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Synthesis of antibacterial and biobased compounds

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Synthesis of antibacterial and biobased compounds

by

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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

2020

DEDICATION

To Dr. George A. Kraus

To my wife

To my parents

Thank you for your love and support

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ABBREVIATIONS

CDI	Carbonyldiimidazole
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
M	Molarity
MCPBA	*meta*-Chloroperoxybenzoic acid
mL	Milliliter
NBS	N-Bromosuccinimide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
rt	Room temperature
PTSA	p-Toluenesulfonic acid
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
THF	Tetrahydrofuran
TMSCN	Trimethylsilyl cyanide

ABSTRACT

Chemical substances isolated from plants or microorganisms play a variety of roles in our society. They work as food sources, provide sustainable energy and cure diseases.

In the first chapter, four natural products and their derivatives exhibiting antibacterial activities were introduced and their total synthesis were described. Biatriosporin D, indanostatin, dihydro eurotiumide B and naphthacemycin A_9 are bioactive hydroquinone/quinone natural products. The acylation and intramolecular Friedel Crafts reaction were the keys steps to the construction of the quinone structure in biatriosporin D. The Hauser-Kraus annulation was successfully applied to the syntheses of hydroquinone structures in indanostatin, dihydro eurotiumide B and naphthacemycin A_9.

In the second chapter, two biobased pyrone compounds were utilized as the starting materials to synthesize a variety of chemical substances. Substituted isophthalates were synthesized from methyl coumalate and vinyl ethers. A variety of alkyl, aryl and heteroaryl isophthalates were prepared. Aldol reactions of dehydroacetic acid at the acetyl group with aldehydes have been achieved. A direct synthesis of pogopyrone A was accomplished in two steps.

CHAPTER 1. SYNTHESIS OF ANTIBACTERIAL COMPOUNDS

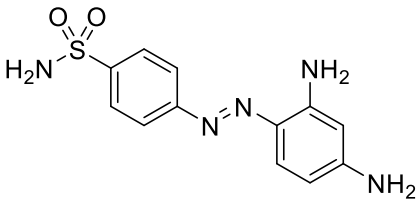
1.1 Introduction

Bacteria, tiny single-celled organisms, were the first life forms existing on earth. They are found all around us. Bacteria exist in the air we breathe, in the water we drink, in the soil we plant, on the surfaces we touch.[1] Bacteria live on and even inside our bodies. Bacteria play essential roles in the earth's ecosystem. They provide nutrients like phosphorus and nitrogen to plants, decompose dead organic substances, and contribute to the cycles of nature. For ourselves, most of bacteria in our bodies are harmless and beneficial.[2] For example, they help degrade the foods that we take and detoxify the poisons we contact. However, some species of bacteria are pathogenic and cause infectious diseases, such as pneumonia, tuberculosis, syphilis and bubonic plague.[3] One of the deadliest pandemics recorded in human history was the Black Death during the Late Middle Ages. It killed 75 to 200 million people in Eurasia and North Africa. The Black Death is now known to be caused by the bacterium *Yersinia* pestis.[4] The disease is treatable by antibiotics.

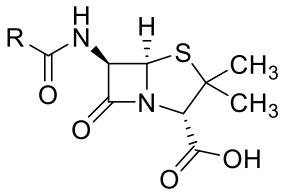
Antibiotics either kill or inhibit the growth of bacteria. They have been used for a thousand years. Ancient civilizations used various plant extracts, such as herbs and honey and even animal feces to treat infections.[5] However, ancient practitioners could not precisely identify or isolate the active components. The modern antibiotics era began with the synthetic arsenic-based pro-drug Salvarsan by Paul Ehrlich in 1909.[6] This discovery was inspired by his work on dyes that certain chemical dyes only color some bacteria cells but not others. Salvarsan was used to treat syphilis in the first half of the 20th century. Later Salvarsan was replaced by Prontosil (Figure 1.1), the first systemically active antibacterial drug.[7] Prontosil is a sulfonamide derivate

and was developed by a research team led by Gerhard Domagk at Bayer. This sulfonamide drug opened a new era in medicine.

In 1928, Alexander Fleming accidentally discovered penicillin (Figure 1.1). Penicillin was introduced on a large scale because of the work of Howard Florey and Ernst Chain who managed to efficiently purify the antibiotic and develop the mass production process. Howard Florey, Ernst Chain and Alexander Fleming shared the 1945 Nobel Prize in Medicine for the discovery of penicillin and its curative effect in various infectious diseases.



Prontosil



Penicillin core structure
Where "R" is the variable group

Figure 1.1 Structure of Prontosil and Penicillin.

The introduction of penicillin marked the beginning of the so-called “golden era” of antibiotics. From 1935 to 1968, the number of new antibiotic substances launched for medical use dramatically increased. Twelve new classes were launched. However, after golden era, the discovery and development of new antibiotics are declining. Only two new classes were introduced between 1969 and 2003 (Table 1.1).[8]

Most of the antibiotic we use today as medicines were discovered and introduced during the golden era. Antibiotics have significantly changed our modern medical history and extended the average human life by 23 years in the past 100 years.[9] However, massive use and misuse of valuable antibiotics since their introduction has resulted in antibiotic resistance. Antibiotic resistance is the ability of bacteria to defeat the antibiotic designed to kill them. This makes existing antibiotic less effective and some infections now impossible to treat, like Methicillin-

resistant *Staphylococcus aureus* (MRSA), and drug-resistant tuberculosis.[10] Resistant bacteria are now widespread in most parts of the world and the number of people who have died from bacterial infections is increasing because the antibiotics have stopped working. Each year in the U.S., at least 2.8 million people are infected with antibiotic-resistant bacteria, and more than 35,000 people die as a result. As long as new drugs keep coming, resistance is not a problem. Therefore, a need for the development of new antibiotics still remains a high priority.

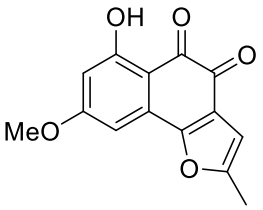
Year introduced	**Class of drug**
1935	Sulphonamides
1941	Penicillins
1944	Aminoglycosides
1945	Cephalosporins
1949	Chloramphenicol
1950	Tetracyclines
1952	Macrolides/lincosamides/streptogramins
1956	Glycopeptides
1957	Rifamycins
1959	Nitroimidazoles
1962	Quinolones
1968	Trimethoprim
2000	Oxazolidinones
2003	Lipopeptides

Table 1.1 History of introduction of new classes of antibiotics.

Most of the antibiotics in current use are natural products or natural product derivatives. Bacterial, fungal, plant, and animal extracts are being screened in the search for new antibiotics.[11] In this chapter, four different antibacterial compounds discovered within past ten years were introduced and their syntheses were described.

1.1.1 Biatriosporin D

Biatriosporin D, a red powder, was isolated from the endolichenic fungus *Biatriospora sp*. (8331C) and reported by Lou and coworkers in 2016 (Figure 1.2).[12] Biatriosporin D showed potent activity against *Candida albicans* strains resistant to fluconazole (an antifungal medication). The minimum inhibitory concentration of biatriosporin D with 80% reduction against the growth of *Candida albicans* was 16 μg/mL. The research on mechanism revealed that biatriosporin D inhibited the function of efflux pumps and reduced the transcriptional expression of the efflux-pump-related genes CDR1 and CDR2.



Biatriosporin D

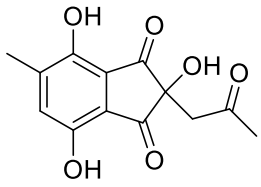
Figure 1.2 Structure of biatriosporin D.

Later, Lou and coworkers reported that biatriosporin D also displayed potent anti-virulence activity by inhibiting adhesion, hyphal morphogenesis and biofilm formation of *Candida albicans*. Morphogenesis is the biological process that causes a cell, tissue or organism to develop its shape.[13] Biofilm formation is a process where microorganisms attach to and grow on a surface and produce extracellular polymers that facilitate attachment and matrix formation, resulting in an alteration in the phenotype of the organisms with respect to growth rate and gene

transcription. Furthermore, Biatriosporin D prolonged the survival of worms infected by *Candida albicans* in vivo. Given the importance of bioactivity of biatriosporin D and that no synthesis has been reported so far, we were interested in making biatriosporin D from organic synthesis.

1.1.2 Indanostatin

Indanostatin was first isolated from the cultured broth of *Streptomyces sp*. RAI20, coming from a soil sample collected at Nagoya Castle Park by Hayakawa and coworkers in 2013 (Figure 1.3).[14] The compound, the first reported 1,3-indanone from bacteria, exhibits potent neuroprotective activity against glutamate toxicity. The neuroprotective activity was examined by the MTT (a yellow chemical) method using C6 rat glioma cells. C6 glioma cells were from rat neural tumors, induced by *N*-nitrosomethylurea. When C6 cells were treated with 100 mM glutamate for 24 hours, about 80% of the cells underwent cell death. Indanostatin partially protected C6 cells against glutamate toxicity with an EC_{50} (half-maximal effective concentration) of 130 nM.



Indanostatin

Figure 1.3 Structure of indanostatin.

Neuroprotective activity refers to the relative preservation of neuronal structure and/or function.[15] Glutamate is a powerful excitatory neurotransmitter that is released by nerve cells in the brain.[16] It is responsible for nerve signaling, for passing chemical messages from one nerve cell to another. At normal concentrations, glutamate is crucial for brain functions such as learning and memory. However, at high concentrations, glutamate's increased cellular activity

results in over-excitation of nerve cells, which eventually leads to cell death. When glutamate causes cellular damage, it becomes glutamate toxicity.

No synthesis of Indanostatin has been reported so far. Given the importance of neuroprotective activity against glutamate toxicity, we were interested in making Indanostatin from organic synthesis.

1.1.3 Eurotiumide B

Eurotiumide A and eurotiumide B were isolated from marine-derived fungus, *Eurotium sp.* XS-200900E6, from the gorgonian *Subergorgia suberosa*, by Wang and coworkers in 2014 (Figure 1.4).[17] Both compounds exhibited potent antifouling activities against the larval settlement of the barnacle *Balanus Amphitrite* with the EC_{50} values ranging from 0.7 to 22.5 μg/mL. Eurotiumide A and B also displayed profound antibacterial activities against *Staphylococcus epidermidis, Bacillus cereus, Vibrio anguillarum,* and *Vibrio parahaemolyticus.*

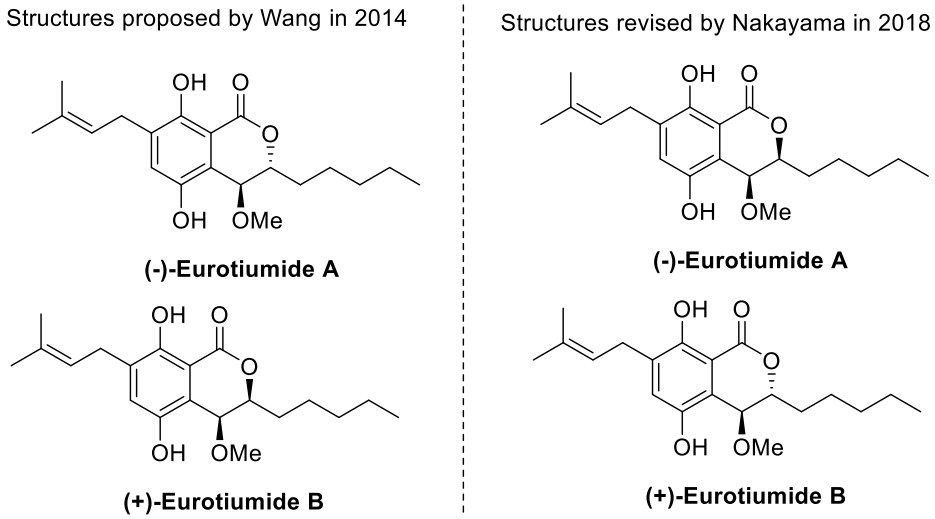


Figure 1.4 Structures of eurotiumide A and B.

Biofouling organisms, like barnacles, bryozoans, mollusks, polychaete, pose a risk to maritime industries in tremendous economic losses and cause a series of environmental problems.[18] In the past, the most used strategy to prevent biofouling is antifouling paints

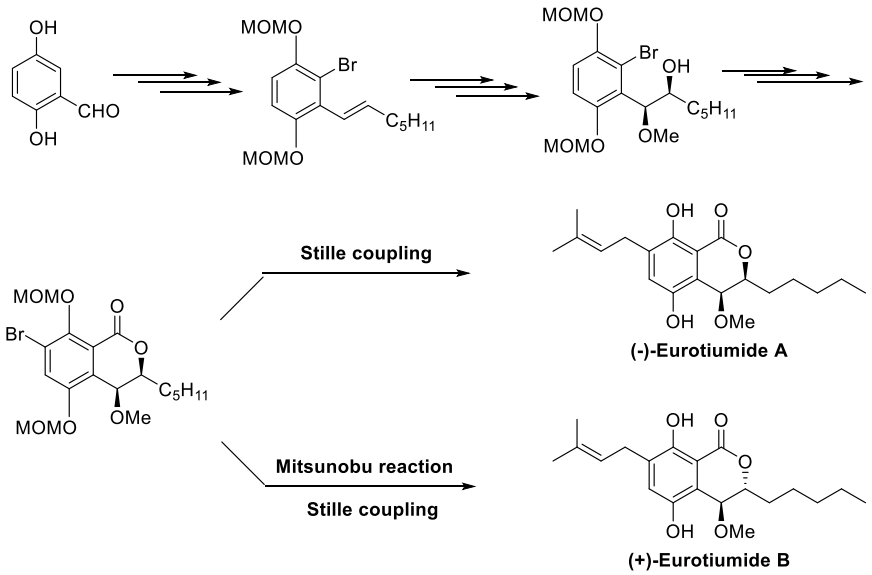
containing copper, lead, mercury, arsenic, or organotins. These paints are effective but difficult to degrade in the environment. They are also toxic to other larger organisms, such as fungi and algae. Therefore, safer antifouling agents without biocidal properties are in urgent demand. Recently, natural products as antifouling agents have drawn the attention of chemists.

Because of the importance of antibacterial and antifouling activities of eurotiumide A and B, Nakayama and coworkers reported the first total synthesis of both compounds in 2018 (Scheme 1.1).[19] They also revised the stereochemistry of eurotiumide A and eurotiumide B (Figure 1.4).

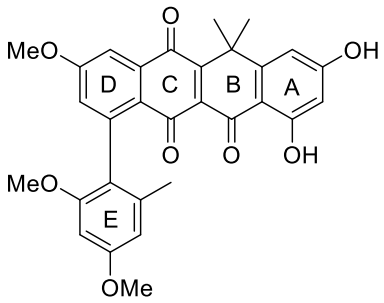
Their synthetic plan started from 2,5-dihydroxylbenzaldehyde. Bromination, MOM (methoxymethyl ether) protection, and then the Julia-Kocienski olefination gave *trans* olefins. Asymmetric epoxidation, followed by epoxide opening reaction, gave a single isomer product. Palladium-catalyzed insertion reaction under carbon monoxide atmosphere followed by bromination generated the bromo substituted lactone. The Stille coupling reaction finally provided the eurotiumide A. When the brominated lactone was treated with the Mitsunobu reaction condition before the Stille coupling reaction, eurotiumide B was formed. The total syntheses' key features are the asymmetric epoxidation, epoxide opening, and palladium catalyzed insertion/lactonization cascade reaction.

1.1.4 Naphthacemycin A_9

Naphthacemycin A_9, isolated from *Streptomyces sp*. KB-3346-5, was reported by Omura and coworkers in 2017.[20] It is comprised of naphthacene structure (A, B, C, and D-rings) and the asymmetric E-ring moiety (Figure 1.5). Naphthacemycin A_9 exhibits both circumventing effect of β-lactam resistance and anti-MRSA activity (methicillin-resistant *Staphylococcus aureus*).[21] It also showed potent anti-VRE (vancomycin-resistant *Enterococcus*) and linezolid-resistant *Staphylococcus. aureus* activities.



Scheme 1.1 Total syntheses of (–)-eurotiumide A and (+)- eurotiumide B.

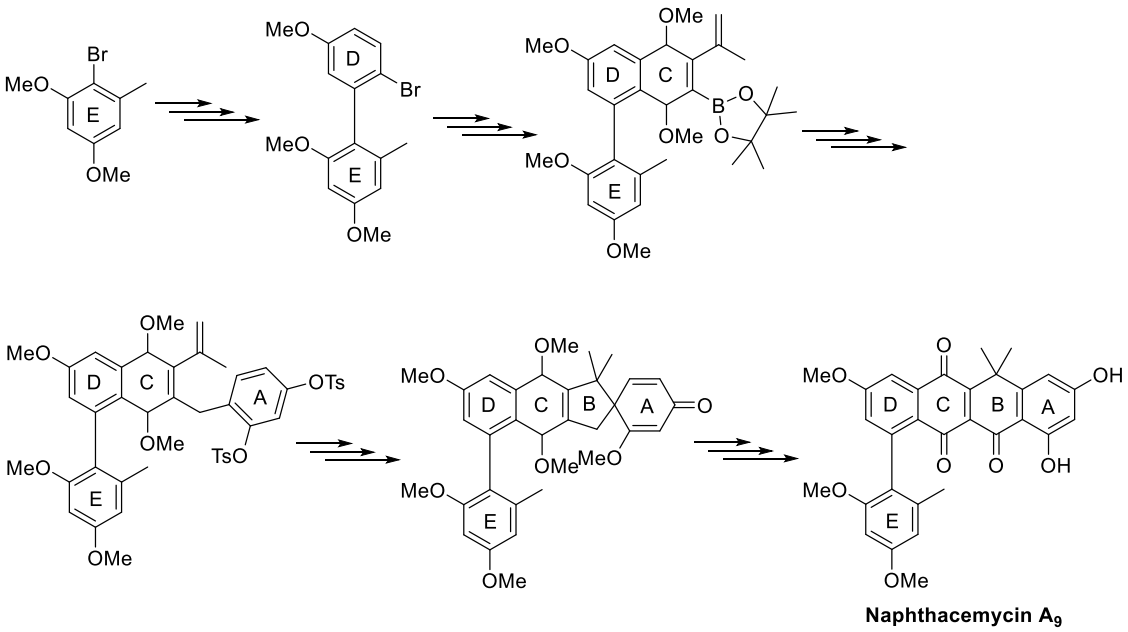


Naphthacemycins A_9

Figure 1.5 Structures of naphthacemycins A_9.

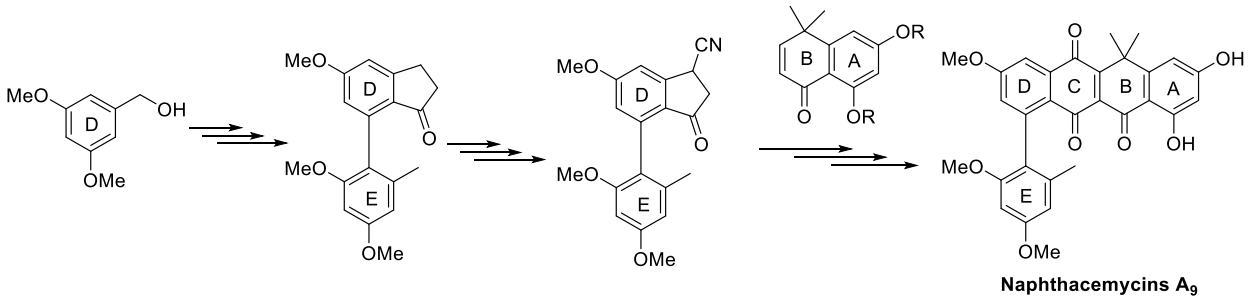
Methicillin-resistant *Staphylococcus aureus* (MRSA) refers to a type of bacteria, resistant to several antibiotics.[22] Several difficult-to-treat infections caused by MRSA have become challenging in the communities due to its high mortality rate. Currently, only a few anti-MRSA drugs, such as vancomycin, teicoplanin, linezolid, and daptomycin, are available to be used against MRSA infections. However, anti-MRSA drugs' side effects and the emergence of drug-resistance strains, such as vancomycin-resistant *Enterococcus* and linezolid-resistant *Staphylococcus aureus*, require the development of new anti-MRSA drugs.

Naphthacemycin A_9 is a good candidate. In 2017, Ōmura and coworkers reported its synthesis for the first time (Scheme 1.2).[23] They started the reaction from trisubstituted aryl bromide. The Suzuki-Miyaura coupling reaction introduced D Ring. The Wulff-Dötz reaction followed by another Suzuki-Miyaura coupling reaction afforded C and A ring. Intramolecular Friedel-Crafts cyclization provided B ring. Overall, they completed the synthesis of naphthacemycin A_9 in 16 steps.



Scheme 1.2 First total synthesis of naphthacemycin A_9.

In 2018, Shia and coworkers reported the second total synthesis of naphthacemycin A_9 (Scheme 1.3).[24] They started the synthesis from disubstituted benzyl alcohol. Biphenyl subunit, D ring and E ring, was constructed through a Suzuki-Miyaura coupling reaction. C ring was generated by a Hauser-Kraus annulation reaction. A and B ring were introduced during the Hauser-Kraus annulation reaction from a synthesized starting material.

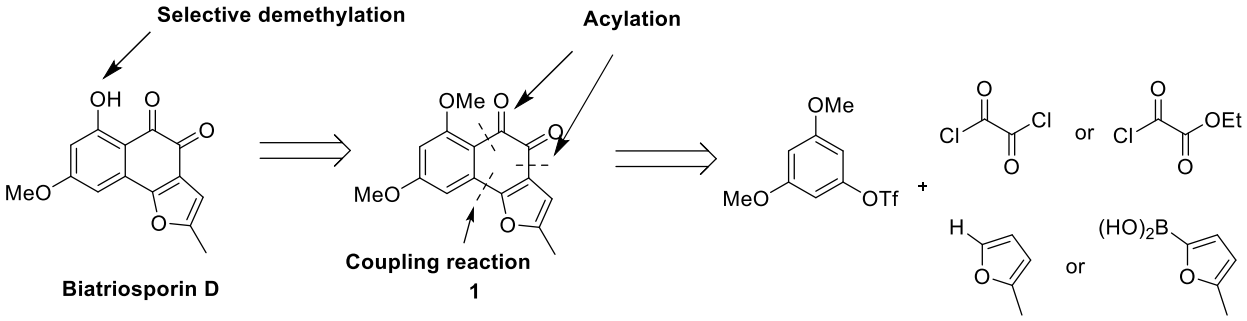


Scheme 1.3 Second total synthesis of naphthacemycin A_9.

1.2 Results and Discussions

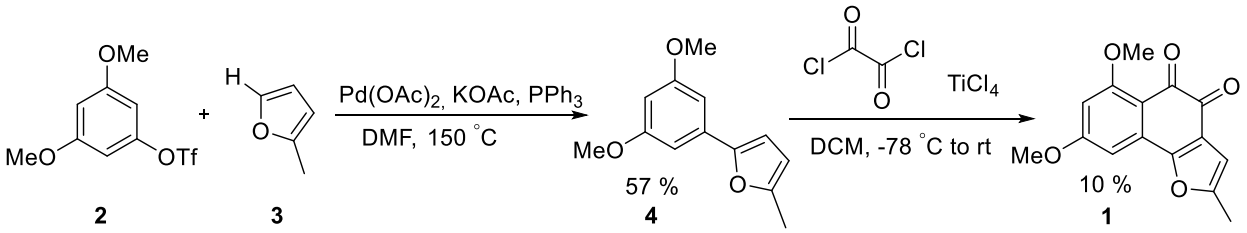
1.2.1 Total synthesis of biatriosporin D

Scheme 1.4 shows the retrosynthetic analysis of biatriosproin D. Biatriosporin D consists of a hydroxyl group, two carbonyl groups, a furan ring and a phenyl ring. As the hydroxyl group is a relatively reactive functional group, forming a hydroxyl group at a late stage could avoid unnecessary protections and deprotections. Selective demethylation from the intermediate **1** could be achieved since one of the methoxy groups is in a carbonyl's ortho position. For the intermediate **1**, the phenyl ring and furan ring could be connected by cross-coupling reactions. Two carbonyl groups could be installed by acylation reactions. The intermediate **1** could be synthesized by combining the following three parts; the phenyl part (triflate protected phenol), the furan part (methyl furan or furan boronic acid), and the dicarbonyl part. Two carbonyl groups could be installed in one step using oxalyl chloride. If multiple steps, ethyl chloroxoacetate is a choice. Since intermediate **1** can be synthesized by acylation and cross-coupling reactions, there are two routes depending on which reaction is performed first.



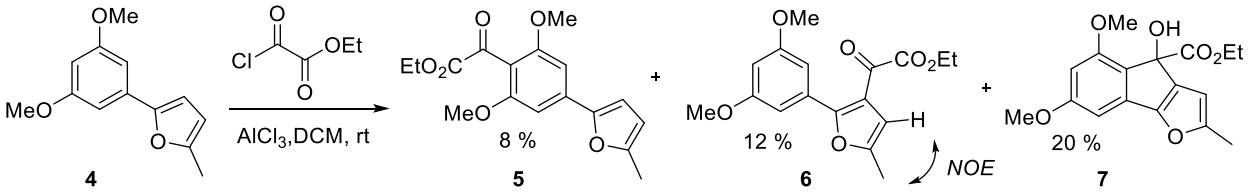
Scheme 1.4 Retrosynthetic analysis of biatriosporin D.

First, we tried route **1**, the cross-coupling reaction followed by acylation (Scheme 1.5). Triflate activated phenol **2** reacts with 2-methyl furan in the presence of palladium acetate and triphenylphosphine to provide the product **4** in 57% yield. Then oxalyl chloride was used to attempt acylation with different Lewis acids.[25-27] Only titanium tetrachloride gave product **1** in 10% yield. Other Lewis acids, like aluminum chloride and tin tetrachloride, failed in the acylation reaction.



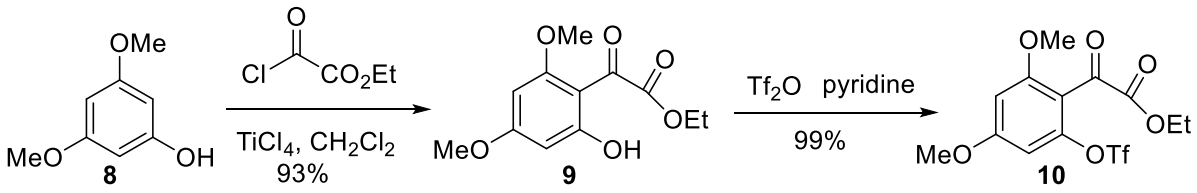
Scheme 1.5 Synthetic route 1.

Then we turned our attention to the stepwise acylation (Scheme 1.6). Acylation of ethyl chloroxoacetate catalyzed by aluminum chloride gave three major products.[28] The first product **5** arises from the acylation on the phenyl ring. The structure is supported by proton NMR data. Product **6** arises from the acylation on the furan ring. The carbonyl and phenyl group are on the same side. This is determined by an NOE (nuclear Overhauser effect) experiment. The third product **7** is the cyclic alcohol. It is supposed to be formed from intermediate **6**. Since only product **6** is desired, the yield is only 12%, limiting further transformations.



Scheme 1.6 Acylation of ethyl chloroxoacetate.

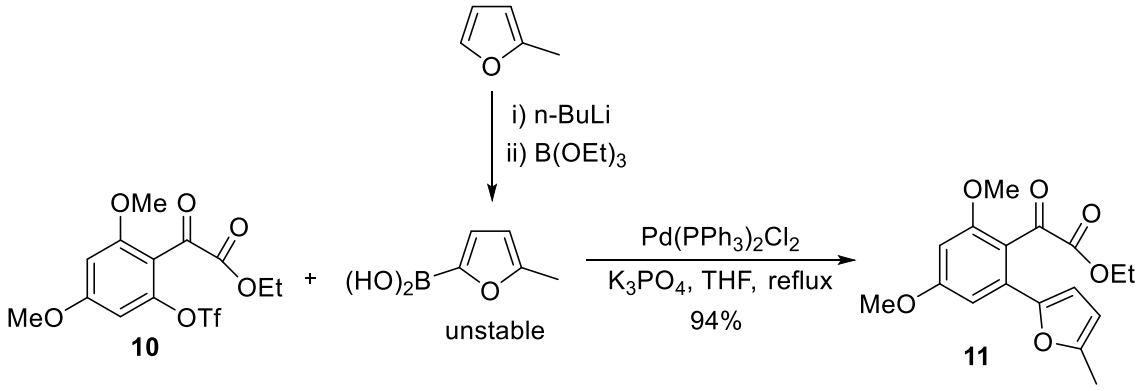
We then explored the second route, acylation followed by the cross-coupling reaction. We started from 3,5-dimethoxy phenol **8**. Acylation of **8** using ethyl chloroxoacetate and titanium tetrachloride occurred and formed the product **9** in 93% yield.[29] Triflate anhydride protected hydroxy group on phenol **9** and produced compound **10** quantitatively (Scheme 1.7).



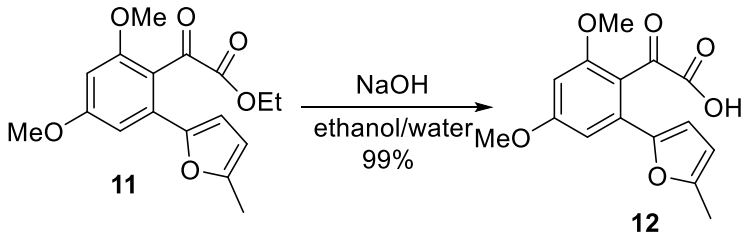
Scheme 1.7 Synthesis of **10**.

The next step is the cross-coupling reaction of compound **10** with (5-methylfuran-2-yl) boronic acid (Scheme 1.8). The furan boronic acid is quite unstable. It needs to be stored at a low temperature. We made the furan boronic acid from 2-methyl furan using butyl lithium and triethyl borate. The Suzuki-Miyaura reaction connected furan boronic acid and compound **10** and provided coupled product **11** in 94% yield.

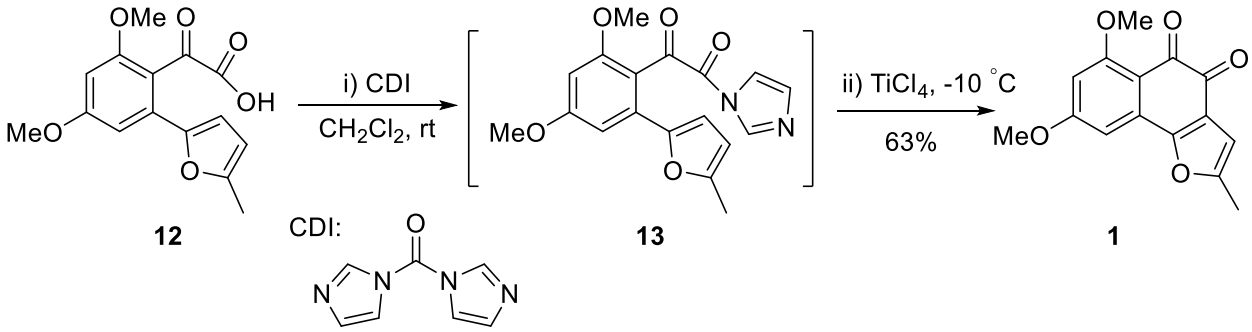
The hydrolysis of compound **11** with sodium hydroxide in ethanol-water provided the keto acid **12**(Scheme 1.9). Conversion of the keto acid **12** into ortho-quinone **1** proved to be difficult. Fortunately, we found that reaction with CDI (carbonyl diimidazole) followed by titanium tetrachloride at -10 °C afforded product **1** in 63% yield.[30] Carboxylic acid **12** reacted with CDI reacted to form amide **13**. The intermediate **13** underwent a Lewis acid catalyzed cyclization to give the product **1**.



Scheme 1.8 Synthesis of **11**.

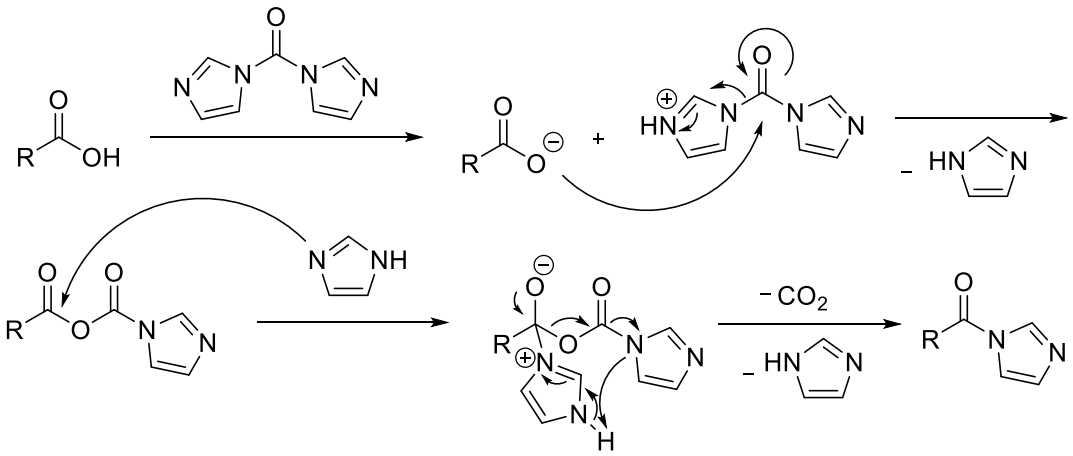


Scheme 1.9 Hydrolysis of compound **11.**



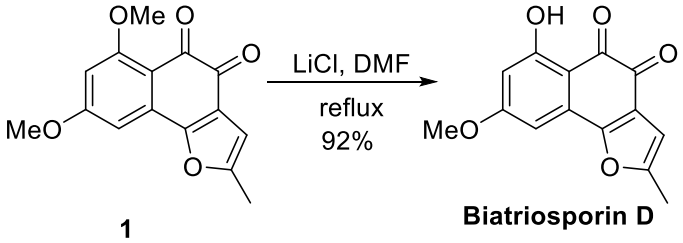
Scheme 1.10 Synthesis of ortho-quinone **1**.

The proposed mechanism of CDI that participated in amide formation from carboxylic acids is shown in Scheme 1.11. The proton transfer goes first. The anhydride is then formed through the attack of the carboxylate to protonated CDI followed by the expulsion of imidazole. The imidazole attacks back to the anhydride. The amide is finally obtained along with carbon dioxide.



Scheme 1.11 Mechanism of CDI participated amide formation.

Ortho-quinone **1** is poorly dissolved in most organic solvents. Attempted deprotection using boron trichloride, boron tribromide or aluminum chloride returned recovered starting material. Finally, lithium chloride in DMF (dimethylformamide) under reflux conditions for two hours selectively demethylated and produced biatriosporin D in 92% yield (Scheme 1.12).[31]



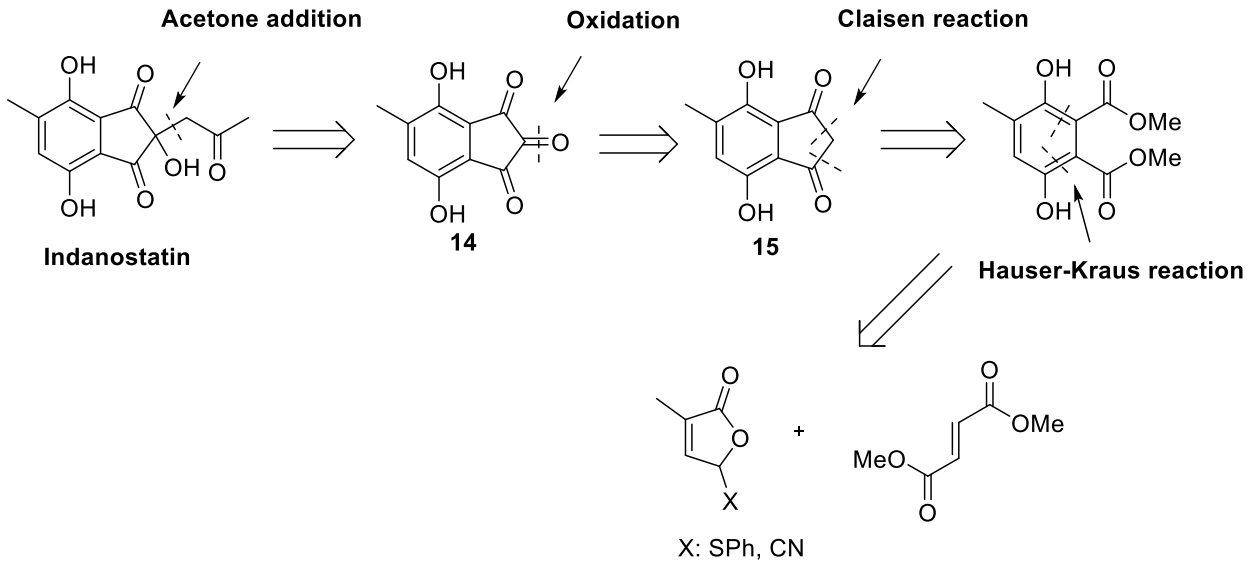
Scheme 1.12 Synthesis of biatriosporin D.

The first synthesis of biatriosporin D was accomplished in six steps from 3,5-dimethoxyphenol. The overall yield is 50% and the key steps are CDI mediated acylation and lithium chloride promoted demethylation.

1.2.2 Total synthesis of (±) indanostatin

Indanostatin has a chiral carbon and its absolute configuration has not been determined. Scheme 1.13 shows the retrosynthetic analysis. Indanostatin could be synthesized from acetone addition to the triketone **14**. The triketone could be obtained through oxidation of methylene

group on indanedione **15**. The intermediate **15** could be formed by the Claisen reaction from the diester hydroquinone. For the hydroquinone, the Hauser-Kraus annulation from butanolide and dimethyl fumarate is a good choice for the formation.

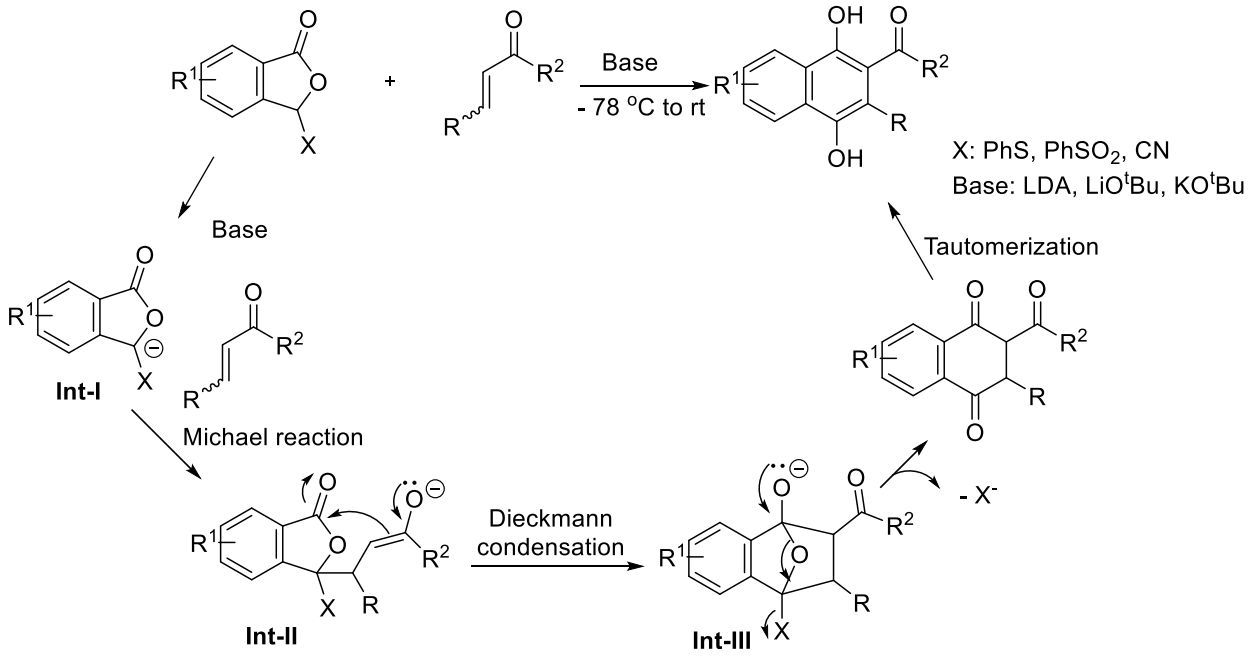


Scheme 1.13 Retrosynthetic analysis of indanostatin.

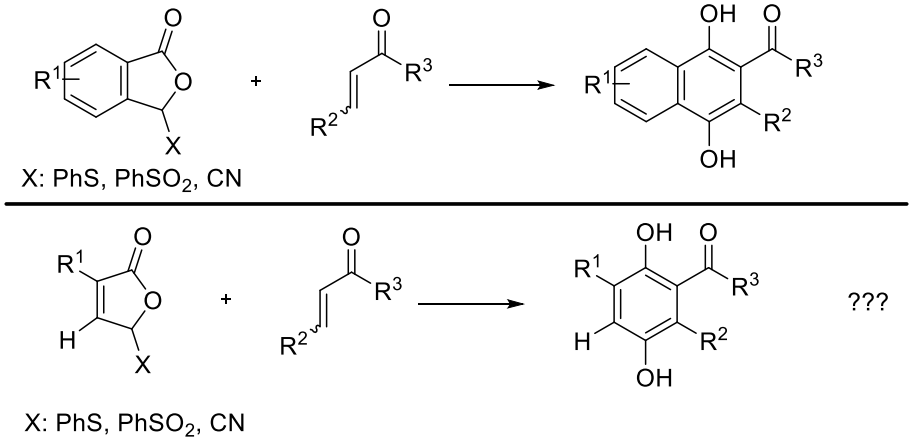
The Hauser-Kraus annulation is the synthesis of naphthalene hydroquinones from phthalides and α, β-unsaturated carbonyl compounds under basic conditions (Scheme 1.14).[32] The phthalide is deprotonated first. The resulting anion underwent the Michael addition with an unsaturated carbonyl compound followed by the Dieckmann condensation. The resulting diketones are tautomerized to naphthalene hydroquinones. Commonly used bases are LDA (lithium diisopropylamide), lithium *tert*-butoxide, or potassium *tert*-butoxide. The X group on phthalides should be an electron-withdrawing leaving group, like cyanide, sulfide or sulfone group. This reaction is named after Dr. Frank Hauser and Dr. George Kraus.[33-35]

In the past, much research focused on the synthesis of naphthalene hydroquinones from phthalides.[36] No one reported the synthesis of benzene-based hydroquinones from substituted lactones (Scheme 1.15). We first explored the phenylthio-substituted lactone reaction with

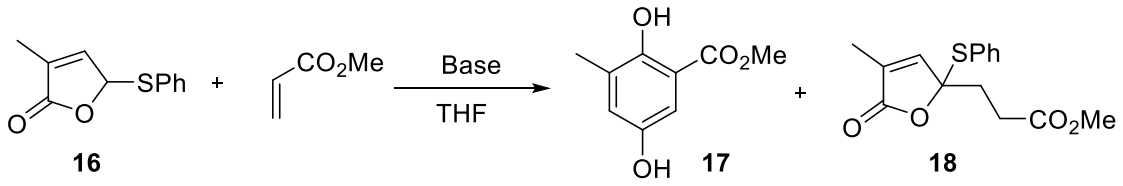
methyl acrylate and different bases (Table 1.1).[37] Two products, the hydroquinone product in 33% yield and the Michael addition product in 60% yield, were obtained when LDA (lithium diisopropylamide) was used. Potassium *tert*-butoxide generated many products. However, lithium *tert*-butoxide gave only hydroquinone **17**. The yield was 82%.



Scheme 1.14 The mechanism of the Hauser-Kraus annulation.



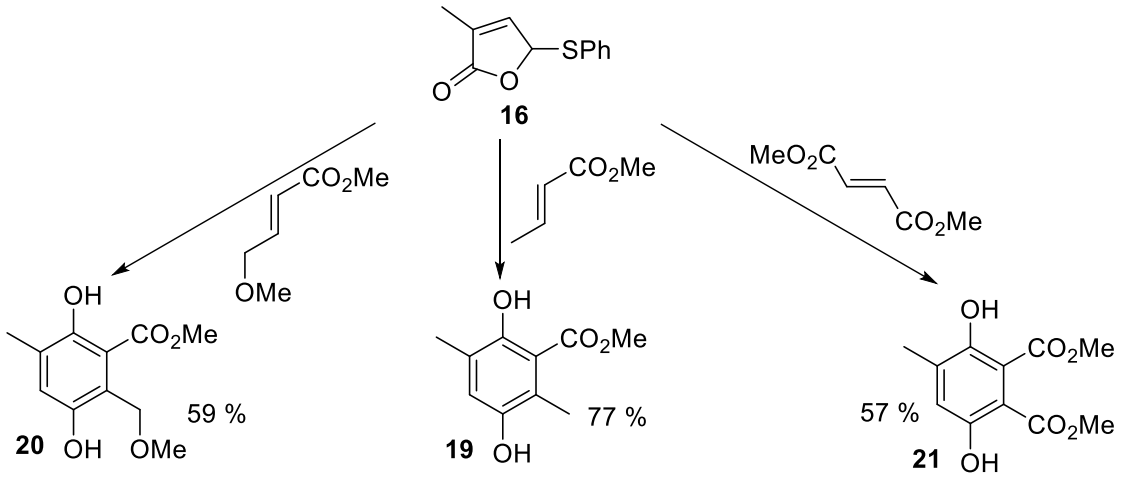
Scheme 1.15 The formation of hydroquinones.



Entry	Base	Temperature	Yield
1	LDA	-78 °C to rt	**17** in 33% and **18** in 60%
2	KO^{t}Bu	rt	Many products
3	LiO^{t}Bu	-78 °C to rt	**17** in 82% and no **18**

Table 1.1 Hauser-Kraus annulation of 5-phenylthiobutenolide.

With the optimal conditions defined, other unsaturated esters were explored with butanolide **16** (Scheme 1.16). Methyl crotonate, methoxy substituted crotonate and dimethyl fumarate all gave only hydroquinones **19** to **21** in 57-77% yields. The product **21** could be used for the synthesis of indanostatin.

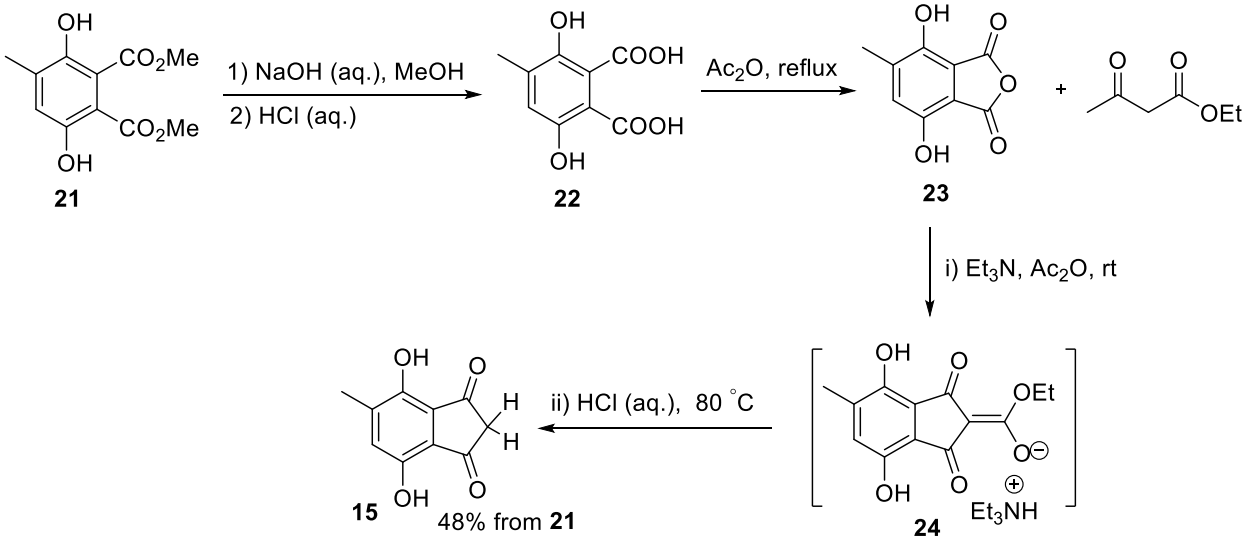


Scheme 1.16 Substrates scope.

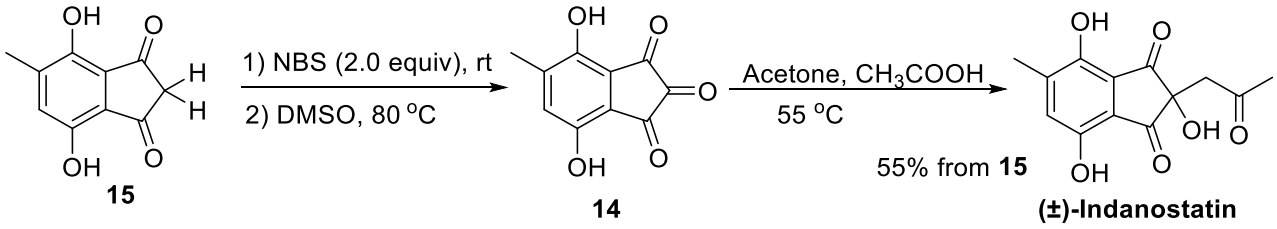
Hydroquinone **21** was hydrolyzed into dicarboxylic acid **22** and then was converted into anhydride **23** with acetic anhydride under reflux conditions. Treatment of the anhydride with ethyl acetoacetate in triethylamine and acetic anhydride gave intermediate **24**. Then hydrochloric

acid at 80 °C converted intermediate **24** to indanedione **15**. The overall yield is 48% from hydroquinone **21** (Scheme 1.17).[38]

The next step is to oxidize the methylene group to the carbonyl group in the presence of the hydroquinone. Strong oxidation agents should be avoided. NBS (*N*-bromosuccinimide) at room temperature dibrominated the methylene group. No bromination occurred on the phenyl ring. Then dibromo compound was heated in DMSO (dimethyl sulfoxide) to generate triketone **14**. The resulting triketone was treated with excess acetone in acetic acid to produce racemic indanostatin in 55% yield (Scheme 1.18).[39]



Scheme 1.17 Synthesis of **15**.



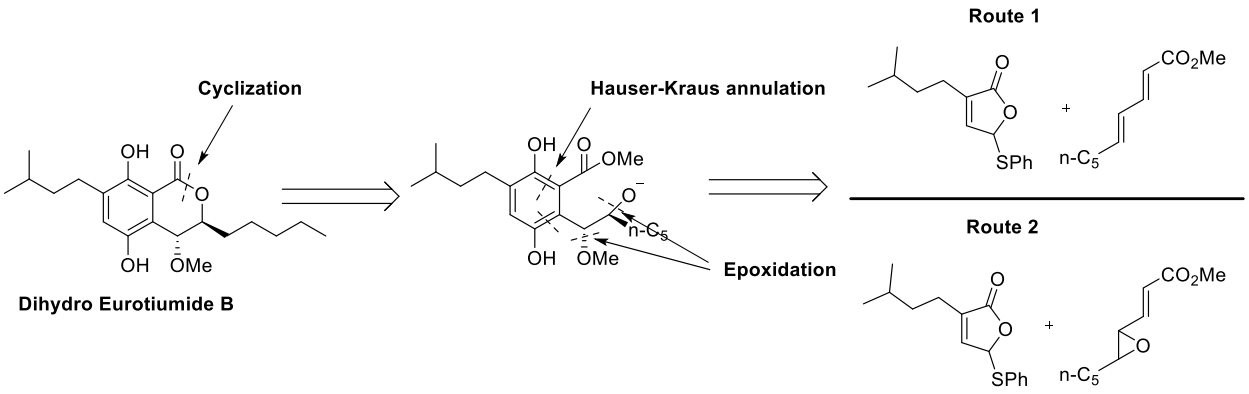
Scheme 1.18 Synthesis of indanostatin

The first synthesis of indanostatin was accomplished in six steps. The overall yield is 15%. Key steps are the Hauser-Kraus annulation and the NBS-DMSO oxidation.

1.2.3 Total synthesis of dihydro eurotiumide B

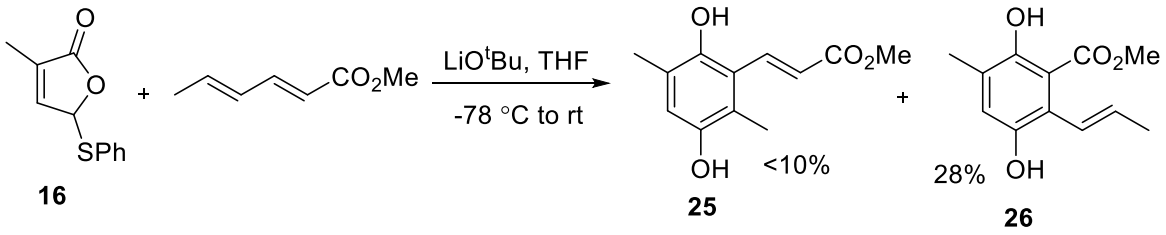
Nakayama and coworker reported the first total synthesis of eurotiumide B in 2018.[19] As part of a program to extend bioactive compounds' applications, we pursue the preparation of the eurotiumide B derivate. Here, a synthesis of dihydro eurotiumide B was described.

Scheme 1.19 shows the retrosynthetic analysis. Dihydro eurotiumide B is a 1,4-hydroquinone lactone. The lactone part could be made by intramolecular cyclization from this intermediate. The intermediate is a hydroquinone and it could be synthesized through Hauser Kraus reaction. As for the two oxygens, they can be installed by ring-opening of the epoxide. Two different routes could synthesize the intermediate. Route 1: Hauser Kraus reaction of a butanolide with a diene ester followed by epoxidation. Route 2: Hauser Kraus reaction of a butanolide with an epoxy acrylate.



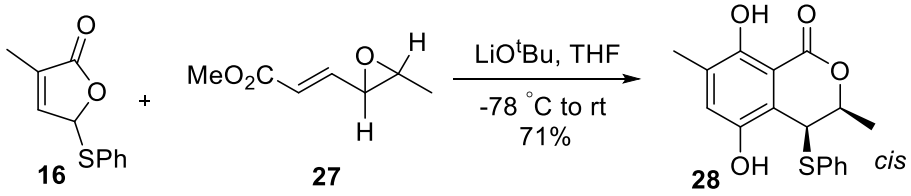
Scheme 1.19 Retrosynthetic analysis of dihydro eurotiumide B.

We first tried route **1**, the Hauser-Kraus annulation of butanolide **16** with methyl sorbate (Scheme 1.20). The reaction gave two major products when using lithium tert-butoxide. Compound **25** does not have the desired regioselectivity. While compound **26** could be used for the further transformation, the yield is 28% yield.



Scheme 1.20 The reaction of methyl sorbate with **26**.

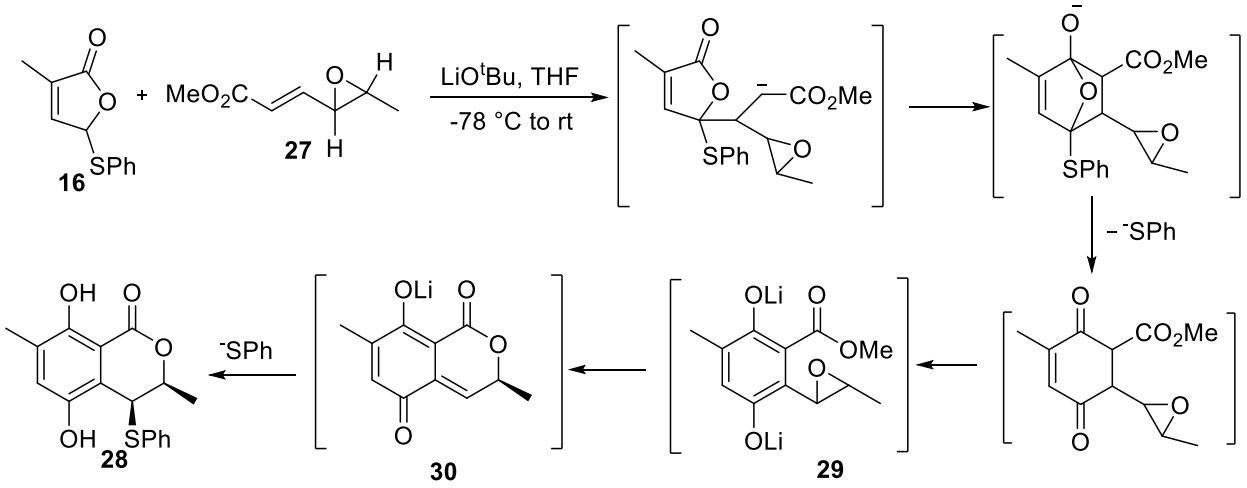
Epoxide **27** was generated from methyl sorbate using the method of Barrow.[40] The Hauser-Kraus annulation using butanolide **16** and epoxide **27** afforded the lactone **28** in 71% isolated yield as shown in Scheme 1.21. The proposed mechanism is shown in Scheme 1.22. The reaction first formed the Hauser-Kraus annulation product **29**. In situ epoxide opening provided the lactone **30**. This step has a literature analogy in Moore's work, which showed that hydroquinones bearing good leaving groups in the benzylic position undergo substitution via a quinone methide type intermediate.[41] The phenylthiolate group produced in the Hauser-Kraus annulation adds back to lactone **30** and finally compound **28** was obtained. The phenylthiol group and methyl group are in a *cis* relationship.



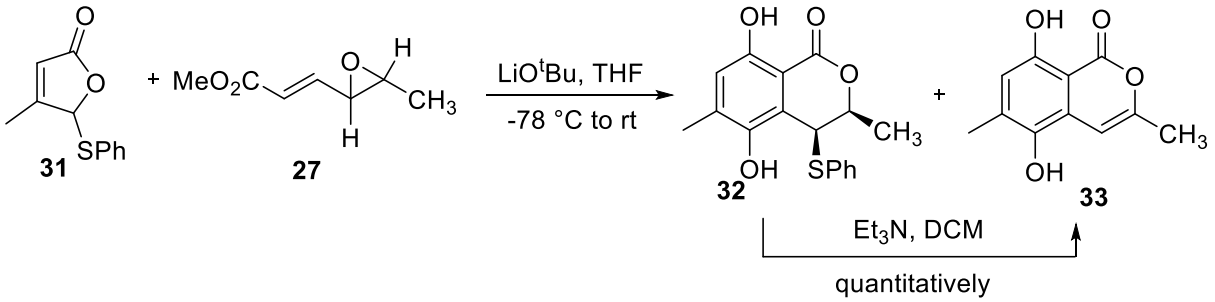
Scheme 1.21 Synthesis of **28.**

In order to better understand the unexpected annulation result, commercially available 4-methyl-5-hydroxybutenolide was converted to **31** using our standard conditions. Reaction with epoxy sorbate **27** under the same conditions used for **16** produced dihydroisocoumarins **32** and an isocoumarin **33** in a 1:2 ratio (Scheme 6). Treatment of mixture of compound **32** and **33** with triethylamine in dichloromethane gave the product **33** only. The overall yield for compound **33** is

69%. The structure of the isocoumarin **33** was supported by comparison to the spectrum of paepalantine.



Scheme 1.22 Mechanism of synthesis of lactone **28**.

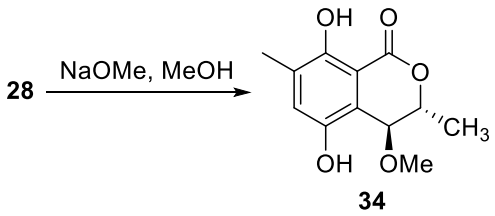


Scheme 1.23 Synthesis of **32** and **33**.

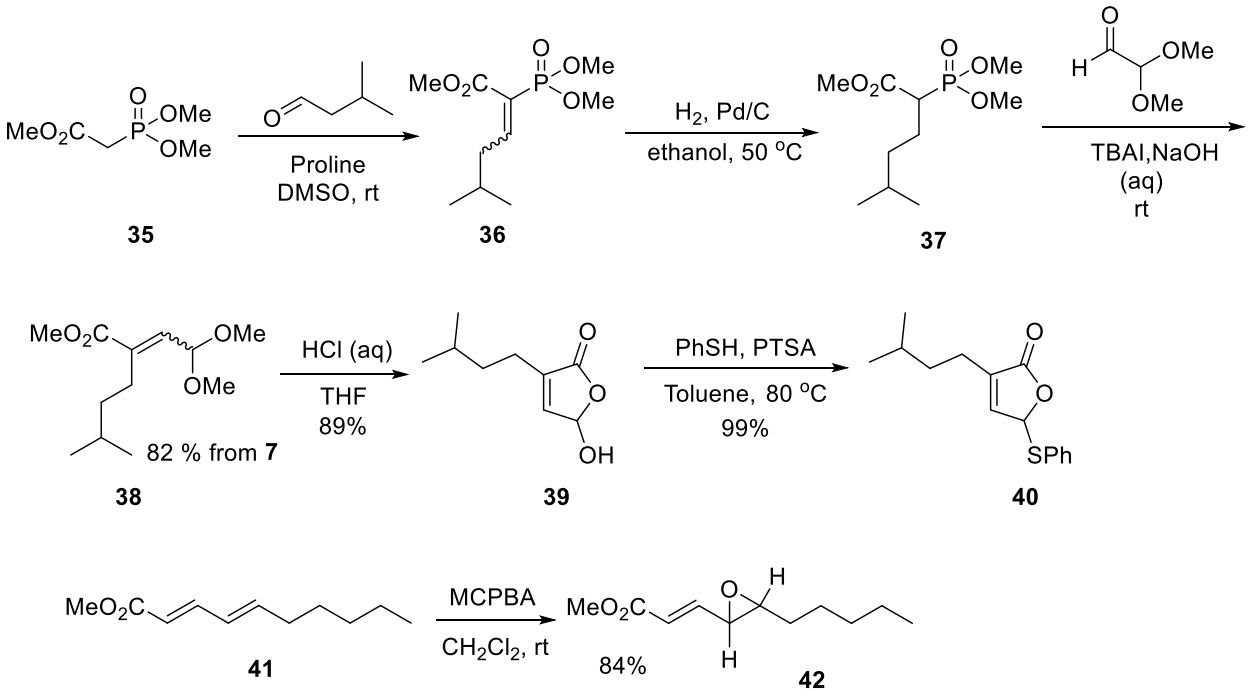
The result from Scheme 1.21 might be applicable to the approach to dihydro eurotiumide B if the conditions for the replacement of the phenylthiol group with a methoxyl group could be identified. After several experiments, we found that using sodium methoxide in methanol at room temperature provided a 54% yield of **9** (Scheme 1.24).

In order to make dihydro eurotiumide B, building blocks **40** and **42** were prepared as illustrated in Scheme 1.25.[42] Phosphonate ester **37** was synthesized from phosphonate **36** through condensation with isovaleraldehyde followed hydrogenation. Then phosphonate ester **37** reacted with the monoacetal of glyoxal to provide a mixture of isomeric esters which was then treated

with hydrochloric acid to hydrolyze the acetal and isomerize the mixture to a hydroxy butanolide **39**. Introduction of the phenylthio group using thiophenol and PTSA (p-toluenesulfonic acid) quantitatively afforded butanolide **40**. Epoxidation of the commercially available ester **41** using MCPBA (*meta*-chloroperoxybenzoic acid) afforded **42** in 84% yield.

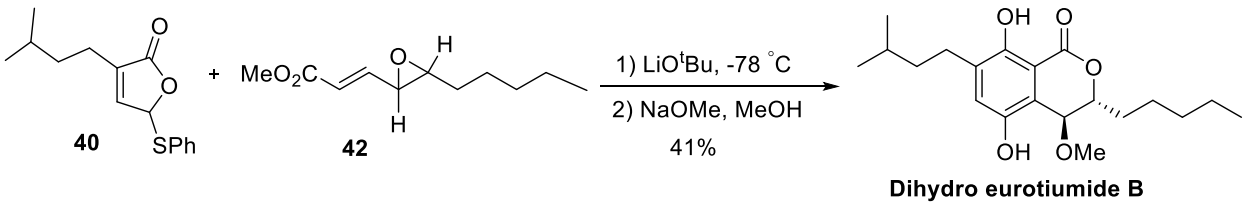


Scheme 1.24 Synthesis of **34**.



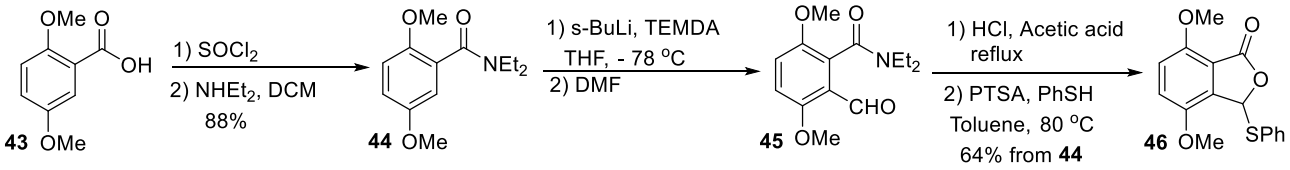
Scheme 1.25 Synthesis of **40** and **42**.

The combination of **40** and **42** using lithium tert-butoxide from -78 °C to ambient temperature followed by addition of methanol generated compound dihydro eurotiumide B (Scheme 1.26) in 41% isolated yield. The *trans*-relationship between the amyl group and the methoxyl group were confirmed by comparison to the NMR spectrum of eurotiumide B.

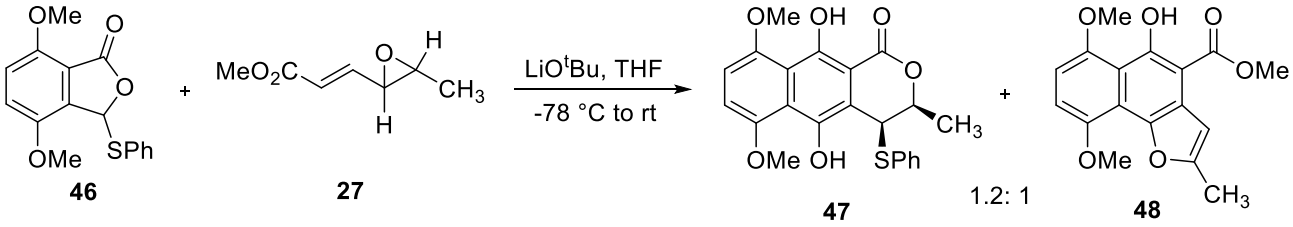


Scheme 1.26 Synthesis of dihydro eurotiumide B.

This chemistry was also applied in the preparation of anhydrofusarubin lactone. Phthalide **46** was readily available from hydroxy phthalide **45** using thiophenol and PTSA (*p*-toluenesulfonic acid) in toluene at 80 °C. Hydroxy phthalide **45** was synthesized from aldehyde **43** in two steps (Scheme 1.27). Reaction of **46** and epoxy sorbate **27** under conditions that had been successful with the phenylthiobutenolide afforded two products, hydroquinone **47** and benzofuran **48** in a 1.2:1 ratio in a 92% combined yield (Scheme 1.28).[43]

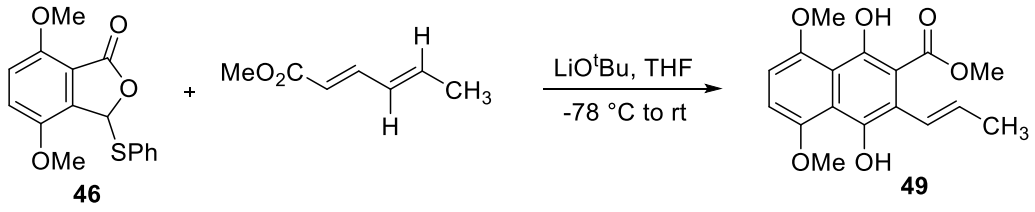


Scheme 1.27 Synthesis of **46**.



Scheme 1.28 Synthesis of **47** and **48**.

The reaction of phthalide **46** with methyl sorbate afforded ester **49** in 81% yield as the only isolated product (Scheme 1.29). The rationale for the high selectivity for 1,4-addition is unclear. Compound **49** represents an advanced intermediate for the synthesis of anhydrofusarubin lactone.



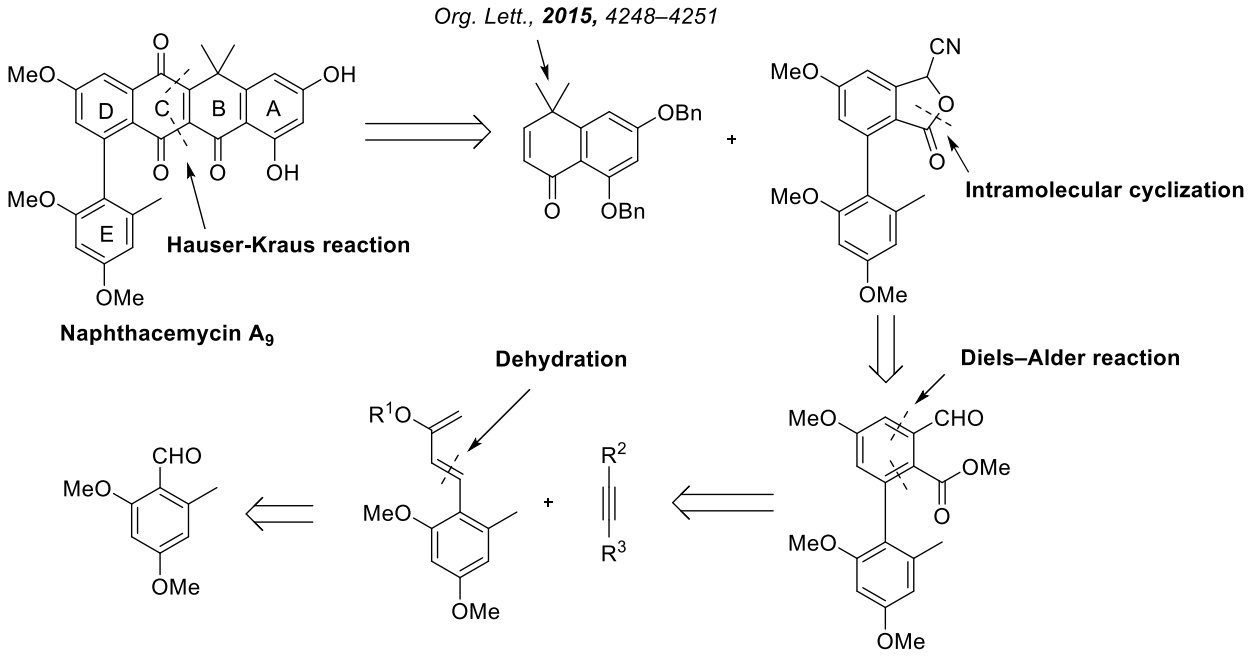
Scheme 1.29 Synthesis of **49**.

The first synthesis of dihydro eurotiumide B has been achieved in seven steps from phosphonate ester **35**. The overall yield is 30%. Key steps are the tandem Hauser-Kraus annulation-reductive thiolation reaction. The highly regioselective annulation of phthalide **46** with methyl sorbate affords an advanced intermediate for the synthesis of anhydrofusarubin lactone.

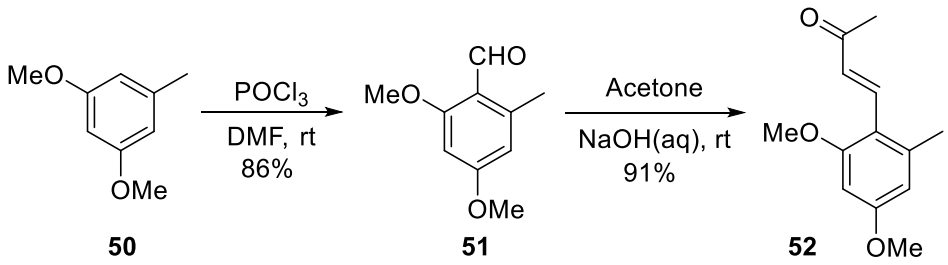
1.2.4 Total synthesis of (±) naphthacemycin A_9

Naphtacemycin A_9 is a 1,4 quinone with two hydroxyl groups. It has a chiral axis and the absolute configuration has not been determined. The C ring could be synthesized by a Hauser-Kraus annulation from cyanide substituted phthalide and benzyl protected enone. The synthesis of the enone was reported from the literature. The biphenyl phthalide could be synthesized through the intramolecular cyclization of biphenyl ester. The Diels-Alder reaction of the diene with alkynes could generate the biphenyl ester. The diene could be obtained through dehydration from the aldehyde (Scheme 1.30).

The synthesis started from dimethoxytoluene **50** (Scheme 1.31). The Vilsmeier reaction using phosphoryl chloride and dimethylformamide provided the aldehyde **51** in 86% yield.[44] Enone **52** was constructed via an aldol reaction with acetone in aqueous sodium hydroxide in 91% yield.

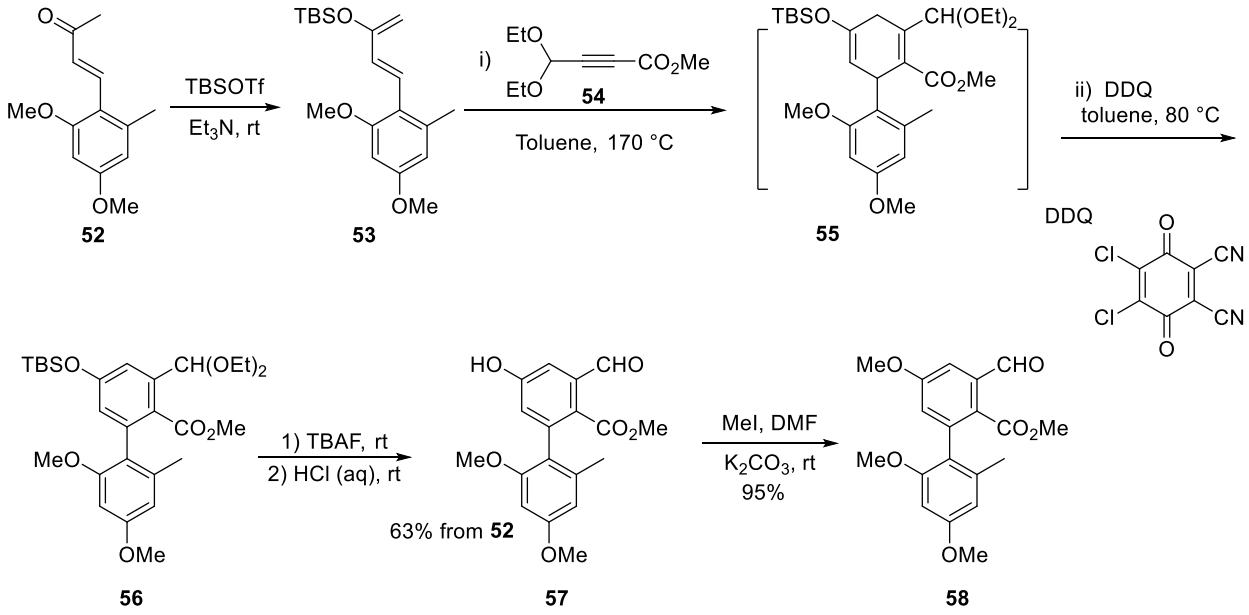


Scheme 1.30 Retrosynthetic analysis of naphthacemycin A_9.



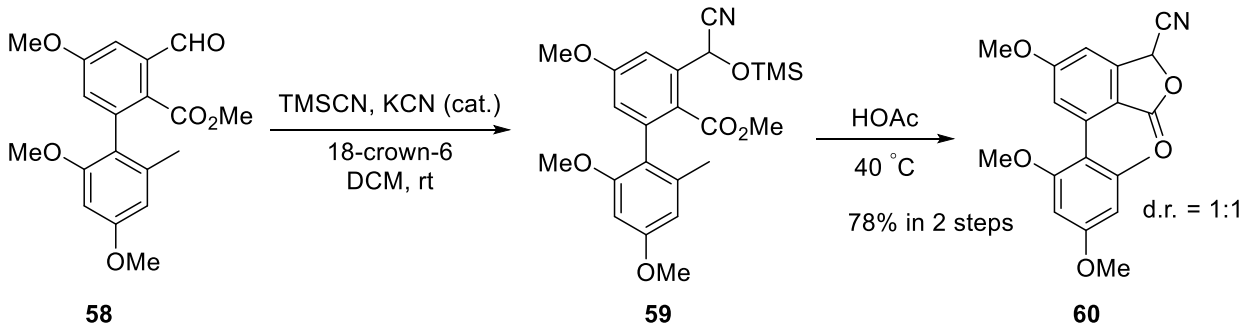
Scheme 1.31 Synthesis of **52**.

TBS triflate (*tert*-butyldimethylsilyl trifluoromethanesulfonate) and triethylamine transferred enone **52** to silyl ether diene **53**. The next step is the Diels-Alder reaction. The reaction of **53** with methyl 4,4-diethoxybutynoate (**54**),[45] an electron-deficient dienophile, in a sealed tube at 170 °C for 40 hours afford a dihydrobiphenyl adduct **55**. DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) oxidation at 80 °C gave biphenyl product **56**. TBAF (tetra-*n*-butylammonium fluoride) removed TBS group and hydrochloric acid hydrolyzed the acetal group to aldehyde **57**. The overall yield is 63% in five steps from compound **52**. Then the hydroxyl group was protected by methyl iodide in 95% yield.



Scheme 1.34 Synthesis of **58**.

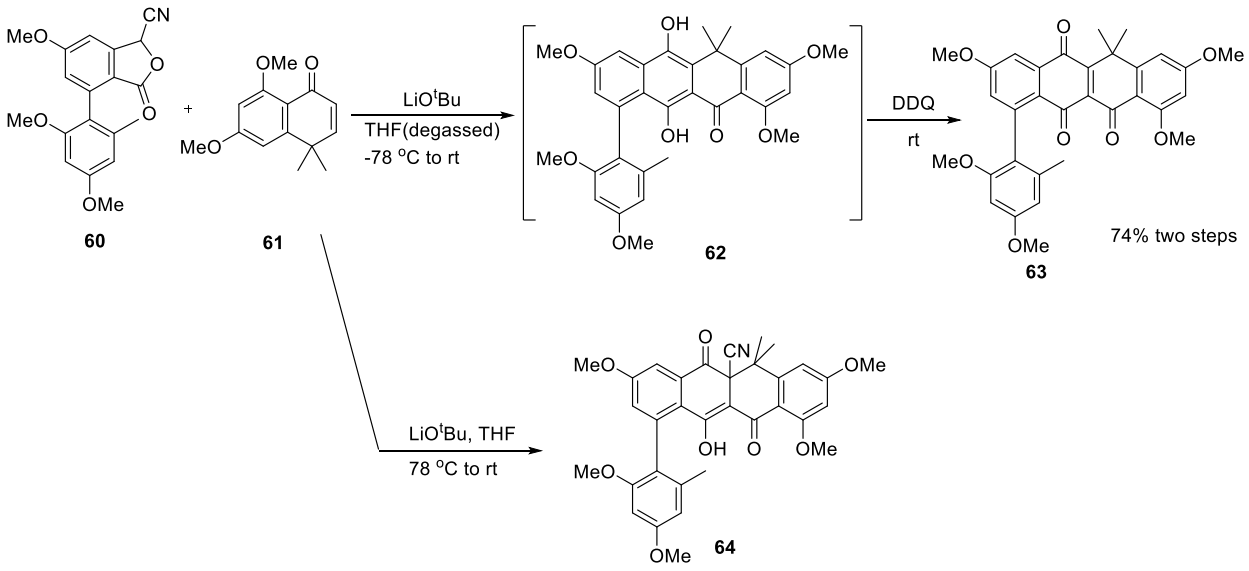
The conversion of **58** to phthalide **60** was achieved through cyanohydrin formation followed by cyclization. TMSCN (trimethylsilyl cyanide) reacted with the aldehyde group of **58** catalyzed by potassium cyanide in the presence of 18-crown-6.[46] Then the adduct underwent cyclization in acetic acid at 40 °C. The transformation gave a diastereomeric a ratio around 1:1.



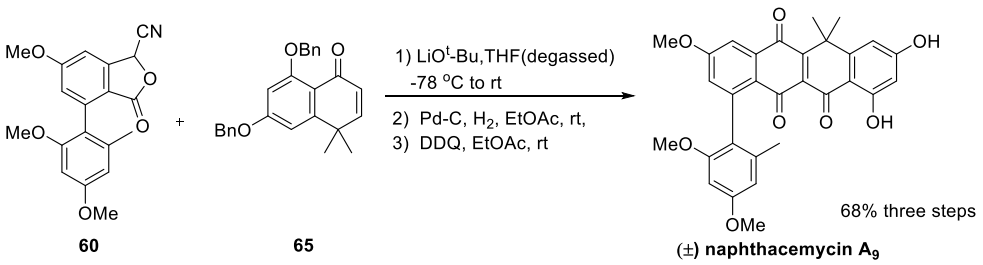
Scheme 1.35 Synthesis of **60**.

Phthalide **60** was then reacted with enone **61**[47] and lithium tert-butoxide in deoxygenated THF (tetrahydrofuran) from -78 °C to ambient temperature to produce a hydroquinone **62** which was oxidized in situ with DDQ to provide a naphthacene quinone **63**, an analog of naphthacemycin A_9, in two steps in 74% overall yield (Scheme 1.36). When the tetrahydrofuran

used in the Hauser-Kraus annulation not was deoxygenated, the compound **64** was the major product, which was supposed to be formed via oxidation of **62** followed by the Michael addition of cyanide. Similarly, with enone **65**[47], naphthacemycin A_9 was prepared by the Hauser-Kraus annulation, removal of the benzyl group and oxidized 1,4 hydroquinone to racemic naphthacemycin A_9. The yield is 68% in three steps.



Scheme 1.36 Synthesis of **63**.



Scheme 1.37 Synthesis of naphthacemycin A_9.

Racemic naphthacemycin A_9 was synthesized in nine steps, the overall yield is in 26%. The key steps are the Diels-Alder reaction and the Hauser-Kraus annulation.

1.3 Conclusion

Total syntheses of four natural products and their derivatives exhibiting antibacterial activities were accomplished. The synthesis of biatriosporin D was started from the Friedel-Crafts reaction of 3,5-dimethoxyphenol followed by triflate protection. The Suzuki-Miyaura reaction of the phenol triflate with a furan boronic acid followed by the hydrolysis afforded the keto acid. Conversion of the keto acid into the ortho-quinone was achieved by using carbonyl diimidazole followed by titanium tetrachloride. Lithium chloride selectively demethylated the ortho-quinone and provided biatriosporin D. The first synthesis of biatriosporin D was accomplished in six steps. The overall yield was 50%. Key steps are the acylation and selective demethylation.

The synthesis of indanostatin started from the Hauser-Kraus annulation of the butenolide and dimethyl fumarate. The resulting hydroquinone was hydrolyzed to the diacid and was then cyclized to the anhydride. The anhydride was then converted into the indanedione. The oxidation of the indanedione using *N*-bromosuccinimide/dimethyl sulfoxide followed by the acetone addition afforded indanostatin. The first synthesis of indanostatin was accomplished in six steps. The overall yield is 15%. Key steps are the Hauser-Kraus annulation and *N*-bromosuccinimide and dimethyl sulfoxide oxidation.

The synthesis of dihydro eurotiumide B was started from the Emmons condensation of a phosphonate with the monoacetal of glyoxal. The acetal hydrolysis and thiophenol addition afforded the butanolide. The Hauser-Kraus annulation of the butanolide with a mono-epoxide of a dienic ester followed by methoxide substitution provided dihydro eurotiumide B. The first synthesis of dihydro eurotiumide B was achieved in seven steps. The overall yield is 30%. Key steps are the tandem Hauser-Kraus annulation-reductive thiolation reaction.

The synthesis of naphthacemycin A_9 was started from the Vilsmeier reaction of 3,5-

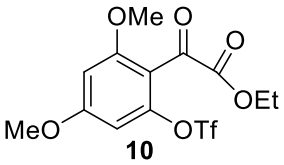
dimethoxytoluene and an aldol-dehydration reaction. The Diels-Alder reaction of the silyloxy diene with the alkyne and DDQ oxidation afforded the biphenyl. The phthalide was achieved through the cyanohydrin formation followed by the cyclization in acetic acid. The resulting phthalide underwent Hauser-Kraus annulation with an enone and produced the hydroquinone. The benzyl deprotection and DDQ oxidation afforded naphthacemycin A_9. Naphthacemycin A_9 was synthesized in nine steps, the overall yield is in 26%. The key steps are the Diels-Alder reaction and the Hauser-Kraus annulation.

1.4. Experimental

General Information

All starting materials were purchased from Sigma-Aldrich, Ambeed, Alfa Aesar, TCI and Oakwood Chemical. Solvents were all purchased from Sigma-Aldrich and Fisher Scientific and were used as received with the following exceptions. Tetrahydrofuran was distilled from lithium aluminum hydride. All reactions were monitored by thin layer chromatography (TLC) and ^{1}H NMR. All yields refer to separated yield after column chromatography unless indicated. TLC was obtained by silica plate using UV light as a visualizing agent or Potassium permanganate solution with heat. All columns were performed with silica gel 60Å, particle size 40-63 μm. ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ or other deuterated solvents on a Varian MR-400 or Bruker Avance III 600 MHz spectrometer. Chemical shifts were reported in parts per million from the solvent resonance as the internal standard ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; DMSO-d_6: δ_H = 2.50 ppm, δ_C = 39.52 ppm; Acetone-d_6: δ_H = 2.05 ppm, δ_C = 29.84 ppm; multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet) and m (multiplet)). High-resolution mass spectra (HRMS) were recorded on an Agilent 6540 QTOF (quadrupole time of flight) mass spectrometer using ESI (electrospray ionization). Melting points were obtained on a Digimelt MPA160 instrument.

General Procedure and Selected Spectrum Data.



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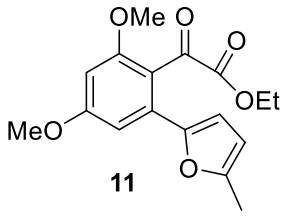
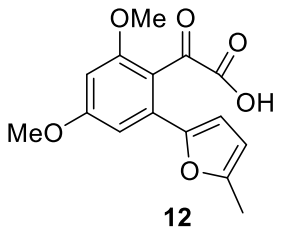
Ethyl 2-(2,4-dimethoxy-6-(((trifluoromethyl)sulfonyl)oxy)phenyl)-2-oxoacetate (10). To a solution of 3,5-dimethoxyphenol (154 mg, 1.0 equiv) in dichloromethane (5.0 mL) was added titanium tetrachloride (208 mg, 1.1 equiv) at -20 °C. Ethyl chlorooxoacetate (150 mg, 1.1 equiv) was added dropwise while maintaining temperature at or below -15 °C. The resulting reaction mixture was stirred for 4 hours. The reaction was quenched by addition of hydrochloric acid (aqueous, 2.0 M) and was extracted with dichloromethane twice. The combined organic solution was washed with water and brine. The organic solution was dried by sodium sulfate. The solvent was evaporated in vacuo and the residue was dissolved in dichloromethane (5.0 ml). To the solution was added pyridine (158 mg, 2.0 equiv) and the solution was cooled to 0 °C. To the reaction mixture, trifluoromethanesulfonic anhydride (338 mg, 1.2 equiv) was added dropwise and the mixture was stirred for an hour. The mixture was diluted with ethyl acetate and was washed with hydrochloric acid (aqueous, 2.0 M), water and then brine. The organic solution was dried by sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel and triflate **10** was obtained as a yellow solid (358 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.48 (d, *J*=2.2, 1H), 6.45 (d, *J*=2.1, 1H), 4.31 (q, *J*=7.1, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 1.32 (t, *J*=7.1, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.80, 165.19, 163.14, 162.29, 149.80, 118.62 (q, *J*=320.7), 110.88, 101.66, 97.86, 62.19, 56.67, 56.22, 14.06. HRMS (ESI-QTOF) calcd for [M + H^+]: 387.0356, found: 387.0356.



11

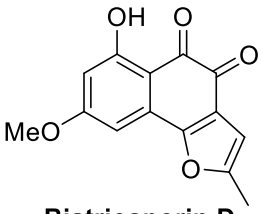
Ethyl 2-(2,4-dimethoxy-6-(5-methylfuran-2-yl)phenyl)-2-oxoacetate (11). Triflate **10** (386 mg, 1.0 equiv), $PdCl_2(PPh_3)_2$ (35.2 mg, 0.05 equiv), 5-methyl-2-furanboronic acid (190 mg, 1.5 equiv) and tripotassium phosphate (425 mg, 2.0 equiv) were added into round flask. To the reaction mixture, degassed tetrahydrofuran (5.0 mL) was added. The mixture was heated under reflux condition overnight. After cooling down, the mixture was diluted with ethyl acetate and was washed with water and brine. The organic solution was dried by sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel and coupling product **11** was obtained as a yellow oil (300 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.67 (d, *J*=2.2, 1H), 6.45 – 6.42 (m, 1H), 6.37 (d, *J*=2.2, 1H), 5.98 (dd, *J*=3.3, 1.0, 1H), 4.18 (q, *J*=7.1, 2H), 3.82 (s, 3H), 3.75 (s, 3H), 2.25 (s, 3H), 1.20 (t, *J*=7.1, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 186.77, 162.61, 161.62, 159.93, 153.31, 149.70, 132.55, 115.71, 110.51, 108.02, 102.66, 97.53, 62.09, 55.99, 55.56, 13.98, 13.53. HRMS (ESI-QTOF) calcd for [M + H^+]: 319.1176, found: 319.1183.



12

2-(2,4-Dimethoxy-6-(5-methylfuran-2-yl)phenyl)-2-oxoacetic acid (12). To a solution of **11** (318 mg, 1.0 equiv) in ethanol (2.5 mL) and water (5.0 mL) was added sodium hydroxide (160 mg, 4.0 equiv) in ice-bath. The mixture was stirred at room temperature for 1 hour. After

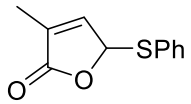
the completion of the reaction, ethanol was removed in vacuo and the residue was acidified by conc hydrochloric acid under an ice-bath. The product **12** was obtained by filtration as a yellow solid (286 mg, 99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.80 (d, *J*=2.1, 1H), 6.73 (d, *J*=3.3, 1H), 6.60 (d, *J*=2.2, 1H), 6.18 (dd, *J*=3.2, 1.2, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 188.91, 162.56, 161.94, 159.32, 152.67, 149.47, 130.72, 115.67, 109.99, 108.33, 102.35, 97.66, 56.17, 55.71, 13.20. HRMS (ESI-QTOF) calcd for [M + H^+]: 291.0863, found: 291.0867.



Biatriosporin D

6-Hydroxy-8-methoxy-2-methylnaphtho[1,2-b]furan-4,5-dione. To a solution of acid **12 (**145 mg, 1.0 equiv) in dichloromethane (3.0 mL) was added carbonyldiimidazole (162 mg, 2.0 equiv). The reaction mixture was stirred at room temperature overnight. The resulting solution was added into a solution of titanium tetrachloride (380 mg, 4.0 equiv) in dichloromethane (2.0 mL) at -10 °C. The reaction mixture was stirred at -10 °C for 5 hours and quenched by addition of hydrochloric acid (aqueous, 2.0 M) and then was extracted twice with dichloromethane. The combined organic solution was washed with saturated sodium bicarbonate solution, water and brine. The organic solution was dried by sodium sulfate. The solvent was evaporated in vacuo and red solid **1** was obtained (87 mg, 63 %). To a solution of solid **1** (54.4 mg, 1.0 equiv) in dimethylformamide (6.0 mL) was added lithium chloride (50.4 mg, 6.0 equiv). The reaction mixture was heated under reflux condition for 2 hours and was cooled down. Dimethylformamide was removed by distillation under reduced pressure. And the residue was acidified by hydrochloric acid (aqueous, 2.0 M) and then was extracted three times by ethyl

acetate. The combined organic solution was washed with water and brine. The organic solution was dried by sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel and product was obtained as red solid (47.4 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.43 (s, 1H), 6.74 (d, *J*=2.3, 1H), 6.41 (s, 1H), 6.31 (d, *J*=2.3, 1H), 3.90 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.12, 175.37, 169.22, 168.20, 158.14, 156.31, 129.59, 122.78, 106.82, 105.39, 104.44, 101.26, 56.31, 13.78. HRMS (ESI-QTOF) calcd for [M + H^+]: 259.0601, found: 259.0597.



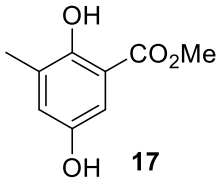
16

3-Methyl-5-(phenylthio)furan-2(5H)-one (16). To a stirred solution of 5-hydroxy-3-methylfuran-2(5H)-one (1.14 g, 10 mmol) in toluene (100 mL) was added p-toluenesulfonic acid (PTSA, 50 mg) followed by thiophenol (1.10 g, 10 mmol), and the mixture was heated at 80 °C for 15 hours. Toluene was removed under reduced pressure. The crude residue was then diluted with ethyl acetate (50 mL) and washed by water and brine and dried over sodium sulfate and concentrated. Purification by column chromatography gives the product as a solid **16** (1.80 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 - 7.46 (m, 2H), 7.40 - 7.28 (m, 3H), 6.96 (p, *J*=1.6, 1H), 6.11 (p, *J*=1.9, 1H), 1.83 (t, *J*=1.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.84, 144.96, 134.12, 132.15, 130.20, 129.27, 129.15, 85.86, 10.59. HRMS (ESI-QTOF) calcd for [M + H]$^+$: 207.0474, found: 207.0470.

General procedure for Hauser-Kraus annulation of 16 for the syntheses of compound 17, 19, 20, 21.

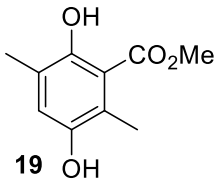
To a stirred solution of **16** (206 mg, 1.0 mmol, 1.0 equiv) in tetrahydrofuran (3.0 mL) was added lithium *tert*-butoxide (1.0 M in THF, 3.0 mL, 3.0 equiv) at -78 °C. And the mixture

was stirred for 30 minutes at the same temperature. The unsaturated ester (1.5 equiv, 1.5 mmol) in tetrahydrofuran (1.0 mL) was added dropwise to the mixture and the mixture was stirred at -78 °C for 30 minutes. Then the mixture was warm to room temperature and stirred overnight. Hydrochloric acid (aqueous, 2 M, 10 mL) was added to quench the reaction and the aqueous layer was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography gives the product.



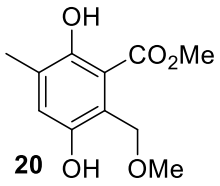
17

Methyl 2,5-dihydroxy-3-methylbenzoate (17). White solid, 150 mg, yield = 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.61 (s, 1H), 7.10 (d, *J*=3.2, 1H), 6.89 (d, *J*=3.2, 1H), 5.54 (br, 1H), 3.89 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.80, 154.32, 147.08, 128.15, 125.17, 112.10, 111.42, 52.48, 15.91. HRMS (ESI-QTOF) calcd for $[M - H]^-$: 181.0506, found: 181.0502.

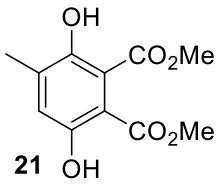


19

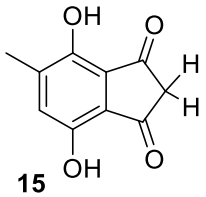
Methyl 2,5-dihydroxy-3,6-dimethylbenzoate (19). White solid, 151 mg, yield = 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.78 (s, 1H), 6.83 (s, 1H), 3.96 (s, 1H), 2.39 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.41, 154.90, 145.75, 124.76, 123.91, 122.33, 112.68, 52.31, 15.98, 14.38. HRMS (ESI-QTOF) calcd for $[M - H]^-$: 195.0663, found: 195.0662.



Methyl 2,5-dihydroxy-6-(methoxymethyl)-3-methylbenzoate (20). White solid, 133 mg, yield = 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.40 (s, 1H), 8.10 (br, 1H), 6.90 (s, 1H), 4.98 (s, 2H), 3.95 (s, 3H), 3.44 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.21, 153.90, 149.28, 127.88, 125.66, 118.16, 110.60, 72.36, 58.51, 52.51, 16.16. HRMS (ESI-QTOF) calcd for $[M - H]^-$: 225.0768, found: 225.0771.

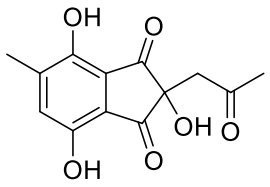


Dimethyl 3,6-dihydroxy-4-methylphthalate (21). White solid, 136 mg, yield = 57%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.95 (s, 1H), 8.89 (s, 1H), 6.89 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.87, 169.45, 152.14, 150.87, 134.80, 124.02, 111.80, 109.74, 52.62, 52.53, 16.44. HRMS (ESI-QTOF) calcd for $[M - H]^-$: 239.0561, found: 239.0559.



4,7-dihydroxy-5-methyl-1H-indene-1,3(2H)-dione (15). To a solution of **21** (240 mg, 1.0 mmol, 1.0 equiv) in methanol (5.0 mL) and water (5.0 mL) was added sodium hydroxide (400 mg, 10.0 equiv) in ice-bath. The mixture was stirred at room temperature for 1 hour. After the completion of the reaction, methanol was removed in vacuo and the residue was acidified by

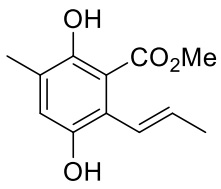
conc hydrochloric acid in ice-bath. The mixture was extracted with ethyl acetate (10 mL x 2) and the combined organic layers were dried over sodium sulfate and concentrated. The residue was dissolved in acetic anhydride (10 mL) and the mixture was heated overnight at reflux and then was cooled down. Acetic anhydride was removed by distillation under reduced pressure. The residue was dissolved in acetic anhydride (2.0 ml) containing triethylamine (1.0 mL) and the solution was treated with ethyl acetoacetate (156 mg, 1.2 mmol). After stirring overnight, hydrochloric acid (aqueous, 6 M, 10 mL) was added to the dark solution at room temperature. The solution was heated to 75 °C for 1.0 hour. Aqueous layer was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over sodium sulfate and concentrated. Hexane was added to the residue and solid was precipitated out. Product was collected by filtration. Brown solid, 92 mg, yield = 48%. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.03 (s, 1H), 9.17 (s, 1H), 7.05 (s, 1H), 3.23 (s, 2H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 200.43, 195.76, 148.25, 146.48, 136.80, 127.19, 126.39, 124.63, 46.41, 16.15. HRMS (ESI-QTOF) calcd for $[M - H]^-$: 191.0350, found: 191.0353.



(±)-Indanostatin

2,4,7-trihydroxy-5-methyl-2-(2-oxopropyl)-1H-indene-1,3(2H)-dione (indanostatin). To a solution of **9** (92 mg, 0.48 mmol, 1.0 equiv) and ammonium acetate (3.7 mg, 0.048 mmol, 0.1 equiv) in diethyl ether (5.0 mL) was added *N*-bromosuccinimide (170 mg, 0.96 mmol, 2.0 equiv). The mixture was stirred at room temperature for overnight. After the completion of the reaction, the solution was diluted with diethyl ether (10 mL) and was washed with hydrochloric acid (aqueous, 1 M, 5 mL) followed by brine. The organic layer was dried over sodium sulfate

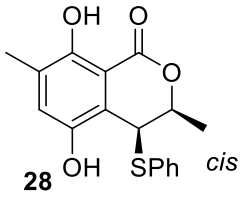
and concentrated. The residue was dissolved in dimethyl sulfoxide (1.0 mL) and heated at 80 °C for 2.0 hours. After the reaction was cooled down, water (1.0 mL) was added to the solution and the mixture was stirred at room temperature for 1.0 hour. Water and dimethyl sulfoxide were removed by distillation under reduced pressure. And the residue was diluted with ethyl acetate (20 mL) and washed with hydrochloric acid (aqueous, 1 M, 10 mL) followed by brine. The organic layer was dried over sodium sulfate and concentrated. The residue was dissolved in acetic acid (1.0 mL) and a few drops of acetone were added to the mixture. The reaction was heated at 55 °C for 6 hours. After cooling down, acetic acid was evaporated in vacuo and the residue was diluted with ethyl acetate (10 mL) was washed with hydrochloric acid (aqueous, 1 M, 5 mL) followed by brine. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography gives the product as a yellow solid, 69.1 mg, yield = 55%. ^{1}H NMR (400 MHz, acetone-d_6) δ = 8.64 (s, 2H), 7.19 (d, *J*=0.9, 1H), 3.39 (d, *J*=1.4, 2H), 2.32 (d, J=0.8, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ = 205.63, 201.18, 198.51, 149.11, 148.07, 137.65, 127.10, 122.73, 121.50, 73.62, 47.61, 28.49, 14.92. HRMS (ESI-QTOF) calcd for $[M - H]^-$: 263.0561, found: 263.0561.



26

Methyl (E)-2,5-dihydroxy-3-methyl-6-(prop-1-en-1-yl)benzoate (26). To a stirred solution of butanolide **16** (206 mg, 1.0 mmol) in tetrahydrofuran (5.0 mL) was added lithium *tert*-butoxide (1.0 M in tetrahydrofuran, 3.0 mL) at -78 °C (dry ice/acetone bath). The mixture was stirred for 30 minutes at the same temperature. Methyl sorbate (151 mg, 1.2 mmol) in THF (2.0 mL) was added dropwise to the mixture and the mixture was stirred at -78 °C for another 30

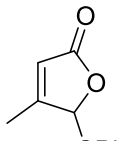
minutes. The mixture was warmed to room temperature and stirred 16 hours. Hydrochloric acid (aqueous, 2 M, 10 mL) was added to quench the reaction and the aqueous layer was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 20:1 (v/v)) gave the product **26** as a yellow oil (62.10 mg, 28%, d.r =3/1, rf = 0.3(hexane/ethyl acetate = 10:1 (v/v))). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.94 (s, 1H), 6.98 (s, 1H), 6.45 (dd, *J*=16.3, 2.0, 1H), 5.75 (dq, *J*=16.4, 6.5, 1H), 5.52 (s, 1H), 3.89 (s, 3H), 2.22 (s, 3H), 1.93 (dd, *J*=6.5, 1.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$){1H}: δ = 171.7, 154.6, 144.8, 129.8, 127.4, 126.9, 123.8, 121.2, 109.8, 52.1, 18.5, 16.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{15}O_4$ 223.0965; Found 223.0968.



28

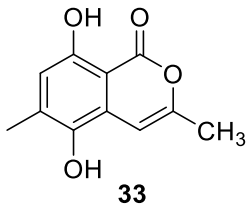
5,8-Dihydroxy-3,7-dimethyl-4-(phenylthio)isochroman-1-one (28). To a stirred solution of butanolide **16** (206 mg, 1.0 mmol) in tetrahydrofuran (5.0 mL) was added lithium *tert*-butoxide (1.0 M in tetrahydrofuran, 3.0 mL) at -78 °C (dry ice/acetone bath). The mixture was stirred for 30 minutes at the same temperature. The epoxide **27** (170 mg, 1.2 mmol) in tetrahydrofuran (2.0 mL) was added dropwise to the mixture and the mixture was stirred at -78 °C for 30 minutes. The mixture was warmed to room temperature and stirred 16 hours. Hydrochloric acid (aqueous, 2 M, 10 mL) was added to quench the reaction and the aqueous layer was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 3:1 (v/v)) gave the product **8** as a solid (224 mg, mp:126-128 °C, 71%,

d.r =3/1, rf = 0.3(hexane/ethyl acetate = 3:1 (v/v))). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.90 (s, 1H), 7.51 - 7.44 (m, 2H), 7.38 - 7.30 (m, 3H), 6.99 (s, 1H), 4.91 (qd, *J*=6.8, 1.4, 1H), 4.90 (br, 1H) 4.45 (d, *J*=1.3, 1H), 2.24 (s, 3H), 1.35 (d, *J*=6.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$){1H}: δ = 168.2, 154.9, 144.4, 134.6, 131.7, 129.3, 128.8, 128.0, 126.7, 118.5, 106.3, 78.4, 44.5, 20.2, 15.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}O_4S$ 317.0842; Found 317.0841.



31

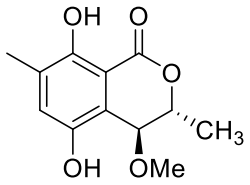
4-Methyl-5-(phenylthio)furan-2(5H)-one (31). To a stirred solution of 5-hydroxy-4-methylfuran-2(5H)-one (1.70 g, 10 mmol) in toluene (100 mL) was added p-toluenesulfonic acid (PTSA, 57 mg, 0.3 mmol) followed by thiophenol (1.10 g, 10 mmol), and the mixture was heated at 80 °C (oil bath) for 15 h. Toluene was removed under reduced pressure. The crude residue was then diluted with ethyl acetate (50 mL), washed by water and brine, dried over sodium sulfate, and concentrated. Purification by column chromatography on silica gel gave the product **6** as yellow liquid. 1.85 g, yield = 90%. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.55 - 7.53 (m, 2H), 7.40-7.34 (m, 3H), 6.02 (m, 1H), 5.77 (dt, *J*=2.9, 1.5, 1H), 2.18 (t, *J*=1.3, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ = 171.3, 164.7, 134.3, 129.3, 129.2, 128.9, 118.8, 89.1, 14.5.HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{11}H_{11}O_4$: 207.0474; found: 207.0471.



33

5,8-Dihydroxy-3,6-dimethyl-1H-isochromen-1-one (33). To a stirred solution of butanolide **6** (206 mg, 1.0 mmol) in tetrahydrofuran (3.0 mL) was added lithium *tert*-butoxide

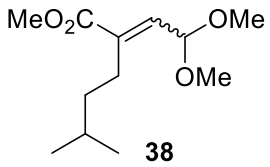
(1.0 M in tetrahydrofuran, 3.0 mL, 3.0 mmol) at -78 °C (dry ice/acetone bath). The mixture was stirred for 30 min at the same temperature. The epoxide **27** (213.0 mg, 1.5 mmol) in THF (1.0 mL) was added dropwise to the mixture, and the mixture was stirred at -78 °C for 30 min. The mixture was warmed to room temperature and stirred 16 h. Hydrochloric acid (aqueous, 2 M, 10 mL) was added to quench the reaction, and the aqueous layer was extracted with ethyl acetate (10 mL × 2). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel gave a mixture of compound **32** and **33**. The mixture was dissolved in dichloromethane (10 mL) and triethylamine (1.0 mL) and was stirred at room temperature for 24 hours. Hydrochloric acid (aqueous, 2 M, 10 mL) was added to quench the reaction, and the aqueous layer was extracted with dichloromethane (10 mL × 2). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel gave product **33** as a yellow solid. 142 mg, yield = 69%, mp 154-156 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ = 10.51 (s, 1H), 6.74 (d, J=0.8, 1H), 6.72 (d, J=1.1, 1H), 2.36 (d, J=0.7, 3H), 2.29 (d, J=1.1, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ = 166.4, 154.9, 153.0, 141.0, 136.1, 125.5, 115.6, 103.3, 99.1, 18.6, 16.6. HRMS (ESI-TOF): m/z [M + H]$^{+}$ calcd for $C_{11}H_{11}O_4$: 207.0652; found: 207.0646.



34

5,8-Dihydroxy-4-methoxy-3,7-dimethylisochroman-1-one (34). Compound **28** (224 mg, 0.71 mmol) was dissolved in methanol (10 mL) and sodium methoxide (192 mg, 3.55 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour. Methanol was removed under reduced pressure. The crude residue was then diluted with ethyl acetate (10 mL)

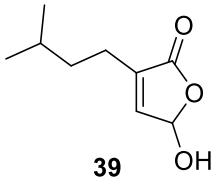
and washed by hydrochloric acid (aqueous, 2 M) and brine and dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 2:1 (v/v)) gave the product **34** as solid (72.6 mg, mp:159-161 °C, 43%, rf = 0.3(hexane/ethyl acetate = 2:1 (v/v))). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.89 (s, 1H), 6.95 (s, 1H), 6.10 (br, 1H), 4.93 (qd, *J*=6.8, 3.8, 1H), 4.62 (d, *J*=3.8, 1H), 3.43 (s, 3H), 2.23 (s, 3H), 1.38 (d, J=6.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$){1H}: δ = 168.5, 154.8, 145.8, 128.9, 126.1, 117.2, 106.1, 78.2, 72.9, 56.4, 18.0, 15.8. HRMS (ESI-TOF) m/z: $[M - H]^-$ Calcd for $C_{12}H_{13}O_5$ 237.0768; Found: 237.0771.



38

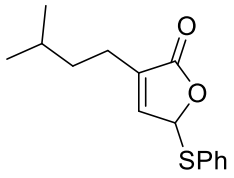
Methyl 2-(2,2-dimethoxyethylidene)-5-methylhexanoate (38). To a solution of proline (1.0 mmol, 115 mg) in dimethyl sulfoxide (3.3 mL), isovaleraldehyde (0.86 g, 10 mmol) was added. After 10 min, trimethyl phosphonoacetatemalonate **35** (1.82 g, 10 mmol) was slowly added and the reaction was stirred 24 hours at room temperature. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (20 mL), sodium bicarbonate solution (saturated, 20 mL) and brine (20 mL). The organic layer was dried over sodium sulfate and concentrated. The residue was added to the suspension of palladium on carbon (10 wt %, 2.11 g, 2 mmol) in ethanol (100 mL). The mixture was stirred for 5 hours at 50 °C (oil bath) under hydrogen atmosphere. After cooling down to room temperature, the mixture was filtrated through Celite and ethanol was removed under reduced pressure. To the residue dissolved in dichloromethane (13 mL), glyoxal dimethyl acetal (1.50 g, 14.3 mmol), tetrabutylammonium iodide (TBAI, 173 mg) and 33 % sodium hydroxide solution (13.00 g) were added. After 30 min of stirring at room temperature, the reaction mixture was extracted with dichloromethane (20 mL

x 3). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 5:1 (v/v)) gave the product **38** as liquid (82%, 1.88 g, Z/E = 1.0, rf = 0.4(hexane/ethyl acetate = 5:1 (v/v))). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.56 (d, *J*=6.5, 1H), 5.73 (d, *J*=6.6, 1H), 5.36 (d, *J*=6.6, 1H), 5.07 (d, *J*=6.5, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.33 (s, 6H), 3.31 (s, 6H), 2.38 - 2.22 (m, 4H), 1.53 (dp, J=13.3, 6.6, 2H), 1.35 - 1.24 (m, 4H), 0.89 (d, *J*=6.6, 6H), 0.86 (d, *J*=6.6, 6H). ^{13}C NMR (100 MHz, $CDCl_3$){1H}:δ = 168.0, 167.7, 137.1, 136.9, 136.0, 134.0, 99.9, 99.3, 53.3, 52.4, 51.9, 51.7, 38.2, 37.4, 32.0, 28.2, 27.6, 25.5, 22.36, 22.35. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{23}O_4$ 253.1410; Found: 253.1413.



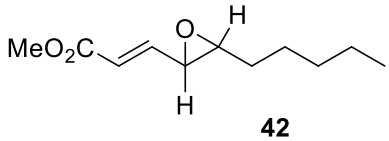
39

5-Hydroxy-3-isopentylfuran-2(5H)-one (39). Compound **38** (2.00 g, 8.7 mmol) was added to the mixture of hydrochloric acid (aqueous, 2 M, 20 mL) and tetrahydrofuran (20 mL). The reaction mixture was stirred at room temperature until the starting material was fully consumed. The reaction was extracted with ethyl acetate (30 mL x 2). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 3:1 (v/v)) gave the product **39** as liquid (1.32 g, 89%, rf = 0.3(hexane/ethyl acetate = 2:1 (v/v))). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.84 (q, *J*=1.6, 1H), 6.11 (s, 1H), 5.06 (br, 1H), 2.47 - 2.15 (m, 2H), 1.66 - 1.52 (m, 1H), 1.47 - 1.38 (m, 2H), 0.90 (d, *J*=6.7, 6H). ^{13}C NMR (100 MHz, $CDCl_3$){1H}: δ = 172.9, 143.8, 143.8, 138.2, 97.3, 36.0, 27.6, 22.9, 22.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{15}O_3$ 171.1016; Found: 171.1015.



40

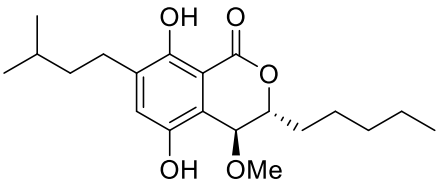
3-Isopentyl-5-(phenylthio)furan-2(5H)-one (40). To a stirred solution of 5-hydroxy-3-isopentylfuran-2(5H)-one **39** (1.70 g, 10 mmol) in toluene (100 mL) was added p-toluenesulfonic acid (PTSA, 57 mg, 0.3 mmol) followed by thiophenol (1.10 g, 10 mmol), and the mixture was heated at 80 ^{o}C (oil bath) for 15 hours. Toluene was removed under reduced pressure. The crude residue was then diluted with ethyl acetate (50 mL) and washed by water and brine and dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 10:1 (v/v)) gave the product **3b** as liquid (2.59 g, 99%, rf = 0.4 (hexane/ethyl acetate = 10:1 (v/v))). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 - 7.46 (m, 2H), 7.37 - 7.30 (m, 3H), 6.88 (q, *J*=1.6, 1H), 6.10 (q, *J*=1.8, 1H), 2.19 - 2.11 (m, 2H), 1.41 (dt, *J*=13.3, 6.7, 1H), 1.27 - 1.18 (m, 2H), 0.85 (d, *J*=2.0, 3H), 0.84 (d, *J*=2.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$){1H}: δ = 172.4, 144.0, 136.7, 134.4, 129.6, 129.1, 85.5, 36.2, 27.5, 23.0, 22.3, 22.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}O_2S$ 263.1100; Found: 263.1101.



42

Methyl (E)-3-(3-pentyloxiran-2-yl)acrylate (42). *Meta*-Chloroperoxybenzoic acid (mCPBA, 4.63 g, 26 mmol) was added to a solution of compound **13** (1.82 g, 10 mmol) in dichloromethane (30 mL) at 0 °C (ice bath), and the mixture was stirred and warmed to room temperature. After 3 hours, the reaction was quenched with sodium thiosulfate solution and extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate solution and

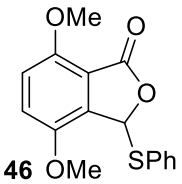
dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 20:1 (v/v)) gave the product **5b** as liquid (1.66 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.68 (ddd, *J*=15.7, 7.1, 1.0, 1H), 6.11 (dd, *J*=15.6, 1.0, 1H), 3.73 (s, 3H), 3.19 (dd, *J*=7.1, 1.1, 1H), 2.87 (ddd, *J*=7.4, 4.2, 1.3, 1H), 1.68 - 1.55 (m, 2H), 1.50 - 1.40 (m, 2H), 1.30 (m, 4H), 0.91 - 0.86 (t, *J*=7.2, 3H). ^{13}C NMR (100 MHz, $CDCl_3$){1H}: δ = 166.1, 145.2, 123.0, 61.5, 56.3, 51.7, 31.9, 31.5, 25.5, 22.5, 13.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{19}O_3$ 199.1329; Found: 199.1325.



Dihydro eurotiumide B

5,8-Dihydroxy-7-isopentyl-4-methoxy-3-pentylisochroman-1-one (dihydro eurotiumide B). To a stirred solution of butanolide **40** (86.0 mg, 0.33 mmol) in tetrahydrofuran (3.0 mL) was added lithium *tert*-butoxide (1.0 M in tetrahydrofuran, 1.0 mL, 1.0 mmol) at -78 °C (dry ice/acetone bath). And the mixture was stirred for 30 minutes at the same temperature. The epoxide **42** (84.8 mg, 0.4 mmol) in THF (1.0 mL) was added dropwise to the mixture and the mixture was stirred at -78 °C for 30 minutes. The mixture was warmed to room temperature and stirred 16 hours. Hydrochloric acid (aqueous, 2 M, 5 mL) was added to quench the reaction and the aqueous layer was extracted with ethyl acetate (5 mL x 2). The combined organic layers were dried over sodium sulfate and concentrated. The residue was dissolved in methanol (6 mL) and sodium methoxide (180 mg) was added. The reaction mixture was stirred at room temperature for 1 hour. Methanol was removed under reduced pressure. The crude residue was then diluted with ethyl acetate (10 mL) and washed by hydrochloric acid (aqueous, 2 M) and brine and dried over sodium sulfate and concentrated. Purification by column chromatography

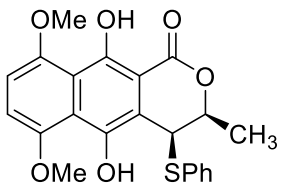
on silica gel (hexane/ethyl acetate = 5:1 (v/v)) gave the product **1b** as solid (47.2 mg, mp: 106-108 °C, 41%, rf = 0.2(hexane/ethyl acetate = 5:1 (v/v))). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.89 (s, 1H), 6.95 (s, 1H), 4.78 (ddd, *J*=8.4, 4.9, 2.8, 1H), 4.66 (d, *J*=2.8, 1H), 3.40 (s, 3H), 2.73 - 2.48 (m, 2H), 1.65 - 1.43 (m, 7H), 1.27 (td, *J*=6.6, 3.2, 4H), 0.94 (d, *J*=6.6, 6H), 0.89 - 0.83 (t, *J*=6.6, 3H). ^{13}C NMR (100 MHz, $CDCl_3$){1H}: δ = 168.7, 154.4, 145.9, 133.7, 125.0, 117.4, 106.5, 82.3, 70.9, 56.1, 38.3, 32.0, 31.3, 27.9, 27.5, 25.0, 22.5, 22.4, 13.9. HRMS (ESI-TOF) m/z: [M - H]$^-$ Calcd for $C_{20}H_{29}O_5$ 349.2020; Found: 349.2020.



46

4,7-Dimethoxy-3-(phenylthio)isobenzofuran-1(3H)-one(46). To a solid of 2, 5-dimethoxybenzoic acid **43** (50 mmol, 9.1 g) in round bottle flask was added thionyl chloride (50 mL), and the mixture was refluxed for 16 hours. Thionyl chloride was removed under reduced pressure. The crude residue was added to a solution of dichloromethane (200 ml) and diethylamine (50 mL) at 0 °C (ice-water bath) and the mixture was stirred at room temperature for 16 hours. Water (100 mL) was added to quench the reaction, and the aqueous layer was extracted with dichloromethane (100 mL x 2). The combined organic layer was washed by water and brine, dried over sodium sulfate, and concentrated. Purification by column chromatography on silica gel gave the product **44** (10.4 g, yield = 88%). Then to a solution of **44** (6.0 g, 25 mmoL) and tetramethylethylenediamine (TMEDA, 4.5 mL, 30 mmol) in tetrahydrofuran (50 mL) was added *sec*-butyllithium (1.4 M, 21.4 mL, 30 mmoL) at -78 ^{o}C and the mixture was stirred at same temperature for 2 hours. Dimethylformamide (7.7 mL, 100 mmoL) was added to the mixture at -78 °C and the mixture was stirred for 30 minutes and then warm to room

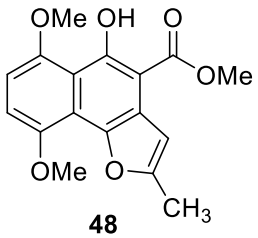
temperature and stirred for another 16 hours. The reaction was quenched by hydrochloric acid (aqueous, 2 M, 20 mL) and the mixture was extracted with ethyl acetate (30 mL x 3). The combined extracts were dried over sodium sulfate and concentrated. The crude reside (**45**) was dissolved in acetic acid (100 mL) and hydrochloric acid (aqueous, 2 M, 100 mL). The resulting solution was refluxed (oil bath) for 16 h. After the reaction was complete, acetic acid was removed under vacuum and the residue was extracted with ethyl acetate (100 mL x 2). The combined organic layer was washed with water and brine, dried over sodium sulfate, and concentrated. To a stirred solution of the obtained crude aldehyde in toluene (250 mL) was added *p*-toluenesulfonic acid(PTSA, 143 mg, 0.75 mmol) followed by thiophenol (2.75 g, 25 mmol), and the mixture was heated at 80 °C (oil bath) for 15 hours. Toluene was removed under reduced pressure. The crude residue was then diluted with ethyl acetate (50 mL), washed with water and brine, dried over sodium sulfate, and concentrated. Purification by column chromatography on silica gel [hexane/ethyl acetate, 3:1 (v/v)] gave the product **46** (4.83 g, 64% yield). White solid; mp 113–115 °C; Rf = 0.25 [hexane/ethyl acetate, 3:1 (v/v)]. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.36 - 7.34 (m, 3 H), 7.32 - 7.28 (m, 3 H), 7.08 (d, J = 8.8 Hz, 1 H), 7.03 (s, 1 H), 3.92 (s, 3 H), 3.78 (s, 3 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 166.3, 151.8, 147.7, 134.9, 133.8, 130.1, 129.5, 129.2, 119.7, 114.6, 113.9, 82.7, 56.8, 56.6. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{16}H_{15}O_4S$: 303.0686; found: 303.0689.



47

Methyl (E)-1,4-dihydroxy-5,8-dimethoxy-3-(prop-1-en-1-yl)-2-naphthoate (47). To a stirred solution of **46** (302 mg, 1.0 mmol) in tetrahydrofuran (3.0 mL) was added lithium *tert*-

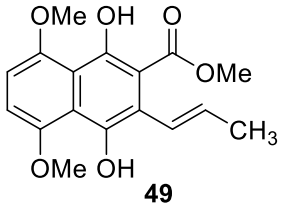
butoxide (1.0 M in tetrahydrofuran, 3.0 mL, 3.0 mmol) at -78 °C (dry ice/acetone bath). The mixture was stirred for 30 min at the same temperature. The epoxide **27** (213.0 mg, 1.5 mmol) in tetrahydrofuran (1.0 mL) was added dropwise to the mixture, and the mixture was stirred at -78 °C (dry ice/acetone bath) for 30 min. The mixture was then warmed to room temperature and stirred 16 hours. Hydrochloric acid (aqueous, 2 M, 10 mL) was added to quench the reaction, and the aqueous layer was extracted with ethyl acetate (10 mL × 2). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate, 3:1 (v/v)) gave the product **47** along with benzofuran **48**. Light brown oil; 206.7 mg, yield = 50%, d.r. = 1/1. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 12.62 (s, 1H), 12.38 (s, 1H), 9.79 (s, 1H), 9.74 (s, 1H), 7.56 (dd, *J*=6.6, 2.9, 2H), 7.49 – 7.45 (m, 2H), 7.33 – 7.31 (m, 3H), 7.19 (ddd, *J*=14.5, 7.8, 6.2, 3H), 6.97 (dd, *J*=11.3, 8.7, 2H), 6.81 (dd, *J*=19.8, 8.7, 2H), 4.88 (tdd, *J*=8.9, 6.8, 4.3, 2H), 4.79 (dd, *J*=9.9, 1.7, 2H), 4.04 (s, 3H), 4.03 (s, 4H), 3.97 (s, 3H), 3.95 (s, 3H), 1.65 (d, *J*=6.4, 3H), 1.32 (d, *J*=6.8, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 170.1, 168.7, 155.9, 155.8, 154.1, 154.0, 149.6, 149.5, 143.0, 141.0, 135.2, 134.7, 134.4, 133.6, 133.0, 129.5, 129.3, 129.1, 128.7, 128.4, 128.0, 120.8, 120.6, 117.6, 117.2, 112.8, 110.1, 109.9, 107.4, 107.0, 102.1, 101.8, 78.0, 77.7, 57.0, 57.0, 46.0, 44.4, 20.0, 18.7. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{22}H_{21}O_6S$: 413.1053; found: 413.1046.



48

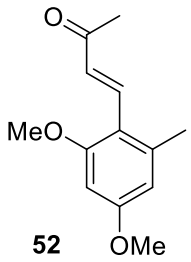
Naphtho[1,2-b]furan-4-carboxylic acid, 5-hydroxy-6,9-dimethoxy-2-methyl-, methyl ester (48). Yellow Solid; mp, 156-158 °C; 132.1 mg, yield = 42%. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 12.53 (s, 1H), 7.04 (d, *J*=8.7, 1H), 6.87 (q, *J*=0.9, 1H), 6.84 (d, *J*=8.7, 1H), 4.08 (s, 3H), 4.07

(s, 3H), 4.04 (s, 3H), 2.60 (d, *J*=0.8, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 171.2, 158.9, 155.6, 153.0, 148.4, 142.5, 124.0, 118.5, 114.2, 110.2, 106.0, 104.7, 100.9, 57.1, 56.7, 52.1, 14.3. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{17}H_{17}O_6$: 317.1020; found: 317.1019.



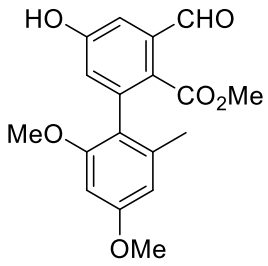
49

Methyl (E)-1,4-dihydroxy-5,8-dimethoxy-3-(prop-1-en-1-yl)-2-naphthoate (49). To a stirred solution of **46** (302 mg, 1.0 mmol) in tetrahydrofuran (3.0 mL) was added lithium *tert*-butoxide (1.0 M in tetrahydrofuran, 3.0 mL, 3.0 mmol) at -78 °C (dry ice/acetone bath). The mixture was stirred for 30 min at the same temperature. Methyl sorbate (189.0 mg, 1.5 mmol) in tetrahydrofuran (1.0 mL) was added dropwise to the mixture, and the mixture was stirred at -78 °C (dry ice/acetone bath) for 30 min. The mixture was then warmed to room temperature and stirred 16 hours. Hydrochloric acid (aqueous, 2 M, 10 mL) was added to quench the reaction, and the aqueous layer was extracted with ethyl acetate (10 mL x 2). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 5:1 (v/v)) gave the product **49** (rf = 0.10 (hexane/ethyl acetate = 1:1 (v/v))). Yellow solid; mp, 109-111 °C; 257.6 mg, yield = 81%. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.64 (s, 1 H), 9.40 (s, 1 H), 6.58 (dq, *J* =16.0, 1.7 Hz, 1 H), 6.55 (d, *J* = 8.3 Hz, 1 H), 6.50 (d, *J* = 8.5 Hz, 1 H), 6.24 (dq, *J* = 16.0, 6.6 Hz, 1 H), 3.94 (s, 3 H), 3.94 (s, 3 H), 3.91 (s, 3 H), 1.92 (dd, *J* = 6.6, 1.8 Hz, 3 H). ^{13}C NMR (150 MHz, CDCl3): δ = 169.1, 150.9, 150.5, 144.2, 143.6, 130.5, 124.5, 118.2, 117.9, 116.4, 114.8, 105.1, 104.1, 56.5, 56.4, 52.3, 19.6. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{17}H_{18}O_6$: 319.1176; found: 319.1175.



52

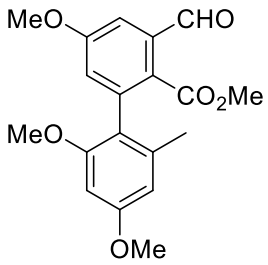
(E)-4-(2,4-Dimethoxy-6-methylphenyl)but-3-en-2-one (52). Phosphoryl chloride (14.5 mL, 0.156 mol) was added dropwise to a solution of 3,5-dimethoxytoluene (19 g, 0.12 mol) in dimethylformamide (100 mL) at 0 °C. The reaction was warmed to room temperature overnight. The reaction was quenched by slowly adding cold water (100 mL). The suspension was further diluted with water (200 mL) and saturated sodium bicarbonate solution (100 mL), stirred overnight. The mixture was extracted with ethyl acetate (150 mL x 3). The combined organic layers were dried over sodium sulfate and concentrated to give **51** as a white powder (19.4 g, 97%) for the next step. To a solution of 2,4-dimethoxy-6-methylbenzaldehyde **51** (9.00 g, 50 mmol) and acetone (37 mL) in ethanol (88 mL) was added aqueous sodium hydroxide (1.25 M, 176 mL). The mixture was stirred at room temperature for 2 hours and then the mixture was subsequently neutralized with hydrochloric acid (aqueous, 2.0 M) at 0 ^{o}C (ice bath). Ethanol was evaporated under vacuum and the water phase was extracted with ethyl acetate (200 ml x 2). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate = 5:1 (v/v)) to afford product **52** (10.0 g, 91%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J*=16.3, 1H), 6.89 (d, *J*=16.3, 1H), 6.38 (d, *J*=2.4, 1H), 6.34 (d, *J*=2.4, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.44 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$){1H} δ = 199.9, 161.6, 161.2, 141.8, 137.6, 128.9, 115.5, 108.0, 96.5, 55.6, 55.5, 27.7, 21.8. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}O_3$ 221.1172, Found: 221.1175.



57

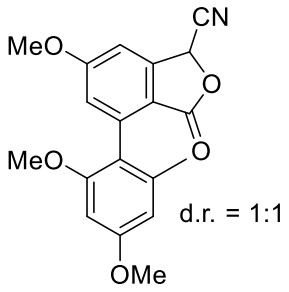
Methyl 3-formyl-5-hydroxy-2',4'-dimethoxy-6'-methyl-[1,1'-biphenyl]-2-carboxylate (57). To a solution of **52** (2.20 g, 10 mmol, 1.0 equiv) and triethylamine (2.10 mL, 1.5 equiv) in dichloromethane (40 mL) at 0 ^{o}C (ice bath) was added dropwise *tert*-Butyldimethylsilyl trifluoromethanesulfonate (3.10 mL, 1.35 equiv). After stirring at room temperature for 2 hours, the solution was poured into saturated aqueous sodium bicarbonate and was extracted with dichloromethane (40 mL x 3). The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography to afford the silyl enol ether as colorless liquid, which was directly used for the next step. The silyl enol ether and methyl 4,4-diethoxybut-2-ynoate **54** (1.87 g, 1.0 equiv) were dissolved in toluene (10 mL) and the reaction mixture was heated at 170 °C (oil bath) for 40 hours in a sealed tube. After cooling to room temperature, the reaction mixture and 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 2.96 g, 1.3 equiv) in toluene (20 mL) was added into a round bottom flask. The mixture was cooled to room temperature after heating at 80 °C (oil bath) for 2 hours and the reaction mixture was diluted with ethyl acetate (50 mL) and filtrated through Celite. The filtrate was then concentrated and the residue was run by flash column on silica gel (hexane/ethyl acetate = 3:1 (v/v)), which directly used for the next step. To the obtained product in tetrahydrofuran (20 mL) solution, tetra-*n*-butylammonium fluoride (TBAF, 1.0 M in tetrahydrofuran, 15 mL) was added dropwise. After stirring at room temperature for 15 hours, the reaction mixture was diluted with ethyl acetate (100 mL) and then washed by aqueous hydrochloric acid (2.0 M) and brine. The organic

layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 2:1 (v/v)) to afford product **57** (2.08 g, 63%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.97 (s, 1H), 7.25 (d, *J*=2.6, 1H), 6.85 (d, *J*=2.6, 1H), 6.38 (d, *J*=2.3, 1H), 6.34 (d, *J*=2.3, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 3.58 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$){1H} δ = 191.3, 168.7, 160.2, 157.8, 157.6, 140.0, 138.6, 135.9, 127.8, 123.9, 120.1, 115.4, 106.4, 96.0, 55.8, 55.4, 52.5, 20.5. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}O_6$ 331.1176, Found: 331.1183.



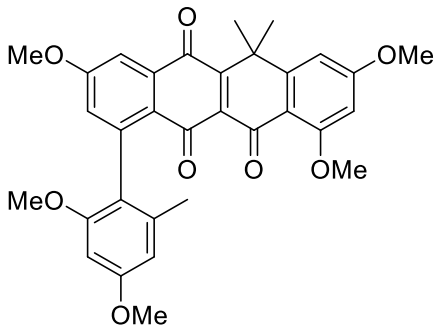
58

Methyl 3-formyl-2',4',5-trimethoxy-6'-methyl-[1,1'-biphenyl]-2-carboxylate (58). To a cooled (0 °C, ice bath) stirred solution of **57** (2.08 g, 6.3 mmol, 1.0 equiv) in dimethylformamide (15 mL) were added potassium carbonate (3.48 g, 4.0 equiv) and methyl iodide (2.67 g, 3.0 equiv). After being stirred at room temperature for 15 hours, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (60 mL x 3). The combined extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 2:1 (v/v)) to afford product **58** (2.06 g, 95%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.10 (s, 1H), 7.40 (d, *J*=2.6, 1H), 6.95 (d, *J*=2.6, 1H), 6.40 (d, *J*=2.3, 1H), 6.35 (d, *J*=2.3, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.66 (s, 3H), 3.58 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$){1H} δ = 190.7, 167.8, 160.6, 160.2, 157.9, 139.7, 138.5, 136.0, 128.7, 122.8, 120.4, 112.0, 106.2, 95.9, 55.8, 55.7, 55.3, 52.2, 20.5. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{21}O_6$ 345.1333, Found: 345.1338.



60

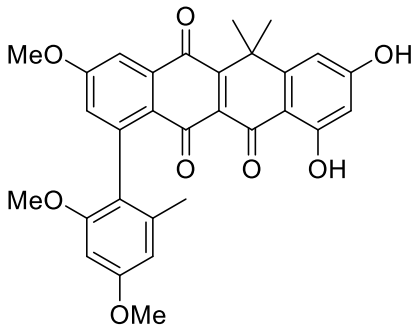
4-(2,4-Dimethoxy-6-methylphenyl)-6-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (60). To a stirred solution of **58** (2.06 g, 6.0 mmol, 1.0 equiv) in dichloromethane (40 mL) at 0 °C (ice bath), was added trimethylsilyl cyanide (832 mg, 1.4 equiv), and a solution of potassium cyanide (10 mg, 0.02 equiv) and 18-crown-6 (34.1 mg, 0.02 equiv) in tetrahydrofuran (3.0 mL). The reaction mixture was stirred at the same temperature for 1.5 hours, and for 30 min at room temperature. The reaction mixture was then concentrated and the residue was dissolved in acetic acid (10 mL) and stirred at 40 °C (oil bath) for 40 hours. The reaction was neutralized by addition of saturated sodium bicarbonate solution until no any bubbles formed. The solution was extracted with ethyl acetate three times and the combined organic layer were washed with water and brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 2:1 (v/v)) to afford product **60** (1.58 g, 78%, dr = 1:1) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.05 (d, *J*=1.4, 1H), 6.94 (d, *J*=2.1, 1H), 6.48 – 6.42 (m, 1H), 6.40 (dd, *J*=6.1, 2.2, 1H), 5.96 (s, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 3.69-3.64 (s, 3H), 2.07-2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$){1H} δ = 166.0, 165.3, 160.8, 158.0, 145.0, 140.8, 137.8, 121.4, 117.0, 115.2, 114.6, 106.7, 105.5, 96.2, 64.4, 56.3, 55.8, 55.4, 20.5. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{18}NO_5$ 340.1179, Found: 340.1186.



63

***7-(2,4-Dimethoxy-6-methylphenyl)-2,4,9-trimethoxy-12,12-dimethyltetracene-5,6,11(12H)-trione* (63)**. To a round bottom flask was charged with cyanophthalide **40** (33.9 mg, 0.1 mmol, 1.0 equiv) and enone **61** (25.5 mg, 1.1 equiv). Degassed dry tetrahydrofuran (2 mL) was then introduced and the resultant solution then cooled to -78 °C (dry ice/acetone bath). Lithium *tert*-butoxide (1.0 M in tetrahydrofuran, 0.3 mL, 3.0 equiv) was then added dropwise via syringe to the stirred reaction mixture. The resulting yellow solution was stirred at -78 °C (dry ice/acetone bath) for 45 min and then at room temperature for 2 hours. Saturated ammonium chloride solution (5 mL) was added to quench the reaction under argon. The aqueous layer was separated and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with water and brine, dried over sodium, filtered, and concentrated. The crude residue was dissolved in ethyl acetate (5 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 30 mg, 1.3 equiv) was added in one portion. After stirring at room temperature for 2 hours, the reaction mixture was diluted by ethyl acetate (15 mL) and then washed by saturate sodium bicarbonate solution (15 mL x 2) and brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 1:1 (v/v)) to afford product **63** (40.0 mg, 74%) as orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J*=1.4, 1H), 6.96 (d, *J*=1.4, 1H), 6.65 (s, 1H), 6.45 – 6.34 (m, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.67 (s, 3H), 2.02 (s, 3H), 1.84 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$){1H} δ = 186.2, 182.0 181.2, 164.3, 162.6, 161.5, 159.9, 157.2, 155.2, 150.0, 140.7, 139.1, 136.8, 136.1, 125.1, 124.5, 121.6, 116.1, 109.8, 106.8, 102.5, 96.9, 96.5, 56.1, 56.0, 55.9, 55.5, 55.3, 39.1, 29.4, 29.4, 20.7. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{31}O_8$ 543.2013, Found: 543.2013.



(±) **naphthacemycin A_9**

7-(2,4-Dimethoxy-6-methylphenyl)-2,4-dihydroxy-9-methoxy-12,12-dimethyltetracene-5,6,11(12H)-trione (naphthacemycin A_9). To a round bottom flask was charged with cyanophthalide **60** (33.9 mg, 0.1 mmol, 1.0 equiv) and enone **65** (42.3 mg, 1.1 equiv). Degassed dry tetrahydrofuran (2 mL) was then introduced and the resultant solution then cooled to -78 °C (dry ice/acetone bath). Lithium tert-butoxide (1.0 M in tetrahydrofuran, 0.3 mL, 3.0 equiv) was then added dropwise via syringe to the stirred reaction mixture. The resulting yellow solution was stirred at -78 °C (dry ice/acetone bath) for 45 min and then at room temperature for 2 hours. Saturated ammonium chloride solution (5 mL) was added to quench the reaction under argon. The aqueous layer was separated and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered, and concentrated. The crude residue was dissolved in ethyl acetate (5 mL) and 10% wt palladium/carbon (40 mg) were added, and then stirred vigorously at room temperature under hydrogen atmosphere(1 atm) for 15 h. The reaction mixture was diluted with ethyl acetate (15 mL) and filtrated through Celite. The filtrate was concentrated and the crude residue was

dissolved in ethyl acetate (5 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 30 mg, 1.3 equiv) was added in one portion. After stirring at room temperature for 2 hours, the reaction mixture was diluted by ethyl acetate (15 mL) and then washed by saturated sodium bicarbonate solution (15 mL x 2) and brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 1:1 (v/v)) to afford product **3** (35.0 mg, 68%) as orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.86 (s, 1H), 7.52 (d, *J*=2.7, 1H), 6.99 (d, *J*=2.6, 1H), 6.54 (s, 1H), 6.43 (s, 1H), 6.38 (s, 1H), 6.21 (d, *J*=1.7, 1H), 3.94 (s, 3H), 3.78 (s, 3H), 3.65 (s, 3H), 2.06 (s, 3H), 1.82 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$){1H} δ = 185.9, 185.2, 182.8, 165.1, 163.8, 162.8, 160.0, 156.8, 155.6, 154.8, 140.3, 137.1, 135.9, 135.7, 125.9, 124.8, 121.0, 110.3, 109.7, 107.0, 105.6, 101.7, 96.5, 56.0, 55.9, 55.3, 39.4, 30.2, 29.7, 20.8. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{27}O_8$ 515.1700, Found: 515.1705.

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CHAPTER 2. SYNTHESIS OF BIOBASED COMPOUNDS

2.1 Introduction

According to the USDA (United States Department of Agriculture), biobased products are "derived from plants and other renewable agricultural, marine and forestry materials. Biobased products generally provide an alternative to conventional petroleum-derived products and include a diverse range of offerings such as lubricants, detergents, inks, fertilizers, and bioplastics." Even though biofuels, like bioethanol and biodiesel, are a major sector of the biobased industry, researchers and firms now also focus on developing biobased compounds from biomass that nearly every industry depends on.[1] Figure 2.1 shows some commercially available biobased compounds. The biobased compounds are eco-friendly as they neither release toxic emissions nor cause pollution.[2] The biobased compounds market expects to reach around 97.2 billion dollars by the end of 2023.

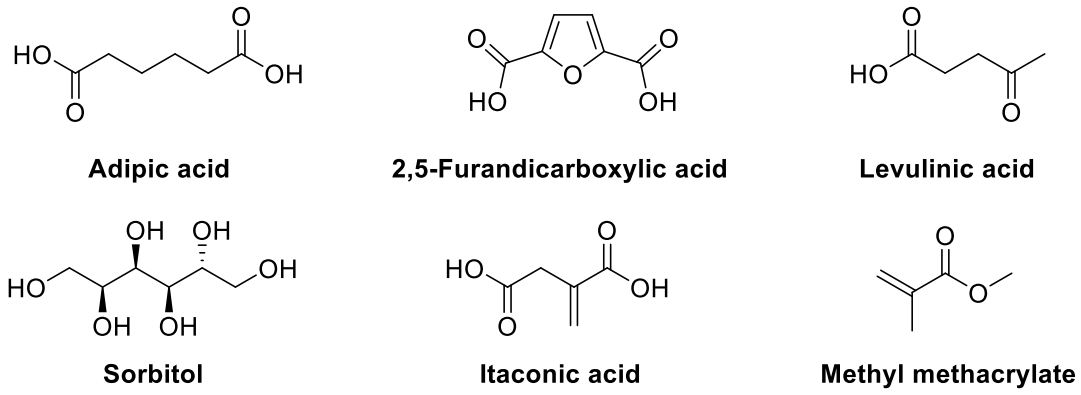


Figure 2.1 Biobased compounds.

Pyrones are a family of six-membered unsaturated cyclic compounds with an oxygen atom in the ring. There are two different pyrone isomers, 2-pyrone and 4-pyrone, depending on the oxygen atom position in the ring (Figure 2.2).[3]

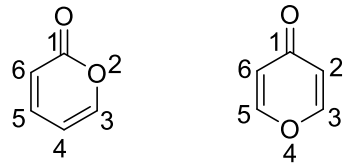


Figure 2.2 Structure of pyrones.

The 2-pyrone unit is abundant in numerous natural products isolated from plants, animals, marine organisms, bacteria, fungi, and insects that exhibit a broad range of biological activities (Figure 2.3).[4] The simplest example, 2-pyrone, is a versatile building block and used in organic synthesis to generate more complex chemical structures because it may participate in various cycloaddition reactions to form bicyclic lactones.

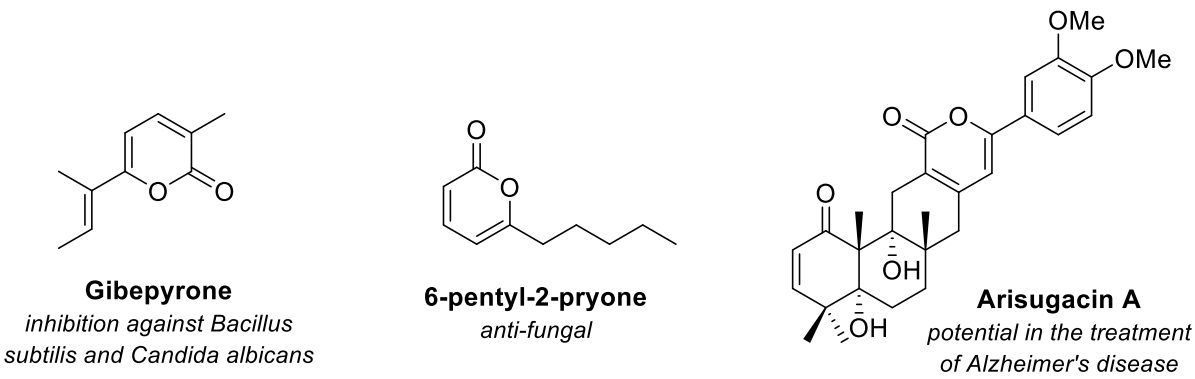
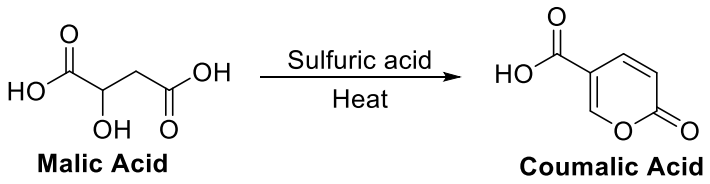


Figure 2.3 Bioactive pyrone natural products.

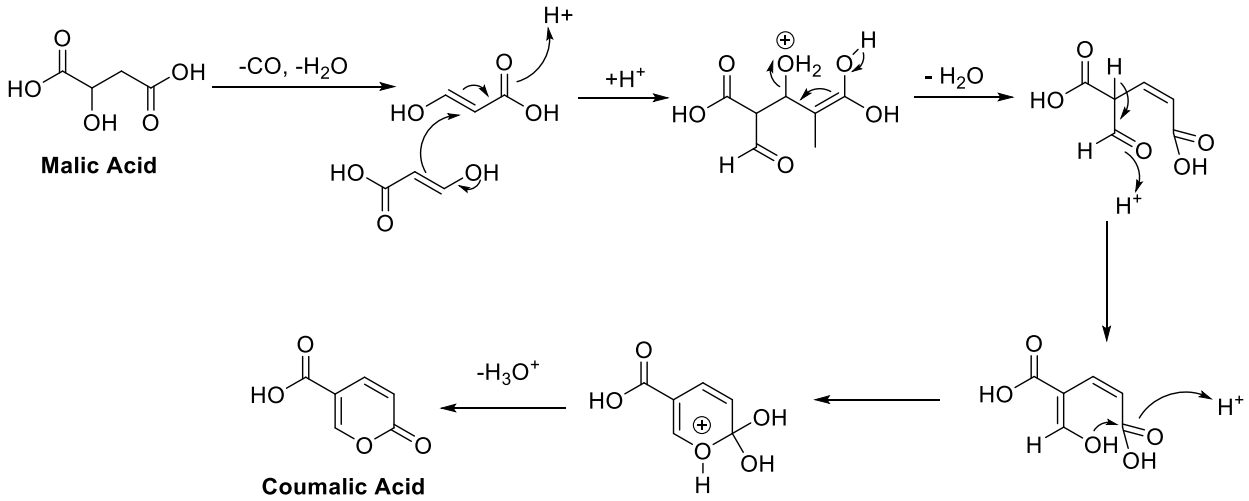
2.1.1 Methyl coumalate

Malic acid occurs naturally in all fruits and many vegetables and is generated during metabolism. It contributes to the sourness in many fruits, like apples and grapes. When malic acid was treated with fuming sulfuric acid, coumalic acid, a 2-pyrone, was formed through a self-condensation process (Scheme 2.1).[5]



Scheme 2.1 Synthesis of coumalic acid from malic acid.

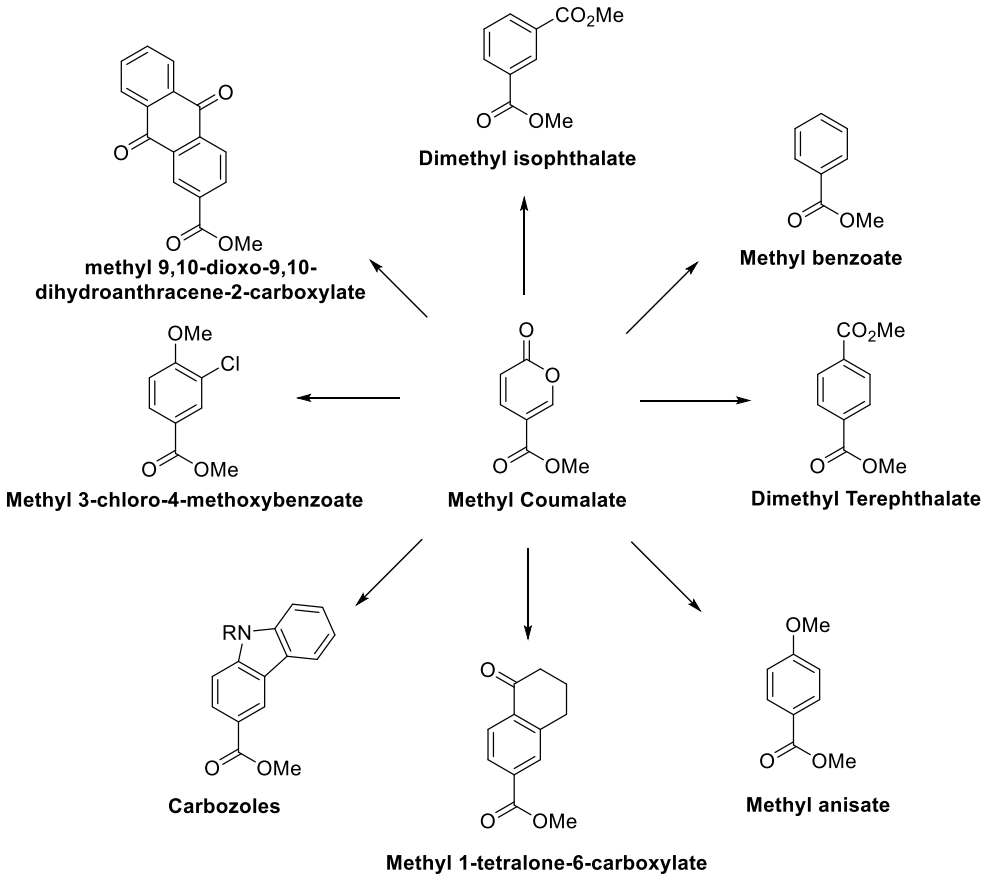
The mechanism of the transformation was also proposed (Scheme 2.2). The reaction proceeds via an acid-catalyzed dehydration/decarbonylation of malic acid to give an initial aldehyde acid enol, which condenses by Michael addition of the enol to the enone, followed by lactonization and dehydration to give the desired coumalic acid. Overall, two moles of malic acid condense to give one mole of coumalic acid with the loss of two moles of carbon monoxide and four equivalents of water.



Scheme 2.2 Mechanism of coumalic acid formation.

Methyl coumalate, formed through the esterification of coumalic acid with methanol, is an electron-deficient pyrone. It reacts with various electron-rich dienophiles in an inverse electron-demand Diels–Alder type reaction. As a team in the Center for Biorenewable Chemicals (CBiRC), the Kraus group has extensively researched the reactivity of methyl coumalate.

In 2011, the Kraus group reported the formation of para-substituted alkyl benzoates from unactivated alkenes and methyl coumalate.[6] The reaction proceeds with excellent regioselectivity during the Diels-Alder reaction. Later, the Diels-Alder reaction of methyl coumalate with alkenes bearing electron-withdrawing groups was discovered.[7] The reaction provides terephthalates or isophthalates. Then, the Kraus group accomplished the Diels-Alder reactions between methyl coumalate and vinyl ethers, ketals or orthoesters.[8-9] They synthesized substituted benzoates. Recently, the Kraus group reported the Diels-Alder reaction of methyl coumlate with acyclic enamines,[10] 3-chloroindoles[11] and hydroxyquinones[12]. (Scheme 2.3).

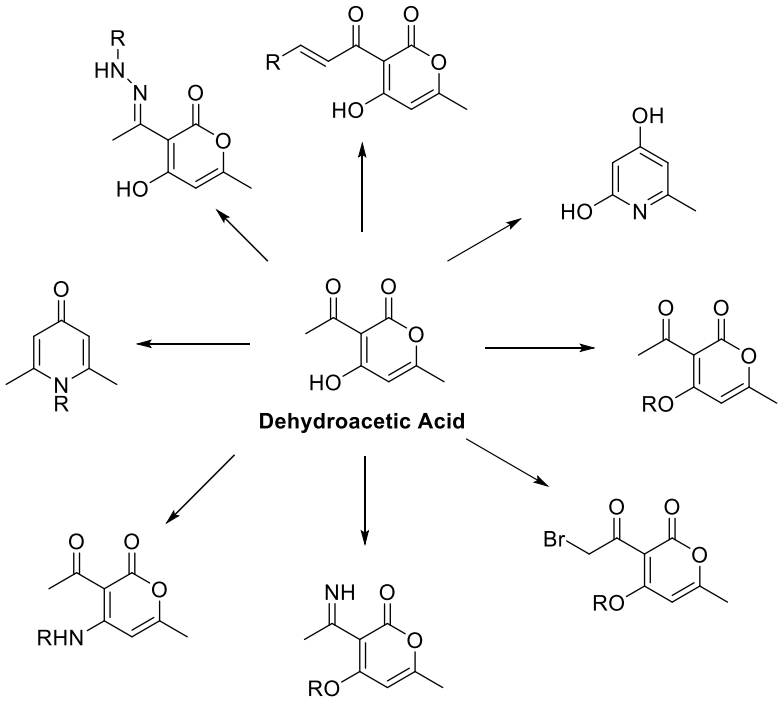


Scheme 2.3 Coumalate platform and valuable applications.

2.1.2 Dehydroacetic acid

Dehydroacetic acid is a pyrone derivate (Figure 2.5). It is isolated from *Solandra nitida*, a flowering plant.[13] Dehydroacetic acid is used as a fungicide and bactericide. It is found in synthetic resins as a plasticizer and in toothpastes as an antienzyme agent. It also works as a food preservative to prevent pickle bloating in squash and strawberries. Because of diverse applications in industry, the reactivities of dehydroacetic acid were widely explored and a variety of dehydroacetic acid derivatives were synthesized.

Scheme 2.4 shows some transformation of dehydroacetic acid. Alkylation, bromination, reactions with primary amines and condensation with aldehydes were all reported.[13] However, aldol reactions via the dianion of dehydroacetic acid have not been reported.

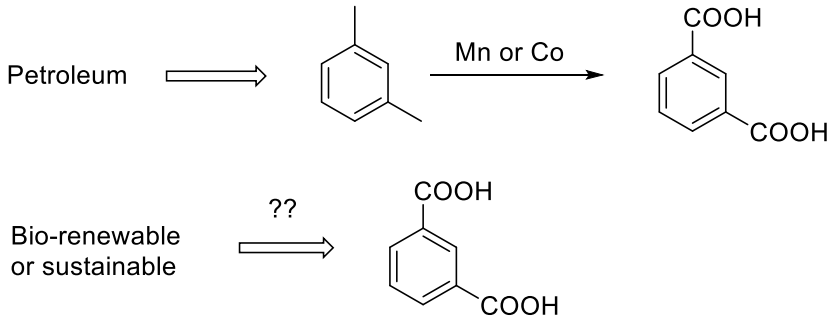


Scheme 2.4 Transformation of dehydroacetic acid.

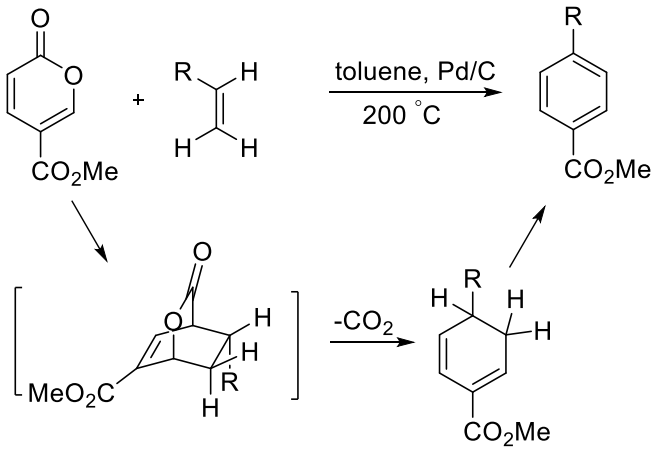
2.2 Result and Discussion

2.2.1 Synthesis of isophthalates from methyl coumalate.

Benzoic acid and isophthalic acid are prepared as commodity chemicals by the benzylic oxidation of toluene or xylene using a cobalt or manganese catalyst (Scheme 2.5).[14] As a team in the Center for Biorenewable Chemicals (CBiRC), we have extensively researched the reactivity of methyl coumalate. We recently reported the synthesis of *para*-substituted benzoic acids by the reaction of methyl coumalate with alkenes.[6] The mechanism involves an in-situ generated bicyclic lactone which loses carbon dioxide and undergoes dehydrogenation providing the aromatic ester, as illustrated in Scheme 2.6.



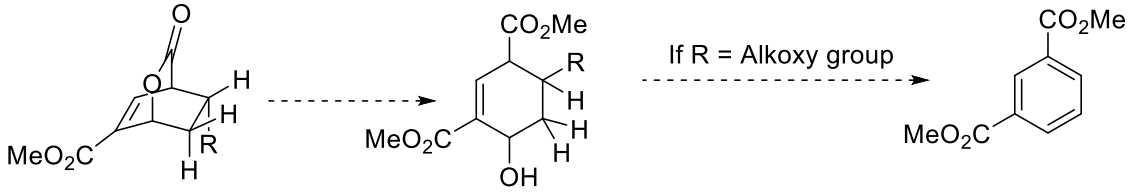
Scheme 2.5 Synthesis of isophthalic acids.



Scheme 2.6 The reaction of methyl coumalate with alkenes**.**

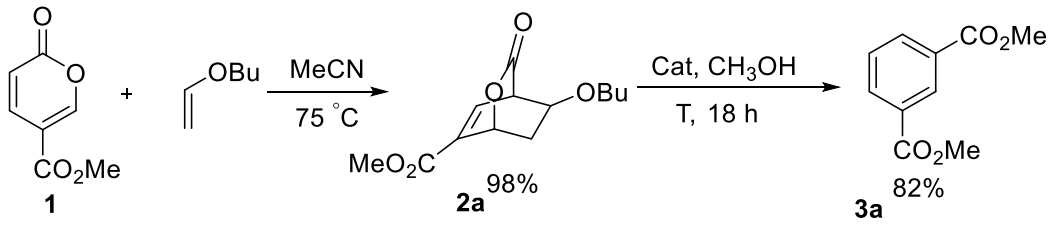
We envisioned that bicyclic lactones from methyl coumalate and enol ethers could offer

an opportunity to open the lactone under basic or acidic conditions. The following elimination reactions will produce isophthalates (Scheme 2.7). This strategy utilizes all of the carbons of methyl coumalate, increasing the atom economy of the transformation.



Scheme 2.7 Envisioned synthesis of isophthalates from methyl coumalate.

The cycloaddition of methyl coumalate with butyl vinyl ether worked well in acetonitrile at 80 °C. The formed bicyclic lactone was explored in a number of acids and bases to determine the optimal conditions for isophthalates formation. The result was shown in Table 2.1. Our best conditions involved five percent of PTSA (p-toluenesulfonic acid) in boiling methanol.



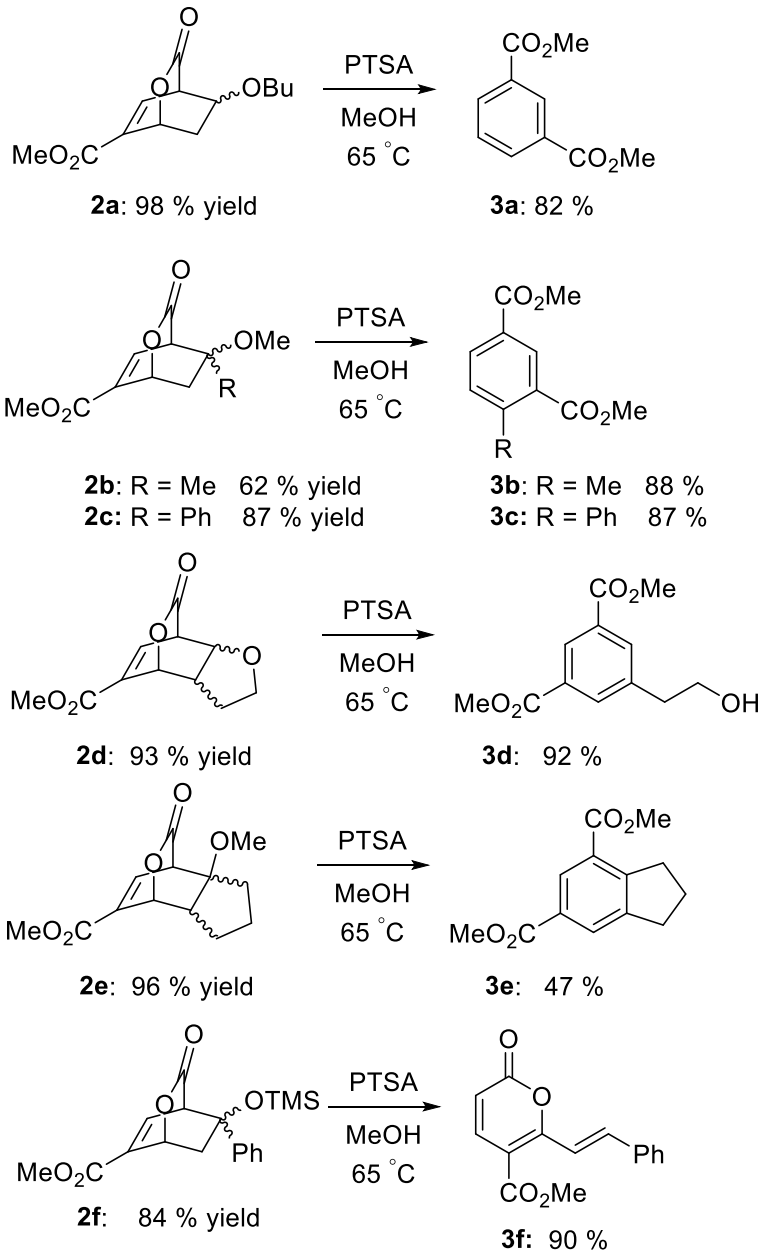
Entry	Cat (5 mol%)	T (°C)	Yield (%)
1	H_2SO_4	65	48
2	CF_3COOH	65	29
3	PTSA	65	82
4	NaOH	65	43
5	K_2CO_3	65	57
6	NaOMe	65	65
7	PTSA	45	47

Table 2.1 Optimization of the aromatization reaction.

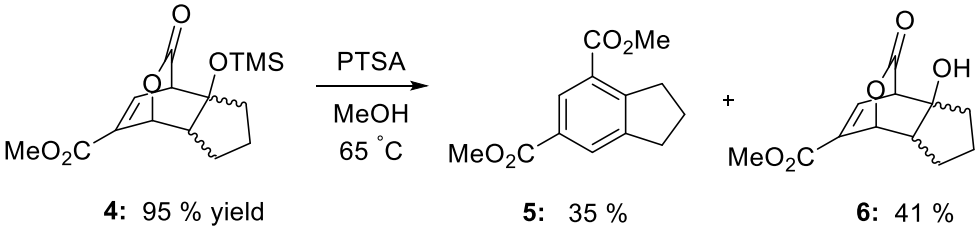
Examples are illustrated below in Scheme 2.8. The yields over the two-step sequence are very good. Aromatization with PTSA in methanol gives good yields of isophthalates. In the case of **3a**, butyl methyl isophthalate was formed in 15% yield. Methyl and phenyl substituted isophthalates **3b**-**3c** were synthesized. We got hydroxyl substituted isophthalate **3d**. Cyclic isophthalate **3e** were obtained. Heterocyclic systems also participate effectively in this transformation. The preparation of a thiophene substituted isophthalate **3f** was achieved in very good overall yield.

The corresponding enol silyl ethers also formed stable adducts with methyl coumalate. However, the adducts do not undergo high-yield aromatization to afford the isophthalates. As shown below in Scheme 2.9, the adduct from the reaction of methyl coumalate with the enol silyl ether of cyclopentanone **4** afforded two main products. Apparently, rapid removal of the silyl ether group in methanol yields an alcohol **6** that undergoes some fragmentation in addition to aromatization.

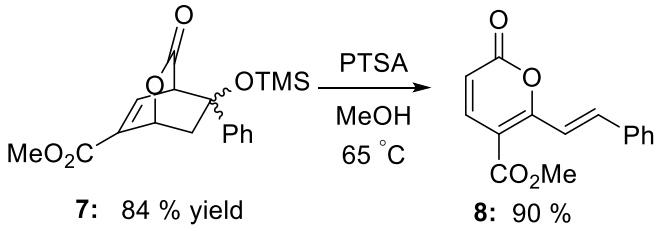
The adduct of the enol silyl ether of acetophenone **7** reacted with PTSA in methanol to afford a product in 90% yield that was clearly not an isophthalate. After examination of the NMR, IR and mass spectrum, we assigned the structure to be pyrone **8** shown in Scheme 2.10. The mechanism of formation is not clear, but likely involves a retro-aldol reaction and an intramolecular hydride shift followed by loss of water.



Scheme 2.8. Isophthalates from lactone intermediates.



Scheme 2.9. Isophthalates from silyloxy lactones.



7: 84 % yield **8:** 90 %

Scheme 2.10. Rearrangement of silyloxy lactone.

The two-step Diels-Alder/aromatization pathway to substituted isophthalates proceeds in high overall yields and is operationally convenient. A variety of alkyl, aryl and heteroaryl isophthalates can be prepared. Adducts of alkyl vinyl ethers afford higher yields of isophthalates than adducts of enol silyl ethers.

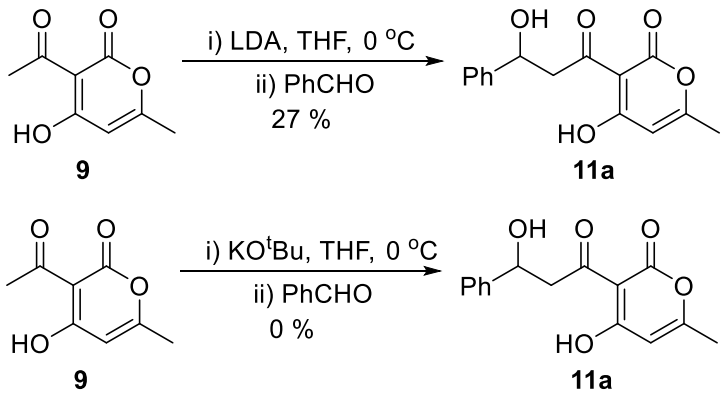
2.2.2 The dianion of dehydroacetic acid: A direct synthesis of pogopyrone A

When we attempted to deprotonate dehydroacetic acid **9** using two equivalents of lithium diisopropylamide, followed by the addition of benzaldehyde, we obtained the expected aldol product **11** in only 27% yield. The majority of the material was starting material. Potassium *tert*-butoxide gave no reactions (Scheme 2.11). Reasoning that the corresponding silyl enol ether **10** might be more reactive, we reacted dehydroacetic acid **9** with dichlorodimethylsilane and triethylamine in dichloromethane at room temperature. This process afforded the silane **10** in 99% yield (Figure 2.4).

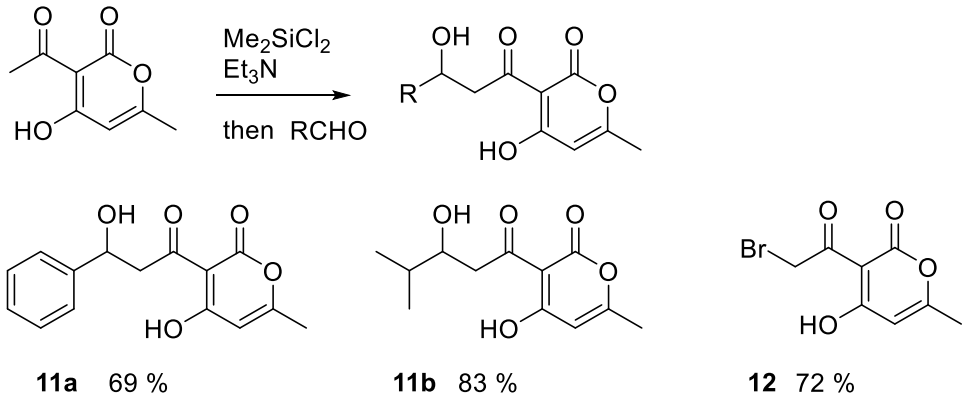
Compound **10**, which could be generated in situ, reacted readily with a number of aldehydes and *N*-bromosuccinimide.[15] Boron trifluoride etherate was an effective Lewis acid catalyst for the aldol reaction. The products and yields are listed in Scheme 2.12.

9 **10**

Figure 2.4 Structures of dehydroacetic acid and silyl enol ether **10**.



Scheme 2.11 Synthesis of **11a**.

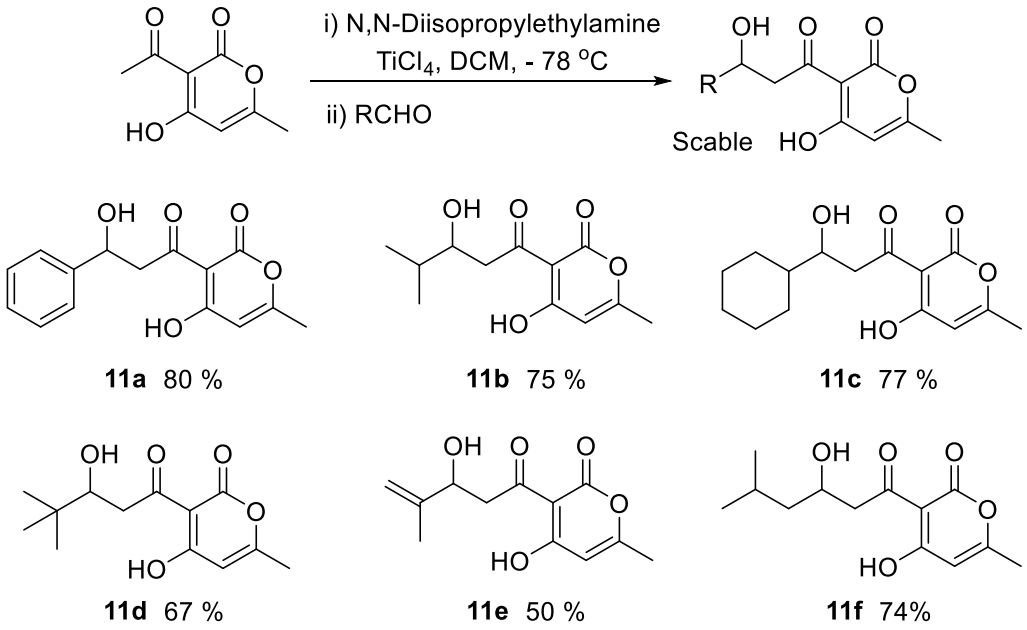


Scheme 2.12 Addition reactions via silyl enol ether **10**.

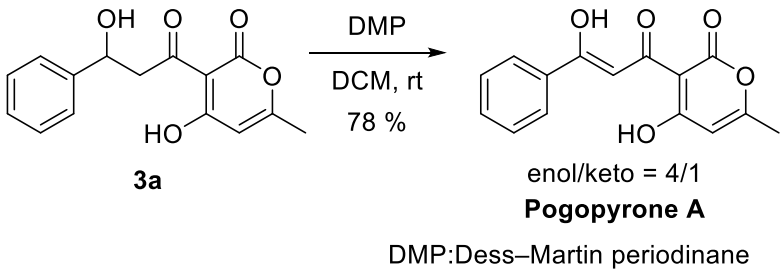
Although **10** made possible the synthesis of compounds on millimole scales, its tendency to decompose during storage prompted us to evaluate other dianion equivalents. Although the boron or tin enolate was unreactive, the titanium enolate, generated via titanium tetrachloride and *N*,*N*-diisopropylethylamine in dichloromethane, afforded an 80% yield of the aldol product **11a** with benzaldehyde. Workup conditions at low temperature were essential to minimize dehydration. The products and yields are shown in Scheme 2.13. This chemistry was scalable and **11b** was synthesized on a 50 mmol scale.

Pogopyrone A is a compound isolated from *Pogostemon heynianus* Benth Syn.[16] Oxidation of **11a** with DMP (Dess–Martin periodinane, an oxidation reagent) afforded a 78%

yield of pogopyrone A(enol/keto = 4:1) (Scheme 2.14).



Scheme 2.13 Addition reactions via titanium enolate.



Scheme 2.14 Synthesis of pogopyrone A.

Selective reactions at the acetyl group of dehydroacetic acid have been achieved via either silyl enol ether **10** or the titanium enolate of **9**. The titanium chemistry can be scaled to make **11b** on a 50 mmol scale. A direct synthesis of pogopyrone A was achieved.

2.3 Conclusion

A variety of biobased compounds were synthesized from methyl coumalate and dehydroacetic acid. The Diels-Alder reaction of methyl coumalate with vinyl ethers afforded stable bicyclic lactones. Substituted isophthalates were synthesized by the treatment of bicyclic

lactones with acids in methanol. A variety of alkyl, aryl and heteroaryl isophthalates can be prepared in high overall yields. The two-step Diels–Alder/aromatization pathway to substituted isophthalates utilized all of the carbons of methyl coumalte and increased the atom economy of the transformation.

Selective aldol reactions at the acetyl group of dehydroacetic acid have been achieved via the either silyl enol ether or the titanium enolate. Boron trifluoride etherate was needed in the transformations via the silyl enol ether. The titanium enolate reacted effectively with various aldehydes. The yields range from 50-80%. Titanium chemistry can be scaled to a 50 mmol scale when isobutyraldehyde was used in the aldol reaction. Oxidation of the adduct with benzaldehyde by using the Dess-Martin periodinane afforded pogopyrone A in excellent overall yield.

2.4. Experimental

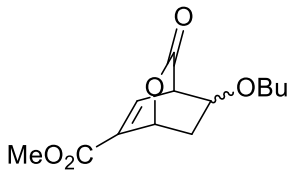
General Information

All starting materials were purchased from Sigma-Aldrich, Ambeed, Alfa Aesar, TCI and Oakwood Chemical. Solvents were all purchased from Sigma-Aldrich and Fisher Scientific and were used as received with the following exceptions. Tetrahydrofuran was distilled from lithium aluminum hydride. All reactions were monitored by thin layer chromatography (TLC) and ^{1}H NMR. All yields refer to separated yield after column chromatography unless indicated. TLC was obtained by silica plate using UV light as a visualizing agent or Potassium permanganate solution with heat. All columns were performed with silica gel 60Å, particle size 40-63 μm. ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ or other deuterated solvents on a Varian MR-400 or Bruker Avance III 600 MHz spectrometer. Chemical shifts were reported in parts per million from the solvent resonance as the internal standard ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; DMSO-d_6: δ_H = 2.50 ppm, δ_C = 39.52 ppm; Acetone-d_6: δ_H = 2.05 ppm, δ_C = 29.84 ppm;

multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet) and m (multiplet)). High-resolution mass spectra (HRMS) were recorded on an Agilent 6540 QTOF (quadrupole time of flight) mass spectrometer using ESI (electrospray ionization). Melting points were obtained on a Digimelt MPA160 instrument.

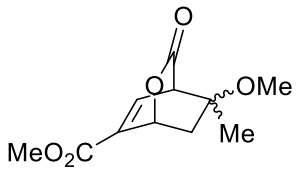
General procedure for D-A reaction of methyl coumalate with enol ethers.

Methyl coumalate (154 mg, 1.0 mmol, 1.0 equiv), enol ether (3.0 mmol, 3.0 equiv) and acetonitrile (1.0 mL) were added to a 15 mL sealed tube. The tube was heated in a 75 °C (oil bath) and stirred for 24 hours. After the reaction, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography.



2a

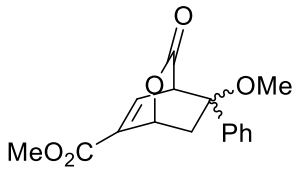
Methyl -8-butoxy-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-6-carboxyl-ate (2a). Colorless oil; 249 mg, yield = 98%**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 - 7.17 (m, 1H), 5.68 - 5.65 (m, 1H), 4.09 (m, 1H), 4.06 - 4.01 (m, 1H), 3.79 (s, 3H), 3.43 (ddd, *J*=8.3, 5.4, 1.8, 1H), 3.35 (ddd, *J*=9.0, 5.4, 1.8, 1H), 2.60 (dddd, *J*=13.3, 7.8, 3.8, 1.5, 1H), 1.59 (d, *J*=1.9, 1H), 1.46 (pd, *J*=6.8, 3.8, 2H), 1.28 (tdd, *J*=14.6, 7.3, 1.6, 2H), 0.87 (td, *J*=7.3, 1.6, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.75, 162.64, 138.43, 135.78, 73.41, 71.44, 69.33, 52.30, 47.63, 34.93, 31.64, 19.28, 13.87. HRMS (ESI-QTOF) calcd for [M + H^+]: 255.1227, found: 255.1226.



2b

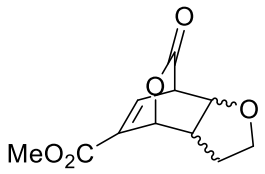
Methyl -8-methoxy-8-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-6-carboxylate (2b).

Colorless oil; 140 mg, yield = 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.22 (dd, *J*=6.2, 2.1, 1H), 5.60 (m, 1H), 3.81 (d, *J*=6.1, 1H), 3.76 (s, 3H), 3.10 (s, 3H), 2.15 (dd, *J*=14.0, 3.6, 1H), 1.84 (dd, *J*=14.2, 1.8, 1H), 1.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.19, 162.70, 139.57, 135.00, 75.66, 73.58, 52.95, 52.21, 50.19, 40.90, 23.97. HRMS (ESI-QTOF) calcd for [M + H^+]: 227.0914, found: 227.0911.



2c

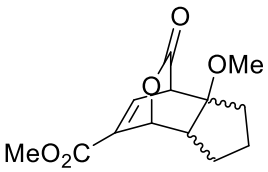
Methyl-8-methoxy-3-oxo-8-phenyl-2-oxabicyclo[2.2.2]oct-5-ene-6-carboxylate (2c). White solid; 250 mg, yield = 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 - 7.30 (m, 3H), 7.24 (m, 2H), 7.16 (m, 1H), 5.78 (m, 1H), 4.24 (d, *J*=6.5, 1H), 3.76 (s, 3H), 3.03 (s, 3H), 2.77 (dd, *J*=14.2, 4.1, 1H), 2.31 (d, *J*=14.3, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.22, 162.52, 140.17, 138.09, 137.68, 129.02, 128.62, 126.90, 81.19, 73.82, 52.43, 52.20, 51.44, 39.70. HRMS (ESI-QTOF) calcd for [M + H^+]: 289.1071, found: 289.1076.



2d

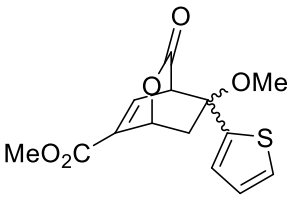
Methyl-8-oxo-2,3,3a,4,7,7a-hexahydro-4,7-(epoxymethano) benzo furan-5-carboxylate (2d). White solid; 208 mg, yield = 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21 (dd, *J*=6.7, 2.0, 1H), 5.52 (m, 1H), 4.30 (dd, *J*=8.7, 3.5, 1H), 4.11 (tdd, *J*=8.6, 4.1, 1.9, 1H), 3.92 (ddt, *J*=7.1, 3.6, 1.7, 1H), 3.87 - 3.80 (m, 1H), 3.79 (s, 3H), 2.66 (dddd, *J*=9.3, 7.9, 6.3, 1.6, 1H), 2.23 - 2.00 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.98, 162.52, 139.14, 138.27, 77.90, 76.50, 71.24, 52.47, 48.80, 43.39, 27.44. HRMS (ESI-QTOF) calcd for [M + H^+]: 225.0757, found:

225.0758.



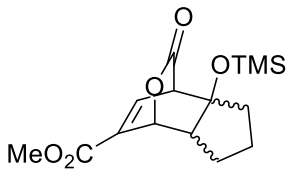
2e

Methyl-7a-methoxy-8-oxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-(epoxy methano)indene-5-carboxylate (2e). White solid; 242 mg, yield = 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 (m, 1H), 5.46 (m, 1H), 3.99 (d, *J*=6.1, 1H), 3.79 (s, 3H), 3.17 (s, 3H), 2.16 (td, *J*=7.7, 6.7, 1.7, 1H), 2.05 (dq, *J*=9.3, 4.7, 3.5, 2H), 1.79 (dtd, *J*=11.7, 6.2, 3.5, 2H), 1.72 - 1.60 (m, 1H), 1.53 (ddd, J=13.8, 8.8, 6.8, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.31, 162.93, 139.56, 136.62, 88.78, 77.21, 52.33, 52.16, 51.28, 50.90, 33.05, 27.66, 27.20. HRMS (ESI-QTOF) calcd for [M + H^+]: 253.1071, found: 253.1068.



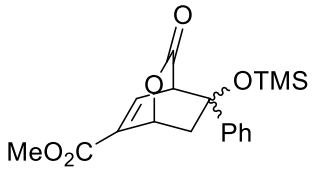
2f

Methyl 8-methoxy-3-oxo-8-(thiophen-2-yl)-2-oxabicyclo[2.2.2]oct-5-ene-6-carboxylate (2f). Oil; 263 mg, yield = 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 (dd, *J*=5.1, 1.2, 1H), 7.09 (dd, *J*=6.6, 2.3, 1H), 6.91 (dd, *J*=5.1, 3.6, 1H), 6.86 (dd, *J*=3.6, 1.2, 1H), 5.80 - 5.68 (m, 1H), 4.18 (d, *J*=6.6, 1H), 3.73 (s, 3H), 3.07 (s, 3H), 2.72 (dd, *J*=14.2, 4.0, 1H), 2.27 (dd, *J*=14.2, 1.6, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.43, 162.36, 144.83, 138.15, 137.14, 126.92, 126.79, 126.41, 78.79, 73.59, 53.99, 52.40, 51.40, 39.36. HRMS (ESI-QTOF) calcd for [M + H^+]: 295.0635, found: 295.0637.



4

Methyl-8-oxo-7a-((trimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-4,7-(epoxymethano)indene-5-carboxylate (4). White solid; 294 mg, yield = 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.22 (dd, *J*=5.0, 0.9, 1H), 5.43 - 5.41 (m, 1H), 3.80 (s, 3H), 3.78 (d, *J*=6.3, 1H), 2.17 (dd, *J*=8.8, 6.6, 1H), 2.11 - 2.01 (m, 1H), 1.98 - 1.88 (m, 1H), 1.86 - 1.68 (m, 3H), 1.61 (m, 1H), 0.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.43, 163.04, 140.94, 136.12, 85.74, 77.44, 55.75, 53.24, 52.34, 39.70, 27.95, 27.05, 2.05. HRMS (ESI-QTOF) calcd for [M + H^+]: 311.1309, found: 311.1316.



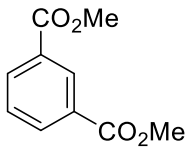
7

Methyl-3-oxo-8-phenyl-8-((trimethylsilyl)oxy)-2-oxabicyclo[2.2.2] oct-5-ene-6-carboxylate (7). White solid; 290 mg, yield = 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 - 7.43 (m, 2H), 7.35 (m, 3H), 7.31 - 7.25 (m, 1H), 5.80 (m,1H), 3.96 (dd, *J*=6.4, 0.7, 1H), 3.84 (s, 3H), 3.02 (d, *J*=3.8, 1H), 2.33 - 2.19 (m, 1H), -0.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.34, 162.93, 144.06, 141.38, 135.43, 128.64, 128.28, 125.82, 77.37, 73.57, 57.73, 52.41, 43.30, 1.64. HRMS (ESI-QTOF) calcd for [M + H^+]: 347.1309, found: 347.1312.

General procedure for the formation of Isophthalates.

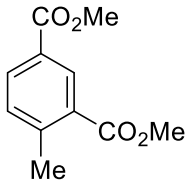
A solution of 0.2 mmol of bicyclic adducts (**2a to 2f, 4, 7**) of methyl coumalate with vinyl ethers, one crystal of p-toluenesulfonic acid (PTSA) and 1.0 mL of methanol was boiled

for 18 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography.



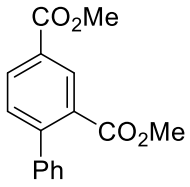
3a

Dimethyl isophthalate (3a). White solid; 37.5 mg, yield = 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.68 (q, *J*=1.6, 1H), 8.22 (dt, *J*=7.8, 1.5, 2H), 7.54 - 7.47 (m, 1H), 3.94 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.38, 133.94, 130.84, 130.70, 128.76, 52.52. HRMS (ESI-QTOF) calcd for [M + H^+]: 195.0652, found: 195.0650.



3b

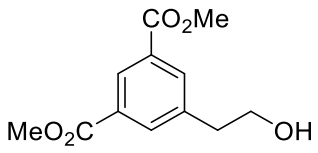
Dimethyl 4-methylisophthalate (3b). White solid; 36.2 mg, yield = 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, *J*=1.9, 1H), 8.02 (dd, *J*=8.1, 1.8, 1H), 7.30 (d, *J*=8.0, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.26, 166.42, 145.68, 132.73, 132.07, 131.99, 129.84, 128.06, 52.31, 52.15, 22.00. HRMS (ESI-QTOF) calcd for [M + H^+]: 209.0808, found: 209.0808.



3c

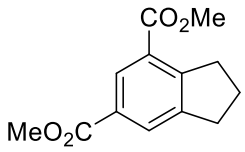
Dimethyl [1,1'-biphenyl]-2,4-dicarboxylate (3c). White solid; 46.9 mg, yield = 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.49 (d, J=1.8, 1H), 8.17 (dd, J=8.0, 1.8, 1H), 7.46 (d, J=8.0, 1H),

7.42 – 7.36 (m, 3H), 7.34 – 7.25 (m, 2H), 3.95 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.29, 166.16, 146.84, 140.27, 132.12, 131.18, 131.07, 129.14, 128.27, 128.22, 127.96, 52.46, 52.29. HRMS (ESI-QTOF) calcd for [M + H^+]: 271.0965, found: 271.0967.



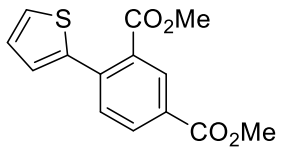
3d

Dimethyl 5-(2-hydroxyethyl)isophthalate (3d). White solid; 43.4 mg, yield = 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50 (q, *J*=1.5, 1H), 8.08 (t, *J*=1.3, 2H), 3.91 (s, 6H), 3.90 (t, *J*=6.5, 2H), 2.95 (t, *J*=6.5, 2H), 1.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.41, 139.95, 134.50, 130.78, 128.93, 63.15, 52.49, 38.74. HRMS (ESI-QTOF) calcd for [M + H^+]: 239.0914, found: 239.0912.



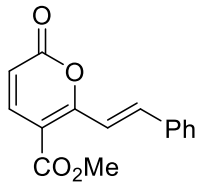
3e

Dimethyl 2,3-dihydro-1H-indene-4,6-dicarboxylate (3e). White solid; 21.7 mg, yield = 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.52 - 8.37 (m, 1H), 8.03 (t, *J*=1.4, 1H), 3.91 (s, 3H), 3.91 (s, 3H), 3.31 (t, *J*=7.6, 2H), 2.96 (t, *J*=7.6, 2H), 2.12 (p, *J*=7.4, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.93, 166.82, 152.32, 146.65, 129.89, 129.26, 128.66, 126.62, 52.37, 52.14, 34.20, 32.43, 25.08. HRMS (ESI-QTOF) calcd for [M + H^+]: 235.0965, found: 235.0965.



3f

Dimethyl 4-(thiophen-2-yl)isophthalate (3f). White solid; 43.6 mg, yield = 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 (t, *J*=2.3, 1H), 8.22 - 8.01 (m, 1H), 7.56 (dd, *J*=8.1, 2.3, 1H), 7.46 - 7.34 (m, 1H), 7.20 - 6.92 (m, 2H), 3.94 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.52, 166.01, 140.87, 138.43, 131.92, 131.84, 131.31, 130.87, 129.37, 127.67, 127.26, 127.14, 52.67, 52.58. HRMS (ESI-QTOF) calcd for [M + H^+]: 277.0529, found: 277.0526.

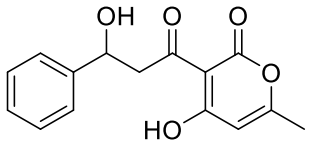


8

Methyl (E)-2-oxo-6-styryl-2H-pyran-5-carboxylate (8). Yellow solid; 46.0 mg, yield = 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 - 7.84 (m, 2H), 7.59 (d, *J*=7.3, 1H), 7.48 (d, *J*=15.8, 1H), 7.47 (m, 3H), 7.08 (d, *J*=15.8, 1H), 6.79 (d, *J*=7.2, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.84, 161.55, 159.80, 144.94, 138.51, 131.65, 130.77, 129.22, 126.01, 121.88, 119.89, 101.79, 51.93. HRMS (ESI-QTOF) calcd for [M + H^+]: 257.0808, found: 257.0810.

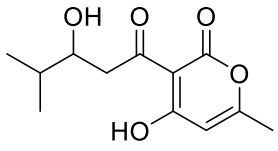
Addition reactions via silyl enol ether 10; general procedure. To a stirred solution of dehydroacetic acid (168 mg, 1.0 mmol) in dichloromethane (5.0 mL) was added dimethyldichlorosilane (129 mg, 1.0 mmol) followed by triethyl amine (202 mg, 2.0 mmol) at 0 °C. The mixture was stirred for 90 minutes at room temperature. Boron trifluoride etherate (284 mg, 2.0 mmol) and aldehyde (2.0 mmol) were added to the flask at 0 °C and the mixture was stirred at 0 °C for 2 hours. Saturated ammonium chloride solution (10 mL) was added to quench the reaction, and the mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 10:1(v/v)) gave the product.

Addition reactions via the titanium enolate; general procedure. To a stirred solution of dehydroacetic acid (168 mg, 1.0 mmol) in dichloromethane (5.0 mL) was added titanium tetrachloride (209 mg, 1.1 mmol) followed by *N*,*N*-diisopropylethylamine(284 mg, 2.2 mmol) at -78 °C. The mixture was stirred for 30 minutes at the temperature. Then aldehyde (1.2 mmol) was added to the flask and the mixture was stirred at -78 °C for 2 hours. Saturated ammonium chloride solution (10 mL) was added to quench the reaction, and the mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 10:1(v/v)) gave the product.



11a

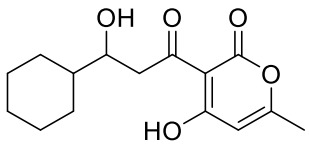
4-Hydroxy-3-(3-hydroxy-3-phenylpropanoyl)-6-methyl-2H-pyran-2-one (11a). Yellow oil, 189 mg, 69% yield (by Si method). 219 mg, 80% yield (by Ti method). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 - 7.39 (m, 2H), 7.40 - 7.31 (m, 2H), 7.32 - 7.24 (m, 1H), 5.97 (s, 1H), 5.26 (dd, *J*=8.1, 3.9, 1H), 3.59 - 3.44 (m, 2H), 3.12 (d, *J*=3.9, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.8, 181.0, 169.6, 161.3, 142.9, 128.5, 127.7, 125.8, 101.5, 100.0, 70.3, 50.5, 20.8. HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for 273.0768; found, 273.0771.



11b

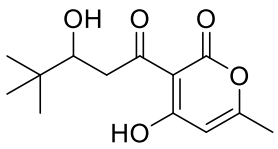
4-Hydroxy-3-(3-hydroxy-4-methylpentanoyl)-6-methyl-2H-pyran-2-one (11b). Color oil, 199 mg, 83% yield (by Si method.) 180 mg, 75% yield (by Ti method). ^{1}H NMR (400 MHz,

$CDCl_3$) δ = 5.96 (s, 1H), 3.90 (ddd, *J*=8.8, 5.5, 2.9, 1H), 3.28 - 3.22 (m, 1H), 3.17 (dd, *J*=16.7, 9.3, 1H), 2.70 (s, 1H), 2.27 (s, 3H), 1.78 (pd, *J*=6.8, 5.6, 1H), 0.98 (d, *J*=4.5, 3H), 0.97 (d, *J*=4.5, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 207.5, 181.0, 169.3, 161.4, 101.5, 100.1, 72.9, 45.8, 33.6, 20.7, 18.5, 17.6. HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for 239.0925; found, 239.0925.



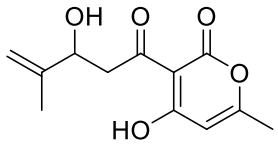
11c

3-(3-Cyclohexyl-3-hydroxypropanoyl)-4-hydroxy-6-methyl-2H-pyran-2-one (11c). White Solid, mp 70-72 °C, 215 mg, 77% yield (by Ti method). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.96 (s, 1H), 3.91 (ddd, *J*=8.9, 5.8, 2.8, 1H), 3.27 (dd, *J*=16.7, 2.9, 1H), 3.19 (dd, *J*=16.7, 9.3, 1H), 2.28 (s, 3H), 1.91 (d, *J*=12.8, 1H), 1.82 – 1.62 (m, 4H), 1.45 (dddt, *J*=11.6, 8.8, 6.0, 2.9, 1H), 1.31 – 0.98 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 207.6, 181.0, 169.3, 161.4, 101.5, 100.1, 72.4, 46.0, 43.5, 28.9, 28.1, 26.4, 26.2, 26.1, 20.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for 281.1384; found, 281.1385.



11d

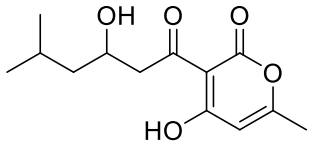
4-Hydroxy-3-(3-hydroxy-4,4-dimethylpentanoyl)-6-methyl-2H-pyran-2-one (11d). Colorless oil, 170 mg, 67% yield (by Ti method). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.95 (s, 1H), 3.79 (d, *J*=10.2, 1H), 3.47 (s, 1H), 3.31 - 3.20 (m, 1H), 3.15 (m, 1H), 2.27 (s, 3H), 0.97 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 207.8, 181.0, 169.3, 161.5, 101.5, 100.2, 75.9, 43.8, 34.9, 25.6, 20.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for 255.1227; found, 255.1228.



11e

4-Hydroxy-3-(3-hydroxy-4-methylpent-4-enoyl)-6-methyl-2H-pyran-2-one (11e).

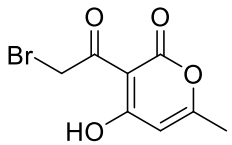
Yellow oil, 119 mg, 50% yield (by Ti method). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.97 (s, 1H), 5.08 – 5.02 (m, 1H), 4.89 (d, J=1.7, 1H), 4.64 – 4.56 (m, 1H), 3.32 (d, J=6.5, 2H), 2.81 (d, J=4.0, 1H), 2.28 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 206.3, 181.0, 169.5, 161.4, 146.0, 111.2, 101.5, 100.0, 71.5, 47.2, 20.7, 18.4. HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for 237.0757; found, 237.0764.



11f

4-Hydroxy-3-(3-hydroxy-5-methylhexanoyl)-6-methyl-2H-pyran-2-one (11f).

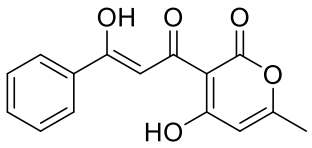
Colorless oil, 188 mg, 74% yield (by Ti method). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 5.97 (s, 1H), 4.24 (ddt, *J*=6.3, 4.4, 2.0, 1H), 3.30 - 3.25 (m, 1H), 3.21 - 3.14 (m, 1H), 2.73 (s, 1H), 2.29 (s, 3H), 1.97 - 1.78 (m, 1H), 1.62 - 1.53 (m, 1H), 1.31 (ddd, J=13.8, 6.7, 3.5, 1H), 0.94 (d, J=6.8, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 207.0, 181.0, 169.4, 161.3, 101.5, 100.0, 66.3, 49.2, 46.1, 24.5, 23.3, 22.1, 20.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for 255.1227; found, 255.1225.



12

3-(2-Bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one (12). To a stirred solution of dehydroacetic acid (168 mg, 1.0 mmol) in dichloromethane (5.0 mL) was added

dimethyldichlorosilane (129 mg, 1.0 mmol) followed by triethyl amine (202 mg, 2.0 mmol) at 0 °C. The mixture was stirred for 90 minutes at room temperature. N-Bromosuccinimide (356 mg, 2.0 mmol) was added to the flask at 0 °C and the mixture was stirred at 0 °C for 2 hours. Saturated ammonium chloride solution (10 mL) was added to quench the reaction, and the mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate = 10:1(v/v)) gave the product **12**. White solid, mp 114-116 °C,178 mg, 72% yield (by Si method, boron trifluoride etherate was not needed). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.01 (s, 1H), 4.70 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 197.3, 181.0, 170.1, 160.6, 101.3, 98.4, 35.2, 20.8. HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for 244.9450; found, 244.9445.



enol/keto = 4/1

Pogopyrone A

. **(Z)-4-Hydroxy-3-(3-hydroxy-3-phenylacryloyl)-6-methyl-2H-pyran-2-one (pogopyrone)**. To a stirred solution of **11a** (137 mg, 0.5 mmol, 1.0 equiv) in dichloromethane (13 mL) was added Dess–Martin periodinane (DMP, 318mg, 1.5 equiv), the mixture was stirred at room temperature overnight. After the reaction, dichloromethane was removed by rotary. Purification by column chromatography on silica gel (hexane/ethyl acetate = 10:1(v/v)) gave the product. Yellow solid, 116 mg, 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 - 7.91 (m, 2H), 7.73 (s, 1H), 7.54 - 7.46 (m, 1H), 7.46 (d, *J*=7.8, 2H), 5.93 (s, 1H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 193.3, 180.0, 177.6, 167.8, 160.9, 133.5, 132.5, 128.7, 127.2, 101.8, 97.6, 95.6, 20.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for 273.0757; found, 273.0757.

2.5 References

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CHAPTER 3. GENERAL CONCLUSION

Four natural products and their derivatives exhibiting antibacterial activities were synthesized. The first synthesis of biatriosporin D was accomplished in six steps. The overall yield is 50% and the key steps are a carbonyl diimidazole mediated acylation and lithium chloride promoted demethylation. The first synthesis of indanostatin was accomplished in six steps. The overall yield is 15%. Key steps are the Hauser-Kraus annulation and the N-bromosuccinimide and dimethyl sulfoxide oxidation. The first synthesis of dihydro eurotiumide B was accomplished in seven steps. The overall yield is 30%. Key steps are the tandem Hauser-Kraus annulation-reductive thiolation reaction. Naphthacemycin A_9 was synthesized in nine steps, the overall yield is in 26%. The key steps are the Diels-Alder reaction and the Hauser-Kraus annulation.

In the second chapter, the transformations of the methyl comalate and dehydroacetic acid provided a variety of biobased compounds. The two-step Diels-Alder/aromatization pathway to substituted isophthalates proceeds in high overall yields and is operationally convenient. Selective aldol reactions at the acetyl group of dehydroacetic acid have been achieved via the either silyl enol ether or the titanium enolate. A direct synthesis of pogopyrone A was achieved.