Norwegian University
of Life Sciences

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Faculty of Chemistry, Biotechnology and food science

Towards Fuligopyrone B: Explorative Work and Route Scouting

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Acknowledgment

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First, I would like to thank Yngve Stenstrøm for giving me the opportunity to take a master's degree in organic synthesis. I would especially thank my supervisors Marius Aursnes and Petros Danielsen Siapkaras for their guidance through my master project. You have provided me with valuable knowledge and helpful guidelines throughout the whole project. In addition, you have shared encouraging words during the "pain periods" and provided a great environment both inside and outside the lab.

"Top notch!"

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Last but not least, I would like to thank my family for always being there for me – through thick and thin. Especially my parents: You have taught me valuable lessons such that hard work always pays off. You have been supportive throughout my whole life.

Sammendrag

I 2023 ble fuligopyron B isolert fra *Fuligo septica*. Ingen betydelig biologisk aktivitet ble påvist, men det ble observert en kraftig UV-absorpsjon ved 325 nm. Dette gav en indikasjon om at fuligopyron B kan fungere som solkrem/solbeskyttelse for den gule fruktmassen på *Fuligo septica*. Hovedmålet med denne oppgaven var å utvikle en syntese mot fuligopyron B og etablere en effektiv prosedyre for regioselektiv klorinering av 4-hydroksy-2-pyronringssystemet. Den planlagte konvergente syntesen av fuligopyron B er basert på to kommersielt tilgjengelige startmaterialer: pyridinium-svoveltrioksid og 3-butyn-1-ol.

Pyridinium-svoveltrioksidsaltet ble omdannet til metyl (2*E*,4*E*)-5-(4-((*tert*-butyldimetylsilyl)oksy)fenyl)penta-2,4-dienoat i en 4-trinns syntese. 2,4-dienoat-et var dermed klar til å bli koblet med 6-(2-aminoetyl)-3-kloro-2-oxo-2*H*-pyran-4-yl acetat i en amidbinding for så å senere danne fuligopyron B. Syntesen av acetatet viste seg å være mer utfordrende. I løpet av dette prosjektet ble 3-butyn-1-ol omdannet til 6-(2-((*tert*-butyldimetylsilyl)oksy)etyl)-3-klor-2-okso-2*H*-pyran-4-yl acetat i en 6-trinns syntese. Et av fokusene ved videre arbeid med dette prosjektet vil dermed være å konvertere silyleteren til et amin for å danne det ønskede acetatet og deretter koble det med 2,4-dienoat-et for å senere danne fuligopyron B.

I løpet av prosjektet ble det også utviklet en ny regioselektiv klorinering av 4-hydroksy-2-pyronringssystemet. Prosedyren involverte NCS og TEB i en elektrofil aromatisk substitusjon, der TEB ble brukt i katalytiske mengder. Den ble testet på flere 4-hydroksy-2-pyronringssystemer med vellykkede resultater. En faktor som viste seg å være et problem ved reaksjonen var imidlertid utbyttet, som var varierende avhengig av skalaen og de forskjellige 4-hydroksy-pyronringssystemene. Det kreves derfor ytterligere forskning for å forbedre protokollen.

Abstract

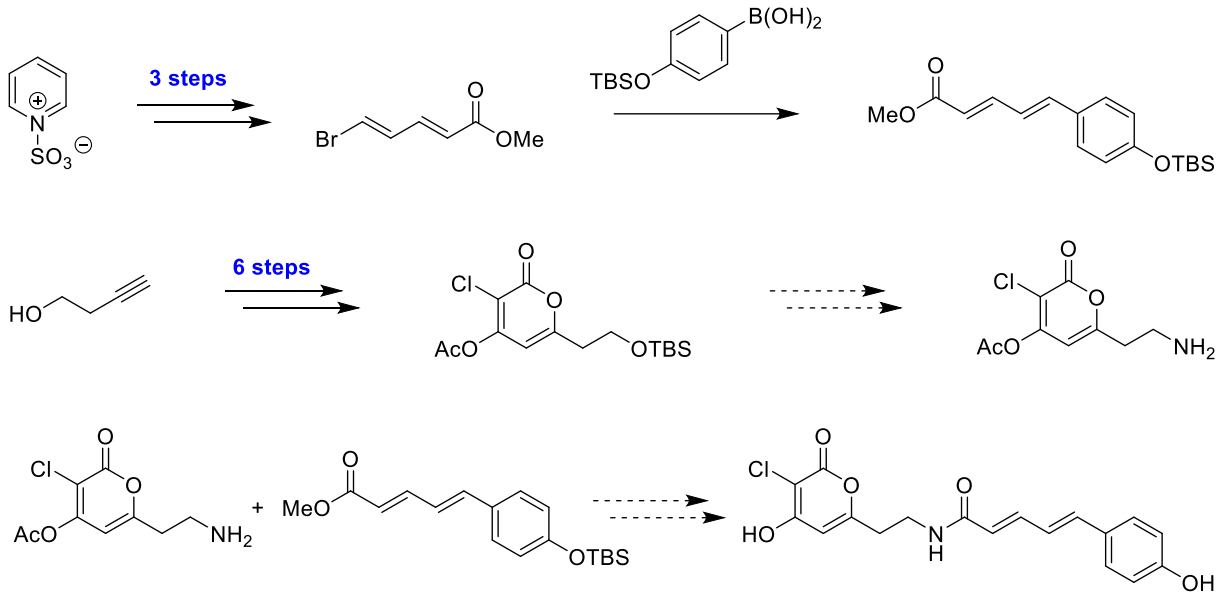
In 2023, fuligopyrone B was extracted and isolated from *Fuligo septica*. No remarkable biological activity was observed. It did, however, have a noteworthy UV-absorption at 325 nm. This indicated a potential function as sun protection for the yellow fruiting body of *Fuligo septica*. The primary objective of this study was to develop a synthesis route for fuligopyrone B and establish an effective procedure for the regioselective chlorination of the 4-hydroxy-2-pyrone ring system. The planned convergent synthesis of fuligopyrone B is based on two commercially available starting materials: pyridinium sulfonate salt and 3-butyn-1-ol.

The pyridinium sulfonate salt was successfully converted into methyl (2*E*,4*E*)-5-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)penta-2,4-dienoate in a 4-step synthesis. The 2,4-dienoate was then ready to be coupled with 6-(2-aminoethyl)-3-chloro-2-oxo-2*H*-pyran-4-yl acetate in an amide formation to later form fuligopyrone B. The synthesis of the acetate proved to be more challenging. During this project 3-butyn-1-ol was converted to 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-chloro-2-oxo-2*H*-pyran-4-yl acetate in a 6-step synthesis. One of the future tasks for this project will therefore be to convert the silyl ether into an amine to form the desired acetate, and then couple it with the 2,4-dieonate to later form fuligopyrone B.

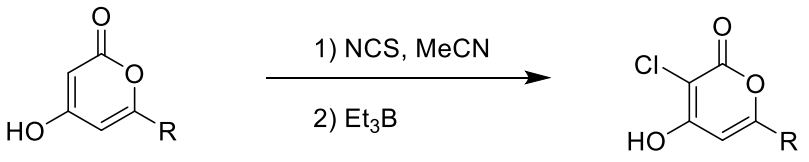
During the project a new regioselective chlorination of 4-hydroxy-2-pyrone ring system was developed in our laboratory. The procedure involved NCS and TEB in an electrophilic aromatic substitution, where TEB is used in catalytic amounts. It was tested on several 4-hydroxy-2-pyrone ring systems with successful outcomes. However, the yield seemed to vary depending on the scale and the different 4-hydroxy-pyrone ring systems. Further research is therefore required to improve the new regioselective chlorination.

Graphical Abstract

Synthetic approach towards fuligopyrone B



Regioselective chlorination of 4-hydroxy-2-pyrone ring systems



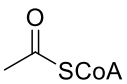
R = CH_3
R = CH_2CH_2OTBS
R = CH_2CH_2OH

Abbreviations

BuLi	Butyllithium
CoA	Coenzyme A
d	Doublet
dd	Double doublet
DCM	Dichloromethane
°C	Degrees Celsius
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
dq	Double quartet
eq	Equivalent
EtOAc	Ethyl acetate
F. septica	*Fuligo septica*
FGI	Functional group interconversion
h	Hour/hours
Hz	Hertz
LDA	Lithium diisopropylamide
m	Multiplet
Me	Methyl
min	Minutes
n	*Normal*
NCS	N-Chlorosuccinimde
nm	Nanometer
p	*Para*
ppm	Parts per million
q	quartet
Rf	Retention factor
rt	Room temperature
s	Singlet

t	*Tert*
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBDPSCl	*Tert*-butyldiphenylsilylchloride
TBS	*Tert*-butyldimethylsilyl
TBSCl	*Tert*-butyldimethylsilylchloride
td	Tripel doublet
TEA	Triethylamine
TEB	Triethylborane
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV	Ultraviolet

Compound Library



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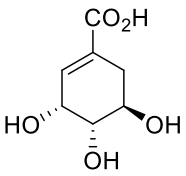

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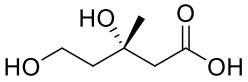

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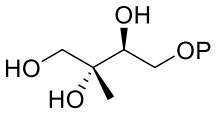

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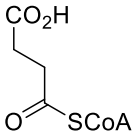

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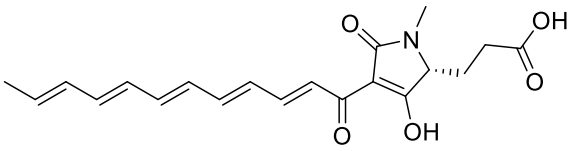

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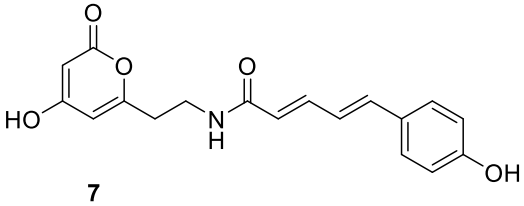

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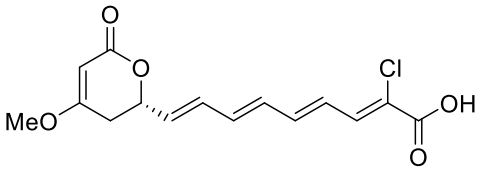

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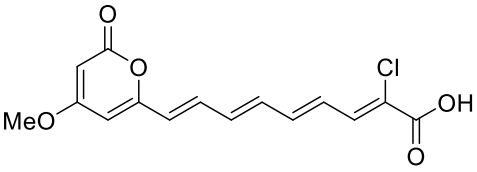

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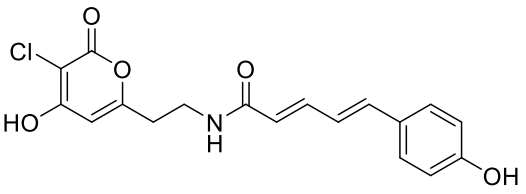

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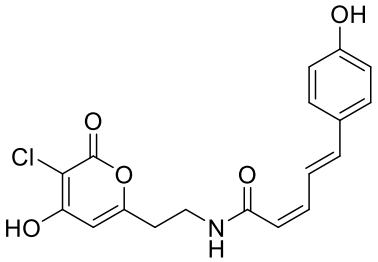

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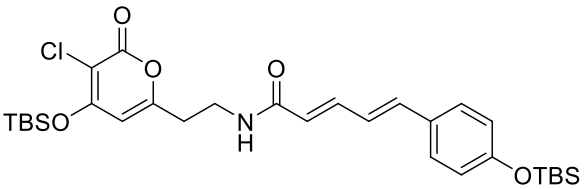

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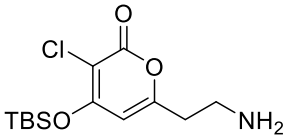

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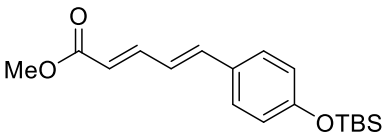

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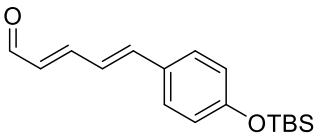

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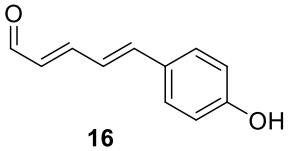

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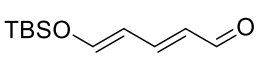

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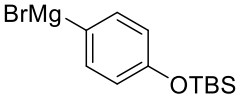

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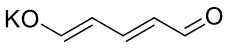

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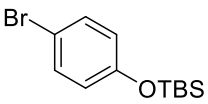

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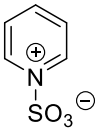

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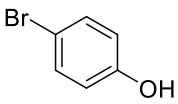

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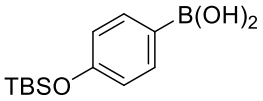

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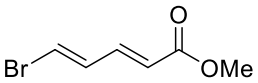

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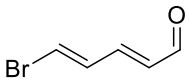

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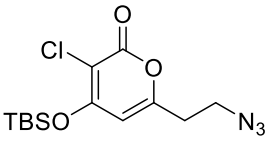

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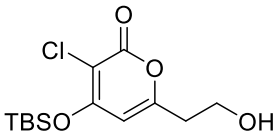

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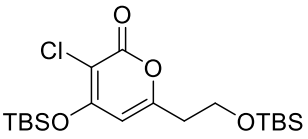

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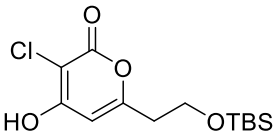

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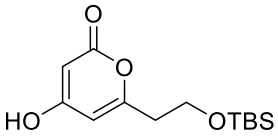

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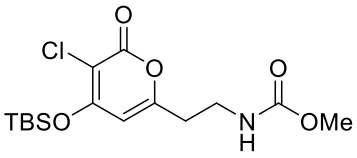

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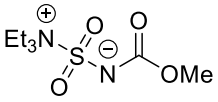

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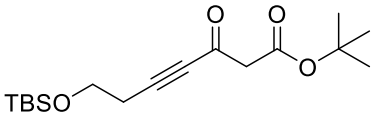

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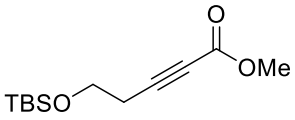

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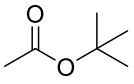

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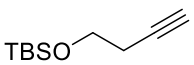

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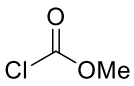

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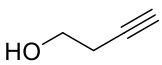

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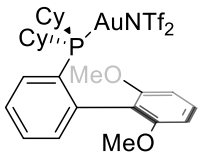

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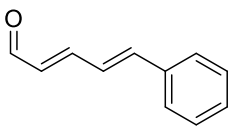

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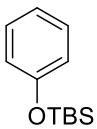

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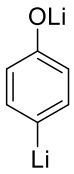

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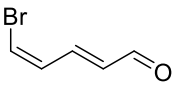

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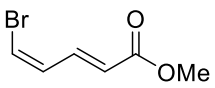

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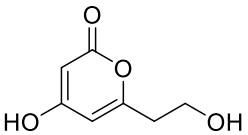

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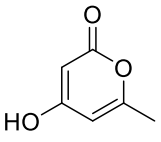

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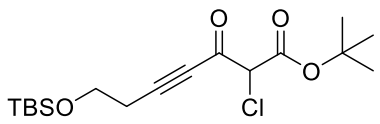

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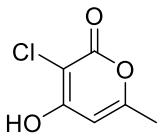

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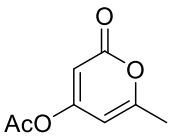

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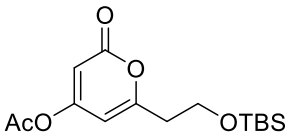

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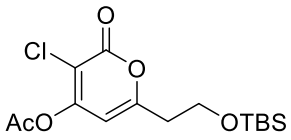

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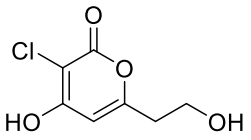

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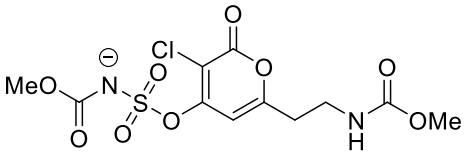

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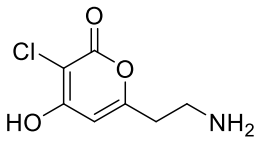

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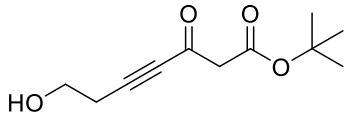

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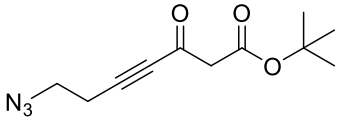

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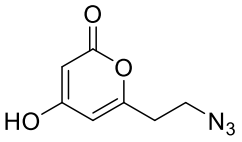

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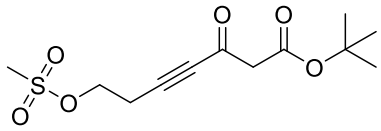

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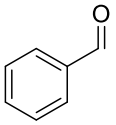

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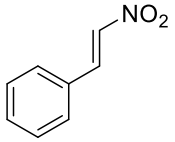

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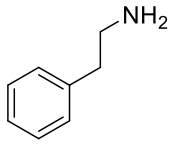

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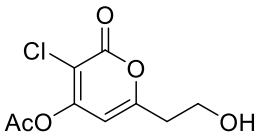

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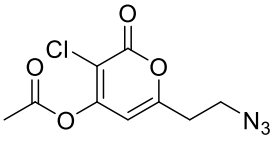

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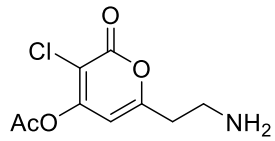

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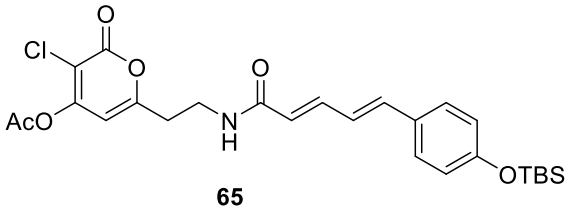

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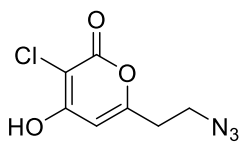

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List of Content

1 Aim of Study

In 1948 it was discovered that *Fuligo septica* (*F. septica*), a yellow fungus, contained yellow pigments with antibiotic activity.[1] Since then, numerous chemical investigations have been conducted on *F. septica*, where several yellow pigments have been discovered. One of these yellow pigments was fuliogpyrone B (**10**), which was discovered in 2023.[2] Fuligopyrone B (**10**) was found to lack any significant biological activity. It did, however, absorb UV-light at 325 nm and may thus work as a temporary sun protection for the fruiting mass of *F. septica*.[2]

There has been no reported synthesis of fuligopyrone B (**10**) and the aim of this project is to establish an effective and convergent synthetic approach to reach this target.

2 Natural Products

2.1 Natural products

Natural products are simply defined as small substances or compounds produced by biological sources.[3] Natural products are commonly classified into primary and secondary metabolites, although there are often an intersection between these categories.[4] Primary metabolites are compounds which are essentially the same in all living organisms, apart from some slight differences.[4] These are involved in growth, development and reproduction of living matter.[5] Examples of primary metabolites are fats, proteins and carbohydrates.[4]

Secondary metabolites are natural compounds found in only specific organisms, or groups of organisms.[4] They contribute to the survival functions of the organisms from which they originate.[6] Examples of secondary metabolites are steroids, alkaloids and polyketides.[7] Usually in organic chemistry the phrase “natural products” means secondary metabolites, since these often have interesting properties.[7]

Secondary metabolites are constructed using building blocks that originate from the primary metabolism.[4] The key building blocks utilized in their biosynthesis derive from the intermediates acetyl coenzyme A (acetyl-CoA) (**1**), shikimic acid (**2**), mevalonic acid (**3**) and methylerythritol phosphate (**4**),[4] shown in **Figure 2-1**.

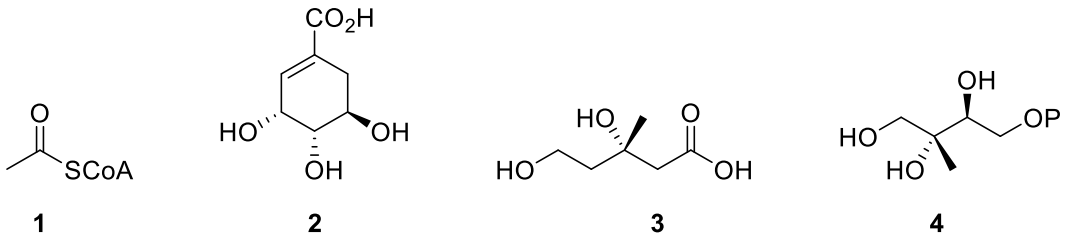
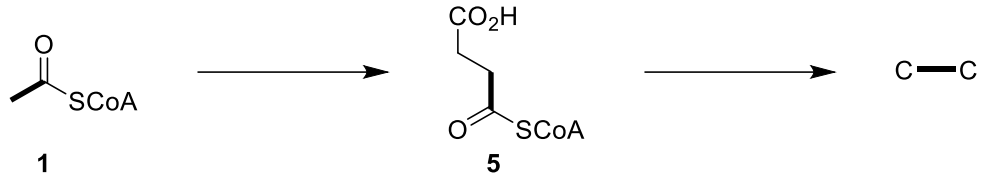


Figure 2-1 Display of four common intermediates from which many building blocks are derived.[4]

Acetyl-CoA (**1**) is an important intermediate which may become a part of an extended alkyl chain within fatty acids or contribute to the structure of an aromatic system, such as phenols. Acetyl-CoA (**1**) is often first converted into the more reactive malonyl-CoA (**5**),[4] shown in **Scheme 2-1**. Both fatty acids and polyketides are made from **1** and **5** in the acetate pathway.[7]



Scheme 2-1 Formation of C-C bonds with **1**.[4]

3 Polyketides

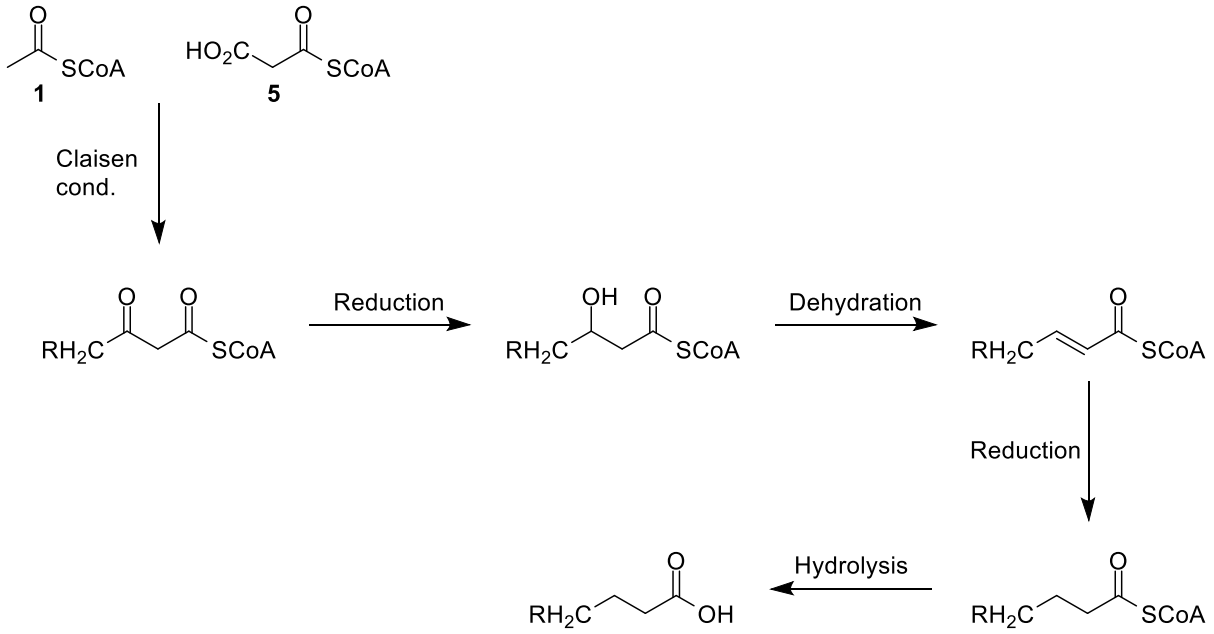
3.1 Polyketides

Polyketides are secondary metabolites with a huge variety with regards to both structure and function. They exhibit a broad range of bioactivities such as antibacterial, antifungal, anticancer and so on. Examples of organisms that can produce polyketides are bacteria, fungi, plants and insects.[8]

As stated earlier, polyketides have huge variety when it comes to structures. They can derive from poly-beta-keto chains, which are built up from **1** and **5**. The ketone on the poly-beta-keto chains can be reduced to later form different types of polyketide systems, such as aromatics, macrolides and fatty acids.[4]

3.2 Fatty acids

Fatty acids are biosynthesized from **1** and **5**, where they produce a beta-keto ester in a Claisen condensation.[4] The keto group is then reduced, which happens after each chain extension. The reduction is carried out through three steps: first the keto group is reduced to an alcohol, then its dehydrated and the double bond is reduced. The reduction is then followed up by hydrolysis to form the acid group.[4] The entire process is shown in **Scheme 3-1**.



Scheme 3-1 Acetate pathway towards fatty acids.[4]

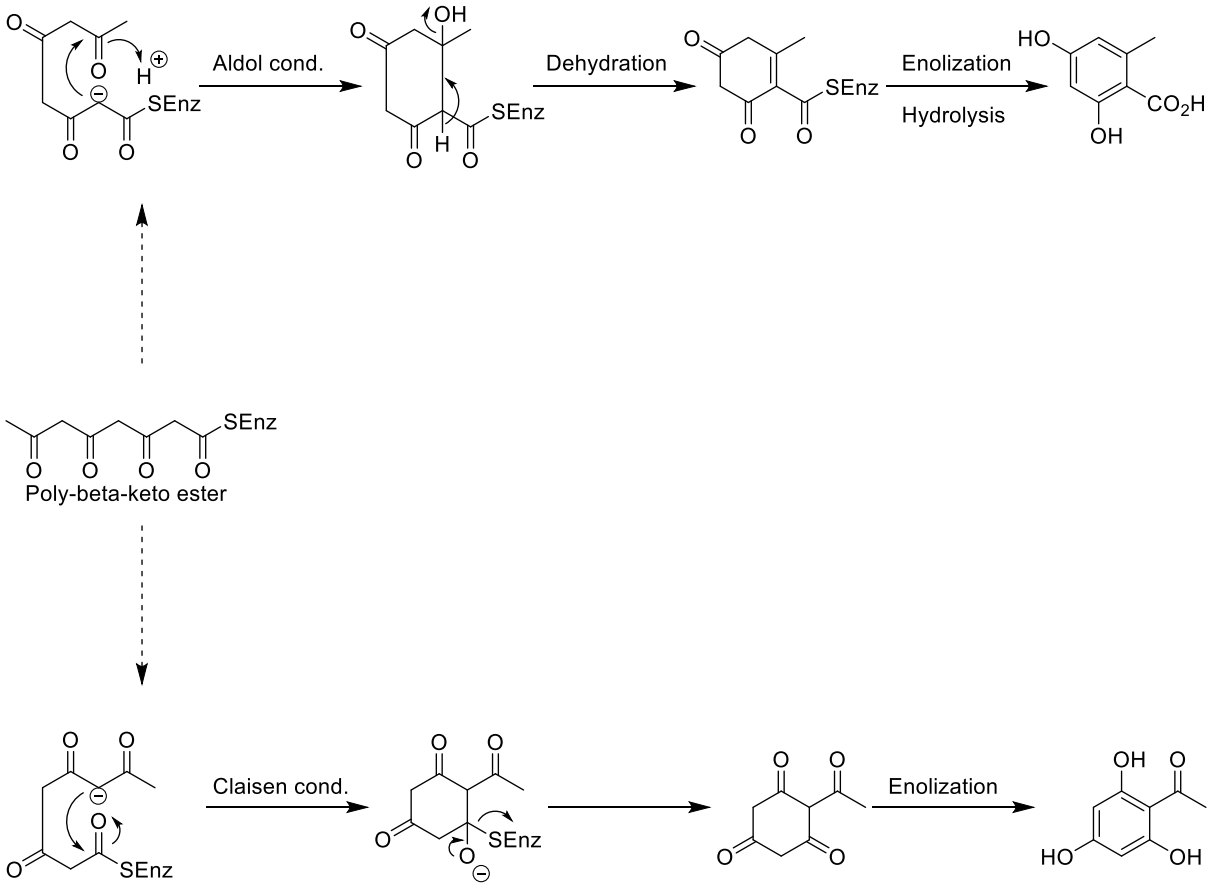
3.3 Macrolides

Macrolides are characterized by a lactone or lactam ring, and they can exist as 14,15 and 16 membered rings.[9] They are biosynthesized in the same way as fatty acids in the acetate pathway, but the degree of the reduction varies. The poly-beta-keto chains can undergo a partial, complete or no reduction at all. Which means they often have diverse chains that can contain carbonyl groups, hydroxyl groups, double bonds and alkane groups.[4]

3.4 Aromatics

Aromatic phenols can be formed from poly-keto chains where no reduction has occurred, and the chains are made up from one **1**, as a starter unit, and three **5**.[4] The chain consisting of four units can then be folded in two ways, where either a Claisen or an aldol condensation can occur. The Claisen condensation is followed up by a reformation of the carbonyl group, where the product is released from the enzyme, and an enolization to form the aromatic ring. The aldol

condensation however, is followed up by a dehydration and an enolization hydrolysis to form the aromatic ring.[4] Both pathways are shown in **Scheme 3-2**.

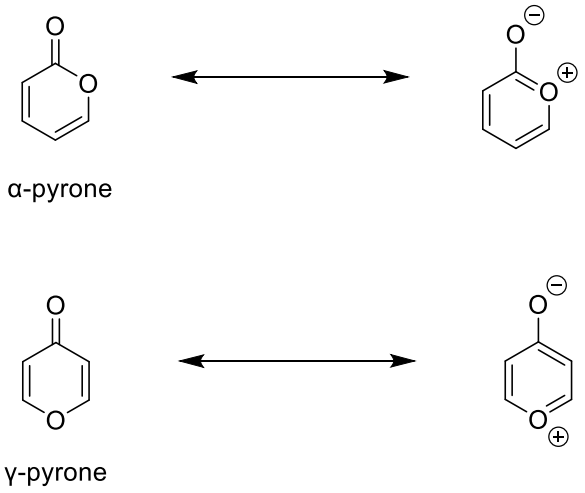


Scheme 3-2 Formation of aromatic phenols though Claisen and aldol condensation.[4]

Aromatic phenols formed from Claisen, and aldol condensation always end up as 1,3-phenols and 1,3,5-phenols. Phenols can also be biosynthesized from shikimic acid (**2**) in the shikimate pathway.[4] Other aromatic compounds can also be biosynthesized to form different aromatic polyketides, such as pyrones.

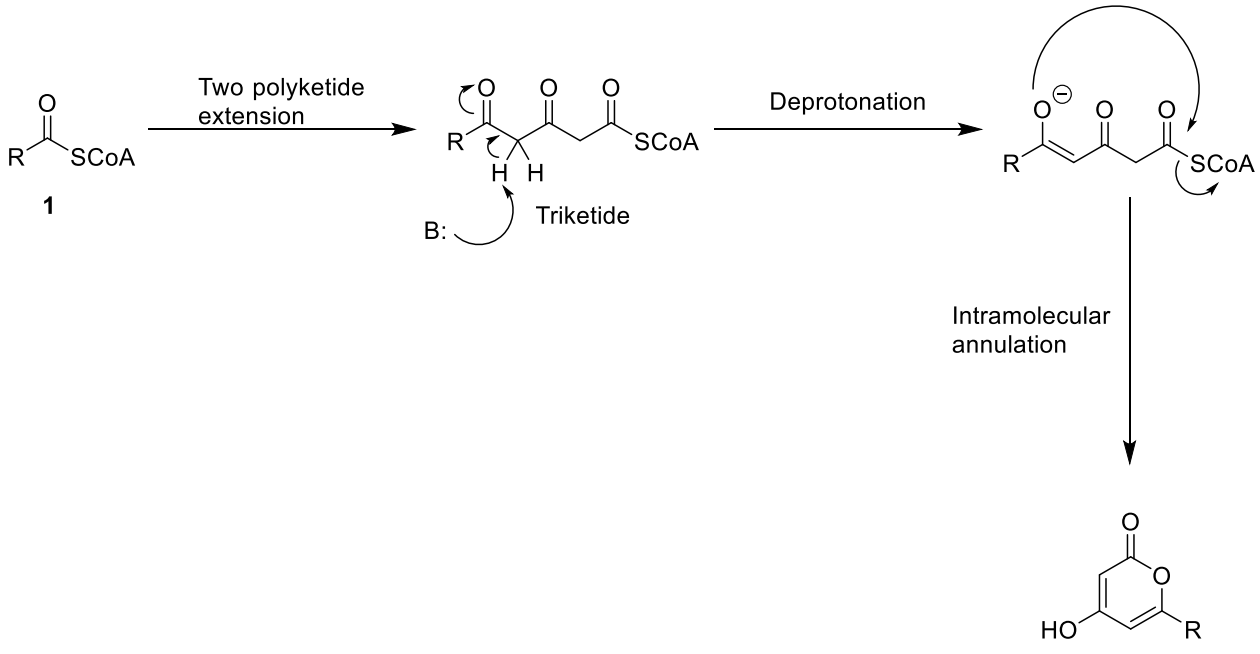
3.5 Pyrones

Pyrones are heterocyclic compounds which consist of an unsaturated six-membered ring with an oxygen atom and a ketone functional group. They are considered to be aromatic,[7] as shown in **Scheme 3-3**.



Scheme 3-3 Alpha-pyrone and γ-pyrone.[7]

The alpha-pyrones in polyketides are bult up from poly-beta-keto chains, which are bult up from three acetyl-CoA (**1**). The three acetyl-CoA (**1**) forms the triketide intermediate via a Claisen condensation. The triketide intermediate then undergoes a cyclization to from an alpha-pyrone.[10] This progress is shown in **Scheme 3-4**. Examples of polyketides containing alpha-pyrones are fuligopyrone (**7**) and fuligopyrone B (**10**).



Scheme 3-4 Formation of an alpha-pyrone from **1**.[10]

4 Fuligopyrone B (10)

4.1 Myxomycetes

Myxomycetes is a class of plasmodial slime molds that can form fruiting bodies under ideal conditions.[11] The classification of these slime molds has been controversial because of their lifecycle. At one point in its lifecycle, it was considered an animal and belonged to the animal kingdom, but in other parts of its lifecycle it was considered a plant and a fungus. In sum, this means it belonged to three different kingdoms: animal, plant and fungi kingdom. Today they are classified as Amoebozoans,[11] which is a division under the domain eukaryotes.[12]

4.2 *Fuligo septica*

Fuligo septica (*F. septica*) is a slime fungus that belongs to the class myxomycetes.[13] It is also referred to as "dog vomit fungus" because of its yellow color and similar texture to dog vomit.[14] The slime fungus is found worldwide and usually habitats on wood, stems, leaves and in bark munch.[13] In 1948 aromatic yellow pigments were isolated from *F. septica* which had antibiotic activity.[1] Since then, there have been numerous chemical investigations of *F. septica*, where several yellow pigments have been discovered. In 1987 the yellow pigment fuligorubin A (**6**) was reported,[15] and the absolute configuration was later confirmed via total synthesis.[16, 17] Later in 1989, fuligopyrone (**7**) was identified.[18] Fuligo acid (**8**) and dehydrofuligoic acid (**9**) were reported in 2009 and 2010.[19, 20] Unfortunately, no biological data was reported for these yellow pigments. It wasn't until later in 2023 that Minns *et al.* isolated and assessed the biological activity of certain yellow pigments.[2]

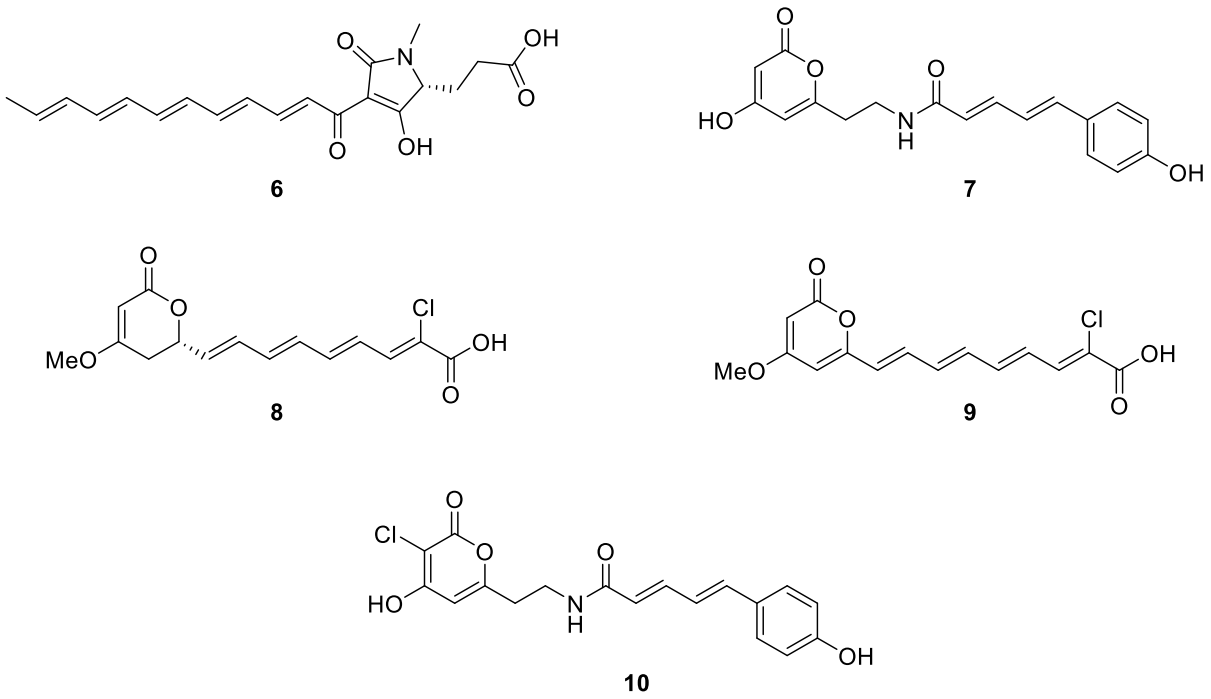


Figure 4-1 Structure of **6**, **7**, **8**, **9** and **10**.[2]

4.3 Extraction and isolation of 7 and 10

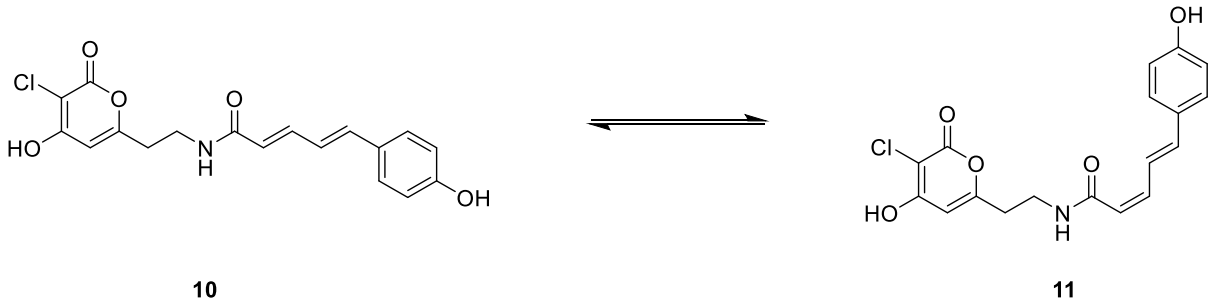
According to work performed by Minns *et al.* they extracted and purified the mixture using HPLC to yield three different pigments: fuligopyrone (**7**), fuligorybin A (**6**) and fuligopyrone B (**10**).[2] The first of which, **7** was identical to the one reported in 1989,[18] while **6** matched the molecular formula and UV-Vis spectrum of the previously reported **6** in 1987.[15] Compound **10** was reported as a new yellow pigment, as it was a 6-chlorinated analogue of **7**. However, there was no data which accounted for the presence of **8** and **9**.[2]

Both **7** and **10** were isolated as yellow solids and the structures were confirmed with HR-ESI(+)-MS analysis, ^{1}H (600 MHz) NMR, ^{13}C (150 MHz) NMR, HMBC, COSY and ROESY. Compound **10** contained one fewer proton and one chlorine more than **7** according to MS. **7** and **10** were almost identical in NMR, except for some minor differences. The chemical shift for one of the protons was missing in **10** and the carbon attached to the chlorine had higher chemical shift in ^{13}C NMR, because of deshielding via the inductive effect.[2]

4.4 Biological activity of 7 and 10

According to Minns *et al.*, **7** and **10** were tested for antibacterial, antifungal, antiprotozoal, cytotoxic, and herbicidal activities. Out of all these trials, they found out that **7** showed weak cytotoxic activity. They then concluded that **7** and **10** exhibited no significant biological activity,

and that it was unlikely that these two pigments were responsible for the antibacterial activity of *F. septica*.[2] However, **7** and **10** had a UV-absorption at 325 nm. This UV-absorption indicates that they may act as an impermanent sunscreen to help protect the fruiting mass from sunlight and thus photodamage.[2] This was tested by exposing a solution of **10** and methanol to direct sunlight for an hour. After 5 minutes an equilibrium was made between (2*E*, 4*E*) **10** and (2*Z*, 4*E*) **11**, where the ratio was 50:50.[2]



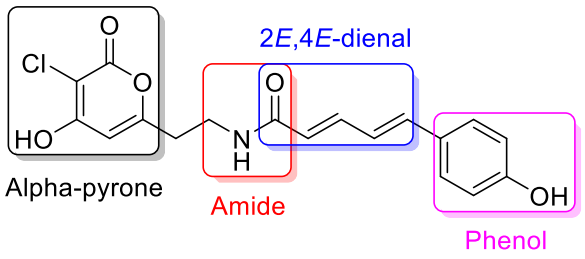
Scheme 4-1 Equilibrium between **(**2*E*, 4*E*) **10** and (2*Z*, 4*E*) **11**.[2]

A total synthesis of **7** has already been established, where its corresponding dimethyl ether was synthesized.[18] There are no reports of an established synthesis of **10**. The aim of the project is to establish a synthetic approach to fuligopyrone B (**10**).

5 Synthetic Approach to Fuligopyrone B (10)

5.1 Synthetic approach to fuligopyrone B (10)

Fuligopyrone B (**10**) consists of a chlorinated alpha-pyrone which is amid bonded to a conjugated aromatic 2*E*,4*E*-dienal system. The product contains no stereogenic centers, which exclude the search for stereoselective reactions and commercially available chiral starting material. The synthesis will be developed over multiple steps in a convergent synthesis.

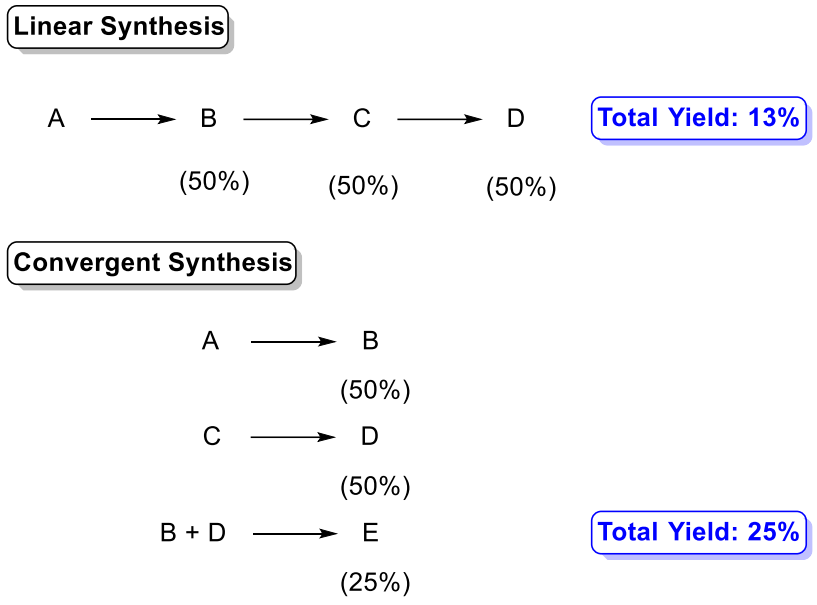


10

Figure 5-1 Structure of fuligopyrone B (**10**).

5.2 Convergent synthesis

In organic chemistry, compounds may be synthesized via a convergent or linear pathway. In a linear synthesis the products are made in a sequential order, where reactant A is synthesized to give product D via B and C. In a convergent synthesis two or more pieces are synthesized independent of each other and are then later coupled together to form the product. In this way yields may be increased,[21] and the *"arithmetic demon*" is avoided.[22] **Scheme 5-1** shows the difference between the total yield for linear and convergent synthesis, when the yield of each step is 50%.



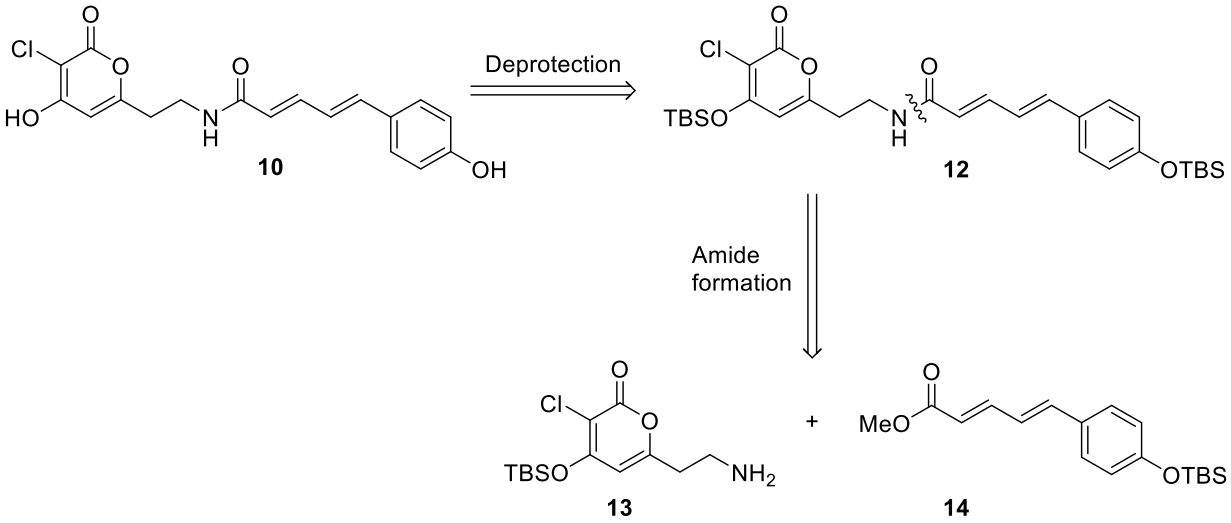
Scheme 5-1 The mathematical difference in yield between theoretical linear and convergent synthesis, where A, B, C, D and E represent reactants and products.[21]

5.3 Protective groups

In some cases, the functional groups which are present during a synthesis project might not be suited for the conditions of future steps. In such cases, a so-called protective group is necessary. This is a group introduced to a functional group to alter it characteristics and hence provide chemoselectivity going forward.[23] In other words, the reactivity of a specific functional group is reduced, to enhance the reactivity of the other functional group. This targeted approach facilitates the desired reaction with the other functional group while minimizing undesired reactions with the less-reactive group. Examples of protecting groups for alcohols are silyl ethers, acetic acid ester, methyl ether and benzyl ether. These protective groups can be removed under specific conditions, some are milder than others. Generally, they are designed to have a chemical "Achilles heel" to facilitate their effective removal.

5.4 The retrosynthetic plan for fuligopyrone B (10)

The synthetic approach towards **10** is described and shown in **Scheme 5-2**, **5-3**, **5-4**, **5-5**, **5-6** and **5-7** as retrosynthetic plans with retrosynthetic disconnection. The retrosynthetic plan starts with a deprotection of the silyl ethers on **12**. It is then followed up by a disconnection of the amide bond in **12** to form the respective reactants amine **13** and ester **14**, shown in **Scheme 5-2**. A convergent retrosynthetic strategy is employed to formulate individual retrosynthetic plans for compound **13** and **14**.



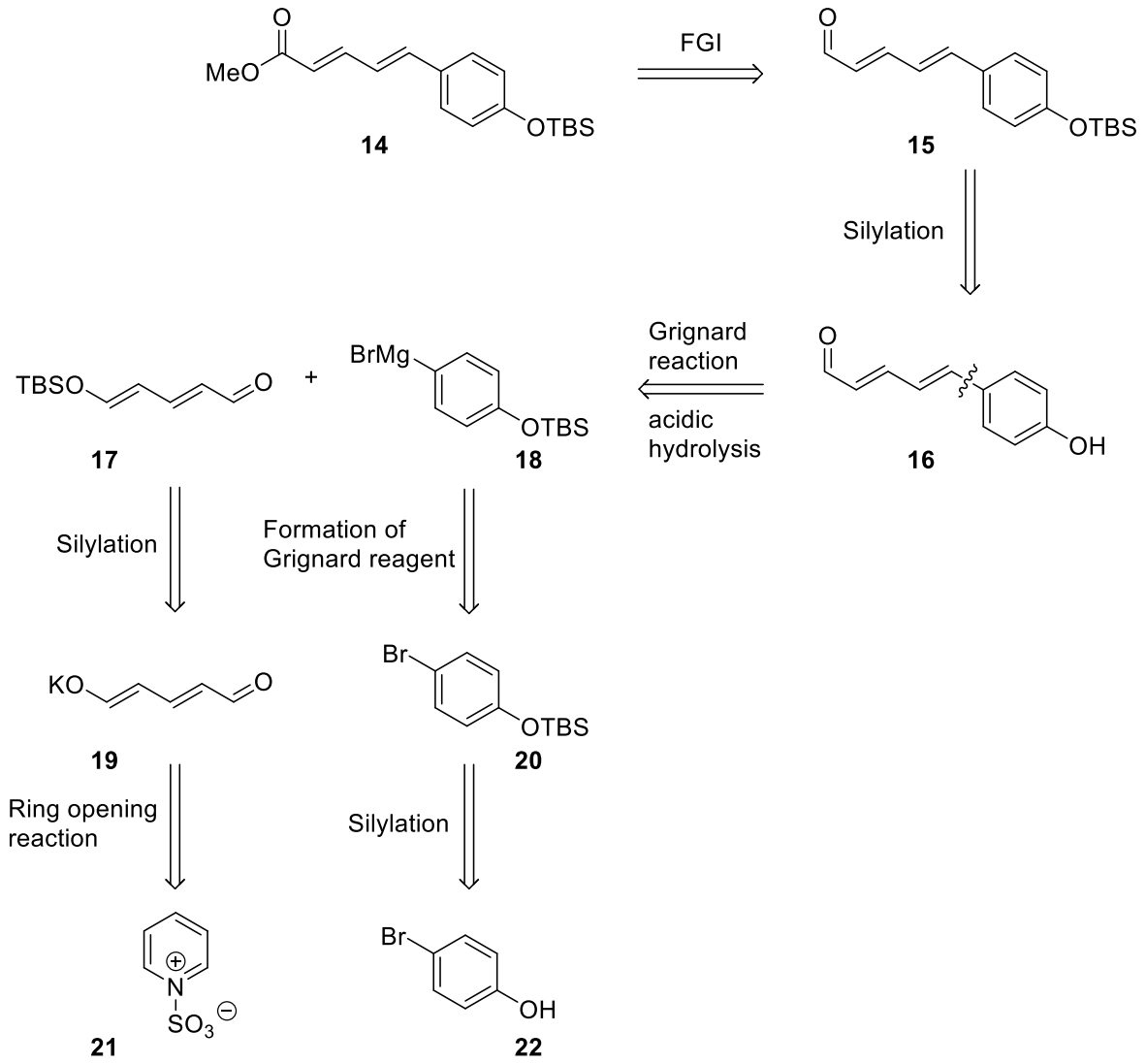
Scheme 5-2 Retrosynthetic disconnection of the amide formation in **12**.

5.5 The retrosynthetic plan for 14

There were two plausible retrosynthetic approaches towards ester **14**. They both have similarities, which are mostly inspired by the work done by Primdahl *et al.*.[24] The two retrosynthetic approaches towards ester **14** are referred to as **A** and **B**, and they are shown in **Scheme 5-3** and **5-4**.

5.6 Retrosynthetic plan A for 14

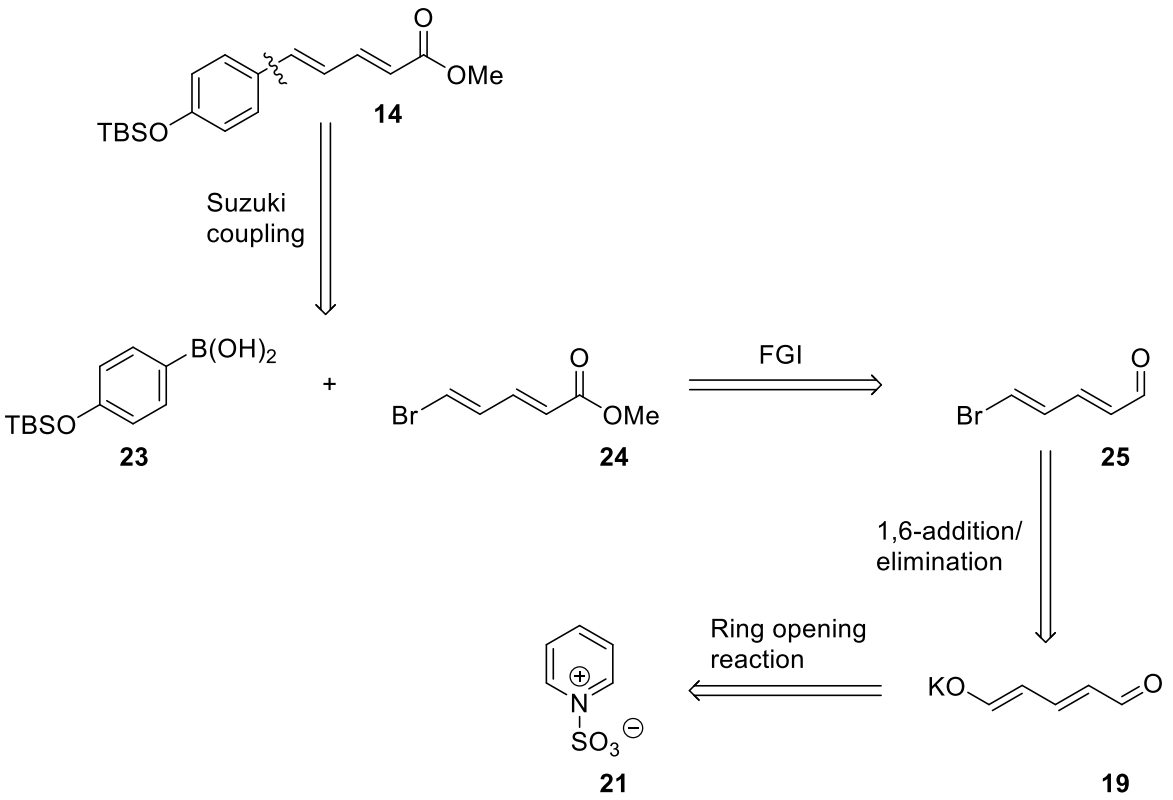
Retrosynthesis **A** is depicted in **Scheme 5-3** and starts with a functional group interconversion (FGI), where the ester in **14** is obtained by an oxidation from the aldehyde in **15**. The silyl ether in **15** is introduced via aldehyde **16**, to protect the alcohol group from oxidation. Aldehyde **16** can be prepared through a Grignard reaction between 2*E*,4*E*-dienal **17** and Grignard reagent **18**,[25] followed up by an acidic hydrolysis. The Grignard reaction utilizes two starting materials, 2*E*,4*E*-dienal **17** and Grignard reagent **18**, which are both in their silyl ether forms. Grignard reagent **18** can be obtained through an umpolung reaction from silyl protected bromophenol **20**, which then again can be obtained from the commercially available *p*-bromophenol (**22**). 2*E*,4*E*-dienal **17** however, can be obtained from the glutaconaldehyde potassium salt (**19**). Glutaconaldehyde salt **19** can be prepared through a ring-opening reaction from the commercially available pyridinium sulfonate (**21**).



Scheme 5-3 Retrosynthetic disconnections of **14** in retrosynthetic pathway **A**.

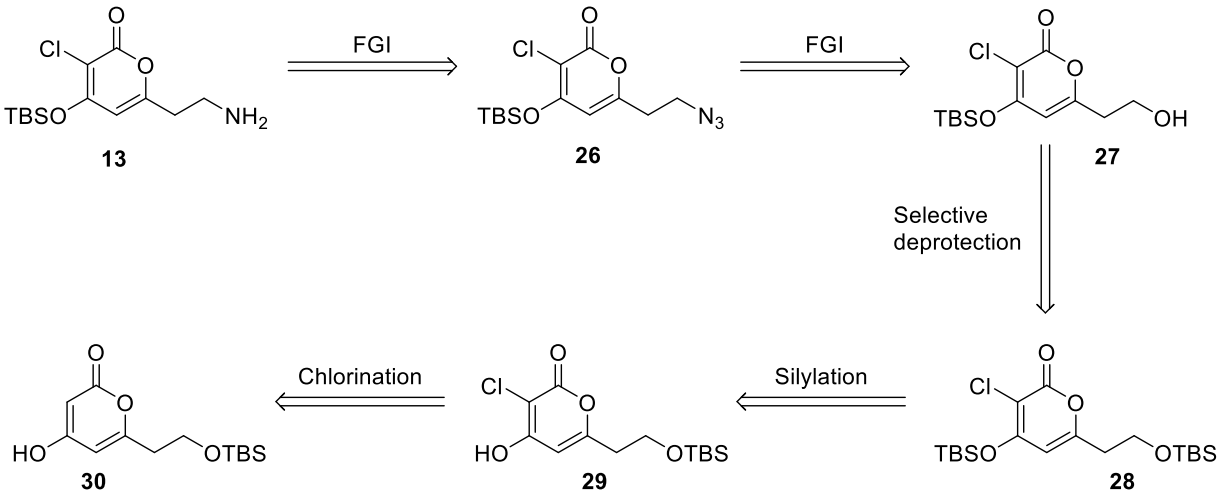
5.7 Retrosynthetic plan B for 14

In retrosynthesis **B**, ester **14** is disconnected with a Suzuki cross-coupling reagent in mind in the forward direction,[26] where the reactants are the commercially available 4-(*tert*-butyldimethylsilyloxy)phenylboronic acid (**23**) and bromo ester **24**. Bromo ester **24** can be obtained through an FGI from bromo aldehyde **25**, where the aldehyde is oxidated to an ester. Bromo aldehyde **25** can be prepared from glutaconaldehyde salt **19** with an addition/elimination reaction, where **19** can be obtained from the commercially available pyridinium sulfonate (**21**).



Scheme 5-4 Retrosynthetic disconnections of **14** in retrosynthetic pathway **B**.

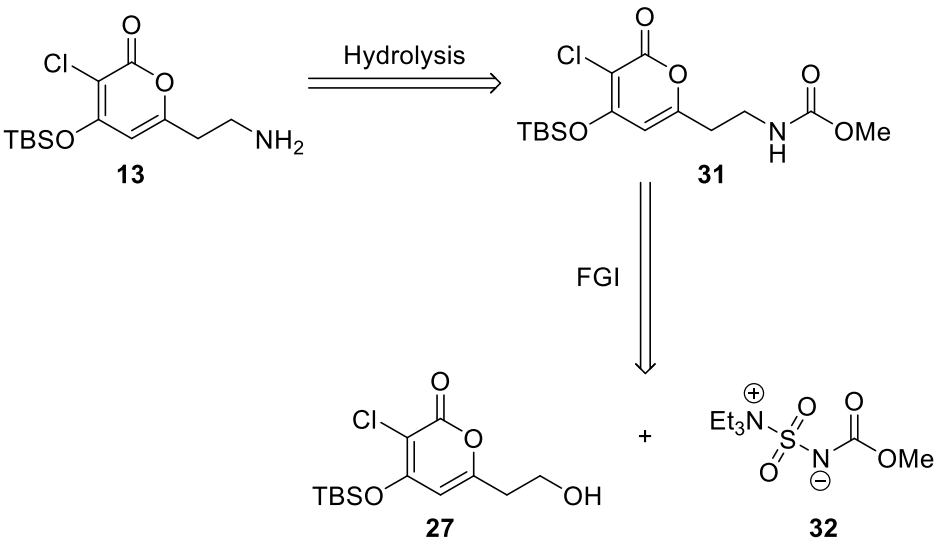
5.8 The retrosynthetic plan for 13



Scheme 5-5 Retrosynthetic disconnections of **13**.

The retrosynthetic plan for **13** starts with a FGI, where the amine in pyrone **13** is obtained from the azide in pyrone **26** through a Staudinger reduction.[27] The azide in **26** can be prepared from pyrone **27** in a Mitsunobu reaction, where the primary alcohol is converted to an azide. The amine on pyrone **13** can also be introduced in another way using Burgess reagent. Through

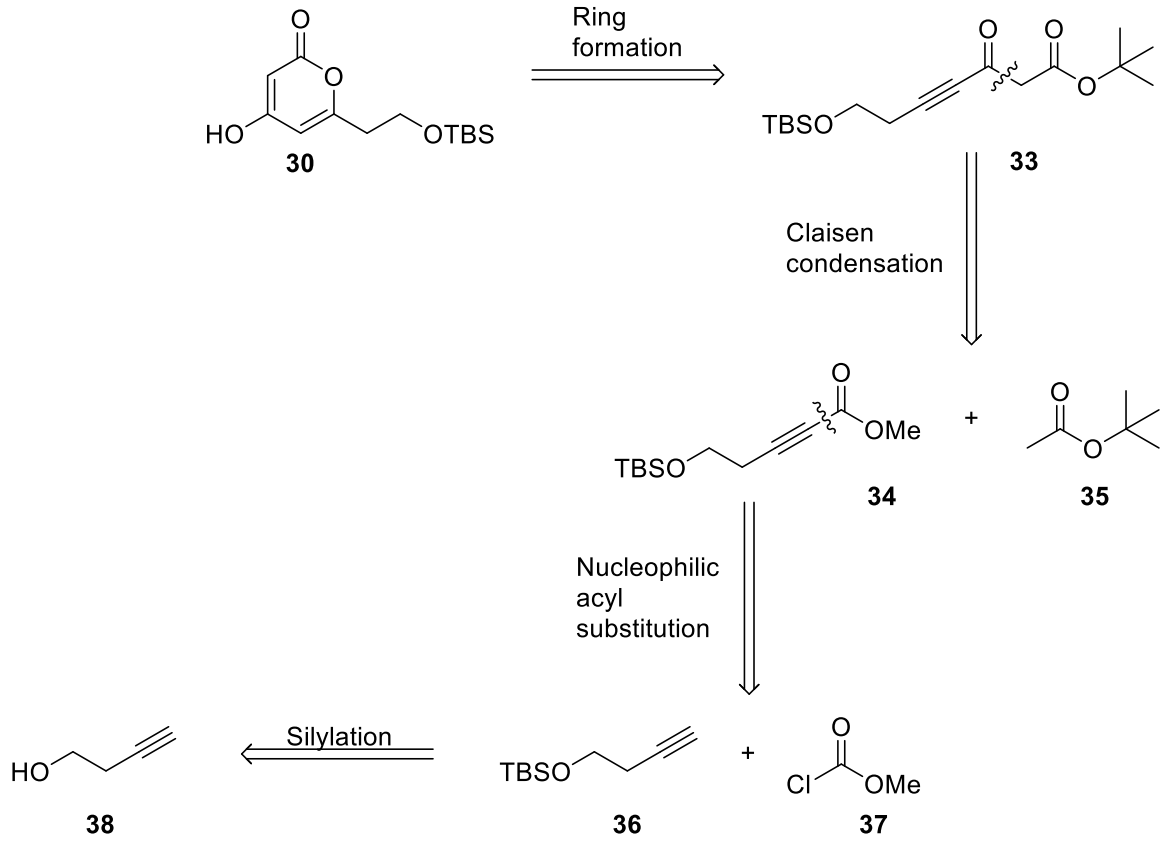
hydrolysis the amine at **13** can be prepared from carbamate **31**, where **31** is obtained from **27** with the commercially available Burgess reagent **32**. This process is shown in **Scheme 5-6**.



Scheme 5-6 Planned formation of the amine in **13** with hydrolysis and the commercially available Burgess reagent **32**.

Pyrone **27** can be obtained from **28** in a selective deprotection, where only the primary silyl ether gets cleaved off. This is inspired by the work done by Sabitha *et al.*, where they use a 50% aqueous methanolic solution of oxone to selective cleave off primary silyl ethers, in the presence of secondary and tertiary silyl ethers.[28] Pyrone **28** can be prepared through a silylation of the phenolic hydroxyl group in **29**, where **29** can be obtained from **30** with a chlorination on the alpha carbon, shown in **Scheme 5-5**.

Chlorine can also be introduced earlier in the retrosynthesis. Instead of introducing it on pyrone **30**, it can be introduced at the alpha carbon on beta-keto ester **33**, depicted in **Scheme 5-7**, which is before the ring closure. The testing of the chlorination will then be conducted before and after the ring closure.



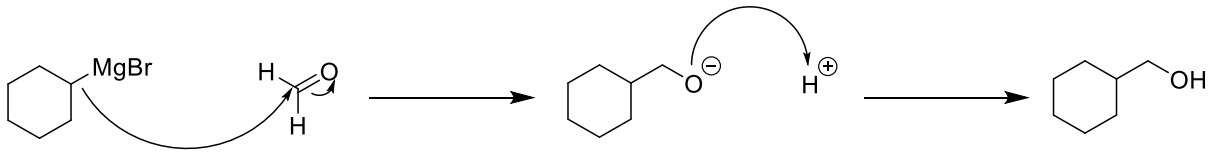
Scheme 5-7 Retrosynthetic disconnections of **13**.

The ring closing off beta-keto ester **33**, where **30** is obtained, is based on the work done by Chaladaj *et al.*.[29] In the their research they synthesize different alpha-pyrones from different beta-keto esters with the help of gold complex **39** as a catalyst.[29] Beta-keto ester **33** can be prepared in a Claisen condensation between methyl ester **34** and the commercially available *t*-butyl acetate (**35**).[30] Methyl ester **34** can be introduced via a nucleophilic acyl substitution between terminal alkyne **36** and the commercially available methyl chloroformate (**37**). At last, **36** can be obtained through a silylation of the commercially available 3-butyn-1-ol (**38**), which is shown in **Scheme 5-7**.

6 Mechanisms

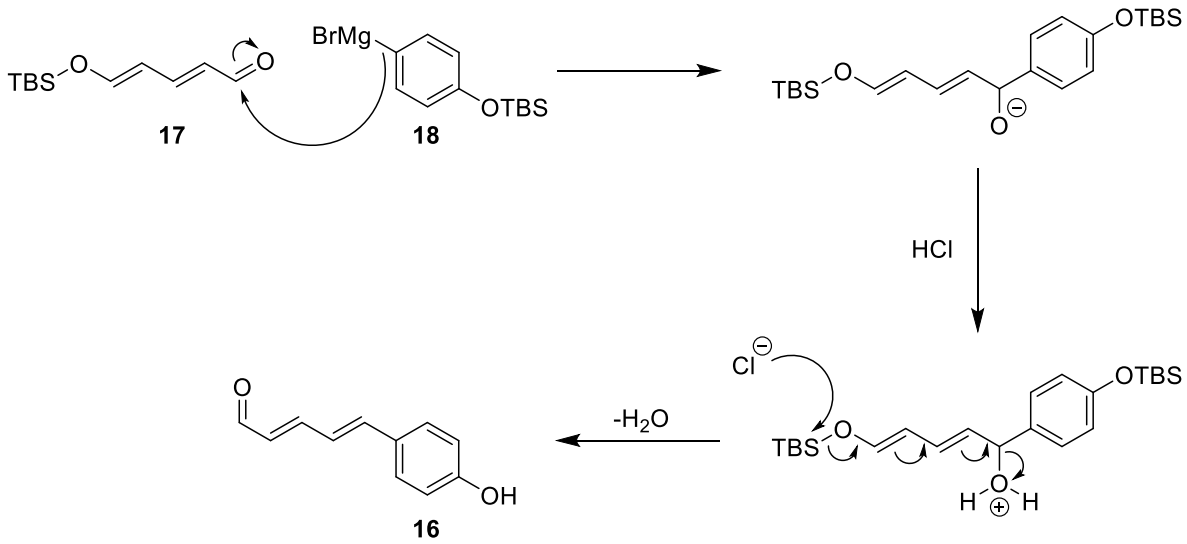
6.1 Grignard reaction

The Grignard reaction was discovered in 1900 by Victor Grignard,[25, 31] who later in 1912 got a Nobel prize for his work.[32] In a Grignard reaction a carbon-carbon bond is made with a nucleophilic Grignard reagent. The Grignard reagent is an organomagnesium reagent with the general formula of RMgX, where X is a halogen, often bromide or chloride. It is prepared in a radical reaction between an organic halide and metallic magnesium, where the solvent usually is ether.[31] The electrophilic site in the Grignard reaction is usually a carbonyl group, and they are often turned into various alcohols when exposed of nucleophilic addition by the Grignard reagent.[33] The mechanism of a Grignard reaction is shown in **Scheme 6-1**, where a formaldehyde is converted to a primary alcohol.



Scheme 6-1 A Grignard reaction between formaldehyde and a Grignard reagent.[7]

The phenol dienal **16** can be obtained through a Grignard reaction between Grignard reagent **18** and the aldehyde in **17**, followed up by acidic hydrolysis.[34] According to their research the acidic hydrolysis will give the more thermodynamically product, which is the *E,E*-dienal.[34] The silyl ethers are expected to be cleaved off, considering the acidic environment.[35] The plausible mechanism is shown in **Scheme 6-2**.

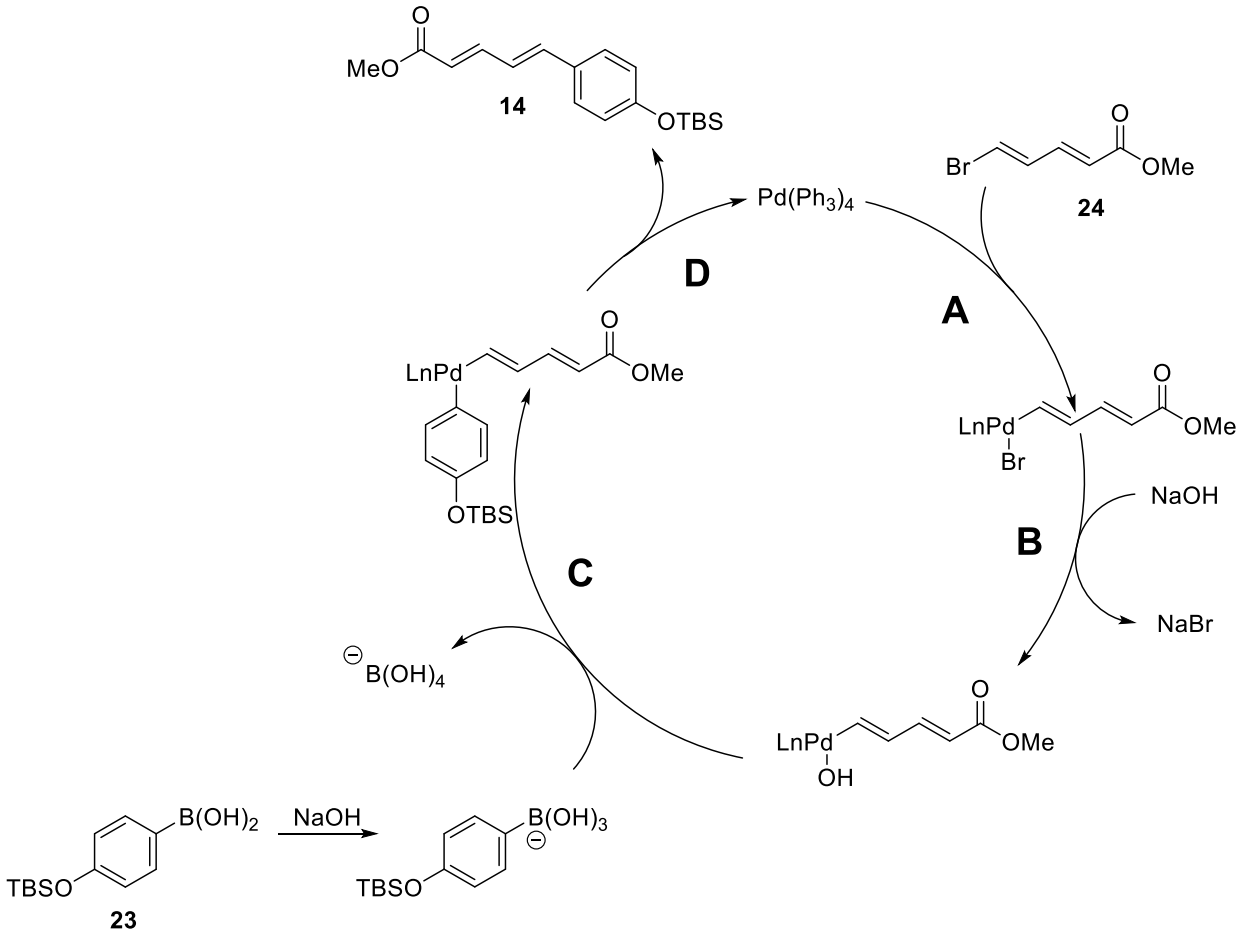


Scheme 6-2 Mechanism of the Grignard reaction between **17** and **18**, followed up by acidic hydrolysis.[34]

6.2 Suzuki reaction

The Suzuki reaction is a cross-coupling reaction between boronic acid and organohalides with palladium(0) complex as catalyst.[26] The reaction takes place in the presence of a base, where examples of common bases employed are NaOH, Na_2CO_3 and $NaHCO_3$.[36] The reaction was discovered and first published by Akira Suzuki,[26] and he shared a Nobel prize with Heck and Negishi for their contribution and discovery of the reaction.[37] The Suzuki reaction is a hugely important reaction for creating carbon-carbon bonds due to its relatively mild reaction conditions, generally affordable stoichiometric reagents and catalytic process.[37]

Ester **14** can be obtained through a Suzuki coupling between boronic acid **23** and organohalide **24**. The palladium catalyst is $Pd(Ph_3)_4$ and the base is Na_2CO_3, which forms NaOH in the presence of water. The conditions and reagents are inspired by work performed by Primdahl *et al.*.[24] The mechanism for the Suzuki coupling between **24** and **23** are shown in **Scheme 6-3**.

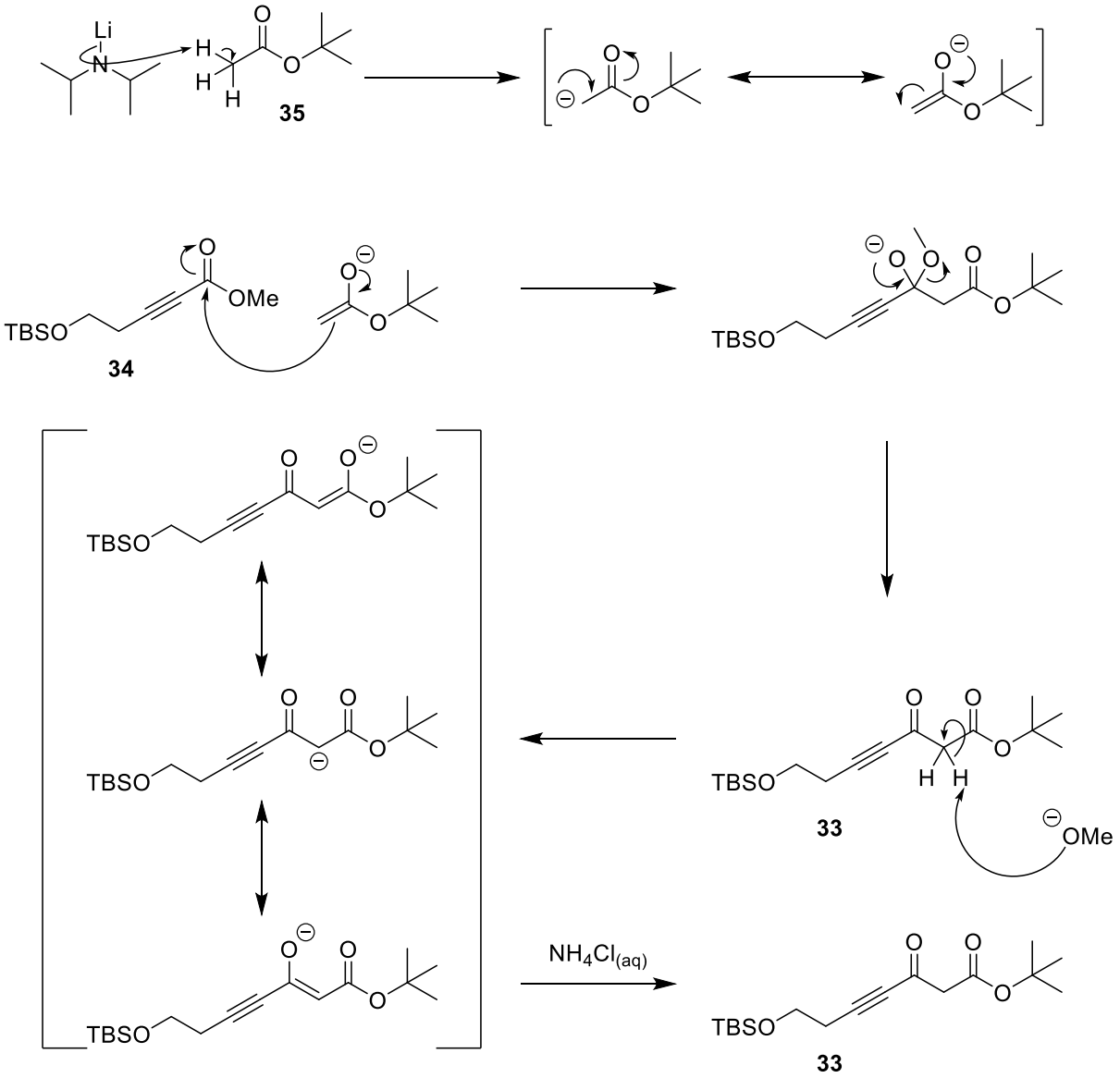


Scheme 6-3 Mechanism of the Suzuki coupling with boronic acid **23** and **24**. A: Oxidative addition, B: Metathesis, C: Transmetalation, D: Reductive elimination.[36]

6.3 Claisen condensation

Claisen condensation is a reaction that forms carbon-carbon bonds between an ester and another carbonyl group in the presence of a strong base. The other carbonyl group can be another ester, ketone or aldehyde, and the reaction produces beta-keto esters.[7] It was discovered and published by Rainer Ludwig Claisen in 1887.[30]

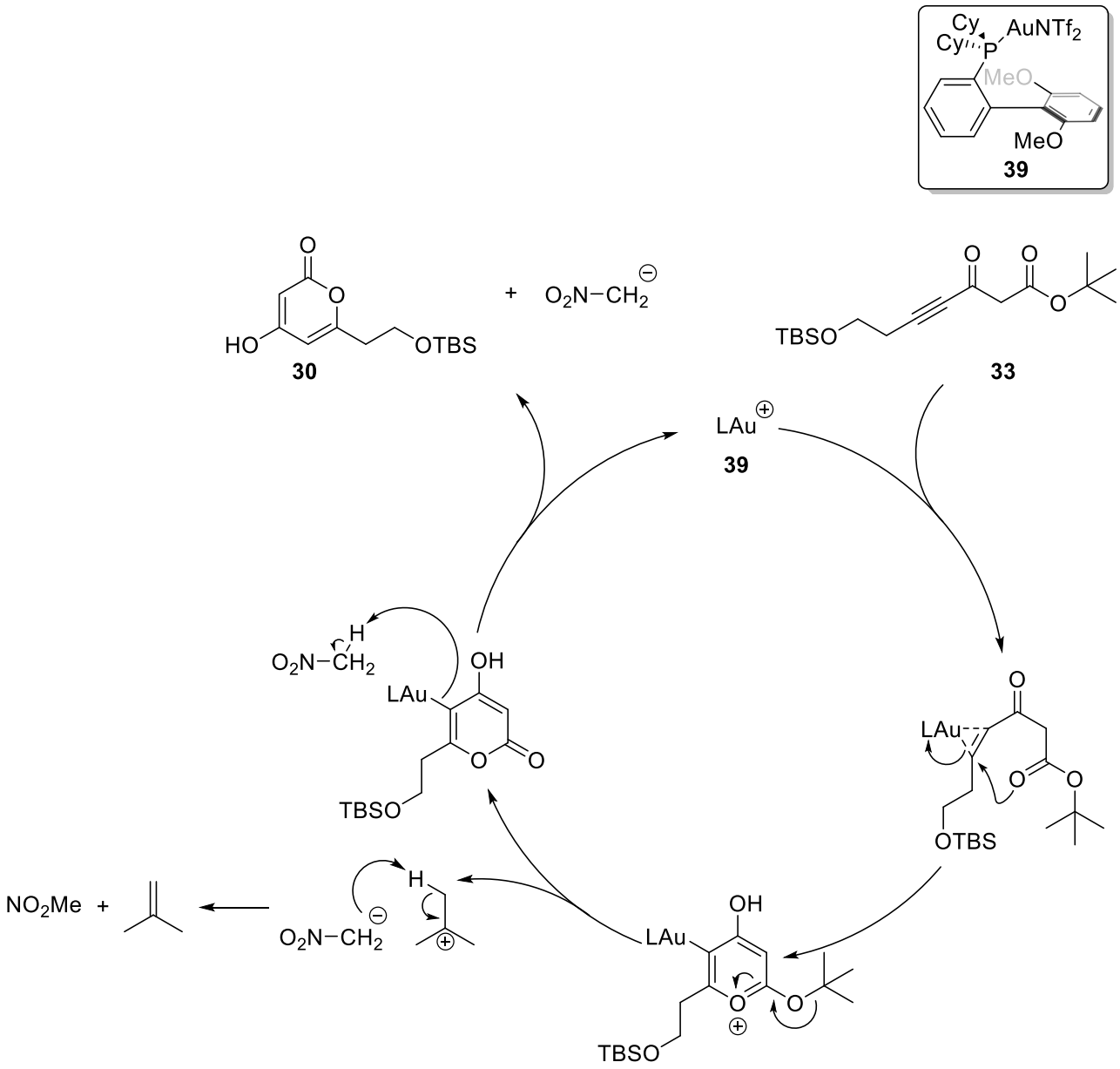
Beta-keto ester **33** can be obtained in a Claisen condensation between **35** and **34** in the presence of lithium diisopropylamide (LDA), where the reaction is quenched with ammonium chloride.[29] The mechanism of this Claisen condition is shown in **Scheme 6-4**.



Scheme 6-4 Mechanism of Claisen condensation between **34** and **35** in the presence of LDA.[7]

6.4 6-endo-dig addition of beta-keto ester 33

Beta-keto ester **33** is converted to pyrone **30** through a 6-endo-dig addition in an acidic environment, with the aid of a gold complex.[29] The gold complex used is [(SPhos)AuNTf$_2$] (**39**, Tf = trifluoromethanesulfonate), also referred to as LAu. According to Chaladaj *et al.* they also used another gold complex as a catalysator, but gold complex **39** was used numerous times on various other beta-keto esters. They also stated that acetic acid or nitromethane with **39** gives the highest reaction rates.[29] The plausible mechanism of the annulation of **33** is shown in **Scheme 6-5**.

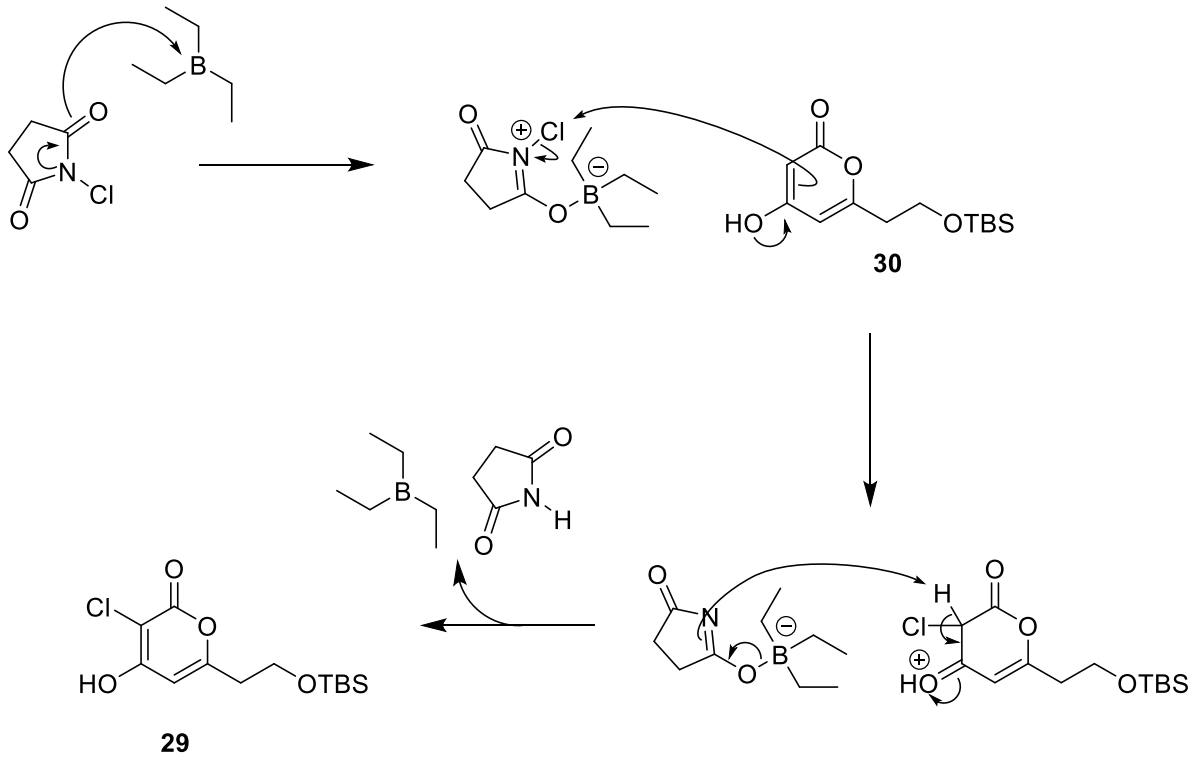


Scheme 6-5 Mechanism of the 6-endo-dig addition of **33** with gold complex **39** in acidic environment.[29]

6.5 Chlorination with N-chlorosuccinimide and triethylborane

A new chlorination method was planned to be tested for the chlorination of **30**, which has not been reported before. The reagents used are N-chlorosuccinimde (NCS) and triethylborane (TEB), where the solvent is acetonitrile (MeCN). A plausible mechanism is shown in **Scheme 6-6**, where it is displayed as an electrophilic aromatic substitution.

In this reaction TEB presumably functions as a catalyst, where it helps the chlorination by "activating" NCS. It makes it easier for the π-electrons in **30** to do a nucleophilic attack on the chlorine atom in NCS, by weakening the N-Cl bond. The by-product is succinimide.



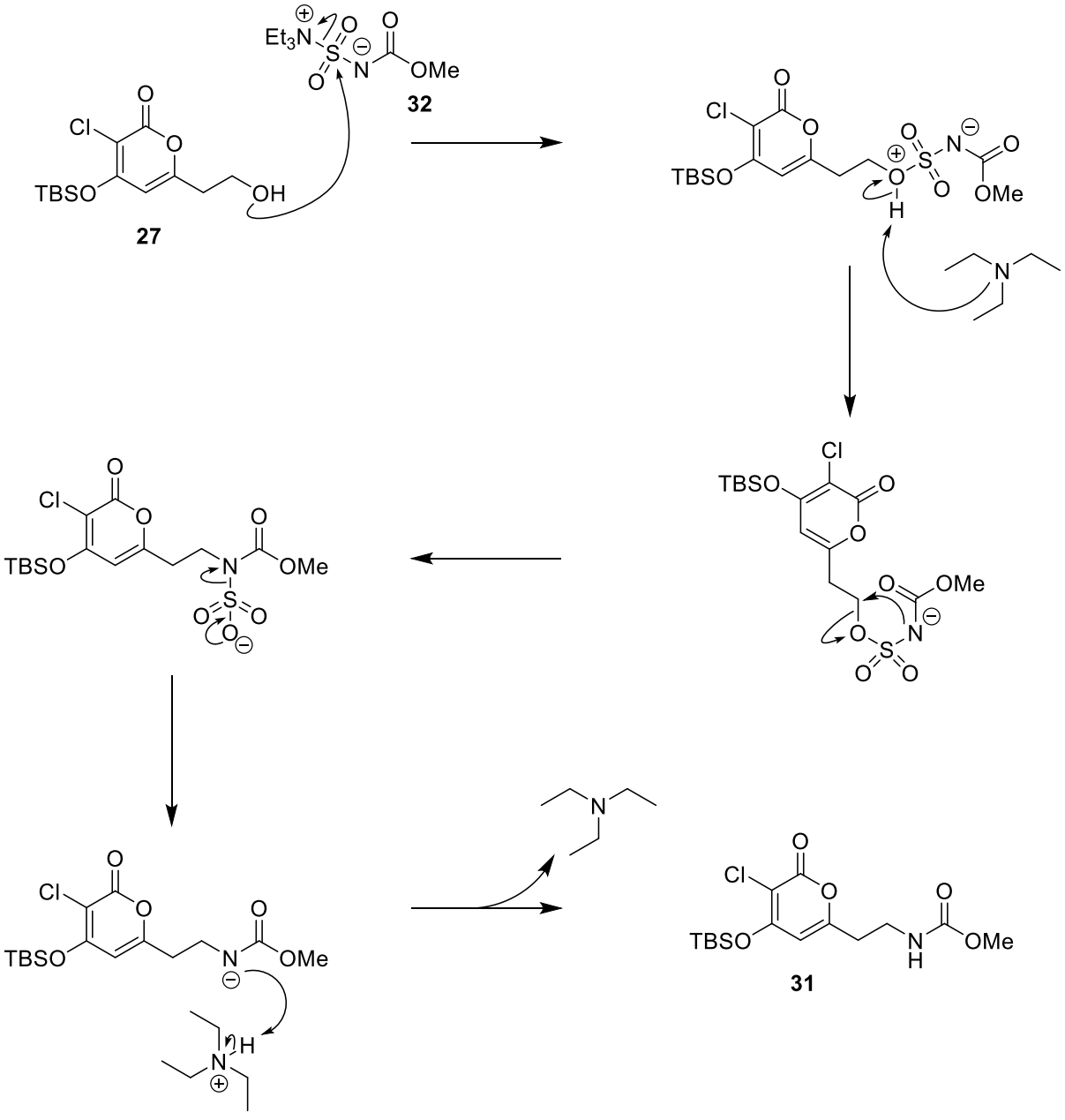
Scheme 6-6 Plausible mechanism for chlorination of **30** with NCS and TEB.

6.6 Burgess reagent

In 1970 an article was published by Burgess *et al.*, where they used an inner salt of (methoxycarbonylsulfamoyl)triethylammonium hydroxide (**32**) to convert secondary and tertiary alcohols to their corresponding alkenes.[38] The reaction occurs in an E_i elimination under mild conditions,[39] and the reagent is now known as Burgess reagent.

Primary alcohols, however, are usually converted to carbamates with Burgess reagent. It is more energetically favored for the primary alcohol to undergo a S_N2 pathway than an E_i

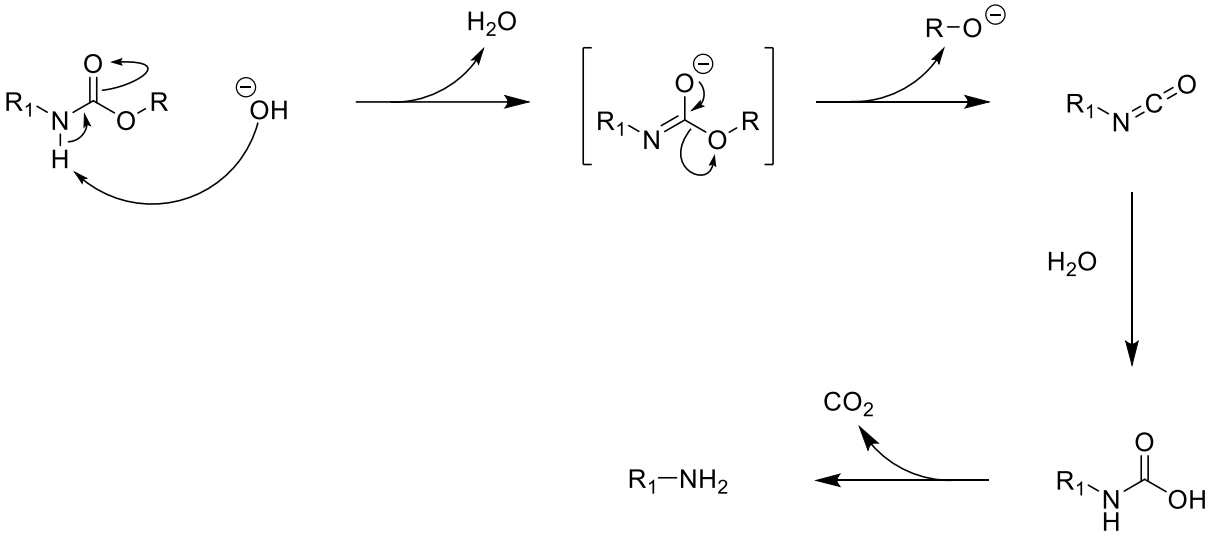
elimination.[38, 40] The plausible mechanism for carbamate formation of **27** is shown in **Scheme 6-7**. The carbamate formation can then be followed up by a basic hydrolysis to convert the carbamate into the corresponding amine.[39]



Scheme 6-7 Plausible mechanism for carbamate formation of the primary alcohol on **27** with Burgess reagent **32**.[39]

The basic hydrolysis of carbamates can follow two plausible mechanisms, dependent upon whether the carbamate in question is N-unsubstituted and N-monosubstituted, or N-disubstituted.[41] The main difference between the mechanisms is how the hydroxyl ion acts in the beginning. When there is a N-disubstituted carbamate, the hydroxyl ion will do a

nucleophilic attack on the carbonyl group and form a carbamate ion intermediate. When there is a N-monosubstituted or N-unsubstituted, the hydroxyl ion will rather deprotonate the amide group.[41] The mechanism for basic hydrolysis of N-unsubstituted and N-monosubstituted carbamates are shown in **Scheme 6-8**.

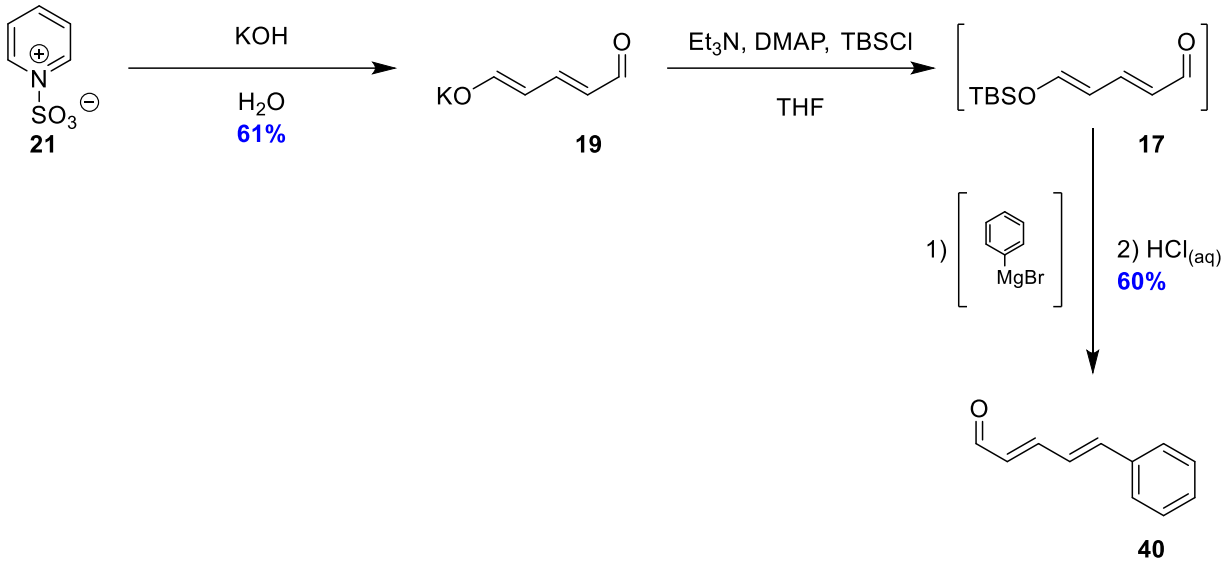


Scheme 6-8 Mechanism for basic hydrolysis of N-unsubstituted and N-monosubstituted carbamates.[41]

7 Results and Discussion

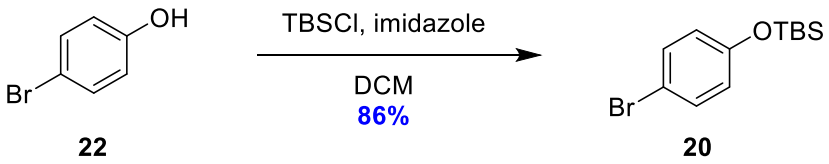
7.1 Synthetic route towards 2*E*,4*E*-dienal 40 and 16

The commercially available pyridinium salt **21** was converted into glutaconaldehyde potassium salt (**19**) with excess amount of aqueous potassium hydroxide.[24] The yields were around 61%.



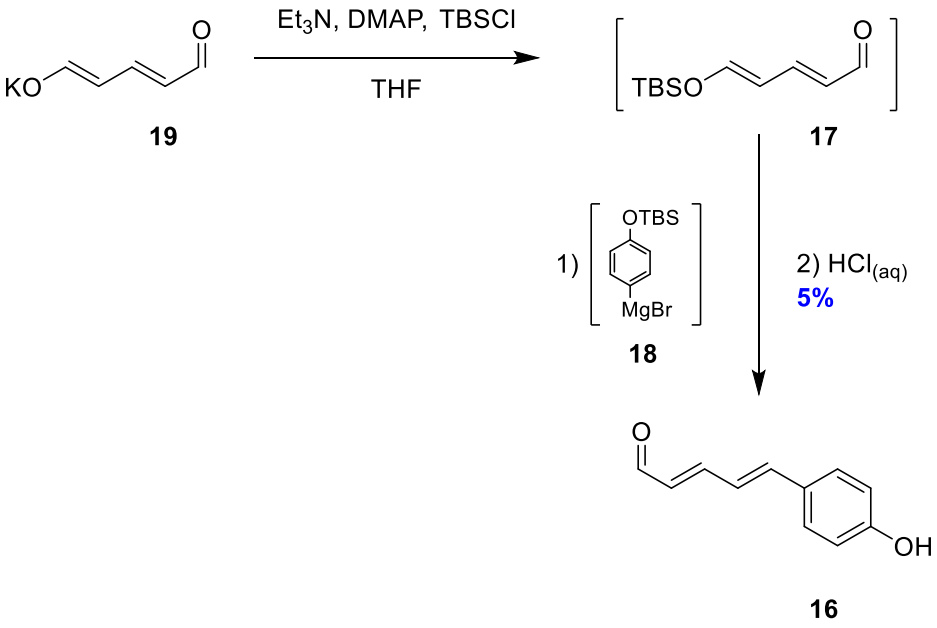
Scheme 7-1 Synthetic route towards **40**.

The glutaconaldehyde salt **19** was protected with TBSCl, using DMAP and triethylamine (TEA), to form silyl ether **17**.[34] Crude silyl ether **17** was treated with commercially available phenylmagnesium bromide followed up by acidic hydrolysis with aqueous HCl, to afford the more thermodynamically *E*,*E*-dienal (**40**) with a yield of 60%.[34]



Scheme 7-2 Protection of the phenol with silyl ether.

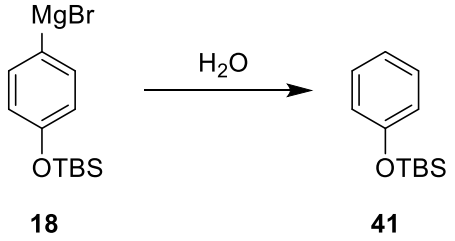
The same procedure was then tried to form 2*E*,4*E*-dienal **16** with a phenol instead of the phenyl group. The Grignard reagent here would then be phenolmagnesium bromide, which would be made from commercially available *p*-bromophenol (**22**). Due to the acidic character of the phenol, the hydroxyl group had to be transformed into a silyl ether. This was done following the procedure described by Kunák *et al.*,[42] which is shown in **Scheme 7-2**. Compound **20** was afforded with a yield of 86%.



Scheme 7-3 Synthetic route towards **16**.

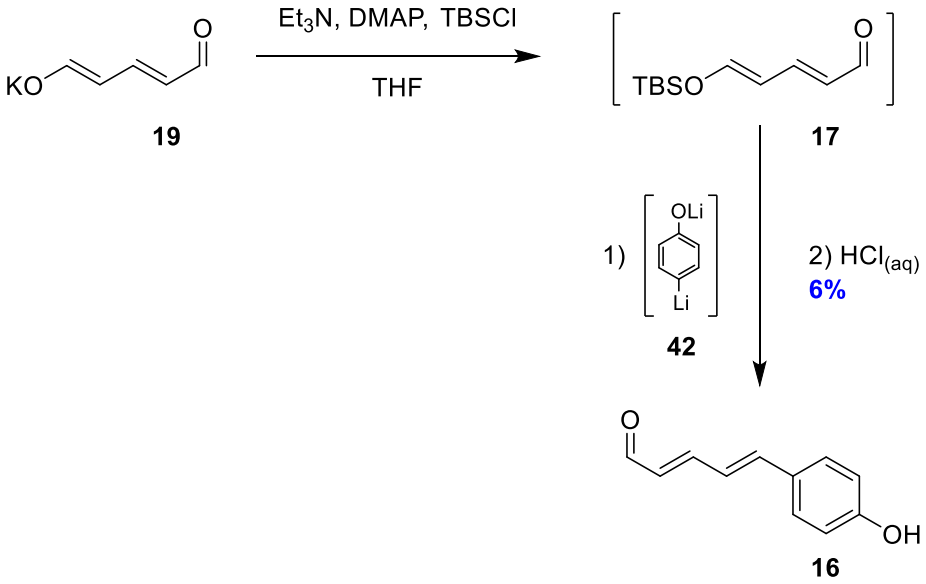
Compound **16** was prepared using the same procedure described in **Scheme 7-1**, where the corresponding silyl ether to phenolmagnesium bromide (**18**) was used as Grignard reagent instead of phenyl magnesium bromide. Grignard reagent **18** was prepared using **20**, magnesium and THF.[43] A crystal of iodine was also used to activate the magnesium.[44] The Grignard solution was directly exposed to the solution of compound **17**, and aqueous HCl was later added to afford compound **16** with a yield at 5%.

Both the TLC and the ^{1}H NMR showed traces of *tert*-butyldimethyl(phenoxy)silane (**41**) as a by-product. The TLC taken before adding aqueous HCl also showed traces of **41**. This indicates that water was present during the reaction as shown in **Scheme 7-4**.



Scheme 7-4 Phenolmagnesium bromide **18** reacting with water.

In an effort to prevent this, both **19** and **20** were dissolved in 2-methyltetrahydrofuran and concentrated *in vacuo* to remove water as part of an azeotrope.[45] Molecule sieves were also employed. These changes did not improve the yield.



Scheme 7-5 Preparation of **16** using lithiation of bromophenol **22**.

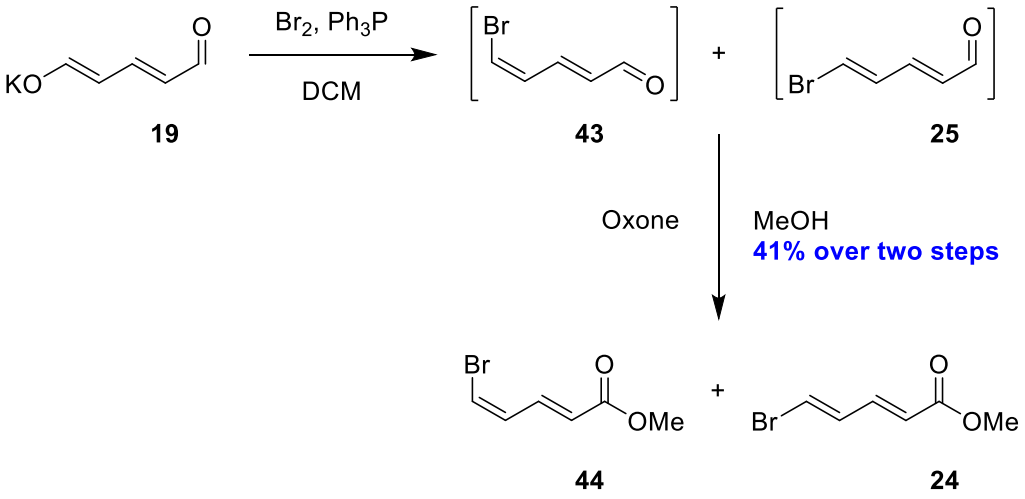
The yields, in the procedure described in **Scheme 7-3**, were too low to go forward with. Again, in an effort to increase the yield, the Grignard reagent was replaced by organolithium compound **42**, shown in **Scheme 7-5**. Organolithium **42** was prepared at -78 °C using *n*-BuLi and *p*-bromophenol (**22**),[46] it was then directly exposed to the solution of compound **17**. The hypothesis was that *n*-BuLi would first deprotonate the hydroxy group and then initiate a lithium halogen exchange reaction to give **42**.[46] An umpolung reaction will result, where the carbon at para-position would go from an electrophile to a nucleophile. The aim was to increase the yield in the synthesis of **16** using organolithium compound as a nucleophile instead of the Grignard reagent. The yield was 6%, which is not a substantial increase. As a last attempt, sodium hydride (NaH) was added first, followed by *n*-BuLi in the preparation of the organolithium compound, to ensure that the phenol got deprotonated cleanly first. The yield was unaffected.

The interpretation of the spectra for compound **16** proves challenging, particularly in instances where the spectra exhibit impurities. Additionally, certain proton shifts in the ^{1}H NMR spectrum appear obscured by the solvent peak. A comparative analysis was conducted with another ^{1}H

NMR spectrum of the same compound, published by a fellow master student.[47] Notably, the spectra display comparable chemical shifts.

7.2 Synthetic route towards 5-bromo-2*E*,4*E*-dienoate (24)

The synthetic route towards **24** has the same start as the synthetic route towards the 2*E*,4*E*-dienals, where glutaconaldehyde salt **19** was prepared from pyridinium salt **21**, shown in **Scheme 7-1**.[24]



Scheme 7-6 Synthetic route towards the isomers **44** and **24**.

Glutaconaldehyde salt **19** was treated with bromide and triphenylphosphine to afford the isomeric bromodienals 2*E*,4*E* **25** and 2*E*,4*Z* **43** in an 1,6-addition/elimination.[24] According to the work done by Primdahl *et al.* the crude product was purified with column chromatography to get rid of excess of triphenylphosphine, and was then treated with oxone and methanol to afford their corresponding methyl esters.[24] Since triphenylphosphine is oxidized to triphenylphosphine oxide in the presence of oxone,[48] the purification was skipped and the crude product was directly converted into the corresponding esters, as shown in **Scheme 7-6**.

The isomeric methyl esters were separated via recrystallization from heptane. The 2*E*,4*E*-isomer **24** was poorly soluble in heptane and would crystallize, while the 2*E*,4*Z*-isomer **44** would be left in the supernatant. The yield of both isomers together was 41%.

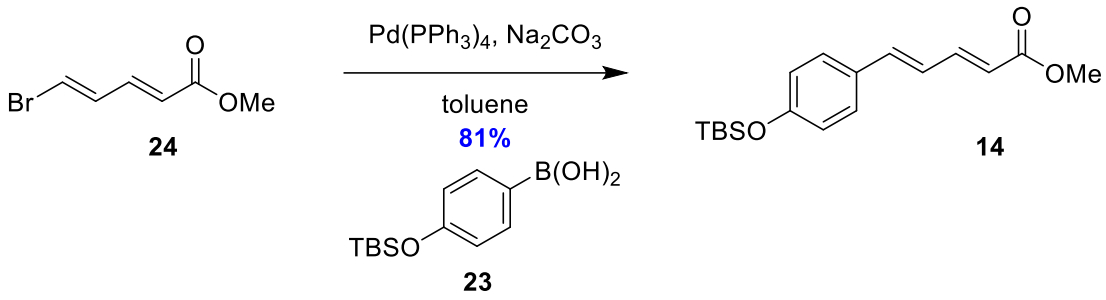
7.3 Problems with the 1,6-addition/elimination of 19

The first two attempts on the 1,6-addition/elimination of **19** did not yield the right results. According to the crude ^{1}H NMR and TLC the two isomers **43** and **25** had not been obtained,

and the spots on the TLC were not identified. Since the reaction had been done before by Primdahl *et al.*,[24] the reaction conditions and reagents were inspected. The only factor that could have made a difference was glutaconaldehyde salt **19**, since this was the only reagent that was not commercially available and was made through the ring opening reaction from **21**. A new batch of **19** was made and tested in the 1,6-addition/elimination. This yielded the right products. The problem with the previous **19** batch was not identified.

Importantly, the problem caused with the above-mentioned glutaconaldehyde salt **19** generated new perspectives in the synthetic route towards 2*E*,4*E*-dienal **16**. The unidentified problem with the old batch of **19** could have been the factor that caused the low yields. It would be interesting and intriguing to conduct further experiments with a new batch of **19** in the future, testing the reaction with both Grignard and organolithium reagents.

7.4 Suzuki coupling between 2*E*,4*E* methyl ester 24 and boronic acid 23

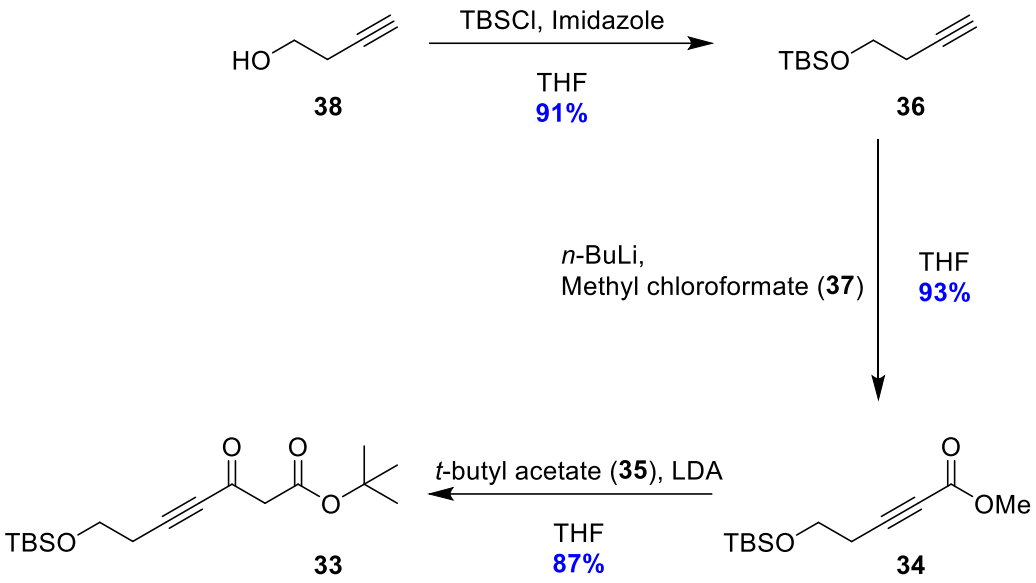


Scheme 7-7 Suzuki coupling with boronic acid **23**.

2*E*,4*E*-methyl ester **24** was successfully coupled with boronic acid **23** in a Suzuki coupling.[24, 26] The commercially available boronic acid **23** was used together with palladium-catalyst $Pd(PPh_3)_4$ and the activating base sodium carbonate, shown in **Scheme 7-7**. Ester **14** was formed in 81% yield.

7.5 Synthetic route towards beta-keto ester 33

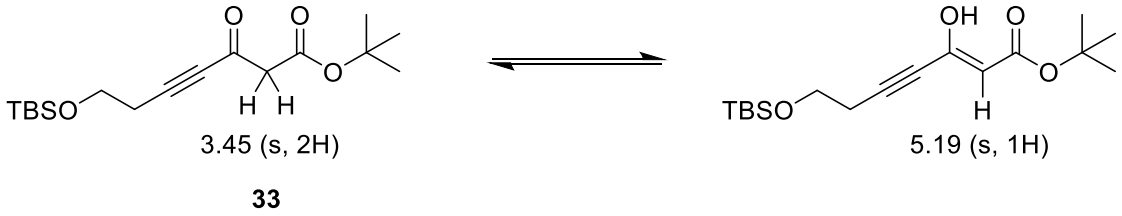
The hydroxyl group on the commercially available terminal alkyne **38** was converted into the corresponding silyl ether **36** using TBSCl and imidazole,[49] shown in **Scheme 7-8**. Terminal alkyne **36** was formed in 91% yield.



Scheme 7-8 Synthetic route towards **33**.

Terminal alkyne **36** was then treated with *n*-BuLi to deprotonate the alkyne. The deprotonated **36** was then treated with commercially available methyl chloroformate (**37**) to afford **34** in 93% yield.[29] The prescribed procedure called for stirring the solution for 3 h following the addition of methyl chloroformate (**37**).[29] However, based on the analysis using TLC, it was observed that the reaction was already completed after 1 h. Consequently, the reaction was quenched at the 1-hour mark.

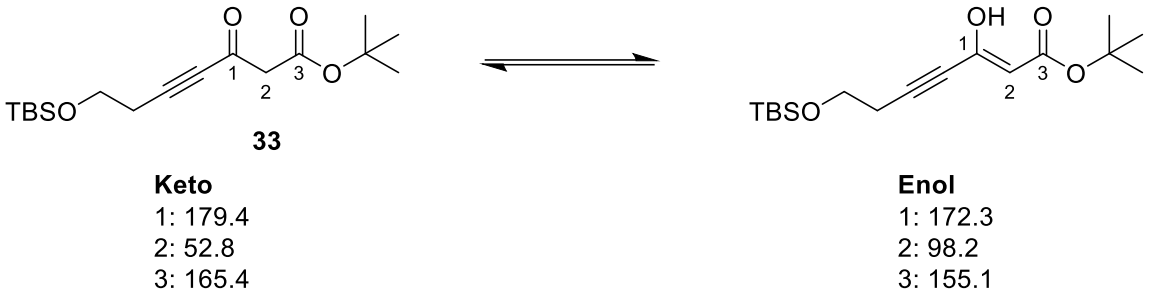
Beta-keto ester **33** was prepared via Claisen condensation in 87% yield by treating *t*-butyl-acetate (**35**) with LDA, followed by addition of methyl ester **34**.[29, 30] The ^{1}H NMR spectrum of **33** showed interestingly a 9:1 ratio of the keto-enol form, as described in **Scheme 7-9**.



Scheme 7-9 ^{1}HNMR shifts for the alpha protons on the different tautomerizations of **33** in ppm.

Both ^{1}H NMR and ^{13}C NMR shifts of this work were confirmed by previously reported data of tautomerization of beta-keto esters.[50] Additionally, purification of compound **33** by flash column chromatography on silica proved to be troublesome. Unidentified decomposed

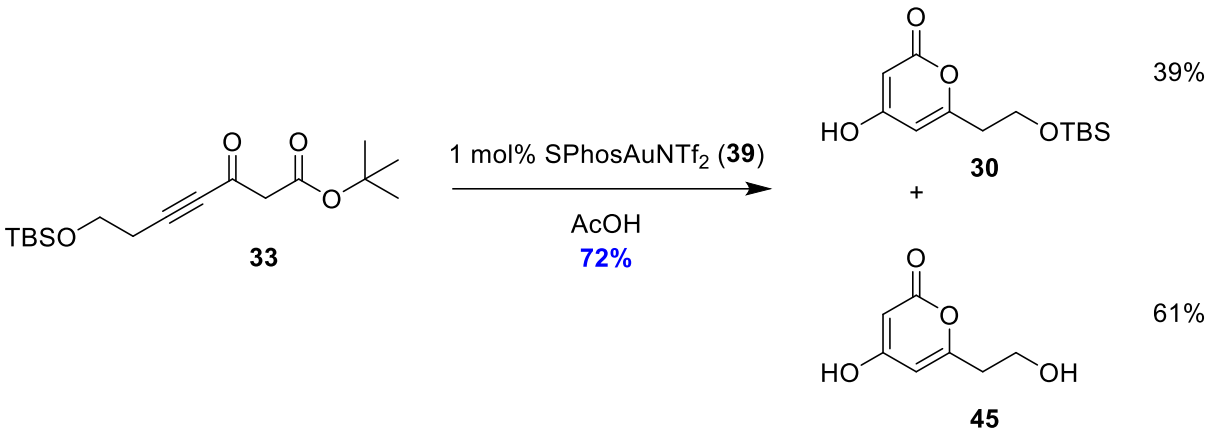
compounds were collected after purification, resulting in filtration through a short pad of silica to avoid this problem.



Scheme 7-10 ^{13}C NMR shifts for beta-keto ester **33** and its tautomer in ppm.

7.6 The 6-endo-dig addition of beta-keto ester 33

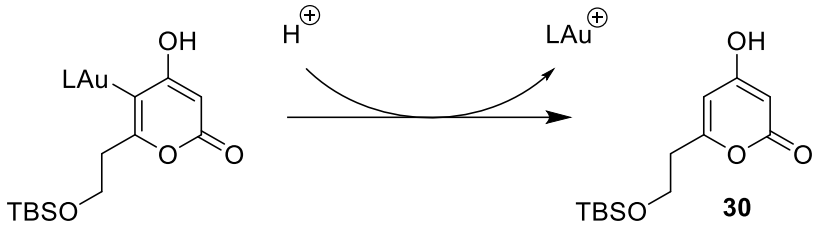
The beta-keto ester underwent a 6-endo-dig addition with gold complex **39** as a catalyst to form alpha-pyrone **30**.[29] Acetic acid was first used as solvent, since it was used on similar compounds in the work done by Chaladaj *et al.*.[29] The acetic acid made the solution too acidic, which resulted in cleavage of the TBS-group, as shown in **Scheme 7-11**. The yield was at 72%, where 39% of the yield was **30** and 61% was **45**.



Scheme 7-11 6-endo-dig addition of beta-keto ester **33** with AcOH as solvent.

To avoid the cleavage of the TBS-group, use of different solvents was investigated. According to Chaladaj *et al.* they used nitromethane, instead of acetic acid, as solvent on some compounds.[29] Nitromethane is of course less acidic than acetic acid, as seen by their pKa-values of 10.3 and 4.75, respectively,[51, 52] which resulted in nitromethane as alternative solvent. Nitromethane as solvent resulted in no cleavage of the TBS-group, but there were traces of beta-keto ester **33** left. A hypothesis was that the protonation step in the annulation mechanism,

shown in **Scheme 7-12**, was probably a slower process now, due to the less acidic solution. To compensate, 2% of gold complex **39** was used. This resulted in full conversion to the desired alpha-pyrone **30**, with a yield of 78%.



Scheme 7-12 The protonation step in the annulation.

7.7 Chlorination attempts on beta-keto ester 33 and pyrone 46

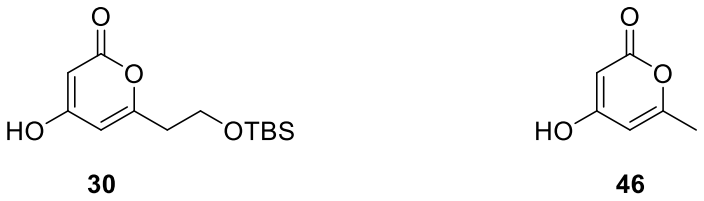
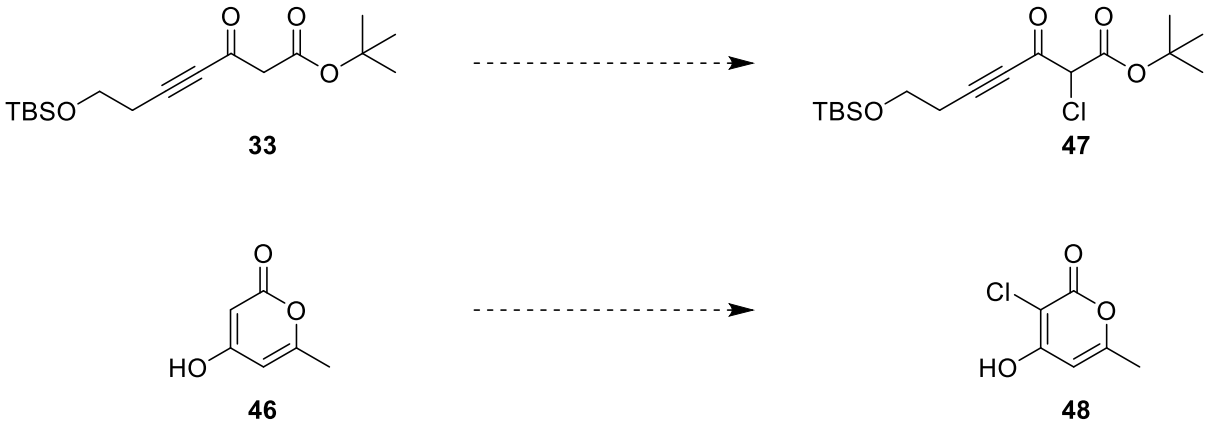


Figure 7-1 Structure of pyrone **30** and pyrone **46**.

The chlorination step proved to be a difficult step which required multiple attempts – both before and after the annulation. It was attempted to chlorinate both beta-keto ester **33** and a pyrone with a similar structure to pyrone **30**. This pyrone was the commercially available 4-hydroxy-6-methyl-2-pyrone (**46**) and is displayed in **Figure 7-1**. The reason pyrone **46** was used instead of **30**, was to save product and time. **Table 7-1** displays all the entries and results.



Scheme 7-13 Chlorination of beta-keto ester **33** and pyrone **46**.

Table 7-1 Reaction conditions for chlorination of both beta-keto ester **33** and pyrone **46**.

Entry	Starting material	Reagents	Solvent	Reaction conditions	Comment	Ref.
7-1-1	**33**	$C_2O_2Cl_2$ (1.20 eq) DMSO (1.20 eq)	DCM	30 min, 0 °C	Desired product not observed	[53]
7-1-2	**33**	NCS (1.05 eq)	DMSO	20 min, rt	Desired product not observed	[54]
7-1-3	**33**	NCS (1.05 eq) D-proline (0.80 eq)	DCM	1 h, 0 °C	Desired product observed, not full conversion	[55]
7-1-4	**46**	NCS (1.05 eq) NH_4Ac (10 mol%)	MeCN	3 h, rt	Desired product observed, not full conversion	[56]
7-1-5	**46**	NCS (1.05 eq) Et_3B (10 mol%)	MeCN	16 h, rt	Desired product observed, not full conversion	*

* 7-1-5 is a new method to chlorinate alpha-pyrones, that has not been reported previously.

Only entry 7-1-3, 7-1-4 and 7-1-5 yielded the desired product. Since 7-1-4 and 7-1-5 introduced chlorine at a later stage in the synthesis, these attempts were tested more to see if there could be a full conversion to the desired product. **Table 7-2** and **7-3** display the different results.

Table 7-2 Reaction conditions for 7-1-4 chlorination of pyrone **46**.

Entry	Starting material	Reagents	Solvent	Reaction conditions	Comment	Ref.
7-2-1	**46**	NCS (1.05 eq) NH_4Ac (10 mol%)	MeCN	3 h, rt	Desired product observed, not full conversion	[56]
7-2-2	**46**	NCS (1.05 eq) NH_4Ac (20 mol%)	MeCN	3 h, rt	Desired product not observed, not full conversion	[56]
7-2-3	**46**	NCS (2.00 eq) NH_4Ac (10 mol%)	MeCN	3 h, rt	Desired product observed, nearly full conversion*, yield: 29%	[56]
7-2-4	**46**	NCS (2.00 eq) NH_4Ac (20 mol%)	MeCN	3 h, rt	Desired product observed, not full conversion	[56]
7-2-5	**46**	NCS (1.50 eq) NH_4Ac (15 mol%)	MeCN	3 h, rt	Desired product observed, not full conversion	[56]

* TLC showed full conversion, but ^{1}H NMR showed traces of the starting material

In **Table 7-2** entry 7-2-3 was the only condition that got nearly full conversion according to the TLC. The ^{1}H NMR specter showed approximately 50% conversion, with a yield of 29%. In **Table 7-3** entry 7-3-5 and 7-3-6 was the one with the highest conversion, with both a conversion of around 80% and a yield around 54%. During the testing of 7-1-5 chlorination, ether was used as extraction solvent. The reason was to try and remove most of the by-product succinimide, since succinimide is not soluble in ether.[57] The spectra showed almost no traces of succinimide after using ether as the extract solvent. Entry 7-3-5 was taken further to test on alpha-pyrone **30**.

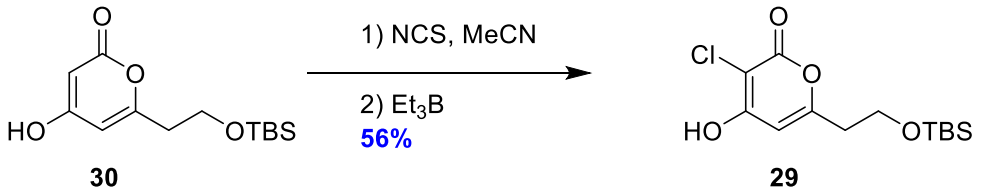
Table 7-3 Reaction conditions for 7-1-5 chlorination of pyrone **46**.

Entry	Starting material	Reagents	Solvent	Reaction conditions	Comment	Yields
7-3-1	**46**	NCS (1.05 eq) Et_3B (10 mol%)	MeCN	16 h, rt	Desired product observed, not full conversion	-
7-3-2	**46**	NCS (1.05 eq) Et_3B (12 mol%)	MeCN	16 h, rt	Desired product observed, not full conversion	-
7-3-3	**46**	NCS (1.05 eq) Et_3B (15 mol%)	MeCN	16 h, rt	Desired product observed, not full conversion	-
7-3-4	**46**	NCS (1.20 eq) Et_3B (20 mol%)	MeCN	16 h, rt	Desired product observed, not full conversion	-
7-3-5	**46**	NCS (1.30 eq) Et_3B (20 mol%)	MeCN	16 h, rt	Desired product observed, nearly full conversion*	54%
7-3-6	**46**	NCS (1.35 eq) Et_3B (20 mol%)	MeCN	16 h, rt	Desired product observed, nearly full conversion*	54%
7-3-7	**46**	NCS (1.30 eq) Et_3B (25 mol%)	MeCN	16 h, rt	Desired product not observed	-
7-3-8	**46**	NCS (1.35 eq) Et_3B (25 mol%)	MeCN	16 h, rt	Desired product not observed	-
7-3-9	**46**	NCS (1.40 eq) Et_3B (30 mol%)	MeCN	16 h, rt	Desired product not observed	-

*Showed full conversion on TLC, but ^{1}H NMR showed traces of the starting material

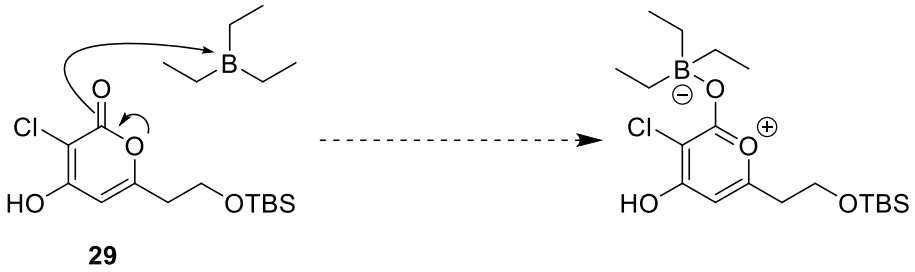
7.8 Chlorination of pyrone 30

Alpha-pyrone **30** was chlorinated with the conditions of entry 7-3-5, to afford **29** in 56% yield. Both TLC and ^{1}H NMR showed traces of the start material.



Scheme 7-14 Chlorination of alpha-pyrone **30**.

A new chlorination attempt was then tried, where it was used more equivalents of NCS and TEB, but that did not give the desired product. The same result was also seen when using more than 20 mol% of TEB on the chlorination attempt with pyrone **46**. The TLC seemed to show the desired product with full conversion, but the chemical shift of the proton in the pyrone ring was slightly different than normally observed in the crude ^{1}H NMR. After the purification with flash, the product was not to be seen on either TLC or in ^{1}H NMR. One possibility is that the carbonyl group in the pyrone could do a nucleophilic attack on TEB to make an anionic four-coordinate boron atom, shown in **Scheme 7-15**, which might explain why it got stuck on the column. However, if this is true, then it should have been stuck in the water phase before the purification, due to the ionic charges.[58] The product was seen in the organic phase. Only adding more of NCS, did not increase the yield or lead to full conversion.



Scheme 7-15 Nucleophilic attack on TEB to form a zwitterion.

The chlorination with conditions 7-3-5 was done multiple times on pyrone **30**, and the yield seemed to be varying. **Table 7-4** displays the different yields of some of the attempts. As stated before, the purification step with flash might be the reason for the lower yields. A solution can be to try and recrystallize **29**, since it is insoluble in the more nonpolar solvents because of its high polarity.

Table 7-4 Reaction conditions and yields for some of the chlorination attempts of alpha-pyrone **30**.

Entry	Starting material	Reagents	Solvent	Reaction conditions	Comment	Yields
7-4-1	**30** 275 mg, 1.02 mmol	NCS (1.20 eq) Et_3B (20 mol%)	MeCN	16 h, rt	Not full conversion	56%
7-4-2	**30** 385 mg, 1.42 mmol	NCS (1.20 eq) Et_3B (20 mol%)	MeCN	16 h, rt	Not full conversion	40%
7-4-3	**30** 303 mg, 1.12 mmol	NCS (1.20 eq) Et_3B (20 mol%)	MeCN	16 h, rt	Not full conversion	35%

On alpha-pyrone **30**, there exist two potential sites for chloride atom attachment, as illustrated in **Figure 7-2**. To assert the correct position, a ^{1}H-^{1}H NOESY experiment was conducted. The NOESY results conclusively established that the chloride atom was attached to carbon 1. This determination was based on the observed interaction of the proton with the protons on carbon 4. The ability of the proton to perceive the protons on carbon 4 implies its presence on the same face of the ring as these protons, affirming the placement of the chloride on the opposite side of the ring, at carbon 1.

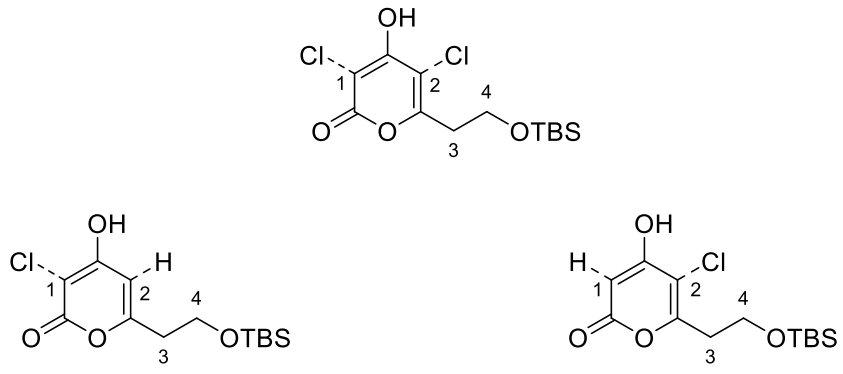


Figure 7-2 Plausible positioning of the chlorine atom on **30**.

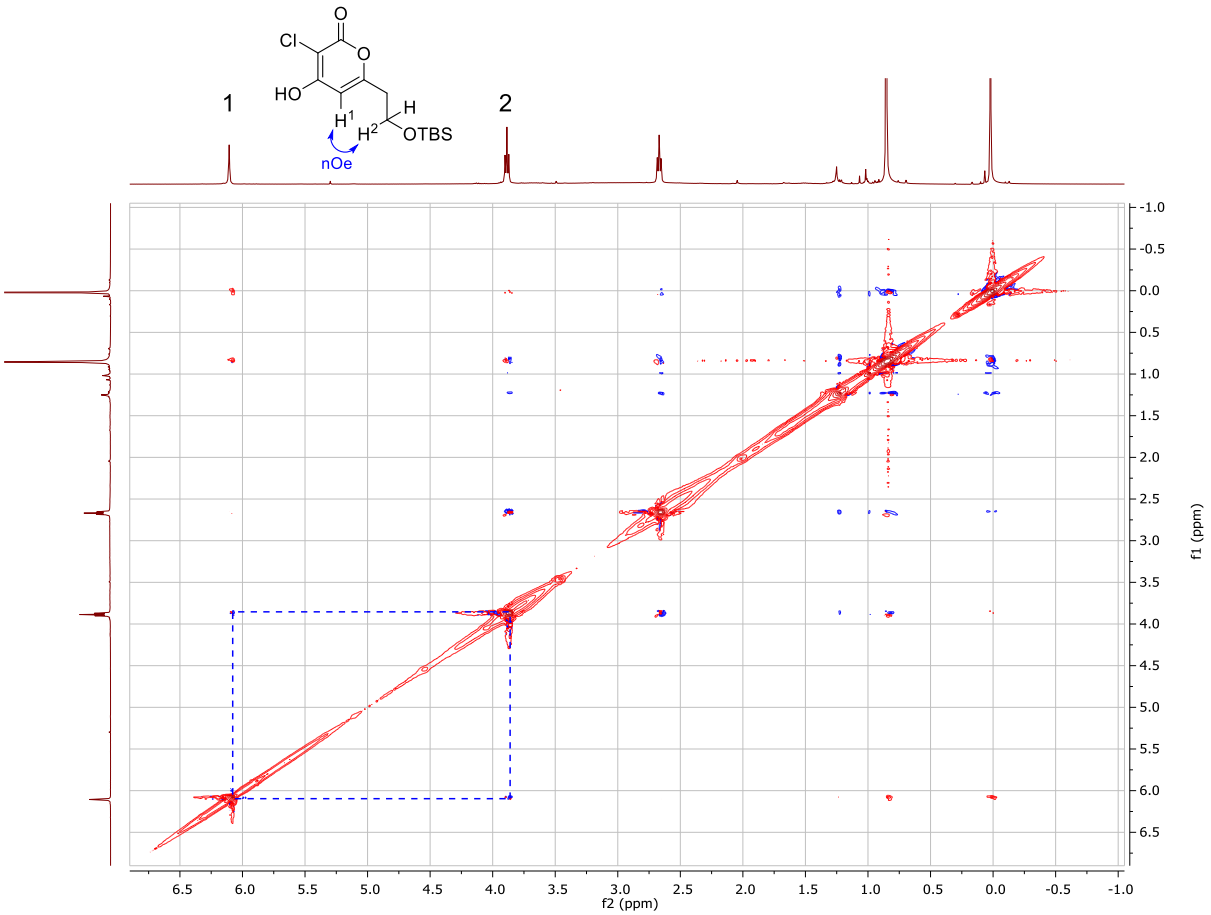
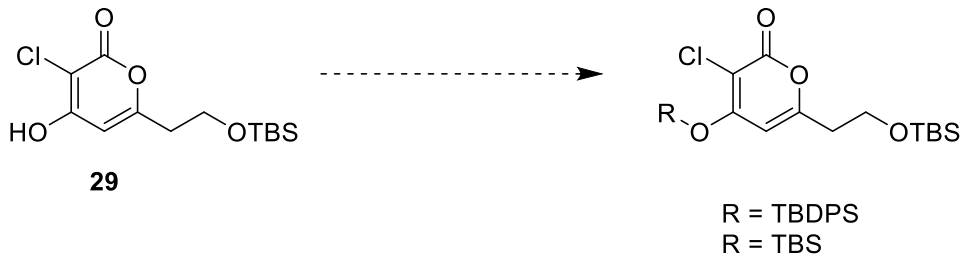


Figure 7-3 ^{1}H-^{1}H NOESY specter of chlorinated alpha-pyrone **29**.

7.9 Silylation of the hydroxyl group on pyrone 29

Alpha-pyrone **29** underwent attempted conversion of its hydroxyl group into a silyl ether by treatment with *t*-butyldiphenylsilyl chloride (TBDPSCl) and TEA.[59] However, no conversion of the starting material was observed. Subsequent efforts were made by employing catalytic amounts of DMAP in an attempt to enhance the silylation process,[60] yet this yielded no progress, mirroring the results of the initial attempt. Notably, starting material **29** exhibited poor solubility in the chosen solvent, dichloromethane (DCM), during both attempts.

Recognizing the solubility challenge, an alternative approach involved utilizing dimethylformamide (DMF) as a more polar solvent.[61] Despite this change, the outcome remained consistent, with no discernible sign of conversion.



Scheme 7-16 Silylation of the hydroxyl group in pyrone **29**.

The hydroxyl group in **29** was then instead treated with TBSCl and imidazole.[42] There were two sets of reactions, one with DCM and another with DMF as solvent. Both attempts showed no conversion. **Table 7-5** is a summary of all the silylation attempts of pyrone **29**.

Table 7-5 Summary of all the silylation attempts of pyrone **29**.

Entry	Starting material	Reagents	Solvent	Reaction conditions	Comment	Ref.
7-5-1	**29**	TBDPSCl (1.10 eq) Et_3N (1.10 eq)	DCM	16 h, rt	No conversion	[59]
7-5-2	**29**	TBDPSCl (1.10 eq) Et_3N (1.10 eq) A crystal of DMAP	DCM	16 h, rt	No conversion	[59]
7-5-3	**29**	TBDPSCl (1.10 eq) Imidazole (2.10 eq)	DMF	5 – 16 h, rt	No conversion	[61]
7-5-4	**29**	TBSCl (1.20 eq) imidazole (1.20 eq)	DCM	16 h, rt	No conversion	[42]
7-5-5	**29**	TBSCl (1.20 eq) imidazole (1.20 eq)	DMF	16 h, rt	No conversion	[42]

7.10 Acetylation of the hydroxyl group on pyrone 29, 30 and 46

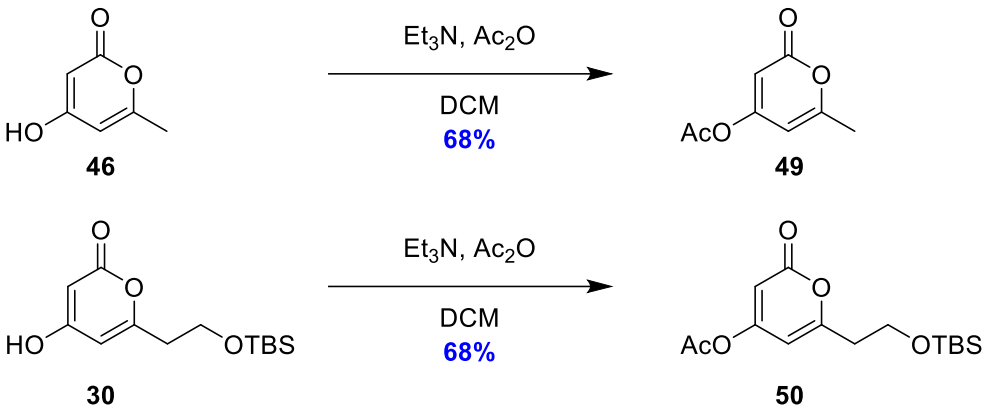
A new protective group had to be found, since the silylation attempts showed no signs of conversion. Converting the hydroxyl group of **29** into the corresponding acetyl protected compound was the next option. Pyrone **29** was treated with acetic anhydride and DMAP in pyridine.[62] According to the TLC and ^{1}H NMR there were no signs of conversion. Another attempt was tried using acetic anhydride and TEA in DCM.[63] Ended up with the same result, no conversion.

Table 7-6 Reaction conditions for acetylation entries on pyrone **29**.

Entry	Starting material	Reagents	Solvent	Reaction conditions	Comment	Ref.
7-6-1	**29**	Acetic anhydride (2.40 eq) A crystal of DMAP	Pyridine	16 h, rt	Desired product not observed	62
7-6-2	**29**	Acetic anhydride (1.36 eq) Et_3N (1.36 eq)	DCM	16 h, rt	Desired product not observed	63

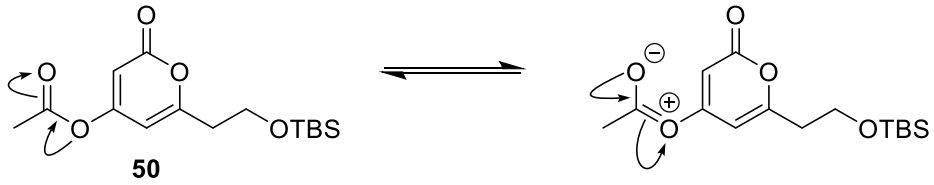
One reason for all the failed attempts of protecting the hydroxyl group in pyrone **29**, could be steric hindrance. There is a possibility that the chloride on the alpha carbon beside the hydroxyl group makes it sterically harder for the oxygen to do a nucleophilic attack on the acetic anhydride and the silyl compounds. The previous acetylation attempt was then tried on pyrone **30**, without the chlorine.

The acetylation was first tried on pyrone **46**, where it was treated with acetic anhydride and TEA in DCM to form pyrone **49** with a yield of 68%.[63] The work up included washing with 1 M HCl. The same conditions were then tried on pyrone **30**, but 1 M HCl was switched with water. The 1 M HCl could cleave off the silyl ether.[64] These conditions afforded pyrone **50** with a yield of 68%.



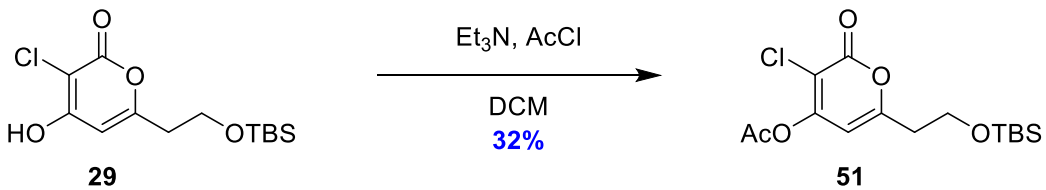
Scheme 7-17 Acetylation of **46** and **30**.

It was then tried to chlorinate pyrone **50** with the conditions of entry 7-3-5. The reaction showed no signs of conversion. The reason could be that the electrons on the oxygen in the hydroxyl group are less available, since the electrons can participate in resonance with the carbonyl group,[65] shown in **Scheme 7-18**. Also, the acetyl group creates more steric hindrance.



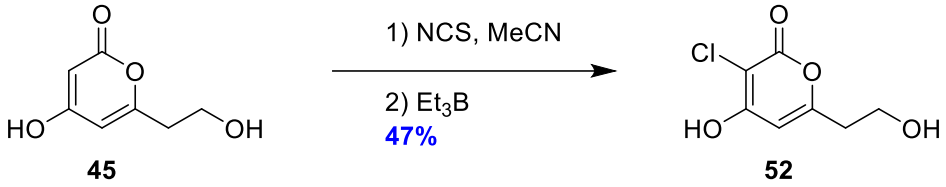
Scheme 7-18 Different resonance structures of the ester in **50**.

Since the chlorination attempt with condition 7-3-5 on **50** failed, the acetylation had to occur after the chlorination. The steric hindrance problem with the chloride atom could be overcome by using a smaller and harder electrophile than acetic anhydride. Another way of acetylation is to use acetyl chloride. This is more reactive and smaller than acetic anhydride.[66] The same procedure as before were tried, but acetyl chloride was used instead of acetic anhydride.[63] This afforded pyrone **51** with a yield of 32%.



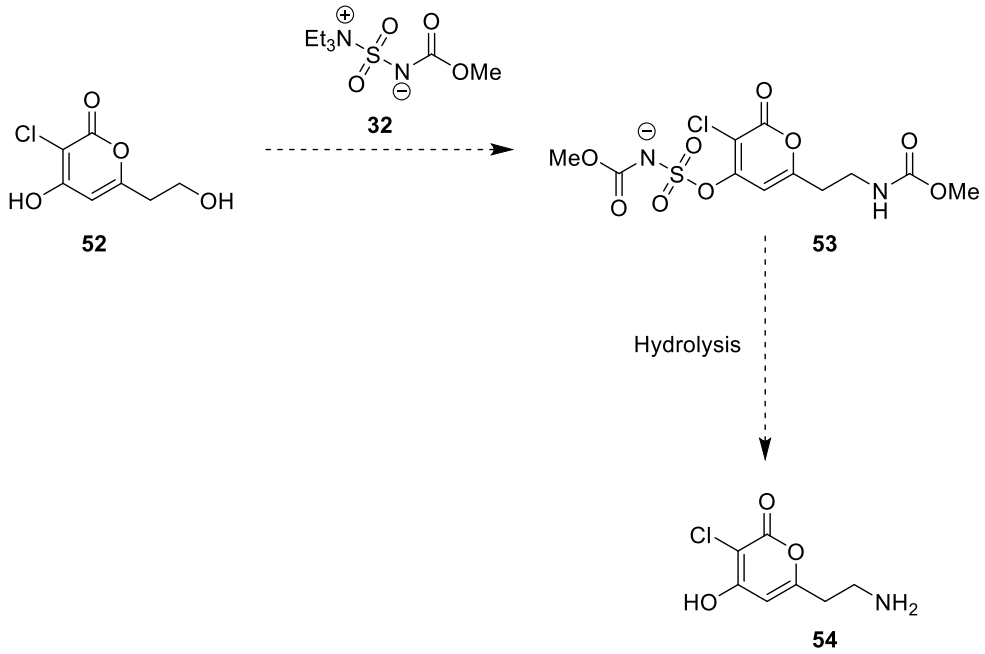
Scheme 7-19 Acetylation of **29** with Acetyl chloride.

7.11 Chlorination of 45 and Burgess reaction



Scheme 7-20 Chlorination of pyrone **45**.

The protection process of the hydroxyl group on pyrone **29** took more time and more attempts than estimated. In the meantime, pyrone **45**, from the annulation with acetic acid, was taken further to see if there was no need for protective groups. Pyrone **45** was treated with the conditions of 7-3-5 to afford pyrone **52**. Since **52** was quite polar, the work up was skipped, and it was taken directly to the purification step. This yielded **52** with 47%.



Scheme 7-21 Formation of amine from a primary alcohol with burgess reagent.

Pyrone **52** was then treated with Burgess reagent **32** at 95 °C to try and afford carbamate **53**.[40] Two equivalents of Burgess reagent were used, since there are two hydroxyl groups available for the burgess reagent. The primary alcohol should be converted into a carbamate, which can then be converted to a primary amine via hydrolysis.[39] The alcohol on the sp^2 hybridized carbon could be converted into the corresponding olefin via an E_i elimination.[39] This is highly unlikely, since the carbon attached to the alcohol is sp^2 hybridized, and E_i rarely happens on sp^2

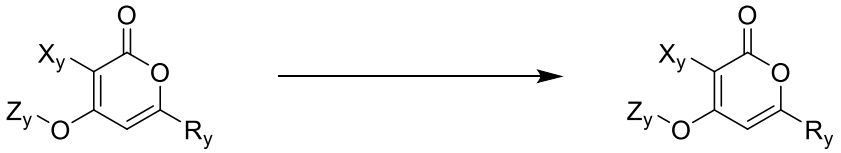
hybridized carbons.[67] However, the alcohol could transform into a sulfamate,[39] shown in **Scheme 7-21**. It should be possible to convert the sulfamate back to an alcohol using acid.

The Burgess reaction was worked up with 5% HCl and water with EtOAc. It was hard to know for certain if the compound would be in the water phase or the organic phase, because of the high polarity. Therefor it was taken TLC's of both the water phase and organic phase. The starting material was observed on the TLC with other several spots. The ^{1}H NMR only showed traces of the starting material. It was concluded that the reaction was not successful.

Table 7-7 Reaction conditions and yield for chlorination of **45** and Burgess reaction with **52**.

Entry	Starting material	Reagents	Solvent	Reaction conditions	Comment	Ref.
7-7-1	**45**	NCS (1.20 eq) Et_3B (20 mol%)	MeCN	16 h, rt	Yield: 47%	-
7-7-2	**52**	Burgess reagent **32** (2.00 eq)	No solvent	1 h, 95 °C	No conversion	[40]

7.12 Summary of all the successful reactions on the different pyrones



X_1: H
X_2: Cl

R_1: CH_3
R_2: CH_2CH_2OTBS
R_3: CH_2CH_2OH

Z_1: H
Z_2: $COCH_3$

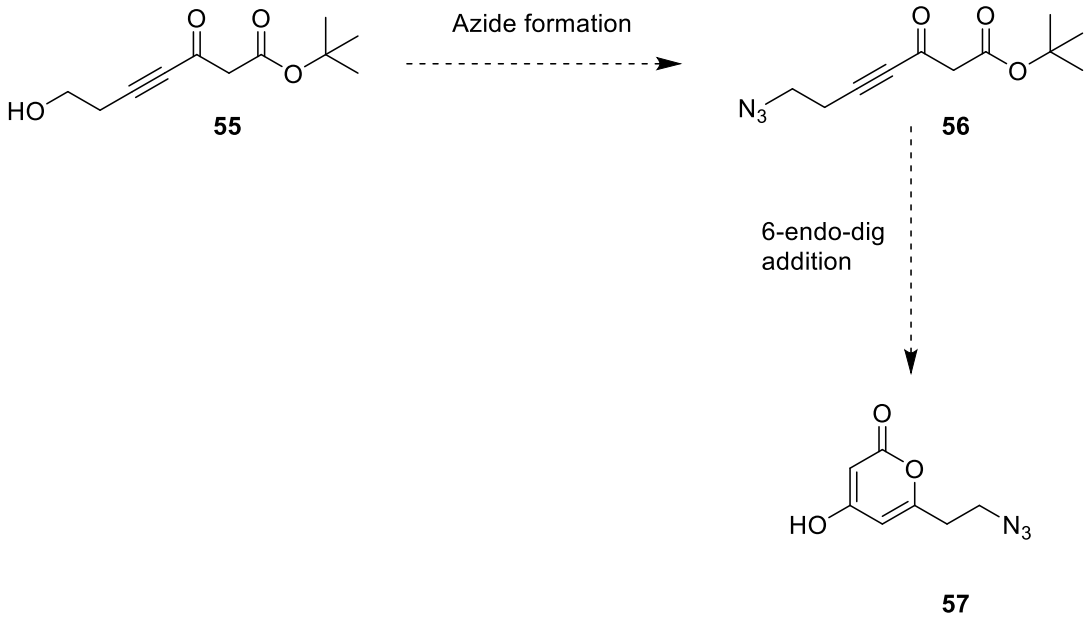
Scheme 7-22 Summary of all the successful reactions on the different pyrones.

Table 7-8 Reaction conditions and yields for all the successful reactions on the different pyrones.

Attempt number	Starting material	Reagents	Solvent	Reaction conditions	Comment	Ref.
7-8-1	**46** X_1, R_1 and Z_1	NCS (2.00 eq) NH_4Ac (10 mol%)	MeCN	3 h, rt	**48** X_2, R_1 and Z_1 yield: 29%	[56]
7-8-2	**46** X_1, R_1 and Z_1	NCS (1.30 eq) Et_3B (20 mol%)	MeCN	3 h, rt	**48** X_2, R_1 and Z_1 Yield: 54%	-
7-8-3	**30** X_1, R_2 and Z_1	NCS (1.20 eq) Et_3B (20 mol%)	MeCN	16 h, rt	**29** X_2, R_2 and Z_1 Yield: 56%	-
7-8-4	**45** X_1, R_3 and Z_1	NCS (1.20 eq) Et_3B (20 mol%)	MeCN	16 h, rt	**52** X_2, R_3 and Z_1 Yield: 47%	-
7-8-5	**46** X_1, R_1 and Z_1	Ac_2O (1.36 eq) Et_3N (1.36 eq)	DCM	16 h, -20 °C to rt	**49** X_1, R_1 and Z_2 Yield: 68%	[63]
7-8-6	**30** X_1, R_2 and Z_1	Ac_2O (1.36 eq) Et_3N (1.36 eq)	DCM	16 h, -20 °C to rt	**50** X_1, R_2 and Z_2 Yield: 68%	[63]
7-8-7	**29** X_2, R_2 and Z_1	AcCl (1.36 eq) Et_3N (1.36 eq)	DCM	16 h, -20 °C to rt	**51** X_2, R_2 and Z_2 Yield: 32%	[63]

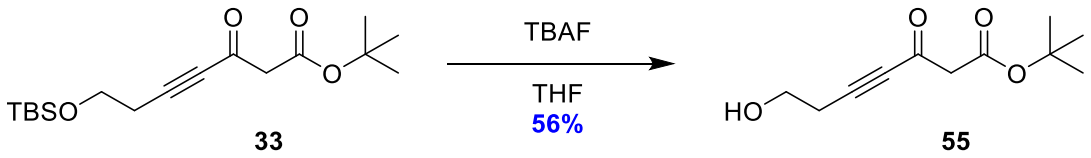
7.13 Azide formation of beta-keto ester 55

A new synthetic plan was tested at the end, since the protection of the hydroxyl group on **29** proved to be more difficult than estimated. The idea was to introduce the azide group earlier in the synthesis, specifically on beta-keto ester **55**. This would resolve in converting the primary alcohol on beta-keto ester **55** into an azide in a Mitsunobu reaction, and then do the 6-endo-dig addition on **56** to form **57**.



Scheme 7-23 A new synthetic route involving azide formation of beta-keto ester **55**.

The first step involves cleaving off the silyl ether on beta-keto ester **33** to form the primary alcohol. Beta-keto ester **33** was treated with tetra-*n*-butylammonium fluoride (TBAF) in THF at rt to afford **55** with a yield of 56%.[68] Both the keto- and the enol-form were spotted in the spectra.



Scheme 7-24 Cleavage of the silyl ether to afford **55**.

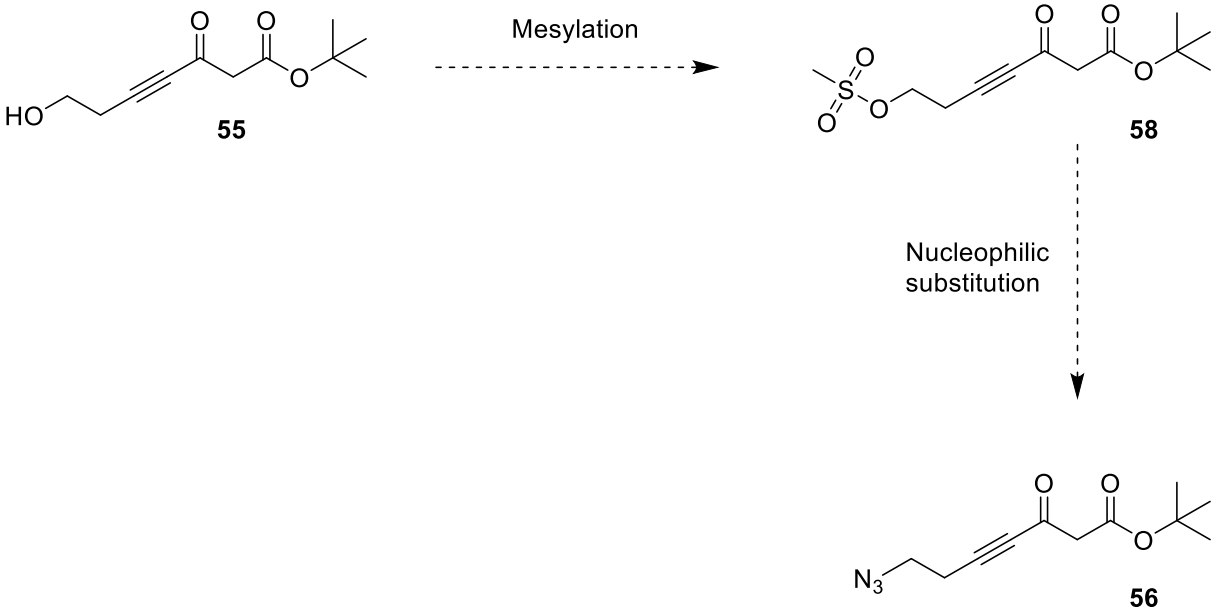
Beta-keto ester **55** was then treated with triphenylphosphine, diisopropyl azodicarboxylate (DIAD) and diphenylphosphoryl azide (DPPA) in a Mitsunobu reaction.[69, 70] The starting material was not present on the TLC, and several other spots had appeared. The crude material

was purified using flash chromatography. However, none of the spots matched with either the starting material or the desired azide **56** in ^{1}H NMR. It was concluded that the reaction did not work, and the different spots were not identified.

Table 7-9 Reaction conditions for Mitsunobu reaction of **55**.

Entry	Starting material	Reagents	Solvent	Reaction conditions	Comment	Ref.
7-9-1	**55**	Ph_3P (1.10 eq) DIAD (1.10 eq) DPPA (1.10 eq)	THF	16 h, 0 °C to rt	The desired product was not spotted	[69]

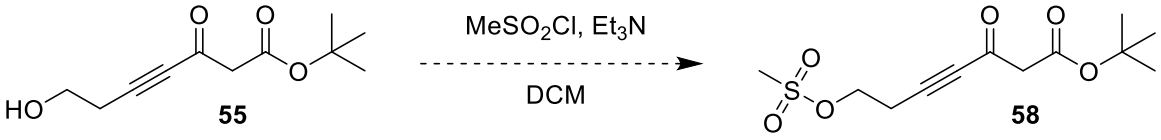
Another way of converting alcohol into an azide, is to first do a mesylation by converting the alcohol into a mesylate. Then the mesylate can be transformed into an azide via a nucleophilic substitution reaction,[71] shown in **Scheme 7-25**.



Scheme 7-25 Another pathway to form an azide using mesylation and nucleophilic substitution.

Beta-keto ester **55** was treated with TEA and methanesulfonyl chloride in DCM to try and afford mesylate **58**.[72] After 16 h of stirring, the TLC showed sign of starting material **55**. However, there were also several other new spots on the TLC. It was added more equivalents of TEA and

methanesulfonyl chloride and it was stirred for another 16 h. There was still sign of the starting material. However, the reaction was extracted, and it was taken crude ^{1}H NMR. The ^{1}H NMR of the crude material looked promising, but it had to be purified to confirm that mesylate **58** had been synthesized. Unfortunately, there was not enough time.



Scheme 7-26 Mesylation of **55**.

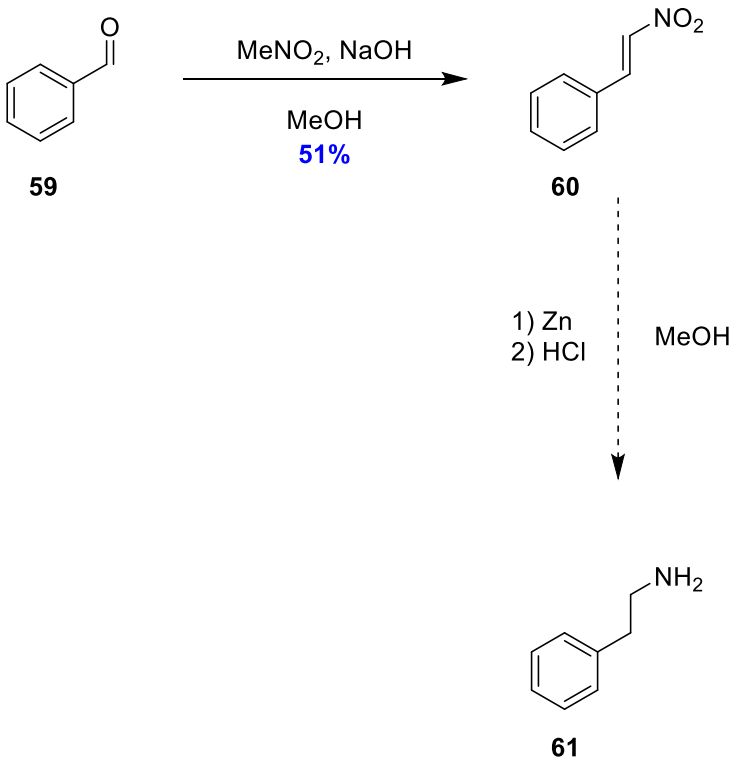
Table 7-10 Reaction conditions for mesylation of **55**.

Attempt number	Starting material	Reagents	Solvent	Reaction conditions	Comment	Ref.
7-10-1	**55**	$MeSO_2Cl$ (1.20 eq) Et_3N (1.20 eq) *	DCM	16 h + 16 h, rt	Several new spots appeared on the TLC and the crude ^{1}H NMR was promising	[72]

* There was added 1.20 eq more of both reagents to try and see if all the start material would react

7.14 Extra: Henry aldol

While waiting for the ordered reagents for the synthesis of **13**, involving the 6-endo-dig process, other ways of making **13** were tried. One plan was to convert an aldehyde into a CH_2-CH_2-NH_2 moiety. The aldehyde would be bonded to a ring structure similar to the desired alpha-pyrone structure. The synthesis involved a Henry aldol to convert the aldehyde into a conjugated nitro group, which further could be reduced to an amine. The test reaction consisted of benzaldehyde and nitromethane, and the synthetic route is displayed in **Scheme 7-27**.



Scheme 7-27 Synthetic route towards **61**.

Benzaldehyde **59** and nitromethane in MeOH was stirred together with a NaOH water solution at 0 °C. It was stirred for 1 h, before it was quenched with aqueous HCl to afford **60**.[73] In the prescribed article the product was purified with chromatography.[73] However, nitro compound **60** was purified with recrystallization in heptane and minimal amount of EtOAc. Nitro compound **60** was soluble in hot heptane and a few drops of EtOAc, but once it was placed in the freezer it fell out as yellow crystals. This afforded **60** with a yield of 51%.

Nitro compound **60** was taken further in a reduction reaction with Zn and concentrated HCl in MeOH,[74] to try and afford **61**. The TLC taken after 8 h was hard to interpret. There were some spots at the baseline, but the crude ^{1}H NMR showed nothing. However, the reaction was quenched with NaOH. The ^{1}H NMR taken after the workup showed nothing. The test was then aborted, and the original synthetic route towards **13** was started.

Table 7-11 Reaction conditions and yield for the henry aldol and reaction conditions for the attempted reduction of **60**.

Entry	Starting material	Reagents	Solvent	Reaction conditions	Comment	Ref.
7-11-1	**59**	$MeNO_2$ (1.00 eq) NaOH (1.20 eq)	MeOH	1 h, 0 °C	Yield: 51%	[73]
7-11-2	**60**	Zn (17.6 eq) Concentrated aq. HCl	MeOH	15 min, -10 °C 8 h, 0 °C	No sign of product	[74]

8 Conclusion and Further Work

Most of the synthetic experiments conducted during this project are incorporated in the summarized **Scheme 8-1**, **8-2**, **8-3**, **8-4**, **8-5** and **8-6** below. The schemes additionally depict unexplored reactions and outline prospective plans for the continuation of this project.

There were two synthetic plans to synthesize ester **14**, where one is depicted in **Scheme 8-1** and the other in **8-2**. The first synthetic plan involved formation of 2*E*,4*E*-dienal **16**. Dienal **16** was successfully made from **19** through a Grignard and organolithium reactions. However, both reactions resulted in poor yields. The poor yields might be a result of a poorly made batch of **19**. Further down the line it could be interesting to test both reactions with a new batch of **19**, to see if the yields can be improved.

The second synthetic route towards **14** involved an 1,6-addition/elimination of **19** to form the isomers **25** and **43**. With a new batch of **19** the isomers **25** and **43** were successfully obtained. The crude isomers were then directly exposed to methanol and triphenylphosphine to yield the ester isomers **44** and **24**. Ester isomers **44** and **24** were separated in a recrystallization where **24** fell out as crystals and **44** remained in the supernatant. Bromo ester **24** was taken further in a Suzuki coupling with boronic acid **23** to successfully produce **14**.

The synthetic route towards **13** started with a silyl protection of 3-butyn-1-ol (**38**) to form silyl ether **36**. Silyl ether **36** was then exposed with *n*-BuLi and later methyl chloroformate (**37**) to produce methyl ester **34**. Methyl ester **34** was taken further in a Claisen condensation to form beta-keto ester **33**, where its respective enol tautomerization was presence in a 9:1 relation. Minimal silica gel was used in the purification step since beta-keto ester **33** seemed to be unstable when exposed with silica for too long.

Beta-keto ester **33** underwent a 6-endo-dig addition with gold complex **39** as a catalyst. At first acetic acid was used as solvent, which later proved too acidic resulting in cleavage of the silyl ether. Acetic acid was then replaced with nitromethane, and this resulted in no cleavage of the silyl ether. However, nitromethane as the reaction solvent also resulted in incomplete conversion. The amount of gold complex **39** was then increased, from 1 mol% to 2 mol%, to afford full conversion to pyrone **30**.

Another way to resolve the cleavage problem in the annulation reaction is to introduce a more robust protection group earlier on, instead of TBSCl. Other more robust silyl ethers could be

tested, for example TBDPSCl. Could also expand to other protection groups than silyl ethers, but they must be stable in both acidic and basic conditions due to the Claisen condensation and the annulation. Examples of other more stable protection groups could be benzyl ether or methyl ether. One challenge associated with the incorporation of a more resilient protection group is the increased difficulty in the subsequent deprotection process.

Pyrone **30** was taken further in a chlorination reaction, that has not been reported yet, to form **29**. In the chlorination reaction TEB and NCS are used to chlorinate alpha-pyrone **30**. The reaction has also been successful on other pyrones such as pyrone **46** and **45**. It was not successful on pyrone **50**, because of less available electrons and the steric hindrance of the acetyl group. The yield of the reaction was proven to be varying, where the cause might be the purification step. There are indications that the product could be retained on the silica column, but additional research is needed to strengthen the theory. Another way of purifying the product could be to recrystallize it, where recrystallization could improve the yields and strengthen the theory regarding the silica column issue.

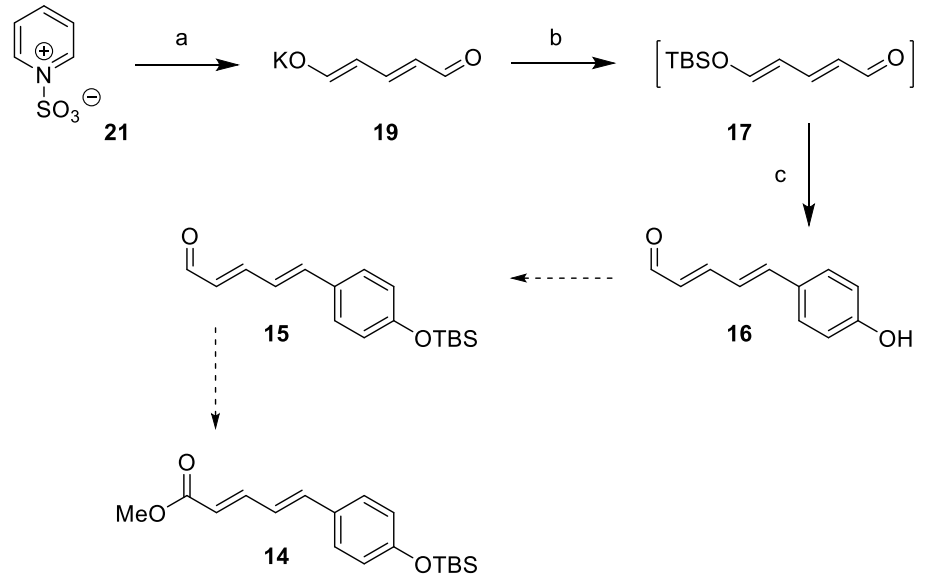
After the chlorination step the hydroxyl group on pyrone **29** needed to be protected. This proved to be a more challenging step than estimated, because of the steric hindrance of chlorine. At first TBDPSCl and TBSCl were tested with no positive results. Then acetylation was tested with acetic anhydride, which also yielded no desired product. At last acetylation was tested again, but with acetyl chloride instead. The reaction was successful and **51** was obtained with a yield of 32%. The yield was not optimal, and further work is needed to improve it.

In addition to enhancing the yield of the acetylation reaction, further efforts should be directed towards the progression towards the desired end-product. Pyrone **51** can then be taken further in a deprotection reaction to obtain **62**, where the alcohol group on **62** can be turned into an azide either through a Mitsunobu reaction or mesylation followed up by nucleophilic substitution. The azide on **63** can be converted to an amine, through a Staudinger reduction, to obtain **64**. Pyrone **64** can then be linked together with **14** in an amide formation, followed up by deprotection of the protecting groups to form fuligopyrone B (**10**).

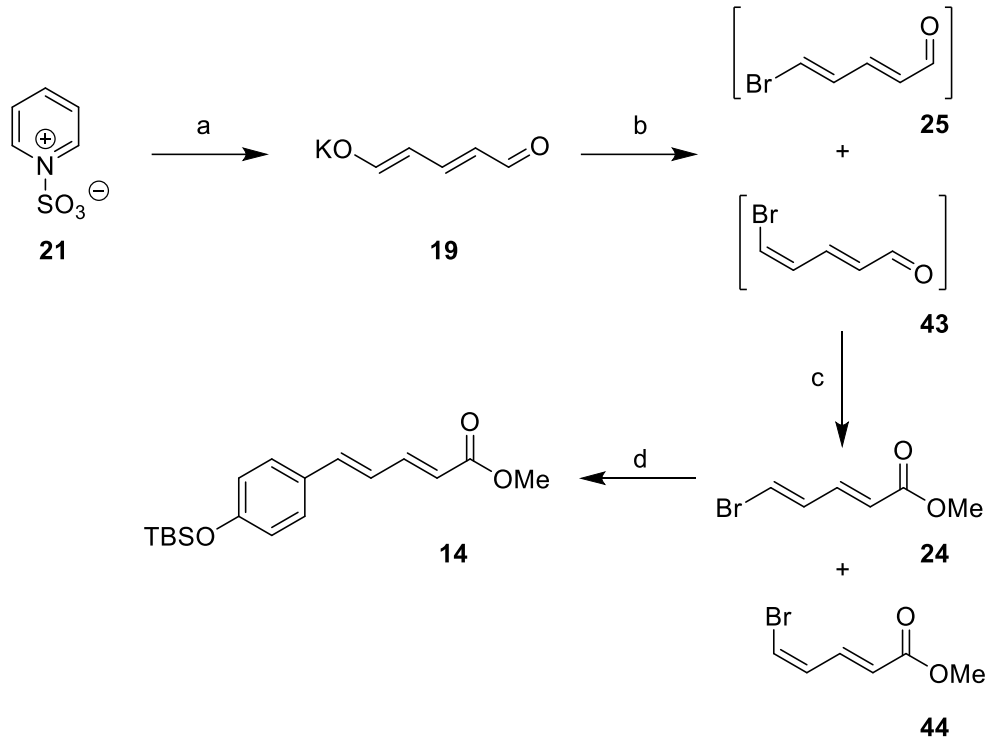
Another pathway towards **64** was also tested, where the azide group was introduced earlier in the synthetic route. It was tested to see if an azide group could be introduced on beta-keto ester **55**, where both Mitsunobu and mesylation reactions were tried. The Mitsunobu reaction resulted in no yields of the desired azide **56**. However, it seems that the mesylation reaction successfully

obtained **58**. A workup of the crude material from the mesylation must be done to conclude that the reaction was successful. If the reaction is successful, then **58** can undergo a nucleophilic substitution to afford azide **56**. Azide **56** can then be taken further in the annulation reaction to afford pyrone **57**, which can be chlorinated to obtain **66**. Then pyrone **66** can be protected with an acetylation reaction and further undergo a Staudinger reduction to afford **64**.

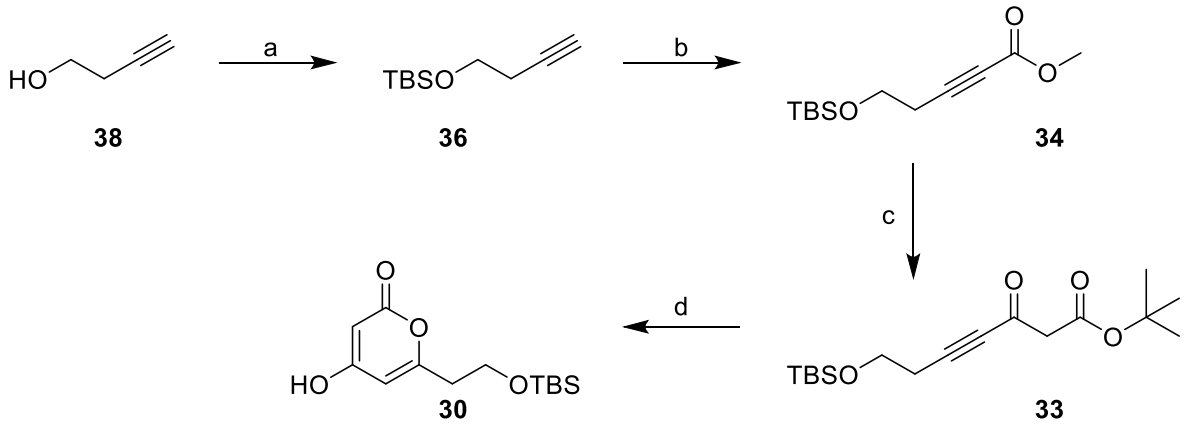
The aim of this project was to obtain a synthetic pathway to fuligopyrone B (**10**) in a convergent synthesis, where the two main building blocks were **64** and **14**. Ester **14** was successfully obtained through a Suzuki coupling at the end. The synthetic route towards **64** proved to be more challenging, where pyrone **51** was the last obtained compound in the synthetic route. Further work on this project will focus on the synthetic route towards **64**. Where the reactions will be optimized and **51** will be taken further to obtain **64**. Compound **64** can be coupled together with the already obtained **14** to later afford fuliopyrone B (**10**). Alternatively, the azide group can be introduced earlier in the synthesis on beta-keto ester **55**, if this is proven to be a more trouble-free pathway.



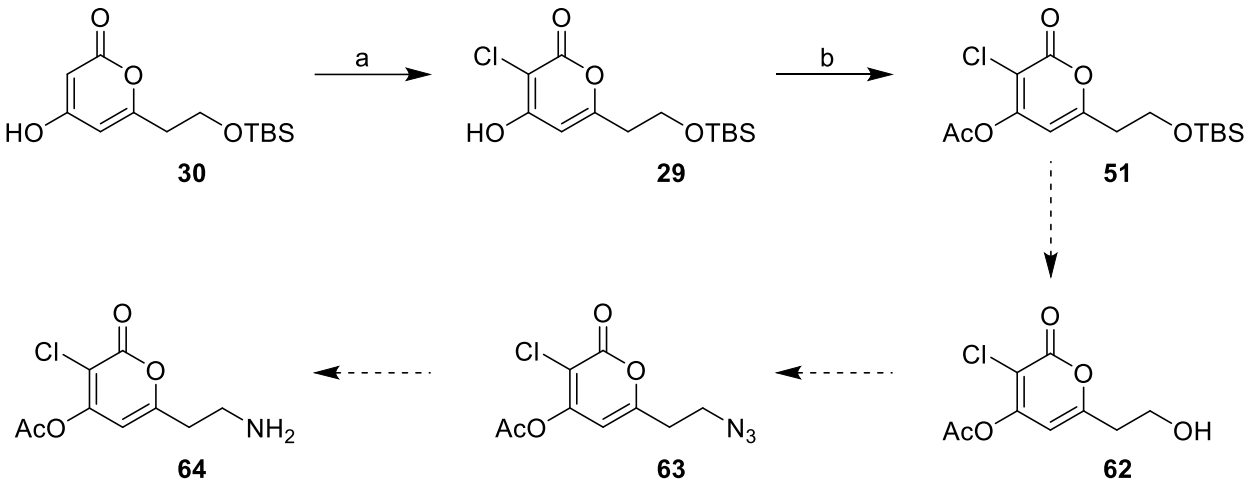
Scheme 8-1 a) NaOH (4.13 eq), water, -20 °C: 1 h, rt: 6 h, 61%, b) Et_3N, DMAP (11 mol%), TBSCl (1.00 eq), THF, rt: 2 h, c) Grignard reagent **18** (1.06 eq)/organolithium **42** (1.10 eq) and $HCl_{(aq)}$, THF, rt: 4 h, 5-6%.



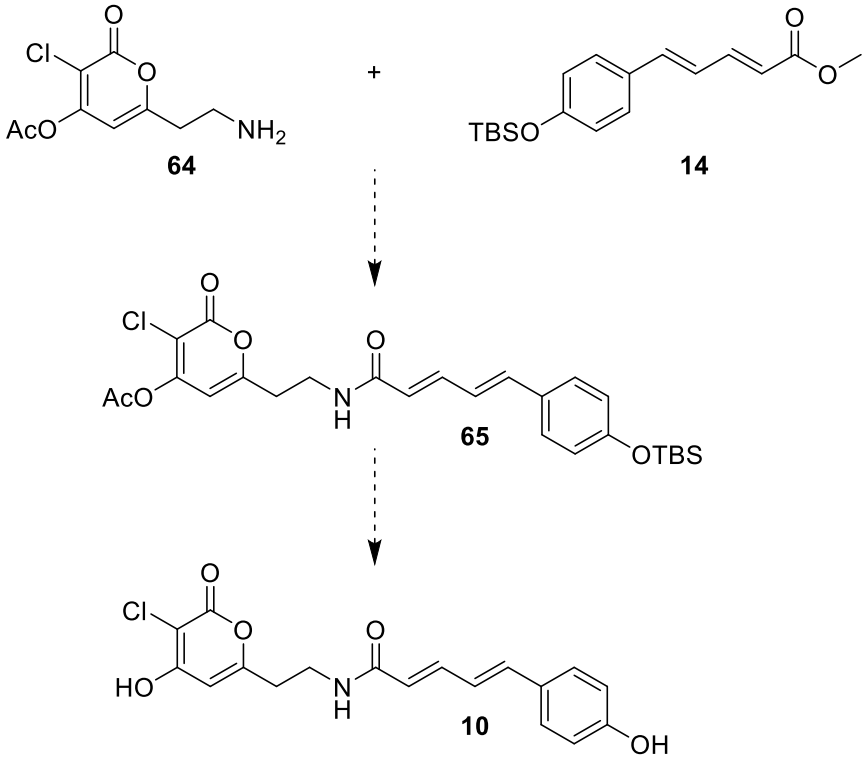
Scheme 8-2 a) NaOH (4.13 eq), water, -20 °C: 1 h, rt: 6 h, 61%, b) Ph_3P (1.35 eq), Br_2 (1.30 eq), DCM, rt: 16 h, c) $KHSO_5$ (1.50 eq), MeOH, rt: 24 h, 41% over all yield of the two isomers **24** and **44** from **19** d) Boronic acid **23** (1.20 eq), $Pd(PPh_3)_4$ (1 mol%), degassed 2 M Na_2CO_3, toluene, 80 °C: 16 h, 81%.



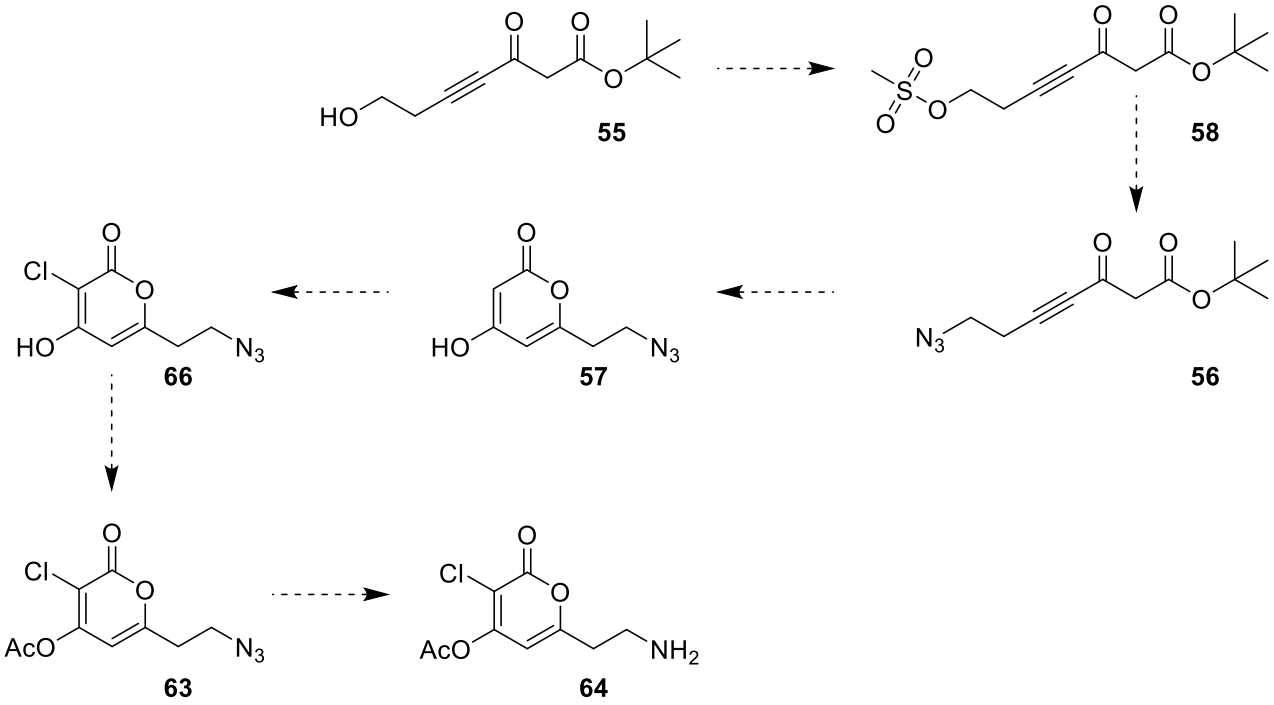
Scheme 8-3 a) TBSCl (1.20 eq), imidazole (2.40 eq), THF, rt: 3 h, 91%, b) *n*-BuLi (1.03 eq), methyl chloroformate (**37**) (1.18 eq), THF, -78 °C: 1 h, 93%, c) LDA (1.30 eq), *t*-butyl acetate (**35**) (1.30 eq), THF, -78 °C: 3 h, 87%, d) SPhosAuNTf2 (**39**) (2 mol%), $MeNO_2$, rt: 24 h, 78%.



Scheme 8-4 a) NCS (1.30 eq), Et_3B (20 mol%), MeCN, rt: 16 h, 56%, b) Acetyl chloride (1.36 eq), Et_3N (1.36 eq), DCM, rt: 16 h, 32%.



Scheme 8-5 Amide formation between **64** and **14**, followed up by a deprotection to form fuligopyrone B (**10**).



Scheme 8-6 An alternative synthetic pathway towards **64**.

9 Experimental Procedures

9.1 General information

All reactions were carried out using Schlenck to keep a controlled atmosphere without water and O_2. The reactions were carried out under N_2-atmosphere, and all glassware was flame dried before use. The reagents utilized were of technical grade and were used without additional purification. Some reagents without septum were transferred to glassware and sealed with septum before it was degassed and filled with nitrogen (This was done three times).

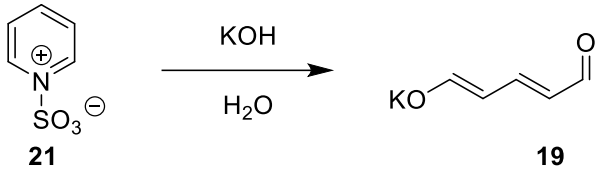
TLC was used to monitor all the reactions, except the synthesis of glutaconaldehyde potassium salt (**19**). Since both starting material and product are salts, it is very hard to monitor it on TLC. TLC was performed on Merck TLC silica gel 60 F254. KMnO4 stain, $FeCl_3$ stain and UV-light were used for development.

Silica gel 60 (SiO_2) (0.040-0.063 mm) from Merck was utilized when flash chromatography was used as a purification method. Dry loading was performed on all pyrones, except in the purification method for 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-oxo-2*H*-pyran-4-yl acetate (**51**). Celite (545) was used as dry loading material.

The NMR spectra were recorded at Bruker Ascend 400-spectrometer. The ^{1}H NMR spectra were recorded at 400 MHz and the ^{13}C NMR spectra were recorded at 101 MHz. Both chloroform ($CDCl_3$) and dimethyl sulfoxide (DMSO-d_6) were used as solvents. The spectra were processed and analyzed in MestReNova.

IR-spectra were recorded at Perkin-Elmer FT-IR instrument (spectrum Bx, 50/60 Hz).

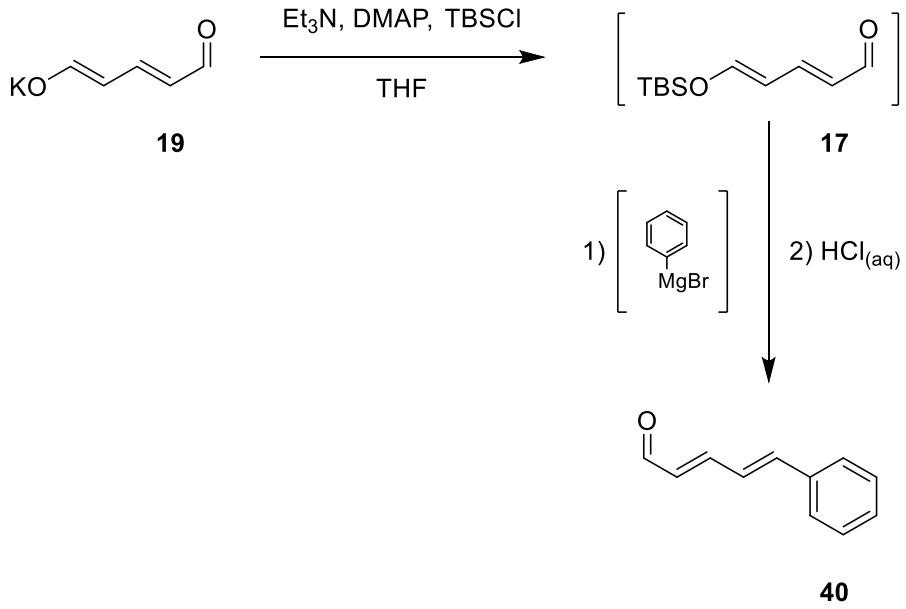
9.2 Potassium (1*E*,3*E*)-5-oxopenta-1,3-dien-1-olate (19)



Scheme 9-1 Synthesis of compound **19**.

Pyridinium-1-sulfonate (**21**) (50.0 g, 0.31 mol, 1.00 eq) was added portionwise over 5 min to a solution of potassium hydroxide (71.8 g, 1.28 mol, 4.13 eq) and water (175 mL) at -20 °C. It was then stirred for 1 h at this temperature before it was warmed to rt and stirred for 6 h or until the solution turned dark brown. The round bottle was then cooled to 0 °C for 15 min and was then filtrated with acetone (4 x 40 mL) using a Büchner funnel. After the filtration it was up concentrated *in vacuo* and dried over night at 4 °C. The product was then added to methanol (700 mL) and activated charcoal (5.00 g), before it was refluxed with effective stirring for 15 min. After that it was immediately prepared for a hot filtration, where it was used more hot methanol (2 x 100 mL) to wash the remaining material in the filtration funnel. The filtrate was then cooled to rt and was up concentrated *in vacuo*. The solid substance was then collected in a Büchner funnel and was washed with acetone (5 x 20 mL) and dried overnight to afford a light brown glutaconaldehyde potassium salt (**19**). Yield: 25.9 g, 61%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 9.2 Hz, 2H), 7.04 (t, J = 13.1 Hz, 1H), 5.11 (dd, J = 13.1, 9.2 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 184.4, 159.8, 106.2. NMR corresponds to previously reported data.[24]

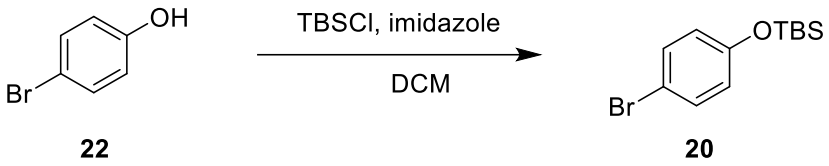
9.3 (2*E*,4*E*)-5-phenylpenta-2,4-dienal (40)



Scheme 9-2 Synthesis of compound **40**.

Triethylamine (5 drops) and 4-dimethylaminopyridin (15.0 mg, 0.12 mmol, 11 mol%) was added to a slurry of glutaconaldehyde potassiumsalt (**19**) (150 mg, 1.10 mmol, 1.00 eq) in dry THF (20 mL) at rt. The mixture was stirred and *tert*-butyldiemthylsilyl chloride (170 mg, 1.13 mmol, 1.03 eq) was added. After 2 h of stirring the reaction mixture was cooled down to 0 °C before a solution of phenylmagnesium bromide (214 mg, 1.18 mmol, 1.07 eq) in THF (1.50 mL) was added. The mixture was warmed to rt over 2 h. After 2 h the solution was diluted with HCl (3 M, 1.50 mL). The solution was then stirred for 2 h (isomerization). The mixture was extracted with EtOAc (3 x 50 mL) and the organic phase was washed with brine. It was then dried ($MgSO_4$), filtrated and up concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, 10% Et_2O in heptane, $KMnO_4$ stain) to afford (2*E*,4*E*)-5-phenylpenta-2,4-dienal (**40**) as a yellow oil. Yield: 104 mg, 60%; Rf = 0.18 (10% Et_2O in heptane, $KMnO_4$ stain); ^1H NMR (400 MHz, $CDCl_3$) δ: 9.62 (d, J = 7.9 Hz, 1H), 7.54-7.48 (m, 2H), 7.41-7.35 (m, 3H), 7.30-7.24(m, 1H), 7.01 (d, J = 7.2 Hz, 2H), 6.27 (dd, J = 15.2, 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 193.7, 152.2, 142.6, 135.7, 131.7, 129.8, 129.1, 127.7, 126.3. NMR corresponds to previously reported data.[75]

9.4 (4-bromophenoxy)(*tert*-butyl)dimethylsilane (20)

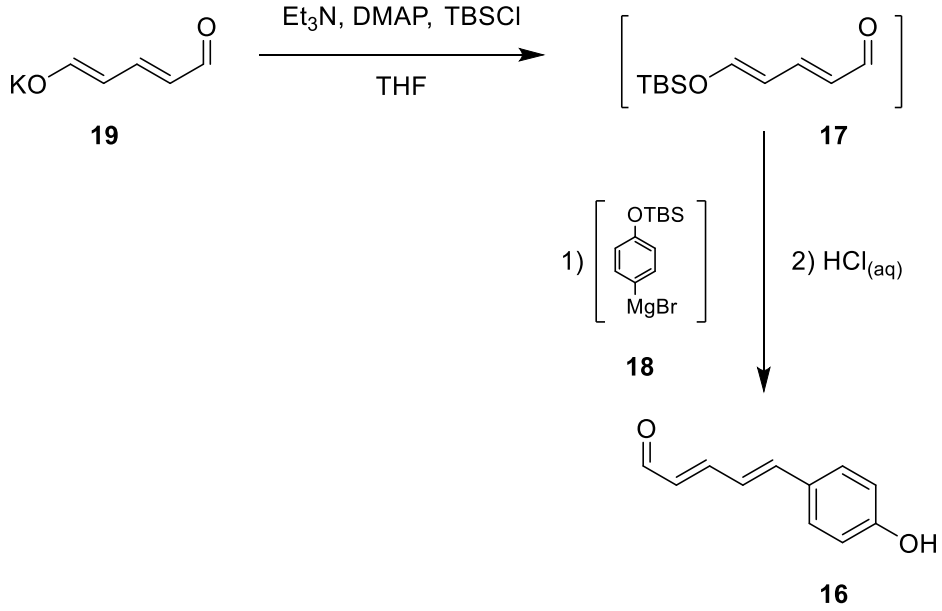


22 **20**

Scheme 9-3 Synthesis of compound **20**.

Tert-butyldimethylsilyl chloride (5.23 g, 34.7 mmol, 1.20 eq) and imidazole (2.36 g, 34.7 mmol, 1.20 eq) was added to a solution of *p*-bromophenol (**22**) (5.00 g, 28.9 mmol, 1.00 eq) and DCM (22.5 mL) at 0 °C. The reaction mixture was then warmed to rt and was stirred for 16 h. It was then filtrated through a short pad of silica gel and washed with heptane (100 mL) to afford (4-bromophenoxy)(*tert*-butyl)dimethylsilane (**20**) as a transparent oil. Yield: 7.14 g, 86%; Rf = 0.36 (heptane, $KMnO_4$ stain); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 8.8 Hz, 2H), 0.99 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.0, 132.4, 122.0, 113.8, 25.8, 18.4, -4.3. NMR corresponds to previously reported data.[42]

9.5 (2*E*,4*E*)-5-(4-hydroxyphenyl)penta-2,4-dienal (16)



Scheme 9-4 Synthesis of compound **16**.

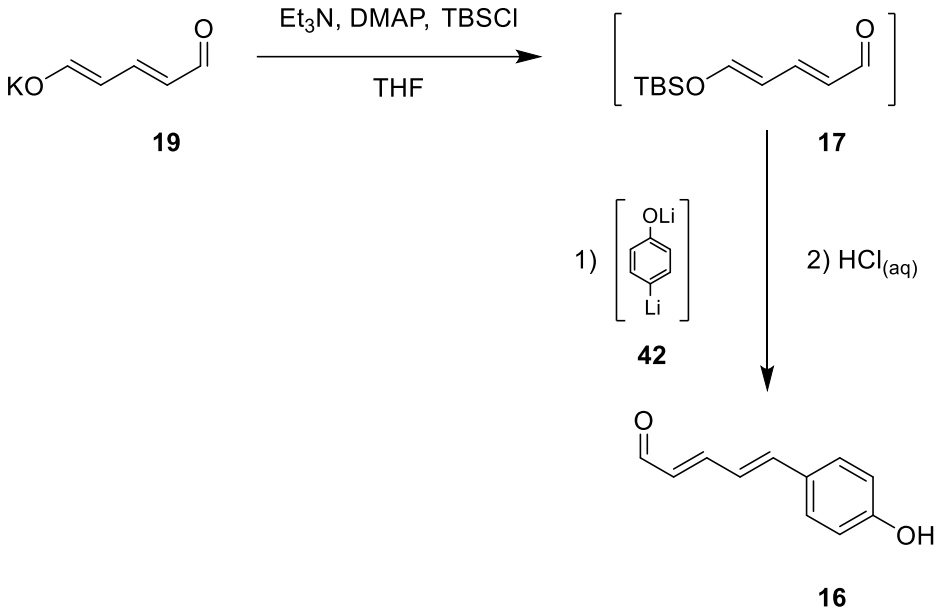
Triethylamine (5-7 drops) and 4-dimethylaminopyridin (30.0 mg, 0.25 mmol, 11 mol%) was added to a slurry of glutaconaldehyde potassium salt (**19**) (300 mg, 2.21 mmol, 1.00 eq) in dry THF (6.00 mL) at rt. The mixture was stirred and *tert*-butyldimethylsilyl chloride (333 mg, 2.21 mmol, 1.00 eq) was added. The mixture (A1) was stirred a minimum of 2 h to afford a solution of **17**.

While A1 was stirring, the Grignard solution was made. Mg (95.0 mg, 3.91 mmol, 1.66 eq) was added to a round flask under nitrogen. A little crystal of Iodin and THF (1.00 mL) was added to activate the magnesium. Silyl protected bromophenol **20** (675 mg, 2.35 mmol, 1.06 eq) in THF (2.35 mL) was added gradually while the mixture was gently refluxed. The mixture was stirred for 2 h.

After 2 h the mixture was poured into A1 at 0 °C, while it was stirring. The solution was warmed to rt over 2 h. After 2 h the solution was diluted with HCl (3 M, 1.50 mL). The solution was then stirred for 2 h (isomerization). It was then extracted with EtOAc (3 x 15 mL) and the organic phase was washed with brine. The organic phase was dried ($MgSO_4$), filtrated and up concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, 30% → 40% EtOAc in heptane, $KMnO_4$ stain) to afford (2*E*,4*E*)-5-(4-hydroxyphenyl)penta-2,4-dienal (**16**) as an orange solid. Yield: 20 mg, 5%; Rf = 0.17 (30% EtOAc in heptane, $KMnO_4$ stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.60 (d, J = 8.0 Hz, 1H), 7.46-7.39 (m, 2H), 6.97 (d, J =

15.4 Hz, 1H), 6.91-6.87 (m, 1H), 6.86-6.83 (m, 2H), 6.72 (s, 1H), 6.23 (dd, J = 15.2, 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 193.8, 157.2, 152.9, 142.4, 130.8, 129.5, 128.8, 124.3, 116.1.

9.6 (2*E*,4*E*)-5-(4-hydroxyphenyl)penta-2,4-dienal (16)



Scheme 9-5 Synthesis of compound **16**.

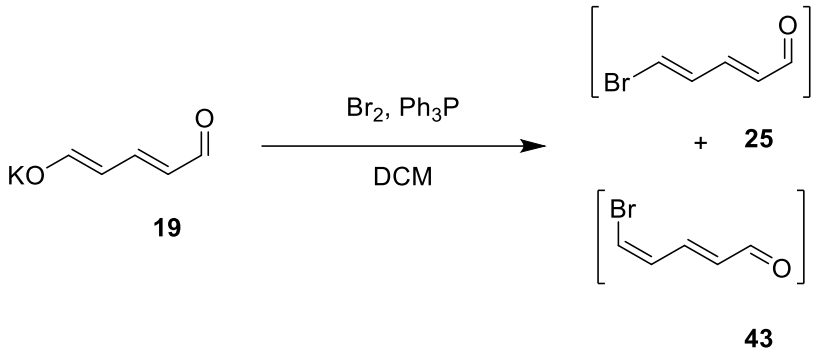
Triethylamine (10 drops) and 4-dimethylaminopyridin (100 mg, 0.82 mmol, 11 mol%) was added to a slurry of glutaconaldehyde potassium salt (**19**) (1.00 g, 7.34 mmol, 1.00 eq) in dry THF (20 mL) at rt. The mixture was stirred and *tert*-butyldimethylsilyl chloride (1.11 g, 7.36 mmol, 1.00 eq) was added. The mixture (A2) was stirred a minimum of 2 h to afford a solution of **17**.

While A2 was stirring, the lithiation of the *p*-bromophenol (**22**) was started. *p*-Bromophenol (**22**) (1.40 g, 8.08 mmol, 1.10 eq) was dissolved in THF (80 mL) and cooled down to -78 °C. *n*-BuLi (1.6 M in hexane, 11.1 mL, 17.8 mmol, 2.20 eq) was added dropwise and the solution was stirred at -78 °C for 45 min.

The lithium phenol solution was then added to A2 at 0 °C. The mixture was warmed to rt over 2 h. After 2 h the solution was diluted with HCl (3 M, 10 mL). The solution was then stirred for 2 h (isomerization). It was then extracted with EtOAc (3 x 50 mL) and the organic phase was

washed with brine. The organic phase was dried ($MgSO_4$), filtrated and up concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, 30% → 40% EtOAc in heptane, $KMnO_4$ stain) to afford (2*E*,4*E*)-5-(4-hydroxyphenyl)penta-2,4-dienal (**16**) as an orange solid. Yield: 76.5 mg, 6%; Rf = 0.17 (30% EtOAc in heptane, $KMnO_4$ stain); ^1H NMR (400 MHz, $CDCl_3$) δ: 9.60 (d, J = 8.0 Hz, 1H), 7.46-7.39 (m, 2H), 6.97 (d, J = 15.4 Hz, 1H), 6.91-6.87 (m, 1H), 6.86-6.83 (m, 2H), 6.72 (s, 1H), 6.23 (dd, J = 15.2, 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 193.8, 157.2, 152.9, 142.4, 130.8, 129.5, 128.8, 124.3, 116.1.

9.7 (2*E*,4*E*)-5-bromopenta-2,4-dienal (25) and (2*E*,4*Z*)-5-bromopenta-2,4-dienal (43)



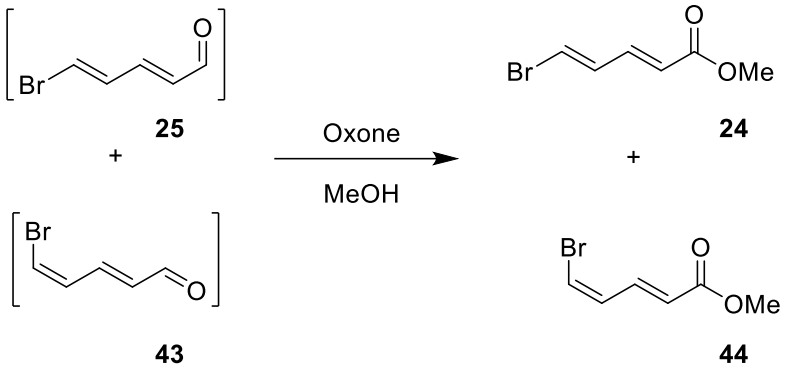
Scheme 9-6 Synthesis of compound **25** and **43**.

Triphenylphosphine (11.2 g, 42.6 mmol, 1.35 eq) was dissolved in DCM (150 mL) and cooled to 0 °C. A solution of bromine (2.10 mL, 41.0 mmol, 1.30 eq) was dissolved in DCM (38 mL) and the solution was added dropwise with efficient stirring (if there was a persistent reddish-brown and yellow color after complete addition of the bromine solution, additional triphenylphosphine was added in small portions until a white slurry appeared). Glutaconaldehyde potassium salt (**19**) (4.30 g, 31.6 mmol, 1.00 eq) was then added in one portion. The reaction mixture was allowed to attain rt and it was stirred overnight. The reaction mixture was then filtered through a short pad of silica gel (SiO_2, DCM, $KMnO_4$ stain) and the crude material was up concentrated *in vacuo*. The crude product was used in the next step of the synthesis (**9.8**) without further purification.

(2*E*,4*E*)-5-bromopenta-2,4-dienal (**25**): Rf = 0.18 (10% Et_2O in heptane, $KMnO_4$ stain)

(2*E*,4*Z*)-5-bromopenta-2,4-dienal (**43**): Rf = 0.24 (10% Et_2O in heptane, $KMnO_4$ stain)

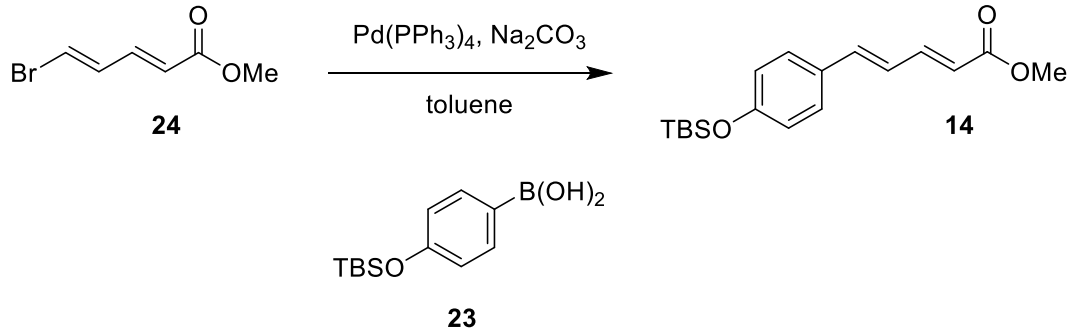
9.8 (2*E*,4*E*)-5-bromopenta-2,4-dienoate (24)



Scheme 9-7 Synthesis of compound **24**.

The crude product obtained from procedure **9.7** was dissolved in dry methanol (200 mL) and then potassium peroxymonosulfate (9.45 g, 30.7 mmol, 1.50 eq) was added in one portion. The flask was flushed with nitrogen and stirred for 24 h. The flask was then placed on a rotary evaporator in order to remove most of the methanol until a slurry was obtained. Next, EtOAc (50 mL) was added, rapid stirring was turned on and an aqueous 1 M solution of HCl was added carefully until all the salts had dissolved. The aqueous phase was extracted with EtOAc (5 x 50 mL), the combined organic phase was dried (Na_2SO_4), filtrated and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO2, 10% Et_2O in heptane, KMnO4-stain) to give a mixture of geometric isomers. The fractions containing the two isomers were combined and the flask was placed on a rotary evaporator in order to remove approximately 80% of the solvent volume. The flask was then placed in a -20 °C freezer which lead to the crystallization of the *E,E*-isomer while the *E*,*Z*-isomer remained in solution. The supernatant was carefully transferred into a new flask and the crystals of the *E,E*-isomer were washed with ice-cold heptane (2 x 5 mL). This process gave pure methyl (2*E*,4*E*)-5-bromopenta-2,4-dienoate (**24**) as white crystals. Combined yield: 2.48 g, 41%; Rf = 0.39 (10% Et_2O in heptane, KMnO4-stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (dd, J = 15.4, 10.5 Hz, 1H), 6.90-6.71 (m, 2H), 5.93 (d, J = 15.3 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.1, 141.4, 135.5, 121.9, 118.1, 51.9. NMR corresponds to previously reported data.[24]

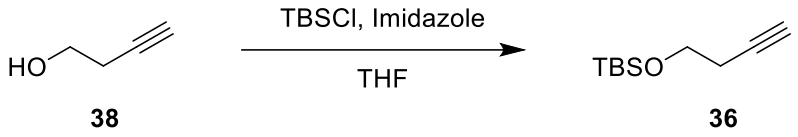
9.9 Methyl (2*E*,4*E*)-5-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)penta-2,4-dienoate (14)



Scheme 9-8 Synthesis of compound **14**.

$Pd(PPh_3)_4$ (12.2 mg, 10.6 µmol, 1 mol%) was added to a solution of (4-((*tert*-butyldimethylsilyl)oxy)phenyl)boronic acid (**23**) (318 mg, 1.26 mmol, 1.20 eq), methyl (2*E*,4*E*)-5-bromopenta-2,4-dienoate (**24**) (200 mg, 1.05 mmol, 1.00 eq), degassed 2.0 M Na_2CO_3 (3.30 mL) and toluene (5.50 mL). The flask was then evacuated and vented with nitrogen (3x) and the reaction mixture was heated to 80 °C and stirred overnight. After completion, the reaction mixture was cooled to room temperature, quenched by the addition of saturated aqueous NH_4Cl (25 mL) and extracted with Et_2O (5 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, 10% Et_2O in heptane, $KMnO_4$ stain) to afford methyl (2*E*,4*E*)-5-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)penta-2,4-dienoate (**14**) as a white solid. Yield: 270 mg, 81%; Rf = 0.25 (10% Et_2O in heptane, $KMnO_4$ stain); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.44 (dd, J = 15.2, 10.8 Hz, 1H), 7.37-7.33 (m, 2H), 6.87-6.71 (m, 4H), 5.94 (d, J = 15.2 Hz, 1H), 3.76 (s, 3H), 0.98 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.8, 156.9, 145.4, 140.5, 129.5, 128.8, 124.4, 120.6, 119.7, 51.7, 25.8, 18.4, -4.2.

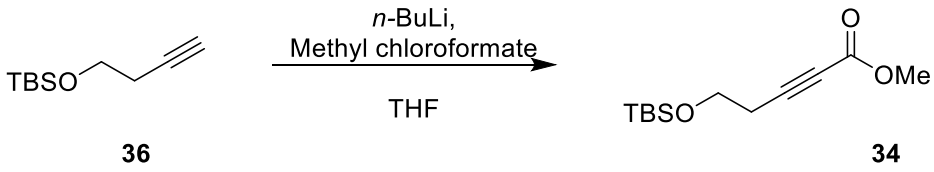
9.10 (But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (36)



Scheme 9-9 Synthesis of compound **36**.

Tert-butyldimethylsilyl chloride (12.9 g, 85.6 mmol, 1.20 eq) was added to a solution of 3-butyn-1-ol (**38**) (5.00 g, 71.3 mmol, 1.00 eq) and imidazole (11.6 g, 171 mmol, 2.40 eq) in THF (109 mL). It was then stirred for 3 h at rt, before it was filtered through a short pad of silica gel (SiO_2, 20% EtOAc in heptane, $KMnO_4$ stain) to afford (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (**36**) as transparent oil. Yield: 12.0 g, 91%; Rf = 0.66 (20% EtOAc in heptane, $KMnO_4$ stain); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.74 (t, J = 7.1 HZ, 2H), 2.40 (td, J = 7.1 HZ, 2.6 HZ, 2H), 1.96 (t, J = 2.6 HZ, 1H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 81.69, 69.4, 61.9, 26.0, 23.0, 18.5, -5.1. NMR corresponds to previously reported data.[76]

9.11 5-((*tert*-butyldimethylsilyl)oxy)pent-2-ynoate (34)

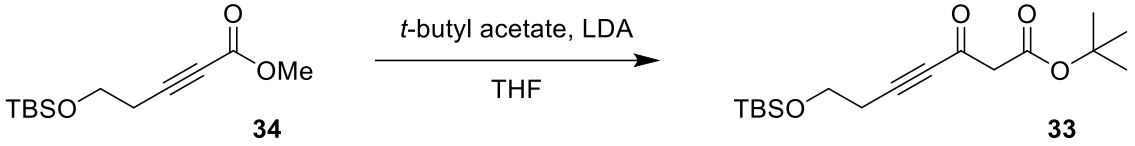


Scheme 9-10 Synthesis of compound **34**.

n-BuLi (1.6 M in hexane, 6.98 mL, 11.2 mmol, 1.03 eq) was added to a solution of terminal alkyne **36** (2.00 g, 10.8 mmol, 1.00 eq) in THF (36.0 mL) at -78 °C. The mixture was stirred at -78 °C for 30 min, before methyl chloroformate (**37**) (1.21 g, 12.8 mmol, 1.18 eq) was introduced. The mixture was then stirred for 1 h at -78 °C, before it was quenched with saturated NH_4Cl-solution (10-20 mL). The mixture was warmed to rt, before it was extracted with EtOAc (3 x 20 mL). After the extraction the organic phase was washed with brine before it was dried (Na_2SO_4) and filtrated. The organic phase was then concentrated *in vacuo*, before it was plugged through a short pad of silica (SiO_2, 20% EtOAc in heptane, $KMnO_4$ stain) to afford methyl 5-

((*tert*-butyldimethylsilyl)oxy)pent-2-ynoate (**34**) as yellow oil. Yield: 2.45 g, 93%; Rf = 0.44 (20% EtOAc in heptane, $KMnO_4$ stain); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.78 (t, J = 6.9 Hz, 2H), 3.75 (s, 3H), 2.54 (t, J = 6.9 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 154.2, 86.9, 73.9, 60.8, 52.7, 25.9, 23.2, 18.42, -5.2. NMR corresponds to previously reported data.[77]

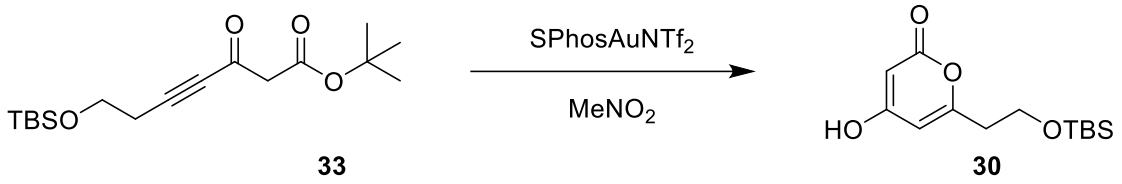
9.12 *Tert*-butyl 7-((*tert*-butyldimethylsilyl)oxy)-3-oxohept-4-ynoate (33)



Scheme 9-11 Synthesis of compound **33**.

n-BuLi (1.6 M in hexane, 10.1 mL, 16.1 mmol, 1.30 eq) was added to a solution of diisopropylamine (2.08 g, 16.1 mmol, 1.30 eq) in THF (22.2 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 50 min, 30 min at 0 °C and cooled to -78 °C. *t*-Butyl acetate (**35**) (1.87 g, 16.1 mmol, 1.30 eq) was then added dropwise to the stirred solution at -78 °C. It was stirred at this temperature for 30 min before the TBS protected ester alkyne (**34**) (3.00 g, 12.4 mmol, 1.00 eq) was slowly added. The stirring was continued at -78 °C for 3 h. The mixture was poured into aqueous saturated NH_4Cl (20-30 mL) and it was extracted with Et_2O (3 x 50 mL). The organic phase was then washed (NH_4Cl), dried (Na_2SO_4), filtrated and concentrated *in vacuo*. The crude material was plugged through a short pad of silica (SiO_2, 7% EtOAc in heptane, $KMnO_4$ stain) to afford *tert*-butyl 7-((*tert*-butyldimethylsilyl)oxy)-3-oxohept-4-ynoate (**33**) as an yellow oil. Yield: 3.52 g, 87%; Rf = 0.44 (20% EtOAc in heptane, $KMnO_4$ stain); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.19 (enol) (s, 1H) 3.78 (t, J = 6.9 Hz, 2H), 3.45 (s, 2H), 2.59 (t, J = 6.9 Hz, 2H), 1.47 (s, 9H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 179.4, 165.4, 93.2, 82.3, 81.3, 60.8, 52.8, 28.1, 25.9, 23.6, 18.4, -5.2.

9.13 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-hydroxy-2*H*-pyran-2-one (30)

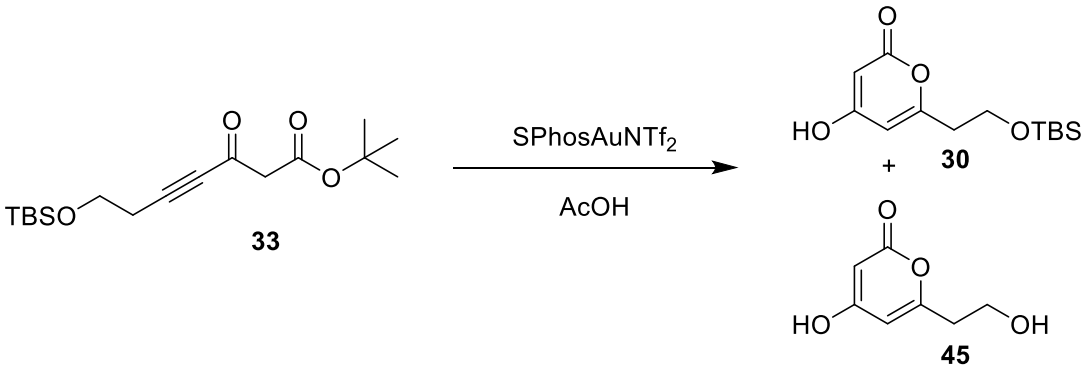


33 30

Scheme 9-12 Synthesis of compound **30**.

A solution of beta-keto ester **33** (479 mg, 1.47 mmol, 1.00 eq) and SPhosAuNTf$_2$ (**39**) (26.1 mg 29.4 µmol, 2 mol%) in $MeNO_2$ (7.00 mL) was stirred for 24 h. It was then concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 50% EtOAc in heptane, $KMnO_4$ stain) to afford 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-hydroxy-2*H*-pyran-2-one (**30**) as a yellow solid. Yield: 311 mg, 78%; Rf = 0.18 (50% EtOAc in heptane, $KMnO_4$ stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.04 (d, J = 2.1 Hz, 1H), 5.58 (s, J = 2.1 Hz, 1H), 3.89 (t, J = 6.1 Hz, 2H), 2.68 (t, J = 6.1 Hz, 2H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.1, 167.8, 164.7, 102.9, 90.8, 59.9, 37.5, 25.9, 18.3, -5.3. NMR corresponds to previously reported data.[78]

9.14 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-hydroxy-2*H*-pyran-2-one (30) and 4-hydroxy-6-(2-hydroxyethyl)-2*H*-pyran-2-one (45)



33 30 45

Scheme 9-13 Synthesis of compound **30** and **45**.

A solution of beta-keto ester **33** (1.52 g, 4.66 mmol, 1.00 eq) and SPhosAuNTf$_2$ (**39**) (41.4 mg, 46.6 µmol, 1 mol%) in HOAc (21.6 mL) was stirred for 24 h. It was then concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 2% MeOH → 5% MeOH in DCM, $KMnO_4$ stain) to afford 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-hydroxy-2*H*-pyran-2-one (**30**) as a yellow solid and 4-hydroxy-6-(2-hydroxyethyl)-2*H*-pyran-2-one (**45**) as a white solid.

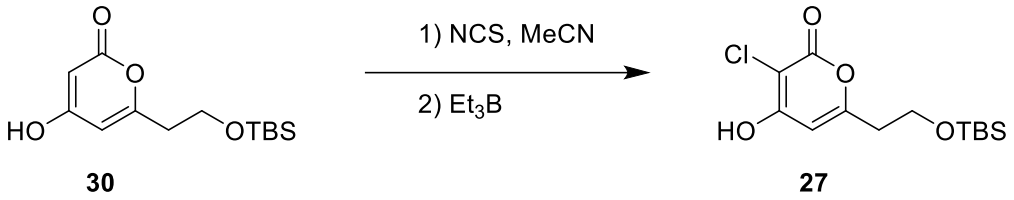
6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-hydroxy-2*H*-pyran-2-one (**30**):

Yield: 250 mg, 20%; Rf = 0.18 (50% EtOAc in heptane, $KMnO_4$ stain); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.04 (d, J = 2.1 Hz, 1H), 5.58 (s, J = 2.1 Hz, 1H), 3.89 (t, J = 6.1 Hz, 2H), 2.68 (t, J = 6.1 Hz, 2H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.1, 167.8, 164.7, 102.9, 90.8, 59.9, 37.5, 25.9, 18.3, -5.3. NMR corresponds to previously reported data.[78]

4-hydroxy-6-(2-hydroxyethyl)-2*H*-pyran-2-one (**45**):

Yield: 385 mg, 53%; Rf = 0.09 (5% MeOH in DCM, $KMnO_4$ stain); ^1H NMR (400 MHz, DMSO-d_6) δ: 5.97 (d, J = 2.0 Hz, 1H), 5.21 (d, J = 2.0 Hz, 1H), 3.63 (t, J = 6.3 Hz, 2H), 2.56 (t, J = 6.3 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 170.4, 164.5, 163.9, 100.8, 88.4, 57.8, 36.7.

9.15 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-chloro-4-hydroxy-2*H*-pyran-2-one (27)

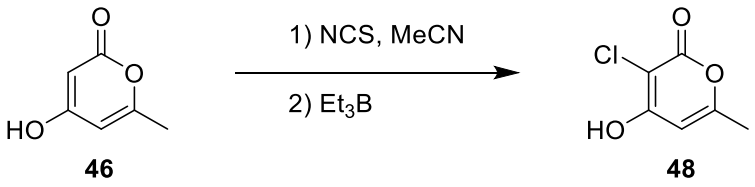


30 **27**

Scheme 9-14 Synthesis of compound **27**.

Pyrone **30** (275 mg, 1.02 mmol, 1.00 eq) and NCS (177 mg, 1.32 mmol, 1.30 eq) were solved in MeCN (2.10 mL) and was flushed with nitrogen. The solution was then stirred while triethylborane (0.20 mL, 0.20 mmol, 20 mol%) in THF (1 M) was added. It was stirred overnight. The mixture was then concentrated *in vacuo* before water (2.50 mL) was added, and it was extracted with Et_2O (4 x 3 mL) before it was dried and filtrated through Na_2SO_4. The organic phase was then concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, 10% MeOH in DCM, $KMnO_4$ stain) to afford 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-chloro-4-hydroxy-2*H*-pyran-2-one (**27**) as an orange solid. Yield: 174 mg, 56%; Rf = 0.28 (10% MeOH in DCM, KMnO4 stain); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.11, (s, 1H), 3.89 (t, J = 6.1 Hz, 2H), 2.67 (t, J = 6.1 Hz, 2H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.1, 162.7, 160.3, 100.3, 98.5, 59.7, 37.3, 25.9, 18.3, -5.3.

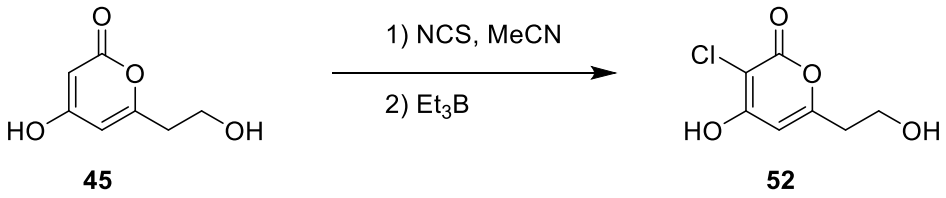
9.16 3-chloro-4-hydroxy-6-methyl-2*H*-pyran-2-one (48)



Scheme 9-15 Synthesis of compound **48**.

4-hydroxy-6-methyl-2-pyrone (**46**) (250 mg, 1.98 mmol, 1.00 eq) and NCS (344 mg, 2.57 mmol, 1.30 eq) were solved in MeCN (3.75 mL) and was flushed with nitrogen. The solution was then stirred while triethylborane (0.40 mL, 0.40 mmol, 20 mol%) in THF (1 M) was added. It was stirred overnight. The mixture was then concentrated *in vacuo* before water (2.50 mL) was added, and it was extracted with Et_2O (4 x 3 mL) before it was dried and filtrated through Na_2SO_4. The organic phase was then concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, 10% MeOH in DCM, $KMnO_4$ stain) to afford 3-chloro-4-hydroxy-6-methyl-2*H*-pyran-2-one (**48**) as a white solid. Yield: 171 mg, 54%; Rf = 0.10 (5% MeOH in DCM, KMnO4 stain); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.13 (d, J = 1.0 Hz, 1H), 2.19 (d, J = 0.9 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 164.9, 160.8, 160.4, 99.9, 95.4, 19.1.

9.17 3-chloro-4-hydroxy-6-(2-hydroxyethyl)-2*H*-pyran-2-one (52)

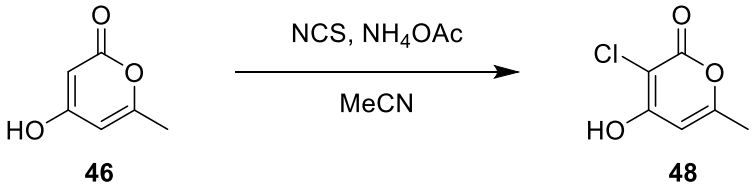


Scheme 9-16 Synthesis of compound **52**.

Pyrone **45** (200 mg, 1.28 mmol, 1.00 eq) and NCS (222 mg, 1.66 mmol, 1.30 eq) were solved in MeCN (2.64 mL) and was flushed with nitrogen. The solution was then stirred while triethylborane (0.26 mL, 0.26 mmol, 20 mol%) in THF (1 M) was added. It was stirred overnight. The mixture was then concentrated *in vacuo* before it was purified by flash column

chromatography (SiO_2, 10% MeOH → 20% MeOH in DCM, $KMnO_4$ stain) to afford 3-chloro-4-hydroxy-6-(2-hydroxyethyl)-2*H*-pyran-2-one (**52**) as a brown solid. Yield: 114 mg, 47%; Rf = 0.13 (20% MeOH in DCM, KMnO4 stain); ^{1}H NMR (400 MHz, acetone-d_6) δ: 6.67 (s, 1H), 4.27 (t, J = 6.1 Hz, 2H), 3.11 (t, J = 6.1 Hz, 2H).

9.18 3-chloro-4-hydroxy-6-methyl-2*H*-pyran-2-one (48)

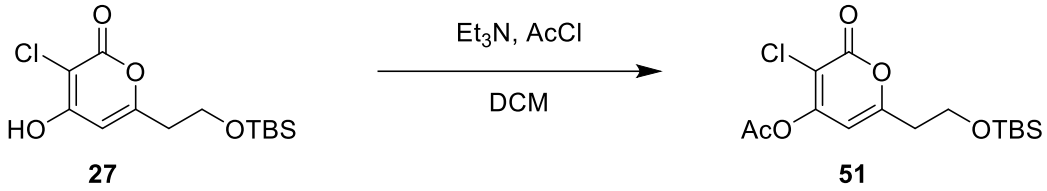


46 **48**

Scheme 9-17 Synthesis of compound **48**.

NCS (211 mg, 1.58 mmol, 2.00 eq) and ammonium acetate (6.17 mg, 0.08 mmol, 10 mol%) was added to a solution of 4-hydroxy-6-methyl-2-pyrone (**46**) (100 mg, 0.79 mmol, 1.00 eq) and MeCN (2.45 mL). The reaction mixture was then stirred for 3 h. The mixture was concentrated *in vacuo* and treated with EtOAc and water mixture (0.75 mL, 1:1). The biphasic mixture was separated, and the aqueous layer was extracted with EtOAc (3 x 0.25 mL), before it was washed (brine), dried ($MgSO_4$), filtrated and concentrated *in vacuo*. The crude material was then purified by flash column chromatography (SiO_2, 0% → 10% MeOH in DCM, $KMnO_4$ stain) to afford 3-chloro-4-hydroxy-6-methyl-2*H*-pyran-2-one (**48**) as a white solid. Yield: 37 mg, 29%; Rf = 0.10 (5% MeOH in DCM, KMnO4 stain); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.13 (d, J = 1.0 Hz, 1H), 2.19 (d, J = 0.9 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 164.9, 160.8, 160.4, 99.9, 95.4, 19.1.

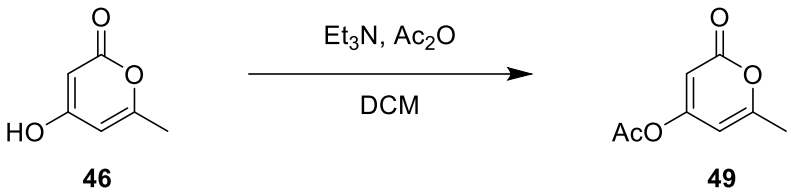
9.19 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-chloro-2-oxo-2*H*-pyran-4-yl acetate (51)



Scheme 9-18 Synthesis of compound **51**.

A solution of acetyl chloride (10.7 mg, 0.14 mmol, 1.36 eq) in DCM (50.0 µL) was slowly added at -20 °C to a solution of pyrone **27** (30.0 mg, 0.10 mmol, 1.00 eq) and triethylamine (14.2 mg, 0.14 mmol, 1.36 eq) in DCM (0.14 mL). Once the addition was complete, the cooling bath was removed and stirring was continued overnight at rt. The mixture was then up concentrated *in vacuo*, and water (1.00 mL) was added. The aqueous layer was extracted with EtOAc (3 x 1 mL) and the combined organic phases were dried and filtrated through Na_2SO_4, before it was up concentrated *in vacuo*. The crude material was then purified by flash column chromatography (SiO_2, 0% → 50% EtOAc in heptane, $KMnO_4$ stain) to afford 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-chloro-2-oxo-2*H*-pyran-4-yl acetate (**51**) as a yellow solid. Yield: 11.2 mg, 32%; Rf = 0.44 (30% EtOAc in heptane, KMnO4 stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.15 (s, 1H), 3.90 (t, J = 6.0 Hz, 2H), 2.70 (t, J = 6.1 Hz, 2H), 2.35 (s, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.9, 161.8, 160.3, 158.4, 110.1, 103.4, 59.7, 37.3, 25.9, 20.8, 18.3, -5.4.

9.20 6-methyl-2-oxo-2*H*-pyran-4-yl acetate (49)

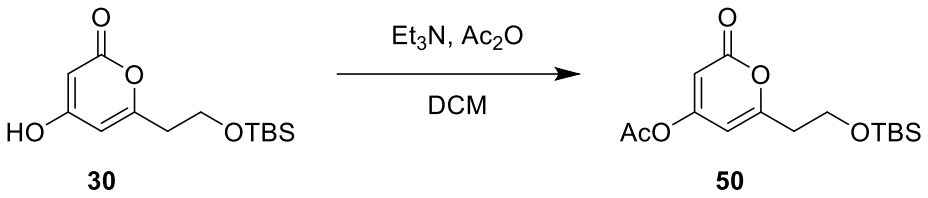


46 **49**

Scheme 9-19 Synthesis of compound **49**.

A solution of acetic anhydride (110 mg, 1.08 mmol, 1.36 eq) in DCM (0.36 mL) was slowly added at -20 °C to a solution of 4-hydroxy-6-methyl-2-pyrone (**46**) (100 mg, 0.79 mmol, 1.00 eq) and triethylamine (109 mg, 1.08 mmol, 1.36 eq) in DCM (1.08 mL). Once the addition was complete, the cooling bath was removed and the stirring was continued overnight at rt. The mixture was washed afterwards with a 1 N aqueous solution of HCl (0.72 mL). The aqueous layer was extracted with DCM (3 x 1 mL) and the combined organic phases were dried (Na_2SO_4), filtrated and up concentrated *in vacuo*. The crude material was then purified by flash column chromatography (SiO_2, 0% → 10% MeOH in DCM, $KMnO_4$ stain) to afford 6-methyl-2-oxo-2*H*-pyran-4-yl acetate (**49**) as a white solid. Yield: 90 mg, 68%; Rf = 0.76 (10% MeOH in DCM, KMnO4 stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.03 (dd, J = 2.0, 0.8 Hz, 1H), 5.95 (dq, J = 1.9, 0.9 Hz, 1H), 2.28 (s, 3H), 2.26 (d, J = 0.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.0, 163.8, 163.4, 163.1, 101.4, 101.2, 21.4, 20.3. NMR corresponds to previously reported data.[63]

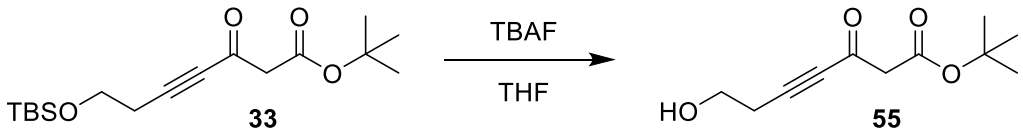
9.21 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-oxo-2*H*-pyran-4-yl acetate (50)



Scheme 9-20 Synthesis of compound **50**.

A solution of acetic anhydride (102 mg, 1.00 mmol, 1.36 eq) in DCM (0.34 mL) was slowly added at -20 °C to a solution of pyrone **30** (200 mg, 0.74 mmol, 1.00 eq) and triethylamine (101 mg, 1.00 mmol, 1.36 eq) in DCM (1.02 mL). Once the addition was complete, the cooling bath was removed and the stirring was continued overnight at rt. The mixture was up concentrated *in vacuo* and water (1.00 mL) was added. It was then extracted with EtOAc (3 x 1.5 mL) before it was dried and filtrated with Na_2SO_4. It was then up concentrated *in vacuo* and purified by flash column chromatography (SiO_2, 0% → 20% EtOAc in heptane, $KMnO_4$ stain) to afford 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-oxo-2*H*-pyran-4-yl acetate (**50**) as an orange/yellow oil. Yield: 158 mg, 68%; Rf = 0.39 (20% EtOAc in heptane, KMnO4 stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.06 (d, J = 2.1 Hz, 1H), 6.03 (d, J = 2.0 Hz, 1H), 3.90 (t, J = 6.1 Hz, 2H), 2.68 (t, J = 6.1 Hz, 2H), 2.28 (s, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.9, 164.4, 163.9, 163.0, 102.4, 101.6, 59.8, 37.6, 25.9, 21.4, 18.3, -5.4.

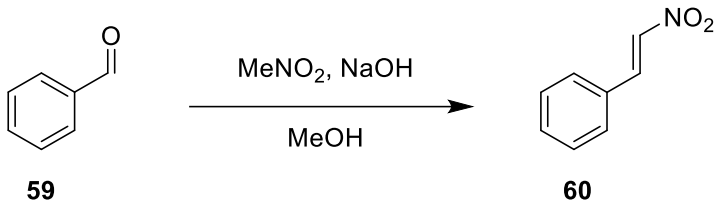
9.22 *Tert*-butyl 7-hydroxy-3-oxohept-4-ynoate (55)



Scheme 9-21 Synthesis of compound **55**.

A solution of beta-keto ester **33** (2.00 g, 6.13 mmol, 1.00 eq) in THF (45.0 mL) was treated with tetra-*n*-butylammonium fluoride (1 M in THF, 15.3 mL, 15.3 mmol, 2.50 eq) at rt. After stirring at rt for 1 h, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (25-30 mL), and brine (25-30 mL). The organic layer was dried (Na_2SO_4), filtrated and concentrated *in vacuo* before it was purified by flash column chromatography (SiO_2, 40% EtOAc in heptane, $KMnO_4$ stain) to afford *tert*-butyl 7-hydroxy-3-oxohept-4-ynoate (**55**) as a brown/yellow oil. Yield: 731 mg, 56%; Rf = 0.22 (40% EtOAc in heptane, KMnO4 stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.22 (enol) (s, 1H), 3.80 (t, J = 6.2 Hz, 2H), 3.47 (s, 2H), 2.64 (t, J = 6.1 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 179.4, 165.8, 93.6, 82.7, 81.6, 60.2, 52.9, 28.1, 23.6.

9.23 (*E*)-(2-nitrovinyl)benzene (60)



Scheme 9-22 Synthesis of compound **60**.

A solution of NaOH (480 mg, 12.0 mmol, 1.20 eq) in water (2.00 mL) was added dropwise to a mixture of benzaldehyde (**59**) (1.06 g, 10.0 mmol, 1.00 eq) and $MeNO_2$ (610 mg, 10.0 mmol, 1.00 eq) in methanol (10.0 mL) at 0 °C. After the complete addition of the NaOH-solution, more methanol (3-5 mL) was added, and it was stirred for 1 h. After 1 h it was taken TLC to see if all the benzaldehydes had reacted. Water (10 mL) was then added, and the solution was poured over into aqueous HCl (4.70 mL conc. HCl in 10 mL water). The mixture was then

stirred for 15 min before it was extracted with DCM (3 x 15 mL). The organic phase was washed (brine), dried ($MgSO_4$), filtrated and up concentrated *in vacuo*. The crude product was then recrystallized by dissolving it in warm heptane and drops of EtOAc until the solution was no longer cloudy. The solution was then placed in a -20 °C freezer overnight. This lead to crystallization of (*E*)-(2-nitrovinyl)benzene (**60**). The supernatant was then carefully transferred into a new flask and the crystals were washed with heptane (3 × 5 mL). This process afforded pure (*E*)-(2-nitrovinyl)benzene (**60**) as yellow crystals. Yield: 761 mg, 51%; Rf = 0.26 (15% EtOAc in heptane, KMnO4 stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J = 13.7 Hz, 1H), 7.59 (d, J = 13.7 Hz, 1H), 7.57-7.54 (m, 2H), 7.53-7.42 (m, 3H). NMR corresponds to previously reported data.[79]

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11 Appendix

A Potassium (1*E*,3*E*)-5-oxopenta-1,3-dien-1-olate (19)

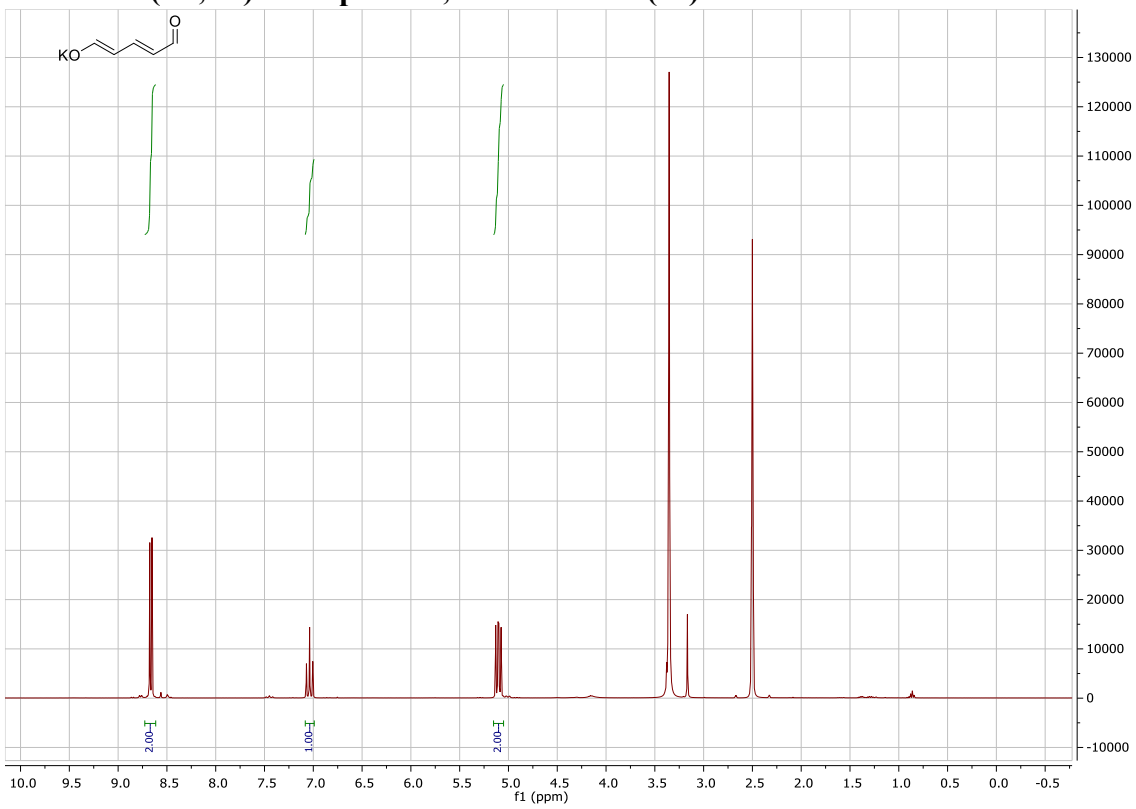

Figure A1 ^{1}H NMR for **19**, 400 MHz, DMSO-d_6.

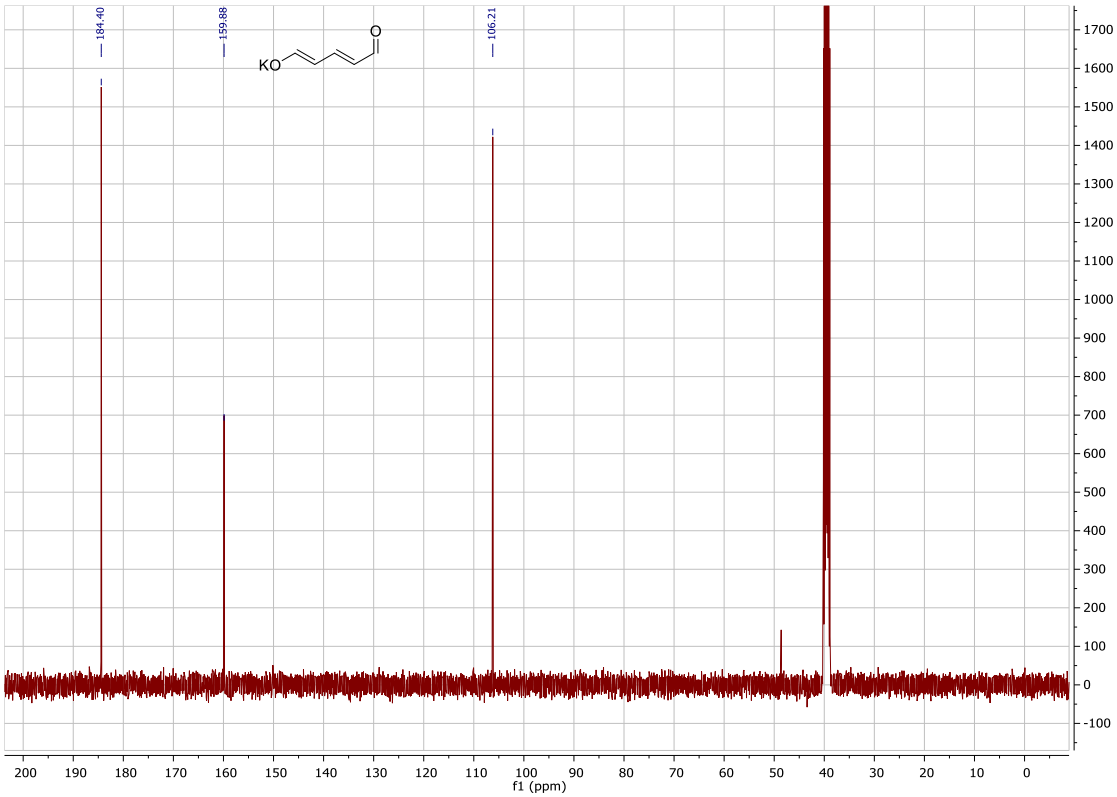

Figure A2 ^{13}C NMR for **19**, 101 MHz, DMSO-d_6.

B (2*E*,4*E*)-5-phenylpenta-2,4-dienal (40)

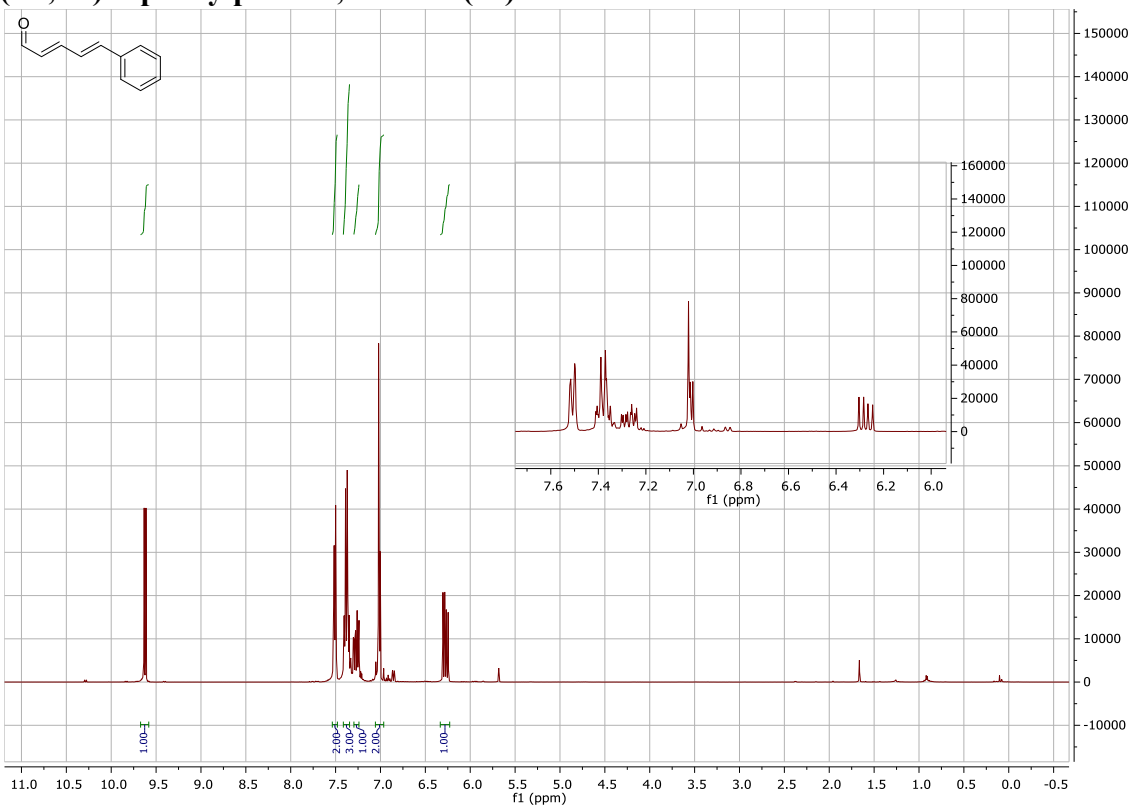

Figure B1 ^{1}H NMR for **40**, 400 MHz, $CDCl_3$.

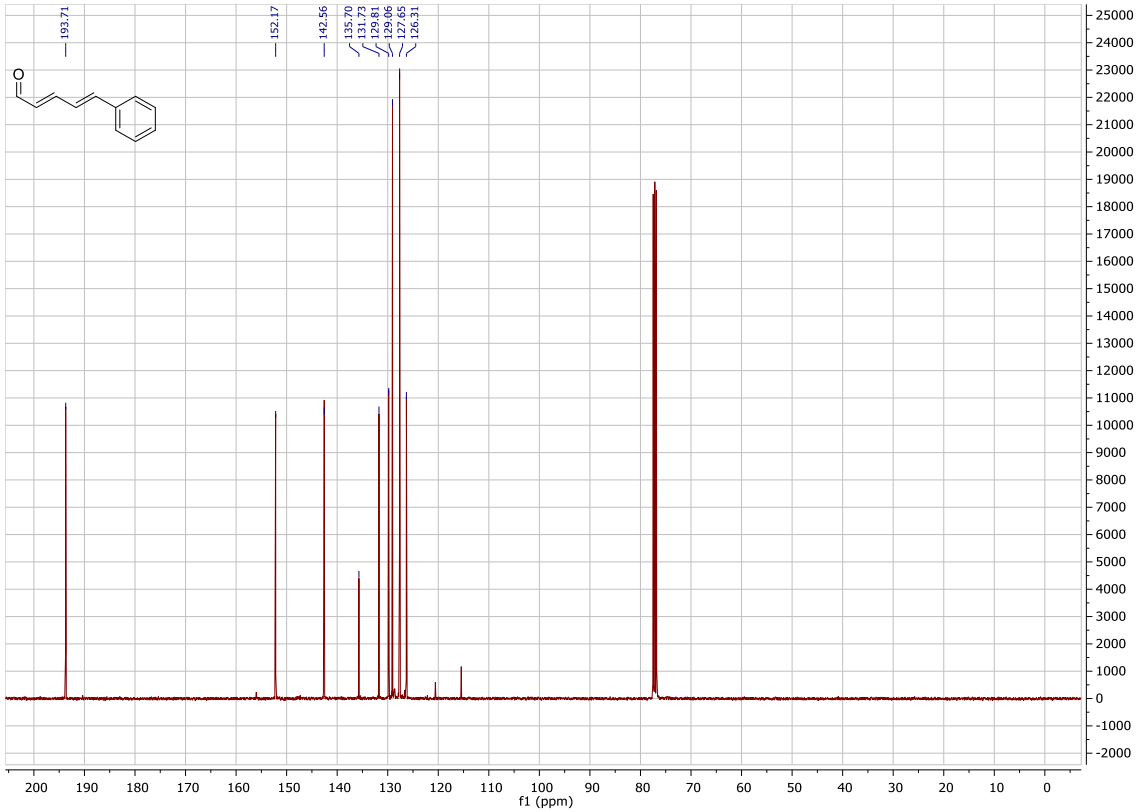

Figure B2 ^{13}C NMR for **40**, 101 MHz, $CDCl_3$.

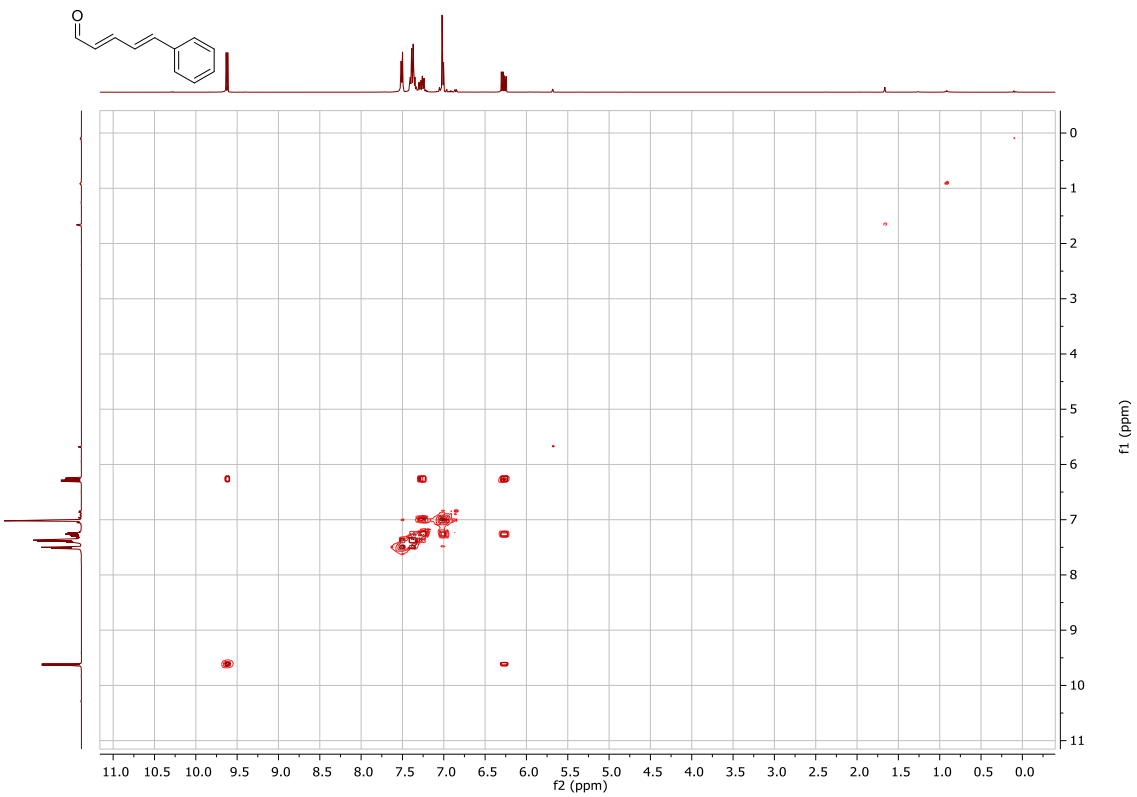

Figure B3 ^{1}H-^{1}H COSY for **40**, 400 MHz, $CDCl_3$.

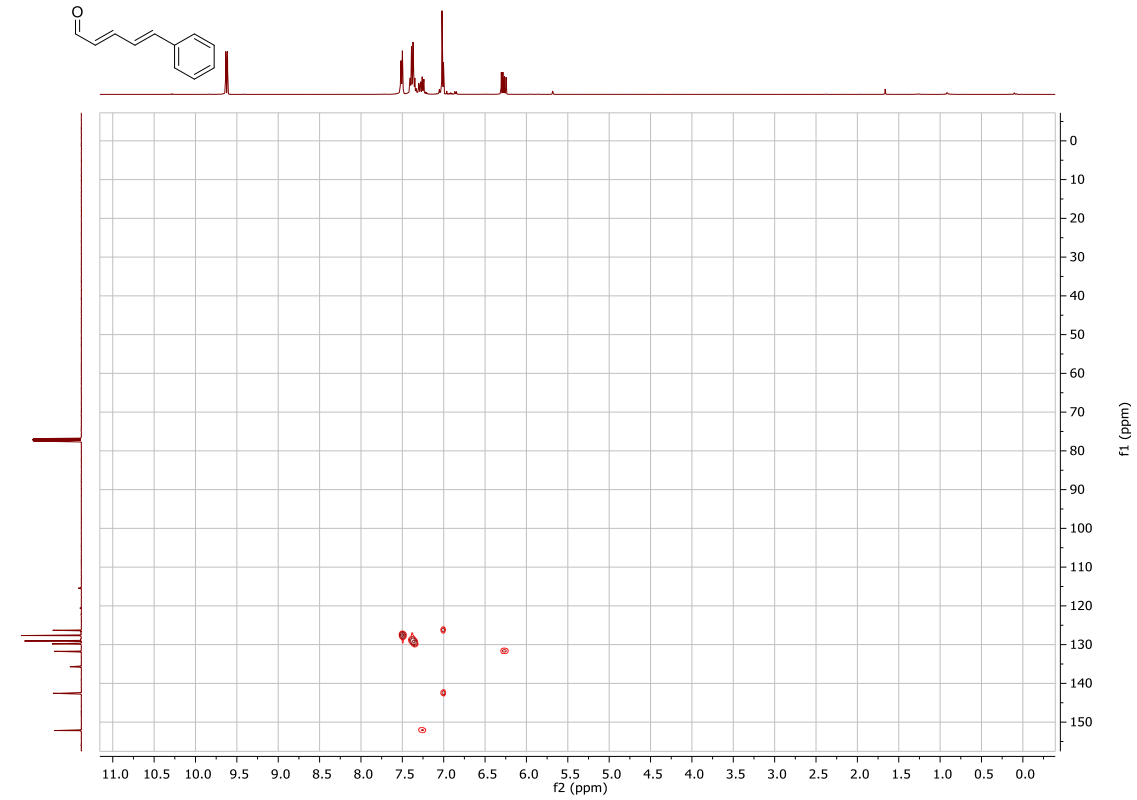

Figure B4 ^{1}H-^{13}C HSQC for **40**, 400 MHz, $CDCl_3$.

C (4-bromophenoxy)(*tert*-butyl)dimethylsilane (20)

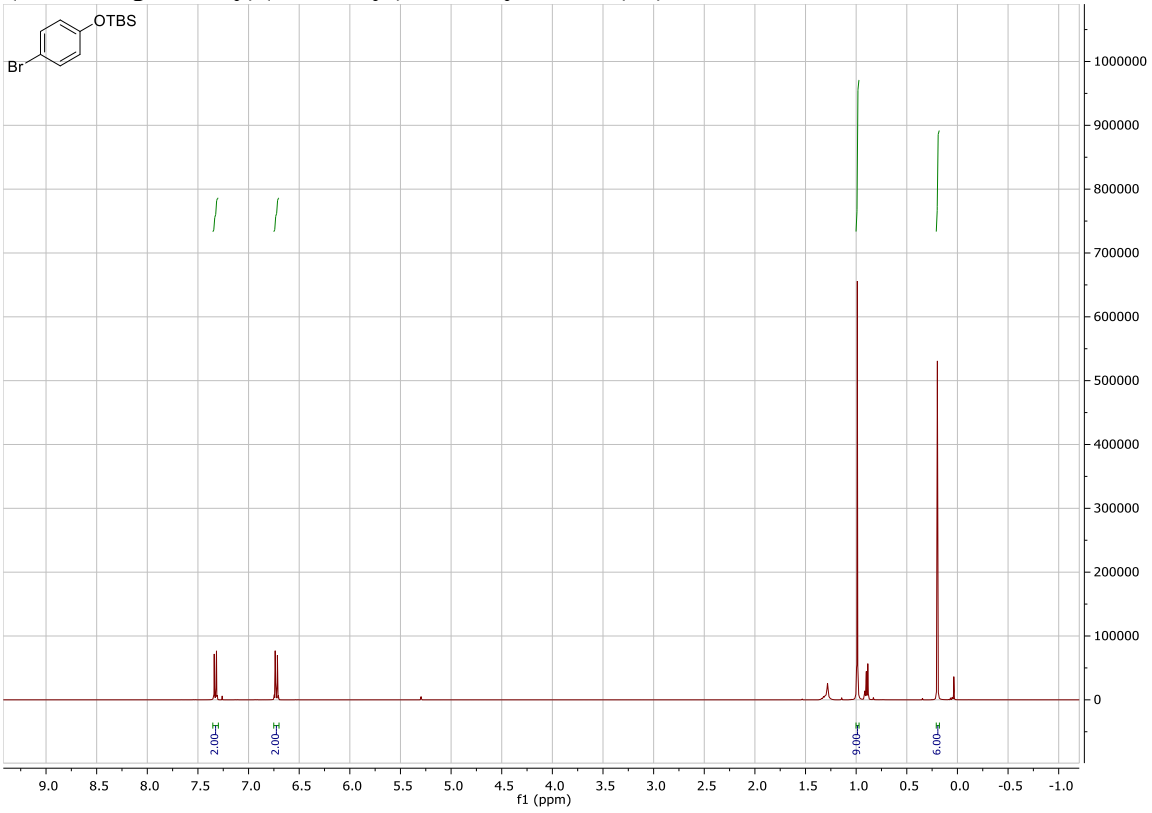

Figure C1 ^{1}H NMR for **20**, 400 MHz, $CDCl_3$.

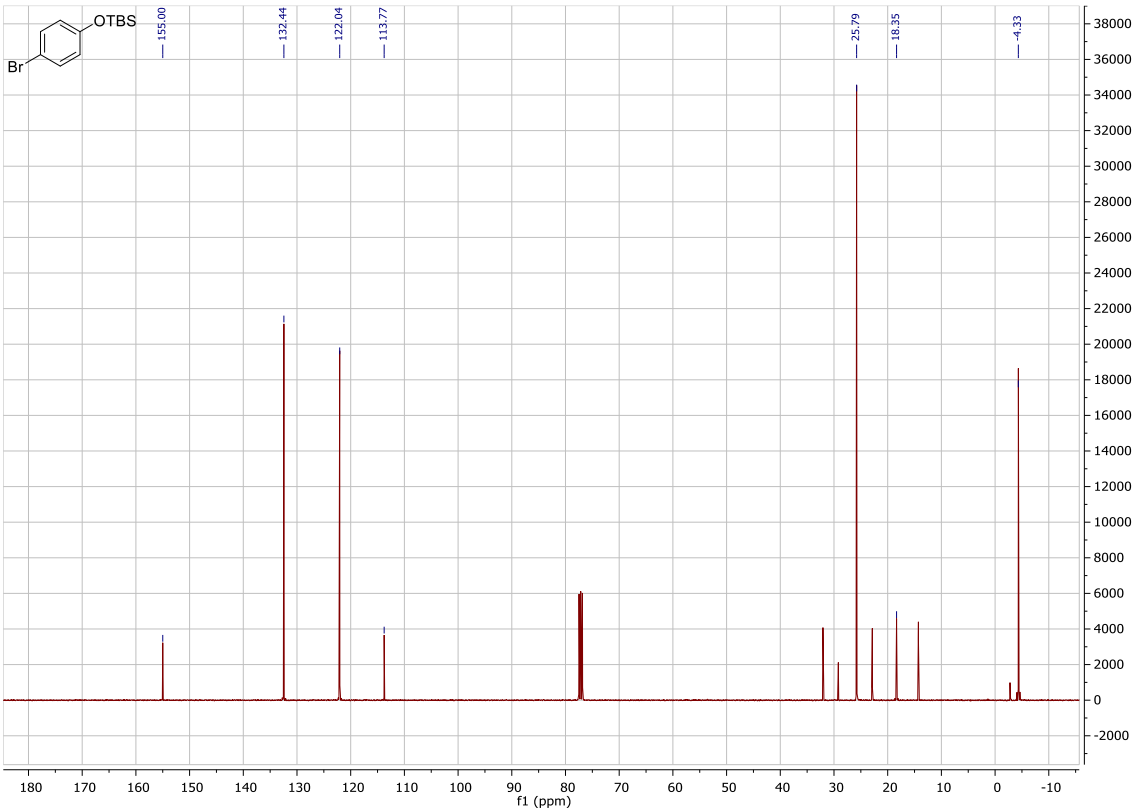

Figure C2 ^{13}C NMR for **20**, 101 MHz, $CDCl_3$.

D (2*E*,4*E*)-5-(4-hydroxyphenyl)penta-2,4-dienal (16)

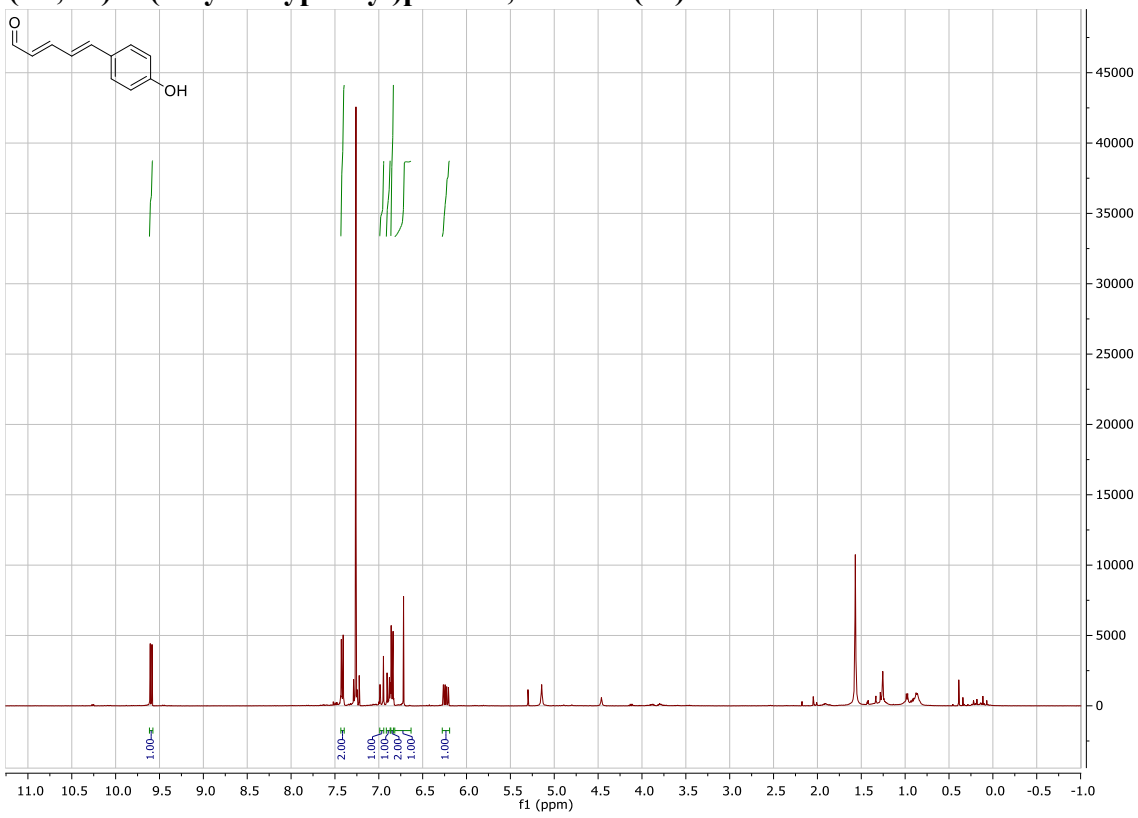

Figure D1 ^{1}H NMR for **16**, 400 MHz, $CDCl_3$.

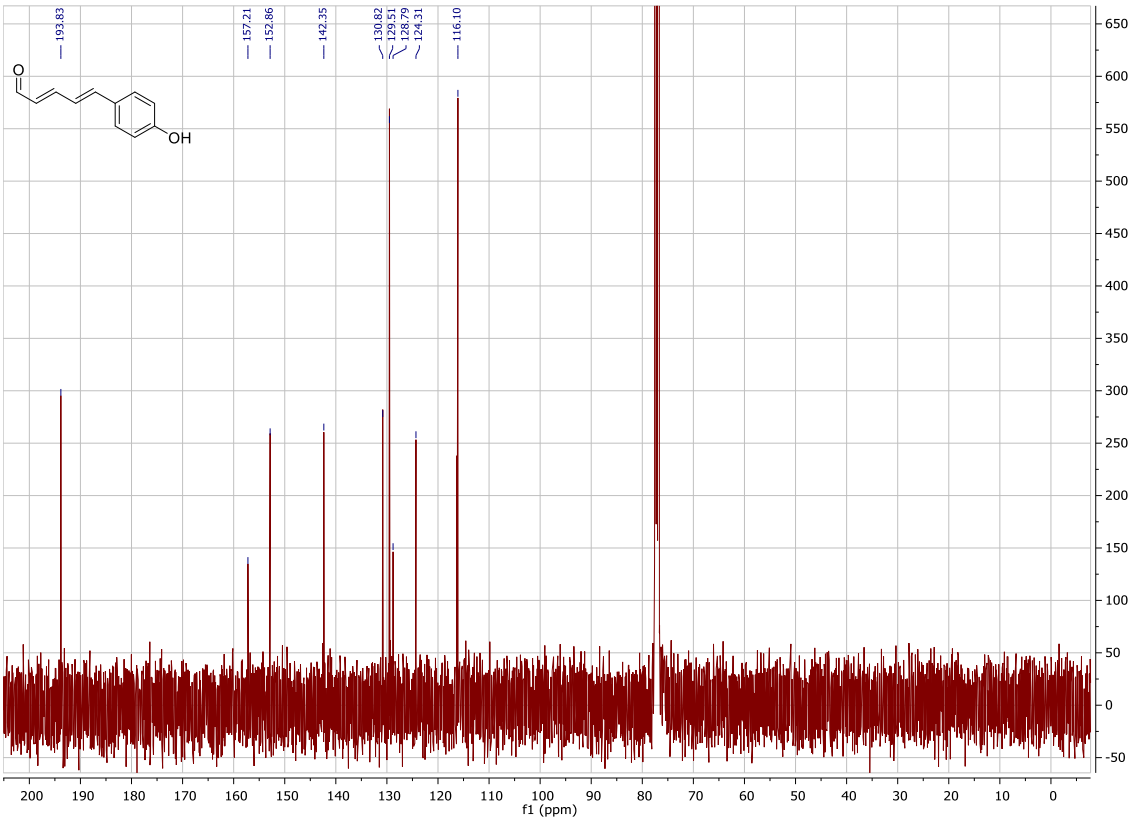

Figure D2 ^{13}C NMR for **16**, 101 MHz, $CDCl_3$.

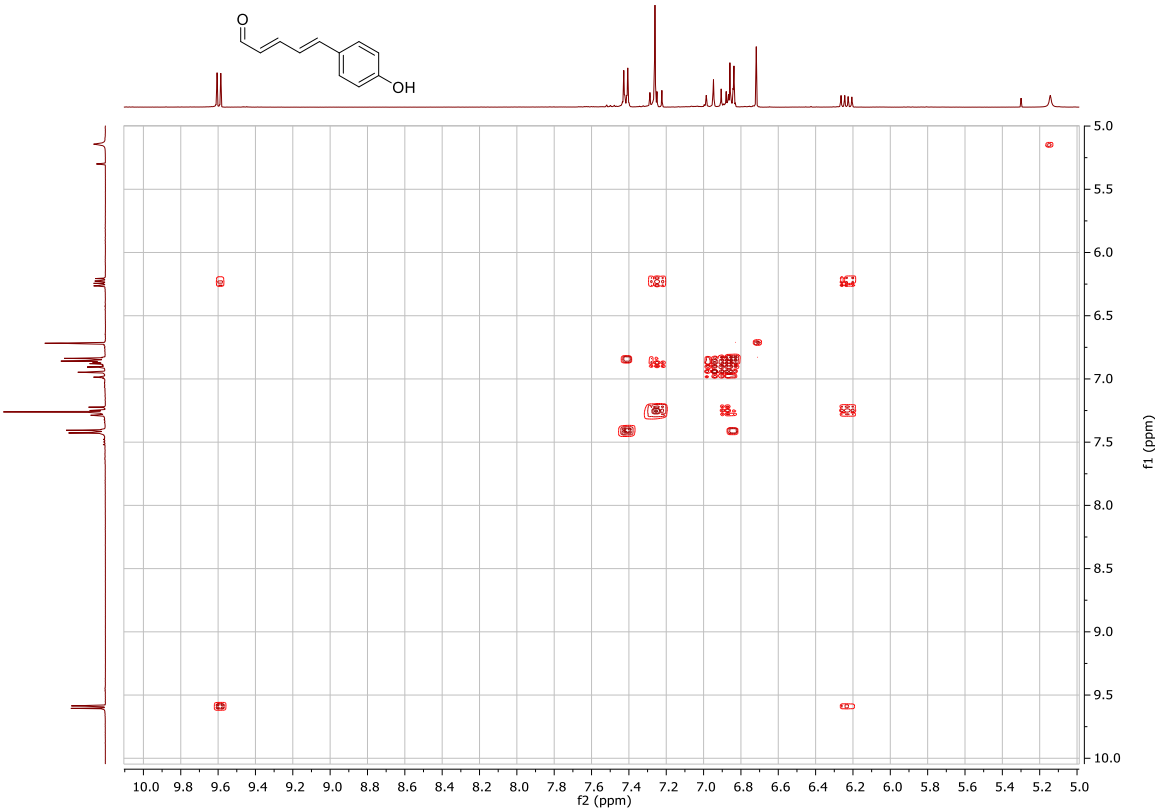

Figure D3 ^{1}H-^{1}H COSY for **16**, 400 MHz, $CDCl_3$.

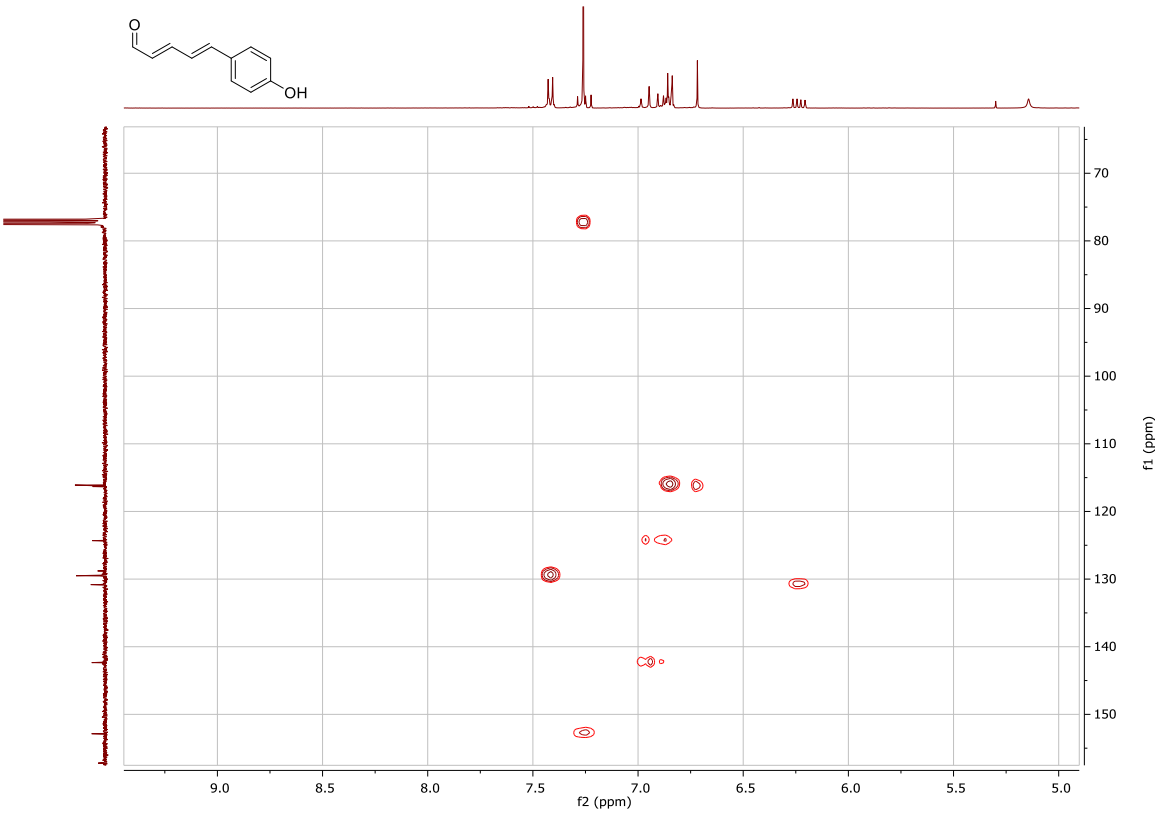

Figure D4 ^{1}H-^{13}C HSQC for **16**, 400 MHz, $CDCl_3$.

E (2*E*,4*E*)-5-bromopenta-2,4-dienoate (24)

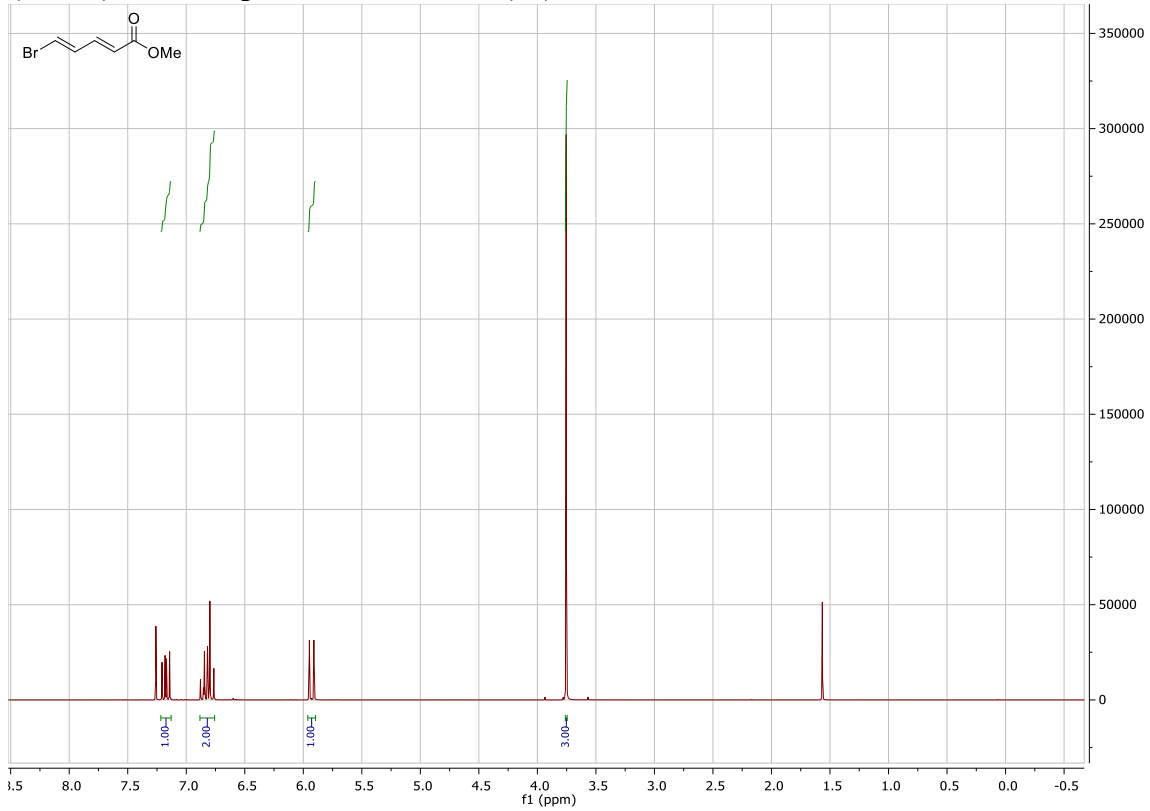

Figure E1 ^{1}H NMR for **24**, 400 MHz, $CDCl_3$.

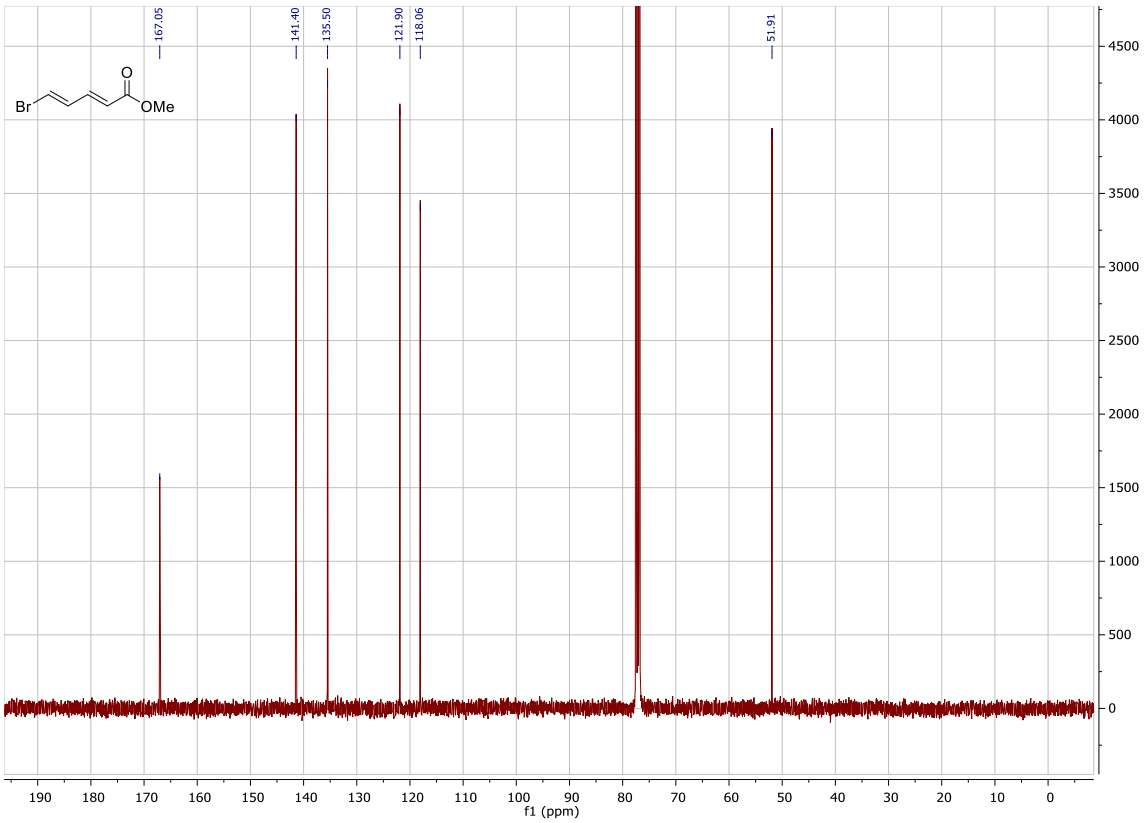

Figure E2 ^{13}C NMR for **24**, 101 MHz, $CDCl_3$.

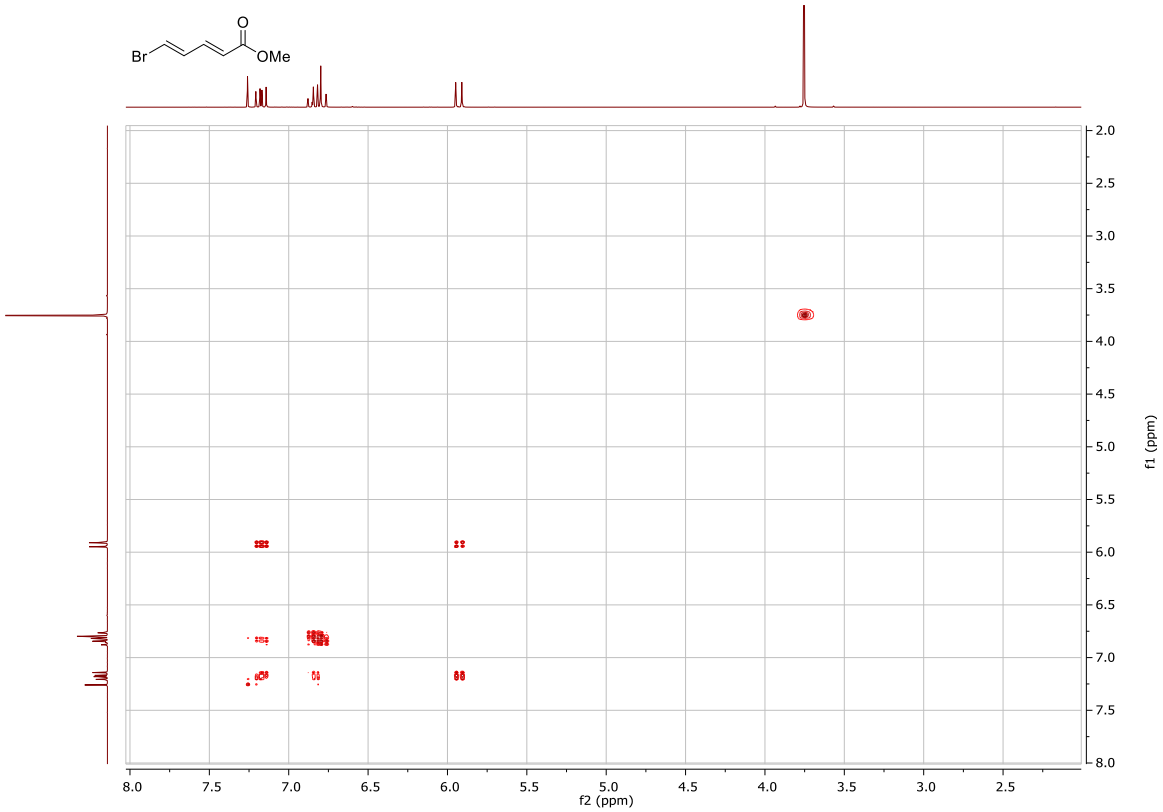

Figure E3 ^{1}H-^{1}H COSY for **24**, 400 MHz, $CDCl_3$.

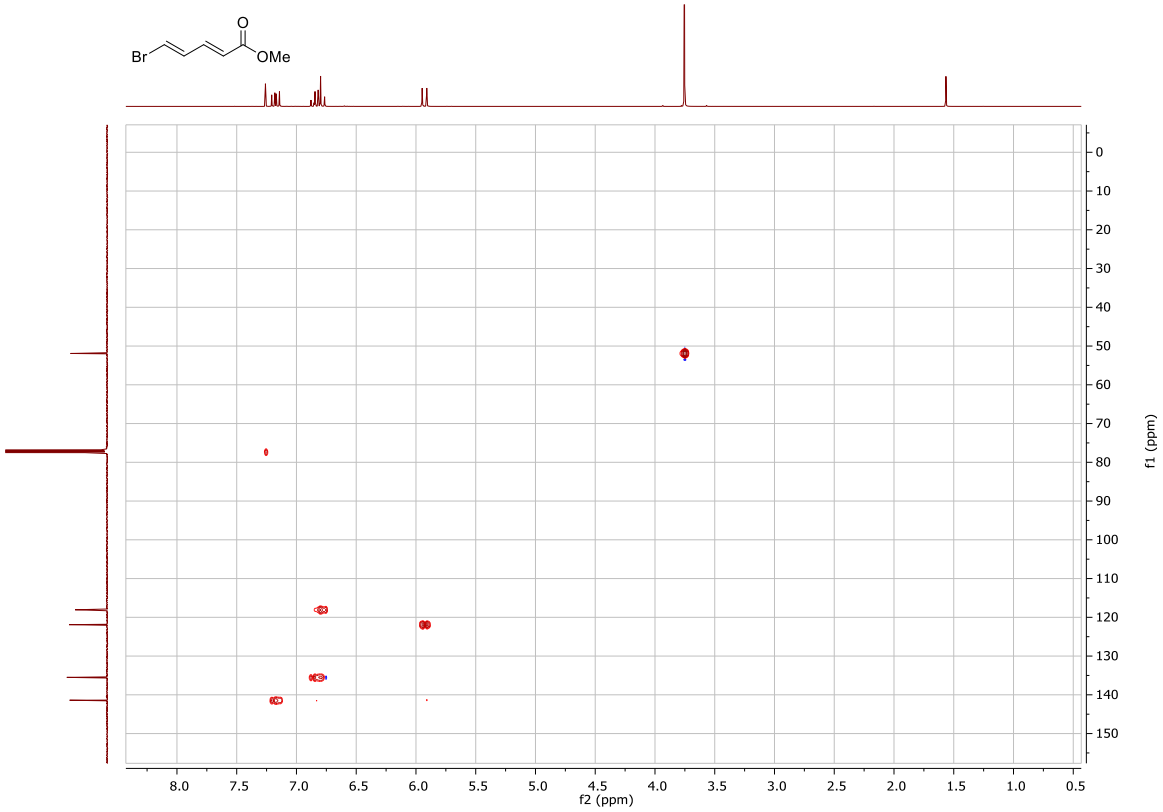

Figure E4 ^{1}H-^{13}C HSQC for **24**, 400 MHz, $CDCl_3$.

F Methyl (2*E*,4*E*)-5-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)penta-2,4-dienoate (14)

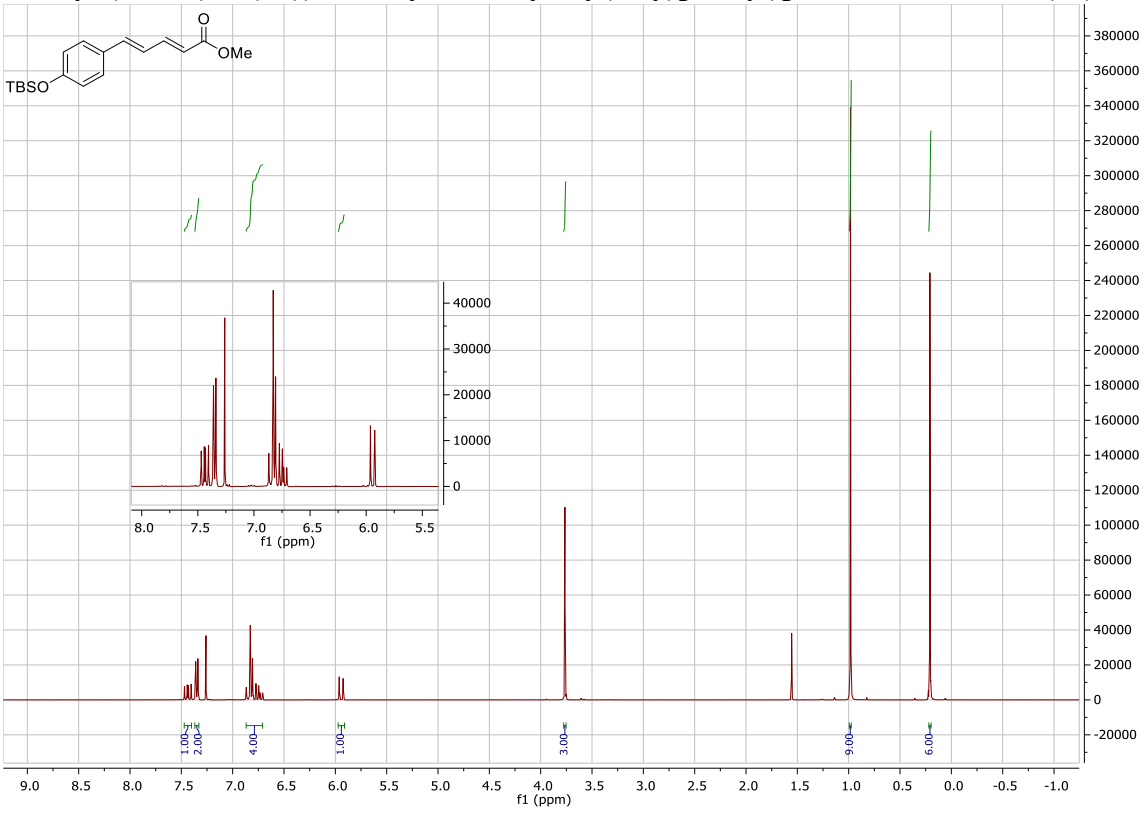

Figure F1 ^{1}H NMR for **14**, 400 MHz, $CDCl_3$.

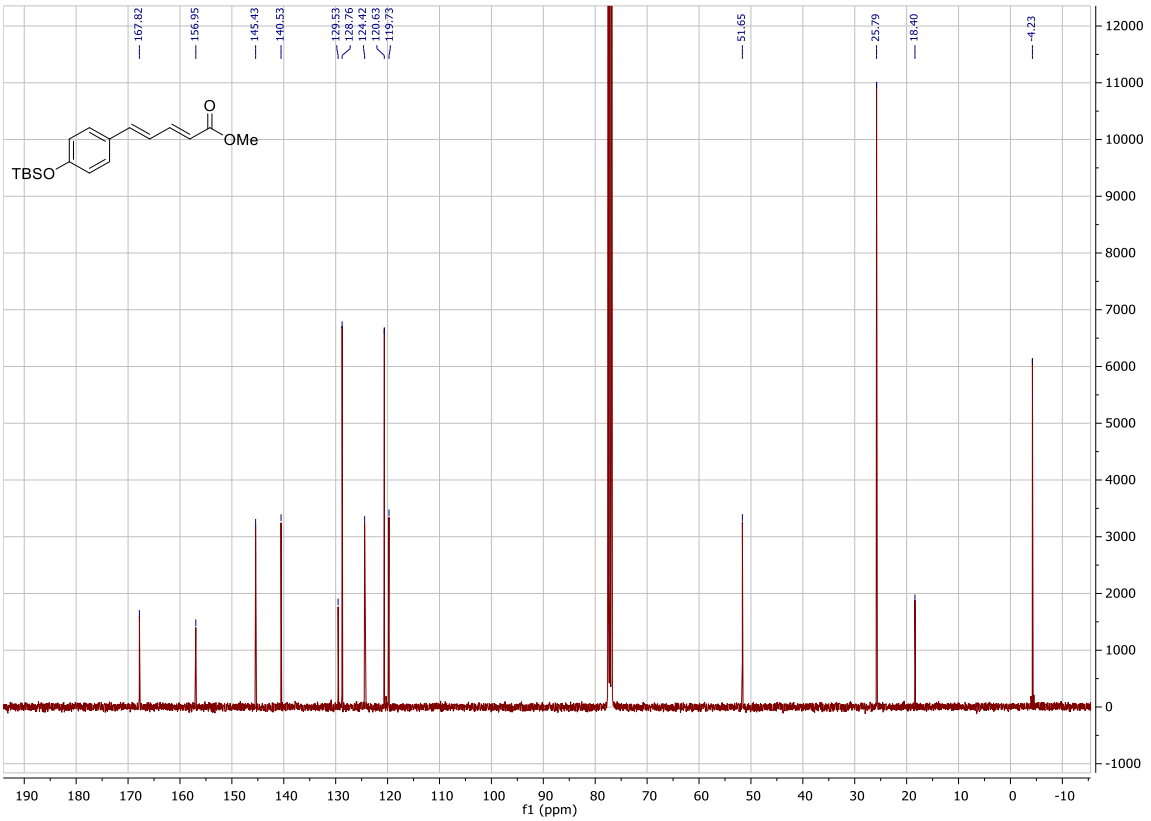

Figure F2 ^{13}C NMR for **14**, 101 MHz, $CDCl_3$.

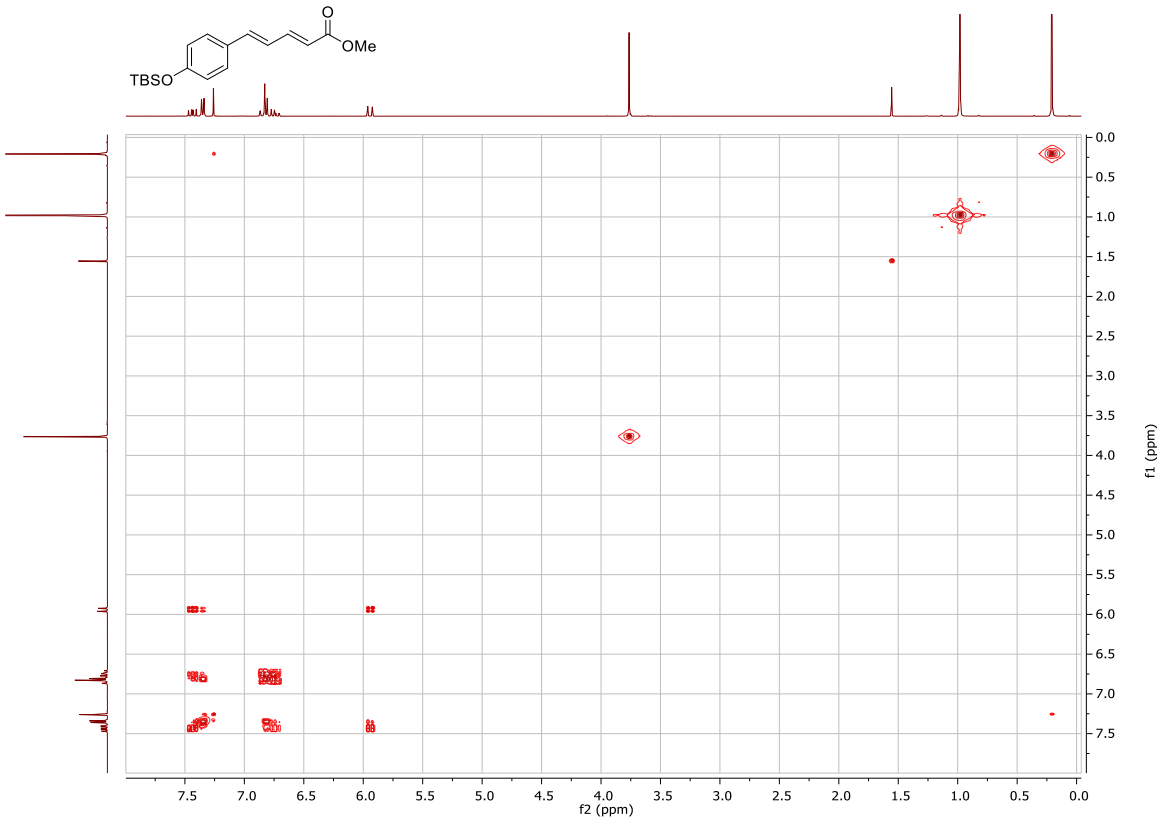

Figure F3 ^{1}H-^{1}H COSY for **14**, 400 MHz, $CDCl_3$.

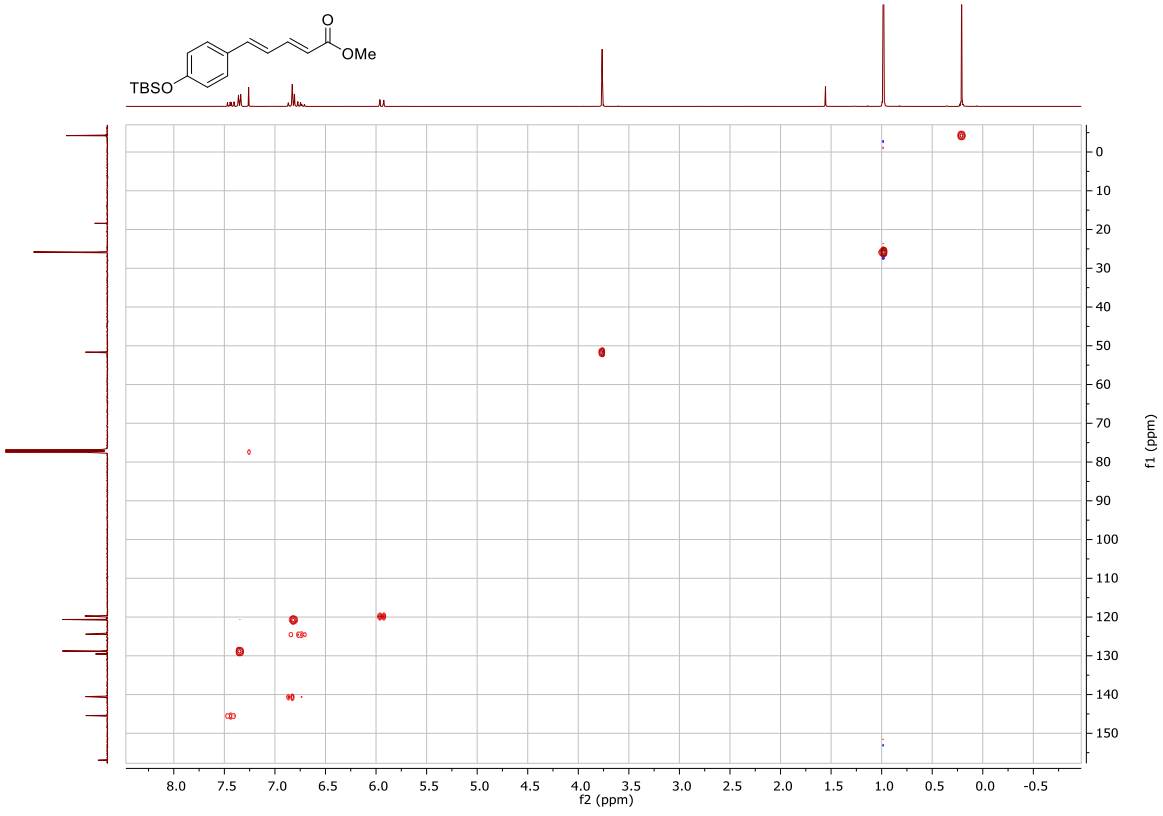

Figure F4 ^{1}H-^{13}C HSQC for **14**, 400 MHz, $CDCl_3$.

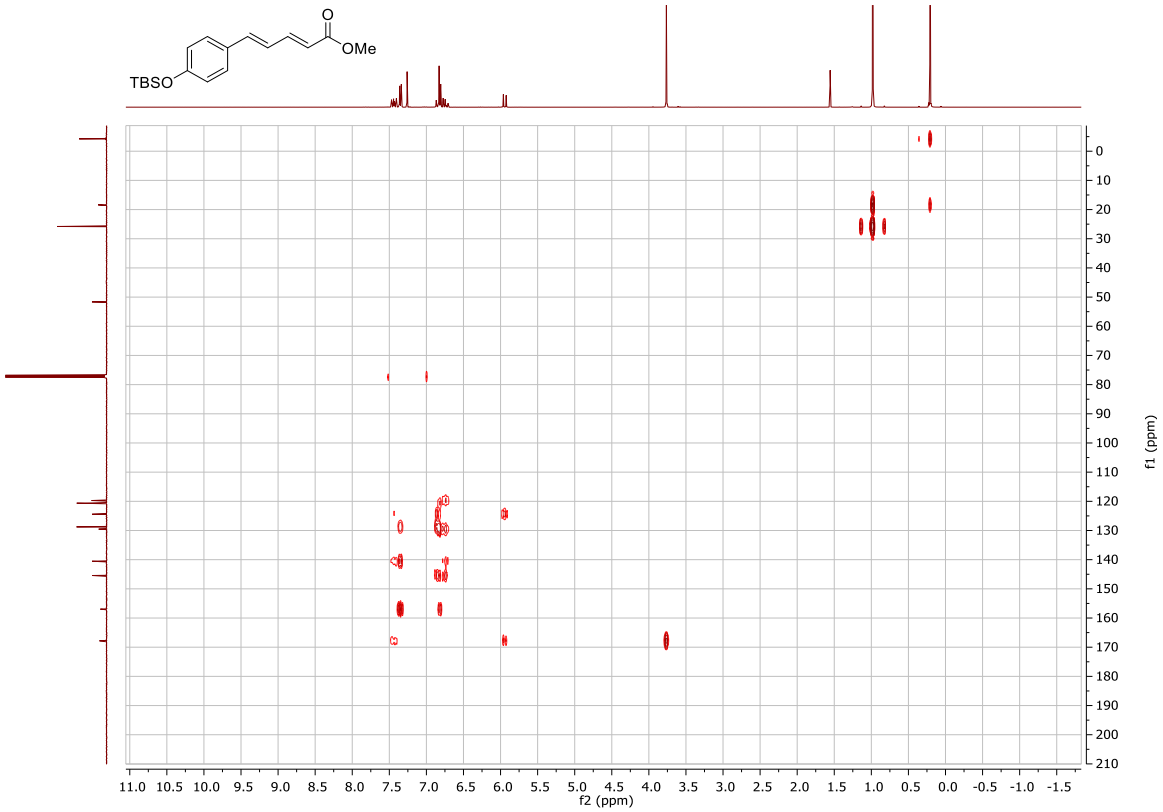

Figure F5 ^{1}H-^{13}C HMBC for **14**, 400 MHz, $CDCl_3$.

G (But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (36)

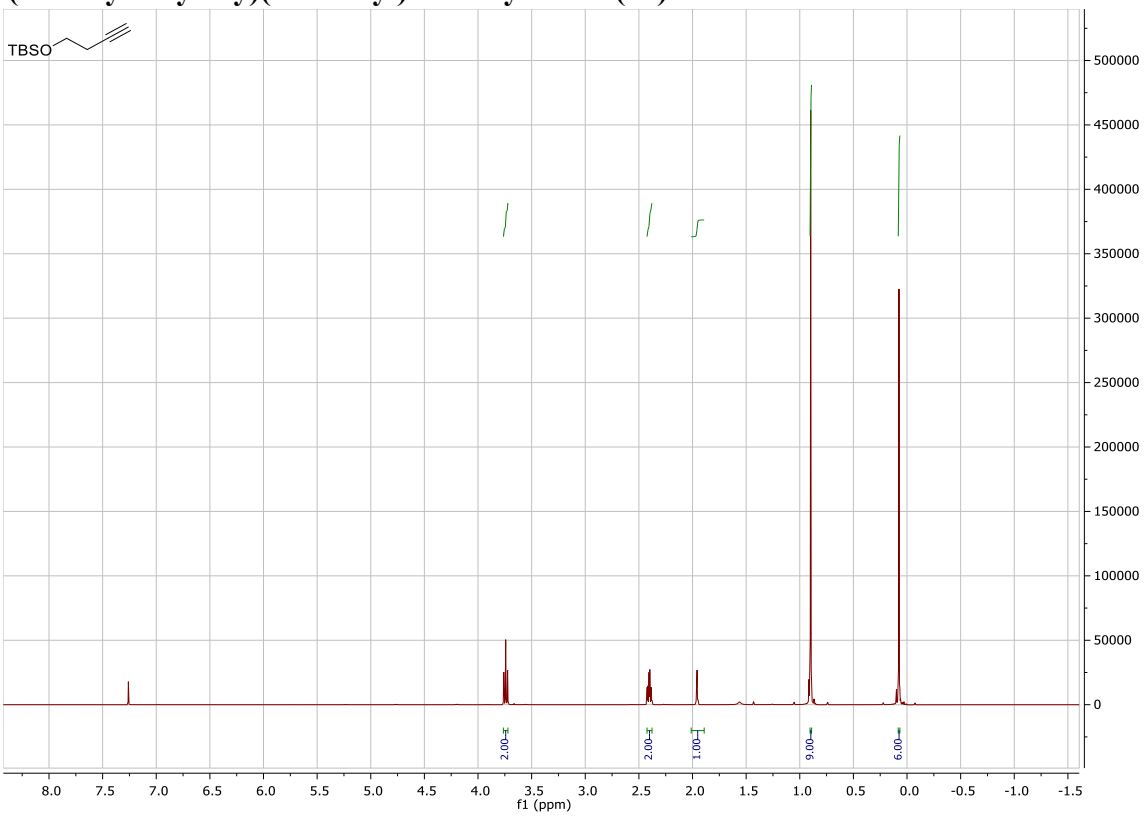

Figure G1 ^{1}H NMR for **36**, 400 MHz, $CDCl_3$.

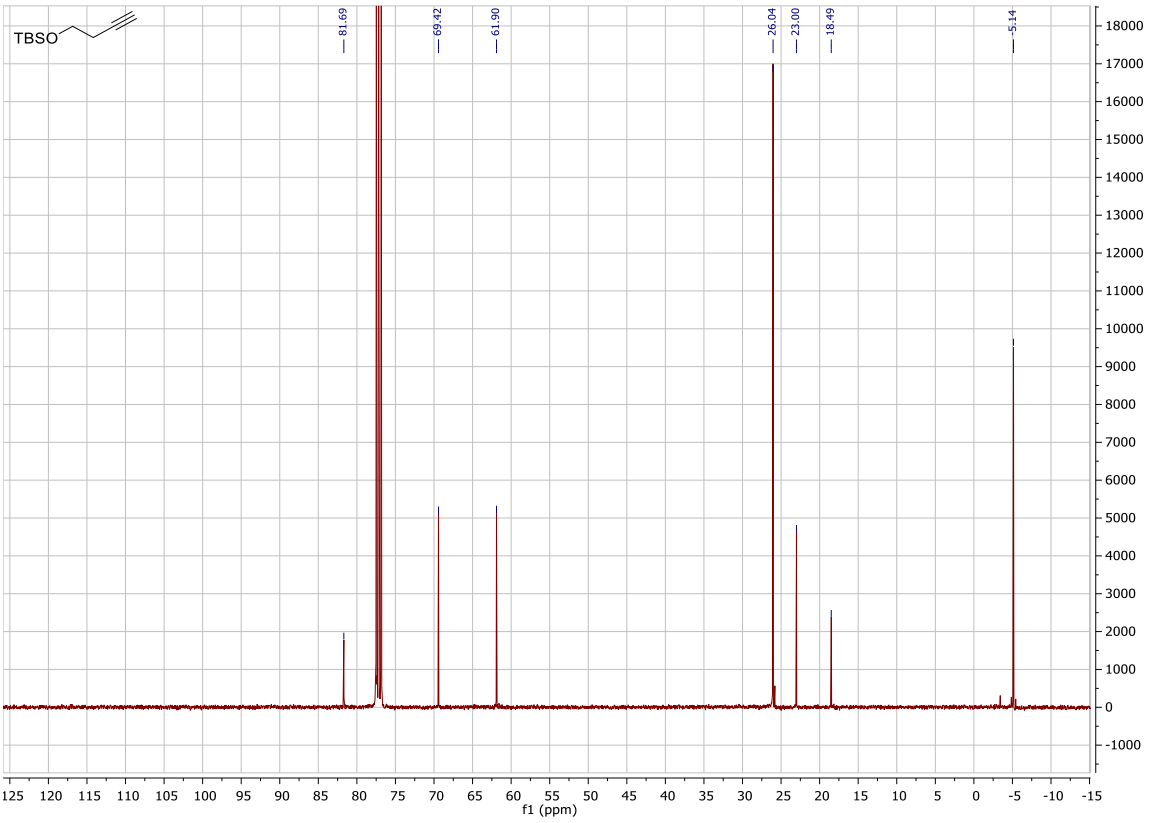

Figure G2 ^{13}C NMR for **36**, 101 MHz, $CDCl_3$.

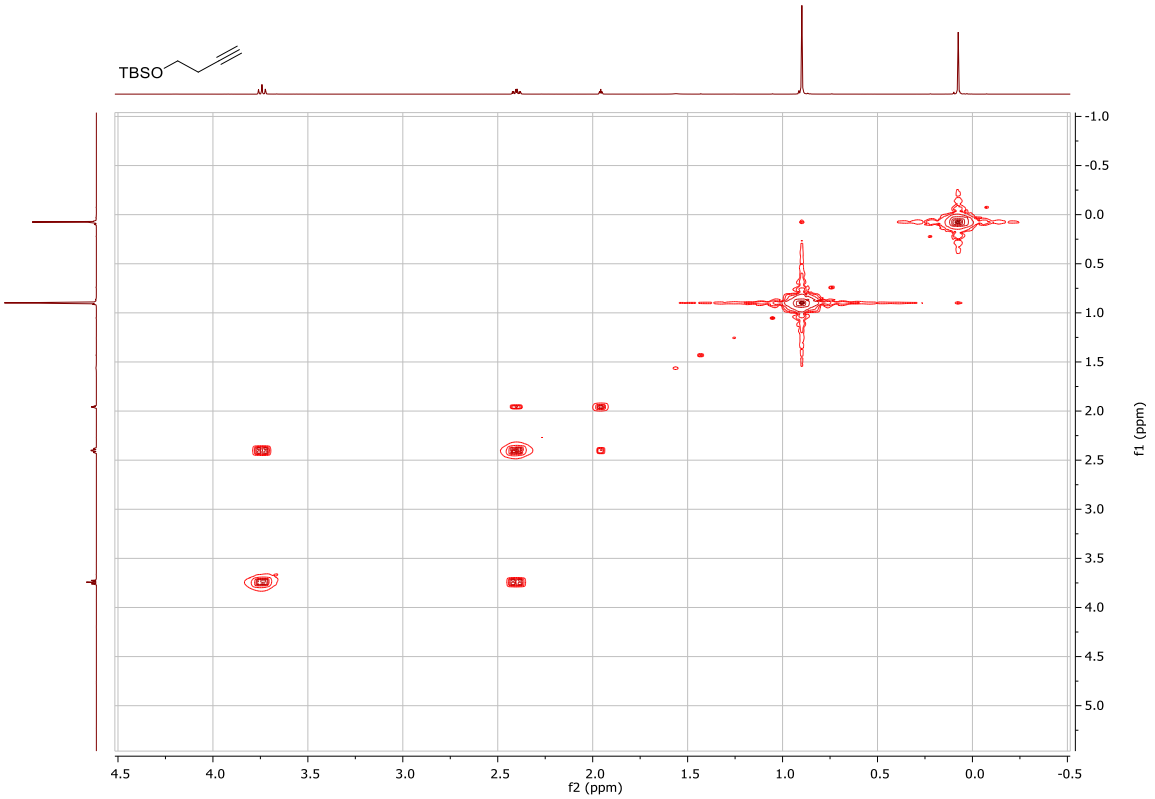

Figure G3 ^{1}H-^{1}H COSY for **36**, 400 MHz, $CDCl_3$.

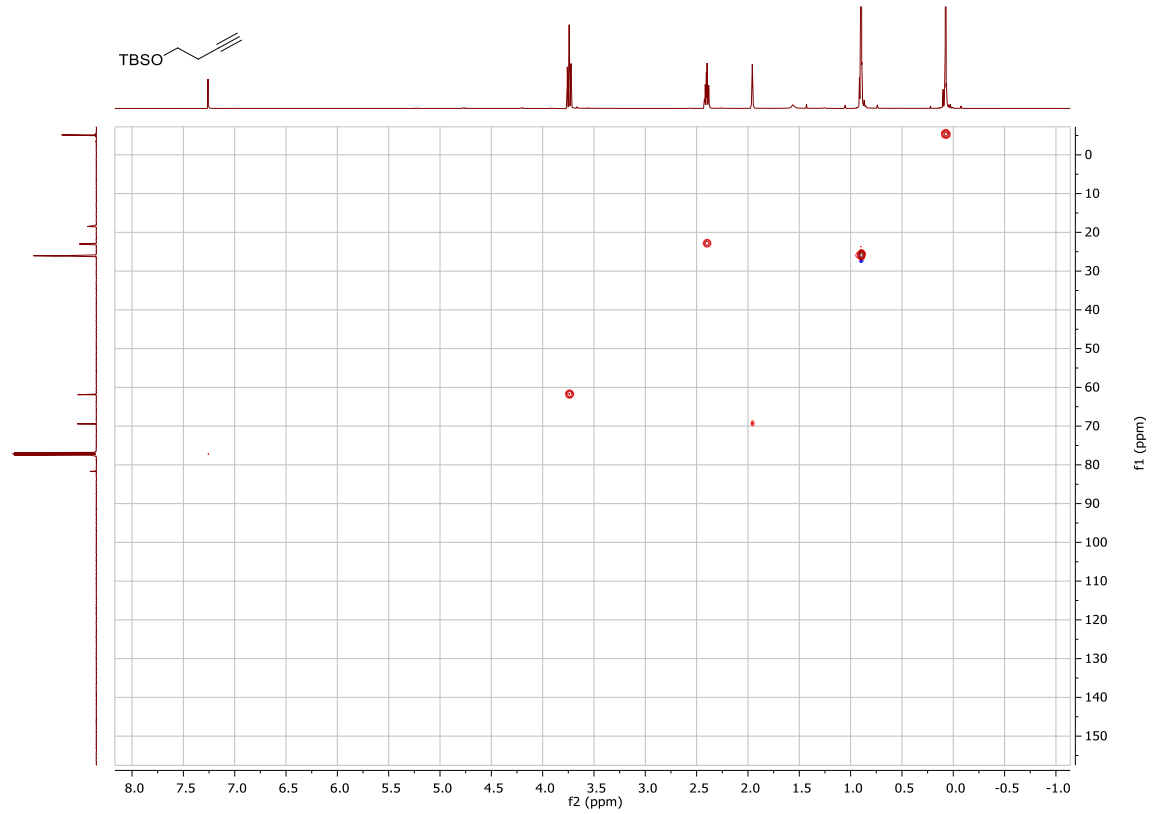

Figure G4 ^{1}H-^{13}C HSQC for **36**, 400 MHz, $CDCl_3$.

H 5-((*tert*-butyldimethylsilyl)oxy)pent-2-ynoate (34)

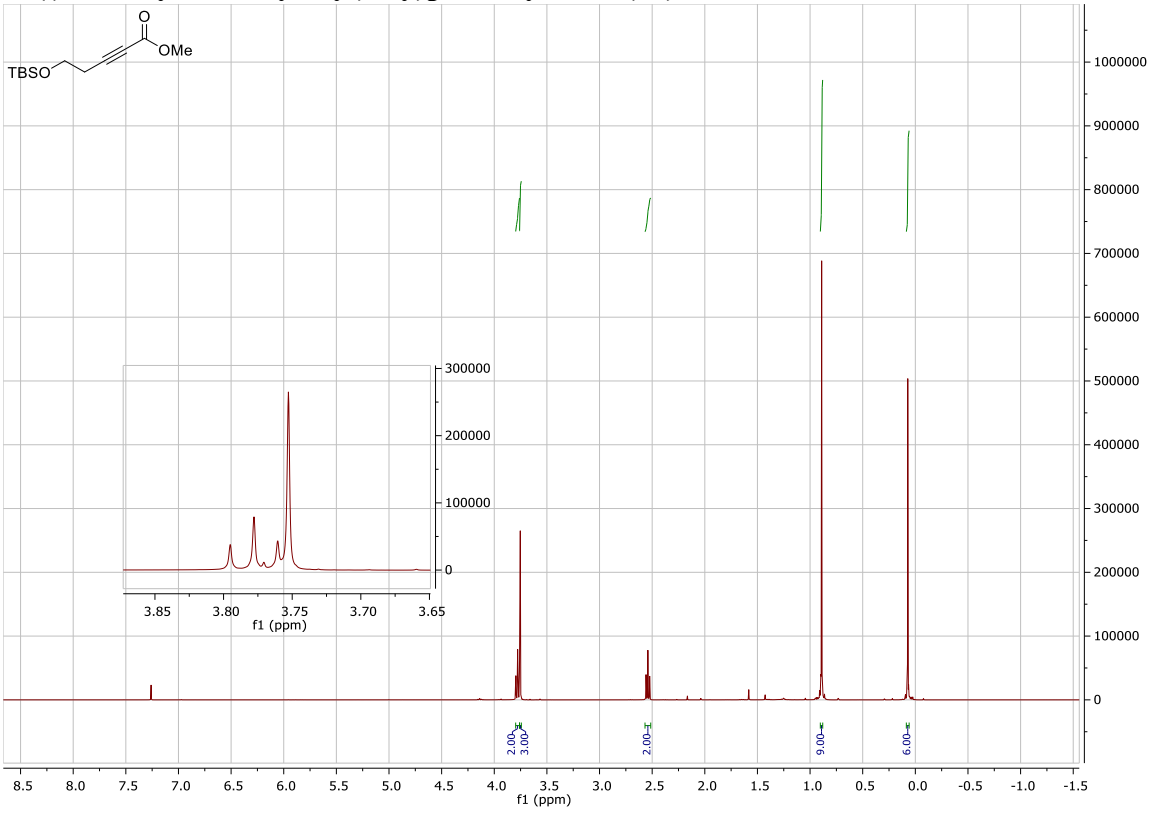

Figure H1 ^{1}H NMR for **34**, 400 MHz, $CDCl_3$.

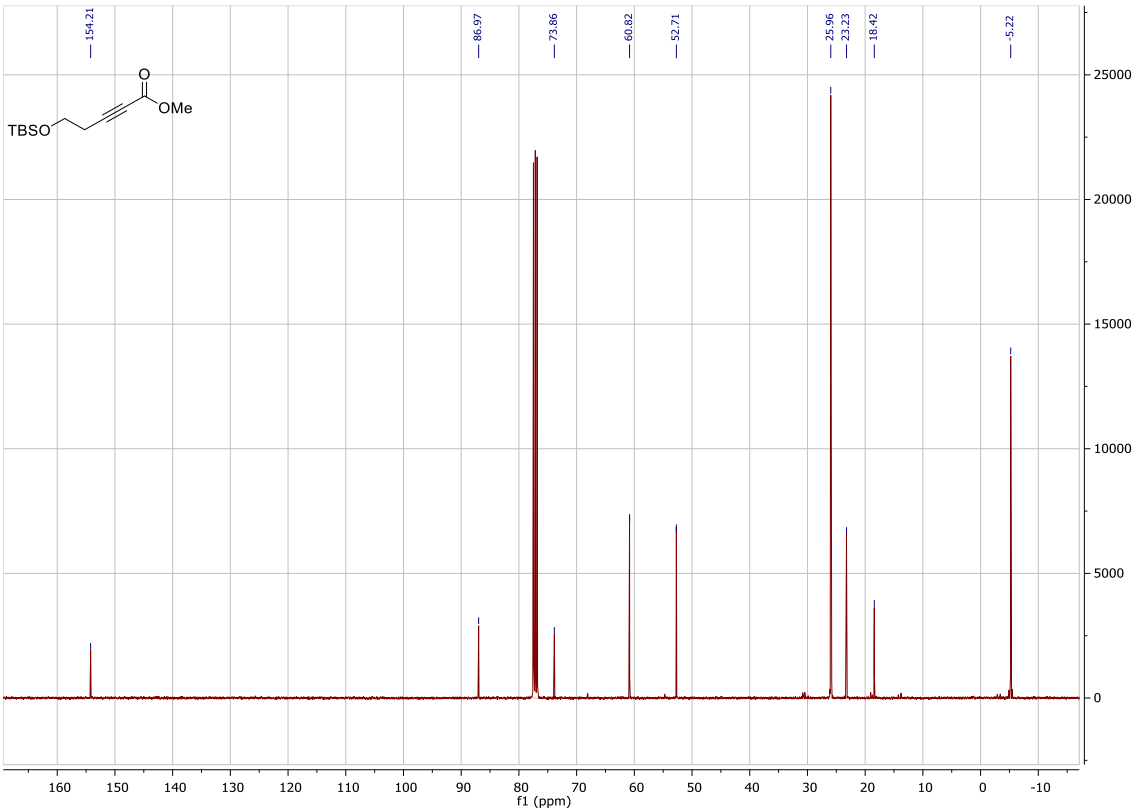

Figure H2 ^{13}C NMR for **34**, 101 MHz, $CDCl_3$.

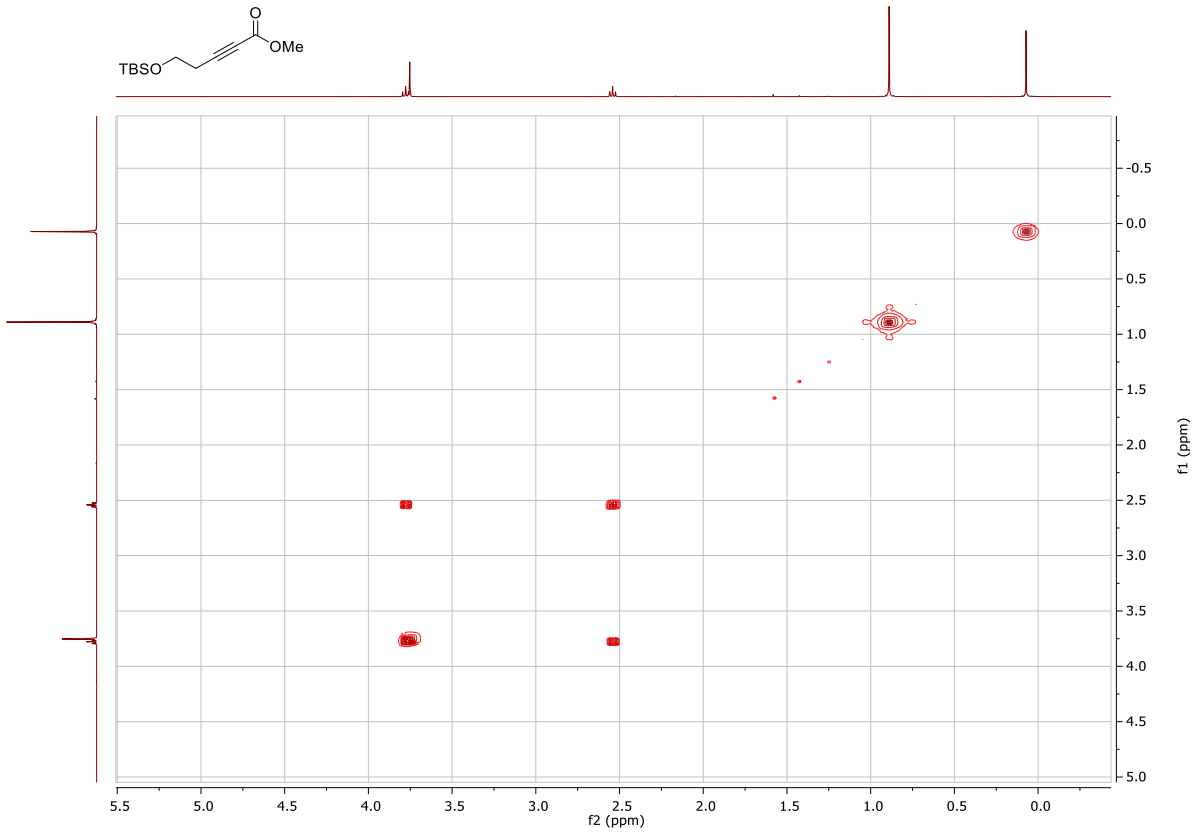

Figure H3 ^{1}H-^{1}H COSY for **34**, 400 MHz, $CDCl_3$.

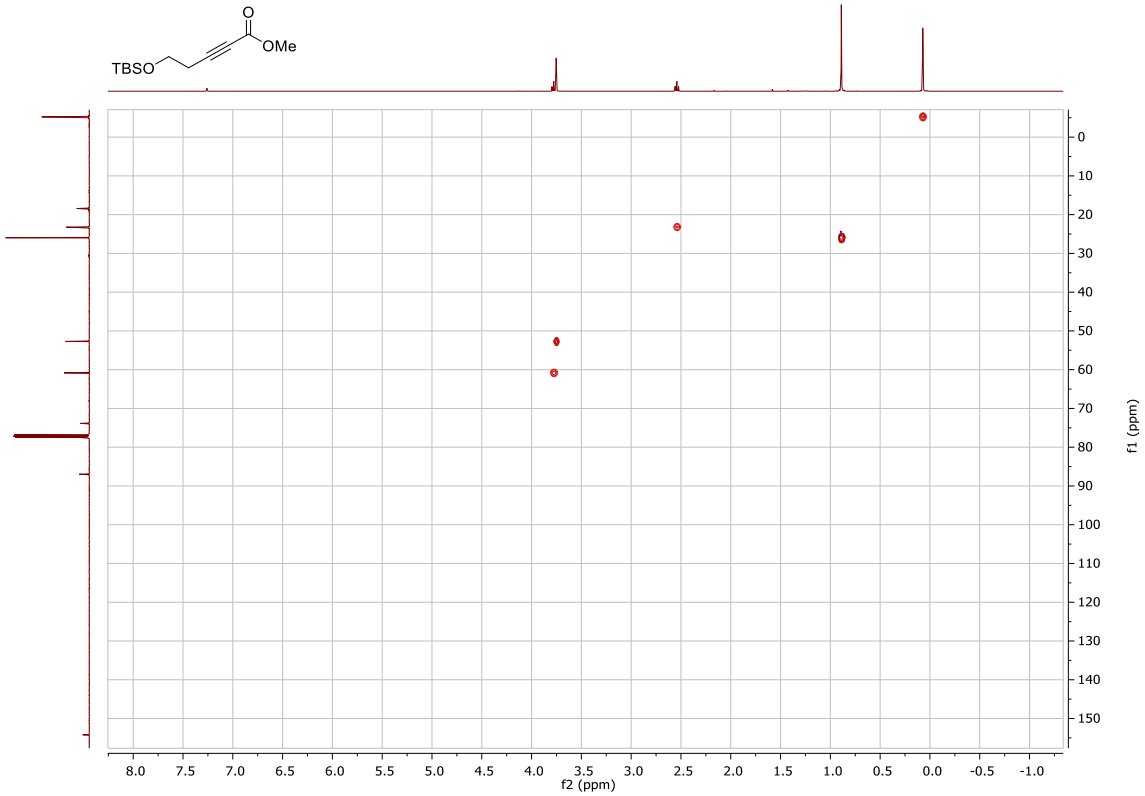

Figure H4 ^{1}H-^{13}C HSQC for **34**, 400 MHz, $CDCl_3$.

I *Tert*-butyl 7-((*tert*-butyldimethylsilyl)oxy)-3-oxohept-4-ynoate (33)

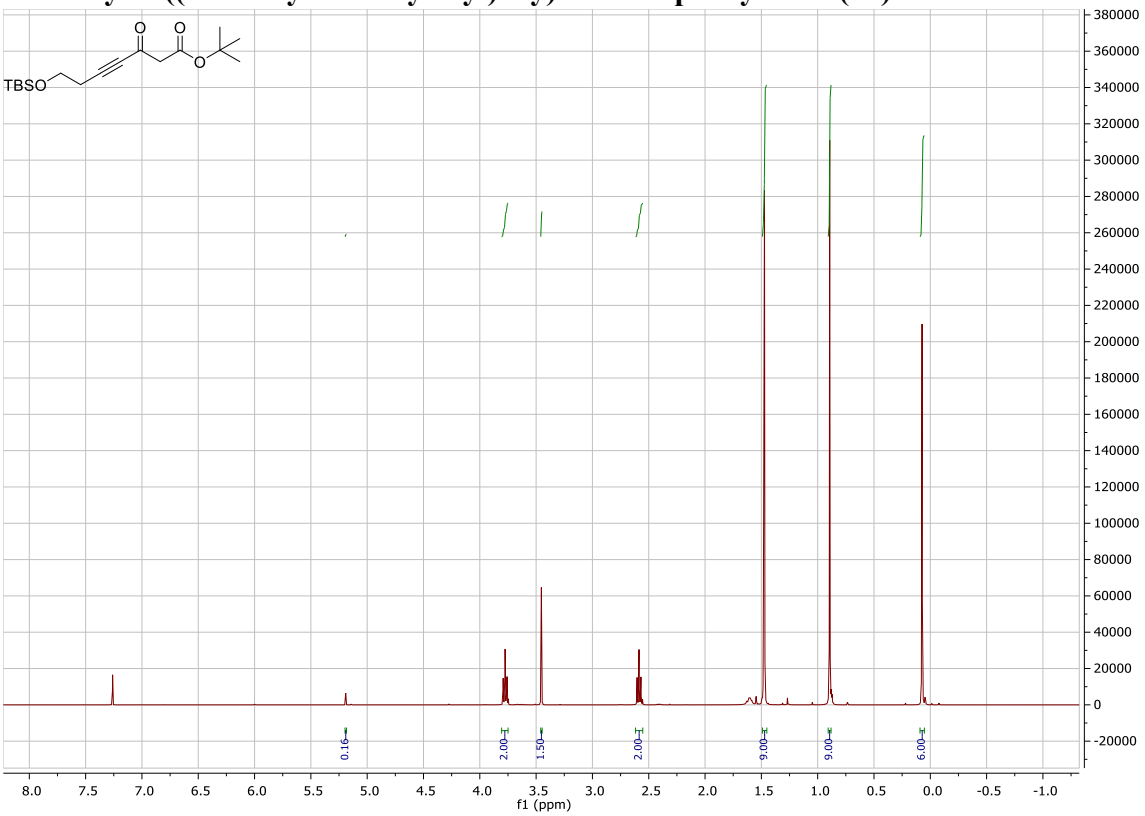

Figure I1 ^{1}H NMR for **33**, 400 MHz, $CDCl_3$.

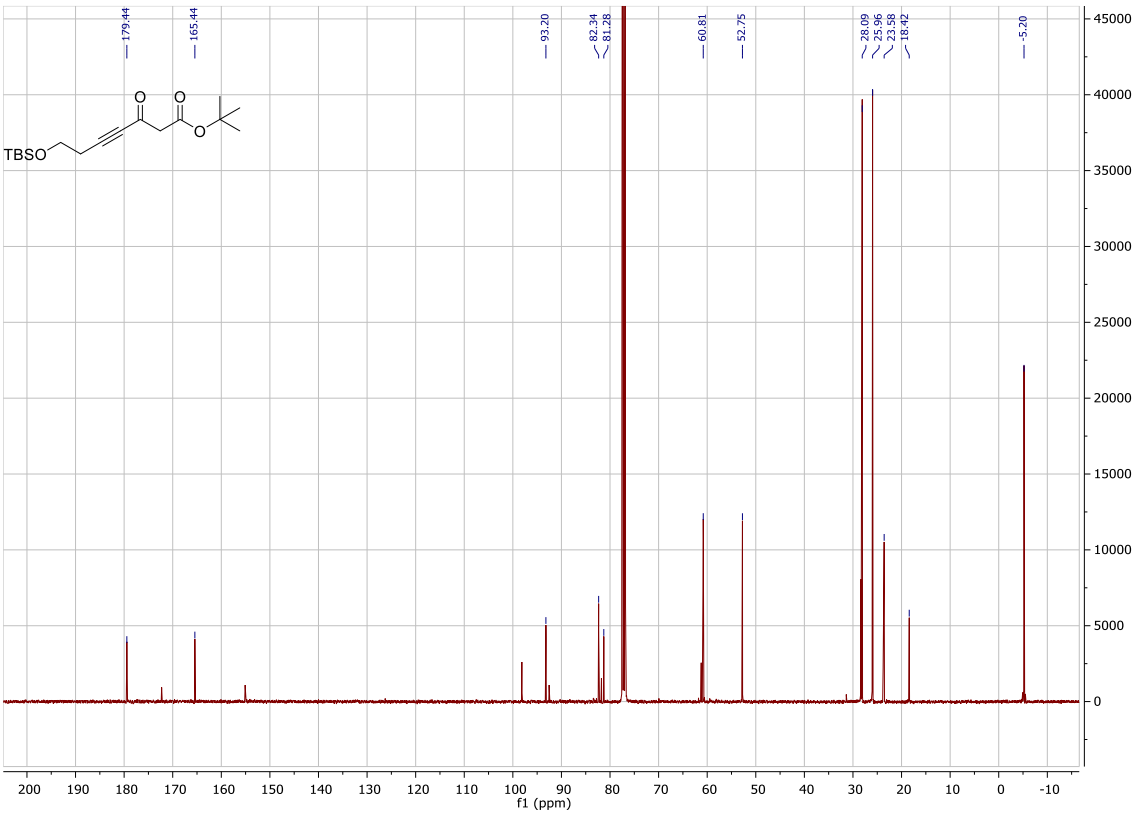

Figure I2 ^{13}C NMR for **33**, 101 MHz, $CDCl_3$.

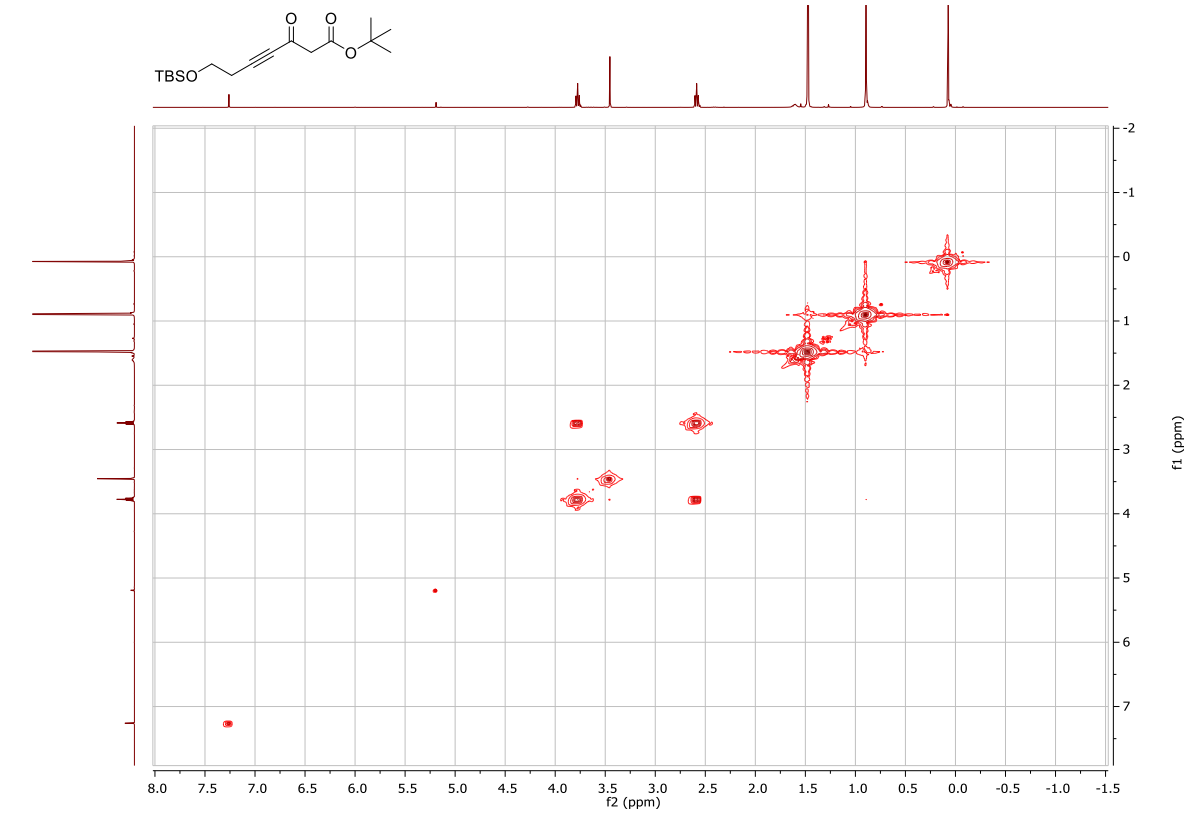

Figure I3 ^{1}H-^{1}H COSY for **33**, 400 MHz, $CDCl_3$.

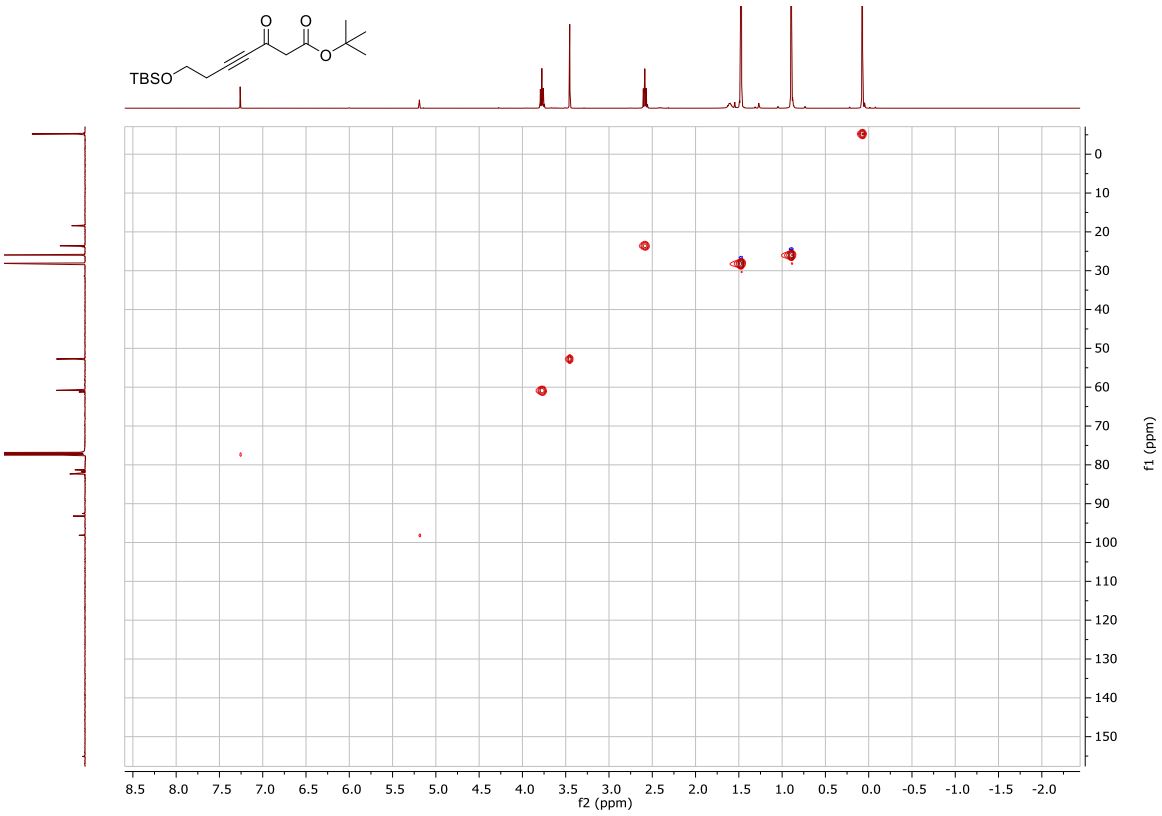

Figure I4 ^{1}H-^{13}C HSQC for **33**, 400 MHz, $CDCl_3$.

J 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-hydroxy-2*H*-pyran-2-one (30)

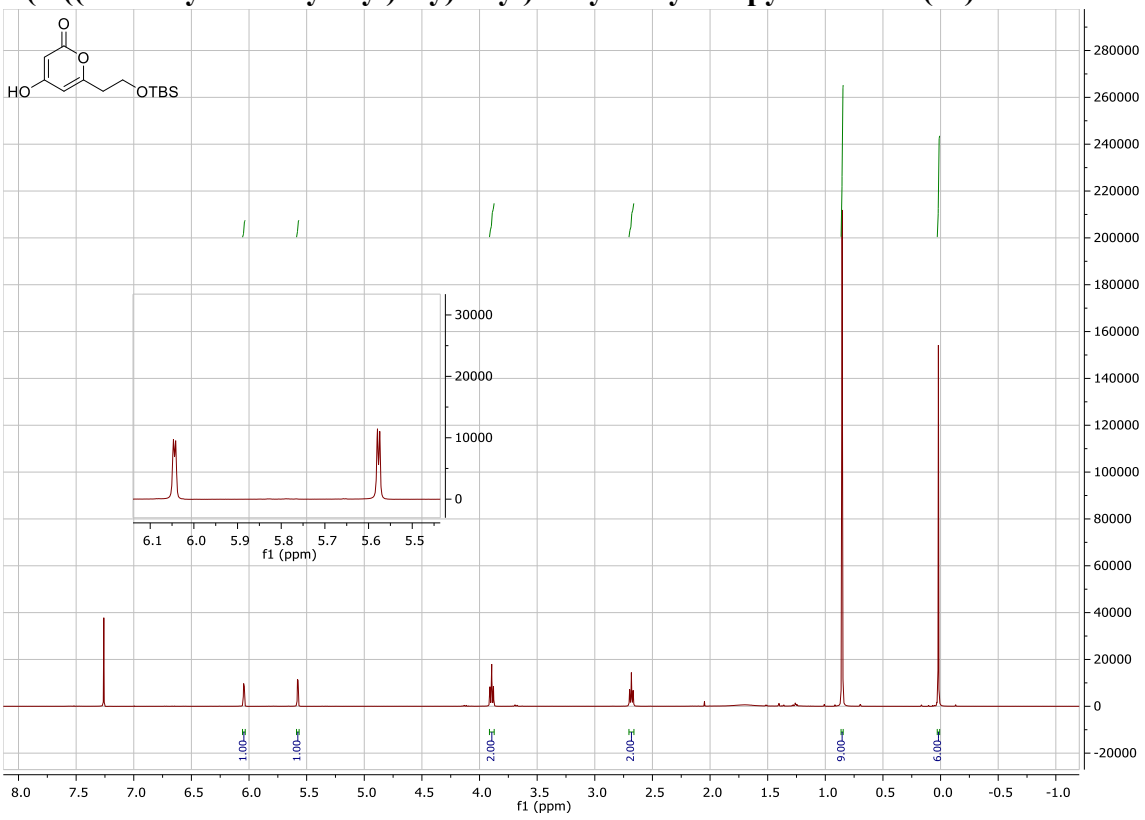

Figure J1 ^{1}H NMR for **30**, 400 MHz, $CDCl_3$.

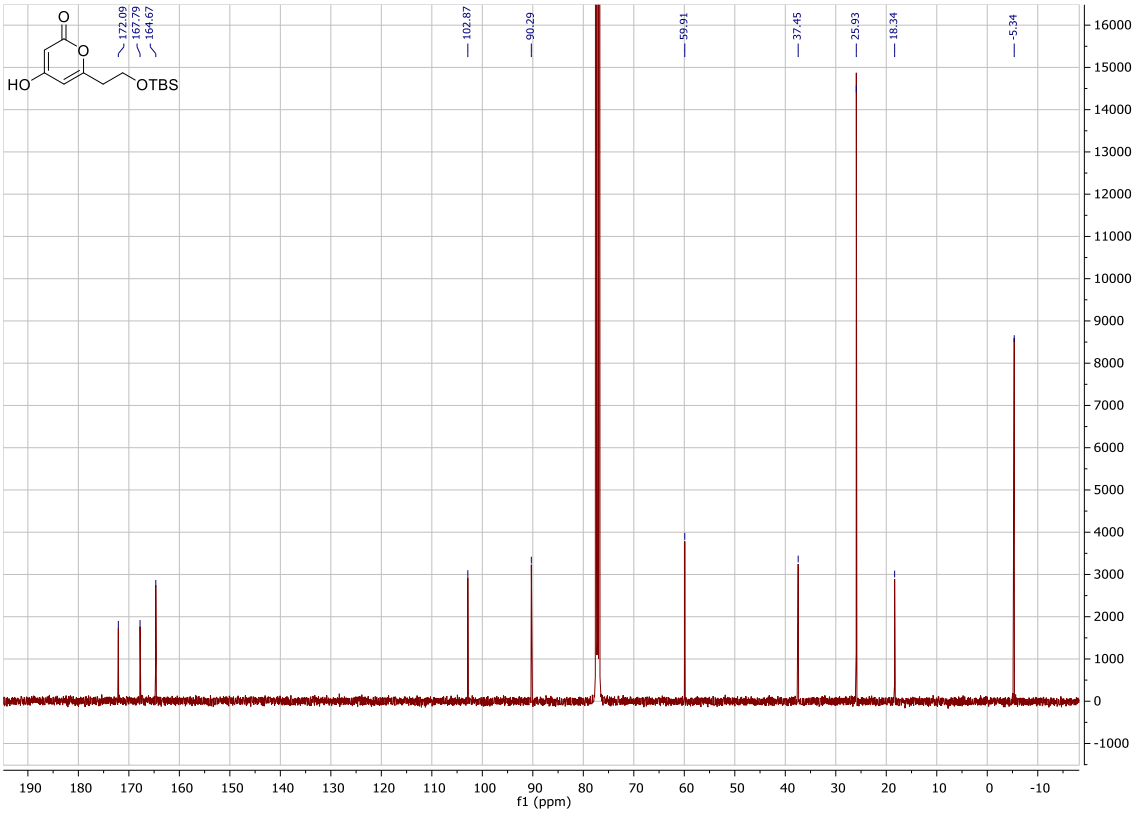

Figure J2 ^{13}C NMR for **30**, 101 MHz, $CDCl_3$.

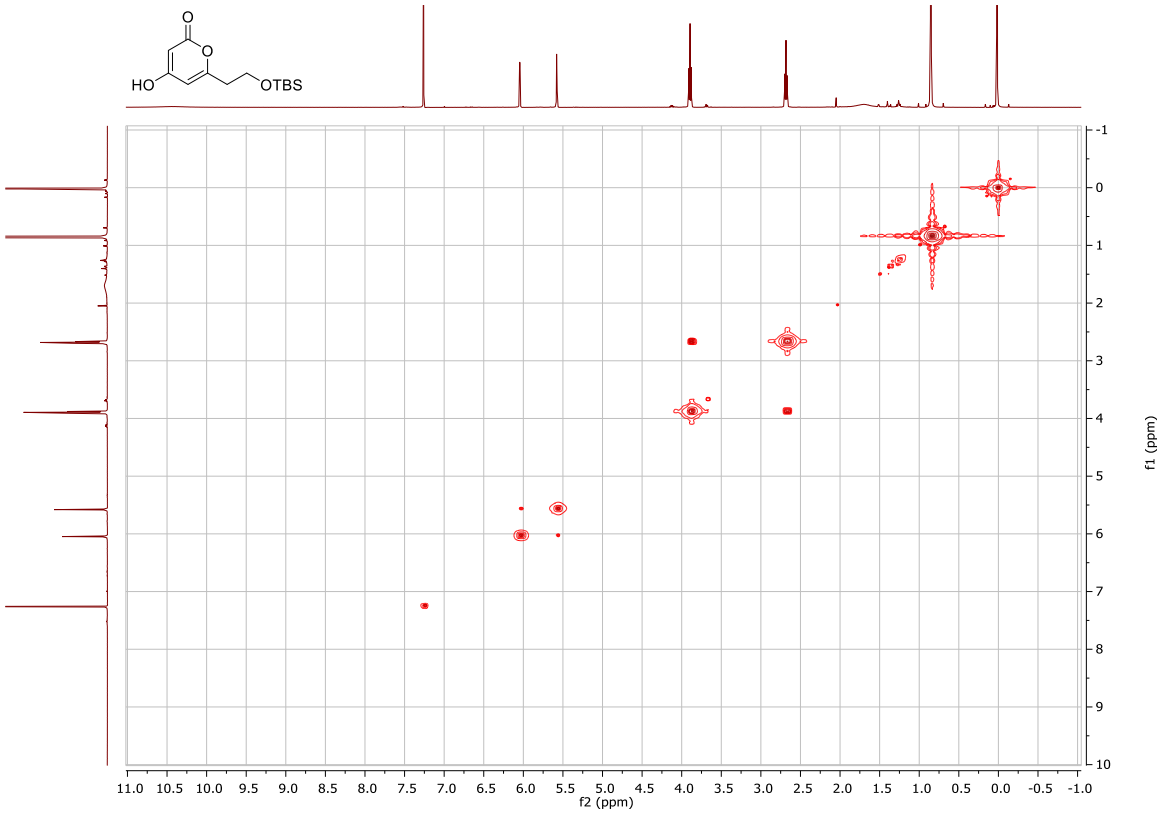

Figure J3 ^{1}H-^{1}H COSY for **30**, 400 MHz, $CDCl_3$.

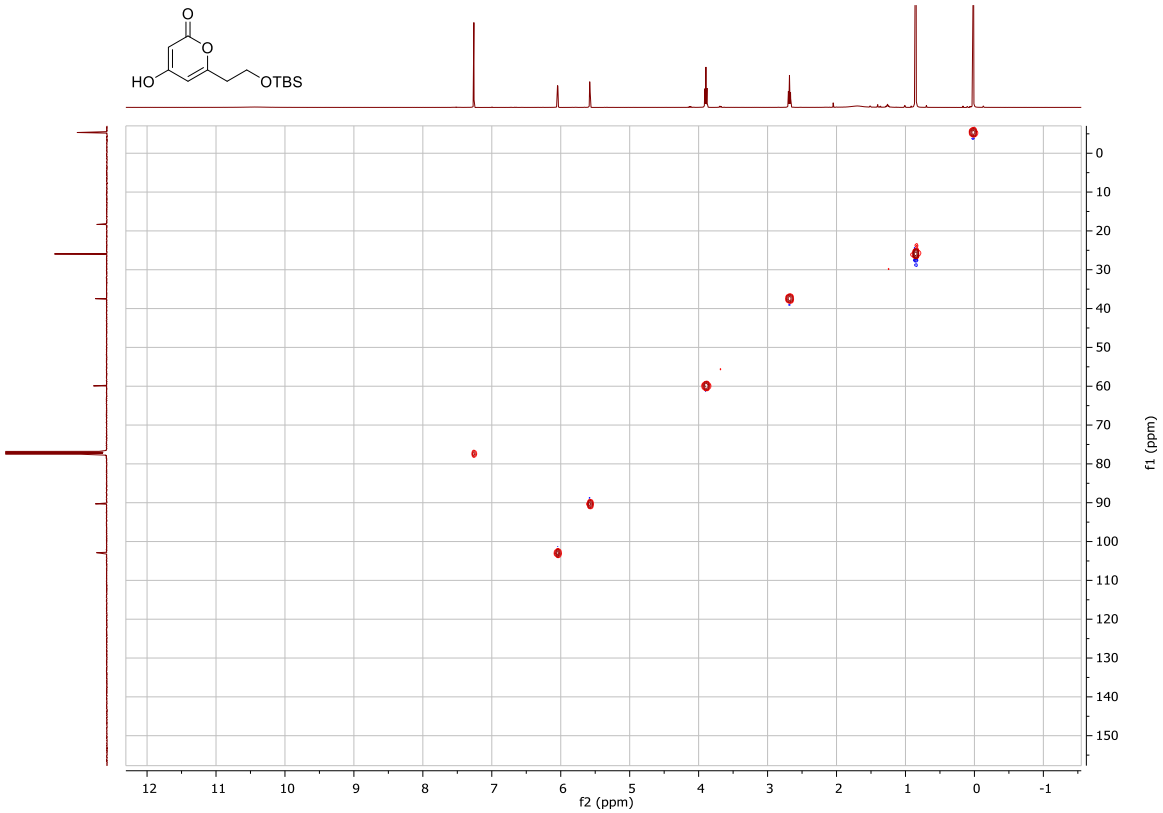

Figure J4 ^{1}H-^{13}C HSQC for **30**, 400 MHz, $CDCl_3$.

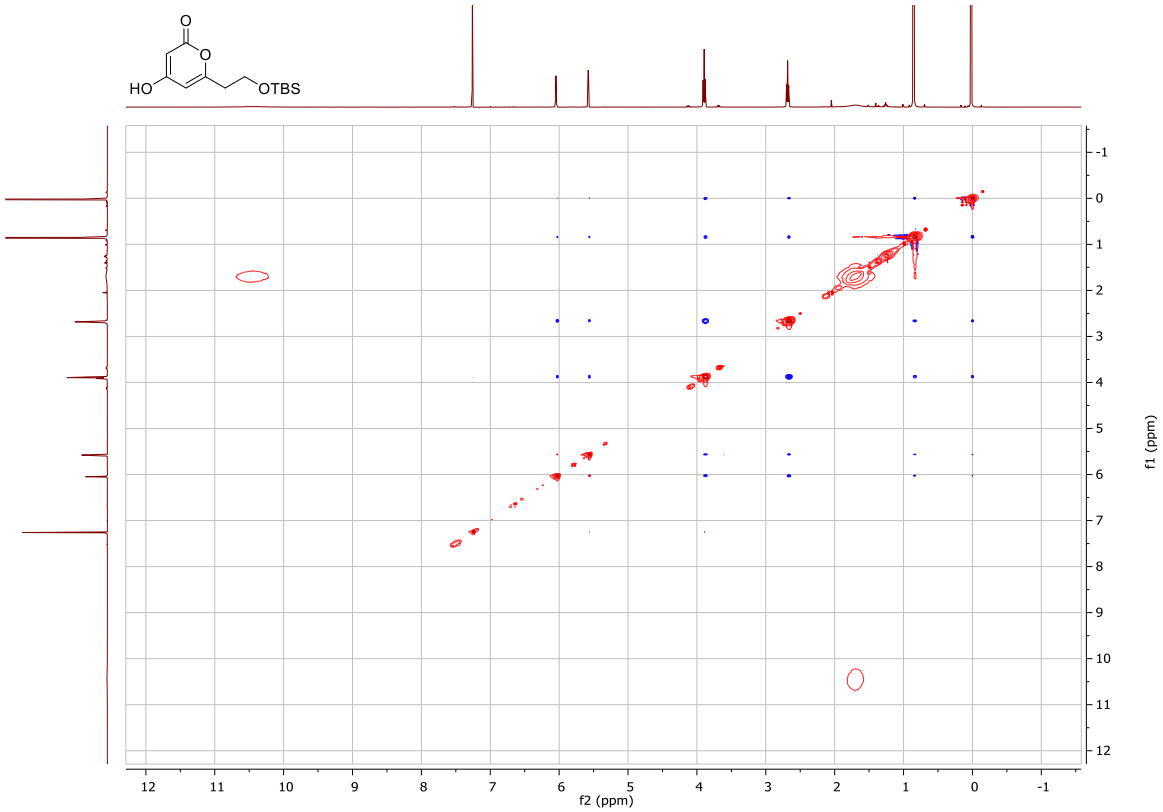

Figure J5 ^{1}H-^{1}H NOESY for **30**, 400 MHz, $CDCl_3$.

K 4-hydroxy-6-(2-hydroxyethyl)-2*H*-pyran-2-one (45)

Figure K1 ^{1}H NMR for **45**, 400 MHz, DMSO-d_6.

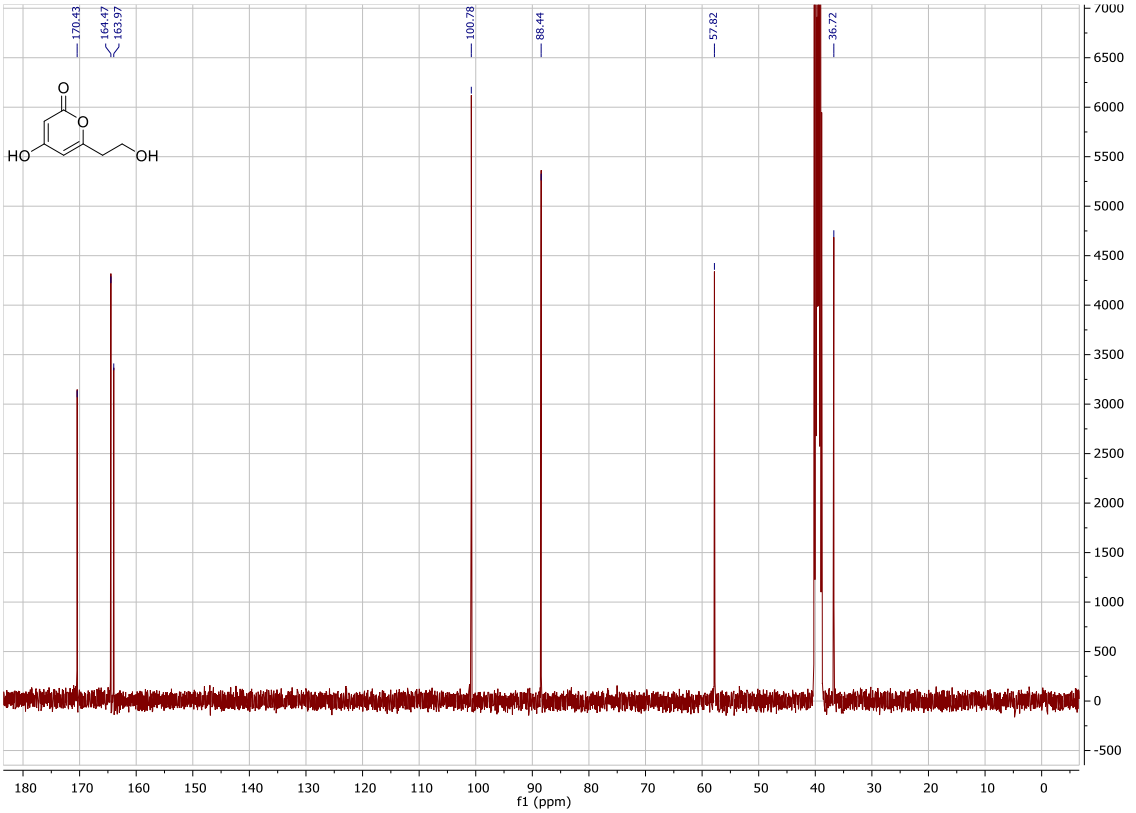

Figure K2 ^{13}C NMR for **45**, 101 MHz, DMSO-d_6.

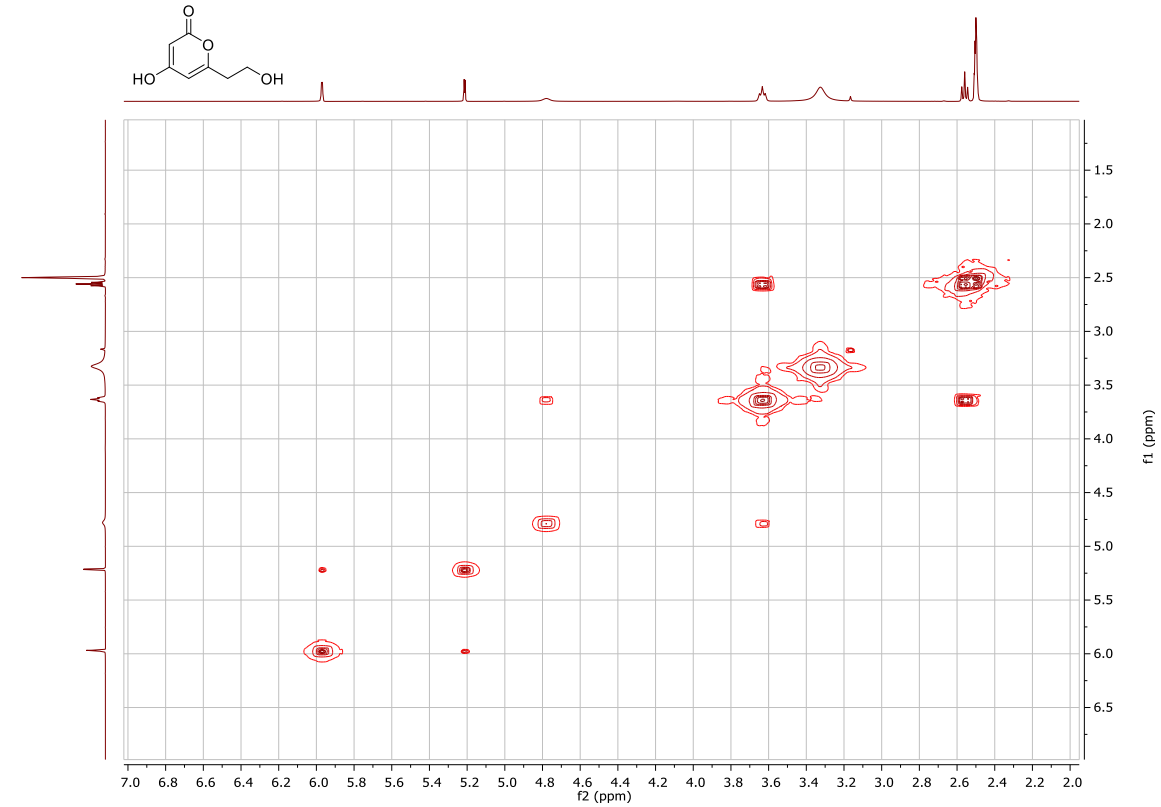

Figure K3 ^{1}H-^{1}H COSY for **45**, 400 MHz, DMSO-d_6.

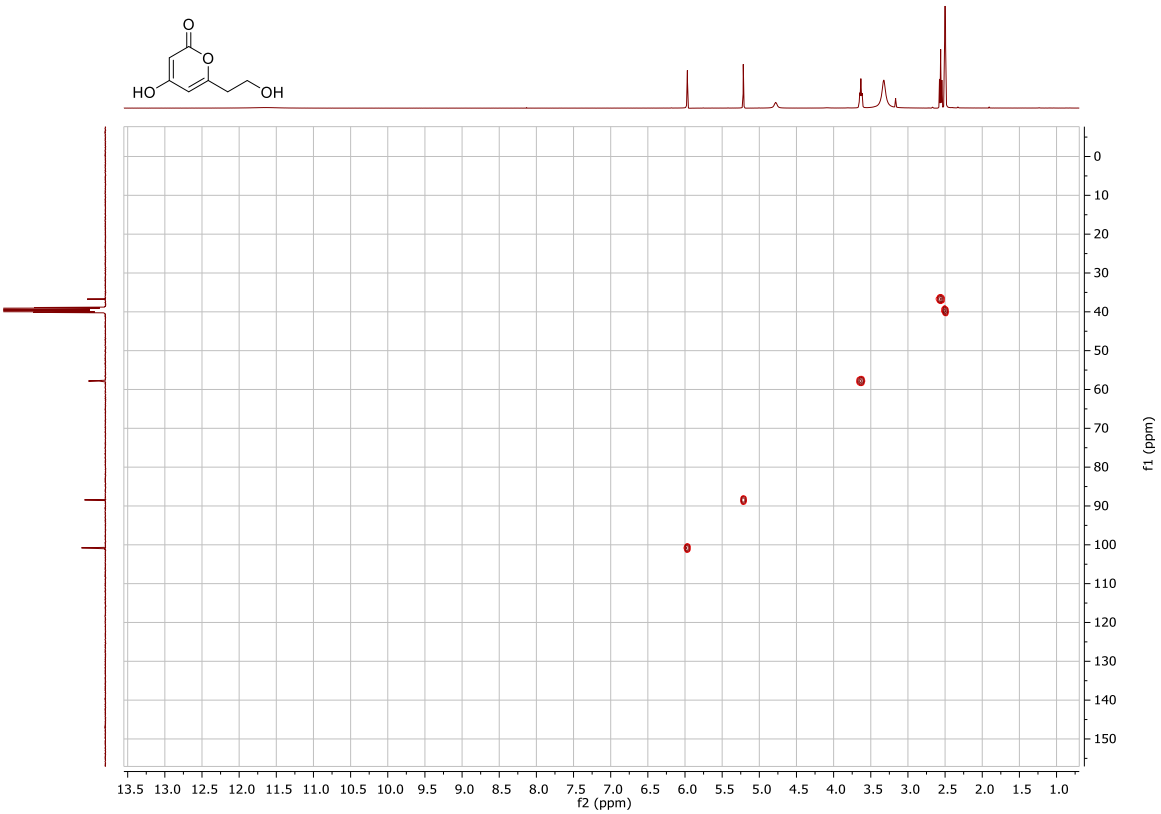

Figure K4 ^{1}H-^{13}C HSQC for **45**, 400 MHz, DMSO-d_6.

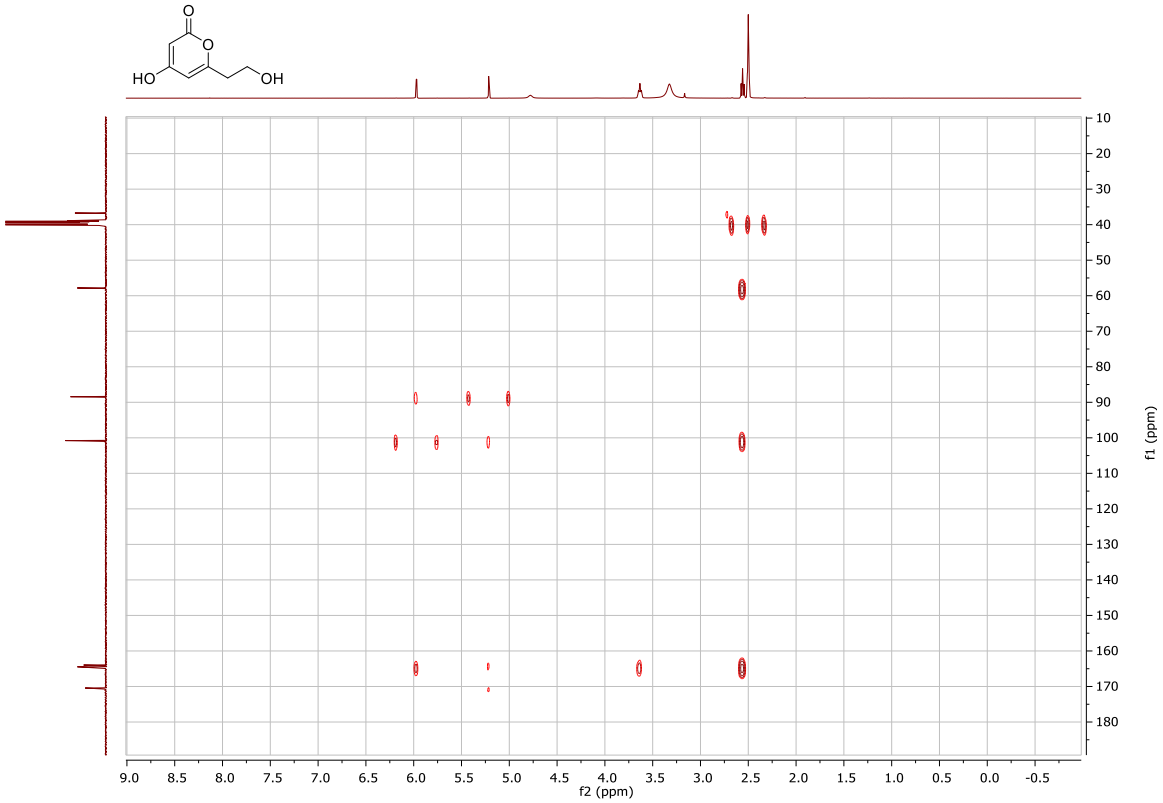

Figure K5 ^{1}H-^{13}C HMBC for **45**, 400 MHz, DMSO-d_6.

L 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-chloro-4-hydroxy-2*H*-pyran-2-one (29)

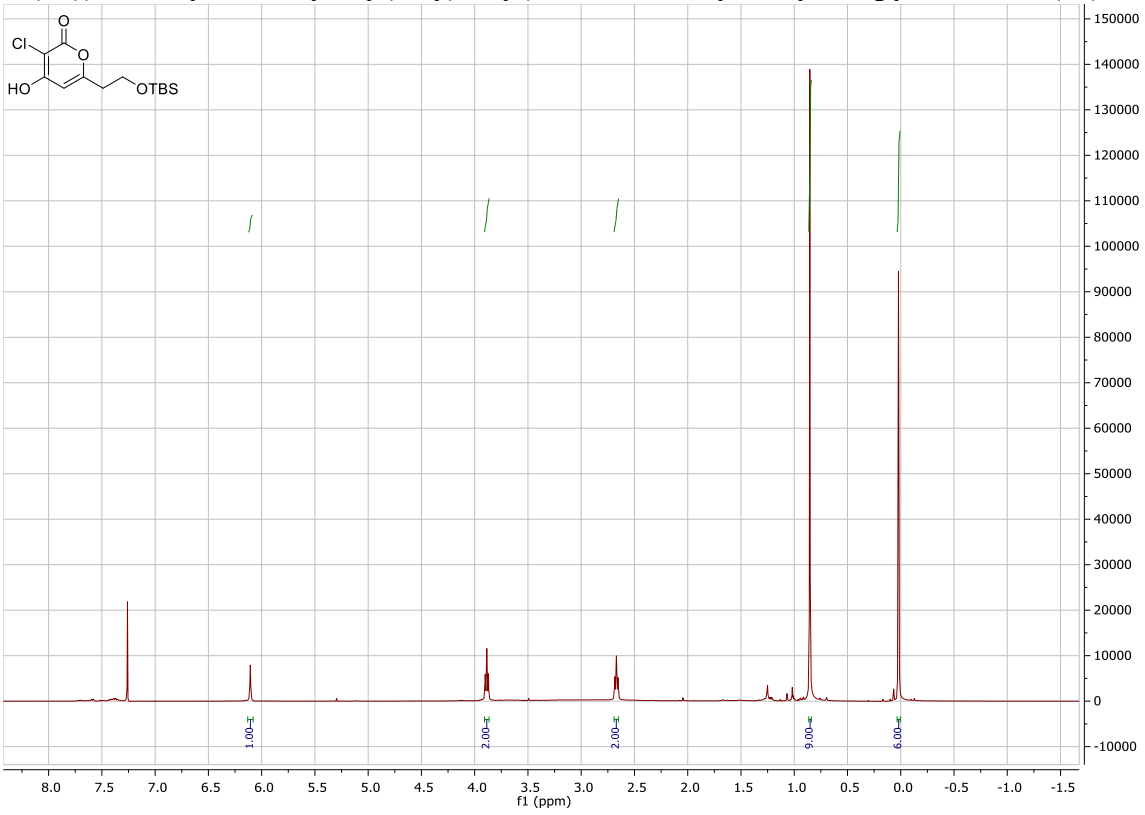

Figure L1 ^{1}H NMR for **29**, 400 MHz, $CDCl_3$.

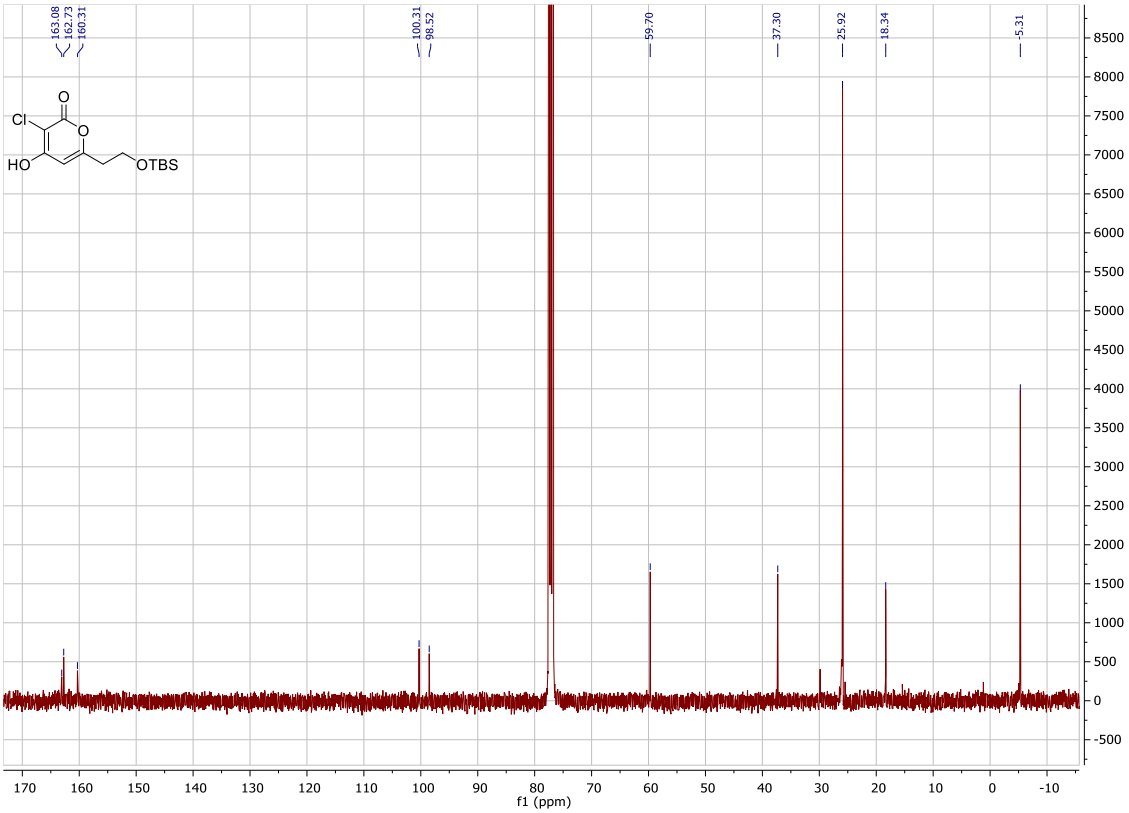

Figure L2 ^{13}C NMR for **29**, 101 MHz, $CDCl_3$.

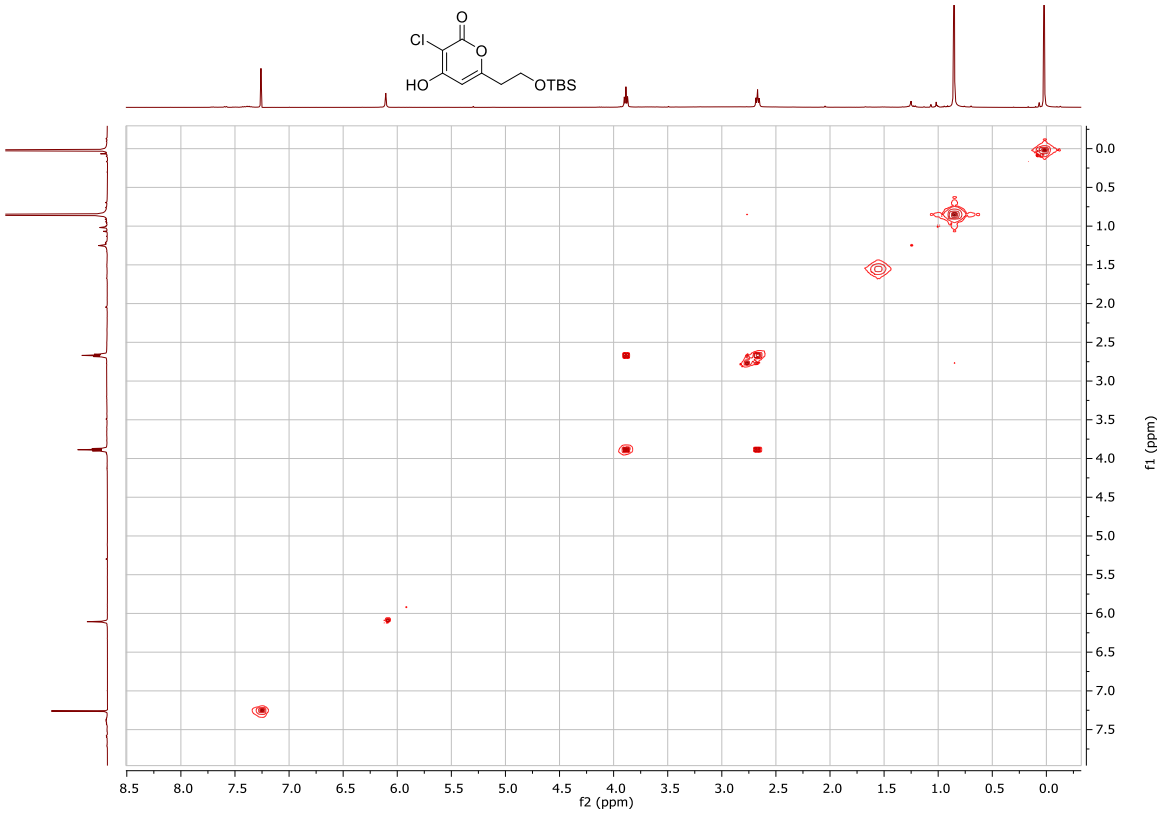

Figure L3 ^{1}H-^{1}H COSY for **29**, 400 MHz, $CDCl_3$.

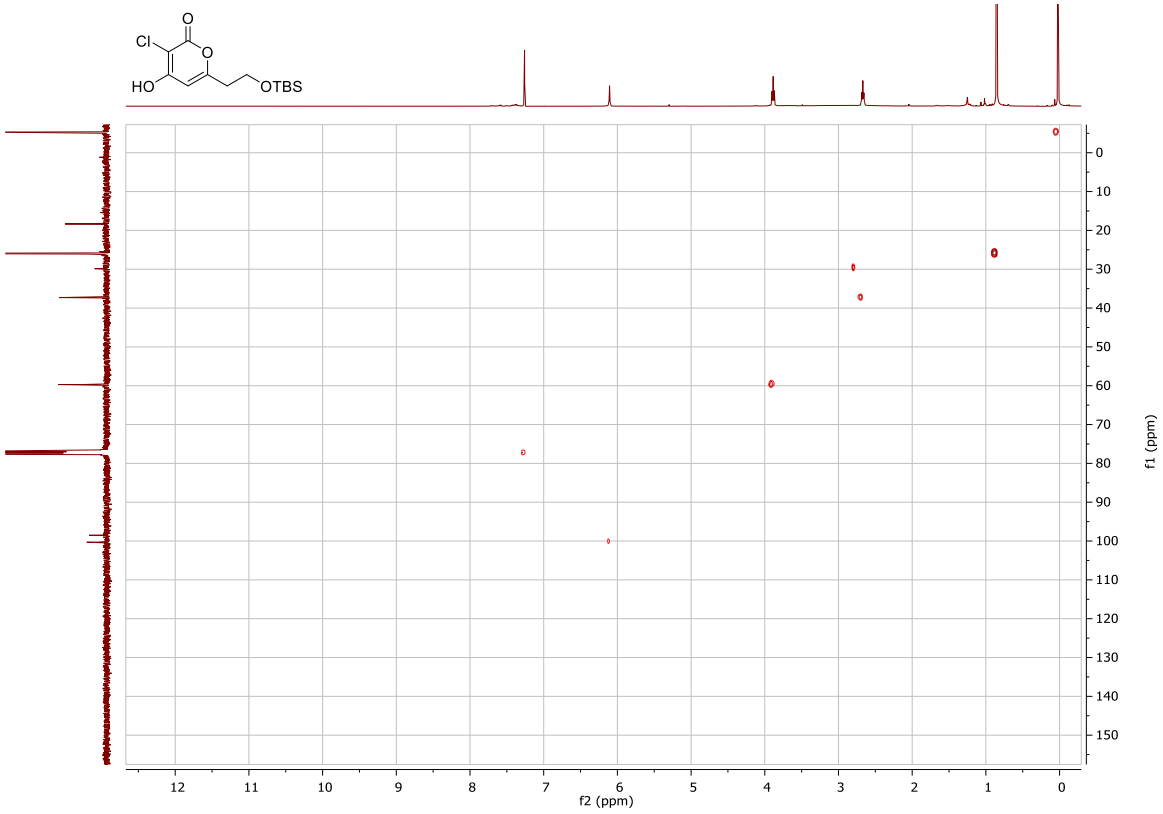

Figure L4 ^{1}H-^{13}C HSQC for **29**, 400 MHz, $CDCl_3$.

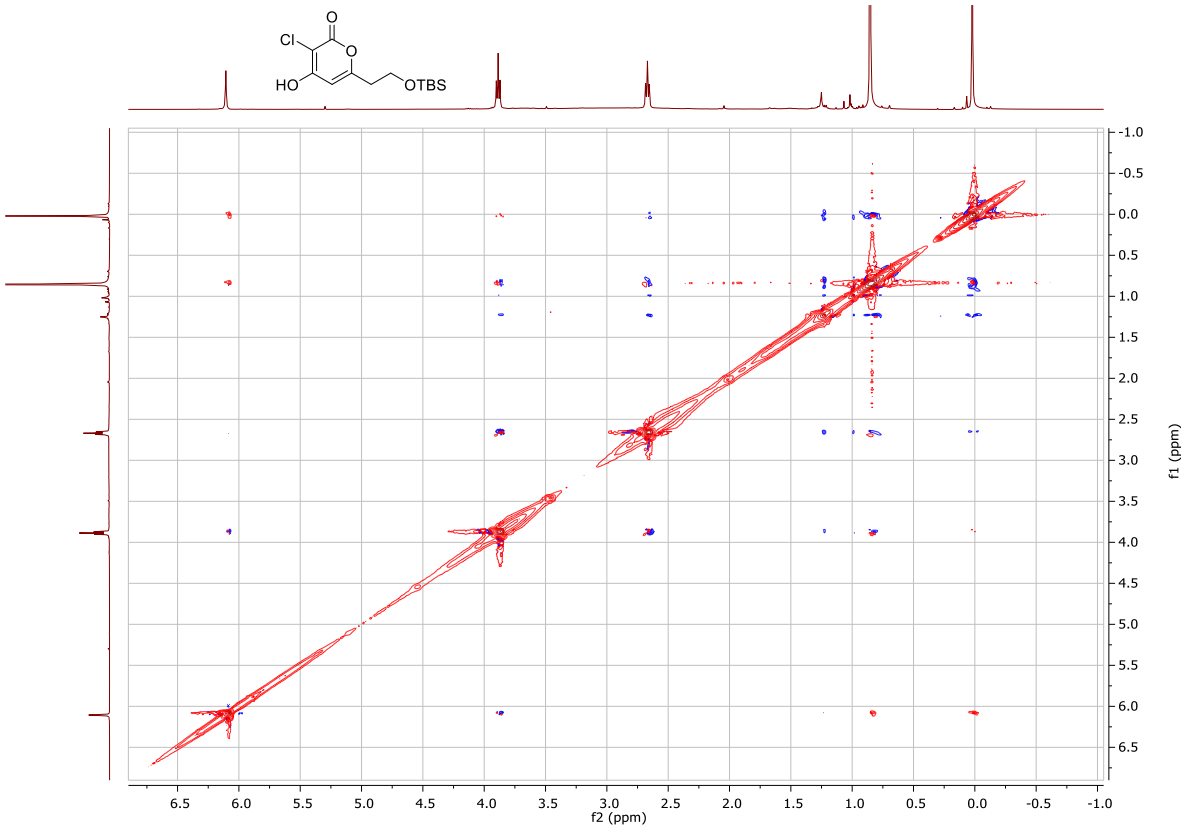

Figure L5 ^{1}H-^{1}H NOESY for **29**, 400 MHz, $CDCl_3$.

Sample ID:2023-09-27T12-13-41
Sample Scans:32
Background Scans:32
Resolution:8
System Status:Good
File Location:C:\Users\Public\Documents\Agilent\MicroLab\Results\\2023-09-27T12-13-41.a2r

Method Name:Default
User:admin
Date/Time:09/27/2023 12:13:41 PM
Range:4000 - 650
Apodization:Happ-Genzel

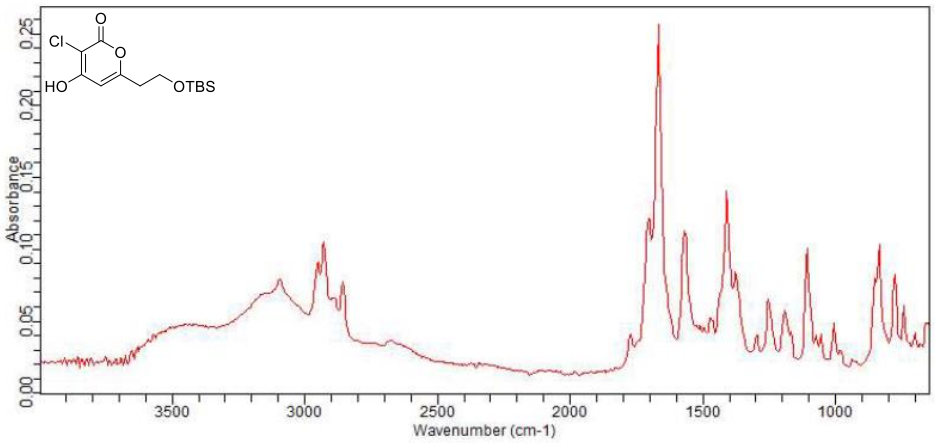

Figure L6 IR spectrum of **29**.

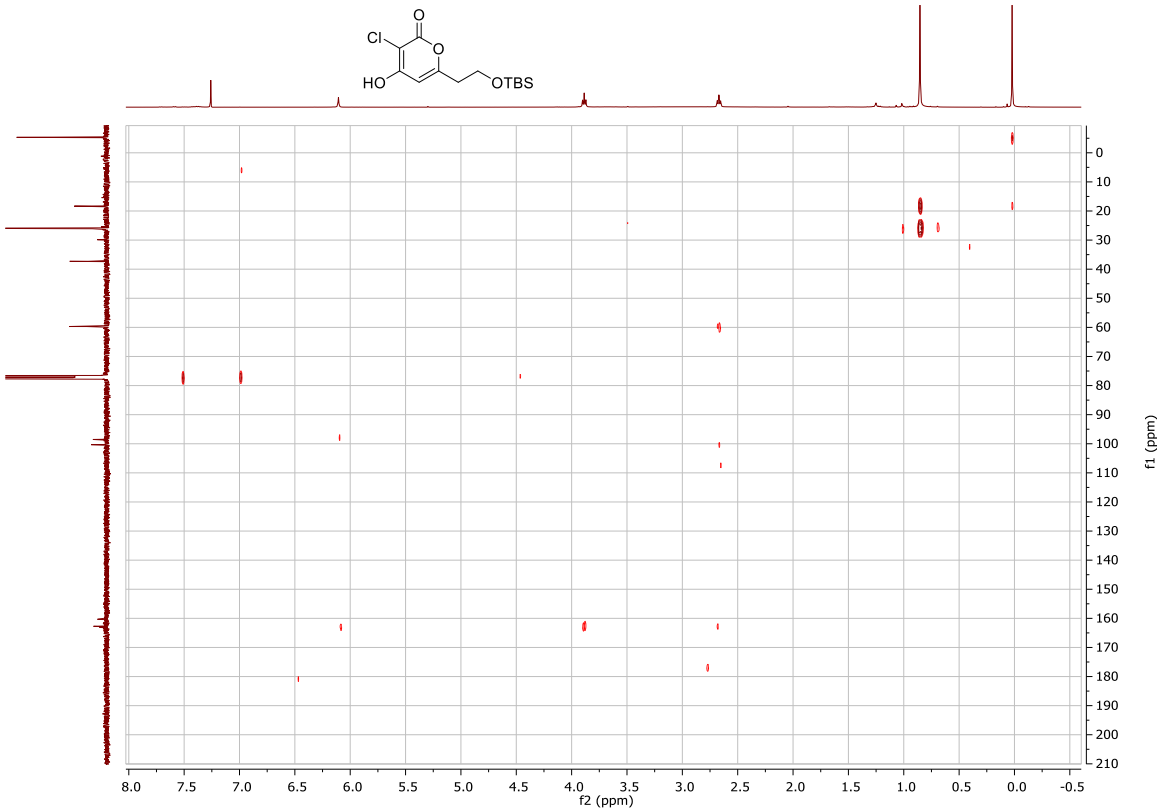

Figure L7 ^{1}H-^{13}C HMBC for **29**, 400 MHz, $CDCl_3$.

M 3-chloro-4-hydroxy-6-methyl-2*H*-pyran-2-one (48)

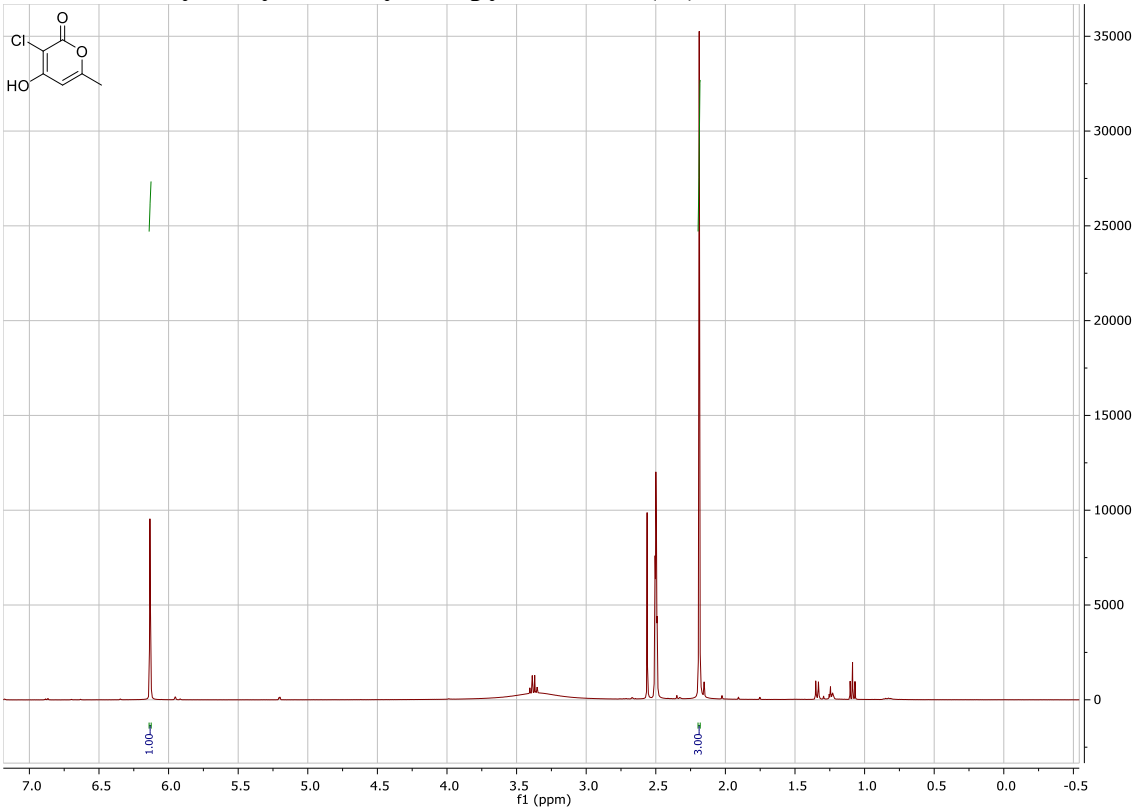

Figure M1 ^{1}H NMR for **48**, 400 MHz, DMSO-d_6.

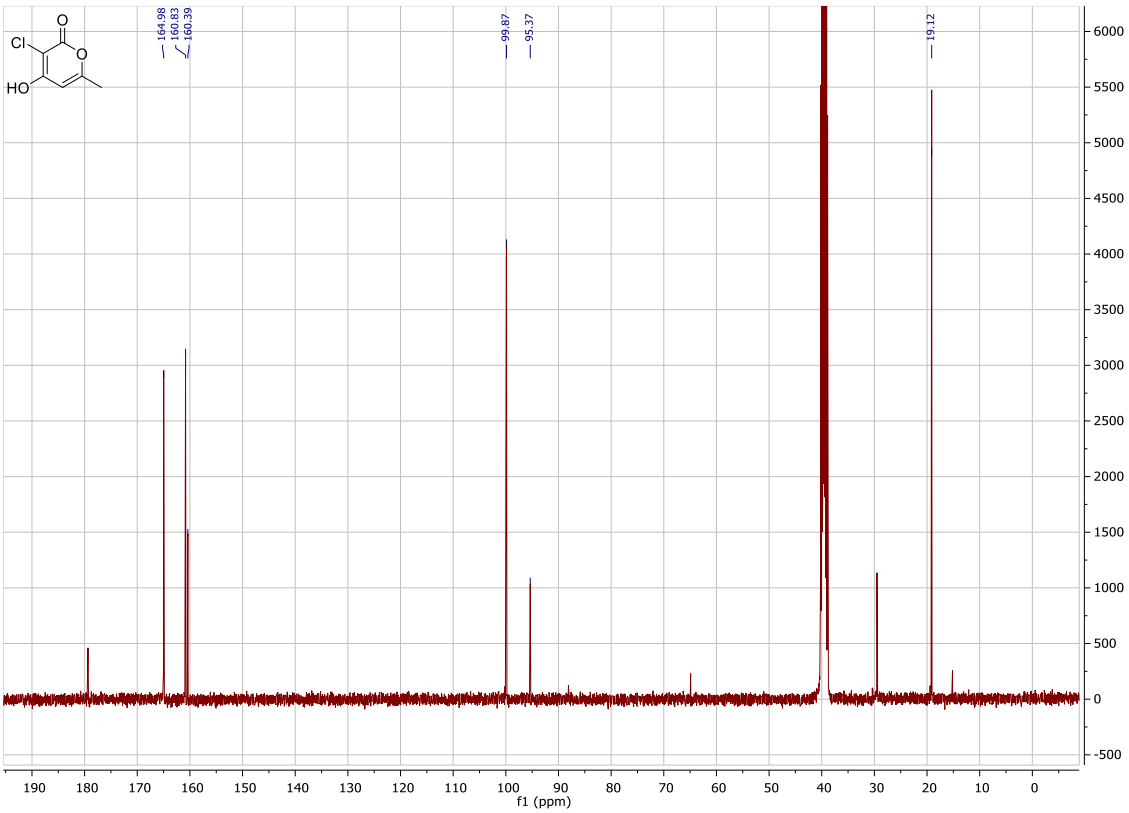

Figure M2 ^{13}C NMR for **48**, 101 MHz, DMSO-d_6.

N 3-chloro-4-hydroxy-6-(2-hydroxyethyl)-2*H*-pyran-2-one (52)

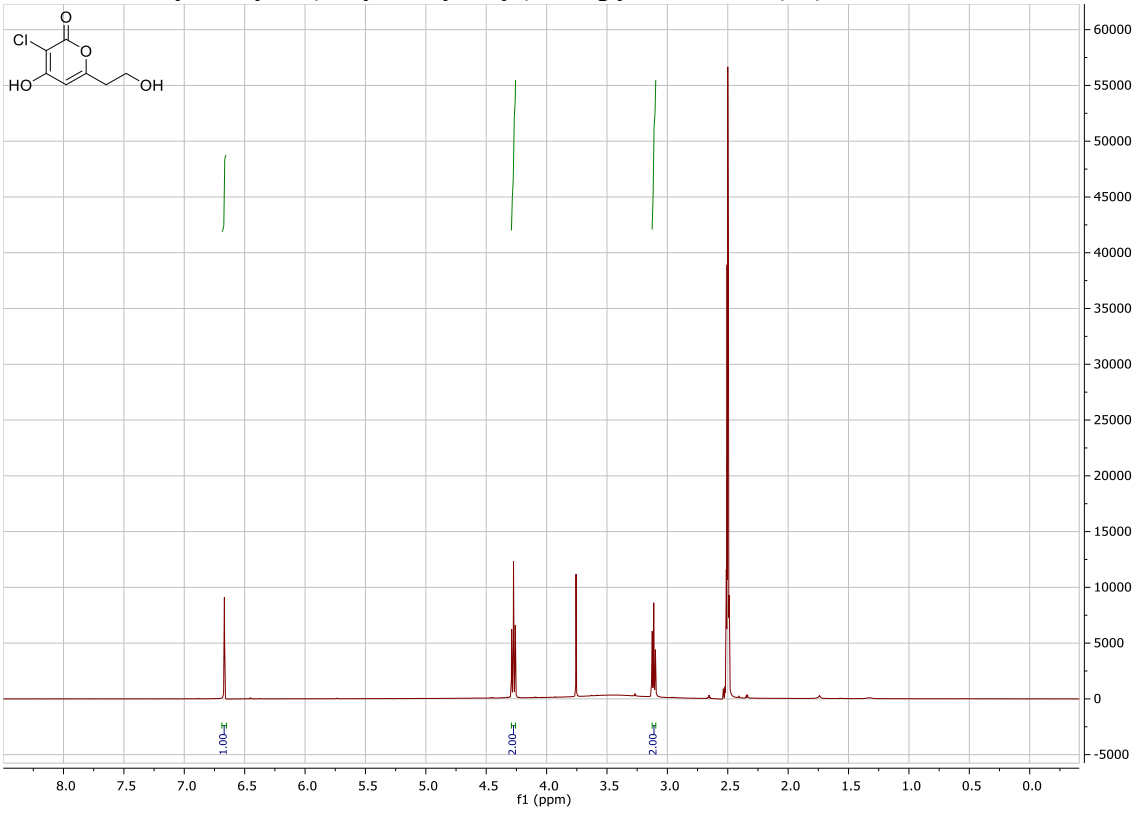

Figure N1 ^{1}H NMR for **52**, 400 MHz, acetone-d_6.

O 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-chloro-2-oxo-2*H*-pyran-4-yl acetate (51)

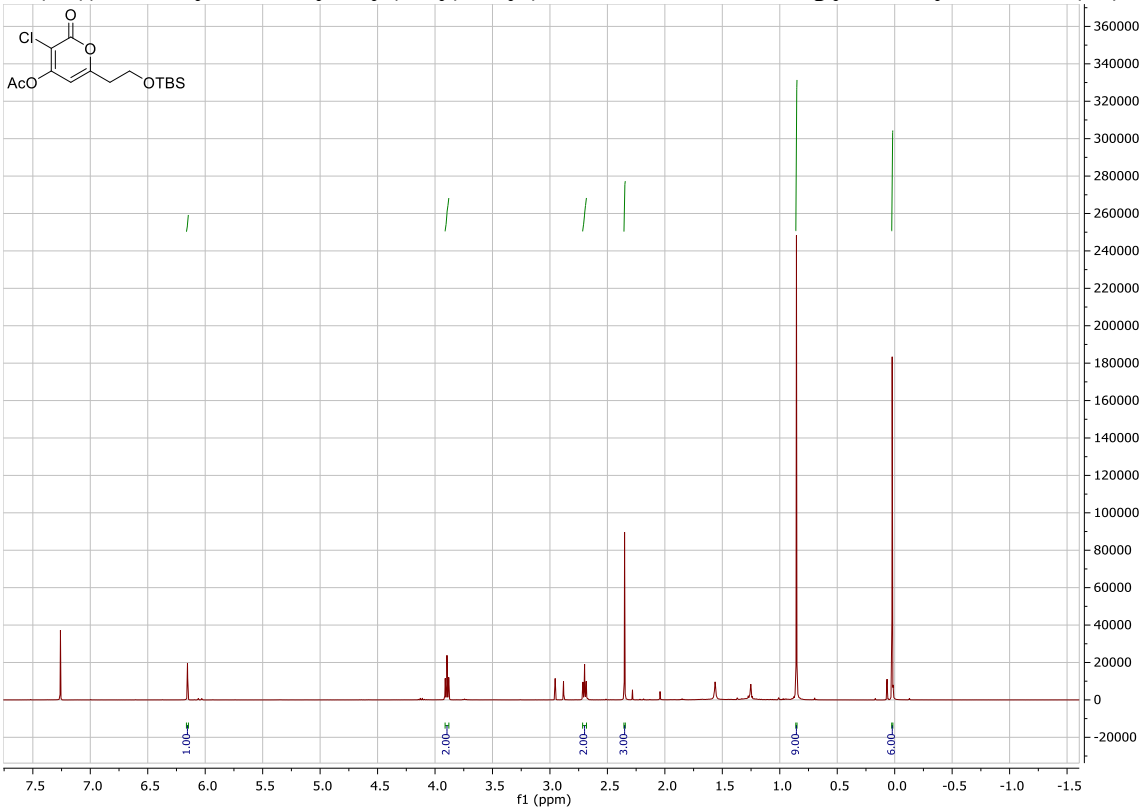

Figure O1 ^{1}H NMR for **51**, 400 MHz, $CDCl_3$.

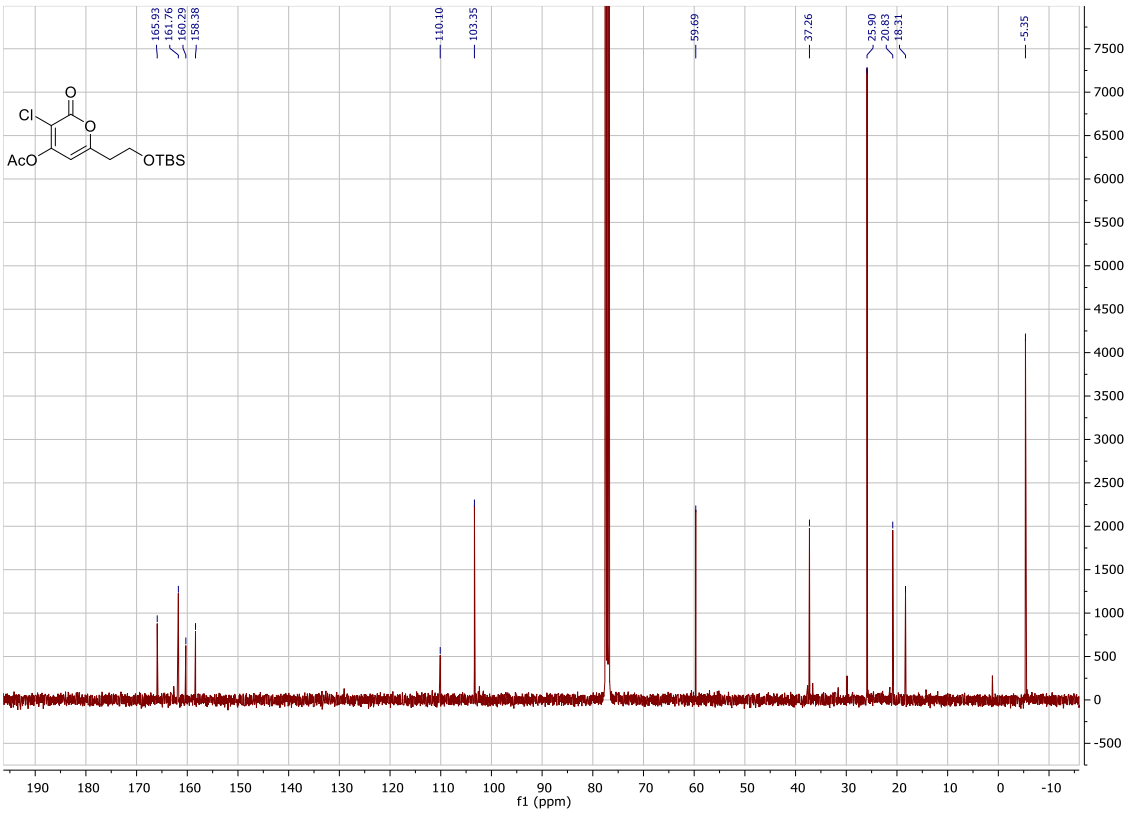

Figure O2 ^{13}C NMR for **51**, 101 MHz, $CDCl_3$.

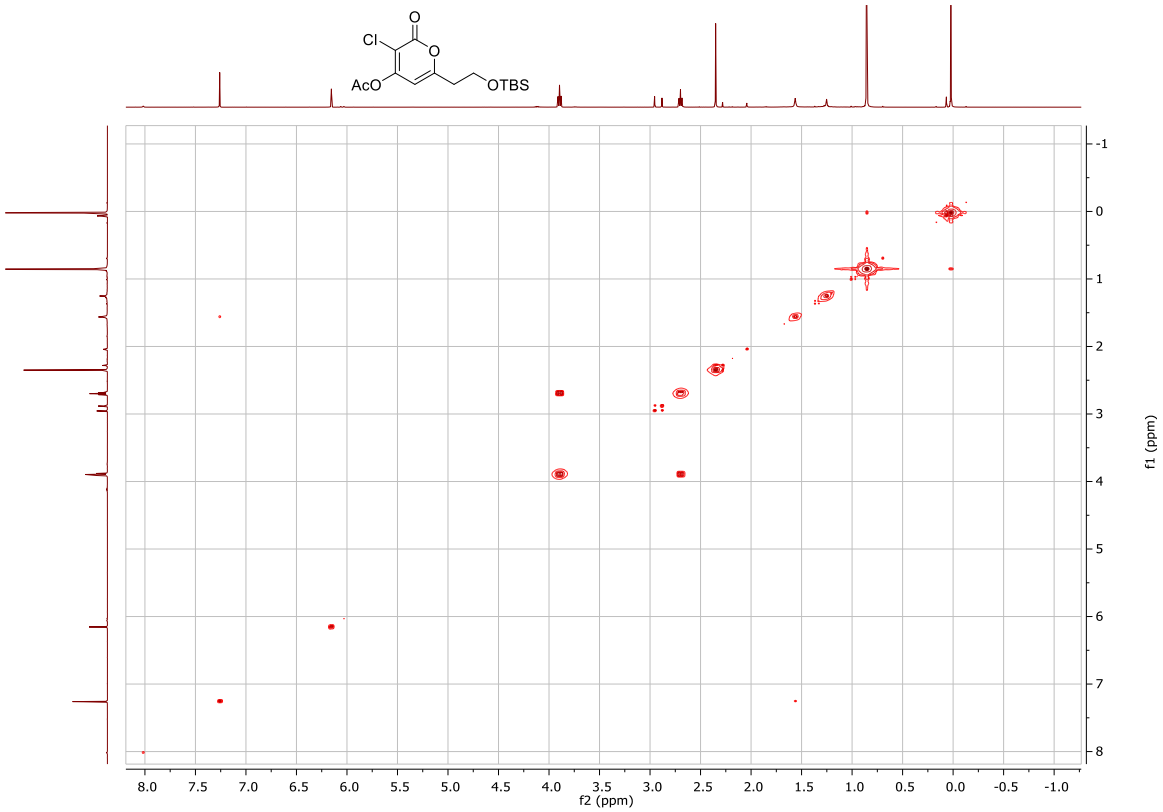

Figure O3 ^{1}H-^{1}H COSY for **51**, 400 MHz, $CDCl_3$.

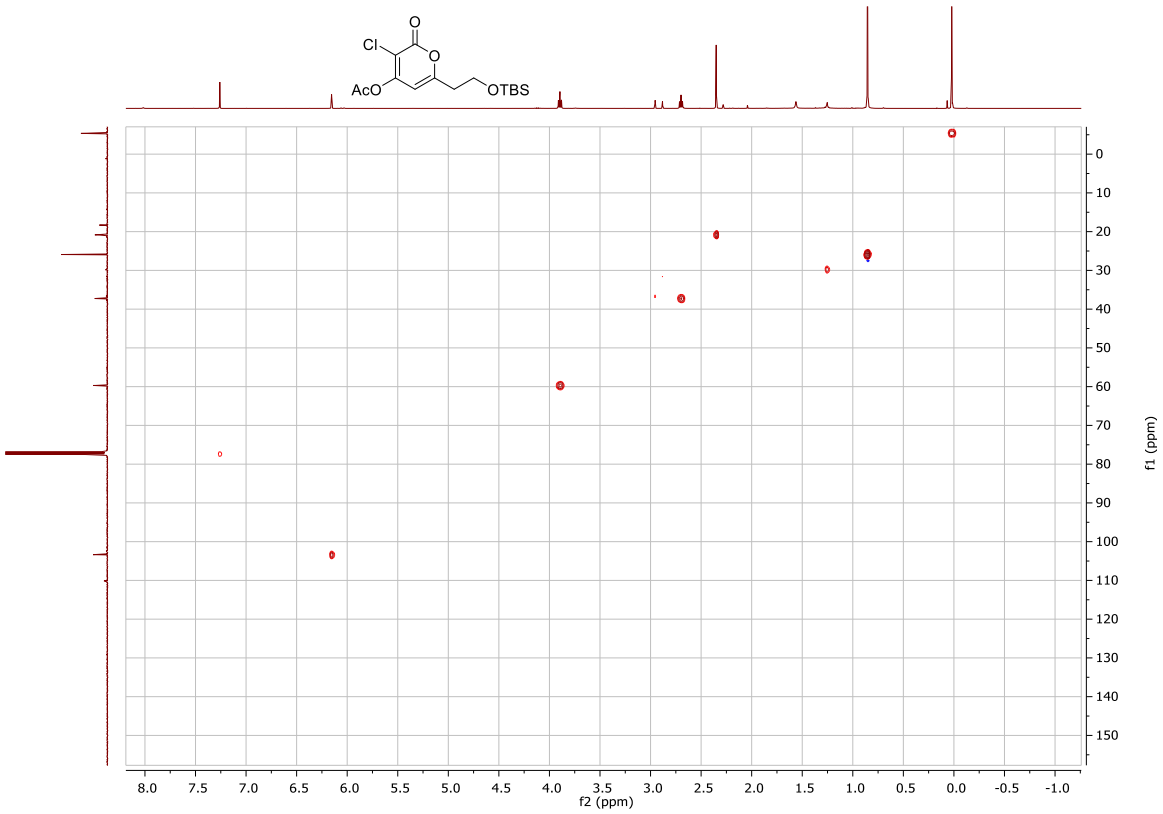

Figure O4 ^{1}H-^{13}C HSQC for **51**, 400 MHz, $CDCl_3$.

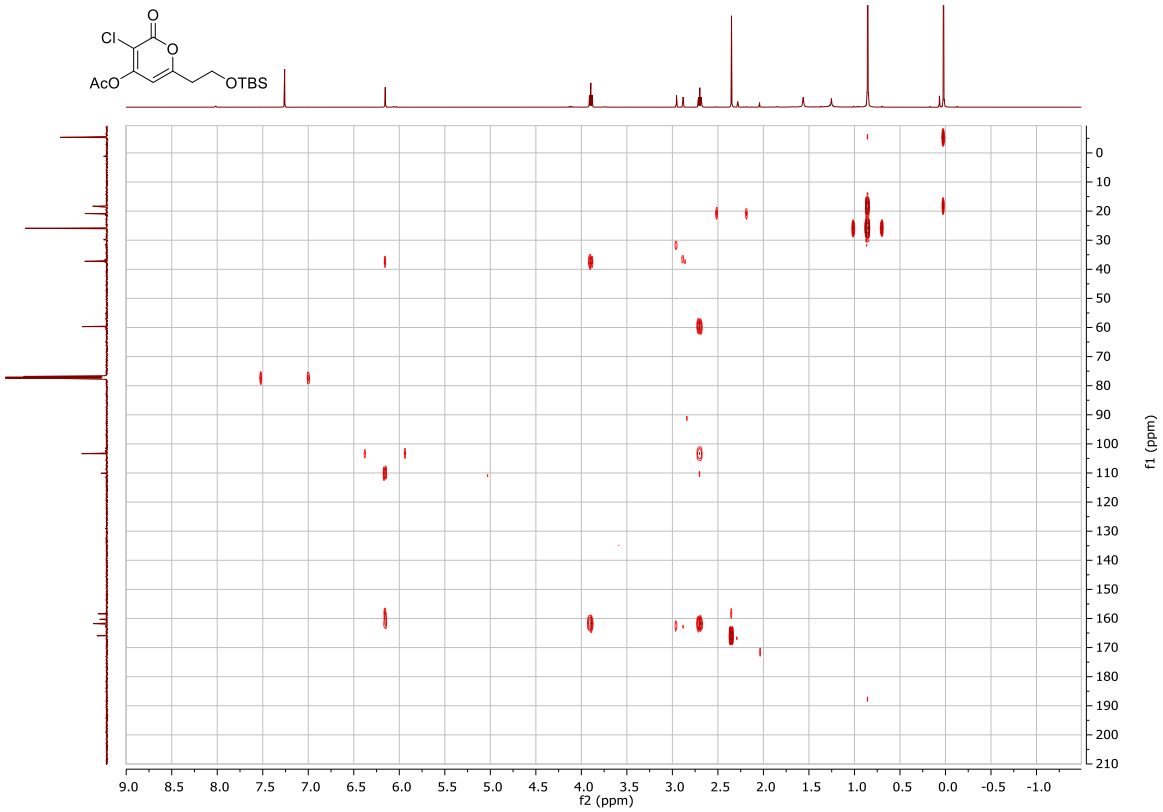

Figure O5 ^{1}H-^{13}C HMBC for **51**, 400 MHz, $CDCl_3$.

P 6-methyl-2-oxo-2*H*-pyran-4-yl acetate (49)

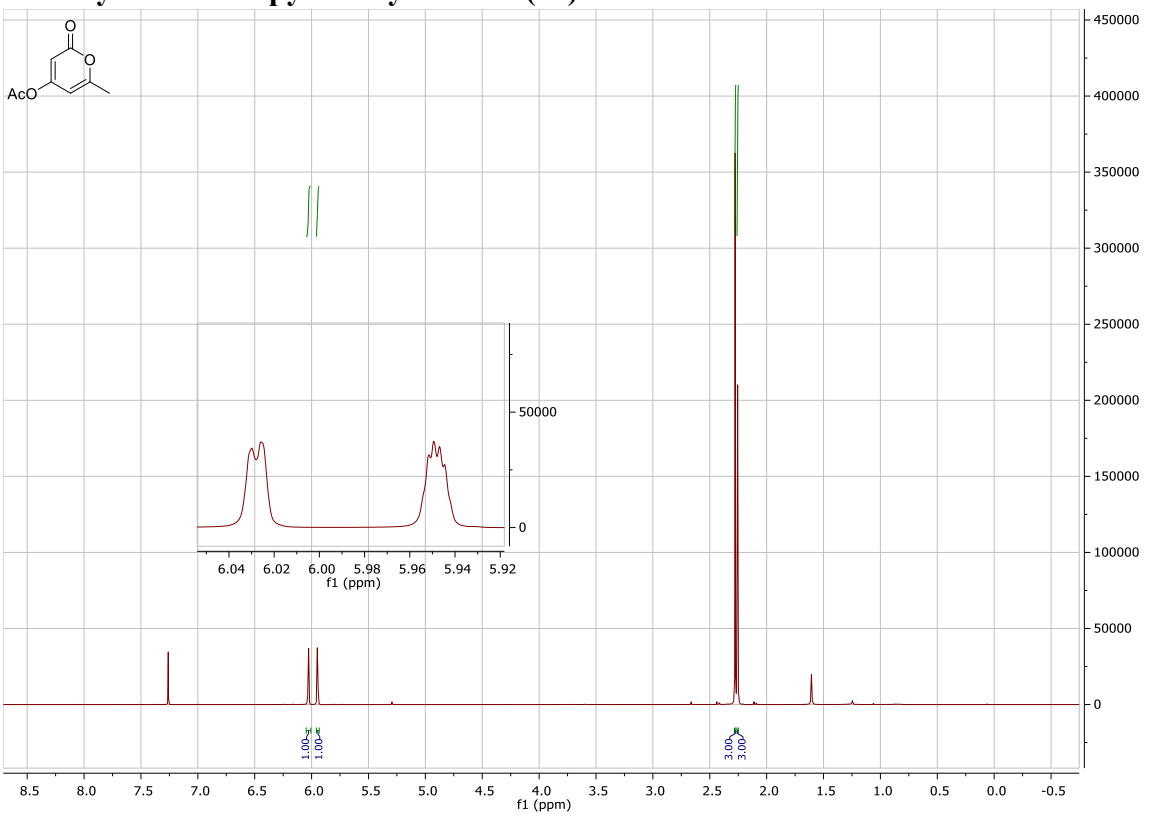

Figure P1 ^{1}H NMR for **49**, 400 MHz, $CDCl_3$.

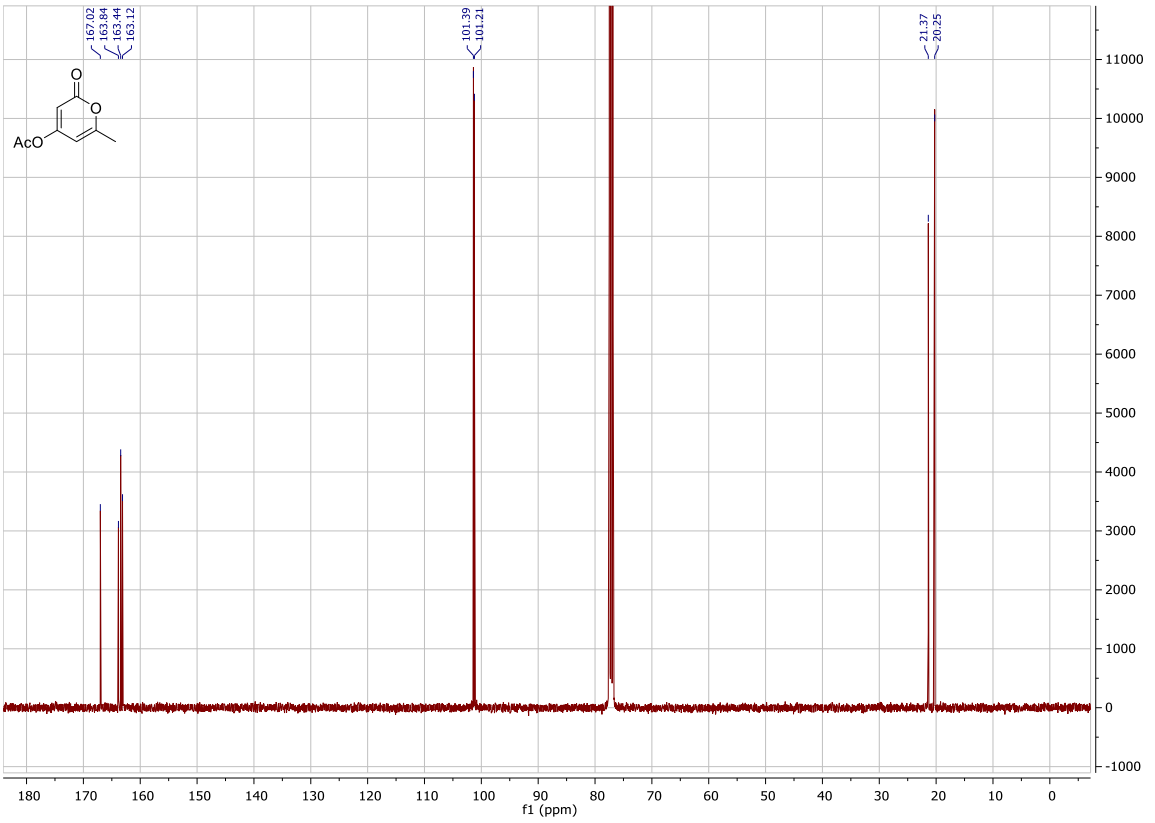

Figure P2 ^{13}C NMR for **49**, 101 MHz, $CDCl_3$.

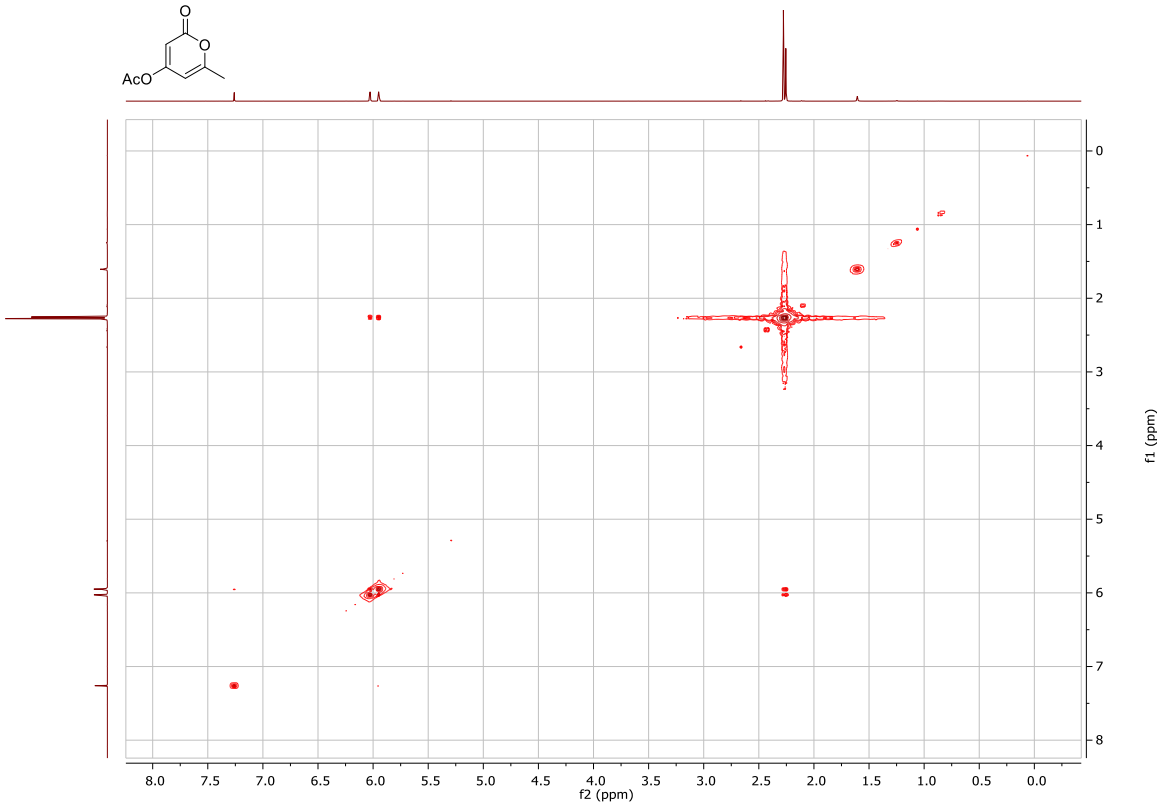

Figure P3 ^{1}H-^{1}H COSY for **49**, 400 MHz, $CDCl_3$.

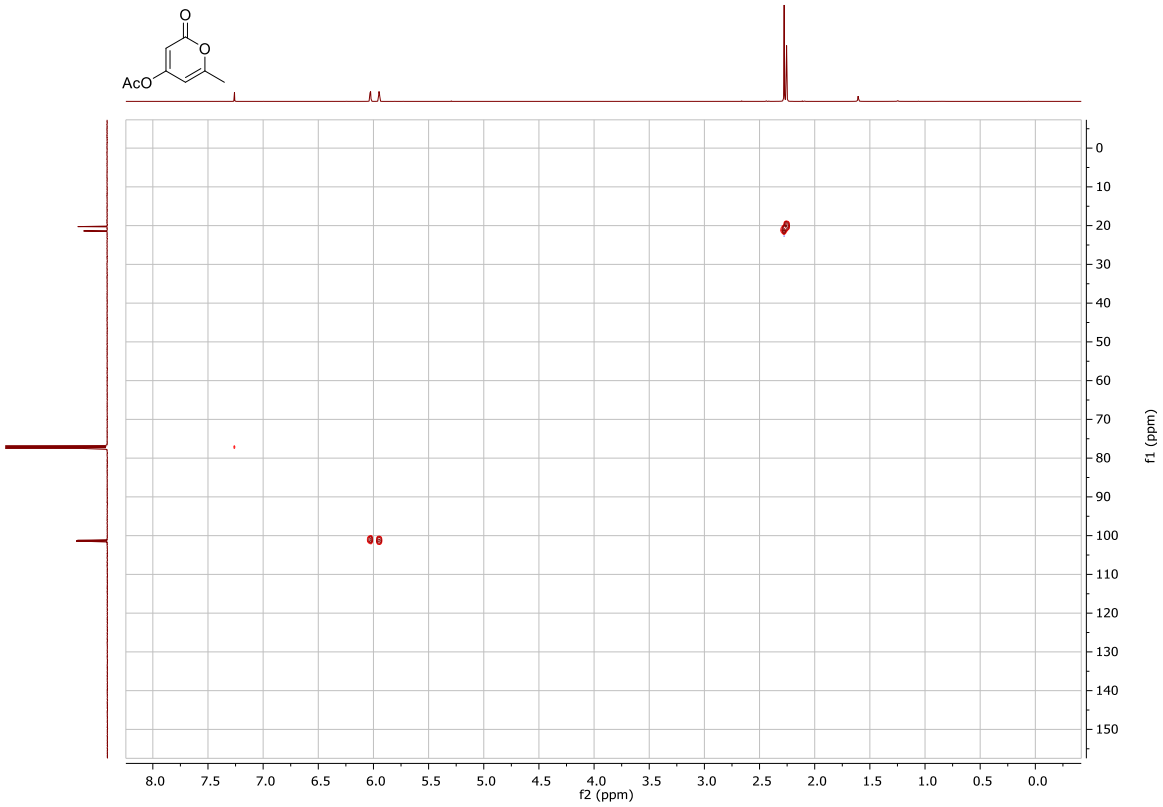

Figure P4 ^{1}H-^{13}C HSQC for **49**, 400 MHz, $CDCl_3$.

Q 6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-oxo-2*H*-pyran-4-yl acetate (50)

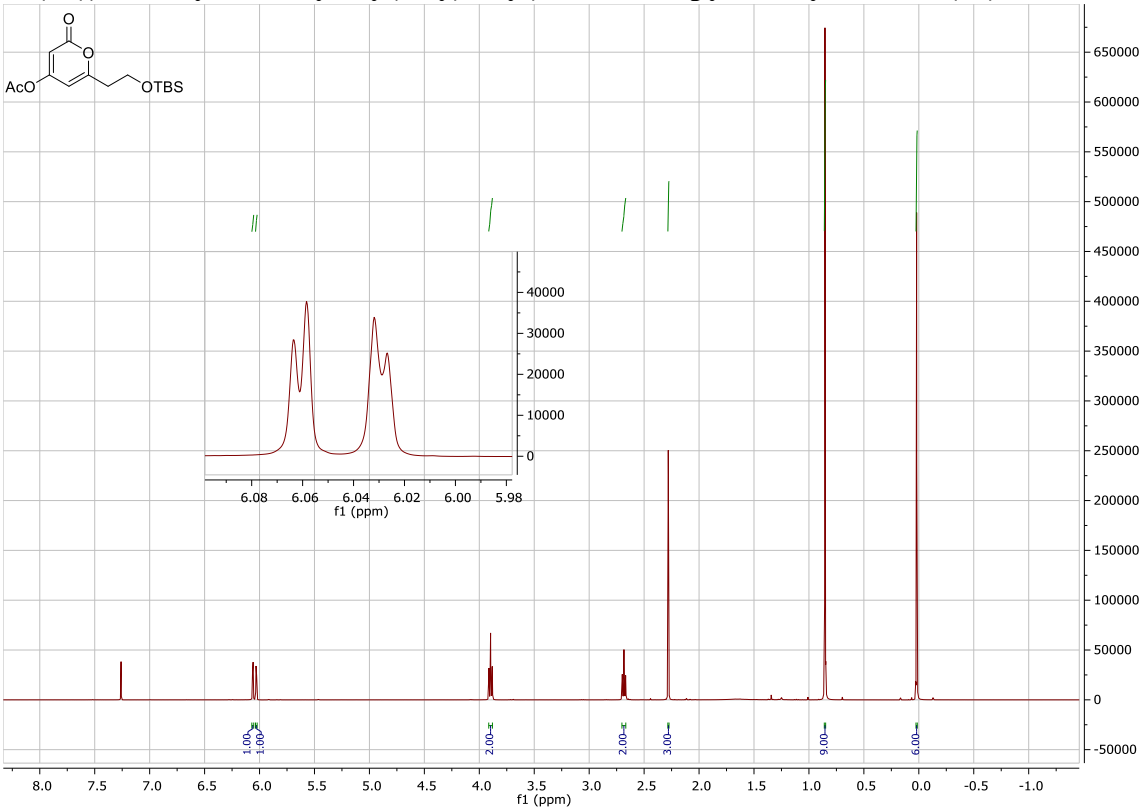

Figure Q1 ^{1}H NMR for **50**, 400 MHz, $CDCl_3$.

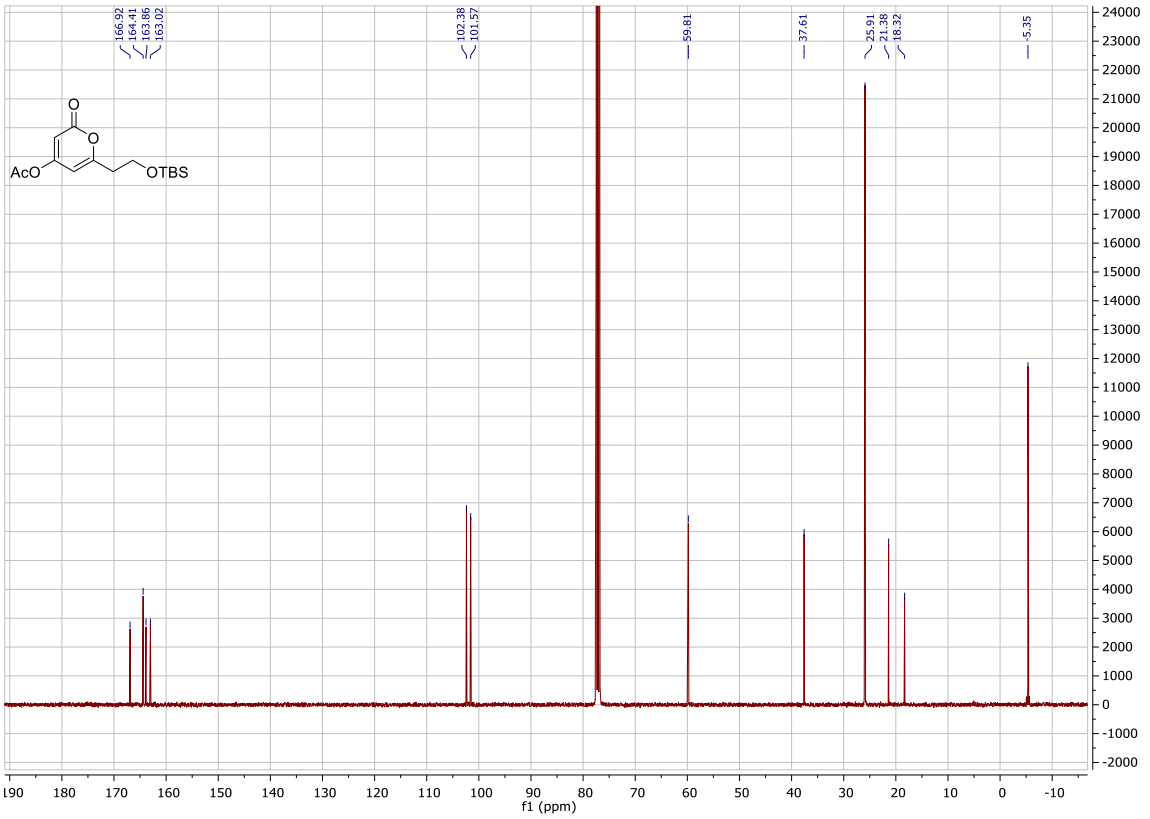

Figure Q2 ^{13}C NMR for **50**, 101 MHz, $CDCl_3$.

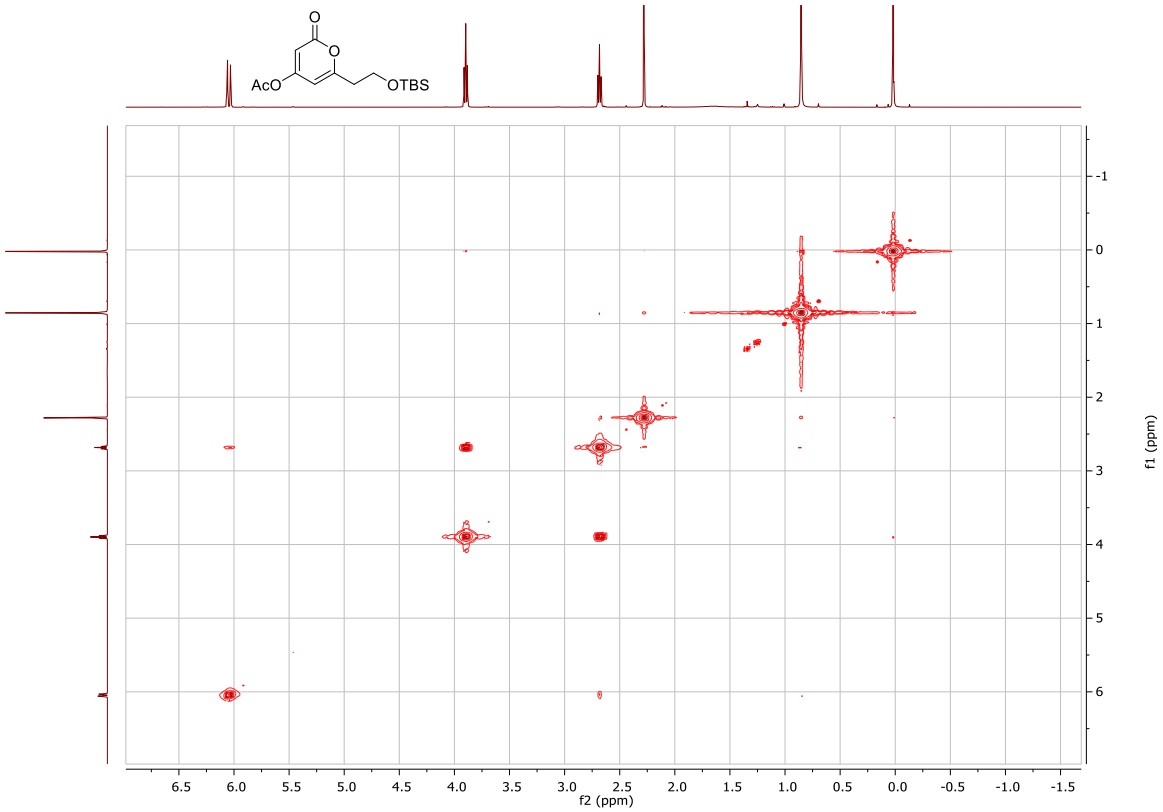

Figure Q3 ^{1}H-^{1}H COSY for **50**, 400 MHz, $CDCl_3$.

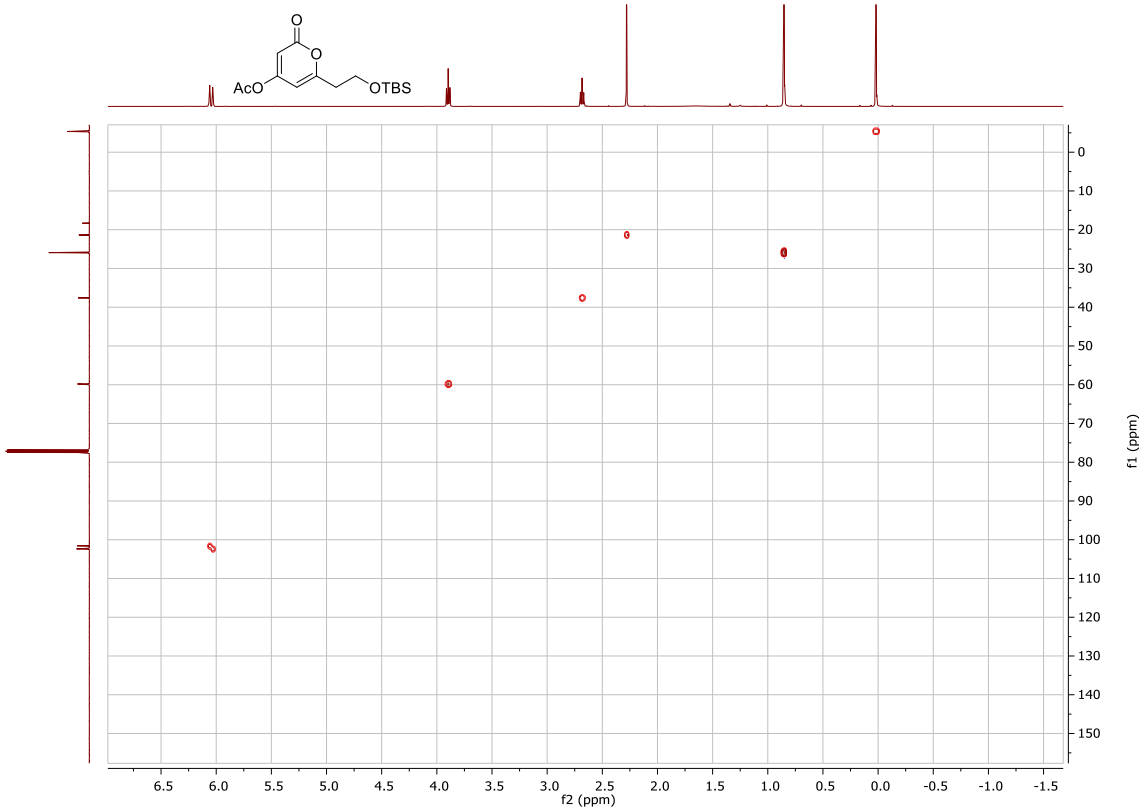

Figure Q4 ^{1}H-^{13}C HSQC for **50**, 400 MHz, $CDCl_3$.

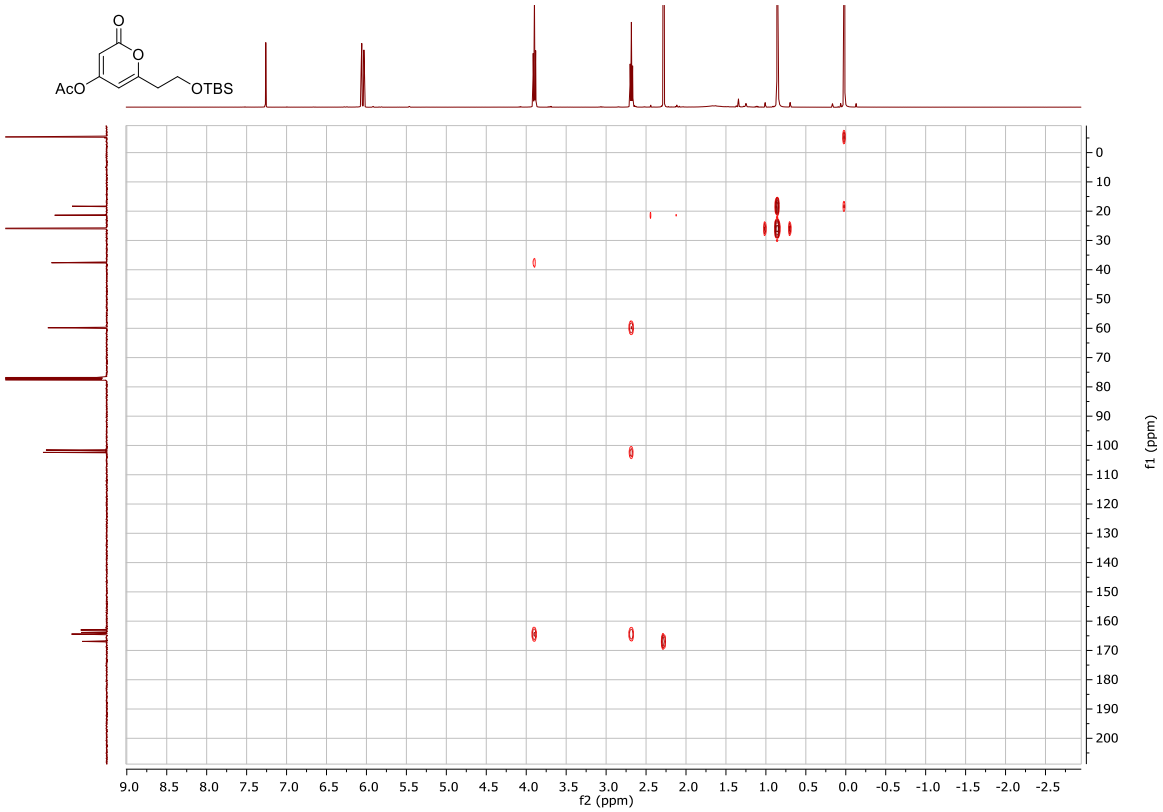

Figure Q5 ^{1}H-^{13}C HMBC for **50**, 400 MHz, $CDCl_3$.

R *Tert*-butyl 7-hydroxy-3-oxohept-4-ynoate (55)

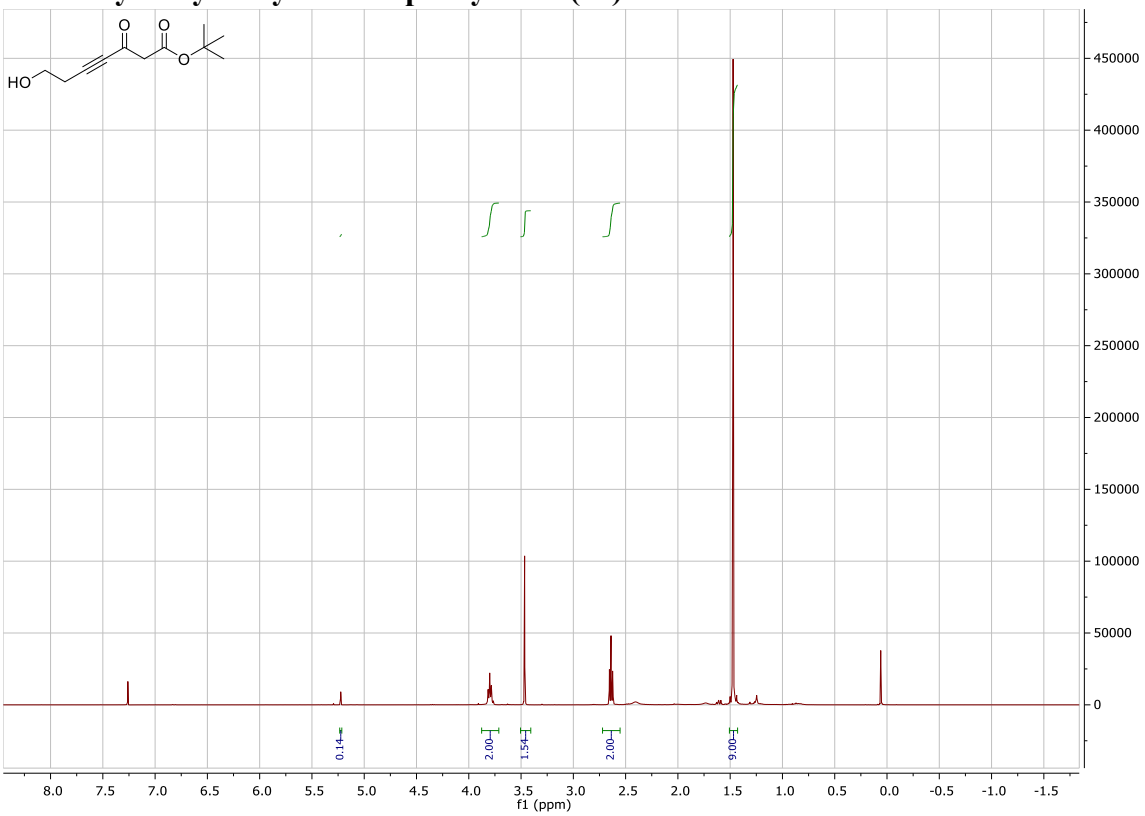

Figure R1 ^{1}H NMR for **55**, 400 MHz, $CDCl_3$.

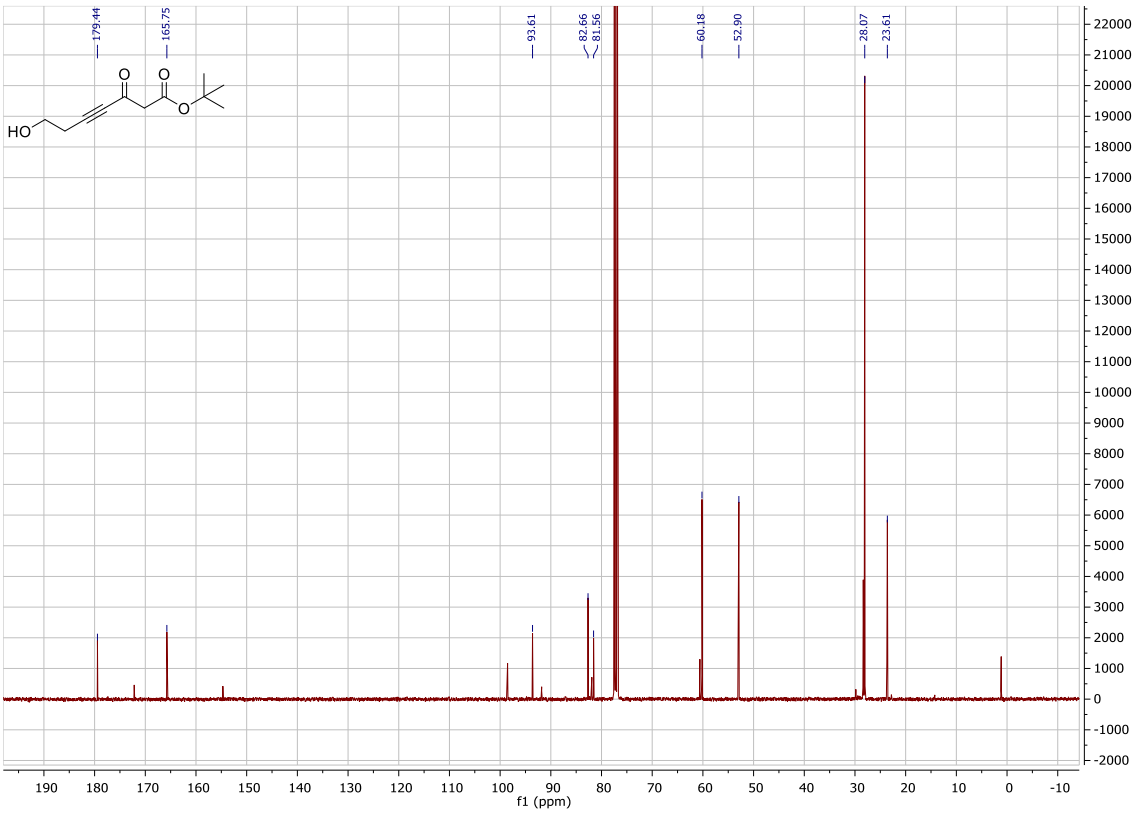

Figure R2 ^{13}C NMR for **55**, 101 MHz, $CDCl_3$.

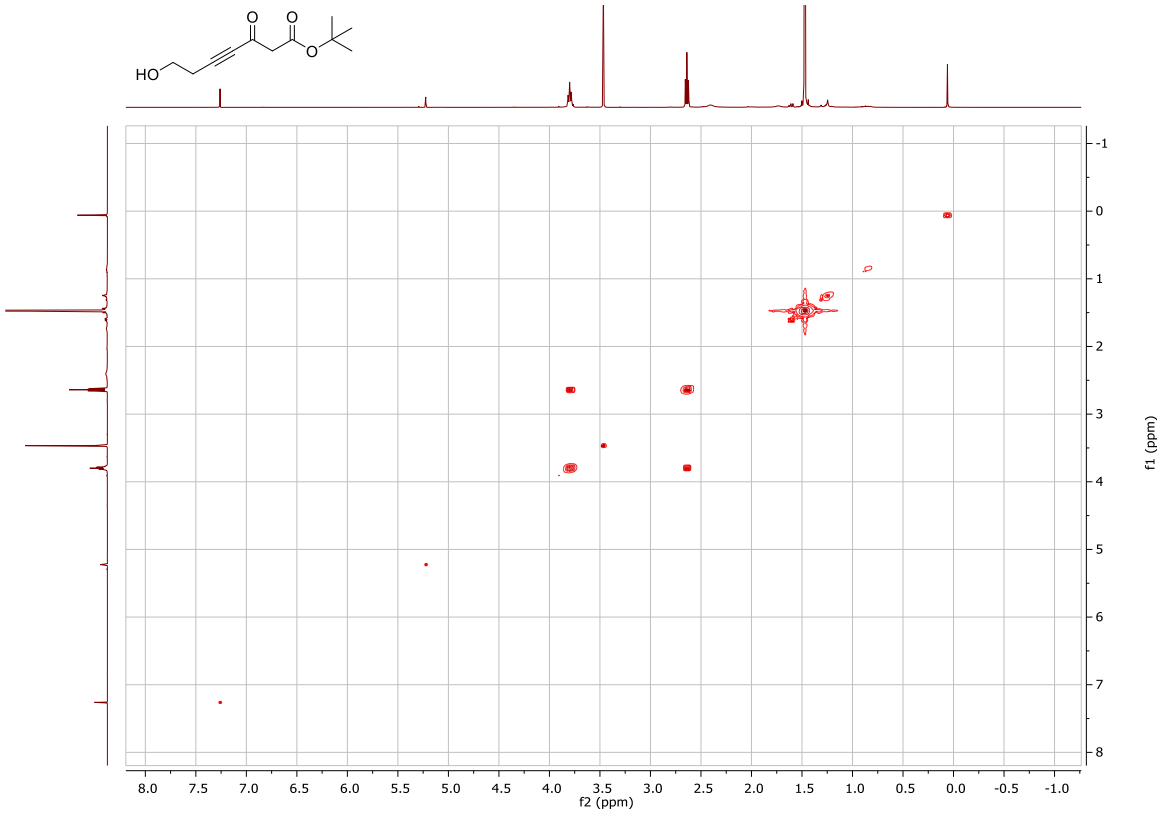

Figure R3 ^{1}H-^{1}H COSY for **55**, 400 MHz, $CDCl_3$.

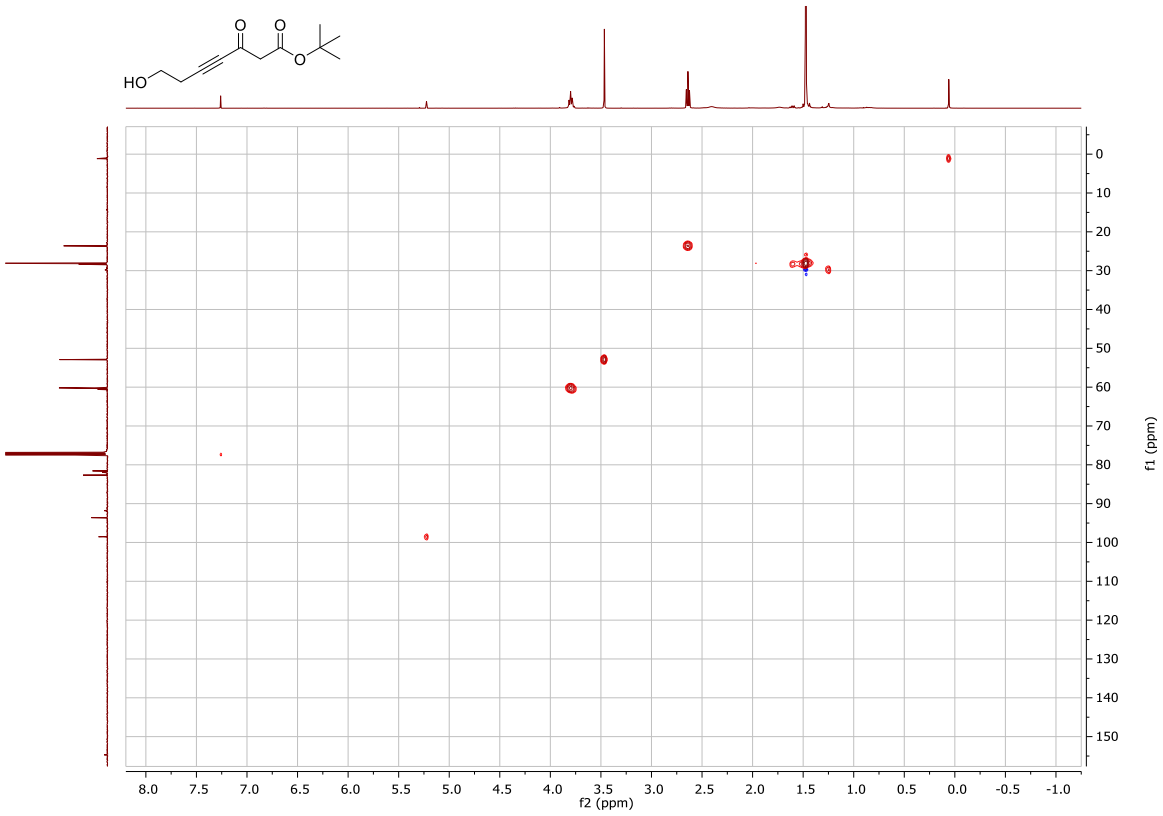

Figure R4 ^{1}H-^{13}C HSQC for **55**, 400 MHz, $CDCl_3$.

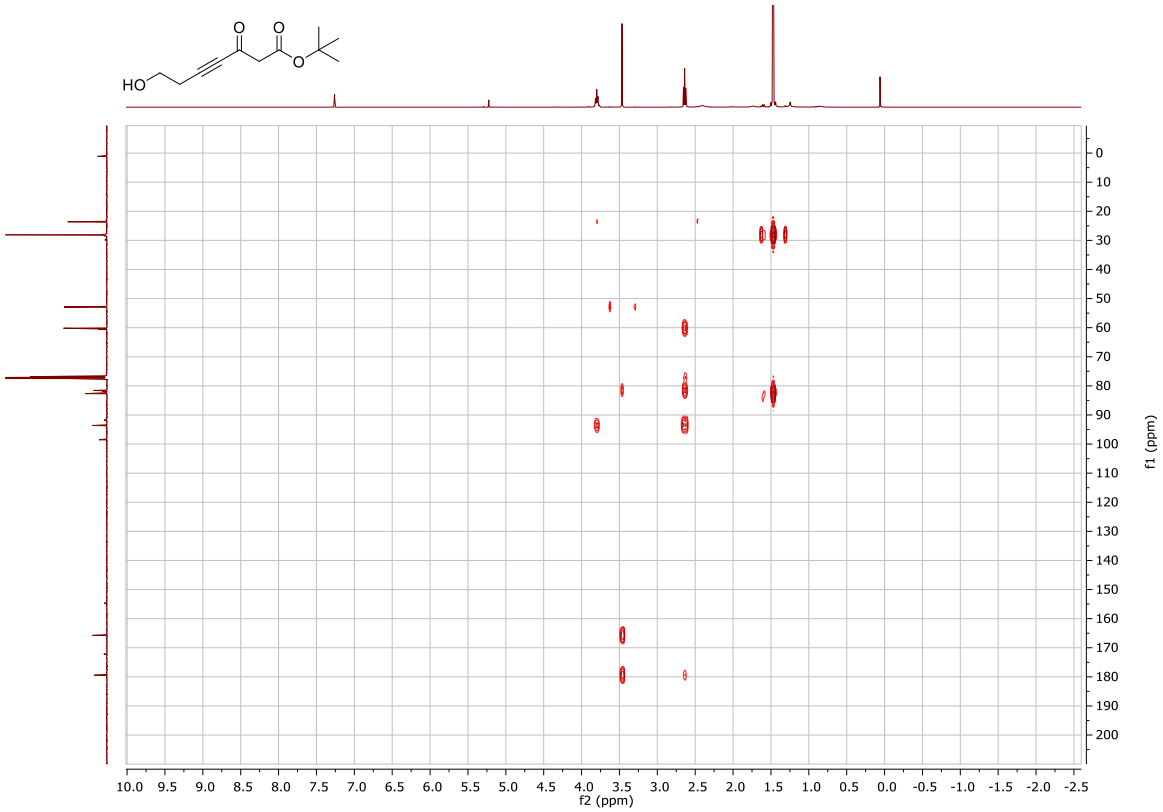

Figure R5 ^{1}H-^{13}C HMBC for **55**, 400 MHz, $CDCl_3$.

S (*E*)-(2-nitrovinyl)benzene (60)

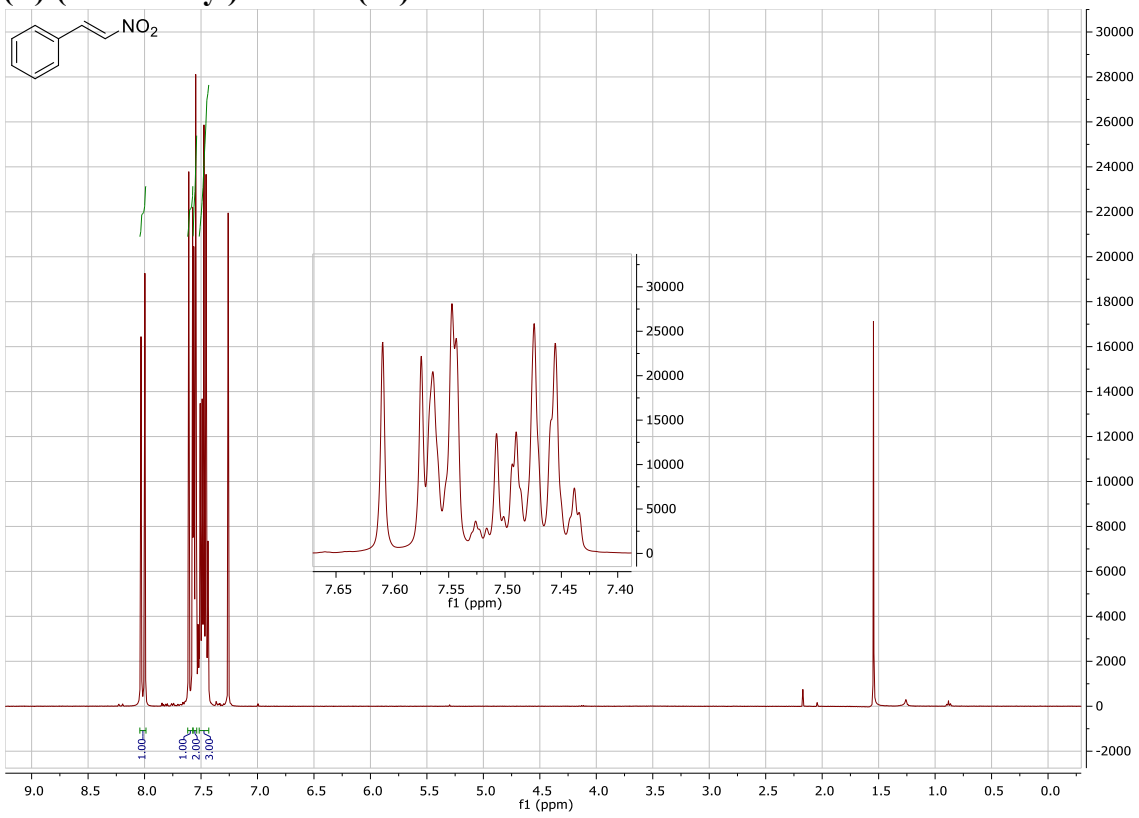

Figure S1 ^{1}H NMR for **60**, 400 MHz, $CDCl_3$.

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