Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Natural Sciences
Department of Chemistry

Victor Hubert Pierre Noilhan

Total Synthesis of Dothideopyrones A-D

Master's thesis in Chemistry
Supervisor: Eirik Johansson Solum
June 2021

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Declaration

I hereby declare that work presented in this thesis have been conducted in full accordance with the rules and regulations for the Master degree of chemistry at the Norwegian University of Sciences and Technologies

Trondheim, June 1st 2021

Victor Hubert Pierre Noilhan

Acknowledgements

The work presented has been done at the Department of Chemistry of the Norwegian University of Science and Technology, Trondheim, from September 1, 2020 to May 31, 2021. It has been supervised by Professor Eirik Johansson Solum.

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I wish to also thank David Liwara, for the conversations we were able to share during our work that were always helpful to use another perspective, and for the mutual help we beneficiated from each other that allowed us to move forward during the most complex parts of our respective projects.

Finally, I would thank my friends and family that supported me during my master at NTNU in a particular period.

Abstract

Dothideopyrone A-D [**1**-**4**] have been isolated from the dothideomycete LRUB20, an endophytic fungus species living in the plant *Leeea rubra*.[1] Their cytotoxic activities have been tested and appeared to be low, but due to the low amount of Dothideopyrones extracted from the natural source, a synthesis pathway had to be found to allow antimicrobial test. The aim of this master thesis was to design and perform the total synthesis of the compounds Dothideopyrone A-D [**1**-**4**].

A first linear synthesis pathway has been designed, starting from a comercially available substituted *α*-pyrone, but quickly appeared to not be feasible due to the difficulties encountered during the Carreira alkynylation step, which is suspected to not be compatible with a *α*-pyrone substrate.

A second convergent synthesis pathway have been designed, which includes the formation and coupling of two building-blocks and the formation of the *α*-pyrone ring, appeared to be more promising. However, the synthesis was not completed due to a lack of time, and all reactions have been successfully conducted with good yield until compound **20**. An attempt to synthesize compound **21** have been made but did not resulted in the isolation of the desired product. This second synthesis pathway will be continued by a new research team, using synthesised compound **14** and **17**, to evaluate the antimicrobial properties of the Dothideopyrones A-D [**1**-**4**].

Sammendrag

Dothideopyrone A-D [**1**-**4**] har blitt isolert fra dothideomycete LRUB20, en endofytisk sopp som lever i planten *Leeea rubra*.[1] Deres cytotoksiske aktiviteter har blitt testet og ser ut til å være lave, men på grunn av den lave mengden av Dothideopyrones ekstrahert fra den naturlige kilden, en syntesevei måtte bli funnet for å tillate antimikrobiell testing. Målet med denne masteroppgaven var å designe og utføre den totale syntesen av forbindelsene Dothideopyrone A-D [**1**-**4**].

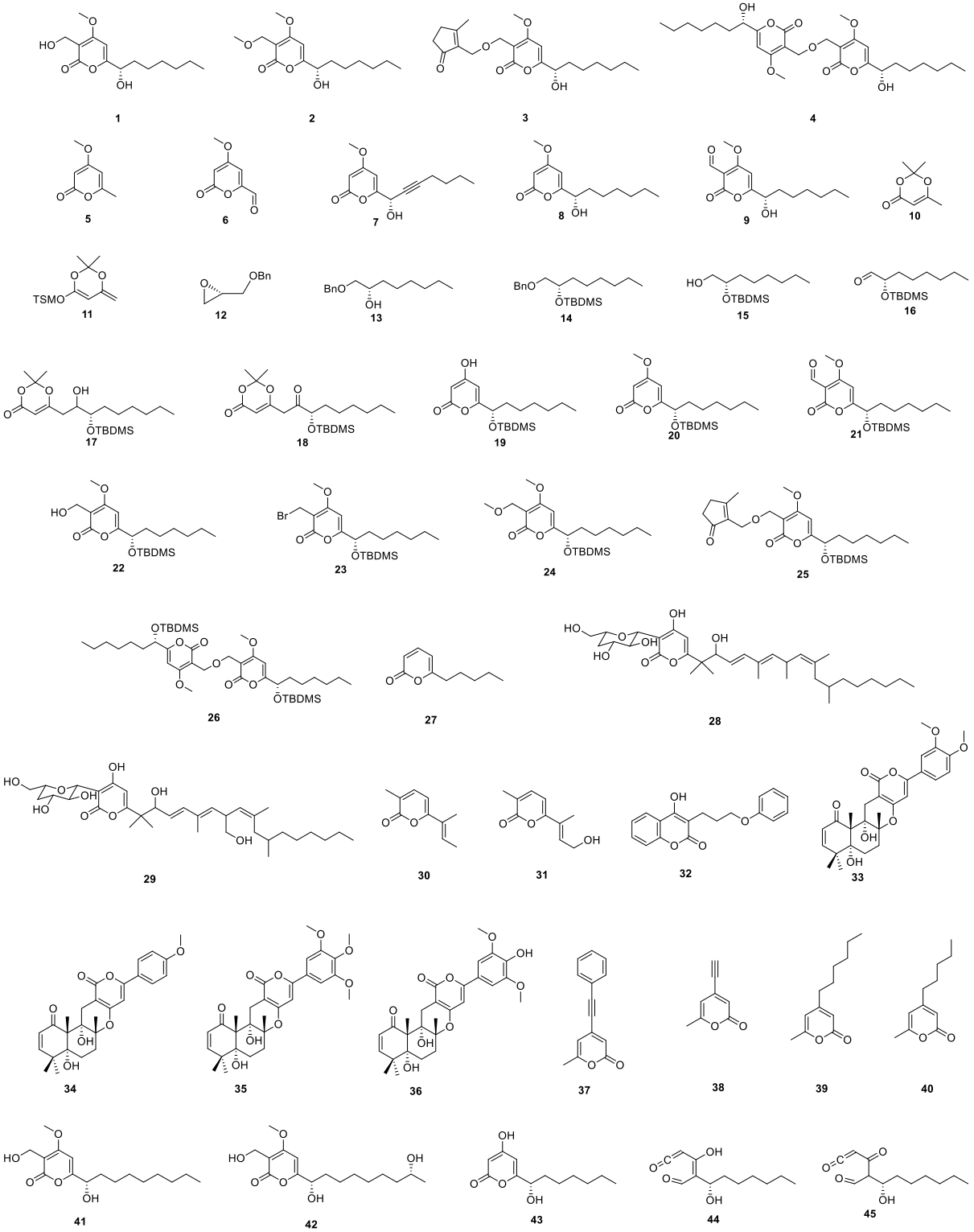
En første lineær syntetisk rute er designet, basert på en kommersielt tilgjengelig substituert *α*-pyron, men syntes raskt ikke å være mulig på grunn av vanskelighetene som oppstod under Carrera-alkynyleringstrinnet, som mistenkes å være uforenlig med et α-pyronsubstrat.

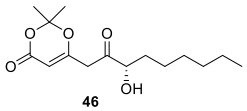
En annen konvergent syntetisk rute er designet, som inkluderer dannelse og kobling av to byggesteiner og dannelsen av *α*-pyronringen, syntes å være mer lovende. Syntesen ble imidlertid ikke fullført på grunn av tidsmangel, og alle reaksjoner har blitt utført i godt utbytte inntil forbindelse **20**. Et forsøk på å syntetisere forbindelse **21** er gjort, men resulterte ikke i isolering av det ønskede produkt. Denne andre syntetiske ruten vil bli videreført av et nytt forskningsteam, som bruker syntetiserte forbindelser **14** og **17**, for å evaluere de antimikrobielle egenskapene til Dothideopyrone A-D [**1**-**4**].

Abbreviations & symbols

AIDS	Acquired Immunodeficiency Syndrome
br	Broad signal
cat.	Catalyst
con	Connection
δ	Chemical shift (ppm)
DCM	Dichloromethane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
EAS	Electrophilic aromatic substitution
eq	Equivalent
FGA	Functional group addition
FGI	Functional group interchange
FGR	Functional group removal
h	Hour(s)
HIV	Human Immunodeficiency Virus
J	Coupling constant (Hz)
LDA	Lithium diisopropylformamide
m	Multiplet
mg	Milligram
min.	Minute(s)
p	Quintet
ppm	Parts per million
q	Quartet
RF	Retention factor
Rt	Room temperature
s	Singlet
S_n2	Bimolecular nucleophilic substitution
t	triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS/TBS	*tert*-butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
^{1}H NMR	Proton nuclear magnetic resonance
^{13}C NMR	Carbon nuclear magnetic resonance

Numbered compounds





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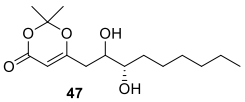

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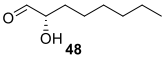

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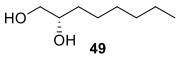

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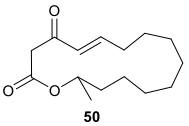

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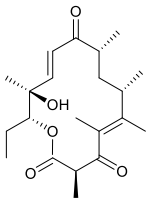

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1. Introduction

Traditionally natural products and their derivatives have been mainstays of antibiotic drugs.[2] Shaped by the evolutionary process, complex organic molecules have emerged from natural sources and from there gone into the clinic for the treatment of various kinds of infections. However, over the last decades, the focus in drug development has shifted into using synthetic compounds and target-based discovery methods. This along with shifting economic and regulatory issues, conspire to move investment in research and development away from the antibiotics arena.[3, 4] The result is a lack of antibiotic drug discovery and hence few new drug candidates reaching the clinic. This situation is in contradiction with the emergence of multi-resistant bacteria that is urging toward the development of new antibiotics to prevent the multiplication of new untreatable bacterial infections globally threatening public health.[5, 6]

Fungal endophytes normally colonize living internal tissues of plants without causing any obvious negative effects or external symptoms. Endophytic fungi may offer either significant benefit to their host plants by producing secondary metabolites that provide protection and survival advantage to the plants. Particular secondary metabolites produced by endophytic fungi are believed to benefit the host plants as they may be plant growth regulators, antimicrobials, antivirals, and insecticidals, or even mediate resistance to some types of abiotic stress.[7-9] Among the metabolites of interest, the Dothideopyrones A-D [**1**-**4**] raised the interest of the research group.

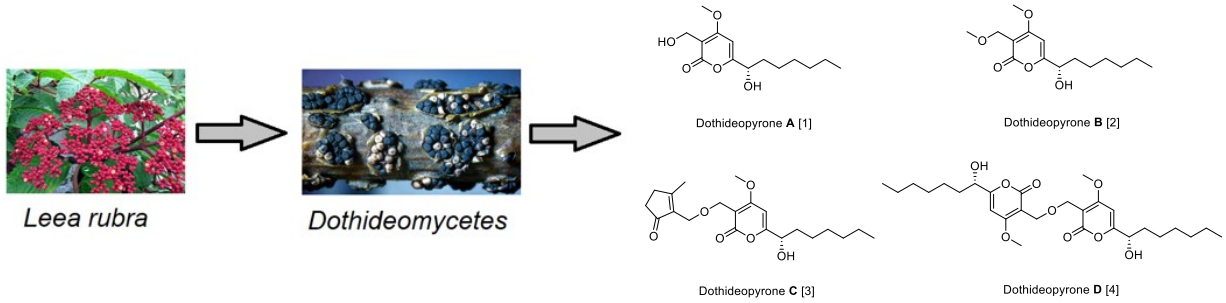
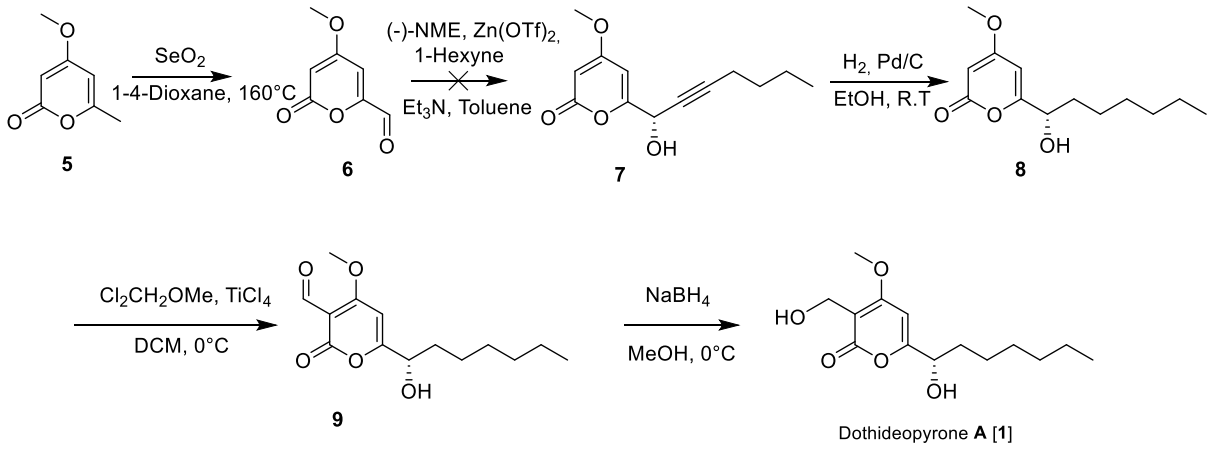


Figure 1.1 : Dothideopyrones A-D [**1**-**4**]

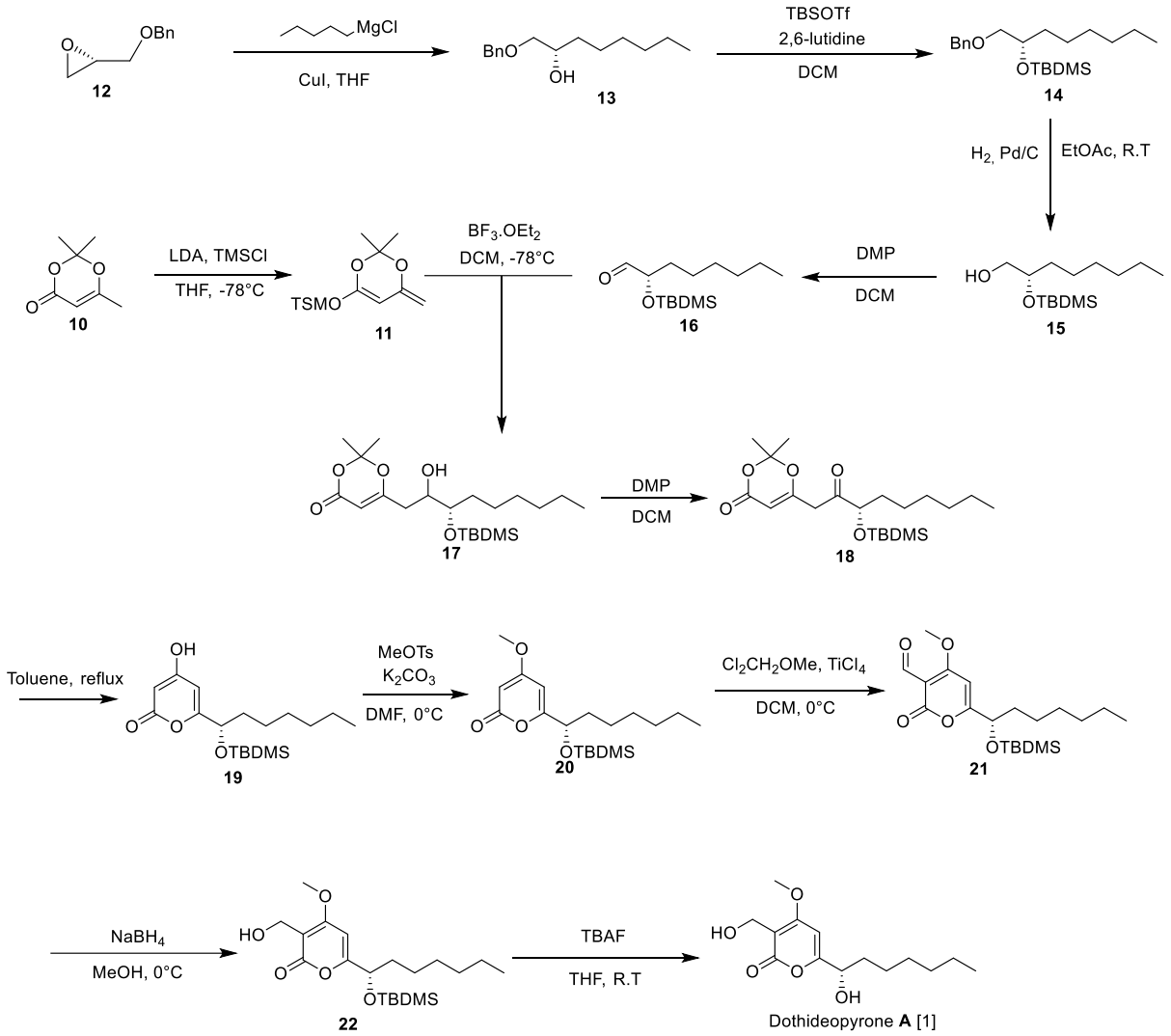
In total 12-126 mg of Dothideopyrone A-D [**1**-**4**] were isolated from the extraction of Dothideomycetes. Initial biological effects proved the compounds not to be cytotoxic in cellular assays using nine different cell lines.[1] However, the compounds were not tested for their ability to inhibit bacterial growth. Within this project we aim to synthesize Dothideopyrone A-D [**1**-**4**] and evaluate the antibacterial properties of the synthesized compounds due to the difficulty to extract a significative amount of those compounds directly from the natural source.

In the initial proposed synthesis, we aimed to use a Carreira alkynylation as a key step to introduce alkyl side chain to the 2-pyrone aldehyde. To achieve the 2-pyrone aldehyde **6** a Riley oxidation of the methyl group was employed. In order to secure the right stereochemistry of the secondary alcohol, obtained after alkynylation with 1-hexyne, (-)-*N*-methyl ephedrine (NME) was used in the reaction as chiral auxiliary. After hydrogenation of the alkyne **7**, a Williamson ether synthesis was proposed to be performed to obtain the methoxy group at the position 4 of the pyrone ring. The installation of the primary alcohol via a Rieche formylation followed by a reduction of the freshly formed carbonyl **9** was then planned to be employed to complete the synthesis of Dothideopyrone A [**1**] in 4 steps, see scheme 1.1.



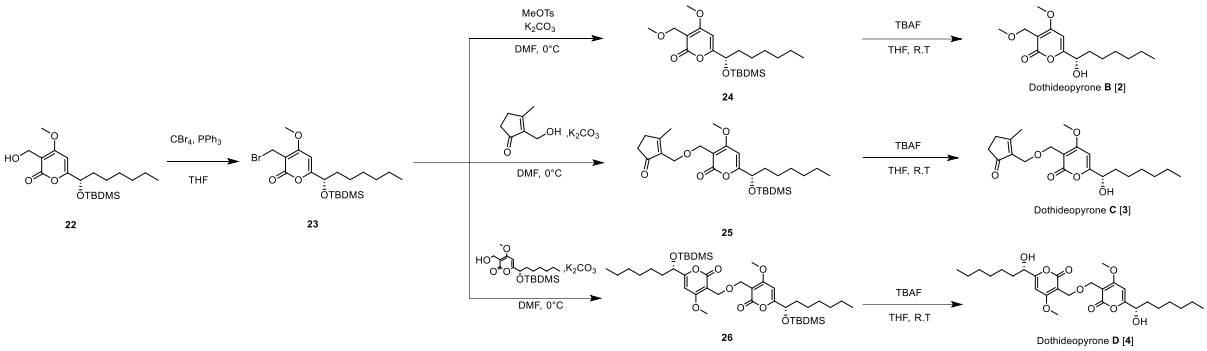
Scheme 1.1 : Proposed linear synthesis of the Dothideopyrone **A** [**1**]

However, this first synthesis pathway was not successful due to the lack of consistency in the results obtained with the Carreira alkynylation, which failed at each try in this project despite the different procedures used. Even if there is no certainty in the cause of those failures, it was suspected that the condition of the Carreira reaction was not suitable to be used on an *α*-pyrone substrate. Considering the difficulties to do the Carreira alkynylation, a new synthesis pathway was elaborated, see scheme 1.2:



Scheme 1.2 : Proposed convergent synthesis of the Dothideopyrone **A** [**1**]

This new pathway consisted of synthesize the 6-substitued 2-pyrone via a vinylogous Mukaiyama aldol-type reaction with the suitable synthesized aldehyde **16**, followed by an oxidation and a *oxo*-Diels-Alder reaction, and then to obtain the Dothideopyrone A [**1**] by performing a methylation of the hydroxyl group on the pyrone **19** and a formylation followed by a reduction to bring the methoxy group at the position 3 of the pyrone. Dothideopyrone B [**2**], C [**3**] and D [**4**] could be then easily obtained via the TBS-protected Dothideopyrone A **22**, by performing a bromination and a Williamson reaction with the suitable alcohol, see scheme 1.3:



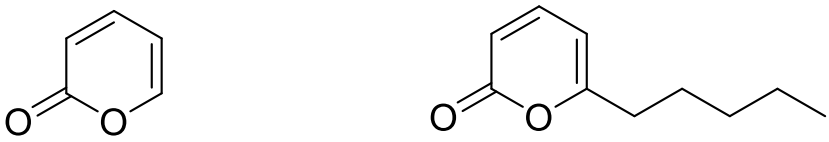
Scheme 1.3 : Proposed synthesis for Dothideopyrones B-D [**2**-**4**]

2. Theory

2.1. 2-pyrones

2.1.1. Previously identified bioactive 2-pyrones

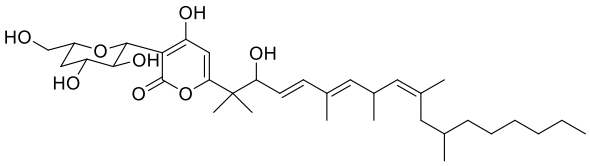
2-pyrone (or *α*-pyrone) is an unsaturated organic compound presenting a cyclic ester function, having for molecular formula $C_5H_4O_2$. 2-pyrone is an abundant motif in natural products, and sources of 2-pyrone compounds is extremely diverse: fungus, plants, animals, bacteria, insects.[10] The importance of 2-pyrone compounds as secondary metabolites has been widely studied and anti-microbial, anti-fungal, cytotoxic, phytotoxic and neurotoxic-properties have been observed. The described properties are giving the organisms presenting those 2-pyrones compound a significative selective advantage that justify the presence and abundance of naturally occurring 2-pyrones.[11] An explicit example can be found in the 6-pentyl-*α*-pyrone **27**, a metabolite of *Trichoderma Asperellum,* which notably induce better resistance in *Arabidobsis thaliana* when co-cultivated together against *Botrytis cinerea* and *Alternaria brassicicola*, two common necrotrophic fungus for many plant species.[12]



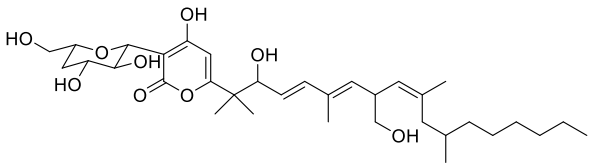
2-pyrone ring 6-pentyl-α-pyrone **27**

Figure 2.1 : 2-pyrone ring and the bioactive 6-pentyl-*α*-pyrone **27**

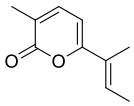
2-pyrones raised the interest of medicinal and organic chemist and many possible therapeutical uses for 2-pyrones have been found since then. Works on extracts from rice cultures *Fusarium semitectum* resulted in the isolation and characterization of two *α*-pyrone **28** and **29** that showed important anti-fungal activity against agent of human mycoses.[13] Gibepyrones A [**30**] and B [**31**] isolated from *Gibberella fujikuroi* showed anti-microbial properties against *Candida albicans* and *Staphylococcus aureus*, two pathogenic agents for humans.[14]



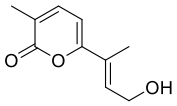
Bioactive Deoxyfusapyrone **28**



Bioactive Fusapyrone **29**



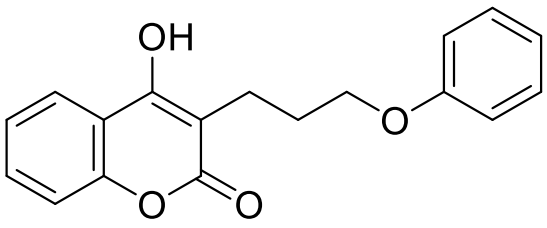
Gibepyrone **A** [**30**]



Gibepyrone **B** [**31**]

Figure 2.2 : Four bioactive compounds [**28**-**31**] against human pathogens presenting a 2-pyrone moiety

Works on the inhibition of the HIV (Human Immunodeficiency Virus) protease – which is a viral agent responsible of the replication of the HIV, and an important target for the treatment of AIDS- allowed to discover 2-pyrone derivatives with therapeutical interest.[15] 4-hydroxy-2-pyrones derivatives have been widely studied and some compounds showed remarkable potency as HIV protease inhibitors. 4-hydroxy-2-pyrone derivatives have become one of the most predominant classes of anti-HIV agent.[16, 17]



Warfarin [**32**]

Figure 2.3 : Warfarin [**32**], registered on the WHO List of Essential Medicines

2-pyrones appeared to have some interest for others medical applications. Arisugasin A [**33**], a 2-pyrone derivative presenting a 6-aryl-4-hydroxypyrone moiety, showed great effectiveness as an acetylcholinesterase inhibitor, a type of bioactive molecule of great interest for the treatment of neurodegenerative diseases, and could be an interesting lead for the treatment of Alzheimer's disease or dementia.[18, 19] Alteration of this compound and other

derivatives (Arisugacin B [**34**], Territrem B [**35**] and Territrem C [**36**]) presenting the 2-pyrone moiety has been isolated, and the presence of the 2-pyrone moiety has been shown to be crucial for the properties of the compounds as inhibitors of Acetylcholinesterase.[19]

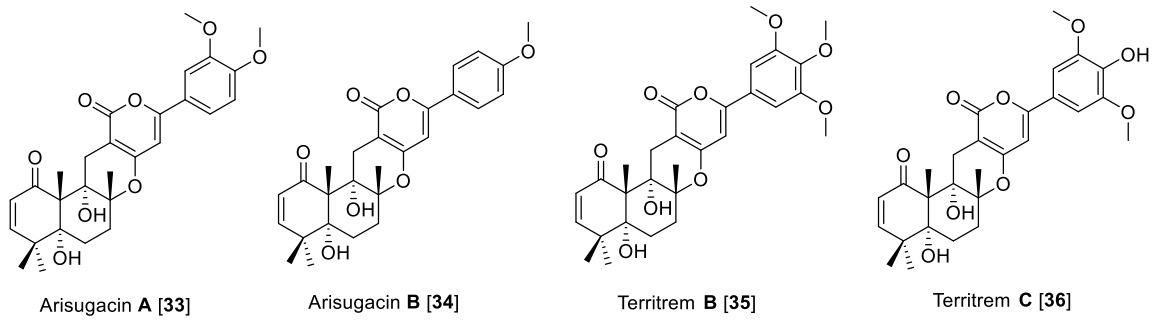


Figure 2.4 : Territrem derivatives [**33**-**36**] with Acetylcholinesterase inhibition activity

2-pyrone compounds can also show cytotoxic activities making the molecules good leads for drug development for cancer treatments. New methods of synthesis for 2-pyrone derivatives allow the synthesis of large array of new derivatives. Fairlamb and co-workers used modern Pd-catalysed cross-coupling processes to synthesized a wide array of 4-substitued-6-methyl-2-pyrone.[20] Screening for cytotoxic and anti-microbial properties showed promising results, as most of the compounds were presenting interesting bioactive properties. Over one third of the compounds presented some anti-proliferation properties to specific cancer cell lines, and anti-microbial screening revealed some potent inhibitors for a number of fungi, bacteria and yeast.[20, 21]

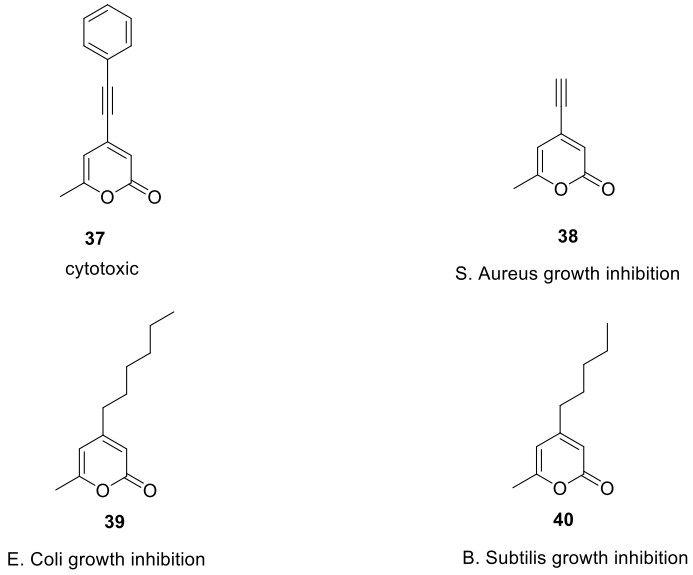


Figure 2.5 : Compound [**37**-**40**] synthesized by Farlamb *et. al.*, mentioned with their bioactive properties

This non-exhaustive list of potential therapeutical uses of naturally occurring or synthetic 2-pyrone compounds is encouraging for the discovery of new bioactive 2-pyrones.

2.1.2. Pyrones reactivity

2-Pyrone are a 6 membered heterogenocylic compound comporting a cyclic ester function and 5 sp^2-hybridized carbons. The 2-pyrone present both aliphatic and aromatic behaviour regarding its reactivity and physical properties, thus 2-pyrones can be implicated in a wide range of reactions, including electrophilic and nucleophilic substitution, cyclization, ring transformation, cycloaddition and photochemical reactions , making it a very flexible synthon opening the way to many derivatives.[22]

Also, due to the increasing interest of organic and medical chemist of 2-pyrones, a consequent number of processes have emerged to prepare new 2-pyrones that cannot be covered exhaustively here, the following will focus on processes relevant for the work performed in order to synthesize the Dothideopyrones A-D [**1**-**4**].[23]

2.1.3. Dothideopyrones

Endophytic fungi is a group of fungi organism that live within a plant without being the cause of any disease to the latter.[8] Those kind of organisms are presumed to be beneficial to the host plant, due to their numerous bioactive metabolites, more specially secondary metabolites, that are believed to offer to the plant antimicrobial, insecticidal, antiviral and other similar protections.[7]

Extracts from two species of endophytic fungus *dothideomycete sp* (LRUB20 & EL003334) allowed the isolation and characterization of 6 new compounds presenting a 2-pyrone moiety : Dothideopyrone A-D [**1**-**4**] (from LRUB20)[1] and Dothideopyrone E-F [**41**,**42**] (from EL003334).[24]

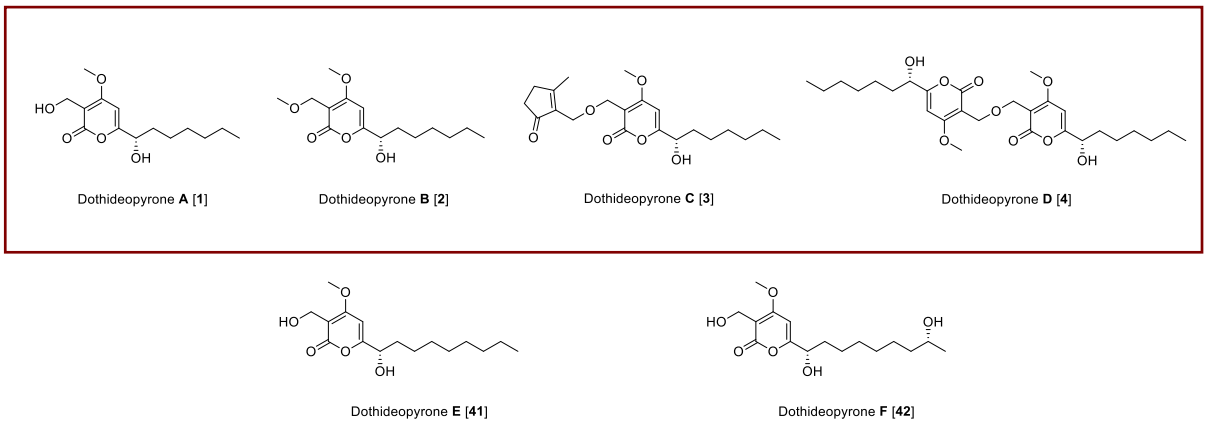


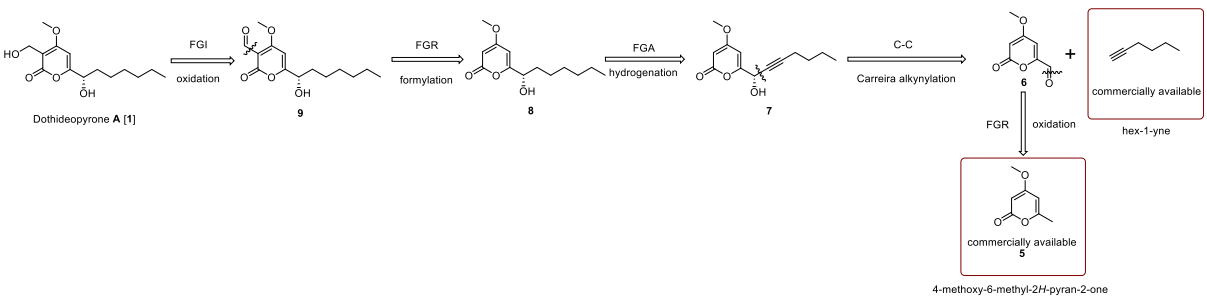
Figure 2.6 : Dothideopyrones [**1**-**4**,**41**,**42**] isolated from endophytic fungus, A-D [**1**-**4**] are the targets of the thesis

Dothideopyrone A-C [**1**-**3**] have been assessed for their cytotoxicity against 9 cancer cell lines and only showed weak to no activity. Dothideopyrone D [**4**] showed a medium cytotoxic activity but none of them appeared to be a promising lead compound for new cancer treatments.[1] Dothideopyrone E-F [**41**,**42**] did not show better cytotoxicity activity, however Dothideopyrone F [**42**] expressed anti-inflammatory properties on a type of microglia cell. This property could limit neuroinflammatory factors that can lead to neurodegenerative diseases.[24]

Still, the anti-microbial potential of the Dothideopyrones A-F [**1**-**4**,**41**,**42**] has not been assessed yet.

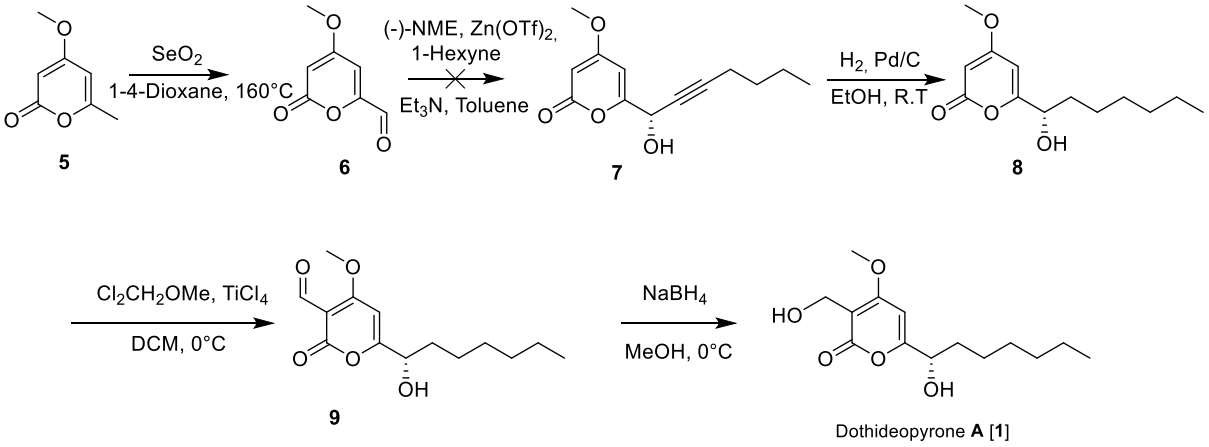
2.2. Retrosynthesis analysis

The project aimed at the synthesis of the compounds mentioned in the previous part, the Dothideopyrones A-D [**1**-**4**]. The strategy to synthetize Dothideopyrone A [**1**] was not obvious and needed further investigations before being performed. A first retrosynthetic analysis is presented below for the Dothideopyrone A [**1**] in scheme 2.1:



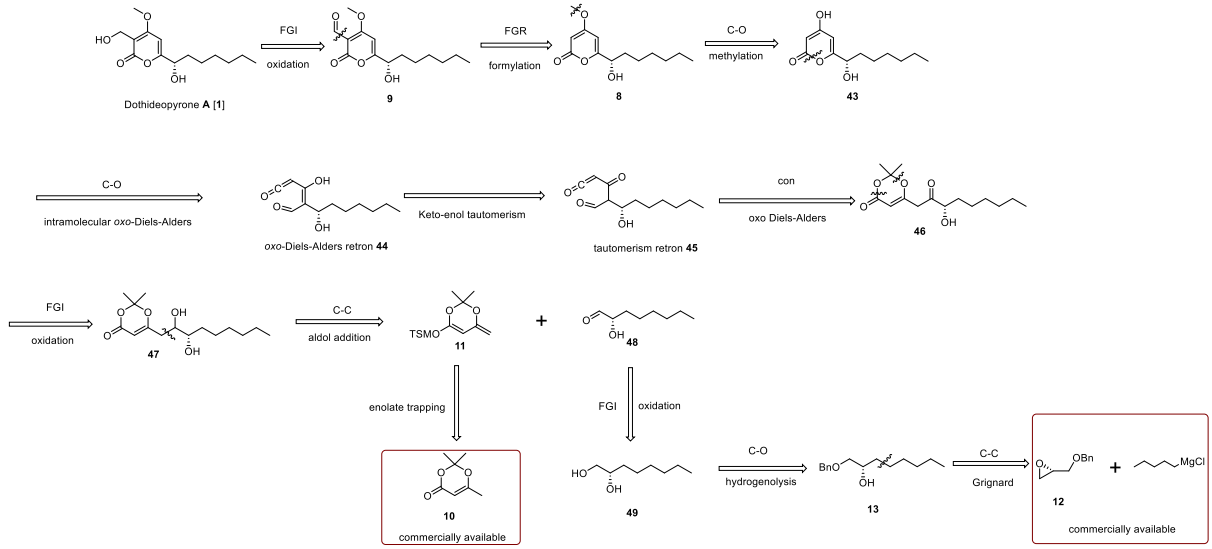
Scheme 2.1 : Retrosynthetic analysis, leading to a linear synthesis strategy

From this first analysis, a linear synthesis strategy emerged. The planned synthesis consisted of forming the chiral secondary alcohol and to connect the alkyl chain to a suitable α-pyrone substrate during the same reaction. To realize such a transformation, the Carreira alkynylation has been considered, as it allows the enantioselective addition of an alkyne on a carbonyl.[25-28] To prepare the suitable α-pyrone substrate **6** a Riley oxidation was considered to oxidize the methyl group at the position 6 of the pyrone. After a hydrogenation of the alkyne, the compound **8** was planned to be obtained. The remaining work to synthesize the Dothideopyrone A [**1**] was to bring a hydroxymethyl group 3 of the pyrone ring. A Rieche formylation followed by a reduction of the carbonyl group formed to finish the synthesis of Dothideopyrone A [**1**] were envisaged. The linear synthesis strategy is presented in scheme 2.2:



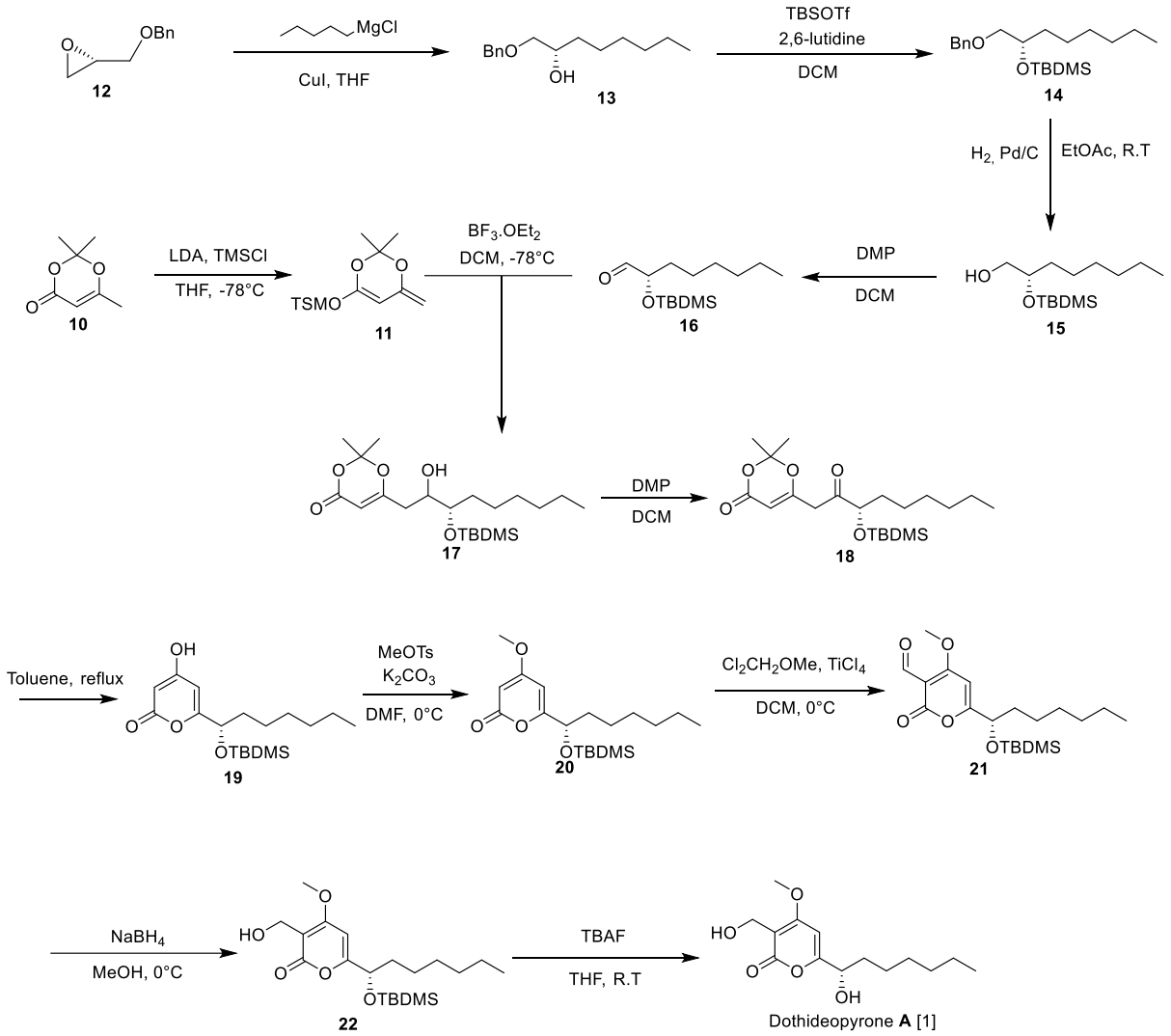
Scheme 2.2 : Proposed linear synthesis for Dothideopyrone A [**1**]

However, this first synthesis strategy was not successful, due to the difficulties encountered to perform the Carreira alkynylation in presence of an α-pyrone ring.[29] Further investigations were needed to find a new way to realize the synthesis of the Dothideopyrone A [**1**], without using the Carreira alkynylation. A second retrosynthetic analysis is presented in scheme 2.3:



Scheme 2.3 : Retrosynthetic analysis, leading to a convergent synthesis strategy

For the second synthesis pathway, a convergent synthesis strategy has been envisaged. The synthesis consisted in the synthesis of two building-blocks, compound **11** and **48**, to then realize a Mukaiyama aldol addition to form a substrate **47** suitable to perform an intramolecular *oxo*-Diels-Alder reaction. This permits to form the already 6 substituted *α*-pyrone intermediate **43** that will, after performing a methylation of the hydroxyl function at the position 4 of the pyrone ring and a formylation followed by a reduction at the position 3, as planned in the initial linear synthesis pathway, the synthesize of the target compound Dothideopyrone A [**1**]. However, a quick look at this retrosynthetic analysis makes the need of protecting the chiral alcohol early in the synthesis obvious, has alcohol oxidation takes place at the third step of the formation of the building-block **48**. Considering the need to protect the chiral secondary alcohol, the proposed convergent synthesis strategy is presented in scheme 2.4:

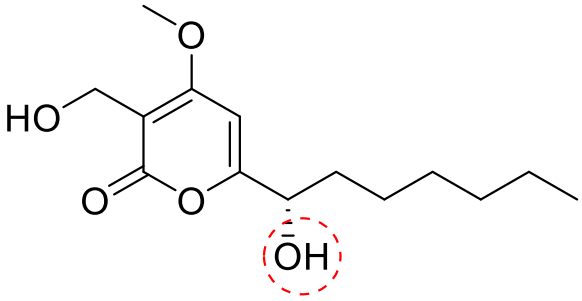


Scheme 2.4 : Proposed convergent synthesis for Dothideopyrone A [**1**]

2.3. Protecting groups

2.3.1. TBDMS protecting group

The Dothideopyrone B-D [**2**-**4**] all result from modifications on the Dothideopyrone A [**1**], which present a primary alcohol at the position 3 of the 2-pyrone ring. To perform the three desired alkylation to obtain Dothideopyrone B-D [**2**-**4**], the secondary alcohol on the Dothideopyrone A [**1**] must be protected. The choice of a protecting group must be done considering few parameters, which are the kind of group that must be protected on the substrate and the reaction conditions that the protected substrate will have to withstand during the remaining of the synthesis. Lastly, the removing of the protecting group should be able to be done without reacting with the rest of the substrate once protection is not necessary anymore.[30, 31]



Dothideopyrone **A** [**1**]

Figure 2.7 : Dothideopyrone A [**1**] present a secondary chiral alcohol needing protection

A lot of options exist for the protection of hydroxy group.[30, 32] The most common way to perform this protection is to use an acetal, an ether oxide, an ether benzylic, an ester or a silyl ether.

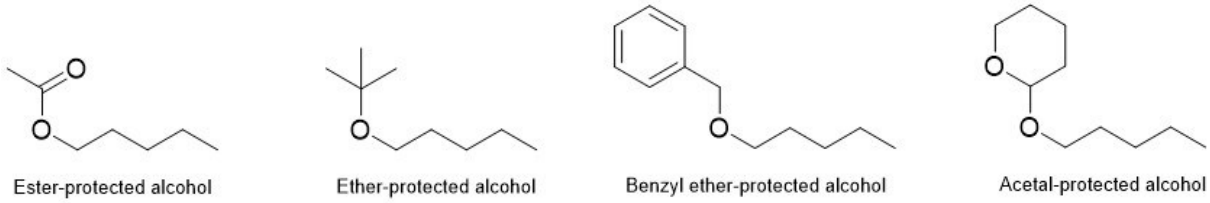
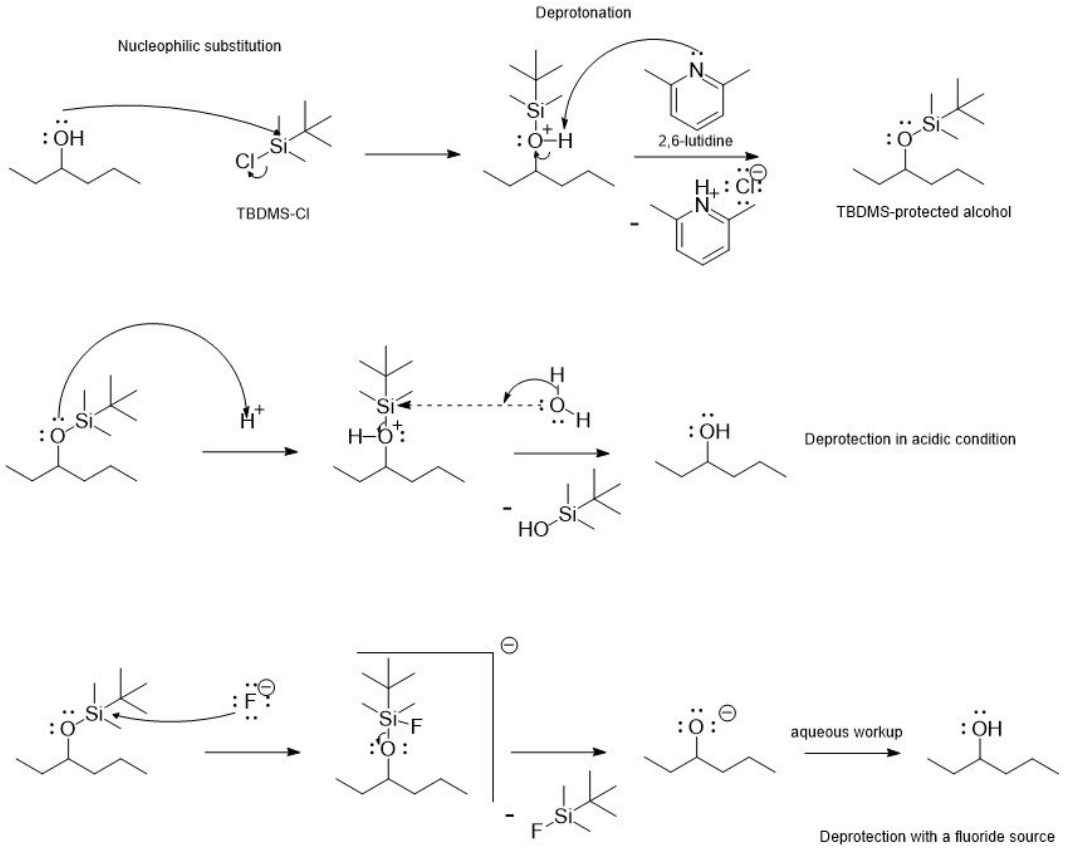


Figure 2.8 : Different protective groups for alcohol function

The use of silyl ether has been chosen to realize the protection of the hydroxy group due to the ease of conversion and deprotection of the alcohol, and the relative stability of the protecting group in the planned reaction condition.

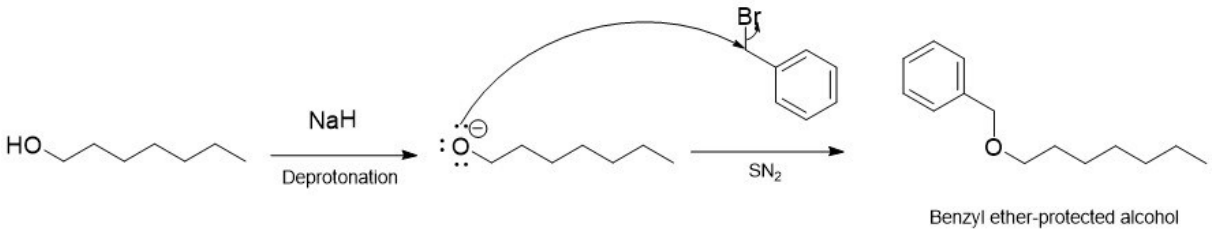
The protecting group chosen was *t*-butyldimethylsilyl ether (TBDMS or TBS).[30] As a silyl ether, TBDMS is stable under most conditions and due to its relative bulkiness compared to other common silyl ether, protect selectively and efficiently primary and secondary alcohols. TBDMS can be easily removed under acidic conditions without compromising most of the other functions sensible in presence of acid. Moreover, a common way to deprotect a TBDMS-protected alcohol is to use a fluoride source, the most common is tetra-*n*-butylammonium fluoride (TBAF). Other sources of fluoride can be considered as metallic NH_4F, aqueous HF, SiF_4 or BF_3. Both the mechanisms for protection and deprotection of an alcohol, using both acidic conditions and a fluoride source are presented in scheme 2.5:



Scheme 2.5 : Mechanism of alcohol protection and deprotection with TBDMS protective group

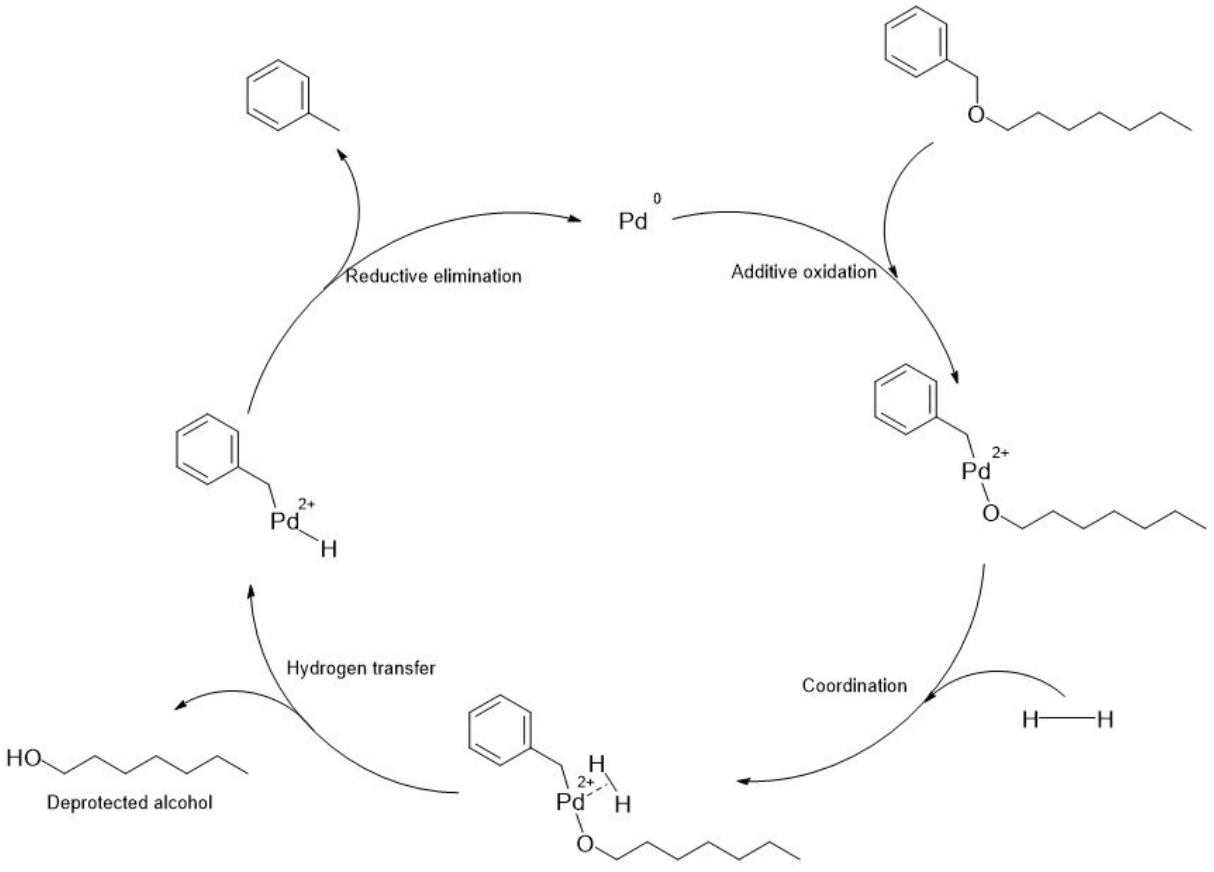
2.3.2. Benzyl deprotection

Hydroxy groups can also be protected by the formation of a benzyl ether.[30, 32] This protective group have the advantage to be extremely robust to a wide range of reaction conditions. However, the protection step itself via a benzyl ether can be difficult, as it can lead to unwanted side reactions due to the usual reaction condition, which is most commonly a Williamson ether synthesis. The mechanism of the reaction itself is a classic, S_N2 type reaction, which the mechanism is shown in scheme 2.6. As an S_N2 reaction, the nucleophilic alkoxide anion attacks the electrophilic carbon of the aromatic halogen, and consequently displaces the halogen atom, resulting in a Walden inversion of the configuration of the chiral center, if the latter is chiral. The formation of the alkoxide anion itself usually necessitates a strong base, as NaH. When the substrate cannot support condition a strong base, milder ones as Ag_2O can be used and lead to decent yield.[33]



Scheme 2.6 : Mechanism of alcohol protection with a benzyl bromide

The deprotection of benzyl-protected alcohol can be carried by performing a palladium-catalyzed hydrogenolysis.[30, 32] This has the advantage to left unaltered most of other protective groups, as it is orthogonal to most of non-ether oxide protective groups. The reaction can be done under H_2 atmosphere in presence of palladium or hydroxy palladium on activated charcoal.[34] The catalytic cycle of this reaction is presented in scheme 2.7. Firstly, an oxidative addition of the benzyl-protected alcohol on the Pd(0) complex takes place. Next, a coordination of the dihydrogen followed by a hydrogen transfer release the alcohol from the complex. The Pd(0) catalyst is then regenerated via a reductive elimination of the toluene.

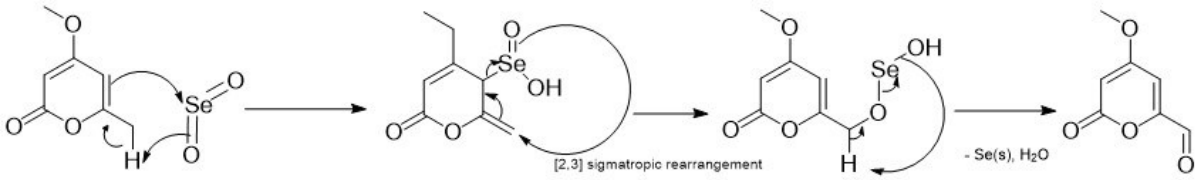


Scheme 2.7 : Catalytic cycle of the hydrogenolysis of benzyl ether

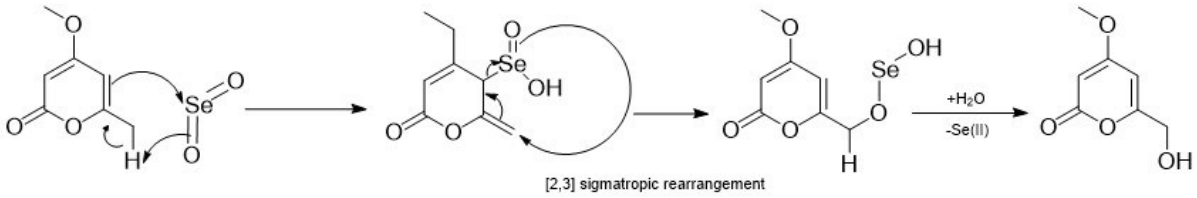
2.4. Riley oxidation

The Riley oxidation, which has been first reported by Riley and co-workers in 1932, is an oxidation reaction mediated via a selenium dioxide reagent.[35] This reaction allows to oxidize either methylene group in position alpha of a ketone, or at the allylic position of an alkene. The oxidation, depending on the reaction condition, can form either a hydroxyl group or a carbonyl group.

The mechanism of the Riley oxidation has been extensively studied since its first appearance in 1932.[36-39] For the allylic oxidation of alkenes, the mechanism consists in 3 major steps. First, an electrophilic ene reaction of the substrate with Selenium dioxide. Following that step, a [2,3] sigmatropic rearrangement takes place that restores the initial position of the C=C double bond. Lastly, a solvolysis of the selenium ester allows to recover the allylic alcohol. Further oxidation led to the carbonyl compound. The mechanism, both for the formation of the allylic alcohol and the carbonyl, are represented in the scheme 2.8.



Riley oxidation into the allylic carbonyl compound



Riley oxidation into the allylic alcohol compound

Scheme 2.8 : Mechanism of Riley oxidation

It is interesting to note that the selectivity of the reaction toward the carbonyl group and the allylic alcohol can easily be determined by the reaction condition. If the carbonyl is the desired product, stochiometric amount or excess of SeO_2 in 1-4 dioxane will lead to the formation of the enone, but using acetic acid or catalytic amount of SeO_2 with *t*-butyl hydroperoxide (^{t}BuOOH) as a stoichiometric oxidant will give better conversion into the allylic alcohol.[36, 37]

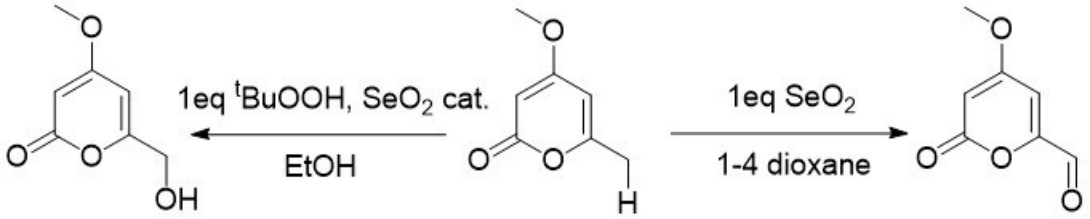


Figure 2.9 : Product of the Riley oxidation depend of the reaction condition

In the case of tri-substituted alkenes, a strong selectivity of the oxidation was observed toward the more substituted end of the C=C liaison. This characteristic indicates that the first step of the selenium-mediated oxidation is electrophilic in nature. For tri-substituted alkenes when more than one carbon can be the site of the oxidation, the reactivity of the reaction follows $CH_2 > CH_3 > CH$. Also, interesting stereoselective properties are observed during the oxidation of geminal-substituted alkene, as the major product is usually the (E)- allylic alcohol, or the corresponding carbonyl in case of further oxidation.[36, 40]

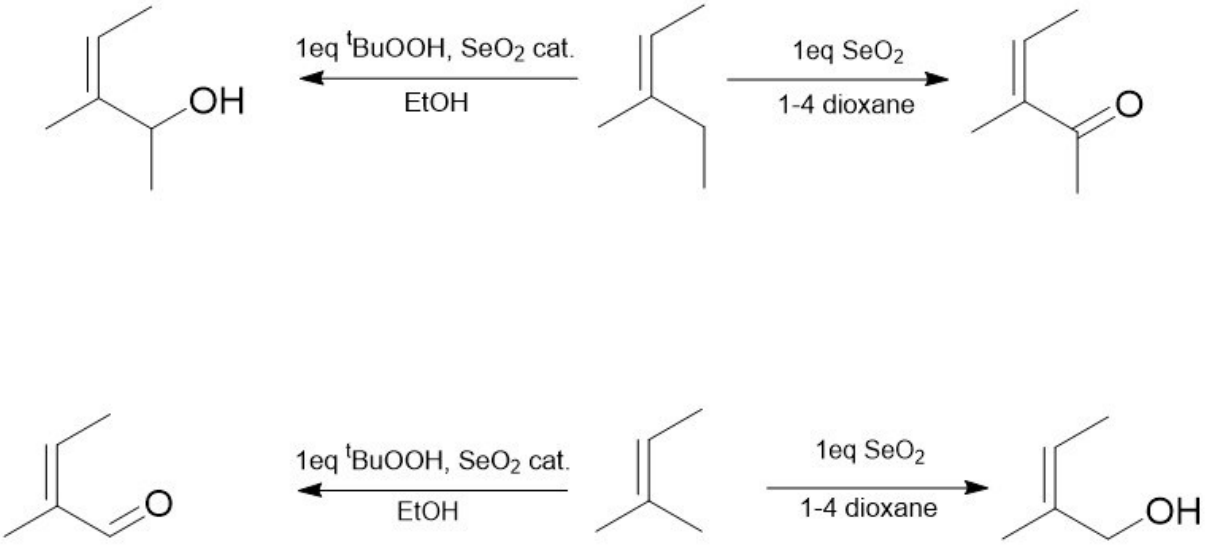


Figure 2.10 : Regioselectivity of the Riley oxidation

2.5. Carreira alkynylation

The Carreira asymmetric alkynylation has been first reported by E. M Carreira and co-workers in 2000[25, 26, 41]. This alkynylation is a new process to realize enantioselective addition of an alkylzinc, prepared *in situ* with an alkyne, on a carbonyl. This process allows to form a C-C bond and selectively a new stereogenic center in a single step. During the last decades, chemists worked extensively on new processes to realize asymmetric addition on carbonyl function.

Such processes, as allylation of carbonyl group or the Mukaiyama aldol addition reaction, necessitate the formation of nucleophiles, such as enol silanes or allylic silanes, that are rarely commercially available and need to be prepared. [26, 42]

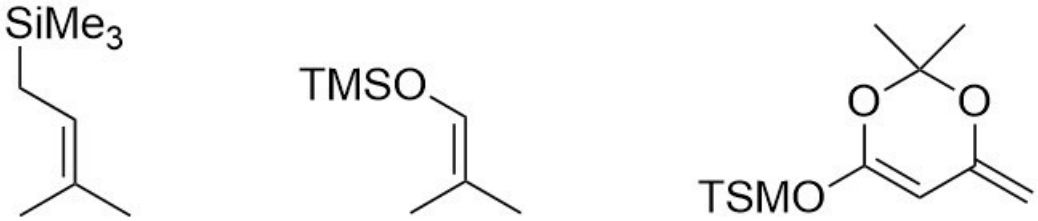


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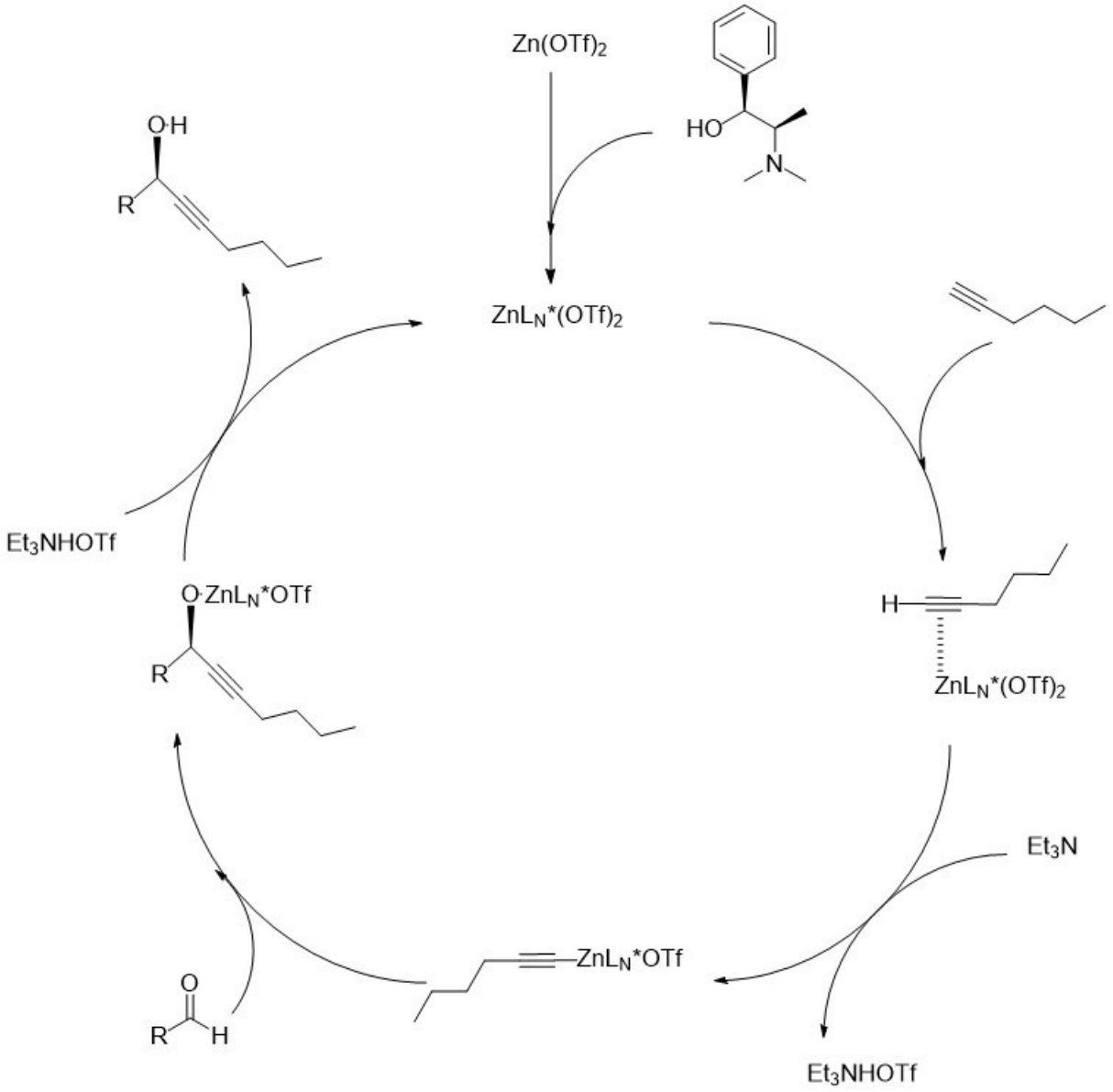
Figure 2.11 : Examples of prepared enol silanes for Mukaiyama aldol addition

The Carreira alkynylation demands the formation of an alkylzinc. Usually, terminal metalated alkynes are prepared with strong bases as metalated amides or carbanions, but those bases are not compatible with the electrophile meant to react with the metalated alkyne, the preparation of the alkylzinc must be done in a separated step. The Carreira alkynylation allows to bypass this constraint by forming the alkylzinc compound *in situ*. The terminal alkyne reacts in presence of the zinc salt $Zn(OTf)_2$ and Et_3N to give the corresponding zinc acetylide, that shows great reactivity with carbonyl functions.

The Carreira alkynylation takes place as presented in the catalytic cycle in scheme 2.9. $Zn(OTf)_2$ acts as the catalytic precursor and is activated by (-)-NME, which will ensure the desired enantioselectivity of the product. Then the alkylzinc is formed, the alkyne ligand is coordinated to the zinc complex, acidifying the terminal C-H bond of the alkyne. The Et_3N allows then a proton abstraction to form the alkylzinc compound. The addition of the aldehyde on the complex, and then a protonation by Et_3NHOTf complete the catalytic circle and regenerate the Zn(II) complex.



Scheme 2.9 : Catalytic cycle of the Carreira alkynylation

2.6. Grignard reaction

The Grignard reaction is a reaction resulting in the formation of a C-C bond, involving a Grignard reagent and an aldehyde, ketone or epoxide. The polarity of the carbon-metal bond of the Grignard reagent, whose the negative charge is localized on the carbon, allows the C-Mg bond to be very reactive and to perform nucleophilic addition. Grignard reagents can be prepared, under dry, inert atmosphere in dry solvent with Lewis base properties, as diethyl ether or THF. The solid magnesium is added followed by the relevant halogenoalkane to obtain, after acidic workup, the Grignard reagent.[43]

Grignard reaction is a very useful procedure to perform nucleophilic addition on carbonyl compound. Also, the Grignard reagent is used in some cross-coupling reactions, the copper catalyzed Corey-House synthesis[44] and the Kumada coupling[45]. Among the many reactions that Grignard reagent can have some interest, a noteworthy one is the opening of an epoxide to obtain a hydroxy group.[46] In this reaction, the Grignard reagent performs a nucleophilic attack on one of the carbons of the epoxide, resulting in its opening and the formation of the alcohol after acidic workup. However, both carbons can be attacked and in case of a substituted epoxide, the wrong regioselectivity could lead to the wrong product. Usually, the nucleophilic attack occurs on the less substituted end of the epoxide. However, report of addition on the most substituted end of the epoxide has been made.[47] The use of copper(I) complex in catalytic amount has been proved useful to assure the right regioselectivity of the reaction.[47-50]

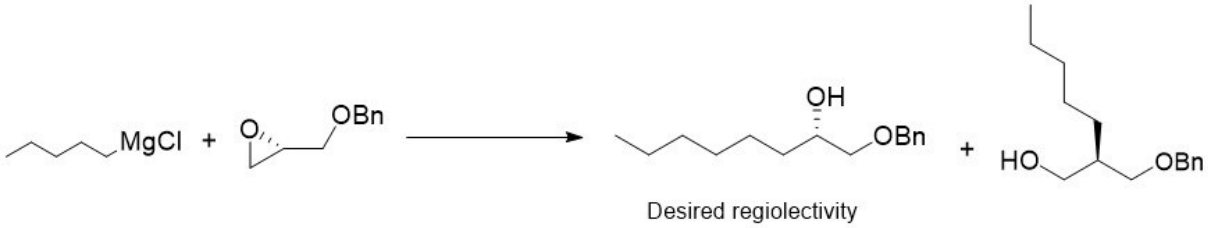
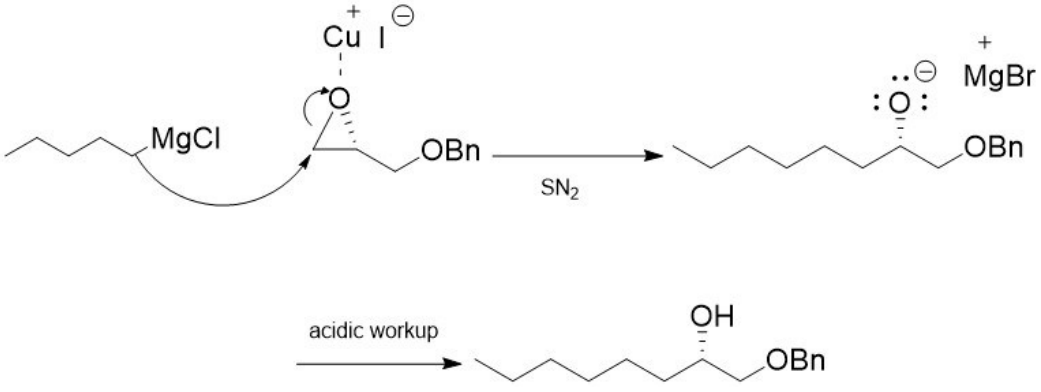


Figure 2.12 : The Grignard reagent can perform a nucleophilic attack on both carbon atoms of the epoxide

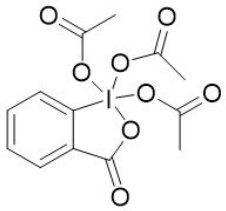
The mechanism of the opening of an epoxide is described in scheme 2.10. The role of the CuX(I) has not been studied in detail in the mechanism, but some option can be ruled out. Organocopper complexes are usually not reactive enough to perform an epoxide opening, so the transmetalation between Mg and Cu is not an option.[51] It is however plausible that the formation of a Gilman-like reactant takes place due to the catalytic amount of CuX(I), And Gilman reactants are reactive enough to open epoxides.[50, 52] The proposed mechanism involves the coordination of the epoxide by the copper catalyst, favorizing the nucleophilic attack on the less substituted carbon of the epoxide.



Scheme 2.10 : Mechanism of the Grignard addition on an epoxide

2.7. DMP oxidation

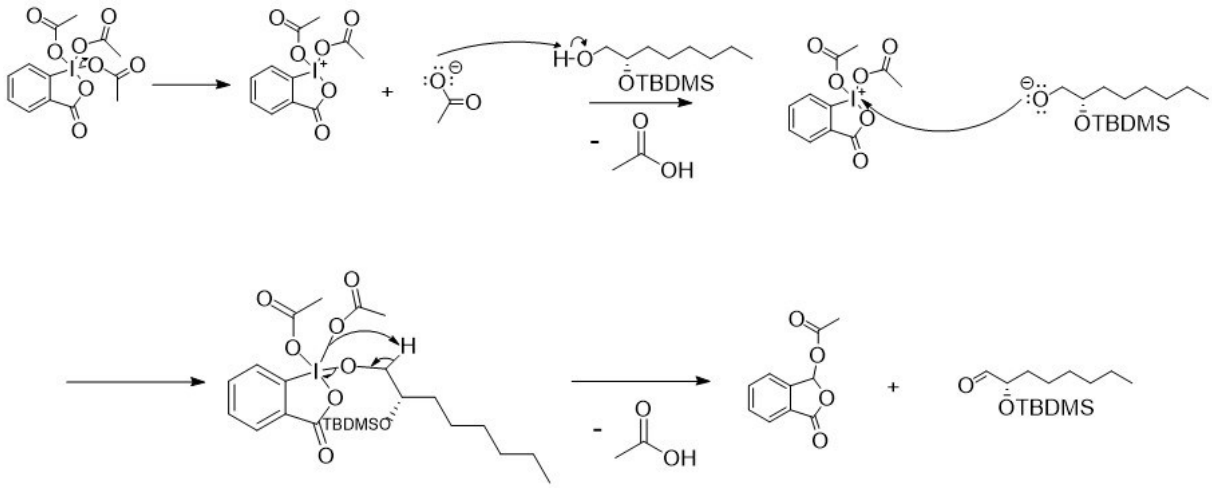
The Dess-Martin oxidation is an oxidation procedure allowing to oxidize primary and secondary alcohols, respectively into aldehyde and ketone. This procedure is based on the use of Dess-Martin periodinane, a hypervalent iodine reagent developed by D. B. Dess and J. C. Martin in 1983.[53] This oxidative agent presents many advantages to chromium-based oxidants and others common oxidants of alcohol, as it can perform with lower reaction time and higher yield, under normal atmosphere without needing large excess of oxidative agent and minimal workup.



Dess-Martin periodinane

Figure 2.13 : The Dess-Martin periodinane allows simple procedure for oxidation of alcohols

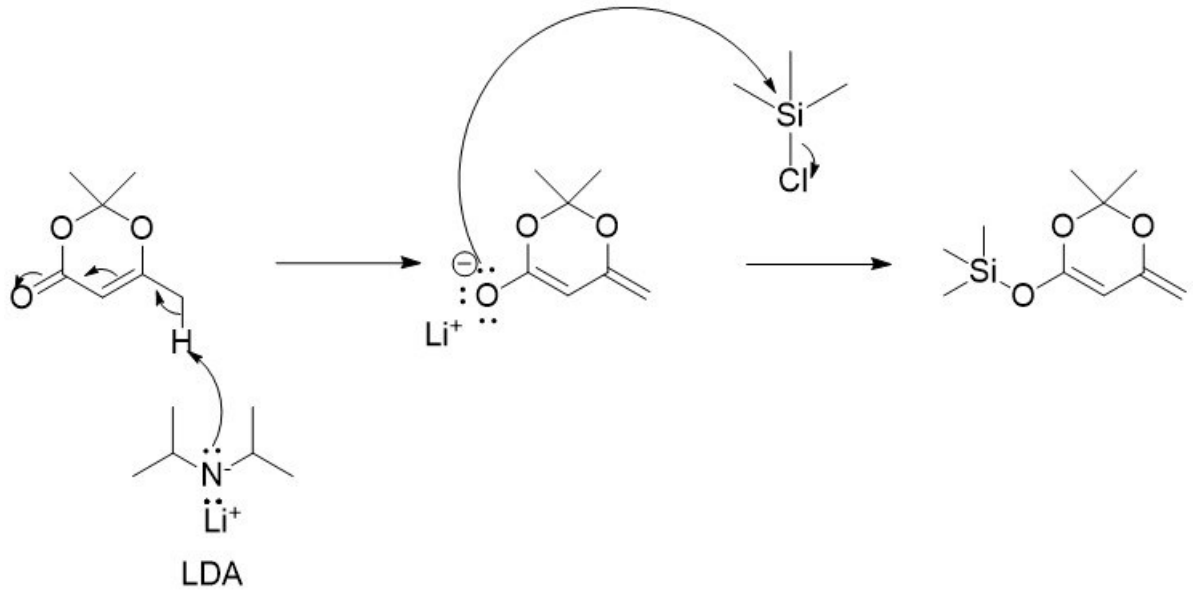
The mechanism of the reaction is presented below. Firstly, the alcohol substitutes one of the acetate group on the iodine atom, followed by a deprotonation of the alcohol which forms acetic acid as a by-product. A proton transfer then allows the formation of the desired carbonyl compound, with another equivalent of acetic acid. As the formation of a carboxylic acid can be problematic in some case, its formation can be buffered with a mild base, like pyridine or 2,6-lutidine.



Scheme 2.11 : Mechanism of the Dess-Martin oxidation

2.8. Mukaiyama aldol addition

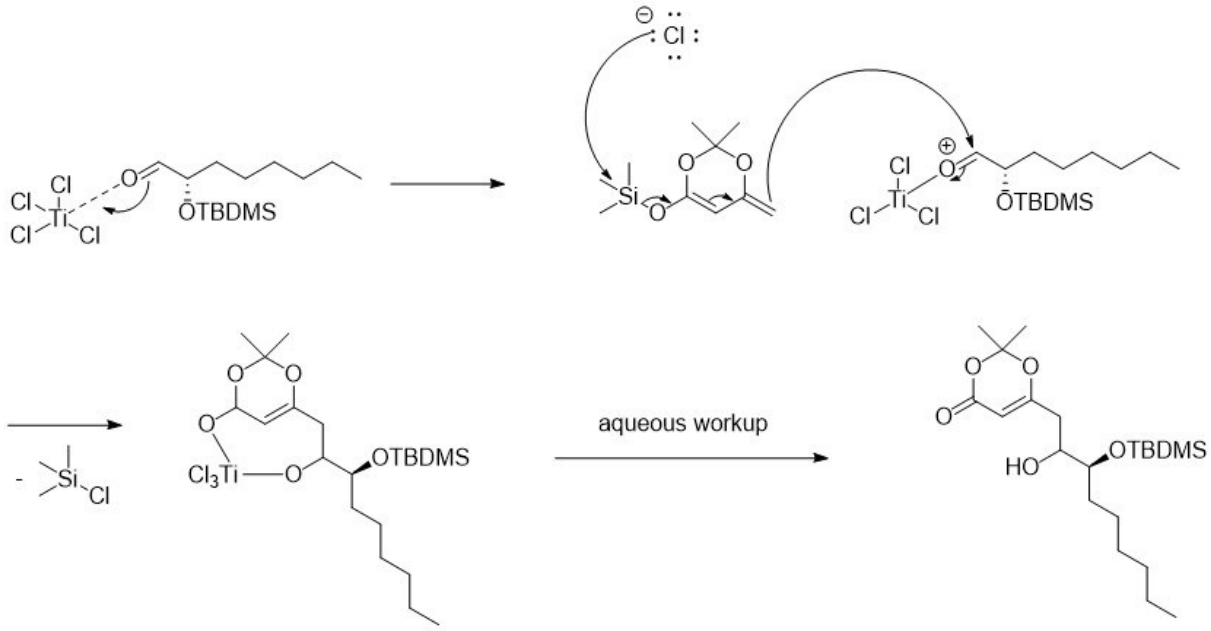
The Mukaiyama aldol addition is an asymmetric aldol addition first reported by Mukaiyama and co-workers in 1973.[42, 54, 55] Aldol additions raised interest of organic chemists as it allows to create new C-C bonds on complex substrates. However, aldol addition can often lead, when the two carbonyl compounds are different, to undesired aldol addition and aldol condensation of the aldehydes under classic basic or acid reaction conditions, greatly reducing yield and consequently effectiveness of such procedures.[56, 57] The use of catalytic procedures, as the Mukaiyama aldol addition, does not suffer from those side reactions, as it involves the prior preparation of a silyl enol ether that will activate the enol and consequently trap the activated aldol hydroxy.[56, 58] The mechanism of formation of the silyl enol ether is presented in the scheme 2.12. The use of a strong base, LDA in the mechanism, at low temperature (-78°C) allows to deprotonate the hydrogen in *γ* position of the conjugated *α*-enone and results in the formation of a lithium dienolate. An S_N2 type reaction of the latter on the electrophilic silicon compound trimethylsilyl chloride results in the formation of the silyl dienol ether. Even if silyl enol ethers are way more stable than lithium enolates, it is important to note that they should be stored under inert atmosphere for only short time frame, as they can suffer degradation.[58]



Scheme 2.12 : Mechanism of the formation of an enol silane

Once the silyl enol ether is prepared, Mukaiyama aldol addition can be performed. The procedure necessitates the use of a strong Lewis acid, as $TiCl_4$, $SnCl_4$ or $BF_3.OEt_2$.[59] The mechanism is presented in scheme 2.13 with a generic Lewis acid. The first step is an electrophilic activation of the aldehyde by the Lewis acid, then the nucleophilic dienol silane

attacks the newly formed electrophilic site of the aldehyde compound leading to the C-C bond formation. An aqueous work up will then allow the formation of the aldol addition product.



Scheme 2.13 : Mechanism of the Mukaiyama aldol addition

2.9. *Oxo*-Diels-Alder reaction

The formation of lactone has been widely studied as it permits the synthesis of variable sizes of lactone ring, a common organic unit encountered under various form in a wide range of natural compounds. Being able to perform those synthesis is a key step in many total synthesis of natural compounds.[60]

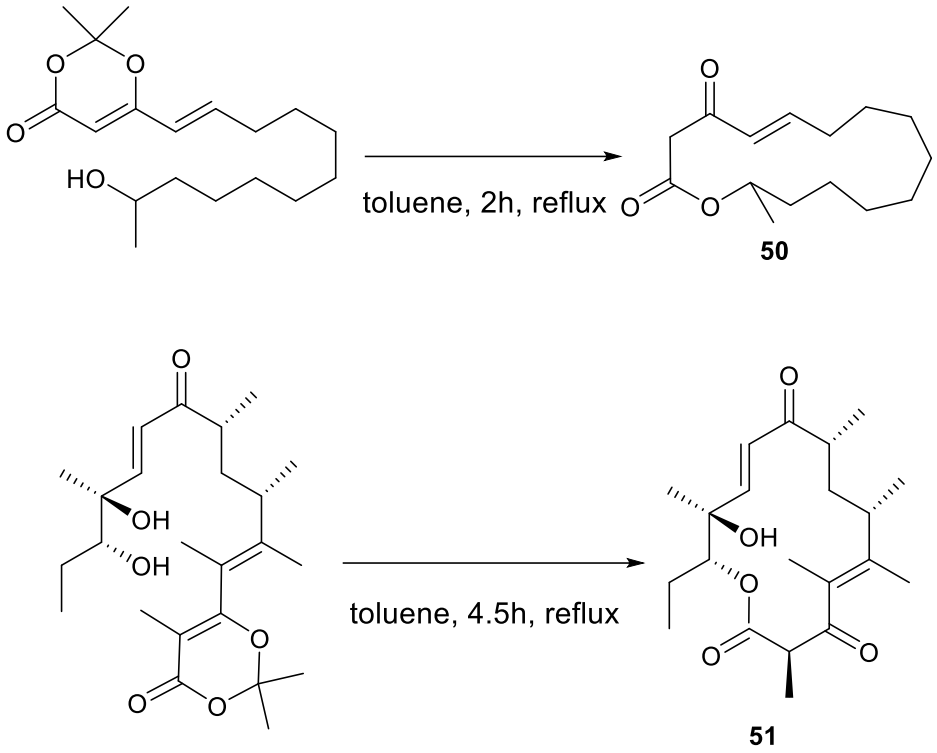
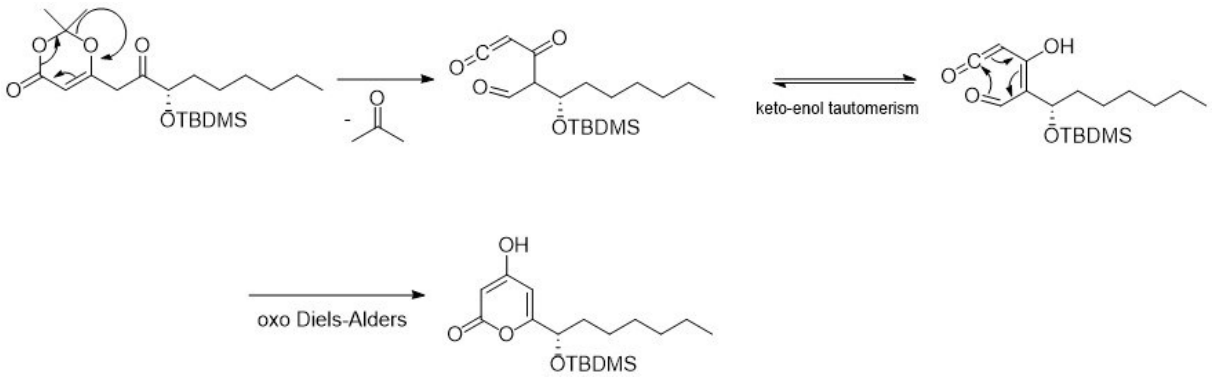


Figure 2.14 : Macrolactones **50** and **51** synthesized by Boeckman *et. al.*[60]

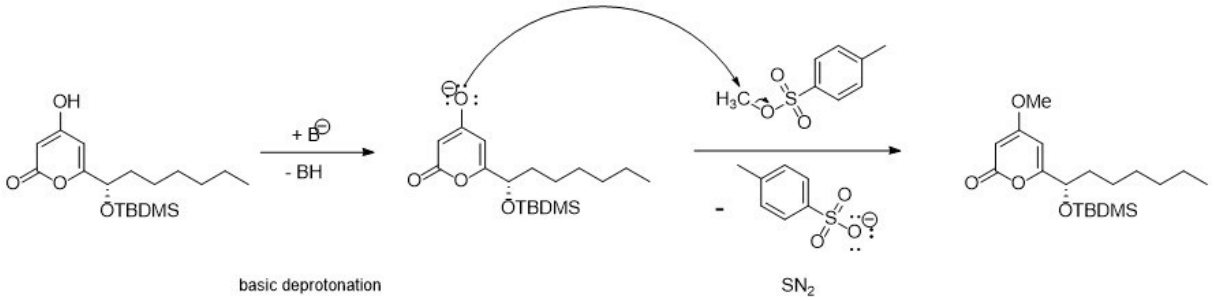
The formation of such lactones follows Baldwin's ring closure rules, that defines favorable and unfavorable ring closure reactions.[61-63] Considering the reaction conditions of the planned synthesis, the Baldwin's rules defined the cyclization as a 6-exo-dig ring closure, as the cyclization takes place by the formation of an electrophilic ketene intermediate[64], which is a favorable closure reaction.[65] Such a reaction has been reported to process effectively under heating in toluene.[65-69] The mechanism of the cyclization reaction is presented in scheme 2.14. Firstly, the intramolecular ketene trapping reaction takes place via a thermal cracking resulting in the displacement of an acetone molecule. Next, the keto-enol tautomerism of the intermediate allows the cyclization via an *oxo*-Diels-Alder reaction[70], as the 4 carbons of the diene must lie in the same plan to perform the latter.[65]



Scheme 2.14 : Mechanism of the *oxo*-Diels-Alder reaction via a [4+2] cycloaddition

2.10. Alcohol methylation

The alkylation of an alcohol function results in the formation of an ether oxide.[71] The mechanism is the one of the Williamson synthesis, and consequently follows a S_N2 type mechanism, as described in the scheme below. The use of a base is needed to activate the nucleophilic character of the alcohol by forming an alkoxide ion *in situ*. The alkoxide ion, once formed, attacks the electrophilic carbon of the alkylating reagent, which can be an alkyl halide or an alkyl tosylate.



Scheme 2.15 : Mechanism of formation of the other oxide via a S_N2

2.11. Rieche Formylation

Formylation reactions are a useful type of reaction in organic synthesis, as they permit the formation of aldehydes, a key function in organic chemistry as they allows a wide range of reaction due to their important reactivity.[72] Formylation of electron-rich aromatic compounds have been extensively studied, as the array of possible products depend greatly on the electron-withdrawing and donating groups on the aromatic compound and their ortho-meta-para director effects, and of the reaction condition.[73, 74] Consequently, many procedures have been developed to ensure formylation as a desired position, considering the aromatic compound involved. The Vilsmeier-Haack process,[75] Gattermann-Koch reaction[76] and hydroformylation are proven procedures of such formylation.[77]

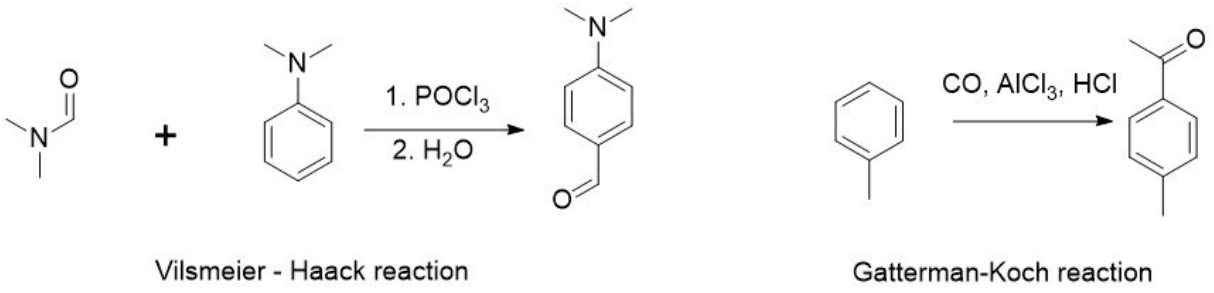


Figure 2.15 : Vilsmeier-Haack and Gatterman-Koch reactions are well studied but dangerous procedures

However, in this project, the desired formylation should take place on the position 3 of a 2-pyrone compound. It has been reported that 2-pyrones can undergoes many electrophilic substitution reactions on their 3 and 5 positions, due to their higher electron density compared to the rest of the 2-pyrone ring.[22] EAS such as trifluoromethylation or formylation have been reported to occur at the 3 position of 2-pyrones.[78, 79]

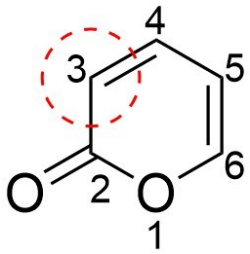
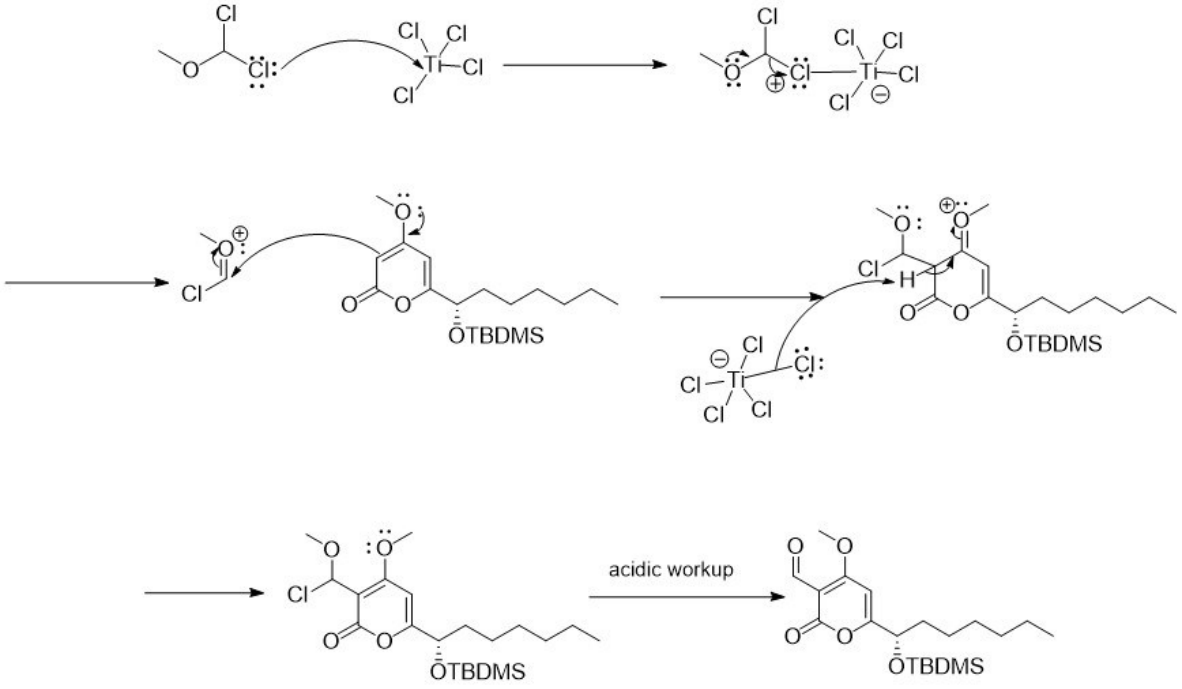


Figure 2.16 : The carbon 3 of the 2-pyrone ring can undergoes electrophilic aromatic substitution

The formylation procedure that has been reported for formylation at the position 3 of a 2-pyrone is the Rieche formylation.[80-82] This procedure was reported by Rieche and co-workers in 1960 mediated by dichloromethyl methyl ether as the formyl agent and $TiCl_4$.[83] The mechanism of the Rieche formylation reaction is presented in scheme 2.16. First, the Lewis acid $TiCl_4$ activates the formyl agent. Next, a nucleophilic attack from the relevant π-bond of the 2-pyrone takes place and formation of the C-C bond occurs. Deprotonation of the hydrogen at position 4 reforms the π-bond. An acidic workup allows the formation of the aldehyde.



Scheme 2.16 : Mechanism of the Rieche formylation reaction

2.12. Reduction of carbonyl group

Reduction of carbonyl group is a common type of reaction used in organic synthesis. Aldehydes and ketones can be reduced into respectively a primary or a secondary alcohol.[84] The reduction of an ester or a carboxylic acid will result in the formation of an aldehyde and an alcohol for the former and an aldehyde and water for the second. Subsequent reduction of the aldehyde formed will result in the obtention of a primary alcohol. When a reduction is performed on a complex substrate, undesired reduction of others carbonyl groups can occur. To prevent that, it is possible to choose a reducing agent that performs a selective reduction on the substrate. The use of $NaBH_4$ will not reduce acid and ester, and $NaBH(OAc)_3$ will allow to reduce aldehydes selectively, without reducing less reactive ketones. [84]

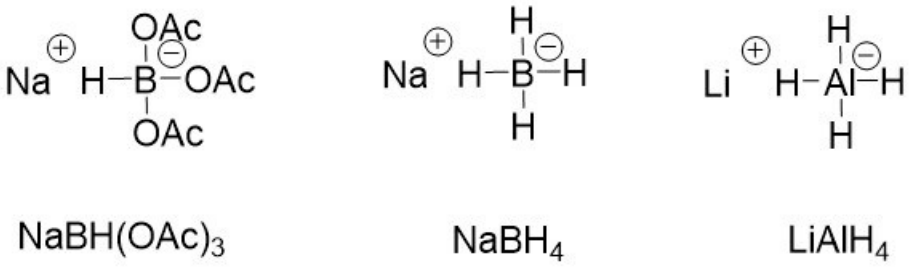
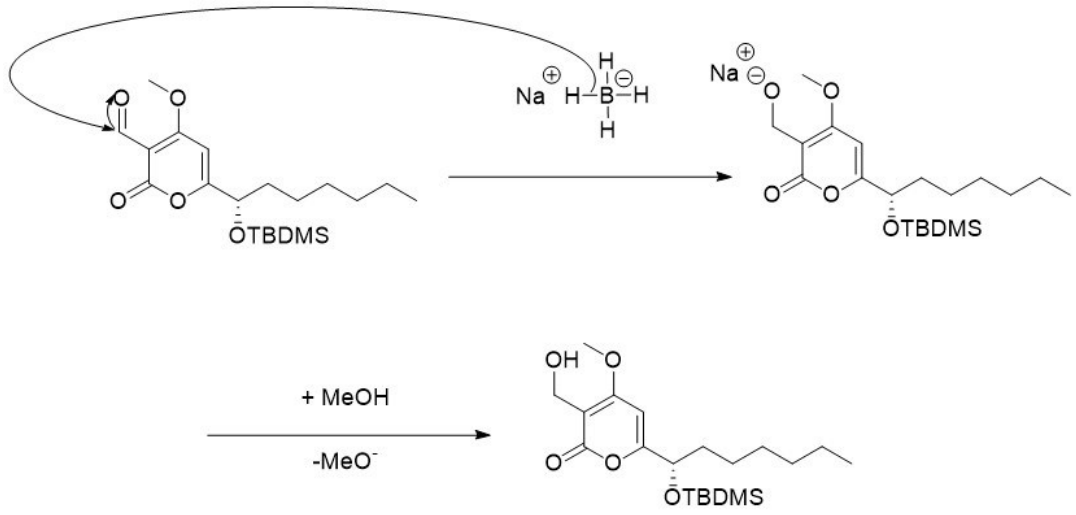


Figure 2.17 : Selective reduction can be performed with the adequate metal hydride

To perform the reduction, the reducing agent allows an ion hydride to realize a nucleophilic attack on the electrophilic carbon of the carbonyl group to form an alkoxide ion. A protonation will then follow due to the protic solvent used, resulting in the completion of the reduction reaction.



Scheme 2.17 : Mechanism of a carbonyl reduction

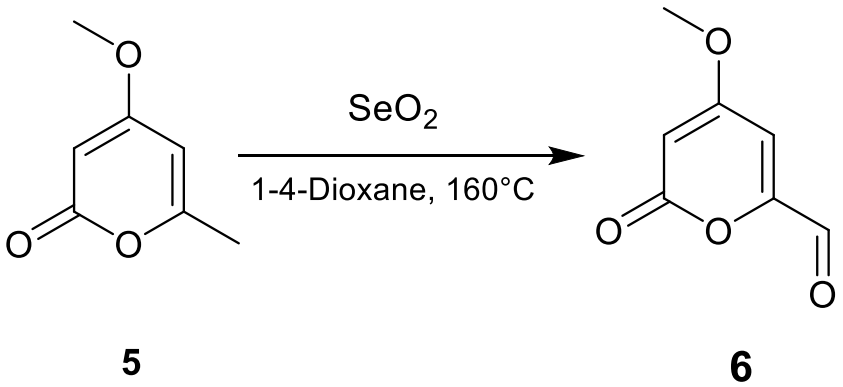
3. Results and discussion

3.1. First pathway, linear synthesis strategy

3.1.1. Compound 6

For the first synthesis considered to reach the Dothideopyrone A [**1**], the first step consisted in the preparation of the suitable aldehyde **6** to realize the Carreira alkynylation. To prepare this aldehyde, a Riley oxidation on a commercially available 2-pyrone **5** derivative substituted in position 4 and 6, respectively by a methoxy group and a methyl group was used. The aim of the Riley oxidation was to perform the oxidation at the allylic position of the C_5=C_6 double bond, on the methyl group. It is notable that, according to the usual reactivity constated in Riley oxidation procedure, the only available site for the oxidation to take place on the substrate was the methyl group, limiting the risk of undesired side reaction.

The reaction has been repeated many times due to the difficulties encountered on the next step, a general description of the procedure is detailed below and shown in scheme 3.1. The compound **6** was synthesized with the commercially available substrate 2*H*-pyrone-2-one-4-methoxy-6-methyl **5** in scale ranging from 264mg to 325mg (57% to 70% yield). The 2*H*-pyrone-2-one-4-methoxy-6-methyl **5** and SeO_2 reagent have been mixed in 1-4 dioxane, in a 50mL sealed tube previously flushed with nitrogen. The reaction was then stirred and heated at 160°C for 4 hours. After the oxidation was completed, the mixture has been diluted with ethyl acetate and filtrated to remove precipitated selenium, then washed with brine. Extraction of the organic layer with ethyl acetate and drying on $MgSO_4$ was performed, the organic layer was then filtrated, and the solvent evaporated. After purification via silica gel column chromatography, the compound **6** was isolated, under the form of light-yellow solid. The ^{1}HNMR was coherent with the formation of the desired compound, the peak at δ = 9.54 ppm integrating for 1 H was characteristic of the formation of an aldehyde.

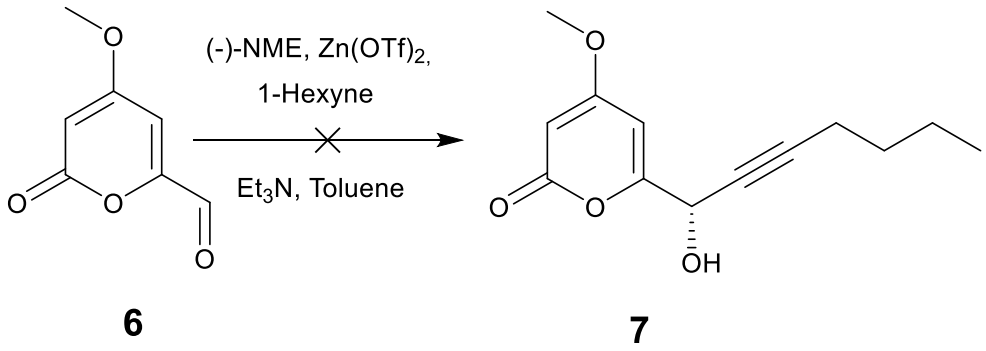


Scheme 3.1 : Synthesis of compound **6** via a Riley oxidation

The small size of the sealed tube, which was the bigger one available, was the principal reason of the need to repeat this procedure many times, consequently this reaction has not been ran at greater scale. However, the procedure has been tested without the sealed tube, refluxed and heated with the aim to scaling up this process. The reaction condition for this procedure involves a high temperature of 160 °C, the 1-4 dioxane having a boiling temperature of 101°C, the temperature had to be lowered to 140 °C due to important bubbling. This resulted in a lower yield, even with a greater reaction time of 20 hours, and the procedure without the sealed tube has been rejected.

3.1.2. Compound 7

The compound **7** was planned to be obtained using the Carreira alkynylation according to a procedure reported by Carreira and co-workers.[41] Despite the different conditions tried in this project, the synthesis of compound **7** illustrated in scheme 3.2 has always resulted to be unsuccessful. A general description of the procedure is detailed below, along a table to summarize the different conditions tested.



6 **7**

Scheme 3.2 : Attempted synthesis of compound **7** via a Carreira alkynylation

To ensure the absence of water moiety for the formation of the alkynzinc compound, $Zn(OTf_2)$ has been put under vacuum overnight before starting the procedure. The glassware used also has been dried in oven. To the $Zn(OTf)_2$, under inert atmosphere, was then added dry DCM, and the (-)-N-methylephedrine. To the mixture was then added the triethylamine and the balloon was stirred for 3 hours before adding the 1-hexyne. After waiting 30 minutes, the compound **6** was added with a slow addition over a period of 12 hours. The reaction was then stirred for a reaction time on a range of 46 to 70 hours. Next, the organic mixture was washed with HCl 1M, H_2O and brine. The organic layer was extracted with DCM, dried on $MgSO_4$. The purification was done via silica gel column chromatography.

Table 3.1 : Reaction conditions tested for the Carreira alkynylation

	Attempt 1[a]	**Attempt 2**	**Attempt 3**	**Attempt 4**[b]	**Attempt 5**	**Attempt 6**
Et_3N eq.	1.2	2.4	1.8	1.5	1.2	1.8
Reaction duration	48h	55h	46h	50h	68h	70h
Total anh. DCM amount	30mL	30mL	15mL	15mL	30mL	15mL
Starting material recovered	Yes	Yes	Yes	Yes	No	No

[a] Addition of compound **6** over 30 minutes, [b] Only starting material was recovered

As stated previously, none of the attempts allowed us to synthesize compound **7**. It is noteworthy that, among the isolated compounds, with the obvious exception of the isolated recovered compound **6**, none of the isolated products presented the characteristic of the *α*-pyrone ring, i.e the peaks for δ = 5.7 ppm (proton H-3) and δ = 6.6 ppm (proton H-5)[85], which is conclusive that a degradation of the *α*-pyrone ring took place. However, in all those cases, the characteristic peak of the aldehyde around δ = 9.48 ppm was not present on the spectrum anymore, and some peaks could be characteristic of an alkyl chain around δ = 1.3-0.9 ppm. Though, peaks of residual ethyl acetate were also present, those peaks could be then characteristic of the hexane used during the column purification, or a superposition of both. Different rotavapors where used for evaporation of solvent after purification during the rest of the project that allowed less to no residual peak. For the attempt 5 and 6, no starting material was recovered, which could indicate that after a long reaction time the pyrone ring is not present anymore.

Considering the spectrum analysis, it can be hypothesized that the reaction condition was unsuitable for an *α*-pyrone substrate, as degradation took place. It is still unclear if the Carreira alkynylation happened on the degraded substrate, as the spectrum were very different from each other. However, it was clear that the Carreira alkynylation could not be used on a *α*-pyrone ring substrate and another synthesis pathway had to be considered.

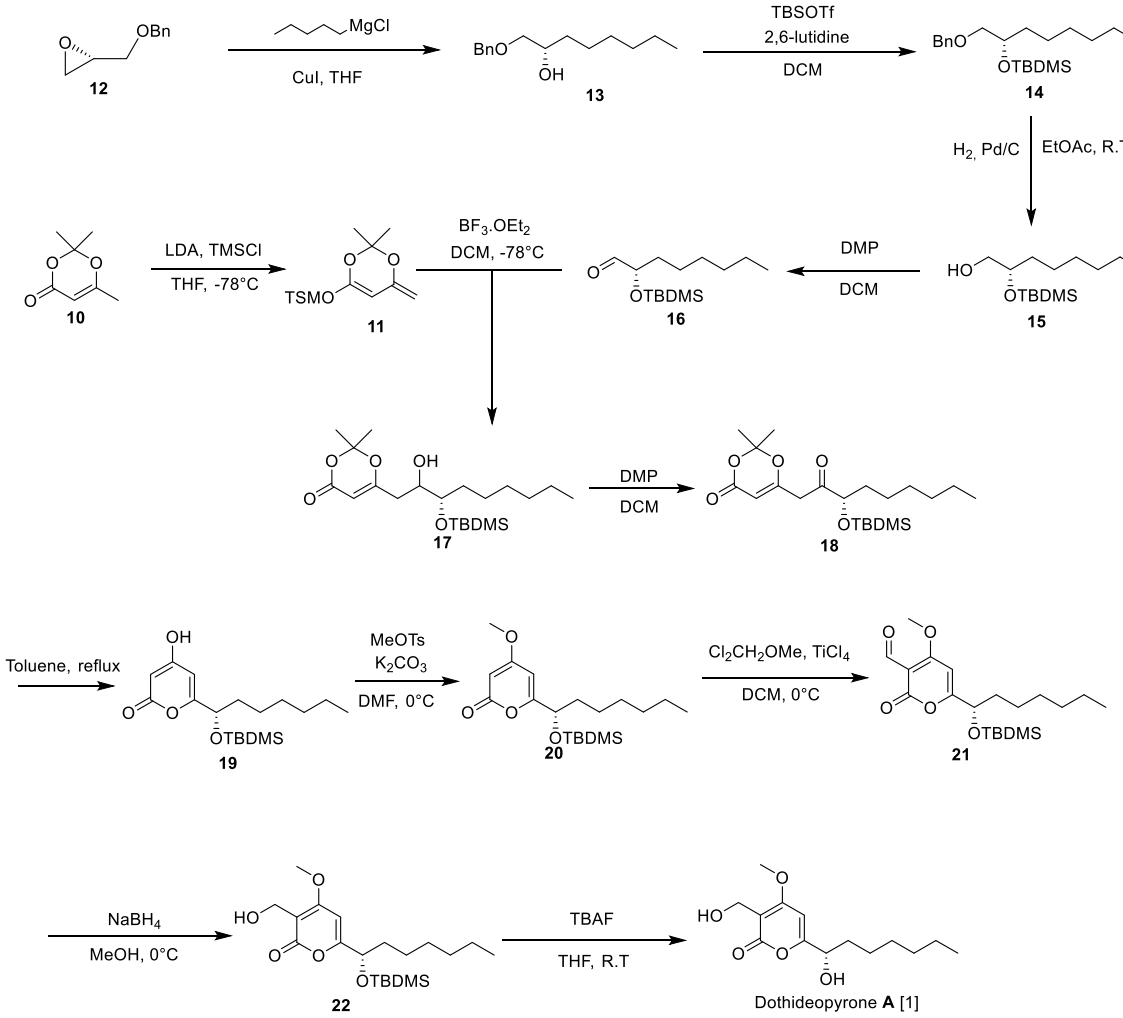
The degradation of the *α*-pyrone ring is suspected to happen due to the basic condition of the reaction. The pyrone, as a cyclic ester, could be opened due to the nucleophilic base, even if the hydrolysis of ester necessitate water, which is unlikely present in the mixture considering the precautions took to run the reaction, and the formation of an amide should not be possible

either, due to the triethylamine being a tertiary amine. The investigation on the actual reaction happening in the degradation of the *α*-pyrone has not been further, as the work on the new synthesis pathway was the new focus. The undesired reaction and the resulting compound(s) have not been determined to this day.

3.2. Second pathway, convergent synthesis strategy

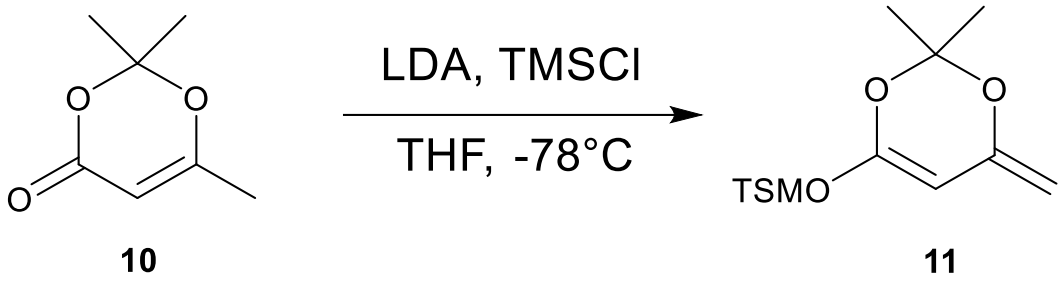
3.2.1. Compound 11

In the second synthesis pathway considered for the total synthesis of Dothideopyrone A [**1**], a convergent synthesis strategy has been conceived and shown in scheme 3.3. In this new synthesis, the construction of two building-blocks was planned, compound **11** and **16**, with the aim to couple them and to form the already 6-substituted *α*-pyrone ring, a methylation of the hydroxy group at the position 4 and the formation of hydroxymethyl group at the position 3 would allow the formation of the Dothideopyrone A [**1**] after deprotection of the secondary chiral alcohol.



Scheme 3.3 : New convergent synthesis pathway for the Dothideopyrone A [**1**]

The preparation of compound **11** shown in scheme 3.4 consisted in the formation of a silyl enol ether to trap the suitable aldol hydroxy that will be needed to perform a Mukaiyama aldol addition with compound **16** in a step described further. The synthesis of compound **11** have been reported to be successful in previous published works[41, 67-69], the same procedure was used here and is described below.



Scheme 3.4 : Synthesis of the enol silane **11**

The lithium diisopropylamide has been prepared *in situ* by mixing *n*-butyllithium and diisopropylamine in anhydrous THF at -78°C, using a dry ice / acetone cooling bath under nitrogen atmosphere. After 50 minutes of stirring at -78°C, the mixture was stirred at 0°C for 30 minutes and then cooled again at -78°C. The commercially available 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **10** was then slowly added in the mixture over a period of 30 minutes. After one more hour of stirring, the silicon electrophilic reagent chlorotrimethylsilyl was then added over a period of 20 minutes and the reaction was then stirred at -78°C for 40 more minutes. Then the mixture was put at room temperature and stirred for an additional 2 hours. The mixture has then been filtrated on $MgSO_4$ under reduced pressure, with the filter cake washed with pentane. The compound **11** has a reported boiling point relatively low, around 32-34°C under high vacuum. To prevent the evaporation of the product, solvent have been evaporated at 100mbar for less than 20 minutes to obtain a dark-orange mixture. The compound **11** has been observed to degrade rather quickly and had to be used shortly after being synthesized. It was possible to store in a sealed balloon filled with nitrogen in a freezer for a week.

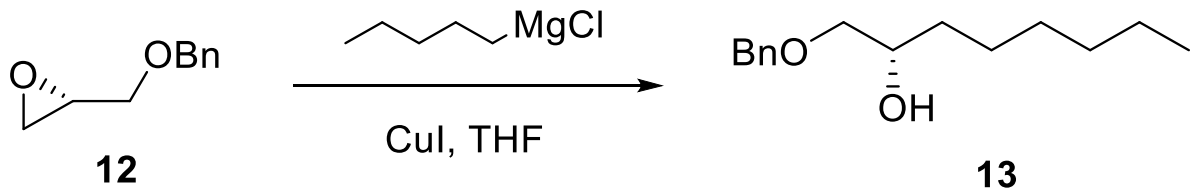
The product has not been purified, has the crude product was expected to be used for the Mukaiyama aldol addition reaction. However, NMR spectrum were analyzed to determine the yield of the compound **11** in the mixture, using the NMR yield determination without internal standard method. Due to the limited evaporation of the solvent, peaks of residual solvent made this analysis more complex. Finally, the calculated yield of the reaction has been determined to be 88%. It is noteworthy to mention that the NMR yield determination without internal standard gives exact result when the mixture is only composed of 2 compounds, as stated above, residuals peaks for the solvents used during the procedure were apparent on the spectrum. In the calculation, an augmentation of the total mass of the mixture will artificially increase the amount of compound **11**. It was then considered that the yield of the

reaction was overestimated, large excess of the crude mixture has been used for the Mukaiyama aldol addition reaction.

It is notable that the reaction has also been performed using commercial prepared lithium diisopropylamide, with results ranging from low to no conversion. The use of commercial prepared lithium diisopropylamide has then been rejected. Also, one of the runs of this reaction with the procedure described in the previous part showed no conversion, despite being run in the same conditions. The reasons could either be the presence of water or acetone moiety in the glassware, degrading the *n*-BuLi, even if it is unlikely present in the mixture considering the precautions took to run the reaction. It could also be due to a longer evaporation of the solvent that would have removed the compound from the mixture. Similar issues were encountered by an-other student working on this reaction on a different project, the exact reasons of those failures have still not been determined.

3.2.2. Compound 13

The synthesis of the second building-block consisted in a 4 steps synthesis to prepare the suitable aldehyde **16** for the Mukaiyama aldol addition. The first step consisted in the preparation of the compound **13** illustrated in scheme 3.5 by performing the regioselective opening of an epoxide to obtain the desired chiral secondary alcohol. To perform this reaction, a Grignard reagent with a copper iodide catalyst has been used to perform a nucleophilic addition on the less substituted carbon of the epoxide ring. The procedure considered has been successfully used by Yadav and co-workers on very similar substrates[49]. The procedure for this reaction is described below.



Scheme 3.5 : Synthesis of compound **13** using a Grignard reagent

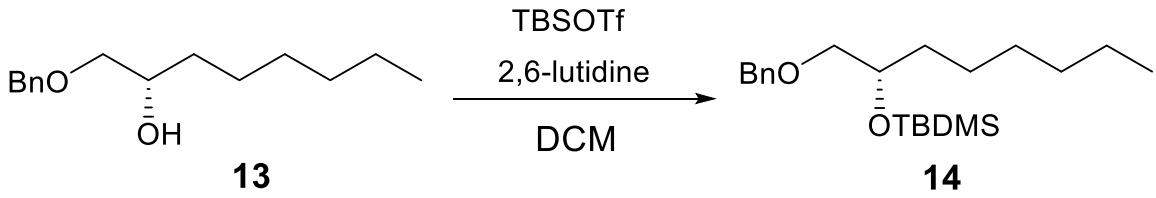
The commercially available Grignard reagent pentylmagnesium chloride and copper iodide were mixed in dry THF under inert atmosphere, the mixture was then cooled at -78°C, using a dry ice / acetone cooling bath. The commercially available epoxide (S)-(+) glycidyl benzyl ether **12** was then added and the mixture was warmed up to -40°C using a dry ice / acetonitrile cooling bath and stirred for 4 more hours. The reaction has then been quenched with NH_4Cl to perform the acidic workup and ensure the formation of the secondary alcohol and the precipitation of the magnesium. The mixture was then filtrated to remove the precipitated

magnesium and extracted with ethyl acetate. The organic layer was then washed with brine and dried on Na_2SO_4. After purification via silica gel column chromatography, the compound **13** was isolated under the form of a colorless oil with a yield of 87%. This reaction has been reconducted with similar yield. The ^{1}HNMR and ^{13}CNMR spectrum analysis of the isolated compound allowed to identify the compound as the desired compound **13**.

Another procedure has been tried, at higher temperature, between -10°C and 10°C, with a slow addition of the epoxide over 30 minutes and a shorter reaction duration.[86] This procedure, initially planned for greater scale, proposed by Alam and co-workers, showed inferior yield (47.3%) and have been rejected.

3.2.3. Compound 14

The second step of the synthesis of the second building-block consisted in the protection of the chiral secondary alcohol of compound **13**. The compound **13** presents, in addition to the chiral alcohol, a benzyl-protected hydroxy group, that will need to be, after deprotection, oxidized to form the suitable aldehyde for the Mukaiyama aldol addition reaction. The protection was then needed to prevent the chiral alcohol to be oxidized, and to be preserved until the end of the synthesis pathway. Also, it was crucial to consider a protective group with deprotection conditions orthogonal to the benzyl protective group already present on the compound **13**. All those considerations have been discussed previously and the protective group chosen was *t*-butyldimethylsilyl (TBDMS or TBS). The procedure to obtain the compound **14** is presented in scheme 3.6 and detailed below.

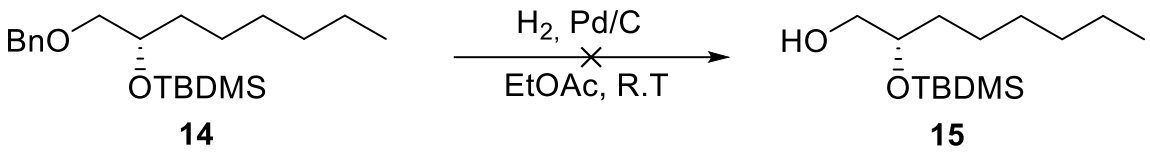


Scheme 3.6 : Protection of the chiral secondary alcohol to obtain compound **14**

The compound **13** was mixed with *t*-butyldimethylsilyl and 2,6-lutidine in dichloromethane and stirred for 2 hours. The reaction was then quenched with water and extracted with DCM. The organic layer was then dried with Na_2SO_4. After purification via silica gel column chromatography, the compound **14** was isolated under the form of a colorless oil with a yield of 85.7%. This reaction has been performed three times in total with similar yield. The ^{1}HNMR and ^{13}CNMR spectrum analysis of the isolated compound was conclusive of the conversion of the hydroxy group into the TBDMS-protected hydroxy group, which identified the isolated compound as the desired compound **14**.

3.2.4. Compound 15

The third step of the synthesis of the second building-block consisted in the deprotection of the benzyl-protected primary alcohol. The deprotection of benzyl-protected alcohol are usually carried with a hydrogenolysis of the ether using a Pd-catalyst under H_2 atmosphere. The reaction is commonly performed in ethyl acetate and results in very good yield. The first procedure used has been adapted from a previous work done by Hatzivassiliou and co-workers on a similar substrate.[87] Unfortunately, the procedure, which is described below and illustrated in scheme 3.7, did not permit the removing of the benzyl protection and the synthesis of compound **15**.

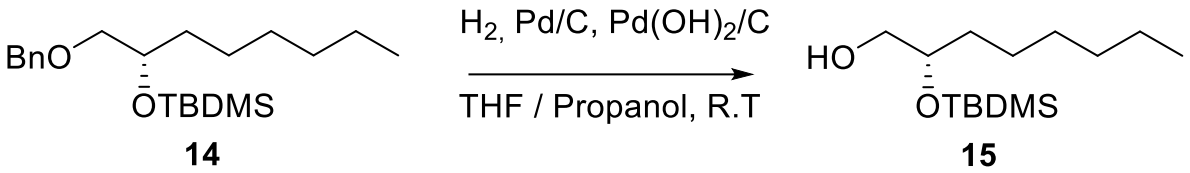


14 **15**

Scheme 3.7 : Attempted hydrogenolysis of the benzyl ether in ethyl acetate

Under inert atmosphere and in a dry balloon, the compound **14** was mixed in ethyl acetate. The palladium on activated carbon catalyst was then added in the mixture and flushed with nitrogen. The balloon was then flushed with H_2 and put under H_2 atmosphere. The reaction was then stirred for 24 hours before being filtrated. It is noteworthy that hydrogenated palladium has to be manipulated cautiously, due to risk of ignition, the filter cake was continuously washed with ethyl acetate to prevent it. After purification via silica gel column chromatography, only the compound **14** was retrieved, presenting the same Rf and NMR spectrum.

The precedent procedure showed no results, despite being performed four times, with conditions usually described for this reaction. Palladium hydroxide on activated carbon has also been tried as a palladium catalyst and showed the same result. More research were done, and it appeared that another research group led by Li and co-workers encountered similar unexpected issues.[88] They proposed an alternative procedure that is described below, with a combination of palladium catalyst, palladium and palladium hydroxide on activated carbon, in a mix of tetrahydrofuran and propanol. This procedure showed satisfying results in the synthesis of compound **15** shown in scheme 3.8.



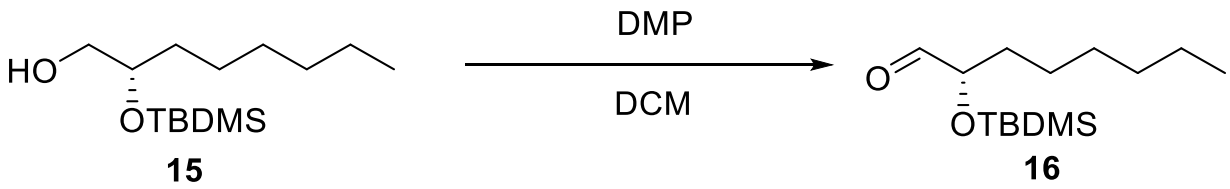
Scheme 3.8 : Successful hydrogenolysis of the benzyl ether to obtain compound **15**

Under inert atmosphere and in a dry balloon, the compound **14** was added to a mix of tetrahydrofuran and propanol, with a ratio of 3:1. The palladium catalysts Pd/C and $Pd(OH)_2/C$ were then added in the mixture, and flushed with nitrogen. The balloon was then flushed with H_2 and put under H_2 atmosphere. The reaction was then stirred for 24 hours before being filtrated. After purification via silica gel column chromatography, the compound **15** was isolated under the form of a colorless oil, with a yield of 55.9%. The ^{1}HNMR and ^{13}CNMR spectrum analysis were conclusive with the removal of the benzyl ring, and thus with the formation of the alcohol. This procedure has been performed two more times with similar yield.

A mechanistic explanation does not exist yet to detail how the combination of the two catalysts allows the reaction to perform when the reported working reaction condition does not. It is also noteworthy that the deprotection of benzyl-protected alcohol is also solvent dependent and showed good reaction rate in THF.[32] As a working procedure has been determined, the focus was made on the rest of the synthesis.

3.2.5. Compound 16

The last step of the preparation of the second-building block consisted in the preparation of the desired aldehyde to perform the Mukaiyama aldol addition. To prepare the compound **16** shown in the scheme 3.9, an oxidation of the freshly deprotected primary alcohol has been conducted using Dess-Martin periodinane. The procedure used to perform this reaction is described below.

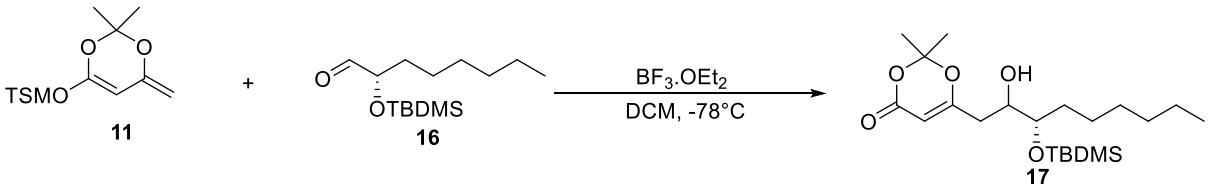


Scheme 3.9 : Synthesis of compound **16** via a Dess-Martin oxidation

The compound **15** was mixed in dichloromethane cooled to 0°C. Then, the Dess-Martin were added, and the cooling bath removed. The reaction was stirred for 4 hours at room temperature before being quenched with $Na_2S_2O_3$. The aqueous phase was extracted with dichloromethane, and the organic layer was dried on Na_2SO_4. After evaporation of the solvent and purification via silica gel column chromatography, the compound **16** was isolated under the form of a colorless oil, with a yield of 80%. The reaction has been performed two more times with similar yield. The ^{1}HNMR and ^{13}CNMR spectrum analysis of the isolated compound was conclusive of the conversion of the primary alcohol into an aldehyde, which identified the isolated compound as the desired compound **16**.

3.2.6. Compound 17

Once the two building-blocks **11** and **16** were synthesized, the next step consisted of performing a Mukaiyama aldol addition to form the compound **17** illustrated in scheme 3.10. Similar reactions involving the compound **11** have been reported to be successful[41, 67-69] and the procedure used, described below, was adapted from those previous works.



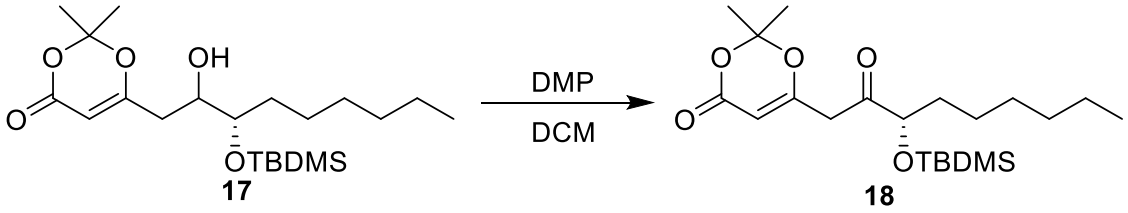
Scheme 3.10 : Synthesis of compound **17** via a Mukaiyama aldol addition

Under inert atmosphere and in a dry balloon, the compounds **11** and **16** were mixed in anhydrous dichloromethane at -78°C, using a dry ice / acetone cooling bath. The Lewis acid needed to perform the electrophilic activation of the aldehyde, $BF_3.OEt_2$, was then added dropwise over a period of 10 minutes. The reaction was then stirred for 1 hour. After that time, the mixture has been quenched with $NaHCO_3$ and extracted with dichloromethane. After being washed with brine, the organic layer has been dried on Na_2SO_4 and the solvent was evaporated. A purification via silica gel column chromatography has been attempted, but the starting material and compound **17** shared similar Rf, which did not allow to separate them. However, the purification allowed to remove some of the impurities with higher Rf in the mixture and the mixture has been used as such in the next step, with the yield calculated over those 2 steps.

To ensure the maximum conversion of the compound **16**, and considering that the yield obtained during the compound **11** synthesis has been overestimated due to the presence of solvent in the mixture, a large excess of the compound **11** has been used.

3.2.7. Compound 18

Once the coupling between the compounds **11** and **16** was done, the aim of the synthesis was to form the suitable *α*-pyrone ring via an *oxo*-Diels-Alder reaction. To be able to perform this reaction, the hydroxyl group formed in the previous step needed to be oxidized to form a ketone as shown in scheme 3.11. The hydroxy group has been oxidized using Dess-Martin periodinane and the procedure followed is described below.

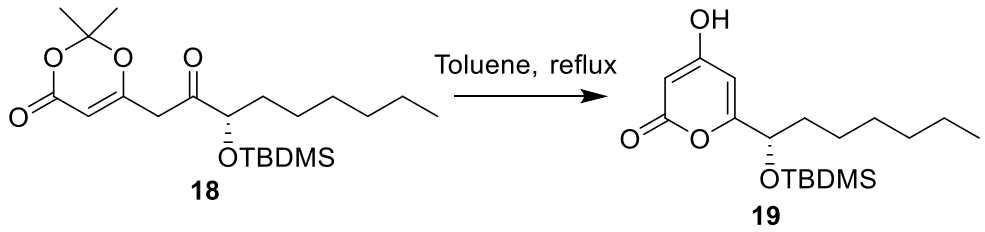


Scheme 3.11 : Synthesis of compound **18** via a Dess-Martin oxidation

The partially purified compound **17** has been mixed in dichloromethane at 0 °C. Then, the Dess-Martin periodinane was added, and the cooling bath removed. The reaction was stirred for 4 hours at room temperature before being quenched with $Na_2S_2O_3$. The aqueous phase was extracted with dichloromethane, and the organic layer was dried on Na_2SO_4. After evaporation of the solvent and purification via silica gel column chromatography, the compound **17** was isolated under the form of a colorless oil. The overall yield of the Mukaiyama aldol addition and the oxidation was 56% over those two steps. The ^{1}HNMR and ^{13}CNMR spectrum analysis of the isolated compound was conclusive of the conversion of the alcohol into a ketone with notably the distinctive peak on the ^{13}CNMR spectra at δ=207 ppm, characteristic of a ketone, which identified the isolated compound as the desired compound **18**.

3.2.8. Compound 19

Once the suitable substrate **18** to perform the intramolecular oxo Diels-Alders has been synthesized, the next step was to form the pyrone ring and so the compound **19** presented in scheme 3.12. Different working procedures have been reported for this reaction[41, 67, 68] and the procedure, which is described below, has been adapted from a method developed by Sato and co-workers, and which has been successfully used in previous reported work.

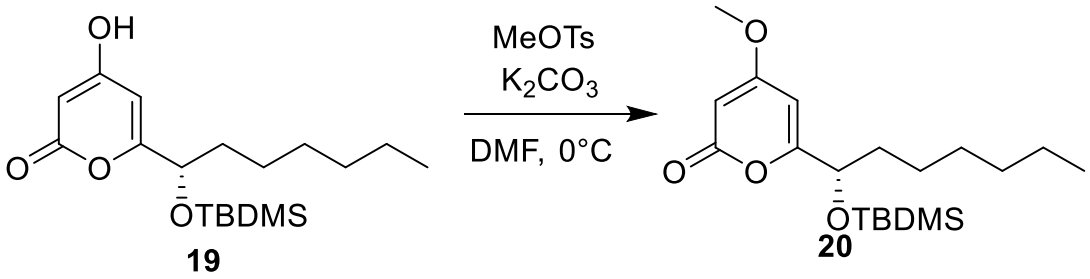


Scheme 3.12 : Synthesis of compound **19** via an intramolecular *oxo*-Diels-Alder reaction

In refluxed anhydrous toluene under nitrogen atmosphere, the compound **18** has been added dropwise over a period of 20 minutes. The reaction has then been stirred and refluxed over a period of 40 minutes, the solvent was then evaporated. After purification via silica gel column chromatography, the compound **19** was isolated under the form of a light-yellow oil with a yield of 51%. The ^{1}HNMR and ^{13}CNMR spectrum analysis of the isolated compound was conclusive of the formation of the *α*-pyrone ring, are the characteristic peaks for δ = 5.58 ppm (proton H-3) and δ = 6.26 ppm (proton H-5) of the *α*-pyrone ring were present on the ^{1}HNMR, which identified the isolated compound as the desired compound **19**.

3.2.9. Compound 20

The compound **19** is close to the Dothideopyrone A [**1**] which is the target compound of this synthesis pathway. The pyrone ring has been formed, with the desired substituent at the position 6 of the cycle. To obtain the Dothideopyrone A [**1**], the hydroxy group at the position 4 of the cycle must be transformed into a methoxy group, a hydroxymethyl group has to be formed at the position 3 and the chiral secondary alcohol must be deprotected. To perform the methylation at the position 4 of the cycle and obtain the compound **20** shown in scheme 3.13, a Williamson ether synthesis reaction has been used. The procedure, described below, has been adapted from a previous synthesis performed by Oikawa and coworker[78, 89], using methyl *p*-toluenosulfonate as the methyl source and K_2CO_3 as the base.



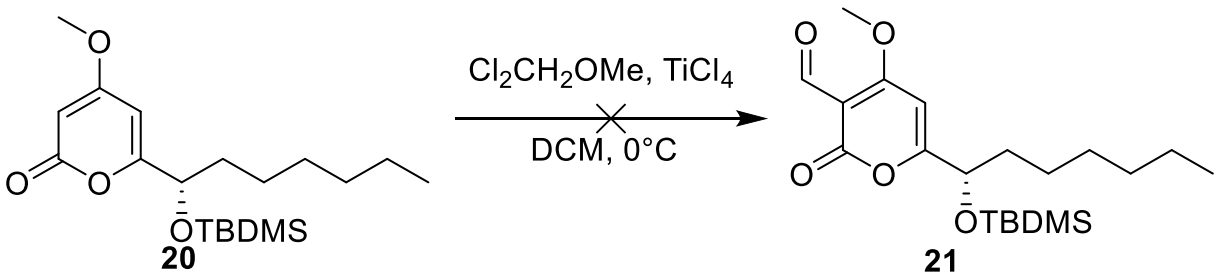
Scheme 3.14 : Synthesis of compound **20** via a Williamson ether synthesis

The compound **19** has been mixed in DMF, cooled at 3 °C. The base K_2CO_3 and the methyl source methyl *p*-toluenosulfonate were then added in the mixture. The cooling bath has then been removed and the mixture was stirred for 18 hours at room temperature. After this duration, the mixture was poured into water and the aqueous phase was extracted with dichloromethane and the combined organic phase were then washed abundantly with water, to remove the DMF, and brine. The organic layer has then been dried on $MgSO_4$ and the solvent was evaporated. A purification via silica gel column chromatography has been attempted, but both the compound **20** and the methyl *p*-toluenosulfonate shared the same Rf and consequently they were not separable via column chromatography. The ^{1}HNMR and ^{13}CNMR spectrum analysis confirmed both the presence of the methyl *p*-toluenosulfonate and the formation of the methoxy group with a characteristic peak for δ = 3.80 ppm. However, due to the important amount of methyl *p*-toluenosulfonate, it was not possible to have a good estimation of the yield and consequently of the quantity of compound **20** synthesized.

3.2.10. Compound 21

During the previous step, a low amount, 31 mg, of a mixture of the compound **20** and MeOTs has been obtained. Still, an attempt of synthesis of the compound **21** have been performed. Even if this attempt appeared to be unsuccessful, the results have to be put into perspective.

This step consisted in performing a Rieche formylation at the position 3 of the *α*-pyrone ring, with the aim to reduce the aldehyde obtained in the next step to obtain the TBS-protected Dothideopyrone A **22**. Such a reaction have been reported to be successful and performed on a less substituted but similar pyrone ring.[78] The Rieche formylation necessitate a strong Lewis acid, $TiCl_4$ in this procedure, and dichloromethyl methyl ether as the formyl agent. The procedure used is described below.



Scheme 3.15 : Attempted formylation to obtain the compound **21**

The compound **20** has been mixed in anhydrous dichloromethane at 3 °C, under nitrogen atmosphere and in dry glassware. The Lewis acid $TiCl_4$ was then added to the mixture, followed by the slow addition, dropwise, of the dichloromethyl methyl ether. The mixture was then allowed to warm at room temperature and stirred for 6 hours. The mixture was continuously

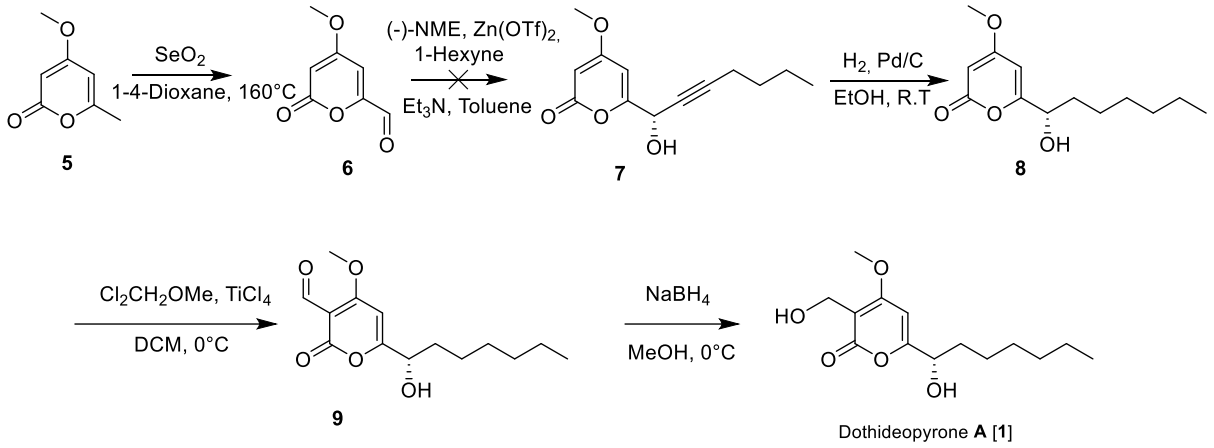
flushed with nitrogen to remove the HCl formed during the reaction. After the 6 hours, the mixture was slowly poured on crushed ice and stirred, then extracted with dichloromethane. The organic layer was then washed with $NaHCO_3$ and brine, then filtrated on $MgSO_4$ and the solvent was evaporated.

This procedure has been attempted twice, however during the first attempt, the continuous flow of nitrogen evaporated the dichloromethane, and the reaction ran dry, the compound was lost. For the second attempt run with 20mg, dichloromethane was regularly added in the mixture to compensate the loss of solvent during the reaction. However, a purification via silica gel column chromatography was only able to retrieve the methyl *p*-toluenosulfonate, which was confirmed with the ^{1}HNMR and ^{13}CNMR spectrum analysis. It is important to precise that after purification, only 2mg of product were retrieved. It is possible that the procedure worked, but due to the low amount of both compound **20** and retrieved product after purification, there was not enough of compound **21** to be able to spot it on TLC or to obtain an exploitable NMR spectrum.

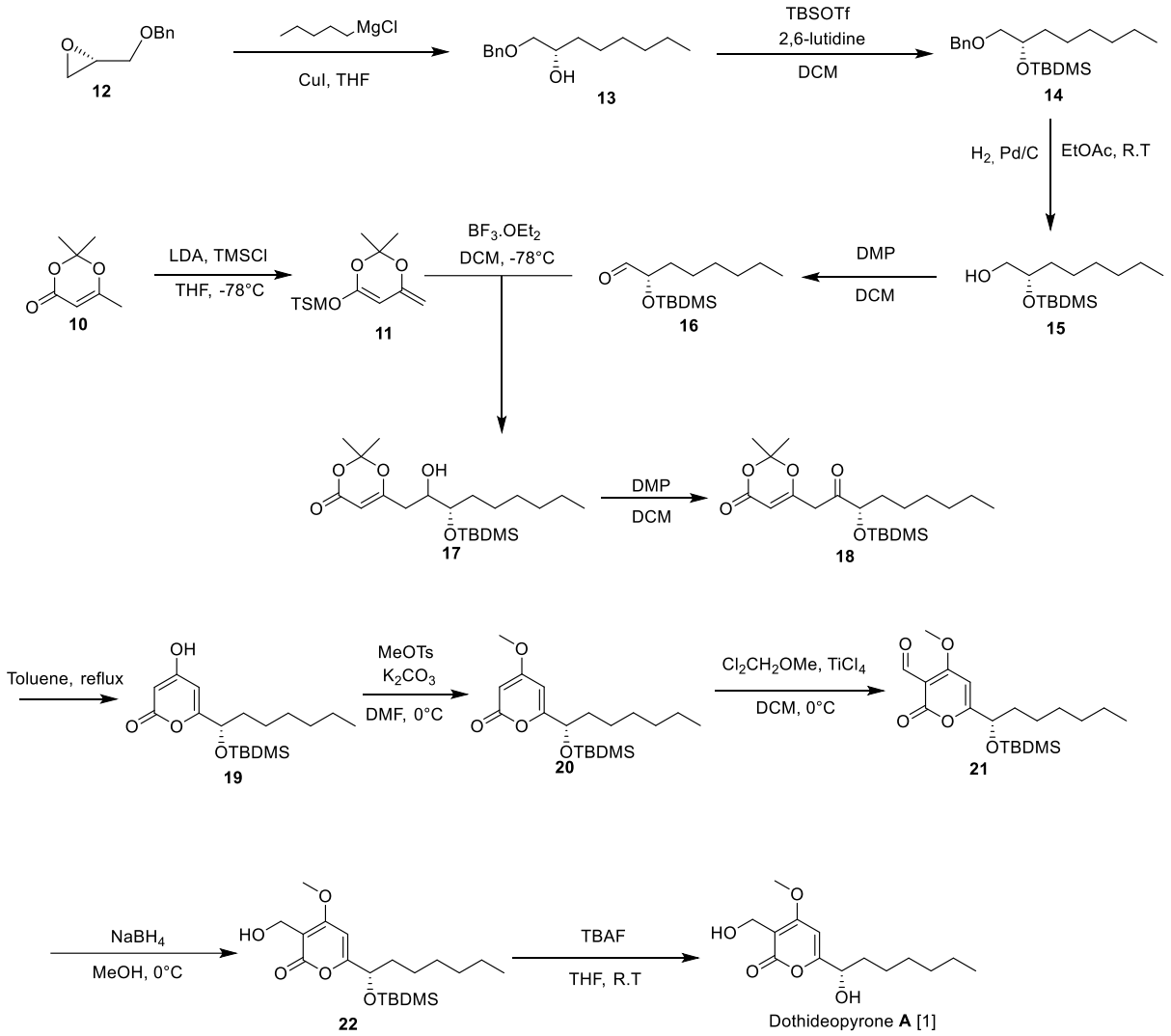
Consequently, this procedure cannot be ruled out based on this attempt alone, further investigations are needed at a greater scale. Unfortunately, such investigations could not be conducted in this thesis due to the lack of available compound **20** at this moment, and the lack of time to perform a full-scale up to obtain it.

4. Conclusion and future work

The aim of the thesis was to perform the total synthesis of the Dothideopyrone A [**1**] and, from that point, to synthesize the Dothideopyrone B [**2**], C [**3**] and D [**4**]. Two synthesis pathways have been considered as seen in scheme 4.1 and 4.2:



Scheme 4.1 : Attempted synthesis of the Dothideopyrone A [**1**] via a linear synthesis strategy, the Carreira alkynylation reaction remained unsuccessful despite the different conditions envisaged



Scheme 4.2 : Attempted synthesis of the Dothideopyrone A [**1**] via a convergent synthesis strategy, the Rieche formylation did not appeared to be successful, further investigations are needed and the reaction could work at a greater scale

The first, linear synthesis pathway has resulted to be unsuccessful due to the Carreira alkynylation condition, unsuitable when used on a α-pyrone ring substrate. The reaction could be investigated further, as the Carreira alkynylation could be an useful reaction for the synthesis of similar compounds.

The second, convergent synthesis pathway appeared to be more promising, even if the Dothideopyrone A [**1**] has not been obtained, mostly due to a lack of time to perform the remaining work. The synthesis of compound **11** to compound **19** have been performed with satisfactory yield, even if the synthesis of compound **15** appeared to be challenging and determination of suitable reaction conditions needed some investigations. The compound **20** has been obtained with mild yield, however in accordance with yield reported in previous

work. The compound **21** has not been isolated nor detected, further investigations are needed to determine if the Rieche formylation can be conducted on the substrate **20**. Such investigations could not be carried during this thesis due to a lack of time to perform an additional scale-up. Consequently, the synthesis of Dothideopyrones B [**2**] , C [**3**] and D [**4**] has not been attempted during this thesis. Overall, 10 compounds were successfully synthesized during this thesis, despite none of the Dothideopyrones have been reached.

Even if the synthesis work carried during this thesis did not allowed to isolate the first target compound Dothideopyrone A [**1**], this thesis has set important stepping stones to perform the total synthesis of all known Dothideopyrones, and to eventual new derivatives. The work performed during this thesis will be continued by another research team using compound **14** and **17** synthesized during the thesis as a starting point. The hopefully resulting compounds Dothideopyrones A-D [**1**-**4**] will then be tested for their antimicrobial activity, with the aim to find a lead compound opening the road to new antibiotics.

5. Experimental section

General information

All reagents and solvents used in the experiments were commercially available, and were used without further purification. All reagents were purchased from Sigma Aldrich. To perform reaction above room temperature (22°C), an oil bath was used for heating purpose. Reaction at 0 °C were performed with a cooling bath of ice and water. Reaction at -40 °C were performed in a cooling bath of acetonitrile and dry ice. Reaction at -78 °C were performed with a cooling bath of acetone and dry ice. Temperature of cooling bath were monitored with an adequate thermometer. All reaction were stirred with a Teflon coated magnetic stir bar. Dry solvents were collected from a Braun MB SPS-800 Solvent Purification System, and filtered and deionized water was used. All reactions were monitored using thin layer chromatography (TLC, silica gel on aluminium plates, F254, Merck). The plates were visualized using UV-light (wave length 254 nm and 365 nm). A potassium permanganate TLC stain were used when adequate. Column chromatography was performed using silica gel (40-63 mesh, 60 A) as the stationary phase, and eluent systems are specified for each separation.

Spectroscopic analysis:

1H NMR and 13C NMR spectra were recorded on a Bruker Avance III HD instrument operating at 400 or 600 MHz for proton and 100 MHz or 150 MHz for carbon. Deuterated chloroform-D_3 was used as solvent. Chemical shifts are reported in d (ppm), calibrated to the solvent signal in chloroform-D (7.26 ppm in 1H and 77.36 in 13C). Coupling constants, *J*, are expressed in Hz. Signals are defined according to their multiplicity: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), p (pentet), m (multiplet), br is used when peak broadening is seen. Missing signals in the 13C spectra are marked by *.

5.1. Synthesis of compound 6

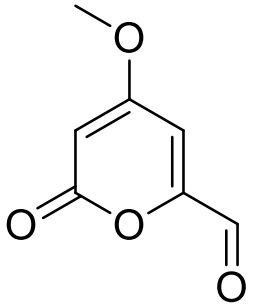
4-methoxy-2-oxo-2H-pyran-6-carbaldehyde (6)

Molecular formula: $C_7H_6O_4$

Formula Weight: 154.12 $g.mol^{-1}$

Aspect: Light-yellow solid

Yield: 65%



6

Procedure:

In a 50mL sealed tube previously flushed with nitrogen, SeO_2 (5eq, 10mmol, 1,109g) and 2*H*-pyran-2-one-4-methoxy-6-methyl (**5**) (1eq, 2mmol, 280mg) were added in 1-4 dioxane (20mL). The reaction was heated at 160°C for 4 hours. The mixture has then been diluted in EtOAc and filtrated, washed with brine, extracted with EtOAc and dried on $MgSO_4$. Evaporation of the solvent and purification via flash chromatography on silica gel (EtOAc/Pentane 1:1) gave the compound (**6**) as a light-yellow solid with a yield of 65% (200mg). This procedure has been repeated five more times, with similar yields.

Characterization: (Appendix A)

^{1}H-NMR (600 MHz, $CDCl_3$-D_3): δ : 9.54 (s, 1H), 6.69 (d, *J* = 2.3 Hz, 1H), 5.76 (d, *J* = 2.3 Hz, 1H), 3.88 (s, 3H),

5.2. Synthesis of compound 7

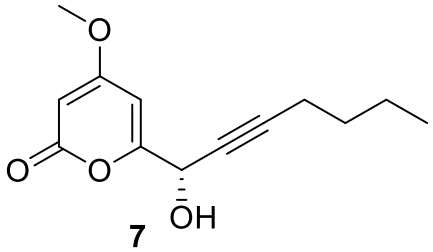
(S)-6-(1-hydroxyhept-2-yn-1-yl)-4-methoxy-2H-pyran-2-one (7)

Molecular formula: $C_{14}H_{18}O_4$

Formula Weight: 250.29 $g.mol^{-1}$

Aspect: N/A

Yield: N/A



7

Procedure:

To $Zn(OTf_2)$ (1.1eq) previously dried under vacuum for 16h has been added DCM. (-)-NME (1.2eq) was then added. Then Et_3N (1.2eq-2.4eq) was added to the mixture and stirred for 3h. Then 1-hexyne (1.1 eq) was added and the mixture was stirred for 30min. Then (**6**) (1eq), diluted in DCM, was slowly added during 12h and the reaction was stirred. The mixture was then washed with HCl, H_2O and brine, the aqueous layer was then extracted with DCM and dried on $MgSO_4$. Filtration and evaporation of the solvent followed by purification via flash chromatography on silica gel (EtOAc/Pentane 1:1) allowed to retrieve the starting material and the degraded starting material. Compound **7** was not isolated nor detected via NMR.

	Attempt A	Attempt B	Attempt C	Attempt D	Attempt E	Attempt F
$Zn(OTf)_2$	1.1eq, 1.1mmol, 400mg	1.1eq, 1.1mmol, 400mg	1.1eq, 1.1mmol, 400mg	1.1eq, 0.66mmol, 240mg	1.1eq, 0.66mmol, 240mg	1.1eq, 0.66mmol, 240mg
(-)-NME	1.2eq, 1.2mmol, 215mg	1.2eq, 1.2mmol, 215mg	1.2eq, 1.2mmol, 215mg	1.2eq, 0.72mmol, 129mg	1.2eq, 0.72mmol, 129mg	1.2eq, 0.72mmol, 129mg
Et_3N	1.2eq, 1.2mmol, 121mg	2.4eq, 2.4mmol, 242mg	1.8eq, 1.8mmol, 182mg	1.5eq, 0.90mmol, 91mg	1.2eq, 0.72mmol, 73mg	1.8eq, 1.08mmol, 110mg
1-Hexyne	1,1eq, 1,1mmol, 90mg	1,1eq, 1,1mmol, 90mg	1,1eq, 1,1mmol, 90mg	1.1eq, 0.66mmol, 54mg	1.1eq, 0.66mmol, 54mg	1.1eq, 0.66mmol, 54mg
6	1eq, 1mmol, 154mg	1eq, 1mmol, 154mg	1eq, 1mmol, 154mg	1eq, 0.60mmol, 93mg	1eq, 0.60mmol, 93mg	1eq, 0.60mmol, 93mg
DCM (ini/**6**)	15mL/15mL	15mL/15mL	5mL/10mL	15mL/15mL	5mL/10mL	15mL/15mL
Reaction duration	48h	55h	46h	50h	68h	70h
Slow addition **6** (Y/N)	N	Y	Y	Y	Y	Y

Table 5.1 : Reaction condition operated for the attempted Carreira alkynylation

Characterization:

Rf: N/A
^{1}H-NMR: N/A
^{13}C-NMR: N/A

5.3. Synthesis of compound 11

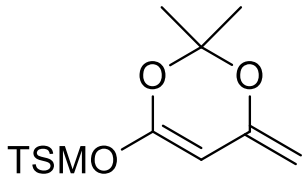
4H-1,3-Dioxin, 2,2-dimethyl-4-methylene-6-[(trimethylsilyl)oxy]- (11)

Molecular formula: $C_{10}H_{18}O_3Si$

Formula Weight: 214.33 $g.mol^{-1}$

Aspect: Brown oil + solid (raw product)

Yield: 88%



11

Procedure:

n-Butyllithium (1.6 M in hexane, 1.1eq, 13,75 mL, 22 mmol) was added to a solution of diisopropylamine (1.1eq, 3.08 mL, 22 mmol) in THF (20 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. 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one **10** (1eq, 2.65 mL, 20 mmol) was added over a period of 30 min and stirring was continued for 1 h before chlorotrimethylsilane (1.2eq, 3.04 mL, 24 mmol) was added over a period of 20 min. After stirring for 40 min the reaction mixture was allowed to reach room temperature, stirred for additional 2 h and filtrated on $MgSO_4$. The filter cake was rinsed with pentane and the filtrate concentrated in vacuo. The compound **11** has not been purified and the crude product was used for the synthesis of compound **17**. The raw mixture had a mass of 5.3g, and the yield has been estimated with the NMR yield determination without internal standard method as 88%

Characterization: (Appendix B)

^{1}H-NMR: Not purified

^{13}C-NMR: Not purified

5.4. Synthesis of compound 13

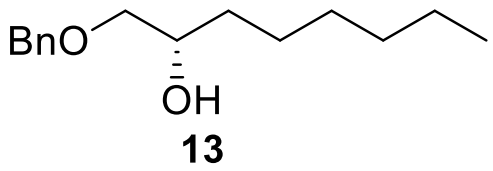
(S)-1-(benzyloxy)octan-2-ol (13)

Molecular formula: $C_{15}H_{24}O_2$

Formula Weight: 236.35 g.mol^{-1}

Aspect: Colorless oil

Yield: 87%



13

Procedure:

At room temperature, pentylmagnesium chloride (2M in THF, 3eq, 36,6mmol, 18.3mL) and CuI (0.05eq, 0.61mmol, 115mg) were mixed in dry THF (20mL). The mixture was then cooled at -78°C and (S)-(+) Glycidyl benzyl ether **12** (1eq, 12.18mmol, 2g) diluted in dry THF (10mL) was added. The mixture has then been warmed up to -40°C and stirred for 4h. The reaction was then quenched with NH_4CL (10mL), extracted with EtOAc. The organic layer was then washed with brine and dried on Na_2SO_4. Evaporation of the solvent and purification via flash chromatography on silica gel (EtOAc/Pentane 4:96 to 1:9) gave the compound **13** as a colorless oil with a yield of 87% (2.505g).

Characterization: (Appendix C)

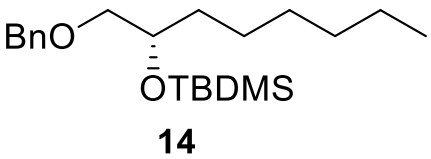
Rf: 0.28 (EtOAc/Pentane 4:96)

^{1}H-NMR (600 MHz, $CDCl_3$-D_3): δ : 7.34 (m, 4H), 7.30 (m, 1H), 4.55 (s, 2H), 3.81 (m, 1H), 3.50 (dd, *J* = 3.0Hz/9.7Hz, 1H), 3.32 (t, *J* = 9.4Hz, 1H), 1.43 (m, 2H), 1.28 (m, 8H), 0.89 (t, *J* = 6.7 Hz, 3H)

^{13}C-NMR (150 MHz, $CDCl_3$-D_3): δ : 138.1, 128.5, 127.8, 127.7, 77.2, 77.0, 76.8, 74.7, 73.4, 70.5, 33.2, 31.8, 29.3, 25.5, 22.6, 14.1

5.5. Synthesis of compound 14

(S)-((1-(benzyloxy)octan-2-yl)oxy)(tert-butyl)dimethylsilane (14)



14

Molecular formula: $C_{21}H_{38}O_2Si$

Formula Weight: 350.61 $g.mol^{-1}$

Aspect: Colorless oil

Yield: 85.7%

Procedure:

(2S)-1-phenoxyoctan-2-ol **13** (1eq, 9.73mmol, 2.3g), 2,6-Lutidine (2eq, 19.46mmol, 2.1g, 2.3mL) and TBSOTf (1.5eq, 14.6mmol, 3.9g, 3.5mL) were stirred in DCM (60mL) for 2h, the reaction has been quenched with H_2O and extracted with DCM. The mixture was then dried on Na_2SO_4. Evaporation of the solvent and purification via flash chromatography on silica gel (EtOAc/Pentane 4:96 to 1:9) gave the compound **14** as a colorless oil with a yield of 85.7% (2.925g).

Characterization: (Appendix D)

Rf: 0.88 (EtOAc/Pentane 4:96)

^{1}H-NMR (600 MHz, $CDCl_3$-D_3): δ : 7.36 (m, 4H), 7.30 (m, 1H), 4.55 (s, 2H), 3.85 (m, 1H), 3.41 (m, 2H), 1.57 (m, 1H), 1.45 (m (br), 2H), 1.31 (m, 8H), 0.92 (m, 12H), 0.09 (dd, *J* = 2.7Hz/5.5Hz, 6H)

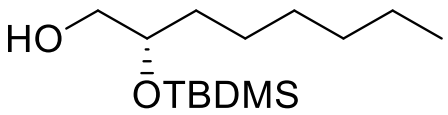
^{13}C-NMR (150 MHz, $CDCl_3$-D_3): δ : 138.6, 128.3, 127.6, 127.5, 77.3, 77.1, 76.8, 74.9, 73.3, 71.6, 34.8, 31.9, 29.5, 25.9, 25.2, 22.7 18.2, 14.1, -4.3, -4.7

5.6. Synthesis of compound 15

(S)-2-((tert-butyldimethylsilyl)oxy)octan-1-ol (15)

Molecular formula: $C_{14}H_{32}O_2Si$

Formula Weight: 260.48 $g.mol^{-1}$



15

Aspect: Colorless oil

Yield: 55.9%

Procedure:

(2S)-1-phenoxyoctan-2-[(tert-Butyldimethylsilyl)oxy-] **14** (1eq, 3.86mmol, 1.3g) is mixed in THF (30mL) / propanol (10mL) with Pd/C 10% (260mg) and $Pd(OH)_2$/C 20% (130mg) under inert atmosphere. The mixture is then flushed with H_2 and put under H_2 pressure and stirred for 24h. The mixture was then filtrated on a celite bed. Evaporation of the solvent and purification via flash chromatography on silica gel (EtOAc/Pentane 5:95 to 1:9) gave the compound **15** as a colorless oil with a yield of 55.9% (587mg).

Characterization: (Appendix E)

Rf: 0.30 (EtOAc/Pentane 5:95)

^{1}H-NMR (600 MHz, $CDCl_3$-D_3): δ : 3.72 (m, 1H), 3.56 (m, 1H), 3.44 (p, *J* = 5.6 Hz, 1H), 1.48 (q, *J* = 7.0 Hz, 2H), 1.28 (m, 8H), 0.90 (t, *J* = 2.9 Hz, 9H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.08 (t, *J* = 3.1 Hz, 6H)

^{13}C-NMR (150 MHz, $CDCl_3$-D_3): δ : 77.2, 77.0, 76.8, 72.9, 66.3, 34.1, 34.0, 31.8, 29.5, 25.9, 25.3, 22.6, 22.3, 18.1, 14.1, -4.4, -4.5

5.7. Synthesis of compound 16

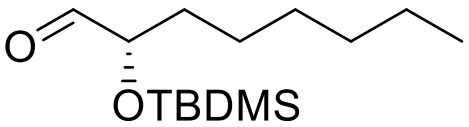
(S)-2-((tert-butyldimethylsilyl)oxy)octanal (16)

Molecular formula: $C_{14}H_{30}O_2Si$

Formula Weight: 258.47 $g.mol^{-1}$

Aspect: Colorless oil

Yield: 80%



16

Procedure:

(2S)-octan-2-[(tert-Butyldimethylsilyl)oxy-]-1-ol **15** (1eq, 1.92mmol, 500mg) is mixed in DCM (18mL) and cooled to 0 °C. DMP (0.3M in THF/Hexane, 1.2eq, 2.3mmol, 8mL) was then added, the cooling bath was removed and the mixture was stirred for 4h. The mixture was then quenched with $Na_2S_2O_3$ (10mL) and extracted with DCM. The organic layer was then washed with brine and dried on Na_2SO_4. Evaporation of the solvent and purification via flash chromatography on silica gel (EtOAc/Pentane 7:93 to 1:9) gave the compound **16** as a colorless oil with a yield of 80% (398mg).

Characterization: (Appendix F)

Rf: 0.63 (EtOAc/Pentane 1:9)

^{1}H-NMR (400 MHz, $CDCl_3$-D_3): δ : 9.58 (d, *J* = 1.7 Hz, 1H), 3.96 (m, 1H), 1.60 (m, 2H), 1.38 (m, 2H), 1.27 (m, 6H), 0.92 (t, *J* = 2.9 Hz, 9H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.07 (d, *J* = 3.6 Hz, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$-D_3): δ : 204.5, 77.7, 77.3, 77.2, 77.0, 76.7, 32.6, 31.6, 29.1, 25.7, 24.6, 22.5, 18.2, 14.0, -4.6, -4.9

5.8. Synthesis of compound 17

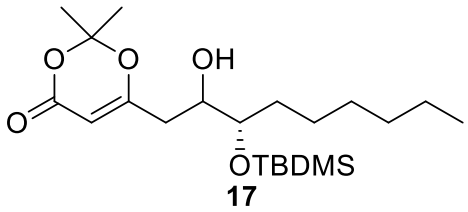
6-(3S)-3-((tert-butyldimethylsilyl)oxy)-2-hydroxynonyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (17)

Molecular formula: $C_{21}H_{40}O_5Si$

Formula Weight: 400.62 $g.mol^{-1}$

Aspect: Colorless oil

Yield: N/A



17

Procedure:

In anhydrous DCM, **11** (Raw product, 3eq, 3.6mmol, 1.4g) and **16** (1eq, 1.2mmol, 300mg) are mixed at -78°C under inert atmosphere. $BF_3.OEt_2$ (1.8eq, 2.1mmol, 298mg, 0.26mL) is then added slowly over a period of 10min, and the mixture was then stirred for 1h. The mixture was then quenched with $NaHCO_3$ (10mL) and extracted with DCM. The organic layer was then washed with brine and dried over Na_2SO_4. Evaporation of the solvent and partial purification via flash chromatography on silica gel (EtOAc/Pentane 2:8) to remove some of the impurities gave the compound **17** as a colorless oil, with some of the starting materials. The product has been used as such for the next step, and the yield have been calculated for the two reactions.

Characterization:

Rf: 0.57 (EtOAc/Pentane 2:8)

^{1}H-NMR: N/A

^{13}C-NMR: N/A

5.9. Synthesis of compound 18

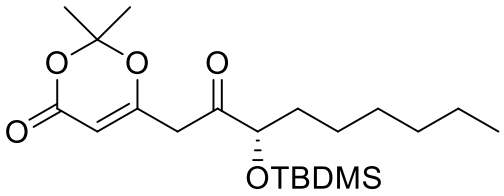
(S)-6-(3-((tert-butyldimethylsilyl)oxy)-2-oxononyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (18)

Molecular formula: $C_{21}H_{38}O_5Si$

Formula Weight: 398.60 $g.mol^{-1}$

Aspect: Colorless oil

Yield: 56% (two steps)



18

Procedure:

17 (Raw product, 1eq, 600mg) is mixed in DCM (30mL) and cooled to 0°C. DMP (0.3M in THF/Hexane, 1.2eq, 1.44mmol, 4.8mL) was then added, the cooling bath was removed, and the mixture was stirred for 4h. The mixture was then quenched with $Na_2S_2O_3$ (10mL) and extracted with DCM. The organic layer was then washed with brine and dried on Na_2SO_4. Evaporation of the solvent and purification via flash chromatography on silica gel (EtOAc/Pentane 2:8 to 4:6) gave the compound **18** as a colorless oil with an overall yield of 56% (200mg) for 2 steps.

Characterization: (Appendix G)

Rf: 0.86 (EtOAc/Pentane 4:6)

^{1}H-NMR (600 MHz, $CDCl_3$-D_3): δ : 5.31 (s, 1H), 4.05 (t, *J* = 6.0 Hz, 1H), 3.48 (s, 1H), 1.70 (d, *J* = 3.9 Hz, 6H), 1.29 (m, 8H), 0.93 (s, 9H), 0.88 (t, *J* = 7.8 Hz, 3H), 0.08 (d, *J* = 12 Hz, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$-D_3): δ : 207.0, 165.3, 160.7, 107.2, 97.0, 77.2, 77.0, 76.8, 41.7, 34.7, 31.6, 29.1, 25.7, 25.1, 25.0, 24.4, 22.5, 18.1, 14.0, -4.8, -4.9

5.10. Synthesis of compound 19

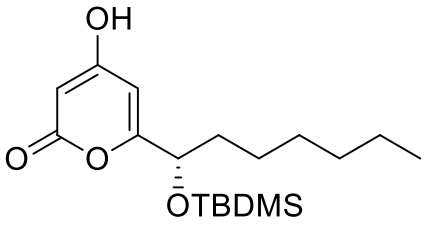
(S)-6-(1-((tert-butyldimethylsilyl)oxy)heptyl)-4-hydroxy-2H-pyran-2-one (19)

Molecular formula: $C_{18}H_{32}O_4Si$

Formula Weight: 340.53 $g.mol^{-1}$

Aspect: Light-yellow oil

Yield: 51%



19

Procedure:

18 (1eq, 45mmol, 180mg) diluted in dry toluene (5mL) is added over 10min in dry refluxed toluene (20mL). The mixture was then stirred and refluxed for 40min. Evaporation of the solvent and purification via flash chromatography on silica gel (EtOAc/Pentane 1:1) gave the compound **19** as a light-yellow oil with a yield of 51% (79mg).

Characterization: (Appendix H)

Rf: 0.3 (EtOAc/ Pentane 1:1)

^{1}H-NMR (600 MHz, $CDCl_3$-D_3): δ : 10.94 (s (br), 1H), 6.26 (d, *J* = 1.7 Hz, 1H), 5.58 (d, *J* = 2.0 Hz, 1H), 4.43 (t, *J* = 5.5 Hz, 1H), 1.71 (m, 2H), 1.27 (m, 8H), 0.91 (s, 9H), 0.86 (t, *J* = 6.7 Hz, 3H), 0.08 (s, 3H), 0.03 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$-D_3): δ : 172.6, 169.3, 167.5, 99.8, 90.1, 77.2, 77.0, 76.8, 71.0, 36.3, 31.7, 29.1, 25.7, 24.3, 22.6, 18.1, 14.1, 14.0, -4.8, -5.0

5.11. Synthesis of compound 20

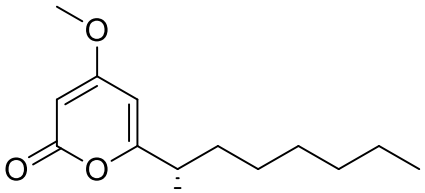
(S)-6-(1-((tert-butyldimethylsilyl)oxy)heptyl)-4-methoxy-2H-pyran-2-one (20)

Molecular formula: $C_{19}H_{34}O_4Si$

Formula Weight: 354.56g.mol^{-1}

Aspect: Light-yellow oil

Yield: 38% (not pure)



20

Procedures:

19 (1eq, 0.23mmol, 80mg) is mixed in DMF (10mL) under nitrogen atmosphere at 0 °C. K_2CO_3 (2eq, 0.46mmol, 64mg) and MeOTs (2eq, 0.46mmol, 85mg) were then added in the mixture. The mixture was then stirred for 18h. The mixture was then poured into water, an extracted with DCM. The aqueous layer was then washed with water (5x10mL), then brine. The mixture was then dried on $MgSO_4$. Evaporation of the solvent and purification via flash chromatography on silica gel (EtOAc/Pentane 1:3 to 1:1) gave the compound **20** as a light-yellow oil with a yield of 38% (31mg). NMR revealed presence of MeOTs in the mixture, which was not separatable via flash chromatography.

Characterization: (Appendix I)

Rf: 0.55 (EtOAc/ Pentane 1:3)

^{1}H-NMR (600 MHz, $CDCl_3$-D_3)^{a,b}: δ : 6.05 (dd, *J* = 0.7Hz/2.3Hz, 1H), 5.39 (d, *J* = 2.4 Hz, 1H), 4.40 (t, *J* = 5.6 Hz, 1H), 3.80 (s, 3H), 2.16 (s, 3H), 1.71 (m, 2H), 1.26 (m, 8H), 0.91 (s, 9H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.08 (s, 3H), 0.03 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$-D_3)^b: δ : 130.1, 129.9, 129.7, 129.7, 128.3, 128.2, 128.1, 127.9, 98.2, 87.7, 77.3, 77.0, 76.8, 71.0, 56.2, 55.9, 36.2, 31.7, 30.9, 29.7, 29.1, 25.8, 24.2, 22.6, 21.8, 21.7, 21.5, 18.1, 14.1, -4.8, -5.0

^{a} Peaks corresponding to MeOTs not reported, ^{b} Sample contaminated by MeOTs

5.12. Synthesis of compound 21

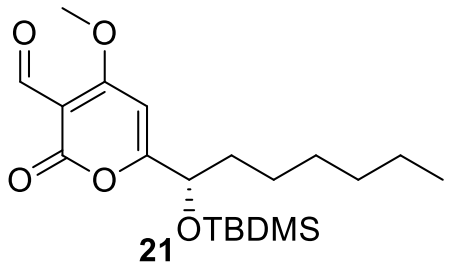
(S)-6-(1-((tert-butyldimethylsilyl)oxy)heptyl)-4-methoxy-2-oxo-2H-pyran-3-carbaldehyde (21)

Molecular formula: $C_{20}H_{34}O_5Si$

Formula Weight: 382.57g.mol^{-1}

Aspect: N/A

Yield: N/A



21

Procedures:

20 (1eq, 0.056mmol, 20mg) was mixed in DCM (10mL) at 0 °C under nitrogen atmosphere. $TiCl_4$ (1M in toluene, 10eq, 0.56mmol, 0.56mL) was then added to the mixture. Dichloromethyl methyl ether (10eq, 0.56mmol, 0.06mL) was then added. A continuous flow of nitrogen was set to remove HCl formed in the balloon. The mixture was warmed to room temperature and stirred for 6h. DCM were added regularly to compensate the evaporation of solvent due to the nitrogen flow. After 6h, the mixture was poured into crushed ice and stirred until the melting of ice. The mixture was then extracted with DCM. The organic layer was then washed with $NaHCO_3$ and brine, then dried on Na_2SO_4. After filtration of the mixture and evaporation of the solvent a purification via flash chromatography on silica gel (EtOAc/Pentane 9:1 to 2:8) was performed and 2mg of a compound were retrieved. NMR showed only presence of MeOTs present in the starting material. Compound **21** was not isolated nor detected.

Characterization:

Rf: N/A

^{1}H-NMR: N/A

^{13}C-NMR: N/A

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Appendix A compound 6

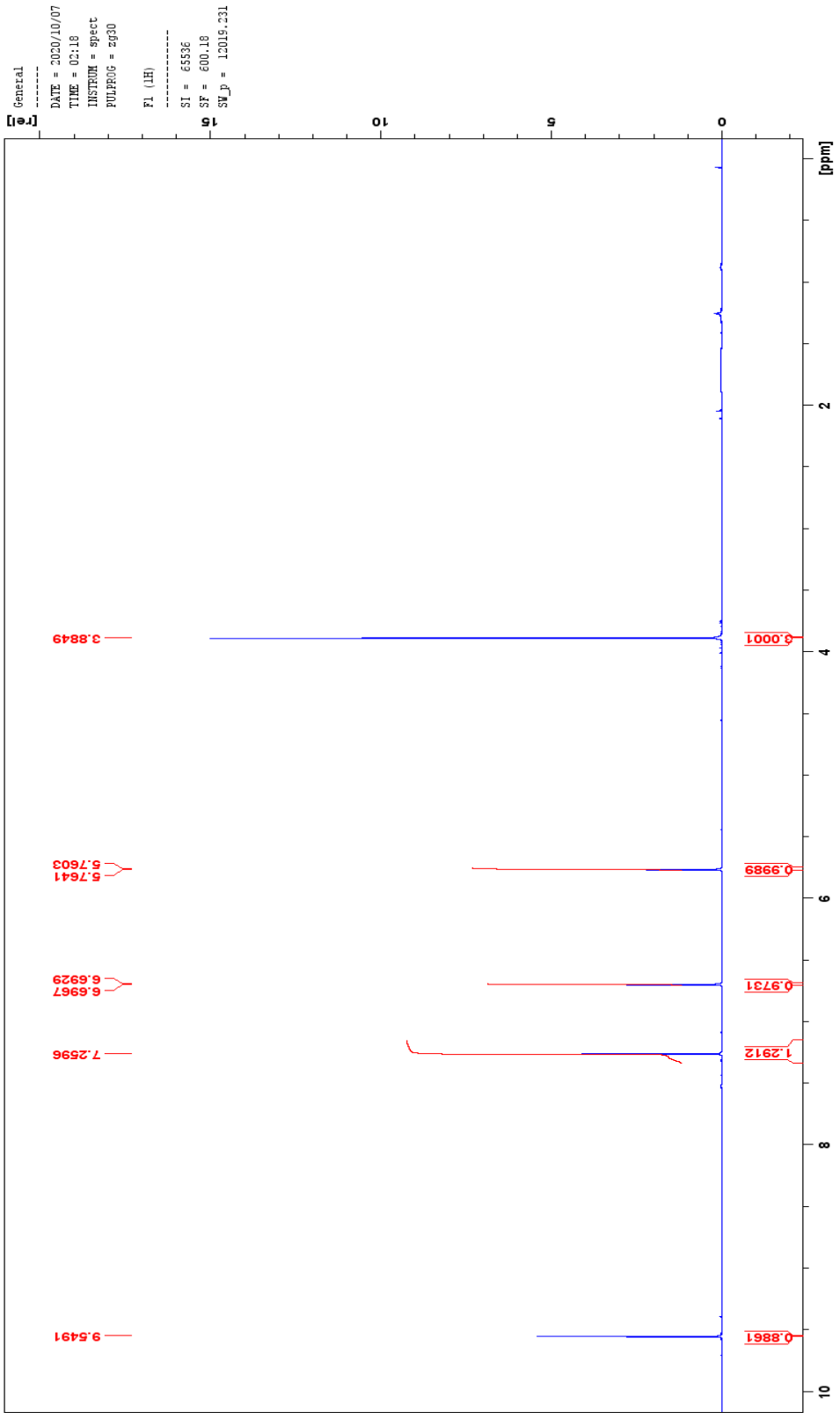


Figure A.1 : ^{1}H NMR spectrum of compound **6**

Appendix B compound 11

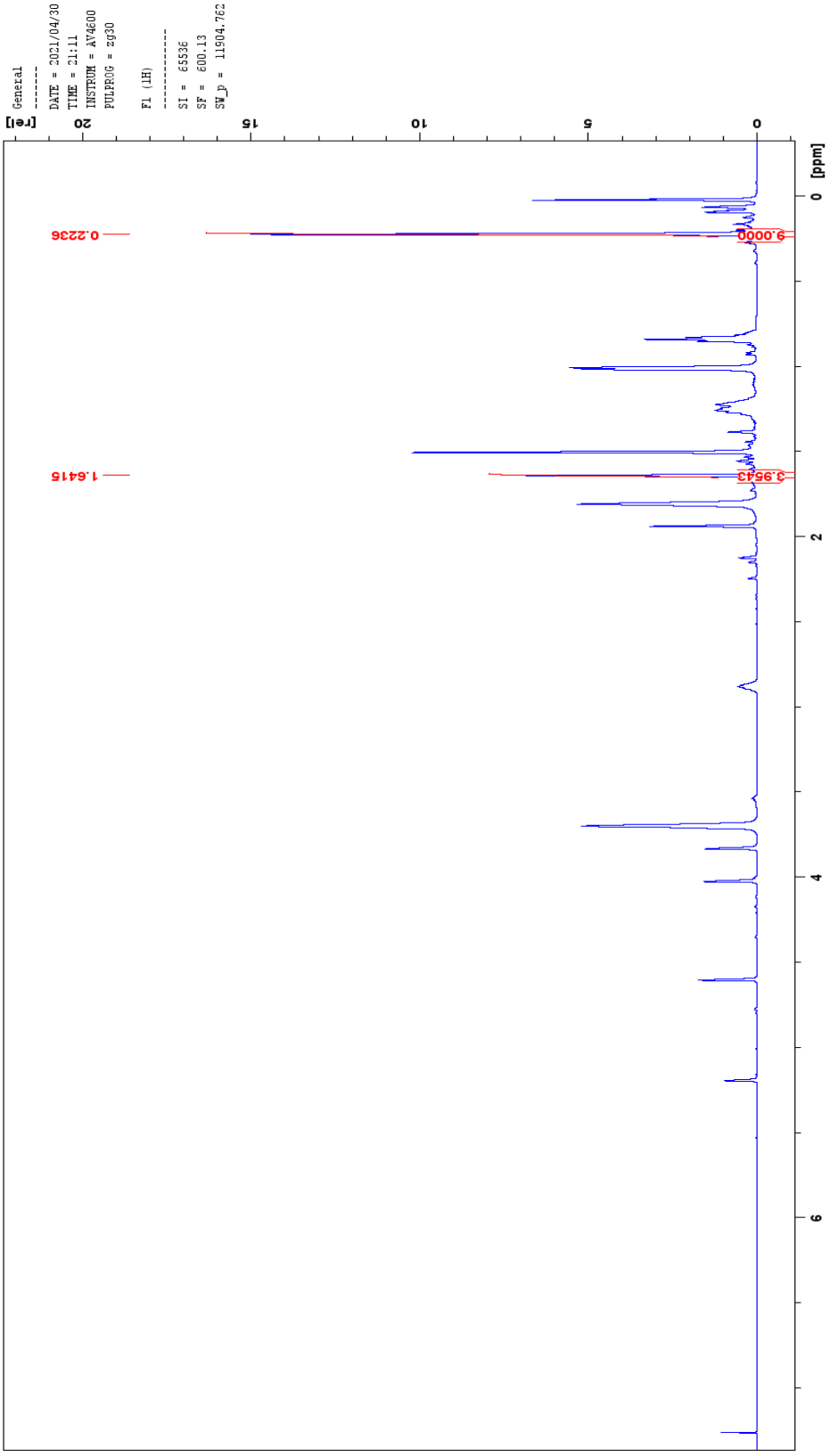


Figure B.1 : ^{1}H NMR spectrum of compound **11** (crude product)

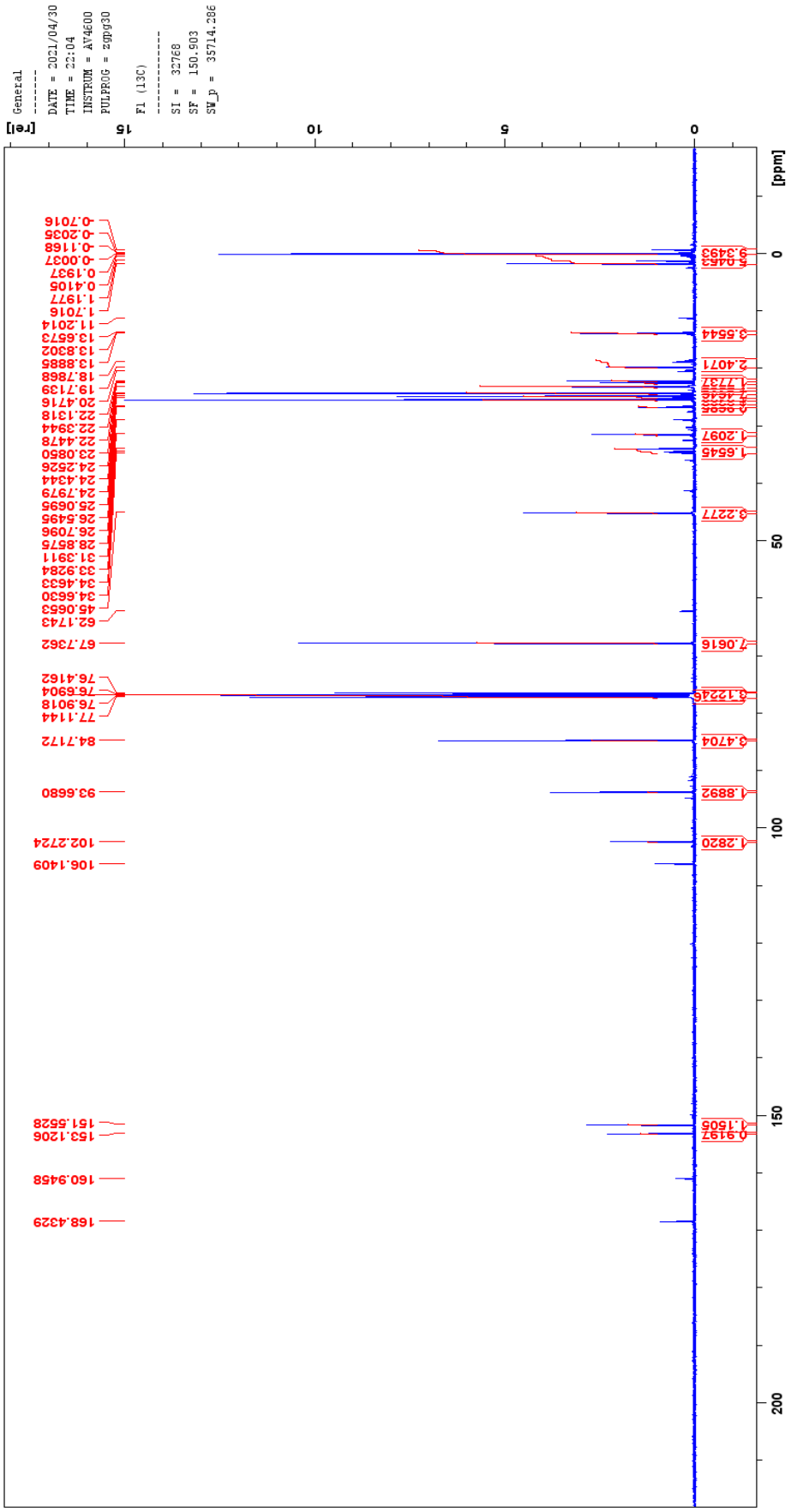


Figure B.2 : ^{13}C NMR spectrum of compound **11** (crude product)

Appendix C compound 13

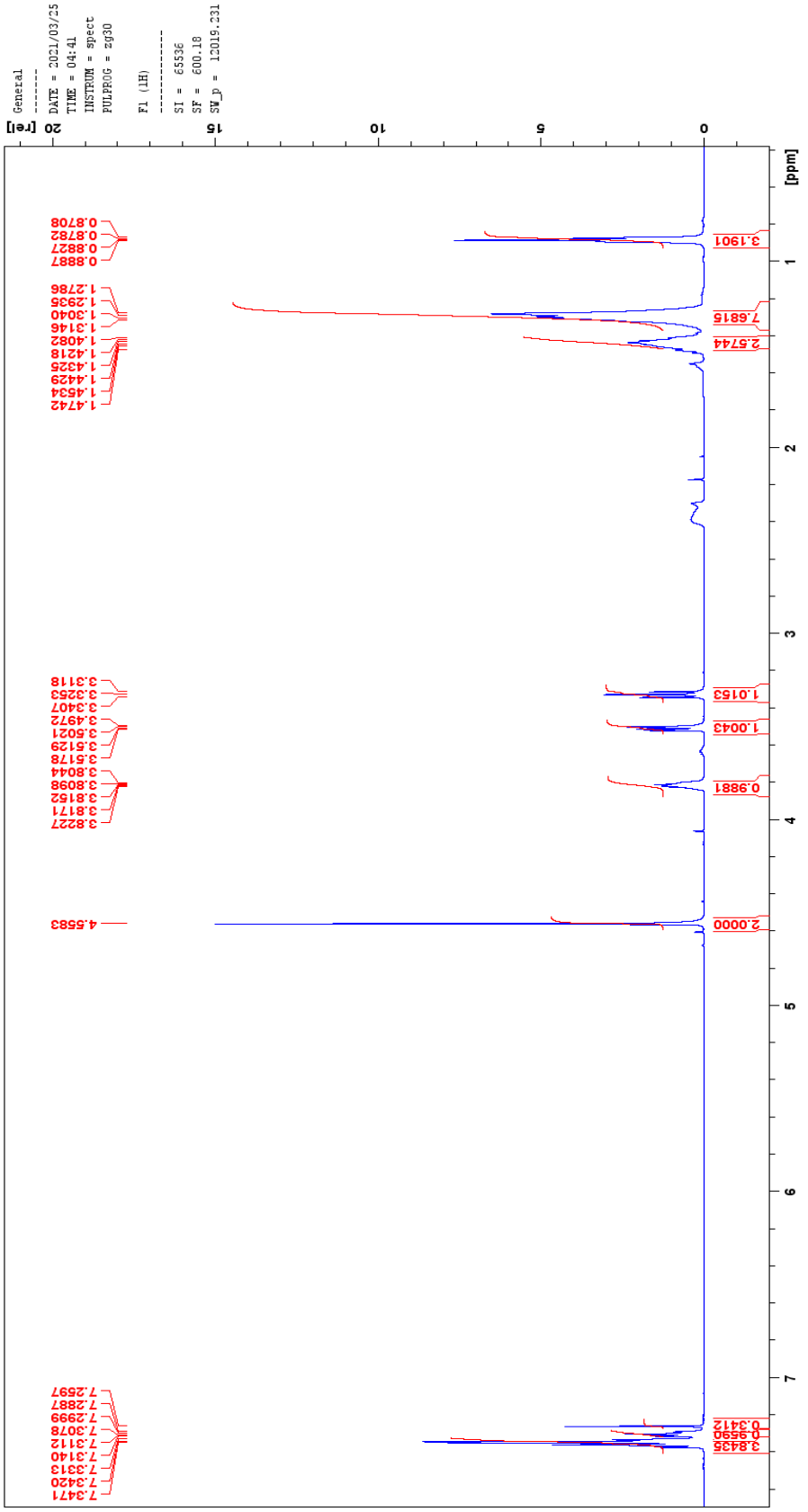


Figure C.1 : ^{1}H NMR spectrum of compound **13**

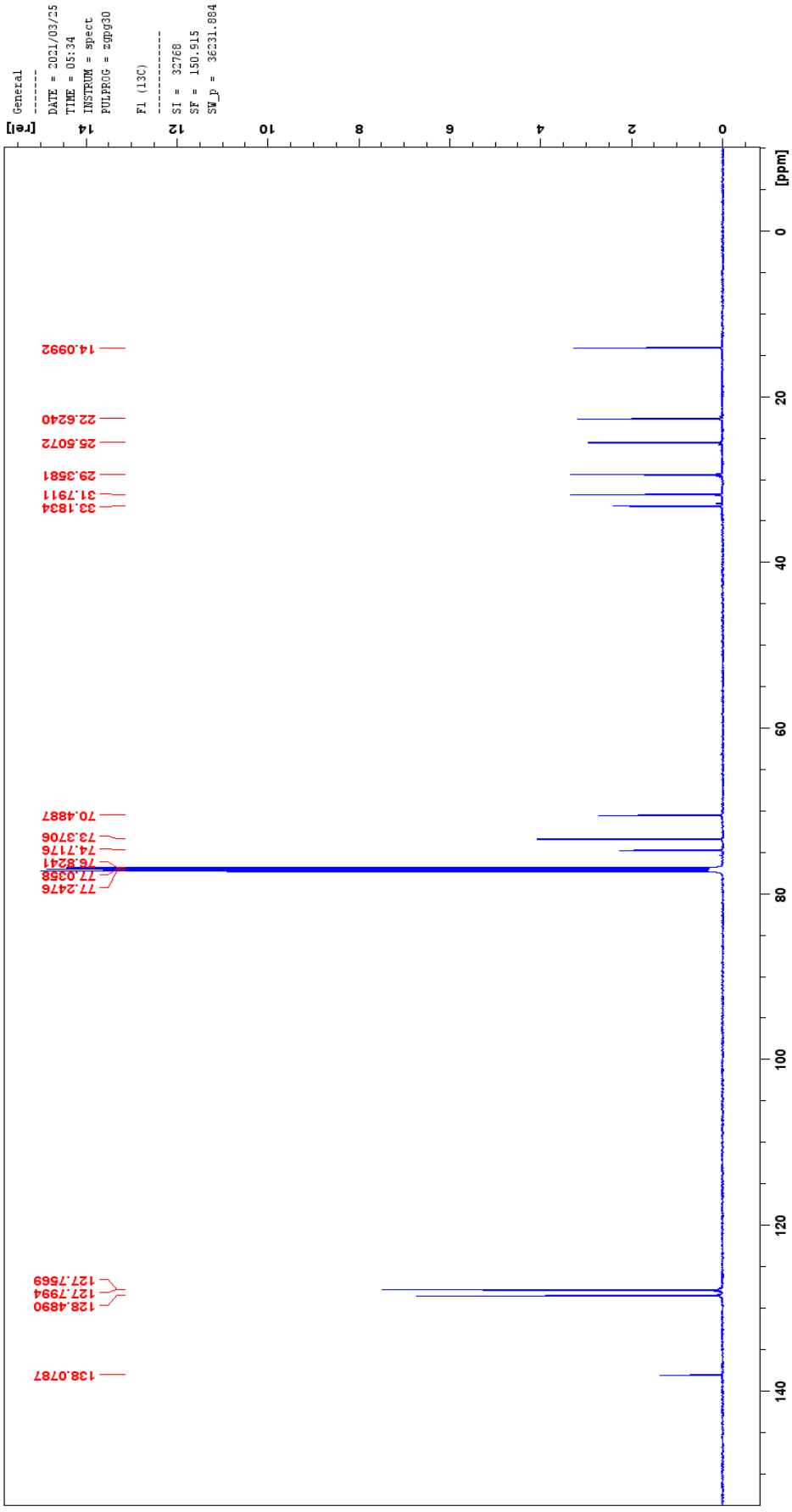


Figure C.2 : ^{13}C NMR spectrum of compound **13**

Appendix D compound 14

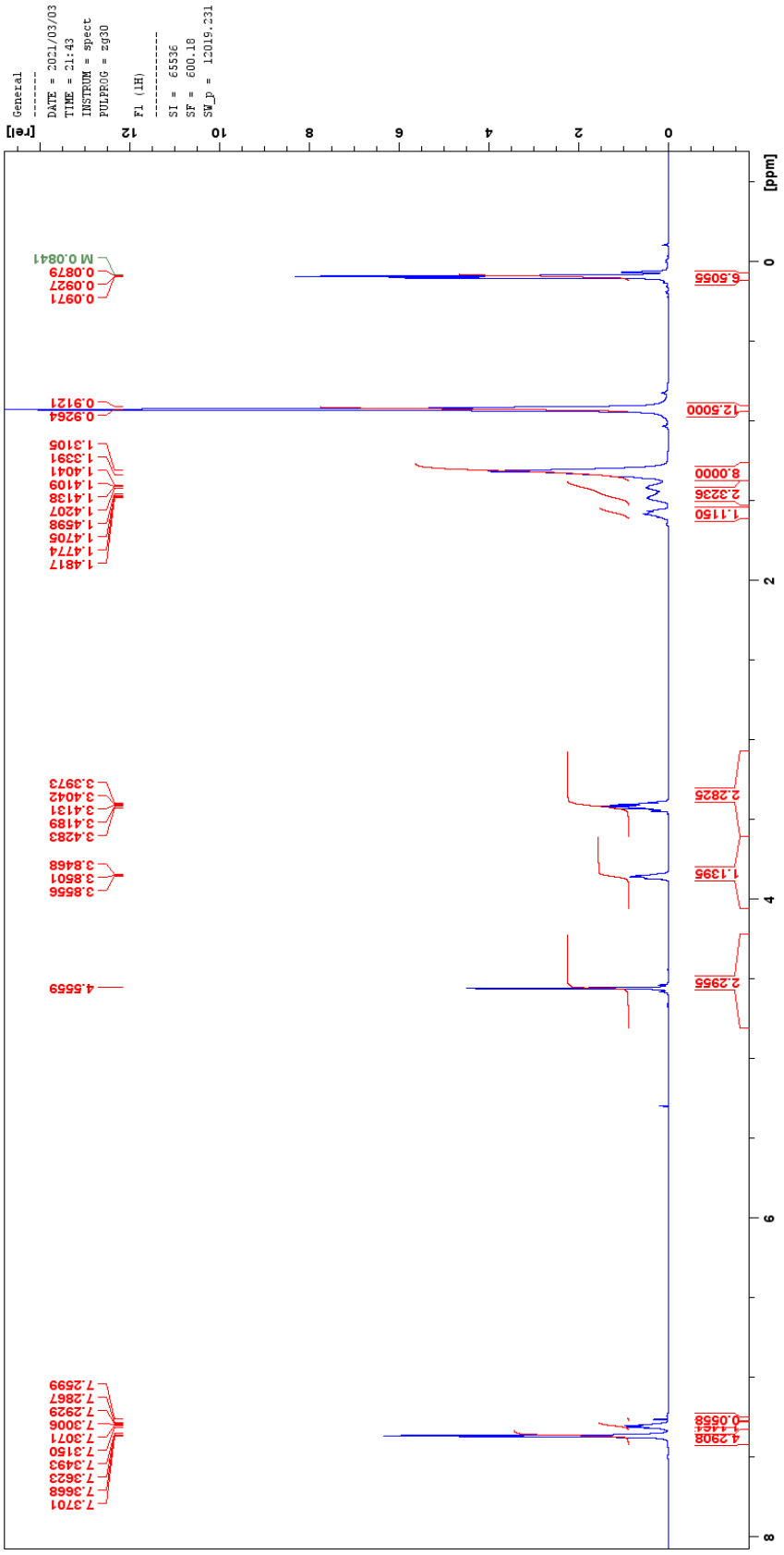


Figure D.1 : ^{1}H NMR spectrum of compound **14**

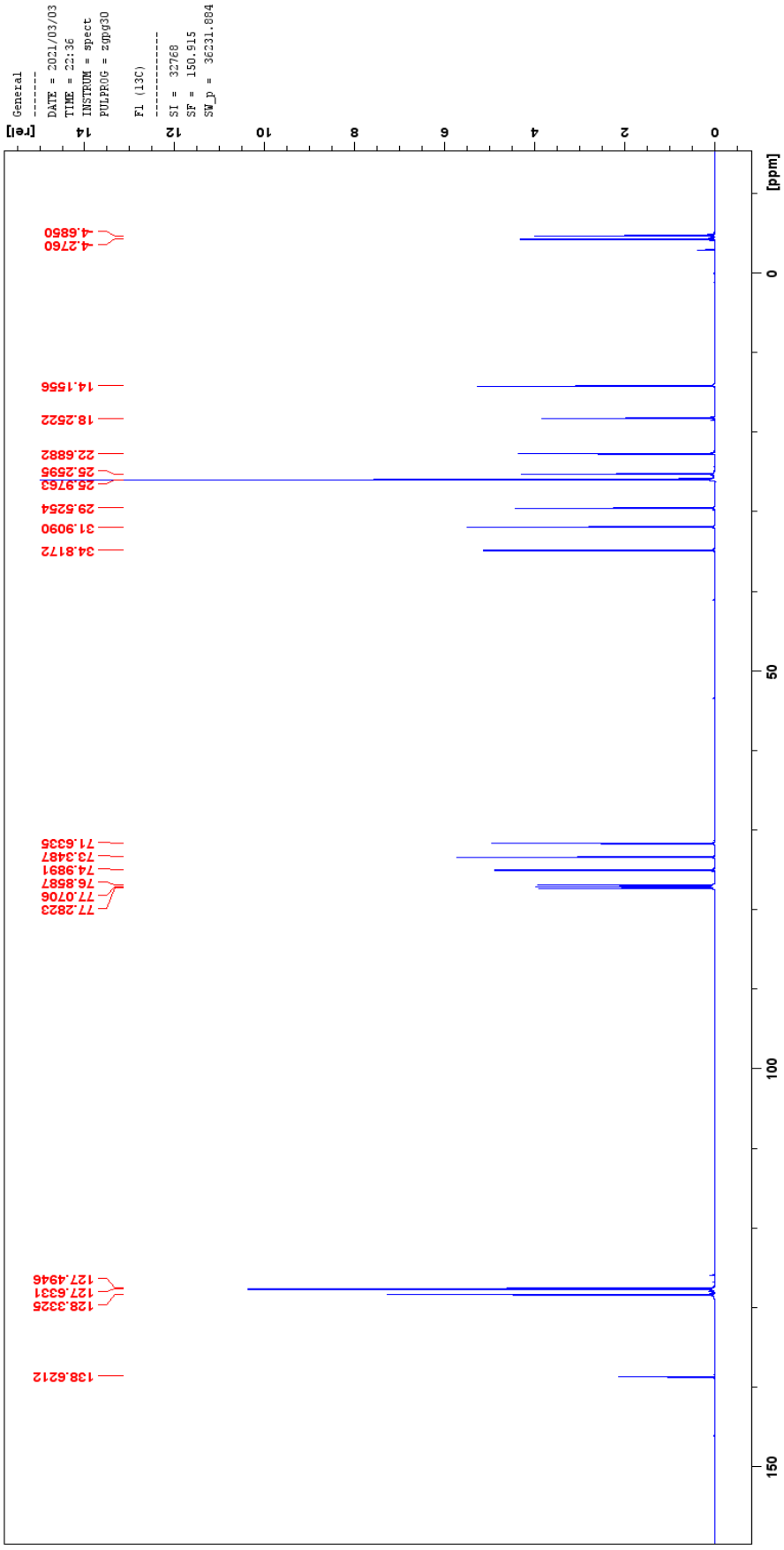


Figure D.2 : ^{13}C NMR spectrum of compound **14**

Appendix E compound 15

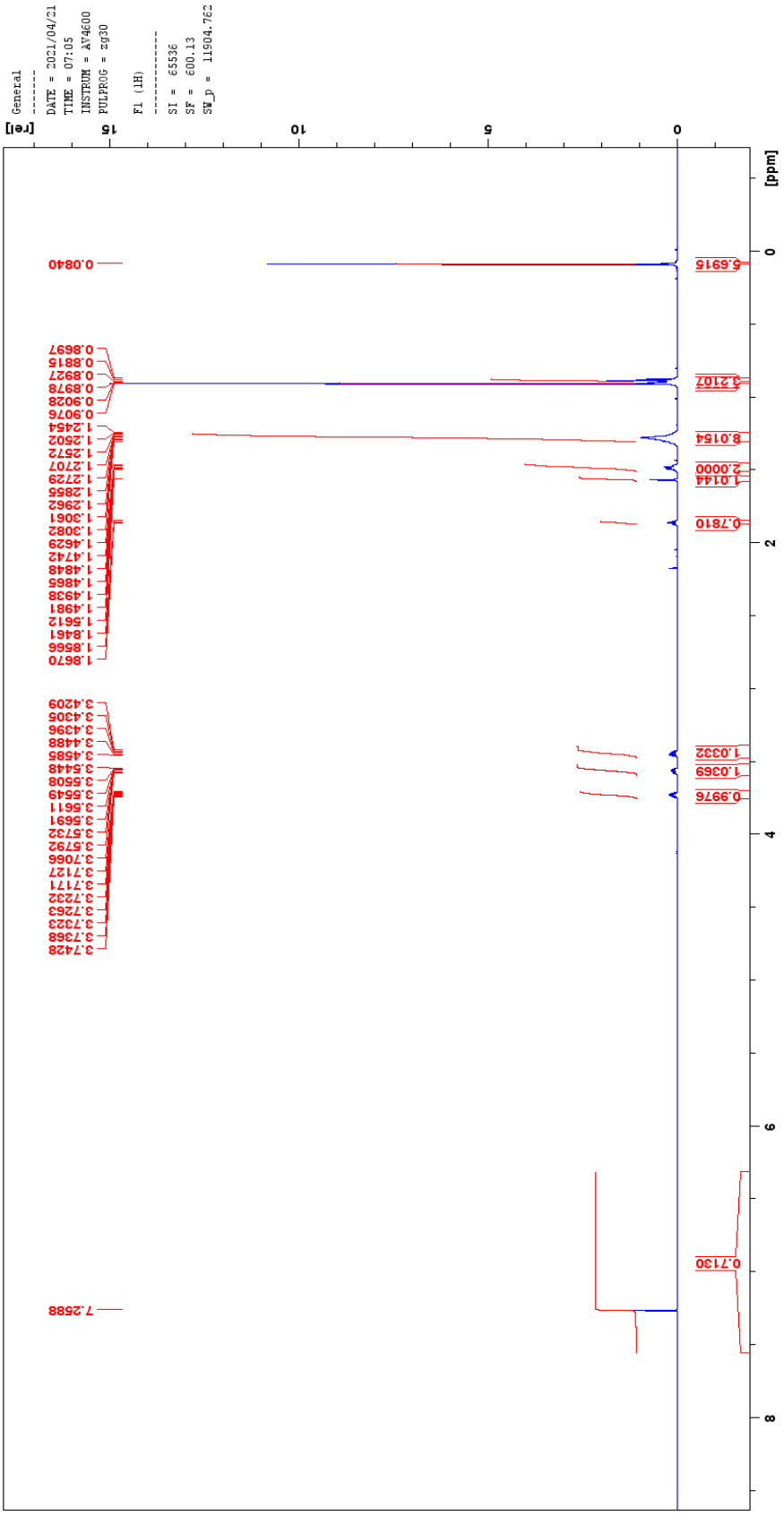


Figure E.1 : ^{1}H NMR spectrum of compound **15**

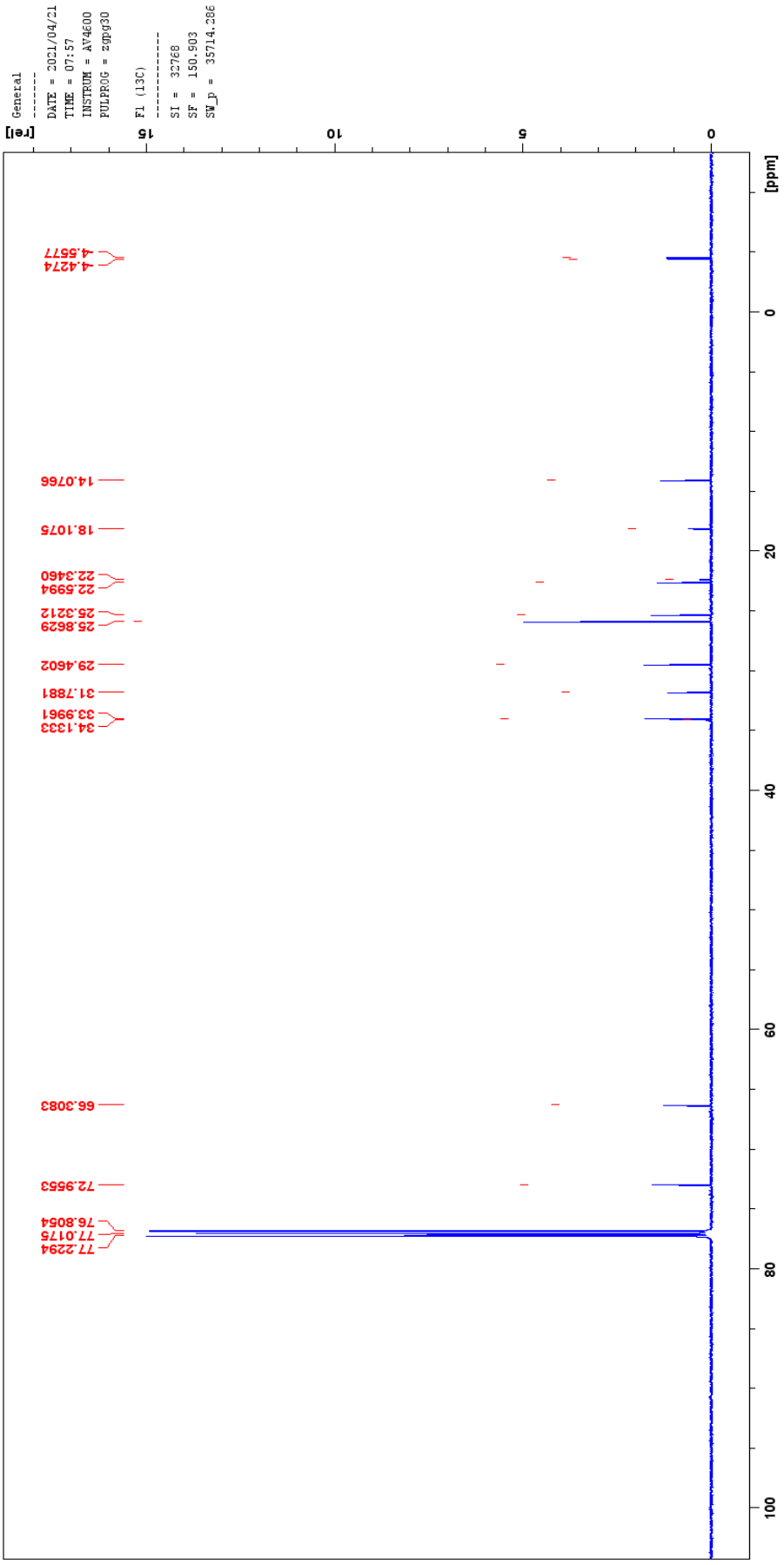


Figure E.2 : ^{13}C NMR spectrum of compound **15**

Appendix F compound 16

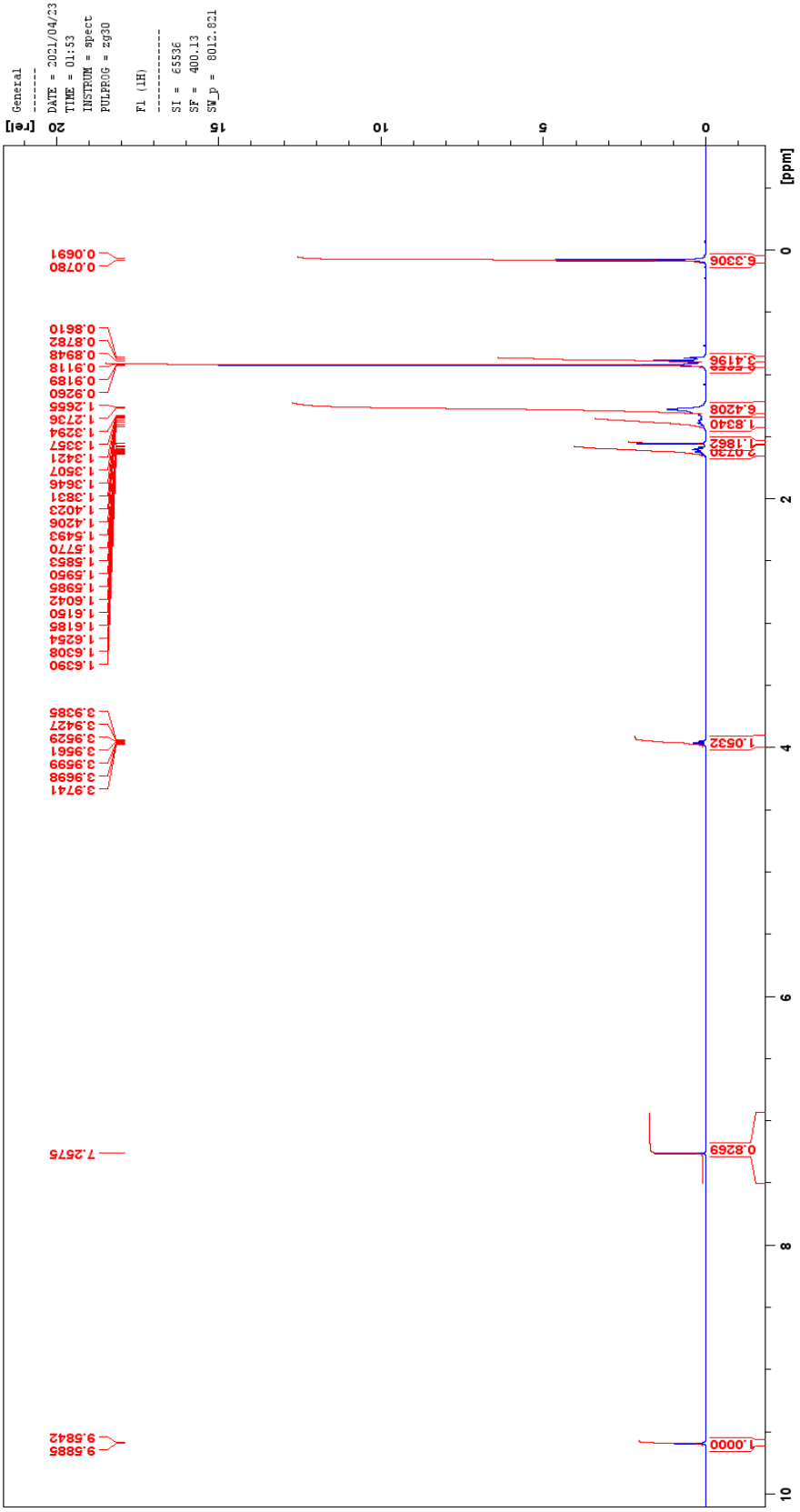


Figure F.1 : ^{1}H NMR spectrum of compound **16**

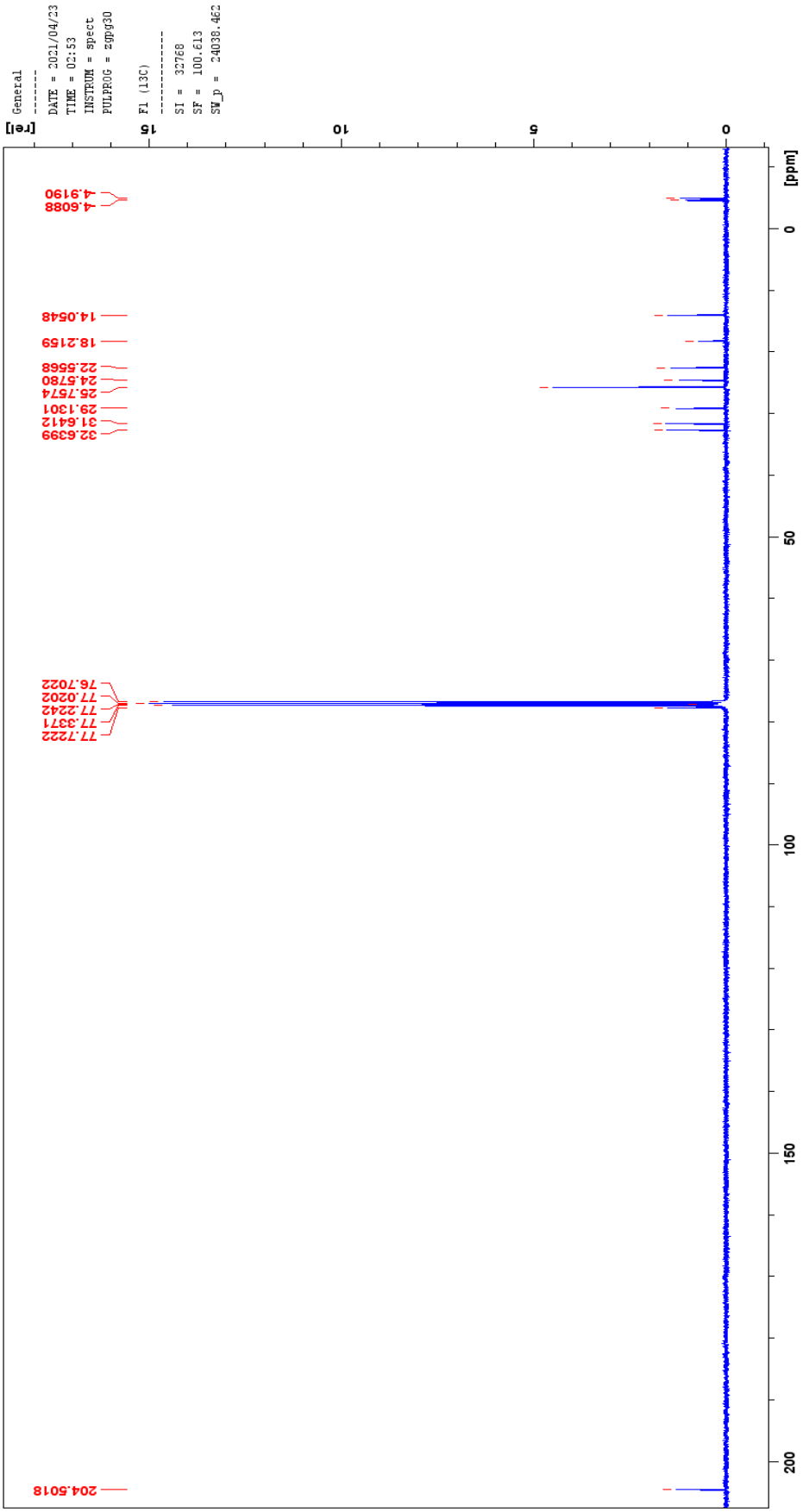


Figure F.2 : ^{13}C NMR spectrum of compound **16**

Appendix G compound 18

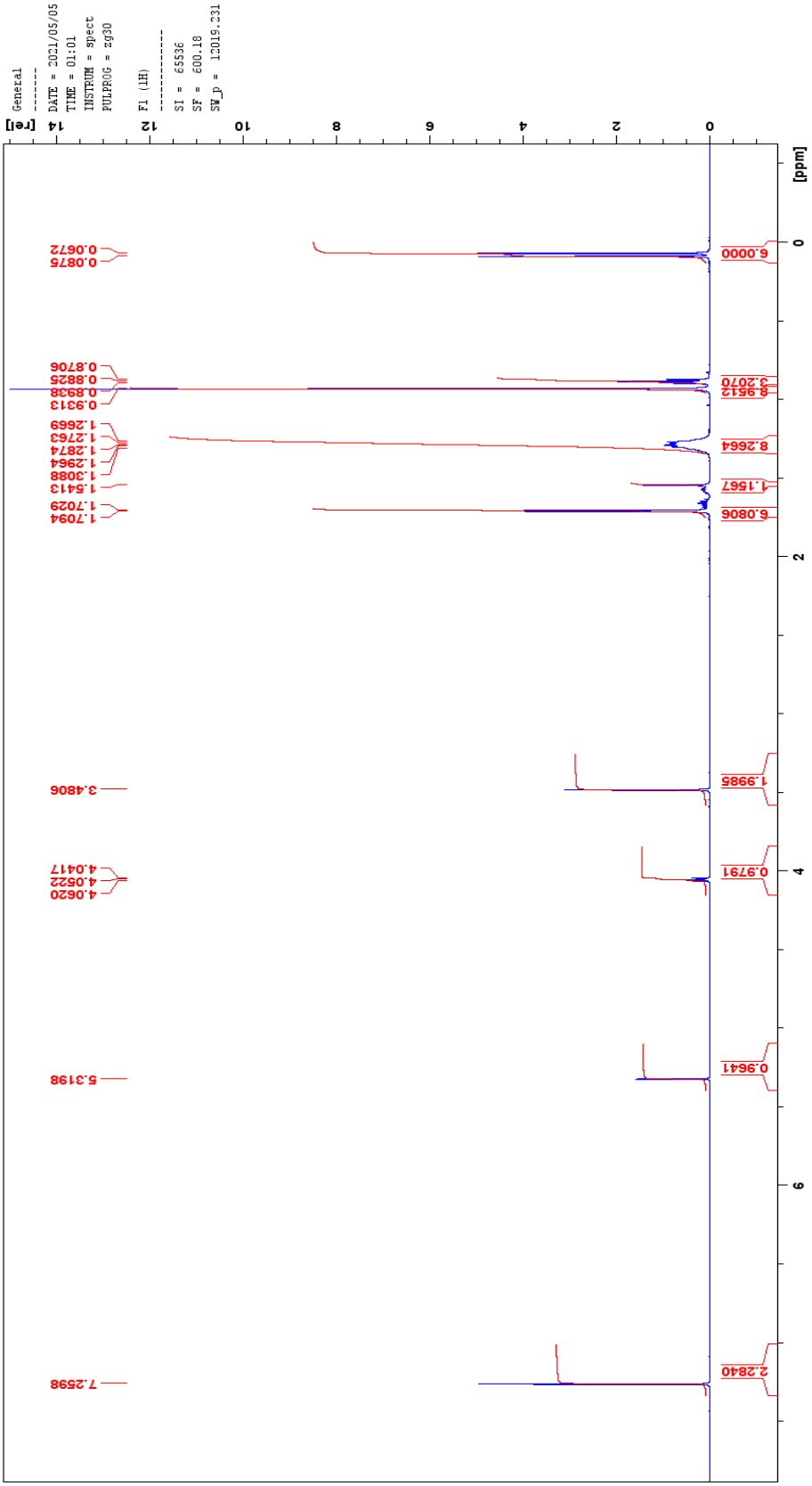


Figure G.1 : ^{1}H NMR spectrum of compound **18**

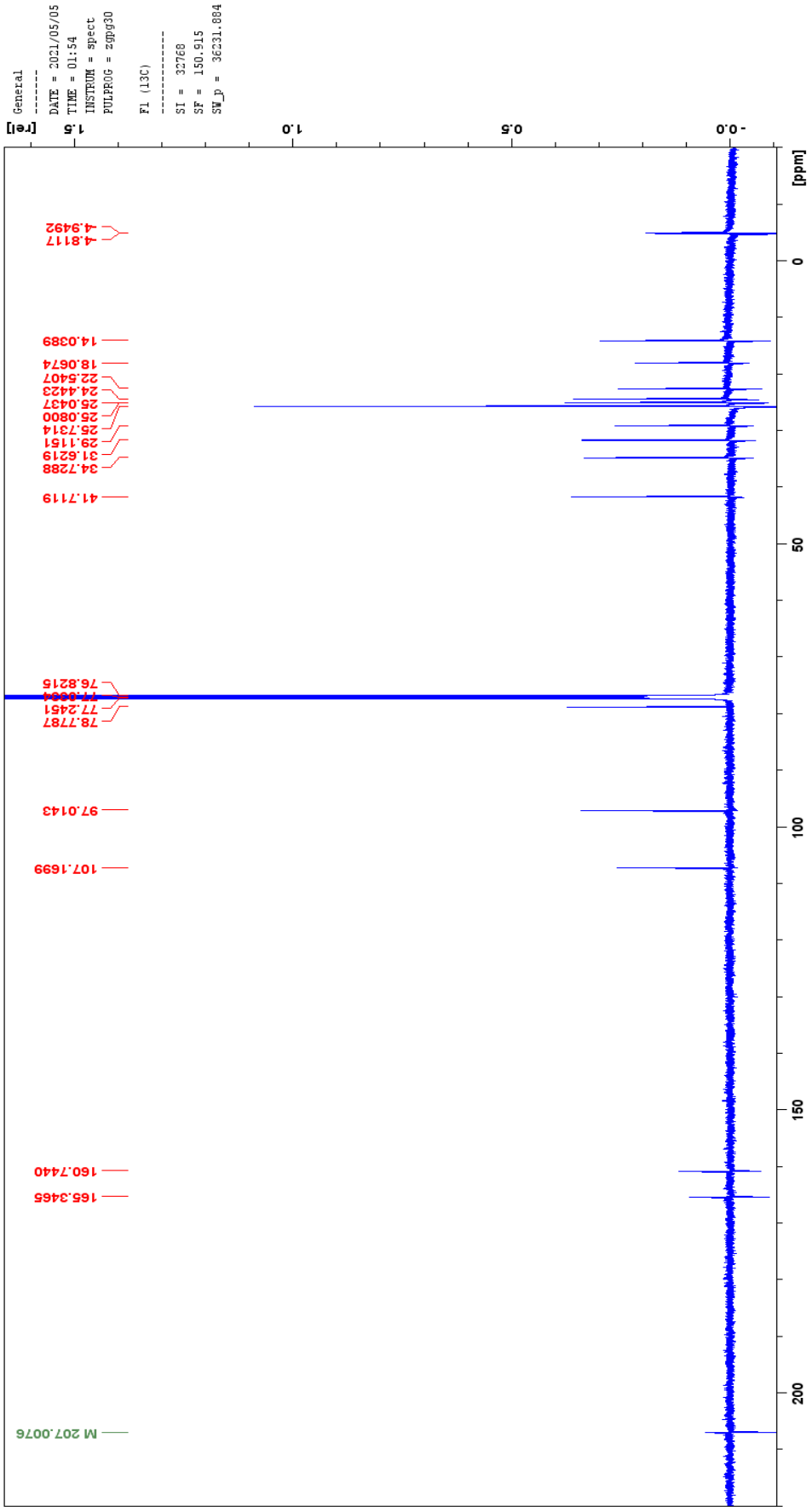


Figure G.2 : ^{13}C NMR spectrum of compound **18**

Appendix H compound 19

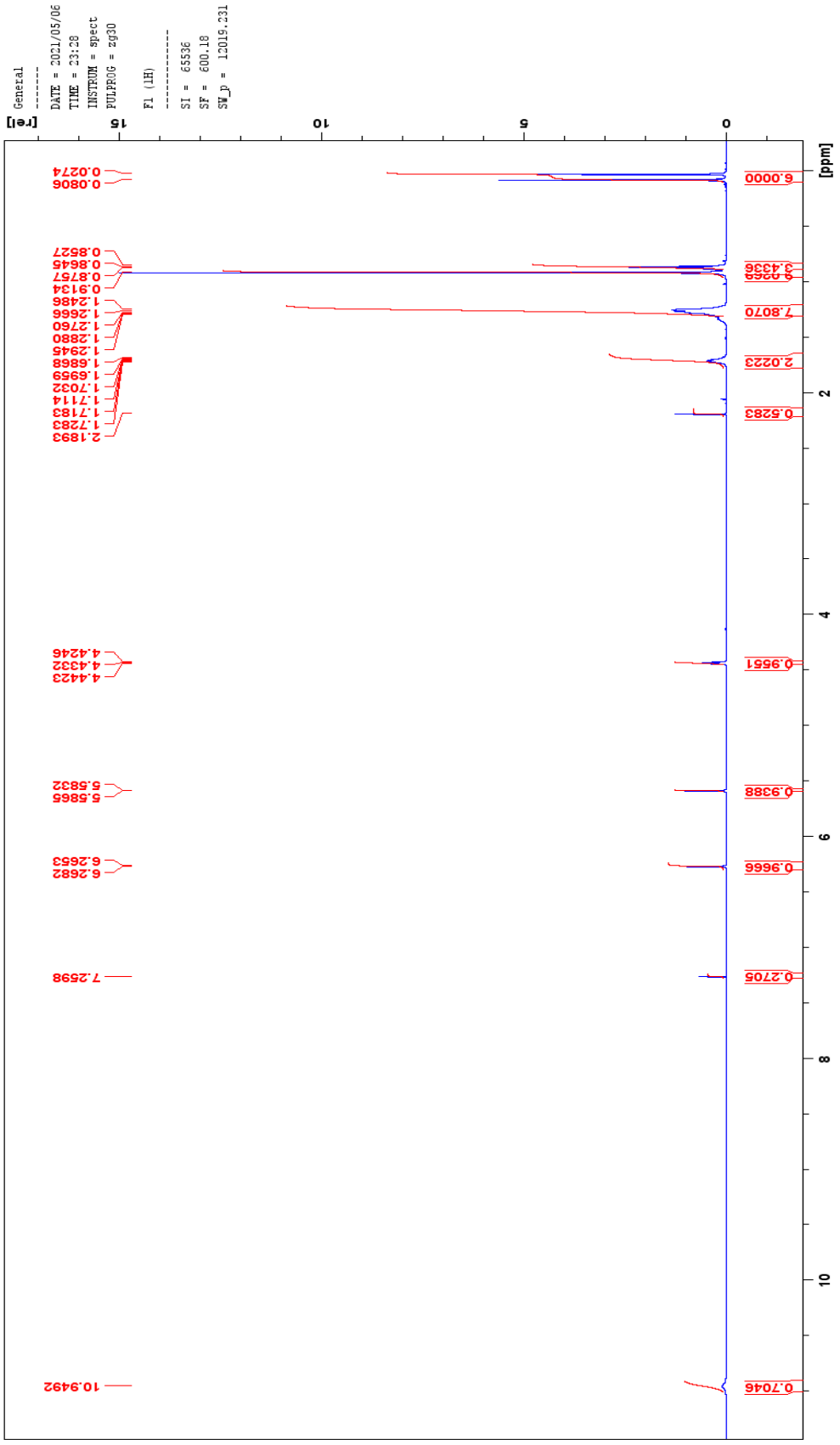


Figure H.1 : ^{1}H NMR spectrum of compound **19**

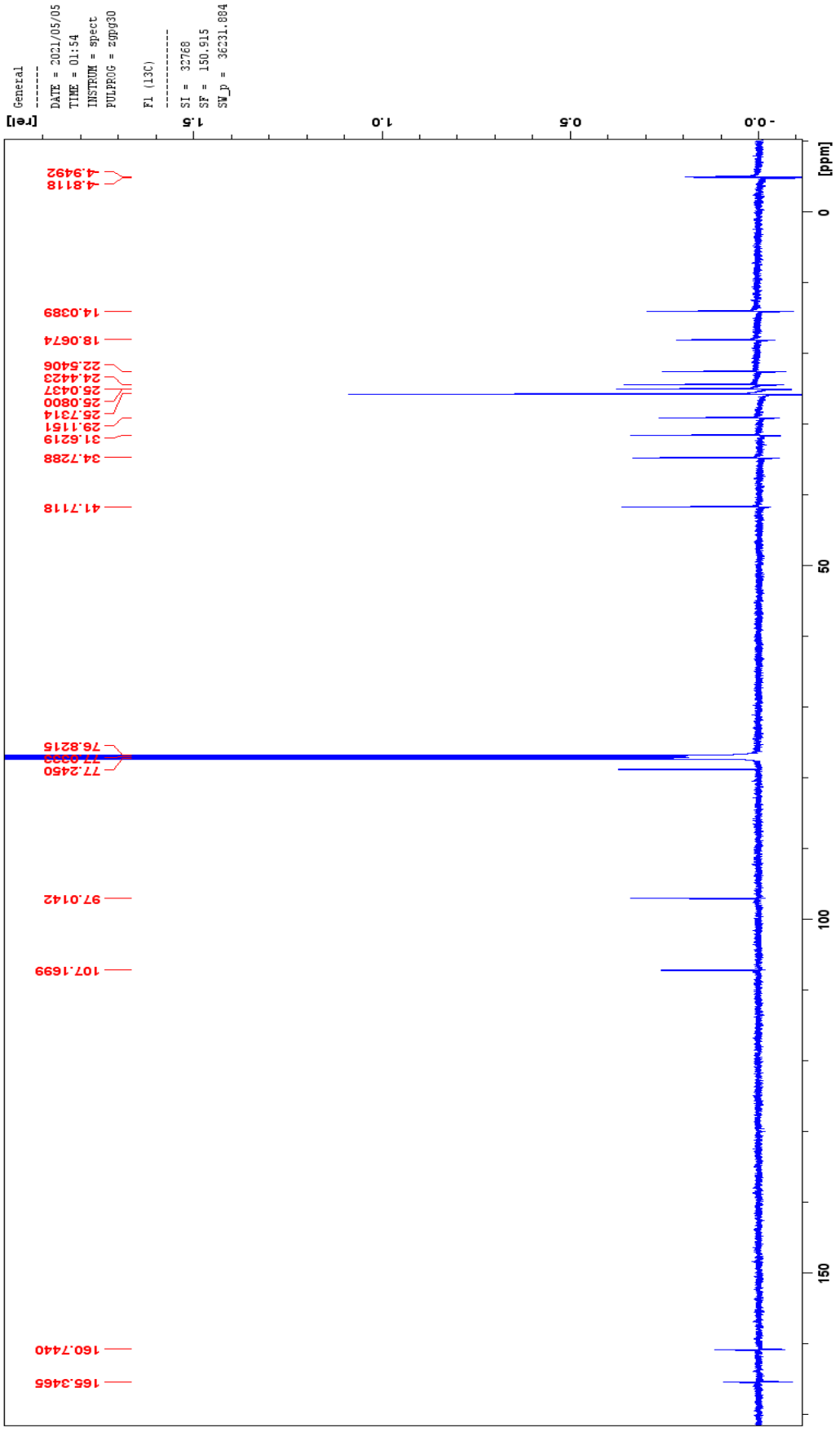


Figure H.2 : ^{13}C NMR spectrum of compound **19**

Appendix I compound 20

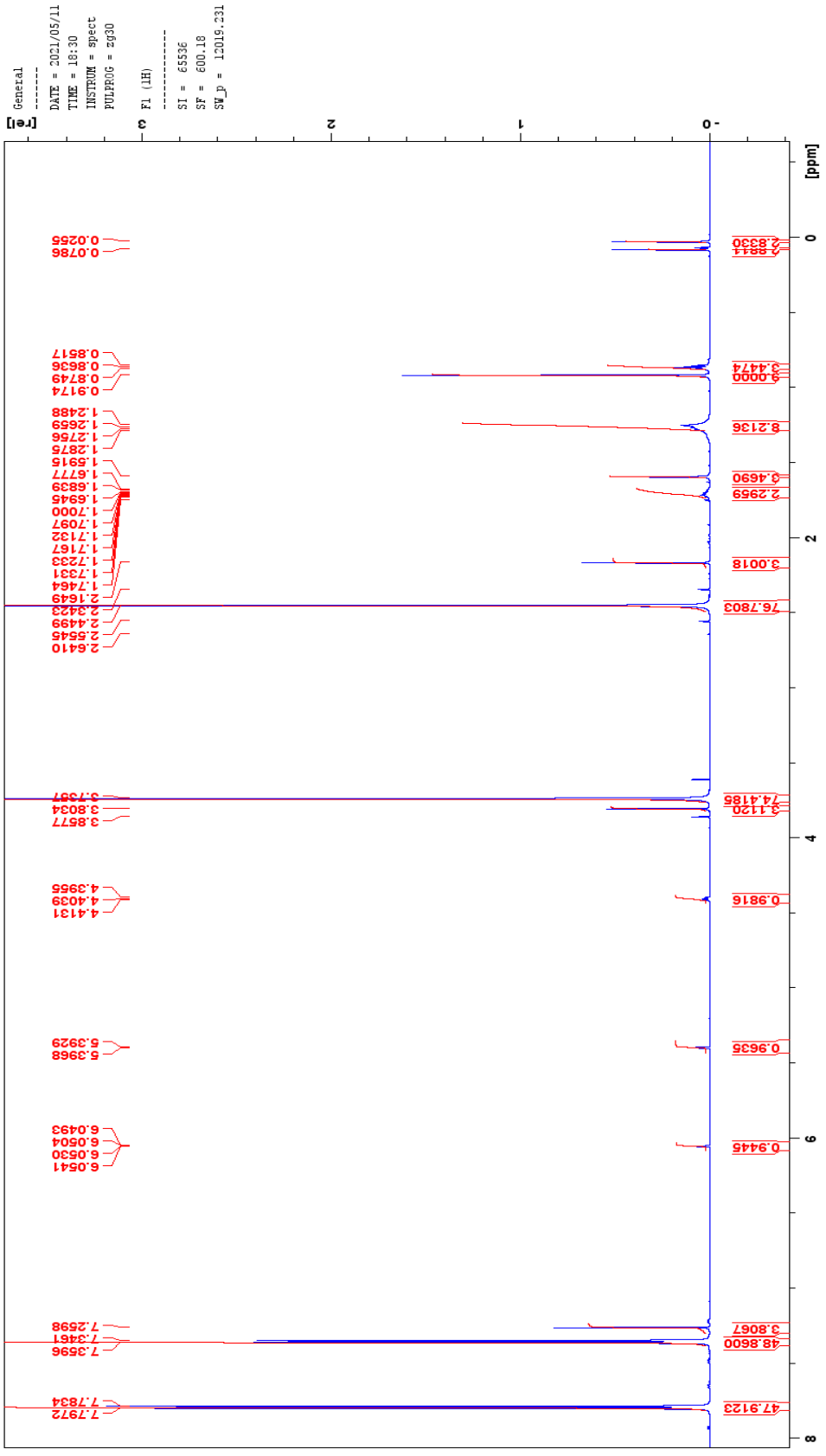


Figure I.1 : ^{1}H NMR spectrum of compound **20**

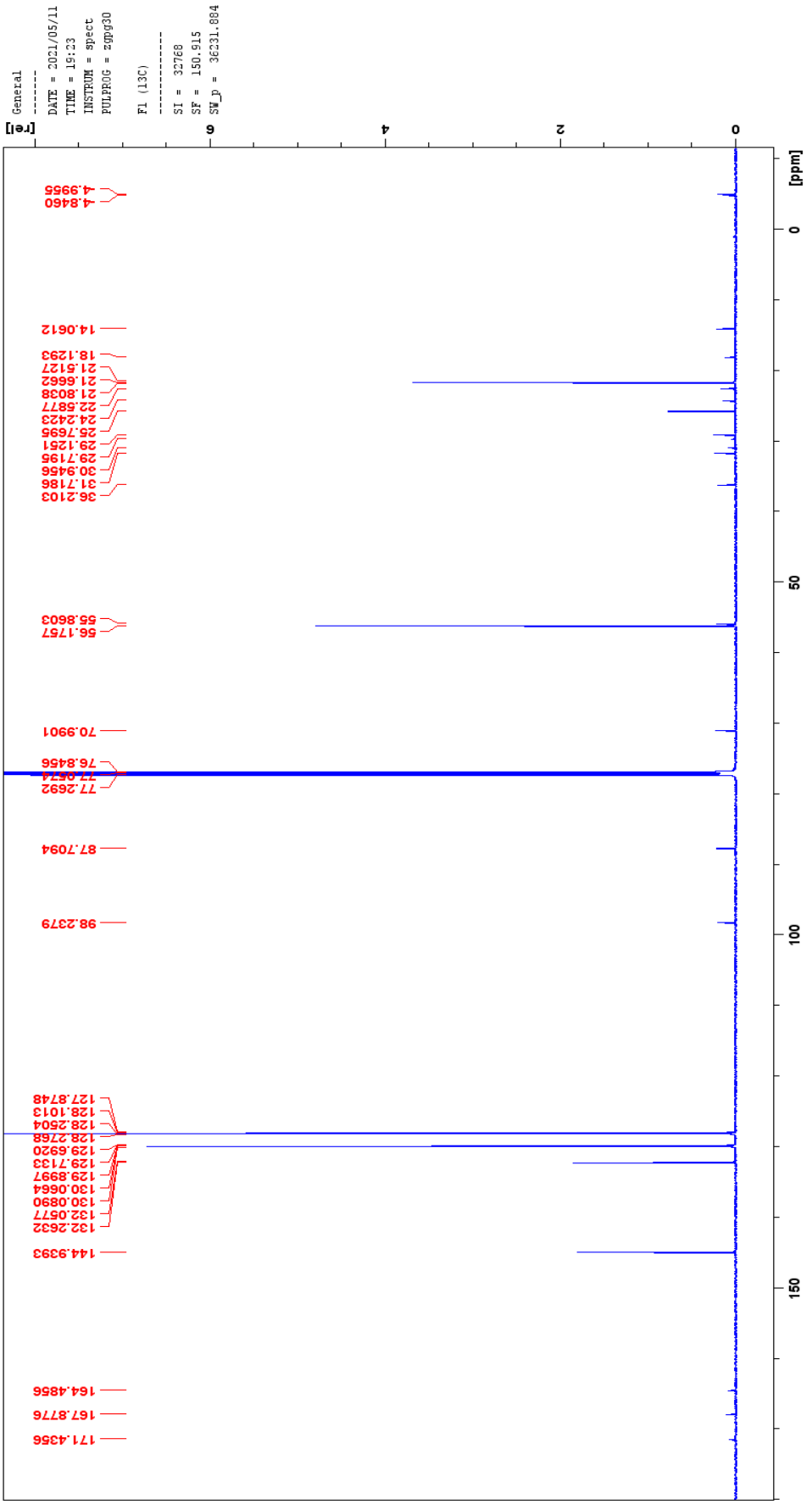
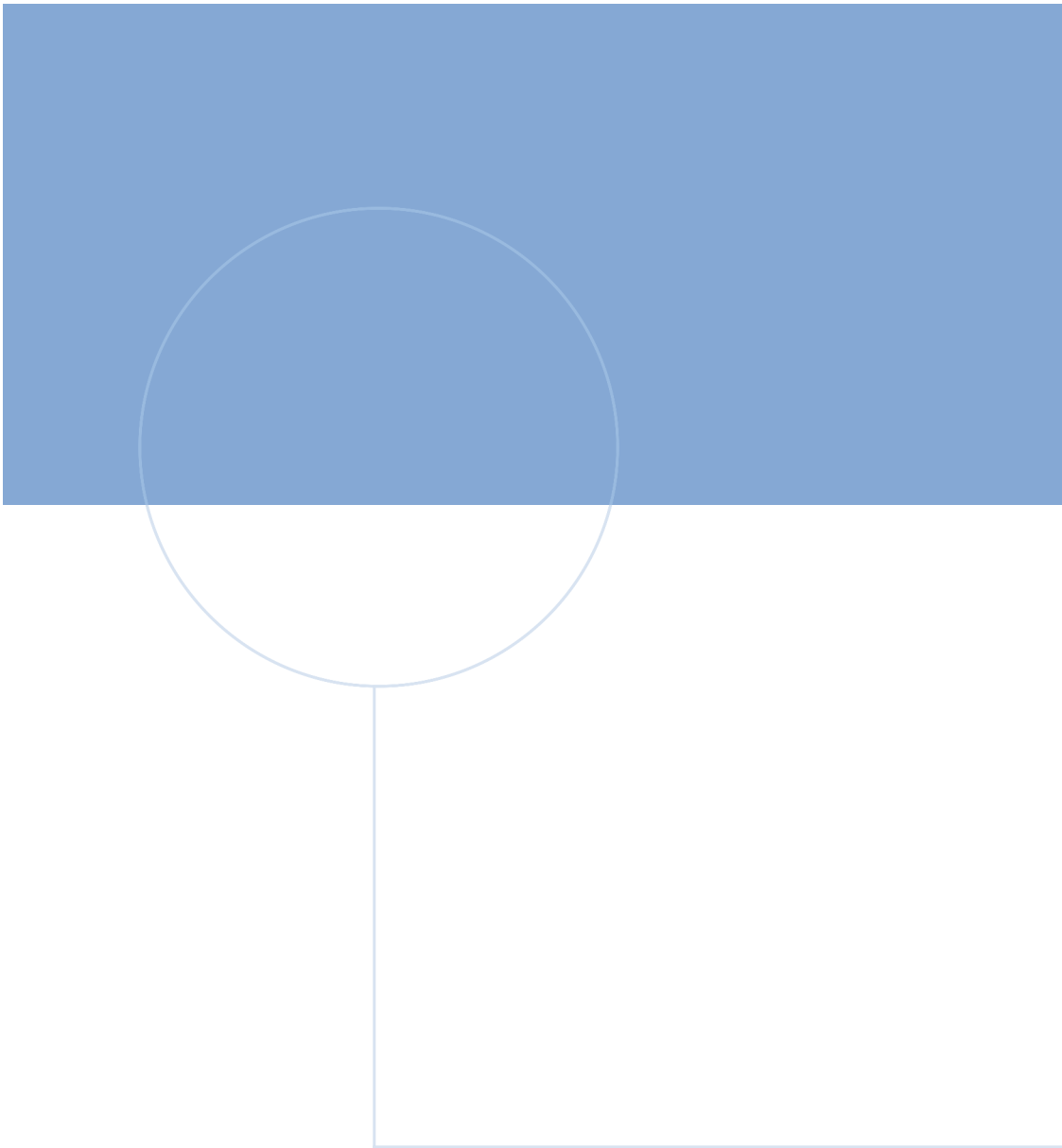


Figure I.2 : ^{13}C NMR spectrum of compound **20**



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