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Understanding the reactivity of triacetic acid lactone

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Understanding the reactivity of triacetic acid lactone

by

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DEDICATION

To my family.

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LIST OF ABBREVIATIONS

Å	angstrom
Ac	acetyl
ACC1	acetyl-CoA carboxylase 1
APCI	atmospheric-pressure chemical ionization
aq.	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl
°C	degrees centigrade
Calcd	calculated
CMF	5-(chloromethyl)furfural
CoA	coenzyme A
δ	NMR chemical shift in ppm downfield from tetramethylsilane
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-Dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublets
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide

E	electrophile
EI	electron ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
$EtNH_2$	ethylamine
Et_2NH	diethylamine
Et_3N	trimethylamine
EtOAc	ethyl acetate
FDCA	2,5-furandicarboxylic acid
g	gram
GC/MS	gas chromatography/mass spectrometry
h	hour
HDP	4-hydroxy-3, 6-dimethyl-2-pyrone
HMDS	hexamethyldisilazane
HMF	5-hydroxymethylfurfural
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
J	coupling constant
L	liter
LDA	lithium diisopropylamide
LiTMP	lithium tetramethylpiperidide
LRMS	Low-resolution mass spectra

K	Kelvin
µ	micron
M	molarity
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
mg	milligram
MHz	megahertz
MICs	minimal inhibitory concentrations
min	minute
mL	milliliter
mm	millimeter
mM	milimolar
mmol	millimole
Mp	megapascal
m.p.	melting point
NBS	N-Bromosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
OMe	methoxy
p	para
PAF	platelet-activating factor

Pd/C	palladium on carbon
Ph	phenyl
PPh_3	triphenylphosphine
ppm	parts per million
2-PS	2-pyrone synthase
PTP1B	Protein tyrosine phosphatase 1B
PTSA	*para*-toluenesulfonic acid
q	quartet
QTOF	quadrupole time of flight
quant.	quantitative
R_f	retention factor
s	singlet
t	triplet
TAL	triacetic acid lactone
TBS	*tert*-butyldimethlsilyl
t-BuOH	*tert*-butanol
t-BuOK	potassium *tert*-butoxide
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	*N, N, N', N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	toluenesulfonyl
UV	ultraviolet

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ABSTRACT

The chemical industry has been dependent on petroleum-derived carbon for commodity chemicals for the past number of decades, but this practice is not sustainable. With the increase of energy demand, biomass has attracted attention for being an inexpensive renewable carbon source. The proposed platform chemical, triacetic acid lactone, can be produced by microbes from glucose. Triacetic acid lactone can subsequently be converted into a multitude of high-value added bio based chemicals via further chemical transformations.

In this dissertation, we explore methods to functionalize triacetic acid lactone to obtain biologically important specialty molecules from biorenewable sources. Chapter 1 of the dissertation describes the synthesis of high value added specialty chemical, pogostone and its analogs from biobased triacetic acid lactone. These high value specialty chemicals are synthesized in high yields and the biological activities are investigated. Chapter 2 discusses an improved aldol protocol for the synthesis of 6-styrenylpyrones from triacetic acid lactone. Styrenyl pyrones are an emerging class of natural products, which exhibit several biological activities. This aldol condensation reaction proceeds in good yields and is compatible with a variety of functional groups. Chapter 3 describes the use of triacetic acid lactone as a common intermediate for the synthesis of 4-hydroxy-2-pyridones and 4-amino-2-pyrones. As demonstrated therein, triacetic acid lactone constitutes a useful platform for the direct introduction of a nitrogen functionality. In summary, triacetic acid lactone represents a convenient biobased platform for a diverse range of important molecules.

CHAPTER I

BIOBASED TRIACETIC ACID LACTONE AS A PLATFORM CHEMICAL

1.1. Introduction

1.1.1. Biomass as a feedstock

The modern society has depended on non-renewable fossil carbon, such as petroleum oil and natural gas, since the beginning of 20th century. However, finding new ways to generate chemicals, energy and materials while decreasing the impact to the environment is essential due to limited global resources and a growing world population, and with increasing individual expectations. Ideal renewable resources can be replenished within a relatively short timescale or are available in a limitless supply. Coal, natural gas and crude oil are the resources which come from fixation of carbon dioxide through photosynthesis. In order to form these materials, nature requires millions of years. These chemicals are known to be non-renewable resources due to their limited supply.

In order to fulfill the world's intrinsic need for energy, chemicals and materials, the chemical and petroleum industry has turned its attention towards to alternative resources. Solar radiation, wind, tides and biomass are known to be the renewable sources. Of these resources, biomass is the only renewable source of carbon, which is abundant and worldwide distributed, for the production of carbon based chemicals and materials.[1-5]

Biomass used in the chemical industry could either be obtained by the cultivation of fast growing, non-edible crops or from waste biomass that is generated from edible crops such as sugar cane, bagasse, corn stover, rice husks and orange peels.[4] Global production of biomass can be divided as 60% terrestrial and 40% aquatic biomass. Only 3% of biomass comes from the cultivated biomass. As shown in the Figure 1, biomass consists of 75% carbohydrates and 20% lignin. The remaining 5% is comprised of triglycerides (fats and oils), proteins and terpenes.[3] Carbohydrates can be classified as storage carbohydrates and structural polysaccharides. Starch, inulin and sucrose are storage carbohydrates and cellulose, hemicellulose and chitin are known as the structural polysaccharides.

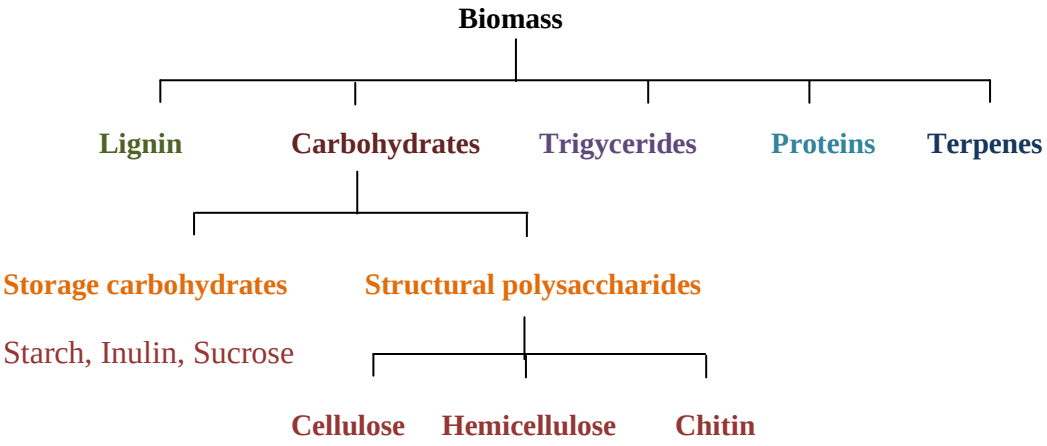


Figure 1. Major categories of biomass.[3]

The use of lignocellulose as a biomass feedstock is advantageous because it is not edible and therefore avoids competition with the food sector. Lignocellulose is composed of 20% of lignin, 40% of cellulose and 25 % hemicellulose as shown in Figure 2. Cellulose is the largest biopolymer. Although lignin is a biopolymer it differs from

cellulose in that it is entirely composed of aromatic subunits. These materials can be used to produce a complex mixture of phytochemicals with high value added applications.[3]

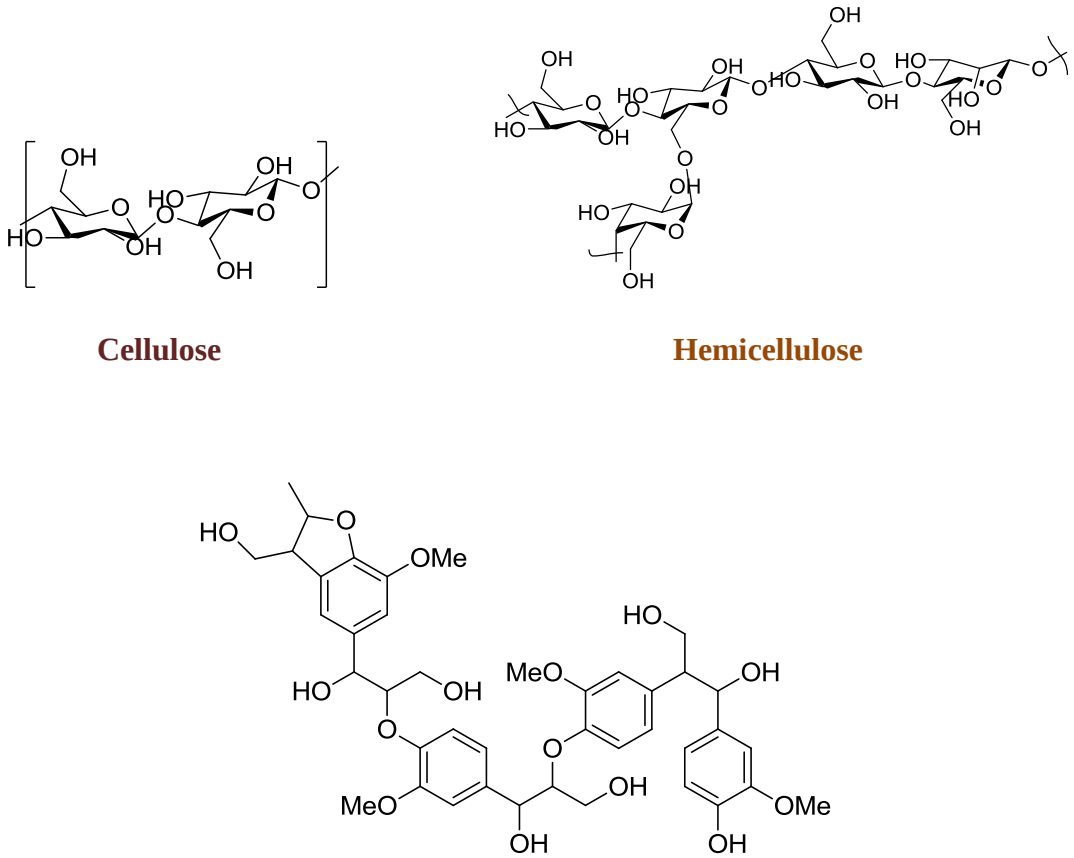


Figure 2. Major components of lignocellulosic biomass.

In order to get either liquid fuels or commodity chemicals, lignocellulose must first be depolymerized and deoxygenated. Pretreatment of biomass is necessary as the large quantities of hemicellulose and lignin act as a protective layer and will change the physical properties and chemical composition of biomass. This can be done in four

different ways: mechanical, chemical, physicochemical, and biological methods and will eliminate the unwanted biomass fraction selectively.

Biomass conversion can be carried out in two ways: thermochemical conversion and biological conversion. Thermochemical conversion can be accomplished by various methods, including liquefaction, combustion, gasification, pyrolysis and torrefaction.

Direct liquefaction converts biomass in to hydrocarbon oil for fuel using a high-pressure thermal decomposition and hydrogenation process. Here, biomass is subjected to elevated pressure (up to 250 bars) and temperature (up to 500 °C). Direct combustion is one of the oldest methods of energy production. Here, biomass is burnt in excess oxygen to release the stored chemical energy. The third method for biomass conversion is by partial oxidation of biomass using an oxidizing agent. This gasification process converts biomass in to syngas which mainly consists of CO and H_2. Another thermal treatment is pyrolysis that decomposes organic biomass in to low molecular weight products in the absence of air or oxygen. Thermochemical conversion of biomass can also be carried out by torrefaction in which the raw biomass is refined to solid fuel.

The biological conversion of biomass involves fermentation and anaerobic digestion. In fermentation microorganisms like bacteria and fungi convert sugars into a wide range of products including biofuels, biochemicals or biomaterials. In anaerobic digestion a mixture of bacteria is involved syntrophic bacteria, fermentative bacteria, acetogenic bacteria and methanogenic bacteria. Under anaerobic conditions, biomass is decomposed to produce biogas (methane and hydrogen) as fuel. Following the hydrolysis step, insoluble organic compounds separate in to water-soluble monomers by hydrolases. Then in acetogenesis stage, hydrolysis products are transforming in to short-chain organic

acids, alcohols, aldehydes and carbon dioxide. Methanogenic bacteria utilize the resulting acetic acid, hydrogen and carbon dioxide to produce methane. With these various conversion methods, biomass can produce a range of biofuels, heat, electricity and chemicals.[1]

1.1.2. Platform molecules

Currently, the plethora of chemicals and materials use in everyday life derive from non-renewable fossil resources such as plastics, synthetic textiles, dyes and pigment, surfactants, agrichemicals, pharmaceuticals, home and personal care products. Therefore, in order to use biomass as a feedstock to the current chemical industry, biomass needs to support and eventually supplant this variety of chemicals and materials.

The modern petrochemical industry is based on a platform chemical approach in which a small set of simple, cheap base chemicals are converted in to vast majority of chemicals and materials demanded by that industry. The research on bio-economy over last 20 years has shown that, biobased chemical industry can deliver the same, through a set of simple, cheap biomass-derived building block chemicals, also referred to as platform chemicals.

The biobased platform molecule concept emerged in the late twentieth century. Simple small molecules derived from biomass can be utilized as building blocks to generate higher value chemicals and materials.[6-7] In 2004, the US Department of Energy (DOE) reported on Top Value Added Chemicals from Biomass, outlining the need of

biobased products in research.[8-9] There are twelve building block chemicals in this report that can be derived from carbohydrates as shown in Table 1.

Table 1. The DOE top chemical opportunities from the carbohydrates, 2004.

The DOE top building block chemicals
1,4 diacids (Succinic, fumaric and malic acids)
2,5- furan dicarboxylic acid
3-hydroxyproionic acid
Aspartic acid
Glucaric acid
Glutamic acid
Itaconic acid
Levulinic acid
3-hydroxybutyrolactone
Glycerol
Sorbitol
Xylitol / arabinitol

This report was later revised and reduced to ten compound classes by Bozell in 2010 after evaluation of recent technological advances.[8] Figure 3 shows chemicals that should be targeted as the chemical industry investigates the production of high value chemicals from biomass. A platform molecule can be converted into a diverse range of products which can be applicable in various industrial sectors.

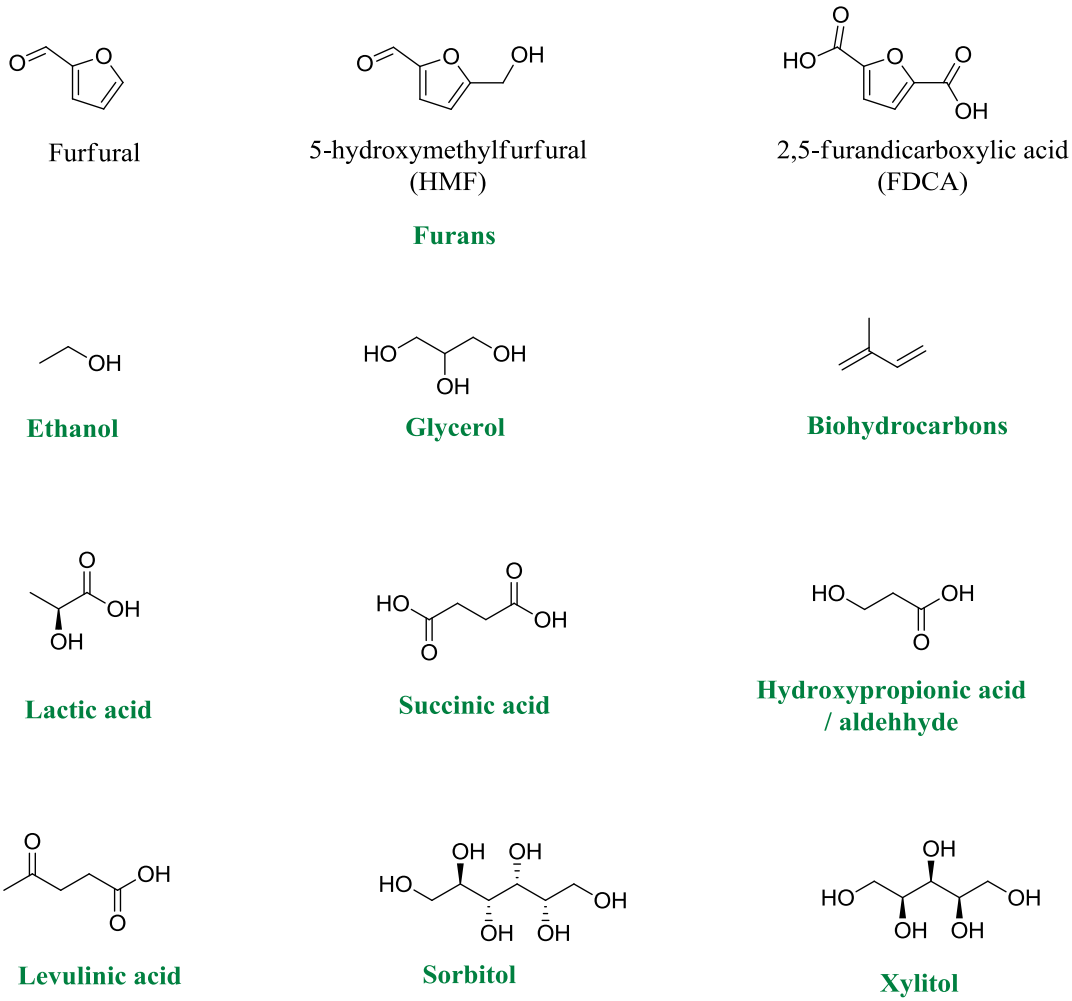


Figure 3. Chemical building blocks from bio-refinery carbohydrates. [8]

In order for a platform molecule to have value to the bio-based industry, it must be useful for the synthesis of the marketable chemicals. 5-(chloromethyl)furfural (CMF) is a platform molecule that has the potential to be converted into a wide range of higher-value added chemicals and materials. Star diagram representation visualizes the full range of chemical transformations for the different functional groups of CMF.[1]

Early efforts towards the preparation of CMF involved treating fructose, sucrose or cellulose with a saturated solution of the hydrogen halide in an organic solvent. CMF's were isolated in 12-30% yields and due to these low yields, several researchers have optimized the reaction conditions. In 2009, an optimized procedure was reported in which either were treated glucose, sucrose, cellulose or corn stover in a biphasic aqueous hydrochloric acid / organic solvent at 80-100 °C in a reactor for 3 hours yielded 80-90% of CMF. [1, 10-13]

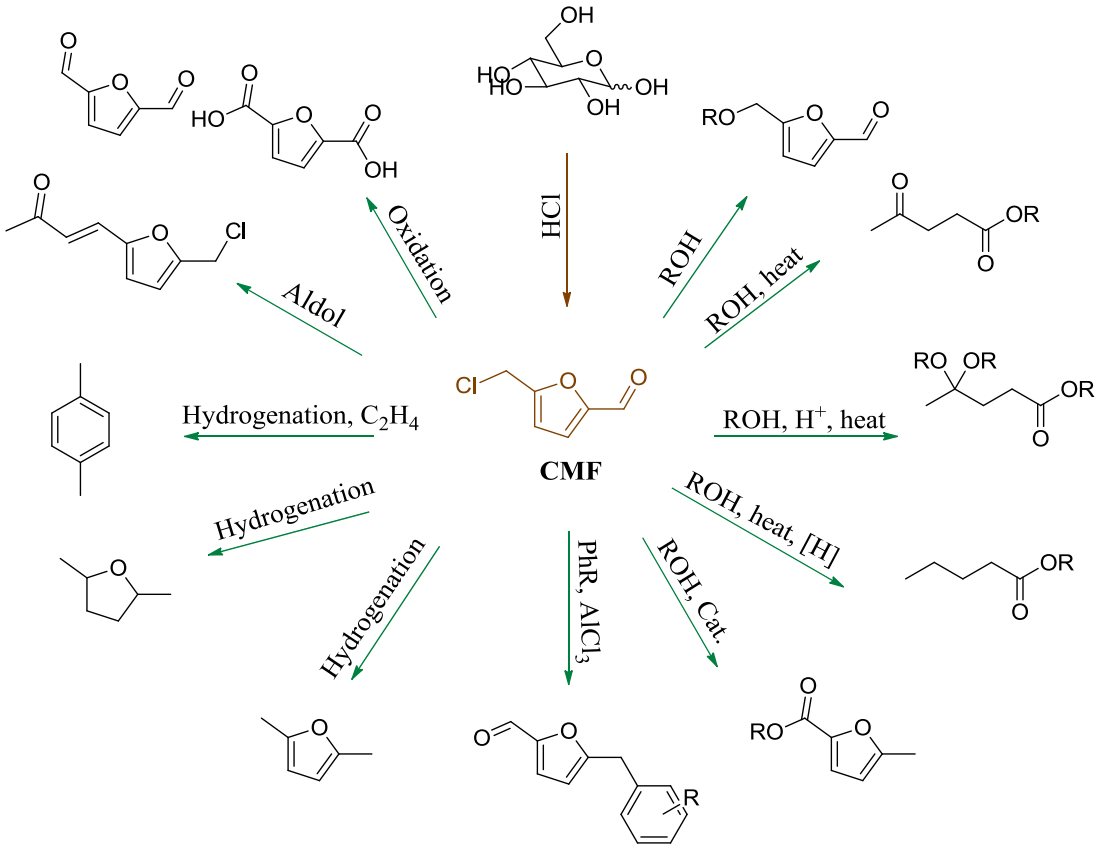


Figure 4. 5-(chloromethyl)furfural as a platform molecule. [1]

CMF is a furan with a formyl and a chloromethyl group substituted at the 2- and 5- positions of the ring. It is a colorless liquid that is obtained by the dehydration of sugar using hydrochloric acid. The reactions of CMF are more like the hydroxymethylfurfural (HMF) reactions, but CMF is more reactive towards nucleophilic substitution at the methylene carbon.

The major two derivative manifolds of CMF are furanic and levulinic as shown in Figure 4. CMF reacts with nucleophiles under mild conditions to give aldehyde condensation products or halide substituted products. In harsher conditions, the furan ring opens to give levulinate products. Reaction with water gives HMF, which is another biobased platform molecule, or the reaction with alcohols at room temperature gives alkoxymethyl furfurals, which can be used as biofuels.[14] Reaction with water or alcohols at elevated temperature produces levulinic acid or esters. Levulinic acid is a key biomass derived platform chemical.[5] Levulinic esters can be used as diesel additives.[15] Further conversion of levulinic acid with alcohols in acidic media, gives levulinate ester acetals. These can serve as novel monomers, plasticisers and solvents. Hydrogenation of levulinic esters gives valeric esters, which show outstanding fuel properties.[16] CMF reaction with alcohol in the presence of *N*-heterocyclic carbene catalyst forms furoate esters, which also show excellent fuel properties.

The Friedel-Crafts reaction yields aryl derivatives, which are useful as biofuel precursors. The complete hydrogenation of CMF gives 2,5-dimethyltetrahydrofurans, a fuel oxygenate. The gentle hydrogenation provides the 2,5-dimethylfuran, a promising biofuel and a precursor for para-xylene. Aldol condensation reactions can be performed when longer carbon chain lengths are required for the diesel like hydrocarbons. Finally,

an oxidation reaction can also be performed with nitric acid to produce 2,5-diformylfuran or 2,5-furandicarboxylic acid (FDCA). FDCA is considered to be a replacement for petroleum derived terephthalic acid.

Platform chemicals are frequently used during the conversion of biomass to commodity or specialty chemicals. There are two strategies of incorporating these into the value chain. Using the drop-in strategy, biomass is converted to a replacement compound, which is currently produced from petroleum feedstock. This strategy is advantageous due to a high market demand for these chemicals. The second strategy that has recently emerged introduces new bio-based chemicals that are currently not in the market. Both approaches contribute to enhance the value of biomass in to the industry.

1.1.3. Biobased triacetic acid lactone

The proposed platform molecules are derived from carbohydrates as depicted in Figure 3, but there are other alternative biobased molecules that can be produced from a various single metabolic pathways. These metabolic pathways have the potential to generate a series of homologous molecules.[2] For example, exploration of the polyketide/fatty acid biosynthetic pathway has potential to produce a series of new platform chemicals.

Several metabolic processes are involved in biosynthetic pathways and these processes carry out the biochemical conversions in molecules in order to install new functionalities at a specific position of the molecule. Understanding the metabolic processes involved in the polyketide/fatty acid biosynthesis, provides the opportunity to

generate a plethora of new platform chemicals. Metabolic pathway engineering is an important tool for the synthesis of complex molecules. Here, the catalytic system in cell metabolism is genetically manipulated to produce structurally diverse and complex molecules.[17]

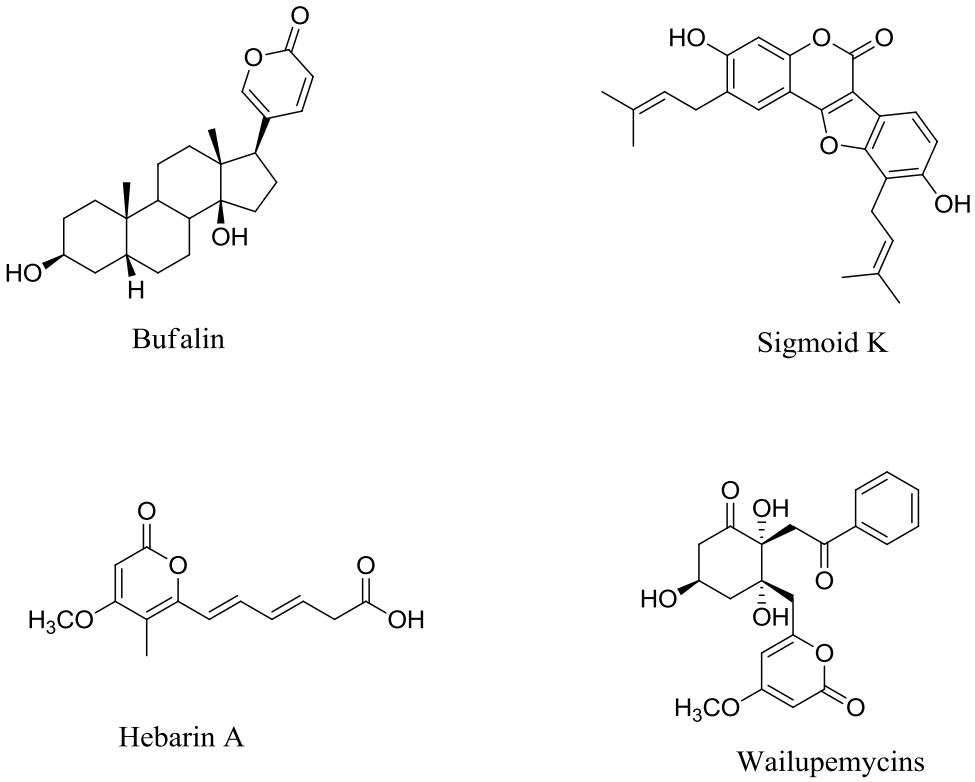
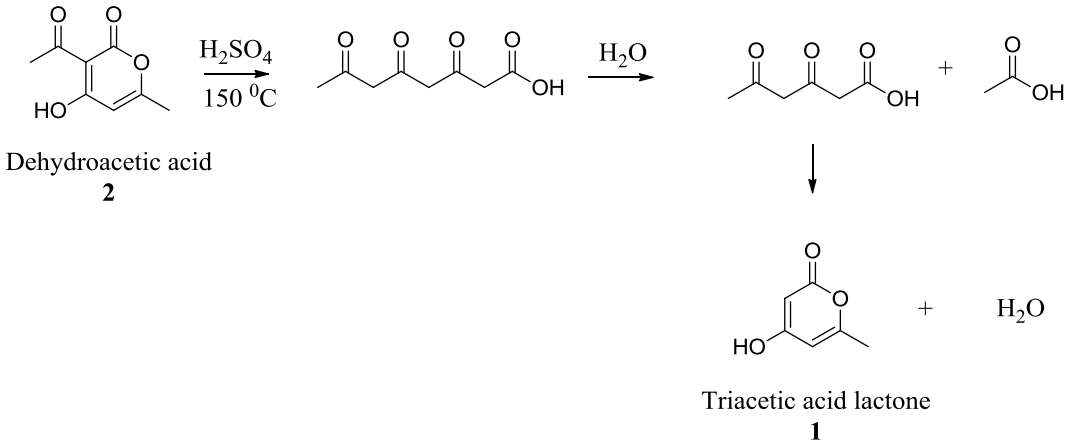


Figure 5. Examples of natural compounds with 2-pyrone functionality.

2-Pyrones are an important classes of compounds that can be generated from biomass by genetically modified polyketide biosynthesis pathways. These can serve as intermediates in the bio-renewable chemical production. Natural compounds containing the 2-pyrone moiety exhibit several biological activities and are valuable pharmaceutical precursors as represented in Figure 5.[18] One of the polyketide sources for natural 2-

pyrones is 4-hydoxy-6-methyl-2-pyrone, which is known as triacetic acid lactone (TAL) **1**. This is commonly known as a triketide derailment product in the polyketide biosynthesis.[19]

Currently, TAL is manufactured in five chemical steps starting with pyrolysis of acetic acid. As illustrated in Scheme 1, the original synthesis of triacetic acid lactone was treating the commercially available dehydroacetic acid **2,** with sulfuric acid at 150 °C, produced TAL.[20]



Dehydroacetic acid
2

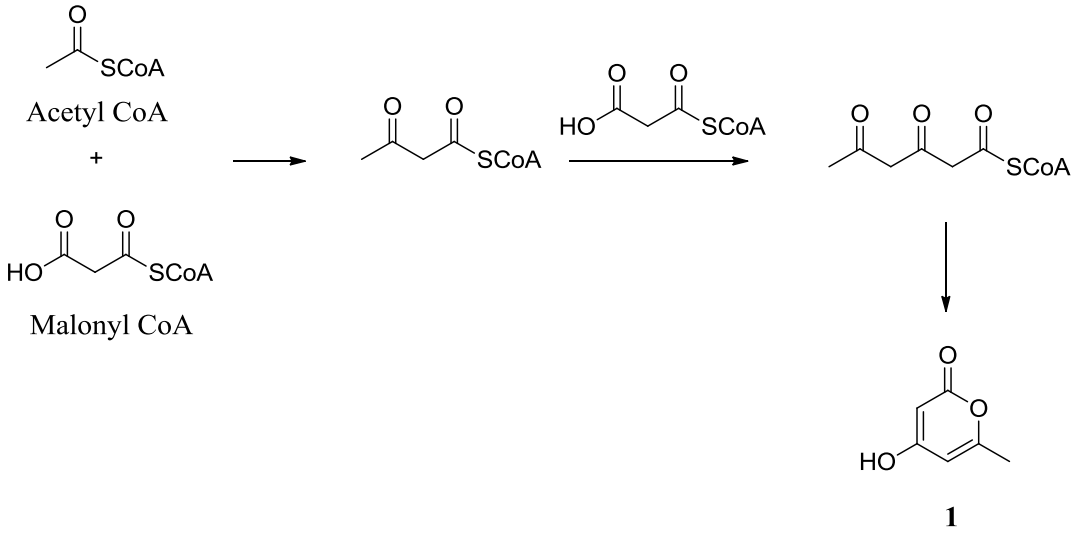
Triacetic acid lactone
1

Scheme 1. TAL from dehydroacetic acid.

Type III polyketide synthase *g2ps1* (2-Pyrone synthase (2-PS)) plays a major role in the direct microbial synthesis of TAL from glucose. This 2-PS enzyme encoded by the *g2ps1* gene, is isolated from *Gerbera hybrida*. Like other type III polyketide synthases, 2-PS is a small protein that uses a single active site for decarboxylation and cyclization reactions.[21-22] Acetyl coenzyme A (acetyl-CoA) is produced by 2-PS which is an initial substrate. Then 2-PS catalyzes the two iterative decarboxylation and condensation of two

extender malonyl-CoA molecules to utilize TAL as detailed in Scheme 2. Both acetyl-CoA and malonyl-CoA are common metabolites in bacteria and eukaryotes.

TAL can be produced either from yeast or *Escherichia coli* by inserting the *g2ps1* gene as a genetically modified fatty acid synthase B gene or genetically modified ketoreductase mutants of the 6-methylsalycilic acid synthase gene (6-MSAS). It has been reported that the TAL shows negative effects on microbial cell growth.[23] TAL is extremely toxic to *E. coli* and showed reduction in growth rate of 25% and 90% in 10 mM and 20 mM TAL respectively and there was no growth observed for 50mM TAL. However, there was no effect on growth to the concentrations up to 200mM TAL in *Saccharomyces cerevisiae. Saccharomyces cerevisiae* is therefore an excellent host for the production of TAL as a result of the minimal toxicity on the microbial cell growth.



Scheme 2. Microbial synthesis of TAL.[19]

Highest TAL titers reported in earlier studies in yeast and bacteria is 2.2 g/L for the *Saccharomyces cerevisiae* strain BY4741. This study showed a 37-fold increase in

TAL concentration with this specific strain. Another study demonstrated that use of the engineered 2-PS enzyme and expressing that strain in *E. coli* increased the production of TAL to 2.1 g/L.[21] In order to adopt TAL as a platform chemical for the production of biorenewable chemicals it is essential that TAL can be produced on an industrial scale. Furthermore, in order to use the lignocellulosic feedstock as the substrate, the strain needs to tolerate to inhibitors that are produced during the deconstruction of these in to monomeric sugars. TAL, which is produced from 2-PS, needs both acetyl and malonyl-CoA. *Saccharomyces cerevisiae* produces malonyl-CoA from acetyl-CoA by acetyl-CoA carboxylase 1 (*ACC1*) enzyme. Acetyl-CoA is produced through multiple pathways in some yeast species. The flux through these pathways is affected by many factors and several metabolic engineering studies have focused in increasing flux to cytosolic acetyl-CoA. The genetic differences between these yeast strains leads to a difference in flux through this pathway and has the potential to increase the capacity to produce TAL.

Cells utilize different metabolic pathways depending on the available carbon source. Alteration of the carbon source and variation of the culture conditions can improve the yield of TAL. Production of TAL from respiratory metabolism for *Saccharomyces cerevisiae* has been studied and cultured with ethanol, glycerol or acetate as the carbon source and the highest TAL yield was obtained when ethanol was used as the carbon source. The concentration of TAL in these studies was 5.2 g/L with an industrial *Saccharomyces* strain and represents the highest titer of TAL reported to date.[21] *Saccharomyces cerevisiae* is an excellent candidate for production of this platform molecule.

1.1.4. 2-Pyrones

As represented in Figure 6, pyran is a six-membered heterocycle baring oxygen in the ring. The pyran ring system is frequently found in bacteria, microbial, plant, insect and animal systems possessing a variety of biological activities. Pyran is not a true aromatic moiety here are four sp^2 carbon atoms and one sp^3 hybridized carbon atom in the ring. The 2-pyrone is a cyclic unsaturated ester in which the sp^3 carbon of the pyran is replaced by a carbonyl functionality. These structures exhibit the chemical and physical properties of alkene and arene compounds.[24-25]

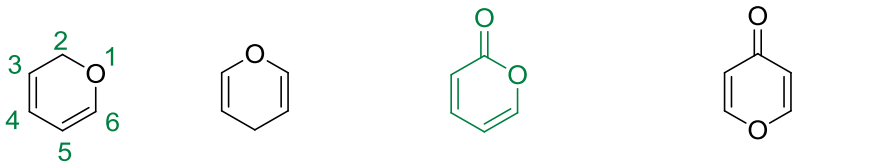


Figure 6. Different pyran ring systems.

The aromatic properties of 2-pyrones have been demonstrated by the reactivity towards electrophilic substitution such as nitration, sulphonation and halogenation. The ability of 2-pyrones to function as dienes and dienophiles in Diels-Alder reactions has been demonstrated their aliphatic character.[26-28]

This ring system is found in plants, animals, marine organisms, bacteria and insects and its involvement in biological actions such as biosynthetic intermediates, metabolites and in defense against other organisms highlight the importance of this moiety in many applications. The 2-Pyrones have been used as precursors in the synthesis

of pharmacological active compounds such as HIV protease inhibitors, antifungals, cardiotonics, anticonvulsants, antimicrobials, pheromones, natural pigments, anti-tumor agents and plant growth regulators as depicted in Figure 7. The 2-pyrones derived from fungi tend to exhibit various cytotoxic, neurotoxic and phytotoxic activities.[24, 29-34]

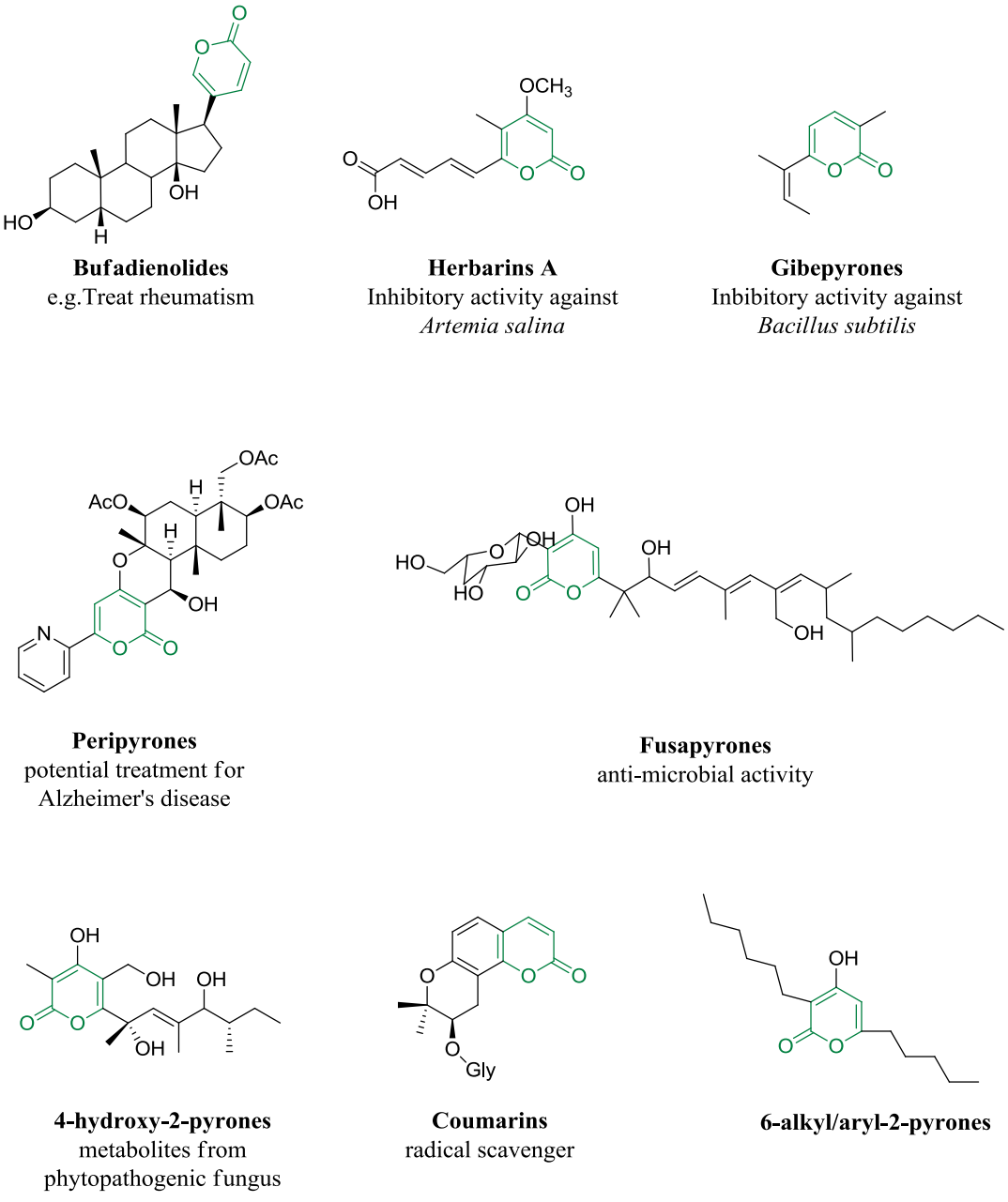


Figure 7. Naturally occurring 2-pyrones of therapeutic importance.[24-25]

Triacetic acid lactone, TAL **1** and dehydroacetic acid **2** are examples for two simple 2-pyrones which are available in biological systems and can be utilized for the synthesis of variety of biological important natural products such as solanopyrones, pheromones, coumarins and inhibitors of α-chymotrypsin and elastase enzymes.[35-39]

1.1.5. Reactions of triacetic acid lactone

The 2-pyrone is a six membered unsaturated lactone ring with four sp^2 hybridized carbons, but the nature of these carbon atoms differs from each other. As illustrated in Figure 8, C-2, C-4 and C-6 positions of the pyrone ring are electrophilic in nature. The C-3 and C-5 positions are prone to electrophilic attacks. The presence of an alkyl, alkoxy or an electron donating group at C-4 and C-6 positions of the ring favors the electrophilic attack on the ring. The presence of an electron withdrawing substituent at C-3 decreases the electron density at the C-4 and C-6 positions and facilitates nucleophilic reactions. The C-6 position is comparatively more prone to nucleophilic attack than the C-4 position. The presence of a leaving group at C-4, such as methoxy, methylsulphonyl and methylsulfinyl, increases the preference for nucleophilic attack at this position.

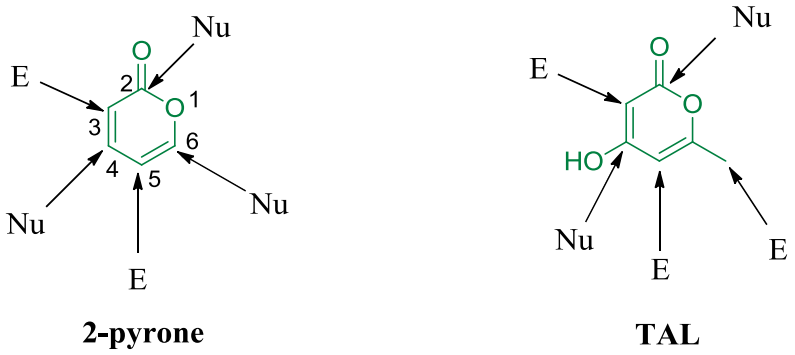
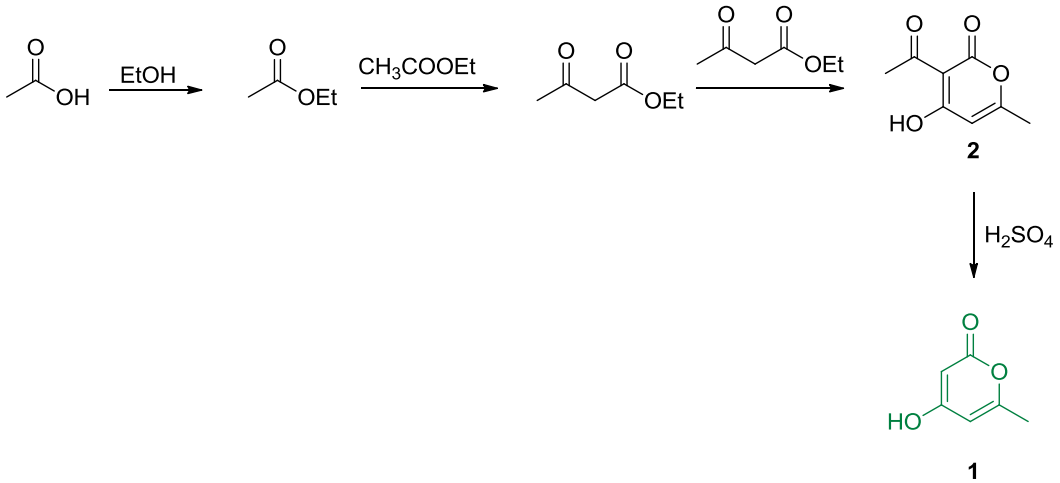


Figure 8. Electrophilic and nucleophilic attack on 2-pyrone and TAL.

The 2-pyrone ring system can behave as a cyclic diene in photochemical and cycloaddition reactions. TAL shows similar electrophilic and nucleophilic carbon character relative to the parent 2-pyrone core. TAL contains an OH group at C-4 and a methyl group at C-6, therefore the C-3 position is more subject to electrophilic attack.

The 2-pyrones, such as 4-hydroxy-6-methyl-pyrone (also denoted as triacetic acid lactone **1**), are biomass derived building blocks for bio-renewable chemicals. In particular, **1** can be obtained by genetically modified polyketide biosynthesis routes from natural sources, or can be produced synthetically from acetic acid as shown in Scheme 3.[20, 24, 40]

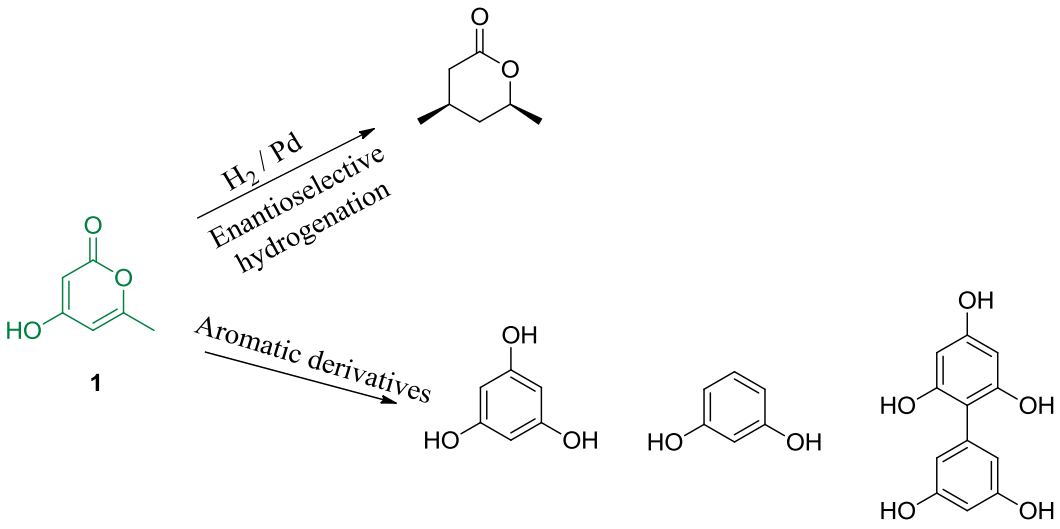


Scheme 3. Synthetic route for TAL from acetic acid.

The most common strategy for the commercial synthesis of TAL is through the acid-catalyzed condensation-cyclisation of β-ketoesters. In the presence of HCl gas the ethyl acetoacetate undergoes the self-condensation and cyclisation to give dehydroacetic acid **2**, which will further deacetylate in the presence of sulfuric acid to yield TAL **1**.[24]

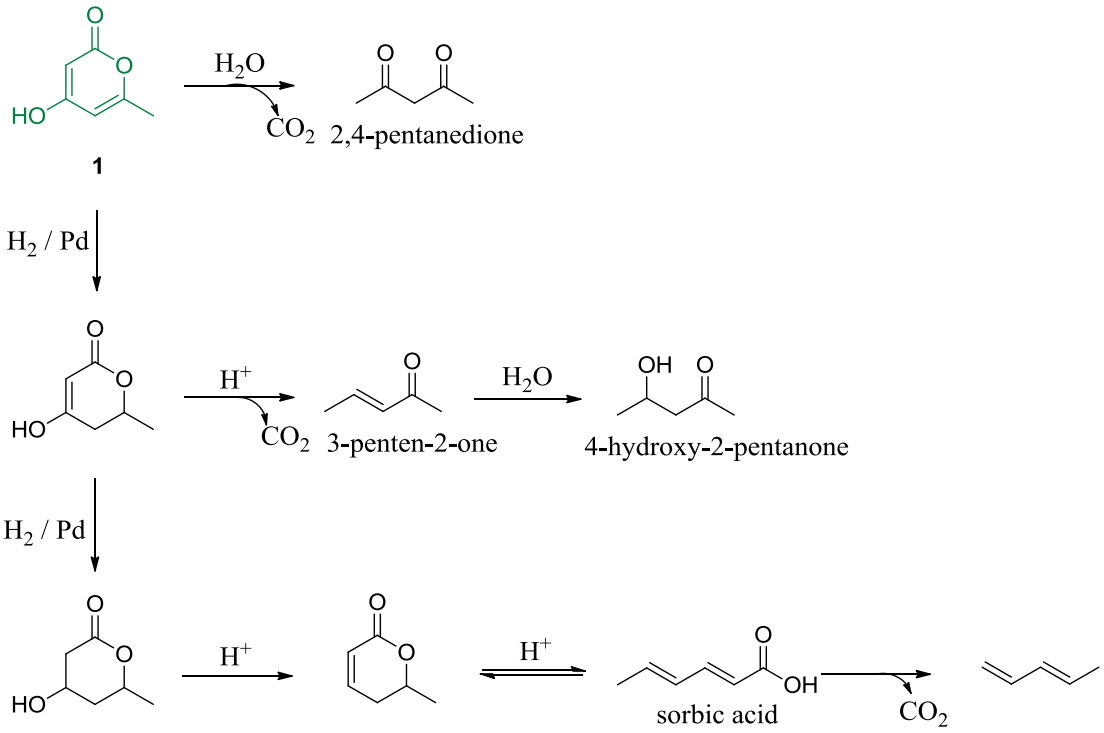
The use of the biosynthesized TAL from glucose and the catalytic upgrade of this material in the integrated strategy has demonstrated the expansion of biologically derived platform chemicals that comes from a single metabolic pathway. This process highlights the potential to produce a series of homologous molecules that can be upgraded in order to functionally displace petrochemicals that are currently in use.

Many reports regarding TAL describe catalytic transformations for the enantioselective synthesis of chemical intermediates for bioactive compounds.[41-44] As exhibited in Scheme 4, derivation of aromatics from TAL has also been reported in literature.[45]



Scheme 4. TAL derivatives

Work has also been reported on the conversion of TAL to products that can directly displace the existing petrochemicals in order to integrate the bio-based chemicals into the current industrial chemical market.[46-47] The hydrogenation of TAL in the presence of a Pd catalyst has been demonstrated in these studies along with the ring-opening and decarboxylation of TAL in water at low reaction temperatures (<373K). These reactions leads to bifunctional chemicals such as 2,4-pentanedione, 3-penten-2-one, 4-hydroxy-2-pentanone, and sorbic acid as illustrated in Scheme 5.



Scheme 5. Bifunctional chemicals from TAL.[46, 47]

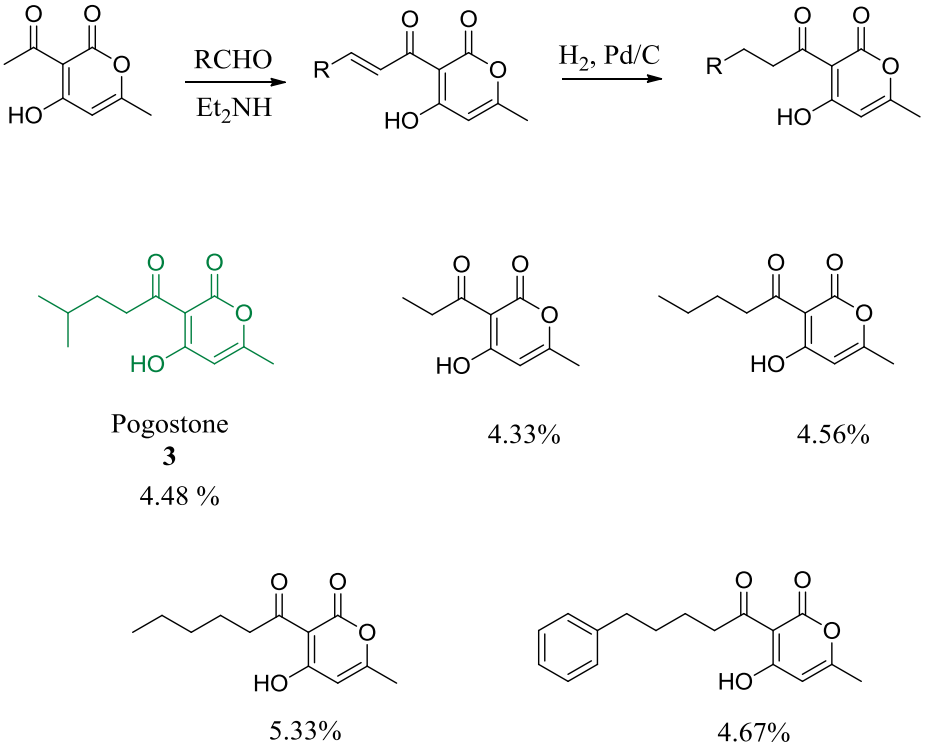
1.1.6. Pogostone from bio-based triacetic acid lactone

There are limited number of studies have been carried out on the bio-based platform chemical TAL. There is a wide range of important molecules that can be obtained from TAL as a result of the 2-pyrone ring. This molecule can be further derived into various specialty chemicals with a good biological activity or which can be widely applied in the perfumes, cosmetics and pharmaceutical industry other than the commodity molecules. These applications have motivated the exploration of new types of pyrones and literature precedent points to the potential for the synthesis of high value added molecules from TAL.

Pogostemonis Herba is the dried aerial part of *Pogostemon cablin* (Blanco) Benth, commonly known as the Patchouli plant from the family Lamiaceae. The plant is native to the tropical regions of Asia and the essential oil of this plant is used as an herbal medicine against common cold, diarrhea, headache and fever. This has been used as an antifungal agent in Chinese traditional medicine. Pogostone **3** is the major chemical marker for this medicinal plant. It has been verified that the active ingredient with 2-pyrone as its nuclear parent, possesses remarkable inhibition activities on *Candida albicans, Cryptococcus neoformans, Penicillium, Rhizopus nigricans, Staphylococcus aureus, Streptococcus* and other periodontopathic bacterias *in vitro* assays. Pharmacological studies on the Patchouli plant have shown that this material exhibits a variety of activities including anti-inflammatory, antinociceptive, anti-emetic, immunomodulatory, antimicrobial actions and inhibitory activity on platelet-activating factor (PAF) activation. Pogostone has displayed a higher activity against all Candia *in*

vivo assays.[48-50] In addition to its biological activities, patchouli has been used in perfumes for centuries. As a result of its pleasant odor it is known as the 'lavender of Asia'. The essential oil of this plant is extracted from the leaves by steam distillation. Recently, due to the strong scent, it is also used in incense, insect repellents and in alternative medicines.

In our study, we targeted molecules that are high value added specialty chemicals. Pogostone is a high value molecule with a commercial value of $ 1600/gram. We designed the synthesis of pogostone from the bio-based platform molecule TAL because of its promising biological activities. There are few reports on the total synthesis of pogostone. Yi and co-workers reported a synthesis for pogostone **3** for anti-bacterial activity evaluation, using the dehydroacetic acid **2**, as the starting material as represented in Scheme 6.

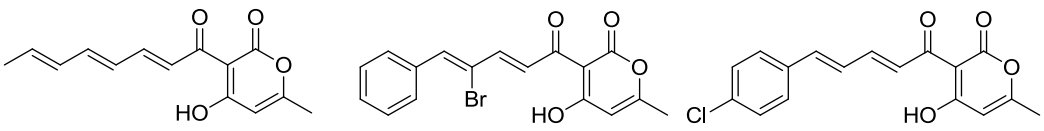


Scheme 6. Reported synthesis of pogostone and its analogs.

In this synthetic approach, an aldol condensation was carried out using the ketone **2** and using isobutyraldehyde. Here, diethylamine was used as the base and the reaction proceeded in dry tetrahydrofuran solution at 0-5 °C for 18 hours. The resultant alkene was hydrogenated with Pd/C using a hydrogenator under 0.1 Mp of pressure for 36 hours at room temperature, to give pogostone in 4.48% yield.[50]

In this report, additional pogostone analogs were synthesized in order to compare the anti-bacterial and anti-fungal activity of molecules derived from different aldehydes. All the analogs were obtained in low yields (~5%) as shown in Scheme 6. However, strong anti-fungal activity was observed when the chain length is either 5 or 6 carbons. With a phenyl group at the terminal carbon, the anti-fungal activity was lost. There were no promising results for the strains evaluated in the anti-bacterial activity studies.

In 2015, Tang and co-workers modified the synthesis of pogostone using a secondary amine catalyst, diphenylprolinol as the base for the aldol condensation.[51] The condensation was carried out at room temperature for shorter time period (2-6 hours), better crystallization method was used for the aldol product, and the hydrogenation time period was also reduced to four hours. The yield of the pogostone was improved to 58% with these synthetic modifications. They introduced 11 other pogostone analogs, containing conjugated alkene chains. Some of these analogs are shown in Figure 9.



3a **3b** **3c**

Figure 9. pogostone analogs with strong biological activities.

Structure **3a,** which contains three double bonds in the side chain of the ring, showed strong anti-bacterial activity against *Staphylococcus aureus*. The presence of an electron withdrawing group in the chain increased the anti-bacterial activity. Compounds containing functional groups with electron donating properties did not show anti-bacterial activity in this study. It has also been reported that the pogostone analogs containing a halogen atom, represented by structure **3b** and **3c**, had very strong cytotoxic activities.[51]

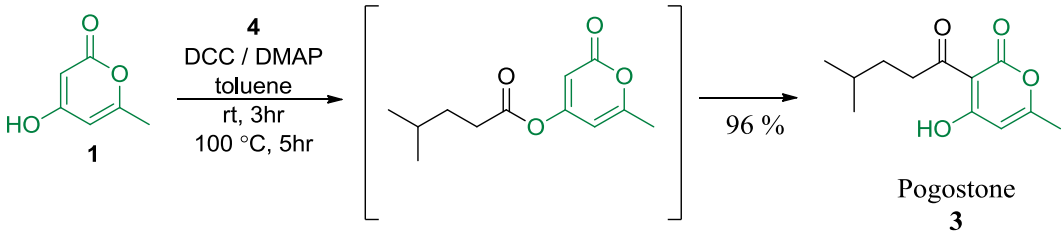
1.2. Results and Discussion

Literature reports on pogostone and its analogs have demonstrated the importance of these molecules as anti-fungal and anti-bacterial agents. The length of the carbon chain at carbon 3 of the pyrone ring notably enhances the anti-bacterial and anti-fungal activities. Pogostone and its analogs are classified as 2-pyrones derivatives and we propose a synthetic strategy to generate pogostone **3** from the platform molecule TAL **1.** In this project we have collaborated with biochemists, microbial engineers and chemical engineers from the NSF engineering research center for biorenewable chemicals (CBiRC).

Pogostone was synthesized using ketone **2** and isobutryaldehyde in an aldol reaction followed by hydrogenation of the resulting alkene. The best yield obtained for pogostone is 58%.[51]We need to think about the ultimate production yield of the target material and the number of synthetic steps involved in order to implement **1** as a biomass platform molecule and as an alternative to petroleum derived chemical building blocks.

We chose a synthetic route to generate pogostone efficiently and easily with these considerations in mind.

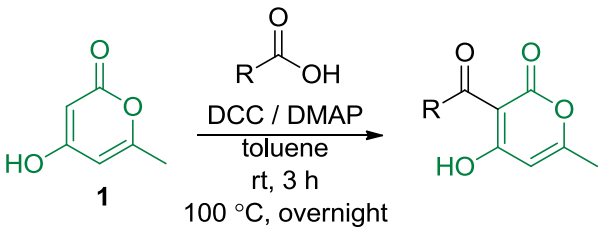
We first synthesized pogostone using commercially available **1** to confirm that the reaction would proceed under the proposed conditions. We conducted the reaction using **1** and commercially available 4-methylpentanoic acid **4** in the presence of *N,N'*-Dicyclohexylcarbodiimide (DCC) and 4-Dimethylaminopyridine (DMAP) which are mild reagents commonly used in the preparation of esters and amides. Using these conditions we were able to prepare 3-acyl-4-hydroxy-2-pyrone from carboxylic acid **4** and **1** in one step. This reaction proceeds through a simultaneous Fries type rearrangement of O-enol acyl group of **1** towards α position of the lactone to get the desired C-acylation product as illustrated in scheme 7.[52-53]



Scheme 7. Pogostone synthesis from TAL.

The reaction was carried under argon at room temperature for 3 hours followed by heating to 100 °C for 5 hours. The crude product was purified by flash column chromatography for purification afforded **3** in 96% yield, the highest yield of pogostone that has been reported to date. The reaction was first carried out in 2.0 mmol scale, but gave similar results when scaled up to 10 grams. With a reasonable set of reaction

conditions at hand, we performed the same reaction using bio-based TAL **1** obtained from the CBiRC. Two bio-based samples of TAL were used which differed only in the purification methods used to isolated the TAL from the biomass broth (in 100% and 94% purity). When we subjected these for the one step synthesis of **3** using same reaction conditions, we were able to get 99% and 93% yields for the 100% pure TAL and 94% pure TAL respectively.



Scheme 8. General reaction for pogostone analogs.

In order to get different analogs for pogostone we followed the same reaction procedure as in Scheme 8, using a range of carboxylic acids. Here, the reaction time was increased from 5 hours to overnight at 100 °C for all carboxylic acids to get better yields. The isolated yields for each product are presented in table 2.

Table 2. Yields of pogostone and its analogs.

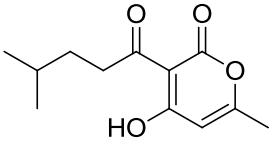
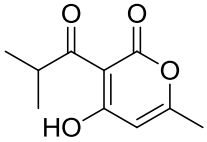
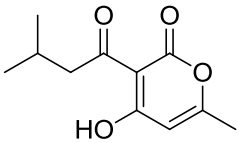
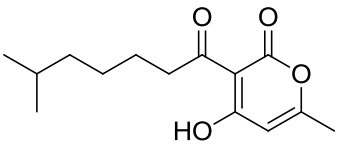
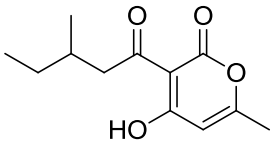
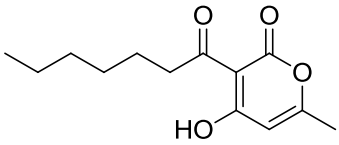
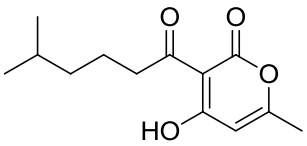
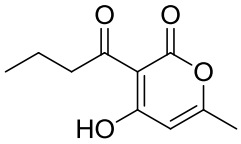
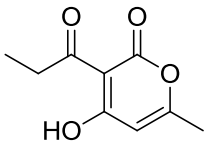
Entry	Carboxylic acid	Product	Yield (%)
1	4-methylpentanoic acid **4**	 **3**	96
2	Isobutyric acid	 **5**	58
3	Isovaleric acid	 **6**	87
4	6-methylheptanoic acid	 **7**	85
5	3-methylpentanoic acid	 **8**	99
6	Heptanoic acid	 **9**	87

Table 2 (continued)

7	5-methylhexanoic acid	 **10**	88
8	Butyric acid	 **11**	95
9	Propionic acid	 **12**	59

The next step in this project was to carry out some biological activity studies for these pogostone and its analogs. For this collaboration with CBiRC and RTI lab we performed preliminary analysis on anti-fungal activities for these nine compounds. Here, they tested on minimal inhibitory concentrations (MICs) against yeast and yeast-like organisms against the pogostone analogs. The results for these experiments are shown in the Table 3.

Table 3. Inhibitory activity against yeast like organisms.

Organism	3	5	6	7	8	9	10
Cryptococcus neoformans	+	--	--	--	--	--	+
Geotrichum capitatum	+	--	+	--	--	--	+
Candida kefyr	+	--	_	--	--	+	_
Candida geochares	+	--	_	--	--	--	+
Candida krusei	+	--	+	--	--	--	+
Yarrowia lipolytica	+	--	+	--	--	--	+
Trichosporon mucoides	--	--	+	+	--	--	+
Protohteca wickehamii	+	+	+	+	+	+	+

+ represents positive inhibitory effect, -- represents no significant inhibitory effect

The activity studies showed that pogostone **3**, **6** and **10** shows inhibitory activity to most of the yeast like organisms so further tests were carried out for these three compounds. Previous reports have shown that some anthropoid controlling studies have been conducted for analog **6.**[54]With that in mind we carried out some entomology studies for pogostone analogs as well.

1.3. Conclusion

There is a pressing need for alternative sources of organic chemicals for the global energy industry. Biomass has been recognized as an alternative source of carbon that can be used to supply this carbon need and several building block chemicals (platform chemicals) have been identified for this approach. Triacetic acid lactone (TAL) has been proposed as a new platform molecule for this purpose. The aim of project is to derive high value added specialty molecules from TAL and to demonstrate its versatile applicability as a platform molecule.

Our first approach for the diversification of TAL was to convert it to the biologically active compound pogostone. We identified a one-step procedure for the synthesis of pogostone and its analogs. Pogostone was isolated in the highest yield reported to date using this effective and convenient method. Eight pogostone derivatives were synthesized with this one-step procedure. These products were generated in high yields following a simple purification and no harsh reaction conditions were required. We obtained pogostone in excellent yields from both commercially available and biomass derived TAL and have demonstrated the scalability of our synthesis of pogostone. We also explored the biological activities for pogostone and its derivatives.

In this chapter we have made considerable advances towards to the synthesis of biologically important natural products from TAL **1**. This work shows that TAL should be pursued as a viable platform molecule for industrial applications.

1.4. Experimental

All starting materials were purchased from Sigma-Aldrich and TCI America; solvents were purchased from Fisher Scientific and used without further purification. All reactions were carried out in flame-dried glassware under argon with dry solvents under anhydrous conditions. All yields refer to isolated products by column chromatography. Thin-layer chromatography (TLC) was performed using commercially available 250 micron silica gel plates (Analtech) using UV light as a visualizing agent. Silica gel 60Å, particle size 0.032 – 0.063 mm, was used for flash column chromatography. ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ on a Varian VXR 300 MHz or Bruker DRX 500 MHz spectrometer. ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to the residual protonated chloroform peak ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm) as an internal reference. Low-resolution mass spectra (LRMS) were recorded on an Agilent 6540 QTOF (quadrupole time of flight) mass spectrometer using ESI (electrospray ionization) or APCI (atmospheric-pressure chemical ionization) or EI (electron ionization) on an Agilent 6890 GC/MS. Melting points were analyzed on a Mel-Temp II capillary melting point apparatus.

Selected Experimental, Physical, and Spectral Data

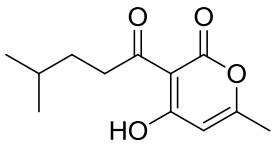
General Procedure: Reaction for pogostone

The synthesis of **3** is representative with the exception of using the appropriate acids for the rest of the compounds **5-12**.

To a flame dried flask the commercially available 98% purity TAL (0.252 g, 2.0 mmol) was added. Dried toluene (5 mL) was added to this flask and stirred. To this suspension, DCC (0.413 g, 2.0 mmol) and DMAP (0.048 g, 0.4 mmol) were added and stirred under argon. Then 4-methylpentanoic acid (0.25 mL, 2.0 mmol) was added to this mixture and was stirred for 3 h at room temperature and was further stirred for 5 h at 100 °C. After cooling to room temperature, the reaction mixture was subjected to filtration. The filtrate was washed twice with toluene (10 mL x 2). The combined toluene solution was concentrated under reduced pressure to give the crude product, which was subjected to silica column chromatography (silica gel, hexane: EtOAc 10:1 as an eluent) to afford **3** (0.429 g, 96%) as a yellow solid.

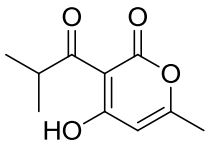
With the use of biomass derived 100 % purity TAL, **3** was obtained in 99% and with the use of 94% purity TAL, **3** was yielded in 93%.

4-hydroxy-6-methyl-3-(4-methylpentanoyl)-2H-pyran-2-one (3)



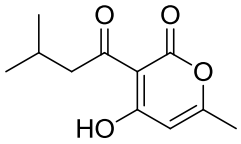
Yellow solid (96% yield): mp 34-35 °C; Rf = 0.64 (silica gel, hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 5.91 (s, 1H), 3.07 (t, 2H), 2.25 (s, 3H), 1.62-1.66 (m, 1H), 1.49-1.56 (m, 2H), 0.93 (d, 6H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 208.3, 181.3, 168.8, 160.9, 101.5, 99.4, 39.7, 32.8, 27.8, 22.4, 20.6 ppm; LRMS (ESI-QTOF) calcd for $C_{12}H_{17}O_4$ $[M + H]^+$ 225.1127, found 225.1121.

4-hydroxy-3-isobutyryl-6-methyl-2H-pyran-2-one (5)



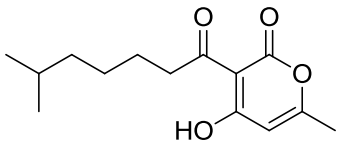
Yellow solid (58% yield): mp 72-74 °C; Rf = 0.33 (silica gel, hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 5.93 (s, 1H), 3.93-3.99 (m, 1H), 2.26 (s, 3H), 1.23 (d, 6H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 212.1, 181.9, 168.8, 160.6, 101.6, 98.5, 37.3, 20.6, 18.39 ppm; LRMS (ESI-QTOF) calcd for $C_{10}H_{13}O_4$ $[M + H]^+$ 197.0813, found 197.0808.

4-hydroxy-6-methyl-3-(3-methylbutanoyl)-2H-pyran-2-one (6)



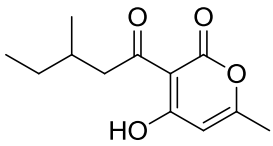
Orange solid (87% yield): mp 75-77 °C; Rf = 0.53 (silica gel, hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ =5.91 (s, 1H), 2.95 (d, 2H), 2.22 (s, 3H), 2.15-2.20 (m, 1H), 0.95 (d, 6H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 207.5, 181.4, 168.8, 161.0, 101.6, 99.7, 50.0, 24.8, 22.6, 20.6 ppm; LRMS (ESI-QTOF) calcd for $C_{11}H_{15}O_4$ $[M + H]^+$ 211.097, found 211.0965.

4-hydroxy-6-methyl-3-(6-methylheptanoyl)-2H-pyran-2-one (7)



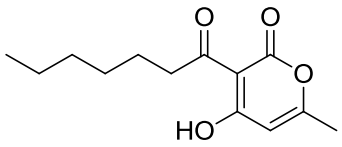
White solid (85% yield): mp 44-45 °C; Rf = 0.68 (silica gel, hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ =5.92 (s, 1H), 3.05 (t, 2H), 2.33 (s, 3H), 1.60-1.64 (m, 1H), 1.44-1.48 (m, 2H), 1.33-1.38 (m, 2H), 1.20-1.22 (m, 2H), 0.84 (d, 6H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ =208.0, 181.3, 168.8, 161.0, 101.6, 99.5, 41.7, 38.7, 33.9, 27.8, 24.2, 22.6, 20.6 ppm; LRMS (ESI-QTOF) calcd for $C_{14}H_{21}O_4$ $[M + H]^+$ 253.144, found 253.143.

4-hydroxy-6-methyl-3-(3-methylpentanoyl)-2H-pyran-2-one (8)



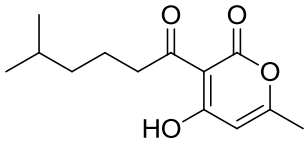
Orange liquid (99% yield): Rf = 0.50 (silica gel, hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 6.15 (s, 1H), 3.10 (dd, 1H), 2.81 (dd, 1H), 2.30 (s, 3H), 1.86-1.89 (m, 1H), 1.32-1.35 (m, 2H), 0.95 (d, 3H), 0.90 (t, 3H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 207.8, 181.5, 168.8, 160.9, 101.6, 99.7, 48.2, 32.4, 30.9, 20.6, 19.2, 11.3 ppm; LRMS (ESI-QTOF) calcd for $C_{12}H_{17}O_4$ $[M + H]^+$ 225.1127, found 225.1958 .

3-heptanoyl-4-hydroxy-6-methyl-2H-pyran-2-one (9)



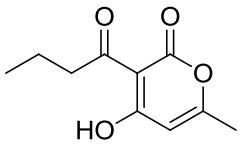
White solid (87% yield): mp 54-55 °C; Rf = 0.59 (silica gel, hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 6.13 (s, 1H), 3.02 (t, 2H), 2.27 (s, 3H), 1.60-1.65 (m, 2H), 1.30-1.33 (m, 6H), 0.87 (t, 3H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 208.1, 181.3, 168.8, 101.6, 99.5, 41.7, 37.1, 31.6, 28.8, 23.9, 22.5, 20.7, 14.1 ppm; LRMS (ESI-QTOF) calcd for $C_{13}H_{19}O_4$ $[M + H]^+$ 239.1283, found 239.1274.

4-hydroxy-6-methyl-3-(5-methylhexanoyl)-2H-pyran-2-one (10)



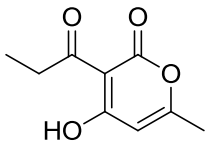
Yellow solid (88% yield): mp 31-33 °C; Rf = 0.64 (silica gel, hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 6.14 (s, 1H), 3.03 (t, 2H), 2.29 (s, 3H), 1.50-1.56 (m, 1H), 1.22-1.28 (m, 4H), 0.87 (d, 6H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 207.9, 181.2, 168.8, 160.98, 101.5, 99.4, 41.8, 38.4, 27.8, 23,7, 22.4, 20.6 ppm; LRMS (ESI-QTOF) calcd for $C_{13}H_{19}O_4$ $[M + H]^+$ 239.1278, found 239.1277.

3-butyryl-4-hydroxy-6-methyl-2H-pyran-2-one (11)



Yellow solid (95% yield): mp 51-53 °C; Rf = 0.60 (silica gel, hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 6.13 (s, 1H), 3.03 (t, 2H), 2.29 (s, 3H), 1.62-1.67 (m, 2H), 0.96 (t, 3H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 207.7, 181.2, 168.8, 160.9, 101.4, 99.4, 43.4, 20.5, 17.2, 13.7 ppm; LRMS (ESI-QTOF) calcd for $C_{10}H_{13}O_4$ $[M + H]^+$ 197.0808, found 197.0807.

4-hydroxy-6-methyl-3-propionyl-2H-pyran-2-one (12)



White solid (59% yield): mp 93-95 °C; Rf = 0.42 (silica gel, hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 5.93 (s, 1H), 3.13 (q, 2H), 2.27 (s, 3H), 1.18 (t, 3H) ppm; ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 208.3, 181.0, 168.8, 161.0, 101.4, 99.3, 35.3, 20.6, 7.7 ppm; LRMS (ESI-QTOF) calcd for $C_9H_{11}O_4$ $[M + H]^+$ 183.0652, found 183.0650.

1.5. References

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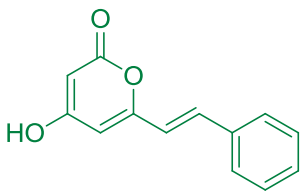
CHAPTER 2

AN IMPROVED ALDOL PROTOCOL FOR THE PREPARATION OF 6-STYRENYLPYRONES[†]

2.1. Introduction:

2.1.1. Styrenylpyrones

Styrenylpyrones are an emerging class of natural products. Biogenetic analysis indicates that these natural products are derivable by the polyketide route initiation by cinnamic acids leading to the 6-styryl-2-pyrones shown in Figure 1.[1]



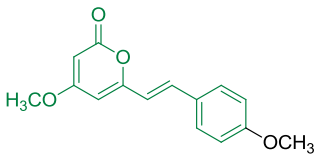
6-styryl-2-pyrone

Figure 1. Core structure of 6-styryl-2-pyrones.

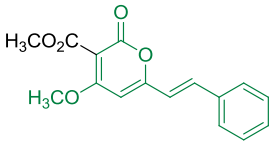
Several naturally occurring 6-styryl-2-pyrones have been isolated from various plants of the genera *Piper, Aniba, Alpinia, Miliusa* and *Ranunculus.* There exists a range of 6-styryl-2-pyrones and their derivatives among *Strophariaceae* and related genera. Micro-organisms are other sources of styrylpyrones. Some of these structures are shown in Figure 2.

[†] Adapted from Kraus, G. A.; Wanninayake, U. K. *Tetrahedron Lett.* **2015**, *56*, 7112–7114 with permission from Elsevier.

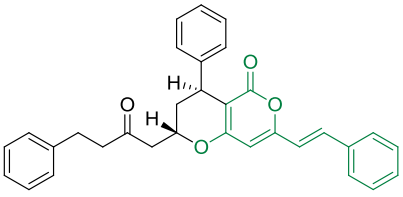
Kavalactones are a class of 6-styryl-2-pyrones found in the kava shrub, known to have a wide variety of effects including anxiolytic, anti-inflammatory, analgesic, nootropic, anticonvulsant and sedative activity caused by numerous interactions with the central nervous system via several mechanisms. They have shown a promising TNF-α (tumor necrosis factor-α) release inhibitory activity as well. The major constituents of the kava rhizome are (+)-kavain (1.8 %), (+)-methysticin (1.2 %), yangonin (1.0 %), demethoxyyangonin (1.0 %), (+)-dihydrokavain (0.6 %), and (+) dihydromethysticin (0.5%) are represented in Figure 3. These kava extracts have long been used as medicine by south Pacific islanders. They have been shown to potently inhibit a wide range of hepatic enzymes, and have potential applications in pharmaceutical and herbal medication.



Yangonin
a kavalactones derivative from the root extracts of *Piper methysticum*



Phelligridin B
isolated from the fruit bodies of the Chinese medicinal fungus *Phellinus igniarius*



Katsumadain A
isolated from the seeds of *Alpinia katsumadai*

Figure 2. Natural occurring 6-styryl-2-pyrones.

The basic skeleton of the natural products isolated from *Polygala sabulosa* (Polygalaceae) greatly resembles that of the kavalactones, isolated from kava (*Piper methysticum*, Piperaceae), which are known for their anxiolytic and antidepressant effects. The natural products derived from *Polygala sabulosa* exhibit anxiolytic-like, hypnosedative, and anticonvulsant effects. These natural 2-pyrones have shown partial binding to the benzodiazepine site, which likely mediates the anxiolytic-like and anticonvulsant effects.[3-7] Some studies have demonstrated the strong inverse correlation in the consumption of styrylpyrone and the incidence of cancer. Various kavalactones have been used in this study.[8]

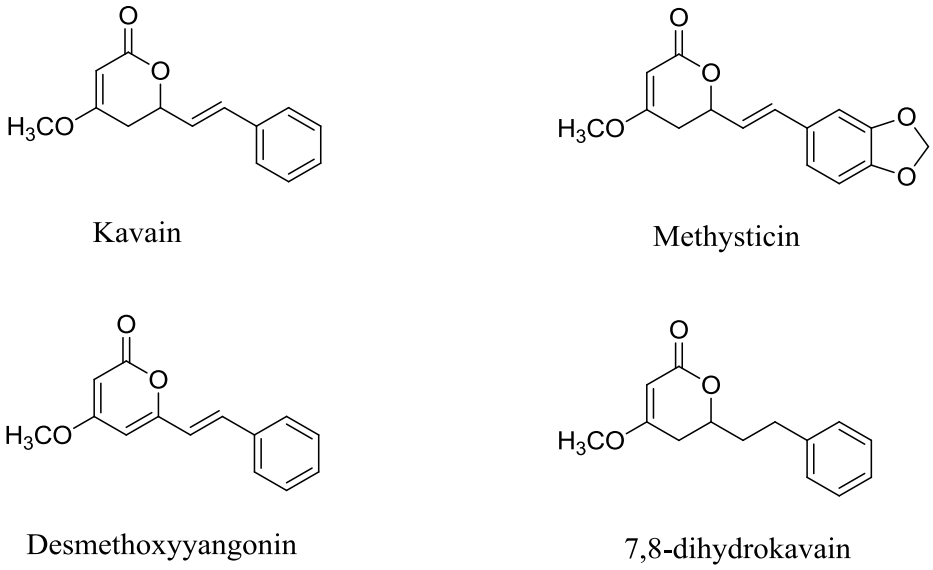


Figure 3. Some of the major constituents of the kava rhizome.

Penstyrylpyrone is a Protein tyrosine phosphatase 1B (PTP1B) inhibitory styrylpyrone type secondary metabolite from marine-derived fungi. This also reduces TNF-α and Interleukin-1 beta (IL-1β) production.[9] *Alpinia speciose* consist of several

kavalactones. The rhizome of these plants is known for its pharmacological activities, and antiulcer and antiplatelet activity.[7]

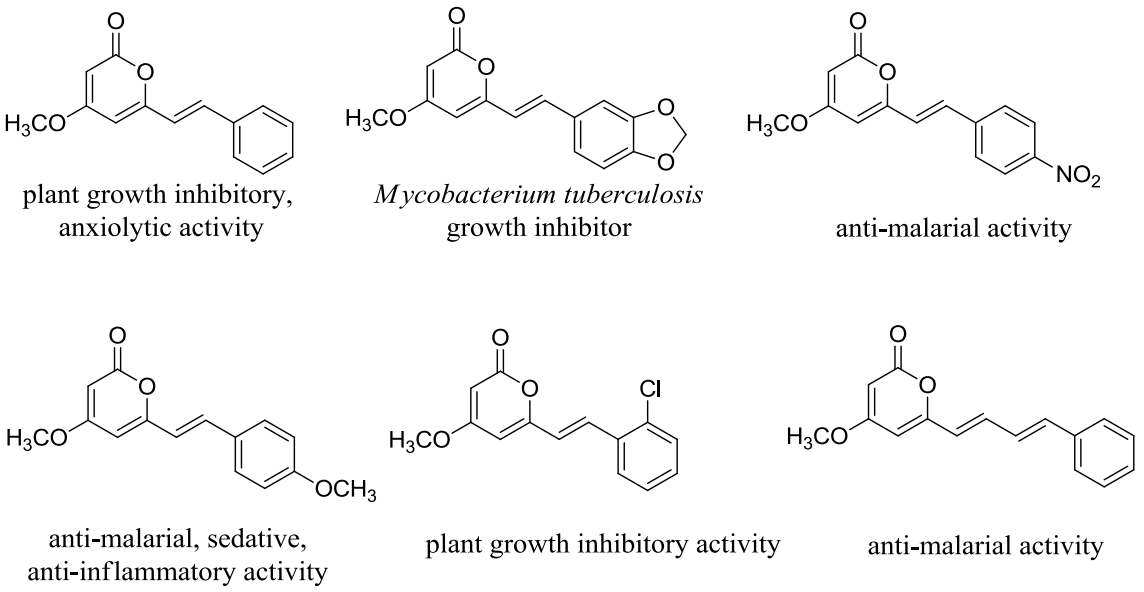


Figure 4. Biological activity of some styrylpyrones.

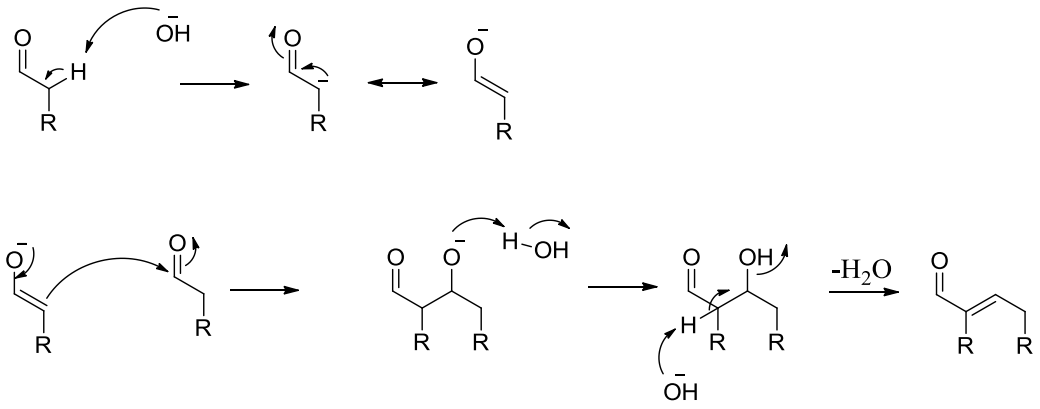
2.1.2. Aldol condensation

Aldol condensations of ketones and aldehydes are widely used in organic chemistry to form carbon-carbon bonds. Reactions can involve the self-condensation of either aldehyde or ketone or the cross condensation of an aldehyde with a ketone. Generally, aldehydes self-condense faster than ketones as the ketone carbonyl is more hindered than, and not as electrophilic as that of aldehyde.

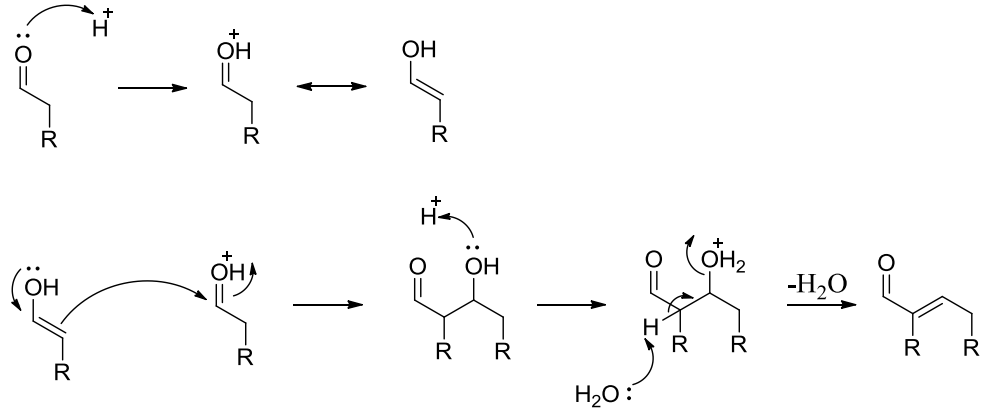
Aldol reactions can be catalyzed both by acids and bases. The aldol reaction occurs first and is followed by a dehydration process that involves the elimination of a

water molecule. The dehydration can happen via two mechanisms as detailed in Scheme 1. One mechanism involves an enolate mechanism when a strong base like potassium *tert*-butoxide, potassium hydroxide or sodium hydride is used. The other pathway involves an acid catalyzed enol mechanism.

Base catalyzed aldol reaction



Acid catalyzed aldol reaction

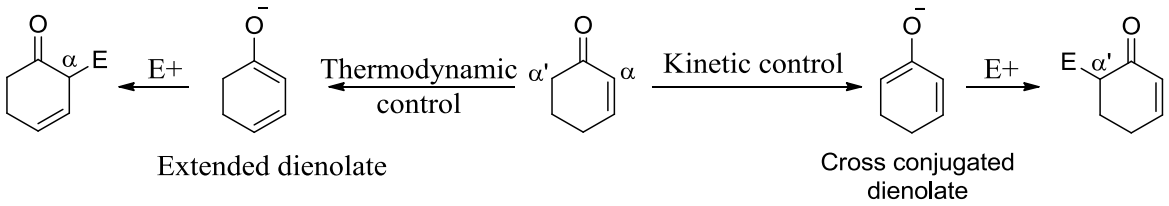


Scheme 1. Acid and base catalyzed aldol condensation.

In the base catalyzed mechanism, the deprotonation of the α-carbon occurs to form an enolate that acts as the nucleophile to attack the carbonyl of the other molecule

forming a carbon-carbon bond. The resultant alkoxide anion is protonated and undergoes an elimination reaction. The acid catalyzed mechanism starts with the protonation of the carbonyl and forms an enol. This enol acts as the nucleophile to attacks the activated carbonyl. Then elimination occurs to remove a water molecule.[11]

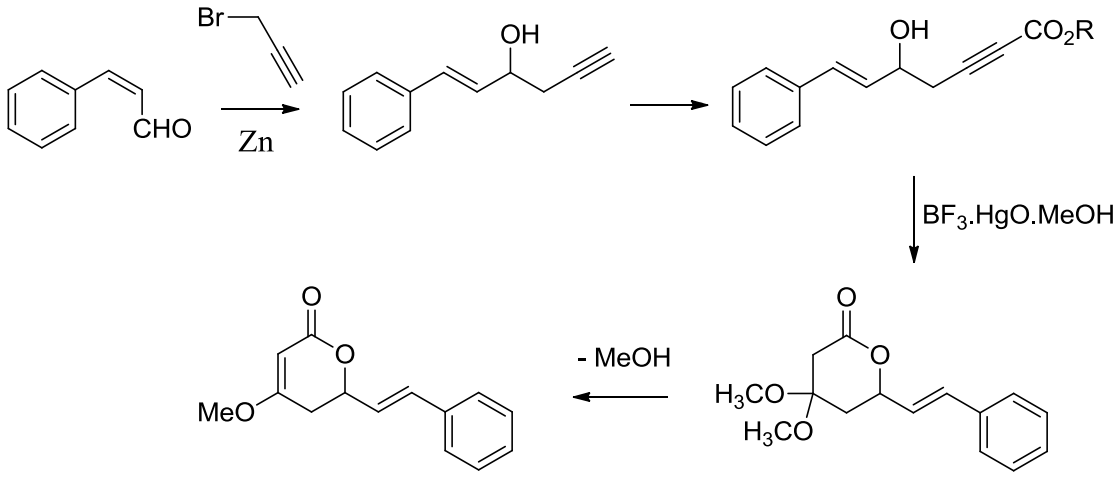
Aldol condensation of α,-β-unsaturated carbonyl compounds is an interesting topic concerning the control of reactivity and selectivity in reactions of conjugated carbonyl compounds. The challenge in these reactions is that the multiple sites are available for enolization and subsequent alkylation. Under kinetic control, such as in reactions with strong bases like LDA (lithium diisopropylamide), cross-conjugated dienolates generally become the dominant species. Under thermodynamic conditions, such as when sodium/ potassium *tert*-butoxide or sodium hydride is used, the extended dienolates tend to be dominant as shown in Scheme 2. The cross conjugated dienolates primarily generate the α'- alkylation products with the given electrophile. In contrast, the extended enolates gives the α-alkylation product.[12]



Scheme 2. Thermodynamic versus kinetic enolate.

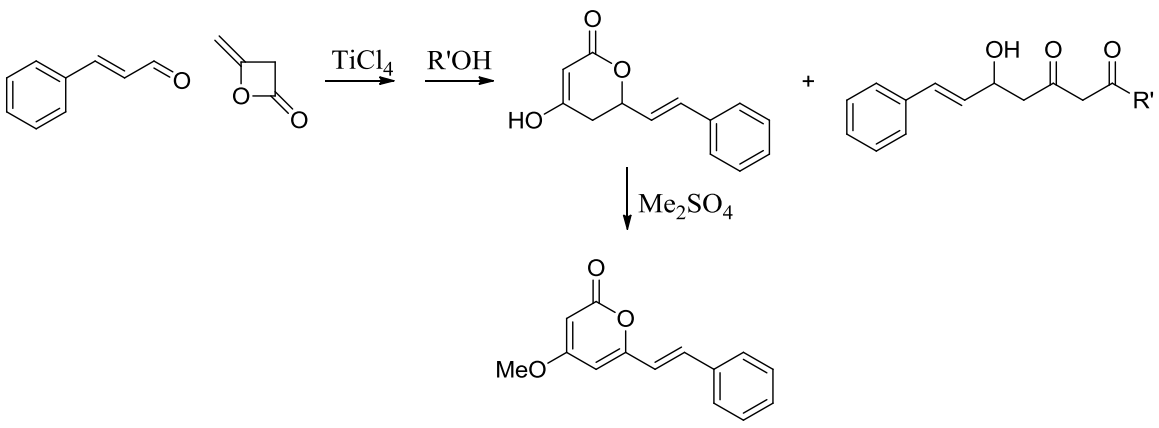
2.1.3. Kavalactone synthesis

There are several reports in literature for the synthesis of 6-styrenyl-2-pyrones, especially the kavalactones due to their promising biological activities. Several Refromatsky reactions have been reported to synthesize kavalactones. Klohs and co-workers have reported a Refromatsky condensation using 4-bromo-3-methoxycrotonoate.[13]



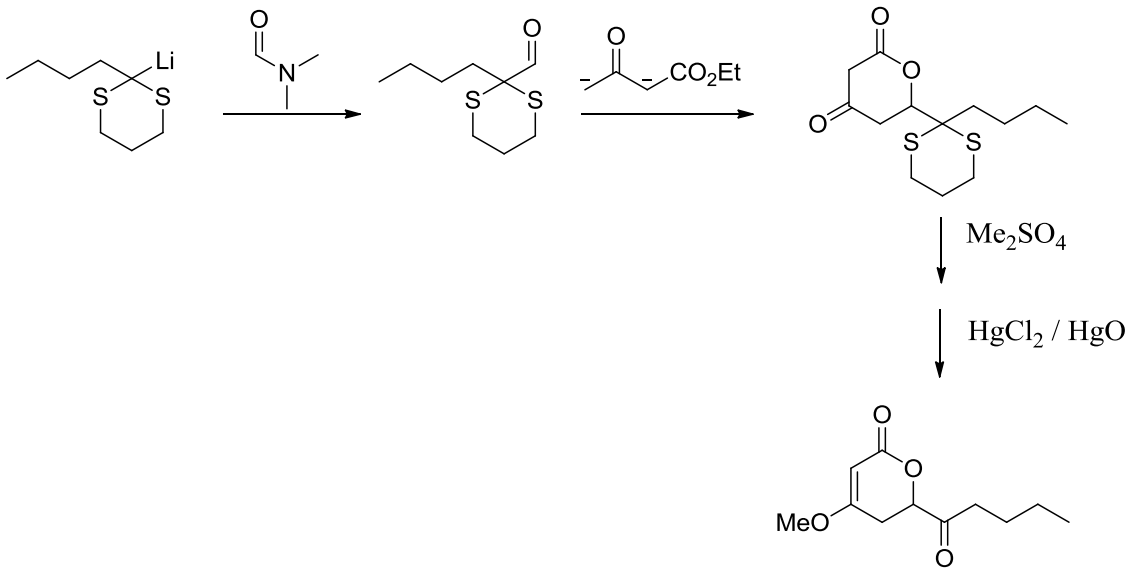
Scheme 3. Kavalactones from 5-hydroxy-2-alkyoic esters.[14]

Fowler and co-workers presented the conjugate addition of methanol to 5-hydroxy-2-alkyoic esters to generate kavalactones as summarized in Scheme 3.[14] Scheme 4 depicts the $TiCl_4$ promoted addition of diketene to aldehyde as reported by Izawa and co-workers to generate kavalactones.[15]

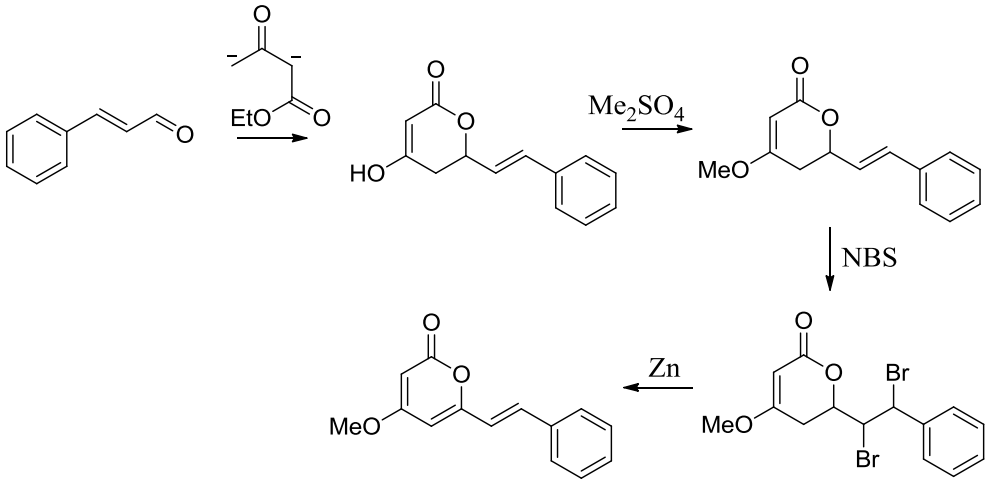


Scheme 4. Kavalactones from diketenes.[15]

Seebach and co-workers reported a strategy for the synthesis of pestalotin using addition of acetoacetate dianion to an aldehyde as illustrated in Scheme 5.[16]

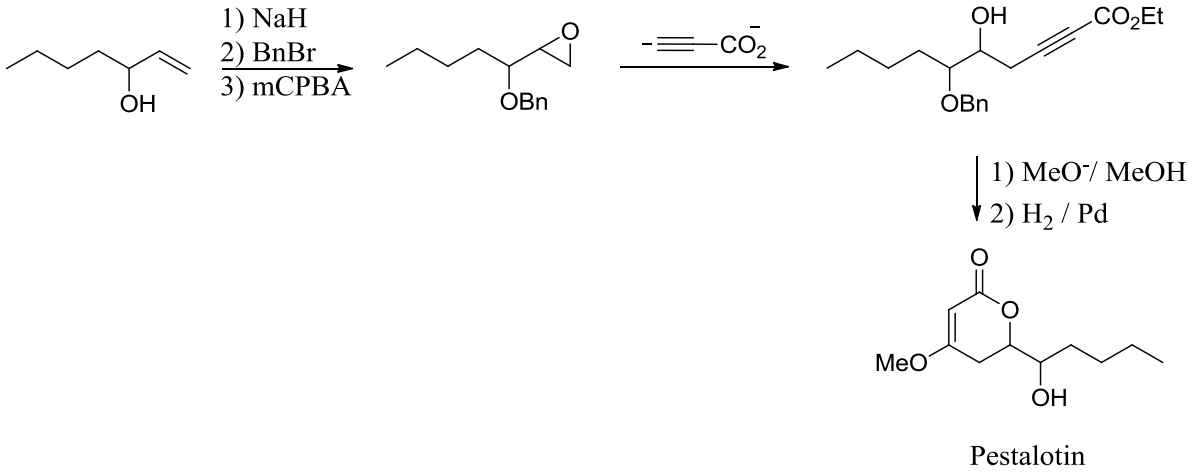


Scheme 5. Pestalotin precursor from acetoacetate dianion.[16]



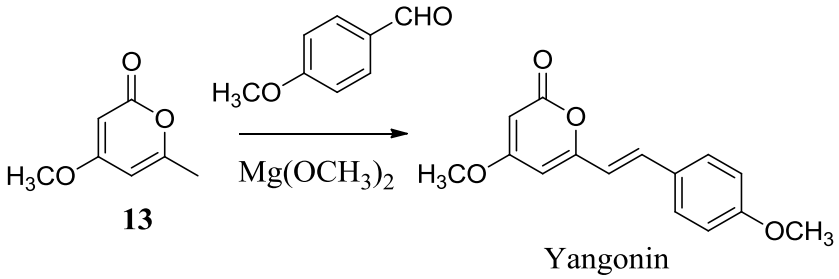
Scheme 6. Kavalactones from acetoacetate dianion. [17]

Reffstrup and co-workers further modified this method to form an aldol-type product as shown in Scheme 6.[17] Scheme 7 represents the work reported by Carlson and co-workers on pestalotin synthesis. They used the propiolic acid dianion as an acyl equivalent.[18]



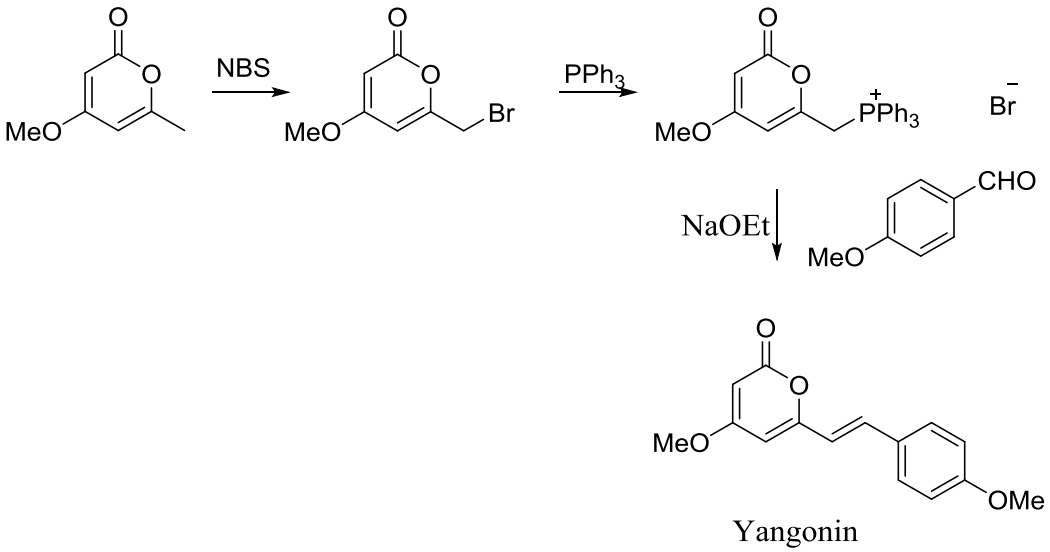
Scheme 7. Pestalotin from propiolic acid dianion. [18]

Bu'Lock and co-workers reported on the synthesis of yangonin, a kavalactone. This work involves an aldol reaction between lactone the triacetic acid methyl ether (TAL-OMe, **13**) and 4-methoxybenzaldehyde in the presence of magnesium methoxide as illustrated in Scheme 8. This method resulted in low yields (33%) for yangonoin.[19]



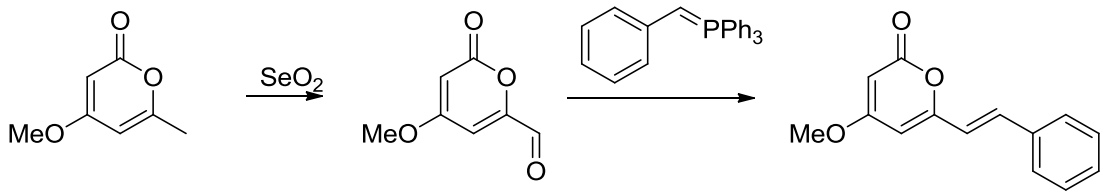
Scheme 8. Kavalactones from TAL-OMe.[19]

Douglas and co-workers reported the same aldol condensation to desmethoxyyangonin using magnesium methoxide and benzaldehyde as the aldehyde.[20] Towards a synthesis of hispidin, Adam and co-workers used the same method as Bu'Lock in their aldol condensation reaction using piperonal and the same base.[21] Another synthesis on yangonin was reported by Bacardit and co-workers using TAL-OMe. In this procedure (as represented in Scheme 9) they formed the ylide from the Wittig reagent using sodium ethoxide and reacted with 4-methoxybenzaldehyde to from yangonin.[22]



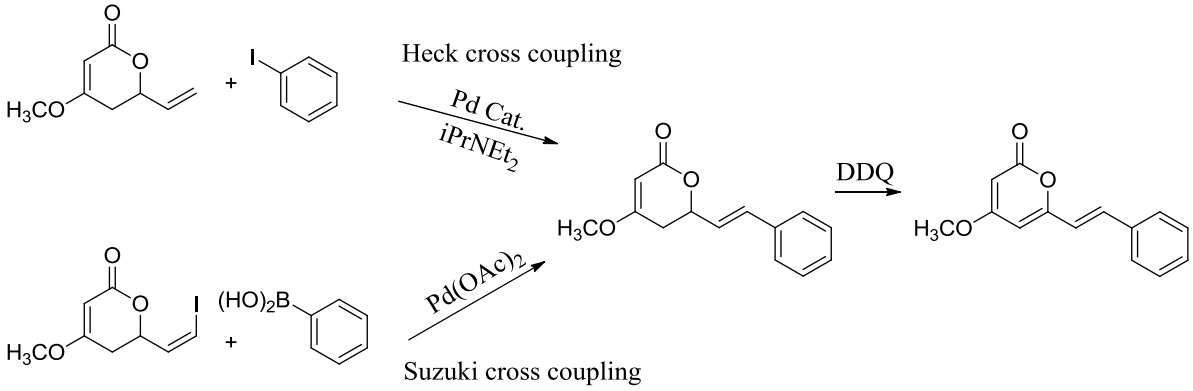
Scheme 9. Kavalactones from 6-bromo TAL-OMe.[22]

Alhough the aldol condensation between TAL-OMe and aromatic aldehydes in the presence of magnesium methoxide occurs at C-6 methyl group of the 2-pyrone, it affords low yields for these reactions. Edwards and co-workers used this method and were able to get 5-6% yields for their compounds.[23] McCracken and co-workers used this method to get yields around 3-20%.[24] Suzuki and co-workers reported another use of TAL-OMe to form kavalactone by condensation of the formyl pyrone and using the appropriate Wittig reagents as shown in Scheme 10.[25]

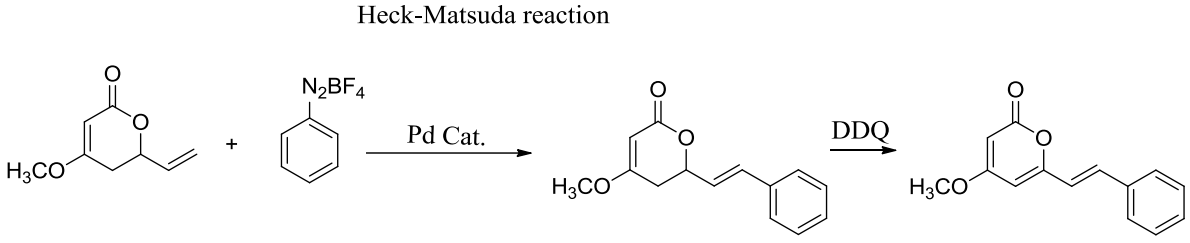


Scheme 10. Kavalactones from Wittig reaction.[25]

Although lithiation of TAL-OMe with LDA or *n*-butyllithium occurs readily, the condensation with an aldehyde occurs at C-3 position of the 2-pyrone giving undesired products in the formation of kavalactones.[26] Amaral and co-workers reported a different method for the synthesis of kavalactones using Heck cross coupling method and Suzuki–Miyaura cross-coupling reactions as detailed in Scheme 11.[27] Soldi and co-workers presented the Heck–Matsuda arylation as a strategy as depicted in Scheme 12, to access kavalactones isolated from *Polygala sabulosa, Piper methysticum* and analogs.[28]



Scheme 11. Kavalactones from Heck and Suzuki coupling.[27]



Scheme 12. Kavalactones through Heck-Matsuda coupling.[28]

2.1.4. TAL anion chemistry

Triacetic acid lactone (TAL, **1**) is a versatile synthon that can potentially serve as a precursor for several important natural products. To obtain the kavalactones from TAL, we needed to activate the C-7 position of TAL as depicted in Figure 5.

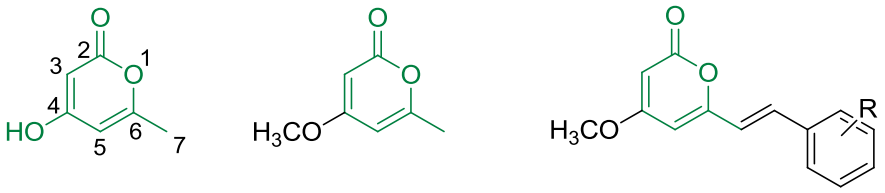
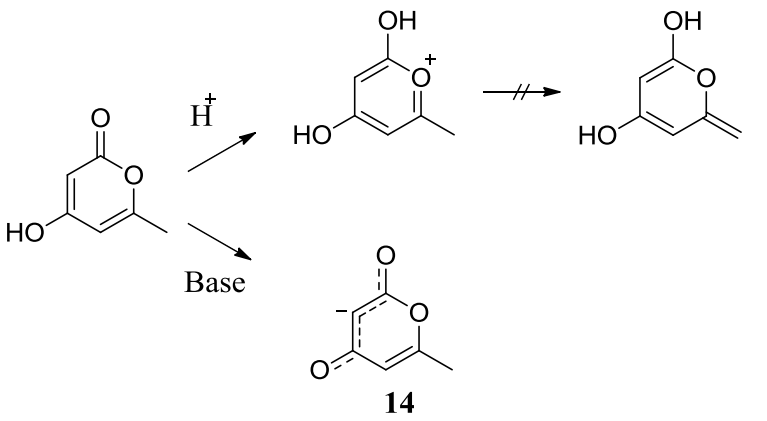


Figure 5. TAL derivatives.

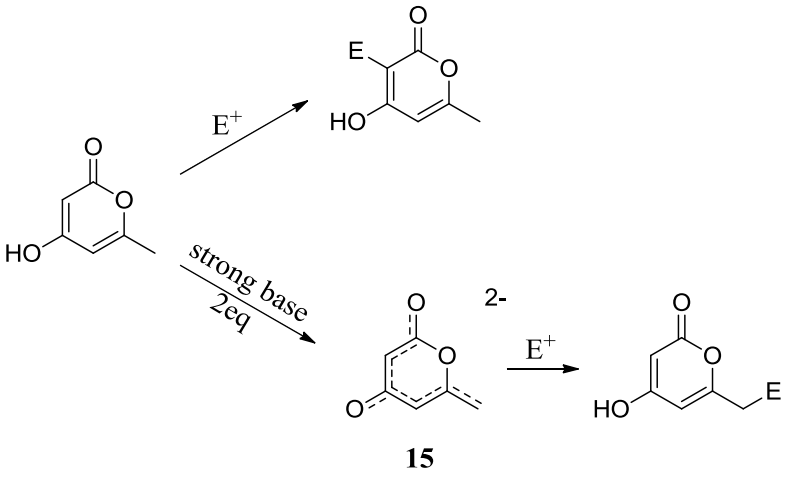
Pyrone **1**, reacts with broad range of electrophiles at C-3 position of the molecule. This is an undesired product since C-7 activation is required to form kavalatones. C-7 activation can occur either by deprotonation or enolization and provides a convenient route to obtain C-7 derivatives.[29]

Deprotonation of C-7 (pKa ~ 9.00) is not readily achieved by basic reagents as the hydroxyl group at C-4 position is more acidic (pKa 5.00),[30] and the anion formed by 4-OH deprotonation does not undergo further deprotonations. The acid-catalyzed enolization of **1** is prevented by the stability of the pyrylium ion formed as shown in Scheme 13.



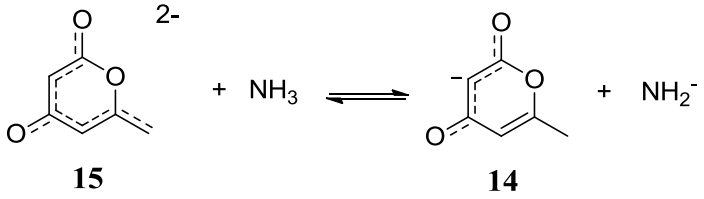
Scheme 13. Enolization and ionization in acidic and basic media.[29]

It has been shown that the C-3 position of **1** is preferred site for attack by electrophiles. Bu'Lock and co-workers have reported a method to overcome this problem by converting **1** to its methyl ether **13**. This method reduces the reactivity of the C-3 position toward electrophiles, where the enolate **14** cannot participate in condensation. Wachter and co-workers have reported that the dianion of **1** would predominantly undergo condensation at C-7 as illustrated in Scheme 14.[29]



Scheme 14. Addition of electrophile (E+) to the anion.[26]

In this report, the dianion was generated in the presence of liquid ammonia, and showed that there exists an equilibrium between monoanion **14** and dianion **15**. This equilibrium was driven towards the monoanion **14** by solubility factors during evaporation of ammonia as shown in Scheme 15.[29]



Scheme 15. Equilibrium between mono- and dianions.[29]

Carpenter and co-workers described the use of LDA and n-butyllithium for the deprotonation of TAL-OMe **13**. The condensation reaction at C-7 is initiated by the deprotonation of TAL-OMe and formation of the carbanion at C-7. The resulting negative charge is delocalized throughout the carbonyl group and π-system of the ring. Studies with strong bases show that kinetically favored deprotonation occurs at C-3, one of the sp^2 carbons of the ring rather than C-7 deprotonation as depicted in Figure 6.

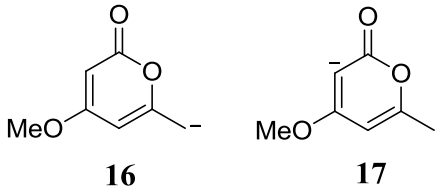
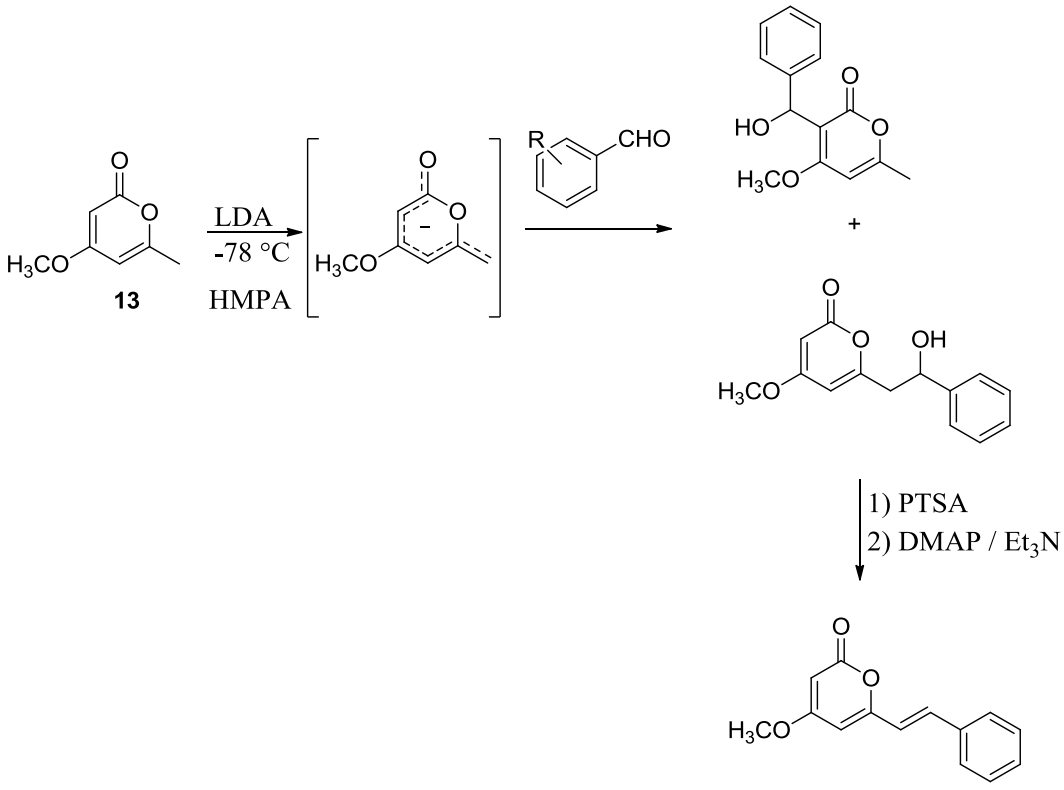


Figure 6. TAL-OMe anions.

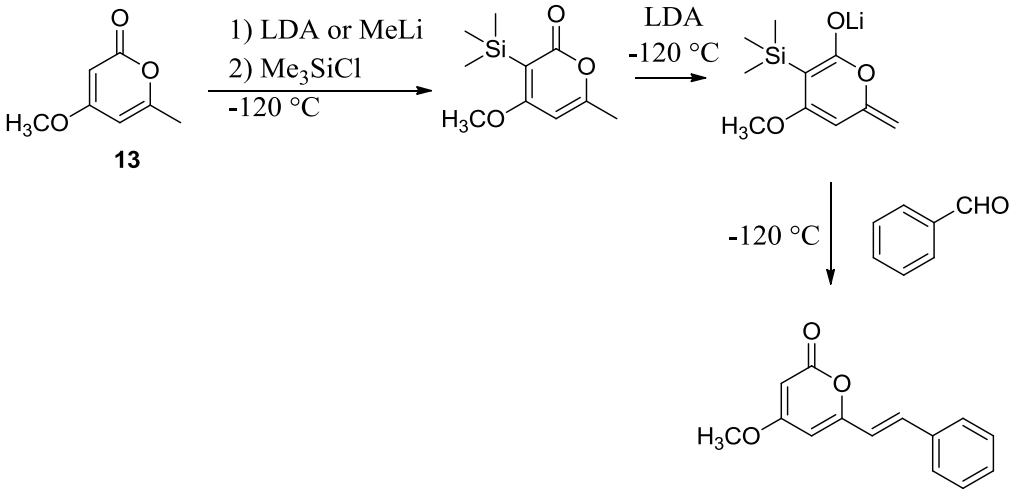
This deprotonation occurs rapidly when *n*-butyllithium (*n*-BuLi) was used.[31] The anion **17** tends to show moderate stability at -78 °C and can be generated with either *n*-BuLi or LDA. The kinetically controlled lithiation occurs at C-3, while the thermodynamically controlled metalation occurs at C-7.[26]

Although the aldol condensation of the methyl ether of TAL and aromatic aldehydes occurs at C-7 in the presence of magnesium methoxide, this method tends produce the condensation product in low yields.[23] The use of LDA or *n*-BuLi as the base generates the undesired product of condensation at C-3.[26] Lyga showed that with the addition of 1 equivalent of hexamethylphosphoramide (HMPA) to the reaction formed a 1:1 ratio of C-7 and C-3 condensation products as illustrated in Scheme 15. An increased ratio of HMPA did not change the ratio of C-3/ C-7 products.



Scheme 15. Aldol reaction in the presence of HMPA.

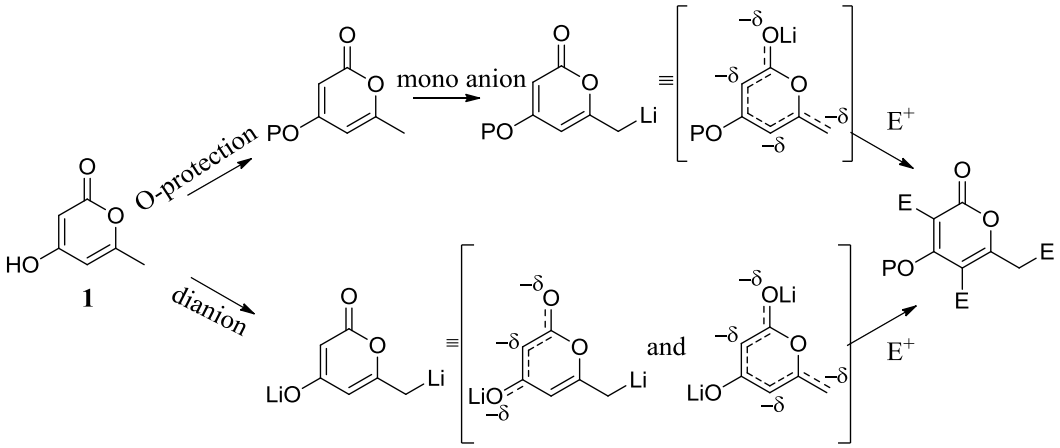
The C-7 aldol product was subjected to *p*-toluenesulfonic acid (PTSA), DMAP and triethylamine (Et_3N) to generate the C-7 elimination product.[32] Further studies have been carried out in order to obtain the C-7 elimination product. Carpenter and co-workers have reported the use of LDA or *n*-BuLi as the base to form C-3 anion at -78 °C. The C-3 anion was allowed to react with trimethylsilyl chloride (TMSCl) at -78 °C to produce the trimethylsilylpyrone.[31] Younis and co-workers carried out the same TMSCl reaction at -120 °C as shown in Scheme 16. The C-3 anion was generated in high yield in the presence of methyllithium. The silylpyrone hinders the ring deprotonation and facilitates the deprotonation at C-7. The TMS protecting group was easily removed following condensation and they were able to generate desmethoxyyangonin kavalactone in moderate yield of 50%.[33]



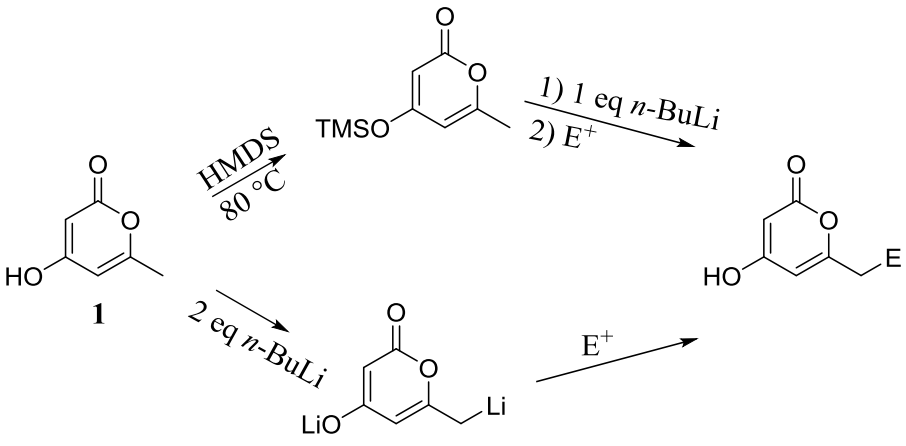
Scheme 16. Synthesis of desmethoxyyangonin kavalactone in the presence of TMSCl.[33]

Zhang and co-workers reported a method of electrophilic substitution to functionalize C-7 of TAL. This involved a temporary monoprotection of C4-OH group

followed by a dianion formation. In this approach, the C4-OH group was capped with a trimethylsilyl group using hexamethyldisilazane (HMDS) and was subsequently deprotonated at C-7 using *n*-BuLi at -78 °C in a one pot/two operation manner. Addition of the electrophile afforded the desired product in moderate yield. The approach toward the target molecule is represented in Scheme 17 and 18. The dianion one-pot/one-operation generated the product in better yield.[34]



Scheme 17. Mono anion and dianion protocol.[34]



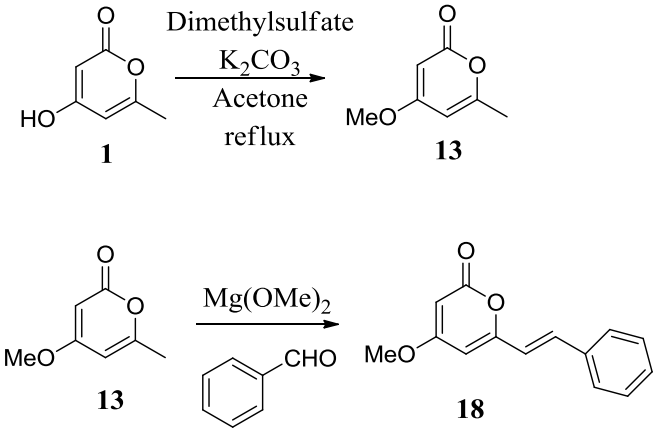
Scheme 18. C-7 electrophilic substitution[34]

Dianion formation in TAL was further investigated by our group using a polar solvent system. In this method, tetrahydrofuran (THF), HMPA and N, N, N', N'-tetramethylethylenediamine (TMEDA) were used as the solvents for better solubility. Exactly 2.4 equivalents of *n*-BuLi were used and the reaction was performed at 0 °C to generated the desired products in moderate yields.[35]

2.2. Results and Discussion

In our studies to understand the chemistry of this molecule and to obtain a broad range of important compounds, we targeted high value added specialty molecules derived from **1**. Kavalactone is one of these specialty molecules.

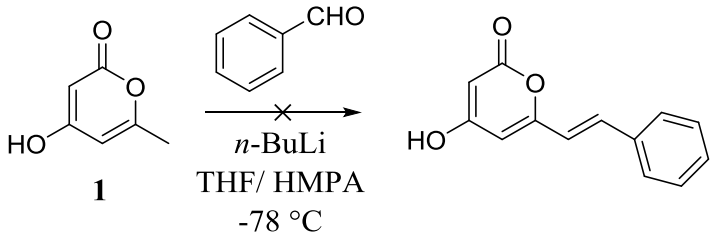
Our first approach to synthesis kavalactone was to use TAL-OMe, **13** in the presence of magnesium methoxide, following the method reported by Bu'Lock.[19] TAL-OMe **13**, was prepared using TAL **1** and dimethylsulfate and compound **13** was produced in 89% yield.[36] A suspension of magnesium methoxide was prepared according to the literature by refluxing magnesium metal in methanol, excess base was used to obtain the aldol product.[37] However, the maximum yield obtained for the aldol condensation product **18** was only 29% when benzaldehyde was used as the aldehyde.



Scheme 19. Aldol condensation to generate kavalactone.

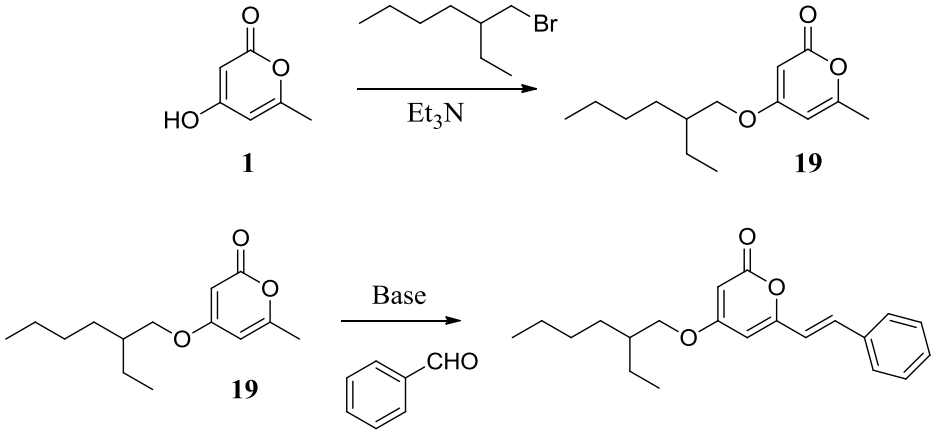
Evaluation of the co-products showed that a Meerwein–Pondorf–Verley reduction of benzaldehyde to benzyl alcohol was a significant side reaction. However, even in the presence of three equivalents of benzaldehyde, there was no significant improvement in the yield.

The dianion of **1** was formed in the presence of *n*-BuLi at -78 °C, but as shown in Scheme 20,[34] no product formed during this reaction. The use of HMPA as the reaction solvent and performing the reaction at -20 °C also, failed to generate the desired product.



Scheme 20. Aldol condensation using *n*-BuLi as the base.

We hypothesized that a bulky protecting group at the C4-OH would sterically hinder the C-3 hydrogen and, we used *tert*-butyldimethylsilyl chloride (TBSCl) to evaluate this hypothesis. Although the analysis of the crude reaction mixture by NMR spectroscopy revealed traces of the desired compound, we were unable to purify the product by column chromatography. Instead, we used 2-ethylhexylbromide to protect the hydroxyl group at C-4. The reaction, illustrated in Scheme 21, proceeded smoothly to yield product **19** in 40% yield.[38]



Scheme 21. Aldol reaction with a protected pyrone **19.**

As described in Table 1, entry 1, protected pyrone **19** was subjected to aldol condensation using one equivalent of LDA as the base, but no significant reaction observed. Using a mixture of HMPA and THF was used as the reaction solvent, we again observed no significant conversion of the starting material, as shown in Table 1, entry 2.[39] However, when potassium *tert*-butoxide (*t*-BuOK) was employed as the base and the *tert*-butanol was used as the reaction solvent, the aldol product was produced in 44% yield, as shown in Table 1, entry 3.

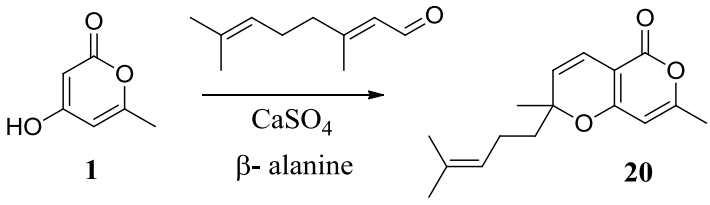
Table 1. Reaction conditions for pyrone **19**.

Entry	Aldehyde	Base	Solvent	Yield (%)
1	Benzaldehyde **35**	LDA	THF	NR
2	**35**	LDA	THF / HMPA	NR
3	**35**	*t*-BuOK	*t*-BuOH	44
4	**35**	*t*-BuOLi	*t*-BuOH	NR
5	Benzyl vailin	*t*-BuOK	*t*-BuOH	√
6	Piperonal **40**	*t*-BuOK	*t*-BuOH	14

NR: No Reaction; √: positive reaction

In an attempt to improve the product yield we used lithium *tert*-butoxide as the base, but there was no new spot on the TLC plate. Using a different aldehyde, benzyl vanillin, we performed the reaction with *t*-BuOK and observed a faint new spot in the TLC plate. Piperonal was used as the aldehyde and the aldol product was obtained in low yield of 14%.

Citral was used to protect the C-3 and C4-OH as shown in Scheme 22, forming compound **20** in 83% yield.[40] We then subjected compound **20** to aldol reaction conditions using LDA as the base, but again observed no reaction.

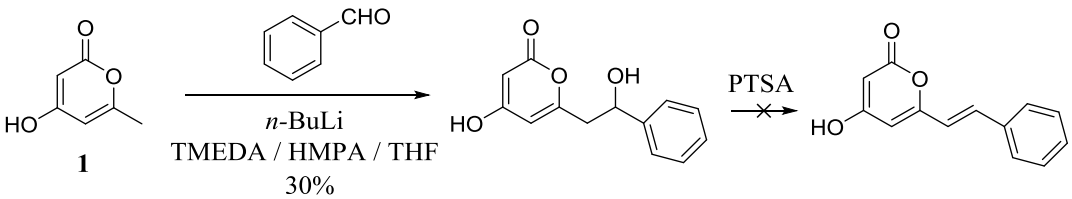


1 **20**

Scheme 22. Protecting TAL with citral.

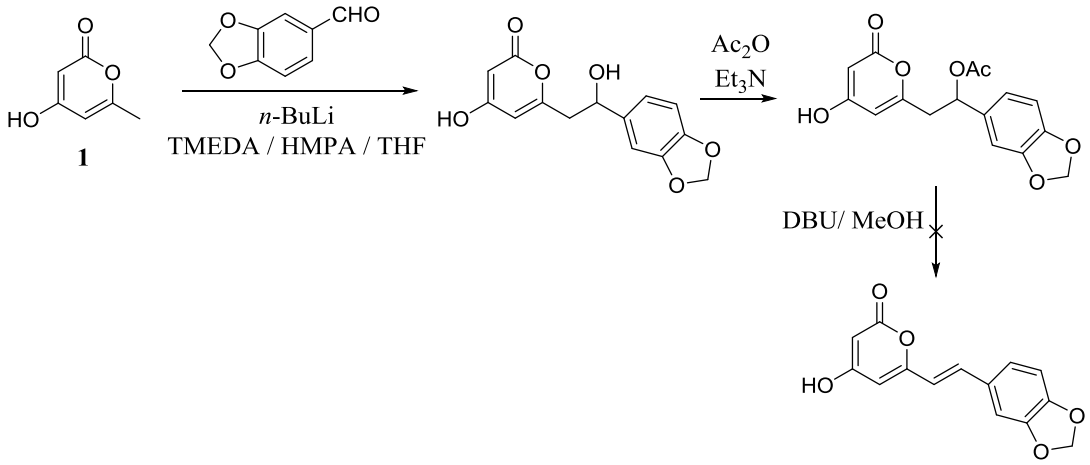
Another non-nucleophilic base, Lithium tetramethylpiperidide (LiTMP) was used to perform the aldol reaction with compound **20** and benzaldehyde. Here also we did not encounter the desired product. We evaluated iodomethane as the electrophile, but the reaction failed to yield product once again. The reaction gave negative results even in the presence of *t*-BuOK as base.

Then we used **1** as the starting material to perform the dianion reaction reported by our group using *n*-BuLi as the base in THF.[35] Benzyl bromide was used as the electrophile and the reaction generated the product in 14% yield. Compound **1** showed poor solubility in THF, therefore we used a TMEDA/ HMPA/ THF solvent system to carry out mono-anion method reported by Zhang and co-workers and the product was formed in 27%. We then performed the mono-anion method using benzaldehyde as the electrophile to form the aldol product in 30% yield as depicted in Scheme 23. In order to drive the elimination reaction, *p*-toluenesulfonic acid (PTSA) was used, but no elimination product was observed. Increasing the amount of PTSA from 1 to 5 equivalents did not produce the elimination product. We protected the OH as an acetyloxy functionality to form, a better leaving group and facilitate the elimination reaction, but again no elimination product was observed.



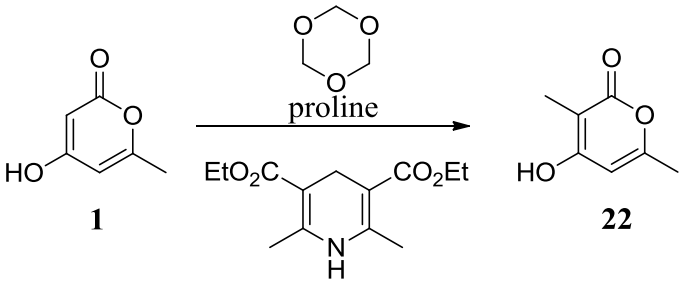
Scheme 23. Dianion strategy for aldol reaction.

We performed a one-pot method using piperonal as the electrophile. Protection of the OH group and generated the aldol product in 21% yield. As illustrated in Scheme 24, OH group was first acetylated and the elimination was performed in the presence of triethylamine (Et_3N) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[41]



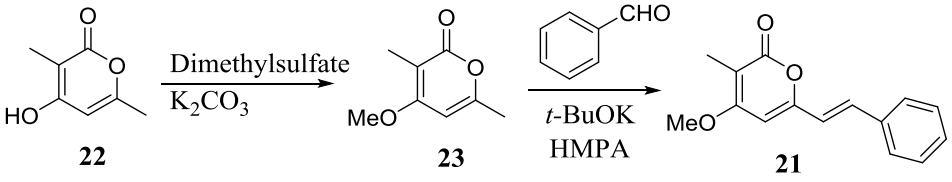
Scheme 24. Aldol condensation with piperonal as the electrophile.

With the idea of modifying the aldol reaction at C-7 of the molecule, we changed our objective to penstyrylpyrone (**21**). This molecule can be achieved from a compound similar to **1**, but contains an extra methyl group at C-3 as shown in Scheme 25.[9] This TAL analog, 4-hydroxy-3,6-dimethyl-2-pyrone (HDP) **22**, can be obtained from **1** by a method developed in our lab using 1,3,5-trioxane and proline in catalytic amount.[35]



Scheme 25. HDP **22** from TAL **1.**

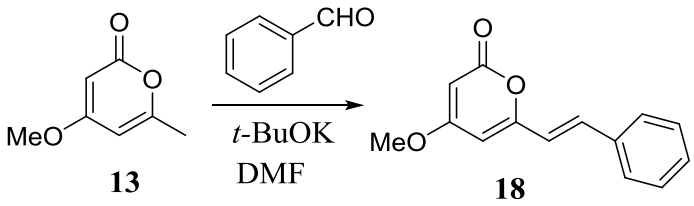
The hydroxyl group of HDP was protected using dimethylsulfate to form the methyl ether HDP-OMe **23** in 89% yield.[42] Aldol reactions were performed with **23** using benzaldehyde, but no positive results were obtained when LDA or LiTMP were used as base. Even the dianion method gave negative results using **22**. As shown in Scheme 26, we performed the aldol reaction in a polar aprotic solvent HMPA with **23** at room temperature using *t*-BuOK solid as the base and this method gave positive results. Analysis of the crude reaction mixture by proton NMR spectroscopy showed *J* coupling values of 16Hz indicating the presence of the *trans*-olefinic hydrogens, which supports formation of the trans-aldol product **21.**



Scheme 26. Aldol condensation with **23.**

We carried out the similar reaction conditions for **13** and were able to get the aldol product **18**. HMPA is known to be a carcinogenic solvent, so we evaluated an

alternative polar aprotic solvent, *N*,*N*-dimethylformamide (DMF). This reaction was carried out using **13** and benzaldehyde with *t*-BuOK as the base at room temperature, and the aldol product was produced in 43% yield as represented in Scheme 27. When 3,4-dimethoxybenzaldehyde was used, it generated the corresponding product **27** in 46% yield.



Scheme 27. Aldol condensation with **13.**

Then we investigated this reaction in the presence of different bases using DMF as the solvent and benzaldehyde as the electrophile. The reaction was carried out using DBU as a base at room temperature and at 70 °C, but did not generate any of the desired products. Phosphazene P_4-*t*Bu, is a strong non-nucleophilic base which was evaluated for the aldol reaction at 70 °C, but again the reaction failed to proceed. Using potassium carbonate as a moderately strong base, the reaction was carried out at room temperature. This reaction did not afford us the product at room temperature, but when heated to 70 °C for 2 days, it gave a positive result.

Table 2. Reaction optimizing conditions for the aldol condensation.[a]

Entry	Pyrone 13 equiv.	*t*-BuOK equiv.	Benzaldehyde equiv.	Temperature / °C	Time / hour	Yield (%)[c]
1	1.0	1.5	1.2	25	12	43
2	1.0	1.5	1.2	0	1	31
3	1.0	2.0	1.2	25	12	10
4	1.0	1.5	1.5	25	48	30
5	1.0	2.0	2.0	70	72	20
6	1.0	3.0	2.0	25	12	27
7	1.0	2.0	2.0	25	12	41
8	1.0	2.0	2.0	25	48	53
9	1.0[b]	2.0	2.0	25	12	56
10	1.0[b]	2.0	2.0	0	12	NR
11	1.0[b]	2.0	2.0	25	48	84

[a]Reactions were carried out with 0.5 mmoL of pyrone. [b]HDP-OMe **23** was used as the pyrone instead of **13**. [c]Isolated yield.

Despite the positive result, we were interested in running this reaction at room temperature so, we returned to using *t*-BuOK in THF solution for the aldol reaction. The reaction was carried out overnight at room temperature and produced the product in 30% yield. We saw a decrease in the yield when *t*-BuOK solution was used, compared to the solid *t*-BuOK. This result indicated that the concentration affects the yield of the aldol reaction. Using solid *t*-BuOK as the base for the aldol reaction, we optimized the reaction conditions and the results of these studies are presented in Table 2.

We optimized the reaction using compound **13** as the pyrone, benzaldehyde as the electrophile, solid *t*-BuOK as the base and DMF as the solvent. The equivalents of each reagent, the reaction temperatures and the reaction times were varied. As the concentration affects the yield of the product, we dissolved the pyrone in minimum amount of DMF.

Table 1, entry 8 showed the maximum yield of 53% for **13** as the pyrone. Here, pyrone **13**: *t*-BuOK: benzaldehyde were used in a ratio of 1: 2: 2 equivalents at room temperature for 48 hours. Decreasing temperature to 0 °C, decreased the yield of the product as presented in Table 2; entry 2. Increasing the temperature to 70 °C and the reaction time for more than 48 hours reduced the yield as shown in Table 2; entry 5.

According to Table 2, entry 7, when the reaction time was less than 48 hours the product yield decreases. When the reaction mixture was charged with 3 equivalents of base, a lower yield of the desired product was observed as presented in Table 2, entry 6. When the equivalents of the electrophile were decreased to 1.2, the yield of the product was also decreased as in Table 2, entry 3. When the pyrone was changed to **23**, as shown in Table 2, entry 11, we observed a significant increase in the product yield (84%) as there was no possibility of forming the anion at C-3 position. Here again the best result for **23** was obtained when the ratio of **23**: *t*-BuOK: benzaldehyde was 1: 2: 2 equivalents at room temperature for 48 hours.

With the optimized reaction conditions in hand, we carried out the aldol reactions using different aldehydes to obtain a series kavalactones. Adducts derived from **23** gave higher yields, as represented in Table 2, entry 2 and 10, due to the absence of acidic hydrogen at C-3.

Table 3. Aldol condensation with varying aldehydes.

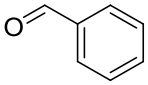
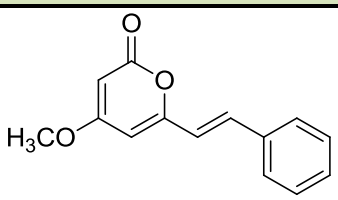
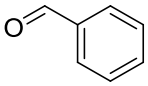
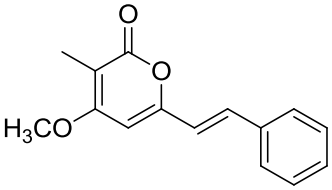
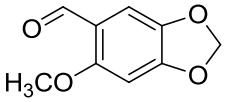
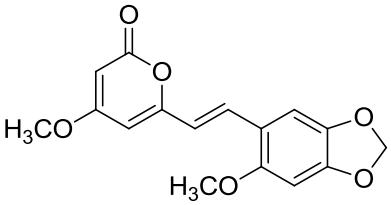
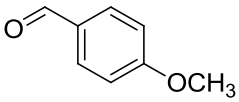
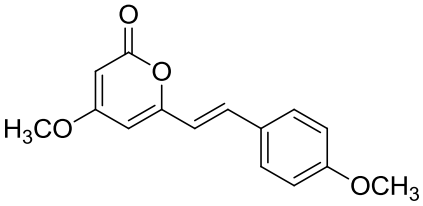
Entry	Pyrone	Aldehyde	Product	Yield (%)
1	**13**	 **35**	 **18**	53
2	**23**	 **35**	 **21**	84
3	**13**	 **36**	 **24**	61
4	**13**	 **37**	 **25**	61

Table 2 (continued)

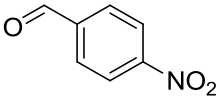
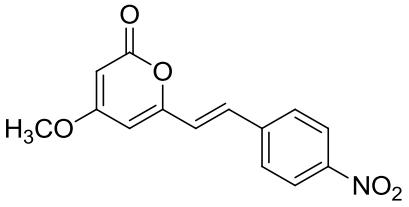
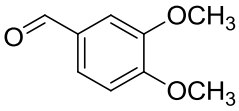
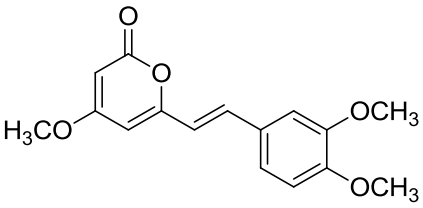
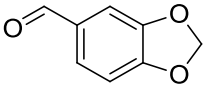
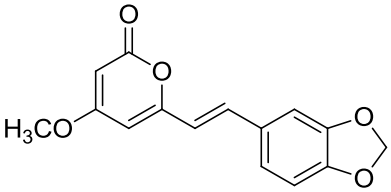
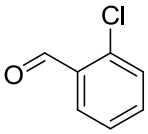
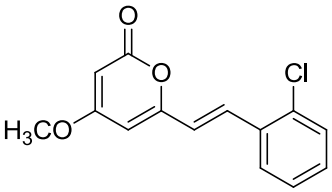
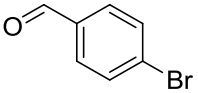
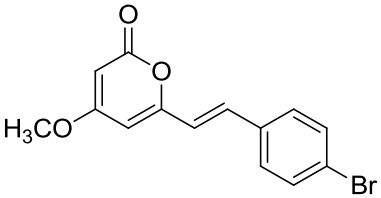
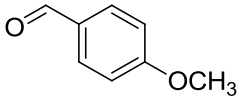
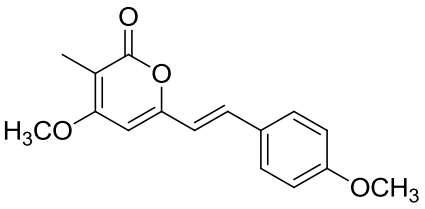
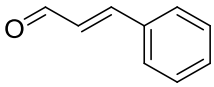
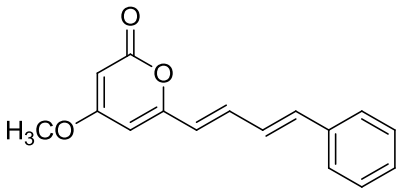
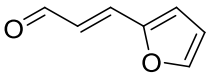
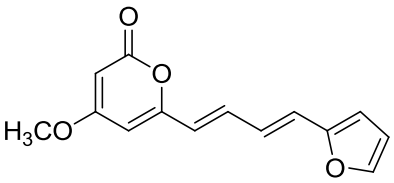
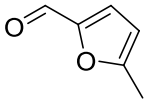
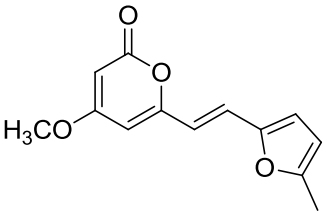
5	**13**	 **38**	 **26**	33
6	**13**	 **39**	 **27**	27
7	**13**	 **40**	 **28**	32
8	**13**	 **41**	 **29**	30
9	**13**	 **42**	 **30**	27

Table 2 (continued)

10	**23**	 **37**	 **31**	63
11	**13**	 **43**	 **32**	39
12	**13**	 **44**	 **33**	7
13	**13**	 **45**	 **34**	23

Functional groups such as ethers, alkenes and acetals were compatible with the reaction conditions. The yield was higher when an electron-donating group was present in the benzene ring as shown in Table 3, entries 3 and 4. The yield of the aldol condensation product was also lower with the presence of a deactivating group as a

substituent as shown in Table 3, entries 5, 8 and 9. We were able to synthesis **21** in 84% yield and this is the first reported synthesis of Penstyrylpyrone **21**. We were also able to obtain the known products in higher yields that what had been previously reported.

2.3. Conclusion

In this chapter we have discussed our second approach to the diversification of TAL. Kavalactones are a group of biologically active high value added specialty compounds. Various strategies have been reported in the literature to make these molecules. However, we have developed an improved protocol for the aldol reaction to generate kavalactones.

Rather than using harsh reaction conditions with high temperatures and expensive catalysts, we modified our reaction to use a convenient base: solid potassium *tert*-butoxide. Solid base was easy to handle during the experiments and can be conveniently measured. We introduced a polar aprotic solvent DMF for the aldol reactions, which is distinct from typical reaction conditions using THF as the solvent. The reaction was carried out at ambient temperature rather than reflux conditions or low temperatures, in which carefully temperature monitoring may be required. The reaction time was extended to 48 hours to reach completion, but these conditions generate the desired products in improved yields relative to literature reports. In addition, this reaction can be conducted in gram scale.

Using the optimized reaction conditions; we were able to report the first total synthesis for Penstyrylpyrone **21** with an excellent yield. We developed the first total synthesis for compound **24** in moderate yield (61%). Lastly, our improved reaction conditions generated desmethoxyyangonin **18** and yangonin **25** in the best yields reported to date.

In this chapter we were able to devise an improved aldol protocol to prepare 6-styrenylpyrones. The optimized reaction conditions afforded the products good yields. This is an operationally convenient method and demonstrates good compatibility with a variety of functional groups.

2.4. Experimental

All starting materials were purchased from Sigma-Aldrich and TCI America; solvents were purchased from Fisher Scientific and used without further purification. All reactions were carried out in flame-dried glassware under argon with dry solvents under anhydrous conditions. All yields refer to isolated products either by column chromatography or by recrystallization. Thin-layer chromatography (TLC) was performed using commercially available 250 micron silica gel plates (Analtech) and preparative thin-layer chromatography was performed using commercially available 1000 micron silica get plates (Analtech). Visualization of TLC plates was effected with short wavelength ultraviolet light (254 nm). Silica gel 60Å, particle size 0.032– 0.063 mm, was used for flash column chromatography. ^{1}H NMR spectra were acquired in $CDCl_3$ on a

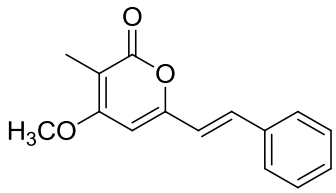
Varian VXR 300 MHz spectrometer. ^{1}H chemical shifts (δ) are given in ppm relative to the residual protonated chloroform peak ($CDCl_3$: δ_H = 7.26 ppm) as an internal reference. High-resolution mass spectra (HRMS) were recorded on an Agilent 6540 QTOF (quadrupole time of flight) mass spectrometer using ESI (electrospray ionization) or APCI (atmospheric-pressure chemical ionization) or EI (electron ionization) on an Agilent 6890 GC/MS. Melting points were analyzed on a Mel-Temp II capillary melting point apparatus.

Selected Experimental, Physical, and Spectral Data

General Aldol Procedure:

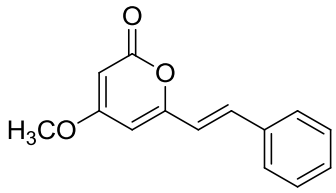
To a stirred solution of 4-methoxy-6-methyl-2-pyrone (0.067g, 0.47mmol) in DMF (1 mL) at room temperature was added benzaldehyde (0.1 mL, 0.95 mmol). Potassium *tert*-butoxide solid (0.1 g, 0.95 mmol) was then added portion wise to it and stirred for 2 days at room temperature. The solution became dark red in color. This was extracted with diethyl ether (3 x 10 mL). For the compounds **24, 25, 26, 27, 32** methylene chloride was used for the extraction. The organic layer was washed with brine (3 x 20 mL), water (5 x 20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography (EtOAc/hexanes) to afford the product.

(*E*)-4-methoxy-3-methyl-6-styryl-2H-pyran-2-one (Penstyrylpyrone) (2**1)**



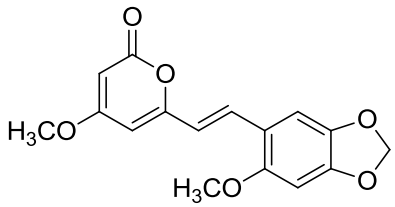
Bright yellow solid (84% yield): mp 197-199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, 2H), 7.49 (d, J = 16 Hz, 1H), 7.40 (d, 2H), 7.35(t, 1H), 6.65 (d, J = 16Hz, 1H), 6.17 (s, 1H), 3.91 (s, 3H), 1.97 (s, 3H) ppm. HRMS (ESI-QTOF) calcd for $C_{15}H_{15}O_3$ $[M+H]^+$ 243.0943, found 243.1016. . ^{13}C NMR data agreed with the literature.[9]

(*E*)-4-methoxy-6-styryl-2H-pyran-2-one (Desmethoxyyangonin) (18)



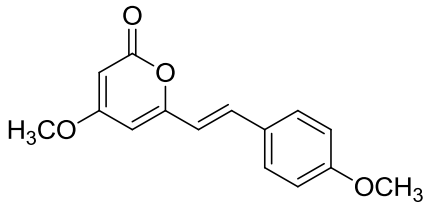
Yellow solid (53% yield): mp 131-133 °C (Lit[27] 134 – 136 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, 2H), 7.48(d, J = 16Hz, 1H), 7.37 (d, 2H), 7.35 (t, 1H), 6.60 (d, J = 16Hz, 1H), 5.94 (d, 1H), 5.50 (d, 1H) 3.82 (s, 3H) ppm. HRMS (ESI-QTOF) calcd for $C_{14}H_{13}O_3$ $[M+H]^+$ 229.0859, found 229.0861. ^{13}C NMR data agreed with the literature.[27]

(*E*)-4-methoxy-6-(2-(6-methoxybenzo[1,3]dioxol-5-yl)vinyl)-2H-pyran-2-one (24)



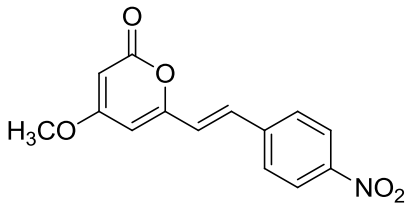
Brown solid (61% yield): mp 187-189 °C (Lit[7] 189 – 191°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 16Hz, 1H), 6.96(s, 1H), 6.52 (s, 1H), 6.47(d, J = 16Hz, 1H), 5.94 (s, 2H), 5.91 (d, 1H), 5.45 (d, 1H) 3.84 (s, 3H), 3.82 (s, 3H) ppm. HRMS (ESI-QTOF) calcd for $C_{16}H_{15}O_6$ $[M+H]^+$ 303.0863, found 303.0867. ^{13}C NMR data agreed with the literature.[7]

(*E*)-4-methoxy-6-(4-methoxystyryl)-2H-pyran-2-one (Yangonin) (25)



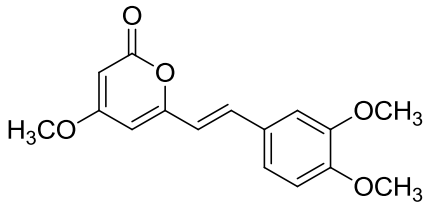
Yellow solid (61% yield): mp 146-148 °C (Lit[27] 148 – 150 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 2H), 7.46(d, J = 16Hz, 1H), 6.91 (d, 2H), 6.46 (d, J = 16 Hz, 1H), 5.88 (d, 1H), 5.46 (d, 1H) 3.89 (s, 3H) ppm. HRMS (ESI-QTOF) calcd for $C_{15}H_{15}O_4$ $[M+H]^+$ 259.0892, found 259.0965. ^{13}C NMR data agreed with the literature.[27]

(*E*)-4-methoxy-6-(4-nitrostyryl)-2H-pyran-2-one (26)



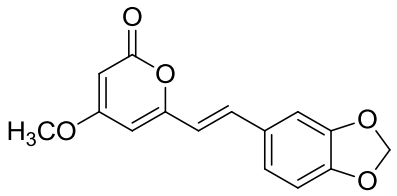
Yellow solid (33% yield): mp 209-211 °C (Lit[10] 211.5 – 214 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, 2H), 7.62 (d, 2H), 7.57 (d, J = 16Hz, 1H), 6.73 (d, J = 16 Hz, 1H), 6.04 (d, 1H), 5.54 (d, 1H), 3.85 (s, 3H) ppm. HRMS (ESI-QTOF) calcd for $C_{14}H_{12}NO_5$ $[M+H]^+$ 274.0637, found 274.0714. ^{13}C NMR data agreed with the literature.[4]

(*E*)-6-(3,4-dimethoxystyryl)-4-methoxy-2H-pyran-2-one (27)



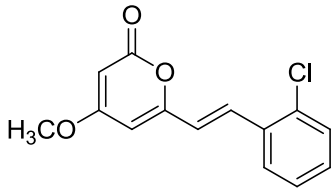
Orange solid (46% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 16Hz ,1H), 7.06 (d, 1H), 7.02 (s, 1H), 6.86(d, 1H), 6.45 (d, J = 16Hz, 1H), 5.91 (d, 1H), 5.47 (d, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H) ppm.

(*E*)-6-(2-(benzo[1,3]dioxol-5-yl)vinyl)-4-methoxy-2H-pyran-2-one (28)



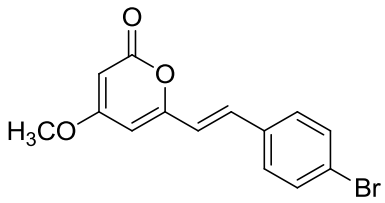
Orange solid (32% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 16Hz ,1H), 7.01 (s, 1H), 6.98 (d, 1H), 6.81(d, 1H), 6.40 (d, J = 16Hz, 1H), 6.00 (s, 2H), 5.90 (d, 1H), 5.48 (d, 1H), 3.82 (s, 3H) ppm.

(*E*)-6-(2-chlorostyryl)-4-methoxy-2H-pyran-2-one (29)



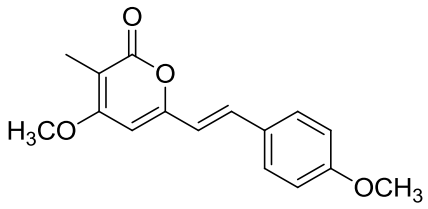
Yellow solid (30% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 16Hz, 1H), 7.57 (d, 1H), 7.47 (d, 1H), 7.33-7.20 (m, 2H), 6.59 (d, J = 16Hz, 1H), 6.00 (d, 1H), 5.53 (d, 1H), 3.84 (s, 3H) ppm.

(*E*)-6-(4-bromostyryl)-4-methoxy-2H-pyran-2-one (30)



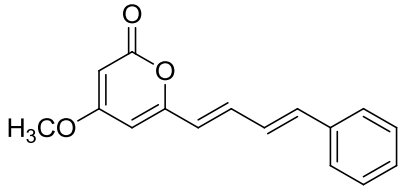
Yellow solid (27% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, 2H), 7.48 (d, J = 16Hz, 1H), 7.36 (d, 2H), 6.56 (d, J = 16Hz, 1H), 5.95 (d, 1H), 5.50 (d, 1H), 3.82 (s, 3H) ppm.

(*E*)-4-methoxy-6-(4-methoxystyryl)-3-methyl-2H-pyran-2-one (31)



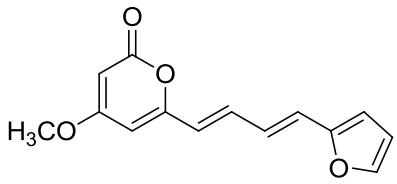
Yellow solid (63% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J = 16Hz, 1H), 7.43 (d, 2H), 6.89 (d, 2H), 6.47 (d, J = 16Hz, 1H), 6.10 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 1.95 (s, 3H) ppm.

4-methoxy-6-((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)-2H-pyran-2-one (32)



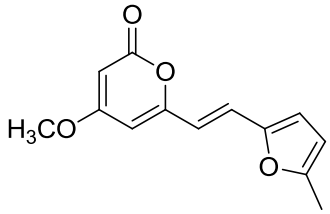
Brownish orange solid (39% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, 2H), 7.41-7.23 (m, 3H), 6.96-6.76 (m, 3H), 6.16 (d, J = 16Hz, 1H), 5.87 (d, 1H), 5.48 (d, 1H), 3.82 (s, 3H) ppm.

6-((1*E*, 3*E*)-4-(furan-2-yl)buta-1,3-dien-1-yl)-4-methoxy-2H-pyran-2-one (33)



Reddish brown solid (7% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, 1H), 6.77 (dd, J = 16Hz, 1H) 6.42-6.44 (m, 3H), 6.13(d, J = 16Hz, 1H) 5.88 (d, J = 16Hz, 1H), 5.86 (d, 1H), 5.46 (d, 1H), 3.82 (s, 3H) ppm.

(*E*)-4-methoxy-6-(2-(5-methylfuran-2-yl)vinyl)-2H-pyran-2-one (34)



Reddish brown solid (23% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 16Hz, 1H) 6.43 (d, J = 16Hz, 1H), 6.40 (d, 1H), 6.06 (d, 1H), 5.87 (d, 1H), 5.45 (d, 1H), 3.82 (s, 3H), 2.33 (s, 3H) ppm.

2.5. References

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CHAPTER 3

TRIACETIC ACID LACTONE AS A COMMON INTERMEDIATE FOR THE SYNTHESIS OF 4-HYDROXY-2-PYRIDONES AND 4-AMINO-2-PYRONES[†]

3.1. Introduction

3.1.1. The 4-hydroxy-2-pyridones

The 4-hydroxy-2-pyridone structure is shown in Figure 1. These compounds are known to exert a range of biological effects ranging from analgesic, antifungal, antibacterial, antimalarial, antiinflamatory, anti-HIV, phytotoxic, antitumoral, antiviral and cytotoxic activity to the induction of neurite outgrowth.[1]

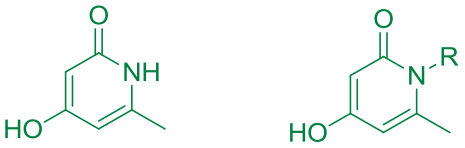
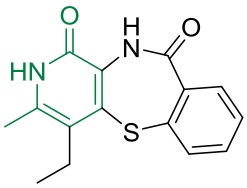


Figure 1. 4-hydroxy-2-pyridones.

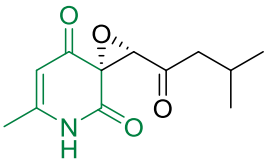
This class of compounds has attracted much attention in the scientific community due to their biological activities. These have resulted in unravelling the biosynthesis of some members which are formed by fungal polyketide synthases via tetramic acids. The 4-hydroxy-2-pyridone moieties have also been used in the synthesis of natural products. New compounds with intriguing architecture have been reported in the past few decades

[†] Adapted from Kraus, G. A.; Wanninayake, U. K.; Bottoms, J. *Tetrahedron Lett.* **2016**, *57*, 1293–1295 with permission from Elsevier.

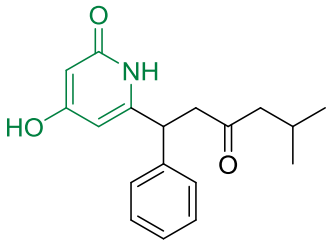
and different new synthetic approaches to synthesize these molecules have been developed. The 2-pyridinones have been used as versatile intermediates in the synthesis of a variety of nitrogen-containing heterocycles, such as pyridine, quinolizidine and inolizidine alkaloids.[1-2] These heterocycles have been used in drug synthesis as templates for novel human chymase inhibitors.[3-7] Fluridone and sapinopyridione are two of the pyridinone compounds with phytotoxic activity.[8] The pyridinone derived bis(pyridyl)methanes exhibit antitumor activity. Some of the structures and their biological activities are illustrated in Figure 2.



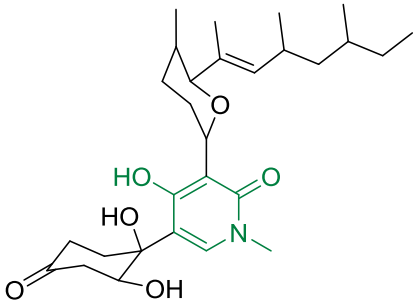
anti-HIV agent



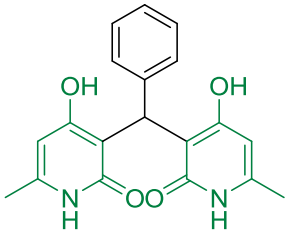
Flavipucine
Phytotoxic activity



Chymase inhibitor

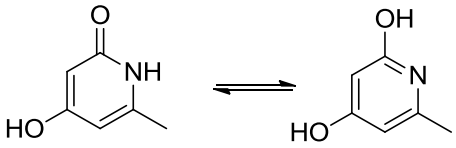


fungistatic activity against
Aspergillus fumigatus



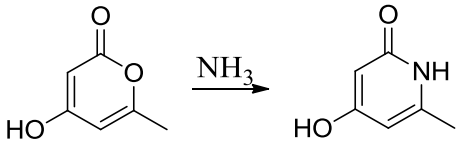
Phytotoxic activity

Figure 2. Biological activity of some 2-pyridones.

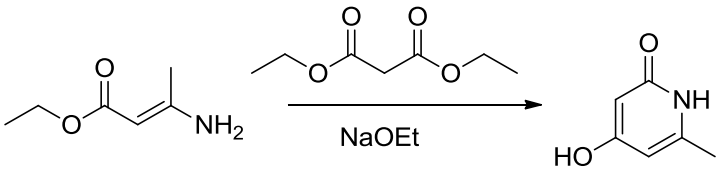


Scheme 1. Possible tautomer forms of 2-pyridone.

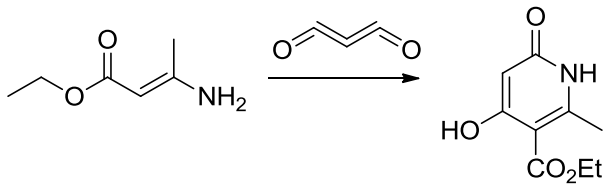
The most prominent feature in 2-pyridone is the amide group. There are two possible tautomers for 2-pyridones as shown in Scheme 1. Collie reported, as shown in Scheme 2, that the 4-hydroxy-6-methyl-2-pyridone can be synthesized from **1** with ammonia.[10] The same pyridone was synthesized by Knovenagel and Fries as represented in Scheme 3, using malonic ester and β-aminocrotonate in a condensation reaction followed by decarboxylation.[11]



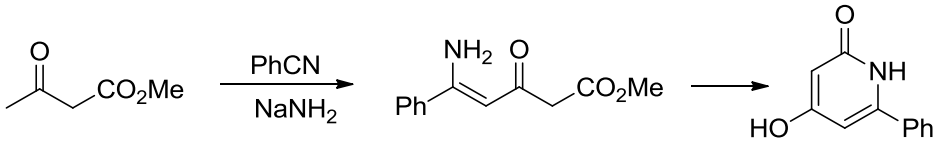
Scheme 2. 2-pyridone from TAL.[10]



Scheme 3. 2-pyridinones from β-aminocrotonate.[11]

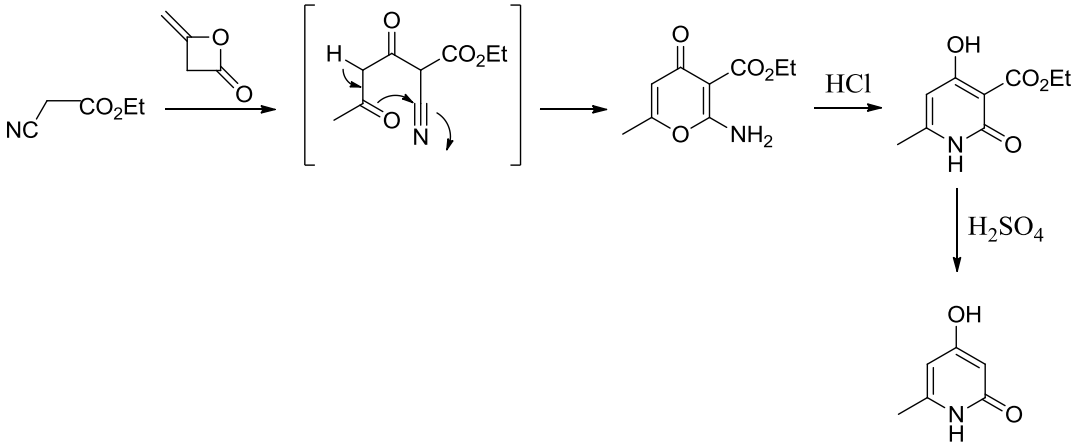


Scheme 4. 2-pyridones from functionalized enamines.[12]

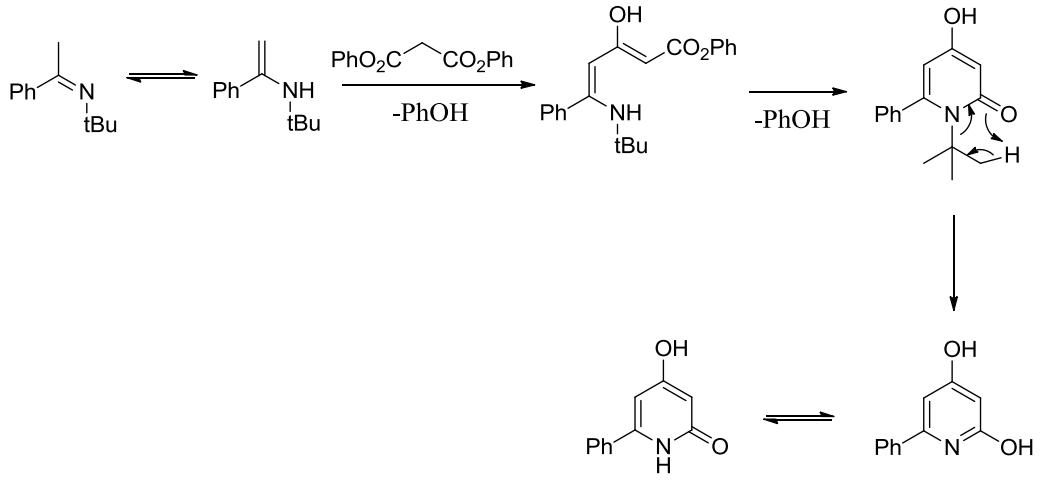


Scheme 5. 2-pyridones from condensation of methyl acetoacetate.[13]

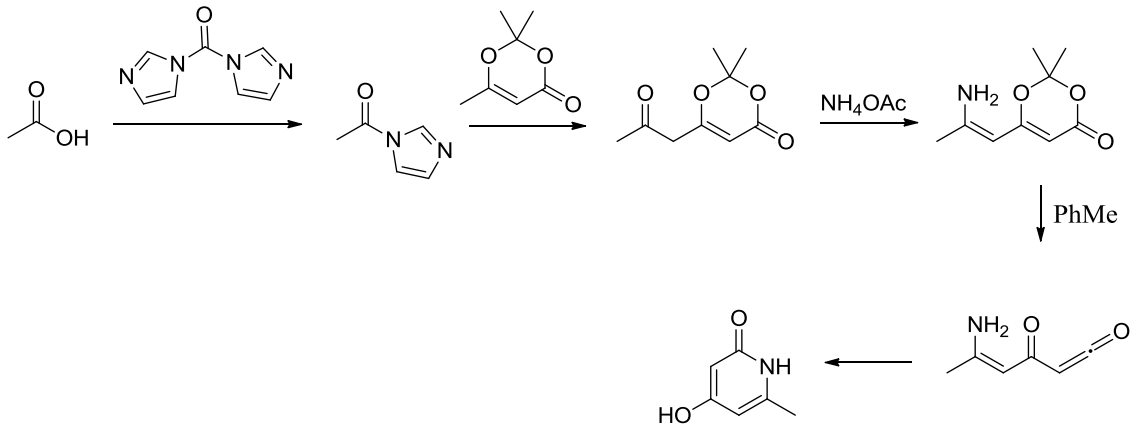
Ziegler and co-workers reported a reaction of functionalized enamines with carbon suboxide (C_3O_2) to give pyridones. This reaction is illustrated in Scheme 4.[12] As shown in Scheme 5, condensation of methyl acetoacetate with benzonitrile followed by cyclization afforded pyridone compounds. This reaction was reported by Huckin and co-workers.[13] Kato and co-workers carried out a reaction of diketene with ethyl cyanoacetate to give ethyl 2-amino-4-pyrones. The 2-amino-4-pyrone was then rearranged in to 2-pyridone in an acidic medium as detailed in Scheme 6.[14]



Scheme 6. Pyridones from the reaction of diketene with ethyl cyanoacetate.[14]

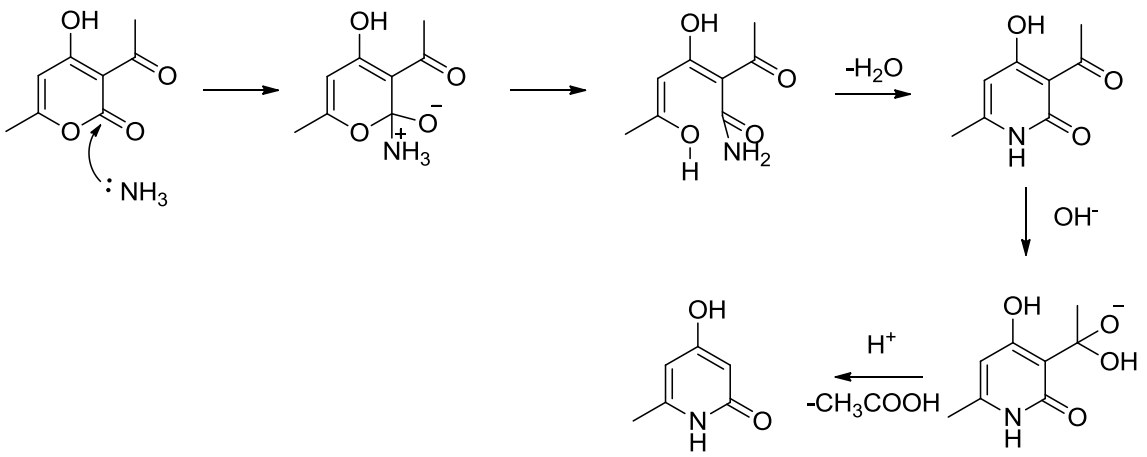


Scheme 7. Pyridones from the reaction of Schiff's bases with diphenyl malonate.[15]



Scheme 8. Pyridinones from enamine-keto-ketenes.

Ito and co-workers reported a reaction of Schiff's bases with diphenyl malonate and subsequent retro-ene reaction with elimination of 2-methylpropene to afford pyridine as shown in Scheme 7.[15] Patel and co-workers mentioned getting pyridones via cyclization of enamine-keto-ketenes as shown in Scheme 8.[16] Wang and co-workers reported the formation of 2-pyridones from dehydroacetic acid with 20% ammonia at 200 °C in low yields. The reaction mechanism for this reaction is depicted in Scheme 9.[17] Stoyanov and Ivanov came up with the use of microwave irradiation method to form pyridone compounds with primary amines starting from **1**.[22]



Scheme 9. Pyridones from dehydroacetic acid.

Few records have mentioned the synthesis of *N*-substituted pyridone compounds. Some examples for *N*-substituted pyridones are shown in Figure 3. These methods mainly involved heating primary amines in an aqueous solution.[18-21]

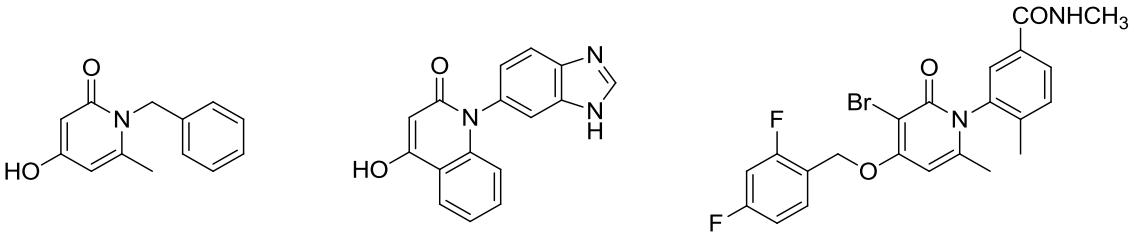
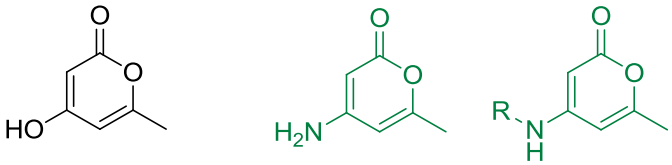


Figure 3. *N*-substituted pyridone compounds.

3.1.2. The 4-amino-2-pyrones

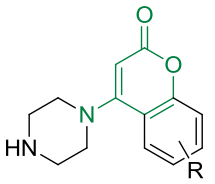
Another class of nitrogen containing pyrones is the 4-amino-2-pyrones. These are analogs of TAL. In the 4-amino-2-pyrone structure, the 4-OH group is replaced by an amine group as depicted in Figure 4. The 4-amino pyrone is a versatile chemical moiety found in a variety of biologically important molecules.



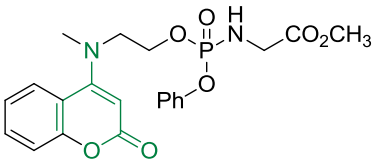
TAL 4-amino-2-pyrones

Figure 4. Structural difference between TAL and 4-amino-2-pyrones.

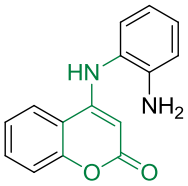
Some of the biological activities exhibited by these molecules are Chitin synthase inhibition activity, human platelet aggregation *in vitro* inhibitory property, antimicrobial activity *in vitro* and potent anti-tumor activity.[23-24] These amino pyrones are also used as a scaffold to synthesize different organic molecules which possess various chemical properties. In the synthesis of polyaromatic compounds which are potential optoelectronic conjugated materials, the amino pyrones play a role as starting materials.[25] Figure 5 depicts some of these molecules with their activities.



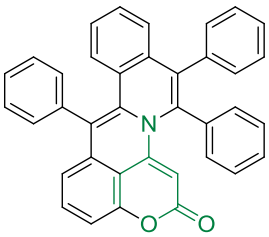
Platelet aggregation inhibitory activity



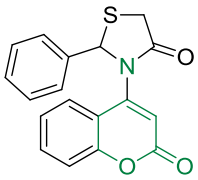
Chitin synthase inhibitory, anti-fungal activity



Anti-tumor activity



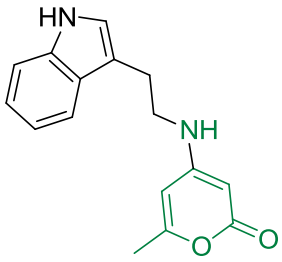
Optoelectronic conjugated material



Anti-tumor activity

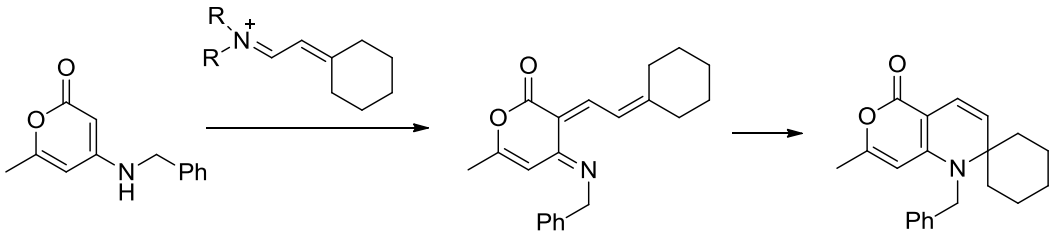
Figure 5. Molecules with a 4-amino-2-pyrone subunit.

Amino-2-pyrone is also a scaffold for the synthesis of Calanolide A, a compound with a potent HIV inhibitory activity as shown in Figure 6.[26] Other than the biological activities, 4-amino-2-pyrones are also used in the formation of azaztriene, which will undergo formal [3 + 3] cycloaddition to afford aza-spirocycles.[27-29] The formation of aza-spirocycles from amino pyrones is shown in Scheme 10.

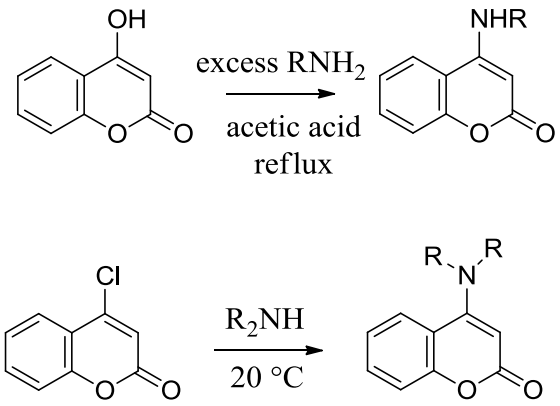


Anti-HIV activity

Figure 6. An amino pyrone with HIV inhibitory activity.



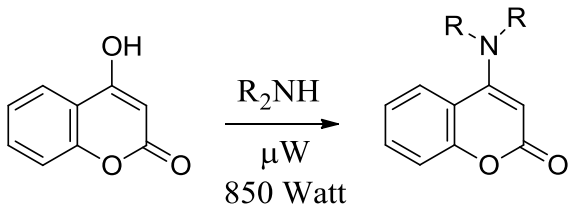
Scheme 10. Azaztriene formation from amino pyrones.



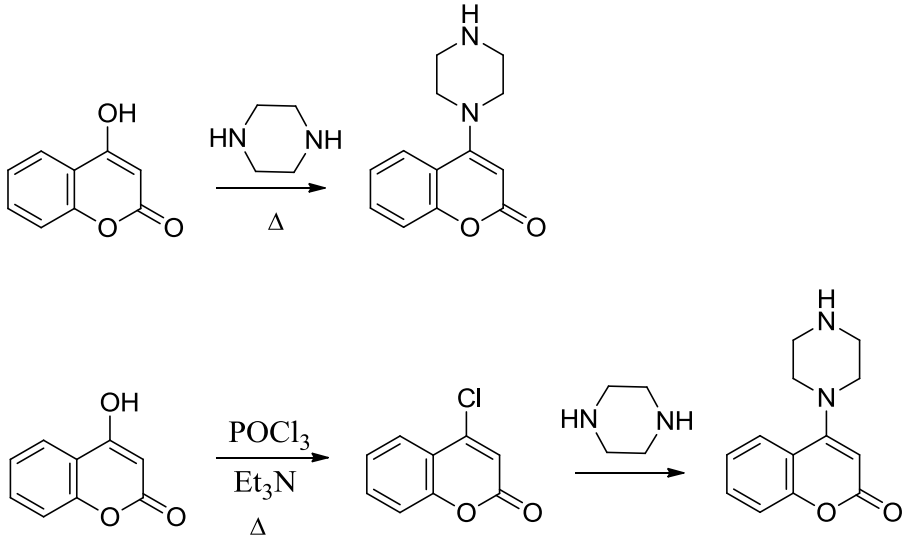
Scheme 11. 4-aminocoumarin from 4-hydroxy or 4-chlorocoumarin.

The 4-amino-2-pyrones can be obtained from different methods as reported in literature. Ivanov and co-workers reported obtaining *N*-substituted 4-aminocoumarins from 4-hydroxy or 4-chlorocoumarin as presented in Scheme 11. The solution mixture was refluxed for 2-20 hours with excess primary amine in a molar ratio of 10:1 amine to 4-hydroxycoumarin in glacial acetic acid. This method was failed with secondary amines. With 4-chlorocoumarin, the secondary amines gave the desired products at 20 °C.[30] The reaction was further modified as shown in Scheme 12, by decreasing the reaction time, by reducing the amount of amines and by improving the reaction conditions for the secondary amines. A microwave irradiation method was carried out to displace the

hydroxyl group of 4-hydroxycoumarin and TAL using 1.2 equivalents of amines without using a solvent.[22]



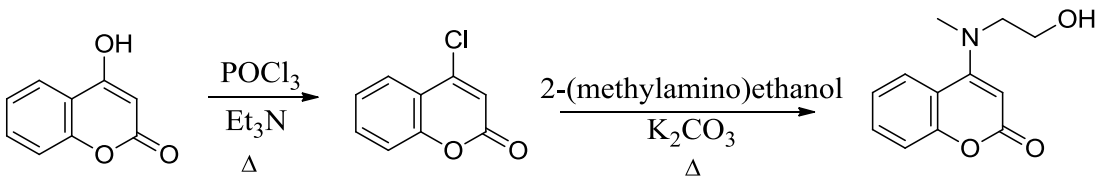
Scheme 12. Microwave irradiation method to get 4-aminopyrones.



Scheme 13. Using secondary amine to get 4-aminopyrones.

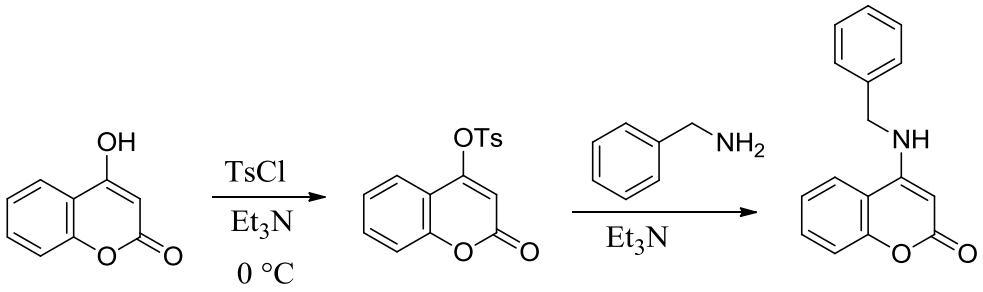
Di Braccio and co-workers reported a method to obtain 4-aminopyrones, using piperazine as the amine for 4-hydroxycoumarin and TAL. One method was to heat excess piperazine and 4-hydroxycoumarin at 160 °C to get 4-aminocoumarin. An alternative method was to heat 4-hydroxycoumarin or TAL with excess phosphorus oxychloride to 130 °C in the presence of triethylamine to get the 4-chloro derivative. The 4-chloro

derivative was then treated with excess piperazine in ethanol at room temperature to obtain the desired product. Both these methods are detailed in Scheme 13.[23]



Scheme 14. N-methylethanolamine as the amine to get 4-aminocoumarins.

Ji and co-workers used a similar method as Di Braccio to get 4-aminocoumarins using N-methylethanolamine as the amine. Reaction details are shown in Scheme 14.[24] Defant and co-workers presented a method to obtain 4-aminopyrones either using 4-hydroxycoumarin or TAL through an intermediate tosylated compound.[26, 31] Various primary amines were used in their method. Scheme 15 represents the details for this reaction of 4-hydroxycoumarin and TAL. The tosylate was a better leaving group and afforded moderate yields.

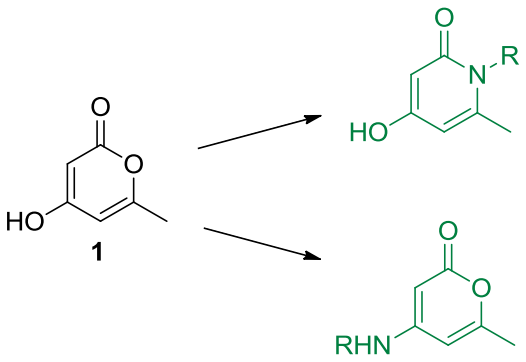


Scheme 15. 4-aminoyrones from the 4-tosyl pyrone intermediate.

3.2. Results and Discussion

The focus of our research was to diversify **1** in order to show its potential as a biomass derived platform molecule. The 4-hydroxy-2-pyridones and the 4-amino-2-pyrones are two different classes of organic molecules which are exhibiting important biological activities. These can be used as scaffolds to build several organic molecules. Because of the importance of these two types of molecules, we targeted simple methods to obtain them.

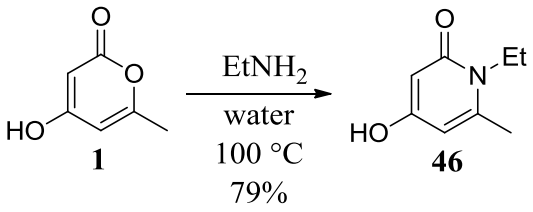
Our focus was mainly on *N*-substituted pyridone compounds as these were less studied in the literature. Mostly, the literature focus had been on 2-pyridones with no substituents on the nitrogen atom. We also focused on 4-amino-2-pyrones. Our target was to get both of these classes of molecules from **1** as a common intermediate as shown in Scheme 16.



Scheme 16. TAL as the common intermediate

Our attempt to make *N*-substituted pyridone was by adapting a method described by Haydon. Compound **1** was used as the starting material and 1.2 equivalents of

ethylamine were mixed. The reaction mixture was heated in water at 80 °C overnight.[20] We optimized the reaction conditions as 1.1 equivalents of ethylamine and mixture was boiled to 100 °C and increased the yield of **46** to 79% as shown in Scheme 17.



Scheme 17. Optimized conditions to get 2-pyridones.

We subjected both aliphatic and aromatic amines to similar reaction conditions to obtain the desired *N*-substituted pyridones. Pyridones were polar solids whose insolubility made them difficult to purify by a silica gel chromatography. The crude product **46** from ethylamine was filtered and washed with ether to give the purified product. The product **47** from butylamine was also purified by washing with ether. Allylamine and m-xylylenediamine did not provide desired products.

As detailed in Table 1, other amines formed the desired products but were unable to be purified with ether washing. Therefore, we tested several solvents to purify the products. As **1** was soluble in acetone and ethyl acetate, we were able to separate the 2-pyridone compounds from **1** by washing the crude product several times in these solvents.

The 4-amino-2-pyrones were made during this reaction for certain amines. These were able to be separated from the 2-pyridones by washing them with either acetone or ethyl acetate. NOE experiments were used to identify the two different types of products,

2-pyridones and 4-amino-2-pyrones. As an example for the product **46**, there was a strong NOE interaction between the methyl group at C-6 and the methylene of the ethyl group.

When octylamine and phenylethylamine were used, as shown in Table 1, entries 4 and 8, both 2-pyridones and 4-amino-2-pyrones were produced. The yields for both 2-pyridones and 4-amino-2-pyrones were quite low for these amines. The maximum yield of 85% was obtained when butylamine was used as represented in Table 1, entry 2. Even with piperonylamine the product yield was 80%. Whether it is an aliphatic or an aromatic amine, the product yield did not show a significant difference. Electron donating groups in the ring of the aromatic amines as shown in Table 1, entries 9 and 10, tend to give better yields compared to the ones without any substituents as in Table 1, entry 5. As presented in Table 1, entry 2, the alkyl amines with shorter chain lengths gave better yields.

Table 1. Results from the reaction of TAL with amines.

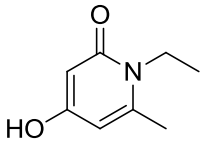
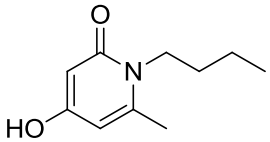
Entry	Amine	Solvent wash	product	Yield (%)
1	Ethylamine	Ether	 **46**	79
2	Butylamine	Ether	 **47**	85

Table 1 (continued)

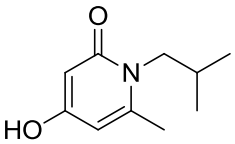
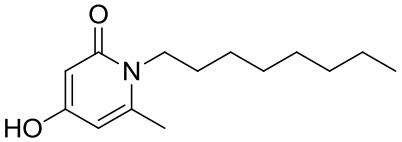
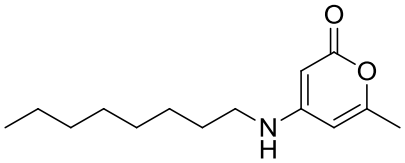
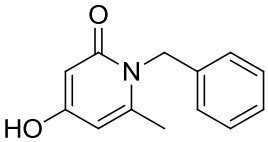
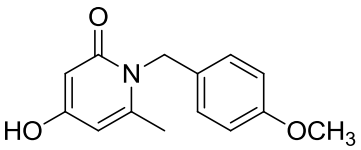
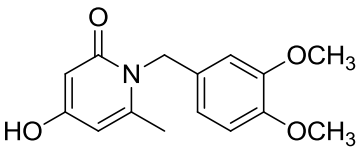
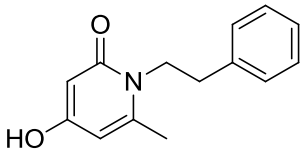
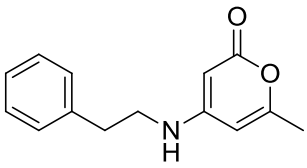
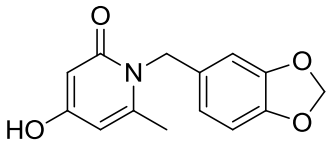
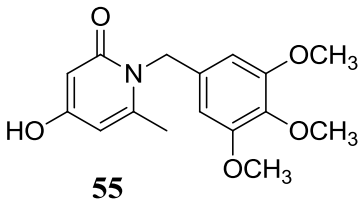
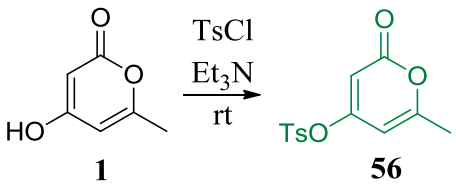
3	Isobutylamine	Ethyl acetate	 **48**	56
4	Octylamine	Ethyl acetate	 **49a**	11
			 **49b**	10
5	Benzylamine	Acetone	 **50**	20
6	4-methoxy-benzyamine	Acetone	 **51**	48
7	3,4-dimethoxy-benzylamine	Acetone	 **52**	24

Table 1 (continued)

8	Phenylethylamine	Acetone	 **53a**	29
		Ethyl acetate	 **53b**	21
9	Piperonylamine	Acetone	 **54**	80
10	3,4,5-trimethoxy-benzylamine	Ethyl acetate	 **55**	69

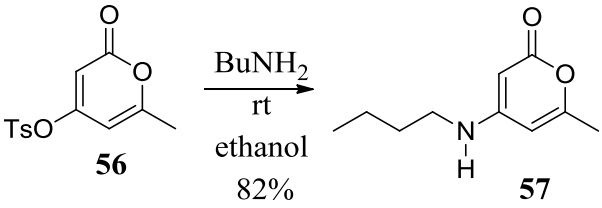
Among the interesting results obtained from Table 1, in entry 4 and 8 we identified that the compound **1** can be an intermediate compound to get both 2-pyridones and 4-amino-2-pyrones. We focused our attention on 4-amino-2-pyrones. With **13** in hand we tried a couple of reactions. The methoxyl group at C-4 is a better leaving group for the C-4 amine substitution. First, we tried to use butylamine as it showed promising results in pyridones. The reaction of **13** with butylamine in DMF was carried out at 70 °C and the starting material was recovered. Using 1: 1.1 molar ratios of **13**: amine we ran the

reaction in methanol at 70 °C in a sealable tube. For butylamine and ethylamine we were able to get positive results. However, this reaction was failed with benylamine, isopropylamine and dimethylamine. We were only able to get the starting material back. Then we changed to the tosylate of TAL. Compound **1** was stirred with tosyl chloride at room temperature as shown in Scheme 18, to obtain TAL tosylate **56** in 96% yield.[33]



Scheme 18. TAL tosylate from TAL.

We conducted our reaction using **56** as the starting material with butylamine in ethanol. This gave an 82% yield of the compound at room temperature as shown in Scheme 19. As detailed in Table 2, with this optimized reaction conditions we tested additional amines. These adducts were not as polar as pyridones, so we were able to separate these from the starting materials by chromatography. There was a strong NOE interaction between the hydrogens at C-3 and C-5 with the methylene in product **57**.



Scheme 19. Optimized conditions to get 4-amino-2-pyrones.

Table 2. The 4-amino-2-pyrones from tosylated TAL.

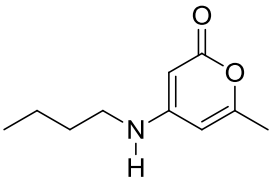
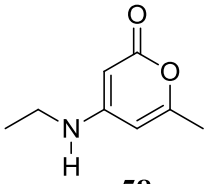
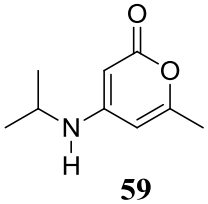
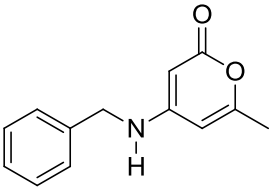
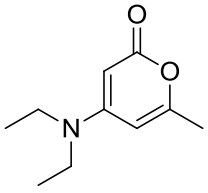
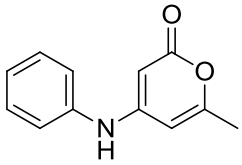
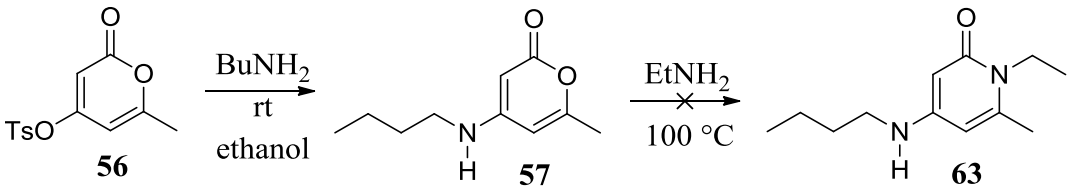
Entry	Amine	Product	Yield (%)
1	Butylamine	 **57**	82
2	Ethylamine	 **58**	51
3	Isopropylamine	 **59**	65
4	Benzylamine	 **60**	32
5	Diethylamine	 **61**	95

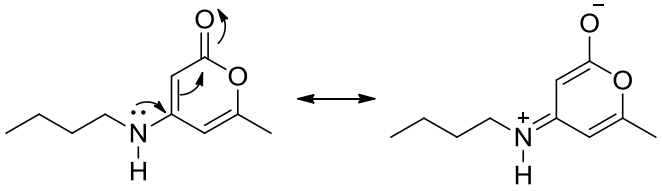
Table 2 (continued)

6	Aniline	 **62**	55

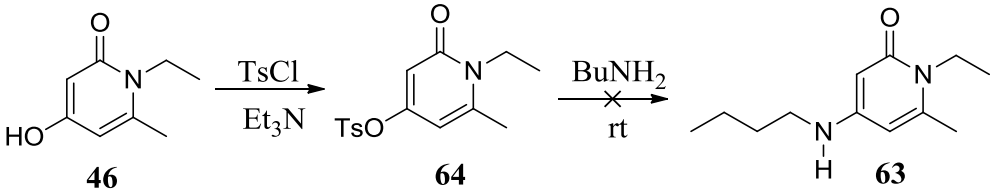
Here, we used both primary and secondary amines as well as both aliphatic and aromatic amines. The best yield was obtained for the secondary amine as shown in Table 2, entry 5. Both aromatic and aliphatic amines gave moderate yields. Then we focused on bis-substitution of the ring to get 4-amino-2-pyridones. We used two different amines to substitute at the two different positions. We used 4-aminopyrone **57** first. After purification of **57**, we subjected it to ethylamine and heated to 100 °C. However, this reaction did return **57** as shown in Scheme 20. The 4-amino group of **57** reduces the electrophilicity of the carbonyl group for a second nucleophile to attack as depicted in Scheme 21.



Scheme 20. Bis-substitution of the ring to afford 4-amino-2-pyridones.



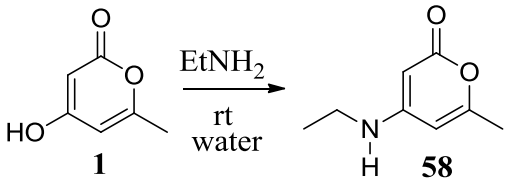
Scheme 21. 4-amino group reducing electrophilicity of the carbonyl group.



Scheme 22. Bis-substitution of the pyrone ring.

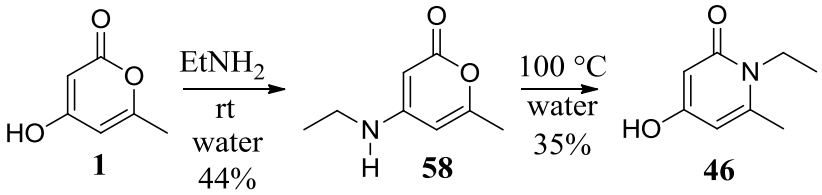
Then we formed the tosylated compound **64** from 2-pyridone **46** and subjected the activated pyridone to butylamine to substitute at the C-4 position to get compound **63** as shown in Scheme 22. Again, the second reaction failed to give the desired bis-substituted product. In this reaction, although there is a good leaving group, the pyridone is less electrophilic.

We subsequently found that **1** reacts with amines at room temperature in water. In an attempt to make 2-pyridones at a lower temperature, we conducted the ethylamine reaction with **1** at room temperature. Surprisingly, we were able to get 4-aminopyrone **58** instead of **46**, as shown in Scheme 23.



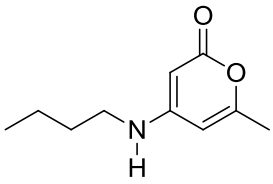
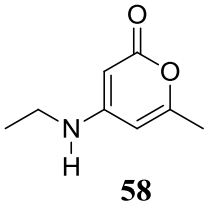
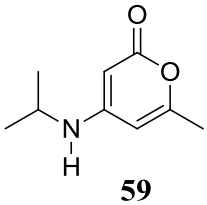
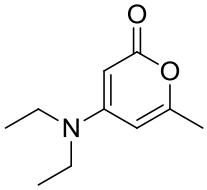
Scheme 23. 4-aminopyrones from TAL.

This is the first reported method of preparing 4-aminopyrones from TAL in water without activating the C-4 position of the ring **1** by a leaving group like a halogen or a tosyl group. We subjected other amines to this reaction conditions and were able to obtain moderate to good yields of products as shown in Table 3. As **58** was obtained using water as the solvent, we subjected it to higher temperatures. As shown in Scheme 24, **58** was boiled in water with a 20% excess of ethylamine to obtain pyridone **46**, which is likely the thermodynamic product. We were able to isolate the product **46** in 35% yield.



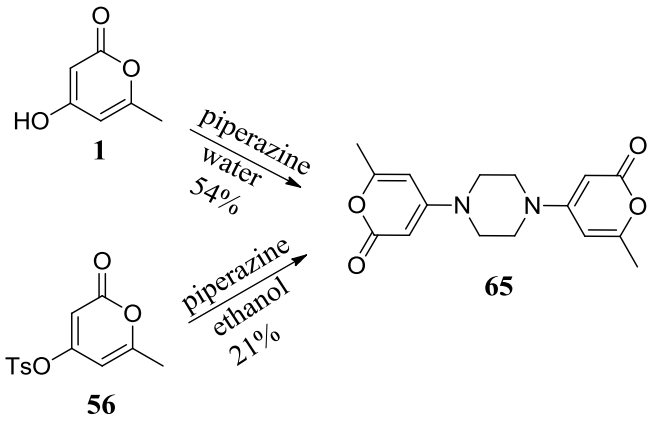
Scheme 24. 2-pyridones and 4-aminopyrones from TAL with an increase in temperature.

Table 3. Reaction of amines with TAL.

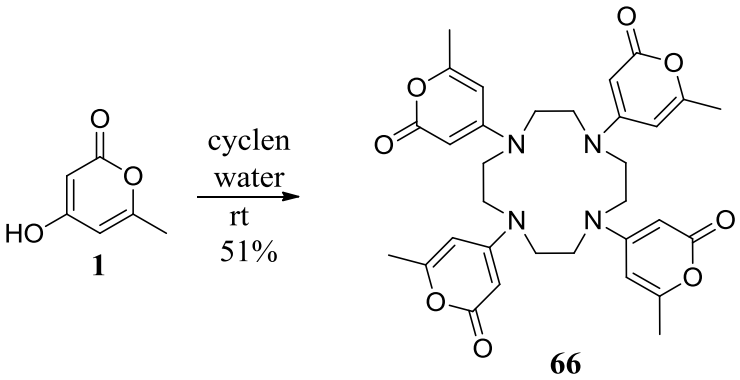
Entry	Amine	Product	Yield (%)
1	Butylamine	 **57**	83
2	Ethylamine	 **58**	44
3	Isopropylamine	 **59**	69
4	Diethylamine	 **61**	47

We performed the reaction with other amines as well, but we did not observe the 4-aminopyrones converting to 2-pyridones. This reaction was only observable for the ethylamine. The reaction was also carried out using diamines. Our reaction was conducted using tosylate **56** with piperazine which afforded the 2:1 adduct **65** in 21%

yield. Later, we found that simply mixing 2 equivalents of **1** with piperazine at room temperature in water give **65** as a cleaner product in 54% as shown in Scheme 25.



Scheme 25. Reaction with diamines.



Scheme 26. Reaction with tetramines.

We further extend this reaction using tetramines which led rapidly to form new materials. Here we used cyclen as the tetramine to get 4:1 adduct **66** in 51% yield using **1** as the pyrone as illustrated in Scheme 26. These cyclic molecules might be used as

ligands to capture metals by coordination through the lone pairs on nitrogen and oxygen atoms. This could be one of the future directions where we can extend the TAL chemistry.

3.3. Conclusion

We have devised an approach to both *N*-substituted pyridones and 4-aminopyrones from the biomass-derived TAL through a simple route. It has advantages over the reported methods, as it is more environmentally benign. Using water as the solvent, we can either convert the TAL to 4-aminopyrones by simply stirring it at room temperature with a desired amine, or we can also boil TAL with an amine to get *N*-substituted pyridones. In both methods we were able to get moderate to good yields for most of the amines and both aliphatic and aromatic amines can be employed. We have extended the reaction to diamines and tetramines and this is the first preparation of these structures.

In this chapter we were able to derive some important scaffolds in organic chemistry, the *N*-substituted pyridones and 4-aminopyrones which can be used to build an array of organic molecules from the biomass derived TAL. Thereby, we have been able to further diversify the range of molecules which can be obtained from biomass-derived platform molecule TAL.

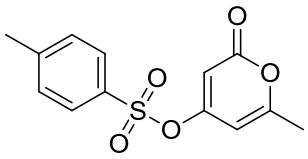
3.4. Experimental

All starting materials were purchased from Sigma-Aldrich and TCI America; solvents were purchased from Fisher Scientific and used without further purification. All reactions were carried out in flame-dried glassware under argon with dry solvents under anhydrous conditions. All yields refer to isolated products either by column chromatography or by recrystallization. Thin-layer chromatography (TLC) was performed using commercially available 250 micron silica gel plates (Analtech) and Preparative thin-layer chromatography was performed using commercially available 1000 micron silica get plates (Analtech). Visualization of TLC plates was effected with short wavelength ultraviolet light (254 nm). Silica gel 60Å, particle size 0.032 – 0.063 mm, was used for flash column chromatography. ^{1}H NMR spectra were acquired in $CDCl_3$ on a Varian VXR 300 MHz or Varian 400 MHz or Bruker DRX 500 MHz spectrometer. ^{1}H chemical shifts (δ) are given in ppm relative to the residual protonated solvent peak ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm; CD_3OD: δ_H = 3.31 ppm, δ_C =49.0 ppm; $(CD_3)_2CO$: δ_H = 2.05 ppm, δ_C = 29.84 ppm) as an internal reference. Low-resolution mass spectra (LRMS) were recorded on an Agilent 6540 QTOF (quadrupole time of flight) mass spectrometer using ESI (electrospray ionization) or APCI (atmospheric-pressure chemical ionization) or EI (electron ionization) on an Agilent 6890 GC/MS. Melting points were analyzed on a Mel-Temp II capillary melting point apparatus.

Selected Experimental, Physical, and Spectral Data

Experimental procedure:

6-methyl-2-oxo-2H-pyran-4-yl 4-methylbenzenesulfonate (**56**)

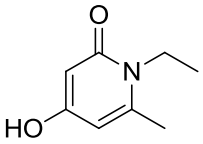


4-Hydroxy-6-methyl-2H-pyran-2-one (triacetic acid lactone, **1**) (0.63 g, 5 mmol) and tosyl chloride (0.955 g, 5 mmol) were dissolved in CH_2Cl_2 (37.5 mL). Triethylamine (2.05 mL, 15 mmol) was added and the reaction mixture was stirred at rt. overnight (23 h). CH_2Cl_2 (50 mL) was added and the organic phase was washed with water (25 mL) and brine (25 mL). The organic phase was dried over $MgSO_4$. After concentration *in vacuo* the crude product was purified by column chromatography using hexane/ethyl acetate (4:1) as eluent to afford the desired product as a colorless solid in 96% yield.[33]:Rf = 0.18 (silica gel, hexanes/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.82 (d, 2H), 7.37 (d, 2H), 6.00 (s, 1H), 5.80 (s, 1H), 2.45 (s, 3H), 2.23 (s, 3H) ppm.

Representative procedure for the preparation of pyridones **46-55**:

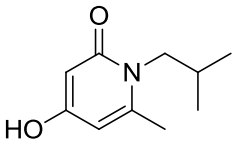
A mixture of triacetic acid lactone (**1**) (0.50 g, 3.96 mmoL, 1 eq) and primary amine (4.35 mmoL, 1.1 eq) in water (2.5 mL) was heated at 100 °C overnight. After completion of the reaction (TLC monitoring), the reaction mixture was cooled and the precipitate was filtered and washed with ethyl acetate and dried under vacuum to obtain the desired product.[20]

1-ethyl-4-hydroxy-6-methylpyridin-2(1H)-one (46)



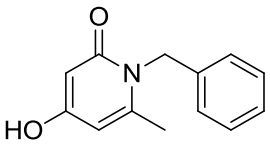
Light brown solid (79% yield): mp 240-242 °C (Lit. 247 °C) [18]; Rf = 0.16 (silica gel, CH_2Cl_2/ EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-d_4) δ = 5.92 (d, 1H), 5.72 (d, 1H), 4.05 (q, 2H), 2.39 (s, 3H), 1.24 (t, 3H) ppm; ^{13}C NMR (126 MHz, Methanol-d_4) δ = 165.7, 164.2, 145.7, 100.6 (2C), 37.1, 17.1, 11.1 ppm; LRMS (ESI-QTOF) calcd for $C_8H_{12}NO_2$ $[M + H]^+$ 154.0868, found 154.0872.

4-hydroxy-1-isobutyl-6-methylpyridin-2(1H)-one (48)



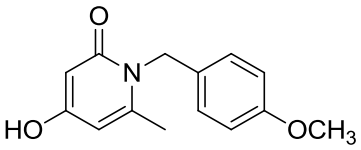
Light brown solid (56% yield): mp 173-175 °C; Rf = 0.35 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-d_4) δ = 5.92 (d, 1H), 5.73 (d, 1H), 3.85 (d, 2H), 2.37 (s, 3H), 2.26-2.05 (m, 1H), 1.04-0.80 (m, 6H) ppm; ^{13}C NMR (126 MHz, Methanol-d_4) δ = 165.4, 164.6, 146.2, 100.5, 94.7, 48.51, 26.2, 17.9, 17.2 (2C) ppm; LRMS (ESI-QTOF) calcd for $C_{10}H_{16}NO_2$ $[M + H]^+$ 182.1181, found 182.1191.

1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one (50)



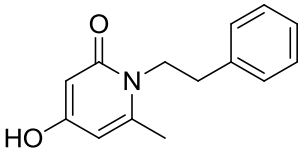
White solid (20% yield): mp 219-220 °C (Lit. 217 °C) [18]; Rf = 0.30 (silica gel, CH_2Cl_2/EtOAc 1:1); ^{1}H NMR (300 MHz, Methanol-d_4) δ = 7.33 (m, 2H), 7.27 (m, 1H), 7.11 (m, 2H), 5.97 (d, 1H), 5.82 (d, 1H), 5.32 (s, 2H), 2.25 (s, 3H) ppm; LRMS (ESI-QTOF) calcd for $C_{13}H_{14}NO_2$ [M + H]$^+$ 216.1025, found 216.1040. ^{13}C NMR data agreed with the literature.[16]

4-hydroxy-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one (51)



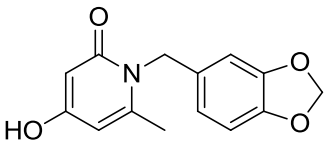
White solid (48% yield): mp 221-225 °C; ^{1}H NMR (300 MHz, Methanol-d_4) δ = 7.27 (d, 2H), 7.07 (d, 2H), 5.86 (d, 1H), 5.50 (d, 1H), 5.19 (s, 2H), 3.77 (s, 3H), 2.20 (s, 3H) ppm; LRMS (ESI-QTOF) calcd for $C_{14}H_{16}NO_3$ [M + H]$^+$ 246.1130, found 246.1142.

4-hydroxy-6-methyl-1-phenethylpyridin-2(1H)-one (53a)



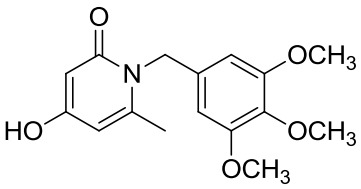
White solid (29% yield): mp 244-247 °C (Lit. 252 °C) [18]; ^{1}H NMR (300 MHz, Methanol-d_4) δ = 7.35-7.14 (m, 5H), 5.85 (d, 1H), 5.77 (d, 1H), 4.17 (t, 2H), 2.97 (t, 2H), 2.12 (s, 3H) ppm; LRMS (ESI-QTOF) calcd for $C_{14}H_{16}NO_2$ [M + H]$^+$ 230.1181, found 230.1173.

1-(benzo[1,3]dioxol-5-ylmethyl)-4-hydroxy-6-methylpyridin-2(1H)-one (54)



White solid (80% yield): mp 206-209 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 6.76 (s, 1H), 6.72 (d, 1H), 6.69 (d, 1H), 5.94 (s, 2H), 5.92 (d, 1H), 5.68 (d, 1H), 5.13 (s, 2H), 2.15 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ = 163.8, 155.3, 147.8, 146.5, 145.6, 133.2, 120.7, 108.6, 108.6, 101.3, 101.3, 99.4, 45.5, 20.4 ppm; LRMS (ESI-QTOF) calcd for $C_{14}H_{14}NO_4$ $[M + H]^+$ 260.0923, found 260.0932.

4-hydroxy-6-methyl-1-(3,4,5-trimethoxybenzyl)pyridin-2(1H)-one (55)



Light yellow solid (69% yield): mp 251-255 °C; ^{1}H NMR (300 MHz, Methanol-d_4) δ = 6.43 (s, 2H), 5.97 (d, 1H), 5.82 (d, 1H), 5.26 (s, 2H), 3.80 (s, 6H), 3.76 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR (126 MHz, Methanol-d_4) δ = 163.4, 159.9, 151.9, 132.0 (2C), 131.4, 115.9, 101.5 (2C), 100.7, 94.5, 58.1, 53.5 (2C), 45.6, 17.5 ppm; LRMS (ESI-QTOF) calcd for $C_{16}H_{20}NO_5$ $[M + H]^+$ 306.1341, found 306.1347.

General procedure for the preparation of 4-aminopyrones (57-62)

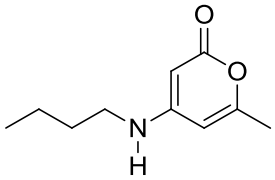
Method A

A mixture of 6-methyl-2-oxo-2H-pyran-4-yl 4-methylbenzenesulfonate (**56**) (0.08 g, 0.3 mmoL, 1 eq) and amine (0.66 mmoL, 2.2 eq) in ethanol (4 mL) was stirred at rt. overnight. After completion of the reaction (TLC monitoring), solvent was evaporated. The crude compound was purified by preparative thin layer chromatography (EtOAc/dichloromethane) to afford the desired product.

Method B

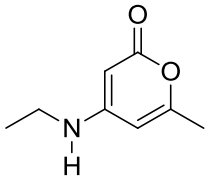
A mixture of triacetic acid lactone **(1)** (0.17 g, 1.4 mmoL, 1 eq) and amine (1.54 mmoL, 1.1 eq) in water (1.5-2 mL) was stirred at rt. overnight. After completion of the reaction (TLC monitoring), solvent was evaporated. The crude compound was purified by preparative thin layer chromatography (EtOAc/dichloromethane) to afford the desired product.

4-(butylamino)-6-methyl-2H-pyran-2-one (57)



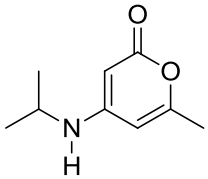
White solid (Method A: 82% yield, Method B: 44% yield): mp >260 °C ^{1}H NMR (300 MHz, Methanol-d_4) δ = 5.75 (s, 1H), 4.86 (s, 1H), 2.93 (m, 2H), 1.64 (m, 2H), 1.41 (m, 2H), 0.93 (t, 3H) ppm; ^{13}C NMR (126 MHz, Methanol-d_4) δ = 160.5, 160.1, 154.4, 102.3, 85.1, 42.1, 37.5, 18.3, 18.0, 11.0 ppm; LRMS (ESI-QTOF) calcd for $C_{10}H_{16}NO_2$ [M + H]$^{+}$ 182.1181, found 181.1176.

4-(ethylamino)-6-methyl-2H-pyran-2-one (58)



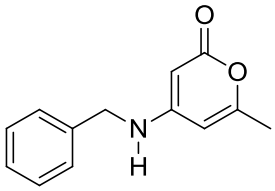
Colorless liquid (Method A: 51% yield, Method B: 83% yield): ^{1}H NMR (300 MHz, Methanol-d_4) δ = 5.92 (s, 1H), 5.72 (s, 1H), 3.32 (m, 2H), 2.39 (s, 3H), 1.24 (t, 3H) ppm; ^{13}C NMR (126 MHz, Methanol-d_4) δ = 163.7, 157.6, 152.7, 97.7, 89.9, 35.1, 27.4, 16.6 ppm; LRMS (ESI-QTOF) calcd for $C_8H_{12}NO_2$ [M + H]$^+$ 154.0868, found 154.0871.

4-(isopropylamino)-6-methyl-2H-pyran-2-one (59)



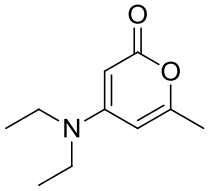
White solid (Method A: 65% yield, Method B: 69% yield): mp >260 °C ^{1}H NMR (300 MHz, Methanol-d_4) δ = 5.76 (s, 1H), 5.21 (s, 1H), 3.63 (m, 1H), 2.13 (s, 3H), 1.20 (d, 6H) ppm; ^{13}C NMR (126 MHz, Methanol-d_4) δ = 165.8, 158.9, 156.7, 97.9, 76.3, 41.9, 19.0 (2C), 16.6 ppm; LRMS (ESI-QTOF) calcd for $C_9H_{14}NO_2$ [M + H]$^+$ 168.1025, found 168.1030.

4-(benzylamino)-6-methyl-2H-pyran-2-one (60)



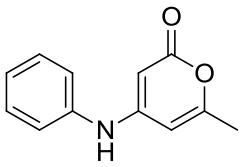
White solid (Method A: 32% yield): mp 126-130 °C; ^{1}H NMR (300 MHz, Methanol-d_4) δ = 7.41 – 7.17 (m, 5H), 5.90 (s, 1H), 4.94 (s, 1H), 4.33 (d, 2H), 2.15 (s, 3H) ppm; LRMS (ESI-QTOF) calcd for $C_{13}H_{14}NO_2$ $[M + H]^+$ 216.1025, found 216.1034.

4-(diethylamino)-6-methyl-2H-pyran-2-one (61)



Yellow solid (Method A: 95% yield, Method B: 47% yield): mp 96-98 °C; ^{1}H NMR (300 MHz, Methanol-d_4) δ = 5.80 (d, 1H), 4.99 (d, 1H), 3.41 (q, 4H), 2.21 (s, 3H), 1.19 (t, 6H) ppm; ^{13}C NMR (126 MHz, Methanol-d_4) δ = 165.5, 160.2, 156.4, 94.7, 77.6, 42.6 (2C), 17.1 (2C), 16.6 ppm; LRMS (ESI-QTOF) calcd for $C_{10}H_{16}NO_2$ $[M + H]^+$ 182.1181, found 182.1189.

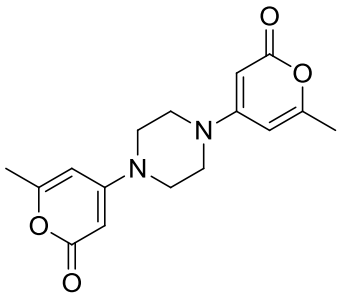
6-methyl-4-(phenylamino)-2H-pyran-2-one (62)



White solid (Method A: 55% yield): mp 192-195 °C (Lit. 195-196 °C) [34] ; ^{1}H NMR (300 MHz, Acetone-d_6) δ = 7.48 – 7.36 (m, 2H), 7.32 – 7.14 (m, 3H), 5.95 (d, 1H), 5.27 (d,

1H), 2.14 (s, 3H) ppm; ^{13}C NMR (126 MHz, Methanol-d_4) δ = 165.5, 160.2, 156.2, 141.3, 127.6 (2C), 123.9, 121.7 (2C), 97.5, 79.5, 16.8 ppm; LRMS (ESI-QTOF) calcd for $C_{12}H_{12}NO_2$ $[M + H]^+$ 202.0868, found 202.0879.

4,4'-(piperazine-1,4-diyl)bis(6-methyl-2H-pyran-2-one) (65)



Method A

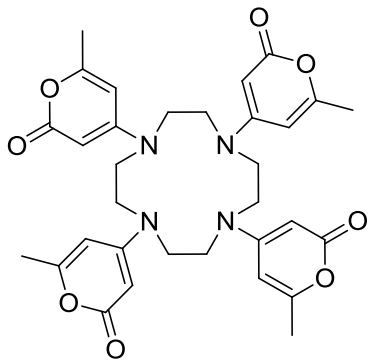
A mixture of 6-methyl-2-oxo-2H-pyran-4-yl 4-methylbenzenesulfonate (**56**) (0.1 g, 0.36 mmoL, 2 eq) and piperazine (0.18 mmoL, 1 eq) in ethanol (8 mL) was stirred at rt. overnight. After completion of the reaction (TLC monitoring), solvent was evaporated. The crude compound was purified by preparative thin layer chromatography (EtOAc/dichloromethane) to afford the desired product as a white solid (21% yield).

Method B

A mixture of triacetic acid lactone **(1)** (0.15 g, 1.2 mmoL, 2 eq) and piperazine (0.6 mmoL, 1 eq) in water (1.5 mL) was stirred at rt. overnight. After completion of the reaction (TLC monitoring), solvent was evaporated. The crude compound was purified by preparative thin layer chromatography (EtOAc/dichloromethane) to afford the desired product as a white solid (54% yield).

^{1}H NMR (300 MHz, Methanol-d_4) δ = 5.77 (s, 2H), 4.86 (s, 2H), 3.11 (s, 8H), 2.14 (s, 6H) ppm; ^{13}C NMR (400 MHz, Methanol-d_4) δ = 179.7 (2C), 169.4 (2C), 161.4 (2C), 105.5 (2C), 87.4 (2C), 42.9 (4C), 18.2 (2C) ppm; LRMS (ESI-QTOF) calcd for $C_{16}H_{19}N_2O_4$ $[M + H]^+$ 303.1345, found 303.1347.

4,4',4'',4'''-(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetrakis(6-methyl-2H-pyran-2-one) (66)



Method B

A mixture of triacetic acid lactone **(1)** (0.14 g, 1.1 mmoL, 4 eq) and cyclen (0.047 g, 0.27 mmoL, 1 eq) in water (2 mL) was stirred at rt. overnight. After completion of the reaction (TLC monitoring), solvent was evaporated. The crude compound was purified by preparative thin layer chromatography (EtOAc/dichloromethane) to afford the desired product as a white solid (51% yield): ^{1}H NMR (400 MHz, Methanol-d_4) δ = 5.67 (s, 4H), 5.03 (s, 4H), 2.92 (s, 16H), 2.05 (s, 12H) ppm; ^{13}C NMR (400 MHz, Methanol-d_4) δ = 179.9 (4C), 169.4 (4C), 161.3 (4C), 105.6 (4C), 87.3 (4C), 43.2 (8C), 18.2 (4C) ppm.

3.5. References

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CHAPTER 4

GENERAL CONCLUSIONS

Tacetic acid lactone as a new biomass derived platform molecule has been proposed in this dissertation. Diversification of triacetic acid lactone to get a variety of biologically important molecules has been described. Chapter 1 focused on the development of a high-value added specialty molecule from triacetic acid lactone. Pogostone is known as an important natural product with a wide range of biological activities. One-step synthesis of pogostone has been derived from the biobased triacetic acid lactone with promising yields. Pogostone and its analogs derived from this synthesis were tested for their biological activities.

Chapter 2 discussed an improved aldol protocol to achieve 6-styrenylpyrones from triacetic acid lactone. The 6-styrenylpyrone is another class of biologically active high value added specialty compounds. A convenient method of forming this class of molecules with lower reaction temperatures and polar solvent conditions has been described. Compared to the previous methods reported, these reaction conditions gave better yields in a simple manner.

Chapter 3 described an approach towards the synthesis of both *N*-substituted pyridones and 4-aminopyrones from the biomass derived TAL through a simple route. It has advantages over the reported methods, as this is a more environmentally benign method. The reaction was carried out in water and can afford either *N*-substituted pyridones or 4-aminopyrones with a change in the temperature in good yields.