

## Design and testing of an ozonolysis reactor module with on-the-fly ozone degassing under flow conditions

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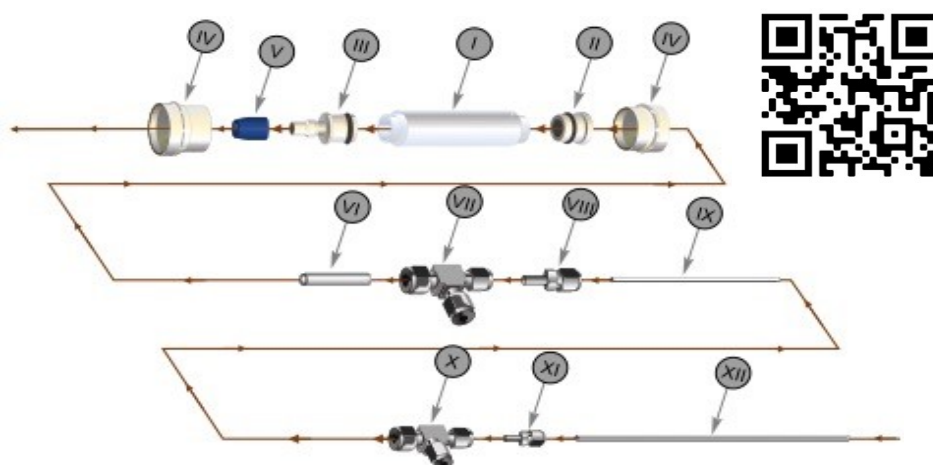
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## 1. Reactor assembly and operation

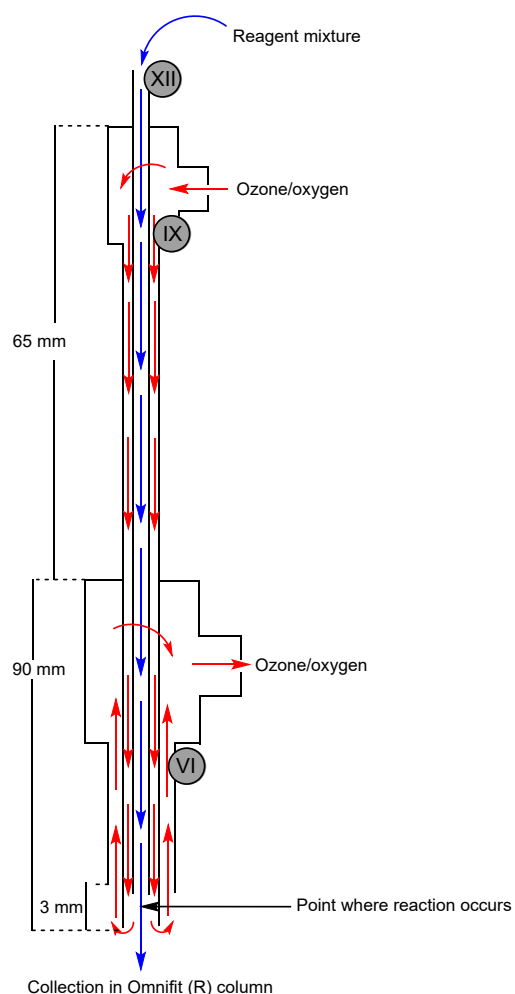
A detailed assembly of the reactor components can be seen in Figure S-1, Table S-1 and Video S-1. A 1/16" stainless steel tube labelled as XII was used for the reagent line which was inserted into a 1/8" stainless steel tube (IX) used to introduce the ozone gas. A Swagelok® bored through reducer XI facilitated the mounting of the 1/16" stainless steel tube into the 1/8" tube at a 1/8" Swagelok® stainless steel union tee X. Employing a similar technique the 1/8" stainless steel tube was then mounted inside a 1/4" PTFE tube VI using a second bored through reducer VIII and a 1/4" Swagelok® stainless steel union tee VII. Finally, the 1/4" PTFE tube VI was mounted inside an Omnifit® column (I) which was reconstructed with a modified top end piece (IV) bored out to adjust to a 1/4" hole which was required to accommodate insertion of the 1/4" PTFE tube (VI). The design of the reactor allowed ozone to be continuously vented on-the-fly and also allowed for various temperature conditions to be investigated ranging from -30 – 0 °C by placing the column module inside a cooling bath. In the cross section of the reactor shown in Figure S-2, one can see the inner tube (XII) carrying the reagent stream mounted inside the ozone/oxygen gas line (IX). The gas is introduced into tube IX via union tee X which in turn is directly connected to the ozone generator. The inner tube (XII) then ends 3 mm before the middle tube (IX) and it is at this point where the ozone and reagent streams mix and the reaction occurs. Finally, the liquid components then drip into the Omnifit® column (I) and the gas is vented into tube VI and vented via union tee VII. The reactor was assembled according to Figure S-1 and S-2. A SmartTrak100 MFC from Sierra was fitted to an oxygen regulator to control the amount of gas flowing into an MP-8000 the ozone generator acquired from [www.a2zozone.com](http://www.a2zozone.com). The ozone generator can produce a maximum of 8 g of O<sub>3</sub>/h.

**Table S-1: Component list for the reactor assembly**

Number	Component part list
I	Omnifit® column 100 x 15 mm o.d.
II	Modified top end piece assembly
III	Original bottom end fitting from Omnifit®
IV	PTFE end fitting
V	Connection cap
VI	PTFE tubing 1/4" (6.35 mm) o.d. x 3/16" (4.8 mm) i.d.
VII	Swagelok® stainless steel union tee, 1/4" (6.35 mm) tube o.d.
VIII	Swagelok® stainless steel bored-through reducer, 1/8" (3.17mm) x 1/4" (6.35 mm) tube o.d.
IX	Stainless steel tubing, 1/8" (3.17 mm) o.d. x 0.080" (2.03 mm) i.d.
X	Swagelok® stainless steel union tee, 1/8" (3.17 mm) tube o.d.
XI	Swagelok® stainless steel bored-through reducer, 1/16" (1.587 mm) x 1/8" (3.17 mm) tube o.d.
XII	Stainless steel tubing, 1/16" (1.587 mm) o.d. x 1/200" (0.127 mm) i.d.



**Figure S-1:** Reactor component assembly with QR code for reactor assembly Video S-1



**Figure S-2:** Cross section of the components fitted into one another

A full illustration of the reactor operations can be appreciated from Figures S-2 and S-3. An HPLC pump, is connected to the solvent inlet of the reactor carrying the solvent/reagent solution, shown in Figure S-3 as liquid in, and in Figure S-2 as tube XII. A second HPLC pump, connected to the outlet of the column reactor, was used to simultaneously remove the solution from the column as it enters, shown in Figure S-3 as liquid out. The introduction of the  $O_2/O_3$  gas was controlled by a SmartTrak 100 MFC, the ozone and the reagent stream mix together in a short 3 mm long “reaction zone” after which the reaction mixture is aspirated into the Omnifit<sup>®</sup> column, and the gas is removed via the 1/4" PTFE tube VI and union tee VII labelled as gas out. The hydroperoxyl stream collected in the Omnifit<sup>®</sup> column upon being pumped out of the column housing is fed into a flask housing the reductant.

## 2. Bubble counting python code

The Python code was run on a Raspberry Pi which had Open-Source Computer Vision (OpenCV) library was installed.[1, 2] OpenCV was used to filter out pixels that were not within a specified colour range. Sudan Red dye was utilised for our set-up, therefore, pixels that were not red were filtered out.

The python script can also be found at the following link:

[https://github.com/JohanvdWesthuizen/bubble\\_counter.git](https://github.com/JohanvdWesthuizen/bubble_counter.git)

Script:

```
# import the necessary packages
from picamera.array import PiRGBArray
from picamera import PiCamera
import numpy as np
import time
import cv2
import os
from datetime import datetime
import os.path

# initialize the camera and grab a reference to the raw camera
capture
camera = PiCamera()
camera.resolution = (640, 480)
camera.framerate = 32
rawCapture = PiRGBArray(camera, size=(640, 480))

# allow the camera to warmup
time.sleep(0.1)

save_path = '/home/pi/Desktop/OpenCV/data'
start_time = datetime.now()
file_name = start_time.strftime("%H-%M-%S")
completeName = os.path.join(save_path, file_name+".txt")
data_file = open(completeName, "w")
```

```

timeout = time.time() + 60*5                                # 5 min from now

all_data = []

# capture frames from the camera
for frame in camera.capture_continuous(rawCapture,
format="bgr", use_video_port=True):
    # grab the raw NumPy array representing the image, then
    initialize the timestamp
    # and occupied/unoccupied text
    time.sleep(0.05)
    #print(datetime.now())
    image = frame.array
    image = image[100:500, 100:400] #Crop y:y+h and x:x+w

    # show the frame
    cv2.imshow("Frame", image)

    hsv_image = cv2.cvtColor(image, cv2.COLOR_BGR2HSV)
    # cv2.imshow("hsv_image", hsv_image)

    #lower mask (0-10)
    lower_red_hsv = np.array([0, 50, 50])
    upper_red_hsv = np.array([10, 255, 255])
    filter1 = cv2.inRange(hsv_image, lower_red_hsv,
upper_red_hsv)
    #upper mask (170-180)
    lower_red_hsv = np.array([170, 50, 50])
    upper_red_hsv = np.array([180, 255, 255])
    filter2 = cv2.inRange(hsv_image, lower_red_hsv,
upper_red_hsv)

    #join the filters
    hsv_filter = filter1 + filter2

    output_hsv = image.copy()

```

```

output_hsv[np.where(hsv_filter == 0)] = 0

cv2.imshow("output_hsv", output_hsv)

output_hsv = cv2.cvtColor(output_hsv, cv2.COLOR_BGR2GRAY)
num_red = cv2.countNonZero(output_hsv)
# print(frame.size)
tot_pix = output_hsv.size
# print(tot_pix)
# print('The number of red pixels is: ' + str(num_red))
ratio = round(((num_red/tot_pix) * 100), 2)

percent_red = ' Percentage red: ' + str(ratio)
data = str(datetime.now()) + percent_red
print(data)
data_file.write(data + '\n')

all_data.append(ratio)
# if len(data) > 20:
#     data.pop(0)
# # roll_avg = round((sum(data) / len(data)), 1)
# roll_avg = round(np.average(data), 2)
# roll_std = round(np.std(data), 2)
# print(f"Rolling average of red: {roll_avg} +-
{roll_std}")

if time.time() > timeout:
    break

key = cv2.waitKey(1) & 0xFF

# clear the stream in preparation for the next frame
rawCapture.truncate(0)

# if the `q` key was pressed, break from the loop
if key == ord("q"):

```



```

        break

    # print(all_data)
    avg = round(np.average(all_data), 2)
    std = round(np.std(all_data), 2)
    print(avg)
    print(std)

    data_file.write('Average: ' + str(avg) + '\n')
    data_file.write('St.dev: ' + str(std) + '\n')

```

### 3. Bubble counting calculation example

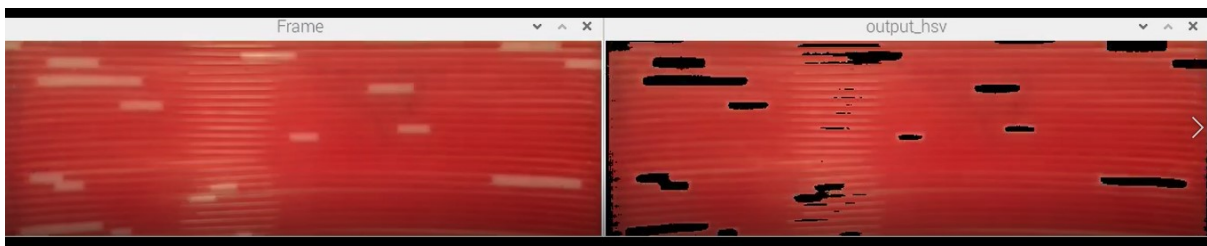
#### Entry 1

- In the case of entry 1 the gas input is 1 sL/h = 1000 mL/h = 16.67 mL/min.
- The gas output is 4.99 %, therefore for every 1 mL there is 0.05 mL gas present and at 1 mL/min there is therefore also 0.05 mL of gas produced per min.
- Therefore, the percentage gas output relative to the gas input is  $0.05/16.67 \times 100/1 = 0.3 \%$ .

#### Entry 2

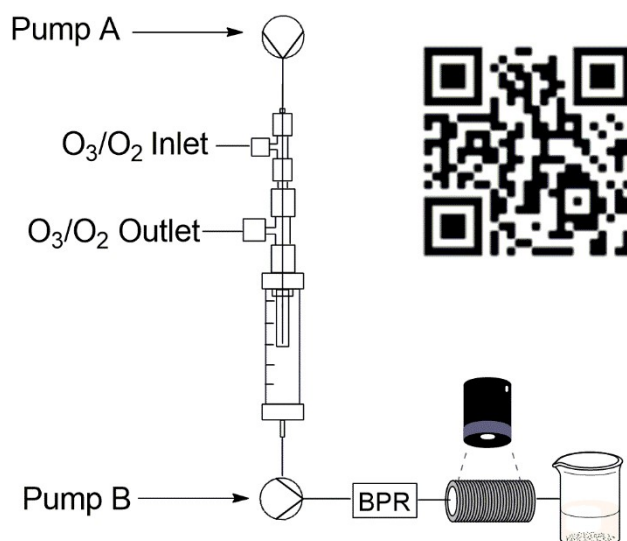
- In the case of entry 1 the gas input is 1 sL/h = 1000 mL/h = 16.67 mL/min.
- The gas output is 8.28 %, therefore for every 1 mL there is 0.0828 mL gas present and at 0.5 mL/min there is 0.0414 mL of gas produced per min.
- Therefore, the percentage gas output relative to the gas input is  $0.0414/16.67 \times 100/1 = 0.25 \%$ .

### 4. Bubble counting picture



**Figure S-3:** Snapshot of the bubble counting for experiment 1 at 1 sL/h and 1mL/min

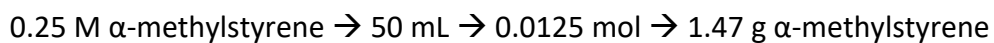
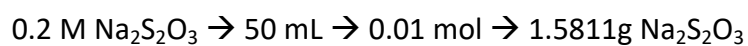
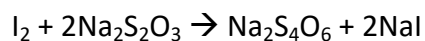
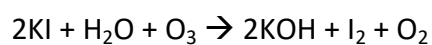
## 5. Bubble counting reactor setup



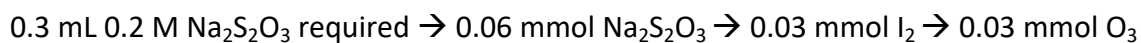
**Figure S-4:** Figure displaying the bubble counting diagram

## 6. Quantification with potassium iodide

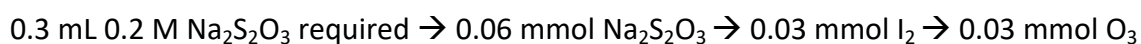
### Titration calculation



### Analysis of headspace gas with no substrate



### Analysis of headspace gas with substrate



## Analysis of headspace gas with substrate

2 mL 0.2 M  $\text{Na}_2\text{S}_2\text{O}_3$  required  $\rightarrow$  0.4 mmol  $\text{Na}_2\text{S}_2\text{O}_3 \rightarrow$  0.2 mmol  $\text{I}_2 \rightarrow$  0.2 mmol  $\text{O}_3$

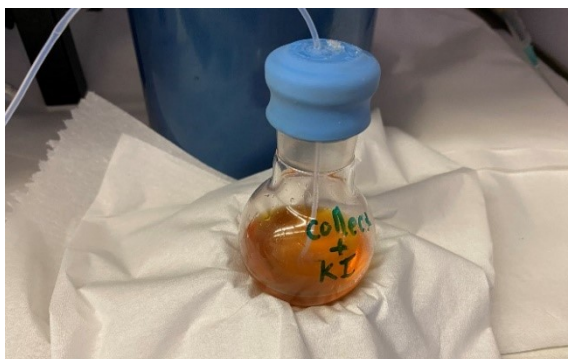
Photos:



**Figure S-5:** 10 mL of 1.0 M KI solution reaction with no substrate present



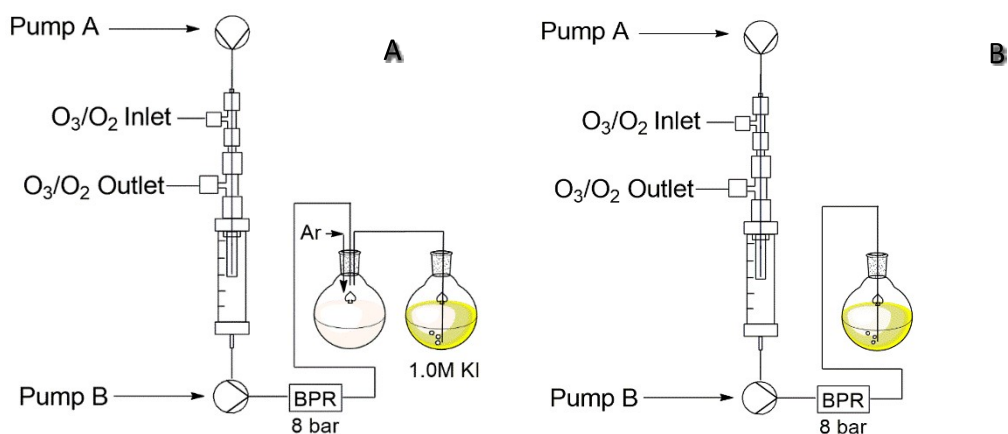
**Figure S-6:** 10 mL of 1.0 M KI solution reaction with 0.25M substrate (alpha-methylstyrene) present



**Figure S-7:** 10 mL of 1.0 M KI solution direct bubbling from the collect stream no substrate present



**Figure S-8:** Pumping 10 % KI solution in Methanol through the reactor



### 7. Reactor set-up for quantification

**Figure S-9:** Reactor set-up for quantification of **A** gas bubbles and **B** gas bubbles and liquid phase using potassium iodide

### 8. Image of reaction mixture “freezing”



**Figure S-10:** Reaction mixture “freezing” below  $-30\text{ }^{\circ}\text{C}$

## 9. Ozone concentration calculation examples

### Table 2, Entry 1

MFC flow rate =  $1.0\text{ sL}\cdot\text{h}^{-1}$

Amount of ozone delivered in 1 h = 8 g

Amount of ozone delivered per mL  $\text{O}_2$  in 1 h =  $8\text{g}/1000\text{mL} = 0.008\text{ g}\cdot\text{mL}^{-1} = 0.384\text{ mmol}\cdot\text{mL}^{-1}$

Volume of  $\text{O}_2$  delivered per min =  $1000\text{ mL}\cdot\text{h}^{-1}/60 = 16.67\text{ mL}$

Amount of  $\text{O}_3$  delivered per min =  $0.008\text{ g}\cdot\text{mL}^{-1} \times 16.67\text{ mL} = 0.133\text{ g} = 6.4\text{ mmol}$

Amount of reagent (0.5 M) delivered per min = 1 mL = 0.5 mmol

### Table 2, Entry 4

MFC flow rate =  $0.75\text{ sL}\cdot\text{h}^{-1}$

Amount of ozone delivered in 1 h = 8 g

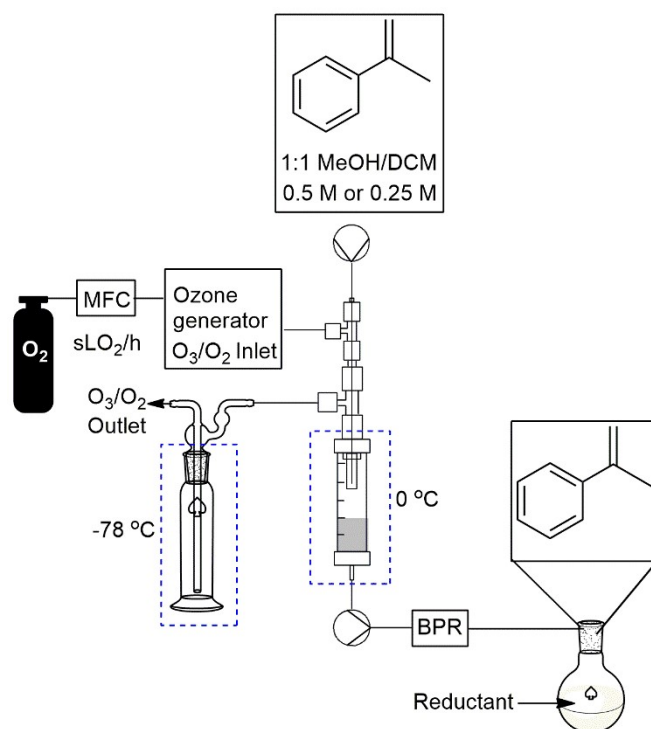
Amount of ozone delivered per mL  $\text{O}_2$  =  $8\text{g}/750\text{mL} = 0.011\text{ g}\cdot\text{mL}^{-1} = 0.512\text{ mmol}\cdot\text{mL}^{-1}$

Volume of  $\text{O}_2$  delivered per min =  $750\text{mL}\cdot\text{h}^{-1}/60 = 12.5\text{ mL}$

Amount of  $\text{O}_3$  delivered per min =  $0.011\text{ g}\cdot\text{mL}^{-1} \times 12.5\text{ mL} = 0.1375\text{ g} = 6.4\text{ mmol}$

Amount of reagent (0.5 M) delivered per min = 1 mL = 0.5 mmol

## 10. Scale-up reactor setup



**Figure S-11:** Reactor set-up for scale-up with cold trap

## 11. Experimental

### i) General Methods and Equipment

All solvents, chemicals and reagents were obtained commercially and used without further purification. Ozone was generated using an MP-8000 ozone generator acquired from [www.a2zozone.com](http://www.a2zozone.com). Gas delivery was controlled through the use of a SmartTrak100 mass flow controller from Sierra. All pumping operations were performed using a Uniqsis Binary pump module instrument plumbed with standard PTFE and stainless steel tubing. Back pressure regulators fitted contained chemically resistant perfluoropolymer and/or Hastelloy components. Yields are calculated from the immediate synthetic precursor, unless otherwise specified.

### ii) Chromatographic separations

The retention factor ( $R_f$ ) values quoted are for thin layer chromatography (TLC) on aluminium-backed Macherey-Nagel ALUGRAM Sil G/UV254 plates pre-coated with 0.25 mm silica gel 60. Spray reagents were used on thin layer chromatography plates for the detection of compounds that were not highly UV active. General reagents used include acidic vanillin, basic  $KMnO_4$ , acidic ceric ammonium sulfate, acidic anisaldehyde.

Macherey-Nagel Silica gel 60 (particle size 0.063 – 0.200 mm) was used as the adsorbent for conventional preparative column chromatography, with a silica to product ratio of 30:1. The silica was packed into a suitable column and the indicated solvent was passed through several times under pressure, until no air bubbles were visible in the column. The crude product was adsorbed onto silica, loaded onto the silica surface and covered with a plug of cotton wool. The elution process was performed using the indicated solvent mixtures either under gravitation or air pump pressure conditions.

### iii) Spectroscopy and physical data

<sup>1</sup>H NMR (300 MHz) and <sup>13</sup>C NMR (75 MHz) spectra were recorded on Bruker AVANCE-III-300 Bruker AVANCE-III-400 spectrometers at 300.13 and 400.13 MHz respectively using standard pulse sequences. All spectra were recorded in deuterated chloroform (CDCl<sub>3</sub> at 7.26 ppm), deuterium oxide (D<sub>2</sub>O at 4.79 ppm) or deuterated dimethyl sulfoxide (d<sub>6</sub>-DMSO at 2.50 ppm) in 5 mm NMR spectroscopy tubes. Chemical shifts,  $\delta$ , are reported in parts per million (ppm), and splitting patterns are given as singlet (s), doublet (d), triplet (t), quartet (q), broad (b) or multiplet (m). Coupling constants, *J*, are expressed in hertz (Hz). In noted cases conversions were determined from <sup>1</sup>H NMR spectra by comparison of integral areas of starting materials and products. All NMR spectra (<sup>1</sup>H and <sup>13</sup>C NMR) were where available compared to known literature spectra.

The LC system used for LC-MS analysis comprised an Agilent 1260 Infinity II series quaternary pump (G7157 A), an Agilent 1260 LC/MSD (G6125 B), an Agilent Infinity 1260 diode-array detector (DAD, G7115 A), and an Agilent 1260 series autosampler (G7129 A). The injection volume was set to 2.5/5  $\mu$ L and DAD data were recorded at several wavelengths at 160 Hz. The system was controlled by OpenLAB CDS ChemStation software (Edition Rev. C.01.04). An Agilent Poroshell 120 EC-C18 column (695975-902, 100  $\times$  4.6 mm i.d., 2.7- $\mu$ m particles) was used. The MS was equipped with an API electrospray-ionization source and configured to run in positive mode at an acquisition rate of 4 Hz (G1948 A/B). LC-UV-MS methods relating to each series of compounds tested are listed in section 11 below.

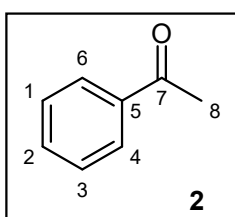
Infrared spectra were obtained on a Bruker ALPHA Platinum ATR spectrometer. The absorptions are reported on the wavenumber (cm<sup>-1</sup>) scale, in the range 400-4000 cm<sup>-1</sup>. The signals are reported: value (relative intensity).

#### iv) Nomenclature and numbering

Compounds are named using the standard International Union of Pure and Applied Chemistry (IUPAC) rules and handbooks. However, the numbering system used to illustrate the diagrams of these compounds is one adopted for convenience and is not meant to reflect the systematic numbering of these compounds.

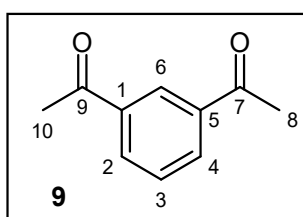
#### General batch procedures

##### Acetophenone (2)



$\alpha$ -Methylstyrene **1** (1.00 g, 8.46 mmol, 1 equiv) was dissolved in 1:1  $\text{CH}_2\text{Cl}_2$ :MeOH (17 mL), and the mixture was cooled to  $-78^\circ\text{C}$ . A stream of ozone gas at a MFC controlled flow rate of  $1\text{ sL}\cdot\text{h}^{-1}$  was bubbled through the solution for 6 minutes and 17 sec, until a blue colour persisted, after which the ozone gas was removed and argon was bubbled through the solution for an additional 10 min to remove any residual ozone. Dimethyl sulfide (0.790 g, 12.7 mmol 1.5 equiv) was added to the mixture, which was then stirred and allowed to warm to room temperature. The suspension was left standing at room temperature overnight after testing negative to peroxide test strips. *Caution!* – *ozonides and peroxy-containing by-products can be explosive*. The mixture was concentrated under reduced pressure, and the residue was taken up in sat. aq.  $\text{NaHCO}_3$  (25 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 25\text{ mL}$ ). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was collected and analysed without any further purification, 0.950 g of the colourless oil **2** was collected equating to 93 % yield. **Rf** = 0.72 (silica gel, 9:1 Hexanes/EtOAc);  $^1\text{H}$  NMR (300 MHz, Chloroform-*d*):  $\delta$  ppm 8.05 – 7.87 (m, 2H,  $\text{H}_4$  &  $\text{H}_6$ ), 7.63 – 7.37 (m, 3H,  $\text{H}_1$ ,  $\text{H}_2$  &  $\text{H}_3$ ), 2.61 (s, 3H,  $\text{H}_8$ ).;  $^{13}\text{C}$  NMR (75 MHz, Chloroform-*d*):  $\delta$  ppm 198.1 ( $\text{C}=\text{O}$ ), 137.1 ( $\text{C}_5$ ), 133.1 ( $\text{C}_2$ ), 128.5 ( $\text{C}_1$  &  $\text{C}_3$ ), 128.3 ( $\text{C}_4$  &  $\text{C}_6$ ), 26.6 ( $\text{C}(\text{O})\text{CH}_3$ ); **IR**  $\nu_{\text{max}}/\text{cm}^{-1}$  1680 (C=O str, s), 1598 (C-C str, s), 1448, 1358, 1263, 955, 758, 688, 586. Analysis of compound acetophenone corresponds with literature results obtained by Xiao and co-workers.[3]

##### 1,1'-(1,3-phenylene)bis(ethan-1-one) (9)

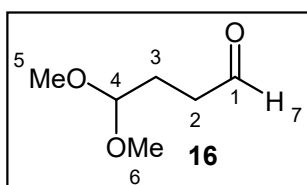


The alkene 1,3-di(prop-1-en-2-yl)benzene **8** (1.03 g, 6.50 mmol, 1 equiv) was dissolved in 1:1  $\text{CH}_2\text{Cl}_2$ /MeOH (13 mL), and the mixture was cooled to  $-78^\circ\text{C}$ . A stream of ozone gas at a MFC controlled



flow rate of 1 sL O<sub>2</sub>/h was bubbled through the solution for 11 minutes and 30 sec, until a blue colour persisted, subsequently argon was bubbled through the solution for an additional 10 min to remove any residual ozone. Dimethyl sulfide (0.605 g, 9.75 mmol, 1.5 equiv) was added to the mixture, which was then stirred and allowed to warm to room temperature. The suspension was left stirring overnight ensuring no residual ozonides were present. The mixture was concentrated under reduced pressure, and the residue was taken up in sat. aq. NaHCO<sub>3</sub> (25 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel. A colourless oil was obtained in 78 % yield. **Rf** = 0.47 (silica gel, 4:1 Hexanes/EtOAc); <sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ ppm 8.51 (q, *J* = 1.6 Hz, 1H, H<sub>6</sub>), 8.14 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 2H, H<sub>2</sub> & H<sub>4</sub>), 7.68 – 7.40 (m, 1H, H<sub>3</sub>), 2.65 (d, *J* = 1.0 Hz, 6H, H<sub>8</sub> & H<sub>10</sub>).; <sup>13</sup>C NMR (75 MHz, Chloroform-*d*): δ ppm 197.2 (2 × C=O), 137.4 (C<sub>1</sub> & C<sub>5</sub>), 132.4 (C<sub>2</sub>), 132.4 (C<sub>5</sub>), 129.0 (C<sub>3</sub>), 127.9 (C<sub>6</sub>), 26.7 (2 × C(O)CH<sub>3</sub>); IR **v**<sub>max</sub>/cm<sup>-1</sup> 3074 (ArC-H str, w), 3005 (C-H str, s), 1681 (C=O str, s), 1592 (C-C str, s), 1481, 1424, 1354, 1286, 1223, 1176, 1118, 1076, 1020, 961, 922, 798, 685, 638, 579, 487. Analysis of compound 1,1'-(1,3-phenylene)bis(ethan-1-one) corresponds with literature results obtained by Xiao and co-workers[3] as well as Ley and co-workers[4]

#### 4,4-Dimethoxybutanal (**16**)

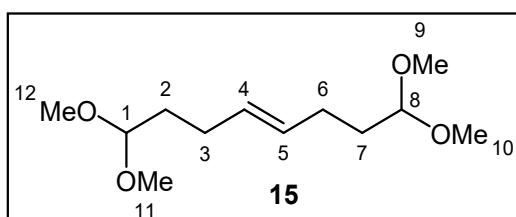


1,1,8,8-Tetramethoxyoct-4-ene, **15** (0.512 g, 2.20 mmol, 1 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and the mixture was cooled to –78 °C. A stream of ozone gas at a MFC controlled flow rate of 1 sL O<sub>2</sub>/h was bubbled through the solution for 4 minutes and 40 sec, until a

blue colour persisted, subsequently argon was bubbled through the solution for an additional 5 min to remove any residual ozone. Triphenyl phosphine (0.865 g, 3.30 mmol, 1.5 equiv) was added to the mixture, which was then stirred and allowed to warm to room temperature. The suspension was left standing at room temperature until 1 hours after testing negative to peroxide test strips (4 hours). The mixture was concentrated under reduced pressure, and the residue was taken up in sat. aq. NaHCO<sub>3</sub> (30 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 mL). The combined organic layers were dried with anhydrous NaSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (90 % Hexane/EtOAc) to afford the product 4,4-Dimethoxybutanal **16** in 67 %. **Rf** = 0.18 (silica gel, 9:1

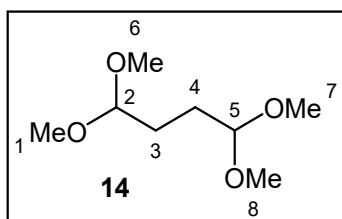
Hexanes/EtOAc);  $^1\text{H}$  NMR (300 MHz, Chloroform-*d*):  $\delta$  ppm  $\delta$  9.77 (t,  $J = 1.5$  Hz, 1H,  $\text{H}_1$ ), 4.38 (d,  $J = 5.4$  Hz, 1H,  $\text{H}_4$ ), 3.34 (s, 6H,  $\text{H}_5$  &  $\text{H}_6$ ), 2.50 (dd,  $J = 7.1, 1.5$  Hz, 2H,  $\text{H}_3$ ), 2.00 – 1.81 (m, 2H,  $\text{H}_2$ );  $^{13}\text{C}$  NMR (75 MHz, Chloroform-*d*):  $\delta$  ppm 201.8 ( $\text{C}_1$ ), 103.8 ( $\text{C}_4$ ), 53.4 ( $2 \times \text{OCH}_3$ ), 38.9 ( $\text{C}_2$ ), 35.3 ( $\text{C}_3$ ); IR  $\nu_{\text{max}}/\text{cm}^{-1}$  3431 (s), 2940 (C-H str, s), 2833, 1721 (C=O str, s), 1445 (C-H bend, m), 1385, 1187, 1126 (C-O str, s), 1054 (C-O str, s), 951, 817, 531. Analysis of compound 4,4-Dimethoxybutanal corresponds with literature results obtained by Nicolaou and co-workers.[5]

### 1,1,8,8-Tetramethoxyoct-4-ene (15)



1,5-Cyclooctadiene, **13** (1.02 g, 9.40 mmol, 1 equiv) was dissolved in 1:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (19 mL), and the mixture was cooled to  $-78$  °C. A stream ozone gas at a MFC controlled flow rate of 1 sL  $\text{O}_2/\text{h}$  for 14 min and 50 sec, then argon was bubbled through the solution for an additional 5 min to remove any residual ozone.  $\text{TsOH}\cdot\text{H}_2\text{O}$  (0.178 g, 0.940 mmol, 0.1 equiv) was added to the mixture, which was then stirred and allowed to warm to room temperature over 2 hours under an atmosphere of argon. DMS (1.00 mL, 14.1 mmol, 1.5 equiv) was then added, and stirring continued for a further 18 hours. The mixture was then concentrated under reduced pressure, and the residue was taken up in sat. aq.  $\text{NaHCO}_3$  (30 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 500$  mL). The combined organic layers were dried ( $\text{NaSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (gradient: 20–33 %  $\text{Et}_2\text{O}$  in hexanes) to afford 1,1,8,8-Tetramethoxyoct-4-ene in a yield of 35 %. **Rf** = 0.56 (silica gel, 9:1 Hexanes/EtOAc);  $^1\text{H}$  5.39 (td,  $J = 4.5, 2.2$  Hz, 2H,  $\text{H}_4$  &  $\text{H}_5$ ), 4.37 (t,  $J = 5.8$  Hz, 2H,  $\text{H}_1$  &  $\text{H}_8$ ), 3.32 (s, 12H,  $4 \times \text{OCH}_3$ ), 2.11 (ddd,  $J = 9.1, 7.5, 5.6$  Hz, 4H,  $\text{H}_3$  &  $\text{H}_6$ ), 1.65 (ddd,  $J = 9.1, 7.6, 5.9$  Hz, 4H,  $\text{H}_2$  &  $\text{H}_7$ );  $^{13}\text{C}$  NMR (75 MHz, Chloroform-*d*):  $\delta$  ppm 129.3, 103.9, 52.6, 32.3, 22.3; IR  $\nu_{\text{max}}/\text{cm}^{-1}$  2947 (C-H str, m), 2830 (C-H str, m), 1728 (m), 1444 (C-H bend, m), 1383 (C-H bend, m), 1365 (m), 1191 (m), 1124 (C-O str, vs), 1063 (C-O str, vs), 994 (w). Analysis of compound 1,1,8,8-Tetramethoxyoct-4-ene corresponds with literature results obtained by Nicolaou and co-workers[5]

### 1,1,4,4-Tetramethoxybutane (14)

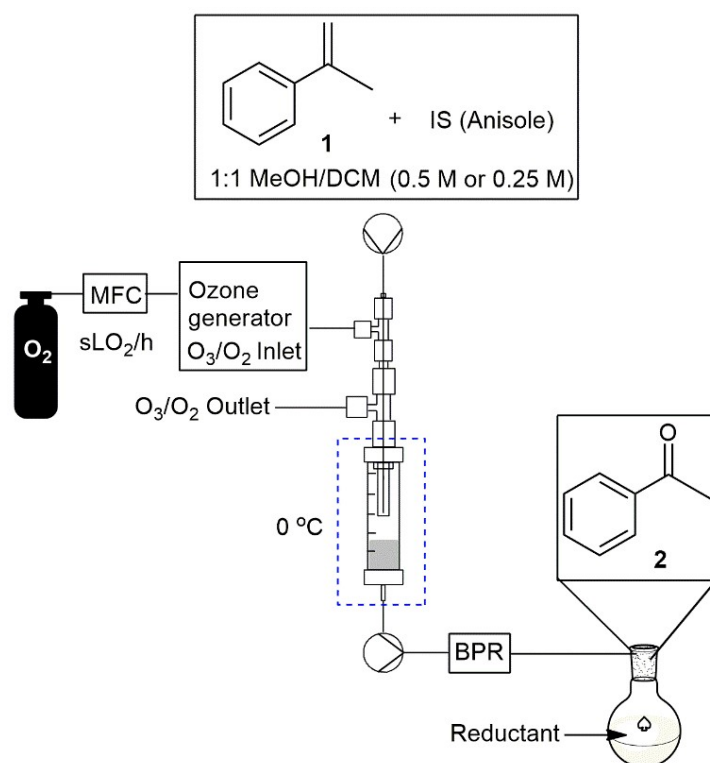


1,5- Cyclooctadiene, **13** (1.02 g, 9.40 mmol, 1 equiv) was dissolved in 1:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH (19 mL), and the mixture was cooled to -78 °C. A stream of ozone gas at a MFC controlled flow rate of 1 sL O<sub>2</sub>/h for 30 min, then argon was bubbled through the solution for an additional 5 min to remove any residual ozone. TsOH·H<sub>2</sub>O (0.178 g, 0.940 mmol, 0.1 equiv) was added to the mixture, which was then stirred and allowed to warm to room temperature over 2 hours under an atmosphere of argon. DMS (1.00 mL, 14.1 mmol, 1.5 equiv) was then added, and stirring continued for a further 18 hours. The mixture was then concentrated under reduced pressure, and the residue was taken up in sat. aq. NaHCO<sub>3</sub> (30 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 500 mL). The combined organic layers were dried (NaSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to afford 1,1,4,4- Tetramethoxybutane in a yield of 76 %. *Rf* = 0.44 (silica gel, 9:1 Hexanes/EtOAc); <sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ ppm 4.39 (t, *J* = 1.9 Hz, 2H, H<sub>2</sub> & H<sub>5</sub>), 3.33 (s, 12H, 4 × OCH<sub>3</sub>), 1.72 – 1.60 (m, 4H, H<sub>3</sub> & H<sub>4</sub>); <sup>13</sup>C NMR (75 MHz, Chloroform-*d*): δ ppm 129.3 (C<sub>2</sub> & C<sub>5</sub>), 52.7 (4 × OCH<sub>3</sub>), 27.5 (C<sub>3</sub> & C<sub>4</sub>); IR *v*<sub>max</sub>/cm<sup>-1</sup> 2939 (C-H str, m), 2831(C-H str, m), 1443(C-H bend, m), 1364, 1192 (m), 1121 (C-O str, vs), 1049(C-O str, vs), 949 (w), 853, 836, 544.

### General flow procedures

#### i) General flow ozonolysis procedure for all substrates

A reactor setup as depicted in **Figure S-11** was employed. A stock solution of the alkene was prepared at a concentration of either 0.25 M or 0.5 M.



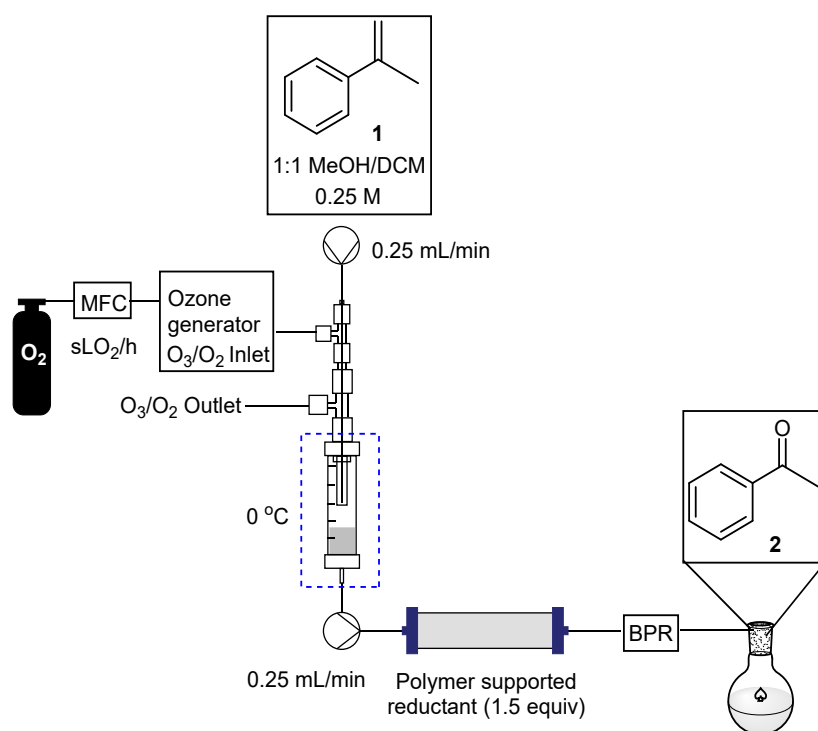
**Figure S-12:** Flow set-up employing offline quench with reductant

**Representative example:**

**Acetophenone 2:** A 0.25 M stock solution was prepared by dissolution of  $\alpha$ -methylstyrene **1** (1.48 g, 12.5 mmol, 1 equiv) in 50 mL 1:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  solvent mixture. From this 10 mL of the stock solution was pumped into the ozonolysis column reactor, held at 0 °C, with a single HPLC pump at various flow rates (0.25 – 1.5 mL/min), simultaneously a constant ozone/oxygen gas stream was introduced into the ozonolysis reactor at a MFC controlled flow rate. A second HPLC pump continuously removed the reaction mixture from the ozonolysis column. The resultant mixture passed through a BPR (8 bar) and into a collection flask housing the reductant DMS (0.280 mL, 3.75 mmol, 1.5 equiv). The reaction mixture was left to stir under batch conditions overnight for 18 hours, after which  $\text{CH}_2\text{Cl}_2$  (10 mL) and saturated  $\text{NaHCO}_3$  (20 mL) was added. The organic layer was separated and washed with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  20 mL). The organic extracts were combined, dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo* to afford the product **Acetophenone 2**.

ii) Flow procedure using polymer supported reductants

The reactor was configured as in **Figure S-12** shown below:

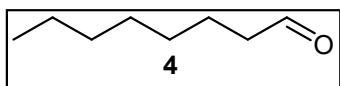


**Figure S-13:** Flow procedure with the addition of a polymer supported reductant housed in a packed bed reactor

#### Representative example:

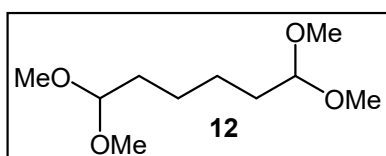
**Acetophenone 2:** A 0.25 M stock solution was prepared by dissolution of  $\alpha$ -methylstyrene **1** (1.48 g, 12.5 mmol, 1 equiv) in 50 mL 1:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  solvent mixture. From this 10 mL of the stock solution was pumped into the ozonolysis column reactor, held at 0 °C, with a single HPLC pump at various flow rates (0.25 – 1.5 mL/min), simultaneously a constant ozone/oxygen gas stream was connected to the ozonolysis reactor at a controlled MFC rate. A second HPLC pump continuously removed the reaction mixture from the ozonolysis column. The resultant mixture passed through a second column reactor housing 1.5 equiv of the polymer supported reductant (polymer supported triphenyl phosphine or Quadrapure<sup>®</sup> TU), after which it passed through a BPR (8 bar) and into a collection flask. The resultant mixture was filtered and extracted from an aqueous layer of  $\text{NaHCO}_3$  (15 mL). The aqueous layer was washed with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  20 mL), all the organic extracts were combined, dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo* to afford the product **Acetophenone, 2**.

#### Nonanal, 4



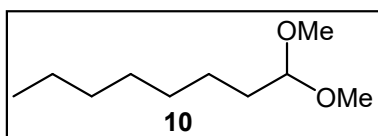
1-Decene, **3** (15mL, 0.25 M, 0.25 mL/min, 1.0 sL/h) was prepared by dissolution in a 1:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH mixture. The reaction material was passed through the ozone reactor by means of an HPLC pump, upon exiting the ozone reactor the mixture was pumped through a second column reactor housing the polymer supported triphenyl phosphine (1.5 equiv). The material was left overnight and processed the following day. An isolated yield of 76 % was recorded for nonanal. <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 9.77 (t, J = 1.9 Hz, 1H), 2.57 – 2.32 (m, 2H), 1.63 (h, J = 7.0 Hz, 2H), 1.43 – 1.12 (m, 10H), 1.02 – 0.82 (m, 3H). Analysis of Nonanal corresponds with literature results obtained from Fiasella and co-workers,[6] however grease can also be noted in the spectrum.

### 1,1,6,6-tetramethoxyhexane, **12**



Cyclohexene, **11** (15mL, 0.25 M, 0.25 mL/min, 1.0 sL/h) and a 1:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH solvent mixture. A yield of 75 – 86 % was recorded depending on reductant used. <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 4.36 (td, J = 5.7, 1.1 Hz, 2H), 3.31 (d, J = 1.5 Hz, 12H), 1.68 – 1.55 (m, 4H), 1.44 – 1.28 (m, 4H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 104.43, 52.65, 32.44, 24.48.

### 1,1-dimethoxynonane, **10**



1-Decene, **3** (15mL, 0.25 M, 0.25 mL/min, 1.0 sL/h) and a 1:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH solvent mixture. A yield of 71 % was recorded. <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 4.29 (t, J = 5.8 Hz, 1H), 3.24 (s, 6H), 1.63 – 1.39 (m, 2H), 1.34 – 1.10 (m, 12H), 0.90 – 0.71 (m, 3H). Analysis of 1,1-dimethoxynonane corresponds with literature results obtained from Mei and co-workers,[Mei, 2009 #829] however grease can also be noted in the spectrum.

### Benzaldehyde, **7** and (Dimethoxymethyl)benzene, **6**

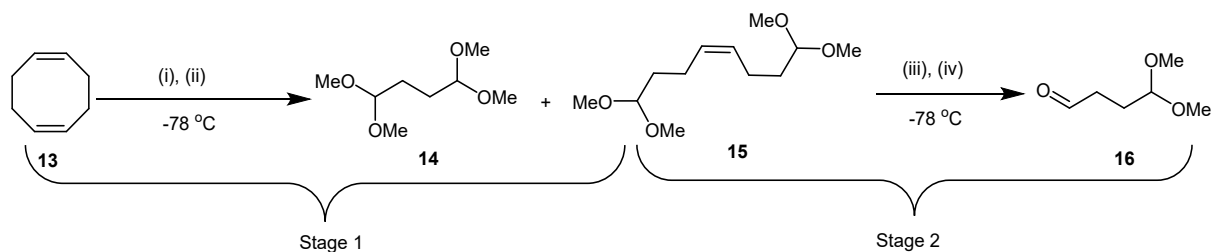
Styrene, **5** (15mL, 0.25 M, 0.25 mL/min, 1.0 sL/h) and a 1:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH solvent mixture. <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 10.02 (s, 1H), 7.91 – 7.86 (m, 2H), 7.66 – 7.60 (m, 1H), 7.57 – 7.50 (m, 2H), 7.48 – 7.42 (m, 2H), 7.40 – 7.30 (m, 3H), 3.33 (s, 6H).

### Phenylmethanol, **17** and (Dimethoxymethyl)benzene, **6**

Styrene, **5** (15mL, 0.25 M, 0.25 mL/min, 1.0 sL/h) and a 1:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH solvent mixture. <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 7.51 – 7.21 (m, 7H), 4.69 (s, 2H), 3.33 (s, 2H).

## 12. Attempted Selective ozonolysis

Further results showing the attempted selective ozonolysis of COD, **13**.



**Figure S-14:** (i) MeOH/DCM O<sub>3</sub>/O<sub>2</sub>, **15** (35 %) **14** (76 %) Batch NMR conversions (ii) TsOH, DMS (iii) DCM O<sub>3</sub>/O<sub>2</sub> (iv) PPh<sub>3</sub>

Table S-1: Flow results for attempted selective ozonolysis of COD, **13**

Entry	MFC flow rate (sL/h)	Flow rate (mL/min)	Reductant <sup>a</sup>	Conc. [M]	Temperature (°C)	Product conversion <sup>b</sup> %
						<b>15 (14)</b>
<b>1</b>	0.3	0.5	DMS, TsOH	0.25	-30°C	82
<b>2</b>	0.3	0.5	DMS, TsOH	0.5	0°C	42 (43)
<b>3</b>	0.5	0.5	DMS, TsOH	0.5	0°C	44 (33)

<sup>b</sup>NMR conversion was determined with an internal standard, These conversion do not reflect isolated yields.

## 13. LC-UV-MS method

### i) Method

**Table S-2:** Method for the optimization of acetophenone on LC-UV-MS

Quat. Pump	
Flow	1 mL/min
Low pressure limit	0.00 bar
High pressure limit	400
Maximum flow gradient	100.00 mL/min
Stop time	8.00 min

Post time mode	off
----------------	-----

#### Channel

Channel	Name	Used	Percentage %
A	Aqueous 10 mM Phosphate buffer 90 % H <sub>2</sub> O/Organic	Yes	30
B	Organic	Yes	70

Organic (50 % MeOH/ACN)

Time (min)	A %	B %	C %	D %	Flow rate (mL/min)	Pressure bar
6.50	30	70	0	0	1	400

Injection mode: Injection with needle wash; Injection volume: 2.5 µL

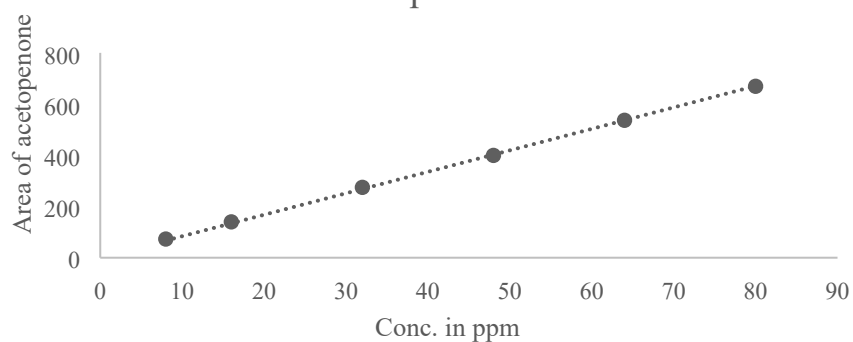
Needle wash location: Flush port; Wash time: 3s; Temperature set: 40 °C

DAD	
Peakwidth	>0.1 min (2 s response time (2.5 Hz))
Slit	4 nm
UV lamp required	Yes
Vis lamp required	Yes
Signals	Wavelength 220, 230 nm

Mass spectrometer detector: Disabled

#### ii) Standard curves for the optimisation of acetophenone (2), anisole and $\alpha$ -methylstyrene (1)

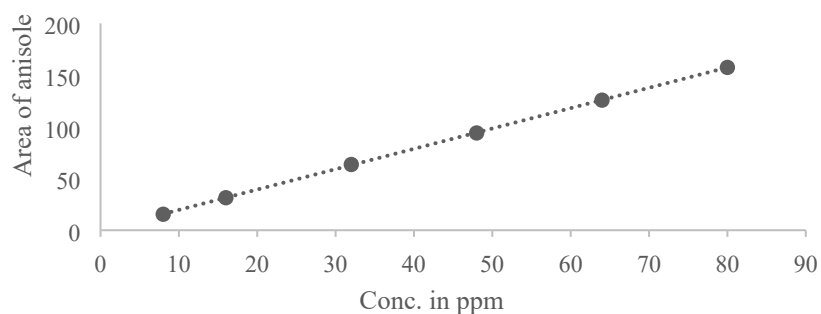
##### Concentration of Acetophenone at 230 nm vs area of Acetophenone



**Figure S-15:** Standard curve for acetophenone **2** at 230 nm

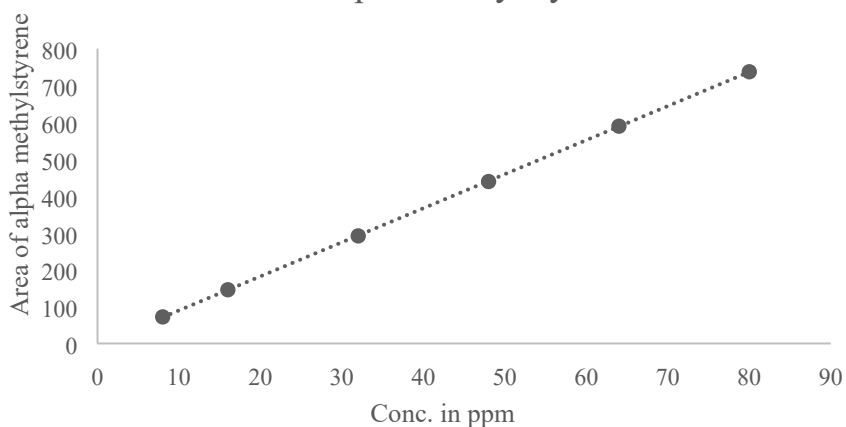


Concentration of Anisole at 230 nm vs area of Anisole



**Figure S-16:** Standard curve for anisole (IS) at 230 nm

Concentration of alpha-methylstyrene at 230 nm vs area of alpha-methylstyrene



**Figure S-17:** Standard curve for alpha-methylstyrene 1 at 230 nm

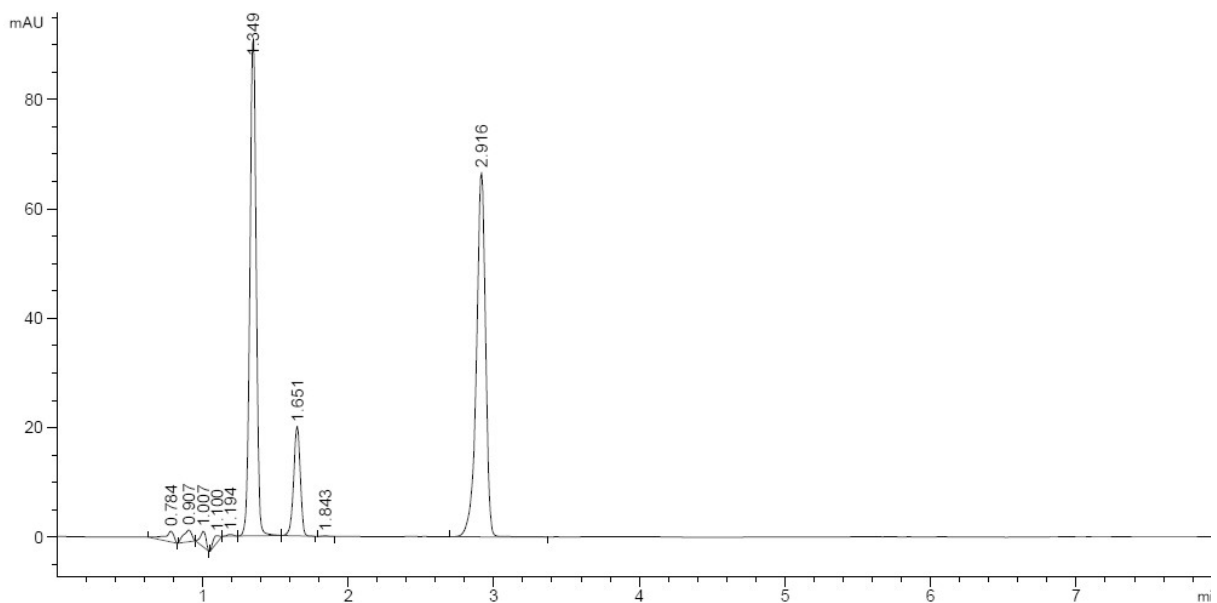
iii) Raw data for standard curves

**Table S-3:** Raw data for standard curves at each concentration

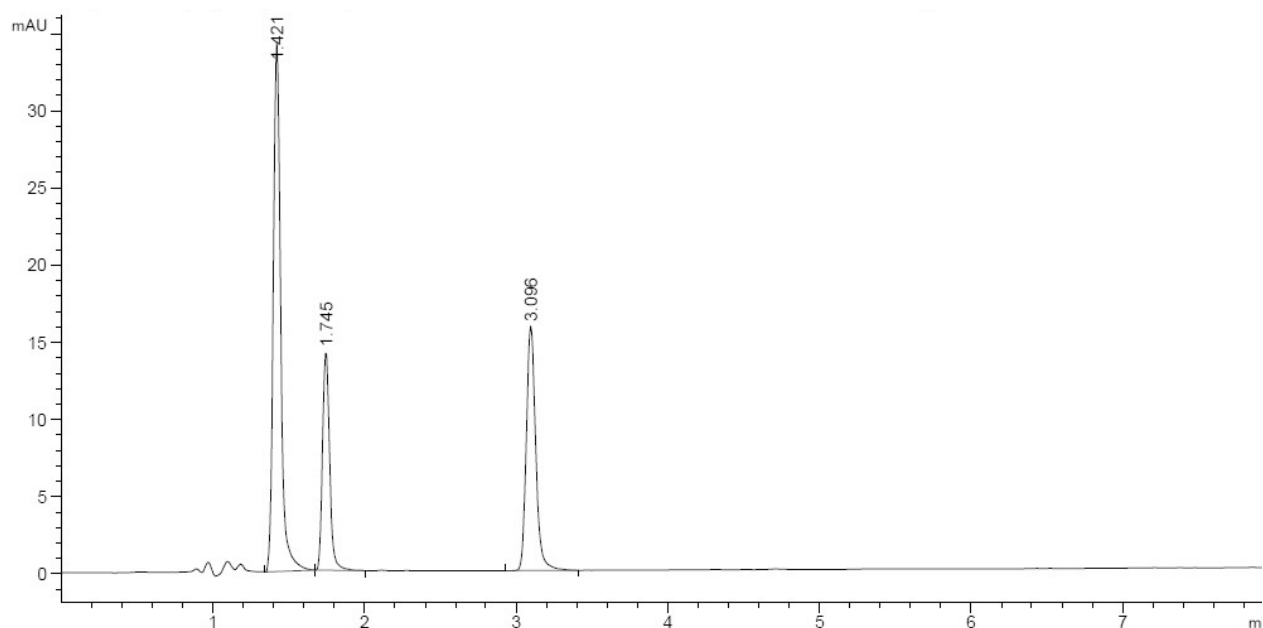
PPM	Area of Anisole	Average Area	Area of Acetophenone 2	Average Area	Area of $\alpha$ -methylstyrene 1	Average Area
8	15.37014	15.44375333	73.47955	72.88869	70.63179	72.11052667
8	15.50195		71.83479		71.82751	
8	15.45917		73.35173		73.87228	
16	31.5877	31.42695667	139.34441	139.9207567	145.59869	145.75742
16	31.25504		140.42378		144.8174	

16	31.43813		139.99408		146.85617	
32	63.50384		274.57397		291.94931	
32	63.48625	63.55721667	275.79395	274.74354	289.99768	291.8440033
32	63.68156		273.8627		293.58502	
48	94.65091		405.74283		443.86386	
48	93.99992	94.03911333	398.28592	399.5198667	438.45407	439.28484
48	93.46651		394.53085		435.53659	
64	125.81603		534.17004		588.37164	
64	125.76982	125.76729	536.19635	536.6272967	593.13678	589.4811
64	125.71602		539.5155		586.93488	
80	158.00154		664.31085		742.12079	
80	157.11839	157.40511	668.84534	669.4324133	737.5351	737.1333233
80	157.0954		675.14105		731.74408	

iv) Example chromatogram from the standard curves



**Figure S-18:** Chromatogram of standard curve at 230 nm for 32 ppm



**Figure S-19:** Chromatogram of FO001.44 sample at 230 nm

**v) Example calculations**

- Each reaction was collected and measured to 30 mL, Concentrations of 0.25 M and 0.5 M were determined exactly the same. With either 10 mL of reagent stock solutions used for 0.25 M or 5 mL of reagent stock solution used.
- From this 1 mL was diluted to a 10 mL volumetric flask.
- A 100  $\mu$ L aliquot from this solution was added to a LC vial and diluted to 1 mL. This equated to a dilution factor of **400**.
- The calculations were completed by taking the average area for the sample and dividing this by the standard curves slope in the case of anisole this was **1.9666**. This value is multiplied by the dilution factor **400** to obtain the concentration in ppm.
- ppm is converted to mg/ml by dividing by a 1000
- Finally, the amount in grams is obtained by multiplying the mg/mL conc. solution with 30 mL

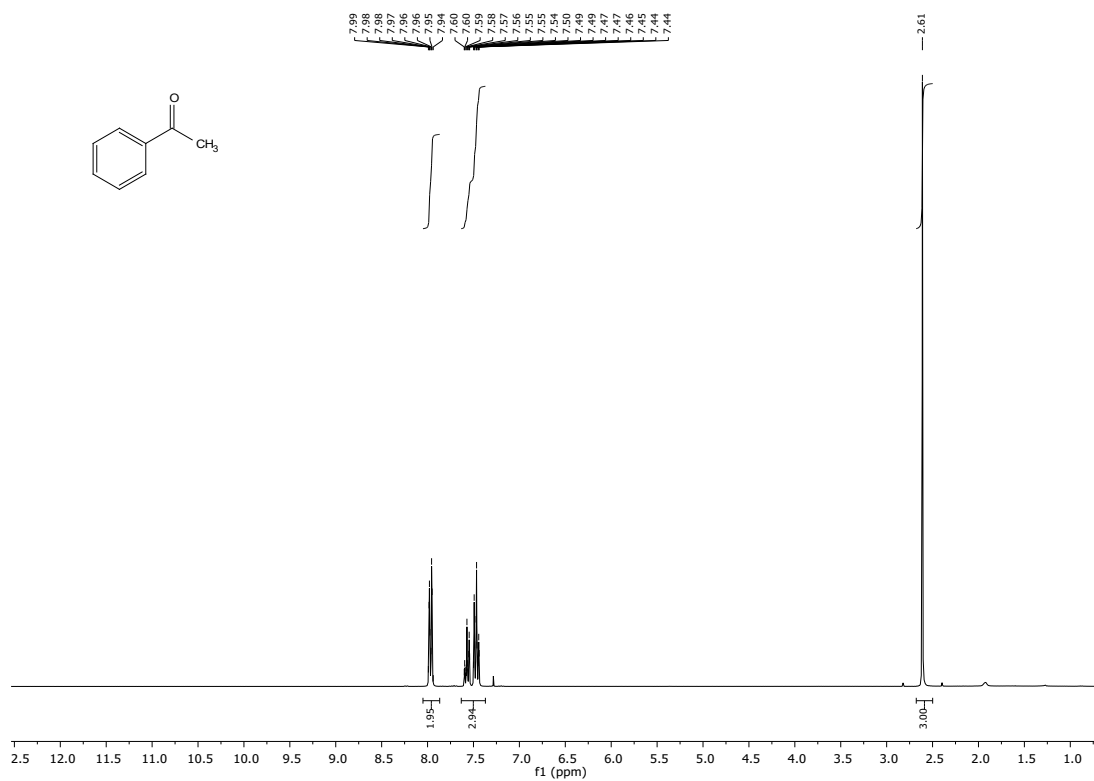
**Table S-4:** Example calculation for Table 2, Entry 9

	<b>Area of anisole</b>	<b>Area of <math>\alpha</math>-methylstyrene</b>	<b>Area of acetophenone</b>	<b>% Yield</b>
Table 2 Entry 9	44.930725	52.897695	146.7188967	68.84
	<b>Conc of anisole</b>	<b>Conc of <math>\alpha</math>-methylstyrene</b>	<b>Conc of acetphenone</b>	
	22.84690583	5.753877238	17.48422769	
	4569.381165 ppm	1150.775448 ppm	6993.691076 ppm	

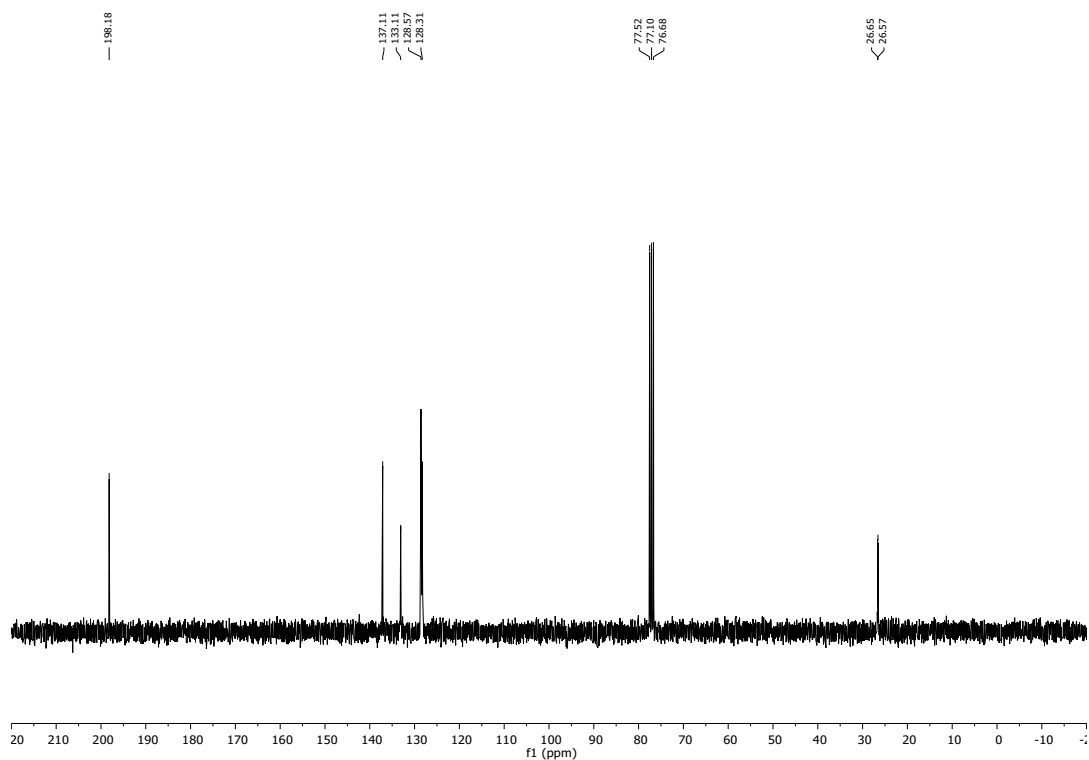
	4.569381165 mg.mL <sup>-1</sup>	1.150775448 mg.mL <sup>-1</sup>	6.993691076 mg.mL <sup>-1</sup>
	274.1628699 g	69.04652686 g	209.8107323 g

## 9. Associated spectra

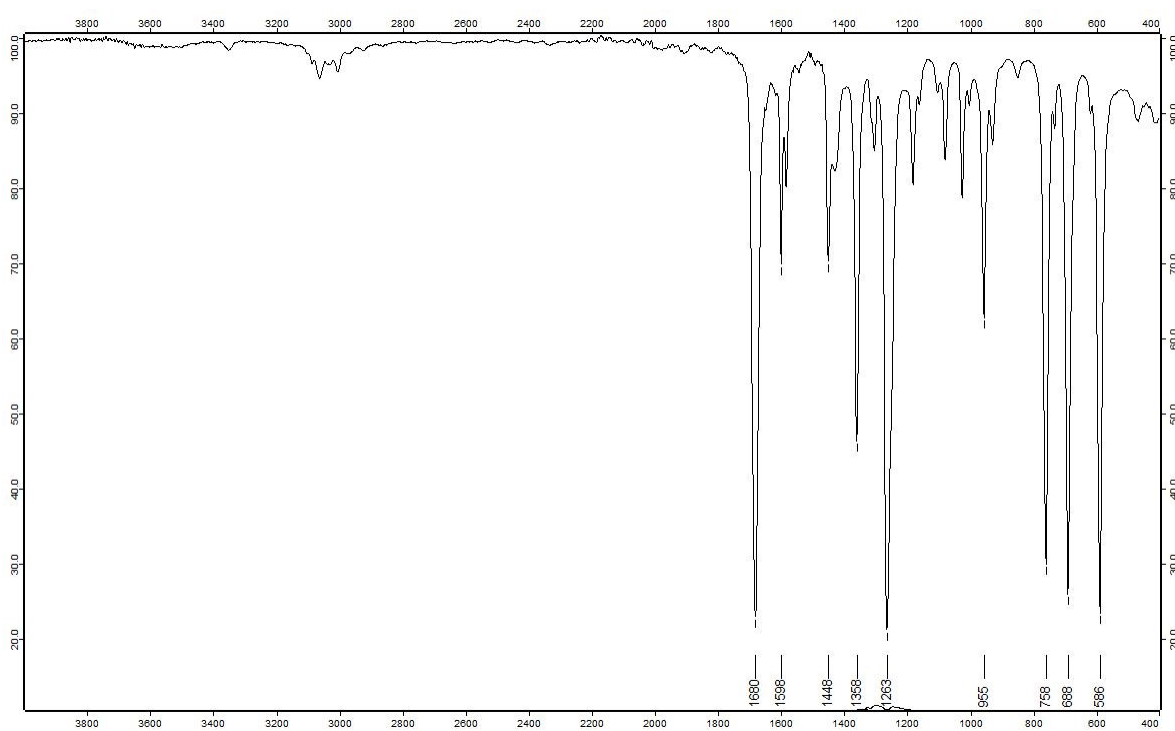
### i) Acetophenone (2)



**Figure S-20:** <sup>1</sup>H NMR spectrum for acetophenone 2

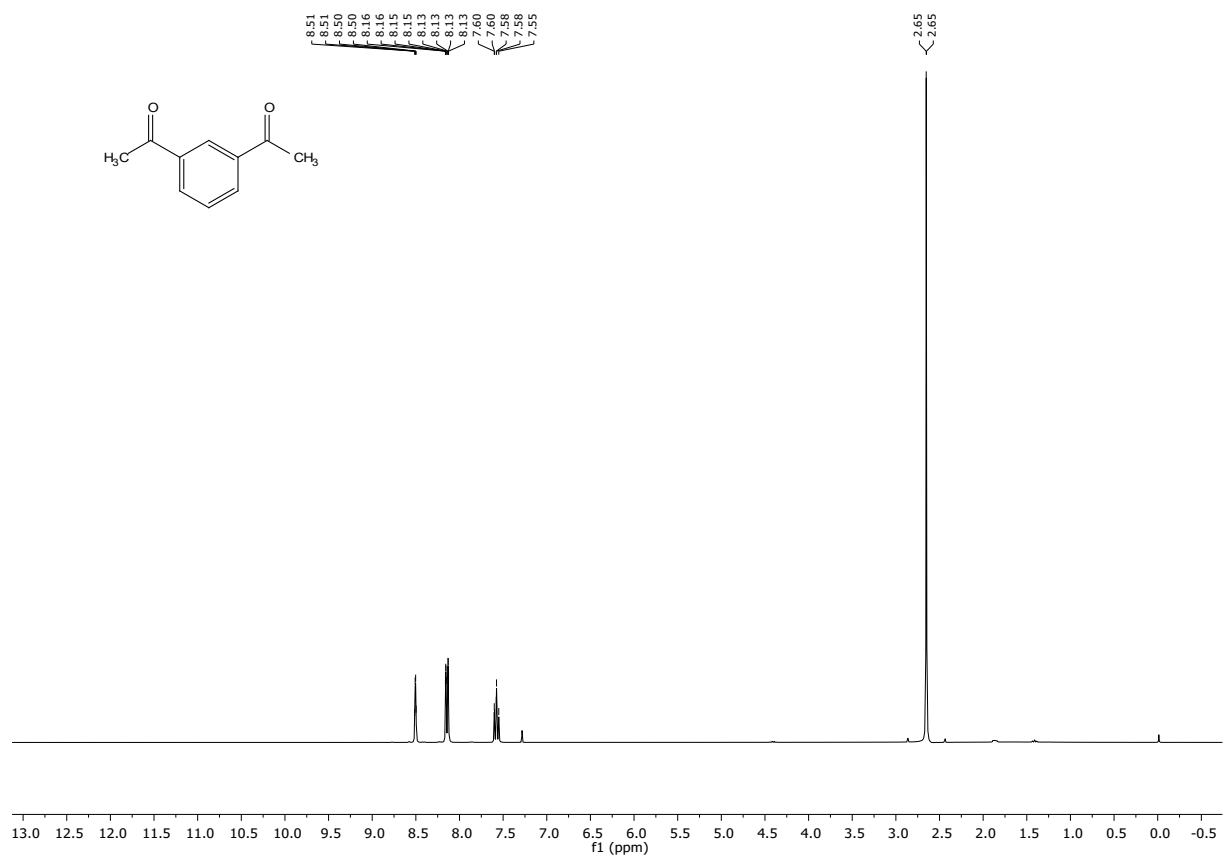


**Figure S-21:**  $^{13}\text{C}$  NMR spectrum for acetophenone **2**

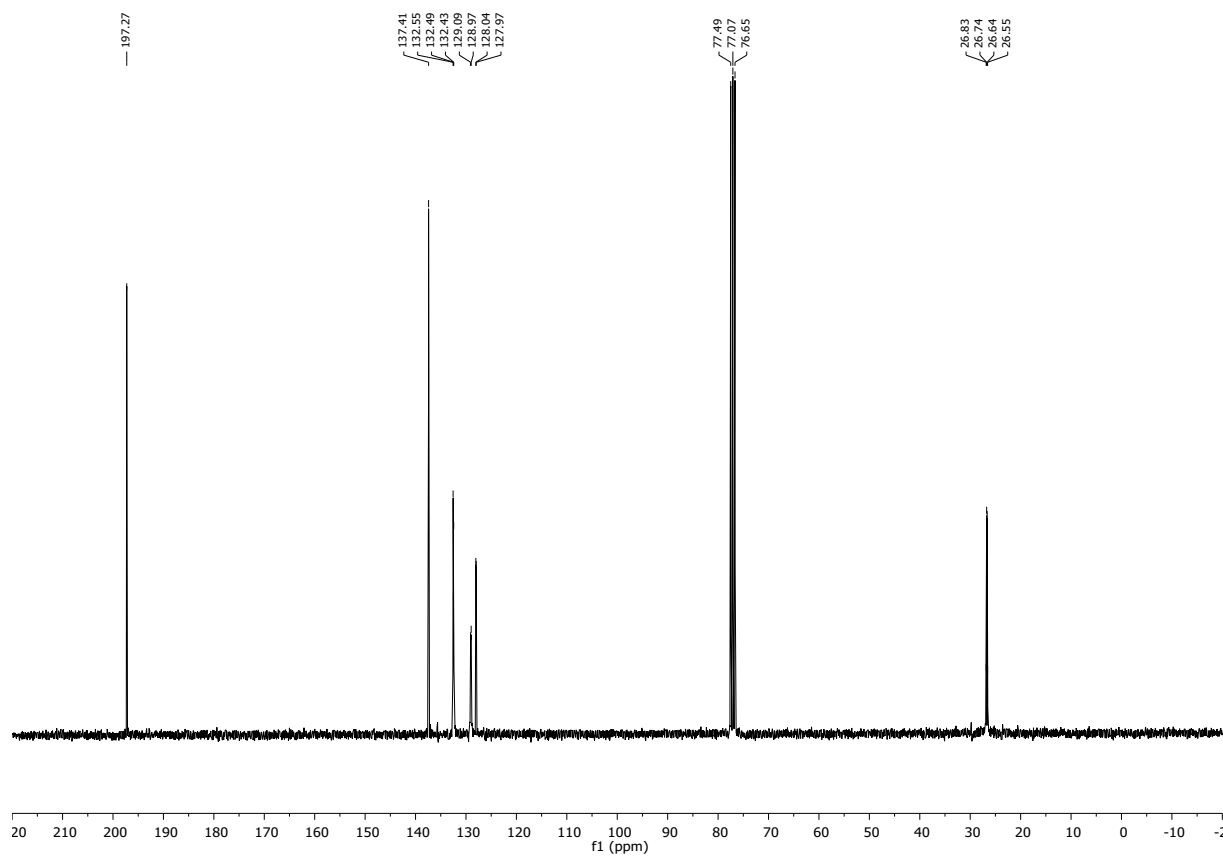


**Figure S-22:** IR spectrum for acetophenone **2**

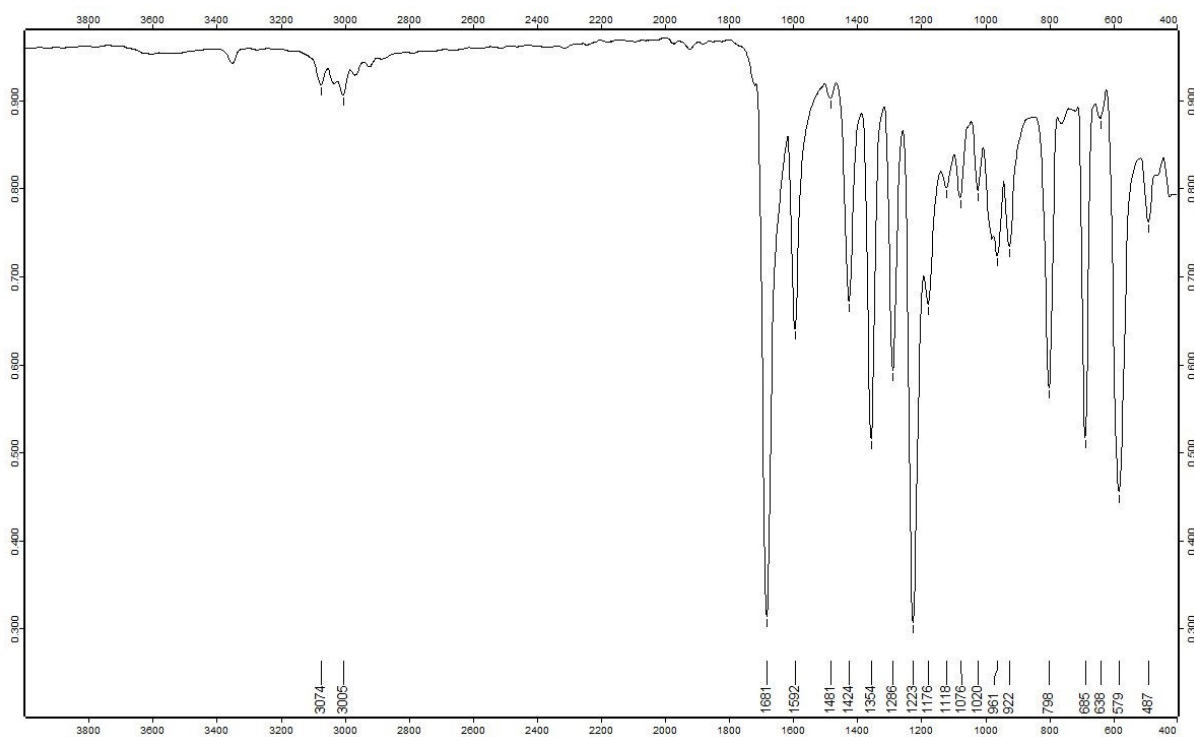
ii) 1,1'-(1,3-Phenylene)bis(ethan-1-one) (9)



**Figure S-23:** <sup>1</sup>H NMR spectrum for 1,1'-(1,3-phenylene)bis(ethan-1-one) **9**

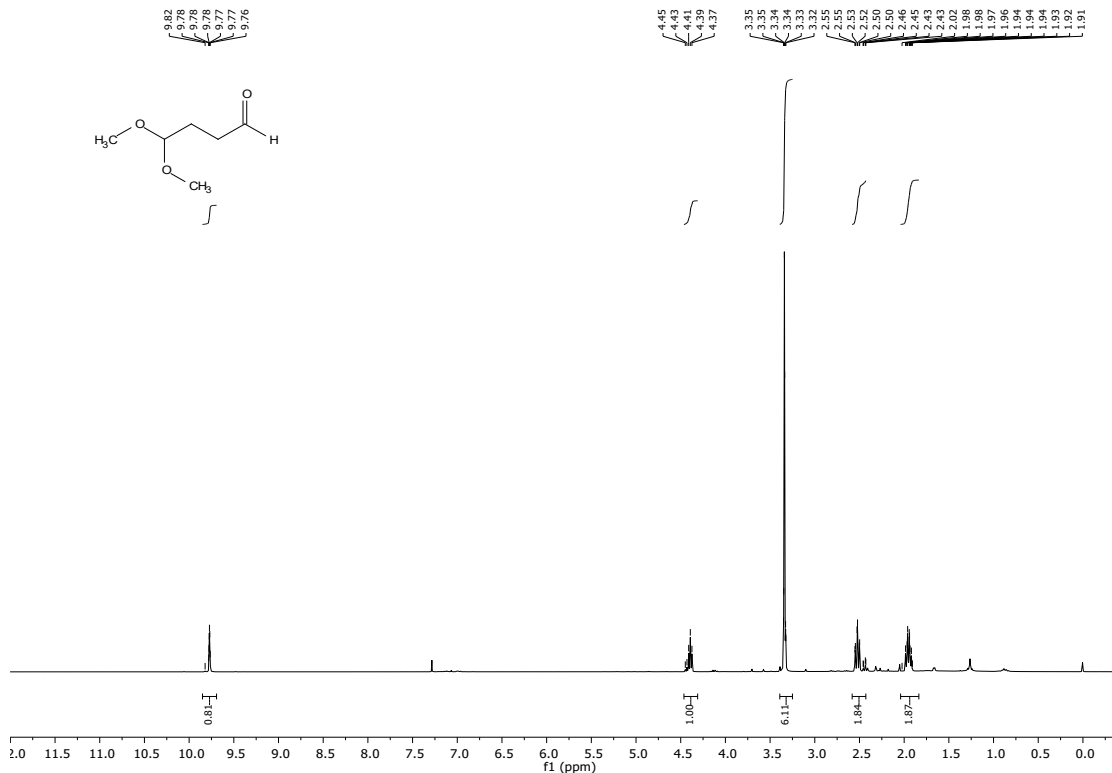


**Figure S-24:**  $^{13}\text{C}$  NMR spectrum for 1,1'-(1,3-phenylene)bis(ethan-1-one) **9**

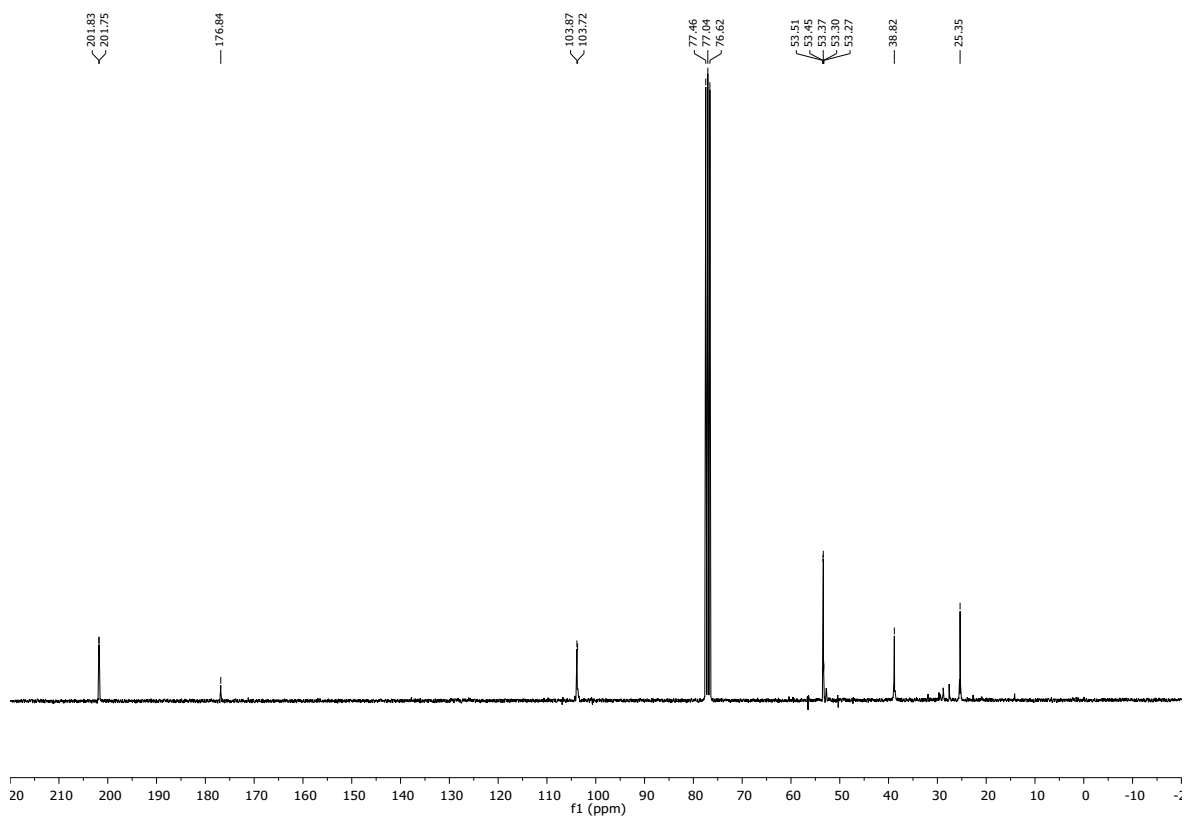


**Figure S-25:** IR spectrum for 1,1'-(1,3-phenylene)bis(ethan-1-one) **9**

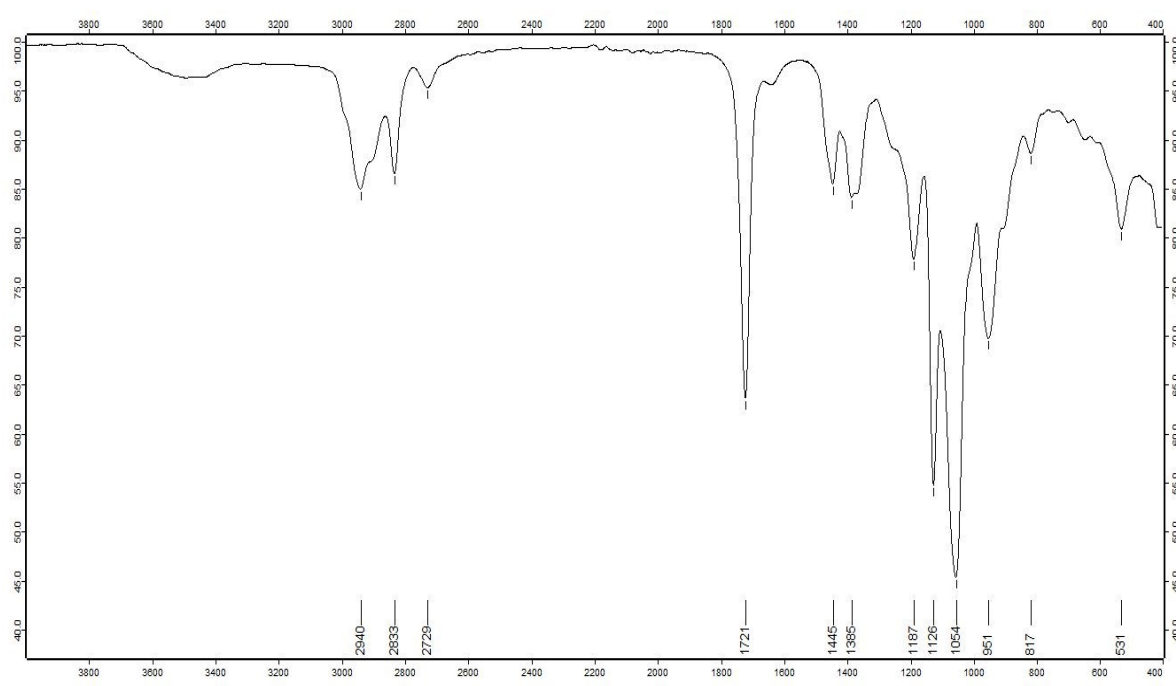
iii) 4,4-Dimethoxybutanal (**16**)



**Figure S-26:**  $^1\text{H}$  NMR spectrum for 4,4-Dimethoxybutanal **16**



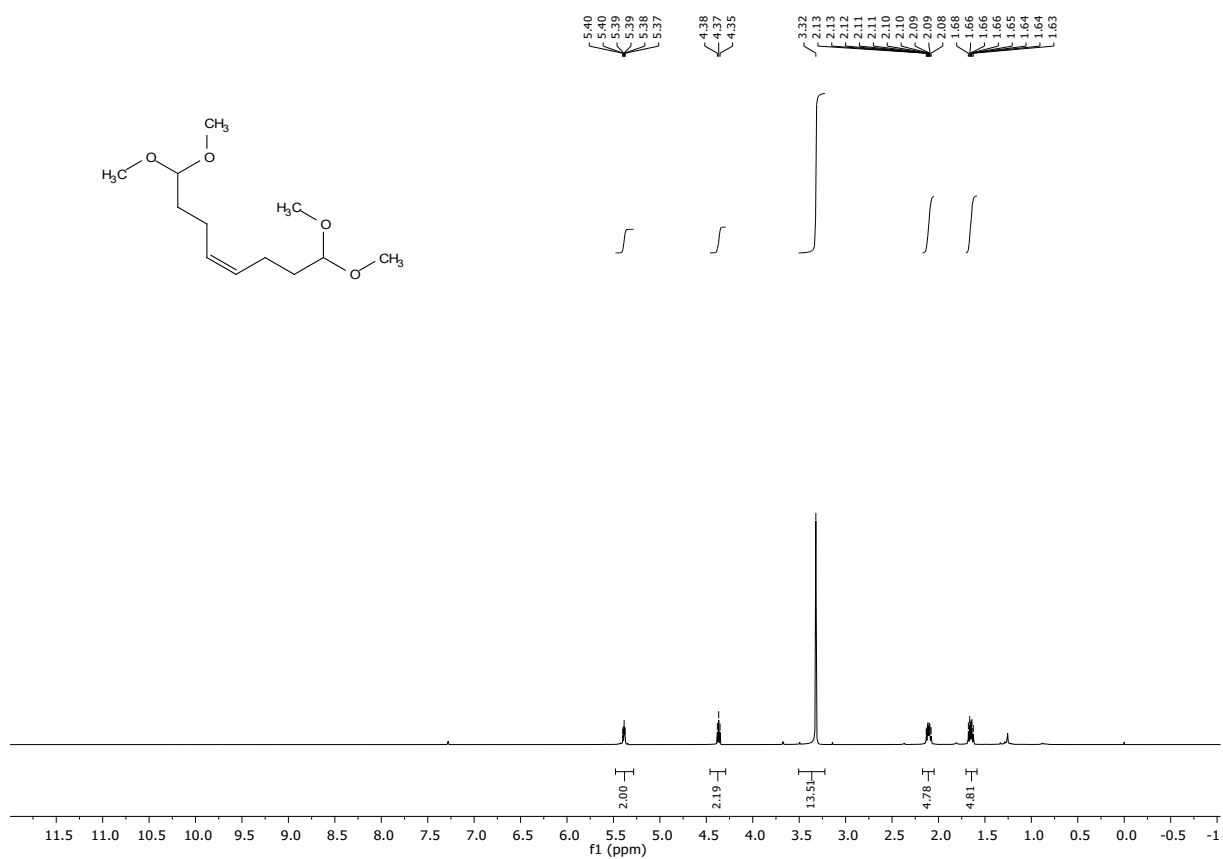
**Figure S-27:**  $^{13}\text{C}$  NMR spectrum for 4,4-Dimethoxybutanal **16**



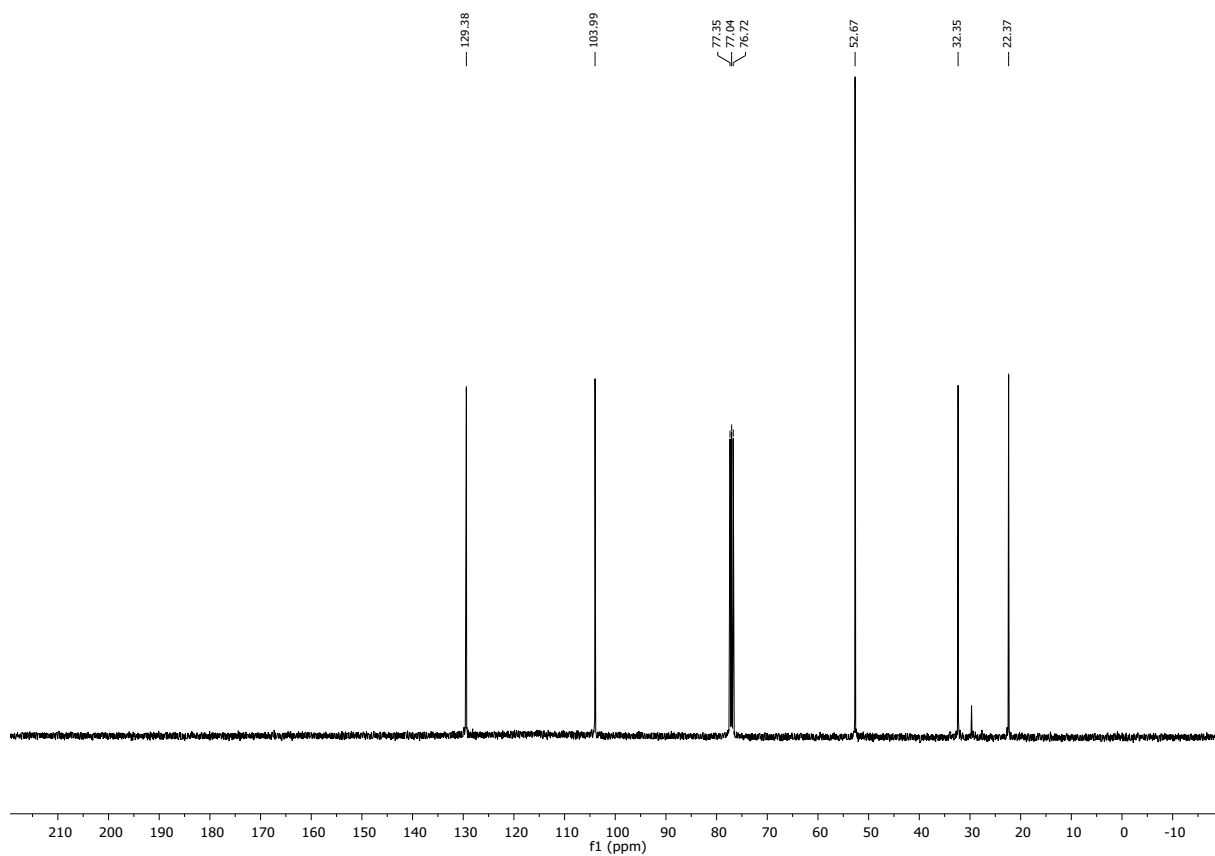
**Figure S-28:** IR spectrum for 4,4-Dimethoxybutanal **16**



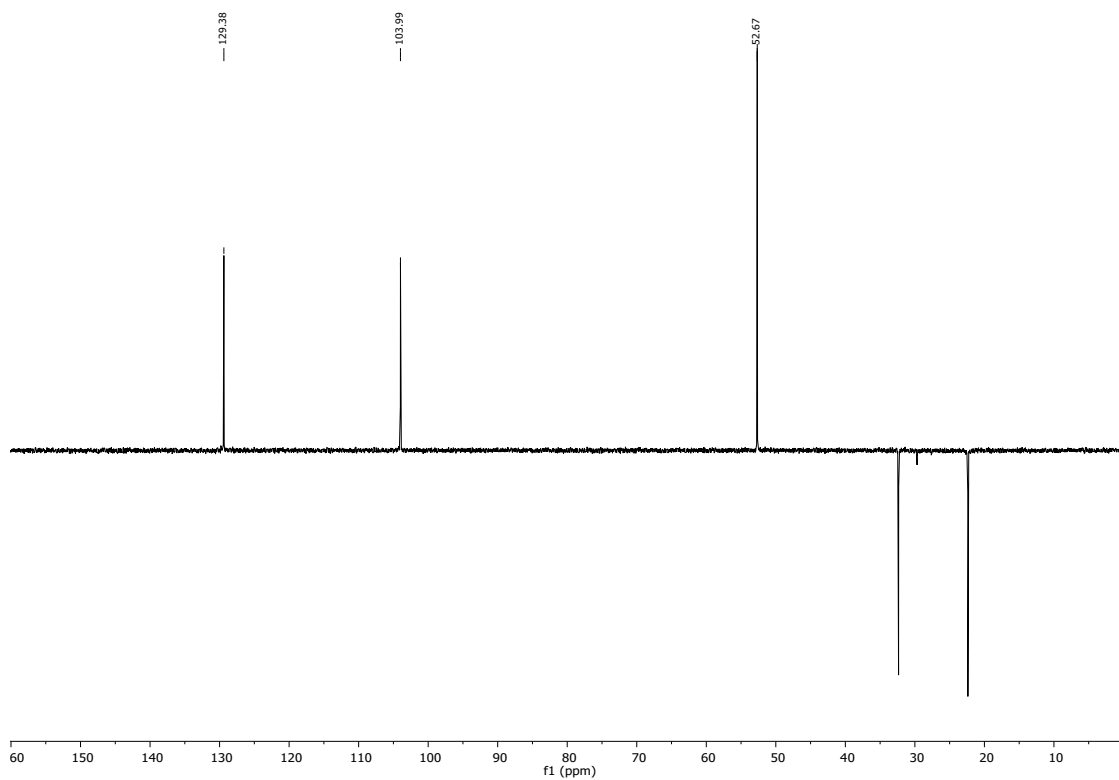
iv) 1,1,8,8-Tetramethoxyoct-4-ene (15)



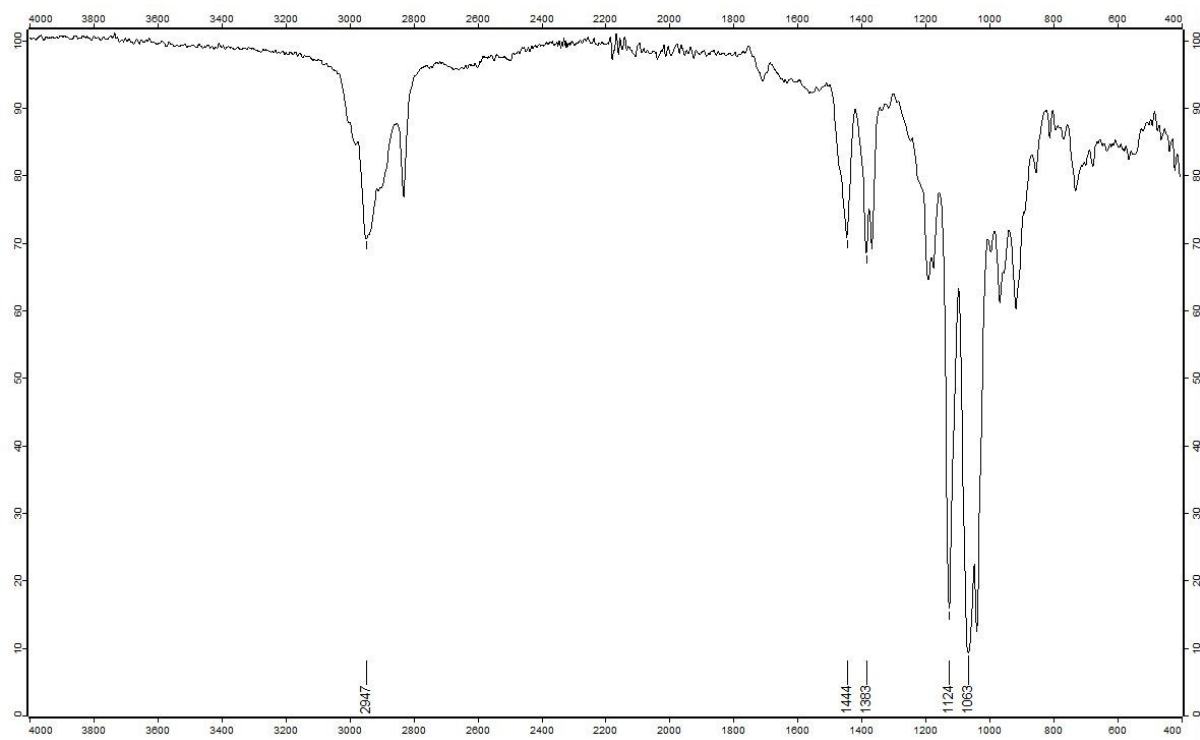
**Figure S-29:**  $^1\text{H}$  NMR spectrum for 1,1,8,8-Tetramethoxyoct-4-ene **15**



**Figure S-30:**  $^{13}\text{C}$  NMR spectrum for 1,1,8,8-Tetramethoxyoct-4-ene **15**

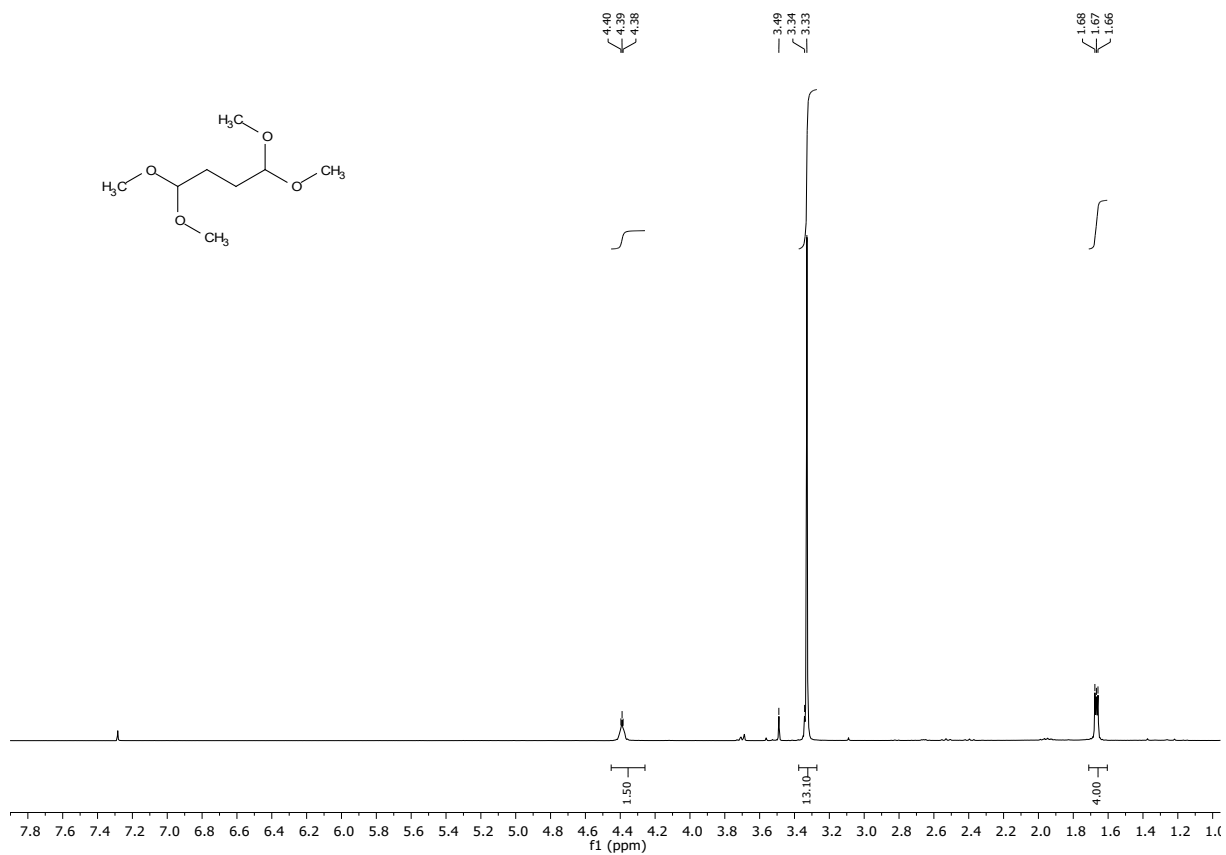


**Figure S-31:** DEPT45 spectrum for 1,1,8,8-Tetramethoxyoct-4-ene **15**

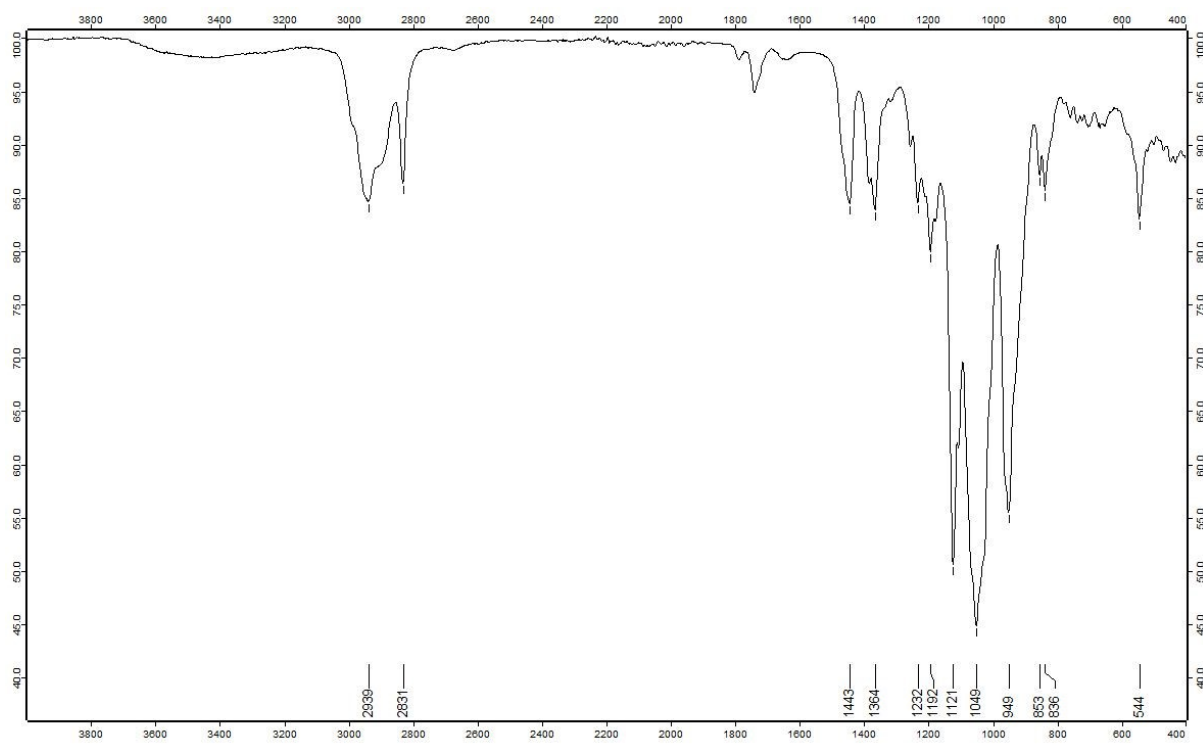


**Figure S-32:** IR spectrum for 1,1,8,8-Tetramethoxyoct-4-ene **15**

v) 1,1,4,4- Tetramethoxybutane (**14**)

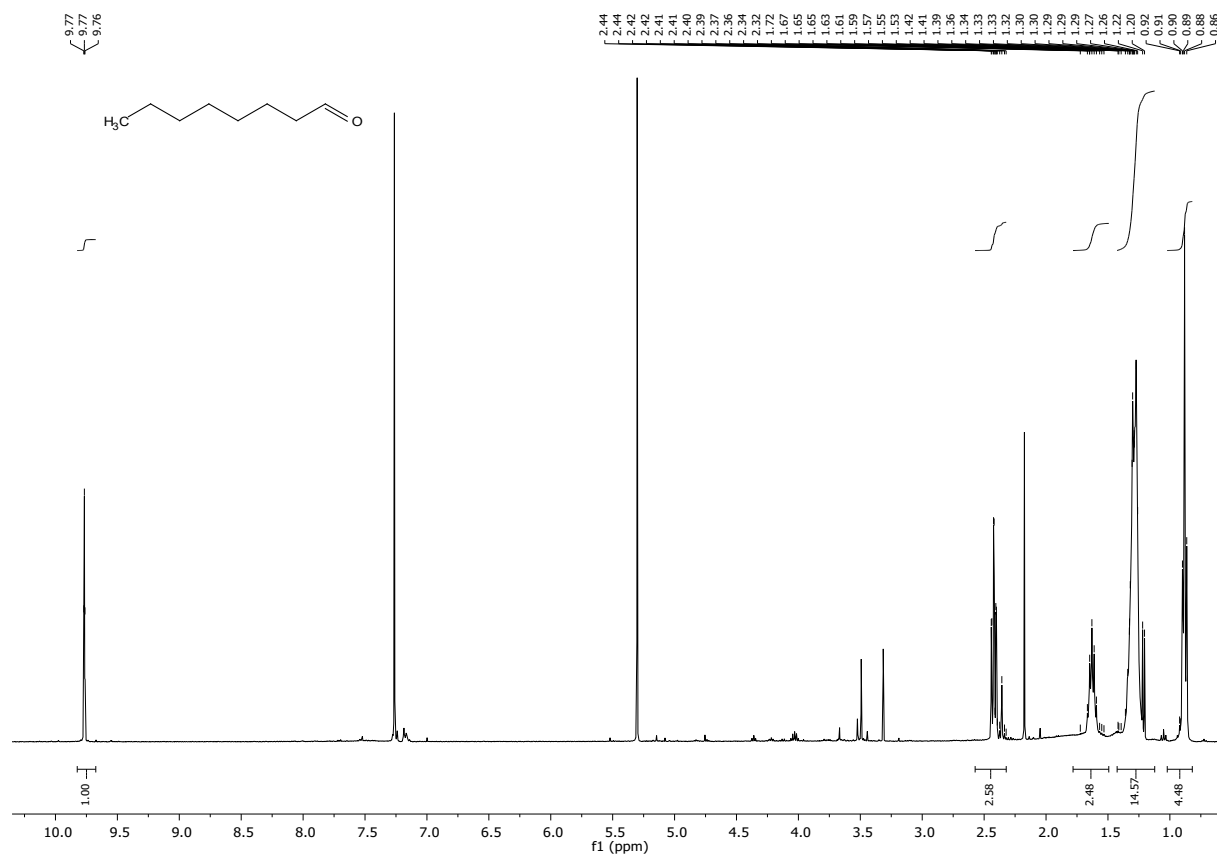


**Figure S-33:** <sup>1</sup>H NMR spectrum for 1,1,4,4- Tetramethoxybutane **14**



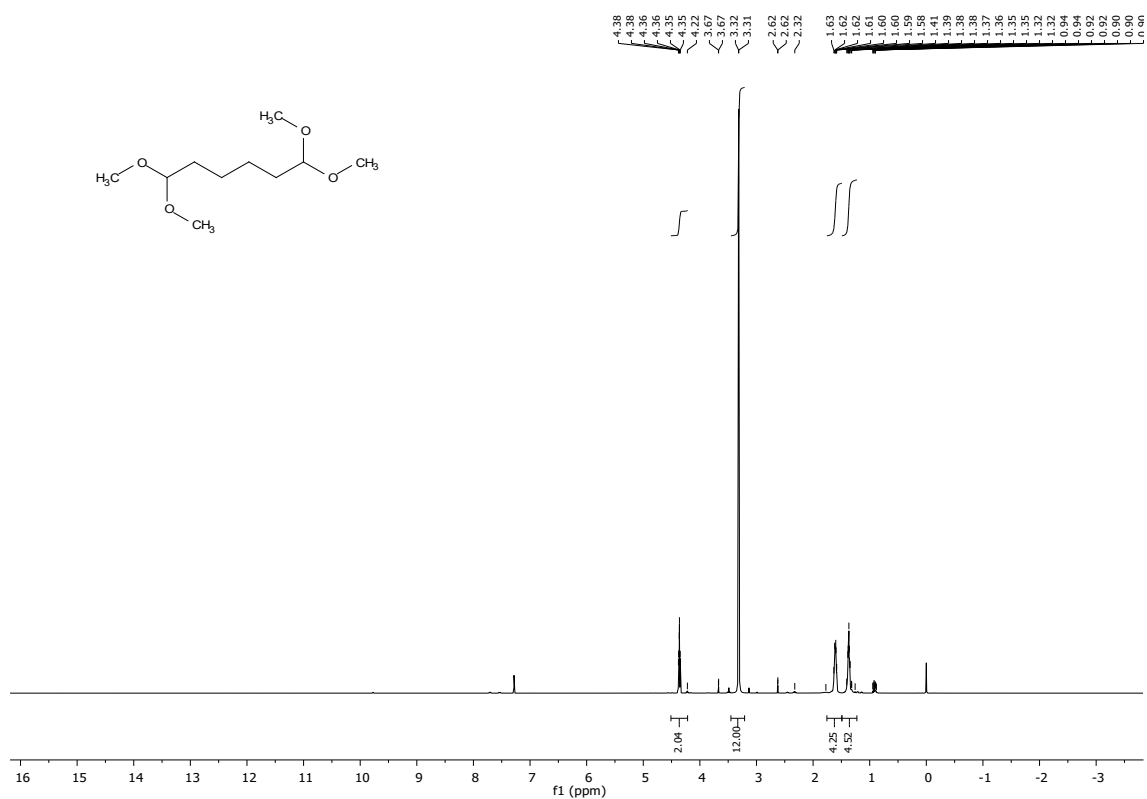
**Figure S-34:** IR spectrum for 1,1,4,4- Tetramethoxybutane **14**

vi) Nonanal (4)

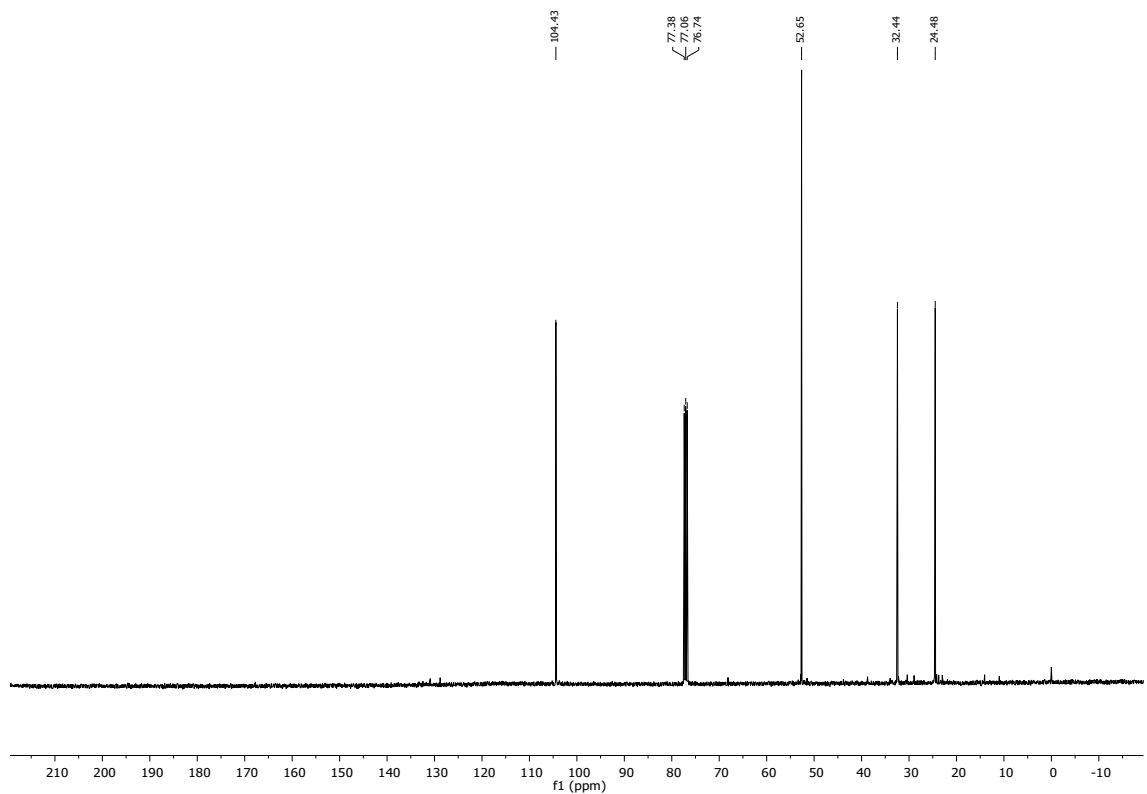


**Figure S-35:**  $^1\text{H}$  spectrum for Nonanal **4**

vii) 1,1,6,6-Tetramethoxyhexane (**12**)

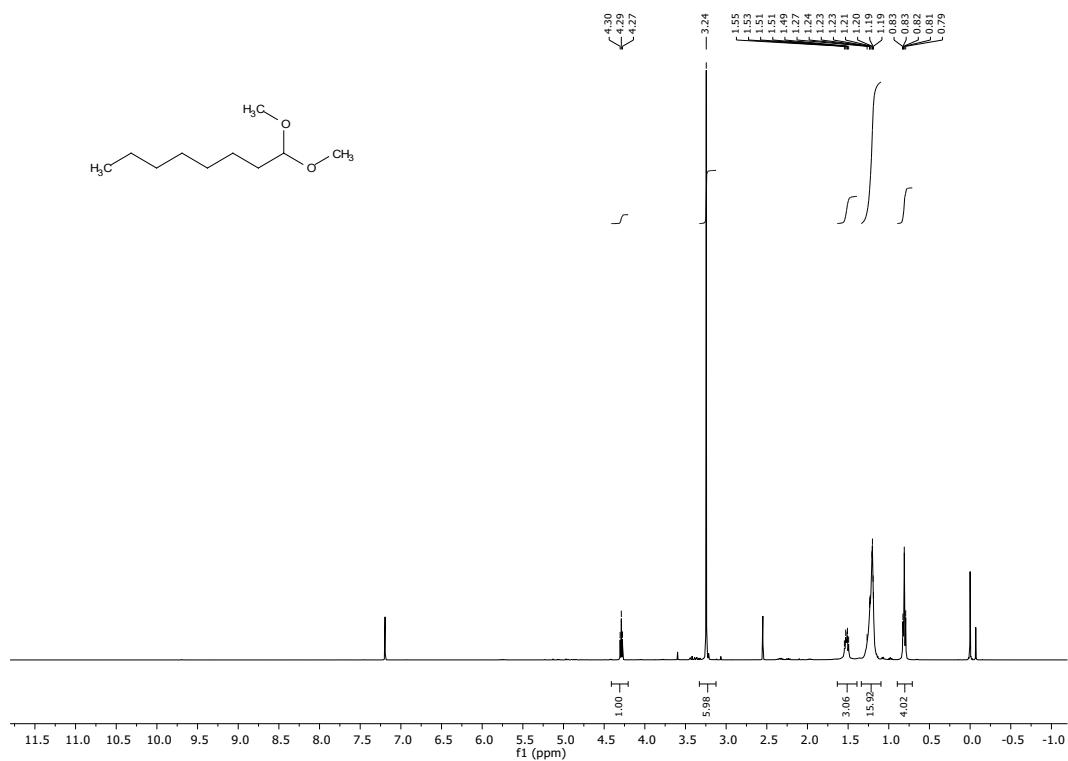


**Figure S-36:**  $^{13}\text{C}$  spectrum for 1,1,6,6-tetramethoxy hexane **12**



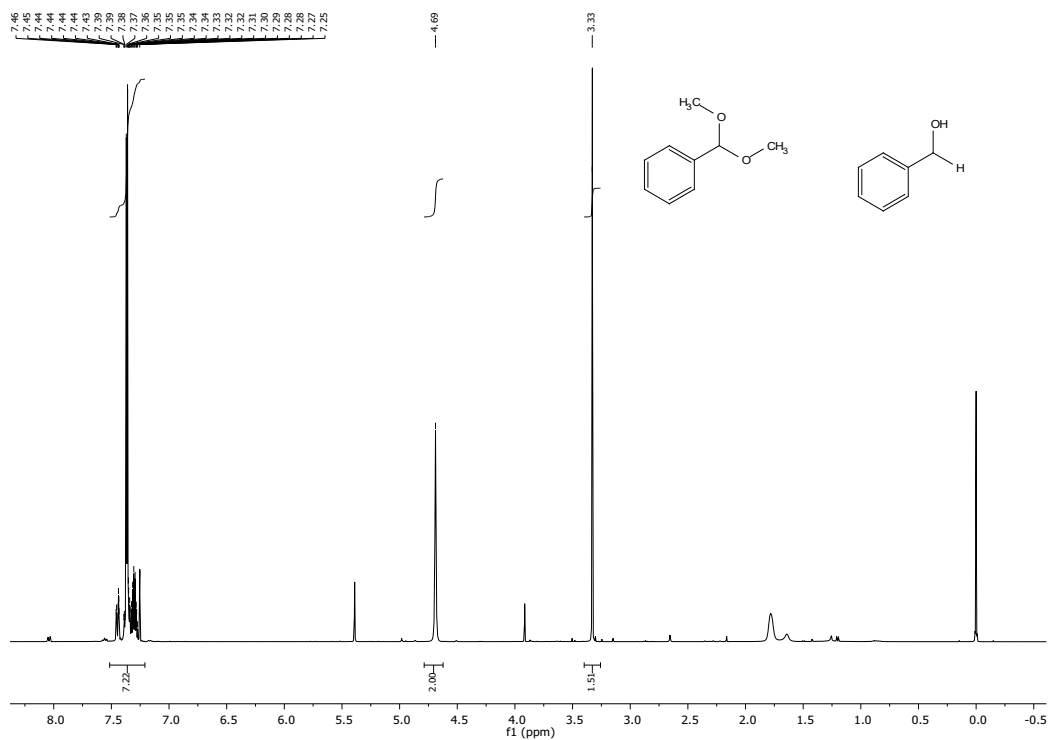
**Figure S-37:**  $^{13}\text{C}$  spectrum for 1,1,6,6-tetramethoxy hexane **12**

viii) 1,1-Dimethoxynonane (10)

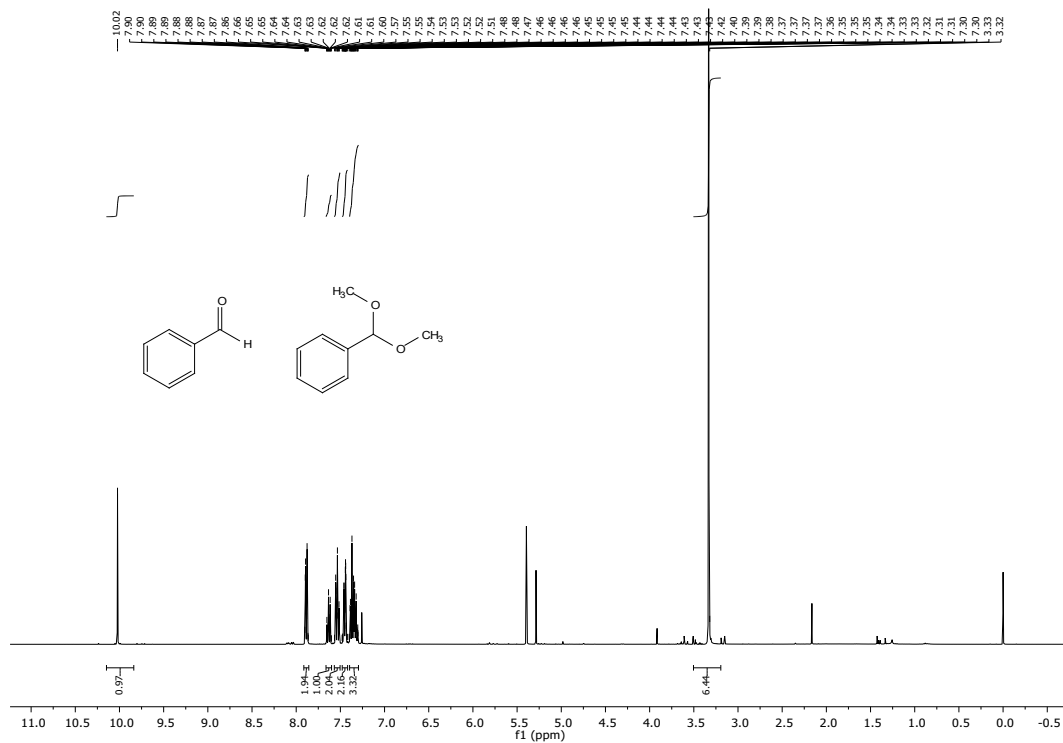


**Figure S-38:**  $^1\text{H}$  spectrum for 1,1-dimethoxynonane **10**

ix) Phenylmethanol (17) and (dimethoxymethyl)benzene (6)

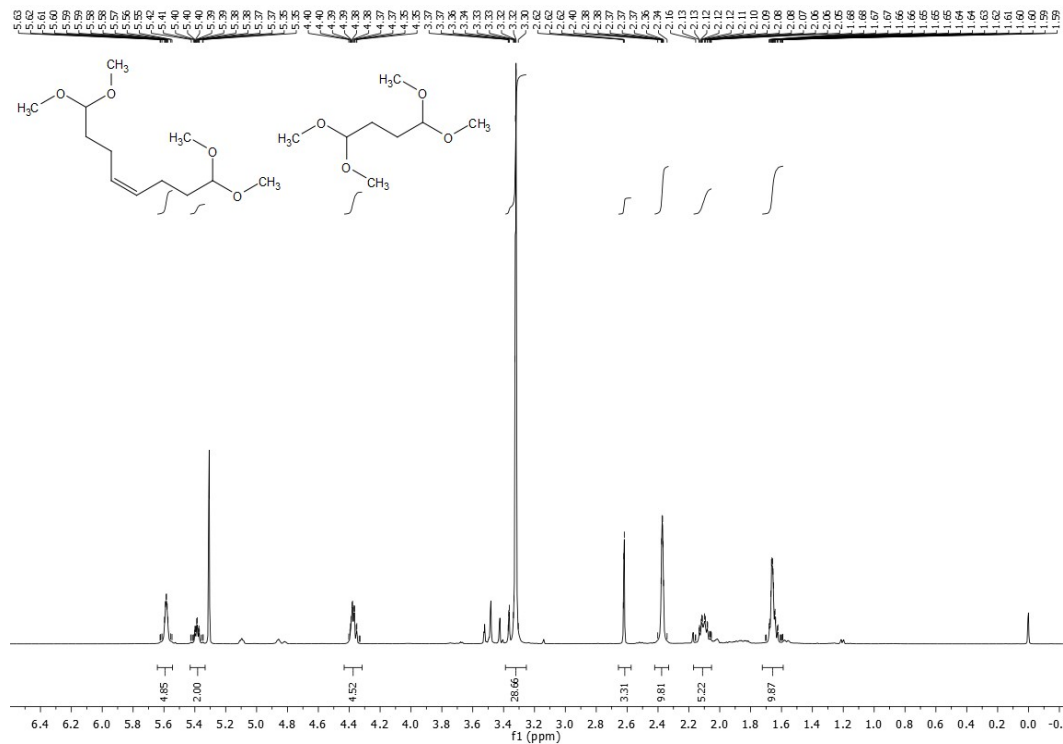


**Figure S-39:**  $^1\text{H}$  spectrum for phenylmethanol **17** and (dimethoxymethyl)benzene **6**  
 x) Benzaldehyde (**7**) and (dimethoxymethyl)benzene (**6**)



**Figure S-40:**  $^1\text{H}$  spectrum for benzaldehyde **7** and (dimethoxymethyl)benzene **6**

xi) 1,1,8,8-Tetramethoxyoct-4-ene **15** and 1,1,4,4-tetramethoxybutane **14**



**Figure S-41:**  $^1\text{H}$  spectrum for 1,1,8,8-Tetramethoxyoct-4-ene **15** and 1,1,4,4-Tetramethoxybutane **14**

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