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A New Synthetic Approach to DMI

Supervisor

Prof. Fabio Aricò

Assistant Supervisor

Dr. Chaimaa Sadraoui

Graduand

Ilenia Pessotto

867709

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SUMMARY

SUMMARY	2
LIST OF ABBREVIATIONS	4
1. INTRODUCTION	1
1.1 From Petro refinery to Biorefinery	1
1.1.1 A brief history of petrol and how it changed the economy.	1
1.1.2 International agreements and the future of climate change.	3
1.2 Biorefinery	4
1.2.1 Differences between petro refinery and biorefinery.	5
1.2.2 The Green Chemistry and the 12 Principle of Green Chemistry	7
1.2.3 Bio-based platform chemicals.....	8
1.3 Dimethylcarbonate, an ambident electrophile	10
1.3.1 Industrial Synthesis of DMC	12
1.4 From D-sorbitol to Isosorbide	14
1.4.1 Synthetic Routes to Isosorbide	15
1.4.2 Isosorbide as bio-based platform chemical.....	17
1.5 From Isosorbide to DMI.....	19
1.5.1 Synthesis of DMI from isosorbide	20
1.5.2 DMI from isosorbide employing nitrogen organo catalysts	22
1.5.3 Possible Reaction Pathways to DMI	23
1.5.4 One-Pot Synthesis of DMI from D-sorbitol.....	25
2. SCOPE	26
3. RESULTS AND DISCUSSION	27
3.1 Methylation of DMI promoted by a heterogeneous catalyst.....	27
3.1.1 Distinctive traits of Zeolites and Hydrotalcites	27
3.1.2 Synthesis of DMI: catalyst screening.....	30
3.1.3 Optimization synthesis of DMI: catalyst screening: amount of catalyst.....	33
3.1.4 Optimization synthesis of DMI: catalyst screening: reaction time	34
3.1.5 Optimization synthesis of DMI: catalyst screening: concentration	35
3.1.6 Optimization synthesis of DMI: catalyst screening: scale-up	36
3.1.7 Synthesis of dimethyl isoidide (DMli) and dimethyl isomannide (DMIm).....	40
3.2 Microwave Synthesis of DMI	42
3.2.1 Versatility and applications of Microwaves	42
3.1.2: DMI synthesis in microwave	44
4. CONCLUSIONS	50
5. MATERIALS AND METHODS	52
5.1 Materials and instruments	52
5.2 General Procedure.....	52
5.2.1 Procedure synthesis of DMI in autoclave: evaluation of catalys (Table 3.1 # 6)	52
5.2.2 Procedure synthesis of DMI in autoclave: evaluation of quantity of catalyst (Table 3.3 # 2)	53
5.2.3 Procedure synthesis of DMI in autoclave: evaluation time of reaction (Table 3.4 # 4)	53
5.2.4 Procedure synthesis of DMI in autoclave: evaluation concentration of reaction (Table 3.5 # 2)	53
5.2.5 Procedure synthesis of DMI in autoclave: scale-up reactions (Table 3.6)	54
5.2.6 Procedure synthesis of DMli in autoclave.....	54
5.2.7 Procedure synthesis of DMIm in autoclave.....	54
5.2.7 Procedure synthesis of DMI in microwave.....	55

A typical microwave reaction was performed as follows: 0.2 g of isosorbide dissolved in 7.0 mL of DMC in the presence of 0.1 mL of NMPy is placed in the quartz vessel to react. The magnetic stirring rod and black disc are then added to the quartz vessel to enable the reaction to better absorb microwaves. The reaction is carried out at 200 °C, with the timing and rates still to be defined.....55

5.3 Characterizations	55
6. APPENDIX.....	57
6.1 Mass Spectra and NMR spectra	57
6.1.1 Characterization of isosorbide	58
6.1.2 Characterization of monomethyl isosorbide (MMI-1)	59
6.1.3 Characterization of dimethyl isosorbide (DMI)	60
6.1.4 Characterization of monomethyl isosorbide (MMI-2)	62
6.1.5 Characterization of monomethoxycarbonyl isosorbide (MCI-1)	63
6.1.6 Characterization of monomethoxycarbonyl isosorbide (MCI-2)	65
6.1.7 Characterization of monocarboxy monomethyl isosorbide (MCMI-1)	66
6.1.8 Characterization of monocarboxy monomethyl isosorbide (MCMI-2)	68
6.1.9 Characterization of di-methoxycarbonyl isosorbide (DCI).....	69
6.1.10 Characterization of dimethyl isoidide (DMli)	71
6.1.11 Characterization of dimethyl isomannide (DMIm)	72
7. BIBLIOGRAPHY	74

LIST OF ABBREVIATIONS

BBPC	Bio-based Platform Chemicals
CO₂	Carbon dioxide
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEC	Diethyl carbonate
DEI	Diethyl isosorbide
DMAP	4-(Dimethylamino)pyridine
DMC	Dimethyl carbonate
DMF	Dimethylformamide
DMI	Dimethyl isosorbide
DMSO	Dimethyl sulfoxide
EC	Ethylene carbonate
EG	Ethylene glycol
EO	Ethylene oxide
GHGs	Greenhouse gases
HMF	5-hydroxymethylfurfural
HSAB	Hard-Soft, Acid-Base Theory
MCI 1-2	Monocarboxymethyl isosorbide
MCFI 1-2	Monocarboxymethyl methyl isosorbide
MMI 1-2	Monomethyl isosorbide
NaOMe	Sodium methoxide
NMPy	N-methyl pyrrolidine
NuH	Nucleophile
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
t-BuOK	Potassium tert-butoxide
TEA	Triethylamine

1. INTRODUCTION

1.1 From Petro refinery to Biorefinery

1.1.1 A brief history of petrol and how it changed the economy.

In the last 150 years, from the Second Industrial Revolution to our days, the increasing use of fossil fuels has allowed the development of numerous sectors, such as energy, materials and chemicals, leading to an exponential social and economic advancement. The petrochemical industry, in the early 1900s, experienced a fast growth driven by scientific research. This research not only led to the development of new chemicals and energy processes, but also enabled the discovery of new materials i.e., synthetic plastics such as polypropylene, polyesters, and elastomers that has been employed for our clothing, building materials, and furnishings commonly used in everyday life (Figure 1.1).^{1,2}

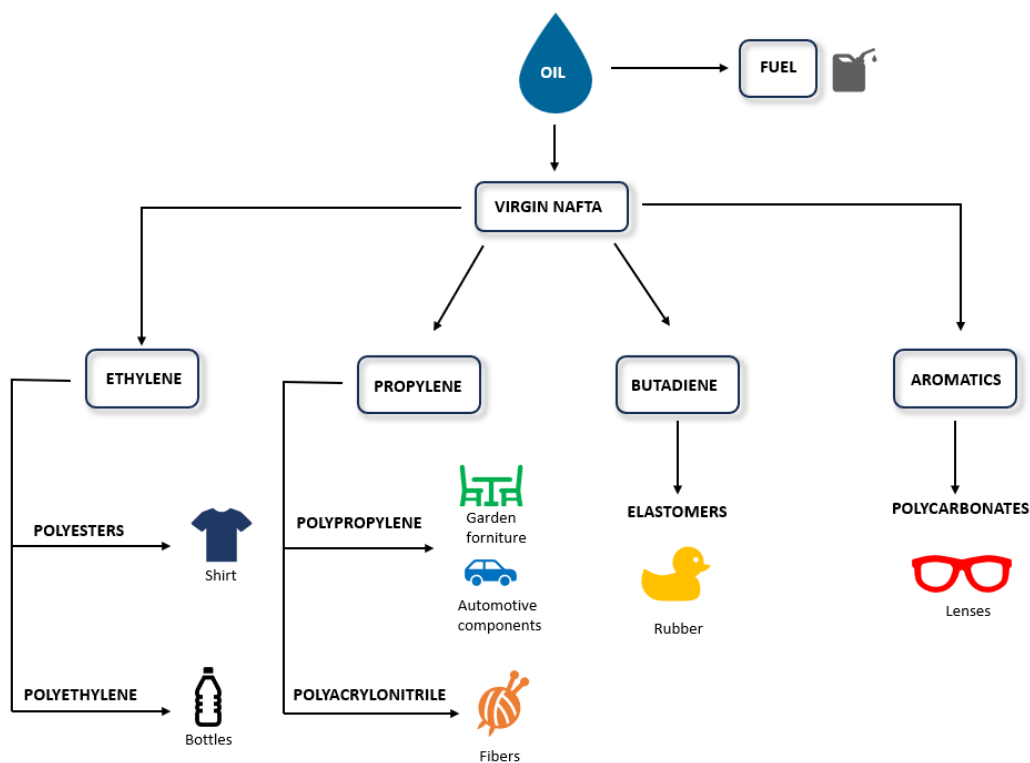
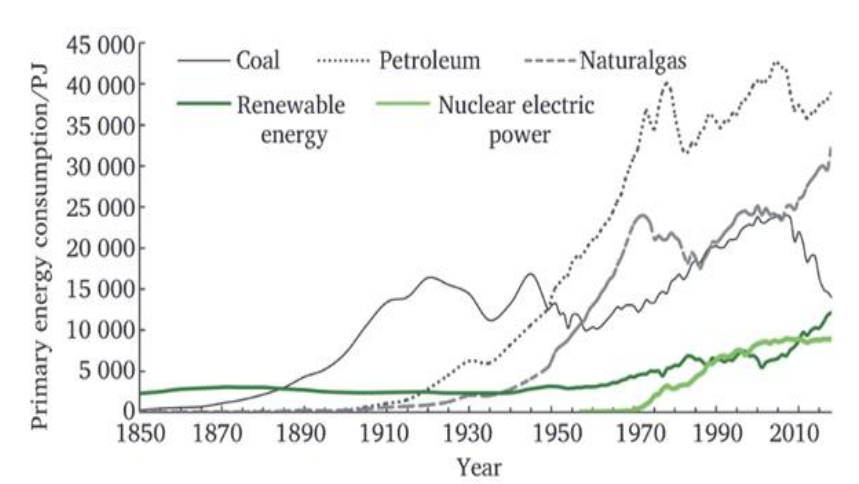


Figure 1.1 The petroleum tree.

Especially in the Third Industrial Revolution in the US - from the 1940s to the 2000s - the continuous growth of energy demand and the development of new technologies promoted a rapid evolution in the industrial world. This transformation promotes technology-intensive in transportation, iron and steel manufacturing, and the chemicals production.

Graphic 1.1 depicts the demand for raw materials that clearly increased drastically in the second part of the 20th century, especially for natural gas and petroleum, which became the main energy source in

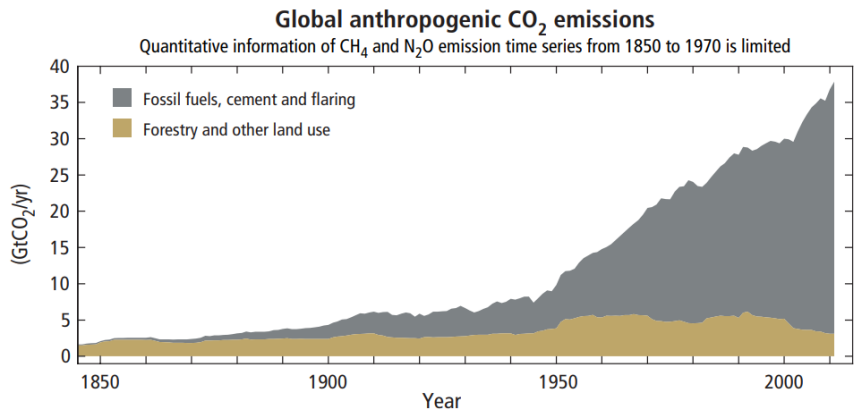
substitution of coal. Oil consumption, for example, rose very rapidly from 8.19 PJ (Petajoule [PJ] = 10^{15} J) in the 1940s to 36.1 PJ in the 1980s. In the same ways, the oil used for energy consumption increased significantly until the nuclear power started to be employed as energy source.



Graphic 1.1: Status of energy consumption in the last 200 years.

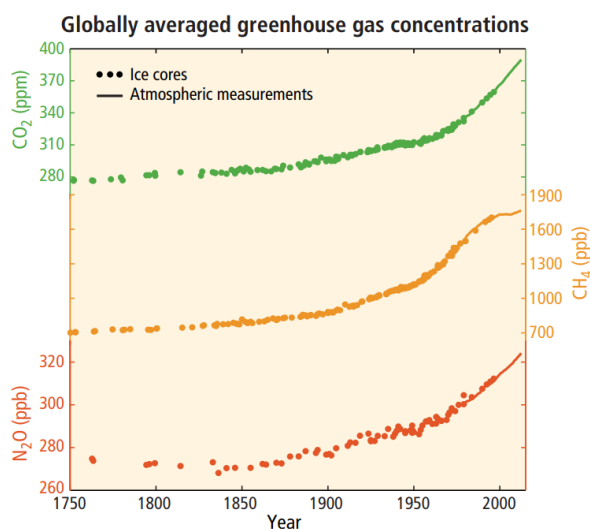
The exploitation of Petro refinery during the 20th century resulted in low production prices for goods and services, allowing the industries to increase productivity and consequently supporting the economic growth of Western countries and improving the living conditions of even the poorest people.^{2 3}

Despite the benefits of petrol, the large consumption of fossil fuels, due to industrialization and urbanization, has, over the years, incremented environmental pollution finally resulting in global warming (Graphic 1.2).



Graphic 1.2: Anthropogenic carbon dioxide emissions in gigatons/year during the Industrial Revolution.

According to scientific reports the anthropogenic emissions of CO₂, NO_x, and CH₄, contribute to the 77% of the total Greenhouse gas (GHGs) emissions in the atmosphere; among these, CO₂ represents 72% of the emissions (Graphic 1.3).⁴



Graphic 1.3: Concentration of different Greenhouse gases in ppm over the years.

This enormous mass of GHGs is released by burning different sources of energy, like coal and natural gas, and oil which is the most consumed. In particular oil use is ascribed to four main macro categories:

- **Energy:** electricity and heat by burning oil, coal, or gas.
- **Manufacturing and steel industry:** manufacturing machines, mining, and several industrial processes require a large quantity of energy and chemicals from fossil fuels.
- **Transportation:** human transport, such as cars, trucks, ships, and planes use internal combustion engines that consume only derivatives from oil (gasoline, diesel) and the trend is growing. Transport releases one-quarter of the global emission of CO₂.
- **Food production:** deforestation, intensive farming, and land use contribute to increased levels of greenhouse gases caused by digestion by cows, production of fertilizers, and energy to run farm equipment.⁵

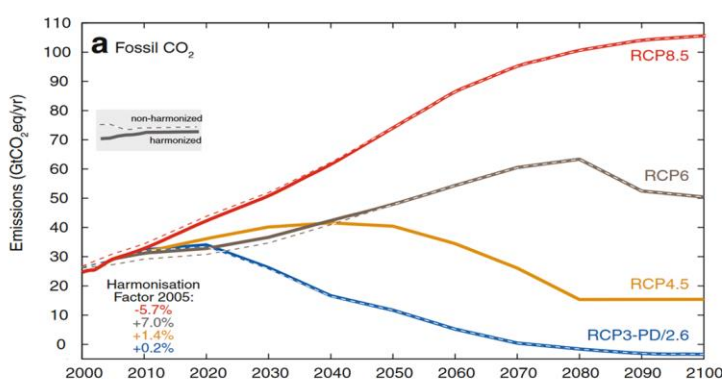
The effects of climate change are undeniable and, especially in the last decade, have caused the intensification of extreme phenomena affecting the environment, animal species and humans with evident social and economic consequences.⁶ Indeed, continuous alarming rate of CO₂ has risen the global temperature of *ca* 1.0 °C leading to drought or intense storms in many sensible regions, with important consequences for agriculture and food.^{7,8}

1.1.2 International agreements and the future of climate change.

The incessant rising of global temperatures due to the presence of greenhouse gases is causing long-lasting and irreversible changes in the climate system. Estimations of GHGs, particularly CO₂ emissions, depend on how much single states will invest in preventing further climate changes.

According to the Representative Concentration Pathways (RCPs), a model that makes assumptions on how socioeconomic choices can change the climate in the future, it is clear that if single states will not make decisions about emissions, there will be an irreversible rise in temperature as shown in Figure 1.4. Multiple lines in the graphic evidence a strong, almost linear relationship between cumulative CO₂ emissions and projected global temperature from now to the year 2100.

Let's consider two extreme cases proposed to the RCPs model (Graphic 1.4): pathway in blue represents an estimate where CO₂ emissions are strongly reduced and global average temperature rise "only" of 1.6 °C with respect pre-industrial period; on the other hand, the pathway in red represents the worst scenario, where temperature reach 4.1 °C by 2100 as a result of continuous grow of carbon dioxide emissions.⁹



Graphic 1.4: RCPs models provided different scenarios for emissions of carbon dioxide during the 21st Century.

In this perspective, it is evident that burning fossil fuels to produce energy and chemical materials is becoming no more sustainable for our planet, in fact, in the last thirty years several international actions have been taken among states to reduce emissions and find alternative solutions to petrol. (Figure 1.2).



Figure 1.2: International climate treaties over the years.

Already in 1987 the Montreal Protocol was established where all participating countries agreed in a treaty to stop the production of substances that damage the ozone layer.¹⁰ Afterward, in 1992, The United Nations Frameworks Conventions on Climate Change (UNFCCC) adopted "Agenda 21" a project encompassing goals and measures to be adopted so to achieve a sustainable development in a faster way.

However, only with the Kyoto Protocol in 1997 (became operational in 2005) it was added in the Agenda 21 a threshold to GHGs emissions i.e., treaty states had to minimize emissions by 5% under 1990s levels.¹¹ In this Century, various agreements occurred, notably the Millennium Development Goals (MDGs) a comprehensive strategy to decrease poverty by 2015. Subsequently, in 2012, the United Nations Conference on Sustainable Development undertook a contract upgrade, and within the same time frame, negotiations started for the elaboration of the Sustainable Development Goals (SDGs). Only in 2015, The United Nations (UN) approved Agenda 2030 for Sustainable Development with its 17 objectives, from human welfare (hunger, poverty, inequality) to environmental protection, that serve as a guide for all countries members of the United Nations to preserve our future (Figure 1.3).¹²



Figure 1.3: Sustainable Development Goals (SDGs).

SDGs promote industry innovation (Goal 9) and responsible consumption and production (Goal 12), two significant elements to pursue against climate change. This is in line with the Paris Agreement which aims to confine temperature rise within 2 °C,¹³ and the 2021 Glasgow UN Climate Change Conference (UNCC) that underlines the necessity of a huge and fast transition of its industries based on fossil fuels, to more sustainable alternatives such as renewable resources as feedstock for energy and materials.¹⁴ This challenging transition starts from the base of industry and promotes a new concept of refinery: the biorefinery.^{13–15}

1.2 Biorefinery

In recent years, biorefinery has emerged as a new form of industry, offering a pathway to a sustainable economy. The concept of biorefinery originated from the Task 42, proposed by the International Energy Agency and Bioenergy (IEAB), an organization established in 1978 and part of the International Energy Agency (IEA), a framework within the Organisation for Economic Co-operation and Development (OECD). IEAB facilitates comprehensive energy programs among its member countries, promoting cooperation and information exchange related to national bioenergy programs, research, and development.¹⁶

As above stated, biorefinery was acknowledged by its establishment in 2007 as a specific IEAB Task 42, and it is defined as “the sustainable processing of biomass into a spectrum of marketable products (food, feed, materials, chemicals) and energy (fuels, power, heat)”.

1.2.1 Differences between petro refinery and biorefinery.

Although the concept of biorefinery is, by name, reminiscent of the conventional refinery, there are several substantial differences between these two types of refinery, mainly concerning the raw material, and the chemical processes used. Conventional refineries use crude oil as main source to obtain different fractions of compounds, like petrol, naphtha kerosene, and diesel, separated from each other by fractional distillation. Moreover, chemical, and thermal treatments (catalytic reforming, steam cracking etc.) allow to obtain aliphatic, aromatic and naphthenic hydrocarbons; the type of products obtained depends heavily on the processes used (Figure 1.4).¹⁷

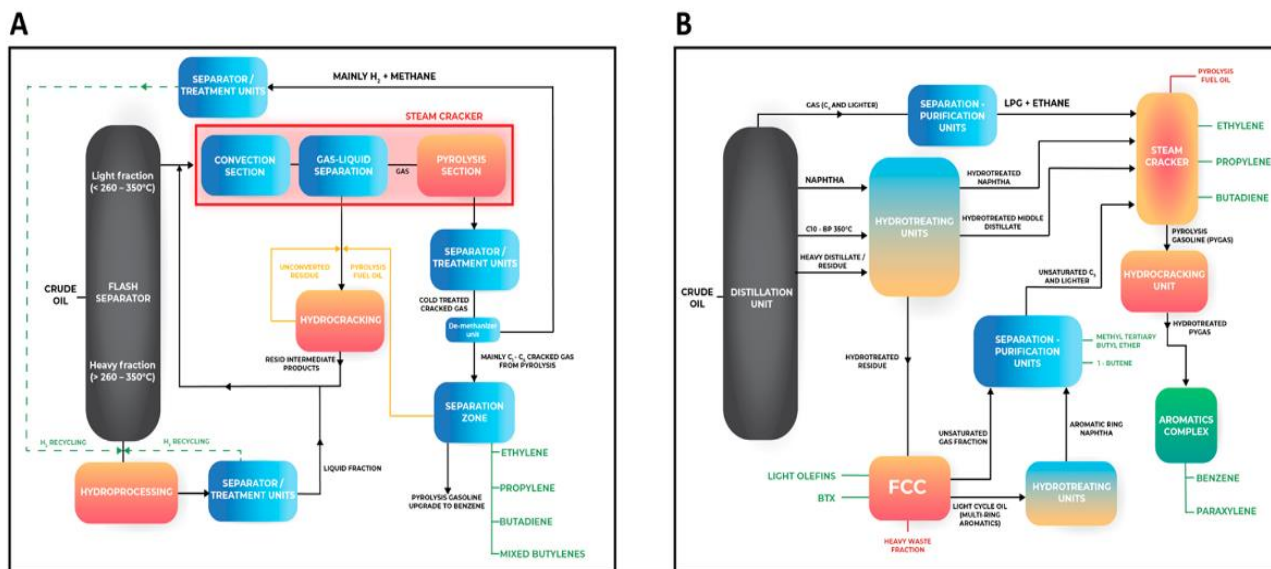


Figure 1.4: Two mainstream refining approaches to maximize products chemicals: (A) steam cracking centred process, (B) fluid catalytic cracking centered process.

On the other hand, biorefinery is based on renewable starting materials- i.e., **biomass** - that play a fundamental role as a counterpart of crude oil.

Biomass is defined as a mixture of biogenic organic-inorganic solid products generated by:

- a) **Natural processes:** containing various constituents originated via photosynthesis or animal/human food digestion;
- b) **Technogenic processes:** derived via processing of the above natural constituents.

Thus, biomass is very heterogeneous meanwhile crude oil which is a homogeneous material. Biomass composition depends on the origin and quality of the constituent material. In this view a classification is necessary that allows the identification of the above mentioned raw material (Table 1.1).¹⁸ Furthermore, the overall composition of biomass can change in quantities not only between different types of

feedstocks, but even within an individual stock.

Generally, biomass is composed of different types of biopolymers like cellulose (35%-50%), hemicellulose (15%-30%), lignin (15%-20%), and in a small quantity of volatiles and ash (1-10%). These differences in compositions are big enough that conversion reactors have to operate under different conditions based on the type of feedstock.¹⁹

Table 1.1: General classification of biomass according to their origin and biological diversity.

Biomass groups	Biomass sub-groups, varieties and species
1. Wood and woody biomass	Coniferous or deciduous; angiospermous or gymnospermous; soft or hard; stems, branches, foliage, bark, chips, lumps, pellets, briquettes, sawdust, sawmill and others from various wood species
2. Herbaceous and agricultural biomass	Annual or perennial and field-based or processed-based such as: 2.1. Grasses and flowers (alfalfa, arundo, bamboo, bana, brassica, cane, cynara, miscanthus, switchgrass, timothy, others) 2.2. Straws (barley, bean, flax, corn, mint, oat, rape, rice, rye, sesame, sunflower, wheat, others) 2.3. Other residues (fruits, shells, husks, hulls, pits, pips, grains, seeds, coir, stalks, cobs, kernels, bagasse, food, fodder, pulps, cakes, others)
3. Aquatic biomass	Marine or freshwater algae; macroalgae (blue, green, blue-green, brown, red) or microalgae; seaweed, kelp, lake weed, water hyacinth, others
4. Animal and human biomass wastes	Bones, meat-bone meal, chicken litter, various manures, others
5. Contaminated biomass and industrial biomass wastes (semi-biomass)	Municipal solid waste, demolition wood, refuse-derived fuel, sewage sludge, hospital waste, paper-pulp sludge, waste papers, paperboard waste, chipboard, fibreboard, plywood, wood pallets and boxes, railway sleepers, tannery waste, others
6. Biomass mixtures	Blends from the above varieties

The heterogeneous composition of biomass is characterized by a broad array of functional groups within the material. The high occurrence of oxidized compounds and the presence of inorganic complexes, particularly in comparison to oil, necessitate diverse processes to achieve building blocks such as ethylene or toluene; furthermore, these processes not always yield a wide range of chemicals.

A diverse combination of biomass materials requires different types of processes, leading to a rather complex classification of biorefineries based on different feedstock, as well, as reactions involved, and high-value products obtained. In this case, IAE Bioenergy Task 42 developed a generic biorefinery classification approach based on four main features: platforms, products (energy and chemicals), feedstock, and conversion processes. Within each category, subcategories delineate the specific products obtained or the main process used:^{20,21}

- 1. Platforms:** these biorefineries are focused on the production of molecules - such as C5 and C6 sugars and oils - then used as intermediates for the synthesis of high value added molecules;
- 2. Products:** in this category, biorefineries are classified based on the use of final products. There are two different types of outcomes for energy production (biodiesel, bioethanol) and material production (fertilizer, glycerine, biomaterials);
- 3. Feedstock:** biorefineries can use dedicated crops, biomasses grown exclusively to be converted into platforms or products, and residues from organic or urban waste;
- 4. Processes:** this classification is more complicated than the previous ones because it includes a wide range of treatments. The most common processes are thermochemical (combustion, pyrolysis), biochemical (fermentation, enzymatic processes), chemical (catalytic processes, esterification, hydrogenation), and mechanical/physical operations (pretreatment, extraction).

This generic classification provides a simple manner to identify a much wider and more complex range of biorefineries, that can use the same starting materials but employ different processes so to achieve specific products (Figure 1.5) This aspect is in contrast with petroleum refineries, where processes are consistently similar.

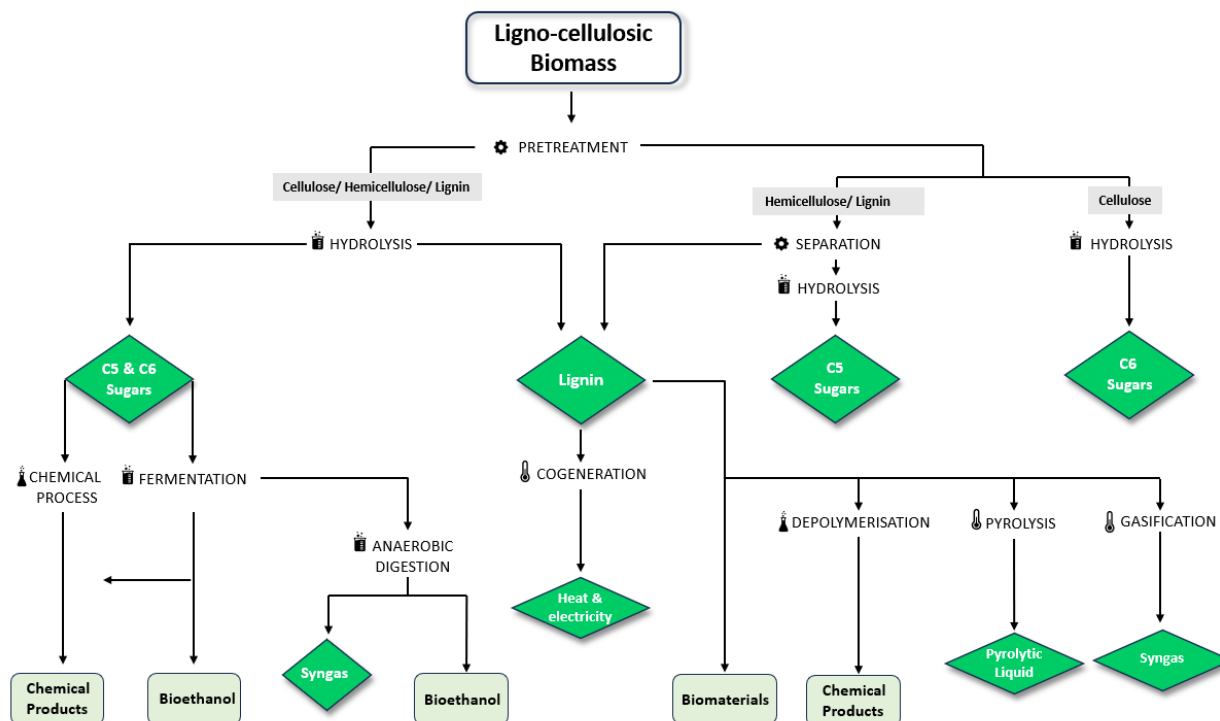


Figure 1.5: Typical processes of lignin cellulosic biomass.

1.2.2 The Green Chemistry and the 12 Principle of Green Chemistry

To pursue a rapid evolution of biorefineries, and to ensure competitive and environmental production, biorefineries need to develop alternative synthetic approaches to the ones classically used for chemical transformation involving chlorine-chemistry and requiring consumptions of large excess of reagents and solvents. In this perspective Green Chemistry can definitely aid and speed this transition. According to the Environmental Protection Agency (EPA) definition, Green Chemistry is *the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances*. Green chemistry applies across the life cycle of a chemical product, including its design, manufacture, use, and ultimate disposal. Green Chemistry, besides aiming to overcome the use of hazardous materials and minimize waste, emphasizes energy conservation, the use of sustainable and renewable feedstocks, and the prevention of any forms of raw material depletion, with a particular focus on water resources.^{22,23}

The core of Green Chemistry scope has been codified in 12 Principles, namely the 12 Principles of Green Chemistry, that provide guidance for the development of chemicals and processes with a greater emphasis on sustainability. These 12 Principles, developed by Paul Anastas and John Warner in 1998, are

applicable to every aspect of the process life cycle, including the raw materials utilised, the efficiency and safety of transformation, and the toxicity and biodegradability of products and reagents used (Figure 1.6).^{24,25}



Figure 1.6: 12 principles of Green Chemistry

1.2.3 Bio-based platform chemicals.

The concept of biorefineries is to transform renewables into a variety of bio-based platform chemicals minimizing, at the same time, waste production and following the principles of Green Chemistry. Bio-based platform chemicals play a fundamental role in biorefinery, as they are molecules derived directly from biomass, incorporating one or more functional groups that can be easily functionalised into a wide range of marketable products, using different type of processes such as chemical, biochemical and physical.

The most promising bio-based platform chemicals were identified in 2004 by the Department of Energy (DOE) as “Top 10 Bio-based Platform Chemicals”, a list implemented in 2010 with other five molecules.

These fifteen molecules were chosen following stringent criteria. In order to be part of this list, molecules are required to be sustainable in all their life-cycle assessments, also, they need to be reactive and functionalised using relatively mild conditions. Just to mention few examples, among bio-based platform chemicals we can find succinic acid (C4), xylitol (C5), lactic acid (C3) and D-sorbitol (C6). These are three Bio-Based Platform Chemicals in which knowledge about chemical and industrial production processes is complete and advanced (Figure 1.7).

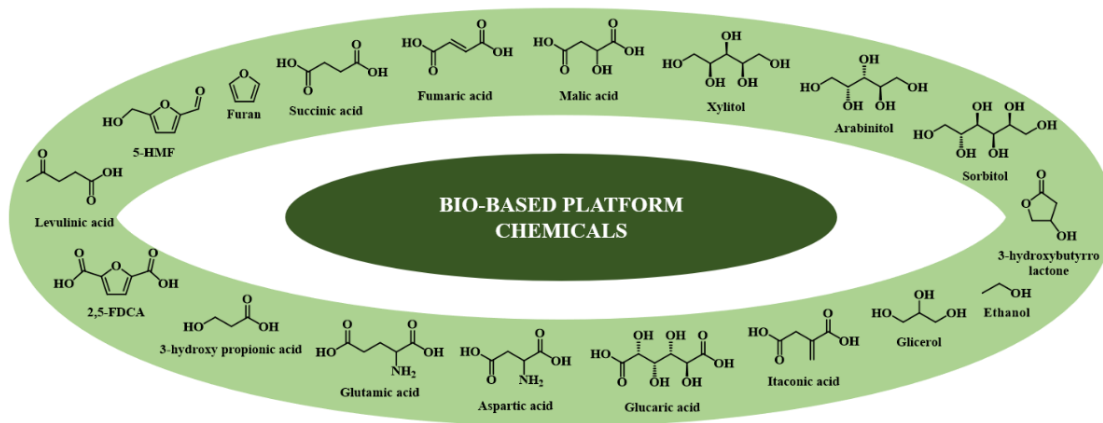


Figure 1.7: The Top 10 Bio-based platform chemicals.

For example, the industrial and scientific knowledge on the synthesis of lactic acid allows this BBPL to have a flourishing market due to its considerable production of 350,000 tons/year. But lactic acid can also undergo numerous transformations: the esterification provides lactate esters, that can be used as a green solvent; reduction following dehydration yields propylene oxide. Lactic acid can also be converted into a biodegradable polymer, polylactic acids, obtained via the polymerization of its dimer called lactide (Figure 1.8).²¹

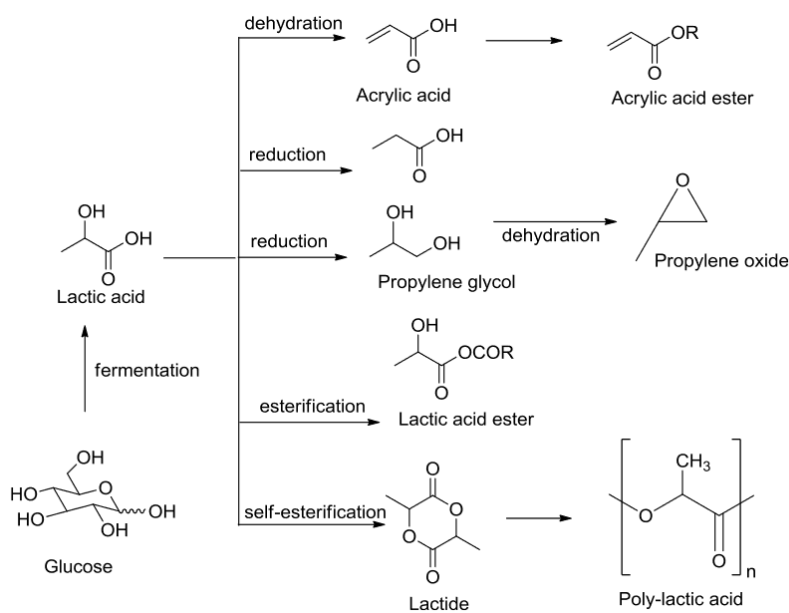


Figure 1.8: Acid lactic and its value-added products.²³

In addition, some chemical industries are focussing on the development of new industrial process for specific bio-based platform chemicals. For example, one of the main protagonists of the BBPC scenario is 5-hydroxymethylfurfural (HMF) also called the “Sleeping Giant” in consideration of its potential industrial applications to create a diverse array of commodities and consumer chemicals. From HMF it is possible to achieve a wide range of monomers like caprolactone, caprolactam, furan dicarboxylic acid that can be in

turn exploit for the preparation of biodegradable and bio-based polymers.

HMF is most commonly prepared via the triple dehydration of D-Fructose and it is now produced on a commercial small scale by AVA Biochem. This company claims to have already prepared a new production plant with a capacity of 5-6 tons/year.^{26, 27}

The strong interest in HMF is also rising by its unique molecular structure, incorporating three very reactive groups such as an alcohol, an aldehyde and a furan unit. This versatility allows HMF to serve as a precursor for a wide range of monomers of bio-based materials, including resins, biofuel additives, solvents and polymers.^{28,29}

In this perspective HMF is a poignant example of the growing interest of industries in Bio-based Platform Chemicals. In fact, according to a UE report, there are two possible types of growth on the potential demand in 2030 for Bio-based Chemical and materials. In the high growth scenario, demand can reach around 16 million tons per year, with a growth rate of 10% per year until 2030; in low growth scenario this rate it is estimated around 3%. In those two cases, the supply of BBPC and materials cannot compensate for the demand, and this is related to the lack of co-processing biorefineries or commercial scale productions.^{20,30}

Despite these issues, biorefinery represents a relatively new research field and as such it is in continuous expansion; it is now essential to integrate biomass processing into traditional refineries as a way to upgrade conventional refineries and make a first step to the green transition.¹⁶

1.3 Dimethylcarbonate, an ambident electrophile

Short-chain dialkyl carbonates (DACs), such as dimethyl carbonate (DMC), diethyl carbonate (DEC), and ethylene carbonate (EC) have attracted increasing attention during the three decades due to their extensive applications in green chemistry (Figure 1.9). Indeed, DACs are green alternatives for toxic and carcinogenic compounds such as phosgene (COCl_2), alkyl halides (RX , $\text{X} = \text{Cl}, \text{Br}, \text{I}$), and dimethyl sulphate (DMS), used for carbonylation reactions and alkylation respectively. In addition, DACs, when used, form only methanol and/or CO_2 as reaction by-products, meanwhile phosgene, dimethyl sulphate and alkyl halides give as by-products inorganic salts which must be appropriately disposed of.

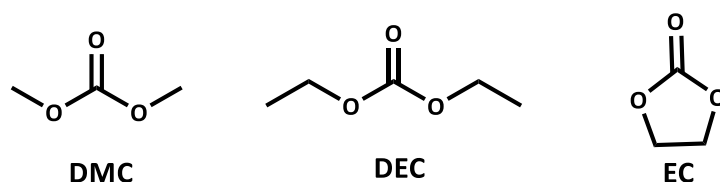


Figure1.9: Short chain DACs.

In particular DMC, (Figure 1.9), which is the methyl ester of carbonic acid, is extensively used in green synthesis both as reagents and solvent in consideration of its physical chemical properties and low

toxicity.

Table 1.2 illustrates a comparison between DMC and water where it is possible to observe its similar physical properties, i.e., density, boiling points, viscosity. DMC is a colourless liquid, and even if it is flammable, it is not a toxic compound for human health or the environment.

Table 1.2: Analogies among DMC with water.

Property	DMC	H ₂ O
M.p. (°C)	4.6	0.0
B.p. (°C)	90.3	100
Density (Kg/m ³)	1.1	1.0
Viscosity (m ² /s)	0.6	1.1
Dielectric constant (C ² /N*m ⁻¹)	3.1	80
Solubility in H ₂ O	13.9	/
Azeotropic mixture	Water, alcohols, hydrocarbons	/

As above stated, DMC is also used as a reagent in numerous chemical reactions. In fact, DMC and DACs in general are an ambident electrophile, able to act as alkylating and/or methoxycarbonylating agents. This peculiar reactivity can be explained by Pearson's theory, specifically the Hard-Soft Acid-Base theory (HSAB). According to this theory, a hard electrophile reacts predominantly with a hard nucleophile, while soft electrophile tends to prefer soft nucleophile. Differences between hard electrophile and soft electrophile based only on empirical observations are summarized in Table 1.3.

Table 1.3: Differences between Hard and Soft electrophiles.

Hard	Soft
Low polarizability	High polarizability
Small dimensions	Large dimensions
High charge density	Low charge density
High oxidation state	Low oxidation state

In the case of DMC (Figure 1.10) the carbonyl moiety is the hard site due to its small dimensions and high charge density given by a direct connection with three oxygens; while the methyl groups are more polarizable so they are the soft sites.^{31,32}

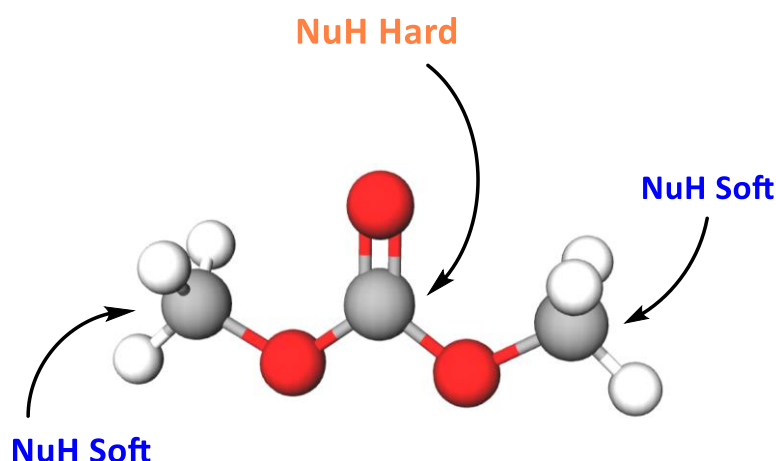
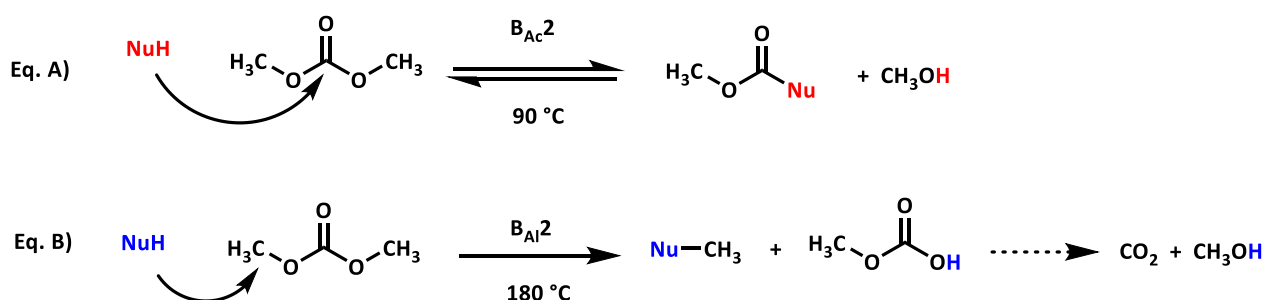


Figure 1.10: Hard and Soft sites of DMC.

This double reactivity of DMC is strongly influenced by the reaction conditions and in particular by the temperature that leads to one of two mechanisms.

At reflux temperature of DMC ($T \approx 90\text{ }^{\circ}\text{C}$) and in the presence of a Hard Nucleophile, DMC acts as a methoxycarbonylation agent; the carbonyl group is attacked by the hard nucleophile (NuH) via base-catalysed bimolecular nucleophilic substitution ($B_{Ac}2$). This is an equilibrium reaction operating under thermodynamic control (Scheme 1.1, **equation A**).

At higher temperatures ($T \geq 150\text{ }^{\circ}\text{C}$), in the presence of a Soft Nucleophile, DMC acts as a methylating agent. The methyl moiety is attacked by the NuH and the methoxycarbonyl anion is released as leaving group. The reaction mechanism is a base catalysed alkylation bimolecular nucleophilic substitution ($B_{Al}2$) and it is irreversible operating under kinetic control (Scheme 1.1, **equation B**).³³



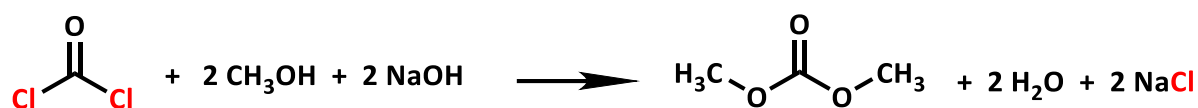
Scheme 1.1: Reaction pathways of DMC: methoxycarbonylation (A), methylation (B).

1.3.1 Industrial Synthesis of DMC

The properties of DMC are long been known, and industrial synthesis has evolved over the years towards more sustainable and safer synthetic routes. In order to be a green solvent or chemical reagent, it is necessary to have a sustainable life cycle assessment, to avoid dangerous industrial procedures, and

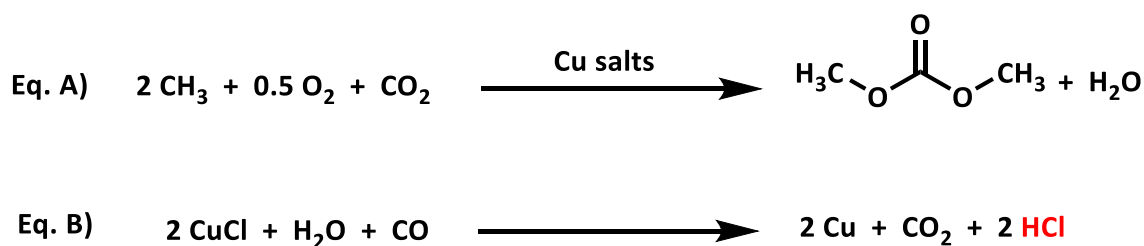
accidental environmental spillage of the product or its derivatives.

The first industrial synthetic route for DMC dates back to the mid-1950s and included the use of phosgene and methanol (Scheme 1.2).



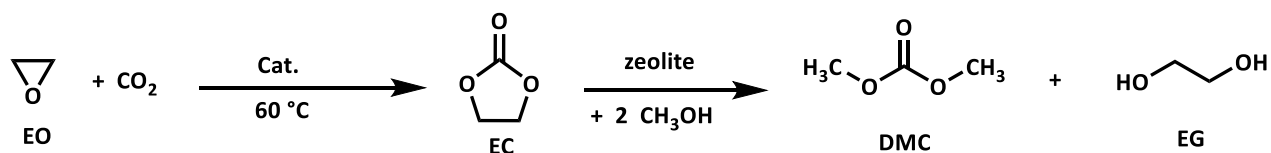
Scheme 1.2: DMC synthesis of DMC from phosgene.

Phosgene is a highly reactive electrophile and an excellent carboxylating reagent, but it is also extremely toxic. So, to avoid the use of phosgene, Enichem in the early 1980's, patented more sustainable synthesis that has supplanted the previous process. This new synthetic approach to DMC consisted of oxidative carbonylation of methanol catalysed by Cu salts, which leads to high yield of DMC. Water was the only by-product formed, however, the presence of copper salts (e.g. CuCl) inevitably led to the formation of HCl resulting in water contamination (Scheme 1.3).^{31,34}



Scheme 1.3: Oxidative carbonylation of methanol (A), and consequence production of HCl (B).

Nowadays, Asahi Kasei's process is the most used industrial route to produce DMC. This synthesis consists of two steps; i) CO₂ insertion in epoxides like ethylene oxide, with MgO as catalysts, ii) transesterification of the so-formed ethylene carbonate (EC) with methanol, catalysed by a zeolite (Scheme 1.4).



Scheme 1.4: Asahi Kasei's synthesis for DMC.

One important aspect that renders greener this process is that carbon dioxide, a by-product of the synthesis of ethylene oxide (EO) via oxidation of ethylene, is reintroduced into the process through an insertion to lead the ethylene carbonate, precursor of DMC. This synthetic path is the greenest technology for the production of DMC, both for recycled CO₂, and for the possibility of selling ethylene

glycol (EG), a by-product that occurs with the formation of DMC. Consequently, Asahi Kasei's synthesis demonstrates a high circular economy, capable of adsorbing 50% w/w of CO₂ per product solvent.^{35,36}

1.4 From D-sorbitol to Isosorbide

The 1,4:3,6-dianhydro-D-glucitol, namely **D-sorbitol** (Figure 1.11), is a natural sugar alcohol present in wild fruits, isolated for the first time in 1872. Due to its use in cosmetics as a humectant and in the confectionery industry as a substitute for D-glucose and D-fructose, the production of D-sorbitol is constantly growing. Nowadays its production is at 800 kt/year globally with a growth rate about 2-3%.^{37,38}

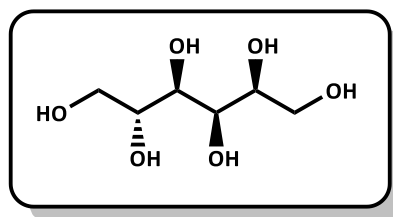
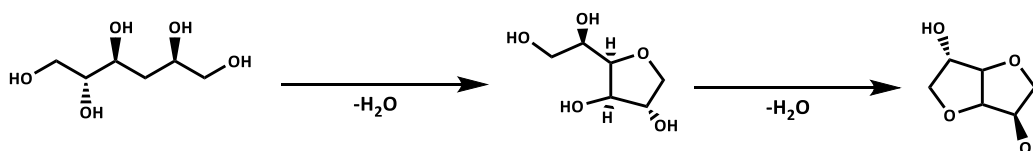


Figure 1.11: D-sorbitol.

D-sorbitol is abundant in cellulose, one of the main components of biomass. It is the reduced form of D-glucose, the monomer of cellulose. To obtain D-sorbitol, it is necessary to extract D-glucose from the biomass through an hydrolysis, followed by a catalytic hydrogenation to convert the D-glucose into a D-sorbitol.³⁹

The crescent interest of this C6 sugar is attributed to its anhydrous sugar alcohols, which include mono-anhydro sorbitol, sorbitan, and di-anhydro-sorbitol, called isosorbide. These compounds serve as reagents for numerous syntheses and are also intermediates of industrial interest (Scheme 1.5).^{40,41}



Scheme 1.5: Dehydration of D-sorbitol.

Isosorbide has a peculiar V-shaped structure due to a 120° disposition of the two tetrahydrofuran rings. Furthermore, the four oxygens integrated into the structure are all in β position each other. The two hydroxyl groups have a different orientation; the hydroxyl group in position 2 is oriented inward the V-shaped cavity, so is referred to as "endo"; meanwhile the hydroxyl in position 5 is directed outward the molecule and is referred to as "exo" (Figure 1.12).

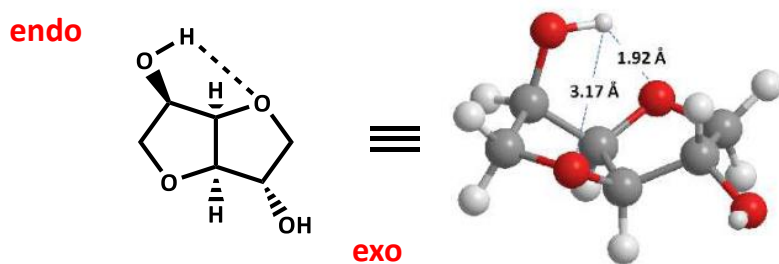


Figure 1.12: "Endo" and "exo" configuration of hydroxyl groups.

As a result, their reactivity differs significantly, in fact, the nucleophilic character of the less sterically hindered group in the *exo* position is generally higher than the one in the *endo* position involved in a strong hydrogen bond. This different configuration of hydroxyl groups in isosorbide results in different chemical, physical, and reactivity properties when compared with its two epimers, isoidide, and isomannide, where the two hydroxyl groups are oriented both in "exo" or "endo" position respectively (Figure 1.13).^{37,41}

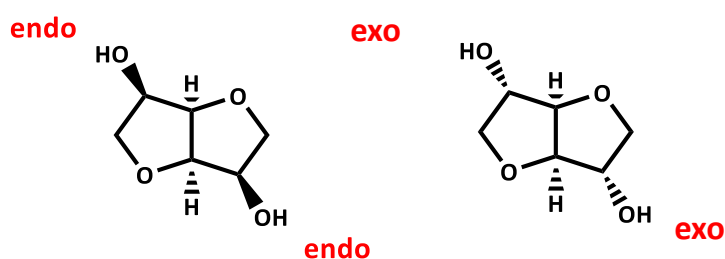


Figure 1.13: Epimers of isosorbide.

1.4.1 Synthetic Routes to Isosorbide

As above stated, cellulose is the primary feedstock to obtain D-sorbitol. Several published studies report that D-sorbitol can be obtained from monosaccharides, but its preparation from cellulose is more attractive from an economic and environmental point of view. Cellulose, however, has low solubility in common organic solvents, and glycosidic bonds are difficult to hydrolysed. As a result, the synthesis of D-sorbitol is quite complex and requires a catalyst with both acid and metallic sites to allow acid hydrolysis and hydrogenation processes (Figure 1.14). In this prospect, several bi-functional catalysts were investigated, like ionic liquids, although the solubility of polysaccharides in these solvents is very low and their actual toxicity has not yet been demonstrated.⁴²⁻⁴⁵

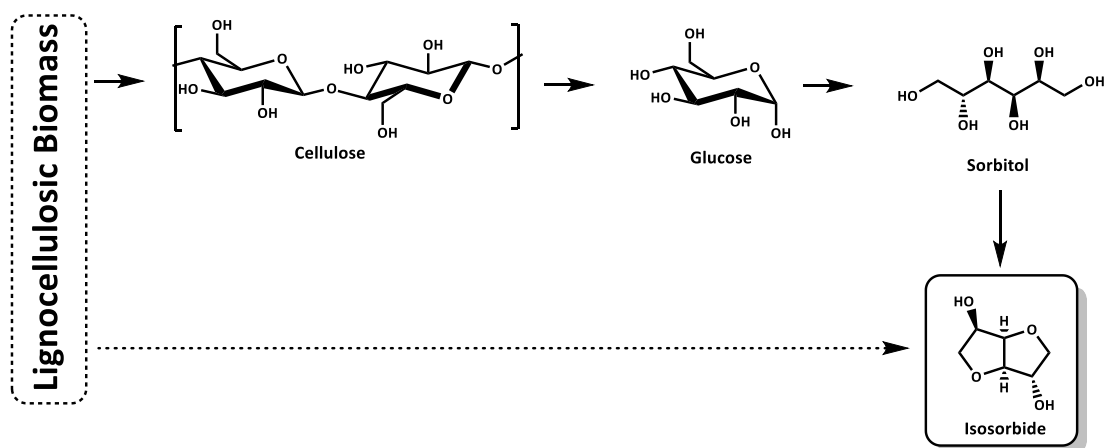


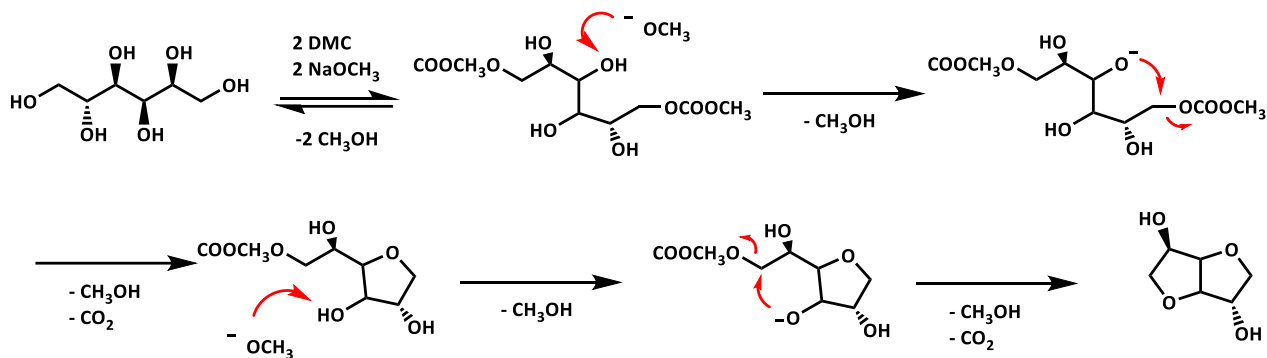
Figure 1.14: Conversion of lignocellulosic biomass in isosorbide.⁴³

As depicted in the Figure 1.14 and scheme 1.5, the synthesis of isosorbide from D-sorbitol requires a double dehydration of sorbitol through 1,4-sorbitan as an intermediate.

The first synthesis of isosorbide was conducted in 1968 by Fleche and co-workers using sulfuric acid as a catalyst at 130 °C in a discontinued reactor with a final yield of 70%. Despite the good yield this approach necessitates a big amount of sulfuric acid and solvent to recover the final product from the reaction mixture.⁴⁰

Recent studies focused on the use of heterogeneous catalysts like oxides, phosphates, or sulphate oxides, and zeolites that are thermally stable aluminium silicate. Zeolites are not efficient like sulfuric acid, but Fukuoka et al. obtain isosorbide with a yield of 76% using zeolite H β with a Si/Al ratio of 75% and without solvents operating at 127 °C. The recovered catalysts can be reutilized up to five times before decreasing its efficiency. Unfortunately, this interesting approach necessitates purification and separation of isosorbide from the reaction mixture.

A promising synthetic route of isosorbide from sorbitol was proposed by Aricò and co-workers, the research group where this thesis work has been conducted. In this approach, isosorbide is reacted in the presence of a strong base with DMC at its reflux temperature (90 °C). In particular, in this approach, DMC plays a double role: reactant and solvent. Following this procedure, isosorbide was recovered in quantitative yield by simple filtration of the base and evaporation of DMC under vacuum. For the total conversion of D-sorbitol in isosorbide, authors used a strong base like sodium methoxide (NaOMe) in large excess, this is because the double cyclization requires 2 equivalents of base, one for each ring formed. The proposed reaction pathway (Scheme 1.6) leading to isosorbide includes two methoxycarbonylation reactions (B_{Ac}2) followed by two intramolecular cyclization (B_{Al}2).



Scheme 1.6: Reaction pathway for isosorbide synthesis.

To avoid the use of an excess of NaOMe, several bases were tested and, among these, 1,8-diazobicyclic [5.4.0] undec-7-ene (DBU) showed the best performance to convert the substrate into isosorbide. Stoichiometric quantities of DBU guarantee the full conversion after 7 hours of reaction contrary to what happens with catalytic quantities, which need more time to bring the conversion to term (Table 1.4).⁴⁶

Table 1.4: Synthesis of isosorbide via DMC chemistry.

Entry	Catalyst	Solvent	DMC (eq.mol.)	Time (h)	Isosorbide (%)	Yield (%) ^b
1	NaOMe (2.0)	MeOH	4	8	80	64
2	NaOMe (2.0)	MeOH	8	8	98	76
3	DBU (1.0)	MeOH	8	7	100	98
4	DBU (0.25)	MeOH	8	7	100	98
5	DBU (0.05)	MeOH	8	24	100	98

The reaction was conducted with D-sorbitol 2.0 g (1.0 eq.) at reflux temperature. Conversion was quantitative. ^b Yield isolated.

1.4.2 Isosorbide as bio-based platform chemical

Isosorbide is a building block with a wide range of applications (Figure 1.14). Thanks to the functionalization of the two hydroxyl groups with different electrophiles, such as DMC, isosorbide can lead to numerous industrially interesting compounds as surfactants, flame retardants, chiral auxiliaries, and monomers for bio-based polyesters or polycarbonate.

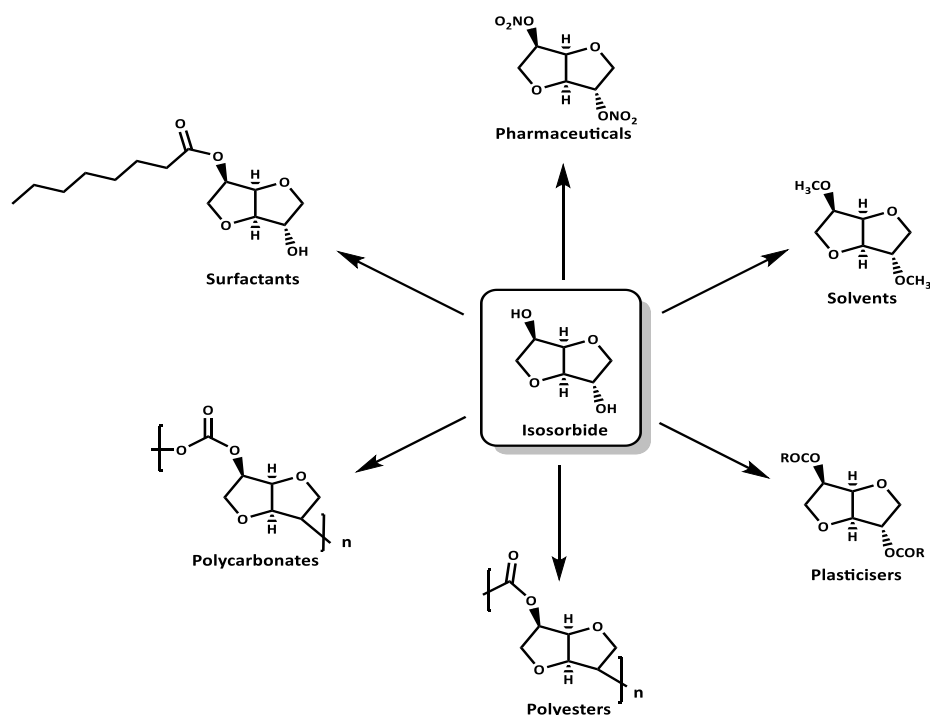


Figure 1.14: Possible applications for isosorbide.

In 2014, 35% of the total isosorbide produced was used to synthesize poly(ethylene-co-isosorbide) terephthalate. Recently Mitsubishi Chemical has introduced isosorbide-based copolycarbonate, called Durabio, in their automobile parts and electronic display, which exhibits superior quality to its petroleum-based analogues incorporating bisphenol A. The higher quality of isosorbide-based polycarbonate than the traditional polycarbonate, is a consequence of the rigid structure of isosorbide which gives high glass transition temperature (T_g) to the polymers (Figure 1.15).

In addition to the rigid structure, isosorbide present diol functionality that can be converted in a wide variety of polymers, including polyesters, polycarbonates or polyurethane. Isosorbides difunctional derivatives were also employed in the synthesis of cross-linked thermoset polymers with high performance property like, for example, isosorbide-methacrylate. This resin presents a T_g bigger than 240 °C with a degradation temperature about 400 °C allowing this material to operate in huge window respect any other know traditional polymers.⁴⁷

Moreover, isosorbide has interesting pharmaceutical and biomedical applications; several polyurethanes, used in biochemical engineering containing isosorbide, are degradable under physiological conditions, and don't affect cell proliferation, a sign of biocompatibility.⁴³

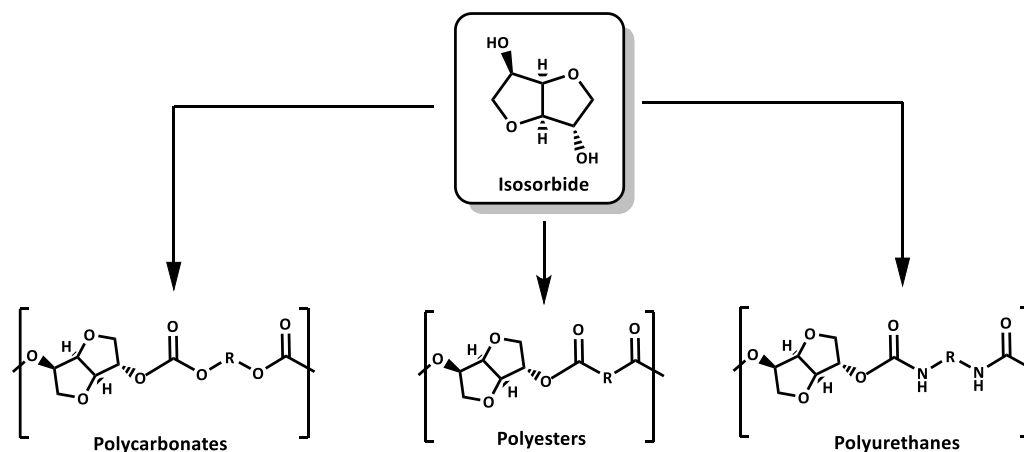


Figure 1.15: Different types of polymers based on isosorbide.³⁸

Isosorbide was also used as a substrate for the synthesis of isosorbide-5-monohydrated (IS-5-MN), isosorbide-2-monohydrated (IS-2-MN) and isosorbide nitrate (ISDN) well known vasodilators for the treatment of cardiac disease.

Recently, synthetic peptides incorporating isosorbide incorporated have been used as inhibitors for the serine protease present in virus responsible for the transmission of several infectious diseases like hepatitis C.⁴⁸

Another interesting derivative of isosorbide is the dimethyl isosorbide (DMI). DMI is extensively used in cosmetics as a humectant agent and to preserve the product from dehydration, but, in recent time, DMI has found interest also as green media due to its interesting physical-chemical characteristics and polarity.^{49,50}

1.5 From Isosorbide to DMI

As previously discussed in paragraph 1.4.1, the functionalization of the two hydroxyl groups of isosorbide can lead to a variety of molecules with diverse applications. One of these is the conversion of isosorbide into dimethyl isosorbide (DMI), which found extensive use as a green solvent due to its high polarity and water solubility; interesting aspects that render it a good replacement for conventional dipolar solvents like dimethylsulfoxide (DMSO) and dimethylformamide (DMF) (Figure 1.16).



Property	DMI
M.p. (°C)	-70
B.p. (°C), 760mmHg	236
Density (Kg/m ³)	1.2
Aspect	pale yellow liquid

Figure 1.16: Structure formula of DMI and some physical properties.

This simple derivative of isosorbide has been efficiently used as a substitute for hazardous solvents, (1,4-dioxane and DMF), for Pd-catalysed cross-coupling reactions, like Suzuki-Miyaura, Mizoroki-Heck, and

Sonogashira reactions.^{49,50} More recently DMI was employed in the preparation of poly(vinylidene fluoride)- and poly(ether sulfone)-based membranes, ideal for ultra and microfiltration processes in water treatments.⁵¹ Moreover, DMI is well-known in cosmetic and pharmaceutical formulations, thanks to its complete miscibility in water, and is used as a co-solvent and penetration enhancer of hydrophilic active substances.⁵²

1.5.1 Synthesis of DMI from isosorbide

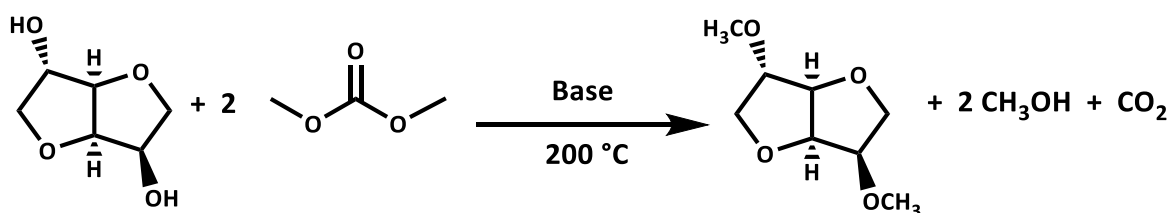
Despite its use as a promising solvent, in literature, there are not many synthetic procedures to DMI which is nowadays mostly produced using methylating agents like alkyl halides. This type of approach is obviously not green, thus several studies have been conducted to avoid the use of toxic and/or halogenated compounds. As an example, methanol and ethanol have been used in the etherification of isosorbide to synthesize DMI and DEI respectively in the presence of different catalysts. Despite several catalysts have been tested, like zeolites, zirconia-base catalysts, or potassium salts of 12-tungstophosphoric acid, selectivity toward DMI and DEI was only about 24 and 34% respectively.^{53,54}

Another interesting example of DMI synthesis, is the use of 1,2-dimethoxyethane as a reagent and solvent. The reaction was conducted at 150 °C in the presence of 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$). This acid-catalysed reaction has led to the quantitative conversion of isosorbide with an 80% selectivity against the DMI. Unfortunately, despite the catalyst was recycled and reused up to three times, there is no information about the isolation procedure of DMI.⁵³

The breakthrough for a greener and less toxic synthesis of DMI takes place with the use of DMC as a methylating agent (Scheme 1.7) (see also Paragraph 1.3).

As mentioned above, DMC, in the presence of a generic NuH, can act as a methylating agent at high pressure and temperature over 150 °C ($B_{Al}2$ mechanism), while at reflux temperature (90 °C), DMC reacts as a methoxycarbonylating agent ($B_{Ac}2$ mechanism). However, there is another aspect to consider when methylation with DMC takes place: the type of nucleophile. In fact, primary and secondary alcohols can give different results when reacted with DMC as methylating agent.

When primary alcohols are methylated with DMC at 180-200 °C, a methoxycarbonylate intermediate is formed which subsequently decarboxylates by losing CO_2 and providing a quantitative conversion for the alcohol. On the other hand, the conversion of secondary and tertiary alcohols is never quantitative and leads to the formation of by-products due to concurrent elimination reaction.⁵⁵



Scheme 1.7: Reaction pathway from DMI with isosorbide and DMC.

On the other hand, investigations conducted on isosorbide demonstrated that its two secondary hydroxyl groups can undergo a selective methylation already at reflux temperature of DMC when the reaction is conducted in the presence of a strong base. This is quite unusual especially in consideration that the reaction of isosorbide with DMC can potentially form eight different compounds (Figure 1.17): monomethoxycarbonyl derivatives (MCI-1, MCI-2), dimethoxycarbonyl isosorbide (DCI), methoxycarbonyl methyl derivatives (MCM1-1, MCM1-2) and three methyl derivatives (MMI-1, MMI-2, DMI). To avoid the formation of these by-products and increased the selectivity and the yield toward DMI, reaction conditions and several bases were tested.

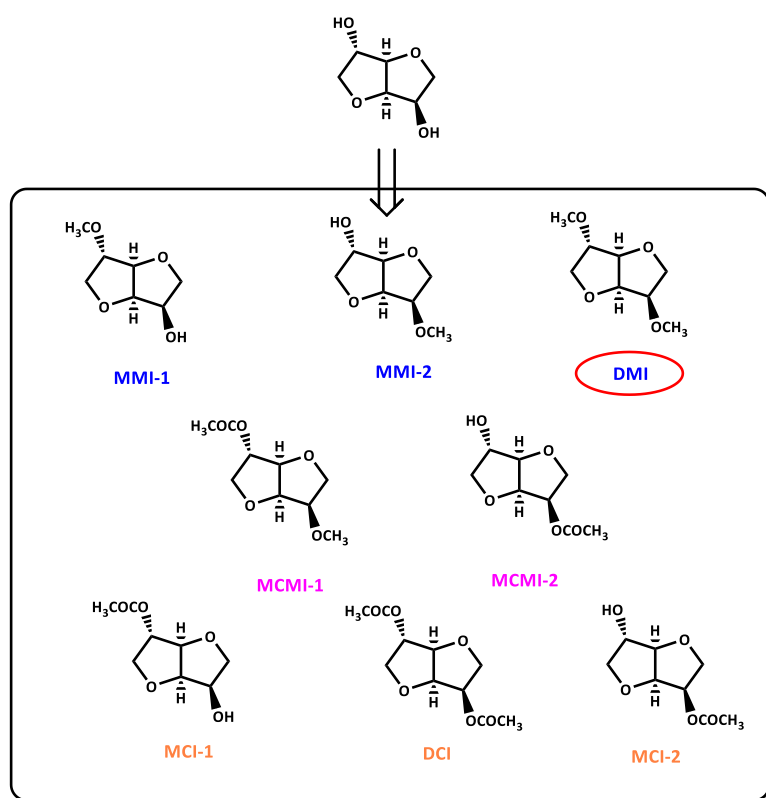


Figure 1.17: Derivates of isosorbide.

First studies were conducted using weak bases (Table 1.5) that have led only to the formation of mono and dimethoxycarbonyl derivatives (MCI-1, MCI-2, DCI); DMI formation was not observed. Only in the presence of strong bases (t-BuOK, NaOMe), the reaction conducted at 90 °C led to a discrete yield of DMI (40% yield) that increased using larger amount of base. (Table 1.5).⁵⁴

Table 1.5: Reactions between Isosorbide and DMC with different bases at 90 °C.

#	Base (eq. mol)	Carboxymethyl derivates			Carboxymethyl methyl derivates		Methyl derivates		
		MCI-1	MCI-2	DCI	MCMI-1	MCMI-2	MMI-1	MMI-2	DMI
1	K ₂ CO ₃ (1.5)	30	7	59 ^b	2	0	0	0	0
2	Cs ₂ CO ₃ ^a	19	4	73 ^b	3	1	0	0	0
3	NaOMe(1.5)	0	1	6	30	12	11 ^b	6	26 ^b
4	t-BuOK(1.5)	0	0	0	37	18	2	2	40
5	NaOMe(2)	1	1	11	36	8	1	1	42 ^b
6	NaOMe(3)	0	0	0	0	0	0	0	100 ^b

Reaction conditions: isosorbide/DMC 1:50 eq. mol.; 20 h; 1 atm; 90 °C. ^a 1w/w. ^b Isolated yield.

Some studies were carried out in an autoclave so to reduce the amount of base used. As reported in Table 1.6, the use of K₂CO₃ in stoichiometric amount led only to 9% selectivity toward DMI. However, when the reaction was repeated at 200 °C, selectivity toward DMI raised considerably to 57%. Similar results were obtained employing t-BuOK.

Table 1.6 : Reactions of isosorbide with DMC in autoclave with different bases and catalysts.

#	Catalyst (eq. mol)	Temp. (°C)	Press. (bar)	Selectivity (GC/MS)%						
				MMI-1	DMI	MMI-2	MCI-1	MCMI 1-2	MCI-2	DCI
1	K ₂ CO ₃	180	8	7	9	10	5	55	2	11
2	K ₂ CO ₃	200	12	4	57	7	0	29	0	0
3	t-BuOK	180	9	13	23	13	2	48	0	1
4	t-BuOK	200	12	5	55	6	0	34	0	0
5	KW2000 ^a	180	11	1	83	3	0	12	0	0
6 ^b	KW2000 ^a	200	20	0	86	2	0	12	0	0
7	KW2000 ^a	200	20	0	91	2	0	7	0	0

Reaction conditions: isosorbide/DMC 1:50 eq. mol.; 24 h, conversion 100%; ^a 1:1 w/w; ^b time reaction 8 h.

The best results were obtained when a heterogeneous catalyst was used, like hydrotalcite KW2000 (Mg_{0.7}Al_{0.3}O_{1.15}), which can theoretically also be reused. The use hydrotalcite led to the total conversion of the starting reagent and a quantitative selectivity toward the DMI when the reaction was performed either at 180 °C or 200 °C.⁵⁶

However, it should be mentioned that the investigation conducted on hydrotalcite was quite preliminary as reaction conditions were never optimized and recycling of the catalyst and large scale reactions were never conducted.

1.5.2 DMI from isosorbide employing nitrogen organo catalysts

The reaction of isosorbide and DMC in autoclave was investigated also in the presence of different nitrogen organo catalysts in 0.5 eq. mol respect to isosorbide (1.0 eq. mol). Selected nitrogen bases included 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-

diazabicyclo[2.2.2]octane (DABCO), Pyridine, N-methylpyrrolidine (NMPy), triethylamine (Et₃N) and 4-dimethylaminopyridine (DMAP). Among them N-methyl pyrrolidine (NMPy) resulted the best performing one (Table 1.7).⁵³

Table 1.7: Synthesis of DMI in the presence of different nitrogen organocatalyst.

#	Base	GC/MS selectivity (%)					
#	Catalyst	MMI-1	DMI	MMI-2	MCI 1-2	MCMI 1-2-	DCI
2	TBD	5	78	0	0	17	0
3	DBU	13	51	0	0	34	0
4	DABCO	8	54	0	0	38	0
5	Pyridine	19	20	11	0	49	0
6	NMPy	2	98	0	0	0	0
7	Et ₃ N	5	95	0	0	0	0
8	DMAP	6	94	0	0	0	0

Reaction condition: Isosorbide: DMC: catalyst 1:50:0.5 eq. mol. Reactions was conducted in an autoclave at 200 °C for 12 h.

Numerous experiments were then undertaken to optimize the methylation and the most favourable reaction condition involve the presence of 0.5 mol eq. of NMPy at 200 °C for 12 hours in an autoclave.

DMI yield remains nearly quantitative in scale-up trials, where the quantity of isosorbide was increased from 1.0 grams up to 10.0 grams. In small scale and large scale trials, DMI was purified respectively using column chromatography and distillation, the recovered product was a transparent liquid (Table 1.8).⁵³

Table 1.8: Scale-up synthesis of DMI.

#	Isosorbide (g)	GC-MS Selectivity (%)			
		MMI-1	DMI	MMI-2	DMI
1	1.0	2	98	0	85 ^b
2	3.0	1	99	0	85 ^b
3	5.0	1	99	0	75 ^b
4 ^a	10.0	8	92	0	65 ^c

Reaction condition: Isosorbide: DMC 1:50 eq. mol, 200 °C for 12 hours in autoclave. Selectivity calculate via GC-MS.^a Reaction condition: Isosorbide : DMC 1:18 eq. mol, 200 °C for 12 hours in autoclave. ^b Purification via distillation. ^c Purification via column chromatography.

1.5.3 Possible Reaction Pathways to DMI

Methylation of isosorbide is a complex process that involves numerous reaction pathways as depicted in Figure 1.24. To understand the possible preferred reaction pathway for DMI formation in the presence of N-MPy, the research group where this thesis was conducted have carefully synthesised all seven methoxycarbonyl and methyl intermediates forming by reaction of isosorbide with DMC.⁵³

After the complete characterization of all seven intermediates, they conducted several experiments, monitoring the reaction over a period of 12 hours. Based on the results collected, the authors have

provided a schematic overview of the reaction pathways leading to DMI via DMC chemistry catalysed by NMPy. In particular, three reactions may occur as reported in Figure 1.18:

1. Methoxycarbonylation via B_{Ac}2 mechanism;
2. Methylation via B_{Al}2 mechanism;
3. Decarboxylation.

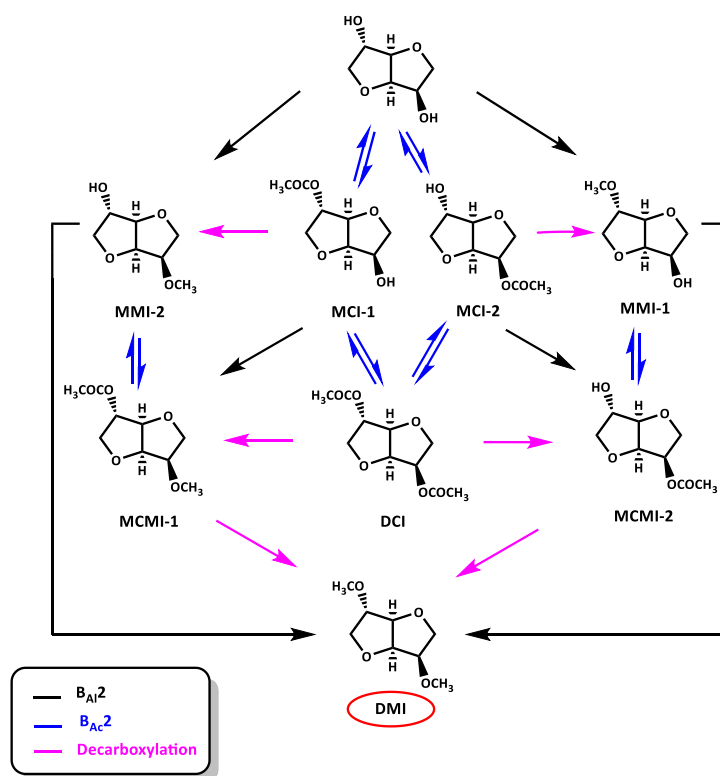


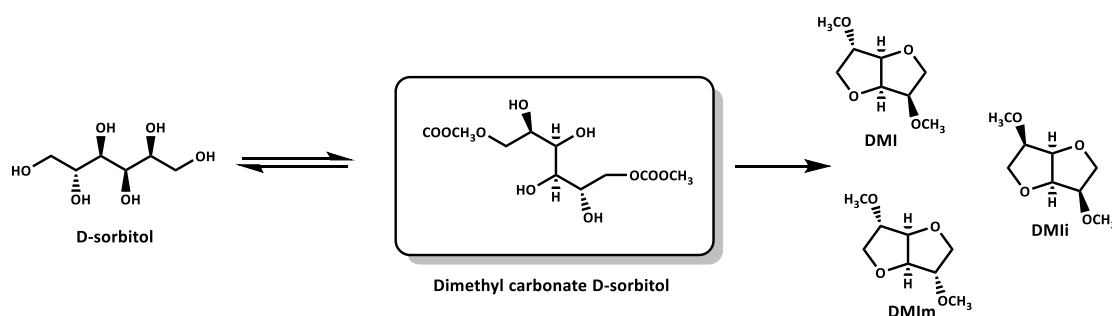
Figure 1.18: Possible reaction pathways.

As seen from Figure 1.18 formation of methyl derivatives of isosorbide can occur with two different mechanisms. One is the direct methylation reaction employing the B_{Al}2 system; alternatively, the second pathway to obtain methyl compound, is the decarboxylation of methoxycarbonyl monomers such as MCI 1-2, MCMI 1-2, and DCI, a procedure not extensively explored among DACs.⁵³

Synthesis for DMI via DMC chemistry was also conducted by heterogeneous and homogeneous acid catalysts like Purolites (CT275DR, Amberlyst-36) and weak acid like oxalic acid, formic acid, and acetic acid respectively. The best result was obtained in autoclave at 200 °C for 6 hour reaction, in presence of Purolites 1:1 weight ratio, that have lead > 75 % of yield in DMI.⁵⁷

1.5.4 One-Pot Synthesis of DMI from D-sorbitol

In literature, several articles report the use of DACs as sacrificial molecules for the synthesis of different heterocycles; as above reported also D-sorbitol was converted into isosorbide according to the same synthetic approach via DMC chemistry. In consideration of this result, it is not surprising that several attempts were made for the one-pot conversion of isosorbide into DMI using DMC both as a cyclization and methylation agent.



Scheme 1.8: From D-sorbitol to DMI and its epimers

To this scope, reactions were carried out in an autoclave in the presence of several catalysts. Directly conversion of D-sorbitol to DMI was not always efficient, especially because one-pot conversion involves numerous subsequent reactions including two methoxycarbonylation reactions and two intramolecular alkylations (Scheme 1.6, Paragraph 1.4.1), followed by double methylation of the two hydroxyl groups. In this view this chemical conversion was performed first at 90 °C for 48 hours, to promote an efficient conversion to isosorbide, and then the temperature was raised to 200 °C for another 24 hours to facilitate the methylation reaction. With this expedient DMI obtained ranges from 41 to 70 % (Table 1.9).

Table 1.9: One-pot synthesis of DMI.

#	Base	Temp. (°C)	Press. (bar)	DMI ^b %	DMIIm ^b %	DMII ^b %
1	Et ₃ N	90/200	85	60	14	26
2	TBD	90/200	26	69	14	17
3	DBU ^c	90/200	58	59	19	22
4 ^a	KW2000	90/200	50	41	0	0

Reaction conditions: D-sorbitol: DMC: catalyst 1:50:1 eq. mol.; ^a Isosorbide: KW500 1:1 w/w; autoclave at 90 °C for 48 h then at 200 °C for 24 h. ^b It was observed the presence of MMI-1 (16%), MMI-2 (11%), MDMI-1 (11%) and MDMI-2 (32%).

For some experiments, it was also observed the presence of dimethyl isomannide and dimethyl isidide possibly due to the epimerization reaction that occurs with the high temperature (Scheme 1.8).⁵⁸

2. SCOPE

The development of the biorefineries requires a considerable economic and scientific effort in the world of research. The goal is to produce high-quality goods and services derived from biomass, serving as excellent substitutes and/or alternatives to products traditionally developed through petroleum chemistry. The identification of D-sorbitol and its cyclic derivative, isosorbide, as bio-based platform chemicals extractable from biomass, has allowed to obtain promising applications of their industrial derivatives that find space in the field of polymers, cosmetics, but also medicine and green solvents.

Given the great interest of research in the development of solvents of renewable origin and with characteristics of low toxicity and danger, the purpose of this thesis study is focused on the synthesis of dimethyl isosorbide (DMI) from isosorbide and dimethyl carbonate (DMC) in the presence of heterogeneous catalysts such as zeolites and commercial hydrotalcite. As reported in the introductions in fact, hydrotalcite have been only preliminary investigated for this chemical transformation.

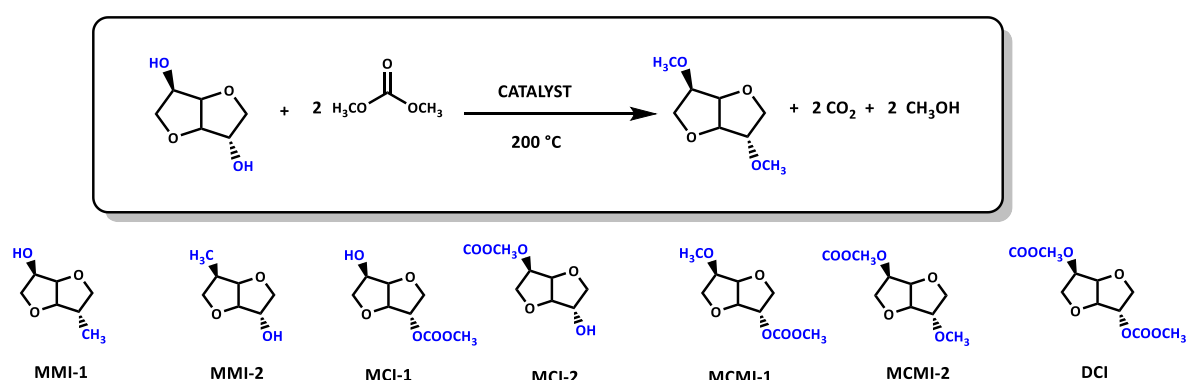
Starting from previous studies conducted mostly in the presence of a base, the objective is to identify optimal reaction conditions for achieving DMI with high selectivity starting from isosorbide. Subsequently, trials will be conducted on a larger scale, with a focus on the recovery and reuse of the catalyst. This approach aligns with the first and ninth principles of Green Chemistry, emphasizing the importance of preventing waste and designing for safer and more sustainable processes.

Finally, the new synthesis will be tested in microwave, an alternative heating method widely used in organic synthesis and recently used for the direct conversion of D-glucose to isosorbide.⁵⁷

3. RESULTS AND DISCUSSION

3.1 Methylation of DMI promoted by a heterogeneous catalyst

The synthesis of DMI has been mainly conducted under basic catalysis conditions given very good results in terms of conversion and selectivity. In the so far found best reaction conditions NMPy resulted the best performing homogeneous catalysts. However, there is a lack of an in-depth study of the methylation of isosorbide employing a heterogeneous catalyst. The only available data can be found in a paper by Aricò and co-workers from 2016, in which they test a range of catalysts including a heterogeneous one: a calcinated hydrotalcite defined as KW2000, tested in an autoclave for up to 20 hours at 200 °C (Scheme 3.1).⁵⁹ However, as above stated, these are preliminary results since reaction conditions were not optimized and the recycling of the catalyst was never addressed.



Scheme 3.1: Synthesis of dimethyl isosorbide.

Based on this information, a series of commercial hydrotalcites and zeolites were chosen to be investigated as heterogeneous catalysts that could give excellent conversion and selectivity towards DMI.

3.1.1 Distinctive traits of Zeolites and Hydrotalcites

The choice to test both hydrotalcites and zeolites comes from their extensive use in heterogeneous catalysis for various organic synthesis applications.^{60,61}

While these minerals share a commonality in their catalytic applications, they exhibit distinct characteristics, including differences in chemical formula, structure, and chemical properties.

Zeolites are aluminosilicates consisting of a tetrahedral structure of SiO_4 and AlO_4 connected by the oxygen atoms at the corners of each tetrahedron. The connection of several tetrahedra leads to the formation of sodalite units, which generate zeolites with different three-dimensional structures where cavities and empty channels, called pores, are present (Figure 3.1).⁶²

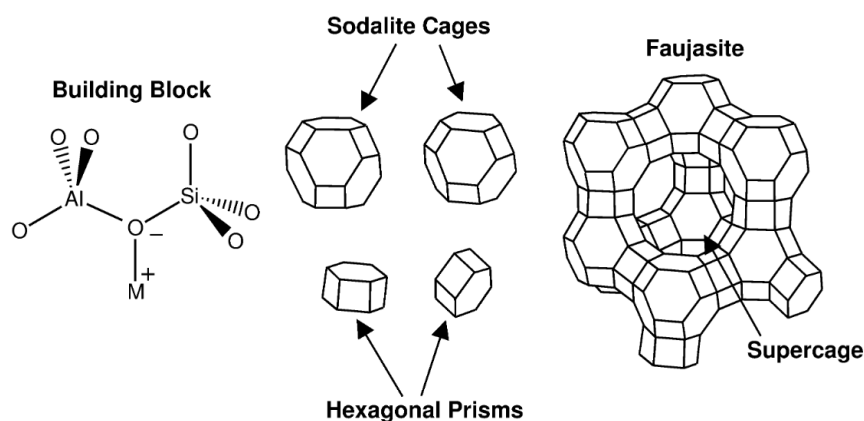


Figure 3.1: A schematic representation of a faujasite, a common zeolite, from structural formula, sodalite cages and 3D structure where is visible the pore (super cage).⁶²

Due to the presence of these internal cavities and the rigid lattice structure, zeolites can absorb molecules smaller than the actual size of the pore. The pore size varies depending on how many oxygens are involved in the formation of the cavity; the presence of eight, ten or twelve oxygens classifies the pores into micropores ($d < 2.0$ nm), mesopores (2.0 nm $< d < 50$ nm) and macropores ($d > 50$ nm), respectively. The arrangement and distribution of the pores and the presence of a defined unit cell -the sodalite unit- gives zeolites different crystal structures (Figure 3.2).^{63,64}

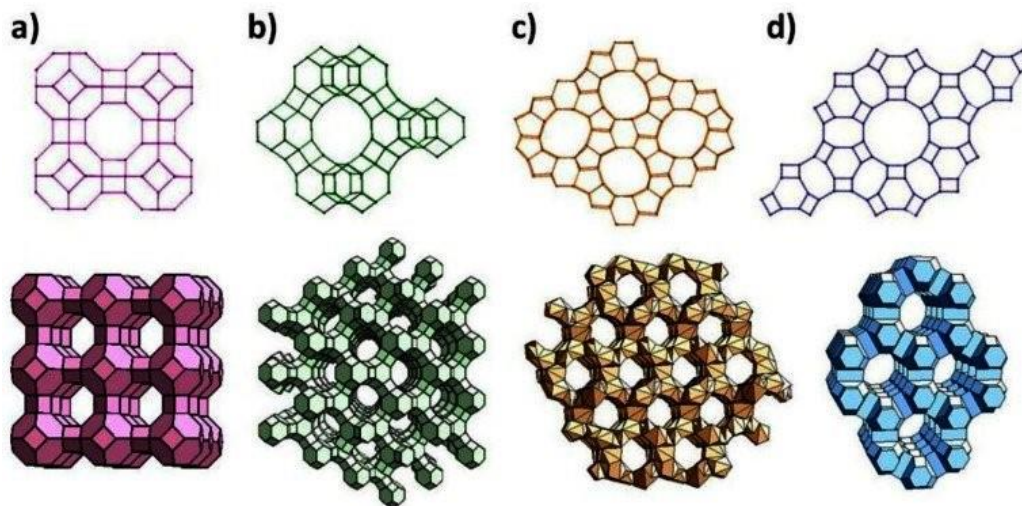


Figure 3.2: Zeolite frameworks: (a) zeolite A (3D, 4.2 Å); (b) zeolite Y (3D, 7.4 Å); (c) zeolite L (1D, 7.1 Å); (d) ZSM-5 silicalite, 2D, 5.3-5.6 Å).⁶³

However, the most important parameter that controls the catalytic properties of zeolites is the aluminium content. In fact, as suggested by their formula $M_{x/n}^{x+} [Al_x Si_y O_{2(x+y)}]^{x-} \cdot zH_2O$, the Si/Al ratio leads to different families of zeolites ranging from zeolites X where the Si/Al ratio is equal to 1 (one Al atom for every Si), to silicalites where the aluminium content is zero and the Si/Al ratio tends to infinity. This ratio is crucial when it comes to catalysis since the AlO_4 tetrahedra are negatively charged, which influences the basicity

of the zeolite. The negative charges present within zeolites is balanced by the presence of cationic counterparts in the cavities, represented by protons or metal ions. These, through ion exchange, can be easily replaced by small ions such as the quaternary ammonium ion.⁶⁰

The catalytic performance of zeolites is linked to factors such as pore width, distribution, and concentration of Brønsted and Lewis acid sites within their structure.

In order to have a reproducible reactions, zeolites employed for catalytic purposes undergo controlled synthesis via hydrothermal processes. This involves the strategic insertion of organic templating agents, facilitating modulation of pore width and channels to achieve the desired catalytic properties.

Hydrotalcites, on the other hand, are clay minerals, both of natural and artificial origin, composed of Mg^{2+} and Al^{3+} octahedra having the general formula of $[Mg_{1-x}Al_x(OH)_2]^{x+} (A^{n-})_{x/n} \cdot mH_2O$. By interconnecting these octahedra form a positively charged two-dimensional lamellar structure, derived from the structure of brucite ($Mg(OH)_2$). Stacked atop one another, these lamellar structures incorporate water molecules and anions, strategically positioned to counterbalance the positive charges within each sheet (Figure 3.3).

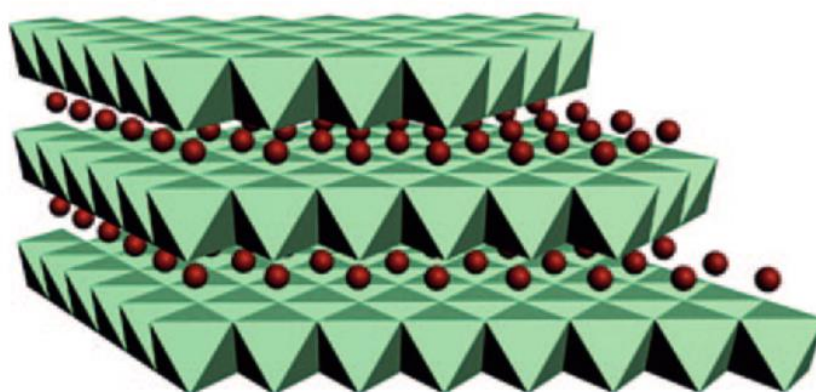


Figure 3.3: Typical structure of hydrotalcites: infinite layers of Mg and Al octahedral (in green) are interspersed with anions (in red).⁶⁵

Due to their lamellar structure and the presence of positive charges, hydrotalcites have a high water adsorption capacity. This occurs as water occupies the basic sites on the surface of each layer, effectively reducing the basic properties of the hydrotalcite. The presence of water within the layers interstices renders the catalytic activity quite inert, requiring adequate calcination. This thermal treatment decomposes the intercalary anions without exceeding the critical temperature at which phase segregation and sintering occurs.

These calcinations processes, called thermal activations, take place between 400 °C and 500 °C, and are prolonged over very long periods of time ranging from overnight to 48 h, to ensure complete dehydration and the development of well-dispersed mixed Mg(Al)O oxides on the porous surface of the hydrotalcite layers (Figure 3.4).

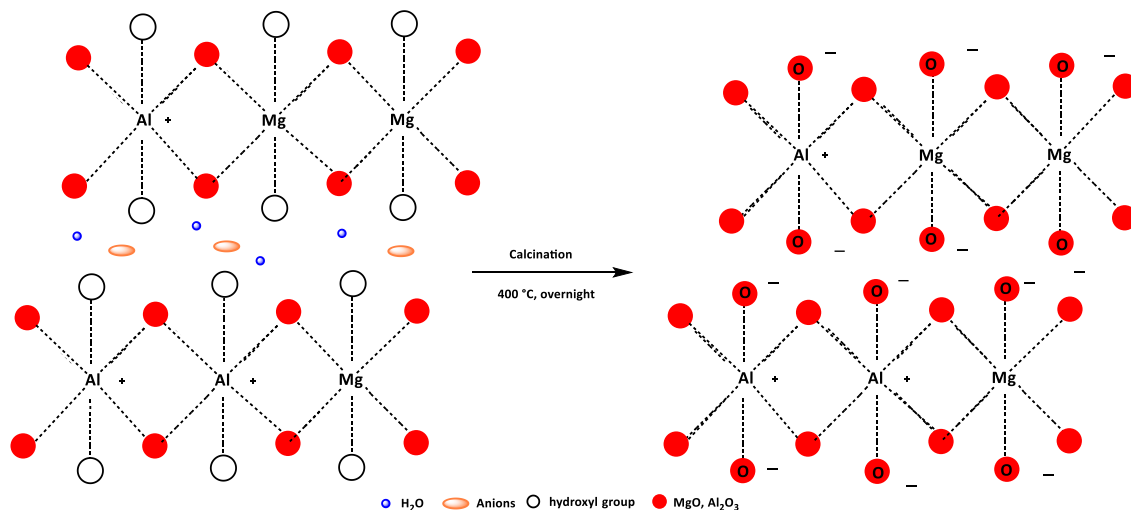


Figure 3.4: Schematic representation of the structure of hydrotalcites before and after calcination.

The formation of these oxides increases the basicity of the hydrotalcite, ensuring a higher catalytic capacity.

Through meticulous control of variables such as cation nature and distribution, counterion nature, morphology and crystal size, hydrotalcites can be tailored with specific characteristics to suit different catalytic applications.^{64–66}

3.1.2 Synthesis of DMI: catalyst screening

In a typical isosorbide methylation reaction conducted in an autoclave, various parameters such as the catalyst type and its quantity, reaction time and concentration were investigated.

The set of experiments was carried out to investigate which heterogeneous catalysts provided better selectivity towards DMI. For this purpose, various commercially employed zeolites and hydrotalcites available in the laboratory were used. Specifically, three zeolites and three hydrotalcites described below were tested (Table 3.1).

Table 3.1: Zeolites and hydrotalcites and their characteristics.

Zeolite	SiO/Al ₂ O ₃	Hydrotalcite	MgO/Al ₂ O ₃
Sodium Y Zeolite (NAY)	5.1	Hydrotalcite Kyowaad 500 (KW 500)	2.4
Ammonium Y Zeolite (AY)	5.0	Hydrotalcite Kyowaad 2000 (KW 2000)	1.8
Ultrastable Y Zeolite (USY)	30.0	Hydrotalcite HT 3 (HT3)	3.0

All reactions were carried out in an autoclave by reacting the isosorbide dissolved in dimethylcarbonate in the presence of the appropriately calcined catalyst at 400 °C for at least one night. The autoclave thus charged was placed in a heating mantle at 200 °C and maintained at autogenous pressure for 12 hours.

The need to conduct reactions in the presence of calcined catalysts is due to the ability of zeolites and hydrotalcites to be highly hygroscopic which greatly limits their catalytic activity. In fact, as seen in section 3.1.1, the presence of ions, and water molecules in the interstices and channels of zeolites, and between the layers of hydrotalcites, prevents isosorbide and DMC molecules from being adsorbed by the surface of these catalysts, limiting, or completely excluding interaction with the active site. Table 3.2 shows some examples of reactions conducted with hydrated catalysts, i.e. catalysts which have not been calcined.

Table 3.2: Reaction conducted with no calcinated catalysts.

#	Cat.	Conversion	GC-MS selectivity (%)					
			MMI-1	DMI	MMI-2	MCI 1-2	MCI 1-2	DCI
1 ^a	HT KW 500	100	0	6	0	1	68	25
2	NAY	12	0	0	0	12	0	0

Reaction conditions: isosorbide: DMC 1.0 g : 30 mL (1:50 eq. mol); isosorbide: catalyst 1:1 w/w; temperature: 200 °C; time: 12 h in autoclave.

Comparing the data in Table 3.2 with the corresponding data in Table 3.3 #2, #6 it is immediately apparent that calcination of the catalyst is mandatory to achieve DMI formation. This could be explained by the increased presence of basic sites on the surface of the hydrotalcites layers, as a result of the calcination thrust, which subtracts most of the hydroxyl groups coordinated with the metal centres of Mg²⁺ and Al³⁺, leaving only the presence of mixed oxides with high basic properties (Paragraph 3.1, Figure 3.4).

Table 3.3 shows the reactions tested with the different catalysts, all opportunely calcined in the muffle furnace before each use.

Table 3.3: catalytic activity evaluation of the different catalysts tested.

#	Cat.	GC-MS selectivity (%)							Yield (%)
		Conv.	MMI-1	DMI	MMI-2	MCI 1-2	MCMI 1-2	DCI	
1	/	65	0	0	0	64	0	1	0
2 ^a	NaY	100	4	20	1	34	13	28	13 ^b
3 ^a	AY	62	2	0	7	26	18	9	/
4 ^a	USY	100	0	49	0	43	3	5	/
5 ^{a,c}	HT KW2000	100	0	90	2	0	0	8	68 ^d
6 ^{a,c}	HT KW500	100	0	100	0	0	0	0	95 ^d
7 ^{a,c}	HT 3	100	0	98	0	0	2	0	26 ^d

Reaction conditions: isosorbide: DMC 1.0 g : 30 mL (1:50 eq. mol); isosorbide: catalyst 1:1 w/w; temperature: 200 °C; time: 12 h, in autoclave. Pressure was about 20 bar when it reached the temperature. ^a Calcinated over night. ^b Yield calculated based on selectivity at GC-MS and weight obtained from the reaction. ^c Hydrotalcites. ^d yield calculated on the reaction crude.

A preliminary test was carried out involved only isosorbide and DMC in the absence of the catalyst (Table 3.3, #1). The outcome resulted mainly in the formation of monomethoxycarbonyl derivatives (MCI 1-2), a sign that only methoxycarbonylation reactions takes place. Methylation - either via direct reaction with DMC or via decarboxylation of methoxycarbonyl derivatives – was never observed.

As for the conversion of isosorbide, this is only about 65 %, which is lower than the total conversion made by the various catalysts.

With regard to the reactions conducted in the presence of zeolites (Table 3.3, #2, #3, #4), a good result was obtained through the use of Ultrastable Y Zeolite (USY), which ensured the formation of DMI with a selectivity of 49 %, which is much higher than that of Sodium Y Zeolite, whose selectivity stopped at around 20 %. In contrast, no DMI formation was observed for Ammonium Y Zeolite.

Still looking at Table 3.2, we note that the best selectivity for DMI is guaranteed by hydrotalcites (Table 3.3, #5, #6, #7), which have guaranteed an almost total conversion of the various intermediates methoxycarbonylated and monomethylated in DMI.

Since the hydrotalcites guaranteed almost complete selectivity towards the DMI, it was possible to evaluate the yield of the reaction directly from the raw reaction. The best result of yield is that given by KW 500, which is almost quantitative, whereas in the case of KW 2000 and HT 3, the yield drops to 65 % and 26 % respectively.

This loss in yields of KW 2000 and HT 3, is much be lower than expected. In fact, once the reaction has taken place, it involves a simple filtration on paper to separate the compound from the rest of the catalyst. The absence of complex synthetic or purification procedures should guarantee an almost quantitative yield of the reaction, which was not observed with the reactions that gave only DMI as the final product. This considerable loss of yield could be explained by the ability of the catalyst to retain the

product within its cavities or layers.

From these initial experiments, out of the catalyst tested, HT KW 500 and HT KW 2000 and USY proved to be the best in converting isosorbide to DMI. As for HT 3, despite the high selectivity, it was decided not to pursue this catalyst due to the low yield obtained respect to the other hydrotalcites.

3.1.3 Optimization synthesis of DMI: catalyst screening: amount of catalyst

Once the screening of the catalysts was completed, the experiments continued by varying the amount of the catalyst within the reaction (Table 3.4)

Table 3.4: Optimisation of dimethyl isosorbide: amount of catalyst.

#	Cat.	Quantity (% wt)	GC-MS Selectivity (%)							Yield (%)
			Conversion	MMI-1	DMI	MMI-2	MCI 1- 2	MCMI 1-2	DCI	
1 ^a	KW2000	50	100	2	36	6	0	55	1	/
2 ^a	KW500	50	100	0	100	0	0	0	0	63 ^b
3 ^a	USY	50	46	6	4	8	14	12	2	/
4 ^a	KW2000	25	98	0	0	1	16	17	64	/
5 ^a	KW500	25	98	1	4	3	13	38	39	/
6 ^a	KW500	10	98	0	0	1	17	23	57	/
7 ^{a,b}	KW500	5	100	0	2	0	1	5	88	/

Reaction conditions: isosorbide: DMC 1.0 g : 30 mL -1:50 eq. mol-; isosorbide: catalyst 1:0.5, 0.25, 0.1, 0.05 w/w; temperature: 200 °C; time: 12 h, in autoclave. Pressure was about 20 bar when it reached the temperature. ^a Calcinated over night. ^b Yield calculated on the reaction crude ^c Presence of unidentified compounds: 4 % .

The minimum amount of catalyst to be included in the reaction was tested on the two hydrotalcites and one zeolite that gave the best results in the first screening approach. Specifically, KW 2000 and KW 500 and USY were tested by reducing the isosorbide/catalyst (w/w) ratio by half, thus working with 50 % wt respect the isosorbide amount. Subsequent tests were carried out by further reducing the amount of catalyst to 25 % by weight, 10 % by weight and 5 % by weight in comparison with isosorbide.

As can be seen from Table 3.4, in first trials conducted with 50 % wt, the hydrotalcites turned out to be the better catalysts compared to the zeolite USY, in terms of conversion and selectivity. In fact, the conversion of zeolite USY was not as quantitative as in the case of the other two hydrotalcites, but stopped at just 46 %, affecting the final selectivity at only 4 % of DMI.

Working with a halved amount of catalyst, it is immediately denoted that KW 500 is better as it always guarantees a full conversion of isosorbide, ensuring the exclusive formation of DMI, contrary to what is observed for KW 2000: selectivity only stops at 36 %.

Lowering the amount of catalyst by beyond 50 % wt did not yield the desired results: DMI is obtained as traces within the mixture, while methoxycarbonylated compounds (MCI, MCMI, DCI) increases significantly as the amount of catalyst is lowered. This fact can be justified by considering how a smaller

quantity of catalyst is more dispersed within the reaction volume, preventing the interaction of the various intermediates necessary to form DMI. The presence of intermediates such as monomethoxycarbonyl derivatives (MCI 1-2), monomethoxycarbonyl methyl derivatives (MCMI 1-2) and dimethoxycarbonyl derivatives (DCI) shows, once again, that DCI is in equilibrium with the MCI 1-2 intermediates. The reduction of the catalyst prevents DCI from converting, first to MCMI 1-2 and then to DMI, through a double methylation via B_{Al}2 and double decarboxylation. In fact, still following Table 3.4, as the catalyst weight decreases, a lower presence of MCMI compound is observed, a sign that the above reactions fail to take place.

3.1.4 Optimization synthesis of DMI: catalyst screening: reaction time

As illustrated in Table 3.4 entry #2, maintaining the reaction at 200 °C for 12 hours with 50 % wt of KW 500 as the catalyst resulted in the complete conversion of isosorbide into DMI. But what happens to the selectivity of the reaction if the reaction time is reduced? The following set of experiments is aimed at investigating the ability of the catalyst to achieve the desired product while reducing the reaction time, in order to find the right compromise between the greater amount of DMI obtained and the minimum heating time. (Table 3.5).

Table 3.5: Optimisation of dimethyl isosorbide synthesis with KW 500: reaction time.

#	Time (h)	GC-MS selectivity (%)							Yield (%)
		Conversion	MMI-1	DMI	MMI-2	MCI 1-2	MCMI 1-2	DCI	
1 ^a	12	100	0	100	0	0	0	0	63 ^b
2 ^a	8	100	0	100	0	0	0	0	80 ^b
3 ^a	6	100	0	100	0	0	0	0	85 ^b
4 ^a	4	100	0	100	0	0	0	0	81 ^b
5 ^a	2	84	1	3	2	26	23	29	/

Reaction conditions: isosorbide: DMC 1.0 g : 30 mL (1:50 eq. mol); isosorbide: KW 500 1:0.5 w/w; temperature: 200 °C; in autoclave. Pressure was about 20 bar when it reached the temperature. ^a Calcinated over night. ^b Yield calculated on the reaction crude.

By lowering the reaction time from 12 to 4 hours, the reaction between isosorbide and DMC proceeded uniquely, ensuring full selectivity towards the target molecule, as seen on GC-MS analysis. Times of less than 4 hours do not guarantee complete conversion of the starting reagent, which then affects the result of the reaction.

Another consideration that can be extrapolated from these data concerns the yield. As mentioned above, despite the few synthetic steps and the absence of purification procedures, the yields are not quantitative. In fact, compared with the reactions carried out with KW 500 at 100 wt %. (Table 3.2 # 6) where the yield was 95 %, those conducted with 50 % wt reported slightly lower yields, varying from 63 %

to a maximum of 85 %. This could again be explained by the ability of the catalyst to adsorb DMI and/or the other intermediates. For example, reactions conducted for 12 hours were set in the evening and treated the following morning, leaving the reacted mixture in the presence of the catalyst for a few hours, which had the necessary time to adsorb DMI into it, limiting the yield. In fact, the 8-, 6- and 4-hour reactions were conducted on the same day, filtering the catalyst from the rest of the mixture as soon as the reaction cooled down. This most likely prevented the catalyst from adsorbing product, limiting the loss of yield.

An attempt was made to recover the adsorbed product by washing the KW 500 with hot methanol. The purpose of the methanol is to dissolve any DMI present in the catalyst, making it possible to quantify the amount of average yield loss, and to have a KW 500 cleaner of organic compounds before calcination in the muffle furnace. This step, however, did not allow an efficient filtration of the catalyst, and the filtrate (methanol plus possible reaction products) is rather cloudy and milky even after several filtration, making it impossible to assess the amount of products adsorbed by the solid support.

3.1.5 Optimization synthesis of DMI: catalyst screening: concentration

Confirmed that the minimum reaction time is 4 hours, the role of the concentration in the reaction outcome was subsequently evaluated (Table 3.6).

Table 3.6: Optimisation of dimethyl isosorbide synthesis with KW 500: concentration.

#	Ratio isosorbide:DMC (eq. mol.)	Isosorbide (g)	GC-MS selectivity (%)							Yield (%)
			Conversion	MMI-1	DMI	MMI-2	MCI 1-2	MCMI 1-2	DCI	
1 ^a	1:50	1	100	0	100	0	0	0	0	81 ^b
2 ^a	1:25	2	100	0	100	0	0	0	0	78 ^b
3 ^a	1:16	3	100	0	84	0	0	16	0	/
4 ^a	1:10	5	94	6	3	7	15	42	21	/

Reaction conditions: quantity of DMC fixed at 30 mL, isosorbide: KW 500 1:0.5 w/w; temperature: 200 °C; time reaction 4 h in autoclave. Pressure was about 20 bar when it reached the temperature. ^a Calcinated over night. ^b Yield calculated on the reaction crude.

To facilitate the experimental process, the set of experiments reported in Table 3.6 was conducted by maintaining a constant volume of DMC while adjusting the quantity of isosorbide based on the selected ratio.

Reactions carried out up to concentrations of 1:25 are still an excellent compromise between the amount of isosorbide reacted and the selectivity for DMI.

However, from the data collected, it appears that the selectivity of DMI worsens as the concentration increases, while the fraction of methoxycarboxylated compounds such as MCI, MCMI and DCI increases.

In fact, reactions conducted at higher concentration, 1:16 eq. mol and 1.10 eq. mol. (Table 3.5, #3, #4), denote a marked decrease in the dimethyl fraction resulting in an increase in methoxycarbonylated intermediates.

A hypothesis that can be advanced for these results could be attributed to the elevated concentration of methanol in reactions carried out at lower dilution. According with the Figure 1.18 (Paragraph 1.5.3), the isosorbide, in addition to directly yielding monomethoxylated products, can undergo mono- and dimethoxycarbonylation reactions that generate one and two moles of methanol, respectively, as a reaction by-product. Since DMC works both as a solvent and as a reagent, it is consumed during the course of the reaction in the same amount of moles of methanol that are formed, effectively increasing the concentration of the reaction. The increase in the concentration of the reaction due to the lower amount of DMC, and the high presence of methanol, locks the reaction into a series of equilibria between mono- and dimethoxycarbonylated products, limiting the formation of methylated products such as DMI, as observed for reactions #3 and # 4 Table 3.6.

3.1.6 Optimization synthesis of DMI: catalyst screening: scale-up

Since the set of experiments maintained a very good conversion of the reagent into DMI, the reactions conducted from here on will be carried out on a larger scale, to see whether the optimized parameter conditions found may also be optimal for a higher quantity of isosorbide.

Table 3.7: Optimisation of dimethyl isosorbide synthesis with KW 500: scale-up.

#	Time (h)	GC-MS selectivity (%)						
		Conversion	MMI-1	DMI	MMI-2	MCI 1-2	MCMI 1-2	DCI
1 ^a	4	97	5	7	5	14	39	27
2 ^a	6	100	8	20	10	2	56	3
3 ^a	12	100	7	32	11	0	0	50
4 ^{a,b}	18	100	4	43	9	0	39	1

Reaction conditions: Isosorbide: DMC 1:25 eq. mol.; isosorbide: 5.0 g; isosorbide: KW 500 1:0.5 w/w; temperature: 200 °C in autoclave. Pressure was about 20 bar when it reached the temperature. ^a Calcinated over night. ^b Presence of unidentified compounds: 3 %.

Not to exceed the capacity and the pressure seal of the autoclaves, the reactions shown in Table 3.7 were carried out with 5.0 g isosorbide.

As expected, 4 hours of reaction time is not sufficient to complete the reaction on a large scale. This is most likely due to the stirring by the magnetic stirrer, which struggles to maintain uniform stirring over the entire mass of reactants placed in the autoclave. Compared with smaller-scale reactions, those conducted on 5 g of isosorbide not only have a larger volume of solvent, but also a fair amount of catalyst is present, which can create local thickening of the reacting mass, reducing those reactions useful for the formation of the desired product. In addition, the presence of 50 % wt of catalyst with respect to

isosorbide appears to be another limiting factor. The meeting between the isosorbide molecules and the catalyst itself seems to be limited by the volume of the reaction which is much greater than in reactions conducted on a smaller scale. In fact, running the same reaction for longer periods of time, 6-, 12- and 18 hours, one notices that the percentage of DMI increases discretely, while the mono- and dimethoxycarboxylated component tends to be less and less, a sign of conversion to DMI. After 18 hours of reaction, in addition to not having a significant amount of DMI (43 %), GC-MS analysis revealed the presence of other unidentified peaks, a sign of a possible decomposition of some product or the presence of secondary reactions taking place over prolonged reaction times.

On a larger scale, it is clear that the amount of catalyst and the time reaction affects the outcome of the presence of DMI. So in order to improve presence of DMI on the reaction, some tests were carried out keeping the amount of catalyst by weight equal to that of the isosorbide reagent (Table 3.8).

Table 3.8: Optimisation of dimethyl isosorbide synthesis reaction with KW 500: scale-up.

#	Time (h)	GC-MS selectivity (%)						
		Conversion	MMI-1	DMI	MMI-2	MCI 1-2	MCMI 1-2	DCI
1 ^a	4	100	6	45	11	0	38	0
2 ^a	6	100	2	66	7	0	25	0
3 ^{a,b}	8	100	0	86	7	0	11	0

Reaction conditions: Isosorbide: DMC 1:25 eq. mol.; isosorbide: 5.0 g; isosorbide: KW 500 1:1 w/w; temperature: 200 °C in autoclave. Pressure was about 20 bar when it reached the temperature. ^a Calcinated over night. ^b Solvent was completely consumed.

In this second set of experiments carried out on 5.0 g of isosorbide, it is clear that only after 4 hours of reaction (Table 3.8, # 1), the reaction ensured the presence of 45 % DMI, which compares significantly with the reaction carried out for 18 hours with 50 % wt of catalyst (Table 3.7, # 4). Both reactions show comparable redistribution of the various intermediates, an indication that the lower amount of catalyst requires a necessary increase in reaction time.

Despite the good results that can be obtained with reactions conducted with catalyst quantities equal to the amount of reactant, experiments performed for times longer than 4 hours have presented a number of difficulties. For example, reaction #2 in Table 3.8, conducted for 6 hours found a reduction in the volume of solvent present in the autoclave with a total loss of 70 %. Implemented the reaction time for 8 hours (Table 3.8, # 3) on the other hand, the solvent loss was total, despite numerous trials, and the absence of leakage from the autoclave used.

This unusual consumption of solvent occurred several times in the course of the experiments conducted for this thesis work, leading the reactions to complete drying out in the most extreme cases, or to a partial loss of solvent that was far from predictable and/or limitable.

In fact, the phenomenon is due to the ability of hydrotalcite to decarboxylate dimethyl carbonate into CO₂

and dimethylether (Me₂O), which together with methanol and the CO₂ of direct formation of the various intermediates generates overpressures of up to 80-90 bar on the scale-up reactions.

The unusual ability of hydrotalcite to decarboxylate the solvent appears to occur in a totally random manner, although the trend to this event was mainly observed in the reactions reported in Table 3.8.

An explanation of why this problem occurs was reported in an article by Selva and co-workers in 2010.⁶⁷

The authors, in fact, sought to understand what variables induced the decarboxylation of the DACs, but in general DMC, in the presence of heterogeneous catalysts, such as zeolites and a hydrotalcite: KW 2000. Firstly, the role of temperature in the decarboxylation of DMC was evaluated. Experiments conducted at different temperatures on KW 2000 hydrotalcites showed that the decarboxylation of DMC is all the more pronounced for temperatures ranging from 150-240 °C, temperatures at which the methylation reaction also takes place. The amount of catalyst is also crucial in the development of this parasitic reaction, an effect observed in most of the reactions in Table 3.8.

Another key factor for solvent decarboxylation appears to be the more or less basic character of the hydrotalcites. The authors point out that basic zeolites have a greater tendency to generate decarboxylation phenomena of DACs. As shown in Figure 3.4 in section 3.2.1, the hydrotalcites, once calcined, present a high presence of mixed magnesium and aluminium oxides, which give the catalyst pronounced basic properties. This could in fact ensure the decarboxylation of dimethyl carbonate, according to a scheme shown below (Figure 3.5).

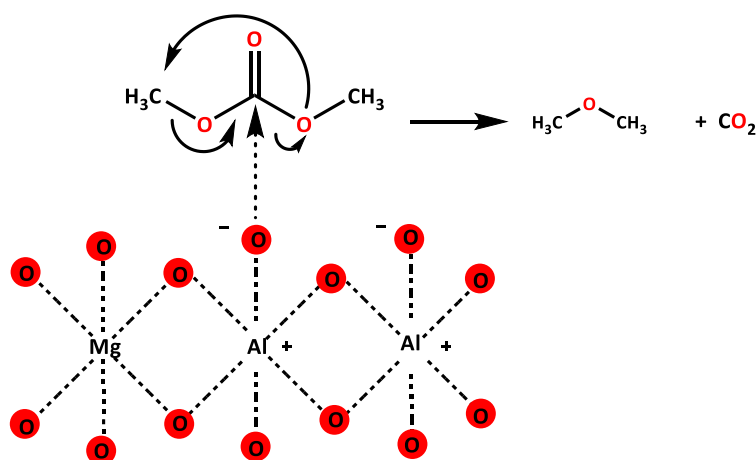


Figure 3.5: Representation of a possible decarboxylation mechanism.

Due to the presence of oxygens on the surface of the hydrotalcite, these can coordinate with the carbonyl carbon of the DMC, bringing increased electron density. Increased charge would loosen the O=C=O bond, releasing a methoxide (⁻OCH₃) group. The latter, recombining with the methoxy group (⁺CH₃) to form dimethyl ether and CO₂. This mechanism may help in interpreting the presence of high pressures during the course of the reaction, however, it is not yet clear how to limit the extent of this problem to avoid unnecessary solvent consumption.

In view of the difficulty of understanding how the various intermediates redistribute in the 8-hour

reaction without the total loss of solvent, it was decided to conduct the catalyst recovery reactions at a temperature of 200 °C for 6 hours in total. Compared with the 4-hour reaction only, the 6-hour reaction gives the reaction a better conversion of the methoxycarboxylate products into the desired final product without having given the total loss of DMI.

Since washing the KW 500 with methanol prevents proper filtration, direct calcination of the hydrotalcite used was chosen to limit the steps.

Once the reaction is complete, the catalyst is filtered on bukner and filter paper, and then placed directly in the muffle furnace for calcination once dry. Calcination overnight at 400 °C seems to be the best solution to restore KW 500. In fact, after the first calcination, only a whitening of the catalyst, a sign of the decomposition of the adsorbed organic compounds, can be seen.

Table 3.9: Optimisation of dimethyl isosorbide synthesis reaction with KW 500 (100 % wt): catalyst recovery.

#	Recovery (#)	Conversion	GC-MS selectivity (%)					DCI
			MMI-1	DMI	MMI-2	MCI 1-2	MCMI 1-2	
1 ^a	1	100	1	76	5	0	18	0
2 ^{a,b}	2	100	0	79	3	0	10	0
3 ^a	3	100	1	87	3	0	9	0

Reaction conditions: Isosorbide: DMC 1:25 eq. mol.; isosorbide: 5 g; isosorbide: KW 500 1:1 w/w; temperature: 200 °C for 6 h in autoclave. Pressure was about 20 bar bar when it reached the temperature. ^aCalcinated over night. ^b presence of unidentified peaks: 8 %.

The recovery of hydrotalcites KW 500 and its re-use after calcination appears to maintain its catalytic capabilities. After three recoveries (4 uses), the selectivity towards DMI remains almost constant as does the remaining composition of the resulting mixture. However, it should be noted that in reaction #2 Table 3.9 the presence of humins (8 %) was detected at GC-MS. The presence of these compounds is probably due to organic residues that did not have time or opportunity to degrade completely during the recalcination step. This could explain the lower amount of crude obtained for the reactions conducted in Table 3.9 and confirm the ability of the KW 500 to retain the reaction products.

The maintenance of catalytic activity over several cycles could be explained by the structure of the hydrotalcite itself. In fact, unlike the structure of zeolites, hydrotalcites do not have a three-dimensional closed-cage structure, but consist of several open layers placed on top of each other (section 3.1.1). Being surfaces arranged in planes, hydrotalcites do not need to maintain specific shapes or cavities for catalytic activity. The two-dimensional plane surface allows them to perform their function directly on one face of the layer, which is less prone to losing its original structure and chemical composition, even over several reactive cycles and after several passes through the muffle furnace.

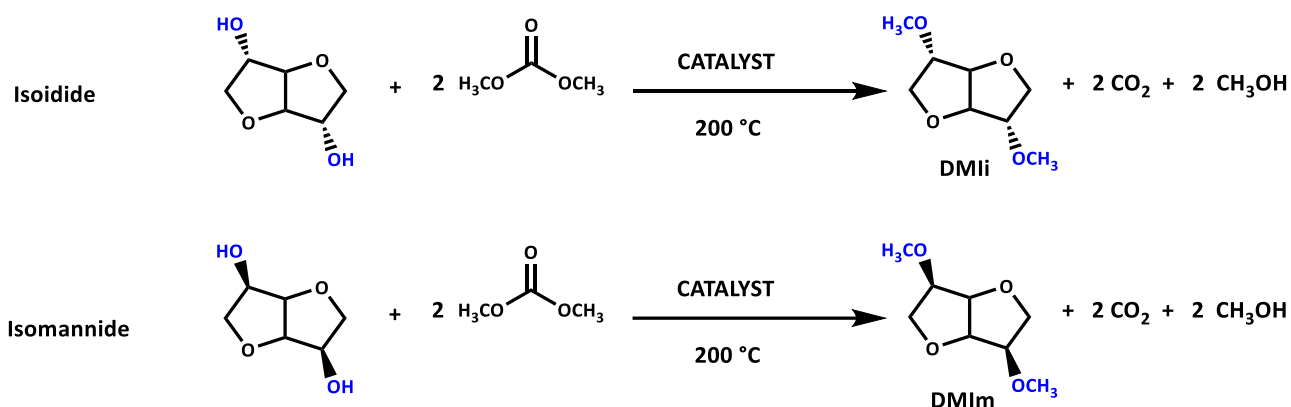
3.1.7 Synthesis of dimethyl isoidide (DMli) and dimethyl isomannide (DMIm)

The two isosorbide epimers, isomannide and isoidide, exhibit different reactivities due to the different orientation of the hydroxyl groups. In fact, the overall reactivity of the three isomers towards a generic methylation reaction with DMC is as follows:



This reactivity actually places isomannide as the epimer most reactive to methylation but least prone to undergo methoxycarbonylation, this being because its two hydroxyls are both in the endo position, a position with greater steric hindrances than the isoidide epimer. The methylation reactions of the two epimers using DMC chemistry is aimed here at assessing whether this reactivity is maintained even in the presence of heterogeneous catalysis, to confirm the proposed theory.

The methylation reactions of the two isoidide and isomannide epimers (Scheme 3.2) were carried out using the best reaction conditions used for Table 3.4.



Scheme 3.2: Reaction synthesis for isoidide and isomannide epimers.

10: Synthesis of dimethyl isoidide and dimethyl isomannide via heterogeneous catalysis.

#	Epimer	GC-MS selectivity (%)							
		Conversion	MMI-1	DMI	MMI-2	MCI 1-2	MCMI-1	MCMI-2	DCI
1 ^a	Isosorbide	100	6	45	11	0	38	0	0
				DMli	MMli 1-2	MClI 1-2	MCMIi 1-2		DCIi
2 ^a	Isoidide	100		49	8	1	42		0
				DMIm	MMIm 1-2	MClIm 1-2	MCMIIm 1-2		DCIm
3 ^a	Isomannide	100		15	41	1	42		1

Reaction conditions: isosorbide: DMC 1.0 g : 30 mL (1:50 eq. mol); isosorbide: KW 500 1:0.5 w/w; temperature: 200 °C; for 4 h in autoclave. Pressure was about 20 bar when it reached the temperature. ^a Calcinated over night.

As can be seen from Table 3.10, #1, there is a greater presence of the MCMI-1 derivative (methoxycarbonyl group in the exo position) than the MCMI-2 derivative (methoxycarbonyl group in the

endo position) of the isosorbide. In fact, the hydroxyl in the exo-position is much less cluttered than the hydroxyl in the endo-position, which favours fast methoxycarbonylation. Methoxycarbonylation on the three epimers, therefore, should proceed in the opposite manner to methylation, effectively making the isoidide more reactive than the isomannide. However, from Table 3.10, for both epimers, the amounts of MCMli and MCMIm are preponderant, but the content of DMli and DMIm changes markedly.

Consider the reaction with the isoidide (Table 3.10, #2). This reaction has a discrete presence of compounds such as DMli (49 %) and MCMli (42 %) while the monomethyl component is very low (8 %). In fact, the isoidide has both hydroxyl groups in the exo position, less sterically encumbered positions that are more likely to undergo both mono- and dimethoxycarbonylation than the direct methylation reaction. The formation of MCl_i and DCli then allow the isoidide to decarboxylate faster, leading the reaction towards the formation of MCMli and subsequently DMli.

On the other hand, in the reaction with isomannide, the presence of monomethylated compounds is high, a sign of direct methylation by endo hydroxyl groups, which is always more likely to occur than the OH group in the exo position, as described above.

However, the high presence of MCMIm compounds in the reaction with isomannide, could be explained by the inability of this of the intermediate to come out of equilibrium with the monomethoxide derivative (MMIm). This could be explained by the inability of the carboxylate group to remain attached to the isomannide structure because it is too cluttered. The equilibrium appears to be equally divided between MMli and MCMli and this could prevent the decarboxylation of the methoxycarbonyl group and the formation of DMIm.

3.2 Microwave Synthesis of DMI

3.2.1 Versatility and applications of Microwaves

As previously discussed, Green Chemistry extends beyond seeking alternative syntheses or environmentally friendly molecules, but also places significant emphasis on minimizing raw material and energy consumption, aligning with the sixth Principle of Green Chemistry. For the synthesis of DMI, an initial consideration involved exploring the use of microwave irradiation.

The heating of a reaction by microwave irradiation is an increasingly explored aspect in Green Chemistry. In comparison to conventional heating methods, microwave irradiation offers the advantage of significantly reducing reaction times, thanks to the capability of electromagnetic waves to directly couple with reactive molecules bypassing thermal conduction. Microwaves have a low energy content and their frequency range between 300 GHz and 300 MHz, and this particular property allows to transfer the heat through thermal radiation that propagates in space by heating the solution directly from the inside to the outside, contrary to what happens in traditional heating (Figure 3.6) ^{68,69}

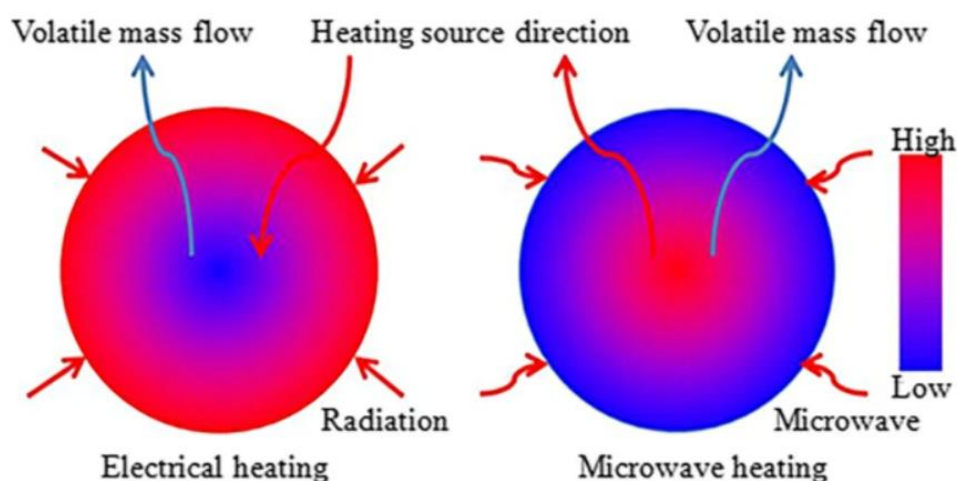


Figure 3.6: Schematical representation of temperature in conventional heating and microwave heating.⁶⁹

This radiative heating phenomenon is also called dielectric heating and it comes from the alignment of molecules with a permanent dipole when subjected to an oscillating electric field E , causing them to orient in accordance with the polarity of the applied field. The continuous change of orientation of the dipole makes the molecules rotate, which tend to collide with each other generating heat, this phenomenon is not observed in molecules that do not have electric dipoles. The capacity to generate heat is particularly pronounced with an increase in the dielectric loss ($\tan \epsilon''$), or the capacity of a molecule -in this case the solvent- to dissipate a certain amount of incoming MW in the form of heat and thus to reach the desired temperature faster.

As shown in Table 3.11, solvents are classified into high ($49.9\text{-}14.6 \epsilon''$), medium ($9.9\text{-}1.1 \epsilon''$), and low ($0.4\text{-}0.04 \epsilon''$) dielectric loss. Often, solvents that exhibit a high dielectric constant (ϵ), therefore a high polarity,

are not always optimal for performing microwave reactions. The most common case concerns water which despite having the highest dielectric constant (80.4 ϵ), is considered as a medium absorber (9.8 ϵ'').⁶⁸

Table 3.11: Dielectric constant and dielectric loss of common solvents.

Solvent	Dielectric constant (ϵ)	High Dielectric Loss (ϵ'')
Ethylene Glycol	37.0	49.9
DMSO	45.0	37.1
Methanol	32.6	21.5
2-Propanol	18.3	14.6
Solvent	Dielectric constant (ϵ)	Medium Dielectric Loss (ϵ'')
Water	80.4	9.9
DMF	37.7	6.1
Acetone	20.7	1.1
Acid Acetic	6.2	1.1
Solvent	Dielectric constant (ϵ)	Lower Dielectric Loss (ϵ'')
Chloroform	4.8	0.4
Dichloromethane	9.1	0.4
Ethyl Acetate	6.0	0.3
Hexane	1.9	0.04

The poor ability of some solvents to not fully absorb radiation at MW, and the poor homogeneity of the solution can, in some cases, lead to the formation of Hotspot phenomena. As reported in Figure 3.7, these hotspots are nothing more than points where radiation at MW are concentrated, generating locally superheating phenomena. This high temperature gradient between a not fully homogeneous zone and the remaining mass leads the solvent to be in the metastable phase, that is, a phase in which the solvent, being at a much higher temperature than the boiling temperature, It can easily explode when stressed.^{68,70}

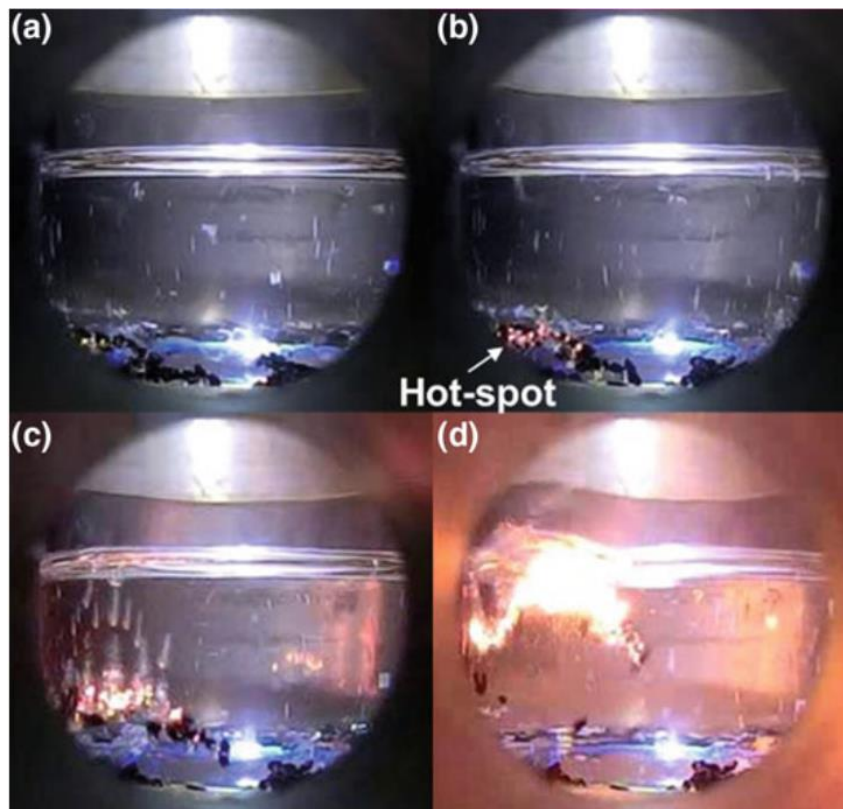


Figure 3.7: Formation of Hotspot with final arc discharge under microwave irradiation.⁶⁸

3.1.2: DMI synthesis in microwave

Given the interesting properties of MW radiation in heating up chemical reactions in a short time, we proceeded to carry out the methylation reaction of isosorbide to DMI by applying the best performing conditions developed for the autoclave.

However, during the investigation phase, the microwave instrument used, a Milestone's Ethos Up, reported some problems that prevented a consistent research activity from being carried out. The tables reported in this section summarise all the experiments tested, highlighting the criticalities that incurred.

The instrument, which dispenses a maximum power of 1900 W, allows to set a temperature and time ramp, and to modify the speed of magnetic stirring. A typical reaction was conducted in a synthesis apparatus consisting of a quartz glassware, in which a magnetic stirrer and a special black disc were placed. Once the glassware has been loaded with the reagents, it is then placed and enclosed in the outer polyetheretherketone (PEEK) tube, which is positioned in a Teflon liner and finally placed inside the MW (Figure 3.8).



Figure 3.8: (Left) glassware in quartz filled with reagents and equipped with magnetic stirrer and black disk; (Centre) tube in PEEK; (Right) Teflon insert charged with tube PEEK and glassware closed with the appropriate cap.

PEEK and Teflon are materials that are totally transparent to microwaves and do not interfere with the heating of the reaction. In contrast, the presence of the special black disc helps to have a more homogeneous absorption of MW within the sample, avoiding the hot-spot phenomena that can occur when a solvent does not absorb microwave radiation well. In fact, reactions are carried out using DMC as a solvent, which does not have a high dielectric loss, and this makes it more difficult to absorb radiation and to bring the reaction to temperature.

It is difficult to find the dielectric loss value of DMC in the literature, but it is possible to derive it roughly by comparing its dielectric constant with that of solvents in which both ϵ' and ϵ'' are known. The dielectric constant of DMC is around 3.2×10^{-7} , an intermediate value between chloroform (4.8) and chlorobenzene (2.6), whose dielectric losses are 0.4×10^{-7} and 0.3×10^{-7} respectively, values which ascribe these three solvents as poor MW absorbers. With these considerations in mind, the first experiments were carried out on a small scale using NMPy as catalyst, keeping the proportions unchanged (isosorbide: DCM 1:50, NMPy 0.5 eq. mol). This first set of experiments was carried out to become familiar with the instrument and to find the right conditions of temperature, wattage, and time to obtain DMI with good yield.

Since a desired power can be set with the microwave, we wanted to investigate the wattage effects on the yield of the reaction. Reported in Table 3.12, we show the effect of different powers while keeping the reaction time fixed at only 15 minutes in order not to risk straining the instrument.

Table 3.12: Reaction conducted with microwave heating: change in wattage.

#	Watt (W)	GC-MS selectivity (%)							Yield (%) ^a
		Conv. (%)	MMI-1	DMI	MMI-2	MCI 1-2	MCM1 1-2	DCI	
1	400	61	22	3	21	3	12	0	1
2	800	>99	2	2	1	14	35	46	2
3	1000	>99	3	4	2	10	53	27	4
4	1400	>99	9	13	6	14	51	7	13

Reaction conditions: isosorbide: DMC 0.2 g : 7 mL -1:50 eq. mol-; isosorbide: NMPy 1:0.5 eq. mol; temperature: 200 °C; time: 15 minutes. (^a) Yield calculated based on selectivity and weight obtained from the reaction.

From a first observation, it seems that the more the power supplied increases, the more the selectivity towards the DMI increases, but only at high wattage can the increase in selectivity be appreciated. The higher the power supplied, the faster the reaction reaches the temperature at which the catalyst, in this case NMPy, can best perform its function, namely the double methylation of the isosorbide. Working with wattages below 1400 W (Table 3.12, #1, #2, #3), the selectivity does not undergo an appreciable change, probably due to the small amount of time given to the reaction, which takes longer to convert the reagent into the desired product. This consideration could also explain the incomplete conversion of the reagent of the reaction performed at 400 W.

As time is another factor influencing the outcome of the reaction, a series of tests were carried out to increase the reaction time, while maintaining a medium to high wattage to ensure rapid conversion of the reagent to DMI. Table 3.13 shows the results obtained.

Table 3.13: Reaction conducted with microwave heating: change in time.

#	Time (min)	GC-MS selectivity (%)							Yield (%) ^a
		Conv. (%)	MMI-1	DMI	MMI-2	MCI 1-2	MCM1 1-2	DCI	
1	30	>99	6	21	4	4	60	4	5
2	60	98	10	28	4	2	52	2	8
3	90	98	7	54	3	0	33	1	12

Reaction conditions: isosorbide: DMC 0.2g : 7 mL -1:50 eq. mol-; isosorbide: NMPy 1:0.5 eq. mol; temperature: 200 °C; wattage 1200 W. (^a) Yield calculated on the basis of selectivity and weight obtained from the reaction.

Once again, the data obtained show a correlation between time and the presence of DMI. However, experiments beyond 90 minutes could not be carried out due to problems with the stability of the power supplied. The use of high wattages and prolonged reaction times lead to instability in the temperature reading, limiting the acquisition of data needed for optimizing the MW reaction.

Therefore, in order to avoid a power overload, it was decided to set the instrument to milder powers and temperatures, specifically 800 W and 180 °C, to ensure an ideal time for increasing the yield of DMI.

Driven by the interest to understand whether the reaction between isosorbide and DMC in the presence of heterogeneous catalyst also occurred under MW heating, a series of syntheses were conducted using KW 500 hydrotalcite. These experiments were conducted under the optimal conditions previously identified for autoclave synthesis (Table 3.14).

Once the reaction was finished and the quartz vessel had cooled down, the resulting mixture was filtered through a paper filter, washed with the minimum volume of DMC, and after the solvent removal by vacuum, the vial was prepared for GC-MS analysis.

Table 3.14: Amount of DMI during the time in MW.

#	Time (min)	Conv. (%)	GC-MS selectivity (%)						Yield (%) ^a
			MMI-1	DMI	MMI-2	MCI 1-2	MCMI 1-2	DCI	
1	30	>99	2	8	3	5	37	44	1
2	45	>99	8	30	5	0	0	56	2
3 ^b	60	>99	0	0	0	14	10	48	0

Reaction conditions: isosorbide: DMC 0.2 g : 7 mL -1:50 eq. mol-; isosorbide: KW 500 1:0.5 eq, mol; temperature: 180 °C; wattage 800 W. (^a) Yield calculated on the basis of selectivity and weight obtained from the reaction. (^b) presence of unidentified peaks.

As indicated in Table 3.14, it is evident that, despite employing lower wattages and temperatures compared to those applied in the autoclave, reactions persisted beyond 45 minutes of heating without reaching completion. As early as one hour into the reaction, the instrument detected signs of instability in the supplied wattage and consequently in the temperature reading, halting the conduct of the experiment.

One of the tests that showed signs of problems in maintaining the set temperature was the reaction conducted for 60 minutes (Table 3.14 # 3), which gave results that were not very consistent with the remaining data in the same table. In fact, again on GC-MS analysis of this test, the presence of other unidentified compound peaks was noted, probably from products that had undergone degradative phenomena, or secondary reactions, due to the uncontrolled temperature changes.

Another fact that we want to highlight about these microwave-conducted tests is the low reproducibility of the experiments in the presence of the heterogeneous catalyst KW 500.

As already mentioned in paragraph 3.1.6, the use of hydrotalcite KW 500 in autoclave leads to totally random and unpredictable solvent consumption phenomena, where in some cases the consumption was totally quantitative, driving the reaction dry and observing high overpressures.

This phenomenon could also be seen with MW heating, especially when the reaction was prolonged in time. Very often, in fact, the solvent content within the quartz vessel was much less than expected or even completely absent. As previously stated, the total consumption of solvent from the reaction environment induces a shift in the reaction equilibrium toward the exclusive formation of DMI, thwarting the outcome of the reaction.

In addition, the total consumption of solvent, which is needed during the reaction phase of the experiment, inevitably leads to problems with the heating of the reaction itself. The absence or little presence of DMC in the reaction generated hot spot phenomena directly in the catalyst mass. This solid support overheating since there is no more presence of the solvent to disperse the excess of heat that was forming locally due to the continuous power supply given by the instrument. One of the reasons for the continuous temperature swings, and the instrument's struggle to bring the temperature to the set temperature (200 °C) is attributed to the solvent itself, the DMC, which having a low dielectric loss did not allow uniform heating of the mass.

Studying the literature in greater depth also revealed how heterogeneous organic reactions (solid/liquid), assisted by microwave radiation, are prone to uncontrolled hotspots, which, in addition to drastically reducing the yield of a reaction, can be dangerous precisely because of the formation of electrical discharges that can ignite the solvents used and damage the equipment.

As reported in literature, in a solid/liquid system irradiated with microwave radiation, hotspots can reach temperature difference values as high as 50 to 100 °C relative to the bulk of the solution. Continuous irradiation with microwaves, which generates such high peaks in temperature and localized on the surface of the catalyst, can give phenomena of reorganization of the catalyst, changing its structure and catalytic capacity, leading to the formation of byproducts.^{71,72}

A relevant example of what has just been written is reported by Horikoshi et al. for the synthesis of 4-methylbiphenyl by Suzuki-Miyaura coupling reaction under microwave irradiation. The reaction, catalyzed by palladium activated on carbon (Pd/AC), in the presence of electric field irradiation generated hotspots that limited the efficiency of the reaction, in contrast to irradiation by magnetic field or even by conventional heating. The formation of hotspots under the pulse of an electric field given by microwaves causes a lowering of the catalytic activity of the catalyst, reducing the product yield and increasing the formation of by-products given by eddy reactions.⁷² This would explain the presence of unexpected compounds, as seen at GC-MS for reactions prolonged for more than 45 minutes.

As explained by the authors themselves, a decline in the performance of a catalyzed reaction occurs when hotspots forms on the surface of the catalyst, which generates particle aggregation phenomena causing loss/obstruction of active sites. This phenomenon become increasingly prevalent the more (I) the shape of the catalyst dust grains is different, and (II) the more the crystal lattice vibrates. The set of lattice vibrations underlies the dielectric loss (ϵ'') ability of a solvent to heat up under microwave pulses. In addition, the shape and distance of the catalyst particles (in this case KW 500) explains the formation of hotspots that block the outcome of the isosorbide methylation reaction. Hotspots, in fact, are nothing more than extremes of the better-known phenomenon called Surface Enhanced Plasmon Resonance (SERP), which is formed when between two ends of catalyst particles, placed at a minimum distance (0.001 mm), the electric field undergoes a drastic increase, eventually generating local electric fields of 11838 V m^{-1} that result in electric arcs (Figure 3.9).^{71,73}

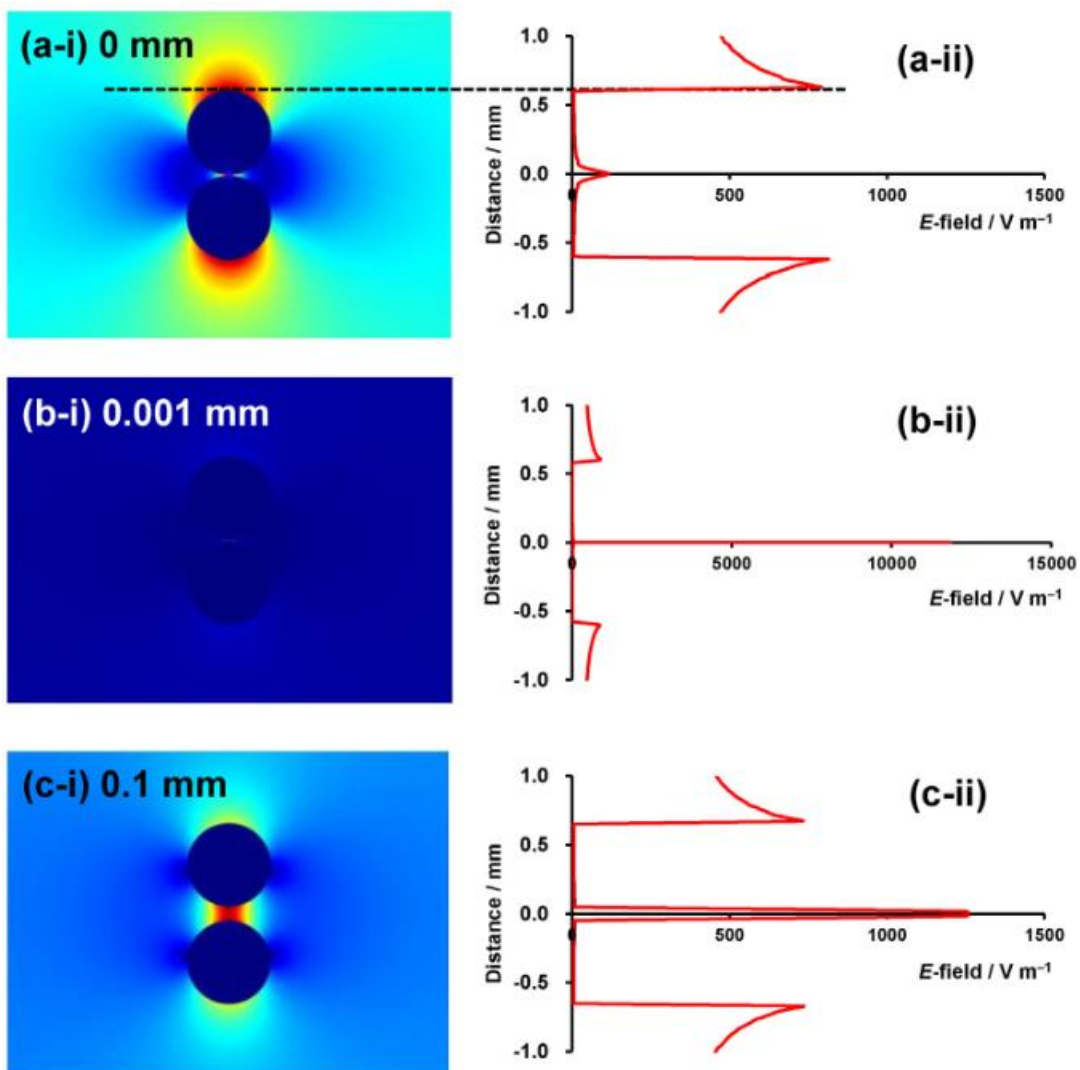


Figure 3.9: Distribution of microwaves' E-field between two nanoparticles of Pd(AC) catalysts simulated by COMSOL multiphysics software. The hotspot is clearly observed in the third image (c-ii), and on the right is reported how the intensity of the E-field growth respect the distance of the particles.⁷¹

4. CONCLUSIONS

The work done in this thesis focused on one of the 15 Bio-Based Platform Chemicals of greatest interest: isosorbide.

This cyclic monosaccharide, which is derived from a double dehydration of D-sorbitol, has a peculiar V-structure, which together with the presence of two hydroxyls with different exo- and endo-configurations, gives the molecule marked reactivity, with potential for developing numerous applications.

One application of this molecule has been the development of an alternative method to the synthesis of dimethyl isosorbide (DMI), a promising green solvent used to replace toxic solvents such as DMSO and DMF.

The aim of this work, therefore, was to synthesize DMI through the use of a heterogeneous catalyst capable of selectively methylating isosorbide and being recycled for multiple reactions.

The first part of the study focused on screening a number of commercial zeolites and hydrotalcites to see which of the chosen proposals could provide better selectivity and reaction yield. The reactions, conducted in autoclave, were set according to the best conditions found for the synthesis of DMI in homogeneous catalysis with NMPy catalyst, found in a previous study (200 °C for 12 hours). KW 500 hydrotalcites proved to be the best catalyst for the isosorbide methylation reaction, ensuring full selectivity towards DMI. The reactions were then continued by evaluating the best amount of catalyst, reaction time, and concentration that could ensure the best performance for the reaction.

Having optimized the process on 1.0 g of isosorbide, the improvements on the reaction were tried on a larger scale (5.0 g). These experiments highlighting how the increase in reaction volume combined with the limited amount of catalyst, and the narrow reaction time, did not guarantee the complete conversion of the carboxylated compounds into the final product. To limit reaction time and improve selectivity, reactions on 5 g of isosorbide require 1:1 wt of catalyst and just 6 hours of reaction time. Increasing the amount of KW 500 to limit the time and energy supplied to the reaction is actually a better compromise for the reaction.

The reuse of KW 500 after prolonged calcinations in the muffle furnace did not seem to affect the catalytic activity of this catalyst, which ensured a homogeneous reaction result even after the fourth recycling.

The study of the reaction between DMC and isosorbide epimers confirmed once again how the different reactivity of the hydroxyl groups of isosorbide is respected even in the presence of heterogeneous catalysts.

As far as microwave DMI syntheses are concerned, it can be said that high wattages greatly accelerate the

development of the reaction; however, it is better to operate at intermediate wattages and lengthen the reaction time in order to allow the DMC to reach temperature in a controlled manner. Syntheses using heterogeneous catalysts, on the other hand, do not seem suitable for microwave radiation-mediated heating. Size and shape of the catalyst particles easily induce the formation of undesirable hot spots that interfere with the success of the reaction.

In conclusion, the methylation of isosorbide via DMC chemistry mediated by hydrotalcites such as KW 500, seems to be a promising synthetic route, both for the selectivity it brings with respect to DMI, and for its ability to be recycled and reused as advocated by Green Chemistry. Further studies will be needed to assess (i) how to limit solvent loss; (ii) how the composition of the catalyst varies after each use; and, (iii) to assess via Green Metrics how green the process is compared to hitherto known DMI synthesis processes.

5. MATERIALS AND METHODS

5.1 Materials and instruments

All the solvents and reagents used were purchased from Sigma-Aldrich, which supplied pure products that did not require further purification.

Hydrotalcites KW 500 and KW 200 were supplied by Kyowa-Chemical Industry Co. company, LTD.

Sodium Y Zeolite (NaY), Ammonium Y Zeolite (AY), Ultrastable Y Zeolite (USY), Hydrotalcite Kyowaad 500 (KW 500), Hydrotalcite Kyowaad 2000 (KW 2000) and Hydrotalcite (HT 3) were all calcined in a muffle furnace at 400 °C for at least one night before being used.

The reactions proposed in this thesis work were conducted by making use of stainless steel autoclaves with a maximum capacity of 100.0 mL provided with an outer heating mantle to which the plate thermocouple can be attached for temperature control. For larger scale reactions (5.0 g isosorbide), larger (220.0 mL) stainless steel autoclaves provided with a thermocouple with attached thermostat for temperature control and special insulated furnace were used. In both cases, the reactions involved heating in the presence of magnetic stirring.

As for microwave reactions, these were carried out by means of Milestone's Ethos Up furnace, using the special experimental set-up equipped with 50.0 mL quartz vessel equipped with magnetic stir bar.

Reactions were monitored by using Agilent Technology GC-MS (GC System 6890 N Agilent Technologies Mass Selective Detector 5973) with silica column (HP-5MS).

The ^1H NMR and ^{13}C NMR spectra were recorded using the company's Bruker 400 MHz and Bruker 300 MHz instrument in CDCl_3 and MeOD.

5.2 General Procedure

5.2.1 Procedure synthesis of DMI in autoclave: evaluation of catalys (Table 3.1 # 6)

A typical 100 mL autoclave reaction was conducted as follows; 1.0 g of isosorbide (Dihydro D-glucitol, 1.0 eq. mol., $6.8 \cdot 10^{-3}$ mol), 30.0 mL of dimethyl carbonate anhydried on molecular sieves (50.0 eq. mol., 0.3 mol) and 1.0 g of KW 500 (isosorbide: KW 500 1.0:1.0 w/w). The reaction was conducted for 12 h at 200 °C, a temperature maintained by thermocouple inserted in the heating mantle, outside the autoclave. The formation of autogenous pressure of about 20 bar measured as soon as the reaction reached temperature was observed during the reaction.

After cooling the autoclave, the reacted contents were filtered on filter paper to separate the solid catalyst from the rest of the reaction, washing it all with about 10.0 mL of DMC. Then the solvent (DMC) was removed by rotavapor and vacuum line, obtaining a straw-yellow liquid mixture (1.3 g). The reaction crude was then first analysed by GM-MS showing only the presence of clean DMI, a finding also

confirmed by ^1H NMR analysis and ^{13}C NMR, obtaining a yield of 68 %.

[5.2.2 Procedure synthesis of DMI in autoclave: evaluation of quantity of catalyst \(Table 3.3 # 2\)](#)

Into a 100 mL autoclave were placed in the following order: 1.0 g of isosorbide (Dihydro D-glucitol, 1.0 eq. mol., $6.8 \cdot 10^{-3}$ mol), 30.0 mL of DMC anhydried on molecular sieves (50.0 eq. mol., 0.3 mol) and 0.5 g of KW 500 (isosorbide: KW 500 1.0:0.5 w/w). The reaction was conducted for 12 hours at 200 °C, a temperature maintained by thermocouple inserted in the heating mantle, outside the autoclave. During the reaction the formation of autogenous pressure of about 20 bar measured as soon as the reaction reached temperature was observed.

After cooling the autoclave, the reaction mixture was filtered on filter paper to separate the solid catalyst from the rest of the reaction that was washed with about 10.0 mL of DMC. Then the solvent was evaporated by rotavapor and vacuum line, obtaining a straw-yellow liquid mixture (0.8 g). The reaction crude was then first analyzed by GM-MS showing only the presence of clean DMI, a finding also confirmed by ^1H NMR analysis and ^{13}C NMR, obtaining a yield of 63 %.

[5.2.3 Procedure synthesis of DMI in autoclave: evaluation time of reaction \(Table 3.4 # 4\)](#)

Into a 100 mL autoclave were placed in the following order: 1.0 g of isosorbide (Dihydro D-glucitol, 1.0 eq. mol., $6.8 \cdot 10^{-3}$ mol), 30 mL of DMC anhydried on molecular sieves (50.0 eq. mol., 0.3 mol) and 0.5 g of KW 500 (isosorbide: KW 500 1.0:0.5 w/w). The reaction was conducted for 4 h at 200 °C, a temperature maintained by thermocouple inserted in the heating mantle, outside the autoclave. The formation of autogenous pressure of about 20 bar measured as soon as the reaction reached temperature was observed during the reaction.

After cooling the autoclave, the mixture was filtered on filter paper to separate the solid catalyst from the rest of the reaction and it was washed with ca 10.0 mL of DMC. Then the resulting mixture was stripped of the supernatant (DMC) by rotavapor and vacuum line, obtaining a straw-yellow liquid mixture (1.0 g). The reaction crude was then first analyzed by GM-MS showing only the presence of clean DMI, a finding also confirmed by ^1H NMR analysis and ^{13}C NMR, obtaining a yield of 81 %.

[5.2.4 Procedure synthesis of DMI in autoclave: evaluation concentration of reaction \(Table 3.5 # 2\)](#)

The reaction between isosorbide and DMC 1.0:25.0 eq. mol. was conducted in a 100 mL autoclave as follows: 2.0 g of isosorbide (Dihydro D-glucitol, 1.0 eq. mol., $13.6 \cdot 10^{-3}$ mol), 30.0 mL of dimethyl carbonate anhydried on molecular sieves (25 eq. mol., 0.9 mol) and 1.0 g of KW 500 (isosorbide: KW 500 1.0:0.5 w/w). The reaction was conducted for 4 h at 200 °C, a temperature maintained by thermocouple inserted in the heating mantle, outside the autoclave. The formation of autogenous pressure of about 20 bar measured as soon as the reaction reached temperature was observed during the reaction.

After cooling the autoclave, the mixture was filtered on filter paper to separate the solid catalyst from the rest of the reaction, then the solid was washed with about 10.0 mL of DMC. Then the solvent was evaporated by rotavapor and vacuum line, obtaining a straw-yellow liquid mixture (1.9 g). The reaction crude was then first analysed by GM-MS showing only the presence of clean DMI, a finding also confirmed by ^1H NMR and ^{13}C NMR analysis, obtaining a yield of 78 %.

5.2.5 Procedure synthesis of DMI in autoclave: scale-up reactions (Table 3.6)

The reaction between isosorbide and DMC 1.0:25.0 eq. mol. Conducted in a 220.0 mL autoclave was as follows: 5.0 g of isosorbide (Dihydro D-glucitol, 1.0 eq. mol., $34.2 \cdot 10^{-3}$ mol), 77.0 mL of dimethyl carbonate anhydriified on molecular sieves (25.0 eq. mol., 0.9 mol) and 2.5 g of KW 500 (isosorbide: KW 500 1.0:0.5 w/w). The reaction was conducted for 18 hours at 200 °C, a temperature maintained by means of a thermocouple inserted in the heating mantle, outside the autoclave. During the reaction the formation of autogenous pressure of about 30 bar measured as soon as the reaction reached temperature was observed.

After cooling the autoclave, the reacted contents were filtered on filter paper to separate the solid catalyst from the rest of the reaction, washing it all with about 10.0 mL of DMC. Then the resulting mixture was stripped of the supernatant (DMC) by rotavapor and vacuum line, obtaining a straw-yellow liquid mixture (5.7 g). The reaction crude was then first analysed by GM-MS showing the presence of DMI (43%) and other reaction intermediates.

5.2.6 Procedure synthesis of DMli in autoclave

A typical 100 mL autoclave reaction was included in the following order: 1.0 g of isoidide (1.0 eq. mol., 0.7 mmol), 30.0 mL of dimethyl carbonate anhydriified on molecular sieves (50.0 eq. mol., 0.3 mol) and 1.0 g of KW 500 (isosorbide: KW 500 1.0:1.0 w/w). The reaction was conducted for 12 h at 200 °C, a temperature maintained by thermocouple inserted in the heating mantle, outside the autoclave. The formation of autogenous pressure of about 20 bar measured as soon as the reaction reached temperature was observed during the reaction.

After cooling the autoclave, the reacted contents were filtered on filter paper to separate the solid catalyst from the rest of the reaction, washing it all with about 10 mL of DMC. Then the resulting mixture was stripped of the supernatant (DMC) by rotavapor and vacuum line, obtaining a straw-yellow liquid mixture (1.3 g). The reaction crude was then first analysed by GM-MS showing only the presence of clean DMI, a finding also confirmed by ^1H NMR and ^{13}C NMR .

5.2.7 Procedure synthesis of DMIm in autoclave

A typical 100 mL autoclave reaction was included in the following order: 1.0 g of isomannide (Dihydro D-

mannitol, 1.0 eq. mol., 0.7 mmol), 30.0 mL of anhydrous dimethyl carbonate on molecular sieves (50.0 eq. mol., 0.3 mol) and 1.0 g of KW 500 (isosorbide: KW 500 1.0:1.0 w/w). The reaction was conducted for 12 hours at 200 °C, a temperature maintained by a thermocouple inserted in the heating mantle, outside the autoclave. During the reaction, the formation of an autogenous pressure of about 20 bar was observed, measured as soon as the reaction reached temperature.

After the autoclave cooled, the contents of the reaction were filtered on filter paper to separate the solid catalyst from the rest of the reaction, washing it all with about 10.0 mL of DMC. Then the resulting mixture was stripped of the supernatant (DMC) by rotavapor and vacuum line, resulting in a straw-yellow liquid mixture (1.3 g). The reaction crude was then first analysed by GM-MS, which showed only the presence of clean DMI, a finding also confirmed by ¹H NMR and ¹³C NMR analysis.

5.2.7 Procedure synthesis of DMI in microwave

A typical microwave reaction was performed as follows: 0.2 g of isosorbide dissolved in 7.0 mL of DMC in the presence of 0.1 mL of NMPy is placed in the quartz vessel to react. The magnetic stirring rod and black disc are then added to the quartz vessel to enable the reaction to better absorb microwaves. The reaction is carried out at 200 °C, with the timing and rates still to be defined.

The reaction mixture is then filtered on a column packed with silica and washed with small aliquots of DMC (5.0-10.0 mL). The excess solvent was then evaporated on a rotavapor and vacuum line, and the reaction blank was analysed by GC-MS.

5.3 Characterizations

- **Isorobitol**

¹H NMR (400 MHz CDCl₃) δ ppm: 4.71-4.68 (t,1H), 4.45-4.42 (t,2H), 4.35-4.31 (q,2H), 4.03-3.92 (m,2H), 3.91-3.87 (m,1H), 3.61-3.57 (q,3H).

- **Monomethyl isosorbide (MMI-1)**

¹H NMR (400 MHz CDCl₃) δ ppm: 4.53 (t,1H), 4.40 (d,1H), 4.19-4.23 (m,1H), 4.01-3.98 (m,1H), 3.85 (dd,1H), 3.82-3.77 (m,2H), 3.52-3.48 (m,1H), 3.32 (s,3H).

¹³C NMR (100 MHz, CDCl₃) δ ppm = 85.63, 85.47, 81.71, 73.65, 73.00, 72.21, 57.20

- **Dimethyl isosorbide (DMI)**

¹H NMR (400 MHz, CDCl₃), δ (ppm): 4.68 (t,1H), 4.54 (d,1H), 4.03-3.92 (m,4H), 3.89 (m,1H), 3.65-3.57 (m,1H), 3.49 (s,3H), 3.40 (s,3H).

¹³C NMR (100 MHz, CDCl₃) δ ppm = 85.87, 81.75, 79.88, 72.98, 69.72, 58.17, 57.11

- **Monomethyl isosorbide (MMI-2)**

¹H NMR (400 MHz CDCl₃) δ ppm: 4.67 (t,1H), 4.40-4.39 (m,1H), 4.26 (m,1H), 3.93-3.85 (m,4H),

3.54-3.48 (m, 1H), 3.41 (s,3H).

^{13}C NMR (100 MHz, CDCl_3) δ ppm = 88.38, 81.82, 79.80, 76.83, 75.92, 70.00, 58.28

- **Monomethoxycarbonyl isosorbide (MCI-1)**

^1H NMR (400 MHz CDCl_3) δ ppm: 5.16 (m,1H), 4.68 (t,1H), 4.57-4.56 (m,1H), 4.35 (m,1H), 4.17-4.14 (dd,1H), 4.06-4.02 (dd,1H), 3.94-3.90 (m,1H), 3.84(s,3H), 3.43-3.59 (m,1H).

^{13}C NMR (100 MHz, CDCl_3) δ ppm = 154.75, 85.40, 81.98, 81.59, 73.67, 73.30, 72.28, 55.14

- **Monomethoxycarbonyl isosorbide (MCI-2)**

^1H NMR (400 MHz CDCl_3) δ ppm: 5.11-5.07(m,1H), 4.93-4.91 (t,1H), 4.44-4.43 (d,1H), 4.38-4.36 (m,1H), 3.95 (m,2H), 3.93-3.86 (m,2H), 3.84 (s,3H)

^{13}C NMR (100 MHz, CDCl_3) δ ppm = 155.21, 88.39, 80.46, 76.96, 76.26, 75.70, 70.41, 55.10

- **Methoxycarbonyl methyl isosorbide (MCMI-1)**

^1H NMR (400 MHz CDCl_3) δ ppm : 5.10-5.09 (m,1H), 4.74-4.72 (t,1H), 4.60-4.59 (m,1H), 4.09 (t,2H), 4.00-3.94 (m, 2H), 3.81 (s,3H), 3.66-3.60 (m,1H), 3.49 (s,3H).

^{13}C NMR (100 MHz, CDCl_3) δ ppm = 154.80, 86.18, 81.75, 81,66, 80.27, 73.45, 70.12, 58.31, 55.05

- **Methoxycarbonyl methyl isosorbide (MCMI-2)**

^1H NMR (400 MHz CDCl_3) δ ppm: 5.03-4.96 (m,1H), 4.77-4.74 (t,1H), 4.41-4.40 (d,1H), 3.95-3.91 (m,1H), 3.86-3.76 (m,4H), 3.73 (s,3H), 3.30 (s,3H).

^{13}C NMR (100 MHz, CDCl_3) δ ppm = 155.17, 85.90, 85.78, 80.59, 76,97, 72.86, 70.16, 57.04, 55.08

- **Dimethoxycarbonyl isosorbide (DCI)**

^1H NMR (400 MHz CDCl_3) δ ppm: 5.17-5.10 (m,1H), 5.8-5.06 (t,1H), 4.92-4.88 (t,1H), 4.55-4.55 (d,1H), 4.12-4.00 (m,2H), 3.97-3.89 (m,2H), 3.83 (s,3H), 3.82 (s,3H)

^{13}C NMR (100 MHz, CDCl_3) δ ppm = 155.12, 154.80, 85.89, 81.24, 80.85, 76.77, 73.26, 70.48, 55.15, 55.10

- **Dimethyl isoidide (DMII)**

^1H NMR (400 MHz CDCl_3) δ ppm: 4.61 (s,2H), 3.91-3.83 (m, 6H), 3.40 (s,6H)

^{13}C NMR (100 MHz, CDCl_3) δ ppm = 85.11, 84.93, 71.85, 57.22

- **Dimethyl isomannide (DMIIm)**

^1H NMR (400 MHz CDCl_3) δ ppm: 4.53 (m,2H), 4.01 (t,2H), 3.90 (m,2H), 3.63 (t,2H), 3.40 (s,6H)

^{13}C NMR (100 MHz, CDCl_3) δ ppm = 81.98, 80.29, 70.95, 58.31

6. APPENDIX

6.1 Mass Spectra and NMR spectra

Temperature ramp rate:

Initial Temperature: 50 °C for 5 minutes

Initial Temperature: 50 °C (hold 5 minutes);

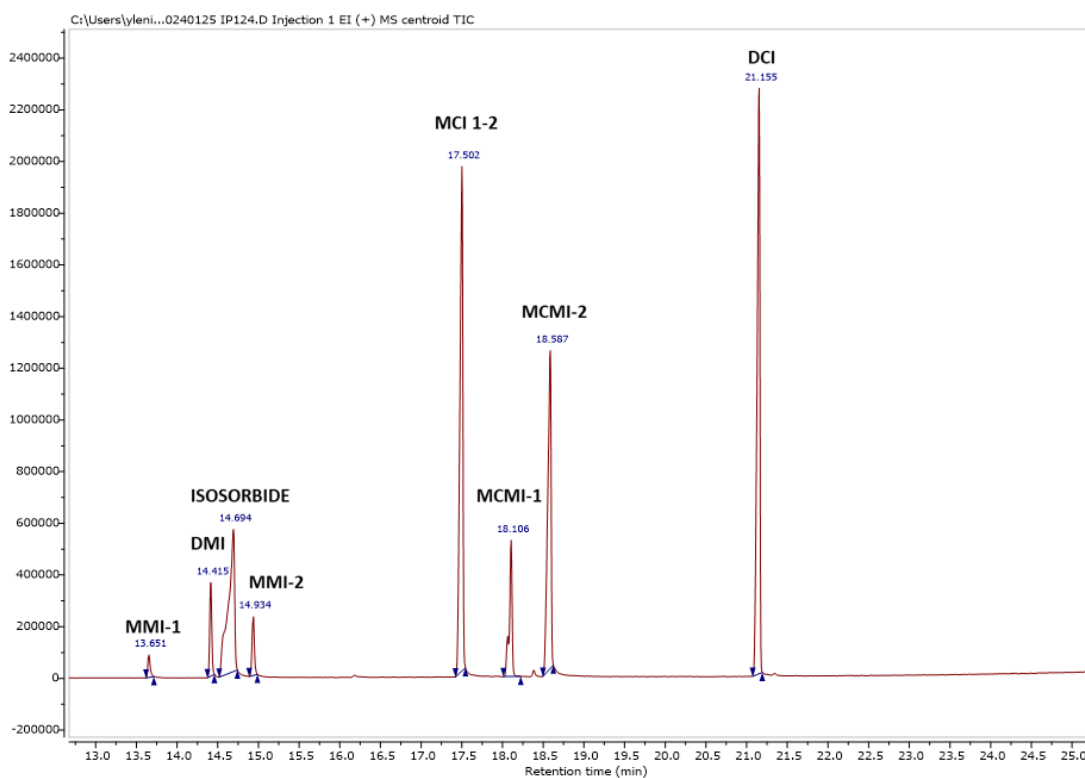
Rate: 10 (°C·min⁻¹);

Final Temperature: 300 °C (hold 20 minutes).

Pressure: 8.8 psi

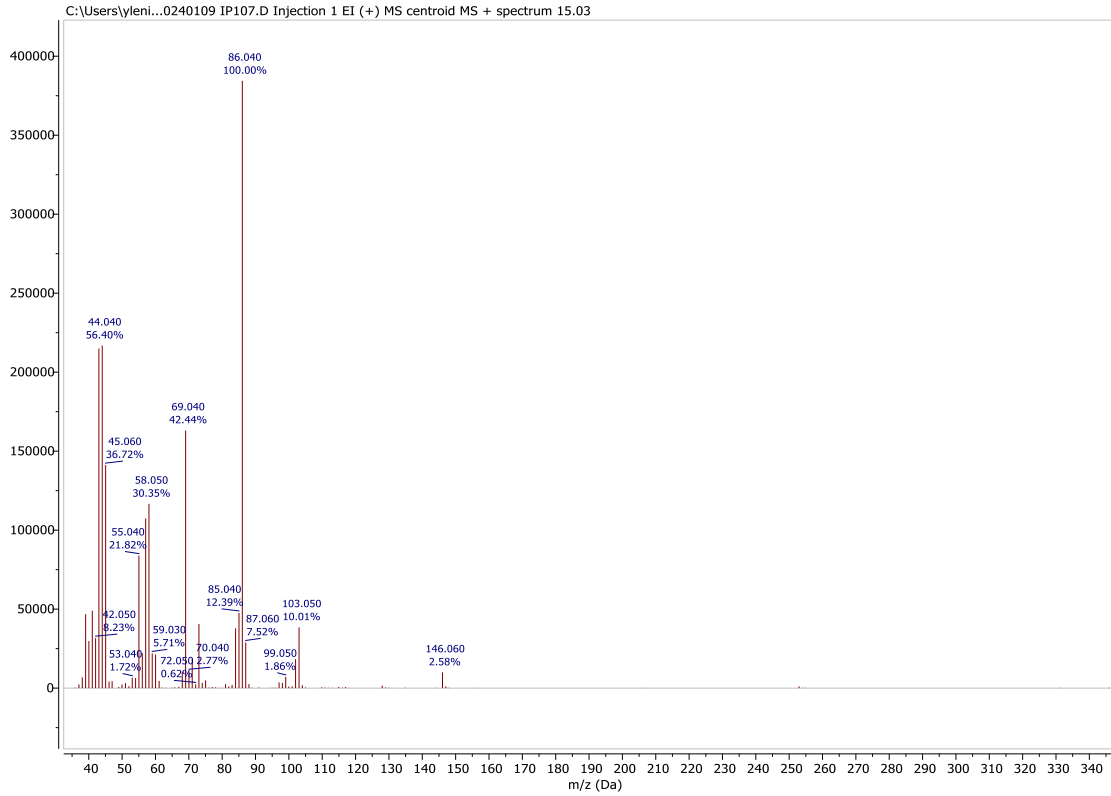
Flow: 13.7 mL/min

Column: Agilent 19091S-433

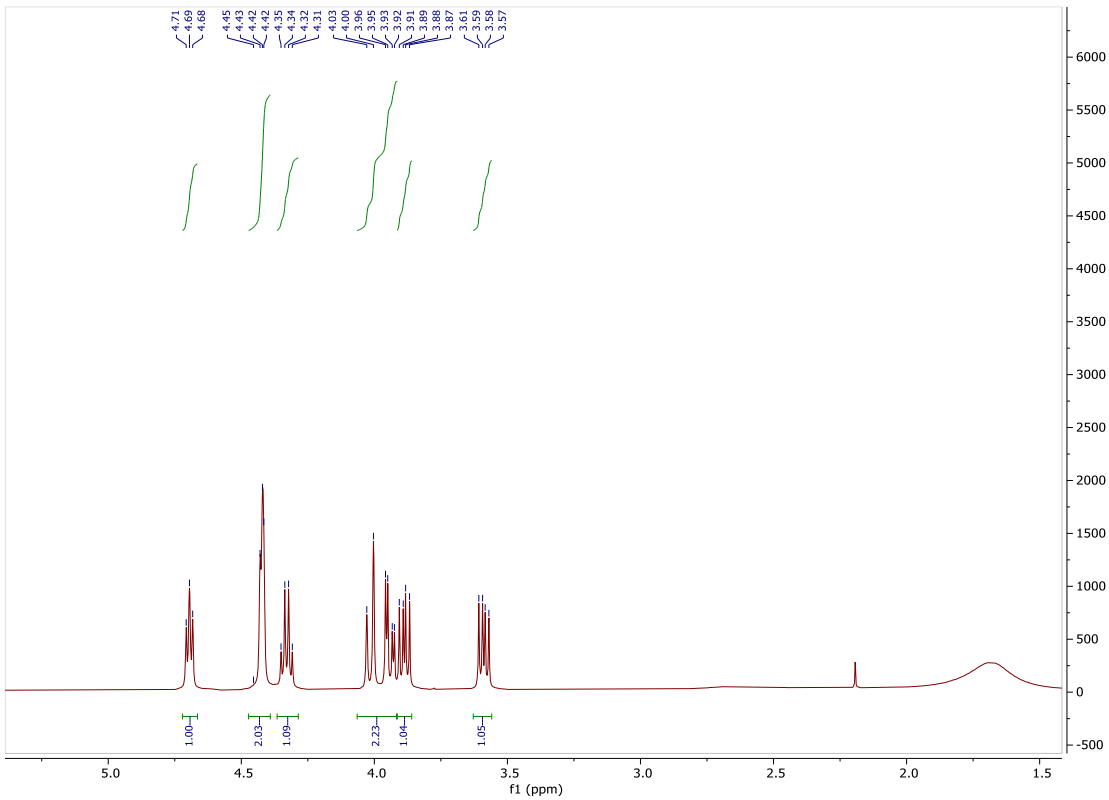


6.1.1 Characterization of isosorbide

- Mass spectra

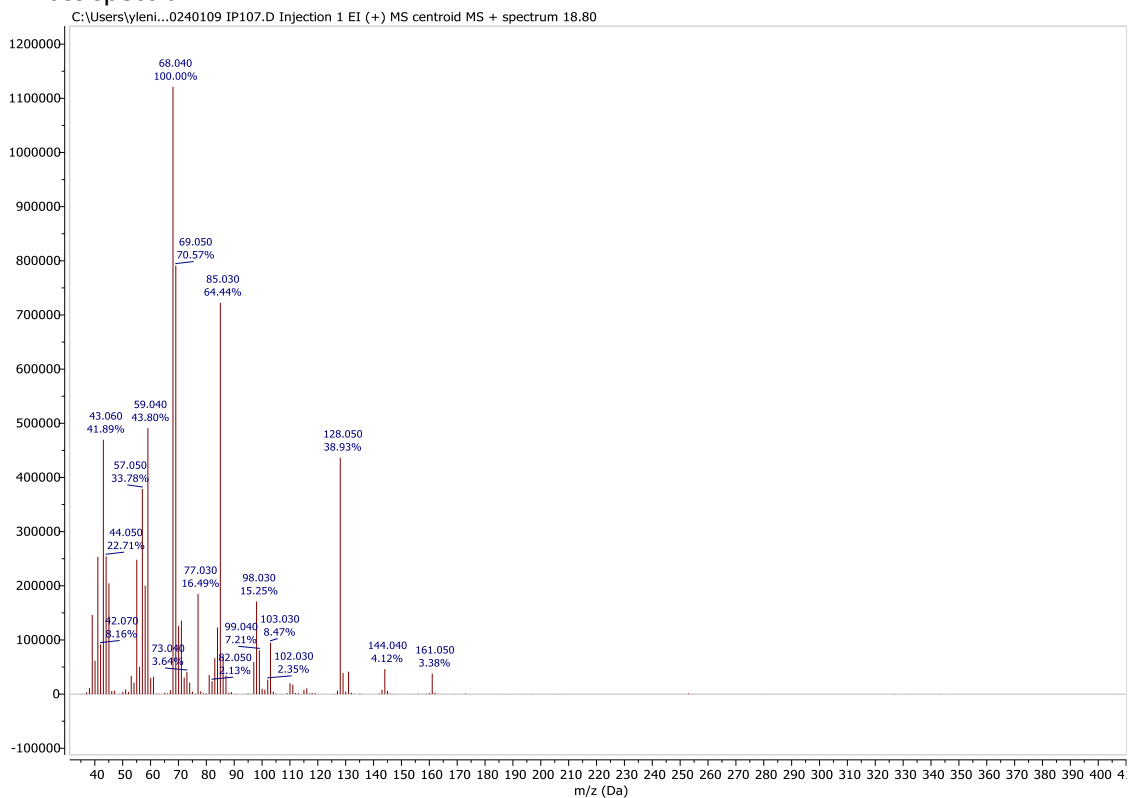


- ^1H NMR, CDCl_3

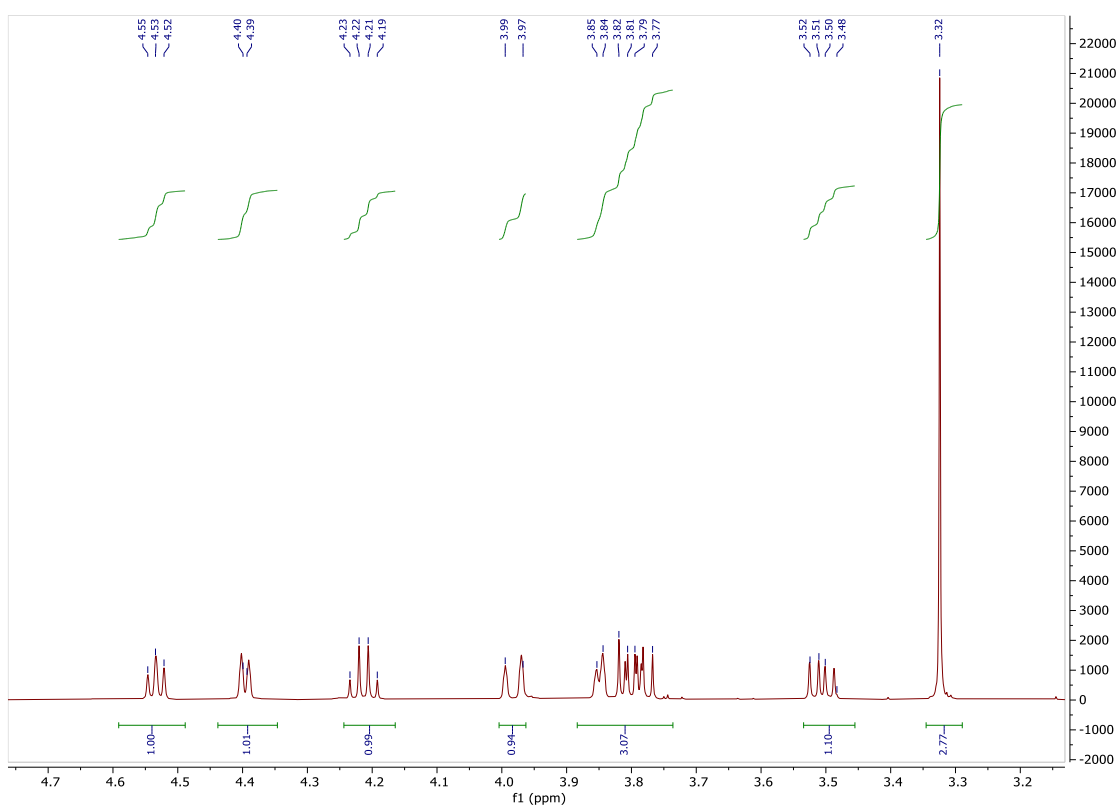


6.1.2 Characterization of monomethyl isorbide (MMI-1)

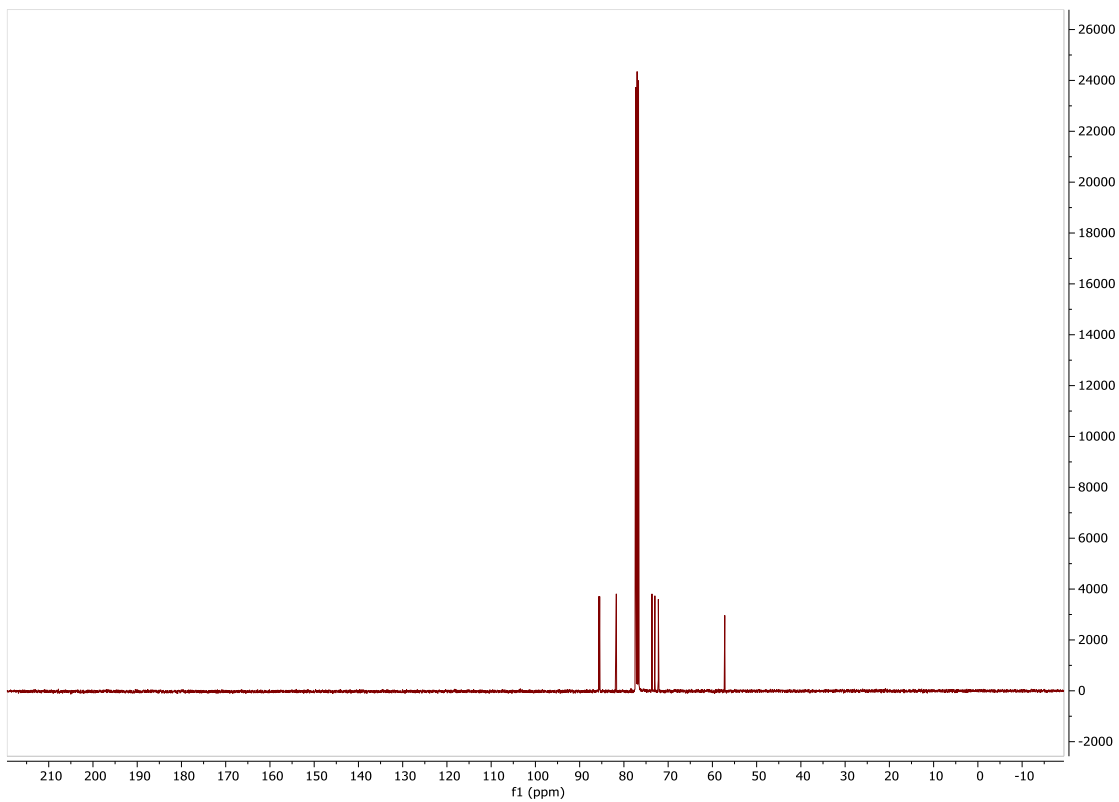
- Mass spectra



- ^1H NMR, CDCl_3

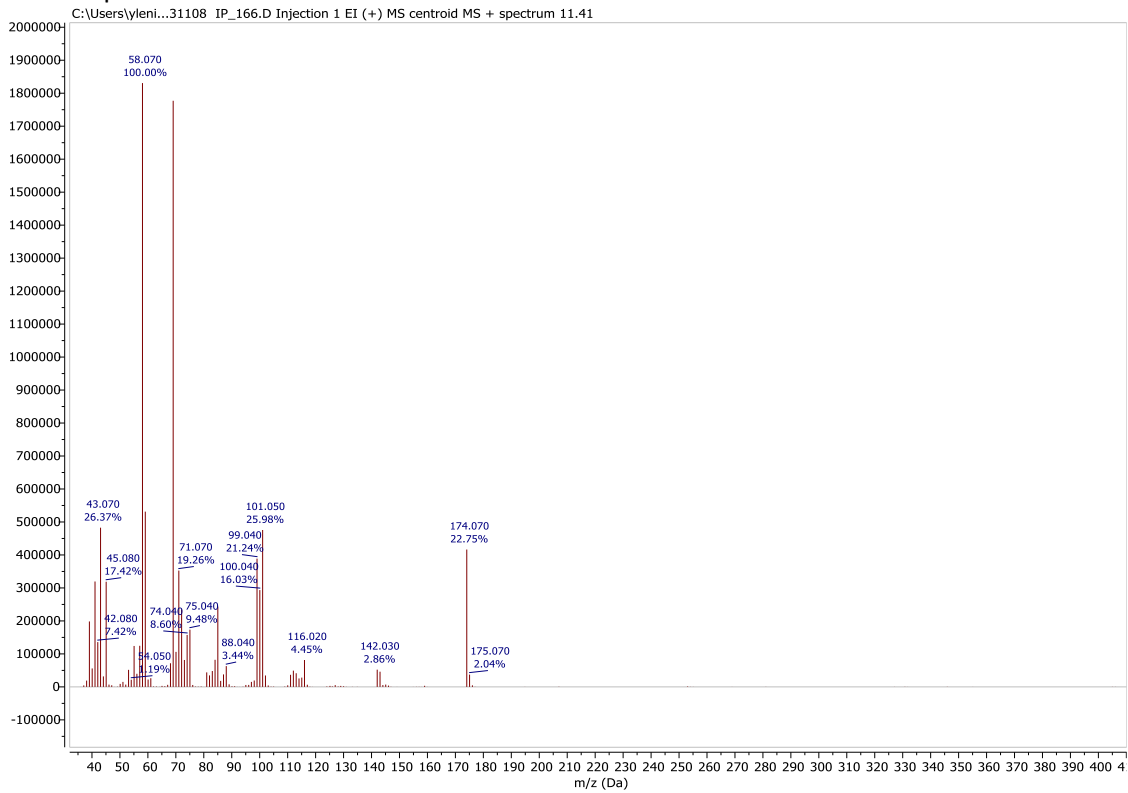


- ^{13}C NMR, CDCl_3

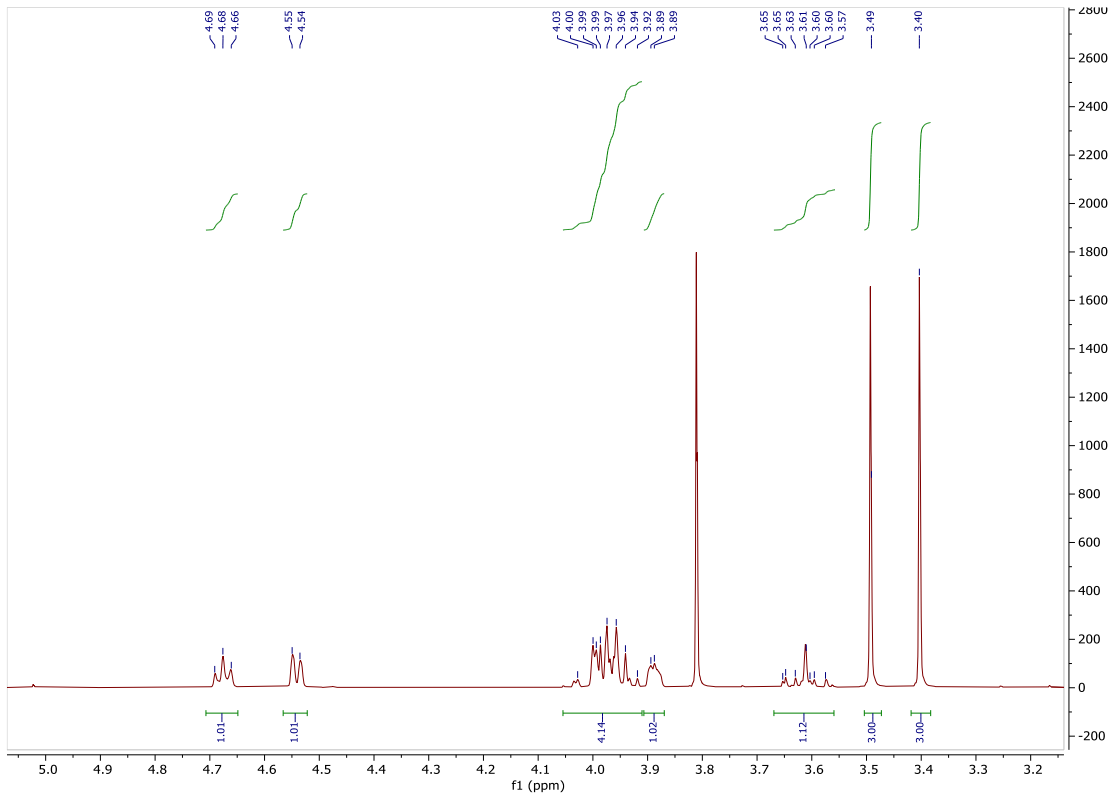


6.1.3 Characterization of dimethyl isosorbide (DMI)

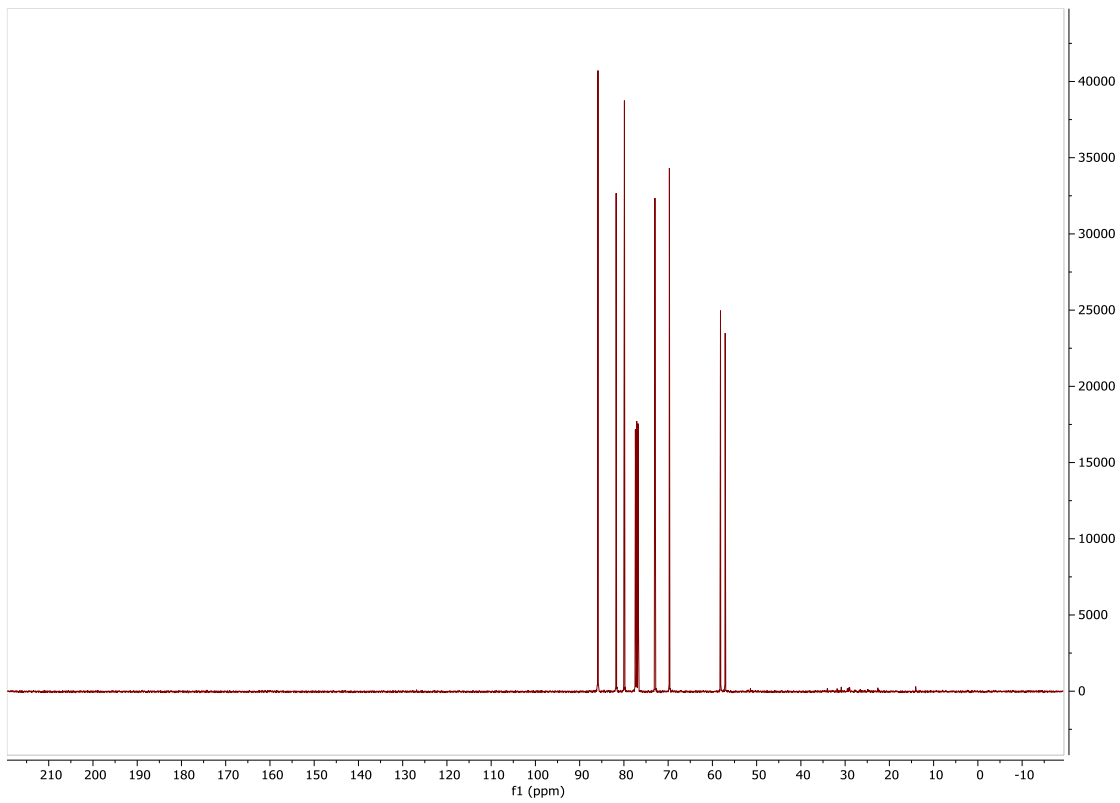
- Mass spectra



• $^1\text{H-NMR}$, CDCl_3

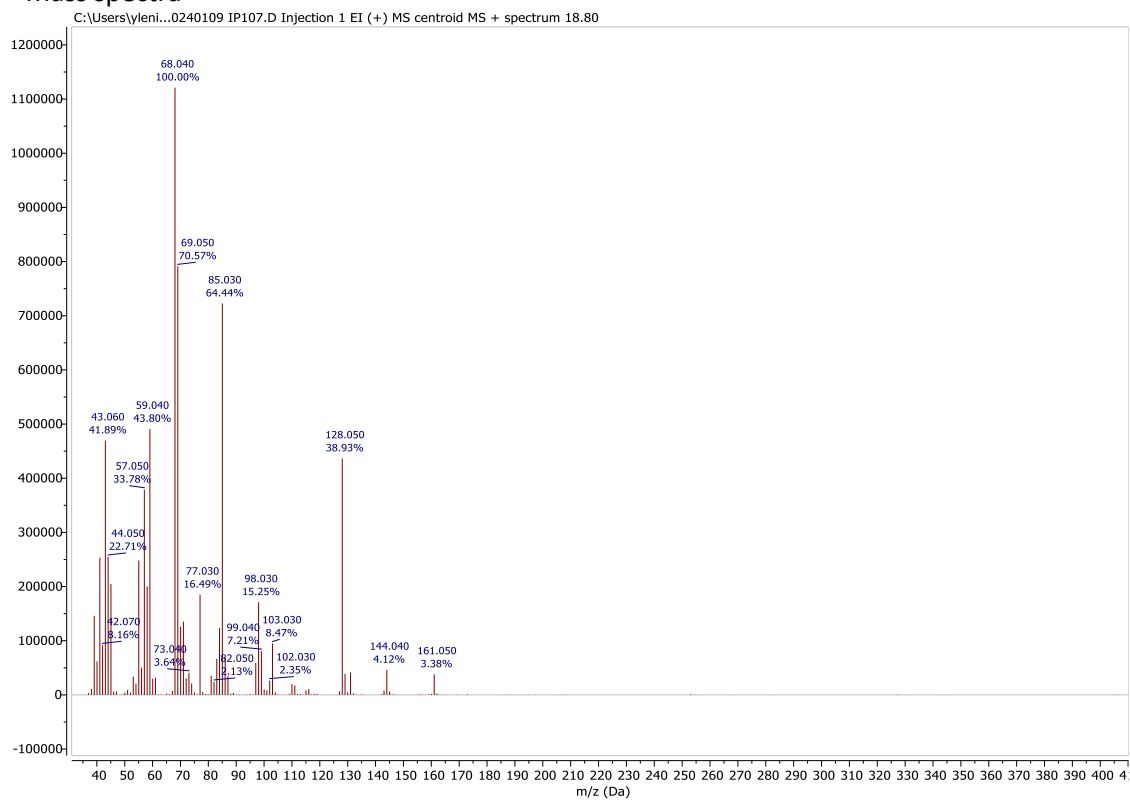


• $^{13}\text{C NMR}$, CDCl_3

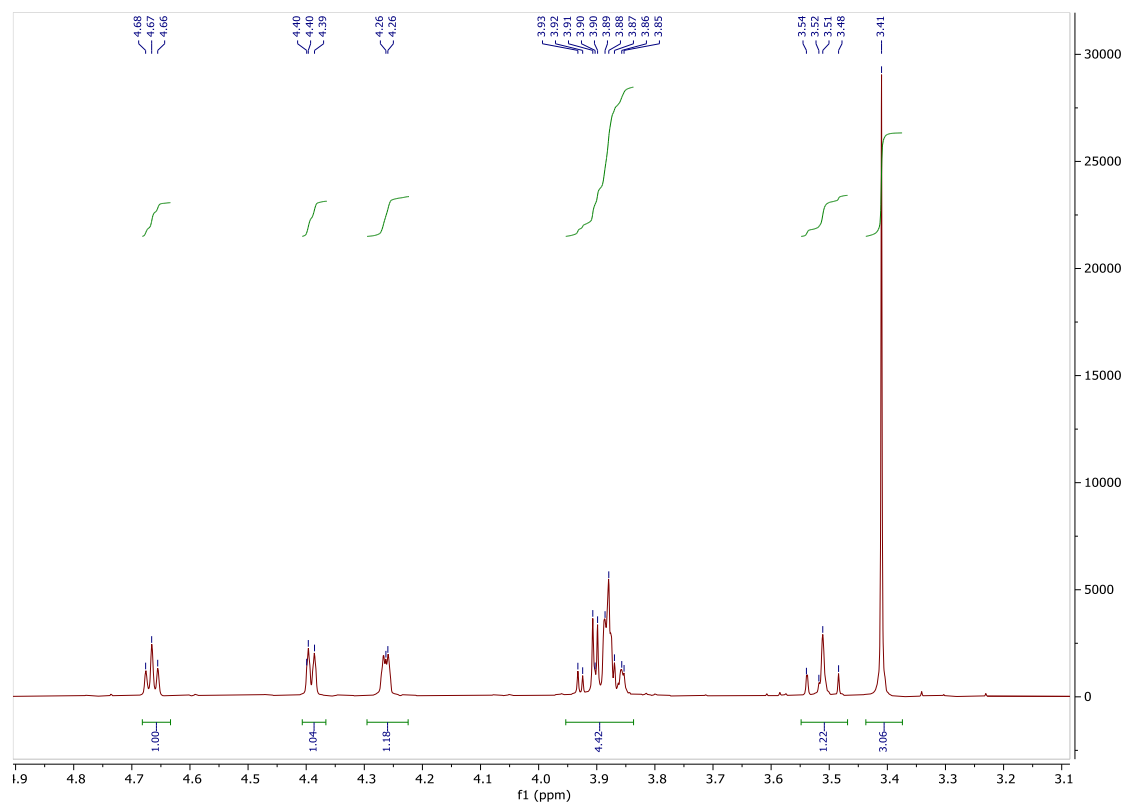


6.1.4 Characterization of monomethyl isosorbide (MMI-2)

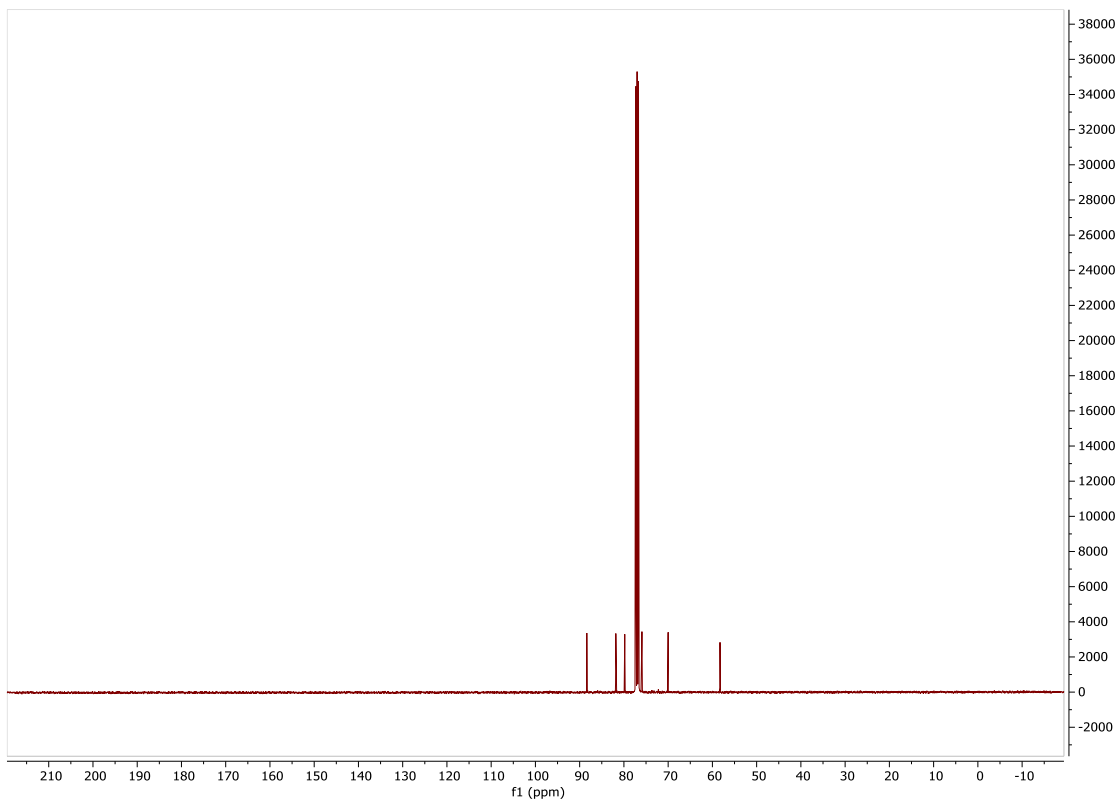
- Mass spectra



- $^1\text{H-NMR}$, CDCl_3

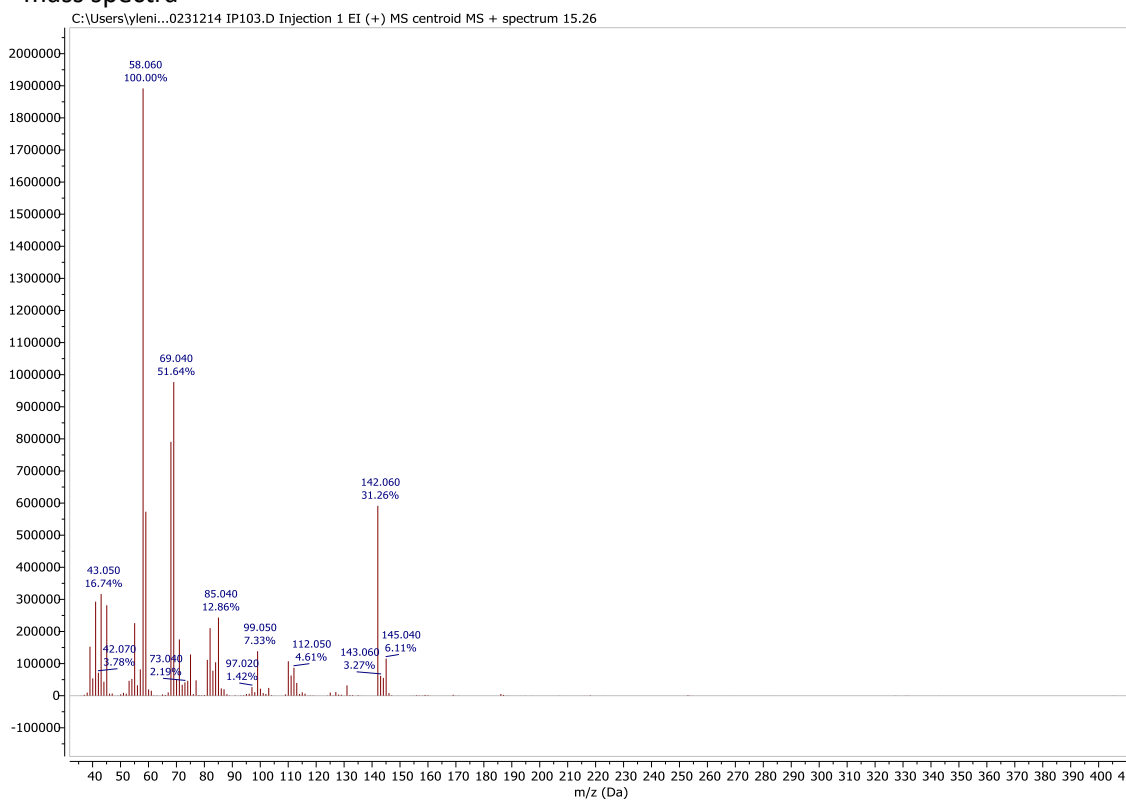


- ^{13}C NMR, CDCl_3

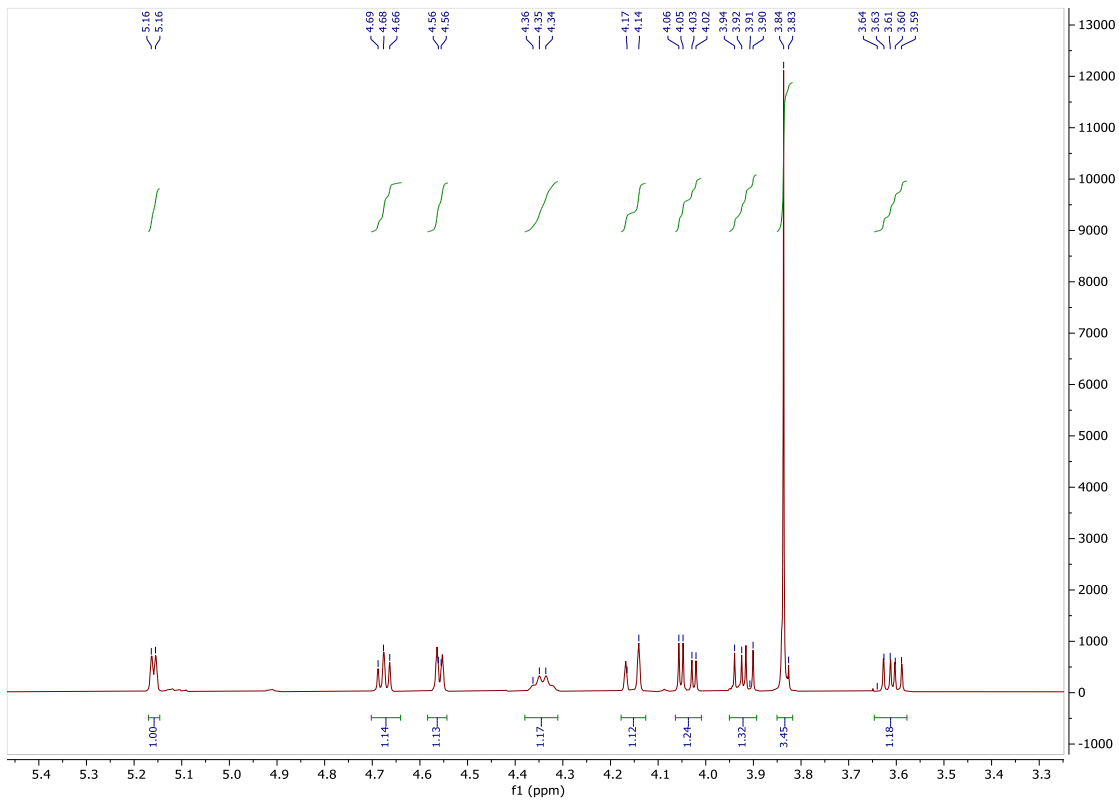


6.1.5 Characterization of monomethoxycarbonyl isosorbide (MCI-1)

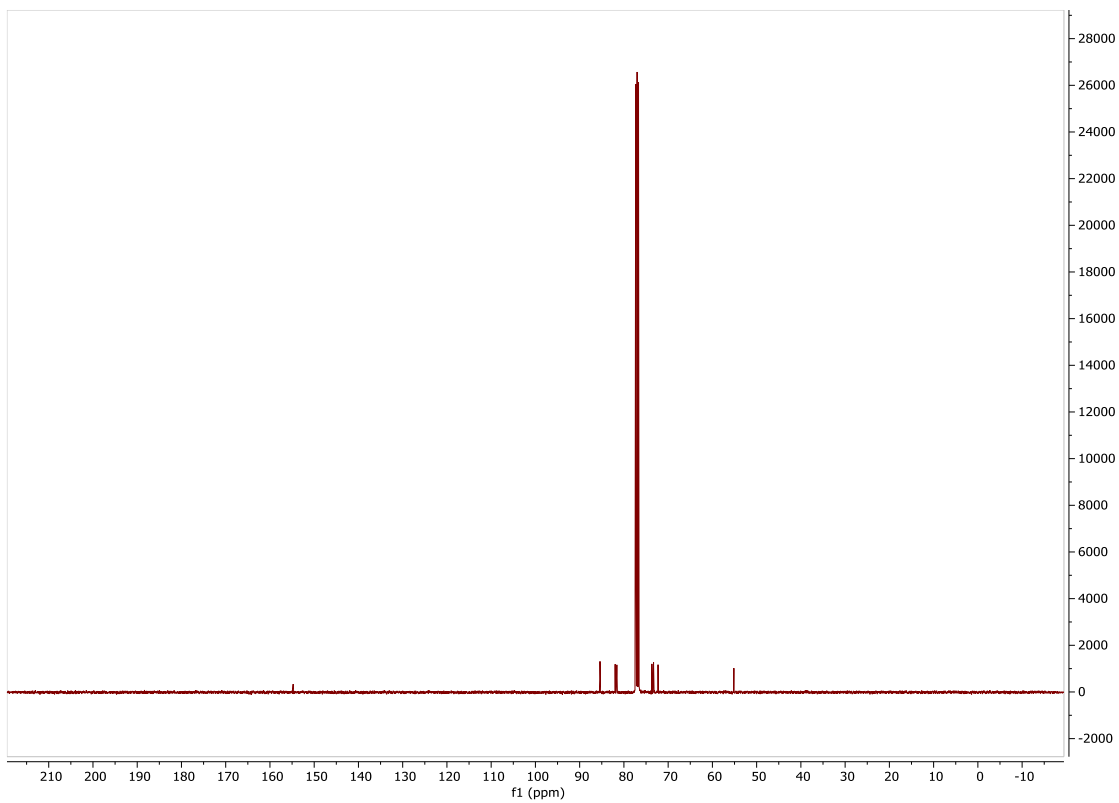
- mass spectra



- ^1H -NMR, CDCl_3

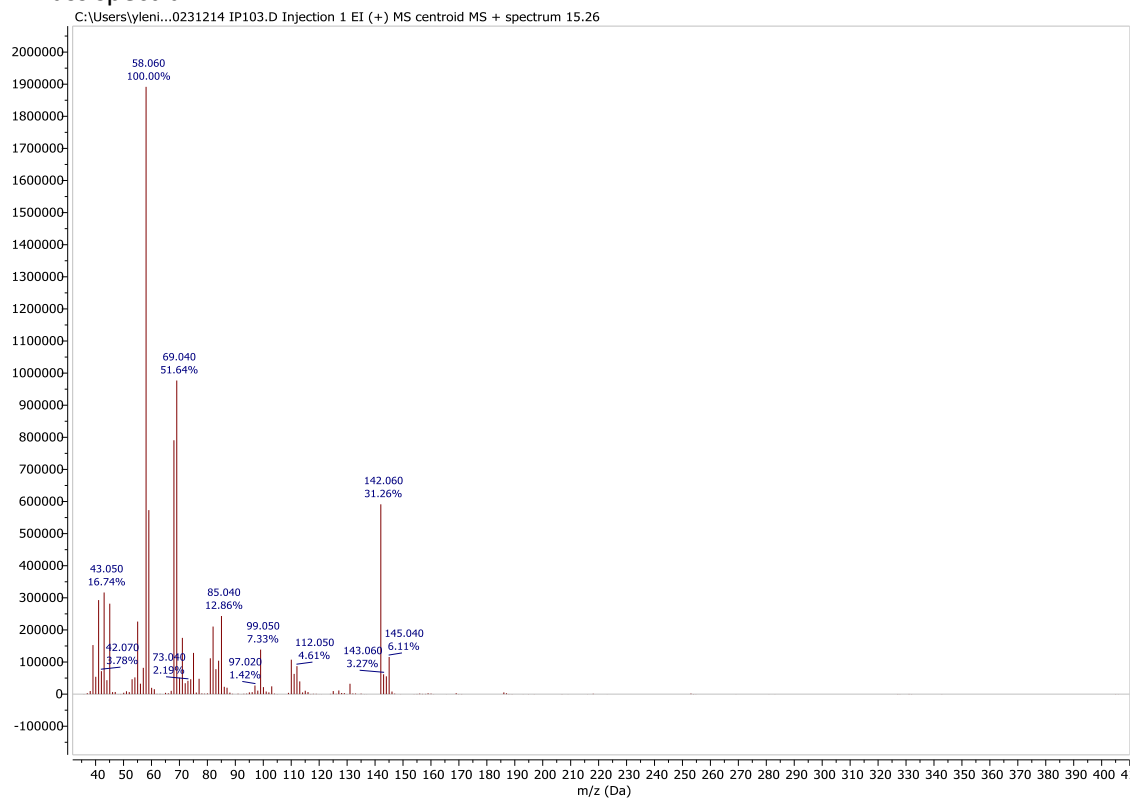


• ^{13}C NMR, CDCl_3

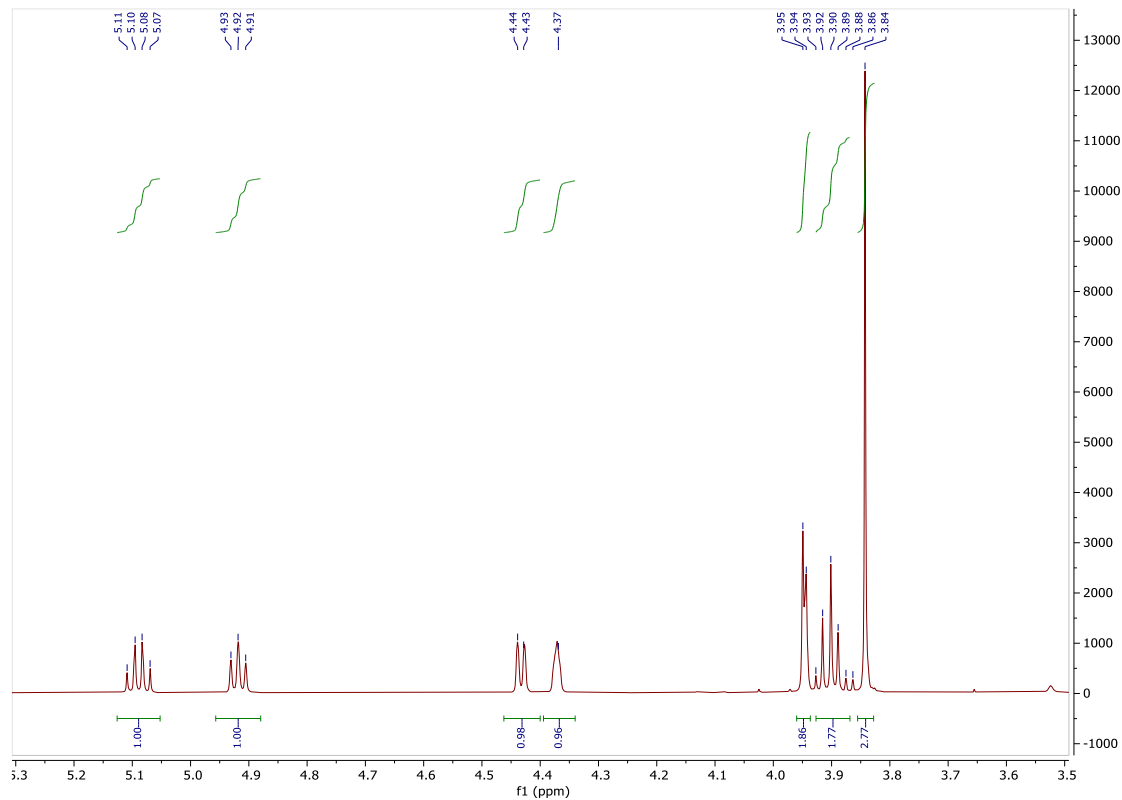


6.1.6 Characterization of monomethoxycarbonyl isosorbide (MCI-2)

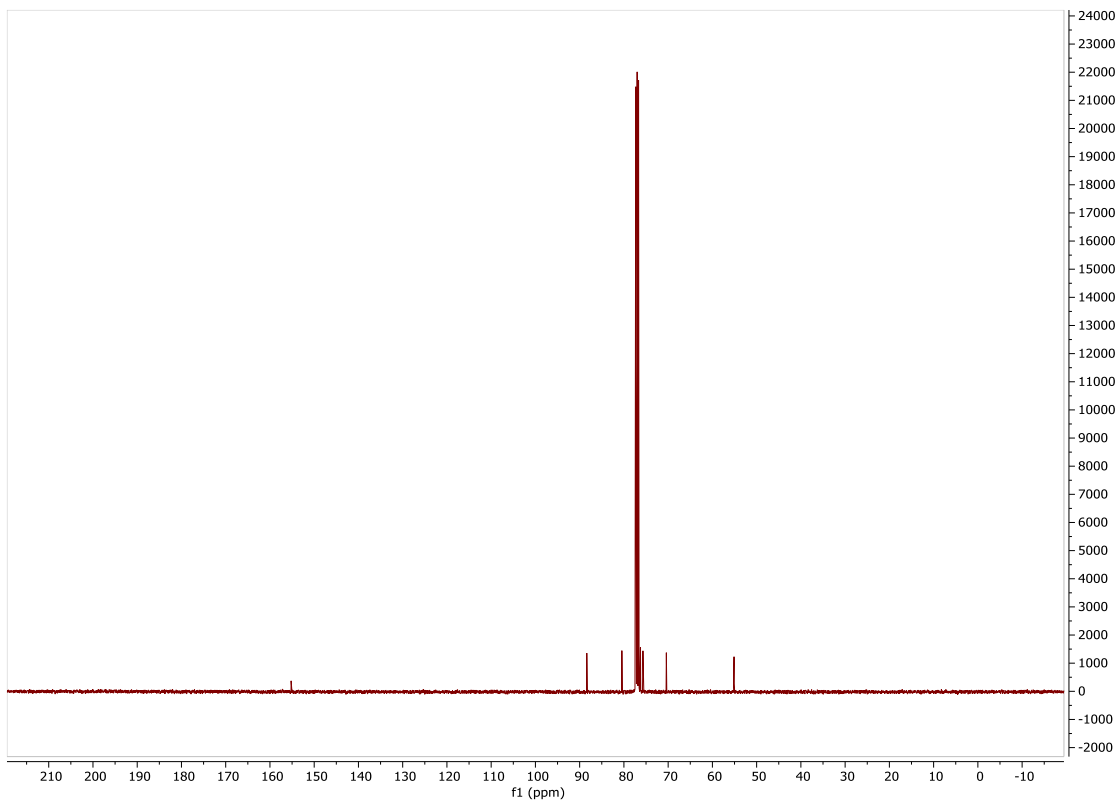
- Mass spectra



- $^1\text{H-NMR}$, CDCl_3

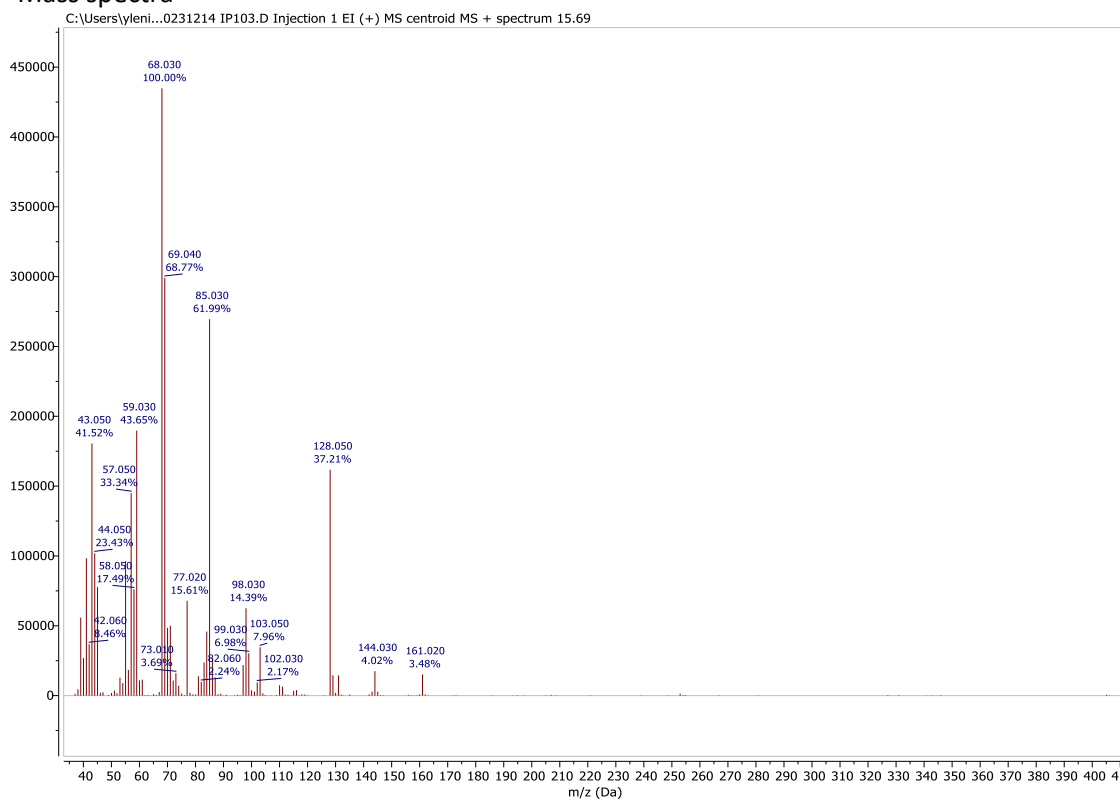


- $^{13}\text{C NMR}$, CDCl_3

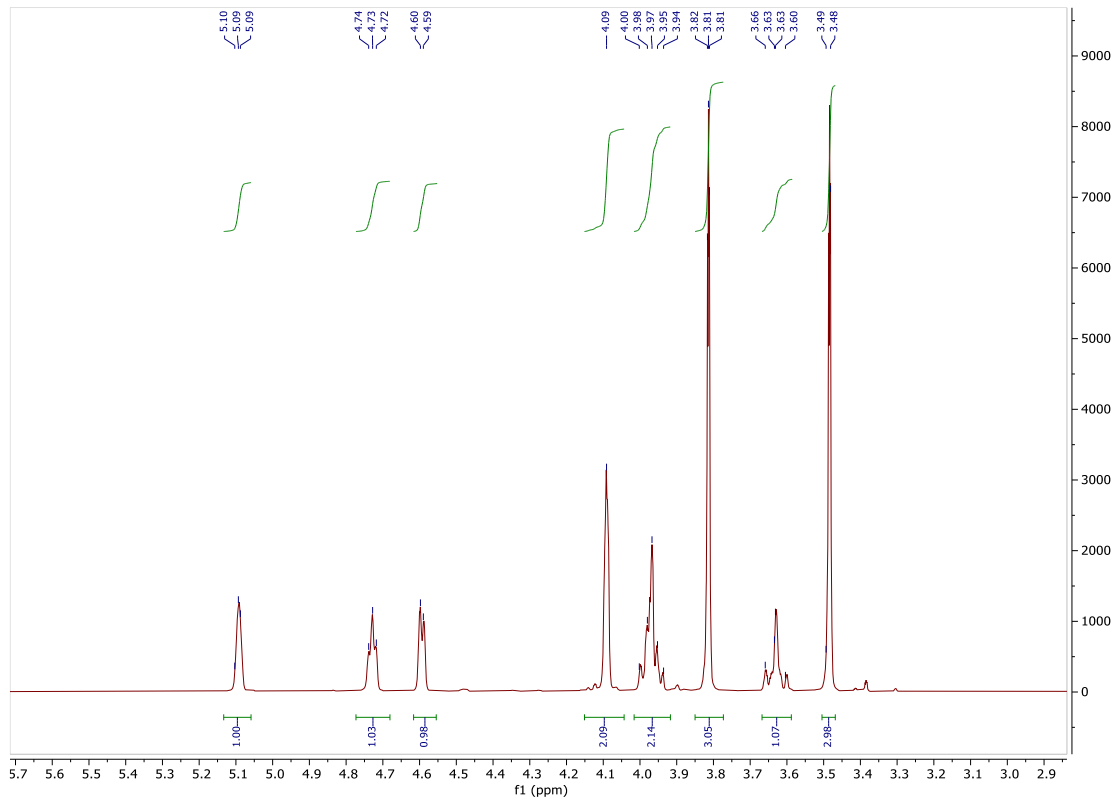


6.1.7 Characterization of monocarboxy monomethyl isosorbide (MCM1-1)

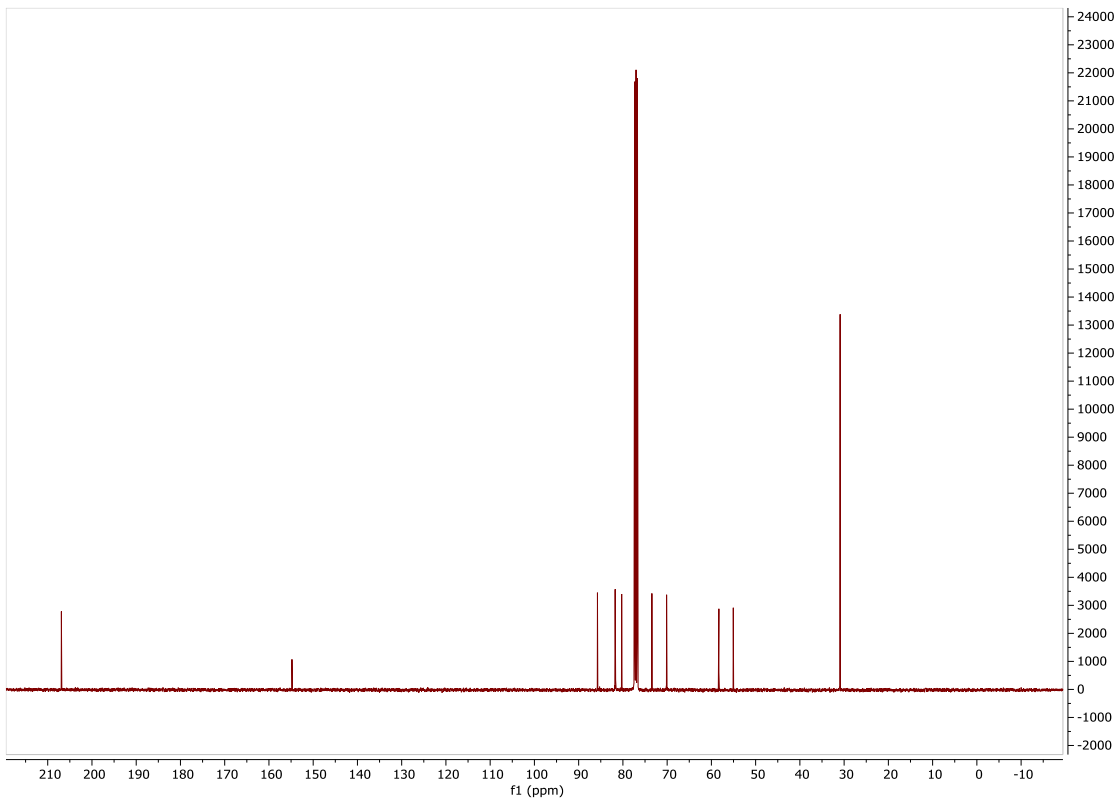
- Mass spectra



• $^1\text{H-NMR}$, CDCl_3

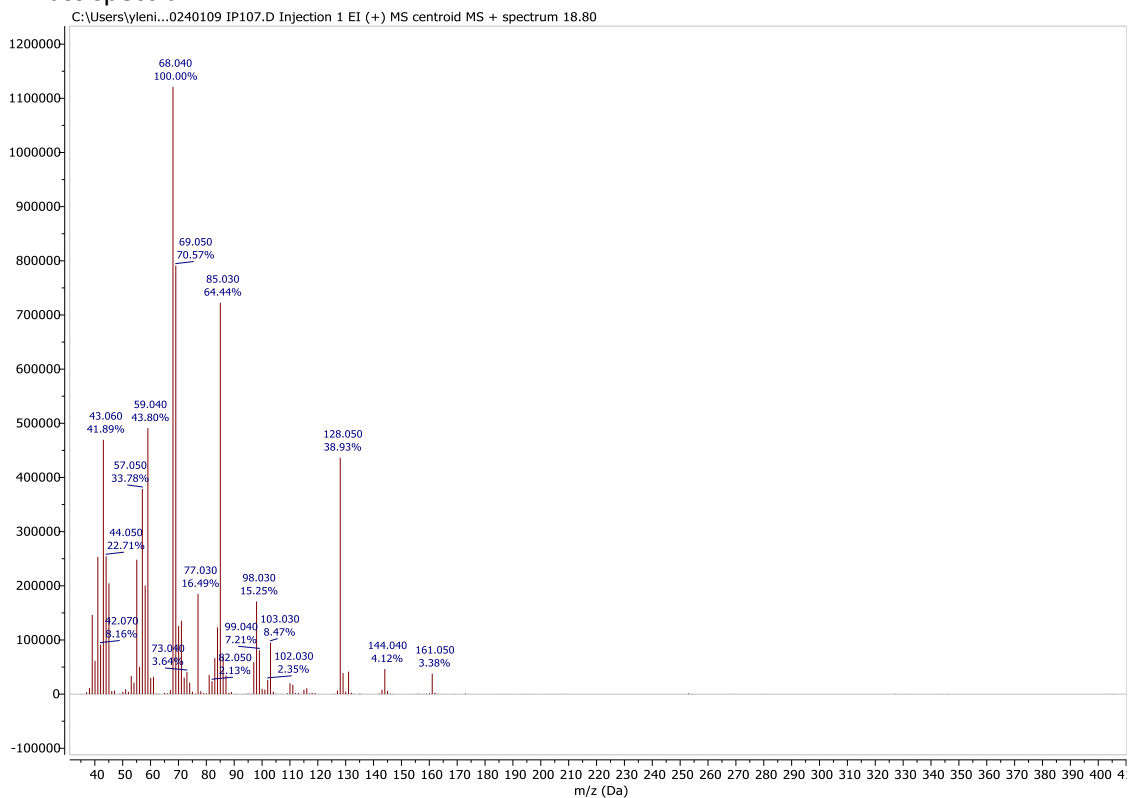


• $^{13}\text{C NMR}$, CDCl_3

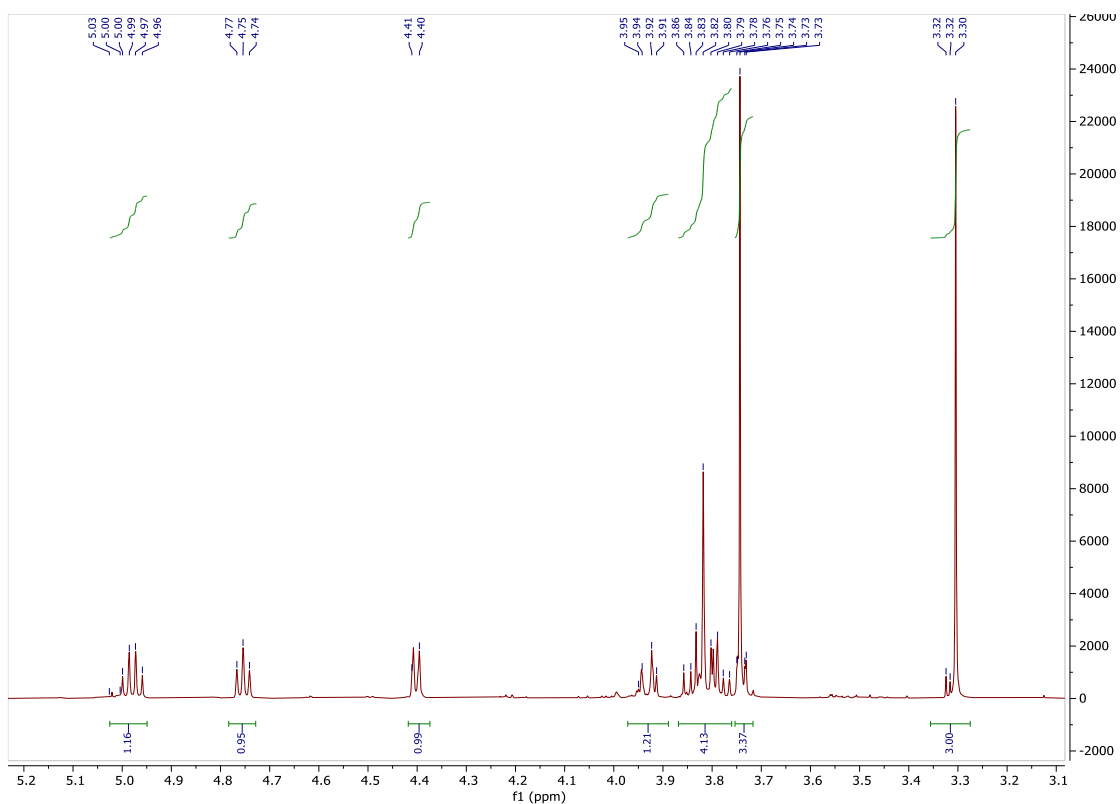


6.1.8 Characterization of monocarboxy monomethyl isosorbide (MCMI-2)

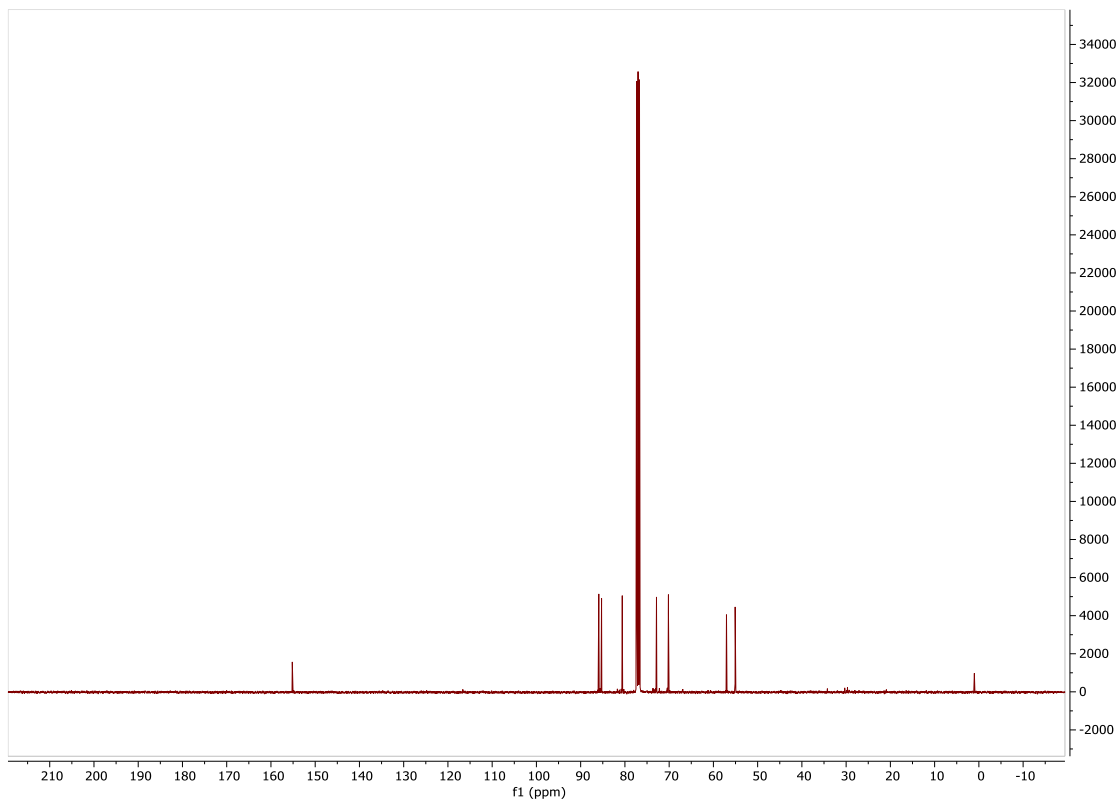
• Mass spectra



• $^1\text{H-NMR}$, CDCl_3

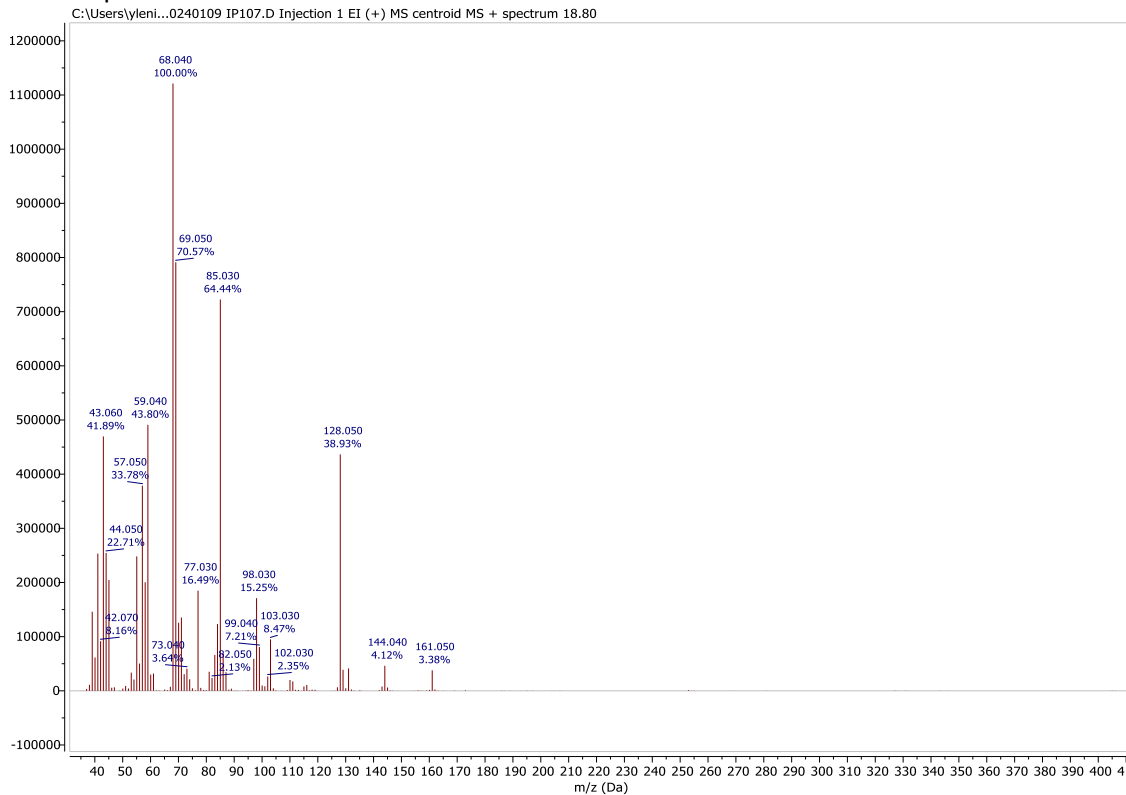


- ^{13}C NMR, CDCl_3

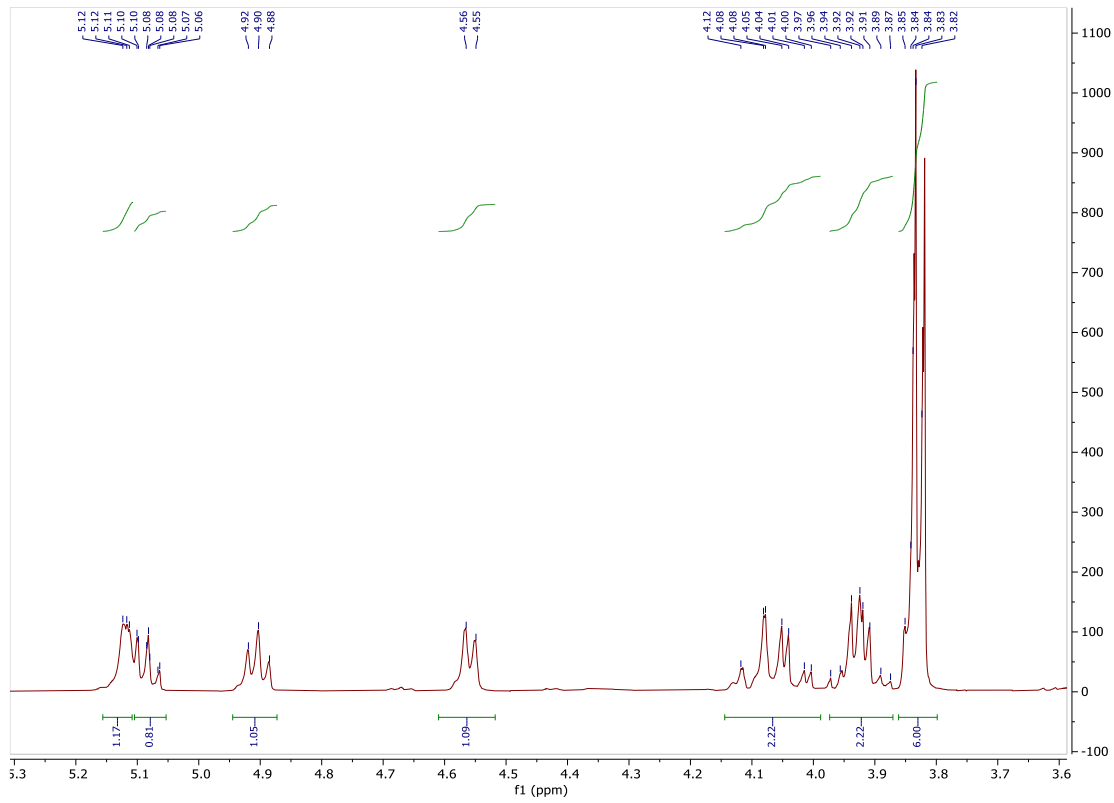


6.1.9 Characterization of di-methoxycarbonyl isosorbide (DCI)

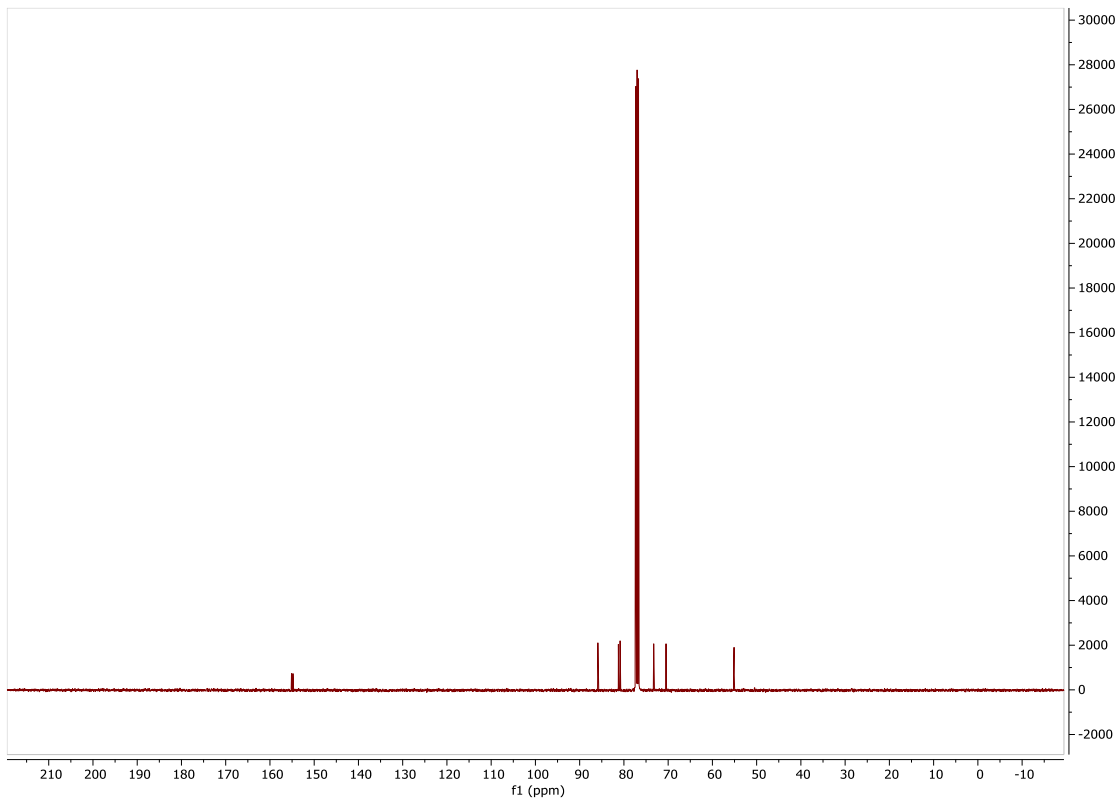
- Mass spectra



• $^1\text{H-NMR}$, CDCl_3

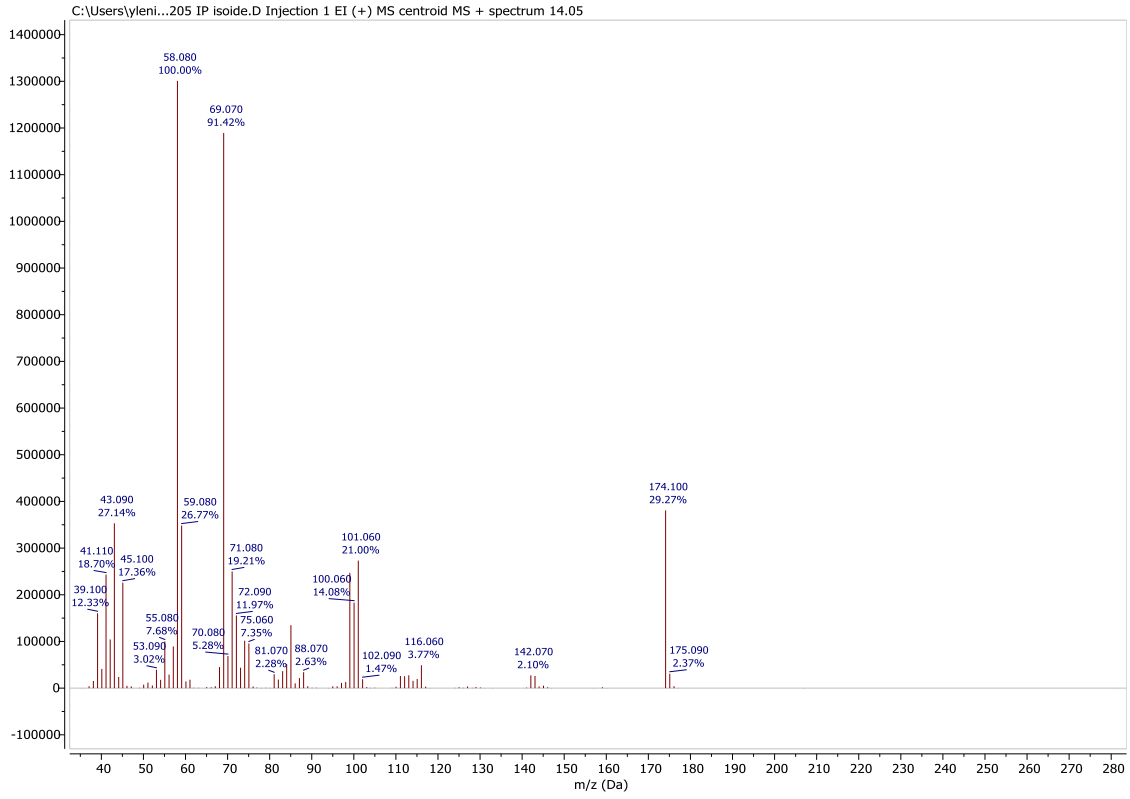


• $^{13}\text{C NMR}$, CDCl_3

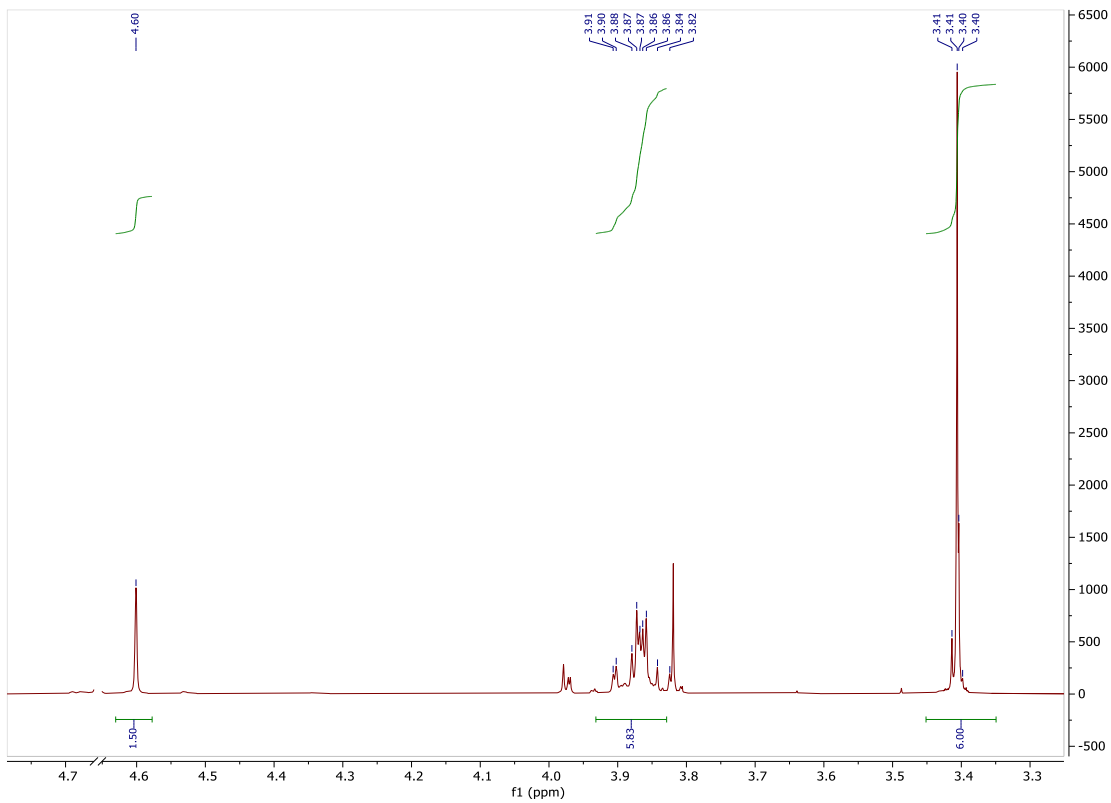


6.1.10 Characterization of dimethyl isoidide (DMli)

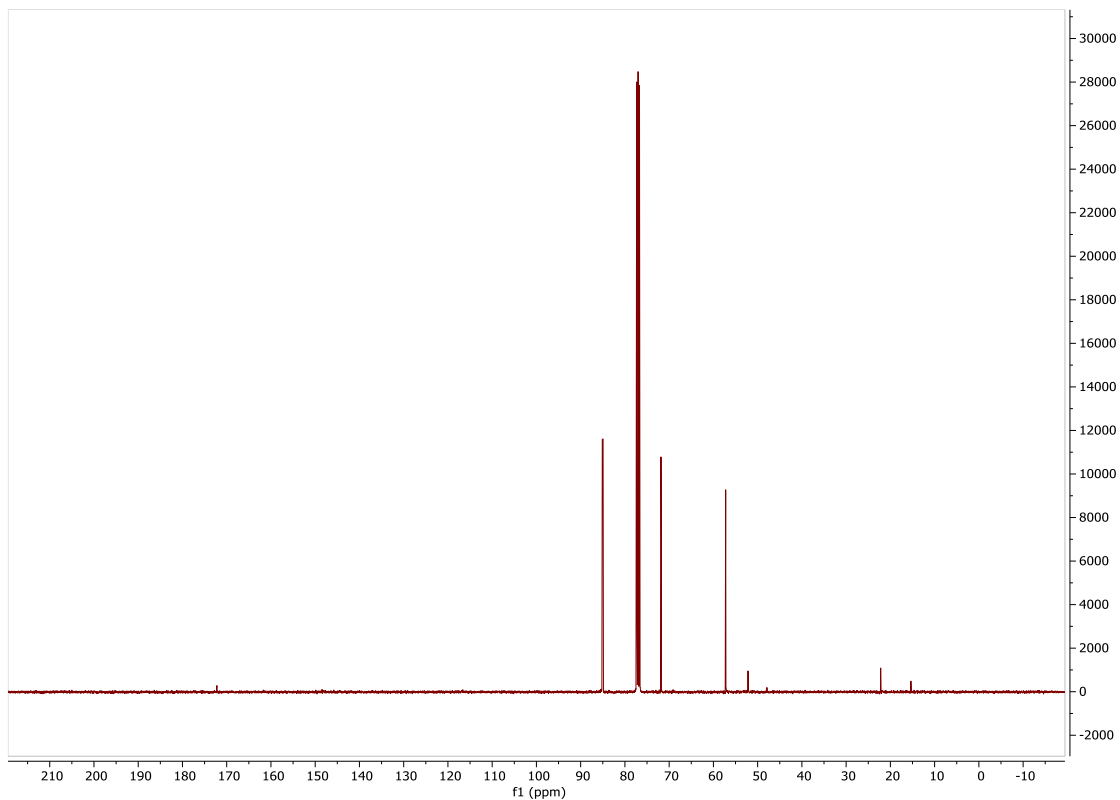
- Mass spectra



- $^1\text{H-NMR}$, CDCl_3

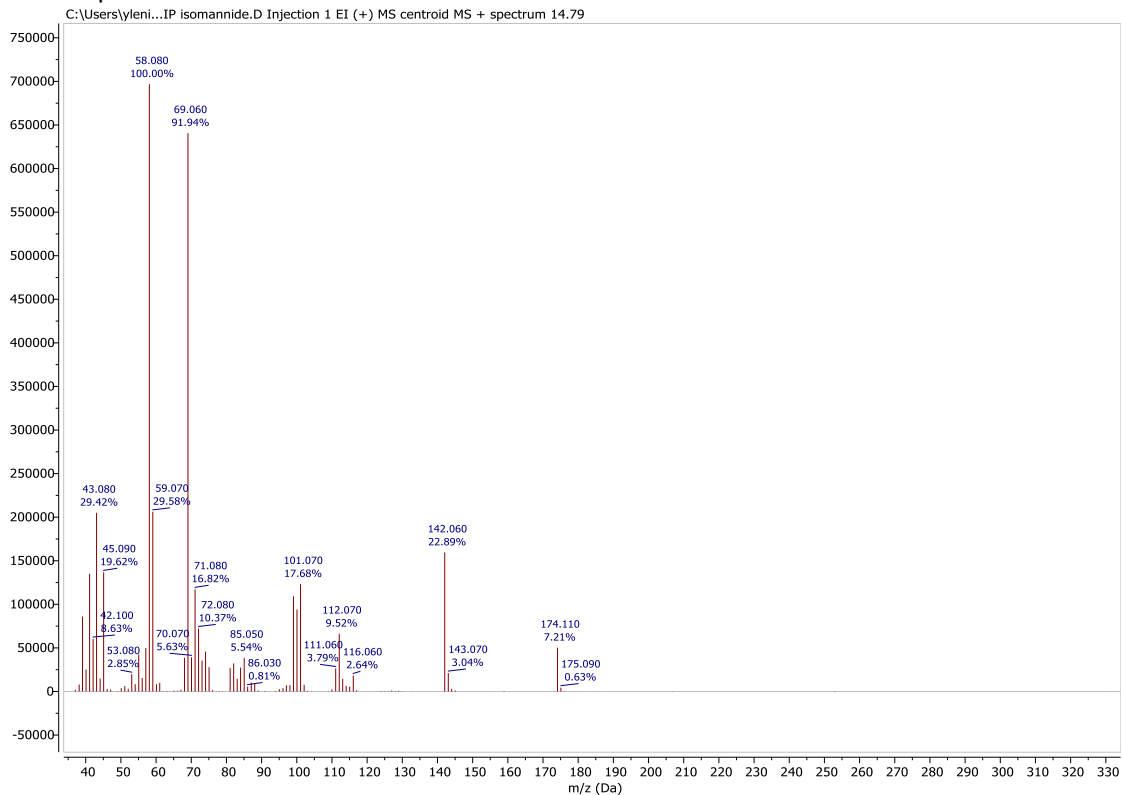


- ^{13}C NMR, CDCl_3

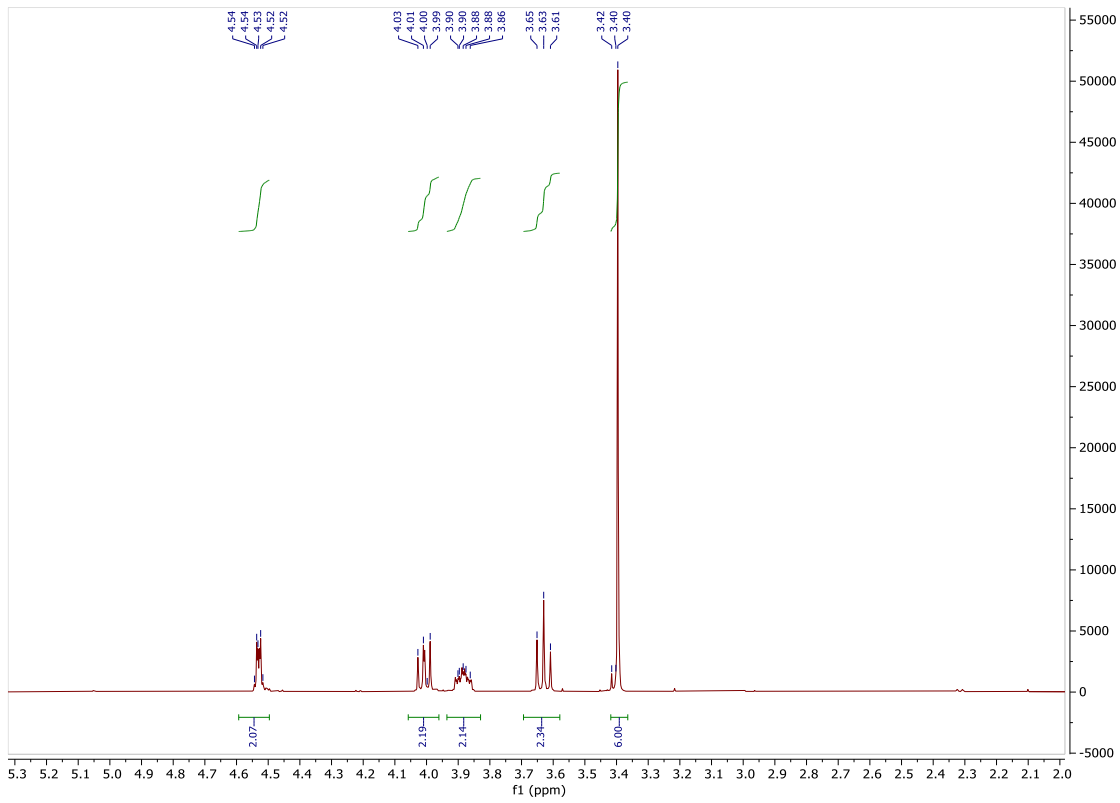


6.1.11 Characterization of dimethyl isomannide (DMIm)

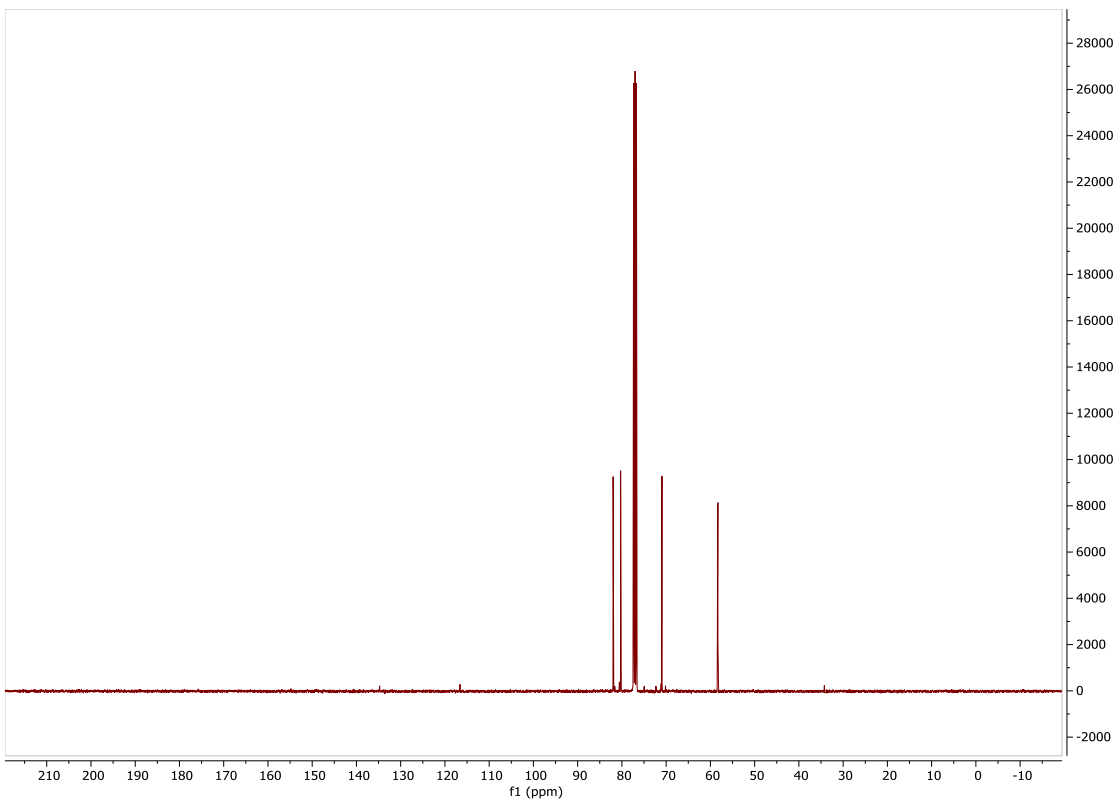
- Mass spectra



• $^1\text{H-NMR}$, CDCl_3



• $^{13}\text{C NMR}$, CDCl_3



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