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Lincenciado em Química Aplicada

[2+2+2] cyclotrimerization in synthesis of selaginpulvilin A and C

Dissertação para obtenção do Grau de Mestre em

Química Bioorgânica

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[2+2+2] cyclotrimerization in synthesis of selaginpulvilin A and C

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Abstract

Since pre-historic ages natural products are employed as medicine by humans. Combinatorial chemistry and high-through-put screening (HTS) process were presented, in the end of the 20th century, has revolutionary methods for the discover of new natural products and their analogues. However, this process failed in reliability, being time-consuming and expensive. Consequently, it left the necessity of finding new affordable techniques to achieve such natural products and analogues. The [2+2+2] cyclotrimerization is a simple yet elegant technique to synthesise a wide variety of functionalized cyclic frameworks. A variety of metals are now used as catalysts in the [2+2+2] cyclotrimerization. Particularly, rhodium catalyst complexes are in the spotlight of chemists, being the $RhCl(PPh_3)_3$, known as Wilkinson's catalyst, the most used. [2+2+2] cyclotrimerization is applied in a variety of fields, including natural products, materials and miscellaneous. An important application of the [2+2+2] cyclotrimerization is the synthesis of fluorene scaffold. The fluorene scaffold in present in a variety of natural products. Selaginpulvilins are a fluorene derivative with a 6-5-6 carbocyclic system. It is an important structure to pharmaceutical industry and has been used in the Traditional Chinese Medicine for the treatment of dysmenorrhea, asthma, and traumatic injury.

In this work we report the use of [2+2+2] cyclotrimerization as a key step for the synthesis of selaginpulvilin A and C. In a first stage of the project the reliability of the technique was investigated by reacting various starting materials in order to determine the scope and limitations of the key transformation. The main objective of this investigation was the determination of an influence of various alkynes upon the course of the cyclotrimerization, in particular on the regioselectivity and reaction yields. It was possible to obtain the respective fluorene scaffold using a variety of alkynes with yields up to 69%.

After the determination of the scope of the [2+2+2] cyclotrimerization the next stage was to employ this technique in the synthesis of selaginpulvilins. It was possible achieve the formal synthesis of selaginpulvilin C. The total synthesis of selaginpulvilin A was not achieved due to difficulties in the last stages of the synthesis. The investigation for the synthesis of this natural product is still undergoing.

Keywords: [2+2+2] cyclotrimerization; Natural products; Fluorene scaffold; Selaginpulvilin A; Selaginpulvilin C

Resumo

Desde as idades pré-históricas que os produtos naturais são utilizados como fármacos pelos seres humanos. A química combinatória e o processo de rastreio de elevada capacidade foram apresentados, no final do século XX, como métodos revolucionários para a descoberta de novos produtos naturais e seus análogos. No entanto, esses processos falharam em confiabilidade, sendo dispendiosos e lentos. Consequentemente, ficou por colmatar a necessidade de encontrar novas técnicas acessíveis para alcançar esses produtos. A [2+2+2] ciclotrimerização é uma técnica simples e elegante para sintetizar uma grande variedade de estruturas cíclicas funcionalizadas. Hoje em dia, existe uma vasta variedade de metais usados como catalisadores na ciclotrimerização. Especificamente, os complexos de ródio são vastamente utilizados, sendo o $RhCl(PPh_3)_3$, conhecido como catalisador de Wilkinson, o mais utilizado. A [2+2+2] ciclotrimerização pode ser aplicada numa variedade áreas, tais como na síntese de produtos naturais, materiais entre diversas outras. Uma aplicação importante da ciclotrimerização é a síntese de fluorenos. Os fluorenos estão presentes numa extensa variedade de produtos naturais. As selaginpulvilin são um derivado do fluoreno com um sistema 6-5-6 carbocíclico. As selinginpulvilin são uma estrutura importante para a indústria farmacêutica, mas também para a industria dos materiais eletrônicos e óticos e tem sido usada na Medicina Tradicional Chinesa para o tratamento de dismenorreia, asma e lesões traumáticas.

Neste trabalho, reportamos o uso da [2+2+2] ciclotrimerização como um passo fundamental para a síntese de selaginpulvilin A e C. Numa primeira fase, foi testado a flexibilidade da técnica reagindo um trieno com uma variedade de alcinos. Os principais objetivos desta investigação foram determinar um alcino adequado para a ciclotrimerização, regioselectividade e rendimentos da reação. Foi possível obter o respetivo fluoreno usando uma variedade de alcinos e com rendimentos até 69%.

Depois de encontrar as condições adequadas para a ciclotrimerização, a próxima fase foi empregar esta técnica na síntese de selaginpulvilin. A ciclotrimerização provou ser uma técnica eficiente para a síntese de selaginpulvilin A e C, pois foi possível alcançar a síntese formal de selaginpulvilin C. A síntese total de selaginpulvilin A não foi alcançada devido a dificuldades nos últimos estágios da síntese.

Palavras-chave: [2+2+2] ciclotrimerização; Produtos naturais; Fluoreno; Selaginpulvilin A; Selaginpulvilin C.

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1. Introduction

1.1. Natural products in drug discovery and development

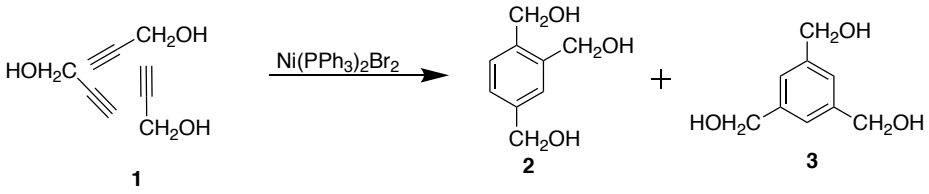
At the end of the 20th century, the pharmaceutical industry invested is resources in combinatorial chemistry and high-through-put screening (HTS) process in order to obtain lead compounds to a determined target. Once a hit is observed, it is necessary to start a process of extraction to obtain the active component. Posteriorly, the active component is transformed and optimized to become a drug. However, this is an expensive and time-consuming process. Other concerns may rise up with this process as well. For instance, after the isolation of an active component, it is necessary a full structural elucidation and may turn out to be an already know natural compound or a patented one. This time consuming and expensive process is not always liable.[1] A more careful analysis at the data presented by Sandra Fox et al. the HTS success rates are presented to be around 50%, which, for the high cost of the process, is not a positive result.[2] Therefore, by the necessity of finding affordable new lead compounds, the scientific community "refocused" their attention to natural products and their derivatives.

Natural products play an important role in modern society. Now more than ever, complex problems require complex solutions and nature can often provide these solutions. Since the pre-historic ages that humans use natural products as medicine. According to fossil records, the use of plants is traced back at least 60000 years.[3] Traditional Medicine is the oldest form of health care and it is still used nowadays, mostly in the western Asia. Traditional medical systems incorporating natural products, mostly plants, as means of therapy can only be traced back only as far as recorded documents of their likeness.[4] Within the period between 1981 to 2014 as many as 1562 drugs were approved by the Food and Drug Administration (FDA). From that number, 67 unaltered natural products were accepted as therapeutical drugs, which corresponded to 4%. However, if it is introduced all the drugs based on natural products (natural products derivatives, mimics of natural products, synthetic drugs based on natural products pharmacophores…) this value escalate to 50%, which represents 785 accepted natural product-based drugs. Half of the drugs approved by the FDA have origin in natural products and in the most diverse areas of therapy (anti-cancer, anti-inflammatory, antibacterial….).[5] Is important to make deeper studies to the natural products reported and used in traditional medicine. There are extensive reports of Traditional Medicine which contain natural products that can be optimized to became more potent therapeutical drugs. Therefore, it is necessary to develop new techniques that will lead to the synthesis of natural drugs or their analogues.

1.2. [2+2+2]-cyclotrimerization

1.2.1. General consideration

The first metal mediated [2+2+2] cyclotrimerization was introduced by Reppe in 1948. They used nickel catalyst to synthetize benzene derivatives **2** and **3** starting from propargyl alcohol (**1**), demonstrated in scheme 1.[6]



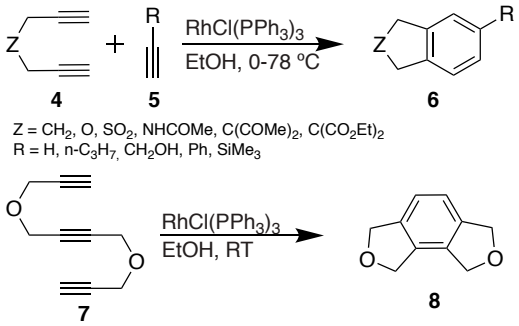
1 2 3

Scheme 1 - First metal mediated [2+2+2] cyclotrimerization reported by Reppe.

Since this discovery, the process has been improved and studies were carried out concerning new transition metals as catalysts. Throughout the last decade, a variety of metals were found suitable for the [2+2+2] cyclotrimerization reaction. Catalysts based on nickel, cobalt, palladium, chromium, ruthenium, rhodium, iron, zirconium, niobium, iridium, and titanium are now being used in the [2+2+2]-cyclotrimerization.[7]

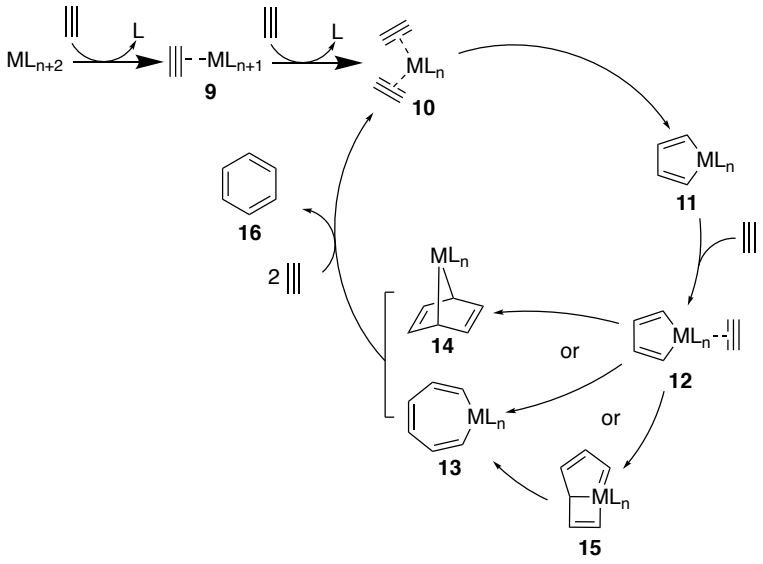
Particularly, rhodium catalyst complexes are in the spotlight of chemists. $RhCl(PPh_3)_3$, known as Wilkinson's catalyst, plays an important role in [2+2+2]-cyclotrimerization. The first use of Wilkinson's catalyst in the [2+2+2] cyclotrimerization was reported by Müller with partially intramolecular [2+2+2] cycloaddition of diynes and external alkynes in the synthesis of substituted benzenes.[8] Since then, Wilkinson's catalyst has been employed in a variety of catalytic reactions. A report from Grigg and co-workers is the first to introduce a partially intramolecular [2+2+2] cyclotrimerization with a catalytic amount of Wilkinson's catalyst, ranging from 0.5-2 mol%.[9] The reactions of internal 1,6-diynes **4** and alkynes **5** required high reaction temperature, in order to obtain high yields of cycloaddition products **6**. In the same paper, an intramolecular [2+2+2] cycloaddition of triynes **7** is reported as well to form the benzodifuran **8** as depicted in scheme 2.

In addition to alkynes, other unsaturated components such as nitriles,[10] isocyanates,[11] olefins,[12] carbonyl compounds,[13] and allylic ethers[14] have been shown to participate in cyclotrimerizations with alkynes, making this strategy a powerful tool to synthesise a wide variety of functionalized cyclic frameworks.



Scheme 2 - A partially intramolecular [2+2+2] cyclotrimerization reaction with internal 1,6-diynes (top) and intramolecular [2+2+2] cycloaddition of triynes (bottom).

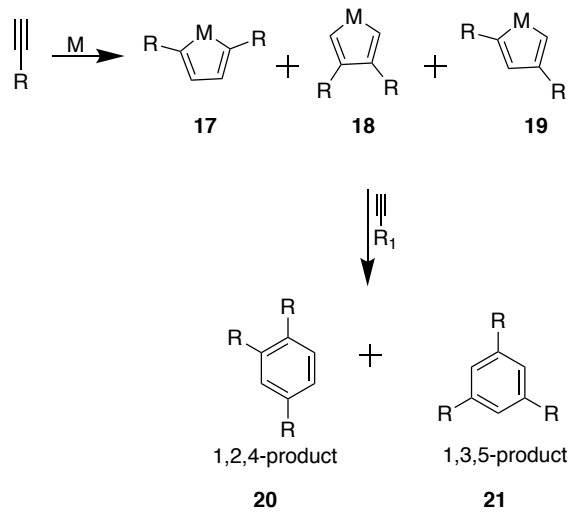
The mechanism of this reaction has been considered as described in scheme 3. Initially, the substitution of two auxiliary ligands by two alkyne moieties takes place. Then, oxidative coupling of the two coordinated alkynes proceeds to give the metallacyclopentadiyne **11**. Coordination of an alkyne to the metallacycle **12** is followed either by: alkyne insertion, forming a planar homoaromatic metallacycloheptatriene **13**; cycloaddition, forming 7-metallanorbornadiyne **14**; or [2+2] cycloaddition, forming compound **15**. Reductive elimination from intermediates **13** and **14** results in the formation of the arene **16** and the transition-metal complex. By reductive elimination, the intermediate **15** proceeds *via* seven-membered metallacycle.[15]



Scheme 3 - Mechanistic insight of [2+2+2] cyclotrimerization to the formation of benzene rings.

1.2.2. Regioselectivity

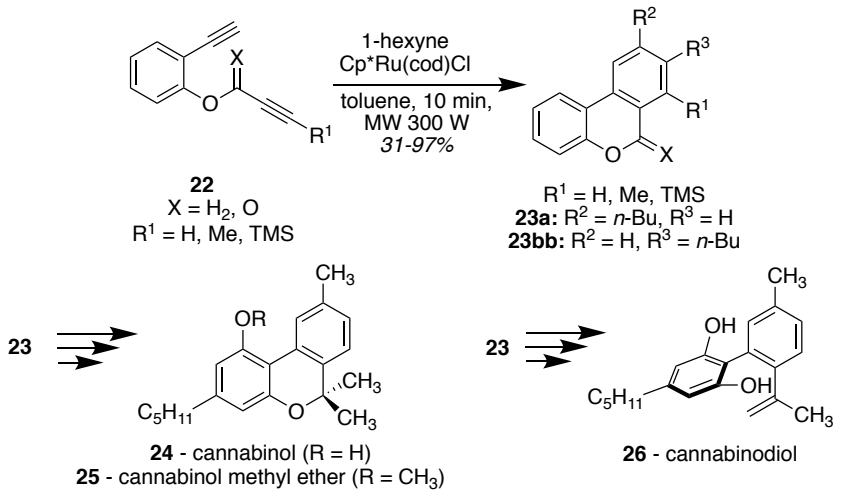
The major problem of the process is the regioselectivity when using unsymmetrical substituted alkynes as starting material due to the possibility to form a large number of regioisomers. Initially the [2+2+2] cyclotrimerization was limited to the use of alkyne homo-cyclotrimerization (use of a single alkyne). With this approach only two possible isomers can be formed, namely 1,2,4-product **20** and 1,3,5-product **21**, depicted in scheme 4. The synthesis *via* alkyne hetero-trimerization (using two or more different alkynes) was troubled by the formation of complex mixtures due to many possible products.[16] However, the trend is changing, and solutions are starting to emerge. The regioselectivity can be influenced by the type of a metal catalyst or its ligands and steric or electronic properties of the substituents of alkynes.[17] Likewise, it is possible to introduce the alkynes stepwise in the reaction mixture in order to predict the outcome of the reaction.[18] Another approach to reduce the number of isomers formed is by tethering the alkynes in a partial intramolecular approach (only 2 alkynes linked) or in a full intramolecular approach (the 3 alkynes linked), as demonstrated in scheme 2. Consequently, in most cases, the number of possible metallacycle intermediates to one leading to the formation of only one isomer. This is obtained due to the favoured formation of one metallacycle by geometrical and entropic restrictions induced by the tether.[19]



Scheme 4 - Regioselectivity of cyclotrimerization of unsymmetrically substituted alkynes.

1.2.3. Applications in synthesis: natural products, materials and miscellaneous.

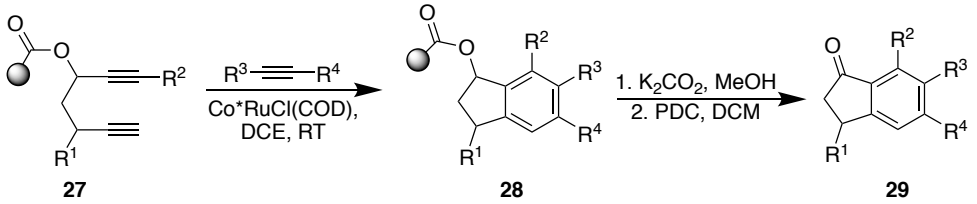
The [2+2+2] cyclotrimerization is a simple and effective method applied in the field of synthesis of natural products. Teske and Deiters reported the synthesis of three different cannabinoid derivatives by using cyclotrimerization. Besides their recreational purposes, cannabinoids are very interesting family of natural compounds. Antiemetic, analgesic, and anticonvulsant properties are some of the most recognised properties by cannabinoids that can be used in medical purposes.[20] The authors reported a partially intramolecular cyclotrimerization approach **22** to obtain the cannabinoid core structure **23,** showed in scheme 5. Using a ruthenium catalyst and microwave irradiation, the authors were able to obtain the core structure in ten minutes with yields ranging from 31 to 97%. The regioisomeric ratio ranges from 70/30 to 95/5 being the **23a** favourable. Cannabinol methyl ether (**25**) was obtained with an overall yield of 50% over 6 steps and cannabinol (**24**) was obtained by deprotection of the methylphenol using a solution of hydroiodic acid with an overall yield of 39%. The cannabinodiol (**26**) was obtained by a different route in 23% yield over 7 steps. This work illustrates the flexibility of the cyclotrimerization approach to the cannabinoid architecture, which enables the rapid introduction of a diverse set of substituents.[21]



Scheme 5 - Cyclotrimerization applied in the synthesis of natural products.

In 2007, Senaiar group reported the synthesis of natural and unnatural indanones *via* solid-supported [2+2+2] cyclotrimerization reactions. Indanones are incorporated in a variety of pharmacologically active compounds and play an important role in medicinal chemistry. Their important biological activities include anti-inflammatory, analgesic, antimicrobial, anticholinergic, anticancer and antimalarial activities.[22] The authors used a solid support in order to

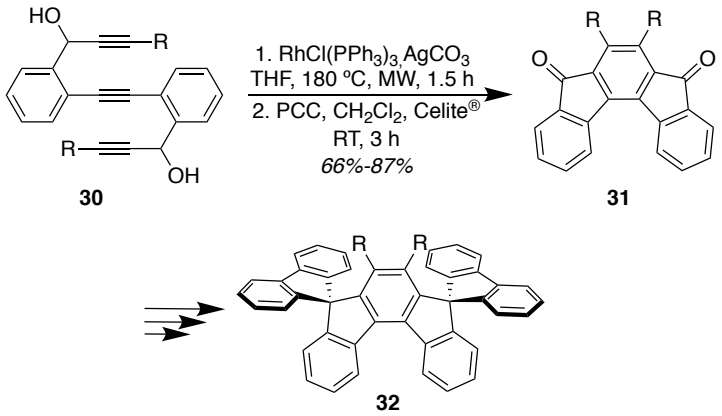
achieve a higher selectivity. By a simple a simple carboxy linker in diyne **27**, that can be easily removed under mildly basic conditions, it was possible to prevent formation of undesired side products. The first attempts for the cyclotrimerization for the formation of the indanone core **28** were carried out using Wilkinson's catalyst, however it led to inconclusive results and cleavage of the diyne from the resin. Through changing the catalyst to Cp*Ru(COD)Cl the reaction occurred smoothly at room temperature, providing the desired indanone core **28**. Subsequently, a simple treatment with K_2CO_3 and MeOH followed by an oxidation with PDC delivered the indanone **29** with high yields, ranging from 58% to 78% over two steps, and high purity.[23]



27 **28** **29**

Scheme 6 - General protocol for the synthesis of the indanone core.

Another field of interest in cyclotrimerization is the material science, especially the synthesis of electronic and optical materials. The recent work reported by Kotora *et al.* demonstrated the application of the cyclotrimerization in the synthesis of spirocyclic fluorenes and indenofluorenes. For instance, 9,9'-spirobifluorenes have been recently employed in solar panels, organic light emitting diodes (OLEDs), transistors, lasers and nonlinear optics.[24] This necessity to produce such complex compounds in high yields lead to the use of different approaches. This was the starting point for the authors, who applied the cyclotrimerization to the production of such complex structures. By using a partial intramolecular approach **30** and Wilkinson's catalyst, they were able to synthesize selectively substituted fluorenes scaffold **31**.[25] The reactions were carried out using 3 mol% of catalyst and high temperatures resulting in high yields ranging from 66% to 87% over two steps. The final indenofluorenes **32** were obtained *via* five-step syntheses with overall yields of 35% to 60%.



Scheme 7 - Synthesis of 9,9'-spirobifluorenes using cyclotrimerization.

Most recently, the cyclotrimerization was applied in a new field. Kotora *et al.* reported last year the synthesis of Bolm's ligand analog **34** applying the cyclotrimerization as a key step. In 1990, Bolm developed ligand **33**, a 2,2-bipyridine scaffold with (*R*,*R*) configuration.[26] Since then, the 2,2-bypiridine family, especially the Bolm's ligand, have been successfully applied in metal-catalysed asymmetric reactions such as cyclopropanation of olefins, alkylation and allylation of aldehydes, hydrosilylation of ketones, allylic oxidation of cycloalkenes, among others.[27,28]

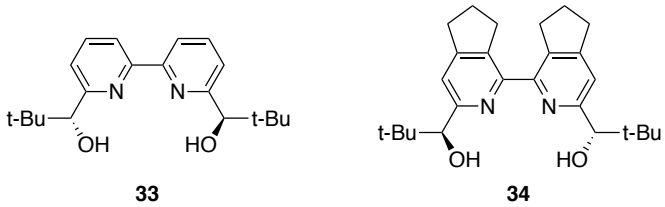
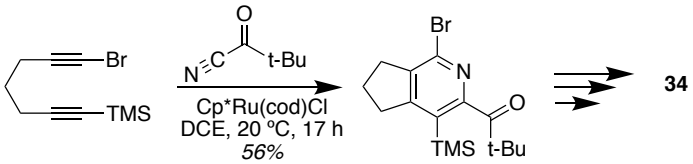


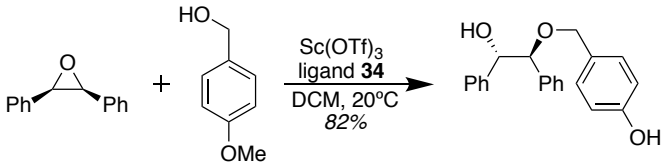
Figure 1 - Bolm's ligand (33) and Bolm's ligand analogue (34)

The key step of the synthesis is depicted in scheme 8. Using a 10 mol% of a ruthenium catalyst in a DCE solution at room temperature the desired substituted pyridine **36** was obtained with 56% yield. Furthermore, they obtained the 2,2-bypiridine **34** with a (*S*,*S*) configuration thanks to an enantioselective reduction of the carbonyl moieties. The ligand was afterwards applied in a variety of enantioselective catalysis achieving promising results. For illustration in scheme 9, the ring opening of cis-stilbene oxide **37** in the presence of ligand **34** gave the product **39** with 82% yield and an excellent enantioselectivity of 98%, which is better than 95% enantioselectivity achieved by Bolm's ligand.[29]



35 **36**

Scheme 8 - Synthesis of Bolm's analog using cyclotrimerization.



37 **38** **39**

Scheme 9 - Aplication of Bolm's analog in ring opening of cis-stilbene oxide

1.2.4. Application in the synthesis of fluorenes

Fluorene was discovered by Marcellin Berthelot in 1867 and has a violet fluorescence, hence its name. For commercial purposes it is obtained from coal tar. Fluorene contains a fused 6-5-6 tricyclic motif with two fused benzene rings at each side of a central cyclopentadiyne ring as depicted in figure 2.[30] Fluorene is capable of numerous chemical reactions, through both the aromatic rings and especially the reactive methylene group. A common reaction is the oxidation of fluorene to fluorenone that can happen at open air. Fluorenone has a planar skeleton with two fused aromatic rings and one carbonyl prochiral centre.[31] In figure 2 are represented some examples of natural products containing the fluorenone scaffold, highlighted in red. Dendroflorin (**40**) is found in a diversity of plants and it was first isolated from *Dendrobium densiflorum* Lidl by the group of Sunil in 1984. Its structure was later confirmed by Zhao in 2001, when dendroflorin was isolated from *D. densiflorum*.[32] In 2009 He and co-workers obtained an interesting fluorenone alkaloid from the radix of *Caulophyllum robustum*. Caulophine (**41)** revealed an anti-myocardial ischemia activity.[33] The related azafluorenone scaffold is a part of the natural products as well. Azafluorenone **42** was firstly isolated from the trunk wood of *Onychopetalum amazonicum* in 1976 by Almeida and it demonstrated phytochemical properties.[34] The fluorenone scaffold can also be found in steroids such as nakiterpiosin (**43).** It was first isolated from the Okinawan sponge *Terpios hoshinota* by Uemura and co-workers in 2003 and belongs to C-nor-D-homo steroids, which are biogenetically originated from steroids with the C-ring contracted and D-ring expanded by one carbon. The C and D ring are indicated in the structure of the nakiterpiosin in figure 2.[35] Consequently, there is the necessity of finding new techniques for the synthesis of the fluorene and fluorenone scaffolds.

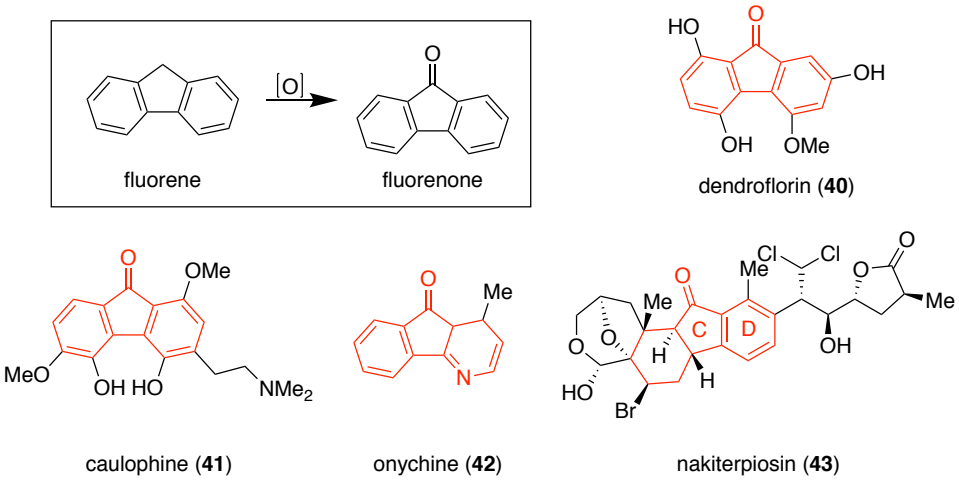
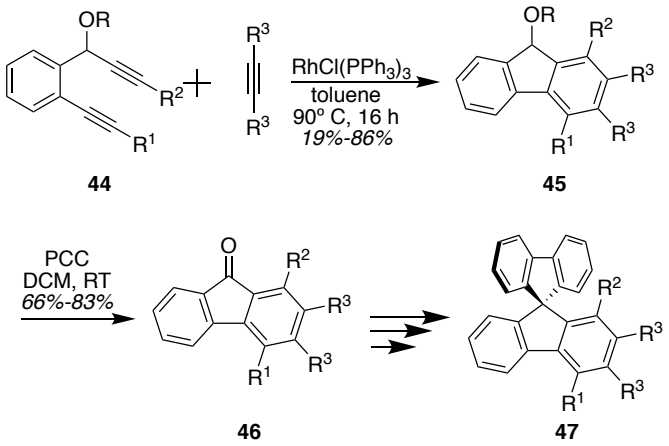


Figure 2 - Natural products containing a fluorene core (red).

In 2015, a selective synthesis of substituted fluorenes and fluorenols, by using cyclotrimerization as a key step, was developed by Kotora *et al.*[25] By employing a partially intramolecular cyclotrimerization approach, diyne **44** was reactred with different alkynes. Compounds **45** were synthesized in yields up to 86% by using 10 mol% of Wilkinson's catalyst and silver carbonate as an additive in toluene at 90 ºC. Furthermore, the oxidation of fluorenols **45** in presence of PCC gave the fluorenones **46**. Lastly, the 9,9'-spirobifluorenes **47** were achieved *via* two-step reaction. This demonstrate that the cyclotrimerization can be applied in the synthesis of selectively substituted fluorenes arising a new pathway to the synthesis of new natural products containing a fluorene core in their structure.



R = H, TBS; R^1 = Ph, nPr; R^2 = Ph, nPr; R^3 = Me, Et, nPr, CH_2OH

Scheme 10 - Synthesis of fluorene core employing the [2+2+2]-cyclotrimerization.

1.3. Selaginpulvilins

1.3.1 Structure, isolation and biological activity

Selaginpulvilins (A-L) have an unprecedented 9,9-diphenyl-1-(phenylethynyl)-9H-fluorene skeleton, depicted in figure 3. The fluorene derivative is a 6-5-6 carbocyclic system with a rigid structure. The selaginpulvilins differ in the C10 and the C12 position, with exception for the selaginpulvilin E (**52**) which contains a lactone ring. The possibilities of the substitution of the C10 position is limited to only two options: hydrogen or phenol. On the other hand, there is a possibility of having a variety of functional groups at the C12 position: hydrogen, phenol, aldehyde, carboxylic acids, among others.[30] It is an important structure to pharmaceutical industry, but also in electronic and optical materials.[36]

Selaginella pulvinata has been used in the Traditional Chinese Medicine for the treatment of dysmenorrhea, asthma, and traumatic injury. Isolation of selaginpulvilins A-D from *S. pulvinata* and their phytochemical study was carried out by Yin *et al.* It was found that they have significant inhibitory activity to phosphodiesterase 4 (PDE4).[37] The IC_{50} values were in the range of 0.11−5.13 μM. The PDE4 is present in the cyclic adenosine-3′,5′-monophosphate (cAMP) signalling cascade and it is responsible for the hydrolysis of cAMP in adenosine 5′-monophosphate (5′-AMP). In figure 4 is briefly illustrated the cAMP signalling cascade.

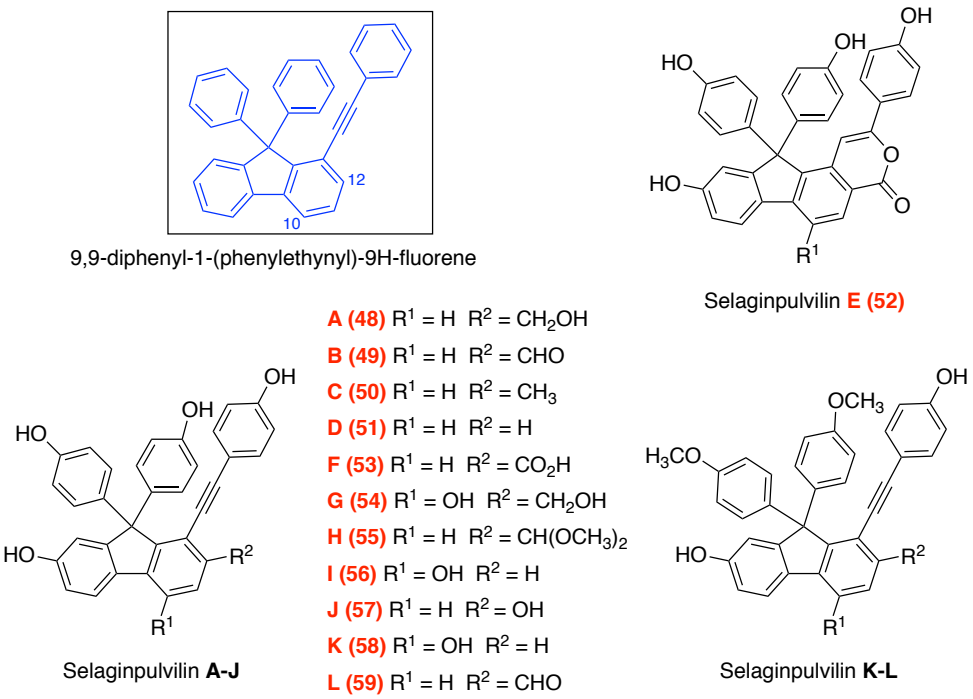


Figure 3 - Structure of Selaginpulvilin A-L and structure of 9,9-diphenyl-1-(phenylethynyl)-9H-fluorene skeleton (blue).

After the stimulation of the cell surface G protein-coupled receptors (GPCRs) by an external agent (hormone, neurotransmitters, etc), activation of the adenylyl cyclases will catalyse the cyclization of adenosine triphosphate (ATP) to cAMP. The cAMP plays an important role in the signalling cascade because it is responsible for the activation of protein kinase (PKA). PKA will, ultimately, be responsible for the production of a cellular response due to the phosphorylation of target proteins.[38] Through modulation of cAMP levels, PDE4 regulates leukocyte responses including the proinflammatory actions of monocytes, T cells and neutrophils, airway and vascular smooth muscle constriction, and neurotransmitter signalling through adenylyl cyclase linked G-protein coupled receptors. Potential diseases for PDE4 inhibitor therapy include asthma, allergic rhinitis, atopic dermatitis, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, psoriasis, Crohn's disease, cancer, Alzheimer's disease, mild cognitive impairment, Parkinson's disease, schizophrenia and depression.[39] Therefore, selaginpulvilins attracted the attention of various organic chemists and several synthetic approaches towards some of these unusual natural compounds were developed.

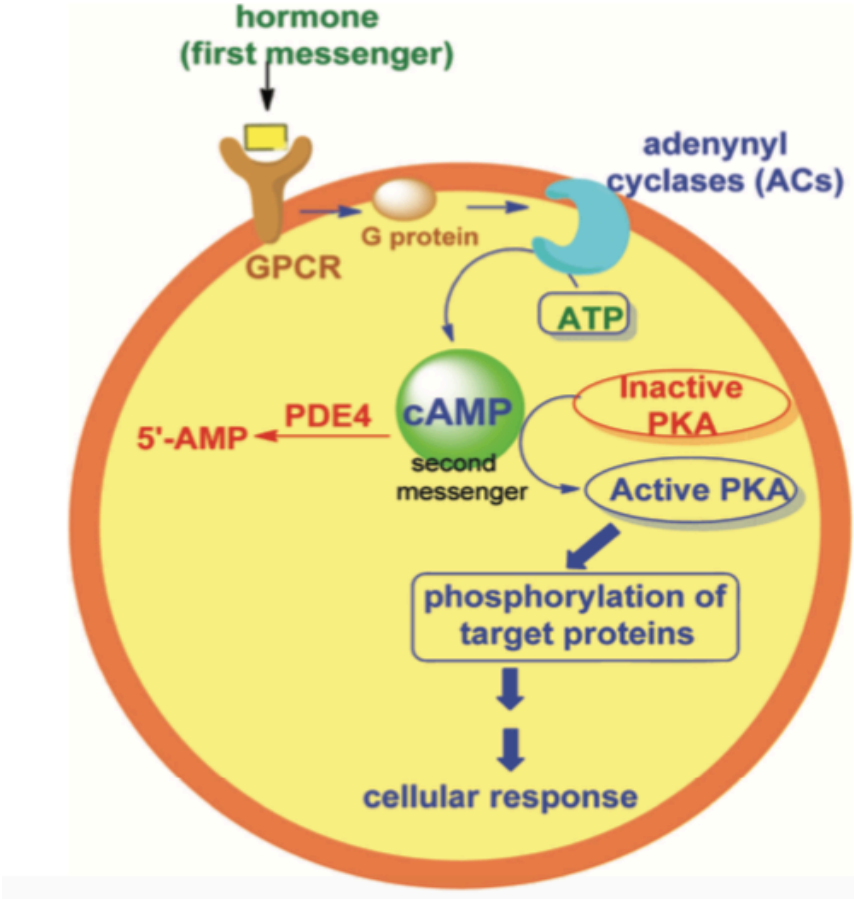
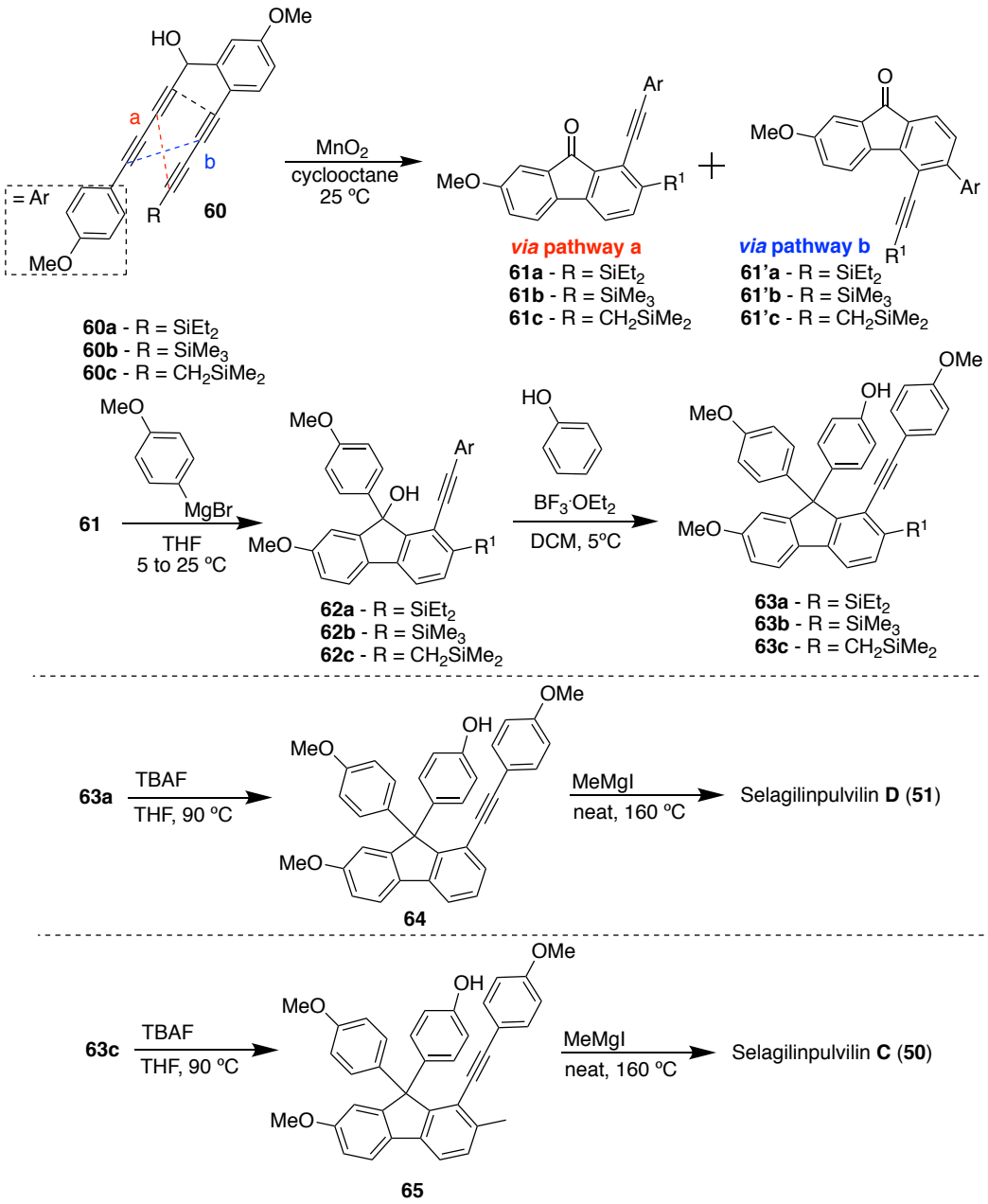


Figure 4 - cAMP signalling cascade, adapted from *Saumitra Sengupta et al*[38].

1.3.2 Previous Synthesis

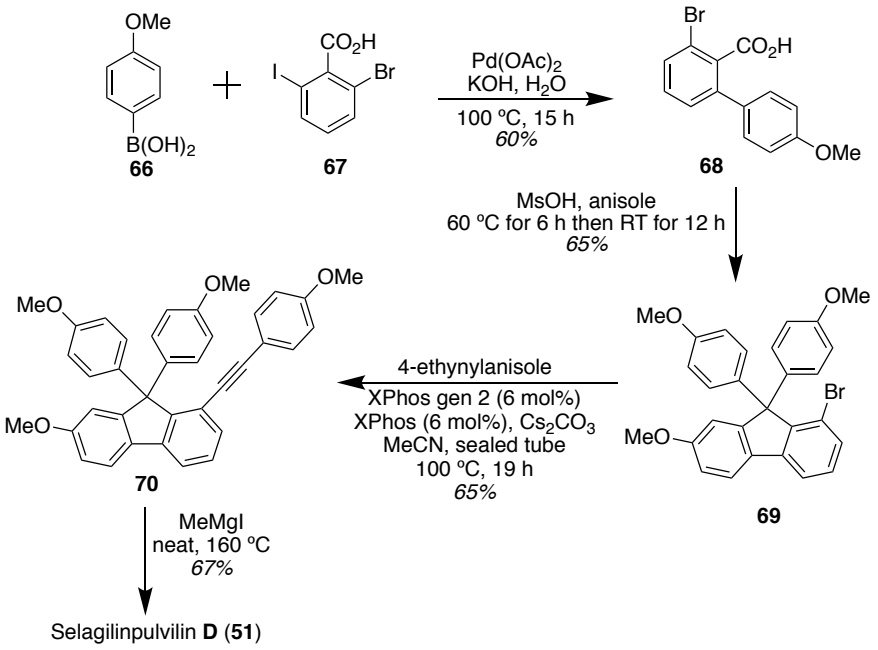
The first total synthesis of selaginpulvilin **C** (**50**) and **D** (**51**) was carried out by Karmakar and Lee in 2016.[40] The reported approach begins with the synthesis of tetrayene **60**, which was then subjected to a hexadehydro Diels−Alder reaction in order to obtain compound **61** with the fluorenone scaffold. The yields were 34% for **61a**, 54% for **61b** and 59% for **61c**, respectively. Nevertheless, the regioisomer **61'** was also formed during the reaction, being the ratio **61a**:**61'a** = 6:1 and **61b**:**61'b** = 5:1. The formation of the regioisomer **61'c** was not reported. Furthermore, the reaction procced to achieve the 9,9-diphenyl-fluorene **63**. With the



Scheme 11 - Synthesis of Selaginpulvilin C and D reported by Karmakar and Lee.

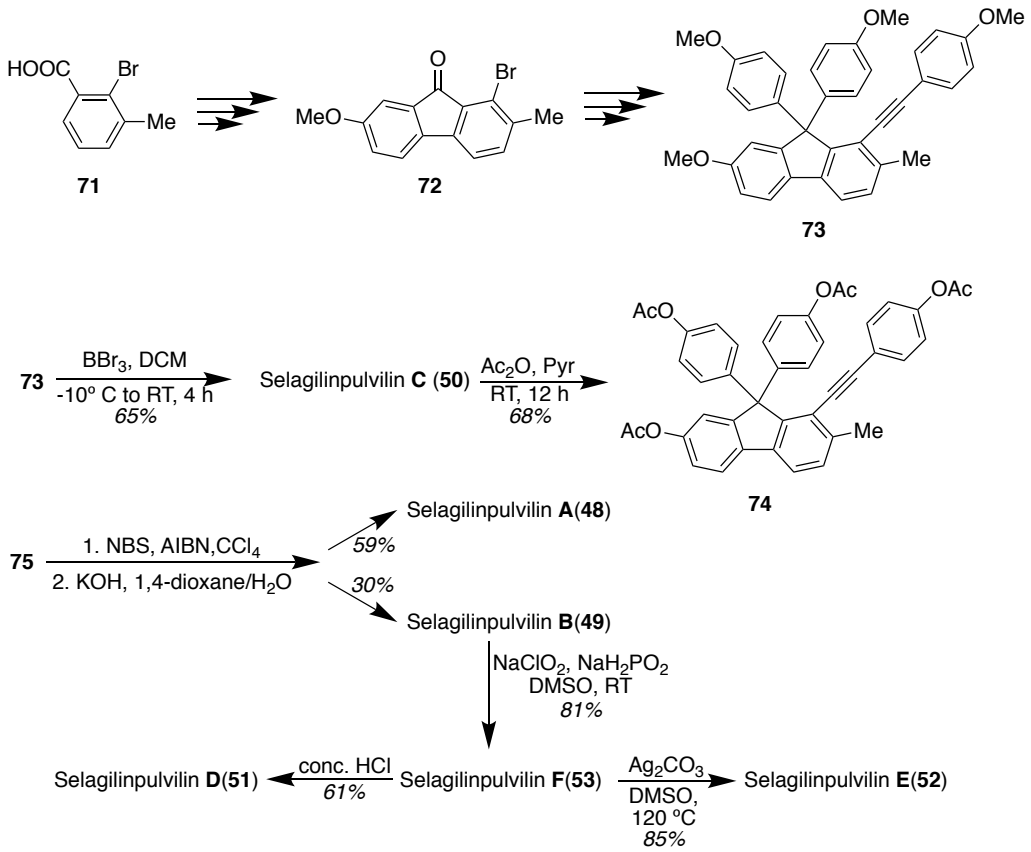
trimethoxy-selaginpulvilin **63a** and **63c** in hands, the authors carried out the desilylation using tetra-*n*-butylammonium fluoride in THF at 5 ºC. The full synthesis of selaginpulvilin **C** and **D** was accomplished by using methylmagnesium iodide at 160 ºC under neat conditions to deprotect the phenols. The elegant total syntheses yielded selaginpulvilin **C** (**50**) in 19% yield over 11 steps and selaginpulvilin **D** (**51**) 1.5% yield.

In the same year, Sowden and Sherburn reported a four-step total synthesis of selaginpulvilin D.[41] It began with the Suzuki-Myiaura coupling of 4-methoxyphenylboronic acid (**66**) with 2-bromo-6-iodobenzoic acid (**67**) giving 2-phenylbenzoic acid **68** in 60% yield. Its heating in methanesulfonic acid produced the fluorenone that was promptly *in situ* converted to compound **69** by a simple addition of anisole. Ensuing Sonogashira coupling with 4-ethynylanisole in the presence of Buchwald's second-generation XPhos precatalyst furnished 4-methoxy-selaginpulvilin D (**70**) in 65% yield. Finally, the total synthesis of selaginpulvilin D (**51**) was accomplished de deprotetcion with methylmagnesium iodide at 160 ºC. The overall yield was 17% over four steps.



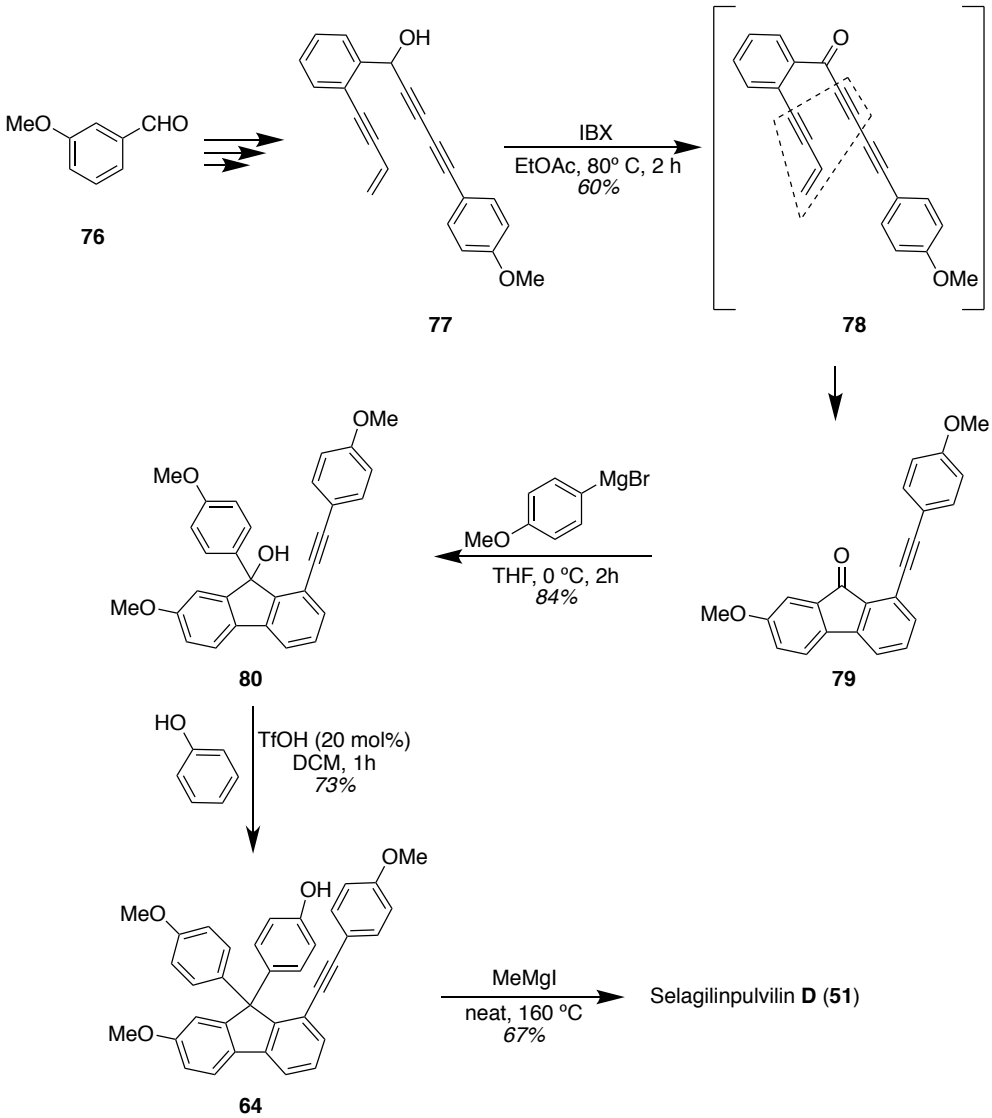
Scheme 12 - Four-step total synthesis proposed be Swoden and Sherburn.

In 2016 Zhang *et al.* reported the total synthesis of selaginpulvilin A.[36] Moreover, several other members of the selaginpulvilin class were prepared by a series of interconversions from selaginpulvilin **A.** Starting with 2-bromo-3-methylbenzoic acid (**71**) they proceed with the Suzuki coupling of 4-methoxyphenylboronic acid followed by Friedel–Crafts-type cyclization to obtain fluorenone **72**. Fluorenone **72** was converted in three steps to the tetramethoxy derivative **73**. The subsequent deprotection of the methoxy groups using boron tribromide provided selaginpulvilin **C** (**50**) in 65% yield. Acetylation of the free phenol groups furnished the peracetate **74**. The series of modifications of **74** allowed to access several other representatives of the selaginpulvilin family. By reacting **74** with NBS and KOH was obtained selaginpulvilin **A** (**48**) and selaginpulvilin **B** (**49**) in 59% and 30% yields, respectively. The oxidation of selaginpulvilin **B** (**49**) gave selaginpulvilin **F** (**53**) in 81% yield. Selaginpulvilin **F** (**53**) was decarboxylated with hydrochloric acid to give selaginpulvilin **D** (**51**) and under Ag-induced intramolecular addition of the carboxylate to the triple bond was obtained selaginpulvilin **E** (**52**).[36]



Scheme 13 - Synthesis of selaginpulvilins A (48)-F (53) proposed by Zhang and co-workers.

In 2017, the formal total synthesis of selaginpulvilin C was achieved by Chinta and Baire [42]. Beginning with 3-methoxybenzaldehyde (**76**) they synthesized triene **77** over a five-step synthesis and with an overall yield of 26%. With triene **77** in hands, the next step was the treatment with IBX in EtOAc at 80 ºC and it resulted in fluorenone **79** *via* a highly selective tetradehydro Diels-Alder with a 60% yield. The rest of the synthesis was very similar to the synthesis executed by Karmakar and Lee in 2016 (see scheme 11).

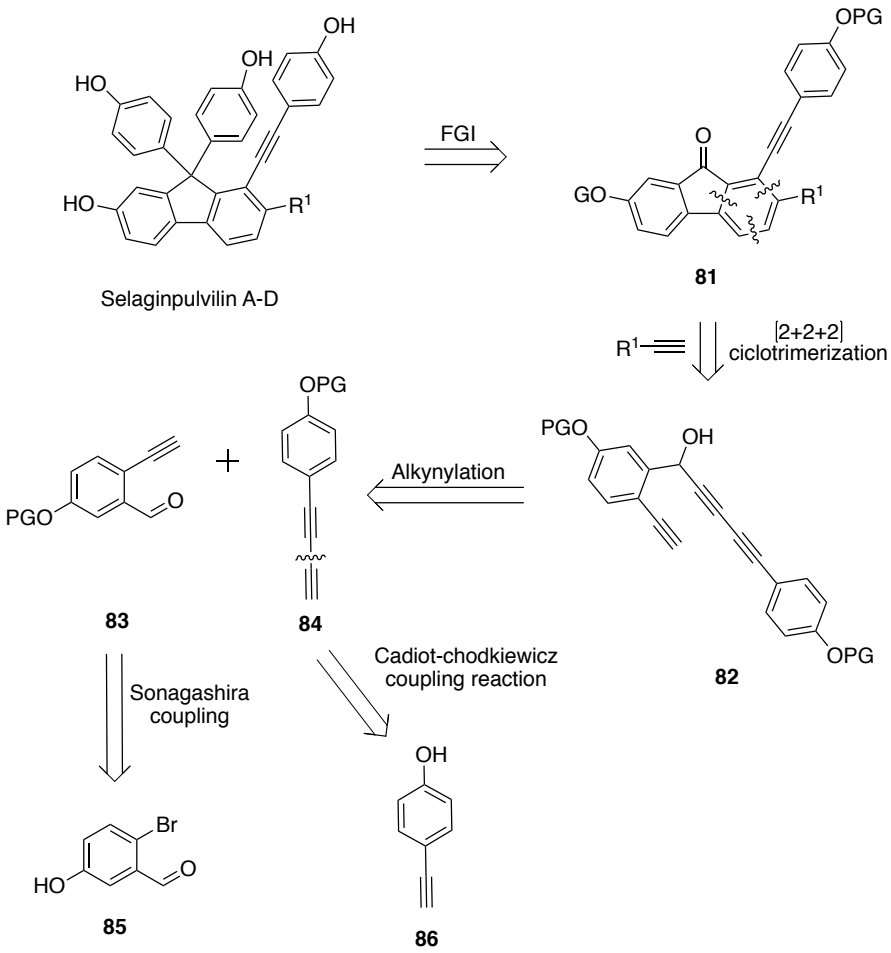


Scheme 14 – Total synthesis of selaginpulvilin D (51) reported by Chinta and Baire.

2. Results and Discussion

2.1. Retrosynthetic analysis

The retrosynthetic analysis of selaginpulvilins is summarized in scheme 15. Through the fluorenone **81** it is possible to introduce the two 9,9-diphenyl substituents *via* Friedel−Crafts arylations. Fluorenone **81** can be assembled *via* [2+2+2] cyclotrimerization using the triene **82** and a numerous possibility of different alkynes. That gives the flexibility to change the functional group in the fluorenone core depending on the desired selaginpulvilin. In terms of designing triene **82**, it can be obtained *via* alkynylation of **83** and **84.** The substrate **83** can be obtained by Sonagashira coupling starting with 2-bromo-5-hydroxybenzaldehyde (**85**). Substrate **84** can be achieved by bromination of 4-ethynylphenol (**86**) followed by Cadiot-Chodkiewicz coupling reaction.



Scheme 15 - Retrosynthetic analysis of Selaginpulvilin A-D.

[2+2+2] cyclotrimerization is a simple and yet elegant technique to synthetize the fluorene core, as described before. The aim of this project is to find suitable conditions for the [2+2+2] cyclotrimerization in order to synthesize a variety of fluorenone cores using different substrates. Moreover, successful application of various alkynes will provide an opportunity to access fluorenols with various substitution, which will open the door to the possibility for the synthesis of unnatural derivatives of selaginpulvilins.

2.2. Scope of the [2+2+2] cyclotrimerization reaction

Various selaginpulvilins differ at the C12 position of the fluorene skeleton (figure 3). Thus, undertaking the outlined synthetic strategy, application of different alkynes will reflect in the formation of various fluorenols, with different substituent at the C12 position. Moreover, the successful synthesis of selaginpulvilins can be only achieved if the key [2+2+2] cyclotrimerization will proceed regioselectivity towards the ortho isomer. Therefore, our initial effort was focused on the determination of the scope of the transformation with respect to the alkyne used. The regioselectivity and the reaction yields were the main objectives of our investigation. Briefly, the reactions were carried in a microwave vial at 90 ºC for 1 hour, loaded with the triene **87**, 5.0 equivalents of alkyne (**88a-88p)** and 10% mol of Wilkinson's catalyst ($(PPh_3)_3RhCl$). The results are demonstrated in table 1. First, Propargyl alcohol **88a** was evaluated as external alkyne in the reaction with triene **87**. Reaction provided 45% yield and a mixture of two regioisomers: ortho **89a** and para **89a'** in ratio 9.5:1. For comparison, reaction with TBS protected propargyl alcohol (**88b**) provided 15% of mixture of regioisomers in ratio 1.4:1 **89b**:**89b'**. This prompted us to investigate more of the alkynes containing free hydroxyl group. For that matter, 2-Methyl-3-butyn-2-ol (**88c**) was used and yielded 24% in a ratio of 1:1.2 of **89c** and **89c'**. It was possible to separate **89c** from **89c'** and both regioisomers were characterized, thus it provides a good opportunity for the discussion, how the ratio and identity of the regioisomers was determined. The ratio of regioisomers was determined by ^1H NMR for all the experiments realized due to the simplicity to detect both regioisomers in a mixture. In particular, the signal of the proton at the methylene bridge of the fluorenol proved to be very useful for the determination of the ratio of the isomers, as depicted in the figure 5, from the red scheme. In figure 5 it is further possible to perceive the aromatic region of regioisomer **89c** (blue), regioisomer **89'c** (green). Since desired regioisomer **89c** is substituted in the C12 position, it only contains a single singlet (at 7.25 ppm), while the remain proton at C10 and C11 position are doublets. On the contrary, the regioisomer **89'c** is substituted in the C11 position. For that reason, is possible to distinguish 3 singlets at 7.25 ppm, 7.47 ppm and 7.68 ppm, the last two corresponding to the proton at C10 and C12 position. These singlets are easily detected on the mixture of regioisomers as proven in the mixture spectrum (red).

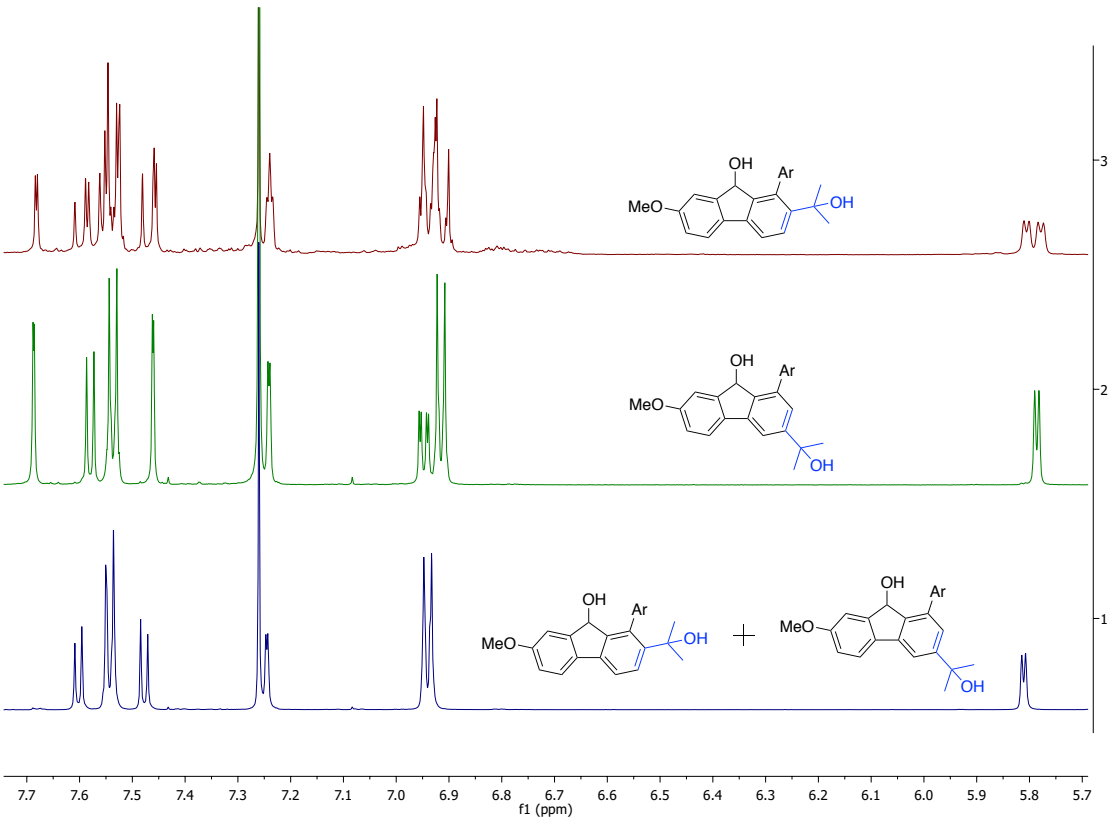
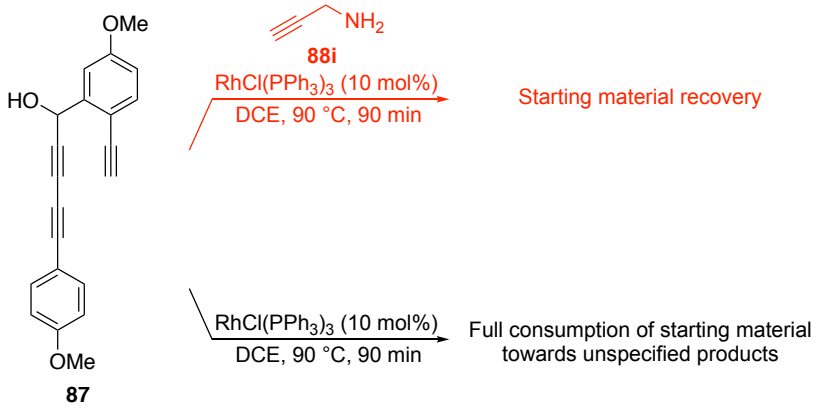


Figure 5 - Overlap 1H NMR spectrum of 89c (blue), 89'c (green) and mixture of 89c and 89'c (red).

Next, we used (*S*)-But-3-yn-2-ol (**88d**), however a complex mixture was obtained and the desired fluorenol **89d** was not isolated. The poor results achieved from the use of tertiary and secondary alcohols (**88b** and **88c**), we refocused the attention in the primary alcohols. For that reason, the length of the chain was studied using the 3-Butynol (**88e**) and the 4-Pentynol (**88f**). Results obtained in the reaction of 3-Butynol (**88e**) and triene **1** were comparable to the that obtained with Propargyl alcohol (**88a**), however, with even enhanced selectivity towards the desired product, which was obtained as a sole regioisomer in 49% yield. By using 4-Pentynol (**88f)**, only the desired regioisomer **89f** was isolated, with the yield of 39%. Furthermore, different functional groups were undertaken in the study. Firstly, Ethyl propiolate (**88g**) was used. However, the respective fluorenol **89g** was not obtained, instead the result was a mixture of unknown products. The results obtained using Propargyl benzoate (**88h**) exceeded expectations. The fluorenol **89h** was obtained with a 52% yield in a ratio of 5.6/1 of **89h** and **89h'**. For a complete scope of the reaction, experiments with functional groups containing nitrogen were performed. The reaction with Propargylamine (**88i**) did not occur and only the starting material was recovered. A control reaction was carried containing only triene **87** and

the Wilkinson's catalyst and all the starting material was consumed, while unidentifiable mixture of products was obtained, as demonstrated in scheme 16. This result suggests that the propargylamine coordinates to the metal and act as a catalyst poison, which results in a suppression of the reaction.

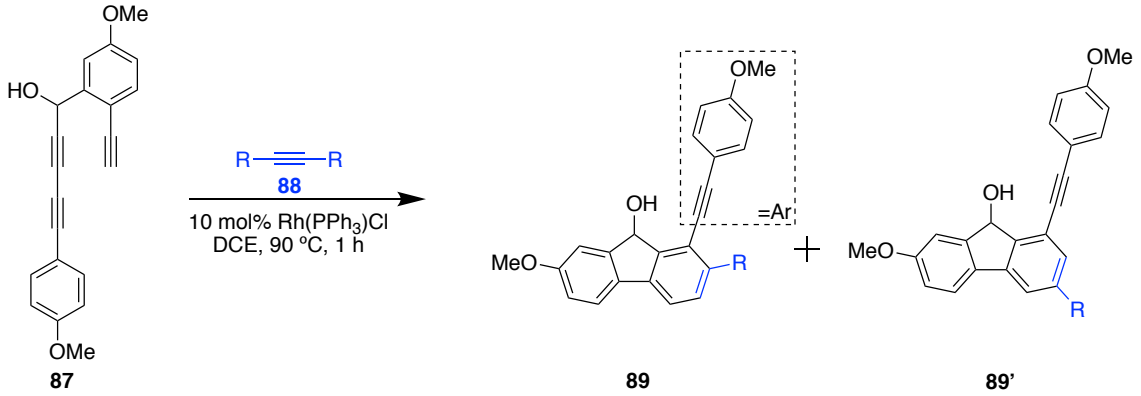


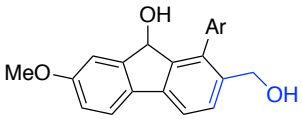
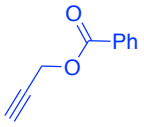
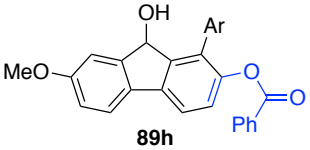
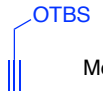
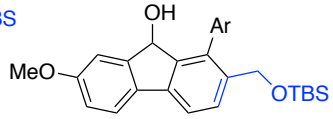
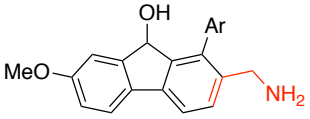
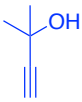
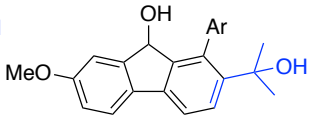
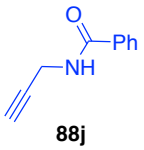
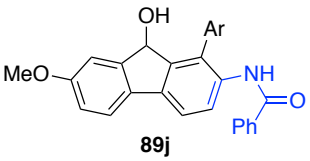
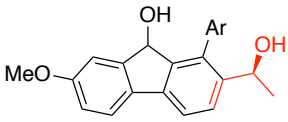
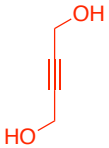
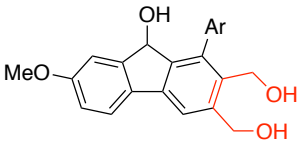
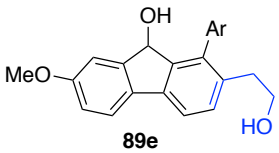
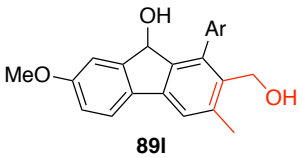
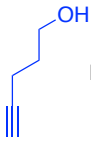
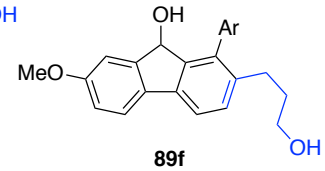
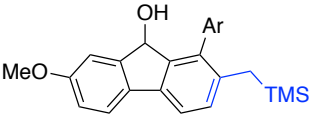
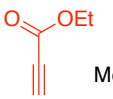
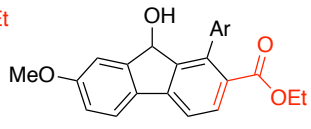
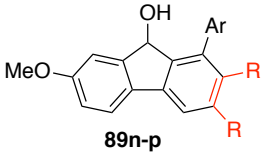
Scheme 16 - Result obtained with the propargyl amine (88i).

On the other hand, results obtained using and *N*-(prop-2-yn-1-yl)benzamide (**88j**) were a surprise, due to the fact that fluorenol **89j** was obtained with a 64% yield in a 13.5/1 ratio of **89j** and **89j'**. Furthermore, experiments with internal alkynes containing polar moieties were carried out. We evaluated 1,4-butynediol (**88k**), a symmetrical alkyne containing two hydroxyl groups. However, the reaction did not occur as expected and the result was a complex mixture. Additionality, 2-butynol **(88l)**, an unsymmetrical alkyne containing a hydroxyl group was used. Desired fluorenol **89l** was not formed and instead the result was a mixture in which products of homodimerization of the starting material were detected.

After the insight into the reactivity of alkynes containing polar groups, the attention was turned on the alkynes lacking such groups. Firstly, it was used the Propargyltrimethylsilane (**88m**), a non-polar terminal alkyne, and it was possible to isolate a mixture of two regioisomers **89m** and **89m'** in a 3.9/1 ratio in a low 14% yield. The next step was the use of symmetrical alkynes such as 3-Hexyne (**88n**), 4-Octyne (**88o**) and Diphenylacetylene (**88p**). The obtained results were similar for all tree experiments. The formation of the desired products was not detected and instead a mixture of homodimerization and further unspecified homooligomerization products was obtained.

Table 1 - Results obtained from the scope of the [2+2+2]-cyclotrimerization.



Alkyne	Product	Yeld/Ratio 89/89'	Alkyne	Product	Yeld/Ratio 89/89'
 88a	 89a	45% 9.5/1	 88h	 89h	51% 5/1
 88b	 89b	15% 1.4/1	 88i	 89i	not formed
 88c	 89c	24% 1/1.2	 88j	 89j	64% 13.5/1
 88d	 89d	complex misture	 88k	 89k	not formed
 88e	 89e	49% 1/0	 88l	 89l	not formed
 88f	 89f	39% 1/0	 88m	 89m	14% 4/1
 88g	 89g	not formed	 88n-p	 89n-p	89n - R = Et, not formed 89o - R = *n*-Pr, not formed 89p - R = Ph, not formed

From the results presented it is possible to draw some conclusions about suitable substrates that can be used in the cyclotrimerization. According to the data displayed tree groups can be shaped: a) terminal alkynes containing a polar moiety; b) terminal alkynes without a polar moiety; c) internal alkynes. The terminal alkynes containing a polar moiety proved to be the most suitable substrates. This is corroborated by the results obtained with alkynes **88a**, **88c**, **88e**, **88f, 88h** and **88j** where the respective fluorenols were obtained in good yields and a good selectivity for the desired regioisomer. However, the steric effect surrounding the alkyne (or the polar moiety e.g. hydroxyl group) must be considered. This can explain the low yield and ratio obtained with 2-Methyl-3-butyn-2-ol (**88c**), since the two-methyl groups can interfere with the coordination of the alcohol to the metal. The terminal apolar alkynes, TBS protected propargyl alcohol (**88b**) and Propargyltrimethylsilane (**88m**), do not have the ability to coordinate to the metal and this fact can explain the low yields and the low ratio obtained. Regarding the internal alkynes, the results were well-defined, the reaction did not occur. All the non-terminal alkynes used, the symmetrical **88k**, **88n-88p** and the unsymmetrical containing a polar moiety **88l**, did not participate in the desired trimerization reaction and the respective fluorenols were not detected in the reaction mixture. Instead we obtained complex mixtures of products, amongst which homodimerization and homooligomerization products were detected by NMR an MS spectrometry.

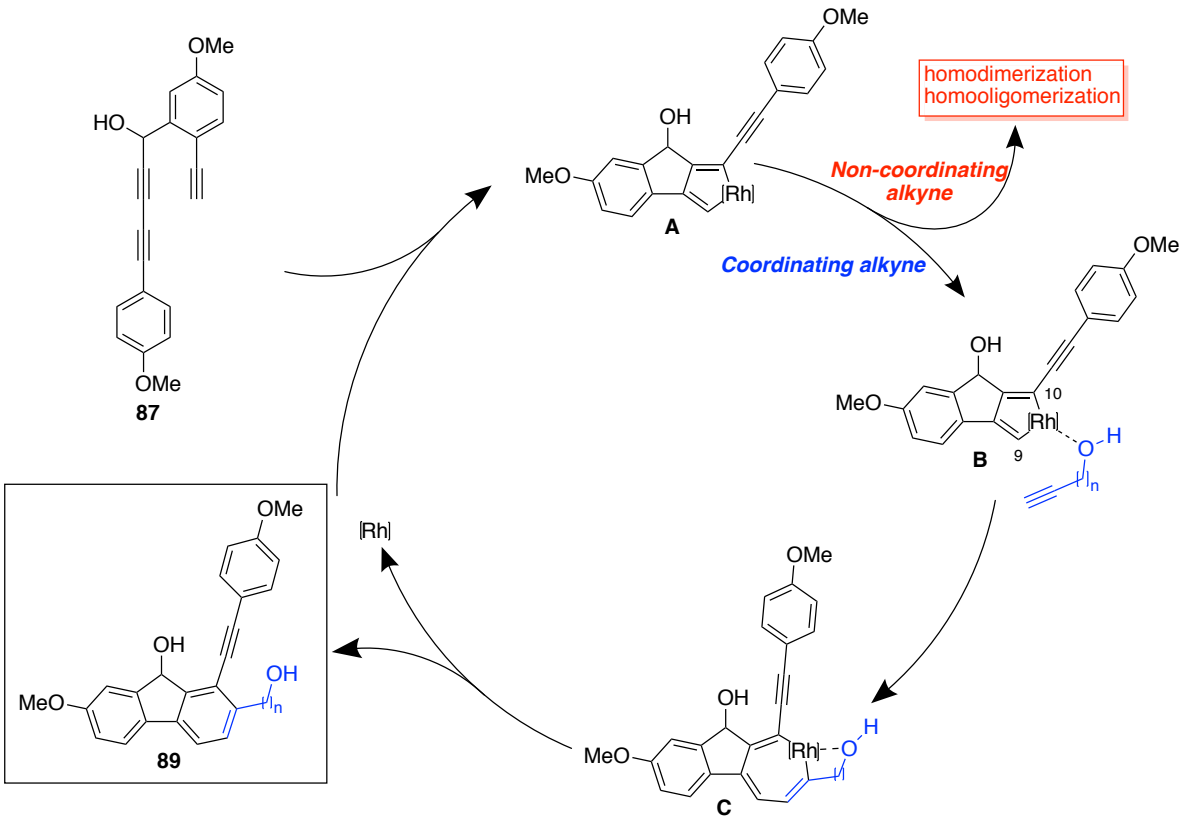
Alongside these results, the mechanism presented in scheme 17 was proposed. Firstly, the coordination of the catalyst to the triene and oxidative coupling of the two coordinated alkynes proceeds to give the metallacyclopentadiyne (**A**). Next, according to the alkyne used, two pathways can take place. If coordination is possible intermediate **B** is preferred. This happens mostly with alkynes containing a polar moiety, such as **88a**, **88e**, **88f**, **88h** and **88j** where the polar moiety will coordinate to the metal. The effect of steric hindrance plays an important role in the coordination to the metal. The evidence is the results obtained from 2-Methyl-3-butyn-2-ol (**88c**). Although the alkyne contains a hydroxy group that can coordinate to the metal, the two methyl groups may prevent this coordination which explains the low yield and poor ratio reported. Moreover, steric hinderance can lead to further destabilization of the intermediate, thus loss of the selectivity as well as the desired reactivity.

On the other hand, if the reaction is carried with an internal alkyne then the intermediate **B** will not be formed, resulting in homodimerization and homooligomerization of the triyne **87** is preferred. This is supported by the results acquired with alkynes **88k**, **88l** and **88n-88p**.

Regarding the regioselectivity of the trimerization, there are two aspects, which can play a role. First, after the coordination, there are two possible sides for the alkyne insertion:

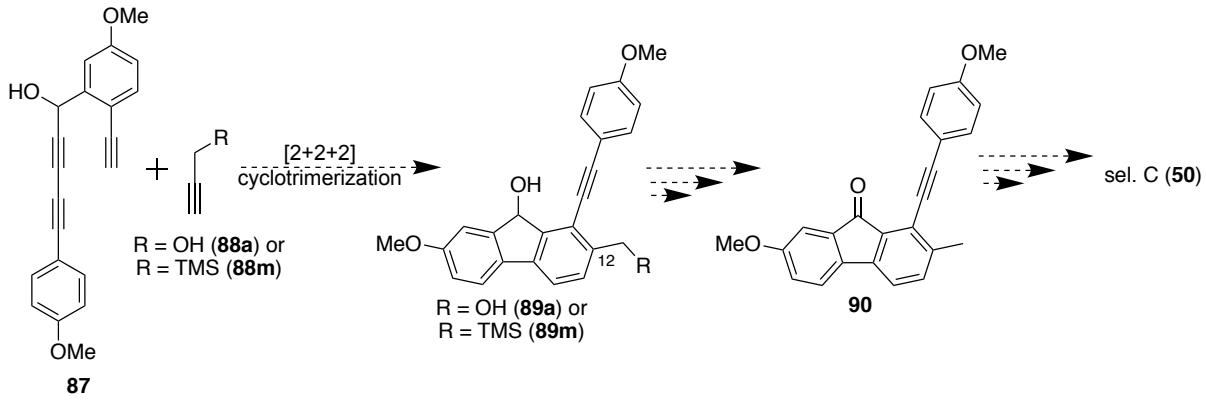
C9-Rh or C10-Rh. Presumably, the insertion will take place on the less sterically hindered C9-Rh side. Second, the coordination of the polar moiety will cause the correct preorientation of the alkyne. Consequently, intermediate metallacycloheptatriene **C** will be formed preferably.

Lastly, a reductive elimination occurs to obtain the fluorenol **89**, which will correspond to the major regioisomer. This model can explain several observations: a) the increased regioselectivity of higher alkyne homologues **88e** and **88f** over Propargyl alcohol (**88a**). For the two earlier, where n = 2 or 3 respectively, the intermediate **C** will form thermodynamically more stable five- and six-membered rings respectively, while the propargyl alcohol will form a four-membered ring. The increased regioselectivity of the amide **88j** over the ester **88h** can be justified by higher Lewis basicity of amides compared to ester, thus, higher ability to coordinate. With this information in hand, the next step was to apply the gained knowledge it in the synthesis of selaginpulvilins.



Scheme 17 - Proposed mechanism for the alkyne insertion.

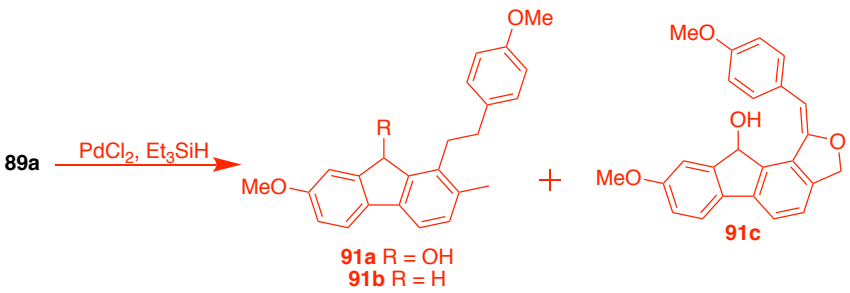
2.3. Synthesis of selaginpulvilin C



Scheme 18 - Approach designed for the formal synthesis of selaginpulvilin C.

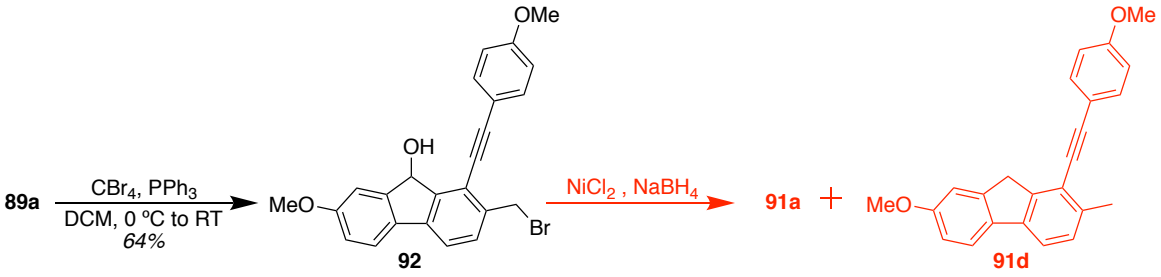
Selaginpulvilin C is a natural product isolated *Selaginella pulvinata*. The proposed synthetic strategy, demonstrated in scheme 18, begin with [2+2+2] cyclotrimerization of triene **87** and alkyne **88a** or **88m** towards the desired fluorenol skeleton **89a** or **89m**, respectively. Consequently, removal of the alcohol moiety (**89a**) or the TMS moiety (**89m**), disclosed in the scheme 18, and oxidation of the secondary alcohol give the fluorenone **90**. Fluorenol **90** was synthesized before and its conversion towards Selaginpulvilin C was described.[40] Thus, by achieving the synthesis of **90** the formal synthesis of selaginpulvilin C can be claimed.

Since selaginpulvilin C contain a methyl group in the C12 position it is necessary to use such alkyne, containing one external carbon building block, such as propyne. From practical reason, a synthon with some cleavable group at the C12 carbon is preferred over propyne. One possibility is the use of Propargyltrimethylsilane (**88m**), application of which would result in the formation of fluorenol **89m** (scheme 17). The TMS moiety could be easily cleaved in order to obtain the desired methyl group in a position C12. However, as exhibited previously (Scope, 1.1), the use of Propargyltrimethylsilane (**88m**) will provide a low yield and a low selectivity for the desired fluorenol, and a complex separation process of regioisomers. Consequently, to avoid these complications, the formal synthesis of selaginpulvilin C began with the [2+2+2] cyclotrimerization of triene **87** and Propargyl alcohol (**88a**) resulting in the fluorenol core **89a** with a 45% and a ratio 9.5/1 of **89a** and **89a'**. At this point, a direct conversion of alcohol to the respective methyl group was attempted, as depicted in scheme 19. Palladium chloride and Triethylsilane, a common system employed for the conversion of benzylic alcohols to the respective alkanes[43], were used in order to reduce primary alcohol **89a** in **90**. However, as a result we obtained a mixture of undesired products, which were identified as products



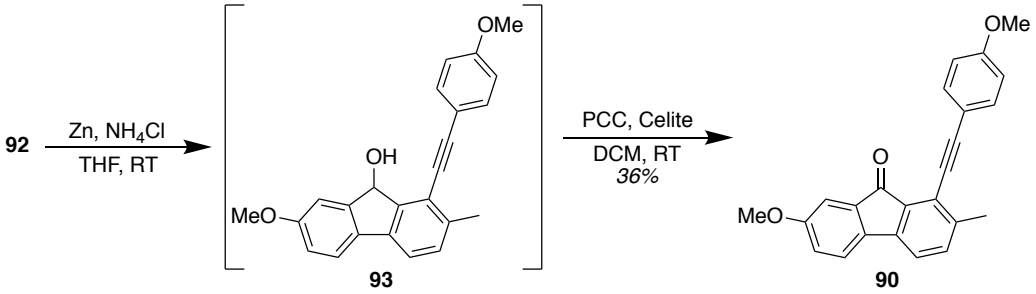
Scheme 19 - Attempt made for direct conversion to the desired fluorenone 90.

of the reduction of the alkyne moiety and/or overreduction of the secondary alcohol resulting in **91a**, **91b**. Compound **91c** result from the nucleophilic attack of the primary alcohol to the alkyne forming a stable tetrahydrofuran ring, most likely catalysed by palladium metal. Due to the difficulty to achieve the direct conversion of alcohol to the respective alkane, a new approach was designed *via* conversion of the alcohol to halide and its subsequent reduction. Therefore, fluorenol **89a** was subjected to the Appel reaction, illustrated in scheme 20. In the presence of Tertrabromomethane and Triphenyl phosphine, bromination yielded 64% of the bromo-fluorenol **92**. Due to instability issues at the open air and silicagel the formation of fluorenol **92** was confirmed only by means of ^{1}H NMR and used quickly in the next step. The reaction product was confirmed by the down shift of protons 25 (annex 6.9). A first attempt of hydrogenation reaction using Nickel chloride and Sodium borohydride did not proceeded as expected, resulting in the side-products **91a** and **91d**. Although it was possible to cleave the bromide with Ni/NaBH$_4$ system, reduction of the alkyne to alkane, **91a**, and cleavage of the secondary alcohol in the C9 position, resulting in florene **91d**, were observed.



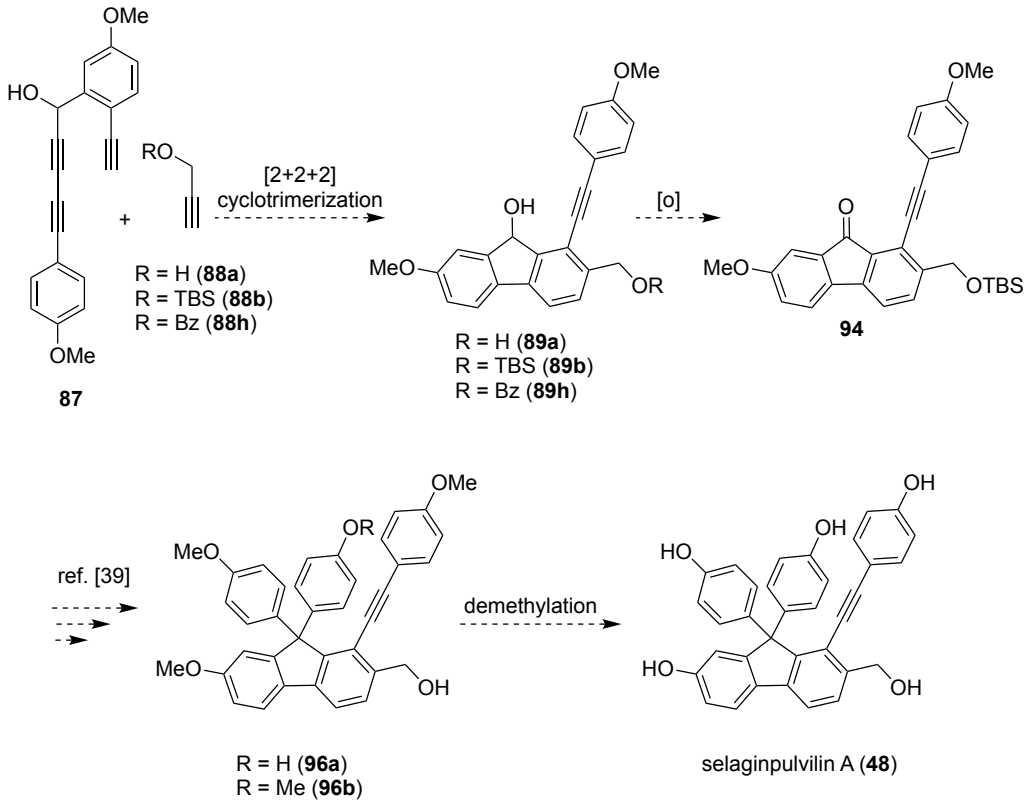
Scheme 20 - Appel reaction and consequent reduction attempt.

Therefore, a mild reduction agent, Zinc powder and Ammonium chloride, was used and is depicted in scheme 21. In this way it was possible to cleave the bromide and obtain the desired fluorenol **93**, containing the methyl group in the C12 position. Without purification, compound **93** was oxidized employing pyridinium chlorochromate and celite®, to achieve the fluorenone **90** with a 36% yield over two steps and complete the formal synthesis of the selaginpulvilin C.



Scheme 21 - Formal synthesis of selaginpulvilin C.

2.4. Synthesis of selaginpulvilin A – First attempt



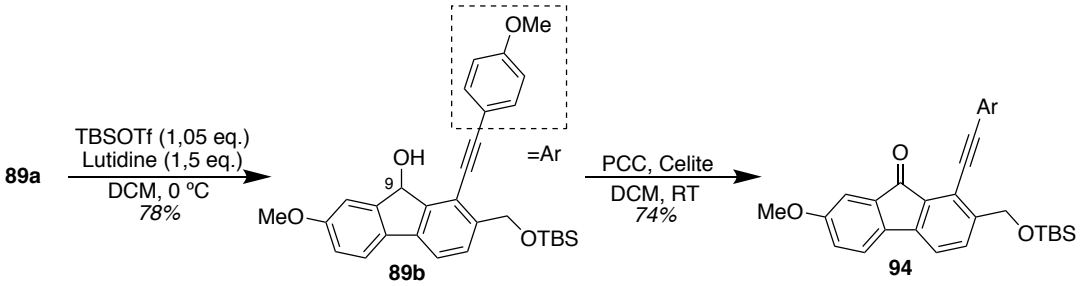
Scheme 22 - Approach designed for the total synthesis of selaginpulvilin A.

Selaginpulvilin A (**48**) contains a methylhydroxy group in the C12 position, illustrated in scheme 22. The formal synthesis of selaginpulvilin A was reported by Chinta and Baire.[44] It proceeded *via* fluorenol **89b**. The introduction of two aromatic moieties then yielded compound **96b** and the formal synthesis was claimed.

Within this part of the master's thesis, we aimed the synthesis of key fluorenone **89** with our methodology and convert it to the known intermediate **94**. Furthermore, we attempted to repeat the chemistry reported by Chinta and Baire[44] for the synthesis of the methylated selaginpulvilin A **96**. The demethylation was attempted as well, in order to finalize the synthesis of the natural product.

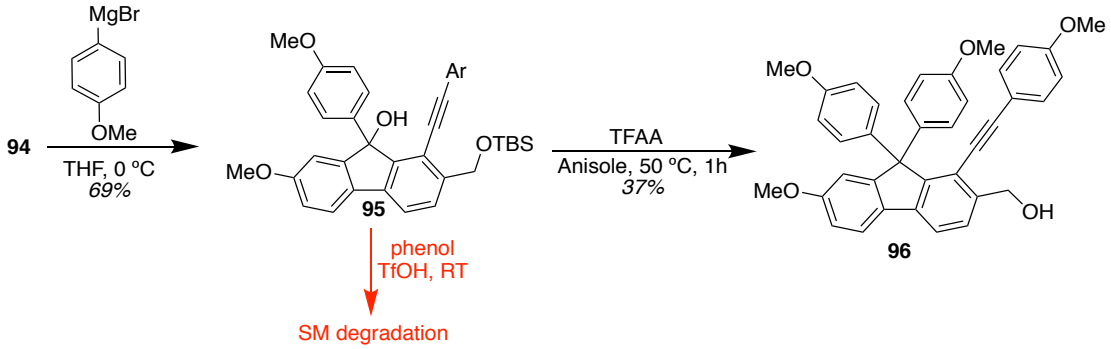
Three candidate alkynes are suitable for the [2+2+2] cyclotrimerization since their application would result in the desired fluorenol skeleton: Propargyl alcohol (**88a**), TBS protected propargyl alcohol (**88b**) or Propargyl benzoate (**88h**). From the scope study (table 1) it is evident that the use of TBS protected propargyl alcohol **88b** leads to a poor result. Application of Propargyl benzoate would lead to the formation of fluorenol **89h**, and two additional steps (deprotection of the benzyl group and protection with the TBS group, would be required). Most

suitable alkyne for the synthesis of fluorenol **89** is Propargyl alcohol (**88a**), since the [2+2+2] cyclotrimerization with triene **87** and Propargyl alcohol (**88a**) provides the best result among the reported alkynes. The relatively good results, compared to the use of alkyne **88b**, compensate for the fact that additional protection step (TBS introduction) is necessary. Hence, the total synthesis of selaginpulvilin A began with [2+2+2] cyclotrimerization of triene **87** and Propargyl alcohol (**88a**) that provided the fluorenol **89a** with a 45% yield and ratio of 9.5/1 **89a**:**89a'**. Next, protection of the primary alcohol was firstly tried with TBSCl, however it resulted in no reaction and only starting material was recovered. Therefore, the next choice was using of TBSOTf, which is more reactive than TBSCl. TBSOTf and Lutidine at 0 ºC yielded 78% of compound **89b** and was easily detected due to the appearance of the characteristic TBS group signal in the ^{1}H NMR, more precisely at 0.95 ppm (9H) and between 0.10 and 0.15 ppm (6H). (annex 6.11). Furthermore, an oxidation reaction took place employing Pyridinium chlorochromate and Celite® to achieve the fluorenone **94** with a 74% yield, showed in scheme 23.



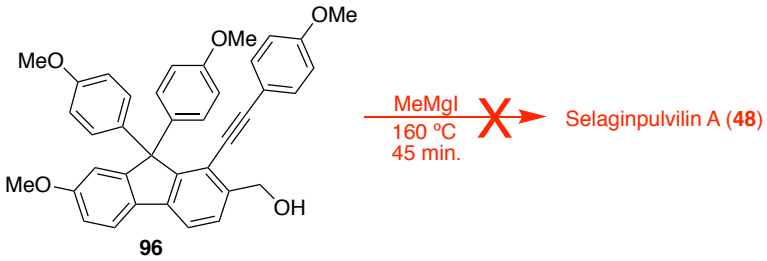
Scheme 23 - Synthesis of fluorenone 94.

The reaction was followed by TLC and the ^{1}H NMR confirms that oxidation was complete (annex 6.12) by the disappearance of the H9 signal at 5.8 ppm on the fluorenone **89b**. With the formation of ketone **94**, the next step was the addition of the anisol group. By using a solution of 4-Methoxyphenylmagnesium, a commercially available Grignard reagent, at 0º C it was possible to obtain tertiary alcohol **95** with a 69% yield, depicted in scheme 24. Having **95** in hands, the attention was turned to the introduction of the second aromatic moiety. Following the literature protocol[40], we first attempted the addition of the second phenol by using Phenol in the presence of Triflic acid. However, the reaction did not occur as expected and degradation of starting material was observed instead. Tetramethoxy-selaginpulvilin A (**96**), was obtained by treatment of alcohol **95** with anisole and Trifluoroacetic anhydride and at 0º C with a 37% yield.



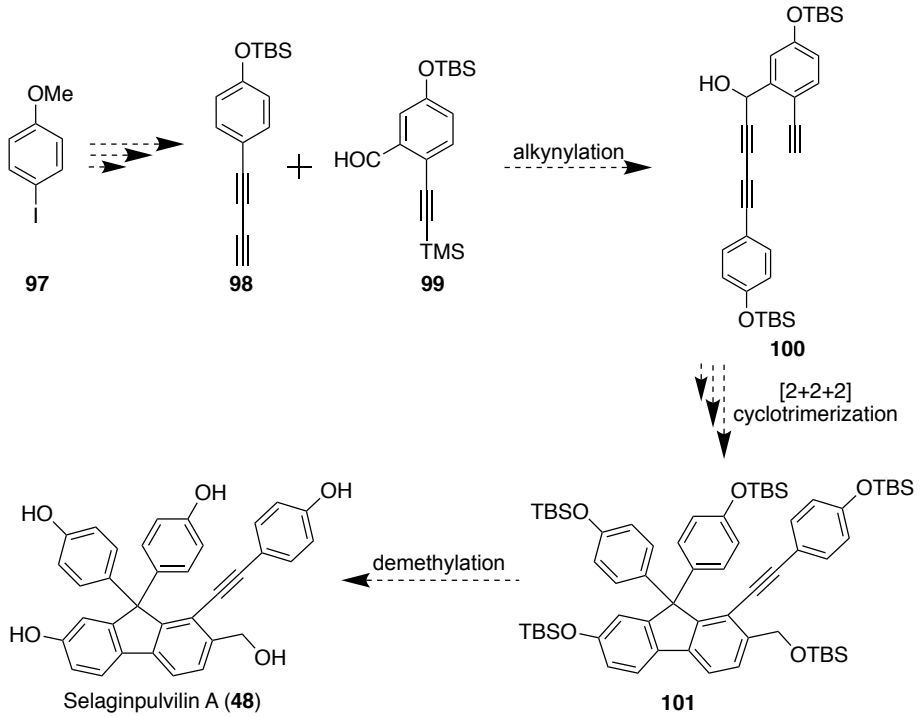
Scheme 24 - Synthesis of Tetramethoxy-selaginpulvilin A 96.

The attempt using Methylmagnesium iodide at 160 ºC under neat conditions as reported by Karmakar and Lee[40], illustrated in scheme 25, did not lead to the desired demethylation, but instead it led to a decomposition of the starting material to an unidentifiable mixture. For that reason, a new approach has been considered with a different protecting group strategy involved. Instead of using methoxy groups as protecting groups of phenols, it was decided to employ TBS protecting group, which should be cleaved in an easier fashion then the methylphenyl ethers (e.g. by reaction with fluorides).



Scheme 25 - Unsuccessful attempt of the total synthesis of selaginpulvilin A (48).

2.5. Synthesis of selaginpulvilin A – Second attempt

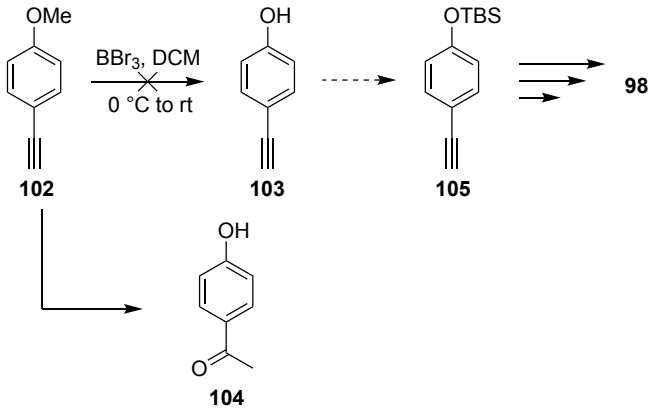


Scheme 26 - New approach designed for the total synthesis of selaginpulvilin A.

A new approach was designed for the total synthesis of selaginpulvilin A, demonstrated in scheme 26. The fluorenol skeleton **101** is still constructed using [2+2+2]-cyclotrimerization, however the protecting groups of the phenols in triene **100** were changed to TBS in order to avoid the complications encountered while attempts to demethylate Tetramethoxy-selaginpulvilin A (**96**)**.** The rest of the strategy remained unchanged. Such an approach should result in the formation of the fully TBS protected selaginpulvilin A **101**. By employing reagents containing fluoride anions (TBAF, HF. pyridine), the cleavage of the TBS ethers should be easily facilitated. The desired cycloaddition precursor, triene containing TBS protecting groups **100** will be prepared by reaction of the diyne **98** and the benzaldehyde **99**.

2.4.1. Synthesis of diyne 98

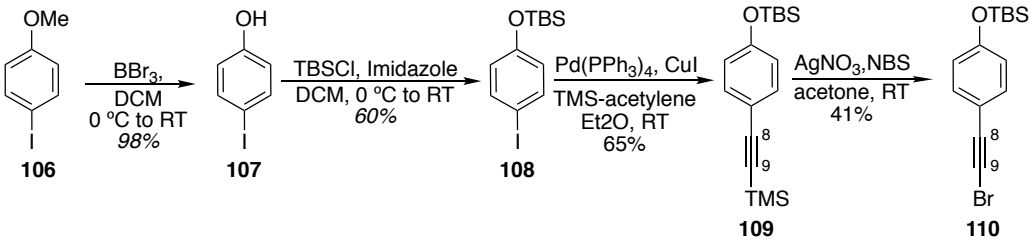
The initial strategy for the synthesis of diyne **98** consisted of demethylation of the 4-Methoxyphenylacetylene (**102**) and further introduction of the TBS group to form the alkyne **103**, which would be further converted into the desired diyne **98**. However, the attempts made to demethylate 4-Ethynylanisole (**102**) using a common demethylation agent Boron tribromide were unsuccessful. Despite the detection of the product in the crude mixture, it was not possible to isolate the desired Phenol and instead, Piceol (**104**) was isolated in all cases. The alkyne moiety in the phenol **103** proved to be extremely prone to a hydration in even a short exposure to the air moisture, which complicated the work-up procedure and this protocol turned out to be unfruitful.



Scheme 27 - Deprotection reaction carried using 4-Ethynylanisole (102).

Introduction of the TBS group needed to be therefore carried out prior the introduction of the alkyne moiety. Hence, the synthesis of the diyne **98,** summarized in scheme 28, begins with the demethylation of 4-Iodoanisole (**106)** using Boron tribromide to obtain Iodophenol (**107**) in 98% yield. It was a simple and clean reaction and the product was obtained by extraction of the crude mixture with DCM without a necessity for an additional purification. The conversion to Iodophenol (**107**) was confirmed by ^{1}H NMR. The demethylation was easily perceived by the disappearance of the peak corresponding to the methyl group at 3.76 ppm. It was also possible to detect the signal of alcohol proton at 4.91 ppm (annex 6.15). A protection of the phenol using TBSCl yielded 60% of the silane **108**. It was easily determined by ^{1}H NMR due to the appearance of the characteristic peaks of TBS at 0.22 ppm (6H) and at 1.01 ppm (9H) (annex 6.16). Afterwards, a Sonagashira coupling of **108** with TMS acetylene using a catalytic amount of Palladium (0) and Copper (I) iodide provided the phenylacetylene **109** in

65% yield**.** Alkyne **109** was then submitted to bromination using silver nitrate and *n*-Bromosuccinimide to obtain the bromoacetylene **110** with a 41% yield. The formation of phenylacetylene **109** was confirmed by ^{1}H NMR by the appearance of the characteristic TMS peak at 0.28 (annex 6.17). Moreover, disappearance of this signal confirmed the consumption of **109** during its conversion to the bromoalkyne. Formation of bromide **110** was further confirmed by analysis of ^{13}C NMR, due to the downshift of C8 and C9 from 105 ppm to 80 ppm and from 92.6 ppm to 48 ppm, respectively (annex 6.18).

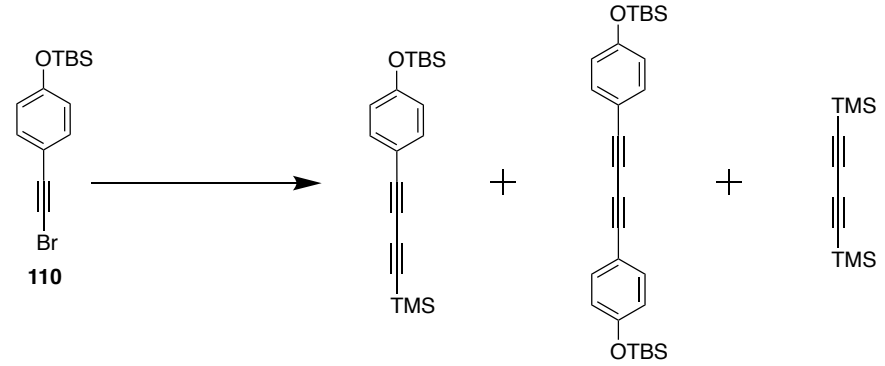


Scheme 28 - Synthesis of the bromoacetylene 110.

In the next step, Cadiot-Chodkiewicz coupling of bromide **110** and TMS-acetylene to form diyne **111** was attempted. However, the reaction suffered a low yield as several side products were detected during the course of the reactions. The structures of the side-products were determined by NMR to be products of homocoupling of the substrates, **112** and **113** (table 2). It was therefore necessary to optimize the reaction conditions by means of catalysts loading, reaction temperature and reagent loadings. The analysis of the crude reaction mixture was carried out by ^{1}H NMR with internal standard (1,2,4,5-tertamethylbenzene). However, difficulties were encountered due to some overlaps in the signals of the product and side-products. Therefore, the obtained values had rather indicative value and are reported in table 2. A control reaction (entry 1) with 1.2 equivalents of TMS-acetylene, 5 mol% of $Pd(PPh_3)_2Cl_2$, 5 mol% of CuI at 40 ºC yielded 37% of the desired product **111**, determined by NMR. The first parameter changed was the TMS-acetylene equivalents. Next reaction was carried out with 1.5 and 2.0 equivalents of TMS-acetylene (entry 2 and 3, respectively). The yields were 32% for reaction with 1.5 and 37% for the reaction with 2.0 equivalents, so it was possible to conclude that the quantity of TMS-acetylene used does not influence the outcome of the reaction. The next parameter changed was the load of CuI from 5 mol% to 2.5 mol%. The reaction with 2.5 mol% of CuI (entry 4) yielded 44% of the desired product. Increasing the catalytic load of $Pd(PPh_3)_2Cl_2$ to 10 mol%, while keeping load of CuI at 5 mol% led to additional improvement and the desired product was formed in 59% (entry 5). Keeping the loading of palladium at 10

mol% and decreasing the load of CuI to 2.5 mol% (entry 6) or 1.0 mol% (entry 7) did not lead to any additional improvement and the desired product was formed in 54% in both cases. Slow addition of the solution of the TMS acetylene over the period of 20 minutes also did not result in any improvement and only 37% of the desired product was formed (entry 8). Last reaction was carried lowering the temperature to 0 ºC (entry 9). The reaction yielded 59% of the desired compound **111**. Optimal conditions were found to be with 1.2 equivalents of TMS-acetylene, 10 mol% of Pd and 5 mol% of CuI. The isolated yield somehow correlated with the NMR determined yield. For instance, product **111** was isolated with a 50% yield with the conditions of entry 9, which was similar to the 59% determined yield by NMR.

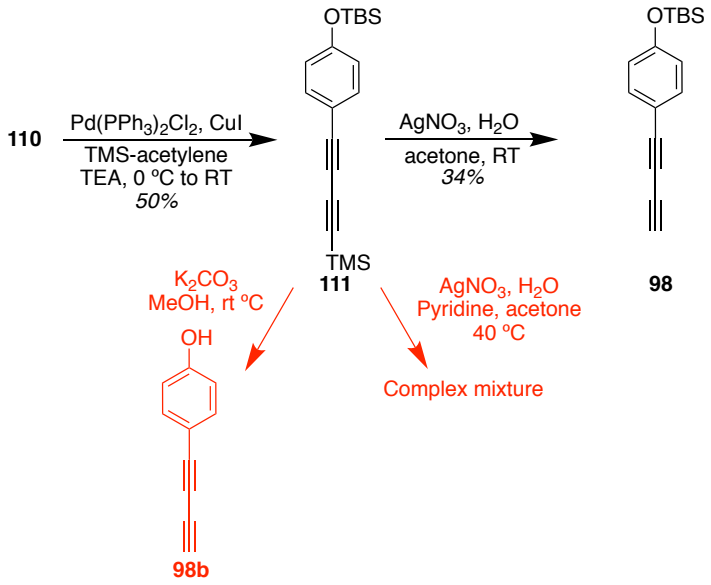
Table 2 - Results obtain for the screening of the Cadiot–Chodkiewicz coupling.



Entry	TMS-acetylene	Pd load (mol%)	CuI load (mol%)	Temperature (ºC)	Yield 111[b]
1	1.2 eq.	5	5	40	37
2	1.5 eq	5	5	40	32
3	2.0 eq.	5	5	40	37
4	1.2 eq	5	2.5	40	44
5	1.2 eq	10	5	40	59(43[c])
6	1.2 eq	10	2.5	40	54
7	1.2 eq	10	1	40	54
8[a]	1.2 eq	10	5	40	37
9	1.2 eq	10	5	0	59(50[c])

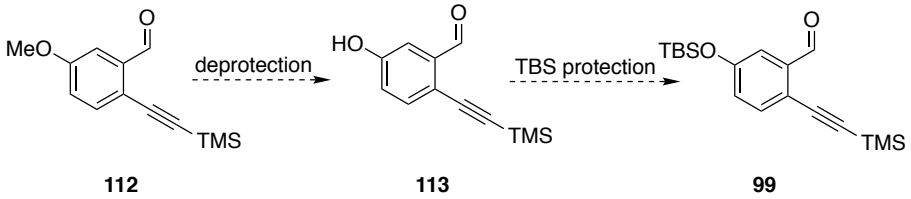
[a] Addition of Starting Material over 20 minutes; [b] NMR yield; [c]Isolated

Following the Cadiot–Chodkiewicz coupling, the standard protocol for desilylation, use of potassium carbonate in methanol, was applied to diyne **111**. Nevertheless, this resulted in the formation of diyne **98b** where both TMS and TBS groups were removed. Alternatively, an attempt was made in the presence of catalytic amount of silver nitrate in a mixture of acetone, pyridine and water which resulted in a formation of a complex mixture of products. Following the literature[45], by removing the pyridine from the system, the desired diyne **98** was obtained with a 34% yield. This conversion was easily detected from ^{1}H NMR analysis by the disappearance of the TMS signal at 0.23 ppm, the appearance of the alkyne proton signal at 2.45 ppm and the presence of the TBS characteristics signals at 0.21 ppm (6H) and 0.98 ppm (9H).



Scheme 29 - Synthesis of diyne **98**.

2.4.2. Synthesis of benzaldehyde 99.

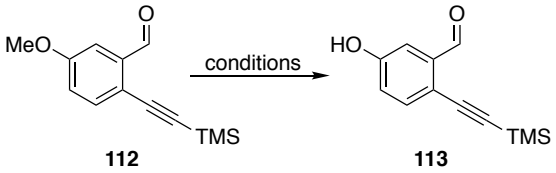


Scheme 30 - Approach designed for the synthesis of the benzaldehyde 99.

With diyne **98** in hands the attention was turned to the synthesis of the benzaldehyde **99**. The synthesis proposed to achieve benzaldehyde **99** is depicted in scheme 30. Using the benzaldehyde **112** firstly a deprotection would take place to remove the methyl protection group and achieve **113**. Then, **113** would be summited to a TBS protection achieve the synthesis of benzaldehyde **99**.

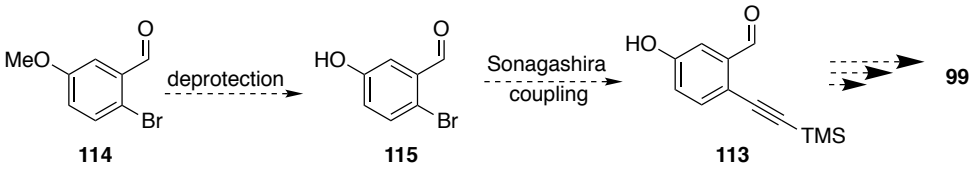
Tree attempts were made to remove the methyl protecting groups of diyne **112** (Table 3). A first attempt was made using Boron tribromide, a second attempt with Potassium iodide and a third attempt with Lithium chloride. The result for the tree attempts was decomposition of the starting material to undefined side-products.

Table 3 - Attempts made to remove the protecting group of diyne 112.



Entry	Reducing agent	Solvent	Temperature (°C)	Result
1	BBr_3	DCM	0	Decomposition
2	TMSCl	CH_3CN	0	Decomposition
3	LiCl	DMF	0	Decomposition

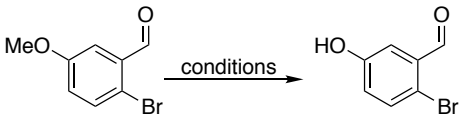
With the unsuccessful attempt with the benzaldehyde **112** a new approach was designed using 2-bromo-5-methoxybenzaldehyde (**114**) as starting material. First step would involve the deprotetction of the phenol to obtain the respective 2-bromo-5-hydroxybenzaldehyde (**115**). Consequently, **115** would be submitted to a Sonagashira coupling and obtain the benzaldehyde **113**. Afterwards, as described previously a protection reaction with TBS and to achieve the desired benzaldehyde **99**.



Scheme 31 - New approach designed for the synthesis of benzaldehyde **99**.

Again, tree attempts to remove the methyl protecting group took place using Boron tribromide, Potassium iodide and Lithium chloride. The result was decomposition of the starting material to an undefined side-product. The work is still under the process.

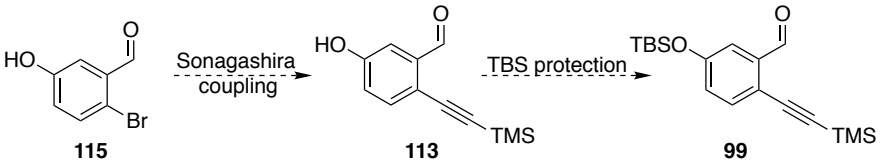
Table 4 - Attempts made to remove the protecting group of diyne **114**.



Entry	Reducing agent	Solvent	Temperature (ºC)	Result
1	BBr_3	DCM	0	Decomposition
2	TMSCl	CH_3CN	0	Decomposition
3	LiCl	DMF	0	Decomposition

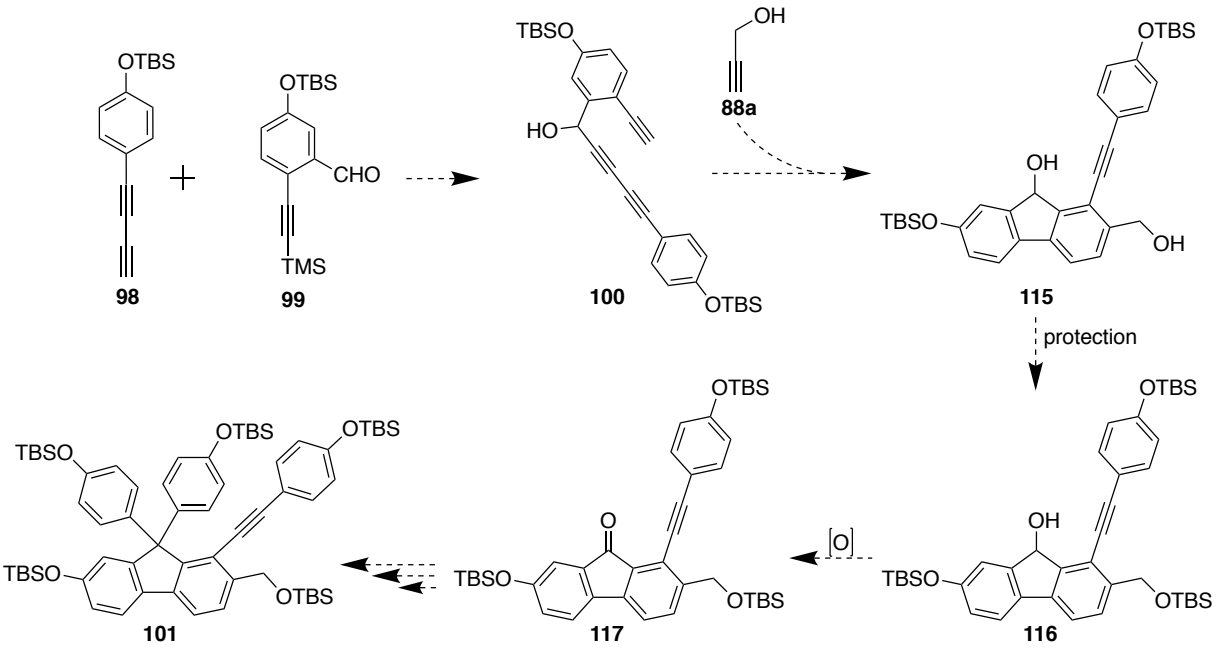
2.6. Future perspectives

To achieve the benzaldehyde **99**, the synthesis should start with 2-Bromo-5-hydroxybenzaldehyde (**115**) a commercially available reagent, as demonstrated in scheme 32. Firstly, Sonagashira coupling will take place between the benzaldehyde **115** and TMS-acetylene to obtain **113**. Afterwards, a TBS protection using for instance TBSCl will provide the desired benzaldehyde **99**.



Scheme 32 - Approach proposed for the synthesis of benzaldehyde 99.

With the diyne **98** and the benzaldehyde **99** isolated and characterized, the next step will be the an alkynylation process to obtain the triene **100**, followed by a [2+2+2] cyclotrimnberization using triene **100** and Propargyl alcohol (**88a**) that will provide the fluorenol **115**. Then, it is necessary to proceed with the protection of the primary alcohol with a TBS group and obtain **116**. Oxidation of **116** will provide the fluorenone **117**, which in turn will be submitted to the addition of two phenolic TBS ethers to achieve the TBS protected selaginpulvilin. A. The total synthesis will be achieved by deprotection of the phenol groups, as exhibited in scheme 33.



Scheme 33 - Approach proposed for the total synthesis of selaginpulvilin A (**48**)

3. Experimental part

3.1. Materials

Wilkinson's catalyst, Propargyl alcohol (99%), Benzoic acid (99%), Propargyl amine (98%), Diisopropylethylamine (99.5%), Triphenylphosphine (99%), Tetrabromomethane (97%), Zinc powder, Celite®, TFAA (99%), Boron tribromide (99.9%), Imidazole (99%), $Pd(PPh_3)_4$ (99%), CuI (99.5%), *N*-butyalmine (99.5%) and $Pd(PPh_3)_2Cl_2$ were purchased from Sigma-Aldrich. Pent-4-yn-1-ol (90%), TBSOTf (97%), *Tert*-butylchlorodimethylsilane (98%) and *N*-bromosuccinimide (99%) were purchased from Fluorochem. 2-Methylbut-3-yn-2-ol (98%) was purchased from Maneko s.r.o. Oxalyl chloride (98%) was purchased from TCI Chemicals. 4-Methoxyphenylmagnesium bromide, 1M solution in THF was purchased from Acros Organics. D-chloroform (99.8%) was purchased from Cambridge Isotope Laboratories, Inc. All the reagents were used without further purification. The solvents used in the above reactions were distilled and dried before use. The reactions were monitored by TLC using Merck TLC silica gel 60 F254 plates, using a UV lamp (254 nm). NMR spectra were measured on a Bruker Avance III spectrophotometer (400 MHz and 600 MHz for ^{1}H NMR and 101 MHz and 151 MHz for ^{13}C NMR, respectively). All chemical shifts δ are reported in ppm. Mass spectrometry was performed on a VG-Analytical ZAB SEQ. Infrared spectra were measured in KBr with a Hermo Nicolet AVATAR 370 FT-IR spectrometer.

3.2. Scope

General procedure for cyclotrimerization with Wilkinson's catalyst RhCl((PPh3)3). A microwave vial was charged with the trialkyne **87** and (32 mg, 0,101 mmol) Wilkinson's catalyst (9 mg, 0.01 mmol, 10% mol.). The atmosphere was exchanged to argon and the mixture was dissolved in dry DCE (2 mL). Alkyne **88** was added, reaction mixture was sealed and heated to 90°C for 1 hour. The reaction mixture was cooled down to room temperature and the solvent was evaporated under reduced pressure. Column chromatography of the residue on silica gel yielded products.

2-(Hydroxymethyl)-7-methoxy-1-((4-methoxyphenyl)ethynyl)-9*H*-fluoren-9-ol (89a). Obtained from the reaction of **87 (**150 mg, 0.474 mmol) and Propargyl alcohol (**88a**) (137 µl, 2.731 mmol) following the general procedure. Column chromatography (15/1, DCM/EtOAc) yielded 85 mg (45%) of the title compound as a light-yellow solid.

Mp 156 °C ($CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.16 (s, 1H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.94 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.66 (d, 8.3 Hz, 1H), 5.55 (d, 8.3 Hz, 1H), 5.27 (t, *J* = 5.0 Hz, 1H), 4.74 (d, *J* = 5.0 Hz, 2H), 3.81 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 149.5, 147.4, 142.2, 139.1, 133.4, 131.9, 127.1, 121.2, 119.1, 118.5, 115.4, 114.8, 114.5, 111.4, 98.2, 84.2, 73.8, 61.7, 55.8, 55.8.

IR (KBr) ν 3327, 2935, 2839, 2208, 1601, 1512, 1293, 1245,1174,1027, 833, 534 cm^{-1}.

HR ESI-MS $[C_{24}H_{20}O_4Na]^+$ 395.1254; found 395.1253.

2-(((*Tert*-butyldimethylsilyl)oxy)methyl)-7-methoxy-1-((4-methoxyphenyl)ethynyl)-9*H*-fluoren-9-ol (89b). Obtained from the reaction of **87 (**150 mg, 0.474 mmol) and *Tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (**88b**) (43 µl, 0.51 mmol) following the general procedure. Column chromatography (1/10 to 1/4, EtOAc/Hexanes) yielded 8 mg (15%) of the title compound as a light-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$δ 7.54-7. 51 (m, 5 H), 7.24 (s, 1H), 6.95-6.91 (ad, 3H), 5.78 (s, 1H), 5.00 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.88 (br, 1H), 0.99 (s 9H), 0.15 (s, 6H).

IR (KBr) 3488, 2956, 2854, 2205 1607, 1512, 1248, 1114, 836 cm^{-1}.

HR ESI-MS $[C_{24}H_{20}O_4Na]^+$ = 509.3119; found 509.2111.

2-(2-Hydroxypropan-2-yl)-7-methoxy-1-((4-methoxyphenyl)ethynyl)-9*H*-fluoren-9-ol (89c). Obtained from the reaction of **87** and 2-Methylbut-3-yn-2-ol (**88c**) (43 µl, 0.506 mmol) following the general procedure. Column chromatography (15/1 DCM/EtOAc) yielded 10 mg (24%) of the title compound and the regioisomer as a light-yellow oil. The regioisomers were separated by preparative thin-layer chromatography using 2/1 Hexane/EtOAc as eluent.

Minor regioisomer 88c: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.54 (ad, 3H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 6.94 (ad, 3H), 5.81 (d, *J* = 4.4 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.05 (s, 1H), 3.02 (d, *J* = 4.4 Hz, 1H), 1.83 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 160.5, 160.4, 148.6, 148.0, 146.8, 139.4, 133.0, 132.1, 125.8, 121.1, 118.9, 116.7, 115.4, 114.5, 110.9, 100.6, 85.3, 75.0, 73.6, 55.7, 55.6, 30.5.

IR (KBr): 3333, 2959, 2923, 2833, 1601, 1506, 1482, 1359, 1284, 1245, 1168, 1126, 1075, 1024, 958, 827 cm^{-1}

HR ESI-MS: $[C_{26}H_{24}O_4Na]^+$= 423.15668; found 423.15701.

Major regioisomer 88c': ^{1} H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 1.6 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.79 (d, *J* = 5.0 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.77 (d, *J* = 5.0 Hz, 1H), 1.79 (s, 1H), 1.65 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 160.4, 160.2, 150.9, 147.1, 145.0, 140.9, 133.3, 132.5, 125.6, 121.2, 119.8, 115.6, 115.3, 114.9, 114.3, 111.0, 94.2, 85.5, 74.6, 72.8, 55.7, 55.5, 32.1.

IR (KBr): 3396, 2962, 2833, 2358, 2208, 1601, 1503, 1455, 1407, 1287, 1242, 1171, 1138, 1096, 1027, 875, 830 cm^{-1}

HR ESI-MS: $[C_{26}H_{24}O_4Na]^+ = [C_{26}H_{24}O_4Na]^+$= 423.1567; found 423.1570.

2-(2-Hydroxyethyl)-7-methoxy-1-((4-methoxyphenyl)ethynyl)-9*H*-fluoren-9-ol (89e). Obtained from the reaction of **87** and But-3-yn-1-ol (**88e)** (36 µl, 0.506 mmol) following the general procedure. Column chromatography (15/1 DCM/EtOAc) yielded 18 mg (49%) of the title compound as a brown solid.

Mp 152 °C ($CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 3H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 1.3 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 6.95 – 6.90 (m, 3H), 5.77 (s, 1H), 3.99 (t, *J* = 6.6 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.16 (t, *J* = 6.6 Hz, 2H), 2.96 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 147.3, 146.7, 139.1, 138.2, 133.2, 132.3, 130.6, 120.9, 120.2, 119.0, 115.2, 114.8, 114.3, 110.9, 98.3, 83.8, 74.8, 63.1, 55.7, 55.5, 37.8.

IR (KBr) 3345, 2998, 2932, 2833, 2358, 2208, 1604, 1509, 1461, 1242, 1102,1027, 809, 531 cm^{-1}

HR ESI-MS $[C_{25}H_{22}O_4Na]^+$= 409.1410; found 409.1414.

2-(3-Hydroxypropyl)-7-methoxy-1-((4-methoxyphenyl)ethynyl)-9*H*-fluoren-9-ol (89f). Obtained from the reaction of **87** and Pent-4-yn-1-ol (**88f**) (43 µl, 0.506 mmol) following the general procedure. Column chromatography (15/1 DCM/EtOAc) yielded 16 mg (39%) of the title compound as a light yellow solid.

Mp 168 °C ($CDCl_3$).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 8.3 Hz, 1H), 7.56 (m, 3H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 2.5 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.94 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.69 – 5.51 (m, 2H), 4.53 (t, *J* = 5.2 Hz, 1H), 3.81 (s, 6H), 3.49 (m, 2H), 2.86 (m, 2H), 1.80 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 159.6, 159.5, 149.0, 147.3, 142.0, 138.0, 133.0, 131.6, 129.3, 120.7, 120.1, 118.8, 115.2, 114.5, 114.1, 111.0, 97.0, 84.8, 73.6, 60.6, 55.42, 55.41, 33.9, 33.6.

IR (KBr) 3273, 2992, 2941, 2878, 2827, 2358, 2205, 1607, 1509, 1455, 1287, 1251, 1171, 1066, 1027, 836, 800, 773, 531 cm^{-1}

HR ESI-MS $[C_{26}H_{24}O_4Na]^+$= 423.1567; found 423.1569.

(9-Hydroxy-7-methoxy-1-((4-methoxyphenyl)ethynyl)-9*H*-fluoren-2-yl)methyl benzoate (89h). Obtained from the reaction of **87** and Prop-2-yn-1-yl benzoate (**88h**) (73 µl, 0.506 mmol) following the general procedure. Column chromatography (15/1 DCM/EtOAc) yielded 25 mg (51%) of the title compound as a mixture of two inseparable isomers (89h:89h' = 5:1) in a form light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.58-7.54 (m, 2H), 7.53-7.51 (m, 2H), 7.51-7.47 (m, 2H), 7.44-7.40 (m, 2H), 7.24 (d, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.82 (d, *J* = 4.7 Hz, 1H), 5.62 (d, *J* = 4.4 Hz, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 2.91 (d, *J* = 4.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 160.6, 160.3, 147.2, 147.0, 140.8, 135.2, 133.4, 133.1, 132.0, 130.3, 130.0, 129.9, 128.5, 121.3, 120.2, 118.9, 115.4, 114.6, 114.3, 110.9, 99.3, 82.9, 74.8, 65.3, 55.7, 55.5.

Characteristic peak of the minor isomer 88'h

^{1}H NMR (400 MHz, $CDCl_3$) δ 5,79 (d, *J* = 4.8 Hz, 1H), 5.40 (s, 2H), 3.85 (s, 3H), 2.83 (d, *J* = 4.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 128.6, 74.6, 66.5.

IR (KBr) 3498, 3055, 2998, 2938, 2833, 2208, 1972, 1718, 1601, 1512, 1485, 1461, 1269, 1245, 1171, 1105, 1021, 830, 806, 710 cm^{-1}.

HR ESI-MS $[C_{31}H_{24}O_5Na]^+$ = 499.1516; found 499.1518.

***N*-(prop-2-yn-1-yl)benzamide.** To a flame dried Schleck tube charged with Benzoic acid (206 mg, 1 mmol) was added anhydrous DCM (5.6 mL), DMF (5 µl) and Oxalyl chloride (171 mL, 2 mmol) dropwise. The reaction mixture was stirred for 3 hours. The solvent was evaporated. The crude was resuspended in DCM (5.6 mL) and was added Propargylamine (96 µl, 1.5 mmol) and Diisopropylethylamine (522 µl, 3 mmol) dropwise. The reaction mixture was stirred for 24 hours. $NaHCO_3$ was added to quench the reaction and an extraction with DCM was proceeded. The organic phase was washed with brine solution and the solvent was evaporated. The purification was proceeded by crystallization (10:1, DCM/EtOAc) yielded 68 mg (43 %) as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.75 (m, 2H), 7.55 – 7.48 (m, 1H), 7.48 – 7.40 (m, 2H), 6.30 (b, NH, 1H), 4.26 (dd, *J* = 5.2, 2.6 Hz, 2H), 2.28 (t, *J* = 2.6 Hz, 1H).

The obtained data agree with those, reported in literature.[46]

***N*-((9-hydroxy-7-methoxy-1-((4-methoxyphenyl)ethynyl)-9*H*-fluoren-2-yl)methyl)benzamide (89j).** Obtained from the reaction of **87** and *N*-(prop-2-yn-1-yl)benzamide (**88j**) (73 µl, 0,506 mmol) following the general procedure. Column chromatography (15/1 DCM/EtOAc) yielded 26 mg (64%) of the title compound as mixture of two inseparable isomers (89j:89‘j = 13.5:1) a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 2H), 7.56 – 7.49 (m, 3H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.44 – 7.37 (m, 2H), 7.24 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H)z, 6.64 (br, 1H), 5.80 (d, *J* = 5.1 Hz, 1H), 4.89 (d, *J* = 5.7 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 2.83 (d, *J* = 5.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 160.5, 160.4, 147.4, 146.8, 140.3, 137.5, 134.7, 133.4, 132.1, 131.6, 130.0, 128.7, 127.2, 127.1, 121.3, 119.8, 119.2, 115.4, 114.4, 111.0, 99.3, 83.3, 74.8, 55.7, 55.5, 43.0.

Characteristic peak of the minor isomer 89’j

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 1H), 7.33, (s, 1H), 4.70 (d, *J* = 5.8 Hz, 2H), 3.85 (s, 3H), 2.83 (d, *J* = 5.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 128.7, 127.0, 114.3.

IR (KBr) 3512, 3288, 3064, 3022, 2962, 2929, 2833, 2361, 2202, 1628, 1607, 1598, 1577, 1512, 1455, 1416, 1338, 1290, 1248, 1171, 1141, 1078, 1027, 991, 836, 806, 695 cm^{-1}**.**
HR ESI-MS $[C_{31}H_{25}NO_5Na]^+$ = 498.1676; found 498.1683.

3.3. Formal synthesis of selaginpulvilin C

2-(Bromomethyl)-7-methoxy-1-((4-methoxyphenyl)ethynyl)-9*H*-fluoren-9-ol (92). To ice-cold mixture of alcohol **89a** (19 mg, 0.052 mmol), Triphenylphosphine (19 mg, 0.073 mmol) and dry DCM (1 mL) was carefully added Tetrabromomethane (19 mg, 0.057 mmol). The reaction was stirred at room temperature for 2 hours. The solvent was then evaporated and the purification of the crude mixture by column chromatography (20:1 DCM/EtOAc) yielded 15 mg (64%) of the bromo-fluorene **92** as a yellow solid. The bromo-fluorene **92** was used without further characterization in the next reaction step, due to is decomposition at open air.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.3 Hz, 1H), 7.47 (q, 2H), 7.24 (d, J = 2.5 Hz, 1H), 6.96 – 6.93 (m, 3H), 5.80 (d, J = 4.9 Hz, 1H), 4.80 (q, J = 9.9 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.84 (d, J = 5.1 Hz, 1H).

7-Methoxy-1-((4-methoxyphenyl)ethynyl)-2-methyl-9*H*-fluoren-9-one (90). Bromofluorene **91** (15 mg, 0.033 mmol) and Zinc powder (13 mg, 0.2 mmol) were weighted into a round bottom flask. Saturated aqueous Ammonium chloride (0.13 mL) and THF (0,07 µl) were added and the reaction mixture was stirred for 2 hours at 25 °C. The unreacted zinc was extracted with water and the desired compound was extracted with ethyl acetate (3 x 1 mL). The organic phases were combined and the solvent was evaporated to obtain fluorene **93.** Without further purification, PCC (9 mg, 0.043 mmol) and Celite (13 mg) were added to the reaction mixture. After addition of DCM (2 mL), the mixture was stirred for 2 hours at room temperature, whereupon it was filtered through Celite and the solvent was evaporated. Purification of the crude mixture by preparative-TLC (8:1, Hexanes/EtOAc) yielded 4 mg (36%) of the desired compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 2H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.29 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.97 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.93 – 6.90 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.50 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 192.5, 160.9, 160.3, 143.1, 140.2, 136.3, 136.0, 134.9, 133.8, 121.5, 121.1, 120.1, 118.5, 115.6, 114.2, 109.3, 100.6, 84.4, 55.9, 55.5, 20.3.

The recorded values are in agreement with the reported data.[44]

3.4. Total synthesis of selaginpulvilin A

3.4.1. First attempt

2-(((*Tert*-butyldimethylsilyl)oxy)methyl)-7-methoxy-1-((4-methoxy-phenyl)ethynyl)-9*H*-fluoren-9-ol (89b). To a flame dried flask on inert atmosphere loaded with **89a** (154 mg; 0.414 mmol) it was added dry DCM. The mixture was stirred and cooled to 0 ºC. TBSOTf (100 µl; 0.434 mmol) and Lutidine (72 µl; 0.620 mmol) were added *via* syringe and the mixture was stirred for two hours. The solvent was evaporated under reduced pressure and purification by chromatography column (9:1 hexanes:EtOAc) yielded 136 mg (78%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 9.0 Hz, 3H), 7.36 (dd, J = 9.8, 7.9 Hz, 2H), 7.19 (d, J = 2.4 Hz, 1H), 6.96 (dd, J = 8.2, 2.5 Hz, 1H), 6.92 (d, J = 8.9 Hz, 2H), 4.96 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 0.98 (s, 9H), 0.16 (s, 6H).

2-(((*Tert*-butyldimethylsilyl)oxy)methyl)-7-methoxy-1-((4-methoxy-phenyl)ethynyl)-9*H*-fluoren-9-one (94). To a flame dried flask on inert atmosphere loaded with **89b** (49 mg; 0.100 mmol) was added dry DCM. PCC (32 mg; 0.149 mmol) and Celite® (42 mg) were added and the mixture was stirred for two hours at room temperature. Filtration through Celite was proceed and the solvent was evaporated. Purification by chromatography column (2:1 hexanes:EtOAc) yielded 36 mg (74%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 9.0 Hz, 3H), 7.36 (dd, *J* = 9.8, 7.9 Hz, 2H), 7.19 (d, *J* = 2.4 Hz, 1H), 6.96 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.92 (d, *J* = 8.9 Hz, 2H), 4.96 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 0.98 (s, 9H), 0.16 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.26, 160.95, 160.35, 143.93, 143.01, 136.36, 135.85, 133.75, 133.37, 131.69, 121.20, 120.11, 118.73, 118.47, 115.30, 114.25, 109.23, 101.11, 82.88, 77.48, 77.16, 76.84, 62.99, 55.83, 55.48, 26.12, 18.59, -5.10.

HR ESI-MS [$C_{30}H_{32}O_4NaSi$] = 507.19621 ; found 507.19605.

The recorded values are in agreement with the reported data.[44]

2-(((*Tert*-butyldimethylsilyl)oxy)methyl)-7-methoxy-9-(4-methoxyphenyl)-1-((4-methoxyphenyl)ethynyl)-9*H*-fluoren-9-ol (95). To a flame dried flask under inert atmosphere loaded with **94** (36 mg; 0.095 mmol) at 0 ºC it was added 2 mL of dry THF. The 4-Methoxy-phenylmagnesium bromide (1.9 µl; 0.191 mmol) was slowly added to the mixture and mixture was stirred for two hours at 0 ºC. Afterwards, the mixture was quenched it NH_4Cl (2 mL) and

the compound was extracted it EtOAc (3 x 5 mL). The organic layer was washed with brine and dried with Na_2SO_4. Purification by chromatography column (10:1 to 4:1 hexanes:EtOAc) yielded 39 mg (69%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 2.1 Hz, 2H), 7.53 (d, *J* = 9.1 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.86 – 6.80 (m, 6H), 4.94 (d, *J* = 4.0 Hz, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.34 (s, 1H), 0.97 (s, 9H), 0.13 (d, *J* = 1.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 160.0, 158.8, 152.2, 150.4, 141.8, 139.5, 135.6, 133.0, 131.2, 127.0, 126.6, 121.1, 119.0, 116.7, 115.0, 114.9, 114.1, 113.7, 110.1, 100.3, 83.9, 82.6, 77.5, 77.2, 76.8, 63.3, 55.6, 55.5, 55.4, 26.1, 18.6, -5.1.

The recorded values are in agreement with the reported data.[44]

(7-Methoxy-9,9-bis(4-methoxyphenyl)-1-((4-methoxyphenyl)ethynyl)-9*H*-fluoren-2-yl)methanol (96). To an inert atmosphere flask containing **95** it was added 70 μL of Anisole and 30 μL of TFAA. The mixture was heated to 50 ºC and stirred for one hour. The compound was extracted with 3 mL EtOAc. The organic layer was washed with 1 mL of $NaHCO_3$ and 1 mL of brine, dried and the solvent was evaporated under vacuum. Purification by chromatography column (4:1 hexanes:EtOAc) yielded 16 mg (37%) of the title compound with a 15% inseparable unspecified impurity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.26 (s, 1H), 7.24 (s, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.84 – 6.82 (m, 3H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.9 Hz, 3H), 4.15 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.74 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 159.6, 158.3, 158.0, 155.8, 152.3, 142.5, 138.8, 135.0, 133.2, 132.7, 132.6, 132.2, 130.4, 130.2, 128.6, 127.4, 120.8, 120.4, 119.0, 118.9, 115.9, 114.0, 114.0, 113.4, 113.2,3 113.1, 113.1, 111.2, 100.6, 86.4, 77.5, 77.2, 76.8, 65.2, 55.6, 55.4, 55.4, 55.4, 39.3.

3.4.2. Second attempt

4-Iodophenol (107). To a flame dried flask containing 4-Iodoanisole (**106**) (500 mg, 3.8 mmol) was added anhydrous DCM (18 mL). The solution was submitted to an ice bath and was slowly introduce 6 mL of Boron tribromide (5.7 mmol) over 5 minutes. The reaction was then heated at room temperature and stirred for 16 hours. After full consumption of the 4-iodoanisole the solution was again submitted to an ice bath and was added 15 mL of cold methanol to quench the remaining unreacted boron tribromide. The mixture was washed it 2 M HCl (2 x 20 mL) and the desired compound was extracted with DCM (3*15 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated to yielded 460 mg (98%) as a pink powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.9 Hz, 2H), 6.63 (d, *J* = 8.9 Hz, 2H), 4.91 (s, 1H). The recorded values are in agreement with the reported data.[47]

***Tert*-butyl(4-iodophenoxy)dimethylsilane (108)**. To a flame dried flask charged with the 4-Iodophenol (**107**) (460 mg, 2.1 mmol) and DCM (11.5 mL) was added the *Tert*-butylchlorodimethylsilane (410 mg, 2.7 mmol) and the Imidazole (185 mg, 2.7 mmol) at 0ºC. The reaction mixture was stirred at the same temperature for 30 minutes and then at room temperature for 24 hours. A white precipitated formed which was filtrated. Purification by chromatography column (hexanes) yielded 424 mg (60%) of the *Tert*-butyl(4-iodophenoxy)dimethylsilane as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 1.01 (s, 9H), 0.22 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 138.4, 122.6, 83.9, 25.8, 18.3, -4.3.

The recorded values are in agreement with the reported data.[48]

***Tert*-butyldimethyl(4-((trimethylsilyl)ethynyl)phenoxy)silane (109).** The Sonagashira coupling was carried in a flame-dried flask containing the *Tert*-butyl(4-iodophenoxy)dimethylsilane (**108**) (422 mg, 1.26 mmol) and the $Pd(PPh_3)_4$ (73 mg, 0.06 mmol). The mixture was suspended in Et_2O (10.5 mL) and stirred for 5 minutes. CuI (24 mg, 0.13 mmol), TMS-acetylene (268 µl, 1.89 mmol) and *n*-butylamine (374 µl, 3,79 mmol) were added and the reaction mixture was stirred for 3 hours. After filtration through celite, the solvent was evaporated and the resulting crude was purified by silica column chromatography (Hexanes) to yield the desired product (250 mg, 65%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 0.99 (s, 9H), 0.26 (s, 9H), 0.20 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 133.6, 120.2, 116.2, 105.4, 92.7, 77.5, 77.2, 76.8, 25.8, 18.4, 0.2, -0.4, -4.3.
The recorded values are in agreement with the reported data.[48]

(4-(Bromoethynyl)phenoxy)(*tert*-butyl)dimethylsilane (110). To a flame-dried flask containing the compound **109** (100 mg, 0.33 mmol) and acetone (4.5 mL) with was added the *N*-bromosuccinimide (76 mg, 0.427 mmol) and the $AgNO_3$ (17 mg, 0.01 mmol). The mixture was stirred for 24 hours. The solvent was evaporated and the resulting crude mixture was purified by silica column (Hexanes) to yield the desired product (42 mg, 41%) as a light yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 2.45 (s, 1H), 0.98 (s, 9H), 0.21 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 134.6, 120.5, 113.7, 77.5, 77.2, 76.8, 75.8, 72.6, 70.9, 68.6, 25.7, 18.8, -4.3.
IR (KBr): 3037, 2956, 2926, 2884, 2854, 1595, 1263, 1165, 940 cm^{-1}

***Tert*-butyldimethyl(4-((trimethylsilyl)buta-1,3-diyn-1-yl)phenoxy)silane (111).** Under inert atmosphere and to a flask containing the compound **110** (100 mg, 0.321 mmol), $Pd(PPh_3)_2Cl_2$ (23 mg, 0.032 mmol) and CuI (3.06, 0.016 mmol) it was added at 0º C TMS-acetylene (89 µl, 0.64 mmol) and TEA (3.5 mL). The mixture was stirred for 1 hour and 0ºC and then 1 hour at room temperature. The solvent was evaporated, and the crude was purified by silica column (Hexanes) to yield the desired product (54 mg, 51%) as a yellow light solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 0.97 (s, 9H), 0.23 (s, 9H), 0.20 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 134.4, 120.4, 114.0, 90.0, 88.3, 77.2, 73.3, 25.7, 18.4, -0.2, -4.3.
IR (KBr): 2959, 2926, 2851, 2205, 2101, 1598, 1509, 1296, 1257, 914, 842, 782 cm^{-1}

(4-(Buta-1,3-diyn-1-yl)phenoxy)(*tert*-butyl)dimethylsilane (98). To a flask containing compound **111** (200 mg, 0.61 mmol) and $AgNO_3$ (16 mg, 0.09 mmol) it was added water (1.10 mL, 61.0 mmol) and acetone (12.5 mL). The mixture was stirred in the dark for 48 hours. The mixture was quenched it NaCl and the acetone was evaporated. Extraction was proceeded

with Et_2O (3 x 10 mL) and the organic layer was washed with brine. The organic layer was purified by silica column (Hexanes) to yield the desired product (53 mg, 34%) as a yellow light solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 2.45 (s, 1H), 0.98 (s, 9H), 0.21 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 134.6, 120.5, 113.7, 77.5, 77.2, 76.8, 75.8, 72.6, 70.9, 68.6, 25.7, 18.4, -4.3.

IR (KBr): 3303, 3037, 2956, 2929, 2857, 2202, 1595, 1503, 1263, 1165, 908, 839, 782 cm^{-1}

4. Conclusion

In this work we reported a successful application of [2+2+2] cyclotrimerization in the synthesis of natural products. In a first stage we tested the robustness and flexibleness of the key transformation. By reacting triene **87** with a variety of alkynes it is possible to determine the scope and limitations of the process and identify such alkynes suitable for the desired reactivity. A suitable alkyne must be a terminal alkyne, otherwise the reaction will not occur, and should contain a polar moiety, capable of a coordination with the metal. Such coordination seems to be crucial for the desired reactivity and regioselectivity. It was therefore possible to propose a model for the process where it is possible to predict the outcome of the reaction based on the alkyne used.

Once the suitable alkynes were established, we employed this process in the synthesis of natural compounds: selaginpulvilin A and C. The synthesis of selaginpulvilin C began with the [2+2+2] cyclotrimerization using the synthetized substrate and propargyl alcohol, that proved to be the most suitable for the synthesis of the desired fluorenol core **89a**. With the desired fluorenol **89a** in hands, attempts were made to promptly achieve the fluorenone **90**. Yet, the attempts were unsuccessful and a new pathway was designed employing the Appel reaction to furnish corresponding bromofluorenol. The formal synthesis of Selaginpulvilin C was finalized by a zinc mediated reduction of bromide to alkane and oxidation of the secondary fluorenol alcohol to the desired fluorenone.

In matter of selaginpulvilin A, it also began with [2+2+2] cyclotrimerization using the synthetized substrate and propargyl alcohol. The total synthesis was not achieved due to complications regarding the demethylations of the methoxy groups. For that reason, a new approach was designed employing TBS protecting groups instead methoxy groups. This approach is still under the investigation.

Although it was not possible to finish the total synthesis of selaginpulvilin A, the [2+2+2] cyclotrimerization proved to be a useful tool for the synthesis of natural compounds, especially the ones containing functionalized cyclic frameworks.

For future work, the synthesis of selaginpulvilin should be completed employing TBS protecting groups which are easily removed. The [2+2+2] cyclotrimerization should also be applied in the synthesis of selaginpulvilins F(**53**) to L(**59**) which were never synthetized in laboratory for the best of my knowledge.

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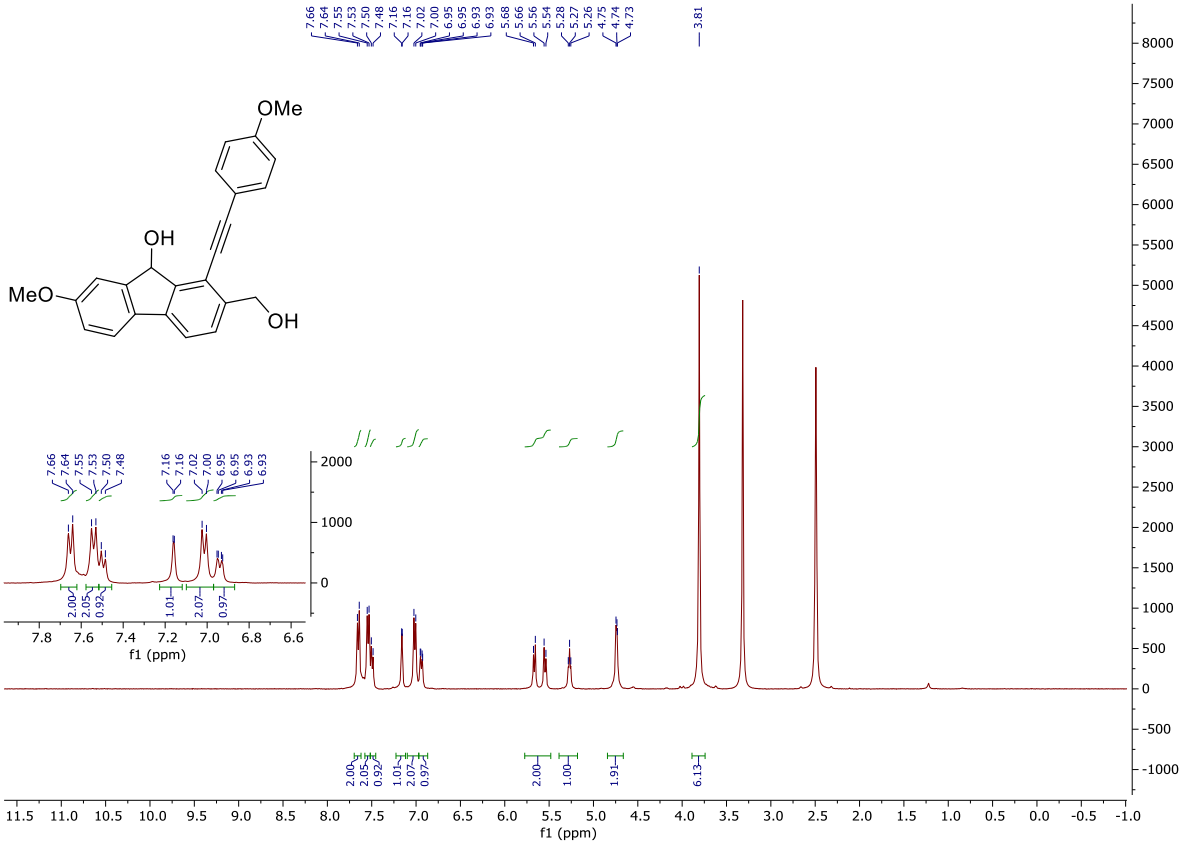
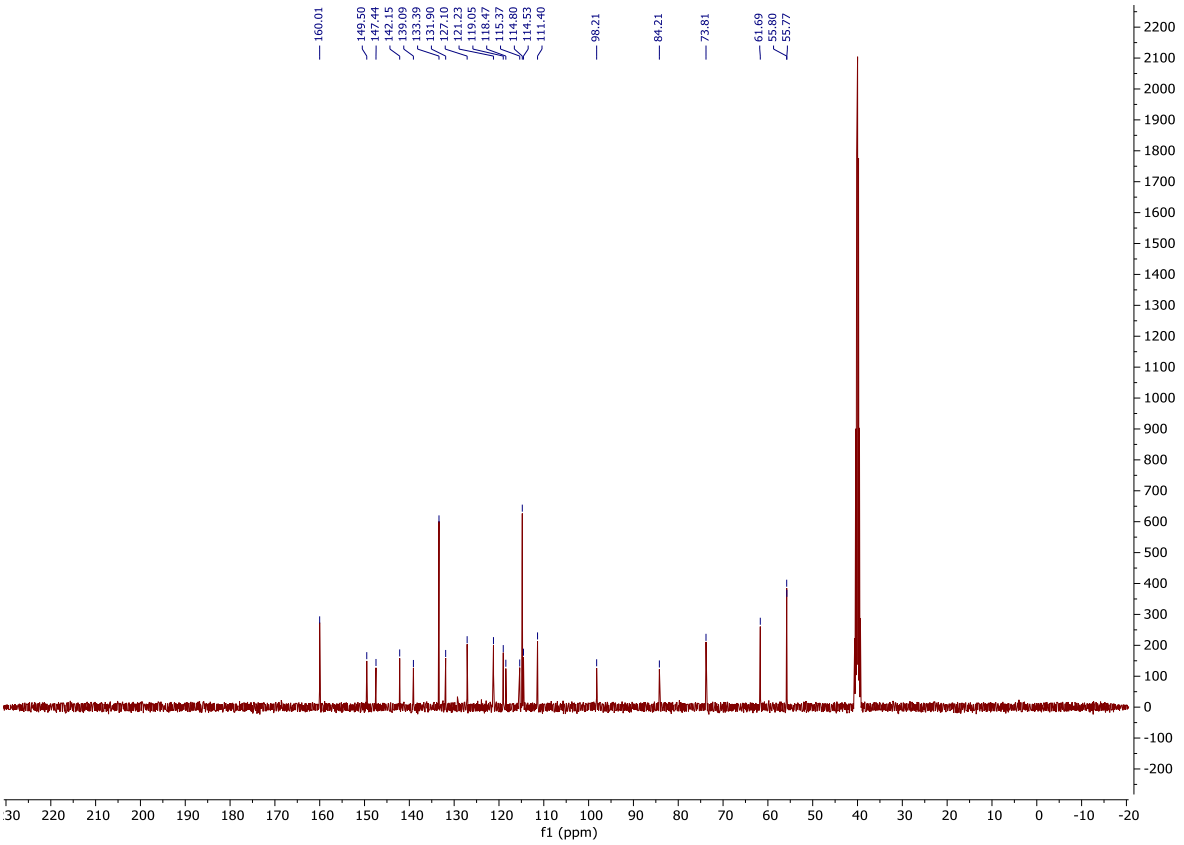
6. Annexes

6.1. Spectral data of 89a





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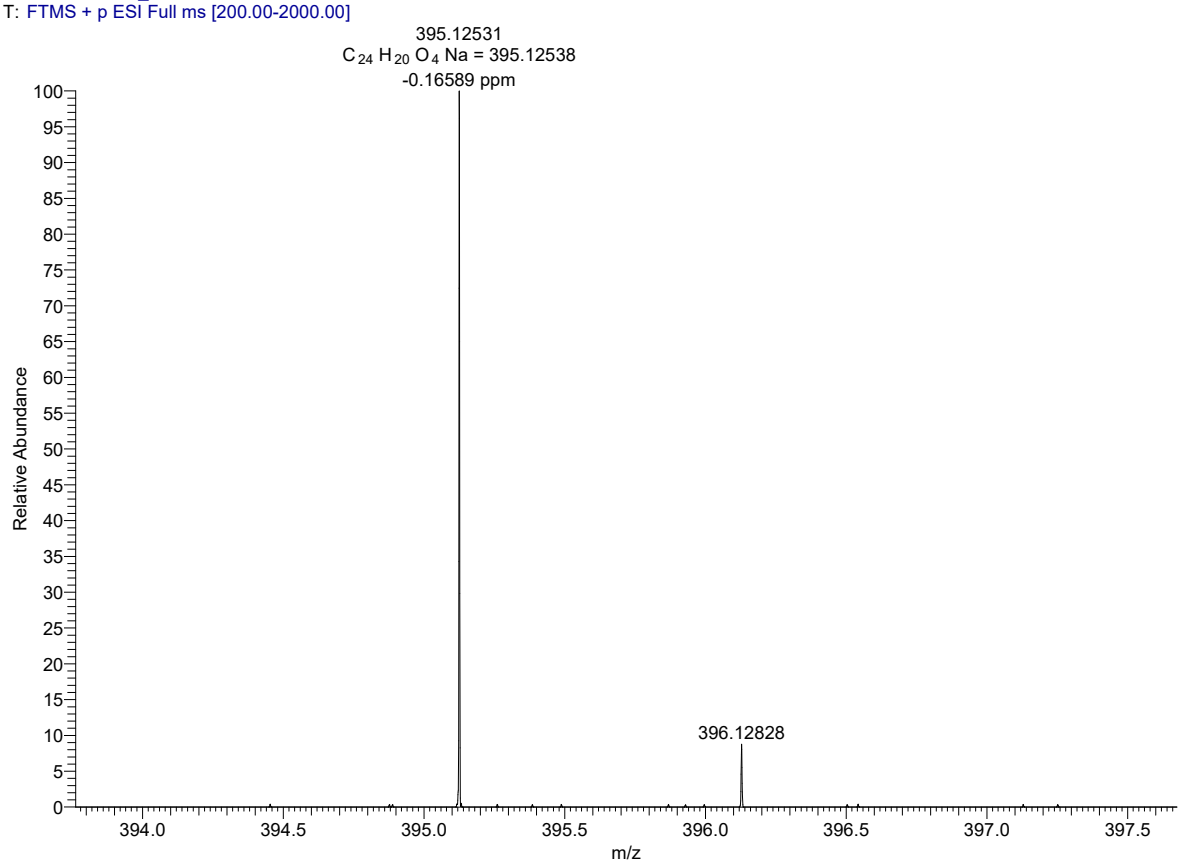
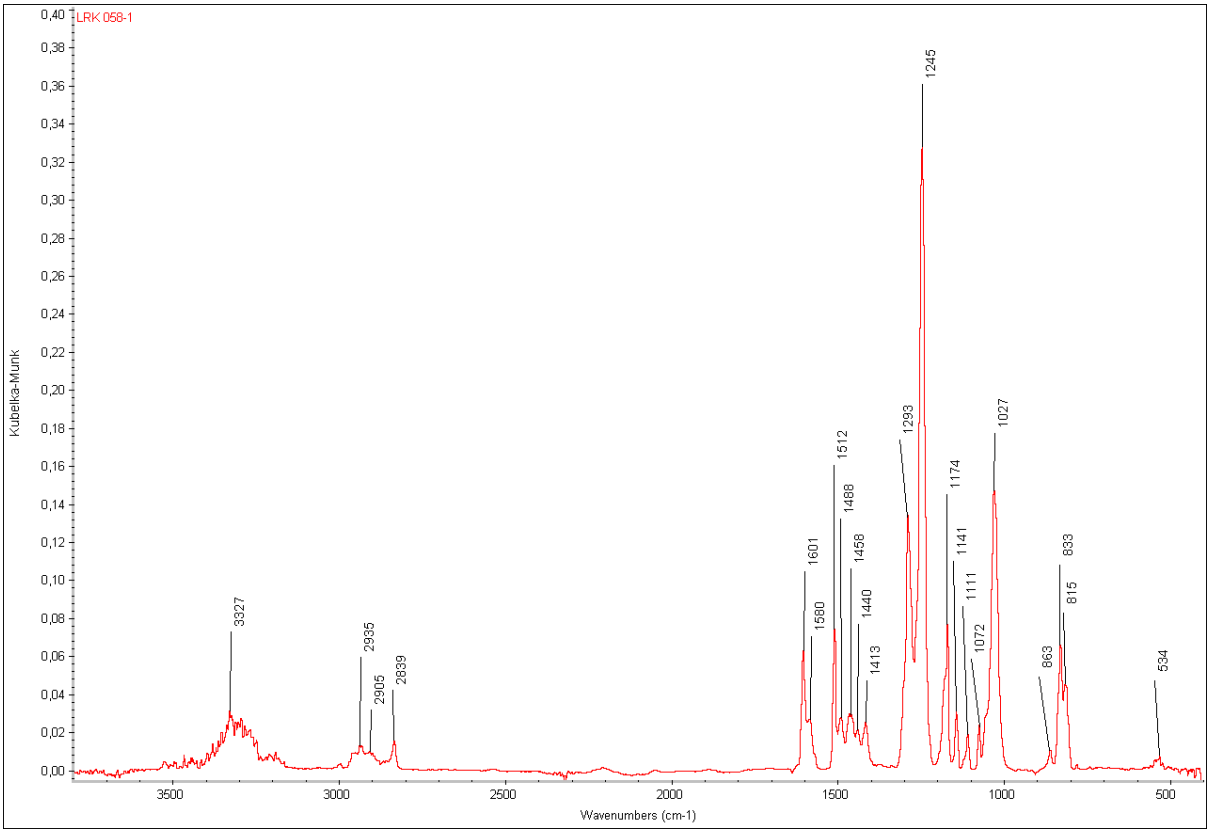
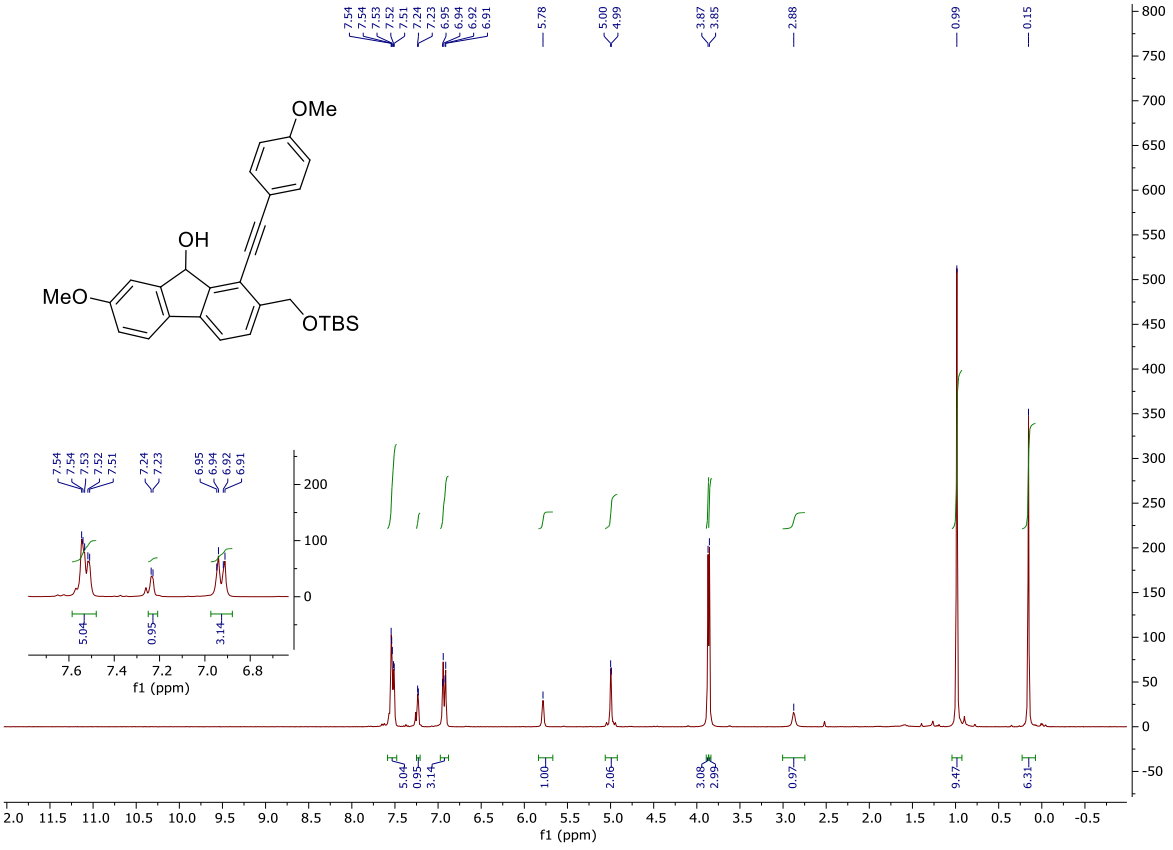
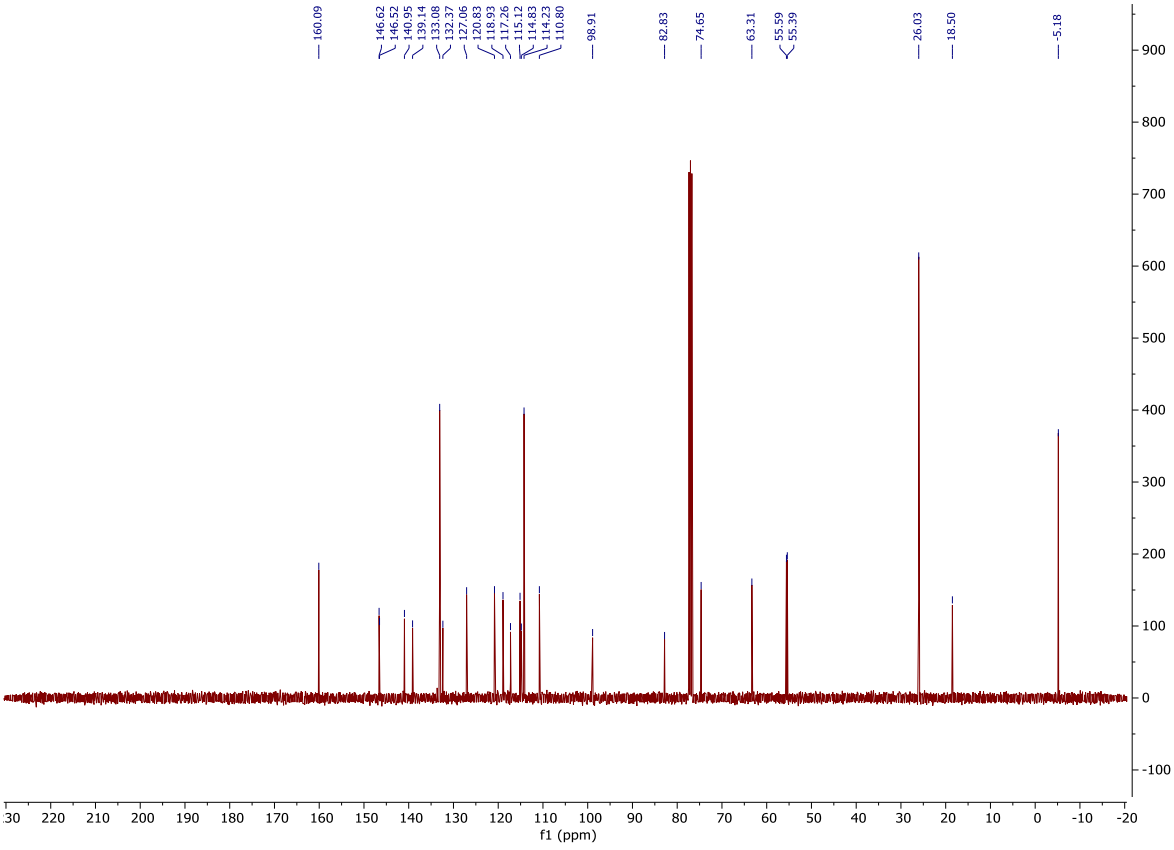


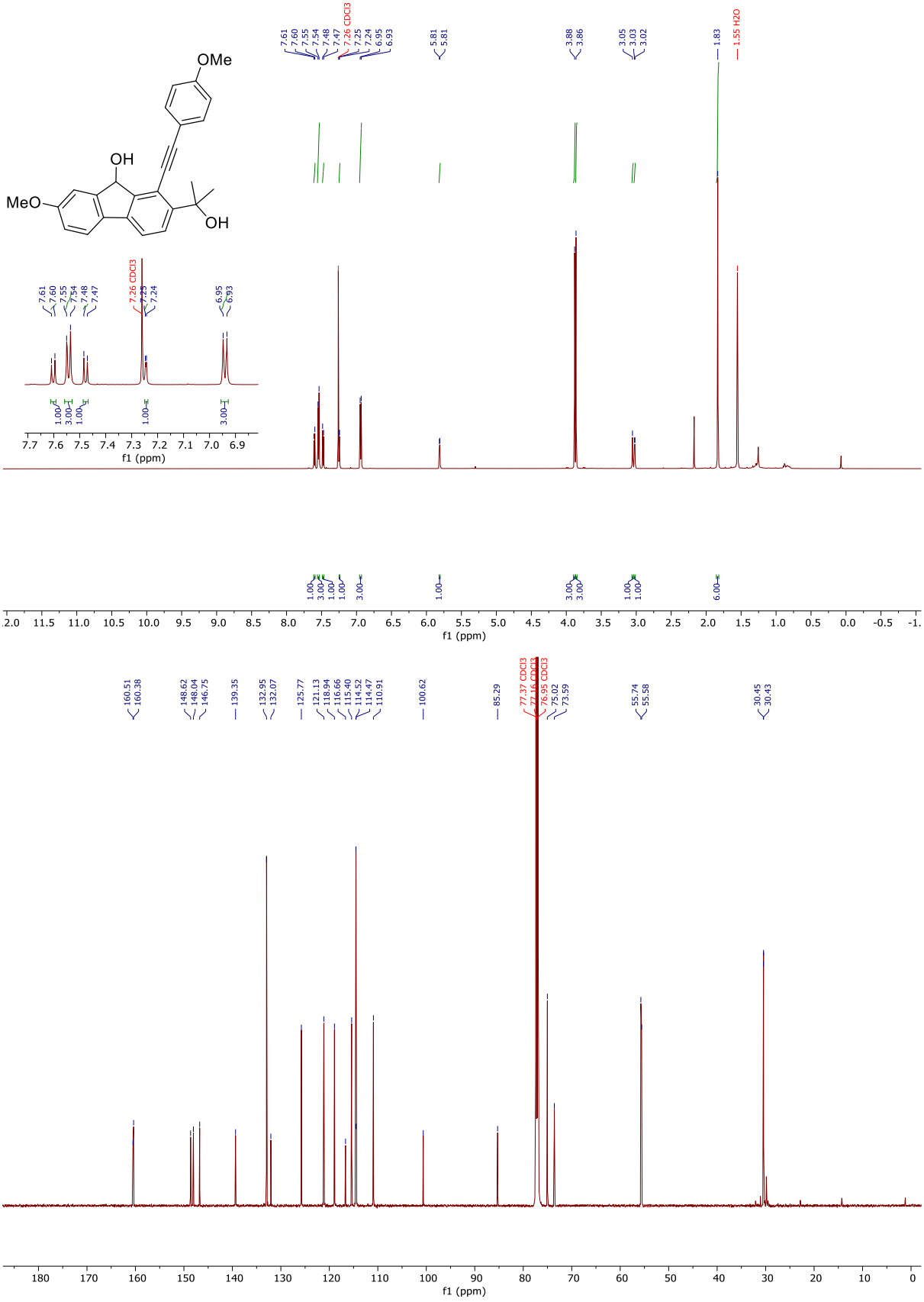


6.2. Spectral data of 89b



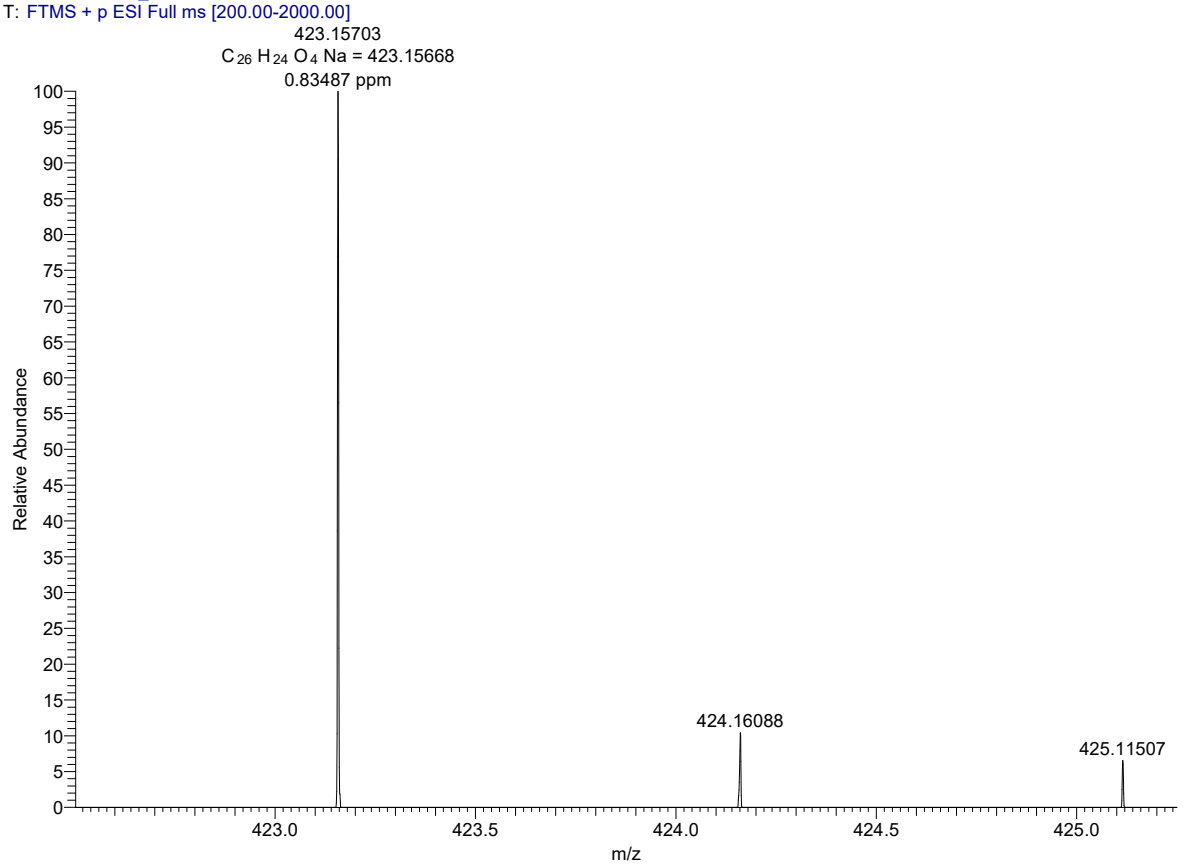


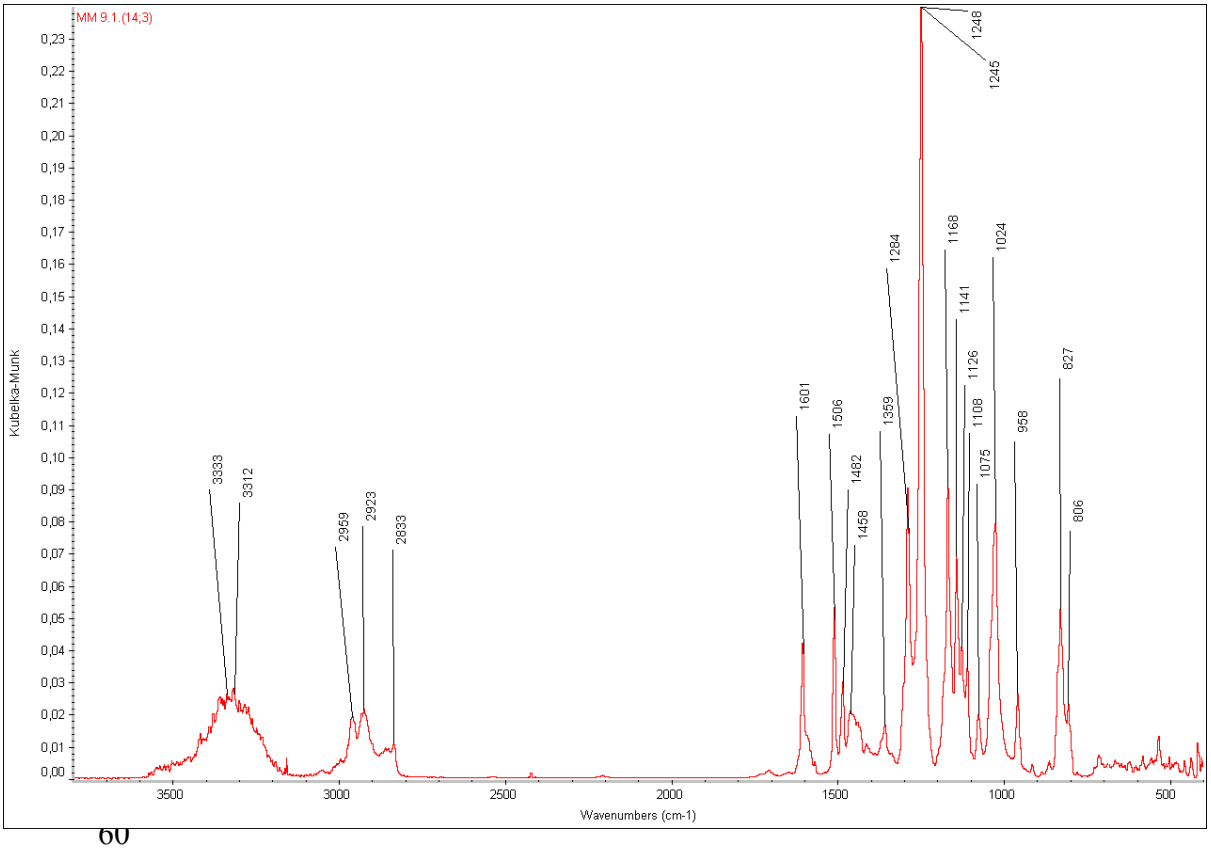
6.3. Spectral data of 89c: minor regioisomer



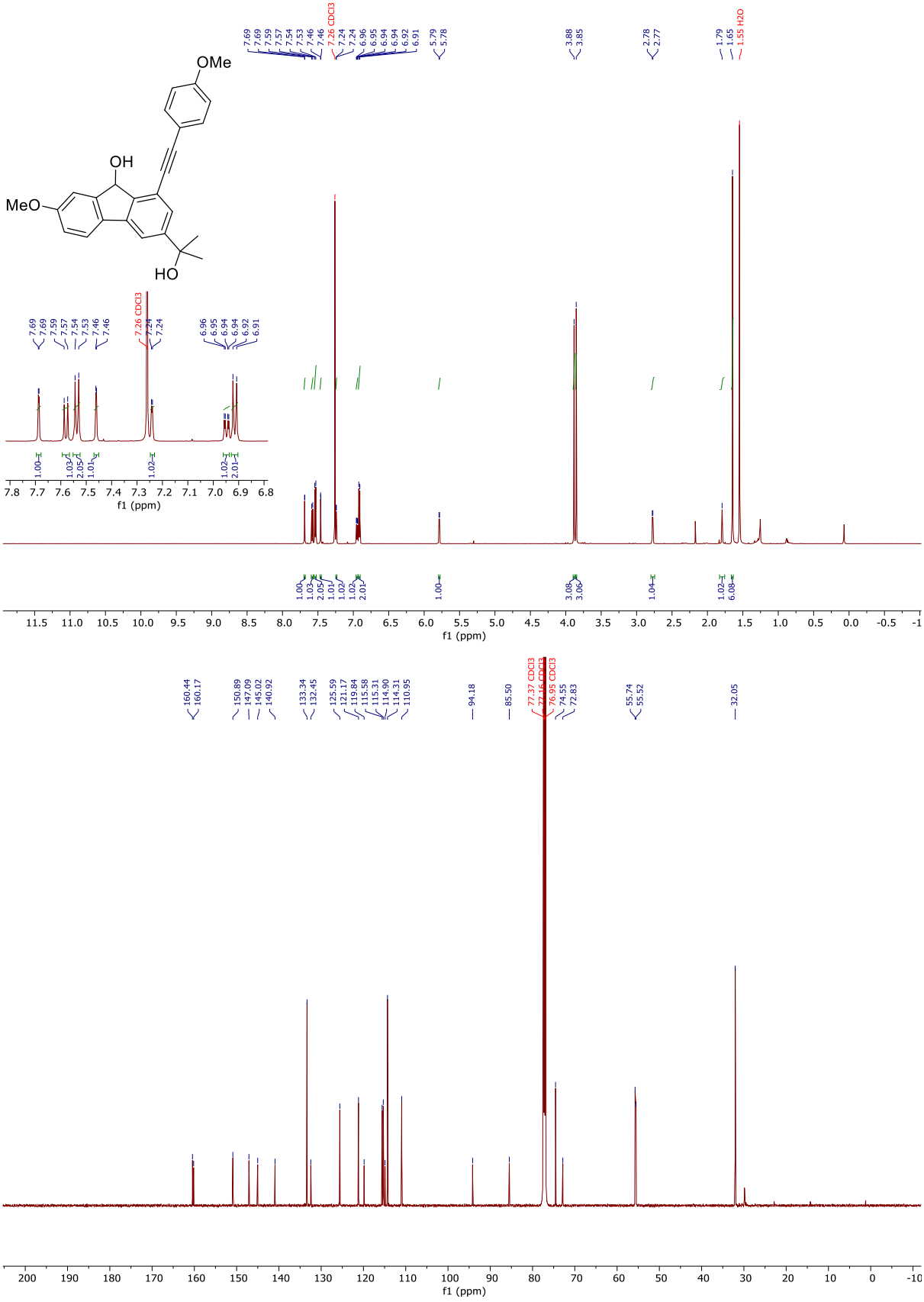
X:\SERVISHR\...\281119servisHR_21 11/28/19 14:27:29 MM9.1-1

281119servisHR_21 #61-62 RT: 1.62-1.64 AV: 2 NL: 2.31E5
T: FTMS + p ESI Full ms [200.00-2000.00]

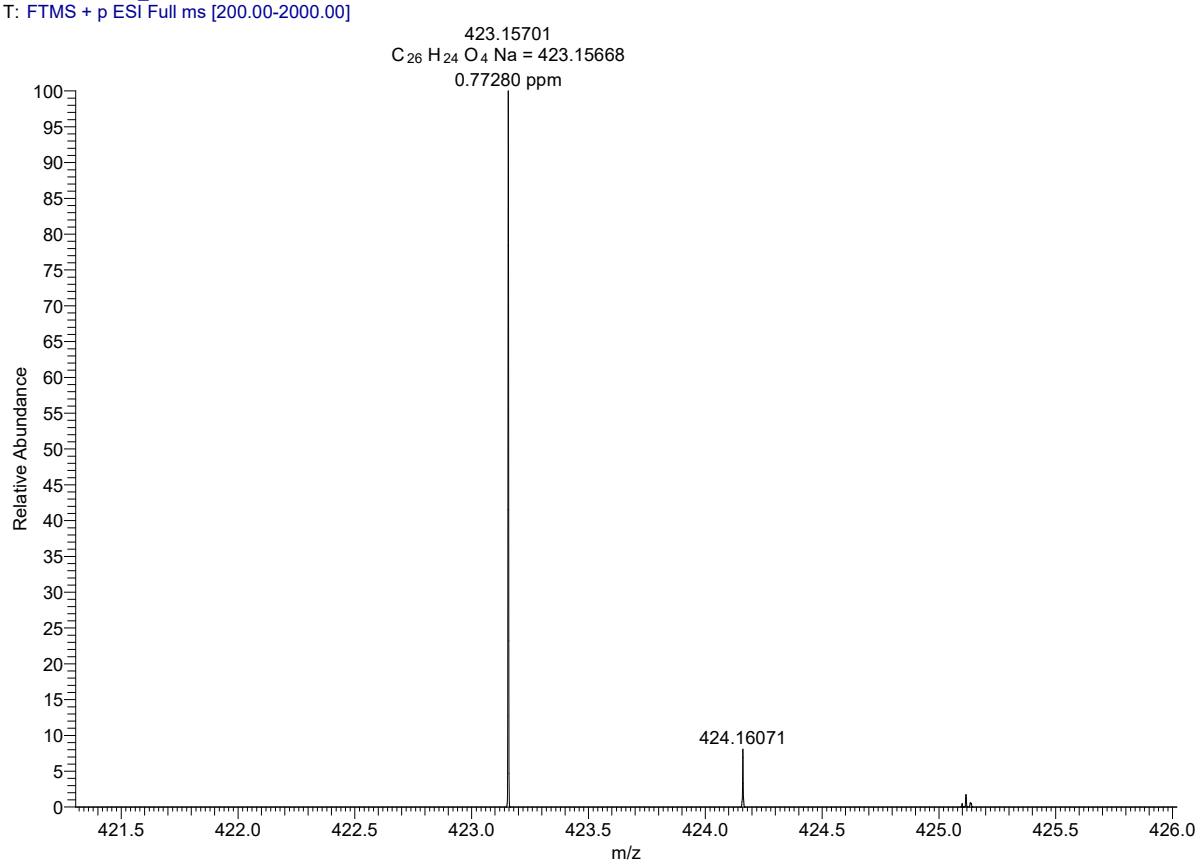


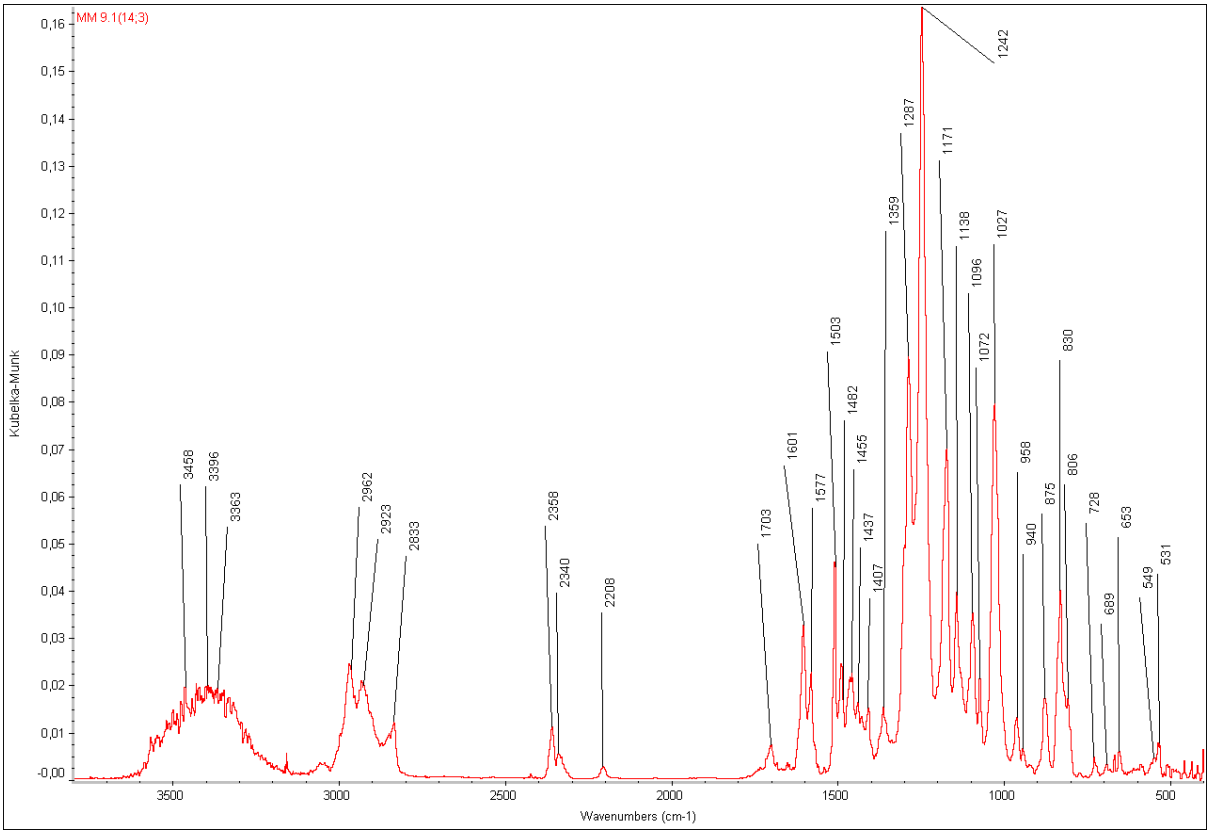


6.4. Spectral data of 89'c:major regioisomer

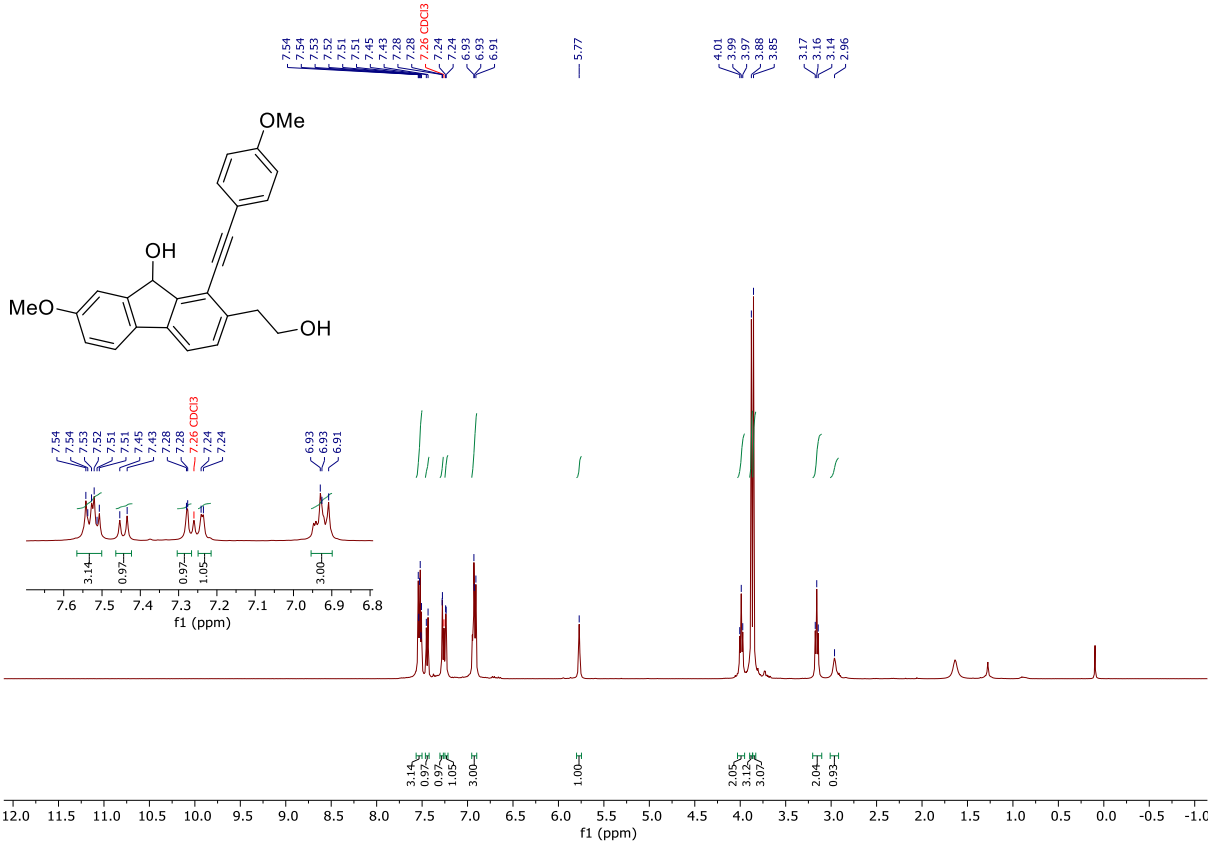


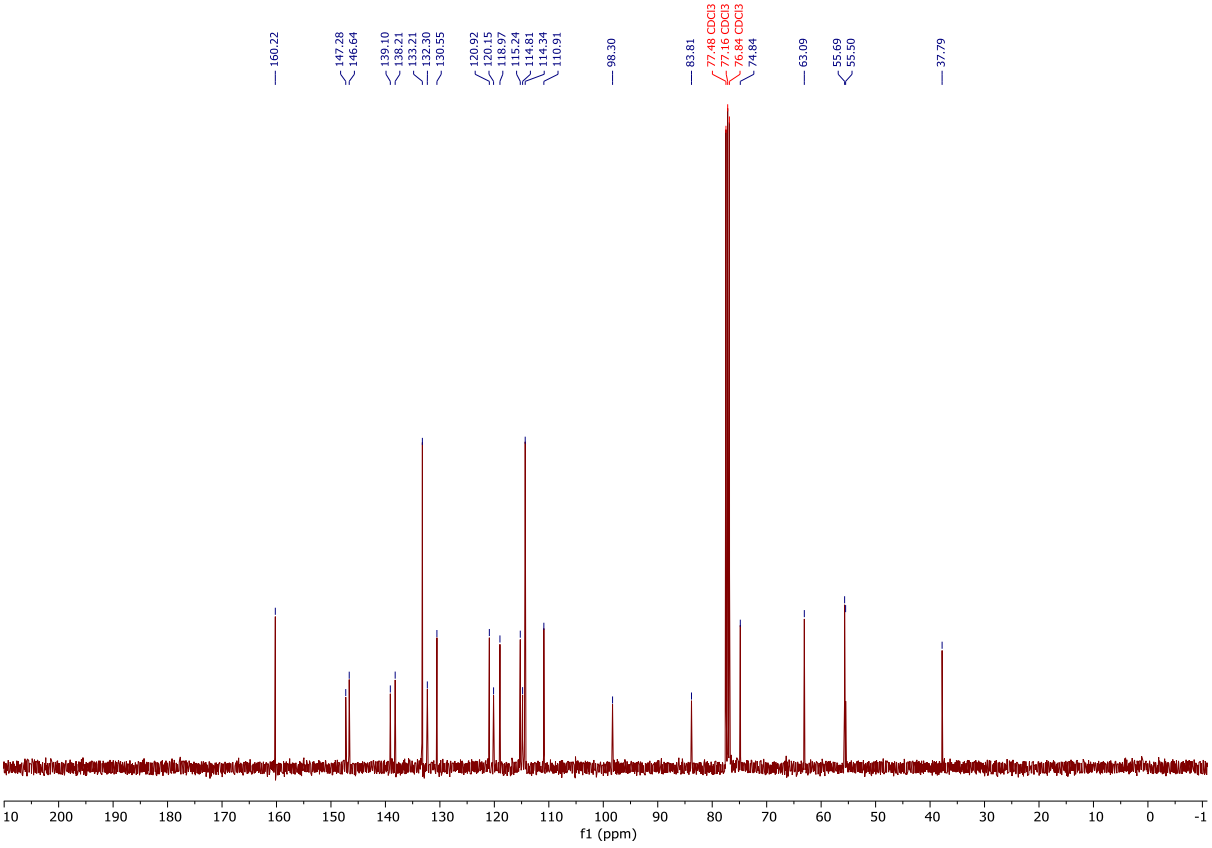
281119servisHR_22 #64-66 RT: 1.70-1.75 AV: 3 SB: 17 0.12-0.28 , 0.09-0.34 NL: 6.77E5
T: FTMS + p ESI Full ms [200.00-2000.00]





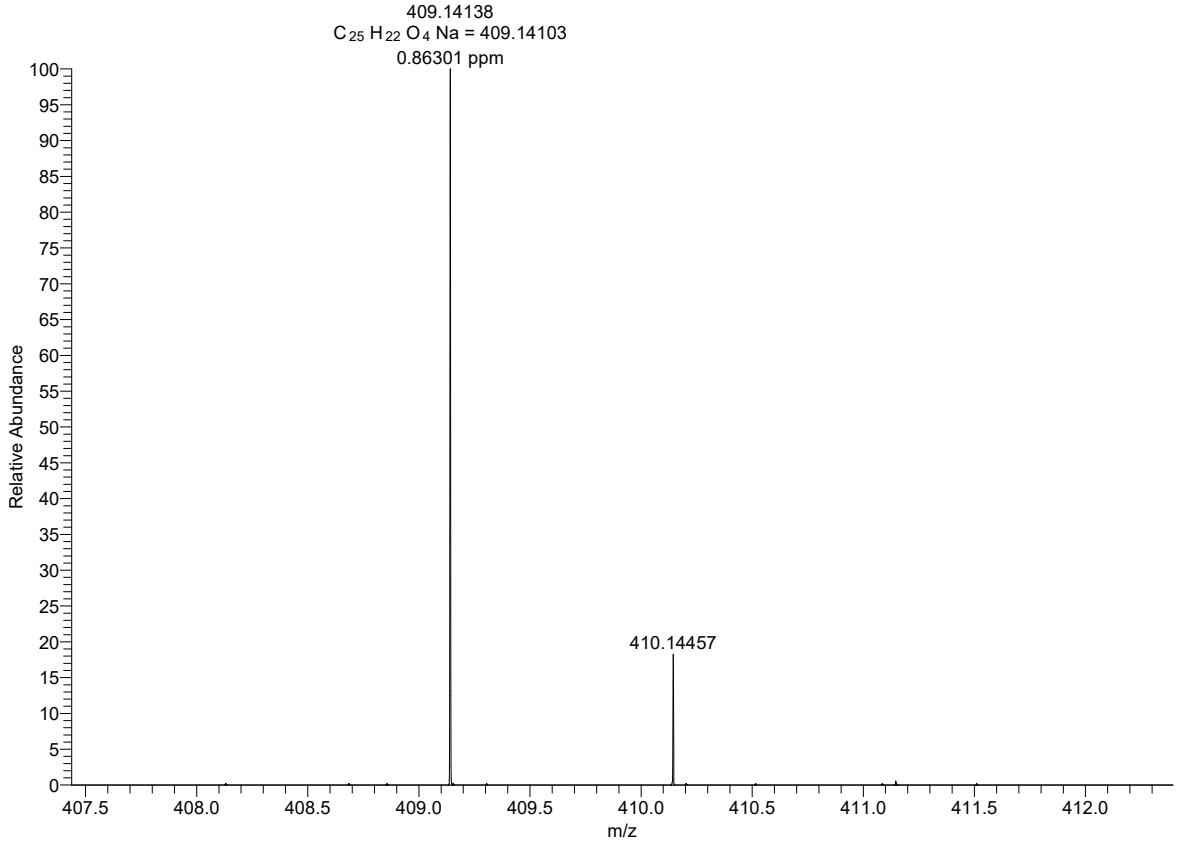
6.5. Spectral data of 89e

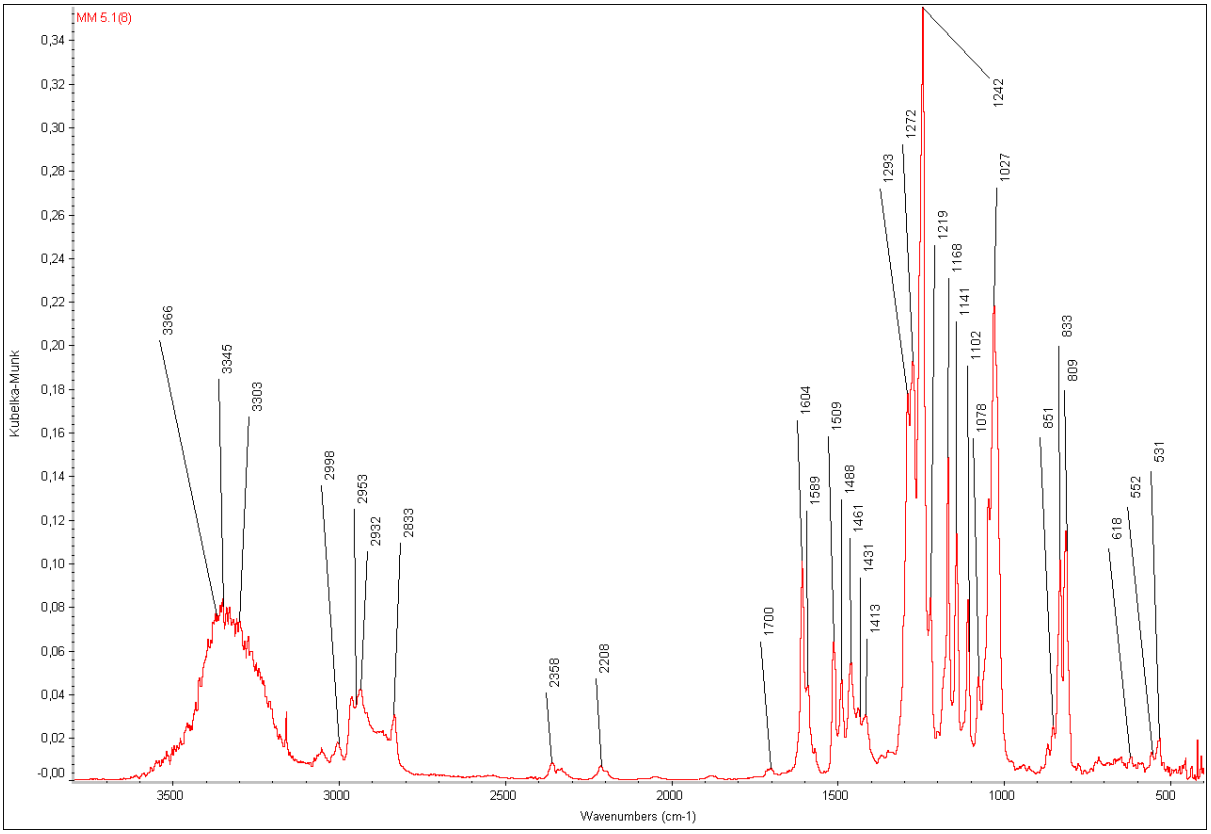




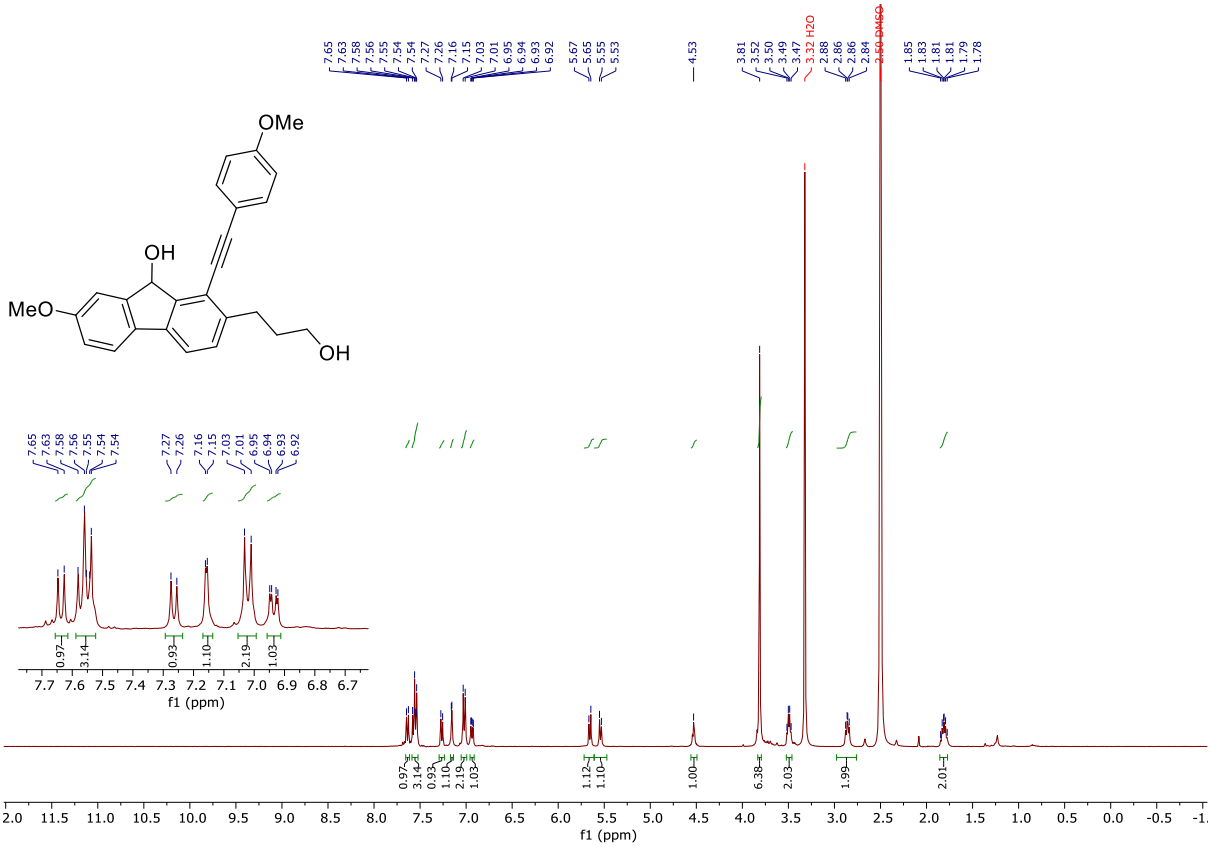
X:\SERVISHR\...\281119servisHR_18 11/28/19 14:15:13 MM5.1(18)

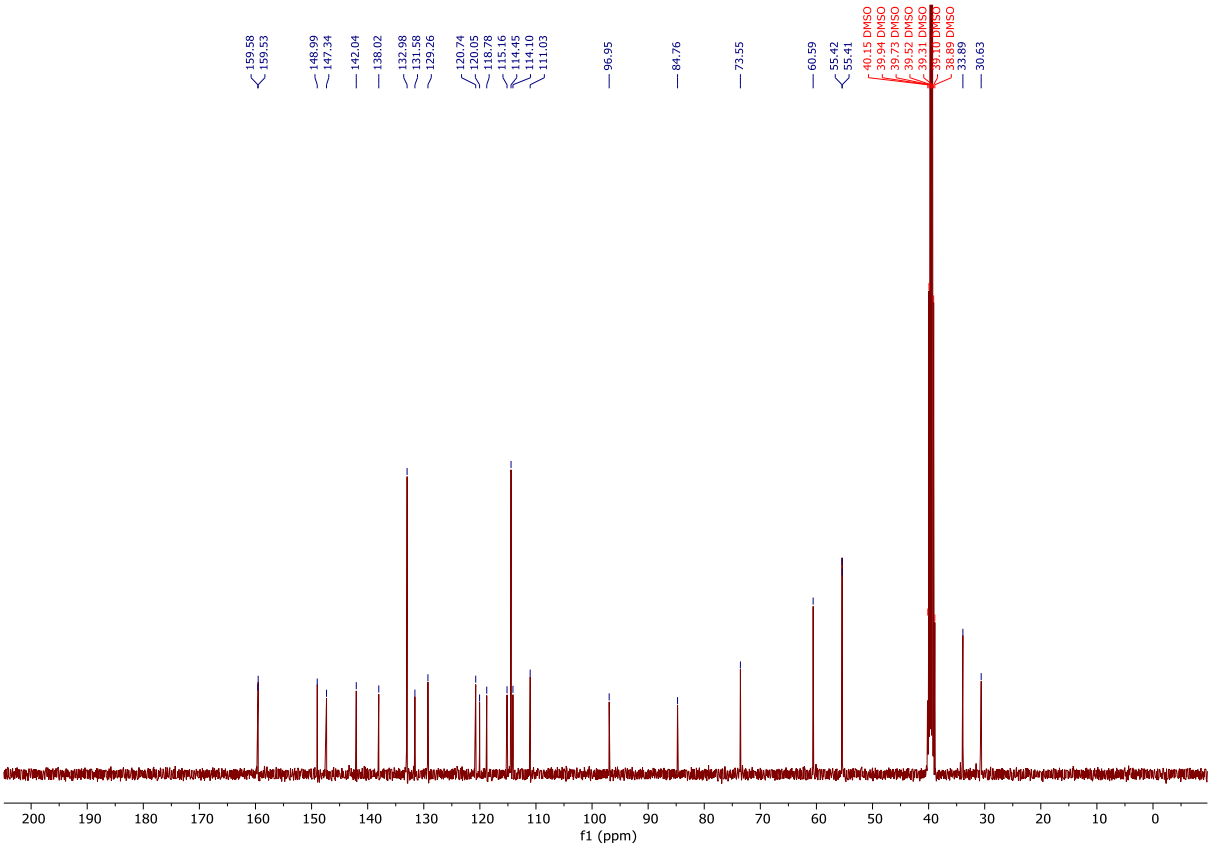
281119servisHR_18 #71-72 RT: 1.89-1.91 AV: 2 NL: 2.46E6
T: FTMS + p ESI Full ms [200.00-2000.00]



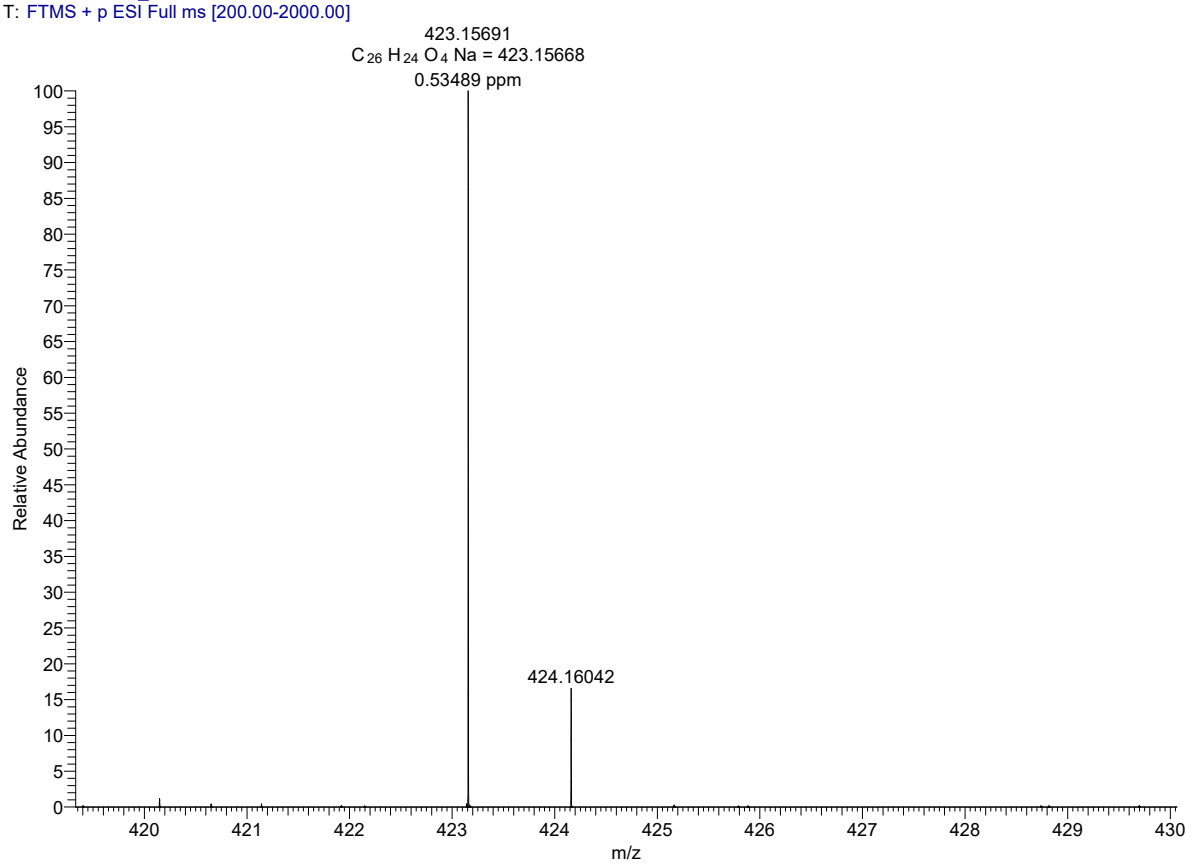


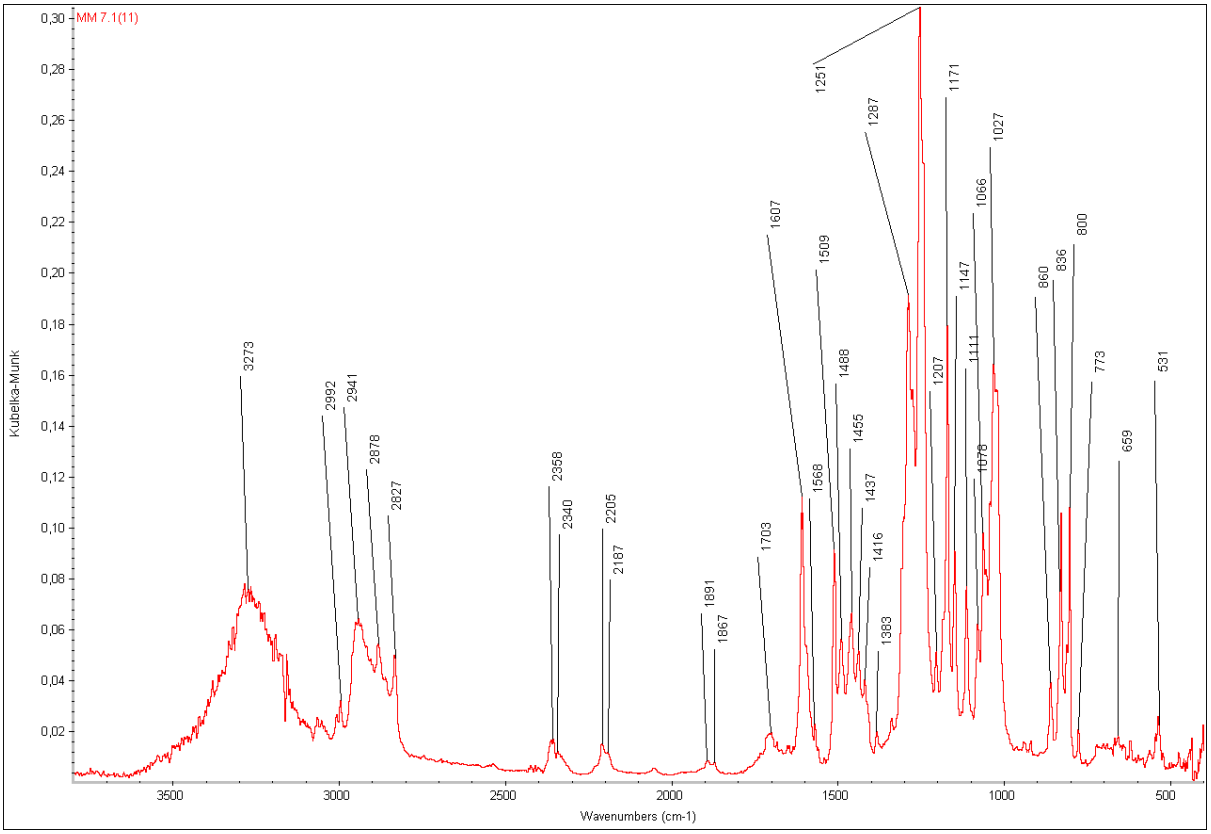
6.6. Spectral data of 89f



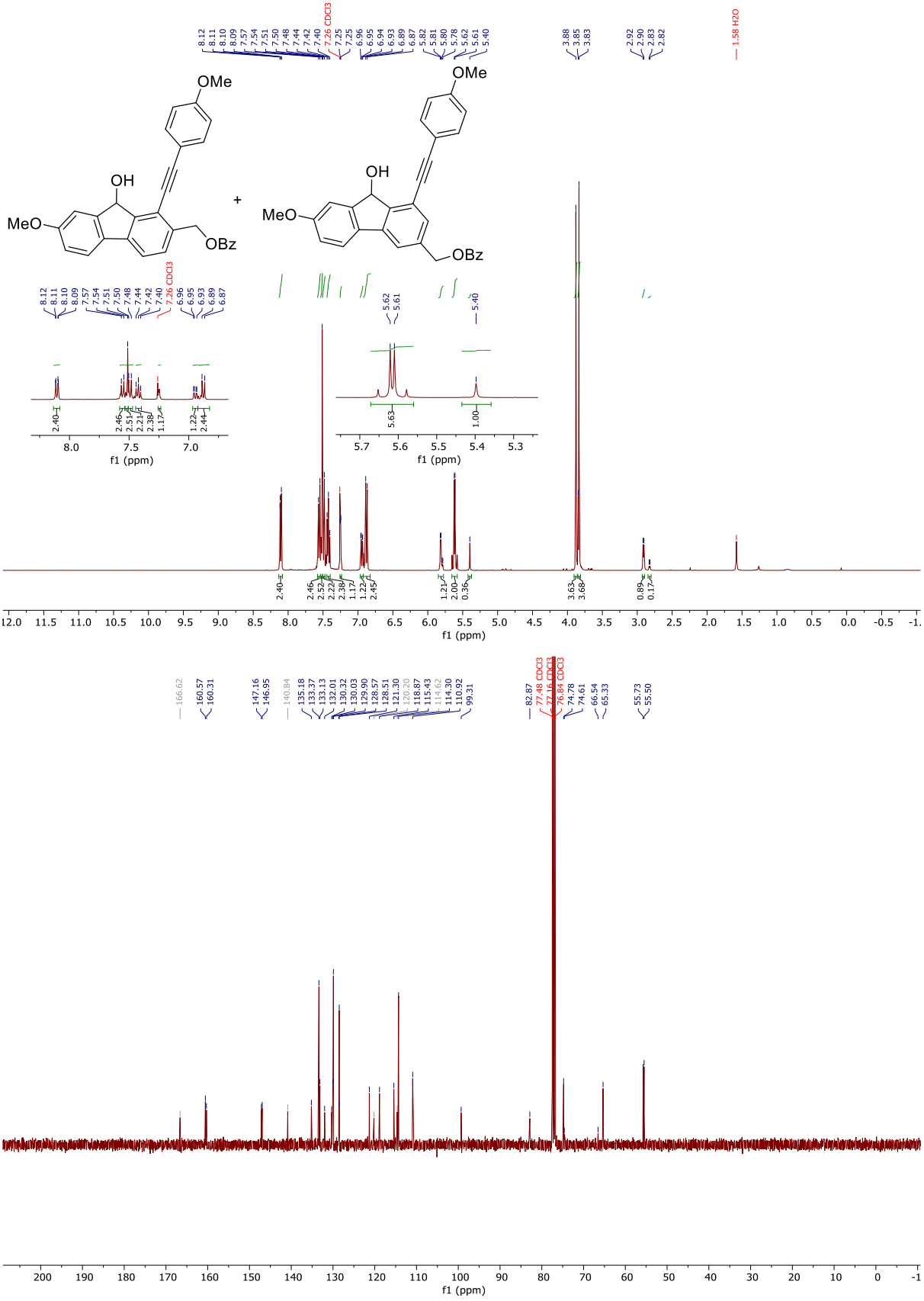


281119servisHR_19 #75-77 RT: 2.00-2.05 AV: 3 NL: 2.13E6
T: FTMS + p ESI Full ms [200.00-2000.00]



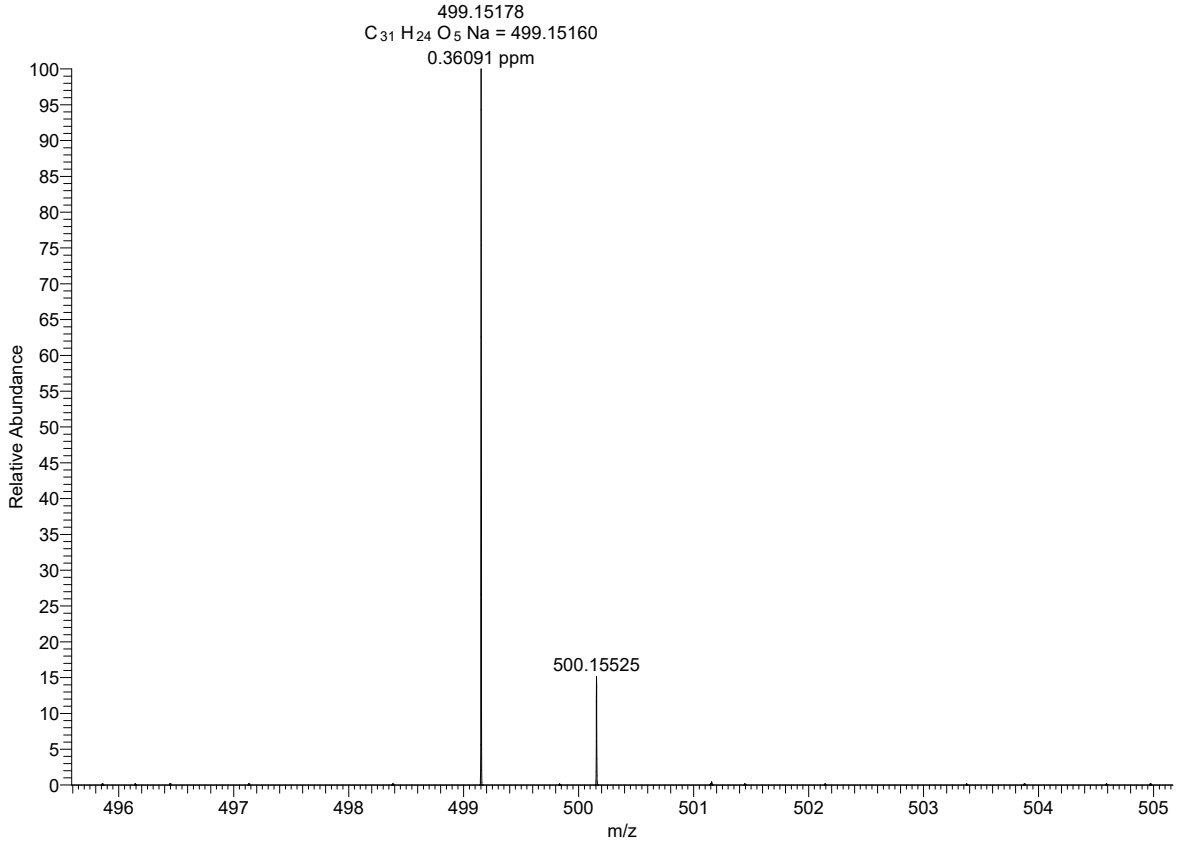


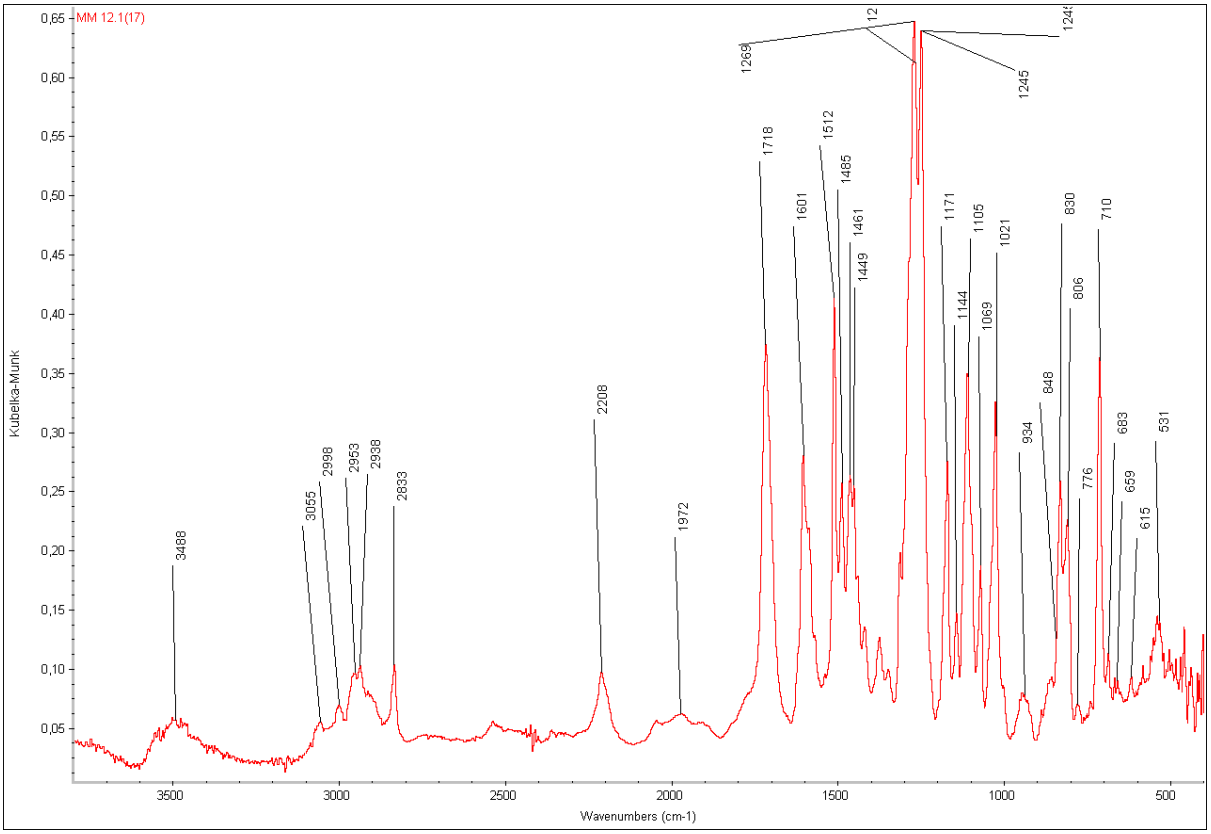
6.7. Spectral data of 89h



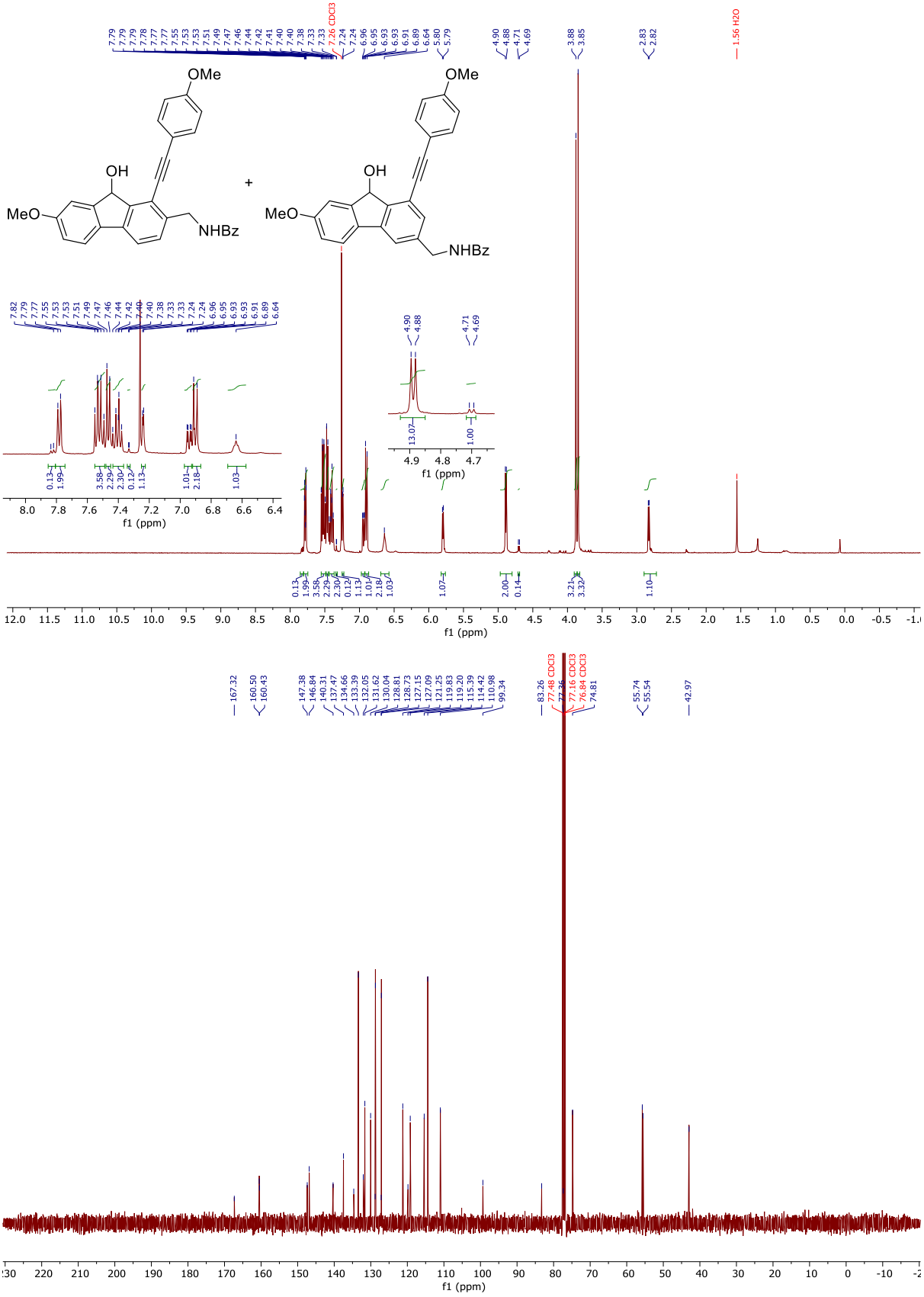
X:\SERVISHR\...\281119servisHR_20 11/28/19 14:23:25 MM12.1(17)

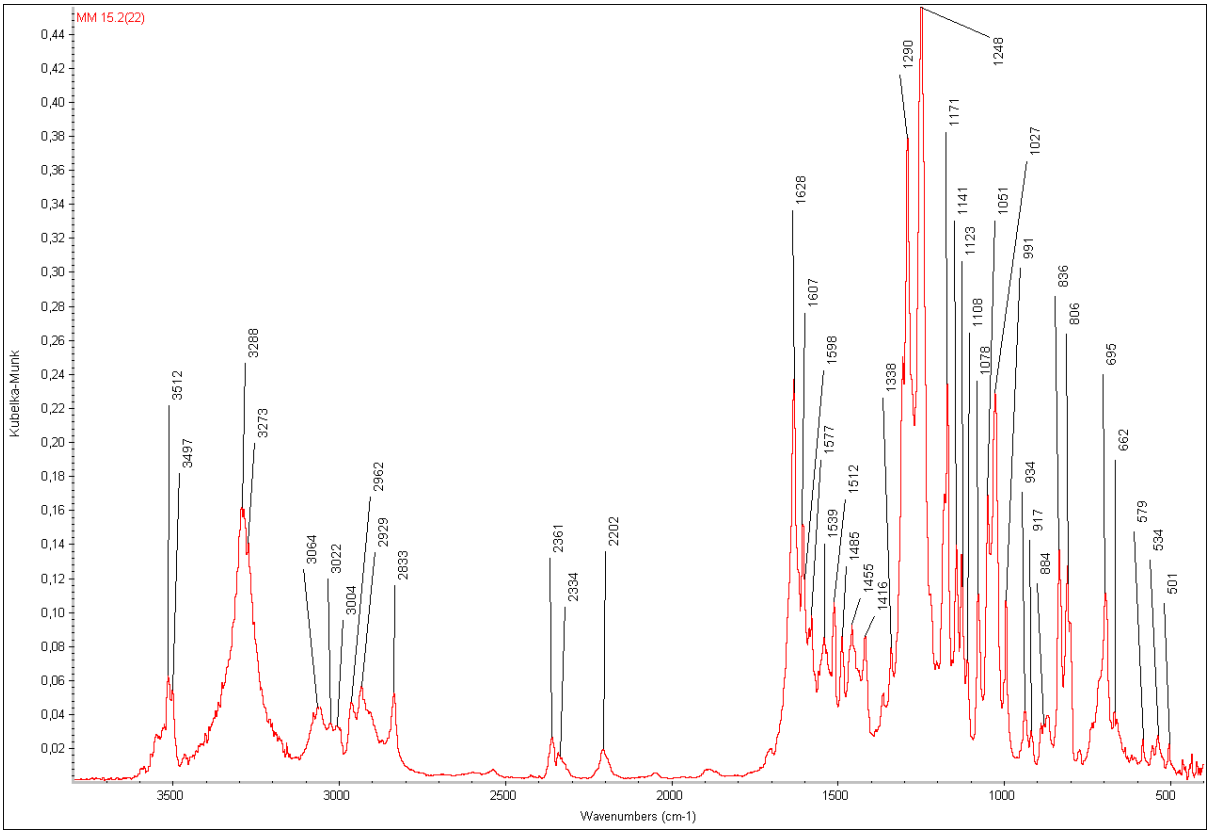
281119servisHR_20 #102-106 RT: 2.73-2.84 AV: 5 NL: 1.08E6
T: FTMS + p ESI Full ms [200.00-2000.00]



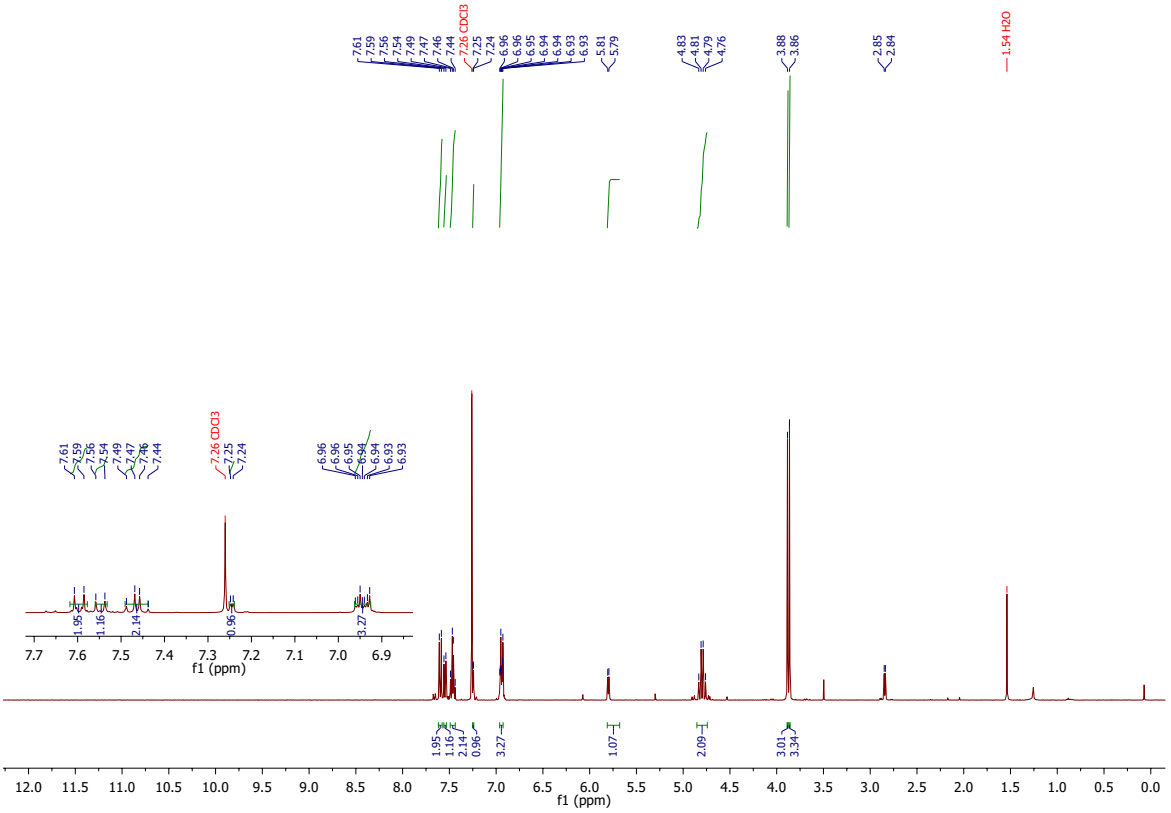


6.8. Spectral data of 89j

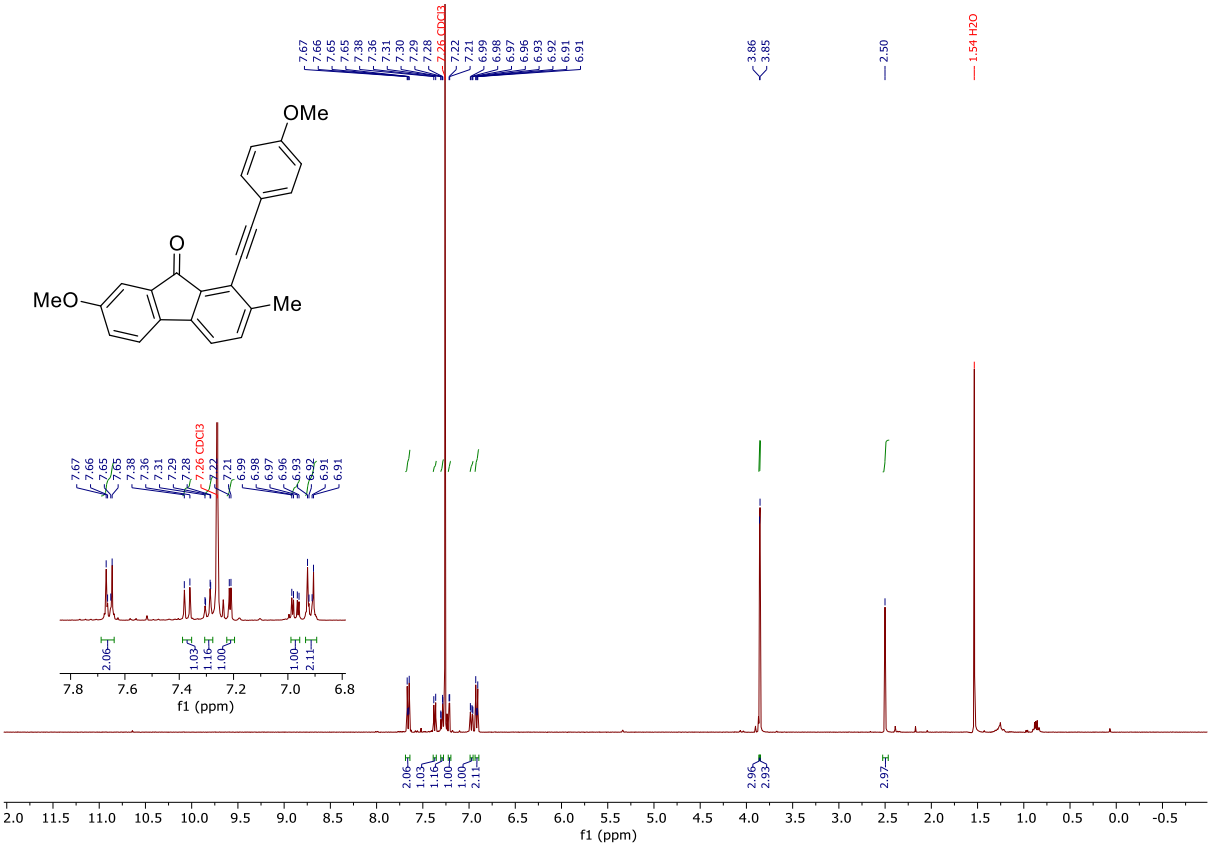


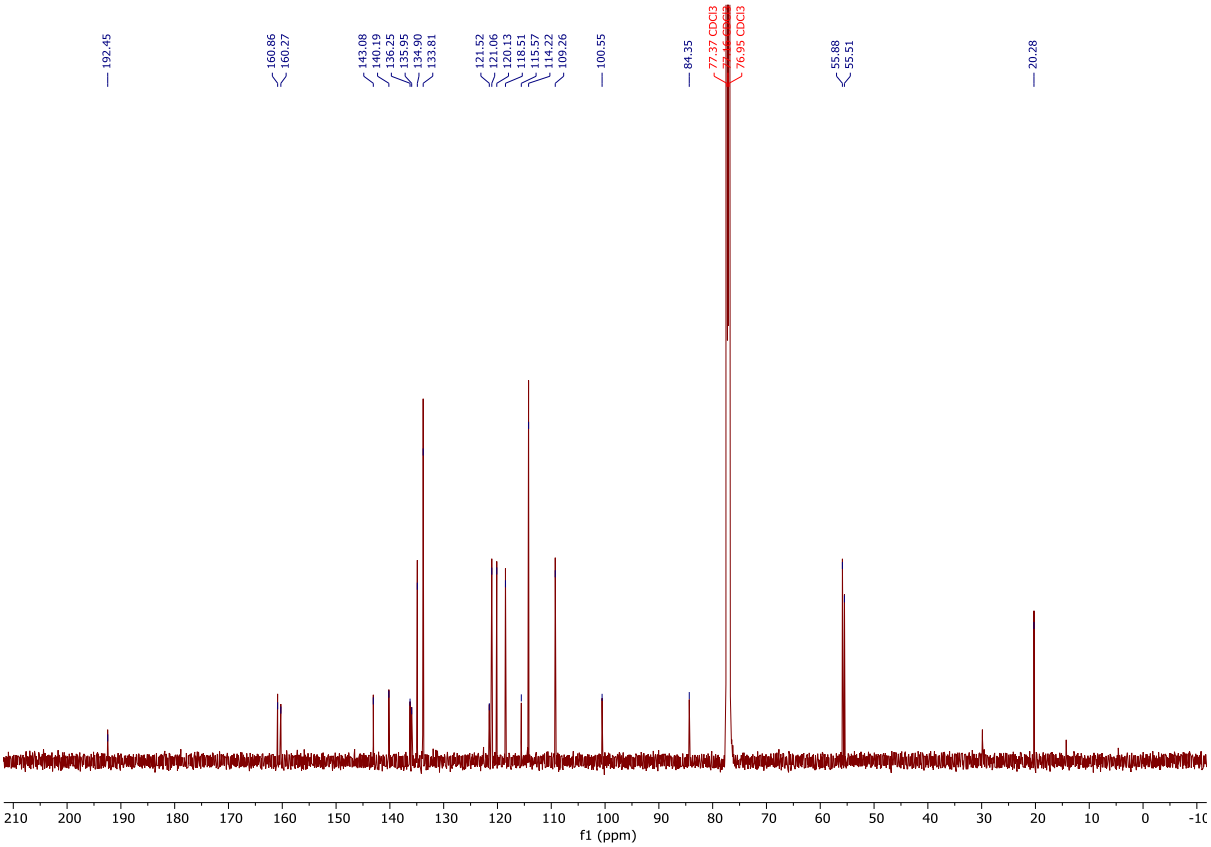

MM 15.2(22)
Kubelka-Munk
Wavenumbers (cm-1)
3512
3497
3288
3273
3064
3022
3004
2962
2929
2833
2361
2334
2202
1628
1607
1598
1577
1539
1512
1485
1455
1416
1338
1290
1248
1171
1141
1123
1108
1078
1051
1027
991
934
917
884
836
806
695
662
579
534
501

6.9. Spectral data of 92

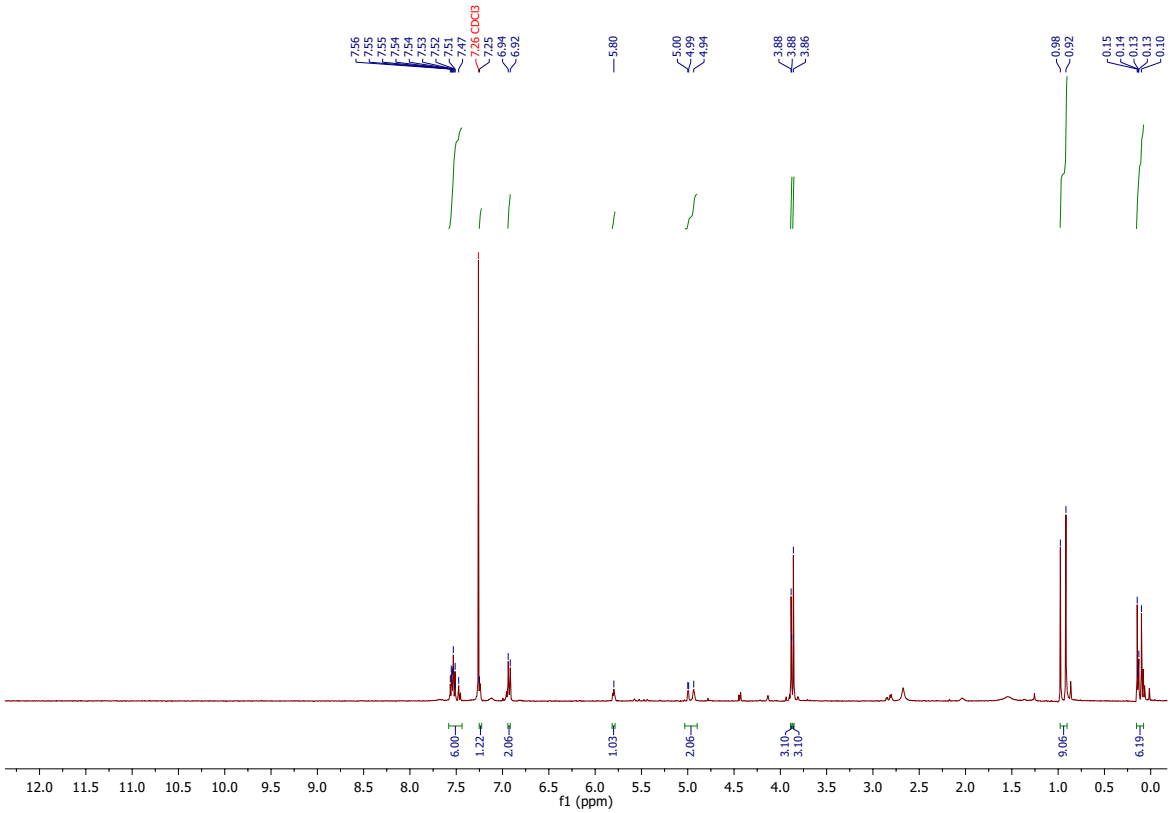


6.10. Spectral data of 90

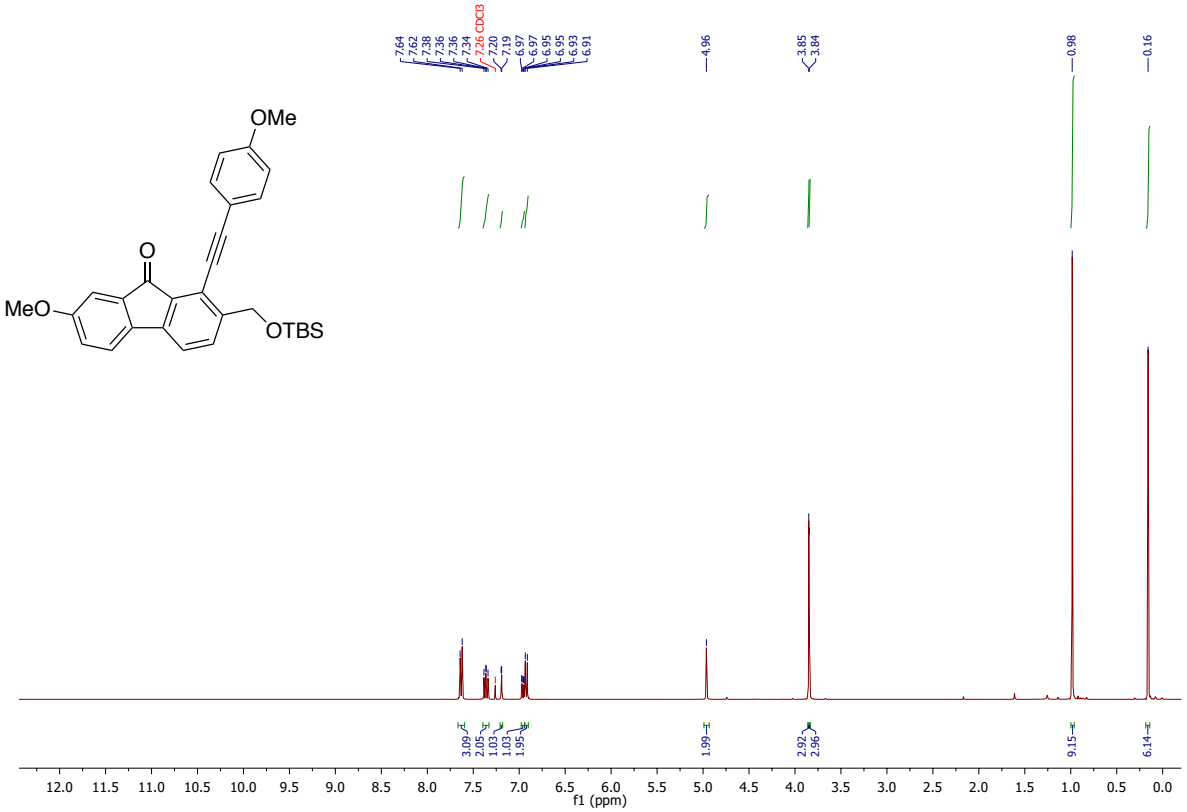


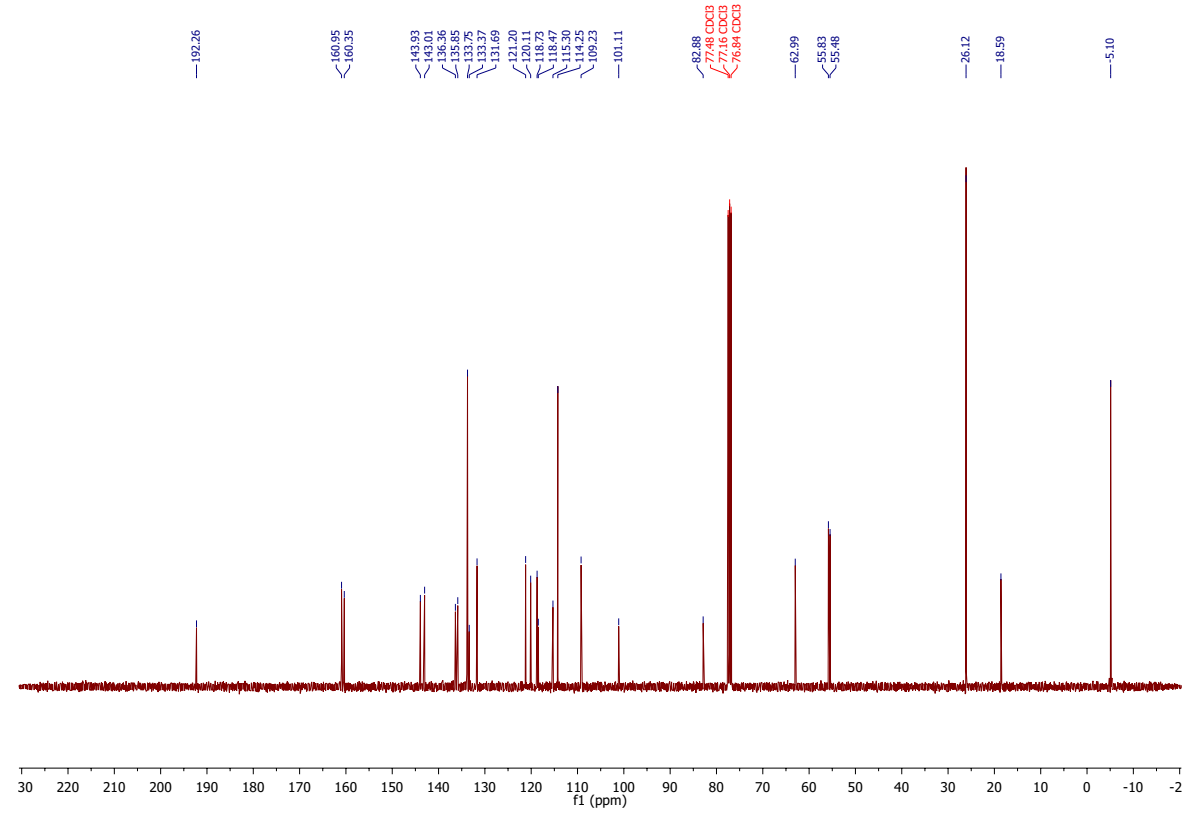


6.11. Spectral data of 89b – TBSOTf aproach



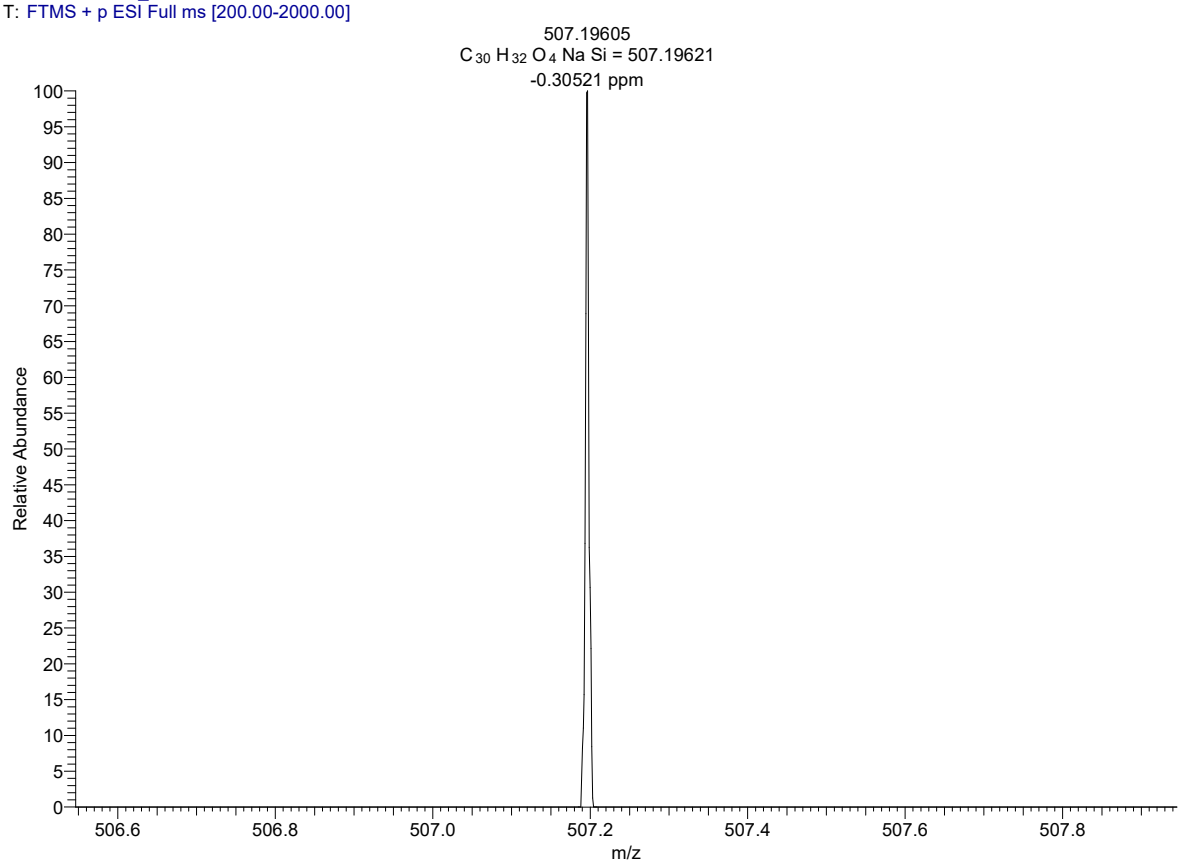
6.12. Spectral data of 94



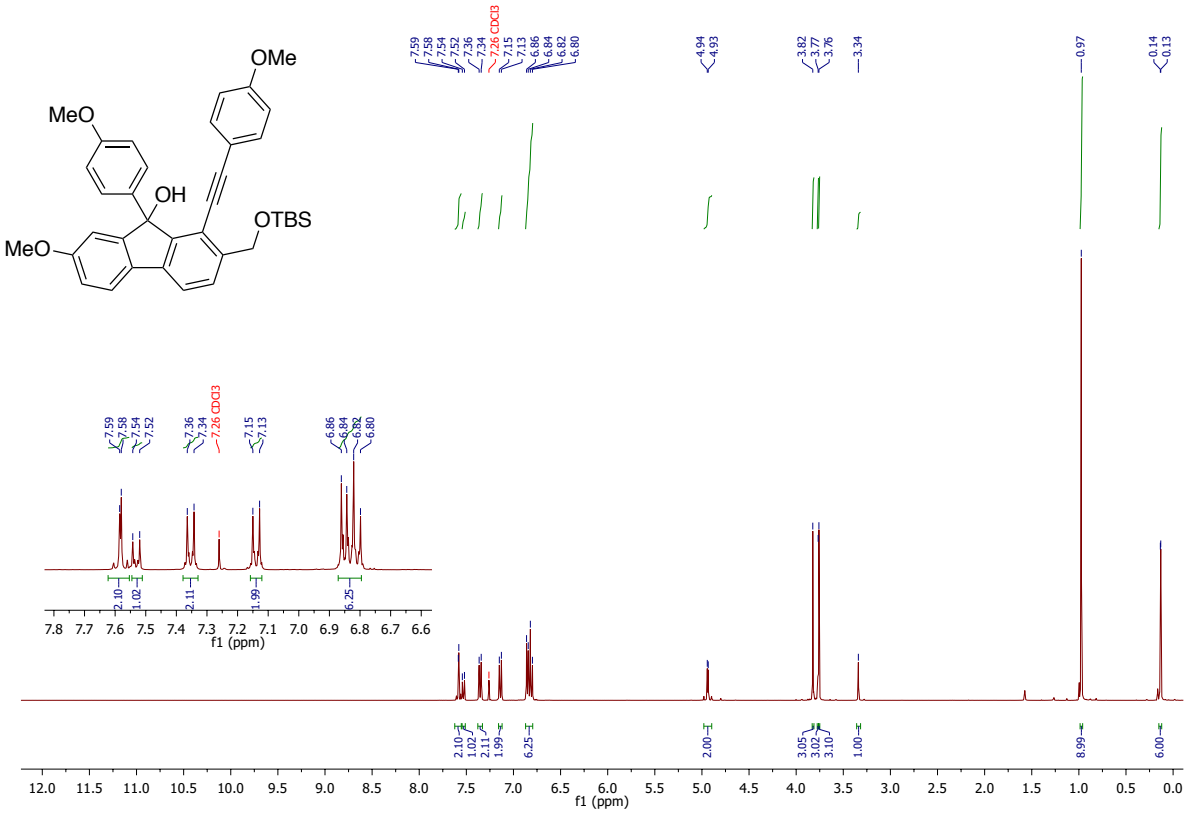


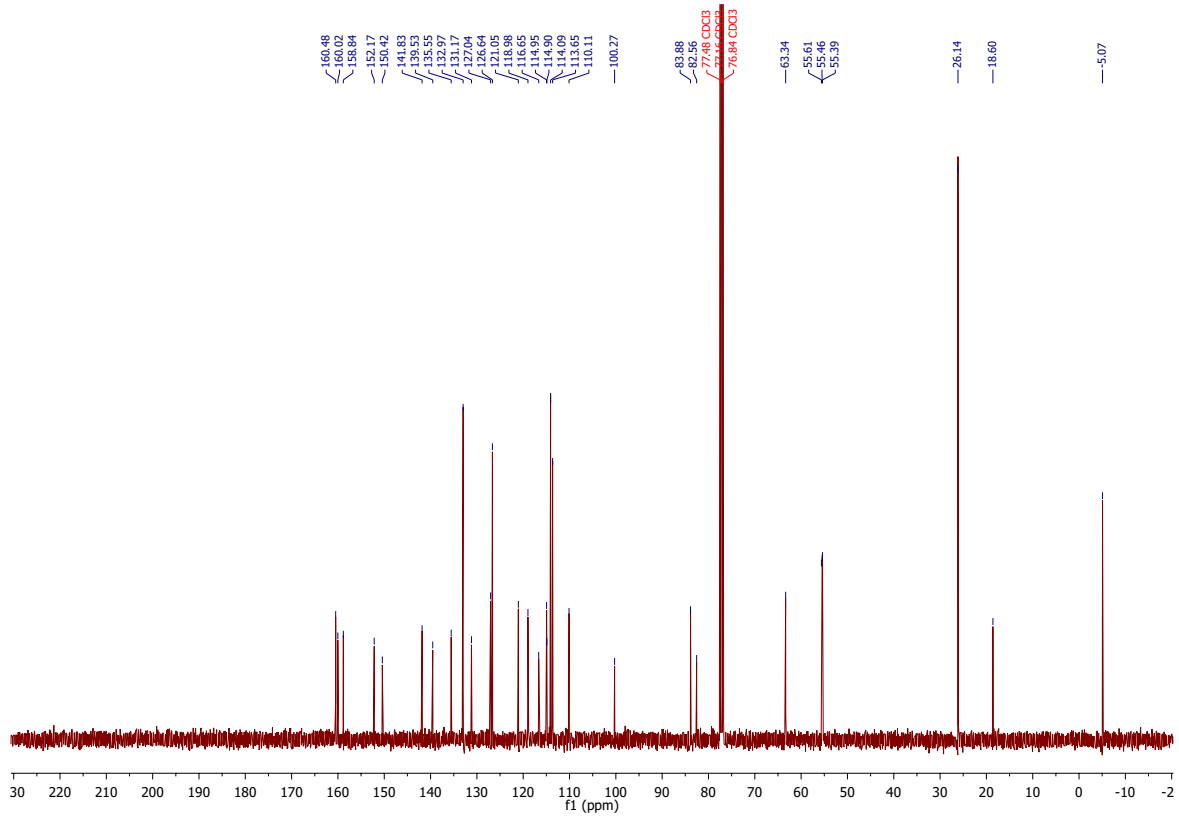
X:\SERVISHR\...\180719servisHR_14 07/18/19 16:01:50 LRK049

180719servisHR_14 #77-79 RT: 2.05-2.10 AV: 3 SB: 18 0.04-0.31 , 0.09-0.25 NL: 3.10E4
T: FTMS + p ESI Full ms [200.00-2000.00]

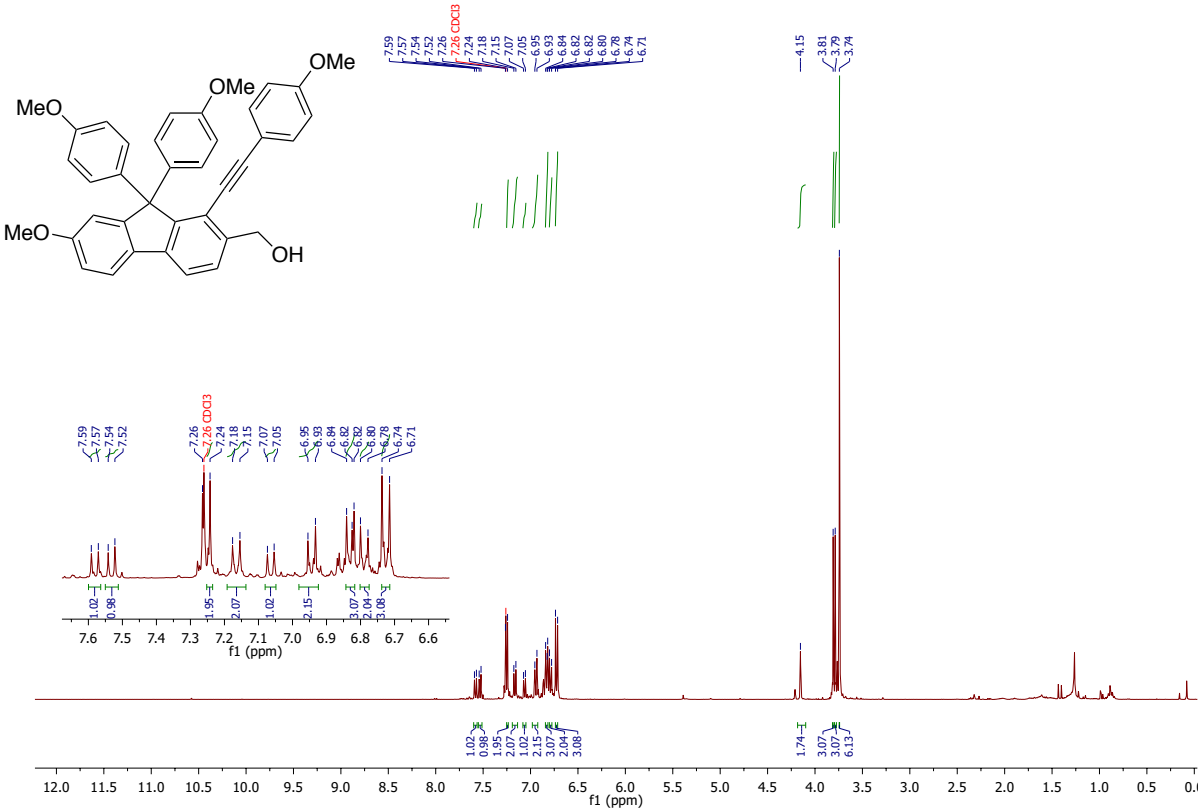


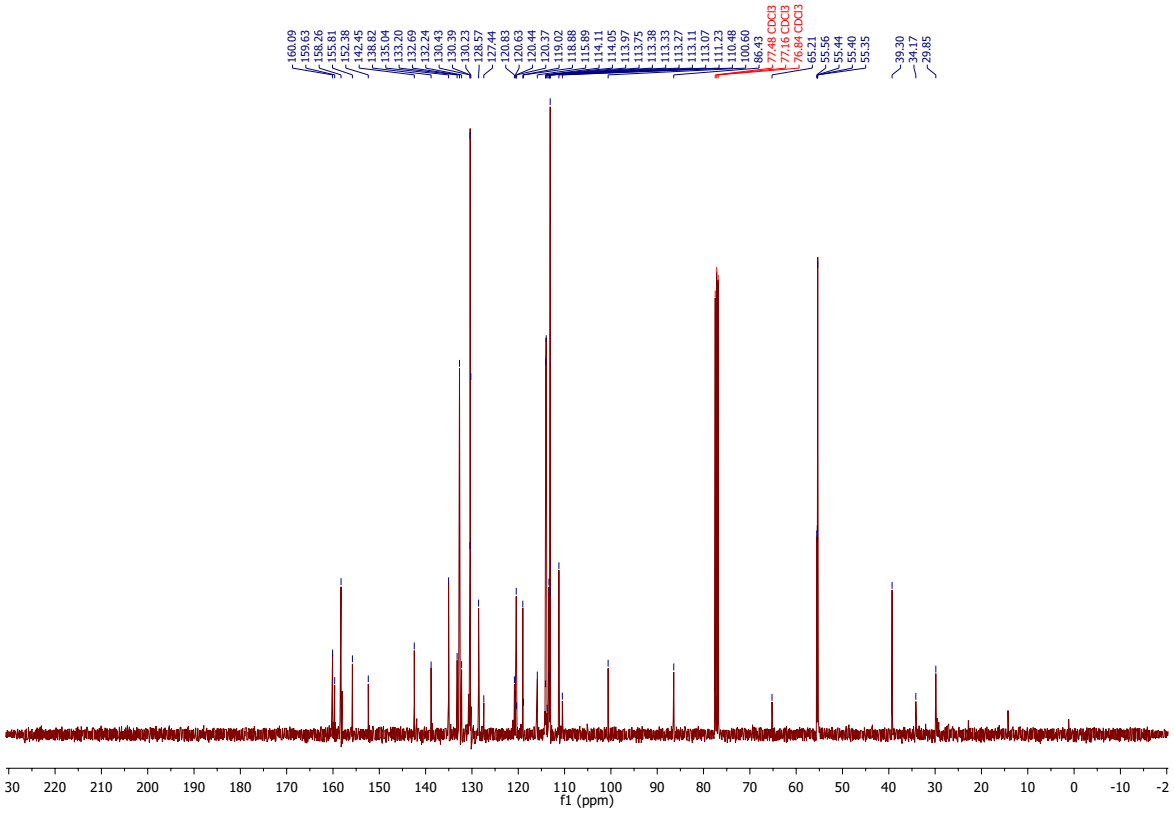
6.13. Spectral data of 95



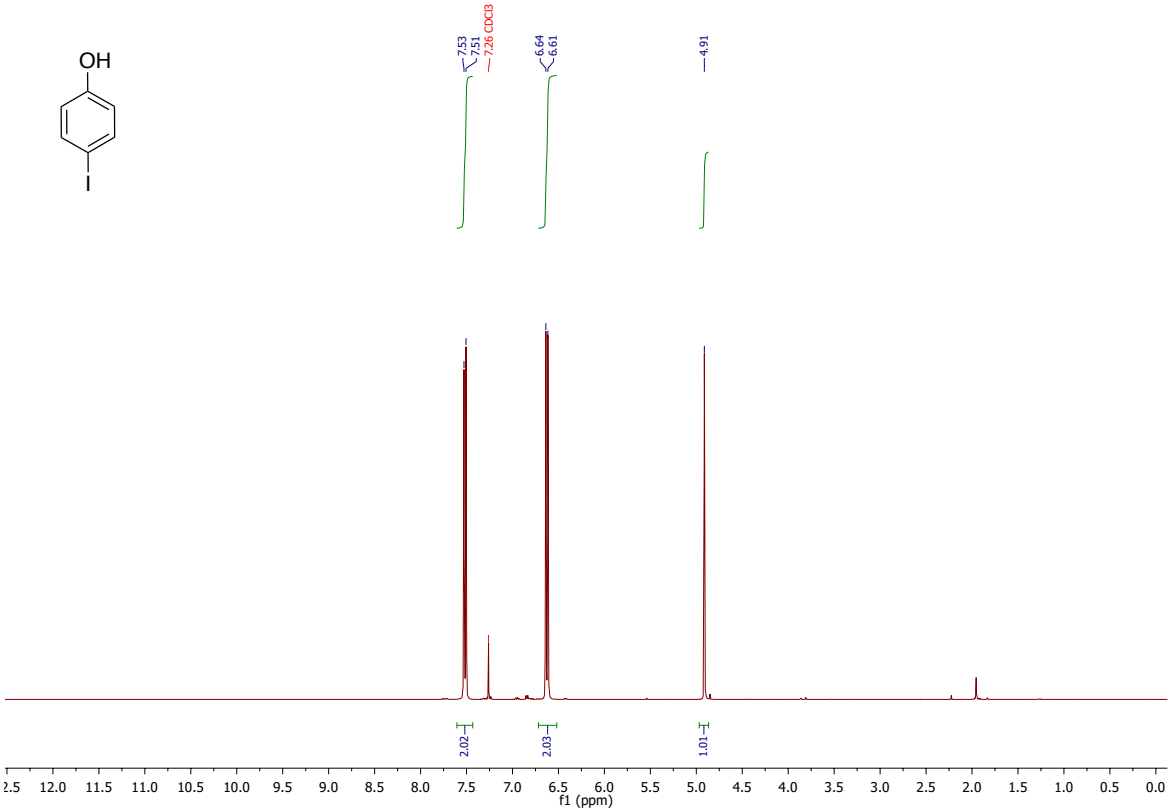


6.14. Spectral data of 96

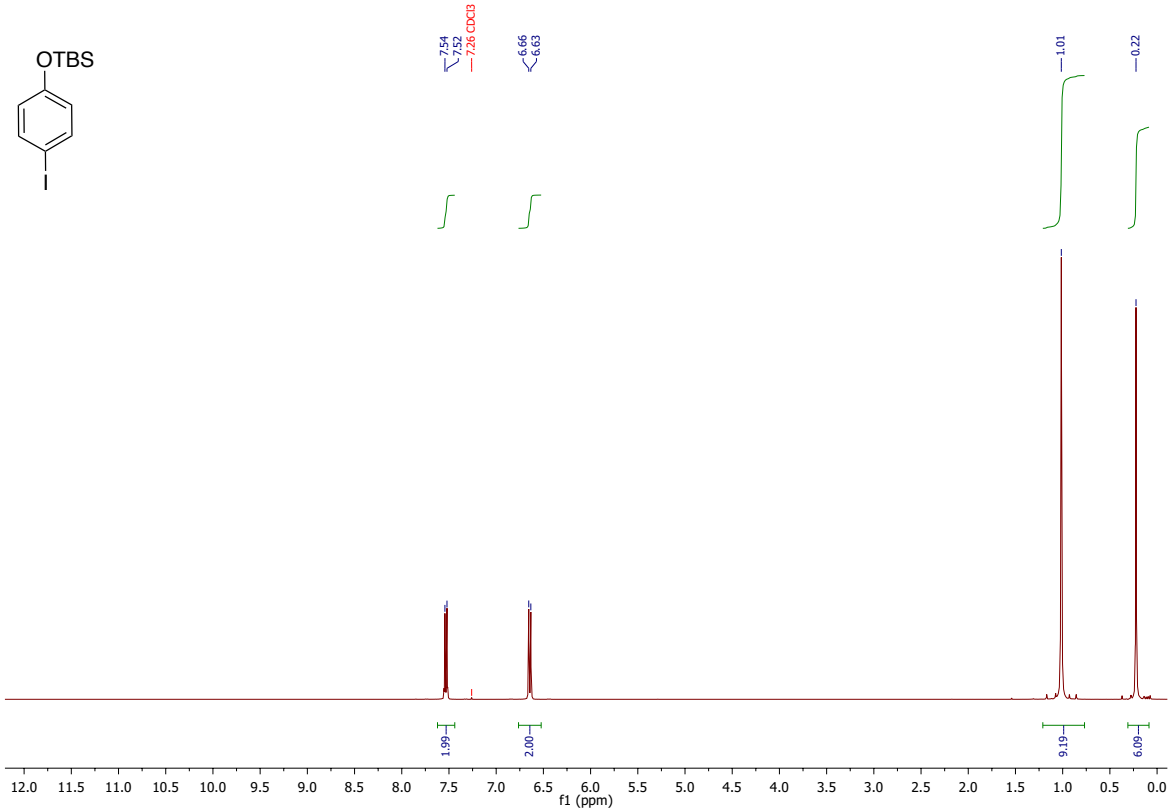


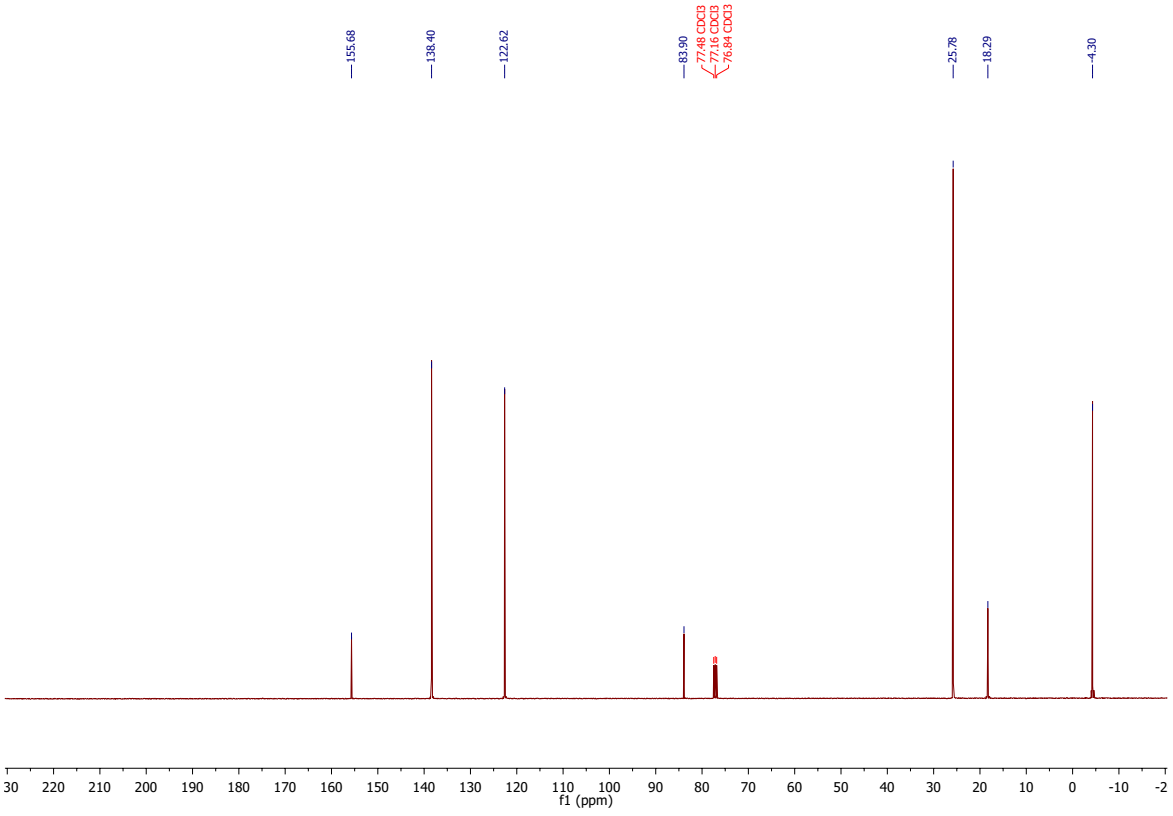


6.15. Spectral data of 4-iodophenol (107)

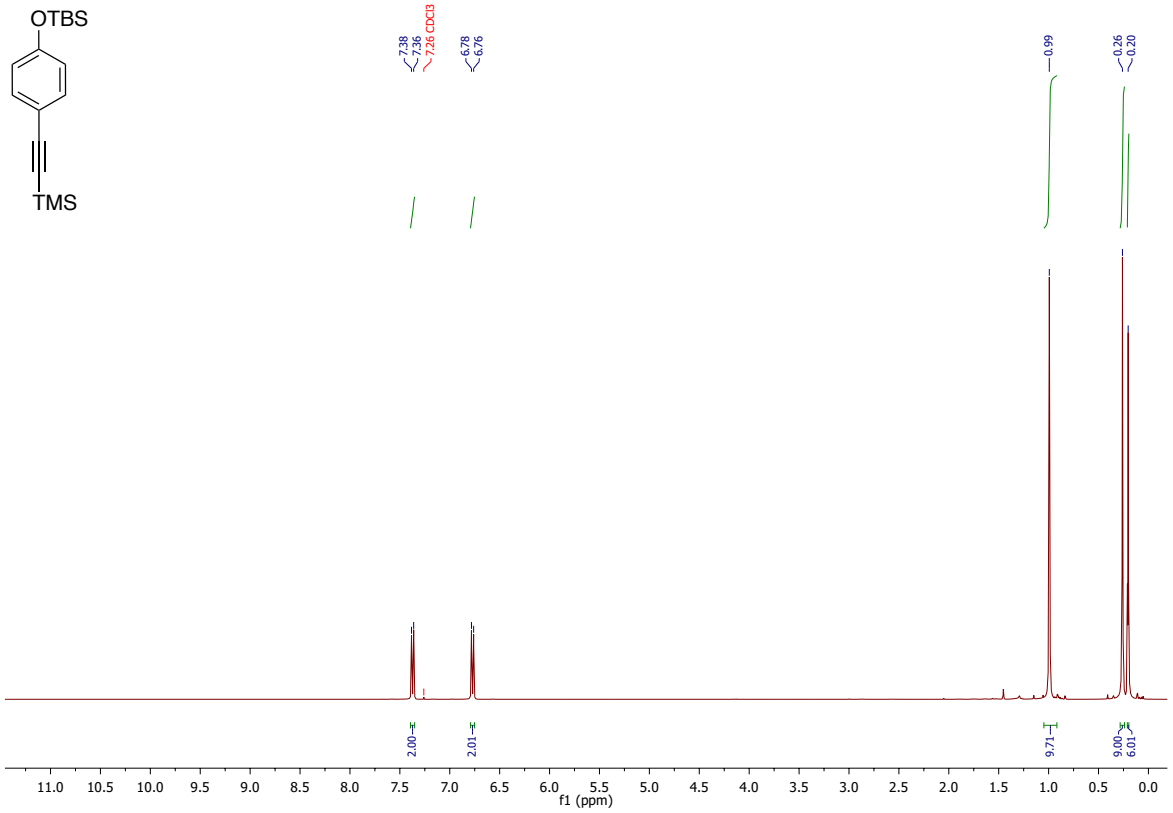


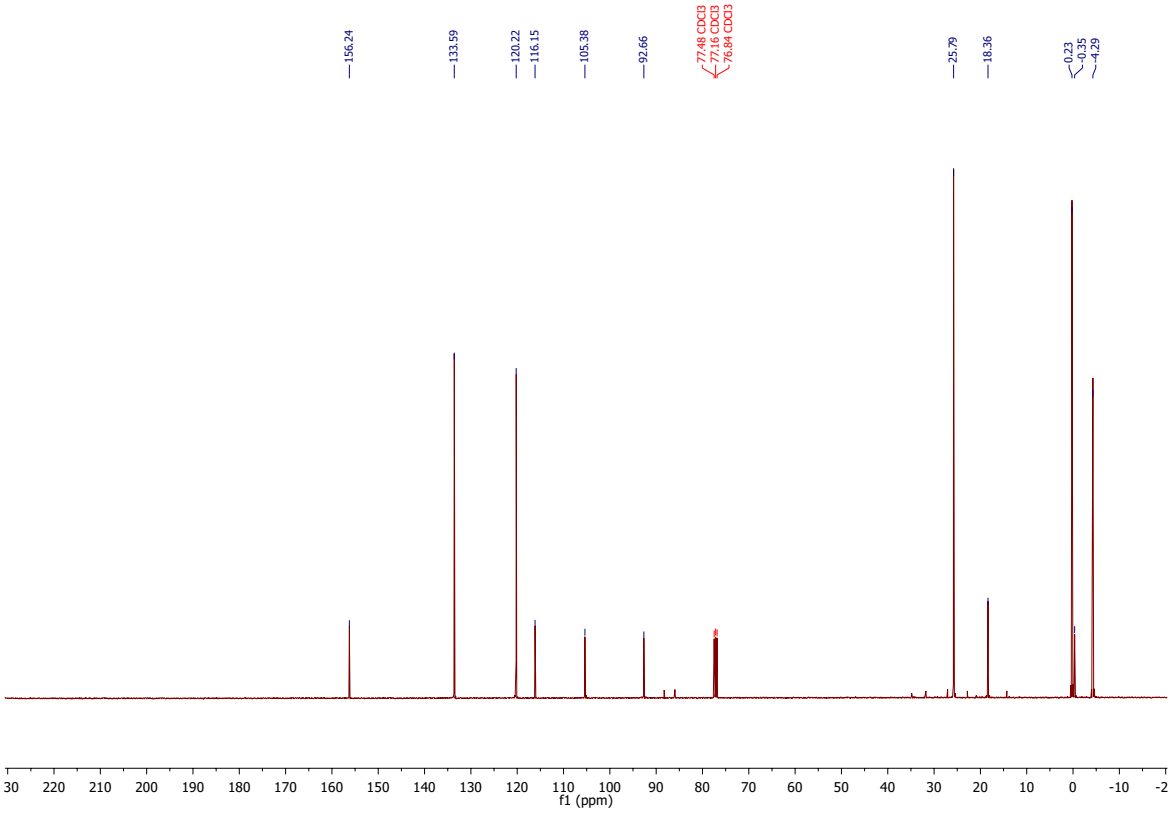
6.16. Spectral data of 108



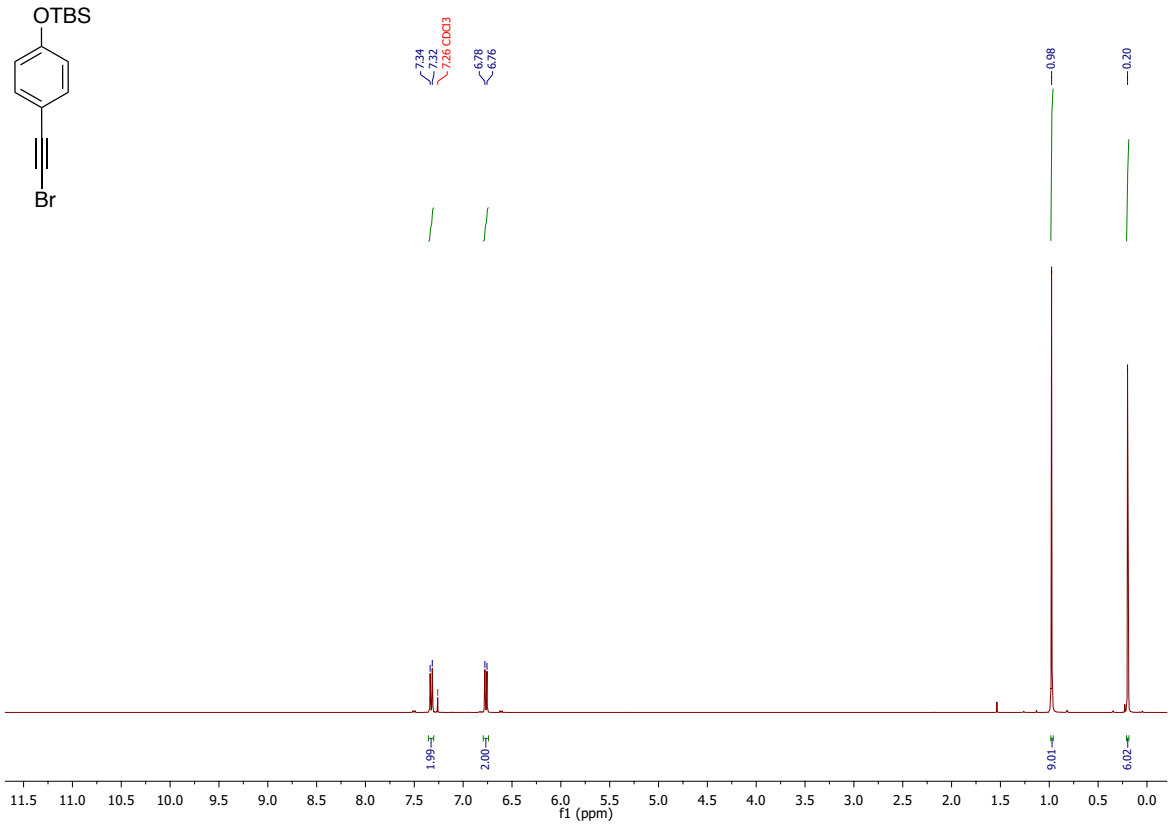


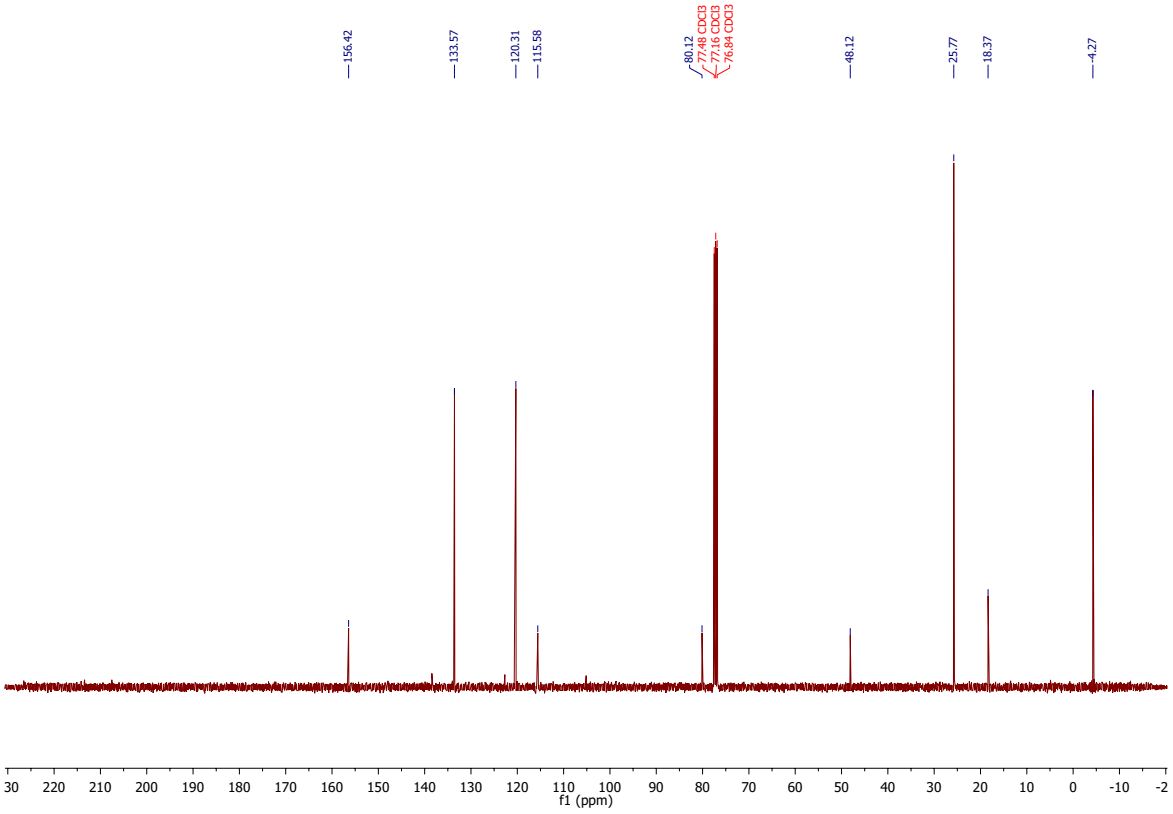
6.17. Spectral data of 109

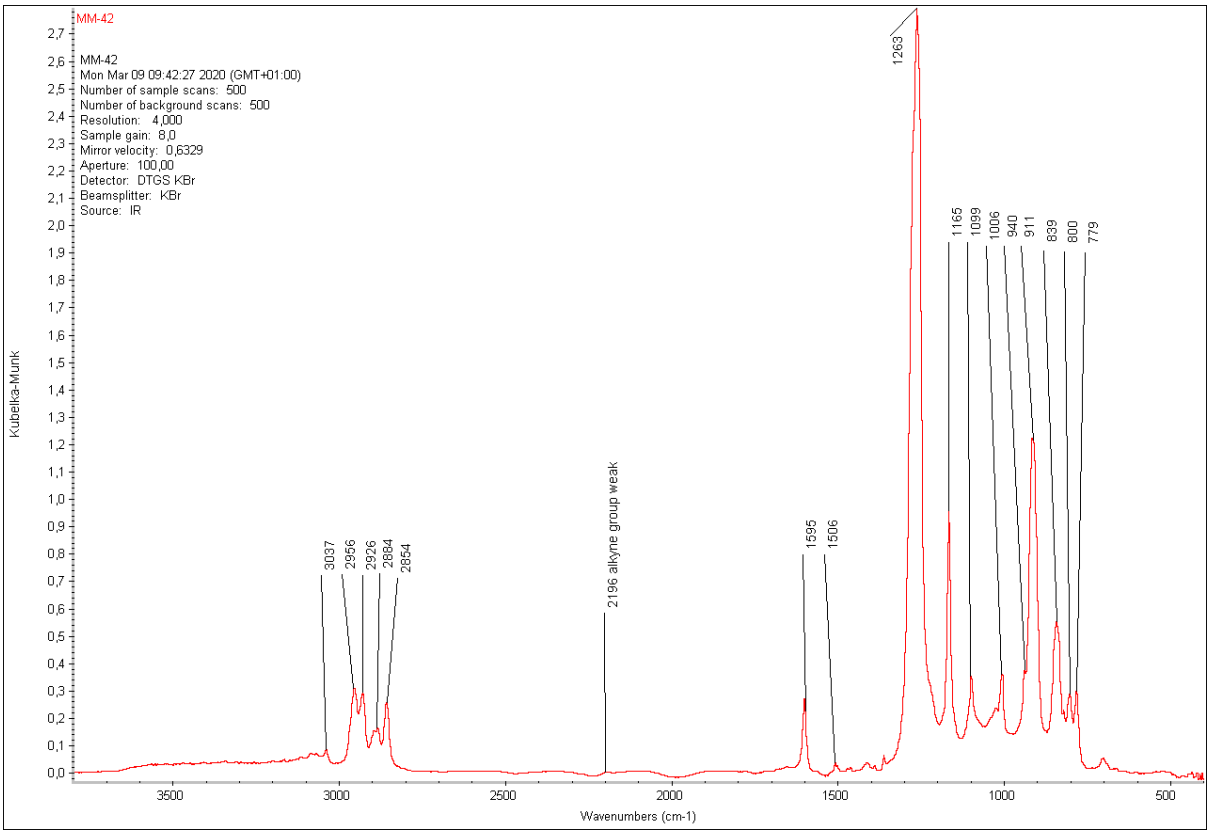




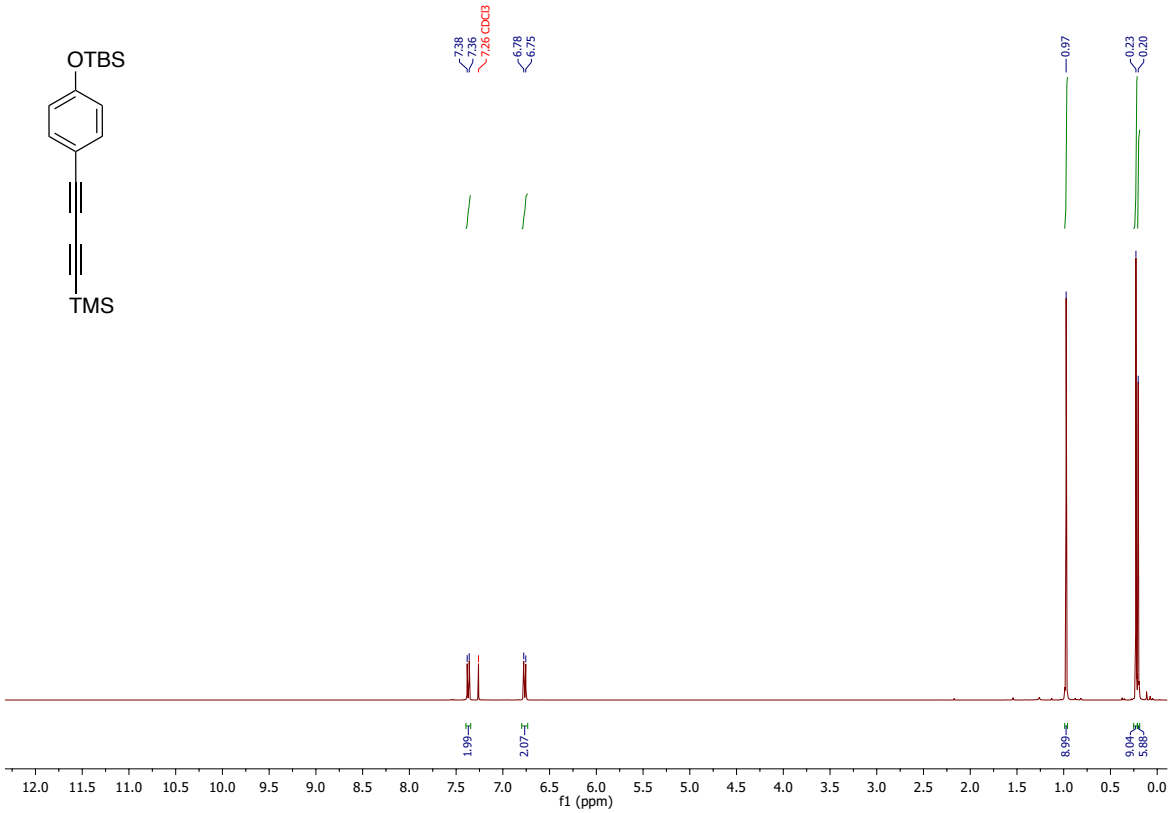
6.18. Spectral data of 110

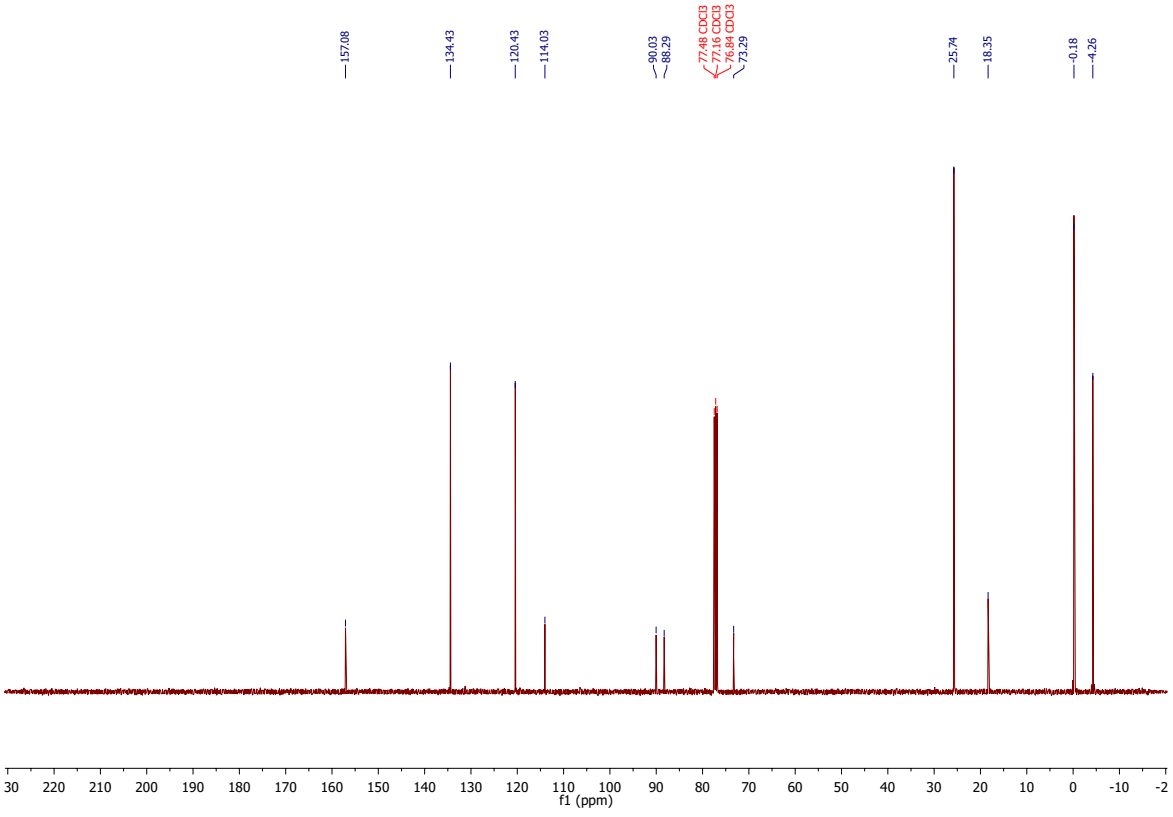


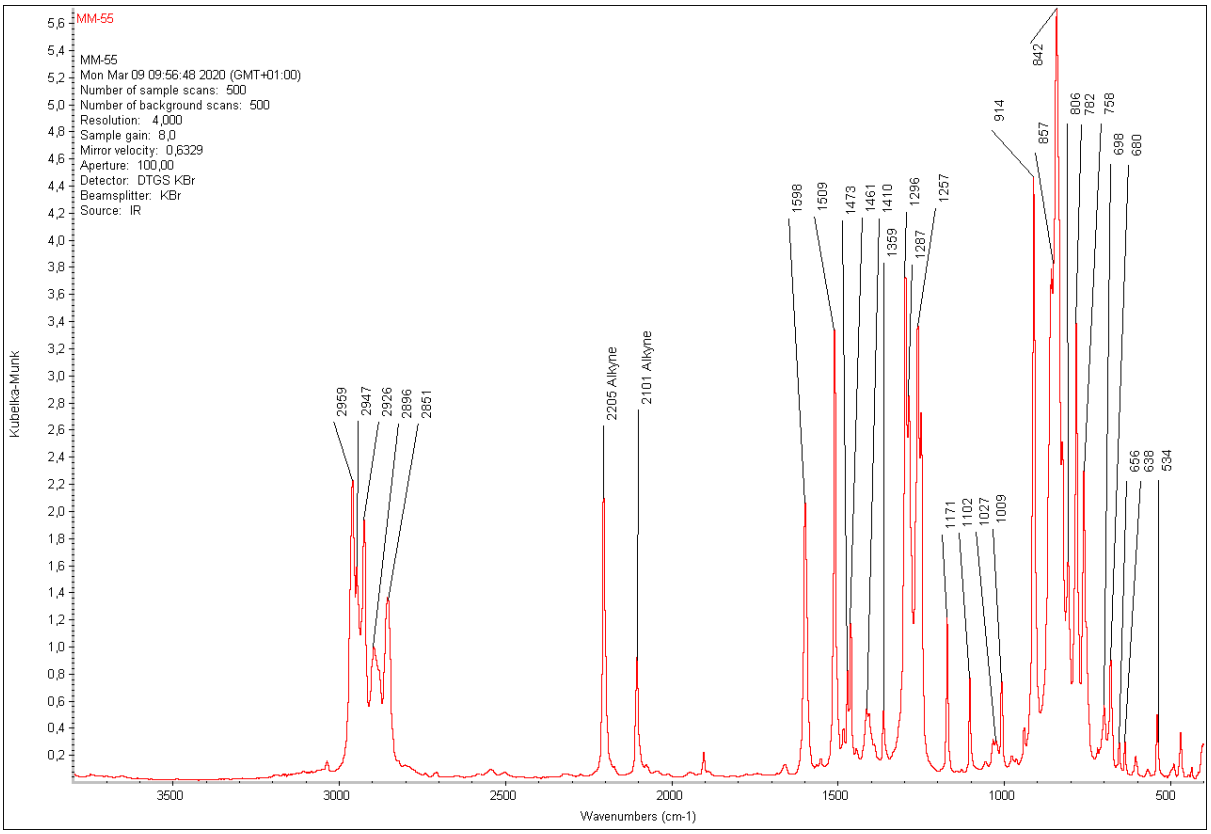



MM-42
MM-42
Mon Mar 09 09:42:27 2020 (GMT+01:00)
Number of sample scans: 500
Number of background scans: 500
Resolution: 4,000
Sample gain: 8,0
Mirror velocity: 0,6329
Aperture: 100,00
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
Kubelka-Munk
Wavenumbers (cm-1)
3037
2956
2926
2884
2854
2196 alkyne group weak
1595
1506
1263
1165
1099
1006
940
911
839
800
779

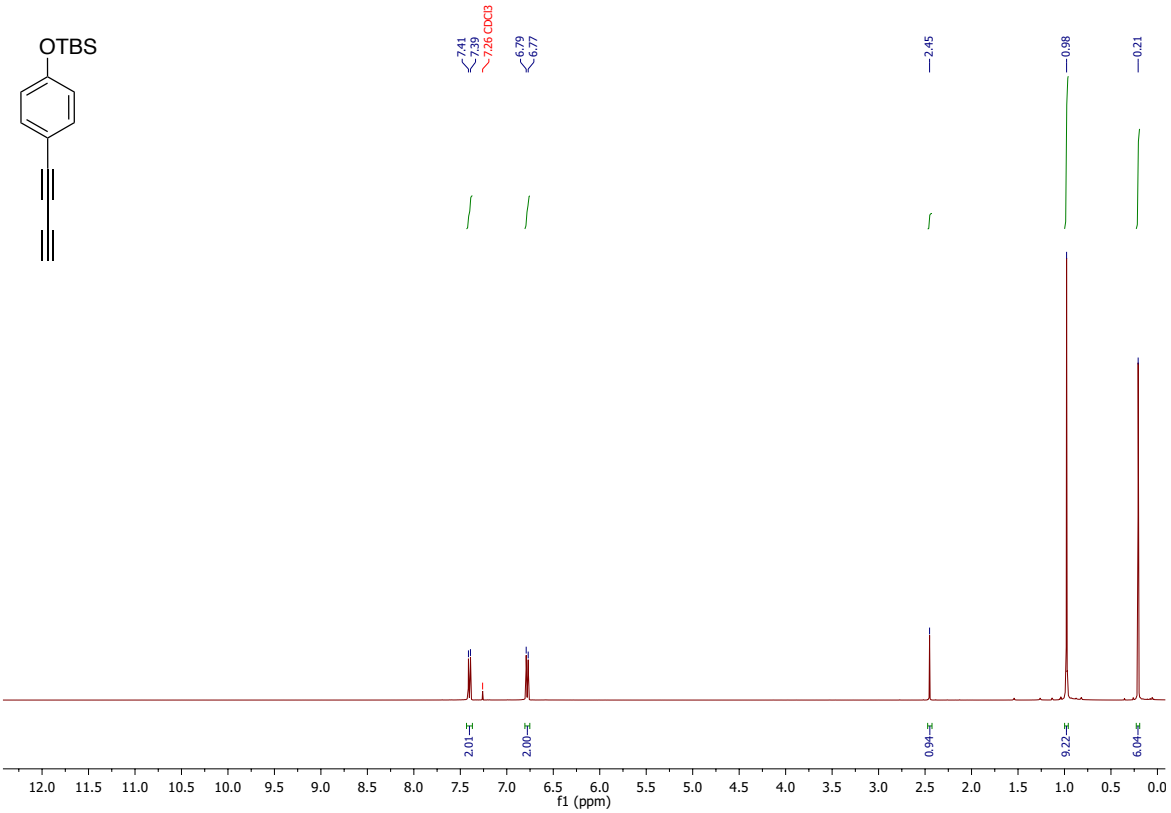
6.19. Spectral data of 111

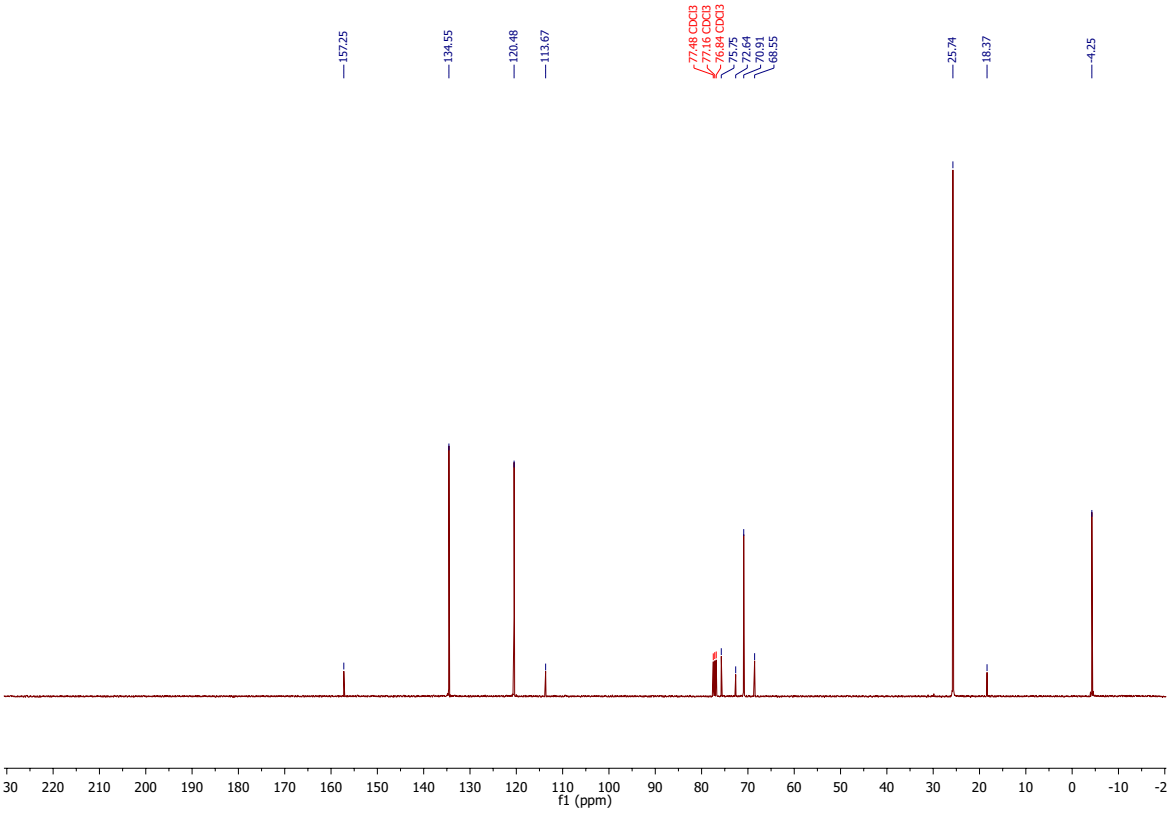


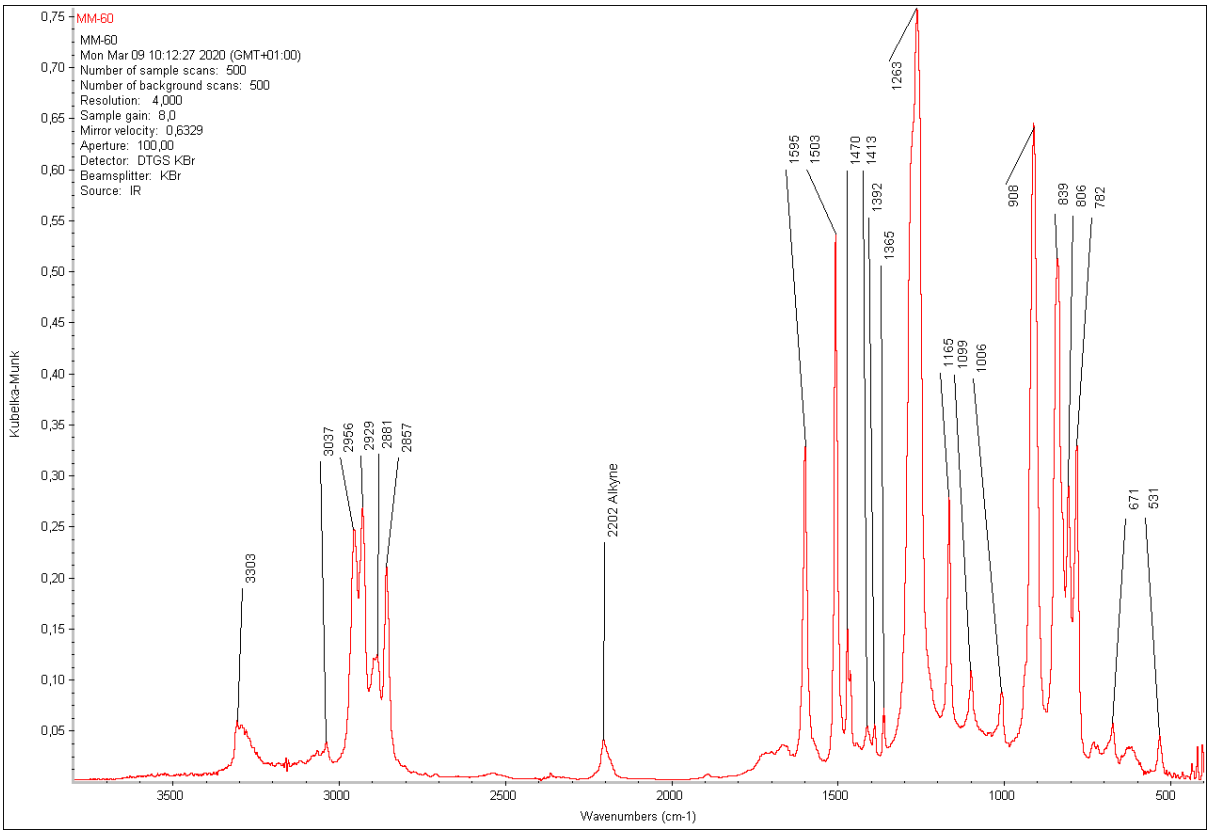



MM-55
MM-55
Mon Mar 09 09:56:48 2020 (GMT+01:00)
Number of sample scans: 500
Number of background scans: 500
Resolution: 4,000
Sample gain: 8,0
Mirror velocity: 0,6329
Aperture: 100,00
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
Kubelka-Munk
Wavenumbers (cm-1)
2959
2947
2926
2896
2851
2205 Alkyne
2101 Alkyne
1598
1509
1473
1461
1410
1359
1296
1287
1257
1171
1102
1027
1009
914
842
857
806
782
758
698
680
656
638
534

6.20. Spectral data of 98






MM-60
MM-60
Mon Mar 09 10:12:27 2020 (GMT+01:00)
Number of sample scans: 500
Number of background scans: 500
Resolution: 4,000
Sample gain: 8,0
Mirror velocity: 0,6329
Aperture: 100,00
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
Kubelka-Munk
Wavenumbers (cm-1)
3303
3037
2956
2929
2881
2857
2202 Alkyne
1595
1503
1470
1413
1392
1365
1263
1165
1099
1006
908
839
806
782
671
531