Catalytic valorisation of terpenes

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Valorisation de produits naturels
Métathèse croisée de terpènes et terpénoides encombrés

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ABSTRACT

Cyclic monoterpenes are important bio-sourced components present in the resin of pine and citrus trees and some of them are currently produced on an industrial scale especially by the fruit juice industry in Brazil. Therefore, any environmentally benign transformation of these terpenes into new useful products should have a strong impact in terms of sustainable economy. Initially, we were especially interested in the functionalization by olefin metathesis of (-)-β-pinene and (-)-limonene, which are bulky unsaturated monoterpenes featuring a terminal disubstituted carbon-carbon double bond. The reaction is catalyzed by Hoveyda-Grubbs type ruthenium catalysts in dimethyl carbonate as green solvent and makes possible the clean introduction of ester and nitrile groups in one step without formation of byproducts. We have shown that the utilization of the internal double bond of a symmetrical cross metathesis partner such as dimethyl fumarate, dimethyl maleate, fumaronitrile, 1,4-diacetoxybut-2-ene, 1,4-dichlorobut-2-ene and 2-methylbut-2-ene was very efficient and selective for the functionalization of β-pinene and limonene in the presence of ruthenium catalysts. The influence of oxygenated functional groups in the terpene partner has also been evaluated with terpenoids derived from limonene bearing a ketone and an epoxide group. In this case, these substrates did not inhibit the cross metathesis with any of the cross metathesis partners and the reactivities followed the general rule found for terpenes. The utilization of internal olefins instead of terminal olefins as cross metathesis partners with bulky cyclic terpenes and terpenoids constitutes an elegant route for the straightforward functionalization of their α,α-disubstituted terminal double bond. All cross metathesis products are new compounds and should be evaluated for valuable properties.

KEY WORDS: Cross-metathesis, Cyclic Terpenes, Ruthenium catalysis, Sustainable chemistry

RESUMO

Monoterpenos cíclicos são importantes componentes de origem biológica presentes na resina de pinus e elementos cítricos, sendo alguns deles atualmente produzidos em escala industrial, especialmente pela indústria de sucos de frutas no Brasil. Portanto, qualquer transformação ambientalmente benéfica desses terpenos em novos produtos pode ter um forte impacto em termos de economia sustentável. Inicialmente, estivemos especialmente interessados na funcionalização por metátese de olefinas como o (-)-β-pineno e (-)-limoneno, que são monoterpenos insaturados volumosos com uma dupla ligação carbono-carbono disubstituída terminal. A reação é catalisada por catalisadores de rutênio do tipo Hoveyda-Grubbs em carbonato de dimetila como solvente verde e possibilita a introdução direta de grupos éster e nitrila em uma única etapa, sem formação de subprodutos. Mostramos que a utilização da dupla ligação interna de um reagente de metátese cruzada simétrico, como fumarato de dimetila, maleato de dimetila, fumaronitrila, 1,4-diacetoxibut-2-eno, 1,4-diclorobut-2-eno e 2-metilbut-2-eno foi muito eficiente e seletiva para a funcionalização do β-pineno e limoneno na presença de catalisadores de rutênio. A influência dos grupos funcionais oxigenados no substrato terpênico também foi avaliada com substratos derivados do limoneno contendo um grupo cetona e um grupo epóxido. Neste caso, estes substratos não inibiram a metátese cruzada com nenhum dos reagentes de metátese cruzada e as reatividades seguiram a regra geral encontrada para os terpenos. A utilização de olefinas internas em vez de olefinas terminais como reagentes de metátese cruzada com terpenos cíclicos volumosos e terpenoides constitui uma rota elegante para a simples funcionalização da dupla ligação terminal α,α-disubstituída. Todos os produtos de metátese cruzada são compostos inéditos e devem ser avaliados quanto às suas propriedades

PALAVRAS-CHAVE: Metátese cruzada, Terpenos cíclicos, Rutênio, Química Sustentável

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To my French supervisors, Dr. Cédric Fischmeister and Prof. Dr. Christian Bruneau, who were a pleasant surprise on my path, from whom I´ve learned immensely. I especially thank them for all the patience and availability they always had in guiding me, whenever I needed it. It was a privilege to be present in an institute of such competence as the *Institut des Sciences Chimiques de Rennes*. I cannot forget to mention the privilege of having also been close to Prof. Pierre Dixneuf, another great reference in the field of Catalysis. To all three, I am immensely grateful for the French (and Breton) cultural experiences they provided me, which I will never forget and I will always miss.

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Summary

1 General Introduction

Terpenes are found in essential oils and constitute a class of natural products that finds direct applications and serves as feedstocks in the flavor and fragrance industry. They have also other potential applications due to their biological properties.[1] They are constructed on the basis of connected isoprene units (2-methyl-1,3-butadiene) and thus contain a number of carbon atoms which is a multiple of five. Terpenoids are chemically modified terpenes, essentially oxygenated derivatives such as alcohols, epoxides, ketones, aldehydes, carboxylic acids and esters. Monoterpenes have already found direct applications in the field of fragrances and flavors[1] and constitute renewable building blocks for the access to sustainable polymers.[2] Several catalytic transformations of natural terpenes, such as oxidation, epoxidation, hydroformylation, hydrogenation, dehydrogenation, isomerization, rearrangement, have been achieved in order to produce added value chemicals for various applications.[3,4,5,6]Recently, computational studies on metathesis transformations of bulky terpenes such as α- and β-pinene in ring opening and cross metathesis with various types of catalysts (Ru, Mo, W) have appeared.[7,8]

Cyclic terpenes such as α-pinene, β-pinene, camphene and limonene (**Figure 1**) are important bio-sourced components present in the resin of pine and citrus trees and are currently extracted on an industrial scale. The world production of turpentine, which contains mainly these terpenes, is estimated at 350.000 tons/year,[9] while that of limonene extracted from the peel of citrus fruits

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produced in fruit juice industry, containing about 90% of limonene,[10] could result in approximately 65 kt per year.[11]

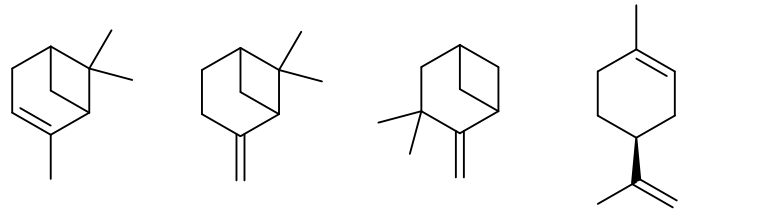

Figure 1: Examples of cyclic terpenes

Olefin metathesis, in particular cross-metathesis, has an enormous potential for direct functionalization of olefins arising from natural resources.[12,13] The possibility of introducing ester, aldehyde, halogen, nitrile functional groups has already been demonstrated starting from 1,2-disubstituted internal double bonds of fatty acid derivatives[14,15] and terpenes featuring the trisubstituted prenyl end[16,17] with electron-deficient olefins, allylic chlorides and esters as cross-metathesis partners.

A few examples of cross-metathesis of gem-disubstituted cyclic olefins with terminal olefins have been reported from methylene-cyclobutane,[18]-cyclopentane and -cyclohexane,[19] and the more difficult cross metathesis of olefins with sterically encumbered exocyclic methylene groups is much less documented.[20,21] (-)-β-Pinene **1** and (-)-limonene **2** have already been involved in olefin metathesis reactions with ruthenium catalysts, especially as chain transfer agents during cleavage of natural polyisoprene rubbers into terpene-

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[21] Wang, Z. I.; Jackson, W. R.; Robinson, A. J. *Org. Lett.* **2013**, 15, 3006–3009.

terminated oligomers[22], and during ring opening metathesis polymerization of dicyclopentadiene to control crosslinking and physical properties of the resulting polymers.[23]

There are only few examples where these terpenes have been used as cross metathesis partners with olefins to form new fine chemicals. Thus, limonene has been reacted with the terminal olefin 1-hexene in the presence of 2 mol% of second generation Grubbs catalyst without solvent to give the expected butyl-substituted limonene as a *E* + *Z* mixture in 40% yield.[24] The extension to the non-conjugated 1,5-hexadiene has led to polyhexadiene together with hexadiene oligomers featuring one or two limonene end. Under these conditions, β-pinene is not reactive, and cross metathesis products have been obtained only with neutral internal olefin partners using a ruthenium catalyst and a large excess of terpene.[24,25] On the other hand, even though the exocyclic double bond of a limonene derivative was reactive in intramolecular ring closing metathesis with an acrylic double bond,[26] a terminal electron-deficient olefin such as an acrylate did not react intermolecularly with these terpenes but only provided the self-metathesis maleate/fumarate mixture.[20] These results showed that beside the nature of the catalyst, which is also a crucial parameter, cross-metathesis of the bulky terpenes **1** and **2** with ruthenium catalysts took place favorably when the cross metathesis partner presented an internal carbon-carbon double bond. This observation provided impetus to investigate the ruthenium-catalyzed cross metathesis of terpenes **1** and **2** with symmetrical functional olefins, in order to generate only one cross metathesis product. These transformations of terpenes via alkene metathesis not only add value to renewables but also involve green catalytic processes.

Initially, we were especially interested in the functionalization of (-)-β-pinene **1** and (-)-limonene **2**, which are bulky unsaturated monoterpenes featuring a terminal disubstituted carbon-carbon double bond. The first substrate is a sterically hindered methylenecyclohexane, and the second corresponds to a

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[26] Li, Y.; Zhang, T.; Lia, Y.L. *Tetrahedron Lett.* **2007**, 48, 1503–1505.

propen-2-ylcyclohexene derivative. We have shown that the utilization of the internal double bond of a symmetrical cross metathesis partner was very efficient and selective for the functionalization of β-pinene and limonene in the presence of ruthenium catalysts. The influence of oxygenated functional groups in the terpene partner has also been evaluated with terpenoids derived from limonene bearing a ketone and an epoxide group.[27,28]

It is worth mentioning that the growing need for environmentally acceptable procedures in the chemical industry, a trend known as "Green Chemistry" or "Sustainable Technology" was taken into account during all the processes we have studied.[29,30] This requires a change from the traditional concepts of process efficiency with a main focus on chemical yields, to environmental values considering reduction of wastes and avoiding the use of toxic and / or dangerous substances at the first stage of a process, in order to develop new efficient sustainable processes.

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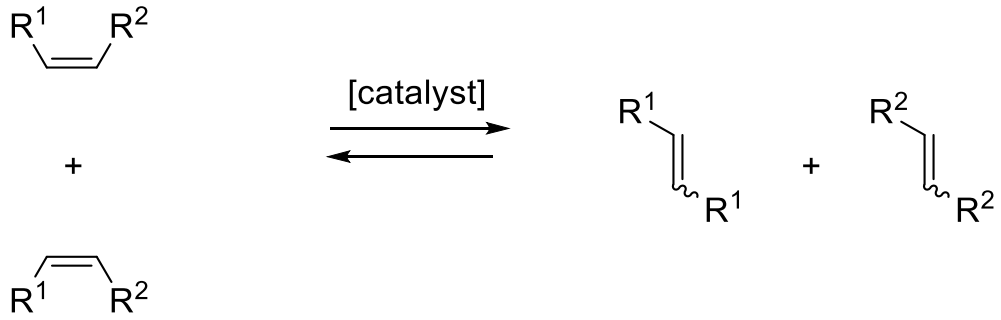
2 Olefin Metathesis

2.1 Introduction

Olefin metathesis is a catalytic reaction involving the cleavage of a double bond and the recombination of the alkylidene fragments, forming two new unsaturated molecules (**Scheme 1**).



Scheme 1: Illustration of the self-metathesis reaction

Historically, olefin metathesis as a synthetic tool has followed an interesting course of evolution, emerging as a truly useful technique by the end of the 20th century. It was first noticed in petrochemical research when a disproportionation of olefins took place on passing them through ill-defined mixtures of metal coordination complexes such as $Mo(CO)_6$/alumina, WCl_6/Bu_4Sn, MoO_3/SiO_2 and $WOCl_4/EtAlCl_2$.[31] Thus from the late 1960's through the early 1980's, the majority of olefin metathesis reactions were carried out with these ill-defined multicomponent systems containing an early transition metal oxide and a main group metal. The olefin metathesis reaction was until then limited to hydrocarbon/fuel chemistry, for the formation of higher olefins from cheaper feedstock such as the Shell Higher Olefin Process (SHOP).[32] In 1971, Chauvin proposed a mechanism to explain the disproportionation of olefins[33] which was acknowledged by the olefin metathesis community. Over time, initial efforts focussed on the development of homogeneous, well-characterized

[31] (a) Eleuterio, H.S. Ger. Pat. 1072811 (**1960**), Chem. Abstr., 55 (1961) 16005; Eleuterio, H.S. U.S. Pat.03074918 (**1963**); (b) Calderon, N.; Chen, H. Y.; Scott, K. W. *Tetrahedron Lett.* **1967**, 3327-3329.
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[33] Herisson, J. L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161-176.

catalysts capable of performing this reaction.[34] Two major players, Schrock and Grubbs skillfully exploited the knowledge gained by preceding metathesis explorers such as Katz[35] and Calderon[31b] and came up independently with the two best-known metathesis catalyst architectures. Since then, olefin metathesis has imposed itself as one of the most powerful synthetic strategies in organic chemistry[36,37] and polymer science,[38,39] and culminated in international recognition by the award of Nobel Prize to Chauvin, Grubbs and Schrock in 2005.

The most important olefin metathesis subtypes are presented in **Scheme 2**. The ring-opening metathesis polymerization (ROMP) of monomers containing strained, unsaturated rings was one of the earliest commercial applications of olefin metathesis. [40] The driving force for ROMP is the ring-strain release,[41] upon going to the polymerized linear products. Ring-closing metathesis (RCM) is widely used in organic synthesis for the synthesis of small cycles (< 8 membered-rings). The driving force for RCM is primarily entropic, because one substrate molecule affords two molecules of product; furthermore, since the small molecules released from this reaction are generally volatile, RCM is practically irreversible and can proceed to completion. On the other hand, cross-metathesis

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[37] (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592-4633. (b) R. R. Schrock, *Angew. Chem., Int. Ed.* **2006**, *45*, 3748-3759. (c) E. S. Sattely, S. J. Meek, S. J. Malcolmson, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 943-953.

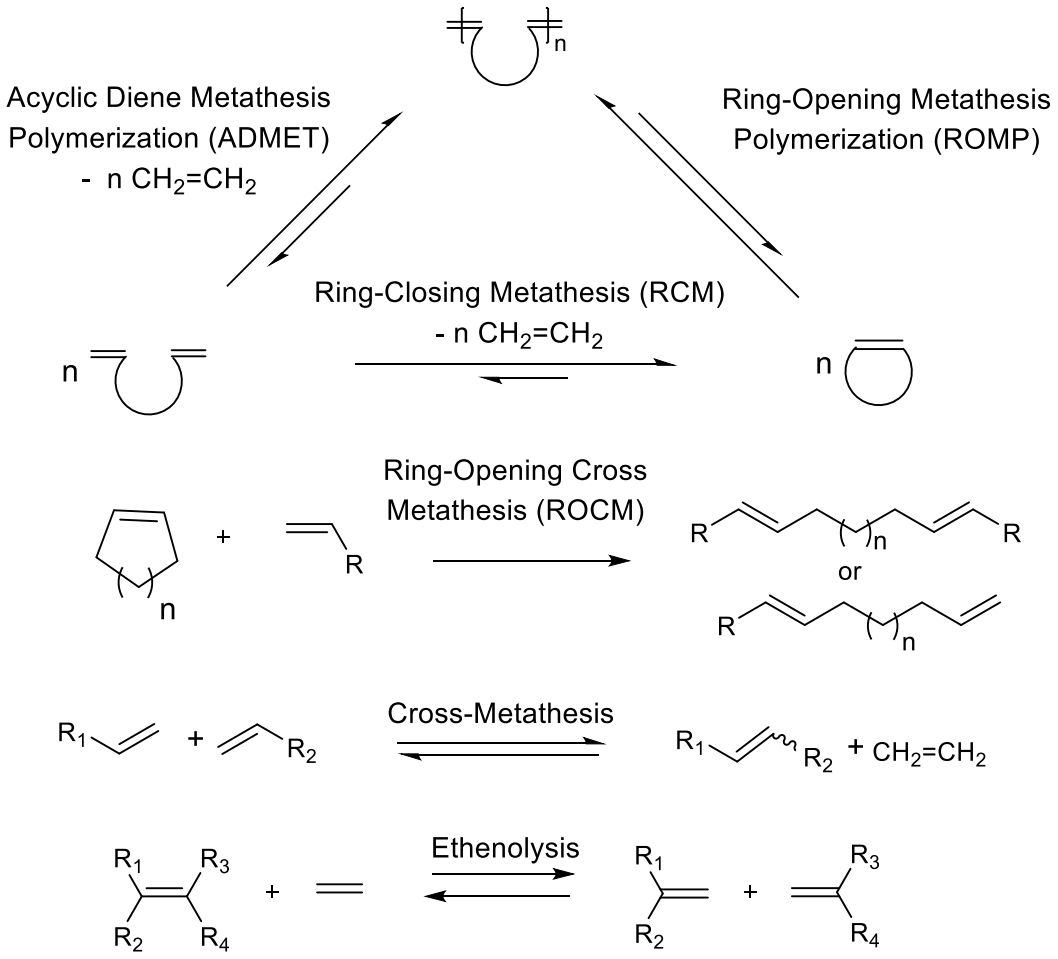
[38] As examples of ROMP see: (a) Grubbs, R. H. Ed. *Applications in Polymer Synthesis*. In *Handbook of Metathesis*; Wiley-VCH: Weinheim, **2003**; Vol. 3. (b) Bielawski, C. W.; Benitez, D.; Morita, T.; Grubbs, R. H. *Macromolecules* **2001**, *34*, 8610-8618. (c) Scherman, O. A.; Rutenberg, I. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 8515-8522. (d) Trimmel, G.; Riegler, S.; Fuchs, G.; Slugovc, C.; Stelzer, F. *Adv. Polym. Sci.* **2005**, *176*, 43-87. (e) Buchmeiser, M. R. Ed. *Metathesis Polymerization* (Advances in Polymer Science), Springer, **2005**. (f) Vygodskii, Y. S.; Shaplov, A. S.; Lozinskaya, E. I.; Filippov, O. A.; Shubina, E. S.; Bandari, R.; Buchmeiser, M. R. *Macromolecules*, **2006**, *39*, 7821-7830.

[39] As examples of ADMET see: (a) Schwendeman, J. E.; Church, A. C, Wagener, K. B. *Adv. Synth. Catal.* **2002**, *344*, 597-613. (b) Baughman, T. W.; Wagener, K. B. *Adv. Polym. Sci.* **2005**, *176*, 1. (c) Mol, J. C. *J. Mol. Catal. A: Chemical* **2004**, *213*, 39-45.

[40] (a) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, **1997**. (b) Slugovc, C. *Macromol. Rapid Commun.* **2004**, *25*, 1283-1297.

[41] Wiberg, K. B. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 312-322.

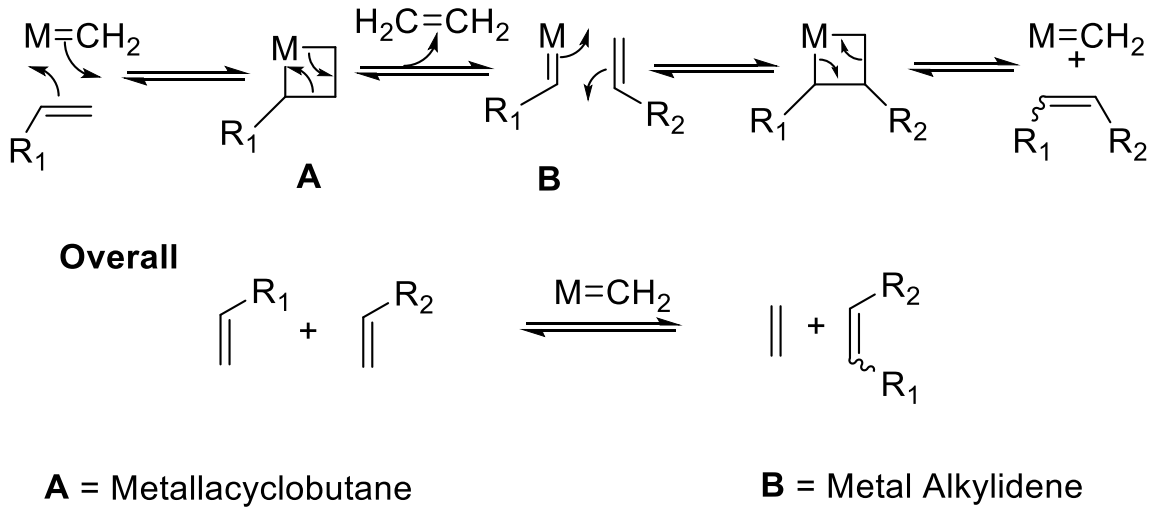
(CM) is more challenging than both RCM and ROMP, as it lacks the entropic driving force of RCM and the ring-strain release of ROMP, which can lead to relatively low yields of the desired cross-product.[51a] Furthermore, selectivity is also an issue to consider as self-metathesis can occur as a side reaction. Practically, both issues can be overcomed using an excess of one of the olefins in order to reach high conversions and ensure high selectivity for the desired cross-metathesis product. For these reasons, CM has been an underutilized metathesis transformation as compared to others. Other types of olefin metathesis reactions include acyclic diene metathesis polymerization (ADMET), ring-opening cross-metathesis (ROCM), and ethenolysis (ethenolysis is the cross-metathesis of ethylene with an internal olefin).



Scheme 2: Most common types of olefin metathesis reactions

2.2 Mechanism of Olefin Metathesis

The first step in the mechanism of olefin metathesis (**Scheme 3**) is the generation of the active, reaction propagating metal alkylidene species (metal-methylidene here). This species coordinates with an olefin to form an unstable, intermediate metallacyclobutane **A** via [2+2] cycloaddition. The metallacycle then collapses to redistribute the olefins via retrocycloaddition to generate a new metal alkylidene **B** with the liberation of an olefin (ethylene). All steps are reversible, possibly nonproductive and in competition with one another. Because of the reversibility of all individual steps in the catalytic cycle, an equilibrium mixture of olefins is obtained. For the metathesis to be productive and useful, it is necessary to shift the equilibrium in one direction. These inceptive mechanistic explorations, followed by highly sophisticated attempts to synthesize metal alkylidenes and metallacyclobutanes, eventually led to the synthesis of various well-defined catalysts for highly efficient and selective olefin metathesis.



Scheme 3: Simplified olefin metathesis mechanism. Metal is shown without ligands for convenience. Major players are metal-alkylidene and metallacyclobutane

The precise role of an olefin metathesis catalyst is to furnish this metal-alkylidene species essential for the reaction. Consideration must be given to the stereochemistry of metathesis products which may be *E* or *Z* or a mixture in

varying proportions.The geometry-determining step is the formation and orientation of reacting olefins in the metallacyclobutane.[42] This knowledge is of importance in the design of stereoselective (*E*/*Z)* olefin metathesis catalysts.[43] Selectivity is also an issue to consider as self-metathesis products can also be produced (R_1=R_1 and R_2=R_2).

2.3 Olefin Metathesis Catalysts

The two most popular metathesis catalyst architectures are the Grubbs and Schrock architectures,[44] respectively based on ruthenium, and molybdenum and tungsten complexes (**Figure 2**).

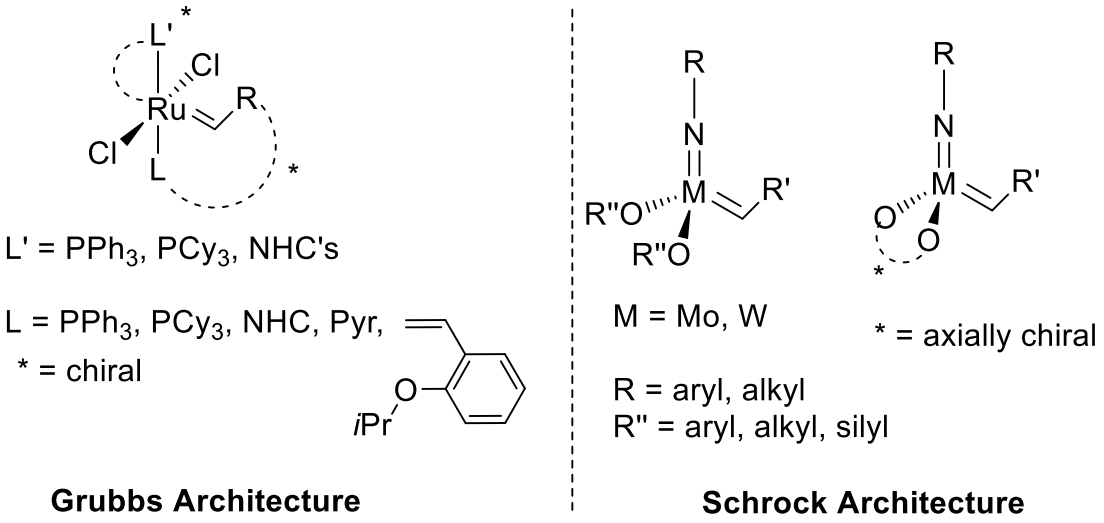


Figure 2: Grubbs and Schrock catalyst (metal alkylidene) architectures

The Grubbs type catalysts are 16 electron species based on ruthenium (IV) complexes, containing two “L” type ligands which can include phosphines (PPh_3, PCy_3), *N*-heterocyclic carbenes (NHC’s), chelating isopropoxystyrene and

[42] Liu, P.; Xu, X.; Dong, X.; Keitz, B. K.; Herbert, M. B.; Grubbs, R. H.; Houk, K. N. *J. Am. Chem. Soc.* **2012**, *134*, 1464-1467.

[43] Shahane, S.; Bruneau, C.; Fischmeister, C. *ChemCatChem* **2013**, 5, 3436-3459.

[44] (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; Dimare, M.; Oregan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875-3886. (b) Odell, R.; McConville, D. H.; Hofmeister, G. E.; Schrock, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 3414-3423. (c) McConville, D. H.; Wolf, J. R.; Schrock, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 4413-4414. (d) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974-3975. (e) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247-2250.(f) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001**, *20*, 5314-5318. (g) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4035-4037.

pyridine (Pyr). On the other hand, Schrock type catalysts are high oxidation state (+VI) tungsten and molybdenum based, containing two aryloxides in its basic form. Some of the most applied catalysts of the two types are shown in **Figure 3**.

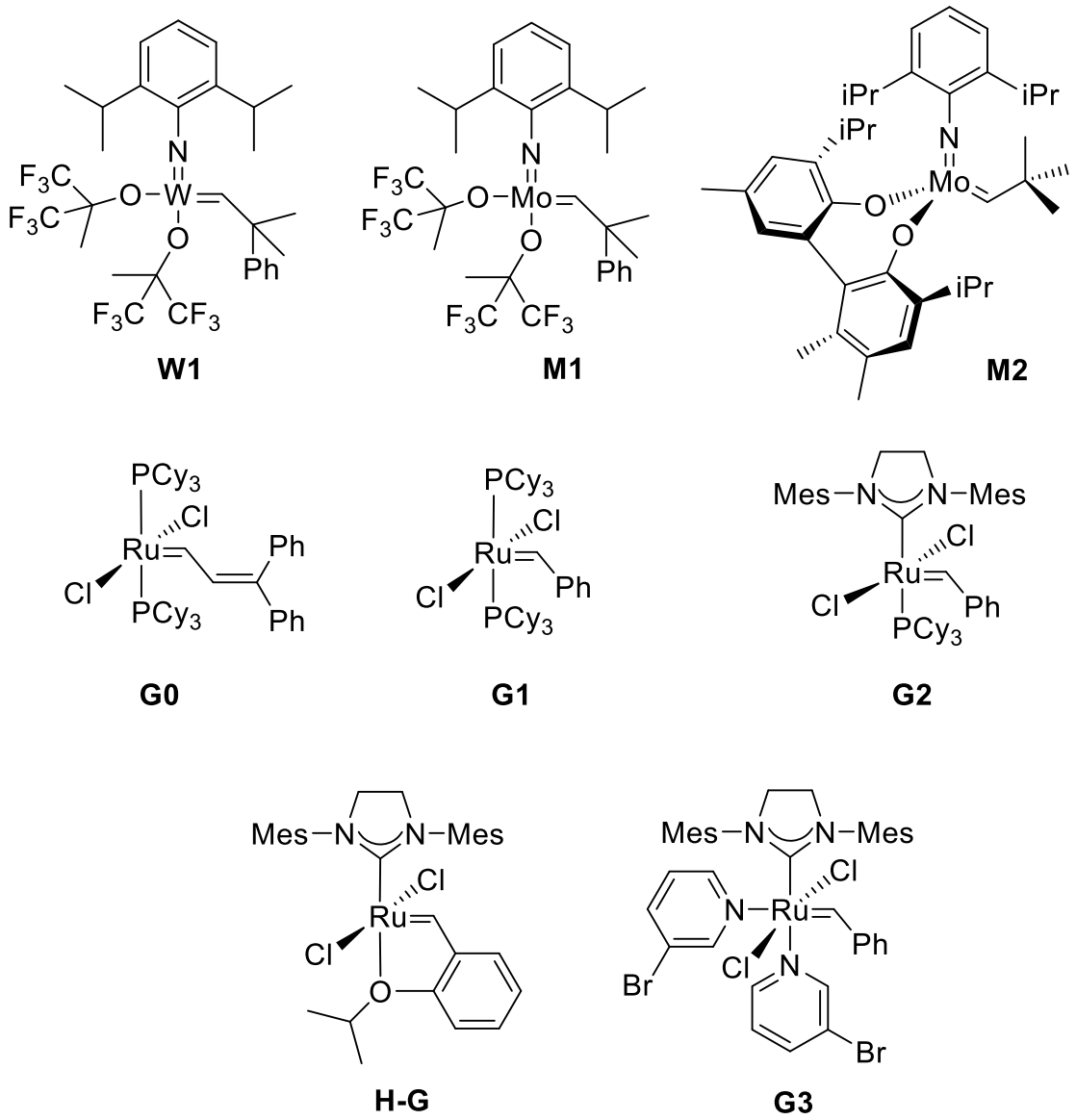


Figure 3: Olefin metathesis catalysts: Schrock tungsten (W1), molybdenum (M1) and chiral molybdenum (M2) complexes, Grubbs first- (G1) and second-generation (G2) catalysts, Hoveyda-Grubbs (H-G) and Grubbs third-generation catalyst (G3)

The first, well-characterized, highly active, neutral tungsten (**W1**) and molybdenum (**M1**) alkylidene complexes were developed by Schrock in 1986.[45] Chiral bridged versions such as (**M2**) have also been used to impart stereoselectivity in metathesis products.[46] Despite the high activities, the low

[45] Schaverien, C. J.; Dewan, J. C.; Schrock, R. R. *J. Am. Chem. Soc.* **1986**, *108*, 2771-2773.
[46] Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592-4633.

stability of these catalysts and limited functional group tolerance remained a drawback, which was offset by the development of air and moisture stable catalysts by Fürstner.[47] The first well-defined, metathesis active ruthenium alkylidene complex (**G0)** was synthesized by Grubbs in 1992.[48] Compared to Schrock catalysts, Grubbs first generation catalysts was characterized with relatively low activities but higher stabilities and was essentially active in polymerization by ROMP. A major breakthrough was achieved with the so-called first generation Grubbs catalyst **G1** which showed improved activity in polymerization but was also capable to perform a number of ring closing metathesis.[49] Second generation (**G2**) [50] and third generation catalysts (**G3**) [51] overcome activity problems posed by **G1** at the same time expanding the substrate scope while the second generation **H-G** catalyst is found to be one of the most stable catalysts within the Grubb's architecture, making its purification over silica gel columns possible.[52] Based on these two broad classes, many more catalysts and catalyst families[53] have been developed for a variety of applications in organic synthesis, material science,[54] medicine,[55] and transformation of renewable resources.[16,56]

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[49] Schwab, P, France, M. B., Ziller, J. W. Grubbs, R. H., *Angew. Int. Ed*. **1995**, *34*, 2039-2041
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[54] For example, Therban®, a Hydrogenated Nitrile Butyl Rubber made using metathesis technology.
[55]Aleron therapeutics makes peptides based on metathesis technology http://www.aileronrx.com/about.php.
[56] (a) Biermann, U.; Bornscheuer, U.; Meier, M. A. R.; Metzger, J. O.; Schaefer, H. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3854-3871. (b) Dupé, A.; Achard, M.; Fischmeister, C.; Bruneau, C. *ChemSusChem* **2012**, 1-7. (c) Miao, X.; Malacea, R.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2011**, *13*, 2911-2919.

3 Transformations of renewable biomass via olefin metathesis

3.1 Introduction

Worldwide demand for cleaner burning fuels and 'clean or green' chemicals has been increasing from the global issues of environmental concern and as fossil ressources stocks will decrease in the next few decades. The depletion of fossil resources along with the unstable price of crude oil and the negative effects of fossil-based fuels and chemicals on the environment accelerated the development and utilization of biomass in the past 20 years.[57,58] This led to a greater utilization of renewable resources to replace the existing fossil-based feedstock for liquid fuels and chemicals.

It is estimated that in 2050, at least 30% by weight of chemicals will be derived from renewable biomass, thus replacing a considerable amount of fossil resources.[59] In favorable market conditions, the production of bulk chemicals from renewable resources is expected to reach 113 million tonnes by 2050, corresponding to 38% of all organic chemical production.[60]

Biomass mainly refers to any organic matter derived from agricultural or forestry sector that is available on a recurring basis (sustainable). It comprises of (highly)-functionalised C, H, O and N- containing materials, a different composition than fossil feedstock which has essentially non-functionalised C and H-based materials.[61] Consequently, moving from fossil to renewable resources implies major modifications and adaptation of the chemical industry that needs to evolve from an oxidation/functionalisation chemistry to a reduction/defunctionalisation chemistry. Of note, most chemicals that are

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[57] Ahmed, M. M.; Narsi, N. S.; Hamza, D.U. *Int. J. Eng. Sci. and Tech. (IJEST)* **2012**, 4, 2, 721-730.
[58] Marshall, A.-L., Alaimo, P. J. *Chem. Eur. J.* **2010**, 16, 4970–4980.
[59] Sanders J.P.M, Clark JH, Harmsen GJ, Heeres HJ, Heijnen JJ, Kersten SRA *et al.*, Process intensifi cation in the future production of base chemicals from biomass. *Chem Eng Process **2012***, 51, 117–136.
[60] Patel, M.K., Crank, M., Dornburg, V., Hermann, B., Roes, L., Hüsing, B *et al*., The BREW Project, Final Report, Utrecht **2006**. Available at: https://www.researchgate.net/publication/27704442_Medium_and_Long-Term_Opportunities_and_Risks_of_the_Biotechnological_Production_of_Bulk_Chemicals_from_Renewable_Resources-The_BREW_Project l [accessed October 28, 2021].
[61] James, H.C., Fabien, I. D. Introduction to chemical from biomass, **2015**. John Wiley and Sons, United Kingdom.

presently produced from petrochemical resources can be replaced by identical compounds from biomass (e.g. bio-based polyethylene from bioethanol) or by biomaterials with comparable properties (e.g. bio-based polylactic acid, PLA, instead of fossil-based polyethylene terephthalate, PET).[62]

The advantages of using biomass rather than petroleum to manufacture chemicals and fuels are believed to include opportunities for less pollution, no net CO_2 contribution to the atmosphere, and more biodegradable and sustainable products.[63-66]

Currently, much of the biomass originating from inedible plant material is considered to be waste and is burned to provide heat and electricity. There is an increasing need for a better utilisation of these waste streams in the future.[67] Hence, converting biomass into a variety of chemicals, biomaterials and energy is one way of minimizing wastes while maximizing the value of biomass. For these reasons, adequate and optimised utilization of crops and waste is generating a wide spread of interest globally.[57,62]

By examining the components of biomass, it is possible to envision their potential for the manufacture of building blocks that can be transformed into useful or potentially useful product families. Of course, the ultimate utility of a particular product family and its synthesis route will depend on the cost of the feedstock and processing, current market volumes and prices, and the potential for new market opportunities.[68]

Vegetable oils and terpenes can be employed for synthesizing products with a higher added value, such as chemicals and fine chemicals. In this sense, one can think of replacing existing chemicals competing directly with those derived from petroleum, or making use of the functional groups existing in biomass components to generate novel products with new and improved properties for replacement of existing chemicals or for new applications.[56,69,70]

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[62] Fiorentino, G.; Ripa, M; Ulgiati, S. *Biofuels, Bioprod. Bioref.* **2016**, 11, 1, 195-214.
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[69] Corma, A., Iborra, S., Velty A. *Chem. Rev.* **2007**, 107, 2411-2502.
[70] Chikkali, S., Mecking, S. *Angew. Chem. Int. Ed.* **2012**, 51, 5802-5808.

Selective biomass conversion to biofuels and useful chemicals requires significant improvements in the current chemical approaches and technologies. These novel strategies will play a key role in the implementation of the bio-based economy relying on renewable resources and will have a significant environmental and societal impact.[71-73]

In addition to merely duplicating existing products derived from fossil resources, the chemistry from renewables opens an opportunity to develop a new portfolio of products that have no equivalence among those presently manufactured by classical synthesis routes from hydrocarbons.[74]

3.1.1 Terpenes and Terpenoids

Natural terpenes and terpenoids[75] are primarily produced by a wide variety of plants, particularly conifers, though also by some insects such as termites or swallowtail butterflies. Terpenes and terpenoids are the major components of resins, steroids and rubbers, which can be found in essential oils of many types of plants and flowers.

Terpenes are biosynthetically derived from isoprene units. The basic molecular formula of terpenes are multiples of $(C_5H_8)_n$ where n is the number of linked isoprene units. The isoprene units may be linked together 'head to tail' to form linear chains or they may be arranged to form rings. Terpenoids are compounds derived from terpenes through chemical modifications. Some terpenoids are also known as isoprenoids. Some authors use the term 'terpene' more broadly, to include the terpenoids.

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[71] (a) A. J. Ragauskas, C. K. Williams, B. H. Davison, G. Britovsek, J. Cairney, C. A. Eckert, W. J. Frederick Jr.,J. P. Hallett, D. J. Leak, C. L. Liotta, J. R. Mielenz, R. Murphy, R. Templer, T. Tschaplinski, *Science*, **2006**, 311, 484; (b) G. W. Huber, S. Iborra, A. Corma, Chem. Rev., **2006**, 106, 4044; (c) P. N. R. Vennestøm,C. M. Osmundsen, C. H. Christensen, E. Taarning, *Angew. Chem., Int. Ed.*, **2011**, 50, 10502-10509.

[72] (a) J. H. Clark, R. Luque, A. Matharu, *Annu. Rev. Chem. Biomol. Eng.*, **2012**, 3, 183; (b) P. Gallezot, *ChemSusChem*, **2008**, 1, 734; (c) M. Besson, P. Gallezot, C. Pinel, *Chem.Rev.*, 2014, 114, 1827; (d) N. Yan, P. J. Dyson, *Curr. Opin. Chem. Eng.*, **2013**, 2, 178; (e) A. M. Ruppert,K. Weinberg, R. Palkovits, *Angew. Chem., Int. Ed*., **2012**, 51, 2564.

[73] Deuss, P. J., Barta, K., de Vries, J.G. *Catal. Sci. Technol.* **2014**, 4, 1174-1196

[74] Gallezot, P. *Chem. Soc. Rev.* **2012**, 41, 1538-1558.

[75] Carrick, J. D. *Recent Advances in the Construction of Carbocycles in Terpene Natural Prodcut Total Synthesis*, **2006**.

As chains of isoprene units are built up, the resulting terpenes are classified sequentially by size as hemiterpenes (C_5H_8), monoterpenes ($C_{10}H_{16}$), sesquiterpenes ($C_{15}H_{24}$), diterpenes ($C_{20}H_{32}$), sesterterpenes ($C_{25}H_{40}$), triterpenes ($C_{30}H_{48}$), and tetraterpenes ($C_{40}H_{64}$) or other polyterpenes $(C_5H_8)_n$. A representative number of examples from this class of natural products containing different numbers of isoprene units are presented in **Figure 4**. For example, myrcene, is an acyclic monoterpene consisting of *two isoprene* units. Biochemical modifications such as oxidation or rearrangement can produce the related monoterpenoids, for instance, geraniol and citral. Monoterpenes can be cyclic as well, a classical example is limonene, that can lead to terpenoids such as menthol or terpineol. Like monoterpenes, sesquiterpenes that consist in three isoprene units can be acyclic or cyclic. Farnesol is a representative of the acyclic sesquiterpene family, while α-cadinene and α-selinene are bicyclic sesquiterpenes. Among diterpenes, phytol is an important precursor of vitamins E and K, and the 14-membered monocyclic diterpene cembrene A, presents a chemical structure that is central to a wide variety of other natural products.[76] Latex is a natural polymer of isoprene (most often *cis*-1,4-polyisoprene), with a molecular weight of 100,000 to 1,000,000; some other natural rubber sources called gutta-percha are composed of *trans*-1,4-polyisoprene, a structural isomer of latex.

In addition to their role as end-products in many organisms, terpenes are major biosynthetic building blocks within nearly every living creature. Steroids, for examples, are derivatives of the triterpene squalene (**Scheme 4**). It is noteworthy that isoprene itself does not undergo the building process, but rather the activated forms, isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP), are the components in the biosynthetic pathway.[77] Vitamin A, another example of terpene, is a vitamin that is needed by the retina of the eye in the form of a specific metabolite, the light-absorbing molecule retinal. It has a β-ionone ring attached to an isoprenoid chain (**Figure 5**). Catalytic transformations of terpenes into a variety of compounds of interest are already

[76] Breitmaier, E. *Terpene: Flavor, Fragrances, Pharmaca, Pheromones*. 2006, WILEY-VCH, .
[77] Swanson, K. M.; Hohl, R. J. *Curr. Cancer Drug Targets*, **2006**, *6*, 15-37.

performed in pharmaceutical, agrochemical, and flavors and fragrances industries.[4]

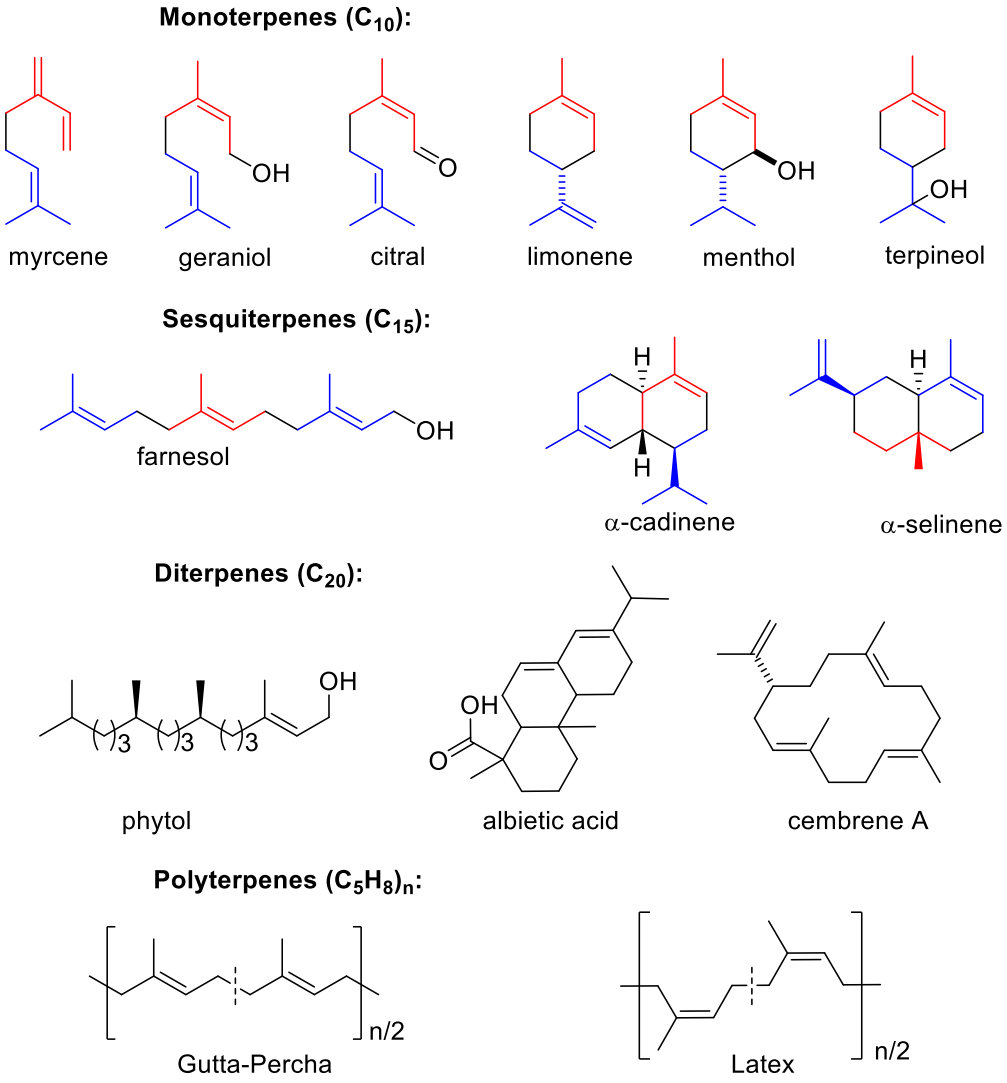
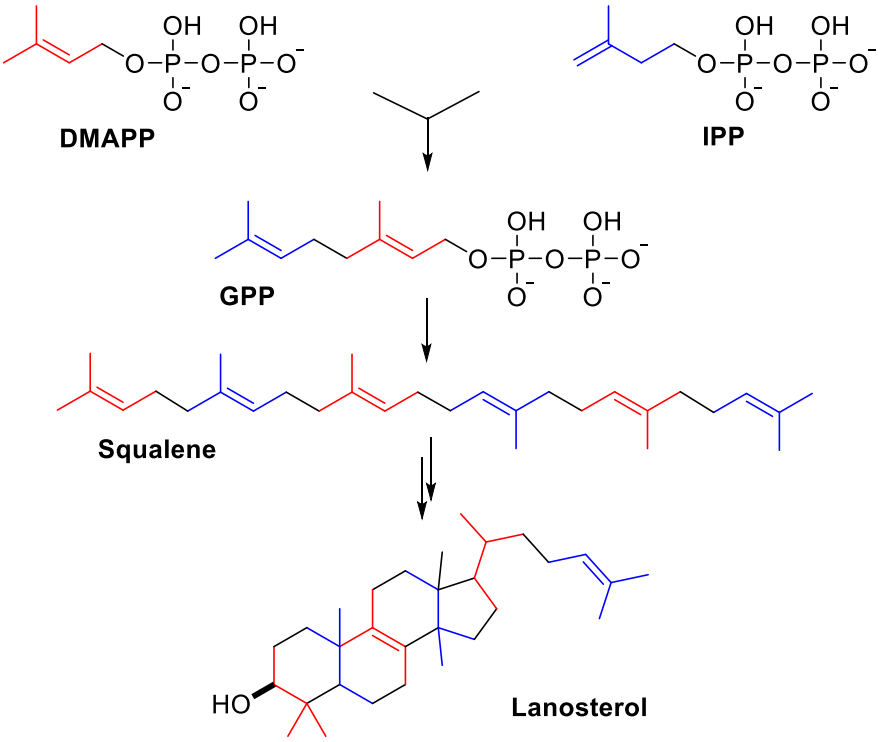


Figure 4: Terpenes containing different numbers of isoprene units



Scheme 4: Simplified version of the Lanosterol steroid synthesis pathway with intermediates isopentenyl pyrophosphate (IPP), dimethylallyl pyrophosphate (DMAPP), geranyl pyrophosphate (GPP) and squalene.

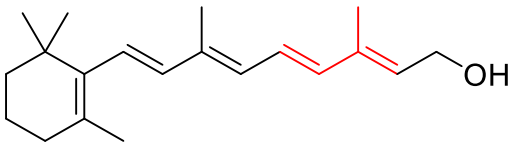


Figure 5: Vitamin A structure.

3.2 Catalytic transformations of terpenes/terpenoids derivatives by cross-metathesis

Olefin cross metathesis is a very practical method to introduce functional groups on a hydrocarbon skeleton and to generate higher internal olefins from simple alkenes. The interest of olefin metathesis for the transformations of terpenoid derivatives into industrially valuable products has been emphasized in a patent.[78] However, although general trends for selective cross metathesis reactions have been proposed,[79] there are not many examples based on terpene

[78] Mauduit, M.; Caijo, F.; Crévisy, C. US2013/0190518 A1, **2013**.
[79] Chatterjee, A. K.; Choi, T. L.; Sanders, D. P. Grubbs, R. H. *J. Am. Chem. Soc.*, **2003**, 125, 11360-11370.

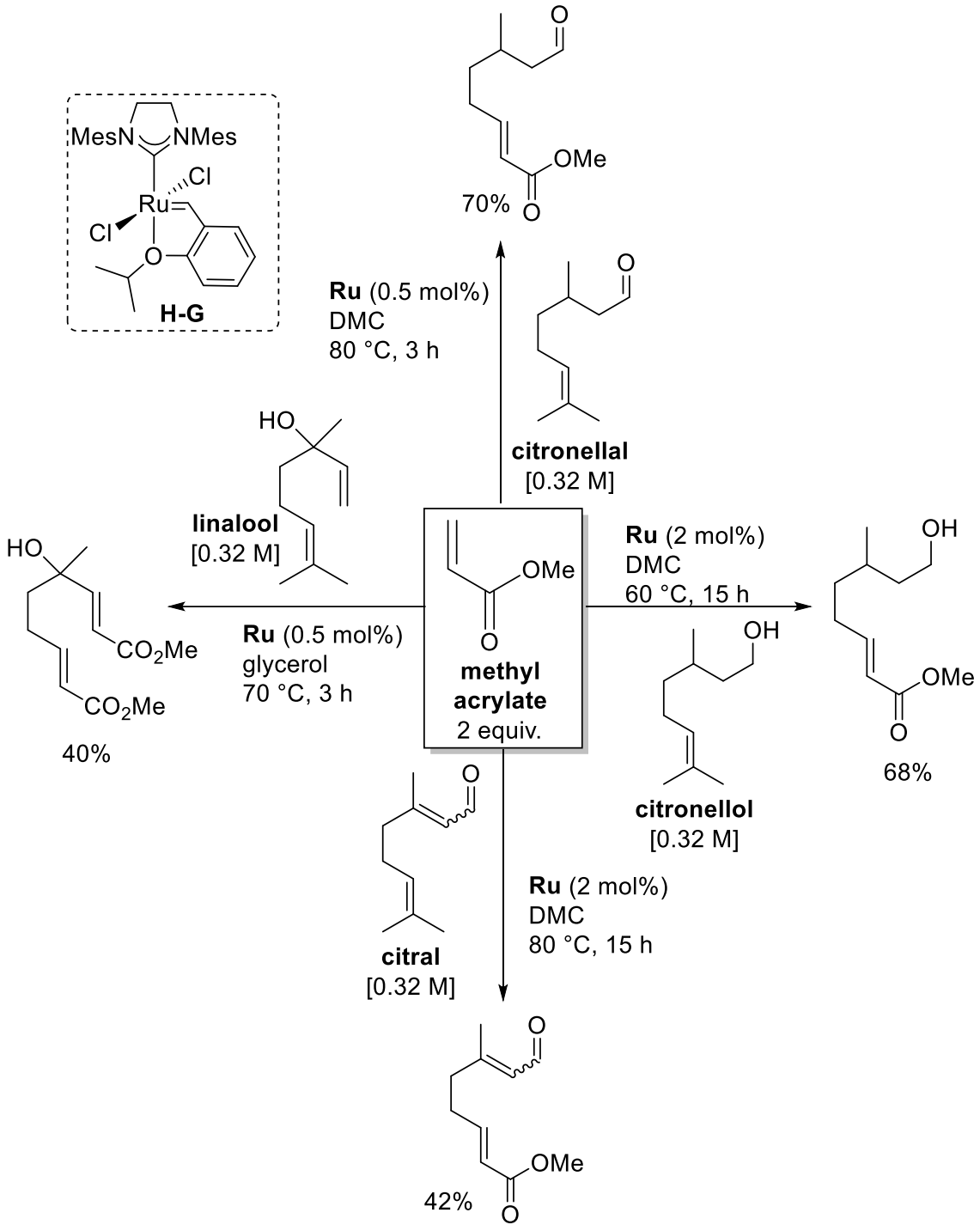
derivatives. Three major types of carbon–carbon double bonds are encountered in terpenes: i) monosubstituted terminal double bonds, ii) trisubstituted double bonds featuring two methyl groups in a 2-methylprop-1-en-1-yl (prenyl) arrangement, and iii) internal endocyclic double bonds. According to the classification described in reference 79, the first ones belong to type I olefins and are subject to fast self-metathesis but also to cross metathesis with olefins of other types. The second ones are olefins of type III with no possibility of self metathesis but prone to react with olefins of type II such as electron-deficient olefins. As far as internal endocyclic double bonds are concerned, they are potential substrates for ring opening metathesis polymerization and copolymerization, and eventually ring opening/cross metathesis sequences.

3.2.1 Cross metathesis of terpenes with electron-deficient olefins

The second generation Hoveyda catalysts have been found to be the most efficient catalysts for cross metathesis of terpenes and terpenoids with acrylic substrates. The cross metathesis of methyl acrylate with the monoterpenes citronellal, citronellol, linalool and citral was successfully achieved in the presence of catalytic amounts of ruthenium catalyst (0.5–2 mol%) in the green solvent dimethyl carbonate (DMC) at 60–80 °C leading to the cross metathesis products isolated in 42–70% yield (Scheme 5).[16] As expected with methyl acrylate as cross metathesis partner, the resulting double bond presented an *E*-configuration, exclusively. Methyl (*E*)-6-methyl-8-oxo-2-octenoate has also been obtained in 40% yield upon cross-metathesis of methyl acrylate (10 equiv.) and citronellal using 2 mol% of catalyst in refluxing dichloromethane for 1 h.[80] Glycerol has also been used as a green solvent for the cross metathesis of citral, linalool and geraniol. In the presence of 2 equiv. of methyl acrylate and 2 mol% of a ruthenium catalyst, full conversions of these terpenoids were obtained at 60–80 °C within 15 h, but the isolated yields of the expected products from geraniol and citral were modest (below 45%).[81] In the case of linalool the terminal and

[80] Yoshikai, K.; Hayama, T.; Nishimura, K.; Yamada, K. I.; Tomioka, K. *J. Org. Chem.*, **2005**, 70, 681-683.
[81] Al-Ayed, A. S. *Asian J. Chem*., **2015**, 27, 3619-3624.

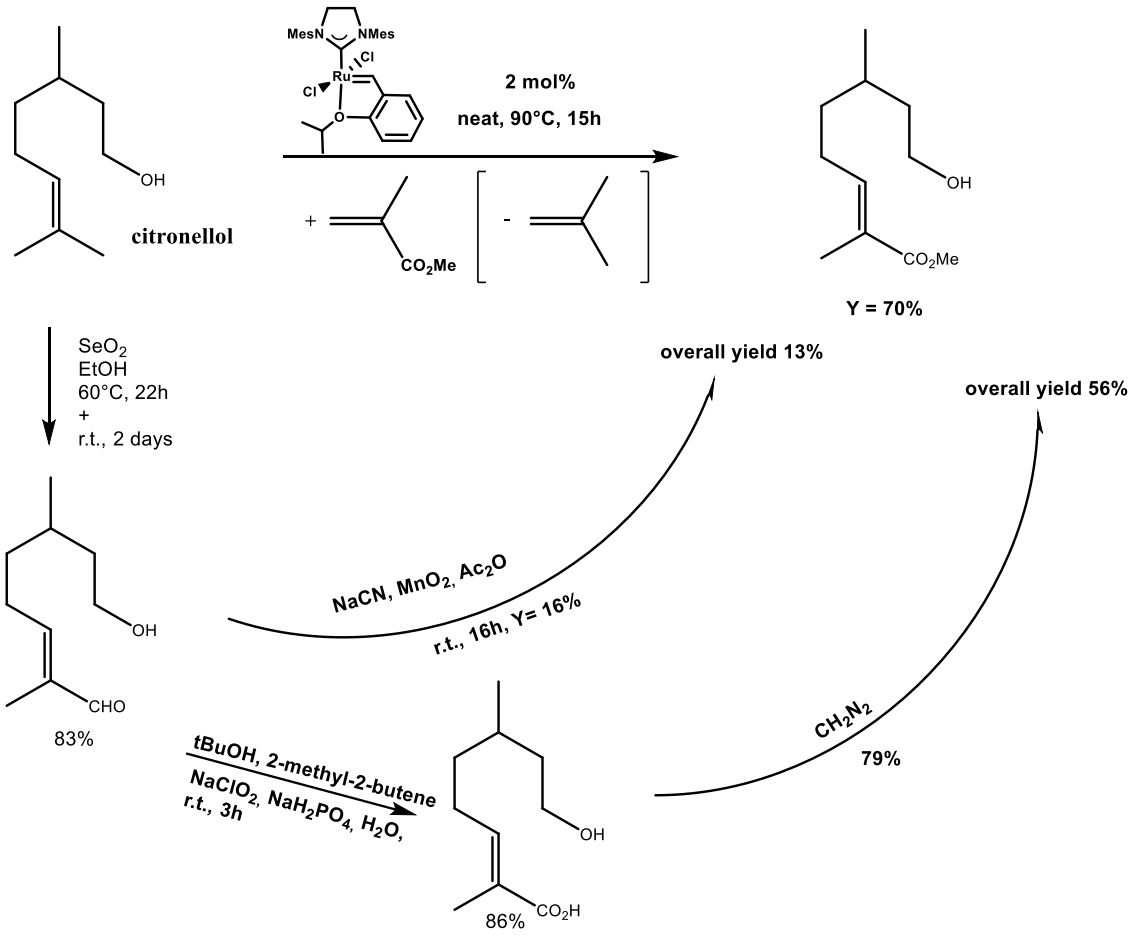
prenyl double bonds were involved in the cross metathesis process leading to the formation of the 1,9-diester with two (*E*)-double bonds in 40% yield obtained with only 0.5 mol% of catalyst (Scheme 5).



Scheme 5: Cross metathesis of terpenoids with methyl acrylate.

Cross metathesis of the more sterically hindered methyl methacrylate required more demanding conditions of temperature. The best conditions for the

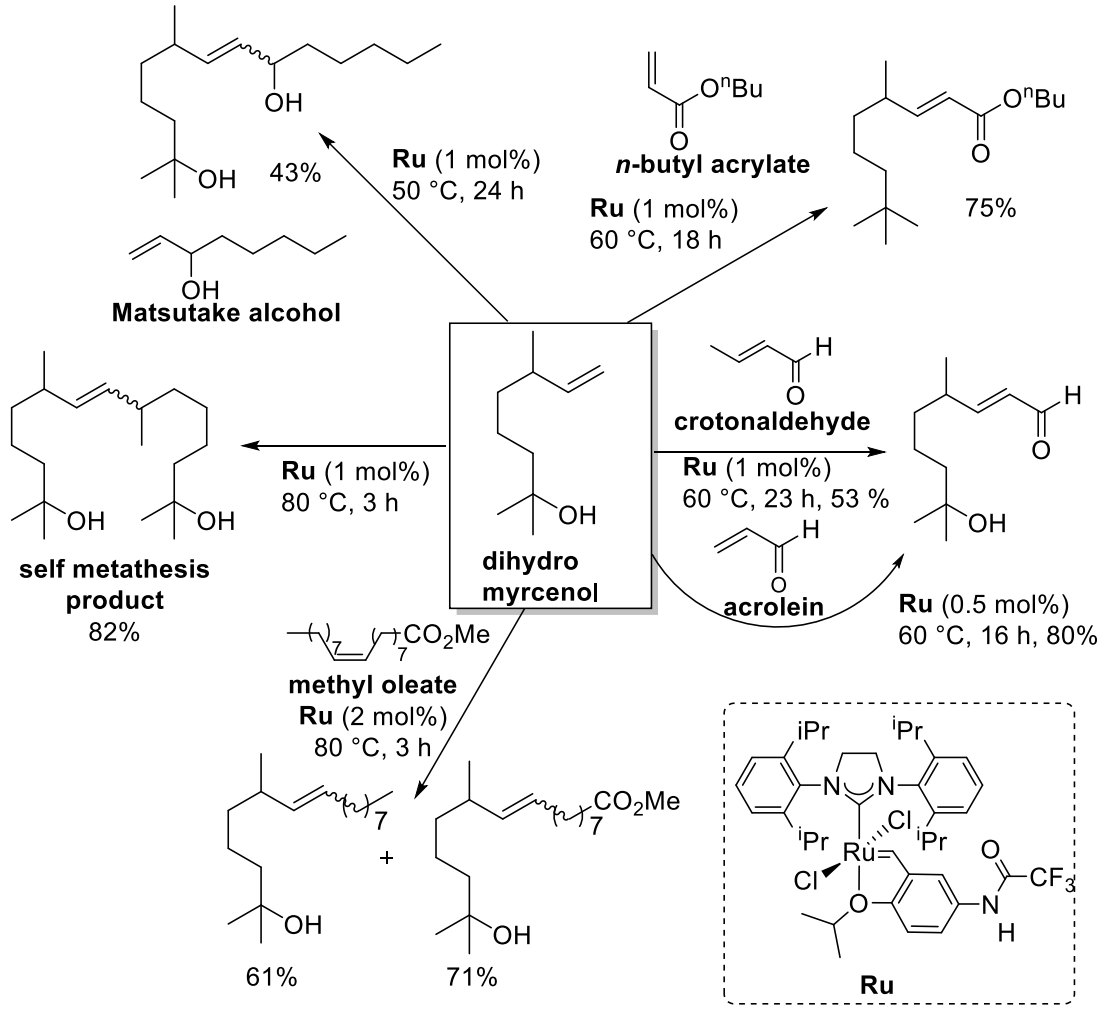
transformation of citronellal, citronellol and citral were obtained under neat conditions at 80–90 °C with 2 mol% of ruthenium catalyst.[16] In these conditions, polymerization of methyl methacrylate occurred making the isolation of the metathesis products more difficult. Again, the reaction was stereoselective and only the (*E*)-isomers were isolated. These products formally correspond to new terpenoids with an oxidized prenyl group obtained without oxidation steps. These reactions constitute a clear example of green catalysis as the new terpenoids were obtained in one step without solvent and avoided the usual 2–3 step synthesis involving hazardous reagents and producing large amount of wastes (**Scheme 6**).[82]



Scheme 6: Cross metathesis of terpenoids with methyl methacrylate.

[82] a) Brown, R. T. Mayalarp, S. P. Watts J., *J. Chem. Soc., Perkin Trans*. **1997**, *1*, 1633-1638; b) Yamaguchi, K., Shinohara, C., Kojima, S., Sodeoka, M., Tsuji, T. *Biosci.Biotechnol. Biochem*., **1999**, *63*, 731-735

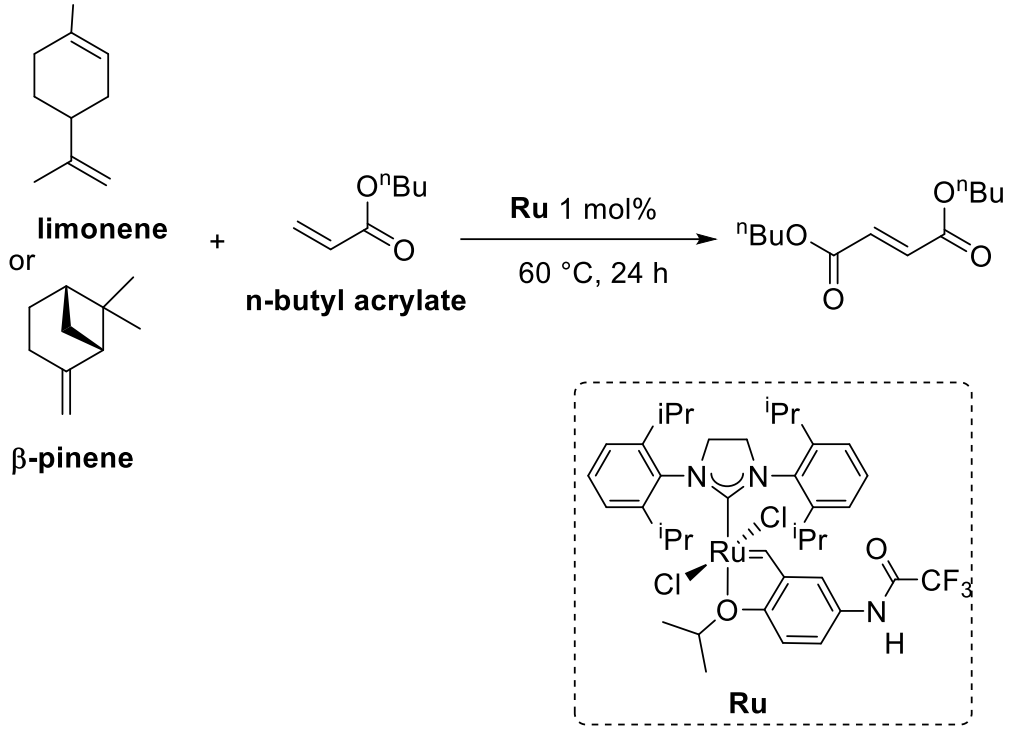
Dihydromyrcenol is a monoterpene derivative featuring only one terminal double bond that has been used in cross metathesis with various partners.[17] In the presence of 1 mol% of the ruthenium catalyst (**Scheme 7**), *n*-butyl acrylate provided the (*E*)-isomer after 18 h at 60 °C without solvent. Lower catalyst loading (0.2, 0.5 mol%) were detrimental to the productivity of the reaction. With the same catalyst, cross metathesis performed at 60 °C with crotonaldehyde and acrolein gave the same product, namely (*E*)-8-hydroxy-4,8,dimethylnon-2-enal, with high stereoselectivity (*E/Z* = 95:5 and 94:6, respectively). Acrolein was more reactive than crotonaldehyde as a lower catalyst loading of 0.5 mol% gave the product in 80% yield after 16 h, whereas crotonaldehyde led to 53% yield of the product after 23 h with 1 mol% of catalyst.



Scheme 7: Cross metathesis of dihydromyrcenol with various olefins.

It is interesting to note that attempts to perform cross metathesis of acrylates with hindered terminal double bonds involved in cyclic terpenes such

as limonene or β-pinene have failed and only the self-metathesis products of the acrylate were obtained (**Scheme 8**).This is quite intriguing since the cross metathesis of acrylates with acyclic terpenes containing a terminal monosubstituted or 2,2-disubstituted double bond or a prenyl non terminal double bond have been carried out successfully with second generation Hoveyda catalysts.



Scheme 8: Cross metathesis of acrylate with various types of acyclic double bonds.

3.2.2 Cross-metathesis of acyclic terpenes with terminal and internal olefins

Terminal olefins of type I[79] such as dihydromyrcenol are known to be prone to self-metathesis. Indeed, this is verified by the formation of a mixture of stereoisomers in 82% yield when dihydromyrcenol was treated at 80 °C for 3 h with 1 mol% of ruthenium catalyst under neat conditions (Scheme 7). When the terminal allylic alcohol (Matsutake alcohol) was used as cross metathesis partner, 43% of product was obtained after 24 h at 50 °C. Much better results were obtained with the internal *cis* double bond of methyl oleate. The two products

corresponding to the reaction of dihydromyrcenol with each side of the double bond of methyl oleate were isolated in 61% and 71% yields. In this case, the (*E*)-stereoisomers were the major ones (*E/Z* = 86:14 and 87:13) but as expected in a much less pronounced selectivity than with electron-deficient olefins such as methyl acrylate, methyl methacrylate, methacrolein, *n*-butyl acrylate, crotonaldehyde and acrolein.

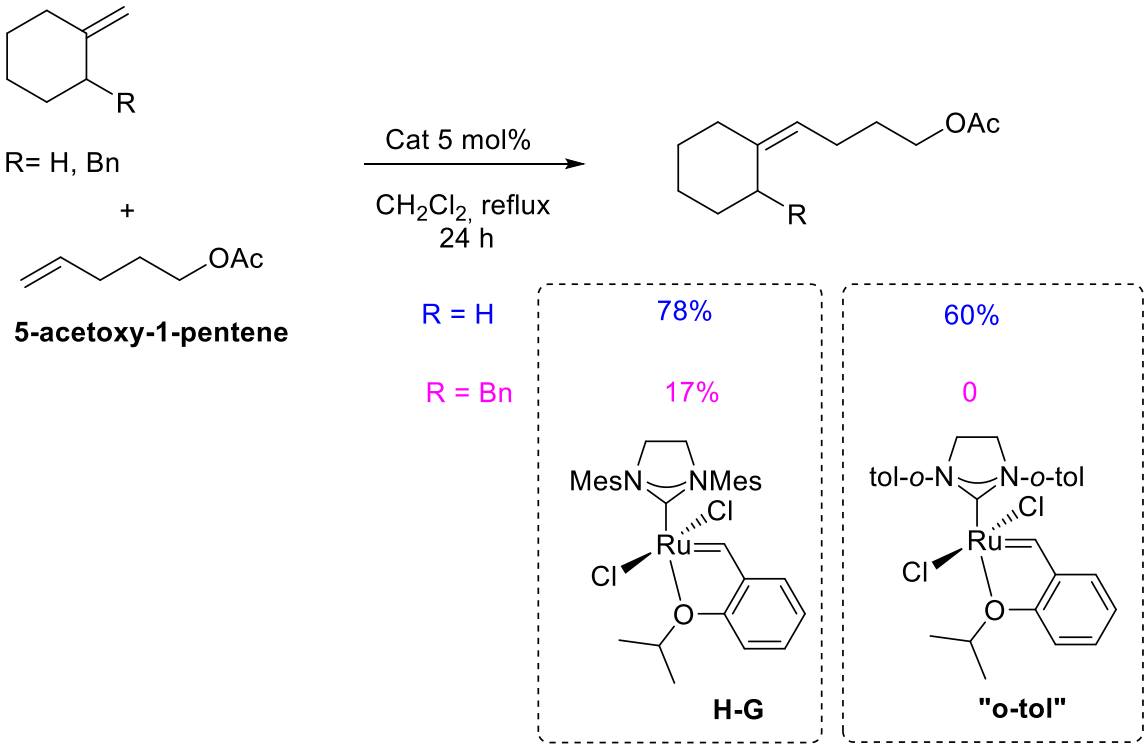
3.2.3 Cross metathesis of cyclic terpenes

Cyclic terpenes are more sterically hindered than the acyclic ones, and the access to the reactive catalytic center might be difficult in some cases. For instance, the lack of reactivity of limonene and β-pinene with *n*-butyl acrylate has been shown (Scheme 8). However, with the non-functional terminal olefin 1-hexene, limonene reacted in the presence of 2 mol% of **G2** at 55 °C without solvent to give the cross metathesis product in 40% yield.[83]

This reactivity of limonene with a terminal olefin has been extended to the production of co-oligomers with 1,5-hexadiene in the presence of the same ruthenium catalyst (1 mol% with respect to the diene) in an excess of limonene as solvent (30 equiv.) at 45 °C. Polyhexadiene was formed together with hexadiene oligomers featuring one or two limonene ends, the proportions of which depended on the 1,5-hexadiene concentration.[83]

It has been shown that cross metathesis of the exocyclic double bond of methylenecyclohexane with the terminal double bond of 5-acetoxy-1-pentene could be achieved efficiently in refluxing dichloromethane for 24 h with various second generation ruthenium catalysts.[84] However, the strong influence of the steric hindrance introduced by a benzyl substituent close to the double bond of methylenecyclohexane was evidenced by a drastic decrease of the yields from 78 to 17% with the Hoveyda-Grubbs catalyst and from 60 to 0% using the Hoveyda-Grubbs catalyst equipped with a less sterically demanding *o*-tolyl-substituted *N*-heterocyclic carbene (**Scheme 9**).[84]

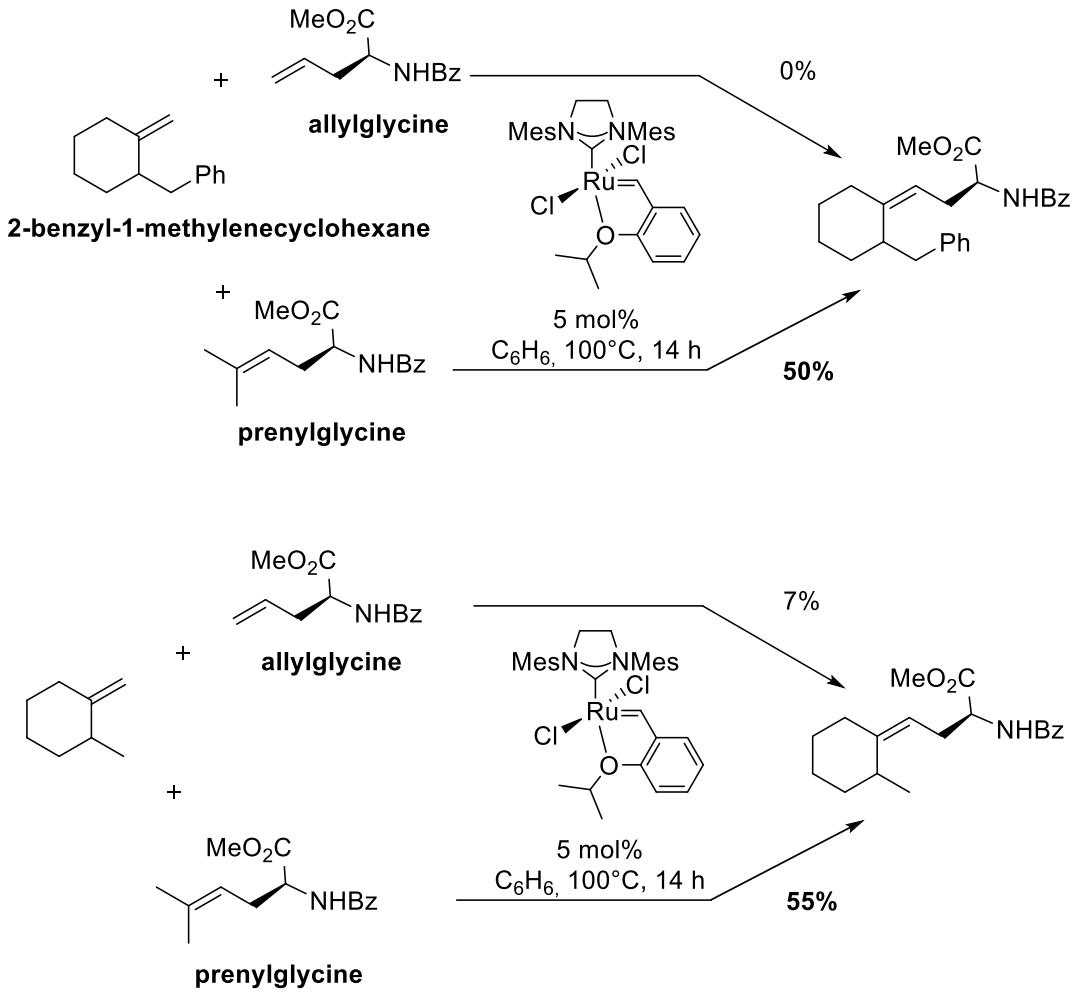
[83] Mathers, R. T.; McMahon, K. C.; Damodaran, K.; Retarides, C. J.; Kelley, D. J. *Macromolecules*, **2006**, 39, 8982-8986.
[84] Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.*, **2008**, 10, 441-444.



Scheme 9: Cross metathesis of methylenecyclohexane with 5-acetoxy-1-pentene

The same absence of reactivity of 2-benzyl-1-methylenecyclohexane was observed when protected allylglycine was used as cross metathesis partner in the presence of 5 mol% of Hoveyda-Grubbs catalyst at 100 °C in benzene.[85] However, it was possible to produce the desired product from the bulky cyclohexane derivative by replacing the terminal double bond of the allyl group of allylglycine by the geminal dimethyl analogue in prenylglycine. Using a large excess of bulky cyclohexane (30 equiv.), the cross metathesis was achieved in 50% yield. The less hindered 2-methyl-substituted methylenecyclohexane exhibited a similar behavior with both cross metathesis partners to lead to desired product (**Scheme 10**).

[85] Wang, Z. I.; Jackson, W. R.; Robinson, A. J. *Org. Lett.* **2013**, 15, 3006-3009.

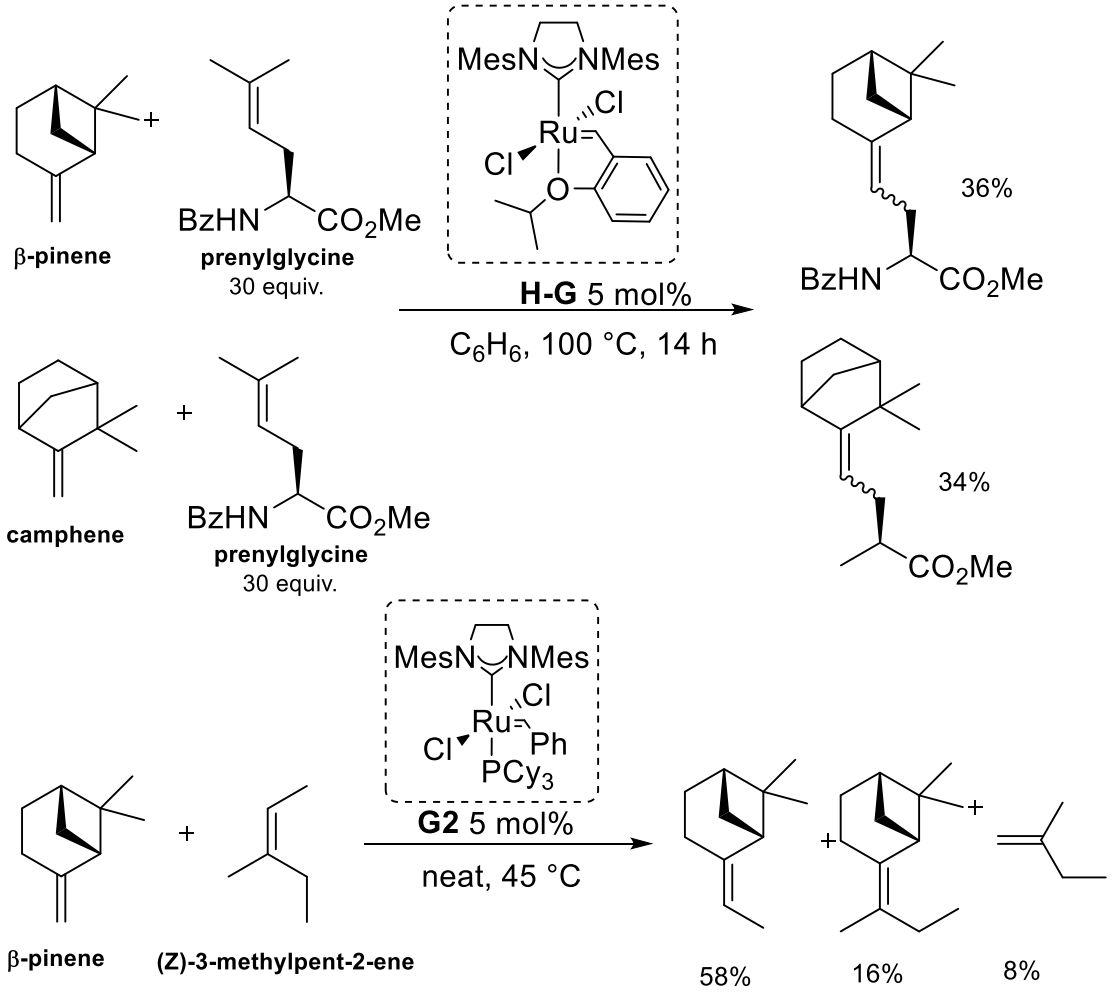


Scheme 10: Influence of steric hindrance on cross metathesis efficiency.

Gratifyingly, this strategy was applied with success for the cross metathesis of bulky terpenes featuring a methylene substituent of a bicyclic structure. Indeed, β-pinene and camphene reacted with prenylglycine in the presence of the Hoveyda-Grubbs catalyst to give the cross metathesis products as mixtures of *E*- and *Z*-isomers in 36 and 34% yield, respectively (**Scheme 11**).[85] Again, with these terpenes, the reaction with the allylglycine partner failed. The cross metathesis with the aliphatic internal olefin (*Z*)-3-methylpent-2-ene with β-pinene has been carried out with 5 mol% of catalyst at 45 °C without solvent and the two possible cross metathesis products have been observed (**Scheme 10**).[86] The general idea to make these cross metathesis reactions with bulky double bonds successful was to favour the productive pathway with respect to the non-productive one (self metathesis of allyl glycine) by playing with the steric

[86] Gutiérrez, S.; Tlenkopatchev, M. A. *Polym. Bull*., **2011**, 66, 1029-1038.

parameters of the cross metathesis partner e. g. on increasing the substitution pattern of the double bond. In this respect, the cross metathesis of β-pinene appeared to be more efficient with a trisubstituted internal olefin as cross metathesis partner (**Scheme 11**). This is in line with the computational studies, which indicated that non-productive metathesis of β-pinene in the presence of another olefin takes place in the presence of second generation ruthenium catalysts via formation of a carbene involving the pinene substrate, and that its self-metathesis does not occur because it is inhibited both by kinetic and thermodynamic factors.[8]



Scheme 11: Cross metathesis involving β-pinene and camphene

The objective of the PhD was the functionalization of bulky unsaturated monoterpenes featuring a terminal disubstituted carbon-carbon double bond (-)-β-pinene and (-)-limonene by olefin metathesis in order to introduce functional

groups such as acrylates. The first substrate is a sterically hindered methylenecyclohexane, and the second corresponds to a propen-2-ylcyclohexene derivative. Inspired by the seminal results on the cross metathesis reactions of bulky terminal olefins with internal olefins, we have first shown that the utilization of the internal double bond of a symmetrical cross metathesis partner such as dimethyl fumarate, dimethyl maleate, fumaronitrile, 1,4-diacetoxybut-2-ene, 1,4-dichlorobut-2-ene and 2-methylbut-2-ene was very efficient and selective for the functionalization of β-pinene and limonene in the presence of ruthenium catalysts. In a second part, the influence of oxygenated functional groups in the terpene partner has also been evaluated with terpenoids derived from limonene bearing a ketone or an epoxide group.[87,88] In both parts, we have investigated the influence of several experimental parameters, catalyst nature, loading, addition mode, solvents, temperature, concentration and reaction time on the reaction outcome. We have dedicated further studies to the identification of the stereoisomers produced thanks to 1D and 2D NMR analysis.

[87] L. Sarmento Fernandes, D. Mandelli, W.A. Carvalho, C. Fischmeister, C. Bruneau, *Catal. Commun*. 135, **2020**, 105893-105901.

[88] L. Sarmento Fernandes, D. Mandelli, W.A. Carvalho, E. Caytan, C. Fischmeister, C. Bruneau, *Applied Cat. A, General.* 623, **2021**, 118284-118290.

4 RESULTS AND DISCUSSION

4.1 Cross-metathesis of non-functionalized terpenes

4.1.1 Objectives

The objective of this firts part was to investigate the ruthenium-catalyzed cross metathesis of terpenes **1** and **2**, respectively β-pinene and limonene, with symmetrical functional olefins, namely acrylic and allylic derivatives such as dimethyl fumarate, dimethyl maleate, fumaronitrile, 1,4-diacetoxybut-2-ene, 1,4-dichlorobut-2-ene and 2-methylbut-2-ene, in order to prepare functionalized and more complex biosourced molecules.

4.1.2 Cross metathesis of acrylic olefins with β-pinene and limonene

4.1.2.1 Cross metathesis of β-pinene 1 and limonene 2 with dimethyl maleate 3 and fumarate 4

We first investigated the cross metathesis reaction of β-pinene **1** with methyl acrylate. Several attempts were carried out under various experimental conditions (2 or 4 equivalents of cross metathesis partner; 1 or 2 mL of solvent; 100 or 130°C) and catalysts (**Ru1** or **Ru2**), but the expected cross-metathesis product was never formed. β-pinene **1** was recovered and only the self-metathesis products dimethyl fumarate **3** and maleate **4** were formed. This is consistent with previous observation reported in the literature.[17]

This result contrasts with the easy formation of cross metathesis products from acrylic acid esters by cross metathesis with non-sterically hindered monosubstituted terminal olefins.[89,90]

Considering some results of the literature indicating that cross metathesis of bulky terpenes in the presence of ruthenium catalysts took place favorably when the cross metathesis partner presented an internal carbon-carbon double bond[91,92,93] including cyclic olefins[94] and polymers,[95] we have investigated the cross metathesis of β-pinene **1** with dimethyl maleate **3** and fumarate **4** as symmetrical functional olefins (**Scheme 12**). Most of the experiments were carried out in a closed Schlenk reactor under argon atmosphere at 100 °C during 15 h in the presence of commercially available second generation ruthenium catalysts **Ru1-Ru2** (**Figure 6**), and the results were based on GC analysis of crude reaction mixtures. The effect of temperature, concentration of substrates, catalyst loading and nature of the solvent were first examined (**Table 1**). Other

[89] a) A. Rybak, M. A. R. Meier, *Green Chem.* **2007**, *9*, 1356-1361; b) U. Biermann, M. A. R. Meier, W. Butte, J. O. Metzger, *Eur. J. Lipid Sci. Technol*. **2011**, *113*, 39-45; c) P. Vignon, T. Vancompernolle, J.-L. Couturier, J.-L. Dubois, A. Mortreux, R. M. Gauvin, *ChemSusChem* **2015**, *8*, 1143-1146; d) A. Behr, J. P. Gomes, *Beilstein J. Org. Chem*. **2011**, *7*, 1-8; e) N. D. Spiccia, E. Border, J. Illesinghe, W. R. Jackson, A. J. Robinson, *Synthesis* **2013**, *45*, 1683-1688; f) T. Jacobs, A. Rybak, M. A. R. Meier, *Appl. Catal. A* **2009**, *353*, 32-35; g) X. Miao, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *ChemSusChem* **2009**, *2*, 542-545 ; h) S. M. Rountree, S. F. R. Taylor, C. Hardacre, M. C. Lagunas, P. N. Davey, *Appl. Catal*. **2014**, *486*, 94-104; i) H. Bonin, A. Keraani, J.-L. Dubois, M. Brandhorst, C. Fischmeister, C. Bruneau, *Eur. J. Lipid Sci. Technol*. **2015**, *117*, 209-216; j) X. Miao, C. Fischmeister, C. Bruneau, P. H. Dixneuf, J.-L. Dubois, J.-L. Couturier, *ChemSusChem* **2012**, *5*, 1410-1414; k) X. Miao, P. H. Dixneuf, C. Fischmeister, C. Bruneau, *Green Chem*. **2011**, *13*, 2258-2271; l) G. A. Abel, K. O. Nguyen, S. Viamajala, S. Varanasi, K. Yamamoto, *RSC Adv.* **2014**, *4*, 55622-55628.

[90] a) A. Behr, S. Toepell, S. Harmuth, *RSC Adv*. **2014**, *4*, 16320-16326; b) A. Behr, J. Pérez Gomes, Z. Bayrak, *Eur. J. Lipid Sci. Technol*. **2011**, *113*, 189-196; c) X. Miao, R. Malacea, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *Green Chem*. **2011**, *13*, 2911-2919.

[91] Z. I. Wang, W. R. Jackson, A. J. Robinson, *Org. Lett*. **2013**, *15*, 3006-3009.

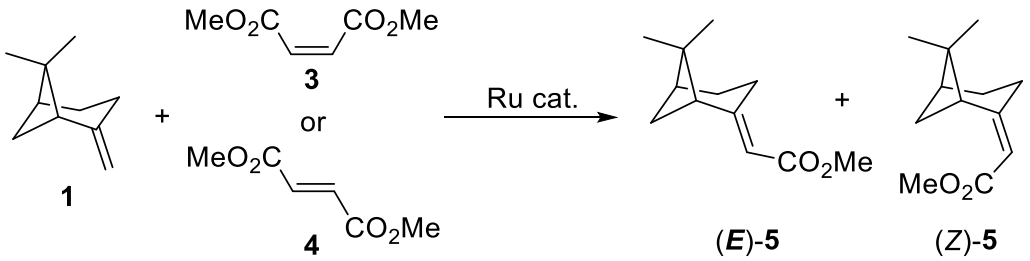
[92] S. Gutiérrez, M. A. Tlenkopatchev, *Polym. Bull*. **2011**, *66*, 1029-1038.

[93] C. Bruneau, C. Fischmeister, D. Mandelli, W. A. Carvalho, E. N. dos Santos, P. H. Dixneuf, L. Sarmento Fernandes, *Catal. Sci. Technol*. **2018**, *8*, 3989-4004.

[94] a) R. T. Mathers, K. Damodaran, M. G. Rendos, M. S. Lavrich, *Macromolecules* **2009**, *42*, 1512-1518; b) J. M. Delancey, M. D. Cavazza, M. G. Rendos, C. J. Ulisse, S. G. Palumbo, R.T. Mathers, *J. Polym. Sci. Part A: Polym. Chem.* **2011**, *49*, 3719-3727.

[95] a) A. Martinez, S. Gutiérrez, M. A. Tlenkopatchev, *Molecules* **2012**, *17*, 6001-6010; b) A. Martinez, S. Gutiérrez, M. A. Tlenkopatchev, *Nat. Sci*. **2013**, *5*, 857-864; c) S. Kongparakul, F. T. T. Ng, G. L. Rempel, *Appl. Catal., A* **2011**, *405*, 129-136; d) S. Kongparakul, F. T. T. Ng, G. L. Rempel, *Top. Catal*. **2012**, *55*, 524-529.

catalysts **Ru3**-**Ru6** depicted in **Figure 6** have been used in other transformations presented later in the manuscript.



Scheme 12: Cross metathesis of β-pinene **1** with methyl maleate **3** and fumarate **4**

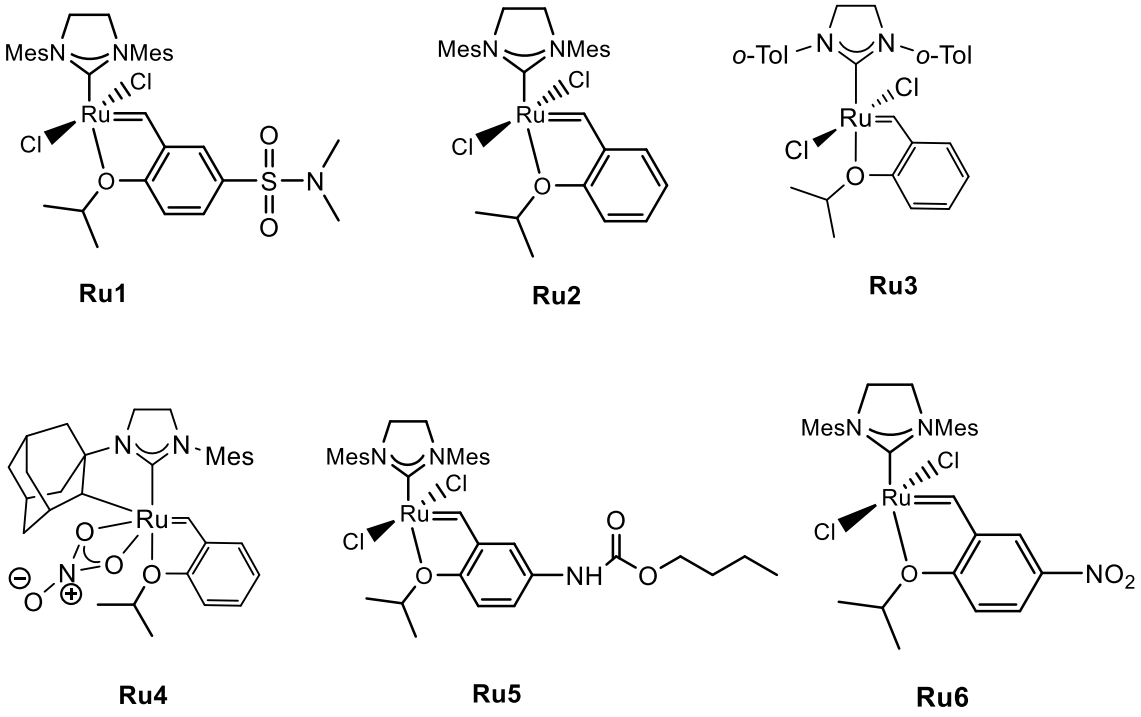


Figure 6: Ruthenium catalysts used in this study.

Table 1: Cross metathesis of β-pinene **1** with methyl maleate **3** and fumarate **4**[a]

Entry	**3** or **4** (mol. ratio)	Catalyst (mol%)	Conc. (mol/L)	T (°C)	Solvent	Conv. (%)[c]	Yield (%)[c](%)[d]	(*E*)/(*Z*) Ratio[e]
1	**3**/**1** (2)	**Ru1** (2.5)	0.37	115	toluene	51	49	62:38
2	**3/1** (2)	**Ru1** (2.5)	0.37	130	toluene	61	57	60:40
3	**3**/**1 (**2)	**Ru1** (2.5)	0.37	100	DMC	55	47	60:40
4	**3**/**1** (4)	**Ru1** (2.5)	0.37	100	DMC	67	66	61:39
5	**3**/**1** (4)	**Ru1** (2.5)	0.074	100	DMC	69	48	61:39
6	**3**/**1** (4)	**Ru1** (5)	0.37	100	DMC	77	70 (66)	62:38
7	**3**/**1** (4)	**Ru1** (5)	0.74	100	DMC	76	72 (48)	62:38
8	**3**/**1** (4)	**Ru1** (2.5)[b]	0.37	100	DMC	52	48	61:39
9	**3**/**1** (4)	**Ru2** (2.5)	0.37	100	DMC	70	68	62:38
10	**3**/**1** (4)	**Ru2** (5)	0.37	100	DMC	85	79 (57)	61:39
11	**3**/**1** (4)	**Ru2** (5)	0.74	100	DMC	91	91 (65)	57:43
12	**3**/**1** (11)	**Ru2** (5)		100	neat	80	80	55:45
13	**3**/**1** (4)	**Ru2** (2.5)[b]	0.37	100	DMC	78	74 (61)	54:46
14	**3**/**1** (4)	**Ru2** (2x2.5)	0.74	100	DMC	97	92	56:44
15	**4**/**1** (2)	**Ru1** (2.5)	0.37	115	toluene	54	52	76:24
16	**4**/**1** (2)	**Ru1** (2.5)	0.37	100	DMC	59	58 (39)	77:23
17	**4**/**1** (4)	**Ru1** (2.5)	0.74	100	DMC	55	47	73:27
18	**4**/**1** (4)	**Ru2** (2.5)	0.37	100	DMC	69	66 (40)	69:31
19	**4**/**1** (4)	**Ru2** (5)	0.37	100	DMC	85	79 (57)	68:32
20	**4**/**1** (4)	**Ru2** (5)	0.74	100	DMC	74	71 (57)	70:30
21	**4**/**1** (11)	**Ru2** (5)		100	neat	57	52 (37)	69:31

[a] General conditions: β-pinene **1** (100 mg, 0.7 mmol), solvent (1, 2 or 10 mL), reaction time (15 h). [b] Slow addition of catalyst in the first 2 h. [c] Conversion and GC yield determined using hexadecane as internal standard. [d] Isolated yield.[e]*E*/Z ratio determined by GC of the crude mixture.

Our first attempts revealed that good conversion of β-pinene **1** into **5** was obtained with the symmetrical electron deficient olefins **3** and **4** in the presence of 2.5 mol% of the fast-initiating Zhan-1-B **Ru1** and the Hoveyda **Ru2** catalysts. It must be noted that the the less hindered catalyst **Ru3** designed for the transformation of bulky reagents was totally inactive under the same conditions. The same result was obtained the *Z*-selective catalyst **Ru4.** In fact, both **Ru3** and **Ru4** and much less stable than **Ru1** or **Ru2** and were likely quickly decomposed.

We found that better results were obtained in the greener solvent dimethyl carbonate than in toluene,[96] which is commonly used in olefin metathesis operating at high temperature. Indeed, a temperature of 100 °C was necessary to get high conversion of the terpene in DMC whereas higher temperatures were necessary in toluene (Table 1 entries 1-3 and 15-17). Consequently, a tempearture of 100 °C was adopted for further investigations. With both olefins **3** and **4**, the effect of the concentration of the terpene was relatively low as conversion remained in the same range when the concentration was varied from 0.074 to 0.74 mol/L with the two catalysts Table 1, entries 4,5; 6,7; 16,17; 19-20). In addition, it was possible to perform the cross metathesis reaction under neat conditions with an excess of fumarate **3** or maleate **4** (entries 12, 21). The catalyst loading and its addition mode was also studied. Doubling this loading from 2.5 mol% to 5 mol% resulted in general in higher conversion (Table 1, entries 4,6; 9,10; 18,19) but full conversion was not achieved. Fractional addition of catalyst which has proved some benefits in a number of olefin metathesis transformation was also attempted with the aim to increase the conversion. If the slow addition of catalyst performed from the begining of the reaction was not efficient (Table 1, entries 4,8; 9,13) the fractional addition of the catalyst (2 x 2.5 mol%) led to an almost full conversion of **3** (Table 1, entry 14, conversion 97%) and 92% yield determined by GC.

It is noteworthy that in a general manner, starting from fumarate or maleate, catalyst **Ru2** provided slightly better conversion of β-pinene **1**. It should also be noted that purification of the products was not easy and resulted in many cases in modest to good yields when compared to GC yields. In all cases, the products were obtained in a mixture of *E* and *Z* stereoisomers identified by NMR studies. As always observed in cross metathesis with acrylates, the *E* isomers was always the major one but in a lower extend than generally observed. Indeed, whatever the conditions used in this study, the *E*/*Z* ratio ranged between 55/45 to 77/23 when it is most often higher than 90/10 in other transformation of less sterically hindered reagents.[97] It should be noticed that using dimethyl fumarate **4** led to a

[96] X. Miao, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *ChemSusChem* **2008**, 1, 813-816.

[97] a) H. Bilel, N. Hamdi, F. Zagrouba, C. Fischmeister, C. Bruneau, *Green Chem.* **2011**, *13*, 1448-1452; b) K. Yoshikai, T. Hayama, K. Nishimura, K.-i. Yamada, K. Tomioka, *J. Org. Chem*. **2005**, *70*, 681-683; c) A. S. Al-Ayed, *Asian J. Chem*. **2015**, *27*, 3609-3624; d) J. Xu, E. J. E. Caro-Diaz, L. Trzoss, E. A. Theodorakis, *J. Am. Chem. Soc*. **2012**, *134*, 5072-5075; e) H. Bilel, N. Hamdi, F. Zagrouba, C. Fischmeister,

slightly higher *E*/*Z* ratio as compared to dimethyl maleate (average value *E*/*Z* = 71:29 from **4**, and *E*/*Z* = 60:40 from **3**). In all cases, due to the presence of an excess of fumarate or maleate, a mixture of these two stereoisomers was observed at the end of the reaction resulting from their self-metathesis reaction. In some cases, dimethyl fumarate was not detected as its self-metathesis preferentially leads to the more stable dimethyl maleate.

A typical GC trace of a crude reaction mixture is presented in Figure 7. It indicates that the two stereoisomers of **5** were formed, which was confirmed by ^{1}H NMR analysis. In the case of cross metathesis with dimethyl maleate, it should also be noticed that dimethyl fumarate was detected by gas chromatography In the crude reaction mixture, as a result of secondary metathesis reactions.

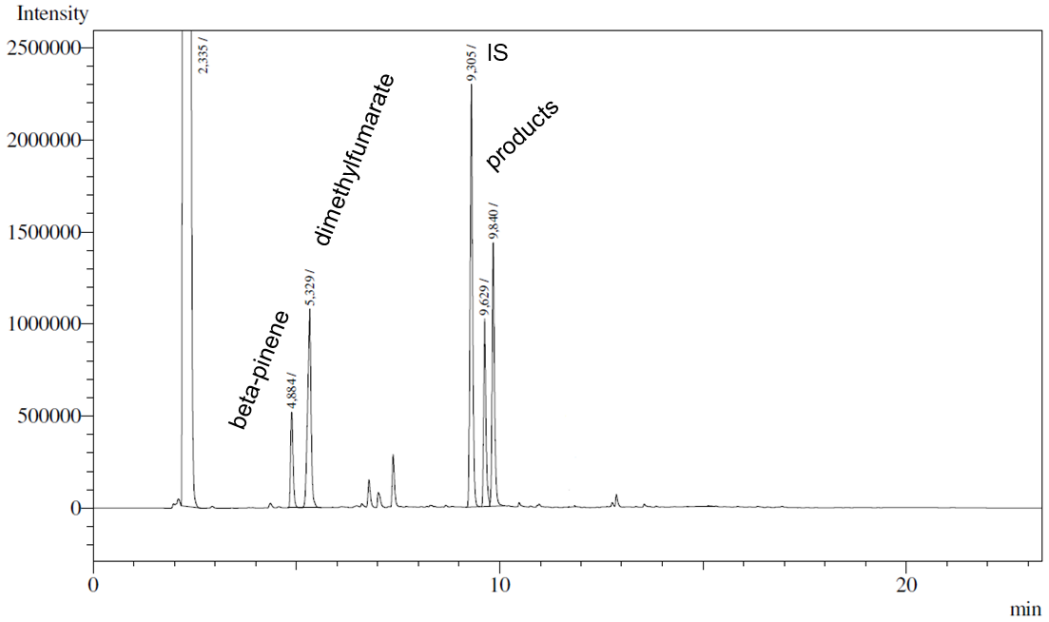


Figure 7: Chromatogram of the crude reaction mixture between β-pinene **1** with dimethyl maleate **3** (IS = Internal Standard = hexadecane)

The new products (*E*)-**5** and (*Z*)-**5** were produced in satisfactory yields but could not be separated by column chromatography. NMR analyses of their mixture based on NOESY and HSQC experiments together with data from the

C. Bruneau, *Catal. Sci. Technol*., **2014**, *4*, 2064-2071; f) V. César, Y. Zhang, W. Kosnik, A. Zielinski, A. A. Rajkiewicz, M. Ruamps, S. Bastin, N. Lugan, G. Lavigne, K. Grela, *Chem. Eur. J*. **2017**, *23*, 1950-1955.

literature on β-pinene **1**,[98,99] made possible the full characterization of each stereoisomer. In particular, the stereochemistry was established by Nuclear Overhauser Effect study, which revealed interaction between the ethylenic proton C(10)H (at 5.49 ppm) with the C(1)H proton in the (*E*)-**5** isomer (at 2.50 ppm), and interaction of the same ethylenic proton C(10)H (at 5.64 ppm) with one of the proton of the methylene group at C(3) in the (*Z*)-5 isomer (at 2.25 ppm). (**Figure 8**)

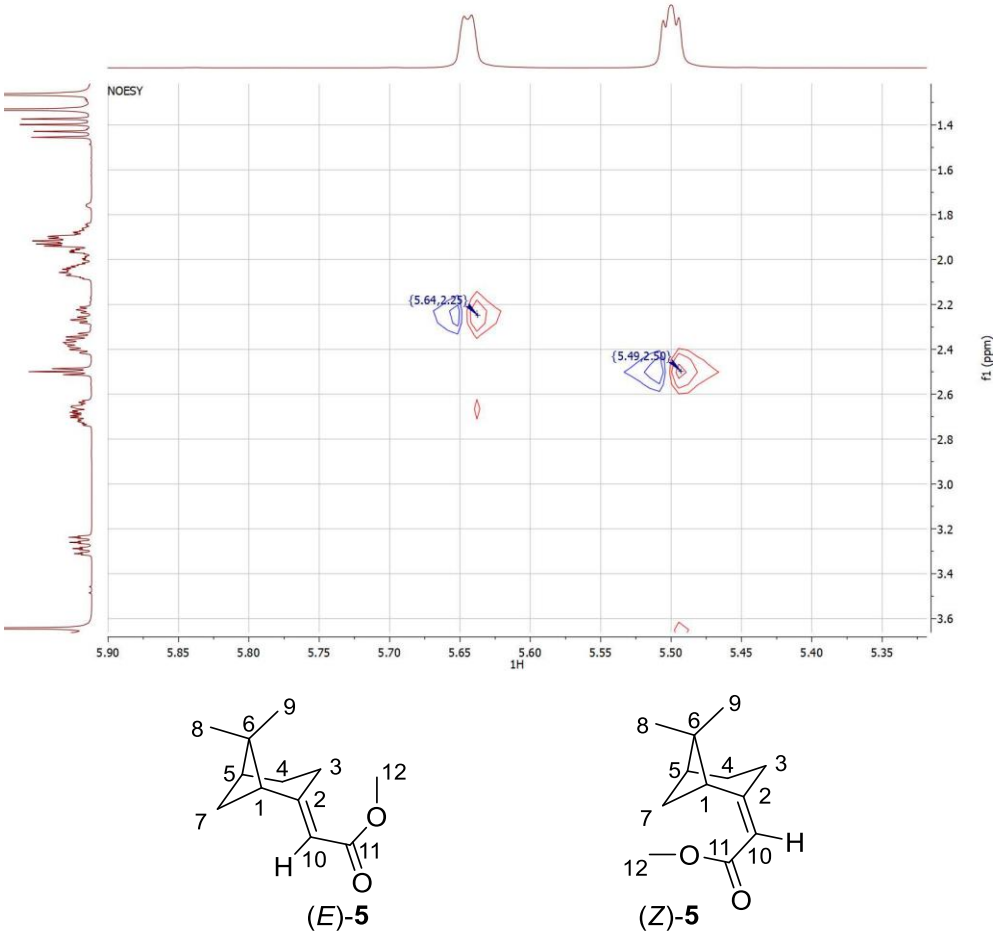
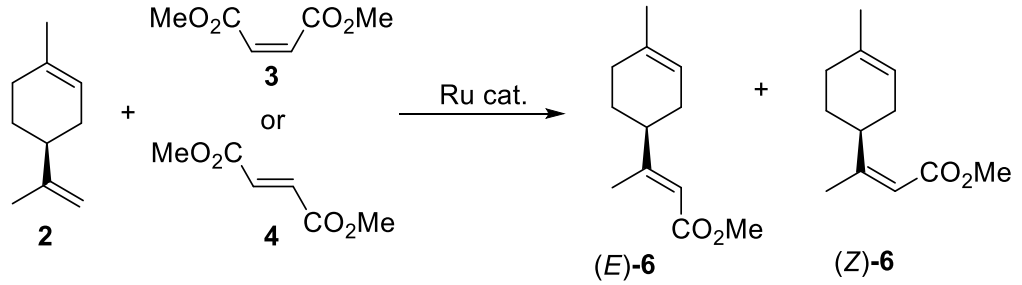


Figure 8: 2D NOESY NMR spectrum of product **5**

The cross metathesis transformation of the less sterically constrained limonene **2** was then investigated with the feedback gained during the study of cross metathesis involving β-pinene **1**. As observed with β-pinene **1,** the reaction of limonene **2** with methyl acrylate was also inefficient and only dimethyl maleate

[98] W. B. Smith, *Magn. Reson. Chem*.**1994**, 32, 316–319.
[99] E. P. Mazzola, J. B. Lambert, C. D. Ridge, *J. Phys. Org. Chem.* **2018**, 31, 3816.

3 and fumarate **4** were formed as previously reported (**Scheme 13**). However, the cross metathesis with the symmetrical maleate and fumarate in the presence of 2.5–5 mol% of **Ru1** and **Ru2** was successful and produced the expected and new acrylic stereoisomers of **6**. Contrary to β-pinene the concentration turned to be an important parameter has depicted by the important drop of the conversion upon moving from a concentration of 0.37 M to 0.74 M (Table 2, entries 2,3). Among the condition tested, the highest conversion of 63% could be obtained with dimethyl fumarate and Ru2 with aa (*E*/*Z*)-**6** ratio of 75:25 (**Table 2**, entry 12). It can be noted that under the conditions of **Table 2**, (2.5 mol% of catalyst **Ru1** or **Ru2**, 0.74 mol/L or 0.37 mol/L, 100°C, 15h) the complexes **Ru3** and **Ru4** were yet inactive.



Scheme 13: Cross metathesis of limonene **2** with methyl maleate **3** and fumarate **4**.

Table 2: Cross metathesis of limonene **2** with methyl maleate **3** and fumarate **4**[a]

Entry	**3** or **4** (mol. ratio)	Catalyst (mol%)	Conc. (mol/L)	T (°C)	Solvent	Conv. (%)[c]	Yield (%)[c] (%)[d]	E/Z ratio[e]
1	**3/2** (2)	**Ru1** (2.5)	0.37	115	toluene	48	11	75:25
2	**3/2 (**4)	**Ru1** (2.5)	0.37	100	DMC	58	10 (10)	74:26
3	**3/2 (**4)	**Ru1** (2.5)	0.74	100	DMC	16		
4	**3/2 (**4)	**Ru1** (5)	0.74	100	DMC	22		
5	**3/2 (**4)	**Ru2** (2.5)	0.74	100	DMC	23		
8	**3/2** (11)	**Ru2** (5)	-	100	neat	26	11	74:26
9	**4/2** (2)	**Ru1** (2.5)	0.37	115	toluene	25	17	80:20
10	**4/2** (4)	**Ru1** (2.5)	0.37	100	DMC	52	48 (10)	77:23
11	**4/2** (4)	**Ru2** (2.5)	0.37	100	DMC	61	57 (16)	76:24
12	**4/2** (4)	**Ru2** (5)	0.37	100	DMC	63	71 (23)	75:25

[a] General conditions: limonene **2** (100 mg, 0.7 mmol), solvent (2 mL), reaction time (15 h). [b] Slow addition of catalyst in the first 2 h. [c] Conversion and GC yield determined using hexadecane as internal standard. [d] Isolated yield.[e]E/Z ratio determined by GC of the crude mixture.

The two cross metathesis stereoisomers were formed as shown by GC analysis of the crude mixture (**Figure 9**) and confirmed by ^{1}H NMR analysis.

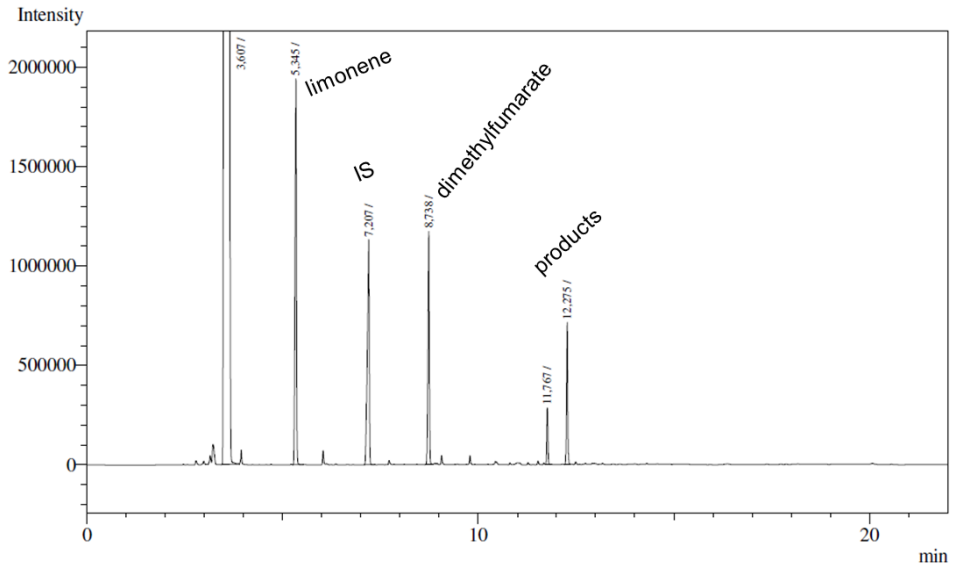


Figure 9: Chromatogram of the crude reaction mixture between limonene 2 with dimethyl maleate **3** .

The nature of the stereoisomers was also unambiguously determined by ^{1}H and ^{13}C NMR. In the (*E*)-isomer **6**, the acrylic proton at C(9) (5.72 ppm) is in interaction with protons at C(3), C(4) and C(5), whereas in the (*Z*)-isomer **6**, the same proton at C(9) (5.67 ppm) is in interaction with the methyl proton at C(10) (1.84 ppm) only) (**Figure 10**).

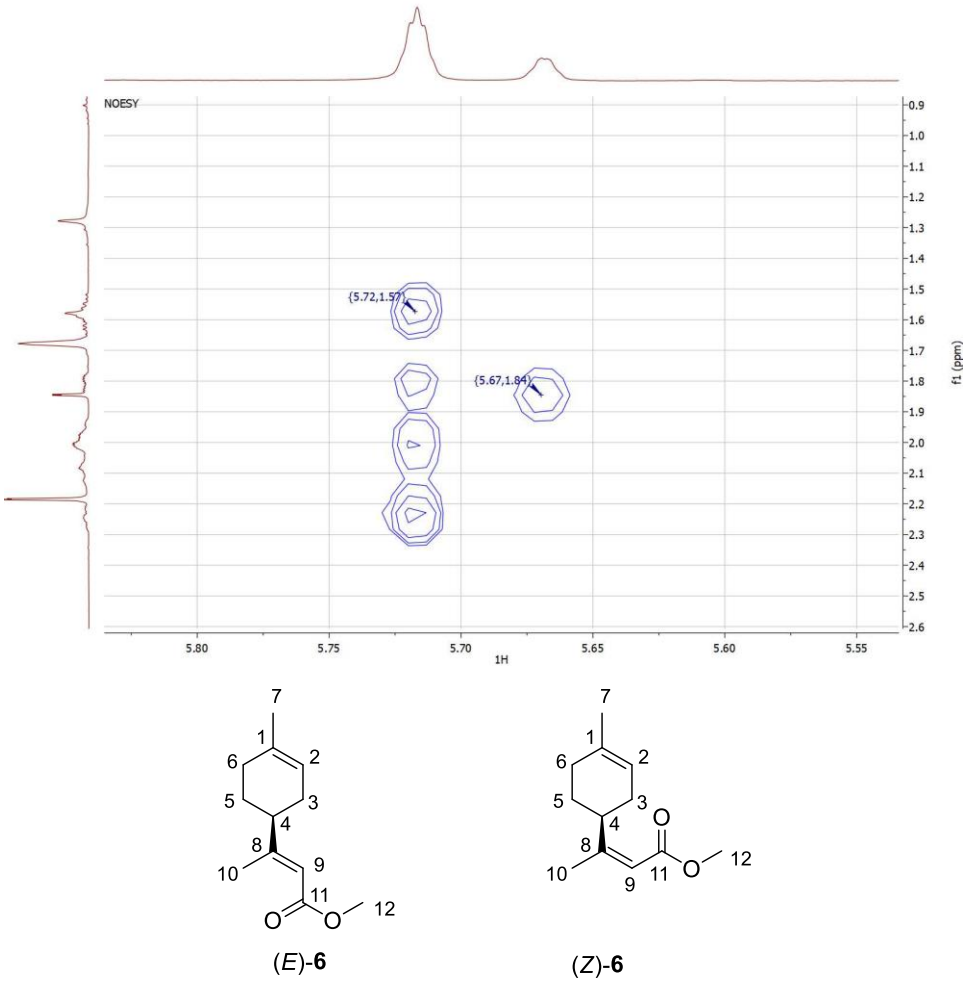
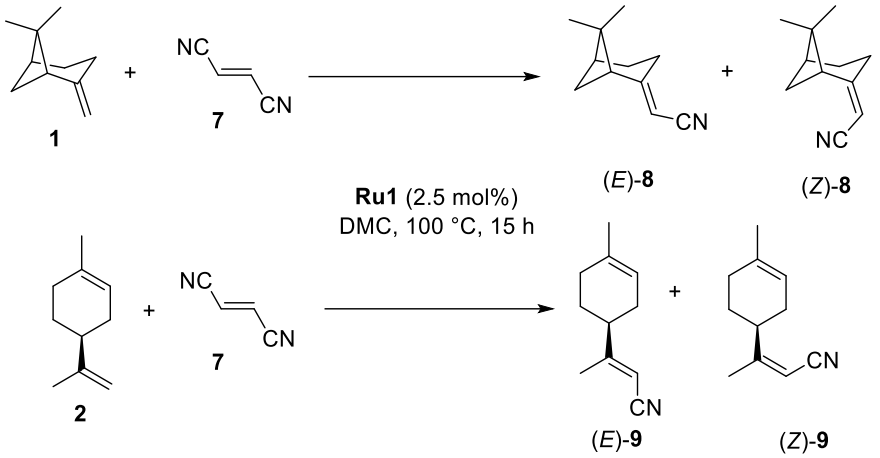


Figure 10: 2D NOESY NMR spectrum of product **6**

4.1.2.2 Cross-metathesis of β-pinene 1 and limonene 2 with fumaronitrile 7

In order to extend and study the scope of the reaction, the cross metathesis of **1** and **2** with acrylonitrile was investigated and did not lead to the cross metathesis product. However, following the principle implemented with acrylates, the use of the symmetrical fumaronitrile **7** led to a mixture of stereoisomers according to **Scheme 14**.



Scheme 14: Cross metathesis of β-pinene **1** and limonene **2** with fumaronitrile **7**

As generally observed in cross metathesis reaction involving nitriles, with this cross metathesis partner, the conversion of β-pinene **1** was much lower than starting from dimethyl maleate **3**. Contrary to cross metathesis reaction with acrylonitrile,[100] the concentration did not have an important impact on the reaction outcome whatever the catalyst used. As depicted in Table 3, slightly better results were obtained with **Ru2** and under optimized conditions, a conversion of 53% was obtained in DMC at 100 °C for 15 h in the presence of 2.5 mol% of catalyst [**Ru2**] with a β-pinene concentration of 0.74 mol/L using the slow addition of the catalyst protocol (**Table 3**, entry 11).

The structure of the stereoisomers has also been determined by NOE experiments and the major stereoisomer was found to be the (*E*)-**8** isomer, which contrasts with all previous results reported with acrylonitrile where the (*Z*)-isomer is the major one.[101] Indeed, interaction between the ethylenic proton C(10)H (at 4.95 ppm) with the C(1)H proton in the (*E*)-**8** isomer (at 2.58 ppm), and interactions of the same ethylenic proton C(10)H (at 5.04 ppm) with one of the protons of the methylene group at C(3) in the (*Z*)-**8** isomer (at 2.40 and 2.70 ppm) were observed in the NOESY spectrum (**Figure 11**).

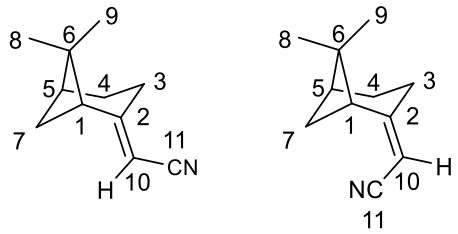
[100] X. Miao, P. H. Dixneuf, C. Fischmeister, C. Bruneau. *Green Chem*. **2011**, 13, 2258-2271.
[101] C. Fischmeister, C. Bruneau, *Beilstein J. Org. Chem*. **2011**, 7, 156-166.

Table 3: Cross metathesis of β-pinene **1** with fumaronitrile **7**[a]

Entry	7 (mol. ratio)	Catalyst (mol%)	Conc. (mol/L)	T (°C)	Solvent	Conv. (%)[c]	Yield (%)[c] (%)[d]
1	**7**/**1** (4)	**Ru1** (2.5)	0.37	100	DMC	32	21 (14)
2	**7**/**1** (4)	**Ru1** (2.5)	0.74	100	DMC	25	18 (10)
3	**7**/**1** (4)	**Ru1** (2.5)	0.05	100	DMC	31	30 (13)
4	**7**/**1** (4)	**Ru1** (5)	0.74	100	DMC	29	21
5	**7**/**1** (4)	**Ru2** (2.5)	0.74	100	DMC	38	30
6	**7**/**1** (4)	**Ru2** (2.5)	0.07	100	DMC	30	22
7	**7**/**1** (4)	**Ru2** (5)	0.74	100	DMC	47	38
8	**7**/**1** (4)	**Ru2** (5)	0.07	100	DMC	39	30
9	**7**/**1** (4)	**Ru2** (5)[b]	0.07	100	DMC	41	32
10	**7**/**1** (4)[b]	**Ru2** (2.5)	0.74	100	DMC	43	33
11	**7**/**1** (4)	**Ru2** (2.5)[b]	0.74	100	DMC	53	42

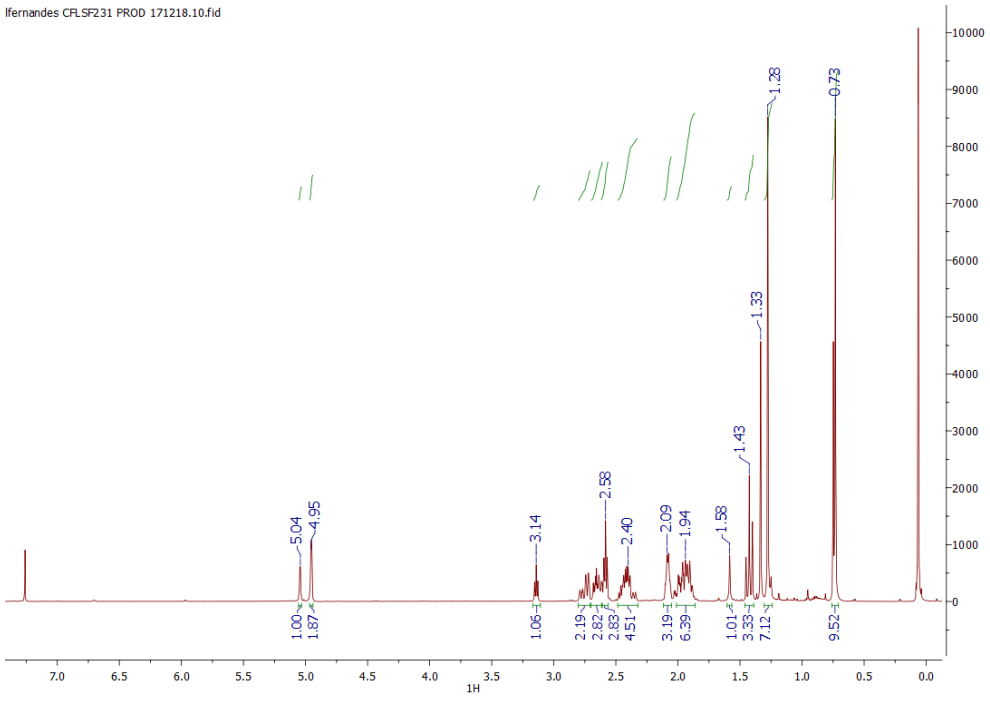
[a] General conditions: β-pinene **1** (100 mg, 0.7 mmol), solvent (1.2 or 10 mL), reaction time (15 h). [b] Slow addition of catalyst in the first 2 h. [c] Conversion and GC yield determined using hexadecane as internal standard. [d] Isolated yield.

The nitrile derivatives **9** could also be formed upon reaction of limonene **2** with fumaronitrile **7** but in the presence of 2.5 mol% of **Ru1** or **Ru2** at 100 °C for 15 h (**Table 4**), low productivity was observed and a maximum conversion of 26% was obtained with **Ru2** with a slow addition of the catalyst protocol (**Table 4,** entry 8). In this case, the (*Z*)-**9** isomer was obtained as the major product (*Z*/*E* = 86:14) (**Figure 12**). Indeed, following attribution of the chemical shift of H(9) and CH_3(10) in the major and minor isomers by COSY experiments, a NOESY experiment evidenced and interaction between H((9), 5.16 ppm) and CH_3((10), 2.09 ppm) in the major isomer whereas not interaction between H((9), 5.10 ppm) and CH_3((10), 1.86 ppm) was observed in the minor isomer.



(*E*)-**8** (*Z*)-**8**

(a)



(b)

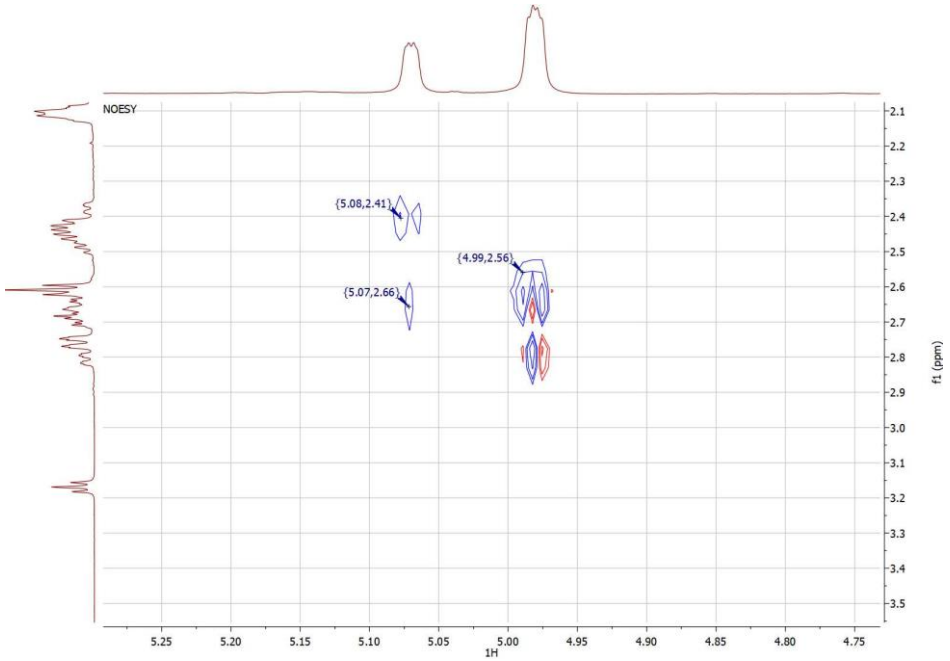


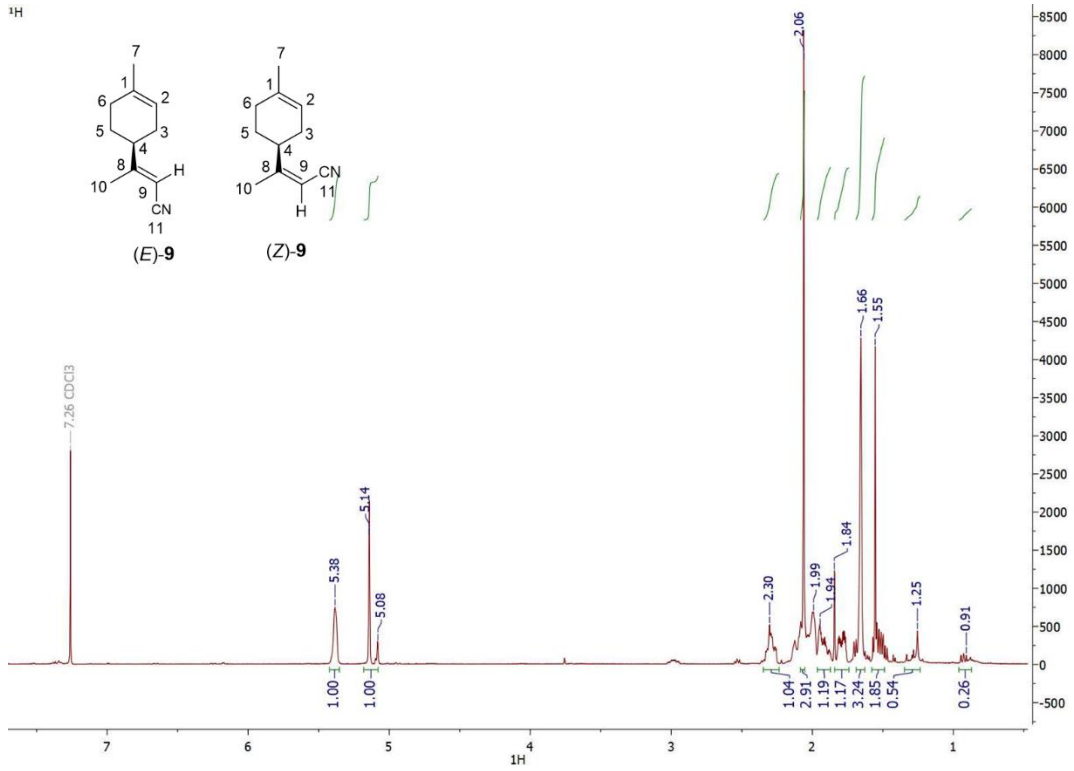
Figure 11: ^{1}H NMR spectrum (a) and 2D NOESY spectrum of product **8**

Table 4: Cross metathesis of limonene **2** with fumaronitrile **7**[a]

Entry	7 (mol. ratio)	Catalyst (mol%)	Conc. (mol/L)	T (°C)	Solvent	Conv. (%)[c]	Yield (%)[c] (%)[d]
1	**7**/**2** (4)	**Ru1** (2.5)	0.37	100	DMC	8	6 (4)
2	**7**/**2**(4)	**Ru1** (2.5)	0.74	100	DMC	17	12
3	**7**/**2**(4)	**Ru1** (2.5)	0.05	100	DMC	13	10 (7)
4	**7**/**2**(4)	**Ru1** (5)	0.74	100	DMC	20	15
5	**7**/**2** (4)	**Ru2** (2.5)	0.74	100	DMC	10	8
6	**7**/**2** (4)	**Ru2** (2.5)	0.07	100	DMC	10	7
7	**7**/**2** (4)	**Ru2** (2.5)[b]	0.07	100	DMC	20	15
8	**7**/**2** (4)	**Ru2** (2.5)[b]	0.74	100	DMC	26	19
9	**7**/**2** (4)	**Ru2** (5)	0.07	100	DMC	11	8
10	**7**/**2** (4)[b]	**Ru2** (5)	0.74	100	DMC	14	11

[a] General conditions: limonene **2** (100 mg, 0.7 mmol), solvent (1,2 or 10 mL), reaction time (15 h). [b] Slow addition of catalyst in the first 2 h. [c] Conversion and GC yield determined using hexadecane as internal standard. [d] Isolated yield.

(a)



(b)

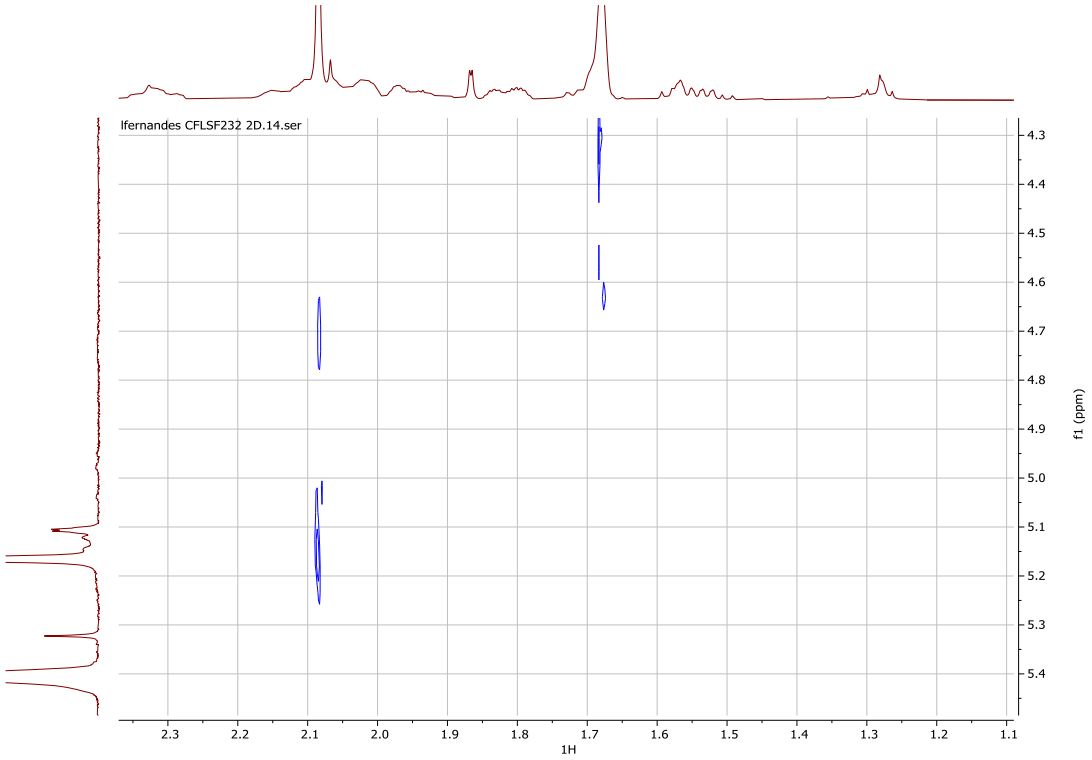
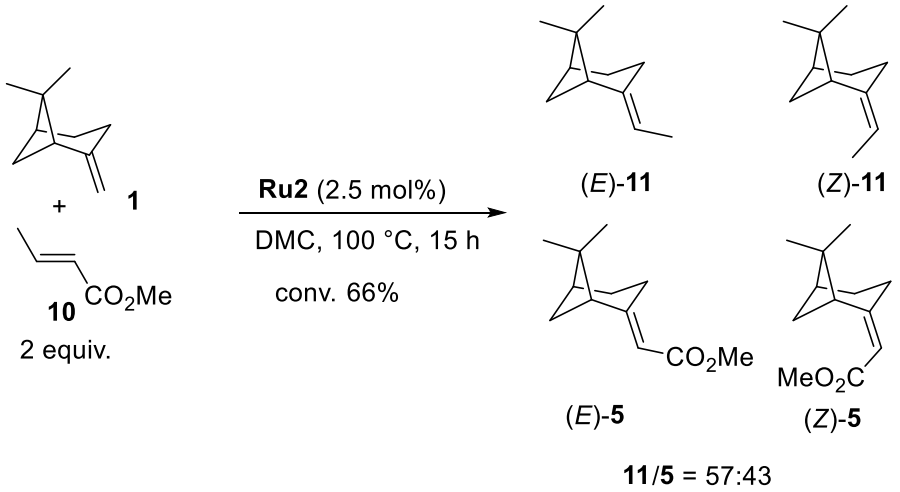


Figure 12: ^{1}H NMR spectrum (a) and 2D NOESY spectrum (b) of product **9**

4.1.2.3 Cross-metathesis of β-pinene 1 and methyl crotonate 10

Following our studies with symmetrical olefins, we have then investigated the cross metathesis of β-pinene **1** with the non-symmetrical methyl crotonate **10** featuring an internal double bond (**Scheme 15**). In the presence of catalyst **Ru2** (2.5 mol%), the cross metathesis reaction of **1** with a twofold excess of **10** took place in DMC ([**1**] = 0.74 mol/L) at 100 °C leading to 66% conversion of β-pinene but the reaction was not selective and beside the functional derivatives **5** (*E*+*Z*), the purely aliphatic stereoisomers of the β-pinene derivative were formed in an almost equimolar amount (**11**/**5** molar ratio of 57:43) as determined by GC analysis of the crude reaction mixture. When the reaction was carried out without solvent in the presence of 5 mol% of **Ru2**, 48% conversion of **1** was obtained and the **11**/**5** ratio was much higher (6.25). As expected, (*E*)-**5** was the major acrylic isomer but the purely aliphatic (*E*)- and (*Z*)-stereoisomers were not separated by GC and thus it was not possible to provide a stereoisomeric ratio.



Scheme 15: Cross metathesis of β-pinene **1** with methyl crotonate **10**

4.1.3 Cross-metathesis of allylic olefins with β-pinene 1 and limonene 2

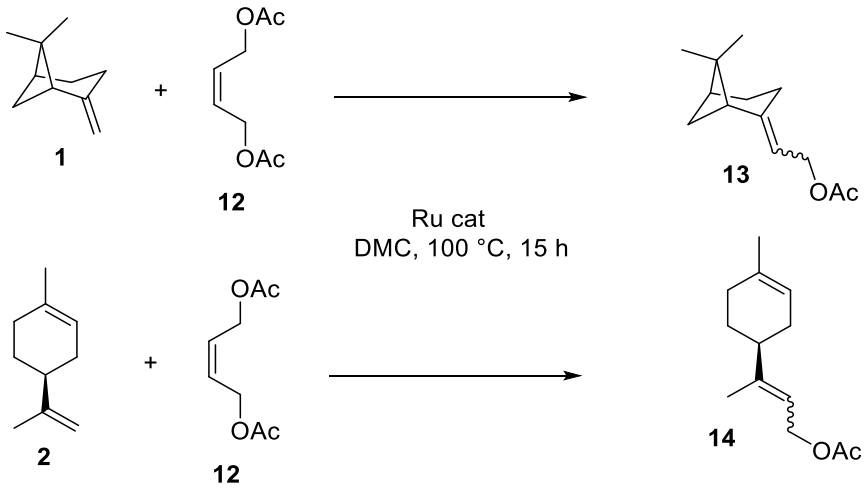
Functional allylic esters and halides are suitable cross metathesis partners to introduce functional groups to the purely aliphatic terpenes **1** and **2**. Using this methodology, natural products including unsaturated fatty esters, acyclic terpenes and lignin-derived allylbenzene derivatives have been functionalized by

cross metathesis with terminal olefinic partners such as allyl acetate and allyl halides or 1,4-diacetoxybut-2-ene as internal olefin.[14]

We initially attempted the cross metathesis of the bulky terpenes **1** and **2** with allyl acetate and allyl chloride featuring a terminal double bond but these attempts were yet unsuccessful. Following the success obtained with the electron deficient dimethyl maleate, dimethyl fumarate and fumaronitrile, we investigated the behavior of the internal olefin-containing *cis*-1,4-diacetoxybut-2-ene and *cis*-1,4-dichlorobut-2-ene.

4.1.3.1 Cross-metathesis of with β-pinene 1 and limonene 2 with cis-1,4-diacetoxybut-2-ene 12

The expected cross metathesis products **13** and **14** were formed in moderate yields when *cis*-1,4-diacetoxybut-2-ene **12** was used (**Scheme 16**). With this cross metathesis partner, the (*E*)-isomers of **13** and **14** were formed as the major products (> 90% (*E*)-**13**, and (*Z*)-**14** was not detected by ^{1}H NMR).



Scheme 16: Cross metathesis of β-pinene **1** and limonene **2** with cis-1,4-diacetoxybut-2-ene **12**

However, the efficiency of these metathesis reactions was much lower with this cross metathesis partner than with acrylic derivatives. The influence of catalyst loading and substrates ratio were not pronounced and conversions reaching 45% of the terpene were obtained under neat conditions with **Ru2** (**Table 5**, entry 9 for **1**, and 15 for **2**).

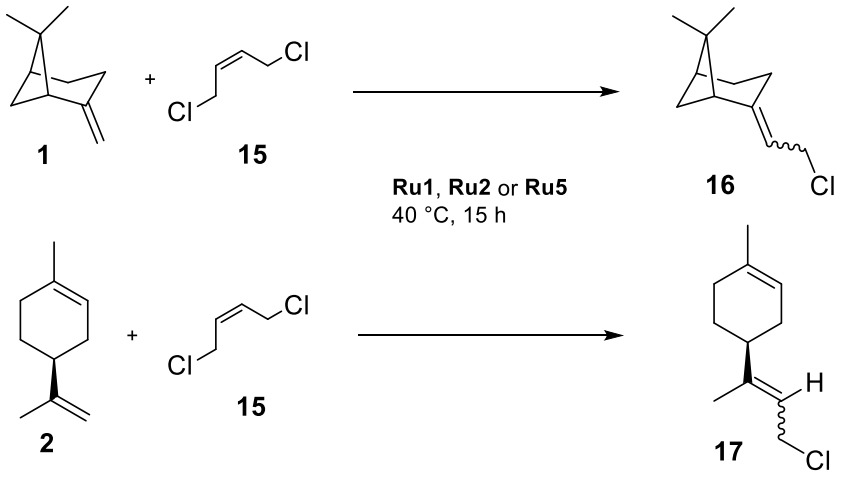
Table 5: Cross metathesis of β-pinene **1** and limonene **2** with *cis*-1,4-diacetoxybut-2-ene **12**[a]

Entry	12/1 or 12/2 (mol. ratio)	Catalyst (mol%)	Conc. (mol/L)	Solvent	Conv. (%)[b]	Yield (%)[b] (%)[c]
1	**12**/**1** (2)	**Ru1** (2.5)	0.37	DMC	19	12 (7)
2	**12**/**1 (**4)	**Ru1** (2.5)	0.37	DMC	15	14 (11)
3	**12**/**1** (4)	**Ru1** (2.5)	0.74	DMC	21	21
4	**12**/**1** (4)	**Ru1** (2.5)	0.74	DMC	24	24 (13)
5	**12**/**1** (8.5)	**Ru1** (2.5)	0.74	neat	31	18 (5)
6	**12**/**1** (8.5)	**Ru1** (5)	0.74	neat	40	30 (26)
7	**12**/**1** (4)	**Ru2** (2.5)	0.74	DMC	17	16
8	**12**/**1** (4)	**Ru2** (5)	0.74	DMC	30	23 (17)
9	**12**/**1** (8.5)	**Ru2** (5)	0.74	neat	45	31 (28)
10	**12**/**2** (4)	**Ru1** (2.5)	0.37	DMC	10	13 (6)
11	**12/2** (4)	**Ru1** (5)	0.74	DMC	9	8 (7)
12	**12/2** (8.5)	**Ru1** (2.5)	0.74	neat	38	17
13	**12/2** (4)	**Ru2** (2.5)	0.74	DMC	8	7
14	**12/2** (4)	**Ru2** (5)	0.74	DMC	8	8 (4)
15	**12/2** (4)	**Ru2** (5)	0.74	neat	45	22
16	**12/2** (4)	**Ru6** (2.5)	0.74	DMC	15	14 (13)

[a] General conditions: β-pinene **1** or limonene **2** (0.7 mmol), solvent (2 mL), 100 °C, reaction time (15 h). [b] Conversion and GC yield determined using tetradecane as internal standard, [c] Isolated yield.

4.1.3.2 Cross-metathesis of β-pinene 1 and limonene 2 with cis-1,4-dichlorobut-2-ene 15

We initially attempted the cross metathesis of terpenes **1** and **2** with the symmetrical internal olefin *cis*-1,4-dichlorobut-2-ene **15** at 100 °C with catalysts **Ru1**, and **Ru2 (Scheme 17)**. The fast initiating **Ru5** catalyst (Figure 7) was also evaluated in this study. In DMC or under neat conditions, the conversions of the terpene were very high, reaching for limonene 86 and 95%, respectively, and 100% for β-pinene (**Table 6,** entries 1, 2, 6, 7).



Scheme 17: Cross metathesis of β-pinene **1** and limonene **2** with cis-1,4-dichlorobut-2-ene **15**

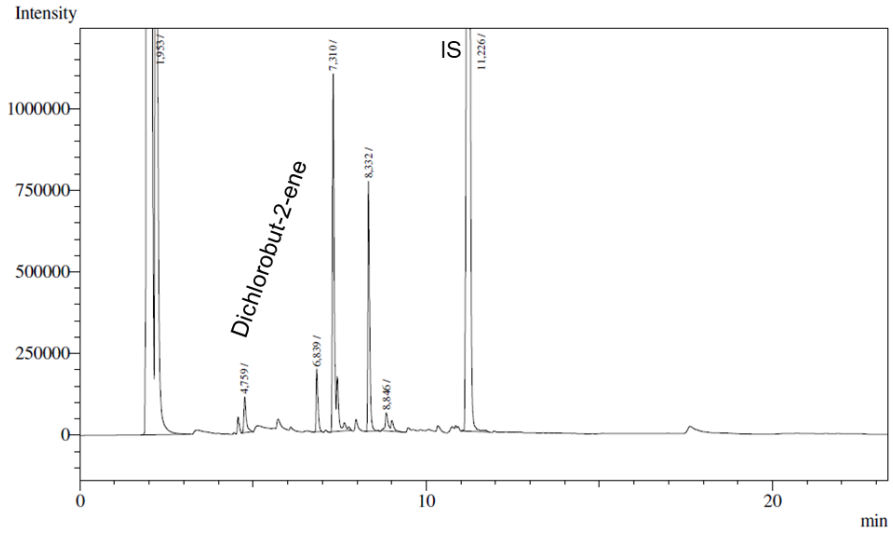
Table 6: Cross metathesis of limonene **1** and β-pinene **2** with *cis*-1,4-dichlorobut-2-ene **15**[a]

Entry	15 (eq.)	Cat (mol %)	Conc. (mol/ L)	T (°C)	Solvent	Conv. (%)[b]	Yield (%)[b] (%)[c]
β-pinene reactions							
1	2	**Ru2** (2.5)	0.74	100	DMC	100	n.d. – n.d.
2	6	**Ru1** (2.5)	1.50	100	neat	100	n.d. – n.d.
3	2	**Ru5** (2.5)	0.74	50	DMC	88	n.d – n.d.
4	2	**Ru1** (2.5)	0.74	50	DMC	78	n.d. – n.d.
5	2	**Ru2** (2.5)	0.74	50	DMC	100	50 - 14
Limonene reactions							
6	2	**Ru2** (2.5)	0.74	100	DMC	86	n.d. – n.d.
7	6	**Ru1** (2.5)	1.50	100	neat	95	n.d. – n.d.
8	2	**Ru5** (2.5)	0.74	50	DMC	63	n.d - 23
9	2	**Ru2** (2.5)	0.74	50	DMC	68	n.d – 28
10	2	**Ru2** (2x2.5)	0.74	50	DMC	64	n.d – n.d.
11	6	**Ru1** (2.5)	1.50	50	neat	44	n.d. – n.d.
12	6	**Ru2** (2.5)	0.74	50	neat	33	n.d. – n.d.
13	6	**Ru2** (5)	0.74	50	neat	34	n.d. – n.d.

[a] General conditions: β-pinene **1** or Limonene **2** (100 mg, 0.7 mmol), solvent (1 or 2 mL), 2 eq. (1.4 mmol) of **6**; time reaction: 15 h.
[b] Conversion and GC yield determined using hexadecane as internal standard.[c] Isolated yield. n.d. – not determined

However, the GC analysis revealed the presence of numerous products in particular with limonene, hence the reaction was non-selective (**Figure 13**).

(a)



(b)

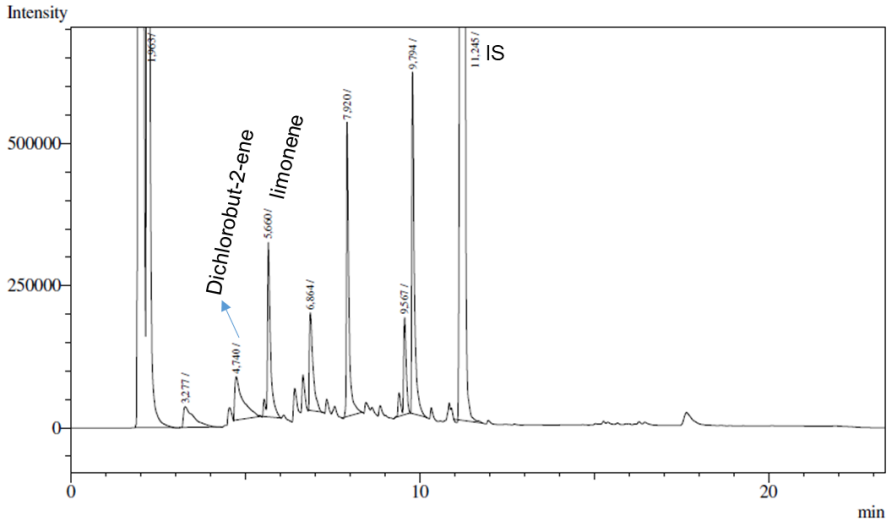


Figure 13: Chromatogram of the crude reaction mixture between β-pinene **1** (a) and limonene **2** (b) with cis 1,4-dichlorobut-2-ene **15** at 100°C

Attemps to improve the selectivity of the reaction were done at lower temperature, i.e. 50 °C. The reactions were performed with catalysts **Ru1**, **Ru2** and **Ru5** at 2.5 mol% catalyst loading in DMC with a twofold excess of **15** or without solvent in the presence of 6 equivalents of **15**. With these cross metathesis partners, the best conditions were obtained in DMC and the conversion after 15 h reached 100% for β-pinene (**Table 6**, entry 5) and 68% for limonene (**Table 6**, entry 9). In the latter case, the conversion was not improved when a second portion of catalyst was added (**Table 6**, entry 10). Under neat conditions, the conversion of limonene were located in the range 36-47% and no beneficial effect was obtained with a higher catalyst loading of 5 mol% (**Table 6**, entries 10, 13). A direct comparison of **Ru1**, **Ru2** and **Ru5** at 50 °C showed the better performances of **Ru2** (Table 6, entries 3-5 and 8-9). The GC analyses of the crude mixture revealed incomplete conversion but clean reactions with only one product formed **(Figure 14),** and for β-pinene reaction, no changes were observed. In the latter case, there was an attempt to isolate the compounds generated but the ^{1}H NMR analysis of the isolated product did not indicate the presence of the desired product **16** (**Figure 15**). Indeed, the ^{1}H NMR spectrum clearly evidenced the presence of a terminal vinyl group with a classical fingerprint : 5.72 (dd, 1H, J= 17.5, 10.9 Hz); 5.23 (dd, 1H, J= 10.9, 1.5 Hz); 5.12 (dd, 1H, J= 17.5, 1.5 Hz).

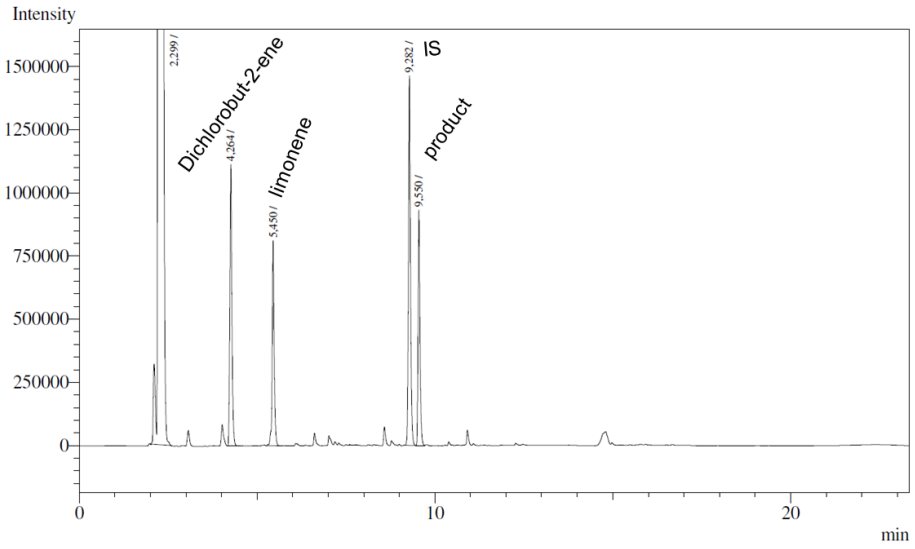


Figure 14: Chromatogram of the crude reaction mixture between limonene **2** (b) with *cis*-1,4-dichlorobut-2-ene **15** at 50 °C

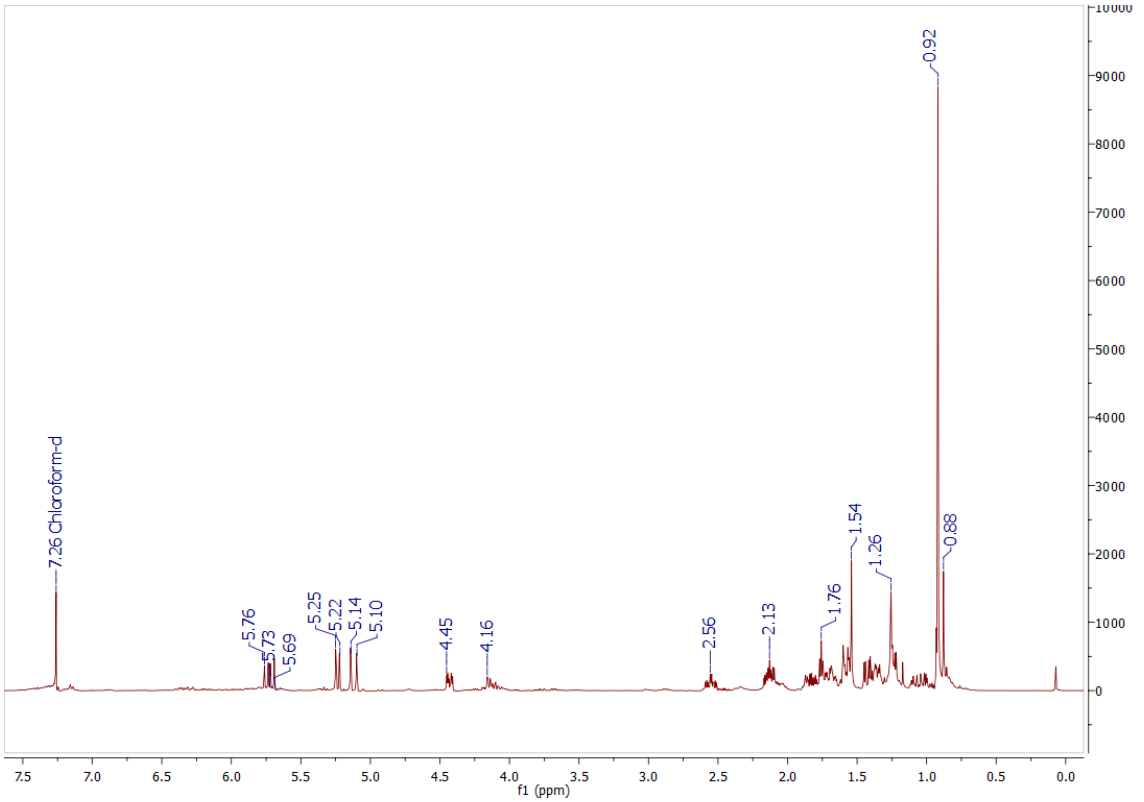


Figure 15: ^{1}H NMR spectrum of the reaction mixture of β-pinene **1** with *cis*-1,4-dichlorobut-2-ene **15**

For the limonene derived product **17,** the NMR analyses showed the presence of a major stereoisomer with only trace amount of the minor isomer (**Figure 16**).

The new terpene derivative **17** was difficult to purify by usual chromatography on silica gel, which led to very low isolated yield, but acceptable results were obtained with elution over alumina (Table 6, entries 8 and 9, 23 and 28%, respectively). The NOESY spectrum of the isolated product showed that the C(11)H_2 protons with a chemical shift of 4.12 ppm were in strong interaction with the protons of the C(10)H_3 group at 1.72 ppm, confirming again in this case the *E*-stereoselectivity of the cross metathesis (**Figure 17**).

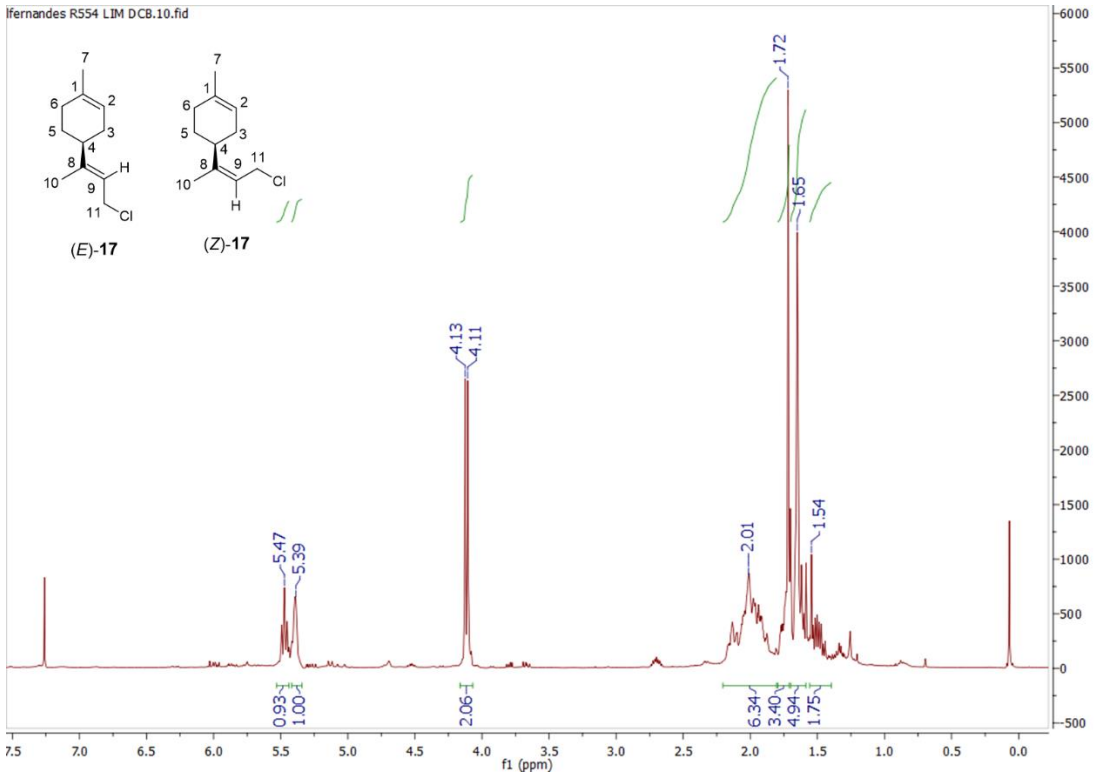


Figure 16: ^{1}H NMR spectrum of the product **17**

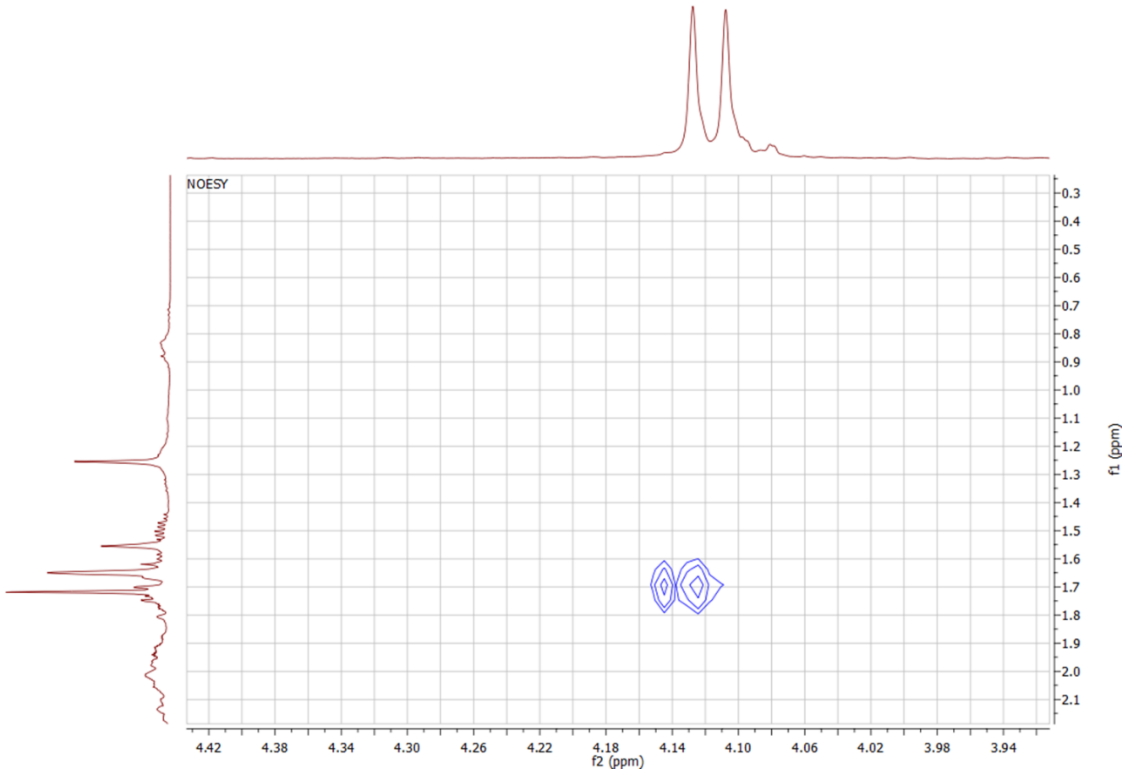
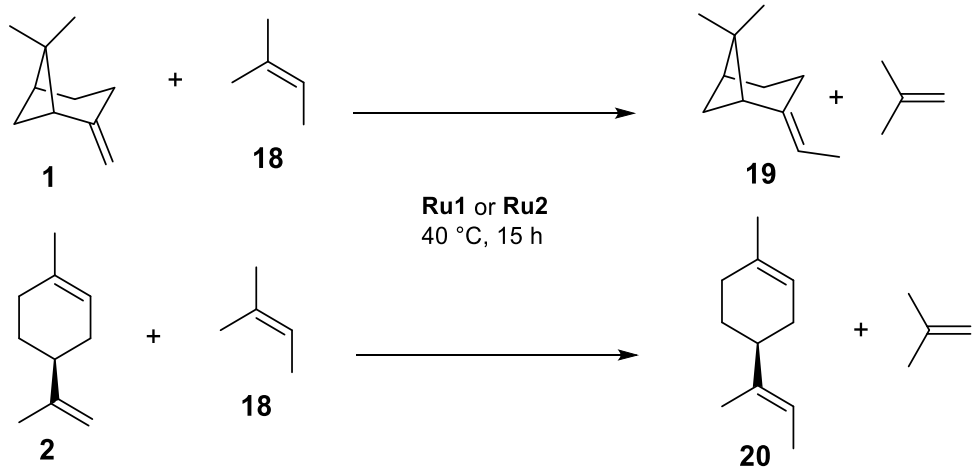


Figure 17: 2D NOESY NMR spectrum of the product **17**

4.1.4 Cross-metathesis of non-functionalized olefins with β-pinene 1 and limonene 2

4.1.4.1 Cross-metathesis of β-pinene 1 and limonene 2 with 2-methylbut-2-ene 18

In line with Tlenkopatchev results who performed the cross metathesis of β-pinene with the purely aliphatic internal olefin 3-methylpent-2-ene catalyzed by the second generation Grubbs catalyst[7], we attempted the cross metathesis of (-)-β-pinene **1** and (-)-limonene **2** with 2-methylbut-2-ene **18 (Scheme 18)**.



Scheme 18: Cross metathesis of β-pinene **1** and limonene **2** with 2-methylbut-2-ene **18**

The reactions were performed in dimethyl carbonate or without solvent at 40 °C with various concentrations of reagents and catalyst loadings. Higher reaction temperatures were not considered due to the low boiling point of 2-methylbut-2-ene **18** (38 °C). When the reaction was carried out in DMC, a fourfold excess of **18** with respect to the terpene was introduced and tetradecane or hexadecane was used as internal standard to evaluate the conversion of the terpene and the yield of product by gas chromatography. When the reaction was performed under neat conditions, an excess of 13 equivalents of **18** with respect to the terpene was used. The first experiments were carried out at 40 °C in DMC with 2.5 and 5 mol% of catalysts **Ru1** and **Ru2** during 15 h (**Table 7**).

Table 7: Cross metathesis of terpenes **1** and **2** with 2-methylbut-2-ene **18**[a]

Entry	18 (eq.)	Catalyst (mol %)	Solvent	Conv. (%)	Yield (%)[b] (%)[c]
(-)-limonene **2**					
1	4	**Ru1** (2.5)	DMC	62	58 – n.d.
2	4	**Ru1** (5)	DMC	65	61 – n.d.
3	4	**Ru2** (2.5)	DMC	65	60 – n.d.
4	4	**Ru2** (5)	DMC	70	66 – n.d.
5	13	**Ru1** (5)	neat	71	67 – n.d.
6	13	**Ru2** (5)	neat	82	76 – n.d.
7	13	**Ru2** (2x2.5)	neat	90	84 – 33
8	13	**Ru2** (2x2.5)	neat	93	87 - 60
9	13	**Ru1** (2x2.5)	neat	76	72 – n.d.
β-pinene **1**					
10	4	**Ru1** (2.5)	DMC	78	73 – n.d.
11	4	**Ru2** (2.5)	DMC	78	72 – n.d.
12	13	**Ru1** (2.5)	neat	87	81 – n.d.
13	13	**Ru2** (2.5)	neat	97	92 – n.d.
14	13	**Ru1** (2.5+1)	neat	86	82 – n.d.
15	13	**Ru2** (2.5+1)	neat	100	95 - 19
16	13	**Ru2** (2.5+1)	neat	100	97 - 56

[a] General conditions: terpene (100 mg, 0.7 mmol), 2-methylbut-2-ene (2.8 mmol in DMC, 9.1 mmol for neat), DMC (2 mL), 40 °C, 15 h, conversion and yield were determined by GC using hexadecane as internal standard. [b] first portion (15 h), second portion (8 h). [c] Isolated yield. n.d.- not determined.

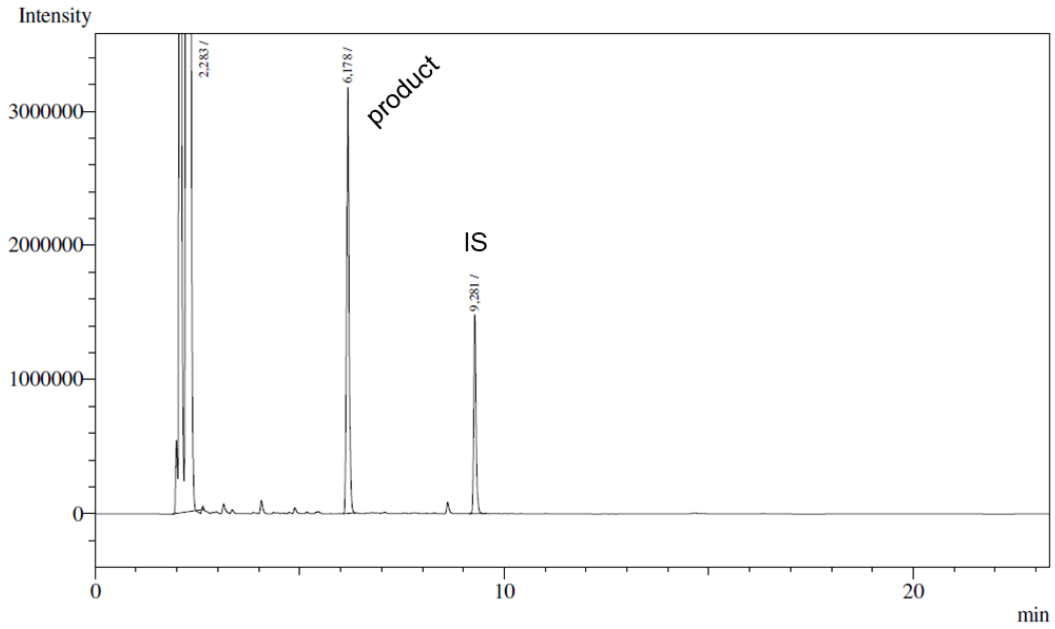
Under these conditions, good conversions were obtained but they were still limited to 70% with limonene **2** and 78% with β-pinene **1**. Because the final products differ from the starting terpene by only one methyl group, it was anticipated that their separation would be difficult and that reaching very high conversion was compulsory to isolate the pure cross metathesis products **19** and **20**. The utilization of 2-methylbut-2-ene **18** both as reagent and solvent led to higher conversions and the addition of the catalyst in two portions allowed to reach 93% conversion of limonene (Table 7, entry 8) and full conversion of β-

pinene (Table 7, entries 15-16). In these metathesis reactions, the Hoveyda catalyst **Ru2** was slightly more efficient than the Zhan catalyst **Ru1**.

The purification of the product was here again difficult as evidenced by the difference between the GC and isolated yields. We noticed that during the drying of the product, we lost a significant amount of these compounds in both reactions. In both cases, the boiling point of the product is expected below 200 °C (bp limonene = 176 °C ; β-pinene = 166 °C). The reaction performed without solvent brought some easier purification with the facile evaporation of the excess of 2-methylbut-2-ene followed by filtration of the catalyst residue over silica gel with pentane as eluent, which was further easily evaporated. With this protocole, pure product **19** was isolated in 56% yield from β-pinene (Table 7, entry 16) and **20** in 60% from limonene (Table 7, entry 8). This strategy was of great importance to obtain the final product in good quantity, since it improved the purification process.

In addition to the expected *E*- and *Z*-stereoisomers (discussed later), the utilization of a non-symmetrical internal olefin might generate two products containing either a methyl- or an *iso*-propyl group. In both cases, the GC analysis of the crude reaction mixture revealed the presence of a major peak (more than 93% area) (**Figure 18**), and the proton NMR spectra showed the presence of an ethylenic proton centered at 5.05 ppm for the pinene derivative **19** and 5.25 ppm for the limonene product **20**. In agreement with this result the GC/MS analysis gave a molecular weight of 150 u corresponding to $C_{11}H_{18}$ (**Figure 19** and **Figure 20**).

(a)



(b)

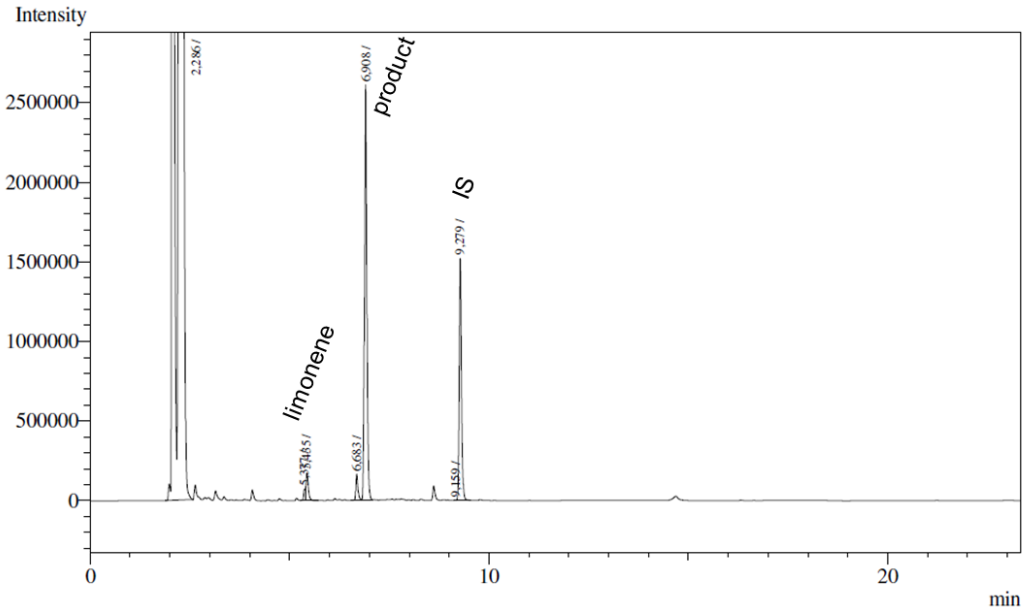
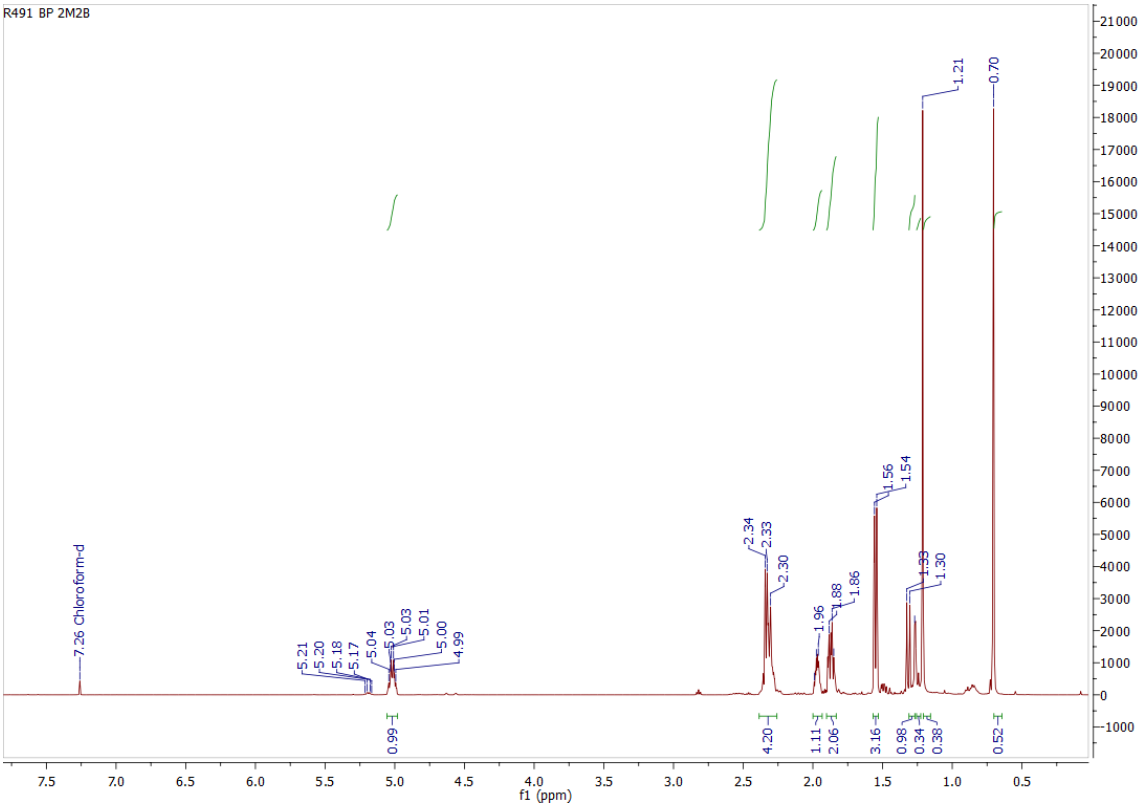


Figure 18: Chromatogram of the crude reaction mixture of the products **19** (a) and **20** (b)

(a)



(b)

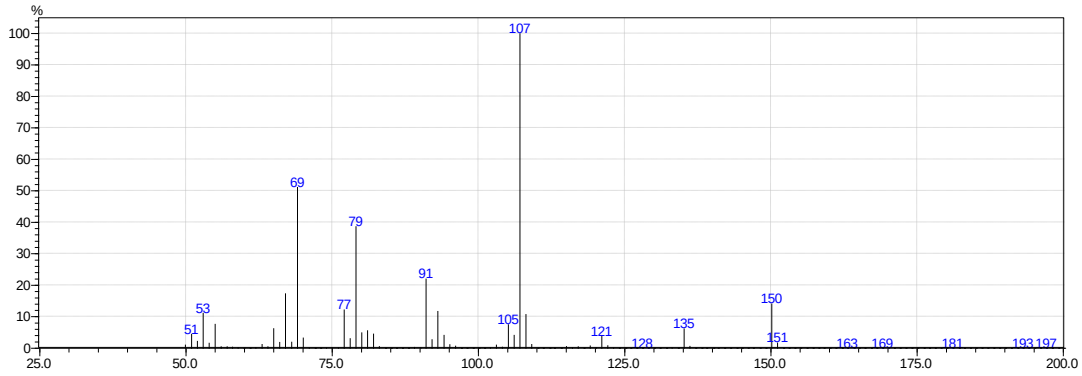
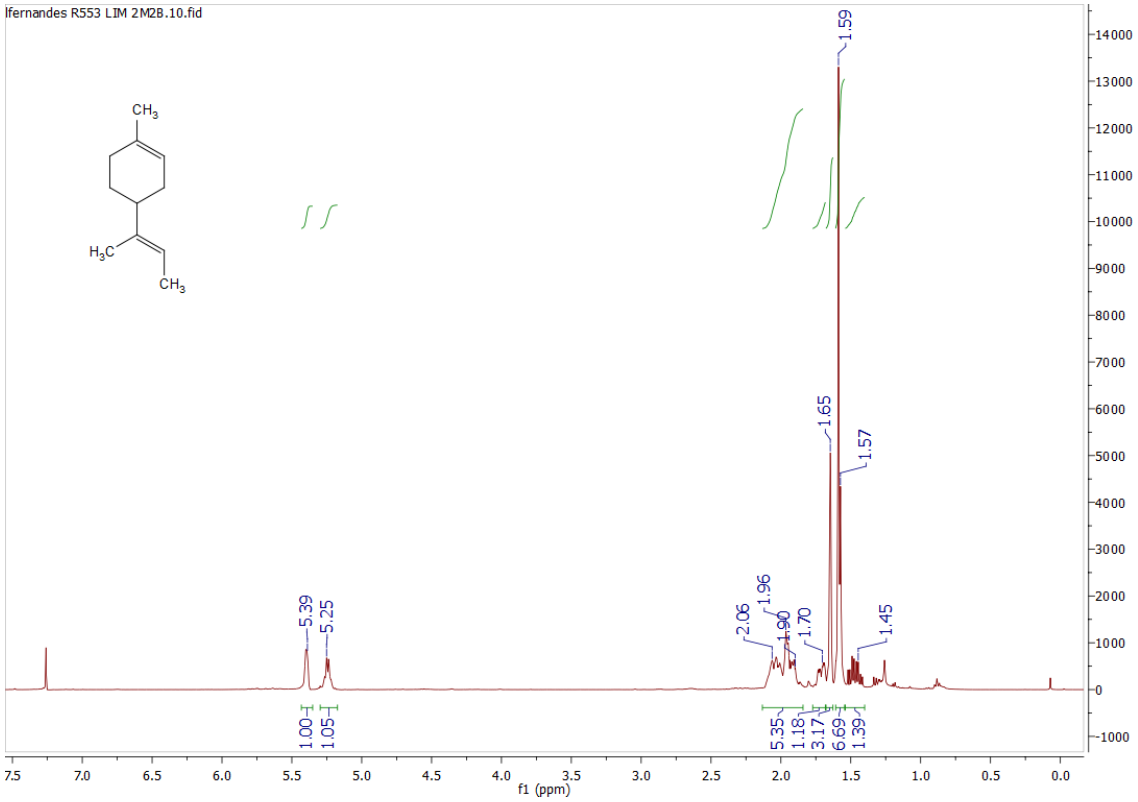


Figure 19: ^{1}H NMR (a) and m/z spectrum (b) of the product **19**

(a)



(b)

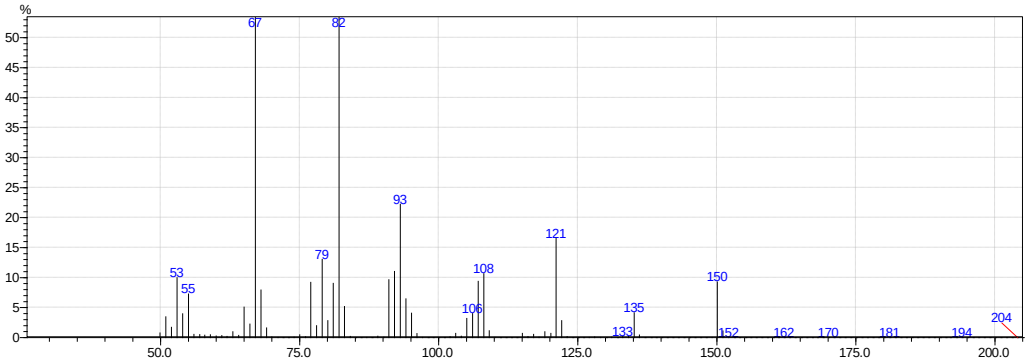


Figure 20: ^{1}H NMR (a) and m/z spectrum (b) of the product **20**

The cross metathesis of the bulky terpenes **1** and **2** with 2-methylbut-2-ene **18** appeared to be regioselective leading to the sole formation of a trisubstituted double bond with elimination of isobutene. This regioselectivity is opposite to what was usually observed in cross metathesis with 2-methylbut-2-ene. Indeed, this simple trisubstituted olefin has been used efficiently for the introduction of a *gem*-dimethyl terminal end to monosubstituted double bonds of

model compounds[102], and in particular the transformation of allyl into prenyl groups for preparation or modification of natural products such as amino acid derivatives [103], flavonoids, coumarines, chromanones, quinolinones [104], in most cases in the presence of the Grubbs second generation catalyst **Ru1** under mild conditions. However, in some cases, the reverse regioselectivity was observed during these prenylation reactions[105] leading to up to 15 % of disubstituted double bond starting from a sterically demanding *o, o'*-diacetoxy allylphenyl structure. The cleavage of methyl oleate containing an internal double bond *via* cross metathesis with 2-methylbut-2-ene revealed that both regioselectivities could be obtained depending on the nature of the catalyst.[106] The cross-metathesis of a sterically hindered vinylheterocyclic substrate with 2-methylbut-2-ene in the presence of the catalyst **Ru2** yielded a mixture of the two regioisomers in a disubstituted/trisubstituted double bond ratio of 2.4/1.0.[107] The regioselectivity leading to the formation of a 1, 2-disubstituted double bond is also exemplified by the cross metathesis of 2-methylbut-2-ene with *n*-butyl acrylate in which the *trans*-*n*-butyl crotonate was formed in 83 % yield[102] due to the higher reactivity of the alkene than the acrylate to generate a ruthenium ethylidene species, as also observed under stoichiometric conditions from the first generation cyclohexyl ester ruthenium carbene $RuCl_2(PCy_3)_2(=CHCO_2Cy)$ and 2-methyl-1-pentene.[108] The above examples reveal that the formation of *gem*-dimethyl olefins is favoured starting from terminal olefins without bulky neighbouring groups, typically allylic fragments, whereas the introduction of steric hindrance, which result in very constrained ruthenacyclobutane intermediates, or electron deficiency at the cross metathesis partner, make the other regioselectivity possible and sometimes preponderant.

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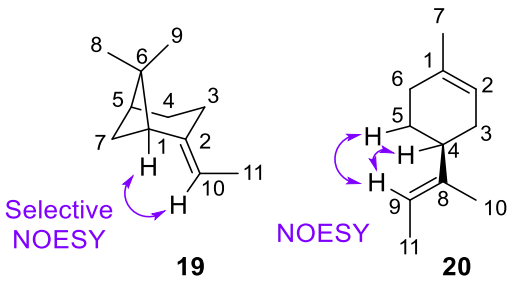
[102] A.K. Chatterjee, D.P. Sanders, R.H. Grubbs, Org. Lett. 4, **2002**, 1939–1942.
[103] (a) J. Elaridi, W.R. Jackson, A.J. Robinson, Tetrahedron Asymmetry 16, **2005**, 2025–2029. (b) B.J. van Lierop, W.R. Jackson, A.J. Robinson, *Tetrahedron* 66, **2010**, 5357–5366.
[104] (a) S.O. Simonetti, E.L. Larghi, T.S. Kaufman, Org. Biomol. Chem. 14, **2016**, 2625–2636. (b) C. Schultze, S. Foß, B. Schmidt, Eur. J. Org. Chem. **2020**, 7373–7384. (c) G. Kwesiga, A. Kelling, S. Kersting, E. Sperlich, M. von Nickisch-Rosenegk, B. Schmidt, J. Nat. Prod. 83, **2020**, 3445–3453. (d) C. Schultze, B. Schmidt, J. Org. Chem. 83, **2018**, 5210–5224. (e) J. Magolan, M.J. Coster, J. Org. Chem. 74, **2009**, 5083–5086.
[105] (a) S. Tischer, P. Metz, Adv. Synth. Catal. 349, **2007**, 147–151. (b) P. Pahari, J. Rohr, J. Org. Chem. 74, **2009**, 2750–2754.
[106] A. Sytniczuk, A. Kajetanowicz, K. Grela, Catal. Sci. Technol. 7, **2017**, 1284–1296.
[107] R.R. Sapkota, J.M. Jarvis, T.M. Schaub, M.R. Talipov, J.B. Arterburn, ChemistryOpen 8, **2019**, 201–205.
[108] M. Ulman, T.R. Belderrain, R.H. Grubbs, Tetrahedron Lett. 41, **2000**, 4689–4693.

Our results are also in line with the calculations of Tlenkopatchev, who predicted that in olefin cross metathesis with trisubstituted olefins the less substituted ruthenium carbene was the most reactive.[2525] The reverse regioselectivity would lead to the formation of a tetrasubstituted double bond with a bulky environment, which is also less favorable. It can be noted that the selectivity in the cross metathesis of β-pinene with **18** was much higher with the Hoveyda catalyst **Ru2** than in the reaction of β-pinene with (*Z*)-3-methyl-2-pentene in the presence of the second generation Grubbs catalyst, which led to a 58:16 mixture of the two regioisomers.[25]

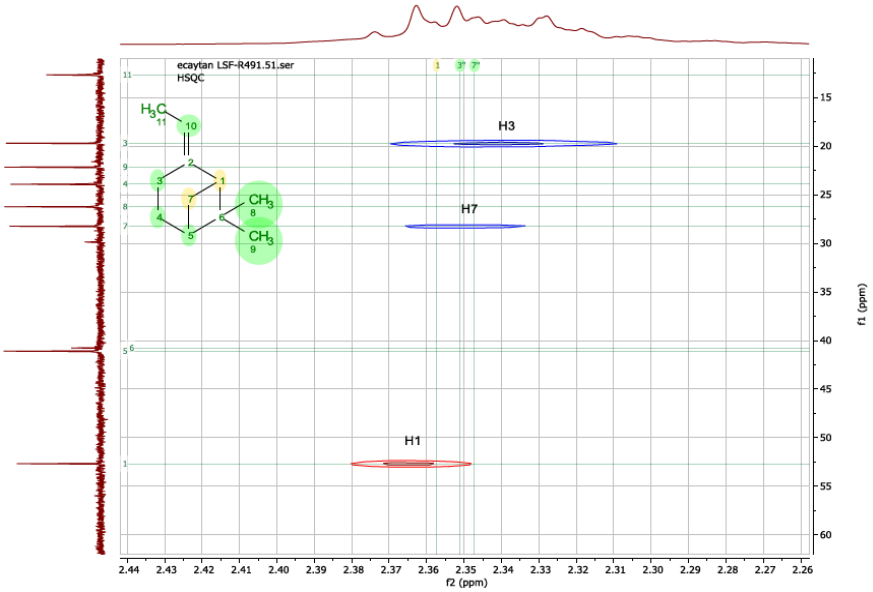
The stereochemistry of the created double bonds was determined by NMR and it was found that the *E*-isomers **19** and **20** were the major products. The stereochemistry was determined using 1D and 2D experiments. First, an HSQC analysis of **19** permitted to identify the contributions of H1, H7 and H3 in the broad ^{1}H signal observed between 2.31 and 2.38 ppm (**Figure 21**, a). Then, a selective 1D NOESY experiment with irradiation of the olefinic H at 5.037 ppm (H10) resulted in an enhancement of the H1 contribution to the braod signal between 2.31 and 3.38, while the contribution of H3 totally vanished (**Figure 21**, b). For **20**, a 2D NOESY experiments showed a strong correlation between H9 nd H4, H5 hence evidencing a *E* configuration (**Figure 21**, c).The very high selectivity in favor of the *E*-isomers was probably due to the presence of a large excess of **18** and high conversion, which promoted secondary cross metathesis of **19** and **20** with **18** in the presence of the second generation ruthenium catalyst leading to isomerization into the thermodynamically favored *E*-isomers and therefore to an increased *E*-stereoselectivity, as observed in other cases of cross metathesis.[109]

[109] (a) T. Ritter, A. Hejl, A.G. Wenzel, T.W. Funk, R.H. Grubbs, Organometallics 25, **2006**, 5740–5745. (b) D.R. Anderson, T. Ung, G. Mkrtumyan, G. Bertrand, R.H. Grubbs, Y. Schrodi, Organometallics 27, **2008**, 563–566.

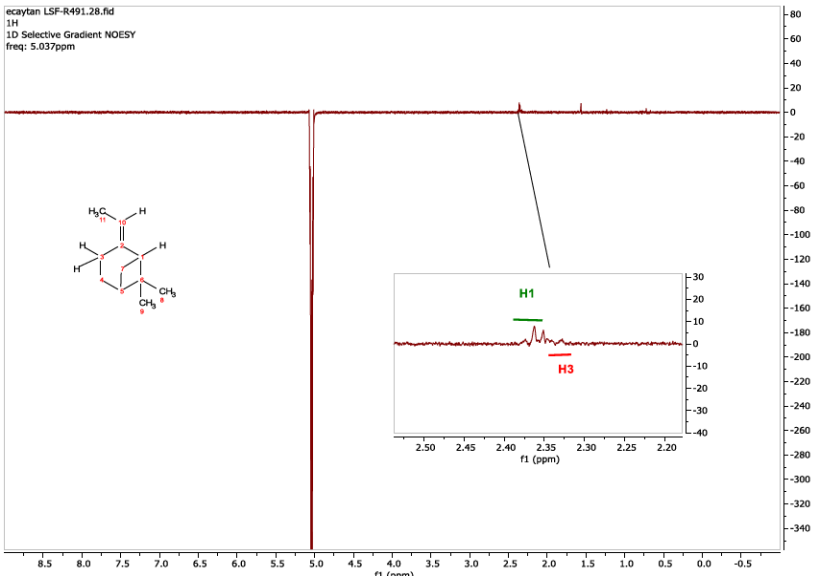

Selective
NOESY
NOESY

19 **20**

(a)


ecaytan LSF-R491.51.ser
HSQC
H3
H7
H1
f2 (ppm)
f1 (ppm)

(b)


ecaytan LSF-R491.28.fid
1H
1D Selective Gradient NOESY
freq: 5.037ppm
H1
H3
f1 (ppm)

(c)

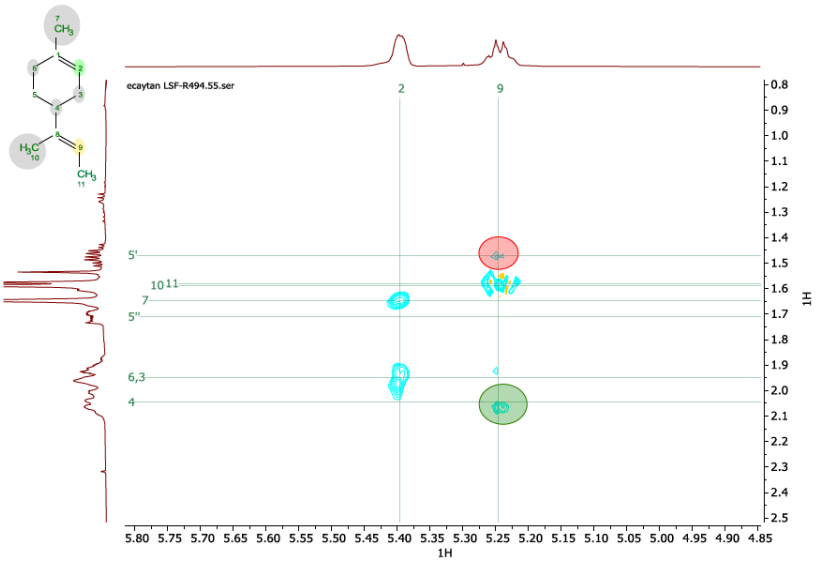
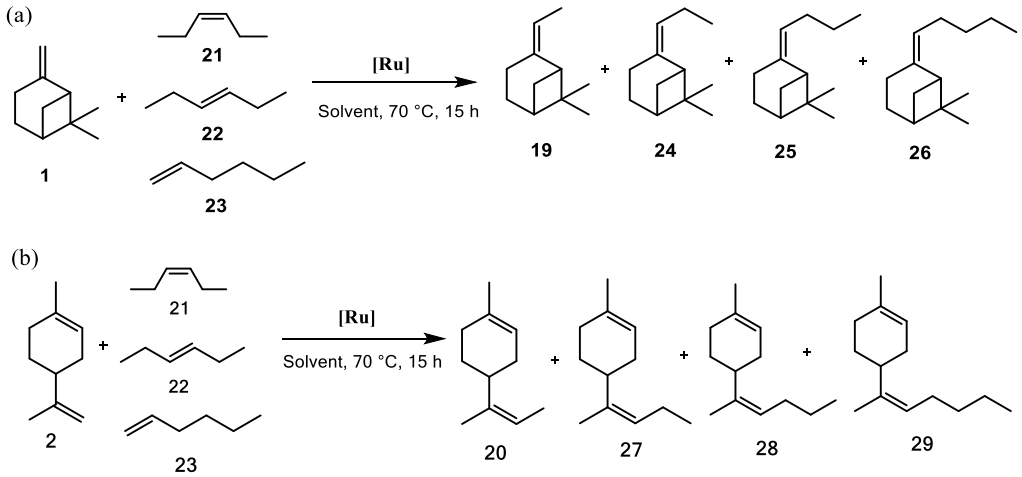


Figure 21: Determination of structures of **19** by HSQC and 1D selective NOESY experiments and **20** by 2D NOESY experiments

4.1.4.2 Cross-metathesis of β-pinene 1 and limonene 2 with cis-hex-3-ene 21, trans- hex-3-ene 22 and hex-1-ene 23

The reactions of terpenes **1** and **2** with the *cis*-**21** and *trans*-**22** forms of hex-3-ene (**Scheme 19**) presented different behaviours (**Table 8** and **Table 9**), obtaining higher values of conversion with the *cis* form and practically no occurrence of reaction when the *trans* form was used. In all cases, the reaction produced several products as a resuts of double-bond migration in the reacting olefins (Scheme 16).



Scheme 19: Cross-metathesis of non-functionalized compounds **21**, **22** and **23** with terpene **1** (a) and **2** (b)

Table 8: Cross-metathesis of β-pinene **1** with *cis*-hex-3-ene **21**, *trans*-hex-3-ene **22** and hex-1-ene **23**

Entry	**21, 22** or **23** (eq.)	Catalyst (mol %)	Solvent	Conv.[b] (%)	GC Ratio			
					(**19**)	(**24**)	(**25**)	(**26**)
1	(**21**) 2	**Ru1** (2.5)	Toluene	89	72	22	6	
2[c]	(**21**) 2	**Ru1**(2.5)	Toluene	87	64	32	4	-
3[d]	(**21**) 2	**Ru1**(2.5)	DMC	60	29	71	0	-
4[d]	(**21**) 4	**Ru1**(2.5)	DMC	55	25	75	0	-
5	(**22**) 2	**Ru1**(2.5)	Toluene	7	30	70	0	-
6	(**23**) 2	**Ru1**(2.5)	Toluene	85	78	9	6	7
7[c]	(**23**) 2	**Ru1**(2.5)	Toluene	6	0	0	0	100

[a] General conditions: terpene (100 mg, 0.7 mmol), solvent (2 mL), 70 °C, 15 h, [b] conversion and yield were determined by GC using hexadecane as internal standard. [c] in the presence of 5 mol% of benzoquinone. [d] in the presence of 10 mol% of benzoquinone

Table 9: Cross-metathesis of limonene **2** with *cis*-hex-3-ene ***21***, *trans*-hex-3-ene **22** and hex-1-ene **23**

Entry	**21, 22** or **23** (eq.)	Catalyst (mol %)	Solvent	Conv.[b] (%)	Ratio			
					(**20**)	(**27**)	(**28**)	(**29**)
1	(**21**) 2	**Ru1**(2.5)	Toluene	70	67	22	8	3
2[c]	(**21**) 2	**Ru1**(2.5)	Toluene	64	45	46	9	0
3[d]	(**21**) 4	**Ru1**(2.5)	Toluene	53	13	83	4	0
4	(**22**) 2	**Ru1**(2.5)	Toluene	12	0	0	0	0
5	(**23**) 2	**Ru1**(2.5)	Toluene	74	68	12	10	10

[a] General conditions: terpene (100 mg, 0.7 mmol), solvent (2 mL), 70 °C, 15 h, [b] conversion and yield were determined by GC using hexadecane as internal standard. [c] in the presence of 5 mol% of benzoquinone. [d] in the presence of 10 mol% of benzoquinone

In spite of the high conversion obtained from the symmetrical *cis*-hex-3-ene **21**, the products that were obtained in larger quantities (**19** and **20**) actually resulted from the metathesis of the terpene with hex-2-ene, a product of isomerization of hex-3-ene. Double-bond migration during olefin metathesis is a known side reaction and previous studies showed that this isomerization can be partially or totally inhibited by the addition of 1,4-benzoquinone to the reaction.[110]

[110] a) S. H. Hong, D. P. Sanders, C. W. Lee, R. H. Grubbs, *J. Am. Chem. Soc*. **2005**, *127*, 17160-17161. b) I. O'Doherty, J. J. Yim, E. A. Schmelz, F. C. Schroeder, *Org. Lett*. **2011**, *13*, 5900. C) O. Kreye, T. Toth,

Thus, when 5 mol% of 1,4-benzoquinone were added to the reaction mixture starting from **1** (Table 8, entry 2) little difference was observed in both the conversion and the product ratio with only a small increase of the relative amount of the expected product **24**, but still the prevalence of the cross metathesis with hex-2-ene (**19**) was observed. In the reaction with **2** (Table **9**, entry 2) the products **20** and **27** resulting from metathesis with hex-3-ene and hex-2-ene, respectively, were formed in equal amounts, which contrasts with the **20**/**27** ratio of 67:22 obtained without 1,4-benzoquinone.

Increasing the amount of 1,4-benzoquinone to 10 mol% favoured the formation of the desired products involving *cis*-hex-3-ene **21** (Table 8 and 9, entries 3), despite a slight decrease of the conversion of the substrates.

In the reactions with *trans*-hex-3-ene **22** (Table 8, entry 5 and Table 9, entry 4) low conversions of the substrates were obtained, with small amount of product obtained in reaction with **1** and no formation of cross metathesis product with **2**.

The reaction of the terpene compounds with hex-1-ene **23** (Table 8, entries 6-7, Table 9, entry 5) was also tested. In the reaction with **1**, the reactions were tested with and without the addition of 1,4-benzoquinone. In the former case a conversion of 85% of the substrate was obtained and the formation of four products, with the product **19** corresponding to cross metathesis with hex-2-ene as the major product. However, by adding 5 mol% of 1,4-benzoquinone the conversion decreases drastically to 6%, but only the product **26** (identified by GC/MS) resulting from cross metathesis with hex-1-ene was formed.

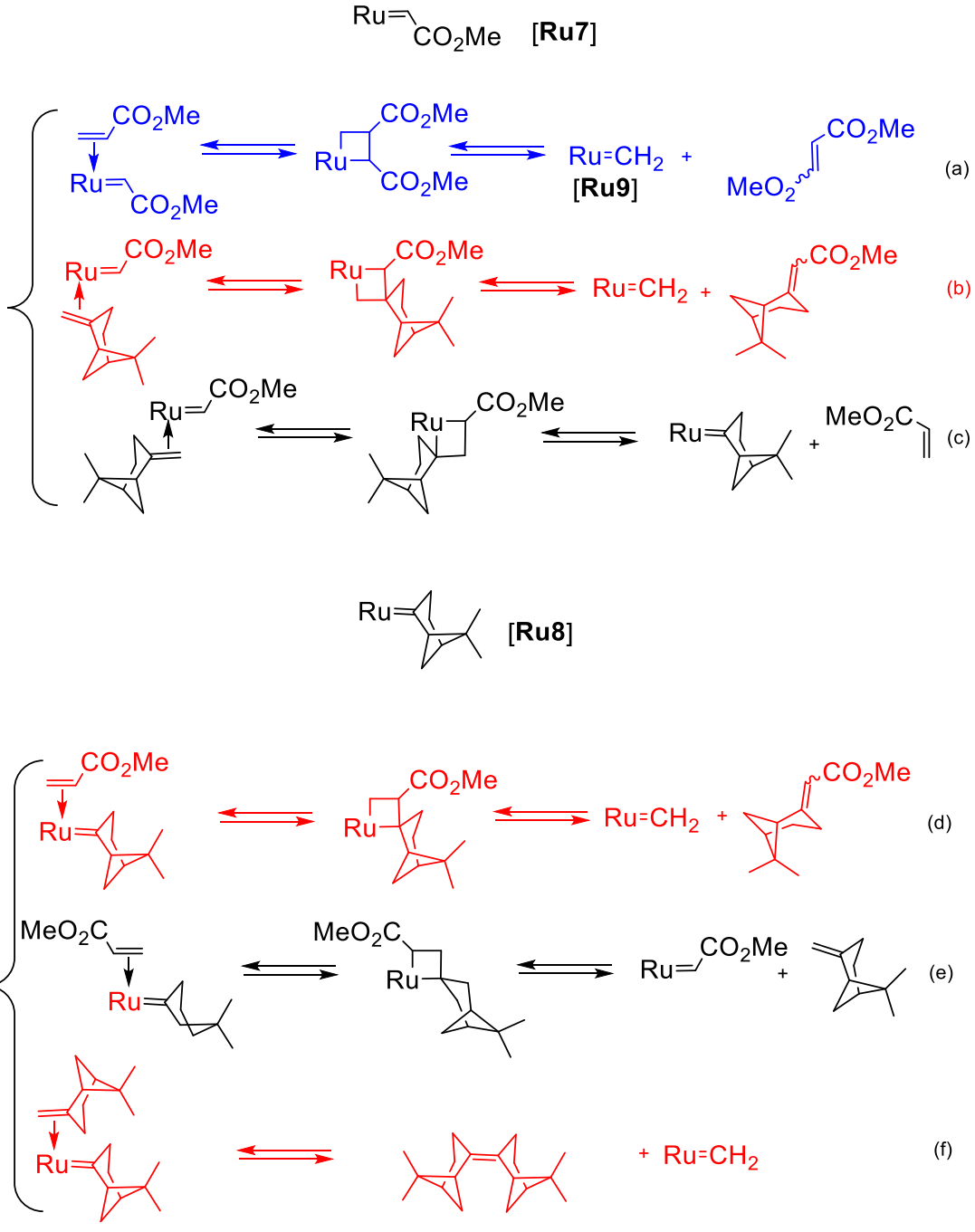
Starting from limonene **2**, a similar behavior was observed when the reaction was carried out without 1,4-benzoquinone (Table 9, entry 5).

The isolation of the obtained products was difficult due to similarity of structures and properties (polarity, boiling point) between starting materials and final products.

M. A. R. Meier, *Eur. J. Lipid Sci. Technol*. **2011**, *113*, 31. d) H. Bilel, N. Hamdi, F. Zagrouba, C. Fischmeister, C. Bruneau, *RSC Adv*. **2012**, *2*, 9584-9589.

4.1.5 Proposed mechanism for cross metathesis with acrylic derivatives

The cross metathesis of terpene **1** with methyl acrylate can formally generate two types of ruthenium carbene species: a methoxycarbonylmethylidene [**Ru7**] and a cyclohexylidene [**Ru8**] (**Scheme 20**).



Scheme 20: Catalytic steps for the cross metathesis of β-pinene 1 with methyl acrylate

[**Ru7**] is a well-known ruthenium enoic carbene intermediate that has been reported in catalytic transformations including self-metathesis of acrylates with second generation ruthenium catalysts, and described as fast initiating but unstable olefin metathesis catalyst.[111] The ruthenium moiety [**Ru8**] has been proposed as active species during the previously reported metathesis transformations of β-pinene with internal olefins [17], and proposed in predictive calculations for cross metathesis of β-pinene with (*Z*)-3-methylpent-2-ene with a second generation Grubbs catalyst.[112] [**Ru7**] can react with methyl acrylate to generate the self-metathesis products **3** + **4** (**Scheme 20**(a)), and with β-pinene, (**Scheme 20**(b)), en route to the expected cross-metathesis product, which is however not formed experimentally. Route (**Scheme 20**(c)) is a non-productive pathway but constitutes nevertheless a pathway for the formation of [**Ru8**]. [**Ru8**] can interact with methyl acrylate according to two regioselectivities. Route (**Scheme 20**(e)) is the non-productive reverse reaction of (**Scheme 20**(c)) and only route (**Scheme 20**(d)) would give the expected product and this one also does not take place experimentally.

The productive interaction of [**Ru8**] with β-pinene (**Scheme 20**(f)) would lead to the self-metathesis product but this reaction is unlikely and not observed as it was shown that the less substituted methylenecyclohexane did not give self-metathesis,[113] and more generally 1,1-disubstituted olefins were reluctant to self-metathesis with ruthenium catalysts.[114] Thus, the sole productive reaction is the self-metathesis of methyl acrylate, which leads to the formation of dimethyl fumarate and maleate (**Scheme 20**(a)).

The same carbenic species [**Ru7**] and [**Ru8**] are formed during the cross metathesis of β-pinene with dimethyl fumarate **4** and maleate **3** (**Scheme 21**).

The interaction of [**Ru7**] with maleate is responsible for the isomerization of the starting olefin into dimethyl fumarate **4** (**Scheme 21**(a)). The route described in **Scheme 21**(b) is the same as the one of **Scheme 20**(b) that is not operative using methyl acrylate.

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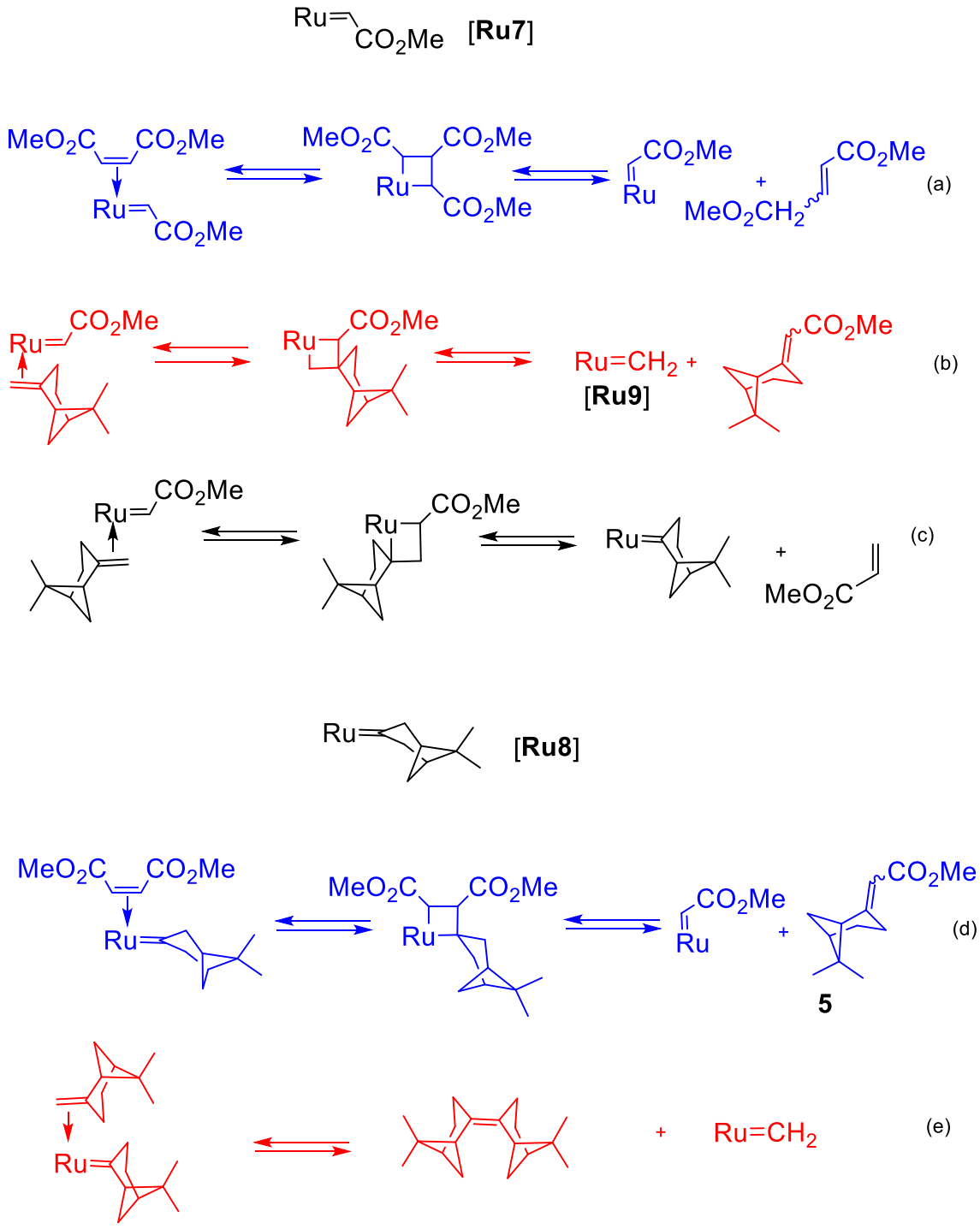
[111] Choi, T. L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417–10418.
[112] Acevedo, A.; Fomine, S.; Gutiérrez, S.; Tlenkopatchev, M.A. *J. Organomet. Chem.* **2014**, *765*, 17–22.
[113] Konzelman, J.; Wagener, K. B. *Macromolecules* **1995**, *28*, 4686–4692.
[114] Chatterjee, A. K.; Choi, T.L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.



Scheme 21: Catalytic steps for the cross metathesis of β-pinene **1** with methyl maleate **3**

In **Scheme 21**, route (c) does not lead to cross metathesis product and route (e) similar to **Scheme 20** route (f) does not take place for steric reason. Finally, from **3** or **4** only routes **Scheme 21** (b) and (d) would lead to the expected cross metathesis product **5**. It is however difficult to conclude which one is the predominant or the sole one. Route (d) represents a similar pathway as the one

proposed by A.J. Robinson for the cross metathesis of an excess of β-pinene (30 equiv.) with isoprenyl olefins[21] and M.A. Tlenkopatchev for the cross metathesis of stoichiometric amounts of β-pinene and the less hindered 3- methylpent-2-ene[112] involving ruthenium carbene species such as [**Ru8**] arising from the terpene. Even though the route described in **Scheme 20** (b) is not productive from methyl acrylate, the same pathway described in **Scheme 21** (b) involving [**Ru7**] and β-pinene might be productive from dimethyl maleate **3** or fumarate **4**. This might be the result of the competitive interaction of [**Ru7**] with acrylates *versus* β-pinene, which is much more favored with methyl acrylate (**Scheme 20**(a) vs **Scheme 20**(b)), considering steric factors and the excess of methyl acrylate hence leading preferentially to the self-metathesis products **3** and **4**.

The steric discrimination is much less important between methyl fumarate or maleate versus β-pinene as depicted in ruthenacycle formation **Scheme 21**(a) and (b)) thus making the productive formation of the cross-metathesis product feasible. It must be noted that a similar competition between self-metathesis versus cross metathesis of acrylate has previously been observed when an acrylate and a moderately hindered gem-disubstituted olefins such as 2-methylheptene or methylenecyclohexane were reacted in the presence of a second generation ruthenium catalyst.[111]

The comparison of the productive pathways in **Scheme 20** and **Scheme 21** reveals that with methyl acrylate a ruthenium methylidene [**Ru9**] is formed, which then generates ethylene to restore [**Ru7**] from methyl acrylate, and that on the other hand, Ru=CHCO$_2$Me [**Ru7**] is generated in the productive routes **Scheme 21**(a) and (d). The formation of [**Ru9**] is known to facilitate decomposition of the catalyst,[115] and the presence of ethylene has also been reported as detrimental to some metathesis reactions,[116] which might contribute to explain the absence of cross metathesis of β-pinene **1** with methyl acrylate. It is also surprising that during the reaction with methyl acrylate, the dimethyl maleate and fumarate, which are generated *in situ* are not involved in further cross metathesis with β-pinene. This observation suggests that the self-

[115] Hong, S.H.; Wenzel, A.G.; Salguero, T.T.; Day, M.W.; Grubbs, R.H. *J. Am. Chem. Soc.* **2007**, 129 7961–7968.

[116] Scholz, J.; Loekman, S.; Szesni, N.; Hieringer, W.; Görling, A.; Haumann, M.; Wasserscheid, P. *Adv. Synth. Catal.* **2011**, 353, 2701–2707.

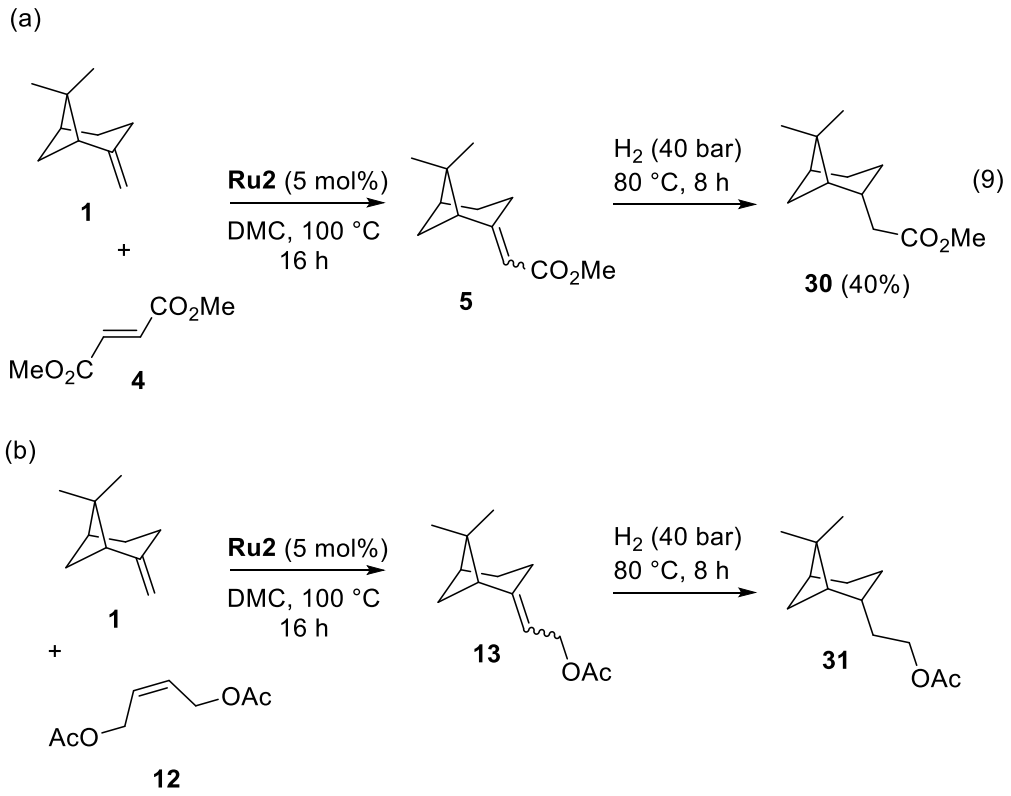
metathesis of methyl acrylate is much faster than the cross metathesis reaction with the terpene and during this transformation after full consumption of methyl acrylate the amount of active catalyst is decreased due to fast decomposition of the catalytic species at 100 °C in the presence of ethylene.

4.1.6 Sequential cross-metathesis/hydrogenation

It is now well established that the ruthenium residues resulting from olefin metathesis transformations are catalysts for subsequent hydrogenation of the formed carbon-carbon double bonds. This catalytic property, which was first used in metathesis polymerization (ROMP and ADMET)/hydrogenation processes[117] has known further developments in sequential cross metathesis/hydrogenation transformations.[118] We have shown that performing first the cross-metathesis reaction of β-pinene **1** with dimethyl fumarate **4** in the presence of 5 mol% of **Ru2** as catalyst in DMC at 100 °C for 16 h and then applying a hydrogen pressure of 40 bar at 80 °C during 8 h led to full conversion of the terpenoid **5** into the saturated ester **30** (**Scheme 22**, **Table 10**, entry 2). ^{1}H NMR analysis confirmed that the *E* and *Z* isomers **5** were quantitativelly hydrogenated into the same product **30** isolated in 40% yield (**Table 10**, entry 1). Using **Ru1** as catalyst (2.5 mol%), the reaction was also successful with a yield of 28% (**Table 10**, entry 2).

Cross metathesis followed by hydrogenation was also performed with the cross metathesis partner *cis*-1,4-diacetoxybut-2-ene **12**. The cross-metathesis was performed under the best conditions (**Table 5**, entry 15) followed by hidrogenation in DMC. In this case, the reaction time of 8 h was not sufficient for full conversion of the cross-metathesis product **13** into the saturated ester **31**, (**Table 10**, entry 3). Full conversion was observed when the hydrogenation reaction time was extended to 24 h. However, the product was isolated in only 2% yield (**Table 10**, entry 4), considering that the cross-metathesis already shows low yield (22%, **Table 5**, entry 15). ^{1}H NMR analysis confirmed that the saturated ester **31** was obtained.

[117] Dias, E.L.; Grubbs, R.H. *Organometallics*, **1998**, 17, 2758–2767.
[118] Miao, X.; Fischmeister, C.; Bruneau, C.; Dixneuf, P.H. *ChemSusChem* **2009**, 2, 542–545.



Scheme 22: Sequential cross-metathesis/hydrogenation between pinene **1** and dimethyl maleate **3** (a) and cis-1.4-diacetoxybut-2-ene **12** (b)

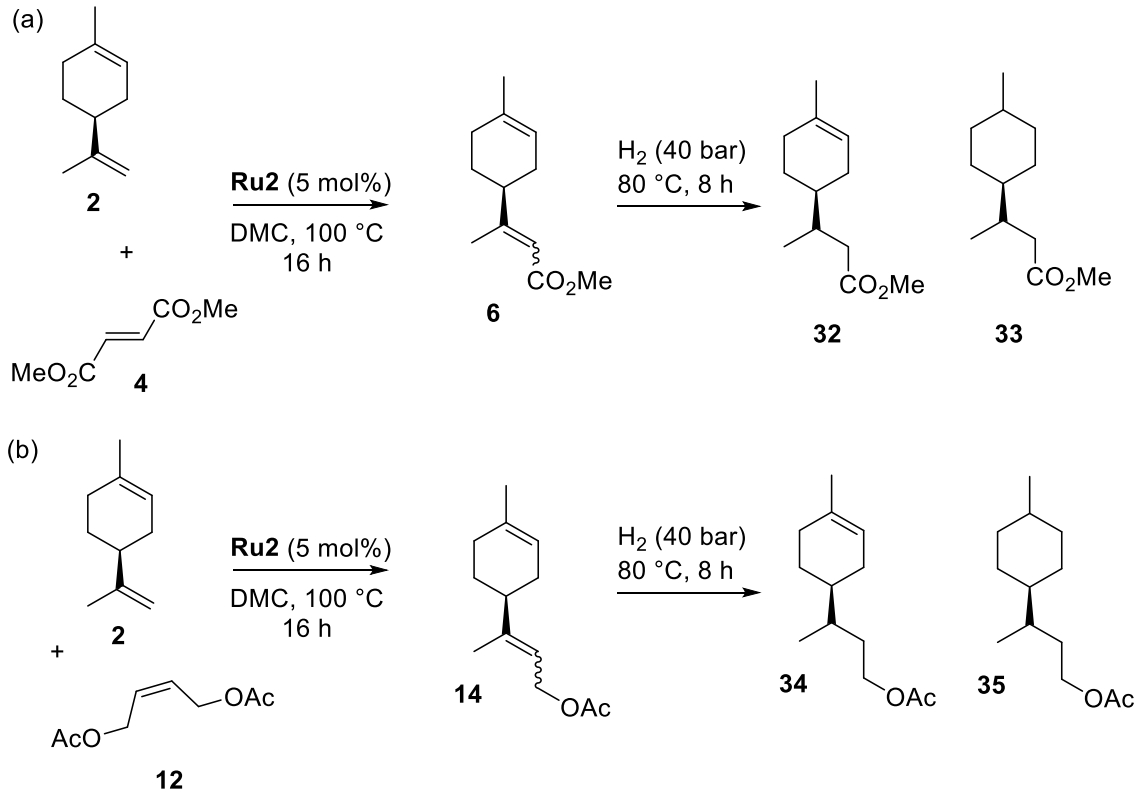
Table 10: Sequential cross-metathesis/hydrogenation between β-pinene **1** and dimethyl maleate **4** and *cis*-1.4-diacetoxybut-2-ene **12**[a]

Entry	4 or 12 (eq.)	Catalyst (mol %)	H_2 (bar)	Temp. (°C)	Reaction time (h)	Yield (%)[b]
1	(**4**) 4	**Ru2** (5)	40	80	8	40
2	(**4**) 2	**Ru1** (2.5)	40	80	8	28
3	(**12**) 2	**Ru2** (5)	40	80	8	**Reaction not complete**
4	(**12**) 2	**Ru1** (2.5)	40	80	24	2

[a] β-pinene (100 mg. 0.7 mmol. 1 eq.). dimethyl fumarate **4** (213 mg. 1.4 mmol. 2 eq.; 426 mg, 2.8 mmol, 4eq.). 1.4-*cis*-diacetoxy-2-butene **12** (234 µL. 1.4 mmol. 2 eq. or 468 µL. 2.8 mmol. 4 eq.). [**Ru1**]: 2.5 mol% (18 µmol. 13.5 mg). [**Ru2**]: 2.5 mol% (18 µmol. 11.5 mg) or 5 mol% (36 µmol. 23 mg). solvent (2 mL DMC). [b] Isolated yield (%).

When performing the sequential cross-metathesis/hydrogenation of limonene **2** with dimethyl fumarate **4** and *cis*-1,4-diacetoxybut-2-ene **12** (**Scheme 23**), we verified the possibility of hydrogenation of both the external and internal

double bond of the limonene structure, and the reaction time of 8 h proved insufficient for full hydrogenation of the product in both reactions (**Table 11**, entries 1 and 3). In the case of the reaction with dimethyl fumarate **4**, with 24 h of hydrogenation it was possible to obtain the fully saturated product **33** (**Table 11**, entry 2). In the reactions with *cis*-1,4-diacetoxybut-2-ene **12**, experimental conditions were tested in order to obtain product **34** with sole hydrogenation of the external double bond, and for this we tested conditions of lower temperature and lower H_2 pressure (**Table 11**, entries 4 and 5), but in both cases mixtures of the two products **34** and **35** were obtained. Keeping the H_2 pressure at 40 bar, temperature of 80 °C and a reaction time of 24 h, the fully saturated product **35** was obtained. ^{1}H NMR analyses confirmed the formation of the fully saturated product.



Scheme 23: Sequential cross-metathesis/hydrogenation between limonene **2** and dimethyl maleate **4** (a) and cis-1.4-diacetoxybut-2-ene **12** (b)

Table 11: Sequential cross-metathesis/hydrogenation between limonene **2** and dimethyl maleate **3** and *cis*-1.4-diacetoxybut-2-ene **12**[a]

Entry	**4** or **12** (eq.)	Catalyst (mol %)	H_2 (bar)	Temp. (°C)	Reaction time (h)	Yield (%)[b]
1	(**4**) 2	**Ru1** (2.5)	40	80	8	Reaction not completed
2	(**4**) 2	**Ru1** (2.5)	40	80	24	8
3	(**12**) 4	**Ru1** (2.5)	40	80	8	Reaction not completed
4	(**12**) 4	**Ru1** (2.5)	35	60	8	Reaction not completed
5	(**12**) 4	**Ru1** (2.5)	20	80	8	Reaction not completed
6	(**12**) 2	**Ru1** (2.5)	40	80	24	2

[a] Limonene **2** (100 mg. 0.7 mmol. 1 eq.). dimethyl fumarate **4** (213 mg. 1.4 mmol. 2 eq. or 426 mg. 2.8 mmol. 4 eq.). 1.4-*cis*-diacetoxy-2-butene **12** (234 µL. 1.4 mmol. 2 eq. or 468 µL. 2.8 mmol. 4 eq.). [**Ru1**]: 2.5 mol% (18 µmol. 13.5 mg). Solvent (2 mL DMC). [b] Isolated yield (%).

4.1.7 Conclusion

The cross metathesis of sterically demanding *gem*-disubstituted olefins with terminal functional olefins in the presence of ruthenium catalysts is known to be a challenging reaction. Based on a few observations from the literature, we have developed a strategy involving more hindered symmetrical functional internal alkenes rather than their terminal metathesis equivalents as cross metathesis partners for cross metathesis with bulky terpenes. Using Hoveyda-Grubbs type catalysts, it was thus possible to introduce ester and nitrile functional groups to β-pinene **1** and limonene **2** *via* cross metathesis with dimethyl fumarate and maleate, fumaronitrile, 1,4-diacetoxybut-2-ene, 1,4-dichlorobut-2-ene under neat conditions or in dimethyl carbonate as a green solvent without production of any byproduct. Considering the non-symmetrical 2-methylbut-2-ene, with this non-functional trisubstituted alkene, the cross metathesis with second generation ruthenium catalysts provided selectively a new trisubstituted double bond at 40 °C with high efficacy. The reaction operated better under neat conditions and led to the *E*-products with very high stereoselectivity.

This cross metathesis reaction provides a straightforward access to new bio-sourced products. Wider catalysts screening involving the most recent

ruthenium and molybdenum complexes might allow improvement of the productivity of these transformations.

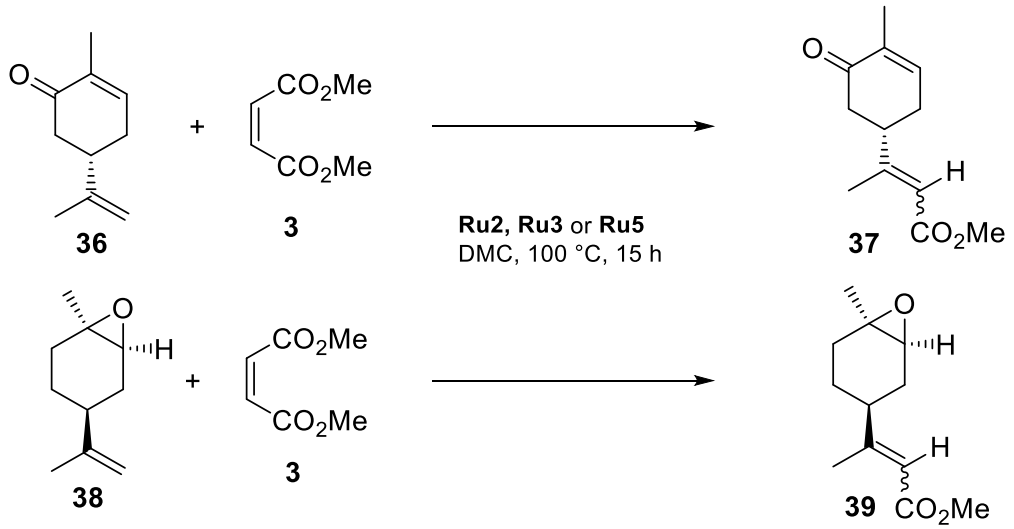
4.2 Cross-metathesis of Terpenoids

4.2.1 Objectives

With the CM method established for the reactions with terpenes **1** and **2**, we explored further reactions with some terpenoids, aiming to verify the influence of functional groups in the metathesis reactivity. We considered to use the compounds (D)-carvone **36**, (+)-*trans*-limonene epoxide **38** and carveol **46**.

4.2.2 Cross metathesis of limonene-derived terpenoids with dimethyl maleate

Having observed similar results with dimethyl maleate **3** and dimethyl fumarate **4** in the previous study, the cross metathesis of (D)-carvone **36** and (+)-*trans*-limonene epoxide **38** was studied only with dimethyl maleate **3** the reaction conditions previously established with β-pinene **1** and (-)-limonene **2**.[87] The reactions were carried out in DMC with a concentration of terpenoid of 0.74 mol/L at 100 °C for 15 h with a fourfold excess of dimethyl maleate (**Scheme 24**).



Scheme 24: Cross metathesis of (D)-carvone **36** and (+)-trans-limonene epoxide **38** with dimethyl maleate **3**.

In the reactions involving (D)-carvone **36**, due to greater availability of analytical reagent, we were able to perform a greater number of reactions in an attempt to obtain better results, especially considering that in the first group of reactions with the cross-metathesis partner **3**, initial conversions ranging from 38 to 52% were obtained whatever the catalyst and catalyst loading (**Table 12**, entries 1-4). Alternatives such as slow addition of catalyst (**Table 12**, entry 5,6) were attempted, but there was no increase in the conversion. The fast initiating catalyst Ru5 was also evaluated but without improvements (**Table 12**, entries 7,8).

Table 12: Cross metathesis of (D)-carvone **36** and (+)-*trans*-limonene epoxide **38** with dimethyl maleate **3**[a]

Entry	3 (eq.)	Catalyst (mol %)	Conc. (mol/L)	Temp. (°C)	Solvent	Conv. (%)[b]	Yield (%)[b] (%)[c]
*(D)-carvone **36***							
1	4	**Ru1** (2.5)	0.74	100	DMC	38	32 – n.d.
2	4	**Ru1** (5)	0.74	100	DMC	37	31 - 27
3	4	**Ru2** (2.5)	0.74	100	DMC	40	34 – n.d
4	4	**Ru2** (5)	0.74	100	DMC	52	49 – 37
5	4	**Ru2** (2x2.5)	0.74	100	DMC	49	45 – n.d.
6	4	**Ru2** (2.5) slow add	0.74	100	DMC	43	38 – n.d
7	4	**Ru5** (5)	0.74	100	DMC	48	43 – n.d.
8	4	**Ru5** (2x2.5)	0.74	100	DMC	48	42 - 37
(+)-*trans*-limonene epoxide **38**							
14	4	**Ru2** (5)	0.74	100	DMC	82	n.d.
15	4	**Ru5** (5)	0.74	100	DMC	74	n.d – (13).

[a] General conditions: : D-Carvone **9** (100 mg, 0.7 mmol), solvent (1 or 2 mL), 4 eq.(2.8 mmol) of **3**, reaction time: 15 h [b] Conversion and GC yield determined using tetradecane as internal standard. [c] Isolated yield n.d. – not determined

GC analysis of the crude reaction mixture (**Figure 22**) indicated that the two stereoisomers of **37** were formed in a ratio of 67:33 which was confirmed by ^{1}H NMR analysis from the integrations of the two signals of the C(4)-H protons at

2.76 and 4.43 ppm and the two –OMe signals at 3.66 and 3.69 ppm (**Figure 23**).[119] The ethylenic protons C(9)-H of the newly created ethylenic double bond in the two stereoisomers presented the same chemical shift centered at 5.70 ppm but the NOESY spectrum of the mixture showed a correlation between the ethylenic proton in the major isomer with the C(4)-H of the carvone ring centered at 2.80 ppm, whereas the C(4)-H of the minor stereoisomer centered at 4.40 ppm did not show any interaction with the C(9)-H proton (**Figure 24**). The interaction of the C(9)-H with the $C(10)H_3$ group was observed only in the minor stereoisomer at 1.87 ppm. These two observations clearly indicated that the *E*-stereoisomer was the major product. It should be noticed that the synthesis of this product mixture was reported in 3 steps and an overall yield of 28% hence highliting the interest of the reported metathesis although a modest 37% yield was obtained.[124]

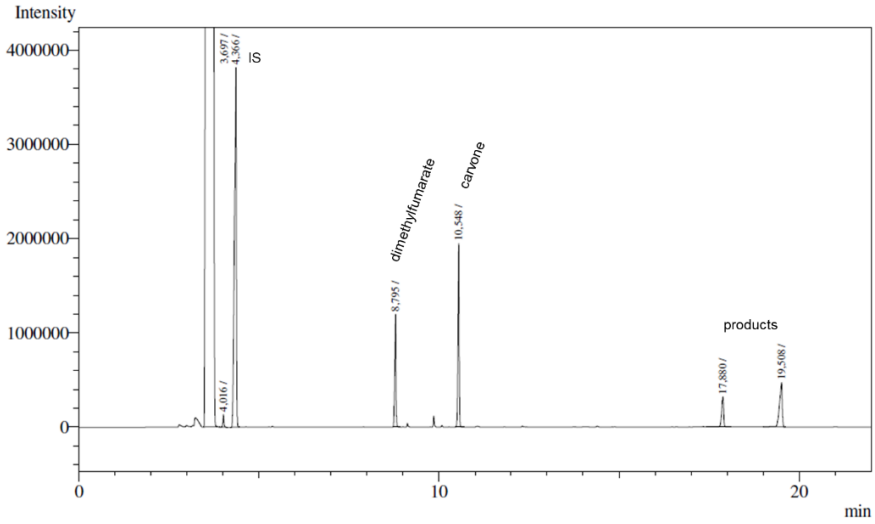


Figure 22: Chromatogram of the crude reaction mixture between (D)-carvone **36** with dimethyl maleate **3**

[119] S. Kamijo, S. Yokosaka, M. Inoue, *Tetrahedron*, **2012**, *68*, 5290-5296.

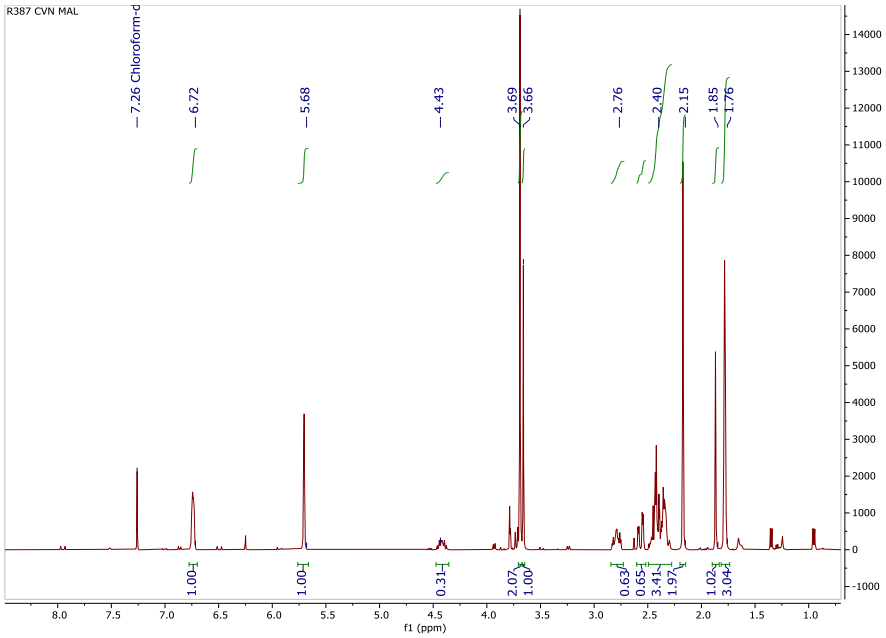


Figure 23: ^{1}H NMR spectrum of the product **37**

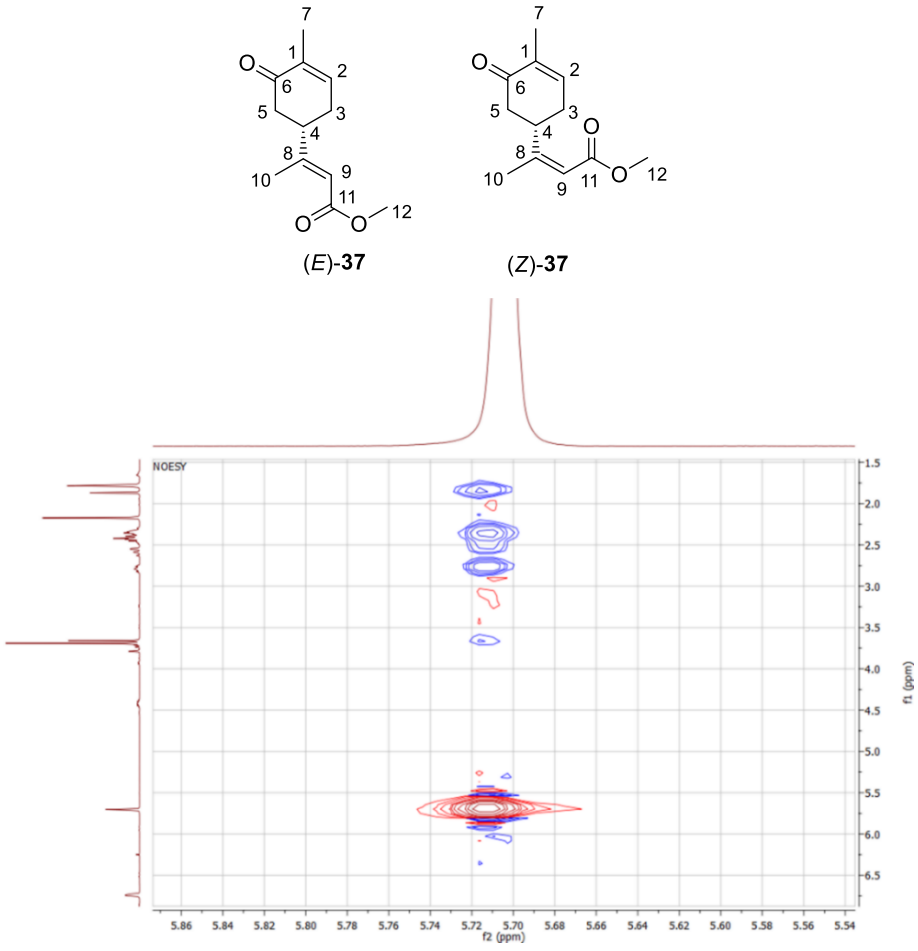


Figure 24: 2D NOESY NMR spectrum of the product **37**

From (+)-*trans*-limonene epoxide **38**, **Ru2** and **Ru5** led to conversions of 82 and 74%, respectively, into **39** (**Table 12**, entries 14-15). The two cross metathesis stereoisomers were produced in a ratio of 65:35 as shown by GC analysis of the crude mixture (**Figure 25**). NOESY experiments showed that in the major isomer, the acrylic C(9)-H proton (at 5.65 ppm) was correlated with protons at C(3), C(4) and C(5), whereas in the minor isomer, the ethylenic proton at C(9) (5.61 ppm) was correlated with the methyl protons at C(10) (1.77 ppm) only (**Figure 26**). The cross-metathesis led therefore preferentially to the formation of the *E*-isomer. Unfortunatly, due to difficult purification, **39** was isolated in a low 13% yield.

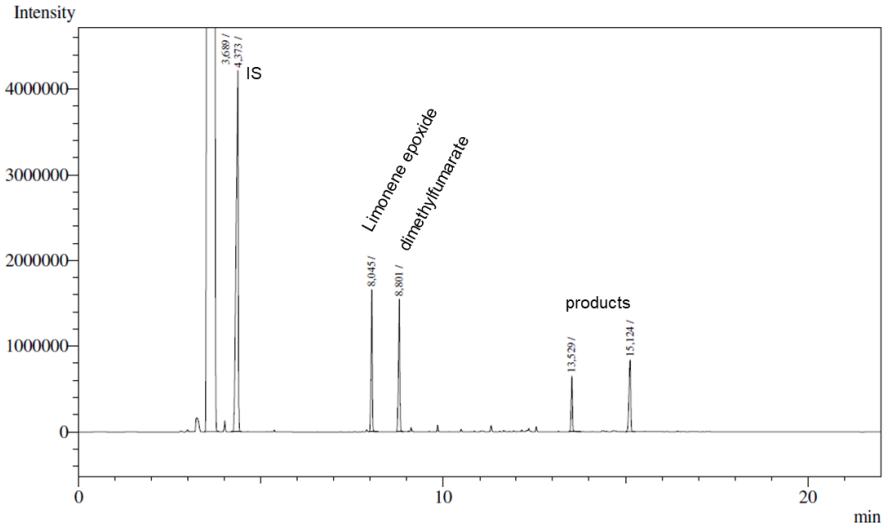


Figure 25: Chromatogram of the crude reaction mixture between (+)-trans-limonene epoxide **38** with dimethyl maleate **3**

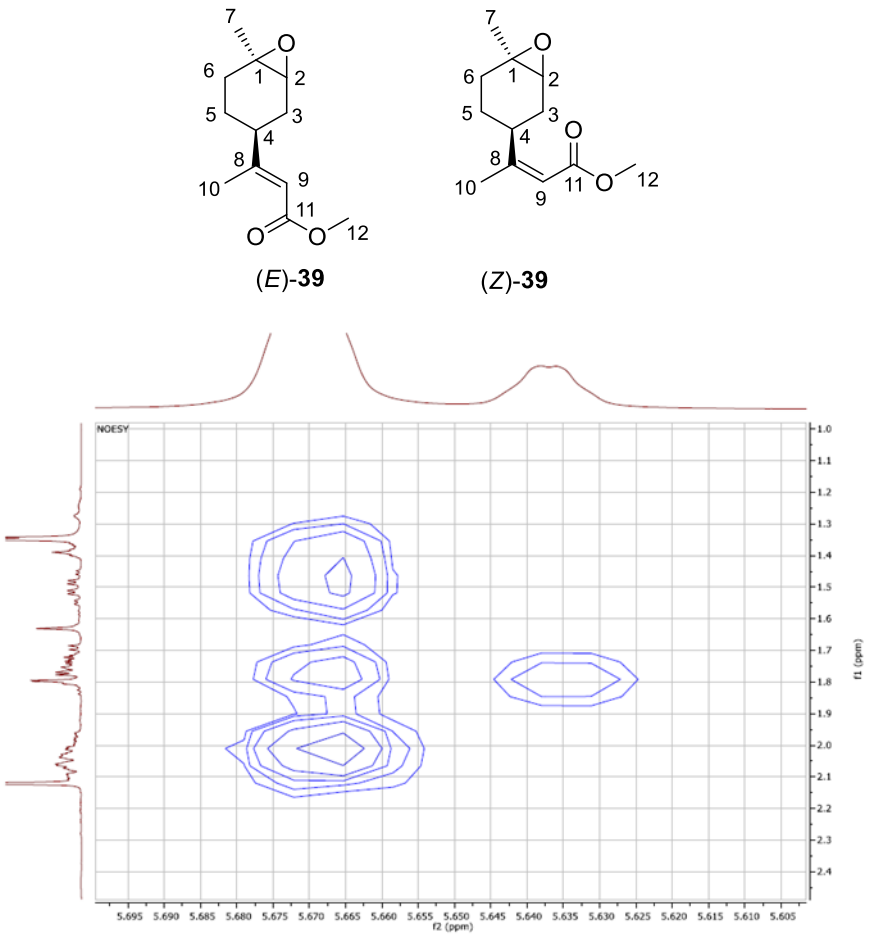
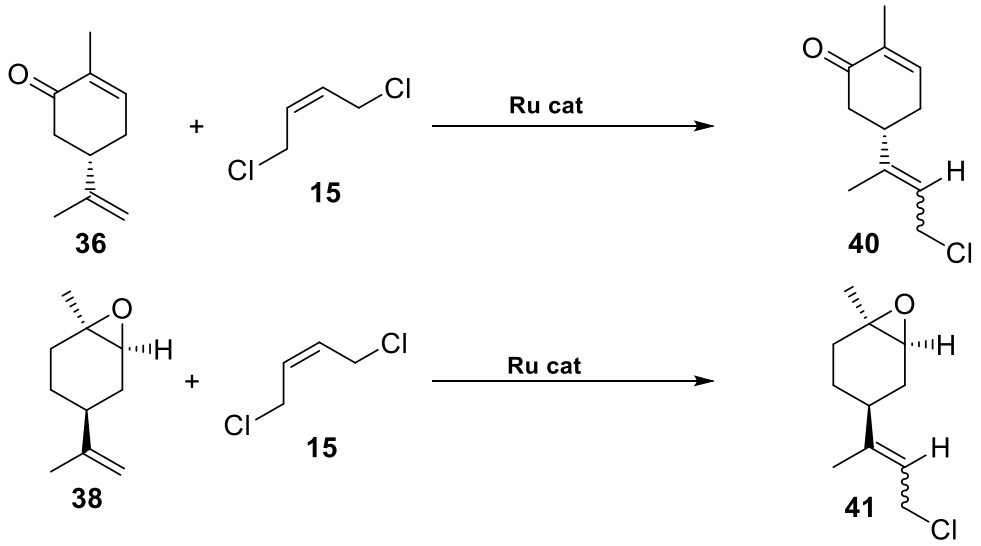


Figure 26: 2D NOESY NMR spectrum of the product **39**

4.2.3 Cross metathesis of limonene-derived terpenoids with *cis*-1,4-dichlorobut-2-ene 15 and *cis*-1,4-diacetoxybut-2-ene 12

The cross metathesis of (D)-carvone **36** and (+)-*trans* limonene epoxide **38** with *cis*-1,4-dichlorobut-2-ene **15** (**Scheme 25**) was investigated and led to similar results as those obtained with limonene since it was possible to reach 52 and 68% conversion, respectively, in DMC at 50 °C in the presence of 2.5 mol% of **Ru2** (**Table 13**, entries 1 and 3). Here again, the purification of the final products proved to be very difficult by column chromatography, where partial decomposition was observed, maybe due to the presence of a chloro group in allylic position. Despite these difficulties, samples of the new terpenoids derivatives **40** and **41** could be isolated in 12 and 15% yield, respectively.



Scheme 25: Cross metathesis of (D)-carvone **36**, and (+)-trans-limonene epoxide **38** with cis 1,4 dichlorobut-2-ene **15**

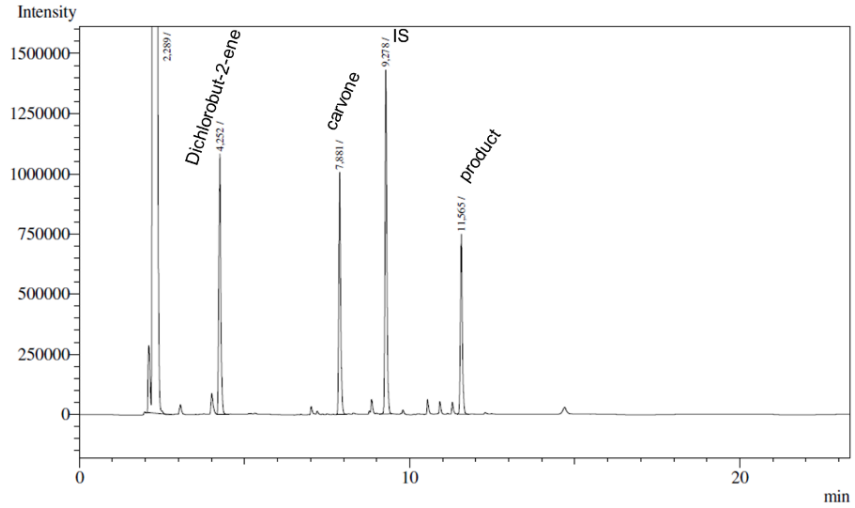
Table 13: Cross metathesis of limonene derivatives with cis 1,4-dichlorobut-2-ene **15**[a]

Entry	Catalyst (mol%)	15/36, or 15/38 molar ratio	Solvent	Conversion (%)	Yield (%)
(D)-carvone **36**					
1	**Ru2** (2.5)	4	DMC	52	37 (12)[c]
2	**Ru2** (5.0)	13	neat	39	-
(+)-*trans*-limonene epoxide **38**					
3	**Ru2** (2.5)	4	DMC	68	(15)[c]
4	**Ru5** (2.5)	4	DMC	64	-

[a] General conditions: terpenoid (100 mg, 0.7 mmol), 1,4-dichlorobut-2-ene **15** (2.8 mmol in DMC, 9.1 mmol for neat), DMC (1 mL), 50 °C, 15 h, conversion and yield were determined by GC using tetraadecane or hexadecane as internal standard. [b] first portion (15 h), second portion (8 h). [c] Isolated yield in parenthesis.

In both cases, the GC analysis of the crude reaction mixture displayed only one peak for the formed products (**Figure 27**).

(a)



(b)

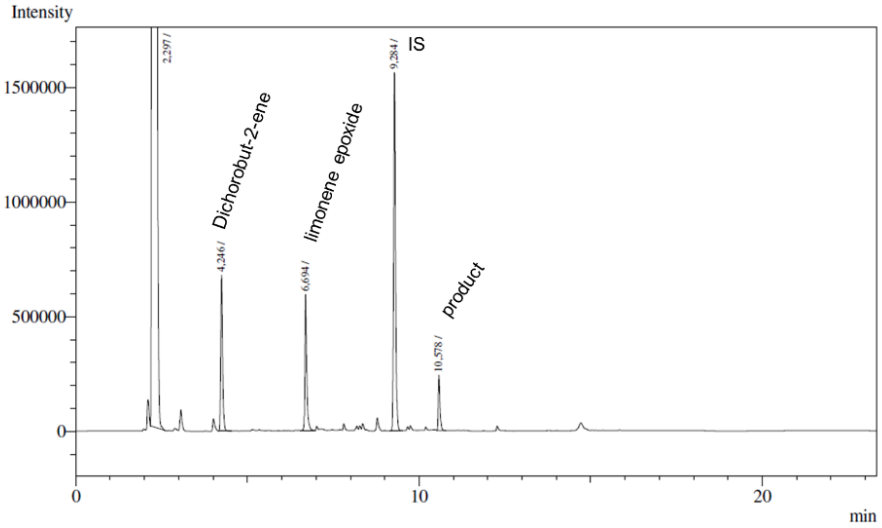


Figure 27: Chromatogram of the crude reaction mixture between (D)-carvone **36** with cis-1,4-dichlorobut-2-ene **15** (a) and (+)-*trans*-limonene epoxide **38** with *cis*-1,4-dichlorobut-2-ene **15** (b)

NOESY NMR allowed to identity the *E* stereoisomer for **40** as an interaction between CH_2 ((11), 4.10 ppm) and CH_3 ((10), 1.74 ppm) was observed whereas no interaction could be observed between H((9), 5.50) and CH_3(10) (**Figure 28**). Compound **41** was also obtained as a single stereoisomer and the NOESY spectrum evidenced the formation of the E-isomer due to the interaction between the CH_3 ((10), 1.76 ppm) and CH_2 ((11), 4.08 ppm) whereas no interaction between this CH_3 and H(9) could be detected (**Figure 29**).

(a)

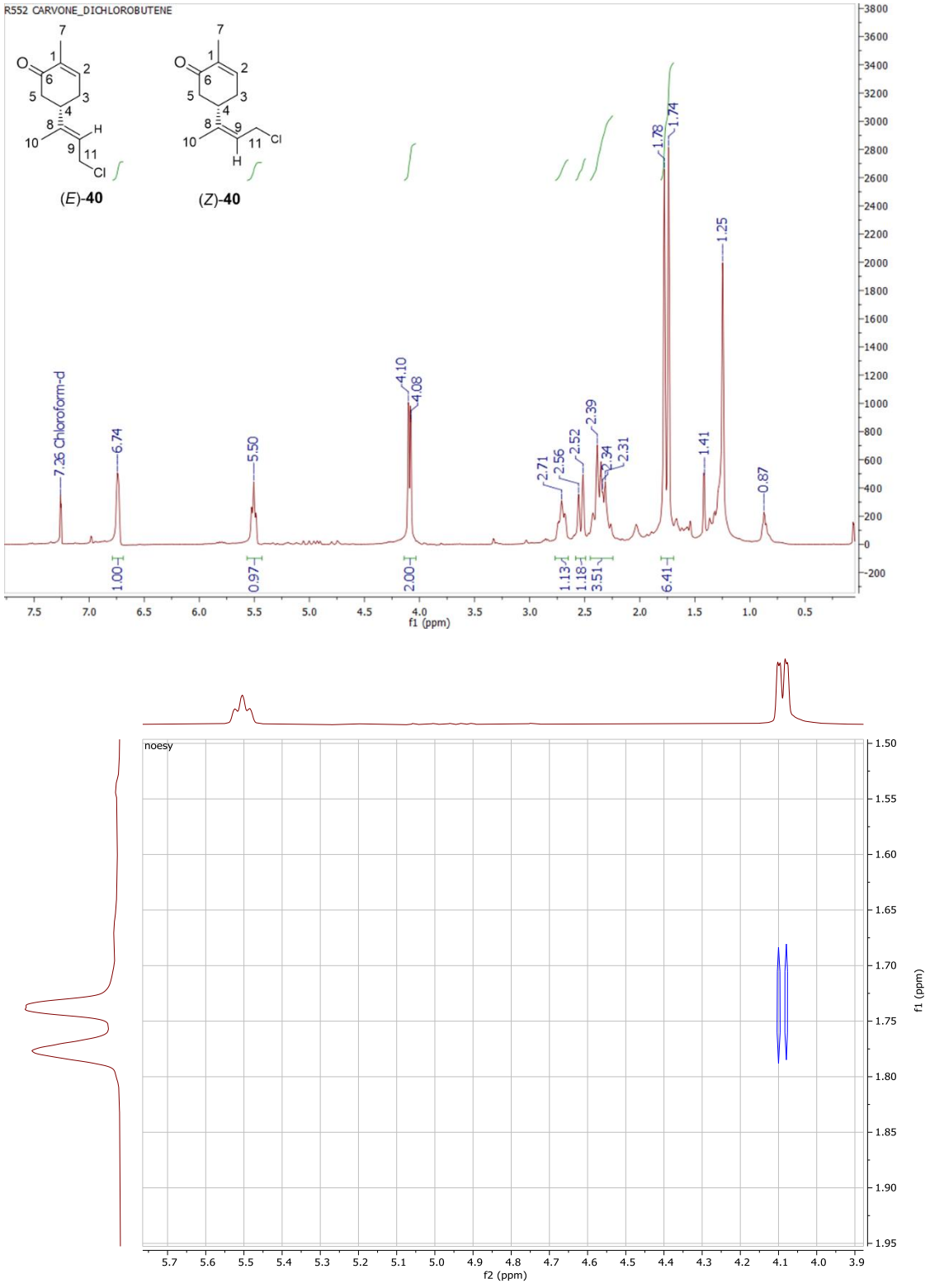


Figure 28: ^{1}H NMR (a) and NOESY (b)spectrum of the product **40**

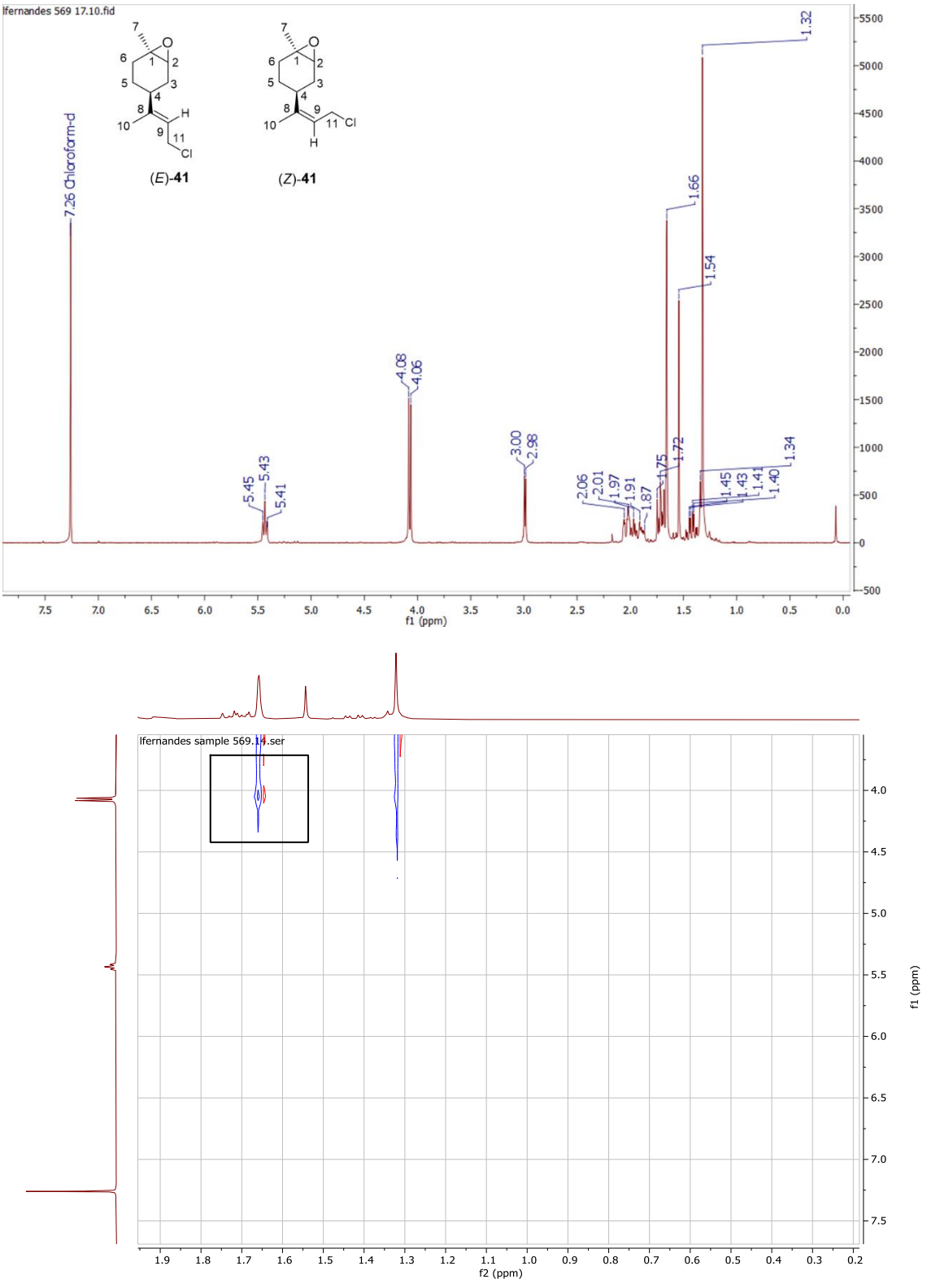
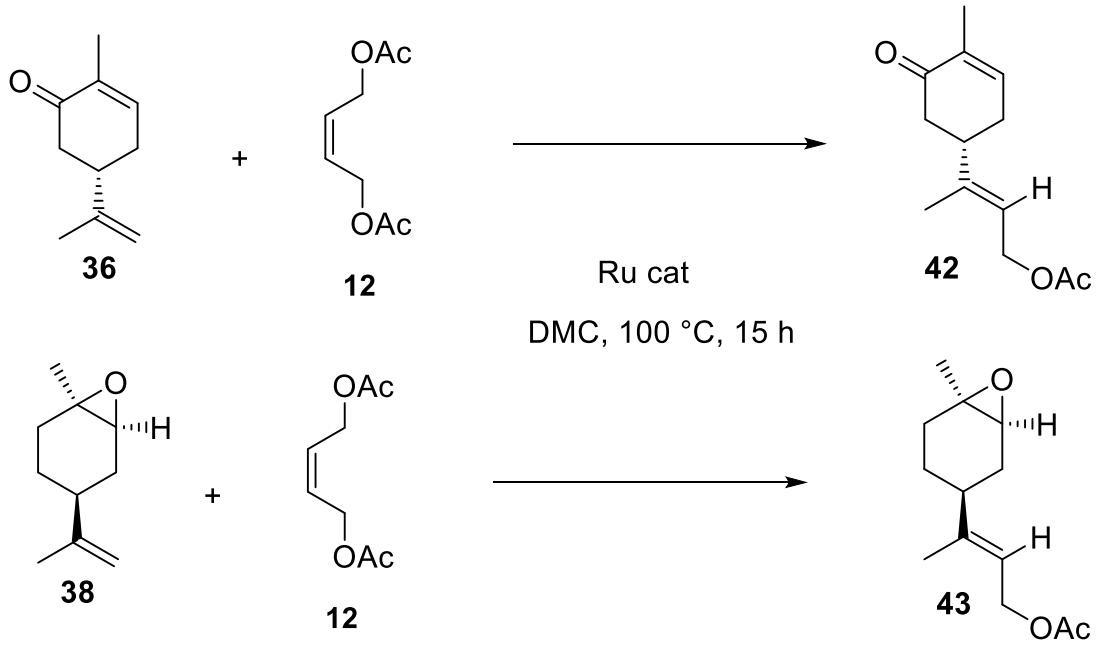


Figure 29: ^{1}H and NOESY spectra of **41**

The reactions with *cis*-1,4-diacetoxybut-2-ene **12 (Scheme 26)** followed the same behavior as the other reactions of this compound with the other

substrates, with low conversion performance in (D)-carvone reactions, achieving maximum conversion of 23% when it was used under neat conditions (**Table 14,** entry 2). The efficacy of the reaction was a little better with (+)-*trans*-limonene epoxide **38** for which a conversion of 59% was reached.



Scheme 26: Cross metathesis of (D)-carvone **36**, and (+)-*trans*-limonene epoxide **38** with *cis*-1,4 diacetoxybut-2-ene **12**

Table 14: Cross metathesis of limonene derivatives with *cis*-1,4-diacetoxybut-2-ene **12**[a]

Entry	**12/36** or **12/38** **(eq.)**	**Catalyst (mol %)**	**Conc. (mol/L)**	**Temp. (°C)**	**Solvent**	**Conv. (%)**[b]	**Yield (%)**[b] **(%)**[c]
*(D)-carvone **36***							
1	4	**Ru2** (5)	0.74	100	DMC	9	4 – n.d
2	8.5	**Ru2** (5)	0.74	100	neat	23	20 –n.d.
(+)-*trans* limonene epoxide ***38***							
3	4	**Ru5** (5)	0.74	100	DMC	56	5 – n.d.
4	4	**Ru2** (5)	0.74	100	DMC	59	6 – n.d.

[a] General conditions: : D-Carvone **36** (100 mg, 0.7 mmol), solvent (1 or 2 mL), 4 eq.(2.8 mmol) of **12**, time reaction: 15 h [b] Conversion and GC yield determined using tetradecane as internal standard. [c] Isolated yield n.d. – not determined

For both substrates, the GC analysis indicate the appearance of only one new peak, probably corresponding to a new product alone or with isomers. The GC/MS analysis did not show the molecular ions at 222 u and 224 u for 42 (**Figure 30**) and 43 (**Figure 31**), respectively. However, several characteristic fragments were detected in both cases. M-HOAc = 162 for **42** and 164 for **43**. For (+)-*trans* limonene epoxide reactions, it can be observed that conversion values are much higher than the GC yields (**Table 14**, entries 3 and 4). Considering the chromatographic analysis of the reaction mixture and the presence of only one peak corresponding to the formation of a new product, this may indicate that some undetected reaction byproducts are being formed. The isolation of the new products was not attempted.

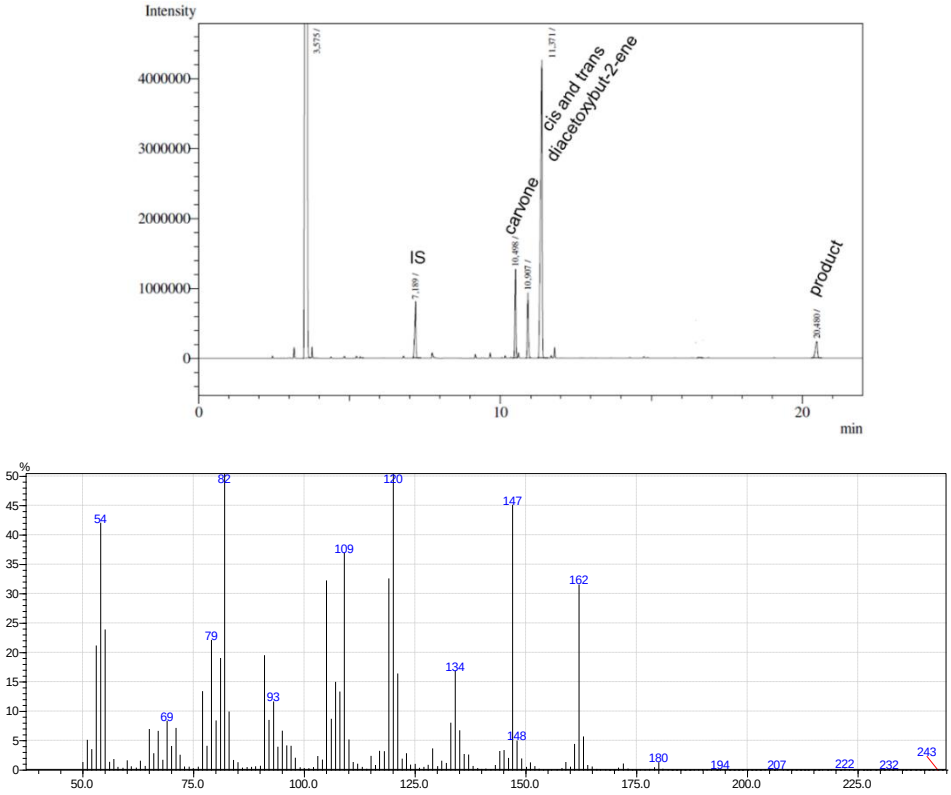


Figure 30: GC/MS chromatogram of the desired product from reaction between *cis*-1,4 diacetoxybut-2-ene **12** with (D)-carvone **36**.

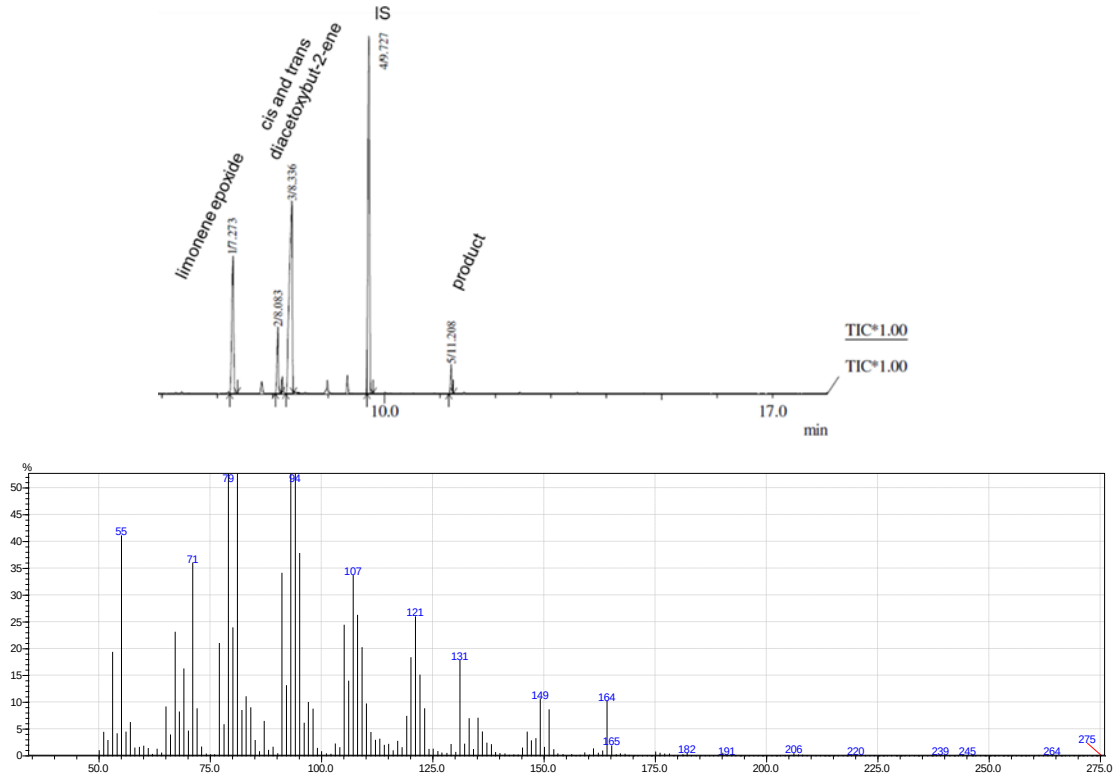
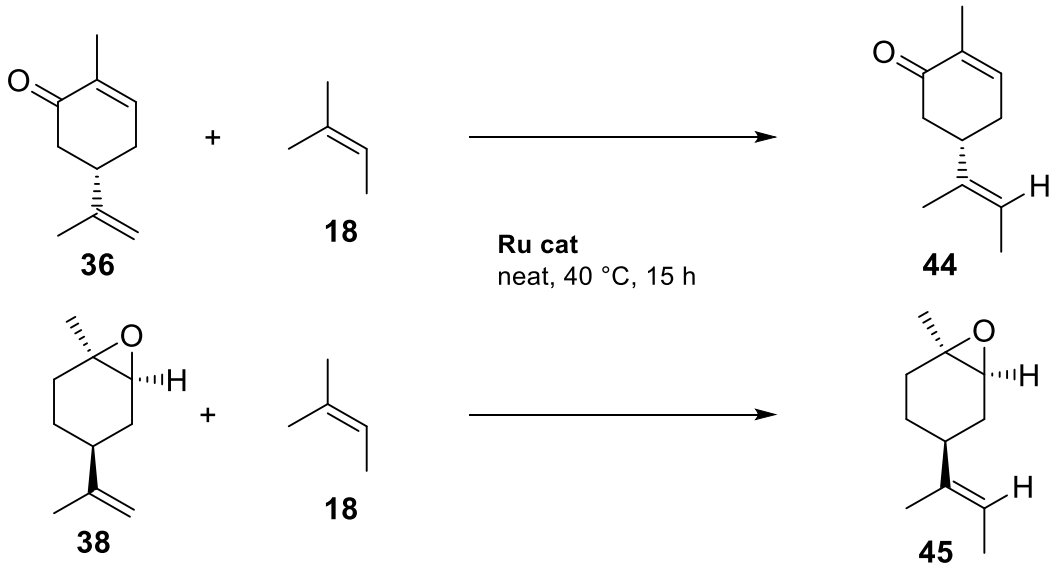


Figure 31: GC/MS chromatogram of the desired product from reaction between cis-1,4 diacetoxybut-2-ene 12 with (+)-trans-limonene epoxide 38

4.2.4 Cross metathesis of limonene-derived terpenoids with 2-methylbut-2-ene 18

As was observed with the terpenes **1** and **2**, the cross metathesis of the terpenoids **36** and **38** with 2-methylbut-2-ene **18** (**Scheme 27**) were most efficiently achieved under neat conditions with the Hoveyda catalyst **Ru2** at 40 °C (

Table 15) and led selectively to trisubstituted olefins. The addition of the catalyst in two portions was beneficial with both substrates to reach full conversion. It can be noted that **Ru1** showed similar catalytic activity as **Ru2,** but **Ru5** appeared to be less efficient (Table 15, entry 7).



Scheme 27: Cross metathesis of (D)-carvone **36** and (+)-*trans*-limonene epoxide **38** with 2-methylbut-2-ene **18**

Table 15: Cross metathesis of (D)-carvone **36** and (+)-*trans*-limonene epoxide **38** with 2-methylbut-2-ene **18**[a]

Entry	**18/36** or **18/38** (eq.)	Catalyst (mol%)	Solvent	Conversion (%)	Yield (%)
(D)-carvone **36**					
1	4	**Ru2** (2.5)	DMC	82	75
2	4	**Ru1** (2.5)	DMC	68	61
3	13	**Ru2** (5)	Neat	92	86
4	13	**Ru2** (2.5 + 1)[b]	Neat	98	95 (73)[c]
5	13	**Ru1** (2x2.5)[b]	Neat	96	91 (58)[c]
(+)-*trans*-limonene epoxide **38**					
6	13	**Ru2** (2x2.5)[b]	Neat	99	89 (34)[c]
7	13	**Ru5** (2x2.5)[b]	Neat	49	40

[a] General conditions: : D-Carvone **36** (100 mg, 0.7 mmol), solvent (1 or 2 mL), 4 eq.(2.8 mmol), 15 h, 40 °C, conversion and GC yield determined using tetradecane as internal standard. [b] first portion 15 h, second portion 8 h [c] Isolated yield

The *E/Z* ratio for **44** and **45** were about 93:7 as determined by GC of the crude reaction mixture (**Figure 32**). In the ^{1}H NMR of the mixture of inseparable *Z*- and *E*-stereoisomers of **44**, only C(4) exhibited a well separated distinct chemical shift. The major isomer signal was in the range 2.55-2.68, whereas the

minor isomer was in the range 3.15-3.38, both of them as multiplets with the same shape (**Figure 33**).

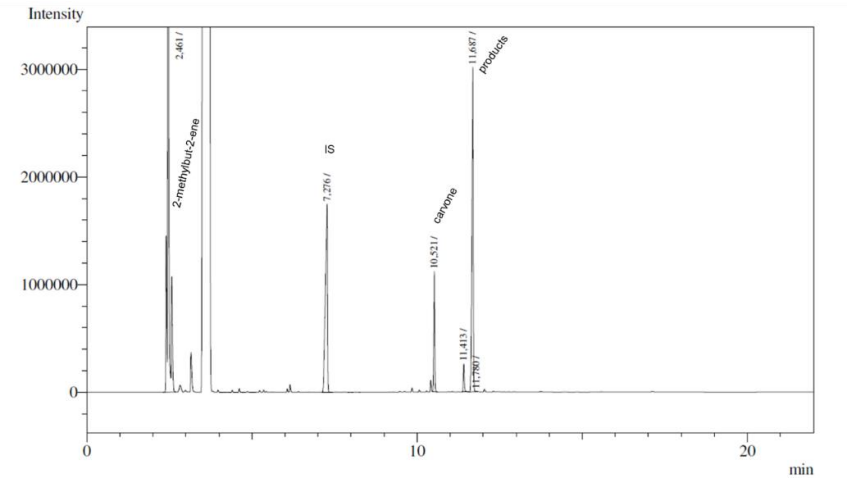


Figure 32: Chromatogram of the crude reaction mixture between (D)-carvone **36** with 2-methylbut-2-ene **18.**

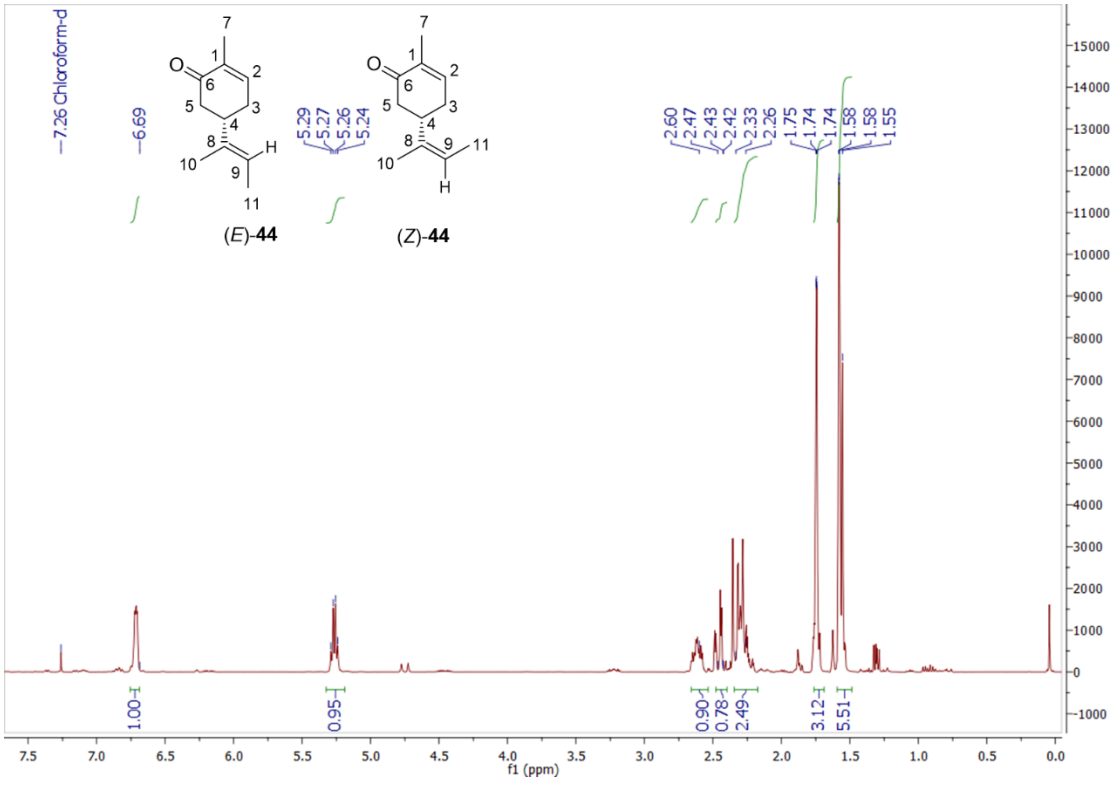


Figure 33: ^{1}H NMR spectrum of the product **44**

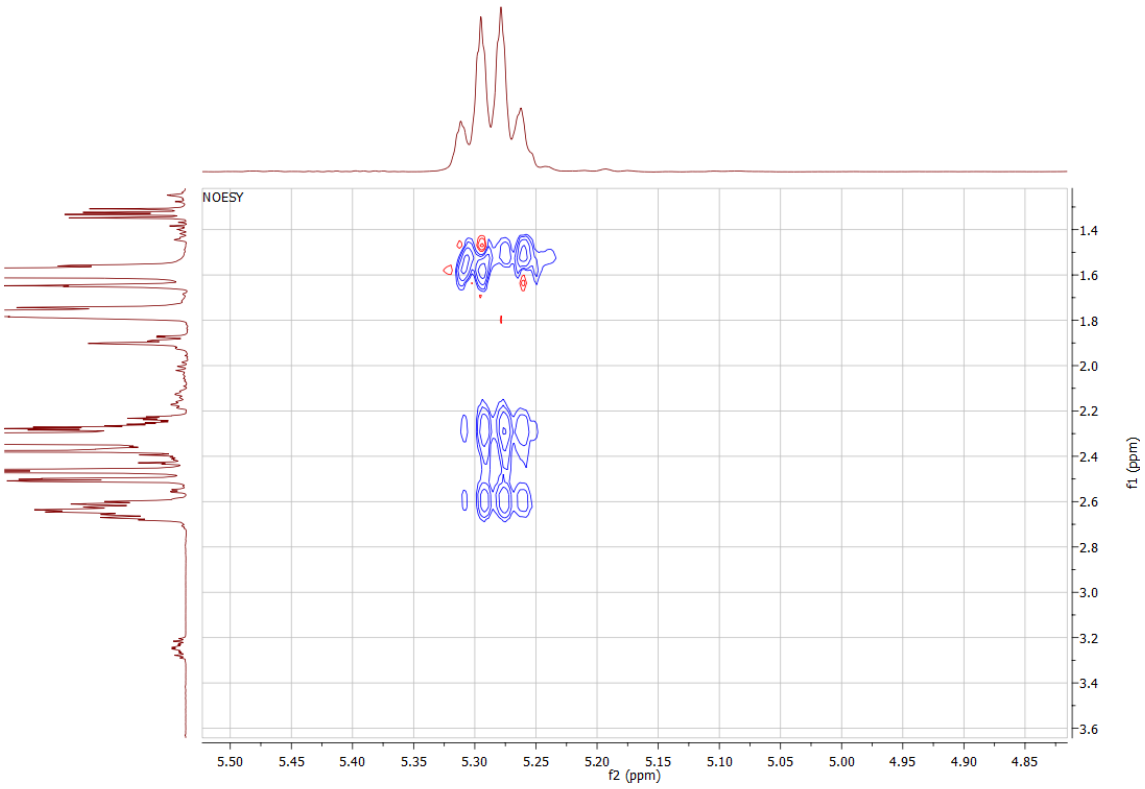


Figure 34: 2D NOESY NMR spectrum of the product **44**

The NOESY experiments showed no interaction between the ethylenic C(9)-H proton (quadruplet at 5.26 ppm) and the C(4)-H centered at 3.25 ppm, whereas it was observed with the other isomer with a signal centered at 2.60 ppm, confirming the *E*-stereochemistry of the major product (**Figure 34**).

For the (+)-*trans*-limonene epoxide **38**, the best result was obtained at 40 °C under neat conditions with **Ru2** added in two portions corresponding to 2.5 mol% each (**Table 13**, entry 6). A conversion of 99% was obtained and product **45** was isolated in 34% yield. The GC analysis of the crude mixture of the reaction performed with **Ru2** showed a unique peak hence only one stereoisomer is produced (**Figure 35**). **Ru5** in this case was much less active leading to only 49% conversion under the same conditions (**Table 13**, entry 7).

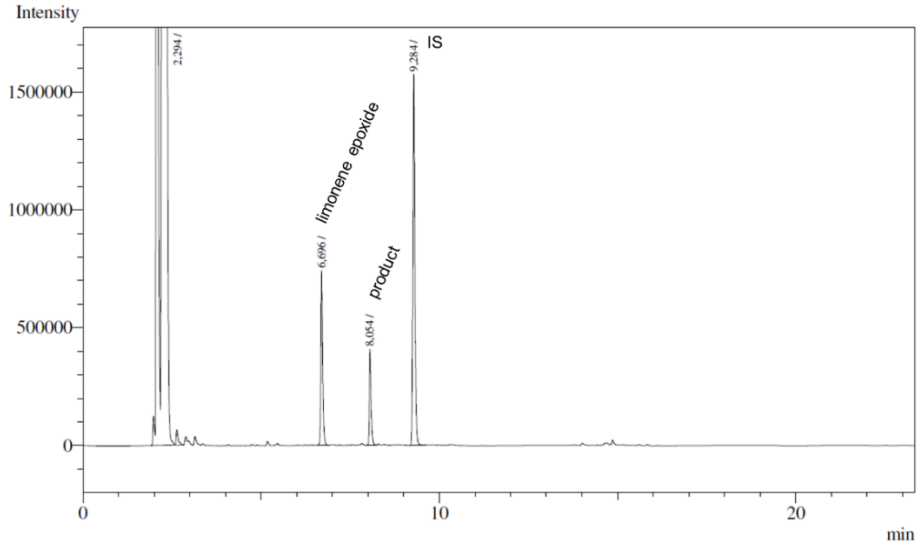


Figure 35: Chromatogram of the crude reaction mixture between (+)-*trans*-limonene epoxide **38** with 2-methylbut-2-ene **18**

The proton NMR showed the presence of only one major product and it was not possible to identify specific signals of the minor stereoisomer (**Figure 36**). However, the NOESY spectrum indicated an interaction of the ethylenic C(9)-H proton (quadruplet at 5.19 ppm) with the C(11)H_3 methyl group (doublet at 1.54 ppm) but none with the C(10)-H_3 methyl group appearing as a singlet at 1.52 ppm, revealing the *E*-configuration of the olefin in this product (**Figure 37**).

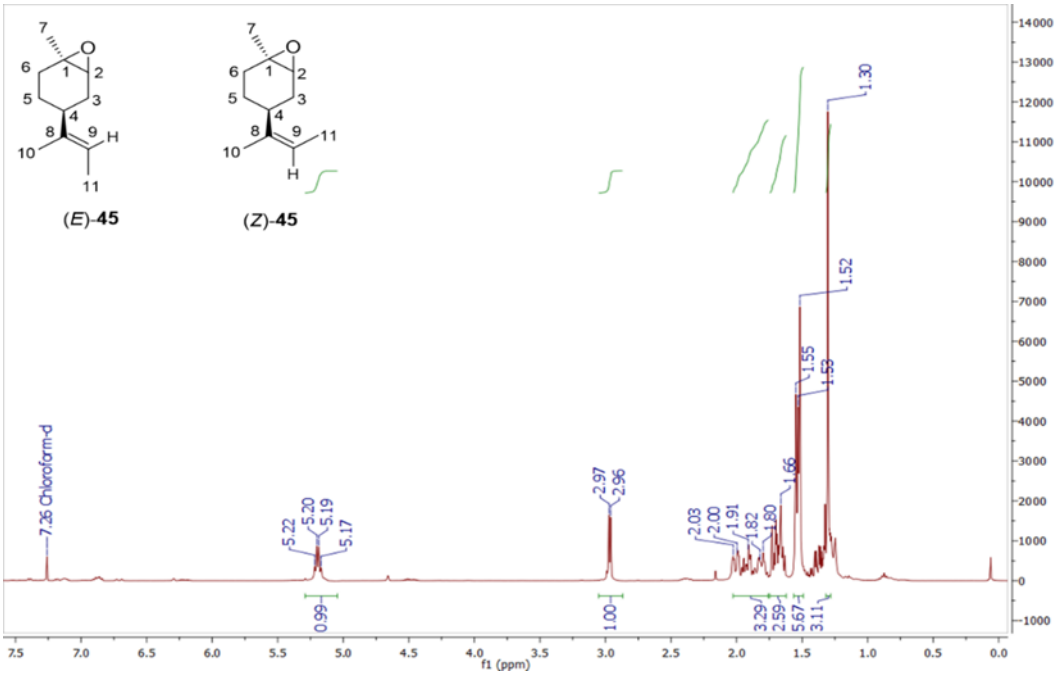


Figure 36: 1H NMR spectrum of the product **45**

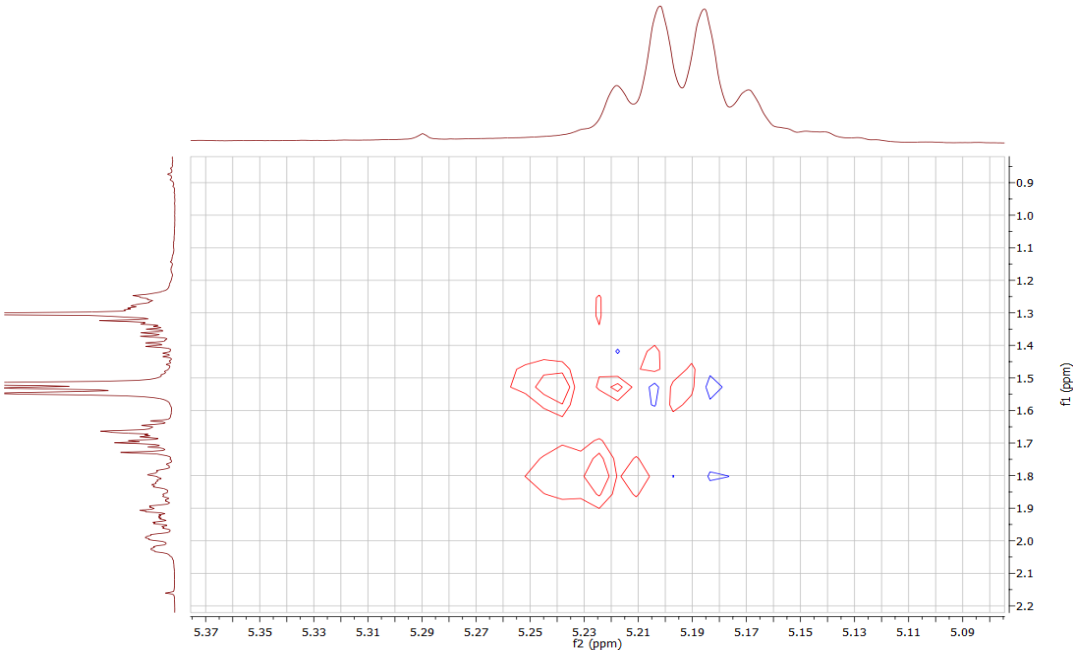
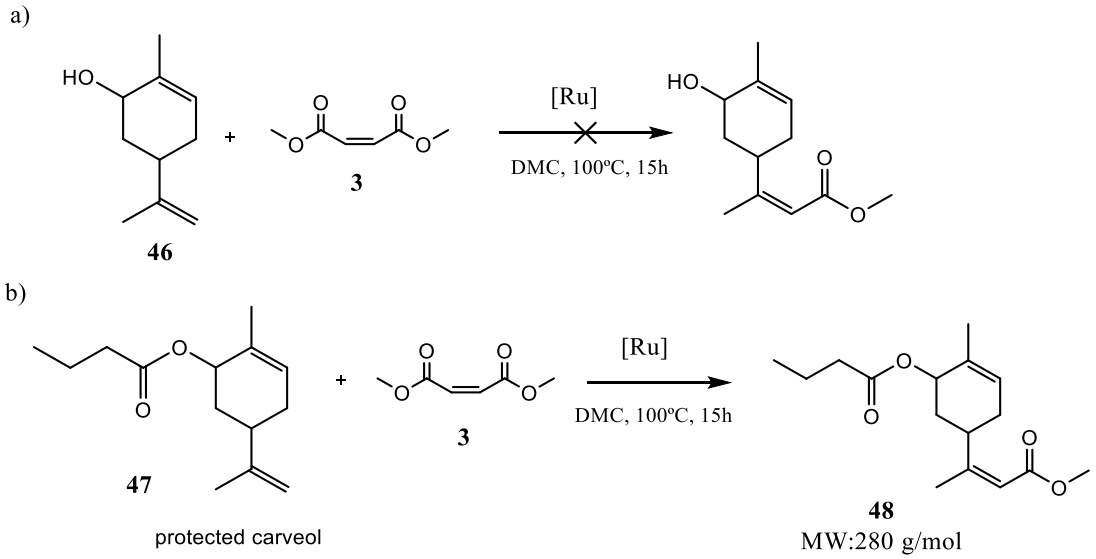


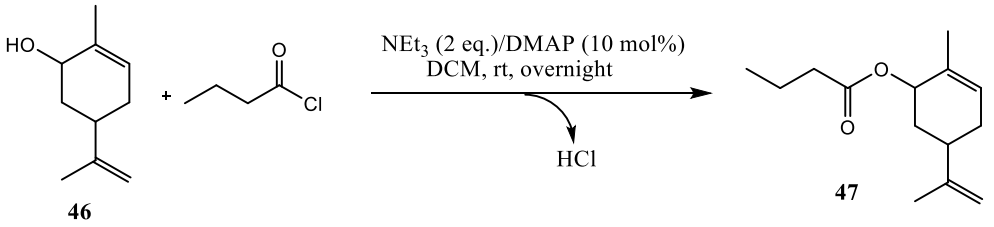
Figure 37: 2D NOESY NMR spectrum of the product **45**

4.2.5 Cross-metathesis of carveol

Carveol is a terpenoid bearing an hydroxy group which is used in cosmetics and food industry. We first attempted the cross-metathesis of carveol **46** with dimethylmaleate **3** (5 mol% **Ru2,** 0.74 mol/L, 100°C, 15h)(**Scheme 28**(a)). Gas chromatography monitoring of this reactions did not reveal any conversion of carveol nor the formation of new peaks referring to reaction products. In this case, the possibility of catalyst poisoning by the hydroxyl group was considered and adopted an alternative route involving protection of this hydroxy group as an ester (**Scheme 29**). The cross metathesis of the protected alcohol **47** with dimethyl maleate then resulted in a conversion of 48% and the formation of the desired product that was identified by the presence of characteristic fragments in the GC/MS spectrum of the reaction mixture (M-CH_3OH = 248; M-$C_3H_7CO_2H$ = 192); **Scheme 28**(b) and **Figure 38**). Due to lack of time, the product was not isolated. It is however established that with this class of terpenoids, additional protection strategies of the functional group and later deprotection are necessary, which needs to be evaluated with more caution.



Scheme 28: Cross-metathesis reactions of carveol **46** with dimethyl maleate **3** (a) and protected carveol **47** with dimethyl maleate **3** (b).



Scheme 29: OH protection of carveol

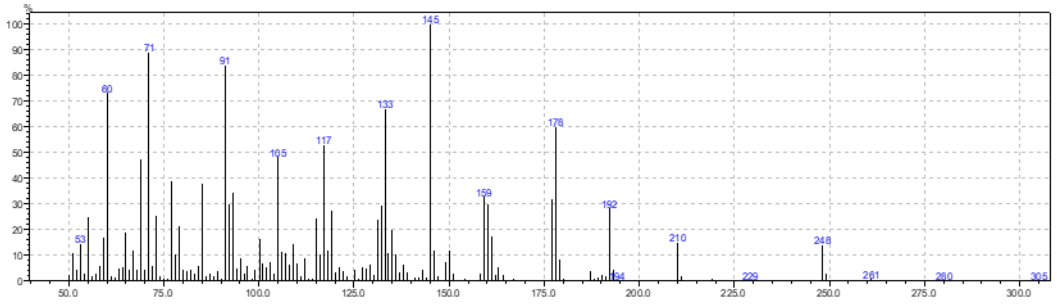


Figure 38: m/z spectrum of the cross metathesis product from protected carveol **47** and dimethyl maleate **3**

4.2.6 Conclusion

The strategy developed for cross metathesis of the sterically hindered β-pinene and (-)-limonene with symmetrical internal olefins such as fumarate, maleate or fumaronitrile has been extended to the terpenoid compounds (D)-carvone, (+)-*trans*-limonene epoxide and carveol**.** The introduction of oxygenated functionalities such as a ketone or an epoxide in (D)-carvone and (+)-*trans*-limonene epoxide did not inhibit the cross metathesis with any of the cross metathesis partners and the reactivities followed the general rule found for terpenes. The situation is different with hydroxyl group which needs to be protected. For all the metathesis reactions that were investigated, the second generation Hoveyda type catalysts **Ru1**, **Ru2** and **Ru5** that are robust and commercially available, exhibited relatively similar reactivities demonstrating the feasibility of these difficult cross metathesis with bulky substrates. The most striking result concerns the utilization of “bulky” internal olefins for the the transformation of bulky terpenes. This counterintuitive situation is the result of complex competitive metathesis reactions where non-productive metathesis pathways are favoured when terminal olefin containing cross-metathesis partners are used. Almost all the cross metathesis products synthesized are new compounds and should be evaluated for valuable properties.

5 GENERAL CONCLUSION

The transformations of terpenes by olefin metathesis is an elegant strategy to access in a single catalytic step a variety of new compounds of potential interest for fragrance and food industry. This route has already been developped with numerous terpenes including acyclic terpenes containing a trisubstituted carbon-carbon double bond such as citronelol, and citronelal. During this PhD research work we have investigated the transformation of cyclic terpenes incorporating a *gem*-disubstituted carbon-carbon double bond such as ß-pinene and limonene. When the cross-metathesis transformations of these compounds was attempted with acrylates such as methyl acrylate, only the self-metathesis product of methyl acrylate was detected. We have developed a strategy involving more hindered symmetrical functional internal alkenes rather than their terminal equivalents as cross metathesis partners for cross metathesis with bulky terpenes. The success of this strategy is based on the balance between productive and non-productive pathways, the latter being privileged when acrylic derivatives are used. We have thus performed the cross metathesis of ß-pinene and limonene with dimethyl maleate, diethyfumarate, fumaronitrile, *cis*-1,4-diacetoxybut-2-ene and *cis*-1,4-dichlorobut-2-ene. Several ruthenium-based second generation catalysts have been evaluated and the Hoveyda catalysts led in general to the best results. All reactions were conducted in dimethyl carbonate, an environmentally friendly and safe solvent or under neat conditions. The results obtained clearly show that the reaction is substrate dependant and required optimization with every single reagent. For instance, the fractional or continuous addition of catalyst proved beneficial only in some cases.

Unsymmetrical olefin partners have also been employed. With methyl-crotonate, the two possible products bearing either an ester or methyl group were obtained. In contrast, when 2-methyl-2-butene was used, the reaction was regioselective leading to the formation of a trisubstituted olefin rather than the tetrasubsituted olefin.

Thanks to the experience gained in the first part, the metathesis transformation was extended to terpenoids containing polar functional groups such as (D)-carvone and (+)-*trans*-limonene. In all cases, the transformations

were less efficient than those involving ß-pinene and limonene but interesting new compounds could be prepared albeit in low yields.

Overall, a number of new products have been synthesised and characterised. The configuration of the newly created carbon-carbon double bond was systematically determined using a set of 1D and 2D NMR experiments which demonstrated that the *E*-olefin was always the major isomer formed. Most products could be isolated but sometimes in very low yield due to the concomitant moderate efficiency of the catalytic reaction and difficult purification.

The efficiency of olefin metathesis for the selective transformation of terpenes offers straightforward and green processes for the access to value-added products from biosourced substrates extracted from renewables. However, future improvements of the catalytic performances will be necessary in some cases. This could be achieved thanks to further optimization of the reaction conditions or use of other metathesis catalysts. Wider catalysts screening involving the most recent ruthenium and molybdenum complexes might allow improvement of the productivity of these transformations.

6 EXPERIMENTAL

6.1 General information

All reactions were carried out with exclusion of air using Schlenk tube techniques.

The reactions were monitored on a Shimadzu 2014 gas chromatograph equipped with a flame ionization detector (GC-FID) and with a 30 m x 0.25 mm x 0.25 µm Equity TM – 1 Fused Silica capillary column using hexadecane or tetradecane as an internal standard. The working conditions were: $°T_{injector}$ = 250 °C, $°T_{detector}$ =280 °C, Column heating program: 80 °C (2 min), 80-250 °C (15 °C/min), 250 °C (10 min). Gas chromatographic analyses coupled to the mass spectrometer (CG-MS) were performed on a Shimadzu QP2010SE, under the following conditions: $°T_{injector}$ = 250 °C, $°T_{detector}$ =250 °C, Column heating program: 50°C (2.3 min), 50-120 °C (50°C/min), 120 °C (4 min) 120-230 °C (100 °C/min), 230 °C (10 min))

The conversion and yield values were calculated using equations 1 and 2, respectively:

$$\textbf{Conversion (\%)} = \frac{\text{mmol initial substrate} - \text{mmol final substrate}}{\text{mmol initial substrate}} \times 100 \qquad \textbf{(1)}$$

$$\textbf{Yield (\%)} = \frac{\text{mmol product}}{\text{mmol theoretical amount of product}} \times 100 \qquad \textbf{(2)}$$

Pure products were obtained by column chromatography on silica gel (Merck Silica Gel 60) using mixtures of heptane and ethyl acetate as the eluent. The chromatographic controls were carried out on aluminium plates covered with silica, revealed by UV fluorescence or by application of a developer such as $KMnO_4$ then dried with a hot air gun.

Elemental analysis data were obtained on a microanalysor (Microanalyseur Flash EA1112 CHNS/OThermo Electron). Products were further analyzed by GC-MS on a Shimadzu QP2010S apparatus.

NMR spectra were recorded at room temperature on a Bruker Avance III 400 MHz spectrometer.

Chemical shifts are expressed in ppm relative to tetramethylsilane using the residual signal of the deuterated solvent as reference. Coupling constants (J) are provided in Hertz. The solvent used was $CDCl_3$ (7.26 ppm for ^{1}H and 77.2 ppm for ^{13}C). The indexation of signals in ^{1}H and ^{13}C NMR were based on COSY, HSQC and HMBC sequences and NOESY (800 ms mixing time) for structure determination. The abbreviations used are as follows: (s) singlet. (d) doublet, (t) triplet, (q) quadruplet, (tq) tripet of quadruplet, (bs) broad singlet and (m) multiplet.

All solvents used are pre-distilled and stored on a pre-activated 3A molecular sieve under an inert argon atmosphere. Commercial reagents have not been further purified.

Monoterpenes and terpenoids were ordered from Sigma Aldrich and have not been further purified: (-)-β-pinene (99%), (S)-(-)-limonene (96%), (D)-carvone (≥96%), (+)-*trans*-Limonene 1,2-epoxide (analytical standard), L-carveol (mixture of cis and trans isomers, ≥95%).

6.2 Experimental procedures

6.2.1 General procedure for cross metathesis reactions

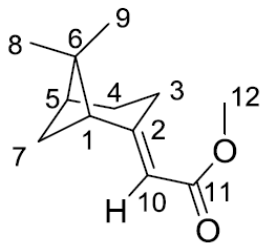
A Schlenk flask containing a magnetic stirrer was loaded with the catalyst (2.5 or 5 mol% of **Ru1** or **Ru2**), closed with a rubber septum and the system was subjected to a vacuum / argon cycle three times. The solvent (when necessary), 50 µl of internal standard (170 µmol of hexadecane or 192 µmol tetradecane), the amount of the cross metathesis reagent (between 2 eq. and 4 eq.) was added with a syringe, and finally the substrate (1 eq., 0.7 mmol). The rubber septum was replaced with a screw cap and the reaction system was heated to the temperature indicated for each type of reaction over a period of 15 hours (overnight). After cooling to room temperature, aliquots were collected for chromatographic and ^{1}H NMR analysis. When appropriate, after concentration under reduced pressure (rotavapor), the crude content was purified on a silica (or alumina) gel chromatographic column for isolation of the product.

6.2.2 General Procedure for Tandem Cross-metathesis of Limonene or β-pinene /Hydrogenation to saturated compounds:

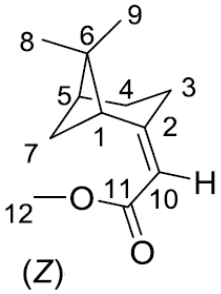
0.7 mmol of unsaturated terpene (1 eq. of **1** or **2**, 100 mg) and the cross-metathesis partner (between 2 eq. and 4 eq. of **3**-**5)** were dissolved under argon in 2 mL of distilled DMC (with internal standard) in dried Schlenk tube and the catalyst (2.5 or 5 mol% of [Ru]-1 or [Ru]-2) was then added. The reaction mixture was heated at 100 ˚C for 15 h (overnight). The crude reaction solution from the cross-metathesis step containing the residual ruthenium was transferred into an autoclave and the reactor was pressurized with 40 bar of H_2. The reaction was stirred at 80 ˚C for the indicated amount of time. After cooling to room temperature and careful release of the pressure, aliquots were collected for chromatographic and ^{1}H NMR analysis. When appropriate, after concentration under reduced pressure (rotavapor), the crude content was purified on a silica gel chromatographic column for isolation of the product.

6.3 Product synthesis and characterization

- **β-pinene/dimethyl maleate cross metathesis product 5**



(*E*)



(*Z*)

In a Schlenk tube under argon, 100 mg (0.7 mmol) of β-pinene and 426 mg of dimethyl fumarate (2.8 mmol) were dissolved in 1 mL of distilled dimethyl carbonate (with hexadecane as internal standard), Hoveyda II catalyst **Ru2** (0.037 mmol, 23 mg, 5 mol%) was then added and the reaction mixture was stirred at 100 °C for 15 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by column chromatography on silica gel (1.5 cm x 12 cm) using a mixture of heptane/ethyl acetate (98:2) as eluent to give 81 mg of **5** as colorless oil (57% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:

Major (*E*) isomer: 0.71 (s, 3H, C(9)H_3); 1.23 (s, 3H, C(8)H_3); 1.34 (d, ^{1}J= 12 Hz, 1H, C(7a)H*H*); 1.79-2.06 (m, 3H, C(5)H + C(4)H2); 2.28-2.39 (m, 1H, C(7s)H*H*); 2.46 (t, ^{3}J= 4 Hz, 1H, C(1)H); 2.57-2.72 (m, 1H, C(3a)H*H*); 3.24 (ddt, ^{2}J= 18 Hz, ^{3}J= 8 Hz, ^{3}J= 2 Hz, 1H, C(3s)H*H*); 3.63 (s, 3H, C(12)H_3); 5.44-5.48 (m, 1H, C(10)H).

Minor (*Z*) isomer: 0.70 (s, 3H, C(9)H_3); 1.29 (s, 3H, C(8)H_3); 1.40 (d, ^{2}J= 12 Hz, 1H, C(7a)H*H*); 1.79-2.06 (m, 3H, C(5)H + C(4)H_2); 2.21 (dt, ^{2}J= 18 Hz, ^{3}J= 4 Hz, 1H, C(3s)H*H*); 2.28-2.39 (m, 1H, C(7s)H*H*); 2.57-2.72 (m, 1H, C(3a)H*H*); 3.60 (s, 3H, C(12)H_3); 3.94 (t, ^{3}J= 6 Hz, 1H, C(1)H); 5.60 (d, ^{4}J= 4 Hz, 1H, C(10)H).

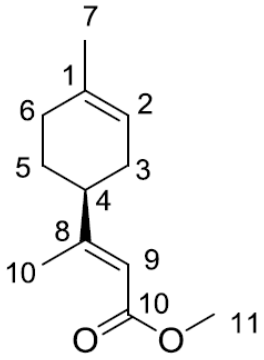
^{13}C NMR (75.5 MHz, $CDCl_3$) δppm:

(*E*) isomer: 22.1 (C(9)); 22.5 (C(3)); 23.7 (C(4)); 26.1 (C(8)); 27.3 (C(7)); 40.5 (C(5)); 40.9 (C(6)); 50.6 (C(12)); 53.8(C(1)); 112.2 (C(10)); 167.0 (C(2)); 169.3 (C(11)).

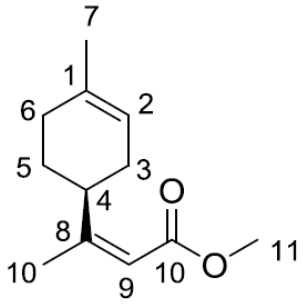
(*Z*) isomer: 21.8 (C(9)), 23.8 (C(4)); 25.6 (C(7)); 26.3 (C(8)); 26.4 (C(3)); 40.4 (C(5)); 41.7 (C(6)); 46.8 (C(1)); 50.6 (C(12)); 112.6 (C(10)); 167.1 (C(2)); 168.1 (C(11)).

GC/MS: Calculated for $C_{12}H_{18}O_2$: 194, found: 194

- **(-)-limonene/dimethyl maleate cross metathesis product 6**



(*E*)



(*Z*)

In a Schlenk tube under argon, 100 mg (0.7 mmol) of limonene and 426 mg of dimethyl fumarate (2.8 mmol) were dissolved in 2 mL of distilled dimethyl carbonate (with hexadecane as internal standard), Hoveyda II catalyst **Ru2** (0.037 mmol, 23 mg, 5 mol%) was then added and the reaction mixture was stirred at 100 °C for 15 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by column chromatography on silica gel (1.5 cm x 12 cm) using a mixture of heptane/ethyl acetate (98:2) as eluent to give 33 mg of **6** as colorless oil (23% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm

Major (*E*) isomer: 1.47-1.62 (m, 1H, C(5)H*H*); 1.65 (broad s, 3H, C(7)H_3); 1.73-1.80 (m, 1H, C(5)H*H*); 1.88-2.14 (m, 4H, C(6)H_2, C(3)H_2); 2.15 (d, 3H ^4J= 4 Hz, C(10)H_3); 2.17-2.26 (m, 1H, C(4)*H*); 3.68 (s, 3H, C(12)H_3); 5.39 (broad s, 1H, C(2)H); 5.67-5.70 (m, 1H, C(9)H).

Major (*Z*) isomer: 1.47-1.62 (m, 1H, C(5)H*H*); 1.65 (broad s, 3H, C(7)H_3); 1.73-1.80 (m, 1H, C(5)H*H*); 1.81 (d, 3H ^4J= 4 Hz, C(10)H_3); 1.88-2.14 (m, 4H, C(6)H_2, C(3)H_2); 2.17-2.26 (m, 1H, C(4)*H*); 3.66 (s, 3H, C(12)H_3); 5.39 (broad s, 1H, C(2)H); 5.62-5.65 (m, 1H, C(9)H).

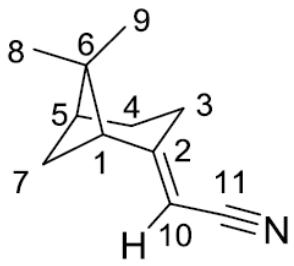
13C NMR (75.5 MHz, $CDCl_3$) δ ppm:

(*E*) isomer: 17.3 (C(10)); 23.5 (C(7)); 27.4 (C(5)); 30.4 (C(3) and C(6)); 44.4 (C(4)); 50.9 (C(12)); 114.0 (C(9)); 120.1 (C(2)); 134.0 (C(1)); 164.5 (C(8)); 167.7 (C(11)).

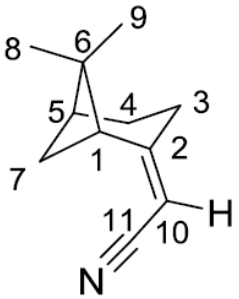
(*Z*) isomer: 20.7 (C(10)); 23.7(C(7)); 27.4 (C(5)); 30.4 (C(3) and C(6)); 44.4 (C(4)); 50.9 (C(12)); 115.7 (C(9)); 120.4 (C(2)); 133.9 (C(1)); 164.7 (C(8)); 166.7 (C(11)).

GC/MS: Calculated for $C_{12}H_{18}O_2$: 194, found: 194

- **β-pinene/fumaronitrile cross metathesis product 8**



(*E*)



(*Z*)

In a Schlenk tube under argon, 100 mg (0.7 mmol) of β-pinene and 218 mg of fumaronitrile (2.8 mmol) were dissolved in 2 mL of distilled dimethyl carbonate (with hexadecane as internal standard), Zhan-1B catalyst **Ru2** (0.018 mmol, 13.5 mg, 2.5 mol%) was then added and the reaction mixture was stirred at 100 °C for 15 h. A sample of the reaction mixture was taken and analyzed by gas

chromatography. The product was purified by column chromatography on silica gel (1.5 cm x 12 cm) using a mixture of heptane/ ethyl acetate (98:2) as eluent to give 16 mg of **8** as colorless oil (14% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:

Major (*E*) isomer: 0.73 (s, 3H, C(9)H_3); 1.28 (s, 3H, C(8)H_3); 1.43 (t, ^{2}J= 12 Hz, 1H, C(7a)H*H*); 1.84-2.04 (m, 2H, C(4)H_2); 2.05-2.13 (m, 1H, C(5)H); 2.32-2.49 (m, 2H, C(3s)H*H*, C(7s)H*H*); 2.58 (t, ^{3}J= 5 Hz, 1 H, C(1)H); 2.61-2.82 (m, 1H, C(3a)H*H*); 4.95 (m, 1H, C(10)H).

Minor (*Z*) isomer: 0.75 (s, 3H, C(9)H_3); 1.33 (s, 3H, C(8)H_3; 1.43 (t, ^{2}J= 12 Hz, 1H, C(7a)H*H*); 1.84-2.04 (m, 2H, C(4)H_2); 2.05-2.13 (m, 1H, C(5)H); 2.32-2.49 (m, 2H, C(3s)H*H*), C(7s)H*H*); 2.61-2.82 (m, 1H, C(3a)H*H*); 3.14 (t, ^{3}J= 4 Hz 1H, C(1)H); 5.04 (m, 1H, C(10)H).

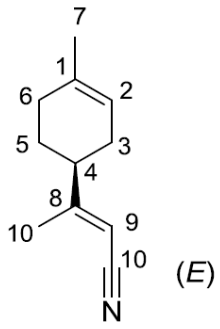
^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm:

(*E*) isomer: 22.1 (C(9)); 23.1 (C(3)); 23.4 (C(4)); 26.0 (C(8)); 26.9 (C(7)); 40.2 (C(5)); 41.8 (C(6)); 52.6 (C(1)); 91.2 (C(10)); 117.2 (C(11)); 173.5 (C(2)).

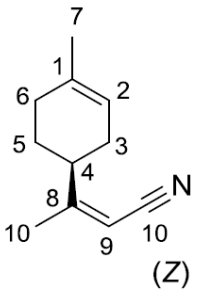
(*Z*) isomer: 21.8 (C(9)), 23.3 (C(4)); 25.2 (C(7)); 26.1 (C(3)); 26.2 (C(8)); 40.2 (C(5)); 42.0 (C(6)); 50.1 (C(1)); 91.2 (C(10)); 117.3 (C(11)); 173.1 (C(2)).

GC/MS: Calculated for $C_{11}H_{15}N$: 161, found 161

- **(-)-limonene/fumaronitrile cross metathesis product 9**



(*E*)



(*Z*)

In a Schlenk tube under argon, 100 mg (0.7 mmol) of limonene and 218 mg of fumaronitrile (2.8 mmol) were dissolved in 10 mL of distilled dimethyl carbonate (with hexadecane as internal standard), Zhan-1B catalyst **Ru2** (0.018 mmol, 13.5

mg, 2.5 mol%) was then added and the reaction mixture was stirred at 100 °C for 15 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by column chromatography on silica gel (1.5 cm x 12 cm) using a mixture of heptane/ ethyl acetate (98:2) as eluent to give 6 mg of **9** as colorless oil (7% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:

Minor (*E*)-isomer: 1.46-1.58 (m, 1H, C(5)H*H*); 1.66 (broad s, 3H, C(7)H_3); 1.75-1.83 (m, 1H, C(5)H*H*); 1.84 (d, 3H, ^{4}J= 1.2 Hz, C(10)H_3); 1.86-1.97 (m, 1H, C(6)H*H*); 1.97- 2.04 (m, 1H, C(3)H*H*); 2.07-2.15 (m, 2H, C(6)H*H*, C(3)H*H*); 2.24-2,37 (m, 1H, C(4)H); 5.06-5.09 (m, 1H, C(9)H); 5.35-5.42 (m, 1H, C(2)H).

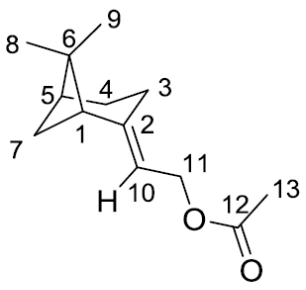
Major (*Z*)-isomer: 1.46-1.58 (m, 1H, C(5)H*H*); 1.66 (broad s, 3H, C(7)H_3); 1.75-1.83 (m, 1H, C(5)H*H*); 1.86-1.97 (m, 1H, C(6)H*H*); 1.97-2.04 (m, 1H, C(3)H*H*); 2.06 (d, 3H, ^{4}J= 1.2 Hz, C(10)H_3); 2.07-2.15 (m, 2H, C(6)H*H*, C(3)H*H*); 2.24-2.37 (m, 1H, C(4)H); 5.12-5.16 (m, 1H, C(9)H); 5.35-5.42 (m, 1H, C(2)H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm:

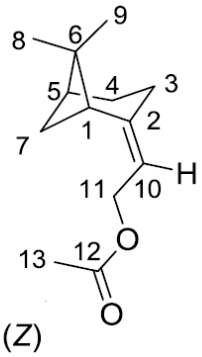
(*Z*+*E*) 19.6 (C(10)); 23.5 (C(7)); 27.2 (C(5)); 29.9 and 30.2 (C(3) or C(6);42.4 (C(4)); 94.3 (C(9)); 117.7 (C(11)); 119.4 (C(2)); 134.2 (C(1)); 169.3 (C(8)).

GC/MS: Calculated for $C_{11}H_{15}N$: 161, found 161

- **β-pinene/*cis*-1,4-diacetoxybut-2-ene cross metathesis product 13**



(*E*)



(*Z*)

In a Schlenk tube under argon, 100 mg (0.7 mmol) of β-pinene and 482 mg of 1,4-*cis*-diacetoxy-2-butene (2.8 mmol) were dissolved in 1 mL of distilled dimethyl

carbonate (with hexadecane as internal standard), Hoveyda II catalyst **Ru2** (0.037 mmol, 23 mg, 5 mol%) was then added and the reaction mixture was stirred at 100 °C for 15 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by column chromatography on silica gel (1.5 cm x 12 cm) using a mixture of heptane/ ethyl acetate (98:2) as eluent to give 25 mg of **13** as colorless oil (17% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:

Major isomer (*E*) 0.71 (s, 3H, C(9)H_3); 1.22 (s, 3H, C(8)H_3); 1.36 (d, ^{1}J= 10 Hz, 1H, C(7a)H*H*); 1.79-1.94 (m, 2H, C(4)H_2); 1.95-2.02 (m, 1H, C(5)H); 2.04 (s, 3H, C(13)H_3); 2.28-2.51 (m, 4H, C(7s)H*H*, C(1)H, C(3)H_2); 4.46-4.65 (m, 2H, C(11)H); 5.15 (tt, 1H, ^{3}J= 6.8 Hz, ^{4}J= 2.5 Hz, C(10)H).

Small traces of (Z), less than 10%

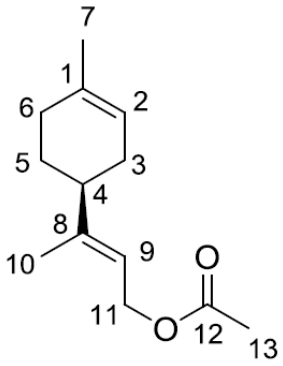
(Z) 0.69 (s, 3H, C(9)H_3); 1.22 (s, 3H, C(8)H_3); 1.46 (d, ^{1}J= 10 Hz, 1H, C(7a)H*H*); 1.79- 1.94 (m, 2H, C(4)H_2); 1.95-2.02 (m, 1H, C(5)H); 2.07 (s, 3H, C(13)H_3); 2.28-2.51 (m, 3H, C(7s)H*H*, C(3)H_2); 2.85 (t, 1H, ^{3}J= 4 Hz), C(1)H); 4.15-3.95 (m, 2H, C(11)H); 5.32- 5.39 (m, 1H, C(10)H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm:

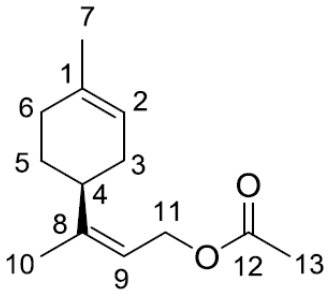
(*E*) 19.7 (C(3)); 21.5 (C(13)); 22.0 (C(9)); 23.7 (C(4)); 26.2 (C(8)); 27.6 (C(7)); 40.8 (C(5)) and (C(6)); 52.5 (C(1)); 61.0 (C(11)); 115.5 (C(10)); 149.5 (C(2)); 171.3 (C(12)).

GC/MS: Calculated for $C_{13}H_{20}O_2$: 208, found: 208

- **(-)-limonene/*cis*-1,4-diacetoxybut-2-ene cross metathesis product 14**



(*E*)



(*Z*)

In a Schlenk tube under argon, 100 mg (0.7 mmol) of limonene and 482 mg of 1.4-*cis*-diacetoxy-2-butene (2.8 mmol) were dissolved in 2 mL of distilled dimethyl carbonate (with hexadecane as internal standard), Zhan-1B catalyst **Ru1** (0.037 mmol, 27 mg, 5 mol%) was then added and the reaction mixture was stirred at 100 °C for 15 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by column chromatography on silica gel (1.5 cm x 12 cm) using a mixture of heptane/ ethyl acetate (98:2) as eluent to give 11 mg of **14** as colorless oil (7% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:

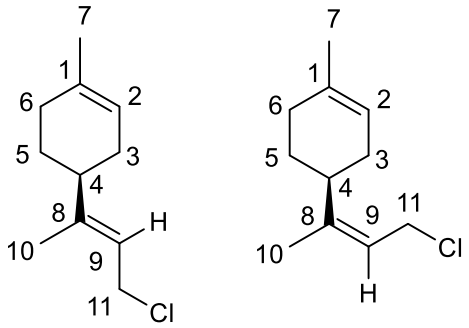
Major isomer: (*E*) 1.42-1.57 (m, 1H, C(5)H*H*); 1.67 (broad s, 3H, C(7)H_3); 1.71 (broad s, 3H, C(10)H_3); 1.74-1.84 (m, 1H, C(5)H*H*); 2.08 (s, 3H C(13)H_3); 1.85-2.30 (m, 5H, C(3)H_2, C(4)H), C(6)H_2); 4.63 (d, 2H, ^{3}J= 6.8 Hz, C(11)H_2); 5.32-5.42 (m, 2H, C(2)H, C(9)H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm:

14.8 (C(10)); 21.2 (C(13)); 23.6 (C(7)); 27.7 (C(5)); 30.6 (C(3)); 30.7 (C(6)); 42.9 (C4)); 61.7 (C(11)); 117.1 (C(9)); 120.6 (C(2)); 133.9 (C(1)); 146.4 (C(8)); 171.3 (C(12)).

GC/MS: Calculated for $C_{13}H_{20}O_2$: 208, found: 208

- **(-)-limonene/*cis*-1,4-dichlorobut-2-ene cross metathesis product 17**



(*E*)-**17** (*Z*)-**17**

In a Schlenk tube under argon, 100 mg (0.7 mmol) of (-)-limonene and 163 µL of *cis*-1,4- dichlorobut-2-ene (1.4 mmol) were dissolved in 1 mL of distilled dimethyl carbonate (with tetradecane as internal standard). **Ru2** catalyst (0.018 mmol, 11.5 mg, 2.5 mol%) was then added and the reaction mixture was stirred at 50 °C for 15 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by filtration with pentane, which was later evaporated by simple distillation to give 38 mg of **17** as colorless oil (28% isolated yield).

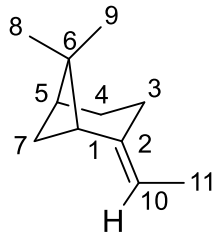
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm

Major (*E*) isomer: 1.42-1.60 (m, 1H, C(5)H*H*); 1.65 (broad s, 3H, C(7)H_3); 1.72 (s, 3H, C(10)H_3); 1.68-1.80 (m, 1H, C(5)H*H*); 1.84-2.22 (m, 5H, C(6)H_2, C(3)H_2, C(4)H) ; 4.12 (d, 2H, *J*= 7.9 Hz, C(11)H_2); 5.34-5.43 (m, 1H, C(2)H); 5.43-5.54 (m, 1H, C(9)H).

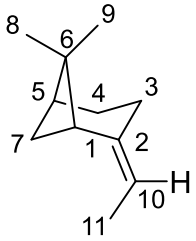
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:

(*E*) isomer: 14.4 (C(10)); 23.6 (C(7)); 27.6 (C(5)); 30.5 and 30.6 (C(3) and C(6)); 41.4 (C(11)); 42.8 (C(4)); 119.1 (C(9)); 120.5 (C(2)); 134.0 (C(1)); 147.1 (C(8)).

- **β-pinene/2-methylbut-2-ene cross metathesis product 19**



(*E*)**-19**



(*Z*)**-19**

In a Schlenk tube under argon, 100 mg (0.7 mmol) of β-pinene was added in 1 mL of 2-methylbut-2-ene (neat reaction). **Ru2** catalyst (0.018 mmol, 11.5 mg, 2.5 mol%) was then added and the reaction mixture was stirred at 40 °C for 15 h. After this time, another 1 mol% of catalyst (5 mg) was added and the reaction stirred for an additional 8 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by filtration with pentane, which was later evaporated by simple distillation to give 61 mg of **19** as colorless oil (56% isolated yield).

The determination of configuration of the major isomer (*E*) was made by 1D gradient selective NOESY (800 ms mixing time) (see spectra section). The accurate chemical shifts of protons was determined using HSQC and 1D selective TOCSY sequences.

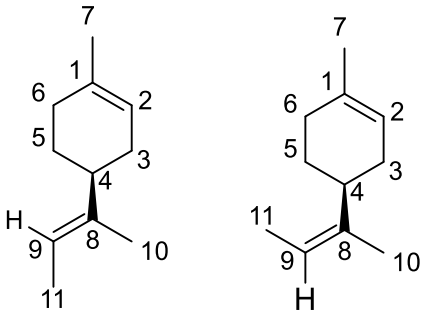
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:

Major (*E*) isomer: 0.70 (s, 3H, C(9)H_3); 1.21 (s, 3H, C(8)H_3); 1.31 (d, ^{1}J= 8.7 Hz, 1H, C(7a)H*H*); 1.55 (d, 3H, J= 6.7 Hz, C(11)H_3); 1.82-1.90 (m, 2H, C(4)H_2); 1.93-2.02 (m, 1H, C(5)H); 2.28-2.39 (m, 4H, C(3a)H*H*)+ C(1)H+ C(7a)H*H*)+ C(3s)H*H*); 5.00-5.08 (m, 1H, C(10)H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:

Major (*E*) isomer: 12.7 (C(11)); 19.7 (C(3)); 22.2 (C(9)); 23.9 (C(4)); 26.2 (C(8)); 28.2 (C(7)); 40.8 (C(6)); 41.1 (C(5)); 52.7 (C(1)); 115.3 (C(10)); 143.1 (C(2)).

- **(-)-limonene/2-methylbut-2-ene cross metathesis product 20**



(*E*)**-20** (*Z*)**-20**

In a Schlenk tube under argon, 100 mg (0.7 mmol) of limonene was added to 1 mL of 2-methylbut-2-ene (neat reaction). **Ru2** catalyst (0.018 mmol, 11.5 mg, 2.5 mol%) was then added and the reaction mixture was stirred at 40 °C for 15 h. After this time, another 2.5 mol% of catalyst was added and the reaction stirred for an additional 8 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by filtration with pentane, which was later evaporated by simple distillation to give 66 mg of **20** as colorless oil (60% isolated yield).

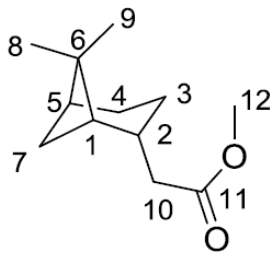
^{1}H NMR (400 MHz, $CDCl_3$) δ **ppm**

Major (*E*) isomer: 1.41-1.55 (m, 1H, C(5)H*H*); 1.58 (d, 3H, J= 5.8 Hz, C(11)H_3); 1.59 (s, 3H, C(10)H_3), 1.65 (broad s, 3H, C(7)H_3); 1.67-1.76 (m, 1H, C(5)H*H*); 1.84-2.14 (m, 5H, C(6)H_2, C(3)H_2, C(4)H); 5.20-5.29 (m, 1H, C(9)H); 5.37-5.44 (m, 1H, C(2)H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:

(*E*) isomer: 13.4 (C(11)); 13.9 (C(10)); 23.6 (C(7)); 28.1 (C(5)); 30.9 (C(3) and C(6)); 43.0 (C(4)); 116.9 (C(9)); 121.1 (C(2)); 133.8 (C(1)); 140.3 (C(8)).

- **β-pinene/dimethyl maleate tandem cross metathesis/hydrogenation product 30**



In a Schlenk tube under argon, 100 mg (0.7 mmol) of β-pinene and 426 mg of dimethyl fumarate (2.8 mmol) were dissolved in 2 mL of distilled dimethyl carbonate (with hexadecane as internal standard), Hoveyda II catalyst **Ru2** (0.037 mmol, 23 mg, 5 mol%) was then added and the reaction mixture was stirred at 100 °C for 16 h. The crude reaction solution from the cross-metathesis step containing the residual ruthenium was transferred into an autoclave and the reactor was pressurized with 40 bar of H2. The reaction was stirred at 80 ˚C for 8 h. After cooling to room temperature, aliquots were collected for chromatographic and 1H NMR analysis. The product was purified by column chromatography on silica gel (1.5 cm x 12 cm) using a mixture of heptane/ ethyl acetate (98:2) as eluent to give 58 mg of **30** as colorless oil (40% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: C12H20O2

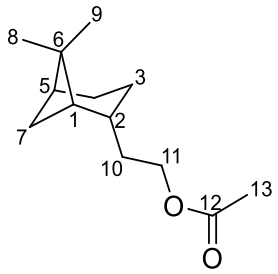
0.93 (d, 1H, ^{2}J= 6 Hz, C(7)H*H*); 1.00 (s, 3H, C(9)H_3); 1.17 (s, 3H, C(8)H_3); 1.37-1.49- (m, 1H, C(3)H*H*); 1.78-2.07 (m, 5H, C(1)H, C(4)H_2, C(5)H, C(3)H*H*); 2.28-2.36 (m, 1H, C(7)HH); 2.38 (dd, 2H, ^{3}J= 7.6 Hz, ^{2}J= 3.6 Hz, C(10)H_2); 2.47-2.57 (m, 1H, C(2)H); 3.64 (s, 3H, C(12)H_3).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm:

21.8 (C(3)), 23.2 (C(9)), 26.2 (C(4)), 28.1 (C(8)), 33.5 (C(7)), 37.7 (C(2)), 38.8 (C(6)), 41.2 (C(5)), 42.0 (C(10)), 46.3 (C(1)), 51.5 (C(12)), 173.9 (C11)).

GC/MS: Calculated for $C_{12}H_{20}O_2$: 196, found 196

- **β-pinene/*cis*-1,4-diacetoxybut-2-ene tandem cross metathesis/ hydrogenation product 31**



In a Schlenk tube under argon, 100 mg (0.7 mmol) of β-pinene and 241 mg of diacetoxy-2-butene (1.4 mmol) were dissolved in 2 mL of distilled dimethyl carbonate (with hexadecane as internal standard), Zhan-1B catalyst **Ru1** (0.018 mmol, 13.5 mg, 2.5 mol%) was then added and the reaction mixture was stirred at 100 °C for 15 h. The crude reaction solution from the cross-metathesis step containing the residual ruthenium was transferred into an autoclave and the reactor was pressurized with 40 bar of H_2. The reaction was stirred at 80 ˚C for 8 hours. After cooling to room temperature, aliquots were collected for chromatographic and ^{1}H NMR analysis. The product was purified by column chromatography on silica gel (1.5 cm x 12 cm) using a mixture of heptane/ ethyl acetate (98:2) as eluent to give 3 mg of **31** as colorless oil (2% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: $C_{13}H_{22}O_2$

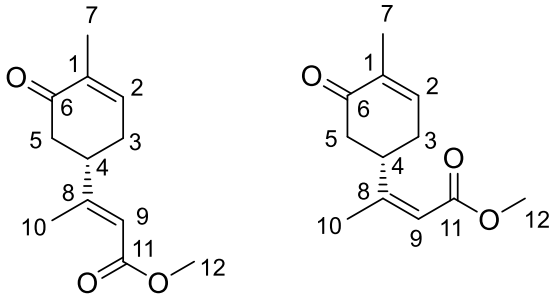
0.89 (d, ^1J= 4 Hz, 1H, C(7a)H*H*); 1.01 (s, 3H, C(9)H_3); 1.18 (s, 3H, C(8)H_3); 1.40-1.57 (m, 2H, C(3)H_2); 1.68-1.77 (m, 2H, C(10)H_2); 1.79-2.01 (m, 4H, C(4)H_2, C(1)H, C(5)H); 2.04 (s, 3H, C(13)H_3); 2.06-2.14 (m, 1H, C(2)H); 2.28-2.38 (m, 1H, C(7)H*H*); 4.15-3.95 (m, 2H, C(11)H_2).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm:

21.2 (C(13)); 22.3 (C(3)); 23.4 (C(9)); 26.5 (C(4)); 28.3 (C(8)); 33.7 (C(7)); 36.5 (C(10)), 38.0 (C(2)); 38.9 (C(6)); 41.5 (C(5)); 46.4 (C(1)); 63.7 (C(11)); 171.4 (C(12)).

GC/MS: Calculated for $C_{13}H_{22}O_2$: 210; found 210.

- **(D)-carvone/dimethyl maleate cross metathesis product 37**



(*E*)-**37** (*Z*)-**37**

In a Schlenk tube under argon, 100 mg (0.7 mmol) of D-Carvone and 380 µL of dimethyl maleate (2.8 mmol) were dissolved in 1 mL of distilled dimethyl carbonate (with hexadecane as internal standard), **Ru2** catalyst (0.037 mmol, 23 mg, 5 mol%) was then added and the reaction mixture was stirred at 100 °C for 15 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by column chromatography on silica gel (1.5 cm x 12 cm) using a mixture of heptane/ethyl acetate (98:2) as eluent to give 52 mg of **37** as colorless oil (37% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:

Major isomer (*E*)-isomer: 1.75-1.81 (m, 3H, C(7)H3); 2.17 (s, 3H, C(10)H3); 2.27-2.49 (m, 3H, C(5)H and C(3)H2), 2.51-2.61 (m, 1H, C(5)H), 2.73-2.85 (m, 1H, C(4)H); 3.69 (s, 3H, C(12)H3); 5.68-5.73 (m, 1H, C(9)H); 6.71-6.77 (m, 1H, C(2)H).

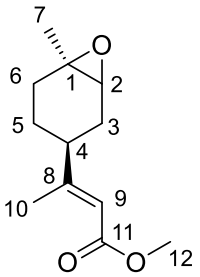
Minor isomer (*Z*)-isomer: 1.75-1.81 (m, 3H, C(7)H3); 1.87 (s, 3H, C(10)H3); 2.27-2.49 (m, 3H, C(5)H and C(3)H2); 2.51-2.61 (m, 1H, C(5)H), 4.35-4.48 (m, 1H, C(4)H); 3.66 (s, 3H, C(12)H3); 5.68-5.73 (m, 1H, C(9)H); 6.71-6.77 (m, 1H, C(2)H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:

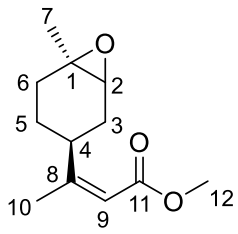
Major isomer (*E*)-isomer: 15.8 (C(7)); 16.9 (C(10)); 30.7 (C(3)); 42.4 (C(5)); 45.2 C(4)); 51.1 (C(12)); 115.7 (C(9)); 135.8 (C(1)); 143.8 (C(2)); 159.5 (C(8)); 167.1 (C(11)); 198.5 (C(6)).

Minor isomer (*Z*)-isomer: 15.9 (C(7)); 20.8 (C(10)); 30.2 (C(3)); 36.9 C(4)); 41.7 (C(5)); 51.1 (C(12)); 117.5 (C(9)); 135.6 (C(1)); 144.5 (C(2)); 159.3 (C(8)); 166.2 (C(11)); 198.8 (C(6)).

- **(+)-*trans*-limonene epoxide/dimethyl maleate cross metathesis product 39**



(*E*)-**39**



(*Z*)-**39**

In a Schlenk tube under argon, 100 mg (0.7 mmol) of (+)-*trans*-limonene epoxide and 380 µL of dimethyl maleate (2.8 mmol) were dissolved in 1 mL of distilled dimethyl carbonate (with hexadecane as internal standard), **Ru2** catalyst (0.037 mmol, 23 mg, 5 mol%) was then added and the reaction mixture was stirred at 100 °C for 15 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by column chromatography on silica gel (1.5 cm x 12 cm) using a mixture of heptane/ ethyl acetate (98:2) as eluent to give 18 mg of **39** as colorless oil (13% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:

Major isomer (*E*): 1.32 (broad s, 3H, C(7)H3); 1.28-1.40; 1.41-1.54; 1.64-1,81; 1,89- 2,12 (m, 7H, C(5)H2,C(6)H2,C(3)H2,C(4)H); 2.09 (d, 3H, J= 1.2 Hz, C(10)H3); 2.97-3.03 (m, 1H, C(2)H); 3.67 (s, 3H, C(12)H3); 5.65 (s, 1H, C(9)H).

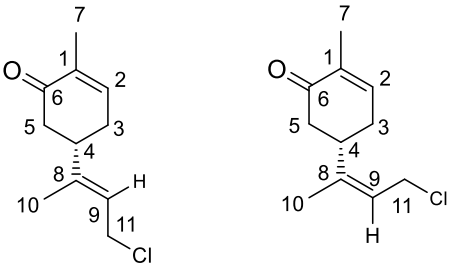
Minor isomer (*Z*): 1.31 (broad s, 3H, C(7)H3); 1.28-1.40; 1.41-1.54; 1.64-1,81; 1,89- 2,12 (m, 7H, C(5)H2,C(6)H2,C(3)H2,C(4)H); 1.77 (d, 3H, J= 1.4 Hz, C(10)H3); 2.97-3.03 (m, 1H, C(2)H); 3.66 (s, 3H, C(12)H3); 5.61 (s, 1H, C(9)H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:

Major isomer (*E*): 16.7 (C(10)); 23.1 (C(7)); 23.9, 29.4, 30.6 (C(3),C(5),C(6)); 43.9 (C(4)); 51.0 (C(12)); 57.5 (C(1)); 58.8 (C(2)); 114.7 (C(9)); 163.1 (C(8)); 167.4 (C(11)).

Minor isomer (*Z*): 20.5 (C(10)); 23.1 (C(7)); 23.9, 29.4, 30,6 (C(3),C(5),C(6)); 43.9 (C(4)); 50.9 (C(12)); 57.5 (C(1)); 59.2 (C(2)); 115.9 (C(9)); 163.1 (C(8)); 167.4 (C(11)).

- **(D)-carvone/*cis*-1,4-dichlorobut-2-ene cross metathesis product 40**



(*E*)-**40** (*Z*)-**40**

In a Schlenk tube under argon, 100 mg (0.7 mmol) of D-Carvone and 163 µL of *cis*-1,4- dichlorobut-2-ene (1.4 mmol) were dissolved in 1 mL of distilled dimethyl carbonate (with tetradecane as internal standard). **Ru2** catalyst (0.037 mmol, 23 mg, 5 mol%) was then added and the reaction mixture was stirred at 50 °C for 15 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by column chromatography on alumina (1.5 cm x 12 cm) using a heptane/ ethyl acetate (98:2) mixture as eluent to give 15 mg of **40** as colorless oil (12% isolated yield).

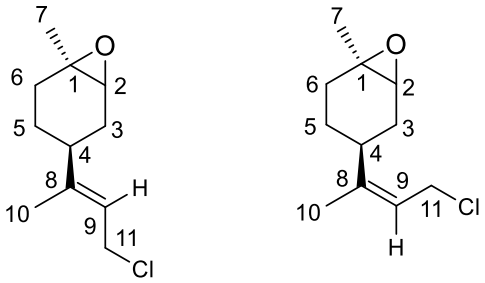
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm

Major (*E*) isomer: 1.74 (broad s, 3H, C(10)H3); 1.78 (broad s, 3H, C(7)H3); 2.22-2.47 (m, 3H, C(3)H*H,* C(5)H*H,* C(3)H*H*); ; 2.50-2.60 (m, 1H, C(5)H*H*); 2.62-2.79 (m, 1H, C(4)*H*); 4.09 (d, 2H, J= 7.7 Hz, C(11)H2); 5.50 (t, 1H, J= 7.4 Hz C(9)H); 6.71-.79 (m, 1H, C(2)H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:

(*E*) isomer: 14.3 (C(10)); 15.8 (C(7)); 31.0 (C(3)); 40.6 (C(11)); 42.8 (C(5)); 44.1 C(4)); 121.1 (C(9)); 135.7 (C(1)); 143.2 (C(8)); 144.4 (C(2)); 199.3 (C(6)).

- **(+)-*trans*-limonene epoxide/ *cis*-1,4-dichlorobut-2-ene cross metathesis product 41**



(*E*)-**41** (*Z*)-**41**

In a Schlenk tube under argon, 100 mg (0.7 mmol) of (+)-*trans*-limonene epoxide and 163 µL of *cis*-1,4-dichlorobut-2-ene (1.4 mmol) were dissolved in 1 mL of distilled dimethyl carbonate (with tetradecane as internal standard). **Ru2** catalyst (0.037 mmol, 23 mg, 5 mol%) was then added and the reaction mixture was stirred at 50 °C for 15 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by column chromatography on alumina (1.5 cm x 12 cm) using a heptane/ ethyl acetate (98:2) mixture as eluent to give 21 mg of **41** as colorless oil (15% isolated yield).

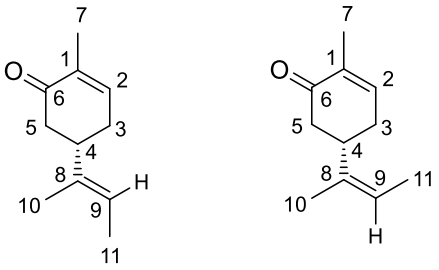
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:

Major isomer: (*E*) 1.32 (s, 3H, C(7)H3); 1.15-1.48 (m, 2H, C(5)H2); 1.66 (s, 3H, C(10)H3); 1.67-1.73 (m, 2H, C(3)H, C(6)H); 1.84-2.08 (m, 3H, C(3)H, C(4)H, C(6)H); 2.99 (d, 1H, J= 5.1 Hz, C(2)H); 4.07 (d, 2H, J= 7.9 Hz, C(11)H2); 5.43 (t, 1H, J= 7.9 Hz, C(9)H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 13.8 (C(10)); 23.0 (C(7)); 23.9 (C(5)), 29.4 (C(3)), 30.6 C(6)); 40.9 (C11)); 42.4 (C(4)); 57.5 (C(1)); 59.0 (C(2)); 119.7 (C(9)); 145.6 (C(8))*.

* This quaternary carbon was not detected under standard 13C conditions due to long relaxation time. However, this quaternary carbon could be assigned thanks to HMBC experiment (see spectra section).

- **(D)-carvone/2-methylbut-2-ene cross metathesis product 44**



(*E*)-**44** (*Z*)-**44**

In a Schlenk tube under argon, 100 mg (0.7 mmol) of (D)-Carvone was added in 1 mL of 2-methylbut-2-ene (neat reaction). **Ru2** catalyst (0.018 mmol, 11.5 mg, 2.5 mol%) was then added and the reaction mixture was stirred at 40 °C for 15 h. After this time, another 1% of catalyst (5 mg) was added for an additional 8 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by filtration with heptane, which was later evaporated in the vacuum line to give 79 mg of **44** as colorless oil (73% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm

Major (*E*) isomer: 1.56 (d, 3H, J= 6.6 Hz, C(11)H3), 1.58 (broad s, 3H, C(10)H3); 1.75 (broad s, 3H, C(7)H3); 2.18-2.37 (m, 3H, C(3)H2*,* C(5)H*H*); 2.48 (ddd, 1H, J= 16.0, 3.7, 1.2 Hz, C(5)H*H*); 2.55-2.68 (m, 1H, C(4)*H*); 5.26 (q, 1H, J= 6.6 Hz, C(9)H); 6.67-6.77 (m, 1H, C(2)H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm

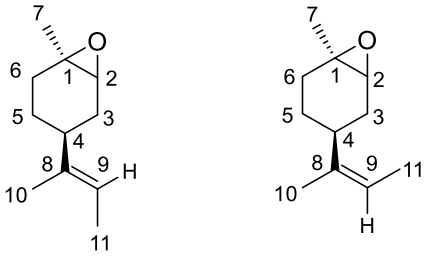
(*E*) isomer: 13.4 (C(11)); 13.7 (C(10)); 15.8 (C(7)); 31.5 (C(3)); 43.4 (C(5)); 44.41 C(4)); 119.1 (C(9)); 135.3 (C(1)); 137.0 (C(8)); 145.0 (C(2)); 200.3 (C(6)).

Minor (*Z*)- isomer : only the C(4)-H entity shows visible different chemical shifts

1H NMR (400 MHz, $CDCl_3$) δ ppm: 3.15-3.28 (m, 1H, C(4)-H)

13C NMR (100 MHz, $CDCl_3$) δ ppm: 36.5 (C(4))

- **(+)-*trans*-limonene epoxide/2-methylbut-2-ene cross metathesis product 45**



(*E*)-**45** (*Z*)-**45**

In a Schlenk tube under argon, 100 mg (0.7 mmol) of (+)-*trans*-limonene epoxide was added in 1 mL of 2-methylbut-2-ene (neat reaction). **Ru2** catalyst (0.018 mmol, 11.5 mg, 2.5 mol%) was then added and the reaction mixture was stirred at 40 °C for 15 h. After this time, another 2.5% of catalyst was added and the reaction stirred for an additional 8 h. A sample of the reaction mixture was taken and analyzed by gas chromatography. The product was purified by filtration with heptane, which was later evaporated in the vacuum line to give 37 mg of **45** as colorless oil (34% isolated yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:

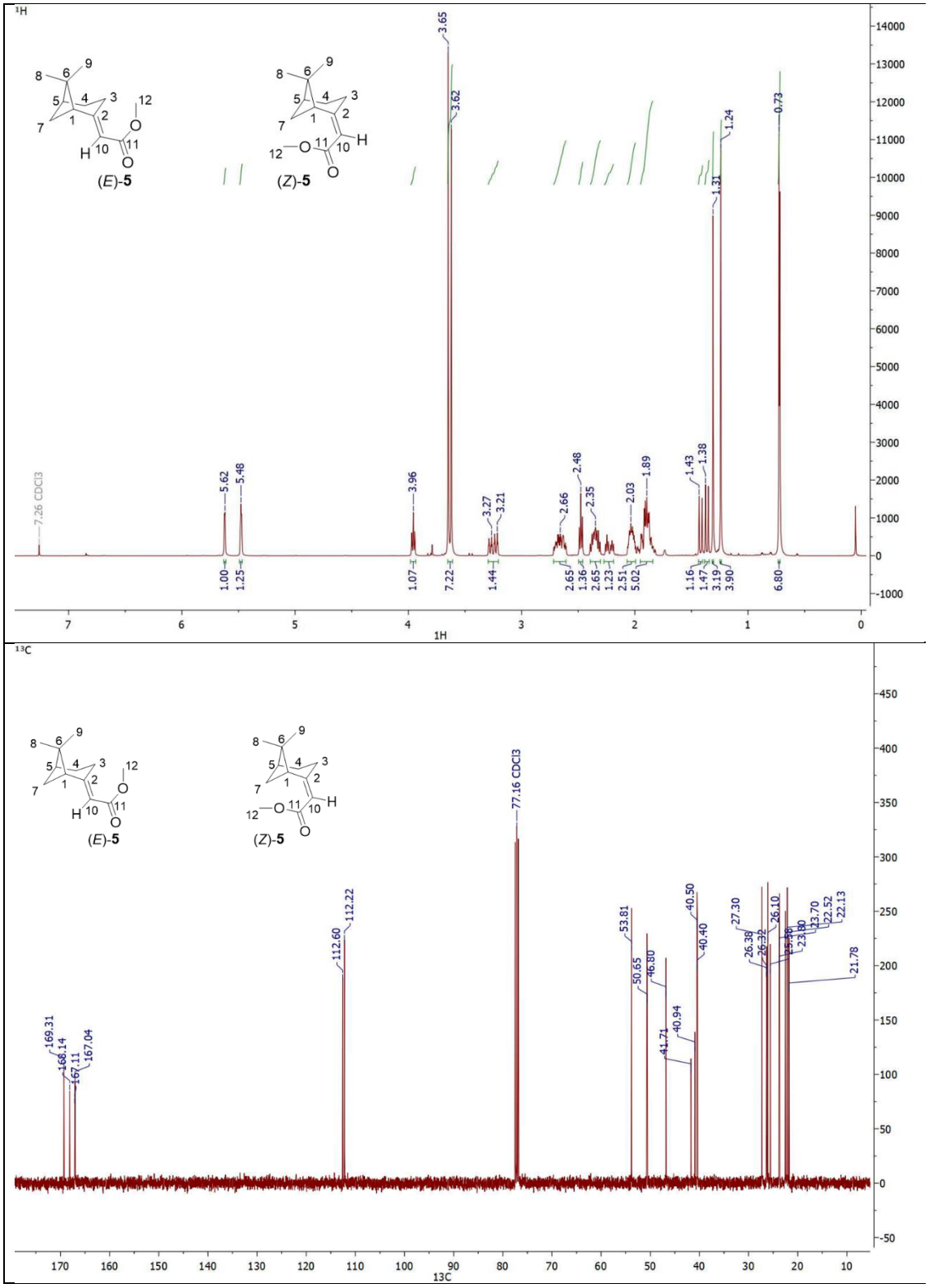
Major isomer (*E*): 1.26-1.43 (m, 2H, C(5)H2); 1.30 (s, 3H, C(7)H3); 1.52 (s, 3H, C(10)H3); 1.54 (d, J= 6.7 Hz, C(11)H3); 1.60-1.75 (m, 2H, C(3)H1, C(6)H1); 1.78-2.07 (m, 3H, C(3)H, C(4)-H, C(6)H);f 2.99 (d, 1H, J= 5.2 Hz, C(2)H); 5.19 (q, 1H, J= 6.5 Hz, C(9)H).

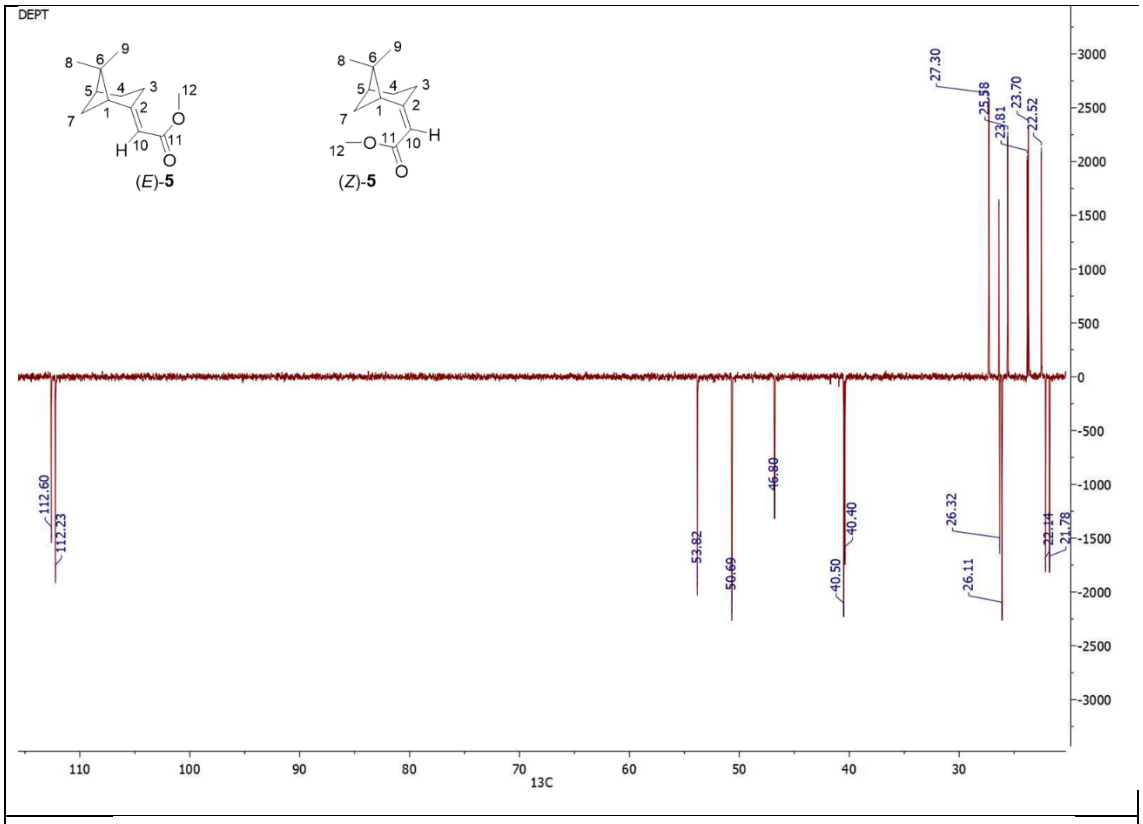
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:

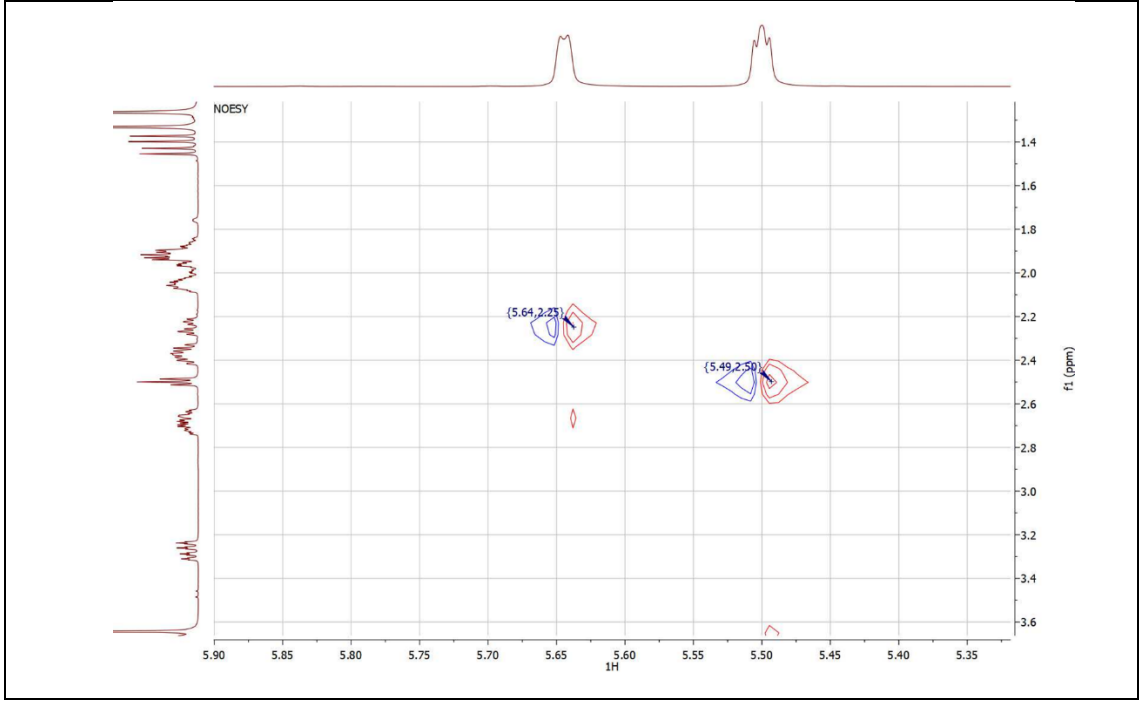
13.4(C(10) and C(11)); 23.3 (C(7)); 24.5 (C(5)); 29.9 (C(6)); 31.0 (C(3)); 42.7 (C(4)); 57.7 (C(1)); 59.6 (C2)); 117.6 (C(9)); 139.3 (C(8)).

6.4 NMR spectra

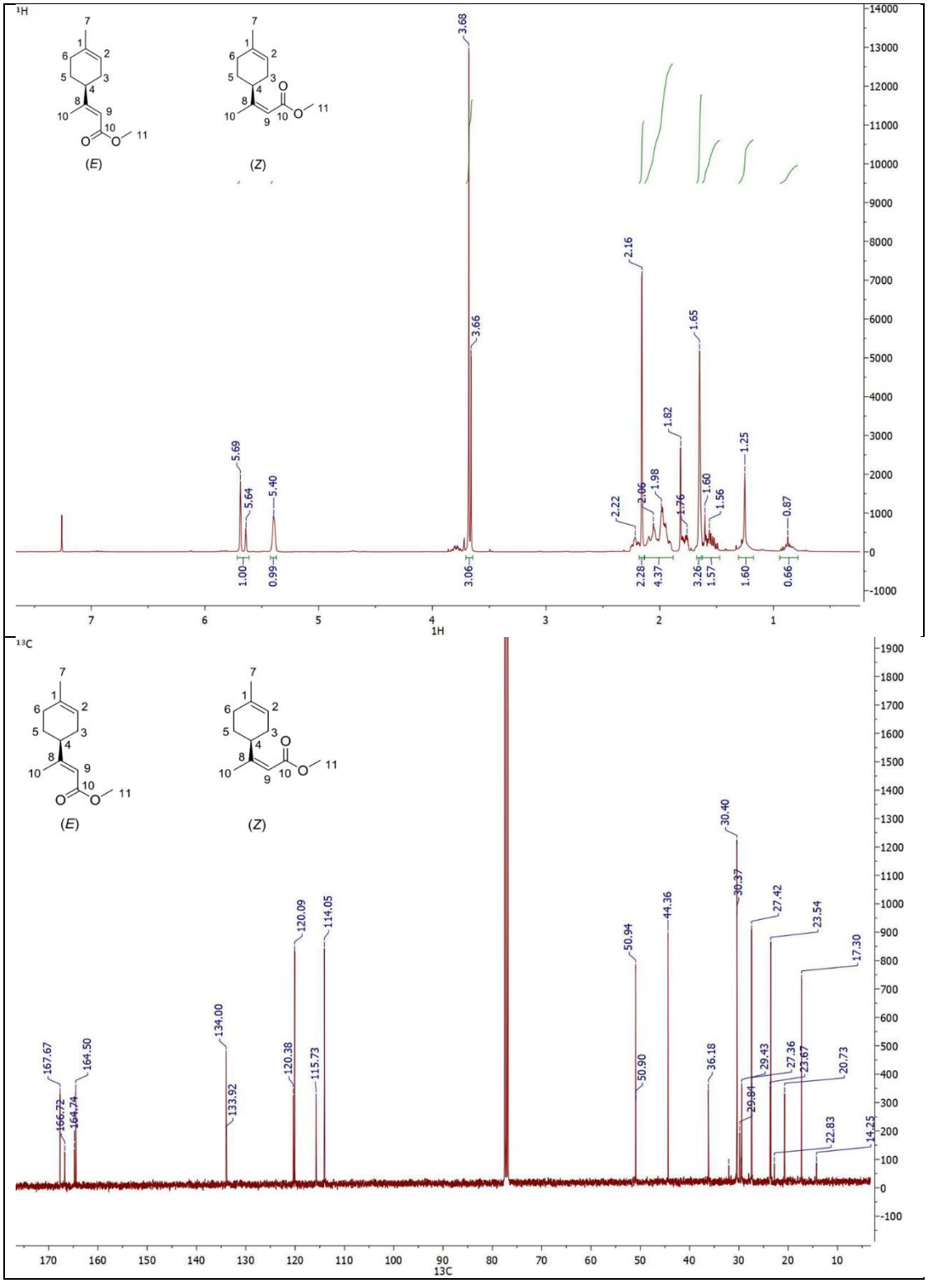
- **β-pinene/dimethyl maleate cross metathesis product 5**

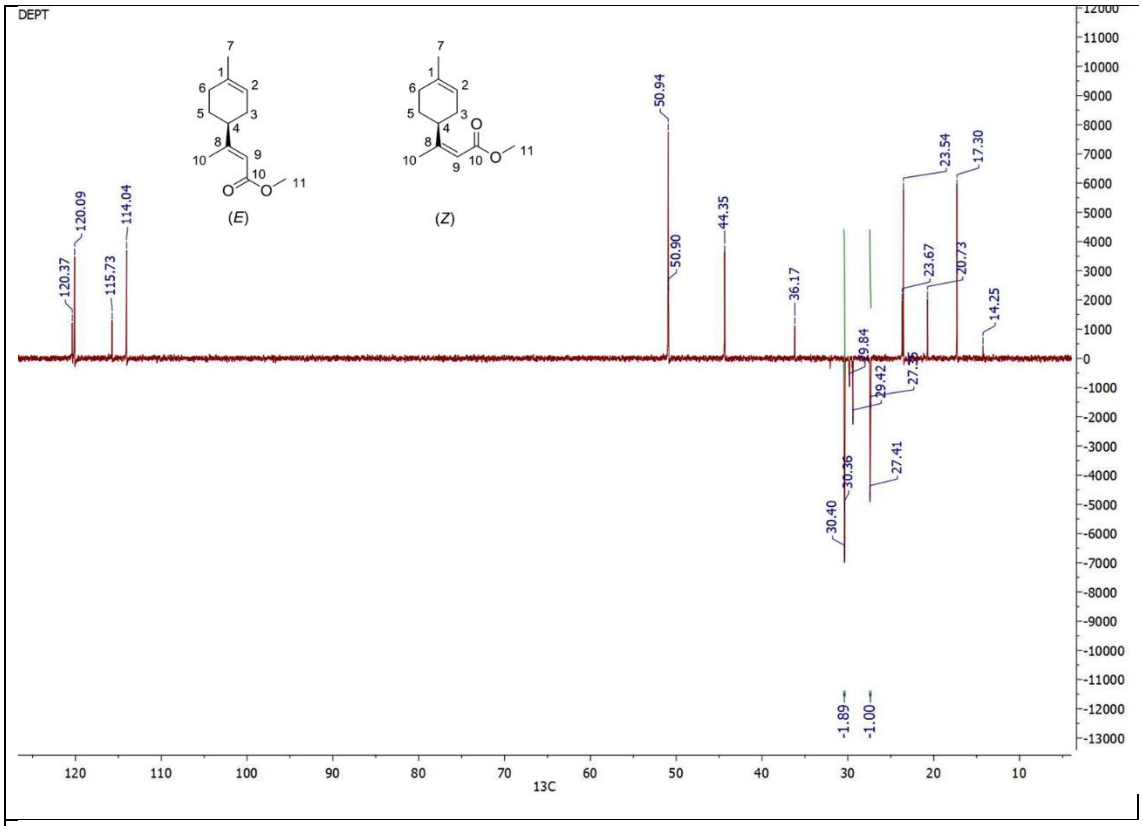


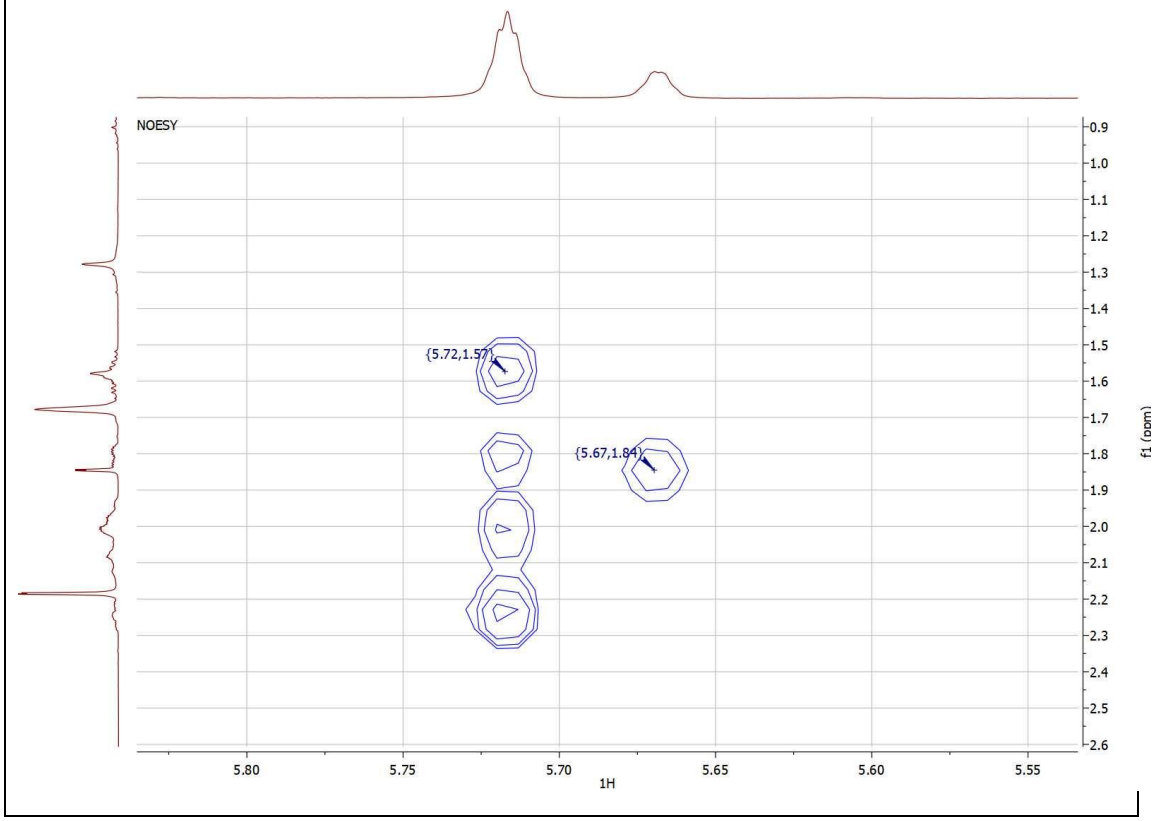

DEPT
(E)-5
(Z)-5
27.30
25.58
23.81
23.70
22.52
112.60
112.23
53.82
50.69
46.80
40.40
40.50
26.32
26.11
22.14
21.78
13C


NOESY
{5.64,2.25}
{5.49,2.50}
f1 (ppm)
1H

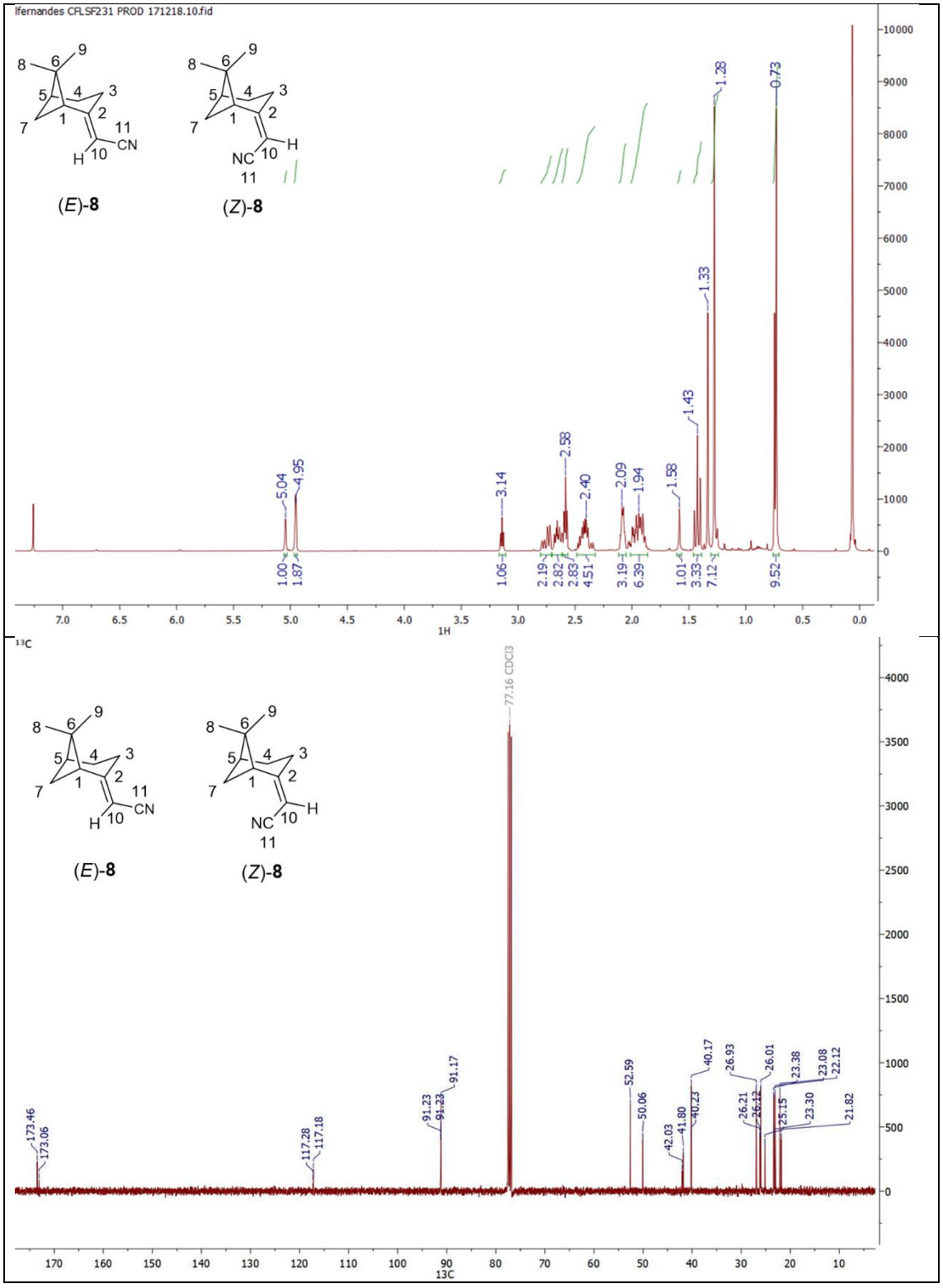
- **(-)-limonene/dimethyl maleate cross metathesis product 6**

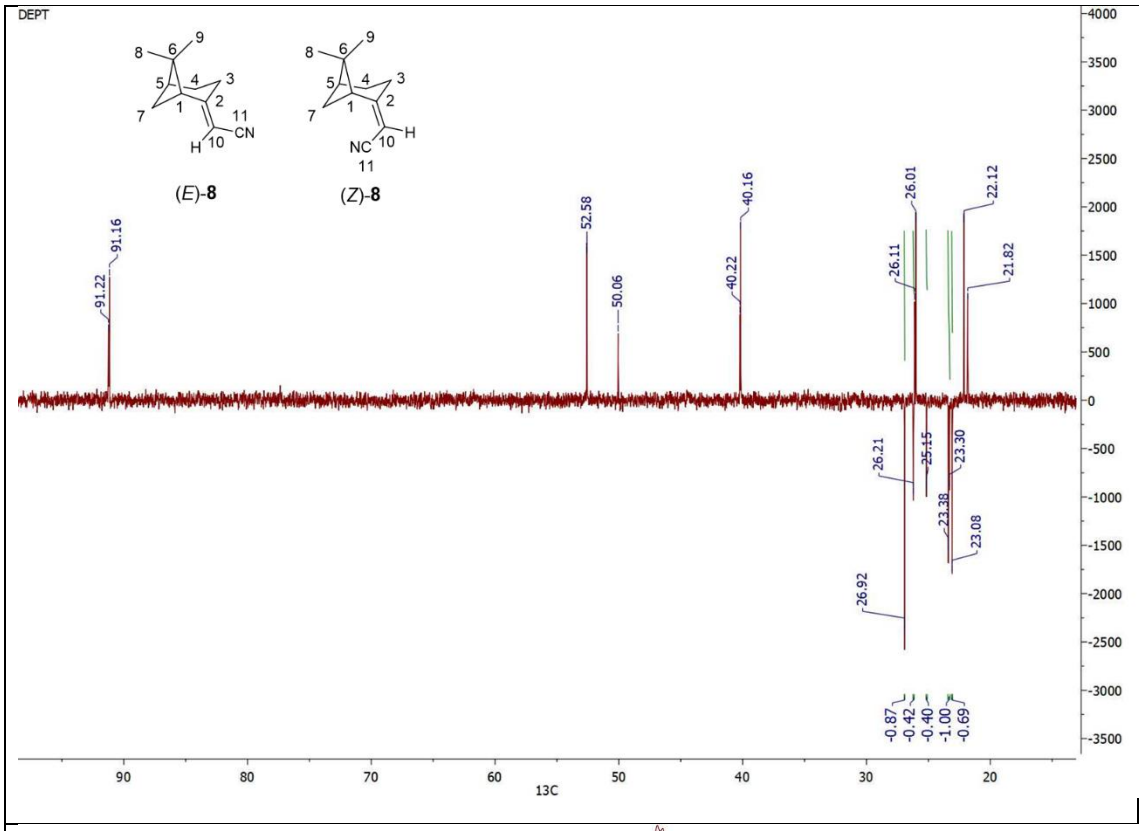


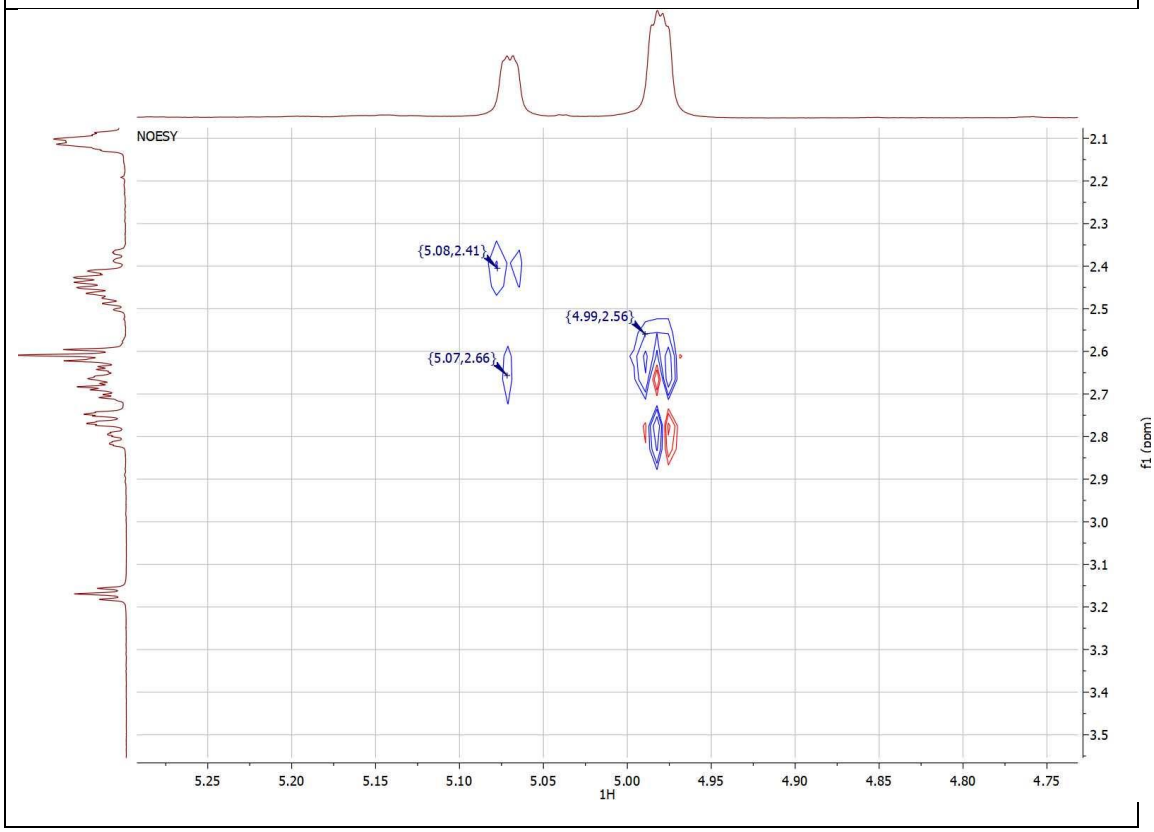

DEPT
(E)
(Z)
120.37
120.09
115.73
114.04
50.94
50.90
44.35
36.17
30.40
30.36
29.84
29.42
27.41
23.54
23.67
20.73
17.30
14.25
-1.89
-1.00
13C


NOESY
{5.72,1.57}
{5.67,1.84}
1H
f1 (ppm)

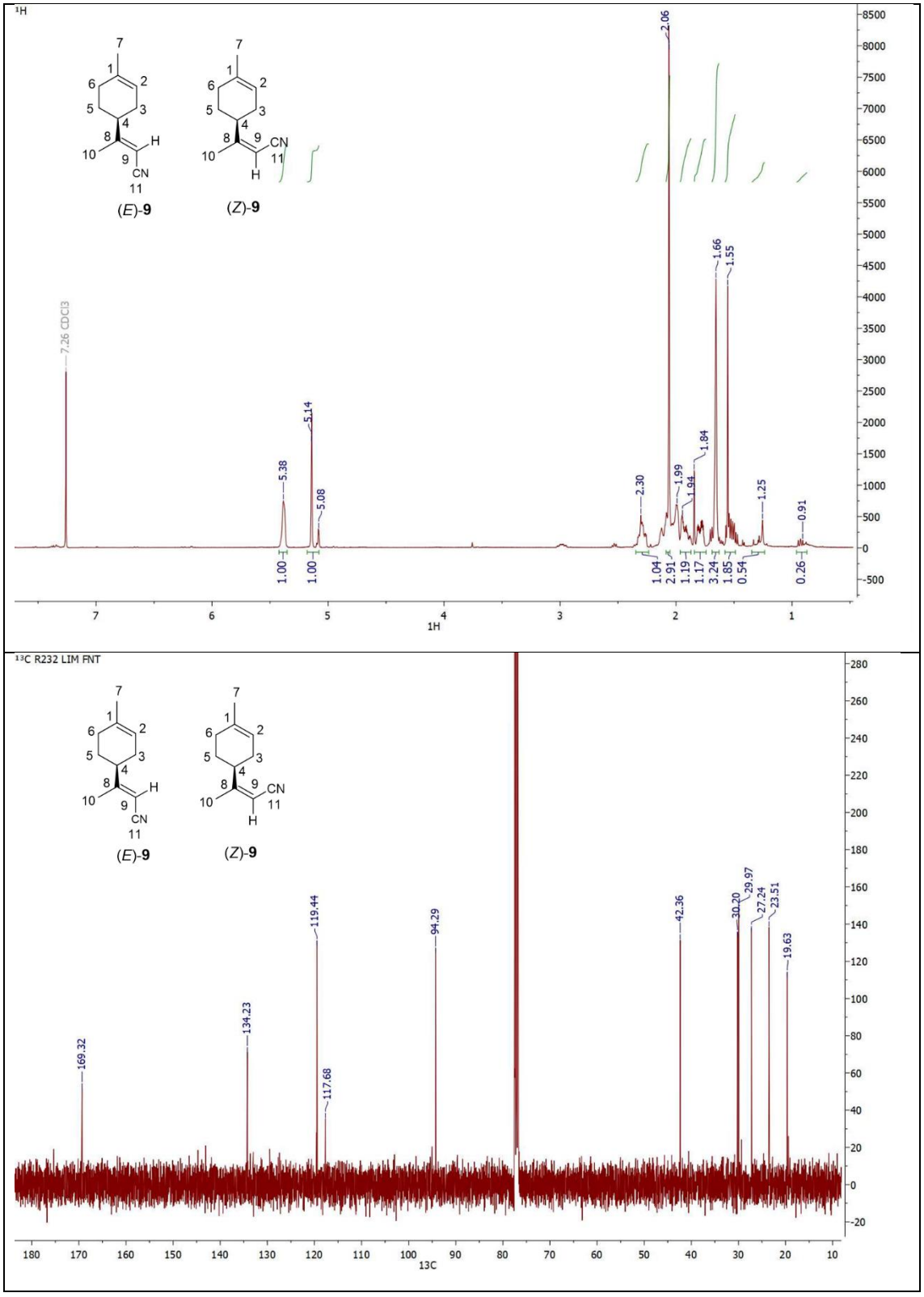
- **β-pinene/fumaronitrile cross metathesis product 8**

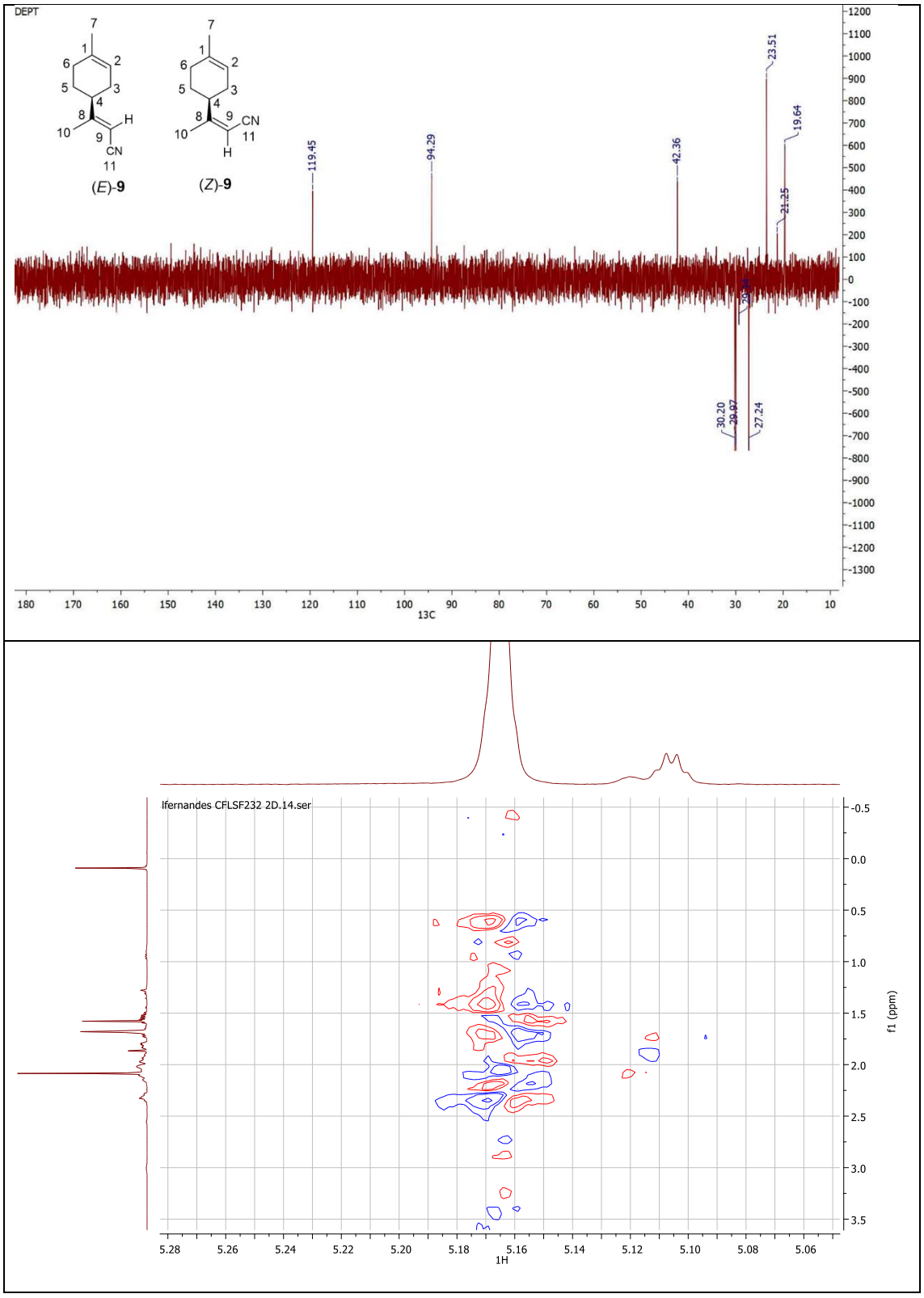



DEPT
(E)-8
(Z)-8
91.22
91.16
52.58
50.06
40.22
40.16
26.92
26.21
26.11
26.01
25.15
23.38
23.30
23.08
22.12
21.82
-0.87
-0.42
-0.40
-1.00
-0.69
13C

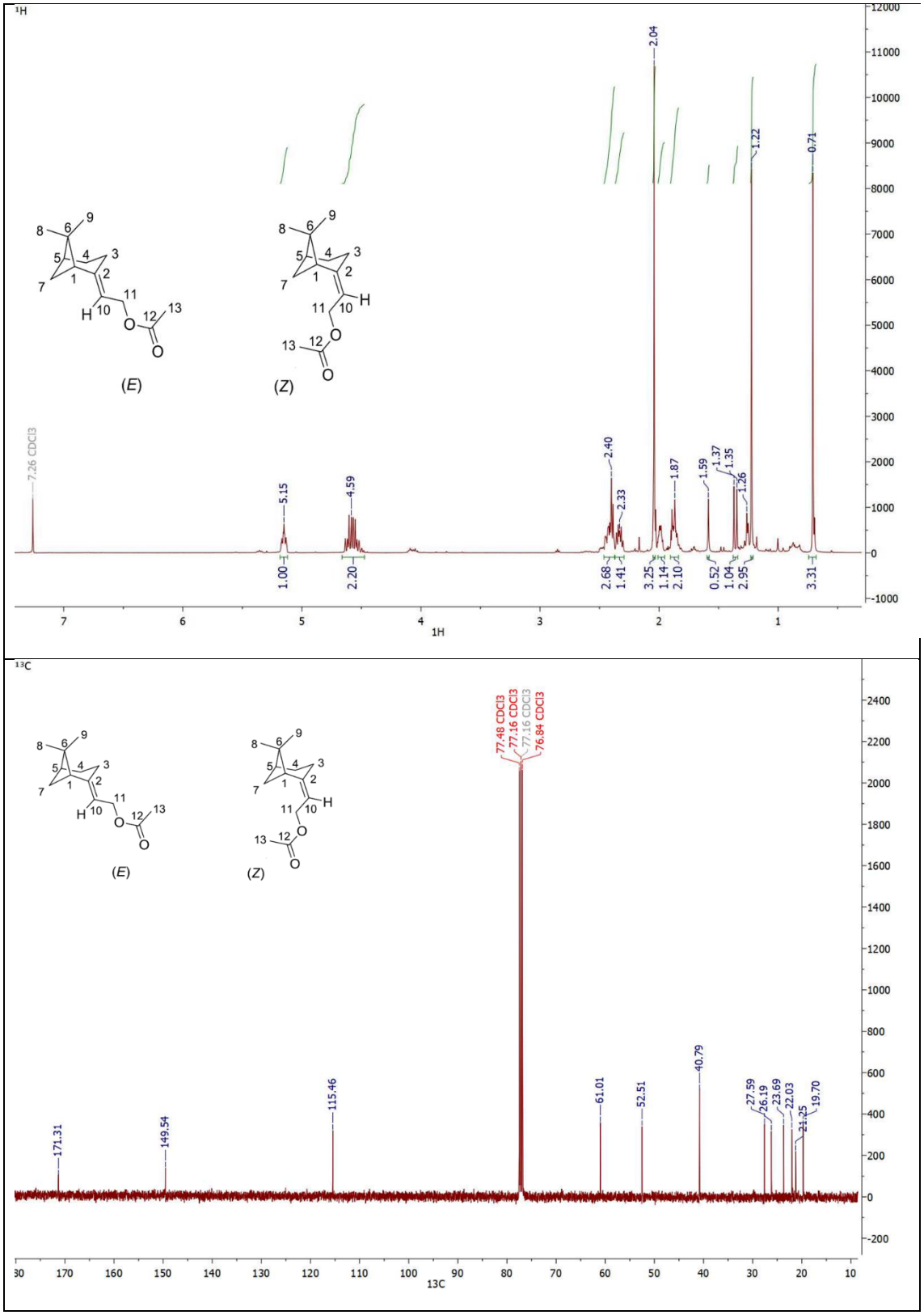

NOESY
{5.08,2.41}
{4.99,2.56}
{5.07,2.66}
1H
f1 (ppm)

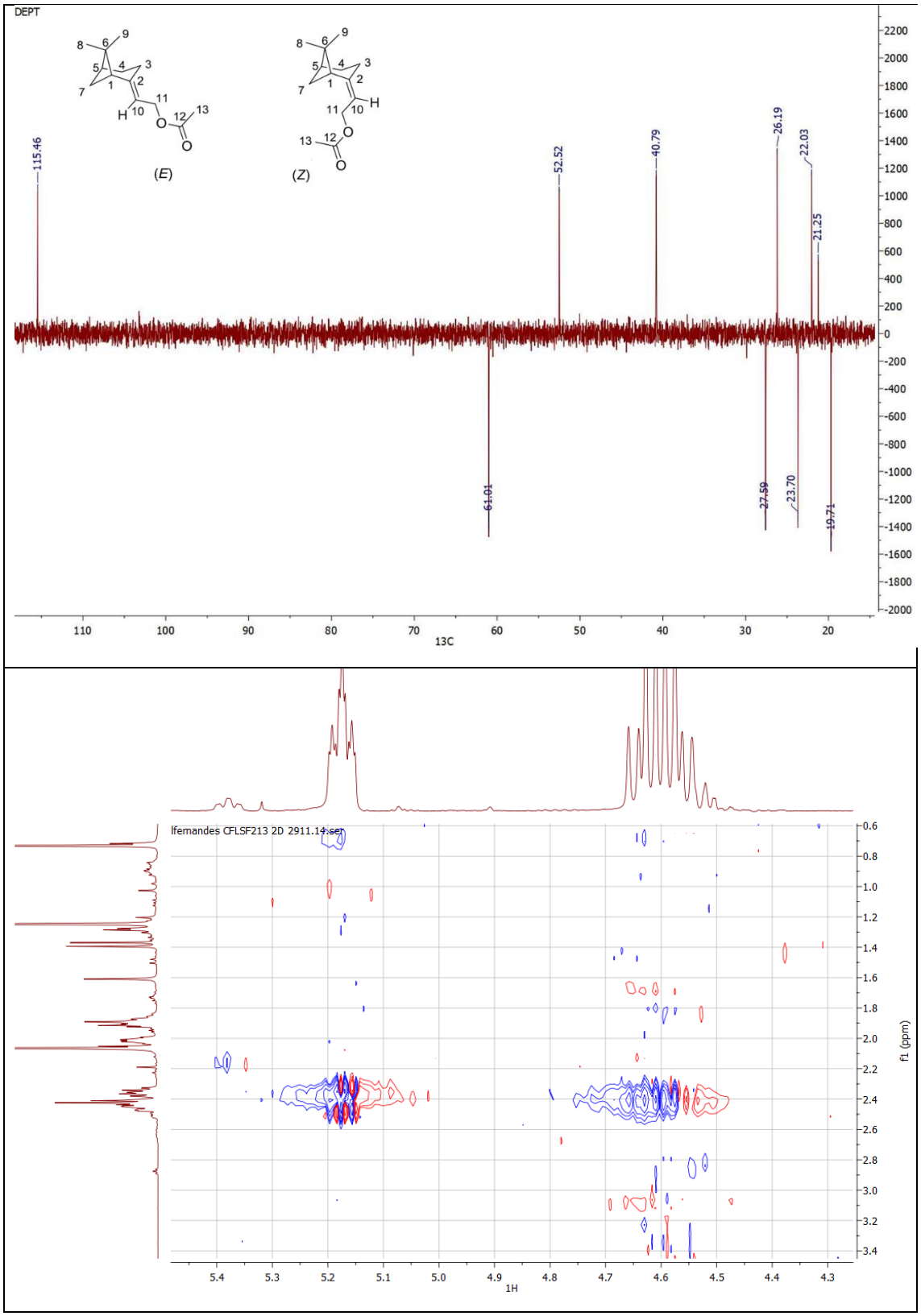
- **(-)-limonene/fumaronitrile cross metathesis product 9**



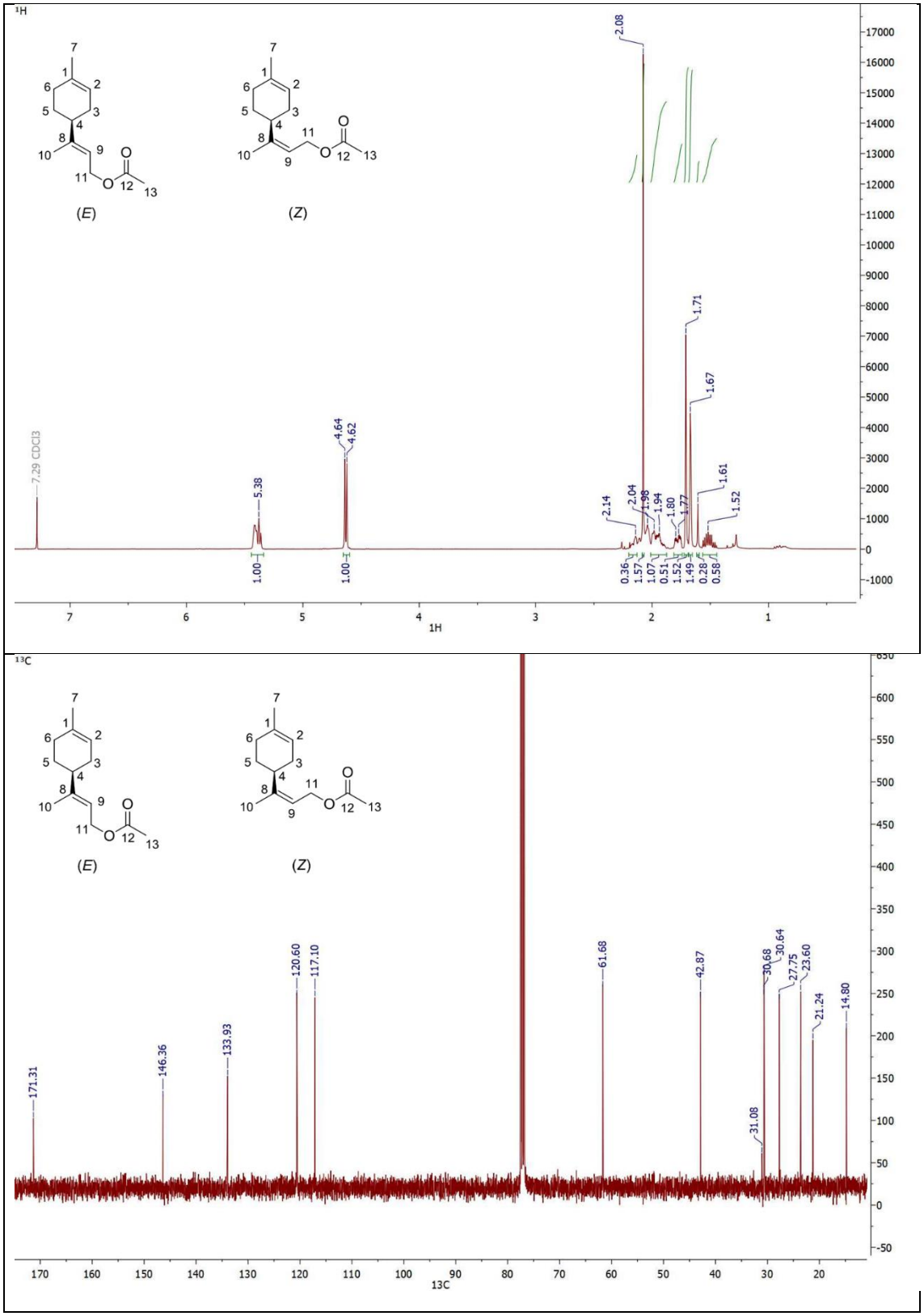

DEPT
(E)-9
(Z)-9
119.45
94.29
42.36
23.51
19.64
21.25
30.20
28.97
27.24
13C
lfernandes CFLSF232 2D.14.ser
1H
f1 (ppm)

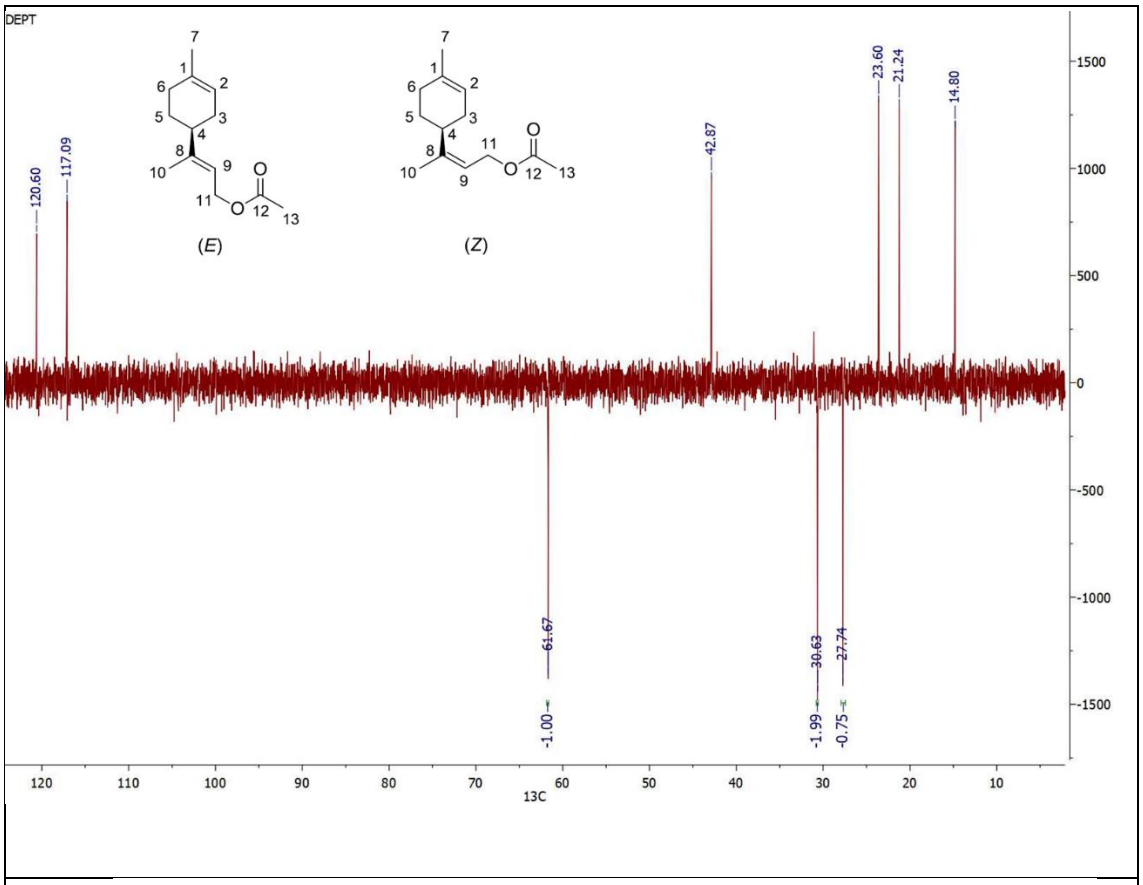
- **β-pinene/*cis*-1,4-diacetoxybut-2-ene cross metathesis product 16**

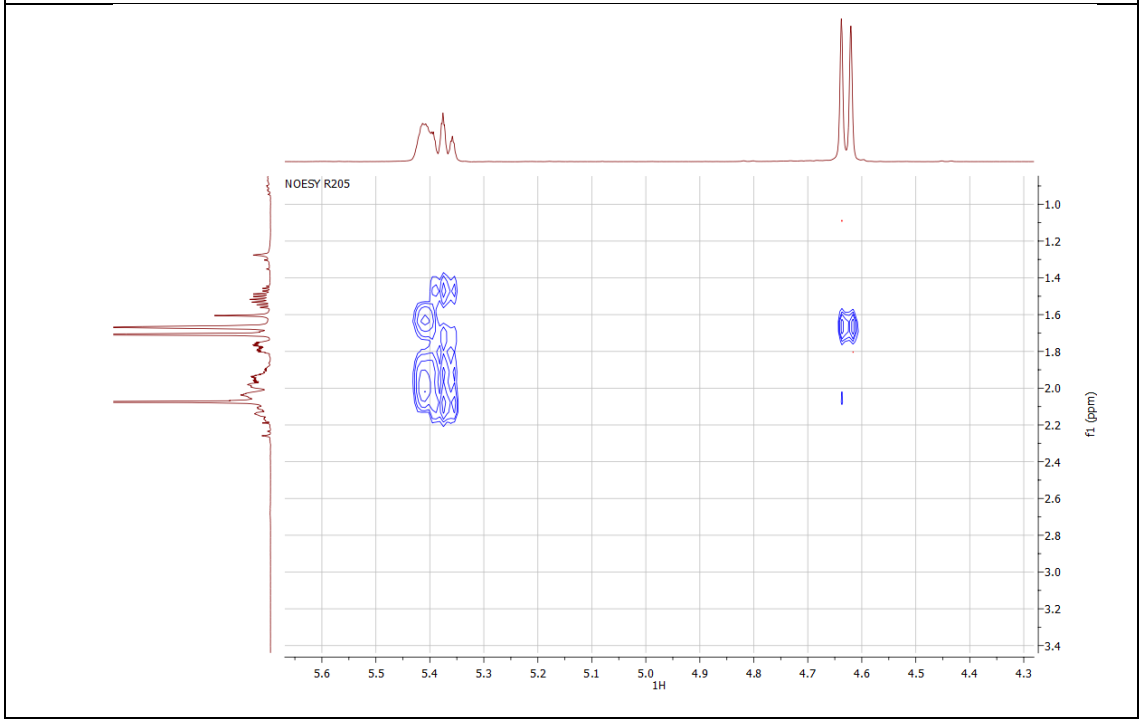



DEPT
(E)
(Z)
115.46
52.52
40.79
26.19
22.03
21.25
61.01
27.59
23.70
19.71
13C
lfernandes CFLSF213 2D 2911.14.ser
1H
f1 (ppm)

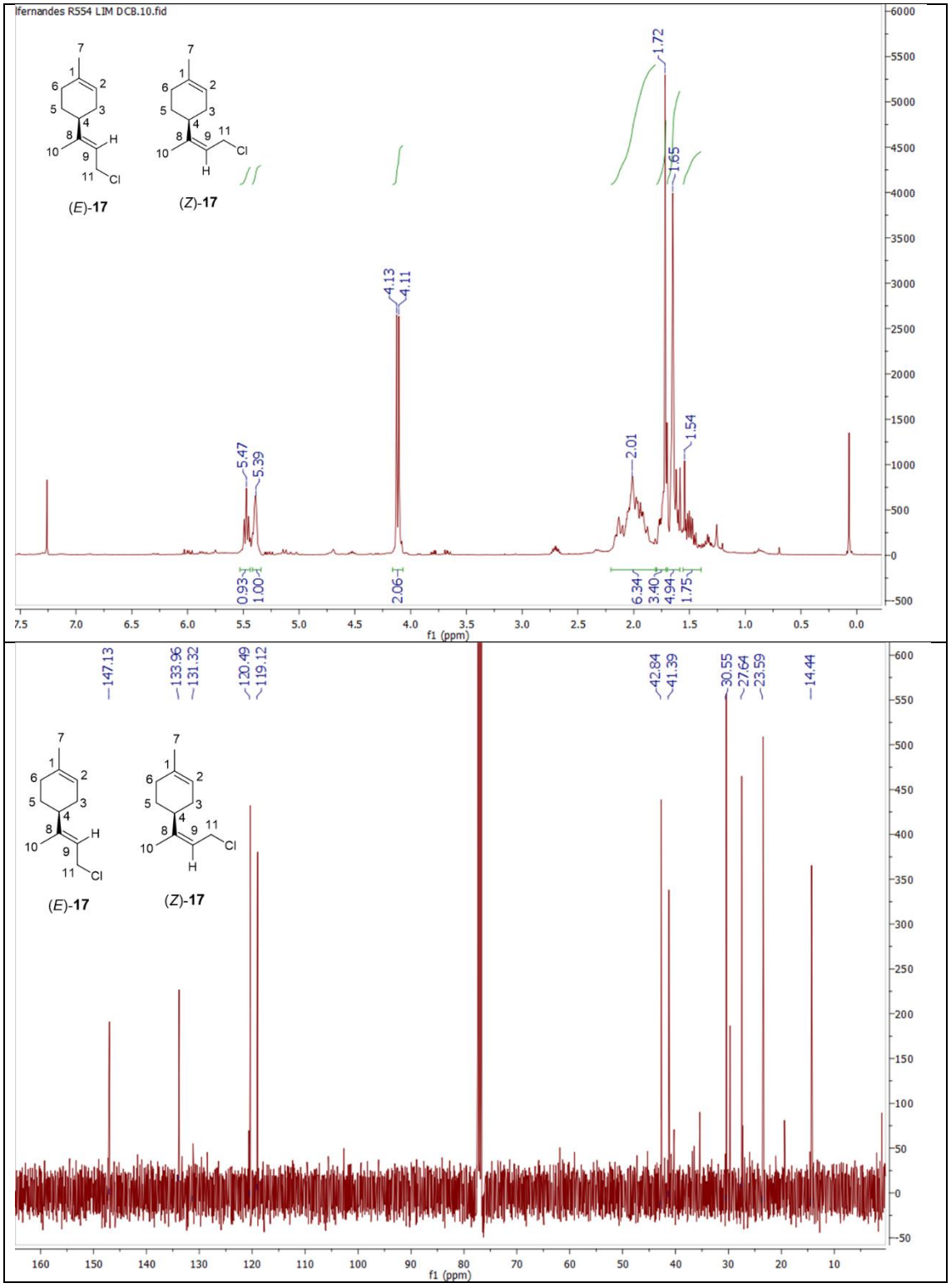
- **(-)-limonene/*cis*-1,4-diacetoxybut-2-ene cross metathesis product 17**

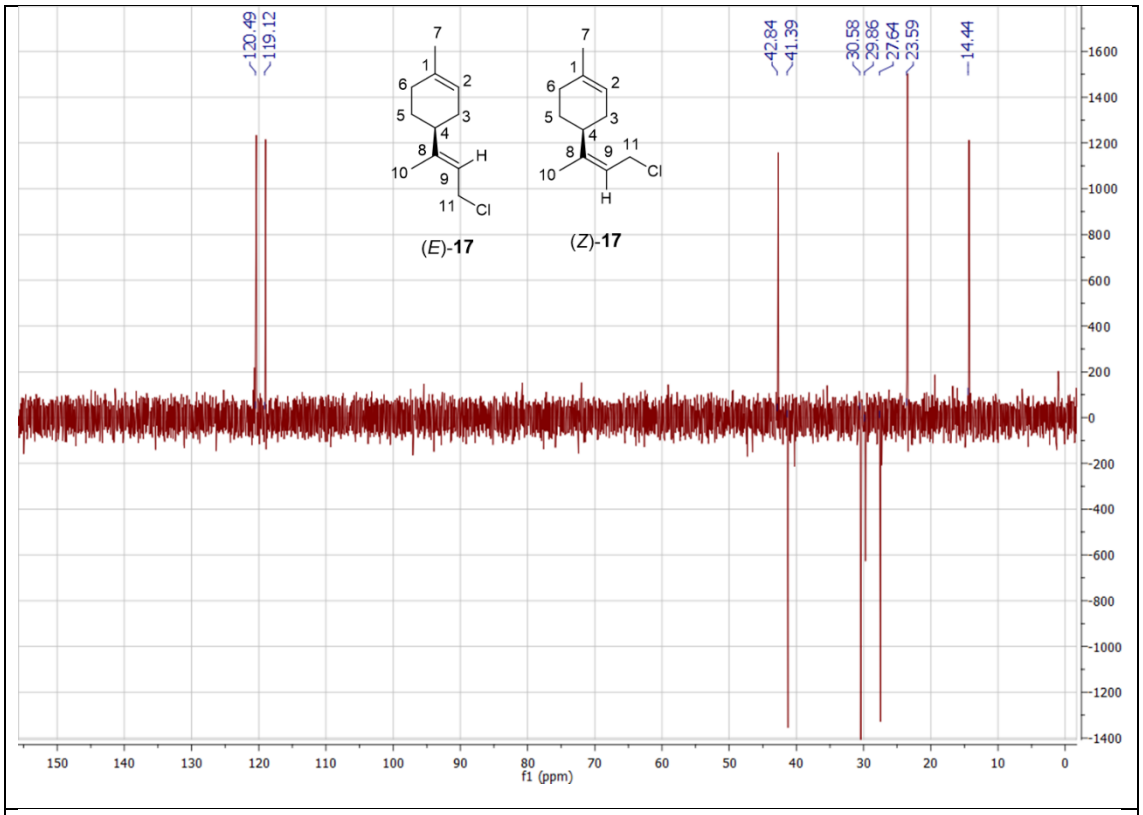


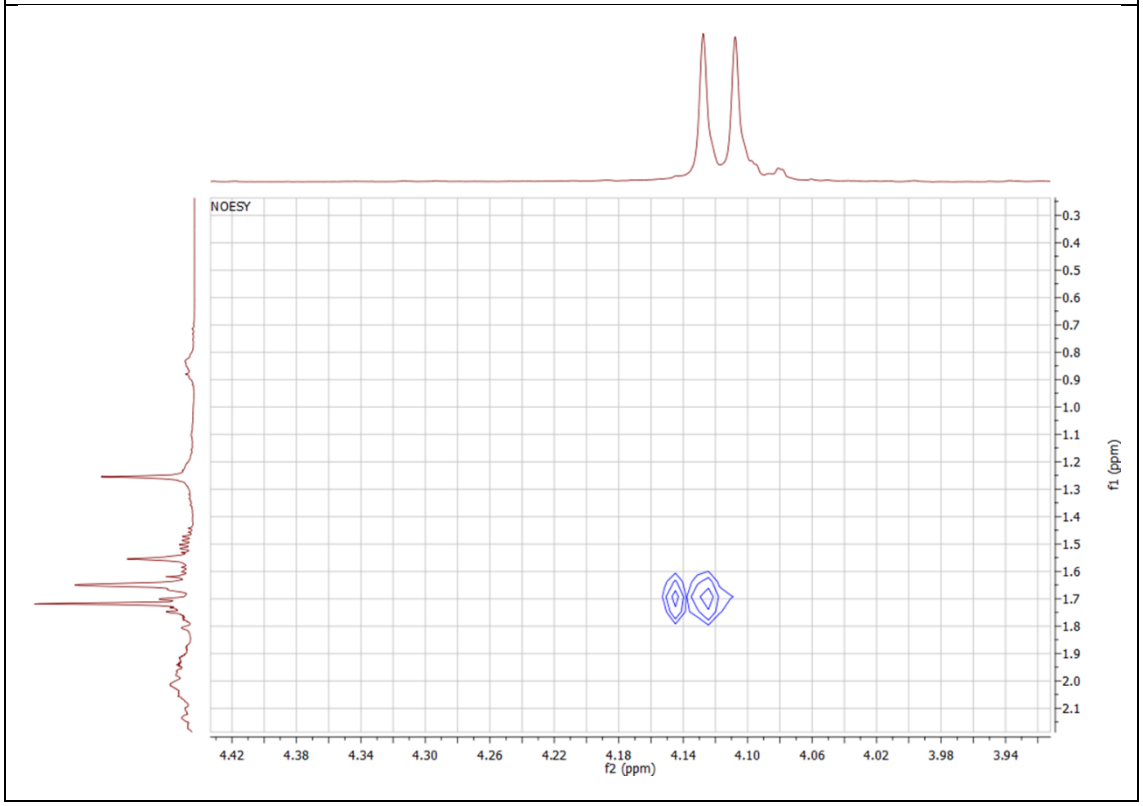

DEPT
(E)
(Z)
120.60
117.09
61.67
42.87
30.63
27.74
23.60
21.24
14.80
-1.00
-1.99
-0.75
13C


NOESY R205
1H
f1 (ppm)

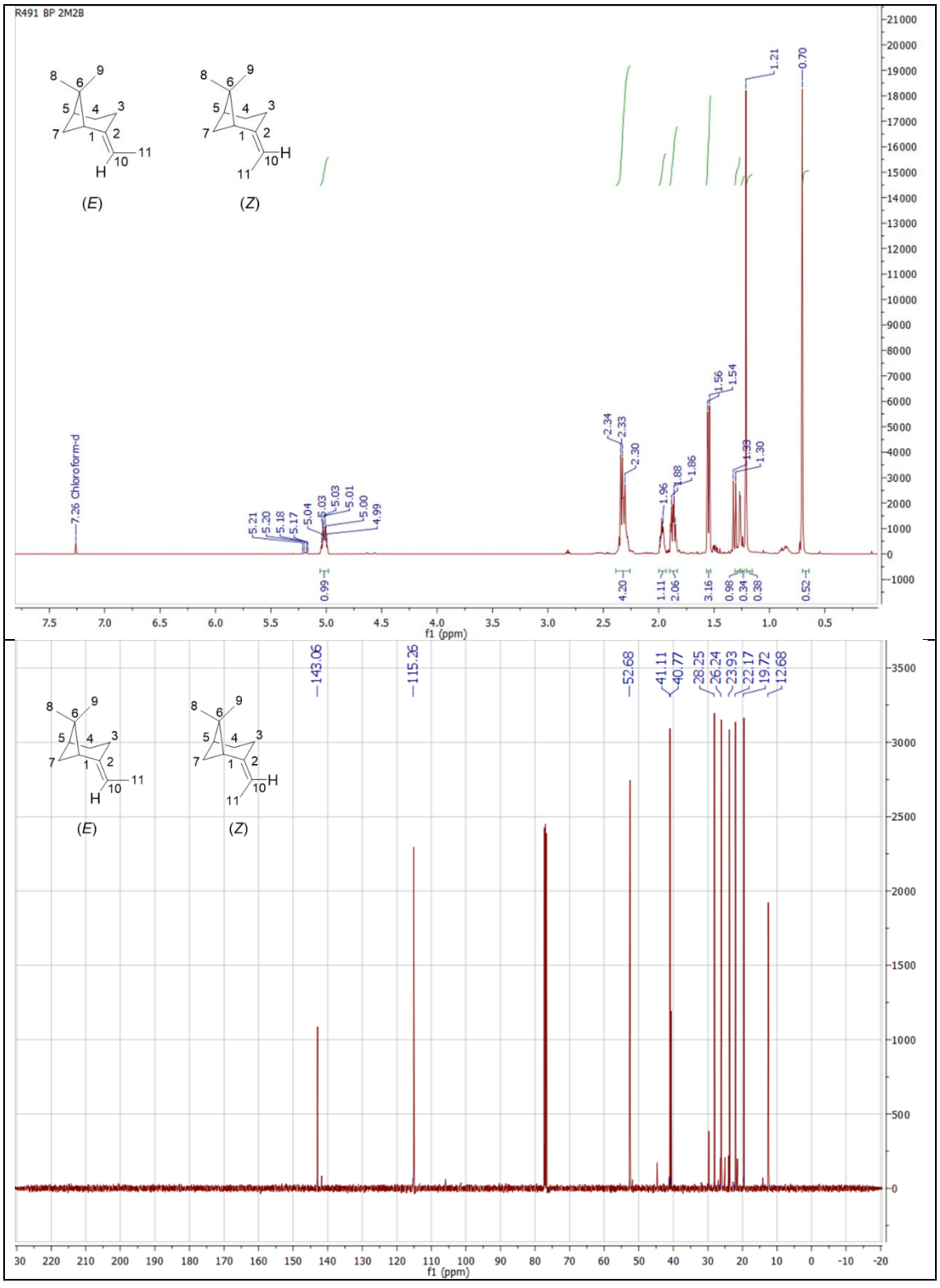
- **(-)-limonene/*cis*-1,4-dichlorobut-2-ene cross metathesis product 17**

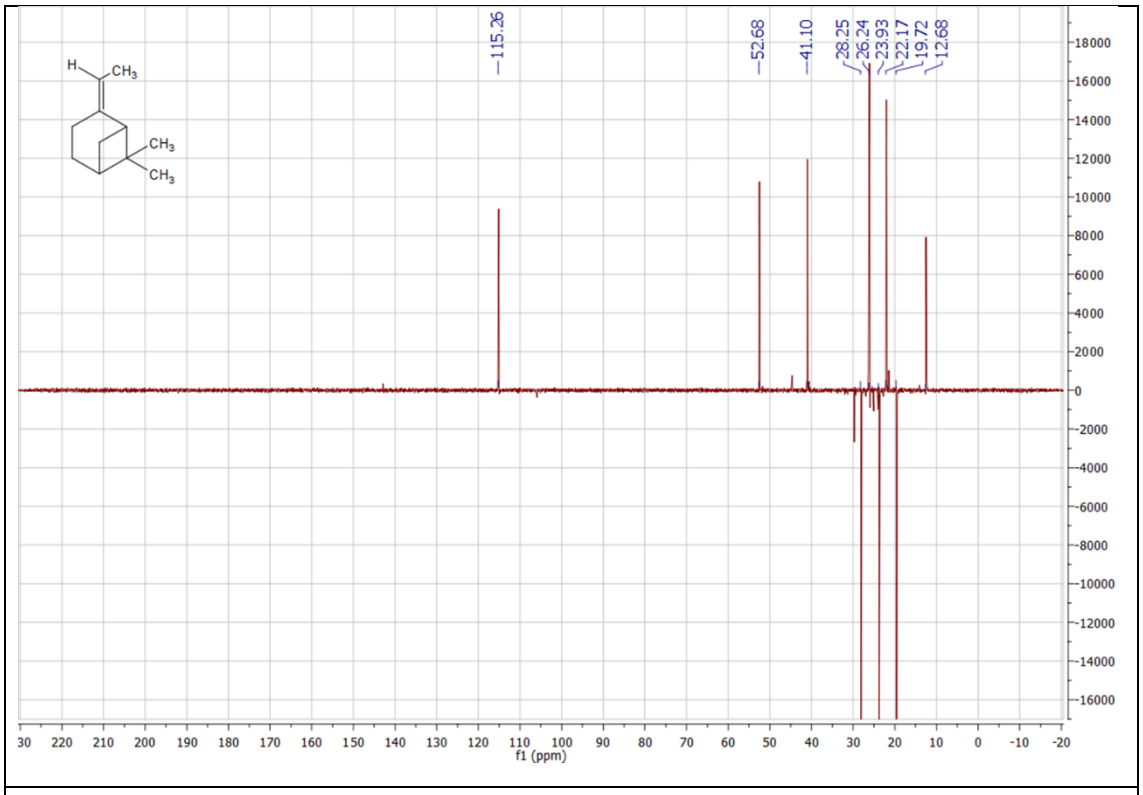


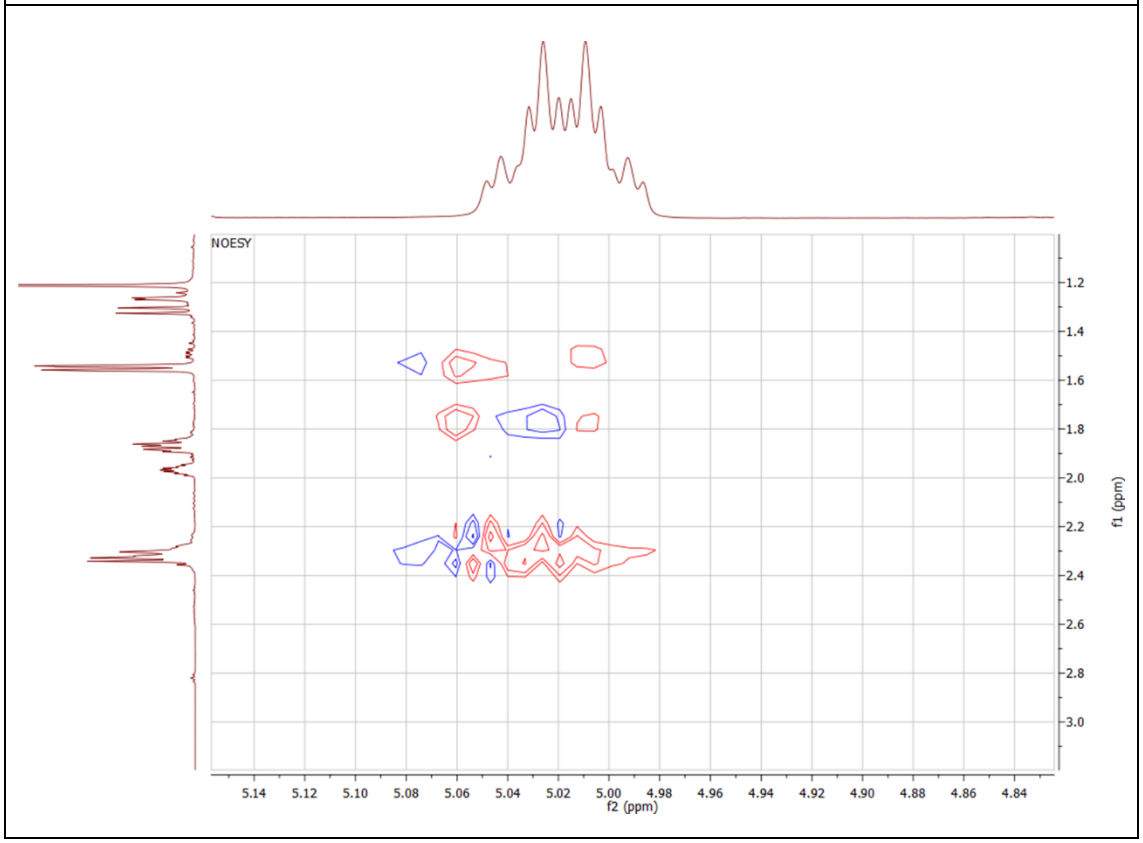

120.49
119.12
42.84
41.39
30.58
29.86
27.64
23.59
14.44
(E)-17
(Z)-17
f1 (ppm)


NOESY
f2 (ppm)
f1 (ppm)

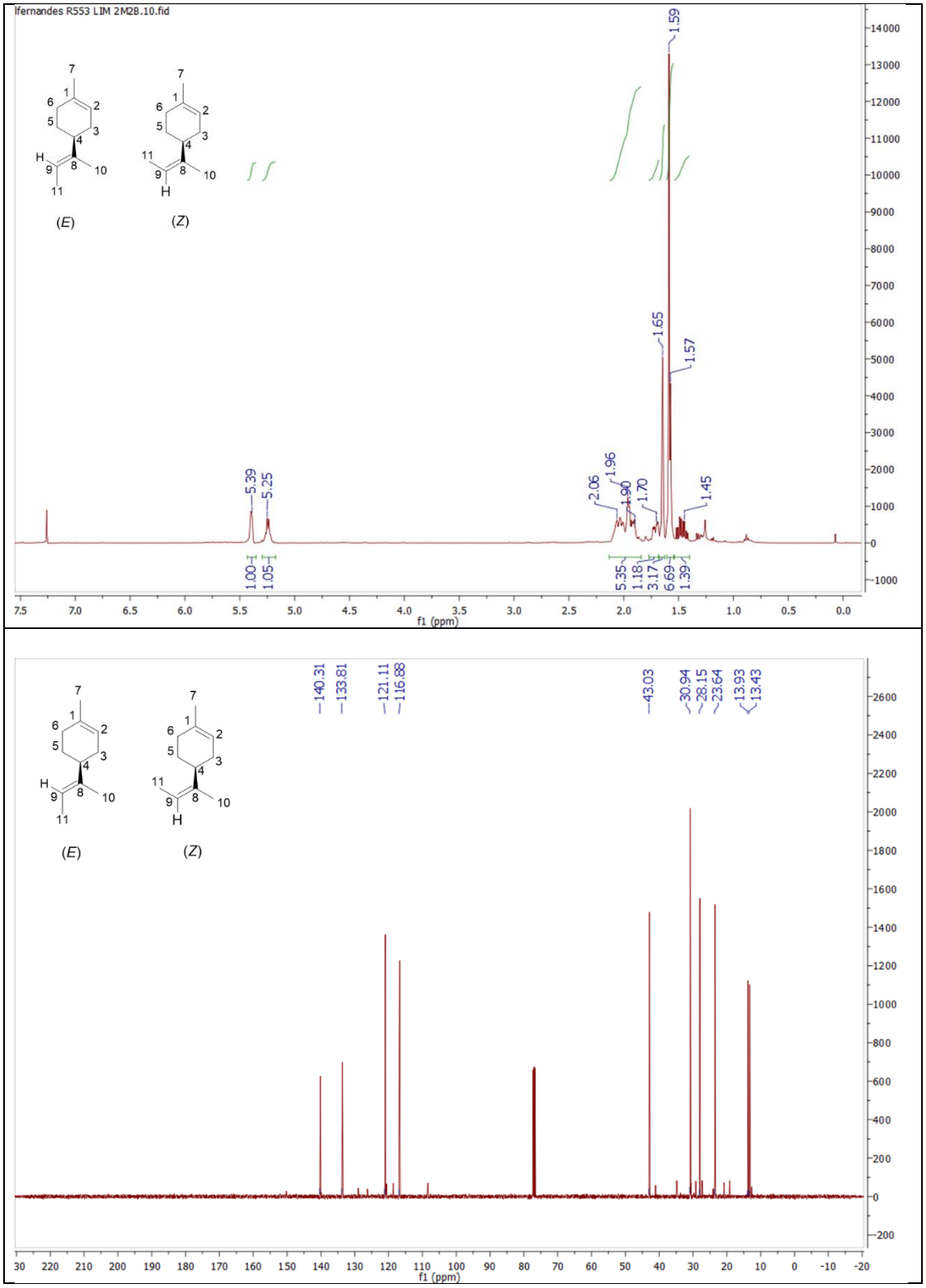
- **β-pinene/2-methylbut-2-ene cross metathesis product 19**

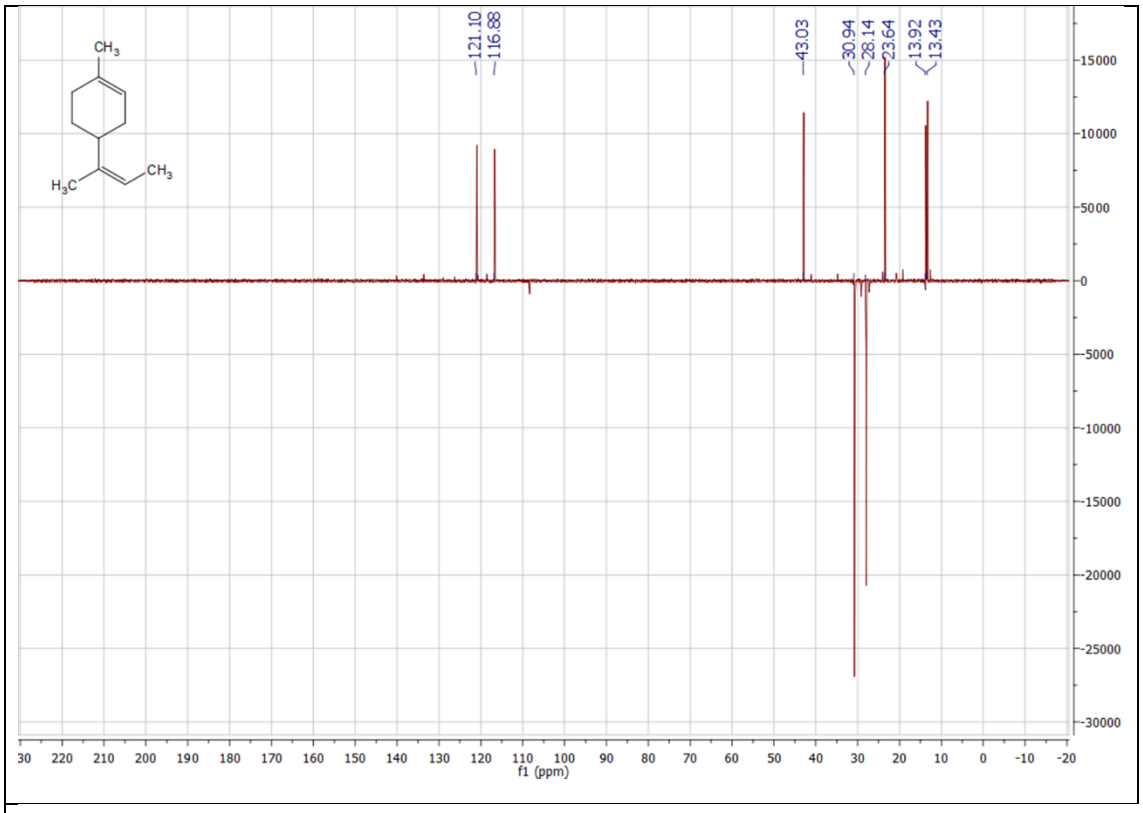


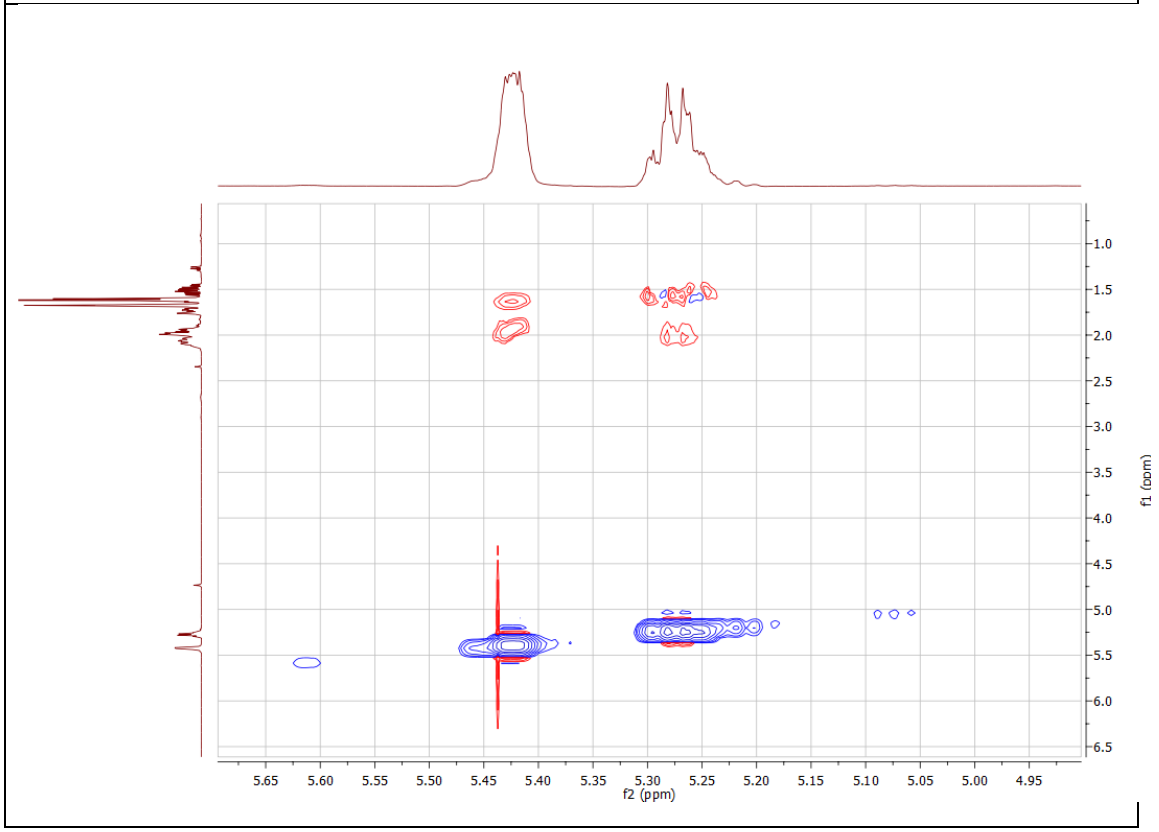

115.26
52.68
41.10
28.25
26.24
23.93
22.17
19.72
12.68
H
CH3
CH3
CH3
f1 (ppm)


NOESY
f2 (ppm)
f1 (ppm)

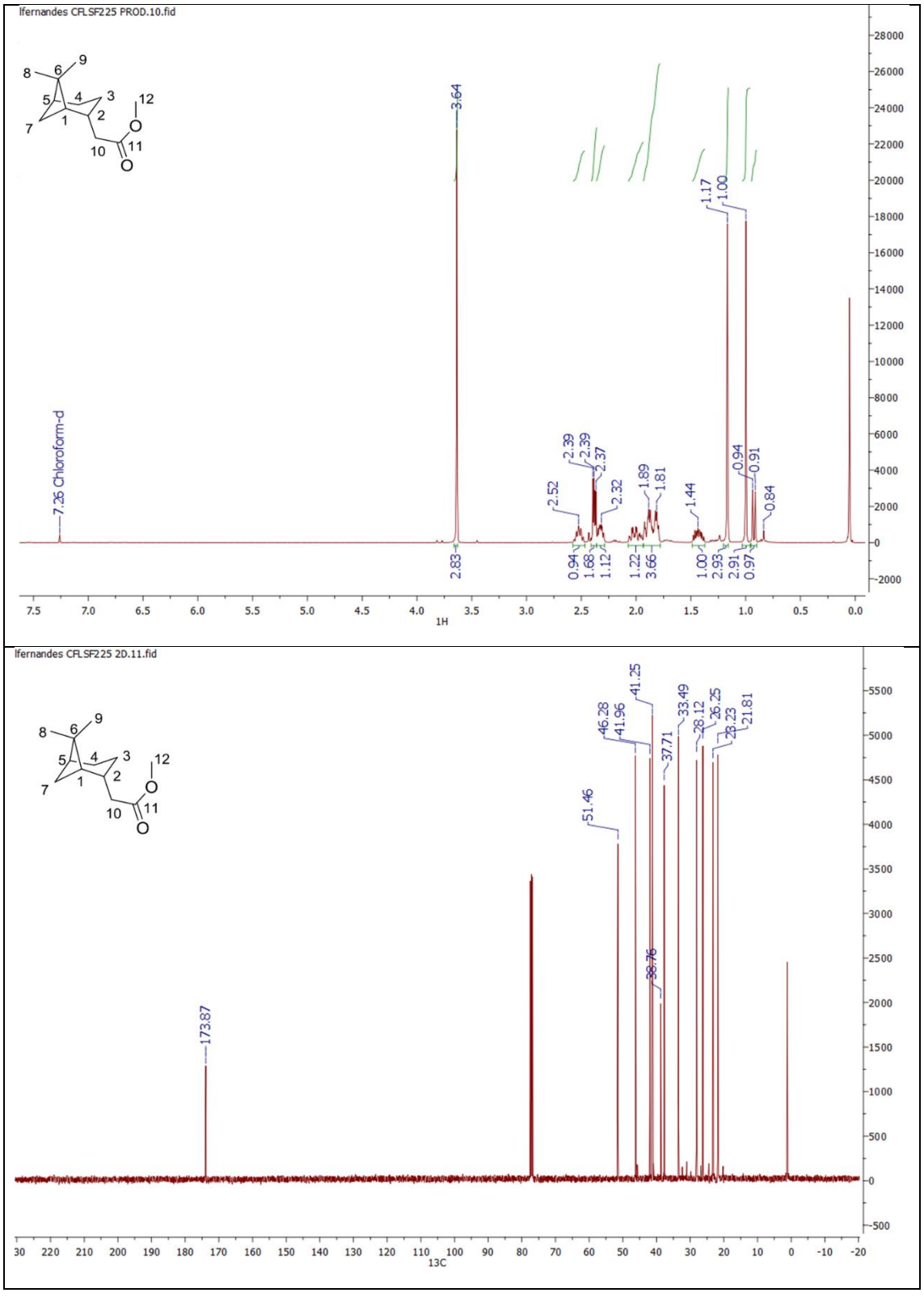
- **(-)-limonene/2-methylbut-2-ene cross metathesis product 20**



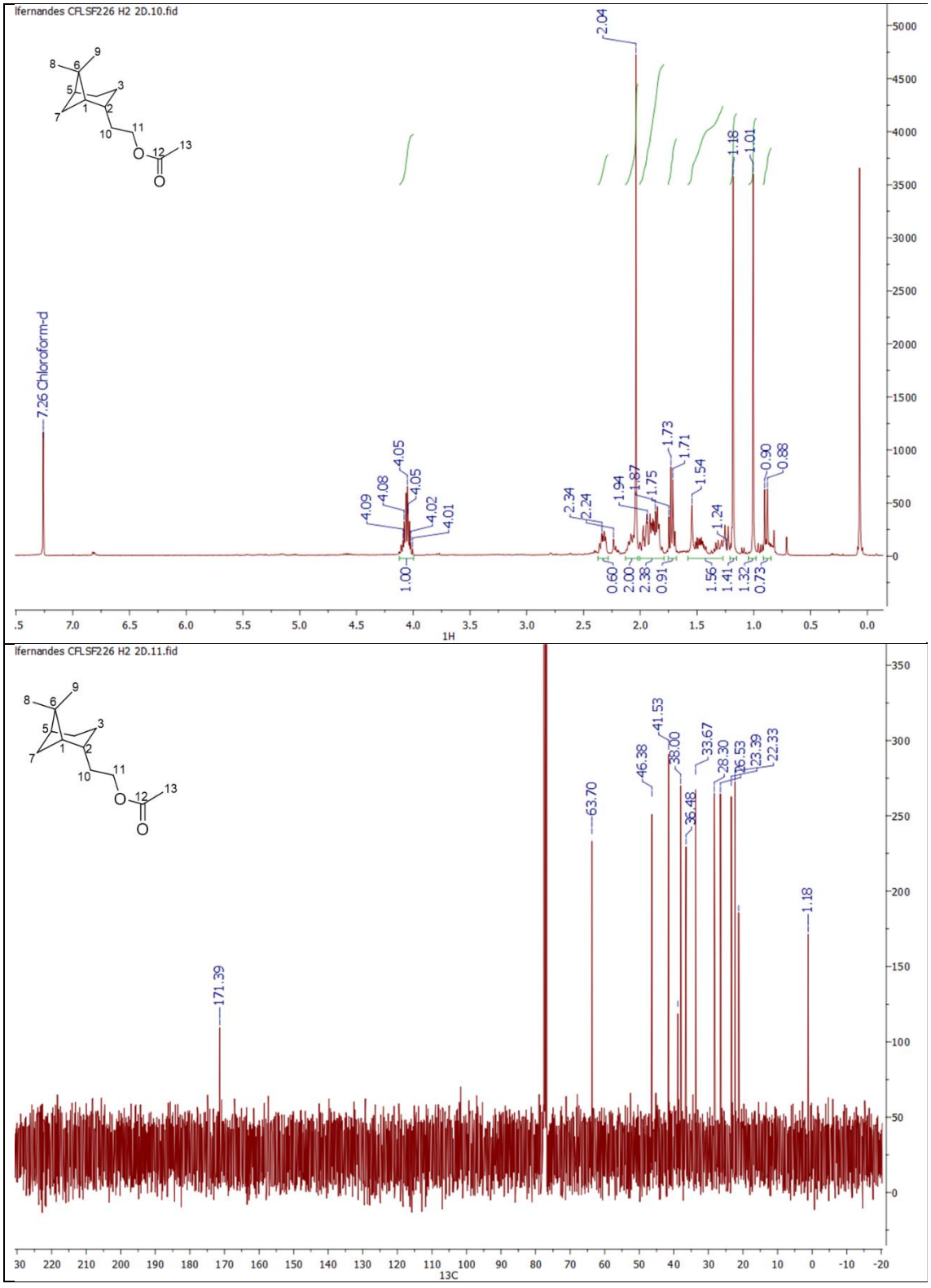

CH3
H3C
CH3
121.10
116.88
43.03
30.94
28.14
23.64
13.92
13.43
15000
10000
5000
0
-5000
-10000
-15000
-20000
-25000
-30000
f1 (ppm)


1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
f1 (ppm)
f2 (ppm)

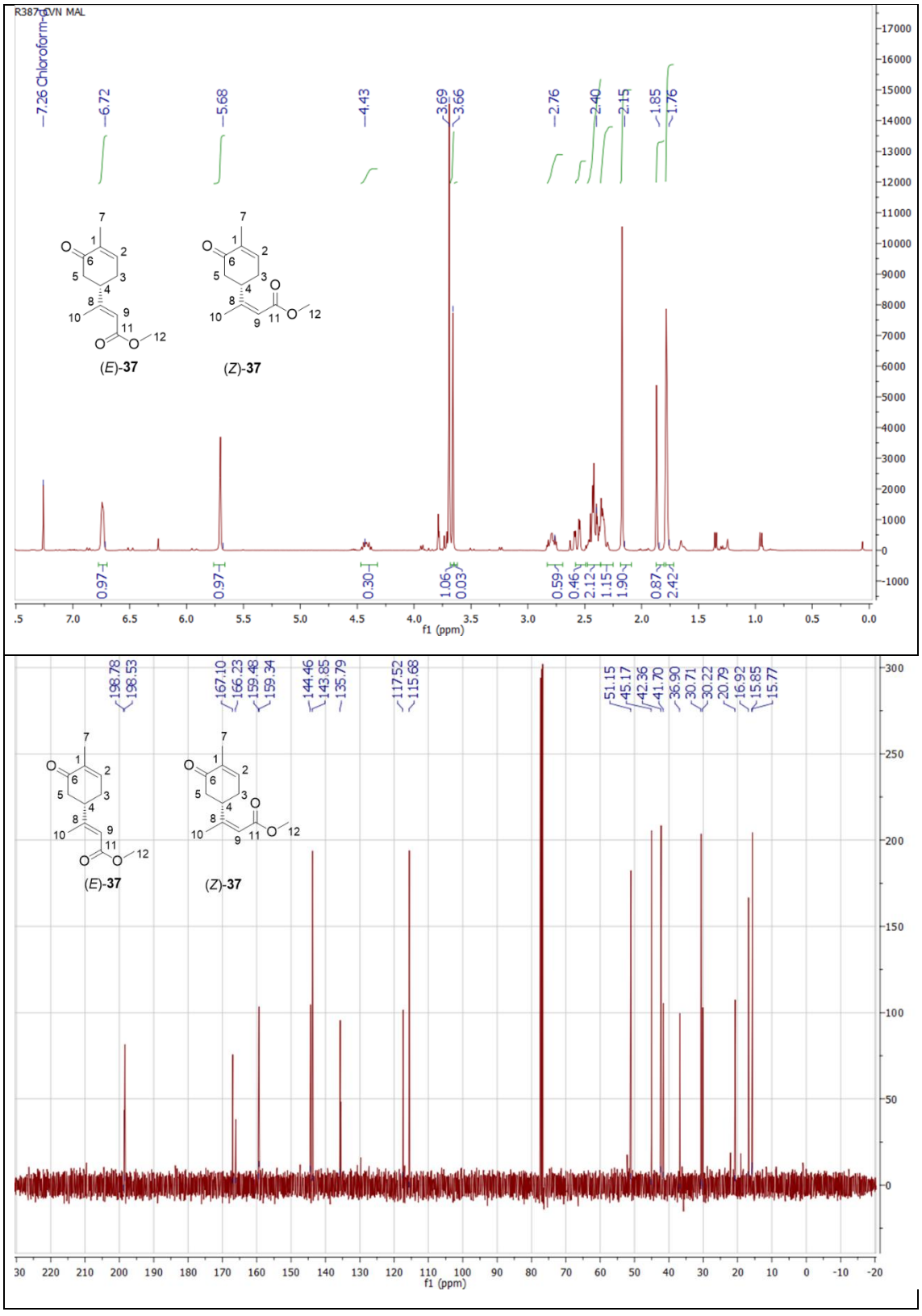
- **β-pinene/dimethyl fumarate tandem cross metathesis/hydrogenation product 30**

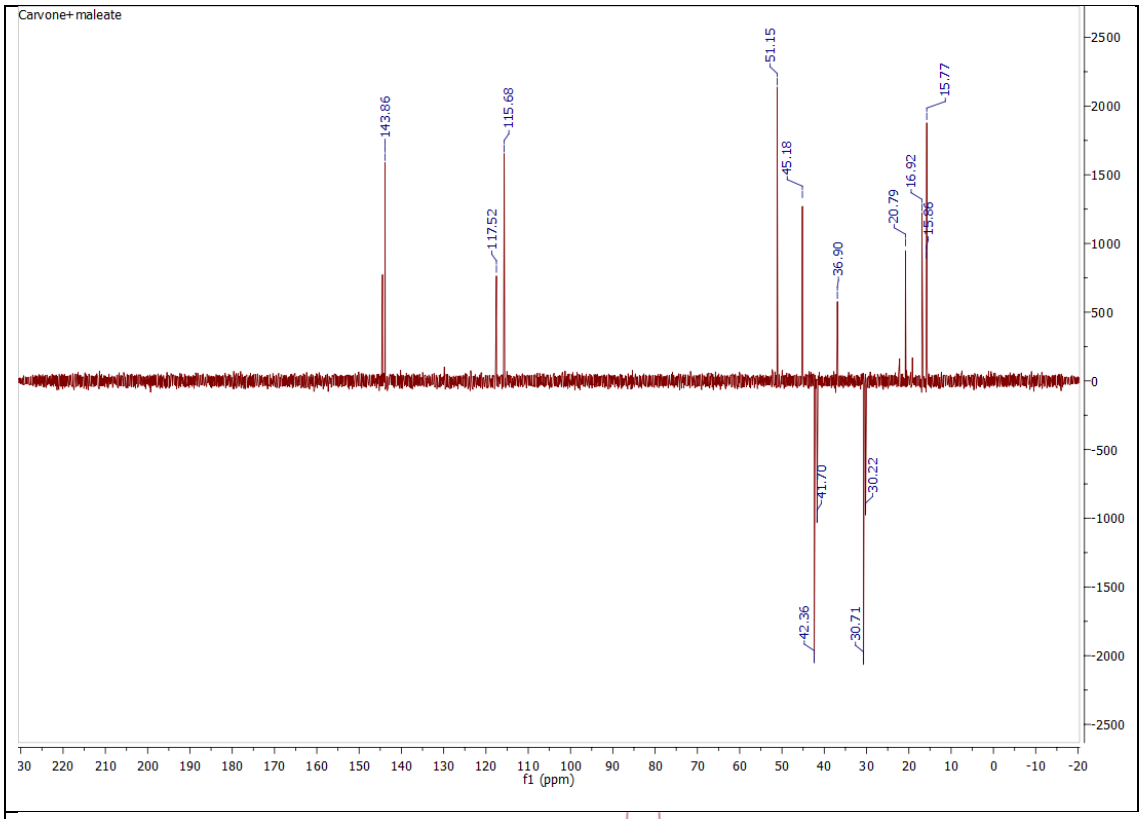


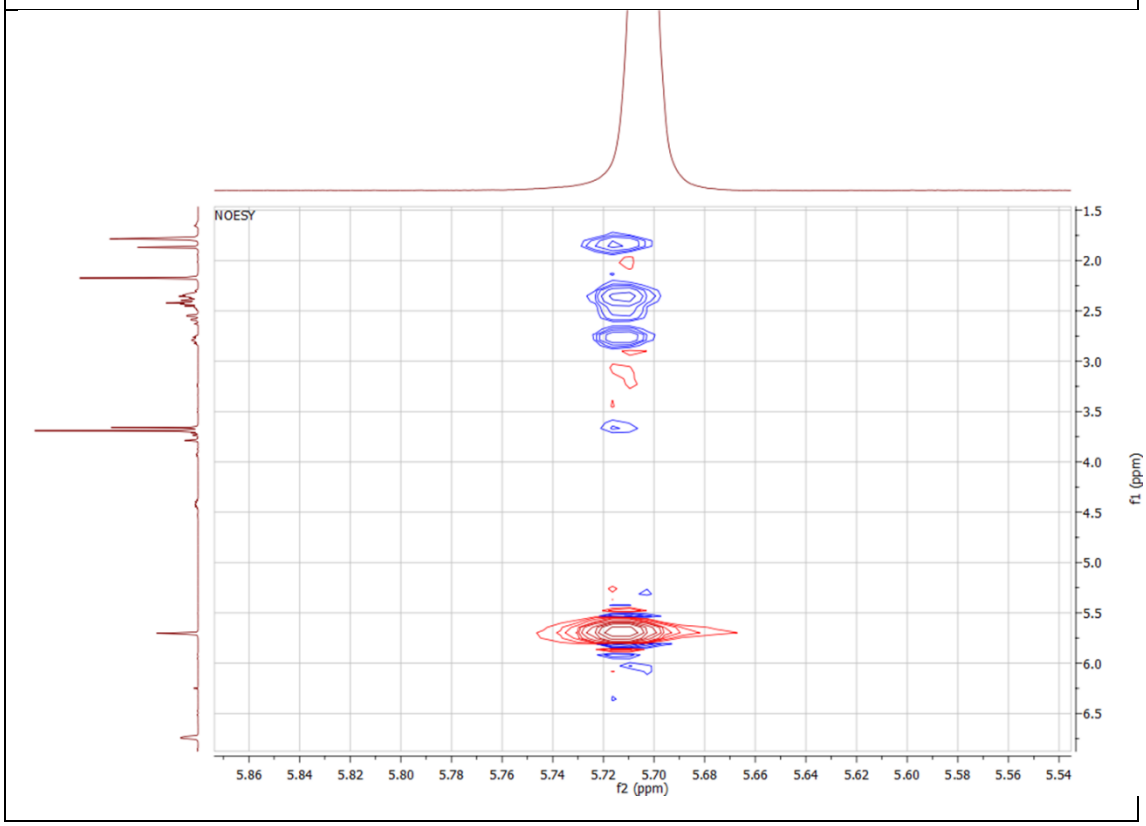
- **β-pinene/*cis*-1,4-diacetoxybut-2-ene tandem cross metathesis/ hydrogenation product 31**



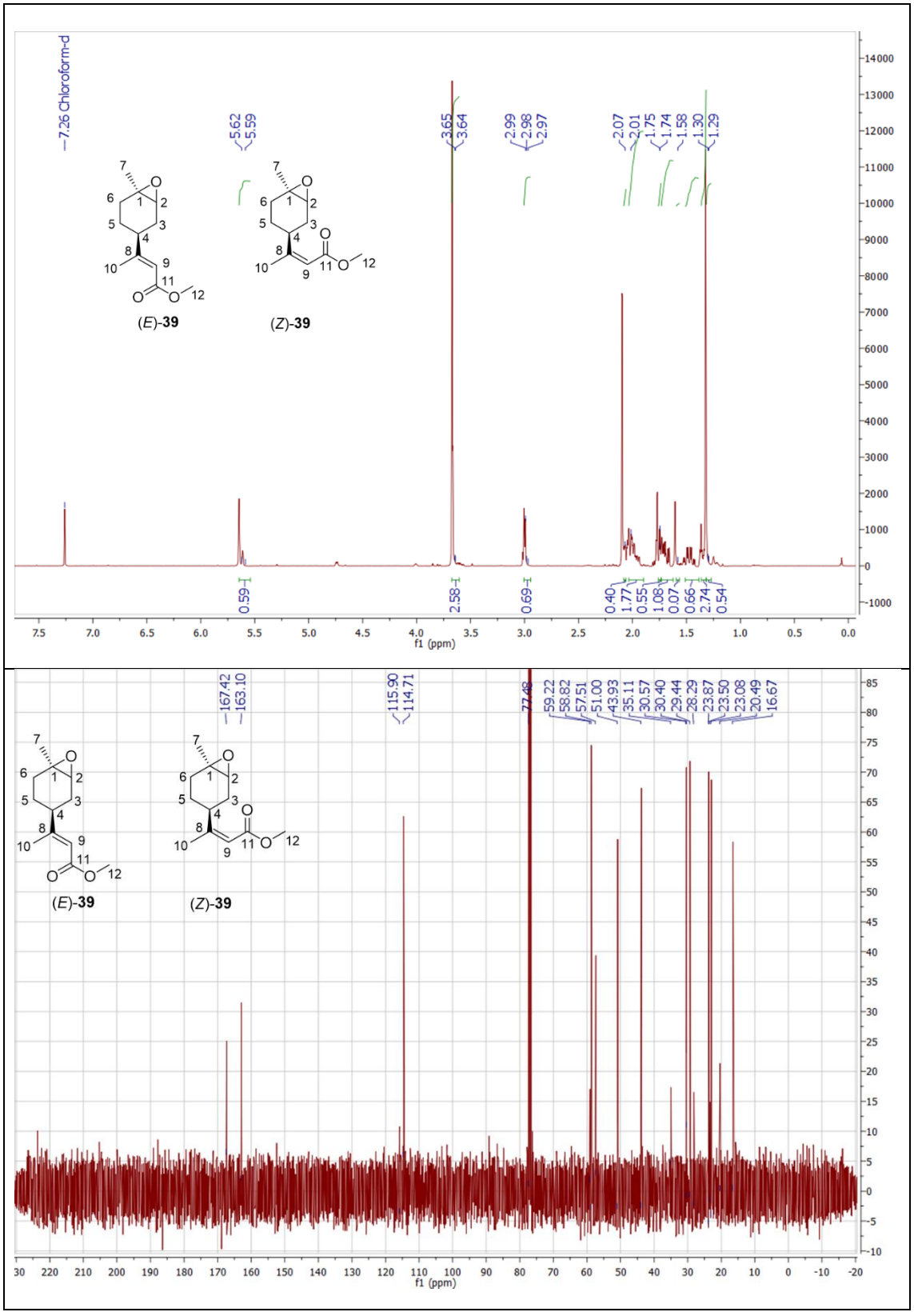
- **(D)-carvone/dimethyl maleate cross metathesis product 37**

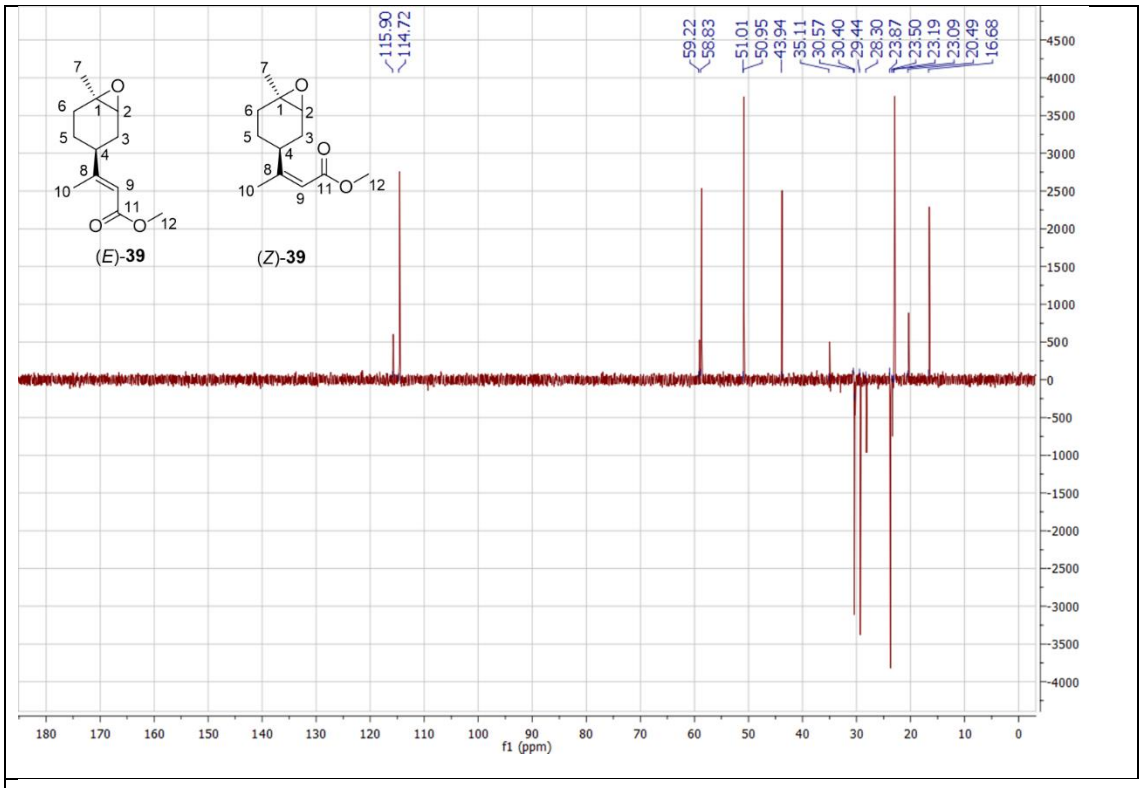


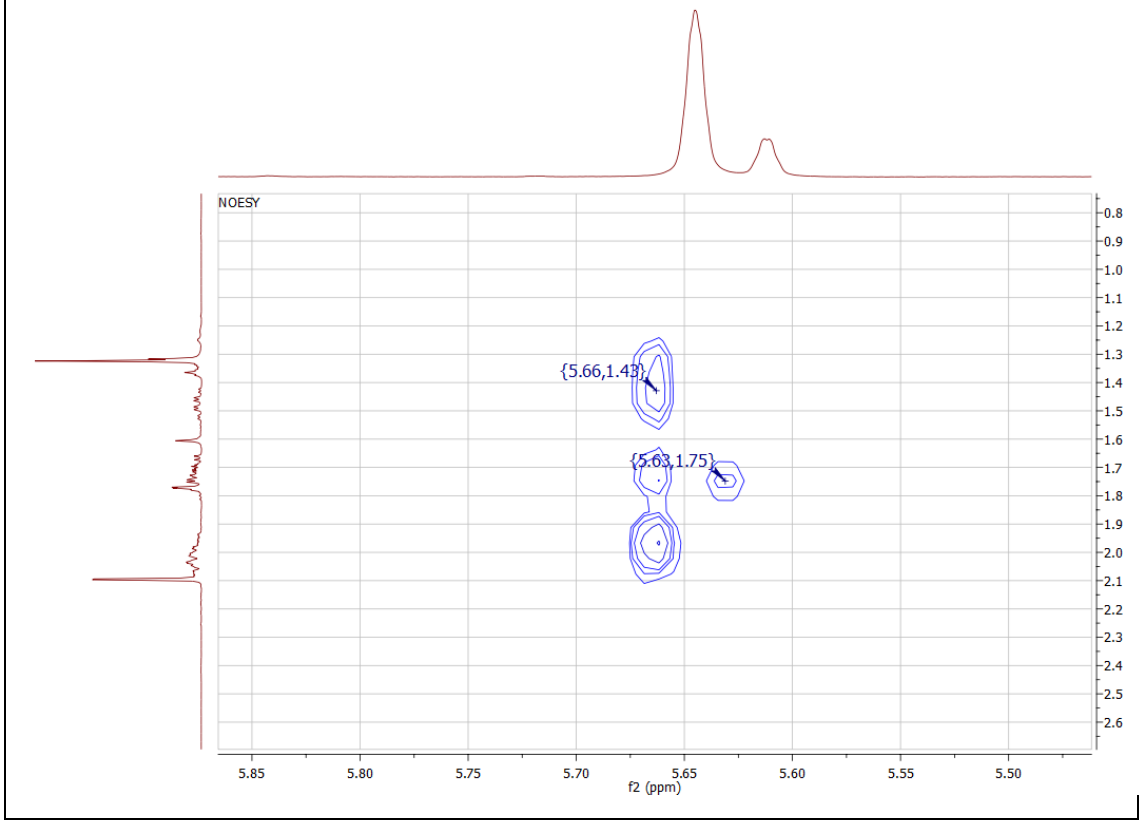

Carvone+maleate
143.86
115.68
117.52
51.15
45.18
36.90
20.79
16.92
15.88
15.77
41.70
30.22
42.36
30.71
f1 (ppm)


NOESY
f2 (ppm)
f1 (ppm)

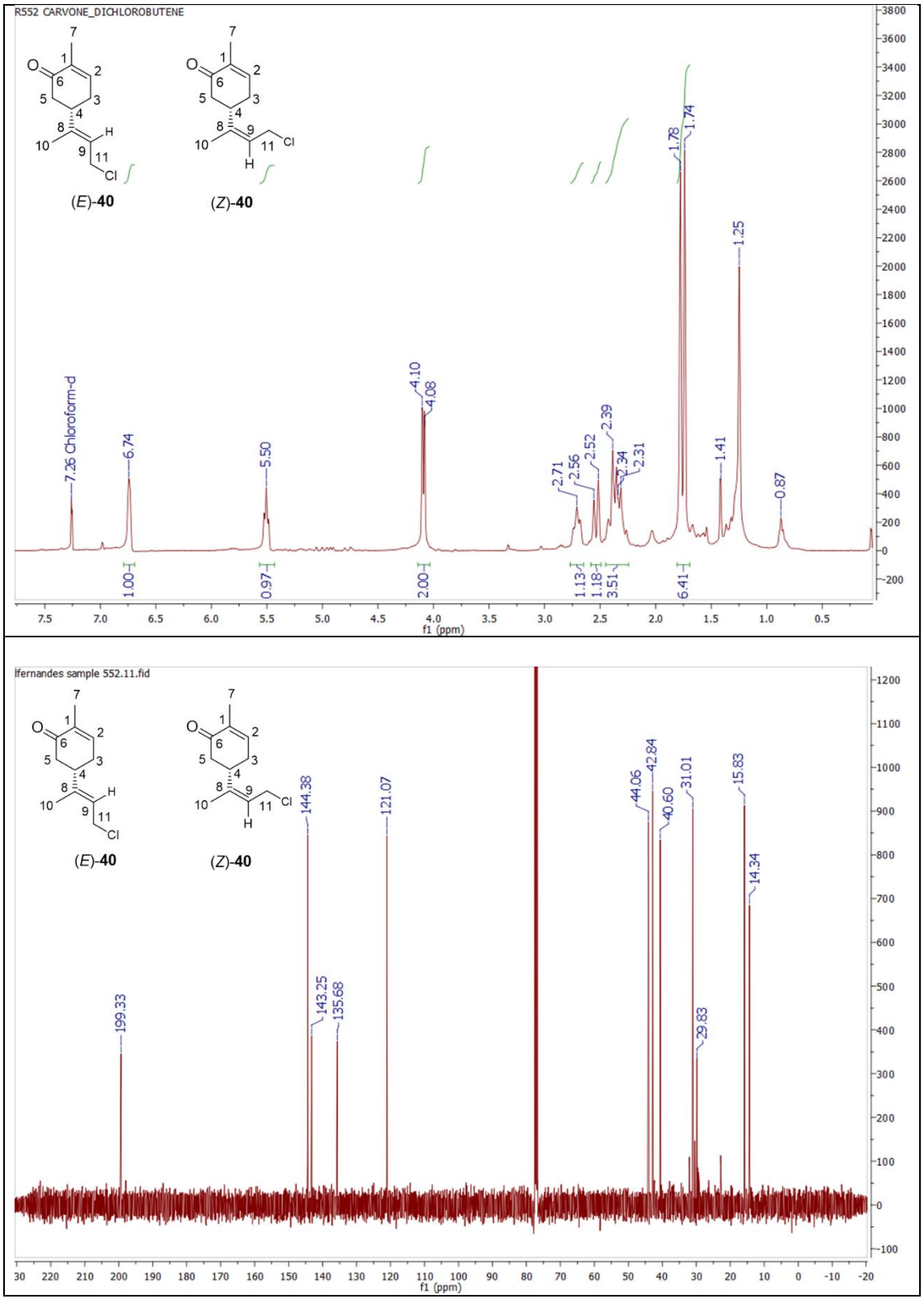
- **(+)-*trans*-limonene epoxide/dimethyl maleate cross metathesis product 39**

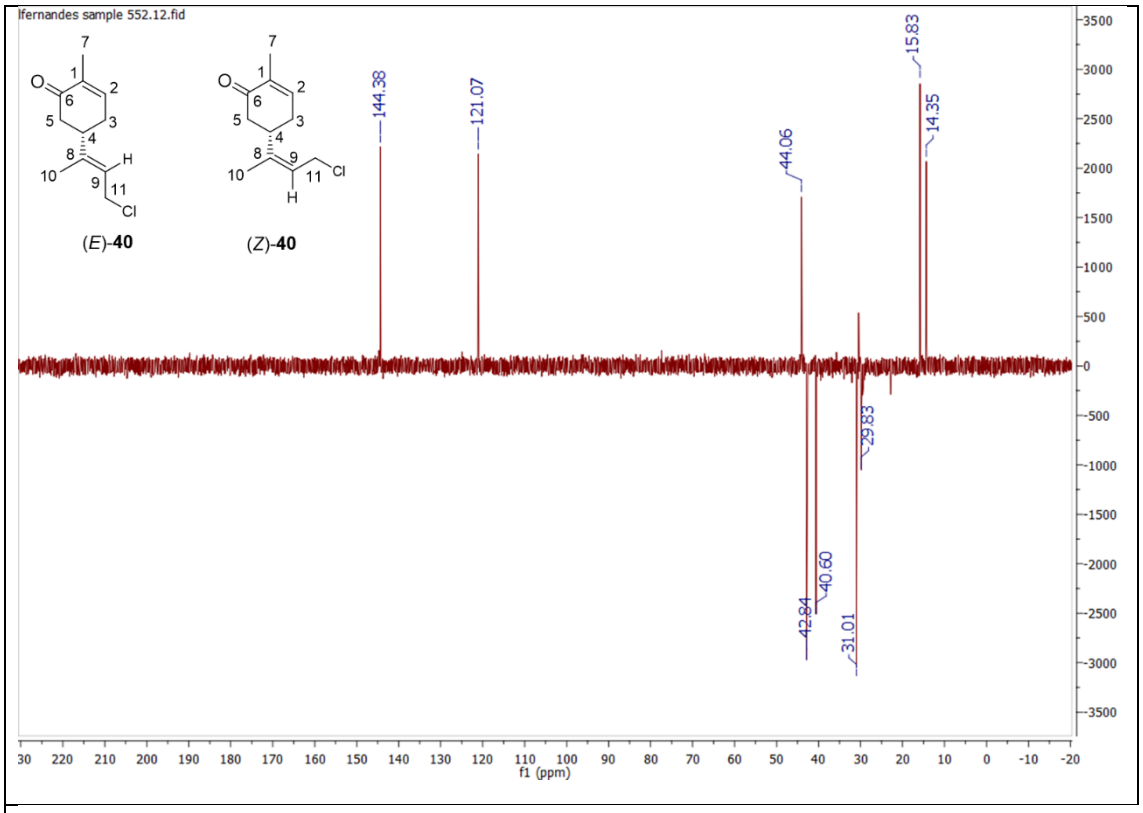


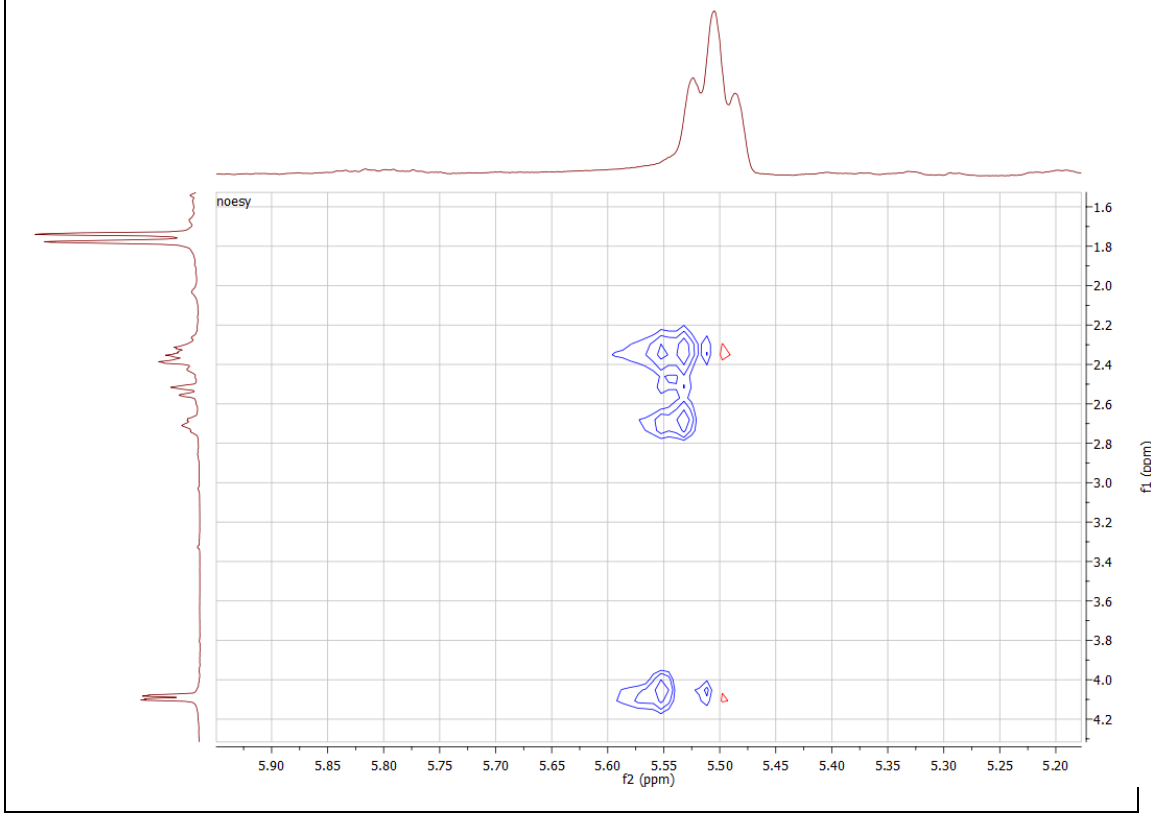

(E)-39
(Z)-39
115.90
114.72
59.22
58.83
51.01
50.95
43.94
35.11
30.57
30.40
29.44
28.30
23.87
23.50
23.19
23.09
20.49
16.68
f1 (ppm)


NOESY
{5.66,1.43}
{5.63,1.75}
f2 (ppm)

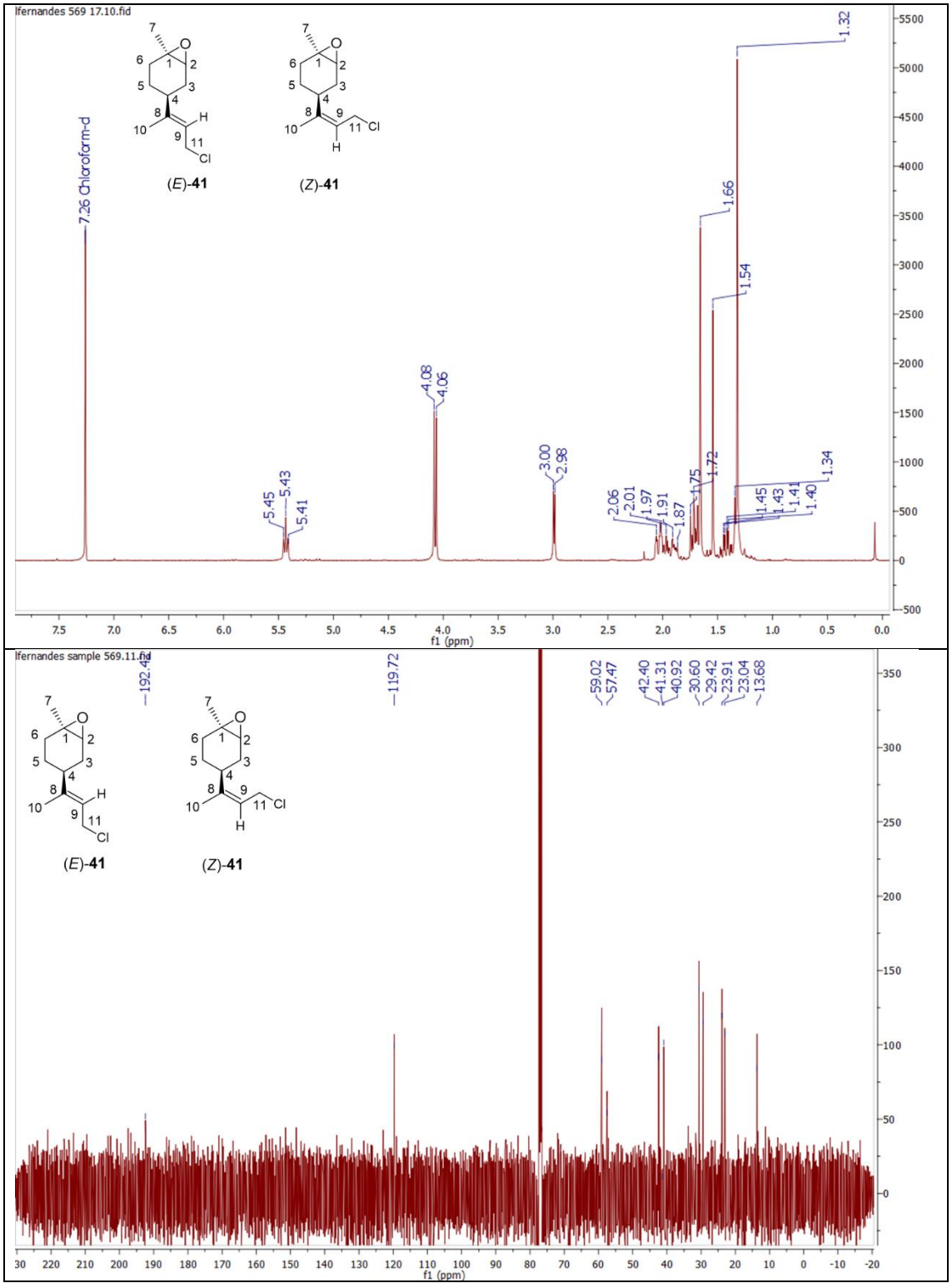
- **(D)-carvone/*cis*-1,4-dichlorobut-2-ene cross metathesis product 40**



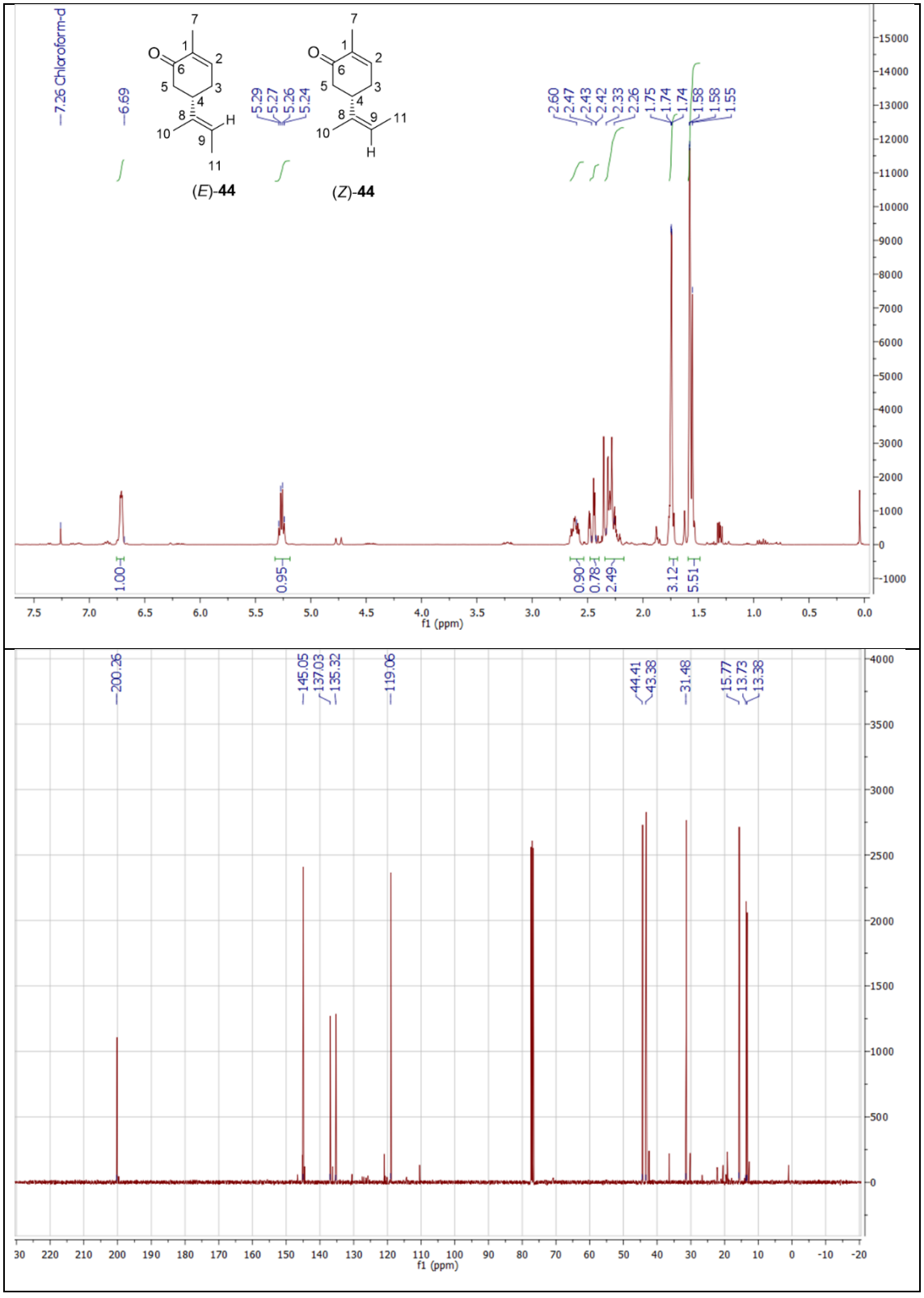

lfernandes sample 552.12.fid
(E)-40
(Z)-40
144.38
121.07
44.06
15.83
14.35
42.84
40.60
31.01
29.83
f1 (ppm)

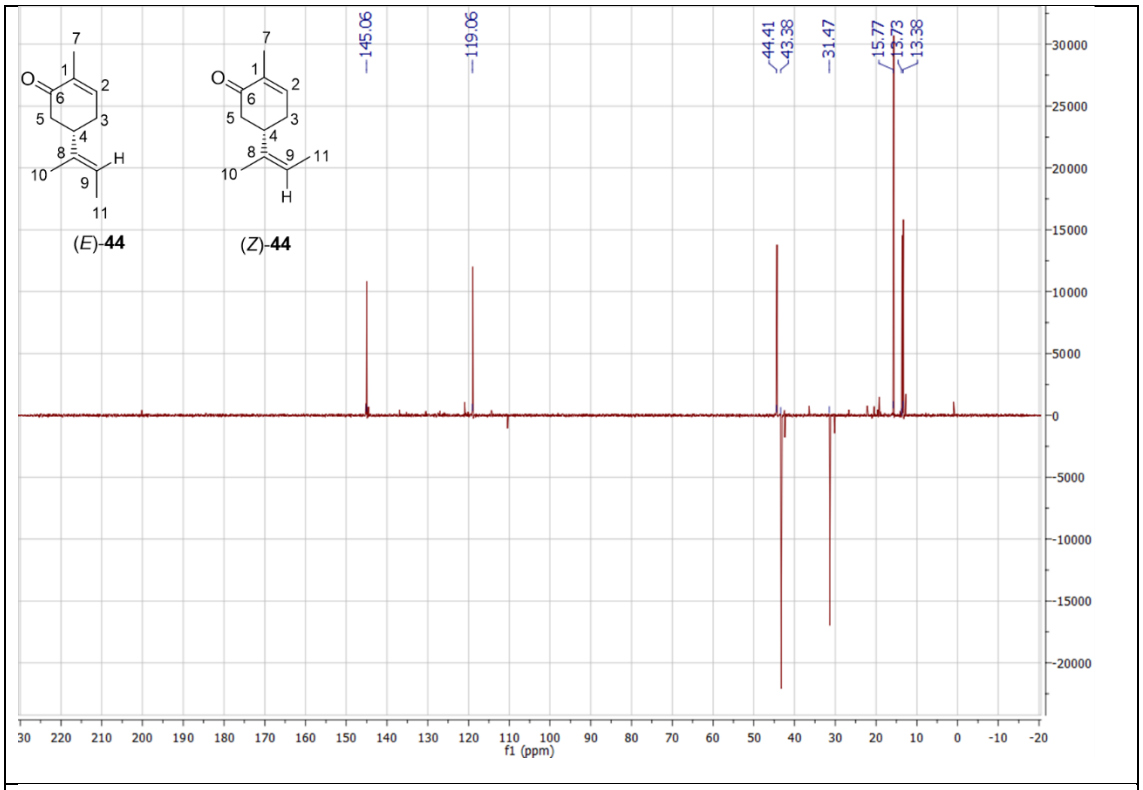

noesy
f2 (ppm)
f1 (ppm)

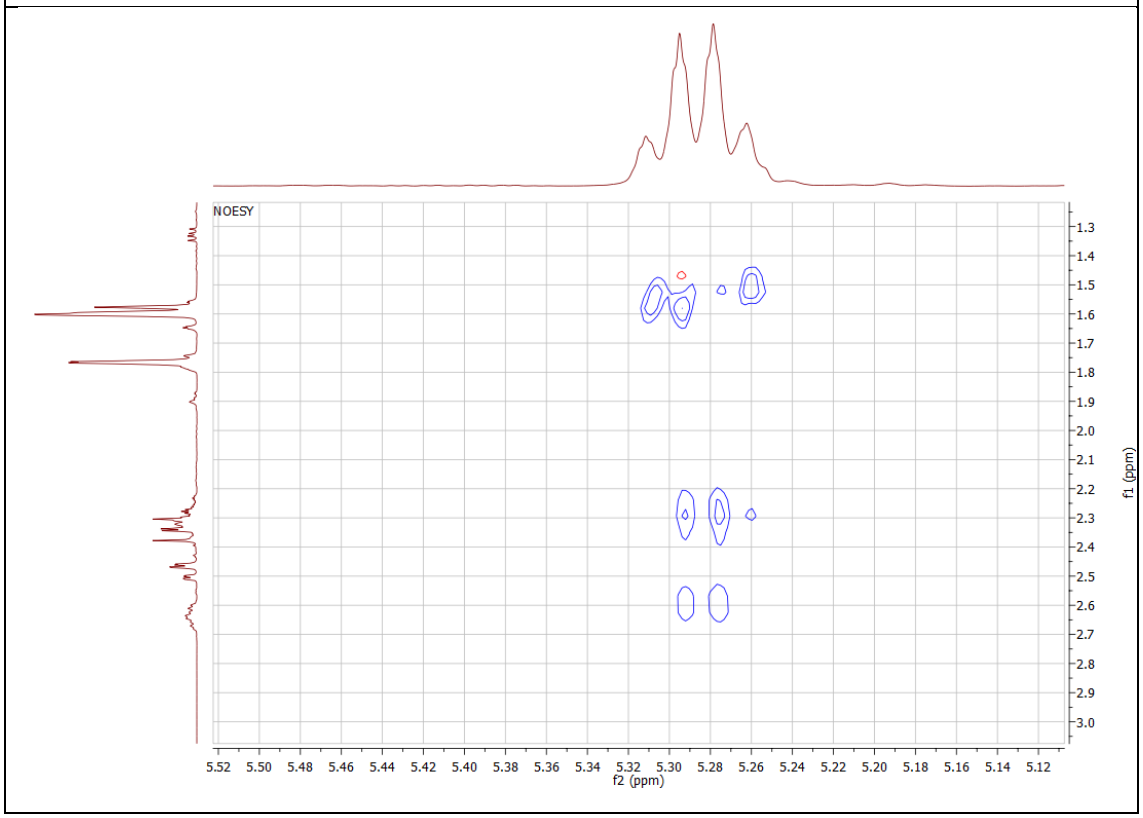
- **(+)-*trans*-limonene epoxide/ *cis*-1,4-dichlorobut-2-ene cross metathesis product 41**



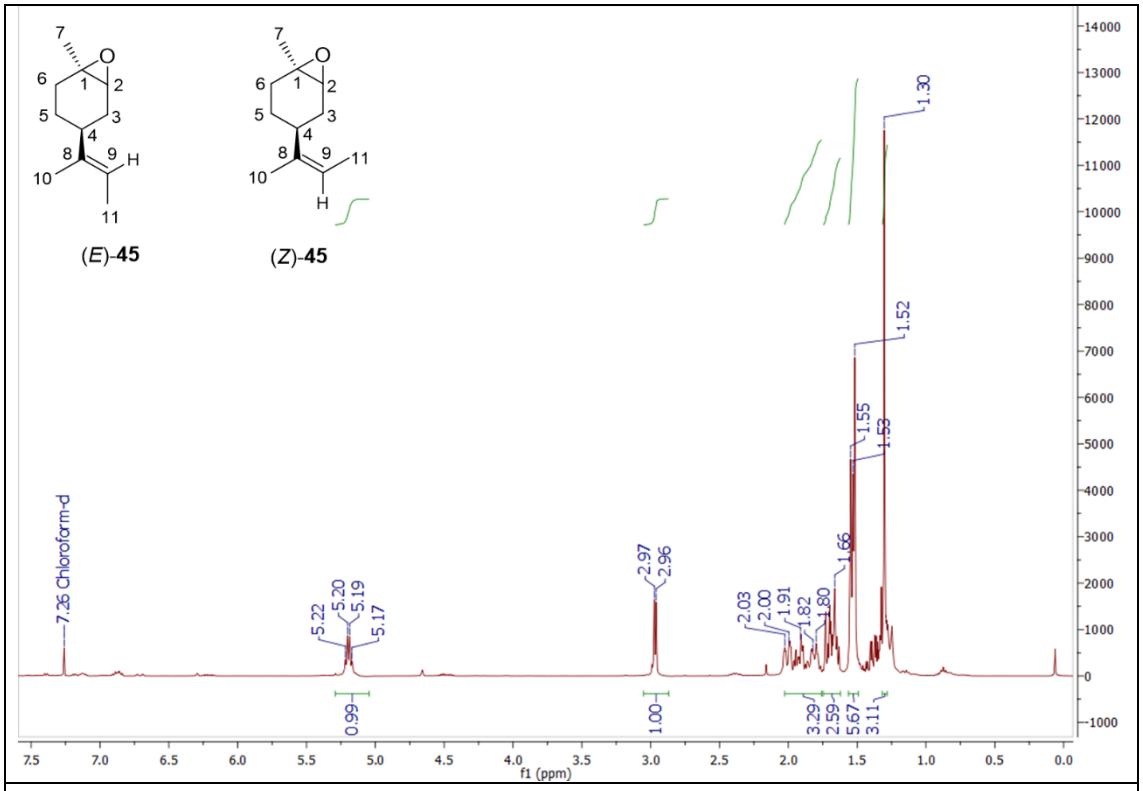
- **(D)-carvone/2-methylbut-2-ene cross metathesis product 44**

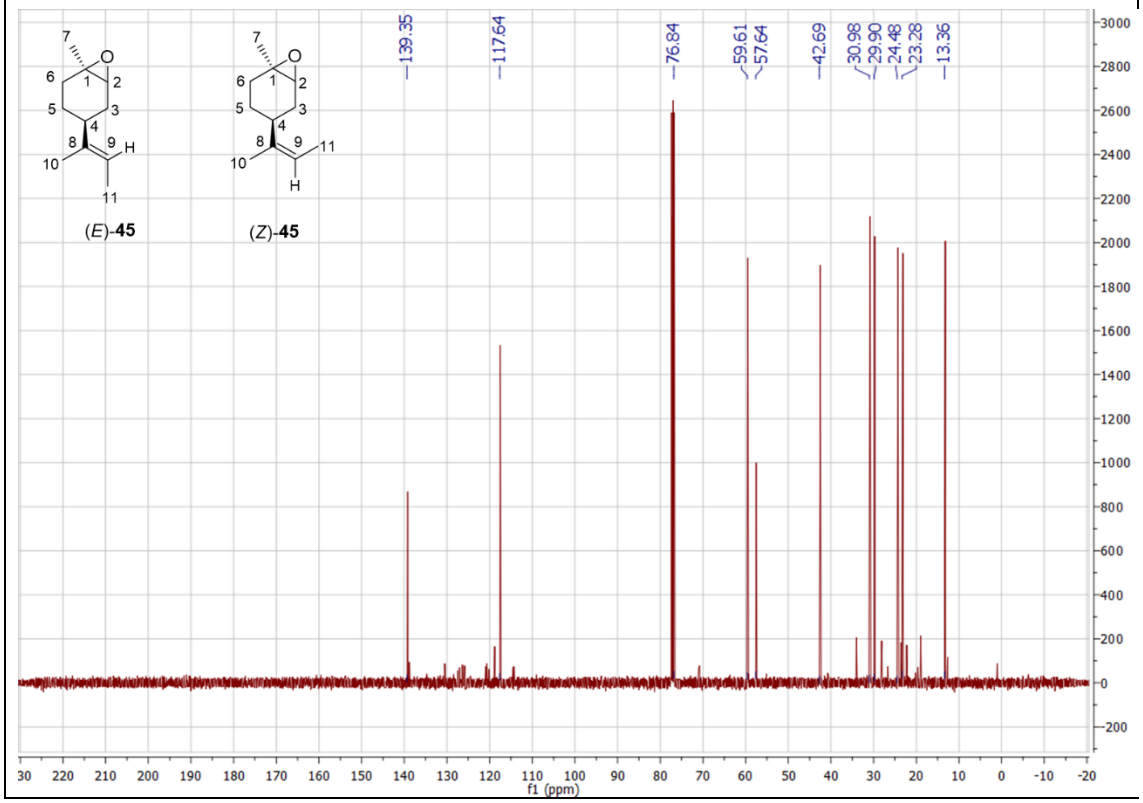


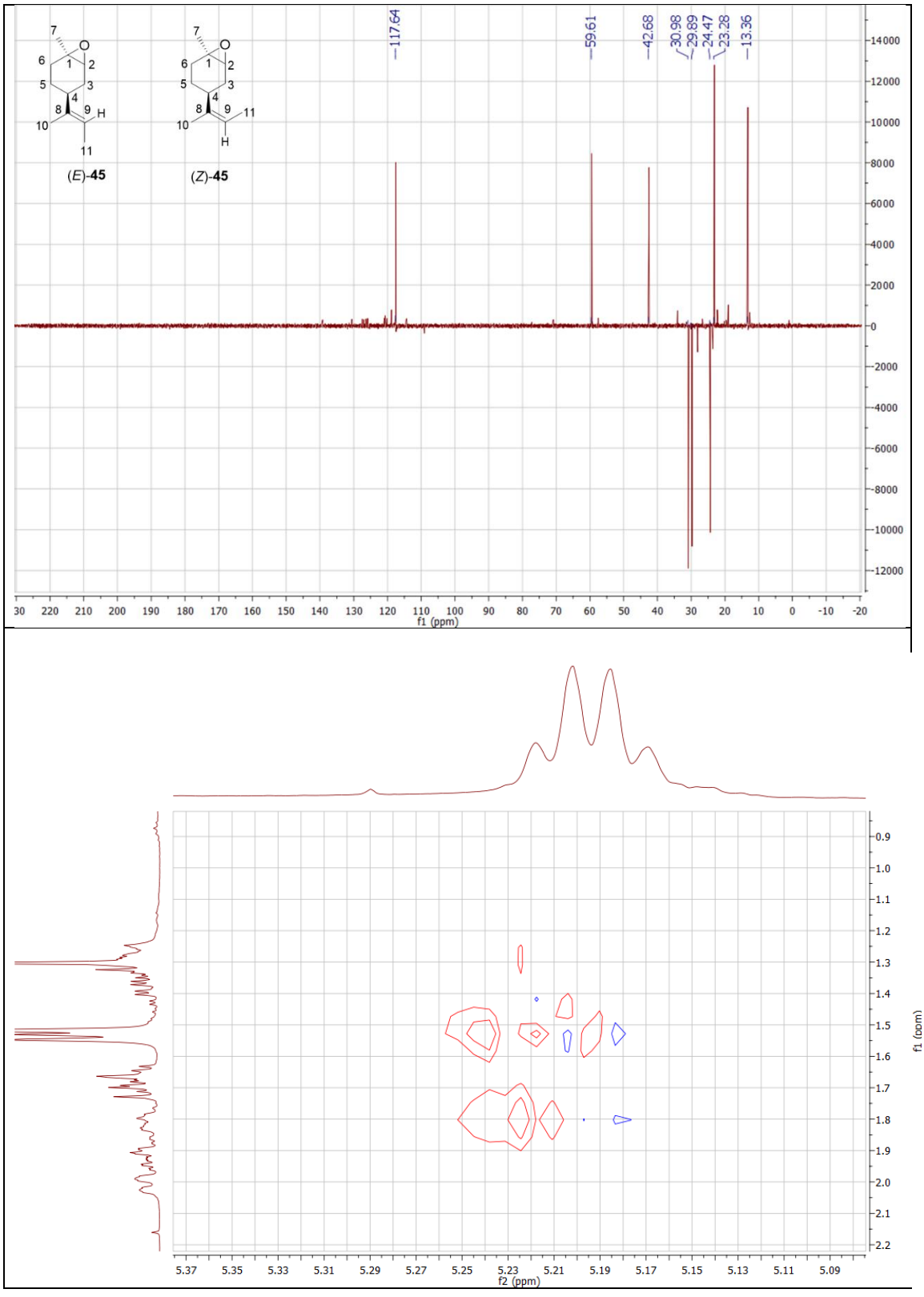

(E)-44
(Z)-44
145.06
119.06
44.41
43.38
31.47
15.77
13.73
13.38
f1 (ppm)


NOESY
f2 (ppm)
f1 (ppm)

- **(+)-*trans*-limonene epoxide/2-methylbut-2-ene cross metathesis product 45**






(E)-45
(Z)-45
117.64
59.61
42.68
30.98
29.89
24.47
23.28
13.36
f1 (ppm)
f2 (ppm)
f1 (ppm)

Résumé étendu de la Thèse: Valorisation catalytique des terpènes

Luciana SARMENTO FERNANDES

Introduction

Les terpènes sont présents dans les huiles essentielles et constituent une classe de produits naturels qui trouvent des applications directes et servent de matières premières dans l'industrie des arômes et des parfums. Ils ont également d'autres applications potentielles en raison de leurs propriétés biologiques.[1] Ils sont construits sur la base d'unités isoprènes connectées (2-méthyl-1,3-butadiène) et contiennent donc un nombre d'atomes de carbone qui est un multiple de cinq. Les terpénoïdes sont des terpènes chimiquement modifiés, essentiellement des dérivés oxygénés tels que des alcools, des époxydes, des cétones, des aldéhydes, des acides carboxyliques et des esters. Les monoterpènes ont déjà trouvé des applications directes dans le domaine des parfums et des arômes et constituent des éléments de base renouvelables pour l'accès à des polymères durables.[2] Plusieurs transformations catalytiques des terpènes naturels, telles que l'oxydation, l'époxydation, l'hydroformylation, l'hydrogénation, la déshydrogénation, l'isomérisation, le réarrangement, ont été réalisées afin de produire des produits chimiques à valeur ajoutée pour diverses applications.[3,4,5,6] Récemment, des études computationnelles sur les transformations par métathèse de terpènes volumineux tels que l'α- et le β-pinène en ouverture de cycle et en métathèse croisée avec différents types de catalyseurs (Ru, Mo, W) sont apparues.[7,8]

Les terpènes cycliques tels que l'α-pinène, le β-pinène, le camphène et le limonène (Figure 1) sont des composants bio-sourcés importants présents dans

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[1] Zwenger, S; Basu, C. *Biotechnol. Mol. Biol. Rev*., **2008**, 3, 1-7.
[2] Winnacker, M. *Angew. Chem. Int. Ed*. **2018**, 57, 14362-14371.
[3] Swift, K.A.D. *Top. Catal.* **2004**, 27, 143-155.
[4] Monteiro, J.L.F.; Veloso, C.O.. *Top. Catal.* **2004**, 27, 169-180.
[5] (a) Ravasio, N.; Zaccheria, F.; Guidotti, M.; Psaro, R. *Top. Catal.*, **2004**, 27, 157-168; (b) Malko, M.; Antosik, A. K.; Wroblewska, A.; Czech, Z.; Wilpiszewska, K.; Miadlicki, P.; Michalkiewicz, B. *Pol. J. Chem. Technol.*, **2017**, 19, 50-58.
[6] Schwab, W.; Fuchs, C.; Huang, F. C. *Eur. J. Lipid Sci. Technol.*, **2013**, 115, 3-8.
[7] Fomine, S. Tlenkopatchev, M. A. *J. Organomet. Chem.*, **2012**, 701, 68-74.
[8] Acevedo, A.; Fomine, S.; Gutiérrez, S.; Tlenkopatchev, M. A. *J. Organomet. Chem.*, **2014**, 765, 17-22.

la résine des pins et des agrumes et sont actuellement extraits à l'échelle industrielle. La production mondiale de térébenthine, qui contient principalement ces terpènes, est estimée à 350 000 tonnes/an,[9] tandis que celle de limonène extrait de l'écorce des agrumes produits dans l'industrie des jus de fruits, qui contient environ 90 % de limonène,[10] pourrait représenter environ 65 kt par an.[11]

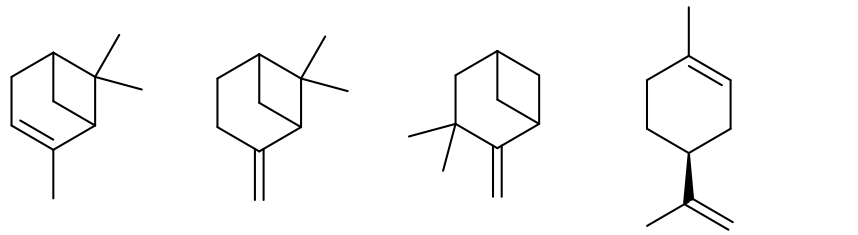

Figure 1: Exemples de terpènes cycliques

La métathèse des oléfines, en particulier la métathèse croisée, présente un énorme potentiel pour la fonctionnalisation directe des oléfines provenant de ressources naturelles.[12,13] La possibilité d'introduire des groupes fonctionnels ester, aldéhyde, halogène, nitrile a déjà été démontrée à partir de doubles liaisons internes 1,2-disubstituées de dérivés d'acides gras[14,15] et de terpènes comportant l'extrémité prényle trisubstituée[16,17] avec des oléfines déficientes en électrons, des chlorures allyliques et des esters comme partenaires de métathèse croisée.

Quelques exemples de métathèse croisée d'oléfines cycliques disubstituées par des gemmes avec des oléfines terminales ont été rapportés à partir de méthylène-cyclobutane,[18] -cyclopentane et -cyclohexane,[19] et la métathèse croisée plus difficile d'oléfines avec des groupes méthylène

[9] Alma, M.H.; Salan, T. *Proc. Petrochem. Oil Ref.* **2017**, 18, 1-12.
[10] Bledsoe Jr.; Kirk-Othmer, J.O. *Encyclopedia of Chemical Technology*, Wiley & Sons Inc., 2000.
[11] Pulidindi, K.; Pandey, H. Dipentene (Limonene) Market, Global Market Insights **2018**.
[12] de Espinosa, L. M. ; Meier, M.A.R. *Top. Organomet. Chem.* **2012**, 39, 1–44.
[13] Bruneau, C.; Fischmeister, C.; Mandelli, D.; Carvalho, W.A.; dos Santos, E.N.; Dixneuf, P.H.; Fernandes, L.S. *Catal. Sci. Technol*. **2018**, 8, 3989–4004.
[14] Jacobs, T.; Rybak, A. ; Meier, M.A.R. *Appl. Catal. A* **2009**, 353, 32–35.
[15] Miao, X.; Dixneuf, P.H.; Fischmeister, C.; Bruneau, C. *Green Chem.* **2011**, 13, 2258–2271.
[16] Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C. *Green Chem*. **2011,** 13, 1448–1452.
[17] Borré, E.; Dinh, T.H.; Caijo, F.; Crévisy, C.; Mauduit, M. *Synthesis* **2011**, 13, 2125–2130.
[18] Kotov, S.V.; Finkel'shtein, E. S.; Chernykh, S.P.; Shabalina, T.N.; Tyshchenko, V.A.; Milovantseva, V.I. *Kinet. Catal.* **2006**, 47, 460–463.
[19] Morrill, C.; Grubbs, R. H. *J. Organomet. Chem.* **2003**, 68, 6031–6034.

exocycliques encombrés stériquement est beaucoup moins documentée.[20,21] Le (-)-β-Pinène 1 et le (-)-limonène 2 ont déjà été impliqués dans des réactions de métathèse d'oléfines avec des catalyseurs au ruthénium, en particulier comme agents de transfert de chaîne pendant le clivage de caoutchoucs polyisoprènes naturels en oligomères terminés par des terpènes,[22] et pendant la polymérisation par métathèse par ouverture de cycle du dicyclopentadiène pour contrôler la réticulation et les propriétés physiques des polymères résultants. des polymères obtenus.[23]

Il n'existe que quelques exemples où ces terpènes ont été utilisés comme partenaires de métathèse croisée avec des oléfines pour former de nouveaux produits chimiques fins. Ainsi, le limonène a été mis en réaction avec l'oléfine terminale 1-hexène en présence de 2 % en moles d'un catalyseur de Grubbs de deuxième génération sans solvant pour donner le limonène substitué par un butyle sous la forme d'un mélange E + Z avec un rendement de 40%.[24] L'extension au 1,5-hexadiène non conjugué a conduit au polyhexadiène ainsi qu'à des oligomères d'hexadiène présentant une ou deux extrémités limonènes. Dans ces conditions, le β-pinène n'est pas réactif et les produits de métathèse croisée n'ont été obtenus qu'avec des partenaires oléfiniques internes neutres en utilisant un catalyseur au ruthénium et un grand excès de terpène.[24,25] D'autre part, même si la double liaison exocyclique d'un dérivé de limonène était réactive en métathèse intramoléculaire par fermeture de cycle avec une double liaison acrylique,[26] une oléfine terminale déficiente en électrons telle qu'un acrylate n'a pas réagi de manière intermoléculaire avec ces terpènes mais a seulement fourni le mélange maléate/fumarate d'auto-métathèse. Ces résultats ont montré qu'outre la nature du catalyseur, qui est également un paramètre crucial, la métathèse croisée des terpènes volumineux 1 et 2 avec des catalyseurs au ruthénium se déroulait favorablement lorsque le partenaire de métathèse croisée présentait une double liaison carbone-carbone interne. Cette observation a incité

[20] Stewart, I. C.; Douglas, C.J.; Grubbs, R. H. *Org. Lett.* **2008**, 10, 441–444.
[21] Wang, Z. I.; Jackson, W. R.; Robinson, A. J. *Org. Lett.* **2013**, 15, 3006–3009.
[22] Martinez, A. ; Gutierrez, S. ; Tlenkopatchev, M. A. *Nat. Sci.* **2013**, 5, 857–864.
[23] Alzari, V.; Nuvoli, D.; Sanna, D.; Ruiu, A.; Mariani, A. *J. Polym. Sci. A Polym. Chem.* **2016**, 54, 63–68.
[24] Mathers, R.T.; McMahon, K.C.; Damodaran, K.; Retarides, C.J.; Kelley, D.J. *Macromolecules* **2006**, 39, 8982–8986.
[25] Gutiérrez, S.; Tlenkopatchev, M.A. *Polym. Bull.* **2011**, 66, 1029–1038.
[26] Li, Y.; Zhang, T.; Lia, Y.L. *Tetrahedron Lett.* **2007**, 48, 1503–1505.

à étudier la métathèse croisée catalysée par le ruthénium des terpènes 1 et 2 avec des oléfines fonctionnelles symétriques, afin de générer un seul produit de métathèse croisée. Ces transformations de terpènes via la métathèse des alcènes ajoutent non seulement de la valeur aux énergies renouvelables, mais impliquent également des processus catalytiques verts.

Initialement, nous nous sommes particulièrement intéressés à la fonctionnalisation du (-)-β-pinène **1** et du (-)-limonène **2**, qui sont des monoterpènes insaturés volumineux présentant une double liaison carbone-carbone disubstituée terminale. Le premier substrat est un méthylènecyclohexane à encombrement stérique, et le second correspond à un dérivé du propène-2-ylcyclohexène. Nous avons montré que l'utilisation de la double liaison interne d'un partenaire de métathèse croisée symétrique était très efficace et sélective pour la fonctionnalisation du β-pinène et du limonène en présence de catalyseurs au ruthénium. L'influence des groupes fonctionnels oxygénés dans le partenaire terpénique a également été évaluée avec des terpénoïdes dérivés du limonène portant un groupe cétone et un groupe époxyde.[27,28]

Résultats et conclusions

La métathèse croisée d'oléfines disubstituées gemmes stériquement exigeantes avec des oléfines fonctionnelles terminales en présence de catalyseurs au ruthénium est connue pour être une réaction difficile. Sur la base de quelques observations de la littérature, nous avons développé une stratégie impliquant des alcènes internes fonctionnels symétriques plus encombrés plutôt que leurs équivalents de métathèse terminale comme partenaires de métathèse croisée pour la métathèse croisée avec des terpènes volumineux. En utilisant des catalyseurs de type Hoveyda-Grubbs, il a donc été possible d'introduire des groupes fonctionnels ester et nitrile dans le β-pinène 1. au β-pinène 1 et au limonène 2 par métathèse croisée avec le fumarate et le maléate de diméthyle,

[27] Fernandes, L.S. ; Mandelli, D. ; Carvalho, W.A. ; Fischmeister, C. ; Bruneau, C. *Catal. Commun.* **2020**, 135, 105893-105900.
[28] Fernandes, L.S. ; Mandelli, D. ; Carvalho, W.A., Caytan, E. ; Fischmeister, C. ; Bruneau, C., *Appl. Cat. A, Gen.* **2021**, 623, 118284-118290

le fumaronitrile, le 1,4-diacétoxybut-2-ène, le 1,4-dichlorobut-2-ène dans des conditions pures ou dans le carbonate de diméthyle comme solvant vert sans production d'aucun sous-produit. En considérant le 2-méthylbut-2-ène non symétrique, avec cet alcène trisubstitué non fonctionnel, la métathèse croisée avec des catalyseurs au ruthénium de deuxième génération a fourni sélectivement une nouvelle double liaison trisubstituée à 40 °C avec une grande efficacité. La réaction a mieux fonctionné dans des conditions pures et a conduit aux produits E avec une stéréosélectivité très élevée..

Cette réaction de métathèse croisée fournit un accès direct à de nouveaux produits bio-sourcés. Une sélection plus large de catalyseurs impliquant les complexes de ruthénium et de molybdène les plus récents pourrait permettre d'améliorer la productivité de ces transformations.

La stratégie développée pour la métathèse croisée du β pinène et du (-)-limonène a été étendue aux composés terpénoïdes (D)-carvone, (+)-trans-limonène époxyde et carvéol. L'introduction de fonctionnalités oxygénées comme une cétone ou un époxyde dans la (D)-carvone et le (+)-trans-limonène époxyde n'a pas inhibé la métathèse croisée avec aucun des partenaires de métathèse croisée et les réactivités ont suivi la règle générale trouvée pour les terpènes. La situation est différente avec le groupe hydroxyle qui doit être protégé. Pour toutes les réactions de métathèse étudiées, les catalyseurs de type Hoveyda de deuxième génération, qui sont robustes et disponibles dans le commerce, ont présenté des réactivités relativement similaires, ce qui démontre la faisabilité de ces métathèses croisées difficiles avec des substrats volumineux.

Le résultat le plus frappant concerne l'utilisation d'oléfines internes "volumineuses" pour la transformation de terpènes volumineux. Cette situation contre-intuitive est le résultat de réactions de métathèse compétitives complexes où les voies de métathèse non productives sont favorisées lorsque des partenaires de métathèse croisée contenant des oléfines terminales sont utilisés. Presque tous les produits de métathèse croisée synthétisés sont de nouveaux composés et doivent être évalués pour leurs propriétés intéressantes. La configuration de la double liaison carbone-carbone nouvellement créée a été systématiquement déterminée à l'aide d'une série d'expériences de RMN 1D et 2D qui ont démontré que l'oléfine E était toujours le principal isomère formé. La plupart des produits ont pu être isolés mais parfois avec un rendement très faible

en raison de l'efficacité modérée concomitante de la réaction catalytique et d'une purification difficile.

L'efficacité de la métathèse des oléfines pour la transformation sélective des terpènes offre des procédés simples et écologiques pour l'accès à des produits à valeur ajoutée à partir de substrats biosourcés extraits de sources renouvelables. Cependant, des améliorations futures des performances catalytiques seront nécessaires dans certains cas. Cela pourrait être réalisé grâce à une optimisation supplémentaire des conditions de réaction ou à l'utilisation d'autres catalyseurs de métathèse. Un screening plus large des catalyseurs impliquant les complexes de ruthénium et de molybdène les plus récents pourrait permettre d'améliorer la productivité de ces transformations.