Continuous Flow Transetherification of Vinylogous Esters and Their Reverse Reaction Using Fe-Catalyst

A thesis submitted towards partial fulfilment of the requirement of BS-MS dual degree program

By

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CERTIFICATE

This is to certify that this dissertation entitled **"Continuous Flow Transetherification of Vinylogous Esters and Their Reverse Reaction Using Fe-Catalyst"** towards the partial fulfilment of the BS-MS dual degree programme at the Indian Institute of Science Education and Research, Pune represents the work carried out by **Mr. Nenavath Parvathalu** at Indian Institute of Science Education and Research under the supervisor of Dr. Boopathy Gnanaprakasam, Assistant Professor, Department of Chemistry during the academic year 2018-2019.

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DECLARATION

I hereby declare that the matter embodied in the report entitled **"Continuous Flow Transetherification of Vinylogous Esters and Their Reverse Reaction Using Fe-Catalyst"** are the results of the work carried out by me at the Department of Chemistry, Indian Institute of Science Education and Research, Pune under the supervisor of Dr. Boopathy Gnanaprakasam and the same has not been submitted elsewhere for any other degree.

Date: 20-03-2019

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Dedicated to my Family, Teachers & Friends

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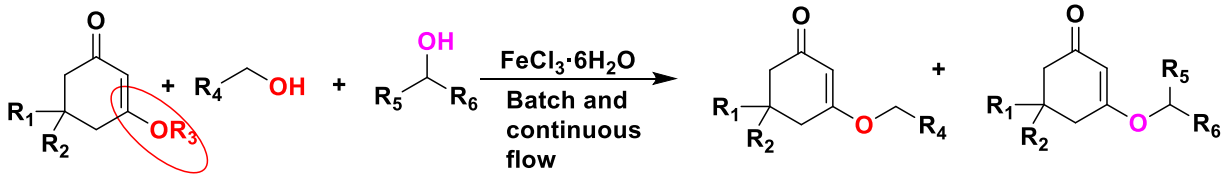
ABBREVIATIONS

DCE	1, 2-Dichloroethane
ACN	Acetonitrile
MeOH	Methanol
EtOAc	Ethyl acetate
KOAc	Potassium acetate
DCM	Dichloromethane
rt	Room temperature
h	Hour
DMF	Dimethylformamide
mL	Millilitre
mmol	Millimole
min	Minute
Hz	Hertz
IR	Infrared
M^+	Metal Ion
NMR	Nuclear magnetic resonance
$CDCl_3$	Deuterated chloroform
IPA	Isopropyl alcohol
ESI	Electron spray ionisation
TMHD	2,2,6,6-Tetramethyl-3,5-heptanedione
DEAD	Diethyl azodicarboxylate
CAN	Ceric ammonium nitrate
THF	Tetrahydrofuran
DMSO	Dimethyl sulfoxide
TMS	Tetramethylsilane
p-TsOH	Para-toluene sulfonic acid
TBAB	Tetra-n-butylammonium bromide

ABSTRACT

Vinylogous esters have been widely used as a key intermediate in synthetic organic chemistry. In particular, they have been used as synthons in natural products and drug synthesis. Many vinylogous esters have been found in the core structure of several compounds having a wide range of biological activity. Furthermore, this type of compounds were also used as a source of dienophiles in Diels-Alder reactions and precursor for many terpenoid syntheses. However, this compound prone to undergoes reversible reaction under acidic environment results in no reaction or poor yields. Therefore, special attention has been considered for their synthesis. Several reported batch conditions poses a serious concern on reversibility, yield and scalability. Therefore novel process which can overcome the batch condition is highly desirable. In this dissertation, we have studied the continuous flow approach for the synthesis of vinylogous esters using environmentally benign, less toxic, cheap, and commercially available Fe-catalyst.

Moreover, this approach is highly efficient, operationally simple, additive free and chemoselective for transetherification of vinylogous esters from different alcohols. We have also studied for the scalability and sequential transetherification using Fe homogeneous and heterogeneous catalyst. Besides, the deprotection of vinylogous esters in water using a catalytic amount of $FeCl_3 \cdot 6H_2O$ (5 mol%) have also been achieved. The synthetic applications of vinylogous esters also shown by coupling reactions, spiro compound synthesis and aromatisation reactions.



Vinylogous esters **Exclusive selectivity on primary alcohols**

- **Electron deficient unsymmetrical ether substrates**
- **Chemoselective and catalytic reaction**
- **Functional group tolerance and solvent free**
- **Continuous multi-transetherification**
- **Batch and continuous flow synthesis**
- **Wide substrate scope and gram scale synthesis**
- **Assisted by chelation of Fe with C=O group**
- **Novel Fe-catalyzed de-alkylation using water**

1. INTRODUCTION

1.1 Ethers

Ethers are a class of organic compounds that contains two alkyl or aryl groups attached by an oxygen atom. Ether functionality has been found in many natural products, pharmaceuticals and serves as key intermediates in organic synthesis (Figure 1).[1, 2] Ether linkage is present in many oligonucleotides and carbohydrates. Due to the inertness of ethers with many chemicals, it exhibits as an excellent solvent for extractions as well as in many chemical reactions. It also serves as an unreactive derivative of alcohols as a protecting group, which is useful in many natural products synthesis to control the reactivity of O-H functionality. Synthesis of ether was reported 100 years ago by Williamson for the symmetrical and unsymmetrical ethers by a classical stoichiometric nucleophilic substitution reaction. The upsurge in the development of environmentally benign non-catalytic and catalytic version produced many approaches towards their synthesis. The most common methods for the synthesis of ethers involves Williamson synthesis, Ullmann coupling and Mitsunobu reaction. Some of the well-known traditional methods of synthesising ethers are described below.

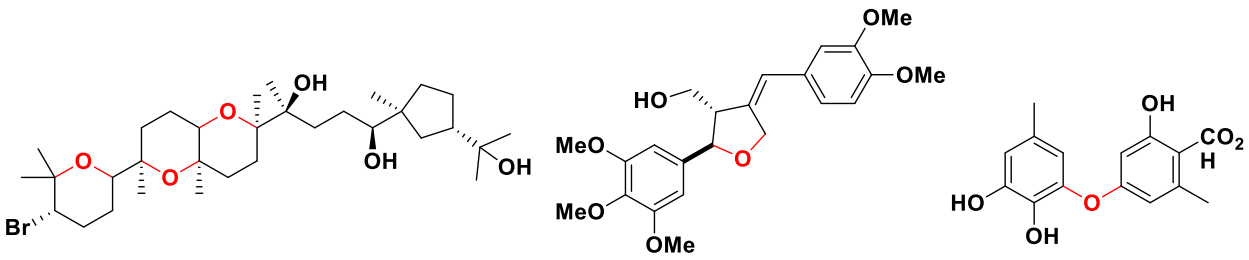


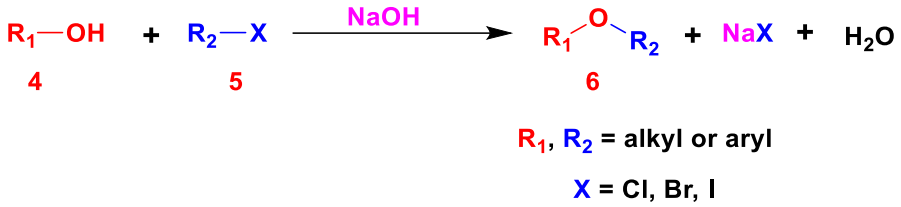
Figure 1. Ether bond containing natural products

1.2 Synthetic approaches for ethers:

- **Williamson synthesis**

In 1850, Williamson reported the first and commonly used approach for the synthesis of unsymmetrical as well as symmetrical ethers, which involves the base-mediated

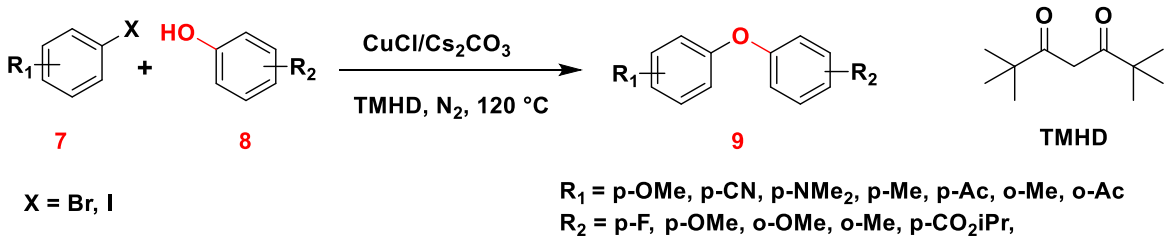
reaction of alcohols or phenols with alkyl or aryl halides (Scheme 1)[3]. Although it has been used in the synthesis of many ethers from the last hundred years, it has some drawbacks *viz.* requirement of the stoichiometric amount of base, inorganic waste, use of toxic halogenated compound and involves multi-step route starting from alcohols.



Scheme 1. Williamson ether synthesis

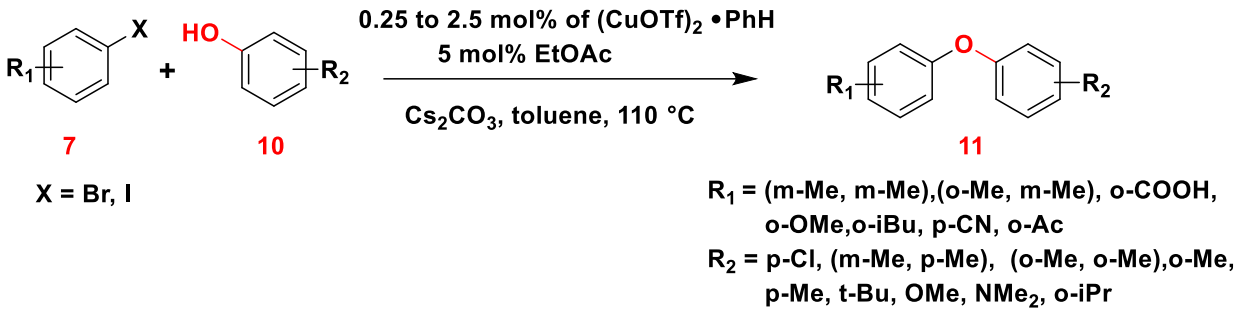
- **Ullmann diaryl ether synthesis**

In 1904**,** Ullmann reported the synthesis of diaryl ethers; which is also a traditional and commonly employed method which involves the coupling of substituted phenols and haloarene using a stoichiometric amount of Cu and carried out under harsh reaction conditions usually at high temperature (Scheme 2).[4a,b] After that many variations have been developed for the catalytic and non-catalytic version for the synthesis of diaryl ethers.[5] Among them, Song and co-workers reported simplified Ullmann ether synthesis with copper (I) catalyst and 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) as a ligand.[6]



Scheme 2. Ullmann diaryl ether synthesis

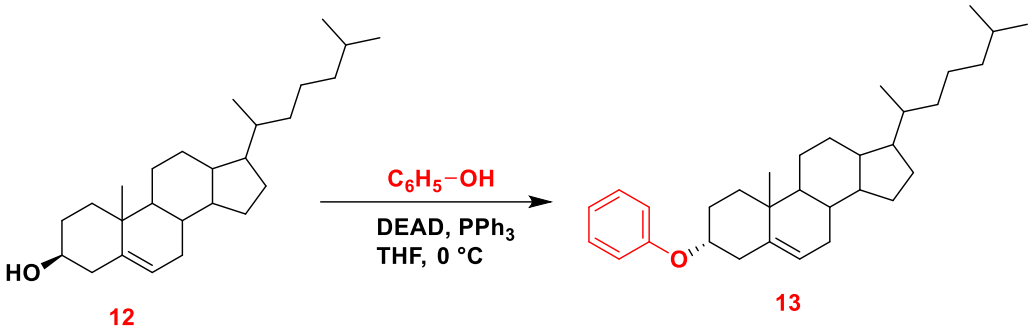
To avoid the use of a stoichiometric amount of base, Buchwald and co-workers developed a catalytic approach for the synthesis of diaryl ethers (Scheme 3). The drawbacks of this protocol are air sensitive Cu-complex and the use of expensive catalyst.[7]



Scheme 3. Catalytic approach for the synthesis of diaryl ethers

- **Etherification using Mitsunobu conditions**

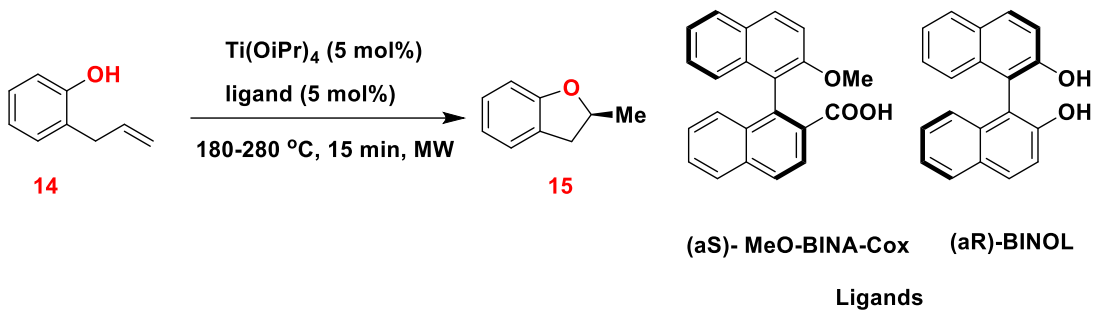
Mitsunobu reaction is extensively used in organic synthesis for the synthesis of amines, ethers, esters and amides.[8,9] To avoid the use of halogenated compounds, Lakoud and co-workers accomplished the etherification and esterification of steroids and terpenes under Mitsunobu reaction conditions and also shown the chemoselectivity with alcohols (Scheme 4).[10]



Scheme 4. Etherification under Mitsunobu conditions

- **Hydroalkoxylation of non-activated alkenes**

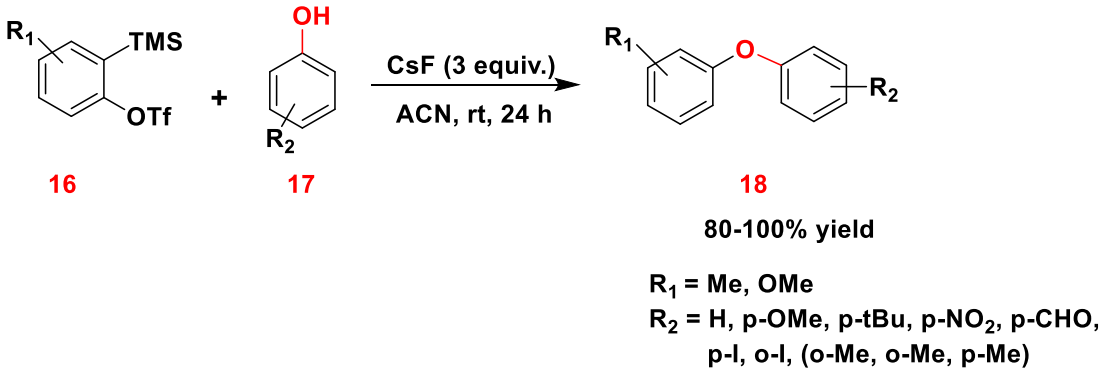
Hintermann group developed a method for the synthesis of asymmetric ethers by using $Ti(OiPr)_4$ as a catalyst in the presence of chiral ligand under microwave conditions at high temperature. This reaction works very well for unactivated alkenes (Scheme 5).[11]



Scheme 5. Synthesis of asymmetric ethers

- **Transition metal free O-arylation of phenols**

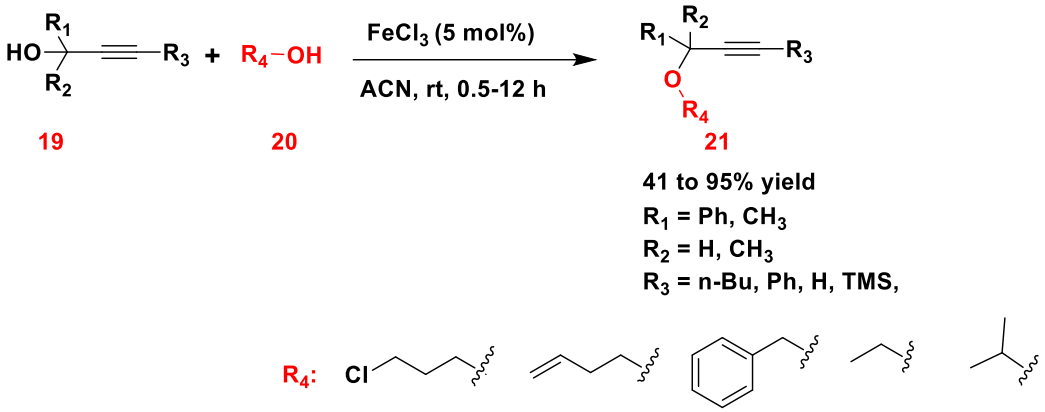
Larock and co-workers reported transition metal free O-arylation of phenols using CsF as a base (Scheme 6).[12] Good to excellent yields of arylated products are achieved under very mild reaction conditions. This chemistry readily tolerates a variety of functional groups.



Scheme 6. Transition metal free O-arylation of phenols

- **The $FeCl_3$-catalyzed etherification of propargylic alcohols**

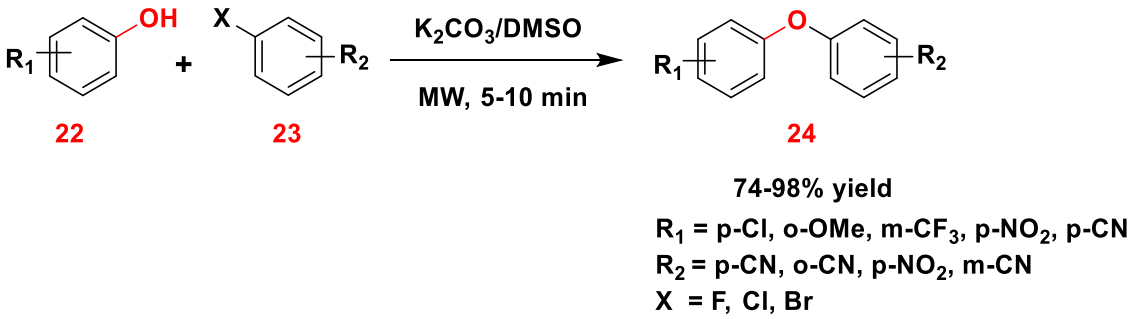
In 2006, Zhan and co-workers reported the etherification of propargylic alcohols with a catalytic amount of $FeCl_3$ (Scheme 7). This method applies to both terminal alkyne and internal alkyne.[13]



Scheme 7. Etherification of propargylic alcohols

- **Microwave-assisted synthesis of diaryl ethers**

To reduce the longer reaction time and to avoid the use of a metal catalyst, Wang and co-workers was developed a method for the preparation of ethers under microwave radiation using substituted phenols, haloarenes and K_2CO_3 (Scheme 8).[14] high to excellent yield was obtained using this method.



Scheme 8. Synthesis of ethers under microwave radiation

1.3 Vinylogous ester

Vinylogous ester (R-O-CH=CHCOR') is a functional group in which C=C bond is placed between a carbonyl and ether groups, an electronically analogous to esters (RCOOR). Vinylogous ester has been found in the core structure of several natural products having a wide range of biological activity.[15,16] Vinylogous esters also used as starting materials for many drug molecules.[17-22] For instance (+)-Kjellmanianone is a compound which contains vinylogous ester moiety which shows antibacterial activity

against gram-positive microorganisms such as *E. coli* K12 and *Bacillus subtilis var niger*.[23] Griseofulvin another drug which is used as medication, that fights infections due to fungus.[24] Artonin E is a prenylated flavonoid compound it has unique medical properties; for instance, it can be used as alleviating most of the human disease. Signal transducer and activator of transcription 3 (STRT3) is an essential protein for cell proliferation and survival. Phaeosphaeride A is a natural product, which contains vinylogous ester and it inhibits the growth of STAT3-dependent U266 protein. STAT3 has an essential role in oncogenesis and STAT3 considered as anti-cancer chemotherapeutic agents.[25] Haterumadienone and Acetoxyhaterumadienone are marine natural products having important biological properties such as antitumor, anti-cancer, antimalarial, anti-HIV, antiviral and immunomodulatory.[26] Few natural products and drug molecule containing vinylogous esters in its core are listed in Figure 2.

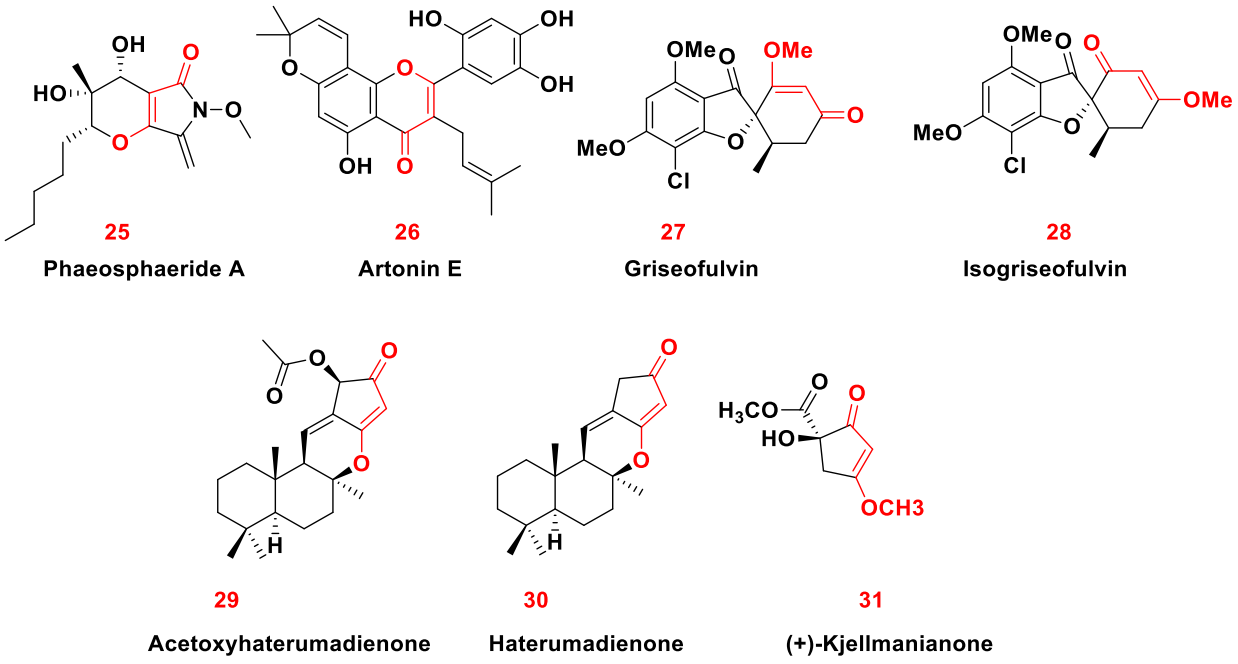


Figure 2. Natural products and drug molecule containing vinylogous esters in its core

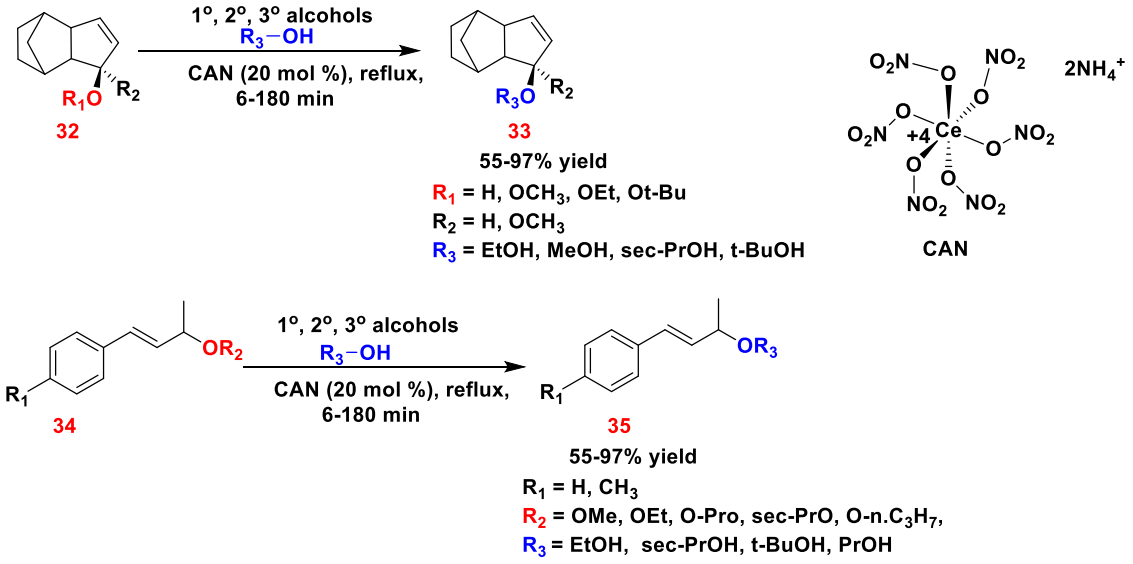
1.4 Transetherification

In addition to the method mentioned above, ether can also be synthesized *via* transetherification reaction. Transetherification is an important transformation in organic chemistry where functional group exchanged with reactant alcohols. Thus,

transetherification is a process of exchange of alkoxy or aryloxy group of ethers with alcohol promoted by a catalytic amount of acid. During the past two decades, several homogeneous catalysts such as Brønsted acid or Lewis acid and transition metal based methodologies were developed for the synthesis of ethers through the transetherification process which encompasses electronically rich substrates containing benzyl and allyl groups. To the best of our knowledge, transetherification vinylogous esters have not been studied yet.

- **Transetherification of allylic and tertiary benzylic ethers**

In 1994, Iranpoor and co-workers examined transetherification using the catalytic amount of ceric ammonium nitrate (CAN) and alcohol as a reagent as well as solvent under reflux conditions (Scheme 9).[27] This reaction was limited to the substrates having allylic and tertiary benzylic substituents. Furthermore, this reaction required high temperature, and only tertiary ethers undergo transetherification reaction.

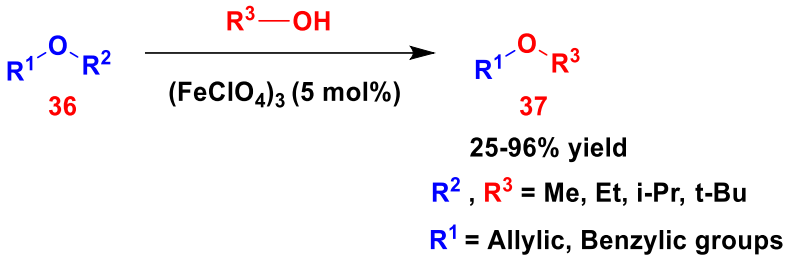


Scheme 9. Transetherification of allylic and tertiary benzylic ethers

- **Iron-catalysed Transetherification of allylic and benzylic ethers:**

In 2000, of environmental benign Iron-catalysed transetherification of allylic and benzylic ethers was reported by Salehi and co-workers (Scheme 10).[28] Although this method

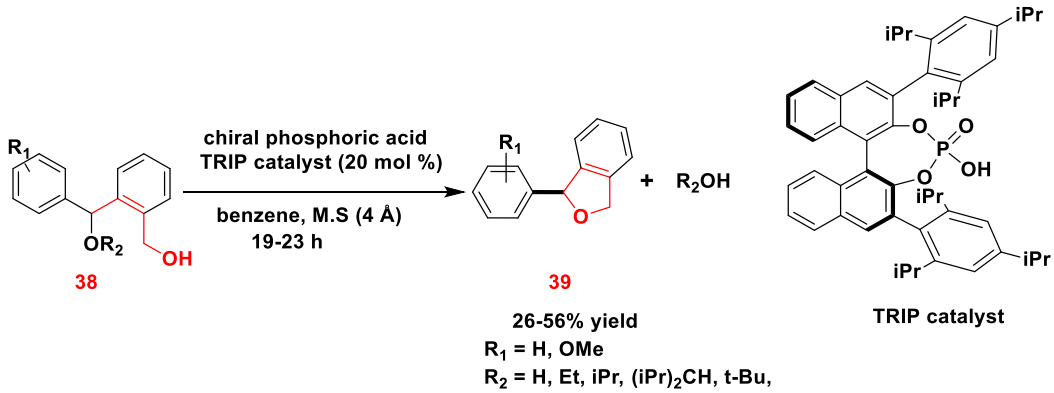
was superior over traditional methods still covers some drawbacks for instance, limited substrate scope, studied with only aliphatic alcohols.



Scheme 10. Transetherification of allylic and benzylic ethers

- **Intramolecular transetherification reactions of hydroxy ethers:**

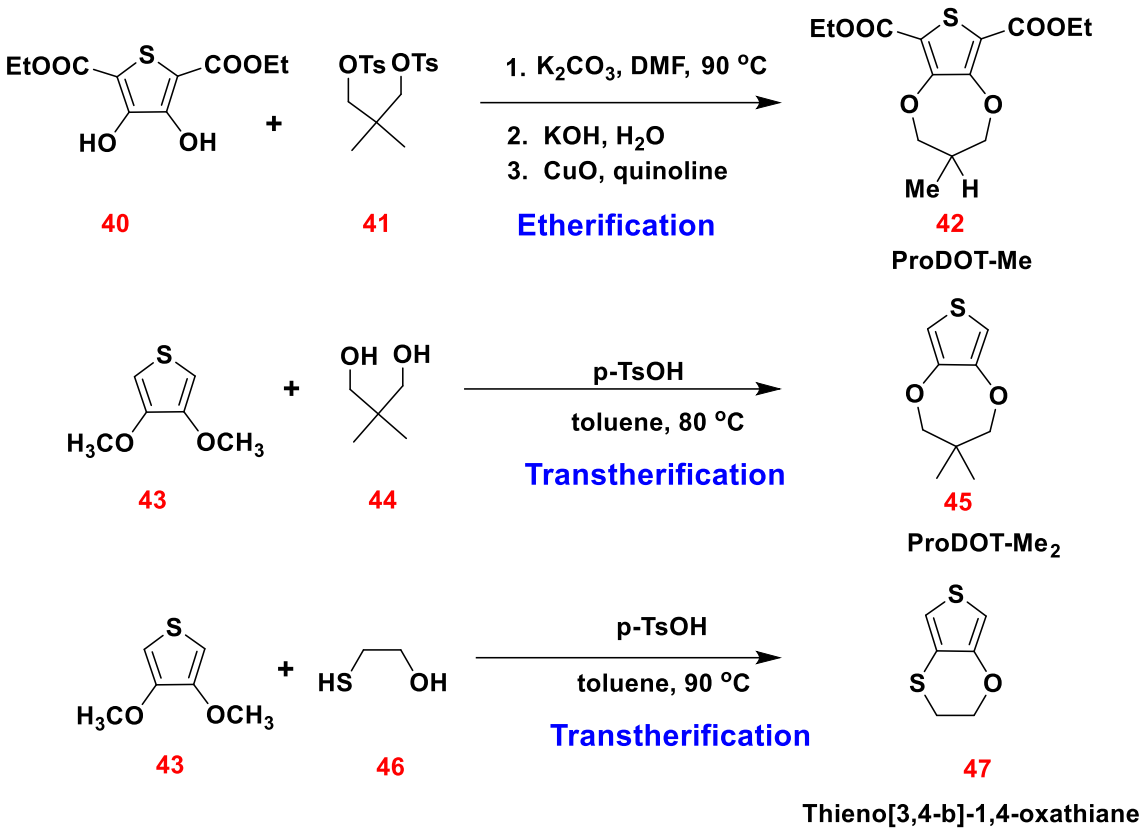
The List and co-workers reported enantioselective intramolecular transetherification of hydroxy ethers (Scheme 11).[29] This is also interesting to form tetrahydrofuran ring by transetherification, but it has some limitation like limited substrate scope, low reaction yield, expensive catalyst and use of carcinogenic benzene as a solvent.



Scheme 11. Intramolecular transetherification hydroxy ethers

- **Etherification and transetherification of thiophene derivatives**

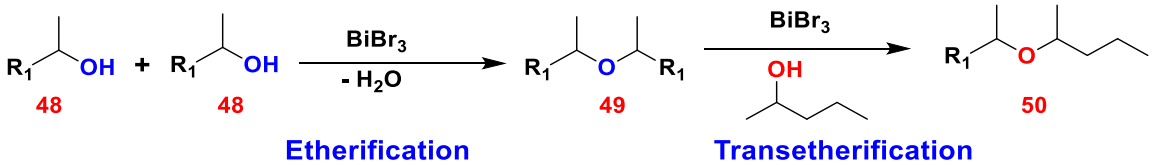
Polysubstituted 3,4-ethylenedioxythiophene (EDOT) is commonly used in several organic optoelectronic devices. In 1999, Reynolds and co-workers synthesised ProDOT-Me and ProDOT-Me$_2$ (Scheme 12).[30a] In 2002, Blanchard and co-workers was synthesised analogous of EDOT through transetherification reaction (Scheme 12).[30b]



Scheme 12. Etherification and transetherification of thiophene derivatives

- **Transetherification of symmetrical ethers with $BiBr_3$:**

Bismuth(III) metal mediated etherification and transetherification was developed under mild reaction conditions using chiral alcohol (Scheme 13). This method is only suitable for symmetrical ethers. Limited substrate scope and use of a stoichiometric amount of $BiBr_3$ was a disadvantage for this method.[31]

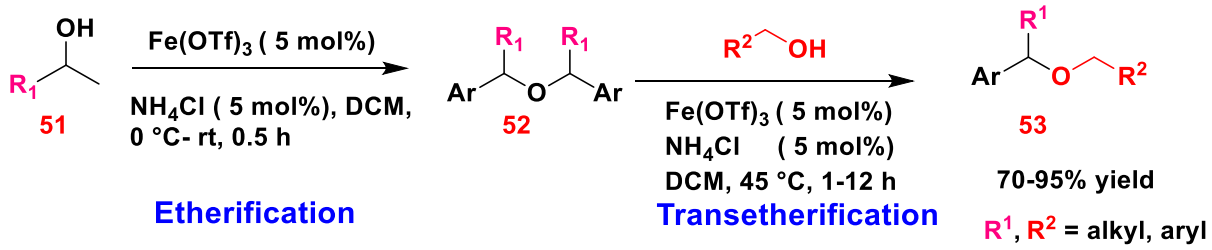


Scheme 13. Transetherification of symmetrical ethers using $BiBr_3$

- **Transetherification of symmetrical ethers:**

Gunanathan and co-workers reported transetherification of symmetrical ethers with primary alcohols by using iron salt in the presence of the external additive (NH_4Cl)

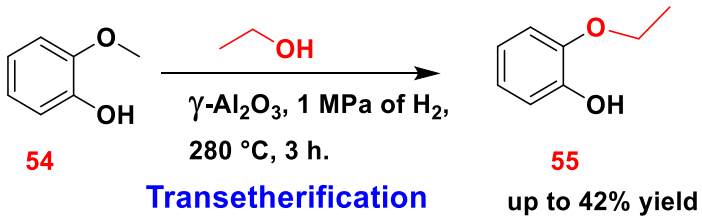
(Scheme 14)[32]. This method was applicable for symmetric ethers, and it suffers some limitation such as no chemoselectivity, limited substrate scope, use of external additives and the expensive moisture sensitive catalyst.



Scheme 14. Transetherification of symmetrical ethers

- **Transetherification of guaiacol to o-ethoxyphenol:**

Apart from the homogeneous catalysis, the environmentally benign and green catalytic system has been developed by Li and co-workers which utilizes the heterogeneous catalytic system for transetherification of guaiacol to o-ethoxyphenol under pressurised hydrogen gas (Scheme 15).[33] Though it was the first heterogeneous catalytic system, but suffers some limitations such as a high temperature and high pressure is required to carry out the reaction.



Scheme 15. Heterogeneously catalysed transetherification

1.5 Flow Chemistry

Continuous flow synthesis is a new technology in organic synthesis. In continuous flow, reagents are continuously flowed in the stream at a particular flow rate and mix where tubes join one another, and the product continuously collected. The large surface area to volume ratio, a result of the small dimensions, provides effective mass and heat transfer rates. Longer reactor lengths, smaller reactor cross-sections and accurate control of reaction parameters make the reaction more efficiently. In

continuous flow synthesis, we can generate a highly unstable intermediate and instantly consume the product in the multistep process.[34,35,36] Continuous flow synthesis has many advantage compared to traditional batch reactions including heat transfer, mass transfer, extreme reaction conditions (high/low temperature, high pressure), easy scale-up, faster reaction, rapid reaction optimisation, and reduction of byproduct, improved yield, improved product quality, enhanced chemical selectivity, easy to maintain the large scale synthesis and we can perform multistep reaction at a time. This technology is convenient for both homogeneous and heterogeneous catalysis. Apart from academia recently continuous flow systems have become very popular in the industry for preparation of fine chemicals, such as an active drug molecule, natural products, etc. The representative continuous flow set up shown in Figure 3.

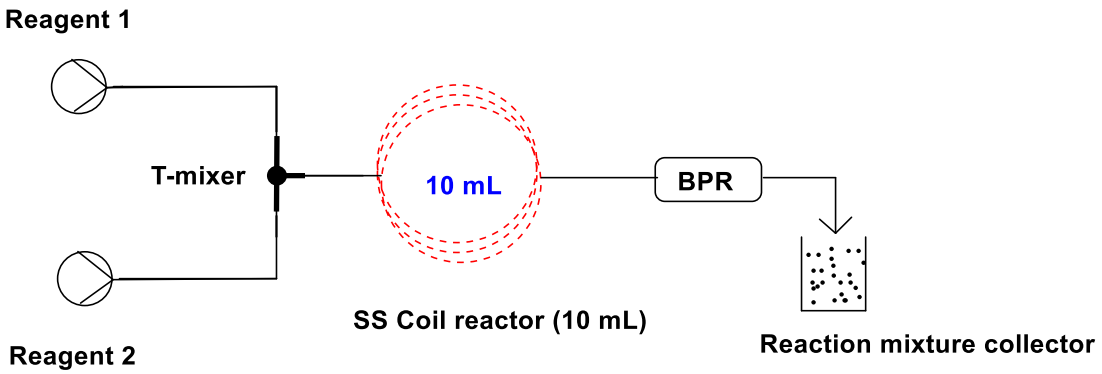


Figure 3. The representative continuous flow set up

2. Methods

2.1 Experimental section

Material and instrumentations:

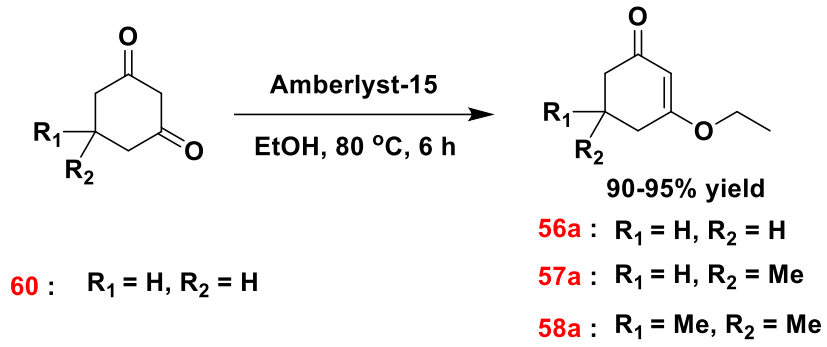
All experiments were carried out in an open atmosphere. All the chemicals used were purchased from commercial sources. Deuterated solvents were used as received. Column chromatography was performed over 100−200 mesh sized silica gel. All the solvents used were dry reagent grade and stored over 4 Å molecular sieves. The iron (III) chloride (product number: 44939) was purchased from Sigma Aldrich. ^{1}H NMR spectra were recorded on, JEOL (400 MHz) and Bruker (400 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectroscopic data were recorded with a 100 MHz. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Chemical shifts have been expressed in ppm units downfield from TMS. All reactions were monitored by Thin Layer Chromatography (TLC). The visualisation was accomplished with UV light and PMA, CAM stain and I_2 followed by heating. High-resolution mass spectra were recorded with Waters-synapt G2 using electrospray ionisation (ESI-TOF). Fourier-transform infrared (FT-IR) spectra were obtained with a Bruker Alpha-E fourier transform infrared spectrometer. The flow chemistry experiments were carried on vaportec R-series.

2.2 Synthetic procedures

Synthesis of starting materials:

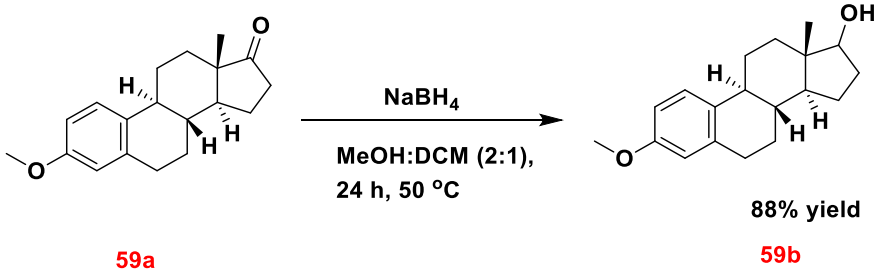
Synthesis of compound 56a, 57a and 58a: In a 100 mL round bottom flask, substituted 1,3-cyclohexadione (1 mmol), and Amberlyst-15 (0.200 g) and 10 mL of alcohol were added and the resulting mixture was refluxed at 80 ^{o}C for 6 h. After the completion reaction, cooled to room temperature, the reaction mixture was filtered and washed with DCM. The organic layer was concentrated under reduced pressure, and

the residue was purified by column chromatography (EtOAc: n-hexane = 30:70) on silica gel to afford the pure vinylogous esters.[37]



Scheme 16. Synthesis of starting materials

Synthesis of compound 59b: Estron-3-methyl ether **59a** (1 mmol) was dissolved in methanol: DCM (2:1). $NaBH_4$ was added portion wise, and the mixture was refluxed for 24 h at 50 °C. After completion of the reaction (monitored by TLC), water was added and extracted with DCM and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure and residue was purified by column chromatography (EtOAc: n-hexane = 25:75) on silica gel to afford the pure product (0.250 g, 88%).[38]



Scheme 17. Reduction of Estron-3-methyl ether

Transetherification reaction procedure:

A. **General procedure for the transetherification of vinylogous ester in batch reaction (56b-56o, 58b, 58c):** In a round bottom flask (10 mL), vinylogous ester (1 mmol), $FeCl_3 \cdot 6H_2O$ (5 mol %) and 3 mL of alcohol was added and allowed to stirred at room temperature (25 °C) in open air for a respective time. After reaction completion, alcohol was removed under reduced pressure; the crude

product was purified by column chromatography (EtOAc: n-hexane = 30:70) on silica gel to afford the pure vinylogous ester.

B. **General procedure for the transetherification of compounds 56p, 56q, 56r, 57b and 58d in batch**: In a seal tube (20 mL), vinylogous ester (1 mmol), $FeCl_3 \cdot 6H_2O$ (5 mol %), alcohols (1 mmol) and DCE (10 mL) were added. Then the tube was sealed, and the reaction vessel was allowed to stir at 80 °C for respective time. After completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (EtOAc: n-hexane = 30:70) on silica gel to afford the pure vinylogous ester.

C. **General procedure for the transetherification of vinylogous ester in a continuous flow:** In 30 mL vial, 0.1 M solution of vinylogous ester (1 mmol) was prepared by adding 10 mL of alcohols and 5 mol% of $FeCl_3 \cdot 6H_2O$. Then sonicated for 5 min to dissolve catalyst completely in the alcohols. Prepared 0.1M solution passed through a tube reactor which has a length of 10 m at 0.2 mL/min flow rate, 1.8 bar pressure at 80 °C. After completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (EtOAc: n-hexane = 30:70) on silica gel to afford the pure vinylogous ester.

Synthesis of compound 60: To the compound **56a** (1 mmol, 0.140 g) in methanol, Iodine (2 mmol, 0.508 g) was added, and the resulting mixture was stirred at 60 °C for 2 h. After completion of the reaction, the reaction mixture was quenched with cold sodium thiosulfate and extracted with ethyl acetate, and the collected organic layer was evaporated and purified by column chromatography (EtOAc: n-hexane = 5:95) on silica gel to afford the aromatised product **60** as a colourless liquid.[39]

Synthesis of compound 61: In a seal tube (20 mL), **56p** (0.280 g, 1 equiv.), TBAB (1 equiv.), KOAc (2.5 equiv.), $Pd(OAc)_2$ (0.02 equiv.) and toluene (7 mL) was added and stirred under N_2 at 130 °C. After 4 h, water was added and extracted with ethyl acetate. The combined organic layers were washed with water and brine solution, passed through sodium sulphate and evaporated the solvent. The crude product was purified by column chromatography (EtOAc: n-hexane = 20:80) on silica gel to afford pure product **61**.[40]

Synthesis of 62: In a seal tube (20 mL) vinylogous ester **56a** (1 mmol), 1-phenylethane-1,2-diol (3 mmol), $FeCl_3 \cdot 6H_2O$ (5 mol %) and DCE were added. Then the seal tube was sealed, and the reaction vessel was allowed to stir at 80 °C for 8 h. After completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (EtOAc: n-hexane = 30:70) on silica gel to afford 58% of the desired product **62**.

2.3 Analytical data for the product:

3-methoxycyclohex-2-en-1-one (56b).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56b** (0.123 g, 3 h, 98%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56b** (0.123 g, 3 h, 98%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (s, 1H), 3.68 (s, 3H), 2.40 (t, *J* = 6.3 Hz, 2H), 2.36 – 2.30 (t, J = 6.88 Hz, 2H), 1.98 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.98, 178.90, 102.46, 55.75, 36.85, 28.95, 21.35. **IR (neat):** 2952.28, 2311.97, 1727.07, 1601.11, 1453.93, 1380, 1232.65, 1183.99, 1001.03, 758.03, 597.32 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_7H_{11}O_2$ $(M+H)^+$: 127.0759, found: 127.0762

3-propoxycyclohex-2-en-1-one (56c).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56c** (0.141 g, 9 h, 92%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56c** (0.151 g, residence time: 50 min, 98%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (s, 1H), 3.78 (t, 2H), 2.39 (t, *J* = 6.3 Hz, 2H), 2.36 – 2.28 (t, 2H), 1.98 (m, 2H), 1.74 (m, 2H), 0.98 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.10, 178.31, 102.82, 70.13, 36.88, 29.16, 22.03, 21.37, 10.54. **IR (neat):** 2953.87, 2315.29, 1724.89, 1590.46, 1458.78, 1369.83, 1226.41, 1179.69 1060.78,

753.04, 601.90 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_9H_{15}O_2$ $(M+H)^+$: 155.1072, found: 155.1078.

3-(hexyloxy)cyclohex-2-en-1-one (56d).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56d** (0.192 g, 9 h, 98%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56d** (0.190 g, residence time: 50 min, 97%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.81 (t, *J* = 6.6 Hz, 2H), 2.39 (t, *J* = 6.3 Hz, 2H), 2.36 – 2.31 (t, *J* = 6.96, 2H), 2.02 – 1.90 (m, 2H), 1.71 (m, 2H), 1.41 – 1.28 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.06, 178.30, 102.83, 68.75, 36.88, 31.56, 29.20, 28.62, 25.73, 22.66, 21.38, 14.12. **IR (neat):** 2944.26, 2834.76, 2310.19, 1718.52, 1589.98, 1465.80, 1298.50, 1110.66, 1034.34, 786.44, 610.97 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{12}H_{21}O_2$ $(M+H)^+$: 197.1542, found: 197.1539.

3-(octyloxy)cyclohex-2-en-1-one (56e).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56e** (0.217 g, 11 h, 97%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56e** (0.219 g, residence time: 50 min, 98%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.81 (t, *J* = 6.6 Hz, 2H), 2.40 (t, *J* = 6.3 Hz, 2H), 2.37 – 2.28 (t, *J* = 7.08, 2H), 1.97 (m, 2H), 1.71 (m, 2H), 1.31 – 1.23 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.02, 178.27, 102.84, 68.76, 36.90, 31.90, 29.35, 29.30, 29.21, 28.66, 26.07, 22.77, 21.40, 14.22. **IR (neat):** 2929.90, 2862.30, 2314.45, 1727.50, 1592.35, 1461.24, 1233.15, 1184.78, 1090.23, 756.55, 607.87 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{14}H_{25}O_2$ $(M+H)^+$: 225.1855, found: 225.1861.

3-(2-methoxyethoxy)cyclohex-2-en-1-one (56f).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56f** (0.165 g, 11 h, 98%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56f** (0.166 g, residence time: 50 min, 98%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1H), 3.99 – 3.95 (m, 2H), 3.70 – 3.67 (m, 2H), 3.42 (s, 3H), 2.45 (t, *J* = 6.3 Hz, 2H), 2.37 – 2.32 (t, *J* = 6.16 Hz, 2H), 1.97 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.95, 177.99, 103.10, 70.26, 67.80, 59.34, 36.87, 29.10, 21.34. **IR (neat):** 3023.28, 2401.97, 1730.21, 1602.11, 1464.39, 1217.26, 1188.16, 1001.03 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_9H_{15}O_3$ $(M+H)^+$: 171.1021, found:171.1031.

3-(3-phenylpropoxy)cyclohex-2-en-1-one (56g).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56g** (0.225 g, 7 h, 98%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56g** (0.225 g, residence time: 50 min, 98%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.23 – 7.15 (m, 3H), 5.32 (s, 1H), 3.83 (t, *J* = 6.4 Hz, 2H), 2.78 – 2.67 (t, *J* = 7.84, 2H), 2.41 (t, *J* = 6.3 Hz, 2H), 2.37 – 2.32 (t, J = 7.04, 2H), 2.09 – 2.02 (m, 2H), 1.98 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.05, 178.14, 141.01, 128.65, 128.51, 126.28, 102.94, 67.73, 36.86, 32.21, 30.19, 29.14, 21.37. **IR (neat):** 3023.67, 2847.54, 2875.98, 2365.45, 1723.13, 1663.91, 1547.80, 1379.97, 1221.50, 1198.80cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{15}H_{19}O_2$ $(M+H)^+$: 231.1385, found:231.1387.

3-(benzyloxy)cyclohex-2-en-1-one (56h).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56h** (0.198 g, 20 h, 98%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56h** (0.198 g, residence time: 50 min, 98%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 5H), 5.48 (s, 1H), 4.89 (s, 2H), 2.47 (t, *J* = 6.3 Hz, 2H), 2.39 – 2.35 (t, J = 6.96, 2H), 2.03 – 1.98 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.95, 177.73, 135.14, 128.86, 128.71, 128.02, 103.55, 70.59, 36.90, 29.19, 21.36. **IR (neat):** 3029.14, 2947.04, 2947.04, 2881.89, 2315.54, 1734.79, 1648.08, 1597.17, 1359.34, 1221.55, 1175.66, 863.08, 743.15 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{13}H_{15}O_2$ $(M+H)^+$: 203.1072, found: 203.1079.

3-(allyloxy)cyclohex-2-en-1-one (56i).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56i** (0.149 g, 10 h, 98%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56i** (0.149 g, residence time: 50 min, 98%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 – 5.91 (m, 1H), 5.39 (m, 1H), 5.36 (s, 1H), 5.30 (m, 2H), 4.37 (dt, *J* = 5.6, 1.3 Hz, 4H), 2.43 (t, *J* = 6.3 Hz, 4H), 2.37 – 2.31 (t, *J* = 7.0 Hz, 2H), 1.98 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.91, 177.56, 131.50, 119.10, 103.30, 69.25, 36.86, 29.12, 21.34. **IR (neat):** 3016.17, 2981.44, 2316.54, 1716.45, 1640.31, 1555.80, 1463.91, 1366.11, 1218.94, 1140.12 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_9H_{13}O_2$ $(M+H)^+$: 153.0916, found:153.0916.

3-((3-methylbut-2-en-1-yl)oxy)cyclohex-2-en-1-one (56j).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one 0.140 g, 1 mmol) to afford vinylogous ester **56j** (0.176 g, 5 h, 98%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56j** (0.176 g, residence time: 50 min, 98%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 – 5.38 (m, 1H), 5.38 (s, 1H), 4.37 (d, *J* = 6.9 Hz, 2H), 2.41 (t, *J* = 6.3 Hz, 2H), 2.38–2.31 (t, *J* = 6.96, 2H), 1.98 (m, 2H), 1.78 (s, 3H), 1.70 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.05, 178.05, 139.86, 118.01, 103.10, 65.55, 36.88, 29.27, 25.94, 21.40, 18.33. **IR (neat):** 2953.38, 2311.97, 1720.17, 1601.11, 1553.93, 1380.22, 1242.55, 1173.79 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{11}H_{17}O_2$ $(M+H)^+$: 181.1229, found:181.1236.

3-(but-3-yn-1-yloxy)cyclohex-2-en-1-one (56k).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56k** (0.065 g, 16 h, 40%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.94 (t, *J* = 6.7 Hz, 2H), 2.63 (td, *J* = 6.7, 2.7 Hz, 2H), 2.42 (t, *J* = 6.3 Hz, 2H), 2.36 – 2.31 (t, *J* =7.0, 2H), 2.03 (t, *J* = 2.7 Hz, 1H), 2.00 – 1.95 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.94, 177.57, 103.17, 70.38, 66.27, 36.83, 29.82, 28.96, 21.28, 19.08. **IR (neat):** 2929.90, 2862.30, 2314.45, 2140.17, 1722.50, 1600.35, 1561.24, 1237.15, 1184.78, 1090.23 cm^{-1}. **HRMS (ESI)** m/z calculated for $C_{10}H_{13}O_2$ $(M+H)^+$: 165.0916, found:165.0920.

3-isopropoxycyclohex-2-en-1-one (56l).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56l** (0.120 g, 9 h, 78%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56l** (0.151 g, residence time: 50 min, 98%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 4.43 (m, 1H), 2.35 (m, 4H), 2.01 – 1.92 (m, 2H), 1.29 (d, *J* = 6.1 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.15, 177.09, 103.14, 71.05, 36.84, 29.77, 21.61, 21.36. **IR (neat):** 2978.67, 2310.65, 1730.60, 1641.95,

1595.51, 1461.11, 1230.90, 1187.26, 1000.27, 757.95, 608.98 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_9H_{15}O_2$ $(M+H)^+$: 155.1072, found:155.1078.

3-(cyclopentyloxy)cyclohex-2-en-1-one (56m).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56m** (0.176 g, 6 h, 98%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56m** (0.176 g, residence time: 50 min, 98%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (s, 1H), 4.64 – 4.57 (m, 1H), 2.34 (dd, *J* = 12.5, 6.3 Hz, 4 H), 1.96 (dd, *J* = 13.0, 6.6 Hz, 2H), 1.89 – 1.82 (m, 2H), 1.82 – 1.78 (m, 2H), 1.78 – 1.68 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.05, 177.34, 103.80, 80.70, 36.83, 32.80, 29.50, 24.23, 21.39. **IR (neat):** 2995.15, 2910.56, 2344.50, 1734.64, 1599.78, 1499.91, 1304.68, 1211.78, 1122.97 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{11}H_{17}O_2$ $(M+H)^+$: 181.1229, found:181.1225.

3-(1-phenylethoxy)cyclohex-2-en-1-one (56n).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56n** (0.112 g, 20 h, 52%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56n** (0.112 g, residence time: 50 min, 52%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.28 – 7.24 (m, 3H), 5.26 (s, 1H), 5.18 (q, *J* = 6.5 Hz, 1H), 2.44 (dd, *J* = 10.5, 6.1 Hz, 2H), 2.27 (td, *J* = 6.2, 2.2 Hz, 2H), 1.98 – 1.91 (m, 2H),1.56 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.05, 176.78, 141.44, 128.93, 128.16, 125.48, 104.71, 36.74, 29.83, 29.49, 23.77, 21.27. **IR (neat):** 3029.14, 2947.04, 2947.04, 2881.89, 2315.54, 1724.79, 1658.08, 1587.17, 1449.34, 1266.11, 1199.44 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{14}H_{17}O_2$ $(M+H)^+$: 217.1229, found:217.1227.

3-(hexan-2-yloxy)cyclohex-2-en-1-one (56o).

Batch: Prepared according to general procedure A, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56o** (0.192 g, 6 h, 98%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 1H), 4.23 (m, 1H), 2.37 – 2.29 (m, 4H), 1.98 – 1.90 (m, 2H), 1.68 – 1.25 (m, 6H), 1.23 (d, J = 6.08 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.07, 177.29, 102.94, 74.80, 36.78, 35.60, 29.59, 27.59, 22.60, 21.29, 19.21, 14.08. **IR (neat):** 2929.90, 2862.30, 2314.45, 1727.50, 1592.35, 1461.24, 1233.15, 1184.78, 1090.23, 756.55, 607.87 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{12}H_{21}O_2$ $(M+H)^+$: 197.1542, found:197.1549.

3-((2-bromobenzyl)oxy)cyclohex-2-en-1-one (56p). Prepared according to general procedure B, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56p** (0.145 g, 24 h, 52%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.43 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.35 (td, *J* = 7.5, 1.2 Hz, 1H), 7.22 (td, *J* = 7.9, 1.8 Hz, 1H), 5.50 (s, 1H), 4.97 (s, 2H), 2.51 (t, *J* = 6.3 Hz, 2H), 2.42 – 2.35 (t, *J* = 7.04 Hz, 2H), 2.03 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.84, 177.35, 134.56, 133.07, 130.07, 129.39, 127.77, 103.81, 69.97, 36.90, 29.03, 21.36. **IR (neat):** 3056.27, 3016.68, 2984.66, 2298.97, 1731.92, 1643.92, 1594.96, 1401.18, 1270.41, 1216.91, 1179.39 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{13}H_{14}BrO_2$ $(M+H)^+$: 281.0177, found: 281.0177.

3-(((3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)cyclohex-2-en-1-one (56q).

Batch: Prepared according to general procedure B, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56q** (0.432 g, 20 h, 90%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 – 5.33 (m, 2H), 4.09 – 3.92 (m, 1H), 3.59 – 3.40 (m, 1H), 2.41 – 2.31 (m, 4H), 2.06 – 1.93 (m, 5H), 1.92 – 1.87 (m, 1H), 1.87 – 1.77 (m, 3H), 1.64 – 1.60 (m, 2H), 1.47 (m, 7H), 1.25 (s, 2H), 1.14 – 1.09 (m, 5H), 1.01 (d, *J* = 7.3 Hz, 5H), 0.93 – 0.90 (m, 4H), 0.86 (dd, *J* = 6.6, 1.3 Hz, 7H), 0.67 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.10, 176.98, 140.91, 139.31, 123.33, 121.85, `103.25, 71.94, 56.85, 56.28, 50.22, 42.45, 40.07 – 39.52, 37.99, 37.40, 37.04, 36.75, 36.34, 35.94, 31.96,

29.68, 28.38, 28.16, 27.67, 24.44, 23.98, 22.97, 22.71, 21.51 – 20.86, 19.52, 18.86, 12.01. **IR (neat):** 3023.79, 2954.91, 2852.40, 2387.87, 1718.30, 1629.40, 1593.84, 1524.58, 1467.16, 1429.53, 1378.29, 1328.47 1001.03, 758.03, 597.32 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{33}H_{53}O_2$ $(M+H)^+$: 481.4046, found:481.4040

3-(((8R,9S,13S,14S)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)oxy)cyclohex-2-en-1-one (56r):

Prepared according to general procedure B, using 3-ethoxycyclohex-2-en-1-one (0.140 g, 1 mmol) to afford vinylogous ester **56r** (0.350 g, 20 h, 92%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 5.37 (s, 1H), 4.13 – 4.04 (m, 1H), 3.78 (s, 3H), 2.86 (m, 2H), 2.40 (td, *J* = 6.1, 3.2 Hz, 2H), 2.36 – 2.32 (m, 2H), 2.02 – 1.94 (m, 3H), 1.54 – 1.29 (m, 8H), 1.25 (s, 4H), 0.88 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.11, 178.06, 157.64, 138.02, 132.47, 126.48, 113.9, 111.67, 103.77, 86.98, 55.36, 49.79, 43.83, 38.64, 37.46, 36.86, 29.91, 29.41, 27.99, 27.38, 26.36, 23.74, 21.38, 12.29**. IR (neat):** 3016.59, 2966.53, 2874.26, 2437.37, 2378.87, 1724.53, 1629.40, 1593.84, 1524.58, 1467.16, 1429.53, 1378.29, 1328.74, 1101.03 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{25}H_{33}O_3$ $(M+H)^+$: 381.2430, found: 381.2430.

3-((2-chlorobenzyl)oxy)-5-methylcyclohex-2-en-1-one (57b).).

Prepared according to general procedure B, using 3-ethoxy-5-methylcyclohex-2-en-1-one (0.154 g, 1 mmol) to afford vinylogous ester **57b** (0.182 g, 24 h, 45%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.30 – 7.26 (m, 2H), 5.45 (s, 1H), 4.97 (s, 2H), 2.52 – 2.40 (m, 2H), 2.27 – 2.18 (m, 2H), 2.08 – 2.00 (m, 1H), 1.09 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.47, 176.59, 133.43, 133.00, 129.84, 129.33, 127.15, 103.37, 67.79, 45.27, 37.22, 29.02, 21.13. **IR (neat):** 3056.27, 3016.68, 2984.66, 2298.97, 1731.92, 1643.92, 1594.96, 1401.18, 1270.41, 1216.91, 1179.39 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{11}H_{16}ClO_2$ $(M+H)^+$:251.0839 found: 251.0839.

5, 5-dimethyl-3-propoxycyclohex-2-en-1-one (58b).

Batch: Prepared according to general procedure A, using 3-ethoxy-5, 5-dimethylcyclohex-2-en-1-one (0.168 g, 1 mmol) to afford vinylogous ester **58b** (0.123 g, 25 h, 68%) as yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.168 g, 1 mmol) to afford vinylogous ester **58b** (0.167 g, residence time: 50 min, 92%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.79 (t, *J* = 6.6 Hz, 2H), 2.27 (s, 2H), 2.20 (s, 2H), 1.80 – 1.70 (m, 2H), 1.07 (s, 6H), 0.98 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.82, 176.55, 101.62, 70.19, 50.88, 43.04, 32.60, 28.43, 22.05, 10.52. **IR (neat):** 2959.17, 2881.44, 2310.50, 1722.54, 1598.80, 1463.91, 1367.11, 1218.58, 1147.97 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{11}H_{19}O_2$ $(M+H)^+$: 183.1385, found: 183.1392.

3-(cyclopentyloxy)-5, 5-dimethylcyclohex-2-en-1-one (58c).

Batch: Prepared according to general procedure A, using 3-ethoxy-5, 5-dimethylcyclohex-2-en-1-one (0.168 g, 1 mmol) to afford vinylogous ester **58c** (0.150 g, 25 h, 72%) as a yellowish oil.

Flow: Prepared according to general procedure C, using 3-ethoxycyclohex-2-en-1-one (0.168 g, 1 mmol) to afford vinylogous ester **58c** (0.150 g, residence time: 50 min, 72%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (s, 1H), 4.60 (m, 1H), 2.21 (s, 2H), 2.19 (s, 2H), 1.89 – 1.55 (m, 8H), 1.05 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.71, 175.52, 102.60, 80.68, 50.80, 43.32, 32.83, 32.60, 28.40, 24.23. **IR (neat):** 2995.15, 2910.56, 2344.50, 1734.64, 1599.78, 1499.91, 1304.68, 1211.78, 1122.97 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{13}H_{21}O_2$ $(M+H)^+$: 209.1542, found:209.1545.

3-((2-chlorobenzyl)oxy)-5, 5-dimethylcyclohex-2-en-1-one (58d). Prepared according to general procedure A, using 3-ethoxy-5, 5-dimethylcyclohex-2-en-1-one (0.168 g, 1 mmol) to afford vinylogous ester **58d** (0.105 g, 25 h, 40%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.31 – 7.27 (m, 2H), 5.48 (s, 1H), 5.00 (s, 2H), 2.37 (s, 2H), 2.24 (s, 2H), 1.10 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.33,

175.50, 133.38, 133.03, 129.83, 129.21, 127.14, 102.59, 67.77, 50.91, 42.95, 32.76, 28.51. **IR (neat):** 3056.27, 3016.68, 2984.66, 2298.97, 1731.92, 1643.92, 1594.96, 1401.18, 1270.41, 1216.91, 1179.39 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{15}H_{18}ClO_2$ $(M+H)^+$: 265.0995, found:265.0999.

3-ethoxycyclohex-2-en-1-one (56a): Yellowish oil (0.133 g, 3 h, 95%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 1H), 3.88 (q, *J* = 7.0 Hz, 2H), 2.38 (t, *J* = 6.3 Hz, 2H), 2.34 – 2.29 (t, J = 7.04 Hz, 2H), 1.96 (m, 2H), 1.35 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.60, 177.79, 102.89, 64.24, 36.89, 29.25, 21.42, 14.31. **HRMS** (ESI) m/z calculated for $C_8H_{13}O_2$ $(M+H)^+$: 141.0837, found:141.0826

3-ethoxy-5-methylcyclohex-2-en-1-one (57a): Yellowish oil (0.138 g, 4 h, 90%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (s, 1H), 3.88 (t, *J* = 7.0, 3.7 Hz, 2H), 2.43 – 2.35 (m, 2H), 2.24 – 2.08 (m, 2H), 2.01 (dd, *J* = 16.4, 11.5 Hz, 1H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.59, 177.18, 102.48, 64.32, 45.27, 37.43, 29.01, 21.12, 14.32. **HRMS** (ESI) m/z calculated for $C_9H_{15}O_2$ $(M+H)^+$: 155.1094, found: 155.1072

3-ethoxy-5,5-dimethylcyclohex-2-en-1-one(58a): Yellowish oil (0.151 g, 5 h, 90%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (s, 1H), 3.88 (q, *J* = 7.1 Hz, 2H), 2.25 (s, 2H), 2.18 (s, 2H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.06 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.47, 176.11, 101.64, 64.30, 50.87, 43.10, 32.62, 28.48, 14.31. **HRMS** (ESI) m/z calculated for $C_{10}H_{17}O_2$ $(M+H)^+$:169.1150, found: 169.1129

(8R,9S,13S,14S)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-ol (59a): (0.250 g, 24 h, 88%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 3.78 (s, 3H), 3.73 (t, *J* = 8.4 Hz, 1H), 2.86 (dd, *J* = 9.3, 6.3 Hz, 2H), 2.32 (m, 1H), 2.23 – 2.07 (m, 2H), 1.98 – 1.91 (m, 1H), 1.88 (m, 1H), 1.75 – 1.65 (m, 1H), 1.58 (s, 3H), 1.48 – 1.32 (m, 5H), 0.78 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.57, 138.14, 132.79, 126.48, 113.95, 111.61, 82.08, 55.36, 50.17, 44.09, 43.41, 39.00, 36.85, 30.75, 29.96, 27.40, 26.47, 23.27, 11.20**. HRMS** (ESI) m/z calculated for $C_{19}H_{27}O_2$ $(M+H)^+$:287.2011, found: 287.2009.

1,3-dimethoxybenzene(60): (0.117 g, 2 h, 85%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 11.0, 5.4 Hz, 1H), 6.54 – 6.51 (m, 2H), 6.48 (t, *J* = 2.4 Hz, 1H), 3.80 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.98, 130.00, 106.29, 100.59, 55.38. **FTIR:** 3095.15, 2910.56, 1599.78, 1554.91, 1304.68, 1211.78, 1122.97 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_8H_{11}O_2$ $(M+H)^+$: 139.0761, found: 139.0761.

2,3,4,6-tetrahydro-1H-benzo[c]chromen-1-one(61): (0.190 g, 4 h, 95%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.9 Hz, 1H), 7.32 (ddd, *J* = 7.9, 1.4, 0.7 Hz, 1H), 7.20 (td, *J* = 7.5, 1.2 Hz, 1H), 7.02 (dd, *J* = 7.5, 0.7 Hz, 1H), 5.12 (s, 2H), 2.62 – 2.50 (m, 4H), 2.00 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.52 (s), 174.19 (s), 128.67 (s), 127.89 (s), 127.03, 124.97, 123.80, 113.20, 69.63, 38.43, 29.02, 20.21. **FTIR:** 3329.14, 2947.04, 2947.04, 2881.89, 2315.54, 1664.08 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{13}H_{13}O_2$ $(M+H)^+$: 201.0915, found:201.0919.

2-phenyl-1,4-dioxaspiro[4.5]decan-7-one(62): (0.134 g, 8 h, 58%)

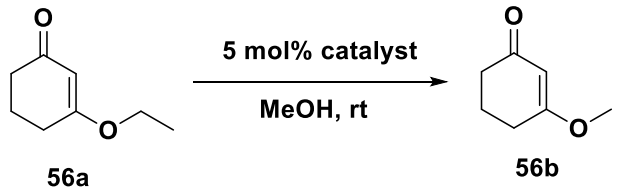
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 5.09 (m, 1H), 4.32 (m, 1H), 3.77 – 3.67 (m, 1H), 2.77 (dd, *J* = 23.2, 14.2 Hz, 2H), 2.37 (t, *J* = 6.7 Hz, 2H), 2.07 (m, 2H), 2.01 – 1.83 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.47, 138.34, 138.05, 128.74, 128.41, 111.12, 78.47, 78.17, 71.78, 52.64, 52.10, 40.40, 35.15, 34.65, 20.18. **FTIR:** 3023.79, 2962.12, 2873.22, 2312.25, 1711.09, 2594.96, 1465.21 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{14}H_{17}O_3$ $(M+H)^+$: 233.3070, found: 233.3075.

3. RESULTS AND DISCUSSION

3.1 Catalyst study

To study the transetherification of vinylogous ester, we have taken 3-ethoxycyclohex-2-en-1-one (**56a**) and methanol as a model substrate to optimise the reaction condition using variety of metal catalyst (5 mol%) and the results are summarised in table 1. Initially, a control experiment was performed in the absence of a catalyst. As a result, there is no transetherification product was observed (Table 1, entry 1). However using 5 mol% $Ru(bpy)_3Cl_2 \cdot 6H_2O$ as a catalyst and 10 equiv. of methanol in ACN solvent afforded desired product 3-methoxycyclohex-2-en-1-one (**56b**) in 40% yield (Table 1, entry 2). Interestingly by using an excess of methanol 90% transetherification product was formed in 11 h (Table 1, entry 3). From this, we confirmed that this is a reversible reaction and need to add an excess amount of alcohol to shift the equilibrium in the forward direction. Surprisingly, **56b** could be obtained in 98% yield in 3 h, when 5 mol% $FeCl_3 \cdot 6H_2O$ was used as a catalyst (Table 1, entry 4). Replacement of $FeCl_3 \cdot 6H_2O$ with other transition metal catalysts, such as Ru-MACHO, $(CH_3COO)_3Mn \cdot 2H_2O$, or $MnCl_2 \cdot 2H_2O$, resulted in no reaction (Table 1, entries 7-10). $[Ru(p\text{-cymene})Cl_2]_2$ significantly proceeded to yield **56b** in 93% yield (Table 1, entry 5). Furthermore salts such as $RuCl_3 \cdot 6H_2O$, $NiBr_2 \cdot 2H_2O$, $CuCl_2 \cdot 2H_2O$, $CoCl_3 \cdot 2H_2O$ and afforded 95, 30, 25, and 40% yields respectively (Table 1, entries 10-13). After screening various catalysts, we found Iron (III) chloride as the best catalyst for the transetherification reaction of the vinylogous ester. The reason to choose iron as a catalyst because it is cheap, environmentally friendly, commercially available and less toxic.

Table 1. Optimisation for transetherification reaction in a batch.



56a **56b**

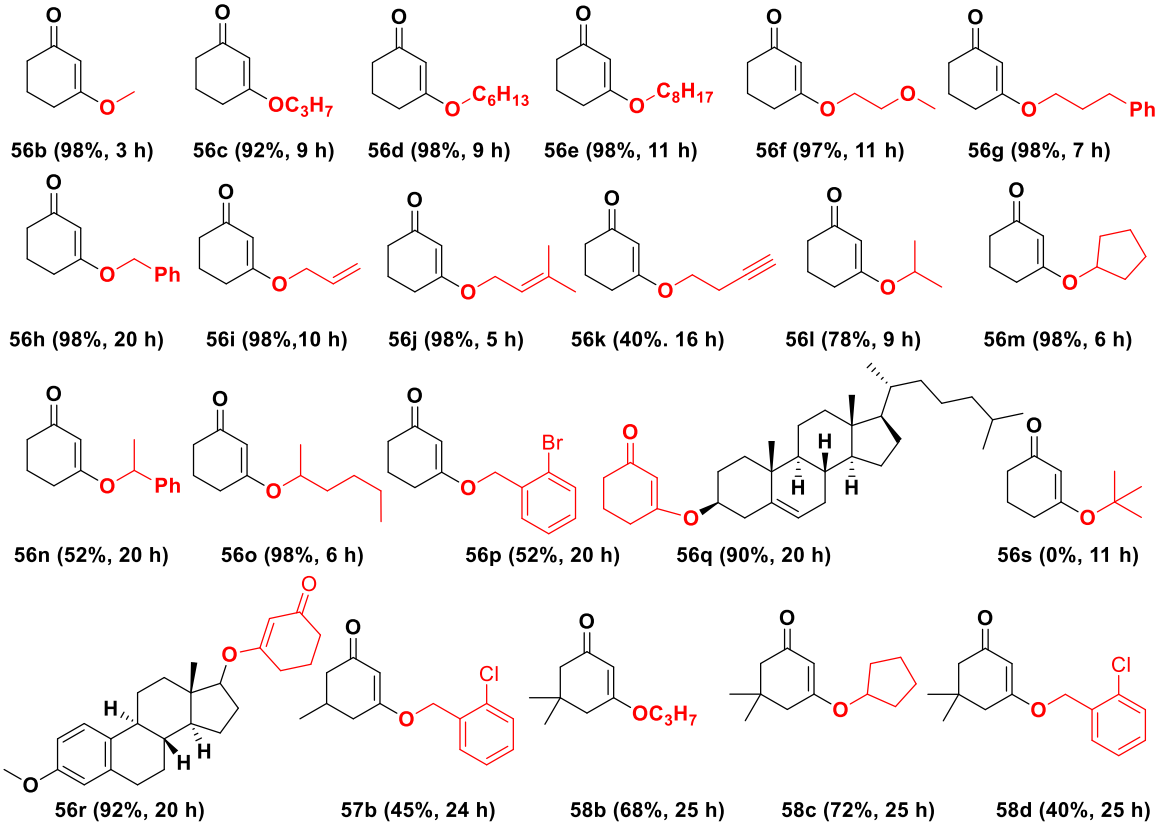
entry	catalyst	MeOH	solvent	time (h)	yield (%)
1	-	10 equiv	-	21	-
2	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	10 equiv	ACN	21	40
3	$Ru(bpy)_3Cl_2$	excess	-	11	90
4	$FeCl_3 \cdot 6H_2O$	excess	-	3	98
5	$[Ru(p\text{-cymene})Cl_2]_2$	excess	-	6	93
6	Fe-zeolite	excess	-	3	95
7	Ru-MACHO	excess	-	40	-
8	$(CH_3COO)_3Mn \cdot 2H_2O$	excess	-	3	-
9	$MnCl_2 \cdot 2H_2O$	excess	-	3	-
10	$RuCl_3 \cdot 6H_2O$	excess	-	3	95
11	$NiBr_2 \cdot 2H_2O$	excess	-	3	30
12	$CuCl_2 \cdot 2H_2O$	excess	-	3	25
13	$CoCl_3 \cdot 2H_2O$	excess	-	3	40

Reaction condition: 56a (1 mmol), catalyst (5 mol%), methanol (2 mL) and were stirred at room temperature, the mentioned yields are isolated yield.

3.2 Substrate scope in batch and continuous flow

With the established optimisation reaction condition in hand, we performed reactions with a variety of vinylogous esters with different aliphatic and aromatic alcohols. Substrate scope for this transformation summarised was Figure 4. We have performed the reaction with primary aliphatic alcohols such as *n*-propanol, *n*-hexanol, and *n*-octanol with **56a** which afforded desired products **56c**, **56d**, **56e** in excellent yield 92, 98, 98% respectively. Furthermore, other substituted primary alcohols such as 2-methoxy ethanol, 3-phenylpropane-1-ol, 2-bromobenzyl alcohol, and benzyl alcohol also reacted well with **56a** to afford **56f**, **56g**, **56h**, **56p** in 97, 98, 98, 52% yield respectively.

Interestingly, this reaction is well tolerant to olefin and alkyne functional groups; for example, allyl alcohol and 3-methylbut-2-en-1-ol reacted smoothly to afford the transetherified products **56i** and **56j** in 98% but in case but-3-yn-1-ol of we got only **56k** only 40% yield. Sterically hindered secondary alcohols such as isopropyl alcohol, cyclopentanol, 1-phenylethanol, 2-hexanol, cholesterol and esterol reacted well with **56a** and gave **56l**, **56m**, **56n**, **56o**, **56q**, **56r** in 78, 98, 52, 98, 90 and 98% yield respectively. Unfortunately, transetherification was unsuccessful with sterically hindered tertiary butanol. Vinylogous ester (**57a**) reacted well with 2-chlorobenzyl alcohol and gaves **57b** in 45% yield. Other substituted vinylogous ester **58a** also reacted well with *n*-propanol, cyclopentanol and 2-chlorobenzyl alcohols gives **58b**, **58c**, **58d** in 68, 72, 40% yield.



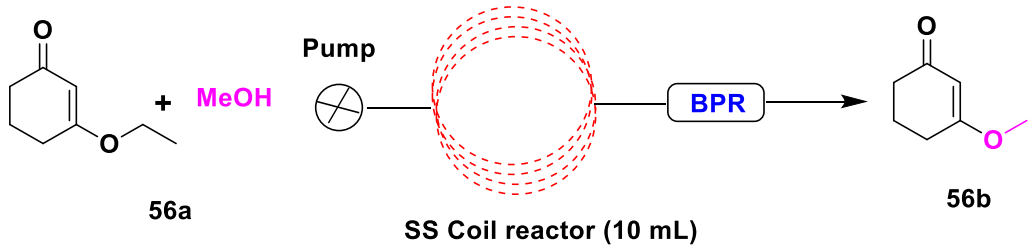
Reaction condition: vinylogous ester (1 mmol), $FeCl_3 \cdot 6H_2O$ (5 mol %), alcohols (2 mL) and the mentioned yields are isolated yield.

Figure 4. Substrates scope under the batch condition

To examine our hypothesis in continuous-flow, initially reactions of 0.1 M of 3-ethoxycyclohex-2-en-1-one (**56a**) with methanol was flowed in continuous flow at 60 °C

as a result no product was observed (Table 2, entry 1). However, flowing the reactants and 3 mol% $FeCl_3 \cdot 6H_2O$ catalyst with 0.2 mL/min flow rate at room temperature providing 3-methoxycyclohex-2-en-1-one (**57a**) in 65% yield (Table 2, entry 2). We continued to evaluate the effect of catalyst loading, temperature, and residence time (Table 2). Increasing both the catalyst loading (5 mol %) and temperature (80 °C) with residence time 50 minutes resulted in the best yield of **57a** around 98% (Table 2, entry 6). There was no improvement in the yield of the reaction while increasing the temperature to 100 °C (Table 2, entry 7).

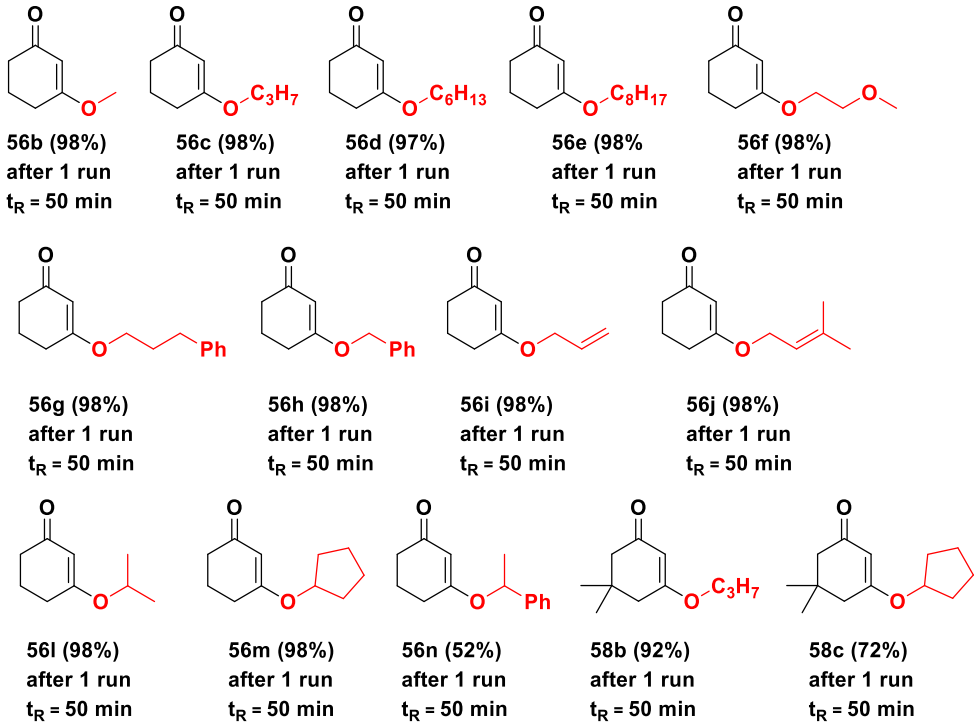
Table 2. Optimisation for transetherification reaction in continuous flow



entry	$FeCl_3 \cdot 6H_2O$ (mol%)	temp. (°C)	flow rate (mL/min.)	t_R (min.)	yield (%)
1	-	60	0.2	50	-
2	3	rt	0.2	50	65
3	3	60	0.2	50	82
4	3	80	0.2	50	85
5	5	60	0.2	50	92
6	5	80	0.2	50	98
7	5	100	0.2	50	98

Having optimised reaction condition in hand, we performed substrate scope for this transformation in a continuous flow, and the results are shown in Figure 5. The yields were generally comparable to the batch reaction, but reactions are completed in a shorter duration of time. A slight decrease in yield of **57o** and **57p** was observed when

the reaction was carried out with cyclopentanol and 1-phenylethanol. To demonstrate gram scale synthetic utility of this strategy, we also conducted in 10 mmol scales transetherification reaction with hexanol, which provided **57c** in 1.9 g (97 %). The full setup for Vapourtec R-series reactor shown in Figure 12.



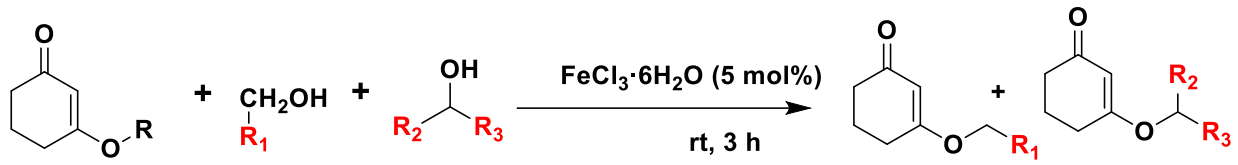
Reaction conditions: All reactions were run on a 0.1 M scale in 10 mL of alcohol using 5 mol% of $FeCl_3 \cdot 6H_2O$ catalyst at 80 °C and maintained at a pressure of 1.2 bar using a BPR, t_R is the residence time, the mentioned yields are isolated yield.

Figure 5. Substrates scope under continuous flow

We also performed chemoselectivity for this transformation with different alcohols. Thus, intermolecular transetherification of vinylogous ester using primary and secondary alcohols was investigated. To this objective, an equivalent amount of methanol and IPA was reacted with vinylogous ester **56a** in the presence of 5 mol% of $FeCl_3 \cdot 6H_2O$ afforded the products **56b** and **56l** in the ratio 60:40% (Table 3, entry 1). Interestingly, high selectivity 95:5% was observed in the case of MeOH/1-phenylethanol mixture (Table 3, entry 2). Primary alcohols reacted rapidly compare to highly hindered secondary alcohols such as diphenylmethanol, bis(4-methoxyphenyl)methanol and phenyl(3-(trifluoromethyl)phenyl)methanol (Table 3, entries 3-5) giving an exclusive

product with primary alcohols. It was found that the reaction efficiency was significantly affected by the steric effect.

Table 3. Optimisation for chemoselective transetherification



entry	vinylogous ester	primary alcohols	secondary alcohols	selectivity based ^{1}H-NMR
1	56a	methanol	IPA	75:25
2	56a	methanol	1-phenylethanol	95:5
3	56a	methanol	diphenylmethanol	100:0
4	56a	*n*-propanol	bis(4-methoxy phenyl)methanol	100:0
5	56a	*n*-hexanol	phenyl(3-(trifluor omethyl)phenyl)methanol	100:0
6	56a	methanol:benzyl alcohol	-	90:10

Subsequently, a sequential transetherification of vinylogous ester was investigated under continuous flow condition. Hence, the vinylogous ester **56a** and 5 mol% of $FeCl_3 \cdot 6H_2O$ in methanol were flown (0.2 mL/min) into the coil reactor at 80 ^oC afforded the product **56b** in 98% yield. The product **56b** in hexanol with 5 mol% of $FeCl_3 \cdot 6H_2O$ was further flowed into the SS coil reactor to provide the **56d** in 98% yield. Further, the product **56d** was continuously transformed into **56m**, and subsequently, the product **56m** was transformed into **56a** in excellent yield under continuous transetherification condition (Figure 6).

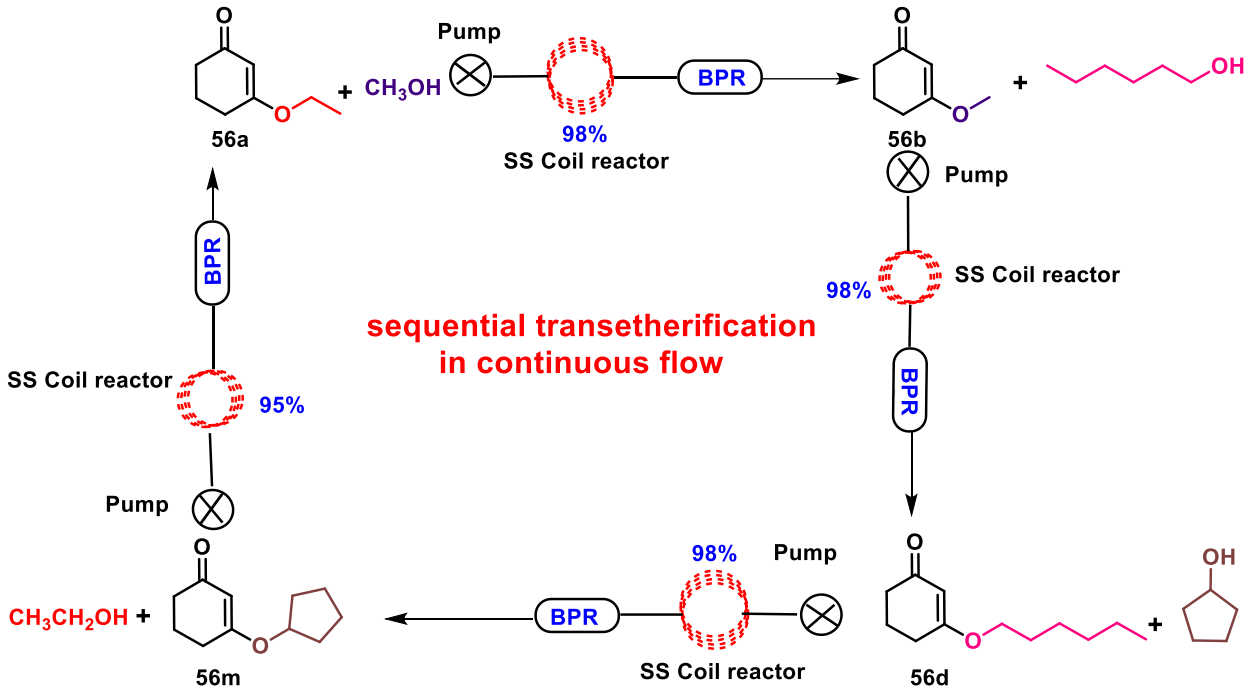


Figure 6. Sequential transetherification under continuous flow

In addition, the catalyst recyclability for this transformation was demonstrated by flowing the vinylogous ester **56a** in methanol to the column packed with Fe-supported on zeolite 13 using syringe addition pump and heated at 60 ^{o}C to afford the product **56b** in 99% yield with residence time t_R = 7 min (Figure 7).

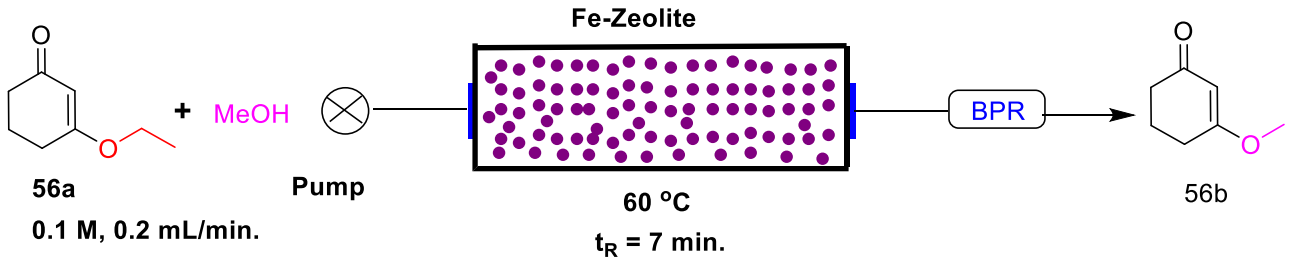
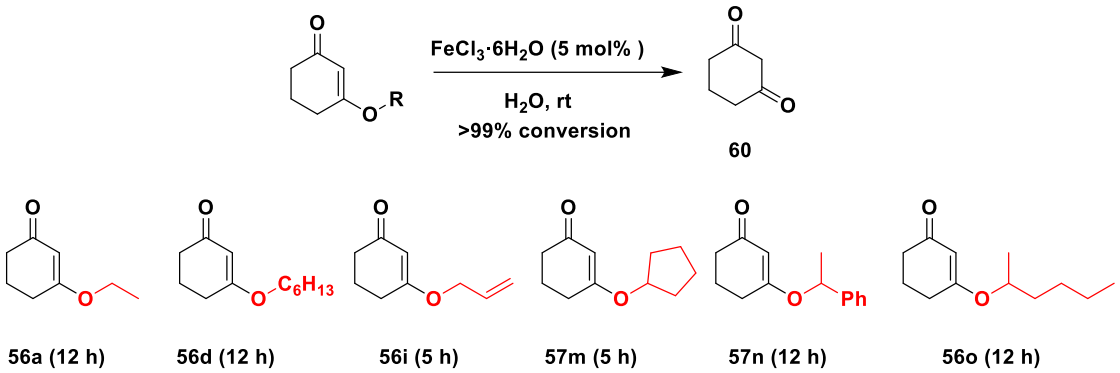


Figure 7. Recyclable Fe-Zeolite catalyzed transetherification under continuous flow

Fe-catalysed hydrolysis of the vinylogous ester:

Next, Fe-catalyzed reversible transformation such as water-mediated hydrolysis of vinylogous esters was investigated. To this direction, a mixture of the vinylogous ester **56a** (1 mmol) and 5 mol% of $FeCl_3{\cdot}6H_2O$ in water was stirred at room

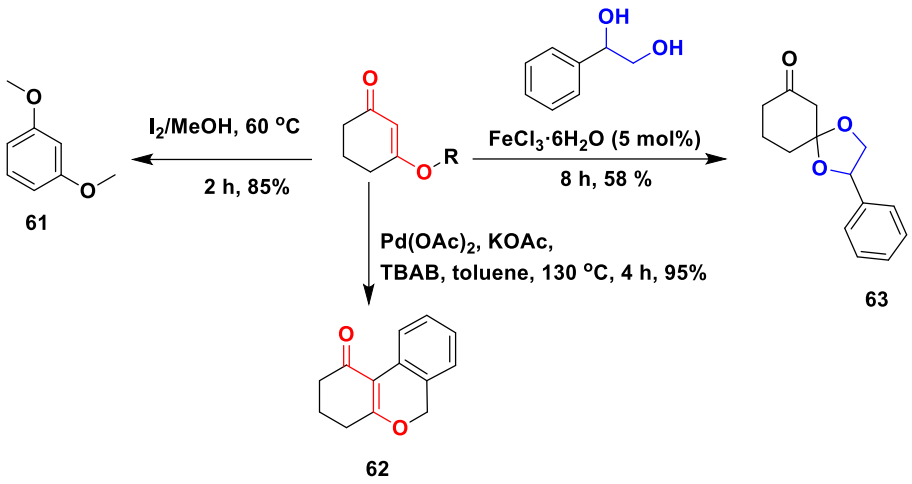
temperature. The reaction was monitored by TLC and observed the complete conversion of the vinylogous ester **56a**. Further, a series of vinylogous ester in the presence of Fe-catalyst was hydrolysed in water as a solvent, and the results are summarised in Scheme 18.



Scheme 18. Fe-catalysed hydrolysis of the vinylogous ester

3.3 Synthetic applications:

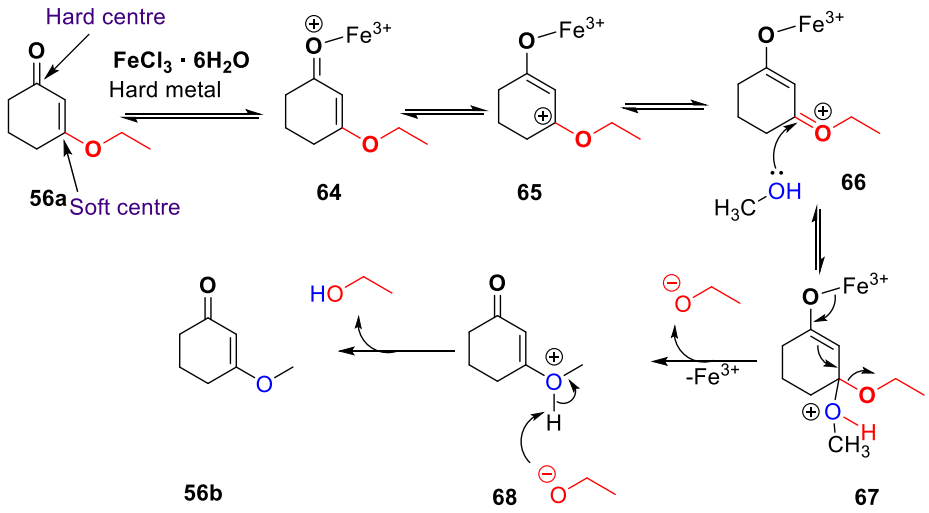
After successful syntheses of the vinylogous ester, we shift our attention to show the the synthetic application of vinylogous ester. The vinylogous ester **56p** was easily converted into 2,3,4,6-tetrahydro-1H-benzo[c]chromen-1-one **62a** *via* Pd-catalysed intramolecular Heck reaction to afford 95% yield. Furthermore, the reaction of **56a** with with I_2 in methanol at 60 °C to afford the corresponding aromatised 1,3-dimethoxybenzene **61** in 85% yield. Interestingly, the reaction of vinylogous ester **56a** and 1-phenylethane-1, 2-diol gives the spiro product 2-phenyl-1, 4-dioxaspiro[4.5]decan-7-one **63** in 58% yield *via* tandem transetherification and 1,4-addition with a conjugated ketone (Scheme 19).



Scheme 19. Synthetic applications of vinylogous esters

3.4 Mechanistic studies

From our experimental observation, a plausible mechanism was proposed for the Fe-catalysed transetherification of vinylogous ester. The C–O bond cleavage of a vinyl ether is known to occur in the presence of the metal catalyst or acid. In contrast to this, vinylogous ester C–O bond cleavage proceeds as shown in Scheme 20 due to the activation of the hard C═O centre which is in conjugation with the vinyl ether. Initially, hard Fe^{3+} coordinates to the hard C═O centre of the cyclic vinylogous ester **56a** to form the intermediate **64** which was confirmed by HRMS and IR. Mass spectra of the crude reaction mixture showed that the peak at m/z 197.0242 corresponds to the intermediate **64** (Figure 11). The IR spectra of the **56a** and $FeCl_3{\cdot}6H_2O$ mixture clearly shows that coordination of Iron to the carbonyl group, the is stretching frequency of carbonyl slowly disappearing in the IR spectra (Figure 9). Further analysis of IR spectra of reaction mixture (**56a**, $FeCl_3{\cdot}6H_2O$ and MeOH) shows decrease in the intensity of a free carbonyl peak, which indicates that C=O coordinated with Iron (III) (Figure 10). Furthermore, intermediate **64** is stabilised with resonance to generate the intermediates **65** and **66**. Finally, the addition of alcohol on oxonium species **66** affords the ketal intermediate **67** and keto-enol tautomerism assisted the elimination of ethanol from the intermediate **67** to gives intermediate **68**. Abstraction of hydrogen from oxonium ion **68** gives product **56b**.



Scheme 20. Plausible mechanism for the transetherification using Fe-catalyst

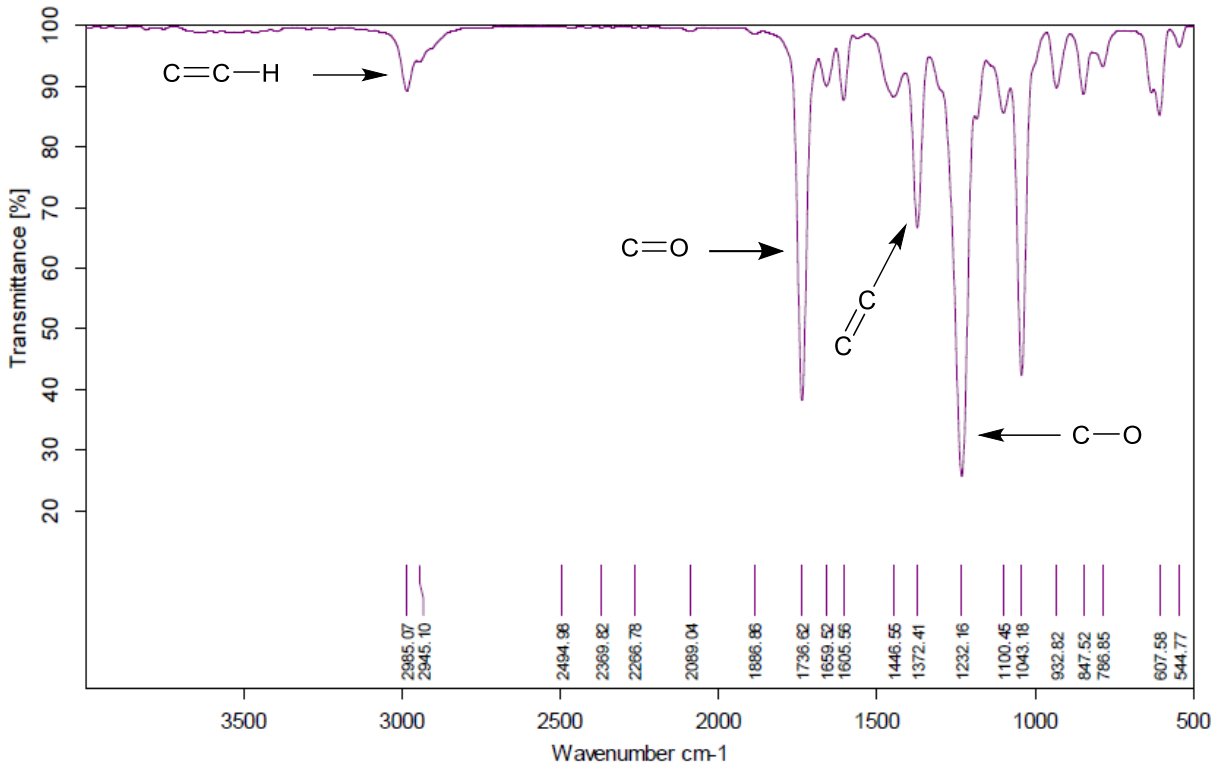


Figure 8. IR spectra of **56a** in DCM

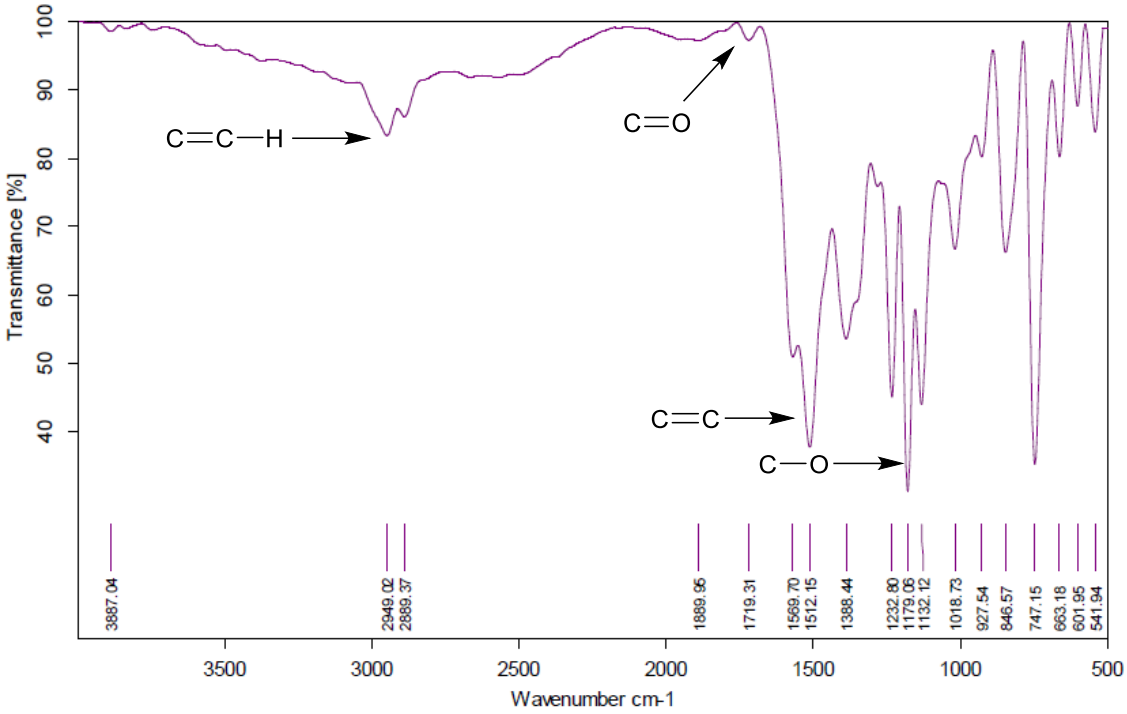


Figure 9. IR spectra **56a** and $FeCl_3 \cdot 6H_2O$ in DCM

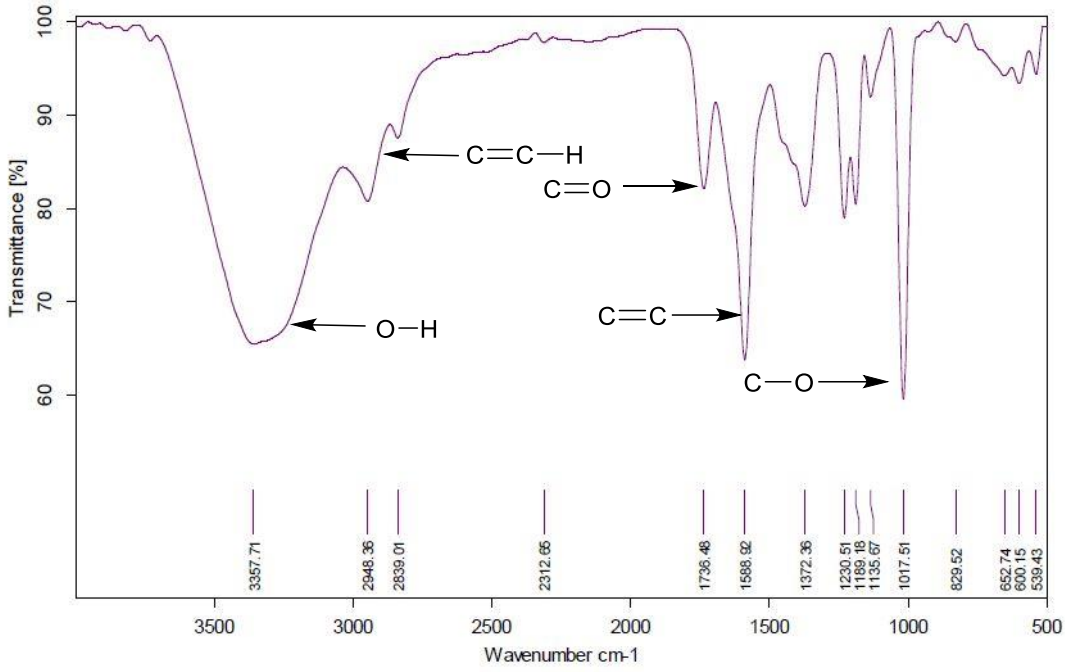


Figure 10. IR spectra of the reaction mixture (**56a**, $FeCl_3 \cdot 6H_2O$, MeOH)

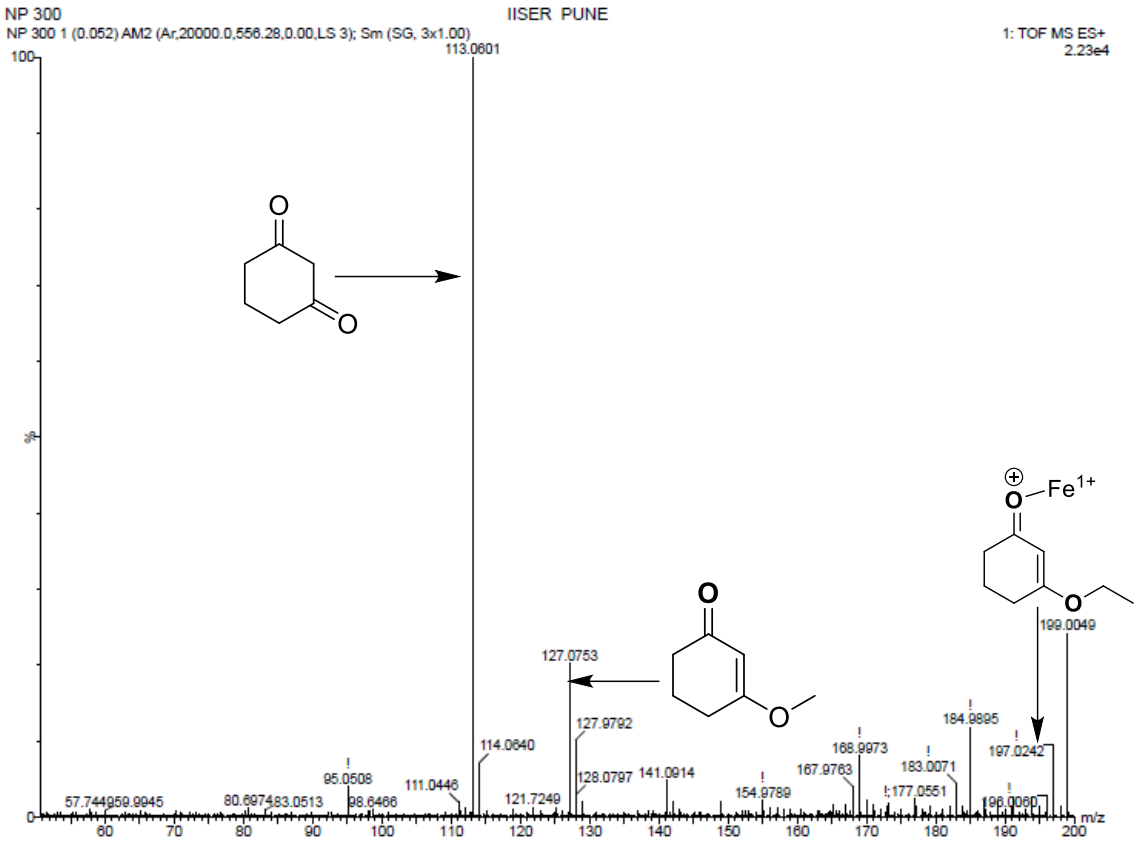


Figure 11a. HRMS of reaction mixture (**56a**, $FeCl_3 \cdot 6H_2O$, MeOH)

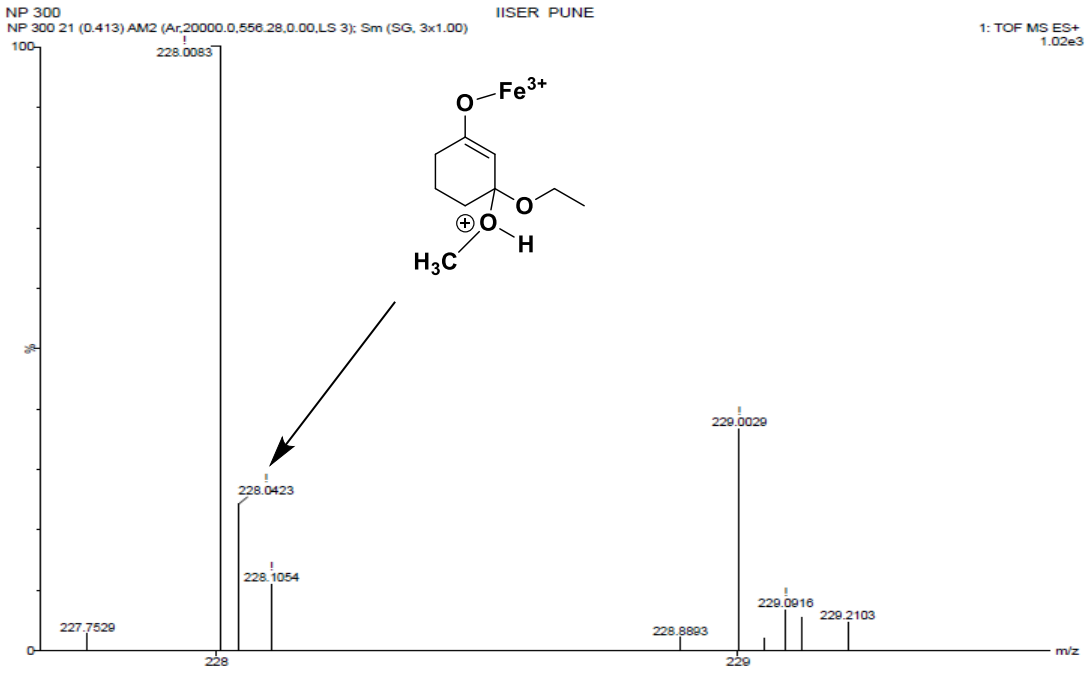


Figure 11b. HRMS of reaction mixture (**56a**, $FeCl_3 \cdot 6H_2O$, MeOH)

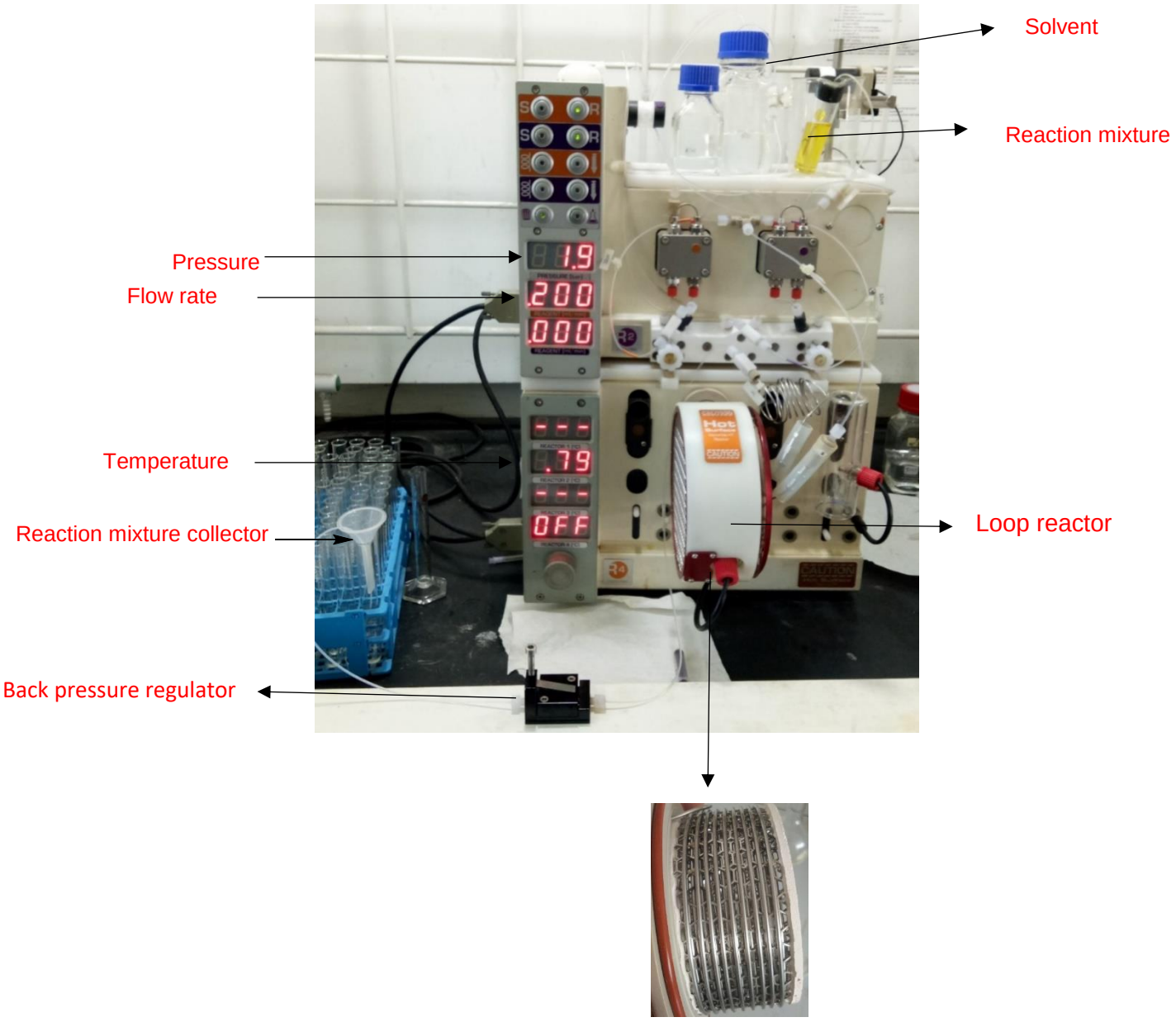


Figure 12. The full setup for vapourtec R-series reactor.

Spectras

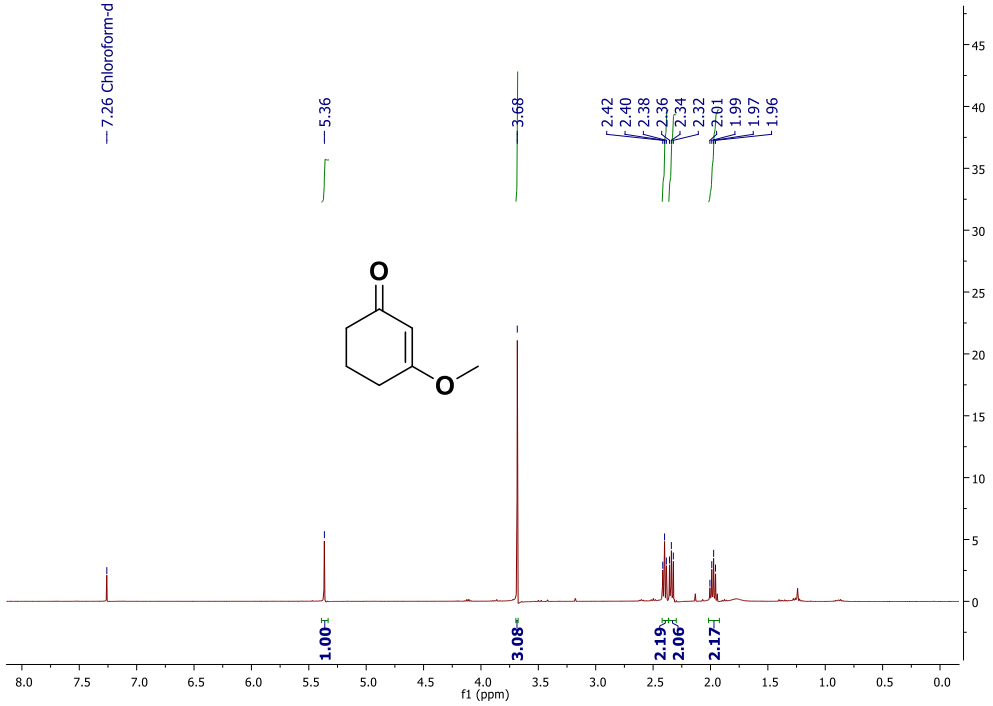


Figure 13. ^{1}H NMR of Compound **56b**

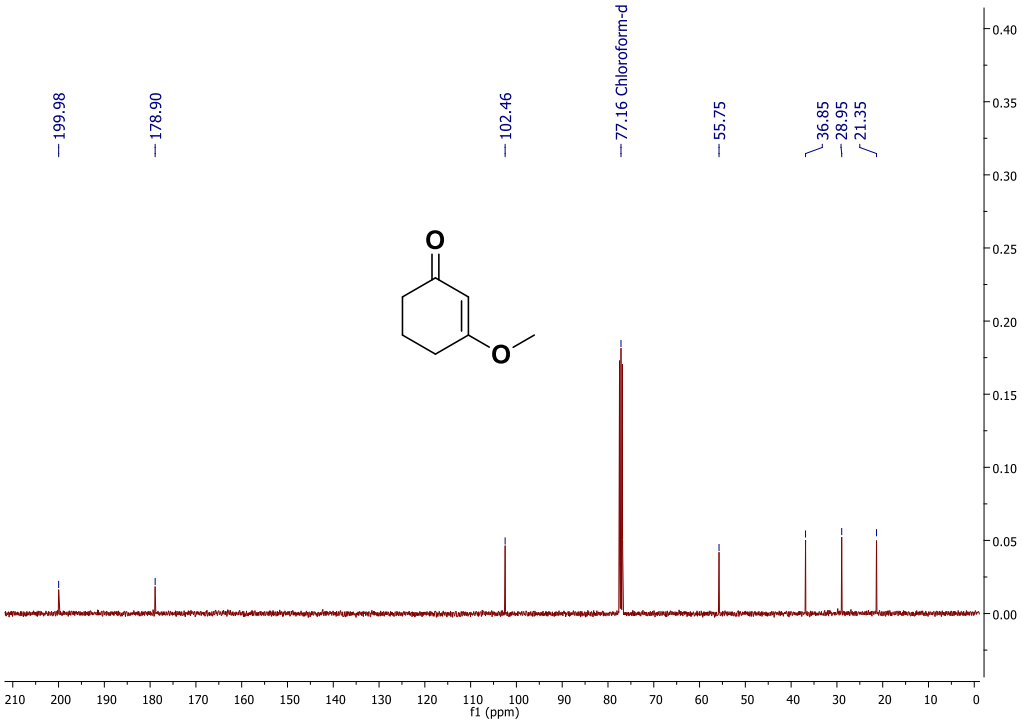


Figure 14. ^{13}C NMR of Compound **56b**

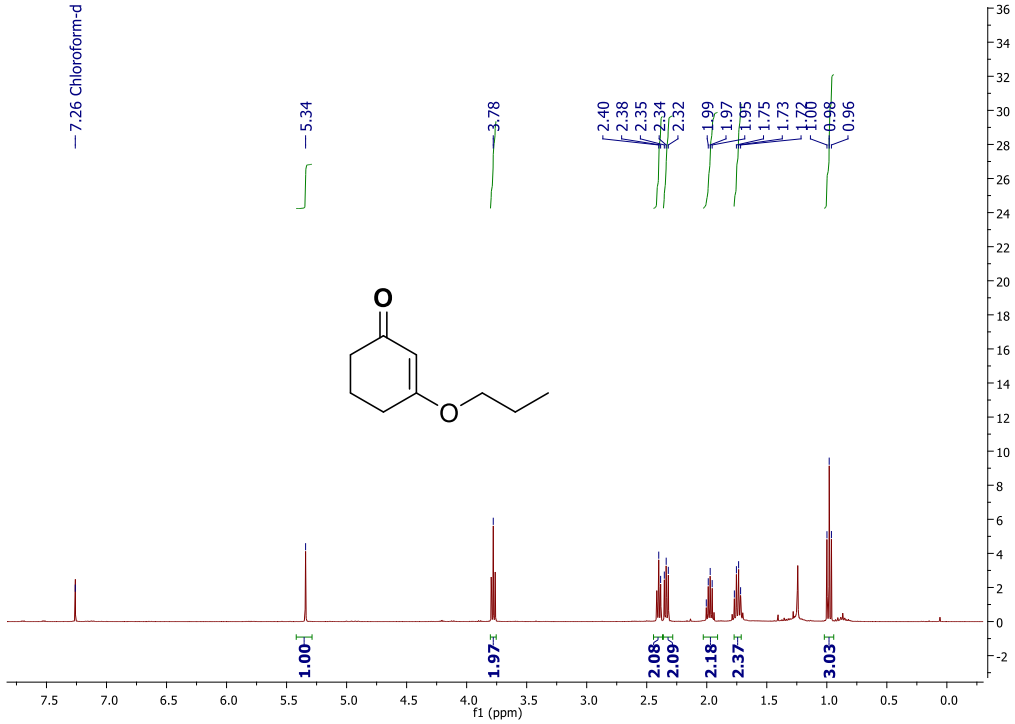


Figure 15. ^{1}H NMR of Compound **56c**

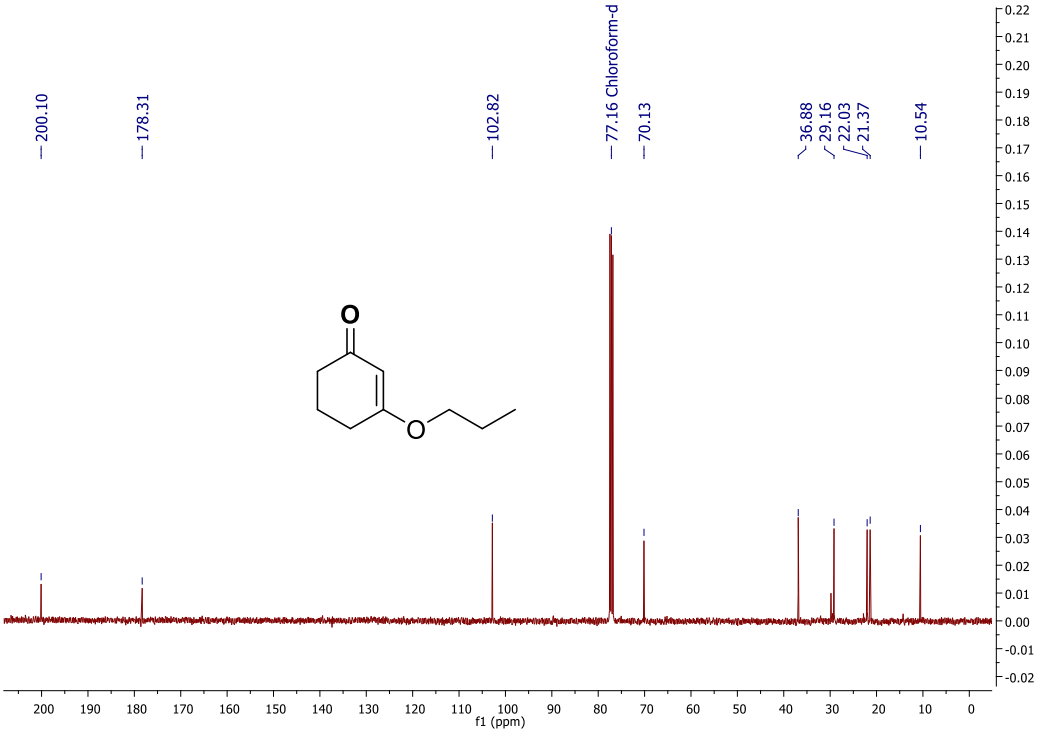


Figure 16. ^{13}C NMR of Compound **56c**

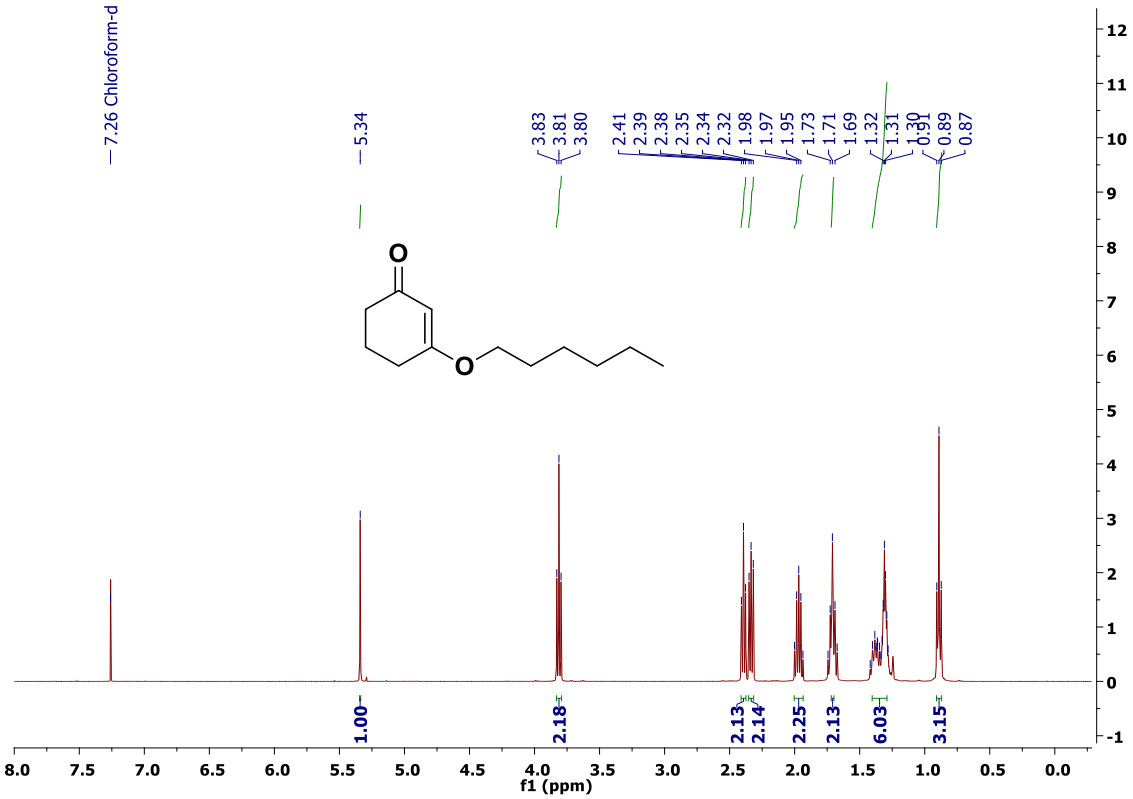


Figure 17. ^{1}H NMR of Compound **56d**

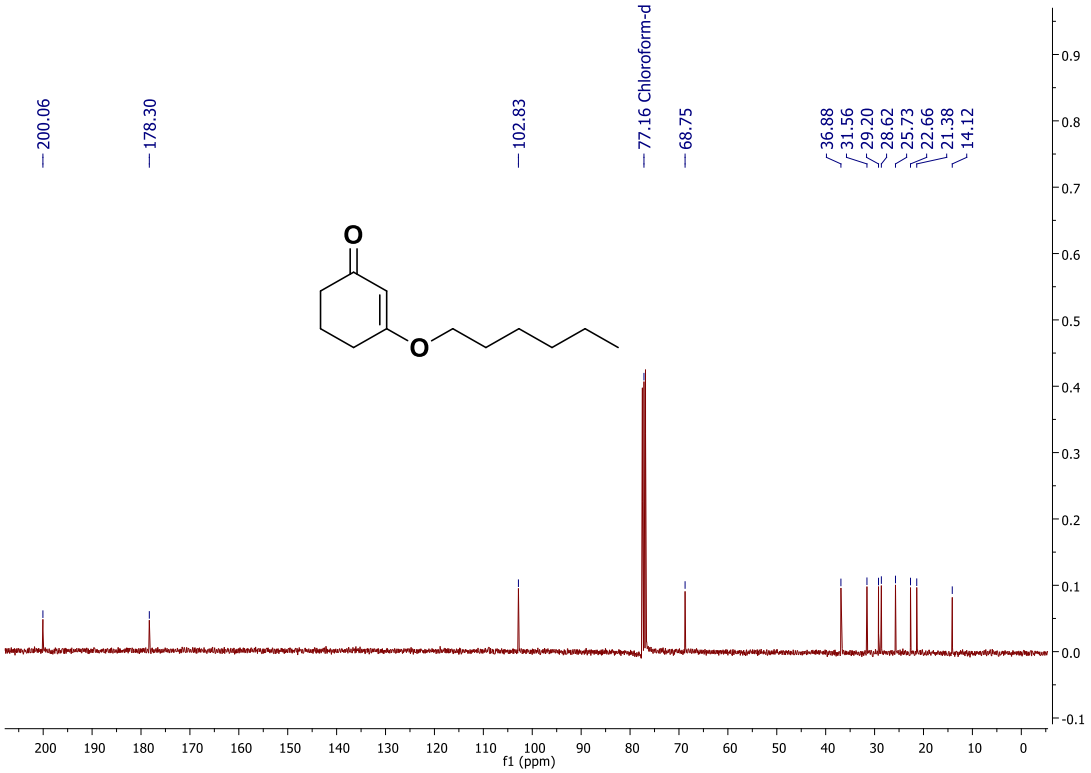


Figure 18. ^{13}C NMR of Compound **56d**

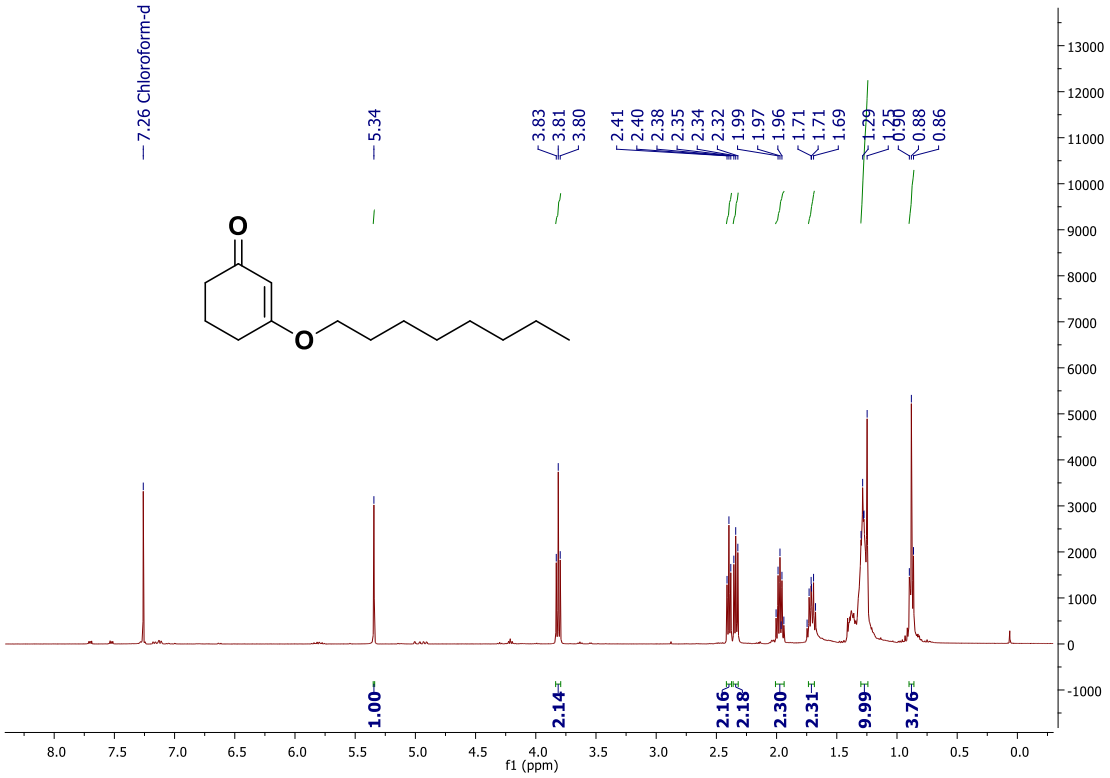


Figure 19. ^{1}H NMR of Compound **56e**

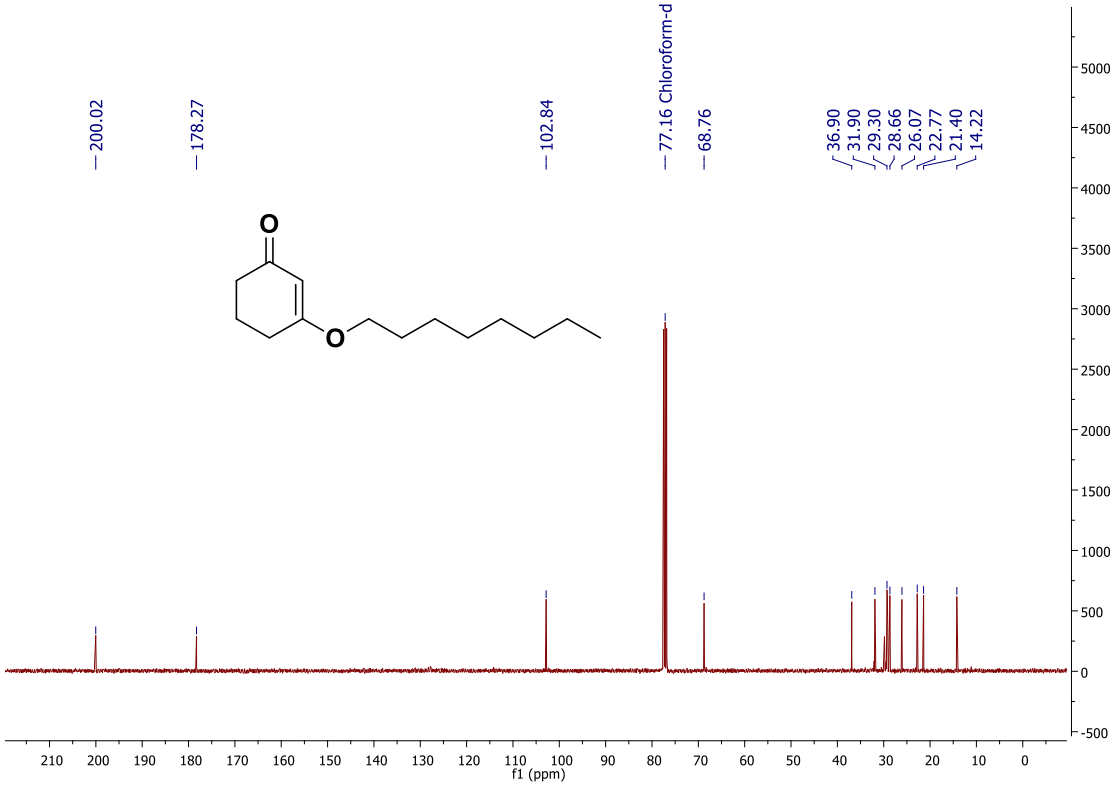


Figure 20. ^{13}C NMR of Compound **56e**

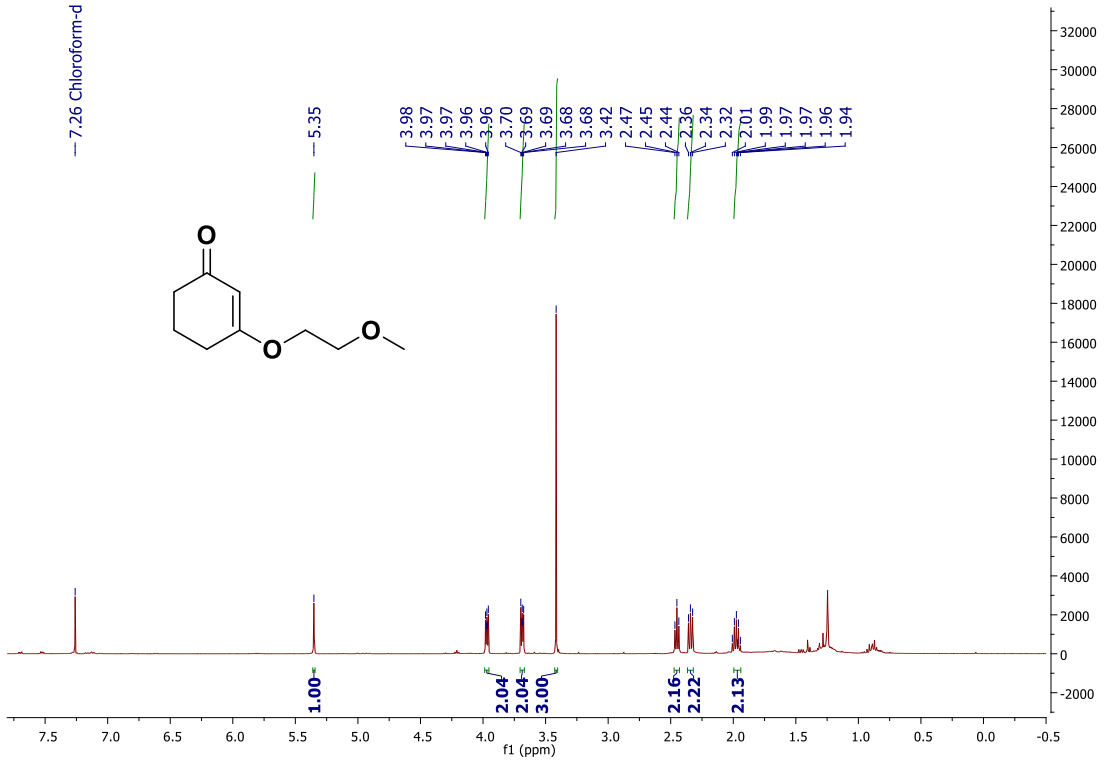


Figure 21. ^{1}H NMR of Compound **56f**

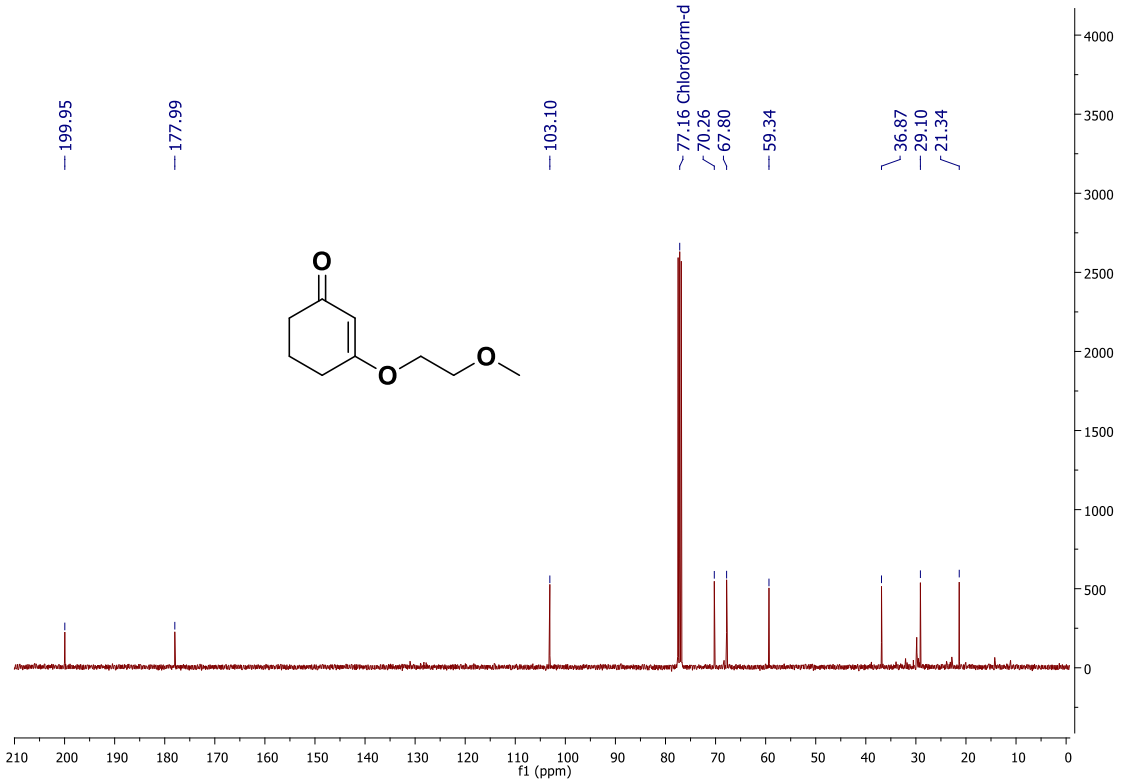


Figure 22. ^{13}C NMR of Compound **56f**

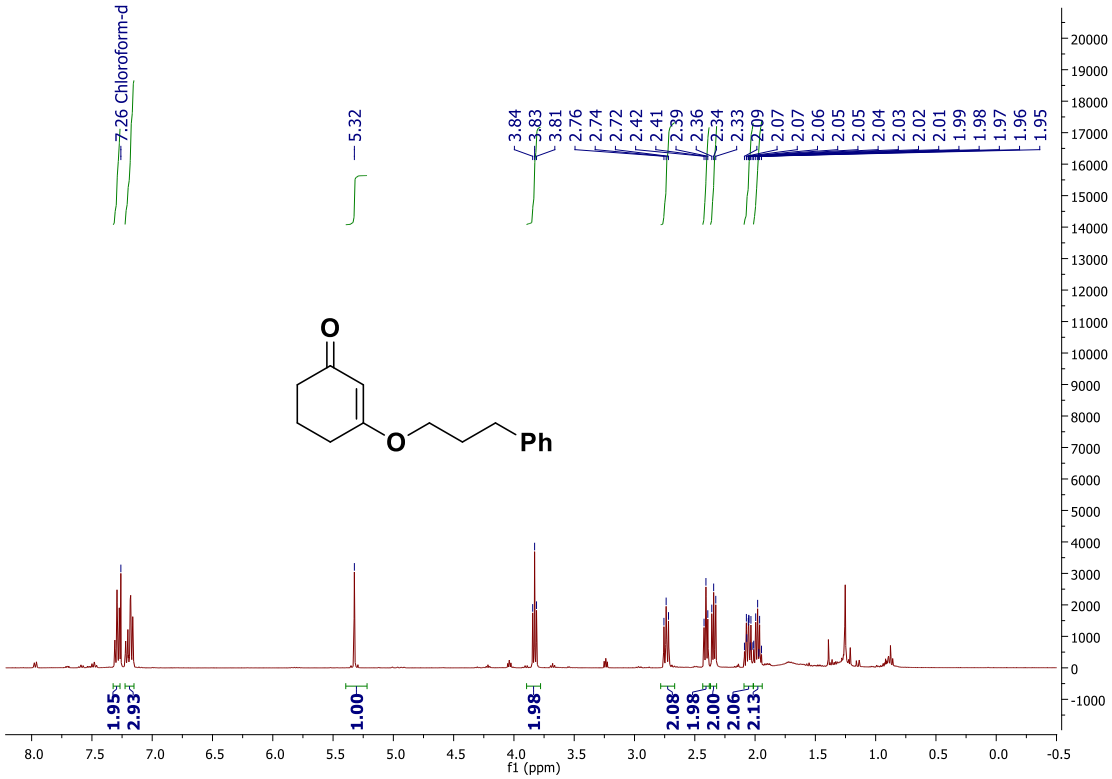


Figure 23. ^{1}H NMR of Compound **56g**

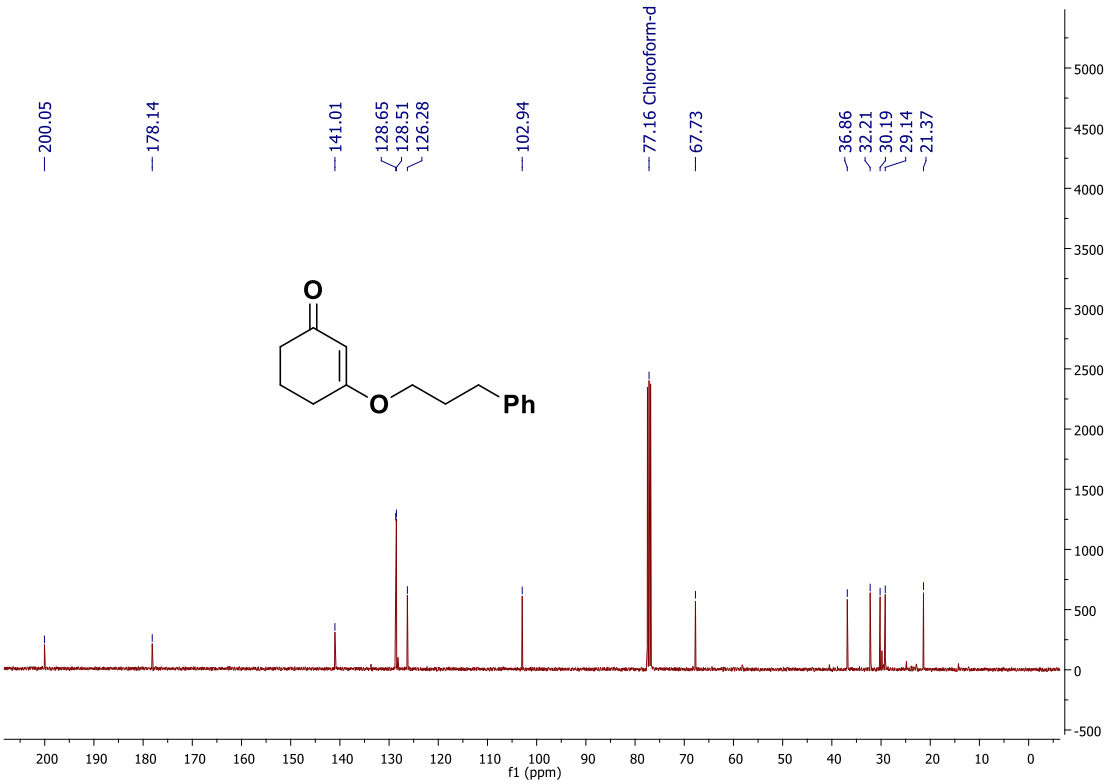


Figure 24. ^{13}C NMR of Compound **56g**

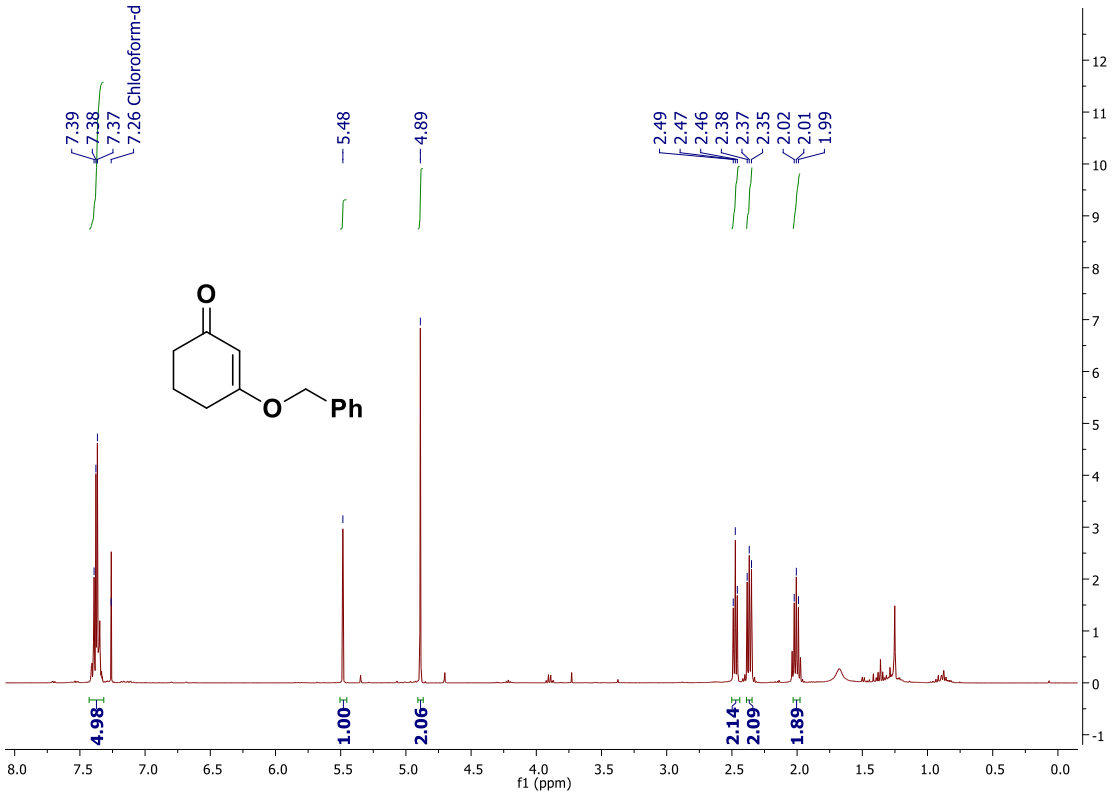


Figure 25. ^{1}H NMR of Compound **56h**

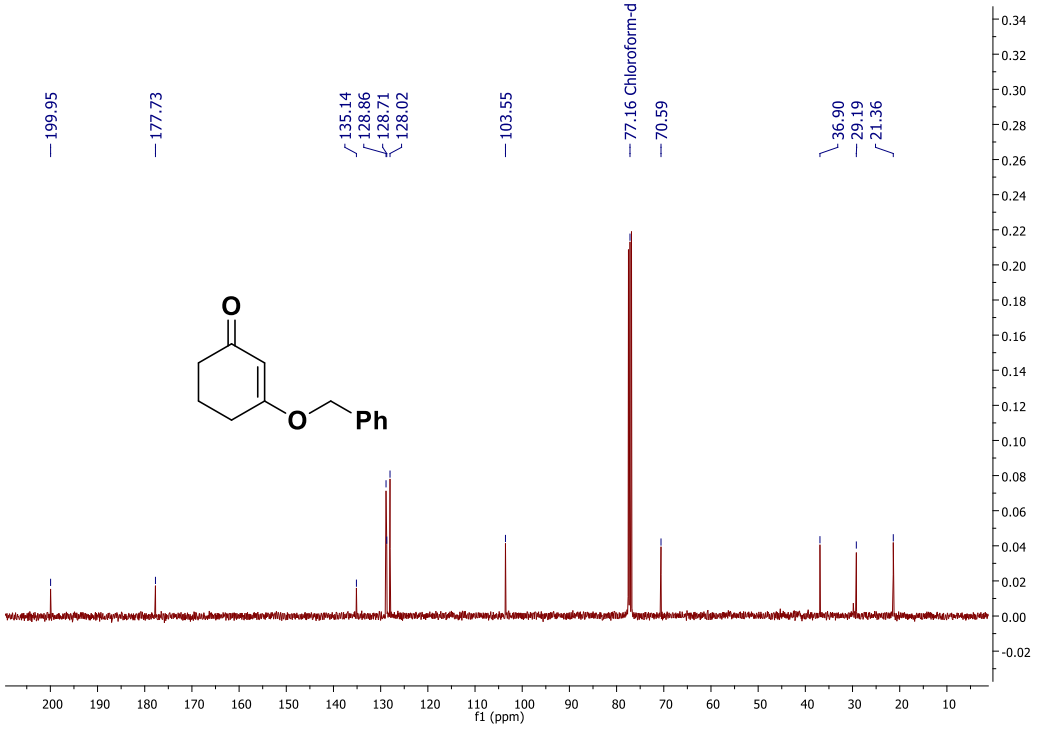


Figure 26. ^{13}C NMR of Compound **56h**

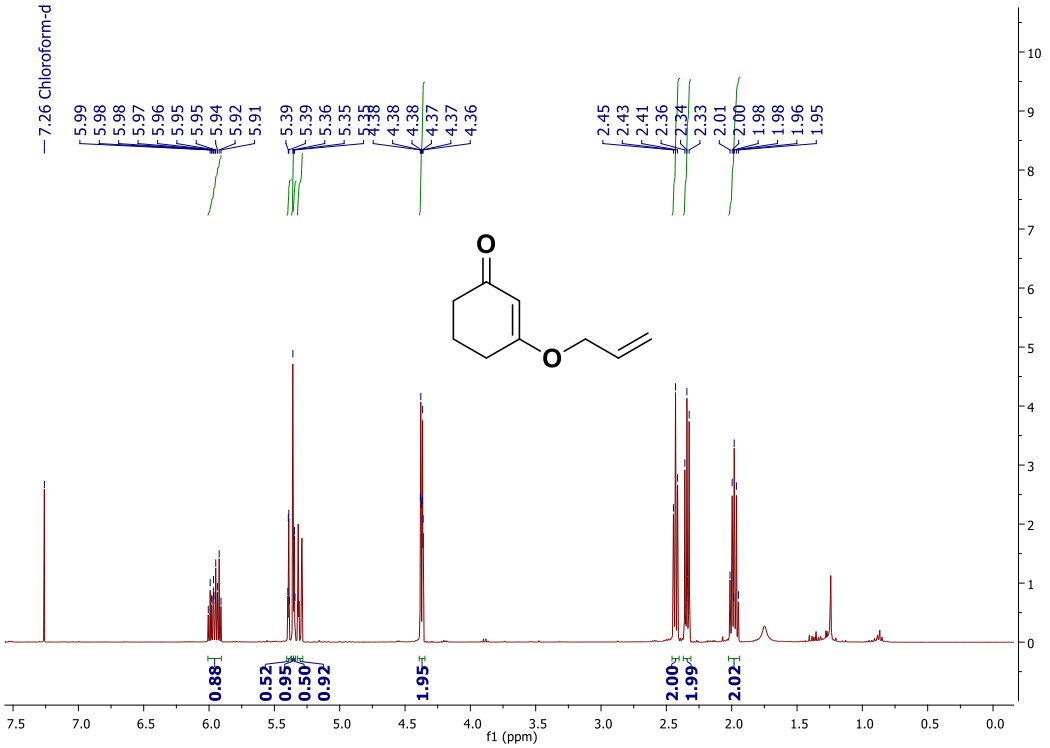


Figure 27. ^{1}H NMR of Compound **56i**

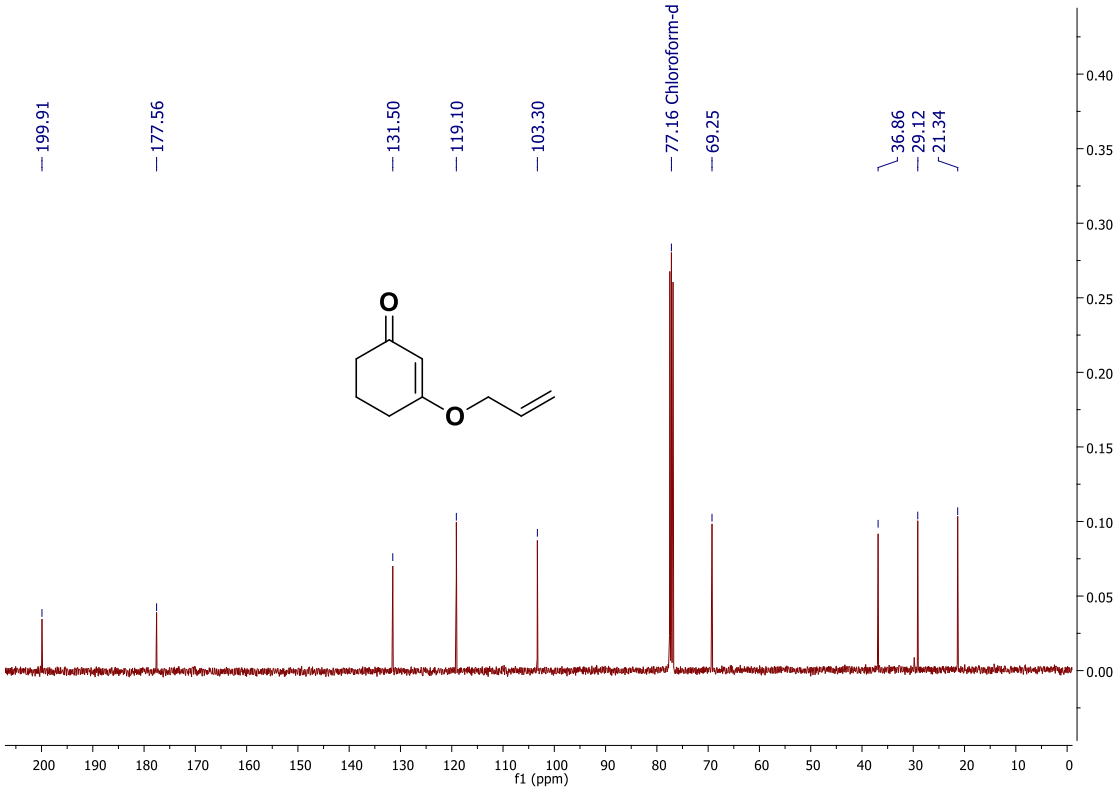


Figure 28. ^{13}C NMR of Compound **56i**

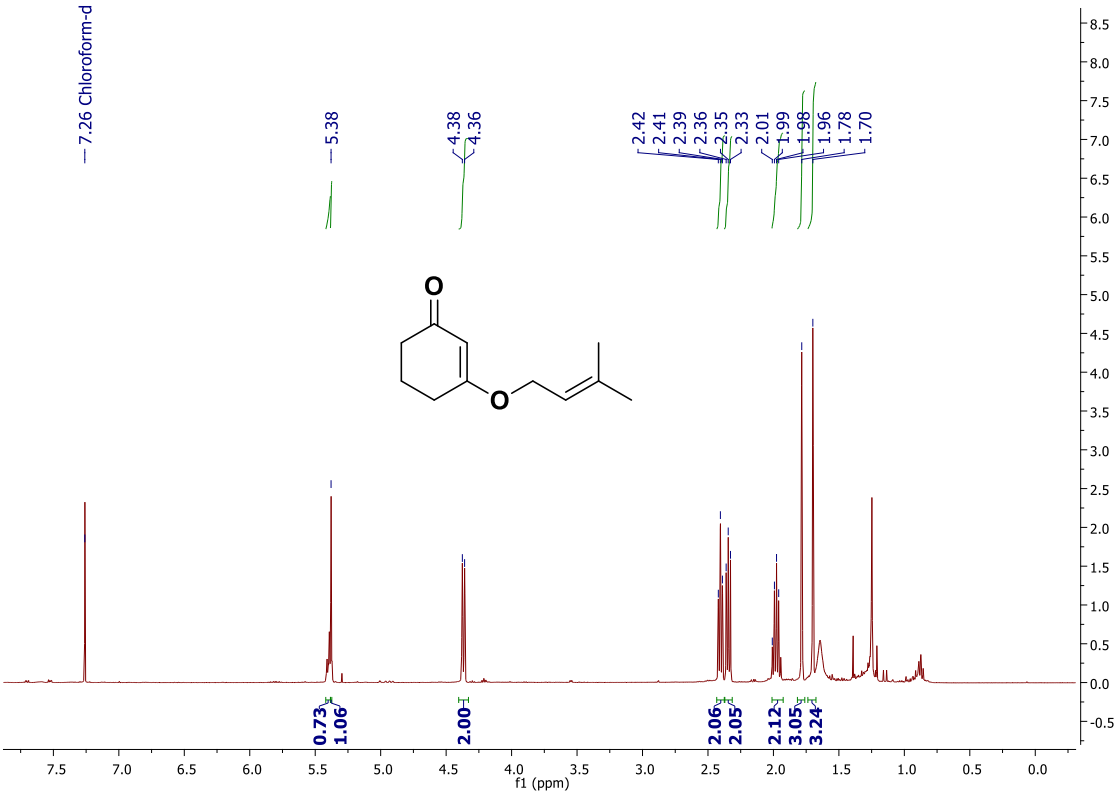


Figure 29. ^{1}H NMR of Compound **56j**

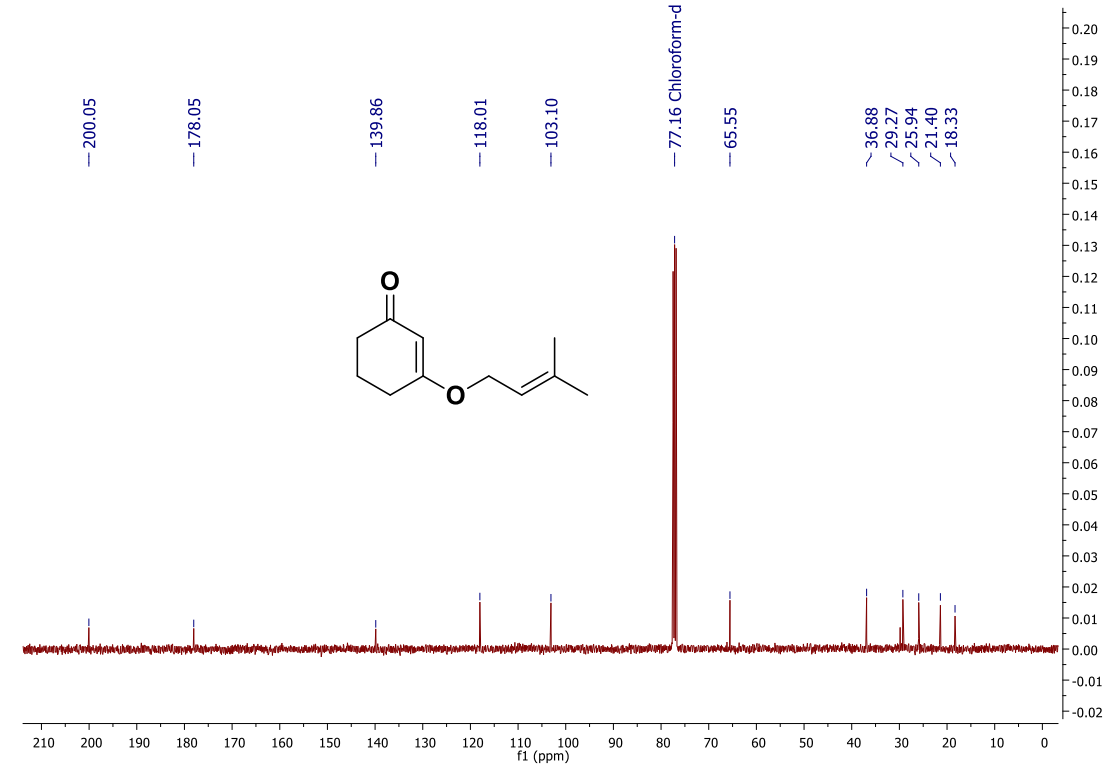


Figure 30. ^{13}C NMR of Compound **56j**

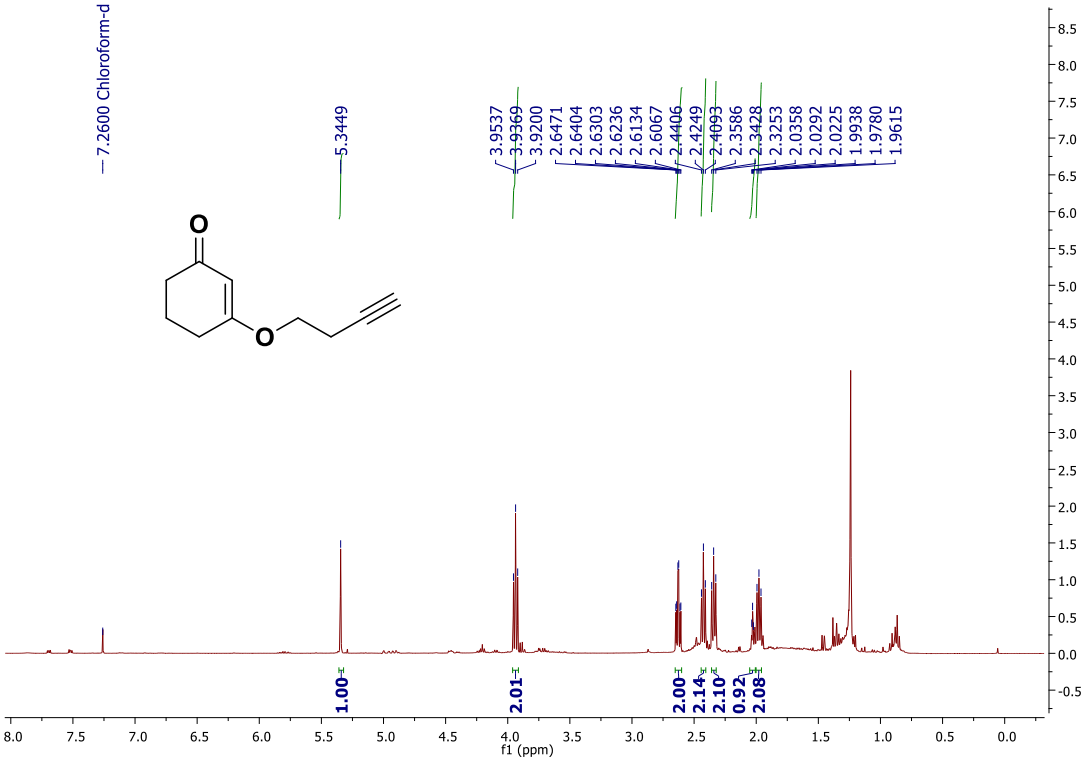


Figure 31. ^{1}H NMR of Compound **56k**

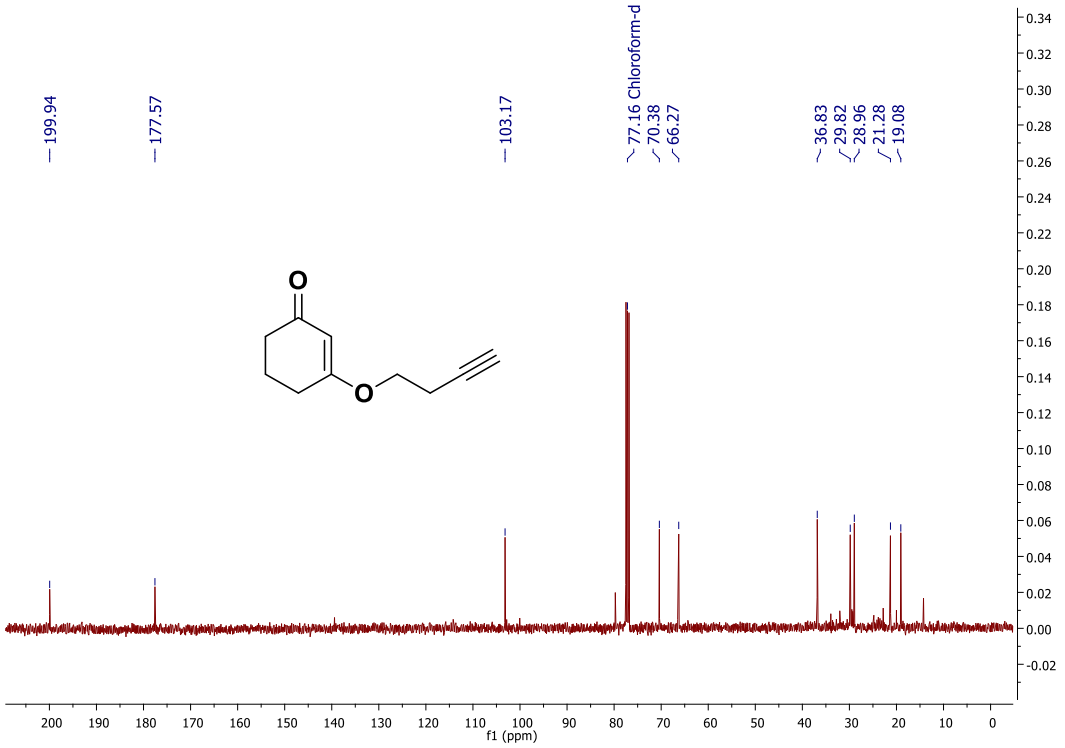


Figure 32. ^{13}C NMR of Compound **56k**

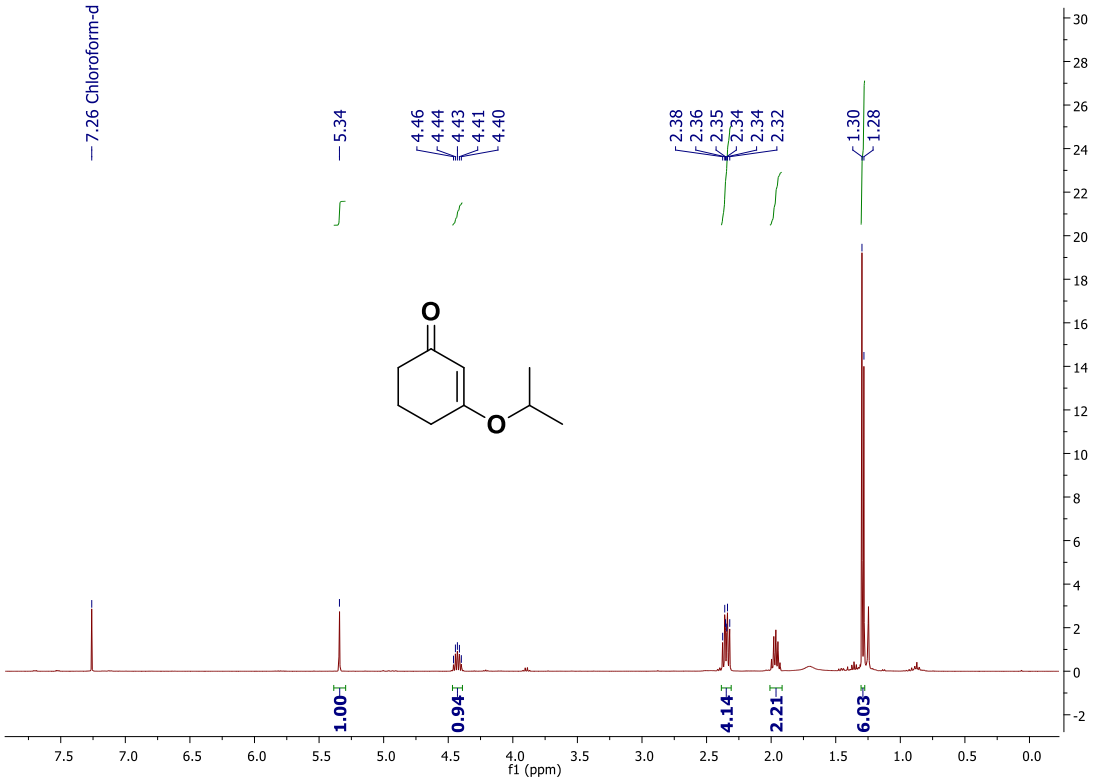


Figure 33. ^{1}H NMR of Compound **56l**

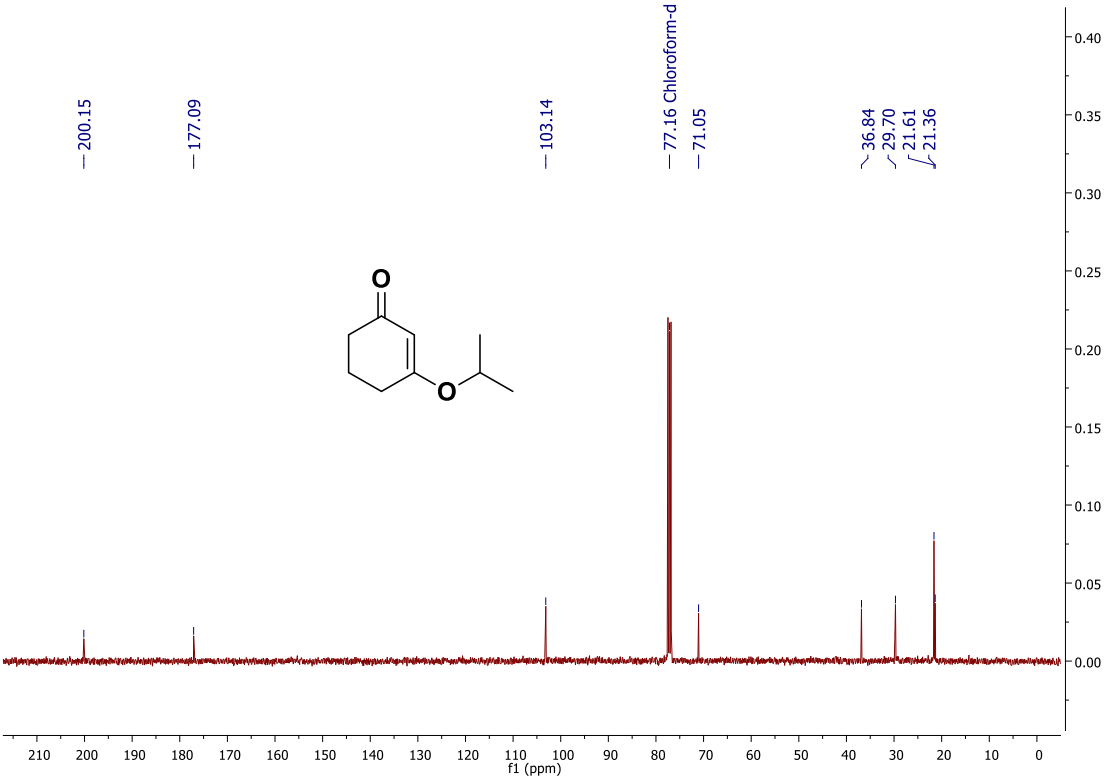


Figure 34. ^{13}C NMR of Compound **56l**

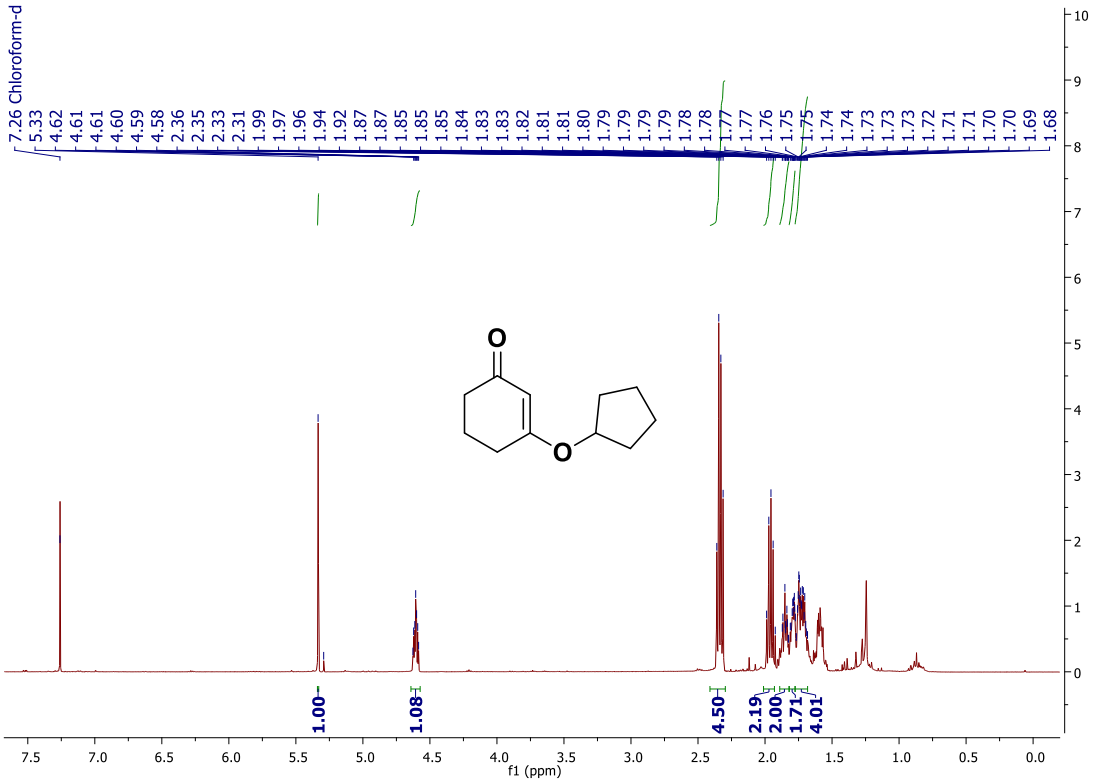


Figure 35. ^{1}H NMR of Compound **56m**

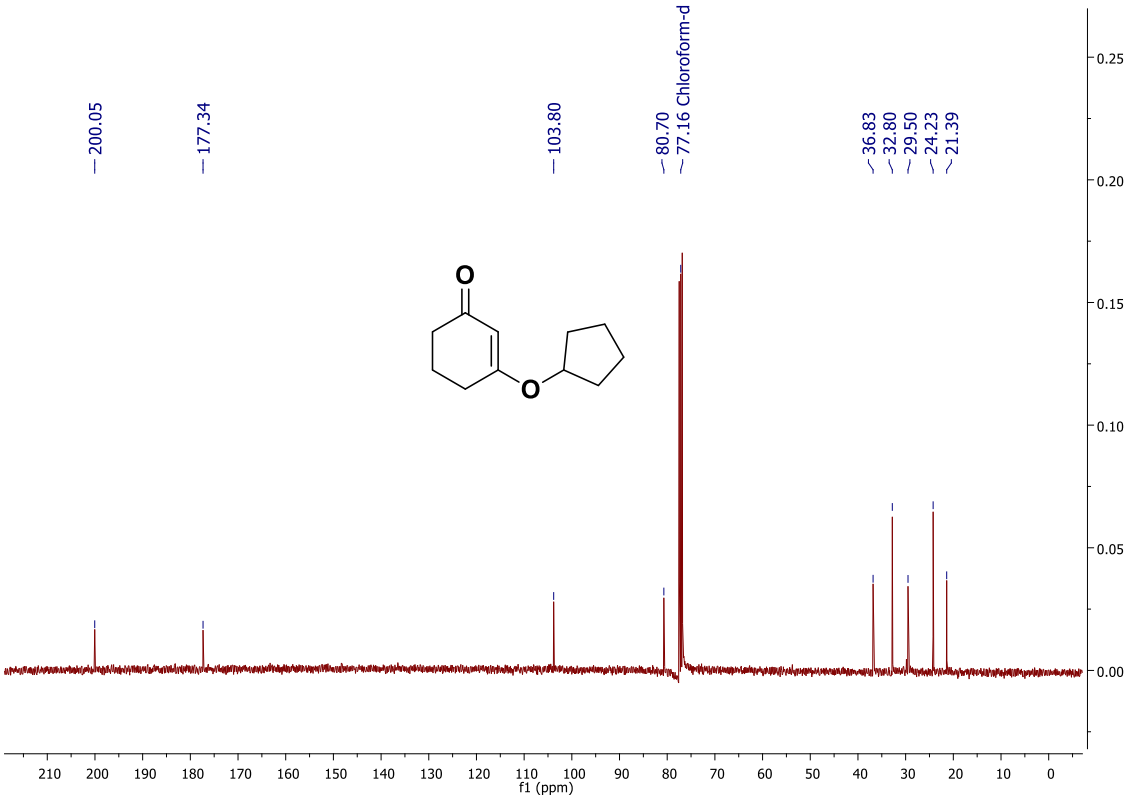


Figure 36. ^{13}C NMR of Compound **56m**

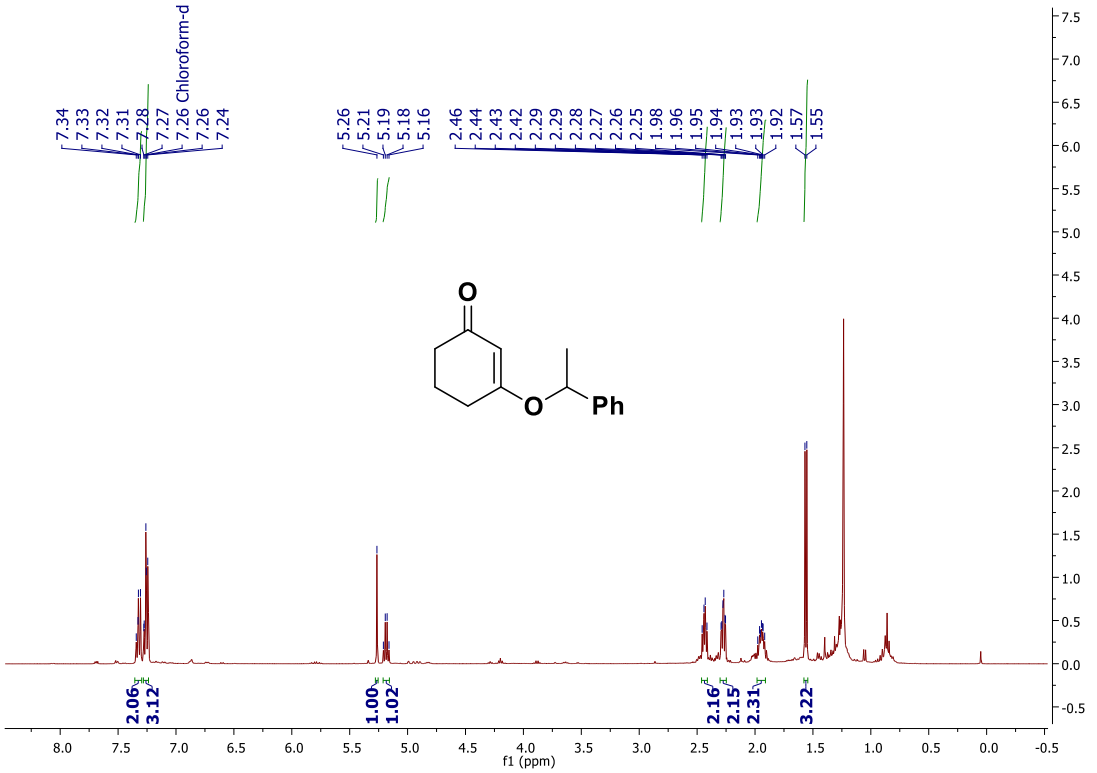


Figure 37. ^{1}H NMR of Compound **56n**

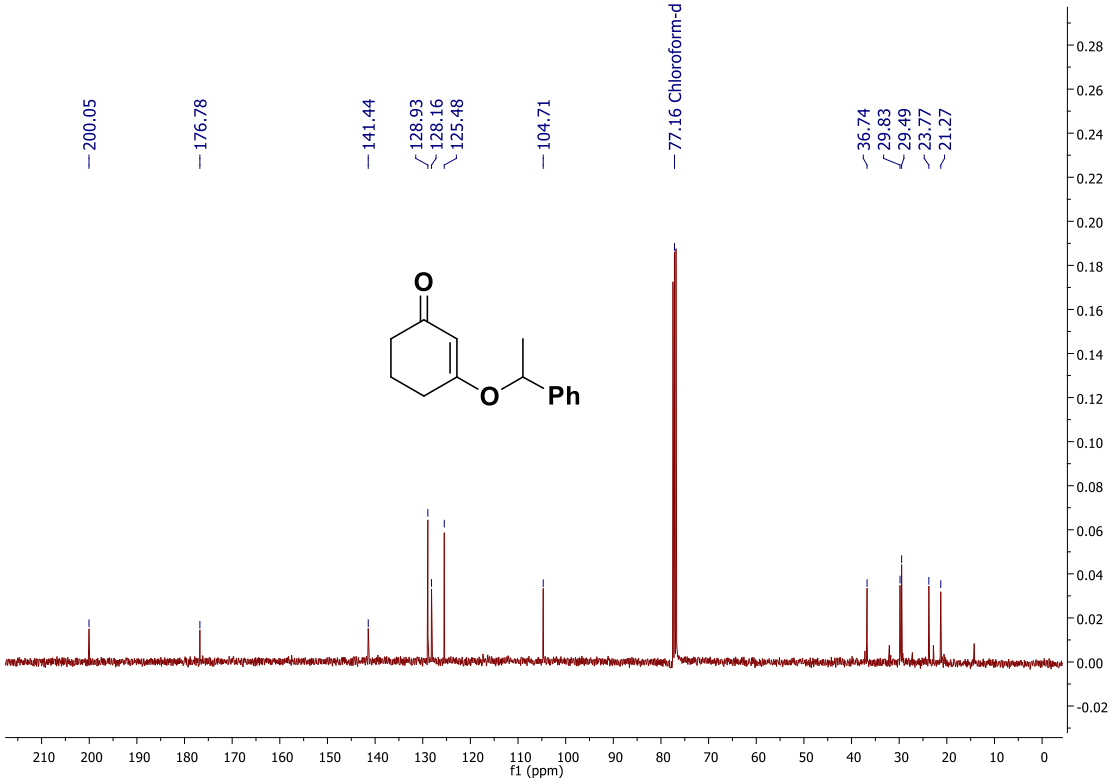


Figure 38. ^{13}C NMR of Compound **56n**

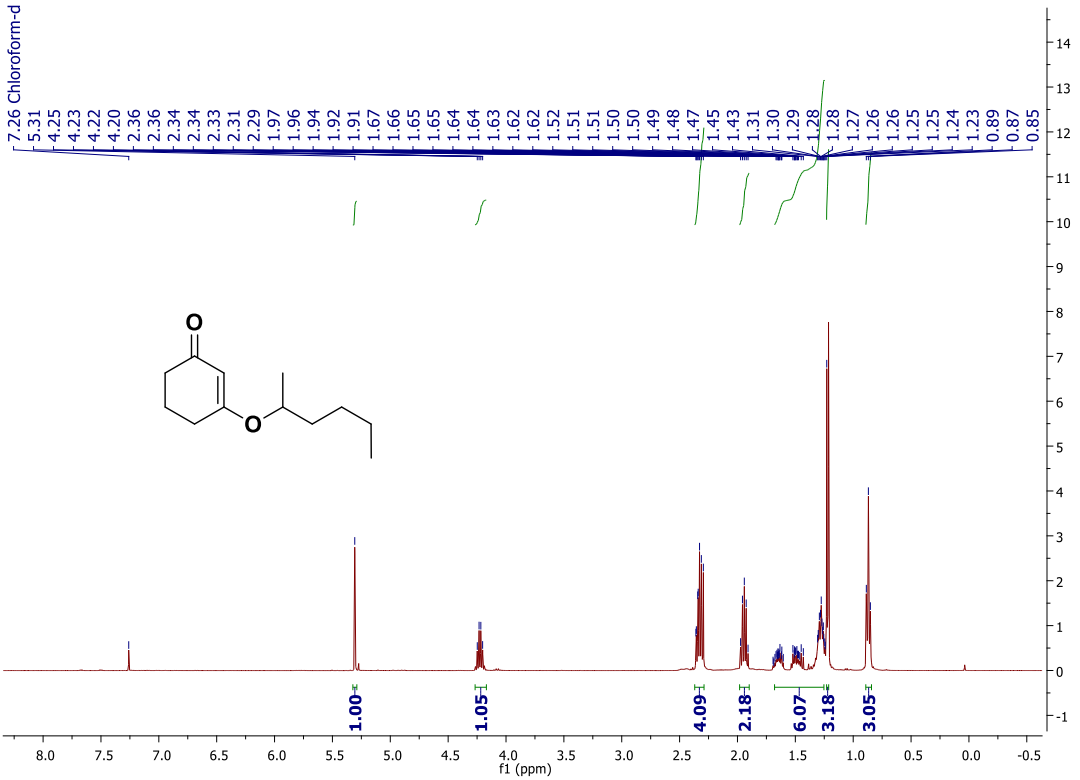


Figure 39. ^{1}H NMR of Compound **56o**

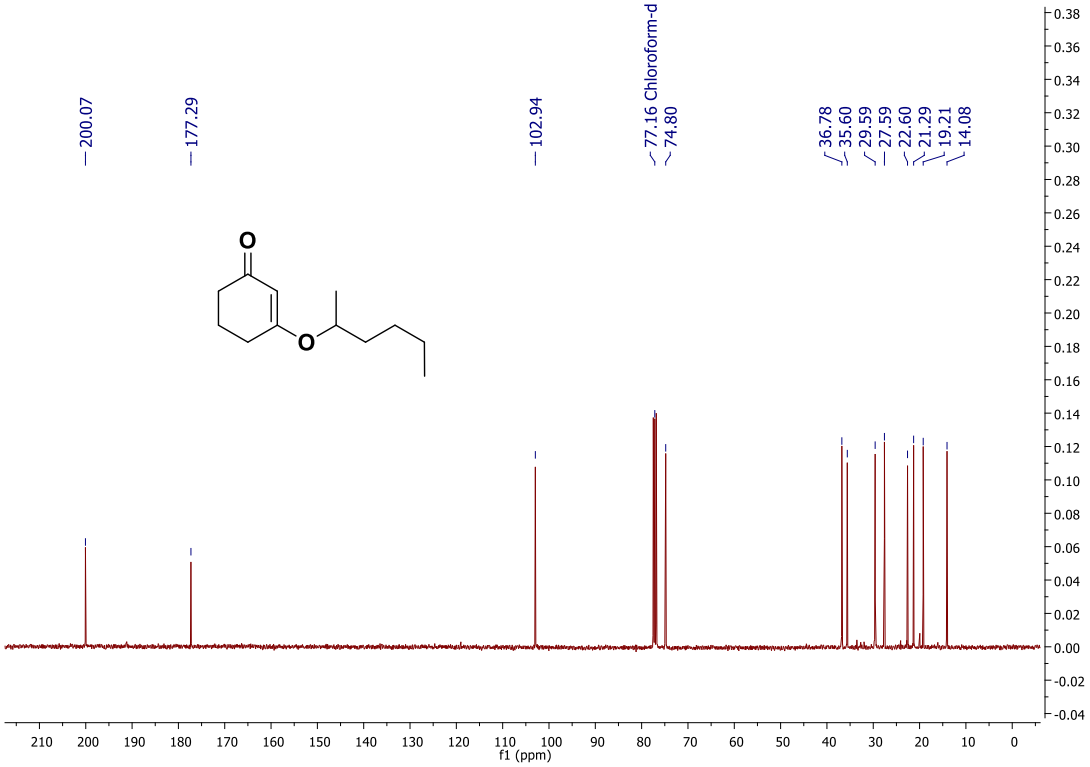


Figure 40. ^{13}C NMR of Compound **56o**

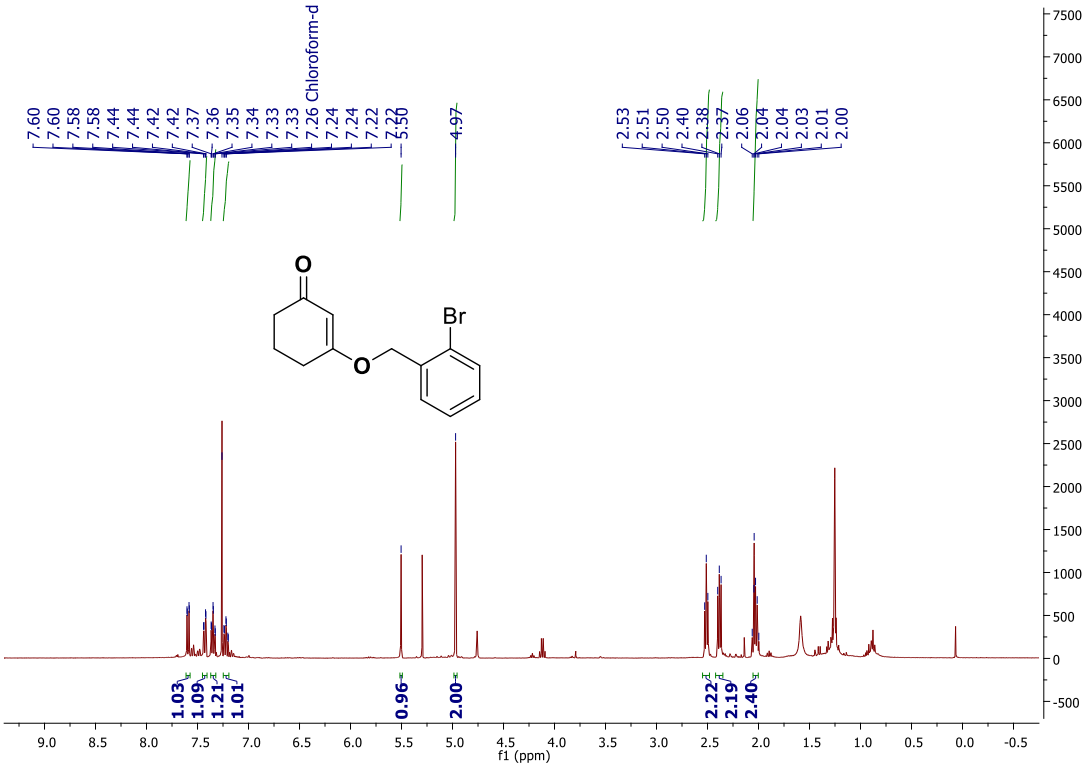


Figure 41. ^{1}H NMR of Compound **56p**

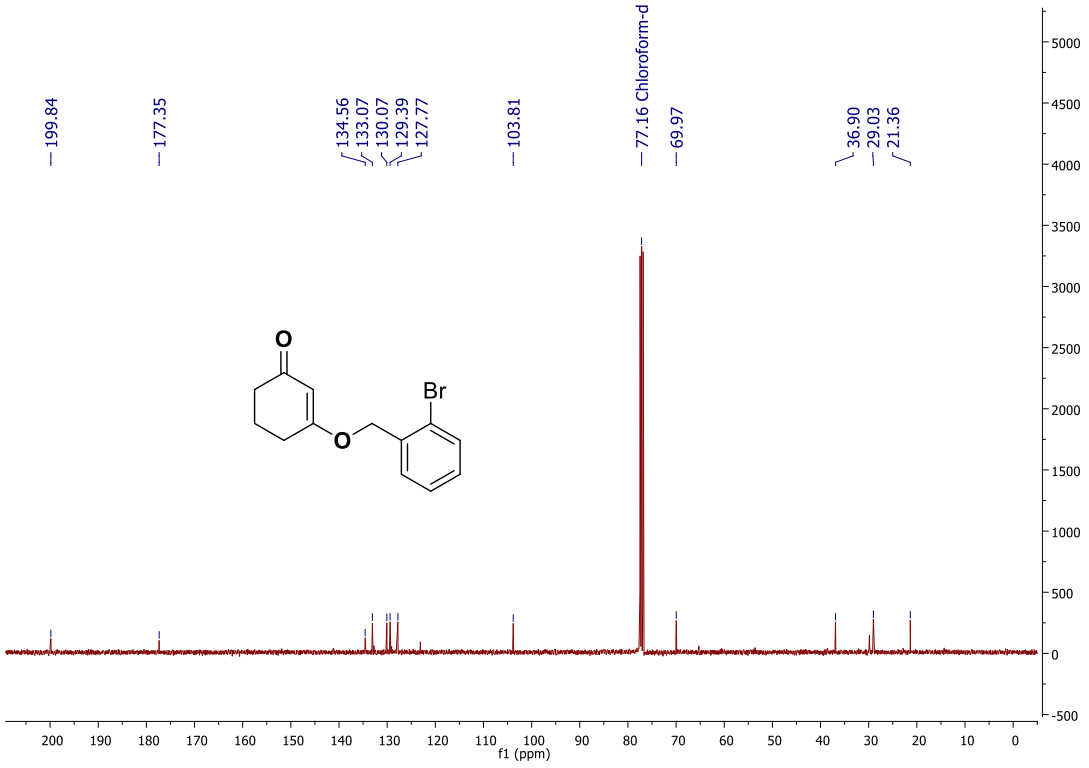


Figure 42. ^{13}C NMR of Compound **56p**

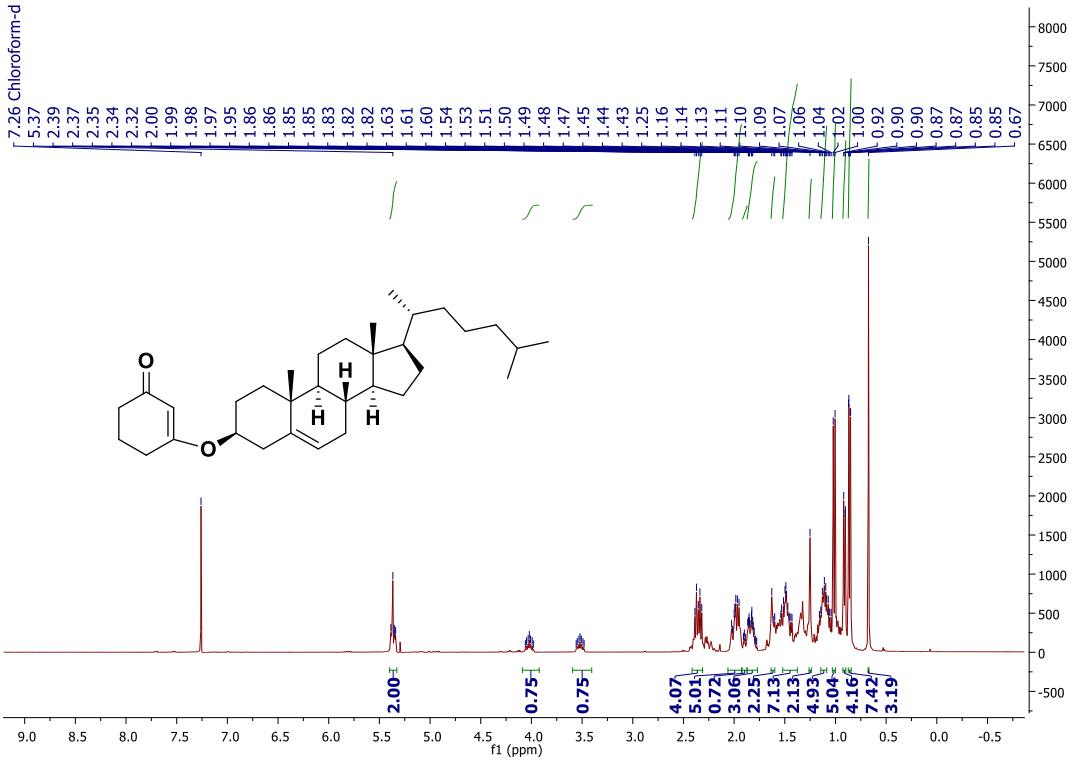


Figure 43. ^{1}H NMR of Compound **56q**

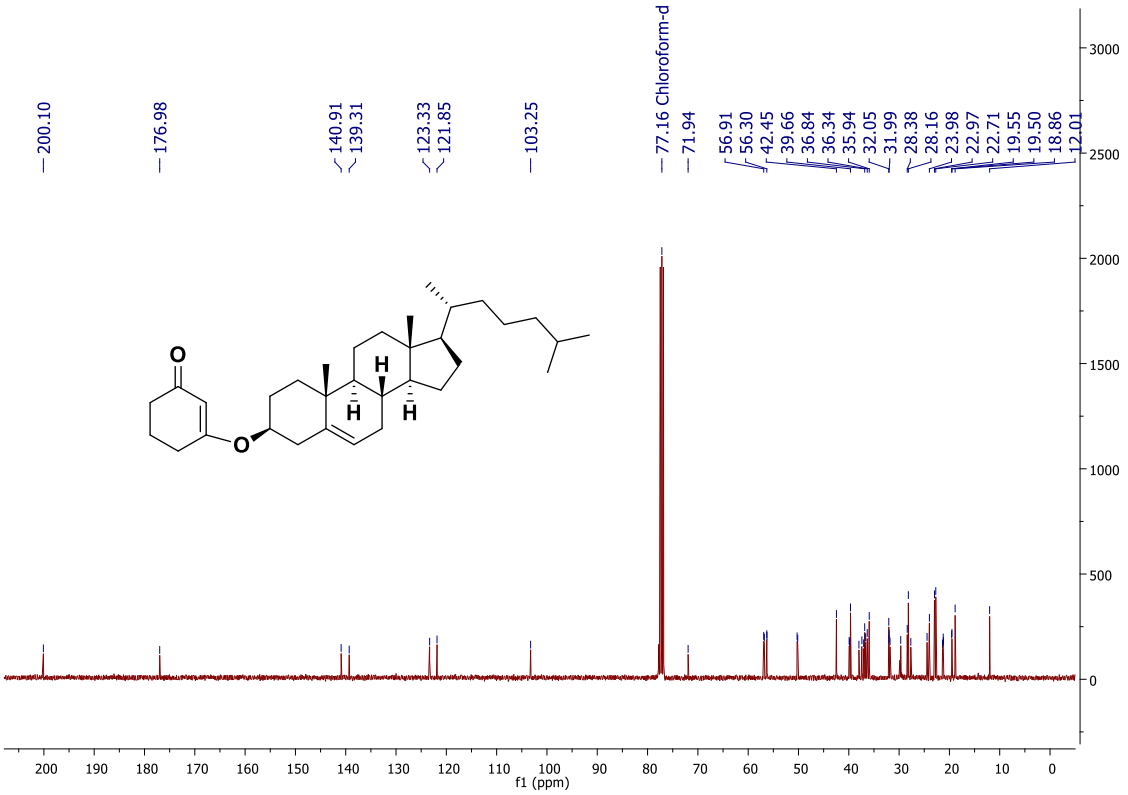


Figure 44. ^{13}C NMR of Compound **56q**

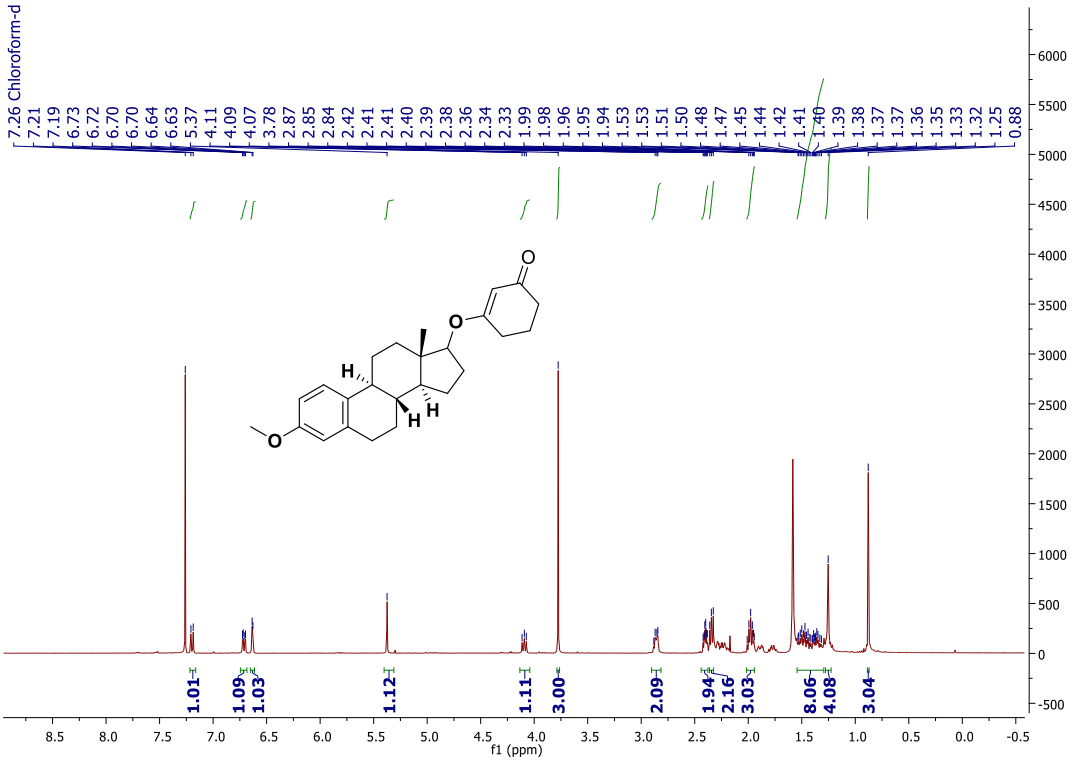


Figure 45. ^{1}H NMR of Compound **56r**

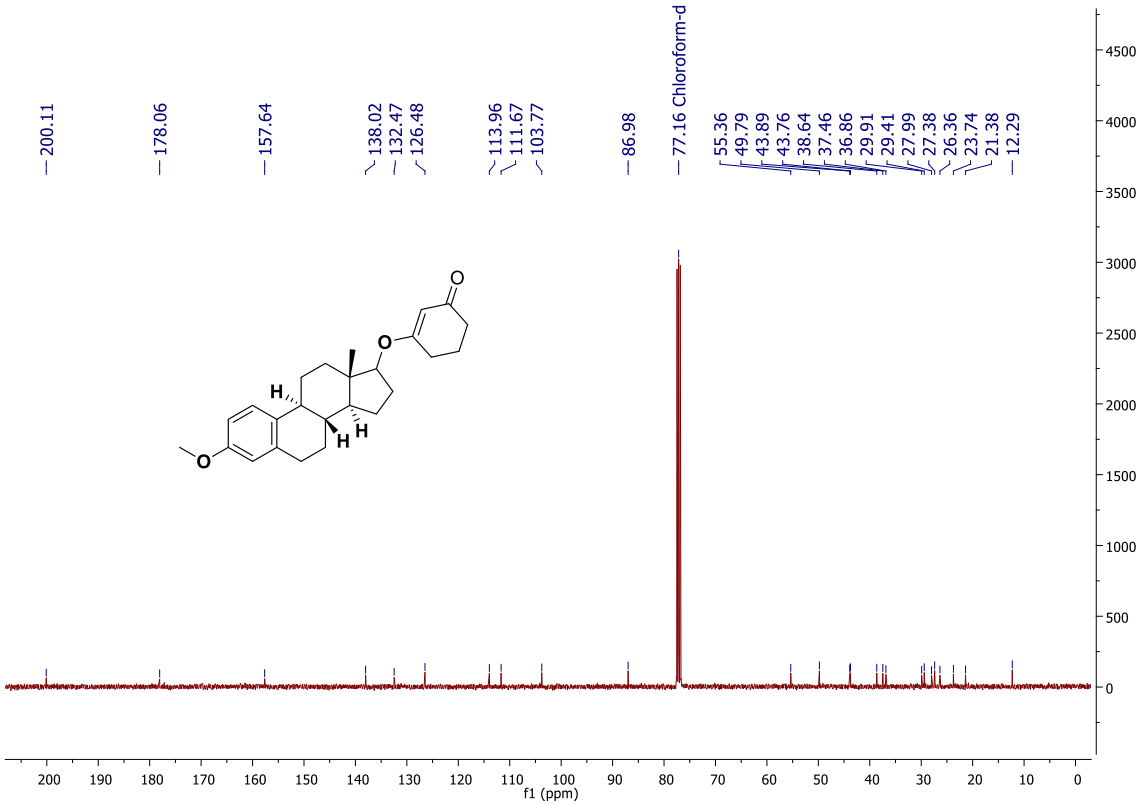


Figure 46. ^{13}C NMR of Compound **56r**

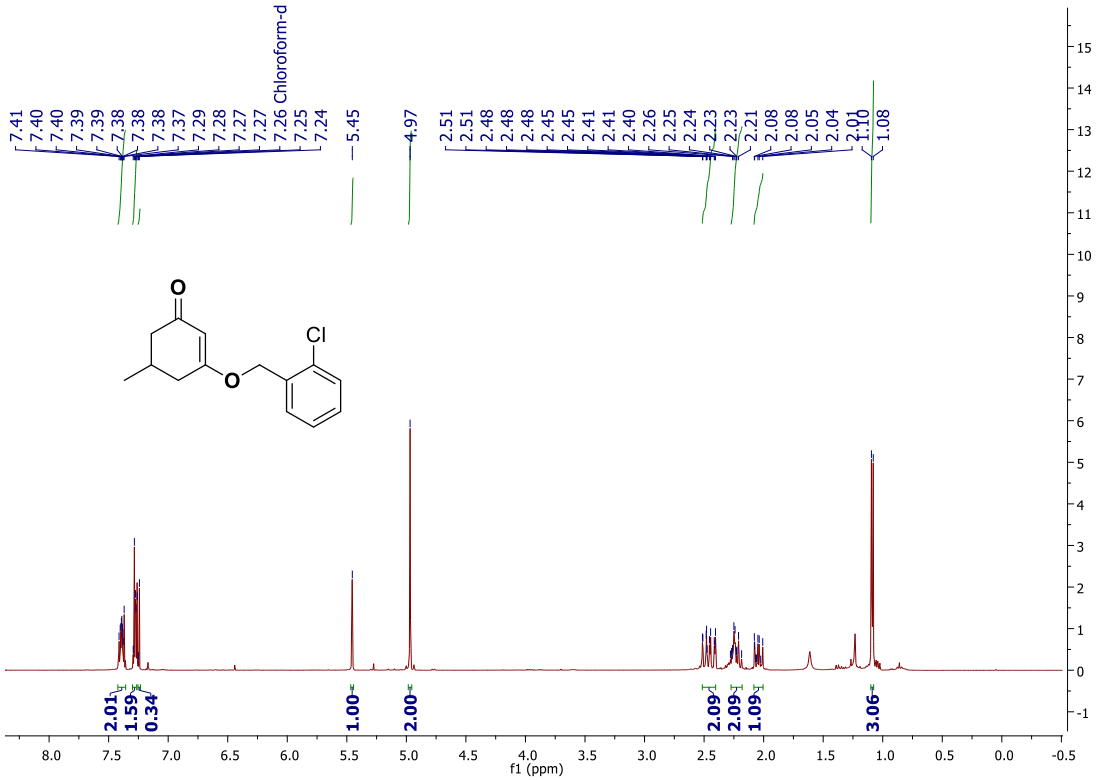


Figure 47. ^{1}H NMR of Compound **57b**

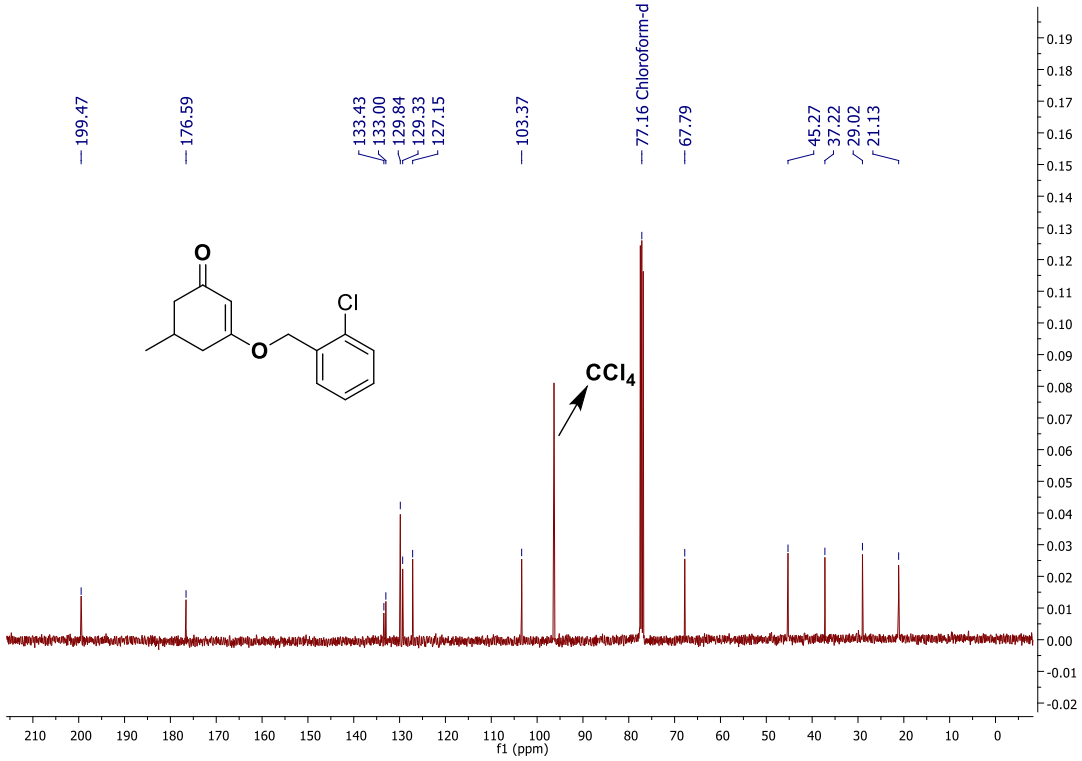


Figure 48. ^{13}C NMR of Compound **57b**

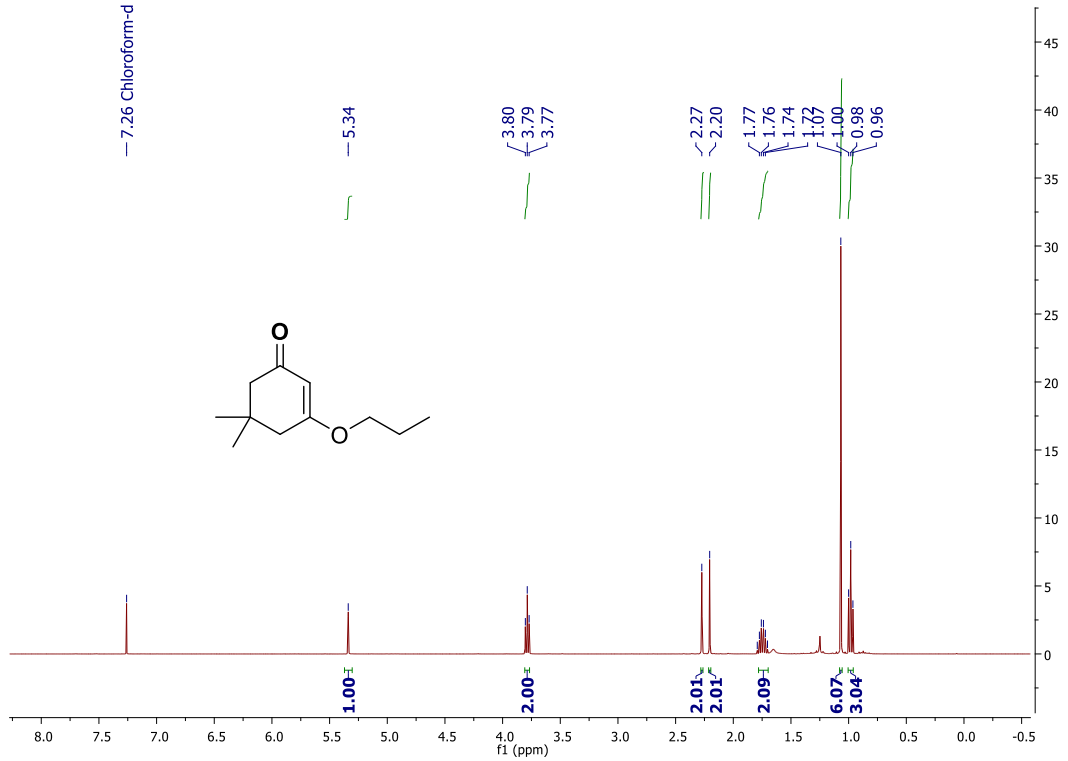


Figure 49. ^{1}H NMR of Compound **58b**

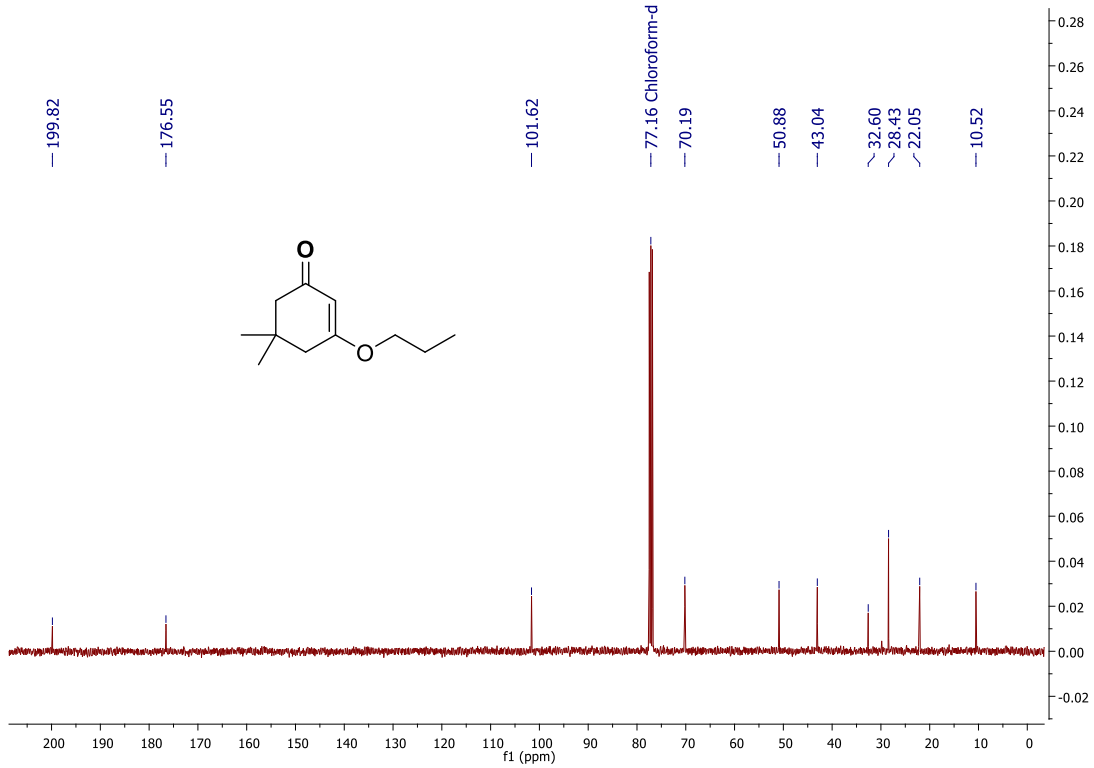


Figure 50. ^{13}C NMR of Compound **58b**

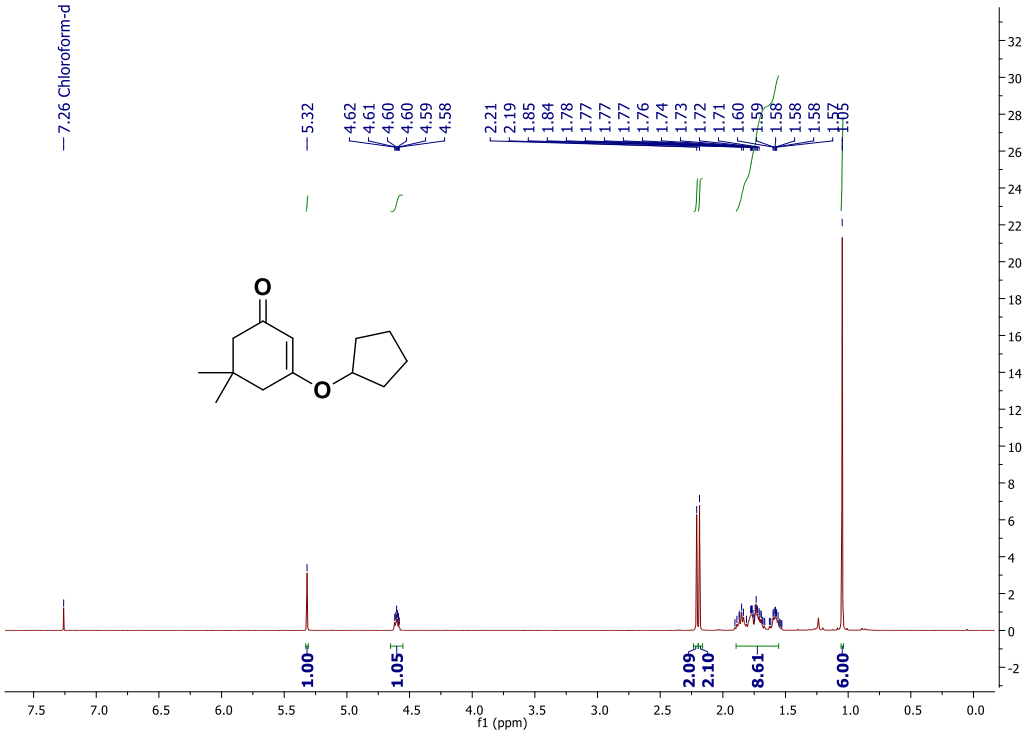


Figure 51. ^{1}H NMR of Compound **58c**

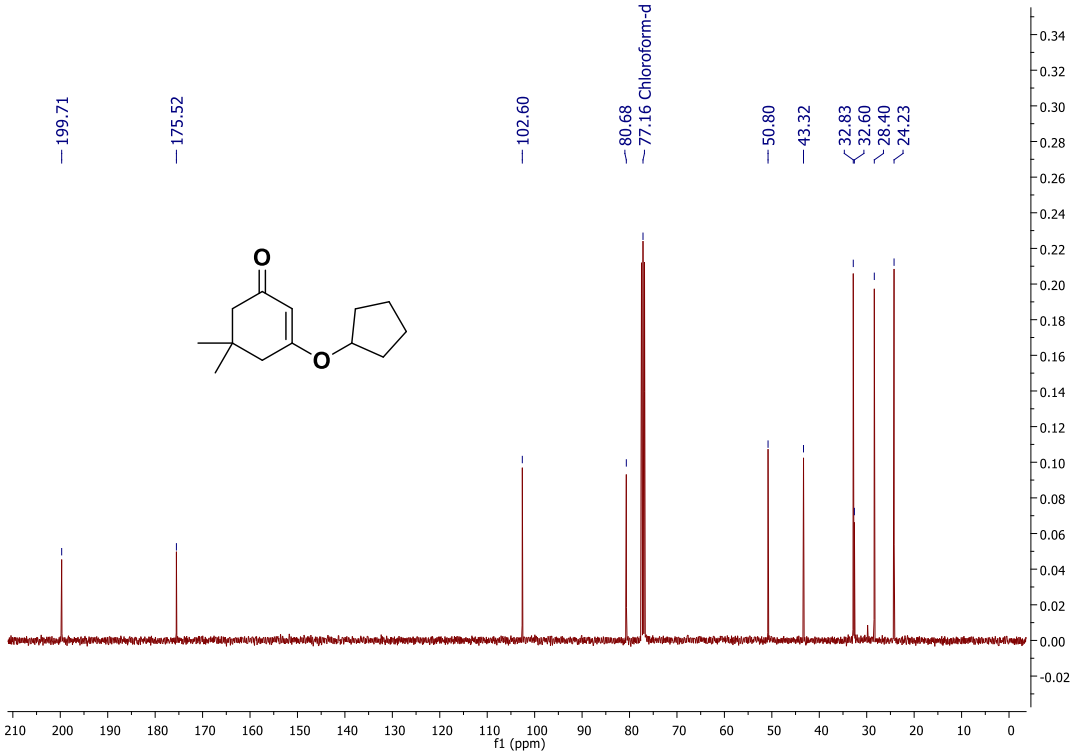


Figure 52. ^{13}C NMR of Compound **58c**

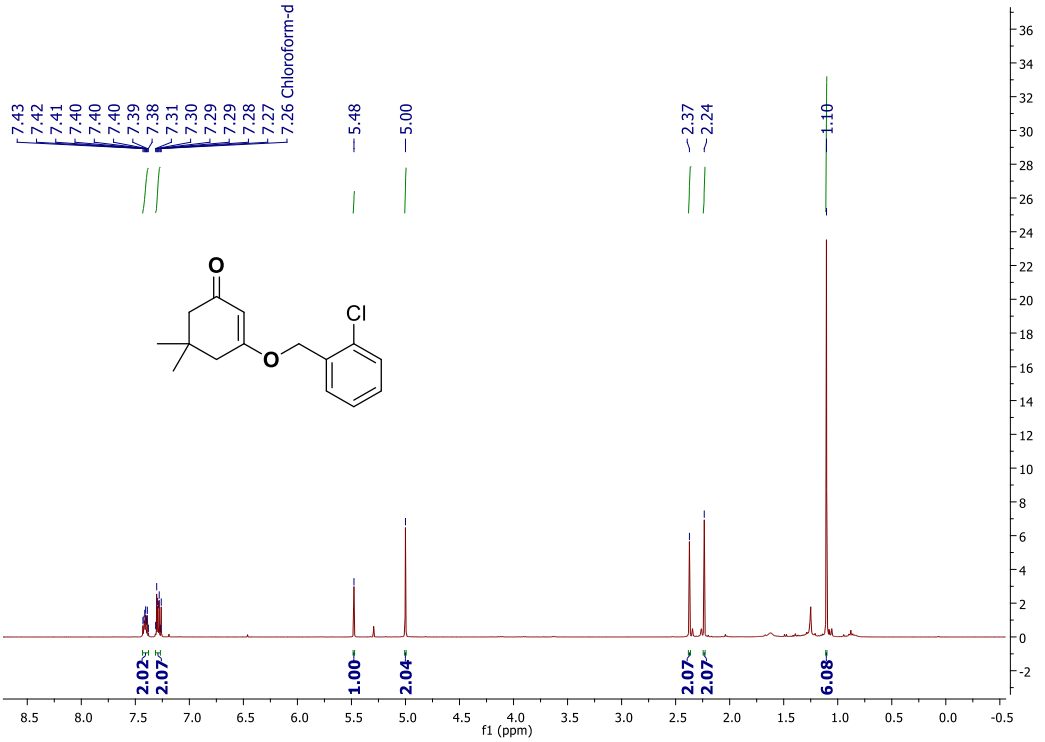


Figure 53. ^{1}H NMR of Compound **58d**

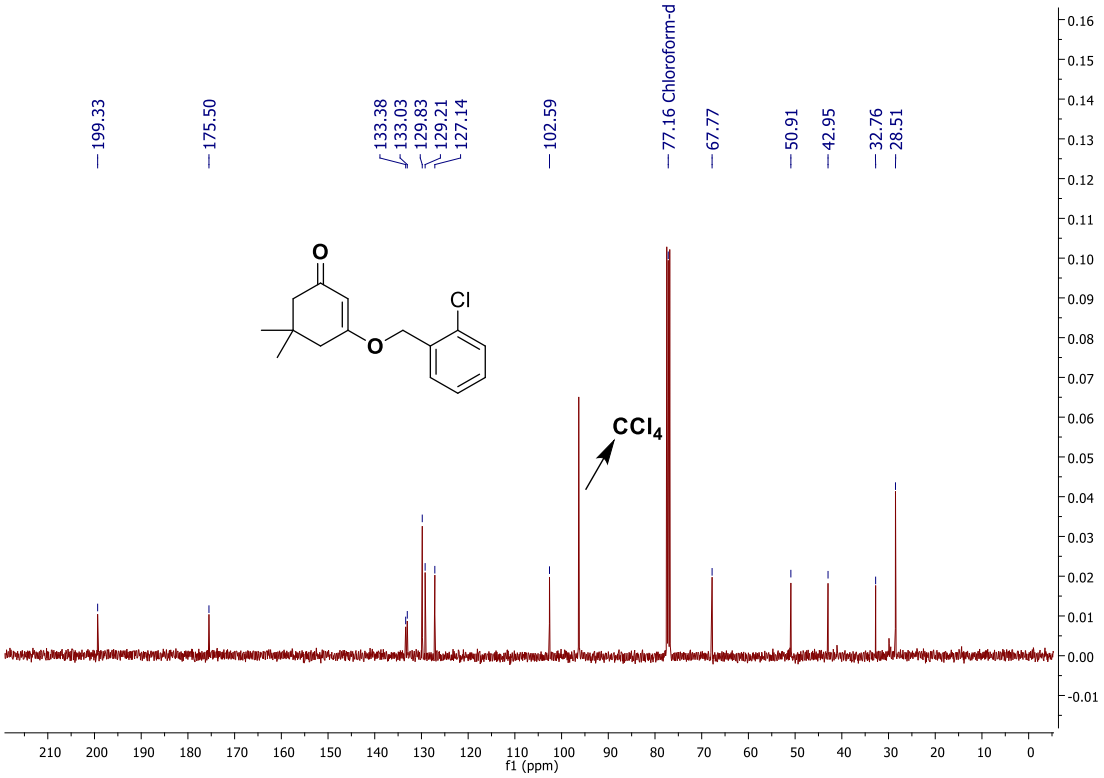


Figure 54. ^{13}C NMR of Compound **58d**

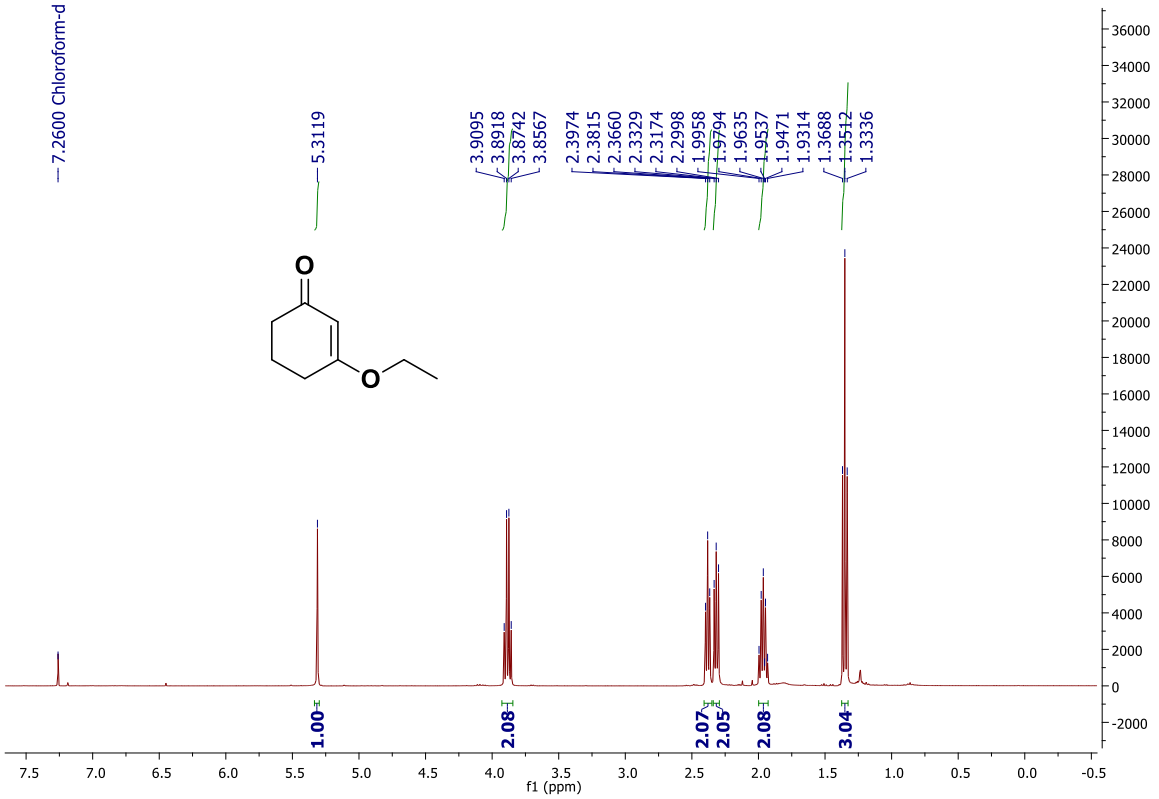


Figure 55. ^{1}H NMR of Compound **56a**

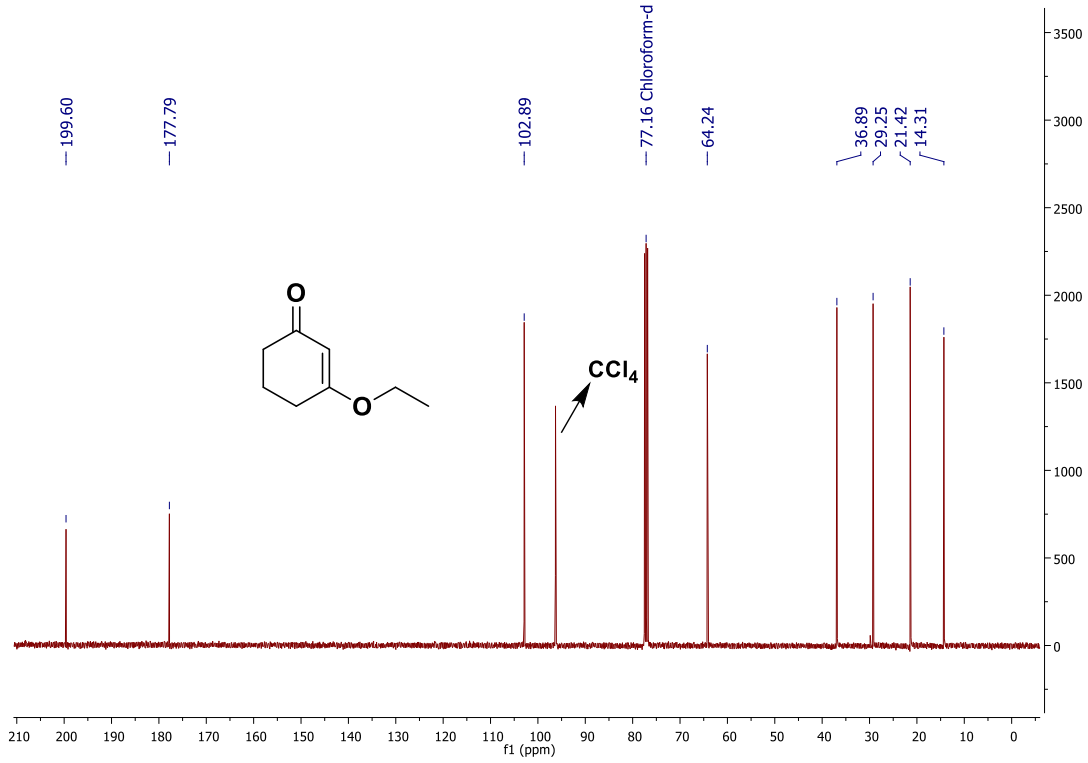


Figure 56. ^{13}C NMR of Compound **56a**

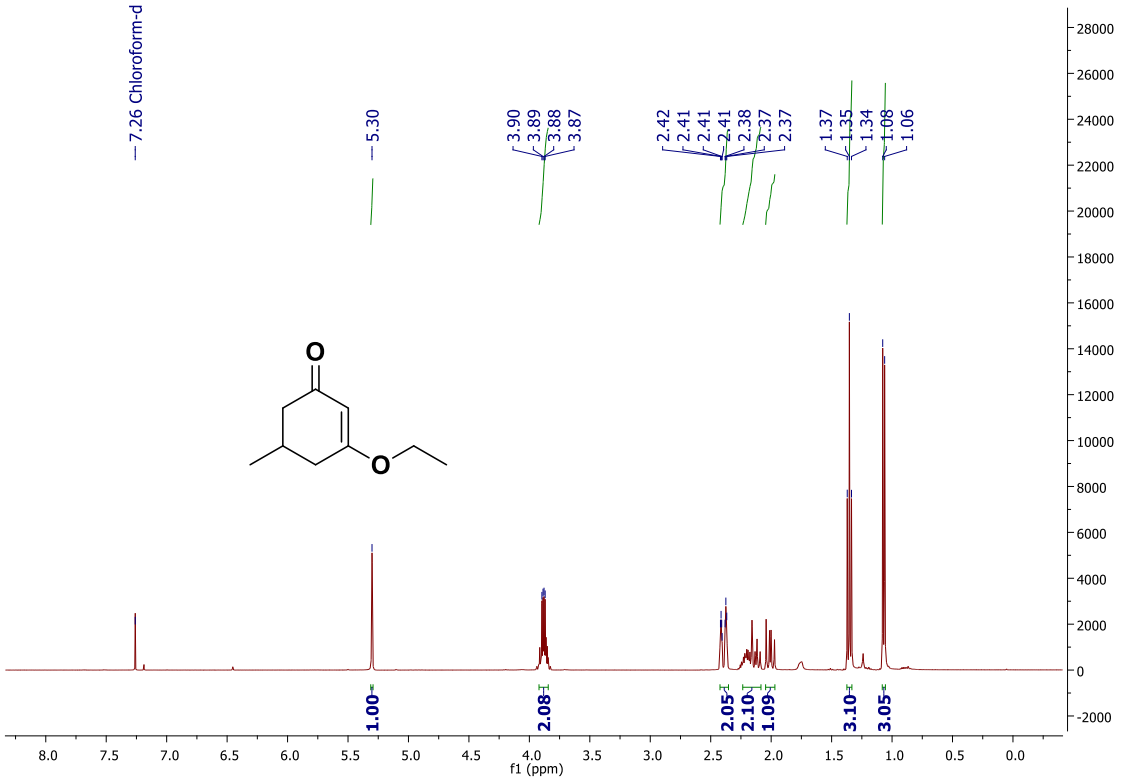


Figure 57. ^{1}H NMR of Compound **57a**

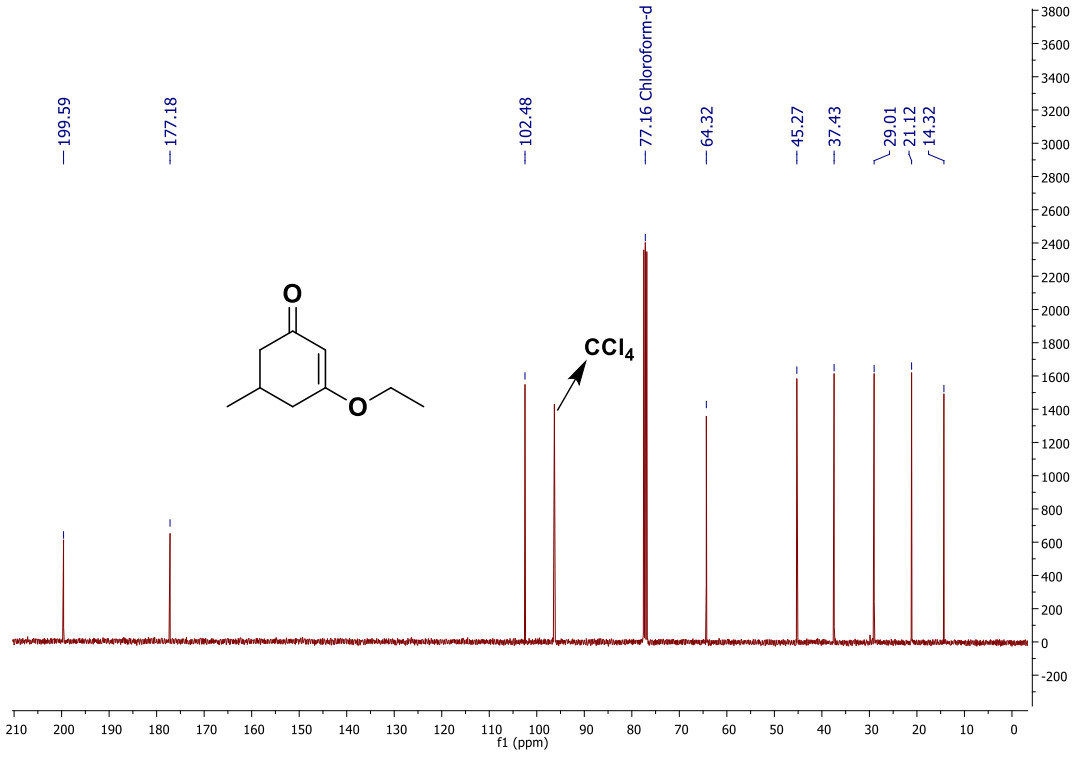


Figure 58. ^{13}C NMR of Compound **57a**

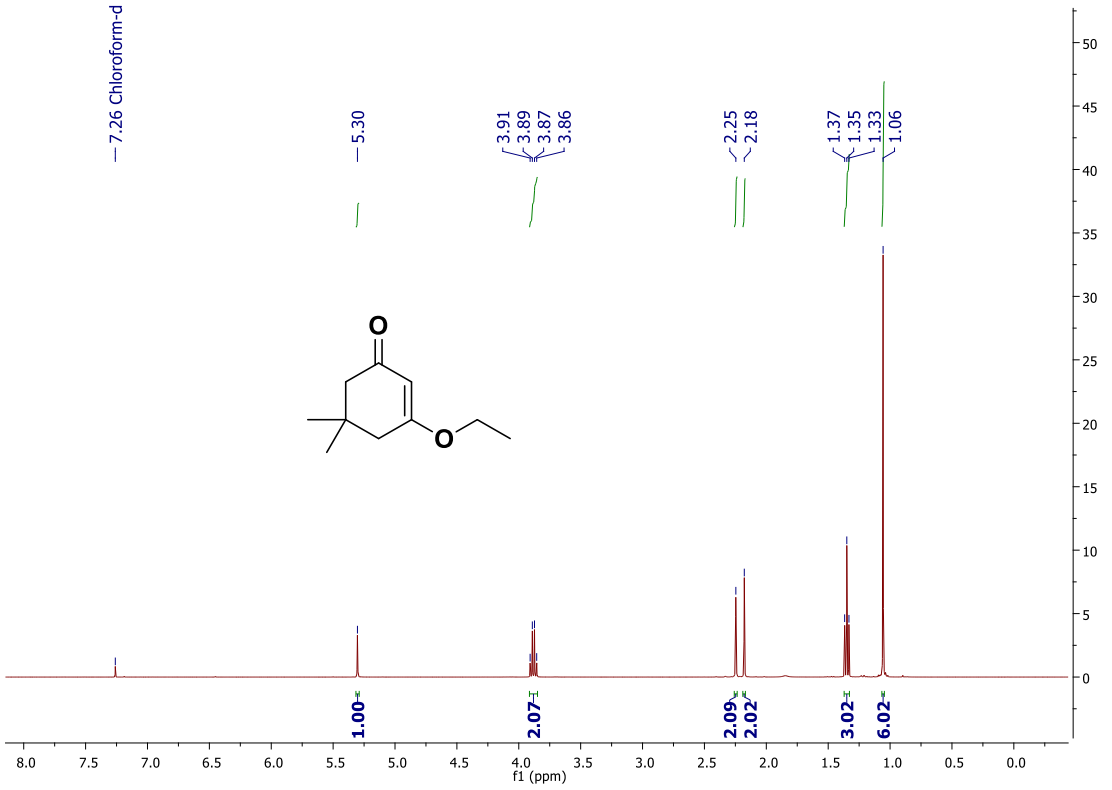


Figure 59. ^{1}H NMR of Compound **58a**

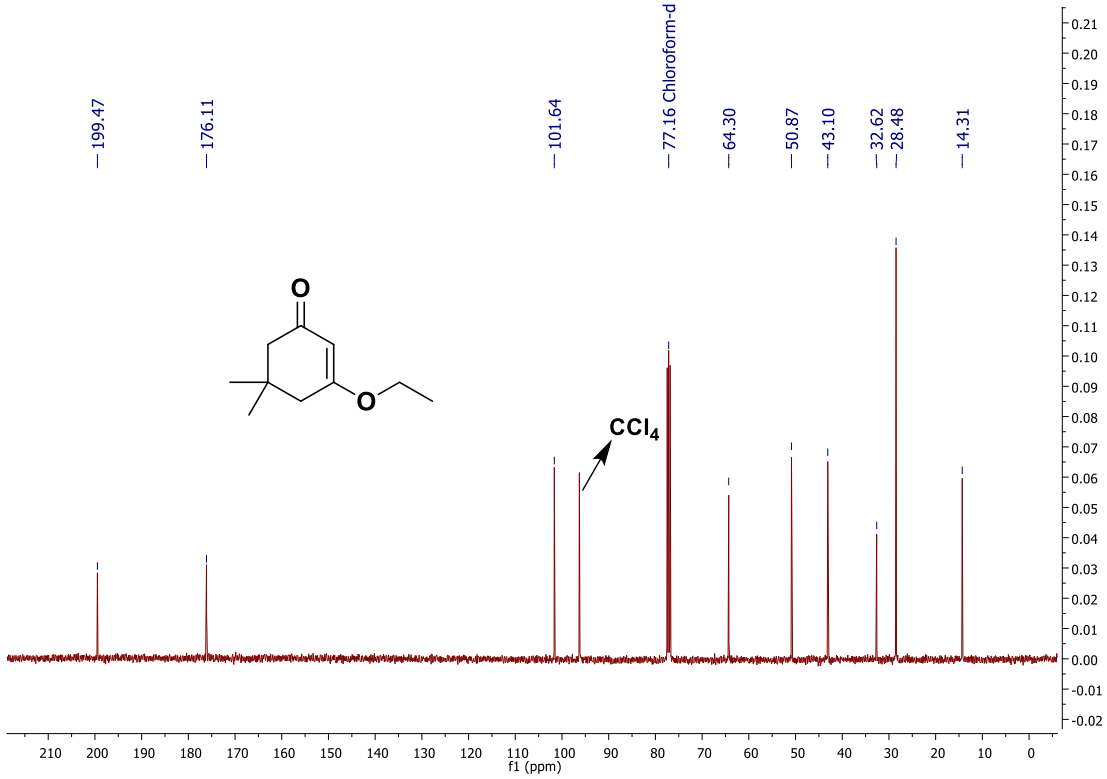


Figure 60. ^{13}C NMR of Compound **58a**

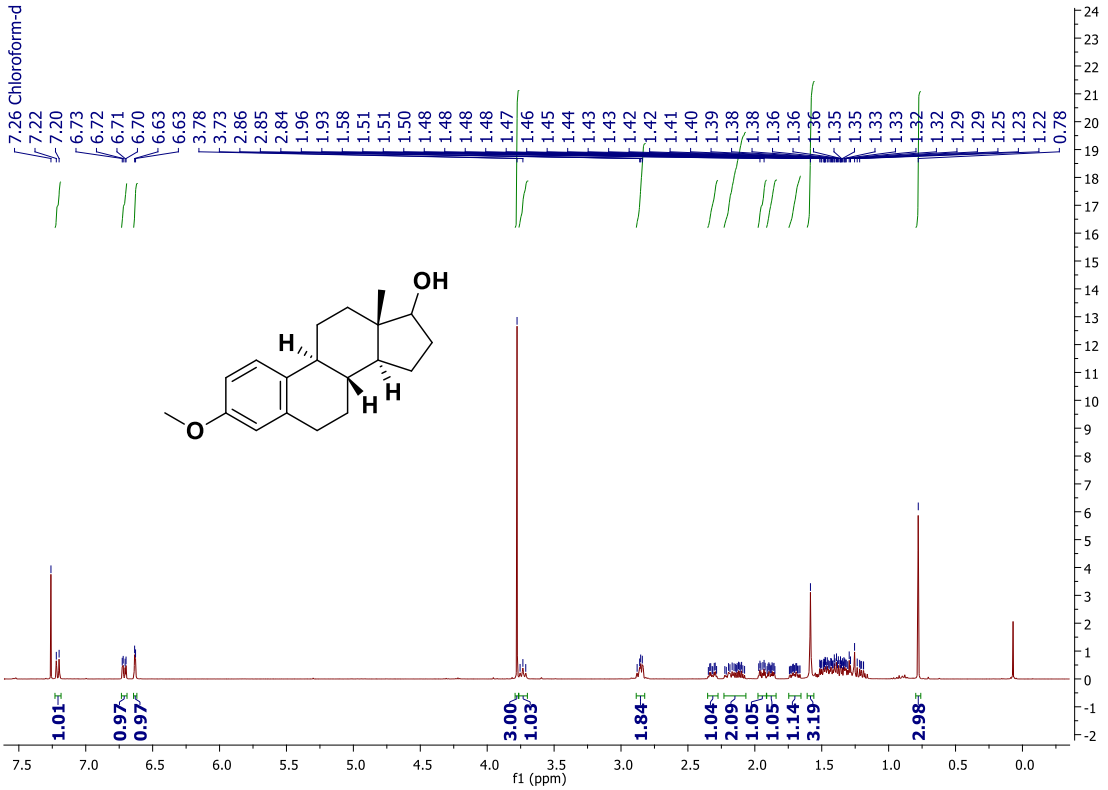


Figure 61. ^{1}H NMR of Compound **59a**

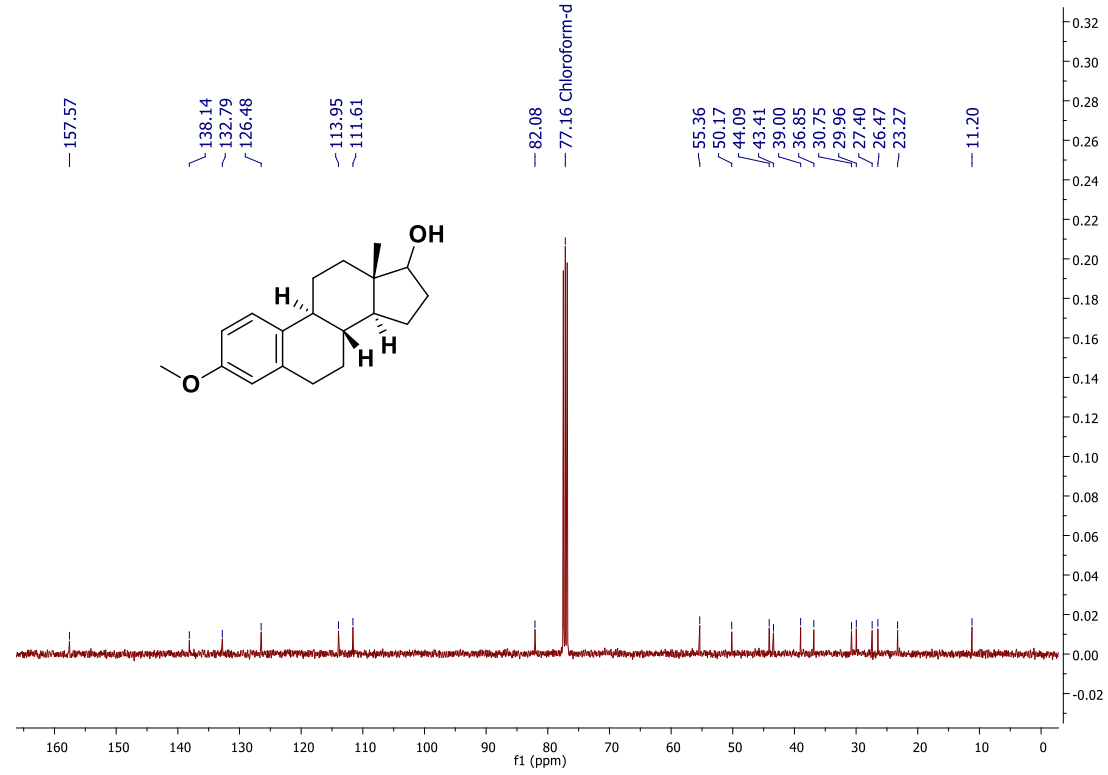


Figure 62. ^{13}C NMR of Compound **59a**

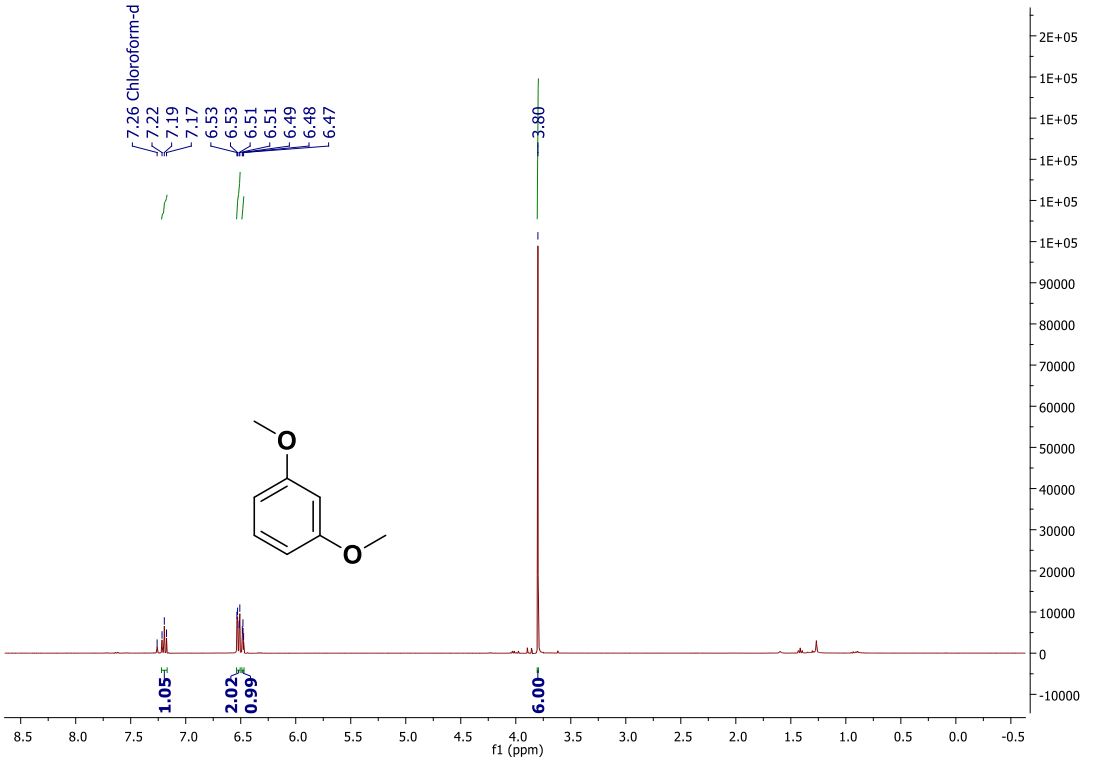


Figure 63. ^{1}H NMR of Compound **61**

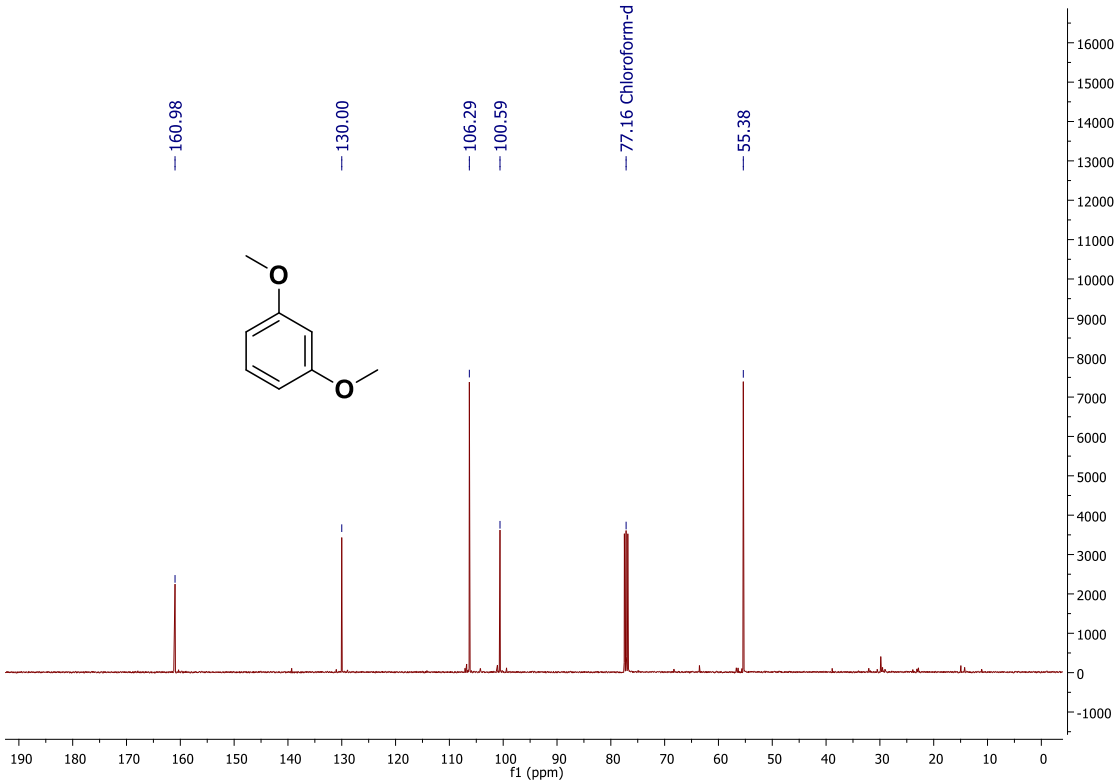


Figure 64. ^{13}C NMR of Compound **61**

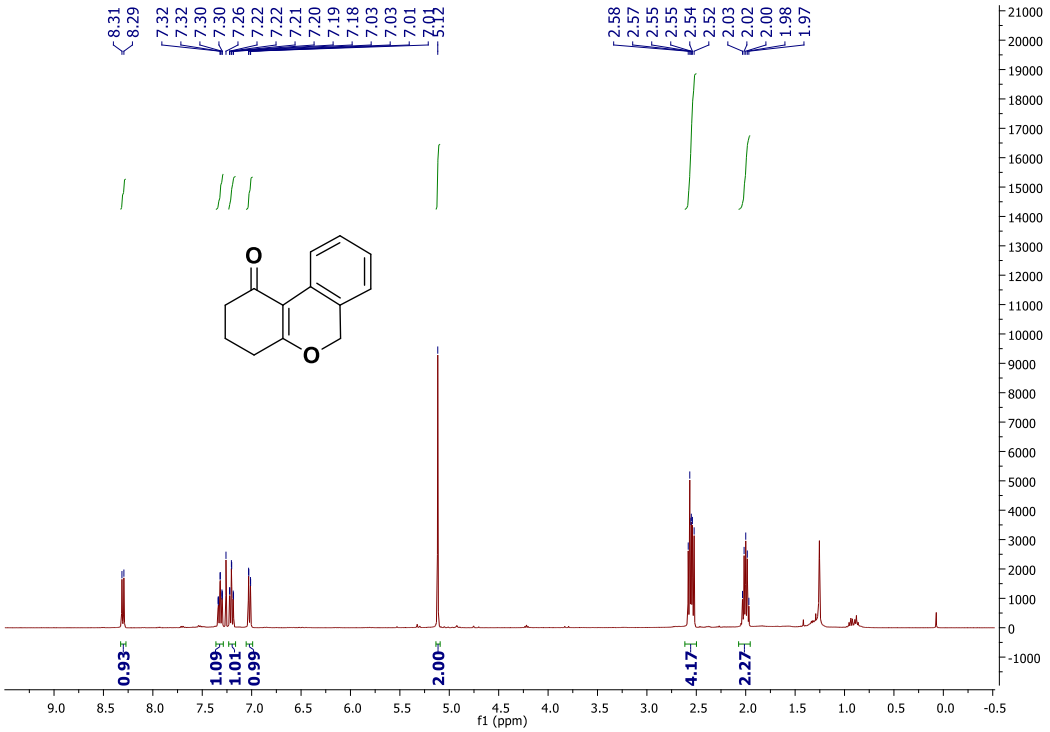


Figure 65. ^{1}H NMR of Compound **62**

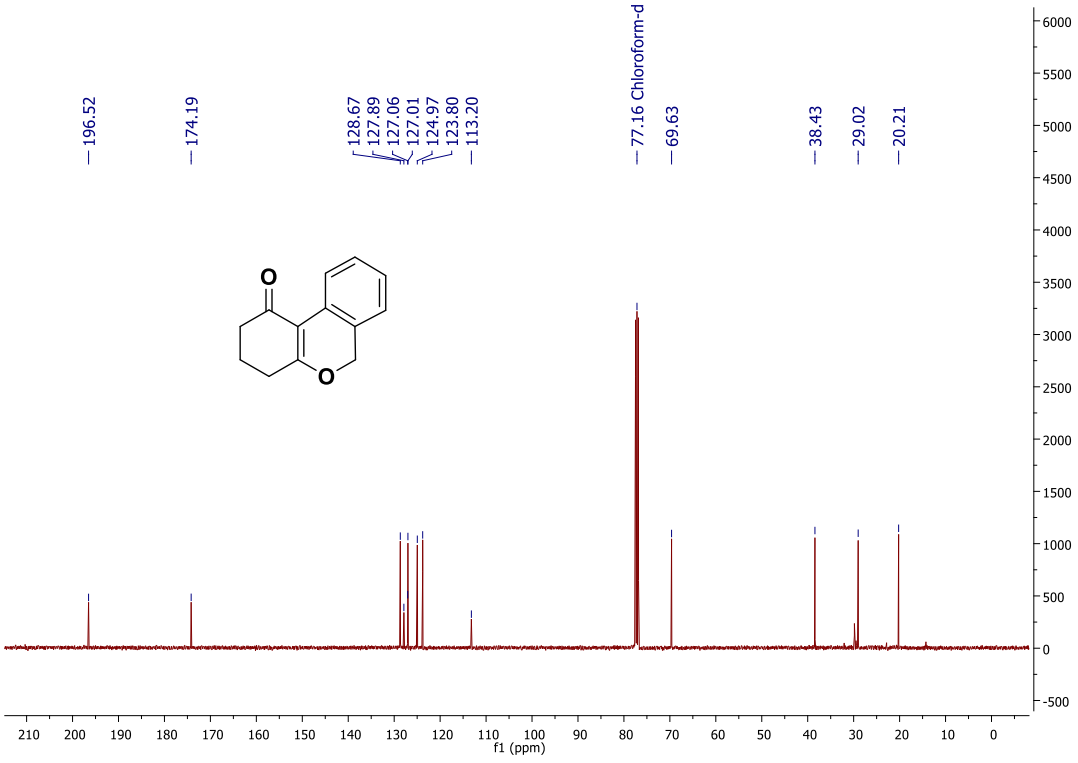


Figure 66. ^{13}C NMR of Compound **62**

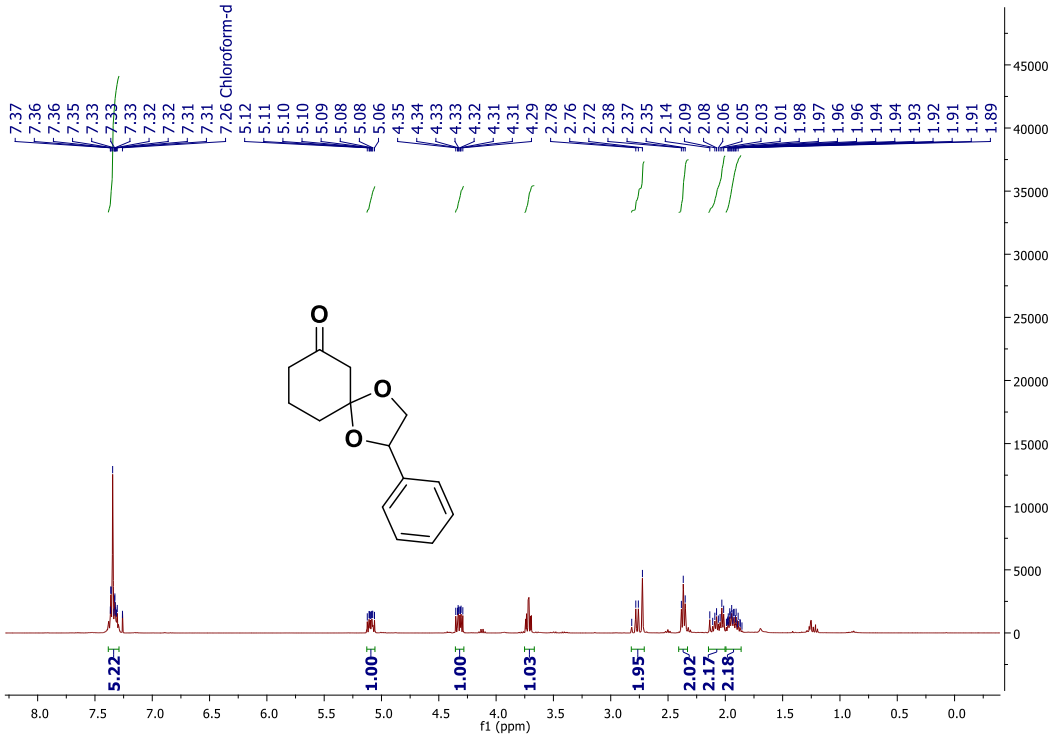


Figure 67. ^{1}H NMR of Compound **63**

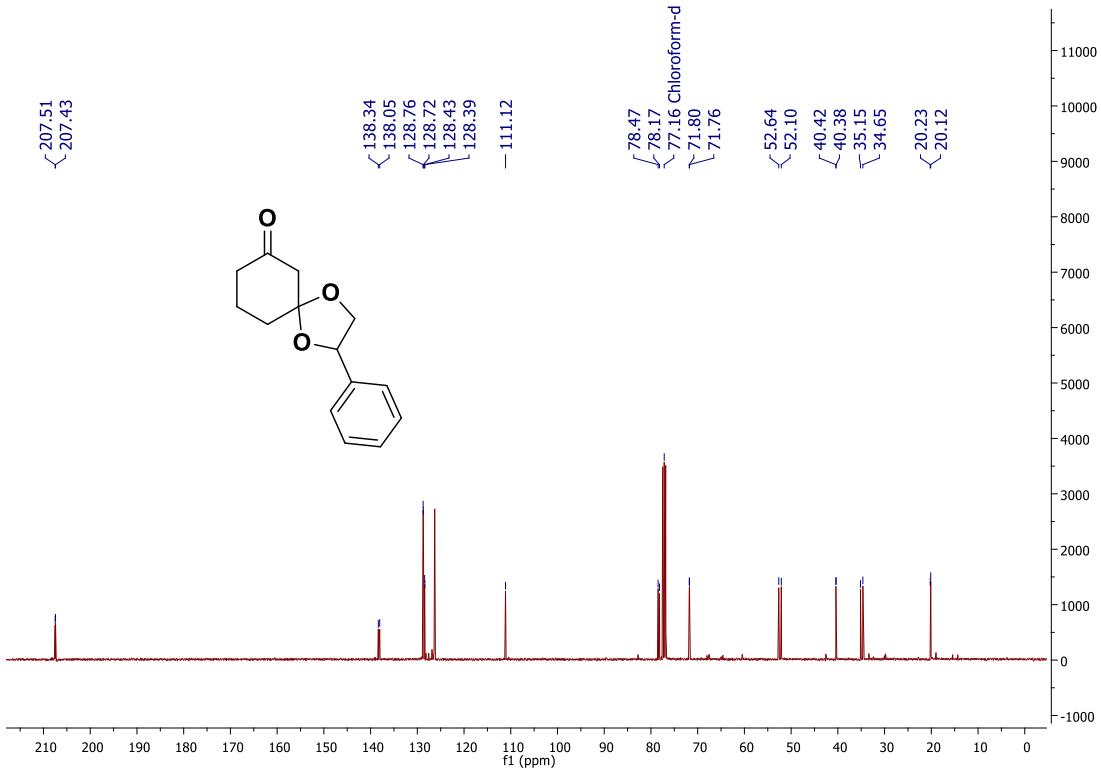


Figure 68. ^{13}**C** NMR of Compound **63**

CONCLUSION

In summary, we have investigated the reactivity of vinylogous ester in the presence of various alcohols using metal-catalyst. This experimental studies developed a selective, mild and efficient method for the transetherification of vinylogous esters using Iron (III) catalyst in good to excellent yield. Furthermore, the reactions were also transformed into the continuous flow and demonstrated gram scale synthesis. In addition, this research also developed a method for deprotection of vinylogous esters to corresponding cyclic β-diketones with 5 mol% of $FeCl_3 \cdot 6H_2O$ by using water as a green solvent. Further studies on the selectivity, high selectivity was observed for primary alcohols over secondary alcohols. Synthetic application of the vinylogous ester were also studied to get the spiro compounds via transetherification and 1,4-addition reaction. We have also successfully synthesised transetherification with biologically important molecules such as Cholesterol and Estrone. All the products were well characterised by NMR, high-resolution mass spectroscopy and Fourier-transform infrared spectroscopy. This work has been published in Organic and Biomolecular Chemistry on 20th February 2019.

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Reversible chemoselective transetherification of vinylogous esters using Fe-catalyst under additive free conditions†

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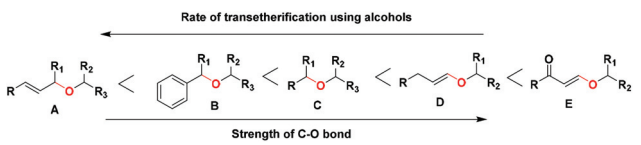
An additive/Brønsted acid/base free, highly efficient and chemoselective transetherification of electron deficient vinylogous esters and water mediated de-alkylation using an earth-abundant Fe-catalyst under very mild reaction conditions is described. This reaction is highly selective to primary alcohols over secondary alcohols, has good functional group tolerance, is scalable to gram scale and a purification free sequential transetherification in a continuous flow mode is demonstrated.

Introduction

Ethers are prevalent motifs in a wide range of natural products, pharmaceuticals, agrochemicals, polymers, fragrances, and materials.[1] Traditionally, Williamson etherification employs stoichiometric sodium alkoxide and alkyl halides to generate symmetrical and unsymmetrical ethers,[2] however, it suffers from a few drawbacks; these include the requirement for a stoichiometric amount of strong base, generation of a stoichiometric amount of inorganic waste, the use of toxic and expensive genotoxic organohalides derived from alcohols, which means that ether synthesis can be a multistep process.[3] During the past few decades, several approaches utilizing homogeneous catalysts such as Brønsted acids or Lewis acids were developed for the synthesis of ethers from diverse functional groups to avoid these shortcomings.[4] Nevertheless although these methods have advantages, they suffer from poor atom economy, the need for stoichiometric additives, limited substrate scope, absence of chemoselectivity and the use of a special stoichiometric reagent for the hydrolysis/ethereal C–O bond cleavage. Alternatively, ethers have been synthesized *via* transetherification reactions by using a metal catalyst with additives and also promoted by a stoichiometric amount of bases and acids[5] which encompasses only electronically rich substrates having benzyl and allyl groups. In general, syntheses of ethers *via* transetherification reactions are reversible in nature; hence an excess amount of alcohol is used to shift the equilibrium in the forward direction in the presence of the catalyst. The relative strength of the C–O bond in various ethers and their reactivities towards various alcohols is shown in Scheme 1.

Ethers having an allyl, benzyl or alkyl group facilitate the C–O bond dissociation *via* resonance stabilization and thus assist the easy substitution of the alkoxy group by the alcohol. On the other hand, this transformation was more difficult with electron deficient ethers such as vinylogous esters due to the conjugated C═O group which makes a stronger alkenyl C–O bond. Hence, the activation of the alkenyl C–O bond and concomitant substitution reaction by various nucleophile is one of the challenges in synthetic organic chemistry, where it is often used to form C–C and C–N bonds in cross-coupling reactions.[6] Moreover, vinylogous esters are electron deficient ethers and are an attractive feedstock for several chemical transformations such as coupling reactions,[7] ene reactions,[8] photocycloaddition reactions,[9] and many other organic transformations.[10]

Development of a metal catalyzed chemoselective transetherification is one of the challenges in synthetic methodology.[11] While transetherifications of ethers having alkyl, allyl, and benzyl substituents have been reported (Scheme 2), the metal-catalyzed transetherification of electron deficient vinylogous esters and chemoselective transetherifications have not been reported in the literature.



Scheme 1 Relative strength and ease of substitution on ethers.

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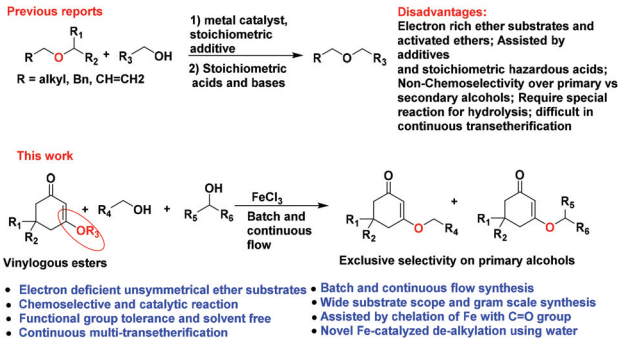
†Electronic supplementary information (ESI) available: Copies of ^{1}H NMR and ^{13}C NMR. See DOI: 10.1039/c9ob00307j

‡These authors contributed equally to this work.



Scheme 2 State of art for the transetherification reaction.

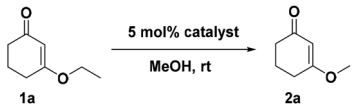
Besides, continuous flow organic reactions are immensely attractive to synthetic chemists since they have several advantages over conventional batch reactions which include improved safety, great efficiency, reproducibility, precise control of reaction conditions, and easy scale-up.[12] Furthermore, vinylogous esters are highly reversible in nature in the presence of the acid/catalyst, which requires a short reaction time to avoid the exposure of the reaction mixture to prolonged acidic or catalytic reaction conditions. Hence, a continuous flow approach can overcome the existing problems associated with the transetherification reaction.

Herein, we report an additive free, highly efficient and chemoselective transetherification of vinylogous esters using an Fe-catalyst in the absence of stoichiometric strong acids or bases. The advantages of this novel approach include that it is easily and rapidly integrable into continuous flow mode, provides purification-free continuous flow sequential transetherification and is scalable to gram scale in a short duration. In addition, a novel approach for the reversible reaction of this vinylogous ester and water-mediated de-alkylation under very mild reaction conditions is also demonstrated.

Results and discussion

To examine the optimal conditions for the transetherification of vinylogous esters, 3-ethoxycyclohex-2-en-1-one (**1a**) was used as a model substrate in the presence of catalytic amounts of various metals. The results are listed in Table 1. In a control experiment, in the absence of a catalyst, no transetherification product **2a** was observed (Table 1, entry 1). A subsequent survey of the reaction by addition of 5 mol% of $RuCl_3{\cdot}6H_2O$ and $[Ru(p\text{-cymene})Cl_2]_2$ catalysts significantly proceeded to yield **2a** in 95% and 93% yield respectively (Table 1, entries 4 and 5). However, this reaction was less efficient with Ru-complexes such as $Ru(bpy)_3Cl_2{\cdot}6H_2O$ in acetonitrile (ACN) and Ru-MACHO (Table 1, entries 2, 3 and 6). To identify an earth-abundant catalyst, this reaction was investigated with Mn, Fe, Co, Ni, and Cu-precursor. No reaction was observed while using Mn-salts such as $MnCl_2{\cdot}2H_2O$, $(CH_3COO)_3Mn{\cdot}2H_2O$ as a catalyst (Table 1, entries 9–10). Other transition metal salts *viz.* Co, Ni, and Cu give a poor yield of **2a** (Table 1, entries 11–13).

Table 1 Optimization for transetherification reaction in batch[a]

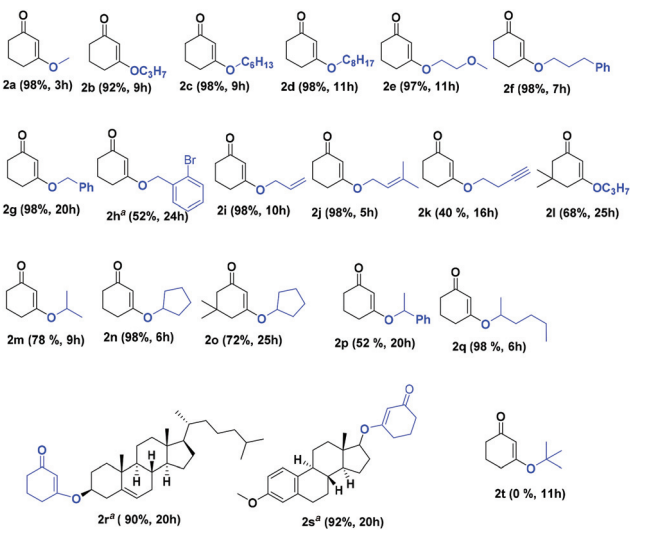


Entry	Catalyst	MeOH	Solvent	Time (h)	Yield (%)
1	—	10	—	21	—
2	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	10	ACN	21	40
3	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	Excess	—	11	90
4	$RuCl_3{\cdot}6H_2O$	Excess	—	3	95
5	$[Ru(p\text{-cymene})Cl_2]_2$	Excess	—	6	93
6	Ru-MACHO	Excess	—	40	—
7	$FeCl_3{\cdot}6H_2O$	Excess	—	3	98
8	Fe-Zeolite	Excess	—	3	95
9	$(CH_3COO)_3Mn{\cdot}2H_2O$	Excess	—	3	—
10	$MnCl_2{\cdot}2H_2O$	Excess	—	3	—
11	$NiBr_2{\cdot}2H_2O$	Excess	—	3	30
12	$CuCl_2{\cdot}2H_2O$	Excess	—	3	25
13	$CoCl_3{\cdot}2H_2O$	Excess	—	3	40

[a] Reaction conditions: **1a** (1 mmol), catalyst (5 mol%), and methanol (2 mL) were stirred at room temperature.

Interestingly, the best-optimized conditions were obtained using 5 mol% $FeCl_3{\cdot}6H_2O$ catalyst in methanol as a solvent to afford **2a** in 98% yield (Table 1, entry 7).

With the optimized conditions in hand, the substrate scope of this reaction was explored further by using a variety of vinylogous esters with various aliphatic or aromatic alcohols. Thus, the reaction of vinylogous ester **1a** with various aliphatic alcohols such as *n*-propanol, *n*-hexanol, and *n*-octanol in the presence of 5 mol% of $FeCl_3$ afforded the respective transetherification product **2b–d** in excellent yield (Scheme 3). Other substituted primary alcohols; 2-methoxyethanol, 3-phenylpropan-



Scheme 3 Substrate scope under batch conditions. Reaction conditions: Vinylogous ester (1 mmol), $FeCl_3{\cdot}6H_2O$ (5 mol%) and alcohol (2 mL), were stirred at room temperature. [a] Vinylogous ester (1 mmol), alcohol (3 mmol), $FeCl_3{\cdot}6H_2O$ (5 mol%) and 1,2-dichloroethane (2 mL) were stirred at 80 °C for 20 h.

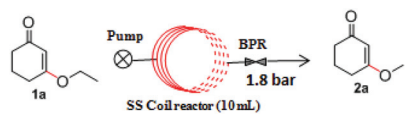
1-ol, benzyl alcohol, and 2-bromobenzyl alcohol also reacted well with **1a** to afford the corresponding products **2e–h** in very good yield (Scheme 3). Interestingly, this reaction is well tolerant to olefin and alkyne functional groups; for example, allyl alcohol, 3-methylbut-2-en-1-ol, and but-3-yn-1-ol reacted smoothly to afford the transetherified products **2i** and **2j** in 98% except for **2k** (40%) (Scheme 3). Substituted vinylogous ester, 3-ethoxy-5,5-dimethylcyclohex-2-en-1-one also reacted well with the *n*-propanol to afford the product **2l** in 68% yield. Fascinatingly, this reaction was effective for sterically hindered secondary alcohols (isopropyl alcohol, cyclopentanol, 1-phenylethanol, 2-hexanol, cholesterol, and esterol) to afford the corresponding products **2m–s** in good to excellent yield (Scheme 3). Unfortunately, sterically hindered tertiary butanol was incompatible with this reaction and did not generate the desired product **2t** (Scheme 3).

To examine our hypothesis for continuous-flow, a flow set up was assembled (Fig. S1, ESI†) by using a pump, coil reactor and back pressure regulator (BPR). Initial reactions of 0.1 M, 3-ethoxycyclohex-2-en-1-one (**1a**) with methanol in continuous flow at 60 °C without any catalyst were unsuccessful (Table 2, entry 1). However, flowing the reactants and 3 mol% $FeCl_3{\cdot}6H_2O$ catalyst with a 0.2 mL min^{-1} flow rate at room temperature provided 3-methoxycyclohex-2-en-1-one (**2a**) in 65% isolated yield (Table 2, entry 2). We continued to evaluate the effect of catalyst loading, temperature, and residence time (Table 2).

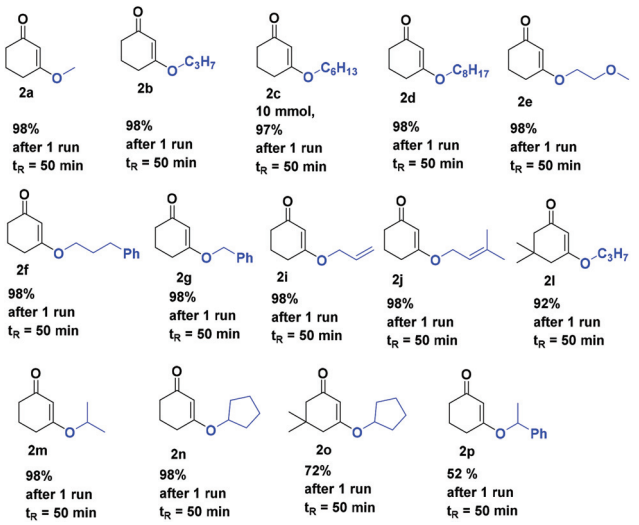
Increasing both the catalyst loading (5 mol%) and temperature (80 °C) with a residence time of 50 minutes resulted in the best yield of **2a** around 98% (Table 2, entry 6). There was no improvement in the yield of the reaction when the temperature was increased to 100 °C (Table 2, entry 7).

With the optimized conditions in hand, we set out to investigate a range of substrates using continuous flow and the results are shown in Scheme 4. The yields were generally comparable to the batch reaction, but reactions are completed in a shorter duration of time (Scheme 4). A slight decrease in yield of **2o** and **2p** was observed when the reaction was carried out with cyclopentanol and 1-phenylethanol. To demonstrate the gram scale synthetic utility of this strategy, we also conducted

Table 2 Optimization for continuous flow



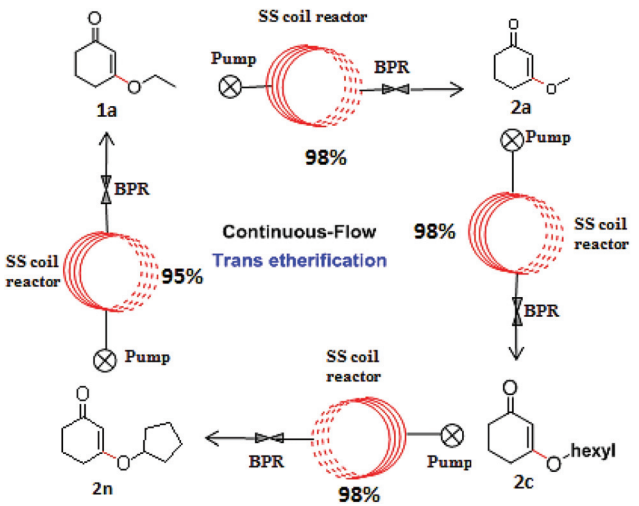
Entry	$FeCl_3{\cdot}6H_2O$ (mol%)	Temp. (°C)	Flow rate (mL min^{-1})	t_R (min)	Yield (%)
1	—	60	0.2	50	—
2	3	rt	0.2	50	65
3	3	60	0.2	50	82
4	3	80	0.2	50	85
5	5	60	0.2	50	92
6	5	80	0.2	50	98
7	5	100	0.2	50	98



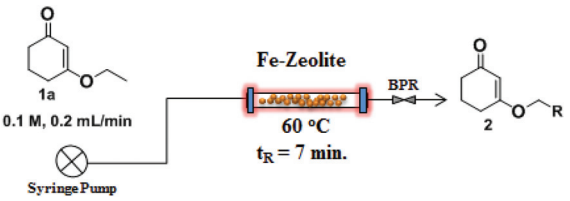
Scheme 4 Substrate scope under continuous flow. Reaction conditions: All reactions were run on a 0.1 M scale in 10 mL of alcohol using 5 mol% of $FeCl_3{\cdot}6H_2O$ catalyst at 80 °C and maintained at a pressure of 1.2 bar using a BPR.

a 10 mmol scale transetherification reaction with hexanol, which provided **2c** in 1.9 g (97%).

Subsequently, a sequential transetherification of a vinylogous ester was investigated under continuous flow conditions (Scheme 5). Hence, the vinylogous ester **1a** and $FeCl_3$ in methanol were pumped (0.2 mL min^{-1}) into the coil reactor at 80 °C affording the product **2a** in 98% yield. The product **2a** in hexanol was further pumped into the SS coil reactor to afford the **2c** in 98% yield. Further, the product **2c** was continuously transformed into **2n** and subsequently, the product **2n** was transformed into **1a** in excellent yield under the continuous transetherification conditions. In addition, the catalyst recyclability for this transformation was demonstrated by flowing the vinylogous ester **1a** in methanol into a column packed



Scheme 5 Sequential transetherification under continuous flow.



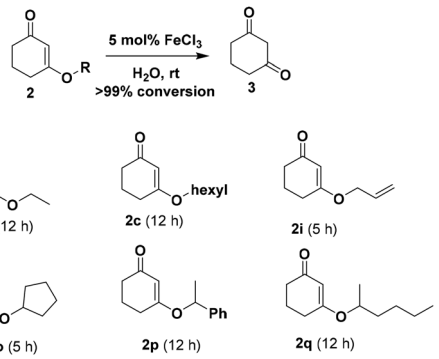
Scheme 6 Recyclable Fe-zeolite catalyzed transetherification under continuous flow mode.

with Fe-supported on zeolite[13] using a syringe addition pump and heated at 60 °C to afford the product **2a** in 99% yield with a residence time t_R = 7 min (Scheme 6).

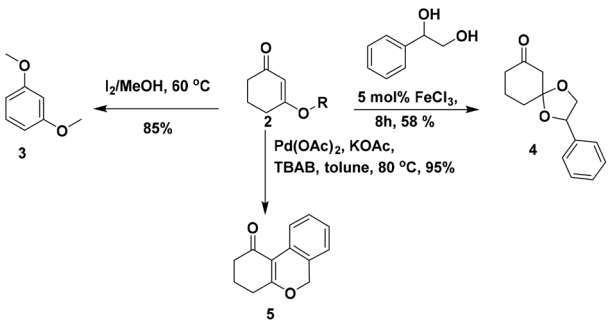
To study the chemoselectivity of the alcohols, we have investigated the intermolecular transetherification of a vinylogous ester using primary and secondary alcohols (Table 3). Thus, an equivalent amount of methanol and IPA was reacted with vinylogous ester **1a** in the presence of 5 mol% of $FeCl_3$ to afford the products **2b** and **2e** in a ratio of 75 : 25% (Table 3, entry 1). Interestingly, selectivity was increased to 95 : 5% in case of a MeOH/1-phenylethanol mixture (Table 3, entry 2). Excellent selectivity (100%) and exclusive reactivity of the primary alcohols was observed while using diphenylmethanol, bis(4-methoxyphenyl)methanol and phenyl(3-(trifluoromethyl)phenyl) methanol (Table 3, entries 3–5). Similarly, higher selectivity (90 : 10) with the aliphatic and less substituted methanol was observed (Table 3, entry 6).

To probe the ether cleavage, Fe-catalysed water-mediated hydrolysis of a vinylogous ester was investigated (Scheme 7). A solution of vinylogous ester **1a** and $FeCl_3$ in water was allowed to stir at room temperature for 5–12 h resulting in complete deprotection of the vinylogous ester to give cyclohexane-1,3-dione (Scheme 7). Under similar reaction conditions other vinylogous esters **2c**, **2i**, **2o**, **2p**, and **2q** were easily hydrolyzed to the respective 1,3-diketones in >99% conversion using 5 mol% $FeCl_3$ under very mild and environmentally benign conditions in 5–12 h.

Next, we have explored the synthetic application of the vinylogous ester (Scheme 8). Thus, the vinylogous ester **2a** was reacted with I_2 in methanol at 60 °C to afford the corresponding 1,3-dimethoxy benzene **3** in 85% yield.



Scheme 7 Fe-catalysed hydrolysis of the vinylogous ester.

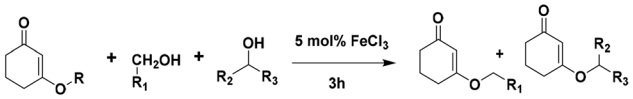


Scheme 8 Synthetic utility of the vinylogous esters.

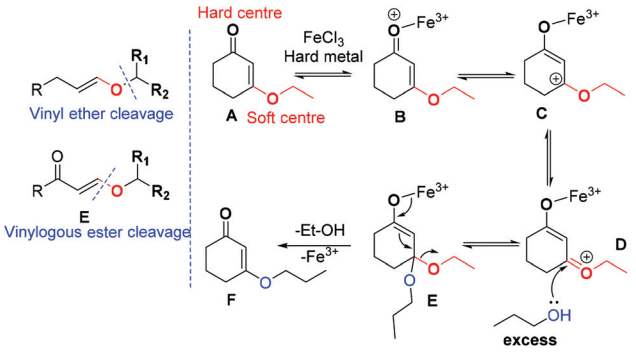
Interestingly, the reaction of vinylogous ester **2a** and 1-phenylethane-1,2-diol afforded the spiro product 2-phenyl-1,4-dioxaspiro[4.5]decan-7-one **4** in 58% yield *via* tandem transetherification and 1,4-addition with a conjugated ketone. Furthermore, the vinylogous ester **2h** was easily converted into 2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromen-1-one **5** *via* Pd-catalysed intramolecular Heck reaction (95%).[7c]

A mechanism for the Fe-catalysed transetherification of the vinylogous ester is proposed in Scheme 9. C–O bond cleavage of a vinyl ether is known to occur in the presence of the metal catalyst or acid. In contrast to this, vinylogous ester C–O bond cleavage proceeds as shown in Scheme 9 due to the activation of the hard C=O center which is in conjugation with the vinyl

Table 3 Chemoselective transetherification



Entry	Vinylogous ester	Primary alcohol	Secondary alcohol	Selectivity based on GC-MS and ^{1}H-NMR
1	**1a**	Methanol	IPA	75 : 25
2	**1a**	Methanol	1-Phenylethanol	95 : 5
3	**1a**	Methanol	Diphenylmethanol	100 : 0
4	**1a**	*n*-Propanol	Bis(4-methoxy phenyl)methanol	100 : 0
5	**1a**	*n*-Hexanol	Phenyl(3-(trifluoromethyl)phenyl)methanol	100 : 0
6	**1a**	Methanol : benzyl alcohol	—	90 : 10



Scheme 9 Plausible mechanism for transetherification.

ether. Initially hard Fe^{3+} coordinates to the hard C═O centre of the cyclic vinylogous ester **A** to form the intermediate **B**. The intermediate **B** is resonance stabilized to generate the intermediates **C** and **D**. Further, the addition of alcohol to the oxonium intermediate **D** to afford the ketal intermediate **E**. Finally, keto–enol tautomerism assisted elimination of ethanol from the intermediate **E** occurs to form the transetherified product **F**.

Experimental

General information and data collection

Materials and methods. All the chemicals were purchased from Sigma Aldrich or Alfa-Aesar. Deuterated solvents were used as received. All the solvents used were dry grade and stored over 4 Å molecular sieves. Column chromatographic separations were performed over 100–200 silica gel. Visualization was accomplished with UV light and phosphomolybdic acid (PMA), cerium ammonium molybdate (CAM) staining followed by heating. Iron(III) chloride (product number: 44939) was purchased from Sigma Aldrich. All the experiments were carried out without maintaining inert conditions. The flow chemistry experiments were carried on a Vaportec R-series system. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using a Bruker 400 MHz or JEOL 400 MHz spectrometer. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra were recorded with Waters-synapt G2 using electrospray ionization (ESI-TOF). Fourier-transform infrared (FT-IR) spectra were obtained with a Bruker Alpha-E Fourier transform infrared spectrometer.

General procedure for the transetherification of enol ethers in a batch reaction (2a–2p)

Vinylogous ester (1 mmol), $FeCl_3{\cdot}6H_2O$ (5 mol%) and 2 mL of alcohol were added to a 10 mL round bottom flask with a magnetic bar and stirred at room temperature (25 °C) in open air for the respective time (Scheme 2, main manuscript). After completion of the reaction, alcohol was removed using vacuum pressure and the crude reaction mixture was purified by column chromatography affording the pure transetherification product.

General procedure for the transetherification of compounds 2h, 2r and 2s in a batch reaction

Vinylogous ester (1 mmol) and $FeCl_3{\cdot}6H_2O$ (5 mol%) were added to a solution of alcohol (1 mmol) in dichloroethane (10 mL). The solution was heated at 80 °C for 20 h. The reaction was allowed to cool to room temperature. The solvent was removed using vacuum pressure and the crude reaction mixture was purified by column chromatography on silica gel with eluent (Ethyl acetate: Hexane (9 : 1)) afforded respective products.

General procedure for the transetherification of enol ether in a continuous flow system

Transetherification reactions were performed in a Vapourtec R-series continuous flow system equipped with a high-temperature SS coil reactor (10 mL, stainless steel, 1.00 mm i.d.). 0.1 M solution of vinylogous ester in different alcohols was passed through tube reactors at 0.2 mL min^{-1} flow rate, 1.8 bar pressure and at 80 °C. After completion of the reaction, alcohol was removed using vacuum pressure and the crude reaction mixture was purified by column chromatography to afford the pure transetherification product.

General procedure for iodine catalyzed aromatization of vinylogous ester (3)

To a solution of compound **1a** (1 mmol, 0.140 g) in methanol, iodine 0.508 g (2 equiv.) was added and the resulting mixture was stirred at 60 °C temperature for 2 h. Once TLC confirmed complete consumption of the starting material, the reaction mixture was quenched with cold sodium thiosulfate and extracted with ethyl acetate. The organic layer was evaporated and purified through column chromatography (10–90% EtOAc in hexane) to obtain the desired compounds **3**.

Representative procedure for coupling reactions: synthesis of 2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromen-1-one (5)

3-((2-Bromobenzyl)oxy)cyclohex-2-en-1-one (280 mg, 1 equiv.), TBAB (1 equiv.), KOAc (2.5 equiv.), $Pd(OAc)_2$ (0.02 equiv.) and toluene (7 mL) were added in sequence to a Schlenk tube and stirred under N_2 at 130 °C. After 3.5 h, water (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (2 × 10 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL), dried and the solvents evaporated. The crude material obtained was purified by column chromatography (silica, 1 : 1 hexane/EtOAc) to afford the product 5 in 95% yield.

Fe catalyzed the hydrolysis of vinylogous esters

To a solution of vinylogous ester in water, $FeCl_3{\cdot}6H_2O$ (5 mol%) was added and the reaction mixture was stirred at room temperature for the respective time (Scheme 7, main manuscript). After completion, the reaction mixture was diluted with ethyl acetate and extracted 3 times with ethyl acetate. The organic layers were dried on sodium sulfate and

concentrated using vacuum pressure affording quantitative yields of 1,3-diketone.

Analytical data for the product

3-Methoxycyclohex-2-en-1-one (2a). Yellowish oil (Batch-0.123 g, 98%; Continuous flow-0.123 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 3.68 (s, 3H), 2.40 (t, J = 6.4 Hz, 2H), 2.34 (t, J = 6.4 Hz, 2H), 2.01–1.93 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 178.9, 102.4, 55.7, 36.8, 28.9, 21.4. FTIR (neat): 2952.28, 2311.97, 1727.07, 1601.11, 1453.93, 1380, 1232.65, 1183.99, 1001.03, 758.03, 597.32 cm^{-1}. HRMS (ESI) m/z calculated for $C_7H_{11}O_2$ (M + H)$^+$: 127.0759, found: 127.0762.

3-Propoxycyclohex-2-en-1-one (2b). Yellowish oil (Batch-0.141 g, 92%; Continuous flow-0.150 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.78 (t, J = 6.5 Hz, 2H), 2.40 (t, J = 6.4 Hz, 2H), 2.34 (t, J = 6.0 Hz, 2H), 2.03–1.92 (m, 2H), 1.80–1.68 (m, 2H), 0.98 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (s), 178.3, 102.8, 77.5, 76.8, 70.1, 36.9, 29.2, 22.0, 21.4, 10.5. FTIR: 2953.87, 2315.29, 1724.89, 1590.46, 1458.78, 1369.83, 1226.41, 1179.69 1060.78, 753.04, 601.90 cm^{-1}. HRMS (ESI) m/z calculated for $C_9H_{15}O_2$ (M + H)$^+$: 155.1072, found: 155.1078.

3-(Hexyloxy)cyclohex-2-en-1-one (2c). Yellowish oil (Batch-0.192 g, 98%; Continuous flow-0.950 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.81 (t, J = 6.8 Hz, 2H), 2.39 (t, J = 6.4 Hz, 2H), 2.34 (t, J = 6.4 Hz, 2H), 2.01–1.93 (m, 2H), 1.71 (p, J = 6.7 Hz, 3H), 1.43–1.36 (m, 2H), 1.13–1.28 (m, 2), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 178.3, 102.8, 68.7, 36.9, 31.6, 29.2, 28.6, 25.7, 22.7, 21.4, 14.1. FTIR: 2944.26, 2834.76, 2310.19, 1718.52, 1589.98, 1465.80, 1298.50, 1110.66, 1034.34, 786.44, 610.97 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{21}O_2$ (M + H)$^+$: 197.1463, found: 197.1469.

3-(Octyloxy)cyclohex-2-en-1-one (2d). Yellowish oil (Batch-0.219 g, 98%; Continuous flow-0.219 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.81 (t, J = 6.6 Hz, 2H), 2.40 (t, J = 6.4 Hz, 2H), 2.34 (t, J = 6.0 Hz, 2H), 2.01–1.93 (m, 2H), 1.77–1.65 (m, 3H), 1.33–1.26 (m, 9H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0, 178.3, 102.8, 68.8, 36.9, 31.9, 29.4, 29.3, 29.1, 28.7, 26.1, 22.8, 21.4, 14.2. FTIR (neat): 2929.90, 2862.30, 2314.45, 1727.50, 1592.35, 1461.24, 1233.15, 1184.78, 1090.23, 756.55, 607.87 cm^{-1}. HRMS (ESI) m/z calculated for $C_{14}H_{25}O_2$ (M + H)$^+$: 225.1854, found: 225.1861.

3-(2-Methoxyethoxy)cyclohex-2-en-1-one (2e). Yellowish oil (Batch-0.164 g, 97%; Continuous flow-0.166 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1H), 3.99–3.94 (dt, J = 8.8 Hz, 1.6 Hz, 2H), 3.72–3.66 (dt, J = 9.5 Hz, 2 Hz, 2H), 3.42 (s, 3H), 2.45 (t, J = 6.4 Hz, 2H), 2.34 (t, J = 6.4 Hz, 2H), 2.02–1.93 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 177.9, 103.1, 70.3, 67.8, 59.3, 36.8, 29.1, 21.3. FTIR (neat): 3023.28, 2401.97, 1730.21, 1602.11, 1464.39, 1217.26, 1188.16, 1001.03 cm^{-1}. HRMS (ESI) m/z calculated for $C_9H_{15}O_3$ (M + H)$^+$: 171.1021, found: 171.1031.

3-(3-Phenylpropoxy)cyclohex-2-en-1-one (2f). Yellowish oil (Batch-0.225 g, 98%; Continuous flow-0.225 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H), 7.23–7.15 (m, 3H), 5.32 (s, 1H), 3.83 (t, J = 6.4 Hz, 2H), 2.74 (t, J = 7.2 Hz, 2H), 2.41 (t, J = 6.4 Hz, 2H), 2.34 (t, J = 6.0 Hz, 2H), 2.09–2.03 (m, 2H), 2.02–1.94 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0, 178.1, 141.0, 128.6, 128.5, 126.3, 102.9, 67.7, 36.9, 32.2, 30.2, 29.1, 21.4. FTIR: 3023.67, 2847.54, 2875.98, 2365.45, 1723.13, 1663.91, 1547.80, 1379.97, 1221.50, 1198.80 cm^{-1}. HRMS (ESI) m/z calculated for $C_{15}H_{19}O_2$ (M + H)$^+$: 231.1385, found: 231.1387.

3-(Benzyloxy)cyclohex-2-en-1-one (2g). Yellowish oil (Batch-0.197 g, 98%; Continuous flow-0.197 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.33 (m, 5H), 5.48 (s, 1H), 4.89 (s, 2H), 2.47 (t, J = 6.4 Hz, 2H), 2.37 (t, J = 6.4 Hz, 2H), 2.05–1.96 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 177.7, 135.1, 128.8, 128.7, 128.0, 103.5, 70.5, 36.9, 29.2, 21.3. FTIR: 3029.14, 2947.04, 2947.04, 2881.89, 2315.54, 1734.79, 1648.08, 1597.17, 1359.34, 1221.55, 1175.66, 863.08, 743.15 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{15}O_2$ (M + H)$^+$: 203.1072, found: 203.1079.

3-((2-Bromobenzyl)oxy)cyclohex-2-en-1-one (2h). Yellowish oil (Batch-0.146 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 8.0, 1.1 Hz, 1H), 7.43 (dd, J = 7.7, 1.5 Hz, 1H), 7.37–7.32 (m, 1H), 7.22 (td, J = 7.9, 1.8 Hz, 1H), 5.50 (s, 1H), 4.97 (s, 2H), 2.51 (t, J = 6.3 Hz, 2H), 2.43–2.35 (m, 2H), 2.08–2.00 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 177.3, 134.5, 133.1, 130.1, 129.4, 127.8, 103.8, 69.9, 36.9, 29.0, 21.4. FTIR: 3056.27, 3016.68, 2984.66, 2298.97, 1731.92, 1643.92, 1594.96, 1401.18, 1270.41, 1216.91, 1179.39 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{14}BrO_2$ (M + H)$^+$: 281.0177, found: 281.0177.

3-(Allyloxy)cyclohex-2-en-1-one (2i). Yellowish oil (Batch-0.149 g, 98%; Continuous flow-0.149 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02–5.90 (m, 1H), 5.36 (qt, J = 1.5, 1.4 Hz, 1H), 5.36 (s, 2H), 5.30 (ddd, J = 10.5, 2.4, 1.3 Hz, 2H), 4.37 (dt, J = 5.6, 1.3 Hz, 2H), 2.43 (t, J = 6.3 Hz, 2H), 2.34 (dd, J = 7.3, 6.0 Hz, 2H), 1.98 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 177.6, 131.5, 119.1, 103.3, 69.2, 36.9, 29.1, 21.3. FTIR: 3016.17, 2981.44, 2316.54, 1716.45, 1640.31, 1555.80, 1463.91, 1366.11, 1218.94, 1140.12 cm^{-1}. HRMS (ESI) m/z calculated for $C_9H_{13}O_2$ (M + H)$^+$: 153.0915, found: 153.0916.

3-((3-Methylbut-2-en-1-yl)oxy)cyclohex-2-en-1-one (2j). Yellowish oil (Batch-0.176 g, 98%; Continuous flow-0.176 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41–5.38 (m, 1H) 5.38 (s, 1H), 4.37 (d, J = 6.9 Hz, 2H), 2.41 (t, J = 6.4 Hz, 2H), 2.35 (t, J = 6.4 Hz, 2H), 1.98 (dd, J = 13.0, 6.5 Hz, 2H), 1.78 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 178.1, 139.7, 118.0, 103.1, 65.6, 36.9, 29.3, 25.9, 21.4, 18.3. FTIR (neat): 2953.38, 2311.97, 1720.17, 1601.11, 1553.93, 1380.22, 1242.55, 1173.79 cm^{-1}. HRMS (ESI) m/z calculated for $C_{11}H_{17}O_2$ (M + H)$^+$: 181.1228, found: 181.1236.

3-(But-3-yn-1-yloxy)cyclohex-2-en-1-one (2k). Yellowish oil (Batch-0.065 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.94 (t, J = 6.7 Hz, 2H), 2.63 (td, J = 6.7, 2.7 Hz, 2H), 2.42 (t, J = 6.4 Hz, 2H), 2.34 (t, J = 6.4 Hz, 2H), 1.98 (t, J = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 177.5, 103.1, 79.7, 70.4, 66.3, 36.8, 28.9, 21.3, 19.1. FTIR (neat): 2929.90, 2862.30, 2314.45, 2140.17, 1722.50, 1600.35, 1561.24, 1237.15, 1184.78, 1090.23 cm^{-1}. HRMS (ESI) m/z calculated for $C_{10}H_{13}O_2$ (M + H)$^+$: 165.0915, found: 165.0727.

5,5-Dimethyl-3-propoxycyclohex-2-en-1-one (2l). Yellowish oil (Batch-0.123 g, 68%; Continuous flow-0.167 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.79 (t, J = 6.8 Hz, 2H), 2.27 (s, 2H), 2.20 (s, 2H), 1.81–1.70 (m, 2H), 1.07 (s, 6H), 0.98 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 176.5, 101.6, 70.2, 50.9, 43.0, 32.6, 28.4, 22.0, 10.5. FTIR: 2959.17, 2881.44, 2310.50, 1722.54, 1598.80, 1463.91, 1367.11, 1218.58, 1147.97 cm^{-1}. HRMS (ESI) m/z calculated for $C_{11}H_{19}O_2$ (M + H)$^+$: 183.1385, found: 183.1392.

3-Isopropoxycyclohex-2-en-1-one (2m). Yellowish oil (Batch-0.120 g, 78%; Continuous flow-0.150 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (s, 1H), 4.43 (dt, J = 12.2, 5.9 Hz, 1H), 2.40–2.31 (m, 4H), 2.01–1.92 (m, 2H), 1.30 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 177.0, 103.1, 70.1, 36.8, 29.6, 21.5, 21.3. FTIR (neat): 2978.67, 2310.65, 1730.60, 1641.95, 1595.51, 1461.11, 1230.90, 1187.26, 1000.27, 757.95, 608.98 cm^{-1}. HRMS (ESI) m/z calculated for $C_9H_{15}O_2$ (M + H)$^+$: 155.1072, found: 155.1078.

3-(Cyclopentyloxy)cyclohex-2-en-1-one (2n). Yellowish oil (Batch-0.176 g, 98%; Continuous flow-0.176 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (s, 1H), 4.64–4.57 (m, 1H), 2.34 (dd, J = 12.5, 6.3 Hz, 4H), 1.95 (dt, J = 9.0, 6.5 Hz, 2H), 1.90–1.82 (m, 2H), 1.82–1.77 (m, 2H), 1.76–1.71 (m, 2H), 1.65–1.56 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 177.3, 103.8, 80.7, 36.8, 32.8, 29.5, 24.2, 21.4. FTIR: 2995.15, 2910.56, 2344.50, 1734.64, 1599.78, 1499.91, 1304.68, 1211.78, 1122.97 cm^{-1}. HRMS (ESI) m/z calculated for $C_{11}H_{17}O_2$ (M + H)$^+$: 181.1228, found: 181.1225.

3-(Cyclopentyloxy)-5,5-dimethylcyclohex-2-en-1-one (2o). Yellowish oil (Batch-0.149 g, 72%; Continuous flow-0.149 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (s, 1H), 4.60 (m, 1H), 2.21 (s, 2H), 2.19 (s, 2H), 1.90–1.56 (m, 8H), 1.05 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 175.5, 102.6, 80.7, 50.8, 43.3, 32.8, 32.60, 28.4, 24.2. FTIR: 3012.15, 2988.66, 2388.57, 1712.54, 1488.98, 1412.81, 1356.12, 1226.88, 1182.27 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{21}O_2$ (M + H)$^+$: 209.1524, found: 209.1545.

3-(1-Phenylethoxy)cyclohex-2-en-1-one (2p). Yellowish oil (Batch-0.112 g, 52%; Continuous flow-0.112 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 7.9, 6.6 Hz, 2H), 7.29–7.23 (m, 3H), 5.26 (s, 1H), 5.19 (q, J = 6.4 Hz, 1H), 2.44 (dd, J = 10.5, 6.1 Hz, 2H), 2.31–2.24 (m, 2H), 1.98–1.89 (m, 2H), 1.56 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 176.7, 141.4, 128.9, 128.2, 125.5, 104.7, 76.8, 36.8, 29.5, 23.8, 21.3. FTIR: 3029.14, 2947.04, 2947.04, 2881.89, 2315.54, 1724.79, 1658.08, 1587.17, 1449.34, 1266.11, 1199.44 cm^{-1}. HRMS (ESI) m/z calculated for $C_{14}H_{17}O_2$ (M + H)$^+$: 217.1228, found: 217.1227.

3-(Hexan-2-yloxy)cyclohex-2-en-1-one (2q). Colourless oil (Batch-0.193 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 1H), 4.23 (h, J = 6.2 Hz, 1H), 2.36–2.29 (m, 4H), 1.99–1.89 (m, 2H), 1.69–1.61 (m, 1H), 1.55–1.42 (m, 1H), 1.34–1.24 (m, 4H), 1.21 (s, 2H), 0.87 (t, J = 7.0 Hz, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 1H), 4.23 (h, J = 6.2 Hz, 1H), 2.37–2.28 (m, 4H), 1.99–1.90 (m, 2H), 1.69–1.60 (m 1H), 1.55–1.43 (m, 1H), 1.34–1.24 (m, 4H), 1.22 (d, J = 2.4 Hz, 2H), 0.90–0.83 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 177.3, 102.9, 74.8, 36.8, 35.6, 29.5, 27.5, 22.6, 21.3, 19.2, 14.1. FTIR (neat): 2929.90, 2862.30, 2314.45, 1727.50, 1592.35, 1461.24, 1233.15, 1184.78, 1090.23, 756.55, 607.87 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{21}O_2$ (M + H)$^+$: 197.1541, found: 197.1549.

3-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[α]phenanthren-3-yl)oxy)-5,5-dimethylcyclohex-2-en-1-one (2r). White solid (Batch-0.349 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (m, 2H), 4.07–3.46 (m, 1H), 2.40–2.31 (m, 3H), 1.01 (d, J = 7.2 Hz, 3H), 0.93–0.90 (m, 3H), 0.87 (d, J = 1.2 Hz, 3H), 0.85 (d, J = 1.2 Hz, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 176.9, 140.9, 139.3, 123.3, 121.8, 103.2, 77.8, 71.9, 56.9, 56.8, 56.3, 56.3, 50.3, 50.2, 42.5, 39.9, 39.8, 39.7, 37.9, 37.4, 37.0, 36.8, 36.6, 36.3, 35.9, 32.0, 31.9, 31.8, 29.8, 29.7, 28.4, 28.1, 27.6, 24.4, 23.9, 22.9, 22.7, 21.3, 21.2, 21.1, 19.6, 19.5, 18.9, 12.0. FTIR (neat): 3023.79, 2954.91, 2852.40, 2387.87, 1718.30, 1629.40, 1593.84, 1524.58, 1467.16, 1429.53, 1378.29, 1328.47 1001.03, 758.03, 597.32 cm^{-1}. HRMS (ESI) m/z calculated for $C_{33}H_{52}O_2$ (M + H)$^+$: 480.3967, found: 480.3967.

3-(((8*R*,9*S*,13*S*,14*S*)-3-Methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[α]phenanthren-17-yl)oxy)cyclohex-2-en-1-one (2s). White solid (Batch-0.349 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.5 Hz, 1H), 6.71 (dd, J = 8.6, 2.8 Hz, 1H), 6.63 (d, J = 2.7 Hz, 1H), 5.37 (s, 1H), 4.09 (dd, J = 8.7, 7.2 Hz, 1H), 3.78 (s, 3H), 2.91–2.82 (m, 2H), 2.39 (dd, J = 6.2, 3.0 Hz, 2H), 2.34 (dd, J = 7.4, 5.8 Hz, 2H), 2.03–1.93 (m, 3H), 0.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 178.1, 157.6, 138.0, 132.5, 126.5, 113.96, 111.7, 103.8, 55.4, 49.8, 43.9, 43.7, 38.6, 37.5, 36.9, 29.9, 29.4, 17.9, 26.4, 23.7, 21.4, 12.3. FTIR (neat): 3016.59, 2966.53, 2874.26, 2437.37, 2378.87, 1724.53, 1629.40, 1593.84, 1524.58, 1467.16, 1429.53, 1378.29, 1328.74, 1101.03 cm^{-1}. HRMS (ESI) m/z calculated for $C_{25}H_{33}O_3$ (M + H)$^+$: 381.2429, found: 381.2430.

1,3-Dimethoxybenzene (3). Colourless liquid (0.117 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, J = 8.2 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 6.48 (t, J = 2.4 Hz, 1H), 3.80 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 130.0, 106.2, 100.6, 77.5, 76.8, 55.4. FTIR: 3095.15, 2910.56, 1599.78, 1554.91, 1304.68, 1211.78, 1122.97 cm^{-1}. HRMS (ESI) m/z calculated for $C_8H_{11}O_2$ (M + H)$^+$: 139.0761, found: 139.0761.

2-Phenyl-1,4-dioxaspiro[4.5]decan-7-one (4). Colourless liquid (0.134 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5H), 5.09 (ddd, J = 10.9, 8.2, 6.1 Hz, 1H), 4.32 (ddd, J = 10.2, 8.3, 6.1 Hz, 1H), 3.72 (td, J = 8.3, 2.9 Hz, 1H), 2.77 (dd, J = 23.2, 14.2 Hz, 2H), 2.37 (t, J = 6.7 Hz, 2H), 2.15–2.01 (m, 2H), 2.00–1.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5 (d, J = 8.4 Hz), 138.4 (s), 138.1 (s), 128.7 (d, J = 4.3 Hz), 128.4 (d, J = 3.4 Hz), 126.3 (d, J = 2.5 Hz), 111.1 (s), 78.32 (d, J = 29.4 Hz), 71.8 (d, J = 4.3 Hz), 52.6 (s), 52.1 (s), 40.4 (s), 35.2 (s), 34.6 (s), 20.2 (d, J = 11.5 Hz). FTIR: 3023.79, 2962.12, 2873.22, 2312.25, 1711.09, 2594.96, 1465.21 cm^{-1}. HRMS (ESI) m/z calculated for $C_{14}H_{17}O_3$ (M + H)$^+$: 233.3070, found: 233.3075.

2,3,4,6-Tetrahydro-1*H*-benzo[*c*]chromen-1-one (5). Yellow solid (0.190 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 7.9 Hz, 1H), 7.32 (t, J = 7.0 Hz, 1H), 7.20 (td, J = 7.5, 1.2 Hz,

1H), 7.02 (dd, J = 7.5, 0.7 Hz, 1H), 5.12 (s, 2H), 2.59–2.51 (m, 4H), 2.00 (dt, J = 12.6, 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 174.1, 128.7, 127.9, 127.0, 124.9, 123.8, 113.2, 69.6, 38.4, 29.0, 20.2. FTIR: 3329.14, 2947.04, 2947.04, 2881.89, 2315.54, 1664.08 cm^{-1}. HRMS (ESI) m/z calculated for $C_{13}H_{13}O_2$ $(M + H)^+$: 201.0915, found: 201.0919.

Conclusions

In conclusion, we have developed a novel, highly efficient and chemoselective catalytic method for the transetherification of a variety of vinylogous esters with various primary and secondary alcohols to afford the substituted vinylogous esters in high yield. Furthermore, this approach was sustainable for all the functional groups tested and easily integrated into a continuous flow mode to produce a variety of vinylogous esters on a large scale. Interestingly, a novel method for de-alkylation of vinylogous esters was also developed by using environmentally benign water and Fe-catalyst. A plausible mechanism was proposed for the transetherification which involves remote C=O group chelation followed by alcohol attack on the double bond.

Conflicts of interest

There are no conflicts to declare.

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