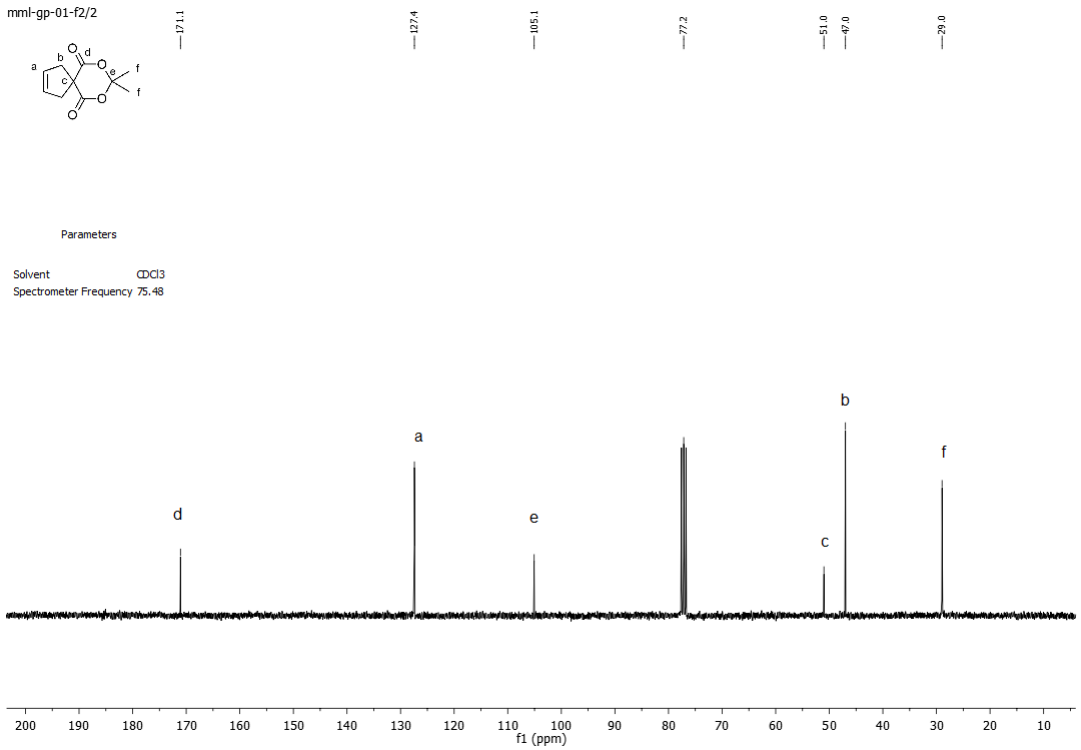


Figure SM 9.3.2.10. ^{13}C NMR spectrum of product **3**. ^{13}C NMR ($CDCl_3$, 75 MHz) : δ = 29.0, 47.0, 51.0, 105.1, 127.4, 171.1.

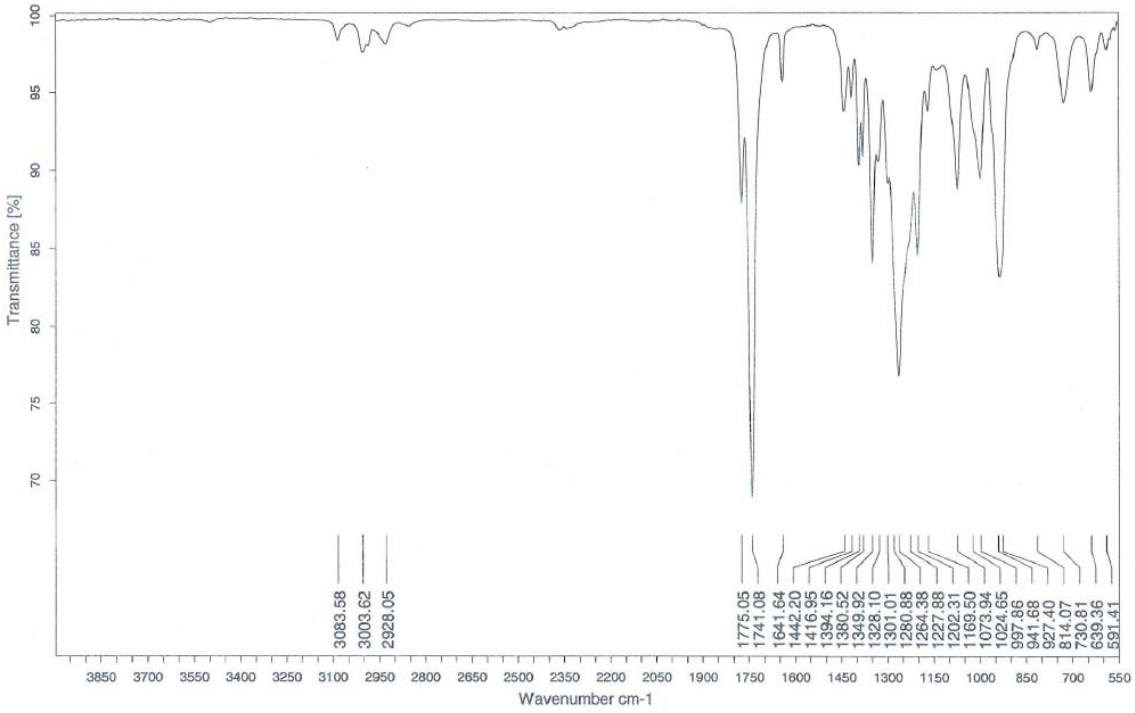
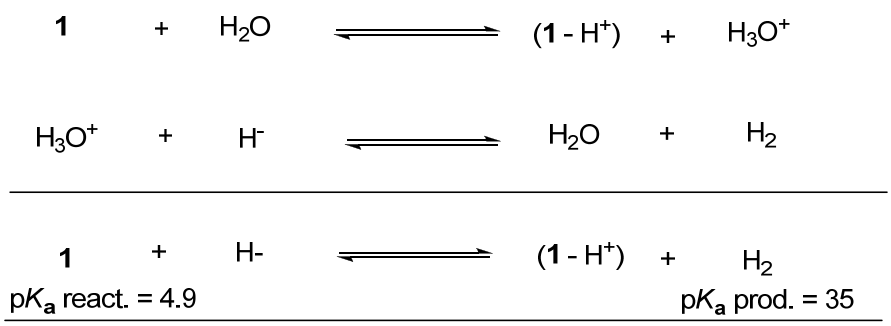


Figure SM 9.3.2.11. IR spectrum of product **3**. 3004, 2928, 1775 ($\nu_{C=O}$ asym.), 1741($\nu_{C=O}$ sym.), 1666 ($\nu_{C=C}$) cm^1.

pK_a analysis

A proton transfer can be regarded as the sum of two K_a equilibria, one written in the forward direction, and the other in the reverse.



The proton transfer reaction is: $10^{[pK_a\,(prod.) - pK_a\,(react.)]} = 10^{[35 - 4.9]} = 10^{30.1}$

So, the deprotonation is virtually total. When a proton transfer K_{eq} is greater than 10^{10}, it can for all practical purposes be considered as irreversible.

Symmetry analysis

A symmetry analysis of product **3** allows assigning a *C_{2V} point group symmetry* ($1C_2$, $2\sigma_v$). Therefore, the following topicity relations can be assigned:

- $CH_{3\ above}$ / $CH_{3\ below}$; H7 $_{up}$ / H10 $_{down}$; H7 $_{down}$ / H10 $_{up}$; H8 / H9: homotopic (exchanged by C_2 axis)
- H7 $_{up}$ / H7 $_{down}$, H10 $_{up}$ / H10 $_{down}$: enantiotopic (exchanged by σ_1)
- H7 $_{up}$ / H10 $_{up}$; H7 $_{down}$ / H10 $_{down}$: enantiotopic (exchanged by σ_2)

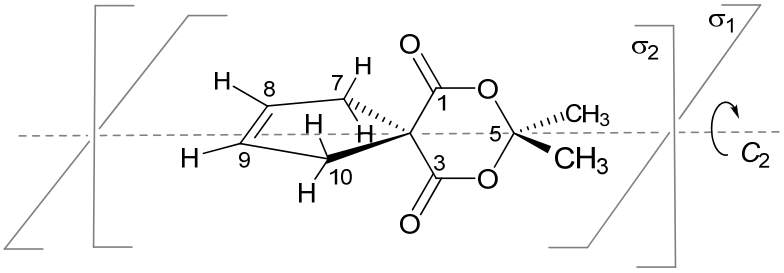


Figure SM 9.3.2.12. Location of the point group symmetry for **3**.

As enantiotopic and homotopic entities in isotropic media are undistinguishable, we can predict that a ^{1}H NMR spectrum of **3** should give rise to only three types of signals [($CH_{3\ above}$ / $CH_{3\ below}$); (H8 / H9); ($H7_{up}$ / $H7_{down}$ / $H10_{up}$ / $H10_{down}$)] with a ratio of 6: 2: 4, as is experimentally observed.