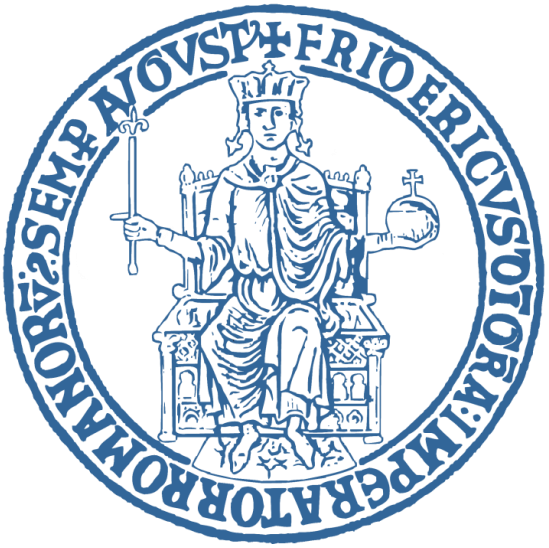
UNIVERSITY OF STUDIES OF NAPLES 'FEDERICO II'

DOCTORAL THESIS IN CHEMICAL SCIENCES (XXVIII CYCLE)

2013-2016



NEW METHODOLOGIES FOR PRODUCTS OF BIOLOGICAL INTEREST BY SUITABLY SUBSTITUTED FURANS

***PhD Student**: Rosalia Sferruzza*

Tutor: Prof. Maria Rosaria Iesce

Supervisor: Dr. Alessandro Pezzella

Co-Tutor: Prof. Marina Della Greca

Coordinator: Luigi Paduano

ABSTRACT

Furans, due to their easy preparation and great synthetic versatility, are widely used as intermediates in organic synthesis and as building blocks in the preparation of a wide number of natural and synthetic compounds interesting from a pharmacological point of view. This encourages to explore for novel preparation methods, and new synthetic applications of this system. In the first part of this thesis one-pot syntheses for new functionalized glycosides and new modified nucleosides of biological interes have been developed. The strategy is based on the preparation of glycosyl furans used as precursors in reactions of [4+2] cycloaddition with singlet oxygen, generated by dye-sensitized photooxygenation, and subsequent elaborations. In this context, novel and highly functionalized spiroketals of sugars were synthetized. The spiroketal moiety represents a privileged substructure since it can be found in many natural products characterized by various important biological properties, from antibiotic to anticancer.

The second part of the thesis was devoted to study polysubstituted furans as precursors of lignan-like compounds. Lignans are widespread plant secondary metabolites holding a large series of bioactivities. Basic structure consists of two phenylpropanoidic units linked in different patterns. To isolate lignans from plant materials is a laborious and expensive process. For this over the years diverse synthetic approaches have been proposed, mainly based on coupling of C_6C_3 units. As an alternative, a novel methodology to obtain $\beta-\beta'$ linked lignan-like products was found, based on the use of aryl substituted furans. In particular, a Tf_2O-mediated Friedel-crafts reaction starting from furyl alcohols was examined and led to furans with lignan backbone. Moreover, in order to explain some peculiar results evidenced in "classical" reactions of the endoperoxides of β,β'-dicarbomethoxy aryl furans, an investigation was carried out on the reactivity of these compounds by examining mainly substituent effects. The synthetic potential was also exploited. The introduction of furan system in the lignan scaffold was inspired by the chemical properties of furans that are efficiently converted into reduced forms as dihydro- and tetrahydrofurans or to oxidized forms as furanones or enediones. Therefore, further elaborations can be expected that enlarge the number of derivatives with lignan bakbone.

CONTEXT

ABSTRACT

CHAPTER 1. INTRODUCTION

Furans: synthesis and reactivity

Dye-sensitized photooxygenation of furans

1A. THE PROJECT

CHAPTER 2. SYNTHESIS OF GLYCOSYL FURANS AND APPLICATIONS IN THE FIELD OF C-GLYCOSIDES AND C-NUCLEOSIDES

2. INTRODUCTION

2A. ONE-POT PROCEDURE FOR NOVEL SPIROKETALS OF MONOSACCHARIDES

RESULTS AND DISCUSSION:

*Synthesis of Glycosyl Furans **2***

*Dye-Sensitized Photooxygenation of Furans **2a**-**2c** and Et_2S Reduction*

2B. ONE-POT PROCEDURE FOR 1,2-PYRIDAZINE *C*-NUCLEOSIDES

RESULTS AND DISCUSSION:

*Preparation of starting β-Glycosyl Furans **3***

Synthesis of 1,2-Pyridazine C-Nucleosides

2C. CONCLUSION

2D. EXPERIMENTAL SECTION

Experimental-part 2A

Experimental- part 2B

CHAPTER 3. SYNTHESIS OF ARYL TRISUBSTITUTED FURANS AND APPLICATIONS IN THE FIELD OF LIGNANS

3. INTRODUCTION

3A. SYNTHESIS OF DIARYL FURANS WITH LIGNAN BACKBONE BY NOVEL FRIEDEL-CRAFTS ALKYLATION

RESULTS AND DISCUSSION:

Synthesis of furans 1

Synthesis of furanyl alcohols 2

Friedel-Crafts alkylation reactions

Antibiotic activity of some derivatives

3B. DYE-SENSITIZED PHOTOOXYGENATION OF ARYL TRISUBSTITUTED FURANS AND APPLICATIONS IN THE FIELD OF LIGNANS

RESULTS AND DISCUSSION:

Synthesis of other furans of type 1

Photooxygenation reactions

Et_2S reduction

Base treatment

Mb-sensityzed photooxygenation of furans 1 in acetone

3C. CONCLUSION

3D. EXPERIMENTAL SECTION

Experimental-part 3A

Experimental- part 3B

CHAPTER 4. CONCLUSION AND PERSPECTIVES

REFERENCES

CHAPTER 1. INTRODUCTION

The name furan comes from the Latin furfur, which means bran. The first furan derivative to be described was 2-furoic acid, by Carl Wilhelm Scheele in 1780 (Senning 2006). Furans are an important class of heterocyclic compounds, often possessing biological properties such as antibacterial, analgesic, antihyperglycemic, antifungal, antitumoral (Manna and Agraval 2009). The furan ring system is the basic skeleton of numerous compounds possessing cardiovascular activities. An iodinated lipophilic furan derivative is widely used in the treatment of ventricular and arterial fibrillation (Verma et al. 2011). Some examples of furans and derivatives are used in the treatment of diabetes (Nakanishi 1974).

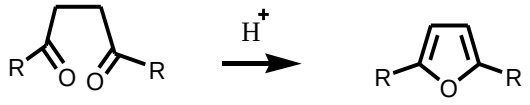
Furans are also versatile building blocks in organic synthesis and are used in the preparation of a wide number of important natural and synthetic compounds (Keay et al. 2008; Wong et al. 2008; Lee et al. 2005). Furans, indeed, find a large number of applications in the field of drugs, pesticides, cosmetics, detergents, polymers, dyes and so on.

Hence, considerable attention is continuously focused on the synthesis of furan derivatives and screening for pharmacological activity and/or for industrial applications.

Furans: synthesis and reactivity

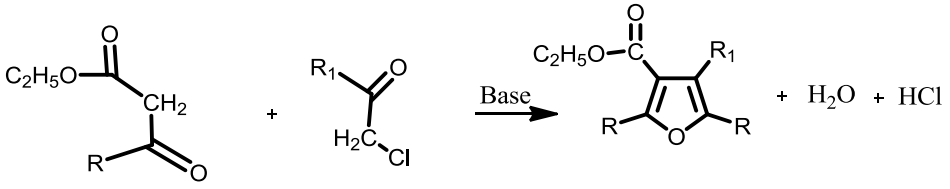
The furan ring is the most popular heterocyclic system due to its versatility in several types of reactions (Donnelly et al. 1984; Sargent et al. 1984; Heaney et al. 1996; Sargent et al. 1979; Shipman 1994; Dean 1982; Bosshard and Eugster 1996) and it is widely used in the synthesis of a lot of important products (Wong et al. 2008; Lee et al. 2005). Hence, chemists have paid considerable attention to the development of ring synthesis and elaborations for this class of heterocycles.

The acid-catalyzed cyclization of 1,4-dicarbonyl compounds and their surrogates, known as the Paal-Knorr synthesis, is one of the most popular methods for the preparation of furans and recently mechanistic details have been disclosed (Amarnath and Amarnath 1995)(**SCHEME 1.1**).



SCHEME 1.1 PAAL-KNORR SYNTHESIS

Noteworty is the synthesis of furan derivatives by treatment of an α-halo ketone and a β-dicarbonyl compound with a base (Feist-Benary furan synthesis) (Carson and Wong 1973) (**SCHEME1.2**).

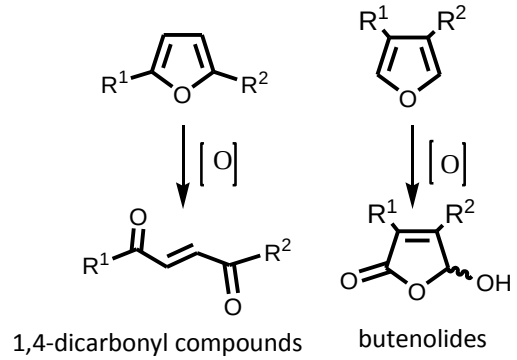


SCHEME1.2 FEIST-BENARY SYNTHESIS

Many derivatives come from elaboration of a starting simple compound, in many cases deriving from natural sources as furfural, furyl alcohol, etc. (Kirk-Othmer 1980).

Furans undergo a wide range of reactions. Typical reactions are electrophilic substitutions, Diels-Alder, reductions and oxidations. Substitution occurs preferentially at C-2 because the intermediate obtained by attaching a substituent at this position is more stable than the intermediate obtained by attaching a substituent at C-3. If both positions adjacent to the heteroatom are occupied, electrophilic substitution will take place at C-3. Diels-Alder reactions lead to a great number of complex structures that are intermediates in the synthesis of natural products (Kappe et al. 1997; Keay et al. 1999). Among these structures are the so- called ' *naked sugars'*, important precursors for *de novo* syntheses of carbohydrates (Vogel 2000; Vogel 1998; Vogel 1990).The reduction into tetra- and dihydrofurans can be carried out under classical metal-catalyzed hydrogenation. Typical catalysts used are Pd/C, Raney nickel and rhodium on alumina (Pei and Pei 2000). Furans can also be oxidized by classical reagents such as peracids, hydrogen peroxide, and metal oxides to give derivatives of synthetic utility and several reviews have been published on this topic (Gingerich et al. 1990; Sauter and Adam 1995; Ciufolini et al. 1998; Merino et al. 2000). Generally, 2,5-disubstituted

furans provide 1,4 dicarbonyl compounds, instead 3,4-disubstituted furans give rise to butenolides (**SCHEME 1.3**).



SCHEME 1.3 SYNTHESIS OF 1,4-DICARBONYL COMPOUNDS AND BUTENOLIDES

Several other procedures for the oxidation of furans are reported. These use reagents including bromine, tert-butyl-hydroperoxide (TBHP), *N*-bromosucinimide (NBS), singlet oxygen, dioxiranes and lead to various structures: in addition to 1,4-enediones and furanones diepoxides, epoxyfuranones, enolesters. Furanones, in particular, show a very interesting structural motif, widely occurring in bioactive natural and synthetic products (Bailly et al. 2008; De Silva et al. 1980; Gunasekera et al. 1996; De Rosa et al. 1995). 1,4-Enediones are versatile systems that can be used as synthons for the preparation of diverse carbo- and heterocyclic compounds (Iesce and Cermola 2012; Merino et al. 2007; Piancatelli et al. 1994). Among oxidation procedures the reaction with singlet oxygen, generated by dye-sensitized photooxygenation, is one of the most used for the mild reaction conditions and efficiency and for the possibility to obtain interesting C-4 functionalities (Iesce et al. 2012; Noutsias and Vassilikogiannakis 2012; Merino et al. 2007; Feringa 1987).

Dye-sensitized photooxygenation of furans

The photooxygenation can be described as a reaction in which a combination of light and oxygen in the presence of a sensitizer allows to introduce oxygenated functions in a given substrate (Iesce et al. 2005).

The reaction is based on the irradiation of a substrate in the presence of oxygen and a catalytic amount of a dye. The latter compound 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 1.4**).

$$^1S \xrightarrow{h\nu} {}^1S^* \xrightarrow{ISC} {}^3S^* \xrightarrow{^3O_2} {}^1S + {}^1O_2$$

^1S=dye; S*= excited dye

SCHEME 1.4 FORMATION OF SINGLET OXYGEN VIA SENSITIZER

The most common sensitizers used in the reactions of photooxygenation are non-toxic dyes with structures that allow large electron delocalization; they can be artificial or natural dyes that absorb visible light. A typical dye is Methylene Blue (MB), the structure of which is shown in **FIGURE 1.1**.

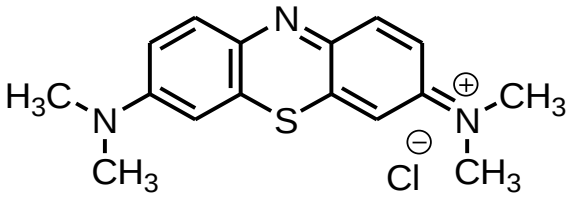
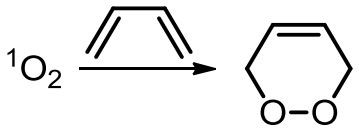


FIGURE 1.1 METHYLENE BLUE STRUCTURE

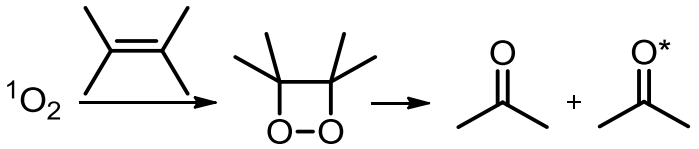
Halogenated or deuterated solvents, low temperatures, use of halogen lamps and the continuous oxygen flow favor the production of singlet oxygen and ensure a long lifetime of this species (order of seconds) (Iesce et al. 2005).

Singlet oxygen is a very reactive species that adds to unsaturated systems to give peroxides and hydroperoxides (Frimer 1985) through the following paths:

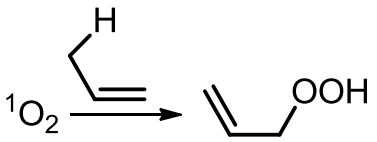
- [4 + 2] Cycloaddition with conjugated dienes



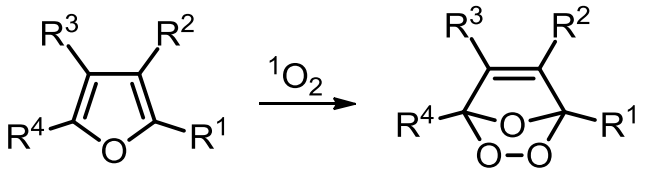
- Addition to a double bond and subsequent fragmentation with the formation of two carbonyl fragments



- Reaction with alkenes having an allylic hydrogen, forming allyl hydroperoxides



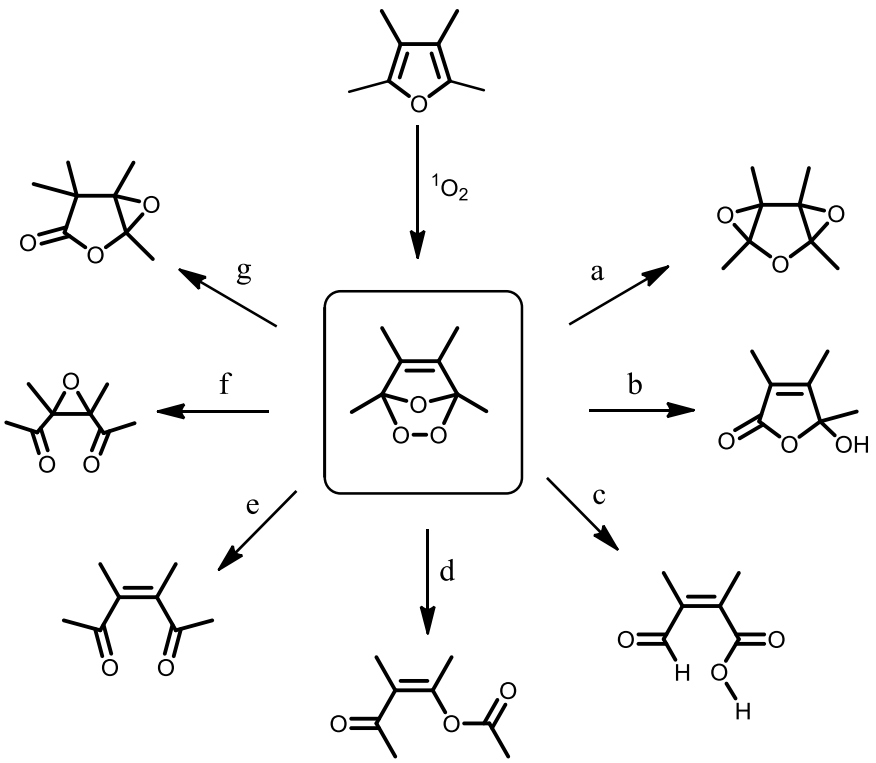
Furan is an excellent substrate for singlet oxygenation reactions. Indeed, singlet oxygen adds to the hetorocycle by a [4+2] cycloaddition, analogue to Diels-Alder reaction, in a quantitative and concerted reaction leading to 2,3,7-trioxabicyclo[2.2.1]-heptenes, also named furan endoperoxides (**SCHEME 1.5**).



SCHEME 1.5 DYE-SENSITIZED PHOTOOXYGENATION

Furan endoperoxides are generally thermally unstable and can afford characteristic rearranged products. Anyhow, the reactivity can be controlled working at subambient temperature. Studies have evidenced that straight correlations exist between the

nature of the substituents present in the bicycle and the stability as well as the type of the observed final products (Graziano et al. 1982; Graziano et al. 1987; Scarpati et al. 1998; Iesce and Cermola 2012). So, the thermal stability of the furan endoperoxides appears to depend on the α-substituents and follows the order Me > Ph > H > OMe. The presence of an electron-withdrawing group at the β position, on 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 (Graziano et al. 1980). The subsequent rearrangements of the intermediate endoperoxide depend on the nature of the α-substituents as well as on the reaction conditions (Iesce and Cermola 2012; Merino et al. 2007; Gollnick and Griesbeck 1985). Epoxides, diepoxides, enol esters, enediones, ketoesters, epoxyfuranones, furanones are some of the products available from the photooxygenation of furans (**SCHEME 1.6**).



SCHEME 1.6 SOME REARRANGEMENTS OF FURAN ENDOPEROXIDES

The reaction of furans with singlet oxygen is widely used in diverse scientific fields. The mild reaction conditions of the dye-sensitized photooxygenation, and the great structural diversity of products available from this simple heterocycle via the corresponding endoperoxide are strongly appealing in organic synthesis. The conversion to butenolides and 1,4-dicarbonyl compounds are the most used applications due to the key roles of these derivatives (Iesce and Cermola 2012; Montagnon et al. 2008; Merino et al. 2007).

As above evidenced, butenolides have found utility as precursors to complex lactone-containing compounds, some of them exhibiting bioactive properties (Noutsias and Vassilikogiannakis 2012). This functionality can be easily introduced by the action of singlet-oxygen-mediated reaction sequences starting from silylated furans (Katsumura et al. 1985; Kernan and Faulkner 1988) or in the presence of a base starting from α,α'-unsubstituted furans (Kernan and Faulkner 1988) or in basic medium (Graziano and Iesce 1985), in water or ionic liquids (Astarita et al. 2009) starting from α- and α,α'-unsubstituted furans. *Cis*-1,4-enediones are prepared by low temperature photooxygenation followed by *in situ* treatment of the intermediate furan endoperoxides with reductants such as triphenylphosphine or dialkyl sulfides (Iesce et al. 2005; Gollnick and Griesbeck 1985; Graziano et al. 1980). These compounds are generally formed almost quantitatively and hence can be used without isolation. Indeed they represent useful synthons for carbo- and heterocyclic compounds (Iesce and Cermola 2012; Merino et al. 2007; Piancatelli et al. 1994).

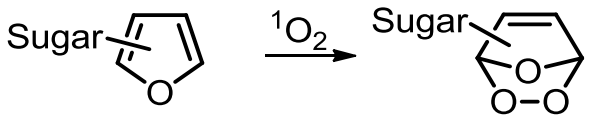
The high propensity of furans to add singlet oxygen also accounts for the wide use of some derivatives as trapping agents in environmental and biomedical analyses (Boule 1999).

1A. THE PROJECT

In this context, the PhD project has aimed to explore novel preparation methods to obtain molecules of biological interest using the furan system as starting material and simple and environmentally procedures.

The work was focused :

- to synthetize glycosyl furans and explore novel applications in the field of glycosides and modified nulclesides using the photooxygenation as key step (**SCHEME 1.7**)



SCHEME 1.7 GENERAL SCHEME OF PHOTOOXYGENATION OF SUGAR FURANS

- to search new approaches to lignan-like compounds starting from opportunely prepared furans
- to investigate the reactivity towards singlet oxygen of novel furan structures.

CHAPTER 2. SYNTHESIS OF GLYCOSYL FURANS AND APPLICATIONS IN THE FIELD OF C-GLYCOSIDES AND C-NUCLEOSIDES

2. INTRODUCTION

Over the years glycosides, due to their importance in natural products chemistry,represent a class of molecules widely studied. Considering the nature of the glycosidic bond between the anomeric carbon (C-1) and the aglycone it is possible to distinguish among *O*-glycosides, *N*-glycosides, *C*-glycosides and *S*-glycosides.

The role of glycosides in biological processes is widely known. Of particular interst are nucleosides. As known, a nucleoside consists simply of a nucleobase bound to either ribose or deoxyribose via beta-glycosidic linkage; nucleosides linked to a phosphate group are the molecular building-blocks of DNA and RNA. Modified nucleosides are represented by compounds that differ from the natural analogous for changes in the sugar structure. Some derivatives have been used as therapeutic drugs. Compounds that act as anti-viral and anti-cancer drugs are *Acyclovir* (Sawdon and Peng 2013; Moustafa et al 2011) or *Azidothymidine*(**FIGURE 2.1**) (Radzio and Sluis-Cremer 2008; Fischl et al. 1990).

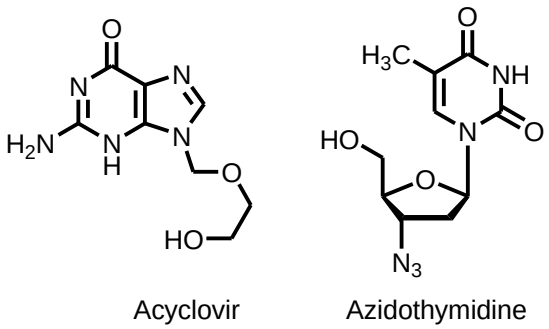


FIGURE 2.1 STRUCTURE OF ACYCLOVIR AND AZIDOTHIMIDINE

The first strongly inhibits herpes virus, while the second inhibits the HIV virus.

There is a further class of modified nucleosides, where the sugar and nucleobases are linked through a β-*C*-glycosidic linkage: the *C*-nucleosides. These derivatives present a carbon-carbon linkageto the anomeric centre and result particularly stable to chemical and enzymatic hydrolysis. In *C*-nucleosides the sugar moiety is often a ribose or deoxyribose and the aglycon part an aryl compound but a variety of other structures are also found.They can exhibit biological properties similar to those of their O- and N-

analogues; some of these molecules exhibit antibacterial, antiviral and antitumour properties. An example of natural *C*-nucleosides is showdomycin (Barrett and Broughton 1986; Hungerford et al. 2003) (**FIGURE 2.2**).

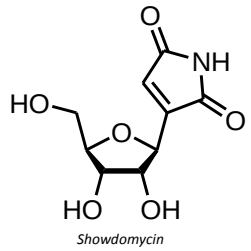


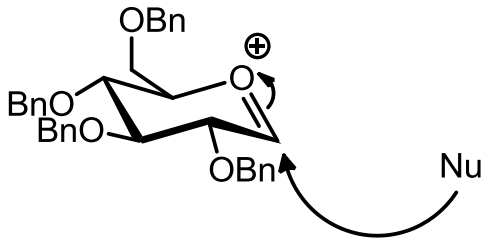
FIGURE 2.2 STRUCTURE OF SHOWDOMYCIN

Showdomycin was isolated in 1964 from *Streptomyces Z-452*. It shows mild activity against Gram-positive and Gram-negative bacteria andit can also stop the growth of tumor cells.

On the basis of these applications it is considered important to develop new molecules that can act in a targeted and effective way, whilst minimizing side effects. *C*-glycosides synthesis is difficult (Wellington and Benner 2006; Picard et al. 2006; Chaumontet et al.2006; Bililign et al.2005) but the field of synthesis of *C*-glycosides and *C*-nucleosides is in continuous development due to searching for new molecules as well as for efficient and environmentally friendly procedures.

The common strategy for the synthesis of glycosides involves a nucleophilic attack on this naturally electrophilic centre. The activation of the anomeric centre is based on a previous reaction which converts the C-1 hydroxyl group in a better leaving group. Over the years a great variety of electrophilic sugars have been prepared and employed (Postema 1995). Glycosyl halides as chlorides, bromides and fluorides have been used extensively in *C*-glycoside preparation as leaving group with different nucleophiles. Another common electrophile is the anomeric *O*-tricholoacetoimidate that leads to *C*-glycosides in good yields. The carbon nucleophiles that have been used as glycosyl acceptors include: olefins, silyl enol ethers, silyl cyanide and organometallics such as organolithium, aluminates and Grignard reagents. For these electrophilic sugars the

products obtained are often α-*C*-glycosides. This general trend can be explained considering that when the sugar electrophile is exposed to Lewis acidic conditions, an intermediate oxonium is formed (**SCHEME 2.1**). Hence, the attack of nucleophile on the intermediate is predominantly from the α-face under control of the anomeric effect. This method is the most generally used, but sometimes it cannot guarantee good results because of the degradation of the selected acceptors due to harsh acidic conditions (Postema 1995; Levy and Tang 1995).



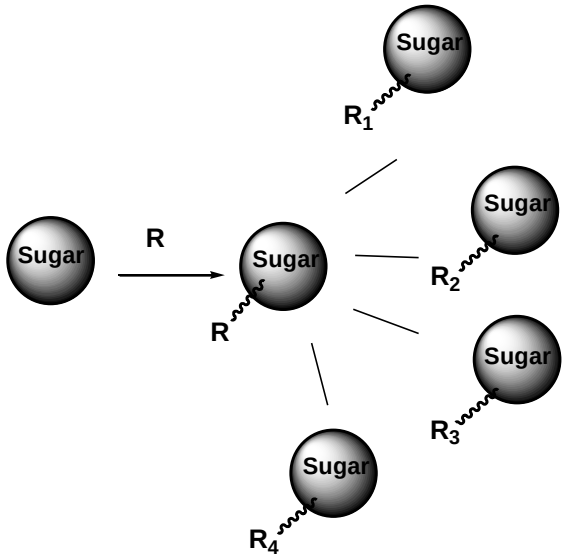
SCHEME 2.1 NUCLEOPHILIC ATTACK TO PYRANOOXONIUM INTERMEDIATE

An interesting approach to achieve β-*C*-glycosides involves the addition of an organometallic reagent to a sugar lactone; the result is normally a mixture of lactols which are selectively reduced to the required β-glycosides.

Considering the relevant biological activity of some natural *C*-nucleosides, the synthesis of these derivatives represents an important field of research. There are several types of strategic approaches to synthesise *C*-nucleosides, that can be divided into two main classes. The first involves direct attachment of the base heterocycle to the C-1 carbon of the D-ribosugar. The second strategy is less general and involves the conversion of a heterocycle precursor, bonded to β-*C*-riboside, to the target molecule (**SCHEME 2.2**). So in effect, the key point of this approach is the stereoselective synthesis of β-*C*-ribosides bearing a useful carbon fragment.

SCHEME 2.2 ALTERNATIVE SYNTHETIC GLYCOSYDES ROUTE

The direct coupling often gives unsuccessful results, for example due to the acid conditions that induce isomerizations or degradations of the aglycone moiety.
The alternative is particularly useful when it allows to prepare a glycosyl precursor bearing an aglycone that can undergo a series of elaborations to give a series of derivatives (**SCHEME 2.3**).



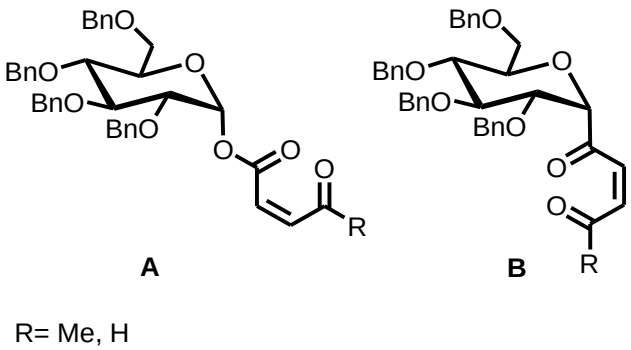
SCHEME 2.3 AN ALTERNATIVE FOR GLYCOSYL PRECURSOR

In this context, in the laboratory where this thesis has been prepared, a strategy has been developed and it is based on the easy oxidability of the furan ring. In particular, glycosyl furans have been prepared and the dye-sensitized photooxygenation has been used as key step in the synthesis of different compounds and, mainly, of glycosyl 1,4-dienones that in turn have been utilized for a large number of structural elaborations.

The photooxygenation of glycosyl furans belongs to synthetic strategies to obtain *C*-glycosides via a *C*-glycoside precursor that is subsequently modified through regio- and stereoselective reactions to obtain the desired molecule. The procedure was applied to substituted furans with monosaccharides to 5 and 6 atoms of carbon and led to

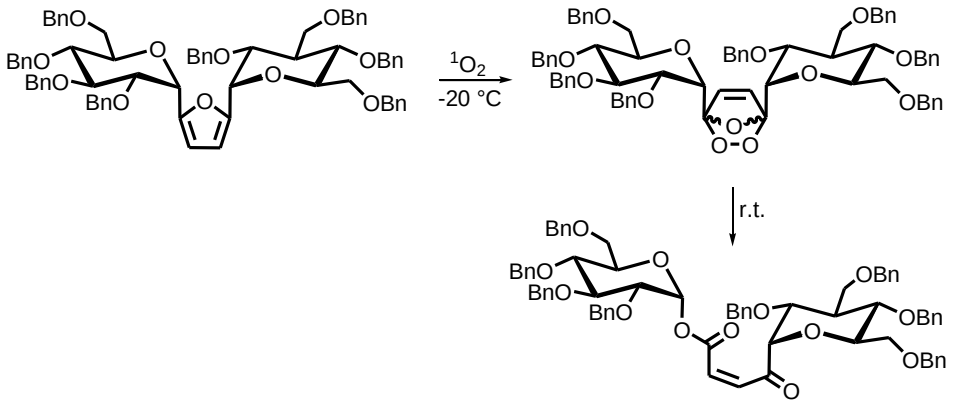
interesting results in the field of the glycoside synthesis (Cermola et al. 2004; Cermola et al. 2005; Cermola and Iesce 2006). The methodology was based on the [4+2] cycloaddition reaction of singlet oxygen to glycosyl furans as starting point and appropriate structural elaborations of the corrisponding endoperoxides. The advantages concern the possibility to synthesize different glycosyl derivatives from a single furan precursor. Furans with glycosidic residues (pentose and hexose) in 2 or 3 position were prepared and photooxygenated. When the residue of the monosaccharide is linked to the starting furan in 2 position, O-glicosides of type A are formed almost quantitatively through a Baeyer-Villiger like-rearrangement which occurs with ritention of configuration to the anomeric carbon (**SCHEME 2.4**).

Cis-C-glicosides of type **B** instead can be obtained almost quantitatively through reduction of the crude photooxygenation mixture with Et_2S at low temperature (**SCHEME 2.4**).



SCHEME 2.4 SOME PRODUCTS OF FOSC OF GLYCOSYL FURANS

Interesting results were obtained by photooxygenation conducted on 2,5-bis(glycosyl)furans (**Scheme 2.5**)(Cermola et al. 2011). These studies allowed to prepare new 1,1'-linked disaccharides separated by a functionalized spacer, structurally related to mimetics of Sialyl Lewis X (sLe^x), a tetrasaccharide involved in inflammatory responses (**FIGURE 2.3**) (Kaila and Thomas 2002; Hiruma et al.1996; Cheng et al. 2000).



SCHEME 2.5 PHOTOOXYGENATION OF 2,5-BIS(2',3',4',6'-TETRA-O-BENZYL-D-GLUCOPIRANOSYL)FURAN

During this study, useful information on the thermal rearrangement of asymmetrical 2,5-bis(glycosyl)furans was obtained. In particular it was demonstrated that *i*) the thermal rearrangement trend depends on steric factors and *ii*) the protecting groups can have an important role in this process.

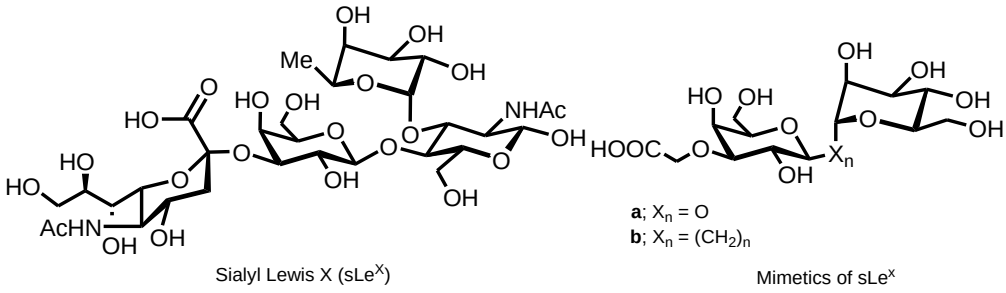
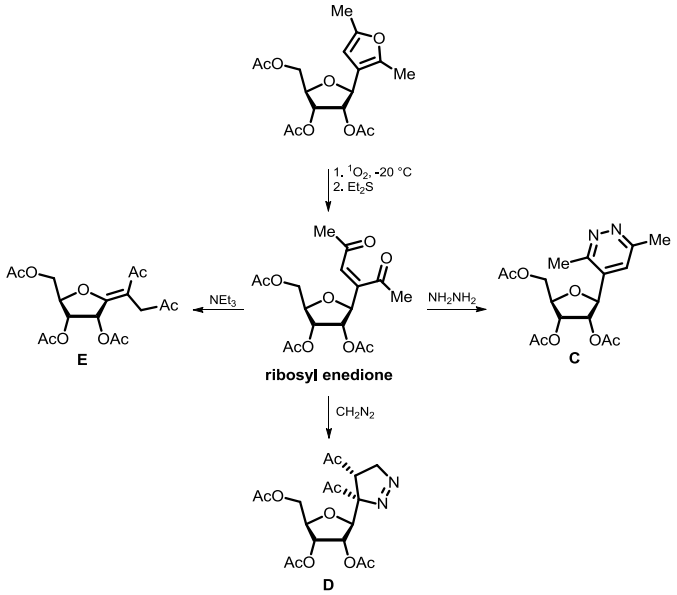


FIGURE 2.3 SIALYL LEWIS X AND MIMETICS

The use of a ribosyl 1,4-diketone, easily obtained by photooxygenation followed by Et_2S reduction provided simple procedures for novel pyridazine C-nucleoside **C** and pyrazoline C-nucleoside **D** (Cermola and Iesce 2006) and new functionalized exo-glycals **E** (Cermola and Iesce 2006) (**SCHEME 2.6**).



SCHEME 2.6 SYNTHETIC APPLICATIONS OF FOSC OF RIBOSYL FURANS

In this context part of the PhD work was focused to use opportunely substituted glycosyl furans and their corresponding endoperoxides, obtained by dye-sensitized photooxygenation, as a possible alternative to common routes to get spiroketals of monosaccharides and novel piridazine C-nucleosides. We were inspired by some results reported in the literature.

2A. ONE-POT PROCEDURE FOR NOVEL SPIROKETALS OF MONOSACCHARIDES

A spyro compound is a bicyclic compound with rings connected via a single atom, also called spiroatom. Although a wide array of ring sizes are possible, the most abundant motifs in Nature are [5.6]-, [5.5]- and [6.6] (**FIGURE 2A.1**).

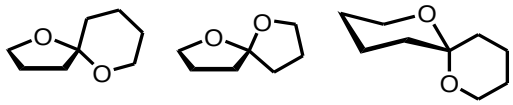
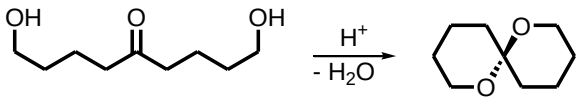


FIGURE 2A.1 EXAMPLE OF SPYROKETALS STRUCTURES

The interest towards this class of molecules is due to the spiroketal moiety represents a privileged substructure since it can be found in many simple or complex natural products characterized by important and assorted biological properties, from antibiotic to anticancer, as spongistatin 1 (Xu et al. 2011), avermectins (Davis and Green 1991), milbemycins (Wang et al. 2011).

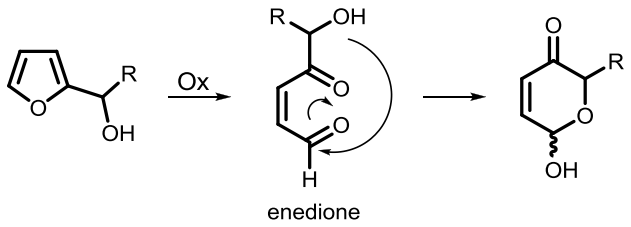
The synthetic approaches to obtain spiroketals are manifold. The most common methods involve the use of oxo-diols as precursors and spiro-cyclizations are subjected to acid-catalyzed in the presence of Lewis or Bronsted acids (**SCHEME 2A.1**) (Venkatesh and Reissig 2008; Castagnolo et al. 2007; Crimmins and O'Mahony 1989).



SCHEME 2A.1 SYNTHESIS OF SPYROKETALS BY RING CLOSURE OF OXO DIOLS

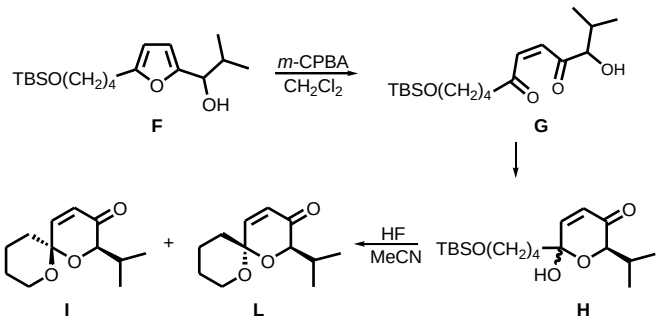
Interesting applications of the traditional method employ Achmatowicz reaction. As above reported, oxidation of a furan system with an oxidising agent, as m-CPBA, PCC, TBHP or with NBS leads to a 1,4-dicarbonylic compound. When the starting furan is a hydroxyalkyl furan, the oxidation leads to a α-hydroxy-1,4-dicarbonyl compound, that cyclizes spontaneously into a functionalized pyranone (Achmatowicz 1981)(**SCHEME**

2A.2).



SCHEME 2A.2 GENERAL MECHANISM OF ACHMATOWICZ REACTION

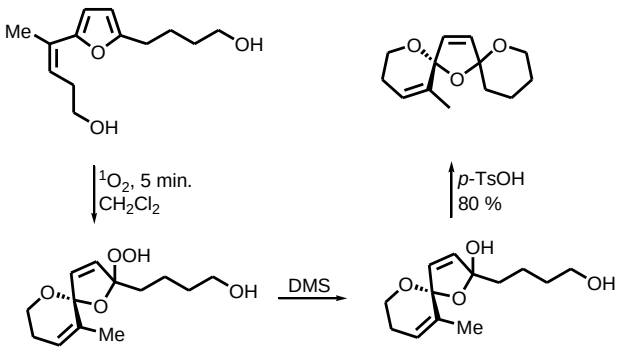
So, spiroketals **I** e **L** are obtained via acid-catalyzed cyclization of piranone **H**, in turn obtained by oxidation with *m*-chloroperbenzoic acid of the appropriately protected furyldiol **F** (**SCHEME 2A.3**).



SCHEME 2A.3 SYNTHESISOF SPIROKETALS VIA ACHMATOWICZ REACTION

The procedure was used for the preparation of functionalized spiro compounds. Their structural elaboration provided important informations in the field of antibiotics family for istance avermectine (Achmatowicz 1981).

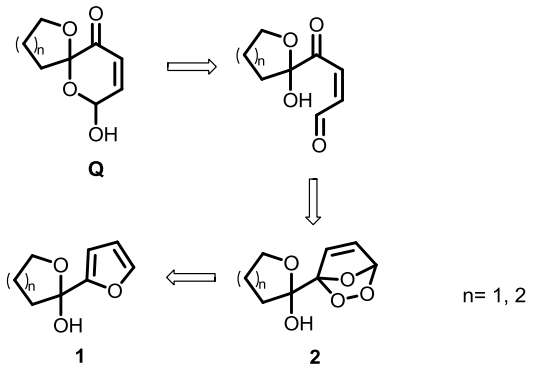
As useful alternative to the oxidation with peracids, recently spiroketals were obtained starting from 2,5-dihydroxyalkylfurans via a dye-sensitized photooxygenation followed by reduction with Et_2S and acid catalyzed cycloaddition (**SCHEME 2A. 4**) (Montagnon et al 2008).



SCHEME 2A.4 SYNTHESIS OF [5,4,5]-BIS-SPIROKETALS

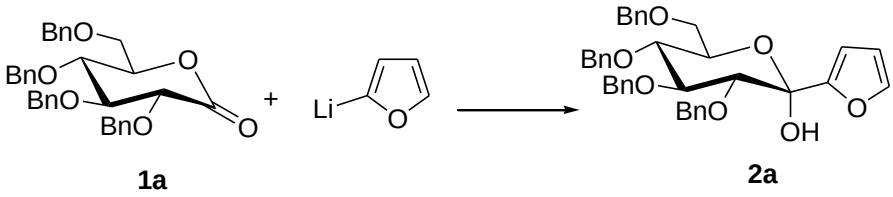
In both cases (**SCHEME 2A.3** and **SCHEME 2A.4**) the reactive intermediate is an enedione obtained by different routes. The photooxygenation followed by reduction presents numerous advantages respect to the oxidation with peracids or other oxidizing agents, due to the use of environmentally friendly oxygen, mild reaction conditions, dyes, and generally it leads to higher yields.

On the basis of these considerations the research was focused to synthetize novel spiroketals of monosaccharides using the following approach:



SCHEME 2A.5 RETROSYNTHESIS FOR [5,4,5]-BIS-SPIROKETALS

Glycosyl derivatives as **2a** were envisaged as suitably substituted starting furans; the synthetic approach to be used was reported in the literature for **2a** and utilizes a glucolactone as **1a** and furyllithium (Czernecki and Ville 1989) (**SCHEME 2A.6**).



1a **2a**

SCHEME 2A.6 SYNTHETIC APPROACH FOR SUGAR FURAN **2a**

RESULTS AND DISCUSSION:

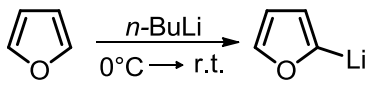
*Synthesis of Glycosyl Furans **2***

Starting 2,3,4,6-*O*-tetrabenzyl-D-glucono-1,5-lactone **1a** was obtained by Swern oxidation of commercially available 2,3,4,6-*O*-tetrabenzyl-D-glucopyranose (Overkleeft et al. 1994) (**SCHEME 2A.7**).

SCHEME 2A.7 SWERN OXIDATION

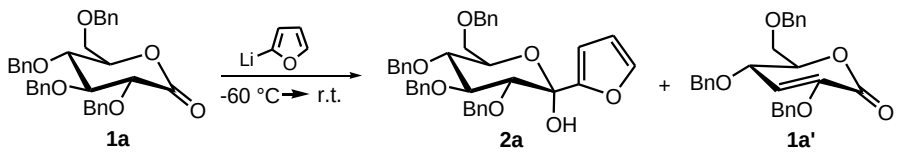
Lactone **1a** was isolated by silica gel chromatography in 95 % yield and was identified by comparison with literature data (Overkleeft et al. 1994).

2-Furyllithium was prepared by adding *n*-butyllithium to a solution of furan in dry tetrahydrofuran (THF) at 0° C and stirring the resulting solution for 4h at room temperature (**SCHEME 2A.8**).



SCHEME 2A.8 2-FURYLLITHIUM PREPARATION

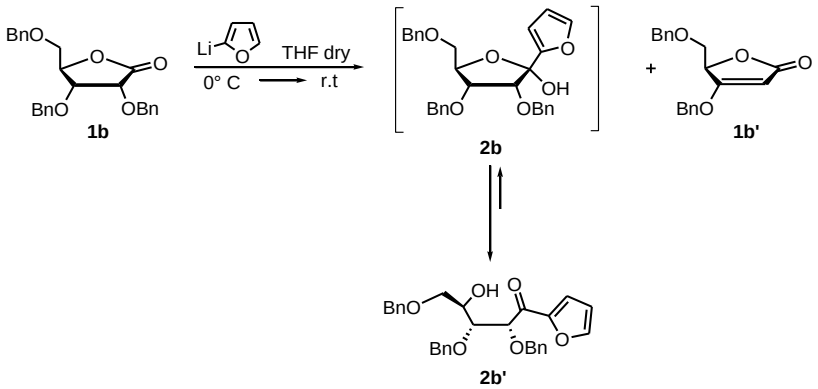
Coupling reaction between 2-furyllithium and lactone **1a** afforded compound **2a** (60 %), together with an unreported product to which, on the basis of spectroscopic NMR data and by comparison with literature data (Rosenblum and Bihovsky 1990), the structure of α,β-unsaturated lactone **1a'** was assigned (**SCHEME 2A.9**).



SCHEME 2A.9 COUPLING REACTION BETWEEN **1a** AND 2-FURYLLITHIUM

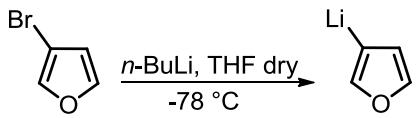
Formation of **1a'** was rationalised through an elimination side-reaction of a benzyl protecting group due to the basic behaviour of 2-furyllithium. Elimination of the benzyl protecting group is reported in the literature by using different metal bases (Rosenblum and Bihovsky 1990).

The synthetic method was then applied to commercially available 2,3,5-tri-*O*-benzyl-D-ribono-1,4-lactone **1b**. Coupling reaction with 2-furyllithium afforded the open chain form **2'b** (58%) as evidenced by ^{13}C NMR spectrum that showed the presence of a signal at 187.6 ppm, a typical value of a ketone function. Only a very little amount of the isomeric ring structure **2b** was present at the equilibrium, as evidenced by ^{1}H NMR spectrum. Silica gel chromatography afforded, as previously observed in the synthesis of **2a**, the corresponding unsaturated sugar **1b'**, which was identified by comparison of its spectral and physical data (mp 82°C) with those reported in literature (Csuk et al.1997) (**SCHEME 2A.10**).



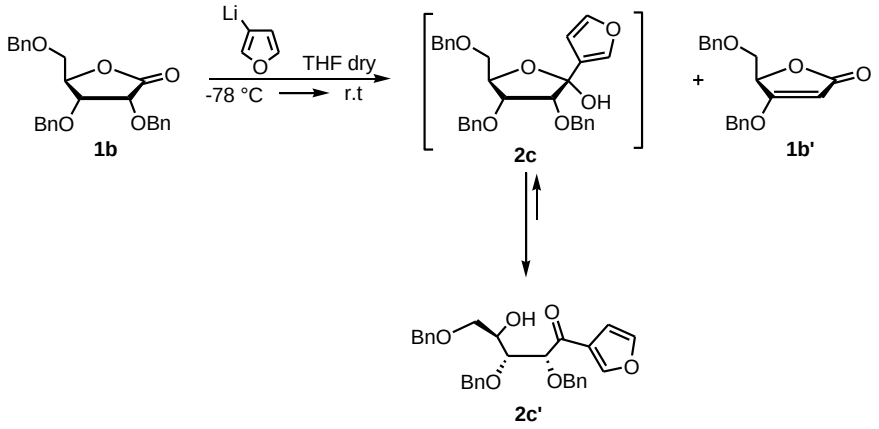
SCHEME 2A.10 SYNTHESIS OF KETAL **2b**

Subsequently, lactone **1b** was coupled with 3-furyllithium. The latter was prepared by halogen-metal exchange process from commercially available 3-bromofuran and *n*-butyllithium, as shown in **SCHEME 2A.11**.



SCHEME 2A.11 HALOGEN-METAL EXCHANGE PROCESS FOR 3-FURYLLITHIUM PREPARATION

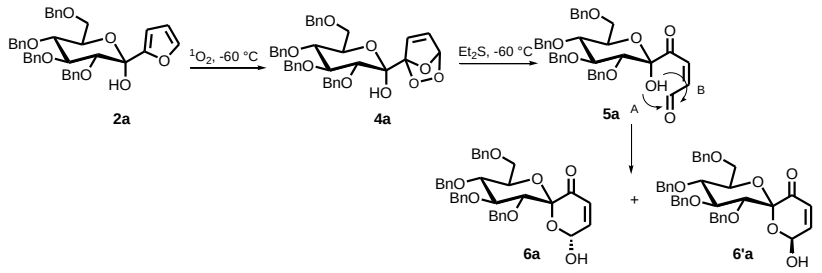
The coupling reaction was conducted at -78°C to prevent the rearrangement of 3-furyllithium to the thermodinamically more stable 2-furyllithium which starts at temperature over -40°C. Also in this case, the ketal **2'c** was isolated after silica gel chromatography (50% yield) along with elimination product **1b'** (**SCHEME 2A.12**). The acyclic structure was assigned on the basis of ^{1}H and ^{13}C NMR data.



SCHEME 2A.12 SYNTHESIS OF THE KETAL **2'c**

*Dye-Sensitized Photooxygenation of Furans **2a**-**2c** and Et_2S reduction*

The photooxygenation reactions of furan **2a** was carried out -60°C using dry dichloromethane in the presence of methylene blue as the sensitizer. The solution was irradiated with a halogen lamp while dry oxygen was bubbling through the solution. When the reaction was complete (TLC), 2 equiv. of Et_2S were added at -60°C. The mixture was maintained at -60°C for 120 min and then kept at -25 °C overnight. The day after the crude reaction was placed at r. t. and the solvent and the excess of sulfide were removed at reduced pressure. A rapid chromatography on silica gel afforded a partial separation of the two products to which, on the basis of mono- and bi-dimensional NMR spectra, structures **6a** and **6'a** were assigned (**SCHEME 2A.13**).



SCHEME 2A.13 FOSC AND REDUCTION TREATMENT OF **2a**

It is to be noted that the ^1H NMR analysis of the residue in $CDCl_3$ showed the presence of two products, in an initial molar ratio of about 1:5 (**FIGURE 2A.2**). They were in equilibrium and after 2 days the molar ratio was almost inverted (2:1) (**FIGURE 2A.3**).

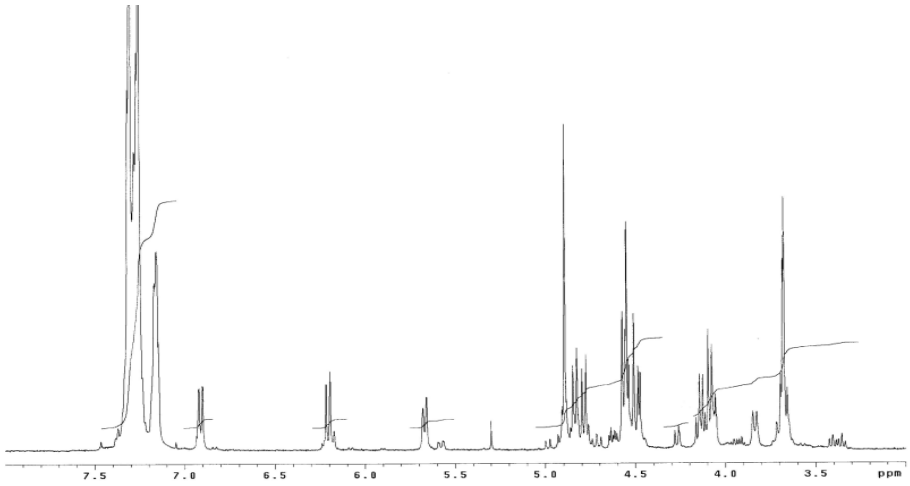


FIGURE 2A.2 EXPANDED ^1H NMR ($CDCl_3$) OF THE CRUDE PHOTOOXYGENATED CH_2Cl_2 SOLUTION OF **2a**

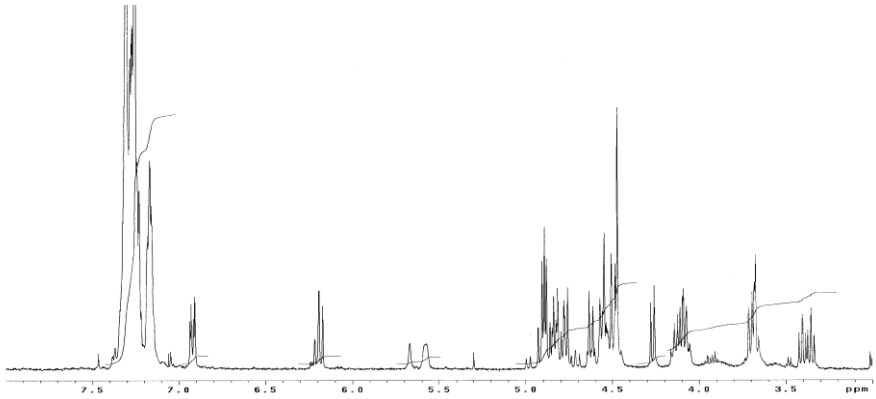


FIGURE 2A.3 EXPANDED ^{1}H NMR OF THE CRUDE PHOTOOXYGENATED MIXTURE OF **2a** AFTER 48h

The configuration α at the C- 2 of both diastereoisomers **6a** and **6'a** was tentatively assigned on the basis of thermodynamic considerations. As reported in the literature, an arrangement with both oxygens in an axial position represents a situation of maximum stability conferred by a double anomeric effect (Venkatesh and Reisseg 2008; Castagnolo et al. 2007; Crimmins and o'Mahony 1989; Deslongchamps 1983; Kirby 1983; Juaristi and Cuevas 1995) (**FIGURE 2A.4**).

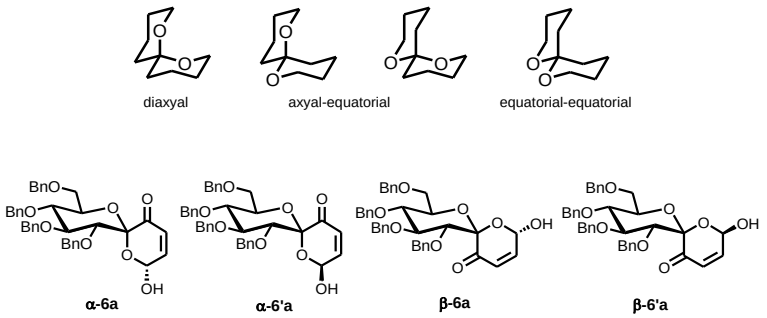
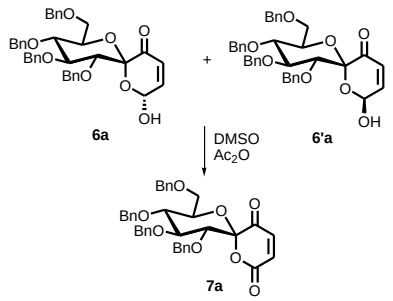


FIGURE 2A.4 POSSIBLE CONFIGURATIONS OF [6.6] SPIROKETALS

The formation of two diastereoisomeric spiro compounds is justified since the attack of the hydroxyl group to the aldehydic carbon of the enedione **5a** can take place from both sides of the plane of the unsaturated system, thus generating both configurations (**SCHEME 2A.13**).

The assignment of diastereomeric structures at the C-2 was confirmed by carrying out

a Swern oxidation on a chromatographic fraction containing the two isomers in the molar ratio of ca 1:1. The reaction led quantitatively to the expected glycosyl derivative **7a**, which was isolated and characterized spectroscopically (**SCHEME 2A.14**).



SCHEME 2A.14 SWERN OXIDATION OF THE MIXTURE OF **6a** AND **6'a**

FIGURE 2A.5 and **FIGURE 2A.6** show the ^{1}H NMR spectra of the mixture of **6a** and **6'a** before and after oxidation. Comparison of the two spectra evidenced the disappearance of the signals of the H-2 protons and the conversion of the signals relative to the protons of the unsaturated system of both diastereoisomers to signals corresponding to a single system CH=CH present in the derivative **7a**.

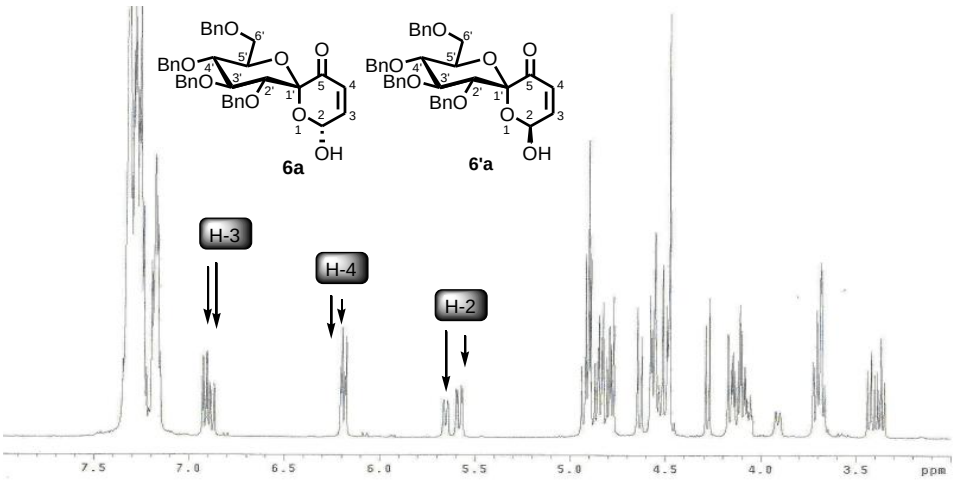


FIGURE 2A.5 ^{1}H NMR ($CDCl_3$) OF THE MIXTURE OF **6a** AND **6'a** USED FOR THE SWERN OXIDATION

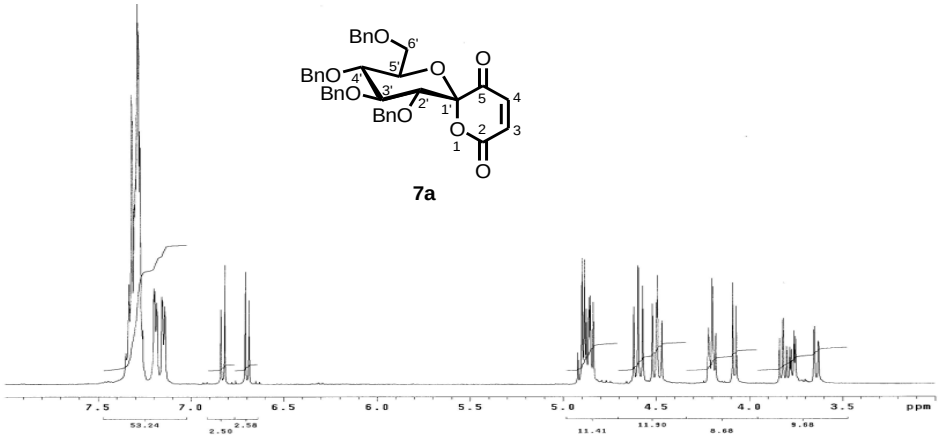


FIGURE 2A.6.5 EXPANDED ^{1}H NMR OF DERIVATE **7a**

Noesy experiments allowed to assign the structure **6a** with the (R)-configuration at the new stereocenter (C-2) to the more stable derivative which was the main product at the equilibrium. These experiments also validated the α-configuration at the sugar-ring of both spiroketals, that is probably ensured by a thermodynamic control since two anomeric effects are in operation in a diaxial arrangement (Deslongchamps 1983), as previously reported in similar cases (**FIGURE 2A.7**).

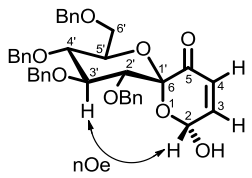
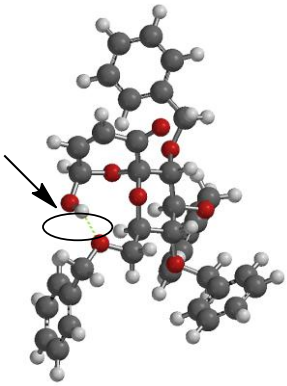


FIGURE 2A.7 NOE EFFECT BETWEEN H-2 AND H-3'

In particular, there was a strong NOE effect between H-2 and H-3' protons of spiro ketal isomer present in higher amount at the equilibrium at r.t. (hence the thermodynamically more stable isomer), thus indicating for this compound structure **6a**. Theoretical calculations*performed on both diastereoisomers were in agreement with the results of NOESY experiments suggesting that spiroketal **6a** is stabilized by an intramolecular hydrogen bond between the new OH group at C-2 and the sugar-ring

oxygen, which is not feasible for **6a'** (**FIGURE 2A.8**). Calculations found that (2R)-**6a** is more stable than (2S)-**6'a** of 3.7 kcal/mol.



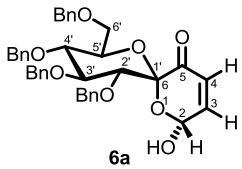
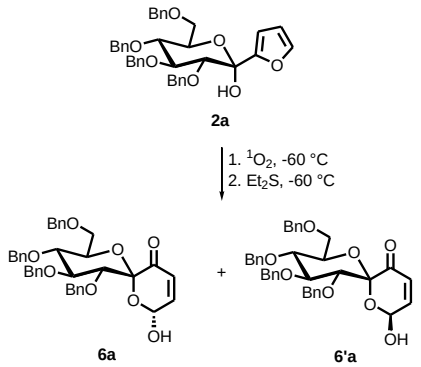


FIGURE 2A.8 HYDROGEN BOND IN SPIRO 6a

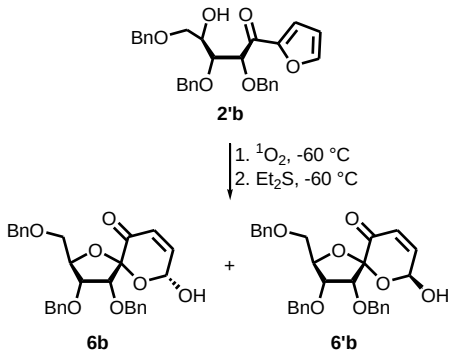
The synthesis of spiro ketals **6a** and **6'a** can be carried out in a one-pot route with total yield 80% as follows:



SCHEME 2A.15 ONE-POT SYNTHESIS OF SPIROKETALA **6a** AND **6'a**

Despite the open form, we decided to use also the ribofuranosyl furan **2'b**, that was photooxygenated and reduced as **2a**. After removal of the solvent under reduced pressure, the residue was analyzed by NMR spectroscopy showing the formation of two diastereomeric products that were obtained in 68% total yield.

Theoretical calculations were performed by SSPARTAN '08 Quantum Mechanics Program. The geometric optimizations (method: HF/3-21G) were performed starting from minimized conformers (conformational analysis by MMFF-molecular mechanics). Energies were calculated running single points by B3LYP/6.31G method.



SCHEME 2A.16 ONE-POT SYNTHESIS OF SPIROKETALA **6b** AND **6'b**

The proton spectrum immediately after solvent removal (**FIGURE 2A.9**) shows the presence of the two products in a molar ratio of 1:7 with a pattern of signals of a system CH=CH-CH-O in the δ range 5.5-7.0, similar to that observed for spiroketals **6a** and **6'a**.

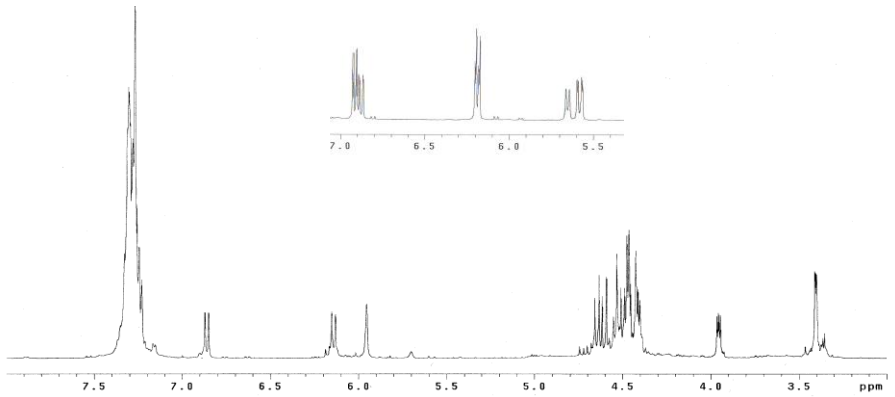


FIGURE 2A.9 EXPANDED ^{1}HNMR OF **6b** AND **6'b**

Also in this case the ratio of the two products changed over time and after 12h they were present approximately in the molar ratio of ca 5:1 (**FIGURE 2A.10**).

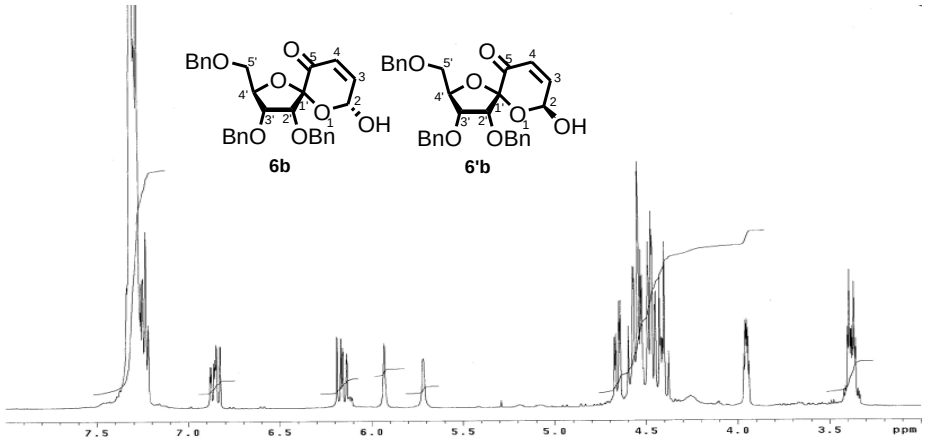
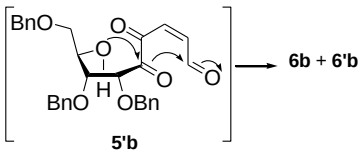


FIGURE 2D.10 ^{1}HNMR SPECTRUM OF **6b** and **6'b** AFTER 12 h IN $CDCl_3$

To these compounds mono- and bi-dimensional spectral data allowed to assign structures **6b** and **6'b**, reported in **SCHEME 2A.16**.

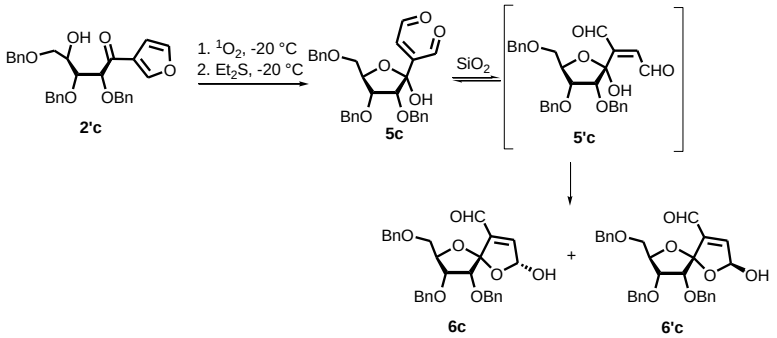
Although the cycloaddition reaction of $^1O_2$ occurred on acyclic derivative **2'b**, it is likely that the enedione **5'b** obtained by reduction in situ of the corresponding endoperoxide **4'b** undergoes a double cyclizations as follows:



SCHEME 2A.17 DOUBLE CYCLIZATION OF THE ENEDIONE **5'b**

Unfortunately, NOESY experiments conducted to assign configurations to the new chiral center C-2, failed. However, the structure **6b** was tentatively assigned to the diastereoisomer present as the main product at the equilibrium on the basis of theoretical calculations* performed on both stereoisomers. These calculations found a lower energy for **6b** than for **6'b** of 2.3 kcal/mol. As observed for **6a**, the calculated structure for **6b** showed the presence of an intramolecular hydrogen bond between the OH and the sugar-ring oxygen.

Finally, the procedure was applied to the sugar-furan **2'c**. As expected, the complete stereoselectivity of the reduction pathway provided the α,β-unsaturated compound **5c,** which presents an unsuitable configuration for cyclization. Anyway, silica gel chromatography promoted an acid-catalyzed isomerization into the enedione **5'c** which quickly cyclized into the new spiroketals **6c** and **6'c** (molar ratio 1:2, overall yields 25%) (**SCHEME 2A.18**).



SCHEME 2A.18 SYNTHESIS OF **6c** AND **6'c**

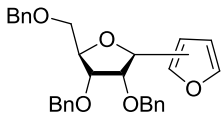
Also in this case NOESY experiments have not allowed to assign the configuration to the two diastereoisomers. As suggested by theoretical calculation*, to the main product the structure (2S)-**6'c** was tentatively assigned which was more stable than (2R)-**6c** of 2.4 Kcal/mol and showed a hydrogen bond between the -OH at C-2 and the oxygen at C-2' of the sugar ring* as already observed for **6a**/**6'a** and **6b**/**6'b**.

Theoretical calculations were performed by SSPARTAN '08 Quantum Mechanics Program. The geometric optimizations (method: HF/3-21G) were performed starting from minimized conformers (conformational analysis by MMFF-molecular mechanics). Energies were calculated running single points by B3LYP/6.31G method.

2B. ONE-POT PROCEDURE FOR 1,2-PYRIDAZINE C-NUCLEOSIDES

RESULTS AND DISCUSSION:

The nucleoside nature of ribofuranosyl furans **2b** and **2c** induced us to explore further applications of sugar furans and the dye-sensitized photooxygenation in order to obtain novel C-nucleosides, in particular novel pyridazine C-nucleosides less substituted than previous reported compound (Cermola and Iesce 2006). For this purpose the suitable novel furans **3** were prepared.

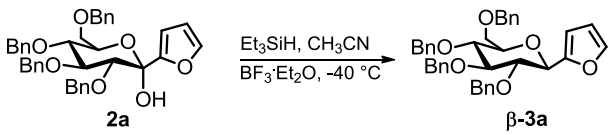


3

*Preparation of starting β-Glycosyl Furans **3***

The procedure employed was a stereoselective reduction of furans **2** with triethylsilane (Et_3SiH) and boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$) as promoter that was previously described for furan **2a** (Czernecki and Ville 1989).

To verify the feasibility, the reduction was firstly performed starting from **2a** by using the reagents under stirring at -40 °C for 1h (**SCHEME 2B. 1**). The resulting *C*-glycoside β-**3a** was isolated in 64% yield and identified by comparison with NMR data reported in literature(Czernecki et al.1989).



SCHEME 2B.1 SYNTHESIS OF**3a**

The stereoselective step of this route leads only to β-glicoside, and this should be due to the anomeric effect that stabilizes the carbocationic intermediate, favouring hydride

attack at α-face (**FIGURE 2B. 1**).

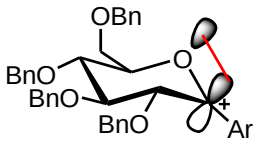
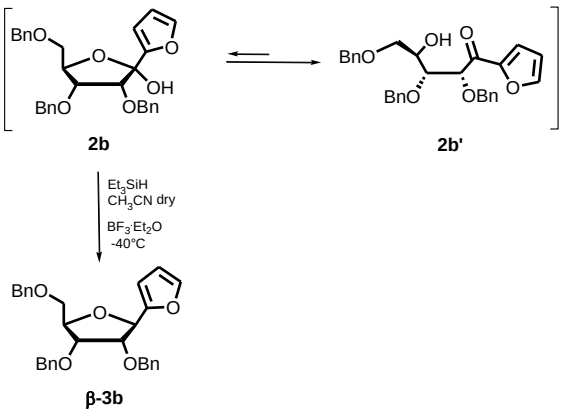


FIGURE 2B.1 CARBOCATIONIC INTERMEDIATE STABILIZED BY ANOMERIC EFFECT

Reduction of **2b/2'b** was conducted in the same condition as above reported for **2a** but required a longer reaction time (4h at -40°C and overnight at rt) owing to the main presence of the open-chain product **2b'** (**SCHEME 2B.2**).



SCHEME 2B. 2 SYNTHESIS OF GLYCOSYL FURAN β-**3b**

Although the ^{1}H-NMR spectrum of the crude reaction mixture showed the presence of the only product β-**3b** (**FIGURE 2B.2**), considerable loss of material occurred during chromatography, according to literature data (Macdonald et al. 1988). Compound β-**3b** was isolated by silica gel flash chromatography in 35% yield.

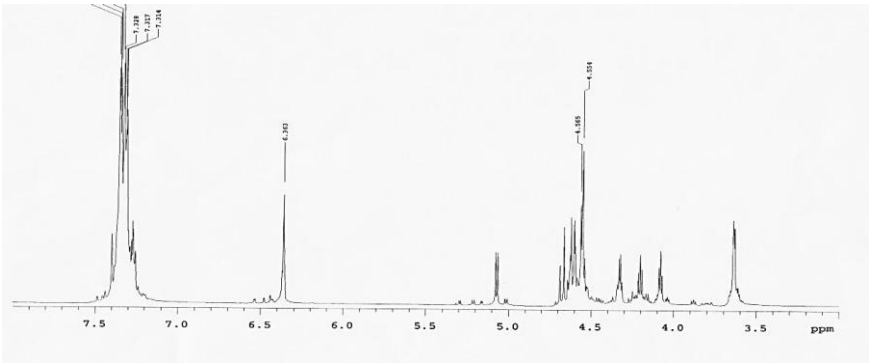


FIGURE 2B. 2 ^{1}H NMR OF THE CRUDE REACTION MIXTURE OF β-**3b**

The 2-(β-ribofuranosyl)furan β-**3b** was fully characterized by mono- and bidimensional NMR data and, in particular, the β stereochemistry at C-1 was confirmed by NOESY experiment which evidenced the *cis* spatial relationship between H-1' and H-4' protons (**FIGURE 2B. 3**).

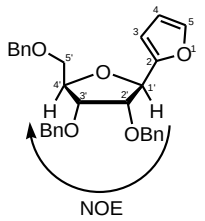
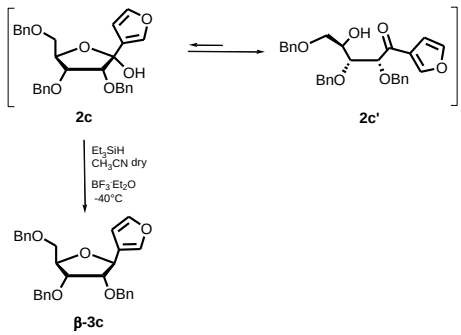


FIGURE 2B.3 NOE EFFECT BETWEEN H-1' AND H-4'

Subsequently, the same procedure was used to obtain 3-(ribofuranosyl) furan β-**3c** that was recovered by chromatography in low yield (30% yield) likely due to considerable loss of product by the adsorbent, as experimented for β-**3b** (**SCHEME 2B.3**).



SCHEME 2B. 3 SYNTHESIS OF GLYCOSYL FURAN β-**3c**

The β-configuration was assigned by NOESY experiment that showed NOE effect between H-1' and H-4' (**FIGURE 2B.4**).

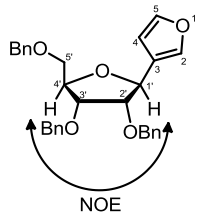
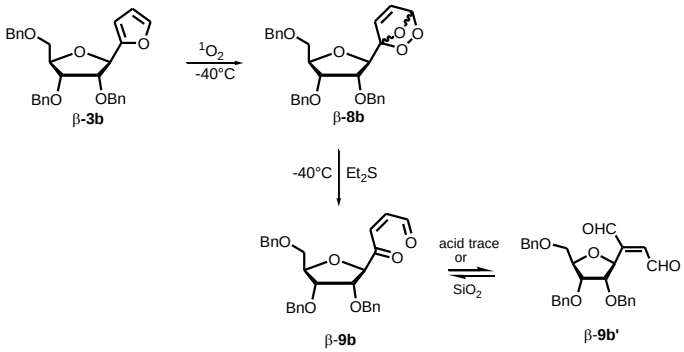


FIGURE 2B.4 NOE EFFECT BETWEEN H-1' AND H-4'

Synthesis of 1,2-Pyridazine C-Nucleosides

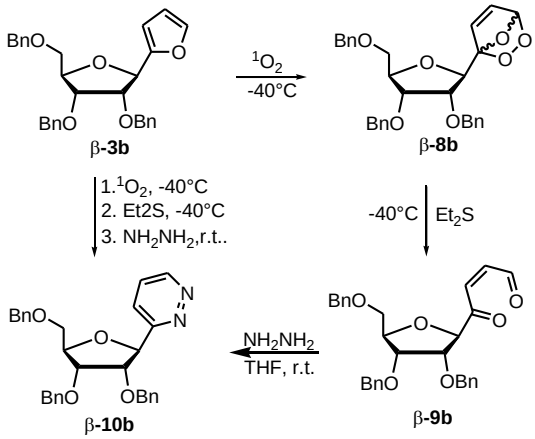
The 2-(β-ribofuranosyl)furan β-**3b** was photooxygenated as described before. When the photooxygenation was complete (TLC), 2 equiv. of Et_2S were added at -40 °C. The mixture was maintained at -40°C for 120 min and then was kept at -25 °C overnight. The low temperature was needed because endoperoxides of 2-(glycosyl)furans are thermally unstable and rearrange rapidly from C- to O-glycosides (Cermola et al. 2004, 2005). Then, the ^{1}H NMR experiment of an aliquot of the mixture showed the α,β-unsaturated-1,4-dicarbonyl glycoside β-**9b**. This was unstable in $CDCl_3$ and isomerized into more stable *trans*-isomer β-**9b'** (**SCHEME 2B.4**). Attempts to purify both *cis*-β-**9b** and *trans*-β-**9b'** failed since they give only polymeric material by chromatography.



SCHEME 2B.4 ENDOPEROXIDES β-**8b** REDUCTION

Attempt to employ the previous procedure (addition of hydrazine chloridrate to a methanolic solution of the crude enone as previously reported (Cermola and Iesce 2006) failed evidently due to conformationally unstability of compound β-**9b** that which rapidly isomerized into *trans*-isomer β-**9b'** that is inadeguate to cyclize with hydrazine.

The expected 3-(β-ribofuranosyl)-pyridazine β-**10b** was however obtained by addition to the crude reduction mixture of a 2M hydrazine solution in THF (**SCHEME 2B.5**).

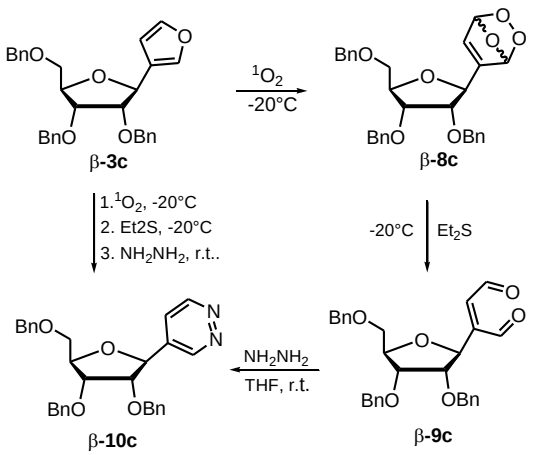


SCHEME 2B.5 ONE-POT SYNTHESIS OF PYRIDAZINE β-**10b**

The ^{1}H NMR spectrum showed the presence of only one product that was purified by silica gel chromatography. To this product mono- and two-dimensional NMR studies

assigned the 3-(β-ribofuranosyl)-pyridazine structure β-**10b**. The β-configuration at C-1' was confirmed by NOESY experiments which evidenced a *cis*-spacial correlation between the H-1' and the H-4' of the sugar ring. Finally, the synthesis of **10b** was realized through a one-pot procedure, as shown in **SCHEME 2B.5**.

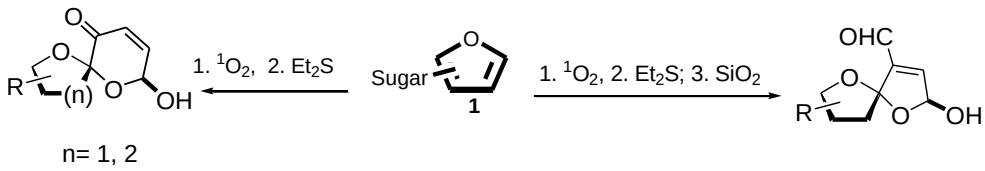
The one-pot procedure was then applied to 3-(β-ribofuranosyl)furan β-**3c**. In this case the photooxygenation was performed at -20°C owing to higher stability of the corresponding endoperoxide. The reaction was checked by TLC and it was complete after approximately 90 min. Then 2 equiv. of Et_2S were added and the mixture was kept at -20 °C overnight. The ^1H NMR spectrum of the crude mixture showed the presence of the glycosyl enedione β-**9c**. In contrast to enedione β-**9b**, this was configurationally stable. Cyclization by addition to the crude β-**9c**, of a 2M hydrazine solution in THF (**SCHEME 2B.6**). led to the corresponding 4-(β-ribofuranosyl)pyridazine β-**10c** that was characterized by mono- and bidimensional NMR spectroscopy. The β-configuration at C-1' was confirmed by NOESY experiments.



SCHEME 2B.6 ONE-POT SYNTHESIS OF PYRIDAZINE β-**10c**

2C. CONCLUSION

In this part of the work two interesting applications of furans have been pointed out in the field of C-glycosides and C-nucleosides. In particular, a one-pot synthetic procedure for novel spiroketals of monosaccharides has been developed starting from suitably prepared glycosyl furans using the photooxygenation as a key reaction.



SCHEME 2C.1 ONE-POT SYNTHESIS OF SPIROKETALS OF MONOSACCHARIDES

The procedure has led successfully to novel spiroketals of monosaccharides with [5.5], [6.5] and [6.6] structtures. These structures are among the most widespread in nature, often present in many bioactive derivates. The method represents a valid alternative, for the good yields and the mild reaction conditions, to other methods reported in the literature that require acidic oxidation conditions or the use of organometallic compounds. The novel spiroketals are highly functionalized in the aglyconic part and are susceptible to further reactions suggesting the possibility of expanding the number of spiroketals of pharmacological interest obtainable starting from one glycosyl furan.

Noteworthy are the novel β-ribofuranosyl furans **3b** and **3c**, that by photooxygenation followed by reduction of the corresponding endoperoxides afford 1,4-dicarbonyl-α,β-unsaturated derivatives which have been tested in cyclization with hydrazine. The latter reaction provides novel pyridazine C-nucleosides β-**10** for which a one-pot procedure has been developed (**FIGURE 2C.1**) . The interest for these derivatives is due to the pyridazine nucleus and its 3-oxo derivatives have been recognized as versatile pharmacophores (Elnagdi et al. 2009). This key subunit is constituted in many biologically active substances with a broad range of biological and pharmaceutical

activities including antibacterial and antifungal activities, 5-lipoxygenase inhibitors and inhibitors of interleukin 1 beta-production.

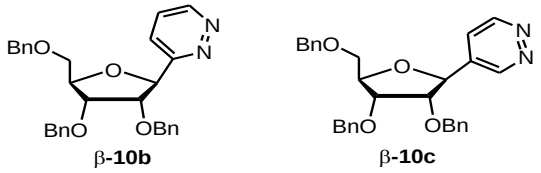


FIGURE 2C.1 PYRIDAZINE C-NUCLEOSIDES β-**10** SYNTHETIZED

2D. EXPERIMENTAL SECTION

Material and Methods: Nuclear magnetic resonance (NMR) spectra were recorded at 500 MHz for [^{1}H] and 125 MHz for [^{13}C] on a Fourier Transform NMR Varian 500 Unity Inova spectrometer. The carbon multiplicity was evidenced by DEPT experiments. The proton couplings were evidenced by ^{1}H-^{1}H COSY experiments. The heteronuclear chemical shift correlations were determined by HMQC (optimized for $^{1}J_{HC}$,140 Hz) and HMBC (optimized for $^{1}J_{HC}$,8 Hz) pulse sequences. ^{1}H–^{1}H proximities through space within a molecule were determined by NOESY. Analytical TLC was performed on precoated silica gel plates (Macherey-Nagel) with 0.2 mm film thickness. Spots were visualized by UV light and by spraying with EtOH-H_2SO_4 (95:5) followed by heating for 5 min at 110 °C. Column chromatography was performed on silica gel (Macherey-Nagel). Furan (Aldrich), 3-bromofuran (Aldrich), acetic anhydride (Aldrich), dry dimethylsulfoxide (DMSO) (Aldrich), 2,3,4,6-tetra-O-benzyl-D-glucopyranose (Aldrich), 2,3,5-tri-O-benzyl-D-ribono-1,4-lactone (Carbosynth), 1.6 M *n*-BuLi solution in hexane (Aldrich), dry tetrahydorfuran (THF) (Aldrich), diethyl sulfide (Aldrich), triethylsilane (Aldrich) and the etherate boron trifluoride ($BF_3{\cdot}Et_2O$) (Fluka) were commercially available.

General procedure of the dye-sensitized photooxygenation: A 0.02 M solution of starting furan (0.25mmol) in dry CH_2Cl_2 was irradiated at the appropriate temperature with a halogen lamp (650 W) in the presence of methylene blue as sensitizer (MB, $1x10^{-3}$ mmol), while dry oxygen was bubbled through the solution. The progress of each reaction was checked by periodically monitoring the disappearance of furan by TLC, or by ^{1}H NMR spectroscopy.

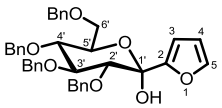
Experimental-Part 2A

Synthesis of lactone 1a: 540 mg (1mmol) of 2,3,4,6-tetra-O-benzyl-D-glucopyranose was dissolved in dry DMSO (2.7mL). Then, acetic anhydride (1.6mL) was added and the resulting solution was stirred at r.t. under argon atmosphere. After *ca* 12 h the reaction was quenched by adding H_2O (*ca*. 10 mL). The organic layer was extracted

with $CHCl_3$, washed with H_2O (5 x 10mL), dried on Na_2SO_4 and filtered. Then, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate 7:3 v/v) affording lactone **1a** (Overkleeft et al.1994) as oil in 95 % yield.

2-Furyllithium: To a solution of furan (68 mg, 1mmol) in dry THF (1.5mL), *n*-BuLi hexane solution 1.6M (0.75mL, 1.2mmol) was added at 0°C. The reaction mixture was stirred at r.t. for 4 h under argon atmosphere before use.

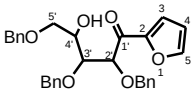
***Synthesis of 2a*:** Lactone **1a** (1.08 g, 2mmol) was dissolved in 5 mL of dry THF, and the resulting solution was cooled to -50°C under argon. A fresh 2-furyllithium solution was then added, and the mixture was stirred for 4 h at -50°C. The temperature was then allowed to rise to r.t. while the mixture was further stirred overnight. Then, the reaction was quenched by adding a NH_4Cl saturated aqueous solution. The organic layer was extracted with ether, drying over Na_2SO_4 and filtered, the solvent was evaporated under reduce pressure. The crude was chromatographed on silica gel (*n*-hexane/ethyl acetate 7:3 v/v) yielding **2a** (60 % yield)as yellow oil (Cermola et al.2014).



2a

2a: oil; **^{1}H NMR** ($CDCl_3$)δ3.70-3.84 (m, 3H, H-6'$_A$, H-6'$_B$ and H-5'), 3.92 (d, 1 H, *J*= 7.5 Hz, H-2'), 4.02 (dd, 1H, *J*= 6.0, 3.2 Hz, H-4'), 4.06 (dd, 1H, *J*= 7.5, 3.2 Hz, H-3'), 4.48 (d, 1H, *J*= 10.5Hz, CH of Bn), 4.52 (d, 1 H, *J*= 10.8 Hz, CH of Bn), 4.61 (d, 1 H, *J*= 8.5 Hz, CH of Bn), 4.63 (d, 1 H, *J*= 10.5 Hz, CH of Bn), 4.69 (s, 2 H, CH_2 of Bn), 4.85 (d, 1H, *J*= 10.8 Hz, CH of Bn), 4.89 (d, 1H, *J*= 8.5 Hz, CH of Bn), 6.41 (dd, 1H, *J*=3.5, 1.9 Hz, H-4), 6.56 (d, 1 H, *J*= 3.5Hz, H-3), 7.21-7.42 (m, 20H, 4 x Ph), 7.43 (d, 1H, *J*= 1.9Hz, H-5); **^{13}C NMR** δ 68.6 (t), 72.3 (d), 73.3 (t), 74.9 (t), 75.0 (d), 75.6 (t), 77.9 (d), 82.5 (t), 82.9 (d), 94.8 (s), 108.2 (d), 110.6 (d), 127.5 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.2 (d), 128.3 (d), 128.4 (d), 137.5 (s), 138.2 (s), 138.3 (s), 138.6 (s), 142.4 (d), 153.8 (s).

Synthesis of 2'b: furyllithium solution kept at -60°C, lactone **1b**(418mg, 1mmol) previously dissolved in 2.4mL of dry THF was added and the resulting mixture was stirred under argon athmosphere at -60°C for 4h. Then the temperature was allowed to rise to r.t. while the mixture was further stirred overnight. Then, the reaction was quenched by adding a saturated aqueous solution of NH_4Cl. The organic layer was extracted with ether (3x30mL), drying over Na_2SO_4 and filtered, the solvent was evaporated under reduce pressure. The crude was chromatographed on silica gel (*n*-hexane/ether 1:1 v/v) yielding **2b**(58% yield) as yellow oil (Cermola et al. 2014).



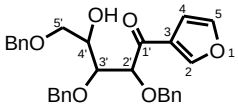
2b

2b: oil; **IR** ($CHCl_3$) ν 3432, 1680, 1600, 1173 cm^{-1}; **^{1}H NMR** ($CDCl_3$)δ3.62 (m, 2H, H-5'$_{AB}$), 4.06 (dd, *J*= 6.6, 4.9Hz, 1H, H-3'), 4.10 (m, 1H, H-4'), 4.50-4.54 (m, 5H, OH and CH_2 of Bn), 4.59 (d, *J*= 11.5 Hz, 1H, CH of Bn), 4.70 (d, *J*= 11.5Hz, 1H, CH of Bn), 4.82 (d, *J*= 4.9 Hz, 1H, H-2'), 6.49 (dd, *J*= 3.3, 1.3Hz, 1H, H-4), 7.08-7.34 (m, 15H, 3 x Ph), 7.35 (d, *J*= 3.3 Hz, 1H, H-3), 7.59 (d, *J*= 1.3 Hz, 1H, H-5); **^{13}C NMR** ($CDCl_3$) δ 70.5 (d), 70.7 (t), 72.8 (t), 73.4 (t), 80.5 (d), 81.6 (d), 112.2 (d), 119.7 (d), 127.6 (d), 127.8 (d), 128.0 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.4 (d), 137.1 (s), 137.5 (s), 138.0 (s), 146.8 (d), 151.9 (s), 187.6 (s); **Anal. calcd**. for $C_{30}H_{30}O_6$: C, 74.06; H, 6.21. **Found**: C, 74.01; H, 6.02.

3-Furyllithium: A solution of 3-bromofuran (146mg, 1mmol) in dry THF (1.5 mL) was kept at -78°C. After 10 min a *n*-BuLi 1.6 M solution (0.75mL, 1.2mmol) was added and the resulting solution was stirred at -78°C for 4 h under argon atmosphere before use.

Synthesis of 2c **:** 3-Furyllithium solution kept at -78°C, lactone **1b** (418mg, 1mmol) previously dissolved in 2.4mL of dry THF was added and the resulting mixture was stirred under argon atmosphere at -60°C for 4h. Then the temperature was allowed to rise to r.t. while the mixture was further stirred overnight. Then, the reaction was quenched by adding a saturated aqueous solution of NH_4Cl (10mL). The organic layer

was extracted with ether (3x30mL), drying over Na_2SO_4 and filtered, then the solvent was evaporated under reduced pressure. The crude was chromatographed on silica gel (*n*-hexane/ether 7:3 v/v) yielding **2c**(50 % yield)as yellow oil(Cermola et al.2014).

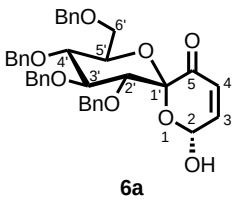


2c

2'c: oil; **IR** ($CHCl_3$) ν 3416, 1685, 1601, 1180 cm^{-1};**^{1}H NMR**($CDCl_3$)δ 2.66 (d, *J*= 4.9 Hz, 1H, OH), 3.60 (m, 2H, H-5'$_{AB}$), 4.03 (m, 2H, H-3' and H-4'), 4.45-4.70 (m, 7H, H-2' and CH of Bn), 6.84 (d, *J*= 1.1 Hz, 1H, H-4), 7.10-7.33 (m, 15H, 3xPh), 7.38 (d, *J*= 1.1Hz, 1H, H-5), 8.23 (s, 1H, H-2);**^{13}C NMR** ($CDCl_3$) δ 70.2 (d), 70.6 (t), 73.2 (t), 73.4 (t), 73.6 (d), 81.1 (d), 84.4 (d) 109.2 (d), 125.8 (s), 127.7 (d), 127.8 (d), 127.9 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.4 (d), 128.5 (d), 137.0 (s), 137.5 (s), 137.9 (s), 143.1 (d), 149.3 (d), 195.3 (s); **Anal. calcd**. for $C_{30}H_{30}O_6$: C, 74.06; H, 6.21. **Found**: C, 73.90; H, 6.08.

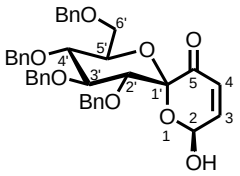
Fosc of furans 2 followed by reduction

Synthesis of spiroketals 6a and 6'a: A 0.02M solution of **2a** in dry CH_2Cl_2 was irradiated at -60°C with a halogen lamp (650W) in the presence of methylene blue as sensitizer sensitizer (MB, 1x10^{-3}mmol), while dry oxygen was bubbled through the solution. The progress of each reaction was checked by periodically monitoring the disappearance of furan by TLC. When the photooxygenation reaction was complete (*ca.* 90 min), 2 equiv. of Et_2S was added to the crude solution at -60°C. After 2h the crude solution was kept at -25°C overnight. Then, the solvent and the Et_2S excess were removed under reduced pressure, and the silica gel chromatography (*n*-hexane/ethyl acetate 7/:3 v/v) afforded spiroketals 6a and 6'a with 80% yield.



6a

6a: oil; **^{1}H NMR** ($CDCl_3$) δ = 3.68(m, 3H, H-6'$_A$, H-6'$_B$ e H-4), 3.85 (d, *J*= 10.8Hz, 1H, OH), 4.04-4.17 (m, 3H, H-2', H-3' e H-5'), 4.47-4.57 (m, 4H, CH_2 del Bn), 4.79 (d, *J*= 10.4 Hz, 1 H, CH del Bn), 4.84 (d, *J*= 10.9Hz, 1H, CH del Bn), 4.90 (s, 2H, CH_2 del Bn), 5.65 (bd, *J*= 10.8Hz, 1H, H-2), 6.19 (dd, *J*= 10.4, 1.2Hz, 1H, H-4), 6.87 (dd, *J*= 10.4, 1.6Hz, 1H, H-3), 7.15-7.38 (m, 20H, 4xPh); **^{13}C NMR** ($CDCl_3$) δ = 68.5 (t), 73.4 (t), 74.0 (t), 75.0 (d), 75.7 (t), 75.9 (t), 78.0 (d), 79.5 (d), 82.6 (d), 87.7 (d), 98.3 (s), 127.0 (d), 127.7 (d), 127.8 (d), 128.0 (d), 128.3 (d), 128.4 (d), 137.3 (s), 137.9 (s), 138.1 (s), 138.4 (s), 147.9 (d), 188.6 (s).



6'a

6'a: oil; **^{1}H NMR** ($CDCl_3$) δ = 3.36 (t, *J*= 9.3 Hz, 1H, H-6$_A$'), 3.41 (dd, *J*=10.4, 9.3Hz, 1H, H-4'), 3.71 (dd, *J*= 9.3, 1.6Hz, 1H, H-6$_B$'), 4.09 (m, 2H, H-3' e OH), 4.27 (d, *J*= 9.8 Hz, 1H, H-2'), 4.48 (s, 2H, CH_2 del Bn), 4.50 (d, *J*= 11.5Hz, 1H, CH del Bn), 4.55 (m, 1H, H-5'), 4.63 (d, *J*= 10.9Hz, 1H, CH del Bn), 4.78 (d, *J*= 10.9Hz, 1H, CH del Bn), 4.83 (d, *J*= 10.9 Hz, 1 H, CH del Bn), 4.90 (m, 2H, CH_2 del Bn), 5.58 (dd, *J*=12.7, 3.3Hz, 1H, H-2), 6.18 (d, *J*= 10.3Hz, 1H, H-4), 6.92 (dd, *J*=10.3, 3.3Hz, 1H, H-3), 7.15-7.38 (m, 20H, 4xPh); **^{13}C NMR** ($CDCl_3$) δ =69.1 (t), 71.9 (d), 73.4 (t), 75.0 (t), 75.5 (t), 75.8 (t), 78.4 (d), 78.5 (d), 83.2 (d), 88.8 (d), 97.7 (s), 124.8 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.2 (d), 128.4 (d), 137.4 (s), 137.7 (s), 138.0 (s), 138.4 (s), 145.7 (d), 188.7 (s).

Synthesis of spiroketals 6b and 6'b: A 0.02 M solution of **2b** in 25mL di CH_2Cl_2 anidro was photooxygenated as reported for furan 2a. When the photooxygenation reaction was complete (ca. 90 min), 2 equiv. of Et_2S was added to the crude solution at -60°C. After 2 h the crude solution was kept at -25°C overnight. Then, the solvent and the Et_2S excess were removed under reduced pressure, and the silica gel chromatography (n-hexane/ethyl acetate 3/:7 v/v) afforded spiroketal **6b** and a fraction with **6'b** in mixture with 6b(ca 2:1) . Yiels 68 %

6b (in mixture with **6'b** in *ca*. 1:1 molar ratio) :**^{1}H NMR**($CDCl_3$) (selected signals) δ 4.26 (bs, 1H, OH), 5.72 (d, *J*= 2.7 Hz,1H, H-2), 6.18 (d, *J*= 10.4, 1H, H-4), 6.88 (dd, *J*= 10.4, 2.7Hz, 1H, H-3); **^{13}C NMR** ($CDCl_3$) (selected signals) δ 69.6 (t), 72.5 (t), 73.0 (t), 73.4 (t), 76.5 (d), 77.3 (d), 83.7 (d), 88.8 (d), 101.8 (s), 125.6 (d), 127.6 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.3 (d), 128.4 (d), 137.5 (s), 137.7 (s), 137.8 (s), 146.3 (d), 188.4 (s).

6'b: **IR** ($CHCl_3$) ν 3420, 1693, 1645, 1455, 1280 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ 3.40 (dd, 2H, H-5'$_{AB}$), 3.96 (dd, *J*=6.6, 3.8Hz, 1H, H-3'), 4.40-4.55 (m, 5H, H-2', H-4', OH, and CH of Bn), 4.60 (d, *J*=12.0Hz, 1H, CH of Bn), 4.64 (d, *J*=12.6Hz, 1H, CH of Bn), 5.94 (bs, 1H, H-2), 6.14 (dd, *J*=10.4, 1.1Hz, 1H, H-4), 6.81 (dd, *J*=10.4, 1.0Hz, 1H, H-3), 7.40-7.80 (m, 15H, 3xPh); **^{13}C NMR** ($CDCl_3$) δ 69.8 (t), 72.7 (t), 73.0 (t), 73.5 (t), 76.7 (d), 77.6 (d), 84.0 (d), 88.6 (d), 102.6 (s), 127.0 (d), 127.6 (d), 127.8 (d), 127.9 (d), 128.1 (d), 128.2 (d), 128.3 (d), 137.3 (s), 137.7 (s), 137.8 (s), 149.1 (d), 188.9 (s).

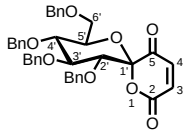
Anal. **calcd**. for $C_{30}H_{30}O_7$ on a diastereomeric mixture of **6b** and **6'b**: C, 71.70; H, 6.02. **Found**: C, 71.54; H, 5.90.

Synthesis of spiroketals 6c and 6'c: A 0.02M solution of **2c** in 25mL di CH_2Cl_2 anidro was photooxygenated as reported for furan 2a. When the photooxygenation reaction was complete (ca. 90 min), 2 equiv. of Et_2S was added to the crude solution at -60°C. After 2h the crude solution was kept at -25°C overnight. Then, the solvent and the Et_2S excess were removed under reduced pressure, and the silica gel chromatography (n-hexane/ethyl acetate 3/:7 v/v) afforded spiroketals **6c** and **6'c** in mixture (ca 2:1) . Yiels 25 %.

Mixture of **5c** and **6c** in *ca*. 1:2 molar ratio:**^{1}H NMR**($CDCl_3$) (selected signals) for **5c**: δ 2.74 (d, *J*=8.2 Hz, 1H, OH), 3.62 (m, 2H, H-5'$_{AB}$), 4.18 (d, *J*=4.4Hz, 1H, H-2'), 4.22 (m, 1H, H-3'), 4.43-4.74 (m, 7H, CH_2 H-4' and CH_2 of Bn), 6.08 (d, *J*= 8.2Hz, 1H, H-2), 6.76 (bs, 1 H, H-3), 7.21-7.35 (m, 15H, 3xPh), 9.70 (s, 1H, CHO); for **6c**δ 3.20 (d, J=7.4 Hz, 1H, OH), 3.62 (m, 2H, H-5'$_{AB}$), 4.02 (d, *J*=4.4Hz, 1H, H-2'), 4.20 (m, 1H, H-3'), 4.43-4.74 (m, 7H, H-4' and CH_2 of Bn), 5.77 (d, *J*=7.4Hz, 1H, H-2), 6.80 (bs, 1H, H-3), 7.21-7.35 (m, 15H, 3x Ph), 9.70 (s, 1H, CHO).**^{13}C NMR**($CDCl_3$) (selected signals) δ 70.2 (t), 70.3 (t), 78.6 (d), 81.3

(d), 82.0 (d), 82.3 (d), 99.5 (d), 99.7 (d), 133.4 (s), 133.5 (s), 133.6 (s), 133.8 (s), 138.2 (d), 138.4 (d), 188.2 (d), 188.3 (d).**Anal**. **calcd**. for $C_{30}H_{30}O_7$ on a diastereomeric mixture of **5c** and **6c**: C, 71.70; H, 6.02. **Found**: C, 71.51; H, 5.85.

Synthesis of spiroketal 7a: A mixture of spiroketals **6a** and **6'a** (0.5 mmol (311 mg)) in molar ratio 1:1 ca, in 1.4mL di DMSO anhydrous. Then, acetic anhydride (0.8mL) was added and the resulting solution was stirred at r.t. under argon atmosphere. After *ca* 12 h the reaction was quenched by adding H_2O (*ca*. 10mL). The organic layer was extracted with $CHCl_3$, washed with H_2O (5x10 mL), dried on Na_2SO_4 and filtered. Then, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate 7:3 v/v) affording spiroketal **7a** in 74 % yield.



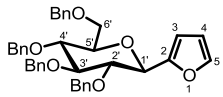
7a

7a:oil; **^{1}H NMR** ($CDCl_3$) δ = 3.64 (dd, *J*=11.3, 1.8Hz, 1H, H-6'$_A$), 3.77 (dd, *J*= 11.3Hz, 3.9, 1 H, H-6'$_B$), 3.82 (t, *J*=9.4 Hz, 1H, H-4'), 4.08 (d, *J*= 9.7 Hz, 1H, H-2'), 4.20 (bt, *J*= 9.4 Hz, 2H, H-3' e H-5'), 4.48 (d, *J*= 12.6 Hz, 1H, CH del Bn), 4.51 (d, *J*=11.5 Hz, 1H, CH del Bn), 4.58 (d, *J*=12.6 Hz, 1H, CH del Bn), 4.61 (d, *J*=10.0Hz, 1H, CH del Bn), 4.84-4.90 (m, 4H, 2x CH_2 del Bn), 6.70 (d, *J*= 10.3Hz, 1H, H-4), 6.83 (d, *J*= 10.3Hz, 1H, H-3), 7.14-7.34 (m, 20H, 4x Ph); **^{13}C NMR** ($CDCl_3$) δ = 67.9 (t), 73.3 (t), 74.7 (d), 75.0 (t), 75.2 (t), 75.8 (t), 77.0 (d), 79.8 (d), 82.1 (d), 101.7 (s), 127.5 (d), 127.6 (d), 127.7 (d), 128.3 (d), 135.0 (d), 136.9 (d), 137.4 (s), 137.9 (s), 138.2 (s), 159.2 (s), 187.5 (s).

EXPERIMENTAL-PART 2B

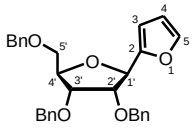
Synthesis of 2-(2',3',4',6'-tetra-O-benzyl-β-D-glucopyranosyl)furan (β-3a): To a solution of 616 mg (1mmol) of **2a** in 10 mL of dry acetonitrile, cooled to -40°C, was added 320 µL (2 equiv.) of triethylsilane and successively, 140 µL (1 equiv.) of $BF_3 \bullet Et_2O$. The solution was stirred at -40°C for 1h, then a saturated aqueous solution of

K_2CO_3 was added (10mL), and the mixture was kept under stirring for 10 min. The organic layer was extracted with ether (3x30 mL), washed with *brine*, dried over anhydrous Na_2SO_4 and filtered. Then the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane/ether 7:3 v/v) affording the β-C-glycoside **β-3a** as white solid in 64% yield which was recognized by comparison with literature data (Czernecki et al.1989).



β-3a

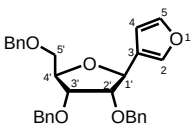
Synthesis of 2-(2',3',5'-tri-O-benzyl-β-D-ribofuranosyl)furan (β-3b): To a solution of 243 mg (0.5mmol) of **2b** in 5.2mL of acetonitrile, cooled to -40°C, were added 240 µL (3 equiv.) of triethylsilane and 70 µL (1 equiv.) of $BF_3 \bullet Et_2O$. The solution was stirred at -40 °C for 4 h and then the temperature was allowed to rise to r.t. while the mixture was further stirred overnight. Then, a saturated aqueous solution of K_2CO_3 was added (10 mL), and the mixture was kept under stirring for 10min. The organic layer was extracted with ether (3x30 mL), washed with *brine*, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was chromatographed on flash silica gel (*n*-hexane/ether 1:1v/v) affording the nucleoside β-**3c** with 35 % yield (Macdonald et al.1988).



β-3b

β-3b: oil; **^{1}H NMR** ($CDCl_3$); δ = 3.61 (m, 2H, H-5'$_A$ and H-5'$_B$), 4.05 (t, J= 4.9 Hz, 1H, H-3'), 4.18 (dd, J= 6.5, 4.9 Hz, 1H, H-2'), 4.30 (m, 1H, H-4'), 4.50-4.66 (m, 6H, CH_2 of Bn), 5.04 (d, J= 6.5Hz, 1H, H-1'), 6.34 (bs, 2H, H-3 and H-4), 7.23-7.33 (m, 15H, 3xPh), 7.34 (bs, 1 H, H-5); **^{13}C NMR**; δ = 70.3 (t), 72.1 (2 x t), 73.4 (t), 76.5 (d), 77.7 (d), 79.9 (d), 81.5 (d), 108.9 (d), 110.3 (d), 127.5 (d), 127.6 (d), 127.7 (d), 127.8 (d), 128.0 (d), 128.3 (d), 137.7 (s), 138.0 (s), 138.2 (s), 142.5 (d), 152.2 (s).

Synthesis of 3-(2',3',5'-tri-O-benzyl-β-D-ribofuranosyl)furan (β-3c): To a solution of 243 mg (0.5 mmol) of **2c** in 5.2 mL of acetonitrile, cooled to -40 °C, was added 240 µL (3 equiv.) of triethylsilane and 70 µL (1 equiv.) of $BF_3 \bullet Et_2O$. The solution was stirred at -40°C for 4h and then the temperature was allowed to rise to r.t. while the mixture was further stirred overnight. Then, a saturated aqueous solution of K_2CO_3 was added (10mL), and the mixture was kept under stirring for 10 min. The organic layer was extracted with ether (3x30mL), washed with *brine*, dried over anhydrous Na_2SO_4 and filtered. Then the solvent was removed under reduced pressure and the residue was chromatographed on flash silica gel (*n*-hexane/ether 1:1 v/v) affording the nucleoside β-**3c** with 30 % yield.

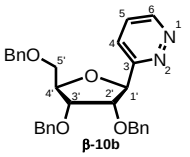


β-3c

β-3c:**mp**: 49–51 °C (hexane); **^{1}H NMR**: δ = 3.56 (d, J= 10.4, 4.4 Hz, 1 H, H-5'$_A$), 3.59 (d, J= 10.4, 4.4Hz, 1H, H-5'$_B$), 3.84 (dd, J= 6.6, 4.9 Hz, 1H, H-2'), 3.99 (dd, J= 4.9, 3.8 Hz, 1H, H-3'), 4.28 (m, 1H, H-4'), 4.48-4.62 (m, 6H, CH_2 of Bn), 4.97 (d, J=6.6 Hz, 1H, H-1'), 6.31 (bs, 1H, H-4), 7.22-7.33 (m, 15H, 3xPh), 7.35 (bs, 1H, H-5), 7.40 (s, 1H, H-2); **^{13}C NMR**: δ = 70.4 (t), 71.9 (t), 72.2 (t), 73.4 (t), 75.7 (d), 77.5 (d), 81.6 (d), 82.2 (d), 108.5 (d), 124.4 (s), 127.6 (d), 127.7 (d), 127.8 (d), 128.0 (d), 128.3 (d), 137.7 (s), 137.9 (s), 138.1 (s), 140.2 (d), 143.2 (d).

One-pot synthesis of 3-(2',3',5'-tri-O-benzyl-β-D-ribofuranosyl)pyridazine (β-10b): A 0.02 M solution of β-**3b** (0.5 mmol) in dry CH_2Cl_2 was photooxygenated as reported in the general procedure. The progress of each reaction was checked by periodically monitoring (TLC) the disappearance of β-**3b**. When the photooxygenation reaction was complete (*ca.* 90 min), 2 equiv. of Et_2S was added to the crude solution at -40°C. After 2h the crude solution was kept at room temperature overnight. Then, the solvent and the Et_2S excess were removed under

reduced pressure, and 2mL of hydrazine solution (2M in THF) were added at the residue. The resulting mixture was stirred at r.t. under nitrogen for 12h. Then, the solvent was removed under reduce pressure, and the silica gel chromatography (*n*-hexane/ethyl acetate 1:1 v/v) afforded the pyridazine *C*-nucleoside β-**10c** with 66 % yield from the starting glycosyl furan.

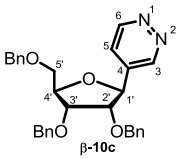


β-10b

β-10b: oil; **^{1}H NMR** ($CDCl_3$); δ= 3.66 (dd, *J*= 10.4, 3.3 Hz, 1H, H-5'$_A$), 3.88 (dd, *J*= 10.4, 2.5 Hz, 1H, H-5'$_B$), 3.97 (dd, *J*= 7.7, 4.9 Hz, 1H, H-3'), 4.31 (dd, *J*=4.9, 2.7 Hz, 1H, H-2'), 4.36 (d, *J*=12.0 Hz, 1H, CH of Bn), 4.44 (m, 1H, H-4'), 4.50 (d, *J*=11.5 Hz, 1H, CH of Bn), 4.56(d, *J*= 12.0 Hz, 1H, CH of Bn), 4.57 (d, *J*= 11.5 Hz, 1H, CHof Bn), 4.74 (d, *J*= 12.0 Hz, 1H, CH of Bn), 4.86 (d, *J*= 12.0 Hz, 1H, CH of Bn), 5.48(d, *J*= 2.7 Hz, 1H, H-1') 7.20 (dd, *J*= 8.8, 4.9 Hz, 1H, H-5), 7.22-7.40 (m, 15H, 3xPh), 7.80 (dd, *J*=8.8, 1.6 Hz, 1H, H-4), 9.03 (dd, *J*= 4.9, 1.6 Hz, 1H, H-6); **^{13}C NMR**; δ= 69.1 (t), 71.7 (t), 72.1 (t), 76.3 (d), 80.9 (d), 81.5 (d), 83.3 (d), 124.9 (d), 126.6 (d), 127.7 (d), 127.8 (d), 128.2 (d), 128.3 (d), 137.7 (s), 138.0 (s), 150.4 (d), 162.8 (s).

One-pot synthesis of 4-(2',3',5'-tri-O-benzyl-β-D-ribofuranosyl)pyridazine (β-10c): A 0.02 M solution of β-**3c** (0.5 mmol) in dry CH_2Cl_2 was photooxygenated as reported in the general procedure. The progress of each reaction was checked by periodically monitoring (TLC) the disappearance of β-**3c**. When the photooxygenation reaction was complete (*ca.* 90 min), 2 equiv. of Et_2S was added to the crude solution at -40°C. After 2h the crude solution was kept at room temperature overnight. Then, the solvent and the Et_2S excess were removed under reduced pressure, and 2mL of hydrazine solution (2M in THF) were added at the residue. The resulting mixture was stirred at r.t. under nitrogen for 12h. Then, the solvent was removed under reduce pressure, and the silica gel chromatography (*n*-hexane/ethyl acetate 1:1 v/v) afforded the pyridazine *C*-nucleoside β-**10c** with 70%

yield from the starting glycosyl furan.



β-10c

β-10c: oil; **^{1}H NMR** ($CDCl_3$); δ= 3.57 (dd, *J*= 10.4, 3.3 Hz, 1H, H-5'$_A$), 3.65 (dd, *J*=10.4, 3.8 Hz, 1H, H-5'$_B$), 3.77 (dd, *J*=7.7, 4.9 Hz, 1H, H-2'), 4.02 (dd, *J*= 4.9, 2.7 Hz, 1H, H-3'), 4.38 (m, 2H, H-4' and CH of Bn), 4.51 (d, *J*= 12.0 Hz, 1H, CH of Bn), 4.56 (d, *J*= 12.0 Hz, 1H, CH of Bn), 4.57(d, *J*= 12.0 Hz, 1H, CH of Bn), 4.60 (s, 2H, CH_2 of Bn), 4.98 (d, *J*= 7.7 Hz, 1H, H-1'), 7.17-7.35 (m, 15H, 3xPh), 7.47 (bd, *J*=5.5 Hz 1H, H-5), 9.00 (d, *J*=5.5 Hz, 1H, H-6), 9.16 (bs, 1H, H-3); **^{13}C NMR**; δ=70.1 (t), 72.7 (t), 73.6 (t), 78.6 (d), 82.7 (d), 83.4 (d), 123.3 (d), 127.7 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.5 (d), 136.9 (s), 137.4 (s), 137.6 (s), 140.3 (s), 149.7 (d), 151.0 (d).

CHAPTER 3. SYNTHESIS OF ARYL TRISUBSTITUTED FURANS AND APPLICATIONS IN THE FIELD OF LIGNANS

3. INTRODUCTION

Due to their numerous preparation methods and the great synthetic versatility, furans have been used in the preparation of a high number of natural and synthetic compounds. In this part of the thesis applications of polysubstituted furans in the field of lignans have been realized.

Lignans are among the main products of the secondary metabolism of the vascular plants. Basic structure consists of two phenylpropanoidic (C_6-C_3) units linked in different patterns. 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 (-)-enterolactone and (-)-enterodiol (**FIGURE 3.1**).

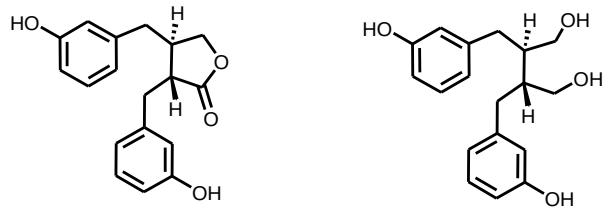
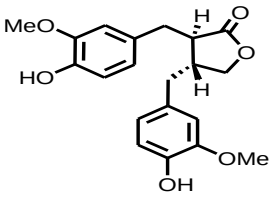


FIGURE 3.1 (-)-ENTEROLACTONE AND (-)-ENTERODIOL

Probably lignans play a key role in the defense mechanisms of the plant; so interest for a possible use in agriculture as environmentally friendly substances for defenses has revived. Lignans possess antimicrobial properties, antifungal, antiviral (Lacret et al. 2012) antioxidant (Belmares et al. 1979; Figgitt et al.1989; Medarde et al. 1995), insecticidal (Oliveto 1972; Osawa et al. 1985; Xue et al. 1992). In recent years these compounds have receved particular attention in pharmacological field for their effects on human health. Indeed they represent a source of phytoestrogens in diets for people who do not consume soy food. There are epidemiological and experimental data, which show a correlation between the uptaking phytoestrogens and a relative risk reduction of a cardiovascular disease, hypercholesterolemia (Adlercreutz and Mazur 1997) menopause, osteoporosis and cancer, in particular cancer to mamelian and

prostate. Many plants containing lignans have been used for centuries as medicinal plants and remedies for various aliments. One of the most diffuse lignans, interesting for cytostatic activity, is matairesinol (**Figure 3.2**) whose antitumoral properties against breast and colon cancers are well known (Thompson et al. 2006).



Matairesinol

FIGURE 3.2 MATAIRESINOL

Lignans derive from the oxidative dimerization of two phenylpropanoid (C_6-C_3) units, The phenylpropanoids units reveal different degree of oxidation and substitution, thus lignans show an enormous structural diversity, and numerous new compounds with structures correlated to lignans are continuously found.

Lignans derive by the shikimic acid pathway (**FIGURE 3.3**) which also produces the aromatic aminoacids: phenylalanine and tyrosine (Jensen 1986).

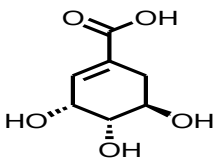


FIGURA 3.3 SHIKIMIC ACID

Lignans can be classified in **classical lignans**, which have the units linked in (8-8') positions, and **neolignans** whose coupling patterns differ from such a β–β' linkage (Saleem et al. 2005).The units can also be linked by an oxygen atom, as in the subclass of **oxyneolignan** (**FIGURE 3.4**).

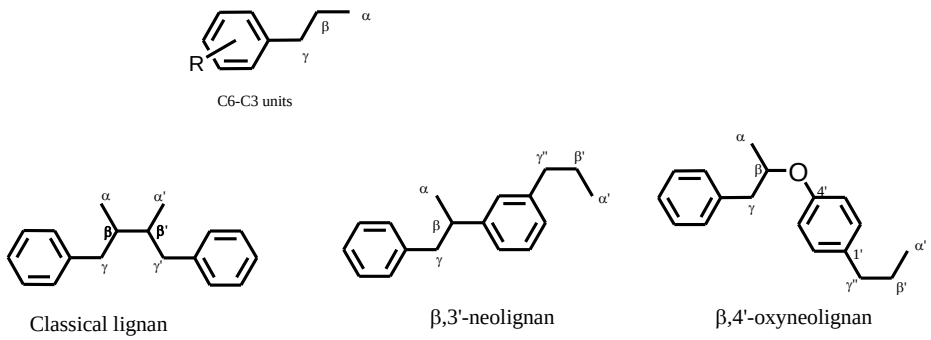


FIGURE 3.4 TYPE OF LIGNANS

The aromatic ring, which is formed starting from the shikimate pathway, may contain substituents such as hydroxyl and methoxyl groups in the 3,4,5 positions (**FIGURE 3.5**).

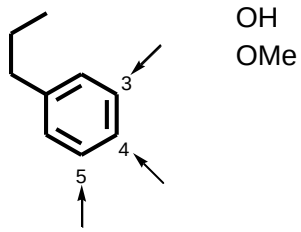


FIGURE 3.5 SUBSTITUENTS ON THE AROMATIC RING OF LIGNANS

Despite the lignans are present in roots, leaves, seeds, rhizomes and fruits of more than seventy families of plants, such sources are not sufficient to "produce" a quantity commercially interesting. Isolation of lignans is very hard-working and of extremely low yields. The interest for these substances in the pharmaceutical and agricultural field, has given substantial impetus to research, aimed at optimizing the production of these substances on a larger scale, also through the development of new synthetic methodologies, industrially applicable with low production costs.

Generally enzymatic and radical reactions have been employed, involving the coupling of phenoxy radicals (Iqbal et al. 1994). A synthetic method for the preparation of lignans (eg. dihydrodyisoeugenol and pinoresinol), starting from C_6-C_3 units has been based on photooxygenation reactions (Della Greca et al. 2008). As an alternative, the

research group have recently recognized the possibility to synthetize lignan-like compounds starting from two units C3-C6 already linked in position β-β' (**FIGURE 3.6**).

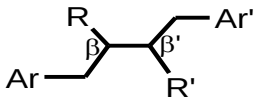


FIGURE 3.6 UNITS C_3-C_6 LINKED IN β-β'

In particular, diarylfuranyl structures of type A-C have been recognized as useful precursors of highly functionalized lignan-like compounds (**FIGURE 3.7**).

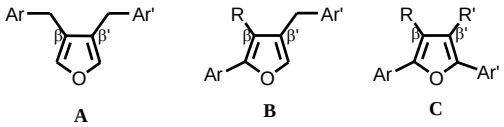
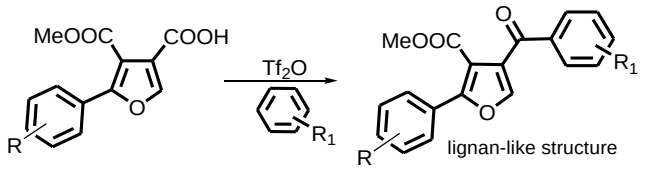


FIGURE 3.7 EXAMPLES OF DIARYLFURANIC STRUCTURES

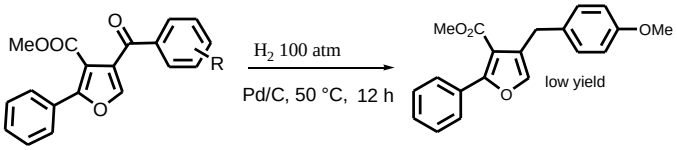
The introduction of furan systems in the scaffold of lignans appeared advantageous not only for the easy preparation of these heterocycles but especially for their high synthetic versatility. As evidenced above, furans are easily converted into reduced forms as dihydro and tetrahydrofurans or in oxidized forms such as furanones, structural units often present in natural lignans, or as versatile enediones (Keay et al. 2005), that in turn can lead to hetero and carbocyclic systems of great interest.The research group has developed a synthetic method for furans with lignan-like structure of the type B (**FIGURE 3A.2**). The procedure employs an innovative Friedel-Crafts (FC) acylation starting from opportunely substituted 2-aryl-4-furoic acids (Comegna et al, 2012). The novelty was the use of trifluoromethylsulfonic anhydride (Tf_2O) as promoter with reduction of steps and without the use of acid catalysts. An inconvenient was the formation of both regioisomers 3- and 4-aroylfurans, although appropriate reaction conditions allowed to obtain the planned appropriate lignan-like 4-aroyl-2-aryl furans as the main products (**SCHEME 3.1**). In the last year, great attention has been focused to the Friedel-Crafts reactions in order to avoid the use of the required stoichiometric metal salts/acids in unfavorable conditions and increase the regioselectivity (kawamura

et al. 2006; Firouzabadi et al. 2004). Tf_2O is one of the most studied and applied catalyst; it is commercially available and known for its utility for the conversion of an OH group into an OTf leaving group.



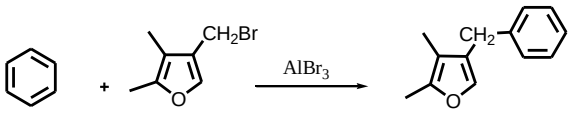
SCHEME 3.1 LIGNAN-LIKE FURANS

In order to bring the arylaroylfuran structure to analogues present in nature, that possess the saturated non-oxidated chain, several attempts were made to reduce the carbonyl functions with unsatisfying results (**SCHEME 3.2**) (Comegna et al. 2012).



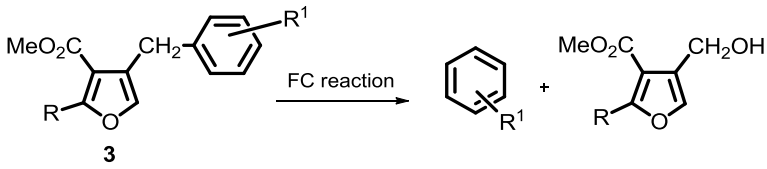
SCHEME 3.2. HYDROGENATION OF CARBONYL FUNCTION

Unsuccessful were some attempts to use the classical reactions of aromatic electrophilic substitution starting from halides in the presence of a Lewis acid (**SCHEME 3.3**).



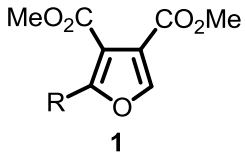
SCHEME 3.3. REACTION OF AROMATIC ELECTROPHILIC SUBSTITUTION

Starting from these results, we decided to explore the possibility to synthetize furans of type **3** by Friedel-Crafts reaction of furanyl alcohol in the presence of Tf_2O (**SCHEME 3.4**).



SCHEME 3.4 FRIEDEL-CRAFTS ALKYLATION

We were encouraged by literature data that reported successful FC alkylation of benzyl alcohols (Khodaei et al. 2012) in the presence of this reagent. The starting furan for furanyl alcohol was recognized a diester derivative as 1, easily prepared (Fan et al. 2005).

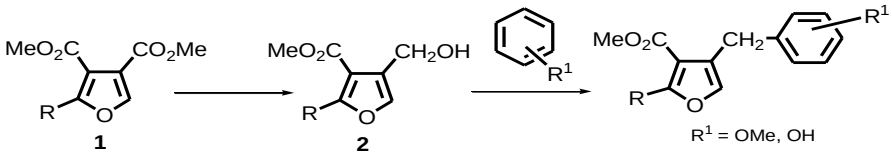


3A. SYNTHESIS OF DIARYL FURANS WITH LIGNAN BACKBONE BY NOVEL FRIEDEL-CRAFTS ALKYLATION

RESULTS AND DISCUSSION:

The following research plan was developed:

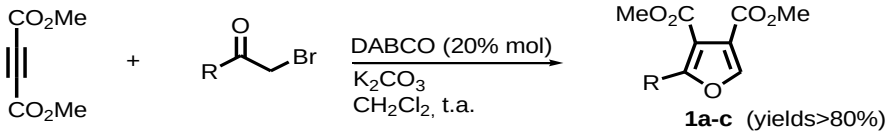
- preparation of furan diester **1**
- reduction of furan **1** to obtain the furanyl alcohol **2**
- Friedel-Crafts alkylation (**SCHEME 3A.1**)



SCHEME 3A.1 RESEARCH DESIGN

*Synthesis of furans **1***

Furans **1a-c** were prepared according to literature procedure (Fan et al. 2005) that involves the use of dimethyl acetylendicarboxylate (DMAD) and α-bromo aryl ketones in the presence of 1,4-diazabycyclo[2.2.2]octane (DABCO) and anhydrous K_2CO_3 (**SCHEME 3A.2**).

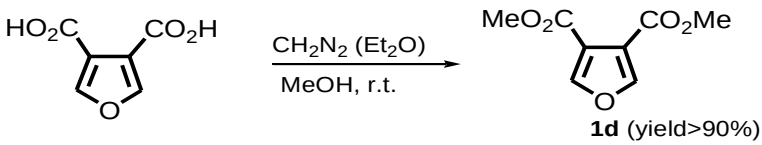


1a-c (yields>80%)

a) R = C_6H_5; **b)** R = 4-$OMeC_6H_4$; **c)** R = 4-BrC_6H_4

SCHEME 3A.2 SYNTHESIS OF FURAN **1a-c**

To verify the role of the aromatic substiuent at 2-posistion, dimethyl furan-3,4-dicarboxylate **1d** was also prepared starting from commercially available furan-3,4-dicarboxylic acid by methylation in the presence of diazomethane in diethyl ether and methanol at rt (**SCHEME 3A.3**). At the end of reaction, chromatography gave derivate **1d** in 90 % yield.

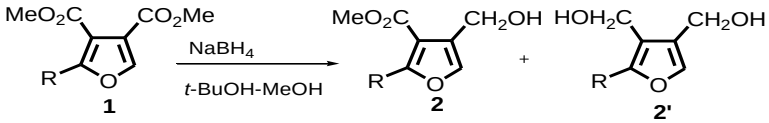


1d (yield>90%)

SCHEME 3A.3 SYNTHESIS OF FURAN **1d**

*Synthesis of furanyl alcohols **2***

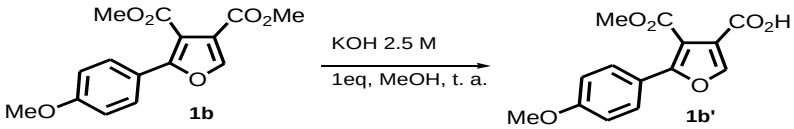
4-(Hydroxymethyl)furans **2a**, **2c**, and **2d** were prepared by $NaBH_4$ reduction of the corresponding dimethyl furan-3,4-dicarboxylates **1a**, **1c** and **1d**. The reaction was carried out in the mixed solvent system t-BuOH/MeOH (Soai et al. 1984) The resulting mixture was refluxed and stopped at ca. 50% conversion (ca. 2h) to avoid a high amount of the corresponding dialcohols (**SCHEME 3A.4**).



a) R = Ph; **c)** R = 4-BrC_6H_4 ; **d)** R =H

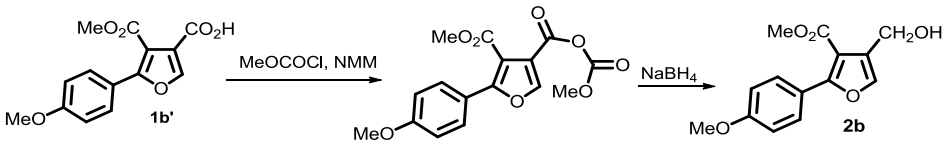
SCHEME 3A.4 FURANYL ALCOHOLS **2** PREPARATION

The reaction was quenched with H_2O and the residue extracted with CH_2Cl_2. The usual work up gave a residue that was purified by preparative silica gel TLC using as eluent hexane/AcOEt. It is interesting to note the regiochemistry of the rroute that reduces only the ester function in 3 position, probably due to steric reasons. The dialcohol **2'** was obtained in small amount after longer reaction time. Attempts to prepare furanyl alcohol **2b** using this procedure failed. An alternative procedure was used (Longobardo et al. 2013) that requires a carboxylic function (**SCHEME 3A.5**). So, the dimethyl ester **1b** was selectively hydrolyzed to 4-(methoxycarbonyl)-5-(4-methoxyphenyl)furan-3-carboxylic acid **1b'** (Lin et al. 2001)



SCHEMA 3A.5 HYDROLYSIS OF FURAN **1b**

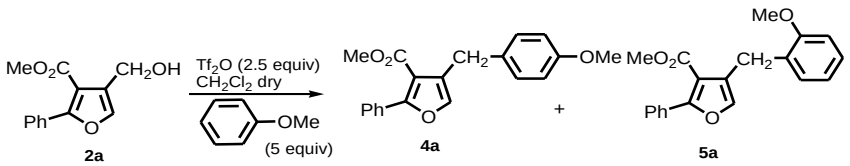
Furoic acid **1b'** was firstly converted to a mixed anhydride using ClCOOMe in the presence of N-methylmorpholine (NMM) and then reduced with $NaBH_4$ in H_2O (**SCHEME 3A.6**) (Longobardo et al. 2013).



SCHEME 3A.6 SYNTHESIS OF FURANYL ALCOHOL **2b**

Friedel-Crafts alkylation reactions

Initially, the reaction of methyl 4-(hydroxymethyl)-2-phenylfuran-3-carboxylate (**2a**) in the presence of Tf_2O was examined with anisole under different conditions (**SCHEME 3A.7**).



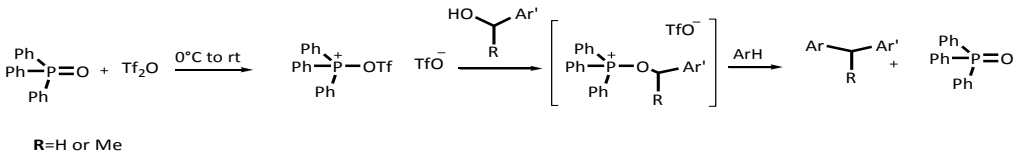
Entry	*Condition*	*T(°C)*	*time (t)*	*Yield*[a]	***4a/5a***
1	Tf_2O	-20°C	20	61	68:32
2	Tf_2O	r.t	4	30	83:17
3	Tf_2O/2,6-lutidine	-20°C	20	62	68:32

[a] Chromatographic yield

SCHEME 3A.7 ALKYLATION REACTIONS OF **2a** IN DIFFERENT CONDITIONS

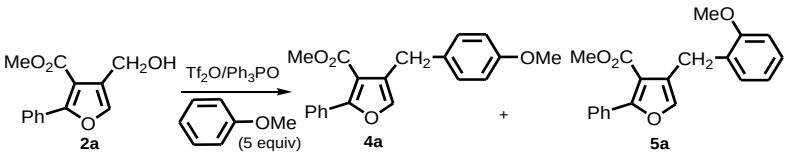
The FC alkylation occurs in all cases regioselectively in favor of the *para*-isomer. The reaction in the presence of only Tf_2O occurs with appreciable yield, mainly at low temperature. The products **4a** and **5a** were formed with a ratio of about 2:1 at -20°C in 20h and 5:1 at rt in 4h. In an attempt to improve the yield, considering that triflic acid (TfOH) is generated, the reaction was also performed in the presence of a non-nucleophilic base, 2,6-lutidine. No effect in total yield nor in the regioisomeric ratio was observed. Previously, these conditions were found particularly useful in Tf_2O-mediated acylations (Della Greca et al. 2013; Grundl et al. 2006; Harmata and Jones 1996).

In the literature Khodaei and Nazari (2012) described a Friedel-Craft alkylation starting from variously substituted benzyl alcohols on different aromatic compounds in the presence of Tf_2O in combination of triphenylphosphineoxide as activating agent. The activation mechanism is described in **SCHEME 3A.8**.



SCHEME 3A.8 ACTIVATION MECHANISM REACTION

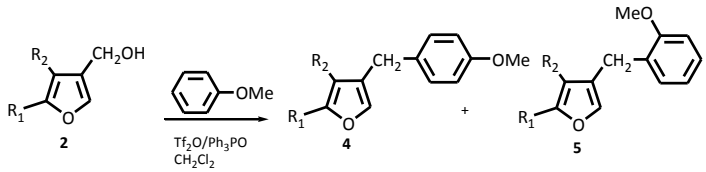
We therefore decided to apply the reaction of **2a** with anisole under the Khodaei procedure. The reaction was carried out at rt for 1h and at 0°C for 5 h. As shown in **SCHEME 3A.9**, also in this case,the isomers **4a** and **5a** were obtained in similar amounts but the reaction time was significantly reduced.



Condition	*T(°C)*	*time(h)*	*Yield(%)*	***4a/5a***
Tf_2O/Ph_3PO	r.t	1	61	60: 40
Tf_2O/Ph_3PO	0	5	56	71:29

SCHEME 3A.9 Tf_2O/Ph_3PO -PROMOTED FRIEDEL-CRAFTS ALKYLATION OF ALCOHOL **2a**

Encoraged by these results, we applied the reaction of anisole under the Khodaei–Nazari procedure (furanyl alcohol, anisole and TPPD in 1:1:1.2 molar ratio, rt) to differently substituted furanyl alcohols **2b**-**2d** and to dialcohol **2a'** (**SCHEME 3A.10**).



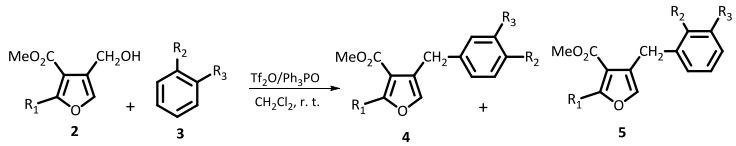
Entry		R_1	R_2	Yield %[a]	**4/ 5**
1	**2a**	C_6H_5	CO_2Me	61	**4a/5a** 60:40
2	**2b**	4-MeO-C_6H_4	CO_2Me	58	**4b/5b** 62:38
3	**2c**	4-Br-C_6H_4	CO_2Me	55	**4c/5c** 61:39
4	**2d**	H	CO_2Me	41	**4d/5d** 58:42
5	**2a'**	C_6H_5	CO_2H	0	

[a]Yield of isolated product after preparative TLC

SCHEME 3A.10 ALKYLATION REACTION OF **2b**-**d** AND **2'a** WITH ANISOLE

As shown in **SCHEME 3A.10**, the reaction occurs except for dialcohol **2'a**. Moreover, the aryl substitution of furan ring appears not essential. In these cases, the ratio of regioisomers is still in favor of **4** due to the lower steric crowding of the corresponding diaryl furan products.

To extend the scope for preparation of lignan-like compounds, starting from furans **2a** and **2b** the alkylation was performed using other aromatic substrates with lignan-typical aryl substitution (Pan et al. 2009; Saleem et al. 2005), such as phenol and 1,2-dimethoxybenzene (**SCHEME 3A.11**).



Entry		R_1		R_2	R_3	Products	Yield %[a]	4/ 5
1	**2a**	C_6H_5	**3a**	MeO	MeO	**4e/5e**	53	100:0
2	**2b**	4-MeO-C_6H_4	**3b**	MeO	MeO	**4f/5f**	62	42:58
3	**2a**	C_6H_5	**3a**	OH	H	**4g/5g**	14	1:99
4	**2b**	4-MeO-C_6H_4	**3b**	OH	H	**4h/5h**	35	20:80
5	**2c**	4-Br-C_6H_4	**3c**	OH	H	**4i/5i**	83	53:47

[a]Yield of isolated product after preparative TLC

SCHEME 3A.11 Tf_2O/Ph_3PO-PROMOTED FRIEDEL-CRAFTS ALKYLATION OF ARENES WITH FURANYL ALCOHOLS **2**

A different position selectivity was observed in the alkylation of 1,2-dimethoxybenzene probably since the electronic effect of the donating substituent is also of importance (Carey and Sundberg 2007). The alkylation worked, although with low yield, even with phenol that gives no reaction starting from benzyl alcohols (Khodaei and Nazari 2012). High regioselectivity at the ortho position of the phenol is observed, as also reported in similar cases (Li and Qu 2012).

Antibiotic activity of some derivatives

In order to evaluate anti-biofilm properties against *Staphylococcus aureus* and *Staphylococcus epidermidis*, some compounds (**5g**, **4i**, **5h** and **5i,** (**FIGURE 3A.1**)) will be tested for the ability to inhibit bacterial biofilms formation. These tests were performed in collaboration with Prof. Buommino (Department of Environmental,

Biological and Pharmaceutical Sciences and Technologies-Second University of Naples)(Prof. Buommino).

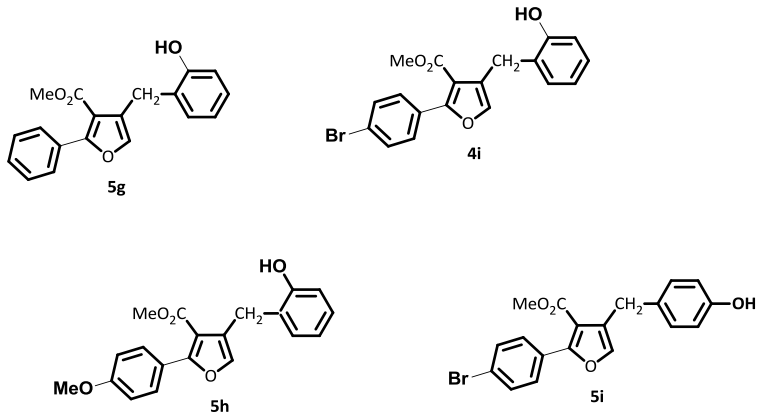


FIGURE 3A.1 LIGNAN.LIKE FURANS TESTED

Bacteria that generate biofilms (Worthington et al. 2012) are highly organized surface-associated communities encased within a self produced extracellular matrix, capable of growing in connection with different biological or inert surfaces such as artificial joints, contact lens or catheters. They cause many health problems, as endocarditis, otitis media, periodontitis, prostatitis,chronic wounds and urinary tract infections. The presence of a matrix prevents the access of antibiotics to the bacterial cells. *Staphylococcus aureus* and *Staphylococcus epidermidis* are two biofilm-forming species, principal aetiological agents of nosocomial infections. In order to evaluate antibiotic properties against *Staphylococcus aureus* and *Staphylococcus epidermidis*, some compounds were tested for the ability to inhibit bacterial growth. In **FIGURE 3A.2** and **FIGURE 3A.3** bacterial growth is shown in terms of turbidity (NTU Nephelometric Turbidity Units), measured at 630 nm. Lower the turbidity more active is the product. As demonstrated in **FIGURE 3A.2** a clear decrease of the growth of *Staphylococcus epidermidis* was observed in the presence of compounds **4i** and **5i**. Compound **5i** displayed the best effects at 32 μg/ml.

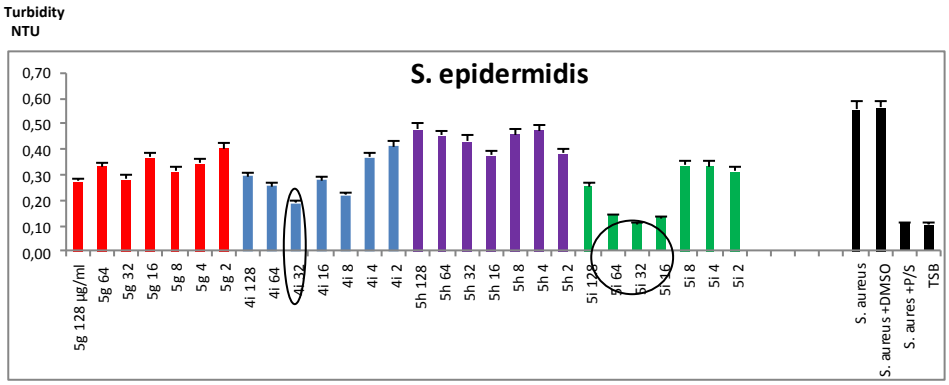


FIGURE 3A.2 THE *S. EPIDERMIDIS* GROWTH IN THE PRESENCE OF COMPOUNDS **5g**, **4i**, **5h** AND **5i**. THE RESULTS ARE EXPRESSED AS TURBIDITY (NTU) COMPARED TO RESPECTIVE CONTROL WELLS

As shown in **FIGURE 3A.3** compounds **5g** and **5h** (at 128 µg/ml and 64 µg/ml), **5i** (at 128 µg/ml ,64 µg/ml and 32 µg/ml) were able to decrease the growth of *S. aureus*.

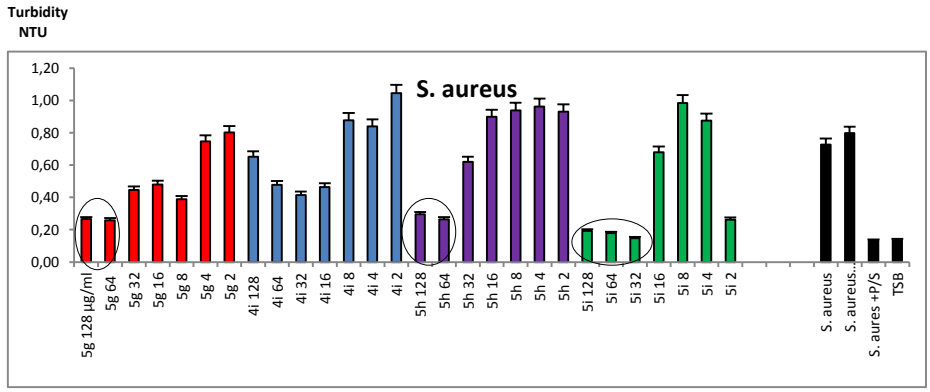
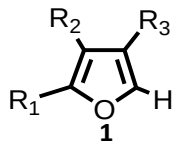


FIGURE 3A.3 EFFECTS OF COMPOUNDS **5g**, **4i**, **5h** and **5i** ON *S. AEREUS* GROWTH. THE RESULTS ARE EXPRESSED AS TURBIDITY (NTU) COMPARED TO RESPECTIVEC ONTROL WELLS

3B. DYE-SENSITIZED PHOTOOXYGENATION OF ARYL TRISUBSTITUTED FURANS AND APPLICATIONS IN THE FIELD OF LIGNANS

In this part attention was paid to the reactivity of trisubstituted arylfurans toward singlet oxygen. During a study directed to the synthesis of compounds with lignan-like structure starting from β, β'-dicarbomethoxy arylfurans some peculiar results were highlighted in"classical" reactions of the related endoperoxides obtained by dye-sensitized photooxygenation (DellaGreca et al. 2013). This prompted to investigate on the reactivity of these furan derivatives by examining mainly substituent effects and to exploit the synthetic potential. In particular, we decided to verify the role of the aromatic group and that of the ester group in two general applications of the photooxygenation of furans, reduction for the preparation of enediones and base treatment for acrylic acids and 4-hydroxybutenolides. As reported above, the nature and position of substituents have a prominent role in the behavior of furan endoperoxides (Iesce et al. 2005; Gollnick et al. 1985; Graziano et al. 1980), and furans as **1** (**FIGURE 3B.1**) were not previously examined.



1

***R*$_1$** Aryl or Alkyl

R$_2$ =***R*$_3$** Ester, ketone or alkylic group

FIGURE 3B.1. TRISUBSTITUED FURANS **1**

Furans examined were substituted in α position by an aryl or an alkyl group while in β positions they have an ester or ketone or alkyl group (**FIGURE 3B.1**).

RESULTS AND DISCUSSION:

Furans **1** examined are reported in **FIGURE 3B.2**

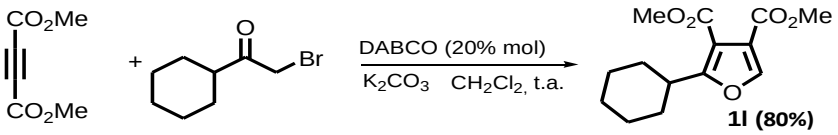
1

Furan	R_1	R_2	R_3
1a	C_6H_5	CO_2Me	CO_2Me
1b	4-MeO-C_6H_4	CO_2Me	CO_2Me
1c	4-Br-C_6H_4	CO_2Me	CO_2Me
1l	C_6H_{11}	CO_2Me	CO_2Me
1m	C_6H_5	CO_2Me	4-$MeOC_6H_4$-CO
1n	C_6H_5	4-$MeOC_6H_4$-CO	CO_2Me
1o	C_6H_5	CO_2Me	CH_2OCOMe
1p	C_6H_5	CO_2Me	4-$MeOC_6H_4$-CH_2

FIGURE 3B.2 FURANS **1** SYNTHETIZED

Synthesis of other furans of type **1**

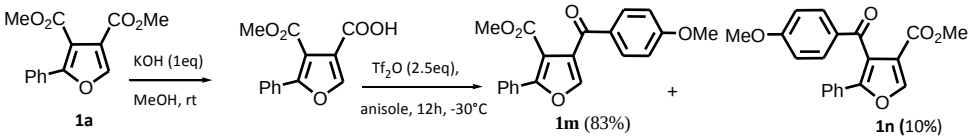
Furan **1l** was prepared according to the literature procedure (Fan et al. 2005) adopted for furans **1a**-**c** (page 70), by DABCO-catalyzed reaction of dimethyl acetylendicarboxylate (DMAD) and 2-bromo-1-cyclohexylethanone, the latter prepared by bromination of cyclohexylethanone (**SCHEME 3B.1**).



SCHEME 3B.1 SYNTHESIS OF FURAN **1l**

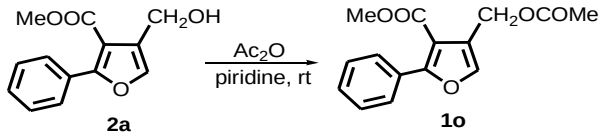
After work-up and chromatography **1l** was obtained in satisfactory yields (80%) and fully characterized.

Furans **1m** and **1n** were obtained by a reported procedure (Comegna et al. 2012), by selective hydrolysis of derivate **1a** to the corresponding acid followed by Tf_2O-mediated Friedel-Crafts acylation (**SCHEME 3B.2**).



SCHEME 3B. 2 PREPARATION OF FURANS **1m** AND **1n**

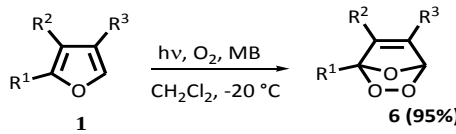
Furan **1o** was obtained by acetylation of alchool **2a** previously synthetized by $NaBH_4$ reduction (**SCHEME 3B.3**).



SCHEME 3B. 3 PREPARATION OF **1O**

Photooxygenation reactions

The photooxygenation reaction was performed under conventional conditions: low temperature (-20°C), dichoromethane as solvent (usually 10^{-2} M) and methylene blue as sensitizer, sunlight lamp, dry oxygen flux. The reaction was checked by TLC (disappearance of furan) and ^{1}H NMR. It was complete within 2-3 h. Endoperoxides were quantitatively formed and they were spectroscopically characterized at r.t. (characteristic CH signal in the δ range 6.80-6.20 typical of an acetalic proton in an unsaturated bicyclic structure (Gollnick et al. 1985;Graziano et al. 1987) In furan system the resonance of H-5 is at δ 7.90-7.96). (**SCHEME 3B.4**)

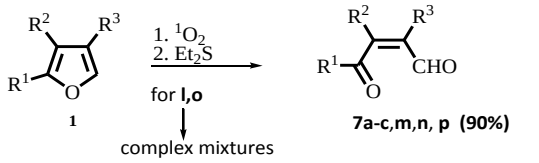


SCHEME 3B.4 DYE-SENSITIZED PHOTOOXYGENATION OF FURANS **1**

Endoperoxides **6a**-**c** and **6l**-**n** exhibited a quite thermal stability while **6o**,**p** quickly converted in a mixture of unidentified products. The peculiar thermal stability of endoperoxides **6a**-**c** and **6l**-**n** can be explained considering that furan endoperoxide stability is significantly increased by the presence of electron-withdrawing groups on the double bond (Graziano et al. 1982). It was suggested that the thermal stability should be due to the delocalization of π electrons in the furan endoperoxide structure by electron-withdrawing groups, and this should ensure that the reactivity of this system lay between that of mono-ozonides of cyclobutadiene derivatives and that of the most stable ozonides of cyclobutene derivatives (Graziano et al. 1982). Reduction and base treatment were however performed starting from all furans **1**. Indeed, the reactivity of furan endoperoxides, even unstable, can be controlled and opportunely addressed working at low temperature (Iesce et al. 2012).

Et_2S reduction

Photooxygenation followed by treatment in situ with Et_2S, led to the expected *cis*-aldehydes **7** in the series **a**-**c**,**m**,**n**,**p** (**SCHEME 3B.5**).

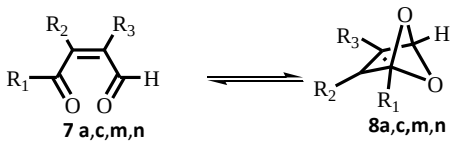


Furan	R_1	R_2	R_3
1a	C_6H_5	CO_2Me	CO_2Me
1b	4-MeO-C_6H_4	CO_2Me	CO_2Me
1c	4-Br-C_6H_4	CO_2Me	CO_2Me
1l	C_6H_{11}	CO_2Me	CO_2Me
1m	C_6H_5	CO_2Me	4-$MeOC_6H_4$-CO
1n	C_6H_5	4-$MeOC_6H_4$-CO	CO_2Me
1o	C_6H_5	CO_2Me	CH_2OCOMe
1p	C_6H_5	CO_2Me	4-$MeOC_6H_4$-CH_2

SCHEME 3B.5 ONE-POT METHODOLOGY FOR ALDEHYDES **7**

These compounds were spectroscopically characterized. The reduction is almost quantitative except for **1n** (>40%) and **1p**(>20%). Despite the low temperature attempts to obtain aldehydes **7l** and **7o** failed since the reactions afforded complex mixtures.

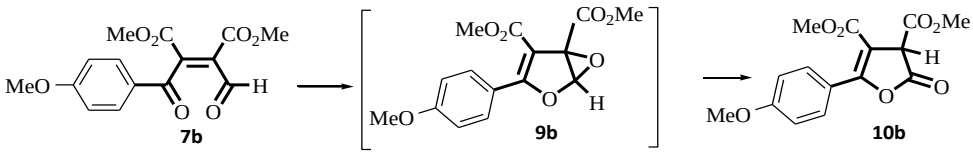
Evidently, reduction competes with thermal conversion and this could be due to different thermal stability of endoperoxides and mildness of the reduction reagent (Et_2S) (Gollnick et al. 1985). Derivatives **7a**,**c**,**m**,**n** (kept at room temperature in $CDCl_3$) converted partly into products to which we tentatively assigned structures **8a**,**c**,**m**,**n** (**SCHEME 3B.6**).



Aldehyde	*R_1*	*R_2*	*R_3*
a	C_6H_5	CO_2Me	CO_2Me
c	4-Br-C_6H_4	CO_2Me	CO_2Me
m	C_6H_5	CO_2Me	4-$MeOC_6H_4CO$
n	C_6H_5	4-$MeOC_6H_4CO$	CO_2Me

SCHEME 3B.6 REARRANGEMENTS OF OXOALDEHYDES **7a**,**c**,**m**,**n** AND SUGGESTED FORMATION PATHWAYS OF 5,6-DIOXABICYCLOHEXENES **8a**,**c**,**m**,**n**

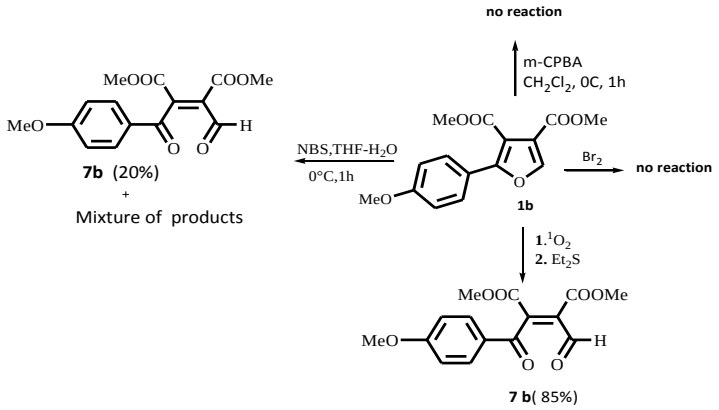
These compounds were not isolated by chromatography and were identified on the basis of NMR data of the mixtures by subtracting NMR signals of aldehydes **7a**-**c**,**n**,**p**. In particular, in the ^{1}H-NMR of the mixture of **7c** and **8c** (1:3 molar ratio) dimethyl 1-(4-bromophenyl)-5,6-dioxabicyclo[2.1.1]hex-2-ene-2,3-dicarboxylate(**8c**) exhibited two doublets at δ 7.44 and 7.38, a singlet at δ 6.13 and two singlet of methoxy signals at δ 3.83 and 3.66. In the HSQC spectrum these protons were correlated to the carbons at δ 131.1, 128.0, 99.6, 53.4 and 52.4, respectively. Furthermore, ^{13}CNMR analysis showed the presence of the quaternary acetalic carbon at δ 107.6. This carbon showed correlations, in the HMBC spectrum, with protons at δ 6.13 and 7.37 assigned to the acetalic and aromatic protons, respectively. The acetalic proton, in the HMBC experiment, gave heterocorrelation with the quaternary carbons at δ 143.4 and 135.5. On contrast, when the reduction mixture from **1b** was kept in $CDCl_3$ and/or chromatographed by TLC, lactone **10b** was isolated (**SCHEME 3B.7**).



SCHEME 3B.7 REARRANGEMENT OF OXOALDEHYDE **7b** AND SUGGESTED FORMATION PATHWAY FOR LACTONE **10b**

A rare example of 5,6-dioxabicyclo[2.1.1]hexane such as **8** has been reported and was obtained by hydroxyhydroperoxy-2,5-dihydrofurans by protic acids (Graziano and Carli 1982). In our cases, formation of **8** could be due to the concomitant presence of the aldehydic group and γ-oxoaryl function that promotes the easy attack of one carbonyl oxygen to the electrophilic carbon followed by ring closure to **8** (**SCHEME 3B.6**). Alternatively, from **7b** silica gel or slightly acid traces promote formation of lactone **10b** and this likely occurs via undetected labile epoxide **9b** (**SCHEME 3B.7**). This trend appears consistent with the electronic effects of the 4-methoxyaryl substituent. Intermediates as **9** have been sometime evidenced by NMR in the oxidation of furans (Adam et al. 1991) as well as rearrangements of epoxides to carbonyl compounds are reported and are particularly favoured in condensed or ester derivatives (Adam et al. 1991b; Baylon and Hanna 1995).

Control experiments conducted starting from **1b**, showed that as expected, owing to electron deficiency these furans , were not oxidized by peracids. In addition, oxidants as bromine or NBS did not react cleanly and afforded mixtures of products (**SCHEME 3B.8**).



SCHEME 3B.8 COMPARISON OF VARIOUS OXIDATION METHODS

On contrast, the photooxygenation followed by reduction is clean and occurs quantitatively as evidenced by the proton spectrum of the crude reaction mixture from **1b** (**FIGURE 3B.3**). Hence, this two-step one-pot reaction represents a useful alternative to oxidize electron-poor furans **1a**-**c**,**n**,**p** respect to classical methods (Merino et al. 2007; Piancatelli et al. 1994; Kobayashi et al. 1998; Gingerich and Jennings 1984).

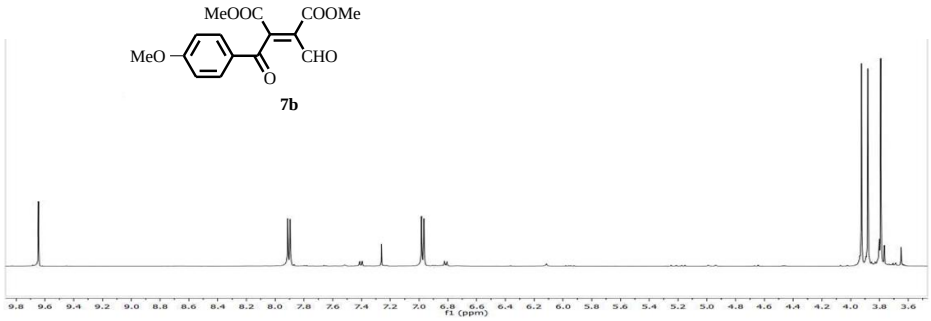
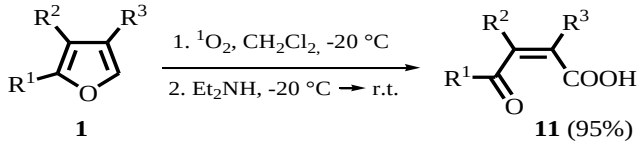


FIGURE 3B.3 ^{1}H NMR SPECTRUM OF THE CRUDE REDUCTION MIXTURE OF **1b**

Base treatment

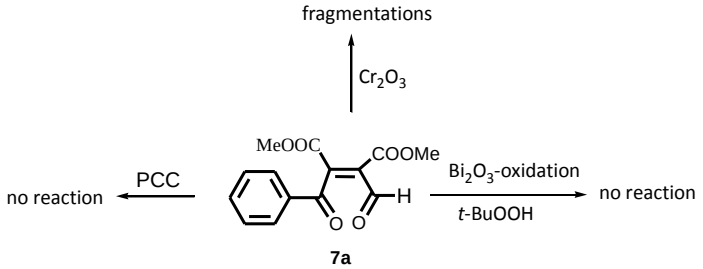
The base treatment was carried out by adding 1.2 equiv of diethylamine to the photooxygenation mixture at low temperature of furans **1a**-**c**,**l**-**o** and the resulting mixture was kept at rt for about 30 min. The base attack to the acid bridged hydrogen (Kernan and Faulkner 1988; Graziano and Iesce 1985) led to an open oxidized product

instead of the expected lactone for all series (**SCHEME 3B.9**). As an example, ^{13}C-NMR spectrum of the mixture from **1a**, in addition to the two signals of ester carbons, showed the presence of two new downfield signals at δ 192.5 and 166.9 due to the aromatic ketone and COOH group, respectively. All acids **11** were obtained in *cis*-configuration.



SCHEME 3B.9 ONE-POT PROCEDURE FOR ACIDS **11**

Similar results were obtained with tertiary amines, as Et_3N or DABCO. Anyhow, the best choice for obtaining acids **11** without further purification turned out to use Et_2NH that can be removed under reduced pressure in the presence of phosphorous anhydride. Having aldehydes **7** in the hands, we tried to oxidize them to acids **11**. All attempts using classical or novel (Lim et al. 2007; Malik and Chakraborty 2010) methods failed leading to the starting aldehydes or tarry mixtures of products (**SCHEME 3B.10**).



SCHEME 3B.10 OXIDATIONS OF ALDEHYDE **7a**

Instead, the one-pot procedure reported in **SCHEME 3B.9** is clean and quantitative as evidenced by the proton spectrum of the crude reaction mixture of **1a** (**FIGURE 3B.3**).

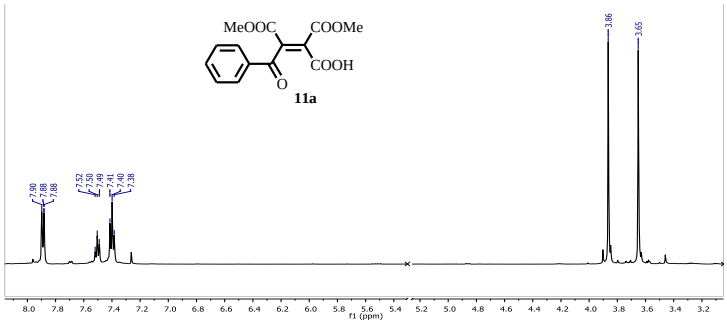
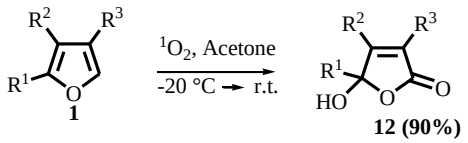


FIGURE 3B.4 ^{1}H-NMR SPECTRUM OF THE CRUDE BASE TREATMENT MIXTURE OF **1a**

*MB-sensityzed photooxygenation of furans **1** in acetone*

Conversion of furans **1a**-**c**,**l**,**m** into the corresponding γ-hydroxybutenolides **12** was readily accomplished in excellent yields when the photooxygenation was carried out in acetone at -20°C and the resulting endoperoxides slowly warmed to r.t. (**SCHEME 3B.11**).



Furan	R_1	R_2	R_3
1a	C_6H_5	CO_2Me	CO_2Me
1b	4-MeO-C_6H_4	CO_2Me	CO_2Me
1c	4-Br-C_6H_4	CO_2Me	CO_2Me
1l	C_6H_{11}	CO_2Me	CO_2Me
1m	C_6H_5	CO_2Me	4-$MeOC_6H_4$-CO

SCHEME 3B.11 ONE-POT PROCEDURE FOR γ-HYDROXYBUTENOLIDES **12**

Under the same conditions furans **1o**,**p** gave complex thermal-conversion mixtures. Also in these cases the reaction was particularly clean as evidenced by the proton spectrum of the crude mixture of **1c** (**FIGURE 3B.5**).

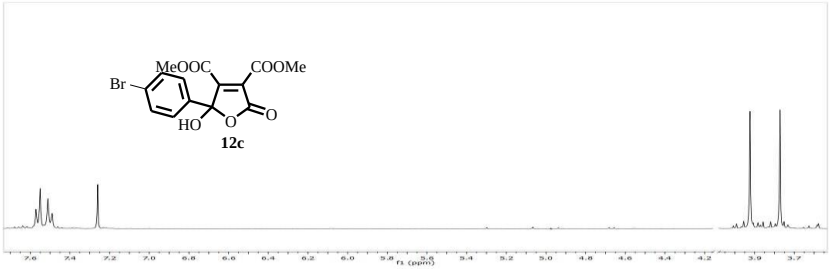
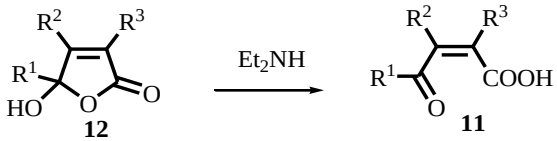


FIGURE 3B.5 ^{1}H-NMR SPECTRUM OF THE CRUDE OXYGENATION MIXTURE OF **1c** IN ACETONE

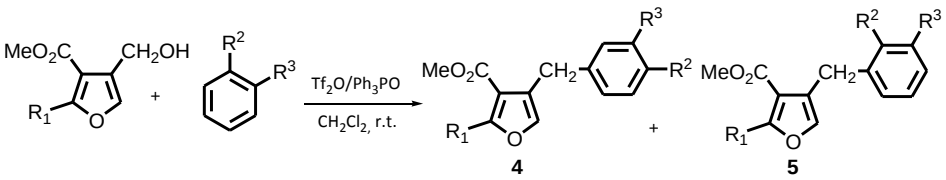
Control experiments showed that when butenolides **12** were treated with Et_2NH they immediately converted to acids **11** confirming that these conditions favour the acid open-form (**SCHEME 3B.12**).



SCHEME 3B.12 CONVERSION OF BUTENOLIDES **12** INTO ACIDS **11**

3C. CONCLUSION

In this part of PhD thesis a novel synthetic method has been developed for the access to diaryl furans of type **4** and **5** with a lignan backbone by a variant of the Friedel-Crafts reaction.



R_1 = C_6H_5, 4-$OMeC_6H_4$, 4-BrC_6H_4, H

R_2= OMe, OH

R_3= H, OMe

SCHEME 3C.1 Tf_2O/Ph_3PO PROMOTED FRIEDEL-CRAFTS ALKYLATION

The results have highlighted that Tf_2O is a promoting agent not only in Friedel-Crafts acylation reactions (Comegna et al. 2012), but also in Friedel-Crafts alkylations. To our knowledge Tf_2O-mediated alkylation of furans was not reported prevously. The reaction uses furanyl alcohols as starting furans and a combination of Tf_2O and Ph_3PO. Under these conditions the reaction time was significantly reduced and temperature from 0°C to r. t. could be used. The alkylation method occurred at room temperature in a short time, with a reduction of step and without acid catalysts. The presence of furan system highlights manifold elaborations of the heterocyclic ring to a variety of product types (Keay et al. 2005; Keay et al. 2008). From a biological point of view, preliminary data obtained by Researchers of the Second University of Naples evidenced an antibiotic activity especially for compound **5i** (**FIGURE 3C.1**) which could be a good candidate as a possible antibiotic.

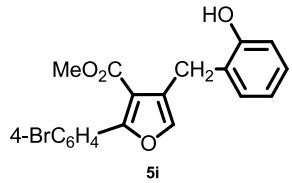
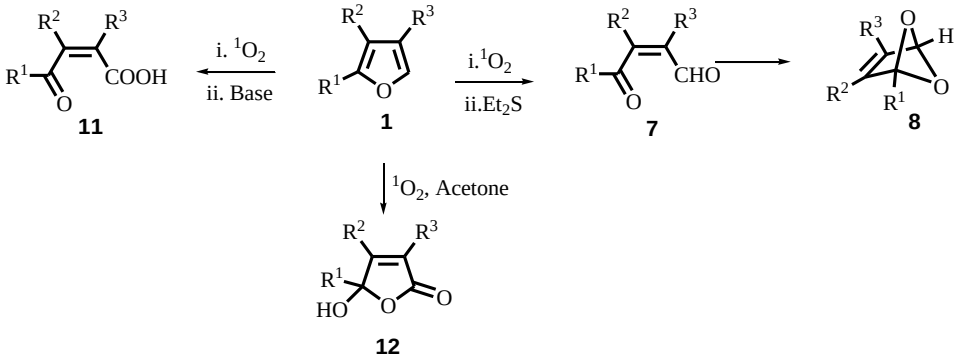


FIGURE 3C.1 COMPOUND **5I**

In addition, studies directed to examine the reactivity of this furan-type and other trisubstituted aryl furans, previously not examined, toward singlet oxygen have led to results particularly interesting and provide more knowledge on the reactivity and synthetic potential of furans. Despite the electrophilicity of singlet oxygen, the high propensity of furan system to add this species overcomes even the negative effects of the electron-withdrawing groups of furans **1**. Substituent effects have evidenced that in the presence of two of these groups and an α-aryl substituent the post-oxidative reactions appear particularly clean and afford useful C-4 synthons in excellent yields. All the reactions are one-pot (**SCHEME 3C.2**) and, due to the cyclic structure of the endoperoxide precursor, occur stereoselectively.



SCHEME 3C.2 APPLICATIONS OF DYE-SENSITIZED PHOTOOXYGENATION OD TRISUBSTITUTED ARYL FURANS

The procedure to aldehydes **7** remains the most useful to obtain enediones from these electron-poor furans if compared with oxidations with peracids or bromine or NBS which do not occur or give not cleanly mixtures(Piancatelli et al. 1994; Kobayashi et al.

1998; Gingerich et al. 1984). Particularly interesting is the high-yield general route for versatile (DellaGreca et al. 2013) acids **11** since attempts to oxidize aldehydes **7** failed using various methods (Lim et al. 2007; Malik et al. 2010). Controlled reaction conditions allow to address the transformation to the corresponding cyclic forms **12**.

During this investigation novel highly functionalized lignan-like compounds have been obtained starting from a single trisubstituted aryl furan as reported for **1a**in **FIGURE 3C.2**.

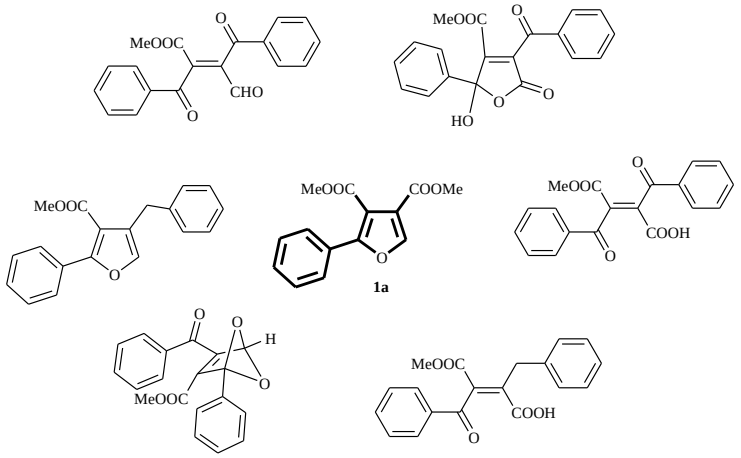


FIGURE 3C.2 FUNCTIONALIZED LIGNAN-LIKE COMPOUNDS FROM ARYL FURAN **1a**

3D. EXPERIMENTAL SECTION

LIST OF ABBREVIATIONS USED:

DABCO = 1,4-diazabicycle[2.2.2]octane

DMAD = dimethylacetilendicarboxylate

EE = diethyl ether

EP = petroleum ether

AcOEt = ethyl acetate

DCM = dichlorometane

MeOCOCl = methylchloroformiate

Tf_2O = anhydride trifluorometansolfonic

r.t. = room temperature

THF = tetrahydrofuran

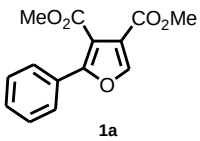
NMM = *n*-methylmorpholine

Materials and methods: All reagents and solvents were obtained from commercial suppliers and used without further purification. 2-Aryldicarbomethoxyfurans (Fan et al. 2005) were synthesized according to the literature; dimethyl furan-3,4-dicarboxylate was commercially available. ^{1}H NMR (400 MHz or 500 MHz) and ^{13}C NMR (100 MHz or 126 MHz) spectra were recorded on a Bruker DRX-400 or INOVA 500 spectrometers at r.t. The carbon multiplicity was evidenced by DEPT experiments. The proton couplings were evidenced by ^{1}H–^{1}H COSY experiments. The heteronuclear chemical shift correlations were determined by HMQC and HMBC pulse sequences. IR spectra were recorded on a Jasco FT/IR-430spectrometer. Electronic impact mass spectra (EI-MS) were recorded on a GC-MS QP5050A (Shimadzu) equipped with a 70 eV EI detector.Thin layer chromatography (TLC) was performed on aluminum plates precoated with Merck Silica Gel 60 F254 as the adsorbent (0.25, 0.50, 1.0 and 2.0 mm). 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).

Experimental-Part 3A

Synthesis of dicarboxymethoxyfurans 1a-c,l: 2.70 mmol of 2-bromoacetophenone and 0.27 mmol of DABCO in 10 ml di DCM. The mixure kept to stirring at room temperature for 30 min, than 4.06 mmol of K_2CO_3 and 1.35 mmol of DMAD were added. The reaction was conducted over nigth (~15 h) in stirring.The mixture reaction was extracted with H_2O and CH_2Cl_2.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: **1a** with EtOAc/EP 10% (85% yield), **1b** with EtOAc/Hex 20% (66% yield), **1c** with EtOAc/PE 10% (70% yield) and **1e** EtOAc/EP 10% (75% yield)

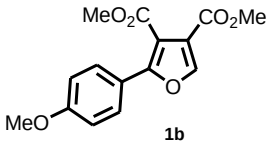
2-FENIL-3,4-DICARBOXYMETHYL FURAN (1a)



1a

1a:^{1}**H NMR** (500MHz) δ : 7.97 (s, 1H, H-5), 7.70 (m, 3H, H-3′- 4′- 5′), 7.40 (d, *J*= 7.4 Hz, 2H, H-2′- 6′), 3.91 (s, 3H, α-OMe), 3.86 (s, 3H, β-OMe); ^{13}**C NMR** (125MHz) δ: 165.0 (C-β), 162.3 (C-α), 154.1 (C-2), 146.3 (C-1′-5′), 128.7 (C-3'-5'), 126.4 (C-2'-6'), 119.8 (C-4), 113.5 (C-3), 52.7 (β-OMe), 52.0 (α-OMe).

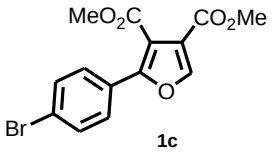
DIMETHYL-2(4-METOXYPHENYL)FURAN-3,4-DICARBOXYLATE (1b)



1b

1b:[1]**H NMR** (500MHz) δ: 7.91 (s, 1H, H-5), 7.67 (d, *J* = 9.0 , 2H, H-2′and 6′), 6.94 (d, *J* =9.0, 2H, H-3′ and 5′), 3.89 (s, 3H, α-OMe), 3.85 (s, 3H, 4′-OMe), 3.84 (s, 3H, β-OMe) ; **[13]C NMR** (125MHz) δ: 165.1 (C-β), 162.6 (C-α), 160.8 (C-4′), 154.9 (C-2), 145.9 (C-5), 114.3 (C-3′-5′),128.4 (C-2′-6′), 121.6 (C-1), 119.9 (C-4), 112.3 (C-3), 52.7 (β-OMe), 52.1 (α-OMe), 55.5 (4′-OMe).

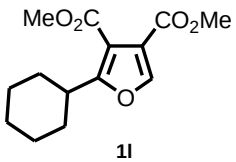
DIMETHYL-2-(4-BROMOPHENYL)FURAN-3,4-DICARBOXYLATE (1c)



1c

1c:[1]**H NMR** (500MHz) δ : 7.96 (s, 1H, H-5), 7.58 (d, *J* = 8.8 , 2H, H-2′and 6′), 7.54 (d, *J* = 8.8, 2H, H-3′ and 5′), 3.90 (s, 3H, α-OMe), 3.86 (s, 3H, β-OMe); **[13]C NMR** (125MHz) δ: 164.5 (C-β), 162.0 (C-α), 153.1 (C-4′),152.0 (C-2), 146.4 (C-5131.9 (C-2′-6′), 127.9 (C-1),), 127.0 (C-3′-5′), 123.7 (C-4), 119.9 (C-3), 52.7 (β-OMe), 52.0 (α-OMe).

DIMETHYL 2-CYCLOHEXYLFURAN-3,4-DICARBOXYLATE (1l)

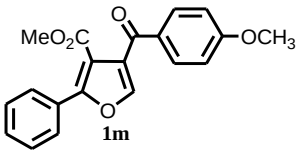


1l

1l:oil;**IR** (CH_2Cl_2) 1735, 1713 cm-1; **[1]H NMR** (500MHz, CDCl3) δ: 7.74 (s, 1H, H-5), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.84 (m, 1H, H-1′), 2.20-1.20 (m, 10H, H-2′-H-5′); **[13]C NMR** (125MHz) δ: 165.9, 163.8, 162.8, 145.2, 118.4, 111.2, 51.9 (x2), 36.8, 30.8 (x2), 26.0 (x2), 25.7; **EI-MS**: m/z = 266.3 [M]+.

Synthesis of furans 1m,n : Furans **1m**and **1n** were prepared according to literature procedures (Comegna et al. 2012).

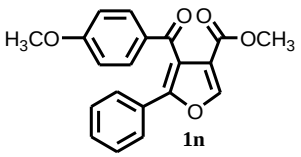
METHYL 4-(4-METHOXYBENZOYL)-2-PHENYLFURAN-3-CARBOXYLATE (1m)



1m

1m:oil;**IR** (CH_2Cl_2): 3021, 2942, 1716, 1612, 1604, 1240, 1035 cm^{-1}; **^{1}H NMR** (500 MHz, CDCl3) 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, -OCH_3), 3.65 (s, 3H, -$COOCH_3$); **^{13}C NMR** (126MHz, $CDCl_3$) 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** m/z= 336.10 $[M]^+$.

METHYL 4-(4-METHOXYBENZOYL)-5-PHENYLFURAN-3-CARBOXYLATE (1n)

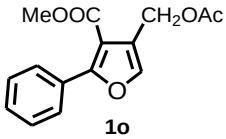


1n

1n: oil; **IR** (CH_2Cl_2): 3020, 1725, 1660, 1598, 1217, 1165 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$) 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, -O*C*H_3), 3.66 (s, 3H, -O*C*H_3); **^{13}C NMR** (100MHz, $CDCl_3$) 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**m/z= 336.10 $[M]^+$.

Synthesis of methyl 4-(acetoxymethyl)-2-phenylfuran-3-carboxylate (1o):

0.5mmol of alcohol **2a** see below in presence of 0.75 ml of acetic anhydride and 0,5 ml of pyridine kept to stirring at room temperature over night. The residue was purified by column chromatography with EtOAc/EP 20% .Derivate **1o** was obtained with a yield of 90%.

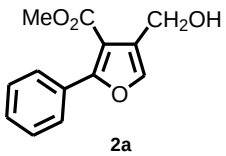


1o

1o:IR (CH_2Cl_2) 1740, 1721 cm-1; **^{1}H NMR** (400MHz, $CDCl_3$) δ: 7.81 (m, 2H, Ar-H), 7.49 (s, 1H, H-5), 7.42 (m, 3H, Ar-H), 5.23 (s, 2H, -CH_2O-), 3.81 (s, 3H, OCH_3), 2.12 (s, 3H, CH_3); **^{13}C NMR** (126MHz, $CDCl_3$) δ 170.6 ($OCOCH_3$), 163.9 ($COOCH_3$), 158.9 (C-2), 140.9 (C-5), 129.7 (C-1'), 129.5 (C-4'), 128.6 (C2' and C-6'), 128.1 (C-3' and C-5'), 122.3 (C-3), 112.3 (C-4), 58.0 (-CH2-), 51.5 (OCH_3), 20.9 ($COCH_3$); **EI-MS**: m/z = 274.3 [M]+.

Furan **1p** (≡ **4a**) was prepared as above.

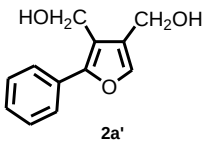
Synthesis of furanyl alcohols 2a,a',c,d: Methanol (4ml) was added over a period of 1h to a refluxing mixture of $NaBH_4$ (175mg, 4.6mmol) and dimethyl 2-phenylfuran-3,4-dicarboxylate (1.2 g, 4.6mmol) in t-BuOH (18ml). The resultant mixture was refluxed for 2h. The reaction was quenched by addition of H_2O (12ml). Most of the organic solvents were evaporated on a rotary evaporator, and residue extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4. After the evaporation of the solvent, the residue was chromatographed on silica gel column using EtOAc-hexane 10% and gave: starting diester (37% yield), **2a** (50% yield) and diol **2a'** (13% yield).



2a

METHYL 4-(HYDROXYMETHYL)-2-PHENYLFURAN-3-CARBOXYLATE (2a) :**IR** (CH_2Cl_2) 3655, 3065, 2990, 1717, 1600, 1282. **^{1}H NMR** (500MHz, $CDCl_3$): 7.71-7.69 (m, 2 H, H-2' and H-6'); 7.45 (s, 1 H, H-5); 7.44- 7.42 (m, 3 H, H-3'- H-5'); 4.63 (s, 2 H, -CH_2O-); 3.81(s, 3 H, MeO). **^{13}C NMR** (126 MHz, $CDCl_3$): 165.2 (COOMe); 159.3 (C-2); 139.8 (C-5); 130.0 (C-1'); 129.5

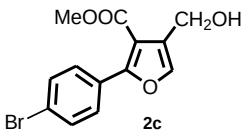
(C-3'and C-5'); 128.8 (C-4'); 128.0 (C-2') e C-6'); 127.3 (C-3); 112.5 (C-4); 55.9 (-CH_2O-); 51.8 (MeO). **EI-MS**: m/z = 232.07 [M]+.



2a'

(2-PHENYLFURAN-3,4-DIYL)DIMETHANOL (2'a): IR (CH_2Cl_2) 3695, 3560, 3065, 2990, 1600, 1282. **^{1}H NMR** (500MHz, $CDCl_3$): 7.59 (m, 2 H, H-2' and H-6'); 7.41 (t, 2 H, J=7.7, H-3' and H-5'); 7.38 (s, 1H, H-5); 7.32 (dd, 1H, J= 10.8, 4.0, H-4'); 4.70 (s, 2H, -CH2O-); 4.56 (s, 2H, -CH_2O-). **^{13}C NMR** (126MHz, $CDCl_3$): 153.1 (C-2); 139.3 (C-5); 130.5 (C-1'); 128.7 (C-3' and C-5'); 128.1(C-4'); 126.7(C-2' and C-6'); 126.5 (C-3); 119.5 (C-4); 55.3(CH_2); 54.5 (CH_2). **EI-MS**: m/z = 204.08 $[M]^+$.

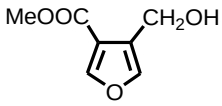
Furan **2c** was prepared using the same procedure of **2a** starting from dimethyl 2-(4-bromophenyl)furan-3,4-dicarboxylate (676 mg, 2 mmol).Yield:43%



2c

METHYL 2-(4-BROMOPHENYL)-4-(HYDROXYMETHYL)FURAN-3-CARBOXYLATE (2c): oil; **IR** (CH_2Cl_2): 3617, 2947, 2918, 3040, 1694, 1476, 1129,912, 835. **^{1}H NMR** (400MHz, $CDCl_3$): 7.58 (d, J=8.3,H-2'and H-6'; 7.55 (d, J=8.5, H-3' and H-5'); 7.44 (s, H-5); 4.61 (s, CH_2); 3.80 (s, Me). **^{13}C NMR** (101MHz, $CDCl_3$):165.1 (*C*OOMe); 157.0 (C-2); 140.0 (C-5); 131.2 (C-3' and C-5'); 130.3 (C-2' and C-6'); 128.8 (C-4'); 127.4 (C-3); 123.9 (C-1'); 112.8(C-4); 55.8 (-CH_2O-); 51.9 (COO*Me*).

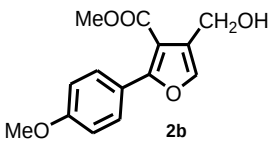
Furan **2d** was prepared using the same procedure of **2a** starting from dimethyl furan-3,4-dicarboxylate (368 mg, 2 mmol), commercially available. Yield:40%



2d

METIL 4-(HYDROXYMETHYL)FURAN-3-CARBOXYLATE (2d): **IR** (CH_2Cl_2): 1708, 1543, 1315, 1143, 1107, 1019. **^{1}H NMR** (400MHz, $CDCl_3$): 7.97 (*s*, 1H, H-2); 7.39 (*s*, 1H, H-5); 4.61 (*s*, 2H, -CH_2O-); 3.86 (*s*, 3H, MeO). **^{13}C NMR** (101MHz, $CDCl_3$): 164.9 (*C*OOMe); 149.3 (C-2), 141.1 (C-5), 125.2 (C-3), 117.8 (C-4), 55.3 (-CH_2O-), 51.9 (COO*Me*);**EI-MS**: m/z = 156.07 [M]+.

Synthesis of furanyl alcohol 2b: To a solution of 4-(methoxycarbonyl)-5-(4-methoxyphenyl)furan-3-carboxylic acid, (735 mg, 2.7mmol) and NMM (391 μl, 3.5 mmol) in THF (8.8 ml) methyl chloroformate (270 μl, 3.5 mmol) was added dropwise at 0°C under stirring. After 2h, the solution was filtered, and the salt was washed with THF (3x2.5ml). A suspension of $NaBH_4$ (147 mg, 3.89 mmol) in H_2O (1ml) was then added dropwise to the filtrate in an ice bath under stirring. After 2h the temperature was allowed to increase to r. t. After 20 min, the solvent was evaporated under reduced pressure and the residue dissolved in EtOAc (15ml). The solution was washed with brine until neutral. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give the crude alcohol that was purified by gel chromatography using EtOAc-n-hexane 30%. Yield 40%



2b

METHYL 4-(HYDROXYMETHYL)-2-(4-METHOXYPHENYL)FURAN-3-CARBOXYLATE (2b): IR (CH_2Cl_2): 3700, 3060, 3040, 1717, 1600, 1282. **^{1}H NMR** (500MHz, $CDCl_3$): 7.67 (br *d*, 2 H, *J* = 8.8, H-2' and H-6'); 7.41 (*s*, 1 H, H-5); 6.95 (*d*, 2 H, *J* = 8.9, H-3' and H-5'); 4.62 (*s*, 2 H, -CH_2O-); 3.86 (*s*, 3 H, MeO); 3.81 (*s*, 3 H, MeO). **^{13}C NMR** (126MHz, $CDCl_3$): 165.3 (*C*OOMe); 160.5 (C-4'); 159.5 (C-2); 139.3 (C-5); 130.3 (C-2') and C-6'); 128.2 (C-3); 122.5 (C-1'); 113.5 (C-3' and C-5'); 111.5 (C-4); 55.9 (-CH_2O-); 55.3 (MeO); 51.7 (COO*Me*). **EI-MS**: *m/z* = 262.28 $[M]^+$.

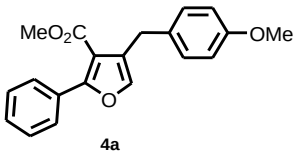
Friedel–Crafts alkylation experiments of furanyl alcohol 2a (Scheme 3a.7): Pure **2a** (58 mg, 0.25 mmol) was dissolved in 2ml of dry solvent (DCM) and then 5 equiv of anisole was added. The mixture was cooled to -20 °C and Tf_2O (2.5 equiv) added dropwise at this temperature. On completion of the reaction (controlled by TLC), the mixture was washed with saturated $NaHCO_3$ solution and extracted twice with ethyl ether. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue that was chromatographed on preparative silica gel TLC using DCM-n-hexane 10% as eluent.

Pure **2a** (58 mg, 0.25 mmol) was dissolved in 2ml of dry DCM and then 5equiv of anisole was added. The mixture was cooled to -20 °C and Tf_2O (2.5 equiv) added dropwise at this temperature. Then 2,6-lutidine (2.5 equiv) was added at the same temperature. The resulting mixture was stirred under N_2 atmosphere at -20° C for 20 h. Work up and purification were performed as reported above.

General procedure for Tf_2O-Ph_3PO mediated Friedel-Crafts alkylation of furanyl alcohols 2: To a solution of Ph_3PO (0.6 mmol) in dry DCM (1 ml), Tf_2O (0.1 ml, 0.6 mmol) was added at 0°C and the mixture was stirred for 15 min at room temperature. Then, arene (0.5 mmol) and furanyl alcohol (0.5 mmol in 1 ml of dry CH_2Cl_2) were added and the mixture was stirred. Upon completion of the reaction (1h), the organic solvent was evaporated and the residue was chromatographed by preparative TLC using EtOAc-n-hexane as eluent.

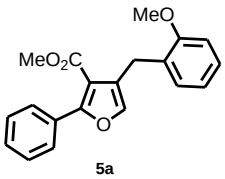
Synthesis of methyl 4-(4-methoxybenzyl)-2-phenylfuran-3-carboxylate (4a) and methyl 4-(2-methoxybenzyl)-2-phenylfuran-3-carboxylate (5a):

Prepared according GP using furanyl alcohol **2a** (116 mg) and anisole (54 mg, 55 μl). Purification was achieved by preparative TLC (*n*-hexane/AcOEt 9:1). **4a(**37%) and**5a** (24%).



4a

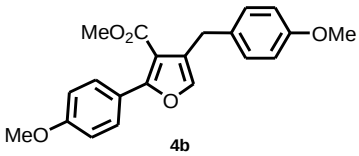
4a: **IR** (CH_2Cl_2): 1715, 1547, 1493, 1441,1213, 1086, 1030. **^{1}H NMR** (400MHz, $CDCl_3$): 7.76 (*d*, 2H, *J* = 7.9, H-2' and H-6'); 7.46–7.36 (*m*, 3H, H-3' and H-5'); 7.18 (*d*, 2H, *J* = 8.4, H-2" and H-6"); 7.04 (*s*, 1H, H-5); 6.86 (*d*, 2H, *J*=8.5, H-3" and H-5"); 3.93 (*s*, 2H, -CH_2-); 3.81 (*s*, 3 H, MeO); 3.75 (*s*, 3 H, MeO).**^{13}C NMR** (101MHz, $CDCl_3$): 164.8 (*C*OOMe); 158.2 (C-4"); 157.9 (C-2); 140.1 (C-5); 131.6 (C-1'); 130.1 (C-1"); 129.7 (C-2"and C-6"); 129.0 (C-4') 128.5 (C-3'and C-5'); 128.1 (C-2' and C-6'); 122.3 (C-3); 113.7 (C-3" and C-5"); 110.4 (C-4); 55.2 (MeO); 51.3 (COO*Me*); 30.3 (-CH_2-). **EI-MS**: *m*/*z* = 322.12 $[M]^+$.



5a

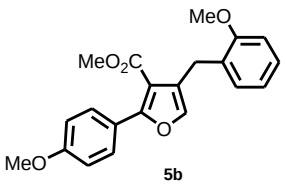
5a: **IR** (CH_2Cl_2): 1715, 1547, 1493,1440, 1215, 1076. **^{1}H NMR** (400MHz, $CDCl_3$): 7.77 (br *d*, 2H, *J* = 7.8, H-2' and H-6'), 7.43-7.35 (*m*, 3 H, H-3' and H-5'), 7.23 (*t*, 1H, *J* = 8.0, H-4"), 7.17 (*d*, 1H, *J* = 7.5, H-6"), 7.00 (*s*, 1H, H-5), 6.90 (*d*and*t*, 3 H, *J* = 7.4, H-3" and H-5"), 3.99 (*s*, 2H, -CH_2-), 3.84 (*s*, 3H, MeO), 3.76 (*s*, 3H, MeO). **^{13}C NMR** (101MHz, $CDCl_3$): 165.8 (*C*OOMe); 157.7 (C-2); 157.5 (C-2"); 140.2 (C-5); 130.8 (C-1'); 130.0 (C-6"); 129.0 (C-4'); 128.7 (C-3); 128.2 (C-3' and C-5'); 128.0 (C-2' and C-6'); 127.5 (C-4"); 126.2 (C-1"); 120.4 (C-5"); 110.3 (C-4 and C-3"); 55.3 (MeO), 51.2 (COO*Me*), 25.2 (-CH_2-). **EI-MS**: *m*/*z* = 322.10 $[M]^+$.

Synthesis ofmethyl 4-(4-methoxybenzyl)-2-(4-methoxyphenyl)furan-3-carboxylate (4b) and 4-(2-methoxybenzyl)-2-(4-methoxyphenyl)furan-3-carboxylate (5b): Prepared according GP using furanyl alcohol **2b** (131mg) and anisole (54mg, 55 µl). Purification was achieved by preparative TLC (*n*-hexane/AcOEt 9:1) and led to **4b** (35%) and **5b** (22%).



4b

4b: **IR** (CH_2Cl_2): 1716, 1535, 1493, 1439, 1213, 1070. **^{1}H NMR** (400MHz, $CDCl_3$: 7.76 (d, J = 8.6, H-2′ and H-6′); 7.19 (d,J = 8.4, H-2′′and H-6′′); 7.01 (s, H-5); 6.97, 6.96 (d, J = 8.4, H-3′ and H-5′); 6.87 (d, J=8.5, H-3′′ and H-5′′); 3.94 (s,CH_2); 3.87 (s, Me); 3.82 (s, Me); 3.76 (s, Me).**^{13}C NMR** (101MHz, $CDCl_3$): 164.8 (*C*OOMe),160.3 (C-4′), 158.6 (C-4″), 158.0 (C-1), 139.5 (C-5), 131.9 (C-1′), 129.9 (C-2′ and C-6′), 129.7 (C-2″ and C-6″), 127.2 (C-3), 122.9 (C-1″), 113.8 (C-3′ and C-5′), 113.5 (C-3″) and C-5″), 55.3 (MeO), 55.3 (MeO), 51.2 (COO*Me*), 30.5 (-CH_2-); **EI-MS**: *m*/*z* = 352.15 $[M]^+$.

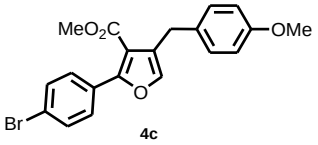


5b

5b: **IR** (CH_2Cl_2): 1716, 1530, 1491, 1439, 1213, 1054, 1019. **^{1}H NMR** (400MHz, $CDCl_3$): 7.76 (*d*, 2 H, *J*=9.0, H-2′ and H-6′); 7.24 (*td*, 1 H, *J*=7.8, 1.7, H-4″); 7.19 (br *d*, 1 H, *J*=7.9, H-6″); 6.98–6.93 (*m*, 4 H, H-5, H-3′, H-5′ and H-5″); 6.91 (*d*, 1 H, *J* = 7.9, H-3″); 4.00 (*s*, 2H, -CH_2-), 3.87 (*s*, 3H, MeO); 3.86 (s, 3H, MeO); 3.77 (s, 3H, MeO). **^{13}C NMR** (101MHz, $CDCl_3$): 165.0 (*C*OOMe); 160.2 (C-4′); 158.3 (C-2); 157.4 (C-2″); 139.7 (C-5); 130.1 (C-6″); 129.9 (C-2′ and C-6′); 129.7 (C-1′); 128.3 (C-3); 127.5 (C-4″); 126.1 (C-1″); 120.5 (C-5″);

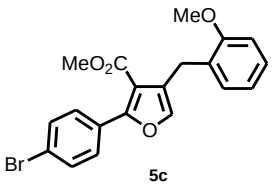
113.8 (C-4); 113.5 (C-3' and C-5'); 110.4 (C-3"); 55.4 (MeO); 55.3 (MeO); 51.2 (*C*OOMe); 25.4 (-CH_2-). **EI-MS**: *m/z* = 352.09 $[M]^+$.

Synthesis of methyl 2-(4-bromophenyl)-4-(4-methoxybenzyl)furan-3-carboxylate (4c) and methyl 2-(4-bromophenyl)-4-(2-methoxybenzyl)furan-3-carboxylate (5c): Prepared according GP using furanyl alcohol **2c** (155 mg) and anisole (54 mg, 55 μl). Purification was achieved by preparative TLC (*n*-hexane/AcOEt 85:15) and led to **4c** (33%) and **5c** (21%).



4c

4c: IR (CH_2Cl_2): 1716, 1611, 1512, 1176, 1078. **^{1}H NMR** (400MHz, $CDCl_3$): 7.66 (*d*, 2H, *J* = 7.3, H-2' and H-6'); 7.54 (*d*, 2H, *J*=7.3, H-3'and H-5'); 7.16 (*d*, 2 H, *J*=7.6, H-2" and H-6"); 7.03 (*s*, 1H, H-5); 6.85 (*d*, 2H, *J*=7.3, H-3" and H-5"); 3.91 (*s*, 2H, -CH_2-); 3.80 (*s*, 3H, MeO); 3.75 (*s*, 3H, MeO).**^{13}C NMR** (101MHz, $CDCl_3$): 164.5 (*C*OOMe); 158.0 (C-4"); 157.0 (C-1); 140.3 (C-5); 131.5 (C-1'); 131.2 (C-3'and C-5'); 129.8 (C-2"and C-6"); 129.6 (C-2'and C-6'); 129.0 (C-1"); 127.5 (C-2); 123.4 (C-4'); 113.8 (C-4, C-3"and C-5"); 55.2 (MeO); 51.4 (COO*Me*); 30.3 (-CH_2-). **EI-MS**: *m/z* = 400.06 $[M]^+$.

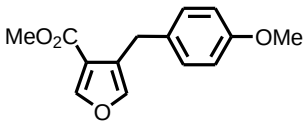


5c

5c:**IR** (CH_2Cl_2): 1716, 1605, 1522, 1175, 1080. **^{1}H NMR** (400MHz, $CDCl_3$): 7.67 (*d*, 2H, *J*= 7.1, H-3'and H-5'); 7.53 (*d*, 2H, *J*=7.1, H-2'and H-6'); 7.23 (*m*, 1H, H-4"); 7.16 (*d*, 1H, *J*=7.4, H-6"); 6.99 (*s*, 1H, H-5); 6.90 (br *t*, 2H, *J*=7.6, H-3"and H-5"); 3.97 (*s*, 2H, -CH_2-); 3.84 (*s*, 3H, MeO), 3.77 (*s*, 3H, OCH_3). **^{13}C NMR** (101MHz, $CDCl_3$): 164.7 (*C*OOMe); 157.2 (C-2"); 156.7 (C-1); 140.5 (C-5); 131.2 (C-3'and C-5'); 130.0 (C-6"); 129.9 (C-2'and C-6');

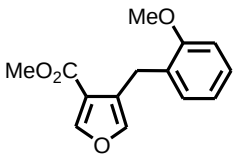
129.2 (C-1'); 127.9 (C-3); 127.6 (C-4"); 126.4 (C-1"); 123.3(C-4'); 120.5 (C-5"); 113.8 (C-4); 110.3 (C-3"); 55.3 (MeO); 51.4 (COO*Me*); 25.3 (-CH_2-). **EI-MS**: *m*/*z* =400.04 $[M]^+$.

Synthesis of methyl 4-(4-methoxybenzyl)furan-3-carboxylate (4d) and methyl 4-(2-methoxybenzyl)furan-3-carboxylate (5d): Prepared according GP using furanyl alcohol **2d** (78mg) and anisole (54mg, 55 μl). Purification was achieved by preparative TLC (*n*-hexane/AcOEt 9:1, two runs) and led to **4d** (29%) and **5d** (17%).



4d

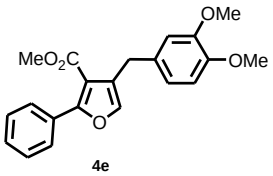
4d: **IR** (CH_2Cl_2): 1722, 1600, 1588, 1494, 1091. **^{1}H NMR** (500MHz, $CDCl_3$): 7.99 (*d*, 1H, *J*=1.7, H-2); 7.18 (*d*, 2H, *J*=8.6, H-2' and H-6'); 7.03 (*d*, 1H, *J*=1.7, H-5); 6.86 (*d*, 2H, *J*=8.6, H-3'and H-5'); 3.95 (*s*, 2H, -CH_2-); 3.82 (*s*, 3H, MeO), 3.81(*s*, 3H, MeO). **^{13}C NMR** (101 MHz, $CDCl_3$): 164.0 (*C*OOMe); 158.0 (C-4'); 149.0 (C-2), 141.7 (C-5); 131.6 (C-1'); 129.6 (C-2'and C-6'); 125.6 (C-3);118.0 (C-4); 113.7 (C-3' andC-5'); 55.1 (MeO); 51.1 (*C*OOMe); 29.4 (-CH_2-). **EI-MS**: *m*/*z* = 246.08 $[M]^+$.



5d

5d: **IR** (CH_2Cl_2): 1720, 1599, 1585, 1490, 1091. **^{1}HNMR** (500MHz, $CDCl_3$): 7.98 (*s*, 1H, H-2), 7.23 (*t*, 1H, *J*=7.8, H-4'); 7.19 (*d*, 1H, *J*=7.1, H-6'); 7.00 (*s*, 1H, H-5); 6.92-6.89 (*d*and*t*, 2H, H-3' and H-5'); 4.01 (*s*, 2H, -CH_2-); 3.84 (MeO); 3.83 (MeO). **^{13}CNMR** (126MHz, $CDCl_3$): 164.1 (*C*OOMe); 157.3 (C-2'); 148.7 (C-2); 142.1 (C-5); 130.1 (C-6'); 128.3 (C-1'); 127.6 (C-4'); 124.4 (C-3); 120.4 (C-5'); 118.2 (C-4); 110.4 (C-3'); 55.3 (MeO); 51.2 (*C*OOMe); 24.4 (-CH_2-). **EI-MS**: *m*/*z* = 246.11 $[M]^+$.

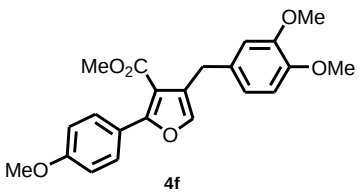
Synthesis of methyl 4-(3,4-dimethoxybenzyl)-2-phenylfuran-3-carboxylate (4e): Prepared according GP using furanyl alcohol **2a** (116 mg) and 1,2-dimethoxybenzene (69 mg). Preparative TLC (*n*-hexane/AcOEt 8:2) gave only isomer **4e**(53%).



4e

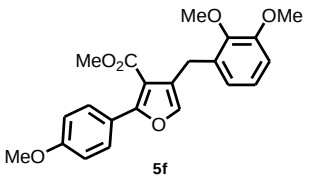
4e: **IR** (CH_2Cl_2): 1715, 1514, 1214, 1139, 1028. **^{1}HNMR** (400MHz, $CDCl_3$): 7.78 (*dd*, 2H, *J* = 7.8, 1.4, H-2'and H-6'); 7.46-7.38 (*m*, 3H, H-3'–H-5'); 7.06 (*s*, 1H, H-5); 6.87-6.78 (*m*, H-2", H-5" and H-6"); 3.96 (*s*, 2H, -CH_2-), 3.90 (*s*, 3H, MeO), 3.88 (*s*, 3H, MeO), 3.78 (*s*, 3H, OCH_3). **^{13}CNMR** (101MHz, $CDCl_3$): 164.7 (*C*OOMe); 158.2 (C-1); 148.9 (C-3"); 147.5 (C-4"); 140.1 (C-5); 132.2 (C-1'); 130.3 (C-1"); 129.2 (C-4'); 128.3 (C-3'and C-5'); 128.1 (C-2' and C-6'); 127.3 (C-3); 120.7 (C-6"); 112.1 (C-2"); 111.4 (C-4); 111.2 (C-5"); 55.9 (MeO);55.9 (MeO); 51.3 (COO*Me*); 30.9 (-CH_2-). **EI-MS**: *m*/*z* = 352.08 $[M]^+$.

Synthesis of methyl 4-(3,4-dimethoxybenzyl)-2-(4-methoxyphenyl)furan-3-carboxylate (4f) andmethyl 4-(2,3-dimethoxybenzyl)-2-(4-methoxyphenyl)furan-3-carboxylate (5f): Prepared according GP using furanyl alcohol **2b** (131 mg) and 1,2-dimethoxybenzene (69 mg). Purification was achieved by preparative TLC (*n*-hexane/AcOEt. 8:2) and led to **4f** (26%) and **5f** (36%).



4f

4f: **IR** (CH_2Cl_2): 1714, 1500, 1177, 1076, 1029. **^{1}H NMR** (400MHz, $CDCl_3$): 7.76 (*d*, 2H, *J* = 9.1, H-2'and H-6'); 7.01 (*s*, 1H, H-5); 6.96 (*d*, 2H, *J*=9.1, H-3' and H-5'); 6.86-6.77 (*m*, 3H, H-2", H-5"and H-6"); 3.95 (*s*, 2H, -CH_2-); 3.89 (*s*, 3H, MeO); 3.88 (*s*, 3H, MeO), 3.87 (*s*, 3H, MeO), 3.77 (s, MeO). **^{13}C NMR** (101MHz, $CDCl_3$): 164.4 (*C*OOMe); 160.3 (C-4'); 158.4 (C-2); 148.8 (C-4"); 147.8 (C-3"); 139.5 (C-5); 132.2 (C-1'); 129.9 (C-2'and C-6'); 129.8 (C-1"); 127.1 (C-3); 120.7 (C-6"); 113.4 (C-3'and C-5'); 112.1 (C-2"); 111.2 (C-5"); 111.1 (C-4); 55.9 (MeO); 55.8 (MeO); 55.3 (MeO); 51.2 (COO*Me*); 31.0 (-CH_2-). **EI-MS**: *m*/*z* = 382.07 $[M]^+$.

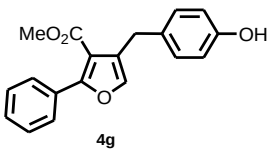


5f

5f: **IR** (CH_2Cl_2): 1715, 1580, 1170, 1076, 1025. **^{1}H NMR** (400MHz, $CDCl_3$): 7.76 (*d*, 2H, *J* = 9.1, H-2'and H-6'); 7.03 (*t*, 1H, *J*=7.8, H-5"); 6.98–6.93 (*s*+*d*, 3H, H-5, H-3'and H-5'); 6.84 (*dd*, 1H, *J* = 8.2, 1.5, H-6"); 6.81 (*dd*, 1H, *J*=7.7, 1.5, H-4"); 4.03 (*s*, 2H,-CH_2-); 3.90 (*s*, 3H, MeO); 3.87 (*s*, 3H, MeO); 3.84 (*s*, 3H, MeO), 3.78 (*s*, 3H, MeO). **^{13}C NMR** (101MHz, $CDCl_3$): 167.7 (*C*OOMe); 160.4 (C-4'); 158.3 (C-2); 152.9 (C-2" and C-3"); 139.7 (C-3); 133.8 (C-2); 130.1 (C-2'and C-6'); 123.7 (C-6"); 122.9 (C-1'); 122.2 (C-5"); 113.4 (C-3'and C-5'); 110.8 (C-4"); 60.6 (MeO); 55.7 (MeO); 55.2 (MeO); 51.3 (COO*Me*); 25.4 (-CH_2-). **EI-MS**: *m*/*z* = 382.10 $[M]^+$.

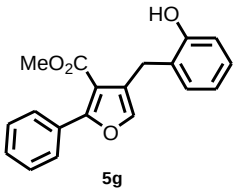
Synthesis of methyl 4-(4-hydroxybenzyl)-2-phenylfuran-3-carboxylate (4g) and methyl 4-(2-hydroxybenzyl)-2-phenylfuran-3-carboxylate (5g):

Prepared according GP using furanyl alcohol **2a** (116mg) and phenol (47mg). Preparative TLC (DCM/AcOEt 9:1) gave **4g** (1%) and **5g** (14%).



4g

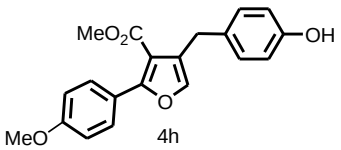
4g: **IR** (CH_2Cl_2): 3200, 1718, 1589, 1492, 1324, 1085. **^{1}H NMR** (400MHz, $CDCl_3$): 7.75 (*dd*, 2H, *J*=8.0, 1.6, H-2'and H-6'); 7.45-7.35 (*m*, 3H, H-3'and H-5'); 7.12 (*d*, 1 H, *J*=8.5, H-2"and H-6"); 7.03 (*s*, 1H, *J*=7.5, H-5); 6.78 (*d*, 2H, *J*= 8.5, H-3"and H-5"); 3.91 (*s*, 2H, -CH_2-), 3.74 (s, 3H, MeO). **EI-MS**: *m*/*z* = 308.07 $[M]^+$.



5g

5g: **IR** (CH_2Cl_2): 3201, 1719, 1589, 1482, 1328, 1080. **^{1}H NMR** (400MHz, $CDCl_3$): 7.66 (*dd*, 2H, *J* = 6.6, 3.1, H-2'and H-6'); 7.44-7.38 (*m*, 3H, H-3'and H5'); 7.20 (*d*, 1H, *J*=7.6, H-6"); 7.15 (*t*, 1H, *J*=7.5, H-5"); 6.92-6.86 (*m*, 2H, H-2"and H-3"); 6.84 (*s*, 1H, H-5); 3.98 (*s*, 2H, -CH_2-), 3.79 (*s*, 3H, MeO). **^{13}C NMR** (101MHz; $CDCl_3$) δ 162.0 (*C*OOMe); 154.4 (C-2); 150.0 (C-2"); 136.6 (C-5); 126.5 (C-6"); 126.2 (C-1'); 125.3 (C-4'); 124.6 (C-2'and C-6'); 124.2 (C-5"); 124.0 (C-3' and C-5'); 122.1 (C-1"and C-4"); 121.8 (C-3); 116.7 (C-3"); 112.6 (C-4); 47.8 (MeO); 20.9 (-CH_2-). **EI-MS**: *m*/*z* = 308.11 $[M]^+$.

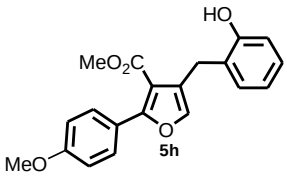
Synthesis of methyl 4-(4-hydroxybenzyl)-2-(4-methoxyphenyl)furan-3-carboxylate (4h) and methyl 4-(2-hydroxybenzyl)-2-(4-methoxyphenyl)furan-3-carboxylate (5h): Prepared according GP using furanyl alcohol **2b** (116mg) and phenol (47mg). Preparative TLC (DCM/AcOEt 9:1) gave **4h** (7%) and **5h** (28%).



4h

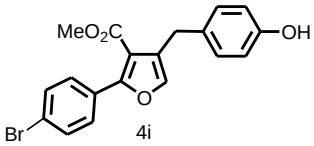
4h: **IR** (CH_2Cl_2): 3200, 1719, 1578, 1492, 1325, 1083. **^{1}H NMR** (400 MHz, $CDCl_3$): δ7.73 (d, 2H, *J*=9.0 Hz, H-2' and H-6'), 7.12 (d, 2H, *J*=8.4 Hz, H-2"and H-6"), 6.99 (s, 1H, H-5), 6.93 (d, 2H, *J*=9.0 Hz, H-3' and H-5'), 6.77 (d, 2H, *J*=8.5 Hz, H-3" and H-5"), 3.90 (s, -CH_2-), 3.85 (s, MeO), 3.73 (s, MeO). **^{13}C NMR** (101MHz; $CDCl_3$): δ 164.7 (*C*OOMe); 160.1 (C-

4'); 153.8 (C-2) and C-4"); 139.4 (C-5); 131.9 (C-1'); 129.8 (C-2', C-6', C-2", and C-6"); 127.1 (C-1"); 122.8 (C-3); 115.2 (C-3') and C-5'); 113.4 (C-3" and C-5"); 112.0 (C-4); 55.2 (MeO); 51.1 (MeO); 30.4 (-CH_2-).**EI-MS**: *m*/*z* = 338.12 $[M]^+$.



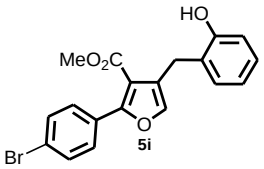
5h:**IR** (CH_2Cl_2): 3201, 1720, 1579, 1486, 1324, 1081. **^{1}H NMR** (400MHz, $CDCl_3$):δ 7.63 (d, 2H, *J*=9.0 Hz, H-2' and H-6'), 7.21 (s, 1H, H-5), 7.19 (dd, 1H, *J*= 7.8, 1.5 Hz, H-6"), 7.14 (m, 1H, H-4"), 6.93 (d, 2H, *J*=9.0 Hz, H-3' and H-5'), 6.90 – 6.86 (m, 2H, H-3" and H-5"), 3.98 (-CH_2-), 3.85 (MeO), 3.79 (MeO). **^{13}C NMR** (101MHz; $CDCl_3$) δ 165.9 (*C*OOMe); 160.3 (C-4'); 158.8 (C-2"); 153.9 (C-2); 139.9 (C-5); 130.4 (C-6"); 130.1 (C-2' and C-6'); 128.0 (C-4"); 126.1 (C-1'); 125.6 (C-1"); 120.6 (C-5"); 122.8 (C-3); 116.5 (C-3"); 113.4 (C-3' and C-5'); 111.3 (C-4); 55.2 (MeO); 51.6 (MeO); 24.9 (-CH_2-). **EI-MS**: *m*/*z* = 338.11 $[M]^+$.

Synthesis of methyl 2-(4-bromophenyl)-4-(4-hydroxybenzyl)furan-3-carboxylate (4i)andmethyl 2-(4-bromophenyl)-4-(2-hydroxybenzyl)furan-3-carboxylate (5i): Prepared according GP using furanyl alcohol **2c** (116mg) and phenol (47mg). Preparative TLC (DCM/AcOEt 9:1) gave **4i** (44%) and **5i** (39%).



4i: IR(CH_2Cl_2): 3201, 1718, 1639, 1495, 1300, 1084. **^{1}H NMR** (400MHz, $CDCl_3$): 7.66 (*d*, 2 H, *J* =10.5 Hz, H-2' and H-6'); 7.56 (d, 2H, *J* = 10.5 Hz, H-3' and H5'); 7.13 (*d*, 2 H, *J* = 8.1 Hz, H-2" and H-6"); 7.06 (s, 1 H, H-5); 6.80 (d, 2H, *J* = 8.1 Hz, H-3" and H-5"); 3.92 (*s*, 2 H, -CH_2-), 3.75 (*s*, 3H, MeO). **^{13}C NMR** (101MHz; $CDCl_3$) δ 164.2 (*C*OOMe); 157.2 (C-4"); 154.0 (C-2); 140.3 (C-5); 132.0 (C-1'); 131.7 (C-2' and C-6'); 129.9 (C-3' and C-5'); 129.8

(C-2″ and C-6″); 128.0 (C-1″); 127.5 (C-3 and C-4′); 113.7 (C-4, C-3″ and C-5″); 51.3 (MeO); 30.5 (-CH_2-). **EI-MS**: *m*/*z* = 386.02 $[M]^+$.

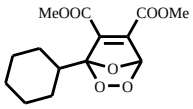


5i

5i: **IR** (CH_2Cl_2): 3202, 1719, 1639, 1497, 1290, 1084. **^{1}H NMR** (400MHz, $CDCl_3$):7.59 (*d*, 2 H, *J* = 6.6 Hz, H-2′ and H-6′); 7.57 (d, 2H, J = 6.6 Hz, H-3′ and H-5′); 7.25 (s, 1 H, H-5); 7.21 (*dd*, 1H, *J* = 7.6, 1.1 Hz, H-6″); 7.15 (*td*, 1 H, *J*=7.7, 1.6 Hz, H-4″); 6.95-6.85 (*m*, 2 H, H-3″ and H-5″); 4.00 (*s*, 2H, -CH_2-), 3.82 (*s*, 3H, MeO). **^{13}C NMR** (101MHz; $CDCl_3$) δ 165.5 (*C*OOMe); 157.2 (C-2); 153.7 (C-2″); 140.8 (C-5); 131.3 (C-3′ and C-5′); 130.4 (C-6″); 130.1 (C-2′ and C-6′); 129.1 (C-1′); 128.0 (C-4″); 126.1 (C-1″); 125.9 (C-3); 121.7 (C-5″); 116.4 (C-3″); 112.9 (C-4); 51.9 (MeO); 24.9 (-CH_2-). **EI-MS**: *m*/*z* = 386.2 $[M]^+$.

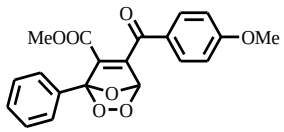
Experimental-Part 3B

Preparation of endoperoxides 6 via Dye-sensitized photooxygenation of furans 1a-c, l-p: A solution of furan **1** (0.5 mmol) in anhydrous dichloromethane 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 **6** was identified by ^{1}H-NMR. Compounds **6a**-**c** were known and were identified by comparison of NMR data with those reported (DellaGreca et al. 2013).



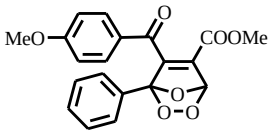
6l

DIMETHYL 1-CYCLOHEXYL-2,3,7-TRIOXA-BICYCLO[2.2.1]HEPT-5-ENE-5,6-DICARBOXYLATE (6l): ^{1}H NMR (500MHz, $CDCl_3$) δ 6.63 (s, 1H), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 2.45 (m, 1H), 2.03-1.17 (m, 10H).



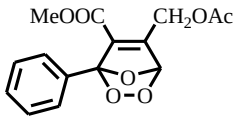
6m

METHYL 6-(4-METHOXYBENZOYL)-4-PHENYL-2,3,7-TRIOXA-BICYCLO[2.2.1]HEPT-5-ENE-5-CARBOXYLATE (6m): ^{1}H NMR (500MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.64 (m, 2H, Ar-H), 7.45 (m, 3H, Ar-H), 6.98 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.72 (s, 1H), 3.88 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3).



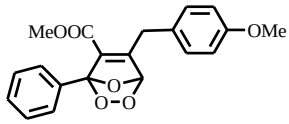
6n

METHYL6-(4-METHOXYBENZOYL)-1-PHENYL-2,3,7-TRIOXA-BICYCLO[2.2.1]HEPT-5-ENE-5-CARBOXYLATE (6n): ^{1}H NMR (500MHz, $CDCl_3$) δ 7.65 (d, *J*=8.6 Hz, 2H, Ar-H), 7.42 (m+d, 7H, Ar-H), 6.80 (s, 1H), 3.88 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3).



6o

METHYL 6-(ACETOXYMETHYL)-4-PHENYL-2,3,7-TRIOXA-BICYCLO[2.2.1]HEPT-5-ENE-5-CARBOXYLATE (6o): ^{1}H NMR (500MHz, $CDCl_3$) δ 7.57 (m, 2H, Ar-H), 7.48 (m, 3H, Ar-H), 6.65 (s, 1H), 5.38 (d, *J* = 15.9 Hz, 1H),5.15 (d, *J* = 15.9 Hz, 1H),3.64 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3).

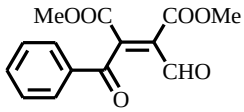


6p

METHYL 6-(4-METHOXYBENZYL)-4-PHENYL-2,3,7-TRIOXA-BICYCLO[2.2.1]HEPT-5-ENE-5-CARBOXYLATE (6p): ^{1}H NMR (500MHz, $CDCl_3$) δ 7.55-7.33 (m, 7H, Ar-H), 6.83 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.21 (s, 1H), 4.21 (m, 2H, -CH_2-),3.78 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3).

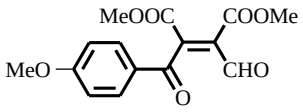
In situ reduction of endoperoxides 6 with Et_2S: To the photooxygenation solution containing the crude endoperoxide **9** at the oxygenation temperature, Et_2S (65 μL, 0.6mmol, 1.2 eq) was added, and the mixture was kept at room temperature for 2-3 h. The excess of Et_2S and the solvent were removed *in vacuo*, and the crude aldehydes **7a-c**,**m** (yields>85%), **7n** (yield>40%) and **7p** (yield>20%) were characterized spectroscopically. No identifiable product was present in the reduction mixtures of furans **1l**,**o**.

Attempts to purify compounds **7a**-**c**,**m**,**n**,**p** by preparative TLC drastically decreased yields. For example, **7a** was obtained as an oil in <20% yield by silica gel TLC using hexane-EtOAc (8:2 v/v) as eluent.



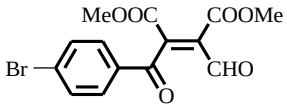
7a

DIMETHYL 2-BENZOYL-3-FORMYLMALEATE (7a): ^{1}H NMR (500MHz, $CDCl_3$) δ 9.95 (s, 1H, CHO), 8.04 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.59 (m, 1H, Ar-H), 6.98 (br t, *J*=7.5 Hz, 2H, Ar-H), 3.89 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3); **^{13}C NMR** (126MHz, $CDCl_3$) 187.6 (CHO), 186.6 (CO), 165.1 (C-4), 162.9 (C-1), 147.0 (C-2), 136.8 (C-3), 134.9 (C-1'), 129.3 (C-2' and C-6'), 129.1(C-3' and C-5'), 128.0 (C-4'), 53.9 (OCH_3), 53.4 (OCH_3); **EI-MS**: *m*/*z*=276.0 $[M]^+$.



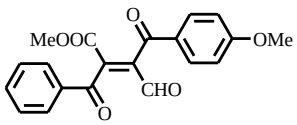
7b

DIMETHYL 2-FORMYL-3-(4-METHOXYBENZOYL)MALEATE (7b): ^{1}H NMR (500MHz, $CDCl_3$) δ 9.64 (s, 1H, CHO), 7.90 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.97 (d, *J*= 9.0 Hz, 2H, Ar-H), 3.92 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3); **^{13}C NMR** (126MHz, $CDCl_3$) δ 187.6 (CHO), 186.6 (CO), 165.1 (C-4), 163.6 (C-1), 163.1 (C-4'), 147.0 (C-3), 137.2 (C-2), 131.9 (C-2' and C-6'), 128.3 (C-1'), 114.5 (C-3' and C-5'), 55.7 (OCH_3), 53.6 (OCH_3), 53.1 (OCH_3); **EI-MS**: *m*/*z* = 306.2 $[M]^+$.



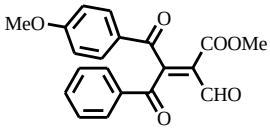
7c

DIMETHYL 2-(4-BROMOBENZOYL)-3-FORMYLMALEATE (7c): ^{1}H NMR (500MHz, $CDCl_3$) δ 9.68 (s, 1H, CHO), 7.77 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.65 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.92 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 188.7 (CHO), 186.5 (CO), 163.2 (C-4), 162.7 (C-1), 147.0 (C-2), 138.0 (C-3), 136.0 (C-4'), 132.5 (C-2' and C-6'), 130.5 (C-3' and C-5'), 128.0 (C-1'), 53.8(OCH_3), 53.2(OCH_3); **EI-MS**: *m/z* = 354.1 $[M]^+$, 356.0 $[M]^+$.



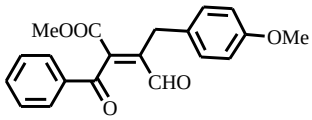
7m

(Z)-METHYL 2-BENZOYL-3-FORMYL-4-(4-METHOXYPHENYL)-4-OXOBUT-2-ENOATE (7m): ^{1}H NMR (500MHz, $CDCl_3$) δ 9.71 (s, 1H, CHO), 8.00 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.88 (d, *J* = 8.8 Hz, 2H, Ar'-H), 7.68 (m, 1H, Ar-H), 7.55 (t, *J* = 7.7 Hz, 2H, Ar-H), 6.98 (d, *J* = 8.9 Hz, 2H, Ar'-H), 3.86 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3); **^{13}C NMR** (126MHz, $CDCl_3$) δ 190.4 (CHO), 187.9 (CO and C-4), 165.1 (C-1), 163.0 (C-4"), 147.1 (C-2), 143.9 (C-3), 135.7 (C-1"), 135.1 (C-1'), 132.4 (C-4'), 131.2 (C-2" and C-6"), 129.4 (C-2' and C-6'), 129.3 (C-3' and C-5'), 114.3 (C-3" and C-5"), 55.6 (OCH_3), 53.4 (OCH_3); **EI-MS**: *m/z* = 352.2 $[M]^+$.



7n

(Z)-METHYL 3-BENZOYL-2-FORMYL-4-(4-METHOXYPHENYL)-4-OXOBUT-2-ENOATE (7n): ^{1}H NMR (500MHz, $CDCl_3$) δ 9.95 (s, 1H, CHO), 8.07-8.01 (m, 4H, Ar-H), 7.61 (t, *J* = 8.9 Hz, 1H, Ar-H), 7.48 (t, *J* = 7.7 Hz, 2H, Ar-H), 6.97 (d, *J* = 8.3 Hz, 2H, Ar'-H), 3.86 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3).

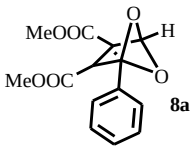


7p

(E)-METHYL 2-BENZOYL-3-FORMYL-4-(4-METHOXYPHENYL)BUT-2-ENOATE (7p): ^{1}H NMR (400MHz, $CDCl_3$) δ 9.61 (s, 1H, CHO), 7.90 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.64 (m, 1H, Ar-H), 7.50 (t, *J* = 7.7 Hz, 2H, Ar-H), 7.27 (obscoured by solvent, 2H, Ar'-H), 6.84 (d, *J*= 8.7 Hz, 2H, Ar'-H), 3.86 (s, 3H, $-OCH_3$), 4.08 (s, 2H, $-CH_2-$), 3.79 (s, 3H, $-OCH_3$), 3.74 (s, 3H, $-OCH_3$).

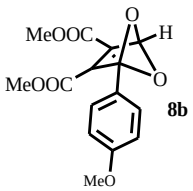
Conversion of Aldehydes 7a,c,m,n to dioxabicyclohexenes 8a,c,m,n:

When these aldehydes were kept in $CDCl_3$ at r.t., they partly converted to compounds **8**. Attempts to isolate the latter by chromatography failed and were characterized in mixture with the corresponding aldehydes.



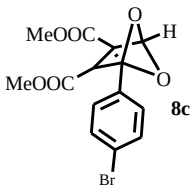
8a

DIMETHYL 1-PHENYL-5,6-DIOXA-BICYCLO[2.1.1]HEX-2-ENE-2,3-DICARBOXYLATE (8a) (7a/8a ca 1:1 molar ratio) :^{1}H NMR (400MHz, $CDCl_3$)δ: 7.68 (m, 2H, Ar-H), 6.14 (s, 1H, CH), 3.80 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3).



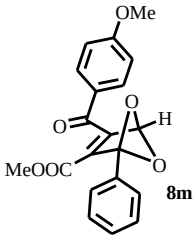
8b

DIMETHYL 1-(4-METHOXYPHENYL)-5,6-DIOXABICYCLO[2.1.1]HEX-2-ENE-2,3-DICARBOXYLATE (8b) (7b/8b ca 9:1 molar ratio):^{1}H NMR (400MHz, $CDCl_3$)δ 7.40 (d, *J*=9.0 Hz, 2H, Ar-H), 6.81 (d, *J*=9.0 Hz, 2H, Ar-H), 6.13 (s, 1H, CH), 3.86 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3).



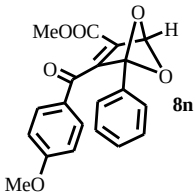
8c

DIMETHYL 1-(4-BROMOPHENYL)-5,6-DIOXA-BICYCLO[2.1.1]HEX-2-ENE-2,3-DICARBOXYLATE (8c) (7c/8c ca 1:3 molar ratio): ^{1}H NMR (400MHz, $CDCl_3$) δ 7.44 (d, *J*=8.2 Hz, 2H, Ar-H), 7.38 (d, *J*=8.2 Hz, 2H, Ar-H), 6.13 (s, 1H, CH), 3.81, (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3); **^{13}C NMR** (101MHz, $CDCl_3$) δ 131.1, 128.0, 107.6, 99.6, 53.4, 52.4.



8m

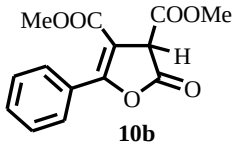
METHYL 3-(4-METHOXYBENZOYL)-1-PHENYL-5,6-DIOXABICYCLO[2.1.1]HEX-2-ENE-2-CARBOXYLATE (8m) (7m/8m ca 9:1 molar ratio): ^{1}H NMR (400MHz, $CDCl_3$) δ 6.13 (s, ^{1}H, CH), 3.83 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3).



8n

METHYL 3-(4-METHOXYBENZOYL)-4-PHENYL-5,6-DIOXA-BICYCLO[2.1.1]HEX-2-ENE-2-CARBOXYLATE(8n) (7n/8n ca 2:1 molar ratio): ^{1}H NMR (400MHz, $CDCl_3$) δ 6.33 (s, 1H, CH), 3.79 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3).

DIMETHYL 5-(4-METHOXYPHENYL)-2-OXO-2,3-DIHYDROFURAN-3,4-DICARBOXYLATE (10b). When the reduction mixture of aldehyde **7b** was kept in CdCl3 at rt and/or chromatographed by silica gel TLC, lactone **10b** was isolated in c.a. 30%.



10b

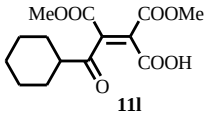
10b: oil; **IR** (CH_2Cl_2) 1813, 1747, 1731, 1604, 1512, cm^{-1}; **^{1}H NMR** (500MHz, $CDCl_3$) δ: 8.06 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.97 (d, *J* = 9.0 Hz, 2H, Ar-H), 4.75 (s, 1H, CH), 3.88 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); **^{13}C NMR** (126MHz, $CDCl_3$) δ: 167.6 (C-2), 165.1 (*C*$OOCH_3$), 162.7 (*C*$OOCH_3$), 162.4 (C-4'), 161.9 (C-5), 131.8 (C-2' and C-6'), 118.6 (C-1'), 114.8 (C-3' and C-5'), 113.6 (C-4), 55.5 (OCH_3), 53.6 (OCH_3), 53.1 (OCH_3), 52.0 (C-3); **EI-MS**: *m*/*z* = 306.0 $[M]^+$.

Oxidations of furan 1b by different routes: To a stirred solution of **1b** (50 mg, 0.17 mmol) in 1 mL of CH_2Cl_2 $NaHCO_3$ (19 mg) was added. The mixture was cooled to 0°C and then *m*CPBA (34 mg, 0.19 mmol) was added. The reaction was kept at r.t. overnight and then worked as reported by Gingerich et al. (Piancatelli et al. 1994; Kobayashi et al.1998; Gingerich et al. 1984) ^{1}H-NMR analysis of the residue indicated the presence of only starting furan **1b**.

Furan **1b** (50 mg, 0.17 mmol) was dissolved in 2 mL of THF-H_2O (4:1) and cooled to 0°C. A stoichiometric amount of NBS was then added portionwise while the temperature was being kept to r.t. overnight. The reaction was then worked as reported by Kobayashi et al. ^{1}H-NMR analysis of the residue indicated the presence of furan **1b** (32%), aldehyde **7b** (20%) and unidentified material (48%).

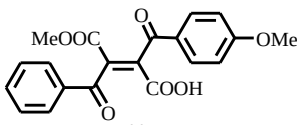
In situ base treatment of endoperoxides 6: Once the conversion of furan into endoperoxide **6** was complete the irradiation was stopped and Et_2NH (62 μL, 0.6 mmol, 1.2 eq) was added, and the mixture was kept at r.t. for 30 min. The solvent and Et_2NH were evaporated and the residue dried in the presence of anhydrous P_2O_5. The crude acrylic acid **11**(yield>90%, except for **11p** purity 55%)was analyzed spectroscopically. Compounds **11a**-**c** were identified according to literature data (DellaGreca et al. 2013).

Attempts to purify acids **11** by silica gel chromatography failed.



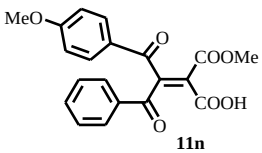
11l

(Z)-3-(CYCLOHEXANECARBONYL)-4-METHOXY-2-(METHOXYCARBONYL)-4-OXOBUT-2-ENOIC ACID (11l): amorphous powder; **IR** (CH_2Cl_2) 1739, 1641, 1255, 1166 cm^{-1}; **^{1}H NMR** (500MHz, $CDCl_3$) δ 9.01(br s, 1H, COOH), 3.83 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.59 (m, 1H), 2.00-1.22 (m, 10H); **^{13}C NMR** (126MHz, $CDCl_3$) δ 203.2 (CO), 166.2 (C-1 and C-4), 163.7(*C*$OOCH_3$), 154.2 (C-2), 138.0 (C-3), 53.3 (OCH_3), 52.9 (OCH_3), 50.4 (C-1'), 28.2 (C-2' and C-6'), 26.0 (C-3' and C-5'), 25.6 (C-4'); **EI-MS**: *m*/*z* = 298.0 $[M]^+$.



11m

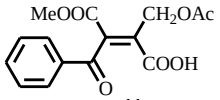
(E)-3-BENZOYL-4-METHOXY-2-(4-METHOXYBENZOYL)-4-OXOBUT-2-ENOIC ACID (11m): amorphous powder; **IR** (CH_2Cl_2) 3054, 1700, 1640, 1570, 1250, 1030 cm^{-1}; **^{1}H NMR** (500MHz, $CDCl_3$) δ 7.94 (d, *J*=9.0 Hz, 2H, Ar-H), 7.88 (d, *J*=9.0 Hz, 2H, Ar-H), 7.49 (t, *J*=7.5 Hz, 1H, Ar-H), 7.39 (t, *J*=7.5 Hz, 2H, Ar-H), 6.90 (d, *J* = 7.5 Hz, 2H, Ar-H), 3.85 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3); **^{13}C NMR** (126MHz, $CDCl_3$) δ 192.1 (2 x CO), 166.3 (C-1), 164.0 (C-4), 163.5 (C-4"), 138.6 (C-2), 136.3 (C-3), 132.7 (C-1'), 131.2 (C-1", C-2" and C-6"), 129.0 (C-3'andC-5'), 128.5 (C-2' and C-6'), 128.4 (C-4'), 114.2 (C-3" and C-5"), 55.5 (OCH_3), 52.7 (OCH_3); **EI-MS** (*m*/*z*) = 368.0 $[M]^+$.



11n

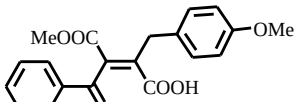
(E)-2-CARBOMETHOXY-3-(4-METHOXYBENZOYL)-4-PHENYL–4-OXOBUT-2-ENOIC ACID (11n): amorphous powder; **IR** (CH_2Cl_2) 1735, 1664, 1594, 1241, 1164 cm^{-1};**^{1}H NMR** (500MHz,

$CDCl_3$) δ 8.05 (br d, *J* = 8.3 Hz, 2H, Ar-H), 8.02 (d, *J* = 8.9 Hz, 2H, Ar'-H), 7.50 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.41 (t, *J* = 7.6 Hz, 2H, Ar-H), 6.91 (d, *J* = 8.9 Hz, 2H, Ar'-H), 3.85 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3); **^{13}C NMR** (126MHz, $CDCl_3$) δ 192.8 (CO), 190.9 (C-4), 166.9 (C-1), 165.8 (*C*$OOCH_3$), 164.1 (C-4"), 148.5 (C-3), 136.4 (C-2), 132.4 (C-2" and C-6"), 129.7 (C-2' and C-6'), 129.6 (C-3' and C-5'), 128.8 (C-4'), 128.5 (C-1'), 127.8 (C-1"), 114.4 (C-3" and C-5"), 55.6 (OCH_3), 51.7 (OCH_3); **EI-MS** (*m/z*) = 368.1 $[M]^+$.



11o

(E)-2-(ACETOXYMETHYL)-3-BENZOYL-4-METHOXY-4-OXOBUT-2-ENOIC ACID (11o) :amorphous powder; **IR** (CH_2Cl_2) 1727, 1676, 1362, 1074 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.8 Hz, 2H , Ar-H), 7.50 (m, 1H, Ar-H), 7.42 (m, 2H, Ar-H), 5.30 (s, 2H, -CH_2-), 3.66 (s, 3H, OCH_3), 2.04 (s, 3H, CH_3); **^{13}C NMR** (101MHz, $CDCl_3$) δ 188.8 (CO), 170.6 (O*C*OCH_3), 169.0 (C-1), 164.2 (C-4), 145.0 (C-2), 136.4 (C-3), 132.4 (C-1'), 132.0 (C-4'), 128.4 (C-2', C-3', C-5' and C-6'), 60.6(-CH_2O-), 52.5 (OCH_3), 20.7 (CH_3). **EI-MS** (*m/z*) = 306.0.

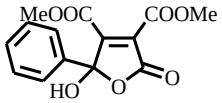


11p

(E)-3-BENZOYL-4-METHOXY-2-(4-METHOXYBENZYL)-4-OXOBUT-2-ENOIC ACID (11p) (60% purity) : **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.85 (br d, *J* = 8.5 Hz, 2H, Ar-H), 7.50-7.04 (m, 5H, Ar-H and Ar'-H), 6.75 (d, *J* = 8.5 Hz, 2H, Ar'-H), 4.13 (s, 2H, -CH_2-), 3.75 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3); **^{13}C NMR** (101MHz, $CDCl_3$) δ 194.7 (CO), 171.0 (C-1), 165.9 (C-4), 158.0 (C-4"), 137.2 (C-3), 137.0 (C-2), 132.3 (C-1'), 131.1 (C-1"), 130.3 (C-2" and C-6"), 128.6 (C-3' and C-5'), 128.3 (C-2', C-4' and C-6'), 113.5 (C-3" and C-5"), 55.2 (OCH_3), 52.1 (OCH_3), 34.8 (-CH_2-).

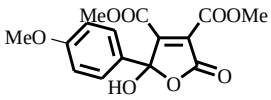
Mb-sensitized photooxygenation of furans 1 in acetone: A solution of furan (0.5 mmol) in anhydrous acetone (27.8 mL, 0.018 M) was irradiated at -20 °C (-60°C for **1o**,**p**) in the presence of methylene blue (MB, 1 mg, 3×10^{-3} mmol) while dry oxygen was bubbled through the solution. The progress of the reaction was checked by periodically monitoring (^{1}H-NMR) until the disappearance of starting furan (typically 2-3 h). After completion of the reaction, the solution was warmed at r.t. and kept at this temperature for 12 h. The solvent was removed under reduced pressure. The crude γ-hydroxybutenolides **12a-c,l,m** (yields > 85%) were spectroscopically characterized. In the other series proton spectra showed complex mixtures.

Compounds **12** could be purified and obtained in similar yields by silica gel filtration using CH_2Cl_2-EtOAc (95:5 v/v).



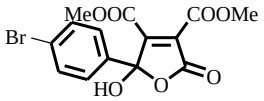
12a

DIMETHYL 5-HYDROXY-2-OXO-5-PHENYL-2,5-DIHYDROFURAN-3,4-DICARBOXYLATE (12a): **IR**(CH_2Cl_2) 3524, 1788, 1744, 1673 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.44 (m, 3H, Ar-H), 2.68 (br s, 1H, OH), 3.92 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3); **^{13}C NMR** (101MHz, $CDCl_3$) δ 165.1 (C-2), 163.3 (*C*$OOCH_3$), 162.4 (*C*$OOCH_3$), 135.0 (C-4), 131.8 (C-3), 131.3 (C-1'), 130.5 (C-4'), 128.7 (C-2' and C-6'), 128.0 (C-5), 126.9 (C-3' and C-5'), 52.9 (2 x OCH_3).



12b

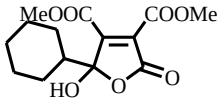
DIMETHYL 5-HYDROXY-5-(4-METHOXYPHENYL)-2-OXO-2,5-DIHYDROFURAN-3,4-DICARBOXYLATE (12b): IR (CH_2Cl_2) 3463, 1802, 1731, 1692, cm^{-1}; **^{1}H NMR** (500MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.97 (d, *J* = 8.4 Hz, 2H, Ar-H), 4.79 (br s, 1H, OH), 3.93 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3); **^{13}C NMR** (126MHz, $CDCl_3$) δ 164.1 (C-2 and (*C*$OOCH_3$), 162.1 (*C*$OOCH_3$), 152.3 (C-4'), 130.6 (C-4), 130.3 (C-3, C-2' and C-6'), 127.5 (C-1'), 114.1 (C-5, C-3' and C-5'), 55.4 (OCH_3), 53.4 (OCH_3), 53.2 (OCH_3).



12c

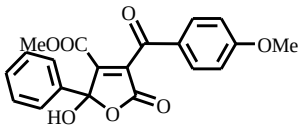
DIMETHYL 5-(4-BROMOPHENYL)-5-HYDROXY-2-OXO-2,5-DIHYDROFURAN-3,4-DICARBOXYLATE (12c)

: **IR** (CH_2Cl_2) 3557, 1799, 1741, 1676 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.55 (d, *J*= 8.6, 2H, Ar-H), 7.51 (d, *J*= 8.6 Hz, 2H, Ar-H), 3.92 (s, 3H, OCH_3), 3.77 (s, 3H, -OCH_3), 2.41 (br s, 1H, OH); **^{13}C NMR** (101MHz, $CDCl_3$) δ 166.8(C-2), 165.5 (*C*$OOCH_3$), 163.6 (*C*$OOCH_3$), 145.2 (C-4), 135.4 (C-3), 131.9 (C-3' and C-5'), 131.7(C-4'), 130.3 (C-1'), 128.6 (C-2' and C-6'), 128.4 (C-5), 53.1 (2 x OCH_3).



12l

DIMETHYL 5-CYCLOHEXYL-5-HYDROXY-2-OXO-2,5-DIHYDROFURAN-3,4-DICARBOXYLATE (12l): **IR** (CH_2Cl_2) 3400, 1787, 1743, 1440, 1041 cm^{-1};**^{1}H NMR** (400MHz, $CDCl_3$) δ 4.91 (br s, 1H, OH), 3.88 (s, 3H, OCH_3), 3.84 (s, 3H, -OCH_3), 2.10 (m, 1H), 1.80-1.02 (m, 10H); **^{13}C NMR** (101MHz, $CDCl_3$) δ 164.5 (C-2), 161.2 (*C*$OOCH_3$), 160.3 (*C*$OOCH_3$), 156.9 (C-4), 127.2 (C-3), 96.3 (C-5), 53.6 (OCH_3), 53.4 (OCH_3), 43.7 (C-1'), 31.0 (C-2' and C-6'), 25.9 (C-3' and C-5'), 23.0 (C-4').



12m

METHYL 5-HYDROXY-3-(4-METHOXYBENZOYL)-2-OXO-5-PHENYL-2,5-DIHYDROFURAN-4-CARBOXYLATE (12m): **IR** (CH_2Cl_2) 3531, 1779, 1734, 1667 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.74 (br d, *J* = 7.0 Hz, 2H, Ar-H), 7.49 (m, 3H, Ar-H), 6.96 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.87 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3); **^{13}C NMR** (101MHz, $CDCl_3$) δ 187.9 (CO), 164.9 (C-2 and $COOCH_3$), 160.7 (C-4"), 135.0 (C-4), 131.7 (C-2" and C-6"), 128.7 (C-3, C-2' and C-6'), 128.2 (C-1'), 127.0 (C-3' and C-5'), 124.3 (C-4'), 121.1 (C-1"), 114.4 (C-3" and C-5"), 113.9 (C-5), 55.5 (OCH_3), 52.8 (OCH_3).

Chapter 4.

CONCLUSION AND PERSPECTIVES

The PhD work has highlighted that furans go on to be an interesting class of heterocycles. New synthetic methods for their preparation and elaboration have been described that provide a significant tool for glycosides and lignan-like compounds with important implications in pharmacological applications. In particular, a novel methodology based on a one-pot process starting from glycosyl furans has been developed for the synthesis of spiro compounds and, in particular, of new chiral [6,6]-, [5,6]- and [5,5]-spiroketals of sugars. The spiroketal moiety represents a privileged substructure since it can be found in many simple as well as complex natural products characterized by important and assorted biological properties, from antibiotic to anticancer. It is to be noted that despite numerous methodologies for spiro compounds few synthetic strategies for derivatives oxidized at the 2-position are reported. Novel pyridazine C-nucleosides have also been synthetized by a one-pot procedure. The pyridazine nucleus and its 3-oxo derivatives have been recognized as versatile pharmacophores and great attention in last years has been devoted to the synthesis of these compounds.

Interesting results have been obtained in the field of polysustituted furans.
Indeed, starting from aryl trisubstituted derivatives a novel synthetic method for diarylfurans with a lignan backbone has been developed using a variant of the Friedel-Crafts reaction. Preliminary biological tests have evidenced antibiotic activities of some derivatives. The presence of furan system in these compounds highlights manifold elaborations of the heterocyclic ring to a variety of product types.
In this context, in the field of dye-sensitized photooxygenation, starting from some trisubstituted furans bearing β,β'electron withdrawing groups, previously not investigated, useful C-4 synthons have been obtained in excellent yields in one-pot manner. All the reaction conditions, based on the combination of photooxygenation with reduction or basic treatment, are particularly mild respect to classical oxidation procedures, often not compatible with functional groups which are frequently present in synthetic intermediates. Hence these procedure represents useful alternatives to classical methods. Many of compounds prepared have various lignan-like structures that confirm the role of furans in the synthesis of interesting products.

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The researches described in this PhD thesis have been presented as oral comunictions in the following Conferences:

- Sferruzza, R.; Cermola, F.; Della Greca, M.; Iesce, M. R. Novel approaches to electron-poor substituted furans and their applications in the synthesis of lignan-like compounds : XVI Convegno Nazionale delle Reazioni Pericicliche e sintesi di etero e carbocicli Matera (Italia), 26-27 Giugno **2015**.

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