PALACKÝ UNIVERSITY

FACULTY OF SCIENCE

Department of Organic Chemistry

# Development of pluripotent reagents of 3rd generation: influence of lactone precursors to reactivity and stability

Bc. Martin Mičic

Master thesis

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I hereby declare that I have elaborated this Thesis independently and that I have listed all literature sources and other sources of information that I used. Neither this work nor a substantial part of it has been submitted for another or the same academic degree.

In Olomouc, 3. 8. 2021 Podpis

I would like to thank my supervisor doc. RNDr. Jiří Pospíšil, Ph.D. for his never-ending support, help and patience. Also, I would like to thank all the members of our research group, as well as the members of the Department of Organic Chemistry, for creating a friendly and inspiring work environment. Many thanks to RNDr. Adam Přibylka, Ph.D. for HRMS, measurements. Finally, I would like to thank the Department of Organic Chemistry for opportunity to go for Erasmus+ study program to Denmark during my master studies.

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Abstrakt: Divergentně orientovaná syntéza je jeden z přístupů jak generovat strukturně různorodé molekuly. Jednou z výzev tohoto přístupu je vývoj a příprava pluripotentních intemediátů. V této diplomové práce se zabýváme vývojem nové generace pluripotentních intermediátů obsahující skelety s THF motivem.



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| Abstract: | Diversity oriented synthesis is one of the approaches how to generate new structurally diverse molecules. One of the challenges of this approach is development and preparation of pluripotent intermediates. In this thesis we focus on development of new generation of pluripotent intermediates with tetrahydrofuran structural motive. |



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In our research group we have previously focused on several ways, how to shorter and made more efficient the synthesis of chemical libraries with high structural diversity. Our best approach opted for the design and development of so-called Pluripotent molecules. Such molecules are special designed to generate in 2-3 steps structural diversity libraries of molecules that can be readily tested against various targets

First generation of our pluripotent molecules was (**PM-1**) developed by Dr. Konrádová led recently to the discover of new mode of action towards leishmanial parasites. The second generation developed by Dr. Kováč (**PM-2**) still awaits to disclose its potential, however it is time to come up with the 3$^{rd}$ generation. The first step towards to the **PM-3** are to be discovered on the next pages of my thesis. So, fasten your seatbelts and let's go dive into the adventure.

# 1 Goals of the thesis

The goals of this thesis were defined as follows:

1) After a brief introduction to the topic to do the literature review about the reactions of lactones with α-methylated sulfones
2) To develop the ways to the **PM-3** generation
3) If the reader of my thesis is interested in these topics than he/she can read through the next pages.

# Table of contents

# List of abbreviations

| | |
|---|---|
| (B/C/P) | Build/couple/pair strategy |
| 3D | Three dimensional |
| Ac | Acetyl |
| APCl | Atmospheric pressure chemical ionization |
| Bn | Benzyl |
| Boc | tert-Butyloxycarbonyl |
| BT | Benzothiazole |
| Bu | Butyl |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-en |
| DCM | Dichloromethane |
| DMAP | 4-Dimethylaminopyridine |
| DNA | Deoxyribonucleic acid |
| DOS | Divergently oriented synthesis |
| ESI | Electrospray ionization |
| Et | Ethyl |
| EWG | Electron withdrawing group |
| eq | Equivalent |
| FG | Functional group |
| GLG | Good leaving group |
| Het | Heterocycle |
| HRMS | High resolution mass spectrometry |
| KHMDS | Potassium hexamethyldisilazane |
| LiHMDS | Lithium hexamethyldisilazane |
| LUMO | Lowest unoccupied molecular orbital |
| Me | Methyl |
| NMR | Nuclear magnetic resonance |
| PCC | Pyridinium chlorochromate |
| PM | Pluripotent molecule |
| ppm | Parts per million |
| PT | Phenyl-tetrazole |
| RNA | Ribonucleic acid |
| RT | Room temperature |
| TBS | *tert*-Butyl-dimethyl silyl |
| TEA | Triethylamine |
| Tf | Triflate |
| THF | Tetrahydrofuran |
| TMS | Trimethylsilyl |
| TOS | Target oriented synthesis |
| UV | Ultra-violet |

# 2 Theoretical part

Since the discovery and further development of the "small organic molecule" concept, scientist were fascinated with the fact that such "small beasts" can have a tremendous impact on the whole living individuals as e.g. humans[1–3].

Thus, very fast they came up with idea, that selected small molecules can be used as drugs or regulators in animal and humans. The moment when biologists started to consider that the "fancy concept with which chemists/alchemists are playing" (molecules) can be somehow exploitable in biology came with the discovery of glucose by Maarggraf in 1747[4]. Later, Wöhler urea synthesis in 1828 changed paradigma that that natural products can be created only by living species and the route to the new drug discovery was opened[5]. 19th and 20th century were then filled with discovery and structure determination of novel small organic molecules as amino acids, vitamins, hormones, neurotransmitters and lipid mediators

In depth study of their function and regulatory process then paved the way to discovery of novel artificial regulators, inhibitants or activators. However, the way from the discovery of novel biological target for small organic molecule and the moment when new small organic molecules "fits" and becomes drug is long and painful. In general, it takes decades and billions of US dollar. And only few from originally tested millions of compounds are selected.

## 2.1 Introduction

There is no strict definition of term small molecule, but most of the definitions says that small molecule is carbon based bioactive compound with molecular weight less than 500 Da. Also, the small molecule is a compound that differ to DNA, RNA and protein macromolecules. Under such definition we can put large number of both synthetic and naturally occurring compounds. And when we refer to "natural" occurring compounds we do refer to the plant secondary metabolites[6].

The important property of small organic molecules within living organisms is the ability to interact specifically with biological targets like proteins. This interaction is general and depends on the compound. The property that makes small molecules efficient "game changers" when they behave in the of the organisms is studied[7].

Traditional sources of small molecules were plants. Ever since the beginning of 19th century, when first pure pharmacologically active compound were isolated from poppy by Friedrich Sertürner[8], natural products were source of drugs or drugable compounds for medicinal chemists. Until rise of synthetic medicinal chemistry in 90's about 80% of new drugs were based on natural products[9]. At that time also biological screening of big chemical libraries

shortened and became more available and access to the novel libraries of the compounds were never easier. However, in early years of 21st century it was more and more obvious that not only the size of the chemical library is important. Therefore, the focus shifted from the size of library to its diversity over the library. Opinion that diversity over the library is kept up to day[3,7].

Over the time the main approaches to the biologically active small molecules changed. The first approach used by alchemists was to mix chemicals that were not necessarily pure and let's see what happens. Their approach was curiosity driven try and mixing up stuff.

Over past century three main approaches how to create small molecules crystalized. First approach was the target-oriented synthesis (TOS) (I wish to have exactly this compound), the second was combinatory chemistry (mix everything and see) and finally the diversity-oriented synthesis (DOS, mix up and create the diversity). These three approaches, even though exploiting synthetic chemistry, are very different when it comes to the (retro)synthetic analysis and application of it in the concept of the approach. (Figure 1)[1]. The next pages will dive deeper into this understanding.

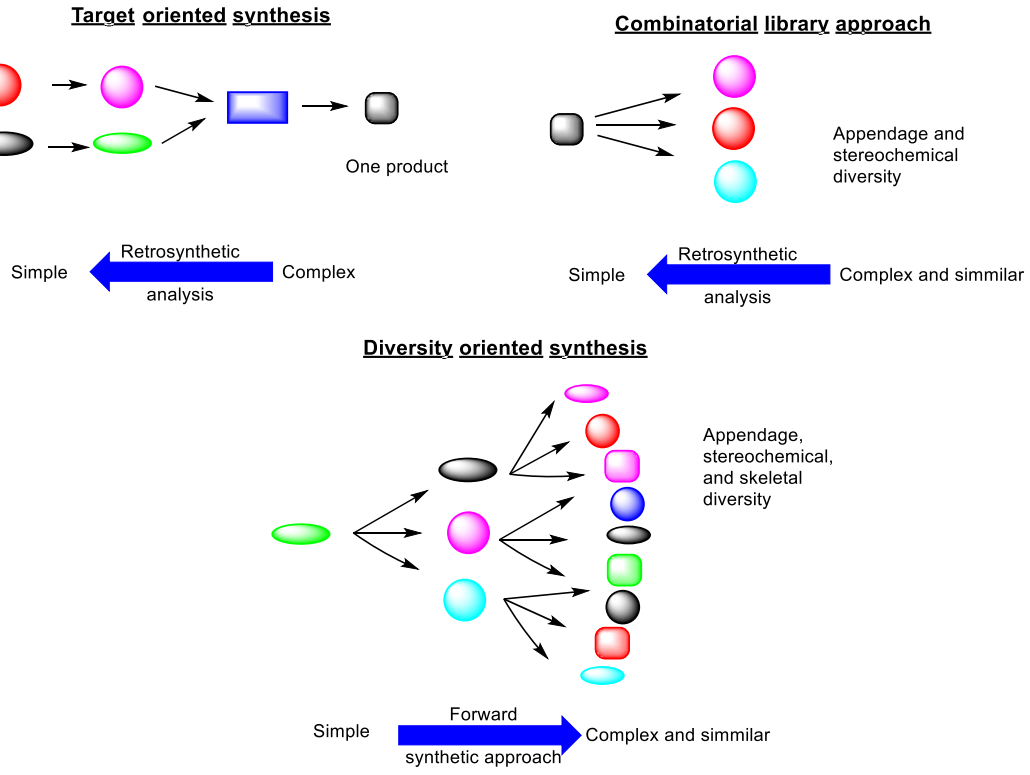


*Figure 1 - Difference between TOS, combinatorial chemistry and DOS*[10]

## 2.2 Target oriented synthesis

TOS is as the name suggest, the synthetic approach that focus on the synthesis of just one specific molecule. This approach it the "approach of the choice" when so called total synthesis of natural products is pursued. This way of synthesis has a long history in organic chemistry[11]. Originally it was designed to proposed structure of newly isolated nature products. The most famous TOS is presumably Woodward's synthesis of vitamin B12, that treat not only the complicated structure of this complex molecule but developed new synthetic methods and methodologies, where the most famous are presumably the Woodward-Hoffmann rules (Nobel prize 1981).

TOS evolved over time, but as the time passed it started to rely more and more on the retrosynthetic analysis. Retrosynthetic analysis is a problem-solving technique, for the synthesis of complex organic molecules. Major strategy of such analysis is to identify main disconnections and based on those to develop a synthetic sequence that leads to commercially available materials.

This synthetic hierarchy was a considerable step forward in synthesis planning and therefore it was not surprising it was recognized by awarding 1990 Nobel Prize in Chemistry to Elias James Corey for "his development of the theory and methodology of organic synthesis".

However, it should be noted that this approach has a drawback. It brings the synthetic chemists to the target molecule. The analogues are left behind. This important feature is of course a problem when medicinal chemistry approaches are considered, because in these cases the analogues are equally important to the targeted molecule.

## 2.3 Combinatory chemistry

Principle of combinatorial chemistry is the synthesis that produce a large quantity of chemical entities that differ at specific positions (e.g. length of carbon chain on ester). As consequence, in this approach a large library structurally very similar compounds are generated. As main feature (from the synthetic methodology in this point) simple chemical groups thus functions are used to achieve this goal.

In this way, chemists can prepare big library of compounds, instead of preparing only a few single entities[12]. For combinatory chemistry is typical use of automatization, solid phase synthesis and high-throughput screening.

## 2.4 Diversity-oriented synthesis

DOS was formed as logic expansion of combinatorial chemistry improving its biggest mistake – rely on quantity over the quality. Thus, under DOS approach the techniques typical to the combinatorial chemistry (high throughput screening, solid phase…) are used, however the main emphasis in the library construction is then given to the diversity.

The diversity is then achieved generating the advanced reagents that possess reaction sites that can be reacted with external building blocks and between each other. As a consequence a library of structurally diverse molecular skeletons is obtained[13].

The goal of DOS is to generate library that differs in appendages, functional groups and stereochemical proprieties, and therefore they will fill chemical space as much as it is possible[14].

For DOS is typical so called forward planning synthetic approach which means that the synthesis starts from simple starting material and in 3-5 steps the library of products is created[15]. Term diversity-oriented synthesis was used for the first time by Stuart Schrieber in early 2000's[11].

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### 2.4.1 Diversity

Term diversity has a broad definition and differs case to case since molecules have many features that can assess them (e.g. molecular mass, lipophilicity, topological features.). In case of DOS term "diversity" is as "the structural diversity" meaning "the diversity in 3D space". Thus, when we refer to the "Structurally diverse library", the library contains a large variety of compounds with different skeletons that causes compound various 3D shape. And it is the 3D shape of molecule that is responsible for the interactions with biologically active macromolecules and therefore determines their biological action. Structural diversity of skeletons within the library then fills in larger chemical space and increases the possibility of "hit". Probability to find biologically active substance on target of unknown molecular structure increases with more covered chemical space.

"Chemical space is defined as the total descriptor space that encompasses all the small carbon-based molecules that could in principle be created". In theory the maximal diversity within the library it can obtain is if all thermodynamically stable molecules that would fill the chemical space are obtained[16].

As can be seen the "chemical space is basically impossible to be filled. However, we need to find the way how to address the way of new chemical library constitution should be done. To do so, four key points that each chemical library should address were determined[3,14,17].

1. Appendage diversity: variation in structural motives around a common skeleton
2. Functional group diversity: variation in the functional groups present
3. Stereochemical diversity: variation in the orientation of potential macromolecule-interacting elements in space
4. Skeletal (scaffold) diversity: presence of distinct molecular skeletons

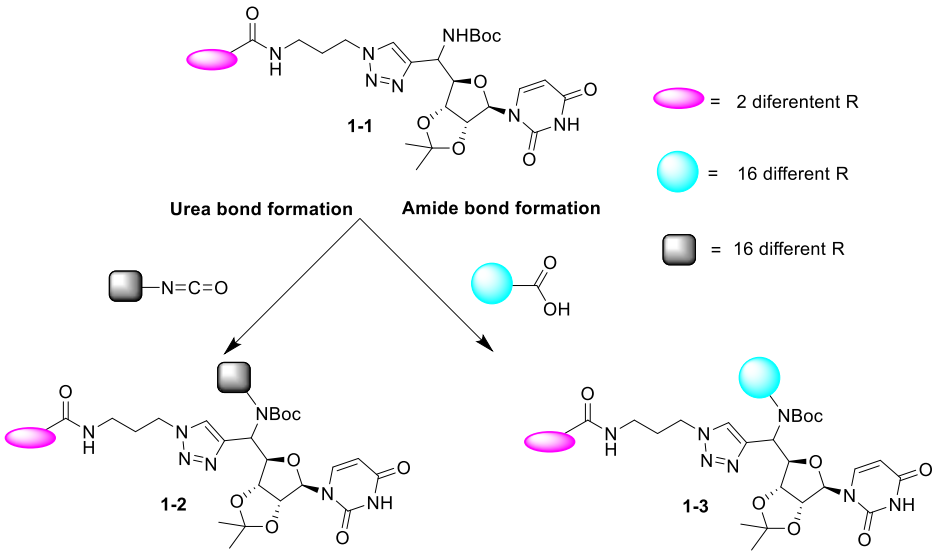
As appendage diversity and functional group diversity is similar in a way of its introduction they will be discussed together in chapter (2.4.2).

### 2.4.2 Appendage and functional groups diversity

The most straight forward approach way how to introduce the diversity is to modify appendages. The term “appendages” refers to the “extremities” of the central molecule. In this context the term refers to all/aryl/heteroaryl chains at the same time it can refer to the functional groups. The difference in modification of these two cases differ in the chemistry. Though both cases will be discussed together in this subchapter.

The chemistry required to achieve these modifications is related to the combinatorial chemistry approach. The advantage of varying appendages is to improve central structure and to vary pharmacokinetic proprieties of it. Modifying substituents is the easiest way how to improve these proprieties[18].

Interesting example of appendage diversity can be found in literature where Cheng and co-workers[19]. The goal of their work was to introduce appendage diversity to uridine-containing library to molecules leading to 5’-uridine based molecules bioactivity potency. Appendage diversity is introduced in the last step via amine functional group This process resulted in formation of 80 individual structures starting from two precursors (Scheme 1).




*Scheme 1– Preparation of 80 compounds with divergent appendages in one step*[19]

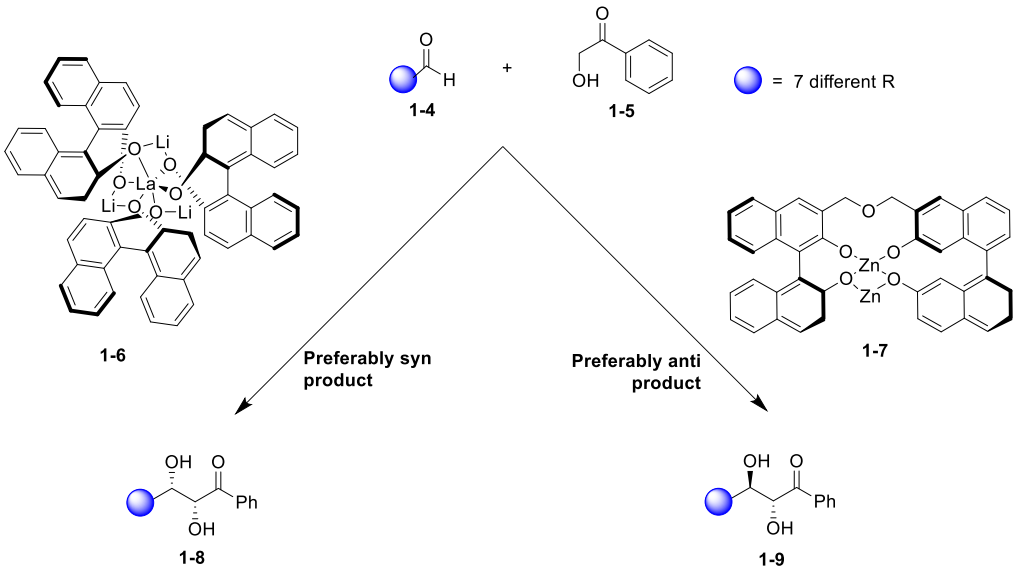
As it was mentioned previously, appendage diversity is a powerful way how to generate a large quantity of compounds starting from single building block in short and efficient manner. The limitations are close structural similarity of produced compounds. As a typical example of this approach can be considered the work of Tan et al. who prepared the library of 2.8 million of compounds in just 6 steps[20].

### 2.4.3 Stereochemical diversity

As mentioned earlier, molecules are three-dimensional structures and the overall shape of them is important. The orientation of individual substituents is crucial for interactions of small compounds with macromolecules. Thus such fact needs to be consider when chemical library is designed[1,14].

By different roads it is crucial to include stereochemical diversity (when possible) to the library design. Thus the processes used to create new stereogenic centers require both, to be selective and generaly applicable[1]. From these criteria, the catalyst approach seems to be the most suitable. Indeed, in this case both possible enantiomers or stereoisomers can be generated by just inverting the ligand that creates chiral environment of the catalsts[21].

As an example of such approach the aldol reaction is one of the most used stereoselective transformations. The example of such reaction that can produce one of the other enantiomer/diastereoisomer is shown on (Scheme 2) [22].




*Scheme 2 - Aldolisation with catalysts providing preferably syn or anti product*[22]

### 2.4.4 Skeletal diversity

Finally, the skeletal diversity. To introduce the skeletal diversity in to the chemical library design is the most challenging part[10]. There are two main strategies how to create skeletal diversity[10,11,14].

First is substrate-based strategy and depends on pre-encoded structures that are called σ-elements. In, such starting materials then generate various diverse substrates by applying common reaction conditions. The diversity is then directly tied to starting pre-encoded structures.

The second, reagent-based strategy, is based on one type of starting compound that includes pluripotent functional groups within the structure (one structure participate in several different reactions) that under different reaction conditions and with different reagents will yield different skeletons.

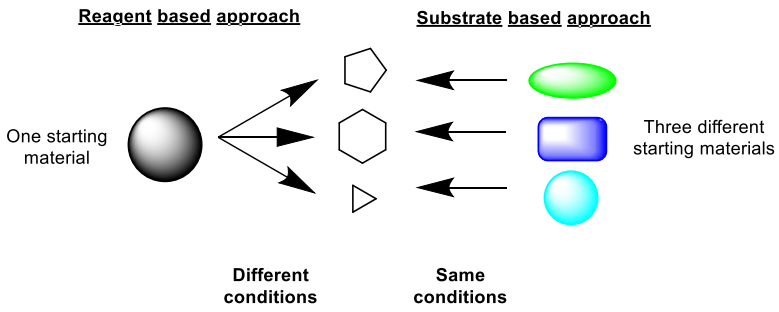
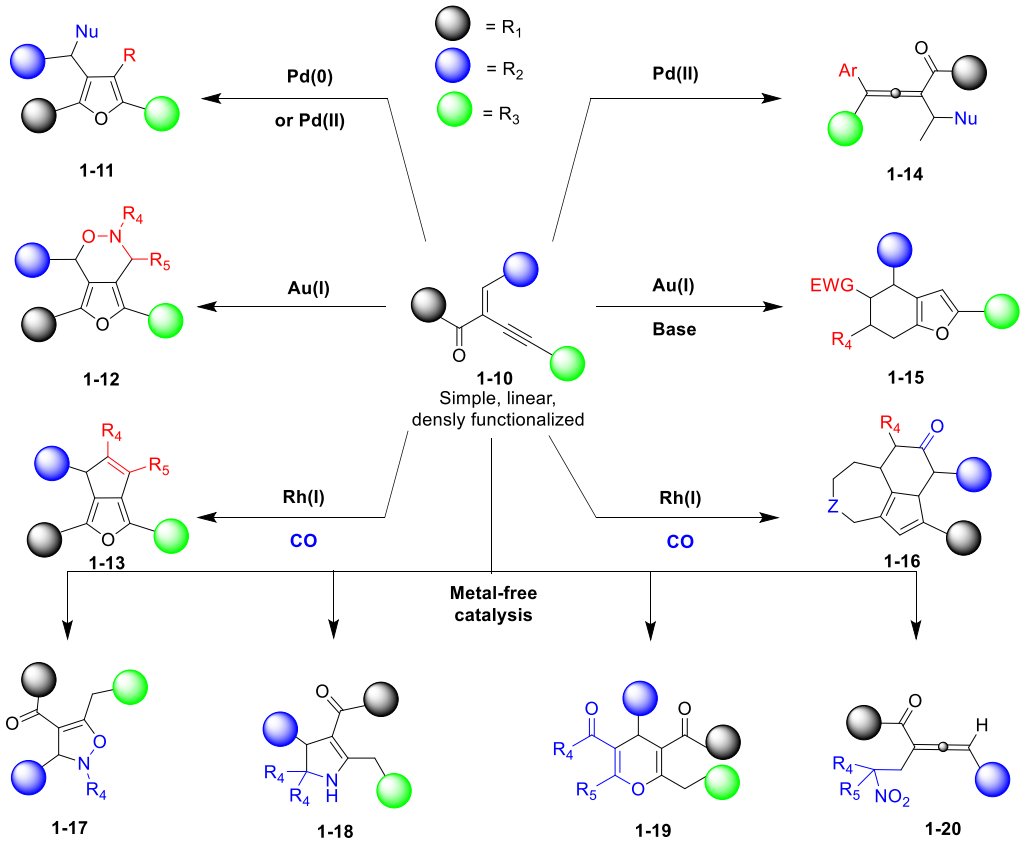



*Figure 2 – Schematic explanation of reagent and substrate-based approaches.*

### 2.4.4.1 Reagent-based approach

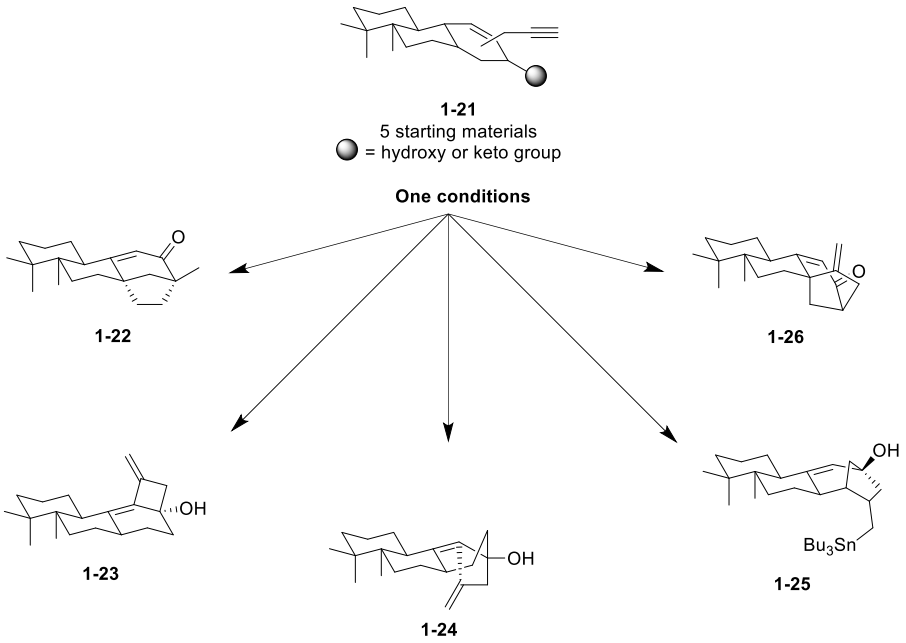
Reagent-based approach uses densely substituted starting molecule with pluripotent functional groups. Such molecules produce diverse scaffolds based on used conditions. Crucial part of such approach is wisely planned staring molecule allowing intramolecular and/or intermolecular modifications through usage of pluripotent function groups. Such example is shown in (Scheme 3)[23].




*Scheme 3– Reagent based approach generating 10 different scaffolds*[23]

### 2.4.4.2 Substrate-based approach

Substrate based approach on the other hand relies on wisely chosen starting material in different way. Diversity is generated by same conditions applied to different substrates which preencode the products as shown in (Scheme 4)[24].




*Scheme 4 – Substrate based approach generating five distinct scaffolds*[19]

### 2.4.5 DOS synthetic approaches

The ambition of chemical libraries with large molecular diversity is a challenge ever since chemists started to address the diversity-oriented synthesis. The whole strategy and planning behind DOS are indeed different to the synthetic approaches used in TOS or combinatorial approach. The progress in this domain was firstly based on the development of reagent and substrate-based. Next build/couple/pair strategy developed from those two approaches and forged a new approach to chemical library constitution[1].

### 2.4.6 Build/Couple/Pair strategy

The stated Build/Couple/Pair strategy (B/C/P) was the evolution and combination of two previous strategies. It is an algorithm that was introduced by Nielsen and Schrieber in 2008[25] and it designs the strategy to create the chemical libraries into three distinctive phases.

**Build** – starting point of synthesis. Basic building blocks (commercial products) are generated. These building blocks must be functionalized

**Couple** – coupling of building blocks to prepare pluripotent intermediates that can be used as in the pair phase

**Pair** – generation of skeletal diversity using intramolecular "pairing" of functionalized groups

Overall, the whole B/C/P strategy should include as few steps as possible to generate diversity and desired products in short and efficient manner. The building blocks should embodied all required functional groups needed for pair phase and at the same time, functional groups that will join together during the couple phase[26].

However, in many cases additional groups are introduced to the structure after Couple step. Pluripotent molecule contain variety of functions that are paired intramolecularly[25].

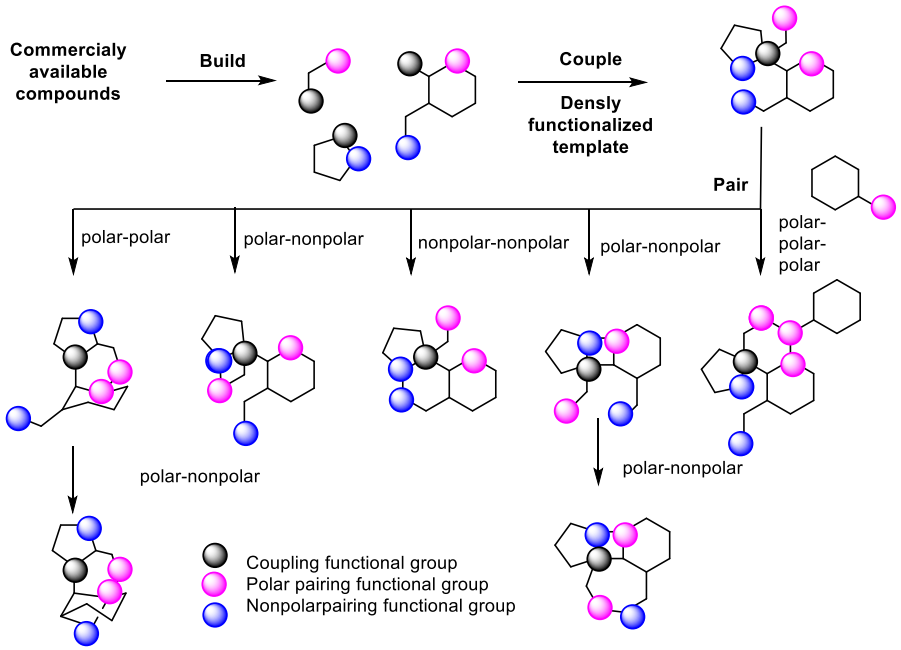
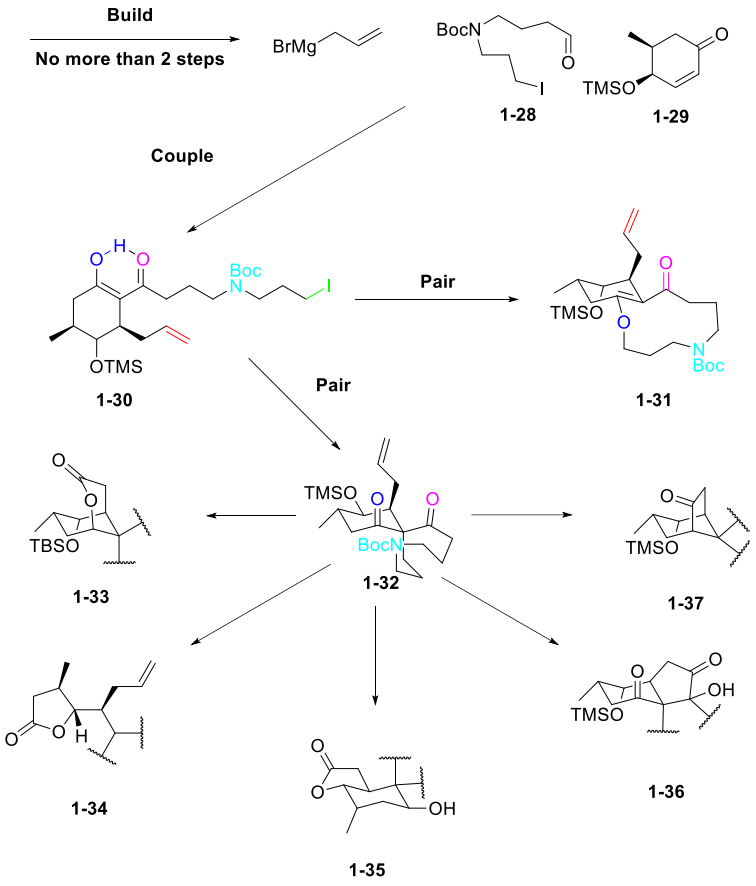



*Figure 3 - Illustrative example of B/C/P strategy*

As an example of key intermediate design can server the pluripotent molecule developed to the library of Lycopodium alkaloid[27] Starting building blocks are either commercially available or readily available in two steps. The couple stage generates an intermediate with all crucial functions required for later pair phase. The pair step then generates key intermediate for synthesis of another five structurally diverse products. In the end, seven complex structures were prepared in no more than two synthetic steps from one key intermediate.




*Scheme 5 – Preparation of 7 different scaffolds from one molecule 1-30 in no more than two steps*[27].

### 2.4.7 Pospisil research group and B/C/P approach

In our group we are focused on the development of new generation of novel pluripotent scaffolds from simple and easily accessible starting materials in fast and efficient way. To do so, in past we have formed our efforts to the design and synthesis on novel pluripotent reagents (PM-molecules), the products of couple step. Such PM is than to be readily transformed to desired product (Pair phase) of new chemical library[28].

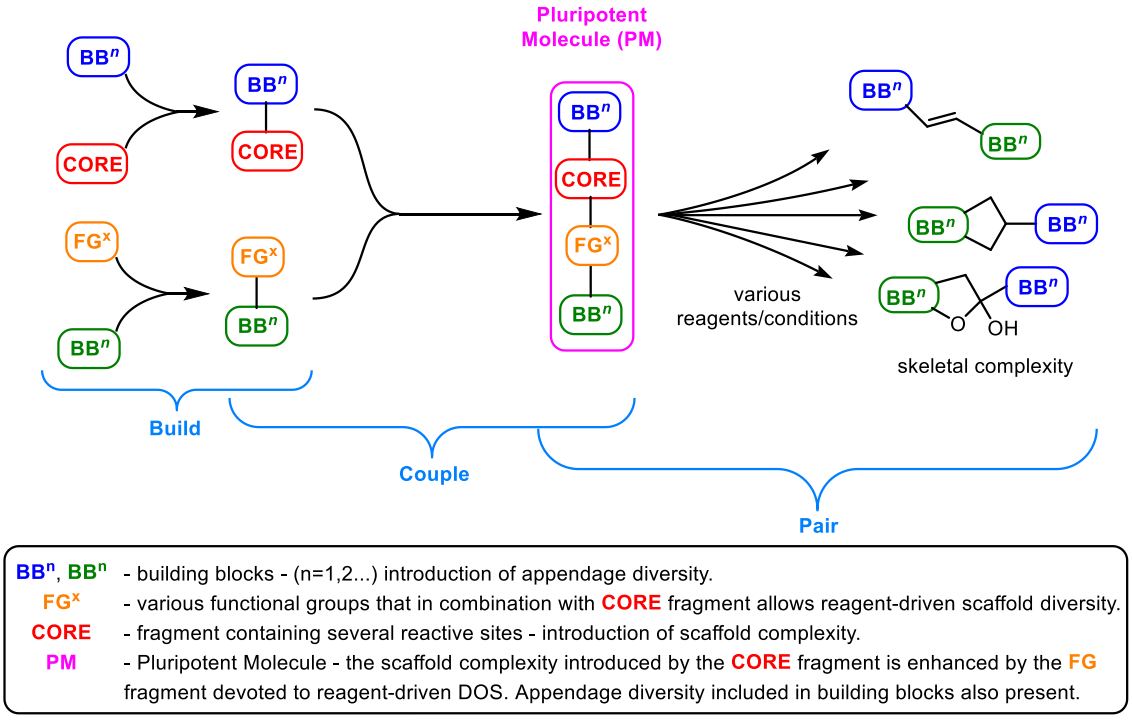



*Figure 4 – Pluripotent Molecules as the key intermediate in the B/C/P strategy*[28]

Crucial step in the design of any PM is to wisely chose the CORE fragment of it. This fragment is responsible to generate (PM), core and furthermore also for modifications in Pair step. Thus the coupling CORE-BB and FG-BB is as important step since this reaction cannot react with other functional groups (side reactions).

Based on our previous experience in the research group, the crucial role of CORE fragment was given to benzothiazole (BT) sulfones[28]. The advantage of heteroaryl is directly connected with the additional reactive sites within the molecule. Acidic hydrogens in $\alpha$ position to sulfone plays also a crucial role in formation of PM in my project. Also, there are other nucleophilic or electrophilic centers with BT-sulfones that can be further exploited. In addition, BT group can be used as electron acceptor (low energy LUMO orbital) or be exchanged with different heteroaryl, aryl or alkyl.

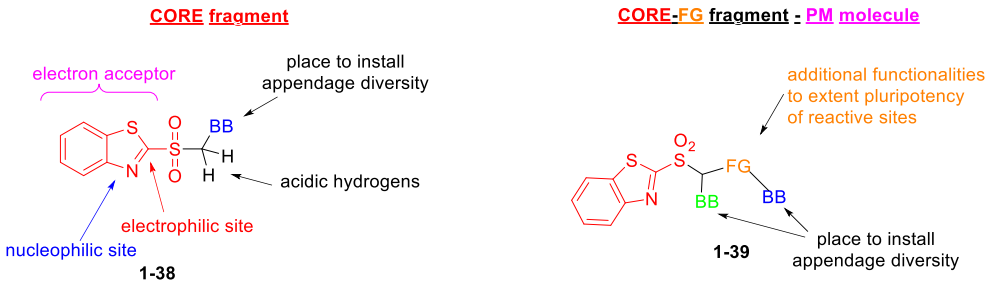
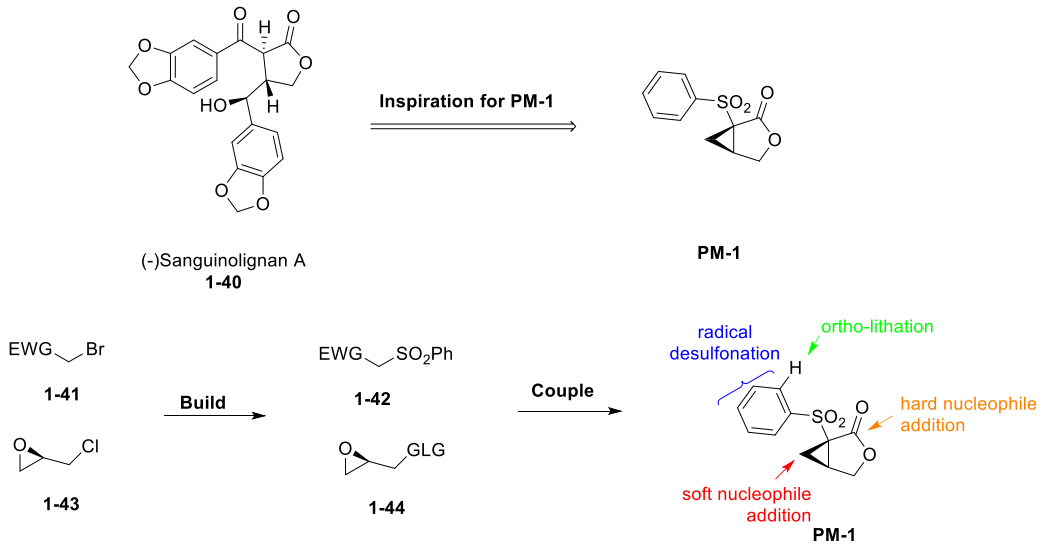



*Figure 5 – Pluripotent molecules based on BT-sulfones*

Previous experiments of our group in the field of heteroaryl sulfones not related to the B/C/P approach can be find in literature[29–32].

### 2.4.8 Previous development of Pluripotent Molecule design in our group

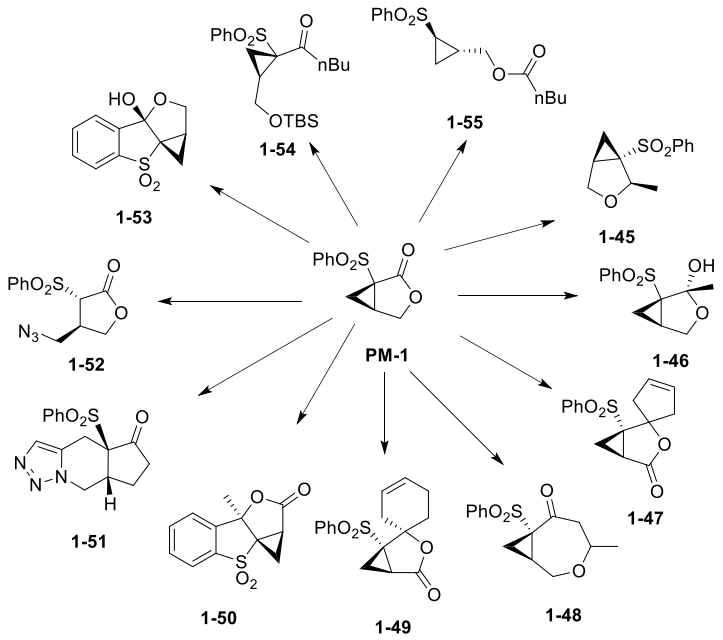
As mentioned PM-design was previously investigated in our group[33,34]. There are three generations of sulfone-based PMs where one of them is not BT-based. During her doctoral Thesis Daniela Koutská (neé Konrádová) used B/C/P approach to constitue lignan natural product inspired library of 10 compounds[35]. **PM-1** was prepared from commercially available materials in two steps and **PM-1** then was modified in 1-3 steps in yields varying from 50-80%. All performed reactions produced the desired compounds with excellent degree of stereoselectivity.




*Scheme 6 – Inspiration for 1st generation of PM and preparation[35].*

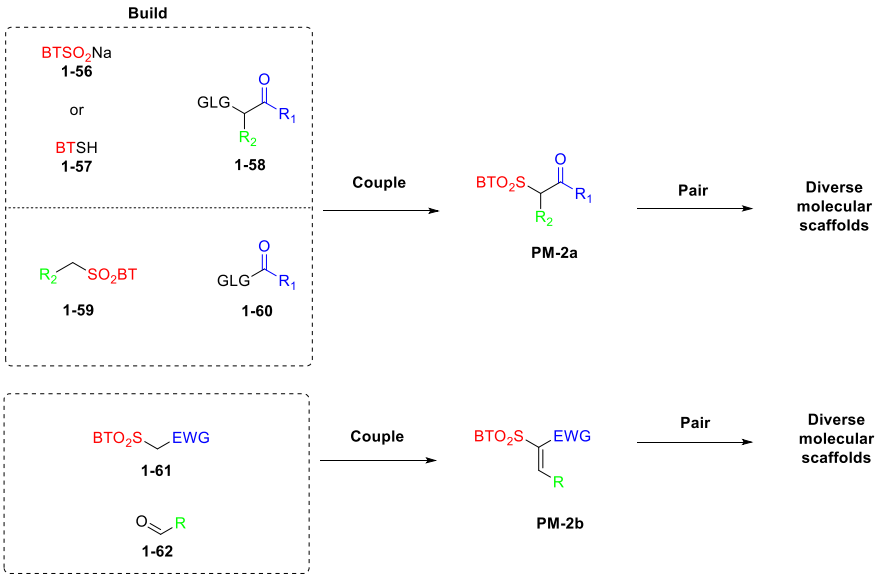
Overall, the library of products constituted of scaffolds as bicycles, tricycles, and tetracyclines, fused or connected spiro compounds were prepared. The chiral compounds were

to be tested for their antileishmanial activity. The results were promising and there are new structural motives with excellent activity were found. These three motives now serve as a starting point to generate new focused library.



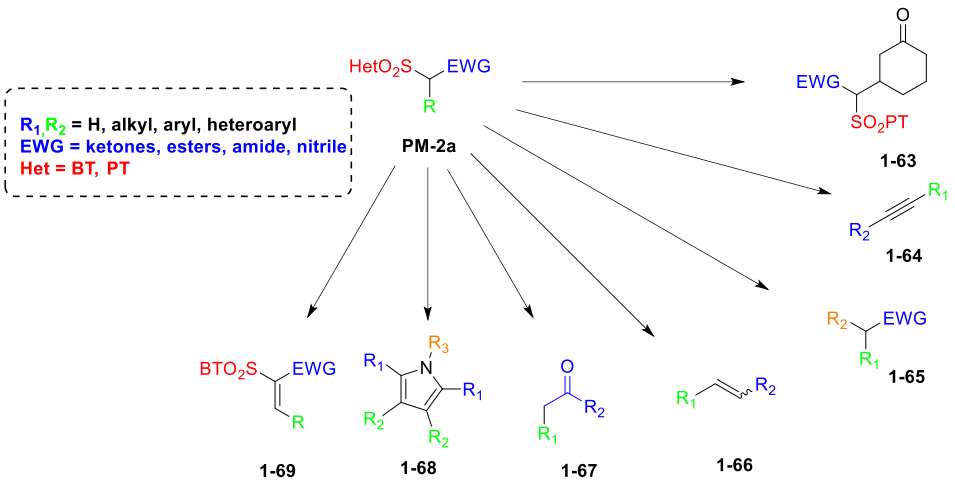

*Scheme 7 – Transformation of PM-1 to structurally diverse molecules*[33].

Next generations of PM + PM-2, are BT-sulfone based and are present in two subclasses, PM-2a and PM-2b (PM-2b is generated from PM-2a). PM-2 molecules were generated and explored in the Ondřej Kováč Doctoral Thesis[34].



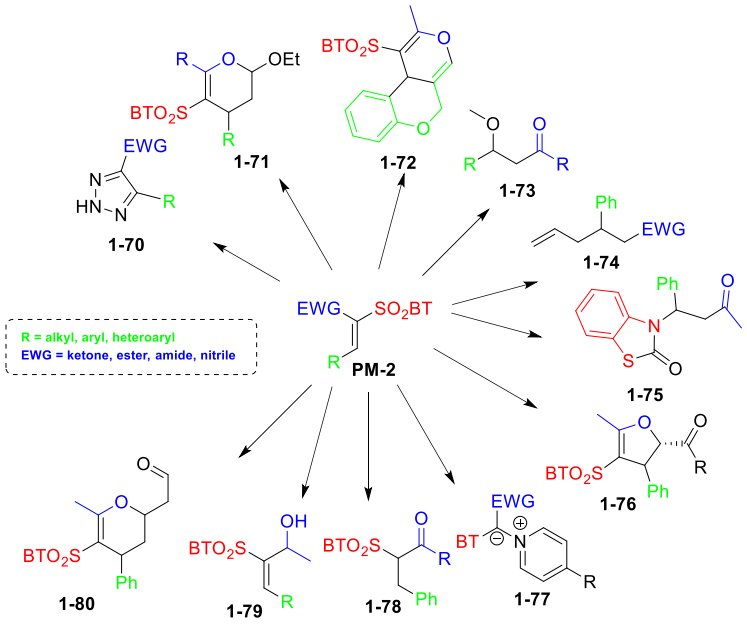

*Scheme 8 – Preparation of PM-2a and PM-2b*[34]

The PM-2a proved to be an excellent reagent to allow one and two-carbon homologation of alcohols. New one-pot protocol for stereoselective formation of C=C bond was also developed[34].




*Scheme 9 – Scope of possible products from PM-2a*[34]

Further evolution of PM-2a to PM-2b then allowed to generate more than 50 different entities. [3+2] and [4+2] cycloadditions, [4+1] cyclization, development as the use of a new type of pyridinium ylides, intramolecular Smiles-type rearrangement, and also the regents can be employed in (4+2) cyclization reaction catalyzed by Hayashi-Jørgensen catalyst[36].

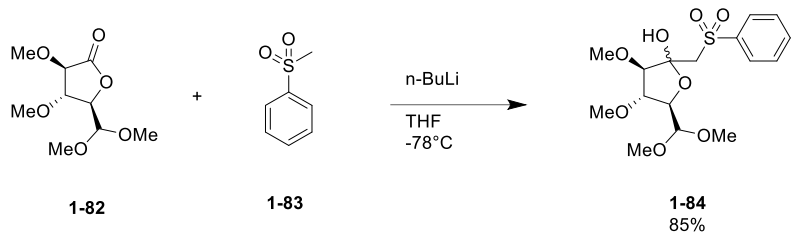



*Scheme 10 - Scope of possible products from PM-2b*[36]

Aim of this diploma thesis is to focus on the development of new 3rd generation of BT-sulfone based pluripotent molecules PM-3 that differs to previous two generations and allows to extend to use of our PM molecules to the field of macrolide chemistry.

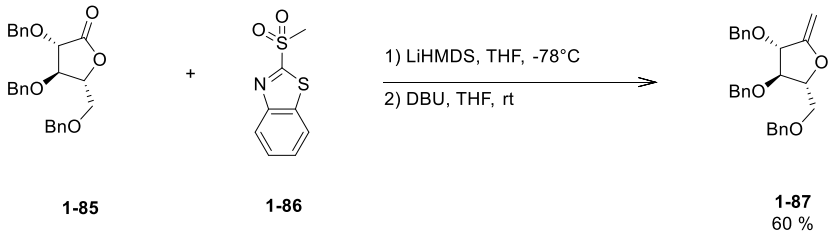
## 2.5 Reactions of lactones with α-methyl sulfones

Reactivity of lactones with α-methyl sulfones is not a topic found often in literature. First mention of α-methyl sulfones used for alkylation of lactone was published in 1997 by Tatsua et al[37]. In the article they prepared progesterone receptor ligands and one of the steps was reaction of lactone with phenyl methyl sulfone in THF with n-BuLi as base with yield of 85% (Scheme 11). However as the NMR or any kind data are not stated for this compound I suspect that it was not isolated and used only as intermediate.



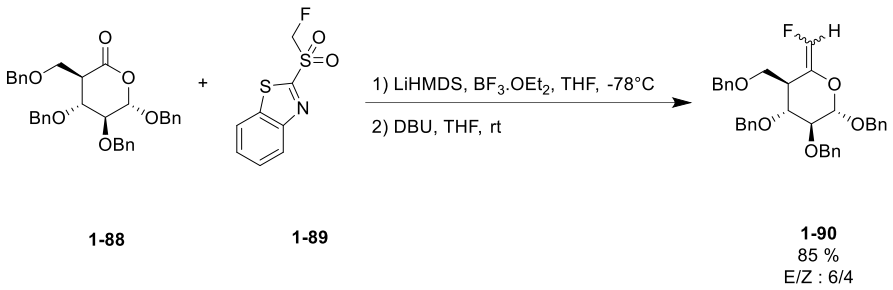

*Scheme 11 – Preparation of 1-84 from lactone **1-82** and sulfone **1-83**[37]*

Other mention of reactions of α-methyl sulfones with lactones can be found in piece published by Gueyrard et. al.[38]. In their article they used 2-(metylsulfonyl)benzo[d]thiazol in olefination reactions with protected sugar derived lactones (example on scheme) (Scheme 12). They used the product as crude in second reaction giving desired *exo*-glycal with 60% yield.




*Scheme 12 – Preparation of exo-glycal **1-87** from lactone **1-85** and sulfone **1-86**[38]*

Further development of this reaction was done with usage of 2-(fluorometylsulfonyl)benzo[d]thiazol allowing synthesis of fluorinated *exo*-glycals (Scheme 13) with yield between 85%[39].

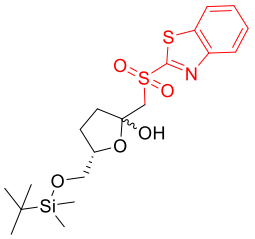



**1-88** **1-89** **1-90** 85 % E/Z : 6/4

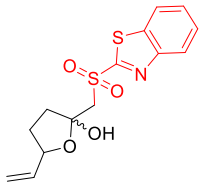
*Scheme 13 - Preparation of fluorinated exo-glycal **1-90** from lactone **1-88** and sulfone **1-89***[38]

# 3 Results and discussion

The following chapter is divided to the two distinct parts that focus on the **PM-3a** and **PM-3b** preparation and modifications.



**PM-3a**



**PM-3b**

First, the retrosynthesis approach to both pluripotent molecules is shown 3.1 and further the synthesis of **PM-3a** and **3b** is discussed in context of B/C/P strategy. The Build part is gathered in the chapter 3.2, the Couple stage (preparation of PM-3 molecules) in chapter 3.3, and finally the modifications **PM-3** molecules in chapter 3.4.

## 3.1 PM-3a and PM-3b retrosynthesis

Aim of my work is to prepare pluripotent molecules **PM-3a** and **PM-3b** and to find out their potency in THF ring-motive containing chemical library constitution.

Targeted pluripotent molecules were planned to be obtained in several steps from methyl benzo[*d*]thiazo-2-yl sulfone **2-3** and lactones **2-1** and **2-4** (Figure 6). In our retrosynthetic approach we expected that lactone **2-1** should be available starting from L-glutamic acid **2-2** via intramolecular lactonization, reduction of carboxylic acid to alcohol, and finally by protecting generated alcohol by TBS group[40]. Similarly, the lactone **2-4** was planned to be prepared starting from butyrolactone **2-6** via base-catalyzed lactone-ring opening[41–44], oxidation of the resulting alcohol to aldehyde[45] (**2-5**), and vinyl magnesium bromide addition[46].

Having obtained the key lactone intermediates, their reaction with BT-sulfone **2-3** (Couple phase) according to our previously reported protocol[31,32] should yielded the desired pluripotent molecules **PM-3a** and **PM-3b**. Finally, the exploration of the reactivity of both **PM-3** molecules e.g. in context of Lewis acid mediated reactions (generation of oxonium) should be carried out to finish up the library constitution.

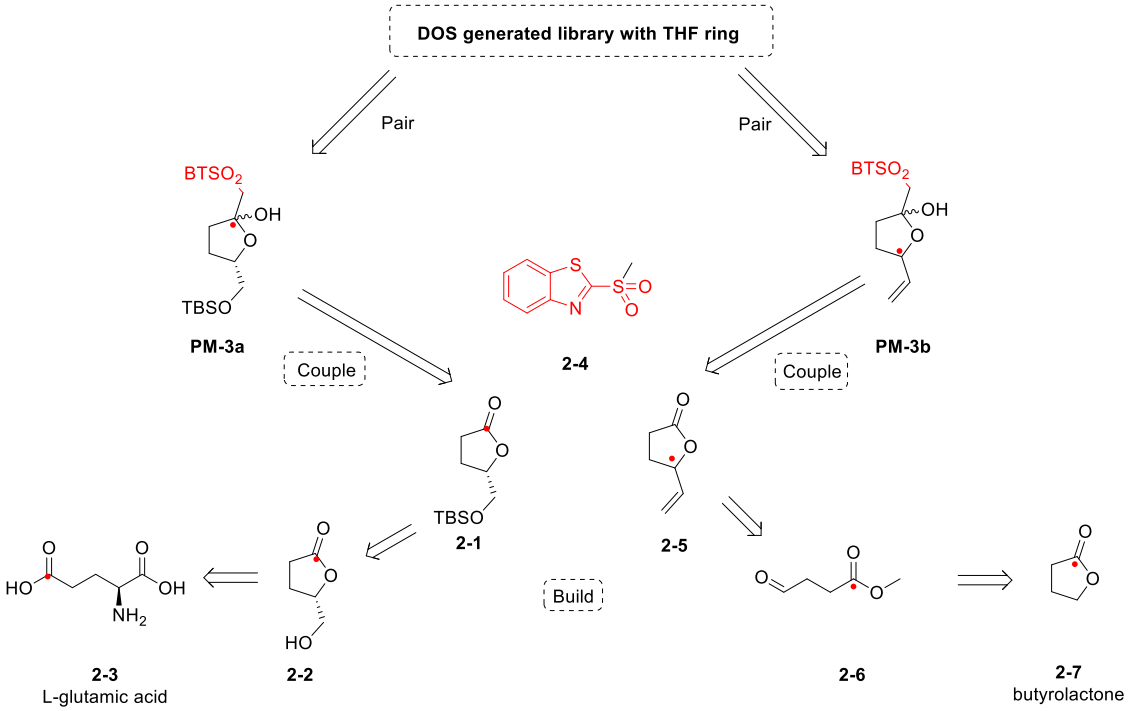



*Figure 6. Retrosynthesis of PM-3 molecules. For better orientation, the key lactone carbonyl atom is highlighted with red dot throughout the Scheme.*

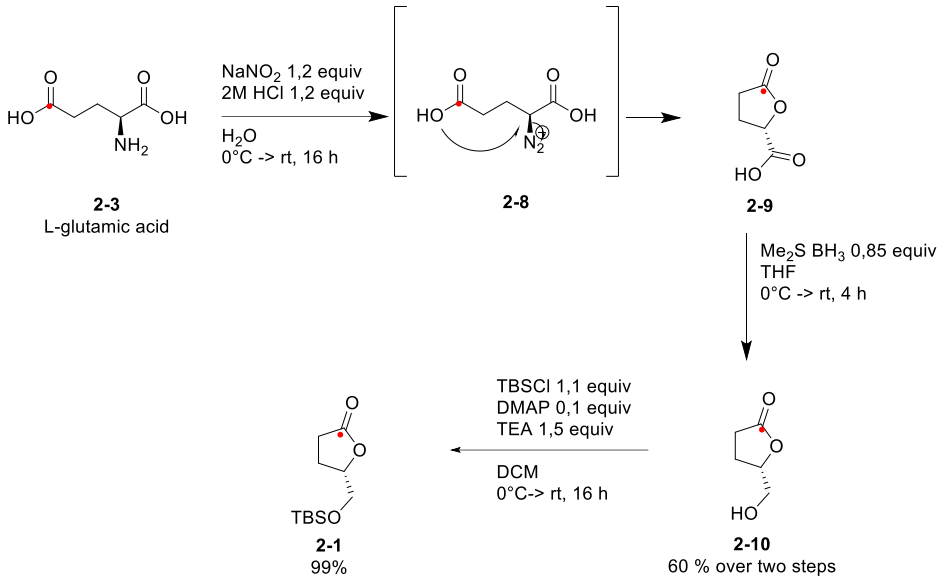
## 3.2 Build phase

### 3.2.1 Preparation of lactone **2-1**

First, we focused on lactone **2-1**. Our choice of the target compound **2-1** was driven by its simple synthesis, availability of the starting material, and also by the presence of a bulky protecting group (TBS) that should effectively direct the stereoselectivity of further transformations planned for the Pair step. In addition, the presence of the bulky -$CH_2$-OTBS group on the lactone skeleton should further allow the stereoselective transformation of **PM-3a** to more substituted derivatives (e.g., by stereoselective *anti*-to methylene-OTBS methylation[40]).

Lactone **2-1** synthesis[40] starts with the transformation of L-glutamic acid **2-3** to the corresponding acid **2-9** (Scheme 14). In this context, amino group was transformed into the corresponding diazo group with help of potassium nitrite, and diazo group then served as a good-leaving group (release of $N_2$) during the subsequent intramolecular lactonization. Generated acid **2-9** was then selectively reduced to alcohol **2-10** with help of $BH_3.SMe_2$ complex. This two-step protocol yielded desired alcohol **2-10** in 60 % yield. Next, primary alcohol in **2-10** was protected in form of TBS ether in quantitative yield. The only drawback of this protocol was the use of $Me_2S.BH_3$ that has due to $SMe_2$ a typical odor. During evaporation it is thus wise to

use a solution of hypochlorite as a “washing” bottle after the safety bottle during the evaporation of all contaminated solutions.




*Scheme 14 – Lactone **2-1** preparation from L-glutamic acid*[40]

The overall yield of **2-1** was 59 % over three steps. The reaction was also carried out in 25g scale without the significant loss in reaction yield.

### 3.2.2 Lactone 2-4 synthesis

The synthesis of vinyl-containing lactone **2-4** was motivated by the stabilization properties of vinylic group to the positive charge in the γ position. We were expecting that when **PM-3b** is generated, the presence of the vinylic group will easy the hemiacetal ring opening and generates qualitatively very different reagent when compared to **PM-3a**. The fact that could be successfully used during the Pair phase-based chemical library constitution.

Lactone **2-4** synthesis starts from butyrolactone **2-6** – inexpensive readily available chemical that is, however, under strict control of low-reinforcement units due to a possible misuse in the drug preparation. In the first step, the compound was trans-esterified with methanol or ethanol (Table 1). This reaction is well-known in the literature[41–44]and we thought it will pose no problems to us to be reproduced. However, none of the conditions we attempted to reproduce either worked or generated in the desired alcohol in good yields and/or reproducible manner (Table 1, entries 1-4). After some evaluation of the reaction conditions, it was observed that the addition of a small quantity of water (1% in MeOH, V/V) brings the conversion of lactone **2-6** to its completion and yields the alcohol **2-11b** in quantitative yield.

*Table 1. Butyrolactone **2-7** trans esterification: Reaction condition optimization*

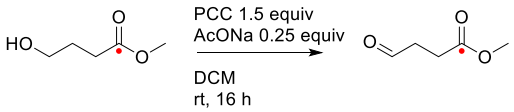

**2-7**
butyrolactone

**2-11**

| Entry | **R** | Conditions | Compound, Literature reported yield [%][a)] | Compound, Isolated yield [%][a)] | Reference to the original protocol |
|---|---|---|---|---|---|
| 1 | Et | $Et_3N$ 1,5 eq, EtOH, 80°C, 16 h | **2-11a**, 96 % | **2-11a**, 50 % | [41] |
| 2 | Me | Amberlyst, MeOH RT, 72 h | **2-11b**, 96 % | **2-11b**, 0 % | [42] |
| 3 | Me | $Et_3N$ 2 eq, MeOH, 60°C, 4 h | **2-11b**, 93 % | **2-11b**, 45 % | [43] |
| 4 | Me | $Et_3N$ 6 eq, MeOH, 60°C, 4 h | **2-11b**, 93 % | **2-11b**, 55% | [44] |
| 5 | Me | $Et_3N$ 2 eq, MeOH, 1 % H20 60°C, 4 h | n/a | **2-11b**, 99% | |

[a)] Refers to pure isolated compound.

Next step was oxidation of alcohol **2-11b** to aldehyde **2-5** (Scheme 15). First attempted reaction conditions relied on the use of PCC reagent developed by Corey[45] in 1975. Since our product is highly volatile, it was observed that the heating bath must be kept under 30°C when reaction solvents are removed under the reduced pressure (increase of reaction yield by cca 10-15%). Another yield improving trick we successfully employed was the use of dry ice cooling of the silica gel (outside) right before the crude aldehyde was loaded on the column chromatography. This prevents local overheating of $SiO_2$ and avoids the undesired side reactions (condensation). Combination of those tricks improved the reaction isolated yields to 45%.



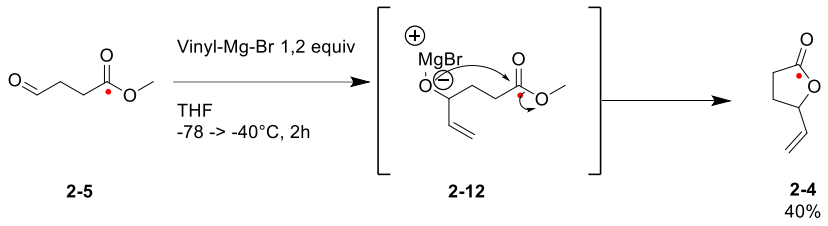

**2-11**

**2-5**
45 %

*Scheme 15 – Oxidation of alcohol **2-11** to aldehyde **2-5**[45]*

To increase the reaction yield of aldehyde **2-5**, additional oxidation methods and reagents were attempted with various outcomes. Dess-Martin oxidation protocol proved to be ineffective in this case (degradation)[47]. Swern oxidation that was accompanied with more demanding reaction set-up yielded the desired product in 40% yield[48]. In addition, the reaction could not be scaled up in our hands.

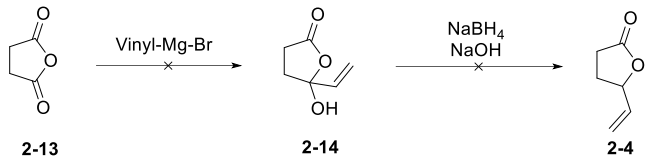
In the last step of the lactone **2-4** synthesis, the addition of the vinyl magnesium bromide to aldehyde of **2-5** should generate alcoholate **2-12** (Scheme 16). Generated alcoholate should then cyclize to yield the desired lactone **2-4**. The given reaction sequence was reproduced, with slight modifications, from the literature[46]**.** The modification we introduced were made for the following reasons: (a) the same equivalents of both, reagent and lactone **2-5**, were used, however, in my case a methyl ester instead of ethyl ester was used; (b) the reaction was setup at -78°C instead of 0°C and further carried out at -40°C, because lower amount of side products was observed in the crude reaction mixture after the reaction work-up (based upon $^1$H NMR analysis of the crude reaction mixtures).




*Scheme 16 – Preparation of **2-4** by Grinard addition to 2-5 followed by intramolecular cyklization*

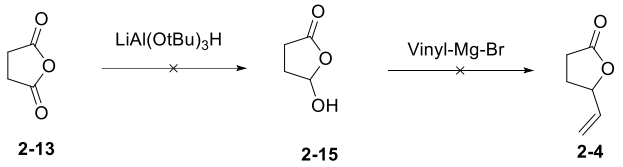
Overall yield of the three-step preparation of lactone **2-4** was 17 %. Within the sequence at least two steps proved to be readily scalable (trans-esterification and oxidation, 25g batch), and Grignard addition/cyclization was carried out on 5g. The trouble maker step is then the oxidation step.

To avoid the oxidation step, two additional approaches to lactone **2-4** were attempted. In the first one, we speculated that the addition of the vinyl-grignard reagent to succinic anhydride **2-13** should yield the corresponding monoadduct **2-14** (Scheme 17). Generated hemiacetal then should in the presence of $NaBH_4$ undergo to the ketone (generated *in situ*) reduction and resulting secondary alcohol would yield upon the solvent evaporation (condensation) the targeted lactone **2-4.**[49] However, this approach miserably failed at my hands.




*Scheme 17 – Preparation of lactone **2-4** from **2-13** by Grinard addition and reduction*[49]

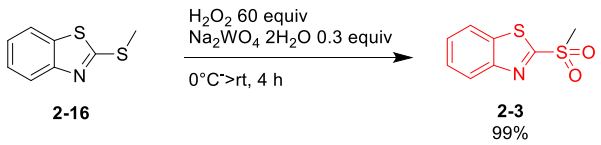
Another possible approach to **2-4** was based on the similar reduction/addition pathway.[49] Also in this case, the reaction sequence started from the succinic anhydride **2-13** (Scheme 18). Unfortunately also in this case we failed to obtain the desired lactone **2-4**.




*Scheme 18 – Preparation of lactone **2-4** from **2-13** by reduction followed by Grinard addition*[49]

### 3.2.3 BT-sulfone **2-3** synthesis

The second building block required for the Couple phase was the 2-(metylsulfonyl)benzo[*d*]thiazol **2-3**. Its synthesis was rather easy and was based on the oxidation of the commercially available and inexpensive sulfide **2-16**. To accomplish this transformation we used hydrogen peroxide-based oxidation of sulfur(II) to sulfur(VI) that was mediated with $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ or $Na_2WO_4\cdot 2H_2O$ pre-catalysts[31]. The reaction yields were in both cases the same and the desired sulfone **2-3** was obtained in both cases in nearly quantitative yields and excellent (>98%) chemical purity (Scheme 19). In both cases the obtained products could be used without any further purification.




*Scheme 19 – Preparation of **2-3** by oxidation of **2-16***[31]

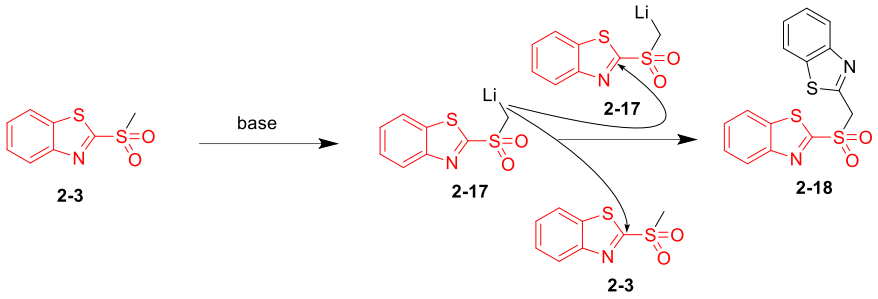
## 3.3 Couple phase

The next stage of our synthesis was the reaction of lactone-building blocks with sulfone **2-3** – Couple phase. Prior I will dive into the reaction attempts and results, it should be noted

that the majority of experiments were carried out on the lactone **2-1** since it is more stable under the reaction conditions and easier to be prepared.

### 3.3.1 Towards the PM-3a synthesis

The connective reunion of lactone **2-1** and sulfone **2-3** was planned to be achieved with use of the C-C connective approach previously developed in our group[36,50]. Condensation reaction is based on the use of metalated sulfone **2-3** as a C-nucleophile that is prepared with help of non-nucleophilic base $[M]N(TMS)_2$. The use of non-nucleophilic base during such process proved to be mandatory to avoid undesired self-condensation of sulfones **2-3** (Scheme 20).



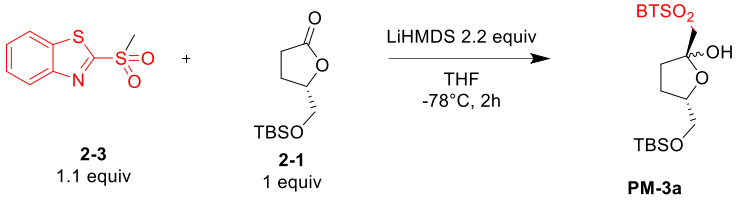

*Scheme 20 – Selfcondenzation of 2-3*[31]

To avoid a self-condensation step, metallated anion of **2-3** has to be prepared (a) at low temperature (-78°C) and (b) in access of nonnucleophilic base (nucleophilic base might also attack electrophilic site of sulfone. With that in mind we modified protocol from this paper which eliminates self-condensation of sulfone **2-3**. The key approach to avoid self-condensation is to add base to cooled down solution of **2-3** and in one or two minutes add a solution of electrophile. This approach proved to be true as we never found any traces of self-condensate side product **2-18** in any crude NMR after condensation with either compound **2-1**, nor **2-4**.

During optimalisation of this reaction we tried slightly different equivalents of reagents, base and temperatures but solvent stayed the same for all tries (

*Table 2*). All the reactions provide pretty good yields, but if the reaction if kept at -78°C for the whole time and it is quenched with aq. sol. of $NH_4Cl$ at -78°C it produces highest yields and least amount of unwanted side products (based on crude 1H NMR spectrums).

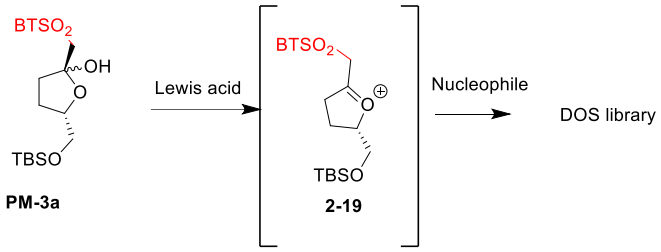
*Table 2. Addition of sulfone 2-3 to lactone 2-1: optimization.*




| Entry | Base (equiv) | Conditions | Yield[a)] |
|---|---|---|---|
| 1 | $LiN(TMS)_2$ (2.2 equiv) | -78°C, 2h | 80 % |
| 2 | $LiN(TMS)_2$ (2.2 equiv) | -78°C->0°C, 4h | 72 % |
| 3 | $KN(TMS)_2$ (2.2 equiv) | -78°C, 2h | 60 % |
| 4 | $KN(TMS)_2$ (2.2 equiv) | -78°C->0°C, 4h | 55 % |

a) Yield of the crude product after the reaction work-up. Determined with help of $^1$H NMR spectroscopy

The Couple phase proceeded best when the most "standard" conditions (2.2 equiv of $LiN(TMS)_2$, -78°C for 2h) were used (Table 2, entry 1). The crude yield of **PM-3a** was 80% (based on $^1$H NMR spectra) with >90% purity. Therefore, it was used as it was for the subsequent experiments. Obviously, the product **PM-3a** was present as a mixture of two diastereoisomers in approx. 1:1 ratio (epimers on the acetal carbon atom). However, since for our next experiments the stereochemistry has no relevance (it is anyway destroyed during the formation of oxonium), the separation of the two was not attempted (Scheme 21).




*Scheme 21. Formation of the oxonium intermediate starting from the **PM-3a** molecule*

Interestingly, it was observed that the diastereomeric ration of *syn* and *trans* **PM-3a** isomers was the same during the coupling step regardless the conditions of the coupling step. However, the situation changed if subsequent transformations (Pair step) were attempted. In such case, if Lewis acid-based conditions were employed ($BF_3{\cdot}Et_2O$ or TMSOTf) and the reaction was terminated with sat. aq. $NaHCO_3$, the ratio alter significantly. In such case the original ration of ~1:1 shifted to 1.81:1 (5.91 ppm major peak, and 5,57 ppm minor peak) and therefore we could successfully attempted to isolate the main peak containing hemiacetal compound and determine its structure as *trans*-**PM-3a**.

Interestingly we were unable to determine (a) the reason why the *trans* hemiacetal is formed preferentially under such reaction conditions, and (b) how it comes that it is stable under the isolation conditions and later on also in the solution during the characterization process.

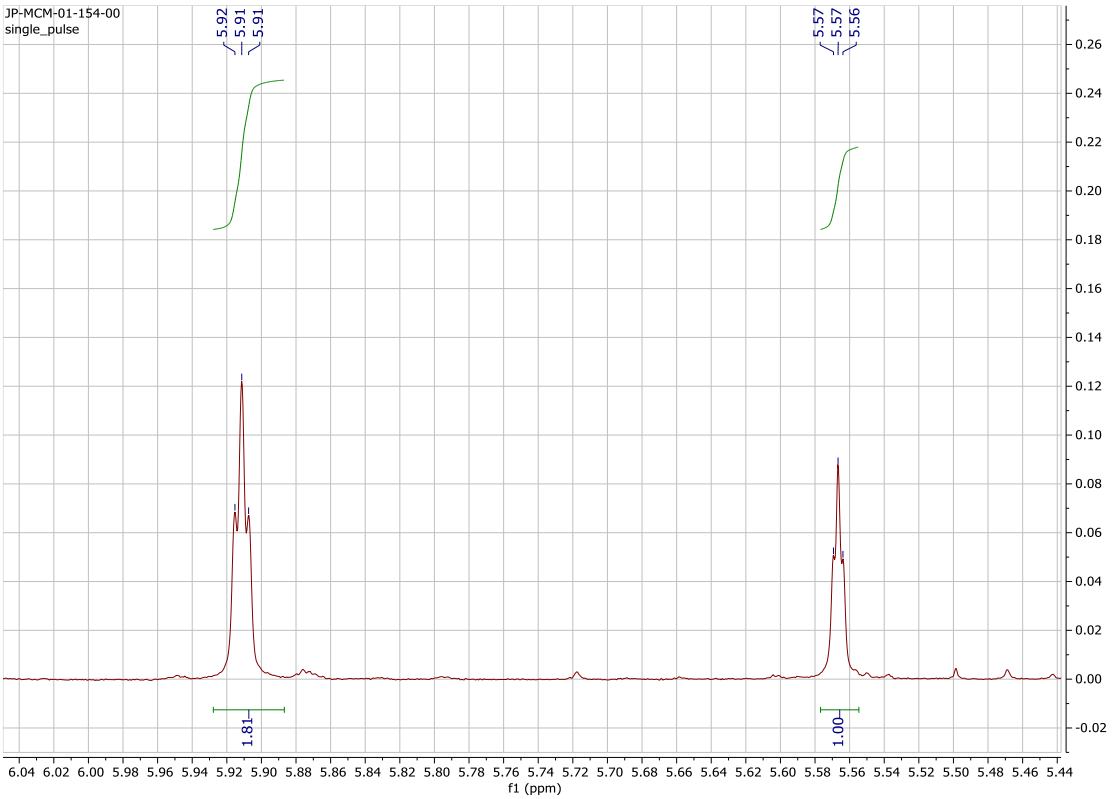
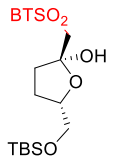


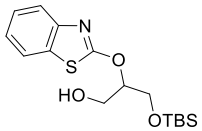

*Figure 7. $^{1}$H NMR spectra (5.44 ppm to 6.04 ppm) of two characteristic peaks of the hemiacetal hydrogen atoms in **PM-3a**.*




*trans* -**PM-3a**

*Figure 8. Major diastereoisomers isolated from the reaction mixture.*

As it was mentioned above, the reaction conditions of the coupling yielded the desired product **PM-3a** in very clean manner. However in case of the KHMDS promoted reaction (Table 2, entry 4) a minor (~10%) side product later on identified as compound **2-20** (Figure 9) was present (identification based on $^{1}$H NMR, $^{13}$C NMR and 2D NMR experiments).

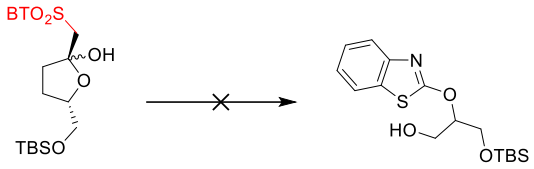



**2-20**

*Figure 9 – Structure of side product **2-20***

The main issue with the compound **2-20** was that we had no idea how the product I formed. First, we expected that **2-20** is generated directly from **PM-3a** molecule either during the reaction or after the reaction work up. To evaluate this hypothesis the **PM-3a** compound was treated with various bases and (Lewis) acids (Table 3). Unfortunately, under no tested reaction conditions we observed the formation of **2-20**. In all cases only starting molecule **PM-3a** was recuperated unchanged.

*Table 3. Evaluation of the **PM-3a** stability under various reaction conditions in DCM.*



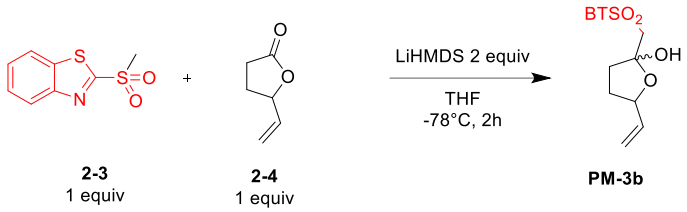

**PM-3a** **2-20**

| Entry | Reagent (equiv) | Conditions | Result |
|---|---|---|---|
| 1 | $BF_3{\cdot}Et_2O$ (2 equiv) | -78°C->0°C, 4h | starting material recuperated |
| 2 | TMSOTf (2 equiv) | -78°C->0°C, 4h | starting material recuperated |
| 3 | KHMDS (2 equiv) | -78°C->0°C, 4h | starting material recuperated |
| 4 | LiHMDS (2 equiv) | -78°C->0°C, 4h | starting material recuperated |

For the time being, the origin of compound **2-20** remains unknown.

### 3.3.2 Preparation of PM-3b

Having an easy access to **PM-3a**, the synthesis of **PM-3b** was evaluated (Scheme 22). Using the same reaction conditions as in the case of **PM-3a** formation (slight difference in reagent stoichiometric ratio due to a worse availability of **2-4**), the desired **PM-3b** was isolated in 20% reaction yield. However at this point it should be noted that even after the tremendous efforts we were unable to isolate the **PM-3b** in sufficiently pure form presumably due to its low stability on silica gel. As in the previous case of **PM-3a**, the desired product **PM-3b** was isolated as a mixture of diastereoisomers.



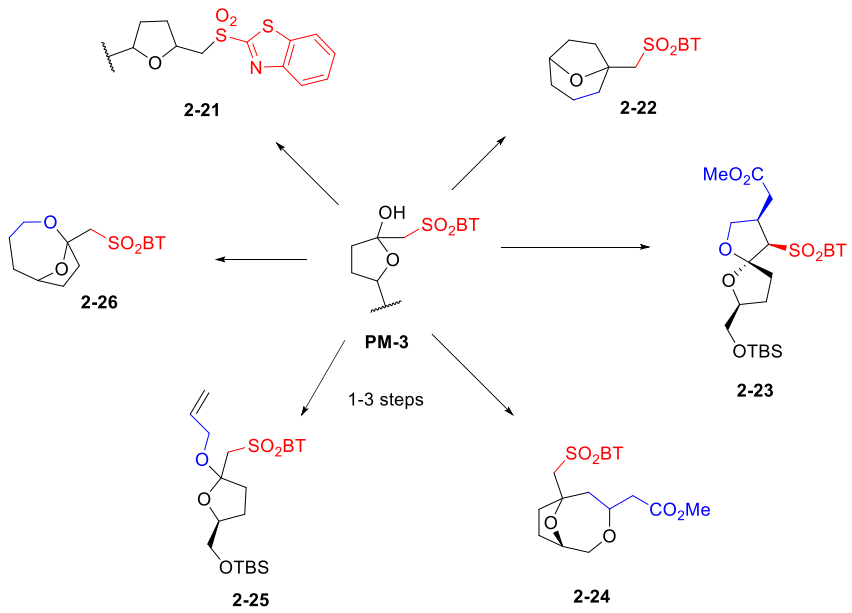

*Scheme 22. Towards **PM-3b** molecule.*

The product was characterized with help of NMR spectra and exact mass.

Due to this disappointing results and the difficulties I had during the lactone **2-4** synthesis, the synthesis of **PM-3b** was abandoned.

## 3.4 Pair phase

Having in hands **PM-3a** and **b** (small amount), the scope and limitations of the Pair phase of our approach could be evaluated. Originally, we planned a vast library that should be readily available via predominantly Lewis acid-mediated sequences (formation of oxonium) that could lead in short and efficient manner to several interesting structures and skeletons (Scheme 23).



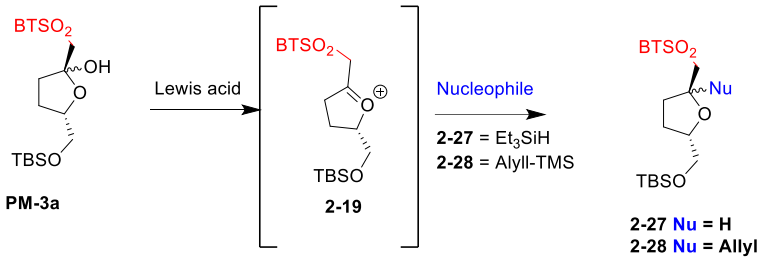

*Scheme 23. A brief overview of planned substructures that would be readily available from **PM-3**-type molecules.*

However, it was soon showed that our approach is not as great as we envisaged and that it faces to severe limitations.

### 3.4.1 The use of **PM-3a** in Pair phase

Our first efforts connected with the **PM-3a** molecule started with the well-known Lewis acid catalyzed oxonium **2-19** formation. Generated oxonium cation then should react *in situ* with nucleophiles as $Et_3SiH$ or allyltrimethylsilane, that were also present in the reaction mixture (Table 4). Unfortunately, under all tested reaction conditions, only starting material was recuperated unchanged after the reaction.

*Table 4. Attempted transformations of **PM-3a** under the Lewis acid conditions.*




| Entry | Acid (equiv) | Nucleophile (equiv) | Conditions | Expected product | Observation[a)] |
|---|---|---|---|---|---|
| 1 | $BF_3{\cdot}Et_2O$ (1.2 equiv) | Allyl-TMS (1.2 equiv) | -78°C, 2h | **2-28** | n.r. |
| 2 | $BF_3{\cdot}Et_2O$ (1.5 equiv) | Allyl-TMS (1.5 equiv) | -78°C, 2h | **2-28** | n.r. |
| 3 | $BF_3{\cdot}Et_2O$ 1,5 eq | Allyl-TMS 1,5 eq | -78°C, 3h | **2-28** | n.r. |
| 4 | $BF_3{\cdot}Et_2O$ 1,5 eq | Allyl-TMS 1,5 eq | -78°C-> RT, on | **2-28** | n.r. |
| 5 | $BF_3{\cdot}Et_2O$ 1,5 eq | Allyl-TMS 15 eq | -78°C-> 0°C, 3 h | **2-28** | n.r. |
| 6 | $BF_3{\cdot}Et_2O$ 1,5 eq | $Et_3SiH$ 1,5 eq | -78°C-> -20°C, 3 h | **2-27** | n.r. |
| 7 | $BF_3{\cdot}Et_2O$ 2 eq | Allyl-TMS 1,5 eq | -78°C-> 0°C, 3 h | **2-28** | n.r. |
| 8 | $BF_3{\cdot}Et_2O$ 2 eq | Allyl-TMS 7 eq | -78°C->- 20°C, 3 h | **2-28** | n.r. |
| 9 | $BF_3{\cdot}Et_2O$ 2 eq | Allyl-TMS 7 eq | RT, on | **2-28** | n.r. |
| 10 | TMSOTf 1,5 eq | Allyl-TMS 5 eq | -78°C->- 20°C, 2 h | **2-28** | n.r. |
| 11 | TMSOTf 2 eq | $Et_3SiH$ 1,5 eq | -78°C -> RT, on | **2-27** | n.r. |
| 12 | TMSOTf 2 eq | $Et_3SiH$ 1,5 eq | -RT, on | **2-27** | n.r. |
| 13 | TMSOTf 3 eq | $Et_3SiH$ 1,5 eq | -78°C, 3 h | **2-27** | n.r. |
| 14 | Et2AlCl 2eq | $Et_3SiH$ 1,5 eq | -78°C-> 0°C, 2 h | **2-27** | n.r. |
| 15 | $Sc(OTf)_3$ 2eq | $Et_3SiH$ 1,5 eq | -78°C-> 0°C, 2 h | **2-27** | n.r. |

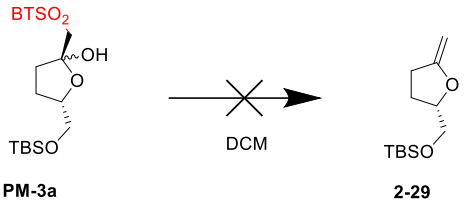
[a)] based on the $^1H$ NMR spectra of the crude reaction mixture. Starting material recuperated unchanged.

Since all our efforts were unsuccessful, it was envisaged that the homoacetal form is presumably too stable. Therefore we suggested that may be under the basic conditions the deprotection of alcohol will lead to the formation of the hemiacetal anion, that can further

undergo to the Smiles rearrangement (as in the case of Julia-Kocienski olefination reaction) and yield the corresponding *exo*-enolether **2-29** (Table 5).

Since we were aware that the presence of strong base as K or LiHMDS has no effect on the structure (Table 3), DBU as non-nucleophilic but strong thermodynamic base was tested. Unfortunately, also in this case no product formation was observed. Only a traces of the **PM-3a** were detected in $^{1}$H NMR spectra along a massive amount of secondary/side products.

*Table 5. Attempted base-promoted elimination of the acetal **PM-3a** to the enolether **2-29**.*

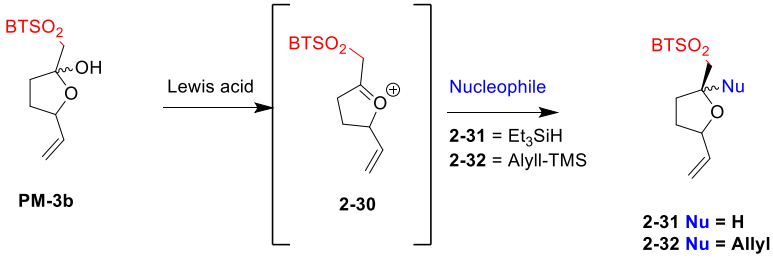



| Entry | Reagent (equiv) | Conditions | Result |
|---|---|---|---|
| 1 | DBU (2 equiv) | -78°C -> RT, 12 h | Unidentifiable mixture |
| 2 | DBU (2 equiv) | -78°C, 1 h | Unidentifiable mixture |

### 3.4.2 PM-3b molecule in Pair phase

Having in our hands some small amount of the desired **PM-3b** molecule, its transformations were also attempted (Table 6). However similarly to the **PM-3a**, no reaction was observed.

*Table 6. Attempted transformations of the **PM-3b** molecule.*




| Entry | Reagents | Conditions | Expected product | Observation |
|---|---|---|---|---|
| 1 | $BF_3{\cdot}Et_2O$ (2 equiv), $Et_3SiH$ (2 equiv), DCM | -78°C -> RT, 12 h | **2-31** | n.r |
| 2 | $BF_3{\cdot}Et_2O$ (2 equiv), Allyl-TMS (2 equiv), DCM | -78°C -> RT, 12 h | **2-32** | n.r. |

| | | | | |
|---|---|---|---|---|
| 3 | TMSOTf (2 equiv), $Et_3SiH$ (1.5 equiv), DCM | -78°C -> RT, 12 h | **2-31** | n.r. |

[a)] based on the $^1H$ NMR spectra of the crude reaction mixture. Starting material recuperated unchanged.

# 4 Conclusions

The main goal of this Theses was to find a way to the **PM-3a** and **b** molecules and to evaluate their suitability for the use in B/C/P sequence of chemical library constitution.

To do so, two key building blocks required for the Coupling step – sulfone **2-3** and its partners lactones **2-1** (three step scalable synthesis) and **2-4** (three step synthesis with 15% overall yield) – were prepared, and the Coupling step was performed. Unfortunately, it was showed that the Coupling step is working in case of lactone **2-1** (80% yield) but was problematic in case of lactone **2-4** (only 20% yield). The product of the later transformation, **PM-3b**, proved to be highly unstable on silica gel and therefore difficult to prepare in pure form.

Nevertheless, having **PM-3a** (substantial amount) and **PM-3b** (only small quantity) in our hands, the desired Pair step of the sequence could be performed. Unfortunately, in this case it was observed that the key intermediates **PM-3a** and **b** completely resists to any of our attempts for their transformation into the desired products. This failure was and is obviously an important drawback of our approach that attempted short and efficient synthesis of vast chemical library inspired with THF motive. In another words, we have demonstrated that the novel generation of pluripotent molecules, compounds **PM-3a** and **PM-3b**, are not suitable for the exploration in the context of DOS and chemical library of small organic molecules constitution.

# 5 Literature


(1) Burke, M. D.; Schreiber, S. L. A Planning Strategy for Diversity-Oriented Synthesis. *Angew. Chemie Int. Ed.* **2004**, *43* (1), 46–58. https://doi.org/10.1002/anie.200300626.

(2) Schreiber, S. L. The Small-Molecule Approach to Biology. *Chemical and Engineering News*. American Chemical Society March 3, **2003**, 51–61. https://doi.org/10.1021/cen-v081n009.p051.

(3) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. Diversity-Oriented Synthesis as a Tool for the Discovery of Novel Biologically Active Small Molecules. *Nature Communications*. **2010**. https://doi.org/10.1038/ncomms1081.

(4) Marggraf, A. S. Experiences Chimiques Faites Dans Le Dessein de Tirer Un Veritable Sucre de Diverses Plantes, Qui Croissent Dans Nos Contrées. *Hist. l'académie R. des inscriptions belles lettres* **1747**, 79–90.

(5) Wöhler, F. Ueber Künstliche Bildung Des Harnstoffs. *Ann. der Phys. und Chemie* **1828**, *88* (2), 253–256.

(6) Schreiber, S. L. Small Molecules: The Missing Link in the Central Dogma. *Nat. Chem. Biol.* **2005**, *1* (2), 64–66. https://doi.org/10.1038/nchembio0705-64.

(7) Tan, D. S. Diversity-Oriented Synthesis: Exploring the Intersections between Chemistry and Biology. *Nat. Chem. Biol.* **2005**, *1* (2), 74–84. https://doi.org/10.1038/nchembio0705-74.

(8) Goerig, M.; Schulte am Esch, J. Friedrich Wilhelm Adam Sertürner-Dem Entdecker Des Morphins Zum 150. Todestag. *Anasthesiol. Intensivmed. Notfallmedizin Schmerztherapie* **1991**, *26* (8), 492–498. https://doi.org/10.1055/s-2007-1000624.

(9) Li, J. W. H.; Vederas, J. C. Drug Discovery and Natural Products: End of an Era or an Endless Frontier? *Science*. July 10, **2009**, 161–165. https://doi.org/10.1126/science.1168243.

(10) Spandl, R. J.; Bender, A.; Spring, D. R. Diversity-Oriented Synthesis; a Spectrum of Approaches and Results. *Org. Biomol. Chem.* **2008**, *6* (7), 1149. https://doi.org/10.1039/b719372f.

(11) Schreiber, S. L. Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery. *Science (80).* **2000**, *287* (5460), 1964–1969. https://doi.org/10.1126/science.287.5460.1964.

(12) Xiang, X. D.; Sun, X.; Briceño, G.; Lou, Y.; Wang, K. A.; Chang, H.; Wallace-Freedman, W. G.; Chen, S. W.; Schultz, P. G. A Combinatorial Approach to Materials Discovery. *Science (80 ).* **1995**, *268* (5218), 1738–1740. https://doi.org/10.1126/science.268.5218.1738.

(13) Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. Stereoselective Synthesis of over Two Million Compounds Having Structural Features Both Reminiscent of Natural Products and Compatible with Miniaturized Cell-Based Assays. *J. Am. Chem. Soc.* **1998**, *120* (33), 8565–8566. https://doi.org/10.1021/ja981746o.

(14) Galloway, W. R.; Spring, D. R. Is Synthesis the Main Hurdle for the Generation of Diversity in Compound Libraries for Screening? *Expert Opin. Drug Discov.* **2009**, *4* (5), 467–472. https://doi.org/10.1517/17460440902916606.

(15) Schreiber, S. L. Molecular Diversity by Design. *Nature* **2009**, *457* (7226), 153–154. https://doi.org/10.1038/457153a.

(16) Dobson, C. M. Chemical Space and Biology. *Nature*. **2004**, 824–828. https://doi.org/10.1038/nature03192.

(17) Spring, D. R. Diversity-Oriented Synthesis; a Challenge for Synthetic Chemists. *Org. Biomol. Chem.* **2003**, *1* (22), 3867–3870. https://doi.org/10.1039/b310752n.

(18) Fergus, S.; Bender, A.; Spring, D. R. Assessment of Structural Diversity in Combinatorial Synthesis This Review Comes from a Themed Issue on Combinatorial Chemistry Edited by Hans-Jö Rg Roth and Prabhat Arya. *Curr. Opin. Chem. Biol.* **2005**, *9*, 304–309. https://doi.org/10.1016/j.cbpa.2005.03.004.

(19) Cheng, W.-C.; Liu, W.-J.; Hu, K.-H.; Tan, Y.-L.; Lin, Y.-T.; Chen, W.-A.; Lo, L.-C. Rapid Synthesis of a Natural Product-Inspired Uridine Containing Library. **2021**, *19*, 29. https://doi.org/10.1021/acscombsci.0c00011.

(20) Crabtree, G. R.; Schreiber, S. L.; Borchardt, A.; Liberles, S. D.; Biggar, S. R.; You, A. J.; Jackman, R. J.; Whitesides, G. M.; Furka, A.; Sebestyén, F.; Asgedom, M.; Dibó, G.; Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J.; Wood, H. B.; Ganem, B.; Mcgowan, D. A.; Berchtold, G. A. *Stereoselective Synthesis of over Two Million Compounds Having Structural Features Both Reminiscent of Natural Products and Compatible with Miniaturized Cell-Based Assays*; UTC, **1996**; Vol. 21.

(21) Crawley, M. L.; Trost, B. M. *Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective*; John Wiley and Sons, **2012**. https://doi.org/10.1002/9781118309872.

(22) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. Direct Catalytic Asymmetric Aldol Reaction: Synthesis of Either Syn-or Anti-α,β-Dihydroxy Ketones. *Journal of the American Chemical Society*. **2001**, 2466–2467. https://doi.org/10.1021/ja015580u.

(23) Qian, D.; Zhang, J. Yne-Enones Enable Diversity-Oriented Catalytic Cascade Reactions: A

Rapid Assembly of Complexity. *Acc. Chem. Res.* **2020**, *53* (10), 2358–2371. https://doi.org/10.1021/acs.accounts.0c00466.

(24) Liu, W.; Yue, Z.; Wang, Z.; Li, H.; Lei, X. Syntheses of Skeletally Diverse Tetracyclic Isodon Diterpenoid Scaffolds Guided by Dienyne Radical Cyclization Logic. *Org. Lett* **2020**, *22*, 7991–7996. https://doi.org/10.1021/acs.orglett.0c02920.

(25) Nielsen, T. E.; Schreiber, S. L. Towards the Optimal Screening Collection: A Synthesis Strategy. *Angew. Chemie Int. Ed.* **2008**, *47* (1), 48–56. https://doi.org/10.1002/anie.200703073.

(26) Spiegel, D. A.; Schroeder, F. C.; Duvall, J. R.; Schreiber, S. L. An Oligomer-Based Approach to Skeletal Diversity in Small-Molecule Synthesis. *J. Am. Chem. Soc.* **2006**, *128* (46), 14766–14767. https://doi.org/10.1021/ja065724a.

(27) Zhang, J.; Wu, J.; Hong, B.; Ai, W.; Wang, X.; Li, H.; Lei, X. Diversity-Oriented Synthesis of Lycopodium Alkaloids Inspired by the Hidden Functional Group Pairing Pattern. *Nat. Commun.* **2014**, *5*. https://doi.org/10.1038/ncomms5614.

(28) Pospíšil, J. Sulfur-Based Methodologies in the Context of Olefination and Diversity-Oriented Synthetic Methods. Habilitation thesis, Palacký University, **2017.**

(29) Blakemore, P. R.; Sephton, S. M.; Ciganek, E. The Julia-Kocienski Olefination. In *Organic Reactions*; John Wiley & Sons, Inc.: **2018;** Vol. 95, pp 1–261. https://doi.org/10.1002/0471264180.or095.01.

(30) Day, J. J.; Neill, D. L.; Xu, S.; Xian, M. Benzothiazole Sulfinate: A Sulfinic Acid Transfer Reagent under Oxidation-Free Conditions. *Org. Lett.* **2017**, *19* (14), 3819–3822. https://doi.org/10.1021/acs.orglett.7b01693.

(31) Pospíšil, J.; Sato, H. Practical Synthesis of β-Acyl and β-Alkoxycarbonyl Heterocyclic Sulfones. *J. Org. Chem.* **2011**, *76* (7), 2269–2272. https://doi.org/10.1021/jo102326p.

(32) Pospíil, J.; Robiette, R.; Sato, H.; Debrus, K. Practical Synthesis of β-Oxo Benzo[d]Thiazolyl Sulfones: Scope and Limitations. *Org. Biomol. Chem.* **2012**, *10* (6), 1225–1234. https://doi.org/10.1039/c1ob06510f.

(33) Konrádová, D.; Bon, D. J. Y. D.; Pospíšil, J. 1-(Phenylsulfonyl)-3-Oxabicyclo[3.1.0]Hexan-2-One as a Building Block in Organic Synthesis. *J. Org. Chem.* **2018**, *83* (19), 12229–12238. https://doi.org/10.1021/acs.joc.8b01625.

(34) Kováč, O. Benzo[d]thiazol-2-yl sulfonyl-based pluripotent molecules in organic synthesis. Doctoral Thesis, Palacký University, **2020**.

(35) Konrádová, D. Biological applications of secondary plant metabolites of phenyl propanoid origins Doctoral Thesis. Palacký University, **2019.**

(36) Kováč, O.; Zálešák, F.; J.-Y. D. Bon, D.; Roiser, L.; Baar, L. V.; Waser, M.; Pospíšil, J.; Pospíšil, J. Trisubstituted Highly Activated Benzo[ d]Thiazol-2-Yl-Sulfone-Containing Olefins as Building Blocks in Organic Synthesis. *J. Org. Chem.* **2020**, *85* (11), 7192–7206. https://doi.org/10.1021/acs.joc.0c00571.

(37) Tatsuta, K.; Yasuda, S.; Kurihara, K. I.; Tanabe, K.; Shinei, R.; Okonogi, T. Total Synthesis of Progesterone Receptor Ligands, (-)-PF1092A, B and C. *Tetrahedron Lett.* **1997**, *38* (8), 1439–1442. https://doi.org/10.1016/S0040-4039(97)00042-7.

(38) Gueyrard, D.; Haddoub, R.; Salem, A.; Said Bacar, N.; Goekjian, P. G. Synthesis of Methylene Exoglycals Using a Modified Julia Olefination. **2004**. https://doi.org/10.1055/s-2005-862364.

(39) Habib, S.; Larnaud, F.; Pfund, E.; Lequeux, T.; Fenet, B.; Goekjian, P. G.; Gueyrard, D. Synthesis of Fluorinated *Exo* -Glycals through Modified Julia Olefination. *European J. Org. Chem.* **2013**, *2013* (10), 1872–1875. https://doi.org/10.1002/ejoc.201201719.

(40) Dake, G. R.; Fenster, E. E.; Patrick, B. O. A Synthetic Approach to the Fusicoccane A-B Ring Fragment Based on a Pauson-Khand Cycloaddition/Norrish Type 1 Fragmentation. *J. Org. Chem.* **2008**, *73* (17), 6711–6715. https://doi.org/10.1021/jo800933f.

(41) Liu, P.; Wang, L.; Dubois, B. G.; Colandrea, V. J.; Liu, R.; Cai, J.; Du, X.; Quan, W.; Morris, W.; Bai, J.; Bishwokarma, B.; Cheng, M.; Piesvaux, J.; Ray, K.; Alpert, C.; Chiu, C. S.; Zielstorff, M.; Metzger, J. M.; Yang, L.; Leung, D.; Alleyne, C.; Vincent, S. H.; Pucci, V.; Li, X.; Crespo, A.; Stickens, D.; Hale, J. J.; Ujjainwalla, F.; Sinz, C. J. Discovery of Orally Bioavailable and Liver-Targeted Hypoxia-Inducible Factor Prolyl Hydroxylase (HIF-PHD) Inhibitors for the Treatment of Anemia. *ACS Med. Chem. Lett.* **2018**, *9* (12), 1193–1198. https://doi.org/10.1021/acsmedchemlett.8b00274.

(42) Anand, R. C.; Selvapalam, N. A Convenient and Mild Procedure for Th Preparation of Hydroxyesters from Lactones and Hydroxyacids. *Synth. Commun.* **1994**, *24* (19), 2743–2747. https://doi.org/10.1080/00397919408010590.

(43) Allegretti, P. A.; Ferreira, E. M. Generation of α,β-Unsaturated Platinum Carbenes from Homopropargylic Alcohols: Rearrangements to Polysubstituted Furans. *Org. Lett.* **2011**, *13* (21), 5924–5927. https://doi.org/10.1021/ol202649j.

(44) Gromek, S. M.; deMayo, J. A.; Maxwell, A. T.; West, A. M.; Pavlik, C. M.; Zhao, Z.; Li, J.; Wiemer, A. J.; Zweifach, A.; Balunas, M. J. Synthesis and Biological Evaluation of Santacruzamate A Analogues for Anti-Proliferative and Immunomodulatory Activity. *Bioorganic Med. Chem.* **2016**, *24* (21), 5183–5196. https://doi.org/10.1016/j.bmc.2016.08.040.

(45) Corey, E. J.; Suggs, J. W. Pyridinium Chlorochromate. An Efficient Reagent for Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds. *Tetrahedron Lett.* **1975**, *16* (31), 2647–2650. https://doi.org/10.1016/S0040-4039(00)75204-X.

(46) Helmboldt, H.; Aho, J. E.; Pinko, P. M. Synthetic Studies toward Pectenotoxin 2. Part II. Synthesis of the CDE and CDEF Ring Systems. *Org. Lett.* **2008**, *10* (19), 4183–4185. https://doi.org/10.1021/ol801585j.

(47) Jeon, J.; Ryu, H.; Lee, C.; Cho, D.; Baik, M. H.; Hong, S. Site-Selective 1,1-Difunctionalization of Unactivated Alkenes Enabled by Cationic Palladium Catalysis. *J. Am. Chem. Soc.* **2019**, *141* (25), 10048–10059. https://doi.org/10.1021/jacs.9b04142.

(48) Kier, M. J.; Leon, R. M.; O'Rourke, N. F.; Rheingold, A. L.; Micalizio, G. C. Synthesis of Highly Oxygenated Carbocycles by Stereoselective Coupling of Alkynes to 1,3- and 1,4-Dicarbonyl Systems. *J. Am. Chem. Soc.* **2017**, *139* (36), 12374–12377. https://doi.org/10.1021/jacs.7b06286.

(49) Canonne, P.; Akssira, M. Synthèses Stéréosélectives Des γ-Lactones Bicycliques Condensées. *Tetrahedron* **1985**, *41* (18), 3695–3704. https://doi.org/10.1016/S0040-4020(01)91390-0.

(50) Bon, D. J. Y. D.; Kováč, O.; Ferugová, V.; Zálešák, F.; Pospíšil, J. One and Two-Carbon Homologation of Primary and Secondary Alcohols to Corresponding Carboxylic Esters Using β-Carbonyl BT Sulfones as a Common Intermediate. *J. Org. Chem.* **2018**, *83* (9), 4990–5001. https://doi.org/10.1021/acs.joc.8b00112.

(51) Fulmer, G. R.; M Miller, A. J.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I.; Beckman, M. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics*. **2010,** *29* (9) 2176-2179. https://doi.org/10.1021/om100106e.

# 6 Experimental part

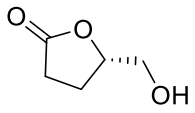
All reactions were performed in round-bottom flasks fitted with rubber septa using the standard laboratory techniques. Reactions sensitive to air and/or moisture were performed under a positive pressure of argon. Reactions run at elevated temperatures were carried out using the metal thermal block and indicated temperatures refers to thermal block temperature. Reactions run at low temperatures were carried out in dry ice-acetone cooling bath, indicated temperatures refers to cooling bath temperature.

All starting materials were purchased from commercial suppliers and used without further purification. Progress of reactions was monitored by thin-layer chromatography (TLC) - aluminum plates pre-coated with silica gel (silica $^{gel}$ 60 $F_{254}$). Visualization of TLC chromatograph was done by a) basic solution of $KMnO_4$, or in case of UV active compounds b) UV lamp with wavelength λ= 256 nm. Column chromatography was performed on silica gel 60 (40-63 µm) from Merck.

$^{1}H$ NMR, and $^{13}C$ NMR spectra were measured on Jeol ECA400II (400 MHz, and 101 MHz, respectively) or Jeol 500 ECA (500 and 126 MHz, respectively) in $CDCl_3$. Chemical shifts are reported in ppm and their calibration was performed (a) in case of 1H NMR experiments on residual peak of non-deuterated solvent δ (CHCl3) = 7.26 ppm and (b) in case of 13C NMR experiments on the middle peak of the 13C signal in deuterated solvent δ (CDCl3) = 77.2 ppm[51].

HRMS analyses were performed on Thermo Exactive Plus high-resolution mass spectrometer with electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCl) and Orbitrap analyzer operating at positive or negative full scan mode in the range of 60-800 m/z.

## 6.1 (*S*)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one, lactone **2-10**[40]



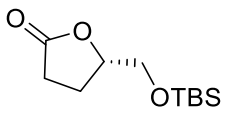

To 1 L round-bottom two necked flask was placed L-glutamic acid (25.0 g, 0.170 mmol, 1 equiv) and it was suspended in $H_2O$ (300 ml) and suspension was cooled to 0°C. A solution of 2M aq. hydrochloric acid (102 mL, 0.204 mol, 1.20 equiv) was added in one portion and the whole mixture become clear. A solution of sodium nitrite (14.1 g, 0.204 mol, 1.20 equiv) in $H_2O$ (300 mL) was added dropwise at 0°C over a period of 1 h (internal temperature should not

overcome 4°C, and the reaction mixture was allowed to warm to RT and stirred for 16 hours. The reaction mixture was concentrated *in vacuo* to a white paste, which was then extracted by boiling ethyl acetate (300 mL). Anhydrous magnesium sulfate (15 g) was added to cold EtOAC layer and the reaction mixture was stirred for additional 1 h, filtered, and concentrated under reduced pressure to yield a clear yellow oil.

Borane-dimethyl sulfide complex (13.7 mL, 0.144 mol, 0.85 equiv) was added dropwise to a solution of the crude oil in THF (250 mL) at 0 °C over a period of 1h. The resulting mixture was allowed to warm to RT and stirred for additional 3h. Methanol (100 mL) was added dropwise, and the resulting solvent mixture was evaporated under reduced pressure to yield a yellow oil. The residue was purified by flash column chromatography ($SiO_2$, EtOAc/petroleum ether = 1:3), and the concentration of relevant fractions yielded the desired product as a yellow oil (12.1 g, 60 %)

$^1$H NMR (400 MHz, Chloroform-*d*) δ (ppm): 4.72 – 4.54 (m, 1H), 3.87 (dd, *J* = 12.5, 2.9 Hz, 1H), 3.63 (dd, *J* = 12.5, 4.6 Hz, 1H), 2.71 – 2.44 (m, 2H), 2.32 – 2.03 (m, 2H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ (ppm): 178.0, 81.0, 64.2, 28.8, 23.2; HRMS (APCl) m/z: [M-H]- calcd. for $C_5H_7O_3$, 115,0401; found 115,0384

## 6.2 (*S*)-5-(((tert-butyldimethylsilyl)oxy)methyl)dihydrofuran-2(3H)-one, Lactone 2-1[40]

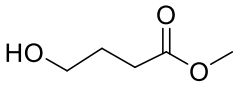



Triethylamine (12.8 mL, 0.156 mol, 1.50 equiv) was added to a solution of (*S*)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (12.1 g, 0.104 mol, 1 equiv), *tert*-butyldimethylsilyl chloride (17.3g, 0.115 mol, 1.1 equiv) and 4-dimethylaminopyridine (1.3 g, 10.4 mmol, 0.10 equiv) in methylene chloride (600 ml) at 0 °C and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was washed with water (2 x 150 mL) and a saturated aqueous solution of sodium chloride (150 mL), dried over magnesium sulfate and concentrated *in vacuo* to yield a clear colorless oil. The crude oil was purified by flash column chromatography ($SiO_2$, EtOAc/hexane = 1:7) and the concentration of relevant fractions yielded the desired product as colorless liquid (30.5 g, 93 %)

$^1$H NMR (400 MHz, Chloroform-*d*) δ (ppm): 4.57 (ddt, *J* = 8.2, 5.1, 3.2 Hz, 1H), 3.85 (dd, *J* = 11.3, 3.3 Hz, 1H), 3.68 (dd, *J* = 11.3, 3.1 Hz, 1H), 2.67 – 2.38 (m, 2H), 2.35 – 2.08 (m, 2H), 0.88

(s, 9H), 0.06 (s, 4H), 0.06 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ (ppm): 177.7, 80.2, 65.1, 28.7, 25.9, 25.7, 23.7, 18.4, -3.5, -5.3, -5.4; HRMS (APCl) m/z: [M+H]+ calcd. for $C_{11}H_{22}O_3Si$, 231.1411; found 231.1401

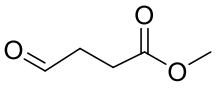
## 6.3 Methyl 4-hydroxybutanoate, 2-11




A solution of γ-butyrolactone (7 g, 81.3 mmol, 1 equiv) and triethylamine (22.6, 163 mmol, 2 equiv) was stirred in methanol (800 mL) and water (8 mL) mixture. The whole mixture was heated to 64°C and stirred for 16 h. The reaction mixture was then cooled to RT and the residue was concentrated *in vacuo* to yield a clear yellowish oil (9.5 g, 99 %).

$^1$H NMR (400 MHz, Chloroform-*d*) δ (ppm): 3.58 (s, 3H), 3.54 (t, *J* = 6.2 Hz, 2H), 2.33 (p, *J* = 7.3 Hz, 2H), 1.76 (tt, *J* = 7.3, 6.2 Hz, 2H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ (ppm): 174.5, 61.5, 51.6, 30.6, 2.6; HRMS (APCl) m/z: [M-$H_2$0]+ calcd. for $C_5H_{11}O_3$, 101,0597; found 101,0597

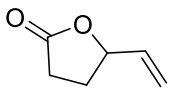
## 6.4 Methyl 4-oxobutanoate, 2-5[45]




Pyridinium chlorochromate (5.47 g , 25.4 mmol, 1.5 equiv) was added to a solution of methyl 4-hydroxybutanoate (2 g, 16.9 mmol, 1 equiv) and sodium acetate (0.34 g, 4.23 mmol, 0.25 equiv) in dichloromethane (150 mL) at 0 °C. The resulting slurry was stirred for 2 hours at 0°C, and then at RT for 16 h. The reaction mixture was diluted with tetrahydrofuran (300 mL), and stirred for additional 15 minutes, filtered over a pad of Celite®, and the filtrate was concentrated under reduced pressure to yield a brow oil. The residue was purified by flash column chromatography ($SiO_2$, EtOAc/petroleum ether = 1:5) and the concentration of relevant fractions yielded the desired product as a clear liquid (0.89 g, 45 %)

$^1$H NMR (400 MHz, Chloroform-*d*) δ (ppm): 9.80 (s, 1H), 3.68 (s, 3H), 2.78 (t, *J* = 6.5 Hz, 2H), 2.62 (t, *J* = 6.8 Hz, 2H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ (ppm): 200.0, 172.8, 52.0, 38.6, 26.4

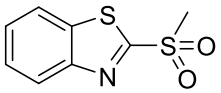
## 6.5 5-vinyldihydrofuran-2(3H)-one, **2-4**



Vinyl magnesium bromide in tetrahydrofuran (6.2 mL, 6.2 mmol, 1.2 equiv; 1.0M solution in THF) was added dropwise to a solution of methyl 4-oxobutanoate (600 mg, 5.2 mmol, 1 equiv) in THF (50 mL) at -78°C over a period of 30 minutes. Next, the reaction mixture was warmed to -40°C over a period of 2 hours, before it was quenched with addition of aq. sat. $NH_4Cl$ (20 mL). The whole mixture was extracted with DCM (3 x 30 mL), and combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography ($SiO_2$, EtOAc/petroleum ether = 1:8) and the concentration of relevant fractions yielded the desired product as clear liquid (0.23 g, 40 %).

$^1$H NMR (400 MHz, Chloroform-*d*) δ (ppm): 5.88 (ddd, *J* = 17.1, 10.5, 6.0 Hz, 1H), 5.36 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.25 (dt, *J* = 10.5, 1.2 Hz, 1H), 5.05 – 4.88 (m, 1H), 2.58 – 2.50 (m, 2H), 2.49 – 2.30 (m, 1H), 2.11 – 1.91 (m, 1H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ (ppm): 177.0, 135.7, 117.6, 80.6, 28.4, 28.4;

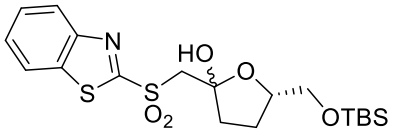
## 6.6 2-(methylsulfonyl)benzo[d]thiazole, **2-3**[32]



A solution of $H_2O_2$ (21.4 mL, 221 mmol, 4.0 equiv; 50% aqueous solution) was added dropwise to a solution of 2-(methylthio)benzo[d]thiazole (5.0 g, 55.2 mmol, 1.0 equiv) and $Na_2WO_4 \cdot 2H_2O$ (0,9 g, 5.51 mmol, 0.1 equiv) in EtOH (92 mL) at 0°C was added. The resulting mixture was stirred at 0°C for 30 min, before the cooling bath was removed and the stirring continued at rt for further 16h. Saturated aqueous $Na_2S_2O_3$ (50 mL) was added and resulting layers were separated. The aqueous layer was extracted with EtOAc (3x100 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The desired product as obtained as a yellowish solid (5,8 g, 99 %) was used in the next step without any further purification.

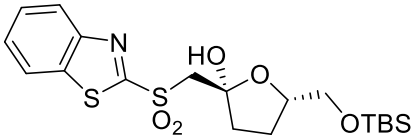
$^{1}$H NMR (400 MHz, Chloroform-*d*) δ (ppm): 8.21 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.02 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.69 – 7.54 (m, 2H), 3.42 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ (ppm): 166.6, 152.6, 136.8, 28.2, 127,9. 125.5, 122.5, 42.6; HRMS (ESI) *m/z*: [M+H]+ calcd. for $C_8H_8NO_2S_2$, 213.9991; found 213.9991.

## 6.7 (5*S*)-2-((benzo[d]thiazol-2-ylsulfonyl)methyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-ol, PM-3a




A solution of lithium bis(trimethylsilyl)amide in THF (1.9 mL, 1.91 mmol, 2.2 equiv; 1.0 M sol in THF) was added to a solution of 2-(methylthio)benzo[d]thiazole (204 mg, 0.96 mmol, 1.1 equiv) in dry THF (10 mL) at -78°C. Resulting mixture was stirred for 1 minute prior a cold solution of (*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)dihydrofuran-2(3*H*)-one (200 mg, 0.86 mmol, 1 equiv) in dry THF (1 mL) was added. Reaction mixture was stirred at -78°C for 2 hours, before aqueous solution of $NH_4Cl$ (5 mL) was added and the whole mixture was extracted with DCM (3 x 10 mL). Combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography ($SiO_2$, hexane:EtOAc = 20:1->12:1) and the concentration of relevant fractions yielded the desired product as yellowish oil (30 mg, 8 %)

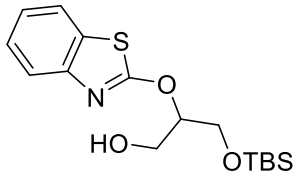
Product *trans*-**PM-3a**
(2S,5S)-2-((benzo[d]thiazol-2-ylsulfonyl)methyl)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-ol




1H NMR (400 MHz, Chloroform-d), δ (ppm) 8.17 (ddd, J = 8.2, 1.4, 0.7 Hz, 1H), 7.97 (ddd, J = 7.9, 1.4, 0.7 Hz, 1H), 7.50 – 7.62 (m, 2H), 5.90 (t, J = 1.7 Hz, 1H), 4.65 (ddt, J = 7.7, 6.0, 3.5 Hz, 1H), 3.82 (dd, J = 11.5, 3.3 Hz, 1H), 3.67 (dd, J = 11.5, 3.6 Hz, 1H), 3.40 – 3.53 (m, 1H), 3.31 (dddd, J = 18.5, 9.8, 6.8, 1.7 Hz, 1H), 2.16 – 2.25 (m, 1H), 2.05 – 2.15 (m, 1H), 1.13 – 1.37 (m, 2H), 0.80

(s, 9H), 0.03 (s, 3H), -0.02 (s, 3H); 13C NMR (101 MHz, Chloroform-d) δ (ppm) = 179.4, 153.1, 136.9, 127.6, 127.4, 125.5, 122.4, 96.7, 86.4, 64.6, 30.9, 29.9, 25.9, 24.9, 18.4, 5.3,

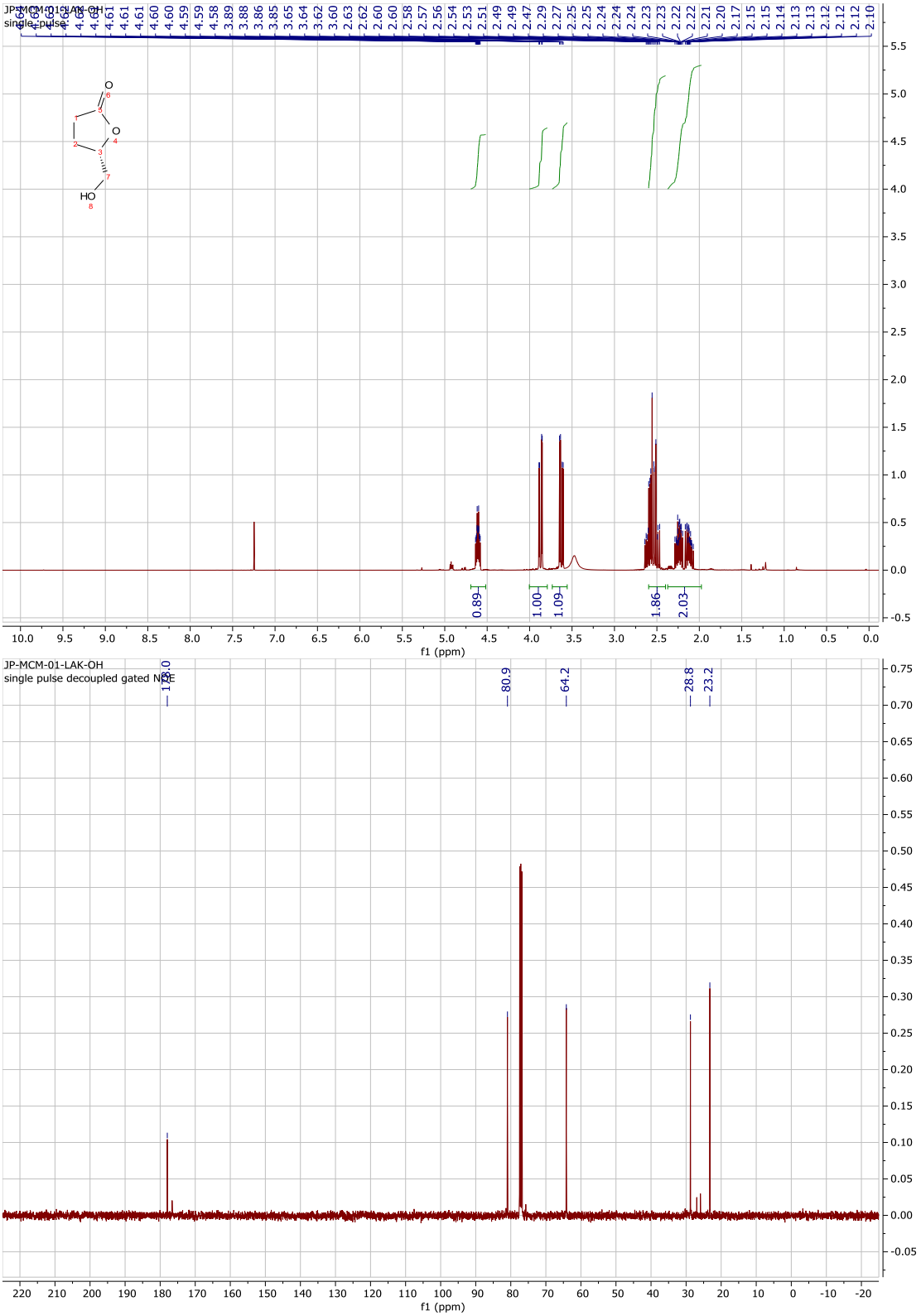
Side product
2-(benzo[d]thiazol-2-yloxy)-3-((tert-butyldimethylsilyl)oxy)propan-1-ol, **2-20**



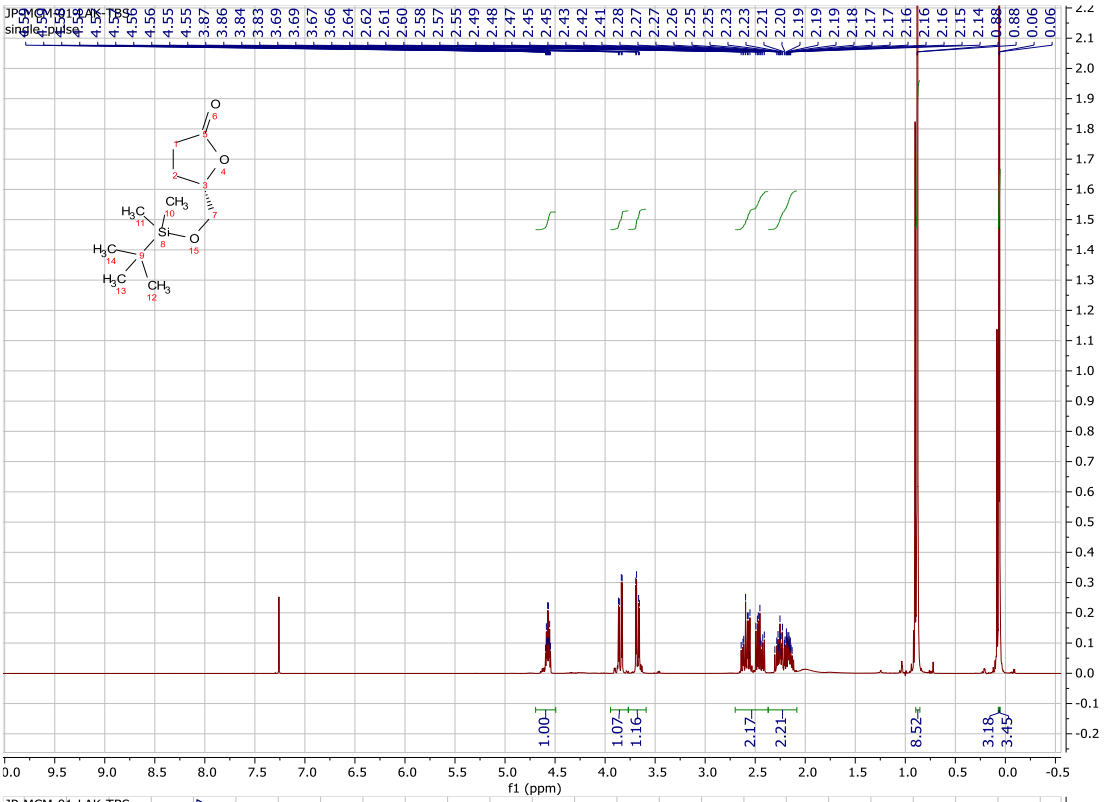

$^{1}$H NMR (400 MHz, Chloroform-*d*) δ (ppm): 8.00 (ddd, *J* = 8.2, 1.3, 0.7 Hz, 1H), 7.92 (ddd, *J* = 8.0, 1.4, 0.7 Hz, 1H), 7.49 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.41 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 5.02 (ddt, *J* = 7.8, 5.2, 2.5 Hz, 1H), 4.12 (dd, *J* = 11.6, 2.6 Hz, 1H), 3.81 (dd, *J* = 11.7, 2.5 Hz, 1H), 3.32 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.64 (dd, *J* = 13.8, 5.3 Hz, 1H), 0.95 (s, 9H), 0.17 (s, 6H);

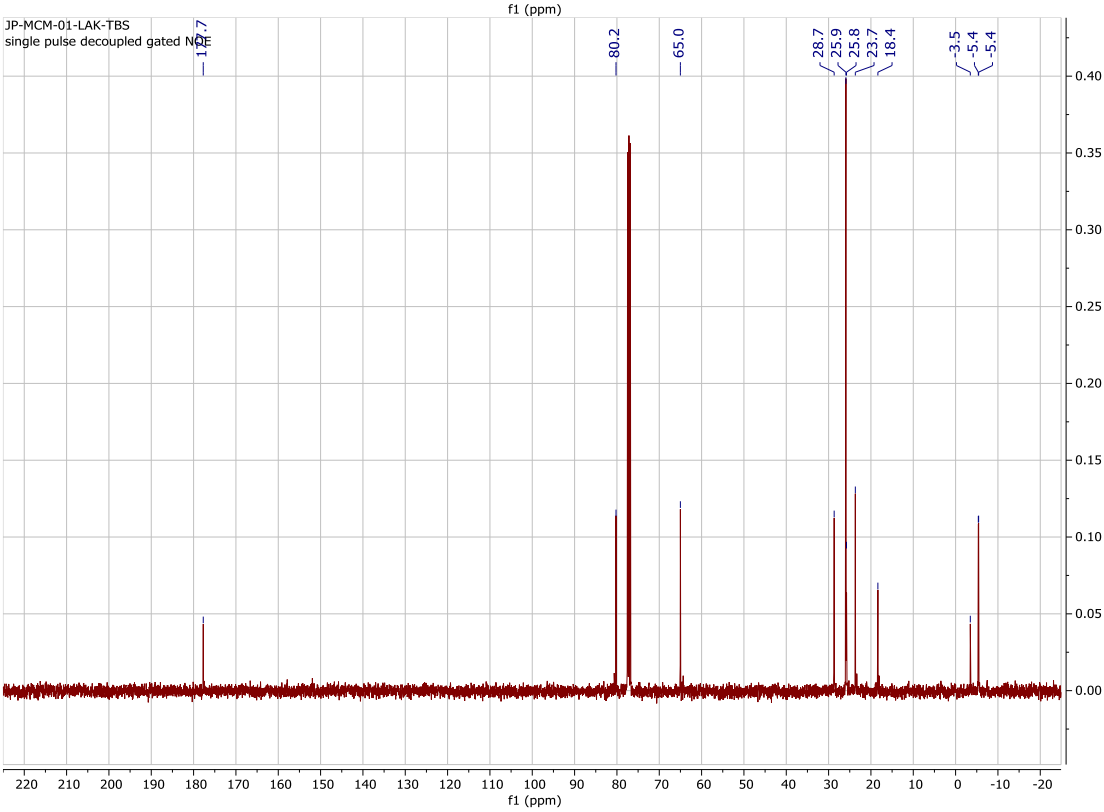
# 7 Appendix

**2-10,** (S)-5-(hydroxymethyl)dihydrofuran-2(3H)-one, $^{1}H$ and $^{13}C$ NMR spectrum

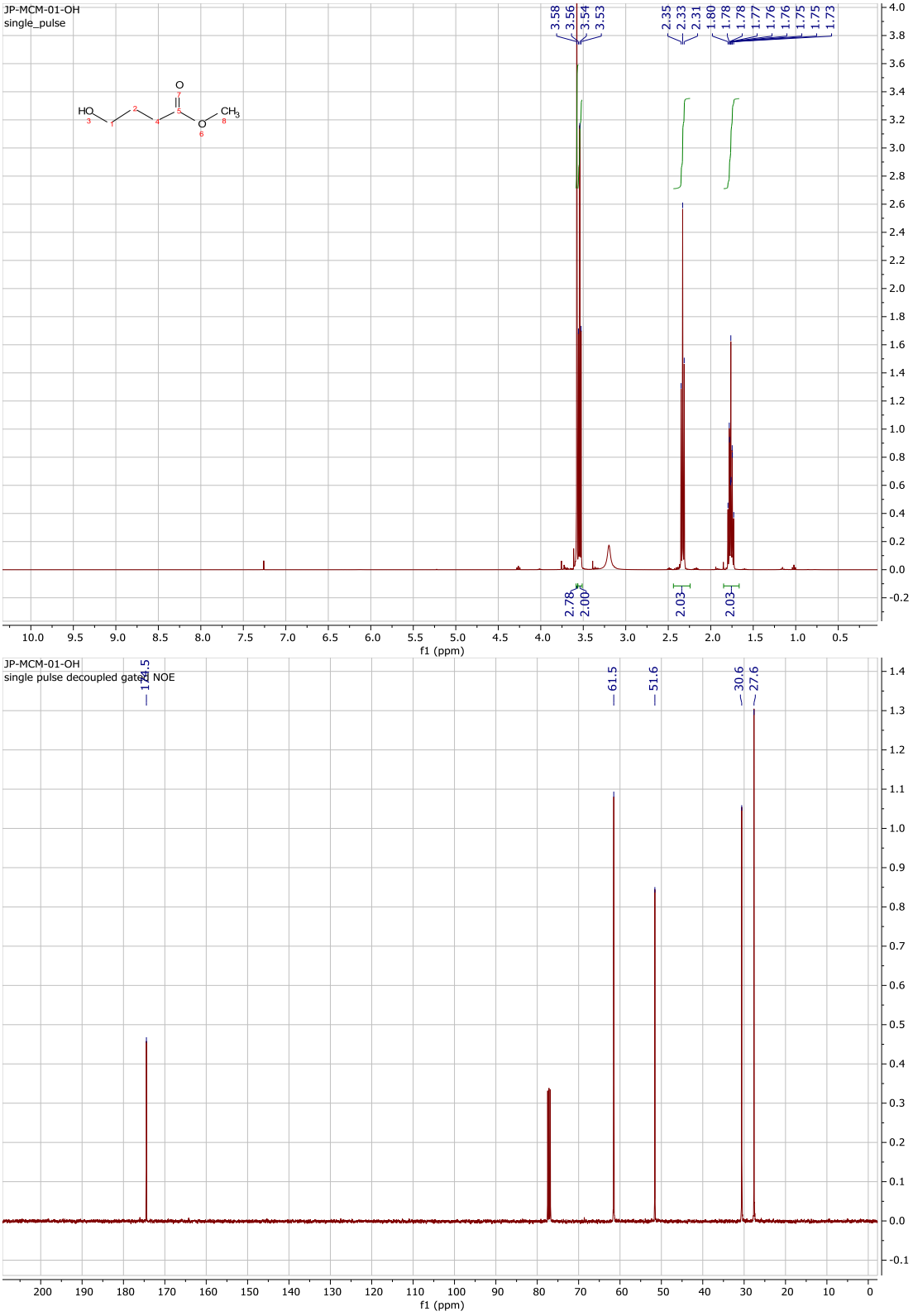


**2-1,** (S)-5-(((tert-butyldimethylsilyl)oxy)methyl)dihydrofuran-2(3H)-one, $^{1}H$ and $^{13}C$ NMR spectrum

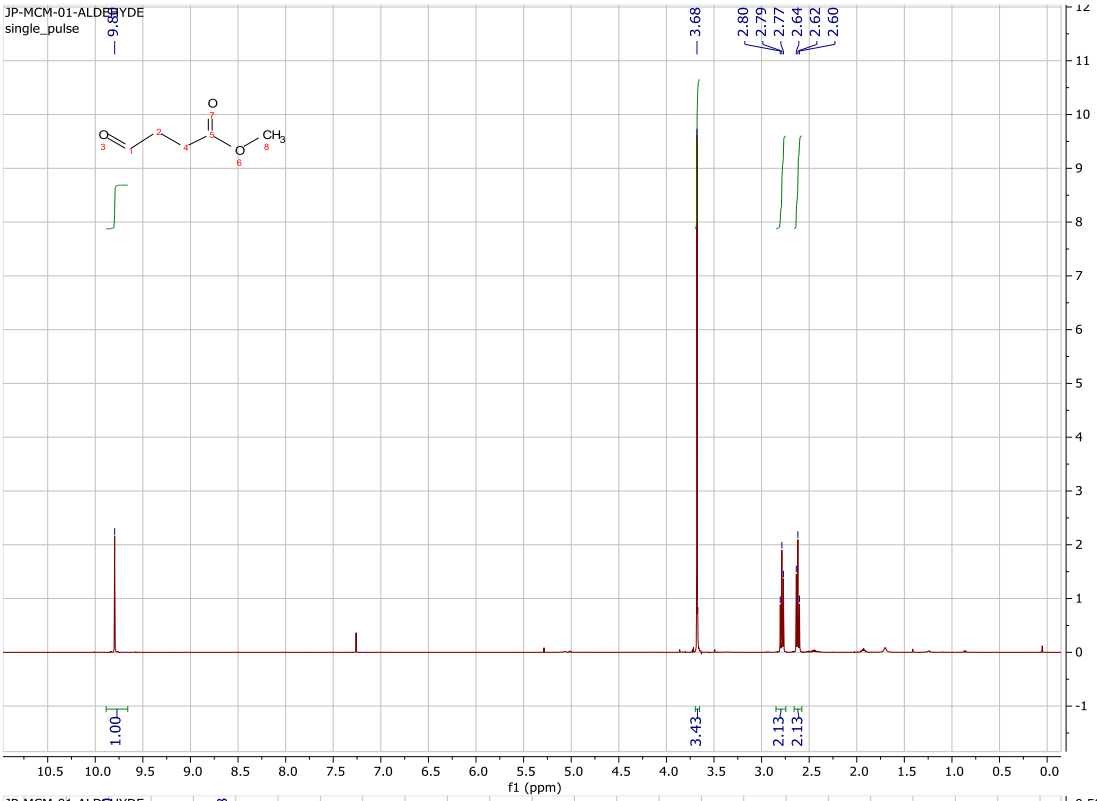


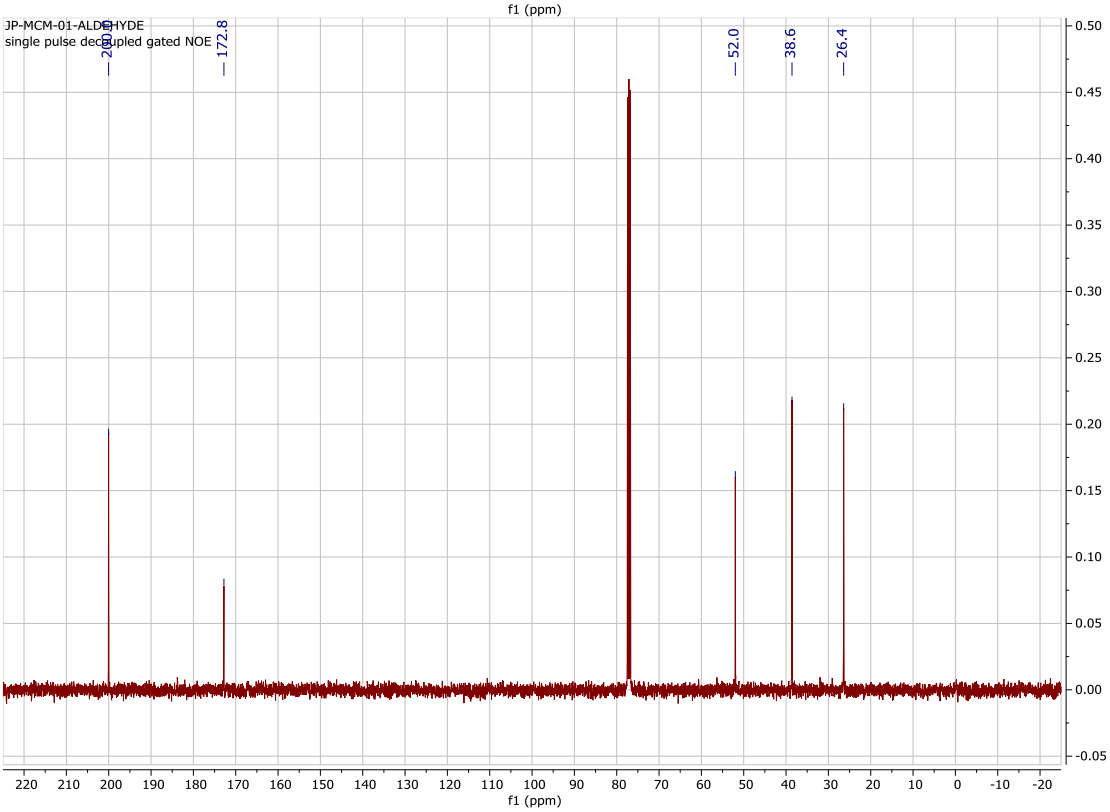



**2-11,** Methyl 4-hydroxybutanoate, $^{1}H$ and $^{13}C$ NMR spectrum

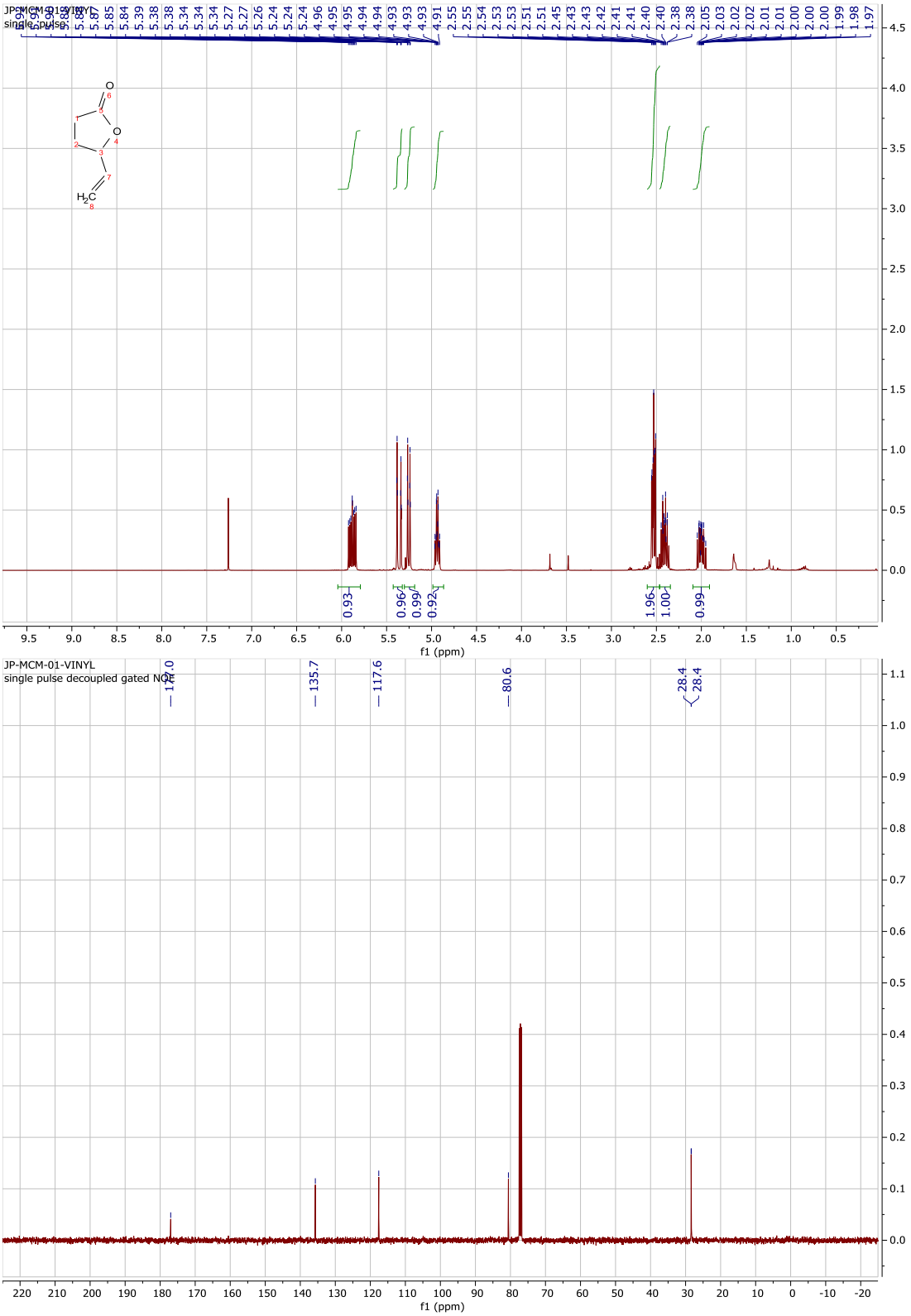


**2-5,** Methyl 4-oxobutanoate, $^{1}H$ and $^{13}C$ NMR spectrum

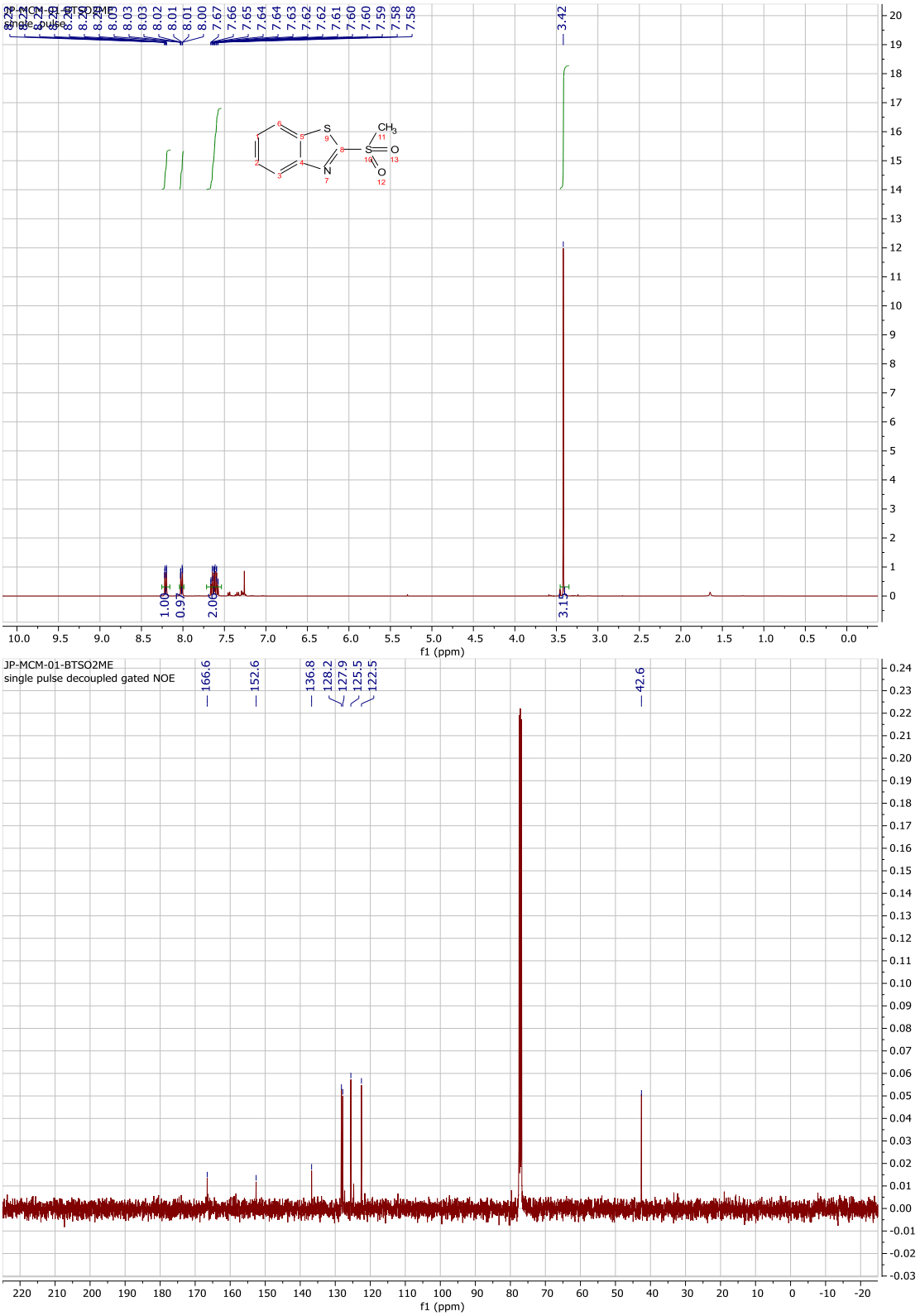


**2-4,** 5-vinyldihydrofuran-2(3H)-one, $^{1}H$ and $^{13}C$ NMR spectrum

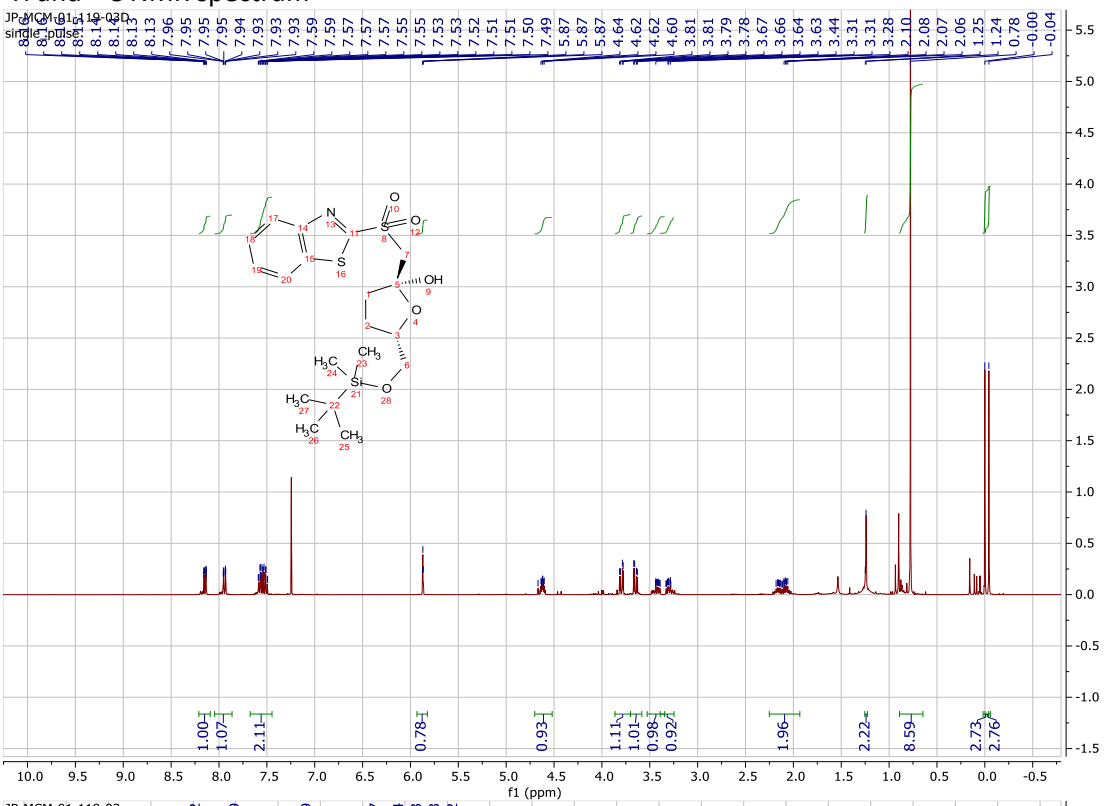


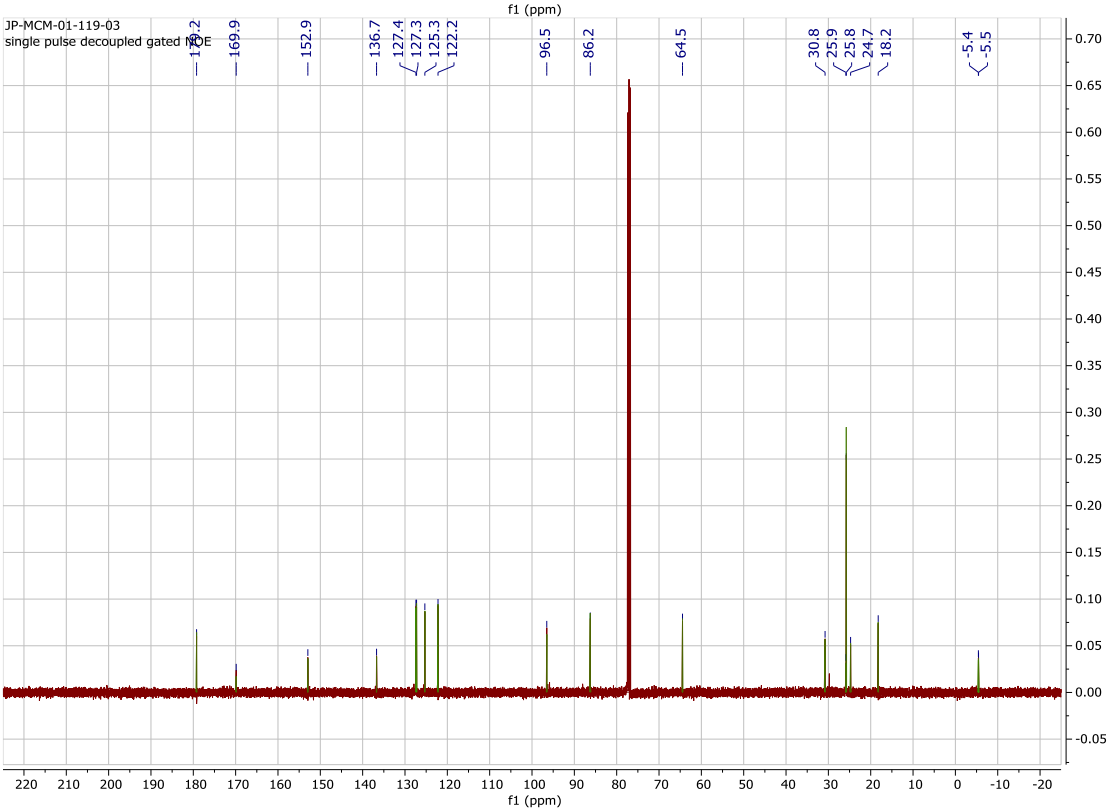
**2-3,** 2-(methylsulfonyl)benzo[d]thiazole, $^{1}H$ and $^{13}C$ NMR spectrum



*trans*-**PM-3a** , (5S)-2-((benzo[d]thiazol-2-ylsulfonyl)methyl)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-ol

$^{1}H$ and $^{13}C$ NMR spectrum



**2-20,** 2-(benzo[d]thiazol-2-yloxy)-3-((tert-butyldimethylsilyl)oxy)propan-1-ol, $^{1}$H NMR spectrum