UNIVERSITY OF NAPLES

"FEDERICO II"

SCHOOL OF MATHEMATICAL, PHYSICAL AND NATURAL SCIENCES

PhD in Chemical Sciences

XXV Cycle (2010-2013)

Course of Synthesis, Structure and Reactivity of Organic Molecules

Synthesis of bioactive natural product analogues

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UNIVERSITÀ DEGLI STUDI DI NAPOLI

"FEDERICO II"

FACOLTÀ DI SCIENZE MATEMATICHE, FISICHE E NATURALI

Dottorato di Ricerca in Scienze Chimiche

Ciclo XXV (2010-2013)

Indirizzo di Sintesi, Struttura e Reattività di Molecole Organiche

Sintesi di analoghi di prodotti naturali bioattivi

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Riassunto

La ricerca di prodotti naturali svolge un ruolo importante sia nella definizione della loro funzione biologica che nella scoperta di nuove molecole. Ad oggi molti farmaci o principi attivi utili alla salute umana sono di origine naturale. Per di più, i prodotti naturali sono stati ampiamente utilizzati per chiarire complessi meccanismi cellulari che portano alla identificazione di importanti obiettivi di intervento terapeutico.

Questo progetto di dottorato è finalizzato alla sintesi di prodotti naturali bioattivi e/o composti analoghi. In particolare, lo scopo è quello di mettere a punto nuove metodologie di sintesi di composti a scheletro lignanico a partire da furani.

I lignani sono metaboliti secondari ampiamente diffusi nel mondo vegetale. Nelle piante i lignani partecipano ai meccanismi difensivi contro l'aggressione dei microrganismi ma, ancor più importante, anche il corpo umano può beneficiare delle loro proprietà antibatteriche, antifungine ed antifeedant. Oltre che in ambito erboristico, infatti, i lignani rappresentano delle sostanze di enorme interesse anche in campo farmacologico, come antiossidanti, antivirali, immunosoppressori. Importanti studi preliminari su alcuni tipi di lignani ne hanno evidenziato un certo ruolo nei meccanismi di prevenzione del cancro, in particolare del seno e del colon.

La struttura dei lignani deriva da unità fenilpropanoidiche (C6-C3), legate tra loro in diversi possibili modi, e che possono essere variamente sostituite ed ossidate. Isolare questi composti da fonti naturali è un processo lungo e dispendioso in termini di lavoro e di costi, e spesso le rese sono molto basse per scopi applicativi. Data, però, la loro importanza in termini di bioattività sono sempre più intensi gli studi per ottenerli mediante sintesi parziale o totale.

In questo progetto di dottorato è stato individuato il 2-aril-3,4-dicarbossimetilfurano come utile precursore di scaffolds C6C3-C3C6 da funzionalizzare per ottenere strutture lignan simili. Nella prima parte del lavoro è stato sviluppato un approccio sintetico per la preparazione di 2-aril-4-aroilfurani, a partire dall'acido 4-furoico (preparato per idrolisi basica selettiva del precursore) mediante acilazione di Friedel-Crafts (FC) utilizzando anidride triflica (Tf_2O). Questo reattivo è risultato vantaggioso perché consente di lavorare con tempi di reazione brevi e senza l'uso di altri catalizzatori acidi. Inoltre, lavorando ad opportune temperature, la reazione è risultata altamente regioselettiva, favorendo la formazione dei prodotti 4-acilati desiderati o degli isomeri 3-acilati, che comunque si ritrovano in miscela. La procedura è stata

estesa a sistemi aromatici opportunamente sostituiti con alcuni dei gruppi tipici di lignani naturali.

Alcuni 2-aril-4-aroilfurani sono stati funzionalizzati mediante reazioni di riduzione e/o fotoossigenazione. In particolare, l'idrogenazione Pd-catalizzata effettuata in differenti condizioni ha portato ad una serie di prodotti, tra cui un tetraidrofurano la cui struttura è analoga a quella di un analogo lignano naturale bioattivo, il Taxiresinolo. Per l'ossidazione, invece, è stata applicata la fotoossigenazione sensibilizzata da coloranti, una valida procedura alternativa ai metodi classici, sia dal punto di vista della *green chemistry*, sia per il coinvolgimento di specie eccitate, come l'ossigeno singoletto ($^1O_2$), la cui reattività spesso differisce da quella allo stato fondamentale. Nonostante l'importanza della reazione dei furani con $^1O_2$ sia ampiamente riconosciuta, sono spesso riscontrati nuovi risultati e spunti sintetici dovuti alla versatilità degli intermedi biciclici che si formano, chiamati *endoperossidi*. A tal proposito, poiché gli α-arilfurani sintetizzati in questo lavoro rappresentano dei sistemi mai studiati precedentemente in quest'ambito, è risultato ancora più interessante sottoporli a fotoossigenazione e successiva elaborazione degli endoperossidi ottenuti. In particolare, la riduzione con Et_2S ha portato ad 1,4-enedioni, che in casi di particolare sostituzione si convertono spontaneamente in strutture lattoniche. Mentre il trattamento basico con Et_2NH ha portato ad acidi 4-oxo-alchenoici, invece che a γ-idrossilattoni come ci si aspettava per quanto riportato in letteratura. I risultati ottenuti, quasi sempre sorprendenti, sono attribuibili alla particolare sostituzione dei furani e all'elevata coniugazione dei sistemi stessi.

In un secondo momento è stata messa appunto una procedura 3-step one-pot a partire sempre dal precursore 2-arilfuranico, fotoossigenato e trattato con base per dare l'acido acrilico. Quest'ultimo è stato sottoposto all'acilazione mediata da Tf_2O che nel precedente approccio sintetico aveva portato a risultati promettenti. In questo caso, però, sono stati ottenuti furanoni 5,5- e 3,5-disostituiti, ugualmente interessanti perché la loro struttura combina il motivo strutturale del furanone, ampiamente diffuso in prodotti naturali e sintetici con proprietà antibiotiche, antifungine, anticancro, e quello di alcuni lignani rari recentemente isolati, come ad esempio il Sacidumlignano D. Anche questa procedura è stata applicata su una serie di substrati arilici opportunamente sostituiti, cercando di ottimizzare le condizioni ed ottenere rese più alte con rapporti isomerici a favore dei prodotti 5,5-disostituiti. In particolare, nel

tentativo di ottimizzare i risultati ottenuti rientra anche l'utilizzo di una base non nucleofila come la 2,6-lutidina, nella reazione di acilazione che ha portato ai medesimi prodotti in rese totali più alte, ma con minore selettività.

Abstract

The chemistry of natural products has made tremendous progress in their fields and has developed a repertoire of transformations to achieve their respective target compounds. Lignans have attracted a great deal of interest over the years due to their wide occurrence in plants and the broad range of biological activities. Lignans show an enormous structural diversity, although their molecular backbone consists only of two phenylpropanoidic (C6-C3) units. They possess significant pharmacological properties, including antitumor, antioxidant, antiviral and cardiovascular actions. Isolation of lignans from plant materials remains highly labor intensive process and the yields are generally low. Therefore, continuous efforts for the development of synthetic methods are made.

In this PhD thesis a strategy allowing the preparation of some furans as precursors of lignan-like compounds is reported. The choice of substituted furan system as starting material for lignan-like compounds is based on two reasons. Firstly, polysubstituted furans are important building blocks for the synthesis of natural and non-natural products, thanks to their ability to undergo a broad range of reactions. Moreover, suitable substituted furans consist of C6C3-C6C3 useful scaffolds. This have a prominent role in synthetic chemistry particularly in oxidation to versatile 1,4-enedione or to furanone ring.

Easily accessible 2-aryl-3,4-dicarboxymethyl furans were recognized as starting precursors of 4-aroyl-2-phenyl furans, interesting products characterized by a *β-β'* linked C6C3-C3C6 backbone typical of lignans. In this thesis a regiodivergent synthetic approach via trifluoromethanesulfonic anhydride (Tf_2O)-mediated acylation is described. Tf_2O is of high current interest in Friedel-Crafts (FC) acylation of carboxylic acids and other substrates. The reaction takes place under neat condition and at low temperatures. Compared to classical FC acylation this route avoids the strong acid conditions and it is highly selective since it reduces the formation of the regioisomer 3-aroyl-2-aryl furan, generally found.

Stimulated by the evident potentiality of the Tf_2O-mediated acylation, this procedure was explored on 4-oxo-2-alkenoic acids, previously prepared by photooxygenation followed by basic treatment. 5,5- And 3,5-diarylfuranones have been obtained in a three-step one-pot manner, then, triflic anhydride-mediated acylation of activated

aromatic substrates. These products appear of particular interest since they combine the presence of a carbon skeleton of some recently isolated rare lignans and a furanone moiety. Furanone structural motif is prevalent in bioactive natural and synthetic products that have shown a wide range of activities, and it is often found in lignan derivatives.

I - Introduction

Natural products have always sparked much interest because of their important properties. For centuries, a lot of molecules of natural sources have been used in folk medicine, in cosmetics and nutrition. Many of them have been useful to better understand some complex cellular and biological processes [1]. The perspective to evaluate a vast number of biologically active natural compounds yet to be discovered and studied seems to be really attractive. Furthermore, natural compounds give new ideas for novel synthetic strategies. Anyway, in the last decades, natural products turned out to be useful as remedy in human health and as suggestion for the design of potential pharmacological molecules, especially in anticancer and antiviral fields. Already in 2006, the FDA (Food and Drug Association) estimated that almost the 70% of worldwide approved drugs were: natural products, semi-synthetic products with a natural core, mimetics of natural products [2a]. These data are in increasing evolution (Figure 1) and a significant number of natural product drugs are actually produced by microbes and/or microbial interactions [2b].

Secondary metabolites are organic compounds that are not directly involved in organisms' normal growth, development or reproduction. They are often restricted to a narrow set of species within a phylogenetic group. These compounds usually have an important function, since they are used as defenses against predators, parasites and diseases, for interspecies competition, and to facilitate the reproductive processes (coloring agent, attractive smells).

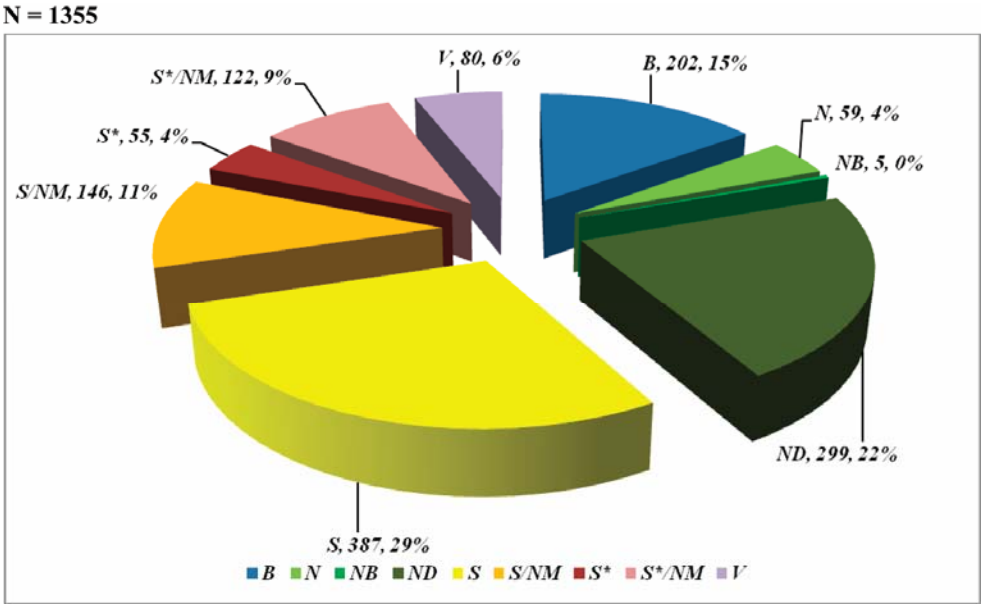


Figure 1. All new approved drugs

1. Lignans

Lignans are a wide class of secondary metabolites occurring in plant woody tissues and roots, and in a wide variety of foods, including seeds (flax, pumpkin, sunflower, sesame), cereals (rye, oats, barley, wheat, oat), fruits (particularly berries), and vegetables [3].

Plant lignans are the main source of phytoestrogens in diets for people who do not consume soy food. The daily phytoestrogen intake by postmenopausal women in the U.S. was estimated to be less than 1 mg/day, with 80% from lignans and 20% from isoflavones [4].

1.1 Structure of lignans

Lignans derive from the oxidative dimerization of two phenylpropanoid (C6-C3) units, and numerous new compounds with structures correlated to lignans are continuously

found. The two phenylpropanoids units reveal different degree of oxidation and substitution, thus lignans show an enormous structural diversity.

Lignans can be classified in *classical lignans* (Figure 2), which have the units linked in *β-β'* (8-8') positions, and *neolignans* (Figure 3) whose coupling patterns differ from such a *β-β'* linkage [5]. The units can be linked also by an oxygen atom, as in the subclass of *oxyneolignan* (Figure 3).

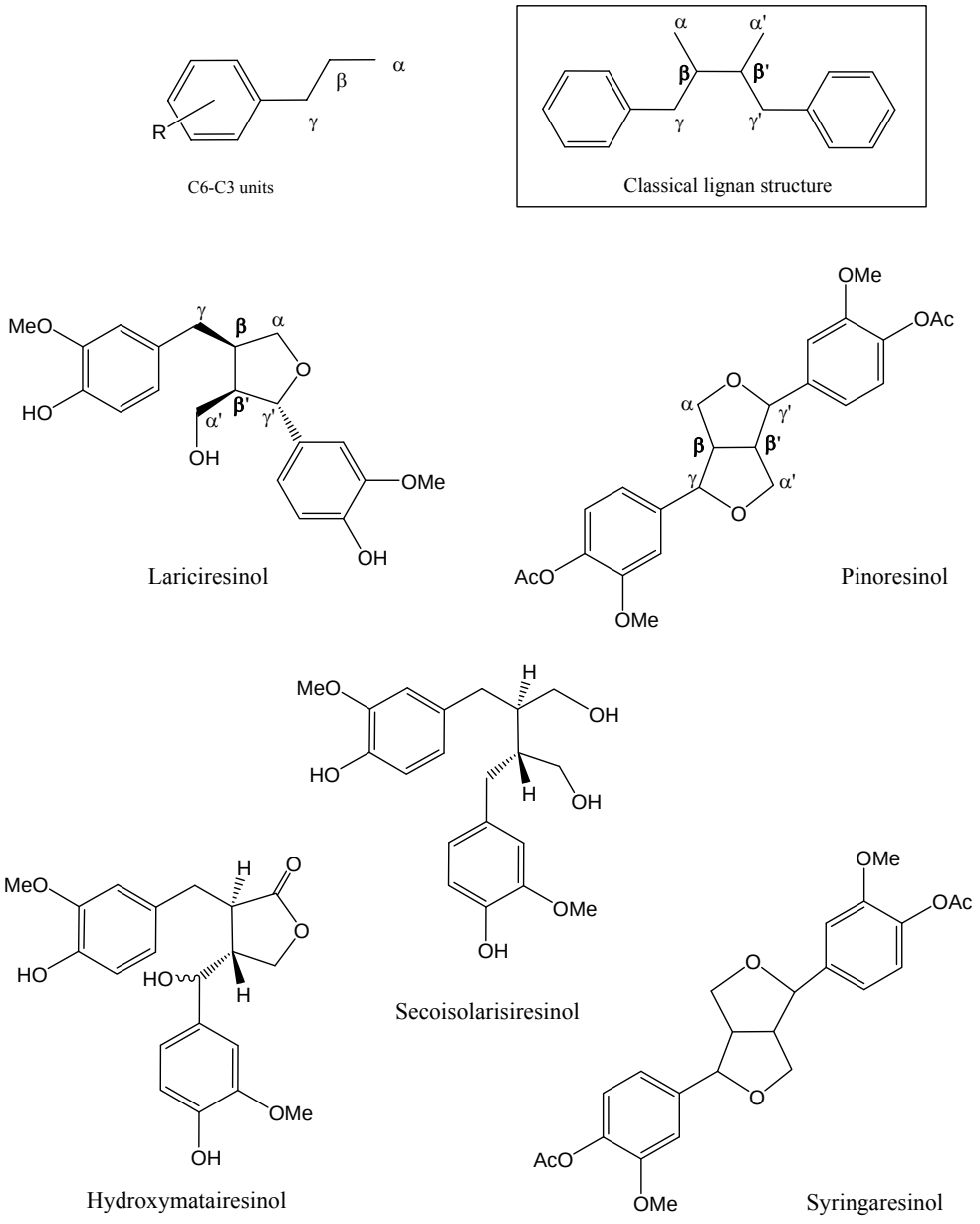


Figure 2. Basic structure of lignans and examples of classical lignans

The main lignans found in knotwood extracts are, for example, Hydroxymatairesinol, Secoisolariciresinol, Pinoresinol, and Lariciresinol (Figure 2) of which some are important dietary lignans found also in our everyday diet.

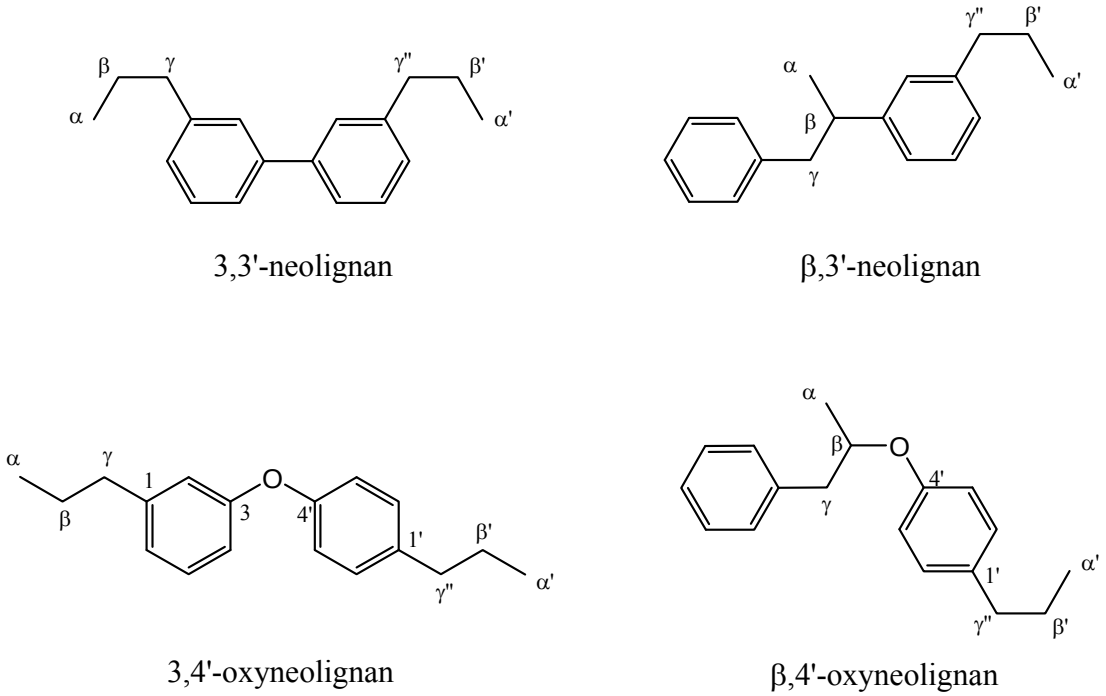


Figure 3. Examples of neolignan and oxyneolignan structures

Typical substituents on 3,4,5 positions of aromatic rings are AcO-, OH- and MeO-groups, in variable number. Really, a further classification for classical lignans may be considered (Figure 4): dibenzylbutans (**CL1**), dibenzylbutyrrolactons (**CL2**), arylnaphtalenes (**CL3**), dibenzocyclooctadienes (**CL4**), 2,6-diarylfurofurans (**CL5**) and substituted tetrahydrofurans (**CL6a-c**) [6].

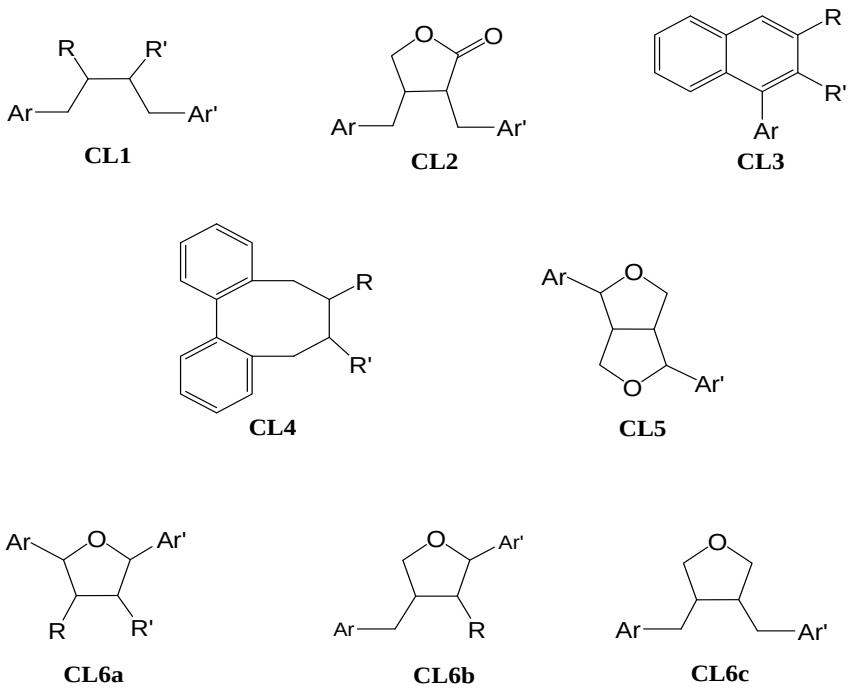


Figure 4. Classification of classical lignans

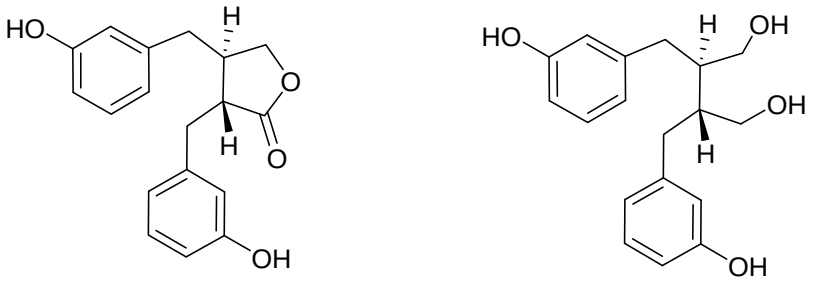
1.2 Biosynthesis of lignans

Lignans and lignins are the major metabolic products of phenylpropanoid metabolism in vascular plants. In wood plants, they typically account for more than 20% of the weight of angiosperms and over 25% of that of the gymnosperms. Together, they constitute some of the most expensive metabolic products generated by plants [7], and derive from the shikimate-chorismate pathway [8] which produces the aromatic amino acids, phenylalanine and tyrosine [9]. The extension of the phenylpropanoid pathway in vascular plants, from phenylalanine onwards, ultimately leads to both the dimeric/oligomeric lignans and the polymeric lignins.

Recently, the biosynthesis of lignans has been revised in relation to the discovery of the dirigent proteins that guide phenolic radical coupling [10]. Lignans are obtained mainly via differential partitioning of the monolignol, coniferyl alcohol, to yield the lignan Pinoresinol, which, in turn, serves as the precursor of both Secoisolariciresinol

and Matairesinol (Figure 2). They are biosynthesized in the cell cytoplasm through the action of enzymes of the phenylpropanoid pathway, in which Phenylalanine Ammonia Lyase (PAL) catalyzes the initial step of the secondary metabolism and Pinoresinol Lariciresinol Reductases (PLR) accelerates the final steps of biosynthesis of lignans.

In plants, lignans show up as glicosides strongly connected to fiber constituents, and are taken in diets as inactive products. Afterwards, they are converted into phytoestrogens by removal of sugar residue by β-galactosidase of intestinal bacteria. Active forms of lignans are the Enterolactone and Enterodiol (Figure 5).



(-)-Enterolactone (-)-Enterodiol

Figure 5. (-)-Enterolactone and (-)-Enterodiol

1.3 Bioactivities of lignans

Lignans play a leading role in plant defense, as suggested by their potent biocidal [11], antiviral, antioxidant [11a, 12], fungicidal, antibacterial properties and cytotoxic activities against pathogens [13]. Antioxidant mechanism and free radical-scavenging properties of lignans were reported [14]. According to the obtained results lignans have shown to be promising antioxidants, mainly due to their good stability.

The most significant aspect of lignans and lignins lies in the fact that, in their absence, vascular plants would not easily survive. Indeed, the continued existence of all terrestrial animal forms somehow or other depends on vascular plants and, hence, on the lignan/lignin biosynthetic pathway. Moreover, it is the differential expression of this pathway that is largely responsible for most of plant biodiversity. The variable deposition of these substances, in terms of their amount and specific composition, can dramatically alter the wood tissues of plants, as well as affect other properties, such as heartwood color, durability and rot resistance, and even their aromatic fragrance.

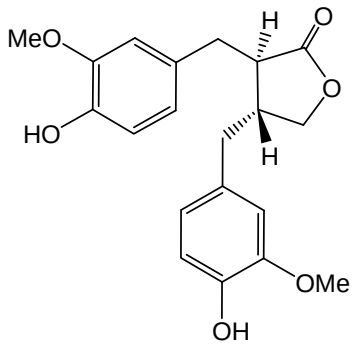
In the last years, much attention has been drawn to lignans thanks to their biological activities. Studies have also shown that high levels of lignans can support healthy weight and glucose metabolism, reducing the risk of insulin sensitivity, metabolic syndrome and diabetes [15].

Thanks to the powerful antioxidant and anti-inflammatory properties of lignans, they are also useful in the prevention of heart diseases. A recent study [16] reported that the main lignan in flaxseed, secoisolariciresinol diglycoside (SDG), was responsible for slowing the progression of plaques and decreasing oxidative stress, which harms the blood vessels' lining. The aryl naphthalene lignin justicidin B, without any chiral center, attracts interest, because of its fungicidal and antiprotozoal properties [17]. It shows antiviral and anti-inflammatory activities as well as inhibition of platelet aggregation [18]. In addition, it is used as a lead compound for the design of antirheumatic drugs [19].

Recent studies report that lignans play an important role in mechanisms preventing tumors. Mammalian lignans such as Enterodiol and Enterolactone, for instance, hinder prostate and breast cancers [20]. In particular, Enterolactone, the primary lignan that circulates in our blood, produces a weak estrogenic activity. Many reports have

revealed that high levels of Enterolactone in our blood help to reduce risk of breast [21], prostate [22] and colon cancers [23], and cardiovascular diseases [24]. It is thought that these phytoestrogens work by mimicking estrogenic activity and preventing the formation of blood vessels to tumors, restricting, thus, their growth. Besides, they disrupt tumor cell multiplication in DNA.

One of the most diffuse lignans, interesting for cytostatic activity, is Matairesinol whose antitumoral properties against breast and colon cancers also are known [25].



Matairesinol

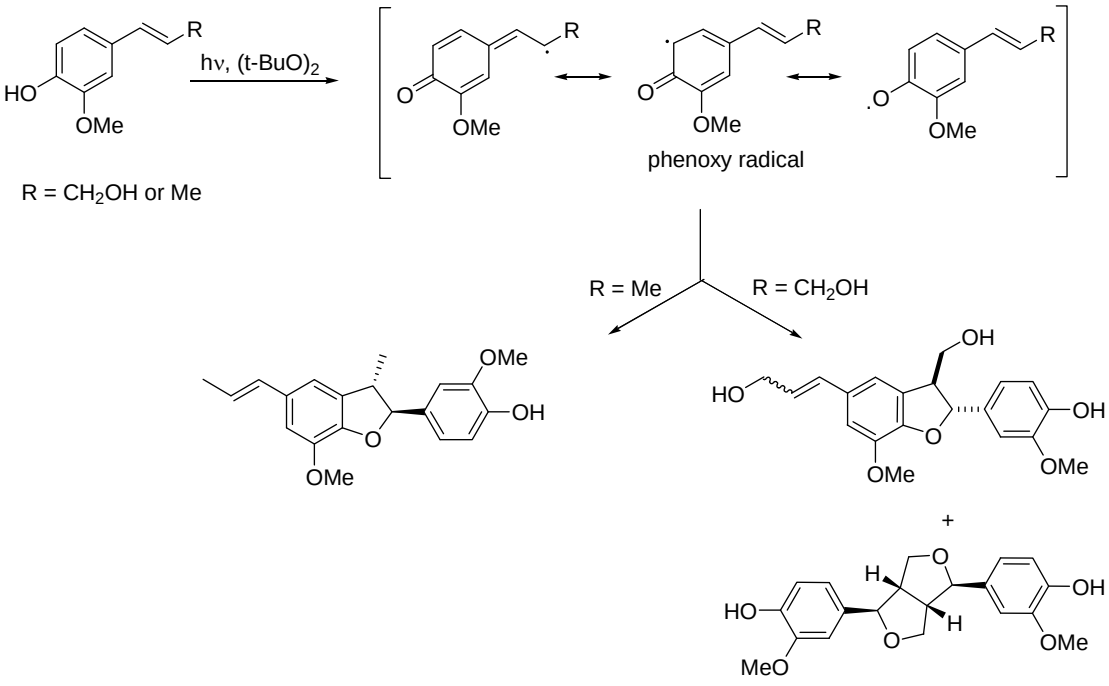
1.4 Synthesis of lignan structures

Direct extraction from plants has been the classical way to obtain lignans. However, this process, added to structural characterization and low yields, is considered quite laborious and expensive [26]. Thus, for a long time, several total and semi-synthetic approaches have been proposed.

One of the most used methodologies to synthesize lignans is enzymatic or chemical oxidative dimerization of derivatives of cinnamyl alcohol and cinnamic acid. Although enzymatic phenoxy radicals coupling leads to well-defined products, they can't be practically used for the mechanism has been unclear and the availability of the enzyme

is low. Chemical coupling has been performed using several oxides agents such as $FeCl_3$ or TTFA (thallium trifluoroacetate) [27], or chiral auxiliary in the asymmetric synthesis [28].

The possibility to prepare some lignans by environmentally-friendly approaches such as photo-induced synthetic methods was reported [29]. Formation of cyclic lignans under light-promoted oxidation is achieved using selective and green conditions. Applying photo-oxidation to isoeugenol and derivatives in presence of peroxides it is possible to obtain pinoresinol, dehydrodiconiferyl alcohol and dehydrodiisoeugenol (Scheme 1).

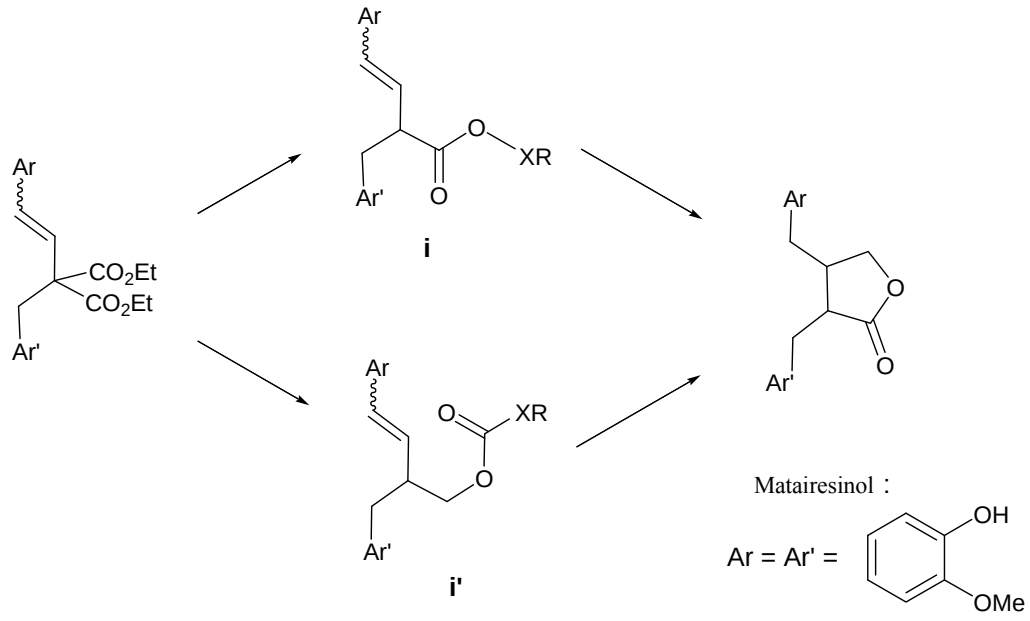


Scheme 1. Light-promoted oxidation of coniferyl alcohol and isoeugenol

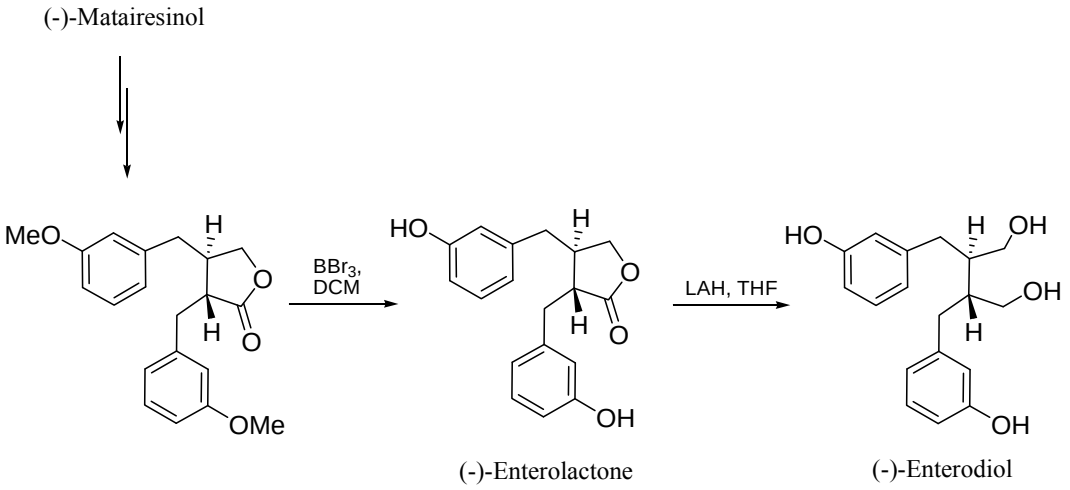
Many synthetic strategies have been proposed for matairesinol and some oxygenated analogues, and radical reactions are often recognized in their total synthesis and analogue dibenzylbutyrolactones [30]. A more recent paper [31] has reported a novel

approach involving a stereoselective radical cyclization of intermediates **i-i'** (Scheme 2).

Matairesinol is also a useful starting material for the synthesis of Enterolactone and enterodiol [32]. Enantiopure products were obtained by a simple procedure of only a few steps (Scheme 3).



Scheme 2. Synthetic approach for dibenzylbutyrolactones



Scheme 3. Synthesis of natural lignans

2. Aim of the project

2.1 Synthetic strategy

A novel approach to obtain lignan structures could be based on the use of synthons with a *β-β'* linked (C6-C3) backbone. For this purpose furan systems **f1-3** (Figure 6) were recognized as suitable scaffolds for further elaboration of lignan structures.

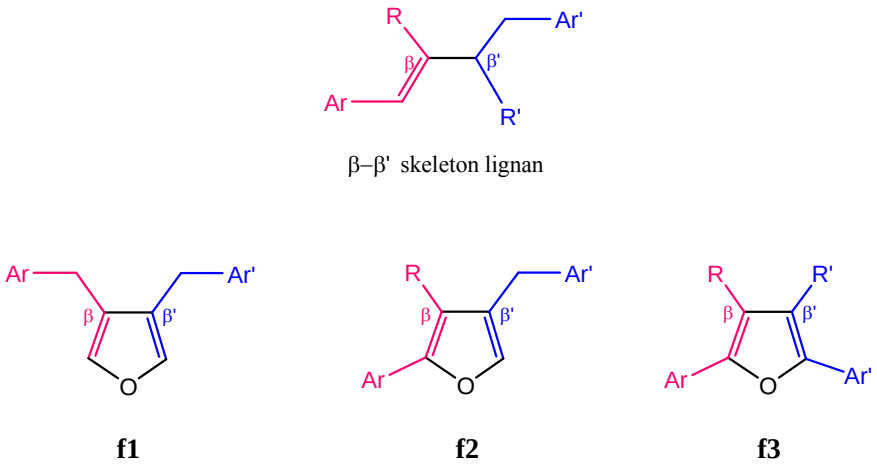


Figure 6. Suitable furan structures for the synthesis of *β-β'* lignan-like compounds

Structural motives of furans and derivatives, as tetrahydrofurans, furofurans and furanones (Figure 2), are widely occurring in lignans. Moreover, furans have also a prominent role in synthetic chemistry, due to their ability to undergo a broad range of reactions [33].

3. Furans

Furans are heterocycles widely distributed in a large number of natural and synthetic substances, endowed with interesting biological activities [34].

3.1 Furan derivative structures in lignans

Antioxidant activity of some furan derivative lignans may be explained in relation to their structural similarity to L-ascorbic acid, which is one of the most common antioxidants. Indeed, some of lignans studied showed an equally good or even better radical-scavenging capacity [14, 36].

Furans find a large number of applications as drugs, pesticides, cosmetics, detergents. Some examples of furans and derivatives with important bioactivities or properties are reported in Figure 7. The benzofuran **a** is used in the treatment of diabetes [37], while **b** is a diterpenic furan, extracted from fruit of *Vitex rotundifolia*, and useful to prevent cardiovascolar disorders [38]. Compounds **c** and **d** are, instead, efficacious pesticides, respectively of natural and synthetic origins [39].

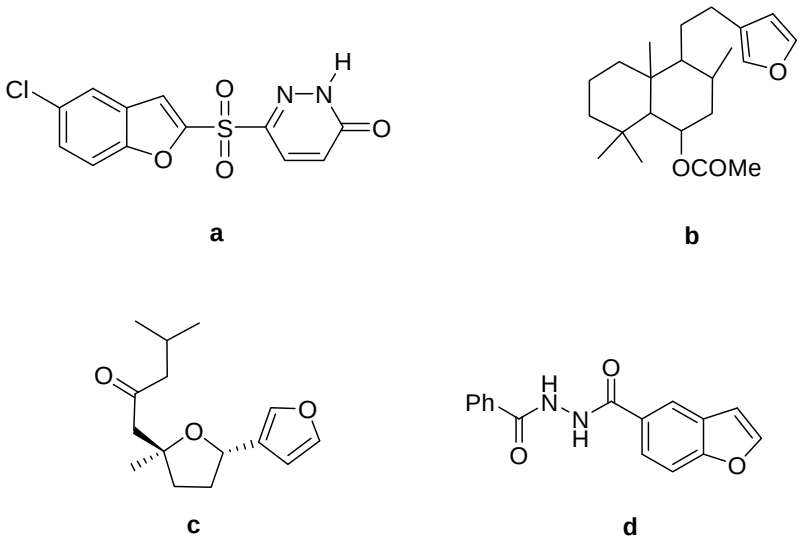


Figure 7. Examples of bioactive furans and derivatives

Due to its ability to undergo a wide range of reactions, this heterocycle is widely used in the synthesis of natural and non-natural products [33, 34a].

Typical reactions of furans are electrophilic substitutions, Diels-Alder reaction, metal-catalyzed reductions and oxidations.

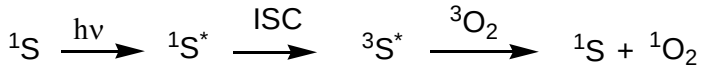
The reduction of furans can be carried out under classical metal-catalyzed hydrogenation. Typical catalysts used are Pd/C, Raney nickel and rhodium on alumina [40].

Several procedures for the oxidation of furans are reported, and lead to various structures, e.g. diepoxides, 1,4-enediones, furanones. The latter, in particular, show a very interesting structural motif, widely occurring in bioactive natural and synthetic products [35a, 41]. The biological importance has induced to develop novel methodologies for their synthesis. Furthermore, furanone structure is a very common backbone of bioactive lignans, as previously shown, for instance, in Figure 2. Similarly enediones are compounds of great synthetic interest and a variety of approaches has been developed for the synthesis of this skeleton [42]. Indeed, by virtue of their multifunctional composition, 1,4-enediones could serve as versatile precursors for heterocycle synthesis, Diels-Alder cycloaddition, Michael addition, as well as many other useful transformations [42, 43].

One of the most used oxidation procedures of furans is the dye-sensitized photooxygenation.

3.2 Dye-sensitized Photooxygenation of furans

The dye-sensitized photooxygenation is based on the irradiation of substrate in presence of catalytic amount of a dye, which usually is a substance easily excited by the absorbance of visible radiations (sunlight), and in coming back to the ground state molecule, it releases the absorbed energy to oxygen that changes its state converting to singlet state (Scheme 4).

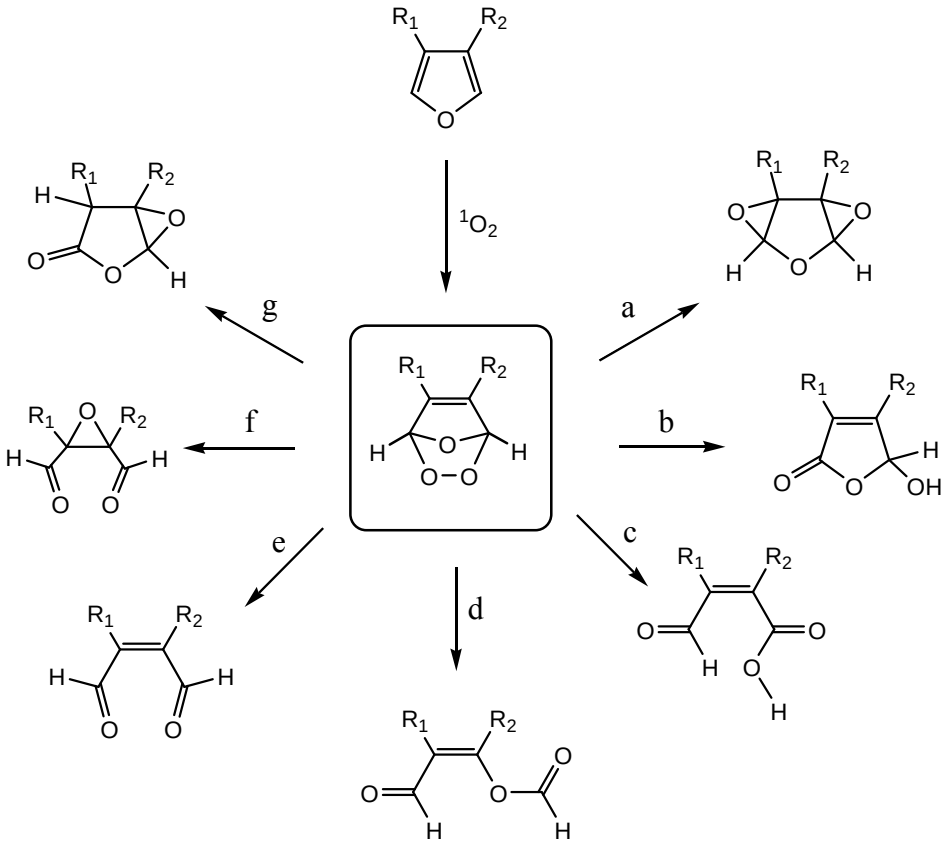


^1S=dye; S*= excitated dye

Scheme 4. Formation of singlet oxygen via sensitizer

Dye-sensitized photooxygenation appears a very promising oxidation route for several advantages as use of molecular oxygen, atom economy, high selectivity of singlet oxygen so that it is widely recognized as efficient and environmentally friendly. Singlet oxygen is a very reactive species that adds to unsaturated systems to give peroxides and hydroperoxides.

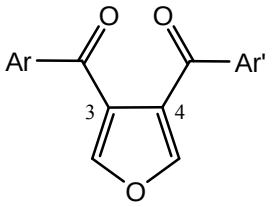
Photooxygenation of furans has been studied extensively from mechanistic and synthetic viewpoints. Singlet oxygen adds to furans in a quantitative and concerted reaction leading to 2,3,7-trioxabicyclo[2.2.1]-heptenes also named *endoperoxides* [44]. These intermediates are generally highly thermally unstable and can afford characteristic rearranged products. The thermal stability of the furan endoperoxides appears to depend on the α-substituent and follows the order Me > Ph > H > OMe [44, 45]. The presence of an electron-withdrawing group at the β position in the furan ring enhances the thermal stability of the corresponding endoperoxides, which may be stable enough to be isolated and characterized by analytical and spectroscopic data [46]. The subsequent rearrangements of the intermediate endoperoxide depend on the nature of the α-substituents as well as on reaction conditions [44, 45, 47]. Epoxides, diepoxides, enol esters, enediones, ketoesters, epoxyfuranones, furanones are only some of the products obtainable from the photooxygenation of furans (Scheme 5).



Scheme 5. Possible rearrangements of furanssendoperoxide

II – Results and Discussion

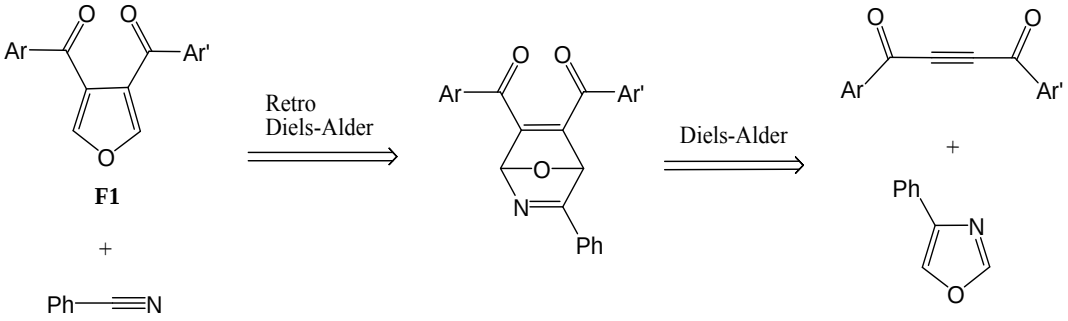
In the first stage of this project, the synthetic targets considered were the 3,4-diaroylfurans type **F1:**



F1

3,4-diaroylfurans

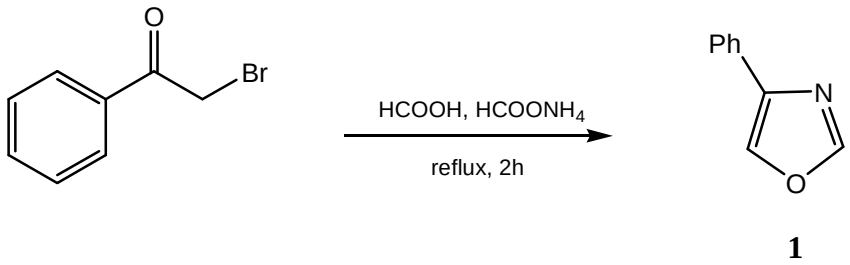
In order to obtain them a methodology involving a Diels-Alder reaction on 4-phenyloxazole and diaroylacetylens was recognized (Scheme 6) [48]. Indeed, by a *retro*-Diels-Alder reaction, the bicyclic intermediate gives furan **F1** and benzonitrile, which is a better leaving group than starting diaroylacetylene. Indeed, a simple procedure has been reported in literature for symmetric and asymmetric alkynyl ketones [49] from alkynylsilanes and halides acids by one-step iodine-catalyzed.



Scheme 6. *Retro*-synthetic analysis of 3,4-diaroylfurans

1. Synthesic approach for 3,4-diaroylfurans

4-Phenyloxazole **1** [50] was prepared by starting from 2-bromoacetophenone and ammonium formate in presence of formic acid (Scheme 7):



1

Scheme 7. Synthesis of 4-phenyloxazole **1**

The reaction was conducted in reflux condition and monitored by TLC analysis. After 2 hours, the reaction mixture was worked-up and chromatographed on silica gel column. The ^{1}H-NMR spectrum of product (21% yield) agreed with that reported for 4-phenyloxazole.

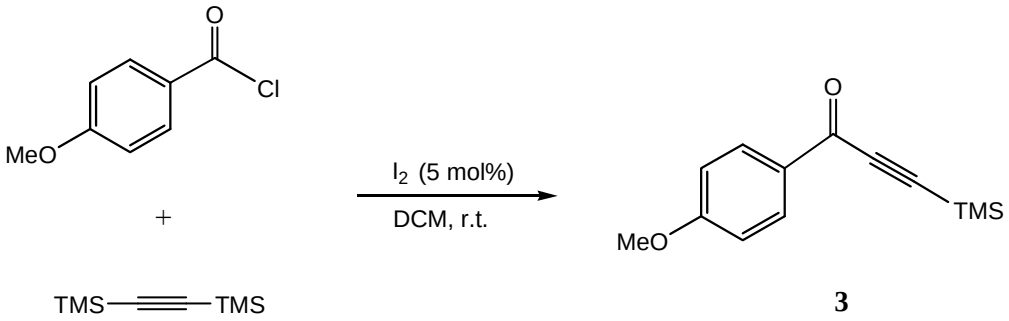
In order to obtain symmetric diaroylacetylenes **2**, the mentioned method was considered (Scheme 8).

2

Scheme 8. Synthesis of symmetric diaroylacetylens **2**

To prepare lignan-like backbone structures opportunely substituted, different aryls were considered. In the first experiments 4-methoxybenzoyl chloride (anisoyl

chloride) was used as aryl substrate, which would have the simplest substituent. Therefore the one-step procedure was applied to bis-(trimethylsilyl)-acetylene and anisoyl chloride (2 eq) in presence of catalytic amount of iodine (Scheme 9). The reaction was conducted in argon atmosphere and in dry DCM. After 20 hours the reaction mixture was worked-up and chromatographed on silica gel column to give a product identified as **3** by comparison of reported NMR data [51].



Scheme 9. Synthesis of trimethylsilyl-monoacyl acetylene **3**

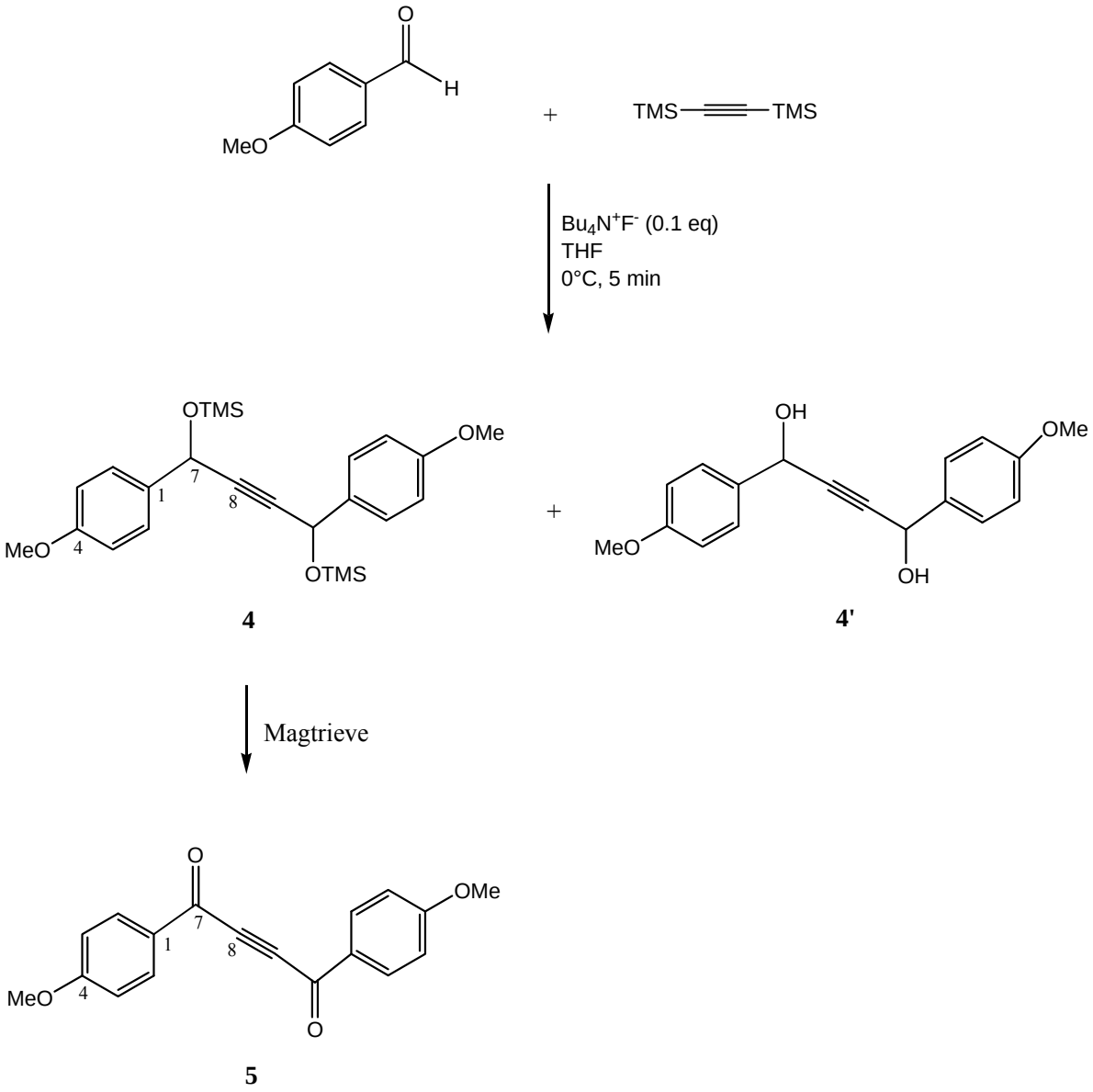
Attempts to apply the same iodine-catalyzed reaction to **3** as starting compound for the synthesis of the corresponding diacylated products were unsuccessful and **3** was recovered unreacted. Thus, other types of reactions were performed to introduce the second anisoyl group on **3**, such as a classical Friedel-Crafts acylation procedure with Lewis acid $AlCl_3$ as catalyst or a reaction catalyzed by $Pd(PPh_3)_2Cl_2$ and CuI in Et_3N [52]. In both cases no reaction occurred.

The same negative results were obtained performing the iodine-catalyzed reaction with other aroyl substrates, such as 3,4-dimethoxy-phenyl and 3,4,5-trimethoxy-phenyl chloride.

The disappointing results that were obtained induced us to use a different method, based on the reaction of anisaldehyde with bis-(trimethylsilyl)-acetylene in the presence of tetrabutylammonium fluoride (TBAF) (Scheme 10) [53]. Indeed it is

known that in basic conditions the protecting group TMS can be eliminated because of the major strength of silicon-fluoride bond than that silicon-carbon [54]. Therefore, the TBAF was added dropwise to the cooled mixture of aldehyde and bis-TMS-acetylene in anhydrous tetrahydrofuran. The reaction was completed in few minutes as shown by TLC analysis which evidenced the disappearance of the aldehyde and the formation of several UV-visible products. Work-up and purification on silica gel column led to the identification of only two products. Compound **4** (20% yield) its the ^{1}H-NMR spectrum showed the presence of a benzylic proton at δ 5.43, and in the ESI-MS spectrum the molecular peak [M^{+}] a *m/z* 442 (Scheme 10) was present. The diol product **4'** was present in very small amount.

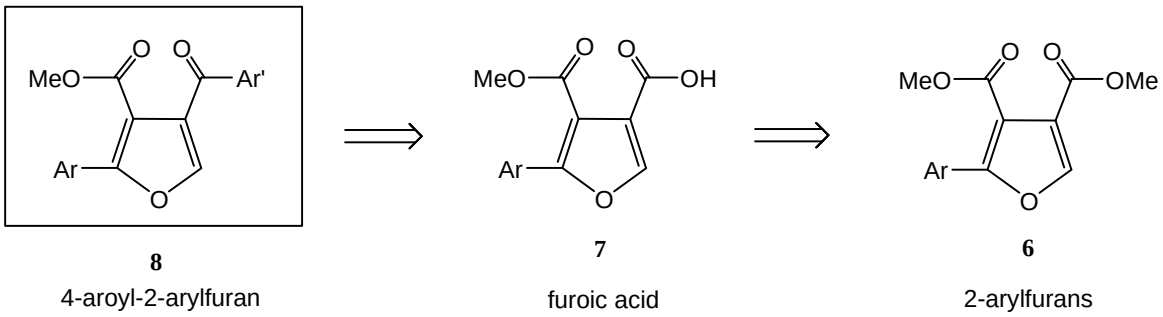
Product **4** was oxidized in mild conditions bypassing the desilylation step. For this purpose the oxidant Magtrieve^{TM} was used (Scheme 10), a very common suitable reagent for selective oxidation of primary and secondary alcohols. Magtrieve^{TM} is a magnetically retrievable oxidizing agent based on reduced form of tetravalent chromium dioxide (CrO_2). It can be easily removed by simple magnetic separation because of ferromagnetic properties [55]. The oxidation reaction was carried out in reflux of toluene for 30 minutes, until the TLC showed the disappearance of **4**. Once Magtrieve^{TM} was removed, the reaction mixture was worked-up and purified by silica gel column chromatography. GC-MS analysis of isolated product of showed a molecular peak [M^{+}] at *m/z* 294, and NMR data were consisted of the structure **5**. ^{1}H-NMR spectrum was very similar to that of **4** but the singlet of benzylic proton at δ 5.43 was absent. ^{13}C-NMR spectrum showed seven signals, in particular singlets at δ 175.1 and 86.0 were attributed to quaternary carbonyl and an acetylenic carbons respectively. However the yield (11%) were not satisfactory for an efficient synthetic strategy.



Scheme 10. Synthesis of diaroylacetylenes **5**

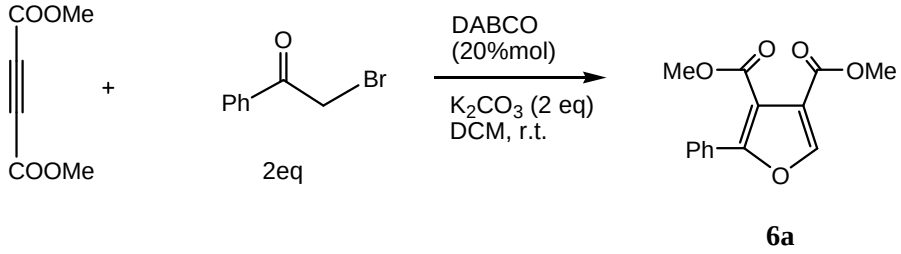
2. Synthesic approach for 2-aryl-4-aroylfurans

These results induced us to consider structures CL6-b (Figure 4) as lignan target, in particular the furan derivative **f2** (Figure 6). For this purpose 2-aryl-3,4-dicarboxymethylfurans **6** were recognized as starting products for 4-aroyl-2-arylfurans **8** as suggested by a *retro*-synthetic analysis (Scheme 11). Indeed, easily accessible furans **6** [56] can be hydrolysed to 4-furoic acids **7**, which should lead to **8** via acylation reaction.



Scheme 11. *Retro*-synthetic analysis of 4-aroyl-2-arylfurans **8** from 2-arylfurans **6**

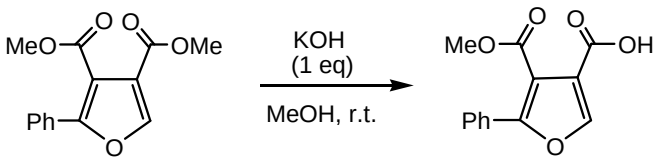
The 2-phenyl-3,4-dicarboxyfuran **6a** was prepared following a reported procedure [56]: a DABCO-catalyzed reaction of dimethyl acetylenecarboxylate (DMAD) with α-bromoacetophenone, in the presence of anhydrous K_2CO_3 (Scheme 12):



Scheme 12. Synthesis of 2-phenylfuran **6a**

After work-up the reaction residue was chromatographed on silica gel leading to **6a** in low yields. Thus, in order to minimize the degradation process of the product, due to the modest acidity of silica, rapid chromatography on flash silica gel column was conducted under nitrogen pressure and 2-phenylfuran **6a** was isolated in 85% yield. Successively, a selective basic hydrolysis in methanol and KOH (1 eq) was performed on furan **6a**. The reaction was conducted at room temperature for 15 hours, leading to 4-furoic acid **7a** in 88% yield (Scheme 13). The regioselectivity in position 4 was

expected because the possibility to hydrolyze asymmetric diesters on less hindrance position is reported [57].

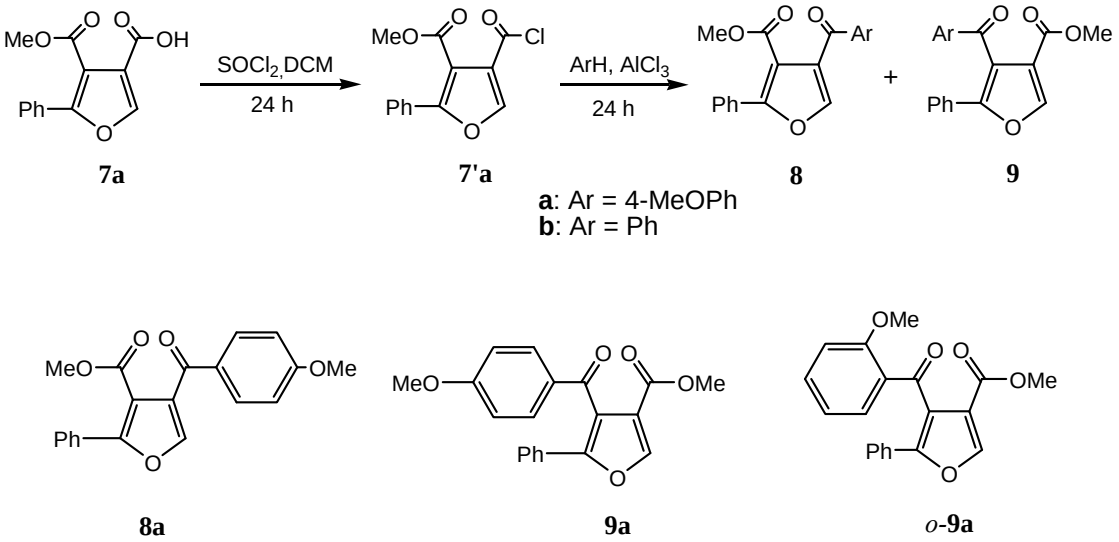


6a **7a**

Scheme 13. Synthesis of 4-furoic acid **7a**

Monoacid **7a** was treated with $SOCl_2$ in dry DCM, and the corresponding chloride **7'a** was subjected to $AlCl_3$-catalyzed Friedel-Crafts acylation reaction [58]. Benzene and anisole were used as aromatic substrates (Scheme 14) and the reaction conditions are summarized in Table 1.

The reaction with benzene was conducted in reflux conditions over night, but no complete conversion of chloride occurred. The work-up and purification led to a mixture of acylated products: the expected 4-benzoylderivative **8b** and isomer 3-benzoylderivative **9b**, in 7:3 ratio.



Scheme 14. Halogenation of monoacid **7a** and Friedel-Crafts acylation reaction on chloride **7'a**

Table 1. Halogenation of monoacid **7a** and Friedel-Crafts acylation reaction on crude chloride **7'a**

Halogenation of **7'a**		Acylation on **7'a**				Time $_{TOT}$ (h)	Yield $_{TOT}$
$SOCl_2$ (Eq)	T (°C)	ArH	Solvent	$AlCl_3$ (Eq)	T (°C)		
1.2	reflux	Benzene	DCM	1.2	reflux	48	60% (**8b** : **9b** = 67 : 33)
1.2	reflux	Anisole	DCM	1.2	r.t.	48	82% (**8a** : **9a** : *o*-**9a)** 68 : 24 : 8)

This result was evidenced by ^{1}H-NMR spectrum analysis, where two singlets at δ 7.79 and δ 8.11 can be attributed respectively to isomers **8b** and **9b**[58]. The similar chromatographic behavior of two isomers made difficult the separation of them and pure **8b** was recovered in poor amount.

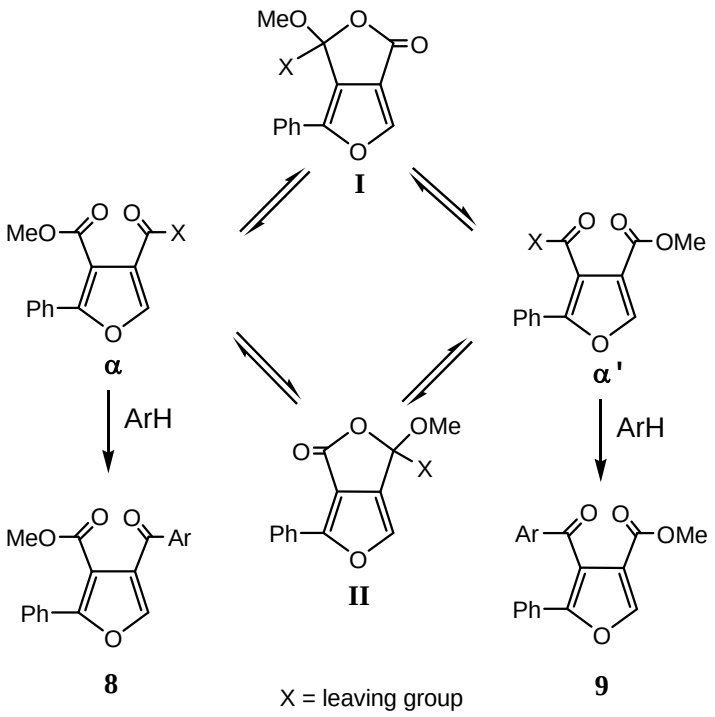
Slightly better results were obtained in reaction with more nucleophilic anisole. This reaction could be conducted at room temperature. The ^{1}H-NMR spectrum of reaction mixture showed three singlets at δ 7.74, δ 8.02 and δ 8.11, respectively attributed to H-

5 protons of **8a**, **9a** and *o*-**9a** in about 68:24:8 ratio. Both *para*- and *orto*-substituted 3-aroylisomers **9a** formed besides the expected **8a**: the *para*-isomer **9a** is favored compared to *orto*-substituted *o*-**9a** because of steric effects.

The formation of both 3-aroyl and 4-aroylfurans, starting from the 4-acyl chloride **α** (X=Cl) could be explained considering that ester and carbonyl chloride groups are sufficiently close to favor the cyclization which leads to intermediates **I** e **II** (Scheme 15) as reported in literature [58]. This interchange is probably due to the required long reaction times.

All the efforts to improve regioselectivity working at lower temperatures failed, because of the very sluggish activation of the furan reactant. These disappointing results induced to explore different acylation procedures reported in the literature. On the other hand great attention in Friedel-Crafts acylation for the synthesis of aromatic ketones is given to their usefulness as intermediates in the preparation of *fine chemicals* and pharmaceuticals [59].

The classical procedure uses acylic chlorides and Lewis acids in excess, thought the work-up is tedious and not environmentally friendly. In order to avoid these problems, several methods based on the use of acylant agents such as carboxylic acids, anhydride, esters have been tested [60]. Currently, there is a great interest for FC acylation, with the aim to minimize some drawbacks of the classical procedure, such as the use of acid chlorides and, generally, high amounts of the metallic oxophilic promoters which cause strongly acidic conditions [61]. New methodologies involve carboxylic acids as acylating agents in the presence of Lewis acid or Brønsted

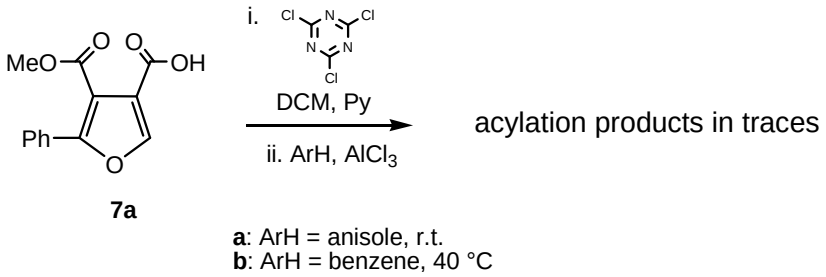


Scheme 15. Interchange mechanism between the ester function and the leaving group by a ring-chain tautomerism

acid catalysts [62], or using anhydrides as activating agents in combination with a catalyst such as *p*-trifluoromethylbenzoic anhydride and $SiCl_4$-$AgClO_4$ [63], trifluoroacetic anhydride and H_3PO_4 [64] or $AlPW_{12}O_{40}$ [65]. A recent methodology applied to acetic and benzoic acids employs trifluoromethylsulfonic anhydride (triflic anhydride) without the use of a catalyst and works in short times and in a large range of temperatures [66]. Anyway, to our knowledge, this methodology has not been applied to furoic acid. Thus, to improve the regioselective synthesis of 4-aroylfurans **8**, acid **7** underwent the study in several conditions based on recent literature.

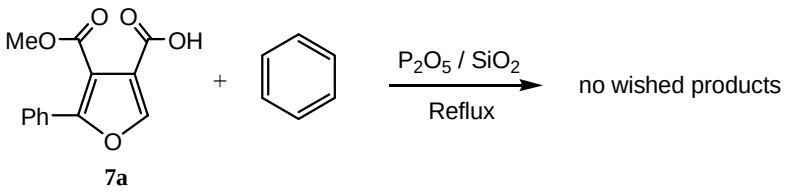
In initial experiments, an acylation reaction was performed on monoacid **7a** with cyanuric chloride, which is generally used to convert in the corresponding chloride in mild conditions and short times carboxylic acids [67]. In this procedure (Scheme 16) monoacid **7a**, dissolved in a 0.1 M solution of DCM, i**s** activated by dropwise addition

of pyridine in presence of cyanuric chloride After few minutes at reaction mixture $AlCl_3$ and aromatic compound are added. The reaction was performed by using both benzene and anisole. Unfortunately, after 15 hours, isomeric ketones were obtained in small quantity in both cases, and a part of the starting product was recovered.



Scheme 16. Acylation of acid **7a** via cyanuric chloride

A recent efficient procedure for the synthesis of aromatic ketones from both aliphatic and aromatic carboxylic acids performs FC acylation reaction in the presence of P_2O_5/SiO_2 [68]. Furthermore, this system (P_2O_5 on silica gel) is easy to prepare and handle, and can be removed from the reaction mixture by simple filtration. The procedure applied on acid **7a** reaction led to only polymeric material (Scheme 17). Probably furan system is quite sensible to the strongly acid conditions [69].



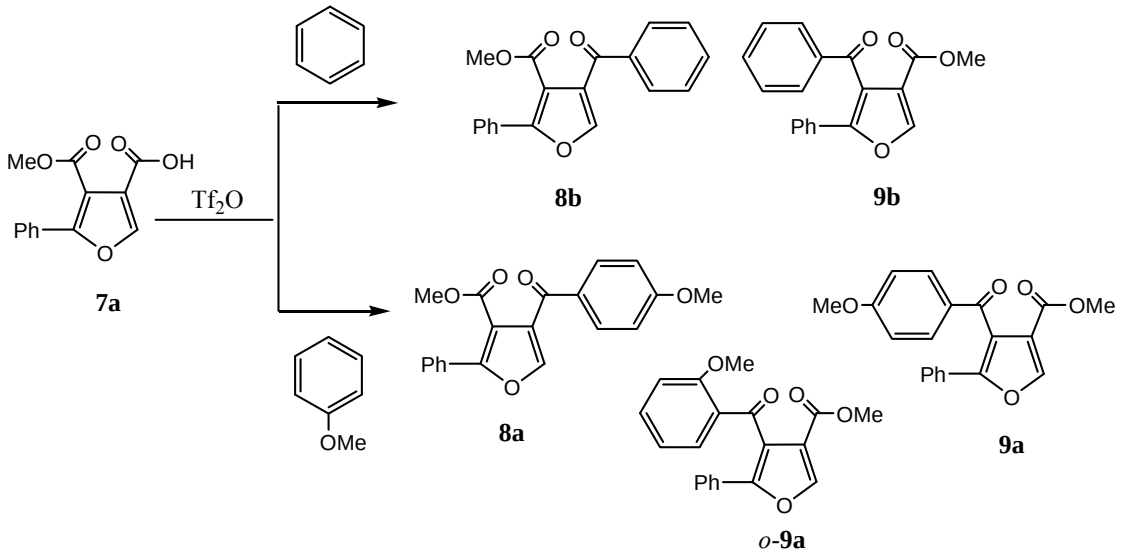
Scheme 17. Acylation of acid **7a** using P_2O_5/SiO_2

Hence, in the search of milder conditions, the use of triflic anhydride as promoter appeared a promising method [66]. According to literature data, Tf_2O forms an intermediate mixed anhydride in short times and a broad range of temperature.

Acylation was performed on acid **7a** in the presence of Tf_2O and benzene (100 eq) (Scheme 18), but no satisfactory results were obtained (Table 2), and reaction didn't go on to completion. Instead higher yields and selectivity were obtained using anisole (100 eq). The analysis of Table 2 shows that 4-aroylderivative **8a** is the main product in neat conditions. Apparently the solvent has no effect on total yields, while it favors the formation of 3-substituted furan regioisomers (**9a**, and *o*-**9a** in traces).

This different reactivity in use of anisole and benzene can be related to the previously analyzed mechanism (Scheme 15). Mixed anhydride is less reactive than acylic chloride, so the nucleophilic aromatic substitution reaction is obtained only with an activated substrate as anisole.

On these considerations, a further aim was to explore the reaction in order to get better yields and/or selectivity for 4-aroylfuran **8a**.



Scheme 18. Acylation of monoacid **7a** via Tf_2O

Table 2. Acylation of monoacid **7a** via Tf_2O with benzene and anisole

ArH	Solvent	Tf_2O (Eq)	T (°C)	Time (h)	Yield (**8a** : **9a**)
Benzene	DCM	1.1	r.t.	24	—
Benzene	—	1.1	80	24	20% (50 : 50)
Anisole	DCM	1.1	r.t.	2	70% (35 : 50 : 15)
Anisole	—	1.1	r.t.	2	72% (67: 24 : 9)

All experiments were performed on acid **7a**, by changing parameters such as temperature, neat conditions or in the presence of a solvent (generally dichloromethane), concentration and order of reagents addition. All conditions and results are reported in Table 3. Thus, reactions are conducted in DCM (entries 1-5) and in neat conditions (entries 6-14), at 40 °C (entries 1-3), at room temperature (entries 4-5) or in 0-30 °C range (entries 8-14). In neat conditions anisole was used in large excess (65 eq) related to the acid and Tf_2O was successively added to the reaction. On the contrary, in the presence of solvent anisole/DCM 1 : 1 was used (entries 1, 4), or a 0.1 M solution of anisole in DCM was added dropwise (entries 2, 3 and 5). In (1-5)

experiments anisole was added to a DCM solution of acid **7a** activated by 1.1 eq of Tf_2O, while at lower temperatures, more equivalents of Tf_2O were used (entries 10, 12-14).

Table 3. Acylation conditions of acid **7a** with anisole via Tf_2O

Entry	Solvent	T (°C)	Tf_2O (Eq)	Time (h)	Yield (**8a** : **9a** : *o*-**9a**)
	In solvent				
1	DCM	40	1.1	2	74% (21 : 63 : 16)
2	DCM/ArH[a]	40	1.1	2	90% (11 : 52 : 37)
3	DCM/ArH 10 eq[a]	40	1.1	3	50% (23 : 69 : 8)
4	DCM	r.t.	1.1	2	70% (36 : 50 : 14)
5	DCM/ArH 5 eq[a]	r.t.	1.1	4	98% (0 : 72 : 28)
	Neat conditions				
6	—	r.t.	1.1	2	72% (67 : 24 : 9)
7	Anisole dropwise	r.t.	1.1	2	62% (66 : 28 : 6)
8	—	0	1.1	3	78% (76 : 19 : 5)
9	Anisole dropwise	0	1.1	3	63% (76 : 19 : 5)
10	—	0	1.5	3	97% (77 : 17 : 6)
11	—	-10	1.1	3	62% (71 : 24 : 5)
12	—	-10	1.5	3	91% (80 : 13 : 7)
13	—	-30	2.0	15	57% (86 : 11 : 3)
14	—	[-30 ÷ -20]	2.5	15	98% (85 : 10 : 5)

[a] Dropwise addition of anisole (0.1 M solution in DCM)

In this case a mixture of acylated regioisomeric products was obtained as in reaction with $SOCl_2$. Starting from the unique acid **7a**, there is a competition between 4-aroylfurans **8a**, **9a** and *o*-**9a** isomers exists. At room temperature, the reaction led to an almost equimolar mixture of regioisomers **8a** and **9a**. In neat conditions, where anisole in excess acts as solvent, the selectivity for **8a** is favored at low temperature.

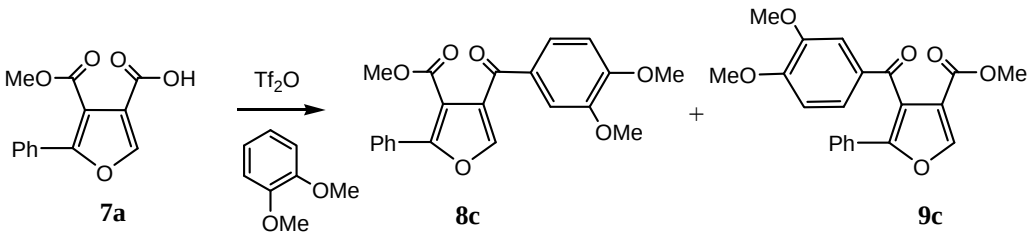
The results obtained can be explained as supposed for 4-aryl chloride (Scheme 15). In this case 4-aryl triflate (α, X = OTf) in equilibrium with 3-aryl triflate (α', X = OTf), through the cyclic intermediates can evolve in regioisomers **8a** and **9a**. At low temperature the product **8a** was formed as major product compared to isomer **9a**. Cyclization process that leads to intermediates is promoted by higher temperatures and

diluted solutions. Hence, thus the equilibrium between mixed anhydrides **α** e **α'** occurs. The Dropwise addition of aromatic substrate (anisole) at room temperature led to almost quantitative formation of **9a**. These experimental evidence suggest that **α** is a more reactive intermediate.

2.1 Tf_2O-mediated FC acylation of other arylic substrates

Promising results obtained induced us to explore the method on a range of other arylic substrates. In particular, compounds were considered with suitable substitution on aromatic ring for the synthesis of 4-aroylfurans, lignan-like precursors. Experiments on acid **7a** were performed starting from the best conditions for anisole, and further attempts were made in order to increase the regioselectivity of acylation in favor of one of the diaroylfuran products.

In the first attempt, it was used as arylic substrate 1,2-dimethoxybenzene (Scheme 15). The obtained results confirmed the role of temperature in regioselectivity, as already suggested by data of anisole. In particular low temperatures favored high total yield of 4-aroylfuran, that is the required product with a suitable substitution on furan (Table 4). Natural lignan derivatives present substituents in positions 4, 3 and 4, or 3,4,5 derived for their biosynthetic pathway [6].



Scheme 19. Acylation on acid **7a** con 1,2-dimethoxybenzene via Tf_2O

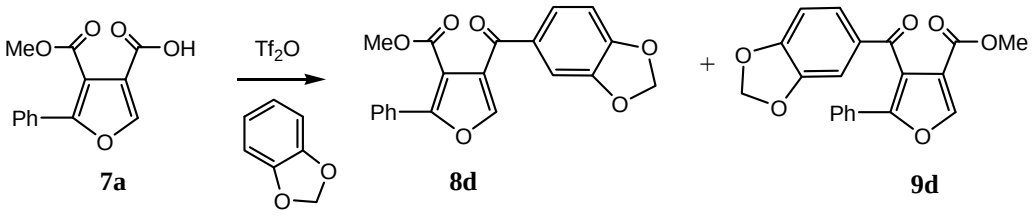
Table 4. Acylation conditions of acid **7a** via Tf_2O with 1,2-dimethoxybenzene

Entry	Solvent	T (°C)	Tf_2O (Eq)	Time (h)	Yield (**8c** : **9c**)
1	DCM	r.t.	1.1	3	87% (42 : 58)
2	DCM/ArH 5 eq[a]	r.t.	1.1	3	63% (11 : 89)
3	DCM/ArH 5 eq[a]	r.t.	1.5	3	86% (11 : 89)
4	DCM	[-30 ÷ -20]	2	15	90% (84 : 16)

[a] Dropwise addition of 1,2-dimethoxybenzene (0.1 M solution in DCM)

Reaction with 1,2-benzodioxole (Scheme 20) gave satisfactory results in formation of both 3-aroyl and 4-aroylfurans, through in lower yields (Table 5).

Differently, acylation with 1,2,3-trimethoxybenzene (Scheme 21) led to high yield, but the selectivity for 4-aroylfuran **8e** is reduced at low temperatures (Table 6).

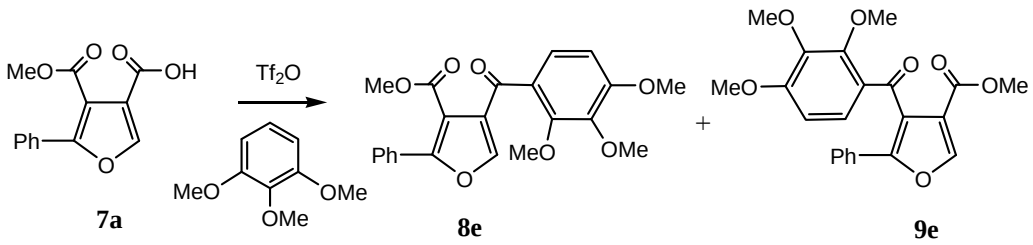


Scheme 20. Acylation on acid **7a** via Tf_2O with 1,2-dibenzodioxole

Table 5. Acylation conditions of acid **7a** via Tf_2O with 1,2-dibenzodioxole

Entry	Solvent	T (°C)	Tf_2O (Eq)	Time (h)	Yield (**8d** : **9d**)
1	DCM	r.t.	1.1	1	56% (25 : 75)
2	DCM/ArH 3 eq[a]	r.t.	1.1	4	41% (0 : 100)
3	DCM/ArH 5 eq[a]	r.t.	1.1	4	46% (0 : 100)
4	DCM/ArH 10 eq[a]	r.t.	2	15	56% (0 : 100)
5	—	-15	2.5	15	68% (80 : 20)
6	DCM	-30	2.0	15	60% (81 : 19)

[a] Dropwise addition of 1,2-dibenzodioxole (0.1 M solution in DCM)



Scheme 21. Acylation on acid **7a** via Tf_2O with 1,2,3-trimethoxybenzene

Table 6. Acylation conditions of acid **7a** via Tf_2O with 1,2,3-trimethoxybenzene

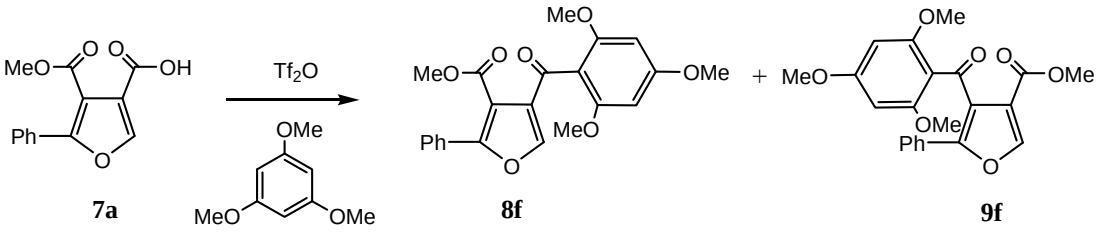
Entry	Solvent	T (°C)	Tf_2O (Eq)	Time (h)	Yield (**8e** : **9e**)
1	DCM	r.t.	1.1	2	84% (57 : 43)
2	DCM/ArH 10 eq[a]	r.t.	2	3	65% (20 : 80)
3	DCM	[-30 ÷ -20]	2	15	98% (67 : 33)
4	DCM	40	1.1	3	65% (20 : 80)

[a]Dropwise addition of 1,2,3-trimethoxybenzene (0.1 M solution in DCM)

Combination of *para*- and *orto*-directing effects due to the position of methoxyl groups on benzene ring as in ketones **8e** e **9e**. Unfortunately, this 2,3,4-substitution pattern on aromatic ring is not common in the natural lignan structure [6].

Acylation reaction on 1,3,5-trimethoxybenzene gave products **8f** e **9f** in good yields (Scheme 22, Table 7)**,** and high regioselectivity for the 4-aroyl furan was observed performing reaction in specific conditions. The 2,4,6-substitution pattern on aromatic ring of products occurs more in neolignan than in lignan structure [6].

All products were isolated by chromatography on silica gel and characterized by ^{1}H NMR, ^{13}C NMR, ESI-MS spectroscopy. In particular, spectrum ^{1}H-NMR of compound **8** have signal of H-5 as a singlet in *chemical shifts* range 7.68 - 7.79 ppm, while for the regioisomer **9** this signal are at lower fields (7.95 - 8.11 ppm). This difference in values is due to the anisotropy of aromatic ring, in compounds **8**, that causes shielding effects on the close proton to the aroyl group [70].



Scheme 22. Acylation on acid **7a** via Tf_2O with 1,2,3-trimethoxybenzene

Table 7. Acylation conditions of acid **7a** via Tf_2O with 1,3,5-trimethoxybenzene

Entry	Solvent	T (°C)	Tf_2O (Eq)	Time (h)	Yield (**8f** : **9f**)
1	DCM	r.t.	1.1	3	50% (100 : 0)
2	DCM	-30	2	4	54% (100 : 0)
3	DCM/ArH 5 eq[a]	r.t.	1.1	3	81% (25 : 75)

[a]Dropwise addition of 1,3,5-trimethoxybenzene (0.1 M solution in DCM)

The analysis of experimental data revealed the possibility to obtain 4-aroylfurans **8** or 3-aroylfurans **9** through a *one-pot* procedure of acylation via Tf_2O on 4-furoic acid **7a**. The regioselectivity of reaction can be addressed choosing different reaction conditions.

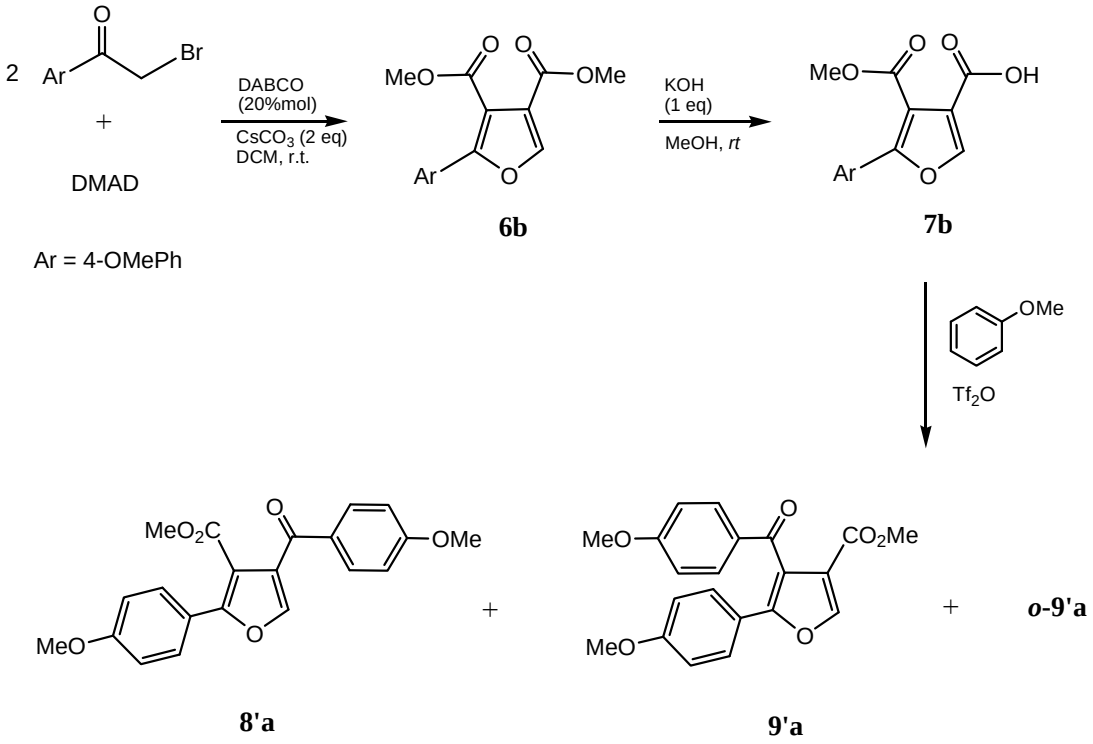
Reaction times are considerably reduced by comparison wuth the classical Friedel Crafts acylation, and work conditions have no effects on them. Dichloromethane turned out to be the best choice to carry out mentioned reactions. Different solvents such as benzene, tetrahydrofuran, acetonitrile, *p*-dioxane are used in order to get higher yields. Anyway, in the first case yields were lower than 80%, whereas in the other solvents no acylation products was formed. The Friedel-Crafts acylation method via Tf_2O for 4-aroylfurans **8** revealed satisfactory for the most aromatic substrates. Some exceptions are observed, for example on reactant 1,2,3-trimethoxybenzene, the reaction behaved in good yields but low selectivity for isomer **8e** (Table 6).

2.2 Tf_2O-mediated FC acylation on 2-(4-methoxyphenyl)furoic acid 7b

In order to investigate the possible effects of a substituted aromatic ring of starting furan, the novel procedure was applied on 2-(4-methoxyphenyl)furoic acid **7b** (Scheme 23). The DABCO-catalyzed reaction of dimethyl acetylene carboxylate with 2 eq of 2'-bromo-4-methoxyacetophenone, led to the best yield (66%) in presence of $CsCO_3$ anhydrous instead of K_2CO_3. Afterwards, the selective hydrolysis of furan **6b** was performed in MeOH and 1.0 eq of KOH 2.5 N for about 3 hours (Scheme 23). Monoacid **7b** was obtained in 70% yield.

As for acid **7a**, the classical Friedel-Crafts acylation, using $SOCl_2$ and $AlCl_3$, was performed on acid **7b**. Nevertheless, this approach led to an equimolar mixture of two regioisomers **8'a** and **9'a**. So, the procedure via Tf_2O was explored in several reaction conditions (Table 8). Based on satisfactory results obtained for monoacid **7a** in anisole strong excess of arene and low temperatures were used. The best selectivity for **8'a** was resulted in entries 2 and 5 (Table 8). Yield of mixture of products was 69%, while isomeric ratio **8'a**:**9'a** was 1.6:1. On the basis of mechanistic hypothesis it is possible to address reaction to the formation of **8'a**, by controlling the temperature.

Although several attempts were performed by tuning the reaction conditions (temperature, presence or absence of solvent, equivalents and order of reagents addition), actually regioisomeric excess of **8'a** was not as satisfactory as could be expected, especially considering the laborious purification of products. Moreover, since acid **7b** is poorly soluble in anisole it was not possible to work at temperatures lower than -30 °C. Reaction in solvent (Table 8, entry 1) in reflux condition led to quite exclusively formation of **9'a**.



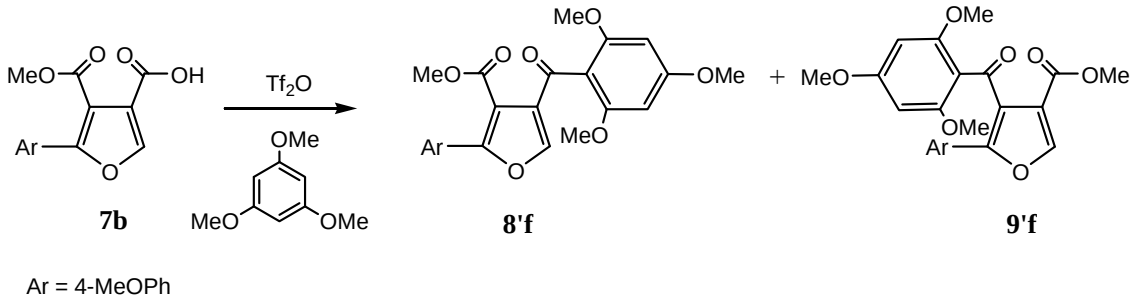
Scheme 23. Acylation on acid **6b** via Tf_2O with anisole

Table 8. Acylation conditions of acid **7b** via Tf_2O with anisole

Entry	Solvent	Tf_2O (Eq)	Anisole (Eq)	T (°C)	Time (h)	Yield %	**8'a:8'a:*o*-9'a**	**8'a:9'a**
1	DCM	1.1	5/DCM[a]	40 rf	4	23	0:4.47:1	0:4.47
2	—	1.2	10	0	4	64	8.4:5.09:1	1.67:1
3	—	1.2	25	-10	3.5	23	2.6:3:1	1:1.6
4	—	1.5	65	-15	72	80	4.45:3.4:1	1.3:1
5	—	2.5	65	-15	72	69	7.3:4.45:1	1.6:1
6	—	2.5	65	-30	o.n.	62	7.7:5.2:1	1.47:1
7	DCM	2.5	5	-30/-10	28	69	1:4.2:1	1:4.2
8	DCM	2.5	5	-20	o.n.	30	1.6:3.3:1	1:2.06
9	DCM	2.5	5	-15/-20	o.n.	gel	—	—
10	DCM	1.1	5/DCM[a]	r.t.	4	56	1:9.92:1.9	1:9.92

o.n. = overnight, rf = reflux ; [a]Dropwise addition of anisole (0.1 M solution in DCM)

The acylation procedure was performed on acid **7b** with 1,3,5-trimethoxybenzene (Scheme 24, Table 9), too. The reactions were conducted in DCM, at different temperatures.



Scheme 24. Acylation on acid **7b** via Tf_2O with 1,2,3-trimethoxybenzene

However, in both cases results were not very satisfactory in terms of isomeric ratio.

Table 9. Acylation conditions of acid **7b** via Tf_2O with 1,2,3-trimethoxybenzene

Entry	Solvent	Tf_2O (Eq)	T (°C)	Time (h)	Yield (**8'f : 9'f**)
1	DCM	1.2	-20	23	63% (1.27 : 1)
2	DCM	1.2	r.t.	22	79% (3.76 : 1)

2.3 Conclusion

A strategy allowing the preparation of either 3-aroyl-2-phenyl- or 4-aroyl-2-phenyl furans, starting from a unique easily accessible mono-acid precursor **6**, has been recognized. This method is based on tunable Tf_2O-mediated FC-acylation and takes advantage of a ring-chain tautomeric interchange occurring on the acylating agent. In particular, temperature turned out to have important effects on regioselectivity. The methodology has been explored on different arylic substrates with typical lignan substitutions. The best conditions leading to a series of *β–β'* lignan-like precursors **8a-f** derivatives are characterized by low temperatures (Table 13).

The method turns out suitable also for regioisomers **9a-f**, whose formation is favoured by higher temperatures (Table 14).

However, less satisfactory appear the results obtained starting from an electron-rich 2-arylfuran.

Table 10. The best Tf_2O-mediated FC-acylation conditions for **8a-f**

Entry		Solvent	T (°C)	Tf_2O (Eq)	Time (h)	Total yield (yield **8**)
a	anisole	—	[-30 ÷ -20]	2.5	15	98% (**8a** 83%)
c	1,2-dimethoxybenzene	DCM	[-30 ÷ -20]	2	15	90% (**8c** 76%)
d	1,2-benzodioxole	—	-15	2.5	15	68% (**8d** 54%)
e	1,2,3-trimethoxybenzene	DCM	[-30 ÷ -20]	2	15	98% (**8e** 66%)
f	1,3,5-trimethoxybenzene	DCM	-30	2	4	54% (**8f** 54%)

Table 11. The best Tf_2O-mediated FC-acylation conditions for **9a-f**

Entry		T (°C)	Tf_2O (Eq)	Time (h)	Total yield (yield **9**)
a	anisole	r.t.	2.5	15	98% (**9a** 98%)
c	1,2-dimethoxybenzene	r.t.	2	15	63% (**9c** 56%)
d	1,2-benzodioxole	r.t.	2.5	15	56% (**9d** 56%)
e	1,2,3-trimethoxybenzene	40	2	15	65% (**9e** 52%)
f	1,3,5-trimethoxybenzene	r.t.	2	4	81% (**9f** 61%)

3. Application of some synthetized furans in the synthesis of functionalized lignan-like compounds

4-Aroyl-2-phenyl-3-methoxycarbonyl furans **8** are very interesting products, since they possess a typical lignan scaffold (Figure 8).

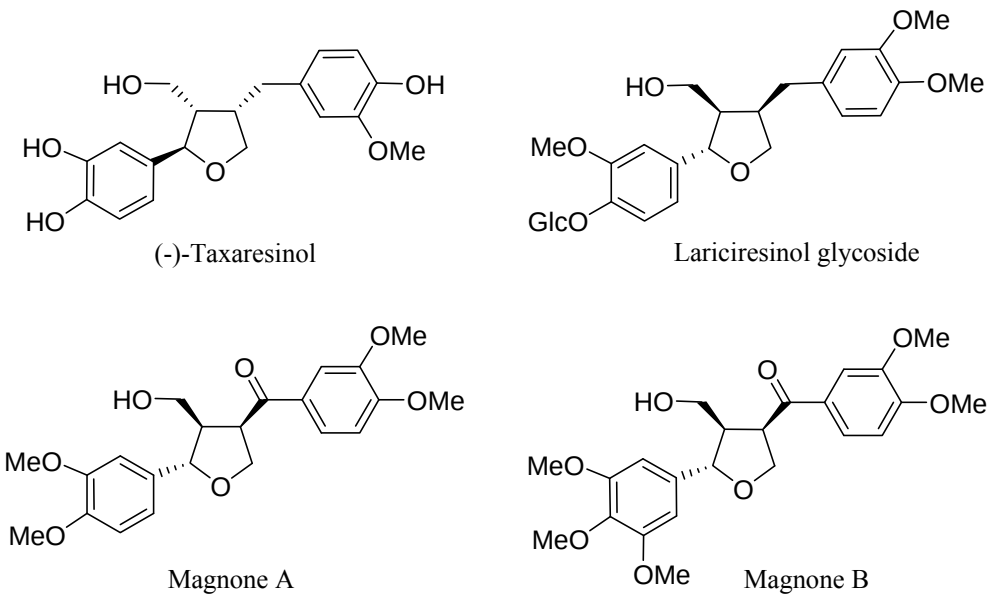


Figure 8. Some examples of natural tetrahydrofuran lignans with anti-inflammatory and antimicrobial activities.

Hence, the possibility to functionalize these products towards lignan-like compounds was explored. In particular, hydrogenation and/or photooxygenation reactions were considered.

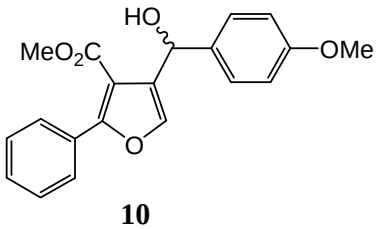
3.1 Hydrogenation of 8a

The hydrogenation of the furan moieties of the obtained 4-aroyl furans **8** would thus offers a versatile and straightforward route to lignan derivatives or analogues thereof. To test this synthetic opportunity, model furan **8a** was hydrogenated under different temperature conditions and at high pressure (100 atm) with Pd on carbon, as already reported for 2-arylfuran-3,4-dicarboxylate esters [57]. Tuning the temperature was indeed useful for obtaining furan derivatives with a differentiated profile of functional groups or the corresponding tetrahydrofuran (Figure 9). In the latter the carbonyl

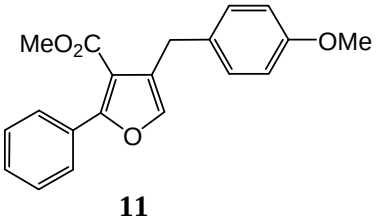
function also underwent reduction to methylenic group because of its di-benzylic character [71].

Furan ring can be readily saturated to yield tetrahydrofuran without ring opening through Pd/C-catalysed hydrogenation in methanol, at low hydrogen pressure and high reaction temperatures [72]. Moreover, it is reported that 2-arylfuran-3,4-dicarboxylate esters can be subjected to a very similar procedure, but at higher pressure in order to avoid the reduction of aryl ring too [40]. On this considerations, the model furan **8a** was hydrogenated, in MeOH dry with 10% Pd/C (Table 10). Preliminary results have evidenced that too high pressures led to the formation of many by-products. After several attempts conducting the reduction at 100 atm the to a less complex mixture of products. Tuning the temperature, furan derivatives with a different functional groups (**10** and **11,** Figure 9) or the corresponding tetrahydrofuran **12** were obtained. These results have induced to investigate the best reaction conditions to promote the synthesis of tetrahydrofuran system **12**.

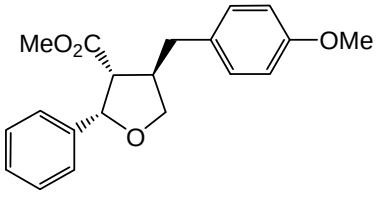
Performing the hydrogenation reaction at room temperature, only reduction of the carbonyl function to hydroxyl group occurs to give **10** which, in turn, was converted in moderate yield to **11** increasing the temperature up to 50 °C. This result can be in according with that is reported hydrogenolysis of the hydroxyl group [71].



10



11



12

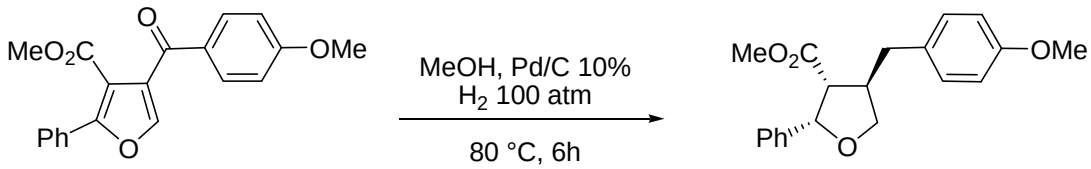
Figure 9. Hydrogenation main products

Hydrogenation of the furan ring led to **12** and occurs at high temperature with high stereoselectivity, evidencing a non-conjugated hydrogenation mechanism [40].

This hydrogenation product **12** is an analogue of tetrahydrofuran plant lignans with antimicrobial (Taxiresinol, Figure 8) and anti-inflammatory activities (Magnone A, Magnone B, Lariciresinol glycoside, Figure 8) [5].

Table 12. Conditions of hydrogenation reaction on product **8a**

Entry	Pressure (atm)	T (°C)	Time (h)	**Products**
1	100	100	7	**12** (50%) and by-products
2	100	150	4	**12** (40%) and by-products
3	120 ÷ 100	156	3	**12** (40%) and by-products
4	100	80	6	**12** (54%)
5	100	50	12	**10** (40%) + **11** (35%)
6	100	r.t.	12	**10** (90%)



8a **12** 54%

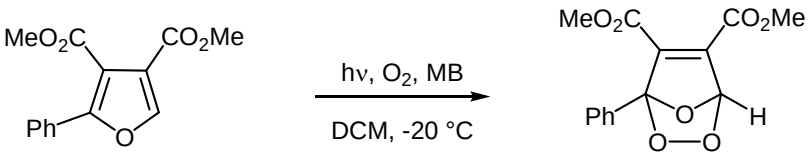
Scheme 23. Hydrogenation reactions on **8a** to **12**

3.2 Photooxygenation of some furan systems

As previously mentioned in the introduction, furans can be easily oxidized and the possibility to apply photooxygenation reactions to obtained furans was explored.

Although the power of the reaction furans with $^1O_2$ is widely recognized [44, 45, 73], new findings are often come up due to the versatility of furan endoperoxides. It has to be noted that peroxides of α-aryl-α'-unsubstituted furans were not previously examined. In particular, we focused on two general applications of the photooxygenation of furans for the preparation of enediones and 4-hydroxybutenolides, compounds of great synthetic interest. *Cis*-1,4-enediones are prepared by low temperature treatment of furan endoperoxides with reductants such as triphenylphosphine or dialkyl sulphides. They generally form almost quantitatively and hence used without isolation. Butenolides are obtained by oxygenation of α and α,α'-unsubstituted furans through a Kornblum-DeLamare rearrangement of the related endoperoxides which occurs in the presence of a base [74], in a basic solvent as acetone [75], water or ionic liquids [76].

Initial experiments were explored on 2-phenylfuran **6a** and the reactivity of corresponding endoperoxide **13** was examined in different conditions (Scheme 24). The photooxygenation reaction was performed in classical conditions such as low temperature (-20 °C), DCM as solvent (usually 10^{-2} M) and methylene blue (MB) as sensitizer, sunlight lamp, dry oxygen flux. The reaction was easily followed by ^1H NMR analysis. Formation of the endoperoxide **13a** was confirmed by the appearance of a characteristic signal at δ 6.80 (typical of acetalic proton in unsatured bicyclic structures [47b, 77] (while singlet of furan system's H-5 is at δ 7.96). The completion of reaction occurred in about 3 hours. Experimental measures for ^1H NMR analysis were rapidly and possibly made at low temperature in order to inhibit the thermal degradation of endoperoxide **13a**. However, it exhibited a quite thermal stability due to the presence of two electron-acceptor groups in β-position [46].



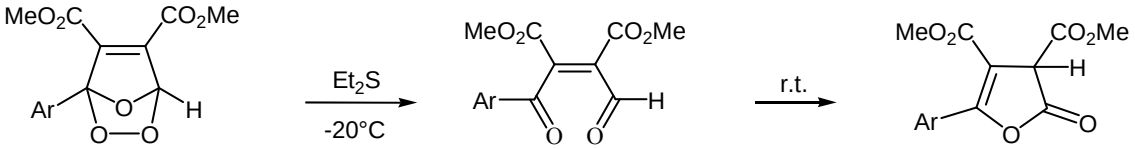
6a **13a**

Scheme 24. Dye-sensitized photooxygenation of 2-phenylfuran **6a**

Attempts were performed on endoperoxide **13** to evaluate thermal reactivity of this intermediate (Scheme 25). However, keeping it for long time at room temperature a complex mixture of products quite difficult to be identified was obtained, as well as warming it rapidly until 80 °C in CCl_4.

3.2.1 Et_2S reduction

As expected, treatment in situ with Et_2S of the endoperoxide **13a** kept at -20°C (Scheme 25) led quantitatively to an enedione identified as aldehyde **14a** by spectroscopic analysis. ^{1}H NMR spectrum showed a singlet at δ 9.68. However, monitoring by NMR the stability of **14a**, a slow complete conversion into lactone **15a** was observed. Indeed, ^{1}H NMR spectrum of sample (kept at room temperature for about 3 hours) showed the singlet δ 4.68, related to H-4 double bond, while the aldehydic signal was disappeared, and ^{13}C NMR showed two carbonylic signals for the ester groups and a lactone carbone.



13
a,b

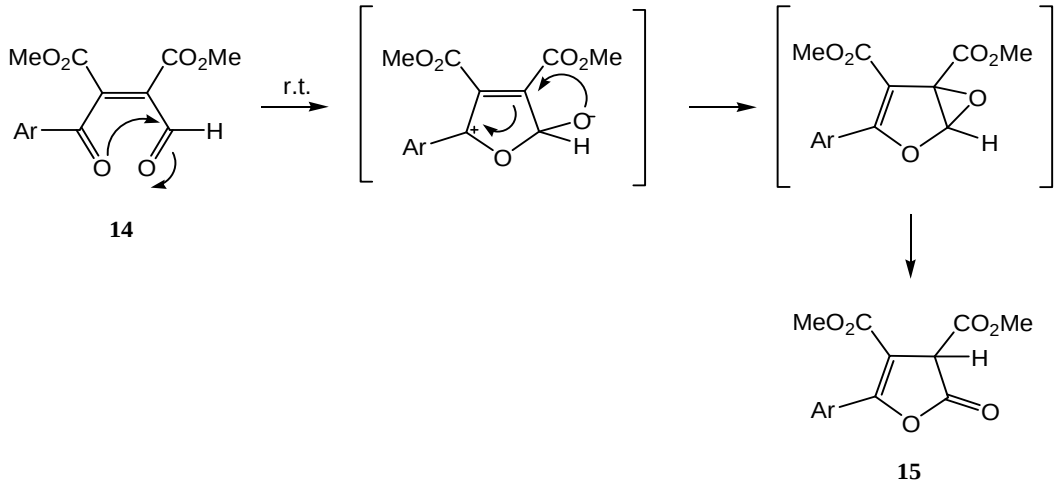
14
a,b

15
a,b

a: Ar = Ph
b: Ar = 4-MeOPh

Scheme 25. Et_2S reduction on endoperoxide **13**

The possible mechanism which explains the formation of lactone, reported in Scheme 26, suggests that a conversion of enedione in epoxide occurs, as observed in other compounds [78]. Then, the epoxide spontaneously converts in the cyclic structure **15** according to its spectral data [79].



14

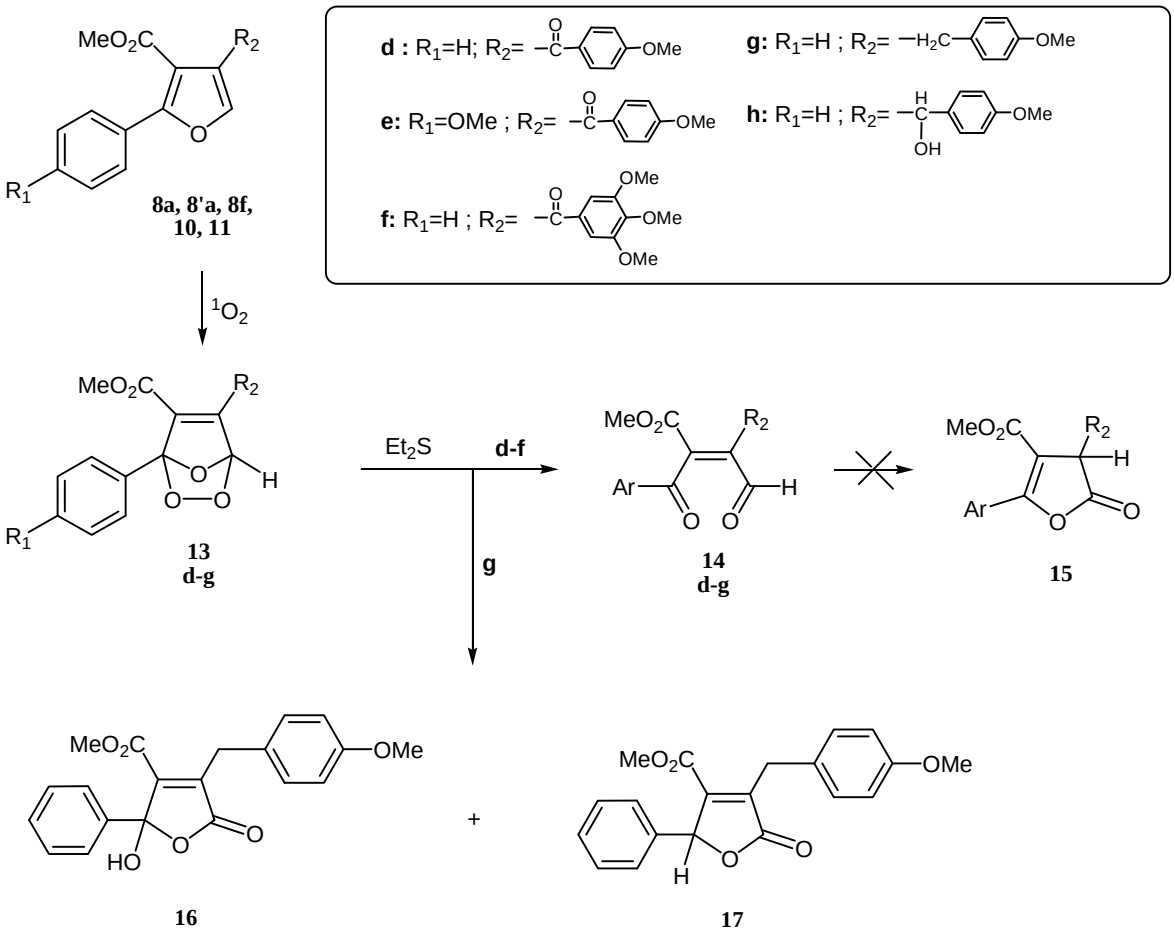
15

Scheme 26. Rearrangement of aldehyde **14** into the lactone **15**

The procedure on analogue 4-methoxyphenylfuran **6b** led to the same results: after formation of aldehyde **14b**, it rearrange in corresponding lactone **15b** (Scheme 26).

Afterwards, the methodology was extended also on 4-aroyl furans **8a**, **8f**, **8'a**, and hydrogenated systems **10** and **11**, chosen in order to obtain lignan-like structures.

Except for **10,** whose endoperoxide degraded, even at low temperature, in unidentified products, all furan systems were quantitatively converted into the corresponding endoperoxides **13** (Scheme 27), which showed a quite thermal stability, as it was evidenced for furans **6**. The reduction with Et_2S on 2-aryl-4-aroylfurans **8a, 8'a** and **8f**, led to the acrylic aldehydes **14**, but no spontaneous conversion into the lactones **15** was observed, though the products were kept in the solvent at room temperature for some days.



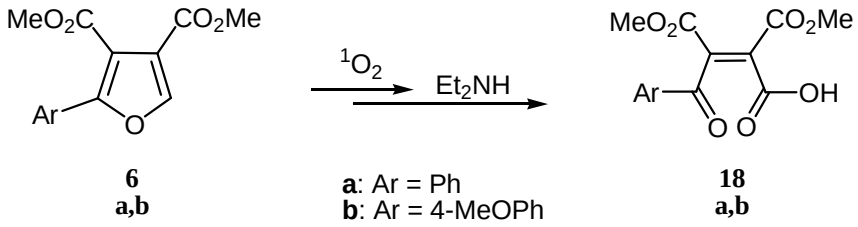
Scheme 27. Photooxygenation followed by Et_2S reduction on furans **8a**, **8'a**, **8f**, **10** and **11**

The reduction with Et_2S, instead, led to a mixture of products different from the expected aldehyde (as evidenced by NMR spectra of mixture). The purification of

mixture by TLC led to two butenolidic products identified as γ-hydroxylactone **16** (25% yield) and lactone **17** (18% yield) by NMR analysis. The formation of the latter is due to the rapid cyclization of the intermediate aldehyde. Product **16** should be formed by a Kornblum-DeLamare rearrangement, likely promoted by Et_2S acting as base instead of reductant.

3.2.2 Basic treatment

In the first experiment the procedure was applied on furan **6a** (Scheme 28).



Scheme 28. Photooxygenation followed by base treatment in situ with Et_2NH on furans **6a,b**

Once formed endoperoxide **13a**, 1.2 eq of diethylamine was added and mixture leaved to room temperature for about 30 minutes (Scheme 28). However, the addition to the endoperoxide **13** at low temperature led exclusively to an opened oxidized structure instead of the expected lactone (Scheme 25). Indeed, in ^1H NMR spectrum of mixture, the predicted singlet of H-5 at about 5 ppm was absent. Moreover, ^{13}C NMR showed two carbonyl signals at δ 192.5 and 166.9, assigned to an aromatic ketone and a -COOH group, respectively. Mass analysis confirmed that product was the acrylic acid **18a**. Actually, this unusual result can be explained by considering the base-mediated conversion of γ-hydroxylactones into the corresponding open structures (Figure 10) [80].

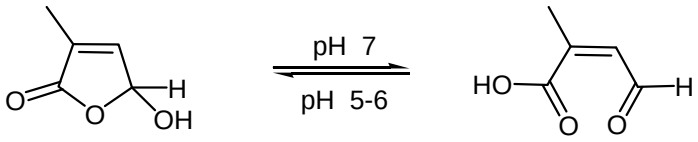
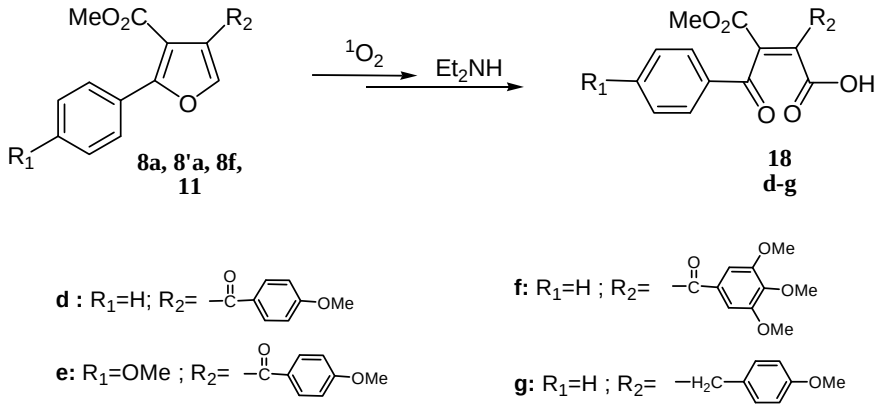


Figure 10. Conversion of γ-hydroxylactone in carboxylic acid

In our case it is likely that γ-hydroxylactone, once rapidly formed, rearranges to the acid open form due to the particular substitution and high conjugation. The same result was obtained also with tertiary amines, as Et_3N or DABCO, or in different slightly basic solvents, as water and acetone. Anyway, the best choice turned out to be Et_2NH which can be removed under reduced pressure in presence of phosphorous anhydride.

The procedure on analogue 4-methoxyphenylfuran **6b** led to acrylic acid **18b** (Scheme 28).

Afterwards, extending the methodology on furans **8a**, **8f**, **8'a**, **11** (already studied in Et_2S reductions) the same result was obtained (Scheme 29).



Scheme 29. Photooxygenation followed by base treatment in situ with Et_2NH on furans **8a**, **8'a**, **8f**, and **11**

So we decided to apply the novel Tf_2O-mediated acylation on opened acid **18a**, in an attempt to improve the synthesis of *β-β'* lignan structures.

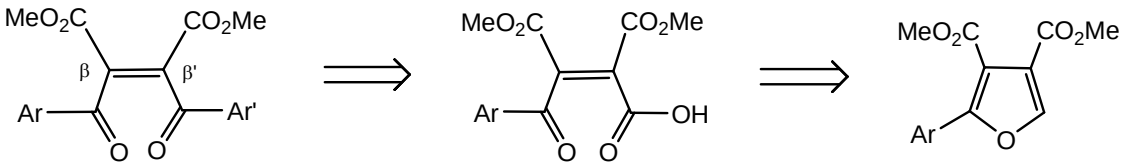
3.3 Conclusion

In order to obtain functionalized lignan-like compounds, the synthetized furans underwent further reactions. In particular, hydrogenation reaction on 4-anisoyl-2-phenyl furans **8a** led to tetrahydrofuran **12** analogue of some bioactive natural lignans in useful yield.

Photooxygenation reaction was explored, followed by Et_2S reduction and/or basic treatment in situ on α-aryl-α'-unsubstituted furans, not previously studied. Endoperoxides **13** exhibited a quite thermal stability due to the presence of two electron-acceptor groups in β-position. In particular, two general procedures for the preparation of enediones and 4-hydroxybutenolides were applied. The α-aryl substitution of furans and their high conjugation gave interesting results. Et_2S reduction of endoperoxides led to expected adehydes **14** whose particular substitutions can favour a rearrangement to lactone structures. Basic treatment with Et_2NH led exclusively to open acid structures probably formed by conversion from the expected γ-hydroxylactones.

4. Preparation of 5,5- and 3,5-diarylfuranones by three-step one-pot procedure

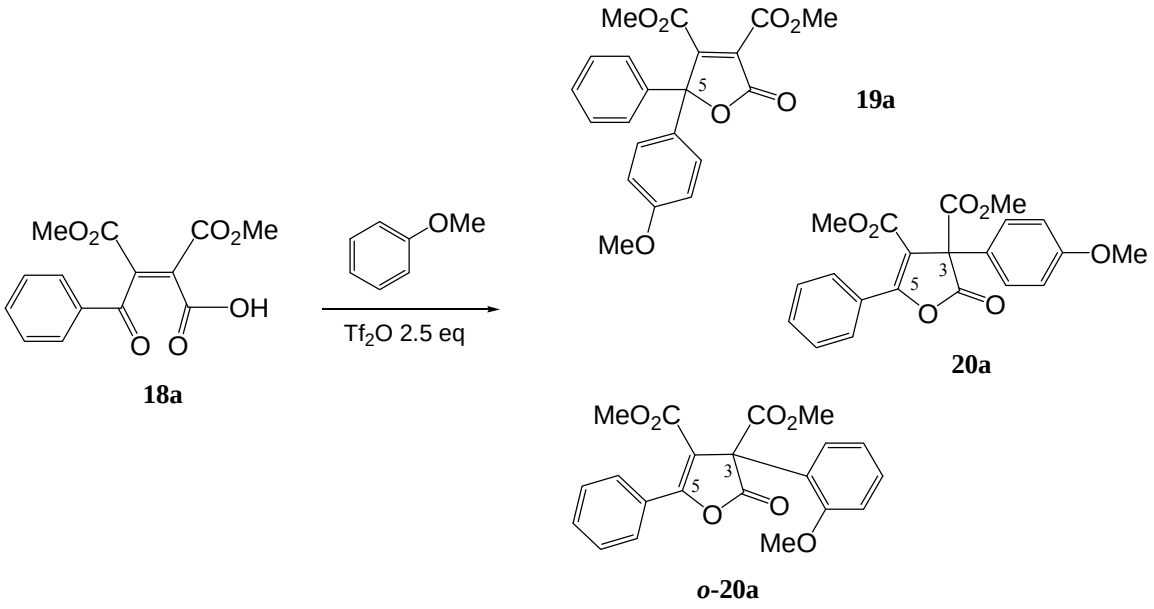
Results previously obtained gave a suggestion to verify the application of acrylic acids prepared. Hence, starting from furans **6** attempts to reach the synthesis of *β-β'* lignan structure anyway applying the novel Tf_2O-mediated acylation on acids **18** (Scheme 30).



18 **6**

Scheme 30. Strategy to obtain *β-β'* lignan structure applying the novel Tf_2O-mediated acylation on acids **18**

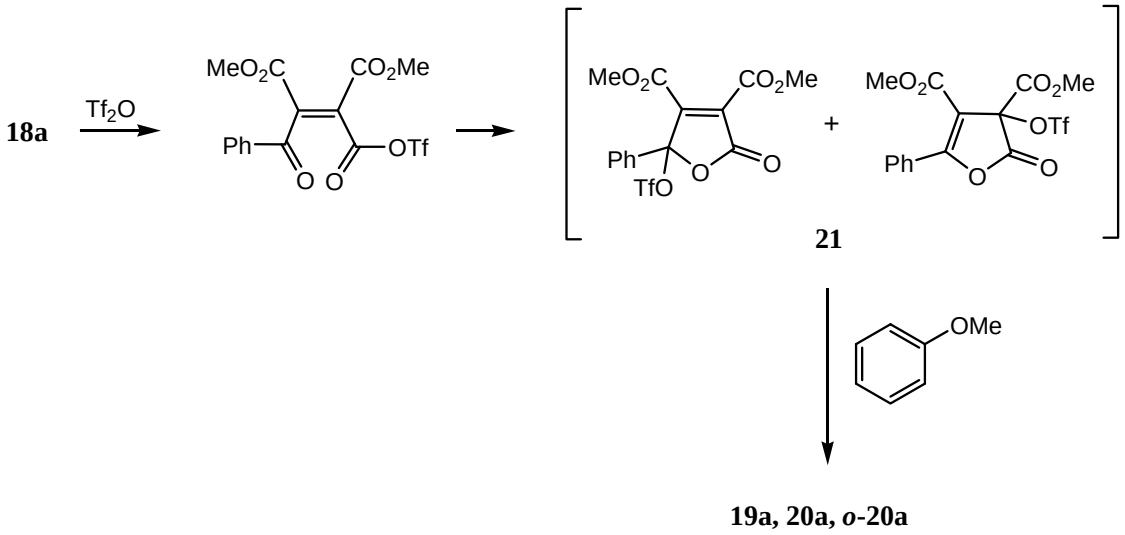
Initially, the investigation of the Tf_2O-catalyzed acylation was tested on pure acid **18a** by using anisole as aryl reagent (Scheme 31).



Scheme 31. Tf_2O-catalized acylation on acrylic acid **18a** with anisole

The reaction was carried out in the best conditions observed for monoacid **7a**: low temperature and absence of solvent. Thus, the acid **18a** was dissolved in 35 eq of anisole, and then 2.5 eq of Tf_2O were added at -20 °C. The reaction was conducted at temperature for 20 hours leading to a mixture of cyclic acylated products identified as the 5,5-diarylfuranone **19a** and the two 3,5-diarylfuranones **20a** and ***o*-20a** (Scheme 31) by NMR analysis. The ^{13}C spectrum of each product showed three esters signals (in a range of δ 170-160.0), and a quaternary carbon at higher field, respectively at δ 91.9, 63.8 and 63.1 for isomers **19a,** and **20a** and ***o*-20a**.

The regioisomeric ratio was in favor of 5,5-disubstituted **19a**, whereas the other ones were obtained in traces (Table 11, entry 1). The formation of cyclic products, though starting from open acid, might be explained supposing an intramolecular addition of the carbonyl to the activated carboxylic function (Scheme 32). Thus, an intermediate like the pseudo anhydrides **21** (or a carbocation) undergo the attack of arene substrate (anisole).



Scheme 32. Proposed conversion of acid **13a** to furanones **13a** and **15a**.

Really, the formation of pseudo anhydrides **21** is supported by ^{1}H NMR spectra acquired immediately after the addition of Tf_2O. A shift at higher field of *ortho* aryl protons was observed by indicating the possible presence of the pseudo anhydrides. This hypothesis accords with analogue results of FC acylation on phthalic acids [81] or alkylated acrylic acids [82], both leading to the 5-arylfuranones.

Diarylfuranones **19a** and **20a** appear of particularly interesting, since they combine the presence of a furanone moiety and a carbon skeleton of some recently isolated rare lignans [83]. Moreover, the structure of 5,5-diarylfuranone **19a** reminds *Sacidumlignan D* (Figure 11), which is a peculiar rearranged tetrahydrofuran lignan [84].

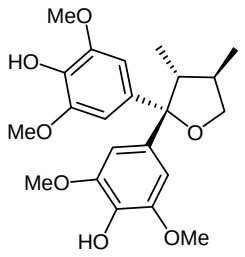


Figure 11. *Sacidumlignan D*, a lignan with a rare structure.

Hence, and considering that 3-arylfuranones have rarely been obtained by FC-acylation [85], the idea to explore the procedure seemed quite attractive.

In order to evaluate a possible effect of solvents, the reaction was performed in DCM by using an excess of anisole (5 eq) and 2.5 eq of Tf_2O, but the result did not change while it appeared to slightly increase the amounts of 3,5-diarylfuranones **20a** and *o*-**20a** (Table 11, entry 2). A lower yield (42%) was also obtained by using highly polar solvent such as acetonitrile, while nitromethane gave a very complex reaction mixture. Further experiments changing the stoichiometry were unsuccessful. The reaction was indeed repeated in the same conditions by using equimolecular amounts of **18a** and anisole in the presence of 1.5 eq of Tf_2O in dichloromethane, giving poor yield (27%). It is likely that the formation of 3,5-diaylfuranone **6a** is promoted by the presence of the aroyl group, which directs the aryl addition also to the 3-position by means of conjugation and/or steric effects [85].

Since the purification of acrylic acid is difficult, acylation reaction was performed on crude acid **18a**. It is previously left in vacuum in presence of P_2O_5 to remove Et_2NH. Analogue results, in terms of yields and isomeric ratio were obtained respect to those of pure acid. Hence, this induced to explore the one-pot 3-steps procedure starting from 2-arylfurans **6**. In particular furans **6a-c** were considered to investigate the reactivity of the substrate, changing the *para* group on phenyl: methoxyl group (**b**) and bromide (**c**) respectively electron-donor and -attractor.

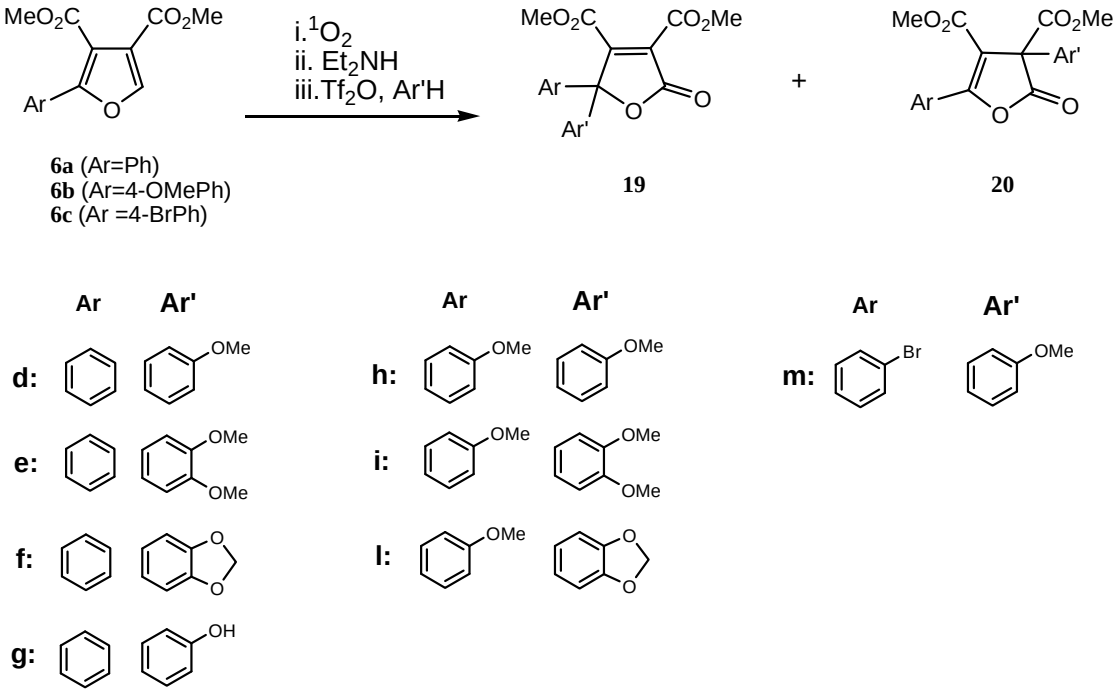
4.1 The three-step one-procedure on other arylic substrates

The acylation was explored by using not only anisole but also other aromatic substrates, with lignan-typical aryl substitution, such as 1,2-dimethoxybenzene, 1,2-

benzodioxole and phenol (Scheme 33). Generally, both solvent conditions and low temperatures were used in these reactions, but some exceptions exist due to particular physical properties of arenes. For instance, the low melting point of 1,2-dimethoxybenzene induced to operate at temperature over 10 °C (Table 13, entries 3-4, 9-10), whereas in other cases only reactions in solvent could be carried out. Indeed, for solid phenol (Table 13, entry 6) necessarily required to be dissolved, while working with 1,2-benzodioxol in neat conditions reaction mixture became after few minutes highly viscous and difficult to follow.

Since all acrylic acids **18** forms in quantitative yields (Scheme 33, step i), the acylation showed that neat conditions and low temperatures favor the 5,5-diarylfuranones **19** except for the reaction with 1,2-dimethoxybenzene (Table 13, entries 3, 4). On the other hands the use of solvent-generally decreased the total reaction yield and, in some cases, led to an inversion of regioselectivity (compare entries 7-8, 12-13 in Table 13).

In all cases diarylfuranones **19** and **20** were formed. Starting from furans **6a** and **6b** with anisole *o*-isomers **20** were also found. The molecular structures were elucidated by ^{1}H and ^{13}C NMR spectroscopy, 2D NMR experiments and MS data. As shown in Table 13, the nature of the aryl substituent on acids **18** has no effect on the furanone formation while the use of the solvents generally decreases the yield. Low temperatures and absence of solvent favor 5,5-diarylfuranones **19** as showed comparing entries 1-2, 6-7, 12-13. In some cases, the use of solvent was effective to reverse the regioselectivity of the acylation in favor of 3,5-diaryl isomers **20** (Table 13, entries 6-7).



Scheme 33. One-pot procedure on furans **6a-c** to furanones **19** and **20**.

Table 13. One-pot preparation of furanones **19** and **20**

	FC Acylation Conditions			Yield $_{TOT}$ (from **6**)	**19 : 20**
	Entry	Solvent	T (°C) / Time (h)		
d	1	-	r.t./20	52%	88 : 12[a]
	2	DCM	-15/2.5	48%	83 : 17[a]
e	3	-	r.t. /18	37%	57 : 43
	4	DCM	0 ÷ 10/2	39%	61 : 39
f	5	DCM	r.t./20	34%	55 : 45
g	6	DCM	r.t./2.5	39%	46 : 54
h	7	-	-20/21	72%	60 : 40
	8	DCM	-20/21	40%	20 : 80
i	9	-	r.t./1.5	89%	23 : 77
	10	DCM	-10/2	50%	18 : 82
l	11	DCM	-10/20	98%	6 : 94
m	12	-	r.t./18	53%	77 : 23[a]
	13	DCM	-10/2.5	35%	45 : 55[a]

a) In these cases ***o*-20** was also obtained, in the (**20**:*o*-**20**) ratios: entry 1 (1:11), entry 2 (7:10), entry 11 (10:13) and entry 12 (20:35)

This also occurs independently from the reaction conditions in the presence of the both highly activated acid **18c** and aromatic compounds like 1,2-dimethoxybenzene (entries 9-10). The acylation on acrylic acids **18** led to products generally with lower yields than the one applied on furoic acid **7** (all over 50%). This result could be connected to the generation of triflic acid in the reaction mixture. Performing acylation reaction in presence of a non-nucleophilic base, it seemed useful to control this problem. Thus, on the basis of literature data [86], 2,6-lutidine was chosen for this purpose. The one-pot procedure was repeated using in the acylation reaction, the base in equimolar quantity in respect to Tf_2O and the same reaction conditions, shown in Table 13, for each prove respectively. The reaction was not applied in the cases leading yet to high yields (Table 13, entries 9 and 11). Results obtained with and without 2,6-lutidine are reported in Table 14.

Table 14. One-pot preparation of furanones **19** and **20** using 2,6-lutidine

	FC Acylation Conditions			**Yield** $_{TOT}$ (from **6**)	**19 : 20**
	Entry	Solvent	T (°C) / Time (h)		
d	1	-	r.t./20	52%	88 : 12[a]
	2	DCM	-15/2.5	48%	83 : 17[a]
e	3	-	r.t. /18	37%	57 : 43
	4	DCM	0 ÷ 10/2	39%	61 : 39
f	5	DCM	r.t./20	34%	55 : 45
g	6	DCM	r.t./2.5	39%	46 : 54
h	7	-	-20/21	72%	60 : 40
	8	DCM	-20/21	40%	20 : 80
i	9	-	r.t./1.5	89%	23 : 77
	10	DCM	-10/2	50%	18 : 82
l	11	DCM	-10/20	98%	6 : 94
m	12	-	r.t./18	53%	77 : 23[a]
	13	DCM	-10/2.5	35%	45 : 55[a]

The comparison of these data shows that higher total yields were really obtained using a non-nucleophilic base, whereas the product ratio was little, if at all, altered.

4.2 Conclusion

A three-steps one-pot mild procedure for highly functionalized 5,5- and 3,5-diarylfuranones was developed.

This methodology involves the same starting precursors **6** and Tf_2O-mediated Friedel-Crafts acylation used in first described procedure. Performing the reaction on crude acrylic acids **18a-c**, cyclic acylated products **19** and **20** were obtained instead of expected open structures. Probably this result is due to an intramolecular cyclization that occurs on activated and highly conjugated system.

Actually, furanones **19** obtained appear of particular interest since they combine the presence of the interesting butenolide moiety and a carbon skeleton of a recently isolated rare lignan as the Sacidumlignan D.

III – Experimental Section

1. Methods and materials

NMR spectra were recorded on 500 MHz spectrometer; ^{1}H NMR recorded at 500 MHz and ^{13}C recorded at 126 MHz. Chemical shifts (δ) are reported in ppm relatively to the residual solvent signal ($CDCl_3$: δ_H 7.26, δ_C 77.0). All reactions involving air or moisture sensitive reagents were carried out under dry argon or nitrogen atmosphere using commercially dry solvents (Sigma-Aldrich 99.7%) stored over molecular sieves.

Thin layer chromatography (TLC) was performed on aluminum plates precoated with Merck Silica Gel 60 F_{254} as the adsorbent (0.25, 0.50, 1.0 and 2.0 mm). Spots were visualized by UV light and developed with 10% H_2SO_4 ethanolic solution. The plates were heated to 130 °C. Flash column chromatography was conducted on Kieselgel 60, 230-400 mesh (Merck), at medium pressure. Column chromatography was conducted on Silica Gel 0.06-0.20 mm mesh (Merck Kieselgel). HPLC analysis on a reverse phase C-18 Phenomenex column 250 x 10 mm (10 μm), and it was performed by LC-8A Shimadzu with a SPD-10A UV-visible *detector*.

The Methylene Blue-sensitized photooxygenations were performed in Pyrex flasks, by irradiation with an external 650-W halogen lamp (Osram, 650 W), thermostat Criocool (Neslab).

2. General experimental procedures

2.1 *Synthesis of phenyloxazole* **1**

α-bromo-acetophenone (650 mg, 3.28 mmol) and ammonium formate (750 mg, 11.9 mmol) were dissolved in 4 mL of formic acid al 98%. The reaction mixture was stirred at room temperature in reflux conditions for 2 h.

Work-up: the reaction mixture was diluted with H_2O (10 mL) and KOH 1.0 M until pH ~ 6, than it was extracted with Et_2O (x3). The organic layers were collected, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue that was purified by flash column chromatography (Et_2O/PE 15%, Et_2O 100%). Yield: 21%

2.2 *Synthesis of 1-(4-methoxyphenyl)-3-(trimethylsilyl)propan-2-yne-1-one* **3**

In an argon atmosphere, iodine (30 mg, 0.118 mmol) was dissolved in 13 mL of DCM *dry*, and 307 µL (2.4 eq, 1.36 mmol) of bis-(trimethylsilyl)-acetylene were added. After 5 min *p*-methoxybenzoyl cloride (441 µL, 3.26 mmol) was added dropwise at 0 °C. The reaction mixture was stirred in argon pressure, at room temperature, over night.

Work-up: the reaction was quenched by addition of H_2O, and the reaction mixture was extracted with DCM (x3). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue that was purified by flash column chromatography (EtOAc/PE 3÷5%). Yield: 68%

2.3 *Synthesis of 1,4-bis(4-methoxyphenyl)but-2-yne-1,4-ditrimethylsilyl-ether* **4**

In THF *dry* (15 mL) 307 µL (1.36 mmol) of bis-(trimetilsilyl)-acetylene and 165 µL (1.36 mmol) of *p*-anisaldehyde were dissolved. After few minutes 68 µL (0.068 mmol) of TBAF 1.0 M were added dropwise at 0 °C. The reaction was conducted in stirring, at -20 °C, for about 20 min.

Work-up: the solvent was removed *in vacuo* and the reaction residue was extracted with H_2O and Et_2O (x3). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue that was purified by flash column chromatography (EtOAc/PE 2÷5%). Yield: 20%

2.4 *Synthesis of 1,4-bis(4-methoxyphenyl)but-2-yne-1,4-dione* **5**

The product **4** (70 mg, 0.158 mmol) was dissolved in toluene (5 mL), and 1.450 g of Magtrieve was added. The reaction mixture was stirred in reflux conditions for about 30 min.

Work-up: the Magtrieve was removed by decantation, and the reaction residue was filtrated on Celite eluting with DCM. The product **5** was purified by silica gel TLC (0.5 mm) in EtOAc/PE 10%. Yield: 11%

2.5 *Synthesis of 2-aryl-3,4-dicarboxymethylfuran* **6**

(2.7 mmol) of α-bromo-arylketone and 0.27 mmol of DABCO were dissolved in DCM (10 mL). The reaction mixture was stirred at room temperature for 30 min, than 2.7 mmol of K_2CO_3 anhydrous and 1.35 mmol of DMAD were added. The reaction was conducted over night (~15 h) in stirring.

Work-up: the reaction mixture was extracted with H_2O and DCM (x3). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue that was purified by flash column chromatography under dry nitrogen pressure. The eluent depended on product: **6a** with Et_2O/Hex 15% (85% yield), **6b** with EtOAc/Hex 10% (66% yield), **6c** with EtOAc/PE 10% (40% yield).

2.6 *Synthesis of 2-aryl-3-methoxycarbonyl-4-furoic acid* **7**

1.0 mmol of 2-aryl-3,4-dicarboxymethylfuran **7** were dissolved in 6 mL of MeOH. Than 400 μL (1 eq) of KOH 2.5 N were added and the reaction mixture was stirred at room temperature over night.

Work-up: the solvent was removed by rotavapor and the reaction residue was extracted with Et_2O and H_2O (x3). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated to give the unreacted furan **6**, while the aqueous one was acidified by dropwise add of HCl 2 N until acid **7** was precipitated. The precipitate was recovered by centrifugation, washed with H_2O, and crystallized to obtain **7a** (in MeOH/H_2O 6:4, 88% yield) and **7b** (in MeOH/H_2O 4:6, 70% yield).

Friedel-Crafts acylation on acids 7

2.7 *Classical procedure with* $SOCl_2$

2-Phenyl-4-furoic acid **7a** (0.85 mmol) was co-evaporated several times with dry toluene and than dissolved in DCM (8 mL). To this solution are added 70 μL (1.2 eq 1.02 mmol) of $SOCl_2$ were added in nitrogen atmosphere. The reaction mixture was stirred, in reflux conditions, over night. Then, the solvent was removed *in vacuo*, and the ^{1}H-NMR analysis of the reaction residue confirmed the quantitive conversion in the acyl chloride **7'a**.

The product **7'a** was dissolved in dry DCM (4 mL) in nitrogen atmosphere. Then anhydrous benzene (2 mL) and 1.2 eq $AlCl_3$ (139 mg, 1.02 mmol) were added. The reaction mixture was stirred, in reflux conditions, but after about 20 h the TLC analysis showed the uncompleted conversion of acyl chloride. The reaction was quenched by dropwise addition of H_2O.

Work-up: the reaction mixture was extracted with DCM (x3). The organic layer was washed with aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and purified by flash

column chromatography. A mixture of acylated products were obtained: **8b** and **9b** with Et_2O/PE 5% (60% yield).

2.8 *Friedel-Crafts acilation with cyanuric chloride on* **7a**

2-Phenyl-4-furoic acid **7a** (0.41 mmol) were co-distilled several times with dry toluene and than dissolved in 3 mL of dry DCM. To this solution 118 mg cyanuric chloride (1.6 eq) and 34 μL (1 eq) of pyridine in DCM were added. After about 15 minutes, 70 mg (1.2 eq) of $AlCl_3$ and 73 μL (2 eq) of benzene, were added to the reaction mixture. The mixture was stirred at room temperature

Work-up: The reaction was quenched by addition of aq. Na_2CO_3 2.5% and extracted with DCM. The organic phase was dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure. The residue was subjected to ^{1}H-NMR analysis which showed the presence of products **8b** and **9b** only in traces. The same results were obtained in anisole leading to **8a** and **9a**.

2.9 *Friedel-Crafts acilation with P_2O_5/SiO_2* on **7a**

2-Phenyl-4-furoic acid **7a** (0.24 mmol) was co-evaporated several times with dry toluene and than dissolved in 5 mL of dry benzene. Than, at this solution 110 mg (1 eq) of P_2O_5/SiO_2, previously prepared, was added. The reaction mixture in the heterogeneous phase was stirred at room temperature overnight.

Work-up: The reaction mixture was diluted with EtOAc and filtered on paper. The organic phase was washed with aq. $NaHCO_3$ 2.5% and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the reaction residue ^{1}H-NMR analysis showed the presence of polymeric material instead of **8b** and **9b**.

Tf_2O-mediated procedure

2.10 *Synthesis of 4-aroyl-2-arylfurans* **8a-f, 8'a,f**

In a typical experiment 0.2 mmol of **7** was co-evaporated times with toluene, the residue was dried and then mixed under nitrogen with the desired arene and dissolved in 1 mL of DCM, excepted for anisole and 1,2-benzodioxole where the substrate was directly dissolved (1 mL). The reaction mixture was stirred at the reported temperature for few minutes. Triflic anhydride (2 or 2.5 eq, see Tables 3-9) was then added. After the complete conversion of the reactant the mixture was diluted with Et_2O (20 mL) and washed with saturated $NaHCO_3$ solution. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue that was purified by column chromatography (mixture of Et_2O/PE).

2.11 *Synthesis of 4-aroyl-2-arylfurans* **9a-f**, **9'a,f**

In a typical experiment 0.2 mmol of **7a** were co-evaporated thrEt2O times with toluene, the residue was dried and dissolved in 1 mL of DCM. Than Tf_2O (0.22 mmol) was added and a solution of the desired arene (1 mmol) in 2 mL of DCM was then added dropwise in 2 h by a syringe-pump. The reaction mixture was stirred at room temperature one more hour was then added. After the complete conversion of the reactant the reaction was diluted with Et_2O (20 mL) and washed with saturated $NaHCO_3$ solution. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue that was purified by column chromatography (mixture of Et_2O/PE).

2.12 *Hydrogenation of* **8a**

Compound **8a** (0.3 mmol) was dissolved in dry MeOH (40 mL) and 10% Pd/C catalyst (20 mg) was then added under nitrogen atmosphere. Hydrogenation was performed at

100 atm and high temperature (for details, sEt2O Table 10).

Work-up: after releasing the pressure, the mixture was filtered and the solvent was removed *in vacuo*. The products were purified by flash chromatography (PE/Et_2O 10 ÷ 30%). Yields: **10** (90%), **11** (35%) and **12** (54%)

Dye-sensitized photooxygenation

2.13 *Preparation of endoperoxides* **13**

A solution of dry furan (0.5 mmol) in anhydrous DCM (27.8 mL, 0.018 M) was irradiated at -20 °C in the presence of methylene blue (MB, 1 mg, 3×10^{-3} mmol) while dry oxygen was bubbled through the solution. The progress of the reaction was checked by periodically monitoring (^{1}H-NMR) until the disappearance of starting furan (typically 2-3 h) and the intermediate endoperoxide **13** was identified by ^{1}H-NMR.

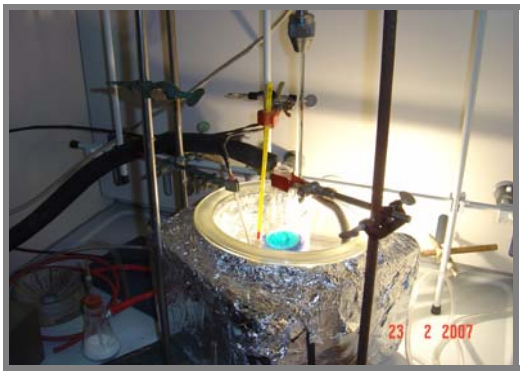


Figure 12. Criocool, acetone bath and thermostatically controlled visible lamp used to conduct photooxygenation reactions.

2.14 *In situ reduction of endoperoxide* **13** *with* Et_2S

Once the conversion of furan into endoperoxide **13** was complete (see **2.10.1**) the irradiation was stopped, and keeping the system at temperature (-20 °C), Et_2S (65 μL, 0.6 mmol, 1.2 eq respect to the furan moles) was added, and the mixture was kept at room temperature for 2-3 h.

Work-up: the excess of Et_2S and the solvent were removed *in vacuo*, and the reaction residue was purified on TLC (MeOH/DCM 2%).

2.15 *In situ basic treatment on endoperoxide* **13**

Once the conversion of furan into endoperoxide **13** was complete the irradiation was stopped, and keeping the system at temperature (-20 °C), Et_2NH (62 μL, 0.6 mmol, 1.2 eq respect to the furan moles) was added, and the mixture was kept at room temperature for 30 min.

Work-up: the solvent was evaporated and the crude acrylic acid **18** was purified on silica gel (Acetone/MeOH) or dried in the presence of anhydrous P_2O_5 for 5 h in order to remove Et_2NH in the one-pot procedure.

2.16 *Synthesis of 5,5- and 3,5-diarylfuranones* **19** and **20**

Crude reagent **18a-c** (0.493 mmol) was dissolved in aromatic compound (35 eq, neat conditions), or in dry solvent (DCM, 2 mL) and then aromatic compound (5 eq) was added. The mixture was cooled to -20 °C and Tf_2O (1.23 mmol, 2.5 eq) was added dropwise at this temperature. The resulting mixture was stirred under N_2 atmosphere at the temperature and for the time reported in Table 11. In the acylation with phenol (Table 13, entry 6), Tf_2O was added dropwise in the acrilic acid **18a** solution (dry DCM, 2 mL) cooled at −20 °C. The mixture was stirred for 30 min, then phenol was added and the resulting mixture warmed to r.t. for 2.5 h.

Work-up: the reaction mixture was washed with saturated aq. $NaHCO_3$ solution and extracted twice with Et_2O. The organic layers were collected, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue that was chromatographed on silica gel with a gradient of PE and EtOAc. Mixture of *p*- and *o*-isomers **20** and ***o*-20** (Table

13, **d** and **m**) were subsequently separated by HPLC using RP-18 column and H_2O:MeOH:MeCN as eluent.

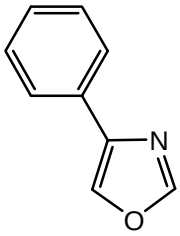
2.17 *Synthesis of 5,5- and 3,5-diarylfuranones* **19d-m**, **20d-m** *using 2,6-lutidine*

Crude reagent **3** (0.493 mmol) was dissolved in aromatic compound (35 eq, neat conditions), or in dry solvent (DCM, 2 mL) and then the aromatic compound (5 eq) was added. The mixture was cooled to −20 °C and Tf_2O (2.5 eq, 1.23 mmol) added dropwise at this temperature. Then 2,6-lutidine (143 μL, 1.23 mmol, 2.5 eq) was added at the same temperature. The resulting mixture was stirred under N_2 atmosphere at the temperature and for the time reported in Table 14.

Work-up: the reaction mixture was washed with saturated aq. $NaHCO_3$ solution and extracted twice with Et_2O. The organic layers were collected, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue that was chromatographed on silica gel with a gradient of PE and EtOAc. Mixture of *p*- and *o*-isomers **20** and ***o*-20** (Table 11, **d, m**) were subsequently separated by HPLC using RP-18 column and H_2O:MeOH:MeCN as eluent.

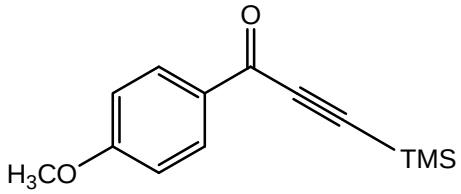
3. Spectroscopic data

4-Phenyloxazole (**1**)



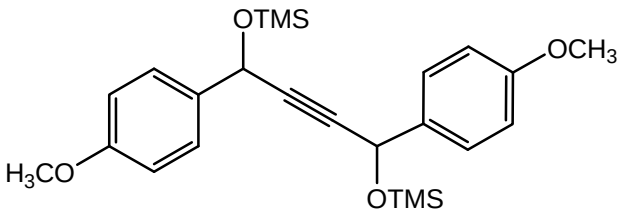
Yellow oil. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 7.94 (brs, 2H, H-Furan), 7.76 (dd, *J* = 7.0, 1.8 Hz, 2H, Ar-H), 7.41 (t, *J* = 7.0 Hz, 2H, Ar-H), 7.31 (t, *J* = 7.0 Hz, 1H, Ar-H); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 150.9, 139.8, 133.3, 130.4, 128.2, 127.6, 125.0; **ESI-MS**: *m*/*z* = 146.0 $[M+H]^+$.

4-Methoxybenzoyl trimethylsilyl acetylene (**3**)



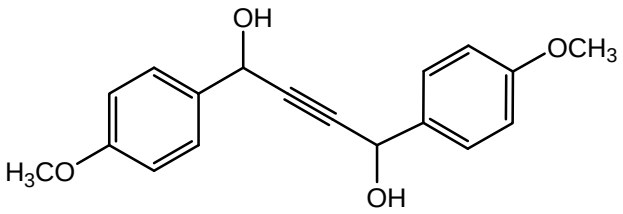
Yellow oil. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.92 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.85 (s, 3H, -OC*H*$_3$), 0.29 (s, 9H, TMS); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 176.2, 164.6, 131.0, 129.9, 113.7, 101.8, 99.5, 55.5, -0.7; **ESI-MS**: *m*/*z* = 236.0 $[M+H]^+$.

Bis-trimethylsilyl ether of *1,4-bis(4-methoxyphenyl)but-2-yne-1,4-diol* (**4**)



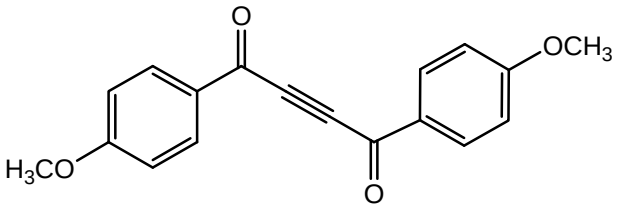
Yellow oil. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.86 (dd, *J* = 8.8 Hz, 2H, Ar-H), 5.50 (s, 1H, H-7), 3.80 (s, 3H, -OC*H*$_3$), 0.15 (s, 9H, TMS); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 159.2, 133.6, 127.8, 113.6, 86.3, 64.4, 55.2, 0.2; **ESI-MS**: *m*/*z* = 443.0 $[M+H]^+$.

1,4-Bis(4-methoxyphenyl)but-2-yne-1,4-diol (**4'**)



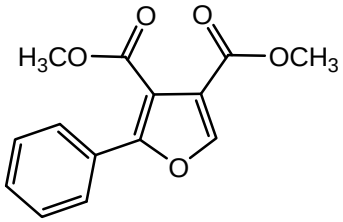
Yellow oil. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.6 Hz, 2H, Ar-H), 6.83 (dd, *J* = 8.6 Hz, 2H, Ar-H), 5.56 (s, 1H, H-7), 3.83 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 159.1, 133.3, 127.3, 113.5, 86.6, 64.4, 55.2; **ESI-MS**: *m*/*z* = 299.3 $[M+H]^+$.

1,4-bis(4-methoxyphenyl)but-2-yne-1,4-dione (**5**)



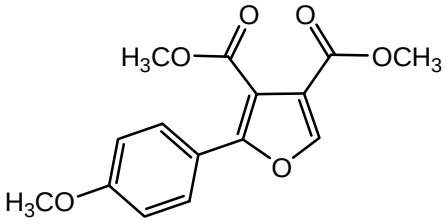
Yellow oil. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 8.15 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.99 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.89 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 175.1, 165.5, 132.3, 130.0, 114.3, 86.0, 55.7; **ESI-MS**: *m*/*z* = 295.0 $[M+H]^+$.

Dimethyl 2-phenylfuran-3,4-dicarboxylate (**6a**)



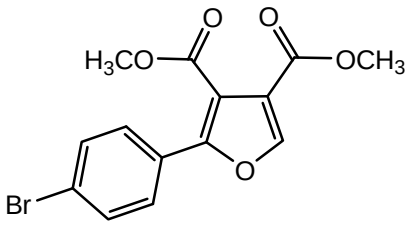
Yellow oil. **IR** (KBr) 3151, 2955, 1717, 1552, 1441, 1282, 1151, 771, 693 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 7.96 (s, 1H, H-Furan), 7.70 (m, 2H, Ar-H), 7.40 (m, 3H, Ar-H), 3.09 (s, 3H, -OC*H*$_3$), 3.84 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 165.1, 162.5, 154.3, 146.5, 130.0, 129.7, 129.0, 126.6, 120.0, 113.8, 53.0, 52.2; **ESI-MS**: *m*/*z* = 261.5 $[M+H]^+$.

Dimethyl 2-(4-methoxyphenyl)furan-3,4-dicarboxylate (**6b**)



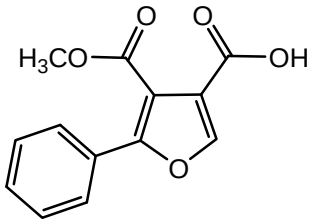
Yellow oil. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.91 (s, 1H, H-Furan), 7.67 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.94 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.89 (s, 3H, -OC*H*$_3$), 3.85 (s, 3H, -OC*H*$_3$), 3.84 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 165.1, 162.6, 160.4, 154.9, 145.9, 128.4, 121.6, 119.9, 114.3, 112.3, 55.5, 52.7, 52.1; **ESI-MS**: *m*/*z* = 291.0 $[M+H]^+$.

Dimethyl 2-(4-bromophenyl)furan-3,4-dicarboxylate (**6c**)



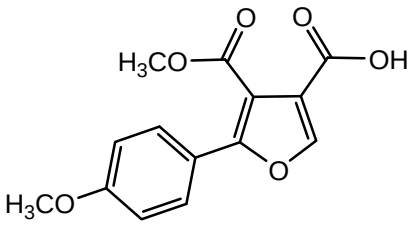
Yellow oil. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.95 (s, 1H, H-Furan), 7.57 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.55 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.90 (s, 3H, -OC*H*$_3$), 3.85 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 164.5, 162.0, 153.1, 146.4, 131.9, 128.0, 127.9, 127.5, 123.8, 119.9, 52.7, 52.0; **ESI-MS**: *m*/*z* = 340.1 $[M+H]^+$.

4-(Methoxycarbonyl)-5-phenylfuran-3-carboxylic acid (**7a**)



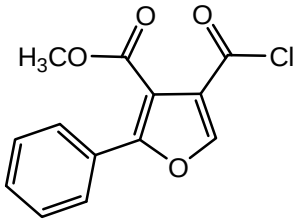
Yellow oil. **IR** (KBr) 3400-3200, 1740, 1694 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.26 (s, 1H, H-Furan), 7.63 (m, 2H, Ar-H), 7.48 (m, 3H, Ar-H), 3.87 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 167.1, 164.5, 160.0, 150.5, 130.3, 129.2, 129.0, 128.2, 120.3, 110.2, 53.1; **ESI-MS**: *m*/*z* = 247.2 $[M+H]^+$.

4-(Methoxycarbonyl)-5-(4-methoxyphenyl)furan-3-carboxylic acid (**7b**)



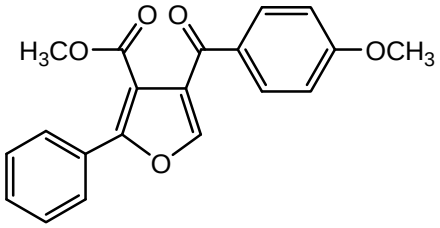
Yellow oil. **IR** (KBr) 3400-32010, 1742, 1692 cm^{-1}. **^{1}H-NMR** (200 MHz) δ 8.21 (s, 1H, H-Furan), 7.56 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.96 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.85 (s, 3H, -OC*H*$_3$), 3.84 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (50 MHz) δ 167.4, 162.6, 161.8, 160.8, 150.1, 130.5, 121.2, 120.2, 113.6, 109.0, 55.3, 53.0; **ESI-MS**: *m*/*z* = 277.0 $[M+H]^+$.

Methyl 2-phenyl-4-(chlorocarbonyl)-3-furoate (**7'a**)



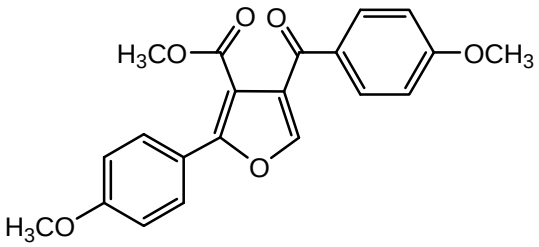
^{1}H-NMR: (200 MHz, $CDCl_3$) δ 8.22 (s, 1H, H-Furan), 7.72 (m, 2H, Ar-H), 7.45 (m, 3H, Ar-H), 3.90 (s, 3H, -OC*H*$_3$).

Methyl 4-(4-methoxybenzoyl)-2-phenyl-3-furoate (**8a**)



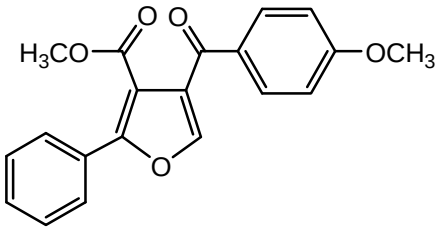
Yellow oil. **IR** (CH_2Cl_2): 3021, 2942, 1716, 1612, 1604, 1240, 1035 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.88 (dd, *J* = 8.4, 1.6 Hz, 2H, Ar-H), 7.74 (s, 1H, H-Furan), 7.46-7.44 (m, 3H, Ar-H), 6.97 (d, *J* = 8.9 Hz, 2H, Ar-H), 3.89 (s, 3H, -OC*H*$_3$), 3.65 (s, 3H, -COOC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 187.4, 164.1, 163.7, 156.2, 143.9, 131.5, 130.9, 129.7, 128.5, 127.8, 120.9, 120.6, 113.9, 111.7, 55.5, 52.0; **EI-MS** for $C_{20}H_{16}O_5$ (*m/z*): M_r (calcd) 336.10, M_r (found) 359.39 $[M+Na]^+$.

Methyl 4-(4-methoxybenzoyl)-2-(4-methoxyphenyl)-3-furoate (**8'a**)



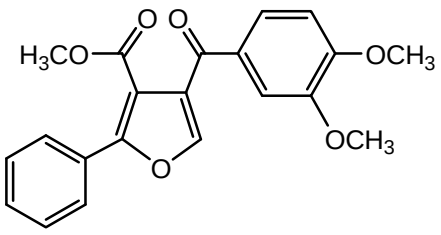
Yellow oil. **IR** (CH_2Cl_2): 3056, 1730, 1661, 1602, 1216, 1159 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.87 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.97 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.96 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.69 (s, 1H, H-Furan), 3.88 (s, 3H, -OC*H*$_3$), 3.86 (s, 3H, -OC*H*$_3$), 3.52 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 187.9, 164.4, 163.9, 161.0, 157.0, 143.5, 131.5, 131.2, 129.6, 127.9, 121.7, 114.2, 114.1, 112.7, 55.7, 55.6, 52.2; **ESI-MS**: *m*/*z* = 367.0 $[M+H]^+$.

Methyl 4-benzoyl-2-phenyl-3-furoate (**8b**)



^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.92-7.87 (m, 3H, Ar-H), 7.79 (s, 1H, H-Furan), 7.60 (m, 1H, Ar-H), 7.50-7.42 (m, 5H, Ar-H), 3.63 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 188.7, 164.1, 156.1, 144.7, 138.1, 133.0, 131.0, 127.9, 127.8, 127.7, 126.2, 114.5, 113.9, 113.9, 52.0; **ESI-MS**: *m*/*z* = 307.3 $[M+H]^+$.

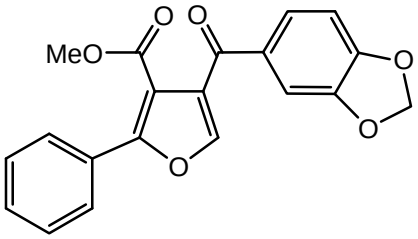
Methyl 4-(3,4-dimethoxybenzoyl)-2-phenyl-3-furoate (**8c**)



Yellow oil. **IR** (CH_2Cl_2): 3020, 1731, 1658, 1598, 1218, 1048 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 10.1, 2.2 Hz, 2H, Ar-H), 7.76 (s, 1H, H-Furan), 7.54-7.44 (m, 5H, Ar-H), 6.92 (d, *J* = 10.1 Hz, 1H, Ar-H), 3.96 (s, 3H, -OC*H*$_3$), 3.95 (s, 3H,

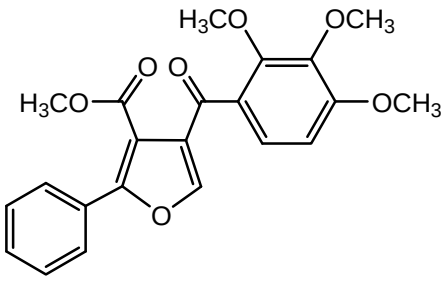
-OC*H*$_3$), 3.66 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 187.4, 164.2, 156.1, 153.5, 149.2, 144.0, 131.0, 129.7, 128.8, 128.5, 127.5, 124.3, 114.0, 110.8, 110.2, 56.1, 52.1; **EI-MS** for $C_{21}H_{18}O_6$ (*m/z*): M_r (calcd) 366.11, M_r (found) 389.32 $[M+Na]^+$.

Methyl 4-(3,4-benzo[d][1,3]dioxole-5-carbonyl)-2-phenyl-3-furoate (**8d**)



Yellow oil. **IR** (CH_2Cl_2): 3052, 1727, 1654, 1605, 1217, 1041 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ 7.90-7.88 (m, 2H, Ar-H), 7.74 (s, 1H, H-Furan), 7.52-7.43 (m, 5H, Ar-H), 6.87 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.08 (s, 2H, -OC*H*$_2$O-), 3.69 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 186.8, 164.2, 156.3, 152.0, 148.2, 143.8, 132.8, 129.7, 128.6, 128.4, 127.5, 125.9, 118.4, 113.6, 108.6, 107.8, 101.9, 52.1; **EI-MS** for $C_{20}H_{14}O_6$ (*m/z*): M_r (calcd) 350.08, M_r (found) 373.62 $[M+Na]^+$.

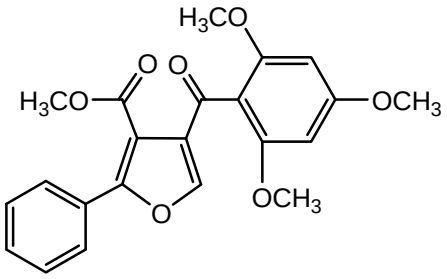
Methyl 4-(2,3,4-trimethoxybenzoyl)-2-phenyl-3-furoate (**8e**)



Yellow oil. **IR** (CH_2Cl_2): 3056, 1729, 1656, 1590, 1217, 1097 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.2, 1.6 Hz, 2H, Ar-H), 7.72 (s, 1H, H-Furan), 7.43 (m, 3H, Ar-H), 7.36 (d, *J* = 8.7 Hz, 1H, Ar-H), 6.72 (d, *J* = 8.7 Hz, 1H, Ar-H), 3.92 (s, 3H, -OC*H*$_3$), 3.89 (s, 3H, -OC*H*$_3$), 3.83 (s, 3H, -OC*H*$_3$), 3.70 (s, 3H, -OC*H*$_3$); **^{13}C-NMR**

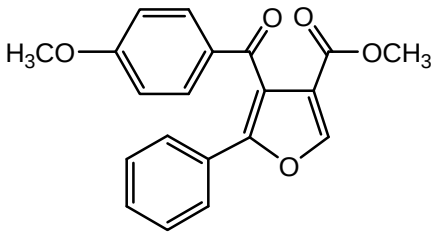
(100 MHz, $CDCl_3$) δ 186.8, 164.5, 157.0, 155.2, 153.3, 145.7, 142.4, 129.6, 128.9, 128.6, 127.2, 126.5, 125.8, 113.6, 106.8, 106.7, 62.0, 61.0, 56.1, 52.1; **EI-MS** for $C_{22}H_{20}O_7$ (*m/z*): M_r (calcd) 396.12, M_r (found) 419.43 $[M+Na]^+$.

Methyl 4-(2,4,6-trimethoxybenzoyl)-2-phenyl-3-furoate (**8f**)



Yellow oil. **IR** (CH_2Cl_2): 3055, 1731, 1666, 1606, 1218, 1131 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.4, 1.6 Hz, 2H, Ar-H), 7.68 (s, 1H, H-Furan), 7.40 (m, 3H, Ar-H), 6.14 (s, 2H, Ar-H), 3.85 (s, 3H, -OC*H*$_3$), 3.81 (s, 3H, -OC*H*$_3$), 3.74 (s, 6H, -OC*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 186.4, 165.4, 162.7, 159.1, 153.7, 147.7, 129.9, 129.2, 128.6, 126.3, 113.2, 111.6, 90.6, 55.9, 55.42, 52.6; **EI-MS** for $C_{22}H_{20}O_7$ (*m/z*): M_r (calcd) 396.12, M_r (found) 420.22 $[M+Na]^+$.

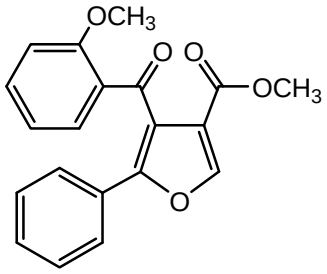
Methyl 4-(4-methoxybenzoyl)-5-phenyl-3-furoate (**9a**)



Yellow oil. **IR** (CH_2Cl_2): 3020, 1725, 1660, 1598, 1217, 1165 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.11 (s, 1H, H-Furan), 7.90 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.55 (dd, *J* = 8.0, 1.7 Hz, 2H, Ar-H), 7.31-7.27 (m, 3H, Ar-H), 6.91 (d, *J* = 8.7 Hz, 2H, Ar-H), 3.85 (s, 3H, -OC*H*$_3$), 3.66 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 190.9, 164.0,

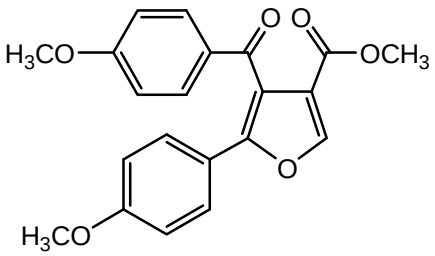
162.4, 152.1, 146.5, 131.8, 130.5, 128.9, 128.8, 125.7, 120.9, 119.6, 114.0, 55.5, 51.7; **EI-MS** for $C_{20}H_{16}O_5$ (*m/z*): M_r (calcd) 336.10, M_r (found) 359.98 $[M+Na]^+$.

Methyl 4-(2-methoxybenzoyl)-5-phenyl-3-furoate (***o*-9a**)



Yellow oil. **IR** (CH_2Cl_2): 3053, 1726, 1657, 1598, 1218, 1040 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.02 (s, 1H, H-Furan), 7.61 (dd, *J* = 9.8, 1.6 Hz, 2H, Ar-H), 7.54 (dd, *J* = 9.8, 1.6 Hz, 1H, Ar-H), 7.45 (t, *J* = 9.8 Hz, 2H, Ar-H), 7.31-7.26 (m, 2H, Ar-H) 6.97 (t, *J* = 9.8 Hz, 3H, Ar-H), 6.91 (d, *J* = 9.8 Hz, 1H, Ar-H), 3.72 (s, 3H, -OC*H*$_3$), 3.60 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 190.7, 162.6, 159.4, 152.5, 145.9, 134.5, 131.9, 131.3, 128.9, 128.8, 128.6, 126.2, 120.4, 113.8, 112.0, 79.2, 55.8, 51.5; **EI-MS** for $C_{20}H_{16}O_5$ (*m/z*): M_r (calcd) 336.10, M_r (found) 359.16 $[M+Na]^+$.

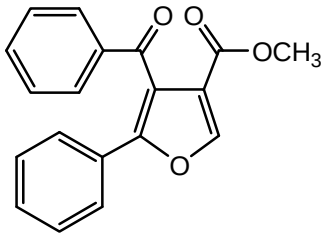
Methyl 4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-3-furoate (**9'a**)



Yellow oil. **IR** (CH_2Cl_2): 3060, 1735, 1668, 1611, 1216, 1166 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.04 (s, 1H, H-Furan), 7.88 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.50 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.89 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.82 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.85 (s, 3H, -OC*H*$_3$), 3.77 (s, 3H, -OC*H*$_3$), 3.64 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$)

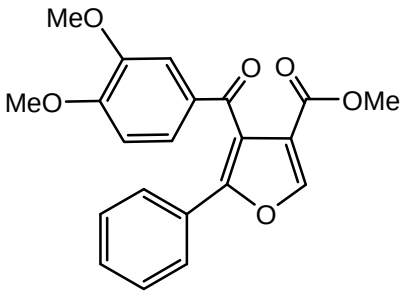
δ 191.3, 164.2, 162.7, 160.3, 152.8, 146.2, 132.0, 131.0, 127.6, 121.9, 120.9, 118.4, 114.4, 114.2, 55.7, 55.5, 51.9; **ESI-MS**: *m*/*z* = 367.0 $[M+H]^+$

Methyl 4-benzoyl-5-phenyl-3-furoate (**9b**)



^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H, H-Furan), 7.91 (m, 2H, Ar-H), 7.57 (m, 3H, Ar-H), 7.42 (m, 2H, Ar-H), 7.30 (m, 3H, Ar-H), 3.63 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 192.3, 162.2, 152.6, 146.5, 137.5, 133.6, 133.0, 131.0, 127.9, 127.7, 120.9, 114.5, 113.9, 113.9, 51.6; **ESI-MS**: *m*/*z* = 307.7 $[M+H]^+$.

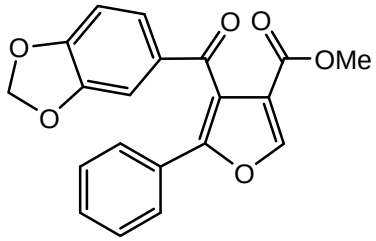
Methyl 4-(3,4-dimethoxybenzoyl)-5-phenyl-3-furoate (**9c**)



Yellow oil. **IR** (CH_2Cl_2): 3057, 1726, 1658, 1592, 1218, 1045 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.10 (s, 1H, H-Furan), 7.66 (d, *J* = 1.9 Hz, 1H, Ar-H), 7.59-7.56 (m, 2H, Ar-H), 7.40-7.27 (m, 3H, Ar-H), 7.33 (d, J = 8.0, 1.9 Hz, 1H, Ar-H), 6.78 (d, *J* = 8.0 Hz, 1H, Ar-H), 3.94 (s, 3H, -OC*H*$_3$), 3.90 (s, 3H, -OC*H*$_3$), 3.67 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 190.8, 162.3, 154.0, 149.3, 146.5, 144.0, 130.6, 129.7,

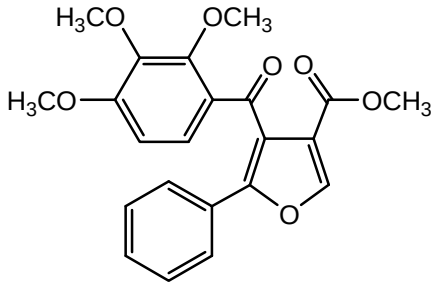
128.7, 127.5, 125.7, 125.3, 120.8, 110.2, 110.1, 110.0, 56.0, 51.7; **EI-MS** for $C_{21}H_{18}O_6$ (*m/z*): M_r (calcd) 366.11, M_r (found) 389.52 $[M+Na]^+$.

Methyl 4-(3,4-benzo[d][1,3]dioxole-5-carbonyl)-5-phenyl-3-furoate (**9d**)



Yellow oil. **IR** (CH_2Cl_2): 3050, 1726, 1663, 1489, 1217, 1041 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.09 (s, 1H, H-Furan), 7.57-7.54 (m, 2H, Ar-H), 7.49-7.41 (m, 2H, Ar-H), 7.34-7.27 (m, 3H, Ar-H), 6.77 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.04 (s, 2H, -OC*H*$_2$O), 3.69 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 190.4, 162.2, 152.5, 152.1, 148.4, 147.4, 146.5, 132.4, 128.6, 128.5, 126.7, 125.6, 120.6, 119.5, 108.4, 108.2, 102.0, 51.7; **EI-MS** for $C_{20}H_{14}O_6$ (*m/z*): M_r (calcd) 350.08, M_r (found) 373.28 $[M+Na]^+$.

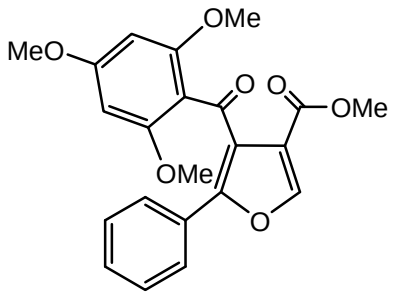
Methyl 3-(2,3,4-trimethoxybenzoyl)-5-phenyl-3-furoate (**9e**)



Yellow oil. **IR** (CH_2Cl_2): 3051, 1726, 1657, 1588, 1218, 1097 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.04 (s, 1H, H-Furan), 7.61-7.57 (m, 2H, Ar-H), 7.30-7.28 (m, 4H, Ar-H), 6.69 (d, *J* = 8.9 Hz, 1H, Ar-H), 3.89 (s, 3H, -OC*H*$_3$), 3.80 (s, 3H, -OC*H*$_3$), 3.69 (s, 3H, -OC*H*$_3$), 3.67 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ 189.6, 162.5, 158.1, 154.8, 151.8, 146.0, 142.3, 129.1, 128.6, 127.3, 125.9, 125.7, 122.7, 120.6,

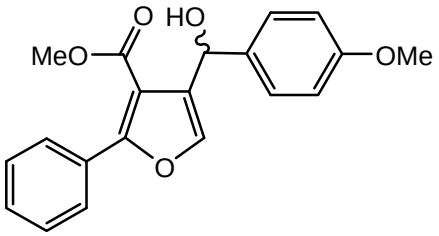
106.8, 61.2, 60.8, 56.0, 51.6; **EI-MS** for $C_{22}H_{20}O_7$ (*m/z*): M_r (calcd) 396.12, M_r (found) 420.55 $[M+Na]^+$.

Methyl 4-(2,4,6-trimethoxybenzoyl)-5-phenyl-3-furoate (**9f**)



Yellow oil. **IR** (CH_2Cl_2): 3056, 1731, 1664, 1604, 1218, 1158 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.93 (s, 1H, H-Furan), 7.66-7.63 (m, 2H, Ar-H), 7.29-7.27 (m, 3H, Ar-H), 6.00 (s, 2H, Ar-H), 3.77 (s, 3H, -OC*H*$_3$), 3.66 (s, 6H, -OC*H*$_3$), 3.64 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 188.0, 163.6, 163.0, 161.0, 154.0, 145.8, 129.5, 128.7 (×2), 128.1 (×2), 127.0 (×2), 120.3, 112.8, 90.7, 56.0, 55.3, 51.5; **EI-MS** for $C_{22}H_{20}O_7$ (*m/z*): M_r (calcd) 396.12, M_r (found) 419.27 $[M+Na]^+$.

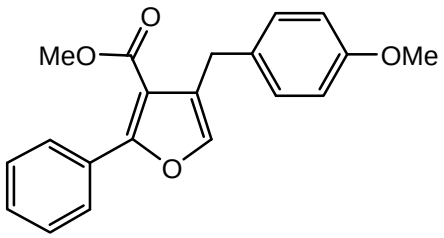
Methyl 4-(hydroxy(4-methoxyphenyl)methyl)-2-phenyl-3-furoate (**10**)



Yellow oil. **IR** (CH_2Cl_2): 3447, 3016, 1692, 1611, 1512, 1214, 1033 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.68-7-65 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.43-7.38 (m, 5H, Ar-H), 7.02 (s, 1H, H-Furan), 6.91 (d, *J* = 8.7 Hz, 2H, Ar-H), 5.90 (bs, 1H, -C*H*OH), 4.43 (bs, 1H, -CHO*H*), 3.82 (s, 3H, -OC*H*$_3$), 3.73 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 165.5, 159.3, 159.0, 140.6, 133.8, 131.4, 130.0, 129.5, 128.7, 128.0, 127.7,

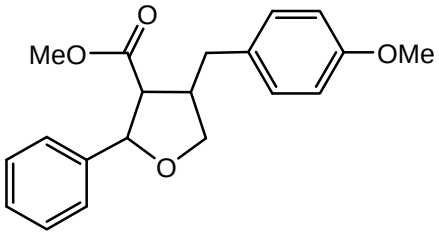
113.7, 112.3, 67.8, 55.2, 51.8; **EI-MS** for $C_{20}H_{18}O_5$ (*m/z*): M_r (calcd) 338.12, M_r (found) 361.39 $[M+Na]^+$.

Methyl 4-(4-methoxybenzyl)-2-phenyl-3-furoate (**11**)



Yellow oil. **IR** (CH_2Cl_2): 3021, 2942, 1716, 1612, 1604, 1240, 1035 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.2, 1.8 Hz, 2H, Ar-H), 7.40 (m, 3H, Ar-H), 7.17 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.03 (s, 1H, H-Furan), 6.86 (d, *J* = 8.6 Hz, 2H, Ar-H), 3.93 (s, 2H, -C*H*$_2$-Ph), 3.80 (s, 3H, -OC*H*$_3$), 3.74 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 164.7, 158.2, 158.0, 140.1, 131.7, 130.2, 129.7, 129.1, 128.3, 128.0, 126.1, 113.8, 113.2, 55.2, 51.3, 30.3; **EI-MS** for $C_{20}H_{18}O_4$ (*m/z*): M_r (calcd) 322.12, M_r (found) 345.76 $[M+Na]^+$.

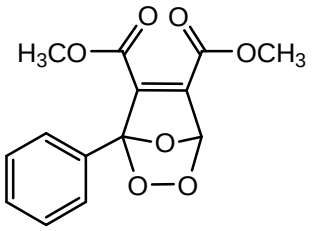
Methyl 4-(4-methoxybenzyl)-2-phenyl-tetrahydrofuran-3-carboxylate (**12**)



Yellow oil. **IR** (CH_2Cl_2): 3006, 2951, 1732, 1661, 1512, 1176, 1034 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.29-7.24 (m, 5H, Ar-H), 7.11 (d, *J* = 6.8 Hz, 2H, Ar-H), 6.84 (d, *J* = 6.8 Hz, 2H, Ar-H), 5.26 (d, *J* = 6.7 Hz, 1H, H2-Furan), 4.34 (t, *J* = 6.4 Hz, 1H, H5b-Furan), 3.79 (s, 3H, -OC*H*$_3$), 3.66 (t, *J* = 6.8 Hz, 1H, H5a-Furan), 3.14 (s, 3H, -COOC*H*$_3$), 3.12 (m, 1H, H3-Furan), 3.08 (m, 1H, H4-Furan), 2.81 (dd, *J* = 11.1, 5.1

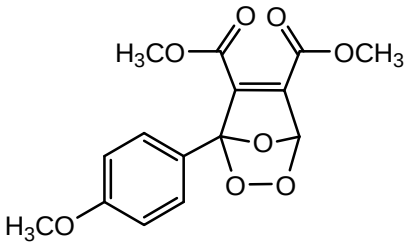
Hz, 1H, -CH_2-), 2.67 (dd, J = 11.1, 6.8 Hz, 1H, -CH_2-Ar); **^{13}C-NMR** (100 MHz, $CDCl_3$) 171.8, 158.1, 138.9, 131.3, 127.9, 127.9, 127.7, 126. 2, 113.9, 82.2, 73.7, 55.8, 55.2, 51.2, 43.7, 37.3; **EI-MS** for $C_{20}H_{22}O_4$ (*m/z*): M_r (calcd) 326.15, M_r (found) 349.54 $[M+Na]^+$.

Dimethyl 1-phenyl-2,3,7-trioxa-bicyclo[2.2.1]hept-5-ene-5,6-dicarboxylate (**13a**)



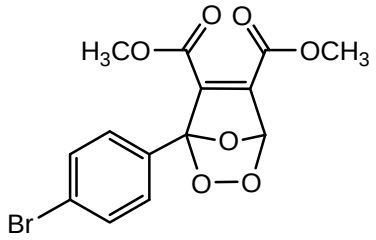
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H, Ar-H), 7.59 − 7.56 (m, 2H, Ar-H), 7.48 − 7.44 (m, 1H, Ar-H), 6.81 (s, 1H), 3.72 (s, 3H, -OCH_3), 3.68 (s, 3H, -OCH_3).

Dimethyl 1-(4-methoxyphenyl)-2,3,7-trioxa-bicyclo[2.2.1]hept-5-ene-5,6-dicarboxylate (**13b**)



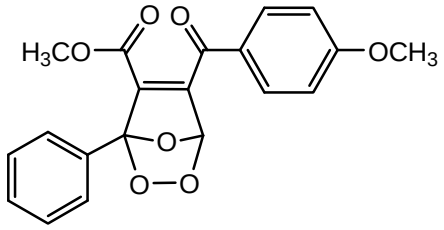
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 9.1 Hz, 2H, Ar-H), 6.97 (d, J = 9.1 Hz, 2H, Ar-H), 6.78 (s, 1H), 3.87 (s, 3H, -OCH_3), 3.84 (s, 3H, -OCH_3), 3.75 (s, 3H, -OCH_3).

Dimethyl 1-(4-bromophenyl)-2,3,7-trioxa-bicyclo[2.2.1]hept-5-ene-5,6-dicarboxylate (**13c**)



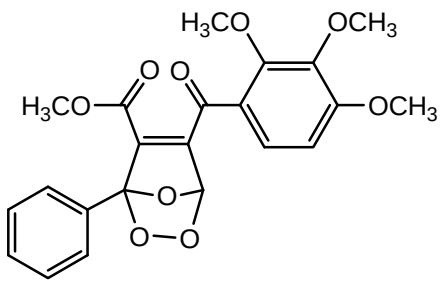
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.47 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.81 (s, 1H), 3.88 (s, 3H, -OC*H*$_3$), 3.74 (s, 3H, -OC*H*$_3$).

6-(4-Methoxybenzoyl)-4-phenyl-2,3,7-trioxa-bicyclo[2.2.1]hept-5-ene-5-carboxylate (**13d**)



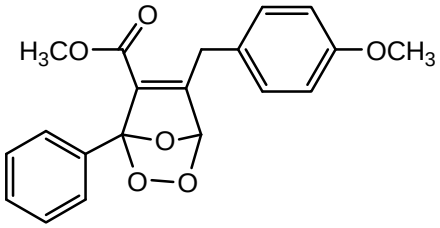
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.98 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.64 (m, 2H, Ar-H), 7.45 (m, 3H, Ar-H), 6.72 (s, 1H), 3.88 (s, 3H, -OC*H*$_3$), 3.38 (s, 3H, -OC*H*$_3$).

6-(2,3,4-Trimethoxybenzoyl)-4-phenyl-2,3,7-trioxa-bicyclo[2.2.1]hept-5-ene-5-carboxylate (**13f**)



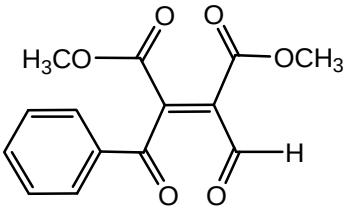
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.62 (m, 2H, Ar-H), 7.60 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.49 (m, 3H, Ar-H), 6.78 (d, *J* = 8.8 Hz, 1H, Ar-H), 6.72 (s, 1H), 3.95 (s, 3H, -OC*H*$_3$), 3.94 (s, 3H, -OC*H*$_3$), 3.88 (s, 3H, -OC*H*$_3$), 3.42 (s, 3H, -OC*H*$_3$).

6-(4-Methoxybenzyl)-4-phenyl-2,3,7-trioxa-bicyclo[2.2.1]hept-5-ene-5-carboxylate (**13g**)



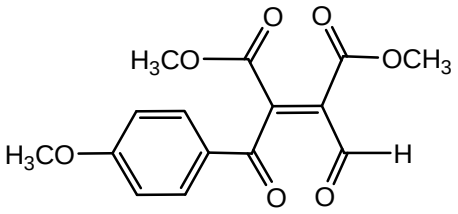
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.60 (m, 2H, Ar-H), 7.48 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.45 (m, 3H, Ar-H), 6.79 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.71 (s, 1H), 3.95 (s, 3H, -OC*H*$_3$), 3.52 (s, 3H, -OC*H*$_3$).

Dimethyl 2-formyl-3- benzoyl--maleate (**14a**)



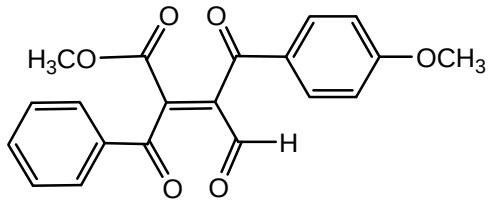
^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H, -CHO), 7.90 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.62 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.56 (t, *J* = 8.0 Hz, 2H, Ar-H), 3.95 (s, 3H, -OC*H*$_3$), 3.81 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 189.9, 188.5, 165.8, 165.5, 160.1, 150.2, 139.5, 135.5, 130.2, 130.1, 53.0, 52.4; **HRMS (ESI)** (*m*/*z*): found 276.0631 $[M+H]^+$; calcd for $C_{14}H_{12}O_6$ 276.0634.

Dimethyl 2-formyl-3-(4-methoxybenzoyl)-maleate (**14b**)



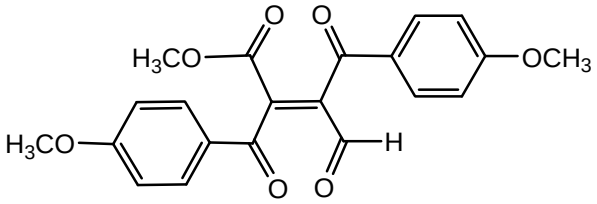
Amorphous powder. **IR** (CH_2Cl_2) 3051, 1712, 1641, 1539, 1255, 1032, 788 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 9.66 (s, 1H, CHO), 7.90 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.93 (d, *J* = 8.6 Hz, 2H, Ar-H), 3.94 (s, 3H, -OC*H*$_3$), 3.90 (s, 3H, -OC*H*$_3$), 3.81 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 188.0, 186.9, 165.4(x2), 163.9, 163.4, 147.3, 137.4, 114.8, 132.2, 55.9, 53.9, 53.4; **HRMS (ESI)** (*m*/*z*): found 306.0740 $[M+H]^+$; calcd for $C_{15}H_{14}O_7$ 306.0738.

(Z)-Methyl 2-benzoyl-3-formyl-4-(4-methoxyphenyl)-4-oxobut-2-enoate (**14d**)



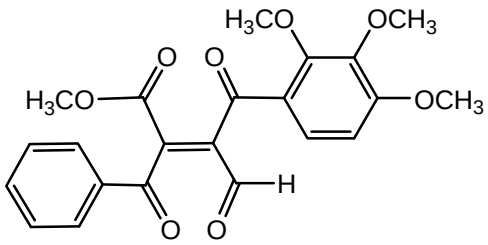
Amorphous powder. **IR** (CH_2Cl_2) 3048, 1715, 1712, 1708, 1641, 1539, 1255, 1032, 788 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 9.69 (s, 1H, CHO), 7.85 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.42 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.40 (t, *J* = 8.4 Hz, 2H, Ar-H), 7.38 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.95 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.93 (s, 3H, -OC*H*$_3$), 3.92 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 191.5, 188.2, 166.5, 165.5, 164.0, 151.3, 138.5, 134.6, 132.0, 131.5, 129.5, 129.4, 114.8, 55.5, 53.5; **HRMS** (**ESI**) (*m*/*z*): found 352.0944 $[M+H]^+$; calcd for $C_{20}H_{16}O_6$ 352.0947.

(Z)-Methyl 3-formyl-2,4-bis(4-methoxybenzoyl)-oxobut-2-enoate (**14e**)



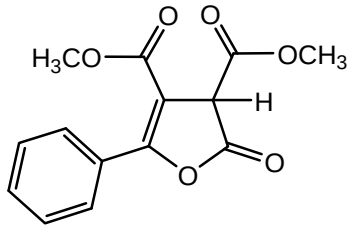
Amorphous powder. **IR** (CH_2Cl_2) 3048, 1719, 1715, 1709, 1640, 1531, 1252, 1033, 788 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 9.69 (s, 1H, CHO), 7.87 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.85 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.98 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.95 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.93 (s, 6H, -OC*H*$_3$), 3.92 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 192.0, 188.2, 166.3, 165.6, 164.5, 151.6, 138.8, 134.6, 132.5, 131.4, 129.4, 114.8, 114.6, 56.4, 55.5, 53.5; **HRMS** (**ESI**) (*m*/*z*): found 352.0944 $[M+H]^+$; calcd for $C_{20}H_{16}O_6$ 352.0947.

(Z)-methyl 2-benzoyl-3-formyl-4-oxo-4-(2,3,4-trimethoxyphenyl)but-2-enoate (**14f**)



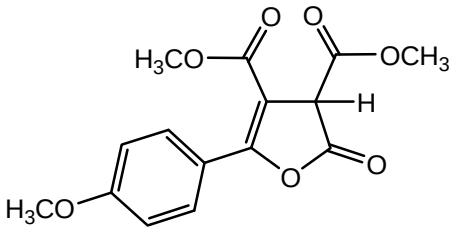
Amorphous powder. **IR** (CH_2Cl_2) 3054, 1710, 1705, 1689, 1640, 1522, 1258, 1031, 780 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 9.60 (s, 1H, CHO), 8.05 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.39 (brt, *J* = 8.7 Hz, 3H, Ar-H), 7.82 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.77 (d, *J* = 8.9 Hz, 2H, Ar-H), 3.97 (s, 3H, -OC*H*$_3$), 3.90 (s, 3H, -OC*H*$_3$), 3.79 (s, 3H, -OC*H*$_3$), 3.55 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 192.4, 191.2, 165.8, 165.1, 158.4, 155.6, 155.0, 141.5, 137.3, 128.8, 125.2, 124.2, 107.4, 68.5, 60.5, 60.6, 56.2, 56.0, 52.3, 52.1; **HRMS** (**ESI**) (*m*/*z*): found 412.1155 $[M+H]^+$; calcd for $C_{22}H_{20}O_8$ 412.1158.

Di-methyl 5-(4-methoxyphenyl)-2-oxo-2,3-dihydrofuran-3,4-dicarboxylate (**15a**)



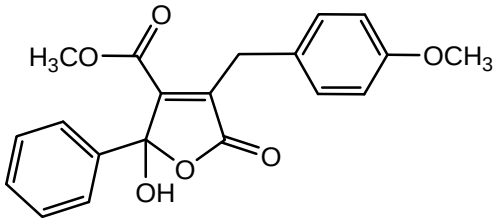
Yellow oil. **IR** (CH_2Cl_2) 2978, 1712, 1680 1652, 1513, 1465, 1174, 1030, 974, 843 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.55 -7.29 (m, 5H, Ar-H), 4.78 (s, 1H), 3.85 (s, 3H, -OC*H*$_3$), 3.83 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 172.7, 161.8, 159.8, 147.0, 141.6, 139.0, 129.7, 127.0, 114.0, 80.5, 55.0, 52.3; **HRMS** (**ESI**) (*m*/*z*): found 306.0740 $[M+H]^+$; calcd for $C_{15}H_{14}O_7$ 306.0743.

Di-methyl 5-(4-methoxyphenyl)-2-oxo-2,3-dihydrofuran-3,4-dicarboxylate (**15b**)



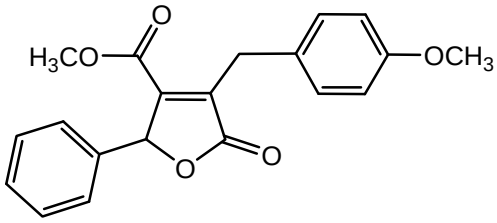
Yellow oil. **IR** (CH_2Cl_2) 2982, 1712, 1701, 1654, 1515, 1465, 1174, 1030, 974, 843 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.97 (d, *J* = 9.0 Hz, 2H, Ar-H), 4.75 (s, 1H), 3.88 (s, 3H, -OC*H*$_3$), 3.84 (s, 3H, -OC*H*$_3$), 3.76 (m, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 172.7, 161.8, 159.8, 147.0, 141.6, 139.0, 130.0, 127.0, 114.0, 80.5, 55.0, 52.3; **HRMS** (**ESI**) (*m*/*z*): found 306.0740 $[M+H]^+$; calcd for $C_{15}H_{14}O_7$ 306.0743.

Methyl 5-hydroxy-3-(4-methoxybenzyl)-2-oxo-5-phenyl-4,5-dihydrofuran-4-carboxylate (**16**)



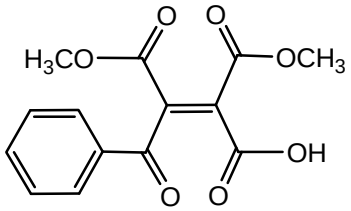
Yellow oil. **IR** (CH_2Cl_2) 2981, 1813, 1756, 1710, 1600, 1515, 1465, 1174, 1030, 974, 843 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.41 (m, 2H, Ar-H), 7.34 (m, 3H, Ar-H), 7.26 (d, *J* = 7.8 Hz, 2H, Ar-H), 6.84 (d, *J* = 7.8 Hz, 2H, Ar-H), 3.76 (s, 3H, -OC*H*$_3$), 3.74 (s, 3H, -OC*H*$_3$), 3.96 (m, 2H, -CH_2-Ph); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.0, 167.2, 157.6, 144.6, 142.7, 135.4, 130.0, 129.7, 129.0, 127.7, 127.1, 114.2, 112.3, 55.8, 52.3, 36.0; **HRMS** (**ESI**) (*m*/*z*): found 354.1101 $[M+H]^+$; calcd for $C_{20}H_{18}O_6$ 354.1103.

Methyl 3-(4-methoxybenzyl)-2-oxo-5-phenyl-4,5-dihydrofuran-4-carboxylate (**17**)



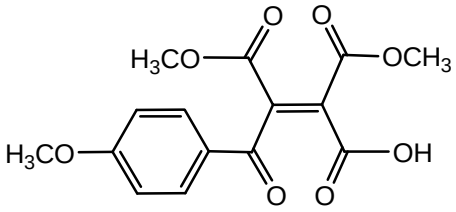
Yellow oil. **IR** (CH_2Cl_2) 2982, 1815, 1752, 1711, 1600, 1515, 1465, 1174, 1030, 974, 843 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 3H, Ar-H), 7.30 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.18 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.84 (t, *J* = 7.8 Hz, 2H, Ar-H), 6.20 (s, 1H), 3.79 (s, 3H, -OC*H*$_3$), 3.75 (s, 3H, -OC*H*$_3$), 3.85 (m, 2H, -CH_2-Ph); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 172.7, 161.8, 159.8, 147.0, 141.6, 139.0, 130.0, 129.7, 129.2, 128.6, 127.0, 114.0, 80.5, 55.0, 52.3, 51.4; **HRMS** (**ESI**) (*m*/*z*): found 338.1156 $[M+H]^+$; calcd for $C_{20}H_{18}O_5$ 338.1154.

3-Benzoyl-4-methoxy-2-(methoxycarbonyl)-4-oxobut-2-enoic acid (**18a**)



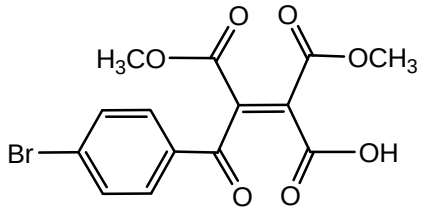
Amorphous powder. **IR** (CH_2Cl_2) 3595 − 3478, 2950, 1742, 1720, 1675, 1605, 1513, 1436, 1172, 1030, 850 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.89 (brd, *J* = 7.6 Hz, 2H, Ar-H), 7.50 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.40 (t, *J* = 7.6 Hz, 2H, Ar-H), 3.86 (s, 3H, -OC*H*$_3$), 3.65 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 192.5, 166.9, 165.6, 163.9, 145.0, 136.6, 134.5, 132.9, 128.6, 128.4, 52.8, 52.4; **HRMS** (**ESI**) (*m*/*z*): found 293.0664 $[M+H]^+$; calcd for $C_{14}H_{12}O_7$ 293.0661.

4-Methoxy-3-(4-methoxybenzoyl)-2-(methoxycarbonyl)-4-oxobut-2-enoic acid (**18b**)



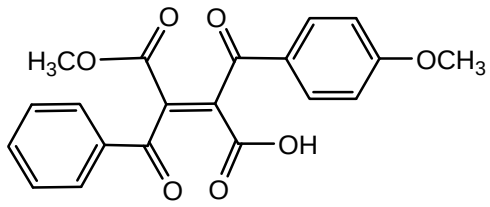
Amorphous powder. **IR** (CH_2Cl_2) 3590 − 3480 (br), 2957, 1740, 1738, 1685, 1600, 1513, 1436, 1172, 1030, 842 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.91 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.90 (s, 3H, -OC*H*$_3$), 3.84 (s, 3H, -OC*H*$_3$), 3.67 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 191.0, 166.7, 166.3, 164.2, 163.3, 140.0, 131.5, 130.9, 130.0, 113.6, 55.4, 52.7, 52.5; **HRMS** (**ESI**) (*m*/*z*): found 323.0772 $[M+H]^+$; calcd for $C_{15}H_{14}O_8$ 323.0767.

3-(4-Bromobenzoyl)-4-methoxy-2-(methoxycarbonyl)-4-oxobut-2-enoic acid (**18c**)



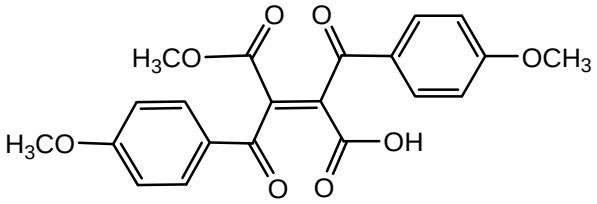
Amorphous powder. **IR** (CH_2Cl_2) 3590 − 3480 (br), 2960, 1742, 1718, 1680, 1601, 1512, 1430, 1170, 1040, 830 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.56 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.87 (s, 3H, -OC*H*$_3$), 3.67 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 191.6, 166.8, 165.5, 163.6, 145.2, 135.4, 131.9, 131.7, 130.3, 128.0, 53.0, 52.4; **HRMS** (**ESI**) (*m*/*z*): found 371.9770 $[M+H]^+$; calcd for $C_{14}H_{11}{}^{79}BrO_7$ 370.9766.

(E)-3-Benzoyl-4-methoxy-2-(4-methoxybenzoyl)-4-oxobut-2-enoic acid (**18d**)



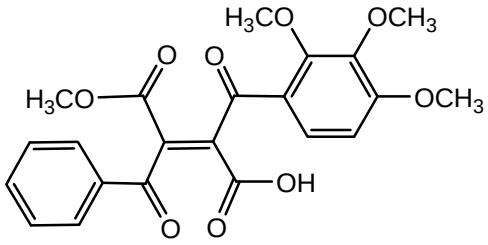
Amorphous powder. **IR** (CH_2Cl_2) 3054, 1700, 1640, 1570, 1250, 1030, 780 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.88 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.49 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.39 (t, *J* = 7.5 Hz, 2H, Ar-H), 6.90 (d, *J* = 7.5 Hz, 2H, Ar-H), 3.85 (s, 3H, -OC*H*$_3$), 3.50 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 192.1, 166.3, 164.0, 163.5, 138.6, 136.3, 132.7, 131.2, 129.0, 128.5, 128.4, 114.2, 114.0, 55.5, 52.7; **HRMS** (**ESI**) (*m*/*z*): found 368.0893 $[M+H]^+$; calcd for $C_{20}H_{16}O_7$ 368.0896.

(E)-4-methoxy-2,3-bis-(4-methoxybenzoyl)-4-oxobut-2-enoic acid (**18e**)



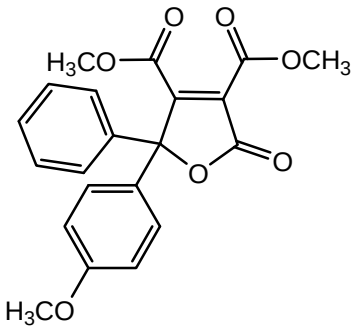
Amorphous powder. **IR** (CH_2Cl_2) 3051, 1705, 1644, 1550, 1255, 1032, 788 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.85 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.90 (d, *J* = 8.0 Hz, 4H, Ar-H), 3.84 (s, 6H, -OC*H*$_3$), 3.50 (s, 3H, -OC*H*$_3$); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 190.4, 164.5, 162.3, 162.1, 161.9, 147.0, 135.6, 129.7, 129.5, 129.3, 127.7, 112.3, 112.2, 53.8, 51.0; **HRMS** (**ESI**) (*m*/*z*): found 398.1005 $[M+H]^+$; calcd for $C_{21}H_{18}O_8$ 398.1002.

(E)-3-benzoyl-4-methoxy-4-oxo-2-(2,3,4-trimethoxybenzoyl)but-2-enoic acid (**18f**)



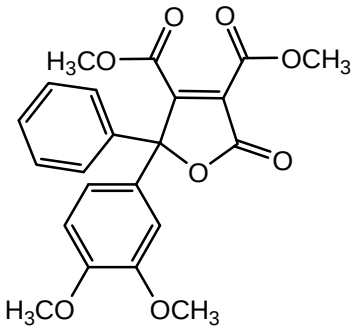
Amorphous powder. **IR** (CH_2Cl_2) 3055, 1715, 1708, 1688, 1640, 1530, 1252, 1033, 788 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.39 (brt, *J* = 8.9 Hz, 3H, Ar-H), 7.82 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.75 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.96 (s, 3H, -OC*H*$_3$), 3.92 (s, 3H, -OC*H*$_3$), 3.78 (s, 3H, -OC*H*$_3$), 3.54 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 193.4, 192.2, 166.2, 165.1, 158.2, 155.2, 155.1, 141.7, 137.4, 128.8, 125.5, 124.1, 107.1, 68.1, 60.9, 60.8, 56.1, 56.0, 52.5, 52.4; **HRMS** (**ESI**) (*m*/*z*): found 428.1105 $[M+H]^+$; calcd for $C_{22}H_{20}O_9$ 428.1107.

Dimethyl 2-(4-methoxyphenyl)-5-oxo-2-phenyl-2,5-dihydrofuran-3,4-dicarboxylate (**19d**)



Yellow oil. **IR** (CH_2Cl_2) 2960, 1760, 1738, 1602, 1441, 1170, 1036, 980, 890 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.38 − 7.29 (m, 5H, Ar-H), 7.23 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.88 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.92 (s, 3H, -OCH_3), 3.81 (s, 3H, -OC*H₃*), 3.75 (s, 3H, -OC*H₃*); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 165.6, 161.5, 161.0, 160.5, 160.3, 136.8, 129.3, 128.6, 128.5, 128.2, 127.7, 126.7, 113.9, 91.9, 55.3, 53.2, 53.1; **HRMS** (**ESI**) (*m*/*z*): found 383.1136 $[M+H]^+$; calcd for $C_{21}H_{18}O_7$ 383.1131.

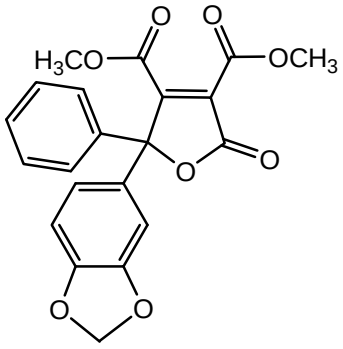
Dimethyl 2-(3,4-dimethoxyphenyl)-5-oxo-2-phenyl-2,5-dihydrofuran-3,4-dicarboxylate (**19e**)



Yellow oil. **IR** (CH_2Cl_2) 2950, 1797, 1748, 1720, 1605, 1507, 1465, 1175, 1018, 968, 838 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.40 − 7.34 (m, 3H, Ar-H), 7.32 (dd, *J* = 8.0, 1.5 Hz, 2H, Ar-H), 6.90 (dd, *J* = 8.4, 2.2 Hz, 1H, Ar-H), 6.83 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.81 (d, *J* = 2.2 Hz, 1H, Ar-H), 3.92 (s, 3H, -OC*H₃*), 3.89 (s, 3H, -OC*H₃*), 3.78 (s, 3H, -OC*H₃*), 3.76 (s, 3H, -OC*H₃*)**;** **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 165.7, 161.6,

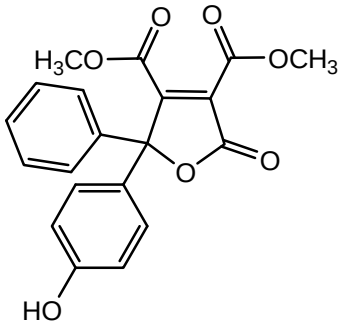
161.4, 160.4, 149.9, 148.9, 136.8, 129.4, 128.8, 128.5, 127.7, 126.3, 120.7, 111.1, 110.7, 91.9, 56.0, 55.9, 53.3, 53.2; **HRMS** (**ESI**) (*m*/*z*): found 413.1239 $[M+H]^+$; calcd for $C_{22}H_{20}O_8$ 413.1236.

Dimethyl 2-(benzo[d][1,3]dioxol-5-yl)-5-oxo-2-phenyl-2,5-dihydrofuran-3,4-dicarboxylate (**19f**)



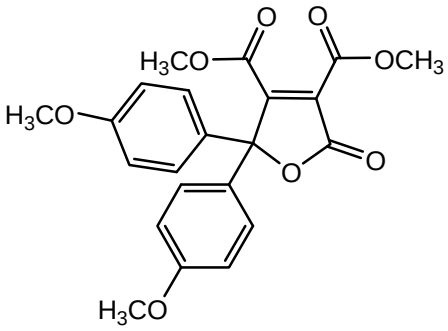
Yellow oil. **IR** (CH_2Cl_2) 3008, 2958, 1795, 1758, 1718, 1604, 1508, 1491, 1182, 1157, 1008, 978, 852 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 3H, Ar-H), 7.33 (d, *J* = 6.9 Hz, 2H, Ar-H), 6.80 (dd, *J* = 9.0, 1.4 Hz, 1H, Ar-H), 6.79 (d, *J* = 1.4 Hz, 1H, Ar-H), 6.74 (d, *J* = 9.0 Hz, 1H, Ar-H), 5.99 (s, 2H, -OC*H*$_2$O-), 3.92 (s, 3H, -OC*H*$_3$), 3.77 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 165.5, 161.4, 161.0, 160.4, 147.9, 136.6, 130.3, 129.4, 128.6, 128.5, 127.6, 127.5, 122.0, 108.5, 108.0, 101.6, 91.7, 53.3, 53.2; **HRMS** (**ESI**) (*m*/*z*): found 397.0929 $[M+H]^+$; calcd for $C_{21}H_{16}O_8$ 397.0923.

Dimethyl 2-(4-hydroxyphenyl)-5-oxo-2-phenyl-2,5-dihydrofuran-3,4-dicarboxylate (**19g**)



Yellow oil. **IR** (CH_2Cl_2) 3009, 2958, 1780, 1758, 1715, 1600, 1510, 1491, 1180, 1010, 981, 846 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.43 − 7.34 (m, 3H, Ar-H), 7.32 (dd, *J* = 8.1, 1.5 Hz, 2H, Ar-H), 7.16 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.80 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.92 (s, 3H, -OC*H*$_3$), 3.75 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 165.9, 161.5, 161.3, 160.5, 156.9, 136.6, 129.5, 129.4, 128.5, 128.4, 127.7, 126.5, 115.4, 92.1, 53.3, 53.2; **HRMS** (**ESI**) (*m*/*z*): found 369.0973 $[M+H]^+$; calcd for $C_{20}H_{16}O_7$ 369.0969.

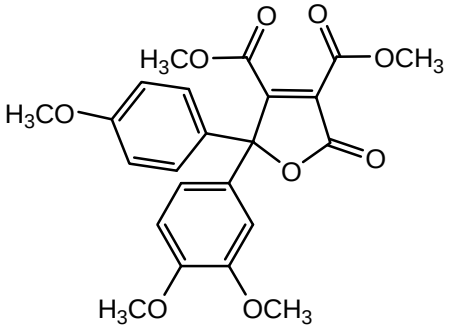
Dimethyl 2,2-bis(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-3,4-dicarboxylate (**19h**)



Yellow oil. **IR** (CH_2Cl_2) 2930, 1780, 1741, 1608, 1461, 1180, 1033, 978, 895 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 9.0 Hz, 4H, Ar-H), 6.88 (d, *J* = 9.0 Hz, 4H, Ar-H), 3.92 (s, 3H, -OC*H*$_3$), 3.82 (s, 6H, -OC*H*$_3$), 3.76 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 165.8, 161.6, 161.3, 160.5, 160.2, 129.2, 128.6, 126.3, 113.8,

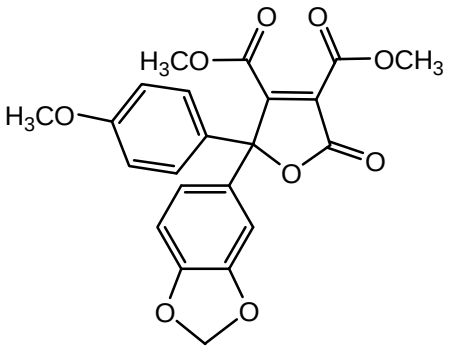
91.8, 55.3, 53.2, 53.1; **HRMS** (**ESI**) (*m*/*z*): found 413.1242 $[M+H]^+$; calcd for $C_{22}H_{20}O_8$ 413.1236.

Dimethyl 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-3,4-dicarboxylate (**19i**)



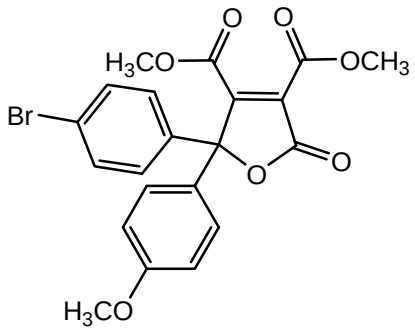
Yellow oil. **IR** (CH_2Cl_2) 3009, 2928, 1780, 1741, 1605, 1514, 1464, 1180, 1027, 995, 841 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.92 – 6.81 (m, 5H, Ar-H), 3.92 (s, 3H, -OC*H*$_3$), 3.89 (s, 3H, -OC*H*$_3$), 3.82 (s, 3H, -OC*H*$_3$), 3.78 (s, 3H, -OC*H*$_3$), 3.76 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 165.8, 161.7, 160.3, 149.8, 148.7, 134.0, 131.8, 129.3, 125.9, 124.0, 120.5, 113.8, 113.7, 110.9, 110.5, 91.5, 55.9, 55.8, 55.3, 53.3, 53.2; **HRMS** (**ESI**) (*m*/*z*): found 443.1349 $[M+H]^+$; calcd for $C_{23}H_{22}O_9$ 443.1342.

Dimethyl 2-(benzo[d][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-3,4-dicarboxylate (**19l**)



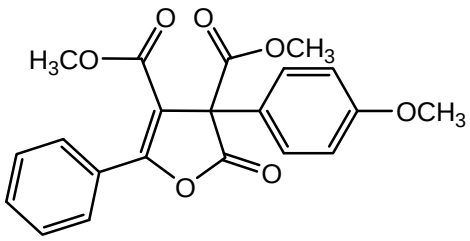
Yellow oil. **IR** (CH_2Cl_2) 3010, 2956, 1780, 1759, 1718, 1601, 1510, 1481, 1185, 1160, 982, 850 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 6.9 Hz, 1H, Ar-H) and 7.00 – 7.84 (m, 6H, Ar-H), 6.00 (s, 2H,-OC*H*$_2$O-), 3.92 (s, 3H, -OC*H*$_3$), 3.82 (s, 3H, -OC*H*$_3$), 3.78 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 165.4, 161.0, 160.8, 160.0, 147.9, 146.5, 136.6, 130.3, 129.4, 128.6, 127.6, 124.5, 121.0, 108.5, 108.0, 101.6, 90.7, 55.0, 53.3, 53.2; **HRMS** (**ESI**) (*m*/*z*): found 427.1041 $[M+H]^+$; calcd for $C_{22}H_{18}O_9$ 427.1029.

Dimethyl 2-(4-bromophenyl)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-3,4-dicarboxylate (**19m**)



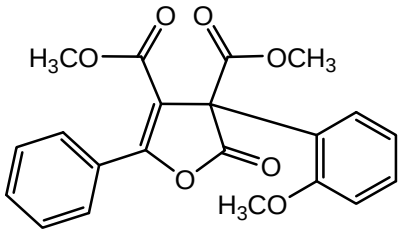
Yellow oil. **IR** (CH_2Cl_2) 3090, 2930, 1750, 1740, 1658, 1608, 1513, 1436, 1343, 1220, 927, 834 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.21 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.19 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.88 (d, *J* = 8.7 Hz, 2H, Ar-H), 3.92 (s, 3H, -OC*H*$_3$), 3.82 (s, 3H, -OC*H*$_3$), 3.77 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 165.4, 161.3, 160.5, 160.3, 160.1, 136.0, 131.7, 129.4, 129.2, 128.1, 127.1, 123.8, 114.0, 91.3, 55.3, 53.3, 53.2; **HRMS** (**ESI**) (*m*/*z*): found 461.0240 $[M+H]^+$; calcd for $C_{21}H_{17}{}^{79}BrO_7$ 461.0236.

Dimethyl 3-(4-methoxyphenyl)-2-oxo-5-phenyl-2,3-dihydrofuran-3,4-dicarboxylate (**20d**)



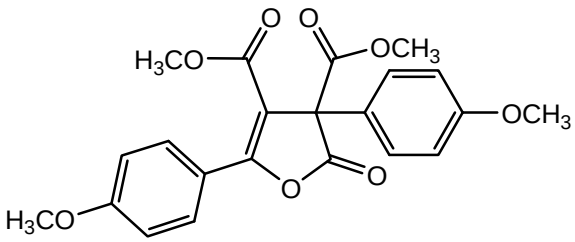
Yellow oil. **IR** (CH_2Cl_2) 2980, 1812, 1755, 1717, 1607, 1510, 1460, 1170, 1032, 970, 841 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.53 − 7.41 (m, 5H, Ar-H), 6.92 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.83 (s, 3H, -OC*H*$_3$), 3.81 (s, 3H, -OC*H*$_3$), 3.68 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.2, 166.8, 162.6, 161.7, 160.0, 132.1, 129.6, 128.9, 128.8, 128.5, 128.2, 114.1, 114.0, 63.8, 55.1, 54.0, 52.0; **HRMS** (**ESI**) (*m*/*z*): found 383.1136 $[M+H]^+$; calcd for $C_{21}H_{18}O_7$ 383.1131.

Dimethyl 3-(2-methoxyphenyl)-2-oxo-5-phenyl-2,3-dihydrofuran-3,4-dicarboxylate (***o*-20d**)



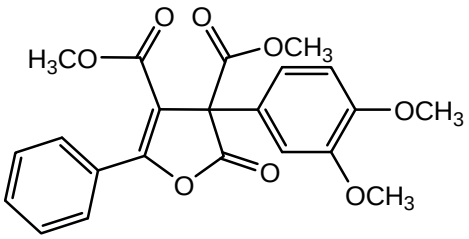
Yellow oil. **IR** (CH_2Cl_2) 2982, 1815, 1752, 1711, 1600, 1515, 1465, 1174, 1030, 974, 843 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.88 (brd, *J* = 7.7 Hz, 2H, Ar-H), 7.57 – 7.43 (m, 5H, Ar-H), 7.33 (t, *J* = 8.8 Hz, 1H, Ar-H), 7.03 (t, *J* = 7.7 Hz, 1H, Ar-H), 3.90 (s, 3H, -OC*H*$_3$), 3.77 (s, 3H, -OC*H*$_3$), 3.56 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.3, 166.5, 162.5, 160.9, 156.5, 131.5, 131.4, 130.1, 129.8, 129.4, 128.1, 127.5, 123.6, 120.9, 111.9, 63.1, 55.8, 53.8, 51.4; **HRMS** (**ESI**) (*m*/*z*): found 383.1133 $[M+H]^+$; calcd for $C_{21}H_{18}O_7$ 383.1131.

Dimethyl 3,5-bis(4-methoxyphenyl)-2-oxo-2,3-dihydrofuran-3,4-dicarboxylate (**20h**)



Yellow oil. **IR** (CH_2Cl_2) 2956, 1813, 1758, 1720, 1606, 1512, 1461, 1172, 1028, 971, 839 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.46 (d, *J* = 9.1 Hz, 2H, Ar-H), 6.99 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.94 (d, *J* = 9.1 Hz, 2H, Ar-H), 3.89 (s, 3H, -OC*H*$_3$), 3.82 (s, 3H, -OC*H*$_3$), 3.81 (s, 3H, -OC*H*$_3$), 3.68 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.3, 167.1, 162.9, 162.6, 161.8, 159.8, 131.8, 131.4, 129.4, 125.5, 118.8, 113.9, 113.6, 63.7, 55.5, 55.3, 53.6, 51.9; **HRMS** (**ESI**) (*m*/*z*): found 413.1240 $[M+H]^+$; calcd for $C_{22}H_{20}O_8$ 413.1236.

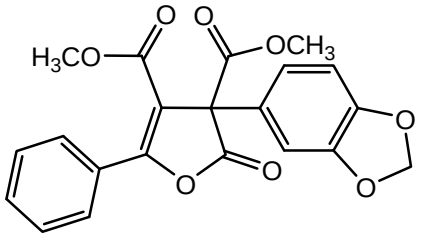
Dimethyl 3-(3,4-dimethoxyphenyl)-2-oxo-5-phenyl-2,3-dihydrofuran-3,4-dicarboxylate (**20e**)



Yellow oil. **IR** (CH_2Cl_2) 2980, 1811, 1756, 1718, 1608, 1505, 1465, 1178, 1032, 971, 839 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.58 – 7.53 (m, 1H, Ar-H), 7.50 (t, *J* = 7.4 Hz, 2H, Ar-H), 7.22 (d, *J* = 2.2 Hz, 1H, Ar-H), 6.95 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar-H), 6.84 (d, *J* = 8.5 Hz, 1H, Ar-H), 3.91 (s, 3H, -OC*H*$_3$), 3.88 (s, 3H, -OC*H*$_3$), 3.84 (s, 3H, -OC*H*$_3$), 3.69 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.1, 166.8, 162.7, 161.7, 149.6, 148.9, 132.1, 129.6, 128.2, 126.7, 125.5,

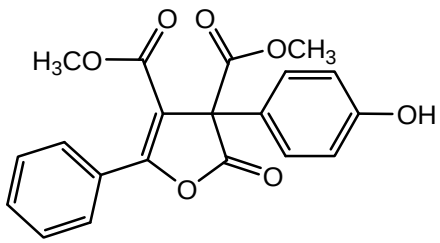
125.3, 120.1, 112.1, 110.8, 63.8, 56.0, 55.9, 53.7, 52.1; **HRMS** (**ESI**) (*m*/*z*): found 413.1240 $[M+H]^+$; calcd for $C_{22}H_{20}O_8$ 413.1236.

Dimethyl 3-(benzo[d][1,3]dioxol-5-yl)-2-oxo-5-phenyl-2,3-dihydrofuran-3,4-dicarboxylate (**20f**)



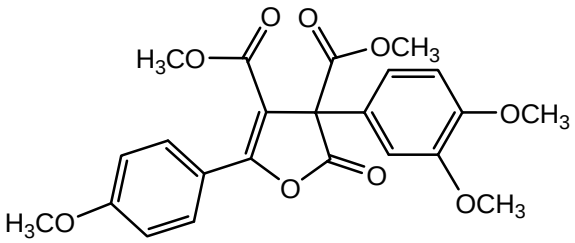
Yellow oil. **IR** (CH_2Cl_2) 3010, 2956, 1815, 1748, 1720, 1605, 1515, 1485, 1176, 1156, 1008, 974, 852 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.55 (brd, *J* = 7.3 Hz, 1H, Ar-H), 7.50 (t, *J* = 7.4 Hz, 2H, Ar-H), 7.13 (brs, 1H, Ar-H), 6.92 (dd, *J* = 8.2, 1.8 Hz, 1H, Ar-H), 6.79 (d, *J* = 8.2 Hz, 1H, Ar-H), 5.98 (s, 2H, -OC*H*$_2$O-), 3.83 (s, 3H, -OC*H*$_3$), 3.69 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.0, 166.6, 162.5, 161.8, 148.2, 147.9, 132.1, 129.6, 128.2, 126.8, 126.6, 121.5, 115.5, 109.3, 108.0, 101.4, 64.0, 53.7, 52.1; **HRMS** (**ESI**) (*m*/*z*): found 397.0936 $[M+H]^+$; calcd for $C_{21}H_{16}O_8$ 397.0939.

Dimethyl 3-(4-hydroxyphenyl)-2-oxo-5-phenyl-2,3-dihydrofuran-3,4-dicarboxylate (**20g**)



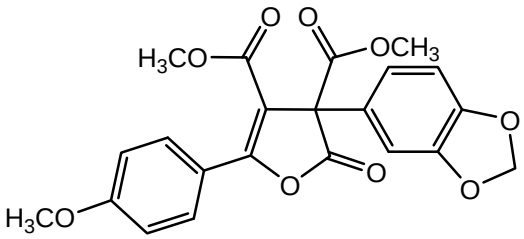
Yellow oil. **IR** (CH_2Cl_2) 3001, 2956, 1810, 1762, 1720, 1601, 1490, 1158, 1008, 980, 850 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.54 (brt, *J* = 7.5 Hz, 1H, Ar-H), 7.50 (brt, *J* = 7.5 Hz, 2H, Ar-H), 7.40 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.84 (d, *J* = 8.7 Hz, 2H, Ar-H), 3.83 (s, 3H, -OC*H*$_3$), 3.68 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.2, 166.9, 162.7, 161.8, 156.2, 132.1, 129.6, 128.2, 126.6, 125.3, 115.5, 110.7, 63.7, 53.8, 52.1; **HRMS** (**ESI**) (*m*/*z*): found 369.0975 $[M+H]^+$; calcd for $C_{20}H_{16}O_7$ 369.0969.

Dimethyl 3-(3,4-dimethoxyphenyl)-5-(4-methoxyphenyl)-2-oxo-2,3-dihydrofuran-3,4-dicarboxylate (**20i**)



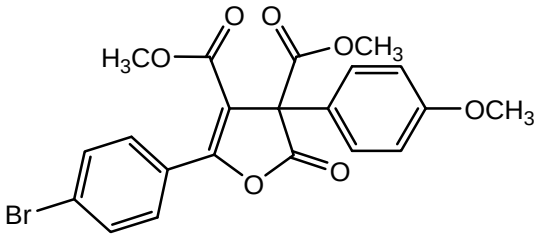
Yellow oil. **IR** (CH_2Cl_2) 3010, 2933, 1810, 1740, 1600, 1518, 1466, 1037, 844 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.21 (d, *J* = 2.1 Hz, 1H, Ar-H), 6.99 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.95 (dd, *J* = 8.5, 2.1 Hz, 1H, Ar-H), 6.83 (d, *J* = 8.5 Hz, 1H, Ar-H), 3.90 (s, 3H, -OC*H*$_3$), 3.89 (s, 3H, -OC*H*$_3$), 3.87 (s, 3H, -OC*H*$_3$), 3.82 (s, 3H, -OC*H*$_3$), 3.69 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 170.2, 167.0, 163.0, 162.7, 161.7, 149.6, 148.8, 131.7, 125.8, 120.2, 118.8, 113.7, 113.6, 112.2, 110.6, 63.5, 56.0, 55.8, 55.4, 53.6, 51.9; **HRMS** (**ESI**) (*m*/*z*): found 443.1352 $[M+H]^+$; calcd for $C_{23}H_{22}O_9$ 443.1342.

Dimethyl 3-(benzo[d][1,3]dioxol-5-yl)-5-(4-methoxyphenyl)-2-oxo-2,3-dihydrofuran-3,4-dicarboxylate (**20l**)



Yellow oil. **IR** (CH_2Cl_2) 3011, 2956, 1813, 1759, 1721, 1605, 1506, 1491, 1180, 1157, 1010, 980, 850 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.12 (d, *J* = 1.9 Hz, 1H, Ar-H), 6.98 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.91 (dd, *J* = 8.2, 1.9 Hz, 1H, Ar-H), 6.78 (d, *J* = 8.2 Hz, 1H, Ar-H), 5.97 (s, 2H,-OC*H*$_2$O-), 3.88 (s, 3H, -OC*H*$_3$), 3.81 (s, 3H, -OC*H*$_3$), 3.68 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 171.0, 166.8, 162.8, 162.7, 161.8, 148.1, 147.8, 131.8, 131.4, 127.1, 121.5, 118.8, 113.8, 109.3, 108.8, 101.4, 63.9, 55.4, 53.6, 51.9; **HRMS** (**ESI**) (*m*/*z*): found 427.1032 $[M+H]^+$; calcd for $C_{22}H_{18}O_9$ 427.1029.

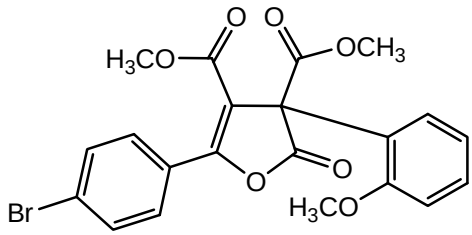
Dimethyl 5-(4-bromophenyl)-3-(4-methoxyphenyl)-2-oxo-2,3-dihydrofuran-3,4-dicarboxylate (**20m**)



Yellow oil. **IR** (CH_2Cl_2) 2928, 1816, 1608, 1590, 1512, 1172, 1149 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.64 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.21 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.85 (d, *J* = 8.9 Hz, 2H, Ar-H), 3.87 (s, 3H, -OC*H*$_3$), 3.81 (s, 3H, -OC*H*$_3$), 3.80 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 169.9, 166.3, 162.4, 159.7, 156.4, 131.4, 130.9, 129.9, 126.2, 123.4, 120.9, 114.2, 111.9,

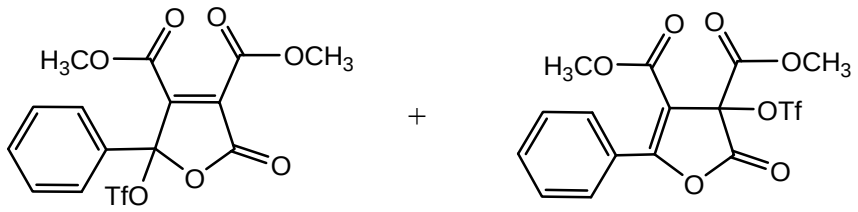
63.4, 55.8, 53.8, 51.5; **HRMS** (**ESI**) (*m*/*z*): found 461.0239 $[M+H]^+$; calcd for $C_{21}H_{17}{}^{79}BrO_7$ 461.0236.

Dimethyl 5-(4-bromophenyl)-3-(2-methoxyphenyl)-2-oxo-2,3-dihydrofuran-3,4-dicarboxylate (***o*-20m**)



Yellow oil. **IR** (CH_2Cl_2) 2930, 1800, 1602, 1592, 1512, 1172, 1150 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.61 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.48 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar-H), 7.33 (td, *J* = 8.0, 1.5 Hz, 1H, Ar-H), 7.04 (t, *J* = 7.8 Hz, 1H, Ar-H), 6.90 (d, *J* = 7.7 Hz, 1H, Ar-H), 3.90 (s, 3H, -OC*H*$_3$), 3.75 (s, 3H, -OC*H*$_3$), 3.57 (s, 3H, -OC*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 169.9, 166.3, 162.4, 159.7, 156.4, 131.6, 131.4, 130.9, 129.9, 129.3, 126.2, 123.4, 120.9, 114.2, 111.9, 63.2, 55.8, 53.8, 51.5; **HRMS** (**ESI**) (*m*/*z*): found 461.0238 $[M+H]^+$; calcd for $C_{21}H_{17}{}^{79}BrO_7$ 461.0236.

Dimethyl 2-oxo-5-phenyl-5-triflate-2,5-dihydrofuran-3,4-dicarboxylate + dimethyl 2-oxo-5-phenyl-3-triflate-2,3-dihydrofuran-3,4-dicarboxylate (**21**)



^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 9.6 Hz, 2H, Ar-H), 7.39 (t, *J* = 9.6 Hz, 1H, Ar-H), 7.36 (t, *J* = 9.6 Hz, 2H, Ar-H), 3.82 (s, 3H, -OC*H*$_3$), 3.73 (s, 3H, -OC*H*$_3$).

List of abbreviations

DABCO = 1,4-diazabicyclo[2.2.2]octane

DCM = dichloromethane

DMAD = dimethyl acetylenecarboxylate

Et_3N = triethylammine

Et_2NH = diethylammine

Et_2O = diethyl ether

EtOAc = ethyl acetate

Et_2S = diethyl sulfide

FC = Friedel-Crafts

Hex = n-hexane

MB = methylene blue

MeOH = methanol

$^1O_2$ = singlet oxygen

o.n. = over night

PE = petroleum ether

rf = reflux

r.t. = room temperature

TBAF = tetrabutylammonium floride

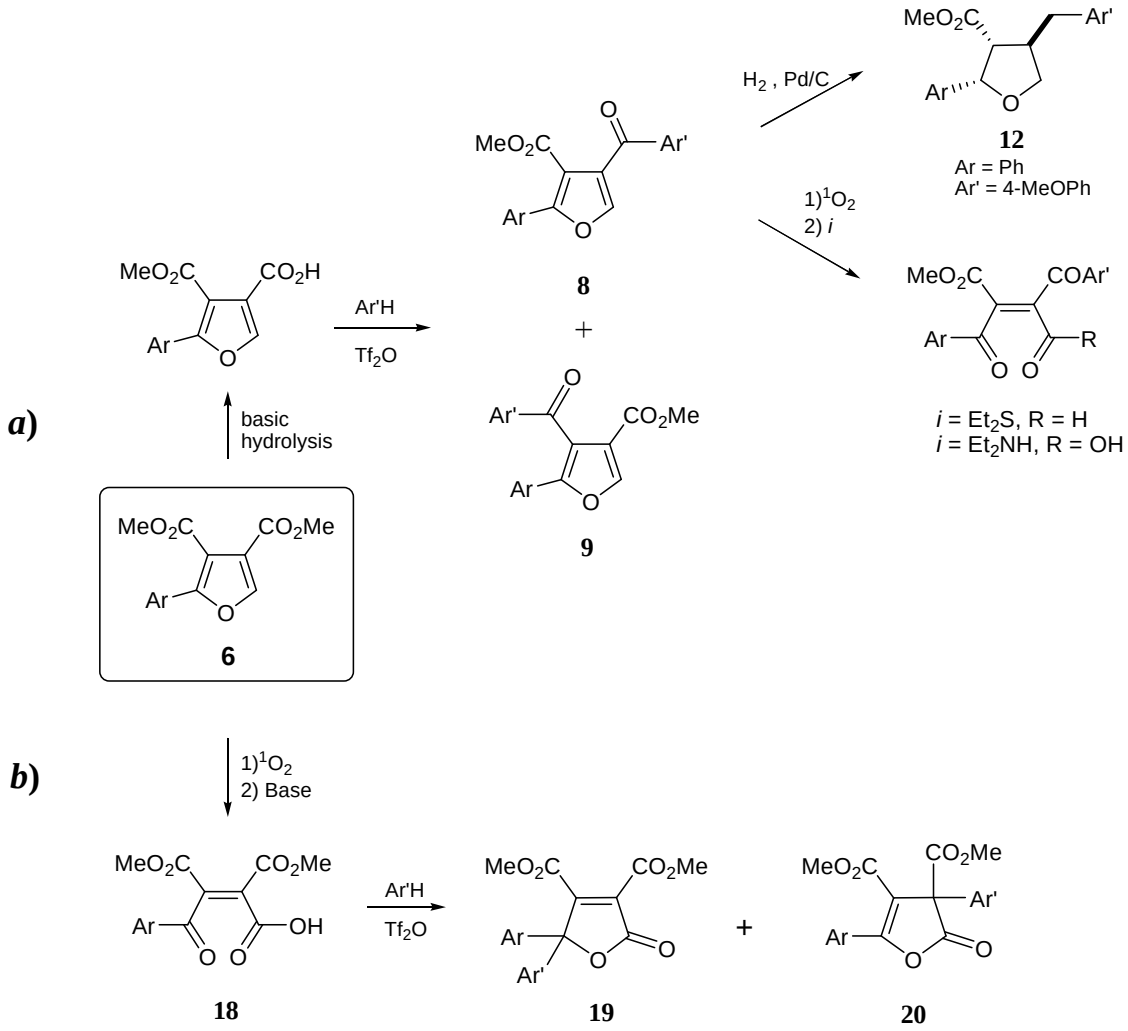
Tf_2O = trifluoromethylsulfonic anhydride (triflic anhydride)

THF = tetrahydrofuran

TMS = trimethylsilyl

IV – Conclusions

In this PhD project novel methodologies were investigated in order to prepare lignan-like compounds. Polysubstituted furans were used as starting materials. Two synthetic procedures were proposed starting from unique precursors 2-aryl-3,4-dicarboxymethylfurans **6**:



Summary Scheme - Novel mild synthetic procedures for lignan-like compounds from unique precursors 2-aryl-3,4-dicarboxymethylfurans **6**

The approach ***a*** was suitable to obtain acylated 2-arylfurans through Tf_2O-mediated Friedel-Crafts acylation. The possibility to prepare regioselectively and in high yields

4- or 3-acylated products was developed by tuning of reaction conditions. In particular, the temperature was turned out to get important effects on selectivity: low temperatures favour 4-acylated products which have a *β-β'* lignan scaffold. The procedure explored on 2-phenylfuran **6a** led to the series of products **8a-f** in satisfactory yields using different arylic substrate with typical lignan substitutions.

The method turned out suitable also to obtain the series of acylated regioisomers **9a-f**, but their structures are not included in those of natural lignans.

The results obtained starting from an electron-rich 2-anisoylfuran **6b** appear less satisfactory.

Applications of some synthesized furans were investigated to obtain differently functionalized lignan-like structures. In particular, their reactivity in reduction and oxidation reactions were studied. Pd/C-catalyzed hydrogenation of 2-phenyl-4-anisoylfuran **8a** led to the corresponding tetrahydrofuran **12** which is an analogue of natural bioactive lignan taxiresinol.

Dye-sensitized photooxygenation was chosen as oxidation method of furans. Although the power of the reaction of furans with $^1O_2$ is widely recognized, new findings are often found due to versatility of furan endoperoxides. We examined the photooxygenation reaction of some synthetized furans since peroxides of α-aryl-α'-unsubstituted furans were not previously examined. In order to obtain oxidated structures as 1,4-enediones and 4-hydroxybutenolides, two general applications of the photooxygenation on were explored. Et_2S reduction led to the corresponding aldehydes **14**, while basic treatment with Et_2NH led exclusively to open acid structures **18** instead of expected γ-hydroxylactones The results obtained could be attributed to the α-aryl substitution of furans and their high conjugation.

In the second part of this project, the three-step one-pot mild procedure ***b*** for highly functionalized 5,5- and 3,5-diarylfuranones was developed. This methodology is similar to the first one, because it involves starting precursors **6** and suitable acrylic acids **18** obtained by photooxygenation and in situ basic treatment. Thus, the Tf_2O-mediated Friedel-Crafts acylation was applied on these open acid forms leading to the mixture of cyclic 5,5- and 3,5-diaryl products. The furanones **19** are particularly interesting since they combine the presence of the intriguing butenolide moiety and a carbon skeleton of a recently isolated rare lignan as the Sacidumlignan D.

V – References

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Acknowledgments

I gratefully thank Prof. Maria Rosaria Iesce for her helpful support, particularly in the photooxygenation section of this work, and Prof. Marina Della Greca for her assistance in the project.