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Synthesis of 2-pyrone containing products and Hibiscone C

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Synthesis of 2-pyrone containing products and Hibiscone C

by

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Program of Study Committee:
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Gregory Phillips
Jacob Petrich
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The student author, whose presentation of the scholarship herein was approved by the program of study committee, is solely responsible for the content of this dissertation. The Graduate College will ensure this dissertation is globally accessible and will not permit alterations after a degree is conferred.

Iowa State University

Ames, Iowa

2018

DEDICATION

To my parents

for encouraging me all the time.

To my grandparents

for the eternal love.

To .

Miss you, grandpa.

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ACKNOWLEDGMENTS

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ABBREVIATIONS

Ac acetyl

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

DCM dichloromethane

dd doublet of doublets

DMA N,N-dimethylacetylamide

equiv equivalent

ESI electrospray ionization

Et ethyl

Et_3N trimethylamine

EtOAc ethyl acetate

FDCA 2,5-furandicarboxylic acid

g gram

GC/MS gas chromatography/mass spectrometry

h hour

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

v

K Kelvin

μ micron

M molarity

m multiplet

m-CPBA meta-chloroperoxybenzoic acid Me methyl

MeOH methanol

mg milligram

MHz megahertz

mL milliliter

mm millimeter

mM milimolar

mmol millimole

m.p. melting point

NBS N-Bromosuccinimide NMR nuclear magnetic resonance Nu nucleophile

OMe methoxy

p para

Pd/C palladium on carbon

Ph phenyl

PPh3 triphenylphosphine

ppm parts per million

2-PS 2-pyrone synthase

PTSA para-toluenesulfonic acid

q quartet

QTOF quadrupole time of flight quant. quantitative

Rf 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

ABSTRACT

2-Pyrone is extremely prevalent in numerous natural products with a broad range of biological activities. Not only structurally complex natural products, but more and more 2-pyrone containing small molecules have also attracted the attention of organic chemists, medicinal chemists and agricultural scientist. Synthesizing valuable 2-pyrone containing products and testing their potential applications are of great importance.

In this dissertation, we summarized the synthesis of two 2-pyrone containing small molecule natural products and explored methods to functionalize triacetic acid lactone, a very promising 2-pyrone compound that has been identified as a bio-privileged molecule. Chapter 1 of this dissertation describes the synthesis of a class of 6-alkyl-2-pyrones and an antileukemic 2-pyrone. Chapter 2 discusses the involvement of triacetic acid lactone in multi-component reaction. The versatility of the bio-based triacetic acid lactone as a platform chemical has been further demonstrated via the 3-component Mannich reaction. The last chapter describes an approach to Hibiscone C, a bioactive and structurally interesting natural product. A strategically new approach to this molecule was depicted.

CHAPTER 1. SYNTHESIS OF 2-PYRONE CONTANING NATURAL PRODUCTS

1.1. Introduction

1.1.1. 2-Pyrones

Pyrones are six-membered unsaturated oxygen containing heterocycles with two double bonds and the oxygen atom was designated as position 1. The pyrone ring is not a true aromatic ring. There are two isomers denoted as 2-pyrone (α-pyrone) and 4-pyrone (γ-pyrone). In view of chemical motifs, 4-pyrone is the vinylogous form of 2-pyrone, which possesses a lactone (Figure 1).

Figure 1. 2-pyrone and 4-pyrone

2-Pyrone is highly abundant in numerous natural products isolated from plants, animals, insects, bacteria, fungi, and marine organisms. It takes part in many different types of biological processes such as key biosynthetic intermediates, as defense against other organisms, and as metabolites. Many 2-pyrone containing compounds exhibit a wide range of biological activities, such as phytotoxic, antibiotic, cytotoxic, neurotoxic and antifungal (Figure 2).[1-3]

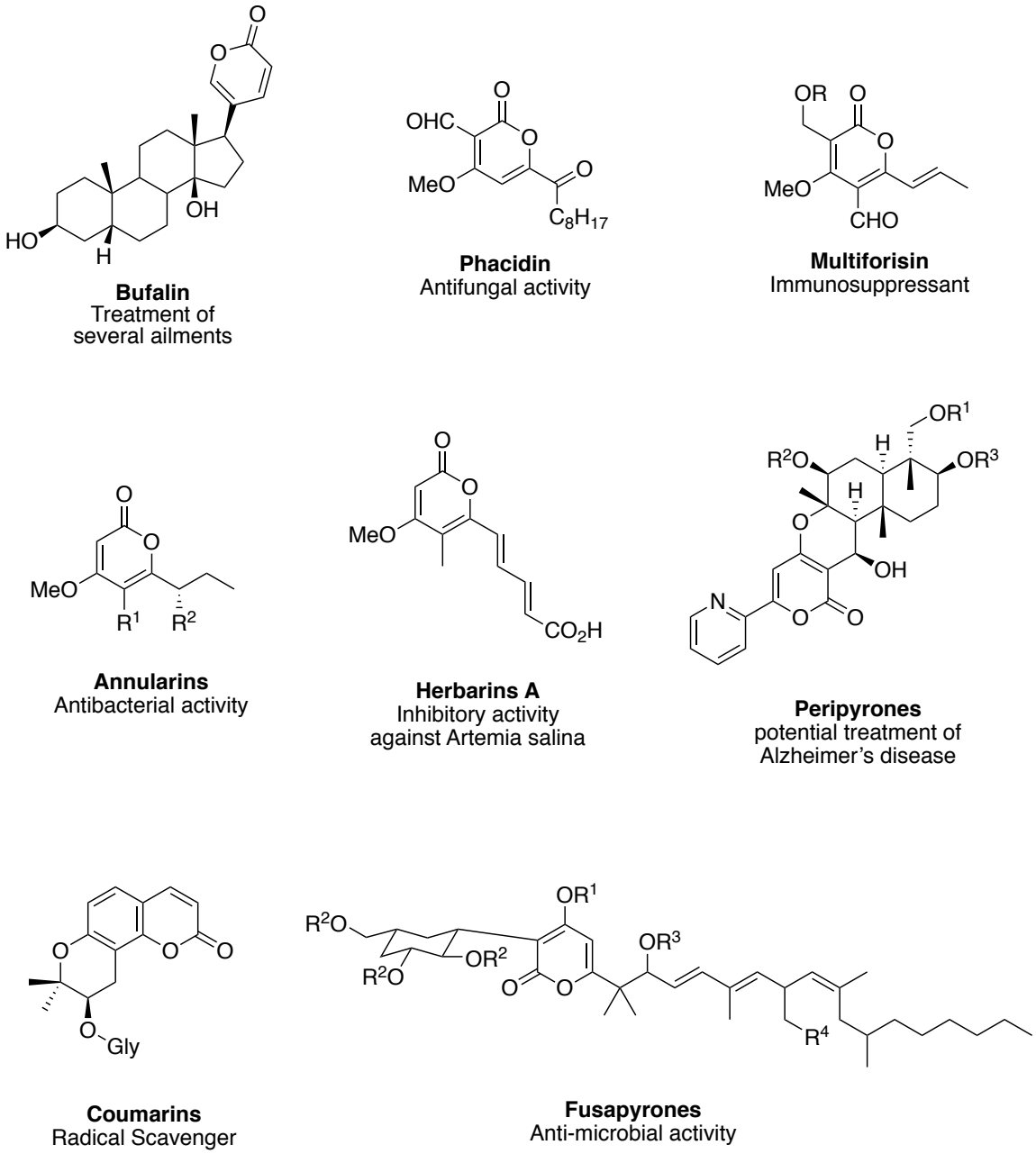


Figure 2. Natural occurring bioactive 2-pyrone containing compounds

Besides, 2-pyrone moieties can serve as versatile synthetic building blocks for organic chemistry and medicinal chemistry. The aromatic potential of 2-pyrones has been demonstrated through their electrophilic substitution reactions such as halogenation, nitration and chloromethylation. It is reported that the C-2, C-4 and C-6 positions of the 2-pyrone are electrophilic and prone to occur nucleophilic attack. An electron-

withdrawing substituent at C-3 could make the C-4 and C-6 positions more electrophilic and thereby favors nucleophilic reactions. And also, the existence of a good leaving group such as methoxy or methylsulphonyl group at C-4 will make this position even much easier to be attacked by nucleophiles. The C-3 and C-5 positions are susceptible to electrophilic attack. The presence of electron-donating groups at C-4 and C-6 positions will facilitate electrophilic substitution reactions (Figure 3).[2-3]

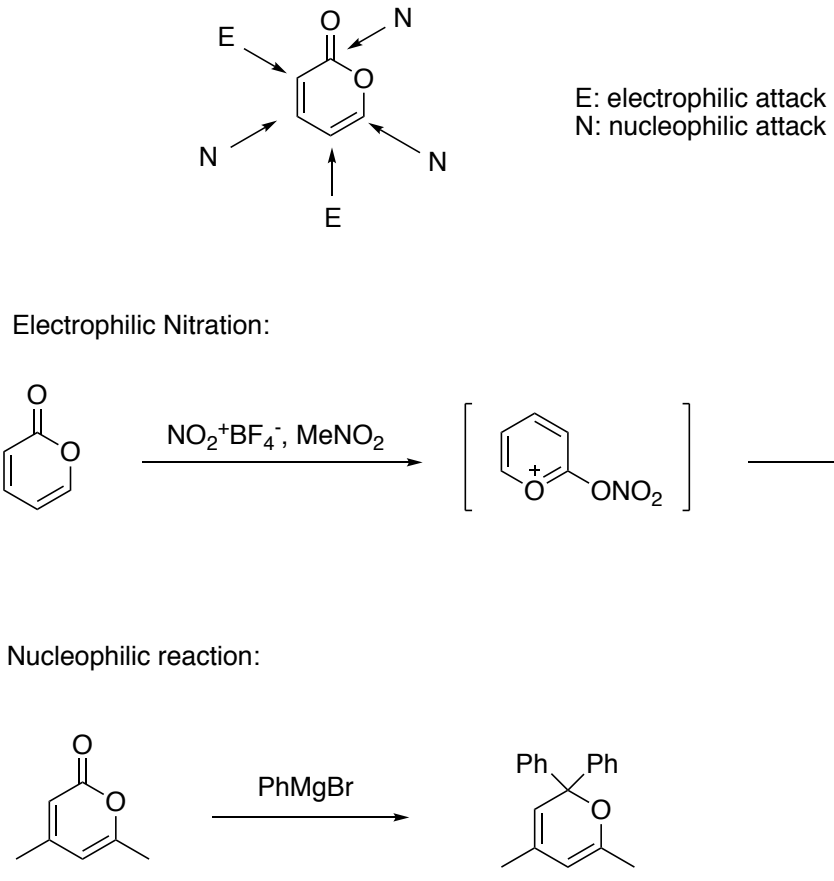
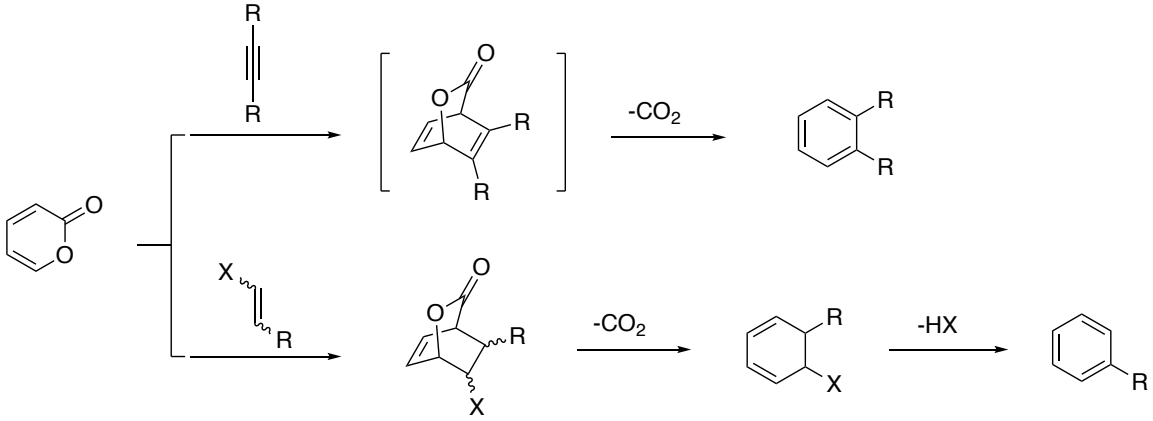


Figure 3. Reactivity of 2-pyrones

Except for nucleophilic and electrophilic reactions, the 2-pyrone moiety showed photochemical and cycloaddition reactivity. In 1931, three years after the first [4+2] cycloaddition reaction was published by Diels and Alder, they reported that 2-pyrones could also involve in these cycloadditions functioning as the diene component.[4] 2-

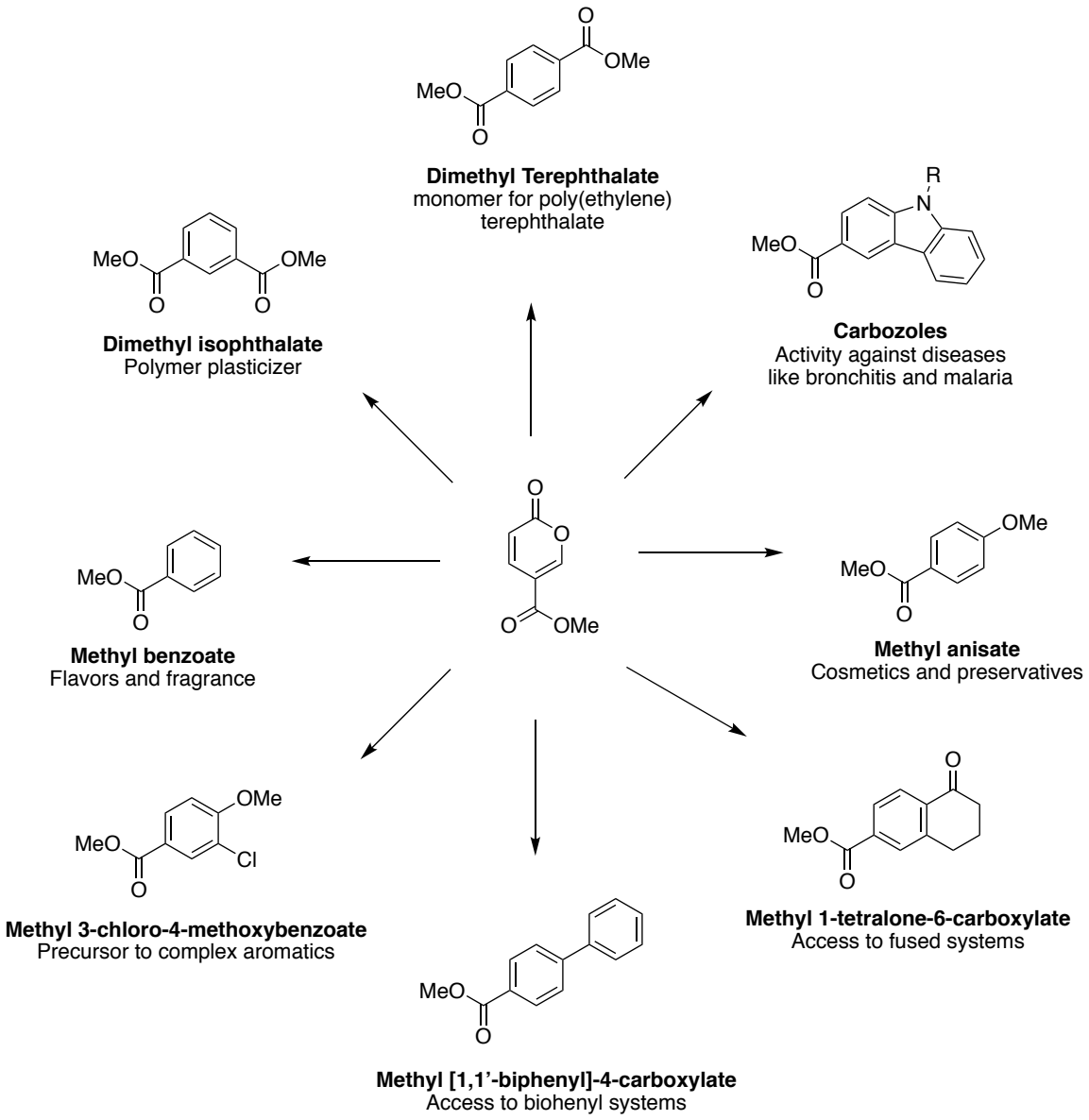
Pyrones have some aromatic character, so they undergo Diels-Alder [4+2] cycloadditions less easily than do most cyclic conjugated dienes. However, under suitable conditions, 2-pyrones can be used effectively in these reactions. As shown in Scheme 1, cycloaddition of 2-pyrone with alkynes generates initially highly strained bicyclooctadienes that readily undergo extrusion of carbon dioxide to form aromatic structures. Cycloaddition with alkenes generates relatively more stable (sometimes isolable) bicyclooctenes, which will lead to dihydrobenzenes by loss of one molecule of carbon dioxide.[5] Ultimate aromatization often occurs when a good leaving group exists in the proper positions.



Scheme 1. Diels-Alder reactions of 2-pyrone with alkynes and alkenes

As part of a project in the Center for Biorenewable Chemicals (CBiRC), the Diels-Alder reactions of methyl coumalate/coumalic acid functioning as diene have been intensively studied in our group. Methyl coumalate and coumalic acid were reported to react with unactivated alkenes with good regioselectivity.[6] The reactions of methyl coumalate with electron-deficient alkenes such as acrolein, acrylonitrile and methyl acrylate have been reported.[7] Those reactions yielded mixtures of meta- and para-substituted benzoates with modest selectivity in favor of the para-isomer. The Kraus group has also optimized the reaction conditions of methyl coumalate with electron-rich

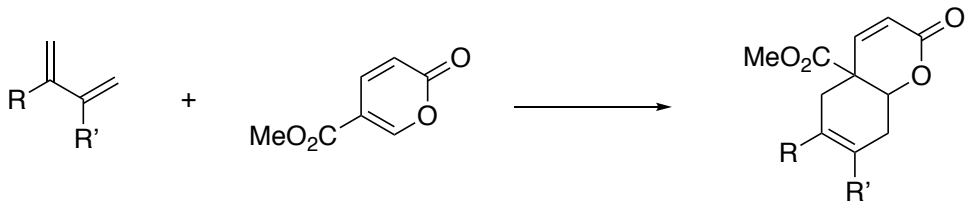
alkenes. The regioselective transformations with ketal and orthoester dienophile equivalents, captodative dienophiles to achieve a formal synthesis of biorenewable terephthalic acid, and substituted indoles to bioactive carbozoles have been successively reported (Scheme 2).[8-11]



Scheme 2. Coumalate platform and valuable applications

There are also a few examples in which the 2-pyrones functioned as dienophile. For example, it was reported that some 2-pyrones could dimerize under high pressure and

photosensitized conditions, the dimers were formed between two equivalents of the pyrone.[12] In another example shown in Scheme 3, methyl coumalate behaved as dienophile and added onto a variety of acyclic dienes.[13]



Scheme 3. Methyl coumalate function as dienophile

1.1.2 6-Pentyl-2-pyrone (6-PP)

The genus *Thichoderma* is an excellent source for bioactive natural products, among them, 6-alkyl-2-pyrones are good examples that have been isolated from various species of genus *Trichoderma*. 6-PP was the first metabolite identified as a fungal product of *Trichoderma viride*.[14] It has a coconut smell and has been reported to be a component of nectarine and peach essence. The flavorant properties of 6-PP have attracted interest in the food industry.[3]

6-PP is a major volatile organic compound (VOC) biosynthesized by *Trichoderma* species and associated with a number of beneficial properties, for example, it promotes plant growth, inhibits primary root growth and shows antifungal activities. It modulates expression of PIN auxin-transport proteins in a specific and does-dependent manner in primary roots. 6-PP promoted the growth of tomato and canola seedlings and pea stems. Tomato plants sprayed with 6-PP had a highly branched root system and increased biomass, which may due to improved nutrient and water acquisition. 6-PP effectively reduced the incidence of *Botrytis cinerea* and *Leptosphaeria maculans* on tomato and canola seedlings; at a concentration of 0.1% (v/v) this compound completely

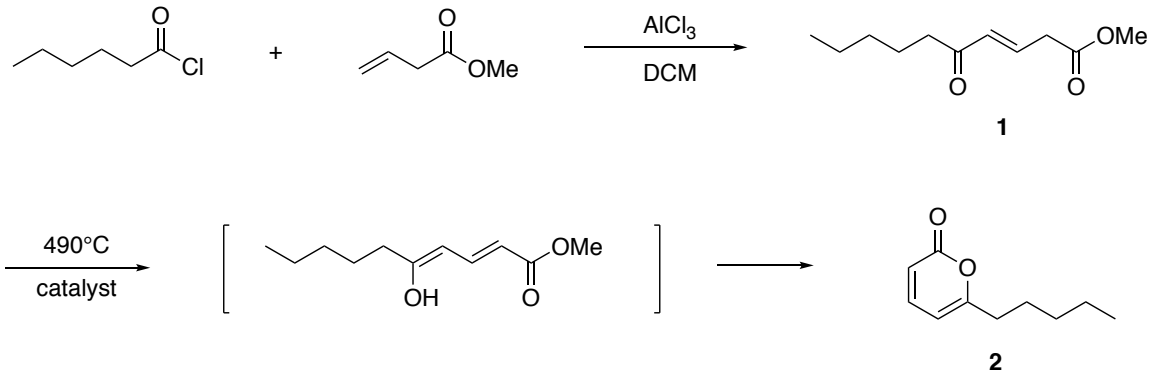
inhibited the outgrowth of *Botrytis cinerea*. It was also proved effective in the control of *Botrytis cinerea* rots in kiwi fruit. Fruit treated with 6-PP was less prone to accelerated ripening.[1, 15-16]

All these biological properties made 6-PP a potential biological control agent (BCA). *Thichoderma* species have proved to be useful BCAs and the best strains produced high quantities of 6-PP.[17] The production of 6-PP by biotechnology in various system has been reported, yields of 2 grams of 6-PP per kilogram of ground corn could be achieved by optimizing the temperature, light, time of harvest and spore inoculation.[18]

6-PP can also be isolated from a marine algicolous fungus of the genus *Myrotherium*. It exhibited a tyrosinase inhibitory activity with IC_{50} value of 0.8 μM, which is more active than kojic acid that is currently been used for functional personal care. The anti-tyrosinase property also made 6-PP potential for skin-coloring effects and therapeutic effects on the local hyperpigmentiaon diseases.[19]

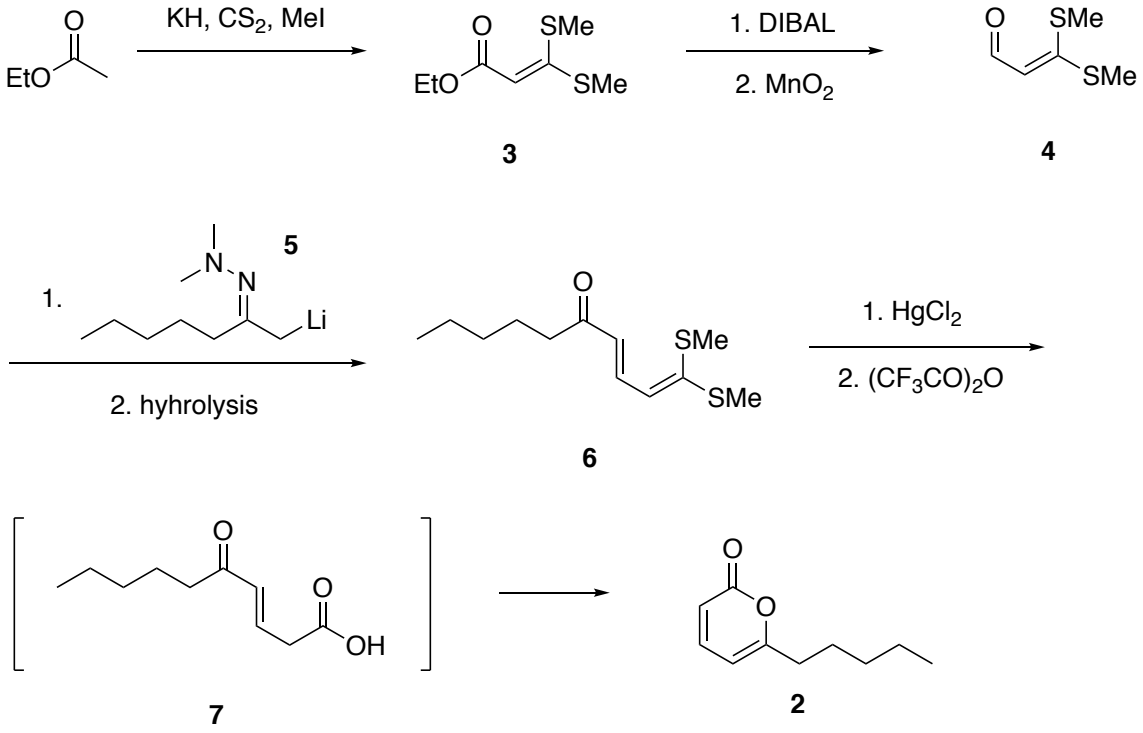
1.1.3 Previous synthesis of 6-alkyl-2-pyrones

In 1975, Pittet and Klaiber reported a general synthesis of 6-alkyl-2-pyrones. The synthesis has been achieved in about 40% overall yield.[20] For example as shown in Scheme 4, acylation of methyl 3-butenoate with hexanoyl chloride under Friedel-Crafts conditions yielded keto ester **1**. Passing the intermediate unsaturated keto ester **1** through a quartz column packed with protruded copper at 490°C gave rise to the final product 6-PP **2**.



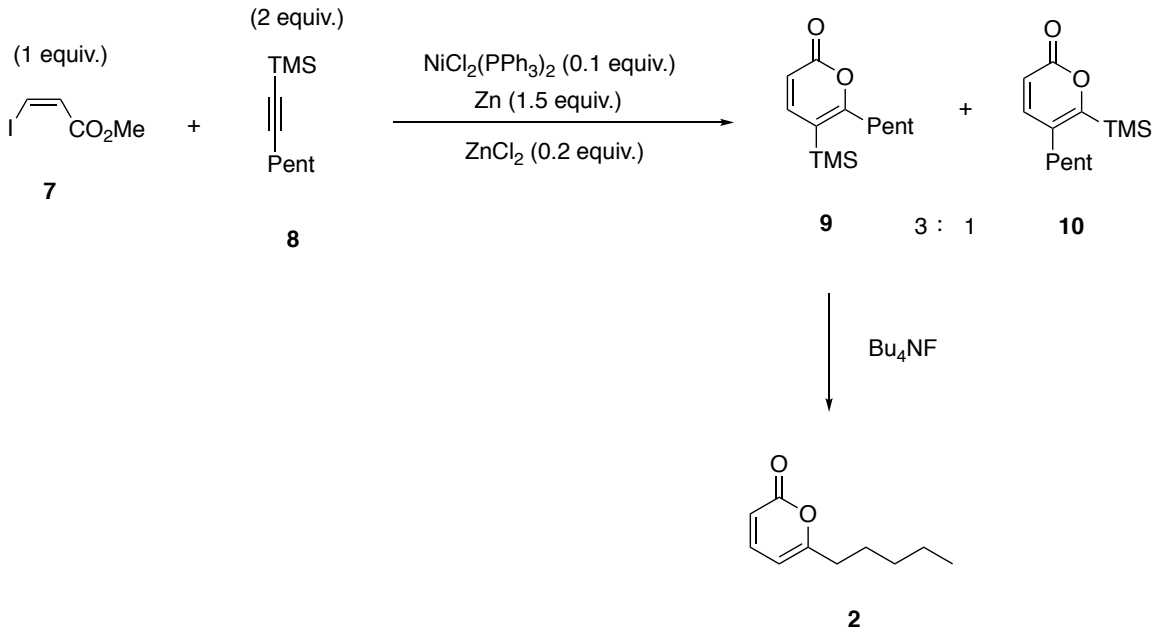
Scheme 4. Pittet synthesis of 6-PP

In 1988, Dieter and Fishpaugh reported synthetic routes to 2-pyrones.[21] The strategy involves a 1,2-nucleophilic addition of a ketone, ester or hydrazone enolate anion to the carbonyl group of a α-oxo ketene dithioacetal or vinylogous thiol ester. The following acid-catalyzed 1,3-carbonyl transposition and enol lactonization afforded the 2-pyrones. For example, ketene dithioacetal aldehyde **4** could be generated from vinylogous thiol ester **3** via DIBAL reduction and subsequent MnO_2 oxidation, due to the difficulty to prepare directly from acetaldehyde in good yield. 1,2-Addition of the hydrozone enolate **5** to aldehyde **4** followed by hydrolysis afforded compound **6**. Subsequent hydrolysis of compound **6** gave an intermediate δ-keto acid **7**, which lactonized to 6-PP **2** (Scheme 5).



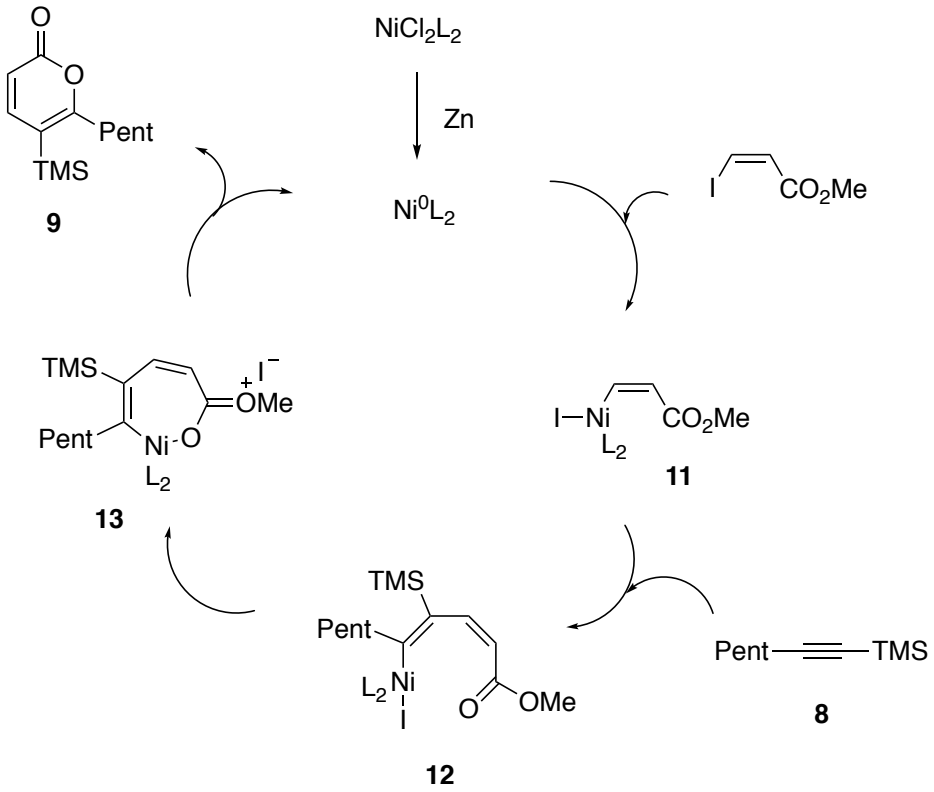
Scheme 5. Dieter synthesis of 6-PP

In 1999, Kotora and co-workers reported a halogen-dependent catalytic reaction of alkynes with halopropenoates towards 6-alkyl-2-pyrones.[22] In this paper, (Z)-3-iodopropenoate was exclusively implemented to generate 2-pyrones whereas (Z)-3-bromopropenoate afforded only cyclopentadienes. As shown in Scheme 6, 1 equivalent of (Z)-3-iodopropenoate reacted with 2 equivalents of alkyne **8** in the presence of 0.1 equivalent of the Ni-phosphine complex catalyst, 1.5 equivalent of Zn and 20 mol % of $ZnCl_2$ afforded a mixture of 5,6-disubstituted pyrone **9** and **10** in 3 to 1 ratio. Further desilylation of **9** using tetrabutylammonium fluoride gave 6-PP.



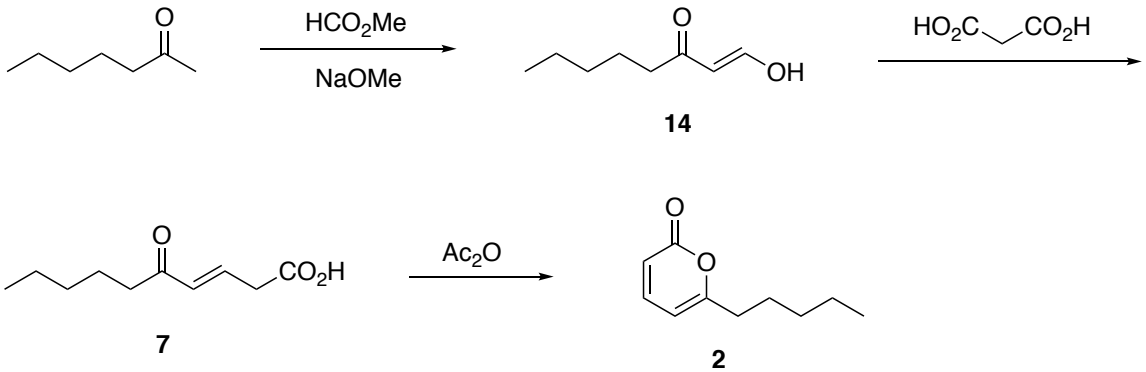
Scheme 6. Kotora synthesis of 6-PP

The mechanism was shown in Scheme 7. The Ni^0 species was formed in the first step by reduction of $NiCl_2(PPh_3)_2$ with zinc powder. Oxidative addition of (Z)-3-iodopropenoate onto Ni^0 gives vinyl nickel compound **11**. Vinylnickel **11** then adds to alkyne **8** forming **12**. Intramolecular attack to the carbonyl group by nickel forms an oxonium salt **13**, which then affords 2-pyrone **9** and methyl iodide via reductive elimination.



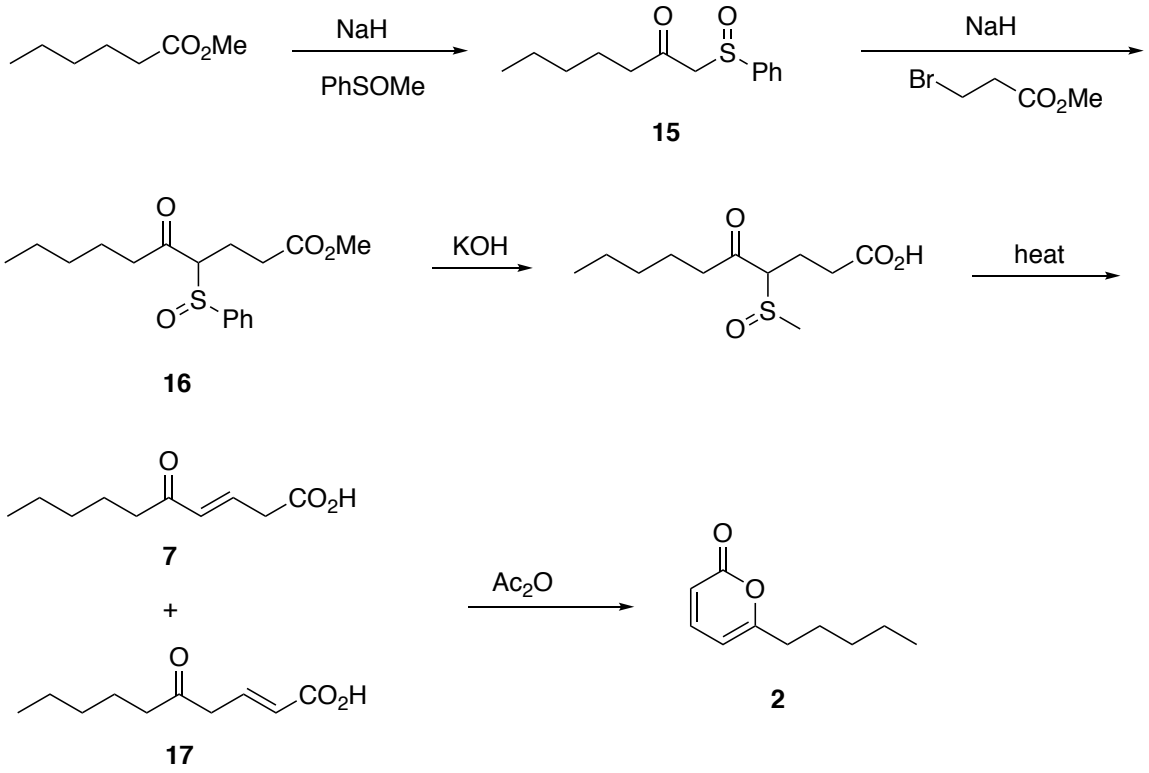
Scheme 7. Mechanism of Ni catalyzed 2-pyrone formation

In 2000, Valla and co-workers reported a general synthesis of 6-alkyl-2-pyrones.[23] As shown in Scheme 8, hydroxymethylene ketone **14** was prepared by formylation of methyl pentyl ketone. Knoevenagel condensation of **14** with malonic acid in the presence of piperidinium acetate under reflux condition yielded the ketoacid **7**, which cyclized quantitatively to the desired product 6-PP **2**.



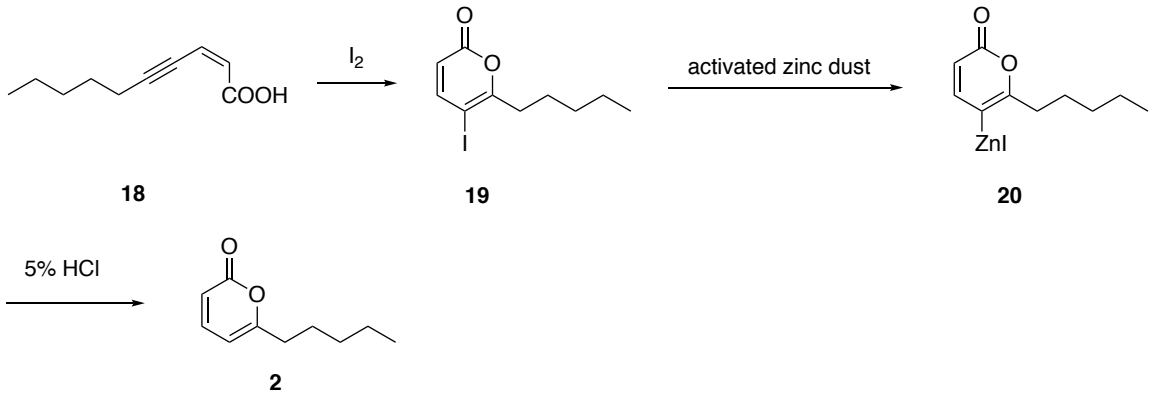
Scheme 8. Valla synthesis of 6-PP

In 2001, Andriamialisoa and co-workers reported a method for the synthesis of 6-pentyl-2-pyrone and its derivatives.[24] As shown in Scheme 9, methyl phenyl sulfoxide reacted with methyl caproate in the presence of sodium hydride to give compound **15**, which then reacted with ethyl-3-bromopropionate to generate compound **16**. The ester **16** was hydrolyzed with potassium hydroxide and the resulting acid underwent thermal elimination of the sulfoxide to provide compound **7** and **17** as a mixture. Cyclization of the crude mixture led to the desired 6-PP in almost quantitative yield. In 2004, they modified the procedure by substituting methyl phenyl sulfoxide by dimethylsulfoxide and ethyl-3-bromopropionate by methyl acrylate. The modification allowed the production of 6-PP with a lower cost and in a large scale.



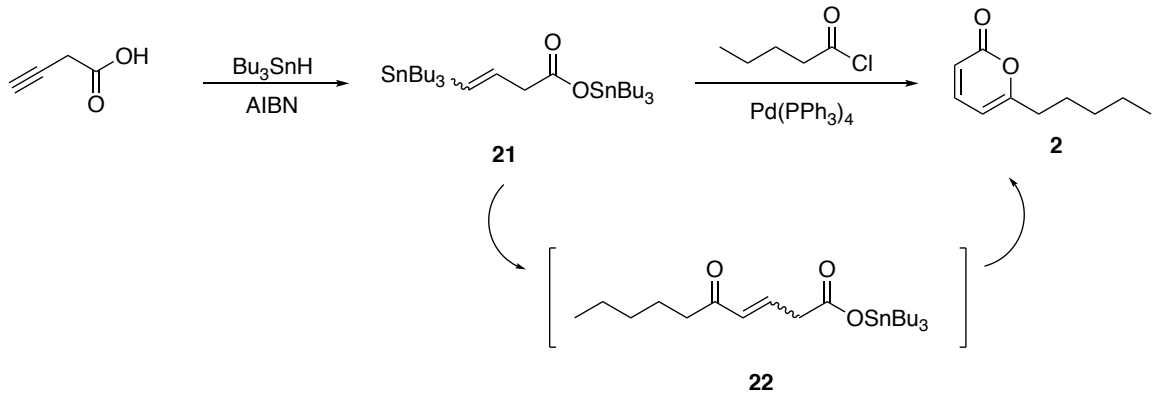
Scheme 9. Andriamialisona Synthesis of 6-PP

In 2001, Bellina and co-workers reported a method where 6-alkyl-5-iodo-2-pyrones **19** can be obtained as major products by reaction of the corresponding (Z)-2-en-4-ynoic acids **18** with iodine and $NaHCO_3$ in CH_3CN. Insertion of activated zinc metal into the carbon-iodine bond could provide the corresponding 5-(iodozinc)-2-pyrones **20**. Hydrolysis of these organometallics gives 6-substituted-2-pyrones in decent yields.[25]



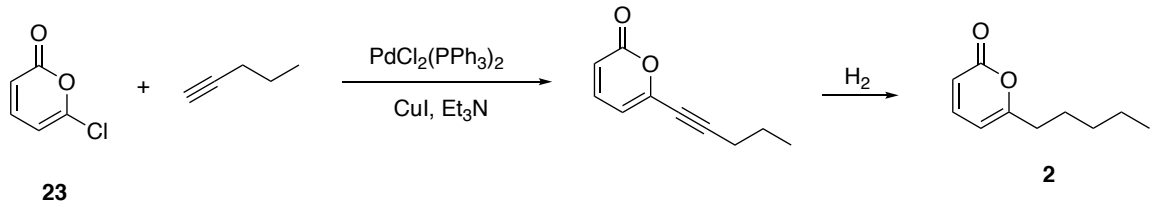
Scheme 10. Bellina synthesis of 6-PP

In 2002, Thibonnet and co-workers reported a synthesis of 6-substituted 2-pyrones where palladium-catalyzed annulation of a functional vinyltin by acyl chlorides was implemented to give the corresponding products.[26] The author demonstrated that the annulation probably proceeds through a Stille/cyclization sequence. For instance, as shown in Scheme 11, the desired vinyltin compound **21** was prepared by radical hydrostannation of 3-butynoic acid as an E/Z mixture. Stille coupling between vinyltin compound **21** and pentanoyl chloride followed by in situ cyclization ultimately generated 6-PP. Mechanistically, Stille reaction would yield the tributylstannyl 5-substituted 5-oxo-3-pentenoate intermediate **22**, the subsequent cyclization then occur through a lactonization reaction on the enol derived from **22**.



Scheme 11. Thibonnet synthesis of 6-PP

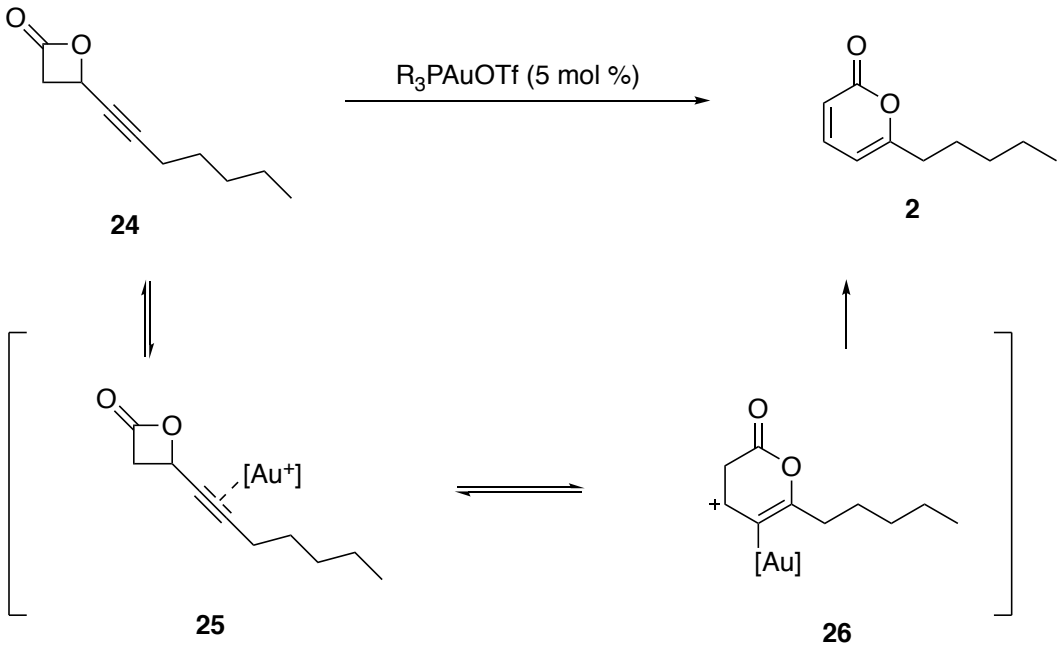
In the same year of 2002, Biagetti and co-workers reported that 6-chloro-2-pyrone **21** can undergo facile Pd/Cu-catalyzed reactions with various terminal alkynes to give rise to the corresponding 6-(1-alkynyl)-2-pyrones in moderate yield, which can be further reduced by hydrogen gas to give 6-(1-alkenyl)-2-pyrones or 6-alkyl-2-pyrones depends on different catalysts (Scheme 12).[27]



Scheme 12. Biagetti synthesis of 6-PP

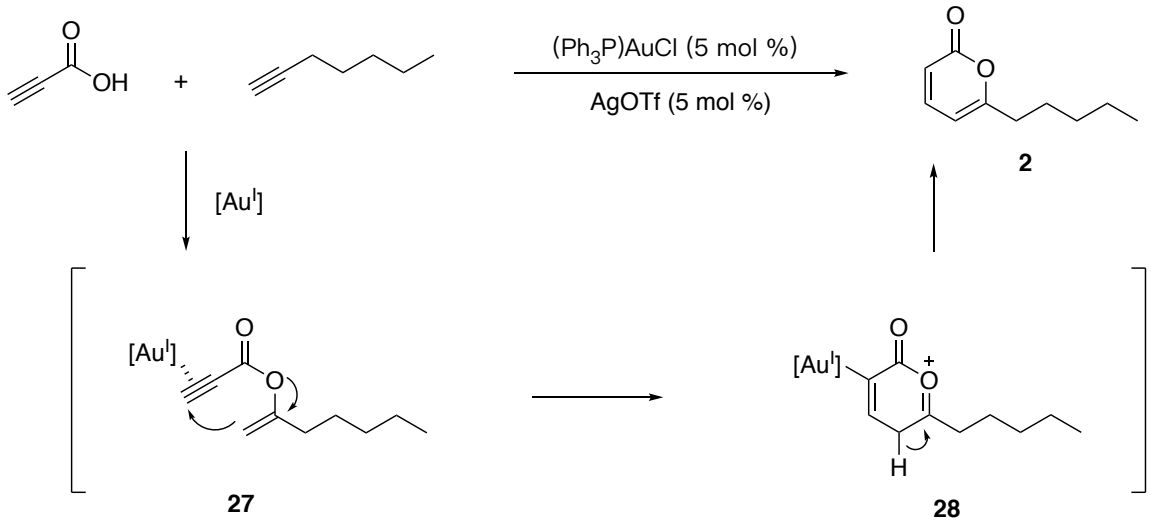
In 2010, Dombray and co-workers reported a straightforward synthesis of substituted 2-pyrones by a gold(I)-catalyzed rearrangement reaction of β-alkynylpropiolactones (Scheme 13).[28] PPh_3AuOTf and $(p\text{-}CF_3Ph)_3PAuOTf$ were determined to be the best catalysts for this rearrangement. The starting β-lactones can be prepared through the cyclocondensation of propargyl aldehydes and acyl halides using an achiral procedure. Mechanistically, Au was thought to coordinate with the triple bond to form a σ-Au complex **25**, which would lead to cationic pyrone gold intermediate **26**,

possibly via either 1,3-oxygen shift or Hashmi-type cyclization. The intermediate **26** then give rise to the desire 2-pyrone products upon proton elimination and protodeauration.



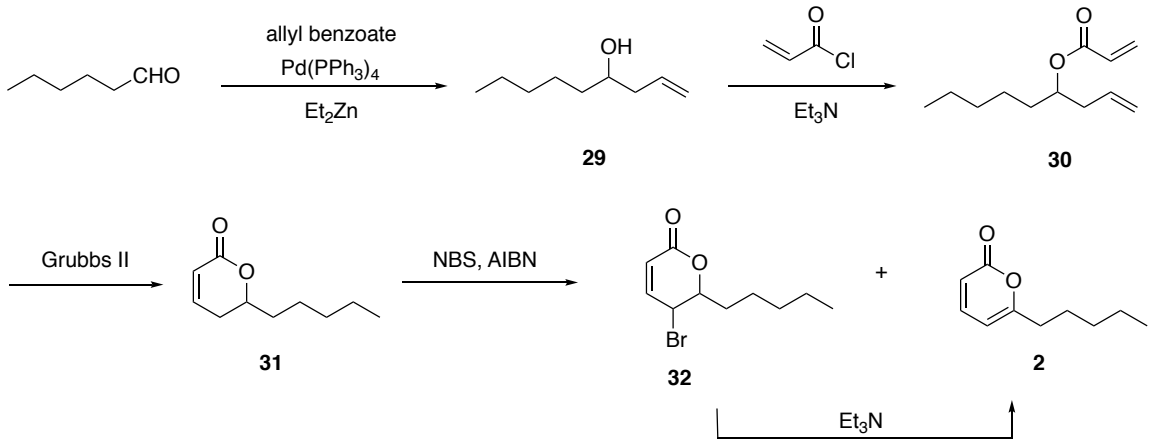
Scheme 13. Dombray synthesis of 6-PP

In 2011, Luo reported a another gold(I)-catalyzed synthesis of 2-pyrones from propiolic acids and alkynes.[29] For instance, as shown in Scheme 14, propiolic acid reacted with heptyne in the presence of 5% $(Ph_3P)AuCl$ and 5% AgOTf to generate 6-PP in 65% yield. Vinyl propiolate intermediate **27** possibly forms under the catalytic condition. The subsequent similar 6-endo cyclization afforded oxocarbenium intermediate **28**, which gave rise to 6-PP via deprotonation and proto-demetalation.



Scheme 14. Luo synthesis of 6-PP

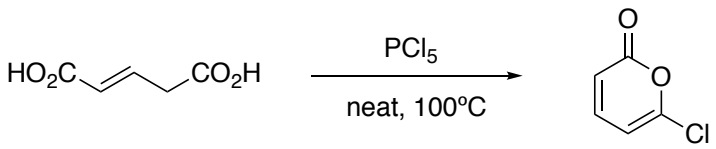
In 2013, Wickel and co-workers reported a synthetic method for 6-alkyl-2-pyrones.[30] As shown in Scheme 15, homoallyl alcohol **29** was synthesized from hexanal and allyl benzoate in the presence of diethylzinc and Pd catalyst. Treatment of **29** with acryloyl chloride in triethylamine gave acrylate ester **30**, which was further transformed into dihydropyrone **31** using the second-generation Grubbs' catalyst. Subsequent radical bromination with AIBN yielded a mixture of 6-PP and compound **30**, which can be converted into 6-PP by treating with triethylamine.



Scheme 15. Wickel synthesis of 6-PP

1.2. Results and Discussion

Since 6-PP possesses a variety of biological activities and as a continuous interest in our group on 2-pyrone chemistry, we wanted to take advantage of the 6-chloro-2-pyrone **23** to access this molecule because it is only one step away from commercially available chemical trans-glutaconic acid.[25, 27] Treatment of trans-glutaconic acid with 2 equivalents of phosphorous pentachloride at 100 °C under neat condition will produce 6-chloro-2-pyrone, which can be used in the next step without further purification but has to be stored in the freezer (Scheme 16). It is noteworthy that only trans-glutaconic acid can be used to generate the desired starting material. Cis-glutaconic acid will exclusively lead to anhydride, which cannot be converted into 6-chloro-2-pyrone by acetyl chloride, by thionyl chloride or by phosphorous pentachloride.[31]



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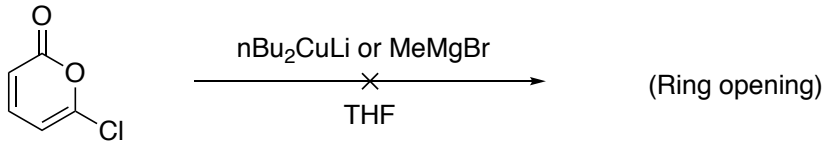
Scheme 16. Trans-glutaconic acid to 6-chloro-2-pyrone

Because of the chlorine atom on C-6, the 6-chloro-2-pyrone is actually a vinylogous acyl chloride and thereby loses its general reactivity as a simple 2-pyrone. C-6 instead of C-2 becomes the most electrophilic position. Several literature have reported that chlorine at C-6 position on some similar 2-pyrone moieties could be substituted by amines.[32-35] We firstly wanted to test if the chlorine atom can be directly substituted by organometallic nucleophiles. Although 6-chloro-2-pyrone has been reported to undergo Sonogashira reactions with a number of terminal acetylenes, there are no reports of

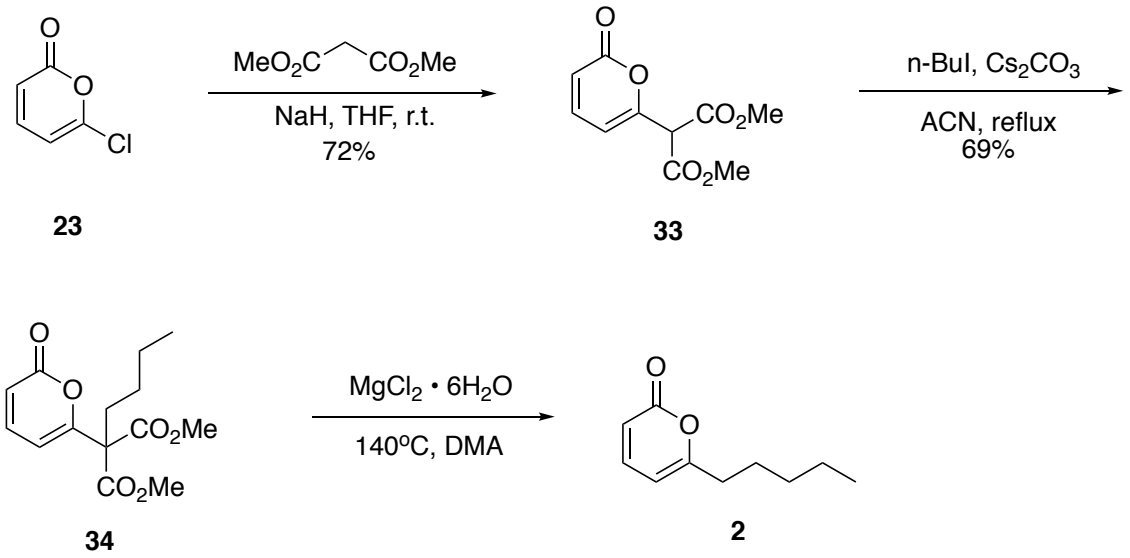
successful additions with organometallic reagents such as cuprates or Grignard reagents.[27, 33, 36]

6-chloro-2-pyrone was treated with Lithium n-butylcuptate (n-Bu_2CuLi) from -78°C to room temperature, no desired product was observed. Instead, crude ^1H NMR might indicate decomposition of starting material. Methyl magnesium bromide also caused ring opening (Scheme 17).



Scheme 17. Reactions between 6-Cl-2-pyrone and organometallics

Reports of nucleophilic substitutions of the chlorine atom on C-6 are rare. Stoltz had reported that nucleophilic substitution of the chlorine in 6-chloro-2-pyrone with dimethyl malonate afforded diester **33** in good yield.[37] Based on this precedent, we were able to obtain pyrone-diester **33** in 72% yield. For the following step, while the use of NaH in THF led to recovered starting material, the use of cesium carbonate in boiling acetonitrile afforded **34** in 69% isolated yield. Probably because of THF is not polar enough for this specific S_N2 substitution. The reaction of **34** under standard Krapcho dealkoxycarbonylation protocol (NaCl, DMSO) led to the recovery of reactant. However, the reaction of **34** in the presence of magnesium chloride hexahydrate in dimethylacetamide (DMA) at 140°C produced 6-PP in 82% yield (Scheme 18).[38]

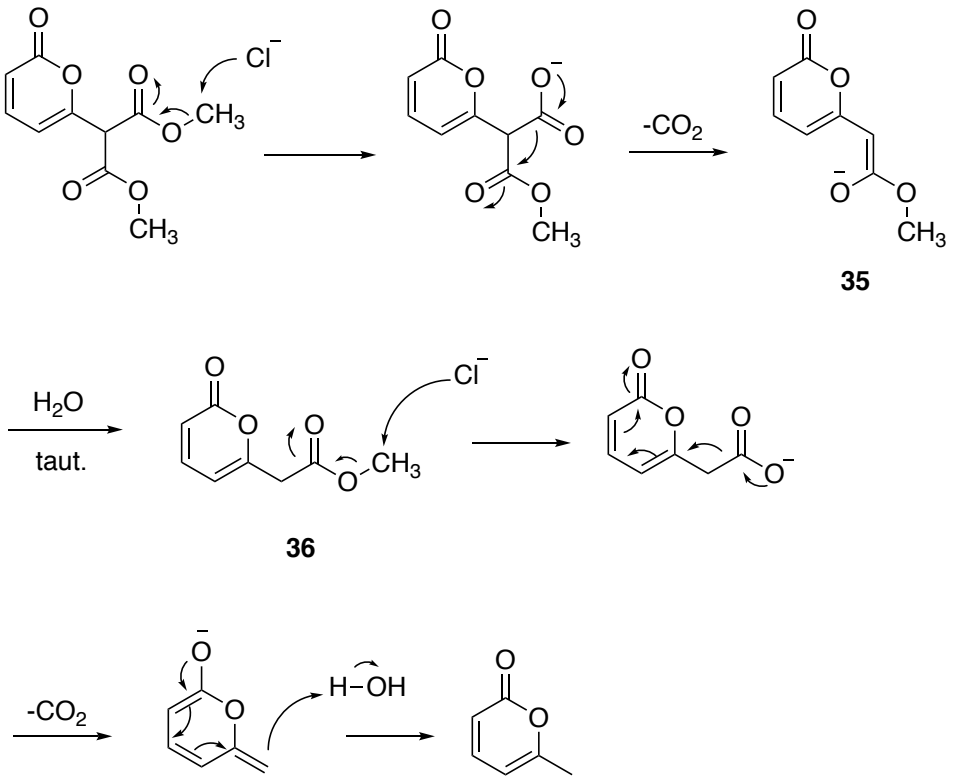


Scheme 18. Synthesis of 6-PP

Esters bearing an electron-withdrawing group at the α-position are important synthetic building blocks for a wide range of reactions like alkylation or conjugated addition reactions. Once the ester part has finished its function in the course of a synthesis, sometimes it needs to be removed, i.e. the ester group needs to be replaced by a proton. Usually the Krapcho dealkoxycarbonylation reaction is the most common and reliable method for accomplishing this conversion in one pot.

Malonates can also be considered as an activated ester and normally, S_N2 type dealkoxycarbonylations of malonates can only afford the monoester/acid. However, in our case, the two esters can be removed in one pot. Mechanistically, as shown in Scheme 19, we think the first dealkoxycarbonylation simply went through the classic Krapcho mechanism, in which the halogen ion attacks the alkyl carbon according to a S_N2-type nucleophilic substitution followed by decarboxylation yields an anionic intermediate **35**, which is protonated by water to generate the monoester **36**. For the second dealkoxycarbonylation step, the anionic intermediate formed after decarboxylation can be stabilized by the conjugated remote carbonyl group on the pyrone ring, which

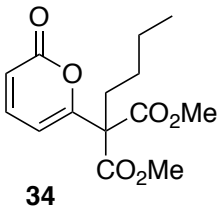
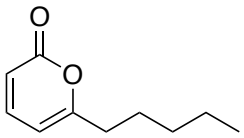
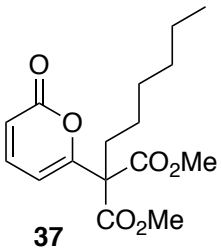
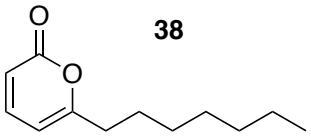
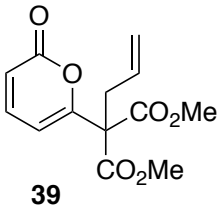
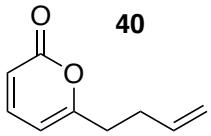
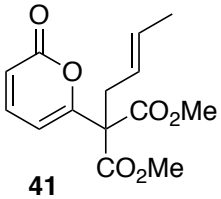
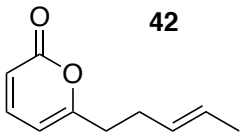
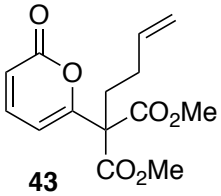
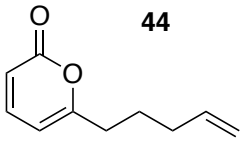
rationalized the reaction. The magnesium ion can form a six-membered transition-state intermediate with oxygen-1 on the pyrone ring and the carbonyl oxygen atom from the monoester, and this might be the reason why magnesium salt can finish the dealkoxycarbonylation while the sodium salt cannot.



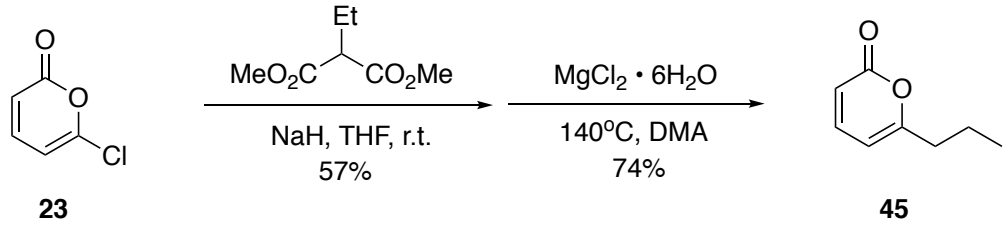
Scheme 19. Mechanism for double dealkoxycarnylation

With the synthetic route established, we reacted diester **33** with several other alkyl halides and the results were summarized in Table 1.

Table 1. Synthesized 6-alkyl-2-pyrones

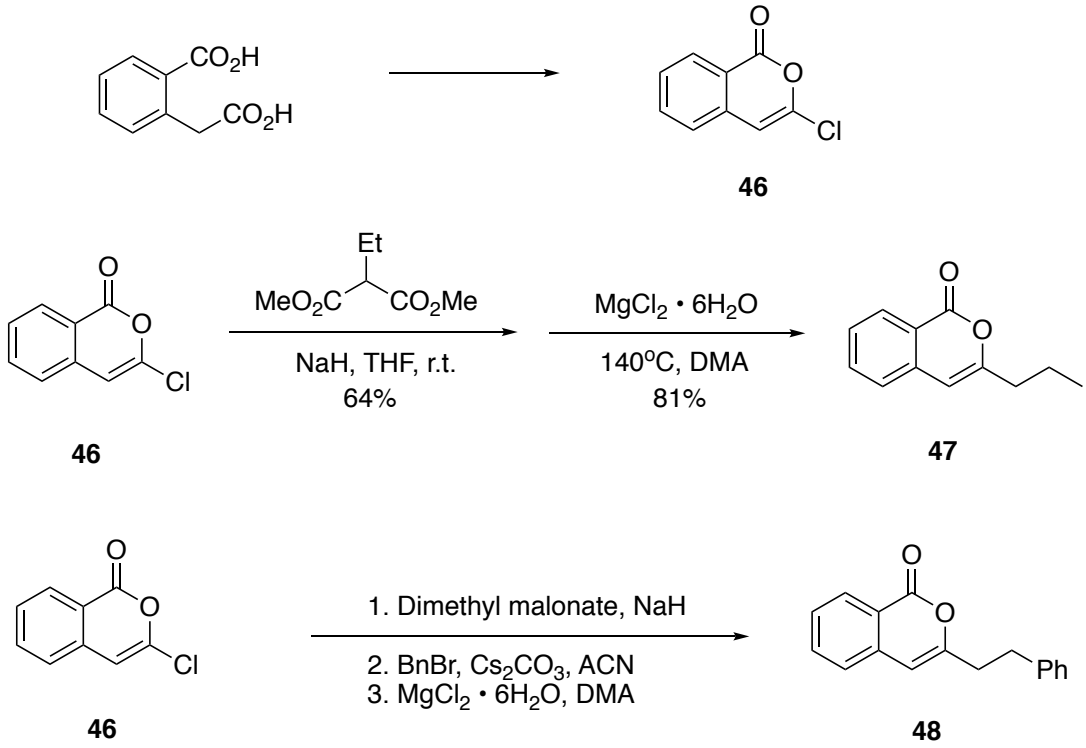
Entry	Alkyl halides	Intermediates	Products	Yields
1	1-iodobutane	 **34**	 **2**	57%
2	1-iodohexane	 **37**	 **38**	58%
3	allyl bromide	 **39**	 **40**	45%
4	crotyl bromide	 **41**	 **42**	51%
5	4-bromo-1-butene	 **43**	 **44**	61%

In addition, 6-Cl-2-pyrone can also directly react with alkyl malonates. Double dealkoxycarbonylation then affords pyrone **45** in 43% overall yield. In practice, the crude adduct can be taken directly on to the next dealkoxycarbonylation step without further purification.



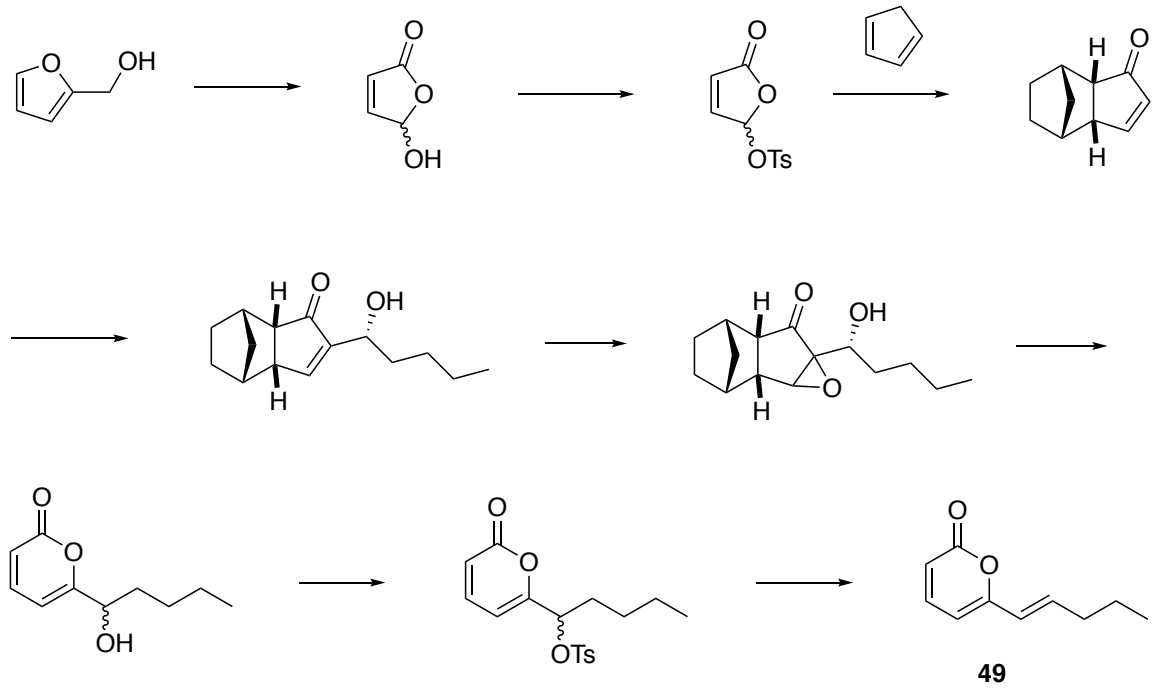
Scheme 20. 6-Cl-2-pyrone directly reacts with alkyl malonate

To expand the reaction scope, 3-chloro isocoumarin **46** was synthesized by treating homophthalic acid with phosphorous oxychloride under neat condition. This compound has been studied in palladium mediated coupling reactions such as the Sonogashira and Suzuki reactions.[39-41] Using the same protocol in Scheme 18, 3-substituted isocoumarins **47** and **48** were synthesized in 52% and 57% yields, respectively (Scheme 21).



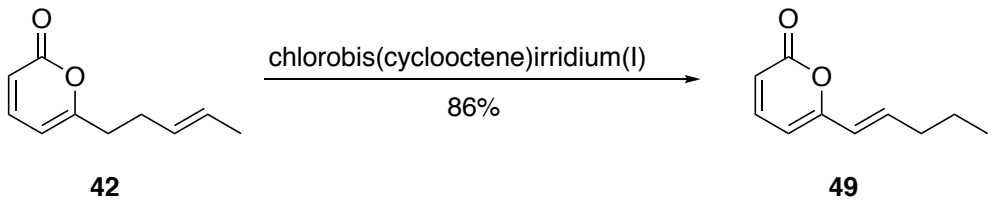
Scheme 21. Synthesis of 3-alkyl isocoumarin

To demonstrate a broader application of this methodology, we synthesized another two natural products using the described protocol as the key step. 6-pentenyl-2-pyrone **49** was isolated as a metabolite from a strain of *Tricoderma viride* and it has been identified as a queen pheromone of the red fire ant, *Solenopsis invicta* and of male mandibular gland secretions of ants of the genus *Camponotus*.[1, 3] 6-Alkenyl-2-pyrones can be synthesized by Sonogashira coupling reactions between 6-chloro-2-pyrone and terminal alkynes, however, terminal alkynes are not as common as alkyl halides. Another way to access this class of compounds can be accomplished by installing a leaving group at C-7 (the carbon adjacent to C-6) followed by elimination reaction, however, installation of a leaving group on this specific carbon is not easy and also, this route needs access to 6-alkyl-2-pyrones even before the leaving group been installed.[42] In 2016, Dobler and Reiser reported a new methodology to this class of compounds (Scheme 22).[43] In their strategy, 6-alkenyl-2-pyrones were synthesized from furfuryl alcohol utilizing a thermal rearrangement of cyclopentadienone epoxides as key step. However, this pathway was synthetically inconvenient suffering from long steps and high temperature requirement.



Scheme 22. Dobler synthesis of 6-pentenyl-2-pyrone.

Taking advantage of the alkene isomerization reaction followed by our protocol, we successfully accomplished the synthesis of 6-pentenyl-2-pyrone. Treatment of the previously synthesized compound **42** with chlorobis(cyclooctene)iridium(I) catalyst in toluene at 85 °C, the double bond migrated towards the pyrone ring to form the most stable conjugated structure **49** as shown in Scheme 23.

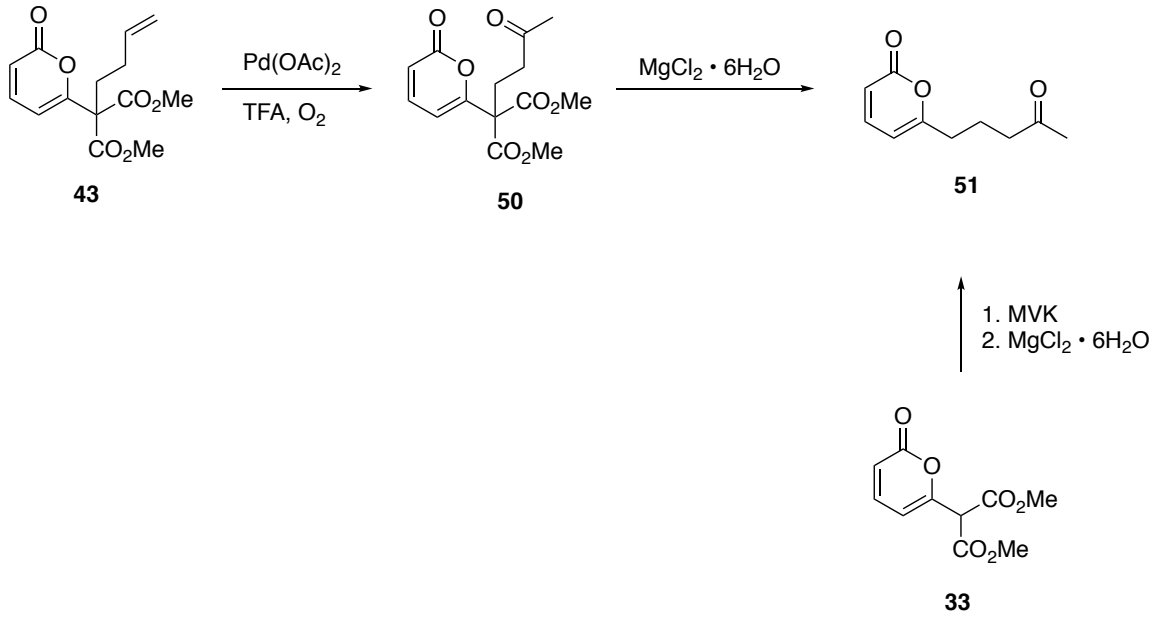


Scheme 23. Synthesis of 6-pentenyl-2-pyrone.

6-(4-Oxopentyl)-2-pyrone, or viridepyranone **51** was another 6-alkyl-2-pyrone analogue isolated from the cultural filtrate of *Tricoderma viride* in 2003 by Evidente.[44] This compound showed antagonistic activity *in vitro* toward *Sclerotium rolfsii*, which is

the causal agent of crown and term rot of artichoke. Bioassays indicated good antifungal activity against *S. rolfsii* at its minimum inhibitory concentration (over 90% inhibition) at 196 µg/mL. It also showed excellent antifungal activity against several different soil-borne pathogenic fungi. The antifungal activity of this compound was even comparable to commercial fungicide Hexaconazole.

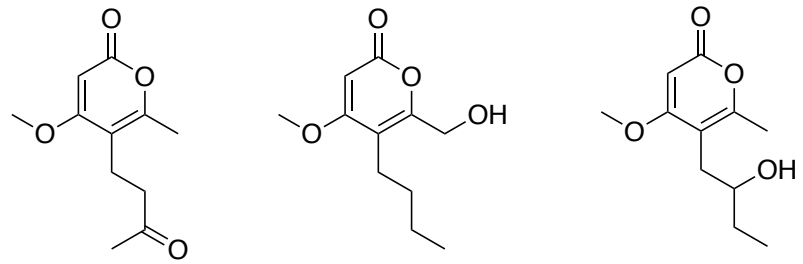
Pyrone **43** was readily prepared from the reaction of **33** with cesium carbonate and 4-bromo-1-butene. Palladium catalyzed Wacker oxidation using oxygen gas followed by double dealkoxycarbonylation afforded viridepyranone in 48% overall yield.[45] Alternatively, reaction of **33** with methyl vinyl ketone and cesium carbonate generated the same intermediate ready for double dealkoxycarbonylation, viridepyronone can be generated in 38% overall yield by this route (Scheme 24).



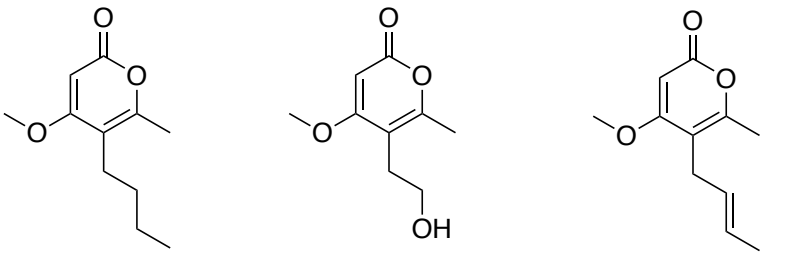
Scheme 24. Synthesis of viridepyronone

After the synthesis of 6-alkyl-2-pyrones, we became interested in another 2-pyrone containing natural product, 4-methoxy-6-methyl-5-(3-oxobutyl)-2-pyrone **52**. It was isolated in 2014 with five other 2-pyrones **53 – 57** from *Alternaria phragmospora*,

an endophytic fungus from *Vinca rosea* leaves (Figure 4). Endophytic fungi can be considered as an unexplored region for novel and bio-avtive secondary metabolites. The genus *Alternaria* was established in 1817, and contains 44 different species. Over 268 metabolites from different species of *Alternaria* have been reported in the past few decades. The isolated metabolites showed a variety of biological activities such as antitumor, herbicide, antimalarial and antimicrobial. This compound **52** showed moderate antileukemic activities against HL60 and K562 cells with IC_{50} values of 0.9uM and 1.5 μM, respectively.[46] Pyrone **52** bears a substituent at the C-5 position and no substituent at the C-3 position. This substitution pattern is rare among pyrone natural products.



52 **53** **54**

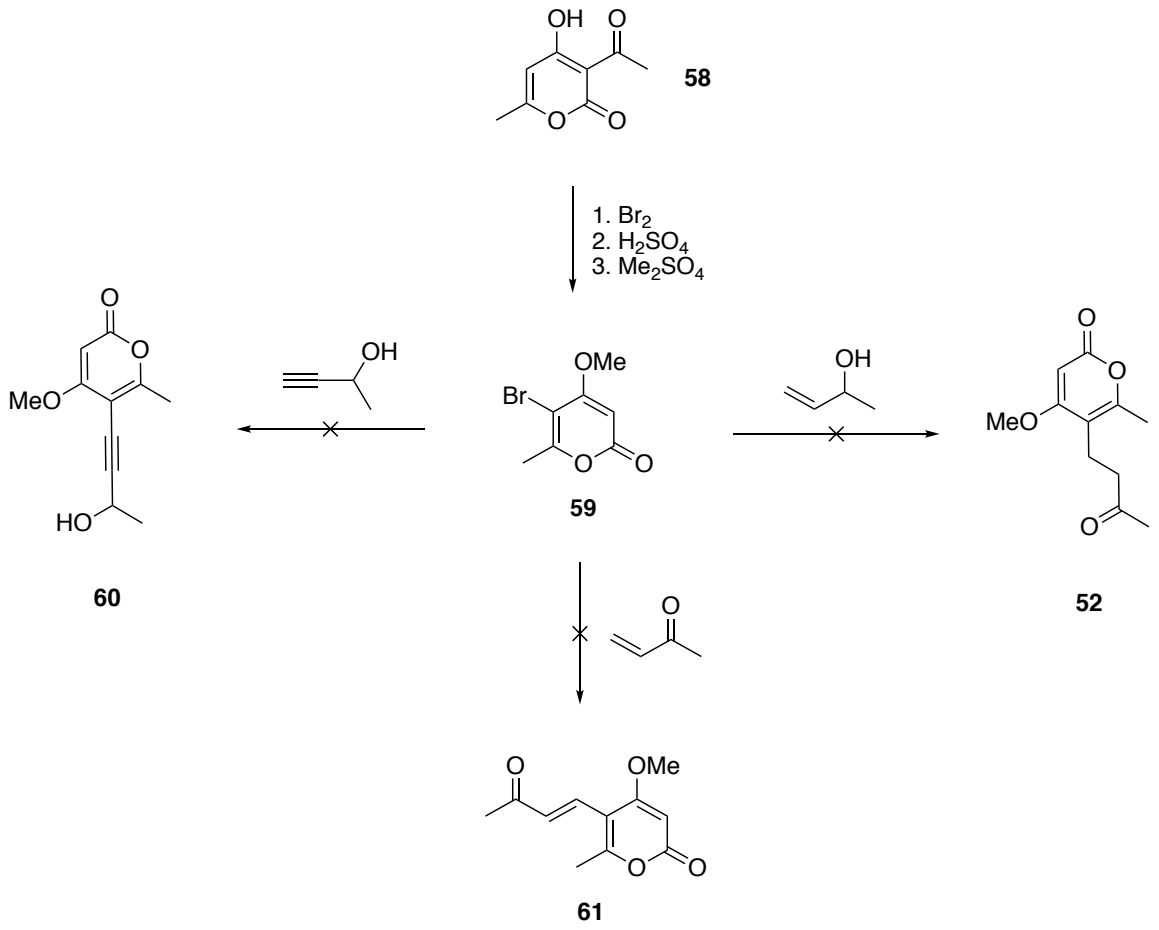


55 **56** **57**

Figure 4. Compounds isolated from *Alterniria phragmospora*

Initially, we wanted to take advantage of the bromopyrone **59**, which can be obtained from commercially available dehydroacetic acid **58** in three steps. With this vinyl bromide compound at hand, we expected to utilize palladium catalyzed coupling reactions to produce **52**, **60** or **61**. Unfortunately, neither the Heck reaction with methyl

vinyl ketone or 1-buten-3-ol nor the Sonogashira reaction with 3-butyn-2-ol afforded the desired product (Scheme 25). Either returned starting material or debromonated products were obtained.

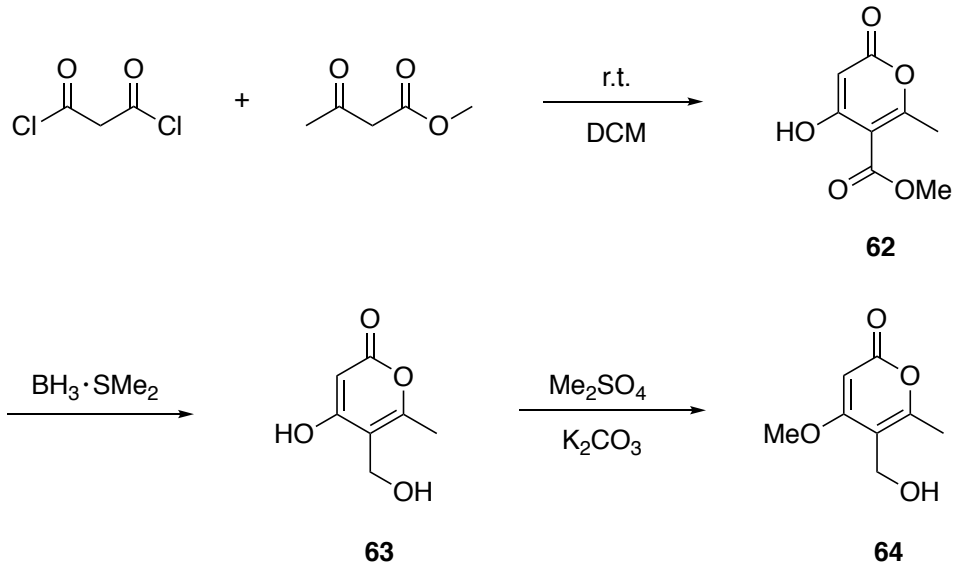


Scheme 25. Attempted coupling reaction of 46.

Coupling reactions of halogenated 2-pyrones have been intensively studied for the past decades. For instance, Sonogashira coupling, Suzuki coupling, Heck coupling and Negishi coupling of 3-, 4-, 6-halogen-2-pyrones have been reported.[47-49] However, 5-halo-2-pyrones are the least active analogue that have only been reported to react with a few aryl/vinyl boronic acids under Suzuki coupling conditions.[48] Steric hindrance might played the key role to decrease the reactivity. For our designed synthetic route,

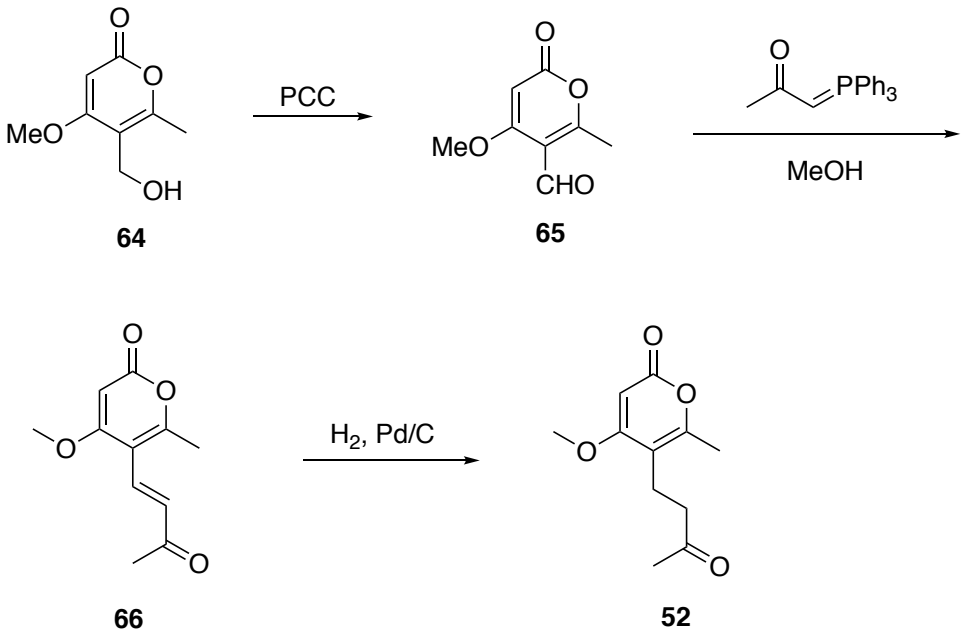
synthesizing the corresponding boronic acid would increase the steps of synthesis, and therefore decrease the efficiency.

Because of the unexpected recalcitrance of **59**, we devised a new approach shown in Scheme 26 focusing on pyrone **62**, readily available from methyl acetoacetate and malonyl chloride. Selective reduction of the ester in pyrone **62** was difficult. Lithium aluminum hydride undoubtedly caused the ring opening; DIBAL-H and sodium borohydride were not effective for this specific reduction. Fortunately, borane-dimethyl sulfide (DMS) complex could selectively reduce esters in the presence of the pyrone lactone, which enabled the selective reduction of **62** in 96% yield.[50] Methylation using dimethyl sulfate provided pyrone **64** in 84% yield. It is noteworthy that methylation prior to DMS reduction will lead to no reaction of the reduction step, suggesting an intramolecular reduction mechanism.



Scheme 26. Synthesis of 51.

Oxidation of **64** using pyridinium chlorochromate (PCC) followed by Wittig reaction using AcCH=PPh_3 led to enone **66** in 92 × 85% yield. This enone could be reduced to **52** using hydrogen gas with Pd/C catalyst in 89% yield.



Scheme 27. Synthesis of antileukemic 2-pyrone 52.

1.3. Conclusion

This chapter contains two projects related to the synthesis of 2-pyrone related compounds. For the first project, we devised a flexible route to the class of 6-alkyl-2-pyrones. The synthetic route commenced from commercially available trans-glutaconic acid and took four steps in total to the desired final products. This synthetic route may not be the most efficient one in terms of steps, but it provides a strategic way to access several products in the same family. Two another 2-pyrone containing natural products were also synthesized using our methodology as the key step. In the second project, an antileukemic 2-pyrone compound was synthesized for the first time. The synthesis started from common chemicals malonyl chloride and ethyl acetoacetate. The straightforward

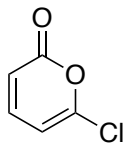
six–step synthesis gave the desired bioactive product in good yield. This is the first synthesis of pyrone **52.**

1.4. Experimental

General Procedures

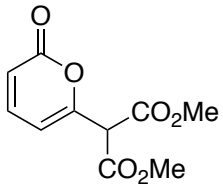
All starting materials were purchased from Sigma-Aldrich; Tetrahydrofuran (THF) was freshly distilled over lithium aluminum hydride and other solvents were purchased from Fisher Scientific and used without further purification. All reactions were carried out in flame-dried glassware under argon with dry solvents under anhydrous conditions. All yields refer to chromatographically isolated products. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.20 mm silica gel plates using UV light as a visualizing agent. Silica gel 60A, particle size 0.032 – 0.063 mm, was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 1.00 mm silica gel plates. ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ on a Varian MR-400 or Bruker Avance III 600 MHz spectrometer. ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to the residual protonated chloroform peak ($CDCl_3$: δH = 7.26 ppm, δC = 77.0 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).

Selected Experimental, Physical, and Spectral Data



6-Chloro-2H-pyran-2-one (23):

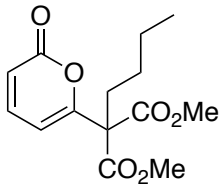
Phosphorus pentachloride (7.86 g, 37.73 mmol) was added to trans-glutaconic acid (techn. 90%, 2.45 g, 18.69 mmol) cooled in an ice bath. The mixture was heated to 100 °C for 10 min, and then cooled to 0 °C. The resulting dark liquid was poured into ice-cooled water (50 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The organic extract was washed with cold aqueous $NaHCO_3$ solution (10%, 3 × 40 mL), dried over anhydrous Na_2SO_4, decolorized with charcoal and concentrated under reduced pressure. The residue was used for next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (dd, J = 9.4, 6.9 Hz, 1H), 6.24 (dd, J = 7.8, 0.8 Hz, 1H), 6.22 (dd, J = 5.2, 0.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.4, 150.0, 144.2, 113.0, 104.1 ppm.



Dimethyl 2-(2-oxo-2H-pyran-6-yl) malonate (33):

To a suspension of sodium hydride (60% in mineral oil, 399 mg, 16.6 mmol, 1.9 equiv.) in THF (50 mL) at 0 °C was added dimethyl malonate (2 mL, 17.5 mmol, 2 equiv.) over 5 minutes. The mixture was warmed to room temperature and stirred for 20 minutes. The solutions was then cooled to 0 °C, and a solution of 6-chloro-2-pyrone (1.1 g, 8.8 mmol, 1 equiv.) in THF (5 mL) was added dropwise over 5 minutes. The reaction was allowed to come to room temperature, and then stirred for two hours. The reaction mixture was acidified to pH 5 by the addition of 2M HCl (aq.). Water was then added (50 mL), and the reaction mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic

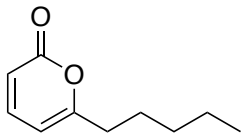
extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was chromatographed (0 - 50% ethyl acetate in petroleum ether on SiO_2) to yield **33** as a yellow oil (1.7 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (dd, J = 9.4, 6.6 Hz, 1H), 6.36 (dd, 1H), 6.30 (dd, 1H), 4.55 (s, 1H), 3.82 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.2, 161.1, 155.4, 142.9, 115.8, 105.6, 56.0, 53.5; HRMS (ESI-QTOF) calcd for $C_{10}H_{10}O_6$ $[M + H]^+$ 227.0550, found 227.0545.



Dimethyl 2-butyl-2-(2-oxo-2H-pyran-6-yl)malonate (34):

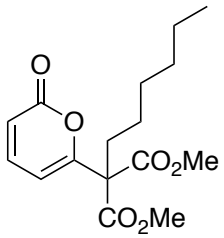
To an ice cold mixture of acetonitrile (3 mL) and Cs_2CO_3 (157.7 mg, 0.48 mmol, 1.1 equiv.) was added a solution of **33** (100.0 mg, 0.44 mmol, 1 equiv.) in acetonitrile (0.5 mL). The reaction was brought to room temperature and stirred for 10 minutes, then cooled to 0 °C. A solution of 1-iodobutane (97.5 mg, 0.53 mmol, 1.2 equiv.) in acetonitrile (0.5 mL) was then added over 5 minutes. The reaction was allowed to warm to room temperature, then brought to reflux and stirred for 14 hours. The reaction was then cooled to room temperature and diluted with saturated NH_4Cl (aq.) (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. The crude oil was chromatographed (0 - 50% ethyl acetate in petroleum ether on SiO_2) to yield **34** as a yellow oil (85.6 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 9.4, 6.8 Hz, 1H), 6.63 (dd, J = 6.8, 0.9 Hz, 1H), 6.25 (dd, J = 9.4, 0.9 Hz, 1H), 3.78 (s, 6H), 2.25 (m, 2H),

1.32 (m, 2H), 1.24(m, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 161.2, 159.4, 143.0, 115.1, 105.2, 62.4, 53.2, 33.8, 26.7, 22.7, 13.8; HRMS (ESI-QTOF) calcd for $C_{14}H_{18}O_6$ $[M + H]^+$ 283.1176, found 283.1177.



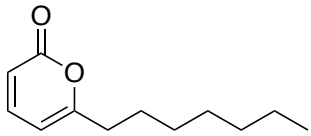
6-Pentyl-2H-pyran-2-one (2):

A mixture of **34** (79.0 mg, 0.28 mmol) and magnesium chloride hexahydrate (114 mg, 0.56 mmol) in DMA (2 mL) was heated at 140 °C (monitored by TLC). The mixture was partitioned between Et_2O (20 mL) and H_2O (20 mL), the Et_2O was dried over anhydrous Na_2SO_4 and concentrated to afford the residue which was chromatographically purified on silica gel to afford the pure product 1 as a yellow oil (38 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, J = 6.1, 3.3 Hz, 1H), 6.17 (dd, J = 9.4, 0.9 Hz, 2H), 5.99 (dd, J = 6.6, 0.8 Hz, 2H), 2.50 (t, J = 7.7 Hz, 3H), 1.73 – 1.63 (m, 2H), 1.40 – 1.29 (m, 4H), 0.93 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 163.0, 143.7, 113.0, 113.0, 102.6, 102.6, 33.8, 31.1, 26.5, 22.3, 13.9; HRMS (ESI-QTOF) calcd for $C_{10}H_{14}O_2$ $[M + H]^+$ 167.1067, found 167.1063.



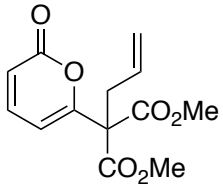
Dimethyl 2-hexyl-2-(2-oxo-2H-pyran-6-yl)malonate (37):

Compound **37** was prepared by using previous described procedure for compound **34** in 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 9.4, 6.8 Hz, 1H), 6.63 (dd, J = 6.8, 0.9 Hz, 1H), 6.25 (dd, J = 9.4, 0.9 Hz, 1H), 3.78 (s, 6H), 2.29 – 2.19 (m, 2H), 1.35 – 1.17 (m, 8H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 161.2, 159.4, 143.0, 115.1, 105.2, 62.4, 53.3, 34.1, 31.4, 29.2, 24.5, 22.5, 14.0; HRMS (ESI-QTOF) calcd for $C_{16}H_{22}O_6$ $[M + H]^+$ 311.1489, found 311.1494.



6-Heptyl-2H-pyran-2-one (38):

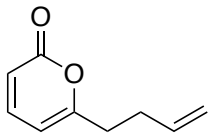
Compound 10 was prepared by using previous described procedure for compound **2** in 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.25 (dd, J = 9.4, 6.6 Hz, 1H), 6.15 (d, J = 9.3 Hz, 1H), 5.96 (d, J = 6.5 Hz, 1H), 2.47 (t, J = 7.7 Hz, 2H), 1.70 – 1.59 (m, 2H), 1.39 – 1.21 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 162.9, 143.7, 113.1, 102.6, 33.8, 31.6, 28.92, 28.89, 26.8, 22.6, 14.0; HRMS (ESI-QTOF) calcd for $C_{12}H_{18}O_2$ $[M + H]^+$ 195.1380, found 195.1381.



Dimethyl 2-allyl-2-(2-oxo-2H-pyran-6-yl)malonate (39):

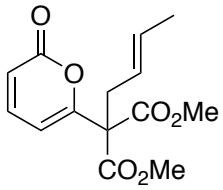
Compound **39** was prepared by using previous described procedure for compound **34** in 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J = 9.4, 6.8 Hz, 1H), 6.56 (dd, J = 6.8,

0.9 Hz, 1H), 6.24 (dd, J = 9.4, 0.9 Hz, 1H), 5.80 – 5.70 (m, 1H), 5.17 – 5.05 (m, 2H), 3.79 (s, 6H), 3.02 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 161.1, 158.8, 142.9, 131.6, 119.9, 115.2, 105.3, 62.6, 53.4, 38.6; HRMS (ESI-QTOF) calcd for $C_{13}H_{14}O_6$ $[M + H]^+$ 267.0863, found 267.0862.



6-(But-3-en-1-yl)-2H-pyran-2-one (40):

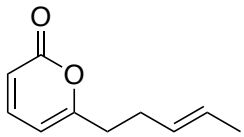
Compound **40** was prepared by using previous described procedure for compound **2** in 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 9.4, 6.6 Hz, 1H), 6.15 (dd, J = 9.4, 0.8, 1H), 5.98 (dd, J = 6.6, 0.9 Hz, 1H), 5.84 – 5.72 (m, 1H), 5.11 – 4.99 (m, 2H), 2.58 (t, J = 7.4 Hz, 2H), 2.46 – 2.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 162.7, 143.6, 136.1, 116.2, 113.3, 102.9, 33.1, 30.7; HRMS (ESI-QTOF) calcd for $C_9H_{10}O_2$ $[M + H]^+$ 151.0754, found 151.0751.



Dimethyl (E)-2-(but-2-en-1-yl)-2-(2-oxo-2H-pyran-6-yl)malonate (41):

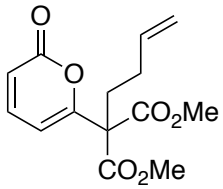
Compound **41** was prepared by using previous described procedure for compound **34** in 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, J = 9.4, 6.8 Hz, 1H), 6.56 (dd, J = 6.8, 0.9 Hz, 1H), 6.21 (d, J = 9.4 Hz, 1H), 5.63 – 5.45 (m, 1H), 5.39 – 5.23 (m, 1H), 3.76 (s, 6H), 2.92 (d, J = 7.2 Hz, 2H), 1.59 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

167.5, 161.1, 159.1, 143.0, 130.8, 123.8, 115.0, 105.3, 62.8, 53.2, 37.6, 18.0; HRMS (ESI-QTOF) calcd for $C_{14}H_{16}O_6$ $[M + H]^+$ 281.1020, found 281.1018.



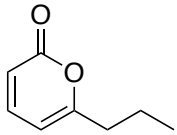
(E)-6-(pent-3-en-1-yl)-2H-pyran-2-one (42):

Compound **42** was prepared by using previous described procedure for compound **2** in 73% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 9.4, 6.6 Hz, 1H), 6.15 (dd, J= 9.4, 0.9 Hz, 1H), 5.96 (dd, J = 6.8, 0.6 Hz, 1H), 5.54 – 5.43 (m, 1H), 5.42 – 5.30 (m, 1H), 2.53 (t, J = 7.6 Hz, 2H), 2.37 – 2.30 (m, 2H), 1.64 (dd, J = 6.2, 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 162.8, 143.6, 128.6, 126.8, 113.2, 102.8, 33.9, 29.8, 17.9; HRMS (ESI-QTOF) calcd for $C_{10}H_{12}O_2$ $[M + H]^+$ 165.0910, found 165.0909.



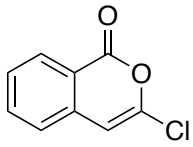
Dimethyl 2-(but-3-en-1-yl)-2-(2-oxo-2H-pyran-6-yl)malonate (43):

Compound **43** was prepared by using previous described procedure for compound **34** in 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, J = 9.4, 6.8 Hz, 1H), 6.63 (dd, J = 6.8, 0.9 Hz, 1H), 6.25 (dd, J = 9.4, 0.9 Hz, 1H), 5.77 – 5.68 (m, 1H), 5.07 – 4.93 (m, 2H), 3.79 (s, 6H), 2.38 – 2.34 (m, 2H), 2.10 – 2.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 161.1, 159.1, 143.0, 136.6, 115.6, 115.2, 105.3, 62.0, 53.3, 33.2, 28.8. HRMS (ESI-QTOF) calcd for $C_{14}H_{16}O_6$ $[M + H]^+$ 281.1020, found 281.1024.



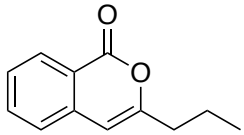
6-Propyl-2H-pyran-2-one (45):

Compound **45** was prepared by using previous described procedure for compound **2** in 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 9.4, 6.5 Hz, 1H), 6.15 (d, J = 9.4 Hz, 1H), 5.97 (dd, J = 6.6, 0.9 Hz, 1H), 2.46 (t, J = 7.5 Hz, 2H), 1.74 – 1.66 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 162.9, 143.7, 113.1, 102.7, 35.7, 20.2, 13.4; HRMS (ESI-QTOF) calcd for $C_8H_{10}O_2$ $[M + H]^+$ 139.0754, found 139.0753.



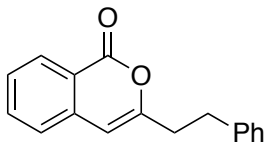
3-chloro-1H-isochromen-1-one (46):

A mixture of homophthalic acid (3.0 g, 16.6 mmol) and phosphorus(V) oxychloride (6.4 g, 42 mmol) is taken in an round-bottom flask. The reaction mixture was stirred at 85 °C for 3 hours and monitored for the completion of the reaction and then was quenched with crushed ice. The contents were left aside for complete precipitation of the crude desired products. The mixture was then filtered through a Buchner funnel and the residue after drying was purified on a silica gel column using hexane/ethyl acetate as eluent to afford **46** (390 mg, 13%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.0 Hz, 1H), 7.66 (td, J = 7.9, 1.2 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.31 (d, J = 7.9 Hz, 1H), 6.46 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 142.8, 137.2, 135.4, 130.1, 128.5, 125.1, 119.4, 104.6 (d, J = 6.6 Hz). HRMS (ESI-QTOF) calcd for $C_9H_5ClO_2$ $[M + H]^+$ 181.0051, found 181.0048.



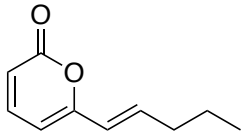
3-Propyl-1H-isochromen-1-one (47):

Compound **47** was prepared by using previous described procedure for compound **2** in 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dt, J= 8.0, 0.6 Hz, 1H), 7.66 (ddd, J = 7.9, 7.3, 1.4 Hz, 1H), 7.44 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 6.25 (s, 1H), 2.50 (t, J = 7.5 Hz, 2H), 1.78 – 1.68 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 158.0, 137.6, 134.7, 129.4, 127.5, 125.0, 120.1, 102.9, 35.4, 20.2, 13.5; HRMS (ESI-QTOF) calcd for $C_{12}H_{12}O_2$ $[M + H]^+$ 189.0910, found 189.0908.



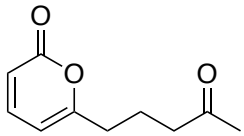
3-Phenethyl-1H-isochromen-1-one (48):

Compound **48** was prepared by using previous described procedure for compound **2** in 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, J = 7.9, 1.3 Hz, 1H), 7.70 (td, J = 7.6, 1.3 Hz, 1H), 7.50 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H), 7.39 – 7.28 (m, 3H), 7.32 – 7.20 (m, 2H), 6.21 (s, 1H), 3.08 (t, J =8 Hz, 2H), 2.88 (t, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 156.9, 140.3, 137.4, 134.7, 129.5, 128.5, 128.3, 127.7, 126.3, 125.1, 120.1, 103.5, 35.5, 33.2; HRMS (ESI-QTOF) calcd for $C_{17}H_{14}O_2$ $[M + H]^+$ 251.1067, found 251.1069.



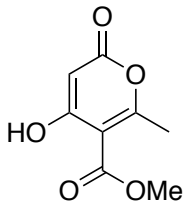
(E)-6-(pent-1-en-1-yl)-2H-pyran-2-one (49):

To a solution of $[Ir(COE)_2Cl]_2$ (27.8 mg, 0.031 mmol) in toluene (2 mL) were added **42** (50.2 mg, 0.31 mmol) and AgO_2CCF_3 (13.7 mg, 0.062 mmol) successively under an argon atmosphere. The resulting mixture was stirred for 2 h at 70 °C. The yellow color of the solution turned dark purple within 5 min of stirring. The solution was filtered to remove AgCl, and the filtrate was evaporated. The crude product was purified by preparative TLC (silica gel, EtOAc:hexanes 2:1) to afforded **49** in 86% yield based on recovered starting material; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 (dd, J = 9.3, 6.7 Hz, 1H), 6.70 (dt, J = 15.6, 7.2 Hz, 1H), 6.16 (d, J = 9.2 Hz, 1H), 6.01 – 5.95 (m, 2H), 2.20 (qd, J = 7.3, 1.4 Hz, 2H), 1.54 – 1.44 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 159.7, 143.8, 139.7, 121.6, 113.7, 103.0, 34.8, 21.8, 13.7; HRMS (ESI-QTOF) calcd for $C_{10}H_{12}O_2$ $[M + H]^+$ 165.0910, found 165.0907.



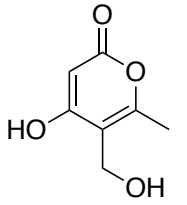
6-(4-oxopentyl)-2H-pyran-2-one (51):

Compound **51** was prepared by using previous described procedure for compound **2** in 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, J = 9.3, 6.6 Hz, 1H), 6.17 (d, J = 10.1 Hz, 1H), 5.99 (d, J = 7.3 Hz, 1H), 2.51 (t, J = 7.3 Hz, 4H), 2.15 (s, 3H), 1.98 – 1.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 165.6, 162.6, 143.6, 113.5, 102.9, 42.1, 32.8, 30.0, 20.8. HRMS (ESI-QTOF) calcd for $C1_0H_{12}O_3$ $[M + H]^+$ 181.0859, found 181.0859.



4-Hydroxy-5-methoxycarbonyl-6-methyl-2-pyrone (62):

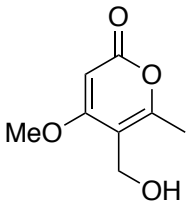
A solution of methyl acetoacetate (11.0 mL, 102 mmol) and malonyl chloride (9.92 mL, 102 mmol) in anhydrous CH_2Cl_2 (300 mL) was stirred at r.t. for 7 days. After which, the mixture was then washed with aqueous sat. $NaHCO_3$. The aqueous layer was acidified with 1% aqueous HCl and the crude product extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the resulting crude residue was subjected to silica gel column flash chromatography (50% EtOAc in hexanes) to give **62** (7.7 g, 41%); R_f = 0.3 (50% EtOAc in hexanes). ^{1}H NMR (400MHz, $CDCl_3$) δ 11.51 (s, 1H), 5.55 (s, 1H), 3.99 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.8, 169.2, 169.1, 161.5, 101.5, 90.1, 53.2, 22.6; HRMS (ESI-QTOF) calcd for $C_8H_8O_5$ $[M+H]^+$ 185.0444, found 185.0441



4-Hydroxy-5-hydroxymethyl-6-methyl-2-pyrone (63):

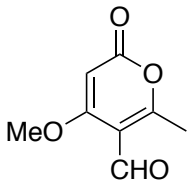
To a solution of **62** (1.08 g, 5.86 mmol) in anhydrous THF (20 mL) was added a solution of $BH_3 \cdot Me_2S$ (2.0M in toluene, 4.4 mL, 8.8 mmol) dropwise at 0 °C. The mixture was allowed to warm up to r.t. and stirred for an additional 2 hours. Anhydrous MeOH was

added and the resulting mixture was stirred for 1 hour before being concentrated under reduced pressure. The crude residue **63** was used for the next step without further purification. ^{1}H NMR (400MHz, DMSO-d6) δ 11.80 (s, 1H), 5.28 (s, 1H), 4.22 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ 170.0, 163.0, 162.3, 111.5, 88.3, 52.9, 17.0; HRMS (ESI-QTOF) calcd for $C_7H_8O_4$ $[M+H]^+$ 157.0495, found 157.0491.



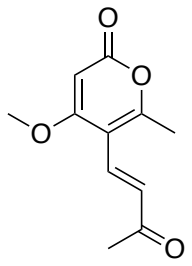
5-Hydroxymethyl-4-methoxy-6-methyl-2-pyrone (64):

To a solution of **63** (910 mg, 5.83 mmol) in acetone (20 mL) were added anhydrous K_2CO_3 (2.4 g, 17.37 mmol) and dimethyl sulfate (1.1 mL, 11.6 mmol). The mixture was refluxed overnight. The mixture was filtered through Celite and concentrated under reduced pressure. Recrystallization of the crude product from EtOAc-hexane gave **64** (992 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (s, 1H), 4.47 (s, 2H), 3.87 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 163.9, 161.1, 110.7, 88.1, 56.3, 55.4, 17.1; HRMS (ESI-QTOF) calcd for $C_8H_{10}O_4$ $[M+H]^+$ 171.0652, found 171.0651.



4-methoxy-6-methyl-2-oxo-2*H*-pyran-5-carbaldehyde (65):

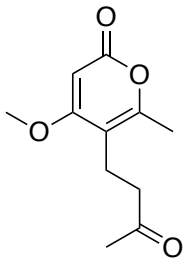
To a solution of **64** (945 mg, 5.55 mmol) in anhydrous CH_2Cl_2 (20 mL) was added PCC (1.4 g, 6.5 mmol) at 0 °C. The mixture was then allowed to warm up to r.t. and stirred overnight. The dark brown mixture was filtered through Celite and the concentrated residue was subjected to silica gel column flash chromatography (50% EtOAc in hexanes) to give **65**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 5.50 (s, 1H), 3.92 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 171.6, 169.8, 161.5, 110.1, 87.1, 56.5, 19.7; HRMS (ESI-QTOF) calcd for $C_8H_8O_4$ $[M+H]^+$ 169.0495, found 169.0491.



4-methoxy-6-methyl-5-(3-oxobut-1-en-1-yl)-2*H*-pyran-2-one (65):

A solution of **65** (450 mg, 2.68 mmol) and ylide (1.02 g, 3.22 mmol) in anhydrous MeOH was stirred for 18 hours. Solvent was evaporated under reduced pressure and the resulting crude residue was subjected to silica gel column flash chromatography (5% MeOH in CH_2Cl_2) to give **65** (475 mg, 85%); R_f = 0.28 (5% MeOH in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 16.3 Hz, 1H), 6.64 (d, J = 16.2 Hz, 1H), 5.50 (s, 1H), 3.87 (s,

3H), 2.40 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 169.6, 163.7, 162.5, 132.5, 130.9, 108.6, 88.2, 56.4, 28.2, 18.9; HRMS (ESI-QTOF) calcd for $C_{11}H_{12}O_4$ $[M+H]^+$ 209.0808, found 209.0804.



4-methoxy-6-methyl-5-(3-oxobutyl)-2*H*-pyran-2-one (52):

A solution of **66** (123.7 mg, 0.59 mmol) in ethanol under H_2 atmosphere (1 atm) was stirred overnight in the presence of 10 mol % Pd/C (10% wt.). After which, the catalyst was removed by Celite and the filtrate was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc:hexanes 2:1) to afforded **52** in 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.42 (s, 1H), 3.79 (s, 3H), 2.56 (s, 4H), 2.22 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 170.4, 164.3, 158.5, 110.0, 87.9, 56.1, 42.5, 29.9, 18.6, 17.2. HRMS (ESI-QTOF) calcd for $C_{11}H_{14}O_4$ $[M+H]^+$ 211.0965, found 211.0961.

1.5. Reference

(1) McGlacken, G. P., Fairlamb, I. J. *Natural product reports*, **2005**, *22*(3), 369.

(2) Goel, A.; Ram, V. J. *Tetrahedron*, **2009**, *65*(38), 7865.

(3) Lee, J. S. *Marine Drugs,* **2015**, *13,* 1581.

(4) Diels, O; Alder, K. *Ann.* **1931**, *490*, 257.

(5) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron,* **1992***, 48*(42), 9111.

(6) Kraus, G. A.; Riley, S.; Cordes, T. *Green Chem.* **2011**, *13*(10), 2734.

(7) Kraus, G. A.; III, G. R. P.; Beck, C. L.; Palmer, K.; Winter, A. H. *RSC Adv.* **2013**, *3*(31), 12721.

(8) Lee, J. J.; Kraus, G. A. *Tetrahedron Lett.* **2013**, *54*, 2366.

(9) Lee, J. J.; Kraus, G. A. *Green Chem.* **2014**, *16*(4), 2111.

(10) Lee, J. J.; III, G. R. P.; Mitchell, D.; Kasuga, L.; Kraus, G. A. *RSC Adv*. **2014**, *4*(86), 45657.

(11) Guney, T.; Lee, J. J.; Kraus, G. A. *Org. Lett.* **2014**, *16*, 1124.

(12) Echter, T.; Meier, H. *Chem. Ber.* **1985**, *118*, 182.

(13) Kende, A. S.; Curran, D. P.; Tsay, Y.-g.; Mills, J.E. *Tetrahedron Lett.* **1977**, 3537.

(14) Collins, R. P.; Halim, A. F. *J. Agric. Food Chem.* **1972**, *20*, 437.

(15) Garnica-Vergara, A.; Barrera-Ortiz, S.; Muñoz-Parra, E.; Raya-González, J.; Méndez-Bravo, A.; Macías-Rodríguez, L.; Ruiz-Herrera, L. F.; López-Bucio, J. *New Phytologist* **2015**, *209*(4), 1496.

(16) Mazzei, P.; Vinale, F.; Woo, S. L.; Pascale, A.; Lorito, M.; Piccolo, A. *J. Agric. Food Chem*. **2016**, *64*(18), 3538.

(17) Andriamialisoa, Z.; Giraud, M.; Labia, R.; Valla, A. *Chemistry and Ecology* **2004**, *20*(1), 55.

(18) Cooney, J. M.; Lauren, D. R.; Jensen, D. J.; Perry-Meyer, L. J. *J. Agric. Food Chem*. **1997**, *45*(7), 2802.

(19) Li, X.; Kim, M. K.; Lee, U.; Kim, S.-K.; Kang, J. S.; Choi, H. D.; Son, B. W. *Chem. Pharm. Bull.* **2005**, *53*(4) 453.

(20) Pittet, A. O.; Klaiber, E. M. *J. Agric. Food Chem*. **1975**, *23*(6), 1189.

(21) Dieter, R. K.; Fishpaugh, J. R. *J. Org. Chem.* **1988**, *53*(9), 2031.

(22) Kotora, M.; Ishikawa, M.; Tsai, F.-Y.; Takahashi, T. *Tetrahedron* **1999**, *55*(16), 4969.

(23) Valla, A.; Zentz, F.; Cartier, D.; Labia, R. *Natural Product Letters* **2000**, *14*(6), 417.

(24) Andriamialisoa, Z.; Giraud, M.; Labia, R.; Valla, A. *Chemistry and Ecology* **2004**, *20*(1), 55.

(25) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*(15), 2859.

(26) Thibonnet, J.; Abarbri, M.; Parrain, J.-L.; Duchêne, A. *J. Org. Chem.* **2002**, *67*(11), 3941.

(27) Biagetti, M.; Bellina, F.; Carpita, A.; Rossi, R. *Tetrahedron Lett.* **2003**, *44*, 607.

(28) Dombray, T.; Blanc Aurélien; Weibel, J.-M.; Pale, P. *Org. Lett.* **2010**, *12*, 5362.

(29) Luo, T.; Dai, M.; Zheng, S.-L.; Schreiber, S. L. *Org. Lett.* **2011**, *13*, 2834.

(30) Wickel, S. M.; Citron, C. A.; Dickschat, J. S. *Eur. J. Org. Chem.* **2013**, *2013*, 2906.

(31) Contforth, J., Hawes, J. E., Mallaby, R., *Aust. J. Chem.* **1992**, *45*, 179.

(32) Gilbreath, S. G.; Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 6172.

(33) Fairlamb, I. J.; Lee, A. F.; Loe-Mie, F. E.; Niemelä, E. H.; Obrien, C. T.; Whitwood, A. C. *Tetrahedron* **2005**, *61*(41), 9827.

(34) Samant, S.; Khatri, A. *Synthesis* **2015**, *47*(03), 343.

(35) Gan, P.; Smith, M. W.; Braffman, N. R.; Snyder, S. A. *Angewandte Chemie* **2016**, *128*(11), 3689.

(36) Fairlamb, I. J. S.; Obrien, C. T.; Lin, Z.; Lam, K. C. *Organic & Biomolecular Chemistry* **2006**, *4*(7), 1213.

(37) Nelson, H. M.; Stoltz, B. M. *Org. Lett.* **2008**, *10*(1), 25.

(38) Gurjar M, Reddy DS, Murugaiah A, Murugaiah S. *Synthesis* **2000**, *2000*, 1659.

(39) Dasaradhan, C.; Kumar, Y. S.; Prabakaran, K.; Khan, F.-R. N.; Jeong, E. D.; Chung, E. H. *Tetrahedron Lett.* **2015**, *56*(6), 784.

(40) Dasaradhan, C.; Kumar, Y. S.; Khan, F.-R. N.; Jeong, E. D.; Chung, E. H. *Tetrahedron Lett.* **2015**, *56* (1), 187.

(41) Kumar, Y. S.; Dasaradhan, C.; Prabakaran, K.; Manivel, P.; Khan, F.-R. N.; Jeong, E. D.; Chung, E. H. *Tetrahedron Lett.* **2015**, *56* (7), 941.

(42) Daoubi, M.; Pinedo-Rivilla, C.; Rubio, M. B.; Hermosa, R.; Monte, E.; Aleu, J.; Collado, I. G. *Tetrahedron* **2009**, *65*(25), 4834.

(43) Dobler, D., Reiser, O. *J. Org. Chem.* **2016**, *81*, 10357−10365

(44) Evidente, A.; Cabras, A.; Maddau, L.; Serra, S.; Andolfi, A.; Motta, A. *J. Agric. Food Chem*. **2003**, *51*(24), 6957.

(45) Wang, Y.-F.; Gao, Y.-R.; Mao, S.; Zhang, Y.-L.; Guo, D.-D.; Yan, Z.-L.; Guo, S.-H.; Wang, Y.-Q. *Org. Lett.* **2014**, *16* (6), 1610.

(46) Metwaly, A. M.; Fronczek, F. R.; Ma, G.; Kadry, H. A.; El-Hela, A. A.; Mohammad, A.-E. I.; Cutler, S. J.; Ross, S. A. *Tetrahedron Lett.* **2014**, *55* (24), 3478.

(47) Fairlamb, I. J.; Lu, F. J.; Schmidt, J. P. *Synthesis* **2003**, *16*, 2564.

(48) Marrison, L. R.; Dickinson, J. M.; Ahmed, R.; Fairlamb, I. J. *Tetrahedron Lett.* **2002**, *43* (49), 8853.

(49) Fairlamb, I. J.; Lee, A. F.; Loe-Mie, F. E.; Niemelä, E. H.; Obrien, C. T.; Whitwood, A. C. *Tetrahedron* **2005**, *61* (41), 9827.

(50) Hsung, R.; Kurdyumov, A.; Muñoz, R. *Synthesis* **2006**, *2006*(11), 1787.

CHAPTER 2.

MULTICOMPONENT REACTION OF TRIACETIC ACID LACTONE

2.1. Introduction

2.1.1 Biomass – a new feedstock resource

A variety of modern industries such as plastics, synthetic textiles, pigment, surfactants, agrichemicals, home and personal care products, pharmaceuticals, polymers, cosmetics and fuel rely on non-renewable petroleum-based chemicals as important raw materials and energy source for production since the beginning of 20th century. However, nature needs millions of years to fix carbon dioxide through photosynthesis to form those resources like coal, crude oil and natural gas. The decreasing fossil reserve, risk of generating environmentally deleterious byproducts and rising oil prices are factors for industries to seek for alternative raw materials and energy source.[1] We need to find new ways to generate energy, food, chemicals and materials to satisfy the growing individual needs and expectations while limiting the damage to earth.

As a result, several efforts have been made to resolve these issues. Ideally, renewable resource can be replenished over short timescale so that can be essentially limitless. Solar energy, wind, tides and biomass are known to be renewable sources, which can be used repeatedly and regenerate naturally if managed appropriately. Among them, biomass is the only renewable source of carbon for production of carbon based chemicals and materials and is worldwide distributed and highly abundant (Figure 1).[1]

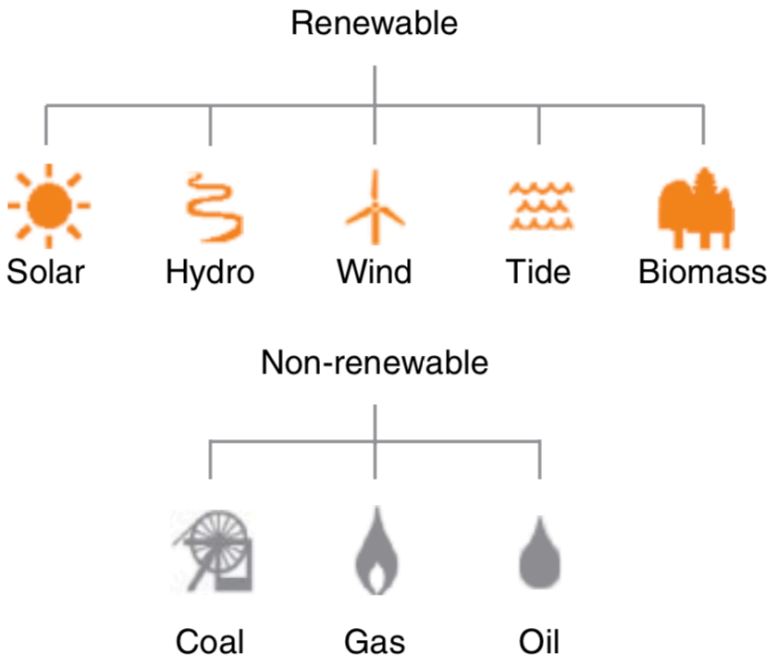


Figure 1. Different types of renewable and non-renewable resources.[1]

Biomass, by definition, is any organic materials come from plants and animals available on a recurring basis. The two most obvious types of biomass are wood and crops; another biomass that people tend to neglect is the waste, such as municipal solid waste, manufacturing waste and landfill gas.[1] Currently, biomass covers approximately ten percent of the global energy supply. In some developing countries, biomass is the only source of fuel for domestic use. More and more people believe that utilization of biomass would be a feasible solution for sustainability.

The biorefinery concept is similar to petroleum refineries, which convert biomass into variety of value-added product including energy, chemical and materials. As estimated, the earth can generate about 10^{11} tons of biomass each year, around 60% of them are terrestrial biomass and rest is aquatic biomass. Biomass consists of 75% carbohydrates and 20% lignin, and the remaining 5% includes triglycerides (fats and oils), proteins and terpenes. Carbohydrates can then be divided into storage carbohydrates and

structural polysaccharides. Starch, inulin and sucrose belong to storage carbohydrate, while cellulose, hemicellulose and chitin are examples of structural polysaccharides.[2]

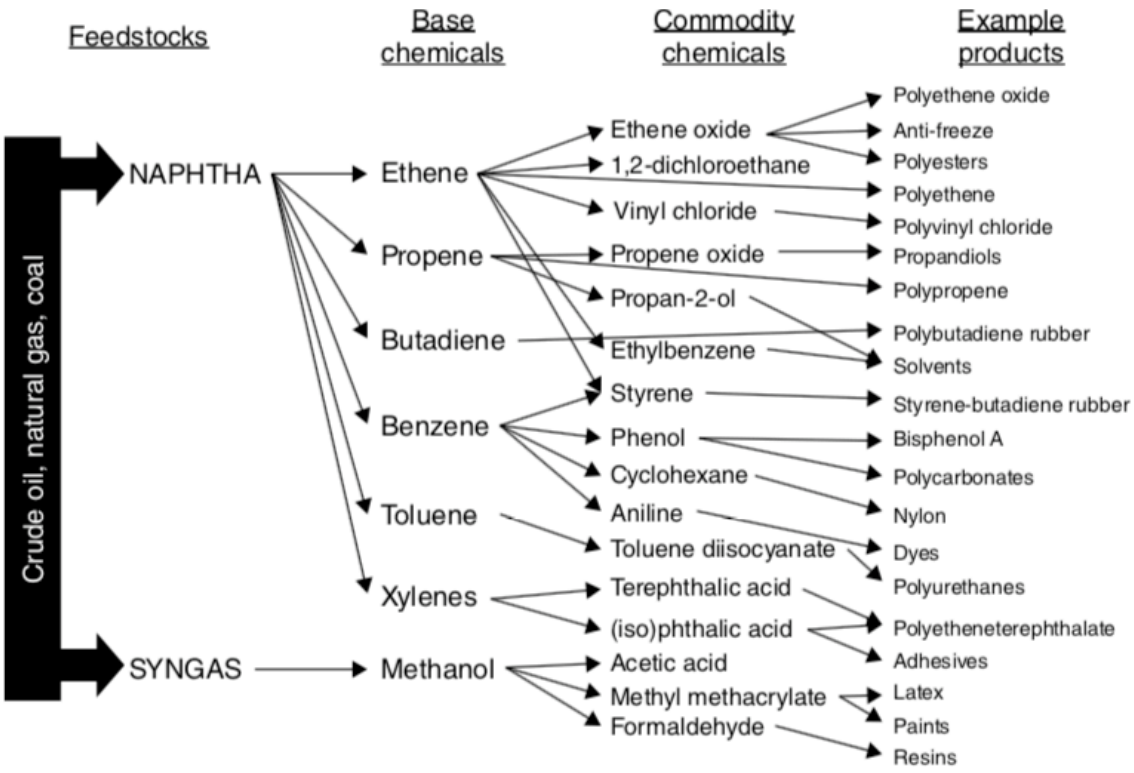
Biomass used in chemical industry could either be obtained by cultivation of fast growing, non-edible crops or from waste that is generated from edible crops such as sugar cane, bagasse, corn stover, rice husks and orange peels. It should be non-edible, a waste material from agricultural processing, or even food waste to avoid competition with the food sector. However, many first-generation biorefineries utilize feedstocks that compete with food or feed. The use of lignocellulosic agricultural residues as a biomass feedstock is advantageous because it is worldwide abundant and is not edible.[1-4] Lignocellulose consists of around 20% lignin, 40% cellulose and 25% hemicellulose.[2]

There are two ways for the biomass conversion: Thermochemical conversion and biological conversion. Thermochemical conversion includes liquefaction, combustion, gasification, pyrolysis and torrefaction. Biological conversion of biomass involves fermentation and anaerobic digestion. Among them, gasification and pyrolysis deal with whole biomass (lignocellulose) leading to upgradable platforms such as syngas and bio-oil, hydrolysis is the most complicated process that requires that lignocellulose is broken into its constitute parts.[1]

2.1.2 Platform molecules

The majority of products and materials produced by modern petrochemical industry are based on a set of cheap and simple building-block molecules, also called as the “base chemicals”. There are seven base chemicals, which are deriving from fossil recourses via cracking, distillation, fractionation and reforming, can be transformed into hundreds of useful products after industrial processes (Scheme 1).[1] The concept of bio-based “platform molecules” is an analogy to the “base chemicals”, it was described as

simple, small molecules from biomass could be utilized as building blocks for higher-value chemicals and materials. The research on bio-economy over the last 20 years has shown that, bio-based chemical industry can deliver the same building block chemicals, through a set of biomass-derived compounds, also referred to as bio-based platform chemicals.



Scheme 1. Simplified view of the fossil-derived chemical industry.[1]

In 2004, the U.S. Department of Energy (DOE) announced the Top 12 Value Added Chemicals that can be produced form sugars via biological or chemical conversions. The twelve molecules could, with further development, be converted to a number of higher-value chemicals or materials. These building block chemicals are molecules with multiple functional groups that possess the potential to be converted into new useful molecules. The twelve platform molecules are 1,4-diacids (succinic, fumaric and malic), 2,5-furan dicarboxylic acid, 3-hydroxy propionic acid, aspartic acid, glucaric

acid, glutamic acid, itaconic acid, levulinic acid, 3-hydroxybutyrolactone, glycerol, sorbitol, and xylitol/arabinitol.[5]

In 2010, after evaluation of recent technological advances, Bozell and co-workers revised the previous bio-based platform molecules list (Figure 2). Two of the criteria of a Top Value Added Chemical are that the compound must display high versatility as a platform that can be functionalized and also the compound and/or its transformation must be relevant and applicable to large-scale process and production.[6]

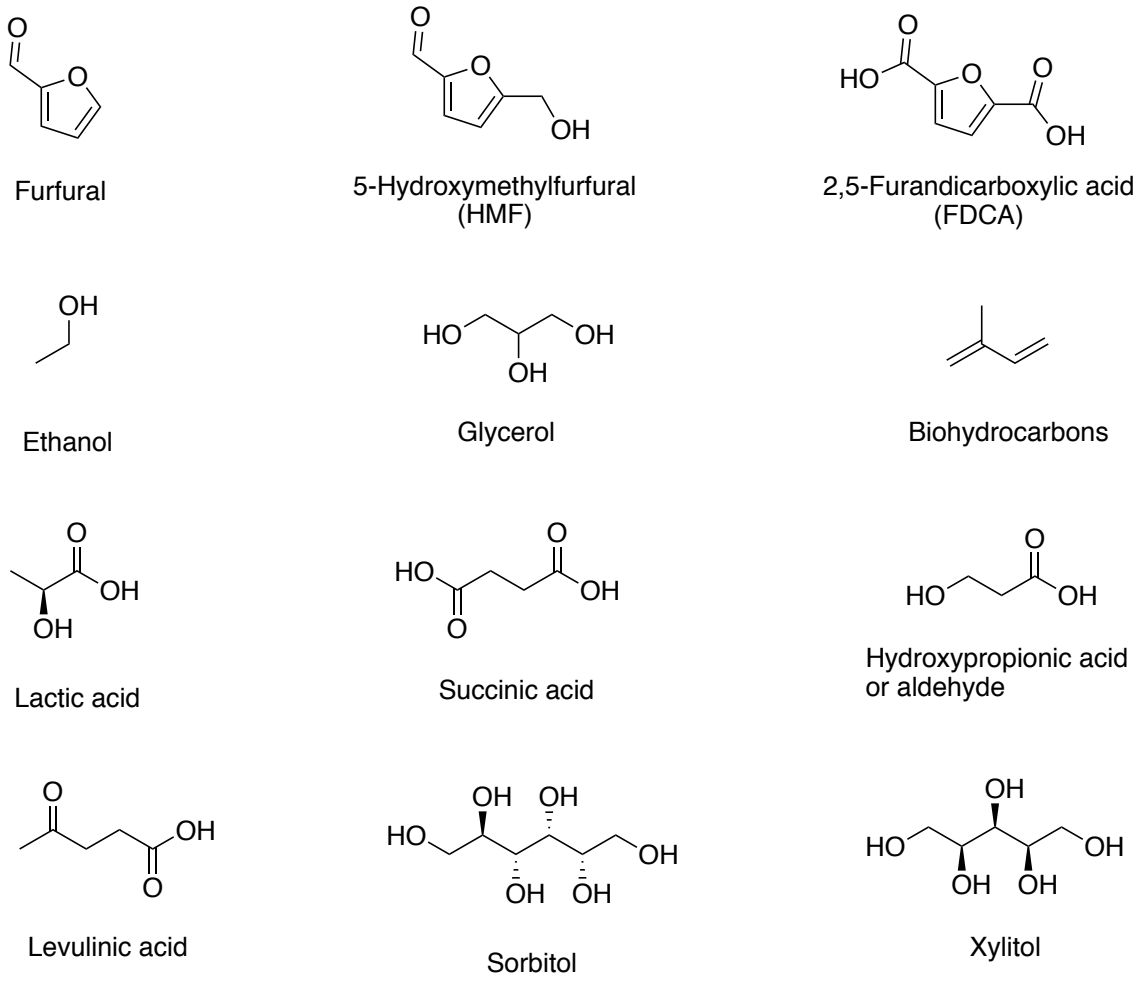


Figure 2. Potential chemical building blocks

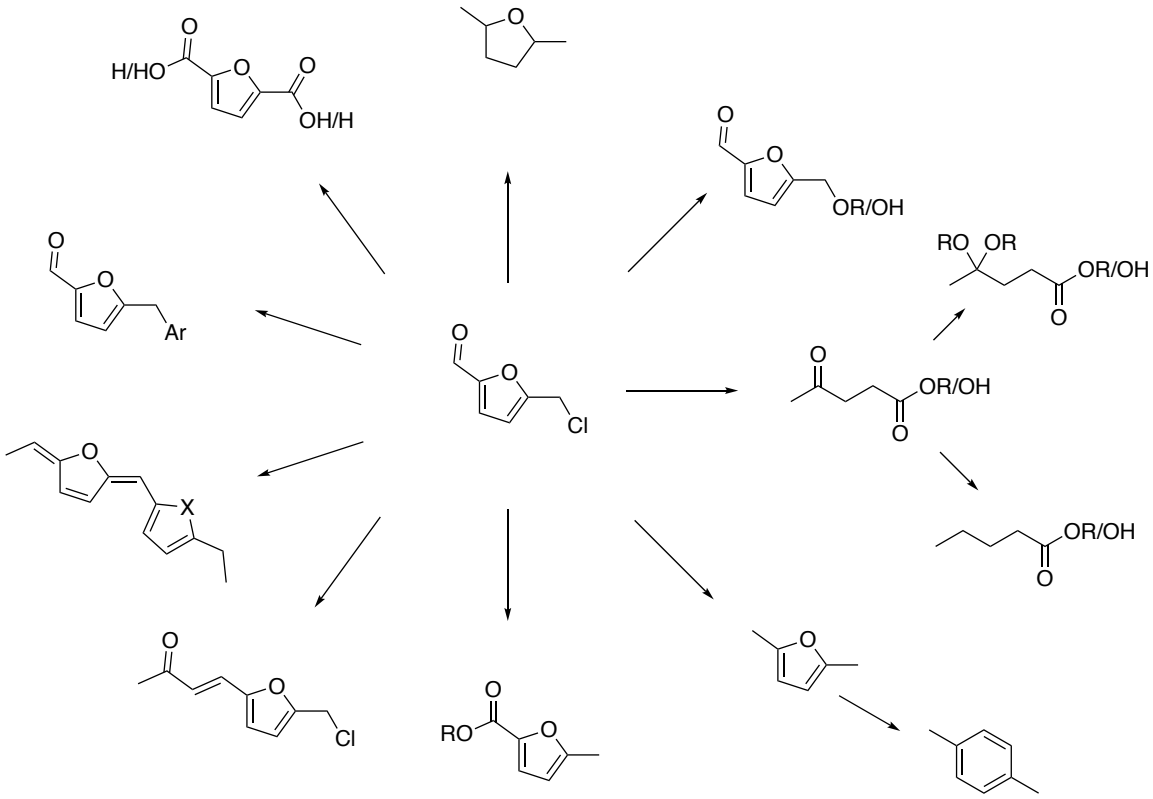
5-(chloromethyl)furfural (CMF) is another good example of bio-based platform molecule. It can be converted into a wide range of higher-value chemicals and materials.

CMF is a furan bearing a formyl and a chloromethyl group at the 2- and 5- position. The reactions of CMF are similar to that of HMF, but the former one is more reactive towards nucleophilic substitution at the methylene carbon. The first preparation of CMF was reported in 1901, treatment of sucrose, fructose or cellulose with an organic solution of the hydrogen halide gave only 12-30% yields. Several researchers have tried to modify the production procedure. An optimized condition was not reported until 2009, whereby sucrose, glucose, cellulose or corn stove could be converted into CMF in 80-90% yield in a biphasic aqueous hydrochloric acid/organic solvent reactor. The method has recently been adapted to a continuous flow reactor to produce CMF, which therefore has been establishes as an alternative to the popular platform molecule HMF.[1]

The star diagram in Scheme 2 shows a range of chemical transformation of CMF. Complete hydrogenation of CMF generates 2,5-dimethyltetrahydrfuran, which is a promising fuel oxygenate. Reaction with water yields HMF, an established bio-based platform molecule. Similarly, Alcohols react with CMF at room to give alkoxymethyl furfurals, which can be considered as biofuels. At higher temperature, it reacts with alcohol or water generates levulinic esters or acid. The former ones have been proposed as diesel additives, while the latter one is also a platform molecule. Treatment of levulinate esters with alcohols in acidic conditions gives the corresponding acetals that have been applied as novel monomers, plasticisers and solvents. Hydrogenation of levulinate esters gives rise to valeric esters, which have showed good fuel properties.

Careful hydrogenation of CMF gives 2,5-dimethylfuran, which is not only biofuel on its own, but also valuable precursor to para-xylene by cycloaddition with ethylene. In the presence of an N-heterocyclic carbene catalyst, CMF react with alcohols generate

furoate esters, which also showed excellent fuel properties. Aldo condensation of CMF or HMF with ketones yields diesel-like hydrocarbons with longer carbon chains. Conjugated, electro-active polymers are produced when CMF reacts with electron-rich aromatics such as pyrrole, furan or thiophene. Fridel-Crafts reaction of CMF yields aryl derivatives. Finally, oxidation of CMF with nitric acid gives either 2,5-diformylfuran or FDCA, the latter one is considered as a renewable replacement for petroleum-derived terephthalic acid.[1]



Scheme 2. 5-(chloromethyl)furfural as a platform molecule

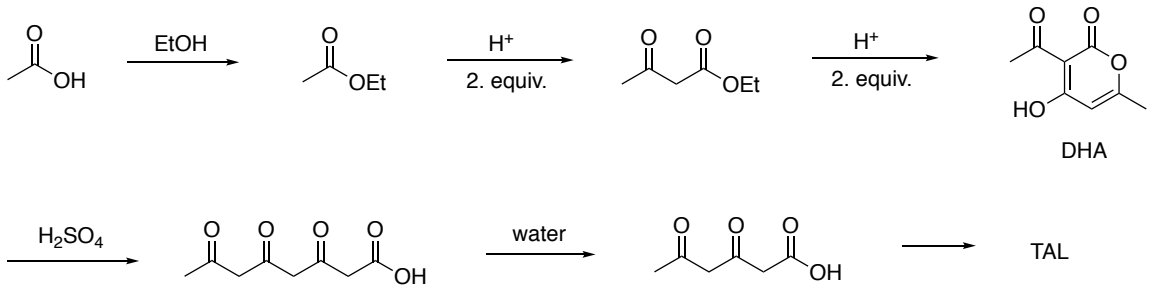
In 2010, Bond and co-workers reported that the United States increase the production of dry biomass from crops and forest wastes at 1.3 billion tons per year, which makes it practical to exploit biomass to produce bio-based platform chemicals.

2.1.3 Bio-based triacetic acid lactone (TAL)

Instead of the proposed platform molecules depicted previously, there are also alternative bio-based privileged molecules that can be produced from various single metabolic pathways. These metabolic pathways have the potential to generate a series of homologous molecules.

Historically, simple 2-pyrones such as TAL and dehydroacetic acid (DHA) are used as precursors for the synthesis of biologically important compounds such as pheromones, elastase enzymes, solanopyrones, α-chymotrypsin and coumarins.[7-8] Recently, studies have shown that TAL can be used as a promising candidate capable of undergoing chemical conversion to sorbic acid and other valuable intermediates.[9]

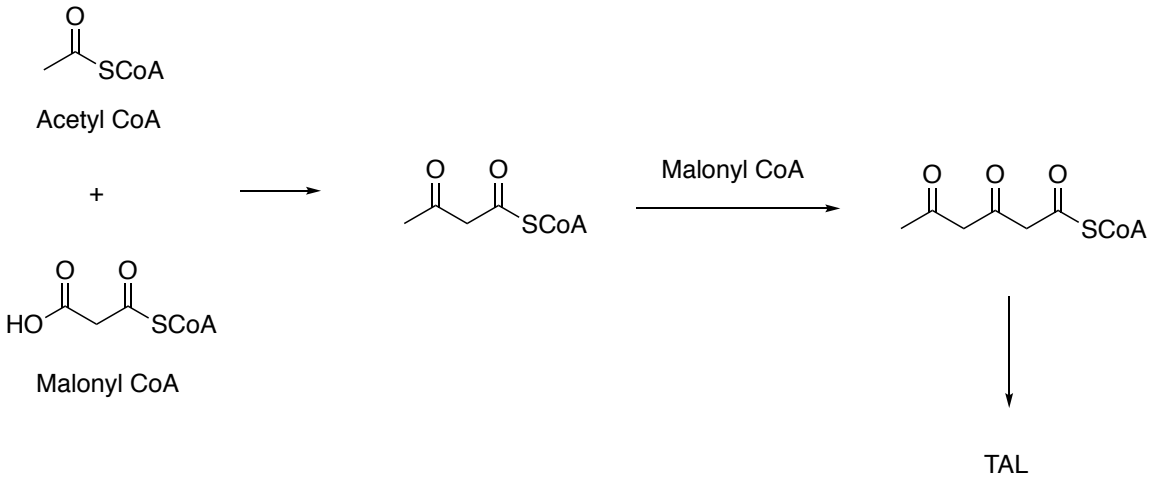
In 1891, Collie reported that when DHA is mixed with sulfuric acid containing around 10 % of water at 130 °C for a few minutes and then pouring into water after cooling down, TAL was separated in crystals. This compound has a much higher melting point than dehydroacetic acid.[10] This is the first report of observation and synthesis of TAL. Currently, TAL can also be produced from acetic acid as shown in Scheme 3.



Scheme 3. Synthesis of TAL from acetic acid

The plant *Gerbera Hybrida* natively produces TAL. GCHS2 was recognized as the key enzyme that participates in the biosynthesis of TAL and for this reason; it is renamed as 2-pyrone synthase (2-PS). The genes that related to the pyrone synthesis were renamed

as g2ps1.[11] 2-PS is a small protein that uses a single active site for decarboxylation and cyclization. The type III polyketide synthase (PKS) 2-PS, encoded by the g2ps1 gene, produces TAL by utilizing acetyl coenzyme A (Acetyl CoA) as an initial substrate and catalyzes the decarboxylation and condensation of two malonyl CoA (Scheme 4).[12]



Scheme 4. Microbial synthesis of TAL

Non-native synthases can also produce TAL. In 2004, Zha and co-workers reported a rational design of a fatty acid biosynthetic pathway, *Brevibacterium ammoniagenes* fatty acid synthase B (FAS-B), which allowed the microbial synthesis of TAL from D-glucose. A maximum titer of 52 mg/L TAL was observed.[13] In 2005, Xie and co-workers reported that a highest concentration (1.8 g/L) and yield (6%) of TAL from glucose were achieved by *S. cerevisiae* expressing the Y1572F mutant of *Penicillium patulum* 6-methylsalycilic acid synthase (6-MSAS).[14] However, the latter two enzymes need phosphopentetheinyl transterase for activation, while the 2-PS does not.

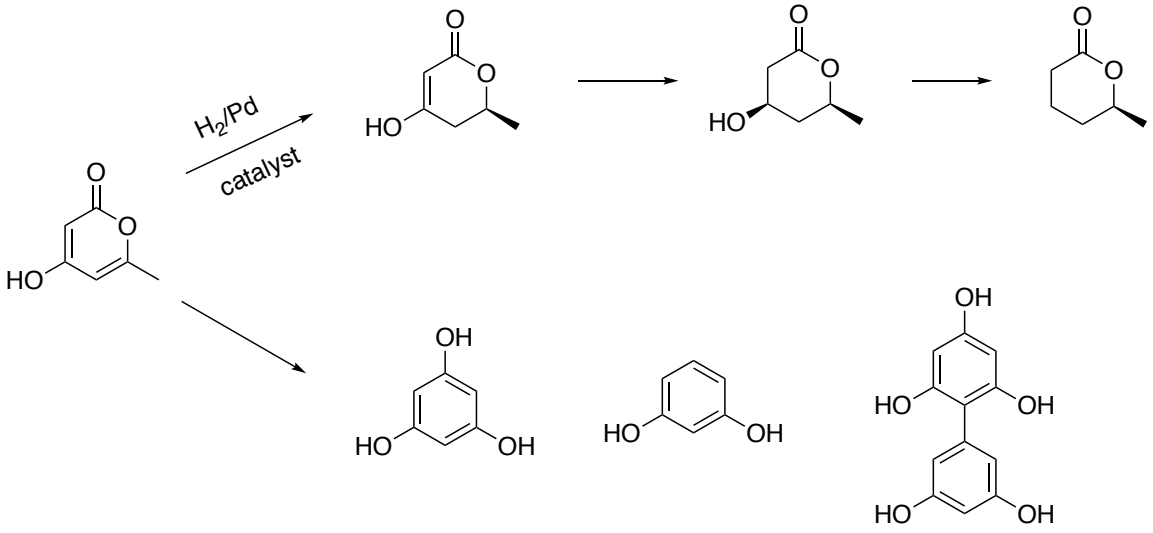
It has been reported that TAL shows negative effects on microbial cell growth. TAL is extremely toxic to *E. coli*. It showed reduction in growth rate of 25% and 90% in

10 mM and 20 mM, respectively and there was no growth observed for 50 mM TAL. However, there was no effect on growth to the concentrations up to 200 mM TAL in *Saccharomyces cerevisiae*.[15] *Saccharomyces cerevisiae* is therefore an excellent host for the production of TAL as a result of the minimal toxicity on the microbial cell growth.

In 2014, Cardenas and Da Silva reported a modified metabolic engineering of *Saccharomyces cerevisiae* for the production of TAL. A highest titer of 2.2g/L and yield of 0.13 g/g glucose TAL was achieved.[15] In the following year, the same group reported a higher TAL titer of 5.2 g/L.[16]

2.1.4 TAL as a potential platform molecule

TAL shows similar electrophilic and nucleophilic characters to its parent 2-pyrone core. TAL possesses an OH group at C-4 position and a methyl at C-6; therefore the C-3 position is more subject to electrophilic attack. Catalytic enantioselective hydrogenation of TAL has been reported by Huck and co-workers.[17-20] Besides, TAL is a precursor for the chemical conversion to the natural product phloroglucinol. Phloroglucinol is a starting material used in the synthesis of various high value bioactive compounds and thermally stable energetic compounds such as 1,3,5-triamino-2,4,6-trinitrobenzene (TATB). Ruduction of phloroglucinol produces resorcinol, which is used in resin and adhesive formulations (Scheme 5).[13, 21-22.]

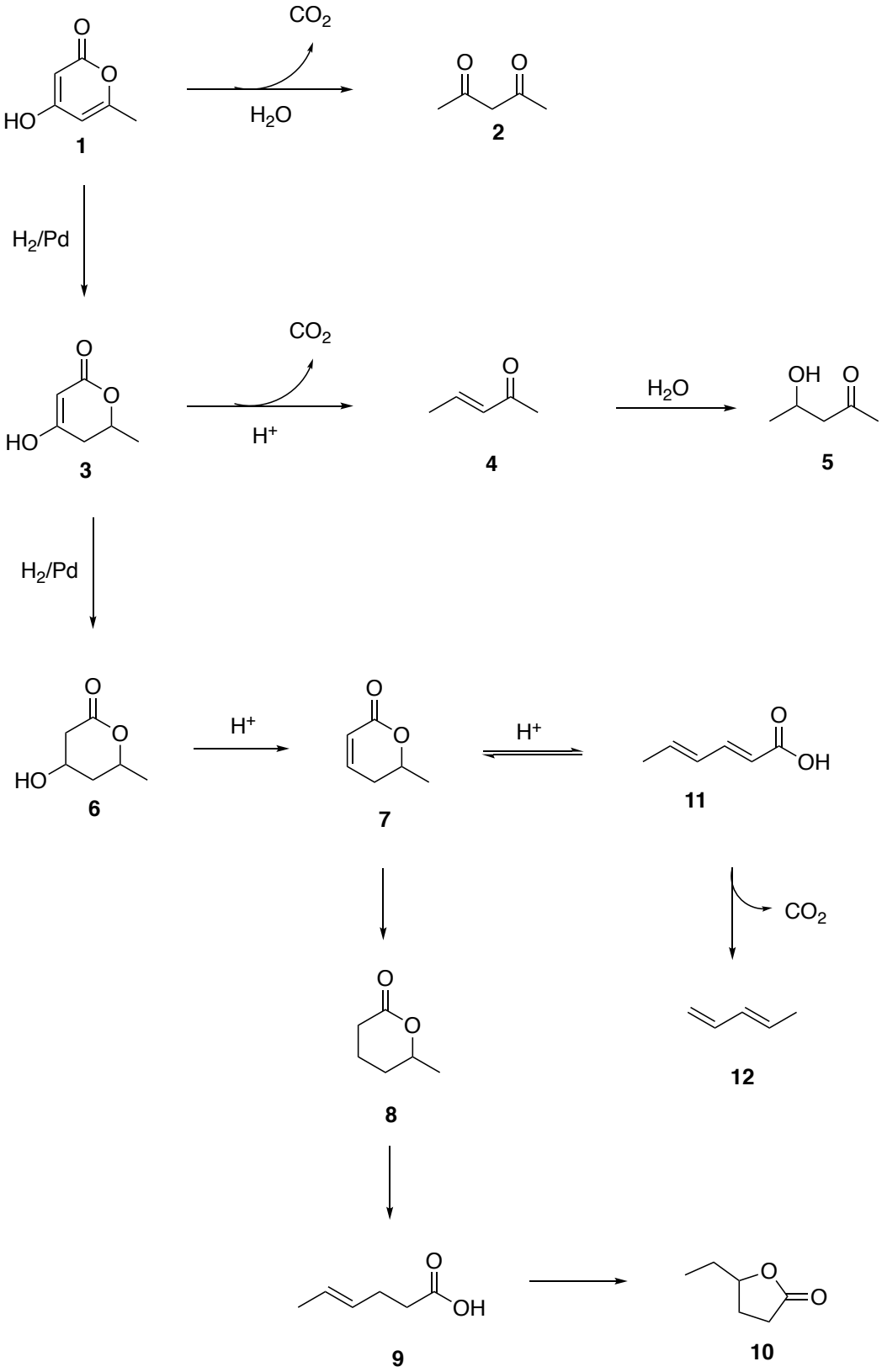


Scheme 5. TAL derivatives.

It also has been reported that TAL can be converted to a range of commercially valuable chemical intermediates and end products (Scheme 6). For instance, TAL undergoes ring opening and decarboxylation in the absence of a catalyst in water, giving acetylacetone **2** and CO_2 as the major products. Acetylacetone **2** is an important commodity chemical that can be used as a fuel additive, in metal plating, in resin modification and in organic synthesis. TAL can be hydrogenated into compound **3** or **6** in the presence of metal catalysts. Ring opening and decarboxylation of **3** in water or THF leads to 3-penten-2-one **4** and 4-hydroxy-2-pentanone **5**, both are bi-functional ketones, valuable chemical intermediate. Dehydration of **6** yields compound **7** and further metal-catalyzed hydrogenation of **7** gives rise to **8**. Subsequent ring opening of **8** leads to the unsaturated acid, hexenoic acid **9**. Hexenoic acid **9** can undergoes ring closure reaction to form γ-caprolactone **10**. Compounds **9** and **10** possess diverse applications, for example, some isomers of **9** were use as flavoring agent in food; Compound **10** is commercially important in food industry, tobacco industry and cosmetic industries. Sorbic acid **11** can be obtained from compound **7** at maximum 64% yield. Sorbic acid **11** is of great

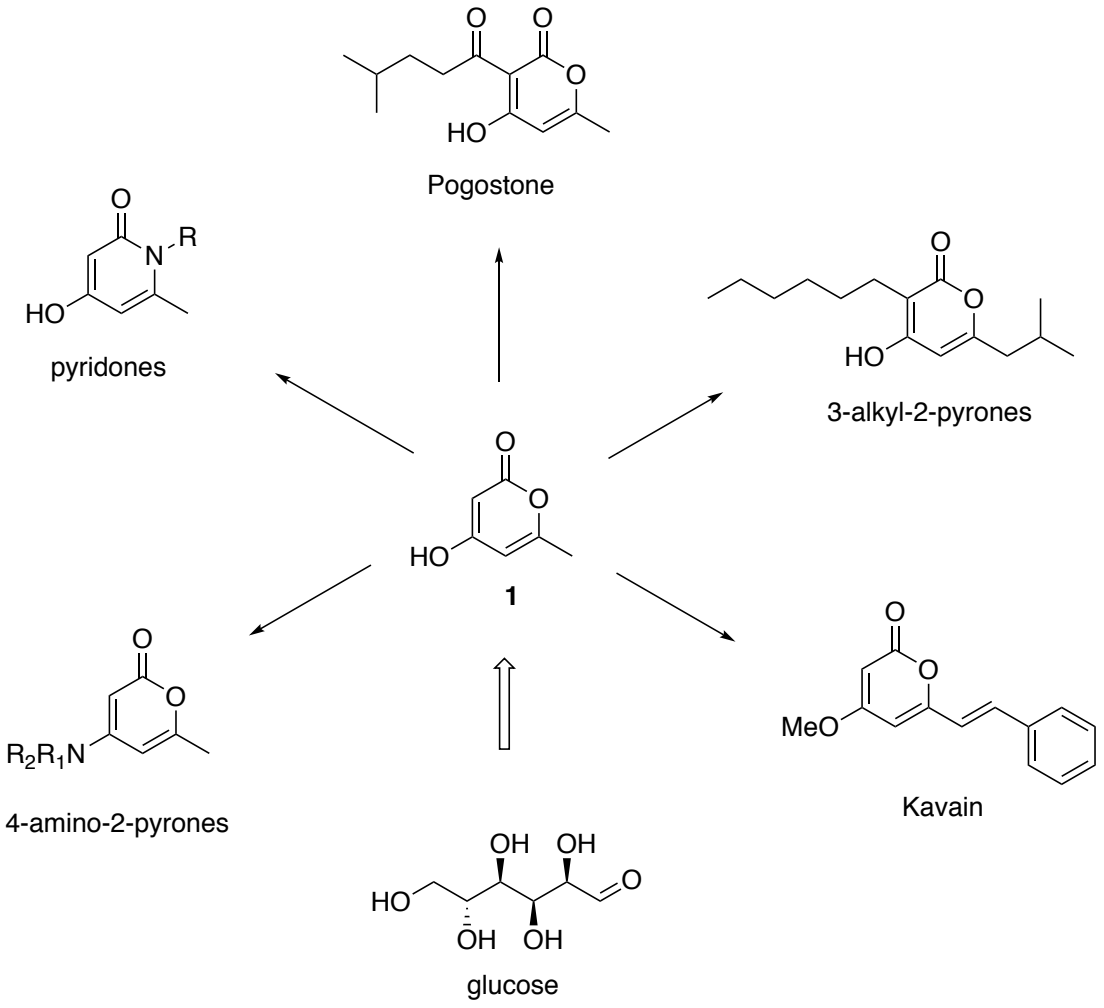
importance in itself. Both **11** and its salt are widely used as preservatives in food industry because of their effective inhibitory properties towards a variety of bacteria and mound while exhibiting low toxicity in mammals. Furthermore, compound **11** has the potential to be used as a monomer and co-polymerize with different compounds. Sorbic acid is currently produced from non-renewable fossil-based chemicals. Further decarboxylation of **11** yields 1,3-pentadiene **12**, a valuable intermediate for making resins, adhesives and plastics.[9]

The Center for Biorenewable Chemicals (CBiRC) is an organization, which is developing the tools, components and materials needed to transform carbohydrate feedstock into bio-based chemicals. As a member of CBiRC, our group also focused on taking advantage of this bio-based privileged TAL and tried to discover the potential of this molecule.



Scheme 6. Bi-functional chemicals from TAL

Scheme 7 shows the chemistry of TAL that has been discovered or studied in our research lab. Acylation of TAL at C-3 directly generates 3-acyl TALs. Pogostone is an example for this class of compounds which possesses a variety of biological activities such as antibacterial and herbicidal. 3-Alkyl-2-pyrones can also be generated via a one-pot Aldol-reduction cascade reaction. Treatment of TAL with corresponding aromatic aldehyde in the presence of t-BuOK in DMF followed by methylation gives styrenylpyrones. 4-amino-2-pyrones and pyridones were also accessible from TAL by controlling reaction conditions.[23-25]



Scheme 7. TAL chemistry from the Kraus Group

2.1.5 Multicomponent reactions and Mannich reaction

Multicomponent reactions (MCRs) are those reactions where three or more reactants come together in a single pot to form a new structure, which contains portions from all the reactants. In an MCR, the product is assembled according to a cascade of chemical reactions and all the reaction equilibria finally merge into an irreversible step yielding the product. Thus, the results are apparently dependent on the reaction conditions: solvent, temperature, concentration, catalyst and, of course, the starting materials. For a successful design of an MCR, it is of importance to have all these concerns solved to form a single main product and do not yield side products.[26]

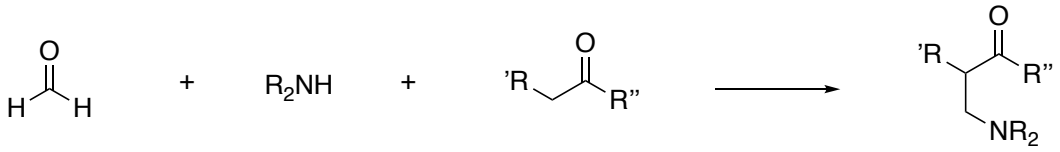
MCRs are known methods to expand the molecular complexity and diversity. A simple mathematical analysis highlights the important character of MCRs. For example, if there is a three-component reaction and we add 10 different reactants for each type of the reactant in one pot, then in principle we can get 1000 (10 × 10 × 10) different products. That means 1000 products can potentially be obtained from only 30 starting materials. MCR is an ideal tool for probe structure-activity relationships.[27]

In the application to the drug discovery process, MCRs provide many advantages over the traditional approaches. Shortened reaction steps usually means shorter development time, lower cost, and less waste generation. Besides, with one-pot reactions, set-up procedure and work-up procedure need to be performed only once, which, to some extent, is apparently superior to multi-step synthesis.[28]

MCRs have been considered as one of the most important processes for the preparation of organic compounds in modern synthetic chemistry. MCR products have attracted much attention of biologists and medicinal chemists due to the predefined

functionalities. Besides of that, MCRs are also welcomed by the superior atom economy, low cost and efficient operation.

The Mannich reaction is a three-component reaction involving a primary or secondary amine, a nonenolizable aldehyde and an enolizable carbonyl compound. The final product is a β-amino carbonyl compound also known as a Mannich base. Reactions between α-methylene carbonyl compounds and aldimines are also considered as Mannich reactions because these imines form between amines and aldehydes. The Mannich reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to form the Schiff base. The Schiff base is an electrophilic acceptor in the next step, which is then attacked by the α-CH-acidic carbonyl compound (nucleophile). The Mannich reaction is also considered as a condensation reaction.[29]



Scheme 8. Mannich reaction

4-Hydroxycoumarin is a structurally analogue of TAL, the β-enol lactone unit provides a very reactive site for both compounds. 4-Hydroxycoumarin is an important fungal metabolite from coumarin. Further fermentative treatment of 4-hydroxycoumarin could lead to the anticoagulant dicoumarol, in which two 4-hydroxycoumarines were linked together by a methylene from formaldehyde at the C-3 position.[30]

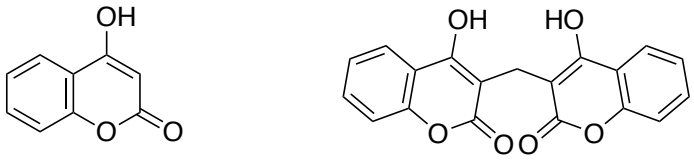


Figure 3. 4-Hydroxycoumarin and Coumarol

In recent years, 3-benzyl substituted 4-hydroxycoumarins have attracted much attention due to their potential application in various fields like biology, medicinal chemistry and clinical chemistry. 3-Benzyl substituted 4-hydroxycoumarins are components of numerous natural products exhibiting a wide range of bioactivities such as anti-HIV, insecticidal, antimalarial and antioxidant properties.[31-32]

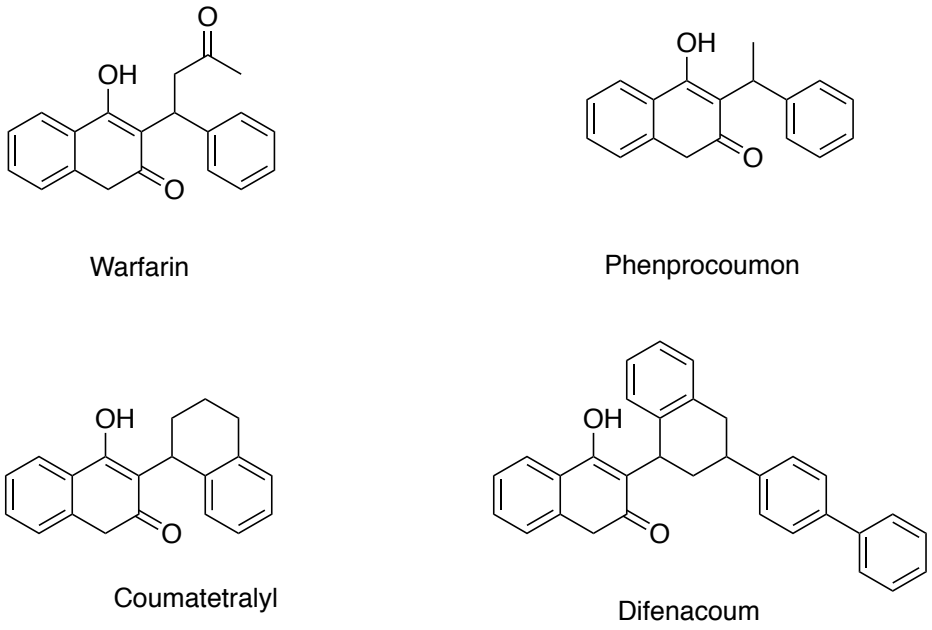
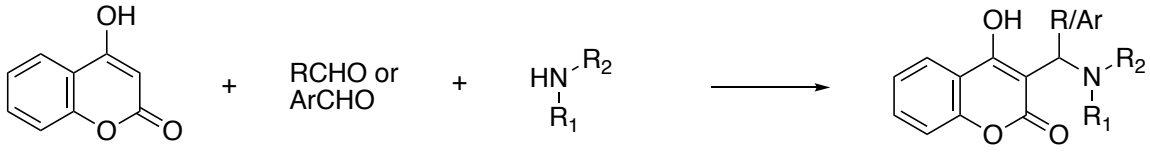


Figure 4. Natural products containing 3-substituted coumarin

The Mannich reaction of 4-hydroxycoumarine has been studied for the past decade and several reaction conditions such as using ionic liquid as the solvent and utilizing metal catalysts have been reported as shown in Table 1.[33-39]

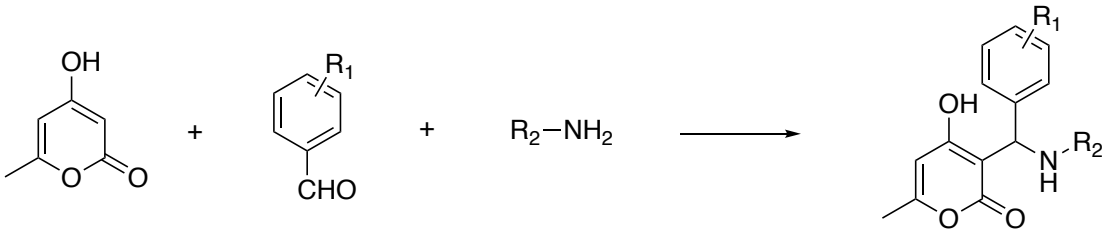
Table 1. Literature methods for Mannich reactions of 4-hydroxycoumarin



Entry	Solvent	Catalyst	Temperature
1	Ionic liquid	-	microwave
2	H_2O	Triton X-100	r.t.
3	toluene	$InCl_3$	r.t. to reflux
4	EtOH	CAN	r.t.
5	H_2O	Nano ZnO	r.t.
6	EtOH	Nano TiO_2	r.t.
7	ACN	Fe_3O_4@ZrO_2/SO_4^{2-}	r.t.
8	EtOH	HCl	reflux

2.2. Results and Discussion

Since TAL has shown promising potential as a bio-based privileged molecule, several new synthetic methodologies based on TAL have been discovered or explored in our group. As a continuous interest in developing renewable chemicals and broadening the chemical transformation of this bio-based starting material, the enol-predominated TAL caused our interest on its potential involvement in Mannich reactions.

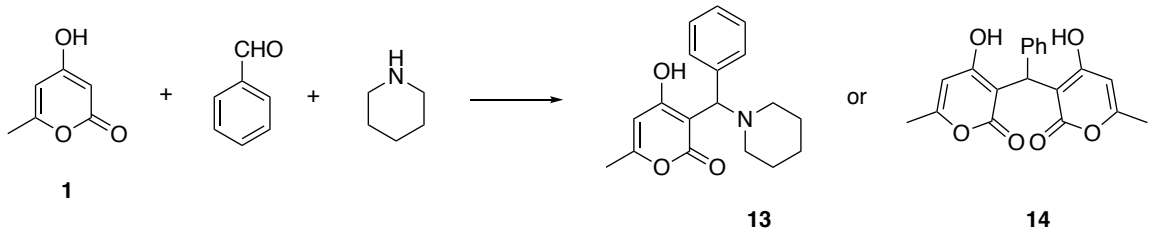


Scheme 9. Mannich reaction of TAL

In this study, we initially optimized the reaction condition using TAL (1.0 mmol), benzaldehyde (1.0 mmol) and piperidine (1.0 mmol) as model substrates. Owing to the

structural similarity between 4-hydroxycoumarin and TAL, we envisaged that their reactivity might be alike. Using the aqueous condition in the presence of a surfactant Triton X-100 reported by Kumar, only starting materials were recovered.[34] When methanol or ethanol was employed as solvents, only bis-adduct where two molecules of TAL and one molecule of the aldehyde were bonded together was observed even if hydrochloric acid or acetic acid were added as catalyst. However, when the reaction was performed in dimethoxymethane or dichloromethane at room temperature, Mannich bases can be obtained as the only products. We also found that when a catalytic amount (5 mol %) of acetic acid was added, it accelerated the reaction rate.

Table 2. Initial reaction condition screening

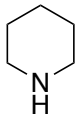
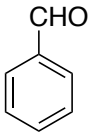
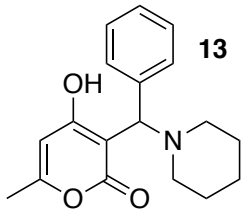
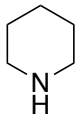
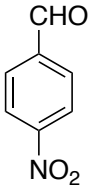
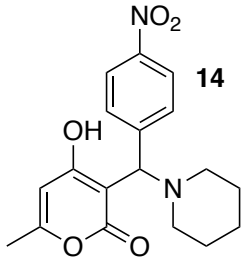
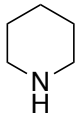
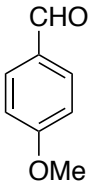
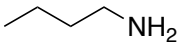
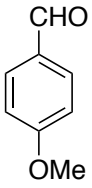
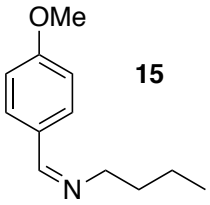


Entry	Solvent	Catalyst	Product	Time	Yield
1	water	Triton X-100	N.R.	16 h	-
2	ethanol	-	**14**	16 h	-
3	ethanol	HCl	**14**	16 h	-
4	ethanol	AcOH	**14**	16 h	-
5	methanol	AcOH	**14**	16 h	-
6	dimethoxymethane	-	**13**	12 h	64%
7	dimethoxymethane	AcOH	**13**	4 h	63%
8	DCM	AcOH	**13**	4 h	65%

With valid conditions at hand, we are interested in how the electron density of the aromatic aldehyde would affect the reaction. As shown in Table 3, the reaction among TAL, 4-nitrobenzaldehyde and piperidine would smoothly generate the desired product

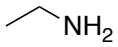
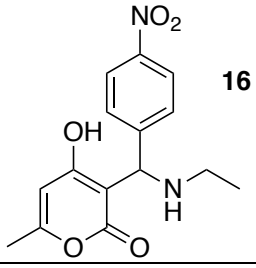
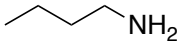
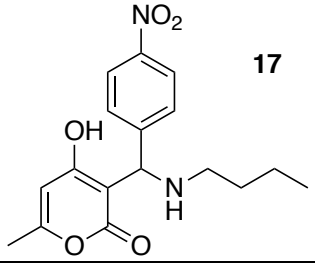
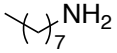
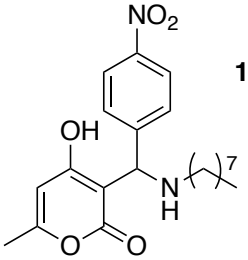
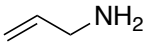
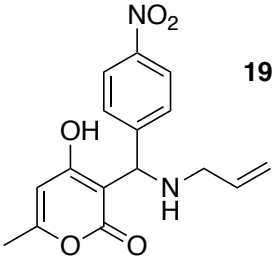
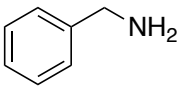
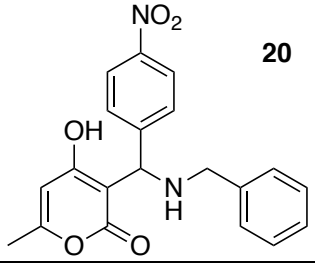
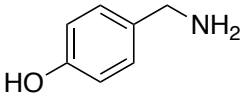
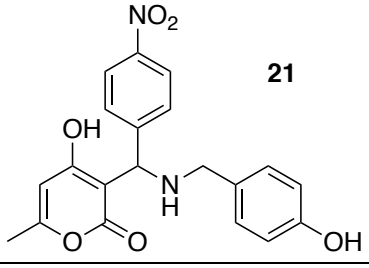
14 in 2 hours in 85% yield, a better yield and shorter reaction time were observed compared to that of the benzaldehyde. However, when 4-methoxybenzaldehyde was employed, only an uncertain product was obtained. The ^{1}H NMR showed the presence of unreacted TAL but lack of the aldehyde proton peak, which we thought due to the generation of the imminium salt. In order to confirm this conjecture, n-butylamine was used instead of piperidine. Under the same reaction condition, the imine intermediate **15** was obtained and confirmed by ^{1}H NMR. The reaction stopped at the intermediate stage and TAL is reluctant to further attack the imine, possibly because the electro-donating group made it less electrophilic.

Table 3. Mannich reaction with different aldehydes

Entry	Amines	Aldehydes	Product	Yield
1			 **13**	65%
2			 **14**	85%
3			[Intermediate]	-
4			 **15**	-

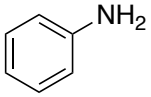
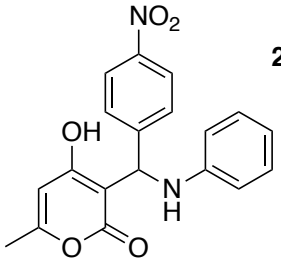
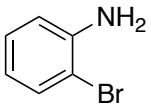
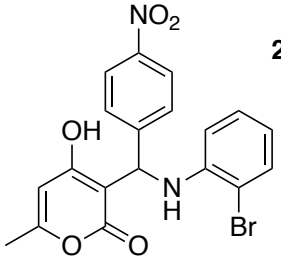
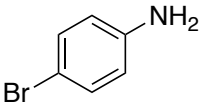
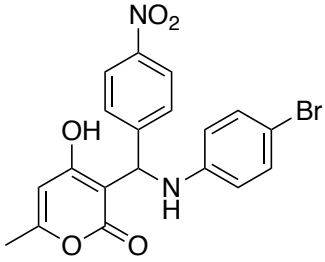
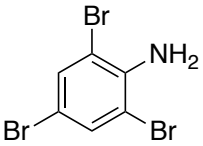
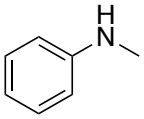
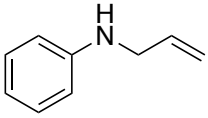
Using the experimentally established reaction condition, the Mannich reaction with TAL, 4-nitrobenzaldehyde and a variety of amines were pursued and the results were summarized in Table 2. Saturated aliphatic primary amines reacted well to produce Mannich bases in good yield (Entry 1 – 3). The reaction with allylamine led to decreased yield (Entry 4). Benzylamine and 4-hydroxybenzylamine were also employed and the corresponding products were generated in decent yield (Entry 5 and 6).

Table 4. Mannich reaction with TAL, 4-nitrobenzaldehyde and primary amines

Entry	Amines	Product	Yiel
1		 **16**	88%
2		 **17**	96%
3		 **18**	84%
4		 **19**	60%
5		 **20**	79%
6		 **21**	72%

Anilines were also used for the Mannich reaction with TAL and 4-nitrobenzaldehyde. The reaction with aniline and 2-bromoaniline led to Mannich base products in relatively low yields (Entry 1 and 2) while the reaction with 4-bomoaniline only generates an unclean and hard-to-purify product. ^{1}H NMR verified the presence of the product but with very low yield and a large amount of byproducts. (Entry 3.) The lower yields and less reactivity possibly due to the weakened N-nucleophilicity induced by the benzene conjugation. The lone electron pair on the nitrogen will partially delocalize to the aromatic ring, which made the nitrogen less nucleophilic. When 2,4,6-tribromoaniline was used in the reaction, no product was observed; steric hindrance possibly played an important role here as well. Besides, two N-substituted anilines were also employed to this reaction; however, no desired product was observed, possibly also due to steric hindrance.

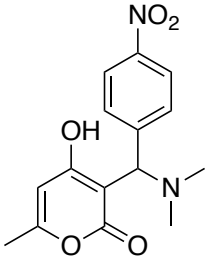
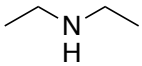
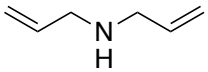
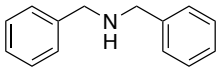
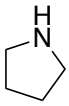
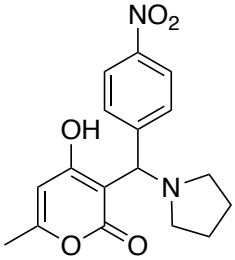
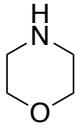
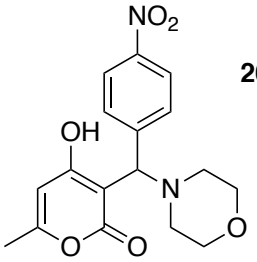
Table 5. Mannich reaction with TAL, 4-nitrobenzaldehyde and anilines

Entry	Amines	Product	Yield
1		 **22**	54%
2		 **23**	52%
3			low yield
4		N.R.	-
5		N.R.	-
6		N.R.	-

With the suspect that acyclic secondary amines are possibly steric hindered for such Mannich reactions, different acyclic secondary amines were employed to test our assumption. Except that only dimethyl amine reacted with TAL and 4-nitrobenzaldehyde, all other amines failed to yield any desired product. However, since piperidine involved

in the reaction pretty well, pyrrolidine and morpholine are two of the most common cyclic amines that we could not ignore. Not surprisingly, both two cyclic amines led to desired Mannich bases.

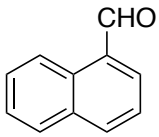
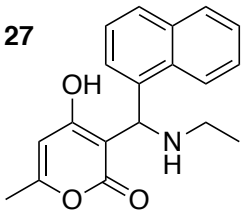
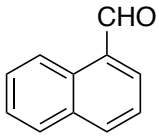
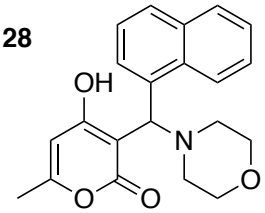
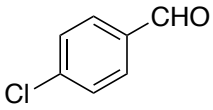
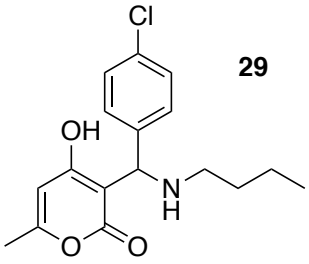
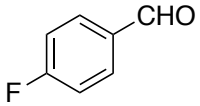
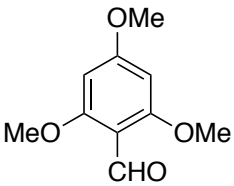
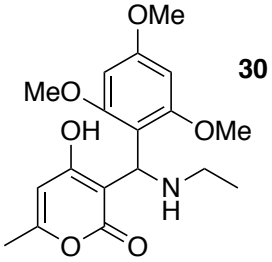
Table 6. Mannich reaction with secondary amines

Entry	Amines	Product	Yield
1		 **24**	85%
2		N.R.	-
3		N.R.	-
4		N.R.	-
5		 **25**	91%
6		 **26**	70%

Besides 4-nitrobenzaldehyde, some other aldehydes were also used to expand the reaction scope. For example, 1-naphthaldehyde involved in the reaction with ethylamine and morpholine to generate the desired Mannich bases in good yields (Entry 1 and 2). 4-

Chlorobenzaldehyde reacted with TAL and butylamine while 4-fluorobenzldehyde could not. To our surprise, 2,4,6-trimethoxybenzaldehyde reacted with TAL and ethylamine to yield the product in 62% yield (Entry 5).

Table 7. Mannich reaction with TAL and different aldehydes

Entry	Aldehydes	Product	Yield
1		**27** 	90%
2		**28** 	89%
3		 **29**	84%
4		N.R.	
5		 **30**	62%

2.3. Conclusion

This chapter has reported an efficient method to extend the library of 3-component TAL-derived Mannich bases. The current proposed method enhances cost efficiency by using AcOH as catalyst in a single-pot reaction. The most noteworthy aspect of this approach is the utilization of the bio-based TAL as one of the starting materials. As a result of this work, the versatility of the bio-based TAL as a platform chemical has been further demonstrated via the 3-component Mannich reaction.

2.4. Experimental

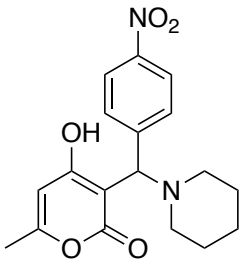
General Procedures

All starting materials were purchased from Sigma-Aldrich; Tetrahydrofuran (THF) was freshly distilled over lithium aluminum hydride and other 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 chromatographically isolated products. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.20 mm silica gel plates using UV light as a visualizing agent. Silica gel 60A, particle size 0.032 – 0.063 mm, was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 1.00 mm silica gel plates. ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ on a Varian MR-400 or Bruker Avance III 600 MHz spectrometer. ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to the residual protonated chloroform peak (CDCl3: δH = 7.26 ppm, δC = 77.0 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).

Selected Experimental, Physical, and Spectral Data

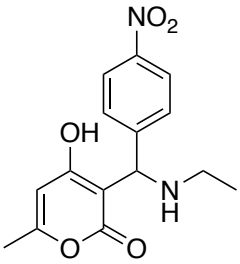
General Procedure: Typical Mannich reaction of TAL

To a dried flask TAL (0.1261 g, 2.0 mmol) was suspended in dimethoxymethane and stoichometric amount of aldehyde (2.0 mmol) was then added. To this suspension, amine (2.0 mmol) was added and stirred. The resulting solution was added a catalytic amount of AcOH, then stirred at room temperature overnight. The resulting solid product was subjected to filtration. The filtrate was washed ten times with petroleum ether (3 mL x 10). The washed solid product was dried in air. For liquid product, crude was subjected to either preparative silica plates or silica column chromatography to obtain the product.



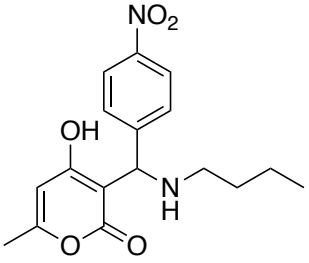
4-hydroxy-6-methyl-3-((4-nitrophenyl)(piperidin-1-yl)methyl)-2H-pyran-2-one (14)

Pale yellow solid (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 5.73 (s, 1H), 4.91 (s, 1H), 3.62 – 3.53 (b, 1H), 2.79 (b, 1H), 2.54 (b, 1H), 2.09 (s, 3H), 1.79 (b, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.4, 164.7, 162.0, 148.0, 144.4, 130.0, 124.3, 104.6, 95.3, 70.0, 55.1, 24.8, 23.0, 20.0 ppm; HRMS (ESI-QTOF) calcd for $C_{18}H_{20}N_2O_5$ $[M + H]^+$ 344.1441, found 344.1447.



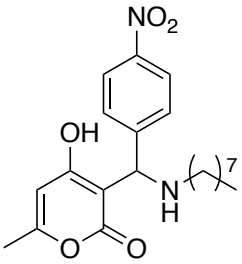
3-((ethylamino)(4-nitrophenyl)methyl)-4-hydroxy-6-methyl-2H-pyran-2-one (16)

Pale yellow solid (88% yield): ^{1}H NMR (400 MHz, DMSO-*d*) δ = 8.21 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 5.48 (s, 1H), 5.27 (s, 1H), 2.87 (q, J = 7 Hz, 2H), 1.96 (s, 1H), 1.16 (t, J = 7Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-*d*) δ = 178.1, 164.6, 159.5, 146.9, 146.4, 128.4, 123.5, 107.4, 90.3, 58.0, 40.7, 19.3, 11.2 ppm; HRMS (ESI-QTOF) calcd for $C_{15}H_{16}N_2O_5$ $[M + H]^+$ 305.1139, found 305.1132.



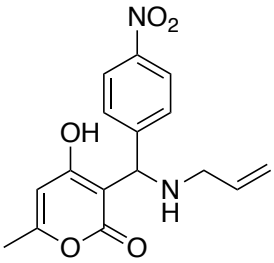
3-((butylamino)(4-nitrophenyl)methyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (17)

Pale yellow solid (96%); ^{1}H NMR (400 MHz, DMSO-*d*) δ = 8.21 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 5.50 (s, 1H), 5.25 (s, 1H), 2.89 – 2.73 (m, 2H), 1.97 (s, 3H), 1.63 – 1.46 (m, 2H), 1.35 – 1.19 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-*d*) δ = 178.0, 164.4, 159.4, 146.9, 146.4, 128.4, 123.5, 107.2, 90.2, 58.9, 45.3, 27.8, 19.3, 19.2, 13.5 ppm; HRMS (ESI-QTOF) calcd for $C_{17}H_{20}N_2O_5$ $[M + H]^+$ 333.1445, found 333.1454.



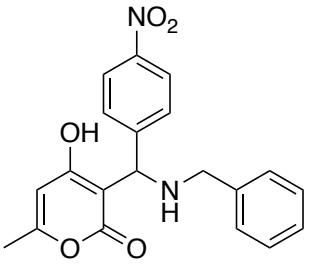
4-hydroxy-6-methyl-3-((4-nitrophenyl)(octylamino)methyl)-2*H*-pyran-2-one (18)

White solid (84%); ^{1}H NMR (400 MHz, DMSO-*d*) δ = 8.21 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 5.49 (s, 1H), 5.24 (s, 1H), 2.86 – 2.81 (m, 2H), 1.97 (s, 3H), 1.59 – 1.51 (m, 2H), 1.32 – 1.27 (m, 10H), 0.84 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-*d*) δ = 178.0, 164.4, 159.4, 146.9, 146.4, 128.4, 123.4, 107.2, 90.2, 58.9, 45.6, 31.1, 28.44, 28.39, 25.9, 25.6, 22.1, 19.2, 13.9 ppm; HRMS (ESI-QTOF) calcd for $C_{21}H_{28}N_2O_5$ $[M + H]^+$ 389.2071, found 389.2075.



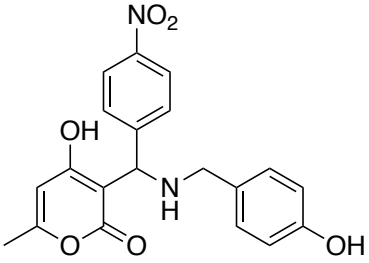
3-((allylamino)(4-nitrophenyl)methyl)-4-hydroxy-6-methyl-2H-pyran-2-one (19)

Pale yellow solid (79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 5.90 – 5.88 (m, 1H), 5.83 (s, 1H), 5.32 (d, 1H), 5.28 (t, 1H), 5.10 (s, 1H), 3.50-3.34 (m, 2H), 2.18 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.7, 164.4, 159.6, 146.9, 146.3, 129.6, 123.6, 122.1, 107.0, 90.5, 57.8, 47.6, 19.3 ppm; LRMS (ESI-QTOF) calcd for $C_{15}H_{16}N_2O_5$ $[M + H]^+$ 317.1108, found 316.1116.



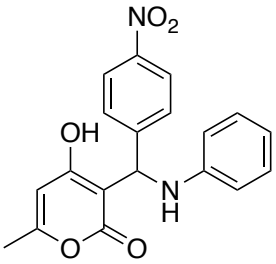
3-((benzylamino)(4-nitrophenyl)methyl)-4-hydroxy-6-methyl-2H-pyran-2-one (20)

Pale yellow solid (79%); ^{1}H NMR (400 MHz, DMSO-*d*) δ = 8.19 (d, J = 8 Hz, 2H), 7.72 (d, J = 8 Hz, 2H), 7.40-7.35 (m, 5H), 5.59 (s, 1H), 5.20 (s, 1H), 4.03 (s, 2H), 2.01 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-*d*) δ = 177.3, 164.3, 159.8, 147.0, 146.8, 133.5, 129.6, 128.5, 128.4, 123.5, 106.5, 91.2, 58.6, 49.3, 19.3 LRMS (ESI-QTOF) calcd for $C_{20}H_{18}N_2O_5$ $[M + H]^+$ 367.1288, found 367.1288.



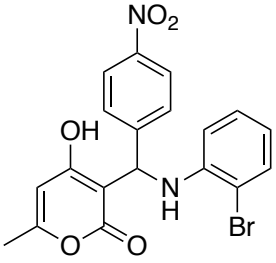
4-hydroxy-3-(4-hydroxybenzyl)amino)(4-nitrophenyl)methyl)-6-methyl-2H-pyran-2-one (21)

Dark yellow solid (72%); ^{1}H NMR (400 MHz, H_2O-*d*) δ = 8.21 (d, 2H), 7.66 (d, 2H), 7.30-7.34 (m, 4H), 5.73 (s, 1H), 5.35 (s, 1H), 4.09 (s, 2H), 1.95 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-*d*) δ =177.8, 173.1, 166.3, 164.6, 159.3, 157.8, 131.2, 130.5, 128.4, 123.4, 115.3, 106.5, 91.2, 57.9, 49.03, 19.32 ppm; HRMS (ESI-QTOF) calcd for $C_{20}H_{18}N_2O_6$ $[M + H]^+$ 383.1223, found 383.1244.



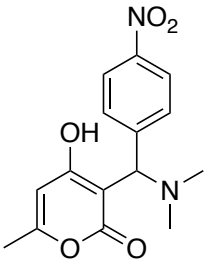
4-hydroxy-6-methyl-3-((4-nitrophenyl)(phenylamino)methyl)-2H-pyran-2-one (22)

Yellow solid (54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13 (d, 2H), 7.65 (d, 2H), 7.24 (d, 2H), 6.94 (t, 1H), 6.87 (d, 2H), 5.93 (s, 1H), 5.77 (s, 1H), 2.19 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-*d*) δ= 177.5, 164.3, 159.9, 146.9, 146.8, 133.3, 129.7, 128.9, 128.7, 128.6, 123.5, 106.7, 91.0, 58.7, 19.3 ppm; HRMS (ESI-QTOF) calcd for $C_{19}H_{16}N_2O_5$ [*M* + H]$^{+}$ 353.1136, found 353.1140.



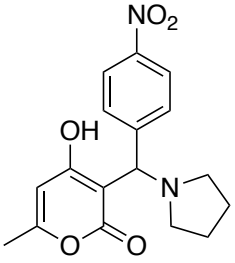
3-(((2-bromophenyl)amino)(4-nitrophenyl)methyl)-4-hydroxy-6-methyl-2H-pyran-2-one (23)

Yellow solid (62%); ^{1}H NMR (400 MHz, DMSO-*d*) δ = 8.19 (d, 2H), 7.69 (d, 2H), 7.50 (d, 1H), 7.18 (t, 1H), 6.74-6.82 (m, 2H), 6.00 (s, 1H), 5.88 (s, 1H), 2.20 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-*d*) δ = 168.7, 165.1, 163.0, 147.8, 143.0, 133.0, 129.0, 128.0, 124.2, 121.6, 114.4, 112.2, 101.7, 91.0, 55.5, 20.0 ppm; HRMS (ESI-QTOF) calcd for $C_{19}H_{15}BrN_2O_5$ [*M* + H]$^{+}$ 431.0258, found 431.0262.



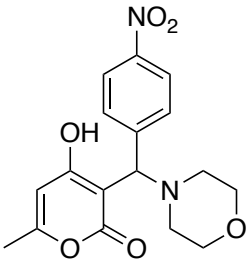
3-((dimethylamino)(4-nitrophenyl)methyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (24)

Bright yellow solid (95%); ^{1}H NMR (400 MHz, DMSO-*d*) δ = 8.22 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.8Hz, 2H), 5.52 (s, 1H), 5.25 (s, 1H), 2.65 (s, 6H), 1.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-*d*) δ = 177.26, 164.0, 159.5, 147.1, 145.5, 128.8, 123.8, 107.0, 91.8, 68.3, 41.9, 19.2; HRMS (ESI-QTOF) calcd for $C_{15}H_{16}N_2O_5$ $[M + H]^+$ 305.1132, found 305.1139.



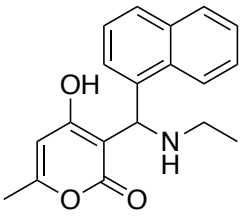
4-hydroxy-6-methyl-3-((4-nitrophenyl)(pyrrolidin-1-yl)methyl)-2H-pyran-2-one (25)

Bright yellow solid (91%); ^{1}H NMR (400 MHz, DMSO-*d*) δ = 8.19 (d, 2H), 7.84 (d, 2H), 5.48 (s, 1H), 5.31 (s, 1H), 3.05 (b, 4H), 1.95 (s, 3H), 1.90 (b, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.6, 164.8, 162.0, 148.0, 144.4, 130.0, 124.3, 104.7, 95.2, 70.0, 52.0, 23.0, 20.0 ppm. HRMS (ESI-QTOF) calcd for $C_{18}H_{20}N_2O_5$ $[M + H]^+$ 331.1288, found 331.1292.



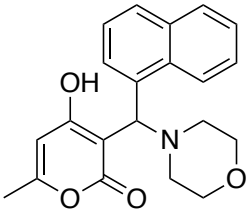
4-hydroxy-6-methyl-3-(morpholino(4-nitrophenyl)methyl)-2H-pyran-2-one (26)

Bright yellow solid (70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (d, 2H), 7.58 (d, 2H), 5.80 (s, 1H), 4.67 (s, 1H), 3.74 (b, 5H), 3.11 (b, 1H), 2.50 (b, 2H), 2.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.3, 163.6, 162.9, 147.7, 144.9, 124.2, 124.1, 101.4, 98.4, 69.3, 66.4, 45.1, 19.9 ppm; HRMS (ESI-QTOF) calcd for $C_{17}H_{18}N_2O_6$ [*M* + H]$^{+}$ 347.1239, found 347.1242.



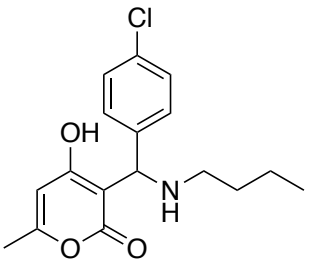
3-((ethylamino)(naphthalen-1-yl)methyl)-4-hydroxy-6-methyl-2H-pyran-2-one (27)

White solid (90% yield): ^{1}H NMR (400 MHz, DMSO-*d*) δ = 8.50 – 8.46 (m, 1H), 7.95 – 7.91 (m, 1H), 7.90 – 7.82 (m, 2H), 7.57-7.47 (m, 3H), 5.95 (s, 1H), 5.5 (s, 1H), 3.01 (q, J = 7.4 Hz, 2H,), 1.96 (s, 1H), 1.21 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-*d*) δ = 178.4, 164.6, 159.0, 134.6, 133.2, 130.7, 128.5, 128.1, 126.3, 125.7, 125.2, 125.1, 124.0, 107.4, 90.2, 54.6, 40.7, 19.2, 11.2; HRMS (ESI-QTOF) calcd for $C_{19}H_{19}NO_3$ [*M* + H]$^{+}$ 310.1438, found 310.1441.



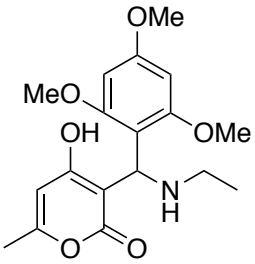
4-hydroxy-6-methyl-3-(morpholino(naphthalen-1-yl)methyl)-2H-pyran-2-one (28)

White solid (89%); m.p. 135-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39 (d, 1H), 7.84 (q, 2H), 7.68 (d, 1H), 7.59 (t, 1H), 7.42 (t, 1H), 7.47 (t, 1H), 5.85 (s, 1H), 5.77 (s, 1H), 3.98 – 2.50 (8H), 2.16 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.3, 164.3, 161.9, 133.8, 133.2, 132.6, 129.4, 129.0, 126.8, 126.0, 125.9, 125.5, 123.3, 102.1, 98.9, 66.2, 63.4, 45.0, 19.9; LRMS (ESI-QTOF) calcd for $C_{21}H_{21}NO_4$ $[M + H]^+$ 352.1543, found 352.1542.



3-((butylamino)(4-chlorophenyl)methyl)-4-hydroxy-6-methyl-2H-pyran-2-one (29)

White solid (89%); m.p. 149-150 °C. ^{1}H NMR (400 MHz, DMSO-*d*) δ = 7.53 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 5.49 (s, 1H), 5.07 (s, 1H), 2.84 – 2.75 (m, 2H), 1.97 (s, 3H), 1.58 – 1.48 (m, 2H), 1.34 – 1.25 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-*d*) δ = 178.2, 164.4, 159.2, 138.1, 132.5, 129.5, 128.2, 107.3, 90.6, 59.3, 45.3, 27.8, 19.3 (2C), 13.5; HRMS (ESI-QTOF) calcd for $C_{17}H_{20}ClNO_3$ $[M + H]^+$ 322.1204, found 322.1205.



3-((ethylamino)(2,4,6-trimethoxyphenyl)methyl)-4-hydroxy-6-methyl-2H-pyran-2-on (30)

White solid (62%); m.p. 150-151 °C. ^{1}H NMR (400 MHz, DMSO-*d*) δ = 6.21 (s, 2H), 5.44 (s, 1H), 5.36 (s, 1H), 3.76 (s, 3H), 3.71 (s, 6H), 2.72 (d, J = 7 Hz, 2H), 1.95 (s, 3H), 1.11 (t, J = 7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-*d*) δ = 178.0, 163.6, 160.8, 159.2, 158.0, 108.0, 106.7, 91.3, 89.5, 56.0, 55.3, 52.2, 41.1, 19.1, 11.4; HRMS (ESI-QTOF) calcd for $C_{18}H_{23}NO_6$ $[M + H]^+$ 350.1598, found 350.1607.

2.5. Reference

(1) Clark, J.; Deswarte, F. *Introduction to Chemicals from Biomass*, **2015**, 1-309.

(2) Sheldon, R. A. *Green Chem.* **2014**, *16*, 950.

(3) Clark, J. H.; Budarin, V.; Deswarte, F. E. I.; Hardy, J. J. E.; Kerton, F. M.; Hunt, A. J.; Luque, R.; Macquarrie, D. J.; Milkowski, K.; Rodriguez, A.; Samuel, O.; Tavener, S. J.; White, R. J.; Wilson, A. J. *Green Chem.* **2006**, *8* (10), 853.

(4) Bomtempo, J.-V.; Alves, F. C.; Oroski, F. D. A. *Faraday Discuss.* **2017**, *202*, 213.

(5) Department of Energy, *Top Value Added Chemicals from Biomass Volume I—Results of Screening for Potential Candidates from Sugars and Synthesis Gas*, 2004.

(6) Bozell, J. J.; Petersen, G. R. *Green Chem*. **2010**, *12*, 539.

(7) McGlacken, G. P., Fairlamb, I. J. *Natural product reports* **2005***, 22*(3), 369.

(8) Lee, J. S. *Marine Drugs* **2015**, *13*, 1581.

(9) Chia, M.; Schwartz, T. J.; Shanks, B. H.; Dumesic, J. A. *Green Chemistry* **2012**, *14,* 1850.

(10) Collie, J. N. *J. Chem. Soc., trans.* **1891**, *59*, 607.

(11) Eckermann, S.; Schröder, G.; Schmidt, J.; Strack, D.; Edrada, R. A.; Helariutta, Y.; Elomaa, P.; Kotilainen, M.; Kilpeläinen, I.; Proksch, P.; Teeri, T. H.; Schröder, J. *Nature* **1998**, *396* (6709), 387.

(12) Tang, S.-Y.; Qian, S.; Akinterinwa, O.; Frei, C. S.; Gredell, J. A.; Cirino, P. C. *J. Am. Chem. Soc.* **2013**, *135* (27), 10099.

(13) Zha, W.; Shao, Z.; Frost, J. W.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126* (14), 4534.

(14) Xie, D.; Shao, Z.; Achkar, J.; Zha, W.; Frost, J. W.; Zhao, H. *Biotechn. Bioeng.* **2006**, *93* (4), 727.

(15) Cardenas, J.; Silva, N. A. D. *Metabolic Engineering*, **2014**, *25*, 194.

(16) Saunders, L. P.; Bowman, M. J.; Mertens, J. A.; Silva, N. A. D.; Hector, R. E. *J. Ind. Microbiol. Biotechnol.* **2015**, *42*, 711.

(17) Huck, W.-R.; Mallat, T.; Baiker, A. *Journal of Catalysis,* **2000**, *193*, 1.

(18) Huck, W.-R.; Bürgi, T.; Mallat, T.; Baiker, A. *Journal of Catalysis,* **2001**, *200*, 171.

(19) Huck, W.-R.; Mallat, T.; Baiker, A. *New Journal of Chemistry,* **2002**, *26*, 6.

(20) Huck, W.-R.; Bürgi, T.; Mallat, T.; Baiker, A. *Journal of Catalysis,* **2003**, *219*, 41.

(21) Hansen, C. A.; Frost, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 5926.

(22) Achkar, J.; Xian, M.; Zhao, H.; Frost, J. W. *J. Am. Chem. Soc.* **2005**, *127*, 5332.

(23) Kraus, G. A.; Basemann, K.; Guney, T. *Tetrahedron Lett.* **2015**, *56* (23), 3494.

(24) Kraus, G. A.; Wanninayake, U. K. *Tetrahedron Lett.* **2015**, *56* (51), 7112.

(25) Kraus, G. A.; Wanninayake, U. K.; Bottoms, J. *Tetrahedron Lett.* **2016**, *57* (11), 1293.

(26) Dömling, A.; Ugi, I. *Angew. Chem. Intl. Ed.* **2000,** *39*, 3168.

(27) Ugi, A.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 734.

(28) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003,** *10,* 51.

(29) Blicke, F. F. *Organic Reactions.* **2001**, *1* (10), 303.

(30) Bye, A.; King, H. K. *Biochemical Journal.* **1970**, *117* (2), 237.

(31) Patil, A. D.; Freyer, A. J.; Eggleston, D. S.; Haltiwanger, R. C.; Bean, M. F.; Taylor, P. B.; Caranfa, M. J.; Breen, A. L.; Bartus, H. R.; Johnson, R. K.; Hertzberg, R. P.; Westley, J. W. *J. Med. Chem.* **1993**, *36*, 4131.

(32) Guilet, D.; Hélesbeux, J.-J.; Séraphin, D.; Sévenet, T.; Richomme, P.; Bruneton, J. *J. Nat. Prod.* **2001**, *64*, 563.

(33) Onkara, P.; Kumar, A. S.; Kanakaraju, S.; Prasanna, B.; Pydisetty, Y.; Chandramouli, G. V. P. *Int J. Pharm. Bio. Sci.* **2013**, *4*, 263.

(34) Kumar, A.; Gupta, M. K.; Kumar, M. *Tetrahedron Lett.* **2011**, *52* (35), 4521.

(35) Zaheer, Z.; Khan, F. A. K.; Sangshetti, J. N.; Patil, R. H. *Chinese Chemical Letters* **2016**, *27* (2), 287.

(36) Ghosh, P. P.; Das, A. R. *Tetrahedron Lett.* **2012**, *53* (25), 3140.

(37) Rao, P.; Konda, S.; Iqbal, J.; Oruganti, S. *Tetrahedron Lett.* **2012**, *53* (39), 5314.

(38) Sangshetti, J. N.; Khan, F. A. K.; Kute, C. S.; Zaheer, Z.; Ahmed, R. Z. *Russian Journal of Organic Chemistry* **2015**, *51* (1), 69.

(39) Ghafuri, H.; Ghorbani, B.; Rashidizadeh, A.; Talebi, M.; Roshani, M. *Appl. Organometal. Chem.* **2017**, *32* (3), 4147.

CHAPTER 3.

A SYNTHRETIC APPROACH TO HIBISCONE C

3.1. Introduction

A series of natural products containing a 2,4-diacylfuran subunit have been isolated and studied since 1945, four examples were selected and shown in Figure 1. Viridin **2** was originally described in 1945 as an antifungal metabolite of *Gliocladium virens*.[1] Belonging to the class of furanosteroids, viridian possesses a highly strained furan ring fused with the steroid skeleton. Viridin exhibits some antibiotic activity against plant pathogens such as *Rhizoctonia solani* and *Pythium ultimum*. Halenaquinone **3** was originally reported in 1983 from a tropical marine sponge.[2] The Halenaquinone family possesses a variety of bioactivities such as antibacterial, antifungal, cardiotonic, cytotoxic and inhibitory activity against enzymes such as protein tyrosine kinase, topoisomerases and myosin Ca^{+} ATPase.[3] Asperfuranone **4** was a novel compound of genomic mining in *Aspergillus nidulans*. It showed anti-proliferative activity in human non-small cell lung cancer A549 cells.[4]

Hibiscone C (Gmelofuran) **5** is a structurally unique furanosesquiterpenoid originally isolated from *Gmelina arborea* in 1978.[5] It was also found in *Hibiscus sp*., the national tree of Jamaica, so the name changed to Hibiscone C.[6] Most recently, it was also isolated from the roots of *Bombax malabaricum*.[7] The Hibiscone family compounds possess a wide range of bioactivities such as inhibition of superoxide anion generation by human neutrophils.[8-9] Hibiscone C has a furan ring as part of a bicyclo [4, 4, 0] decane system, which is commonly found in a number of natural products. Compared with some other natural products within the furanosteroids family, Hibiscone C is structurally

simpler and less studied. Recently, it has been reported that Hibiscone C competitively inhibited the phosphatidylinositol-3-kinase (PI_3K) activity in intact cells, slowed proliferation and induced cell death. Therefore this compound might serve as a productive scaffold for the development of therapeutically relevant PI_3K inhibitors.[10]

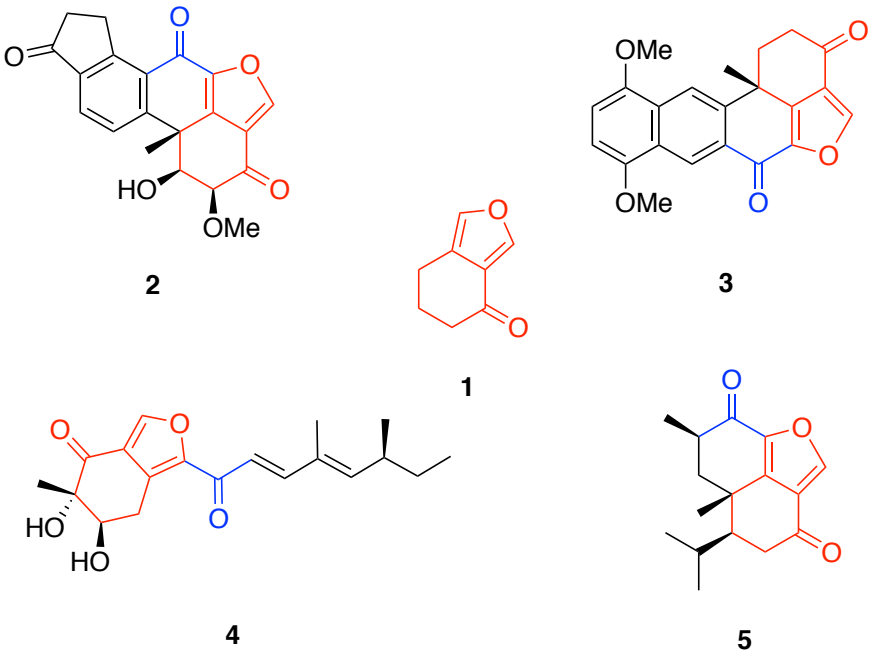
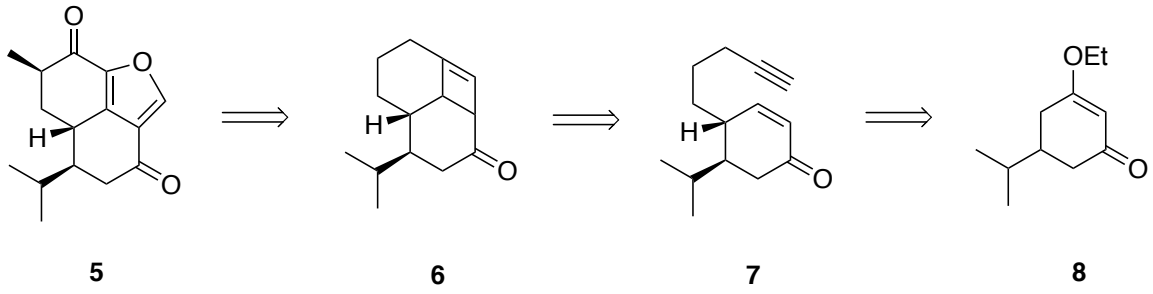


Figure 1. 2,4-Diacylfuran containing natural products

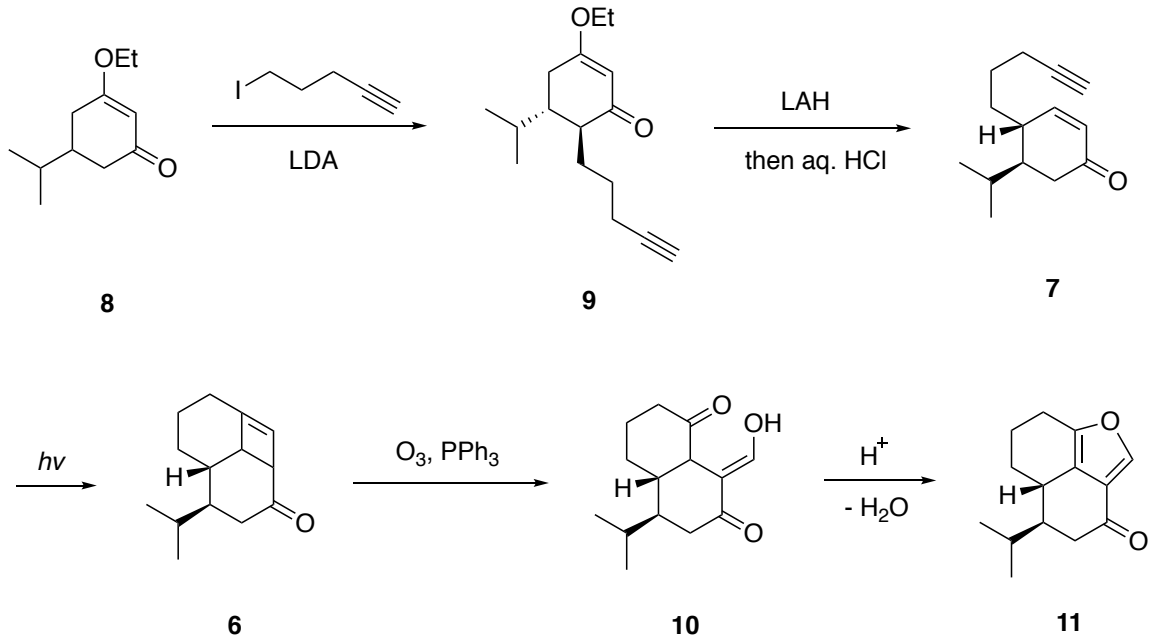
There have been four reported syntheses of Hibiscone C. The Smith group reported the first total synthesis of (±)-Hibisocne C in 1982, in which an intramolecular alkyne-enone [2+2] photochemical cycloaddition was utilized to form a cyclobutene intermediate.[11-12] Ozonolysis and acidic cyclization led to the final product. The retro-synthetic analysis is shown in Scheme 1.



5 **6** **7** **8**

Scheme 1. Retrosynthesis of (±)-Hibiscone C

The synthesis started with the alkylation of β-ethoxyenone **8**, followed by Stork-Danheiser sequence (LAH reduction followed by acid work-up) gave alkyne-enone compound **7** in 60% yield. Irradiation of **7** in dilute hexane under argon for 24 hours generates compound **6** in 60% yield. Ozonolysis of **6** followed by acid-catalyzed dehydration led to furan **11** in 50% yield over two steps.



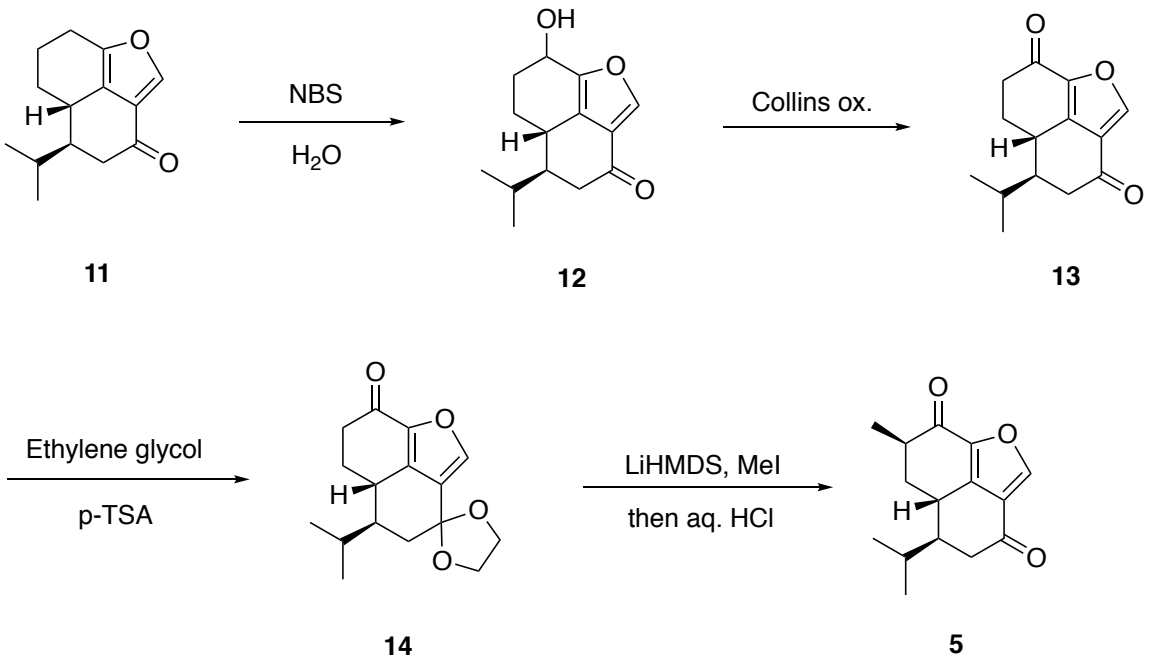
8 **9** **7**

6 **10** **11**

Scheme 2. Synthesis of furan 11

In order to generate the second carbonyl group, allylic oxidation by Collins reagent was employed initially because many simple furan rings are quite stable to the Collins reagent. However, direct oxidation caused extensive decomposition. Compound

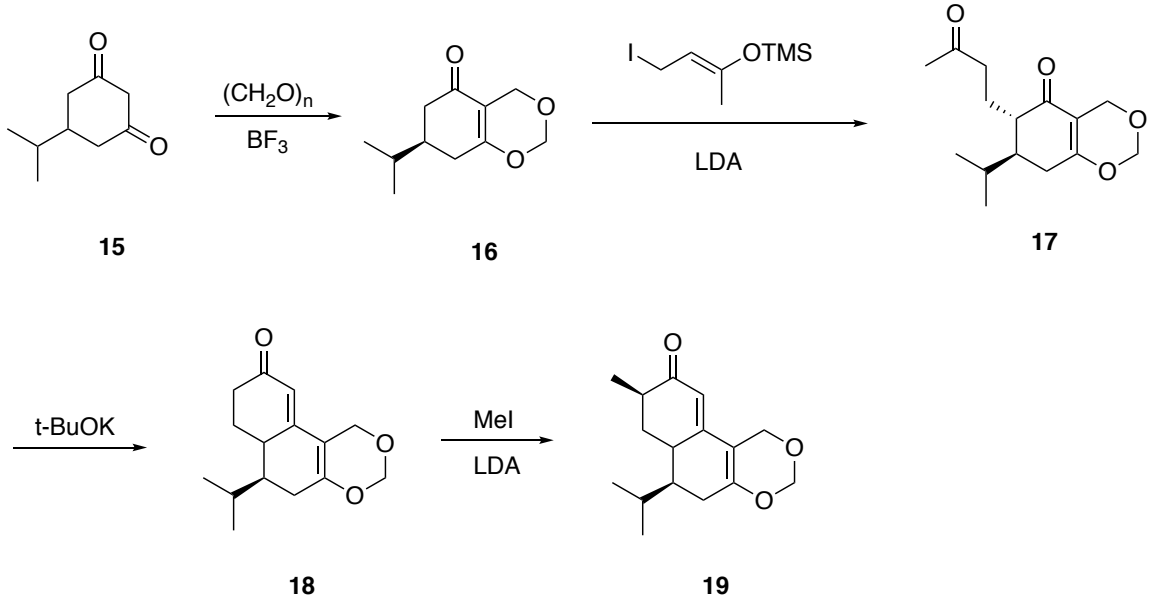
11 also suffered deconstruction from attempted selenium dioxide oxidation. The most effective oxidation of **11** was accomplished by a two-step NBS/water-Collins oxidation protocol in 25% yield over two steps. Selective mono-protection of the specific carbonyl group was furnished by exposure **13** into ethylene glycol under acidic condition. Despite the modest yield (40%), the separation of the desired monoketal **14** is practically feasible from the remainder of the reaction mixture (i.e., starting material and other ketalization products). Deprotonation of **14** by LiHMDS followed by addition of excess methyl iodide and acidic hydrolysis afforded racemic Hibiscone C in 64% yield, accompanied by less than 7% of the equatorial methyl epimer.



Scheme 3. Smith Synthesis of (±)-Hibiscone C

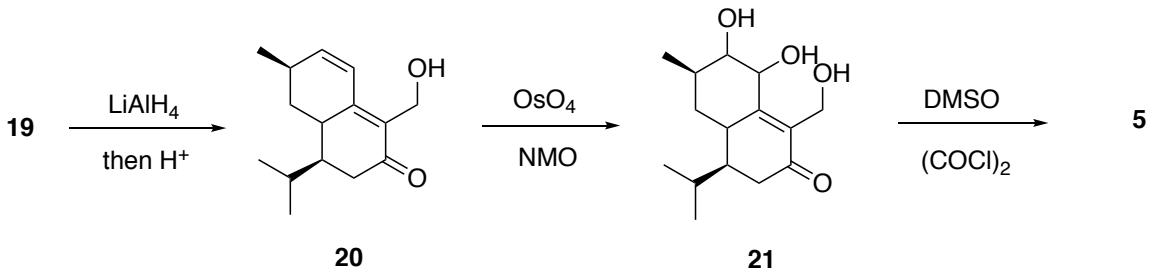
In 1999, Kraus group reported a seven-step synthesis of racemic Hibiscone C starting from 5-isopropyl-1,3-cyclohexanedione **15**.[13] Reaction of **15** with formaldehyde in the presence of boron trifluoride afforded **16** in 92% yield. Treatment of **16** with LDA followed by the silyl enol ether of 4-iodo-2-butanone gave a diketone **17**. Intramolecular

aldol condensation of **17** with potassium tert-butoxide in t-BuOH yielded enone **18**. Methylation of **18** using LDA provided **19** in 95% yield as a single isomer.



Scheme 4. Synthesis of compound 19

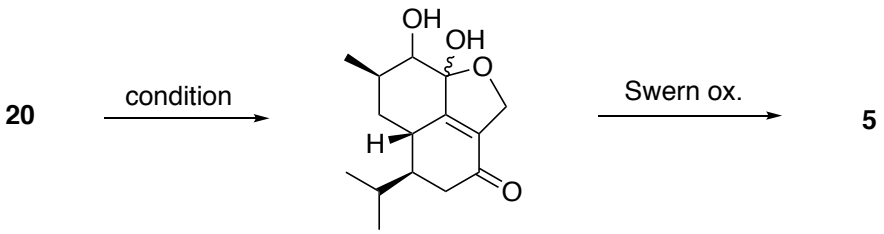
Employing Stork-Danheriser sequence (LAH followed by acidic work-up) with compound **19** produced the rearranged hydroxyl enone **20** in almost quantitative yield. The following dihydroxylation with Osmium tetroxide and N-methylmorpholine N-oxide (NMO) provided triol **21**. The triol was oxidized with 2.5 equivalents of Swern reagent to generate Hibiscone C in 85% isolated yield.



Scheme 5. Kraus Synthesis of (±)-Hibiscone C

Based on the Kraus' synthesis of Hibiscone C in 1999, Goess reported a modified synthesis of Hibiscone C ten years after, due to the failure of obtaining the triol **21** under

the same dihydroxylation condition Kraus reported.[14] In this paper, they utilized a different set of reagents ($K_2OsO_4/K_3Fe(CN)_6$) that has been found to mediate regioselective dihydroxylations on a range of conjugated dienes. Under this condition cyclized diol **22** was isolated in 86% yield instead of the desired triol **21**. Exposure **21** to Swern oxidation condition simultaneously generates Hibiscone C in quantitative yield.



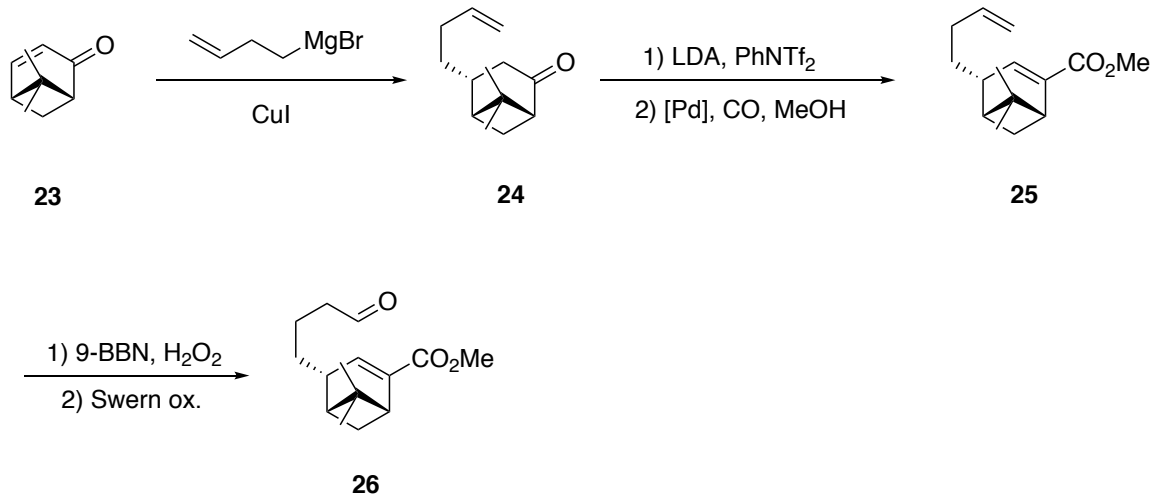
22

condition: $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $CH_3SO_2NH_2$, K_2OsO_4, t-BuOH, H_2O

Scheme 6. Goess Synthesis of (±)-Hibiscone C

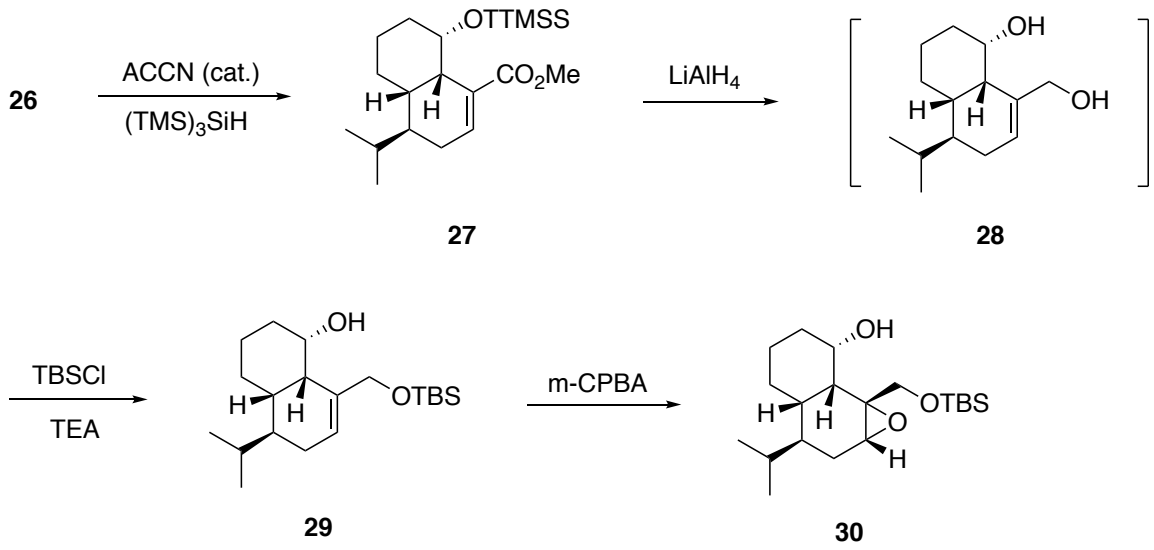
In 2017, Luo reported an asymmetric total synthesis of (−)-Hibiscone C and this is the first asymmetric synthesis to be reported to date.[15] The synthesis was achieved using a radical cyclization/fragmentation cascade strategy.

The asymmetric synthesis of (−)-Hibiscone C started from the chiral enone (+)-apoverbenone **23** readily available from (−)-β-pinene in three steps. Copper iodide catalyzed diastereoselective Michael addition *trans* to the bridge carbon using Grignard reagent could be achieved due to the steric hindrance of the *gem*-dimethyl group. Transforming the resulting single diastereomer ketone **24** into the enol triflate followed by Palladium catalyzed methoxycarbonylation led to **25**. Classical hydroboration-oxidation of **25** generated aldehyde **26**.



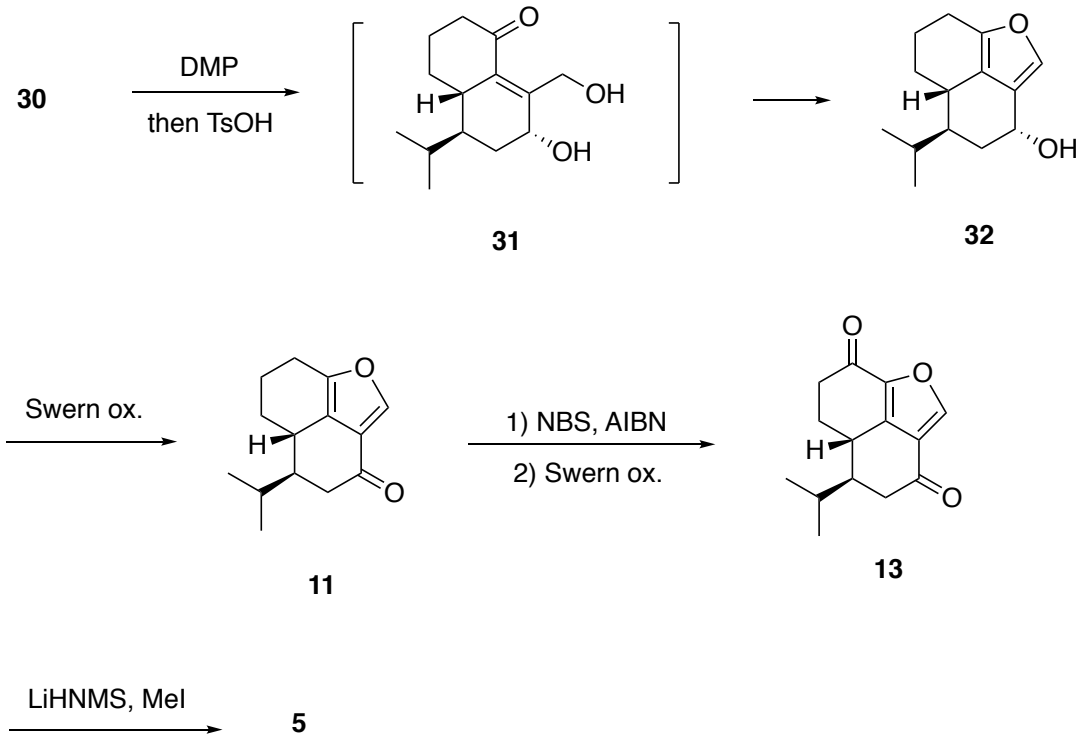
Scheme 7. Synthesis of aldehyde 26

For the transformation of **26** to **27**, tris(trimethylsilyl)silane with a catalytic amount of 1,1'-azobis(cyclohexyl)carbonitrile (ACCN) provided the best cyclization/ring-ruptured product as a single diastereomer in 83% yiled. Reduction of **27** using LAH was accompanied by the loss of tris(trimethylsilyl)silyl group, leading to diol **28**, which was monoprotected to generate **29** in 77% yield over two steps. The hydroxyl-directed epoxidation of **29** generated **30** in 68% yield.



Scheme 8. Synthesis of compound 30

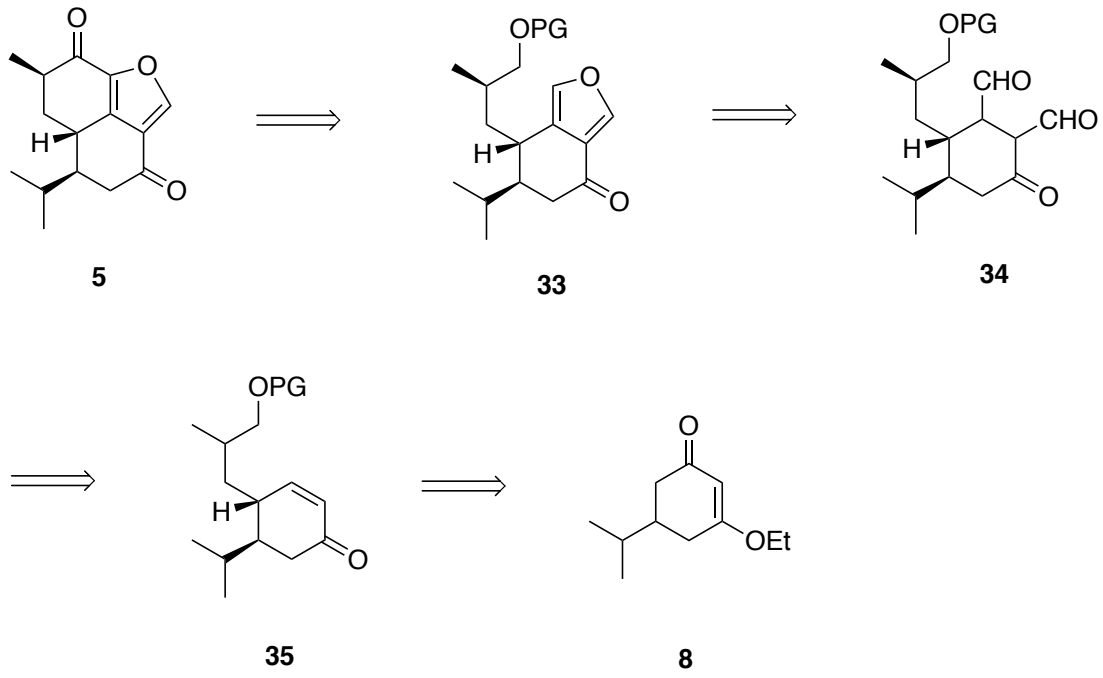
Compound **32** was generated by treatment of **30** with Dess-Martin Periodinane followed by p-toluenesulfonic aicd in THF/H_2O. The one pot cyclization/aromatization was achieved presumably via intermediate **31**. Swern oxidation of **32** yielded **11**. Taking advantage of the previous conditions reported by Smith and Kraus, (−)-Hibiscone was achieved.



Scheme 9. Luo Synthesis of (−)-Hibiscone C

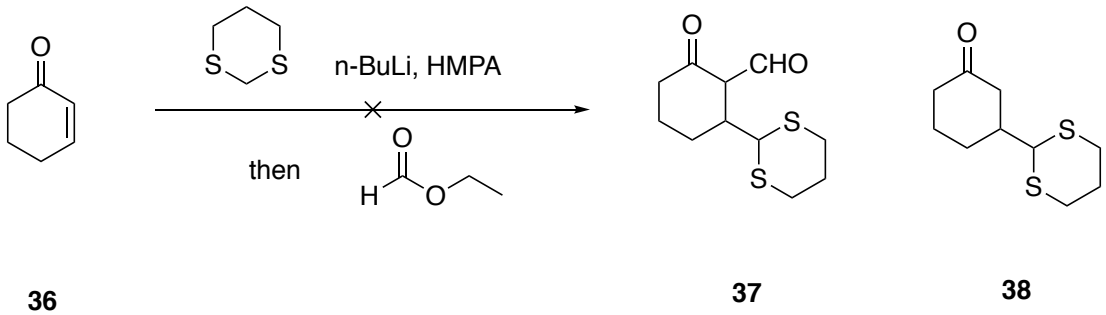
3.2. Results and Discussion

All these four routes constructed the furan ring prior to the installation of the 2-acyl group via redox manipulations. Due to the increased interest in the bioactivity of Hibiscone C, we were prompted to synthesize this compound in a strategically different route. Originally we wanted to take advantage of the Paal-Knorr furan synthesis to establish the core structure **1** and the retrosynthesis was shown in Scheme 10.



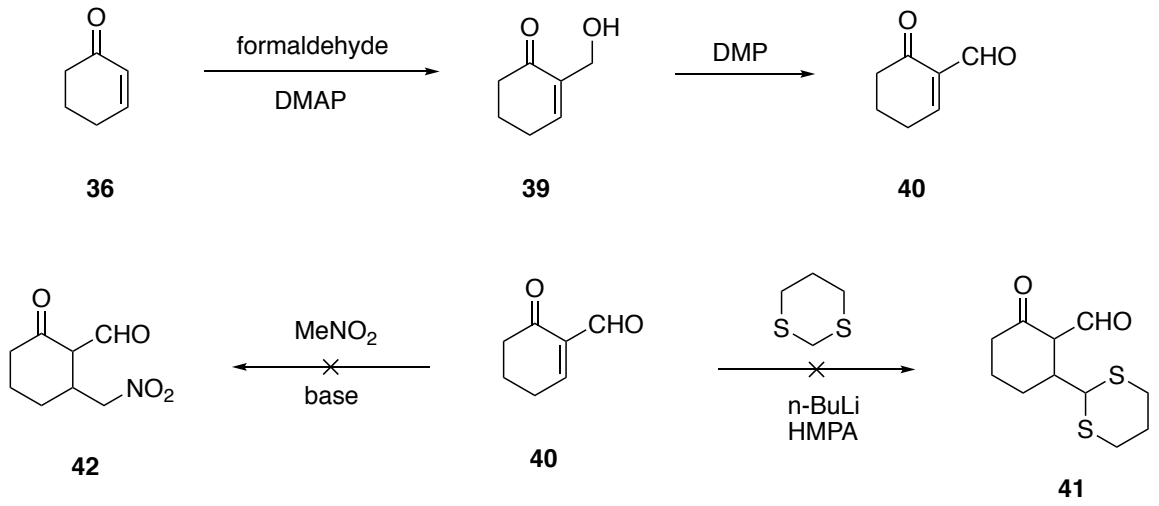
Scheme 10. Initial retrosynthesis

From the retrosynthesis above, we consider the transformation of **35** to **34** as the key step. 2-Cyclohexenone **36** was initially chosen as the starting material for the study. We wished to take advantage of the Michael Addition between 2-lithio-1,3-dithiane and 2-cyclohexen-1-one and trap the reaction intermediate with ethyl formate to generate compound **37**, however, only compound **38** was obtained. It is noteworthy to point out that when allyl bromide was employed to trap the reaction intermediate, the allyl group could be installed at the α-position of the carbonyl.



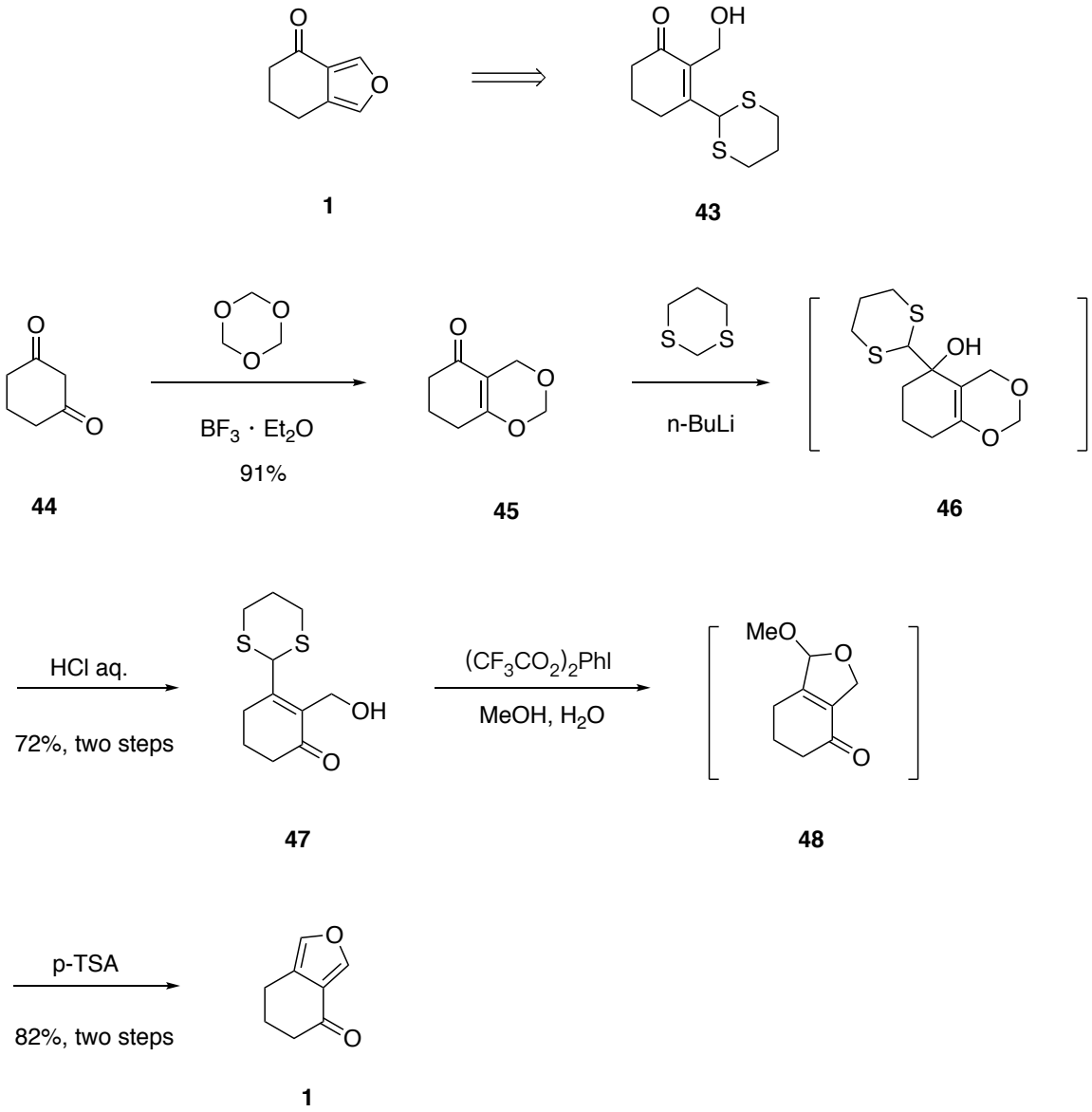
Scheme 11. Attempted Synthesis of 37

Cyclohexenone **40** was then synthesized via Bayllis-Hilman reaction followed by DMP oxidation.[16] However, Michael addition between 2-lithio-1,3-dithiane and **40** did not give any desired product **41**. The anion of nitromethane also failed to yield the desired product **42**, possibly due to the instability of compound **40**.



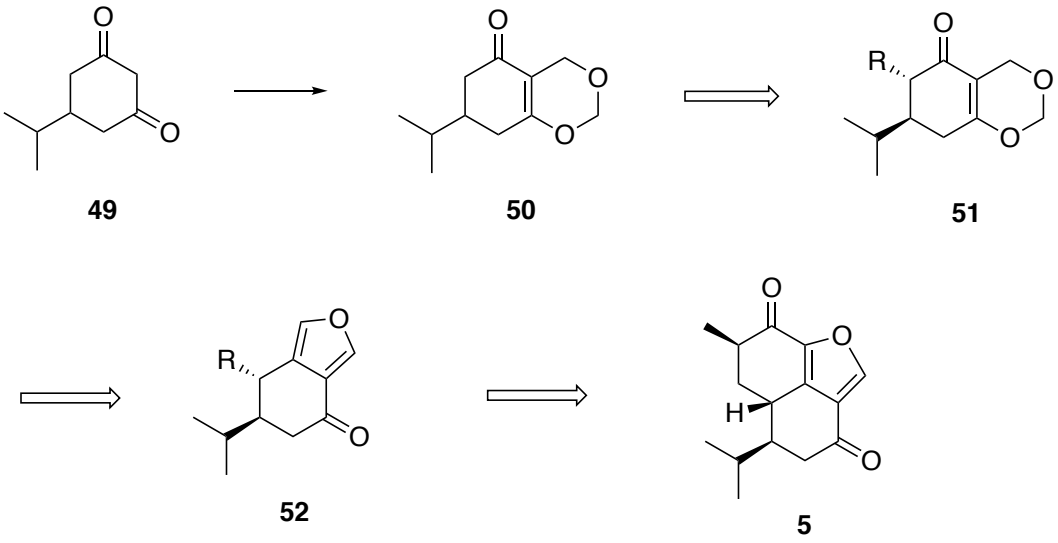
Scheme 12. Attempted synthesis of 41 and 42

From the inspiration by structure **39**, we envisaged that the core structure **1** could also come from intermediate **43** as shown in Scheme 13. The dioxin **45**, which has been utilized as an intermediate for the synthesis of Hibiscone C by Wan and Kraus, attracted our attention.[13,17-19] Treatment of 1,3 cyclohexanedione **44** with 2-lithio-1,3-thiane followed by addition of aqueous HCl generated tertiary alcohol **46**, which could be further transformed into our desired intermediate **47** after addition of aqueous HCl.[20-21] The Stork-Danheiser sequence can be done in one pot. Treatment of **47** with [bis(trifluoroacetoxy)]iodobenzene in a 9:1 mixture of methanol and water at room temperature, gave compound **48**, further fragmentation by p-TSA gave the desired product **1** in 50% overall yield from 1,3-cyclohexanedione.[22]



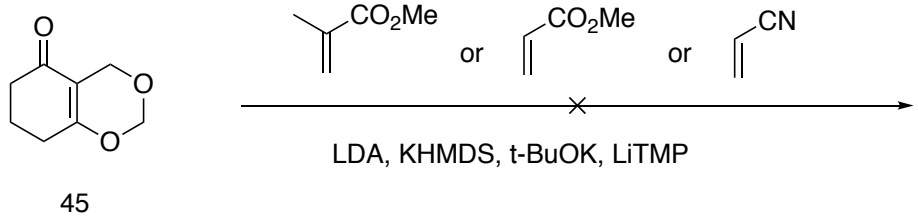
Scheme 13. Synthesis of 1

With the established reaction route at hand, we sought to use the new methodology to access Hibiscone C. As shown in Scheme 14, dioxin **50** could be easily made from diketone **49**. The question then became what is the R group we should install on structure **51**.



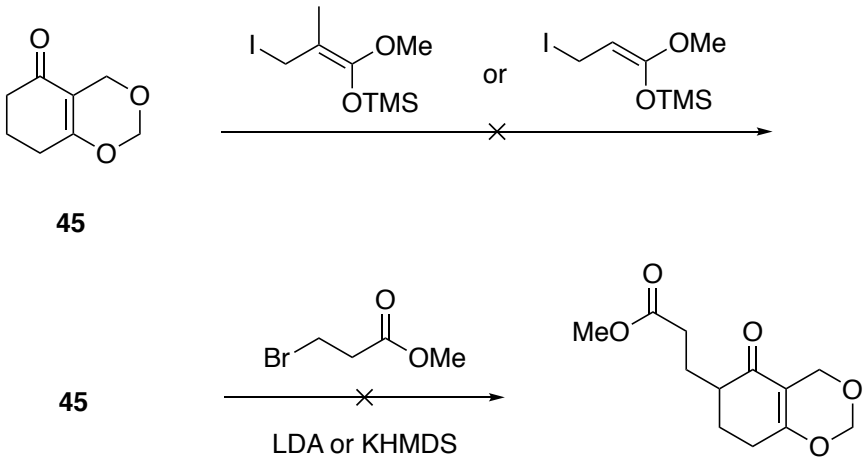
Scheme 14. Synthetic plan

First we tried to take advantage of the Michael addition reaction to access **5**; however, no reaction occurred when methyl methacrylate, methyl acrylate or acrylonitrile were utilized as the Michael accepter. Attempting to transform **45** into an enamine using pyrrolidine and p-TSA did not afford any desired product. Only starting materials were recovered.



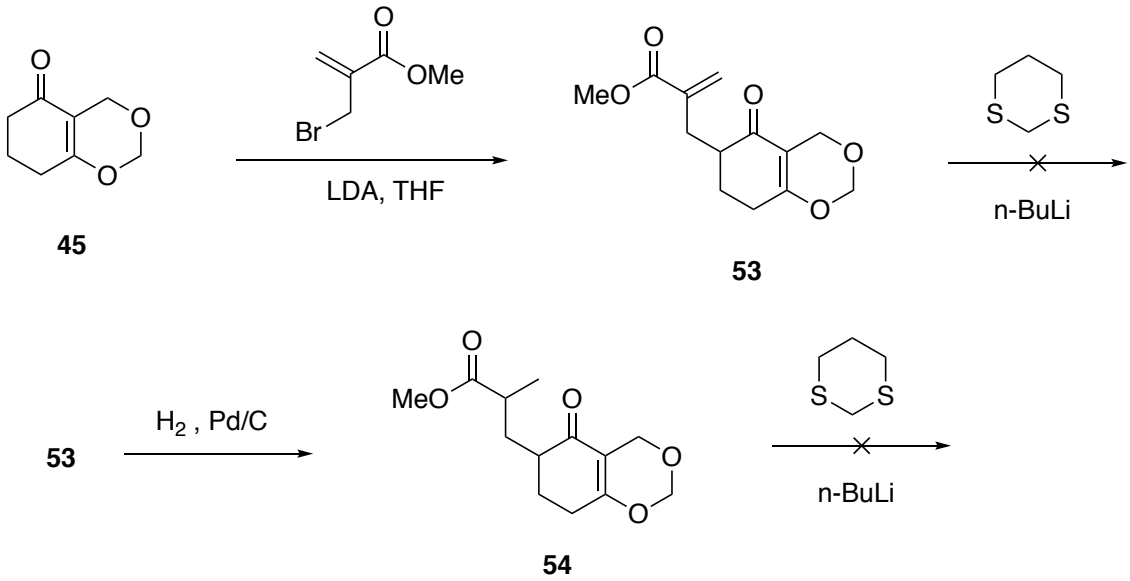
Scheme 15. Attempted Michael Addition of 45

Due to the recalcitrance of the Michael addition, the idea of utilizing the silyl enol ether of acrylates (the adducts of TMSI with methyl acrylate or methyl methacrylate) was tried. However, the in situ generated silyl enol ether did not work for our case. Starting materials were recovered. Reaction of **45** with methyl 3-bromopropionate also did not give any desired product, possibly due to the tendency of β-elimination.



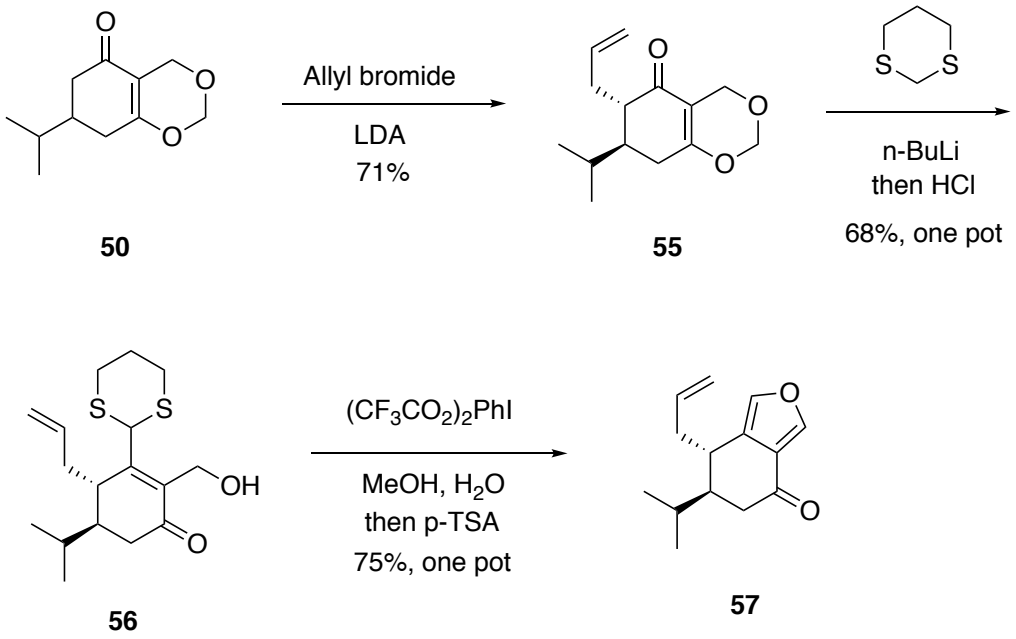
Scheme 16. Attempted synthesis

To avoid the possibility of the β-elimination of the reactant, methyl 2-(bromomethyl)acrylate was utilized. Compound **53** was obtained. However, the subsequent dithiane chemistry failed and only returned starting material. Reduction of the double bond on the side chain did not help for the dithiane chemistry. Possibly due to the steric hindrance, the 2-lithio-1,3-dithiane can no longer access the carbonyl group.



Scheme 17. Attempted synthesis

Allyl bromide was then employed because the terminal double bond could be potentially transformed into the functional groups we need. Treatment of **50** with allyl bromide and LDA gave compound **55** in 71% yield. Using the previously established protocol for **1**, acylfuran **57** could be obtained in 36% overall yield from **50**.

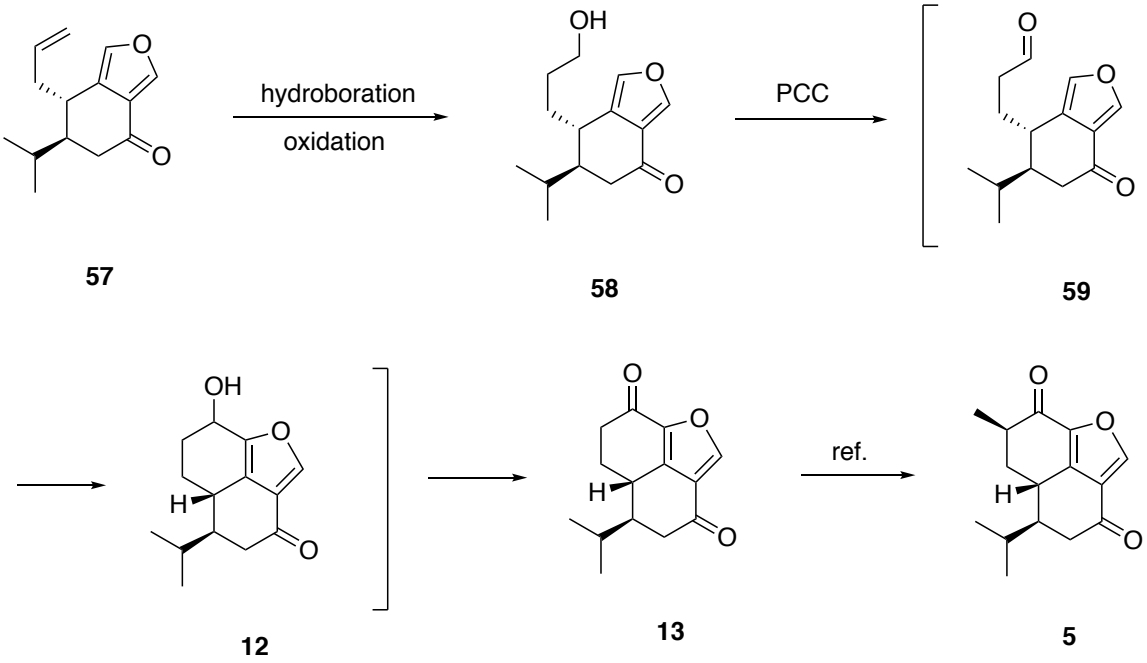


Scheme 18. Synthesis of acylfuran 57

With compound **57** at hand, all the skeletal carbons have been set up for Hibiscone C. Different hydroboration-oxidation conditions were tested and we found that utilizing catecholborane in the presence of Wilkinson's catalyst followed by sodium perborate oxidation is the only effective method for this step (Table 1).[23] In the presence of 4 equivalent of PCC, compound **13** can be achieved in one pot via an oxidation/Friedel-Crafts/oxidation cascade sequence. The last methylation step has been reported previously.

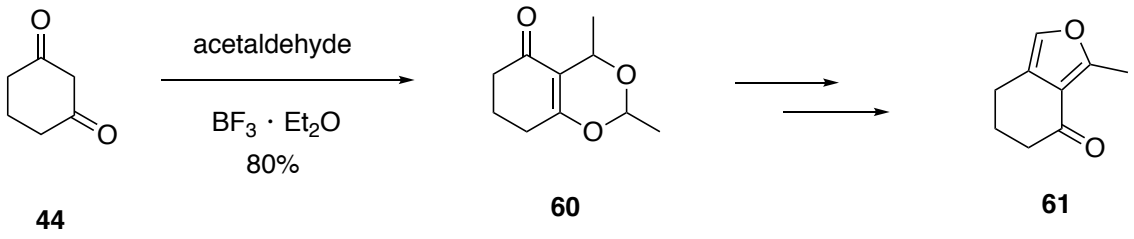
Table 1. Hydroboration-oxidation condition screening

Entry	Conditions	Results
1	BH_3·THF, then $NaBO_3$·$4H_2O$	No product observed
2	9-BBN, then H_2O_2, NaOH	N.R.
3	BH_3·THF, 2.5 eq. cyclohexene, then $NaBO_3$·$4H_2O$	No product observed
4	BH_3·SMe_2, 2.5 eq. cyclohexene, then $NaBO_3$·$4H_2O$	No product observed
5	Catechol borane, then $NaBO_3$·$4H_2O$	N.R.
6	Pinacolborane, then then $NaBO_3$·$4H_2O$	N.R.
7	Catechol borane, $(PPh_3)_3RhCl$ then $NaBO_3$·$4H_2O$	55%



Scheme 19. Synthesis of (±)-Hibiscone C

It is also noteworthy to mention that compound **61** could also be synthesized using the same protocol.



Scheme 20. Synthesis of 61

3.3. Conclusion

The bicyclic core structure **1** of Hibiscone C was achieved in 3 steps from commercially available 5-isopropyl-1,3-cyclohexanedione in 50% overall yield. The demethyl Hibiscone C precursor was synthesized using the methodology discovered herein in 12 % yield. This is a strategically new approach to Hibiscone C and has the potential to be employed in other 2,4-diacylfuran containing natural products.

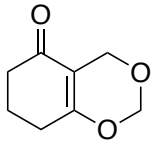
3.4. Experimental

General Procedures

All starting materials were purchased from Sigma-Aldrich; Tetrahydrofuran (THF) was freshly distilled over lithium aluminum hydride and other 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 chromatographically isolated products. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.20 mm silica gel plates using UV light as a visualizing agent. Silica gel 60A, particle size 0.032 – 0.063 mm, was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 1.00 mm silica gel plates. ^{1}H and ^{13}C NMR spectra were acquired in

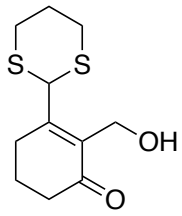
$CDCl_3$ on a Varian MR-400 or Bruker Avance III 600 MHz spectrometer. ^1H and ^{13}C chemical shifts (δ) are given in ppm relative to the residual protonated chloroform peak ($CDCl_3$: δH = 7.26 ppm, δC = 77.0 ppm) as an internal reference. High-resolution mass spectra (HRMS) were recorded on an Agilent 6540 QTOF (quadrupole time of flight) mass spectrometer using ESI (electrospray ionization).

Selected Experimental, Physical, and Spectral Data



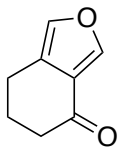
4,6,7,8-tetrahydro-5H-benzo[d][1,3]dioxin-5-one (45)

To a stirred solution of 1,3-cyclohexanedione (1.12 g, 10 mmol) and 1,3,5-trioxane (3.6 g, 40 mmol) in DCM was added $BF_3 \cdot Et_2O$ (2.84 g, 20 mmol) dropwise at room temperature. The resulting solution was stirred at room temperature for another 16 hours, at which time it was filtered through a short pad of Celite, which was rinsed with two 25 mL portions of DCM. The resulting solution was cooled to 0 °C and slowly quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). Standard extractive workup, followed by silica gel chromatography (elution with Hexane/Ethyl Acetate = 2:1) gave 1.4 g (91%) of **1** as yellow oil. R_f = 0.43 (Hexane/Ethyl Acetate = 1:1).



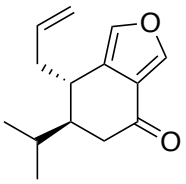
3-(1,3-dithian-2-yl)-2-(hydroxymethyl)cyclohex-2-en-1-one (47)

To a solution of 1,3-dithiane (574 mg, 4.8 mmol) in 12 mL THF at -78 °C was added n-BuLi (2.5 M in hexane, 4.4 mmol, 1.7 mL) dropwise, the resulting solution was stirred at the same temperature for an hour and then brought to 0 °C for another 30 minutes. The solution was then cooled down to -78 °C before the solution of **1** (566 mg, 3.67 mmol) in 6 mL THF was added dropwise. The resulting solution was slowly warm up to room temperature and stirred for 6 hours. The solution was cooled to 0 °C and 4 mL 2 M aqueous HCl was added, the resulting solution was brought to room temperature and stirred for 12 hours. Standard extractive workup by EtOAc, followed by silica gel chromatography (elution with Hexane/Ethyl Acetate = 2:1) gave 645 mg (72%) of **1**. R_f = 0.27 (Hexane/Ethyl Acetate = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 1H), 4.47 (d, J = 6.0 Hz, 2H), 3.03 (ddd, J = 14.8, 12.6, 2.4 Hz, 2H), 2.93 – 2.83 (m, 2H), 2.63 (t, J = 5.9 Hz, 2H), 2.45 – 2.38 (m, 2H), 2.11 – 2.18 (m, 1H), 1.93 – 2.03 (m, 2H), 1.83 – 1.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 156.2, 135.5, 56.4, 50.6, 37.5, 31.0, 28.0, 25.0, 22.1; HRMS (ESI-QTOF) calcd for $C_{11}H_{16}O_2S_2$ $[M+H]^+$ 245.0664, found 245.0663.



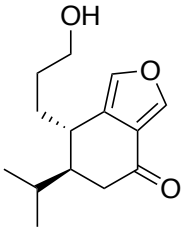
6,7-dihydroisobenzofuran-4(5H)-one (1)

To a solution of **1** (319 mg, 1.31 mmol) in a mixture solvent of 4.5 mL methanol and 0.5 mL water at 0 °C, [Bis(trifluoroacetoxy)iodo]benzene (1.13 g, 2.62 mmol) was added portionwise. The reaction was brought to room temperature and stirred for half an hour before p-TSA (500 mg, 2.62 mmol) was added. The resulting mixture was heated at 65 °C for 6 hours, then cooled to room temperature and 10 mL water was added. Standard extractive workup by EtOAc, followed by silica gel chromatography (elution with Hexane/Ethyl Acetate = 2:1) gave 146 mg (82%) of **1**. R_f = 0.71 (Hexane/ EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 1.4 Hz, 1H), 7.25 (q, J = 1.4 Hz, 1H), 2.66 (td, J = 6.2, 1.4 Hz, 2H), 2.47 (t, J = 8.0 Hz, 2H), 1.98 – 2.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 144.1, 138.1, 124.5, 124.0, 39.6, 24.0, 19.5; HRMS (ESI-QTOF) calcd for $C_8H_8O_2$ $[M+H]^+$ 137.0597, found 137.0601.



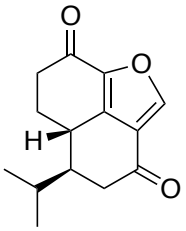
7-allyl-6-isopropyl-6,7-dihydroisobenzofuran-4(5H)-one (57)

Compound **1** was prepared by using previous described procedure for compound **1** in xx% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 1.5 Hz, 1H), 7.30 (t, J = 1.4 Hz, 1H), 5.73 – 5.85 (m, 1H), 5.13 – 5.08 (m, 1H), 5.07 (d, J = 1.5 Hz, 1H), 2.95 – 2.86 (m, 1H), 2.59 (dd, J = 17.0, 3.8 Hz, 1H), 2.54 – 2.47 (m, 1H), 2.44 – 2.35 (m, 2H), 1.89 – 1.76 (m, 2H), 0.89 (dd, J = 16.3, 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 143.5, 139.0, 135.3, 127.3, 123.5, 117.1, 45.3, 38.6, 37.1, 33.0, 27.7, 21.1, 17.9. HRMS (ESI-QTOF) calcd for $C_{14}H_{18}O_2$ $[M+H]^+$ 219.1380, found 219.1378.



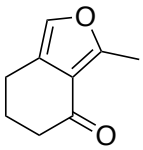
7-(3-hydroxypropyl)-6-isopropyl-6,7-dihydroisobenzofuran-4(5H)-one (58)

A solution of 1 () in THF was added to a dried round bottom flask charged with $Rh(PPh_3)_3Cl$ () with stirring. The solution was cooled to 0 °C, and catecholborane () was added with stirring. The reaction was stirred for 2 hours, and then H_2O (1 mL) and sodium perborate ($NaBO_3 \cdot 4H_2O$) were sequentially added. The resultant solution was removed from the ice bath andstirred vigorously at room temperature for 16 hours, whereupon the mixture was transferred to a separatory funnel containing H2O (4 mL), and the layers were separated. The aqueous phase was extracted with DCM (4 × 4 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified via flash chromatography, eluting with XXX to afford xx mg of 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 1.4 Hz, 1H), 7.26 (s, 1H), 3.64 (t, J = 6.4 Hz, 1H), 2.87 – 2.81 (m, 1H), 2.59 (dd, J = 17.2, 4.1 Hz, 1H), 2.41 (dd, J = 17.2, 6.7 Hz, 1H), 1.82 – 1.52 (m, 6H), 0.86 (dd, J = 15.7, 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 144.0, 139.0, 127.4, 123.4, 62.6, 46.1, 42.8, 38.7, 33.0, 29.3, 28.1, 21.2, 18.6; HRMS (ESI-QTOF) calcd for $C_{14}H_{20}O_3$ $[M+H]^+$ 237.1485, found 237.1492.



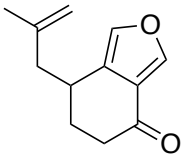
5-isopropyl-5,5a,6,7-tetrahydro-3H-naphtho[1,8-bc]furan-3,8(4H)-dione (5)

PCC () was added to a stirred solution of 1 () in 3 mL dry DCM. After 6 hours at room temperature the solution was diluted with 10 mL diethyl ether and the supernatant liquid was passed through a short pad of silica using EtAcO to was the insoluble black reside. Silica flash column gave 1 in xx% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 2.96 (td, J = 11.4, 4.8 Hz, 1H), 2.72 – 2.55 (m, 3H), 2.48 – 2.39 (m, 1H), 2.34 (dd, J = 16.8, 13.3 Hz, 1H), 2.07 (dtd, J = 13.9, 6.9, 2.7 Hz, 1H), 1.89 (ddt, J = 13.9, 11.3, 2.9 Hz, 1H), 1.82 – 1.68 (m, 1H), 0.98 (dd, J = 23.5, 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 185.0, 147.3, 145.8, 145.7, 123.3, 48.0, 39.9, 38.7, 34.2, 29.7, 26.7, 20.9, 15.5. HRMS (ESI-QTOF) calcd for $C_{14}H_{16}O_3$ $[M+H]^+$ 233.1172, found 233.1173.



3-methyl-6,7-dihydroisobenzofuran-4(5H)-one (61)

Compound **1** was prepared by using previous described procedure for compound **1** in xx% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 2.64 (td, J = 6.2, 1.4 Hz, 2H), 2.57 (s, 3H), 2.47 (t, J = 8 Hz, 2H), 2.01 (tt, J = 7.3, 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 157.4, 134.8, 124.9, 118.2, 40.1, 24.2, 20.0, 14.0; HRMS (ESI-QTOF) calcd for $C_9H_{10}O_2$ $[M+H]^+$ 151.0754, found 151.0750.



7-(2-methylallyl)-6,7-dihydroisobenzofuran-4(5H)-one

Compound **1** was prepared by using previous described procedure for compound **1** in xx% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 1.5 Hz, 1H), 7.37 (s, 1H), 4.88 (s, 1H), 4.80 (s, 1H), 3.04 – 2.95 (m, 1H), 2.71 – 2.63 (m, 1H), 2.56 – 2.39 (m, 2H), 2.29 – 2.22 (m, 1H), 2.17 – 2.08 (m, 1H), 1.81 (s, 3H), 1.79 – 1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 145.2, 142.9, 138.7, 128.8, 123.2, 112.9, 43.1, 38.4, 29.9, 29.5, 22.1.

3.5. References

(1) Brian, P. W.; McGowan J. C. *Nature* **1945**, *156*, 144

(2) Roll, D. M.; Scheuer, P. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *105* (19), 6177.

(3) Nakamura, M.; Kakuda, T.; Qi, J.; Hirata, M.; Shintani, T.; Yoshioka, Y.; Okamoto, T.; Oba, Y.; Nakamura, H.; Ojika, M. *Biosci. Biotechnol. Biochem.* **2005**, *69* (9), 1749.

(4) Wang, C. C. C.; Chiang, Y.-M.; Praseuth, M. B.; Kuo, P.-L.; Liang, H.-L.; Hsu, Y.-L. *Basic & Clinical Pharmacology & Toxicology* **2010**, *107* (1), 583.

(5) Joshi, K.; Singh, P.; Pardasani, R.; Pelter, A.; Ward, R.; Reinhardt, R. *Tetrahedron Lett.* **1978**, *19* (47), 4719.

(6) Ferreira, M. A.; King, T. J.; Ali, S.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 249−256.

(7) Zhang, X.; Zhang, S.; Xuan, L. *Heterocycles* **2008**, *75*, 661− 668.

(8) Cheng, L.-Y.; Liao, H.-R.; Chen, L.-C.; Wang, S.-W.; Kuo, Y.-H.; Chung, M.-I.; Chen, J.-J. *Fitoterapia* **2017**, *117*, 16.

(9) Ryoo, I.-J. *J. Microbio. Biotechno.* **2010**, *20* (8), 1189.

(10) Besley, C.; Rhinehart, D. P.; Ammons, T.; Goess, B. C.; Rawlings, J. S. *Bioorganic & Medicinal Chemistry Letters* **2017**, *27* (14), 3087.

(11) Koft, E. R.; Smith, A. B. *J. Am. Chem. Soc.* **1982**, *104*, 5568.

(12) Koft, E. R.; Smith, A. B. *J. Am. Chem. Soc.* **1984**, *106*, 2115.

(13) Kraus, G. A.; Wan, Z. *Synlett.* **2000**, *2000*, 363−364.

(14) Ungureanu, S.; Meadows, M.; Smith, J.; Duff, D. B.; Burgess, J. M.; Goess, B. C. *Tetrahedron Lett.* **2011**, *52*, 1509.

(15) Lu, Y.; Yuan, H.; Zhou, S.; Luo, T. *Org. Lett.* **2017**, *19* (3), 620.

(16) Adary, E. M.; Chang, C.-W.; Auria, D. T. D.; Nguyen, P. M.; Polewacz, K.; Reinicke, J. A.; Seo, H.; Berger, G. O. *Tetrahedron Lett.* **2015**, *56* (2), 386.

(17) Bolte, M.; Crow, W.; Yoshida, S. *Aust. J. Chem.* **1982**, *35* (7), 1411.

(18) Smith, A. B.; Dorsey, B. D.; Ohba, M.; Lupo, A. T.; Malamas, M. S. *J. Org. Chem.* **1988**, *53* (18), 4314.

(19) Majetich, G.; Grove, J. L. *Heterocycles* **2012**, *84* (2), 963.

(20) Kakde, B. N.; Bhunia, S.; Bisai, A. *Tetrahedron Lett.* **2013**, *54* (11), 1436.

(21) Bisai, A.; Parida, A.; Sharique, M.; Kakde, B.; Ghosh, S. *Synthesis* **2015**, *47* (19), 2965.

(22) Khanapure, S. P.; Manna, S.; Rokach, J.; Murphy, R. C.; Wheelan, P.; Powell, W. S. *J. Org. Chem.* **1995**, *60* (6), 1806.

(23) Delorbe, J. E.; Lotz, M. D.; Martin, S. F. *Org. Lett.* **2010**, *12* (7), 1576.

CHAPTER 4.
GENERAL CONCLUSION

2-Pyrone containing small molecule natural products have attracted more and more attention due to the diverse bioactivities. In the first chapter, two synthetic projects were discussed. The first one focused on the development of a flexible route toward a class of 6-alkyl-2-pyrone compounds, among which, 6-pentyl-2-pyrone is of great interest for its wide range of beneficial properties to plants and viridepyronone possesses promising antifungal activity. The second projects described a straightforward six-step synthesis of an antileukemic 2-pyrone for the first time.

Chapter 2 studied the triacetic acid lactone (TAL) involved three-component Mannich reaction. Acetic acid was found to be an effective catalyst for this reaction, which enhanced its feasibility and cost efficiency. The utilization of bio-based TAL as one of the reaction further demonstrated that TAL is a promising bio-based platform molecule.

Chapter 3 focused on a synthetic approach to natural product Hibiscone C. Umpolung type Stork-Danheiser sequence was discovered for the first time to access the core structure of Hibiscone C. As a structurally simpler and less studied member in the furanosteroids family, this compound showed a promising PI_3K inhibitory activity. The synthetic route also offered a new method to access other compounds in this family.