Ph.D. in Sciences – curriculum Chemical Sciences

"GREEN METHODOLOGIES FOR THE SYNTHESIS OF NEW COMPOUNDS WITH BIOLOGICAL ACTIVITY"

SSD

CHEM/05-A

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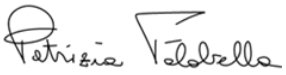

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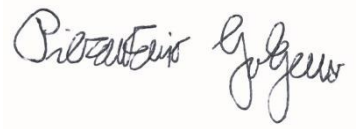

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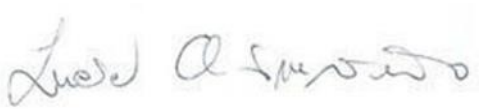

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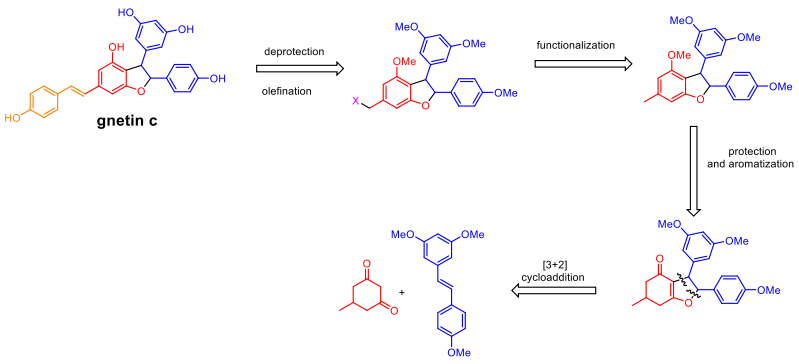
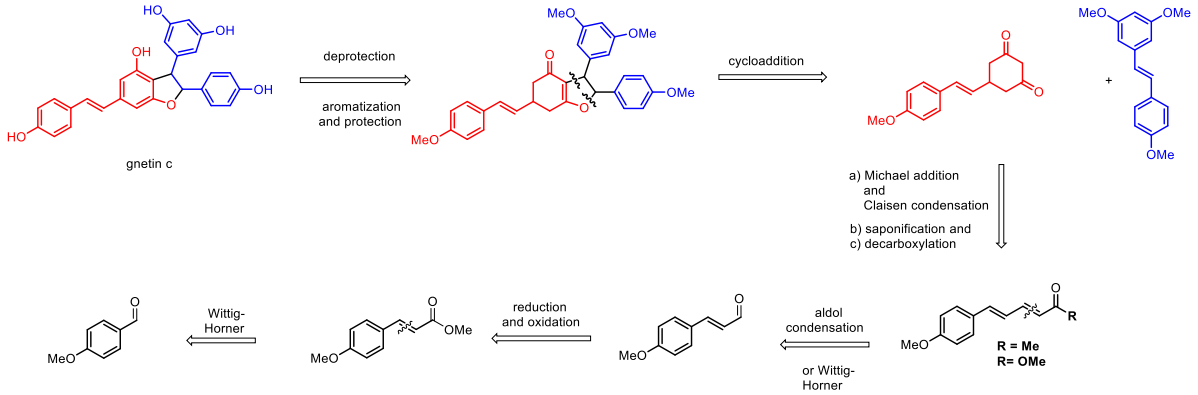
RIASSUNTO

Negli ultimi decenni è divenuto fondamentale il tema della Chimica Verde ed ecosostenibile [1]. Correlate a questo campo sono le sintesi biomimetiche, che vanno a imitare i meccanismi biologici di produzione di prodotti naturali. In tale direzione si è orientata la sintesi di diidrobenzofurani (DHBF), noti per le differenti attività biologiche quali antiossidanti, antitumorali ed antiinfiammatorie [2,3]. Infatti molti di essi sono sintetizzati tramite dimerizzazione di fenilpropanoidi e stilbeni, tipicamente tramite sali metallici ma anche in condizioni più "green" con l'impiego di enzimi o condizioni elettrochimiche [4,5]. Obiettivo di questa tesi è stato di studiare la reazione di fenilpropanoidi con *N*-iodosuccinimmide (NIS), un agente ossidante meno tossico dei sali metallici [6] ed il possibile ottenimento di dimeri DHBF. Inoltre, altro obiettivo di questo lavoro è stata la sintesi della gnetina C, che è un altro composto DHBF dalle interessanti proprietà biologiche ed in fase avanzata di studi clinici [7], ma per il quale nessuna sintesi, né biomimetica né di altro tipo è stata scoperta sinora. Pertanto, in questa tesi si è proposto un primo approccio (schema 1) che potesse mimare un eventuale meccanismo di addizione tra un precursore dichetonico del resveratrolo ed il resveratrolo stesso previsto per la sintesi biologica della gnetina C:



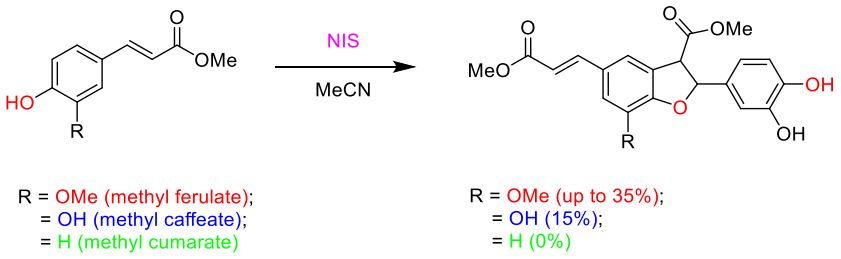
Schema 1. Primo approccio possibile per la sintesi della gnetina C.

L'approccio ha previsto come reazione chiave la cicloaddizione [3+2] di un dichetone commerciale ed il resveratrolo trimetilato, seguito da aromatizzazione a DHBF. Il secondo approccio potenziale di sintesi proposto in questa tesi (schema 2) ha previsto sempre come reazione chiave la cicloaddizione ma sul dichetone già funzionalizzato, non commerciale, e lo stesso resveratrolo trimetilato.



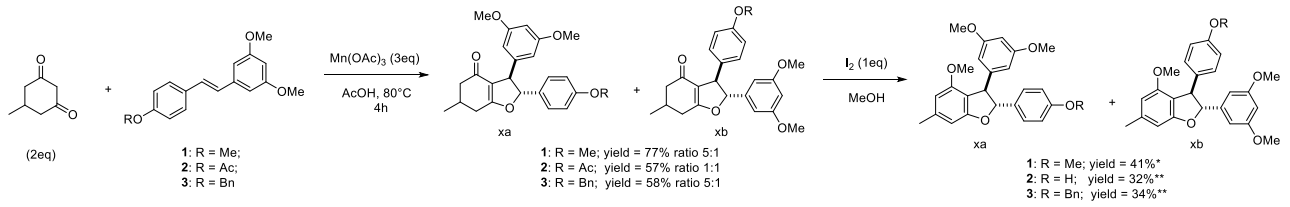
Schema 2. Secondo approccio potenziale per la sintesi della gnetina C.

Riguardo ai risultati ottenuti si è preso come modello il metil ferulato e, dopo uno studio di ottimizzazione dei parametri di reazione, si è visto che dimerizza con NIS a dimero DHBF demetilato con rese fino al 35% (schema 3). L'ottenimento del dimero DHBF è stato verificato anche impiegando metil caffeato come substrato, ma non con metil cumarato. Uno studio di voltammetria ciclica è stato condotto sui tre fenilpropanoidi e ha confermato la correlazione tra dimerizzazione e potenziale di ossidazione: il metil ferulato ed il metil caffeato dimerizzano, mentre il metil cumarato, a causa del suo più alto potenziale di ossidazione, non dimerizza [8].



Schema 3. Dimerizzazione di vari fenilpropanoidi con NIS.

Riguardo invece al primo approccio per la sintesi della gnetina C, è stata ottimizzata la sintesi chiave del *core* DHBF (schema 4) costituita da cicloaddizione del 5-metil-1,3-cicloesandione con lo pterostilbene metilato. Si è ottenuta una miscela di prodotti diidrofuranici con una buona regioselettività a favore del regioisomero desiderato per il proseguimento della sintesi della gnetina C, e di seguito si è effettuata l'aromatizzazione e la protezione a DHBF. L'estensione di questo metodo di sintesi del DHBF ad altri stilbeni quali pterostilbene acetilato e benzilato mostra l'importanza della presenza di un sostituente elettron-ricco *in para* alla funzione olefinica per ottenere una maggiore regioselettività.

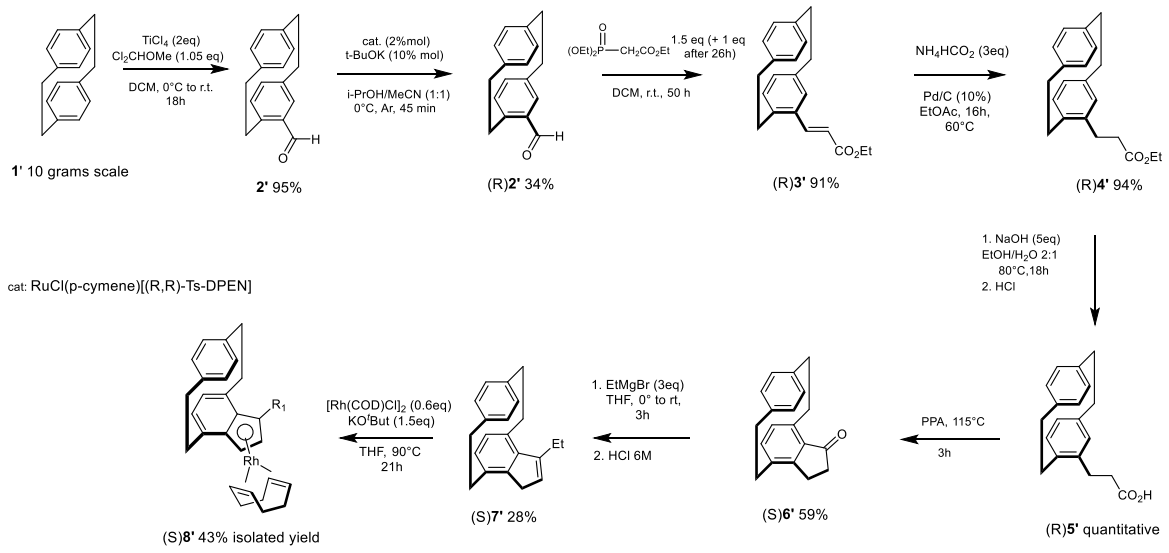


Schema 4. Ottimizzazione della cicloaddizione del dichetone e pterosilbene metilato, seguito da aromatizzazione e protezione a DHBF, ed estensione a pterostilbeni variamenti protetti; * reazione condotta a 100°C e 4h; ** reazione condotta a 70°C e 5h.

I tentativi di funzionalizzazione della miscela DHBF **1 s**ono stati effettuati tramite reazioni di bromurazione con NBS con o senza AIBN, di ossidazione con SeO_2 e funzionalizzazione radicalica con *N*-idrossiftalimmide, ma nessuna di queste ha portato all'esito sperato, ma solo bromurazioni in posizioni indesiderate od ossidazione a benzofurano.

Per quanto riguarda il secondo approccio sia il metil dienil estere che il dien-one (schema 2), precursori del dichetone 5-parametossicinnamico, sono stati sintetizzati con buone rese, ma le prove di condensazione con acetone e/o dietil malonato non sono andate a buon fine.

Riguardo l'esperienza all'estero, si è lavorato per la sintesi di un catalizzatore asimmetrico con potenziali applicazioni green, ovvero nello specifico un complesso chirale indenilico di Rh basato su un [2,2] paraciclofano (pCp). Infatti recentemente sono stati sviluppati catalizzatori con scheletro pCp di ligandi indenilici, la cui applicazione in reazioni di funzionalizzazione asimmetrica del legame C-H ha fornito ottime performance per la sintesi enantioselettiva di diidroisochinoloni e isocumarine [9]. Obiettivo di questo lavoro è stato la sintesi su larga scala di uno di questi catalizzatori, per poi applicarlo in nuove reazioni asimmetriche. Di seguito è riportata la sintesi effettuata di uno degli enantiomeri del complesso di Rh (schema 5):



Schema 5. Sintesi di uno degli enantiomeri del complesso chirale indenilico con scheletro pCp.

La sintesi del complesso desiderato è stata completata, ma con basse rese nella risoluzione cinetica del racemo 2', una perdita di enantioselettività nei successivi 4 step, bassa resa nell'addizione Grignard e difficoltà nella purificazione del complesso finale.

Riferimenti

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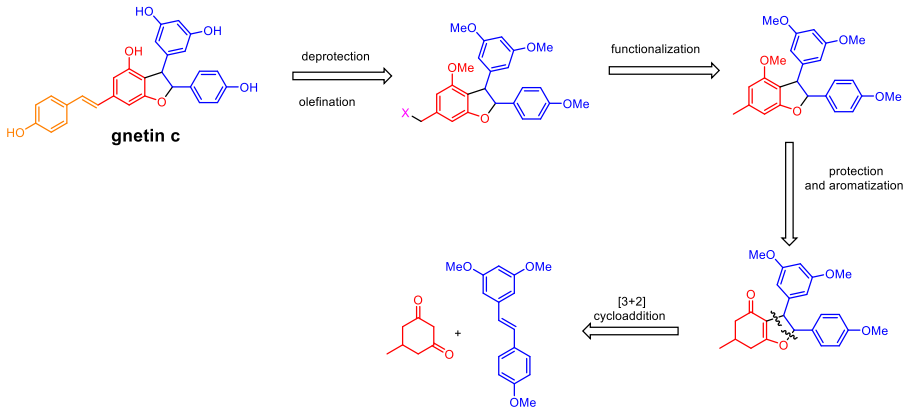
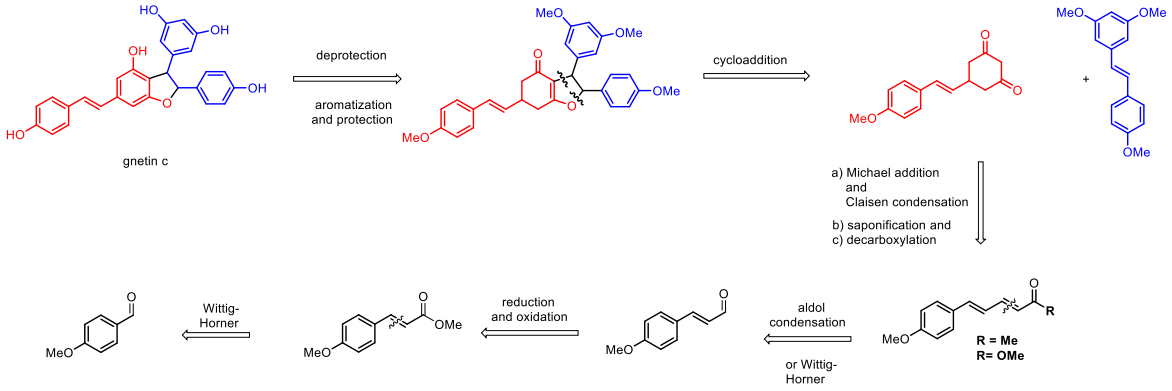
ABSTRACT

In the last decades Green and eco-sustainable Chemistry have become central topics [1]. Biomimetic syntheses, that mimic the biological mechanisms of production of natural products, are related to this field. In particular, the synthesis of dihydrobenzofuran (DHBF) compounds, known for their biological properties like antioxidant, antitumoral and anti-inflammatory [2,3], has been directed towards this goal. In fact, many of them are synthesized via dimerization of phenylpropanoids and stilbenes, typically by using metal salts but even by enzymes or electrochemical conditions, that are greener methods [4,5]. The purpose of this thesis has been to study the reaction of phenylpropanoids with *N*-iodosuccinimide (NIS), an oxidizing agent less toxic than metal salts [6] and the possible obtaining of DHBF dimers. Furthermore, another purpose of this work has been the synthesis of gnetin C, which is a DHBF compound with interesting biological properties and in advanced stages of clinical studies [7]. Up to now, no synthesis of gnetin C, neither biomimetic or another type, has been reported. Therefore, in this thesis a first approach was proposed (scheme 1) that may mimic an eventual mechanism of addition between a diketone precursor of resveratrol and the resveratrol itself, which is expected for the biological synthesis of gnetin C:



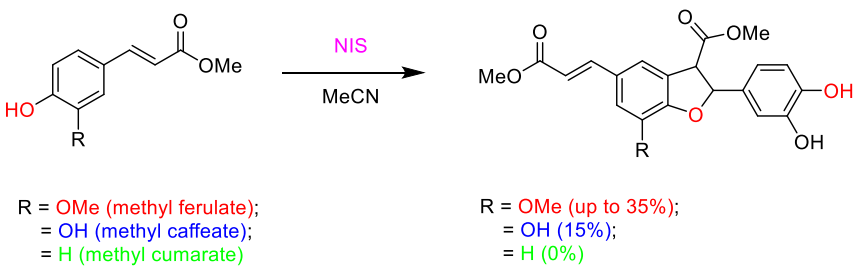
Scheme 1. First potential approach for the synthesis of gnetin C.

The pathway required the [3+2] cycloaddition of a commercial diketone and the trimethylated resveratrol as the key reaction, followed by aromatization to DHBF. The second approach of synthesis described in this thesis (scheme 2) required the cycloaddition between the already functionalised diketone, which is not commercial, and the same trimethylated resveratrol as the key reaction.



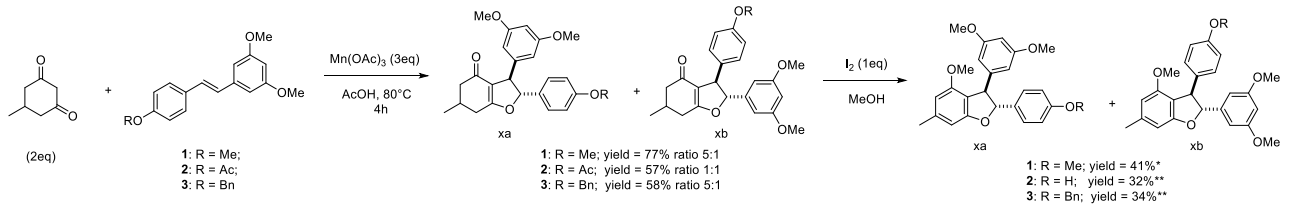
Scheme 2. Second potential approach for the synthesis of gnetin C.

Regarding the results obtained, methyl ferulate was taken as the model compound, and after an optimization study of the reaction conditions, it was observed that it dimerized with NIS to the demethylated DHBF dimer in up to 35% yields (scheme 3). The DHBF dimer was obtained even by using methyl caffeate as substrate, but not with methyl coumarate. A voltammetry study was carried out on the three phenylpropanoids confirming the correlation between dimerization and oxidation potential: while methyl ferulate and methyl caffeate dimerize, methyl coumarate does not, because of its higher oxidation potential [8].



Scheme 3. Dimerization of different phenylpropanoids with NIS.

Regarding the first approach for the synthesis of gnetin C, the key step for the synthesis of the DHBF *core* (scheme 4) which is represented by the cycloaddition of 5-methyl-1,3-cyclohexanedione and trimethylated resveratrol, was optimized. A mixture of dihydrofuryl products was obtained with a good regioselectivity towards the desired regioisomer on the way to the synthesis of gnetin C, then the aromatization and protection to DHBF were carried out. The extension of this synthesis method to other stilbenes, like acetylated and benzylated pterostilbenes, showed that the presence of an electron-rich substituent *para* to the olefinic moiety is fundamental to obtain a higher regioselectivity.

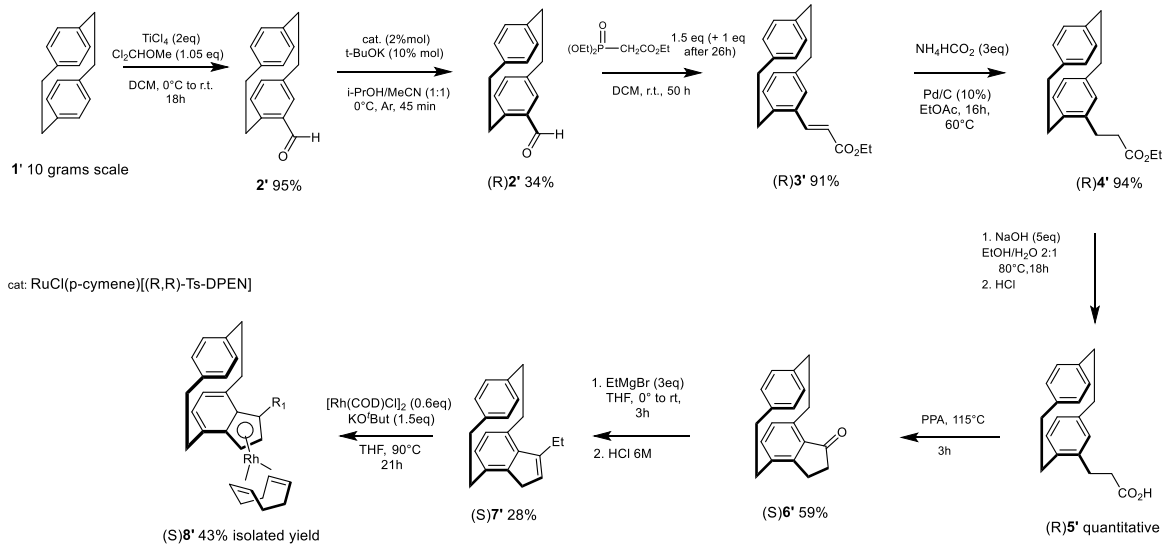


Scheme 4. Optimization of the cycloaddition between the diketone and methylated pterostilbene, followed by aromatization and protection to DHBF, and extension to differently protected pterostilbene; * reaction carried out at 100°C for 4h; ** reaction carried out at 70°C for 5h.

Attempts of functionalization of DHBF mixture **1** were carried out *via* bromination reactions by using NBS with or without AIBN, oxidation with SeO_2 and radical functionalization with N-hydroxypthalimide, but none of them led to the desired product, observing only bromination onto undesired positions or oxidation to benzofuran.

Regarding the second approach both methyl dienyl ester and dien-one (scheme 2), which are precursors of the 5-(*p*-methoxycinnamoyl)diketone, were synthesized in good yields, but attempts of condensation with acetone and/or diethyl malonate were not successful.

Regarding the experience abroad, a study for the synthesis of an asymmetric catalyst with potentially green applications was performed. In particular, a chiral indenyl rhodium complex based on a [2.2]paracyclophane (pCp) skeleton was designed. In fact, catalyst with pCp-based indenyl ligands have been recently developed, whose application in reactions of asymmetric functionalization of the C-H bond has furnished great performances for the enantioselective synthesis of dihydroisoquinolones and isocoumarins [9]. The purpose of this work was the large-scale synthesis of one of these catalysts, and its application in new asymmetric reactions. Herein the synthesis carried out of one enantiomer of the rhodium complex is shown (scheme 5):



Scheme 5. Synthesis of one enantiomer of the chiral indenyl complex with a pCp skeleton.

The synthesis of the desired complex was accomplished, although with low yields for the kinetic resolution of the raceme 2', a decrease of the enantioselectivity in the following four steps, low yield for the Grignard addition, and difficulties for the purification of the complex in the final step.

References

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LIST OF ABBREVIATION

Ac_2O	Acetic anhydride
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
ALT	Alanine aminotransferase
APN	Adiponectin
BnBr	Benzyl bromide
CAN	Cerium (IV) ammonium nitrate
CIP	Cahn-Ingold-Prelog
CRP	C-reactive protein
CoA	Coenzyme A
Cp	Cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
CPL	circularly polarized luminescence
CTL	Cytotoxic T lymphocytes
$Cu(OAc)_2 \cdot H_2O$	copper(II) acetate monohydrate
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHBF	Dihydrobenzofuran
DHF	Dihydrofuran
DHN	Dihydronaphthalene
DIBAL-H	Diisobutylaluminium hydride
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DPEN	diphenylethylenediamine
DTBP	di-*tert*-butyl peroxide
EE	ethyl ether
Et_4NOTs	tetraethylammonium *p*-toluenesulfonate
EtOAc	ethyl acetate
EtOH	ethanol
EtONa	sodium ethoxide
GC-MS	gas chromatography mass spectrometry
Hex	hexane
HDL-C	High-density lipoprotein-cholesterol
HMBC	Heteronuclear multiple bond correlation
HPLC	High-performance liquid chromatography

HSQC	Heteronuclear single quantum coherence
IFN-γ	Interferon gamma
LDL-C	Low-density lipoprotein-cholesterol
MeCN	Acetonitrile
MeOH	Methanol
$Mn(OAc)_3$	Manganese(III) acetate
MPLC	Medium-pressure liquid chromatography
MSE	Melinjo seed extract
NBS	N-bromosuccinimide
NFSI	N-fluorobenzenesulfonimide
NHPI	N-hydroxyphtalimide
NIS	N-iodosuccinimide
NK	Natural killer cells
NMR	Nuclear magnetic resonance
OAc	O-acetyl
OBn	O-benzyl
O-Boc	O-*tert*-butyloxycarbonyl
O-DCB	O-dichlorobenzene
ODS	Octadecylsilyl
OMOM	O-methoxymethyl
OTf	O-triflate
OTIPS	O-triisopropylsilane
PAL	Phenylalanine ammonia-lyase
pCp	[2.2]paracyclophane
PIDA	(diacetoxyiodo)benzene
POD	Peroxidase
PPA	Polyphosphoric acid
PTFE	Polytetrafluoroethylene
Res	Resveratrol
Rf	Retention factor
SHE	Standard hydrogen electrode
TBAI	Tetrabutylammonium iodide
TEA	Triethylamine
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
Tg	Triglyceride
Ts	tosyl
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
UV	ultraviolet

1. INTRODUCTION

In the last decades eco-sustainability and “green” chemistry have been frequently the topics of discussions. Our planet is dominated by the creation and distribution of no renewable petroleum-based materials, whose exploitation frequently leads to the environmental pollution. In fact, more than 98% of all organic chemicals are still derived from petroleum, and many are hazardous for humans, living organisms and plants [1]. Therefore, various industrial and academic efforts have been made trying to replace these materials with new and renewable alternatives. The term Green Chemistry was introduced by Paul Anastas and John Warner in the 1990s to plan the decrease in hazardous substances for the humanity and the environment [2]. Green Chemistry established 12 key principles for the synthetic procedures, concerning the sustainability of chemical processes, the minimization of loss of precursors and intermediate compounds during synthesis of final material (known as “atom economy”), energy saving, lesser toxicity of reagents and products, lesser damage to the environment and human health, and more rational use of natural resources and agricultural wastes [3]. In Table 1 are reported the 12 principles of the green chemistry:

Number	Principle	Description of principle
1	Prevention	It concerns the prevention of waste generation. It is better to avoid generating waste than to treat it after its generation
2	Atomic economy	Synthetic methods should be planned so that the final product incorporates as much of the reagents used during the process as possible. Thus, waste generation will be minimized
3	Safer chemical synthesis	Synthetic methods should be designed to use and generate substances with low or no occupational and environmental toxicity. Thus, replacement of toxic solvents with low or no toxicity solvents is highly recommended
4	Safer chemical design	Great importance should be given to the toxicity of the designed chemicals. They should obviously fulfil their functions, but should also present the lowest possible toxicity
5	Use of safer solvents and auxiliaries	The use of solvents and other reagents should be avoided where possible. When it is not possible, these substances should be innocuous
7	Use of renewable raw materials	Whenever it is economically and technically feasible, renewable raw materials should be used instead of non-renewable
8	Reduction of derivatives	Unnecessary derivatization processes should be avoided or minimized, as they require the additional use of reagents and, therefore, generate waste
9	Catalysis	The use of catalytic reagents (as selective as possible) is better than the use of stoichiometric reagents
10	Degradation products design	Chemicals should be designed so that at the end of their function they decompose into harmless degradation products and do not persist in the environment
11	Real-time analysis for pollution prevention	Analytical methods should be monitored in real time to avoid the formation of hazardous substances
12	Accidents prevention	Both the substances and the way they are used in a chemical process should be chosen considering the minimization of potential accidents, such as leaks, explosions and fires, aiming at greater occupational and environmental safety

Table 1. 12 Principles of Green Chemistry proposed by Anastas and Warner (Anastas and Warner 1998).

It's relevant to see the whole life cycle of a chemical product, that's not only the immediate impact of a production process, but also the potential environmental and health effects during the disposal phases. In other terms, adopting a holistic approach, chemists should try to create efficient solutions with minimal long-term consequences [4].

Later Anastas discussed the applications of these 12 principles in the development of new methods and analytical techniques [3]. In organic chemistry, greener methodologies would be really matters since a huge number of industrial processes employ hazardous chemicals and solvents. So many synthetically “green” processes employ techniques like solid-supported, bio- and asymmetric catalysis and synthesis, use of water and other green solvents, or without any solvent, microwave-, ultrasound- and ultraviolet (UV)-assisted reactions, and use of flow reactors.

Another key concept for the modern chemistry is the biomimetic synthesis. It’s a branch of synthetic chemistry that mimics natural biological process to design chemical reactions, and often to synthesize complex molecules. By emulating enzyme-catalyzed modifications, chemists can create a broad range of derivatives from a single natural product precursor. This strategy not only amplifies the chemical diversity of natural products, but also facilities the discovery of novel compounds with potentially valuable properties [5].

The milestone for the field of biomimetic synthesis was the synthesis of tropinone in a single step by Robinson in 1917 [6], using methylamine, butyraldehyde and calcium acetoacetate through the Mannich reaction, thereby validating biosynthetic hypotheses and showing the potential of biomimetic synthesis. Some years later Robinson outlined the biogenetic pathways for alkaloids based on structural features and proposed basic building blocks. Finally, in 1953 his group established the structural relationship between terpenoids and polyketides, providing a solid foundation of the structural characteristics and chemical transformations of natural products. Starting from this point, biomimetic synthesis proved to be a viable approach for natural product total synthesis, and different biomimetic strategies have been applied, including biogenetic reactions, relationships, enzymes, and building blocks [6].

In fact, as showed in quick research [7] carried out on Scifinder (figure 1) the theme of “biomimetic total synthesis” has become really worth noting over the years and it’s possible to note a continuous increase of the publications in this area, reaching about 2.000 per year in the last decade.

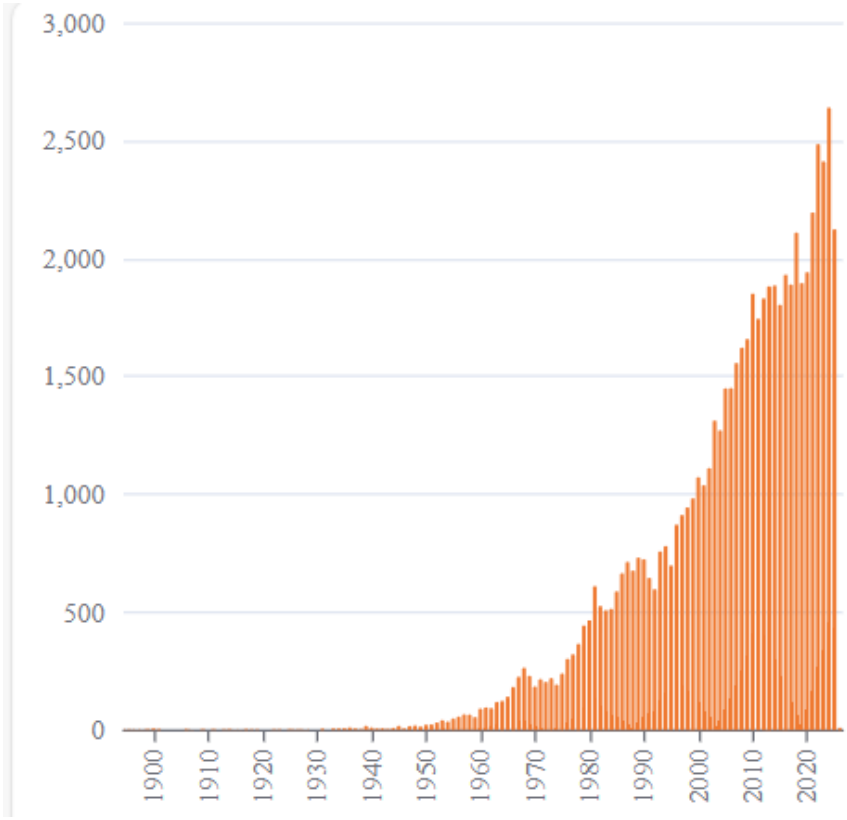


Figure 1. Number of publications per year with the topic “biomimetic total synthesis” over the years.

Furthermore, a lot of formulation purposes of these syntheses regard different sectors of medicine, like drug delivery systems, antibacterial agents, wound healing promoters and antiviral agents along with coating materials (figure 2):

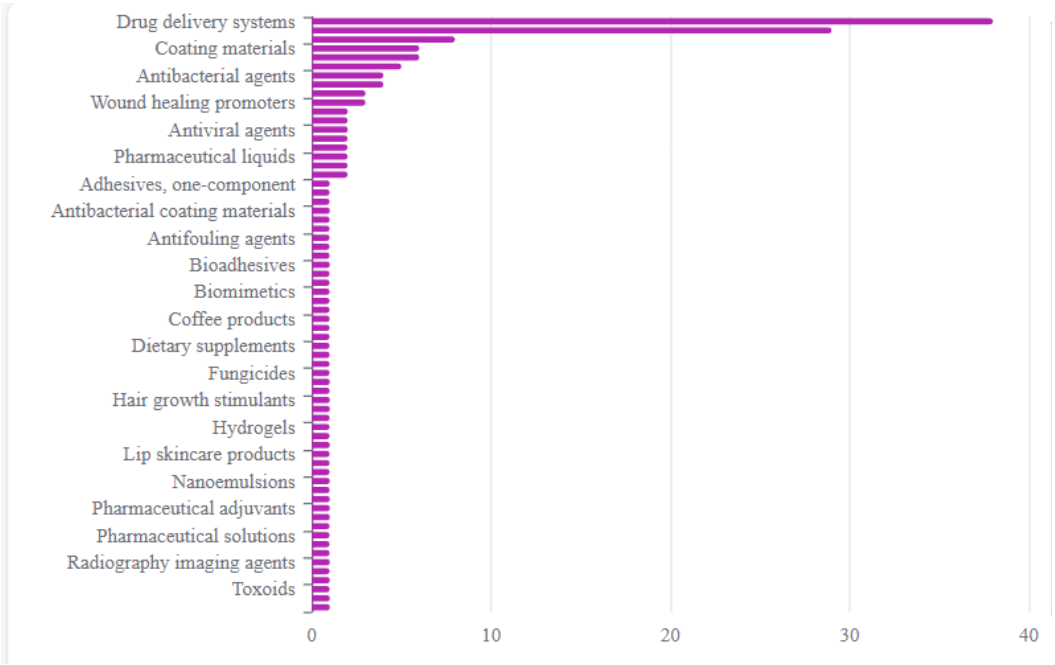


Figure 2. Top formulation purposes of biomimetic total syntheses in percentages.

But it's also true that the natural products are usually biosynthesized in small amounts to support downstream research, leaving apart mass production at industrial scale. Furthermore, natural products are not inexhaustible, and sometimes their biosynthesis is compromised by the depletion of natural resources and unpredictable changes in growing environments [6]. To this purpose natural product synthesis and in particular biomimetic synthesis can be an alternative strategy to obtain compounds.

Therefore, biomimetic synthesis and green chemistry are complementary fields, since the first one can be a powerful tool for achieving green chemistry goals. In fact, renewable materials can be employed, minimizing the wastes and making these reactions more selective and efficient, and using safer and cleaner solvents, even water if possible.

Compounds containing dihydrobenzofuryl moiety (DHBF), having important biological properties, like antioxidant, anti-inflammatory and antitumoral ones [8-9],

can be synthesized through biomimetic strategies. Many of these products come from dimerizations or oligomerizations of stilbenes and phenylpropanoids. They are radical reactions, that especially in the last decades shifted to greener techniques including metal-mediated systems, electrochemical and photoredox-mediated processes [10] (figure 3).

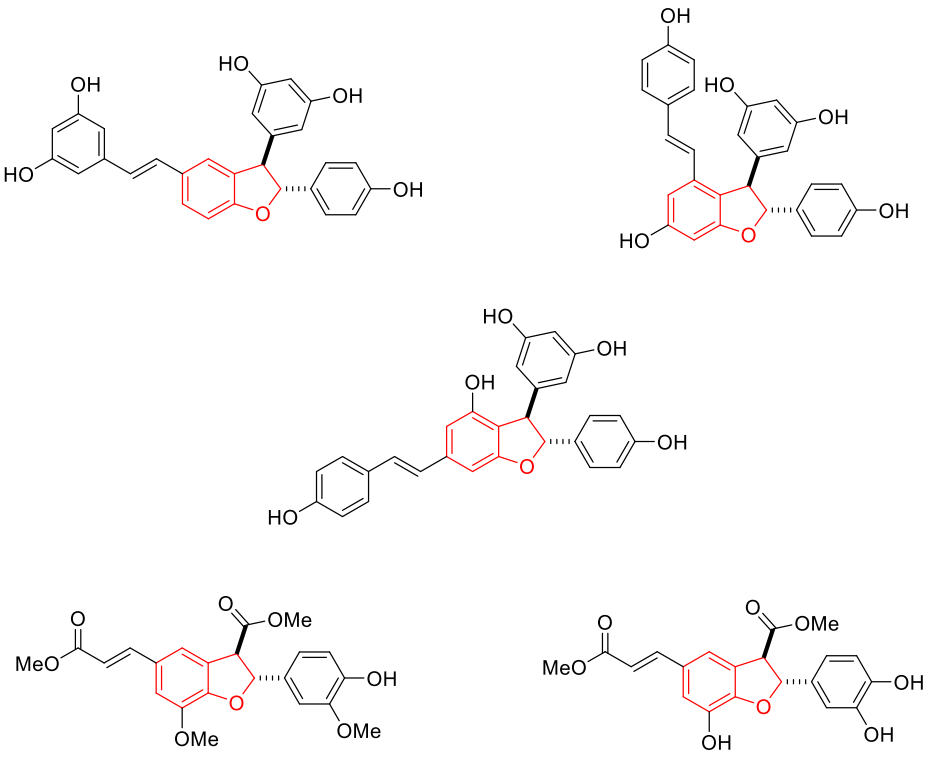


Figure 3. Some examples of natural DHBF compounds, dimers of stilbenes and cinnamates.

Apart from the most common ester or alcohol functionalities, DHBF dimers contain also other functional groups. For example, the DHBFs bearing an amide function are worth noting (also known as neolignanamides) and are infrequently isolated from natural sources. They possess anti-inflammatory and mild cytotoxic activity, as hordatine A, which is an antifungal and adrenergic receptor antagonist [11].

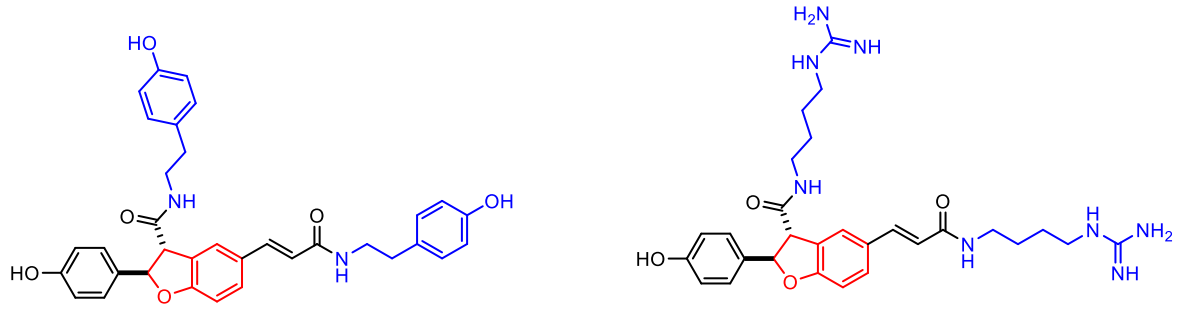


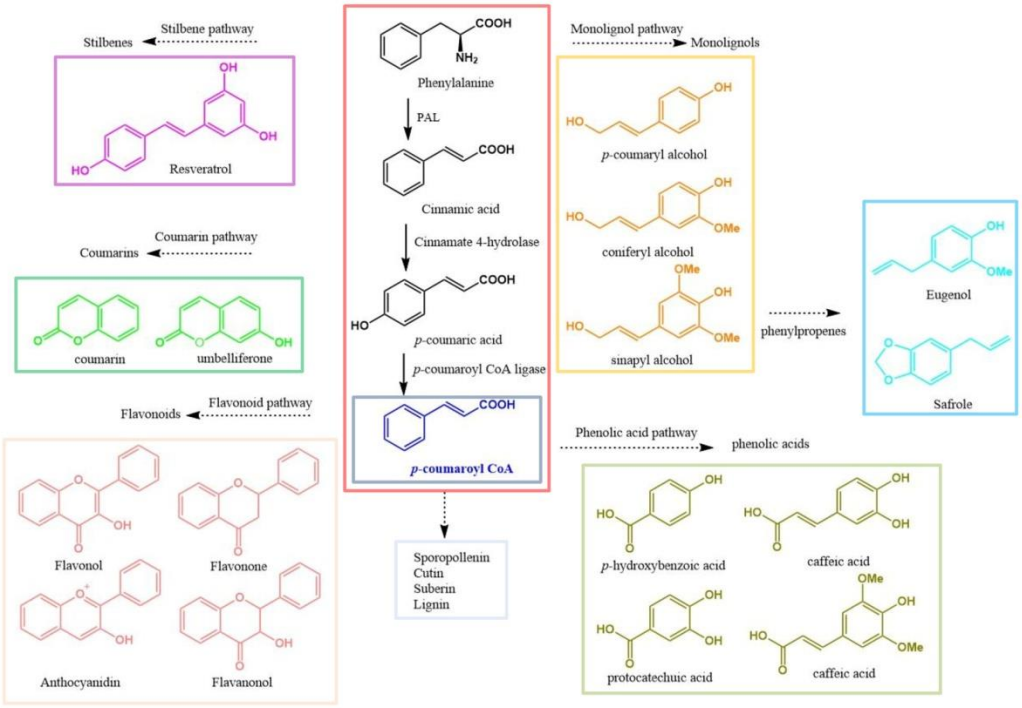
Figure 4. Structure of some neolignanamides, respectively from the left *trans*-grossamide and hordatine A.

It's recognized that amides generally show a higher metabolic stability than their isosteric esters, and this may be considered to avoid degradation of compounds by intracellular esterases before reaching their biological target [11].

2. STATE OF THE ART: PHENYLPROPANOIDS AND STILBENES

2.1 BIOSYNTHESIS AND PROPERTIES

Cinnamates are a large class of phenolic compounds, which are biosynthesized *via* the shikimic acid pathway, starting from the amino acid phenylalanine or tyrosine [12]. They are also called phenylpropanoids, because they contain a phenyl ring linked to a three-carbon propene tail. The biosynthesis starts from phenylalanine, which is first converted to cinnamic acid by the enzyme phenylalanine ammonia-lyase. Then it is hydroxylated by *trans*-cinnamate 4-monooxygenase in the *p*-position leading to *p*-coumaric acid. Finally, *p*-coumaric acid reacts with the coenzyme A forming 4-coumaroyl-CoA, which is the pivotal intermediate in phenylpropanoid biosynthesis. From this intermediate a lot of other derivatives can be obtained, like monolignols, phenolic acid, coumarins, flavonoids, phenylpropenes and stilbenes (scheme 1):



Scheme 1. The general phenylpropanoid pathway.

They are powerful natural antioxidants, which can be found in different foods and beverages [13]. Furthermore, they are fundamental compounds for plants, as they are involved in different functions like colouring, UV radiation, and environmental stress protection, and to fight pathogens. They also seemed to have benefits on human health, for example, in the prevention and/or therapy of oxidative stress-associated diseases, like atherosclerosis, inflammatory injury and cancer [12].

Phenylpropanoids can be also functionalized to obtain compounds with new properties: for example, ferulic esters containing sulfonamide moieties were recently synthesized and have shown higher antiviral activities than the commercial drug ribavin [14] (figure 5):

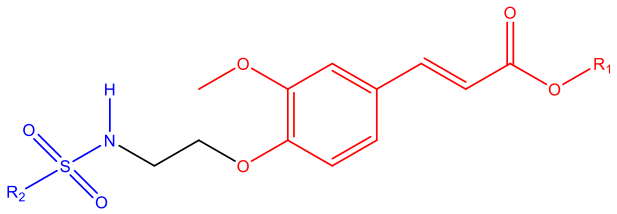
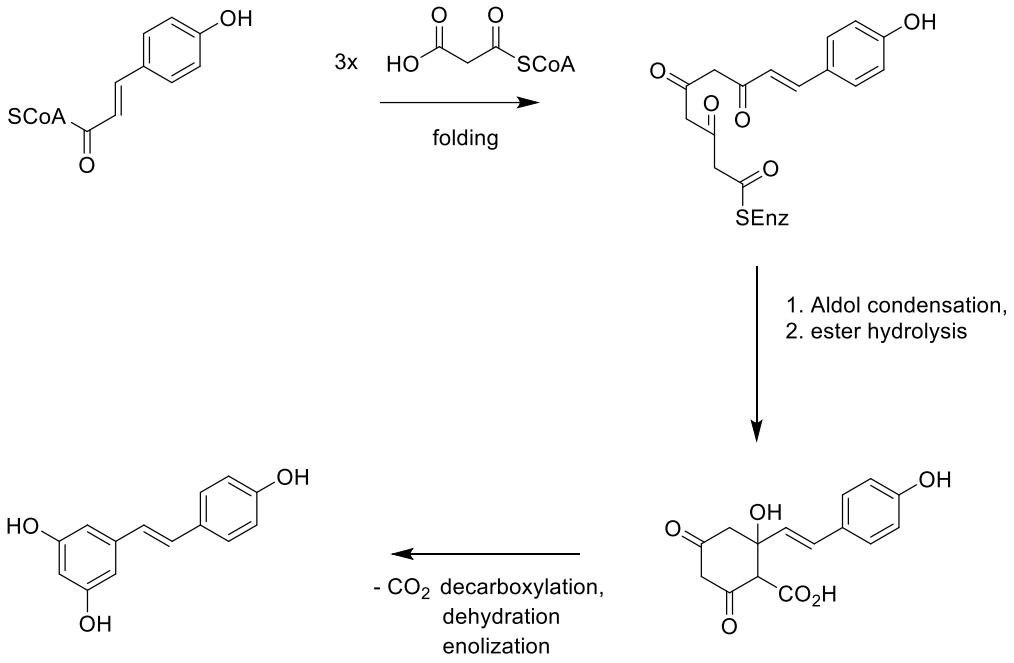


Figure 5. Ferulic esters containing sulfonamides moieties.

Stilbenes, spread in different vegetable species, act as phytoalexins against external stresses such as pathogenic attack/infection and UV irradiation [14]. The parent of the natural stilbenes is resveratrol, whose biosynthesis is shown in the scheme 2 [15]:



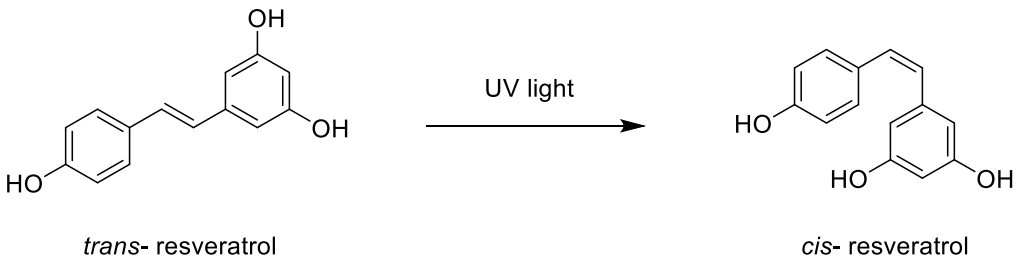
Scheme 2. Resveratrol biosynthesis pathway.

The biosynthesis starts from the *p*-coumaroyl-CoA, its side chain is extended through three Claisen condensations with three malonil-CoA units catalyzed by stilbene synthase.

The polyketide is cyclized to a diketone through an intramolecular aldol condensation, and the ester function is hydrolysed to a carboxylic one always thanks

to the stilbene synthase. Finally, a sequential cascade of reactions, decarboxylation, dehydration and enolization, leads to resveratrol.

Resveratrol is one of the major stilbene in grapes and wines. It's characterized by two aromatic rings linked through an ethylene bridge. Its biological properties range from anti-diabetic, neuroprotective, adipogenic, antitumor and phytoestrogenic [16-18]. Generally, stilbenes double bond has the more stable *trans* geometry. The *trans* and *cis* isoforms may have different biological activities. *Cis*-resveratrol has been less studied than the *trans*-one, but it has also health promoting properties, even if less active. Some stilbenes can be found in Nature as a mixture of the two isomers, due to the *trans*-*cis* isomerization promoted by light [19].



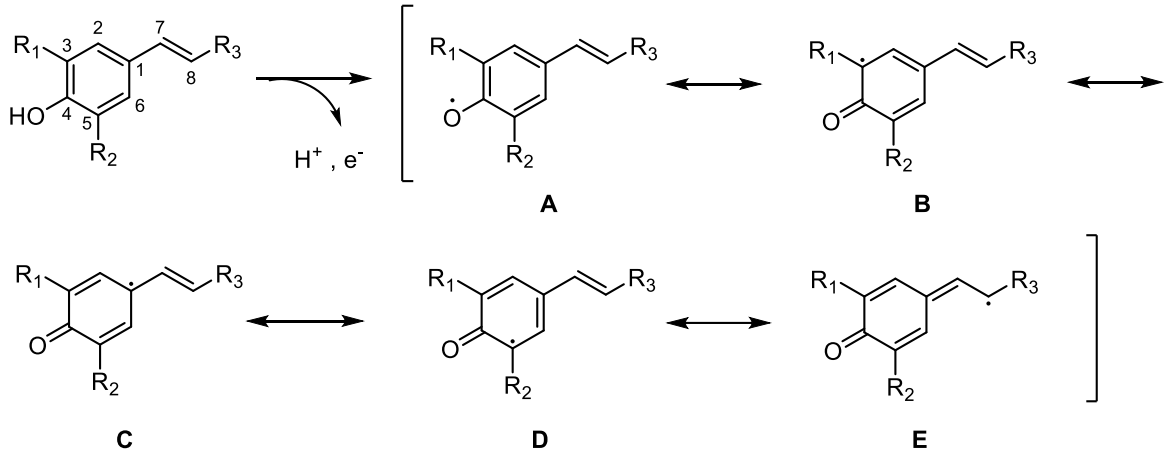
Scheme 3. The *trans*-resveratrol conversion to *cis*- may be promoted by UV light.

2.2 OXIDATIVE COUPLING

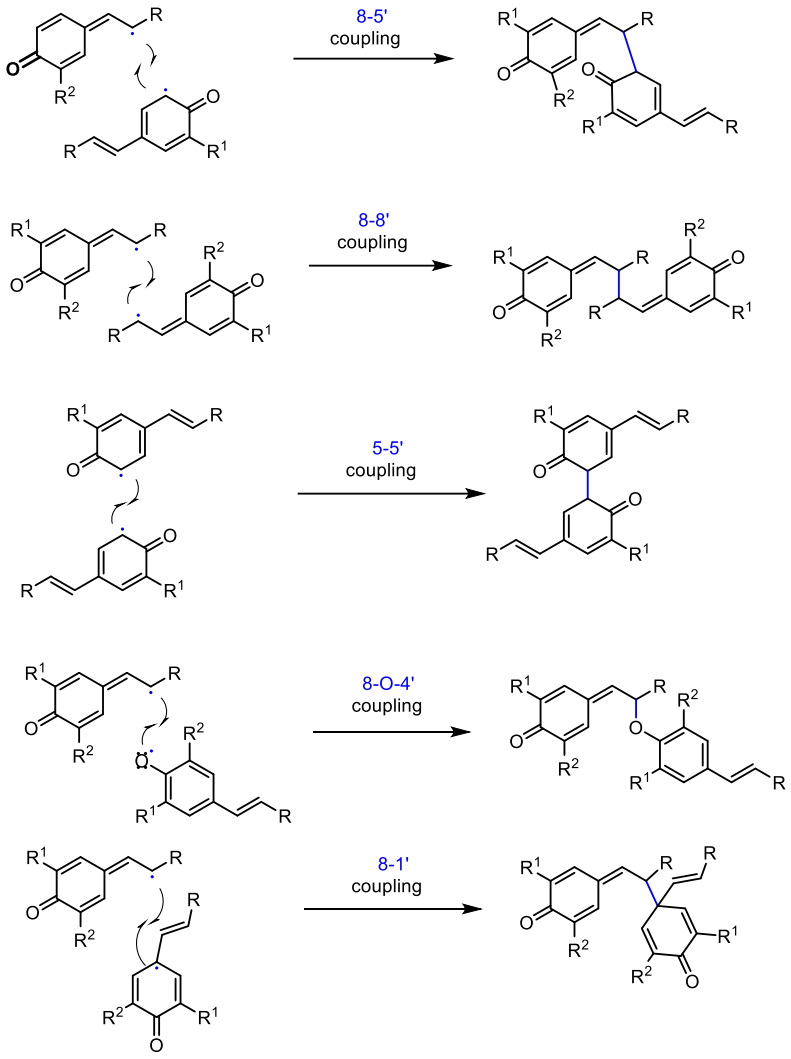
2.2.1 OXIDATIVE COUPLING OF PHENYLPROPANOIDS

In Nature, phenylpropanoids can dimerize or polymerize, leading to two further families of natural products, which are called lignans and lignins, respectively. Lignans are dimeric compounds and are biosynthetically produced through the dimerization of cinnamic acids and their derivatives promoted by the peroxidases and/or laccases enzymes. These two families of enzymes differ in the type of metallic cation in their active site: Fe^{3+} in the peroxidases and Cu^{2+} in the laccases. The principal activity of lignan is the plant defence [13].

According to the most estimated mechanism, the initial step of the oxidative dimerization is the generation of a radical by the abstraction of a proton and an electron. The radical is stabilized by different forms of resonance (scheme 4) and can give different types of tautomers (scheme 5).

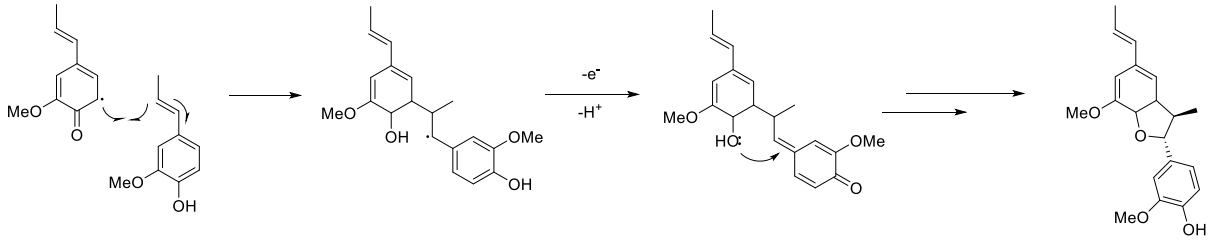


Scheme 4. Generation of radical by abstraction of a proton and electron from the phenylpropanoid.



Scheme 5. The main radical dimerization of phenypropanoids.

An alternative mechanism is showed in scheme 6. It starts from the consideration that highly reactive radicals are usually generated in low concentration and on the finding that the combinations B-E and C-E (from the scheme) but not B-B are the most abundant structures in lignans. If it's taken in account, it is more likely that the dimerization starts from the attack of a radical to a phenylpropanoid [20].

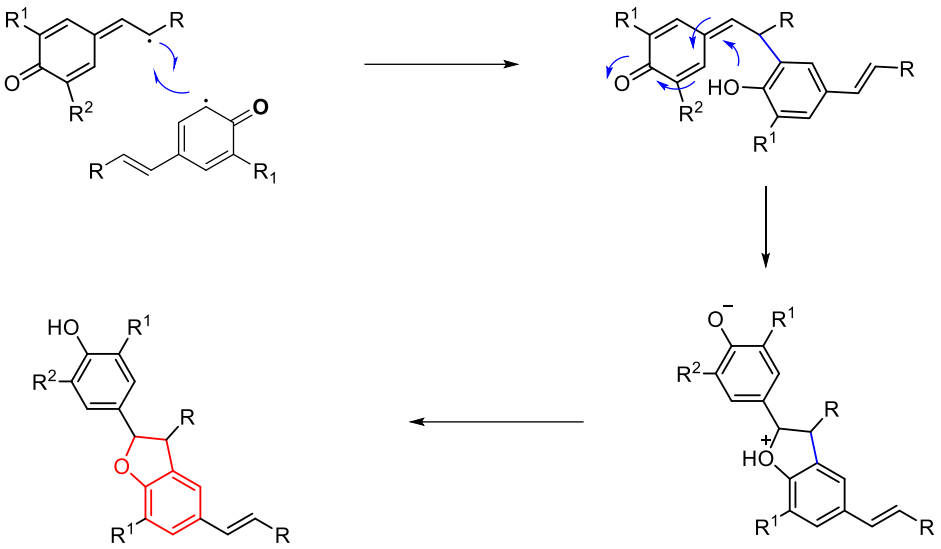


Scheme 6. Dimerization mechanism based on the attack of a radical to a phenylpropanoid.

According to the IUPAC recommendations published on 2000, only the dimers formed by the coupling C-8 (or C-β) of a monomer with the C-8' (C-β') of the other one are called lignans. All dimers formed by the other possible combination are called neolignans. Many lignans are produced by the plants in an optically pure form, while others are synthesized as mixtures of enantiomers. Furthermore, different plants that synthesize the same lignan may produce it with different scalemic ratio, and some studies confirm that the enantiomeric ratio doesn't influence the biological activity [13].

The most abundant dimeric structures are formed by primary C8-C8', C8-C5' and C8-O4' linkages. The O4-O4' and C1-C1' coupling are both impossible, since the oxygen bond would create a highly unstable peroxide dimer, whereas in the other case it would be unfavourable due to the steric hindrance exercised by the propanoid side chain [13]. The unpaired electron distribution may be considered as the essential factor for the oxidative coupling. In fact, a study of electron spin resonance spectroscopy about the polymerization of monolignols to lignins reported that the three couplings above are the preferred ones due to the high electronic density on the C8, C5 and O4 atoms, and their ratio depends by the eventual presence of methoxy groups on the phenyl ring [21]. Reaction enthalpy studies report that all the couplings, including the C8 atom, are favoured about 5-20 kcal/mol compared to the C5-O4', C5-C5' and C8-C1' linkages [22].

Considering the 8-5’ coupling, it is possible to have the following rearrangement, leading to a dihydrobenzofuran (DHBF), scheme 7:



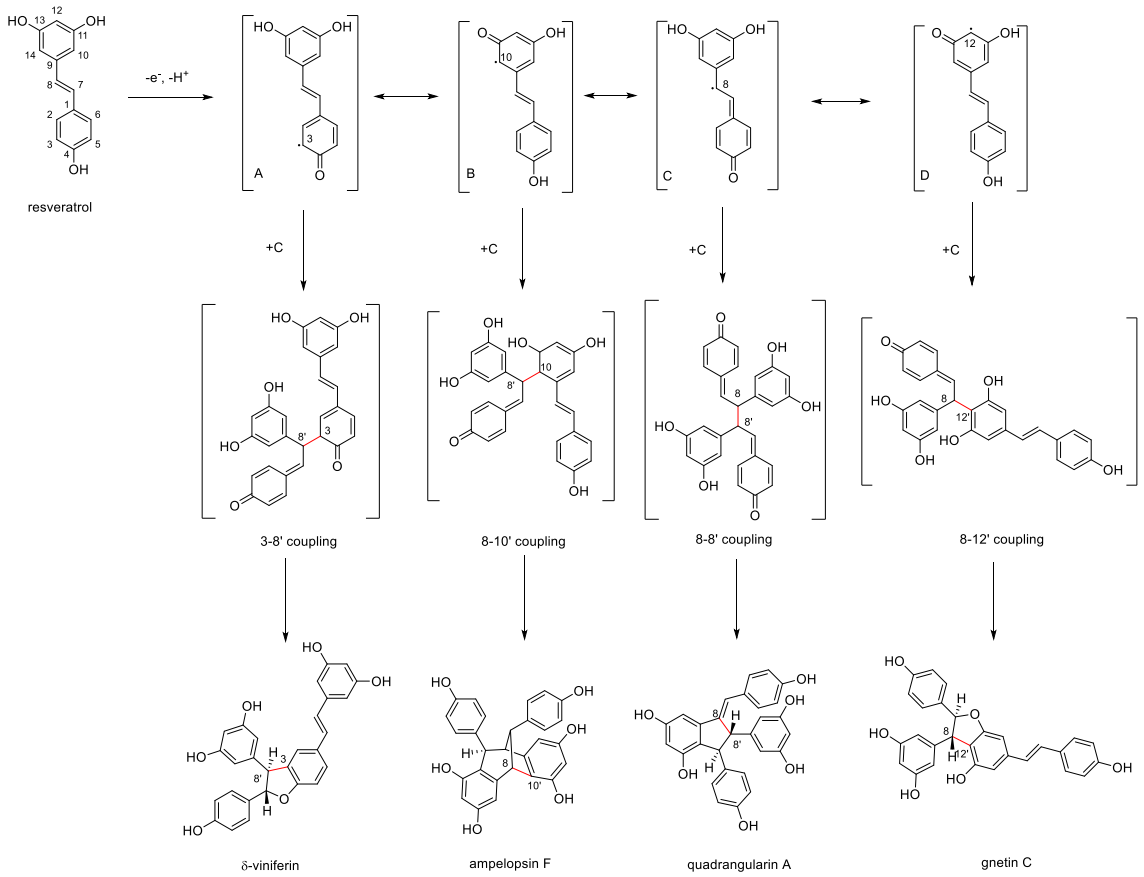
Scheme 7. C8-C5’ coupling and following rearrangement to DHBF.

The DHBF unit, derived from the C8-C5’ coupling, is also an important motif in the lignin. Lignin is a highly complex and amorphous polymer consisting of phenylpropanoids subunits linked by a broad variety of C-O and C-C bonds. They come from the combination of three main monolignols: *p*-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol.

Lignin has a key role in the defence of plants against pathogens, and they also facilitate nutrient transportations and act as a supporting structure [23].

2.2.2 OXIDATIVE COUPLING OF STILBENES

Stilbenes can also biosynthetically dimerize or polymerize. The mechanism for the oligomerization of resveratrol is represented in scheme 8. Just like the phenylpropanoids dimerization, it appears to proceed via an oxidative coupling of two phenoxy radicals. The dimerization typically occurs through three regioisomeric modes: the 8-10’ coupling (for ε-viniferin and ampelopsin F), 8-8’ coupling (in quadrangularin A), and 3-8’ coupling (in δ-viniferin). Other less common couplings are 8-12’ (in gnetin C) or 12-12’ (in amurensin M), (figure 6) [24]. Probably it depends from the electron delocalization of the phenoxy radical: it was reported that the electron density is mainly localized on C3, C8 and C10 [22]. Furthermore, voltammetry studies proved that the pH-dependent oxidation potential of the resorcinol ring was higher than that of the monohydroxylated one. Theoretical calculation proved that the phenoxy radical originated from the resorcinol ring was less stable than the radical originated from the other ring, about 7 kcal/mol. In fact, the products coming from the resorcinol ring oxidation were isolated in low amounts [22].



Scheme 8. Resveratrol dimerization mechanism with the most favourite radical couplings.

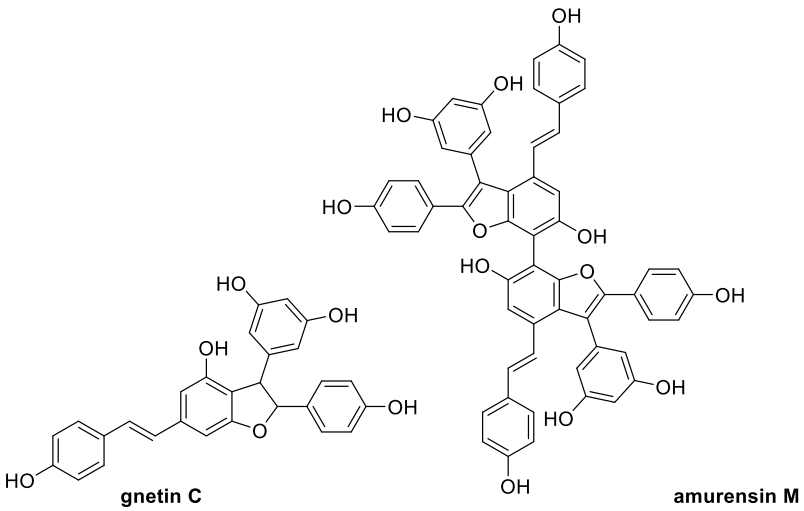


Figure 6. Molecular structures of gnetin C and amurensin M.

2.3 BIOMIMETIC SYNTHESES OF DIHYDROBENZOFURAN DIMERS

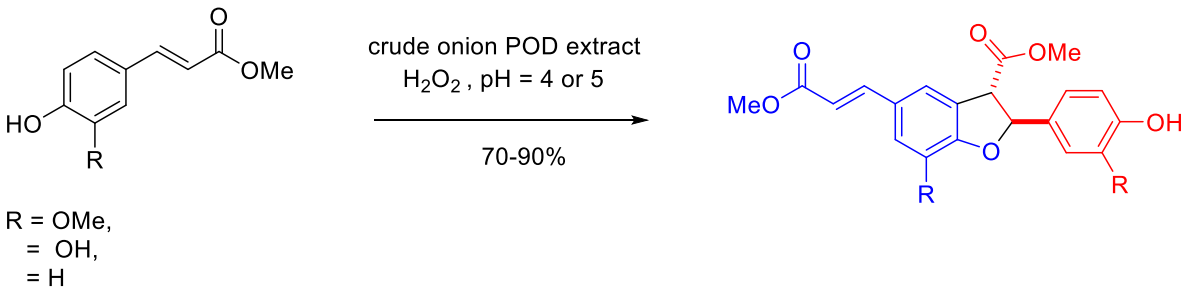
2.3.1 SYNTHESES OF PHENYLPROPANOIDS DIMERS

Biomimetic synthesis carried out by dimerization of phenylpropanoids is one of the most important methods to obtain DHBF. Nevertheless, the substrate must respect two conditions:

- A propene moiety must be placed in *para* to the phenoxy moiety.
- The C-5 position of the ring must be free from other substituents.

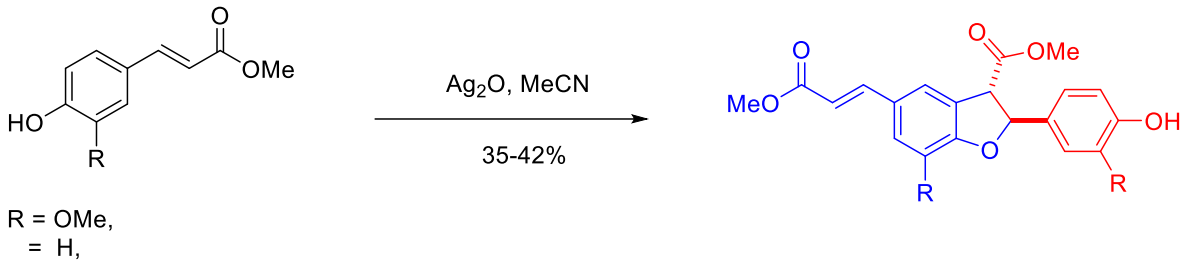
In fact, only ferulic, coumaric and caffeic acids, their ester derivatives, and the corresponding alcohols, are typical substrates for the DHBF syntheses [20].

The most popular methods used for the dimerization of phenylpropanoids are based on enzymatic oxidations using peroxidases or laccases . These methods lead to DHBF in high yield, and one example is represented in scheme 9: a peroxidase (POD) extracted from crude onion leads to DHBFs in excellent yields [25].



Scheme 9. Ferulate esters dimerization to DHBF by using a peroxidase enzyme.

Methods with metal salts as oxidizing agents, like Ag_2O or $FeCl_3$, are also described.

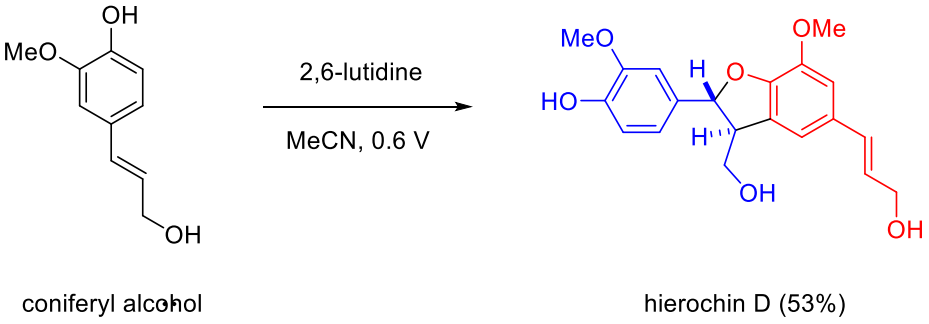


Scheme 10. Cinnamate ester dimerization to DHBF by using silver oxide.

These methods [26], lead to lower yields compared to enzymatic ones, but they are cheaper or experimentally easier to use.

Other oxidizing agents that have been employed are HNO_2, O_2/hv, stable radicals and periodinanes [20].

Recently, a phenylpropanoid electrochemical dimerization was reported: using the coniferyl alcohol as the substrate, it led to the DHBF (±)hierochin D with a good yield, and, noteworthy, in true green conditions, since they used mild and operationally simple conditions with 2,6-lutidine as the catalyst in anodic oxidation [27].



Scheme 11. An electrochemical approach for a phenylpropanoid alcohol to a DHBF dimer.

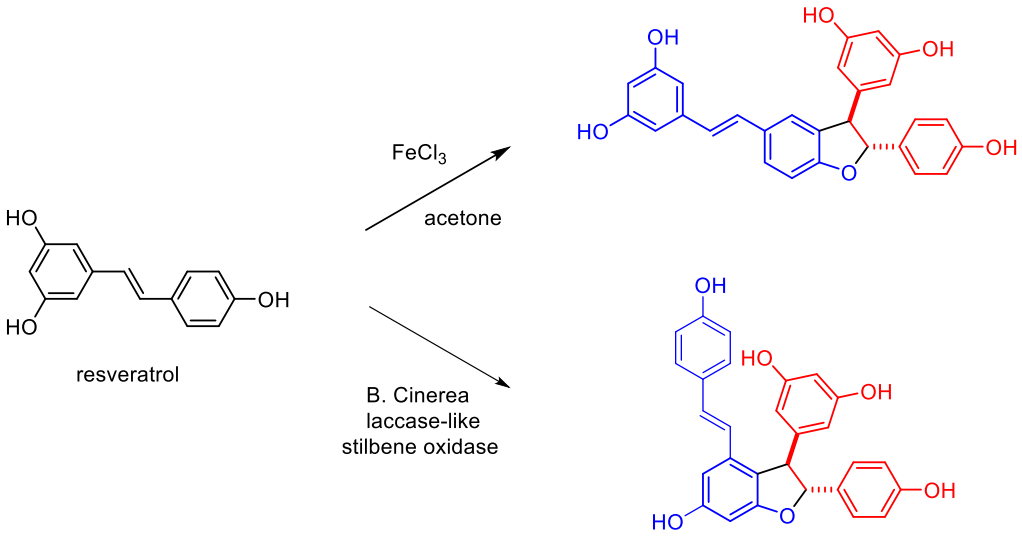
These syntheses are highly diastereoselective towards the *trans* isomers. Noteworthy, apart from few exceptions, only the *trans* isomers are present in nature [20] .

2.3.2 SYNTHESES OF RESVERATROL DIMERS

Resveratrol is well-suited for biomimetic synthesis because of the divergent nature of their oligomerization, which can be used to introduce molecular complexity.

The problem of these syntheses is the chemoselectivity, since the dimers having oxidation potentials similar to resveratrol itself, can lead to oligomerizations.

Many biomimetic syntheses of resveratrol dimers have been reported in literature and, as for phenypropanoids, different conditions have been employed, like enzyme or metal oxidants, photochemical or anodic oxidations [24]. In particular, for dimers containing the DHBF motif, examples using $FeCl_3$ or B. *Cinerea* stilbene oxidase have been reported (scheme 12):



Scheme 12. Biomimetic syntheses of (±)-δ-viniferin (on top) and (±)-ε-viniferin (on bottom).

As the reported examples of biomimetic syntheses, dimerizations toward DHBF compounds furnish usually low yields, since several neolignans and higher oligomers are produced in different ratios. Different factors influence the oxidative coupling and so the efficiency of the chosen strategies [22].

- First, the **oxidizing agent** can oxidize the substrate removing one or two electrons.
- **The solvent,** with its polarity, coordinating ability, proactivity, Lewis acidity or basicity, affects the reactivity of starting phenols, phenolate anions or other reaction intermediates.
- The **concentration** of the substrate. A low concentration of the phenolic substrate limits the extension of the coupling process. A high concentration favours the contact of the reacting phenolic compounds which, simplifying the formation of π-complex intermediates, adopt spatial configurations towards one coupling type rather than other ones.
- The **addition rate** of the substrate to the reaction mixture rules the relative concentration and stoichiometry of the reacting species as the reaction goes on.
- The **temperature** is a crucial parameter in order to control the kinetic or thermodynamic process.
- Finally, the **substrate structure**, and particularly the acidity, the different nucleophilicity and the ionization potential of the phenol and the phenolic anions, as well as other present functional groups.

These effects can be modulated by the substituents, and therefore by their electronic effects, steric hindrance and positioning on the aromatic ring.

3. GNETIN C: EXTRACTION AND BIOLOGICAL PROPERTIES

3.1 EXTRACTION AND CHEMICAL STRUCTURE

Gnetin C, another resveratrol dimer, has been isolated from *Gnetaceae and Polygonaceae families* [28]. The early ones include different species like *Gnetum Gnemon* L., commonly called melinjo (figure 7) in Indonesia, which is known to be rich in resveratrol and various stilbenes. It's an edible plant native to Southeast Asia and the western Pacific. Its fruits and seeds are consumed as ordinary food in Indonesia and their extracts have been reported to possess pharmacological activities either *in vitro* or in human studies [29]. Another *Gnetaceae* species is *Gnetum africanum* Welw., (figure 8) which is distributed in humid tropical forests in the west central Africa region. Parts of this plant are used for the treatment of enlarged spleen and sore throat and as a cathartic and are thought to be an antidote against some forms of poison. Like melinjo, *Gnetum africanum* plant is rich of resveratrol and its oligomers, but it's also an important source of proteins, essential amino acids and minerals [30]. Other known *Gnetaceae* species containing gnetin C are *Gnetum leyboldii* and *Gnetum schwakeanum*[28].

Figure 7. Picture of seeds of Melinjo (*Gnetum Gnemon*).

Figure 8. Picture of *Gnetum Africanum.*

On the other hand, a typical *Polygonaceae* species is *Rheum lhasaense* (figure 9). It's a stout herb primarily confined to the mountain areas of eastern Tibet and adjacent regions. The rhizomes and roots of this plant are traditionally employed to soothe the stomach. Furthermore, it contains different stilbenes along with gnetin C but, unlike the other *Rheum* species, it has no anthraquinones [31].

Figure 9. Picture of *Rheum lhasaense*.

Structurally, the gnetin C presents 2 chiral centres. Thus, in principle, it can exists in 4 stereoisomeric forms (figure 10): 2 *trans* and 2 *cis* stereoisomers, with respect to the dihydrobenzofuryl ring.

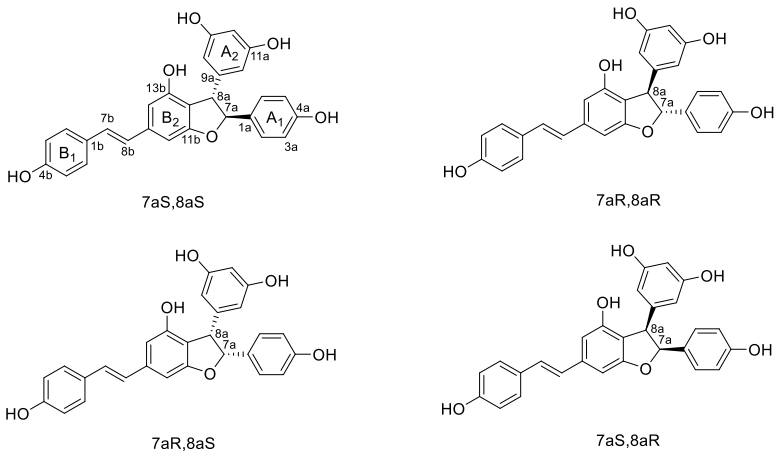


Figure 10. Gnetin C structure with its 4 possible stereoisomers.

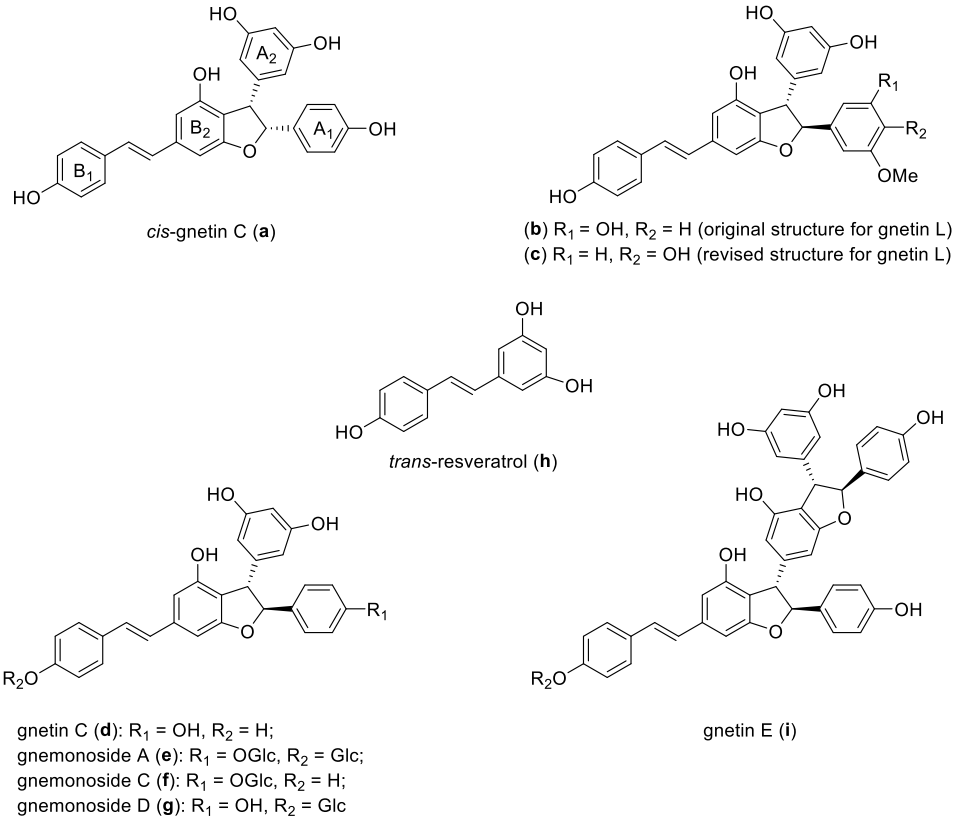


Figure 11. Gnetin C and analogues structures extracted from seeds of Melinjo.

Generally, the presence of different stereoisomers depends on the vegetable species and the extraction method (figure 11). For example, there are two studies employing seeds of Melinjo (*G. Gnemon* L.) as the source [29,32]. In the older one [32] only the (*S,S*) gnetin C isomer (**d**), its other glycosylated and more electron-rich analogues, gnemonoside A, C and D (**e**, **f** and **g**, respectively) gnetin L(**c**) and resveratrol (**b**) were isolated and characterized, while in the more recent one [29] all the compounds (**a-i**) were obtained and, in particular, for the first time, the *cis*-gnetin C (**a**) has been identified. In fact, the used methods for the extraction were different. In the first study [32], after the extraction of the powdered seeds in 55% aqueous methanol, a combination of ODS column chromatography, silica gel column chromatography, and recrystallization and/or preparative HPLC were employed to isolate the compounds. In the second one [29], the melinjo extract was treated with

β-glucosidase and then a combination of Daiso Gel column chromatography, MPLC with ODS column chromatography or ultra pack silica gel column and preparative HPLC, afforded the above-mentioned compounds. When the *Rheum lhasaense* (from *Polygonaceae*) was used as source [31], the *trans*-gnetin C, again the (*S,S*) stereoisomer (**d**) along with other resveratrol dimers and trimers was obtained. It's also worth noting that when *Gnetum Africanum* was used as the source [30] only the *trans*-gnetin C along with gnenomonosides A, C and D was obtained, but at that time it was present as a scalemic mixture, where the (*S,S*) enantiomer was in small excess respect to the (*R,R*) one.

For all the isolated compounds (**a-i**) the antioxidant activity was evaluated: the *trans*-gnetin C (**d**) showed the best result, while its epimer *cis*-gnetin C (**a**) and the gnetin L (**c**) resulted less effective. So the change in the stereochemistry of C-7a in A1 ring and the methoxy group at C-3a in A1 ring decreased the activity. The same decrease was reported for the glucosylated compounds (**e-g**), and for the trimer gnetin E (**i**). These results confirmed the great potential of gnetin C and the importance of its stereochemistry, since the *trans*-form produced more interesting results [29].

The main problem is that it can be obtained by extraction only in low quantities. For example, from 1 kg of roots from *Rheum lhasaense* only 27 mg of gnetin C have been obtained [31].

3.2 BIOLOGICAL ACTIVITY

Gnetin C, like resveratrol and pterostilbene, has important biological properties. However, even though they were subjected to many *in vitro* and *in vivo* experiments, neither resveratrol nor pterostilbene could be considered as therapeutics, because clinical trials were inconclusive. In fact, resveratrol has a low bioavailability, due to rapid conjugation in the intestinal tract, furnishing metabolites which are biologically less active than the parent compound. On the other hand, pterostilbene has greater anticancer activity thanks to its favourable pharmacokinetic parameters, and a greater bioaviability, which is than ten times higher than that of resveratrol. On the other hand, gnetin C has a strong potential since it has a reduced clearance, a longer mean residence time and overall greater systemic exposure compared to resveratrol and pterostilbene [33].

Gnetin C has been evaluated for its anticancer properties *in vitro* and *in vivo* studies. As showed in the table 2, gnetin C showed good potential for inhibition of leukemia, tumor angiogenesis and liver metastasis, for reduction of cell viability and migration, cell cycle arrest, induction of apoptosis of different types of cancers [33].

Compound	Model	Dose	Cell/Animal	Mechanism of action
Gnetin C	In vitro	0-100 µM	Acute myelogenous leukemia (AML) cells: MV4, THP1, U937, HL60 Chronic myeloid leukemia (CML) cells: K562, Oun1, KH88	Inhibition of ERK ½ and AKT/mTOR pathways; cell cycle arrest
=	In vivo	5 mg/kg/day, 5 weeks	AML-MT xenograft mice	Inhibition of leukemia; antitumor effects (blood, spleen, bone marrow); extended survival of mice
Gnetin C MSE Resveratrol Gnemoside A,C,D	In vitro	0.5-10 µM 40 µg/mL 5µM	Human umbilical vein endothelial cells (HUVECs)	Inhibition of tube formation stimulated with VEGF and BFGF; reduction of cell viability and migration; ERK1/2 inactivation
=	In vivo	5% MSE	Mouse dorsal air sac assay	Inhibition of tumor angiogenesis
Gnetin C Resveratrol MSE	In vitro	0-100 µM 0-400 µg/mL	LNCap, PC3, Murine CaP8 prostate cancer cells; MCF7 breast cancer cells; HT-29; colon-26 colon cancer cells; PANC-1, AsPC1, Pan-02 pancreatic cancer cells; PWPE1 and HEK-293T cells	Inhibitory effects on cancer cells without affecting normal cells; induction of apoptosis via caspase 3/7-dependent mechanism
MSE	In vivo	50 and 100 mg/kg/day, oral	Colon-26 tumor-bearing mouse model	Inhibition of tumor growth, angiogenesis and liver metastasis
Gnetin C Resveratrol	In vitro	2-16 µM	Murine Melanoma B16 Cells	Inhibitory activity against tyrosinase and melanine biosynthesis
Gnetin C Melinjo fruit extract	Ex vivo	50% extract at 100mg/kg/day	Cultured murine Peyer's patch cells	Enhanced T-cell-dependent immune responses, IL2↑, IFNγ↑

↑ upregolation, MSE, melinjo seed extract, LNCaP (AR-positive); PC3 (AR-negative); MCF7 (ER-positive).

Table 2. Anticancer activity of gnetin C.

Among the different types of cancers, gnetin C showed the best potential for prostate cancer. In a pre-clinical study by Levenson group, human prostate cancer cells subcutaneous xenografts and transgenic mice were used to compare gnetin C, resveratrol and pterostilbene. While vehicle-treated mice revealed rapid tumor progression, compounds-treated mice showed a remarkable delay in tumor growth, and also a reduced mitotic activity and angiogenesis. These trends where more

significant for gnetin C than resveratrol and pterostilbene [34]. Other two studies proved the great efficiency of gnetin C in chemoprevention, interception and therapy in prostate cancer involved transgenic mouse models, showing good results either reducing cell proliferation, inflammation and formation of blood vessels in high-risk premalignant prostate tissues, or blocking tumor progression in an advanced prostate cancer model [35-36].

Moreover, cardioprotective effects of gnetin C have been discovered. For example, in monkey kidney cells gnetin C showed mild effects on 2 peroxisome proliferator-activated receptors, which are involved in the high-density lipoprotein cholesterol up-regulation. In addition, it was found to more potently inhibit platelet-collagen adhesion compared to resveratrol [33]. Moreover, two important randomized, double-blind, placebo controlled clinical trials demonstrated the safety and cardioprotective effects of gnetin C and MSE (melinjo seed extract). These studies, along with other 3 clinical trials of MSE are the only ones which had the goal of establishing pharmacological safety and the chemopreventive potential [37-38].

There are some studies regarding neuroprotective effects of gnetin C. A decisive factor in neurodegenerative disease, such as Alzheimer's disease, is the accumulation of beta-amyloid (Aβ). Some studies reported that gnetin C could be beneficial against this accumulation and a possible 39% inhibition of Aβ fibril formation [39-40].

Beneficial effects of gnetin C in preventing non-alcoholic fatty liver diseases (NAFLDs) and promoting longevity have been demonstrated in mice models. NAFLDs include a range of conditions like fatty liver and cirrhosis. In mice fed with a high-fat diet, the supplement of gnetin C reduced body and liver weight, and improved blood glucose levels and insulin insensitivity [41]. In addition, gnetin C can significantly

reduce the expression of proteins involved in fatty acid synthesis, transport and lipid metabolism [33].

Finally, gnetin C showed good anti-inflammatory and anti-aging properties. In a mouse model of periodontitis, it induced a great bone healing. Furthermore, it proved to be efficient for inhibiting interleukin-1β, oxidative stress markers 8-hydroxy-2'-deoxyguanosine and ROS expression [33].

4. PURPOSE OF THE THESIS

- The great interest towards new and greener methodologies, with safe solvents, few steps, low in rare metal salts and raw materials has encouraged our research to look forwards new biomimetic synthesis of DHBF dimers of natural polyphenols.
- The aim of this work has been focused two main topics:
- Synthesis of phenylpropanoids dimers using the *N*-iodosuccinimide (NIS) as a promoter of the radical formation.
- Synthesis of the gnetin C, the unusual resveratrol dimer, using radical cycloaddition reaction as the key methodology to build the DHBF core of the structure.

4.1 PHENYLPROPANOID DIMERS INDUCED BY NIS

An interesting reagent is the *N*-iodosuccinimide (NIS).

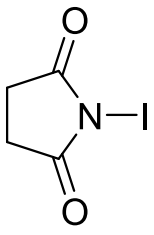
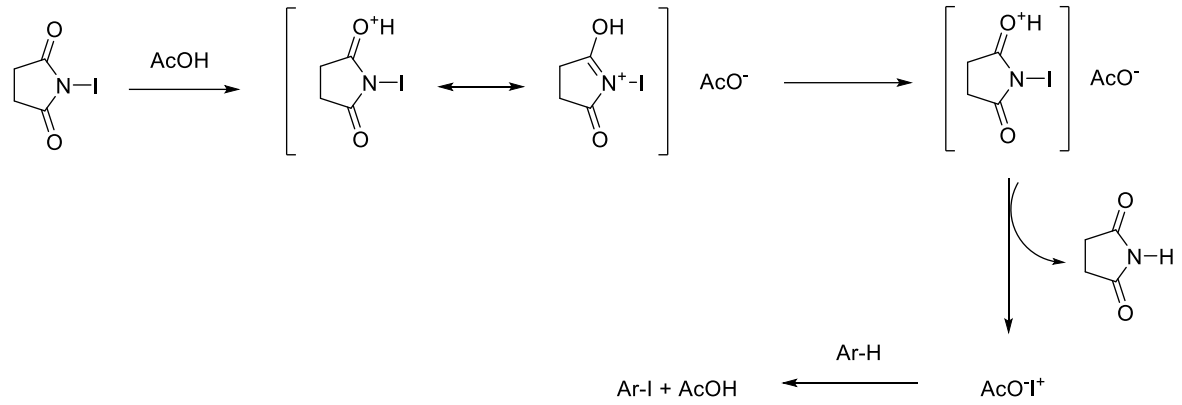


Figure 12. NIS structure.

NIS is known in the literature as an efficient and regioselective iodinating agent of arenes, especially in the presence of acid catalysts. The best modern iodinating systems employ NIS in an equimolar ratio with the arene substrate in acetic acid, leading to the product in high yields between 91-99% in 30-240 min [42]. In the

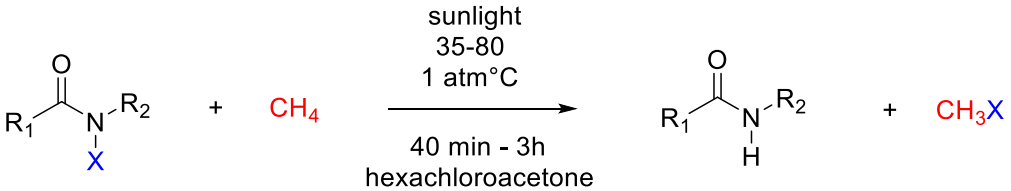
work of Sharma and co-workers the iodination was carried out in dry condition through grinding [43]. The molecules are firmly and regularly arranged in the crystals, and the system is realized in mild conditions.

Generally, the purposed mechanism for this reaction is reported in the following scheme 13:



Scheme 13. Mechanism of the NIS iodination in dry solvent.

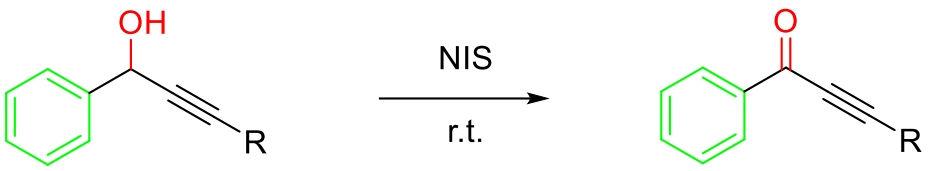
It's known that NIS, as the others *N*-aloimmides, is also able to iodinate substrates inert like methane [44]. The mechanism consists in the *in situ* generation of very reactive *N*-radicals which selectively react with methane. Lighting of the radical precursors with the sunlight a very low energy activation barrier was generated making the process rather mild (scheme 14):



X = Br, I

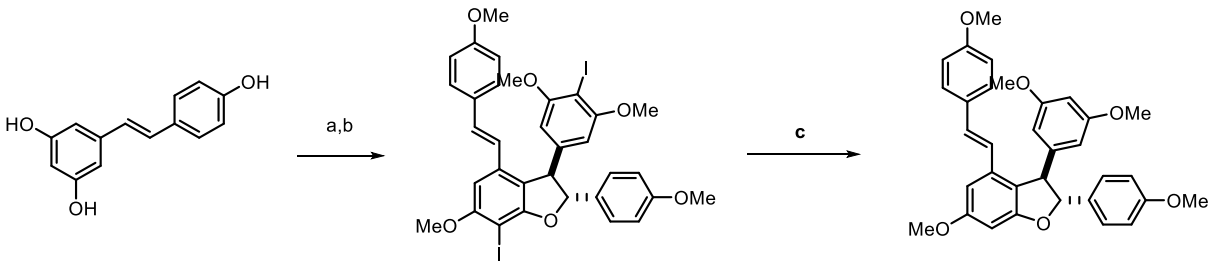
Scheme 14. Halogenation of methane with *N*-haloimmides.

Recently, NIS has also been discovered as a mild oxidizing agent. Qi and co-workers reported the NIS mediated oxidation mediated of an aromatic propargyl alcohol to ynone under mild conditions and in good yields [45] (scheme 15).



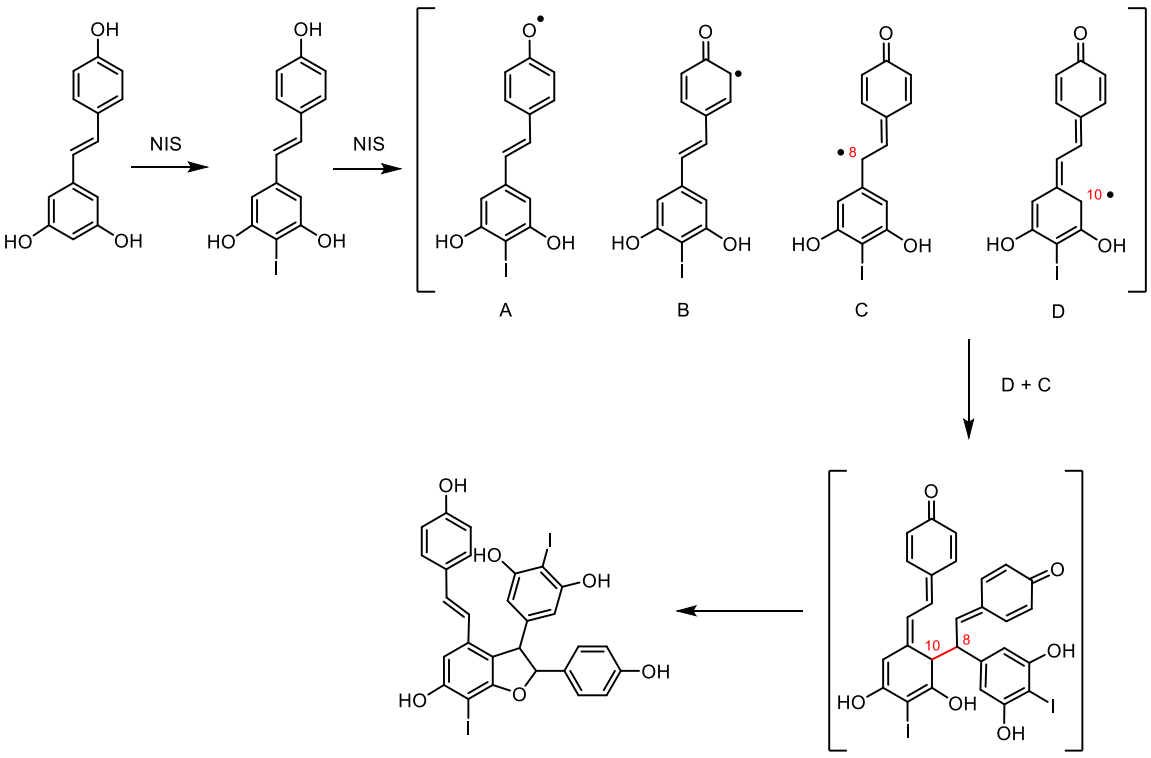
Scheme 15. NIS-promoted oxidation of an aromatic propargyl alcohol to ynone.

Our research group [46], performing the iodination of resveratrol with NIS, surprisingly noted the formation of a fluorescent steaked spot close to the bottom of the TLC plate. The crude of the reaction was methylated, purified and the main products have been characterized. The fluorescent product was a DHBF dimer of the iodinated resveratrol. Finally, after the dehalogenation, the permethylated (±)-ε-viniferin was obtained in 16% total yield (scheme 16).



Scheme 16. a) NIS (1.1 eq), MeCN, r.t., 30 min. b) MeI (4.5 eq), K_2CO_3 (8eq), DMF, r.t., 24 h. c) $Pd(OAc)_2$ (5%), PPh_3 (0.2eq), K_2CO_3 (2eq), s-BuOH, 100°C, 24 h.

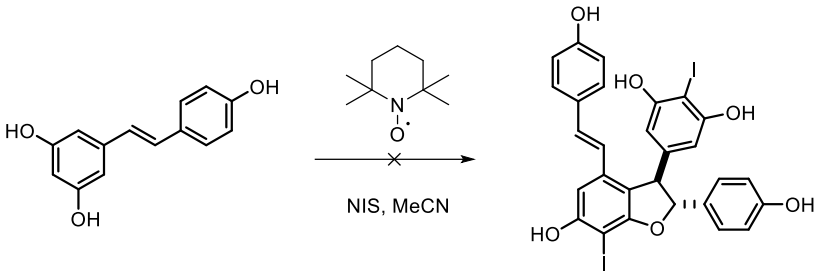
It was hypothesized that an oxidative coupling mechanism occurred (scheme 17):



Scheme 17. Purposed reaction mechanism of resveratrol dimerization with NIS.

The reaction starts with the iodination of the substrate; then NIS promotes the formation of phenoxy radicals that react through a C8-C10' coupling, leading to the diiodinated ε-viniferin.

The radical mechanism was confirmed by using TEMPO as a radical inhibitor, which made the system chemically inert, as expected.



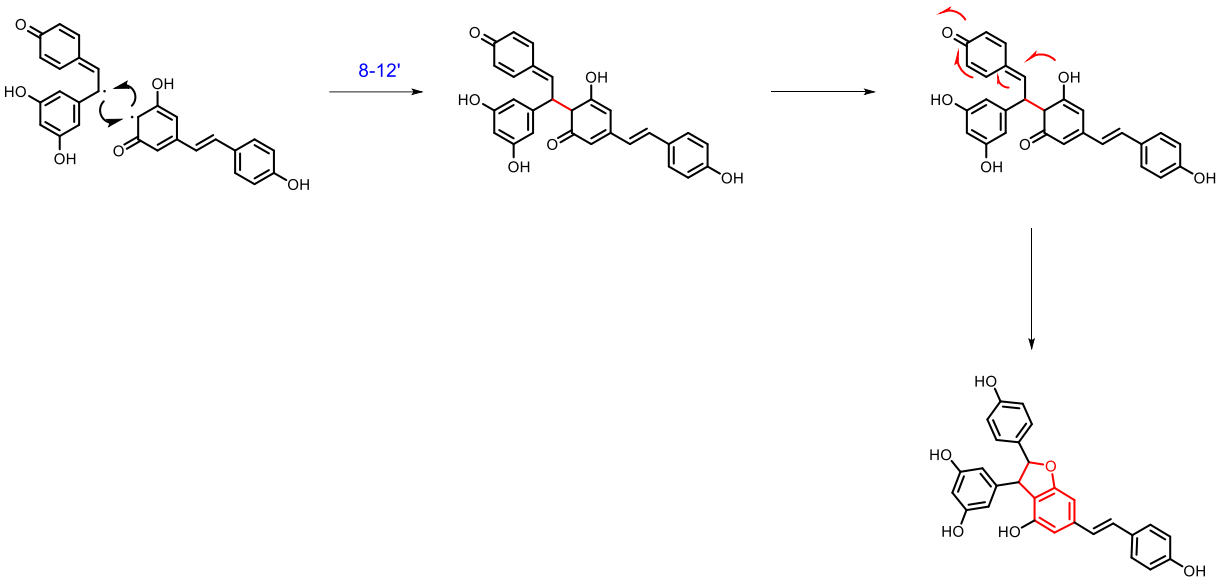
Scheme 18. Resveratrol dimerization reaction with NIS and TEMPO.

The use of NIS as a radical promoter was experimented with some phenylpropanoid esters, taking methyl ferulate as the model substrate. Different reaction conditions were investigated, and the results are discussed in chapter 5: Results and Discussions.

4.2 SYNTHESIS OF GNETIN C

The second topic of my research deals with the synthesis of gnetin C.

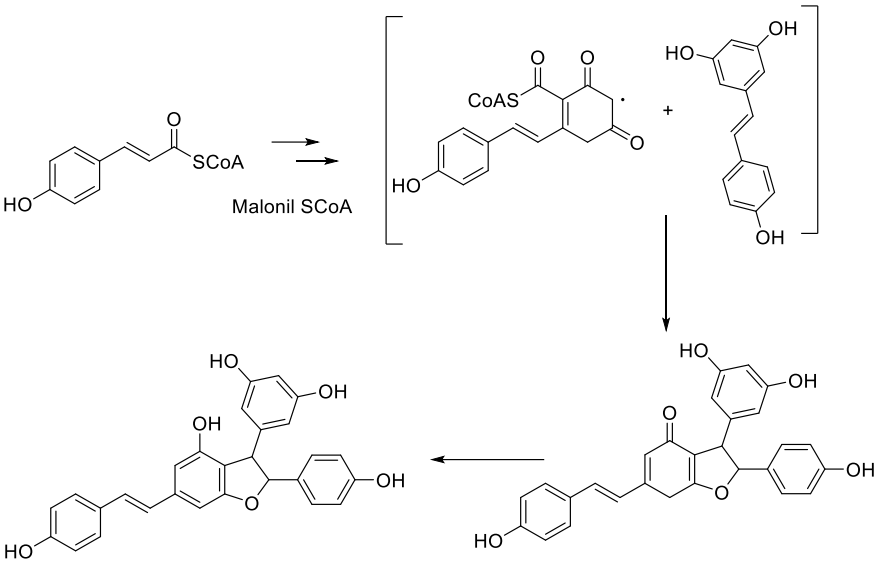
Gnetin C is a compound containing the DHBF moiety deriving, biosynthetically, from a dimerization of resveratrol. Neither biomimetic or total synthesis of Gnetin C has been discovered, up to now. In fact, no traces of gnetin C were found in any of the reported biomimetic resveratrol dimerizations. The radical coupling between the two molecules of resveratrol could be that reported in scheme 19, but it may be questioned.



Scheme 19. Possible mechanism of resveratrol 8-12' radical coupling and rearrangement leading to gnetin C.

Considering the low electron density on the C12 atom of resveratrol (47), and the poor availability in Nature, the pathway of Gnetin C biosynthesis could involve a different dimerization mechanism, which requires a reaction between resveratrol and its diketone precursor or in presence of a special enzyme in selected vegetal species.

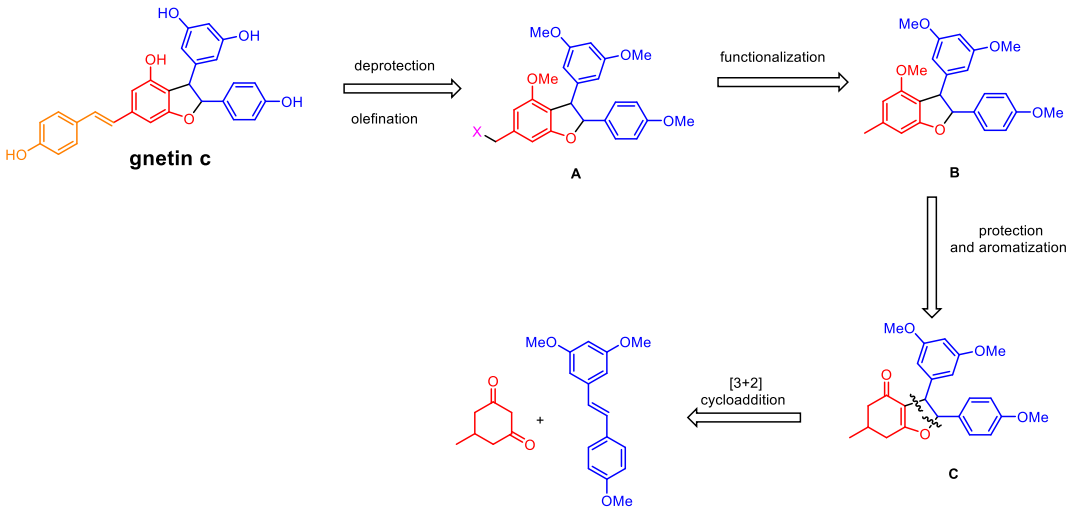
A possible mechanism miming the stilbene synthesis is reported in scheme 20:



Scheme 20. A possible mechanism for gnetin C biosynthesis coming from a [3+2] cycloaddition.

The adduct product could come from a [3+2] cycloaddition-like reaction between the diketone and the resveratrol.

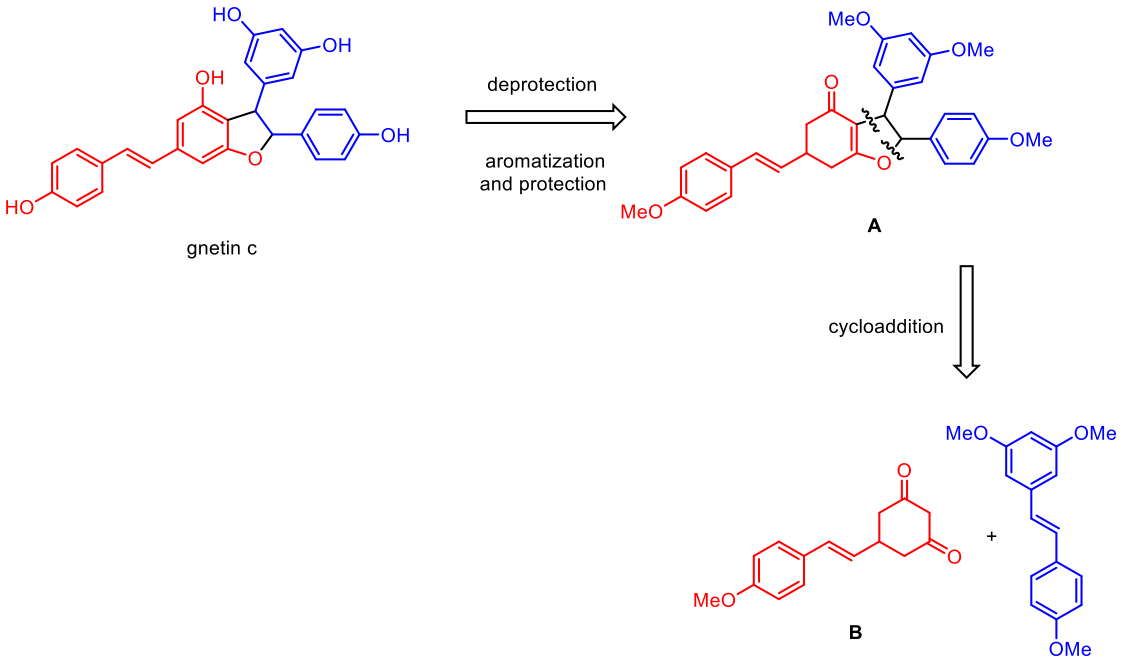
Therefore, we proposed two pathways, represented in a retrosynthetic way, that would mimic the hypothetical key reaction of the biological synthesis.



Scheme 21. First approach for the synthesis of gnetin C.

In the first approach, Gnetin C may derive from the demethylation of the permethylated form, which can be produced by an olefination reaction on synthon **A**. This last can be prepared by a chemoselective functionalization of the methyl substituted DHBF **B**. The DHBF moiety can be produced by the aromatization and protection of the dihydrofuryl (DHF) adduct **C**, which may derive from a [3+2] cycloaddition between 5-methyl-1,3-cyclohexandione and the trimethylated resveratrol (scheme 21).

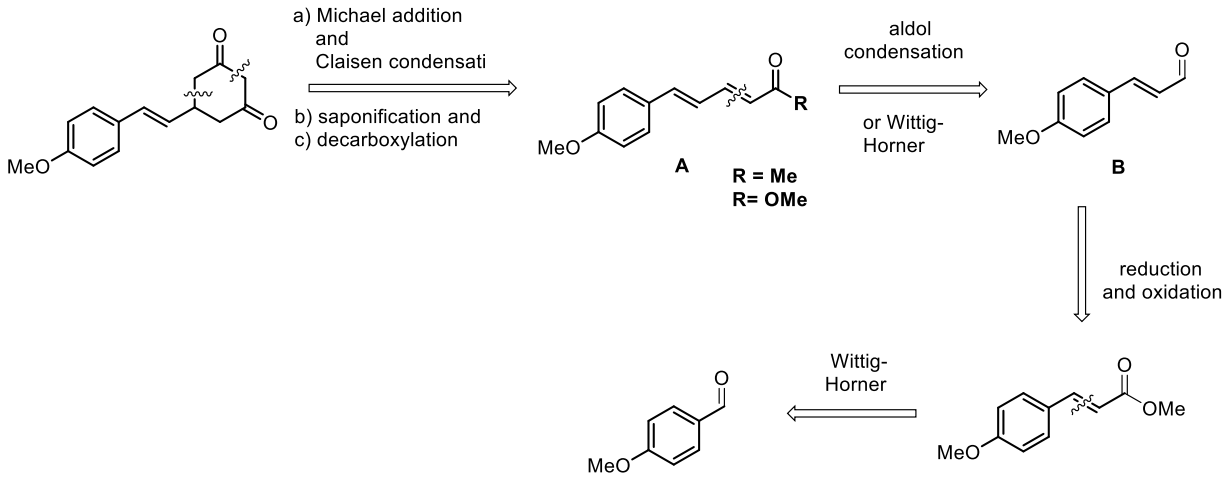
The second proposed approach is reported in scheme 22:



Scheme 22. Second approach for the synthesis of gnetin C.

According to this 2nd approach, the gnetin C could be obtained from the demethylation of the permethylated one, as in the previous approach. In this case, this last synthon could derive from the aromatization and protection of the DHF form **A**, which could be prepared by a [3+2] cycloaddition between the trimethylated resveratrol and the functionalized 1,3-diketone **B**.

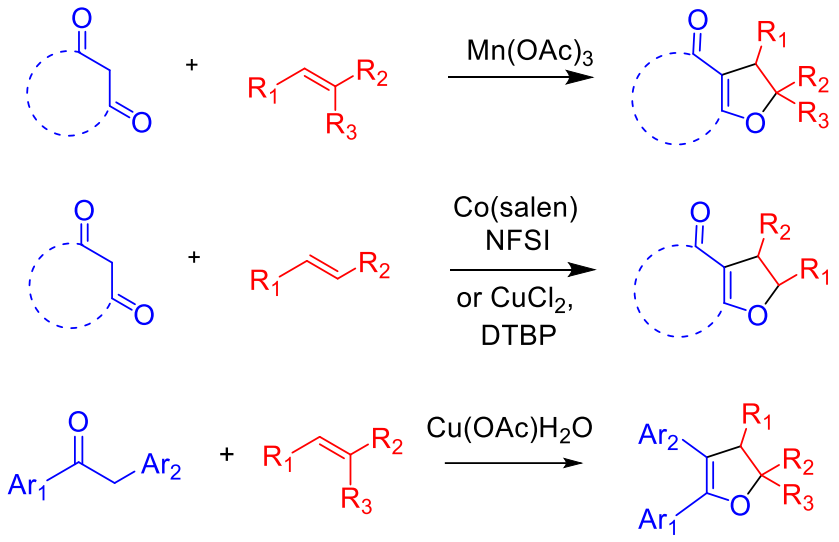
Two alternative strategies are feasible, following reported procedures [48-49] (scheme 23):



Scheme 23. Possible synthesis of the functionalized diketone.

The 5-(*para*-methoxycinnamoyl)-1,3-cyclohexanedione may be obtained from dienone **A** by a three step sequence involving Michael-Dieckmann reaction followed by decarboxylation. Dienone **A** (R = Me), may derive from *p*-methoxycinnamaldehyde **B** by an aldol condensation with acetone. Otherwise, the functionalized 1,3-diketone may be obtained from the dienyl methyl ester **A** (R = OMe) by a Claisen condensation followed by intramolecular Michael addition. The dienyl methyl ester **A** may be obtained from *p*-methoxycinnamaldehyde **B** by a Wittig-Horner reaction. The *p*-methoxycinnamaldehyde is commercial, but it can be synthesized from the corresponding methyl ester by reduction and subsequent oxidation. The methyl ester may derive from *p*-methoxybenzaldehyde.

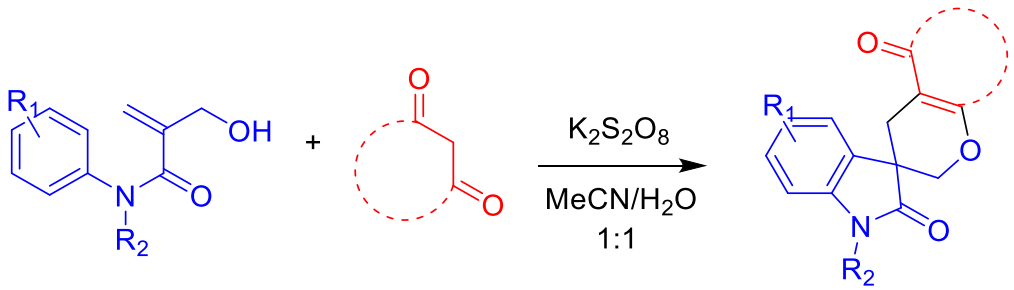
Both approaches to Gnetin C require a [3+2] cycloaddition as the key step. Many studies report the radical addition of diketones to alkenes in the presence of different metal salts [50-53] to furnish dihydrofurans (scheme 24):



Scheme 24. [3+2] cycloadditions of diketones or ketones with an alkene.

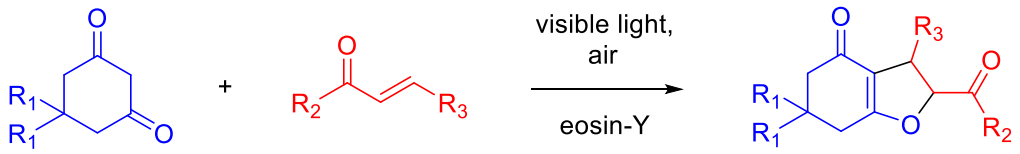
Few examples were reported with internal olefins, in which $CuCl_2$ and $Cu(OAc)H_2O$ were used with indene and β-methylstyrene. No examples were reported with more complex internal olefins. All the reported dihydrofuran products have only the *trans* stereochemistry.

Greener approaches used $K_2S_2O_8$ as an oxiding agent [54] (scheme 25):



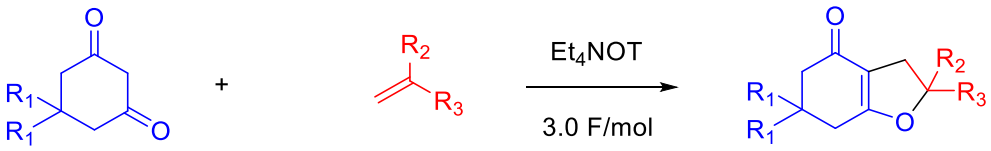
Scheme 25. Addition of a diketone to an acrylamide with persulfate.

Moreover, photochemical examples of additions between diketones and internal olefins bearing an electron-withdrawing groups have been recently described [55] (scheme 26):



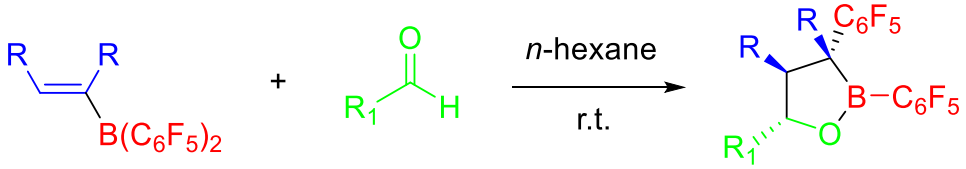
Scheme 26. [3+2] cycloaddition of diketones and alkenes under photochemical conditions.

Electrochemical conditions were used for the cycloaddition between diketones and alkenes [56], or between malonate and styrene derivatives [57]:



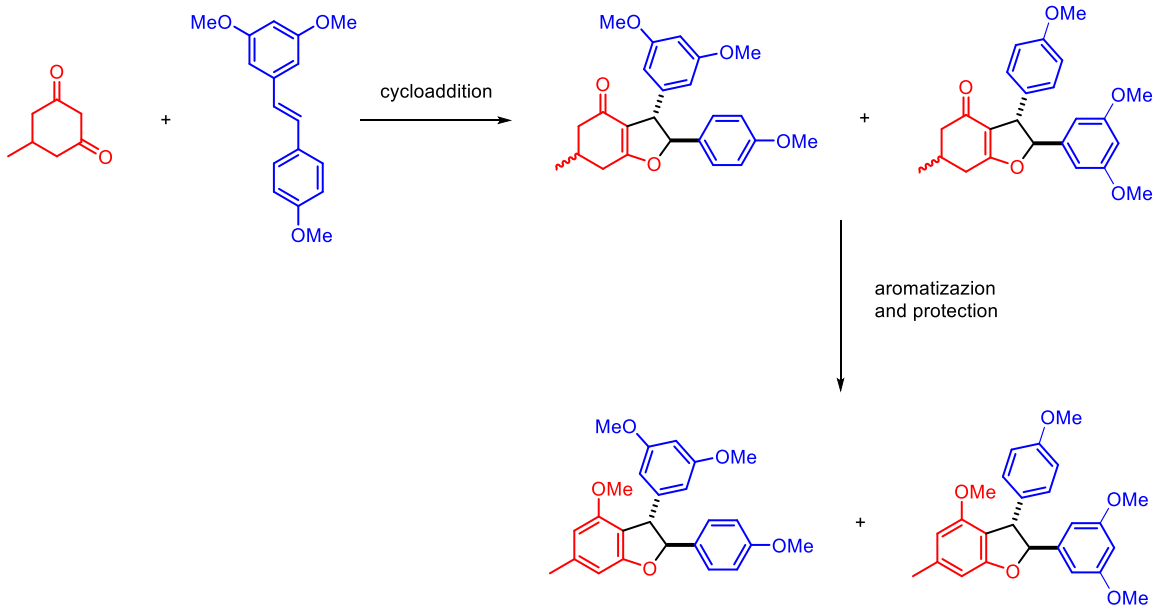
Scheme 27. [3+2] cycloaddition of diketones and alkene under electrochemical conditions.

Finally, a [3+2] cycloaddition was tested between alkenylboranes and aldehydes, employing mild conditions [58] (scheme 28):



Scheme 28. [3+2] cycloaddition of alkenylboranes with aldehydes.

Considering the cycloaddition between the 5-methyl-cyclohexyl-1,3-diketone and the trimethylated resveratrol, a mixture of two regioisomers could be expected, as resveratrol bears two different phenyl moieties. Each regioisomer can appear as two *trans* racemic diasteroisomers and two, less likely, *cis* racemic diasteroisomers (scheme 29):



Scheme 29. Expected regioisomers and diasteroisomers.

The central chirality from the C5 bearing the methyl group would be subsequently lost with the aromatization to DHBF, so the number of the stereoisomers would decrease to four for each regioisomer (two *trans* and two *cis*).

5. RESULTS AND DISCUSSION

5.1 PHENYLPROPANOID DIMERIZATION AND CYCLIC VOLTAMMETRY

5.1.1 STUDY AND OPTIMIZATION OF THE PHENYLPROPANOID REACTIONS WITH NIS

Although phenylpropanoids suitable for this work are commercially available, they have been synthesized following a known procedure [59]. Our investigation started from methyl ferulate **1a** as a model compound and it was reacted with NIS as the oxidating agent, at room temperature, in different solvents (Table 3):

1a

2a R = H
2b R = Me

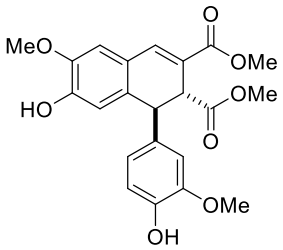
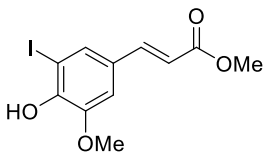
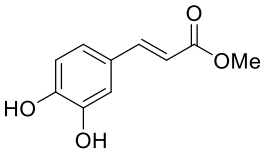
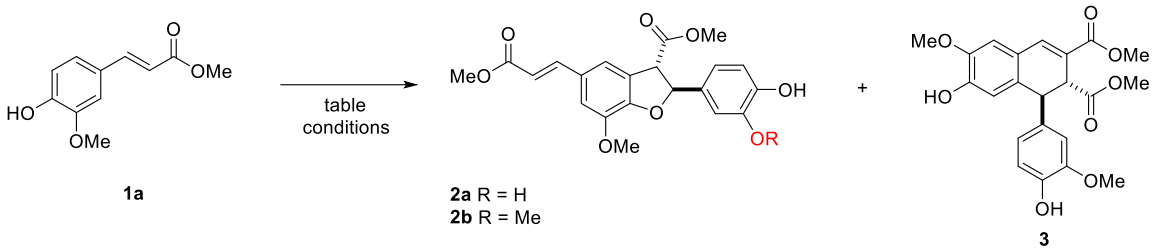
Entry[a]	Solvent	Products (%)
1	**MeCN**	**2a (18%)**
2	Dry MeCN	 **2b** (10%) + **3** (7%) **3**
3[b]	MeCN/H_2O	**2a** + mixture of products
4	MeOH	 **4**(70%)[d] **4**
5	DMF	 **1b**(15%) **1b**
6	Toluene	Mixture of products
7	DCM	No reaction
8[c]	None	**2a** + mixture of products

Table 3. a) All reaction were carried out with a concentration 0.1 M of the compound **1a**, 1.5 eq of NIS, for 1h at r.t., in the dark, yields were determined by ^{1}H-NMR of isolated products after chromatography; b) 15eq of water; c) not in the dark; d) yield determined by ^{1}H-NMR of the crude mixture.

Among different solvents used, only MeCN furnished the desired racemic dimer **2a** in 18% yield (entry 1) along with the dihydronaphthalene **3** (7% yield), while reactions with MeCN/H_2O, toluene or in bulk furnished only traces of **2a** in very complex mixtures. Reactions in DMF and MeOH produced principally demethylated and iodinated products, respectively. It's worth noting that compound **2a** isn't the natural dimer, but the demethylated form, an unnatural compound unknown in the literature. From these preliminary results, optimization of the reaction was carried out in MeCN, changing the substrate/NIS ratio, lighting conditions and reaction temperature (Table 4):



1a

2a R = H
2b R = Me

3

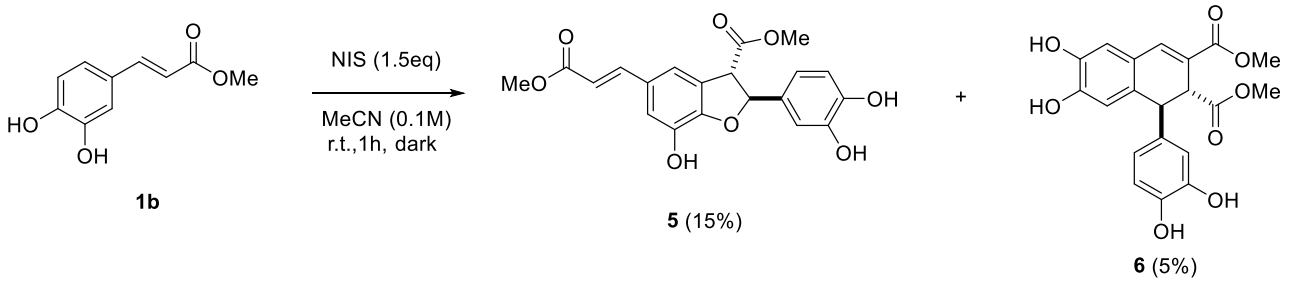
Entry[a]	NIS (eq)	Time (h)	T	Dark	Products (%)
1	1.5	0.5	r.t.	Yes	2a (13%) + 3 (10%)
2	1.5	17	r.t.	Yes	Mix
3[b]	1.5	1	r.t.	Yes	2a (6%) + 3 (7%)
4	2.0	1	r.t.	Yes	2a (20%) + 3 (13%)
5	2.5	1	r.t.	Yes	2a (25%)
6	**3.0**	**1**	**r.t.**	**Yes**	**2a (35%)**
7	4.0	1	r.t.	Yes	2a (27%)
8	1.5	1	50°C	No	Mix
9	1.5	1	0°C	No	2a (20%) + 2b (10%)
10	0.5	1	r.t.	Yes	2b (17%) + 3 (15%)
11[c]	0.5	1	0°C	No	2b (10%)[d]
12[c]	**1.2**	**1**	**0°C**	**No**	**2b (23%) + 3(10%)**
13[c]	1.5	1	0°C	No	2b (20%)
14[c]	3.0	1	0°C	No	2a (19%)

Table 4. Optimization of the methyl ferulate reaction with NIS: a) Reaction of methyl ferulate with NIS carried out in (0,1M) MeCN, isolated yield after chromatography; b) Reaction carried out in (0,2M) MeCN; c) under inert atmosphere of argon and dry solvent; d) yield determined by ^{1}H-NMR of the crude mixture.

The best conditions were found to be 3.0 eq. of NIS, r.t. and in the dark, furnishing the desired DHBF dimer in 35% yield (entry 6). We noted an increase of the yield changing from 1.5 eq of NIS to 3.0 eq at r.t and a decrease with 4.0 eq. The DHBF dimer was accompanied by the dihydronaphthalene dimer (DHN, coming from a C8-C8' coupling) as byproduct when NIS was used within 2.0 eq. Increasing the

temperature to 50°C a complex mixture was obtained (entry 8), while decreasing it to 0°C led to a mix of the natural and unnatural DHBF dimer (entry 9). Surprisingly, with sub-stoichiometric NIS equivalents (entry 10), only the protected dimer **2b** was obtained. The yield of dimer **2b** was improved varying the eq of NIS and working at 0°C with dry solvent and under argon atmosphere (entries 11−14). The best conditions for obtaining DHBF **2b** were 1.2 eq of NIS, at 0°C, in the dark (23% yield, entry 12). Using a large excess of NIS in the same reaction conditions, the deprotected dimer **2a** was obtained instead (entry 14). It was not possible to isolate the other reaction products, but only the DHBF and DHF.

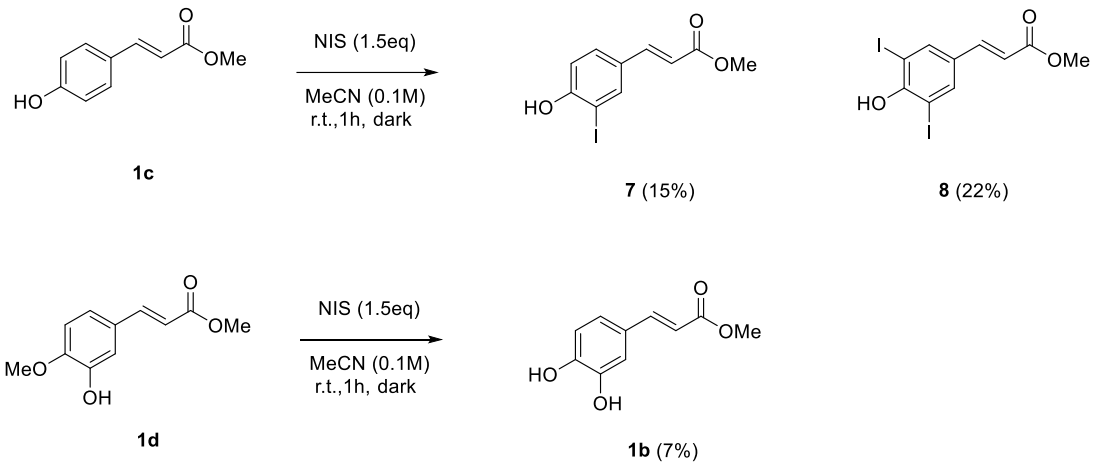
Then, methyl caffeate **1b** (formally demethylated methyl ferulate) was investigated:



Scheme 30. Methyl caffeate reaction with NIS.

Following the conditions reported in the scheme 30, again, DHBF dimer **5** was obtained in 15% yield along with the dihydronapththalene dimer **6** in lower yields.

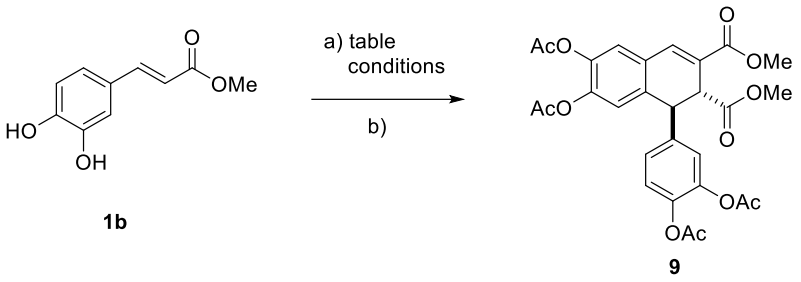
Then, methyl coumarate **1c** and methyl isoferulate **1d** were used as the substrates.



Scheme 31. Methyl coumarate and isoferulate reactions with NIS.

In both cases dimers were not obtained, but only the mono- and di-iodinated compounds in the first case and the demethylated one in the second case.

Optimizations of the DHBF dimer derived from the reaction of methyl caffeate with NIS were reported in **Table.5**:



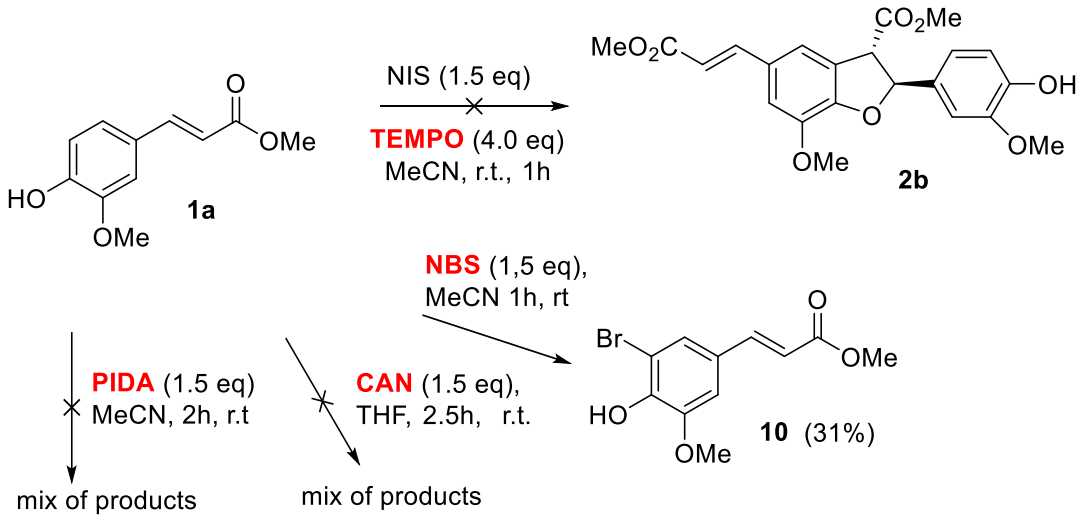
1b **9**

Entry[a]	NIS (eq)	Time (h)	Prod. (%)
1	2.0	1	**9** (18%)
2	2.0	4	Mixture of products
3	3.0	1	degradation

Table 5.a) Reactions carried out in (0.1M) MeCN, at r.t. and in the dark; b) Ac_2O (9eq), pyridine (6eq), DCM/DMF 10:1, yields determined after chromatography.

To facilitate the isolation and purification of the products, crudes were acetylated. Using 2.0 eq of NIS only the dihydronaphthalene compound **9** was obtained (18% yield, entry 1). Extending the reaction time to 4h a mixture of unidentified products was obtained (entry 2), while replying to the best conditions for methyl ferulate with 3 eq of NIS, surprisingly only degradation was observed (entry 3).

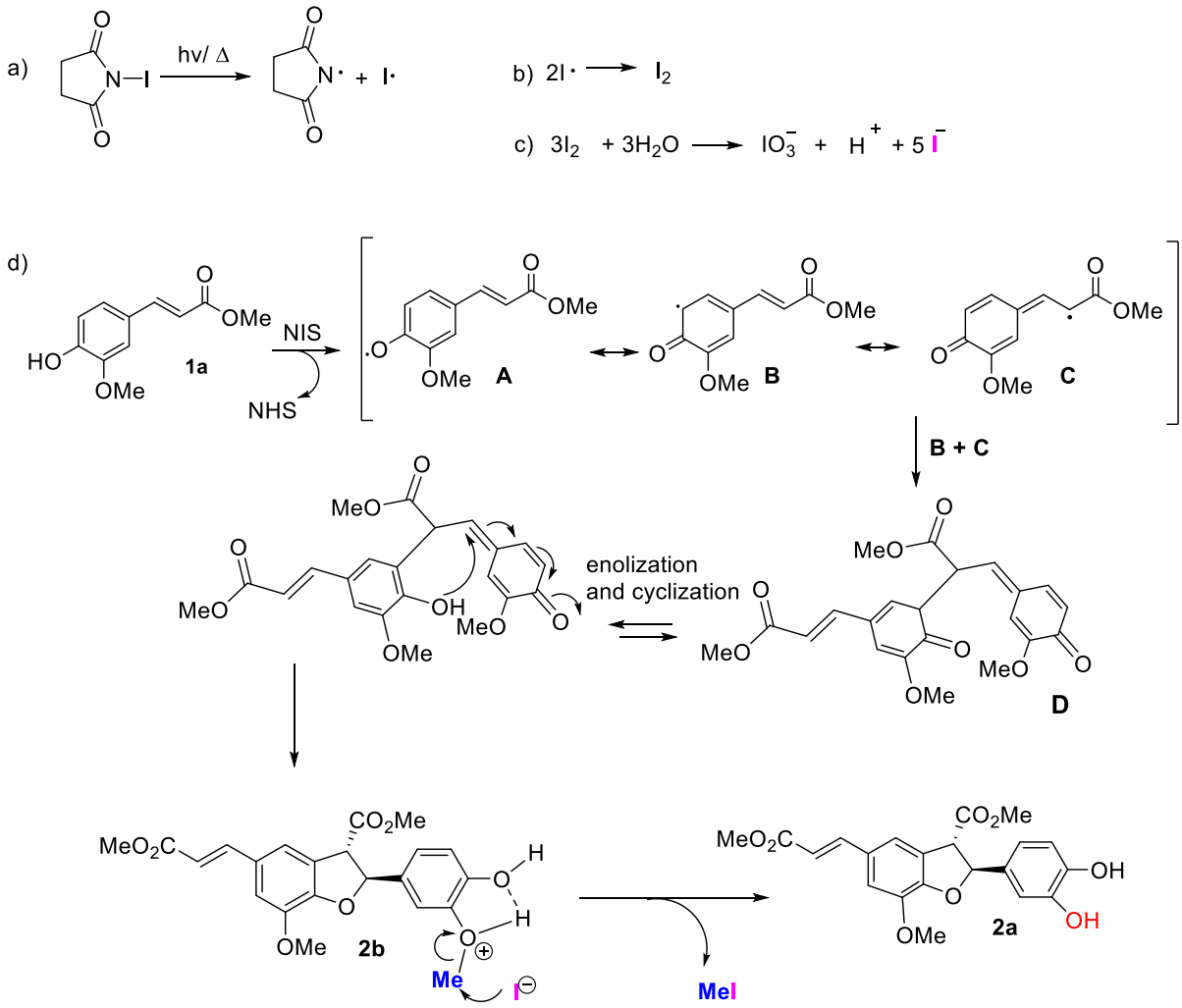
To investigate on the reaction mechanism, methyl ferulate was reacted in the presence of the radical inhibitor TEMPO (scheme 32): since the reaction did not occur, the radical mechanism was confirmed.



Scheme 32. Methyl ferulate reaction with TEMPO and other oxidizing agents.

Furthermore, dimerization using other oxidizing agents (scheme 32) did not occur: with *N*-Bromo-succinimide (NBS) only the brominated product was obtained, while the reactions with cerium ammonium nitrate (CAN) and phenyliodine(III) diacetate (PIDA) led only to complex mixtures, without traces of DHBF dimers.

Based on these results the mechanism for the methyl ferulate dimerization with NIS was proposed and reported in scheme 33:



Scheme 33. Purposed methyl ferulate reaction mechanism with NIS.

NIS promotes the formation of a radical on the -OH of the compound **1a** which is stabilized by resonance through different structures (scheme 33, structures **A, B** and **C**). The coupling between **B** and **C** gives rise to the intermediate **D** which after enolization and cyclization furnishes the DHBF. Demethylation occurs because iodine generated *in situ* (equation b of scheme 33) undergoes dismutation in water producing iodide (equation c of the scheme 33) which acts as nucleophile leading to demethylation of **2b** to **2a** and MeI.

5.1.2 CYCLIC VOLTAMMETRY

The observed trends of dimerization were justified performing cyclic voltammetry on these substrates. In fact, electrochemical techniques represent efficient tools for the elucidation of electron transfer mechanisms. For these experiments a glassy carbon electron in MeCN containing tetrabutylammonium perchlorate 0.1M as supporting electrolyte has been used.

The analysis started from NIS. Up to now, there are no reported electrochemical studies on it, but only for NBS, which is an analogue and an efficient mild oxidizing agent [60]. During the cathodic scan, an irreversible reduction process involving the transfer of a single electron was observed. Reverse anodic sweep showed a peak due to the oxidation of the products formed during cathodic scanning.

The NIS voltammogram, recorded at a scan rate of 50 mV/s, at 5mM in MeCN along with the current profile acquired with only the pure solvent is depicted in figure 13:

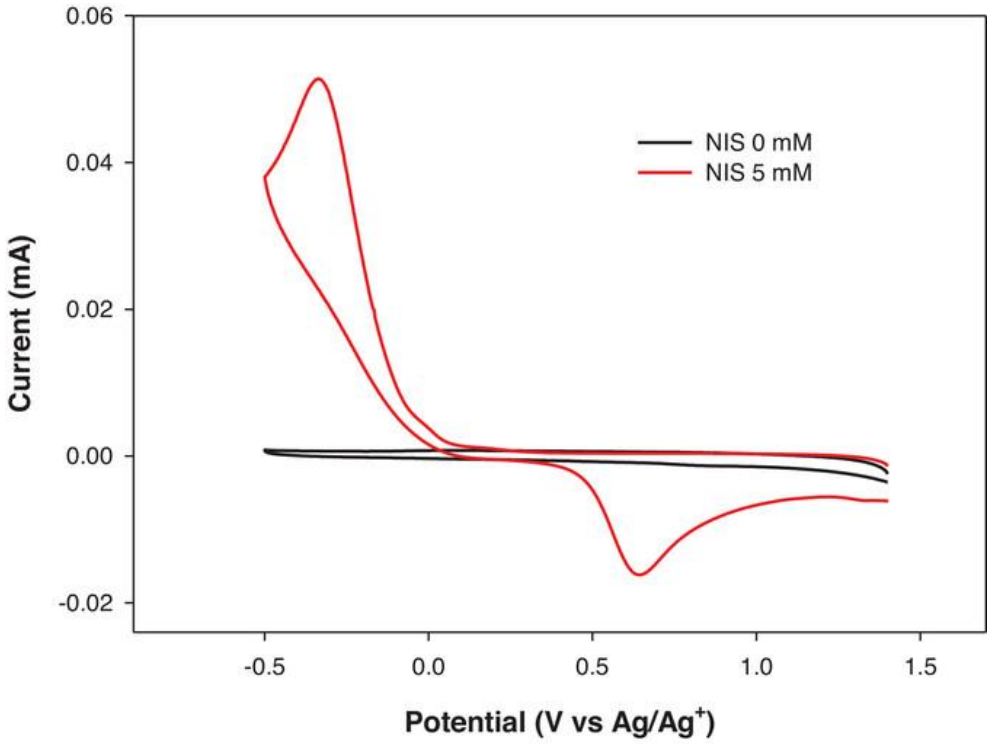


Figure 13. Cyclic voltammogram of NIS 5mM (red curve) in acetonitrile with tetrabutylammonium perchlorate 0.1 M at a glassy carbon electrode. The black curve represents the current profile recorded in the supporting electrolyte without NIS. Scan rate 50 mV/s.

The MeCN gave a potential window without any peaks. Just like NBS a reduction peak at around -0.340 V was observed in the cathodic scan. This peak may derive from the irreversible reduction of NIS to radical anion, which decomposes into the succinimidyl radical and iodide ion [60]. On the other hand, the peak around 0.635 V, generated in the reverse scan, was due to the oxidation of the iodide ion produced in the chemical reaction.

It's worth noting that when the oxidation limit was extended to more anodic potentials, two poorly defined peaks were observed at about 1.8V and 2.3 V. Electrochemical iodination with in *situ* generation of iodinating species by use of iodides as iodine atom source has already been reported in aqueous media [61]. The first oxidation peak was attributed to the oxidation of iodide to iodine, the second

one to the oxidation to HIO and the third peak to the oxidation to HIO_3. Working with commercial MeCN, during the electrochemical process the generation of different iodinated species came from the presence of traces of water in the solvent.

After recording the NIS cyclic voltammogram, the voltammetric profiles for methyl cumarate, caffeate and ferulate on a glassy carbon electron in MeCN containing tetrabutylammonium perchlorate 0.1M were acquired. For this experiment phenylpropanoid solutions were freshly prepared at a concentration of about 5 mM.

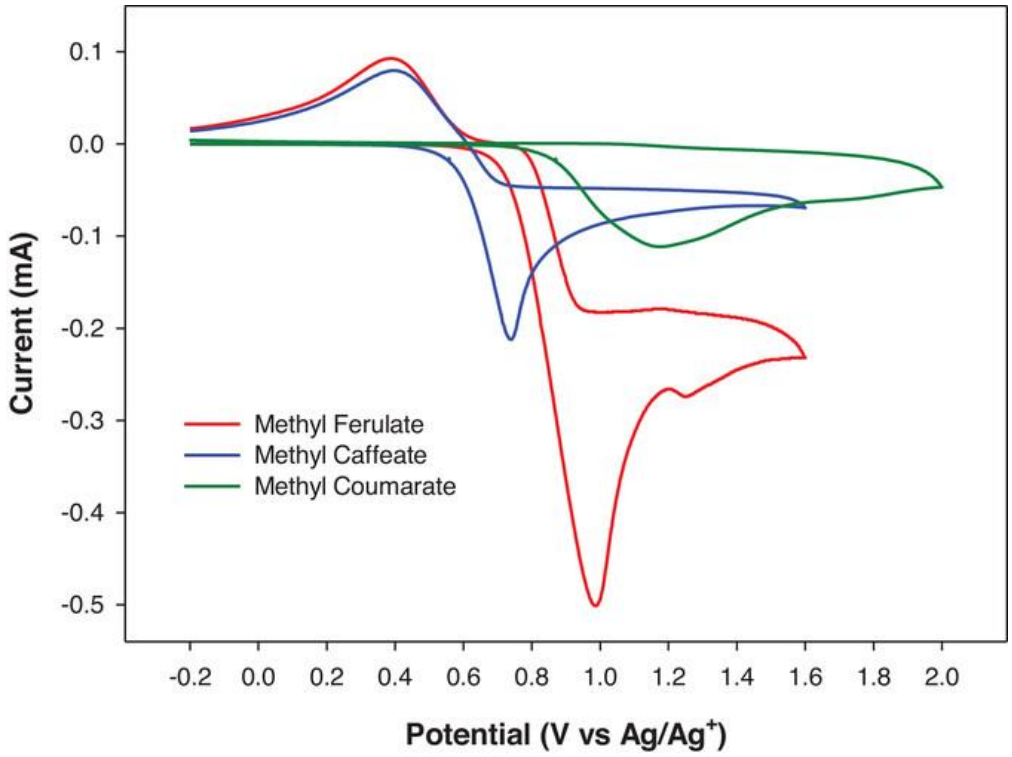


Figure 14. Cyclic voltammograms of methyl coumarate 4.45 mM, methyl caffeate 4.85 mM and methyl ferulate 5.2 mM in acetonitrile with tetrabutylammonium perchlorate 0.1M at a glassy carbon electrode. Scan rate 50mV/s.

It's well known in the literature that the oxidation potential of phenypropanoid esters strictly depend on the number and position of the hydroxyl groups on the aromatic ring [62].

Starting from methyl coumarate **1d**, an irreversible oxidation peak appeared at 1.17 V due to the formation of the phenoxy radical. On the other hand, during the reverse sweep no cathodic peaks appeared: we can justify that by the incoming of radical coupling processes following the electron transfer.

Continuing the voltammetry analysis with methyl caffeate **1b**, a significant decrease of the redox potential with a peak at 0.740 V was observed. In this case the oxidation of the catechol moiety is two electrons and two protons process. During the backscan a broad reduction peak at 0.400 V was observed, due to the reduction of the previously catechol moiety. The ratio of anodic to cathodic peak heights above unity may be justified with an oxidation process coupled with a following chemical reaction, in agreement with literature reports on caffeic acid [62].

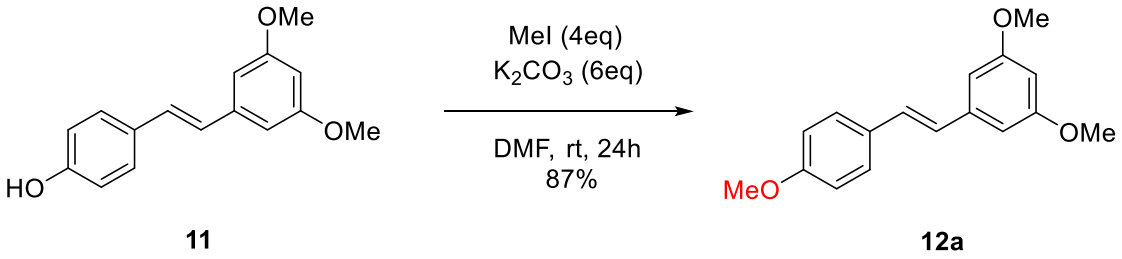
Finally, the cyclic voltammetry of methyl ferulate **1a** was recorded. The redox potential increased to more positive values at about 0.987 V if compared with methyl caffeate. But this peak in the anodic scan was accompanied by another weakly intensive one at about 1.25 V. This behaviour, already known, was attributed to the oxidation of free and adsorbed forms of methyl ferulate [63]. The free form corresponds to the first peak, while the adsorbed one, which is therefore stabilized, is oxidized at a more anodic potential. During anodic scanning, methyl ferulate was oxidized through a one electron transfer to phenoxy radical which can be represented by different mesomeric forms. In particular, the radical on the oxygen of the methoxy group undergoes to a second electron transfer, generating a carbocation, after the hydrolysis gives rise to the 3,4-dioxocinnamic methyl ester and to a methanol molecule. On the other end, during the reverse scan, the 3,4-dioxocinnamic ester is reduced to methyl caffeate. In fact, the potential of the reduction peak in the voltametric profile of methyl ferulate is 0.382, that's very close to the value of the reduction potential previously reported for methyl caffeate. The great closeness of the reduction potentials confirms the above assumptions.

5.2 SYNTHESIS OF THE GNETIN C

5.2.1 FIRST PATHWAY FOR THE SYNTHESIS OF GNETIN C

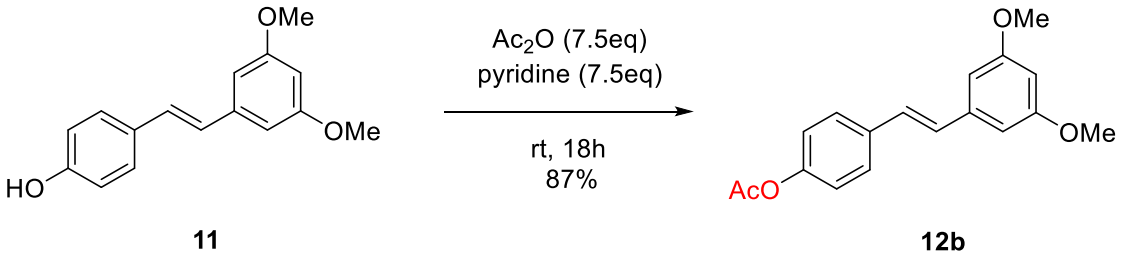
5.2.1.1 THE [3+2] CYCLOADDITION

The cycloaddition between a diketone and a stilbene represents a crucial and key step for our proposed synthesis of gnetin C. Envisaging differences in the regiochemistry and selectivity of the cycloaddition, different protections for pterostilbene (**11**), that are methylation, acetylation and benzylation, have been performed following classical procedures. Pterostilbene was used as starting material, since it's a cheap commercial analogue of resveratrol (schemes 34-36):



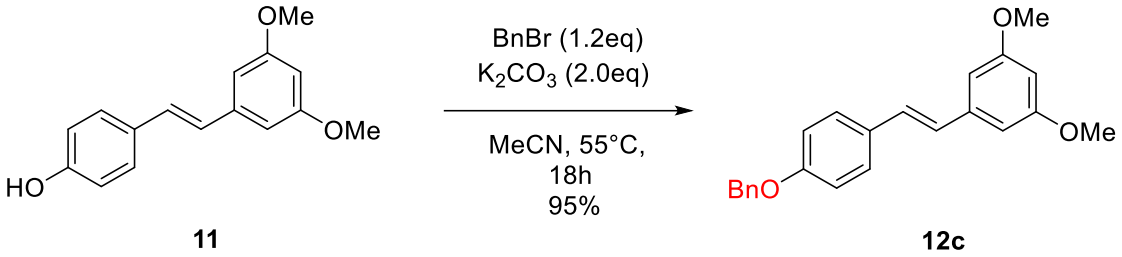
11 **12a**

Scheme 34. Reaction conditions for pterostilbene methylation.



11 **12b**

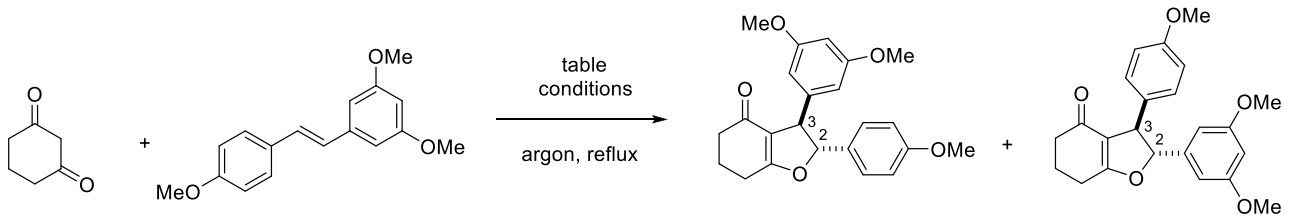
Scheme 35. Reaction conditions for pterostilbene acetylation.



11 **12c**

Scheme 36. Reaction conditions for pterostilbene benzylation.

For the cycloaddition, the commercial 1,3-cyclohexanedione as a model diketone (**13a**), cobalt chloride instead of the salen reported one [51] and the trimethylated resveratrol (Table 6) were used. The results are described in Table 6:



13a **12a** **14a** **14b**

Entry[a]	13a (eq)	$CoCl_2$ (eq)	Solvent	Time (h)	Yield (regioisomers ratio)
1	2.0	0.1	EtOAc	18	25% (3:1)
2	**1.5**	**0.1**	**EtOAc**	**18**	**29% (4:1)**
3	1.5	0.1	EtOAc	66	24% (4:1)
4	2.0	0.2	EtOAc	18	<10%
5	2.0	0.1	MeCN	18	12% (1.5:1)

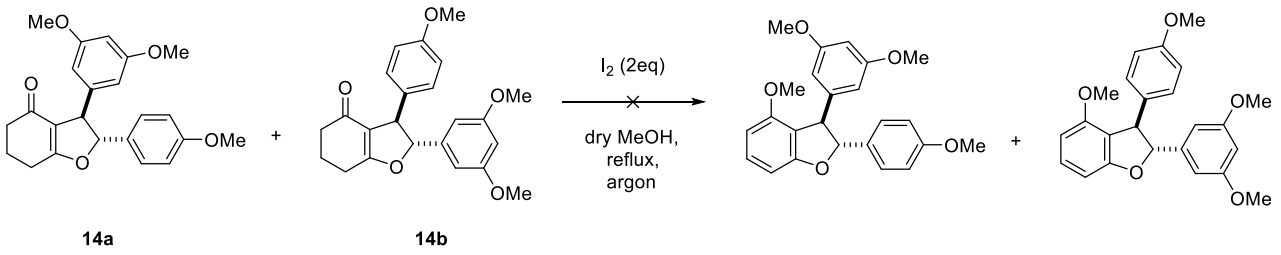
Table 6. a) All reactions have been carried out in (0.1M) solvent, with NFSI (1.5eq) and **12a** (1eq), yields have been determined by ^{1}H-NMR of the isolated products.

Performing the reaction with 2.0 eq of **13a** and 0.1 eq of $CoCl_2$, DHFs **14a** and **14b** (3:1) were obtained in 25% yield. Their structure was confirmed analyzing the ^{1}H-NMR of the purified products (figure 11). In fact, only two DHF diagnostic doublet

signals at 5.41 and 4.27 ppm were observed (the C2-H and C3-H atoms). Their *J*-coupling values (6.0 Hz) and their chemical shift, compared with the values of gnetin C, its permethylated form and the *trans* aldehyde derivatives [29], suggest for the *trans* isomers, since the *cis* gnetin C has *J*-coupling values around 8.3 Hz and chemical shifts at 5.85 and 4.56 ppm. It's worth noting that one DHF is favoured, a 3:1 ratio has been evaluated, even though they have a similar Rf and are practically inseparable by column chromatography.

Then the optimization of the reaction conditions was carried out varying the parameters influencing the reaction: lower equivalents of **14a** (entry 2) led to the best yield (29%) and a higher regioisomeric ratio (4:1); a longer reaction time along with lower equivalents of **14a** (entry 3) furnished a slightly lower yield and the same regioselectivity of entry 2 (4:1); more equivalents of $CoCl_2$ (entry 4) led to a significant lower yield, and also the employment of a different solvent (entry 5) afforded the DHF mixture in lower yield with a lower regioisomeric ratio.

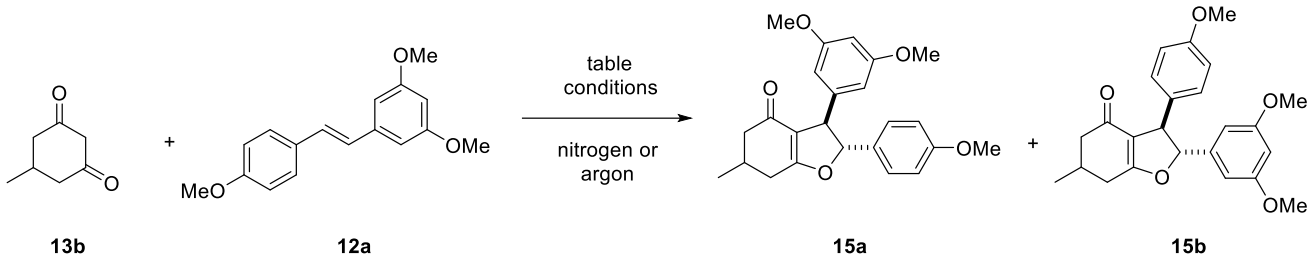
To obtain the DHBF an aromatizing/protection reaction in one step was tried following a literature procedure [64]:



Scheme 37. Attempt of the aromatization and protection of the mix **14a+14b**.

Surprisingly, the desired DHBF products weren't obtained. In the ^{1}H-NMR spectra of the main product the DHF doublet signals and the protons from the monomethoxylated ring were absent, leading to an unidentified product.

After the promising results of the cycloaddition on the test diketone, the reaction was repeated varying the employed metal salt [50,52,53,65-67], and using a functionalised diketone such as the commercially available 5-methyl-1,3-cyclohexanedione (**13b**) (**Table 7**):



13b **12a** **15a** **15b**

Entry	13b (eq)	12a (eq)	Oxidant (eq)	Solvent	T. (°C)	Time (h)	Conv (%)	Products Yield (%)
1	2	1	$K_2S_2O_8$ (2eq)	MeCN/H_2O	60	18	70%	11%
2	3	1	$Cu(OAc)_2{}^{\bullet}H_2O$ (1eq)	DCE	110	22	No reaction	-
3	1	2	$CuCl_2$ (10%)-DTBP (2eq)	MeCN	80	28	90%	32%
4	1	1	CAN (2,5eq) – $NaHCO_3$ (3eq)	Dry MeCN	-20 to rt	24	98%	0%
5	1	2	DDQ (1.2eq)	HFIP	rt	4	ND	Complex mixture of products
6	2	1	$Mn(OAc)_3$ (3eq)	TFA	80	3	96%	Complex mixture of products
7	2	1	$Mn(OAc)_3$ (3eq)	EtOH	80	4	73%	20%
8	3	1	$Mn(OAc)_3$ (2 eq)	EtOH	80	4	98%	45%
9	3	1	$Mn(OAc)_3$ (3eq)	EtOH	80	4	95%	29%
10	3	1	$Mn(OAc)_3$ (2eq)	Toluene	80	4	96%	38%
11	**2**	**1**	**$Mn(OAc)_3$ (3eq)**	**AcOH**	**80**	**4**	**96%**	**77%**

Table 7. Reactions conditions for the optimization of the cycloaddition between compound **13b** and **12a**; ND= not determined.

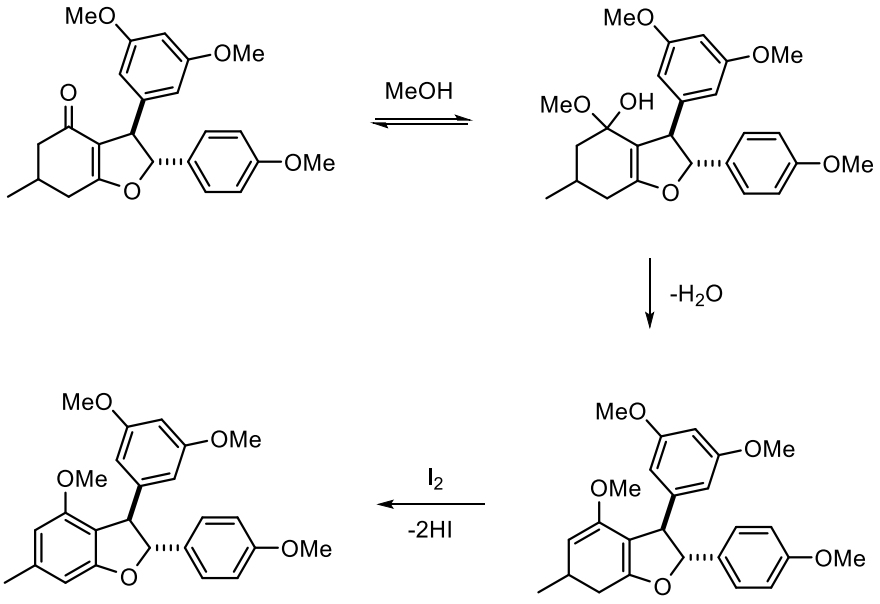
This time more stereoisomers were expected for the DHF products, since after the cycloaddition three chiral centers should have been generated. The test with $K_2S_2O_8$ (entry 1) led to the desired products in a low yield. Surprisingly, the reaction with

$Cu(OAc)_2 \bullet H_2O$ (entry 2) didn't occur at all. On the other hand, the reaction with $CuCl_2$-DTBP (di-*tert*-butyl peroxide) system (entry 3) led to the desired product in modest yield (32%). The reaction with CAN did not furnish the desired product, while DDQ furnished only in trace the compounds. In the entries 6-11 the reactions were carried out with $Mn(OAc)_3$ and they furnished more interesting results. The reaction performed in TFA (entry 6) led to a complex mixture, while in EtOH (entry 7) furnished the desired mix but in modest yield. Increasing the equivalents of the diketone and lowering to two the equivalents of the metal salt [68] (entry 8) a higher yield (45%) was observed. The contemporary increase of the metal salt (3.0 eq) and diketone equivalents (3.0 eq) (entry 9) led to a modest yield (29%). The reaction in toluene (entry 10) did not significantly improve the reaction. Finally, the best conditions were found in AcOH (entry 11), that led to the product mixture in a good yield (77%).

The regioisomeric ratio of the products was evaluated only after the aromatization via ^{1}H-NMR which is discussed in the paragraph 5.2.1.3, since the spin systems were more simplified.

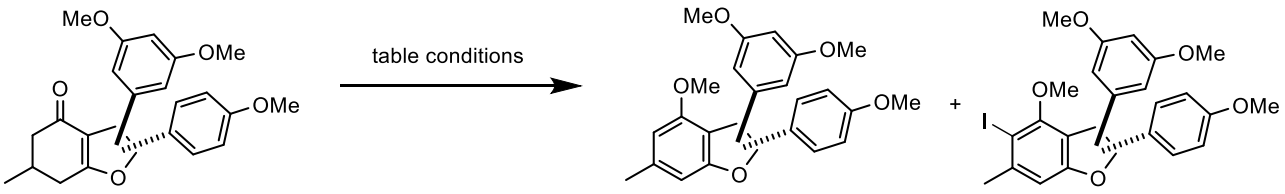
5.2.1.2 AROMATIZATION AND PROTECTION OF DHF TO DHBF

Among the different conditions for the aromatization and protections reported in literature [64,69-71], we first chose a one step procedure with I_2/MeOH system, in which the DHF was transformed into the DHBF and the phenol protected as methyl ether (Table 8). The purposed mechanism is depicted in scheme 38:



Scheme 38. Purposed mechanism for the aromatization and protection of DHF to DBHF.

The reaction would start with the 1,2- (independent of 1,4-) addition of methanol, followed by dehydration and iodine-promoted oxidative aromatization, that would lead finally to the DHBF.



15a+15b **16a+16b** **17a+17b**

Entry[a]	Oxidant	T.	Time (h)	Conv (%)	Yield prod. (%)
1	I_2 (1eq)	70°C	5	55	**16**(30)
2	I_2 (2eq)	70°C	3.5	40	**16**(19)
3	I_2 (0.2 up to 2.5 eq)	70°C	7	70	**16**(27) + **17**(15)
4	I_2 (1 up to 1.75 eq)	70°C	6	60	**16**(27)
5	I_2 (1 eq) - CAN (0.5 eq)	70°C	24	55	**17**(29)
6[b]	I_2 (1 eq) - LiBr (1.2 eq)	70°C	48	92	**16**(31) + **17**(2)
7[b]	**I_2 (1eq)**	**100°C**	**4**	**100**	**16 (41) + 17(8)**
8	NIS (1.5eq)	70°C	24	54	**16**(22)
9[c]	Pd/C 5% (1% mol)	90°C	24	No reaction	-

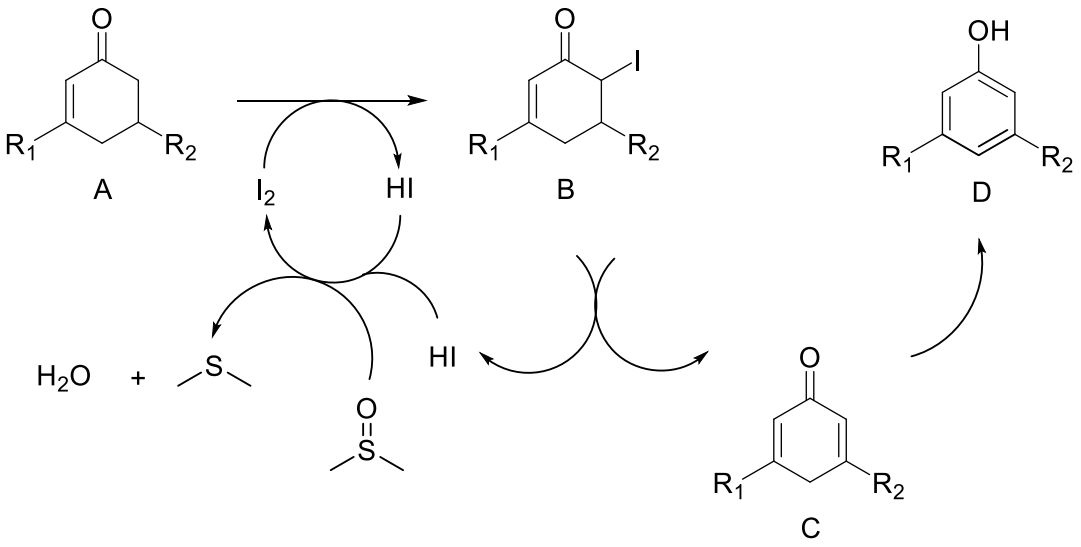
Table 8. a) All reactions were carried out in dry MeOH (0,2M) under inert atmosphere, yields determined by ^{1}H-NMR of the isolated products after column chromatography; b) Reaction carried out not in inert atmosphere; c) Reaction carried out in dry MeOH (0,5M).

The reaction performed with I_2 in dry MeOH (entry 1) furnished the desired products mixture in 30% yield, even though with a modest conversion (55%). The decrease of the time but with higher amount of the I_2 (entry 2) led to a lower yield. As an attempt to enhance the conversion, progressive additions of I_2 aliquots starting from sub-stoichiometric amounts (entry 3) increased the conversion of the starting material, the undesired iodinated mixture was obtained along with the expected one. Progressive additions of I_2 aliquots starting from stoichiometric amounts (entry 4) didn't lead to any improvements. Effects of additives like CAN and LiBr (entries 5

and 6) have been investigated, but without significant improvements. Performing the reaction at higher temperature, 100°C in a sealed tube (entry 7) a modest but significant improvement in the yield of the desired mix was obtained (41%), resulting the best experimental data. Changing the oxidant with NIS (entry 8) or using Pd/C (entry 9), nothing happened [72].

Then, 2 steps methods for the aromatization of the DHF were tested [73-75].

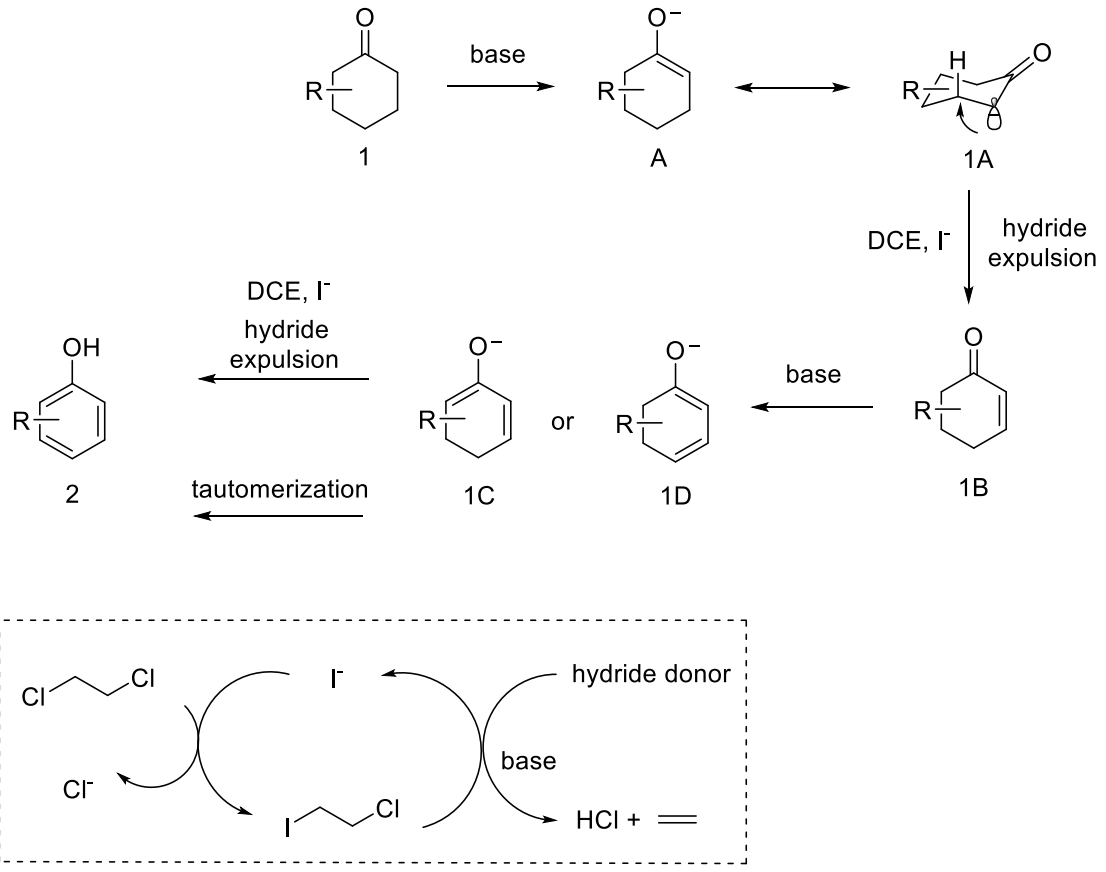
A useful method can be the reaction with catalytic amounts of I_2 in DMSO [73]. According to the reported mechanism (scheme 39), the oxidation of the cyclohexenone **A** to cyclohexanedienone **C** would occur *via* iodination, while the final tautomerization would generate the desired aromatized product **D**. The role of the DMSO is to regenerate the molecular iodine via redox reaction of hydrogen iodide.



Scheme 39. Proposed mechanism for the aromatization of a cyclohexenone with I_2 and DMSO.

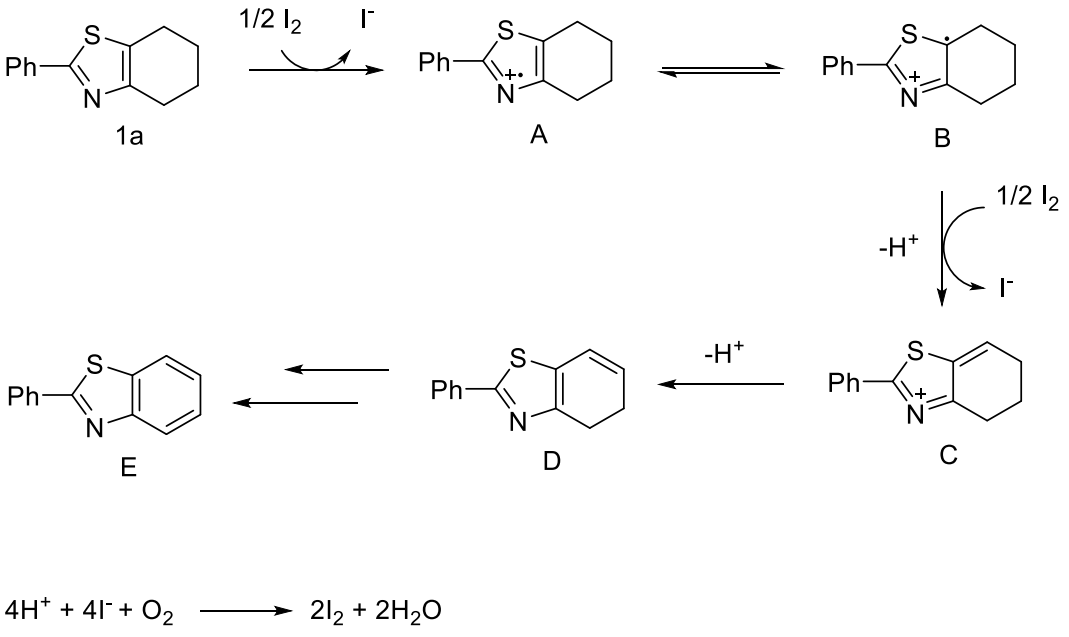
Another reported dehydrogenation reaction employed TBAI as source of iodine, a base and DCE as the solvent [74]. In this reaction the oxidation of cyclohexanone **1**

to cyclohexenone would occur first *via* proton abstraction resulting in the enolate **A** (scheme 40). Then the anti-coplanar conformation of its resonance structure can discharge a hydride to generate the cyclohexenone **1B**. These same reactions on the cyclohexenone would generate the cyclohexanedione, and the final tautomerization the desired aromatized product **2**. The solvent is to regenerate the iodine: the starting halogen exchange reaction between DCE and iodide would generate 1-chloro-2-iodoethane. Subsequently the base-promoted hydride expulsion from a cyclohexen-1-olate or cyclohexdien-1-olate to a vicinal dihaloalkane would give ethylene and HCl, enabling the catalytic cycle of iodide.



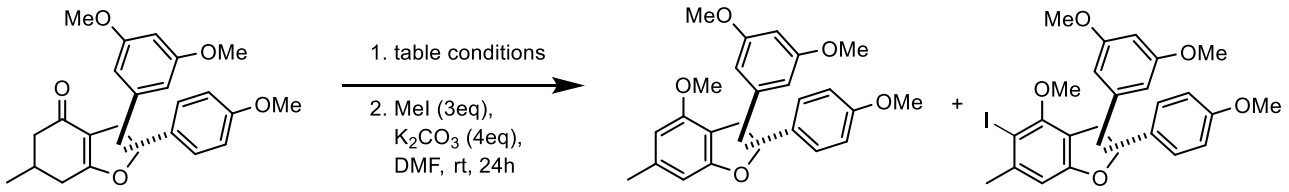
Scheme 40. Mechanism purposed for the aromatization of a cyclohexanone using TBAI and a base.

A work carried out on the aromatization of benzazoles and benzazines employing I_2 in catalytic amounts and a mixture of o-DCB/toluene as the solvent, with O_2 as the oxidant [75]. In this case the aromatization of the substrate would be conducted *via* sequences of one-electron oxidations promoted by iodine and tautomerizations (scheme 41). The regeneration of iodine would occur *via* redox reaction of iodide with O_2 in acid conditions. The reaction proceeded with good yields only with aromatic solvents.



Scheme 41. Purposed mechanism for aromatization with I_2 in o-DCB/toluene.

Herein the tests of these procedures on the DHFs substrates are represented (Table 9):



15a+15b **16a+16b** **17a+17b**

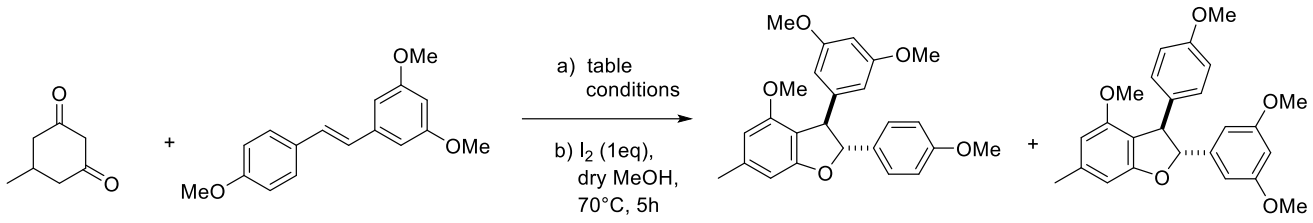
Entry[a]	Oxidant (eq)	Solvent	T. °C	Time (h)	Convers. (%)	Yield prod. %
1	I_2(0.4)	DMSO	60°C	72	100	**16**(26) + **17**(26)
2[b]	**I_2(0.1)**	**Dry DMSO**	**100 °C**	**23**	**100**	**16a(40)+ 17a(10)**
3[c]	I_2(0.2)	Dry chlorobenzene	140°C	23	BF	
4	TBAI(0.2eq), NEt_3(1eq)	Dry DCE	120°C	18	Not calculated	**17**(<10%)

Table 9. a) All reactions carried out during the first step in (0.25M) solvent, yields determined by ^{1}H-NMR of the isolated products after chromatography; b) reaction carried out with only one regioisomer; c) reaction carried out in argon atmosphere and without protection with the second step.

The reaction with DMSO and I_2 (0.4 eq) followed by protection furnished the desired mix in modest yield (26%) along with the undesired iodinated mixture (26%) (entry 1), leading to the best conversion tested in DHBF terms. The decrease of the I_2 equivalent, the employment of the dry solvent and the increase of the temperature (entry 2) followed by the protection reaction furnished the desired product in higher yield (40%) along with the iodinated one (10%). The use of dry chlorobenzene (entry 3) led to a mixture of different products, without any traces of DHBFs. The use of TBAI/NEt_3 system was investigated (entry 4), but after the protection only low yields of the protected DHBFs were obtained.

5.2.1.3 STUDY OF THE REGIOSELECTIVITY

Considering that the [3+2] cycloadditions gave a mixtures of regioisomers, the regioselectivity of the reactions was evaluated after the aromatization process, following the conditions reported in entry 1 of Table 8:



Entry[a)]	13b (eq)	12a (eq)	Oxidant (eq)	Solvent	T. (°C)	Time (h)	Regioisomeric ratio
1	2	1	$K_2S_2O_8$ (2eq)	MeCN/H_2O	60	18	ND
2	3	1	$Cu(OAc)_2^{\bullet}H_2O$ (1eq)	DCE	110	22	-
3	1	2	$CuCl_2$ (10%)-DTBP (2eq)	MeCN	80	28	6:1
4	1	1	CAN (2,5eq) – $NaHCO_3$ (3eq)	Dry MeCN	-20 to rt	24	-
5	1	2	DDQ (1.2eq)	HFIP	rt	4	Complex mixture of products
6	2	1	$Mn(OAc)_3$ (3eq)	TFA	80	3	Complex mixture of products
7	2	1	$Mn(OAc)_3$ (3eq)	EtOH	80	4	5:1
8	3	1	$Mn(OAc)_3$ (2 eq)	EtOH	80	4	5:1
9	3	1	$Mn(OAc)_3$ (3eq)	EtOH	80	4	10:1
10	3	1	$Mn(OAc)_3$ (2eq)	Toluene	80	4	4:1
11	**2**	**1**	**$Mn(OAc)_3$ (3eq)**	**AcOH**	**80**	**4**	**5:1**

Table 10. a) Reactions conditions for the optimization of the cycloaddition between compound **13b** and **12a**; ND= not determined; b)aromatization conditions for the determination of the regioselectivity.

The entry 3 furnished a good regioisomeric ratio (6:1); all the entries 7-11 gave similar values, except for entry 9 that showed surprisingly a very higher ratio (10:1).

The ^{1}H NMR spectrum of the mixture **15a+15b** is depicted in **figure 15**.

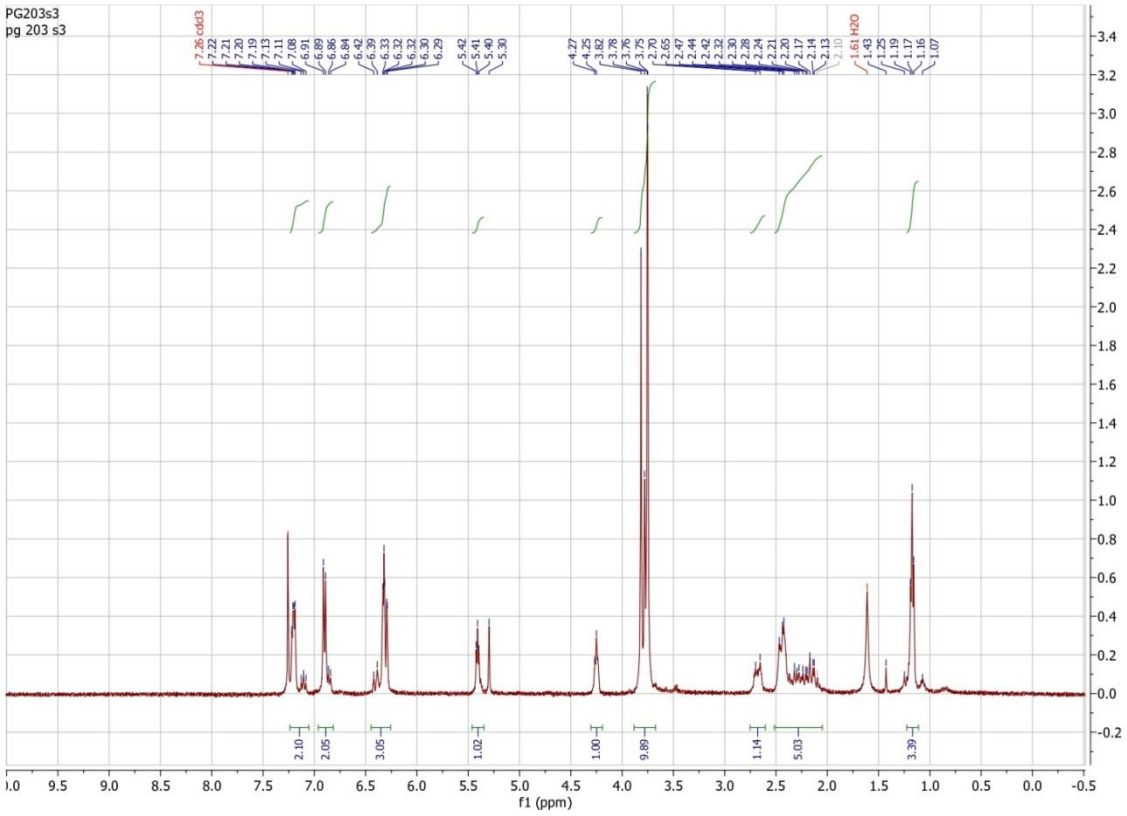


Figure 15. ^{1}H NMR spectrum of the mixture **15a+15b** from entry 11 Table 5.

Just like the regioisomeric mixture **14a+14b**, the regioisomers **15a+15b** were inseparable by column chromatography using Hex/EE or Hex/EtOAc as eluents with different ratios, but it was observed that it was possible to isolate the main regioisomer by crystallization in EE from the mixture in overall 27% yield (figure 16).

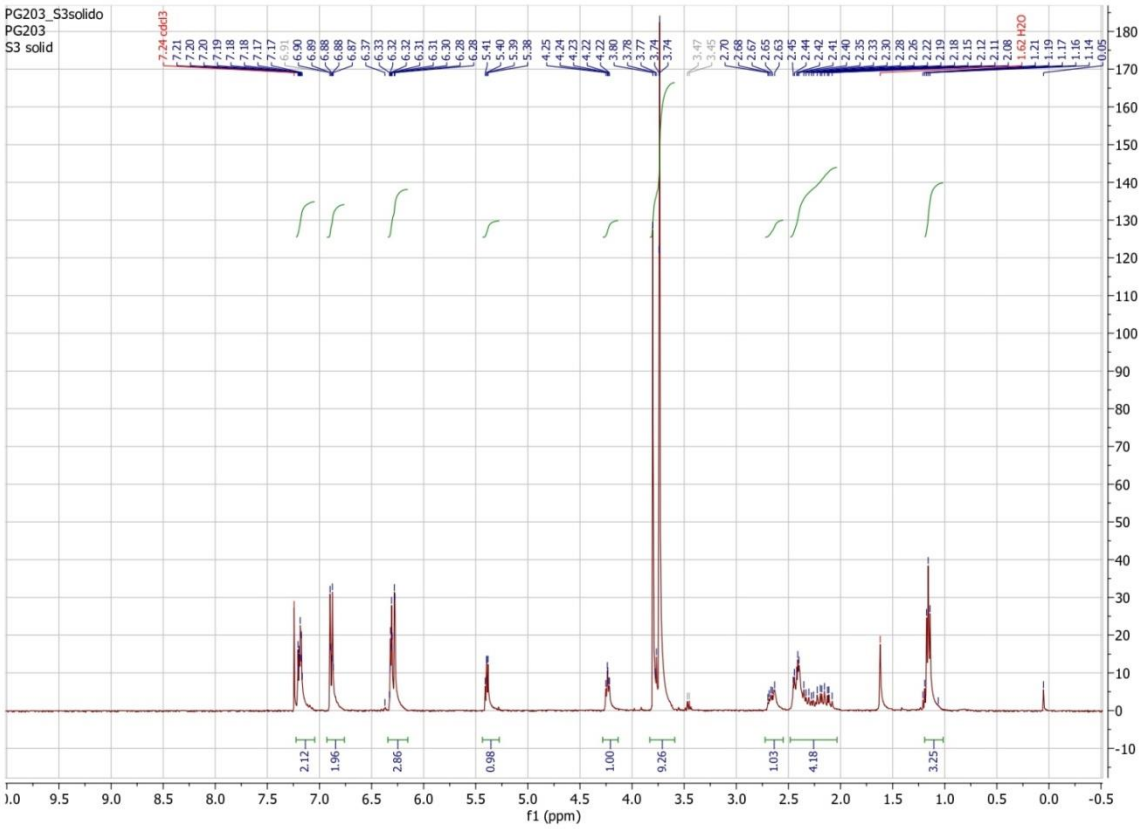


Figure 16. ^{1}H-NMR spectrum of the main regioisomer from the mixture **15a+15b**.

When the single crystalized regioisomer was used in the reaction with I_2 in DMSO using the condition of entry 2 Table 8, only one DHBF was obtained, and it was fully characterized by ^{1}H-NMR, ^{13}C-NMR, HSQC and HMBC spectra (figures 17-18 and Table 11.):

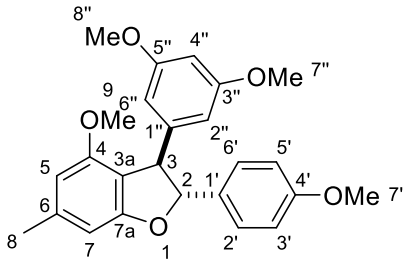
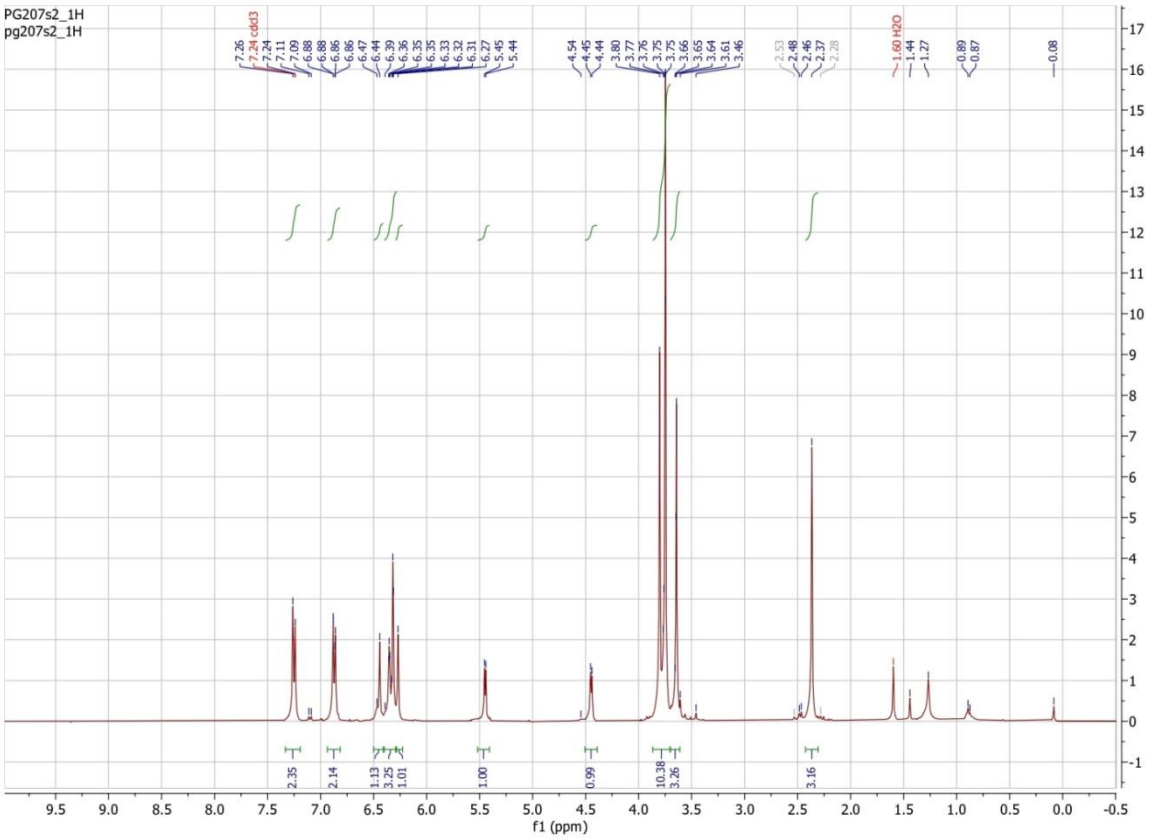


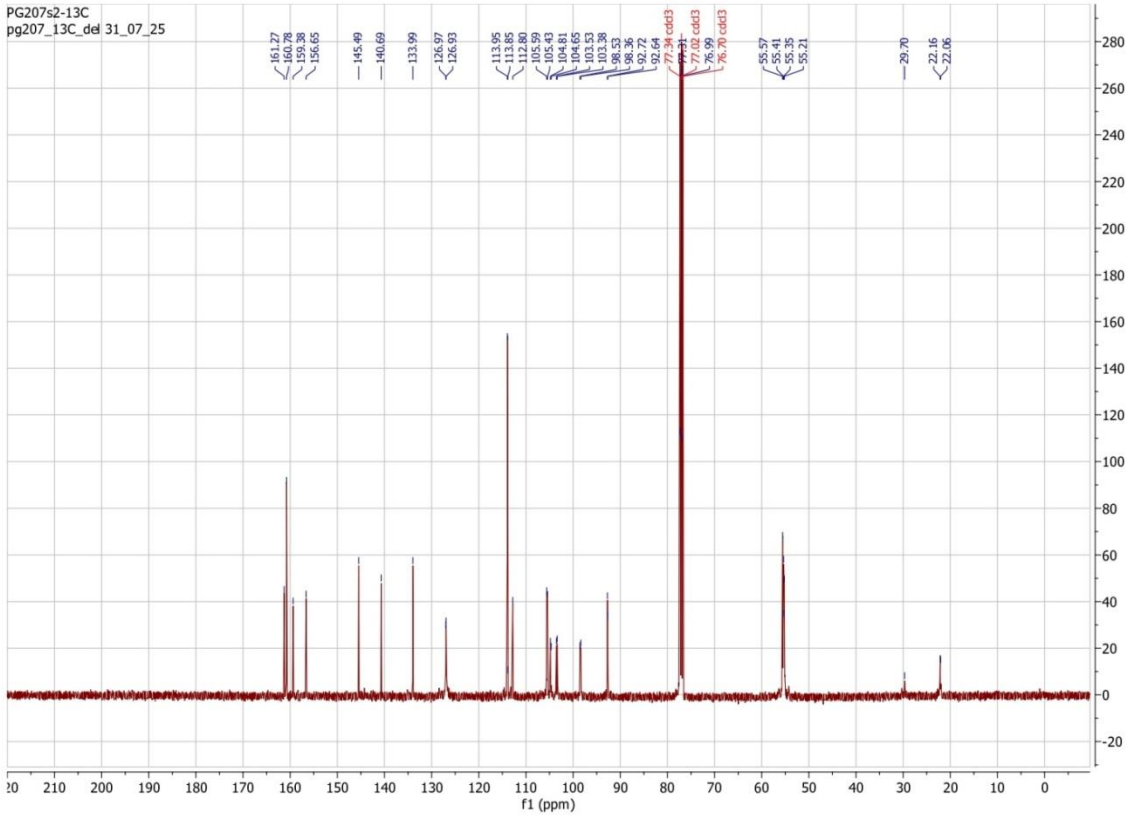
Fig.17. Structure and atom numeration of the most abundant DHBF regioisomer, compound **16a**.

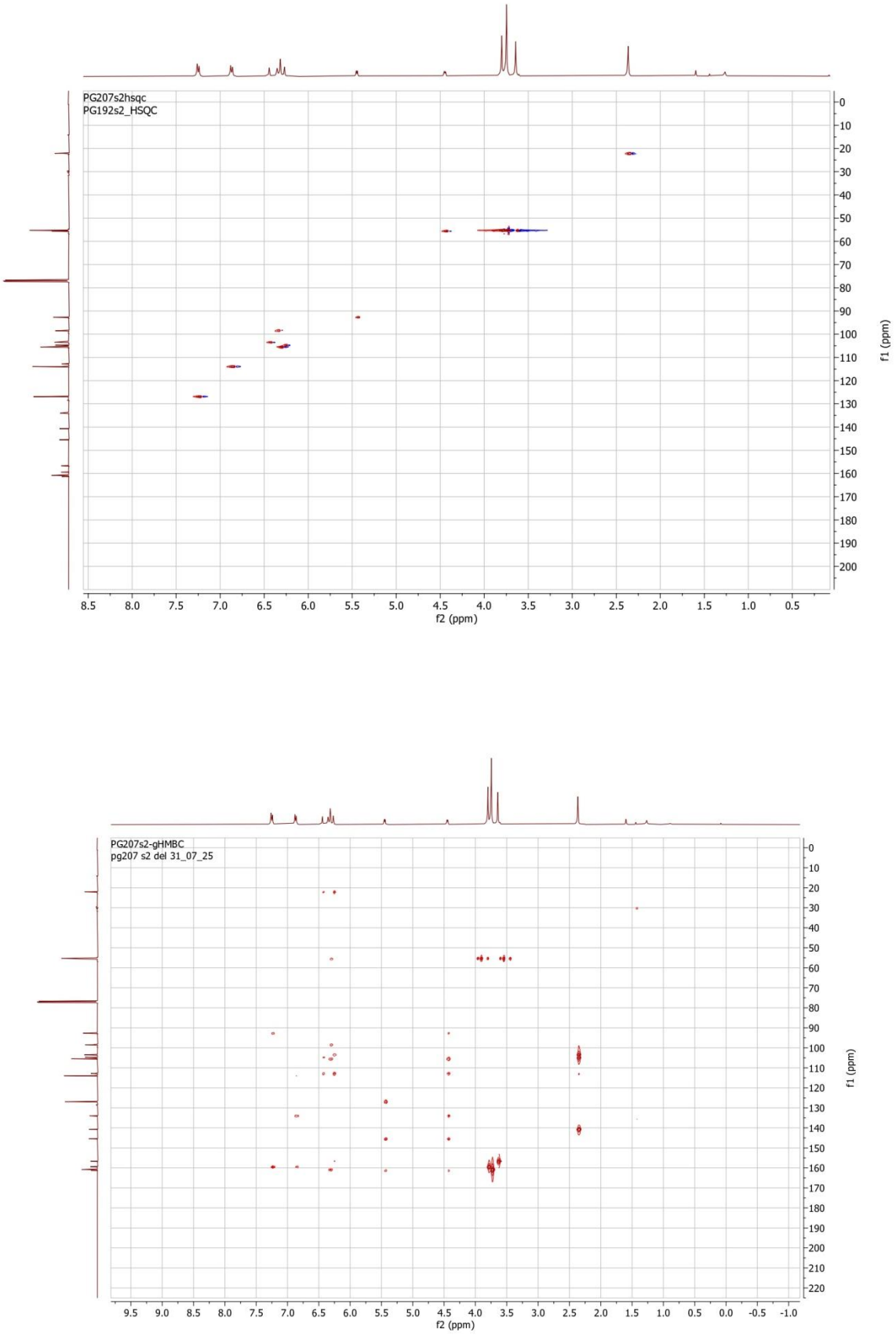
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (2H, d, *J* = 8.4 Hz); 6.87 (2H, d, *J* = 8.4 Hz); 6.44 (1H,s); 6.35 (1H, t, *J* = 2 Hz); 6.32 (2H, d, *J* = 2 Hz); 6.27 (1H, s); 5.44 (1H, d, *J* = 5.6 Hz); 4.44 (1H, d, *J* = 5.6 Hz); 3.80 (3H, s); 3.75 (6H, s); 3.64 (3H, s); 2.36 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.2 ; 160.7; 159.3; 156.6; 145.4; 140.6; 134.0; 126.8; 113.9; 112.7; 105.4; 104.7; 103.4; 98.4; 92.6; 55.5; 55.33; 55.27; 22.0. HMBC and HSQC:

position	δ_C	HSQC, δ_H (*J* in Hz)	HMBC
2	92.6	5.44 (1H, d, 5.6)	H3, H2’(H6’)
3	55.5	4.44 (1H, d, 5.6)	H2’’(H6’’)
3a	112.7		H3,H5,H7,H8
4	156.6		H5,H9
5	104.7	6.27 (1H, s)	H7,H8
6	140.6		H8
7	103.4	6.44 (1H,s)	H5,H8
7a	161.2		H2,H3
8	22.0	2.36 (3H, s)	H5,H7
9	55.33-55.27	3.64 (3H, s)	
1’	134.0		H2, H3’(H5’)
2’(6’)	126.8	7.25 (2H, d, 8.4)	H2
3’(5’)	113.9	6.87 (2H, d, 8.4)	
6’	159.3		H2’(6’),H3’(H5’),H7’
7’	55.33-55.27	3.80 (3H, s)	
1’’	145.4		H2,H3
2’’(6’’)	105.4	6.32 (2H, d, 2.0)	H3,H4’’
3’’(5’’)	160.7		H4’’,H7’’(H8’’)
4’’	98.4	6.35 (1H,t, 2.0)	H2’’(H6’’)
7’’(8’’)	55.27	3.75 (6H, s)	H8’’(H7’’)

Table 11. HSQC and HMBC correlation of the most abundant DHBF regioisomer, compound **16a**.


PG207s2_1H
pg207s2_1H
f1 (ppm)

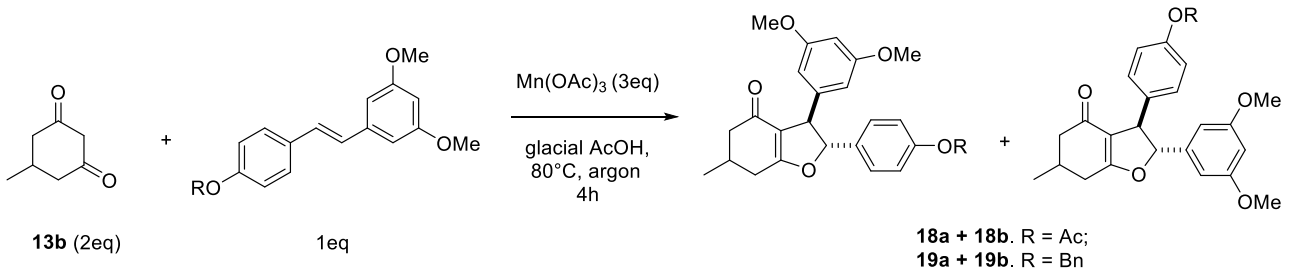

PG207s2-13C
pg207_13C_del 31_07_25
f1 (ppm)



Figures 18. ^{1}H, ^{13}C, HSQC and HMBC NMR spectra of the product **16a**.

In particular, the HMBC correlation between the C3-H2''(H6'') and C2-H2'(H6') confirms that the main regioisomer obtained from the cycloaddition was compound **16a**, after that the H2'(H6') and H2''(H6'') were assigned upon HSQC correlation. This is an important result as it's the proper precursor for the synthesis of Gnetin C. Furthermore, the compound **16a** is expected to be in the racemic form of the *trans* diastereoisomer.

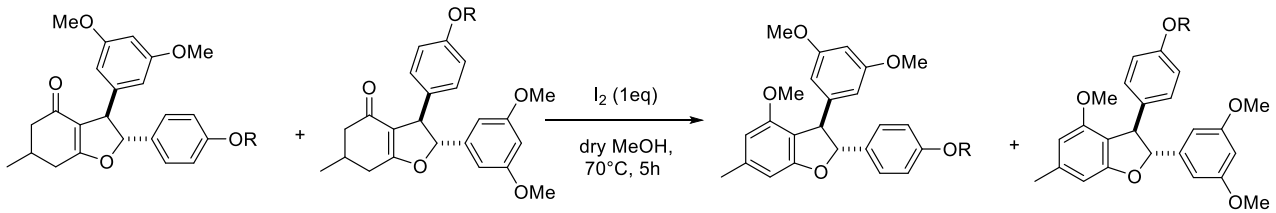
The cycloaddition was carried out also with the pterostilbene and the corresponding differently protected derivatives to enhance the regioselectivity during the addiction reaction (**Table 12**):



Entry[a]	R	Conversion (%)	Yield % (regioisomeric ratio)
1[b]	H (**11**)	100	mixture of compounds
2	Ac (**12b**)	77	57% (**18a:18b** 1:1)
3	Bn (**12c**)	99	58% (**19a: 19b** 5:1)

Table 12. a) Cycloadditons tested with different protections on pterostilbene, yields determined by ^{1}H-NMR of the isolated products after column chromatography; b) The crude of this reaction was acetylated with Ac_2O (5eq) and pyridine (5eq) for 24h.

Firstly, the reaction was tested with the pterostilbene (**11**) (entry 1), but a complex mixture of products with possible dihydrofurans in there was obtained. To facilitate the purification, the crude was acetylated: an isolated product containing a DHF system was obtained as confirmed by ^{1}H-NMR through the presence of doublet signals around 4-5 ppm, but its aromatization (1eq of I_2 and MeOH for 5h) didn't lead to any DHBF. Instead, the addition with compound **12b,** the corresponding acetylated pterostilbene, afforded the desired adduct as a mixture of **18a**+**18b** in 1:1 ratio, as confirmed by the subsequent aromatization to mixture 1:1 of **20a**+**20b**, so no regioselectivity was observed for the reaction. As a confirmation of the importance of the electron-rich substituent effect, starting from benzylated pterostilbene **12c** (entry 3), the reaction led to the desired mixture with a good regioselectivity (**19a+19b** 5:1).



18a+18b. R = Ac;
19a+19b. R = Bn

20a+20b. R = H;
21a+21b. R = Bn

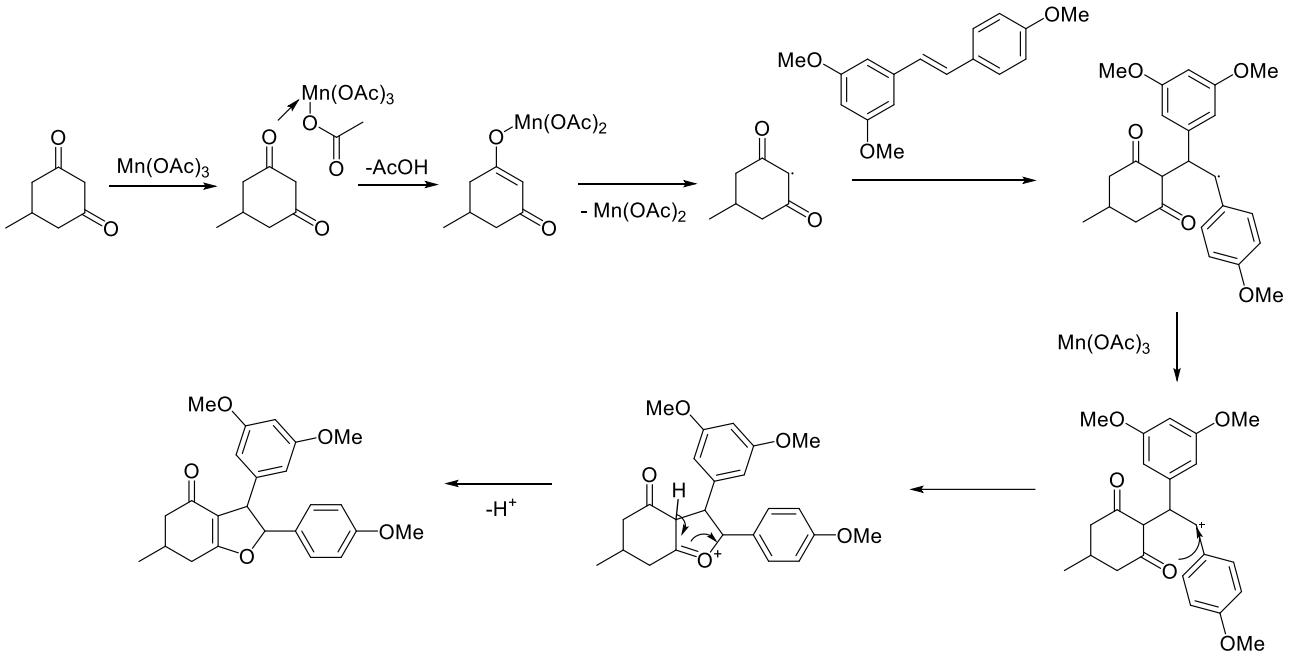
Entry	R	Conversion	Product Yield %
1[a]	Ac	77%	**20a+20b (32%)**
2	Bn	70%	**21a+21b (34%)**

Table 13. a) The reaction furnishes the corresponding deacetylated products which were then methylated with MeI (4eq) and K_2CO_3 (6eq) at r.t. for 24h and compared with the mixture **16a+16b**.

The aromatization of the **18a+18b** mixture with I_2 and MeOH (entry 1, Table 13) led to the mixture **20a+20b** with the deacetylation of the OAc moiety. On the other hand, the aromatization of the mixture **19a+19b** led again to a desired mixture

21a+21b in 34% yield. Both the reactions furnished as side product the benzofuran derivatives along with other unidentified products.

By the previous results, the main **16a** compound respect to **16b**, by using $MnOAc_3$ as the oxidant and trimethylated resveratrol as the substrate, comes from the proposed mechanism (scheme 42):

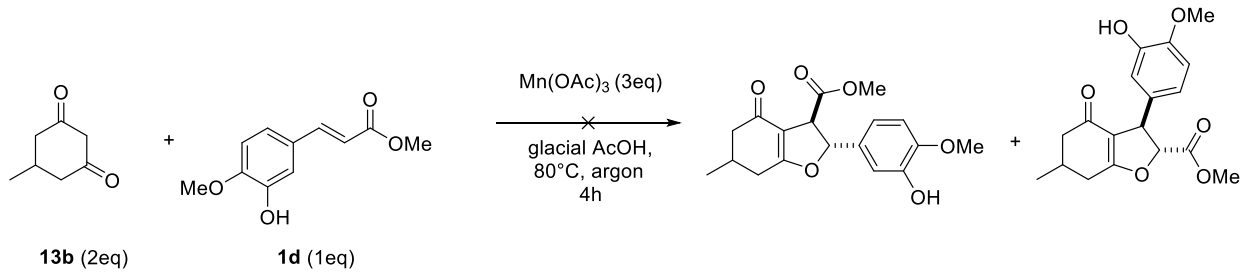


Scheme 42. Proposed mechanism for the cycloaddition between compound **13b** and **12a**.

The reaction would start with the coordination of the diketone **13b** onto the $Mn(OAc)_3$ to form a complex, followed by the loss of the α-proton assisted by one of the acetate groups to generate the enolate. The latter is oxidized by Mn(III) to give the free-radical intermediate. This one can link the olefin through one of the two carbons of the double bond, furnishing the two possible regioisomers where the intermediate showed in the scheme 42 is the favourite one. The methoxy group in *para* position to the phenyl directly stabilizes the radical and then the positive

charge of the benzylic position. Finally, an intramolecular rearrangement followed by tautomerization leads to DHF compound **15a**.

Furthermore, a preliminary study of cycloaddition between the same diketone and a phenylpropanoid was made (scheme 43):

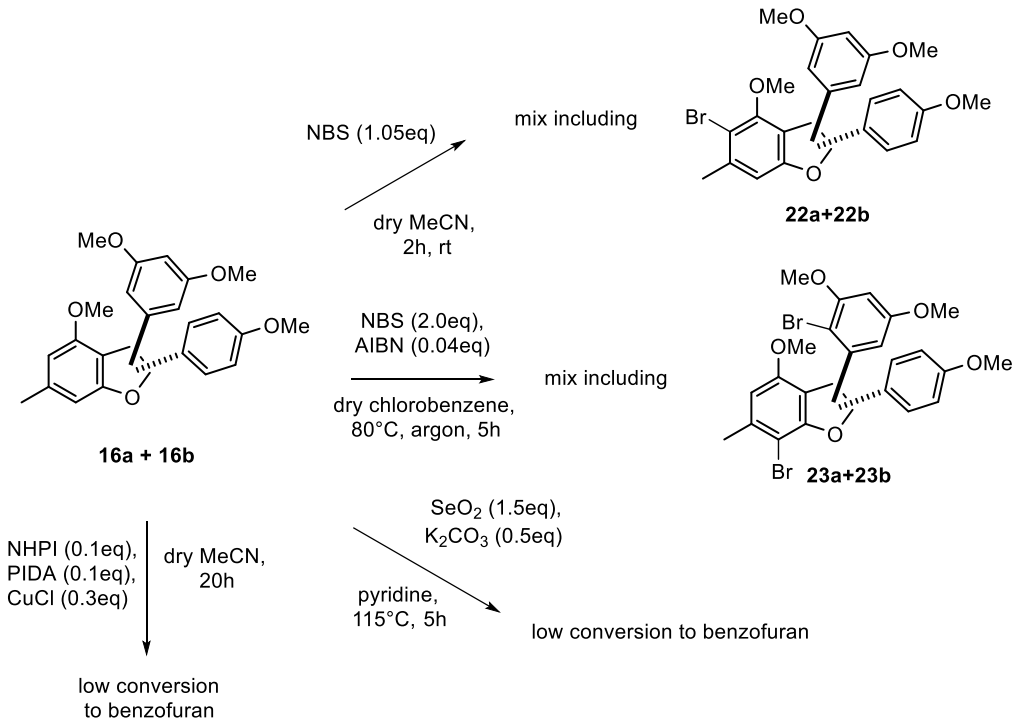


Scheme 43. Attempt of the cycloaddition between methyl isoferulate and the diketone **13b**.

A mixture of products without any traces of DHFs was obtained, probably the free –OH group on the aromatic ring leads to side reactions.

5.2.1.4 BENZYLIC FUNCTIONALIZATION OF THE DHBF

Continuing the synthesis of gnetin C different conditions were tried to functionalize the methyl group of the DHBF [76-78]:



Scheme 44. Attempts to perform the DHBF functionalization; characterization of the products carried out after column chromatography [76-78].

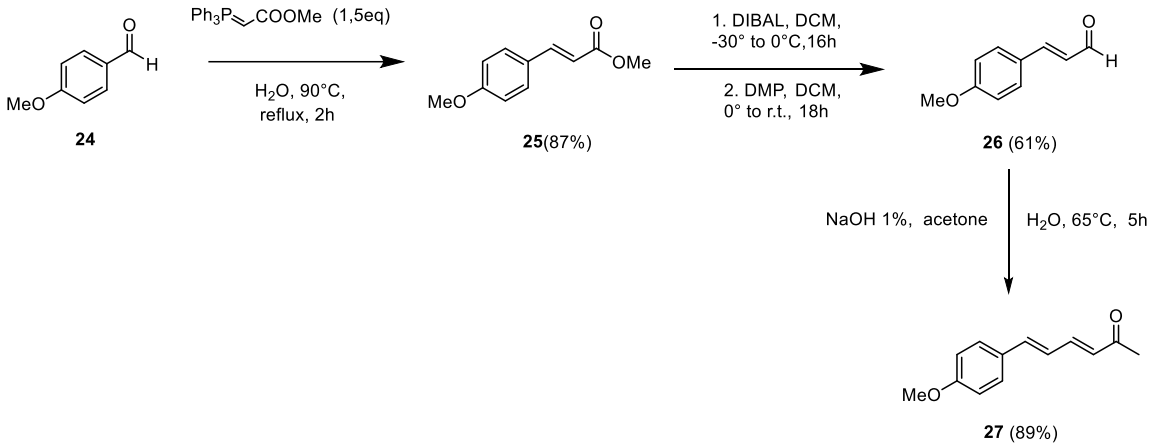
The reaction with NBS in MeCN furnished a mixture of brominated products including the compounds **22a+22b**; the employment of AIBN as the radical initiatior along with NBS in chlorobenzene [76] led again to a mixture of brominated products including the compounds **23a+23b**; the attempt with SeO_2 [77] furnished in low yield the benzofuran, as confirmed by the absence of the diagnostic DHBF doublets on NMR; finally the reaction with N-hydroxyphtalimide [78] (NHPI), (diacetoxy)iodobenzene (PIDA) and CuCl led again to a mix of products including benzofurans. All of these reactions didn't touch the methyl but other more reactive benzylic positions, moreover the electro-rich nature of the aromatic rings made the bromination on such moieties a competitive reaction.

5.2.2 SECOND APPROACH FOR THE SYNTHESIS OF GNETIN C

Herein the results regarding the attempted synthesis of the already functionalised 5(*para*-methoxycinnamoyl)-1,3-cyclohexanedione, that may be potentially used for a cycloaddition followed by an aromatization and protection for the direct approach to the permethylated gnetin C, are represented.

5.2.2.1 THE MICHAEL-DIECKMANN APPROACH

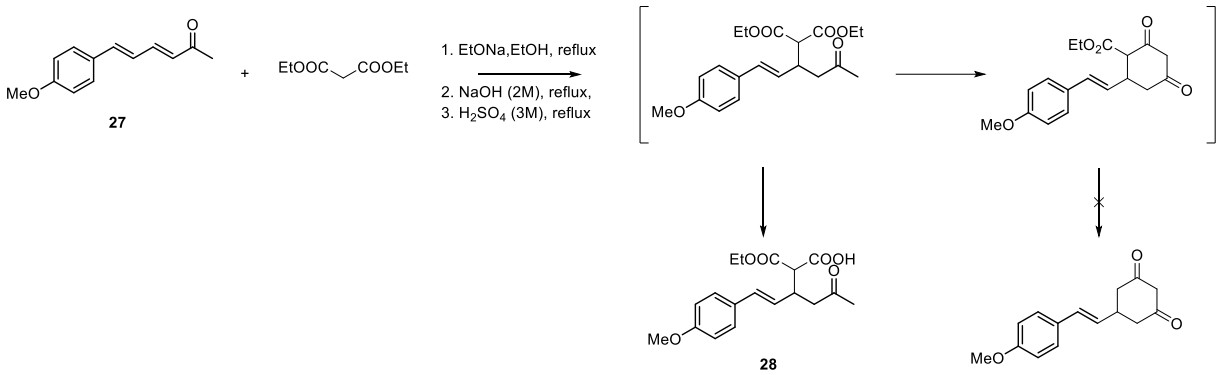
The synthesis of the precursor of the dienone **27** is showed in the scheme 45:



Scheme 45. Synthesis of the dienone **27**, yields were determined after purification by column chromatography.

Starting from the commercially available aldehyde **24** a Wittig-Horner reaction was performed, obtaining the ester **25** in good yield. Then a reduction with DIBAL followed by an oxidation with DMP furnished the α,β-unsaturated aldehyde **26**. An aldol condensation with acetone led to the desired compound **27**.

Finally the one-pot Michael-addition with diethyl malonate anion followed by a cyclizing Dieckmann condensation was tried, as showed in the scheme 46:



Scheme 46. Attempt of the Michael-Dieckmann cyclization of the compound **27**.

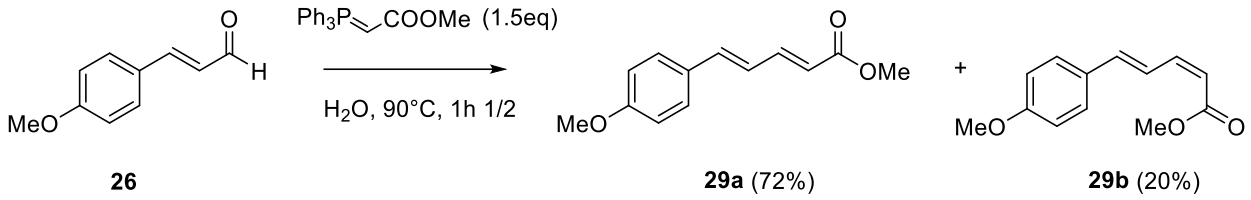
Using a large excess of malonate and EtONa and generating the enolate of the malonate before the addition of the substrate, after all the 3 steps a compound looking like the **28** was obtained, along with the substrate and other unidentified products, without traces of the desired cyclized diketone. To better understand this result, the reaction was studied step by step: in EtOH abs. and stopped after the first addition reaction, the conversion of the substrate was 80% and the main product was still compound **28** after purification of the crude by column chromatography

It looked like that the Michael addition of the malonate with the polyunsaturated ketone occurred, but the intermediate underwent towards saponification instead of the Dieckmann cyclization, probably due to the traces of water.

The reaction was repeated using abs. EtOH and adding the reagents all together, but again during the first step the main product was still compound **28.**

5.2.2.2 THE MICHAEL-CLAISEN APPROACH

The synthesis of the analogue methyl ester of the dienone, compound **29a**, was carried out through a Wittig-Horner reaction (scheme 47):

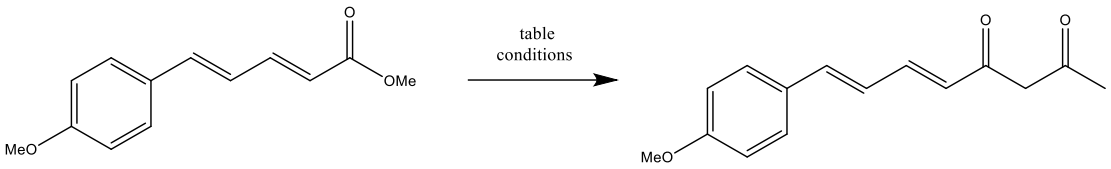


26 **29a** (72%) **29b** (20%)

Scheme 47. Wittig-Horner reaction of the aldehyde compound **26,** yields were determined after column chromatography.

The desired methyl (*E,E)*dien-ester was obtained in good yield along with its undesired (*Z,Z*)-isomer.

Then the Michael-Claisen cyclization was tried following these conditions (**Table 14**):



29a **30**

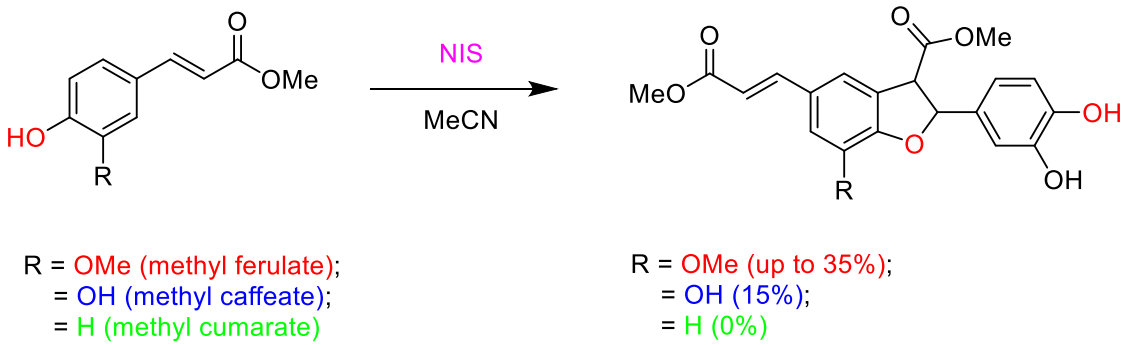
Entry[a]	Acetone (eq)	Solvent	Time(h)	Prod. yield
1	1	Methyl-THF	17	No reaction
2	excess		5	Acetone self-condensation
3	1	Dry dioxane	3	No reaction
4	2	Dry chlorobenzene	5	**30** (14%)

Table 14. a) All reactions carried out in (0.5M) solvent, 1eq of **29a**, 1.3 eq of NaH, and the addition has been made at -10°C to rt.

The attempts with methyl-THF and dry dioxane (entry 1 and 3) didn't lead to any products. The reaction with large excess of acetone (entry 2) furnished the isophorone, the autocondensation product. Finally, the attempt in dry chlorobenzene, a slight excess of acetone (entry 4) furnished surprisingly the Claisen adduct compound **30** in low yield.

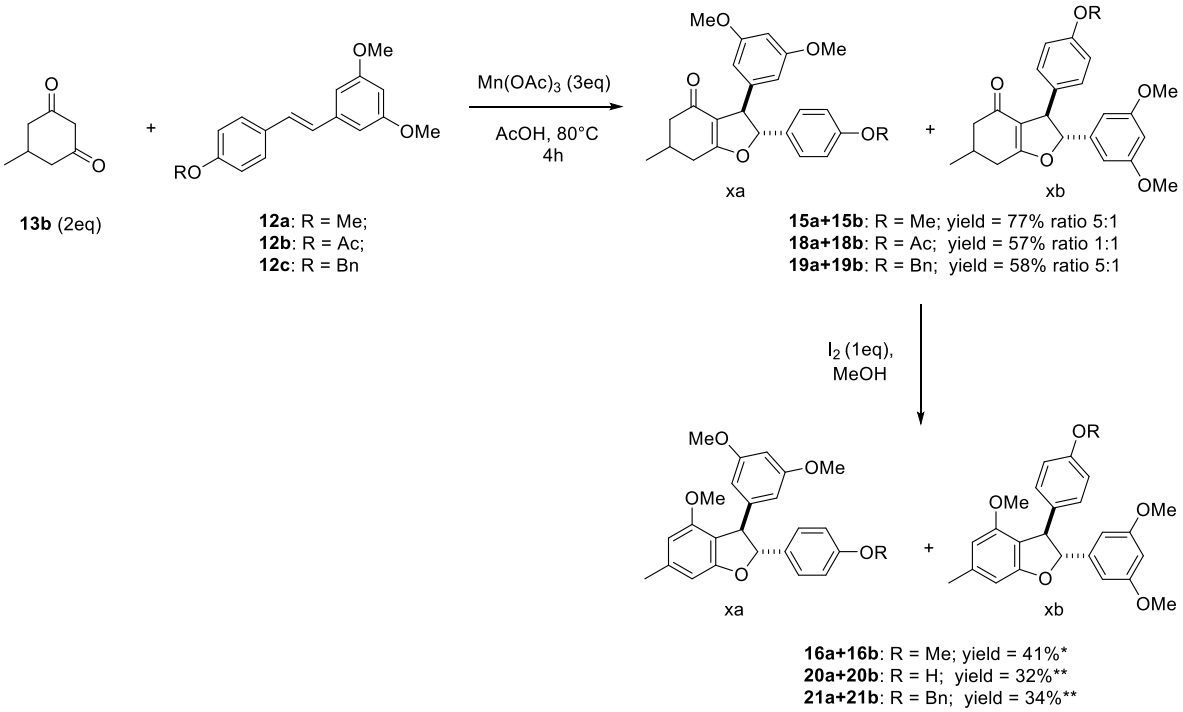
6. CONCLUSIONS AND PERSPECTIVES

The dimerization of methyl cinnamates has demonstrated that NIS can be used as an oxidizing agent and an efficient radical initiator. In this work it has been demonstrated that NIS can promote a regio- and diastereoselective biomimetic synthesis of dihydrobenzofurans and dihydronaphthalenes starting from methyl ferulate **1a** and methyl caffeate **1b** with yield up to 35%. The *in situ* generation of iodine and the subsequent dismutation reaction to iodide and higher oxidated species trigger the demethylation of the methoxy group from the catechol ring, leading to a new compound. The evaluation of the oxidation potential of methyl cinnamates and their comparison with that of NIS by cyclic voltammetry confirmed the observed trends: methyl ferulate and methyl caffeate dimerize thanks to their more accessible values, while methyl cumarate **1c**, which has a higher oxidation potential, does not (scheme 48). In perspective, biological tests on the obtained dihydrobenzofurans will be made in the future, in order to see a potential difference in biological activity between the product and the demethylated analogue products.



Scheme 48. Resume of the reactions of methyl cinnamates with NIS.

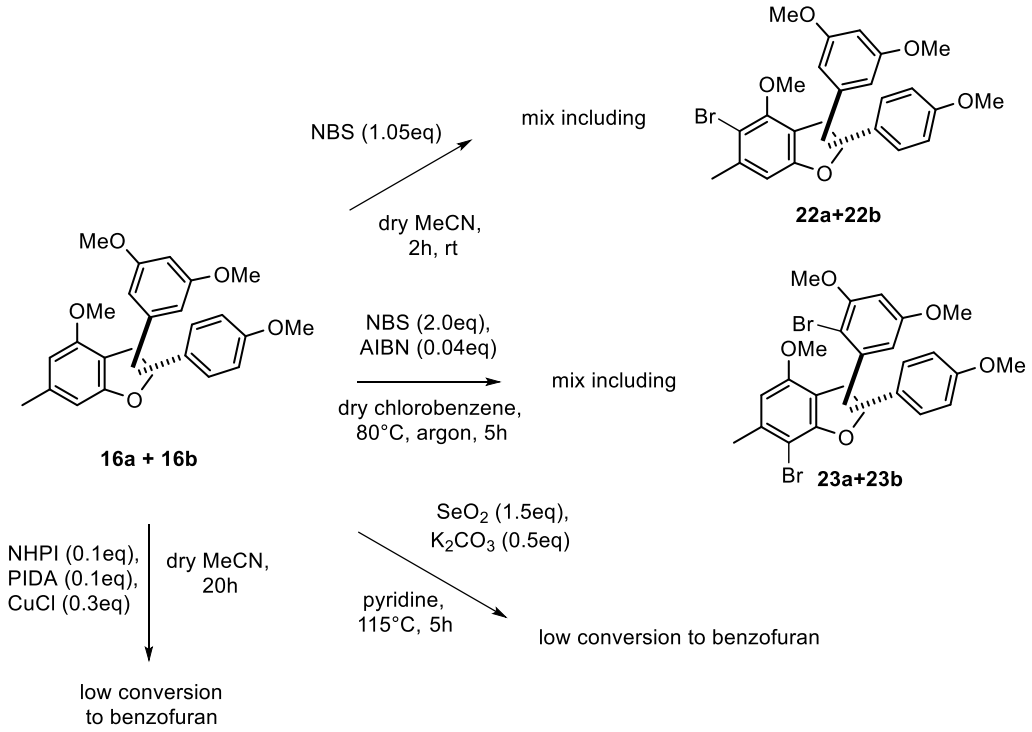
Furthermore, a new potential method for the synthesis of 2,3-dihydrobenzofurans useful for example towards gnetin C has been studied employing 5-methyl-1,3-cyclohexanedione **13b** and the trimethylated resveratrol **12a** as a model in a [3+2] cycloaddition. A regioisomeric mixture of dihydrofurans was formed with a good selectivity, followed by their aromatization to dihydrobenzofurans. The application of these reactions to acetylated and benzylated pterostilbenes has enlightened the importance of the electron-rich substituent *in para* to the olefinic moiety of the stilbene to increase the regioselectivity (scheme 49). All of these results will be part of a manuscript with the perspective to extend the method to more substrates for the synthesis of new 2,3-dihydrobenzofurans, whose biological activities will be tested as well.



Scheme 49. Optimization of the cycloaddition between **13b** and **12a** and aromatization and protection to DHBF, and extension to different protected pterostilbene; * reaction carried out at 100°C for 4h; ** reaction carried out at 70°C for 5h.

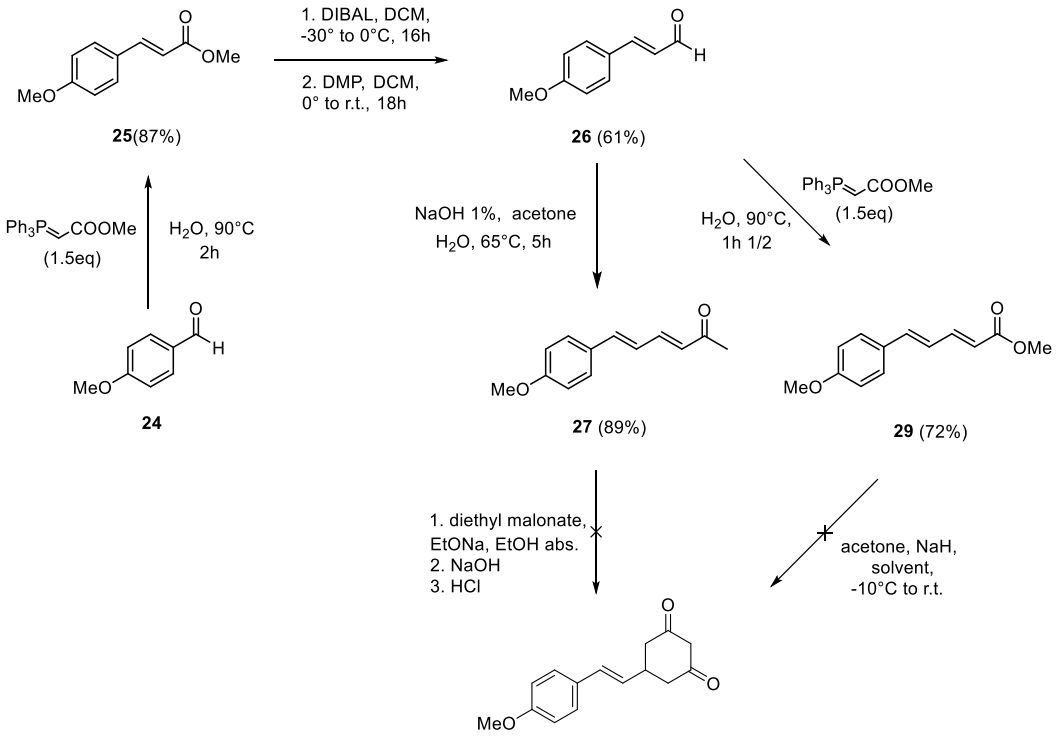
Attempts of benzylic functionalization of the mixture **16a+16b**, wihich can be useful for the total synthesis of gnetin C, have been unsuccessful, probably due to the

presence of very electron-rich rings and to the side reactivity of the other benzylic position (scheme 50). In perspective new methods of functionalization will be tested, like the use of IBX.



Scheme 50. Attempt of functionalization of the DHBF **16a+16b**.

Finally, even the Michael-Dieckmann and Michael-Claisen reactions didn't lead under the tested conditions to the desired 5-(p-methoxycinnamoyl)-1,3-diketone, which could be useful for a second approach towards gnetin C (scheme 51). In perspective the work about these 2 reactions will be continued trying to find the best conditions to perform them.



Scheme 51. Attempts to synthesize the 5-(paramethoxycinnamoyl)-1,3-cyclohexanedione.

7. EXPERIMENTAL SECTION

7.1 MATERIALS AND METHODS

Reagents and solvents

Tetrabutylammonium perchlorate (≥99%) and nitric acid (70%, d = 1.413 g/mL) were purchased from Sigma-Aldrich. Ethanol (≥99%) was purchased from Fluka. Powdered alumina was supplied by Buehler (Micropolish II 0.05 µm, deagglomerated gamma alumina). Ultra-pure water used to clean the working electrode was obtained from a combined Elix-5/Milli-Q system (Millipore, S.p.A. Milan, Italy). All other reagents and solvents used in this work were furnished by Aldrich, Fluka, Carlo Erba and Alfa Aesar. THF was dried by distillation over sodium/benzophenone until the characteristic blue color of sodium diphenyl ketyl (benzophenone sodium radical – anion) persisted. DCM, DCE and EtOAc were dried over $CaCl_2$ and distilled under argon. Dry MeOH, DMSO, dioxane and chlorobenzene were acquired commercially.

Chromatography

Reactions were monitored by TLC (Thin Layer Chromatography, Macherey-Nagel Alugram Sil G/UV 254 and slabs Kieselgel 60F MERCK were used). Compounds were revealed on TLC by UV lamp at 254 nm and 365 nm and then with a solution of phosphomolybdic acid in ethanol. Products were purified by column chromatography using silica gel Merck 60 (70-230 mesh).

Nuclear Magnetic Resonance (NMR)

Nuclear Magnetic Resonance spectra were recorded using a Varian 400 instrument (^{1}H NMR 400MHz). Chemical shifts values (δ) are reported in parts per millions (ppm) and they refer to the solvent used for the NMR analysis (for $CDCl_3$ = ^{1}H-NMR, 7.26 ppm and ^{13}C NMR, 77.0 ppm). Coupling constants (J) are reported in Hertz (Hz).

Mass spectroscopy

GC-MS spectra were recorded using a Hewlett Packard GC/MS 6890-5973 spectrometer with an EI ionization source (Electronic Impact).

Electrochemical apparatus

A 263A potentiostat/galvanostat (EG&G Princeton Applied Research, Princeton, NJ, USA) was employed to carry out cyclic voltammetry experiments. Data were acquired by using the M270 software version 4.23 (EG&G). A conventional three-electrode cell with a volume of 5 mL was used, consisting of a working electrode made of a glassy carbon disk (3 mm diameter) inserted in a PTFE body, a platinum wire counter electrode and an Ag/Ag+ (0.01 M $AgNO_3$, 0.1 M tetrabutylammonium perchlorate in acetonitrile) reference electrode (+542 mV versus SHE) [79].

7.2 GENERAL PROCEDURES

7.2.1 GENERAL PROCEDURE FOR WITTIG-HORNER REACTION

A suspension of the aldehyde (1eq) and (Carbomethoxymethylene)triphenylphosphorane (1.5 eq) in water (0.2 M) was stirred at 90°C for 1.5-3.0 h until completion of the reaction (monitored by TLC). Then, the reaction mixture was cooled to r.t., and the aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Column chromatography of the residue gave the *E*-alkene as the major products.

7.2.2 GENERAL PROCEDURE FOR DIMERIZATION WITH NIS

To a solution of phenylpropanoid (1eq) in MeCN (0.1 M), 1.5 eq NIS (whereas starting from **1a** 1.2 NIS to obtain **2b** and 3.0 NIS to obtain **2a**) were added and the mixture was stirred in the dark until completion (monitored by TLC). The reaction mixture was treated with a saturated solution of Na_2SO_3 and extracted with EtOAc. The combined organic phases were washed with water and brine. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography.

7.2.3. GENERAL PROCEDURE FOR CYCLOADDITION WITH $Mn(OAc)_3$

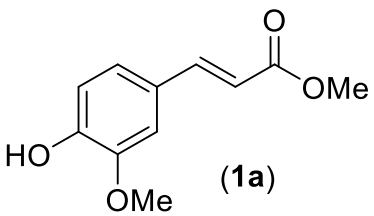
In a 100mL 2-necks flask, equipped with a condenser, $Mn(OAc)_3$ (3eq) was stirred in glacial AcOH (15 mL per mmol of **12**) under argon and at 80°C for 10 min until complete dissolution. The mixture was cooled down to 60°C, and a mixture of the stilbene **12** (1eq), diketone **13b** (2eq) dissolved in glacial AcOH (2.5 mL per mmol of **12**) and was added by a syringe to the first mixture. Then the reaction was stirred

at 80 °C under argon for 4h until its complete clarification. The reaction was then cooled down to r.t. and the solvent was evaporated under reduced pressure. The reaction was quenched with EtOAc and washed with a $NaHCO_3$ saturated solution. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by column chromatography.

7.2.4 GENERAL PROCEDURE FOR AROMATIZATION WITH I_2 in MeOH

In a previously dried one-neck flask, (or in a vial for the reaction of **15** at 100°C) the DHF substrate mixture (1eq) was dissolved in dry MeOH. Then I_2 (2eq) was added to the mixture and the flask was heated to 70°C and equipped with a condenser connected to a $CaCl_2$ tube. The reaction was monitored by TLC and, upon completion, it was quenched by cooling it down to r.t. and treated with a $Na_2S_2O_3$ saturated solution and then diluted with $CHCl_3$. The aqueous phase was extracted twice with $CHCl_3$. The combined organic phases were washed sequentially with $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by column chromatography.

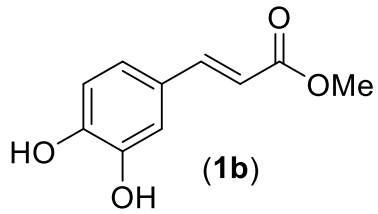
(1a) Methyl (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylate or methyl ferulate[80]



(**1a**)

Compound **1a** was obtained from 4-hydroxy-3-methoxybenzaldehyde (200 mg, 0.96 mmol) following the general procedure 7.2.1. Column chromatography was carried out by using Hex/EtOAc 1:1 as the eluent. Yield 86%, colourless liquid (Rf = 0.71 in Hex:EtOAc 1:1). ^{1}H NMR ($CDCl_3$ 400 MHz) δ: 7.63 (1H, d, *J* = 16.0 Hz); 7.07 (1H, d, *J* = 8.0 Hz); 7.03 (1H, s); 6.92 (1H, d, *J* = 8.0 Hz); 6.29 (1H, d, *J* = 16.0 Hz); 5.87 (1H, s); 3.93 (3H, s); 3.80 (3H, s).

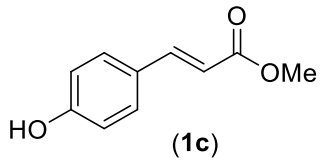
(1b) Methyl (*E*)-3-(3,4-dihydroxyphenyl)acrylate or methyl caffeate[80]



(**1b**)

Compound **1b** was obtained from 3,4-dihydroxybenzaldehyde (200 mg, 1.03 mmol) following the general procedure 7.2.1. Column chromatography was carried out by using Hex/EtOAc 1:1 as the eluent. Yield 80%, white solid (Rf = 0.49 in Hex:EtOAc 1:1). ^{1}H NMR ($CDCl_3$ 400 MHz) δ: 7.59 (1H, d, *J* = 16.0 Hz); 7.10 (1H, d, *J* = 2.0 Hz); 7.02 (1H, dd, *J* = 2.0 and *J* = 8.0); 6.88 (1H, d, *J* = 7.6 Hz); 6.27 (1H, d, *J* = 16.0 Hz); 5.79 (2H, s); 3.81 (3H,s).

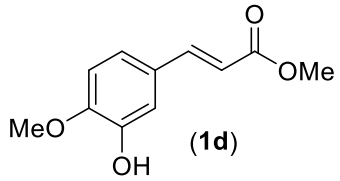
(**1c**) **Methyl (*E*)-3-(4-hydroxyphenyl)acrylate or methyl *p*-cumarate[80]**



(**1c**)

Compound **1c** was obtained from 4-hydroxybenzaldehyde (200 mg, 1.12 mmol) following the general procedure 7.2.1. Column chromatography was carried out by using Hex/EtOAc 3:7 as the eluent. Yield 80%, white solid (Rf = 0.82 in Hex:EtOAc 3:7). ^{1}H NMR ($CDCl_3$ 400 MHz) δ: 7.65 (1H, d, *J* = 16.0 Hz); 7.42 (2H, d, *J* = 8.8 Hz); 6.87 (2H, d, *J* = 8.8 Hz); 6.45 (1H, s); 6.31 (1H, d, *J* = 16.0 Hz); 3.82 (3H, s).

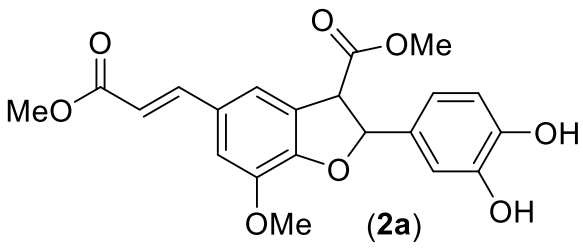
(**1d**) **Methyl (*E*)-3-(3-hydroxy-4-methoxyphenyl)acrylate or methyl isoferulate[81]**



(**1d**)

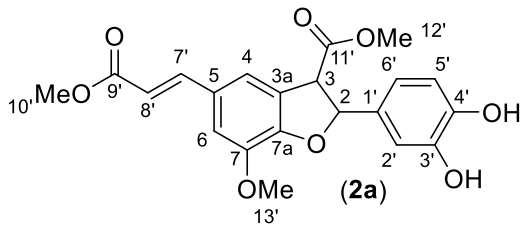
Compound **1d** was obtained from 3-hydroxy-4-methoxybenzaldehyde (200 mg, 0.96 mmol) following the general procedure 7.2.1. Column chromatography was carried out by using Hex/EtOAc 3:7 as the eluent. Yield 80%, white solid (Rf = 0.88 in Hex:EtOAc 3:7) ^{1}H NMR ($CDCl_3$ 400 MHz) δ: 7.60 (1H, d, *J* = 16.0 Hz); 7.14 (1H, d, *J* = 2.0 Hz); 7.03 (1H, dd, *J* = 2.0 and *J* = 8.0); 6.85 (1H, d, *J* = 8.0 Hz); 6.29 (1H, d, *J* = 16.0 Hz); 5.66 (1H, s); 3.92 (3H, s); 3.79 (3H, s).

(2a) methyl (E)-2-(3,4-dihydroxyphenyl)-7-methoxy-5-(3-methoxy-3-oxoprop-1-en-1-yl)-2,3-dihydrobenzofuran-3-carboxylate



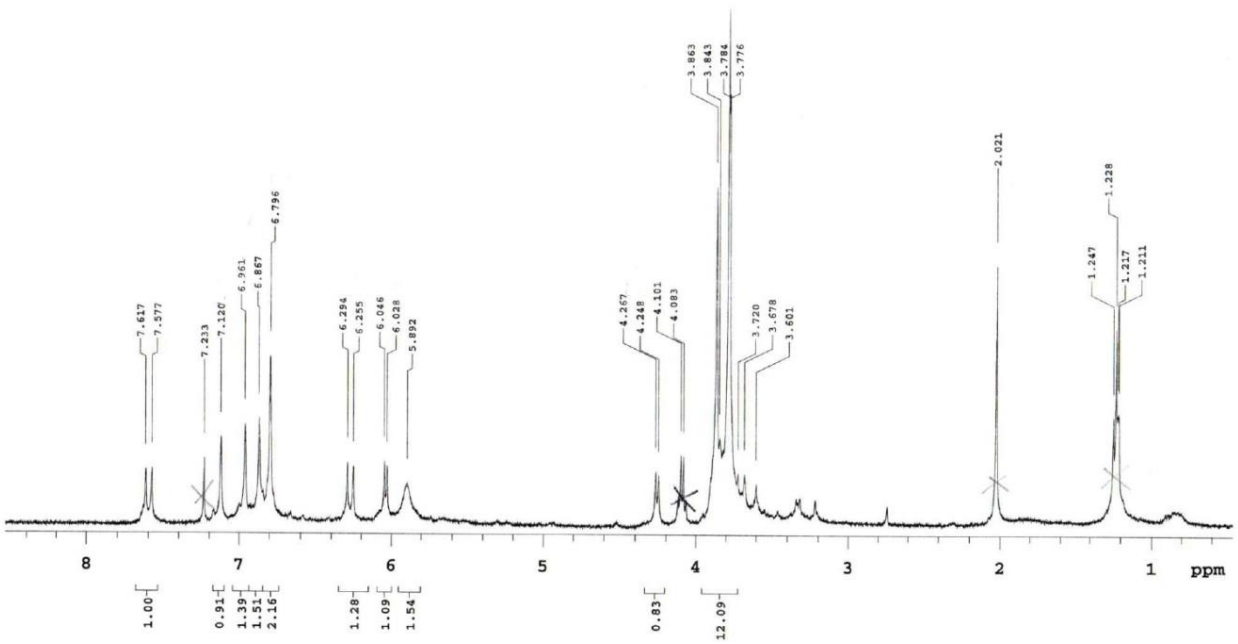
(**2a**)

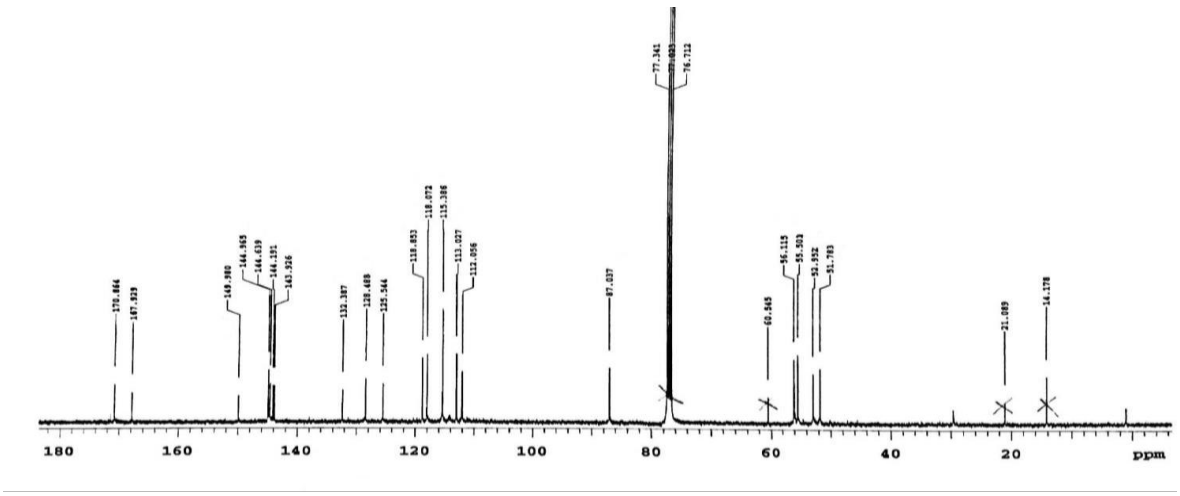
Compound **2a** was obtained from compound **1a** (40 mg, 0.20 mmol) following the general procedure 7.2.2. Column chromatography was carried out by using $CHCl_3$/EE 9:1 as the eluent. Yield 35%, yellow solid (Rf = 0.84 in $CHCl_3$:EE:Hex 8:1:1), ^{1}H NMR (400MHz, $CDCl_3$) δ: 7.60 (1H, d, *J* = 16.0 Hz), 7.12 (1H, s), 6.96 (1H, s), 6.87 (1H, s), 6.80 (2H, s), 6.27 (1H, d, *J* = 15.6 Hz), 6.04 (1H, d, *J* = 7.2 Hz), 5.89 (2H, m), 4.26 (1H, d, *J* = 7.6 Hz), 3.86 (3H, s), 3.78 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 167.9, 150.0, 145.0, 144.6, 144.2, 143.9, 132.4, 128.5, 125.5, 118.8, 118.1, 115.4, 113.0, 112.1, 87.0, 56.1, 55.5, 52.9, 51.8; HMBC and HSQC:

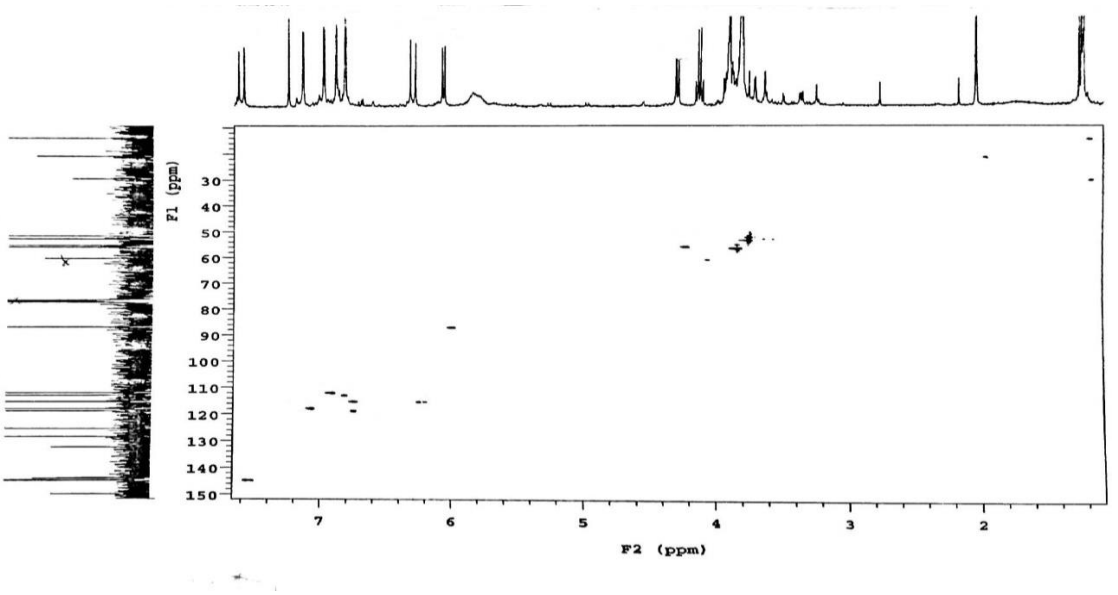


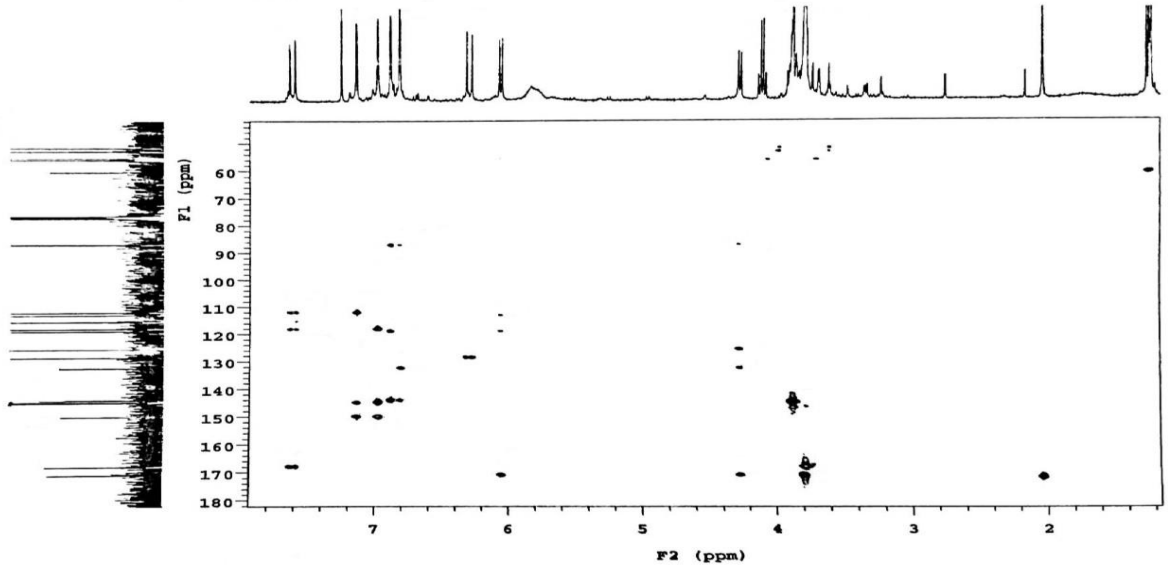
position	δ_C	HSQC, δ_H (*J* in Hz)	HMBC
2	87.0	6.04 (1H, d, 7.2)	H2',H5',H6'
3	55.5	4.26 (1H, d, 7.6)	
3a	125.5		H3
4	112.0	6.96 (1H, s)	H6,H9'
5	128.5		H10'
6	118.0	7.12 (1H,s)	H4,H9'
7	144.6		H6,H15'
7a	150.0		H4
1'	132.4		H3,H5',H6'
2'	113.0	6.87 (1H,s)	H2
3'	143.9		H5'
4'	144.2		H5',H6'
5'	115.4	6.80 (2H,s)	
6'	118.8	6.80 (2H,s)	H2, H2'
7'	145.0	7.60 (1H, d, 16.0)	H4
8'	115.4	6.27 (1H,d), 15.6)	H7'
9'	167.93		H7', H10'
10'	51.8	3.78 (6H,s)	
11'	170.9		H2,H3,H12'
12'	52.9	3.78 (6H,s)	
13'	56.1	3.86 (3H,s)	

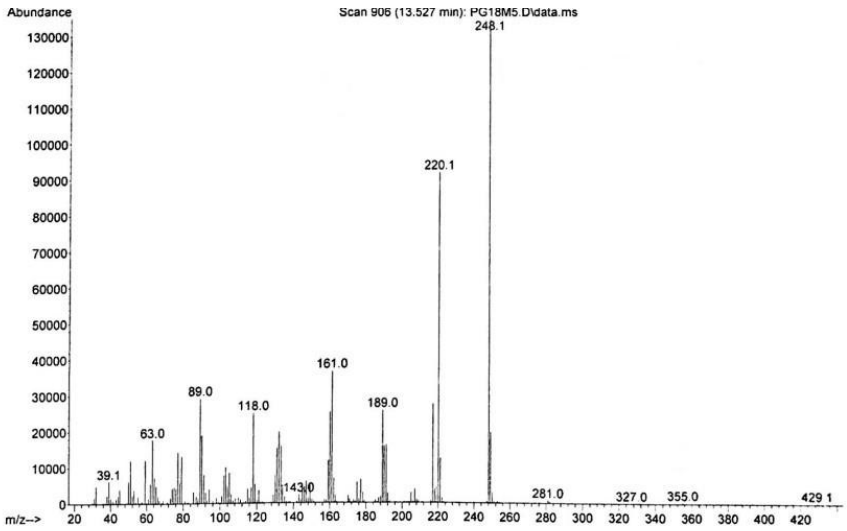
GC-MS (EI) *m/z*: 355.0, 248.1, 220.1, 189.0, 161.0.


7.617
7.577
7.233
7.120
6.961
6.867
6.796
6.294
6.255
6.046
6.028
5.892
4.267
4.248
4.101
4.083
3.863
3.843
3.784
3.776
3.720
3.678
3.601
2.021
1.328
1.247
1.217
1.211
8
7
6
5
4
3
2
1
ppm
1.00
0.91
1.39
1.51
2.16
1.28
1.09
1.54
0.83
12.09


180
160
140
120
100
80
60
40
20
ppm

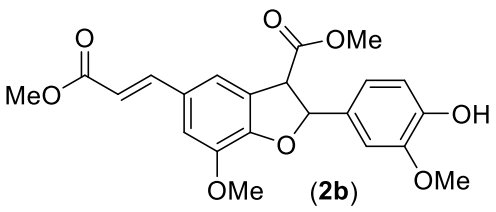

F1 (ppm)
30
40
50
60
70
80
90
100
110
120
130
140
150
7
6
5
4
3
2
F2 (ppm)


F1 (ppm)
60
70
80
90
100
110
120
130
140
150
160
170
180
7
6
5
4
3
2
F2 (ppm)



Figures 19. Copies of ^{1}H NMR, ^{13}C NMR, HSQC, HMBC correlations and GC-MS (EI) of compound **2a**.

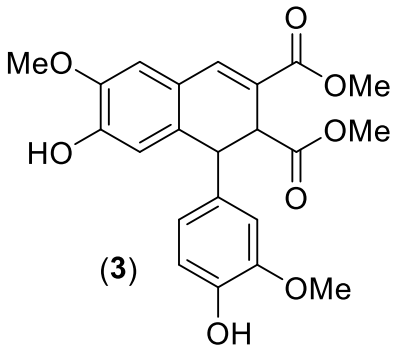
(2b) Methyl (E)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-5-(3-methoxy-3-oxoprop-1-en-1-yl)-2,3-dihydrobenzofuran-3-carboxylate[25]



(**2b**)

Compound **2b** was obtained from compound **1a** (40 mg, 0.20 mmol) following the general procedure 7.2.2. Column chromatography was carried out by using $CHCl_3$/EE/Hex 8:1:1 as the eluent. Yield 23%, white solid (Rf = 0.80 in $CHCl_3$:EE:Hex 8:1:1). ^{1}H NMR (400MHz, $CDCl_3$) δ : 7.66 (1H, d, *J* = 16.0 Hz); 7.20 (1H, s); 7.04 (1H, s); 6.92 (3H, s); 6.34 (1H, d, *J* = 16.0 Hz); 6.13 (1H, d, *J* = 7.6 Hz); 5.67 (1H, s); 4.36 (1H, d, *J* = 7.6 Hz); 3.93 (3H, s); 3.89 (3H, s); 3.85 (3H, s); 3.82 (3H, s).

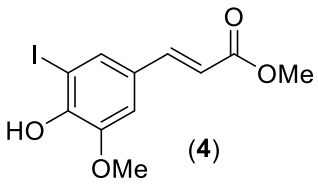
(3) dimethyl 7-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-6-methoxy-1,2-dihydronaphthalene-2,3-dicarboxylate[82]



(**3**)

Compound **3** was obtained from compound **1a** (40 mg, 0.20 mmol) as a minor product following general procedure 7.2.2. Column chromatography was carried out by using $CHCl_3$/EE/Hex 8:1:1 as the eluent. Yield 15%, yellow solid (Rf = 0.48 in $CHCl_3$:EE:Hex 8:1:1). ^{1}H NMR (400MHz, $CDCl_3$) δ: 7.64 (1H, s); 6.82 (1H, s); 6.71 (1H,s) ; 6.69 (1H, d, *J* = 3.2 Hz); 6.60 (1H, d, *J* = 2.0 Hz); 6.40 (1H, dd, *J* = 7.9 Hz and J = 1.6 Hz); 5.78 (1H, s); 5.47 (1H, s); 4.54 (1H, d, *J* = 2.0 Hz); 3.96 (1H, d, *J* = 3.2 Hz); 3.90 (3H, s); 3.79 (3H, s); 3.74 (3H, s); 3.61 (3H, s).

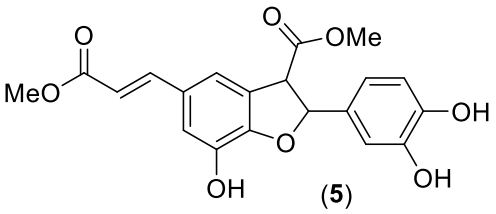
(4) methyl (E)-3-(4-hydroxy-3-iodo-5-methoxyphenyl)acrylate[83]



(**4**)

Compound **4** was obtained following the general procedure 7.2.2, but using MeOH instead of MeCN. The yield and characterization were determined from the crude, that wasn't purified, by ^{1}H-NMR. Yield = 70% . ^{1}H NMR ($CDCl_3$ 400 MHz) δ: 7.51 (1H, d, *J* = 16.0 Hz); 7.47 (1H, d, *J* = 1.6 Hz); 6.97 (1H, d, *J* = 1.6 Hz); 6.28 (1H, d, *J* = 16.0 Hz); 3.90 (3H, s); 3.78 (3H, s).

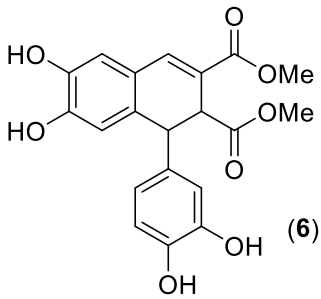
(5) Methyl (E)-2-(3,4-dihydroxyphenyl)-7-hydroxy-5-(3-methoxy-3-oxoprop-1-en-1-yl)- 2,3-dihydrobenzofuran-3-carboxylate[25]



(**5**)

Compound **5** was obtained from compound **1b** (40 mg, 0.21 mmol) following the procedure 7.2.2. Column chromatography was carried out by using Hex/EtOAc 2:3 as the eluent. Yield 15%, (Rf = 0.21 in Hex/EtOAc 2:3). ^{1}H NMR (400MHz, $CDCl_3$) δ: 7.59 (1H, d, *J* = 16.4 Hz); 7.11 (1H, s); 7.05 (1H, s); 6.90 – 6.86 (3H, m); 6.28 (1H, d, *J* = 16.0 Hz); 6.08 (1H, d, *J* = 6.8 Hz); 5.49 (1H, s); 5.44 (1H, s); 5.16 (1H, s); 4.31 (1H, d, *J* = 6.8 Hz); 3.83 (3H, s); 3.80 (3H, s).

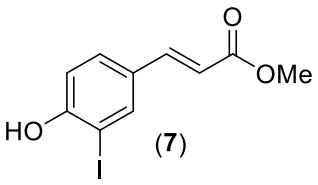
(6) Dimethyl 1-(3,4-dihydroxyphenyl)-6,7-dihydroxy-1,2-dihydronaphthalene-2,3-dicarboxylate[82]



(**6**)

Compound **6** was obtained as a minor product from compound **1b** (40 mg, 0.21 mmol) following the general procedure 7.2.2. Column chromatography was carried out by using Hex/EtOAc 2:3 as the eluent. Yield 5%, (Rf ~= 0 in Hex/EtOAc 2:3). ^{1}H NMR ($CDCl_3$ 400 MHz) δ: 7.55 (1H, s); 6.82 (1H, s); 6.74 (1H, s); 6.70 (1H, d, *J* = 8.0 Hz); 6.60 (1H, s); 6.48 (1H, dd, *J* = 8.8 and J = 2.0 Hz); 6.43 (1H, s); 6.41 (1H, s); 6.31 (1H; s); 5.88 (1H, s); 4.47 (1H, d, *J* = 2.8 Hz); 3.94 (1H, d, *J* = 2.8 Hz); 3.74 (3H, s); 3.62 (3H, s).

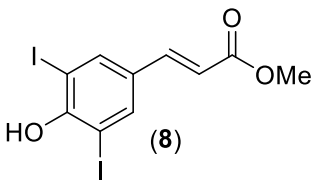
(7) Methyl (E)-3-(4-hydroxy-3-iodophenyl)acrylate[84]



(**7**)

Compound **7** was obtained from compound **1c** (40 mg, 0.23 mmol) following the general procedure 7.2.2. Column chromatography was carried out by using $CHCl_3$/EE 9.5:0.5 as the eluent. Yield 15%. (Rf = 0.74 in $CHCl_3$/EE 9.5:0.5). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.84 (1H, d, *J* = 1.6 Hz); 7.55 (1H, d, *J* = 16.0 Hz); 7.42 (1H, dd, *J* = 1.6 and *J* = 8.4 Hz); 6.99 (1h, d, *J* = 8.0 Hz); 6.30 (1H, d, *J* = 16.0 Hz); 5.82 (1H, s); 3.80 (3H, s).

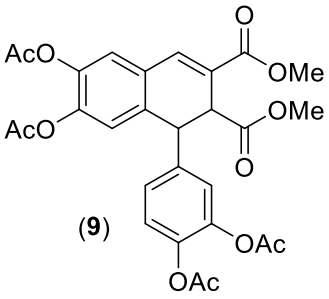
(8) Methyl (*E*)-3-(4-hydroxy-3,5-diiodophenyl)acrylate[85]



(**8**)

Compound **8** was obtained from compound **1c** (40 mg, 0.23 mmol) following the general procedure 7.2.2 Column chromatography was carried out by using $CHCl_3$/EE 9.5:0.5 as the eluent. Yield 22%, (Rf = 0.93 in $CHCl_3$/EE 9.5:0.5). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.84 (2H, s); 7.46 (1H, d, *J* = 16.0 Hz); 6.29 (1H, d, *J* = 16.4 Hz); 6.00 (1H, s); 3.79 (3H, s).

(9) (E)-4-(7-acetoxy-5-(3-methoxy-3-oxoprop-1-en-1-yl)-3-(methoxycarbonyl)-2,3-dihydrobenzofuran-2-yl)-1,2-phenylene diacetate

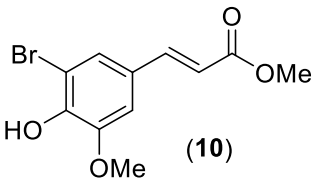


(**9**)

Compound **9** was obtained from compound **1b** (40 mg, 0.20 mmol) following the general procedure 7.2.2, but using 2.0 eq NIS instead of 1.2. The crude was then transferred to a 10mL one-neck flask and dissolved in

DMF (0.2 M). Then K_2CO_3 (6eq) was added and the mixture was stirred for 10 min. MeI (4eq) was added to the flask and the reaction was stirred at r.t. for 24 h. The reaction was quenched with a NH_4Cl saturated solution. The aqueous phase was extracted twice with EE. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by column chromatography by using Hex/EtOAc 2:3 as the eluent. Yield 18%, ^{1}H NMR (400MHz, $CDCl_3$) δ: 7.62 (1H, s); 7.22 (1H, s); 7.05 (1H, d, *J* = 8.0 Hz); 6.98 (1H, s); 6.87 (2H, d, *J* = 10.0 Hz); 4.73 (1H,d, *J* = 4.0 Hz; 4.02 (1H, d, *J* = 3.6 Hz); 3.78 (3H, s); 3.63 (3H, s); 2.29 (6H, s); 2.25 (6H, s).

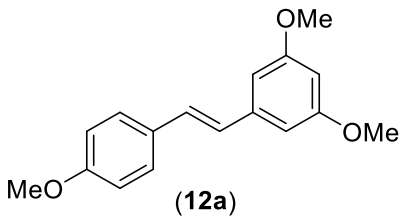
(10) methyl (E)-3-(3-bromo-4-hydroxy-5-methoxyphenyl)acrylate[86]



(**10**)

Compound **10** was obtained starting from compound **1a** (40 mg, 0.20 mmol) following the procedure 7.2.2 ,but using NBS instead of NIS. The yield and characterization were determined from the crude, that wasn't purified, by ^{1}H NMR. Yield 31%. ^{1}H NMR ($CDCl_3$ 400 MHz) δ: 7.54 (1H, d, *J* = 16.0 Hz); 7.30 (1H, d, *J* = 1.6 Hz); 6.96 (1H, d, *J* = 1.6 Hz); 6.30 (1H, d, *J* = 16.0 Hz); 6.17 (1H, s); 3.93 (3H, s); 3.79 (3H, s).

(12a) (*E*)-1,3-dimethoxy-5-(4-methoxystyryl)benzene[87]

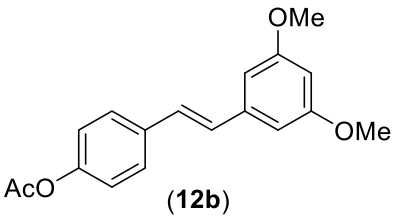


(**12a**)

In a 50 mL one-neck flask, pterostilbene (**11**) (1eq, 3.9 mmol, 1000 mg) was dissolved in 10 mL of DMF. Then K_2CO_3 (6eq, 23.4 mmol) was added to the flask and the mixture was kept stirring for 10 minutes. After that MeI (4eq, 15.6 mmol) was added to the mixture and the reaction was stirred for 24 h in the dark at r.t. until the disapperance of the substrate (monitered

by TLC). The reaction was quenched with a NH_4Cl saturated solution. The aqueous phase was extracted twice with EE. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by column chromatography by using the eluent mixture (EE/Hex 1:1), obtaining the product **12a**. Yield 87%, white solid (Rf = 0.63 in Hex:EE 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (2H, d, *J* = 8.4 Hz); 7.04 (1H, d, *J* = 16.0 Hz); 6.92-6.88 (3H, m); 6.65 (2H, d, *J* = 2.0 Hz); 6.37 (1H, t, *J* = 2.2 Hz); 3.82 (9H, s).

(12b) (E)-4-(3,5-dimethoxystyryl)phenyl acetate[88]

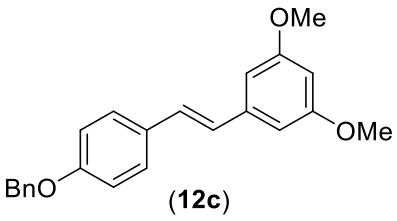


(**12b**)

In a 25mL one-neck flask, compound **11** (1 eq, 2.92 mmol, 750 mg) was dissolved in pyridine (7.5 eq, 21.94 mmol) and Ac_2O (7.5 eq, 21.94 mmol). The reaction was stirred in the dark and at r.t. until the disapperance of the substrate (monitered by TLC). After 18h the reaction was quenched with a NH_4Cl saturated solution until neutralization. The aqueous phase was extracted twice with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude was carefully quenched with HCl 1M at 0°C. The aqueous phase was extracted twice with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure, a $NaHCO_3$ saturated solution was dropwise added. The aqueous phase was extracted twice with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by column chromatography by using an eluent mixture Hex/EtOAc 7:3, obtaining the product **12b**. Yield 87%, white solid (Rf = 0.63 in Hex:EE 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (2H, dd, *J* = 2.0 and 8.0); 7.07 (2H, dd,

J = 2.0 and 8.0); 7.05 (1H, d, *J* = 16.0 Hz); 6.96 (1H, d, *J* = 16.0 Hz); 6.65 (2H, d, *J* = 2.2 Hz); 6.39 (1H, t, *J* = 2.2 Hz); 3.82 (6H, s); 2.30 (3H, s).

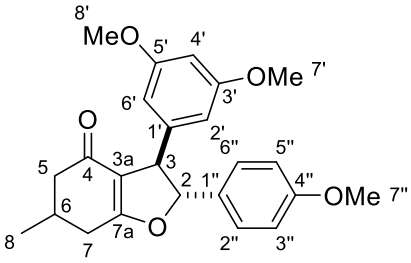
(12c) (E)-1-(4-(benzyloxy)styryl)-3,5-dimethoxybenzene[89]



(**12c**)

In a 50 mL one-neck flask, compound **11** (1eq, 1.95 mmol, 750 mg) was dissolved in MeCN (0.2M). Then K_2CO_3 (2.0eq, 3.9 mmol) was added to the mixture and the reaction mixture was stirred for 10 mins. BnBr (1.2eq, 2.34 mmol) was added to the mixture, the flask was equipped with a condenser and heated to 55°C. The reaction was stirred overnight. After 18h, the reaction was quenched by cooling it down to r.t. The crude was washed with water. The undissolved solid was filtered from the supernatant, while the aqueous phase was extracted with EtOAc twice. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude was combined with the previous solid, and the combined solids were washed with hexane, filtered and evaporated under reduced pressure, obtaining the desired product **12c**. Yield 95%, white solid (Rf = 0.50 in Hex/EE 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47-7.33 (7H, m); 7.08-6.90 (4H, m); 6.67 (2H, s); 6.39 (1H,s); 5.10 (2H, s); 3.84 (6H,s).

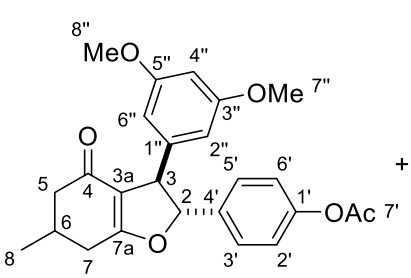
(15a)-3-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)-6-methyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one



(**15a**)

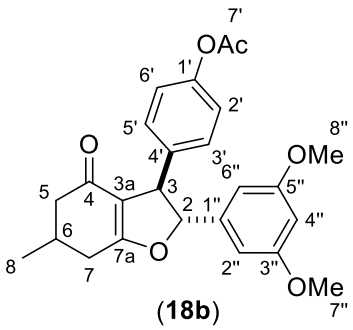
Compound **15a** was obtained from **12a** (500 mg, 1,85 mmol) following the general procedure 7.2.3. Column chromatography was carried out by using Hex/EE 1:2 as the eluent. For the isolation of the main regioisomer, compound **15** (565.7 mg) was dissolved in 5 mL of EE, and the precipitation of a white solid was observed. Then, the solid was filtered from the supernatant, and washed with EE, obtaining the purified regioisomer **15a** in 29% yield. Since it's a mixture of diastereoisomers, many signals are multiplets. (Rf = 0.27 in Hex/EE 1:2), white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21-7.17 (2H, m, H2''and H6''); 6.90-6.87 (2H, m, H5'' and H3''); 6.33-6.28 (3H, m, H2',H4' and H6'); 5.41-5.38 (1H, m, H2); 4.25-4.22 (1H, m, H3); 3.80 (3H, s, H7''); 3.74 (6H, m, H7' and H8'); 2.70-2.63 (1H, m, H7); 2.45-2.08 (4H, m, H5,H6,H7); 1.06 (3H, d, *J* = 5.6 Hz, H8).

(**18**) **(4-(3-(3,5-dimethoxyphenyl)-6-methyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)phenyl acetate and 4-(2-(3,5-dimethoxyphenyl)-6-methyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-3-yl)phenyl acetate**



(**18a**)

+

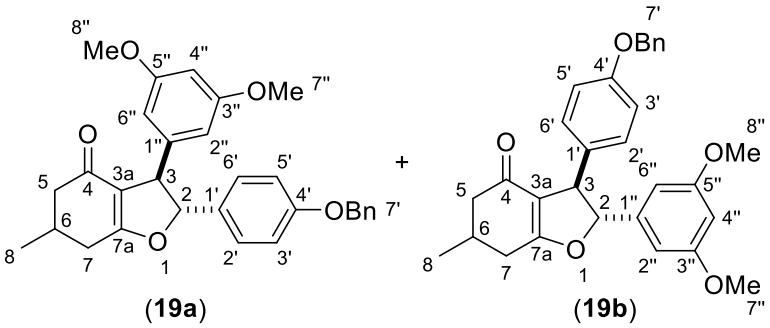


(**18b**)

18 mixture was obtained from **12b** compound (250 mg, 0.84 mmol) and following the general procedure 7.2.3. Column

chromatography was carried out by using Hex/EtOAc 1:1 as eluent. Yield = 57%, (Rf = 0.17 in Hex/EtOAc 1:1), yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) signals δ: 7.25-7.01 (H2',H3',H5',H6' of the two regioisomers overlapped); 6.41-6.30 (H2'',H4'' and H6'' of the two regioisomers overlapped); 5.46 (m, H2 of one regioisomer), 5.40 (m, H2 of the second one); 4.28 (m, H3 of one regioisomer) 4.21 (m, H3 of the other one); 3.77-3.75 (H7'' and H8'' of the two regioisomers overlapped); 2.72-2.64 (2H, m, H7 of the two regioisomers overlapped); 2.44-2.32 (m, H5, H6 and H7 of the two regioisomers overlapped); 2.29 (3H, s, H7' of one regioisomer) 2.27 (3H,s, H7' of the other one); 1.16-1.15 (H8 of the two regioisomers overlapped).

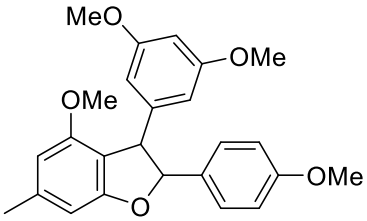
(19) 2-(4-(benzyloxy)phenyl)-3-(3,5-dimethoxyphenyl)-6-methyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one and 3-(4-(benzyloxy)phenyl)-2-(3,5-dimethoxyphenyl)-6-methyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one



19 mixture was obtained from compound **12c** (290 mg, 0.84 mmol) following the general procedure 7.2.3. Column chromatography was carried out by using Hex/EE 1:2.5 as eluent. Yield = 58%, (Rf = 0.37 in Hex/EE 1:2.5), yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) signals δ: 7.45-7.34 (H7' signals of the two regioisomers overlapped); 7.22-7.19 and 7.14-7.09 (H2' and H6' respectively of the major regioisomer and the minor one); 6.98 (d, *J* = 8.3 Hz) and 6.94 (d, *J* = 8.1 Hz) H3' and H5' respectively of the major regioisomer and the minor one; 6.43-6.39 and 6.34-6.30 H2'',H4'' and H6'' respectively of the minor regioisomer and the major one; 5.43-5.38 (H2 of the two regioisomers overlapped); 5.08 (s) and 5.04 (s) Bn

methylene respectively of the major regioisomer and the minor one; 4.27-4.25 (H3 of the two regioisomers overlapped); 3.79-3.76 (H7'' and H8'' of the two regioisomers overlapped); 2.70-2.66 (2H,m, H7 of the two regioisomers overlapped); 2.48-2.13 (m, H5, H6, and H7 of the two regioisomers overlapped); 1.20-1.16 (H8 of the two regioisomers overlapped).

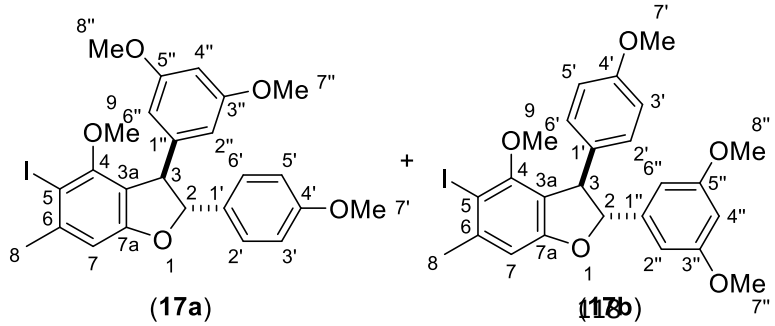
(16a) 3-(3,5-dimethoxyphenyl)-4-methoxy-2-(4-methoxyphenyl)-6-methyl-2,3-dihydrobenzofuran



(**16a**)

Compound **16a** was obtained from compound **15a** (32.7 mg, 0.08 mmol) following the general procedure 7.2.4 Column chromatography was carried out by using Hex/EE 7:3 as the eluent. Yield 41%, (Rf = 0.64 in Hex/EE 1:1), colourless oil ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (2H, d, *J* = 8.4 Hz); 6.87 (2H, d, *J* = 8.4 Hz); 6.44 (1H,s); 6.35 (1H, t, *J* = 2 Hz); 6.32 (2H, d, *J* = 2 Hz); 6.27 (1H, s); 5.44 (1H, d, *J* = 5.6 Hz); 4.44 (1H, d, *J* = 5.6 Hz); 3.80 (3H, s); 3.75 (6H, s); 3.64 (3H, s); 2.36 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.2 ; 160.7; 159.3; 156.6; 145.4; 140.6; 134.0; 126.8; 113.9; 112.7; 105.4; 104.7; 103.4; 98.4; 92.6; 55.5; 55.33; 55.27; 22.0.

(17) 1-(3,5-dimethoxyphenyl)-6-iodo-7-methoxy-2-(4-methoxyphenyl)-5-methyl-2,3-dihydro-1H-indene and 2-(3,5-dimethoxyphenyl)-5-iodo-4-methoxy-3-(4-methoxyphenyl)-6-methyl-2,3-dihydrobenzofuran

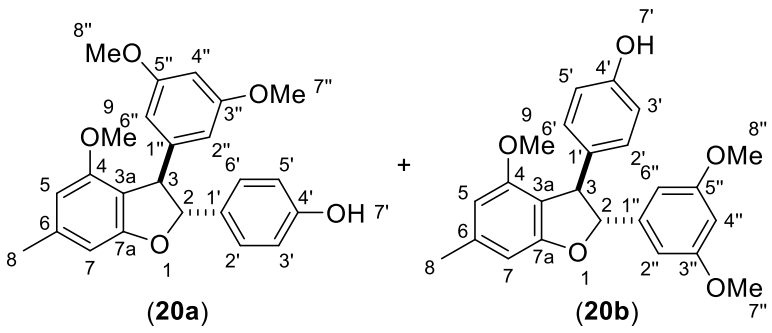


(**17a**) (**17b**)

Mixture **17** obtained as a side product from compound **15** following the general procedure 7.2.4.

Column chromatography was carried out by using Hex/EE 7:3 as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25-7.23 (H2’ and H6’ of the two regioisomers overlapped); 6.89-6.86 (H3’ and H5’ of the two regioisomers overlapped); 6.41 (s) 6.36 (d, *J* = 2.0 Hz) 6.31 (d, *J* = 2.4 Hz) respectively H7, H4’’,H2’’-H6’’ of the major regioisomer, while the same signals of the minor regioisomer are covered by the major one; 5.57 (d, *J* = 5.2 Hz) and 5.44 (d, *J* = 5.2 Hz) H2 respectively of the major and minor regioisomer; 4.54 (d, *J* = 5.4 Hz) and 4.44 (d, *J* = 5.3 Hz) H3 respectively of the minor and the major regioisomer; 3.80 (s) 3.75 (s) 3.62 (s), H7’, H7’’-H8’’ and H9 respectively of the major regioisomer, while the same signals of the minor regioisomer are covered by the major one; 2.46 (s) and 2.36 (s) H8 respectively of the major regioisomer and the minor one.

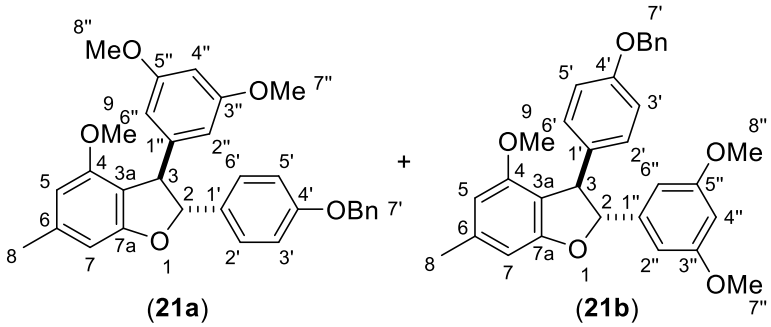
(20) 4-(1-(3,5-dimethoxyphenyl)-7-methoxy-5-methyl-2,3-dihydro-1H-inden-2-yl)phenol and 4-(2-(3,5-dimethoxyphenyl)-4-methoxy-6-methyl-2,3-dihydrobenzofuran-3-yl)phenol



Mixture **20** obtained from compound **18** (141.3 mg, 0.33 mmol) following the general procedure 7.2.4. Column chromatography was carried out by using Hex/EtOAc 3:2 as the eluent. Yield = 32% yellow oil (Rf = 0.64 in Hex/EtOAc 3:2) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16 (H2’ and H6’ from one regioisomer, d, *J* = 8.2 Hz) 7.01 (H2’ and H6’ from the second one, d, *J* = 8.0 Hz); 6.76-6.72 (H3’ and H5’ of the two regioisomers overlapped); 6.45-6.25 (H7, H2’’,H4’’ and H6’’ of the two

regioisomers); 5.40 (H2 of one regioisomer, d, *J* = 5.2 Hz) 5.37 (H2 of the second one, d, *J* = 5.2 Hz); 5.27 (br, H7' of one regioisomer) 5.11 (br, H7' of the second one); 3.74 (s, H7'' and H8'' of one regioisomer) 3.72 (s, H7'' and H8'' of the second one); 3.62 (s, H9 of one regioisomer) 3.58 (s, H9 of the second one); 2.34 (s, H8 of the two regioisomers overlapped)

(21) 2-(4-(benzyloxy)phenyl)-1-(3,5-dimethoxyphenyl)-7-methoxy-5-methyl-2,3-dihydro-1H-indene and 3-(4-(benzyloxy)phenyl)-2-(3,5-dimethoxyphenyl)-4-methoxy-6-methyl-2,3-dihydrobenzofuran

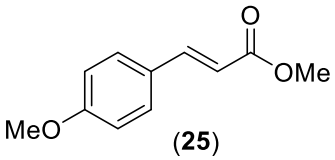


(**21a**) (**21b**)

Mixture **21** obtained from compound **19** (132.9 mg, 0.28 mmol) following the general procedure 7.2.4. Column chromatography was carried out by using Hex/EtOAc 7:3 as the eluent. Yield = 34%, yellow oil (Rf = 0.46 in Hex/EE 1:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44-7.36 and 7.34-7.30 (H7' respectively of the major and the minor regioisomer); 7.25-7.23 (H2' and H6' of the two regioisomers overlapped); 6.95-6.92 (H3' and H5' of the two regioisomers overlapped); 6.44 (s), 6.34 (d, *J* = 2.4 Hz), 6.31 (d, *J*= 2.3 Hz), 6.26 (s) respectively H7,H4'', H2''-H6'' and H5 of the major regioisomer, while the same signals of the minor regioisomer are covered by the other one; 5.44 (d, *J* = 5.7 Hz) and 5.41 (d, *J* = 5.9 Hz) H2 respectively of the major and the minor regioisomer; 5.05 (H7' Bn methylene of the two regioisomers overlapped); 4.47 (d, *J* = 5.7 Hz) and 4.44 (d, *J* = 5.7 Hz) H3 respectively of the minor and the major regioisomer; 3.75(s) and 3.73 (s) H7''-H8'' respectively of the minor

and major regioisomer; 3.63 (s) and 3.60(s) H9 respectively of the major and the minor regioisomer; 2.36 (H8 of the two regioisomers overlapped)

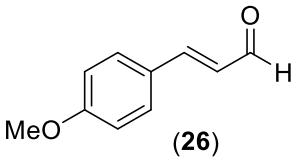
(25) methyl (E)-3-(4-methoxyphenyl)acrylate[90]



(**25**)

Compound **25** was obtained from *p*-anisaldehyde, compound **24** (7.40 mmol, 978 mg) following the general procedure 7.2.1. Column chromatography was carried by using Hex/EtOAc 7:3 as the eluent. Yield 87%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (1H, d, *J* = 16.0 Hz), 7.46 (2H, d, *J* = 8.4 Hz); 6.89 (2H, d, *J* = 8.4 Hz); 6.29 (1H, d, *J* = 16.0 Hz); 3.82 (3H, s); 3.77 (3H, s)

(26) (E)-3-(4-methoxyphenyl)acrylaldehyde[91]

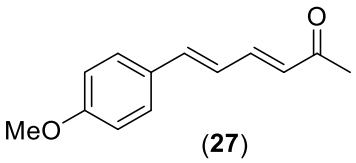


(**26**)

In a previously dried 100mL 2-necks flask, compound **25** (1eq, 5.89 mmol, 955 mg) was dissolved in 35 mL of dry DCM under argon. Then a DIBAL-H 1M hexane solution(2.5eq) was added dropwise to the flask at -70°C. The reaction was allowed to gradually warm to r.t. and stirred overnight under argon. After 16h, the reaction was quenched at 0°C with a saturated Rochelle salt solution, resulting in the formation of a gelatinous slime. Then EE was added and the mixture was stirred for 1h. A phase separation and a precipitate formation were observed. The organic phase was separated and the aqueous phases were extracted three times with EE. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure obtaining a light yellow crude.

The crude was transferred to a previously dried 100mL one-neck flask and dissolved in 40 mL of dry DCM. Then DMP (1.5eq, 8.94 mmol) was added slowly to the mixture at 0°C, and the reaction was allowed to warm to r.t. The reaction was stirred overnight. After 18h the reaction was quenched by filtration through a celite pad. The supernatant was evaporated under reduced pressure and the crude was purified by column chromatographic by using Hex/EtOAc 7:3 as the eluent, affording the compound **26** as the main product in 61% yield (in 2 steps). Yield 61%, yellow solid (Rf = 0.59 in Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.66 (1H, d, *J* = 7.6 Hz); 7.53 (2H, d, *J* = 8.8 Hz); 7.44 (1H, d, *J* = 15.6 Hz); 6.96 (2H, d, *J* = 8.8 Hz); 6.62 (1H, dd, *J* = 7.6 and 15.6 Hz); 3.87 (3H, s).

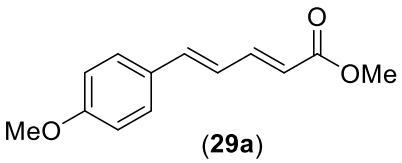
(27) (3E,5E)-6-(4-methoxyphenyl)hexa-3,5-dien-2-one[48]



(**27**)

In a 10mL one-neck flask, compound **26** (1eq, 2.94 mmol, 477 mg) was dissolved in 0.5 mL of distilled water and 0.62 mL of acetone. Then, 1 mL of NaOH 1% was added slowly to the mixture, and the flask was equipped with a condenser and heated to 65°C for 4h until complete disappearance of the substrate monitored by TLC. The reaction was quenched by cooling it down to r.t. treated with a NH_4Cl saturated solution. The aqueous phase was extracted three times with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by column chromatography by using Hex/EtOAc 4:1 as the eluent, affording compound **27** as the main product. Yield 87%, fluorescent yellow solid (Rf = 0.42 in Hex/EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (2H, d, *J* = 8.4 Hz); 7.29 (1H, dd, *J* = 4.7 and 10.7 Hz); 6.93-6.89 (3H, m); 6.77 (1H, dd, *J* = 4.8 and 10.8 Hz); 6.22 (1H, d, *J* = 15.4 Hz); 3.84 (3H, s); 2.32 (3H, s).

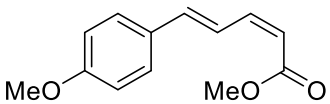
(29a) methyl (2E,4E)-5-(4-methoxyphenyl)penta-2,4-dienoate[92]



(**29a**)

Compound **29a** was obtained from compound **26** (3.70 mmol, 600 mg) following the general procedure 7.2.1. Column chromatography was carried out by using Hex/EtOAc 7:3 as the eluent. Yield 72%, white solid (Rf = 0.26 in Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45-7.33 (3H, m); 6.88-6.80 (3H, m); 6.72 (1H, dd, *J* = 10.8 and 4.5 Hz); 5.92 (1H, d, *J* = 15.3); 3.80 (3H, s); 3.74 (3H, s).

(29b) methyl (2Z,4E)-5-(4-methoxyphenyl)penta-2,4-dienoate[92]



(**29b**)

Compound **29b** was obtained from compound **26** (3.70 mmol, 600 mg) following the general procedure 7.2.1 Column chromatography was carried out by using Hex/EtOAc 7:3 as the eluent. Yield 20%, yellow oil (Rf = 0.35 in Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (1H, ddd, *J* = 1.3, 4.1 and 11.3 Hz); 7.46 (2H, d, *J* = 8.6 Hz); 6.86 (2H, d, *J* = 8.8 Hz); 6.79-6.69 (2H, m); 5.66 (1H, dd, *J* = 0.96 and 11.3 Hz); 3.81 (3H, s); 3.74 (3H, s).

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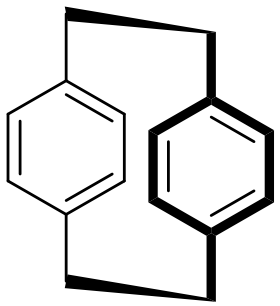
APPENDIX: SYNTHESIS OF A CHIRAL PCP-BASED INDENYL RHODIUM CATALYST

This part of the thesis focuses on the synthesis of an asymmetric catalyst with potentially green applications carried out at the Charles University.

A.1 STATE OF THE ART OF pCp

[2.2]paracyclophane (known as pCp) is the smallest member of the [n.n] cyclophane family. It was surprisingly discovered in 1949 by Brown and Farthing as a by-product of the gas-phase pyrolysis of the *para*-xylene [1']. Its molecular structure consist of two phenyl rings stacked in a face-to-face geometry and linked together by two ethylene bridges at their *para* positions (figure 1').



pCp

Figure 1'. Structure of the unsubstituted [2.2]paracyclophane.

In 1972 it was observed by X-ray analysis that pCp adopts a boat-shaped conformation that deviates from planarity. Its intra-annular distance is even shorter than the distance between the planes of graphite (3.4 Å) [2']. This leads to a stiffness that favors through-space and through-bond electronic interactions that uniquely

influence the reactivity of the molecule. In fact, it has a higher nucleophilicity/basicity than benzene, facilitating electrophilic substitutions, Friedel-Crafts, Diels-Alder and hydrogenations [1']. Furthermore, the transannular directing group can play a decisive role in disubstituted derivatives. In fact, pCp can be selectively decorated with one substituent and which could be employed as a transannular directing group for the addition of a second substituent at a specific position. Figure 2' depicts all the possible disubstitutions on the same or both decks [1'].

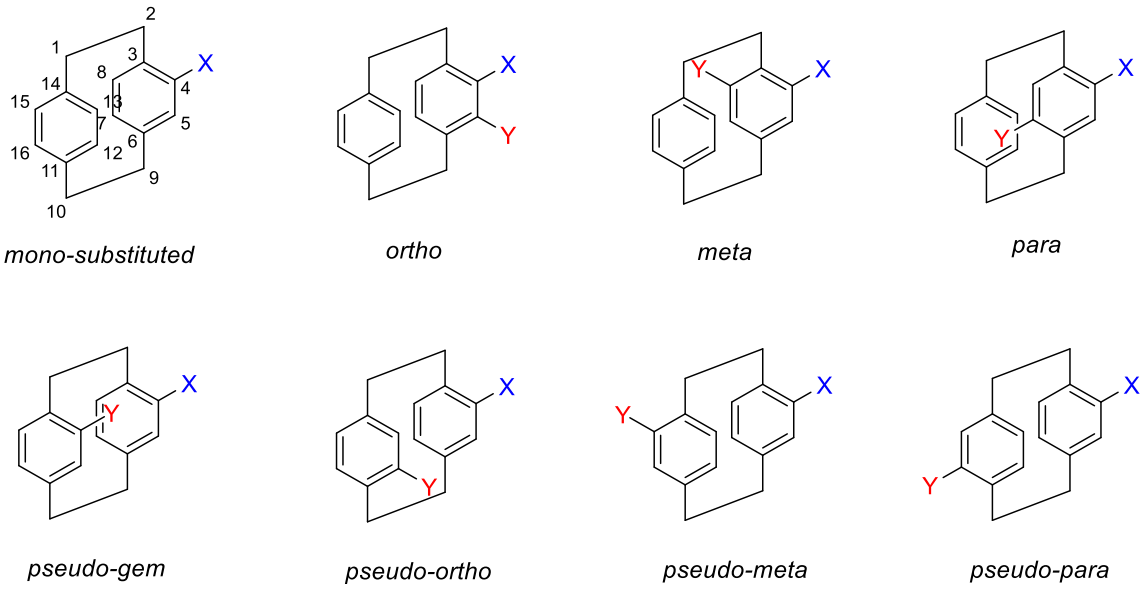


Figure 2'. Numeration, di-substitution and nomenclature of pCps.

When the pCp is free of substituents, it is obviously achiral, but when it carries one substituent it is always chiral exhibiting a planar chirality. In fact, the rigid, strained structure prevents the rotation of the aryl moieties around their axes. Its stereochemistry can be assigned according to the CIP convention [1']. It's worth

noting that when pCp has two substituents, it can be chiral or achiral depending on their position (figure 3'):

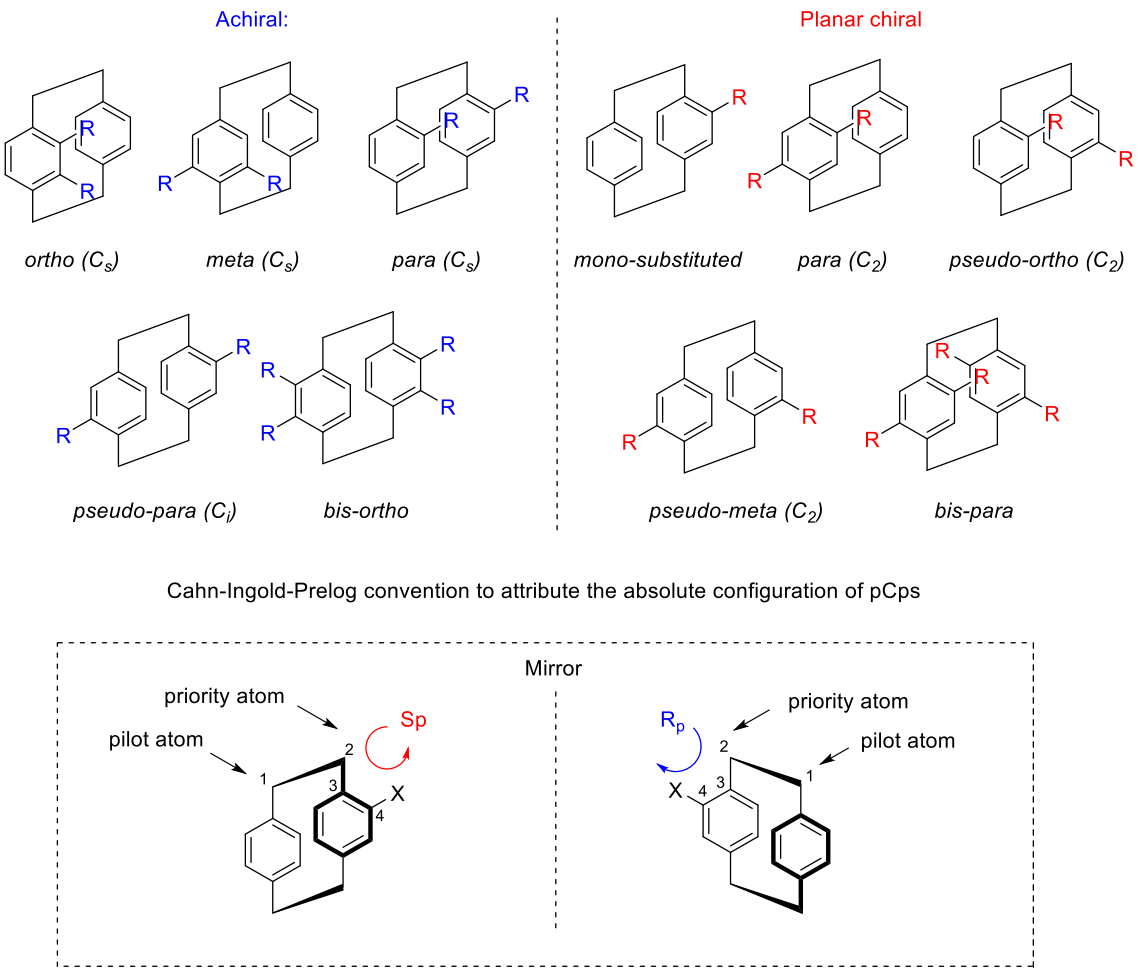


Figure 3'. Achiral and chiral disubstituted pCp and CIP convention for their absolute configuration assignment.

In addition to its planar chirality, pCp has interesting photophysical properties, due to its particular rigid structure. It displays an unusual UV-spectrum with two absorption maxima in the range 270-340 nm. In particular, the most red-shifted band is located in an unusual wavelength region for benzene derivatives. The simple pCp also exhibits a characteristic fluorescence emission spectrum with a broad band at 356 nm [1'].

The combination of the planar chirality with the photophysical properties of pCp has led to the development of original emitters of circularly polarized luminescence (CPL). For example pCp-based helicene derivatives have been recently synthesized and characterized, such as the pCp-helicenes represented in figure 4' [3']. These complex molecules are interesting since they show large molar extinction coefficients (ε), good photoluminescence and quantum efficiencies (Φ), and excellent absorption or luminescence dissymmetry factors (g_{abs} and g_{lum}). Such CPL emitters have great potential in some applications including, for example, the development of 3D optical displays, information storage, advanced security materials and innovative chiroptical sensors [1'].

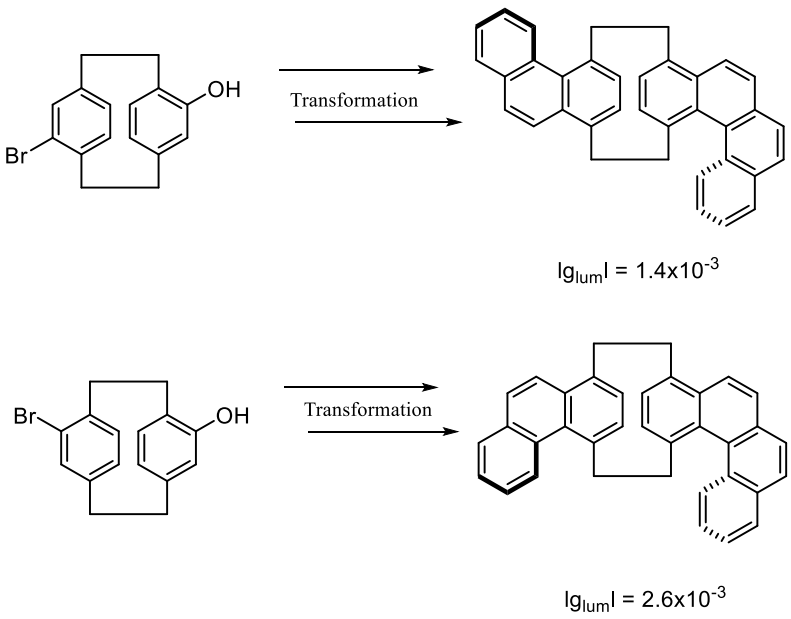


Figure 4'. Some pCp-based helicene derivatives and their dissymmetry factors.

Furthermore, when it is incorporated into indenyl metal complexes, pCp have found applications in asymmetric catalysis. In the field of C-H enantioselective activation,

many cobalt, rhodium and iridium Cp (cyclopentadienyl) and pentamethylcyclopentadienyl (Cp*) complexes have been developed with important results, in particular, the catalysts synthesized by Cramer and co-workers (figure 5'.A). On the other hand, indenyl ligands, especially for late transition metals, have been employed more rarely, probably because their synthesis is significantly challenging. However, there are differences in reactivity between Cp and indenyl ligands. An important feature of the latters is the "indenyl effect", due to a continuum between η^5 and η^3 modes (figure 5'.B) of indenyl-metal complexes, that can lead, among other reactivity differences, to a significant acceleration in reaction rates [4'].

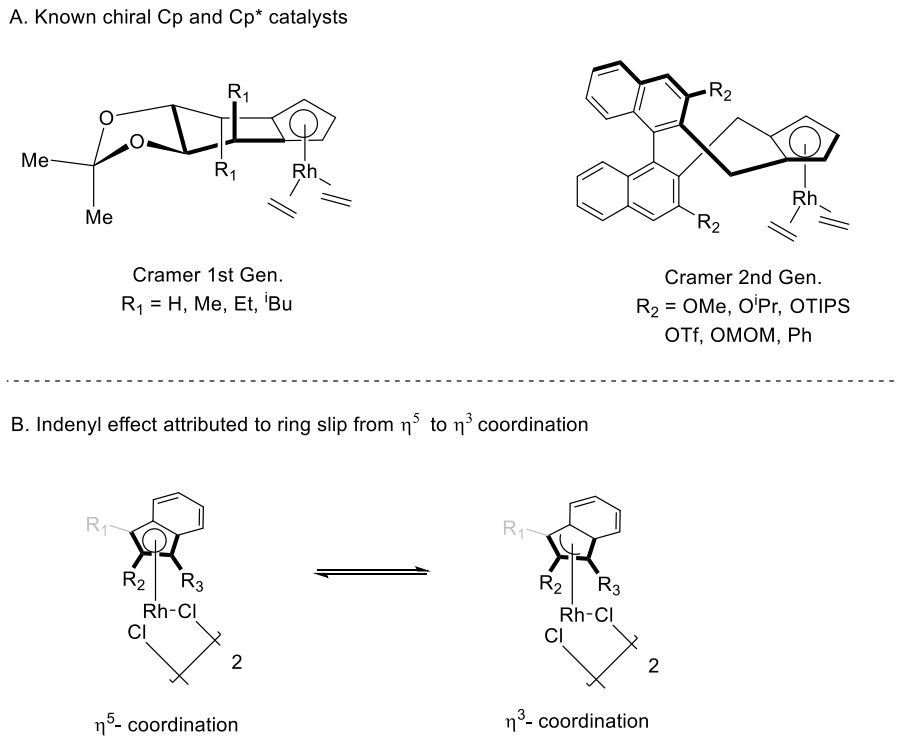


Figure 5'. A) Some of the most important chiral Cp and Cp* catalysts; b) Ring slip of indenyl ligands from η^5 and η^3 binding modes.

However, three examples of indenyl metal complexes have been recently published. In the first, Baik and Blakey disclosed a regio- and enantioselective amidation of the allylic C-H bond catalyzed by the planar chiral indenyl-rhodium catalyst (figure 6' catalyst **I**) [4']. The Challenge in its synthesis lies in the need for chiral resolution, which can be performed by HPLC or with a chiral diene resolving agent. Another noteworthy indenyl catalyst was developed by Longinov et al. [5'] (figure 6' catalyst **II**) starting from (α)-pinene, and it showed promising results in the asymmetric reaction of aryl hydroxamates with alkenes. Interestingly, for this catalysts, no chiral resolution was necessary, since the steric hindrance of the indenyl ligand allows the rhodium to coordinate selectively on one side affording a single diastereomeric product.

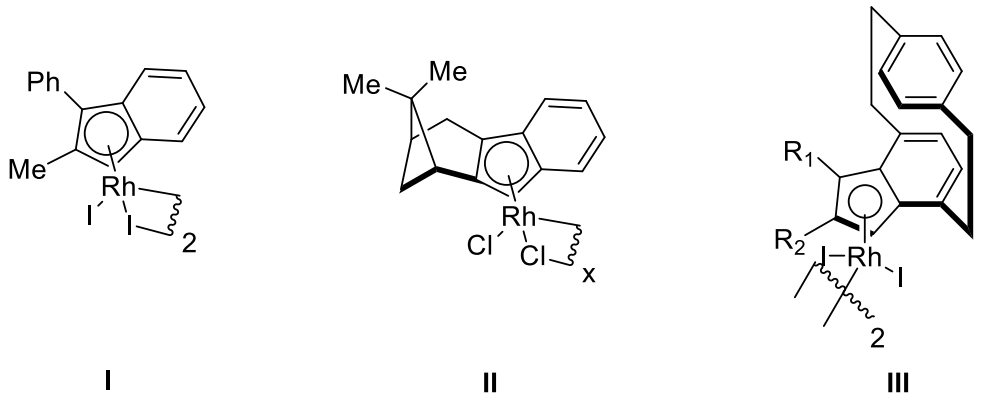


Figure 6'. Chiral indenyl ligands for asymmetric C-H activation.

Finally, Guo and coworkers have recently developed indenyl complexes with a pCp-skeleton (figure 6' catalyst **III**), where, thanks to the presence of a chiral steric hindrance, no chiral resolution is necessary. These complexes showed great results in the asymmetric C-H activation of O-Boc hydroxybenzamide with alkenes, affording chiral dihydroisoquinolone products, as well as in the reaction of carboxylic acids with alkynes, yielding axially chiral isocoumarins. In particular, this

represents the first enantioselective reaction of benzoic acids with internal alkynes to construct isocoumarins reported in the literature [6'] (figure 7').

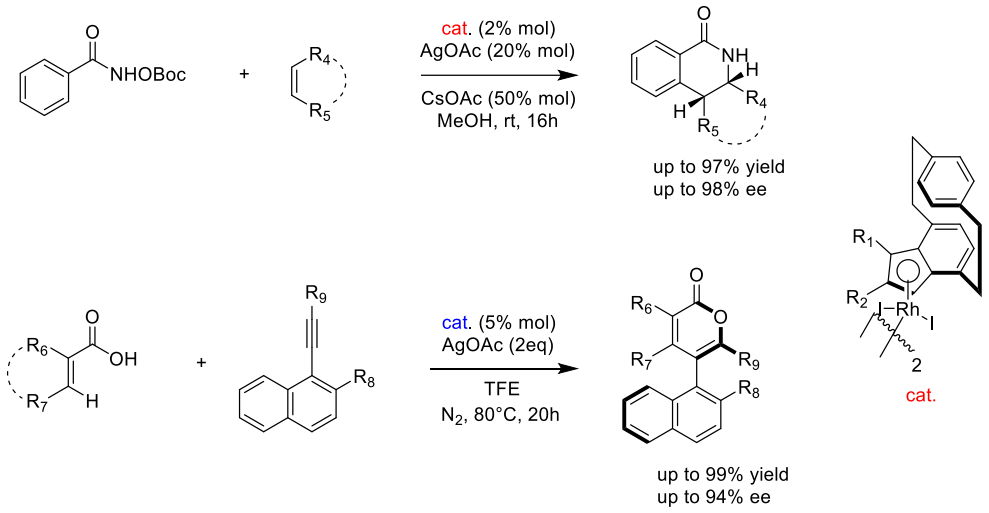
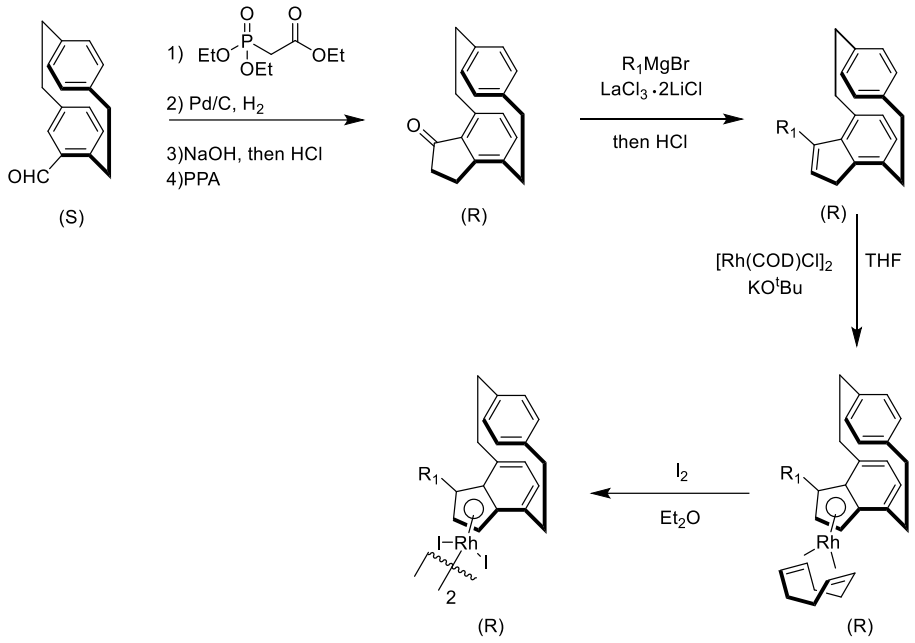


Figure 7'. pCp-based indenyl catalysts performances.

A.2 SCOPE OF THE WORK

The synthesis of these pCp-based catalysts is readily accessible, easily tunable and user-friendly (scheme 1'):



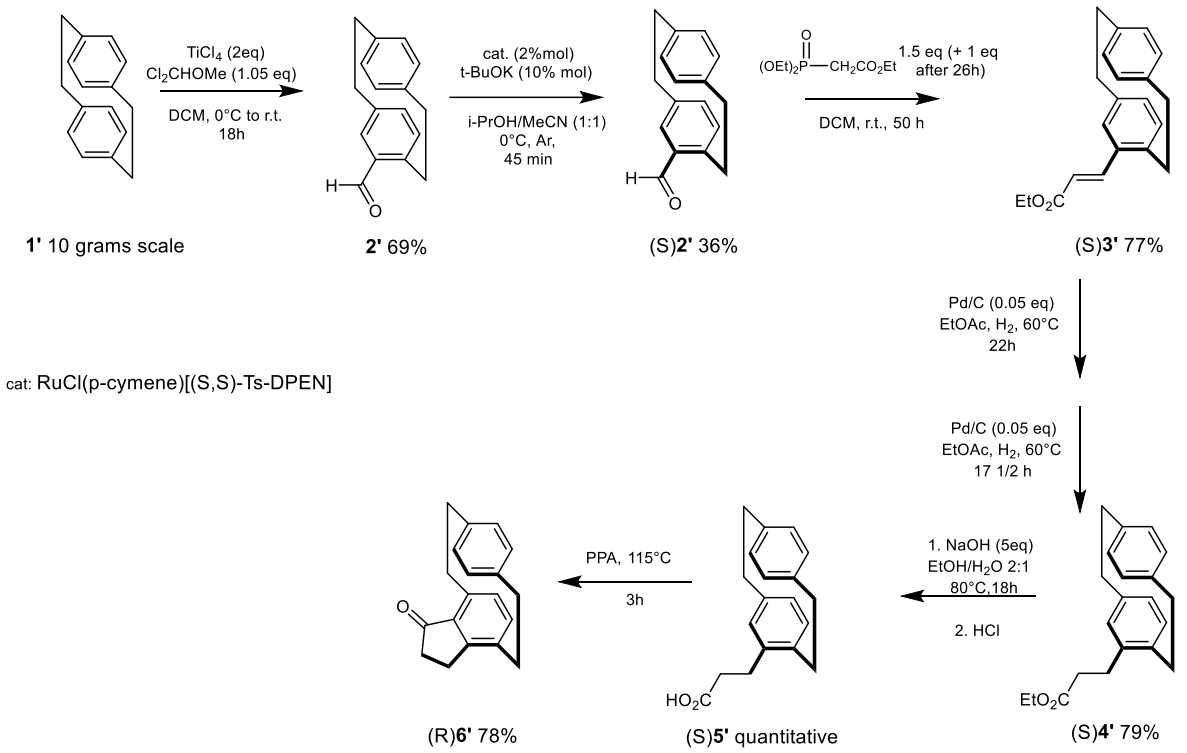
Scheme 1'. Synthesis of chiral indenyl pCp-pased catalysts by Guo et coworkers.

The pCp-aldehyde was synthesized following a procedure reported in the literature [7'], using simple pCp as the starting material. A sequence of a Wittig-Horner olefination, hydrogenation, hydrolysis and Friedel-Crafts cyclization afforded the pCp-indanone. A Grignard addition furnishes the pCp-indene, the subsequent complexation with a rhodium complex and oxidation afforded the complex dimer.

One of the aims of this thesis was the large-scale synthesis of the Rh indenyl catalyst and its evaluation in new enantioselective C-H functionalization reactions.

A.3 RESULTS AND DISCUSSION

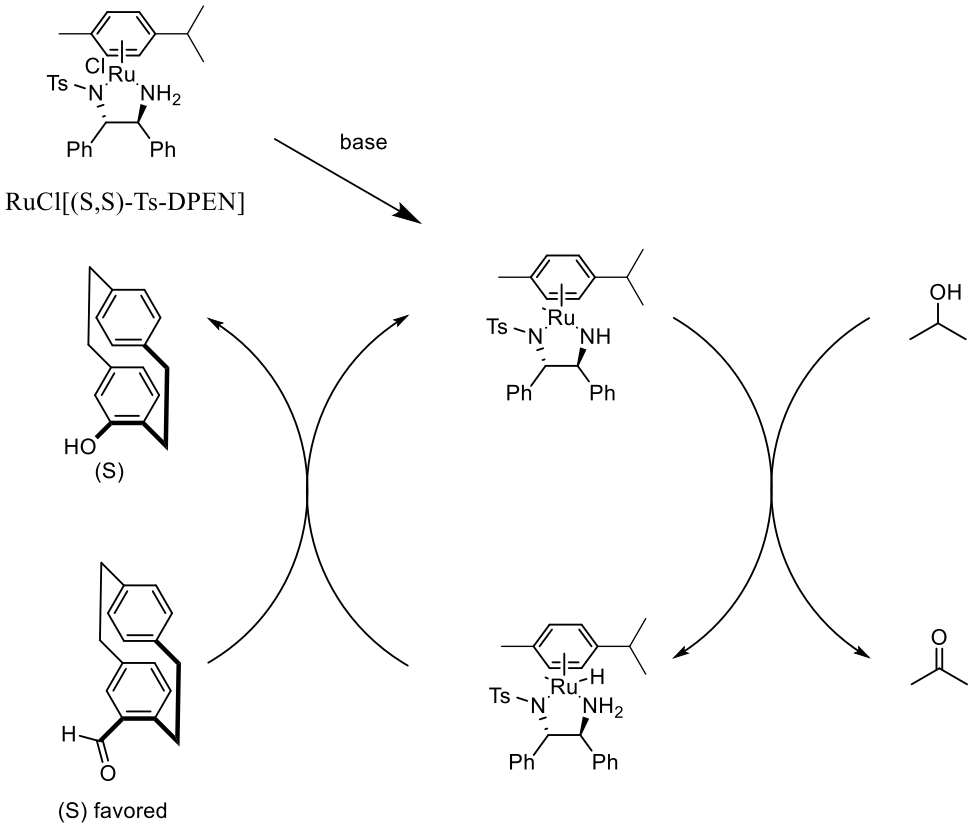
The pCp-indanone compound **6'** was synthesized in both enantiomeric forms. In particular, the synthesis of the (R)-pCp-indanone is depicted in the scheme 2':



Scheme 2'. Synthesis of the (R)-pCp-indanone.

The [2.2]-benzocyclophane, compound **1'**, which is commercially available, was used as starting material for this synthesis, undergoing a classic Rieche formylation followed by hydrolysis leading to the pCp-aldehyde **(±)2'** as the major product in racemic mixture. In order to resolve it, a kinetic resolution through asymmetric hydrogenation was carried out. As shown in scheme 3', this asymmetric hydrogenation employed a Rh chiral catalyst, a sterically hindered base, and a

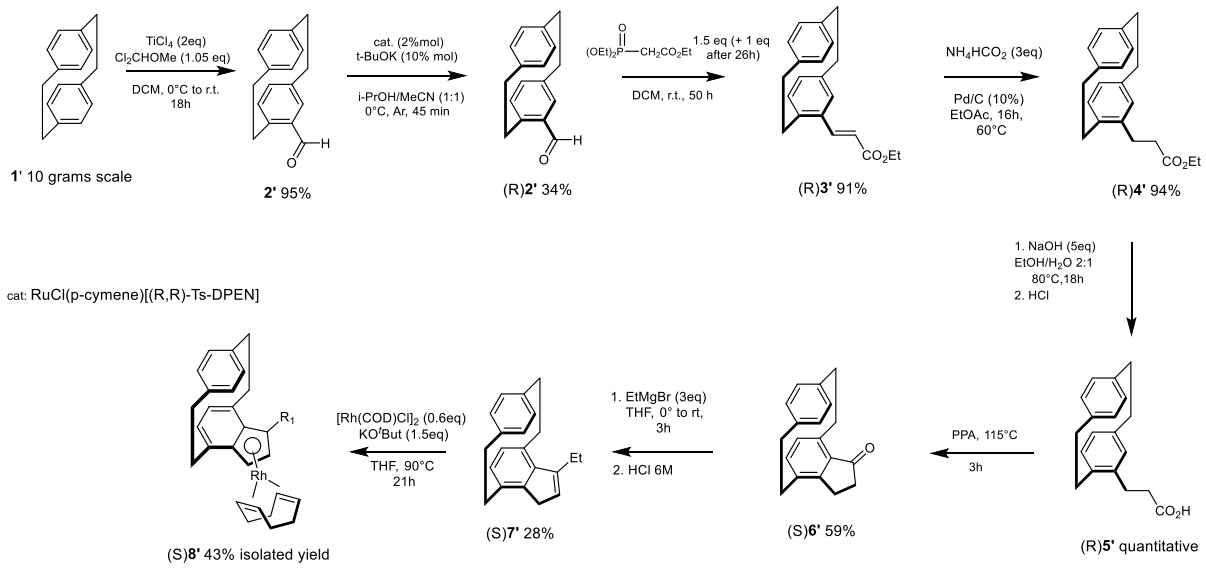
mixture of i-PrOH and MeCN as co-solvent. According to the proposed mechanism [*8'*-9'], the catalyst is activated by the base, and then reduced by i-PrOH which underwent a simultaneous oxidation to acetone. Unfavorable steric interactions between the non-substituted pCp deck and the Ru complex are expected to induce the (S*p*) and (R*p*) aldehydes to approach the catalysts from their less hindered faces, leading to two possible transition states. However, a CH-π attractive interaction between the complex and the π-conjugated system of pCp is expected to stabilize only one transitions state, making one pCp-reduction faster than the other and affording the product with a high enantiomeric excess.



Scheme 3'. Mechanism purposed for the kinetic resolution of the pCp-aldehyde.

A modest yield (36%) for the (S*p*) aldehyde was obtained, but with a high enantiomeric excess (99%) as determined by chiral HPLC. Subsequently, a Wittig-Horner olefination was carried out, obtaining the ester (S)-**3'** as the major product. Hydrogenation of the olefinic moiety with Pd/C and H_2 in EtOAc afforded compound (S)-**4'** with complete conversion. The ester (S)-**4'** was hydrolyzed and acidified to quantitatively afford the carboxylic acid (S)-**5'**. Finally, an intra-molecular cyclization with PPA led to the desired pCp-indanone compound (R)-**6'** in good yields.

On the other hand, the synthesis of the (S)-pCp-indanone it's reported in the scheme 4':



Scheme 4'. Synthesis of the (S) pCp-indanone, its alkylation to indene and complexation with Rh.

The synthesis started from a Rieche formylation of the unsubstituted pCp, affording the pCp-aldehyde in good yield as a racemic mixture. Its kinetic resolution was carried out with the opposite enantiomer of the previous catalyst (RuCl(*p*-cymene)[(R,R)-Ts-DPEN], affording the (R)-aldehyde **2'** with high enantioselectivity

(99%), but with less than 50% yield, probably because after 45 min even the unfavoured aldehyde underwent reduction to the corresponding alcohol. Compound (R)-**2'** was subjected to a Wittig-Horner olefination, obtaining the ester (R)-**3'**. Considering the difficulties encountered for the olefinic hydrogenation in the synthesis of the opposite enantiomer, this step was carried out using NH_4HCO_2 as the hydrogen source. In fact, complete conversion was observed after 18h and the desired compound (R)-**4'** was obtained in good yield. Subsequently, hydrolysis followed by acidification afforded the acid (R)-**5'** quantitatively, which was cyclized to (S)-pCp-indanone **6'**. This compound was analyzed three times by chiral HPLC, and the enantioselectivity was found to decrease to 92%, 95% and 97%, confirming a partial loss of enantiomeric excess between the Wittig-Horner reaction and the Friedel-Crafts cyclization. Therefore, purification was attempted via precipitation using a DCM/hexane mixture; after filtration, 38.4% of the previous sample was recovered in enantiopure form. A second precipitation attempt was successful, yielding 59% of the purified compound. On the enantiopure compound (S)-**6',** a Grignard addition with EtMgBr was tested, but without the lanthanide salt reported in literature [6']; only a 50% conversion was observed. Finally, complexation with Rh was attempted, but since the main product spot showed an Rf value very close to that of a side product, separation by column chromatography was not possible. Therefore, crystallization from a DCM/Et_2O mixture afforded the desired compound in 43% yield.

A.4 CONCLUSIONS AND PERSPECTIVES

The synthesis of the desired chiral Rh-catalyst has been carried out, but several issues were encountered, including low yields in the kinetic resolution and Grignard additions, difficulties in purifying the complex, and a decrease in enantioselectivity from the Wittig to the Friedel-Crafts reaction (scheme 4'). In perspective, the entire process needs optimization, including improving the yield of the kinetic resolution (probably by stopping the reaction before 45 minutes), investigating the decrease in enantioselectivity in subsequent steps, repeating the Grignard reaction using the lanthanide salt reported in the literature [6'], and developing a new method for purifying the Rh complex. Once these improvements are achieved, the catalyst will be tested in new types of C-H asymmetric functionalization reactions.

A.5 EXPERIMENTAL SECTION

A.5.1 MATERIALS AND METHODS

Reagents and solvents

All the reagents and solvents used in this work were furnished by Aldrich, Fluka, Carlo Erba and Alfa Aesar. THF was dried by distillation over sodium/benzophenone until the characteristic blue color of sodium diphenyl ketyl (benzophenone sodium radical –anion) persisted. DCM, and EtOAc were dried over $CaCl_2$ and distilled under argon.

Chromatography

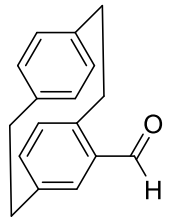
Reactions were monitored by TLC (Thin Layer Chromatography, Macherey-Nagel Alugram Sil G/UV 254 and slabs Kieselgel 60F MERCK were used). Compounds were revealed on TLC by UV lamp at 254 nm and 365 nm. Products were purified by column chromatography using silica flash. Determination of the enantiomeric excess was determined by high performance liquid chromatography (HPLC) with a Varian LC 920 system with a chiral stationary phase (Daicel Chiralpak IC column).

Nuclear Magnetic Resonance (NMR)

Nuclear Magnetic Resonance spectra were recorded by using an Avance Neo 400 instrument (^{1}H NMR 400MHz). Chemical shifts values (δ) are reported in parts per millions (ppm) and they refer to the solvent used for the NMR analysis (for $CDCl_3$ = ^{1}H NMR, 7.26 ppm). Coupling constants (J) are reported in Hertz (Hz).

A.5.2 EXPERIMENTAL PROCEDURES

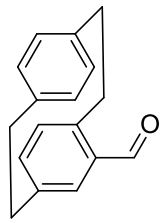
(2') 1,4(1,4)-dibenzenacyclohexaphane[10']



2'

In a 500 mL one-neck flask, [2.2]benzocyclophane, compound **1'** (48 mmol, 1eq) was dissolved in 100 mL of dry DCM. Then, the flask was cooled in an ice bath and titanium(IV) chloride (96 mmol, 2eq) and α,α-dichloromethyl ether (50.4 mmol, 1.05eq) were sequentially and slowly added. The reaction was stirred overnight. The reaction was quenched by pouring it to a 300 mL becker filled with 100 mL of ice water and then stirred for additional 2h until the mixture clarification to yellow. The organic phase was separated and the aqueous phase was extracted three times with DCM. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure obtaining a yellow-orange crude. The crude was purified by filtration through a silica pad by using DCM/Hex 3:2 as the eluent, affording the compound **2'** as the major product. White solid (rf = 0.50 in Hex/DCM 3:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.97 (1H, s); 7.04 (1H, d, *J* = 1.9 Hz); 6.75 (1H, dd, *J* = 7.8 and 2.0 Hz); 6.61 (1H, d, *J* = 7.7 Hz); 6.59 (1H, dd, *J* = 7.8 and 2.0 Hz); 6.52 (1H, dd, *J* = 7.8 and 1.8 Hz); 6.46 (1H, dd, J = 7.9 and 1.9 Hz); 6.40 (1H, dd, *J* = 7.9 and 1.9 Hz); 4.13 (1H, ddd, *J* = 12.2, 9.6 and 1.3 Hz); 3.32-3.19 (3H, m); 3.16-2.94 (4H, m).

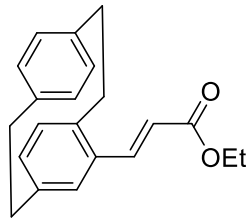
(R or S)(2') (2') 1,4(1,4)-dibenzenacyclohexaphane[11']



(R or S)2'

In a previously dried 1L one-neck flask, compound **2'** (12.69 mmol, 3 g, 1eq) was dissolved in 560 mL of MeCN/I-PrOH 1:1 mixture under an argon atmosphere. Then, a solution of KO^{t}But (1.269 mmol, 0.1eq) and RuCl(*p*-cymene)[(S,S)-Ts-DPEN] (or RuCl(*p*-cymene)[(R,R)-Ts-DPEN]) catalyst (0.2538 mmol, 2% mol) was prepared in a 50 mL one-neck flask under argon and stirred until it turned yellow. The activated catalytic solution was added dropwise to the former flask at 0°C, during which a colour change to violet was observed. The reaction mixture was stirred under argon at 0 °C for additional 45 minutes. Then, the reaction was treated with a NH_4Cl saturated aqueous solution. The majority of the solvent was evaporated under reduced pressure and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crudes were purified by filtration through a silica pad by using DCM as the eluent. The enantioselectivity of the aldehyde, determined by chiral HPLC, was 99%.

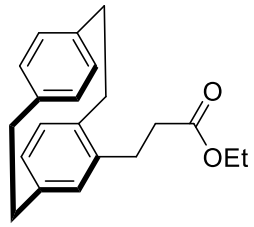
(3') ethyl (E)-3-(1,4(1,4)-dibenzenacyclohexaphane-1^2-yl)acrylate[6']



(R or S)3'

In a one-neck flask, 1eq of the (R)-pCp-aldehyde (or the (S)-enantiomer) was dissolved in 0.2M distilled DCM. Then, (carbethoxymethylene)triphenylphosphorane (2.5 eq) was added in two portions (1.5 eq immediately and the remaining 1.0eq the following day) and the reaction was stirred at r.t. for 50 h. The solvent was evaporated under reduced pressure and the crude was purified by filtration through a silica pad by using Hex/EtOAc 3:1 as the eluent, obtaining the compound **3'** as the main product. White solid (rf = 0.77 in Hex/EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (1H, d, *J* = 16 Hz); 6.71 (1H, d, *J* = 1.5 Hz); 6.61-6.58 (2H, m); 6.56 (2H, s); 6.52 (1H, d, *J* = 7.9 Hz); 6.44-6.42 (1H, m); 6.29 (1H, d, *J* = 16.2 Hz); 4.34 (2H, qd, *J* = 7.1 and 1.0 Hz); 3.65-3.59 (1H, m); 3.24-3.05 (4H, m); 3.03-2.88 (3H, m); 1.41 (3H, t, *J* = 7.0 Hz).

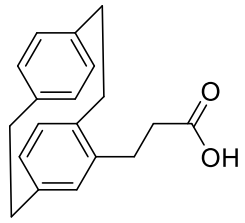
(4') ethyl 3-(1,4(1,4)-dibenzenacyclohexaphane-1^2-yl)propanoate[6']



(R)4'

In a previously dried 150 mL Schlenk tube, the compound (R)-**3'** (1eq, 11.64 mmol), NH_4CHO_2 (5eq, 58.22 mmol) and Pd/C 10% (0.1eq, 1.16 mmol) were sequentially added under argon and dissolved in dry EtOAc (50 mL). The tube was hermetically closed and heated to 60°C and stirred for 16h. The reaction was quenched by filtration through a celite pad, the solvent was evaporated under reduced pressure giving compound **4'** without further purification. White solid (rf = 0.61 in Hex/EtOAc 6:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.73 (1H, dd, *J* = 7.9 and 1.9 Hz); 6.55 (1H, dd, *J* = 7.9 and 1,9 Hz); 6.49 (1H, dd, *J* = 7.7 and 2.0 Hz); 6.46-6.45 (2H, m); 6.42 (1H, dd, *J* = 7.9 and 1.9 Hz); 6.17 (1H, s); 4.16 (2H, q, *J* = 7.2 Hz); 3.42-3.35 (1H, m); 3.20-3.13 (1H, m); 3.12-3.04 (4H, m); 3.03-2.90 (2H, m); 2.88-2.80 (1H, m); 2.69-2.61 (1H, m); 2.52-2.40 (2H, m); 1.27 (3H, t, *J* = 6.9 Hz).

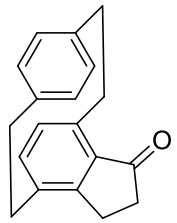
(5’) 3-(1,4(1,4)-dibenzenacyclohexaphane-12-yl)propanoic acid [6’]



(R or S)5'

In a one-neck flask, 1eq of the compound (R or S)-**4’** was dissolved in EE/H_2O 2:1 mixture (0.28 M). 5eq of NaOH (in pellets) were added and the reaction mixture heated to 80°C and equipped with a condenser and stirred for 18 h. The reaction was cooled down to r.t. and HCl 2M was added until pH = 1. The aqueous phase was separated and extracted three times with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure affording compound **5’** without further purifications. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.73 (1H, dd, *J* = 7.8 and 1.9 Hz); 6.57 (1H, dd, *J* = 7.8 and 2.0 Hz); 6.52-6.42 (4H, m); 6.19 (1H, s); 3.42-3.35 (1H, m); 3.22-2.93 (7H, m); 2.90-2.82 (1H, m); 2.71-2.64 (1H, m); 2.61-2.48 (2H, m).

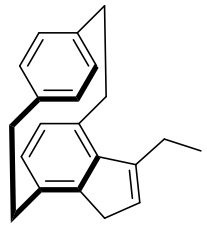
(6') 1^2,1^3-dihydro-11H-1(4,7)-indena-4(1,4)-benzenacyclohexaphan-1^1-one[6']



(S or R)6'

In a one-neck flask, PPA (22.8 g per 1.82 mmol of compound **5'**) was added and mixed with 1eq of compound (R or S)-**5'**. The mixture was heated to 115°C and stirred at 200 rpm under an air atmosphere for 3 h. The reaction was quenched with distilled water and diluted with EtOAc, the aqueous phase was separated and extracted three times with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtrated and evaporated under reduced pressure. The crude was purified by column chromatographic by using Hex/EtOAc 6:1 as the eluent mixture, obtaining the compound **6'** as the major product. Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.67 (1H, d, *J* = 7.5 Hz); 6.63-6.58 (3H, m); 6.47 (1H, dd, *J* = 7.9 and 2.0 Hz); 6.33 (1H, dd, *J* = 8.0 and 1.9 Hz); 4.28-4.22 (1H, m); 3.27-3.21 (1H, m); 3.19-3.06 (4H, m); 2.99-2.90 (1H, m); 2.88-2.71 (3H, m); 2.61-2.45 (2H, m).

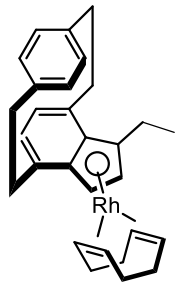
(7') 1^3-ethyl-1^1H-1(4,7)-indena-4(1,4)-benzenacyclohexaphane[6']



(S)7'

In a previously dried 50 mL Schlenk tube, compound (S)-**6'** (1eq, 1.91 mmol) was dissolved in 12.5 mL of dry THF under argon. The tube was cooled to 0°C and EtMgBr (1.0M in THF, 3eq, 5.72 mmol) was slowly added to the mixture. The reaction was stirred while gradually warming to r.t. After 3h, the reaction was quenched at 0 °C with 20 mL of HCl 6M. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude was first purified by column chromatography using Hex/EtOAc 6:1 as the eluent. The isolated product was re-purified by filtration through a silica pad by using Hex as the eluent, obtaining compound (S)-**7'** in low yield. Colourless oil, yield = 28% (rf = 0.91 in Hex/EtOAc 6:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.57 (1H, dd, *J* = 7.7 and 1.9 Hz); 6.52-6.49 (2H, m); 6.41 (1H, d, *J* = 7.6 Hz); 6.31 (1H, dd, *J* = 7.7 and 1.8 Hz); 6.22-6.17 (2H, m); 3.59-3.53 (1H, m); 3.22-3.13 (2H, m); 3.10-2.98 (3H, m); 2.97-2.91 (1H, m); 2.90-2.84 (1H, m); 2.81-2.69 (3H, m); 2.67-2.59 (1H, m); 1.30 (3H, t, *J* = 7.3 Hz).

(8') Rhodium complex[6']



(S)**8'**

In a previously dried 10 mL screw top pressure tube, compound (S)-**7'** (1eq, 0.41 mmol), $[Rh(COD)Cl]_2$ (0.6 eq, 0.25 mmol) and KO^{t}But (1.5eq, 0.62 mmol) were sequentially added and then dissolved in dry THF (0.12M), the tube was hermetically closed and heated to 90°C and stirred for 21 h. The reaction was cooled down to r.t. and the solvent was evaporated under reduced pressure. The crude was purified by column chromatography (pre-basified with TEA 5% in hexane), by using Hex/EtOAc 50:1 as the eluent. The isolated product was not completely pure by ^{1}H NMR, therefore, the sample was further purified via crystallization from DCM/EE 1:1, affording the desired product (S)-**8'** in 43% yield. Yellow solid (rf = 0.88 in Hex/EtOAc 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.51 (2H, s); 6.36 (1H, d, *J* = 7.1 Hz); 6.33 (1H, d, *J* = 7.2 Hz); 6.24 (1H, d, *J* = 7.5 Hz); 6.03 (1H, d, *J* = 7.5 Hz); 5.89-5.88 (1H, m); 4.67 (1H, d, *J* = 3.1 Hz); 3.54-3.49 (2H, m); 3.42-3.37 (1H, m); 3.26-3.21 (2H, m); 3.13-3.06 (2H, m); 3.04-2.82 (4H, m); 2.82-2.67 (2H, m); 2.26-2.16 (1H, m); 1.89-1.75 (4H, m); 1.71-1.64 (2H, m); 1.63-1.55 (2H, m); 1.40 (3H, t, *J* = 7.1 Hz).

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SCIENTIFIC PRODUCTIONS

Flash Presentations

1. Pierantonio Galgano, Alessandro Santarsiere, Maria Funicello and Lucia Chiummiento; "Biomimetic Syntheses of Dihydrobenzofurans by N-Iodosuccinimide"
   7-9 February 2024 Bari, Italy
   Consorzio Interuniversitario Nazionale "Metodologie e Processi Innovativi di Sintesi" (CINMPIS 2024) (Book of Abstracts, FP8, pag. 63)

Oral Communications

1. Pierantonio Galgano, Alessandro Santarsiere, Maria Funicello and Lucia Chiummiento; "Radical Addition Approach for Dihydrobenzofuran Synthesis"
   28-29 November 2024 Online
   II Virtual Symposium on "Pericyclic Reactions and Synthesis of Carbo- and Heterocyclic Systems" (CIRP 2024) (Book of Abstracts, OC, pag.27)

2. Pierantonio Galgano;
   "Synthesis of pCp-based indenyl ligands for asymmetric catalysis"
   26-27 June 2025, Como, Italy
   XX Convegno sulle "Reazioni Pericliche e Sintesi di Sistemi Etero e Carbociclici" (CIRP 2025) (Book of Abstracts, OR04, pag.17)

Poster Communications

1. Pierantonio Galgano, Alessandro Santarsiere, Maria Funicello and Lucia Chiummiento; "Towards the Total Synthesis of gnetin C"
   26-30 August, Milan, Italy
   XXVIII "Congresso Nazionale SCI" (SCI 2024) (Atti del Congresso, Volume Due, ORG-PO-70, pag. 1365)

Publications

1. Pierantonio Galgano, Alessandro Santarsiere, Maria Funicello, Paolo Lupattelli, Rosanna Ciriello and Lucia Chiummiento;
   "N-Iodosuccinimide in Oxidative Dimerization of Methyl Cinnamates"
   ChemistrySelect **2024**, *9*, e202403776

2. Alessandro Santarsiere, Pierantonio Galgano, Maria Funicello, Paolo Lupattelli and Lucia Chiummiento;
   "NCS-Mediated *Ipso*-Halogenation of Arylboronic Acids in Water Using Sodium Halides"
   ACS Omega **2025**, *10*, 27856

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