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Final Thesis

The synthesis and reactivity of enol esters with diols: competitive transesterification and acetalization reactions

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ABSTRACT

A general solvent-free protocol for the synthesis of isopropenyl esters (iPEs) was developed and applied to different carboxylic acids, even renewable ones, and their acyl chlorides derivatives. Isopropenyl acetate (iPAc), a cheap and non-toxic reagent, was used as a "isopropenyl synthon" to synthesize the desired iPEs from benzoic, *p*-methoxybenzoic, octanoic, phenylbutyric, levulinic, oxalic, malonic and succinic acids, in the presence of sulfuric acid as a catalyst. At 90°C and atmospheric pressure, yields of isolated products were typically major than 90%. Brønsted-acidic ionic liquids (BAILs) were also tested to catalyze the reaction. Upon simple modifications including the use of chloroform ($CHCl_3$) as a solvent and resin Amberlyst-15 (Amb-15) as a heterogeneous acid catalyst, the procedure was extended to dicarboxylic acids, such as oxalyl chloride and succinyl chloride.

The reactivity of iPEs was then investigated by exploring the acid-catalyzed reaction of some of the synthesized iPEs, *i.e.* isopropenyl- benzoate, octanoate and phenylbutyrate with model diols as 1,2-propanediol and ethylene glycol, and Amberlyst-15 resin as a catalyst. Under such conditions, the occurrence of an initial transesterification process induced the release of acetone (from the enol leaving group) which, in turn, triggered a competitive acetalization reaction. This study examined the effects of experimental conditions (T, p, solvent and type of reactor) on the relative extent of the two competitive transformations. For comparison, also iPAc was tested. Of the several investigated approaches, most reliable and interesting results were achieved at 70-90°C in an autoclave under moderate pressure (N_2, 8 bar). This procedure showed that different esters exhibited different reactivity, but conditions could be tuned to allow not only a complete conversion of diols (limiting reagents), but also a control of the two sequential (tandem) reactions so that co-product acetone was quantitively consumed for the acetalization process. Accordingly, the corresponding selectivities towards the ester and the acetal as final derivatives were close to 50% each, thereby approaching the theoretic values expected by the stoichiometry. To this purpose, cyclopentyl methyl ether (CPME) was used as a reaction solvent.

Keywords: *isopropenyl esters, transesterification, acetalization, tandem-type reactions.*

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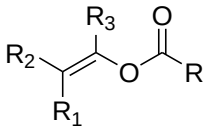
1. INTRODUCTION

1.1. Enol esters: synthesis and reactivity

An initial overview is offered on the synthesis and reactivity of enol esters with a major focus on those compounds used throughout this Thesis work.

Enol esters (EEs) are characterized by the presence of a carbon-carbon double bond adjacent to an ester group (Scheme 1.1).



Scheme 1.1. The general structure of enol esters.

1.1.1. Synthesis

Several synthetic pathways have been reported for the synthesis of EEs. One of the simplest and certainly the most readily available enol ester is isopropenyl acetate (iPAc), that is prepared industrially from the reaction of ketene (obtained upon thermal cracking of acetic acid) and acetone in the presence of strong acid catalysts (Scheme 1.2).[i,ii]

Scheme 1.2. Industrial synthesis of production of isopropenyl acetate (iPAc).

Isopropenyl acetate (iPAc) is a non-toxic, inexpensive, colorless liquid sourced from conventional suppliers such as Aldrich. Due to its chemical versatility, many efforts are under way to develop more sustainable protocols for the production of iPAc starting from bio-based reagents, particularly by using both renewable acetic acid from the catalytic reforming of biomass waste streams[iii] and renewable acetone from the well-known ABE fermentation technology.[iv]

Other general strategies for the synthesis of EEs are summarized in Scheme 1.3. One of the first method, dated back to 1940s, was based on the transvinylation of isopropenyl acetate with carboxylic acids in the presence of mercury (II), ruthenium (II), rhodium (II), platinum (II) and palladium (II) as catalysts (Eq. 1).[v] Although the procedure provided rare valuable homologues of iPAc, even on a large scale, many alternative protocols were investigated, aimed at avoiding both the usage of the highly toxic compounds (especially, mercury-based ones), and the quick deactivation of catalysts. A subsequent option was reported in the early 60s when the esterification of carboxylic acids with light EEs,

specifically iPAc and vinyl acetate, was reviewed under the classical Fisher conditions in the presence of sulphuric acid as a catalyst.[vi] The desired reaction occurred, but a not negligible formation of anhydride by-products was observed. The esterification of dicarboxylic acids (C_9-C_{14}: azelaic, sebacic, do-, tri-, and tetra-decanedioc acids) with iPAc was also examined: in this case however, mercury acetate/BF_3 proved a better catalyst to achieve the corresponding diisopropenyl esters.[vii]

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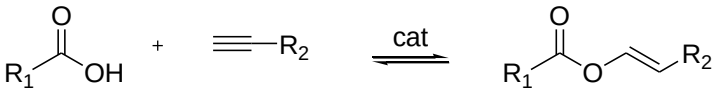
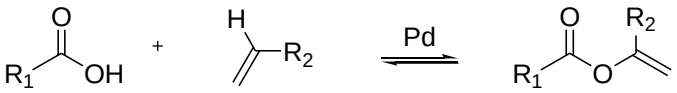


cat = Pd, Rh, Ru, Ir

(**5**)



Scheme 1.3. General strategies for the synthesis of enol esters.

An effective route was proposed in 1995, starting from silyl enol ethers that were discovered as selective enolating agents of acyl chlorides, in presence of copper (I) catalyst (Eq. 2).[viii] Another process for the synthesis of enol acetates was the vapour-phase oxyacylation of olefins with acetic acid (Eq. 3). This reaction was implemented on an industrial scale in the presence of a supported palladium (II) catalyst.[13] A good general method was discovered by using the catalytic hydroxycarbonylation of alkenes or alkynes (Eqn. 4 and 5): the reaction proved effective under mild conditions so that several carboxylic acids could be used affording a great variety of enol esters.[ix,x]

1.1.2. Reactivity

EEs are a class of versatile compounds that can be used for several synthetic goals. Some examples have been already illustrated in Scheme 1.3, describing the preparation of EEs. Other significant applications are in the acylation of alcohols,[xi,xii] in catalytic α-alkylations with both alcohols and silyl ethers,[xiii,xiv] in Michael additions to α,β-unsaturated carbonyl compounds,[xv] in decarboxylative Heck olefination reactions to produce vinyl arenes,[xvi] and in asymmetric hydrogenations to get both chiral α-hydroxy esters and alcohols (if acyl deprotection follows).[xvii,xviii]

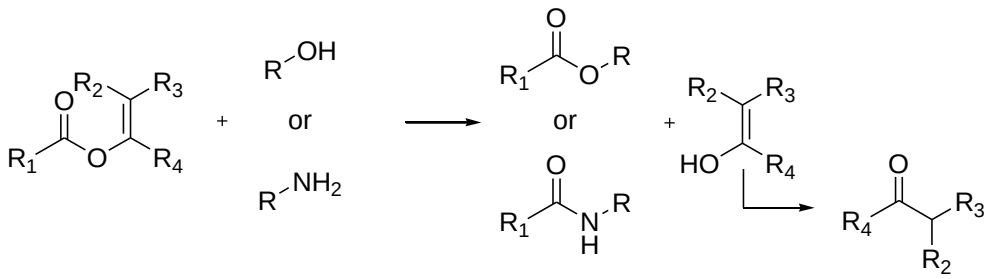
Due to the interest for this Thesis work, a more in-depth analysis is devoted to acylation reactions mediated by EEs, specifically for the case of alcohols and amines. These processes, namely transesterifications and ammidations, are extensively used in multi-step sequences for the preparation of fine chemicals and the protection of labile synthons.[xix,xx] Conventional strategies for these reactions include more often carried acyl chlorides and anhydrides as reactants, and acidic or basic catalysts such as $Sn(OTf_3)$, $TiCl_4/AgClO_4$, $CoCl_2$, etc.., or pyridine, triethylamine and 4-(dimethylamino) pyridine, etc., respectively. Moreover, combined mixtures of Lewis acids and bases have been reported.[xxi] Scheme 1.4 illustrates general ammidation and esterification procedures with conventional reagents.

Starting fr

Scheme 1.4. Transesterification and ammidation reactions using acyl chlorides and anhydrides (Eq. 1 and 2, respectively).

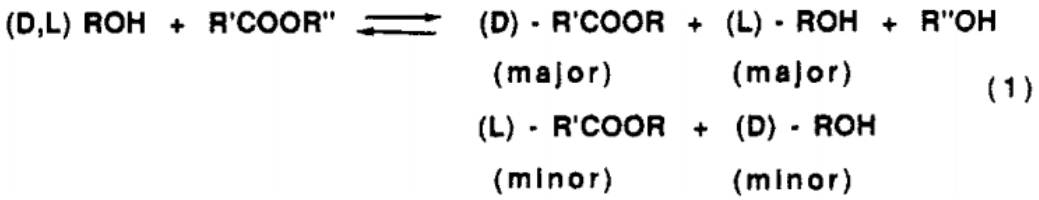
These protocols however, pose drawbacks from both the environmental standpoint and the synthetic efficiency. Most remarkable ones are the toxic/corrosive nature of reactants (anhydrides and mostly, chlorides), the co-formation of stoichiometric salts/acids to be disposed of, and the use of excess reagents or high temperatures to shift rightwards the involved equilibria. Yet, it should also be mentioned that: i) anhydrides and chlorides often lack selectivity for either primary or secondary hydroxyl groups; ii) functions such as dienes, epoxides, acetals and silyl ethers can be susceptible to acidic cleavage, and iii) (basic) catalysts may be air-sensitive and flammable.

As mentioned above, enol esters can be an alternative to prevent these problems. A first advantage is that both transesterification and ammidation protocols promoted by EEs do not suffer from the onset of reverse reactions because the leaving group is an enol which rapidly tautomerizes to the corresponding ketone (or aldehyde in case of vinyl esters), thereby making the overall process irreversible (Scheme 1.5).



Scheme 1.5. Not reversible transesterification and ammidation reactions mediated by EEs.

Moreover, the co-product carbonyl compound can be often isolated and used as a reagent or a solvent for other purposes. The literature reports several reactions in which either isopropenyl and homologue enol esters have been used as acyl sources. One remarkable example described the use of EEs in the bio-catalyzed kinetic resolution of racemic alcohols.[xxii] Enzymes, specifically lipases, catalyze the acylation of a number of hydroxy compounds; however, when conventional esters are used, the reversible nature of the transesterification reaction reduces, if not hinders completely, the stereoselectivity of the process (Scheme 1.6).



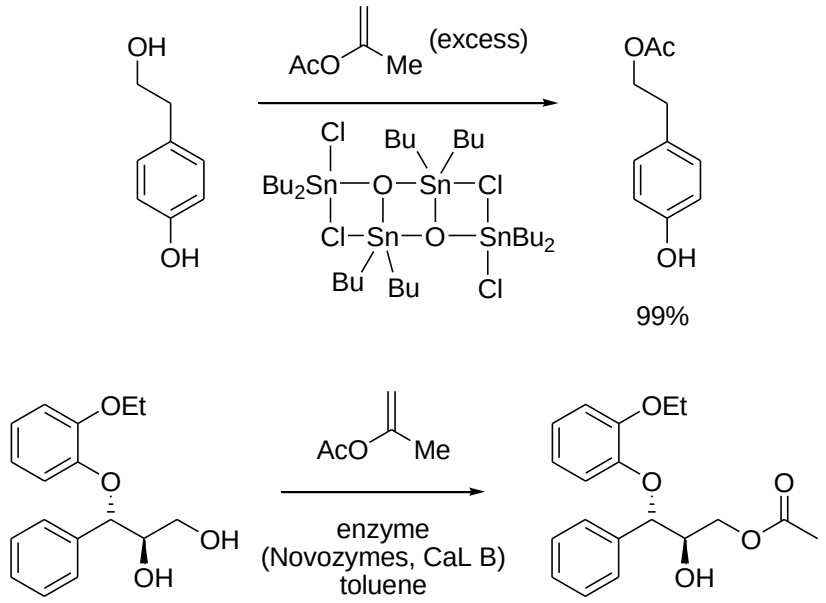
Scheme 1.6. Kinetic resolution of racemic alcohols.

If the D isomer is a better substrate than the L isomer for the enzyme, accumulation of the D ester and the unreacted L alcohol will be observed. In the reverse reaction, however, the D ester is a better substrate which turns back to D alcohol. The enantiomeric excesses of both the D ester and the L alcohol will, therefore, decrease progressively as the extent of the reverse reaction increases. Under the same conditions (lipase catalyst), the problem is overcome by acylating alcohols with enol esters which make the process irreversible: ee up to 98% can be reached. A similar investigation was carried out for the lipase (from *Alcaligenessp*) catalyzed reaction of several secondary alcohols with isopropenyl acetate, demonstrating that acetate esters products were preferentially formed with an R configuration (27 examples reported).[xxiii]

Other examples include EEs-promoted O-acylations catalyzed by metal salts and complexes. In this context, selective transesterifications of vinyl acetate with both primary and secondary alcohols were described in the presence of $PdCl_2$ or $[Bu_4N][Fe(CO)_3(NO)]$ (Scheme 1.7):[xxiv, xxv]

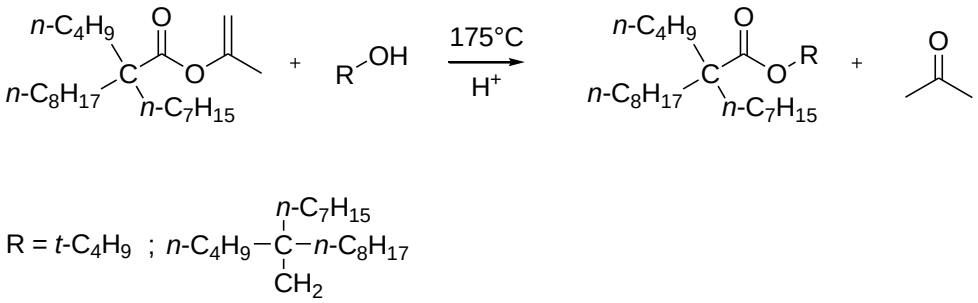
Scheme 1.7. Examples of selective O-acylations with EEs catalysed by metal salts and complexes.

More recently, an analogous protocol expanded the reaction scope to phenols which were converted to the corresponding aryl acetates using DABCO as an organocatalyst. [xxvi] Interesting results were also described when the reaction of polyfunctional substrates including polyols bearing primary and secondary hydroxyls and phenol groups, and aminoalcohols, was explored. It was noticed that using *iso*-propenyl acetate as the acyl source, catalytic and biocatalytic methods proved successful for the exclusive protection of primary alcohols (Scheme 1.8, top),[xxvii, xxviii] while under solventless and catalyst-free conditions, aminoalcohols underwent a highly chemoselective reaction to yield only amide products (Scheme 1.8, bottom).[17]



Scheme 1.8. Selected examples of chemoselective acylation reactions induced by isopropenyl acetate. Top: acylation of 4-(2-hydroxyethyl)phenol and a diol; bottom: acylation of aminoalcohols.

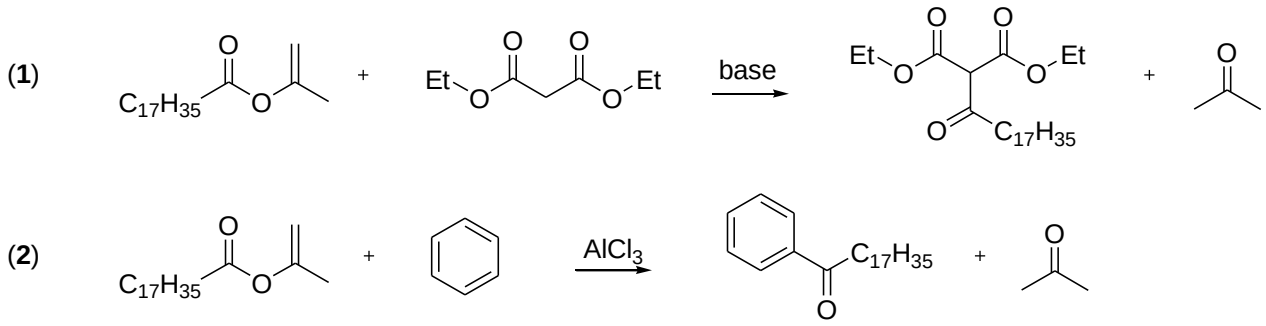
Isopropenyl esters were also claimed as acylating agents of both sterically hindered alcohols and weakly nucleophilic amides to produce the corresponding esters and N-acyl amides (and imides), respectively.[xxix,xxx] These strategies are illustrated in Scheme 1.9 where a mechanistic hypothesis is shown for the reaction of amides (bottom). *p*-Toluenesulfonic acid (PTSA) was the catalyst in all cases.



Scheme 1.9. Top: the transesterification of sterically hindered alcohols by isopropenyl2,2-dibutyldecanoate[29]. Bottom: a mechanistic hypothesis for the acid-catalysed acylation of amides with isopropenyl esters[30].

In the first step, isopropenyl ester is activated through the protonation of the C=C bond which originates a carbocation as a reactive electrophile (Eq. 1). This species is then subjected to an attack by the amide (despite its poor nucleophilicity) which affords intermediate **B** and restores the catalyst (Eq. 2). An intramolecular rearrangement brings to the final acylated product via the release of acetone whose formation becomes the driving force of the overall process (Eq. 3).

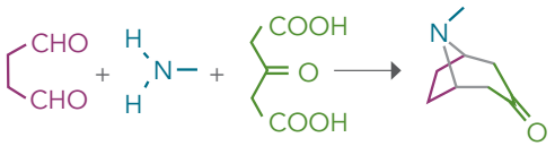
Enol esters were reported also as C-acylating agents. Scheme 1.10 reports two examples in which isopropenyl stearate was used to acylate diethyl malonate under basic conditions, and benzene in the presence of aluminium chloride as catalyst (Friedel-Kraft type reaction).[xxxi]



Scheme 1.10. C-acylation reactions mediated by isopropenyl stearate under basic and Lewis acidic conditions.

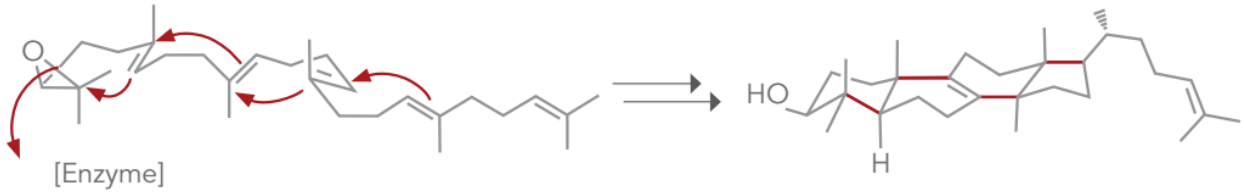
1.1.3. Tandem reactions: a new perspective for enol esters

Tandem reactions are extensively used in modern organic synthesis because they allow atom economic pathways with reduced purification and separation steps.[xxxii] To cite a couple of models, the synthesis of tropinone published more than a century ago by Robison represents one of the most known examples of multiple reactions occurring in one-pot for the preparation of an alkaloid (Scheme 1.11).[xxxiii]



Scheme 1.11. Synthesis of tropinone by sequential reactions involving an intramolecular double Mannich reaction of succynaldehyde, methyl amine, and 3-ketoglutaric acid (3-oxopentanedioic acid).

Another fascinating case is the cyclization of squalene oxide to produce a precursor for steroids such as lanosterol (Scheme 1.12).[xxxiv]



Scheme 1.12. The cyclization of squalene oxide.

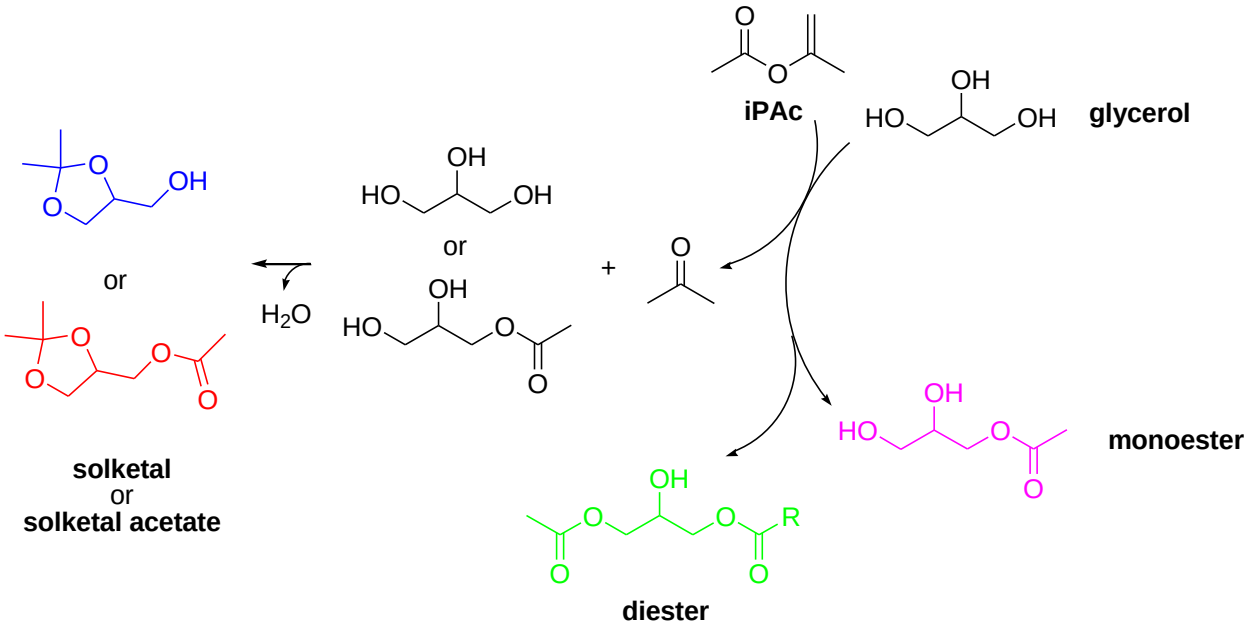
The literature refers indifferently to cascade, tandem, and domino reaction to describe such processes. “Tandem” means literally "one after another" and, as a general principle, this concept is usually associated to two or more close elements with combined effects to drive/activate simultaneously the same system. Specifically, tandem reactions can be envisioned as a set of transformations positioned one behind the other in a way which often suggests a time-dependent sequence of events. However, multiple processes may also occur concurrently as, for example, in concerted mechanisms. This observation explains the need to specify how a set of considered reactions happen,[xxxv] and it helps to introduce one of the main aspects studied in this Thesis work.

As a part of the research interests of our group on the upgrading of bio-based derivatives (compounds of renewable origin), we recently explored the reaction of glycerol with enol esters, more specifically with isopropenyl acetate (iPAc) aimed at developing a sustainable protocol for the synthesis of mono- and di-acetates of glycerol and acetin as well.[xxxvi] Under catalyst-free conditions, this investigation proved that the selective preparation of acetine could be achieved in the continuous-flow mode at relatively high T and P (300 °C and 50 bar, respectively) (Scheme 1.13, top); however, at a lower temperature (180 °C),

the batch reaction of glycerol and iPAc showed the occurrence of both transesterification and acetalization processes (Scheme 1.13, bottom)

Scheme 1.13. The reaction of glycerol with iPAc: i) synthesis of acetine in the CF-mode (top); ii) the formation of products from both transesterification and acetalization reactions (bottom, batch conditions). Bold % indicates selectivities towards shown products.

The results clearly highlighted that once acetone was released by the transesterification of glycerol with iPAc, it could be entrapped by the same reactant glycerol to form either (2,2-dimethyl-1,3-dioxolan-4-yl)methanol, well-known commercially as solketal, and its acetate derivative [(2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate].



Scheme 1.14. Occurring synthetic pathways during the transesterification/acetalization processes of glycerol.

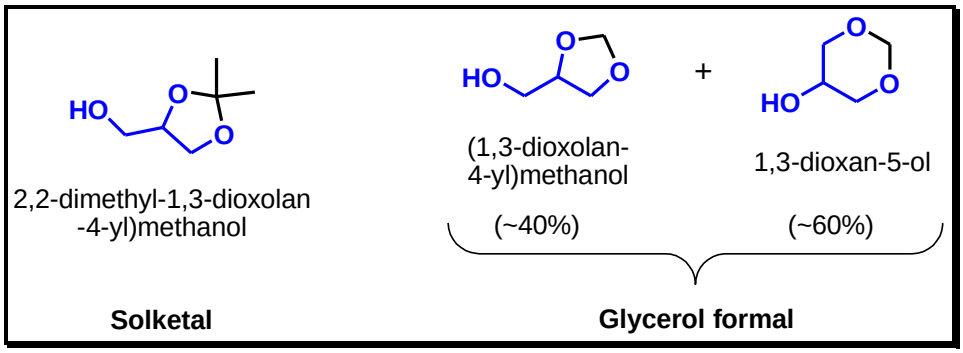
The overall sequence exemplified the case of tandem cascade events, in which two processes were intrinsically coupled: specifically, they both occurred under the same experimental conditions, but the transesterification reaction took place first, thereby

providing the environment suitable to induce the second acetalization step (Scheme 1.14).[xxxvii]

This observation prompted our research group to consider the potential of the dual-reaction system to maximize its carbon economy by improving the selectivity of the involved processes. In other words, by a full exploitation of acetone co-produced from the transesterification of isopropenyl esters, for the concurrent synthesis of acetals. For the interest in this subject, the following paragraph will overview salient details of acetals and the acetalization reaction with an eye to the use of glycerol, and diols as ethylene glycol and propandiol which have been used in this Thesis work.

1.2. Acetalization

Linear and cyclic acetals are usually prepared by the condensation of an aldehyde or a ketone with an alcohol (or a diol/polyol) in the presence of an acid catalyst. Owing to their stability to aqueous and non-aqueous bases, to nucleophiles including powerful reactants such as organometallic reagents, and to hydride-mediated reductions, acetals are among the best-known protecting groups for carbonyl compounds.[xxxviii] Acetals however, may be of interests also for their use as such. This is for example, the case of glycerol-derived cyclic acetals (GAs: glycerol acetals) of which representative model compounds are solketal (right, Scheme 1.15) and glycerol formal (GlyF, existing as a mixture of isomers; left, Scheme 1.15), deriving from the reaction of glycerol with acetone and formaldehyde, respectively.



Scheme 1.15. Right: five mebered acetal of solketal (commercially available as 97% pure isomer); left: glycerol formal is commercially available as a 3:2 mixture of six- and five-membered ring isomers.

GAs find major applications as safe solvents and additives in the formulation of injectable preparations, paints, plastifying agents, insecticide delivery systems and flavour.[xxxix] Specifically, effective scents are obtained by the reactions of glycerol with phenylacetaldehyde and vanillin, which lead to hyacinth and vanilla fragrances, in the presence of strong acids such as PTSA, HCl, H_3PO_4 and acidic divinylbenzene-styrene

resins.[xl] These compounds are in the list of the Flavor and Extract Manufacturers Association (FEMA-GRAS) regulated by the US Food and Drug Administration (FDA).[xli] Moreover, the stability of GAs to oxidative conditions and their miscibility with biodiesel blends, have been key features for their potential use as renewable diesel additives.[xlii]

The use of 1,2-diols as acetalization reagents obviously leads to the synthesis of 5-membered cyclic products. In particular, the acid-catalysed reactions studied in this work, i.e. the acetalization of 1,2-propandiol and ethylene glycol with acetone forms 2,2,4-trimethyl-1,3-dioxolane and 2,2-dimethyl-1,3-dioxolane, respectively (Scheme 1.16)[xliii, 44].

Scheme 1.16. The acetalization of ethylene glycol and 1,2-propanediol with acetone.

Several papers report on the acetalization of ethylene glycol by using both both Brønsted and Lewis acid catalysts.[xliv, xlv, xlvi] For example, yields as high as 95% on the desired product (2,2-dimethyl-1,3-dioxolane) were claimed at ambient temperature with HCl in dimethyl silicon dichloride (Me_2SiCl_2). Interestingly, a highly effective continuous-flow procedure was also described in the presence of acid resins (Deloxan Asp or Amberlyst-15) as heterogeneous catalysts and supercritical CO_2 as the solvent.[xlvii] By contrast, a poorer literature is available on the synthesis and isolation of 2,2,4-trimethyl-1,3-dioxolane (TMD) from 1,2-propandiol and acetone. Very recently (this year), a protocol claiming a quantitative chromatographic yield of the ketal was reported using a new catalytic system comprised of silicotungstic acid ($H_4SiW_{12}O_{40}$) modified by 8-Hydroxy-2-methylquinoline.[xlviii] Though, the product was not isolated. A method patented in 2013 described that the same reaction took place with 75% conversion of propanediol and full acetalization selectivity over Amberlyst 36 catalyst.[43] In this case, the ketal was distilled, but data on the its isolated yield were still not offered. A more accurate procedure combining the use of 4 Å molecular sieves and Amberlyst-15, finally provided the TMD isolation: only a 35% yield was reached.[xlix] Notwithstanding the apparently simple conditions for acetalization reaction, this analysis shows that an efficient synthesis of TMD is not an easy task due to the tricky separation of the product from unconverted or excess reactants.

1.2.1. Acetalization catalysts

As mentioned in the previous paragraph, acid compounds are the most common catalysts for the acetalization reaction, though neutral systems have been also reported.[I] Among the latter, for example, N-Bromosuccinimide (NBS) may selectively catalyze the 1,3-dioxanation of several carbonyl compounds (Scheme 1.17).[Ii]

Scheme 1.17. Synthesis of a model acetal using NBS.

Going back to acid catalysis, sulfonated polystyrene-based resins are some of the most used heterogeneous systems to perform the synthesis of acetals. Of these solids, commercial Amberlyst-15 and Amberlyst-36 are representative examples whose general structure and salient properties are summarized in Scheme 1.18 and Table 1.1.[Iii, Iiii] These materials are usually available in the form of porous small beads (0.5-1 mm diameter) with a high surface area. Ion-exchange properties make the resins suitable for separation, purification, and decontamination processes, while the high acidity can be exploited for catalysis purposes.

Scheme 1.18. Polystyrene sulfonated structure of an acid exchange resin (left) and a representative picture of the resin beads (right).

Table 1.1. Comparison of the major properties of Amberlyst-15 and Amberlyst-36.

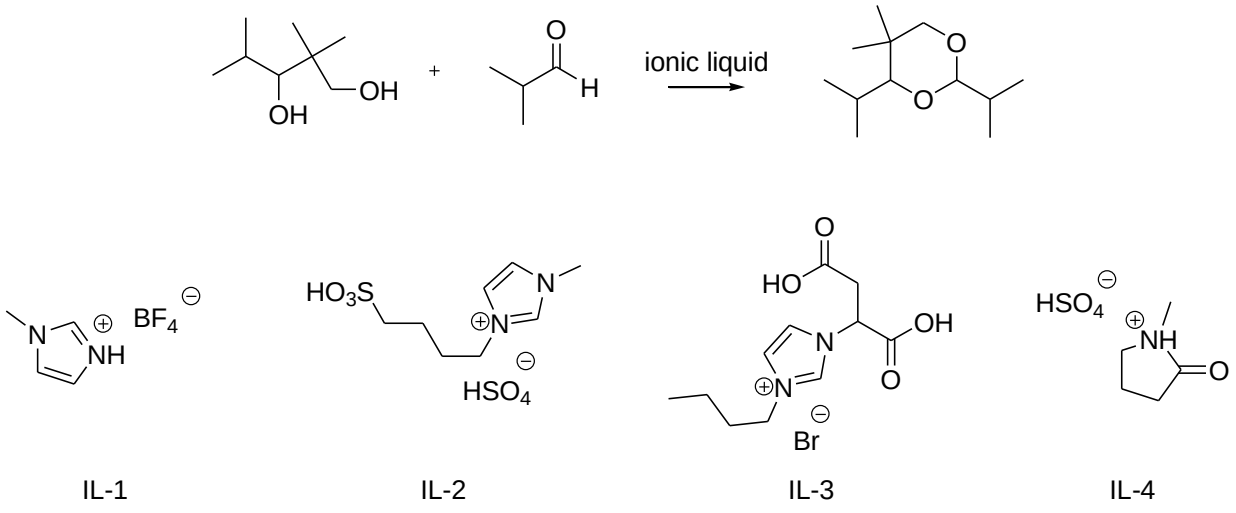
Parameter	Amberlyst-15	Amberlyst-36
Ionic form	H^+form	H^+form
Concentration of activesites	≥ 4.7 meq/g	>5.4 meq/g
Moisture holding capacity	52 to 57%	51-57%
Particle size	0.600-0.850 mm	<0.425 mm

Average pore diameter	300 Å	240 Å
Total pore volume	0.40 mL/g	0.20 mL/g
Maximum operating temperature	120 °C	150 °C

Relevant applications include the preparation of GAs: for example, at T≤ 70°C, Amberlyst 15 has been reported to catalyze the reaction of glycerol with butanal or acrolein with very high selectivities to the corresponding acetals (>90%), while at 50–110°C, Amberlyst-36 is active for a high yield synthesis of glycerol formal from glycerol and formaldehyde.[liv] These resins, more specifically Amberlyst-15, have been extensively used throughout this Thesis work, for the catalysis of concurrent processes of transesterification and acetalization (see Scheme 1.19).

Scheme 1.19. Amberlyst-15 as tandem acetalization/transesterification processes catalyst.

Finally, Brønsted acid ionic liquids (BAILs) have also been described as acetalization catalysts. A typical example is shown in Scheme 1.20: several BAILs proved effective in the reaction of isobutyraldehyde with 2,2,4-trimethyl-1,3-pentanediol (TMPD) for the synthesis of 2,4-diisopropyl-5,5-dimethyl-1,3-dioxane. [lv]



Scheme 1.20. The acetalization reaction of isobutyraldehyde and TMPD (top) catalyzed by Brønsted acidic ionic liquids (bottom).

1.3. The Green Chemistry point of view

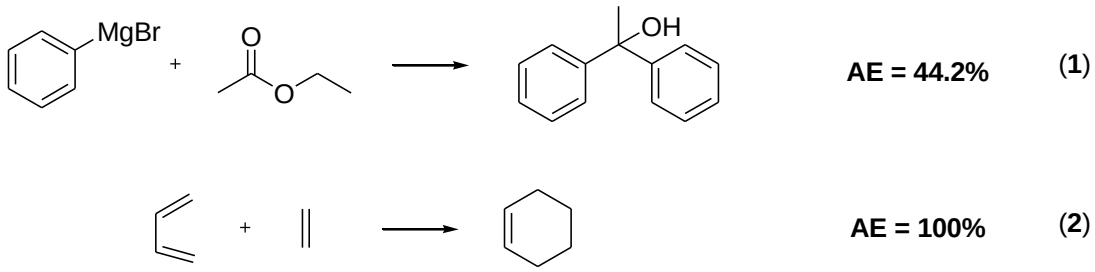
1.3.1. Atom and carbon economy

The definition of Green Chemistry is “designing chemical products and processes to reduce or eliminate the use and generation of hazardous substances”.[lvi, lvii] The Green Chemistry framework is based on twelve principles, introduced in 1998 by Paul Anastas and John Warner [lviii], which serves for designing new chemical products and processes. These principles can be summarized with an acronym, proposed by S. L. Y. Tang et al., the so called “PRODUCTIVELY”, which involves all the green chemistry features.[lix, lx] Among the whole principles, an immediate, direct way for evaluating the greenness of a process is throughout the green metrics, such as Atom Economy (AE) and Carbon Economy (CE), Enviromental Factor (EF), Reaction Mass Efficiency (RME), Effective Mass Yield (EMY) and Mass Index or Mass Intensity (MI), Stoichiometric Factor (SF) and Material Recovery Parameter (MRP). The following description will focus its attention on the AE and CE parameters, due to their importance for the description of the tandem synthesis of esters and acetals.

In 1990 Barry Trost introduced the Atom Economy or Atom Efficiency (AE) metric[lxi], defined as follows:

$$AE = \frac{MW\ of\ the\ desired\ product}{\sum MWs\ of\ all\ the\ reagents} \cdot 100$$

AE is referred to the concept of maximizing the incorporation of the reagents’ atoms into the products, in order to produce the less possible waste. As consequence, the ideal reaction would incorporate all the reactants’ atoms. It is a theoretical parameter that brings to easy access to the reaction efficiency. As an example, the comparison between a Grignard reaction and a Diels Alder reaction is made in order to illustrate the AE prospective (Scheme 1.21).



Scheme 1.21. The nucleophilic substitution (Eq. 1) is a lower atom economical reaction than a concerted one, such as a Diels Alder reaction (Eq. 2).

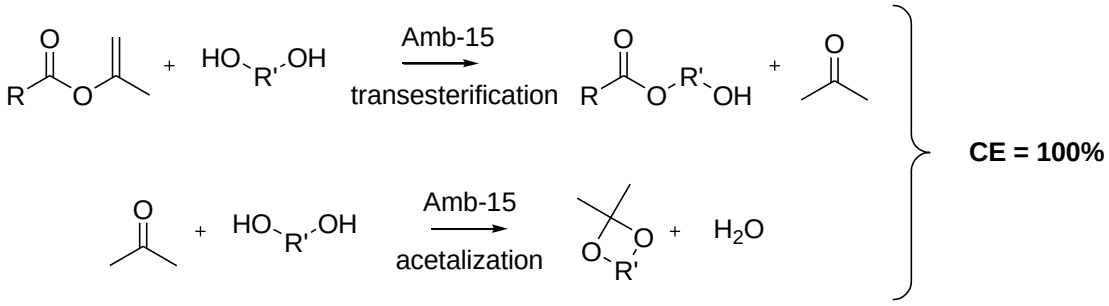
Eq. 1 shows an example of a Grignard reaction that belongs to the category of the substitutions. Due to their intrinsic characteristics, substitutions are not listed among the atom-economical reactions, indeed the substitution of a functional group with another involves the release of a leaving group. Conversely, the Diels Alder reaction (Eq 2) is an

excellent example of atom-economical reaction[61]; it is a concerted cycloaddition in wich all the reactants are incorporated into the product.

When only the C atoms are considered, the AE becomes Carbon Economy (CE), also called Carbon Efficiency as well.[61] An expression for CE is

$$CE = \frac{C\ mass\ in\ the\ desired\ product}{\sum C\ mass\ of\ all\ the\ reagents} \cdot 100$$

The concept of CE is applied to the tandem synthesis as the second objective of the Thesis work (see below Paragraph 1.4). Model isopropenyl esters and 1,2-diols reacted, under Ambelyst-15 catalysis, for synthesizing, throughout a sequential tandem process, both esters and acetals (Scheme 1.18). Two competitive reactions occur, as described in Scheme 1.22.



Scheme 1.22. The Carbon Economy (CE) of the tandem transesterification/acetalization reactions is always 100%.

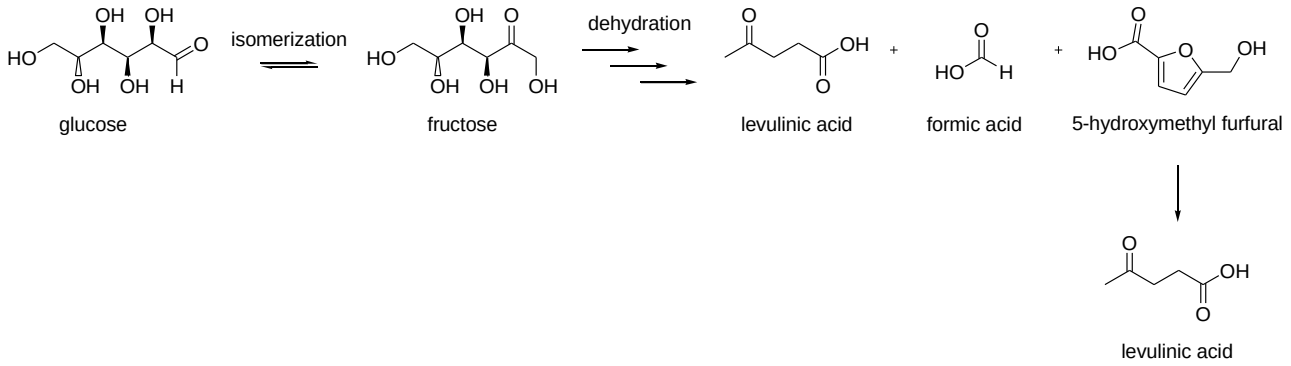
The CE of the overall synthesis is 100%. The strategy of exploiting the acetone co-product formation during the transesterification for the subsequent production of acetals is the key feature that justifies these high CE values.

1.3.2. Towards sustainability: renewable resources

Nowadays, Green Chemistry has not only to follow the twelve global principles, but also to drive towards the usage of renewable feedstocks when chemical synthesis are performed. This simple idea can be summarized as follows: why have I to use a conventional reagent for making my synthesis, instead of something else that is renewable? Considering also that, in some cases, the source of these sustainable product is waste, their cost would be competitive if compared to the fossil ones. Within this scenario, this thesis project aims to develop chemical routes for adding value to a selection of renewable compounds.

Malonic, succinic and levulinic acids. Malonic, succinic and levulic acids are three well-fitting examples of chemicals which can be industrially produced from renewable resources at an industrial scale. Starting from malonic acid, Lygos, Inc., a Lab in Berkeley, California, has developed a patent method for fermentative production of malonic acid[lxii]

The fermentative system, consisting in genetically modified Pichia Kudriavzevii, fed by oxygen, glucose and fermentation media, can produce 10 Mpounds/year of crystalline malonic acid, with a purity up to 99.9%. Starting again from various glucose sources, huge quantities of succinic acid are provided by a variety of genetically engineered microorganisms; [lxiii] fermentative succinic acid production is very competitive, for example if compared to an important petrochemical feedstock such as maleic anhydride[63]. To conclude, levulinic acid is a cellulose derivative and a wide range of processes are reported for its production. The dehydration of different hexose under acid catalysis is the classical way of synthesizing LA[lxiv] (Scheme 1.23).



Scheme 1.23. Dehydration of C-6 sugars for the synthesis of levulinic acid.

Ethylene glycol (EG) and 1,2-propanediol (PD). EG is listed among bulk chemicals.[lxv] Its conventional industrial production is led to the ethylene oxide process [lxvi] but some alternative chemical pathways have been developed aiming at the development of a biobased production. An example of feasible bioprocess uses *Escherichia Coli* through the action of a small group of enzymes, leading to a theoretical 90% yield of EG.[65] PD is a natural product and, nowadays, it is considered a commodity. Relevant biochemical routes can be enclosed among the most competitive pathways for the synthesis of PD. [lxvii] Furthermore, racemic mixtures of PD can be obtained also through chemical hydrogenolysis , starting from sugars.[lxviii] Another starting material for the PD synthesis is glycerol that can be reduced under homogeneous or heterogeneous catalysis.[lxix, lxx] On the other hand, for what is concerned with fermentative processes an example is represented in Figure 1.1.[67]

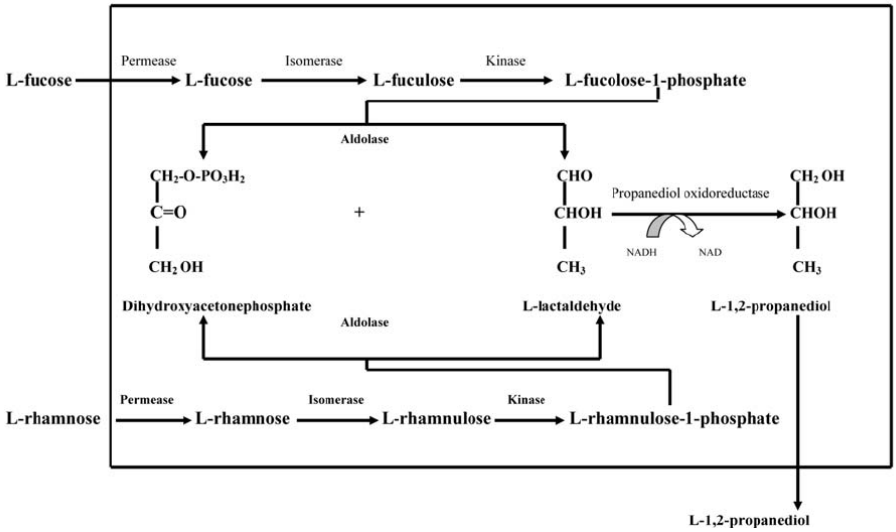
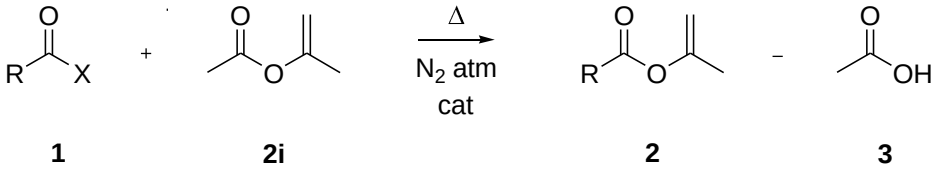


Figure 1.1. Schematic bioroutes for the synthesis of PD (reproduced from Ref. .

1.4. Aim and summary of the work

The present work has been aimed at a double objective.

The first one has dealt with the synthesis of a small library of isopropenyl esters (iPEs), all derived from commercial isopropenyl acetate (iPAc). To this purpose, two major routes have been devised which included the use of iPAc for the catalytic esterification of carboxylic and dicarboxylic acids (octanoic, benzoic, p-methoxybenzoic, phenybutyric, levulinic, succinic, malonic, oxalic acids), and the acyl nucleophilic substitution of acyl chlorides (octanoyl, benzoyl, p-methoxybenzoyl, phenybutyryl, succinyl, malonyl, oxalyl chlorides) (Scheme 1.20).



Scheme 1.20. iPEs were synthesized starting from iPAc and both carboxylic acids or acyl chlorides.

Different catalysts such as strong protic compounds (sulfuric and *p*-toluensulfonic acids) and Brønsted acid ionic liquids (BAILs) as $BSMIMHSO_4$ and $HMIMBF_4$, and different batch conditions with both open and closed (autoclaves) reaction vessels were explored.

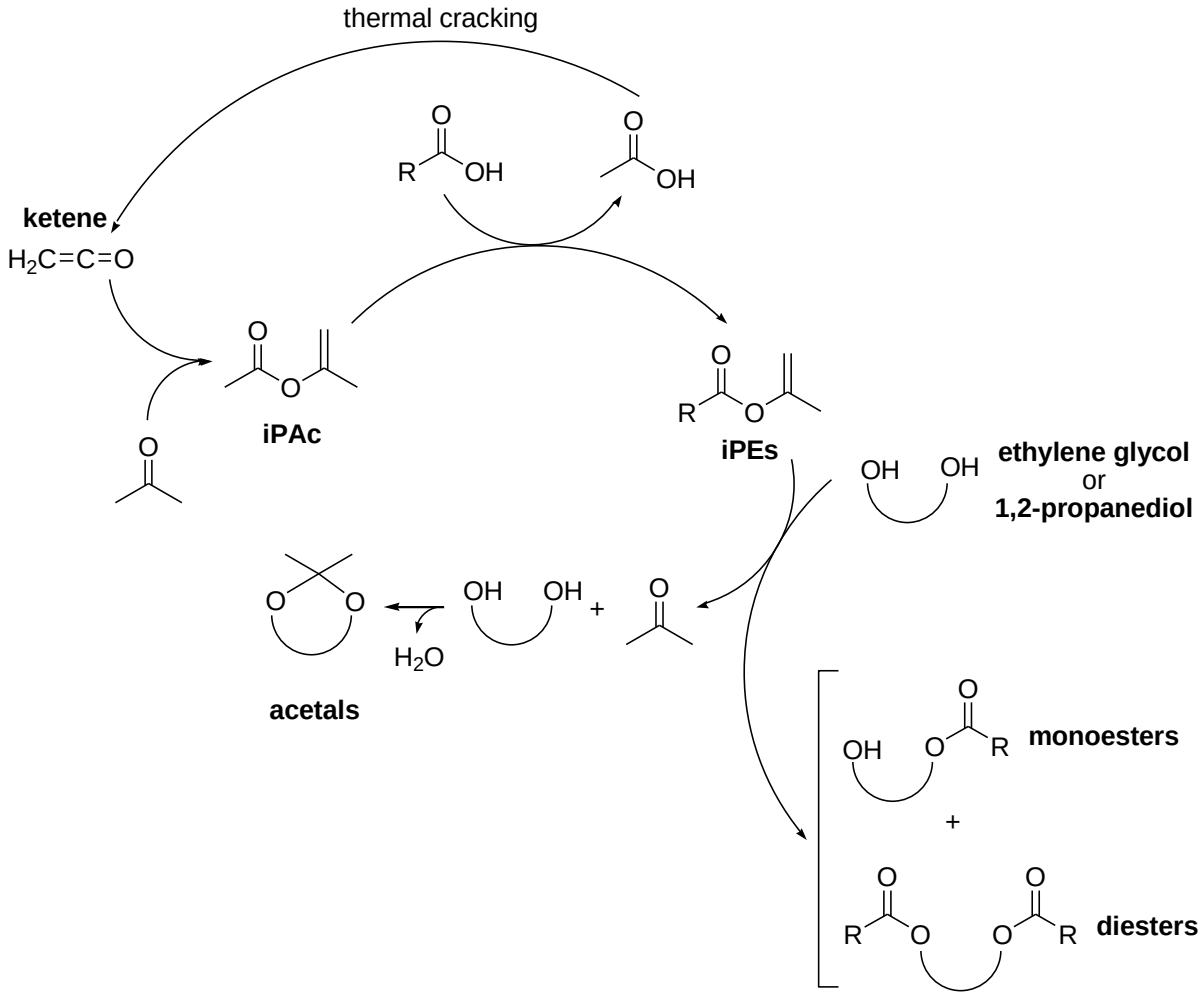
Results highlighted that the nature of carboxylic acids could remarkably affect the reaction outcome: the expected iPEs were observed, but the selectivity was sometimes undermined by the co-formation of the corresponding anhydrides. As an example, starting from octanoic and phenylbutyric acids, the isopropenyl octanoate and phenylbutyrate esters were isolated in a 31% and 39% yield, respectively. In all cases, an excess iPAc amount was used (acid:iPAc = 10 mol/mol), the ester serving simultaneously as reagent and solvent.

Acyl chlorides proved both more reactive and selective than carboxylic acids. The corresponding reactions usually gave higher yields of the desired iPEs (90-99%), though stoichiometric amounts of chloride salts formed and needed to be disposed of.

Syntheses of iPEs were carried out on a molar scale for the preparation of 10-15 g of products.

The second objective of this work was focused on the comparative investigation of the reactivity of some isopropenyl esters of Scheme 1.20 with model 1,2-diols as ethylene glycol (EG) and 1,2-propanediol (PD). The concept behind this research was to devise a protocol by which a catalytic tandem cascade reaction could be implemented as illustrated in Scheme 1.21.

To improve the overall sustainability of the process, once the reaction of iPEs with diols yielded the corresponding esters, the strategy aimed at an *in-situ* exploitation of the co-product acetone to form acetals as further derivatives. Accordingly, a quantitative carbon economy could be achieved releasing only water as a by-product.



Scheme 1.21. Total carbon economical processes for the synthesis of mono- and di-esters, concurrently with acetals. iPAc is produced throughout the reaction of ketene, deriving from the recycling of acetic acid by thermal cracking, with acetone.

Several effects were considered including not only the nature of reactants (both diols and iPEs), but also the change of experimental conditions/parameters such as temperature and pressure, the type of reactor (open vessel and autoclave), and the use of solvents. Amberlyst-15 was always used as a catalyst for sequential transesterification and acetalization processes.

The investigation demonstrated that the reaction could be optimized to obtain the desired products (a mixture of a diol-derived monoester and an acetal) with selectivities approaching the theoretical values (50% for each of two components). For example, the concept was proved the reaction of 1,2-propandiol with iPAc: at 90 °C and 8 bar (autoclave), a substantial equimolar mixture of acetal and monoester was achieved in the presence of cyclopentylmethyl ether as the solvent. The same held true when other iPEs were used, such as isopropenyl octanoate and isopropenyl phenybutyrate. By contrast, due to high reactivity of primary OH groups of ethylene glycol (EG), the reaction with iPEs

formed preferentially esters derivatives: both mono- and di-esters of EG were noticed with selectivities ranging between 45-99% for the monoesters and 0-30% for the diesters, respectively. Only minor amounts of the corresponding acetal were obtained.

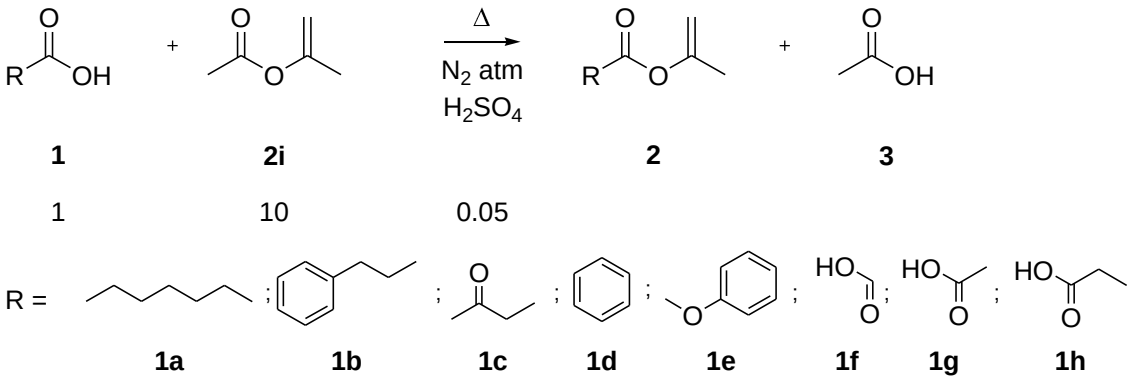
Overall, the study offers a basis to discuss on the relative reactivity of enol esters and diols as well as a route to exploit the synthetic potential of the tandem sequence and improve its carbon efficiency.

2. SYNTHESIS OF ISOPROPENYL ESTERS

State of the art and aim. The synthesis of esters is typically performed by reacting carboxylic acids or their derivates with an excess amount of an alcohol. An alternative way of synthesizing esters is by a transesterification. Transesterification reaction have been broadly discussed in the literature, involving different type of catalysts (acids, bases, etc.) [cfr. Articoli transesterificazioni]. Isopropenyl acetate was proved to be an interesting acylating agent for different type of substrates, in the absence of catalysts and solvents, due to its the peculiar reactivity (see isopropenyl acetate paragraph). For this reason, it was developed a small library of isopropenyl esters (iPEs), starting from isopropenyl acetate, bearing different acyl backbone. The attention was focused on the preparation of bio-based iPEs, developing a sustainable and reproducible synthetic protocol, relying on solventless reaction and on the use of acid catalysis. The method followed the procedure described by Rothmann et al. for the synthesis of isopropenyl stearate [cfr. Rothmann], in which the sulfuric acid-catalyzed interchange of stearic acid with iPAc brings to the formation of the respective more hindered enol ester.

2.1. FROM ACIDS

The reactivity of different acids with isopropenyl acetate (iPAc) as esterifying agent was investigated. Octanoic (**1a**), phenylbutyric (**1b**), levulinic (**1c**), benzoic (**1d**), p-methoxybenzoic (**1e**), oxalic (**1f**), malonic (**1g**) and succinic (**1h**) carboxylic acids were tested. The synthesis were conducted under H_2SO_4 acid catalysis, with a molar ratio between the substrates and iPAc of 1:10. In order to standardize the protocol, nitrogen atmosphere (N_2 atm) was generated into the batch system. Initially, typical reaction conditions are reflux temperature of iPAc and solventless conditions. A general reaction scheme is given in Scheme 2.1:



Scheme 2.1. Transesterification reaction between carboxylic acids and isopropenyl acetate.

The isopropenyl synthon interchange occurs producing the respective iPEs and acetic acid (**3**), that could be detected by GC-MS. Numerical results of conversion and selectivity are reported in Table 2.1*:*

Table 2.1. Experimental results obtained for the reaction of carboxylic acids with isopropenyl acetate.

Substrate	Time (h)	Conversion (%GC-MS)	Selectivity of 2 (%GC-MS)
1a	3	>99	88
1b	2	97	85
1c	0.5	>99	-*
1d	2	87	54
1e	2	75	26
1f	1	>99	-**
1g	1	>99	-**
1h	1	>99	-***

*the main product is α-angelica lactone; **it is not possible to detect any product (GC-MS/NMR); ***the main product is succinic anhydride.

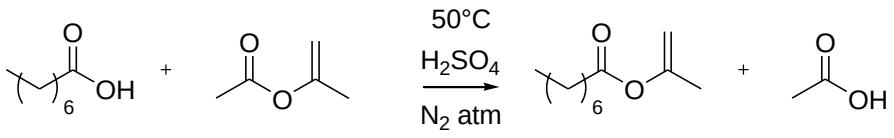
As we can see in Table 1 the method did not give the same results of conversion and selectivity for each carboxylic acid. Substrates **1a**, **1b** showed the highest selectivity towards the esters formation. For what concerns levulinic acid (**1c**) and succinic acid (**1h**), the formation of the iPEs was not observed and α-angelica lactone, succinic anhydride, respectively, were the unique obtained products. Finally, the reaction of substrates **1f**, **1g** with iPAc gave no detectable products by GC-MS (no peaks were seen in the chromatogram) and brought to a series of multiplets in H^1NMR, C^{13}NMR spectra. So, it was not possible to understand which compounds were formed.

During a further investigation, some tests have been made for each substrate without the use of H_2SO_4 as catalyst, maintaining the other conditions equal to the ones described in Scheme 2.1. In these way none reaction took place and the desired iPEs were not formed.

2.1.1. Effect of temperature and catalyst

Octanoic acid (**1a**) was selected as model compound for studying the effect of the temperature and of the catalyst due to its higher reactivity towards the isopropenyl interchange reaction.

Temperature. The reaction of substrate **1a** was carried at a lower temperature (50°C) than reflux of iPAc for 4h**,** as described in Scheme 2.2.



1a **2i** **2a** **3**

1 10 0.05

Scheme 2.2. Effect of the temperature in the synthesis of iPEs.

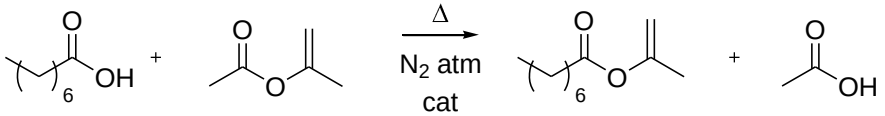
Comparative Table 2.2 includes the temperature-tests.

Table 2.2. Comparison between the tests carried at different temperatures.

T (°C)	Conversion (%GC-MS)	Selectivity of 2a (%GC-MS)
50	88	15
Reflux	>99	88

From Table 2.2 it is possible to observe that the temperature lowering to 50°C decreases both conversion and selectivity of substrate **2a**. Caprilic anhydride (CA, 22%) and octanoyl acetate (OA, 63%) were the main observed products by GC-MS; their isolation and characterization was not possible due to difficulties in separating the substrates **2a**, CA and OA by flash chromatography. Moreover, distillation was not feasible because of the products degradation.

Catalyst. In order to avoid the usage of sulfuric acid as catalysts, two Brønsted acid ionic liquids (BAILs), $BSMIMHSO_4$ and $HMIMBF_4$ respectively, and p-toluensolfonic acid (p-TSA) were investigated for the reaction of **1a** with iPAc (**2i**). Also for these tests the reaction conditions were maintained equal to the ones of the initial tests (reflux temperature, nitrogen atmosphere, molar ratio substrate:iPAc = 1:10). The synthesis were carried for 4h. Scheme 2.3 summarizes the catalysts-tests.



1a **2i** **2a** **3**

1 10 0.05

cat = $BSMIMHSO_4$; $HMIMBF_4$; p-TSA

Scheme 2.3. Variation of the catalyst for the synthesis of **2a**.

Table 2.3 describes the effect of the catalysts.

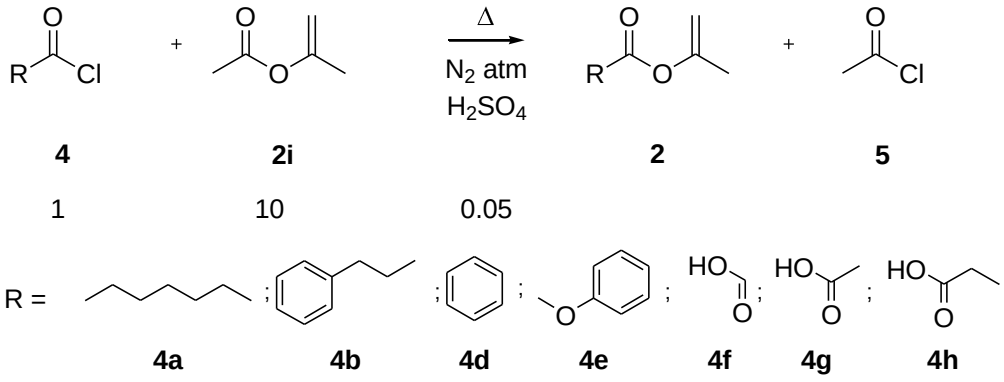
Table 2.3. BAILs and p-TSA for the synthesis of **2a**.

Cat	Conversion (%GC-MS)	Selectivity of 2a (%GC-MS)
$BSMIMHSO_4$	91	52
$HMIMBF_4$	81	-
p-TSA	95	18

From the data reported in Table 2.3 it can be noted that $HMIMBF_4$ is not an effective catalyst for the synthesis of **2a**, bringing to a OA selectivity of 46% and a CA selectivity of 39% (the remaining 15% of selectivity comprehends other various not-characterized products). Conversely, $BMIMHSO_4$ (with a higer broensted acidity) seems to be a better acid catalyst for the transesterification reaction. Indeed, when using $BMIMHSO_4$, an increase of conversion to the corresponding isopropenyl ester (**2a**) was observed, leading also in this case to the formation of CA (8%), OA (28%) and other by-products (12%). Finally, under p-TSA catalysis the isopropenyl ester **2a** was observed with a low selectivity together with other different not-characterized products.

2.2. FROM CHLORIDES

Acyl chlorides were used as substrates for the synthesis of iPEs. The aim of these test was to increase the reactivity of the reagents in order to reach higher conversions and improve the selectivity. Likewise the above tests, octanoyl (**4a**), phenylbutyryl (**4b**), benzoyl (**4d**), p-methoxybenzoyl (**4e**), oxalyl (**4f**), malonyl (**4g**) and succinyl (**4h**) chlorides reacted with iPAc by acid catalysis, at reflux temperature and under nitrogen atmosphere. Also for these synthesis the molar ratio of substrate:iPAc was maintained 1:10. Levulinyl chloride was not investigated because of some problems during its synthesis (see below). The reaction scheme is summarised in Scheme 2.4*:*



Scheme 2.4. Reaction of acyl chlorides with isopropenyl acetate.

Results of conversion and selectivity for the different acyl chloride scope are reported in Table 2.4*:*

Table 2.4. Experimental results of the reaction of acyl chlorides with iPAc.

Substrate	Time (h)	Conversion (%GC-MS)	Selectivity of 2 (%GC-MS)
4a	2	97	93
4b	1	>99	94
4d	4	75	97
4e	3	>99	>99
4f	4	>99	-*
4g	4	>99	-**
4h	1	>99	>99

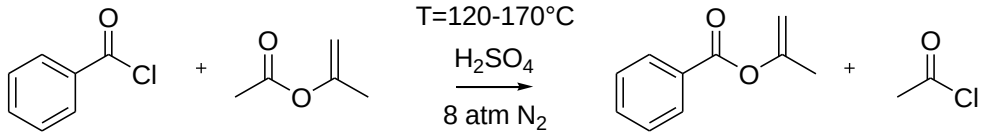
*not possible to detect any product by GC-MS or to identify one or more compounds by NMR; **detected a compound by GC-MS but it was not possible to isolate it.

From Table 2.4 it is possible to see that, as expected, the use of chlorides as substrate gives better results of conversion and selectivity, compared to the corresponding carboxylic acids. For example, isopropenyl succinate (**4h**) could be selectively obtained from the corresponding acyl chloride, differently from what observed in the previous synthesis with the respective acid. On the other hand, for substrates **4f**, **4g** some analytical problems were noticed, as already described for substrates **1f**, **1g** (see carboxylic acids paragraph). Oxalyl chloride (**1f**) was totally converted in some undetectable compounds by GC-MS (maybe too much volatile) and malonyl chloride (**1g**) brought to a product that could not be isolated and, than, characterized.

2.2.1. Effect of temperature and comparison between octanoyl (5a) and benzoyl (5d) chloride

The reactivity of benzoyl chloride (**4d**) was investigated varying the reaction temperature, in order to increase its conversion (it gave the lowest conversion results) and, furthermore, it was compared with substrate **4a** for what concerns the usage of different catalysts and the temperature.

Temperature. The reaction of benzoyl chloride (**4d**) was carried in autoclave for 2h, under 8atm of N_2 pressure, with the same molar ratio 1:10 between **4d** and iPAc, and increasing the temperature. The reaction scheme is summarized in Scheme 2.5:



4d **2i** **2d** **5**

1 10 0.05

Scheme 2.5. Reaction of **4d** with isopropenyl acetate.

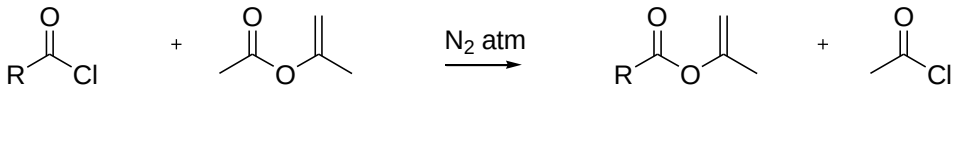
Quantitative results are reported in Table 2.5:

Table 2.5. Experimental results for the reaction between **4d** and iPAc performed in an autoclave reactor.

T (°C)	Conversion (%GC-MS)	Selectivity of 2d (%GC-MS)
120	72	97
150	88	95
170	85	85

From the data of Table 2.5, it is possible to observe that at 120 °C the selectivity towards **2d** is similar to the one observed in reflux conditions (Entry 3, Table 2.4) and conversion is increased at almost 90% setting the temperature at 150°C. At 170°C the selectivity of **2d** decreases and the conversion remains almost the same. To conclude, a final test in autoclave was carried on for 5h instead of 2h, with a conversion of 80% and a **2d** selectivity of 95%.

Comparison. Some preliminary tests for comparing the reactivity of benzoyl chloride (**4d**, the least reactive of the acyl chlorides tested) against octanoyl chloride (**4a**, one of the most reactive acyl chlorides tested) were made, changing the temperature in presence or absence of an acid catalyst (Scheme 2.6).



4 **2i** **2** **5**

1 10

R = ;

4a **4d**

Scheme 2.6. Comparative investigation between substrates **4a**, **4d**.

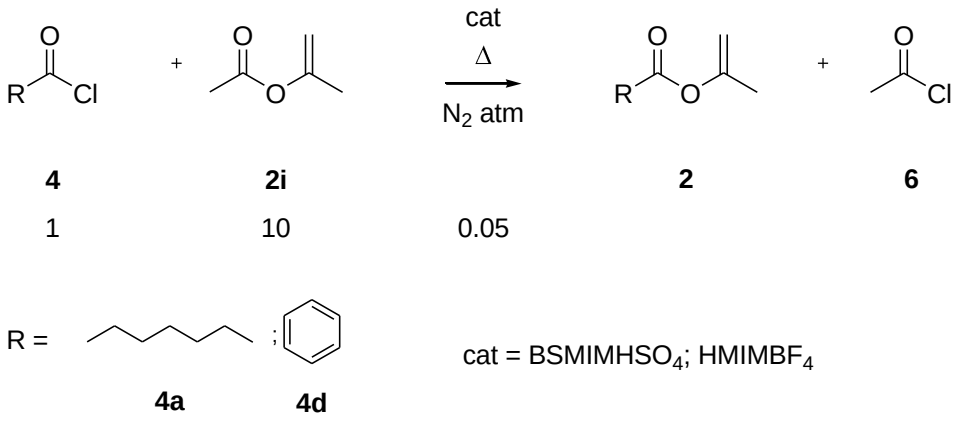
The molar ratio substrate:iPAc was maintained constant for all the tests to 1:10, as the reaction time (4h). The temperature was varied (50°C, reflux and 150°C), the acid catalyst (H_2SO_4) was involved only for the tests at 50°C and reflux temperature. For the catalyst-free tests at 150°C an autoclave reactor, under 8 atm of N_2, was used. Results are summarized in Table 2.6:

Table 2.6. Comparison between substrates **4a**, **4d**.

	H_2SO_4 (0.05%mol); T = 50°C		***H_2SO_4 (0.05%mol); T = reflux***		***Cat-free; T = 150°C***	
Substrate	**Conversion**	**Selectivity of 2**	**Conversion**	**Selectivity of 2**	**Conversion**	**Selectivity of 2**
4a	65	-	>99	88	80	14
4d	10	-	75	97	9	14

Table 2.6 highlights that for each test substrate **4a** shows a higher reactivity compared to **4d**, considering conversion results. For what concerns the tests with sulfuric acid at 50°C, the selectivity does not promote the isopropenyl esters (iPEs) formation in favor of the symmetrical and unsymmetrical anhydrides formation. To conclude, also at 150°C without catalysts the production of the two anhydrides was detected together with low production of iPEs.

During a further investigation, the BAILs $BSMIMHSO_4$, $HMIMBF_4$ catalyzed the synthesis of iPEs for 4h, starting from acyl chlorides **4a**, **4d**. Scheme 2.7 describes the reaction conditions for octyl and benzyl chloride.



Scheme 2.7. Synthesis of iPEs from acyl chlorides in presence of BAILs.

Table 2.7 shows the synthesis results:

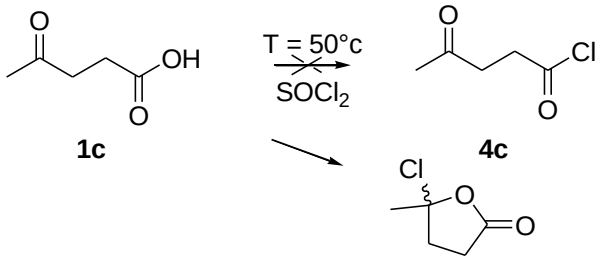
Table 2.7. Usage of BAILs as catalysts.

	BSMIMHSO$_4$		*HMIMBF$_4$*	
Substrate	**Conversion**	**Selectivity of 2**	**Conversion**	**Selectivity of 2**
4a	30	70	44	-
4d	89	63	65	-

As shown in Table 2.7 $BSMIMHSO_4$ seems to direct the synthesis towards the iPEs formation with medium-high selectivities as opposed to $HMIMBF_4$. Also for these reactions, the formation of by-products (symmetrical and unsymmetrical anhydrides) could not be avoided.

2.3. Levulinic acid derivatives tests

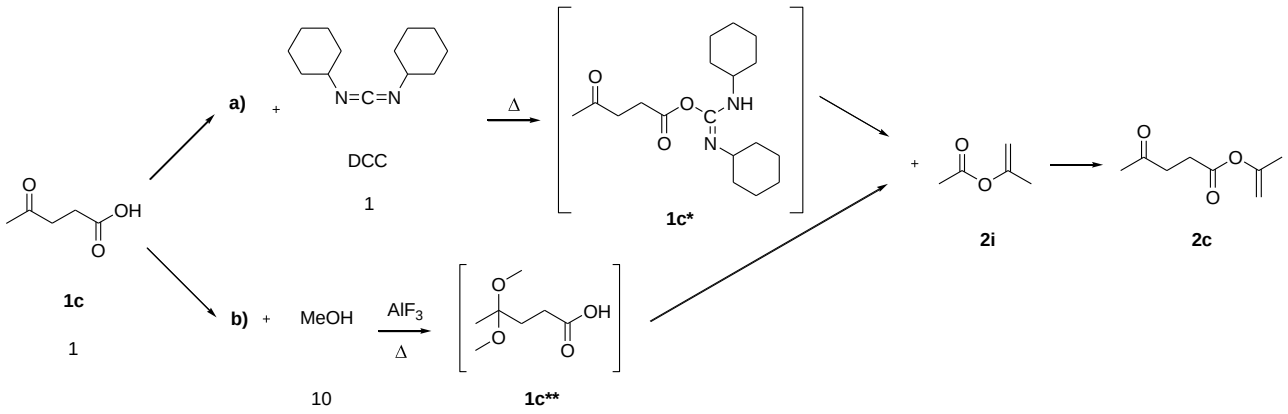
First of all, it is important to underline that an unexpected result was obtained during the synthesis of levulinyl chloride from levulinic acid. The reaction was carried using $SOCl_2$ (excess 1:10% mol), as shown in Scheme 2.8:



Scheme 2.8. Synthesis of levulinyl chloride (**4c**).

From Scheme 2.8 it is possible to understand that the reaction lead to the formation of the corresponding cyclic product, quantitatively. For this reason, it was not possible to use levulinyl chloride as substrate for the reaction with isopropenyl acetate (see Scheme 2.4).

In order to find a suitable method for the synthesis of isopropenyl levulinate (**2c**) some alternative pathways were seeked (Scheme 2.9). The **a**) synthesis involves dicicloesylcarbodiimide (DCC), that can let the –OH group of **1c** be a better leaving group and, so, it can be more active towards the transesterification with iPAc. In the **b**) pathway another synthetic protocol is described, where the ketonic group of **1c** is protected through an acetalization with methanol, in order to avoid the cyclization to α-angelica lactone of levulinic acid under acid catalysis, during the transesterification step (see …).



Scheme 2.9. Alternative pathways for the synthesis of isopropenyl levulinate (**2c**).

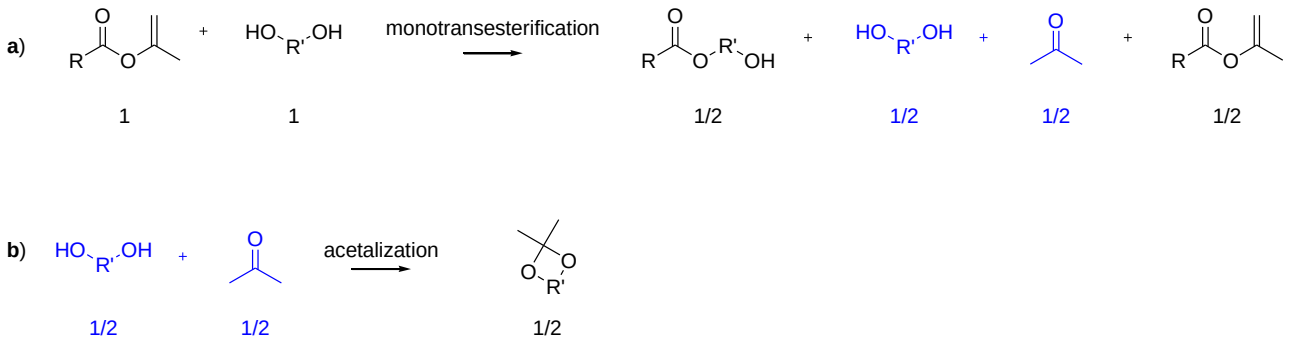
These two alternatives were not successful:

- **a)** The intermediate **1c*** was synthesized with a theoretical yield of 53% (by GC-MS) and it could not be isolated by chromatography or crystallization;
- **b)** The esterification of the acid was mainly observed with formation of the corresponding methyl levulinate and a small quantity of compound **1c**** (25% by GC-MS). Despite of this, different techniques were tested for the **1c**** isolation, such as chromatography, crystallization and distillation, but it was not possible to purify it.

For these reasons the second synthetic step, that involves iPAc for the production of the isopropenyl ester **2c** was not investigated.

2.4. ISOPROPENYL ESTERS (iPEs) REACTIVITY: TANDEM SYNTHESIS OF ESTERS AND ACETALS

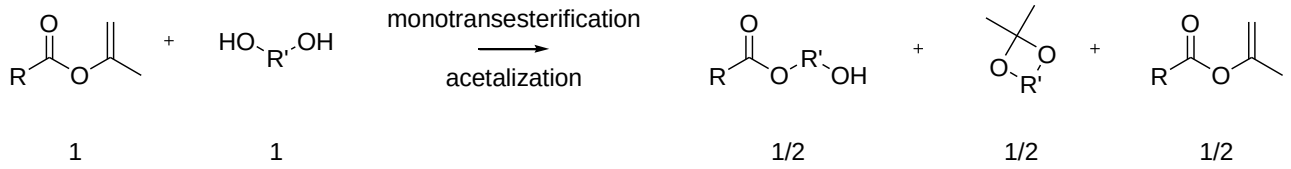
State of the art and aim. To the best of our knowledge there are no reported examples of reaction between iPEs and ethylene glycol (**7**) or 1,2-propanediol (**6**). In this context the aim of the second part of the work was to investigate this new, unexplored field of iPEs reactivity, through a tandem reaction of transesterification and acetalization. The exploitation of the acetone by-product production is tied to the monotransesterification process, that, in an ideal, theoretical way, can bring to the formation of half mole of the respective diol (1,2-propanediol or ethylene glycol) and half mole of acetone (Eq **a**, Scheme 2.10). These half moles of acetone and diols can react together in a second acetalization step (Eq **b**, Scheme 2.10), leading to the formation of half mole of acetal.



Scheme 2.10. a) monotransesterification of iPEs; **b**) acetalization of diols with acetone by-product.

Globally, the synthesis gives half a mole each of monoester, acetal and initial iPE, as shown in Scheme 2.11.

Global synthesis:



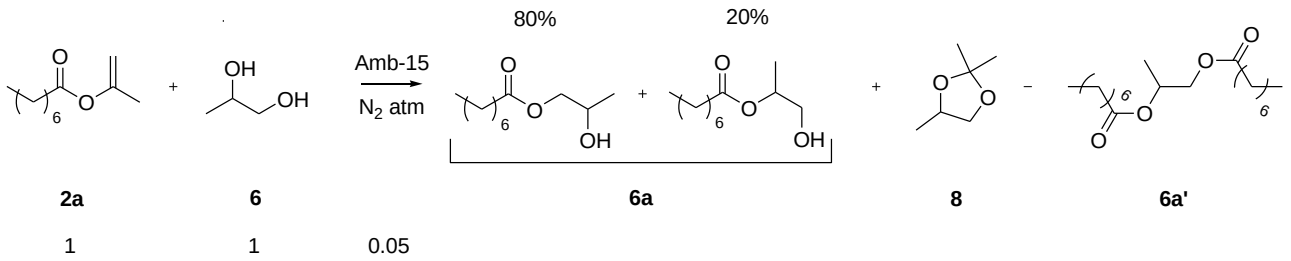
Scheme 2.11. Global tandem synthesis of monoesters and acetals.

Amberlyst-15 was chosen as transesterification-acetalization catalyst, due to its Brønsted acidity that can activate the substrates towards both the processes (see introduction). Some tests were made in order to optimize the synthesis, varying temperature, pressure, dilution of the system, type of solvent, time and type of reactor. It was considered that the optimization was reached when the acetals formation was as high as possible (no more than theoretical 50%).

2.5. iPEs and 1,2-propanediol

2.5.1. Optimization: isopropenyl octanoate and 1,2-propanediol

Isopropenyl octanoate (**2a**) was chosen as model compound for the transesterification-acetalization process optimization. In all the following synthesis, substrate **2a** reacted with 1,2-propanediol (**6**) under resin Amberlyst-15 (Amb-15) catalysis (molar ratios 1:1:0.05 respectively) and the system was standardized throughout nitrogen atmosphere generation (Scheme 2.12).



Scheme 2.12. Isopropenyl octanoate (**3a**) tandem process optimization.

The products detected by GC-MS were characterized as the monoester (**6a**), the diester (**6a'**) and the acetal (**8**).

For all the following tests the conversion was calculated on 1,2-propanediol (**6**), because it was involved in both the processes of transesterification and acetalization.

Time. The first optimized parameter was the time. The reactions were carried in solventless conditions, at the temperature of 90°C (Scheme 2.12) and a self-made reactor, structured as shown in Figure 2.1, was used. The molecular sieves (3Å), were used in order to catch the water by-product, produced during the acetalization process, in order to obtain the highest possible yield of the acetal (**8**). This reactor was developed in two "levels": in the first one the reaction mixture was put and the second one was used as ground for the molecular sieves. The time was varied from 1 to 4 hours. In Figure 2.2 the results are reported.

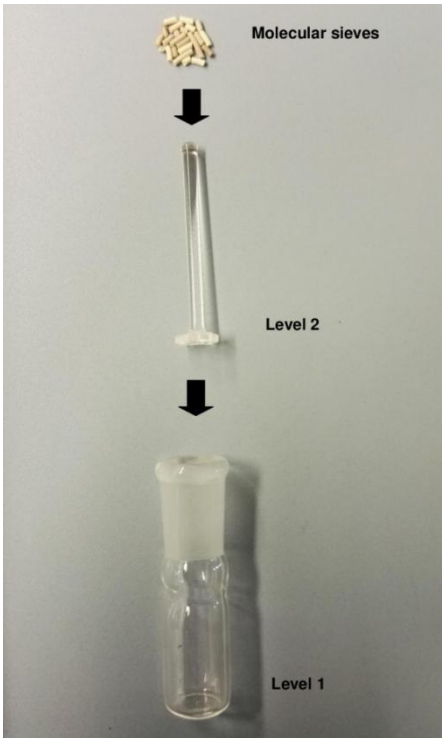


Figure 2.1. Self-made reactor for the synthesis of iPEs.

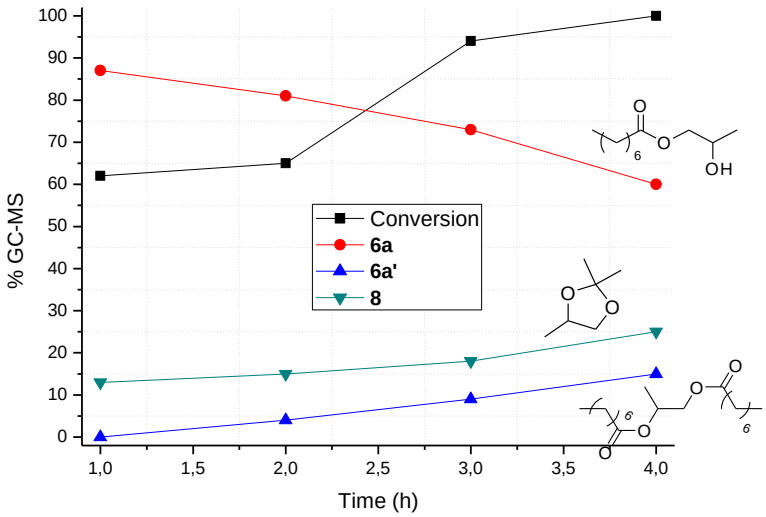


Figure 2.2. Trend of the time tests

In Table 2.8 the results of Figure 2.2 are summarized.

Table 2.8. Numerical results of the time-tests.

Time (h)	Conversion (%GC-MS)	Selectivity of 6a (%GC-MS)	Selectivity of 6a' (%GC-MS)	Selectivity of 8 (%GC-MS)
1	62	87	-	13
2	65	81	4	15
3	94	73	9	18
4	>99	60	15	25

The optimized condition was considered the one in which the maximum conversion was reached. Since after 4h no more 1,2-propanediol was detected, this was chosen as the "best" time for the tandem synthesis and all the following tests were carried on for 4h.

Dilution (batch). The effects of diluting the system were studied using tetrahydrofuran (THF) and cyclopentyl methyl ether (CPME) as solvents (addition of 1 mL and 2.5 mL each to a mixture of substrates **2a** (2.72 mmol) and **6** (2.72 mmol), respectively). The mixtures of **2a** and **6** reacted for 4h in the same reactor used for the time tests (see Figure 2.1), at 70°C when THF was used and at 90°C for CPME, respectively. The dilution effects are shown in Figure 2.3, Figure 2.4.

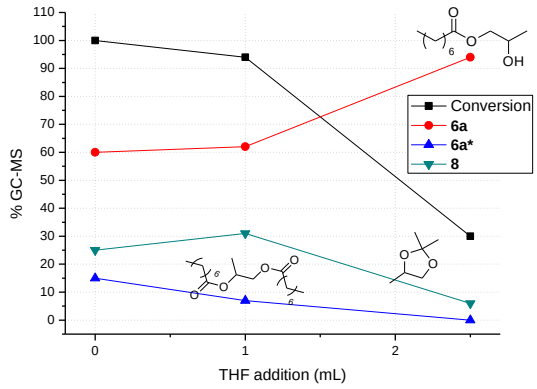


Figure 2.3. Dilution effects using THF.

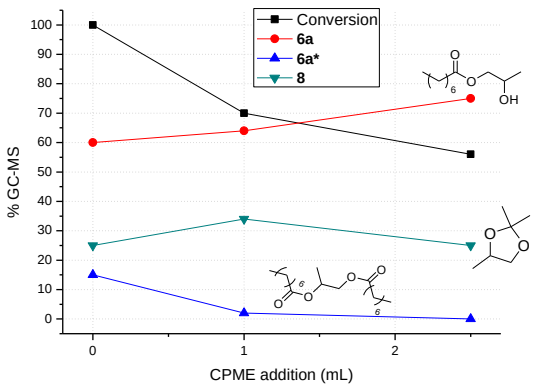


Figure 2.4. Dilution effects using CPME.

Table 2.9 summarizes the dilution tests results.

Table 2.9. Dilution tests.

	THF				*CPME*			
Solvent addition (mL)	**Conversion (%GC-MS)**	**6a***	**6a'***	**8***	**Conversion (%GC-MS)**	**6a***	**6a'***	**8***
-	>99	60	15	25	>99	60	15	25

1	47	62	7	31	70	64	2	34
2.5	30	94	-	6	56	75	-	25

* Selectivity of the substrates in %GC-MS.

As far as conversion is concerned, from Table 2.9 it is possible to observe that, both with THF and CPME, the more the system is concentrated the more conversion is increased. Furthermore, the highest selectivity of **8** is reached with an addition of 1 mL of solvent and the formation of the diester (**6a'**) is decreased at lower concentrations, in both cases again.

1 mL of solvent was considered the optimized concentration, due to the highest selectivity of substrate **8** and CPME was selected as top solvent because of its higher boiling point (106°C vs. 68°C) and its lower hygroscopicity compared to THF.

Reactor. Besides the reactor of Figure 2.1, the autoclave system was tried due to the possibility of caging in a closed volume the acetone by-product, pushing the equilibrium towards the acetal formation. Three comparative routes were driven for 4h at 90°C: the first one involved solventless conditions, in the second and third ones CPME was added (1 ml and 2.5 mL) to a mixture of **2a** (2.72 mmol) and **6** (2.72 mmol). The autoclave was pressurized with 8 atm of nitrogen in order to let the acetone by-product remain as much as possible in the liquid phase, instead of in the vapor one. In Table 2.10 are reported the results of the reactor tests.

Table 2.10. Autoclave tests.

	BATCH REACTOR				*AUTOCLAVE*			
CPME addition (mL)	**Conversion (%GC-MS)**	**6a***	**6a'***	**8***	**Conversion (%GC-MS)**	**6a***	**6a'***	**8***
-	>99	60	15	25	92	65	23	12
1	70	64	2	34	84	43	9	48
2.5	56	75	-	25	75	59	-	41

* Selectivity of the substrates in %GC-MS.

As shown in Table 2.10, the autoclave system seems able to improve the selectivity of **8,** but only with the usage of CPME. It is important to underline that in Entry 2 of Table 2.10 the theoretical maximum selectivity of the acetal was almost reached and for this reason the autoclave was considered the best suitable system for the tandem synthesis.

Moreover, it is interesting to investigate the dilution trend obtained in autoclave, that gives similar results to the batch conditions. In Figure 2.5 the autoclave dilution trend is shown.

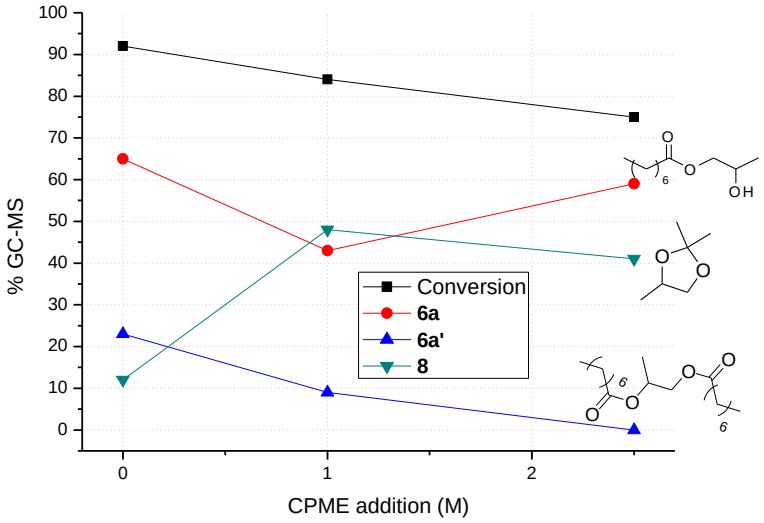


Figure 2.5. Autoclave dilution tests.

In the same way of what concerns the batch dilution tests, conversion in decreased when the concentration is lowered and the highest selectivity towards the acetal (**8**) formation is reached for a CPME addition of 1 mL. Furthermore, the diester (**6a'**) formation is strongly dependent on the dilution, too, getting a minimum selectivity at the lowest concentration tested.

Temperature. After varying the time, the mixture concentration and the type of reactor, another altered parameter was the temperature. All the trials were made in an autoclave system, under 8 atm of nitrogen, with a mixture concentration of 1.52 M (addition of 1 mL CPME) and for 4 h, changing the temperature from 70°C to 110°C. In Figure 2.6 are shown the effects of the temperature variation.

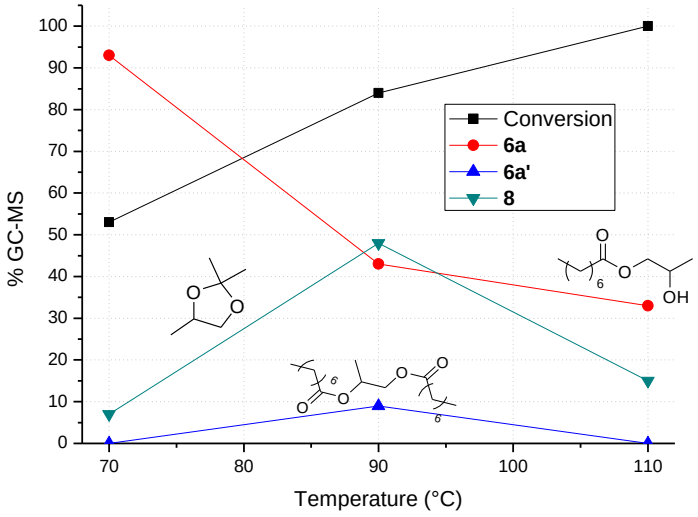


Figure 2.6. Selectivity and conversion trends for the temperature tests.

The results are written down in Table 2.11.

Table 2.11. Autoclave temperature tests.

Temperature (°C)	Conversion (%GC-MS)	Selectivity of 6a (%GC-MS)	Selectivity of 6a' (%GC-MS)	Selectivity of 8 (%GC-MS)
70	53	93	-	7
90	84	43	9	48
110	>99	33	-*	15

*an uncharacterized product (37% selectivity by GC-MS) was synthesized, instead of the diester (**6a'**).

Comparing the results of Table 2.11 it is possible to observe that the formation of the monoester (**6a**) diminishes with increasing the temperature and the conversion has an opposite trend. Moreover, at 110°C the synthesis of an unexpected compound was detected; this compound was not isolated and characterized, due to some separation difficulties. To conclude, at 90°C the condition were considered optimized because of the **8** selectivity was maximized.

Pressure. Initially, the effect of pressurizing the autoclave system with CO_2 instead of N_2 was investigated. A test at 8 atm was made with CO_2 in the same condition described for Entry 2 of Table 2.11 and compared with the one made with the inert gas N_2. It was demonstrated that the gas switch did not influence both the products (**6a**, **6a'** and **8**) selectivity and the conversion, bringing to the possibility of using carbon dioxide in place of nitrogen for pressurizing the system. After that preliminary test, the CO_2 pressure was varied from 8 to 40 atm, maintaining the temperature at 90°C and the mixture concentration at 1.52 M for all the tests. The results are reported in Figure 2.7.

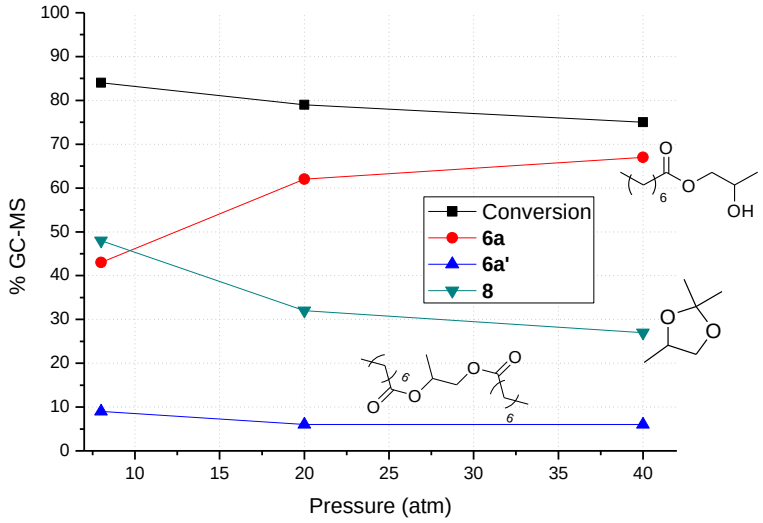


Figure 2.7. Trends of the pressure tests.

From Figure 2.7 it is possible to understand that the selectivity towards the monoester formation can be driven by increasing the pressure, at the expense of the acetal and diester formation. Furthermore, the conversion seems to be slightly influenced by the pressure, with a decreasing when the pressure is enhanced. In Table 2.12 the numerical data are shown.

Table 2.12. Data of the pressure tests.

Pressure (atm)	Conversion (%GC-MS)	Selectivity of 6a (%GC-MS)	Selectivity of 6a' (%GC-MS)	Selectivity of 8 (%GC-MS)
8	84	43	9	48
20	79	62	6	32
40	75	67	6	27

The optimized pressure was considered 8 atm.

Molecular sieves. Another self-made reactor was designed for carrying the autoclave synthesis with a system as similar as possible to the one of Figure 2.1. Also this reactor was developed in two "levels", where in the first one the reaction took place and where in the second one were put the molecular sieves. In Figure 2.8 is reported a "small version" of the Figure 2.1 reactor.

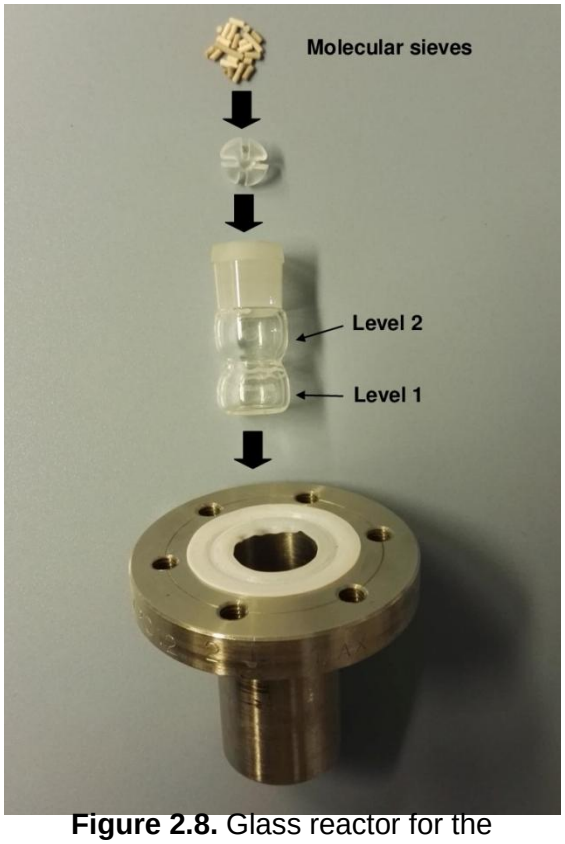


Figure 2.8. Glass reactor for the tandem synthesis in autoclave, under molecular sieves treatment.

The synthesis were carried at 90°C, for 4h and under 8 atm of nitrogen pressure; maintaining these parameters constant, two comparative tests were made in absence of solvent and adding 1 mL of CPME to a mixture of **2a** (2.72 mmol) and **6** (2.72 mmol). Table 2.13 shows the obtained data.

Table 2.13. Effect of the molecular sieves usage.

	WITHOUT MOLECULAR SIEVES				*WITH MOLECULAR SIEVES*			
CPME addition (mL)	**Conversion (%GC-MS)**	**6a***	**6a'***	**8***	**Conversion (%GC-MS)**	**6a***	**6a'***	**8***
-	92	65	23	12	93	63	6	31
1	84	43	9	48	59	81	-	19

* Selectivity of the substrates in % GC-MS.

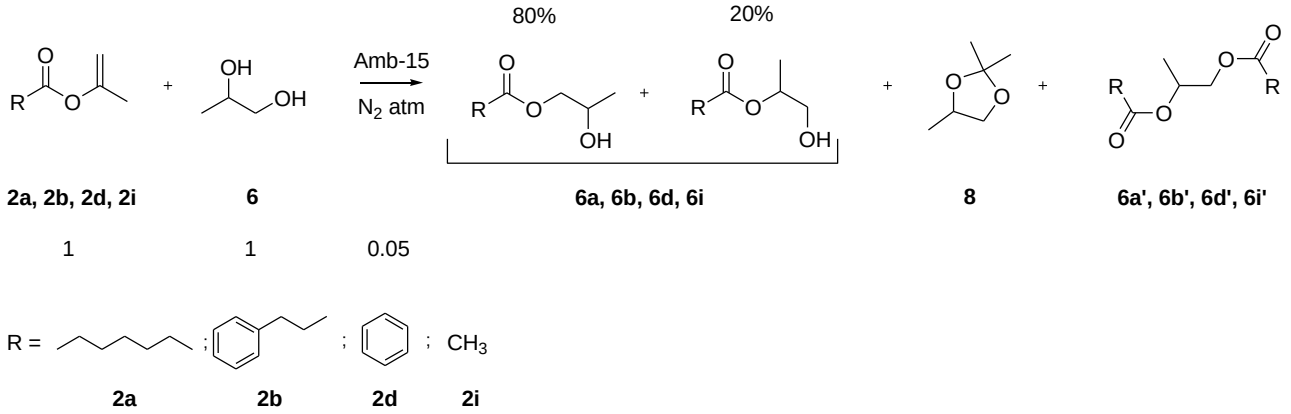
From Table 2.13 it is possible to observe that molecular sieves improve the selectivity of **8** only in solvent-free conditions and in both cases decrease the formation of the diester **6a'**. Because of the highest selectivity towards substrate **8** was reached without the usage of molecular sieves, the final optimized conditions (highlighted in Table 2.13) are:

- Time: 4h;
- Solvent: CPME;
- CPME addition: 1 mL;
- Reactor: autoclave;
- Temperature: 90°C;
- Pressure: 8 atm.

2.6. COMPARATIVE TANDEM SYNTHESIS STARTING FROM iPEs: ISOPROPENYL ACETATE, OCTANOATE, PHENYLBUTYRATE AND BENZOATE

2.6.1. iPEs and 1,2-propanediol

Some iPEs, isopropenyl octanoate (**2a**), phenylbutyrate (**2b**) benzoate (**2d**) and acetate (**2i**), were chosen for the comparative investigation about their different reactivity with 1,2-propanediol (**6**). The reaction conditions were varied in order to get some information about the temperature, reactor, type of system and dilution effects. In all the following synthesis, substrates **2a**, **2b**, **2d**, **2i** reacted with 1,2-propanediol (**6**) under resin Amberlyst-15 (Amb-15) catalysis (molar ratios 1:1:0.05 respectively) and the system was standardized throughout nitrogen atmosphere generation (Scheme 2.13).



Scheme 2.13. Comparative tandem transesterification/acetalization synthesis starting from different iPEs.

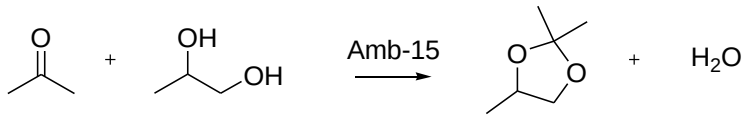
The reaction conditions were chosen due to the possibility of comparing the iPEs reactivity in the most exhaustive way possible, but not forgetting the best results obtained for substrate **2a**.

The detected products by GC-MS were characterized as the monoesters (**6a**, **6b**, **6d**, **6i**), the diester (**6a'**, **6b'**, **6d'**, **6i'**) and the acetal (**8**).

For all the following tests the conversion was calculated on 1,2-propanediol (**6**), because it was involved in both the processes of transesterification and acetalization.

Isopropenyl benzoate (**2d**) demonstrated an atypical reactivity, different from the one described in Scheme 2.13. When substrate **2d** reacted with **6** the main product was benzoic acid (**1d**) in almost every test, apart from those in which molecular sieves were used. In these last cases, the **1d** formation could be decreased between 30-50%, underlining that isopropenyl benzoate is a water-sensitive compound in the reaction

conditions reported in Scheme 2.13. In order to justify the presence of a stoichiometric amount of water in the reaction mixture two different ways are possible: i) the reagents water content; ii) the water formation during the acetalization process (Scheme 2.14)



9 **6** **8**

Scheme 2.14. Acetlization process between acetone (**9**) and 1,2-propanediol (**6**).

i) For the measurement of the **2d** and **6** water content Karl Fischer titration was adopted, …

ii) The isopropenyl benzoate hydrolysis can be almost completely justified by the 1:1 (mol:mol) formation of water during the acetalization. Since the acetal selectivity was ≥60% (by GC-MS) in every test, the 60% production of isopropenyl benzoate can be related to point ii) process.

In lights of all these considerations substrate **2d** was not included among the compared substrates.

Dilution (batch). Initially, the effect of varying the relative concentrations of the substrates was studied in the batch reactor of Figure 2.1. 2.72 mol of substrates **2a**, **2b**, **2i** reacted with 2.72 mol of **6**, the temperature was set at 90°C, CPME was used as solvent (1 mL and 2.5 mL) and the reaction took place for 4h. Table 2.14 summarizes the results of these tests.

Table 2.14. Comparative dilution tests of iPEs reactivity.

	CPME addition: 1 mL				*CPME addition: 2.5 mL*			
Substrate	**Conversion (%GC-MS)**	**6a/6b/ 6i***	**6a'/6b'/ 6i'***	**8***	**Conversion (%GC-MS)**	**6a/6b/ 6i***	**6a'/6b'/ 6i'***	**8***
2a	>99	57	13	30	>99	68	9	23
2b	70	64	2	34	56	75	-	25
2i	>99	47	6	46	>99	53	8	30

* Selectivity of the substrates in % GC-MS.

Table 2.14 highlights that for each substrate the dilution of the mixture decreases the selectivity of **8**, favoring the monoester (**6a**, **6b**, **6i**) formation. The diesters (**6a'**, **6b'**, **6i'**) selectivity seems not to be heavily influenced by the usage of different amounts of solvent and the conversion changes only for substrate **2a**. Indeed, for what is concerned with conversion, substrates **2b** and **2i** demonstrate a higher reactivity than **2a**, bringing to the reaction completion also when the mixture was diluted. To conclude, it is important to underline at first that, for a CPME addition of 1 mL, from substrate **2i** it is almost possible

to raise the theoretical yield (50%) of acetal (**8**) and that the less activity of compound **2a** led to no formation of diester (**6a'**) in a much diluted system (2.5 mL).

Dilution (autoclave). During a further investigation, mixtures of iPEs **2a**, **2b**, **2i** (2.72 mmol) with **6** (2.72 mmol) in CPME (addition of 1mL and 2.5 mL) reacted also in the autoclave system. These synthesis were compared together and with three other tests (one for each iPE), driven in solventless conditions. For each test the temperature was set at 90°C and the synthesis was carried for 4h. The comparative results of selectivity and conversion among substrates **2a**, **2b**, **2i** are shown in Figure 2.9, Figure 2.10, Figure 2.11.

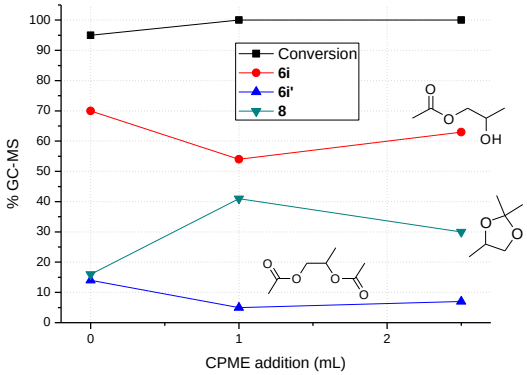


Figure 2.9. Isopropenyl acetate (**2i**) autoclave dilution tests.

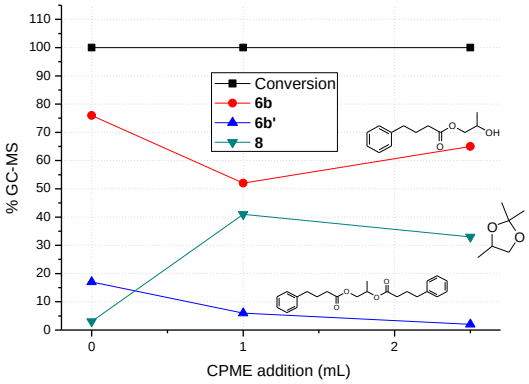


Figure 2.10. Isopropenyl phenylbutyrate (**2b**) autoclave dilution tests.

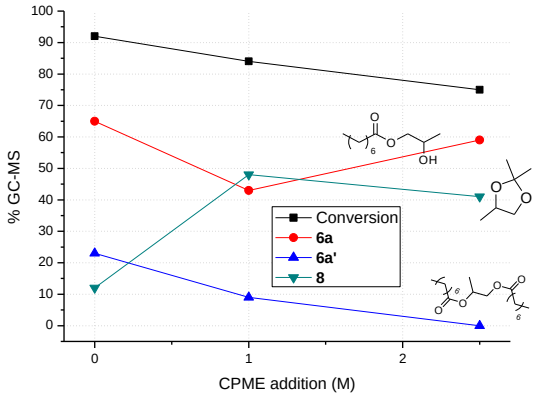


Figure 2.11. Isopropenyl octanoate (**2a**) autoclave dilution tests.

Figures 2.9, 2.10, 2.11 show that the selectivity has the same trend in each diagram, letting substrates **2a**, **2b**, **2i** share similar reactivity. On the other hand, a first observable difference is concerned with conversion: substrate **2a** cannot lead to total conversion of **6** in no condition and, in contrast, for substrates **2b**, **2i** conversion is almost quantitative in each case. The formation of the acetal (**8**) is maximized for all iPEs when 1 mL CPME was added to the mixture, decreasing both when the system was diluted or much concentrated. Despite the case of isopropenyl acetate (**2i**), for both substrates **2a**, **2b** the dilution

disadvantages the synthesis of the diester (**6a'**, **6b'**), favoring the monoester formation. To conclude, the investigated iPEs show similar reactivity in terms of selectivity and, also, it was demonstrated that isopropenyl octanoate (**2a**) seems to be the less active compound among them (it brought to lowest conversions). For completeness, in Table 2.15 are reported the numerical data.

Table 2.15. Comparative autoclave dilution tests for iPEs.

	*Substrate **2a***				*Substrate **2b***				*Substrate **2i***			
Addition (mL)	**Conv.***	**Sel. 6a***	**Sel. 6a'***	**Sel. 8***	**Conv.***	**Sel. 6b***	**Sel. 6b'***	**Sel. 8***	**Conv.***	**Sel. 6i***	**Sel. 6i'***	**Sel. 8***
-	92	65	23	12	>99	76	17	3	95	70	14	16
1	84	43	9	48	>99	52	6	41	>99	54	5	41
2.5	75	59	-	41	>99	65	2	33	>99	63	7	30

* the data are reported in % GC-MS.

Temperature (autoclave). The temperature was varied from 70°C to 110°C in the autoclave system. The mixture concentration was set at 1.52 M (1 mL of CPME was added to a mixture of 2.72 mmol each of substrates **2a**, **2b**, **2i** with **6**, respectively) and the reaction was carried for 4h. The effects on selectivity and conversion are reported in Figures 2.12, 2.13, 2.14.

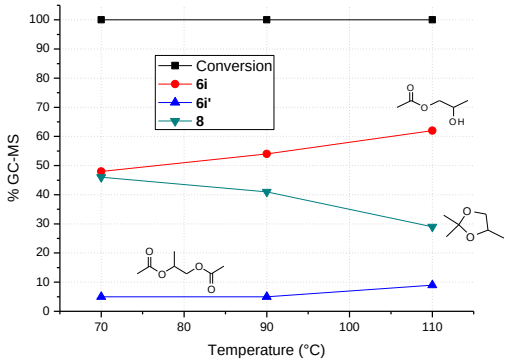


Figure 2.12. Isopropenyl acetate (**2i**) autoclave temperature tests.

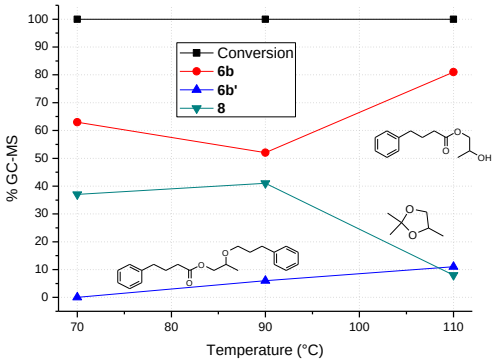


Figure 2.13. Isopropenyl phenylbutyrate (**2b**) autoclave temperature tests.

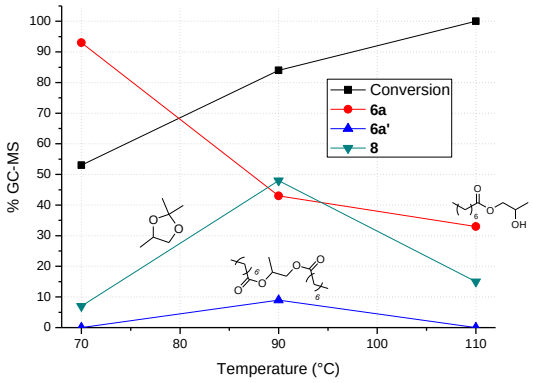


Figure 2.14. Isopropenyl octanoate (**2a**) autoclave temperature tests.

As it is possible to see from Figures 2.12, 2.13, 2.14, the variation of temperature highlights some differences in the reactivity of the substrates. Substrates **2b** and **2i** are more active, since the conversion is >99% (by GC-MS) for each tests, than compound **2a** that brings to total conversion only when the temperature was set at 110°C. The acetal (**8**) selectivity in hugely influenced by the temperature when substrate **2a** reacts, with its highest formation at 90°C. For what is concerned with substrates **2b**, **2i,** compound **8** was synthesized nearing the theoretical 50% selectivity both at 70, 90°C and decreasing its formation at 110°C. The monoesters trend can be described as follows: the more compounds **6b**, **6i** were produced, the more the temperature was increased; the more **6a** was produced the more the temperature was decreased. The diesters **6b'** and **6i'** were detected in every condition and **6a'** was formed only at 90°C. To conclude, from all these considerations it is possible to understand that substrate **2a** shows different reactivity when compared to **2b**, **2i**. The numerical results of the temperature tests are shown in Table 2.16.

Table 2.16. Comparison of iPEs reactivity, varying the temperature.

	*Substrate **2a***				*Substrate **2b***				*Substrate **2i***			
T (°C)	**Conv.***	**Sel. 6a***	**Sel. 6a'***	**Sel. 8***	**Conv.***	**Sel. 6b***	**Sel. 6b'***	**Sel. 8***	**Conv.***	**Sel. 6i***	**Sel. 6i'***	**Sel. 8***
70	53	93	-	7	>99	63	-	37	>99	48	5	46
90	84	43	9	48	>99	52	6	41	>99	54	5	41
110	>99	33	-	15	>99	81	11	8	>99	62	9	29

* the data are reported in % GC-MS.

Molecular sieves (autoclave). The system of Figure 2.8 was used for the comparative reactions of iPEs. The effect of molecular sieves was investigated at 90°C in absence of

solvent and adding 1 mL of CPME to a mixture of **2a**, **2b**, **2i** (2.72 mmol) with **6** (2.72 mmol). All the synthesis were carried for 4h. Table 2.17 reports the results.

Table 2.17. Effect of molecular sieves in the comparative reactions of iPEs.

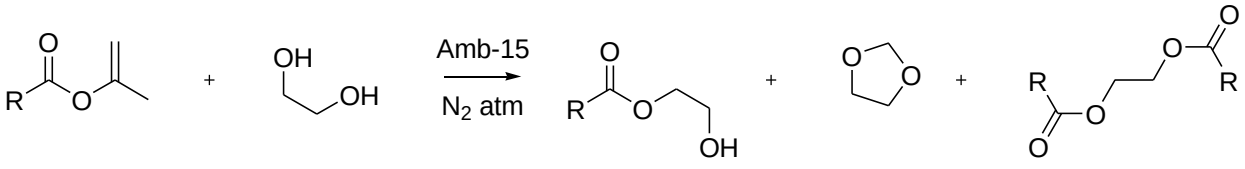
	*Substrate **2a***				*Substrate **2b***				*Substrate **2i***			
Addition (mL)	**Conv.***	**Sel. 6a***	**Sel. 6a'***	**Sel. 8***	**Conv.***	**Sel. 6b***	**Sel. 6b'***	**Sel. 8***	**Conv.***	**Sel. 6i***	**Sel. 6i'***	**Sel. 8***
-	93	63	6	31	>99	82	15	7	94	69	11	20
1	59	81	-	19	>99	79	8	13	>99	63	7	30

* the data are reported in % GC-MS.

From Table 2.17 it is possible to see that the usage of molecular sieves seems not to improve the formation of the acetal **8** (see also Table 2.15), as opposed to what was expected (water caging by molecular sieves would have increased the selectivity of **8**). Moreover, the selectivity and conversion trends cannot be evenly described for all the substrates, due to the no reproducible reaction set-up (*vide infra* discussion).

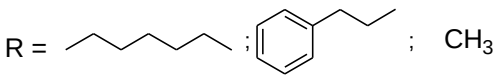
2.6.2. iPEs and ethylene glycol

During a further investigation, isopropenyl octanoate (**2a**), phenylbutyrate (**2b**) and acetate (**2i**) reacted with ethylene glycol (**7**); all the synthesis were carried under resin Amberlyst-15 (Amb-15) catalysis (molar ratios 1:1:0.05 respectively) and the system was standardized throughout nitrogen atmosphere generation (Scheme 2.13).



2a, 2b, 2i **7** **7a, 7b, 7i** **9** **7a', 7b', 7i'**

1 1 0.05



2a **2b** **2i**

Scheme 2.13. Comparative tandem transesterification/acetalization synthesis starting from different iPEs.

The effects of varying the type of reactor, the temperature and the mixture concentration were investigated. The reaction conditions were chosen in order to compare the reactivity of 1,2-propanediol with ethylene glycol, studying the influence of the most effective parameters variation for the reactions of iPEs with **6**.

The detected products by GC-MS were characterized as the monoester (**7a**, **7b**, **7i**), the diesters (**7a'**, **7b'**, **7i'**) and the acetal (**9**).

For all the following tests the conversion was calculated on ethylene glycol (**7**), because it involves both the processes of transesterification and acetalization.

Reactor. Initially, the autoclave system was compared to the batch one (Figure 2.1). Mixtures of iPEs **2a**, **2b**, **2i** (2.72 mmol) with **7** (2.72 mmol) in 1 mL of CPME reacted at 90°C for 4h, in both autoclave and batch reactors. When the autoclave synthesis were performed, the pressure was set at 8 atm, pressurizing the system with nitrogen. The results are reported in Table 2.18.

Table 2.18. Effects of the reactor variation in the tandem synthesis with ethylene glycol.

	*Substrate **2a***				*Substrate **2b***				*Substrate **2i***			
Reactor	**Conv.***	**Sel. 6a***	**Sel. 6a'***	**Sel. 9***	**Conv.***	**Sel. 6b***	**Sel. 6b'***	**Sel. 9***	**Conv.***	**Sel. 6i***	**Sel. 6i'***	**Sel. 9***
Batch	>99	76	3	21	>99	69	21	10	>99	48	31	21
Autoclave	70	77	-	23	>99	80	8	12	>99	42	32	26

* the data are reported in % GC-MS.

From Table 2.18 it is possible to understand that the type of reactor does not highly influence the selectivity and the conversion. Only for substrate **2a** the autoclave system seems to lower the conversion of ethylene glycol, confirming that isopropenyl octanoate is the less active tested compound (see also …). Furthermore, in order to compare the reactivity of **6** vs. **7**, some graphics are shown in Figures 2.15, 2.16, 2.17.

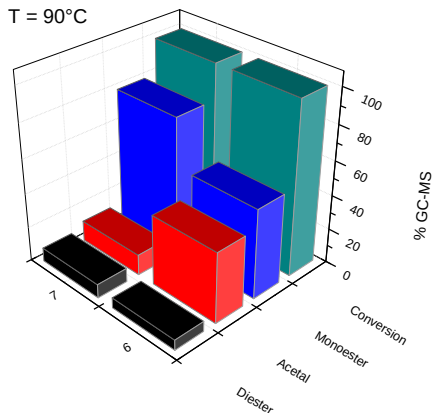


Figure 2.15. Isopropenyl octanoate (**2a**) autoclave comparative reactions with **6**, **7** (T = 90°C)

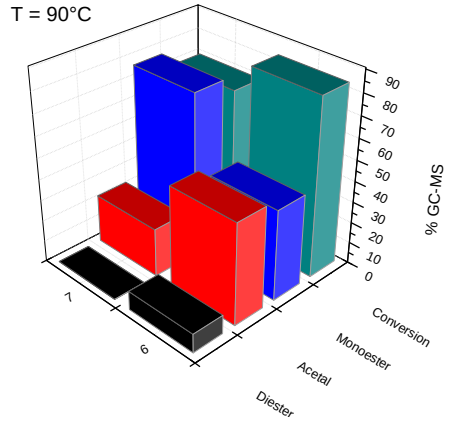


Figure 2.16. Isopropenyl phenylbutyrate (**2b**) autoclave comparative reactions with **6**, **7** (T = 90°C)

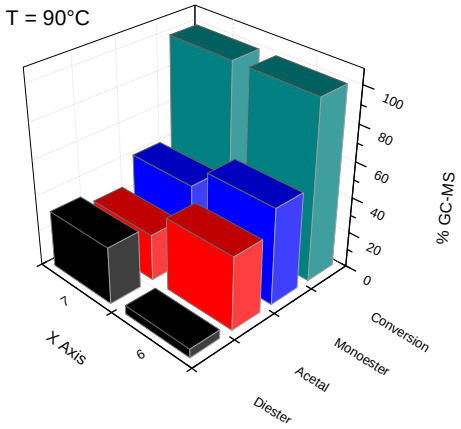


Figure 2.17. Isopropenyl acetate (**2i**) autoclave comparative reactions with **6**, **7** (T = 90°C).

First of all, the above diagrams show that 1,2-propanediol (**6**) brings to higher selectivity of **9** for each isopropenyl tested (**2a**, **2b**, **2i**), when compared to substrate **7**. Despite isopropenyl acetate, ethylene glycol seems to improve the selectivity of the monoester at the expense of acetal **9** but, in contrast, the highest selectivity of the diester is reached just with **7** and **2i**. For what is concerned with conversion, ethylene glycol reacts almost in the same way of **6**.

Temperature (autoclave). Mixtures of substrates **2a**, **2b**, **2i** (2.72 mmol) with **7** (2.72 mmol) in 1 mL of CPME reacted for 4h in an autoclave system, under 8 atm of nitrogen, at the temperature of 70°C and then of 90°C. The effects of the temperature variation are described in Table 2.19.

Table 2.19. Effects of the temperature variation in the tandem synthesis with ethylene glycol.

	*Substrate **2a***				*Substrate **2b***				*Substrate **2i***			
T (°C)	**Conv.***	**Sel. 6a***	**Sel. 6a'***	**Sel. 9***	**Conv.***	**Sel. 6b***	**Sel. 6b'***	**Sel. 9***	**Conv.***	**Sel. 6i***	**Sel. 6i'***	**Sel. 9***

70	30	>99	-	-	>99	86	6	8	>99	43	29	27
90	70	77	-	23	>99	80	8	12	>99	42	32	26

* the data are reported in % GC-MS.

Considering one compound at a time, substrate **2a** is the less active among the three ones tested, because it brings to low conversion. On the other hand, the slow reactivity of **2a** can be exploited for synthesizing selectively the monoester **6a** (see Entry 1, Table 2.19), without the formation of both **9** and **6a'**. Substrates **2b**, **2i** are related to total conversion of ethylene glycol, also when the temperature was set at 70°C. Compound **6b** was the major product for the reaction of isopropenyl benzoate (**2b**) and, when isopropenyl acetate (**2i**) reacted, the selectivity cannot be controlled also at 70°C.

In Figures 2.18, 2.19, 2.20 the comparison between ethylene glycol and 1,2-propanediol is described (T = 70°C, autoclave system).

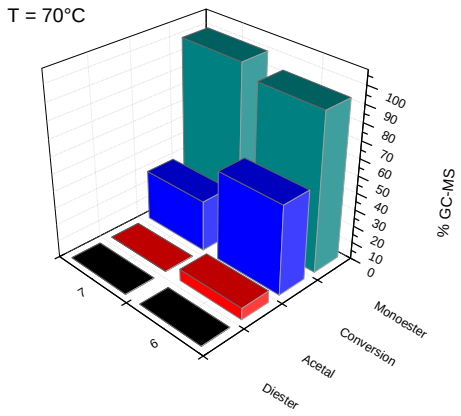


Figure 2.18. Isopropenyl octanoate (**2a**) autoclave comparative reactions with **6**, **7** (T = 70°C)

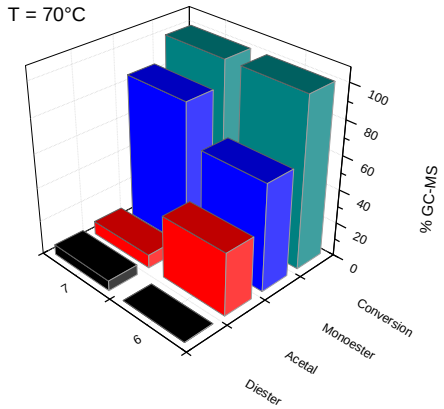


Figure 2.19. Isopropenyl phenylbutyrate (**2b**) autoclave comparative reactions with **6**, **7** (T = 70°C)

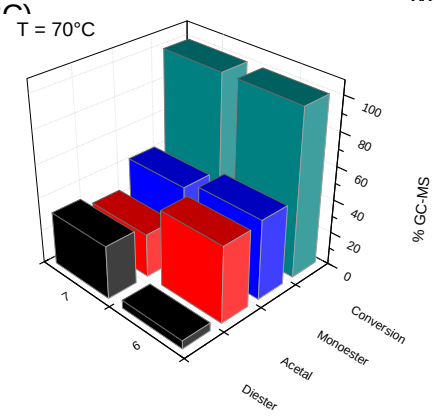


Figure 2.20. Isopropenyl acetate (**2i**) autoclave comparative reaction with **6**, **7** (T = 70°C).

Ethylene glycol (**7**) seems to decrease the acetal (**9**) formation, when compared to **6**, in all the tests made. Moreover, compound **7** improves the synthesis of the monoesters (**6a**, **6b**, **6i**), reaching >99% selectivity with isopropenyl octanoate (**2a**). A peculiar result was

obtained for compound **2i** in the reaction with ethylene glycol: a 29% of diester **6i'** was synthesized at 70°C and 32% at 90°C (see Entry 2, Table 2.19), contrasting with the data obtained in the same conditions for substrates **2a**, **2b**. To conclude, the conversion is almost quantitative for all the tests.

Dilution (autoclave). Compounds **2a**, **2b**, **2i** (2.72 mmol) reacted with **7** (2.72 mmol) at 90°C, for 4h, using CPME as solvent (addition of 1 mL and 2.5 mL). Table 2.20 reports the results.

Table 2.20. Effects of the mixture dilution in the tandem synthesis with ethylene glycol.

	*Substrate **2a***				*Substrate **2b***				*Substrate **2i***			
Addition (mL)	**Conv.***	**Sel. 6a***	**Sel. 6a'***	**Sel. 9***	**Conv.***	**Sel. 6b***	**Sel. 6b'***	**Sel. 9***	**Conv.***	**Sel. 6i***	**Sel. 6i'***	**Sel. 9***
1	70	77	-	23	>99	80	8	12	>99	42	32	26
2.5	95	80	2	18	>99	86	6	8	>99	43	29	27

* the data are reported in % GC-MS.

The dilution does not much influence both the conversion and selectivity in the reaction of iPEs (**2a**, **2b**, **2i**) with **7**. Despite of this aspect, once again substrate **2a** is the less active, considering the conversion results reported in Table 2.20.

3. EXPERIMENTAL SECTION

3.1. Materials and Methods

Reagents and solvents were purchased from commercial sources and used as received unless otherwise stated. MeOH, $CHCl_3$, tetrahydrofuran (THF), $CDCl_3$, H_2SO_4, Na_2CO_3, benzoic acid, *p*-methoxybenzoic acid, octanoic acid, levulinic acid, succinic acid, succinic acid, dimethyl malonate, oxalyl chloride, malonyl chloride, benzoyl chloride, ethylene glycol, 1,2-propanediol, molecular sieves (3Å), Resin Amberlyst-15 and isopropenyl acetate (iPAc) were purchased from Sigma Aldrich (now Merck). Phenylbutyric acid, $SOCl_2$, AlF_3 and dicicloesylcarbodiimide (DCC) were purchased from Fluka. Cyclopentylmethyl ether (CPME) was purchased from Zeon. Octanoyl chloride, phenylbutyryl chloride, *p*-methoxybenzoyl chloride and succinyl chloride were prepared according to a reported procedure. Brønsted acid ionic liquids (BAILs) $BSMIMHSO_4$ and $HMIMBF_4$ were synthesized according to reported literature procedures [cfr. b209, bails] [cfr. catalysis, bails].

Analysis and characterizations were performed with the following analytical instruments:

- GC/MS consisting of a GC Agilent Technologies 6890N, equipped with a capillary column HP-5 (30 m x 0.32 mm, film width: 0.25 µm), coupled with a mass detector Agilent Technologies 5975 working at 70 eV.
- GC/MS consisting of a GC Agilent Technologies 7890A, equipped with a capillary column Elite-624 (30 m x 0.32 mm, film width: 0.18 µm), coupled with a mass detector Agilent Technologies 5975C working at 70 eV.
- GC consisting of a GC hp 5890, equipped with a capillary column Elite-624 (30 m x 0.32 mm, film width: 0.18 µm), coupled with a FID detector.
- NMR Spectrometer Bruker AV400, operating at 400.

GC/MS samples were diluted with diethyl ether, methanol, THF or toluene, depending on the compounds' solubility. ^{1}H NMR and ^{13}C NMR spectra were collected at 25°C (298 K) in deuterated chloroform ($CDCl_3$) or in deuterium oxide (D_2O). In ^{1}H and ^{13}C experiments, chemical shifts were reported in δ values referenced on the residual solvent signal.

3.2. General procedure for the synthesis of isopropenyl esters (iPEs) in batch

From carboxylic acids (Procedure A). The carboxylic acid of choice (1 equiv.) was mixed with an excess of isopropenyl acetate (**2i**, 10 equiv.) in a three-necked round-bottom flask, equipped with a magnetic stir bar, a nitrogen vesicle, a rubber septum, a glass stopcock and a reflux condenser. Then the acid catalyst of choice (0.05 equiv.) was added and the

system was dried by four evacuation/back-fill cycle, using N_2 as the inert gas. The reaction mixture was kept under an inert atmosphere of N_2, stirred vigorously at 400 rpm and heated at reflux temperature by means of a pre-heated oil bath kept at T = 90°C. Each reaction was sampled at given time intervals and monitored offline by GC-MS analysis, until stable conversion values were reached. Upon reaction completion, the mixture was washed tree times (3x10 mL) with a saturated aqueous Na_2CO_3 solution, then extracted three times (3x10 mL) with Et_2O, dried and concentrated *in vacuo* by rotary evaporator. Finally, product isolation was achieved by flash column chromatography. The procedure was successfully performed for the synthesis of isopropenyl octanoate (**2a**), isopropenyl phenylbutyrate (**2b**), isopropenyl benzoate (**2d**) and isopropenyl p-methoxybenzoate (**2e**).

From acyl chlorides (Procedure B). In a three-necked round-bottom flask, equipped with a magnetic stir bar, a nitrogen vesicle, a perforable rubber septum and a reflux condenser, the appropriate amount of. Then, the system was dried by four evacuation/back-fill cycle, using N_2 as the inert gas and it was kept under N_2. The acyl chloride of choice (1 eq) was added under N_2 atmosphere; the mixture was stirred vigorously at 400 rpm and heated at reflux temperature by means of a pre-heated oil bath kept at T = 90°C. Each reaction was sampled at given time intervals and monitored offline by GC-MS analysis, until stable conversion values were reached. Upon the reaction completion, the mixture was washed three times (3x10 mL) with a saturated aqueous Na_2CO_3 solution, then extracted three times (3x10 mL) with Et_2O, dried and concentrated *in vacuo* by rotary evaporator. Finally, product isolation was achieved by flash column chromatography. The procedure was successfully performed for the synthesis of isopropenyl octanoate (**2a**), isopropenyl phenylbutyrate (**2b**), isopropenyl benzoate (**2d**) isopropenyl p-methoxybenzoate (**2e**) and isopropenyl succinate (**2h**). Isopropenyl oxalate (**2f**) and isopropenyl malonate (**2g**) required an additional solvent ($CHCl_3$) and an heterogeneous acid catalyst (Amberlyst-15), instead of sulfuric acid.

Using $CHCl_3$ as a solvent (Procedure C). In a three-necked round-bottom flask, equipped with a magnetic stir bar, a nitrogen vesicle, a perforable rubber septum and a reflux condenser, the appropriate amount of isopropenyl acetate (**2i**, 10 eq) was mixed with equivalent quantities of the catalyst of choice (0.05 eq) and 10 mL of $CHCl_3$. Then, the system was dried by four evacuation/back-fill cycle, using N_2 as the inert gas and it was kept under N_2. The acyl dichloride of choice (**4f**, **4g**, 1 eq) was added under N_2 atmosphere; the mixture was stirred vigorously at 400 rpm and heated at reflux temperature by means of a pre-heated oil bath kept at T = 90°C. Every reaction was

sampled at given time intervals and monitored offline by ^{1}H NMR analysis, until stable values of conversion were reached.

3.3. General procedure for the synthesis of isopropenyl esters (iPEs) in autoclave

Procedure D. The acyl chloride of choice (1 equiv.) was mixed with an excess of isopropenyl acetate (10 equiv.) in a pierced glass reactor, inlaid in a 20 mL stainless steel autoclave. Then, the catalyst of choice was added (0.05 eq). The system was dried by means of four N_2-vacuum cycles and then pressurized with N_2.(p = 8 atm). The autoclave was heated using an aluminum block pre-heated at T = 120-170 °C. Every reaction was carried out for a pre-determined length of time and final conversion was determined by GC/MS analysis. Isopropenyl octanoate (**2a**) and isopropenyl benzoate (**2d**) were synthesized following this procedure.

3.4. Characterization data

3.4.1. Prop-1-en-2-yl octanoate (isopropenyl octanoate, 2a)

i. According to procedure A, isopropenyl acetate (3.531 g, 35.3 mmol), octanoic acid (**1a**: 0.512 g, 3.55 mmol), in presence of sulfuric acid (17.4 mg, 0.17 mmol) as catalyst afforded **2a** in 31% isolated yield as a viscous pale yellow oil.

ii. According to procedure A, isopropenyl acetate (3.471 g, 34.7 mmol), octanoic acid (**1a**: 0.508 g, 3.52 mmol) in presence of $BSMIMHSO_4$ (55.0 mg, 0.17 mmol) as catalyst afforded **2a** in 45% yield by GC/MS.

iii. According to procedure A, isopropenyl acetate (3.460 g, 34.7 mmol), octanoic acid (**1a**: 0.501 g, 3.50 mmol) in presence of $HMIMBF_4$ (30.0 mg, 0.16 mmol) as catalyst afforded **2a** in 0% yield by GC/MS.

iv. According to procedure B, isopropenyl acetate (3.202 g, 32.0 mmol), octanoyl chloride (**4a**: 0.521 g, 3.20 mmol) in presence of sulfuric acid (16.8 mg, 0.17 mmol) as catalyst afforded **2a** in 90% yield, by GC/MS.

v. According to procedure B, isopropenyl acetate (3.082 g, 30.8 mmol), octanoyl chloride (**4a**: 0.451 g, 3.08 mmol) in presence of $BSMIMHSO_4$ (47.1 mg, 0.15 mmol) as catalyst afforded **2a** in 56% yield, by GC/MS.

vi. According to procedure B, isopropenyl acetate (3.462 g, 34.8 mmol), octanoic acid (**1a**: 0.498 g, 3.48 mmol) in presence of $HMIMBF_4$ (30.2 mg, 0.17 mmol) as catalyst afforded **2a** in 0% yield by GC/MS.

vii. According to procedure D, isopropenyl acetate (3.080 g, 30.8 mmol), octanoyl chloride (**4a**: 0.449 g, 3.08 mmol) afforded after 4h **2a** in 8% yield, by GC/MS at 150°C.

^{1}H NMR (400 MHz, 25°C, $CDCl_3$, ^{1}H) δ (ppm relative to TMS): 4.71 (p, J = 1.19 Hz, 1H), 4.68 (dd, J = 1.33, 0.61 Hz, 1H), 2.39 (t, J = 7.51 Hz, 2H), 1.94 (d, J = 1.15 Hz, 3H), 1.67 (m, 2H), 1.32 (m, 8H), 0.90 (m, 3H).

^{13}C{H} NMR (400 MHz, 25°C, $CDCl_3$) δ (ppm relative to TMS): 171.74, 152.86, 101.68, 34.19, 31.46, 28.84, 28.72, 24.73, 22.40, 19.39, 13.86.

GC/MS (relative intensity, 70 eV) *m/z*: 128 (9), 127 (100), 109 (9), 67 (5), 57 (98), 55 (18), 43 (24), 42 (8), 41 (20), 39 (8).

3.4.2. Prop-1-en-2-yl 4-phenylbutanoate (isopropenyl phenylbutyrate, 2b)

i. According to procedure A, isopropenyl acetate (3.041 g, 30.4 mmol), phenylbutyric acid (**1b**: 0.497 g, 3.02 mmol) in presence of sulfuric acid (14.8 mg, 0.15 mmol) as catalyst afforded **2b** in 39% isolated yield as a viscous pale yellow oil.

ii. According procedure B, isopropenyl acetate (2.894 g, 28.0 mmol), phenylbutyryl chloride (**4b**: 0.512 g, 2.80 mmol) in presence of sulfuric acid (13.7 mg, 0.14 mmol) as catalyst afforded **2b** in 94% yield, by GC/MS.

^{1}H NMR (400 MHz, 25°C, $CDCl_3$, ^{1}H) δ (ppm relative to TMS): 7.32 (m, 2H), 7.23 (td, J = 6.73, 1.65 Hz, 3H), 4.73 (p, J = 1.21 Hz, 1H), 4.70 (dd, J = 1.35, 0.61 Hz, 1H), 2.71 (dd, J = 8.28, 6.95 Hz, 2H), 2.43 (t, J = 7.46 Hz, 2H), 1.95 (d, J = 1.10 Hz, 3H).

^{13}C{H} NMR (400 MHz, 25°C, $CDCl_3$) δ (ppm relative to TMS): 171.67, 153.10, 141.37, 128,61, 128.55, 126.17, 102.09, 35.17, 33.76, 26.60, 19.70.

GC/MS (relative intensity, 70 eV) *m/z*: 148 (10), 147 (100), 129 (16), 117 (4), 105 (5), 92 (5), 91 (75), 65 (7), 39 (4).

3.4.3. Prop-1-en-2-yl 4-oxopentanoate (isopropenyl levulinate, 2c)

i. According to procedure A, isopropenyl acetate (4.307 g, 43.1 mmol), levulinic acid (**1c**: 0.501 g, 4.31 mmol) in presence of sulfuric acid (21.1 mg, 0.22 mmol) as catalyst afforded **2b** in 0% yield by GC/MS.

3.4.4. Prop-1-en-2-yl benzoate (isopropenyl benzoate, 2d)

i. According to procedure A, isopropenyl acetate (4.31 g, 43.1 mmol), benzoic acid (**1d**: 0.515 g, 4.21 mmol) in presence of sulfuric acid (20.5 mg, 0.21 mmol) as catalyst afforded **2d** in 16% isolated yield as a viscous brown oil.

ii. According to procedure B, isopropenyl acetate (3.777 g, 37.7 mmol), benzoyl chloride (**4d**: 0.531 g, 3.77 mmol) in presence of sulfuric acid (18.5 mg, 0.18 mmol) as catalyst afforded **2d** in 94% yield, by GC/MS.

iii. According to procedure B, isopropenyl acetate (3.554 g, 35.5 mmol), benzoyl chloride (**4d**: 0.521 g, 3.71 mmol) in presence of $BSMIMHSO_4$ (56.5 mg, 0.17 mmol) as catalyst afforded **2d** in 21% yield, by GC/MS.

iv. According to procedure B, isopropenyl acetate (3.564 g, 35.7 mmol), benzoyl chloride (**4d**: 0.518 g, 3.53 mmol) in presence of $HMIMBF_4$ (30.3 mg, 0.18 mmol) as catalyst afforded **2d** in 0% yield, by GC/MS.

v. According to procedure D, isopropenyl acetate (3.554-3.643 g, 35.5-35.6 mmol), benzoyl chloride (**4d**: 0.521-0.534 g, 3.71-3.79 mmol) and H_2SO_4 (17.9-18.6 mg, 0.17-0.18 mmol) or no catalyst, after 2-4h and at T = 120-170°C afforded **2d** in 5-90% yield, by GC/MS.

^{1}H NMR (400 MHz, 25°C, $CDCl_3$, ^{1}H) δ (ppm relative to TMS): 8.09 (m, 2H), 7.59 (m, 1H), 7.47 (m, 2H), 4.83 (m, 2H), 2.05 (dd, J = 1.16, 0.55 Hz, 3H).

^{13}C{H} NMR (400 MHz, 25°C, $CDCl_3$) δ (ppm relative to TMS): 164.82, 153.37, 133.40, 130.06, 128.56, 102.43, 19.78.

GC/MS (relative intensity, 70 eV) *m/z*: 106 (8), 105 (100), 77 (36), 51 (9).

3.4.5. Prop-1-en-2-yl 4-methoxybenzoate (isopropenyl p-methoxybenzoate, 2e)

i. According to procedure A, isopropenyl acetate (3.235 g, 32.3 mmol), p-methoxybenzoic acid (**1e**: 0.523 g, 3.44 mmol) in presence of sulfuric acid (16.8 mg, 0.17 mmol) as catalyst afforded **2e** in 7% isolated yield as a viscous brown oil.

ii. According to procedure B, isopropenyl acetate (2.932 g, 29.3 mmol), p-methoxybenzoyl chloride (**4e**: 0.511 g, 2.93 mmol) in presence of sulfuric acid (14.3 mg, 0.14 mmol) as catalyst afforded **2e** in >99% yield, by GC/MS.

^{1}H NMR (400 MHz, 25°C, $CDCl_3$, ^{1}H) δ (ppm relative to TMS): 8.05 (m, 4H), 4.80 (m, 2H), 3.87 (s, 3H), 2.04 (dd, J = 1.15, 0.55 Hz, 3H).

^{13}C{H} NMR (400 MHz, 25°C, $CDCl_3$) δ (ppm relative to TMS): 132.97, 132.16, 114.28, 113.84, 102.29, 55.74, 55.61, 19.88.

GC/MS (relative intensity, 70 eV) *m/z*: 136 (8), 135 (100), 107 (7), 92 (10), 77 (12), 64 (5), 63 (4).

3.4.6. Diprop-1-en-2-yl oxalate (isopropenyl oxalate, 2f)

i. According to procedure A, isopropenyl acetate (5.411 g, 54.1 mmol), oxalic acid (**1f**: 0.487 g, 5.41 mmol) in presence of sulfuric acid (26.4 mg, 0.27 mmol) as catalyst afforded **2f** in 0% yield by GC/MS.

ii. According to procedure B, isopropenyl acetate (3.923 g, 39.1 mmol), oxalyl dichloride (**4f**: 0.497 g, 3.91 mmol) in presence of sulfuric acid (19.1 mg, 0.19 mmol) as catalyst afforded **2f** in 0% yield by GC/MS.

iii. According to procedure C, isopropenyl acetate (3.941 g, 39.4 mmol), oxalyl dichloride (**4f**: 0.502 g, 3.95 mmol) in presence of resin Amberlyst-15 (60.1 mg) as catalyst afforded **2f** in >99% yield by ^{1}H NMR.

^{1}H NMR (400 MHz, 25°C, $CDCl_3$, ^{1}H) δ (ppm relative to TMS): 4.42 (q, J = 7.18 Hz, 4H), 1.42 (t, J = 7.15, 6H).

3.4.7. Diprop-1-en-2-yl malonate (isopropenyl malonate, 2g)

i. According to procedure A, isopropenyl acetate (5.951 g, 59.2 mmol), malonic acid (**1g**: 0.512 g, 4.92 mmol) in presence of sulfuric acid (24.2 mg, 0.24 mmol) as catalyst afforded **2g** in 0% yield by GC/MS.

ii. According to procedure B, isopropenyl acetate (3.534 g, 35.4 mmol), malonyl dichloride (**4g**: 0.500 g, 3.55 mmol) in presence of sulfuric acid (17.3 mg, 0.18 mmol) as catalyst afforded **2g** in 0% yield by GC/MS.

iii. According to procedure C, isopropenyl acetate (3.68 g, 36.7 mmol), malonyl dichloride (**4g**: 0.517 g, 3.66 mmol) in presence of resin Amberlyst-15 (58.9 mg) as catalyst afforded **2g** in 50% yield by ^{1}H NMR.

3.4.8. Diprop-1-en-2-yl succinate (isopropenyl succinate, 2h)

i. According procedure A, isopropenyl acetate (4.38 g, 43.6 mmol), succinic acid (**1h**: 0.515 g, 4.36 mmol) in presence of sulfuric acid (21.4 mg, 0.21 mmol) as catalyst afforded **2h** in 0% yield by GC/MS.

ii. According to procedure B, isopropenyl acetate (3.23 g, 32.3 mmol), succinyl dichloride (**4h**: 0.501 g, 3.23 mmol) in presence of sulfuric acid (15.8 mg, 0.16 mmol) as catalyst afforded **2h** in 84% isolated yield as a viscous pale yellow oil.

^{1}H NMR (400 MHz, 25°C, $CDCl_3$, ^{1}H) δ (ppm relative to TMS): 4.69 (m, 4H), 2.73 (s, 4H), 1.91 (dd, J = 1.23, 0.57 Hz, 6H).

^{13}C{H} NMR (400 MHz, 25°C, $CDCl_3$) δ (ppm relative to TMS): 170.23, 152.88, 102.12, 29.18, 19.43.

GC/MS (relative intensity, 70 eV) *m/z*: 141 (32), 102 (5), 101 (100), 73 (7), 58 (4), 55 (11), 43 (6), 41 (7).

3.5. General procedure for the synthesis of acyl chlorides, using $SOCl_2$

In a round-bottom flask, equipped with a magnetic stir bar and a reflux condenser, the appropriate amount of carboxylic acid or anhydride (1 eq) was mixed with equivalent quantity of thionyl chloride (4 eq). The reaction mixture was stirred continuously (400 rpm) and heated at reflux temperature by means of a pre-heated oil bath kept at T = 80°C. Every reaction was sampled at given time intervals and monitored offline by GC/MS or ^{1}H NMR, ^{13}C NMR analysis, until no more carboxylic acid was present in the system. After the reaction completion, the excess thionyl chloride was removed under vacuum and the respective acyl chloride was obtained with no further purification. The procedure was successfully performed for the synthesis of octanoyl chloride (**4a**), phenylbutyryl chloride (**4b**), p-methoxybenzoyl chloride (**4e**) and succinyl chloride (**4h**).

3.6. Characterization data

3.6.1. Octanoyl chloride (4a)

Following the general procedure for the synthesis of acyl chlorides, octanoic acid (**1a**: 3.109 g, 21.6 mmol) and $SOCl_2$ (10.271 g, 86.4 mmol) afforder **4a** in >99% isolated yield. GC/MS (relative intensity, 70 eV) *m/z*: 134 (6), 133 (4), 128 (7), 127 (85), 119 (5), 111 (5), 109 (9), 105 (6), 98 (59), 97 (18), 93 (12), 91 (23), 85 (35), 84 (100), 83 (34), 82 (79), 80 (18), 79 (12), 78 (34) 70 (21), 69 (39), 67 (16), 63 (12), 57 (67), 56 (36), 55 (89), 43 (61), 42 (39), 41 (84), 39 (33).

3.6.2. 4-phenylbutanoyl chloride (phenylbutyryl chloride, 4b)

Following the general procedure for the synthesis of acyl chlorides, phenylbutyric acid (**1b**: 3.026 g, 18.4 mmol) and $SOCl_2$ (8.756 g, 73.6 mmol) afforder **4b** in >99% isolated yield. GC/MS (relative intensity, 70 eV) *m/z*: 182 (M^+, 14), 147 (51), 146 (14), 129 (7), 117 (8), 105 (11), 104 (95), 92 (8), 91 (100), 78 (6), 77(6), 65 (16), 63 (6), 51 (6), 39 (6).

3.6.3. 4-methoxybenzoy chloride (4e)

Following the general procedure for the synthesis of acyl chlorides, phenylbutyric acid (**1e**: 3.245 g, 21.3 mmol) and $SOCl_2$ (10.149 g, 85.3 mmol) afforder **4e** in >99% isolated yield. GC/MS (relative intensity, 70 eV) *m/z*: 136 (9), 135 (100), 107 (8), 92 (16), 77 (19), 64 (8), 63 (9).

3.6.4. Succinyl dichloride (4h)

Following the general procedure for the synthesis of acyl chlorides, succinic anhydride (2.976 g, 29.8 mmol) and $SOCl_2$ (14.2 g, 119.2 mmol) afforder **4h** in >99% isolated yield.

3.7. General procedure for the tandem reactions of acetalization/transesterification

Costum-made batch reactor. A costum-made reactor, shown in Figure 2.1, was filled with resin Amberlyst-15 (0.05 eq, 17.8-16.7 mg), the chosen isopropenyl ester (1 eq, 1.45-1.67 mmol), the diol (1 eq, 1.44-1.67 mmol) of choice and the requested amount of solvent (0-2.5 mL); then the reactor was equipped with a reflux condenser, it was dried by four N_2-vacuum cycles and it was kept under N_2. The temperature was set among 70-90°C and every reaction was carried out for a pre-determined length of time. Final conversion and selectivity were determined by GC/MS analysis and quantified (for substrates **2a** and **2i**) using a calibration curve.

Costum-made autoclave reactor. A costum-made reactor, shown in Figure 2.8, was filled with resin Amberlyst-15 (0.05 eq, 17.5-16.9 mg), the chosen isopropenyl ester (1 eq, 1.48-1.63 mmol), the diol (1 eq, 1.49-1.62 mmol) of choice and the requested amount of solvent (0-1 mL); then the reactor was inlaid into a 20mL stainless steel autoclave, it was dried by four N_2-vacuum cycles and it was pressurized with 8atm of N_2. The temperature was set at 90°C and every reaction was carried out for 4h. Final conversion and selectivity were determined by GC/MS analysis and quantified (for substrates **2a** and **2i**) using a calibration curve.

Autoclave reactor. A pierced glass reactor, inlaid in a 20 mL stainless steel autoclave, was filled with resin Amberlyst-15 (0.05 eq, 17.8-16.7 mg), the chosen isopropenyl ester (1 eq, 1.44-1.67 mmol), the diol (1 eq, 1.42-1.65 mmol) of choice and the requested amount of solvent (0-2.5 mL); then the reactor was dried by four N_2-vacuum cycles and it was pressurized with 8-40atm of N_2 or CO_2. The temperature was set among 70-110°C and every reaction was carried out for 4h. Final conversion and selectivity were determined by GC/MS analysis and quantified (for substrates **2a** and **2i**) using a calibration curve.

3.8. Characterization data

3.8.1. 2,2,4-trimethyl-1,3-dioxolane (8)

GC/MS (relative intensity, 70 eV) *m/z*: 101 (37), 72 (15), 59 (8), 58 (8), 43 (100), 42 (22), 41 (17).

3.8.2. 2,2-dimethyl-1,3-dioxolane (9)

GC/MS (relative intensity, 70 eV) *m/z*: 101 (5), 73 (100), 59 (8), 57 (10), 45 (42), 42 (10).

3.8.3. 2-hydroxypropyl acetate (6i)

GC/MS (relative intensity, 70 eV) *m/z*: 87 (12), 75 (8), 58 (5), 45 (9), 43 (100).

3.8.4. 1,2.diacethoxy propane (6i')

^{1}H NMR (400 MHz, 25°C, $CDCl_3$, ^{1}H) δ (ppm relative to TMS): 5.12 (pd, J = 6.56, 3.59 Hz, 1H), 4.09 (m, 2H), 2.05 (d, J = 5.80 Hz, 6H), 1.24 (d, J = 6.55 Hz, 3H).

^{13}C{H} NMR (400 MHz, 25°C, $CDCl_3$) δ (ppm relative to TMS): 170.72, 170.41, 68.21, 66.07, 21.14, 20.74, 16.44.

GC/MS (relative intensity, 70 eV) *m/z*: 116 (3), 100 (3), 87 (8), 58 (3), 43 (100).

3.8.5. 2-hydroxypropyl octanoate (6a)

GC/MS (relative intensity, 70 eV) *m/z*: 158 (14), 128 (8), 127 (100), 118 (18), 115 (21), 101 (22), 100 (12), 98 (18), 87 (55), 84 (18), 74 (36), 59 (28), 58 (46), 57 (79), 55 (48), 45 (41), 43 (48), 41 (52).

3.8.6. Propylene glycol dicaprilate (6a')

^{1}H NMR (400 MHz, 25°C, $CDCl_3$, ^{1}H) δ (ppm relative to TMS): 5.13 (pd, J = 6.49, 3.59 Hz, 1H), 4.08 (m, 2H), 2.29 (td, J = 7.49, 5.92 Hz, 4H), 1.61 (p, J = 7.35 Hz, 4H), 1.26 (m, 20 H), 0.86 (m, 6H).

^{13}C{H} NMR (400 MHz, 25°C, $CDCl_3$) δ (ppm relative to TMS): 177.85, 177.55, 68.33, 66.26, 34.86, 34.53, 32.06, 32.03, 29.46, 29.42, 29.30, 25.37, 25.29, 22.97, 16.90, 14.41.

GC/MS (relative intensity, 70 eV) *m/z*: 203 (23), 200 (17), 186 (36), 185 (100), 140 (19), 128 (58), 127 (100), 113 (41), 101 (27), 100 (100), 84 (37), 57 (100), 55 (50), 43 (44).

3.8.7. Propdiolmonofenilbut

GC/MS (relative intensity, 70 eV) *m/z*: 222 (M^+, 5), 147 (46), 118 (24), 105(25), 104 (88), 91 (100), 65 (23), 58 (24), 45 (18).

3.8.8. Propdiolo difenilbut

GC/MS (relative intensity, 70 eV) *m/z*: 147 (44), 117 (16), 104 (61), 101 (55), 91 (72), 65 (16), 43 (100).

3.9. Calibration curves set-up

The quantification of substrates **6**, **6a'**, **6i'**, **8** was made throughout a calibration curve. The selectivity of **6a**, **7a** was calculated as follows:

Selectivity (**6a** or **6i**) = 100 – [Selectivity (**6a'** or **6i'**) + Selectivity (**8**)]

4-(methoxymethyl)-2,2-dimethyl-1,3-dioxolane (solketal metyl ether, **10**) was used in place of substrate **8** for the preparation of the calibration curve, due to some difficulties during the isolation of the acetal **8** (see introduction). Indeed, it was demonstrated that the analytical response of compound **8** and **10** was highly similar. For each compound four solutions were made in order to build the calibration curve (100 ppm, 300 ppm, 500 ppm,

700 ppm, respectively) and they were analyzed by GC-MS. In Figure 4.1, Figure 4.2, Figure 4.3, Figure 4.4, the calibration curves for compound **6**, **6a'**, **6i'**, **8,** are reported.

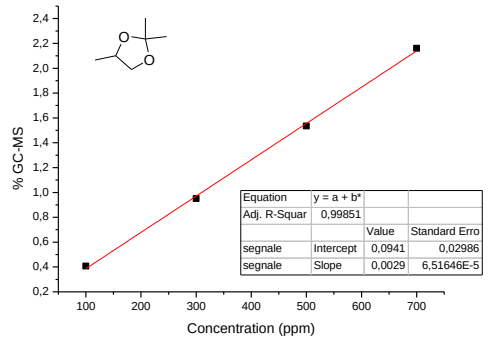


Figure 4.1. Calibration curve of the acetal **8**.

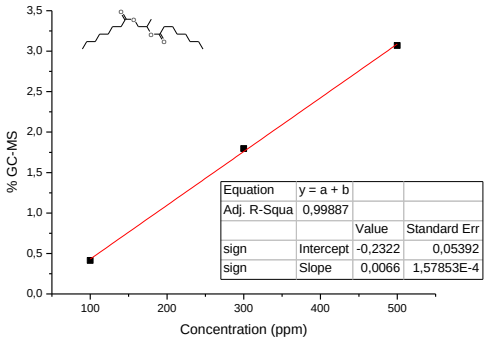


Figure 4.2. Calibration curve of compound **6a'**.

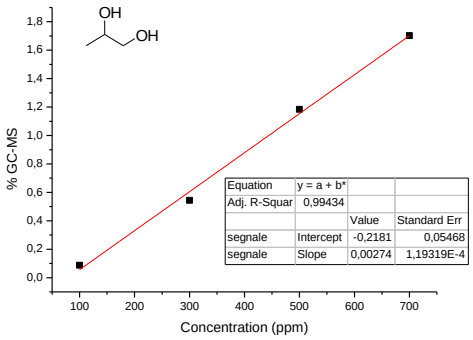


Figure 4.3. Calibration curve of compound **6**.

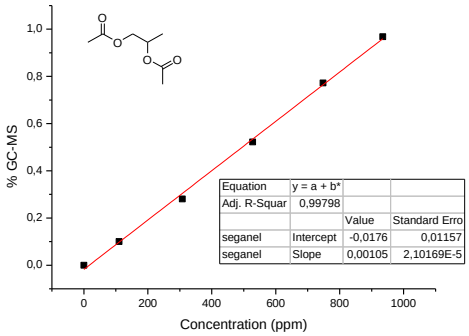


Figure 4.4. Calibration curve of compound **6i'**.

4. APPENDIX

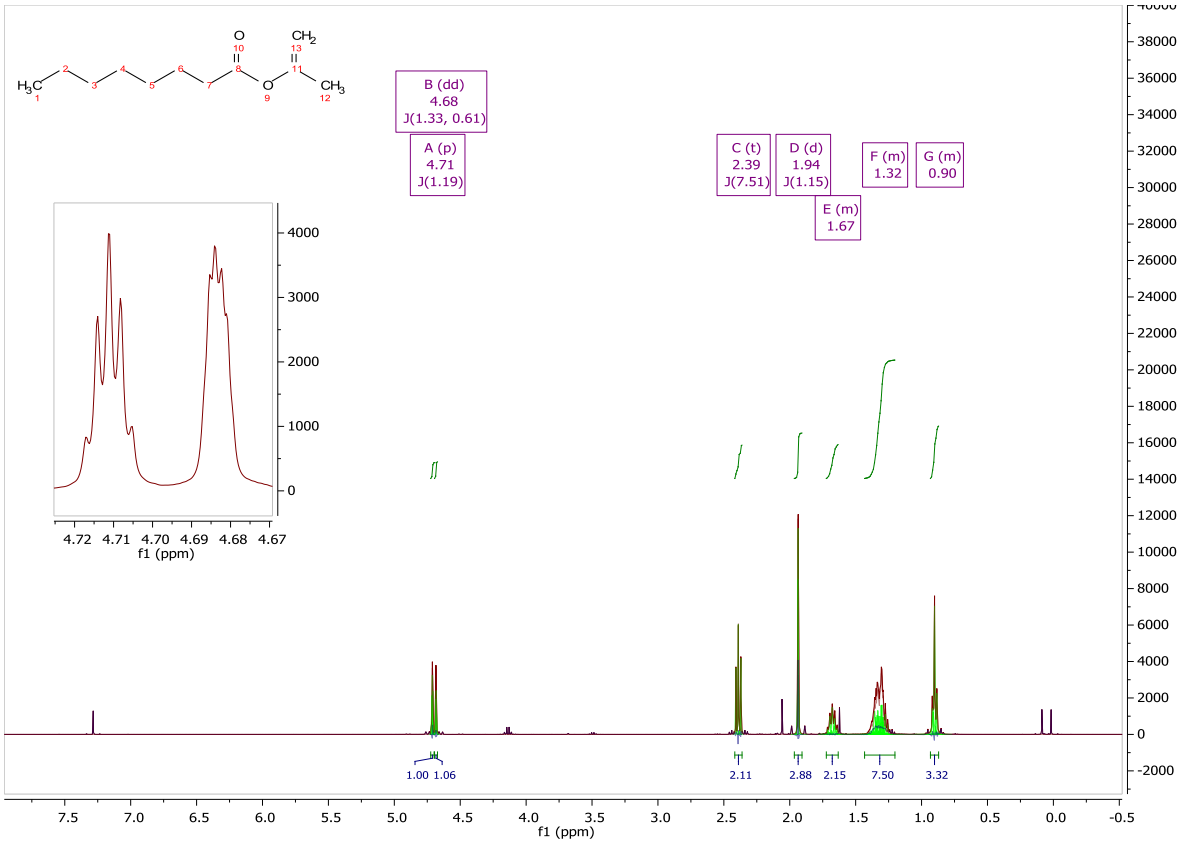


Figure 4.5. ^{1}H NMR spectrum of prop-1-en-2-yl octanoate (**2a**) in chloroform-*d*$_1$.

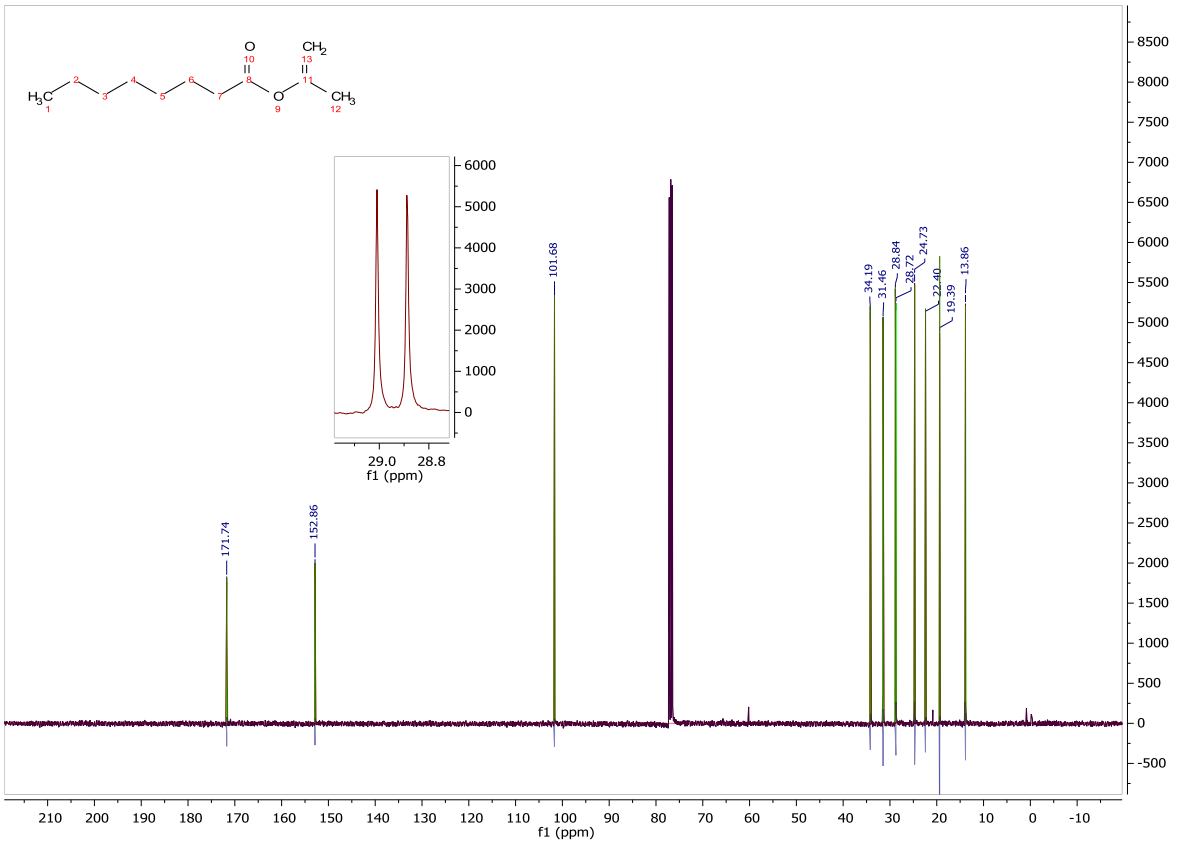


Figure 4.6. ^{13}C NMR spectrum of prop-1-en-2-yl octanoate (**2a**) in chloroform-*d*$_1$.

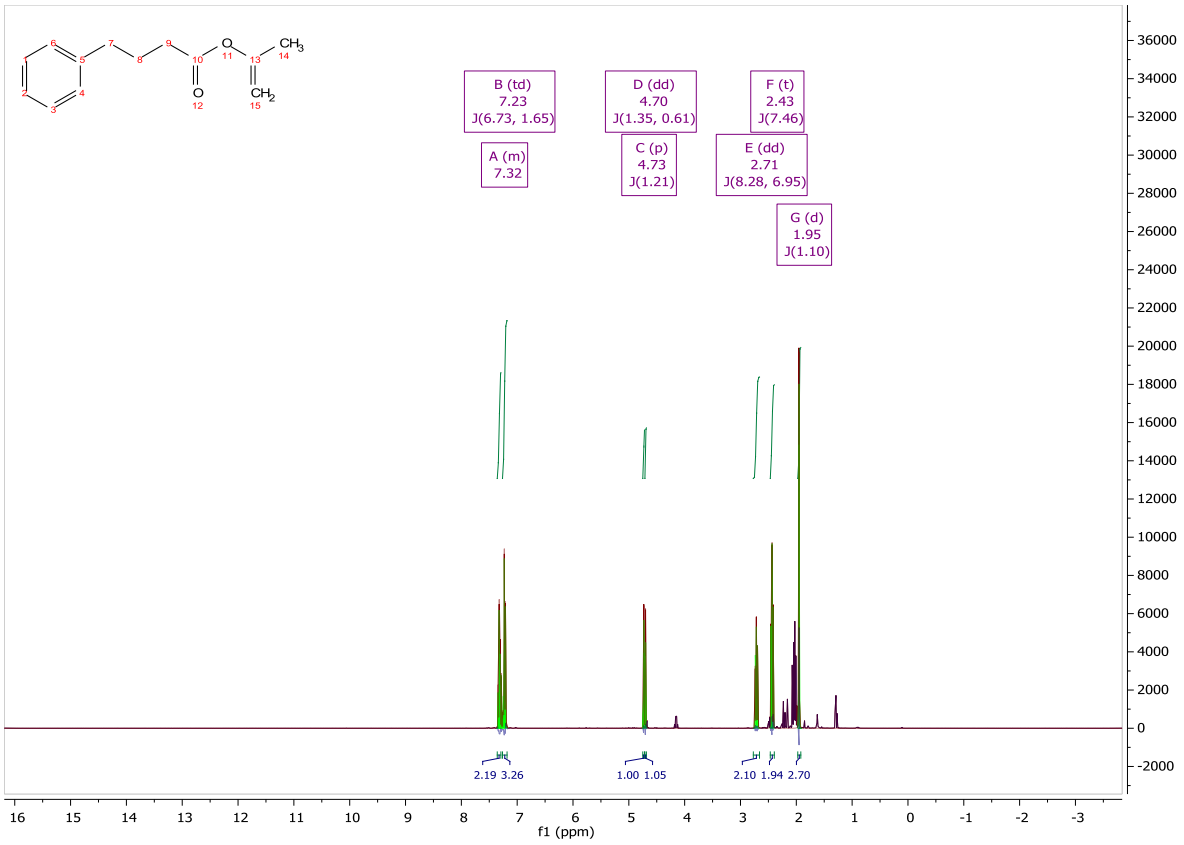


Figure 4.7. ^{1}H NMR spectrum of prop-1-en-2-yl 4-phenylbutanoate (**2b**) in chloroform-d_1.

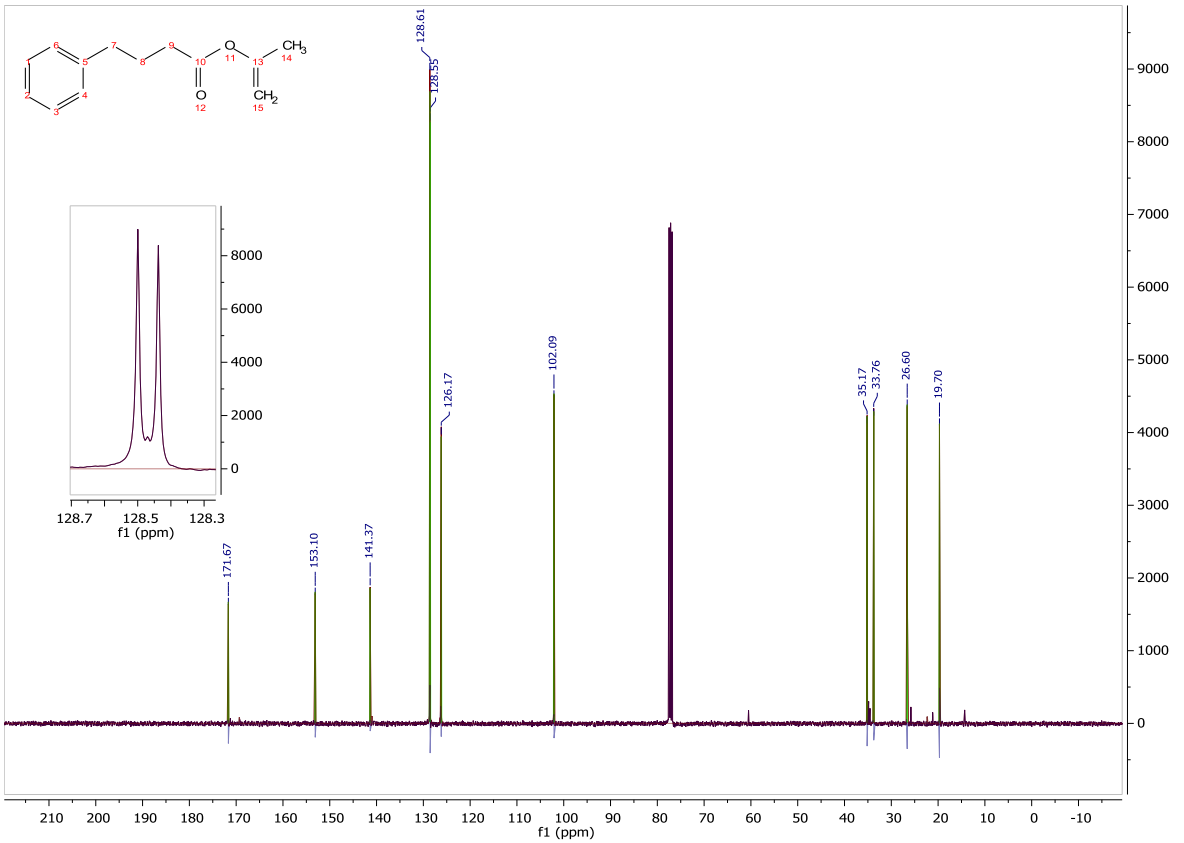


Figure 4.8. ^{13}C NMR spectrum of prop-1-en-2-yl 4-phenylbutanoate (**2b**) in chloroform-d_1.

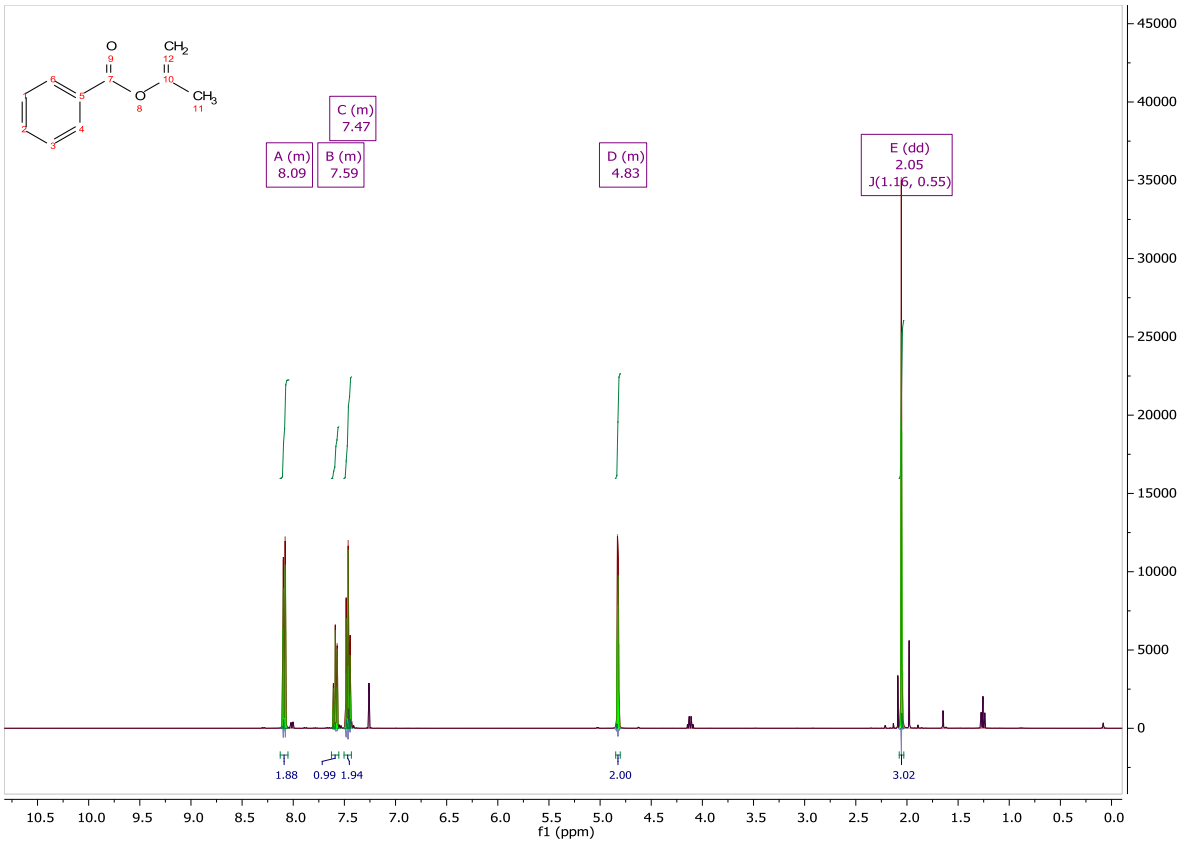


Figure 4.9. ^{1}H NMR spectrum of prop-1-en-2-yl benzoate (**2d**) in chloroform-d_1.

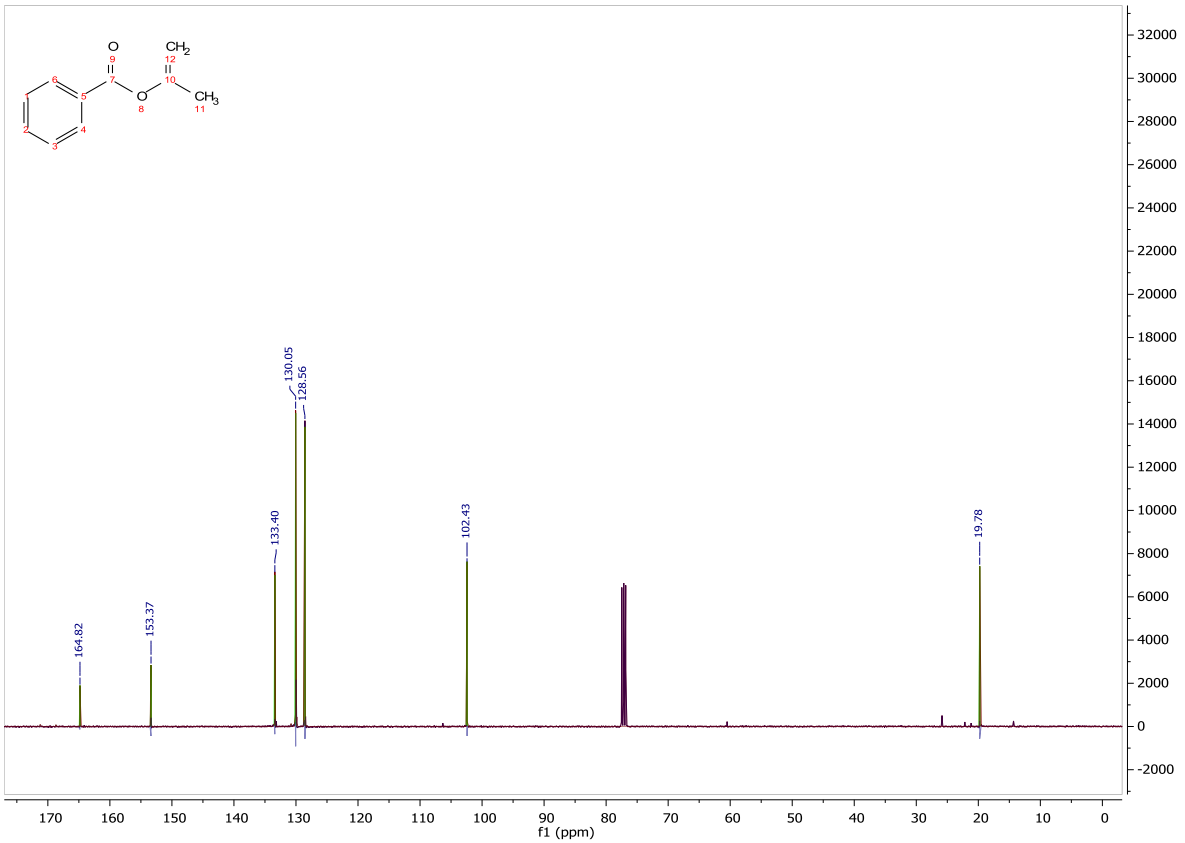


Figure 4.10. ^{13}C NMR spectrum of prop-1-en-2-yl benzoate (**2d**) in chloroform-d_1.

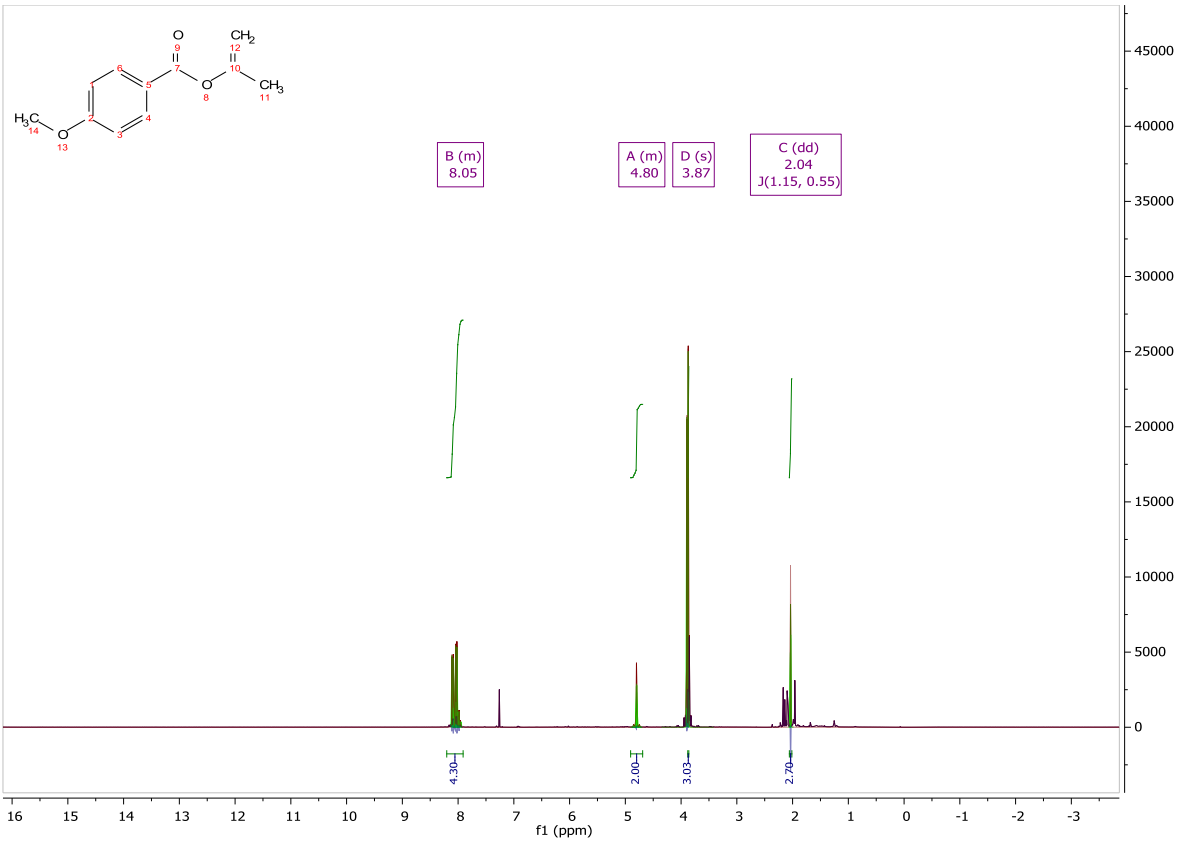


Figure 4.11. ^{1}H NMR spectrum of prop-1-en-2-yl 4-methoxybenzoate (**2e**) in chloroform-*d*$_1$.

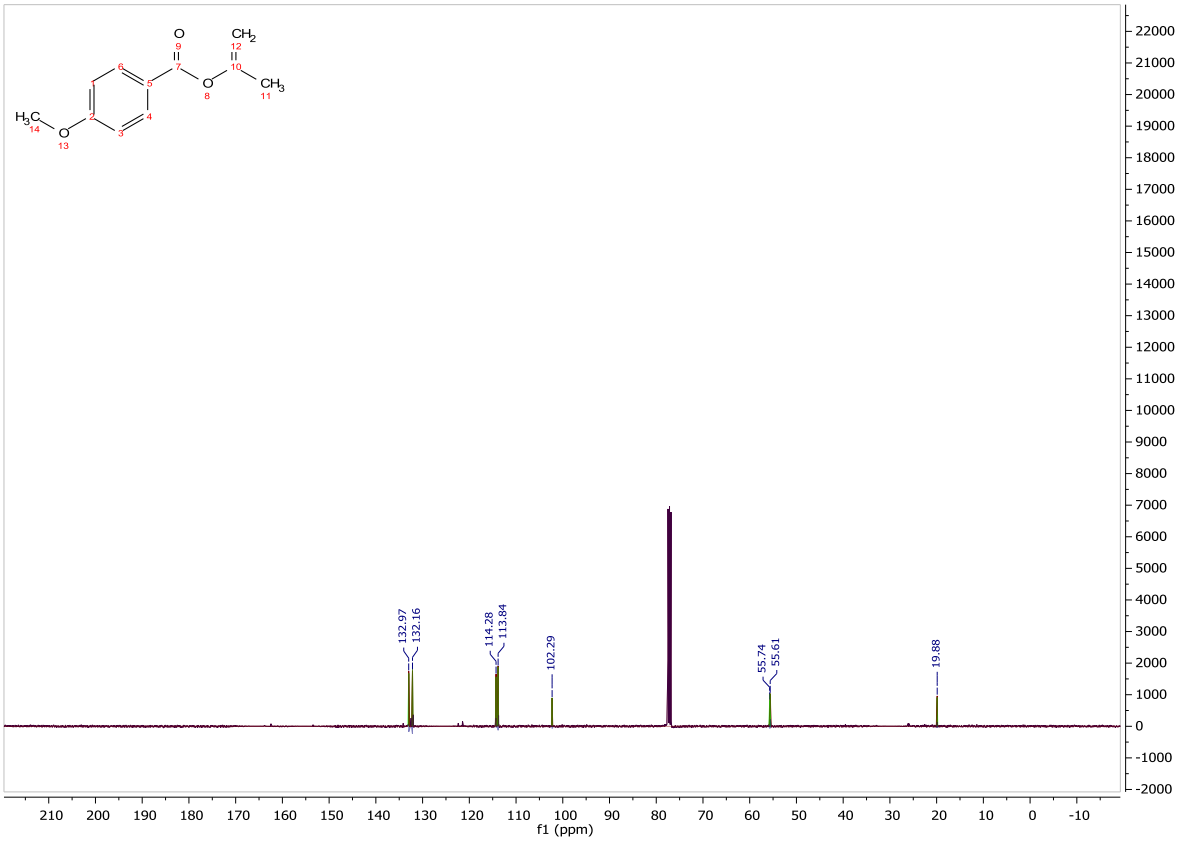


Figure 4.12. ^{13}C NMR spectrum of prop-1-en-2-yl 4-methoxybenzoate (**2e**) in chloroform-*d*$_1$.

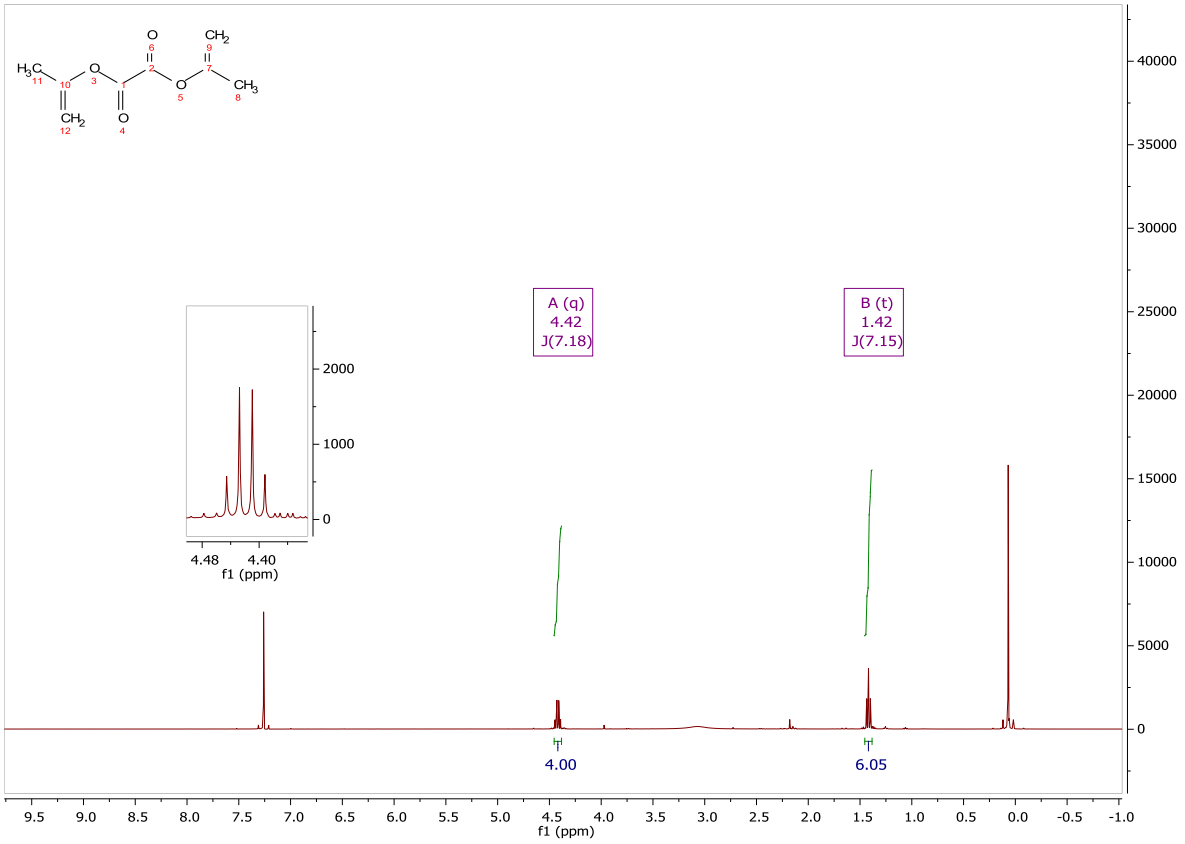


Figure 4.13. ^{1}H NMR spectrum of diprop-1-en-2-yl oxalate (**2f**) in chloroform-*d*$_1$.

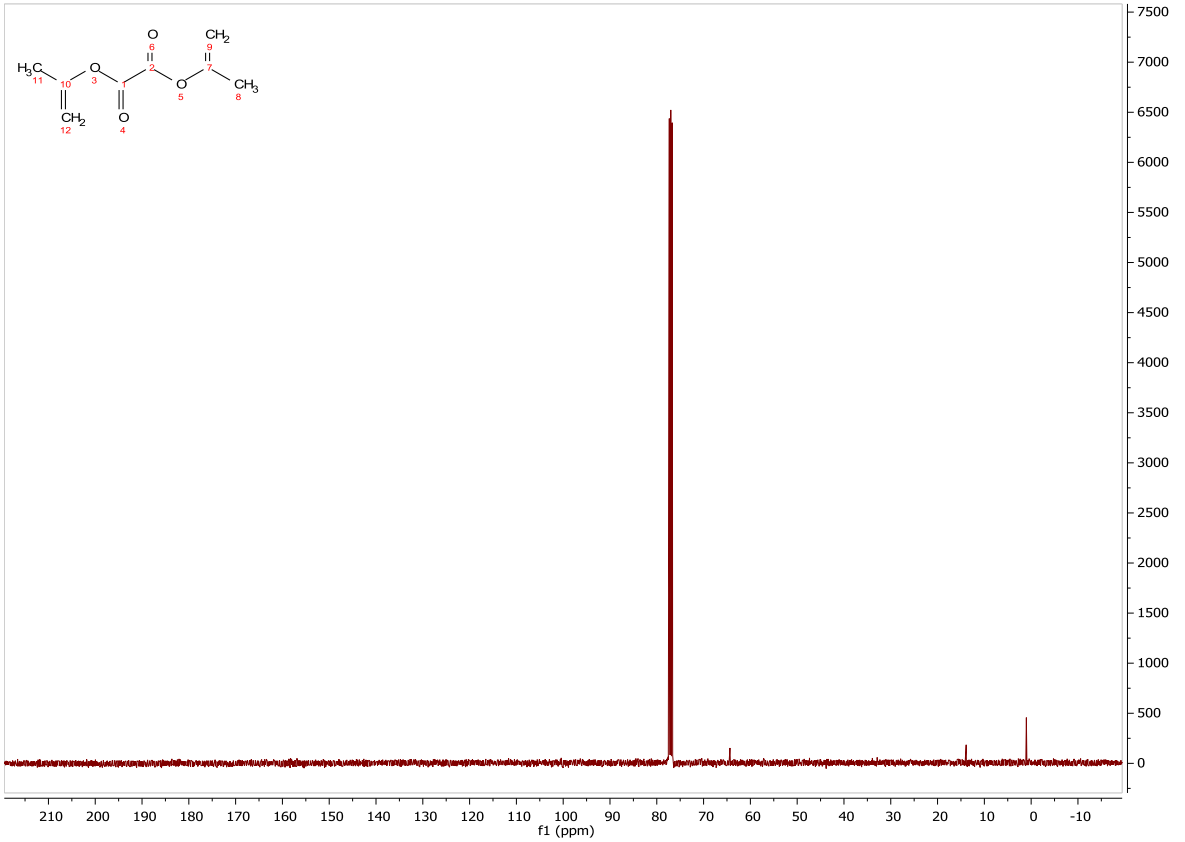


Figure 4.14. ^{13}C NMR spectrum of diprop-1-en-2-yl oxalate (**2f**) in chloroform-d_1.

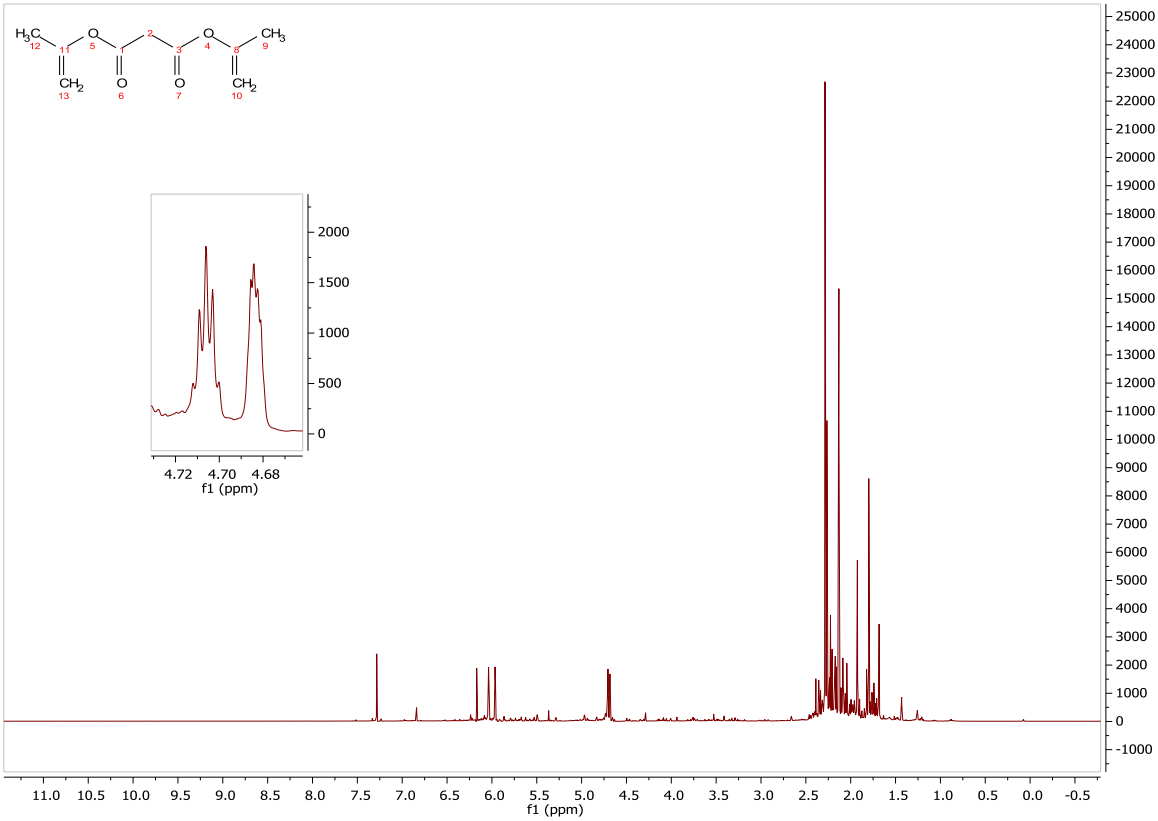


Figure 4.15. ^{1}H NMR spectrum of diprop-1-en-2-yl malonate (**2g**) in chloroform-d_1.

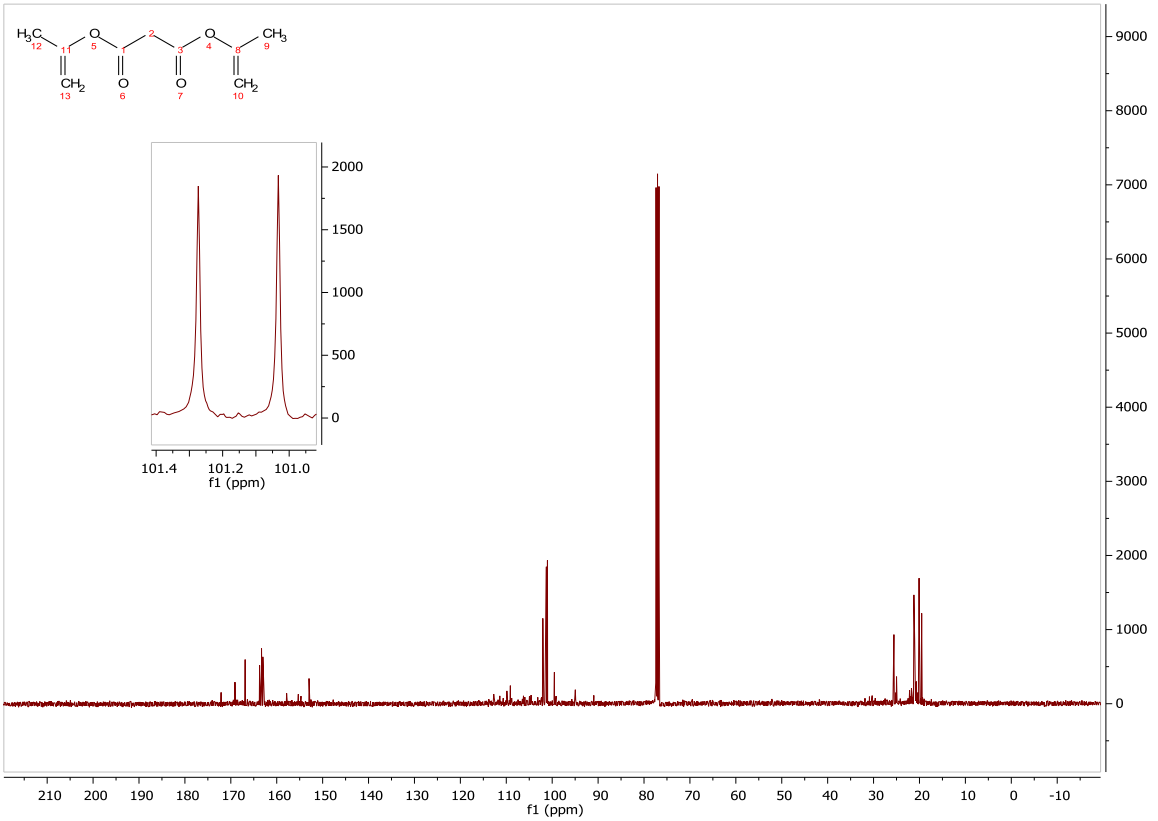


Figure 4.16. ^{13}C NMR spectrum of diprop-1-en-2-yl malonate (**2g**) in chloroform-d_1.

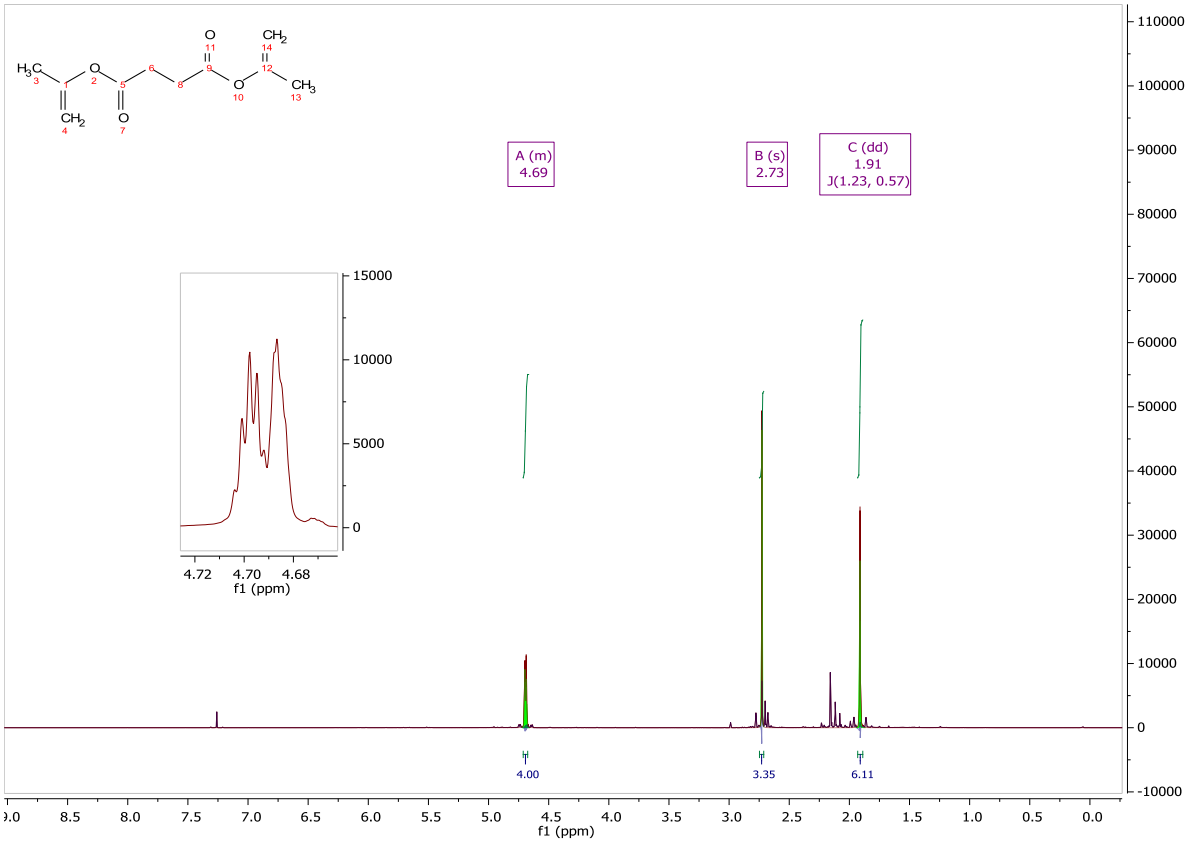


Figure 4.17. ^{1}H NMR spectrum of diprop-1-en-2-yl succinate (**2h**) in chloroform-*d*$_1$.

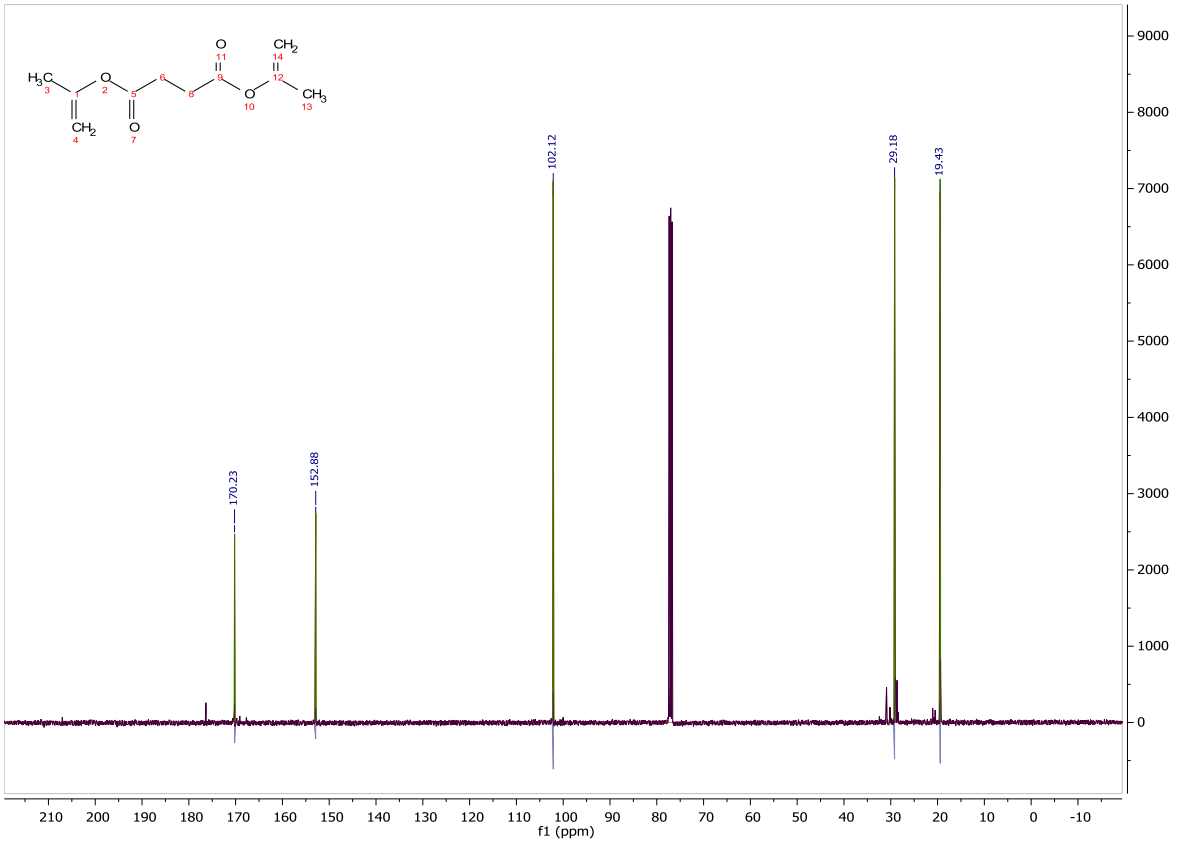


Figure 4.18. ^{13}C NMR spectrum of diprop-1-en-2-yl succinate (**2h**) in chloroform-*d*$_1$.

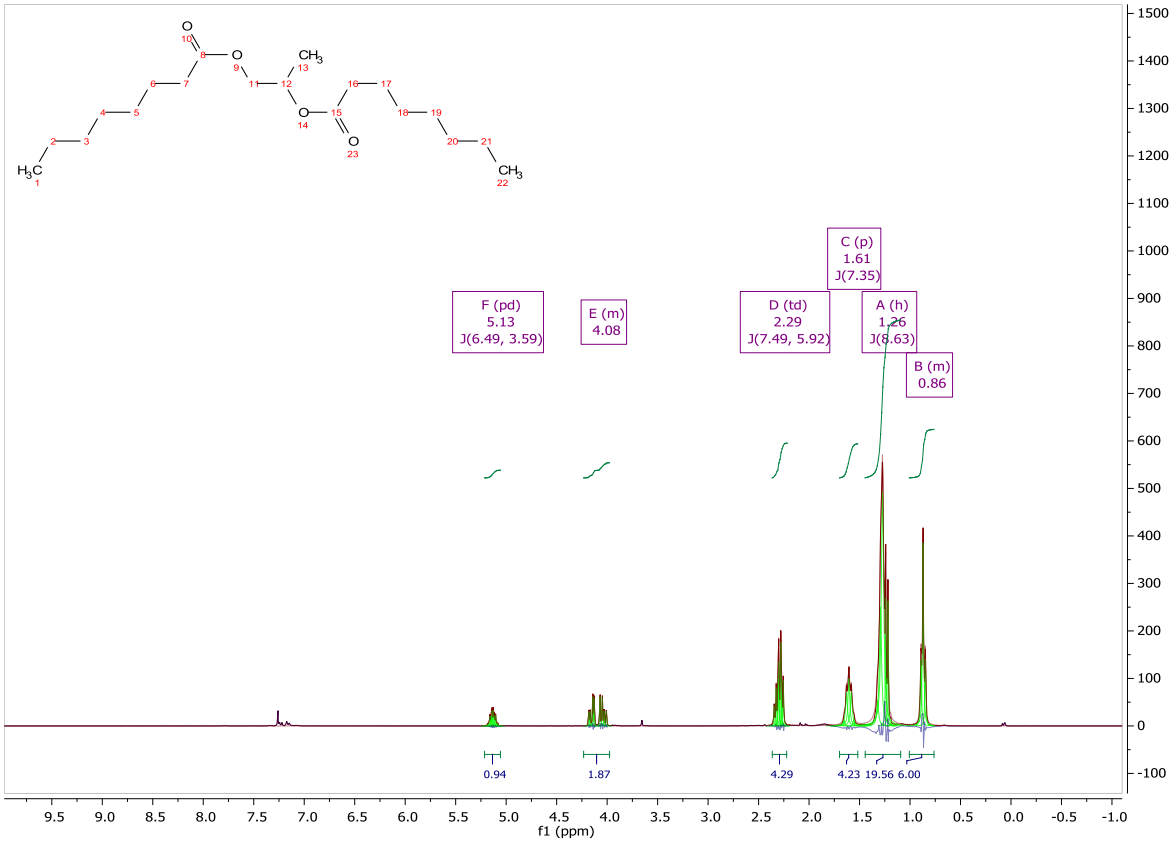


Figure 4.19. ^{1}H NMR spectrum of propylene glycol dicaprilate (**6a'**) in chloroform-d_1.

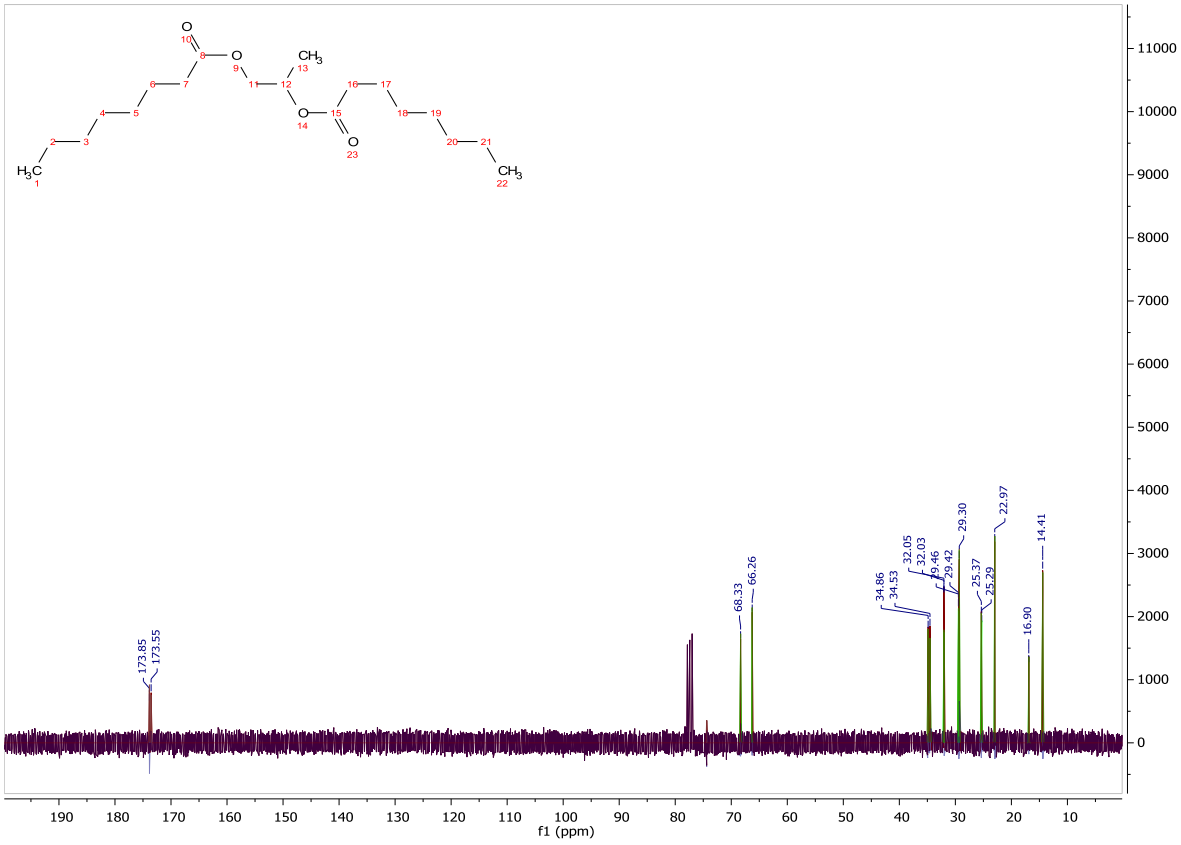


Figure 4.20. ^{13}C NMR spectrum of propylene glycol dicaprilate (**6a'**) in chloroform-d_1.

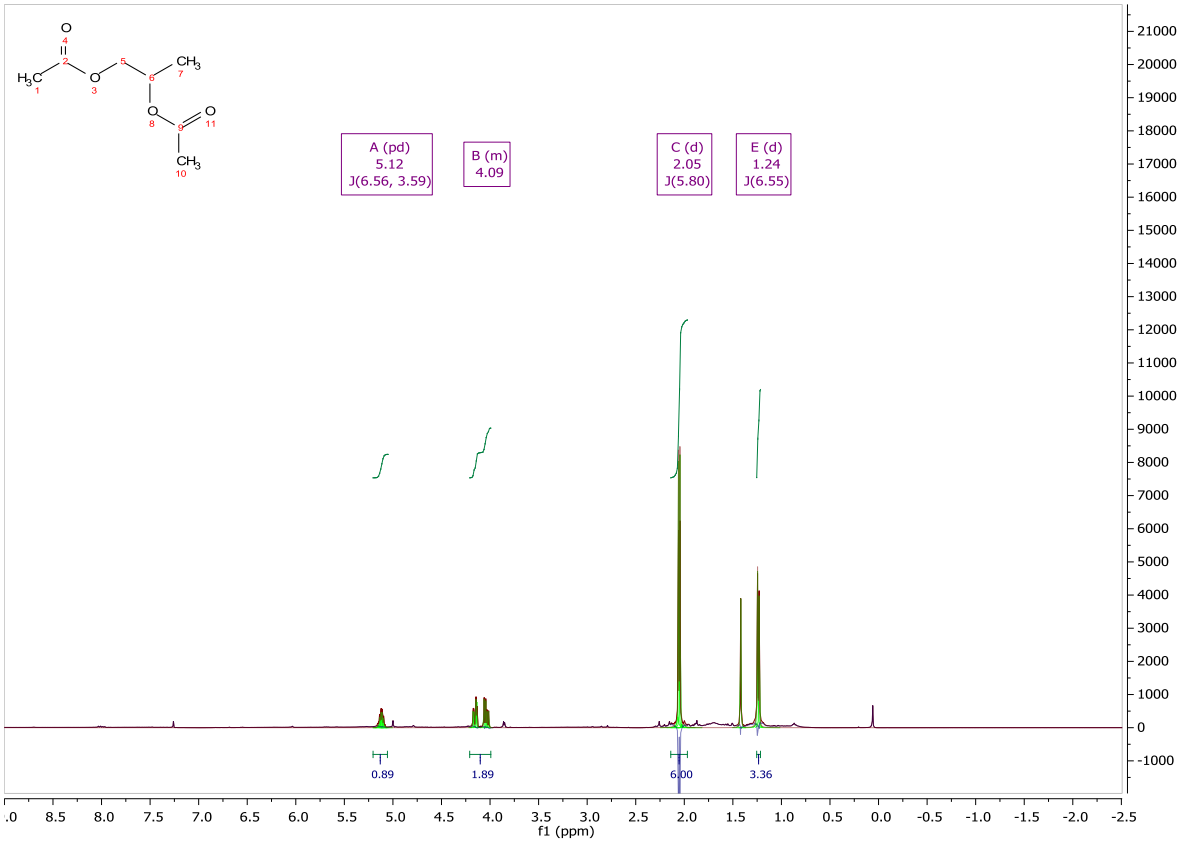


Figure 4.21. ^{1}H NMR spectrum of 1,2.diacetoxy propane (**6i'**) in chloroform-d_1.

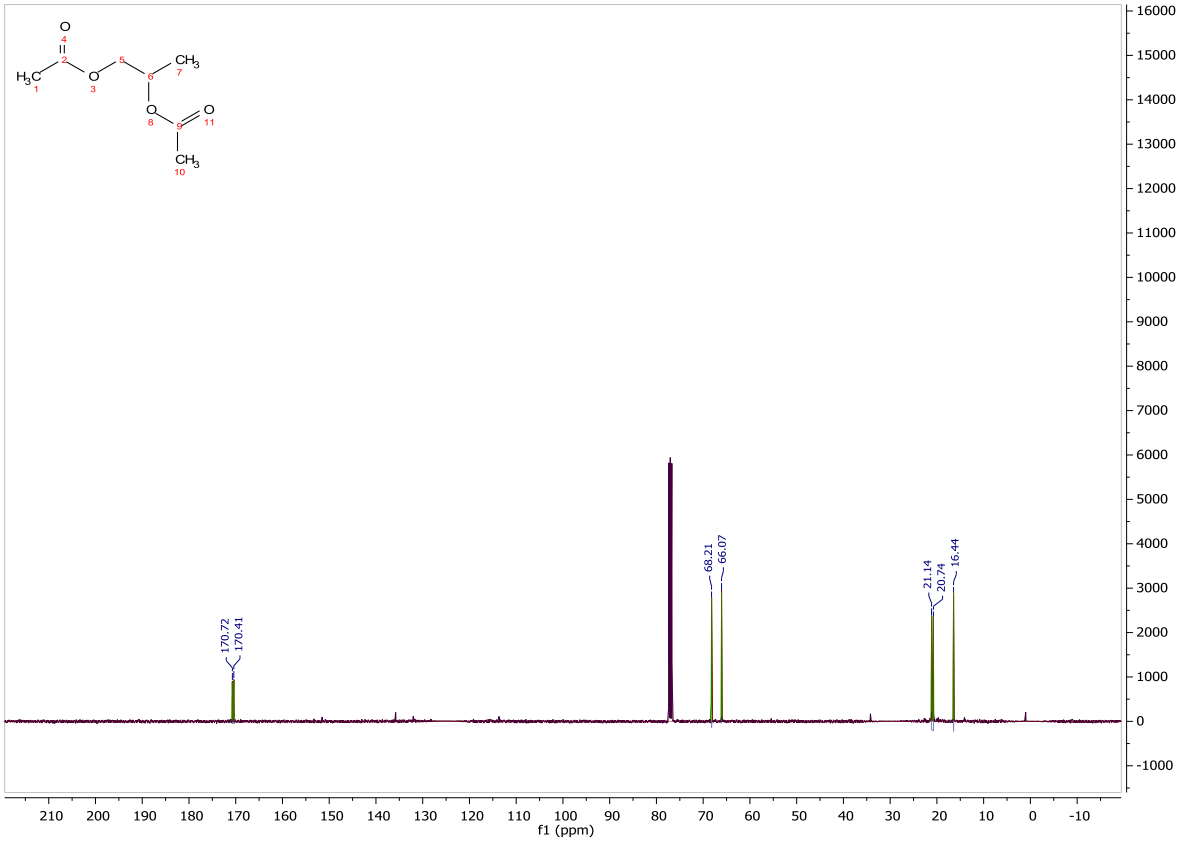


Figure 4.22. ^{13}C NMR spectrum of 1,2.diacetoxy propane (**6i'**) in chloroform-d_1.

References

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