2011

# Lead compounds from nature: Synthesis of natural xanthones and chroman aldehydes that inhibit HIV-1

John Henry Mengwasser
*Iowa State University*

# Lead compounds from nature: Synthesis of natural xanthones and chroman aldehydes that inhibit HIV-1

by

**John Henry Mengwasser**

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:
George A. Kraus, Major Professor
Gregory Phillips
Klaus Schmidt-Rohr
Arthur Winter
Yan Zhao

Iowa State University

Ames, Iowa

2011

## TABLE OF CONTENTS

CHAPTER 1. GENERAL INTRODUCTION 1

CHAPTER 2. Synthesis of 1,7-dioxygenated xanthone natural products 2

Introduction 2

Results and Discussion 24

Experimental 36

References 45

CHAPTER 3. Synthesis of chroman aldehydes that inhibit HIV-1 55

Introduction 55

Results and Discussion 66

Experimental 73

References 80

CHAPTER 4. Selective metalation of 4,6-dibromorescorinol dimethyl ether with LiTMP 84

Introduction 84

Results and Discussion 90

Experimental 95

References 99

CHAPTER 5. GENERAL CONCLUSIONS 102

ACKNOWLEDGEMENTS 103

# CHAPTER 1. GENERAL INTRODUCTION

Organic chemistry is a science central to interdisciplinary research between fields such as molecular biology and medicinal chemistry. Knowledge of natural product structures and an understanding of how these structures interact with biomolecules can lead to valuable therapeutics.

Central to this study is the synthesis of natural products and natural product derivatives with the goal of discovering structures that are most beneficial at inhibiting diseases, particularly HIV-1. The synthetic approaches incorporate environmentally benign methodologies, regioselective reactions and key intermediates that can be easily elaborated into a diverse set of analogues valuable for structure-activity relationship studies.

# CHAPTER 2: SYNTHESIS OF 1,7-DIOXYGENATED XANTHONE NATURAL PRODUCTS

## INTRODUCTION

Xanthone (from the Greek, meaning yellow) is the chemical compound dibenzo-γ-pyrone (Figure 1).[1] There are nearly one thousand known naturally-occurring derivatives.[2-4] In a literature survey covering naturally occurring xanthones from January 2000 to December 2004, Vieira and Kijjoa reported 278 new xanthones.[5] In a survey covering 2005-2008, El-Seedi reported 122 new natural xanthones.[6] Xanthones are secondary plant metabolites that have been isolated from higher plant families, fungi and lichens. The families *Clusiaceae* and *Gentianaceae* are the major sources. Xanthones attract considerable interest because of their taxonomic importance in some families[7] and because of their potential as therapeutic agents.[8]

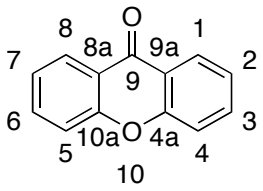



**Figure 1**. Xanthone nucleus and numbering.

## ISOLATION

All parts of the plant can contain xanthones, which can be extracted with organic solvents and then separated by chromatography on silica gel or HPLC.[3] After separation, xanthones have been identified by comparison with authentic samples by TLC. Determining the structure of naturally occurring xanthones is most commonly accomplished from the $^{1}H$ NMR, $^{13}C$ NMR, UV, IR, and MS data. In 2004, Bo and Liu

emphasized capillary electrophoresis in a review of methods used to separate pharmacologically active xanthones.[9] Bioactive xanthones have also been isolated by bioassay-guided fractionation methods by monitoring biological activities, including: antibacterial,[10] antifungal,[11] antiviral,[12,13] trypanocidal,[14,15] and cytotoxic activities against human carcinoma cell lines.[13-15]

## CLASSIFICATION

Xanthones can be classified into six main groups: simple oxygenated xanthones, xanthone glycosides, prenylated xanthones, xanthonolignoids, bis-xanthones, and miscellaneous xanthones. The main groups are subdivided according to the degree of oxygenation into non-, mono-, di-, tri-, tetra-, penta-, and hexaoxygenated xanthones. Simple xanthones contain simple substituents such as hydroxy, methoxy or methyl.

### Simple nonoxygenated xanthones

Xanthone (**1**) and methylxanthones (**2**-**5**) (Figure 2) were observed in crude oils from off-shore Norway and reported by Oldenburg and co-workers in 2002.[19] This was the first description of xanthones in fossil organic matter. Formation of these compounds may have occurred by diagenetic products, oxidation of xanthenes in the reservoir, or by geosynthesis from aromatic precursors.

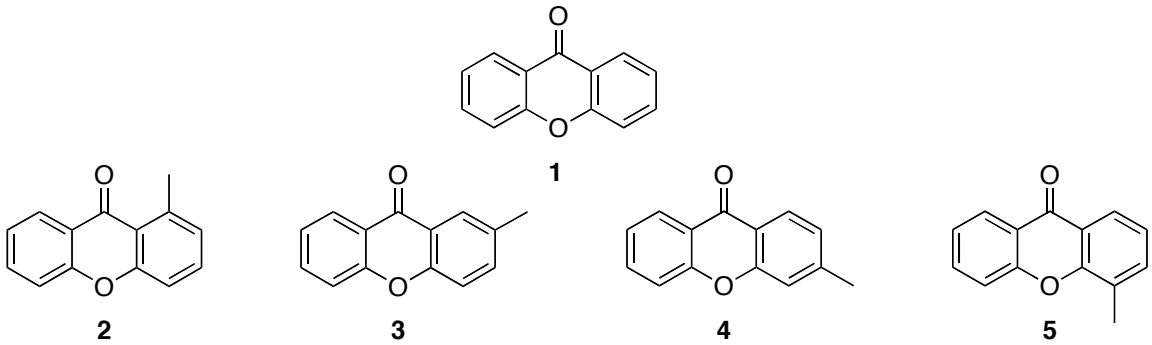



**Figure 2.** Nonoxygenated xanthones from crude oils

**Simple monooxygenated xanthones**

This class of xanthones has few naturally occurring members. 3-(2-Hydroxyethoxy)-xanthone (**6**)[20] and 2-carbomethoxy-6-methoxyxanthone (**7**)[21] (Figure 3) are examples from *Hedychium gardnerianum* and *Calophyllum teysmannii* var. *inophylloide*, respectively. Xanthone **8** is a phytotoxic compound isolated from the fungus *Guanomyces polythrix*.[22]

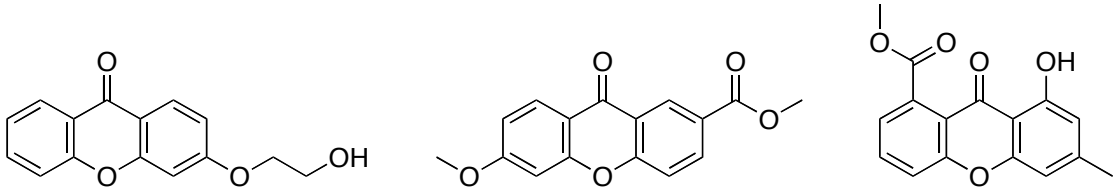



**Figure 3.** Monooxygenated xanthones

**Simple dioxygenated xanthones**

Dioxygenated xanthones are more common. Among examples are euxanthone (**9**) and 1-methoxy-7-hydroxyxanthone (**10**) found in *Hypericum perforatum* (Figure 4).[23]

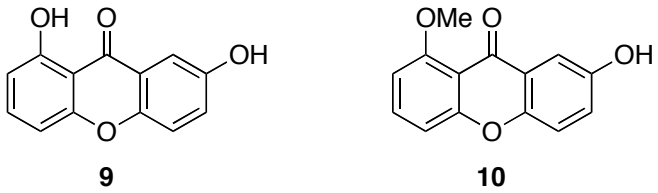



**Figure 4.** Dioxygenated xanthones from *Hypericum perforatum*

**Simple trioxygneated xanthones**

There are more examples of trioxygenated xanthones than there are of dioxygenated xanthones. The first xanthone ever isolated—gentisine, 1,7-dihydroxy-3-methoxyxanthone[24]—is trioxygenated. Another example is 1,3-dihydroxy-5-methoxyxanthone-4-sulfonate (**11**) (Figure 11), which was isolated from *Hypericum*

*sampsonii* in 2004.[25] This sulfonated xanthone was cytotoxic against the P388 (mouse lymphocytic leukemia) cancer cell line. Cratoxyarborenone F (**12**) is another xanthone isolated from *Hypericum perforatum*.[23] Compound **12** possessed moderate cytotoxicity toward a human oral epidermoid carcinoma (KB) cancer cell line.[26]

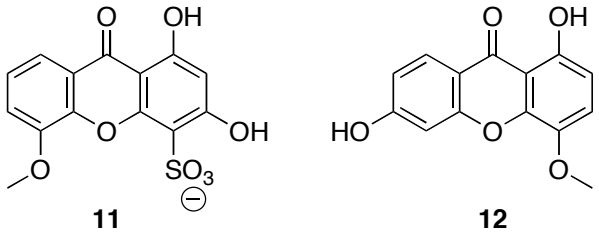
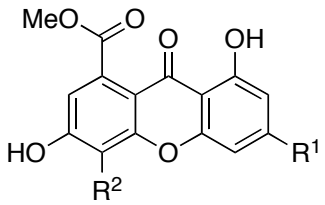



**Figure 5.** Cytotoxic trioxygenated xanthones from *Hypericum*

**Simple tetraoxygenated xanthones**

There are more examples of tetraoxygenated xanthones than there are of trioxygenated xanthones. Three tetraoxygentated xanthones (**13**, **14** and **15**) (Figure 6) were isolated from *Leiothrix curvifolia* and *Leiothrix flavenscens*, herbaceous monocotyledons native to Brazil.[71]



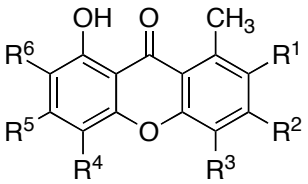

**13** $R^1$ = OMe $R^2$ = OMe
**14** $R^1$ = OMe $R^2$ = OH
**15** $R^1$ = OH $R^2$ = OH

**Figure 6.** Tetaoxygenated xanthones from *Leiothrix*

**Simple pentaoxygenated xanthones**

This is a small but growing group as 27 pentaoxygenated xanthones were isolated between January 2000 and December 2004,[5] including drimiopsins A, B and D[72] (**16**, **17**

and **18**, respectively) (Figure 7) from *Drimiopsis maculata*, a South African plant used by the Zulu to treat digestive disorders in children.

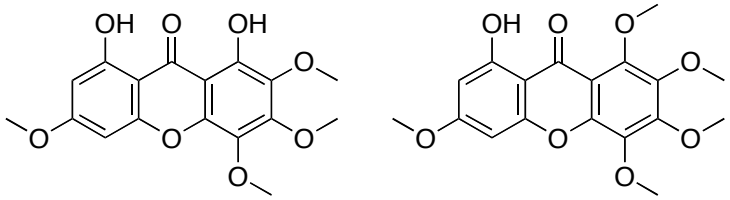



| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ |
|---|---|---|---|---|---|---|
| **16** | H | OH | H | OMe | OH | OMe |
| **17** | H | OH | H | OMe | OMe | OMe |
| **18** | H | OH | OMe | OMe | OH | H |

**Figure 7.** Pentaoxygenated xanthones from *Drimiopsis maculata*

**Simple hexaoxygenated xanthones**

This subgroup has the highest degree of oxygenation of known naturally occurring xanthones. Examples include eustomin (**19**)[27,28] and demethyleustomin (**20**)[27-29] (Figure 8) They were extracted from two *Centaurium* species.



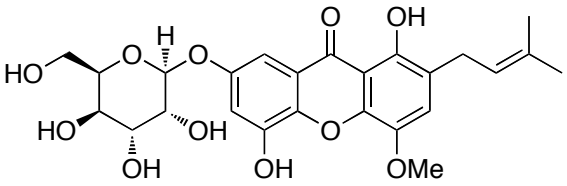

**19** **20**

**Figure 8.** Hexaoxygenated xanthones from *Centaurium*

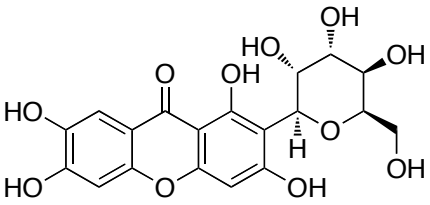
**Glycosylated xanthones**

This group is further divided into *O*-glycosides and *C*-glycosides. The most common oxygenation is tetraoxygenated, and the families *Gentianaceae* and *Polygalaceae* are the greatest sources of both subgroups.[5] An example of a *O*-glycoside is umbilicaxanthoside A (**21**) (Figure 9), which was isolated from the lichen *Umbilicaria*

*proboscidea* that was collected in the Ural Mountains of Russia.[73] Mangiferin (**22**)[74] is an example of a *C*-glycoside. Rats that had been injected with mangiferin displayed enhanced object recognition memory.




**21**




**22**

**Figure 9**. *O*- and *C*-glycosides

**Prenylated xanthones**

Examples of common five-carbon units of prenylated xanthones are 3-methylbut-2-enyl (substituent **A**), 3-hydroxy-3-methylbutyl (substituent **B**) and 1,1-dimethylprop-2-enyl (substituent **C**) (Figure 10).[5] These substituents can cyclize with the *ortho* hydroxyl group to form 2,2-dimethylpyrano (as in **23**),[30] 2,2,3-trimethylfuran (as in **24**),[31] and 2-isopropenyldihydrofuran (as in **25**)[25] (Figure 11). The benzofuran and benzopyran structural motifs generated in this way are privileged structures present in numerous bioactive natural products.[76] Recently, from *Psorospermum molluscum* harvested from the Madagascar rain forest, Kingston and co-workers[77] isolated psoroxanthin (**26**) and 8-(4′-hydroxyprenyl)-1,7-dihydroxyxanthone (**27**) (Figure 12). Psoroxanthin showed promising cytotoxic activities. It is related structurally to psorospermin (**28**),[78] an angular furoxanthone with a reactive epoxide substituent. Compound **28** was isolated from the African plant *Psorospermum febrifugum*, and it possesses biological activity in the 9KB cell culture and *in vivo* P388 mouse leukemia systems.

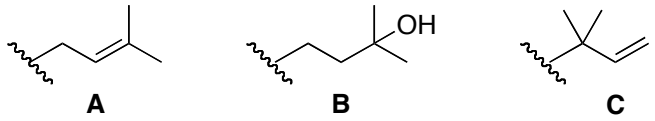



**Figure 10.** Five-Carbon Substituents

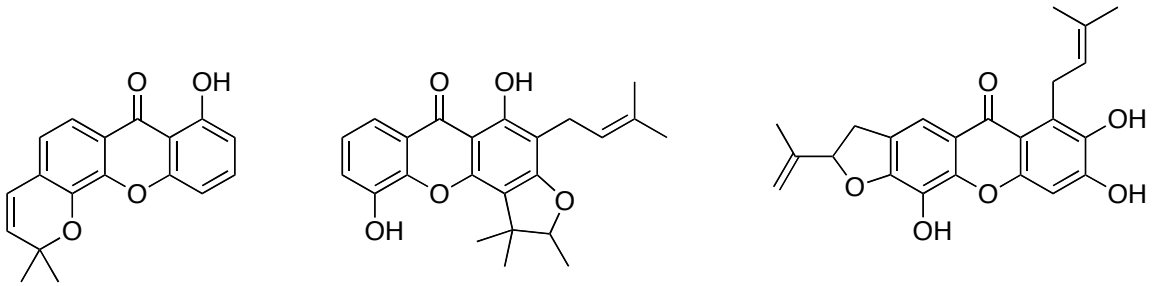



**Figure 11.** Products from the cyclization of five-carbon substituents with a *o*-hydroxyl group

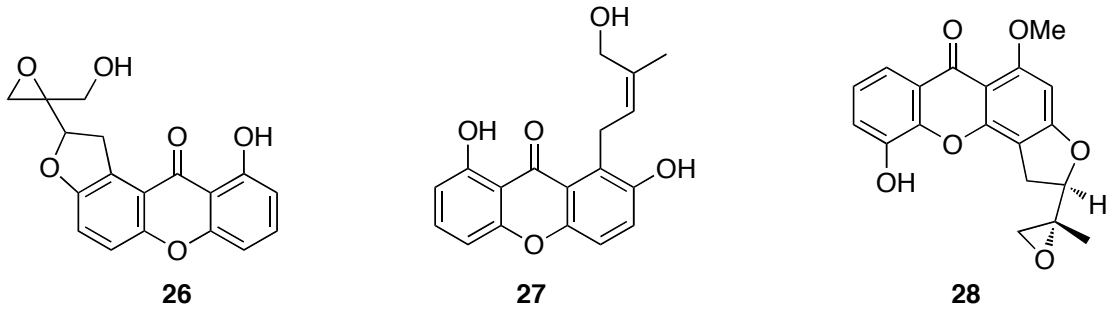
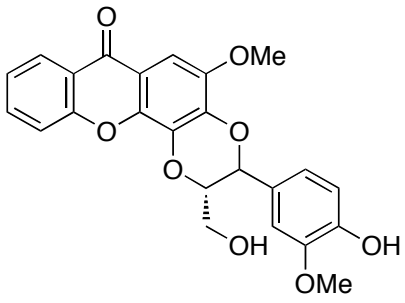



**Figure 12.** Xanthones from *Psorospermum molluscum* (**26**, **27**) and psorospermin (**28**) from *Psorospermum febrifugum*

**Xanthonolignoids**

This group is relatively small. Kielcorin (**29**) (Figure 12) is a representative example. It was isolated from *Kielmeyera variabilis*.[10,32]

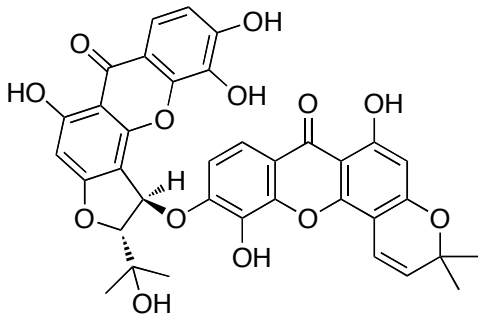



**29**

**Figure 13.** Kielcorin, a xanthonolignoid from *Kielmeyera variabilis*

**Bis-xanthones**

An example of a bis-xanthone is jacarelhyperol A (**30**) (Figure 14), which was isolated from *Hypericum japonicum* in 2002 by Ishiguro and coworkers.[33]

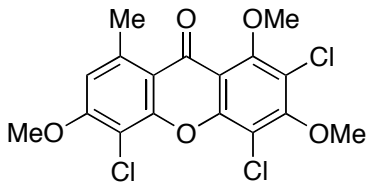



**30**

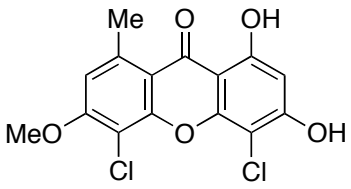
**Figure 14.** Jacarelhyperol A, a bis-xanthone from *Hypericum japonicum*

**Miscellaneous**

Xanthones with unusual substituents have been isolated that do not fit in any of these groups. These are classified as miscellaneous. Examples include two chlorinated compounds (**31**[34] and **32**[35]) from *Dimelaena lichen* (Figure 15).




**31**




**32**

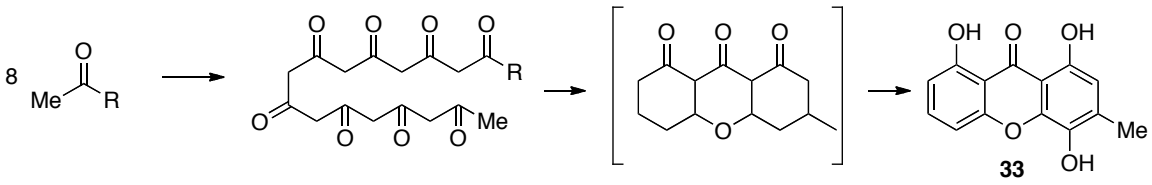
**Figure 15.** Miscellaneous xanthones from *Dimelaena lichen*

## BIOSYNTHESIS OF XANTHONES

Biosynthesis of xanthones has been thoroughly investigated *in vivo*[36] and *in vitro* with labeled intermediates.[37,38] The studies concluded that two processes are involved: the acetate polymalonic pathway and the mixed shikimate acetate pathway.

### Acetate polymalonic route

Xanthones in fungi and lichens are derived from acetate units.[39,40] An example of the acetate polymalonic mechanism was proposed by Birch for the biosynthesis of ravelenin (**33**) from *Helminthosporium ravenelii* (Scheme 1).[40]

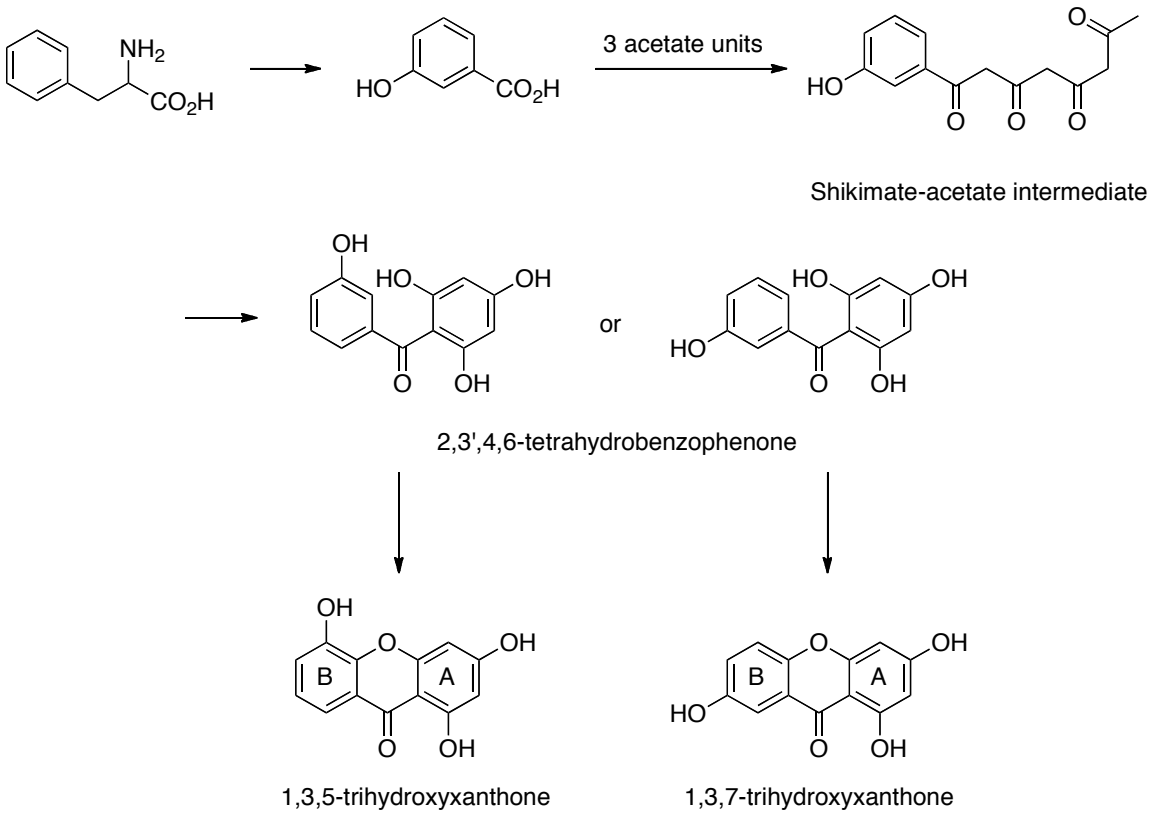



**Scheme 1.** Biosynthesis of ravenelin by the acetate polymalonic pathway

### Mixed shikimate acetate pathway

Xanthones of higher plants are biologically synthesized from shikimate and acetate.[41] Phenylalanine—formed from shikimate—loses two carbon atoms from the side chain and is oxidized to *m*-hydroxybenzoic acid (Scheme 2). This condenses with three acetate units to give the intermediate that cyclizes into a substituted benzophenone. An oxidative phenol coupling reaction forms the central ring, completing the xanthone.[42] Proof of this pathway came from studies on *Gentiana lutea* by Atkinson[43] and Gupta and Lewis.[38] Plants fed $^{14}$C-labeled phenylalanine produced xanthones with the label only observed in ring B, while plants fed $^{14}$C-labeled acetate yielded xanthones with the label only in ring A.

The intramolecular reaction of benzophenone also occurs by other mechanisms, including: quinone addition,[44] dehydration between hydroxyl groups on ring A and ring B (2,2´-dihydroxybenzophenone),[45] or formation and then rearrangement of a spirodienone.[41,46]




**Scheme 2.** Biosynthesis of xanthones by the mixed shikimate acetate pathway

**SYNTHESIS OF XANTHONES**

Naturally occurring xanthones contain different types of substituents in different positions, which leads to a diverse array of structures and pharmacological activities.[47] The structures of naturally occurring xanthones are limited by the biosynthetic pathways. Therefore, a main objective of the synthesis of new derivatives is to develop more diverse and complex xanthones for biological activity and structure-activity studies.[48] Distillation

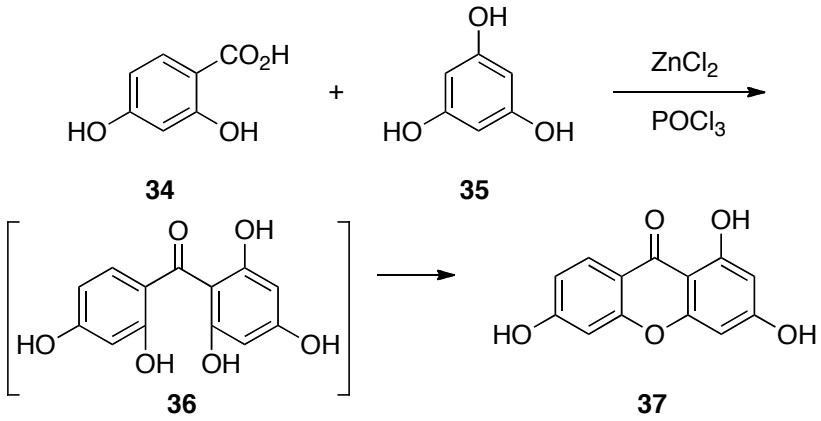
of a mixture of phenol, a *o*-hydroxybenzoic acid and acetic anhydride was one of the first methods used for synthesizing xanthones.[49,50] Milder conditions have been developed since then.

**Classical Methods**

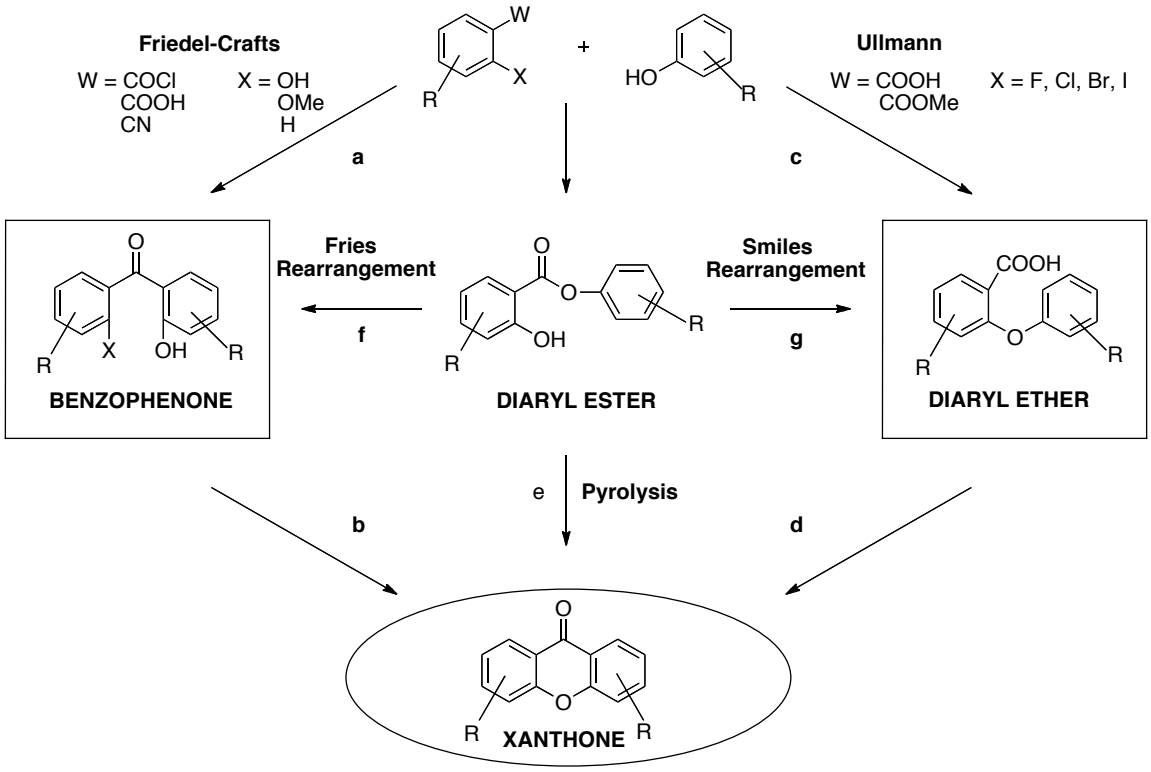
There are three traditional methods for the synthesis of simple xanthones: the Grover, Shah, and Shah (GSS) reaction, the synthesis *via* benzophenone intermediates, and the synthesis *via* diphenyl ether intermediates.

**Grover, Shah, and Shah reaction**

Hydroxyxanthones such as **37** are prepared from accessible starting materials using the GSS reaction (Scheme 3). It requires derivatives of salicylic acid such as **34** and an activated phenol such as phloroglucinol (**35**). These are heated in the presence of $ZnCl_2$ and $POCl_3$.[51] The benzophenone intermediate (**36**) is not isolated during this one pot procedure. The procedure has been modified to give better yields by substituting the phosphorus oxychloride-zinc chloride catalyst with phosphorus pentoxide-methanesulfonic acid (Eaton's reagent).[52]




**Scheme 3.** Grover, Shah, and Shah reaction

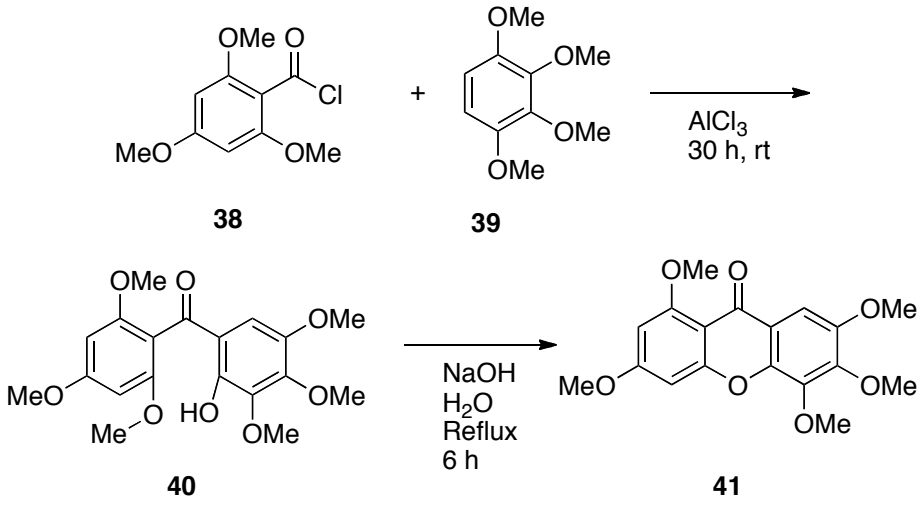



**Scheme 4.**[48] Conventional methods for the synthesis of xanthones

**Synthesis *via* a benzophenone intermediate**

The GSS reaction does not always give the required products, and unwanted demethylations may occur, which led Quillinan and Scheinmann to develop an alternative method.[53] Their efficient general synthesis involves formation of 2-hydroxy-2´-methoxybenzophenones, followed by the quantitative elimination of methanol in the presence of alkali to give xanthones (**a** – **b** in Scheme 4).[48] They used the method to synthesize benzophenones, and mono- to pentaoxygenated xanthones. The Friedel-Crafts acylation of 1,2,3,4-tetramethoxybenzene (**39**) with 2,4,6-trimethoxybenzoyl chloride (**38**) in the presence of aluminum chloride in ether gave 2-hydroxy-2´,3,4,4´,5,6´-hexamethoxybenzophenone (**40**) (Scheme 5). The structure of **40** was established from the $^{1}$H NMR spectrum: the two phloroglucinol protons resonated as a singlet. The *ortho*-

monodemethylation occurred selectively at the more electron rich *ortho*-ether function of the benzophenone because this group is able to coordinate with the Lewis acid and the carbonyl group for the demethylation reaction.[54] Cyclization of **40** with aqueous alkali gave the 1,3,5,6,7-pentamethoxyxanthone (**41**).

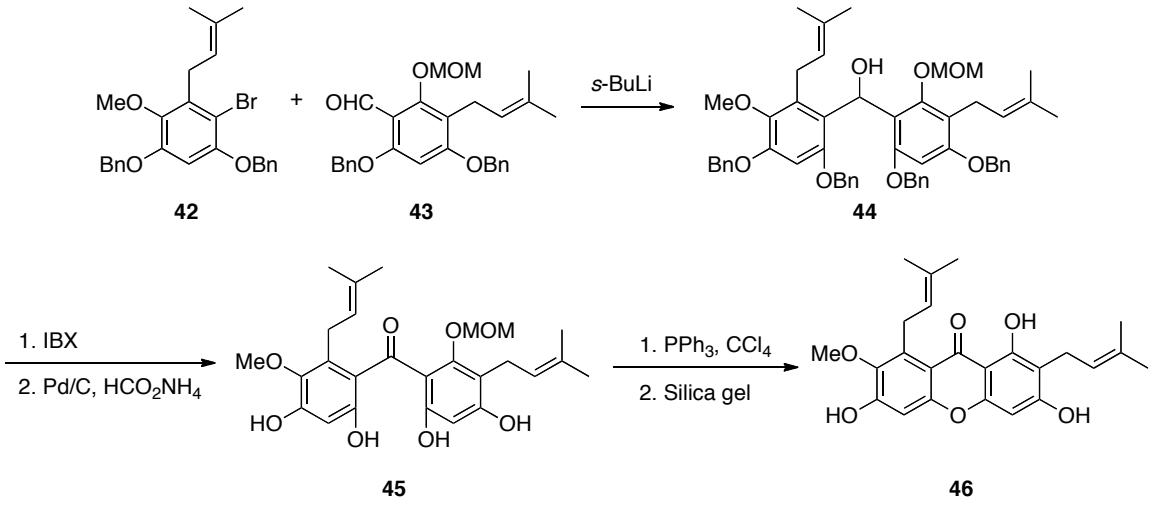



**Scheme 5.** Benzophenone intermediate from a Friedel-Crafts acylation

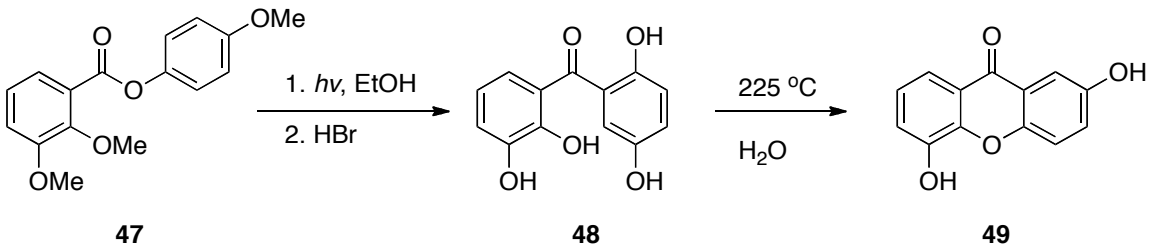
Nishiyama and co-workers used the benzophenone approach in the first direct synthesis of α-mangostin, a potent inhibitor of the acidic sphingomyelinase.[55] Coupling between the anion of **42** and aldehyde **43** provided benzhydrol **44**, which was oxidized with 2-iodoxybenzoic acid (IBX) and then deprotected to benzophenone **45** (Scheme 6). The key cyclization reaction was achieved with $PPh_3$-$CCl_4$. The transformation may begin with phosphorylation of the phenols followed by abstraction of triphenylphosphine oxide. MOM deprotection occurred simultaneously.

Another way to access the benzophenone intermediate is through the photo-Fries rearrangement of diaryl esters, (pathway **f** in Scheme 4). Finnegan and Merkel wanted 2,5-dihydroxyxanthone (**49**) (Scheme 7).[56] Using the GSS reaction conditions with 2,3-

dimethoxybenzoic acid and 1,4-dimethoxybenzene, they did not get the xanthone since demethylation was the primary reaction. Therefore, the diaryl ester **47** was transformed into benzophenone **48** using a photo-Fries rearrangement followed by demethylation with hydrogen bromide. When heated in a sealed tube with water, **48** underwent cyclodehydration forming the xanthone.



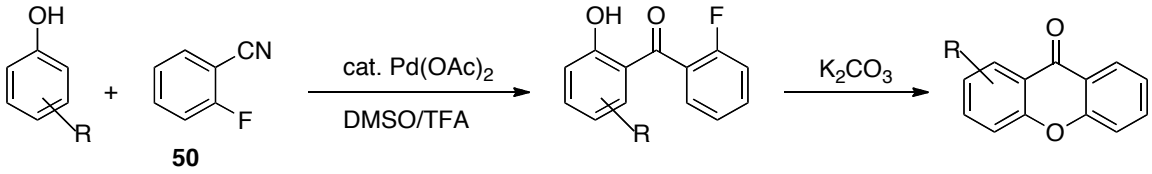

**Scheme 6.** Synthesis of α-mangostin *via* benzophenone




**Scheme 7.** Benzophenone from a photo-Fries rearrangement

Larock and Zhou reported the synthesis of benzophenones using a palladium-catalyzed C—H addition of arenes to nitriles.[57] Using simple phenols and 2-fluorobenzonitrile (**50**) as starting materials, followed by intramolecular cyclization, various xanthones were prepared from cheap, readily available starting materials in moderate yields (Scheme 8). It is proposed that this chemistry involves palladium-

catalyzed C—H activation of the simple arene, followed by an unusual carbopalladation of the nitrile.




**Scheme 8.** Benzophenones from Pd-catalyzed C—H addition of arenes to nitriles

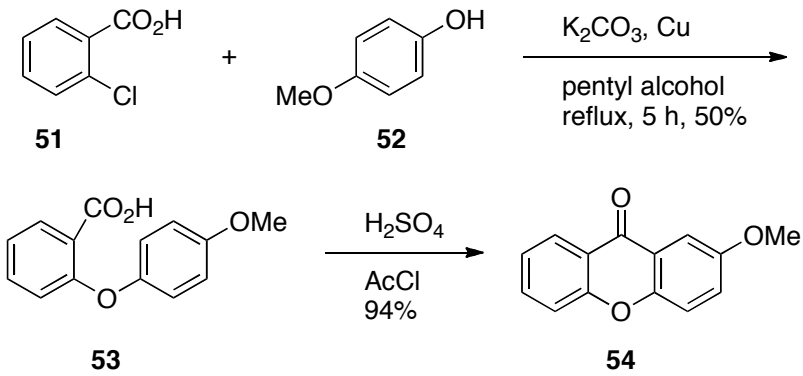
**Synthesis *via* a diphenyl ether intermediate**

Diaryl ethers can be synthesized by the Ullmann condensation[58] between phenols or sodium phenolates and *o*-halogenated benzoic acids, followed by electrophilic cycloacylation of the 2-aryloxybenzoic acids to prepare xanthones, (pathway **c** – **d** in Scheme 4). A disadvantage of this method is the low yield common to Ullmann condensations.

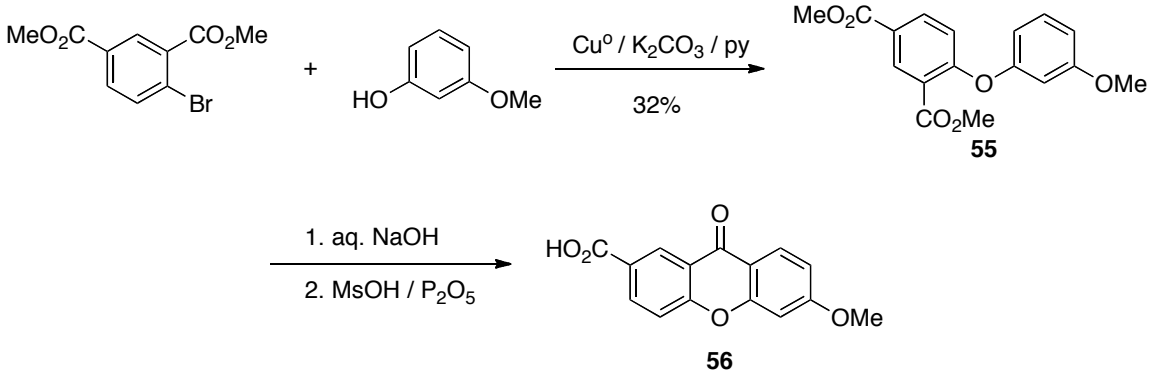
2-Carboxy-4´-methoxydiphenyl ether (**53**) was obtained in a 50% yield when *o*-chlorobenzoic acid (**51**) was condensed with *p*-methoxyphenol (**52**) in hot pentyl alcohol, potassium carbonate, and catalytic copper bronze (Scheme 9).[59] When the reaction was carried out using the original method of Ullmann and Zlokasoff, the yield was 30%. Cyclization to xanthone **53** occurred in 94% yield when a solution of the ether in acetyl chloride and concentrated sulphuric acid was heated to distill off acetyl chloride. When polyphosphoric acid (PPA) was used, cyclization occurred in 84% yield.

Jackson required gram quantities of xanthone **56** (Scheme 10) as part of his effort to develop potent and specific leukotriene $B_4$ receptor antagonists.[60] The Ullmann coupling between 4-bromo-1,3-benzenedicarboxylic acid dimethyl ester and 3-methoxyphenol yielded **55** in only 32%. In the cyclization step, phosphorus pentoxide-

methanesulfonic acid (Eaton's reagent) was used instead of PPA because the latter is difficult to work with in large quantities.

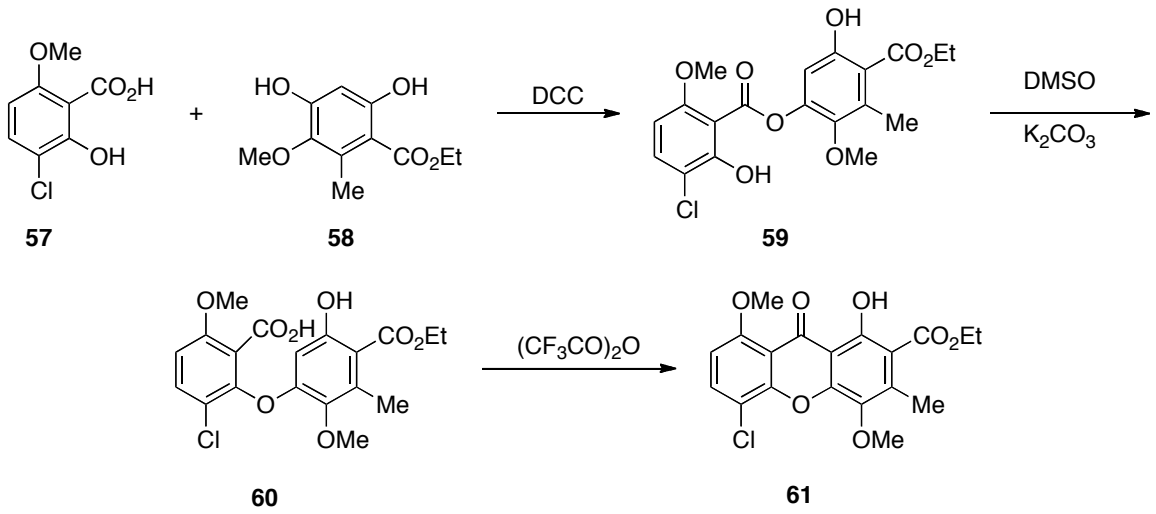



**Scheme 9.** Ullmann ether synthesis followed by cyclization to a xanthone




**Scheme 10.** Eaton's reagent used to cyclize a diaryl ether to a xanthone

The Smiles rearrangement is another way to access the diaryl ether intermediate (pathway **g** in Scheme 4). Elix and co-workers developed this method to synthesize **61** during their study of xanthones from the lichen *Rinodina thiomela* (Scheme 11).[61] Ester **59** was prepared by condensation of acid **57** and phenol **58** in the presence of *N,N´*-dicyclohexlcarbodiimide (DCC). Treating **59** with potassium carbonate in anhydrous dimethyl sulfoxide effected the Smiles rearrangement to carboxylic acid **60** in 63% yield. This was treated with trifluoroacetic anhydride to give the xanthone.

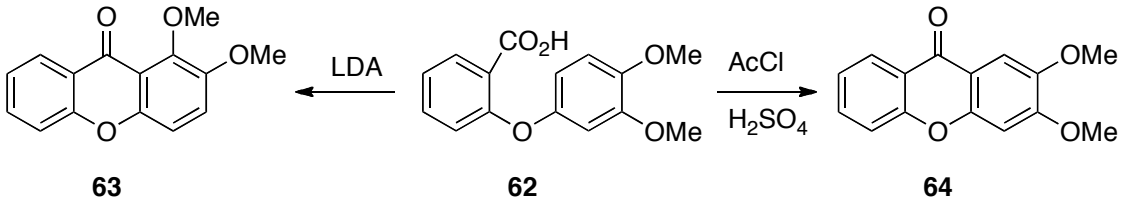



**Scheme 11.** Diaryl ether from a Smiles rearrangement

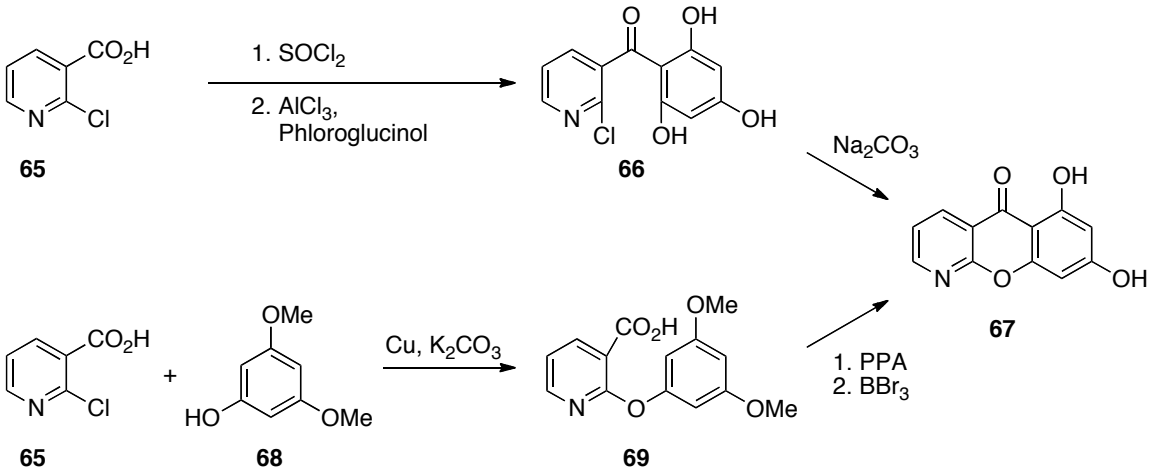
Improvements have been made in the synthesis of 1,2-dioxygenated xanthones through direct metalation of diphenyl ether intermediates using lithium diisopropylamide (LDA).[62] Traditional Friedel-Crafts acylation resulted in mixtures in an attempt to synthesize 1,2-dihydroxyxanthone.[48] The anionic cyclization tactic with LDA avoids the harsh conditions and isomeric mixture separation problems normally observed in the Friedel-Crafts reaction.[62] Sousa synthesized 1,2- and 2,3-dihyroxyxanthone, **63** and **64**, respectively (Scheme 12), from a common intermediate, carboxylic acid **62**.[63] Directed metalation with LDA resulted in **63**, while electrophilic cyclization with acetyl chloride resulted in **64**.

Intermolecular acylation reactions generally give higher yields than Ullmann ether syntheses. Therefore, acylation followed by cyclization is the more often used strategy.[48] For example, xanthone **67** (Scheme 13) was obtained in 51% yield from 2-chloronicotinic acid (**65**) after treatment with thionylchloride, followed by the acylation of phloroglucinol in the presence of aluminum trichloride to give ketone **66**, followed by

treatment with aqueous sodium carbonate to effect cyclization.[64] An Ullmann condensation of **65** with phenol **68** gave diaryl ether **69**, which was treated with PPA to effect cyclization and then $BBr_3$ to demethylate to **67** in 41% overall yield.[65]




**Scheme 12.** 1,2-Dioxygenated xanthones from anionic cyclization *vs*. 2,3-dioxygenated xanthones from acidic conditions



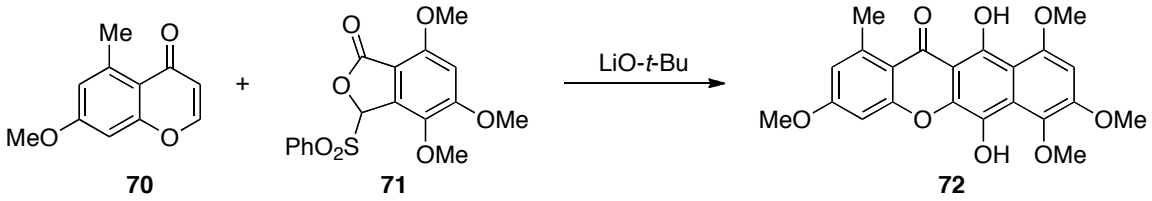

**Scheme 13.** Friedel-Crafts route, 51% over three steps. Ullmann condensation route, 41%

**New Methods**

Although the classical methods towards xanthones continue to be used to synthesize newly discovered compounds, new methods have been developed. Aims of the new methods include constructing densely oxygenated xanthones in a regioselective manner, reducing the number of steps, making the conditions more mild, and eliminating toxic reagents.

**Hauser's Method**

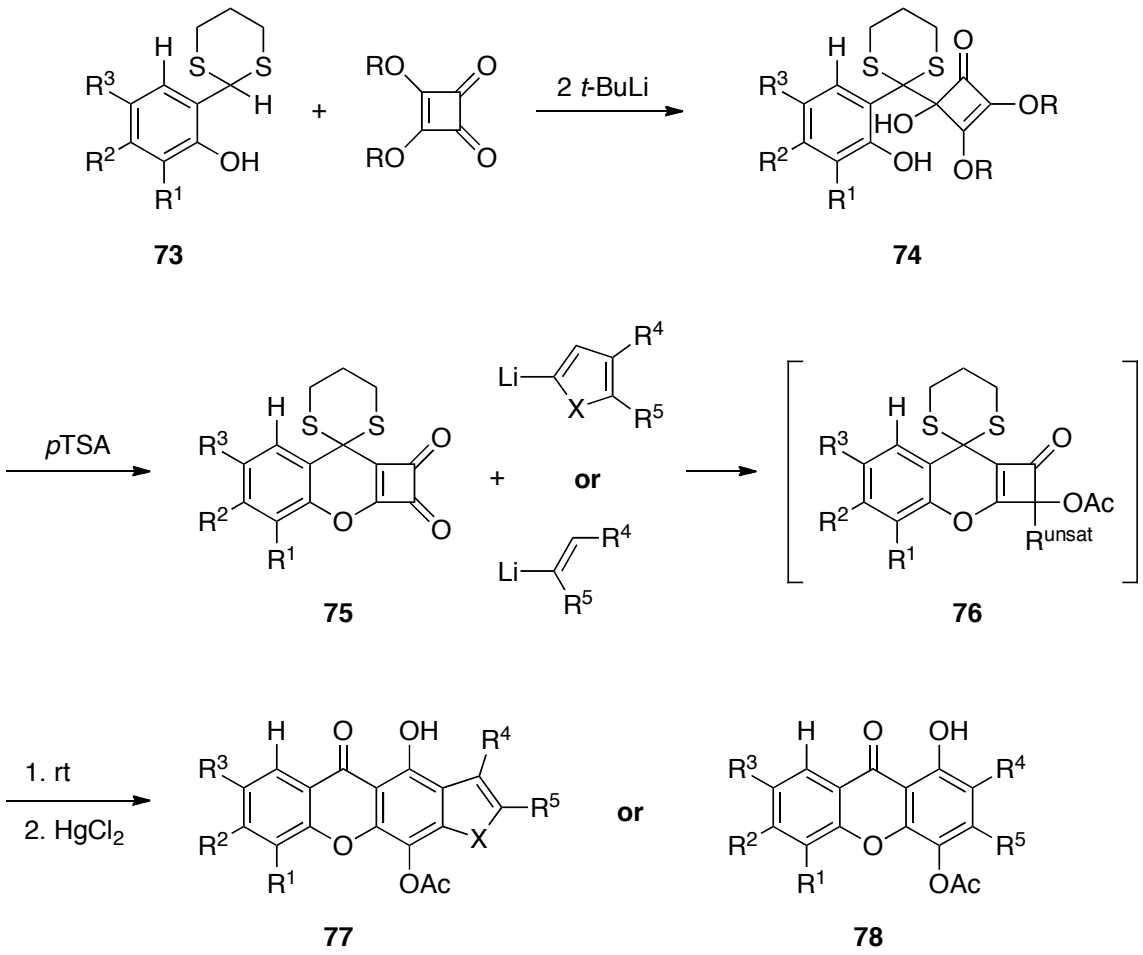
Hauser used the sulfone annelation strategy in a regiospecific preparation of the benz[*b*]xanthen-12-one ring system.[66] Condensation of the anion of phthalide **71** with chromone **70** gave **72** in 27% yield (Scheme 14).




**Scheme 14.** Regiospecific preparation of the benz[*b*]xanthen-12-one ring system

**Liebeskind Method**

Liebeskind's method[67] used dithiane-protected γ-benzopyrone-fused cyclobutenediones **75** (Scheme 15) to regioselectively synthesize a variety of highly-substituted xanthones (**78**) and xanthones fused to aromatic and heteroaromatic rings (**77**). These were readily accessed on a large scale from dialkyl squarates and the dianions of 2-(*o*-hydroxyphenyl)-1,3-dithianes (**73**). The 1,2-adducts (**74**) were treated with *p*-toluenesulfonic acid monohydrate (*p*TSA), which resulted in cyclization to **75**. Nucleophilic addition of different alkenyl, aryl, and heteroaryl anions to **75** occurred at the less sterically hindered ketone. The 1,2-adducts were quenched with acetic anhydride. Some of the *O-acylated* adducts (**76**) derived from aromatic anions could be purified and characterized, but it was more efficient to warm the crude adducts to room temperature and then isolate the benzannulated products. Treatment with $HgCl_2$ completed the synthesis of xanthones.

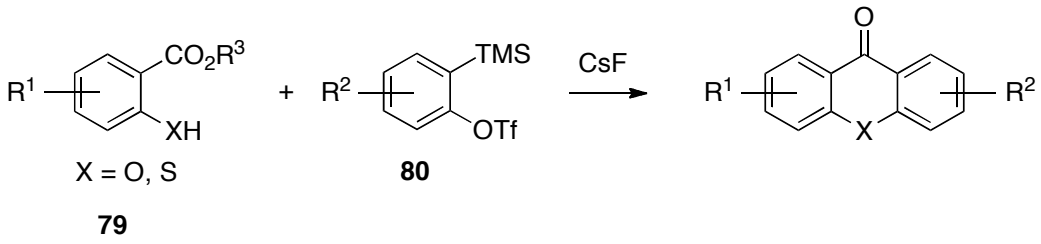



**73** **74** **75** **76** **77** **78**

**Scheme 15.** Benzannulation with cyclobutenediones

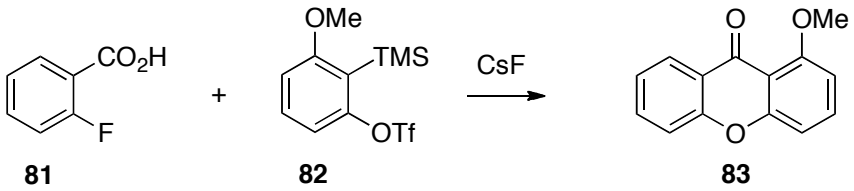
### Larock's One Step Methods

Most syntheses of the xanthone skeleton involve multiple steps, harsh reaction conditions, strong acids, and/or toxic metals. Using Kobayashi's[68] mild approach to arynes from silylaryl triflates, Larock and Zhao[69] developed a general, one-pot approach to xanthones, thioxanthones and derivatives. The reaction of *o*-(trimethysilyl)aryl triflates (**80**, Scheme 16), salicylates (**79**) and CsF afforded xanthones and thioxanthones through a mechanism that proceeds by a tandem intermolecular nucleophilic coupling, followed by intramolecular electrophilic cyclization.




**Scheme 16:** One-pot synthesis of xanthones and thioxanthones

Larock and Dubrovskiy[70] in 2010 developed a second one-step route to xanthones. This procedure uses *o*-(trimethylsilyl)aryl triflates and CsF to generate an aryne, which inserts into the C—O bond of readily available *o*-halobenzoic acids. After subsequent rearrangements, nucleophilic aromatic substitution with a phenolate formed *in situ* results in cyclization of the pyrone. The reaction between *o*-fluorobenzoic acid (**81**) and 3-methoxybenzyne precursor 3-methoxy-2-(trimethylsilyl)phenyl triflate (**82**) with CsF provided 1-methoxyxanthone (**83**) in 71% yield (Scheme 17). Only one regioisomer was formed since the reaction is controlled electronically.[70]

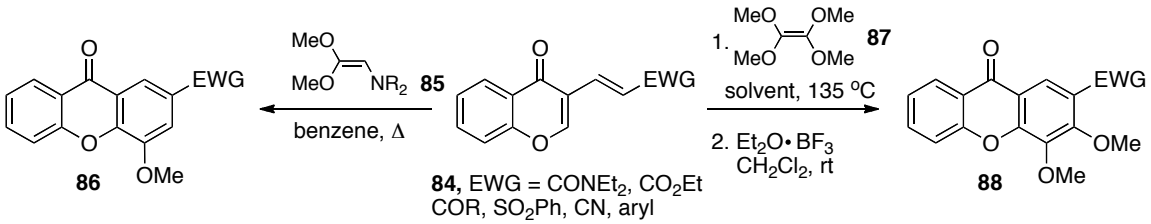



**Scheme 17.** Intermolecular C—O addition of a carboxylic acid leading to a xanthone

**Inverse electron demand Diels-Alder approach**

Bodwell and co-workers[75] synthesized a series 2 substitued 4-methoxyxanthones (**86**, Scheme 18) and 3,4-dimethoxyxanthones (**88**) using a cascade of reactions initiated by an inverse-electron-demand Diels-Alder reaction (IEDDA). The dienes were electron-deficient chromones (**84**) and the dieneophiles were either 1-(2,2-dimethoxyvinyl)pyrrolidine (**85**) or tetramethoxyethene (**87**). For experiments employing

**87**, the series of reactions—IEDDA/elimination (MeOH)/elimination (MeOH)—was interrupted after the first elimination, which led to unaromatized byproducts. Treatment with $Et_2O{\cdot}BF_3$ converted the byproducts to xanthones.




**Scheme 18.** Inverse-electron-demand Diels-Alder approach

**KRAUS APPROACH TO XANTHONES**

The use of herbal medicines is increasing.[79] The Food and Drug Administration (FDA) does not regulate herbal medicines since they are classified as dietary supplements. The second most sold herbal medicine in the United States is St. John's Wort—*Hypericum perforatum*—which is used as an anti-anxiety drug, as an antiviral and as a topical wound-healing agent. The commercial preparation is a mixture of at least ten compounds, including hypericin and hyperforin, which are well know and thought to be the active antidepressant ingredients.[80] However, it is necessary to understand the biological activities of all the major components to avoid unfavorable drug interactions. As mentioned above (Figure 4), the 1,7-dioxygenated xanthones euxanthone (**9**) and 1-methoxy-7-hydroxyxanthone (**10**) are found in St. John's Wort.

Euxanthone shows potential as a pharmaceutical because of its biological activities: it promotes neurite outgrowth by selectively activating the MAP kinase pathway,[81] it showed inhibitory effects on the growth of *Plasmodium falciparum* with $IC_{50}$ values in the milligram/milliliter level,[82] and it inhibited HIV-1 reverse transcriptase

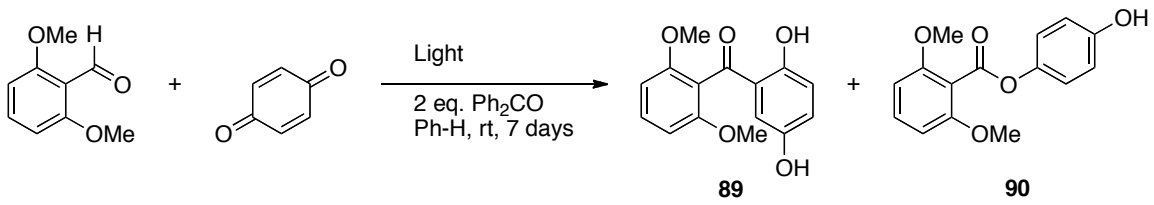
with $IC_{50}$ values at the milligram/milliliter level.[83] In a vasodilation assay, both xanthones **9** and **10** exhibited relaxing activity on the contractions evoked by potassium chloride in rat thoracic aorta rings in a dose-dependent manner.[84] Patel and Trivedi synthesized euxanthone by heating hydroquinone and ethyl 2,6-dihydroxybenzoate in boiling diphenyl ether.[85] The transformation proceeds through a diaryl ester intermediate, which rearranges to the xanthone by pyrolysis (pathway **e** in Scheme 4). Our synthetic route to **9** requires three steps from two commercially available starting materials and is amendable to scale up.

After establishing our route to simple 1,7-dioxygenated xanthones, we made progress towards the synthesis the prenylated 1,7-dioxygenated xanthones from *Psorospermum molluscum* (**26**, **27**, Figure 12). During isolation, Kingston used the *Escherichia coli* SOS PQ37 chromotest assay—a DNA reactivity assay—to guide the fractionation of the plant extract.[77] Compound **26** displayed highly potent SOS activity. It is likely that **26** is a biogenetically derived oxidation product of **27**.[77] The isolated quantities of **26** were too small to determine the stereochemistry, so synthesis is required.

## RESULTS AND DISCUSSION

The key step of our synthetic route to the simple 1,7-dioxygenated xanthone core was the photoacylation[86] of benzoquinone with 2,6-dimethoxybenzaldehyde (Scheme 19). The Kraus lab developed the photoacylation of quinones as a benign alternative to certain Friedel-Crafts reactions. Advantages of this reaction include atom economy, readily available and stable starting materials, and generality concerning the aldehyde component. Adducts from the reaction have been used in syntheses of benzodiazepines

and natural products such as frenolicin.[86c] Concerning benign chemistry, a disadvantage of the procedure is the use of hydrocarbon solvents such as benzene and acetonitrile. However, supercritical carbon dioxide (SC-$CO_2$) has been reported as an alternative solvent and was used in the benzophenone-mediated photoacylation of 1,4-benzoquinone with benzaldehyde or butyraldehyde.[86e] In a large-scale application of the photoacylation, Mattay and co-workers used a *t*-butanol-acetone mixture (3:1, 80 L) as the solvent for the acylation of 1,4-napthoquinone (500 g) with butyraldehyde (4 kg).[87] Before we synthesized **89**, a hindered aldehyde had not been used because the reaction generates an acyl radical, which could undergo an intramolecular 1,5-hydrogen atom transfer prior to coupling with the quinone.[88]

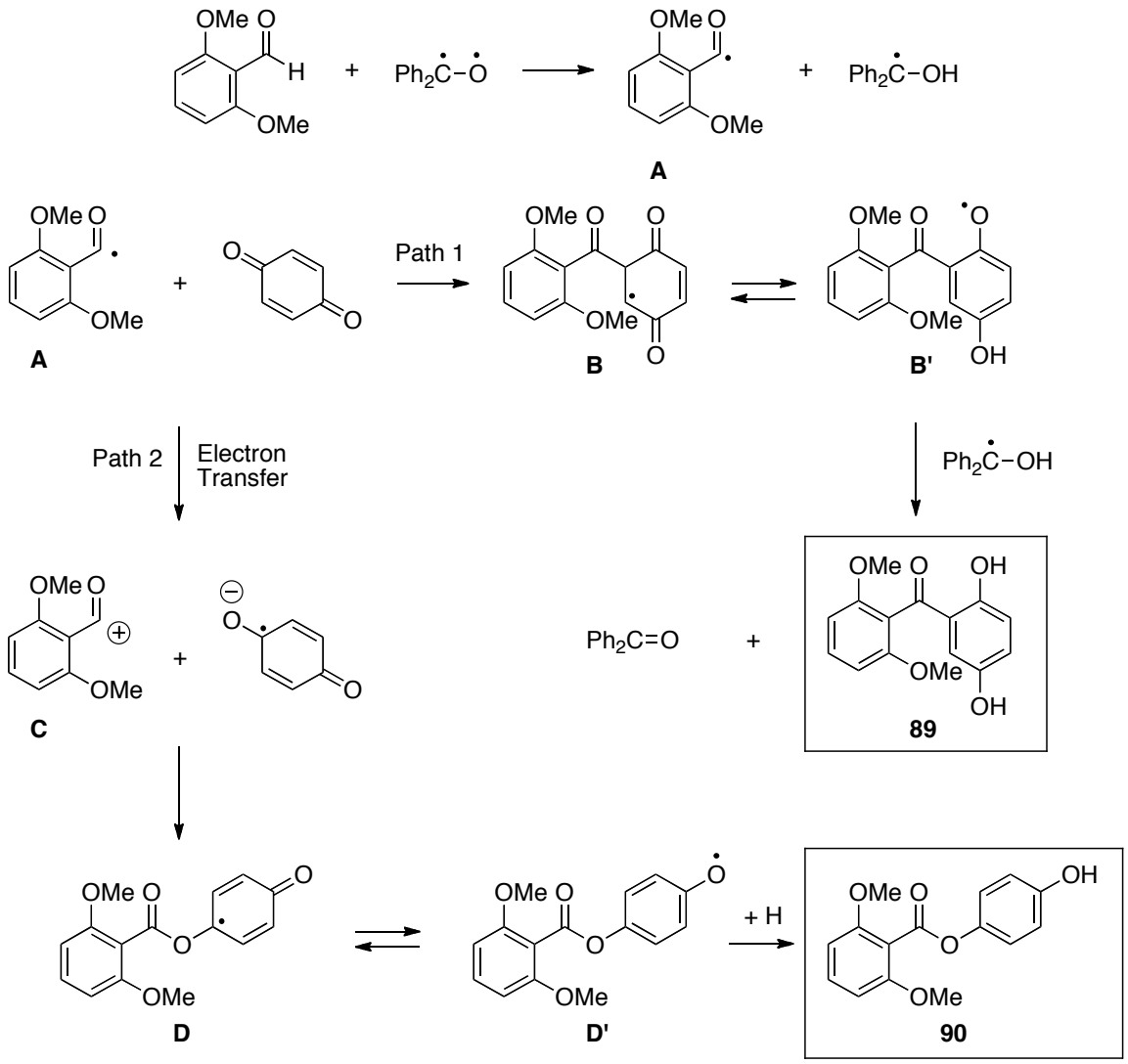



**Scheme 19.** Photoacylation reaction with benzoquinone

The benzophenone-mediated reaction generated the desired adduct **89** and a byproduct, monoester **90**. The two adducts and unreacted 2,6-dimethoxybenzaldehyde were inseparable by column chromatography, so acid-base extraction was used to separate the phenolic products from the recovered aldehyde and benzophenone.

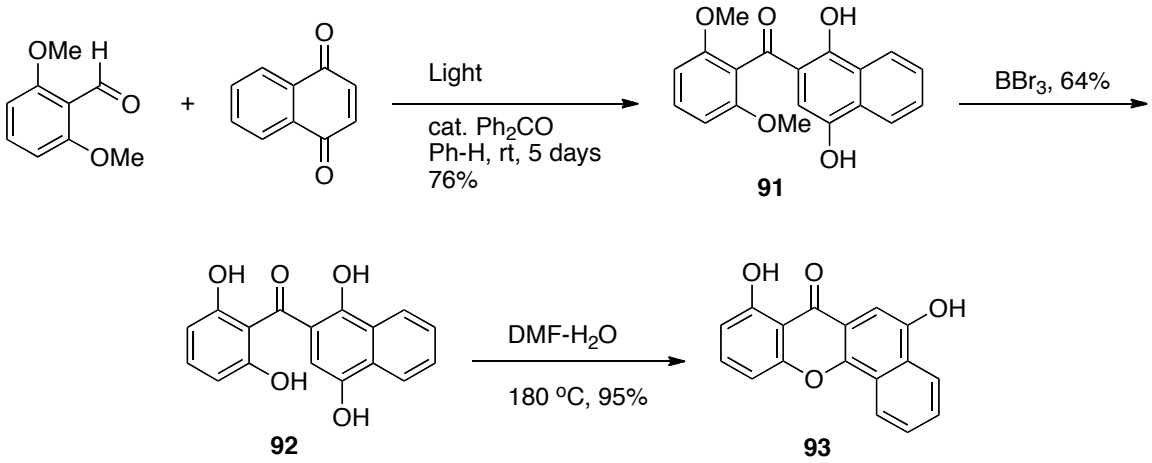
Possible pathways (Scheme 20) leading to **89** and **90** begin with hydrogen atom abstraction[86b, 89] from the formyl group of 2,6-dimethoxybenzaldehyde by the triplet excited state of benzophenone to generate the acyl radical **A**. In Path 1, **A** then adds 1,4 to the quinone, resulting in stabilized semiquinone radicals **B** and **B′**. Finally, the benzhydrol radical donates a hydrogen atom to regenerate benzophenone and produce hydroquinone **89**. In Path 2[90], a single electron transfer between **A** and benzoquinone

gives the acylium ion **C** and a radical anion, which couple to form stabilized radicals **D** and **D′**. In the last step, hydrogen abstraction produces **90**.



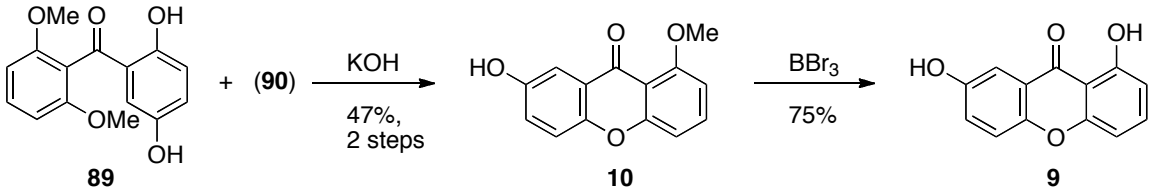

**Scheme 20.** Mechanisms leading to **89** and **90**

We synthesized **91** in 76% yield from naphthoquinone to show the scope of this reaction (Scheme 21). Monoester formation was not observed. Adduct **91** was demethylated with boron tribromide to give **92**, which was cyclized to xanthone **93** in 95% yield with heating at 180 °C for 16 hours.




**Scheme 21.** Synthesis of 5,8-dihydroxy-7H-benzo[c]xanthen-7-one (**93**)

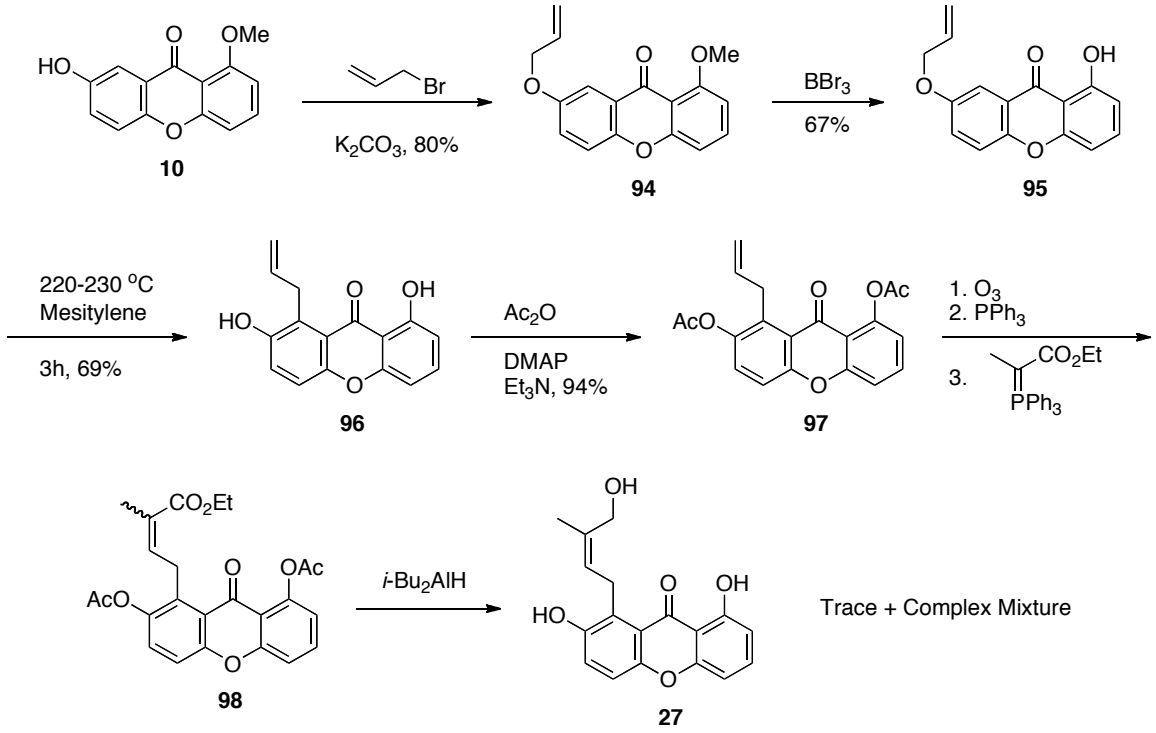
To synthesize xanthone **10**, we treated adduct **89** (along with monoester **90**) with potassium hydroxide in methanol at 100°C for 12 hours to afford compound **10** in 47% yield over two steps.[91] Demethylation of **10** with boron tribromide afforded euxanthone (**9**) in 75% yield.



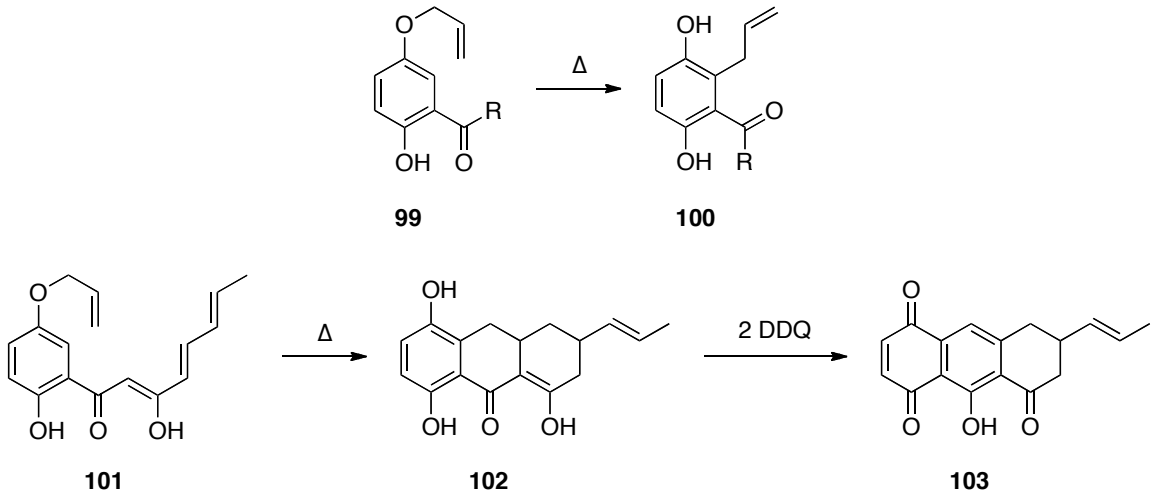

**Scheme 22.** Synthesis of 1-methoxy-7-hydroxyxanthone and euxanthone

Our synthetic effort towards **27** is outlined in Scheme 23. The key step in this series was the selective *ortho*-Claisen rearrangement to place the allyl group at the position *ortho* to the carbonyl, intermediate **96**. The rearrangement of allylphenyl ethers to *o*-allylphenols forms a mixture of isomers when the system is unsymmetrical.[93] However, certain *m*-acyl groups do have a directing effect. Ketones such as **99** rearrange exclusively to **100** (Scheme 24).[94] Kraus and Fulton synthesized polycyclic systems by

coupling the rearrangement with an intramolecular Diels-Alder reaction using ketone **101**. Aromatization of the central ring with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) afforded naphthoquinone **103**.




**Scheme 23.** Synthesis of hydroxyprenylated xanthone **27**

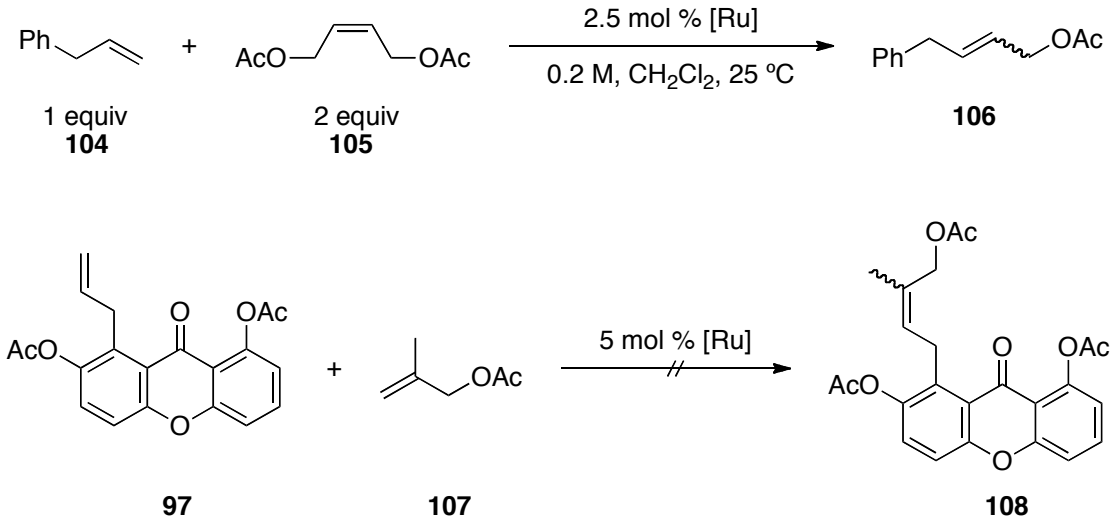



**Scheme 24.** Regioselective *ortho*-Claisen rearrangements

Allylation of **10** afforded xanthone **94** in 80% yield. To determine whether or not an *ortho*-hydroxy group is necessary to effect selectivity in rearrangement, we heated the *O*-methyl xanthone (**94**) at 200 ºC in a sealed tube with toluene. This resulted in a complex mixture. Therefore, we selectively removed the *O*-methyl group using boron tribromide in methylene chloride to afford a 67% yield of **95**. However, the reaction was not clean. In addition to recovered starting material, di-dealkylation gave euxanthone as a byproduct. Euxanthone could be selectively allylated at the 7-postion to give **95** in 57% yield. The *ortho*-Claisen rearrangement cleanly gave dihydroxyxanthone **96** in 69% yield, when the allyl ether was heated at 220-230 ºC for three hours in a sealed tube with mesitylene. Acetylation of the hydroxy groups using acetic anhydride, 4-dimethylaminopyridine (DMAP) and triethyl amine gave diacetate **97** in 94% yield. Next, ozonolysis and *in situ* Wittig reaction[95] with the stabilized ylide ethyl 2-(triphenylphosphoranylidene)propanoate[96] furnished a mixture of *E* and *Z* α,β-unsaturated esters **98** in 43% yield. The major product was the *E* isomer since stabilized ylides furnish high *E* selectivity.[97] We did not isolate the aldehyde and we used mild conditions to effect the Wittig reaction since the aldehyde's stability was a concern owing to the mutually benzylic and α-hydrogen atoms. When we made progress towards **26**, the aldehyde was isolated.

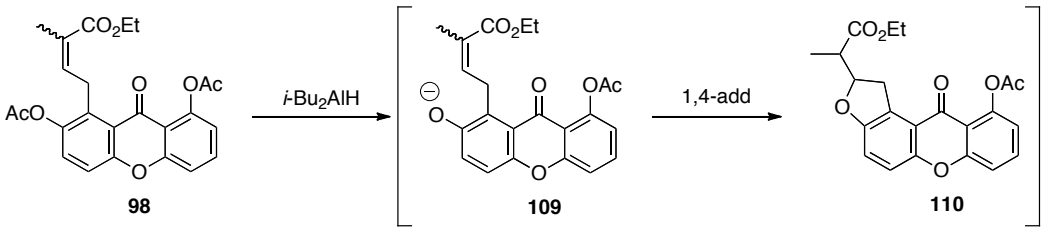
It should be noted that before employing the oxidation/*in situ* Wittig reaction protocol, we attempted a ruthenium catalyzed cross metathesis (CM). Grubbs has successfully coupled allyl benzene (**104**) and 1,4-diacetoxy-2-butene (**105**) (Scheme 25).[98] The two components behave similarly in the CM reaction, so 2 equiv of **105** (corresponding to 4 equiv of allylacetate) were used to increase the statistical yield of the heterocoupled product **106**. The reaction produced a six-component mixture of *E*/*Z*

heterocoupled **106**, *E/Z* 1,4-diacetoxy-2-butene, and *E/Z* homocoupled allylbenzene. The first and second-generation catalysts were compared. The second-generation was more active than the first-generation since the former had faster reaction times and higher total conversions. However, the *E/Z* ratio for the first-generation was ~5 throughout the course of the reaction, while the *E/Z* ratio for the second-generation was ~3 early in the reaction then rising to ~10 as the conversion increased. With this information, we used the first-generation catalyst to couple allylxanthone **97** with 2-methylallylacetate (**107**). Unfortunately, the reaction returned the xanthone starting material and produced *E/Z* homocoupled **107**. The same result was reached with the second-generation catalyst.



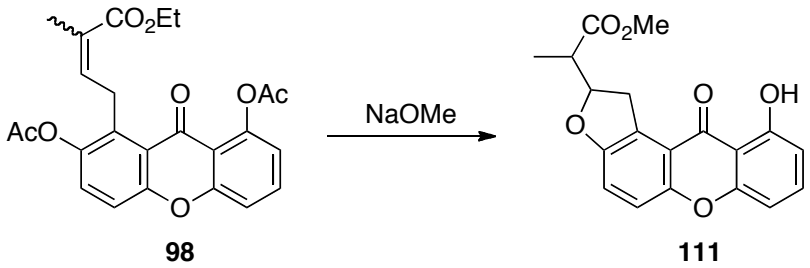

**Scheme 25.** CM reactions between allyl benzenes and allyl acetates

Although the *E,Z*-selectivity of the Wittig reaction was not in our favor, we fortunately did have a small percentage of the *Z*-olefin ready for reduction to the natural product **27**. Using diisobutylaluminium hydride (*i*-$Bu_2AlH$), several attempts all resulted in complex mixtures. Considering an alternate pathway the reaction could take (Scheme 25), if the phenoxide formed *ortho* to the unsaturated ester (**109**), conjugate addition could result, leading to the benzofuran **110**.




**Scheme 25.** A possible side reaction during the reduction step

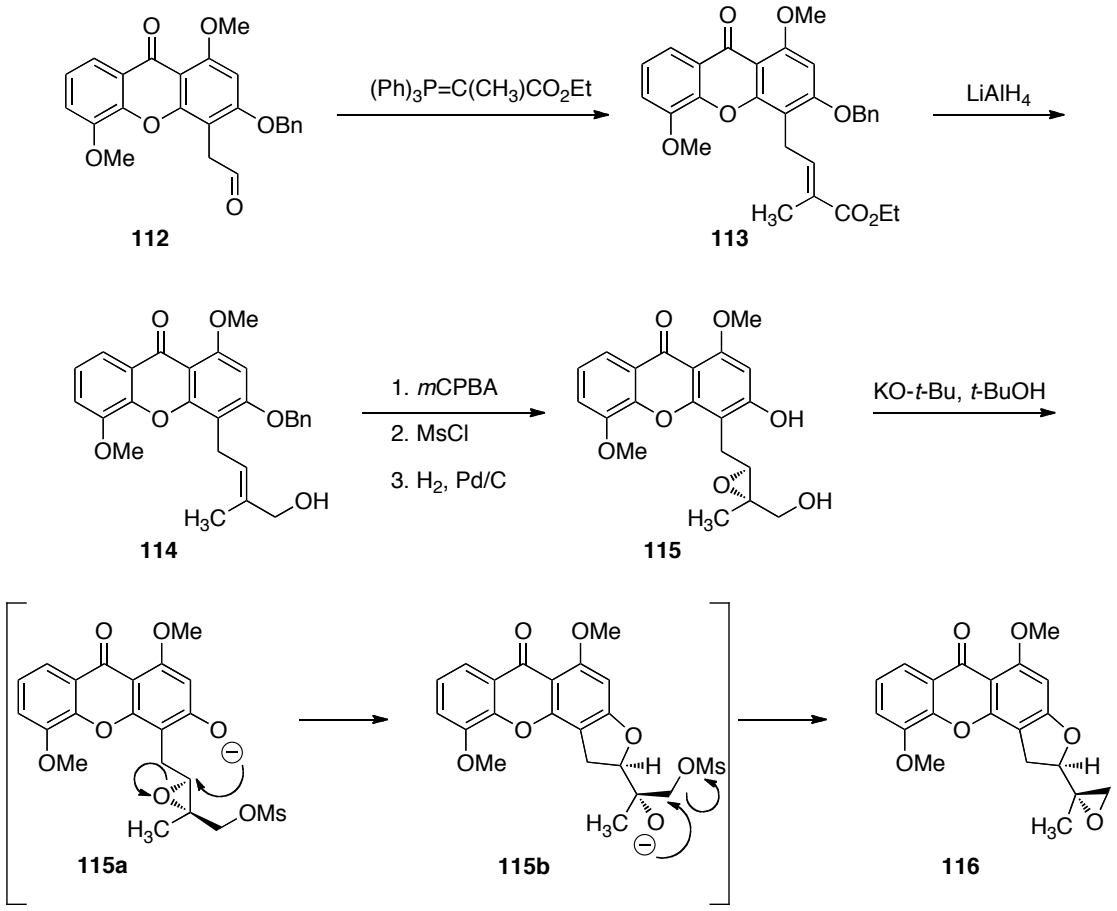
To investigate the cyclization reaction, **98** was treated with sodium methoxide (Scheme 26). Methanolysis, Michael addition and transesterification occurred to afford one compound (**111**) in 97% yield.




**Scheme 26.** Treatment of **98** with NaOMe affords a benzofuran

The ease of cyclization coupled with the difficulty in preparing the *Z*-olefin encouraged us to make a synthetic attempt toward the furanoxanthone **26**, psoroxanthin. As mentioned above, it is structurally related to psorospermin (**28**), which Kupchan first isolated in 1980.[78] In 1987, Cassady assigned the absolute stereochemistry[99] as 2´*R*,3´*R*, and he confirmed the assigned configuration with the total synthesis[100] of the $O^5$-methyl-(±)-2´*R*,3´*S* epimer. Schwaebe completed the first total synthesis[101] of psorospermin in 2005.

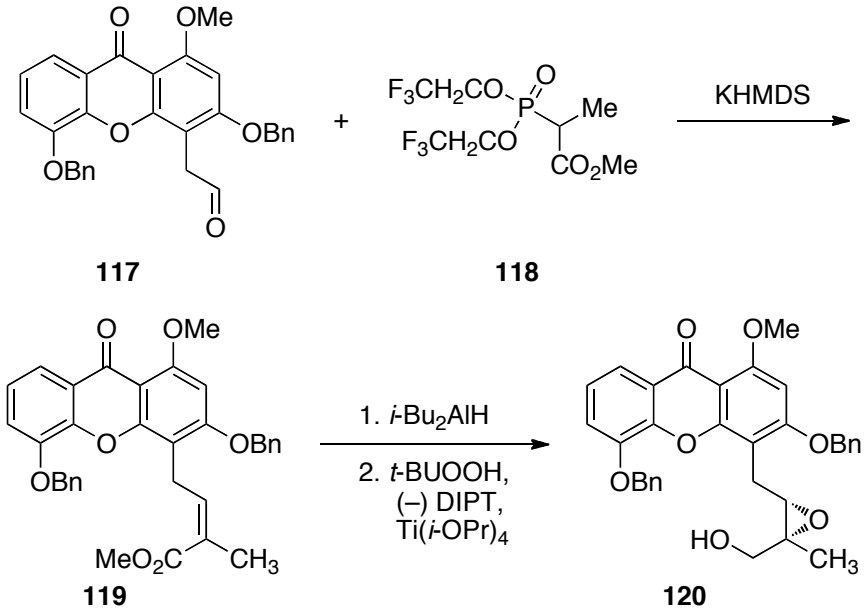
Scheme 27 shows Cassady's synthesis[100] of $O^5$-methyl-(±)-2´*R*,3´*S*-psorospermin beginning with a key intermediate, aldehyde **112**. The Wittig reaction of it with (carbethoxyethylidene)triphenylphosphorane gave the ester (*E*)-**113** in 47% yield. That assignment was based on $^1$H NMR chemical shift correlation. The vinyl proton resonated at $\delta$ 6.87 (6.60 calcd for *E* isomer, and 6.03 for *Z*). Diisobutylaluminum hydride did not effect the reduction, so lithium aluminum hydride was used to afford allylic alcohol **114** in 50% yield. Epoxidation with *m*-chloroperbenzoic acid (*m*CPBA) produced racemic epoxides in 70% yield. The allylic alcohol was mesylated and then the benzyl phenol was deprotected to give **115**. Treatment with potassium *tert*-butoxide in *tert*-butyl alcohol produced the phenoxide ion (**115a**) that opened up the epoxide in an $S_N2$ reaction, which formed the furan ring as the alkoxide ion left. That anion (**115b**) participated in a second $S_N2$ reaction, which formed the epoxide as the mesylate left. The stereochemical outcome of Cassady's zipper-type reaction was set by the stereochemistry of ester **113** and the racemic mixture of epoxides.




**Scheme 27.** Cassady's zipper-type reaction

In Schwaebe's total synthesis of psorospermin,[101] he set the (2´*R*,3´*R*)-stereochemistry of the natural product by selectively forming the *Z*-olefin, **119** (Scheme 28), using the *Z* Horner—Emmons method developed by Still and Gennari.[102] Schwaebe also was able to differentiate the 1- and 5-hydroxys, which allowed for the selective protections and deprotections necessary to complete the synthesis. Aldehyde **117** was added to a solution of trifluoroethylphosphonoester **118** and $KN(SiMe_3)_2$/18-crown-6, which resulted in a 10:1 ratio of the *Z*/*E* unsaturated ester. Crystallization afforded pure *Z*

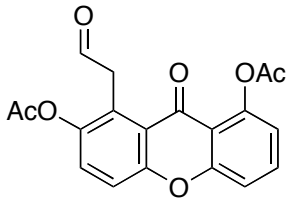
olefin **119** in 76% yield. Reduction with *i*-$Bu_2AlH$ gave the allylic alcohol in 42% yield. Sharpless epoxidation[103] produced **120** in 78% yield with a 70% ee.




**Scheme 28.** Steps establishing the stereochemistry in Schwaebe's total synthesis of psorospermin

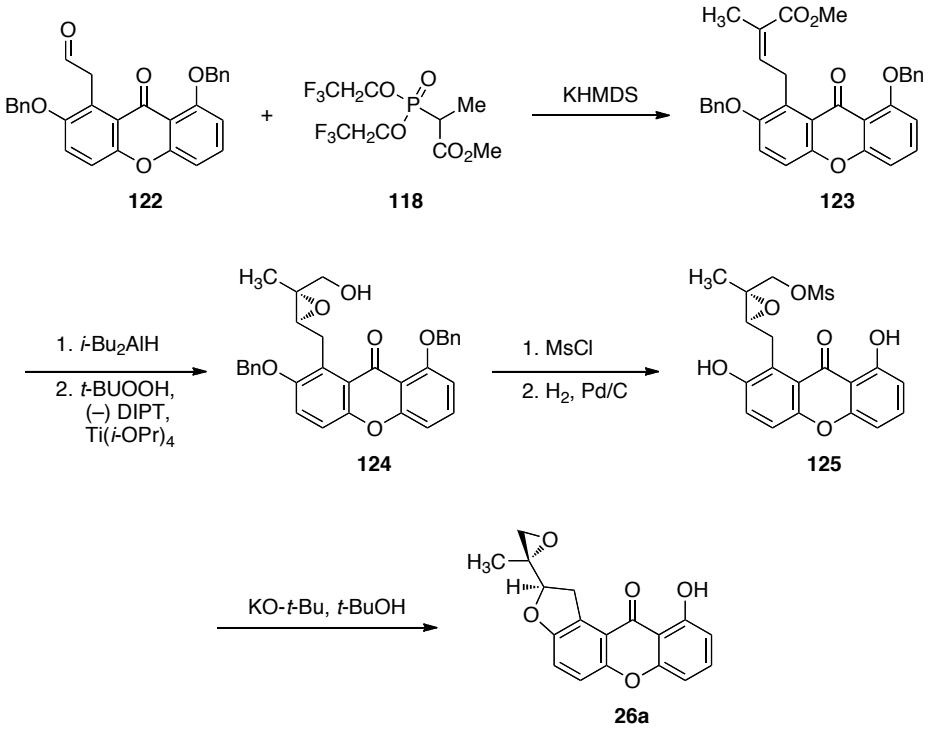
**FUTURE WORK**

We could selectively synthesize derivatives of **26** with Schwaebe's method using the *E* and the *Z*-olefins with (–) DIPT and (+) DIPT. Scheme 29 outlines the synthesis of 2´*R*,3´*R* derivative, **26a**. Instead of using aldehyde **121** (Figure 16), which was isolated and stable, the dibenzyl aldehyde **122** would be used to avoid cyclization during the reduction step.




**121**

**Figure 16**




**Scheme 29.** A planned synthesis of 2´*R*,3´*R* derivative, **26a**

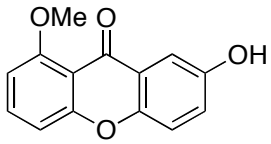
## CONCLUSION

Two bioactive components from *Hypericum perforatum* have been synthesized by direct routes. These results further extend the synthetic utility of the photoacylation of

quinones. Progress was made toward the first total synthesis of psoroxanthin using a regioselective *ortho*-Claisen rearrangement.

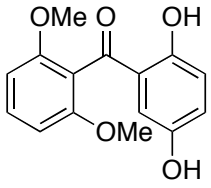
**EXPERIMENTAL**

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Dichloromethane, benzene and diisopropyl amine were distilled over calcium hydride. All experiments were performed under an argon atmosphere unless otherwise noted. Organic extracts were dried over anhydrous magnesium sulfate. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Varian 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for $^1H$ and 77.23 ppm for $^{13}C$), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.



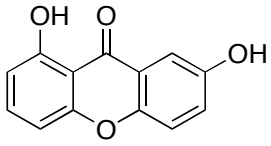

*1-Methoxy-7-hydroxyxanthone* (**10**): A 2.5 cm x 20 cm Pyrex test tube was charged with 2,6-dimethoxybenzaldehyde (544.6 mg, 3.24 mmol), benzoquinone (354 mg, 3.27 mmol), and benzophenone (1.32 g, 7.22 mmol). The tube was equipped with a stir bar, charged with dry benzene (45 mL) and sealed. The solution was degassed with argon (15

min) and irradiated in a Rayonet photochemical reactor (7 days). Crystals precipitated out of the reaction mixture. The mixture was poured into a 250 mL round bottom flask, the tube was rinsed with acetone and the solvents were removed by distillation on a rotary evaporator. Five percent NaOH (20 mL) was poured into the flask and then the aqueous solution was poured into a separatory funnel and extracted with ether (3x 20 mL). The aqueous layer was cooled to 0 °C, acidified with concentrated HCl and then extracted with ether (3x 20 mL). The organic layer was concentrated *in vacuo* to reveal a dark yellowish-brown tar (850.4 mg), which was a mixture of **89** and the monoester (**90**). The mixture was transferred to a pressure tube with MeOH (30 mL). The tube was equipped with a stir bar, charged with KOH (1.74 g, 31 mmol), sealed at 0°C, and heated at 110°C (24 h). The solution was poured into ice, acidified with concentrated HCl and extracted with EtOAc (3x 20 mL). The organic layer was dried over $MgSO_4$ then concentrated. Purification by column chromatography (EtOAc:hexanes, 1:4 → 2:3) removed methyl-2,6-dimethoxybenzoate and hydroquinone. **10** was eluted with 1:1 → 9:1 EtOAc:hexanes as a beige solid (371.7 mg, 1.53 mmol) in 47% over two steps, which crystallized from MeOH as yellow needles, m.p. 238-240 °C (lit.[104] 238-240 °C). All spectra were identical with those previously reported.[104]

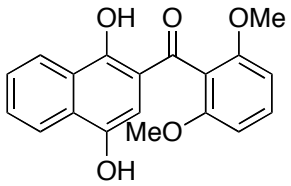



*(2,5-Dihydroxyphenyl)(2,6-dimethoxyphenyl)methanone* (**89**): $^1$H- NMR (acetone-$d_6$) δ 11.71 (s, 1H), 7.46 (t, $J$ = 8.00 Hz, 1H), 7.09 (dd, $J$ = 8.00 Hz, $J$ = 4.00 Hz, 1H), 6.87 (d,

*J* = 8.00 Hz, 1H), 6.80 (d, *J* = 8.00 Hz, 2H), 6.70 (d, *J* = 4.00 Hz, 1H), 3.73 (s, 6H); HRMS (EI) m/z calcd. for $C_{15}H_{14}O_5$ 274.0841, found 274.0846.

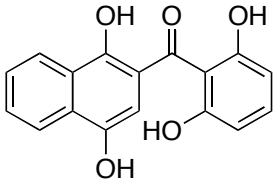



*Euxanthone* (**9**): To a stirred suspension of **10** (152.1 mg, 0.628 mmol) in $CH_2Cl_2$ (30 mL) at –78 °C was added 1.0 M $BBr_3$ solution in $CH_2Cl_2$ (0.942 mL, 0.942 mmol). The reaction mixture was slowly allowed to warm to rt, stirred overnight, cooled to 0 °C, quenched with water, and extracted with $CH_2Cl_2$. The combined organic layers were washed with water, dried (brine, $MgSO_4$), filtered, concentrated *in vacuo*, and purified by column chromatography (15% EtOAc in hexanes) to afford **1** as yellow needles (107.1 mg, 0.469 mmol, 75% yield) m.p. 236-238 °C (lit.[105] 236-238 °C).

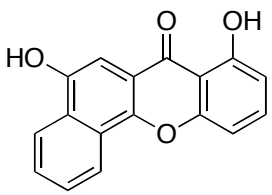



*(1,4-Dihydroxynaphthalen-2-yl)(2,6-dimethoxyphenyl)-methanone* (**91**): A 2.5 cm x 20 cm Pyrex test tube was charged with naphthoquinone (98 mg, 0.62 mmol), 2,6-dimethoxybenzaldehyde (95 mg, 0.565 mmol) and benzophenone (31 mg, 0.17 mmol). Dry benzene (19 mL) was added then the solution was degassed with argon (15 min). It was irradiated in a Rayonet photochemical reactor (5 days). Crystals precipitated out of the reaction mixture. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (hexanes-EtOAc 19:1→1:3) to afford 139 mg (76%) of **91** as bright yellow needles, m.p. 194-196 °C; $^1$H-NMR ($CDCl_3$): δ 13.31 (s, 1H), 8.52 (d, *J* = 8.00 Hz, 1H), 8.08 (d, *J* = 8.00 Hz, 1H), 7.68 (t, *J* = 8.00 Hz, 1H), 7.59 (t, *J* = 8.00 Hz,

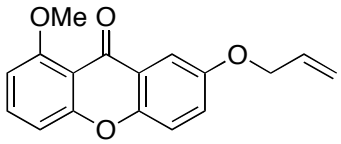
1H), 7.38 (t, *J* = 8.00 Hz, 1H), 6.64 (d, *J* = 8.00 Hz, 2H), 6.54 (s, 1H), 4.84 (s, 1H), 3.74 (s, 6H); $^{13}$C-NMR ($CDCl_3$): δ 200.4, 157.8, 157.4, 143.0, 131.4, 129.9, 129.8, 126.1, 124.8, 121.8, 116.8, 113.9, 107.7, 104.2, 56.2; HRMS (EI) m/z calcd. for $C_{19}H_{16}O_5$ 324.0998, found 324.0998.




*5,8-Dihydroxy-7H-benzo[c]xanthen-7-one* (**92**): An oven-dried 50-mL round bottom flask equipped with a stir bar was charged with benzophenone **91** (27.3 mg, 0.0842 mmol) and $CH_2Cl_2$ (3.0 mL). Then $BBr_3$ (337 μL, 1.0 M in $CH_2Cl_2$, 0.337 mmol) was added in drops over 1 min. The deep red solution was stirred at rt for 8 h and then cooled to 0 °C before quenching with 2 mL $H_2O$. The mixture was warmed to rt, diluted with $CH_2Cl_2$ (20 mL), poured into a separatory funnel and then the organic layer was washed with $H_2O$ (2x 20 mL), brine (1x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford an orange solid that was purified by column chromatography (hexanes:EtOAc; 3:2) to afford the tetrahydroxybenzophenone as an orange solid (16 mg, 0.0540 mmol, 64%); $^1$H-NMR (acetone-$d_6$): δ 8.67 (s, 1H, exchangeable with $D_2O$), 8.57 (s, 1H, exchangeable with $D_2O$), 8.44 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1 H), 7.62 (t, *J* = 8.0 Hz, 1 H), 7.18 (t, *J* = 8.0 Hz, 1 H), 6.78 (s, 1 H), 6.55 (d, *J* = 8.0 Hz, 2 H); $^{13}$C-NMR (acetone-$d_6$): δ 202.3, 156.3, 145.5, 132.0, 130.9, 130.2, 127.1, 126.7 (overlap of two C), 124.8, 123.1, 115.9, 115.4, 108.1, 107.9.

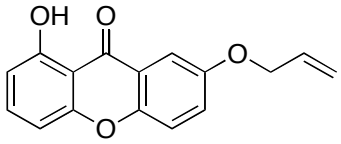


*5,8-Dihydroxy-7H-benzo[c]xanthen-7-one* (**93**): A pressure tube was equipped with a stir bar and charged with the *5,8-Dihydroxy-7H-benzo[c]xanthen-7-one* (18.9 mg, 0.0638 mmol), $H_2O$ (1.6 mL) and DMF (1.0 mL). The resulting solution was sealed at 0 °C and then heated for 16 h at 180 °C. A yellow solid precipitated. The mixture was cooled to 0 °C before opening and diluting with EtOAc (10 mL). The mixture was poured into a separatory funnel. The organic layer was washed with $H_2O$ (2x 10 mL) and brine (1x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow solid that was purified by column chromatography (hexanes:EtOAc; 9:1) to afford the xanthone **93** as a yellow solid (17 mg, 0.064 mmol, 95% yield); $^1$H-NMR (DMSO-$d_6$): δ 12.72 (s, 1 H, exchangeable with $D_2O$), 8.60 (d, *J* = 8.0 Hz, 1 H), 8.27 (d, *J* = 8.0 Hz, IH), 7.81 (dt, *J* = 8.0 Hz, 2H), 7.73 (t, *J* = 8.0 Hz, IH), 7.34 (s, 1 H), 7.26 (d, *J* = 8.0 Hz, IH) 6.82 (d, *J* = 8.0 Hz, IH); $^{13}$C-NMR (DMSO-$d_6$) δ 181.5, 161.0, 155.8, 150.5, 147.8, 137.0, 130.2, 129.5, 128.4, 124.6, 123.3, 123.1, 116.8, 110.4, 109.0, 107.9, 98.8.

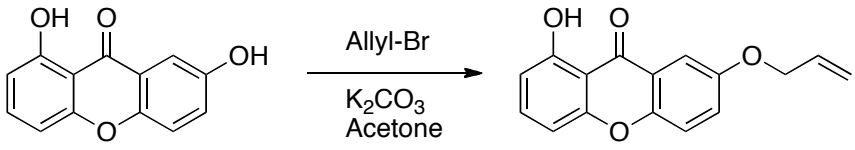



*7-(Allyloxy)-1-methoxy-9H-xanthen-9-one* (**94**): In a 100 mL round bottom flask fitted with a stir bar, 1-methoxy-7-hydroxyxanthone (390.1 mg, 1.610 mmol) was taken up in dry acetone (30 mL). Anhydrous $K_2CO_3$ (447.2 mg, 3.22 mmol) was added to the solution at 0 °C. To the suspension was added allyl bromide (292.8 mg, 205 μL, 2.42 mmol) in acetone (1 mL) over 1 min. The flask was fitted with a heat exchanger and boiled overnight. The mixture was cooled to rt then filtered though Celite and rinsed with acetone. The filtrate was concentrated *in vacuo* then purified by column chromatography (EtOAc:hexanes, 1:1) as a yellowish solid (362 mg, 1.28 mmol, 80 %). $^1$H-NMR (acetone-$d_6$) δ 7.67 (t, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 3 Hz), 7.44 (d, *J* = 8.0 Hz), 7.36 (dd, *J*

= 8.0 Hz, 3.0 Hz), 7.05 (d, *J* = 8.0 Hz), 6.93 (d, *J* = 8.0 Hz), 6.16-6.07 (m, 1H), 5.47 (d, *J* = 16 Hz, 1H) 5.29 (d, *J* = 12 Hz, 1H) 4.68 (d, *J* = 4 Hz, 2H), 3.95 (s, 3H). $^{13}$C-NMR ($CDCl_3$) δ 176.1, 160.5, 157.9, 154.7, 149.6, 134.5, 132.6, 124.2, 123.1, 118.5, 118.0, 111.9, 109.8, 107.3, 105.0, 69.2, 56.3.

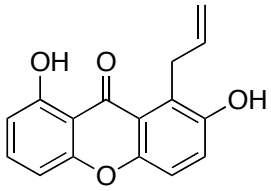



*7-(Allyloxy)-1-hydroxy-9H-xanthene-9-one* (**95**): Dissolved **94** (367 mg, 1.30 mmol) in dry $CH_2Cl_2$ (30 mL), stirred and cooled to –15 °C. Added $BBr_3$ (0.650 mmol, 0.650 mL of 1.0 M solution in $CH_2Cl_2$) dropwise. Slowly allowed the solution to warm to rt overnight. TLC showed a mixture of the desired product, euxanthone and starting material. The reaction mixture was cooled to 0 °C, quenched with sat. aq. $NH_4Cl$, then extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was isolated by column chromatography on silica gel: 5% EtOAc in hexanes eluted the product, 15% eluted euxanthone and 30-75% eluted starting material. The product (232 mg, 0.865 mmol, 67%) was a yellow solid.$^1$H-NMR (300 MHz, $CDCl_3$) δ 12.67 (s, 1H) 7.63 d, *J* = 2.8 Hz, 1H), 7.59 (t, *J* = 8.4 Hz, 1H) 7.44-7.37 (m, 2H), 6.93 (d, *J* = 8.4 Hz), 6.79 (d, *J* = 8.4 Hz, 1H), 6.11-6.05 (m, 1H), 5.48 (d, *J* = 18.4 Hz, 1H), 5.36 (d, *J* = 10.8 Hz, 1H), 4.65 (d, *J* = 5.2 Hz, 2H); HRMS (EI) m/z calcd. for $C_{16}H_{12}O_4$ 268.0736, found 268.0743.

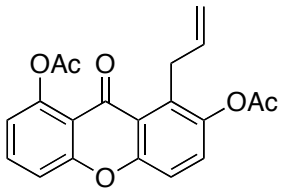



*7-(Allyloxy)-1-methoxy-9H-xanthen-9-one* (**95**) from euxanthone (**10**): In a 100 mL round bottom flash fitted with a stir bar, euxanthone (107.1 mg, 0.469 mmol) was taken up in dry acetone (15 mL). Anhydrous $K_2CO_3$ (130 mg, 0.936 mmol) was added to the slurry at

0 °C. To the solution was added allyl bromide (63 mg, 44 μL, 0.521 mmol) dropwise over 1 min. The flask was fitted with a heat exchanger and boiled overnight. The mixture was cooled to rt then filtered though and rinsed with acetone. The filtrate was concentrated *in vacuo* then purified by column chromatography (5% ethyl acetate in hexanes) as a yellowish solid (71.4 mg, 0.266 mmol, 57 % yield).

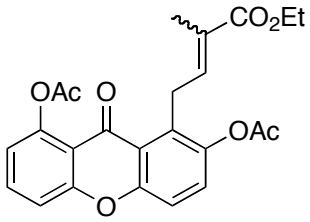



*1-Allyl-2,8-dihydroxy-9H-xanthen-9-one* (**96**): A pressure tube was charged with **95** (232.2 mg, 0.8226 mmol) and mesitylene (10 mL), equipped with a stir bar, cooled to 0 °C, sealed, and then heated at 220-230 °C for 3 h. After cooling to rt, the tube was opened and the reaction mixture was deposited on a column of silica gel in hexanes. The column was flushed with hexanes to remove mesitylene and then eluted with ethyl acetate in hexanes. 5% eluted starting material and 10% to 20% eluted the product (160 mg, 69%), a yellow solid. $^{1}$H-NMR ($CDCl_3$, 400 MHz) δ 7.55 (t, $J$ = 8.4 Hz, 1H), 7.34-7.53 (m, 2H), 6.86 (d, $J$ = 8.4 Hz, 1H), 6.75 (d, $J$ = 8.0 Hz, 1H), 6.20-6.10 (m, 1H), 5.17-5.11 (m, 2H), 4.30 (d, $J$ = 6 Hz, 2H). $^{13}$C-NMR (acetone-$d_6$, 100 MHz) δ 184.8, 162.2, 155.9, 151.8, 151.7, 137.0, 136.8, 126.3, 124.2, 118.9, 116.9, 114.3, 109.8, 109.1, 106.4, 31.1; HRMS (EI) m/z calcd. for $C_{16}H_{12}O_4$ 268.0736, found 268.0737.

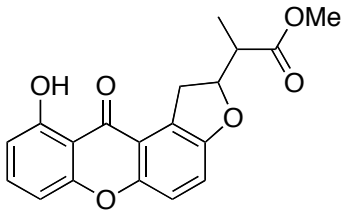



*8-Allyl-9-oxo-9H-xanthene-1,7-diyl diacetate* (**97**): Dissolved the diol (159.7 mg, 0.5953 mmol) and DMAP (7.3 mg, 0.06 mmol) in dry THF (15 mL) at rt with stirring. Added $Ac_2O$ (0.169 mL, 1.79 mmol) followed by dry $Et_3N$ (0.249 mL, 1.79 mmol). After 3 h,

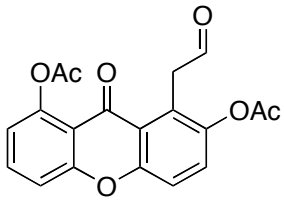
quenched with sat. aq. $NH_4Cl$ then extracted with ether. Dried the organic layer over $MgSO_4$ and concentrated *in vacuo* to reveal a white solid (198 mg, 0.562 mmol, 94%), which was used without further purification. $^1$H-NMR (acetone-$d_6$, 400 MHz) δ 7.63 (t, *J* = 8 Hz, 1H), 7.58 (d, *J* = 8 Hz, 1H), 7.53-7.48 (m, 2H), 7.08 (d, *J* = 8 Hz, 1H), 5.08 (d, *J* = 17 Hz, 1H), 4.94 (d, *J* = 12 Hz, 1H), 4.01 (d, *J* = 8 Hz, 2H)), 2.38 (s, 3H) 2.35 (s, 3H).




*8-(4-Ethoxy-3-methyl-4-oxobut-2-en-1-yl)-9-oxo-9H-xanthene-1,7-diyl diacetate* (**98**). In a 100 mL round bottom flask fitted with a stir bar, the allyl diacetate **97** (136.6 mg, 0.388 mmol) was dissolved in dry $CH_2Cl_2$ (10 mL). The flask was plugged with cotton and cooled to –78 °C. Ozone was bubbled through the solution until the blue color persisted (10 min). The solution was then purged with Ar (20 min) followed by addition of solid $PPh_3$ (152.5 mg, 0.5816 mmol). The mixture was stirred at –78 °C for 1.5 h and then the ice bath was removed. After warming to room temperature, the stabilized Wittig salt (633 mg, 1.94 mmol) was added in $CH_2Cl_2$ (5 mL). The reaction mixture was stirred at rt overnight then concentrated *in vacuo* to reveal a rose-colored residue, which was purified by column chromatography: 5% ethyl acetate in hexanes followed by 50% to afford the title compound (72.6 mg, 0.616 mmol, 43% yield). $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.66 (t, *J* = 8.4 Hz, 1H) 7.40-7.34 (m, 3H), 6.97 (d, *J* = 6.9 Hz, 1H), 6.68 (t, *J* = 6.3 Hz, 1H), 4.18-4.11 (m, 4H, overlap of Ar**CH$_2$**- and –O**CH$_2$**$CH_3$), 2.44 (s, 3H), 2.35 (s, 3H), 2.06 (s, 3H), 1.24 (t, *J* = 7.2 MHz)




*Methyl 2-(10-hydroxy-11-oxo-2,11-dihydro-1H-furo[3,2-a]xanthen-2-yl)propanoate* (**111**). In a 25 mL round bottom flask, **98** (14.5 mg, 3.31 x $10^{-2}$ mmol) was dissolved in dry MeOH (5 mL). The solution was cooled to 0 °C and then a solution of 1.04 M NaOMe in MeOH (67 μL, 7.0 x $10^{-2}$ mmol) was added dropwise. The reaction mixture was slowly warmed to rt and then quenched with 1 N HCl. After extraction with ether, the organic layer was washed with water, dried (brine, $MgSO_4$) and concentrated *in vacuo*. Column chromatography with 5-10% ethyl acetate in hexanes afforded the product (11 mg, 3.23 x $10^{-2}$ mmol, 97%). $^1$H-NMR ($CDCl_3$, 400 MHz) δ 7.56 (t, *J* = 8 Hz, 1H), 7.27 (d, *J* = 8 Hz, 1H), 7.18 (d, *J* = 8 Hz, 1H), 6.89 (d, *J* = 8 Hz, 1H), 6.75 (d, *J* = 8 Hz, 1H), 5.21-5.12 (m, 1H), 4.00-3.91 (m, 1H), 3.74 (s, 3H), 3.65-3.55 (m, 1H), 2.87-2.79 (m, 1H), 1.34 (d, *J* = 7 Hz).




*9-Oxo-8-(2-oxoethyl)-9H-xanthene-1,7-diyl diacetate* (**121**): A 100-mL round bottom flask was charged with **97** (62.6 mg, 0.1777 mmol) and $CH_2Cl_2$ (10 mL), fitted with a stir bar and plugged with cotton. While cooling to –78 ºC, first ozone was bubbled through the solution for 20 min and then Ar was bubbled through for 20 min. Then solid triphenyl phosphine (70 mg, 0.267 mmol) was added all at once and stirring continued for 1 h before the ice bath was removed and the solution was allowed to warm spontaneously to rt. The reaction mixture was then concentrated *in vacuo* and purified on a column of

$SiO_2$, first with five percent ethyl acetate in hexane followed by 1:1 to afford the title compound (25.7 mg, 0.0725 mmol, 41% yield); $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.69 (t, *J* = 8.5 Hz), 7.51-7.44 (m, 2H), 7.39 (dd, J = 8.9 Hz, 1.1 Hz, 1H), 6.99 (dd, J = 7.83 Hz, 1.1 Hz, 1H), 4.22 (s, 2H), 2.44 (s, 3H) 2.35 (s, 3H). $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 197.6, 177.2, 169.7, 169.1, 156.5, 154.3, 150.1, 145.8, 134.7, 129.2, 126.9, 120.7, 118.4, 118.3, 115.8, 115.1, 41.5, 21.2, 20.8; HRMS (EI) m/z calcd M + 1 for $C_{19}H_{15}O_7$ 355.0812, found 355.0816.

**REFERENCES**


1. Roberts, J.C. Naturally occurring xanthones. *Chem. Rev.* **1961,** *61*, 591-605.

2. Pres, V.; Nagem, T.J. Trioxygenated naturally occurring xanthones. *Phytochemistry*, **1997**, *44*, 191.

3. Peres, V.; Nagem, T.J. Naturally occurring pentaoxygenated, hexaoxygenated and dimeric xanthones: A literature survey. *Quim. Nova*, **1997,** *20*, 388-397.

4. Peres, V.; Nagem, T.J.; de Oliveira, F.F. Tetraoxygenated naturally occurring xanthones. *Phytochemistry*, **2000,** *55*, 683-710.

5. Vieira, L.M.M.; Kijjoa, A. Naturally-Occuring Xanthones: Recent Developments. *Curr. Med. Chem.*, **2005,** *12,* 2413-2446.

6. El-Seedi, H.R.; El-Ghorab, D.M.H.; El-Barbary, M.A.; Zayed, M.F.; Goeransson, U.; Larsson, S.; Verpoorte, R. Naturally Occurring Xanthones; Latest Investigations: Isolation, Structure Elucidation and Chemosystematic Significance. *Curr. Med. Chem.* **2009,** *16*, 2581.

7. Mandal, S.; Das, P.C., Joshi, P.C. *J. Indian Chem. Soc.*, **1992,** *69*, 611.

8. Diderot, N.T.; Silvere, N., Etienne, T. Xanthones as therapeutic agents: chemistry and pharmacology. *Adv. Phytomed.* **2006,** *2*, 273.

9. Bo, T.; Liu, H., Separation methods for pharmacologically active xanthones, *J. Chromatogr. B*, **2004,** *812*, 165-174.

10. Pinheiro, L.; Nakamura, C.V.; Filho, B.P.D.; Ferreira, A.G.; Young, M.C.M.; Cortez, D.A.G. Antibacterial xanthones from *Kielmeyera variabilis* Mart. (Clusiaceae). *Mem. Inst. Oswaldo Cruz*, **2003,** *98*, 549.

11. Fukai, T.; Yonekawa, M.; Hou, A.-J.; Nomura, T.; Sun, H.-D.; Uno, J. Antifungal Agents from the Roots of *Cudrania cochinchinensis* against *Candida, Cryptoccoccus,* and *Aspergillus* Species. *J.Nat Prod.*, **2003,** *66,* 1118.

12. Don, M.-J.; Huang, Y.-J.; Huang, R.-L.; Lin, Y.-L., New Phenolic Principles from *Hypericum sampsonii*. *Chem. Pharm. Bull.*, **2004,** *52*, 866.

13. Groweiss, A.; Cardellina, II, J.H.; Boyd, M.R., HIV-Inhibitory Prenylated Xanthones and Flavones from *Maclura tinctoria*. *J. Nat. Prod.*, **2000,** *63*, 1537.

14. Abe, F.; Nagafuji, S.; Okabe, H.; Higo, H.; Akahane, H., Trypanocidal Constituents in Plants 2. Xanthones from the stem bark of *Garcinia subelliptica*. *Biol. Pharm. Bull.*, **2003,** *26*, 1730.

15. Abe, F.; Nagafuji, S.; Okabe, H.; Akahane, H.; Estrada-Muniz, E.; Huerta-Reyes, M.; Reyes-Chilpa, R., Trypanocidal Constituents in Plants 3. Leaves of *Garcinia intermedia* and Heartwood of *Calophyllum brasiliense*. *Biol. Pharm. Bull.*, **2004,** *27*, 141.

16. Thoison, O.; Fahy, J.; Dumontet, V.; Chiaroni, A.; Riche, C.; Tri, M.V.; Sévenet, T. *J.* Cytotoxic prenylxanthones from *Garcinia bracteata*. *Nat. Prod.*, **2000,** *63*, 441.

17. Nkengfack, A.E.; Azebaze, G.A.; Vardamides, J.C.; Fomum, Z.T.; van Heerden, F.R. A prenylated xanthone from *Allanblackia floribunda*. *Phytochemistry*, **2002,** *60*, 381.

18. Pettit, G.R.; Zhang, Q.; Pinilla, V.; Herald, D.L.; Doubek, D.L.; Duke, J.A. Isolation and Structure of Gustastatin from the Brazilian Nut Tree *Gustavia hexapetala*. *J. Nat. Prod.*, **2004,** *67*, 983.

19. Oldenburg, T.B.P.; Wilkes, H.; Horsfield, B.; van Duin, A.C.T.; Stoddart, D.; Wilhelms, A. Xanthones—novel aromatic oxygen-containing compounds in crude oils. *Org. Geochem.*, **2002,** *33*, 595.

20. Carvalho, M.J.; Carvalho, L.M.; Ferreira, A.M.; Silva, A.M.S. A new xanthone from *Hedychium gardnerianum*. *Nat. Prod. Res.*, **2003,** *17*, 445.

21. Kijjoa, A.; Gonzalez, M.J.; Pinto, M.M.M.; Silva, A.M.S.; Anantachoke, C.; Herz, W. Xanthones from *Calophyllum teysmannii* var. *inophylloide*. *Phytochemistry*, **2000,** *55*, 833.

22. Macías, M.; Gamboa, A.; Ulloa, M.; Toscano, R.A.; Mata, R. Phytotoxic naphthopyranone derivatives from the coprophilous fungus *Guanomyces polythrix*. *Phytochemistry*, **2001,** *58*, 751.

23. Yin, Z.-Q.; Wang, Y.; Ye, W.-C.; Zhao, S.-X. Chemical constituents of *Hypericum perforatum* (St. John's wort) growing in China. *Biochem. Systematics Ecol*. **2004,** *32*, 521-523.

24. Henry and Caventou. *J. Pharm. Chim*., **1821,** *7*, 178-179.

25. Hong, D.; Yin, F.; Hu, L.-H.; Lu, P. Sulfonated xanthones from *Hypericum sampsonii*. *Phytochemistry*, **2004,** *65*, 2595.

26. Seo, E.-K.; Kim, N.-C.; Wani, M.C.; Wall, M.E.; Navarro, H.A.; Burgess, J.P.; Kawanishi, K.; Kardono, L.B.S.; Riswan, S.; Rose, W.C.; Fairchild, C.R.; Farnsworth, N.R.; Kinghorn, A.D. Cytotoxic Prenylated Xanthones and the Unusual Compounds Anthraquinobenzophenones from *Cratoxylm sumatranum*. *J. Nat. Prod*., **2002,** *65*, 299.

27. Valentao, P.; Andrade, P.B.; Silva, E.; Vicente, A.; Santos, H.; Bastos, M.L.; Seabra, R.M. Methoxylated xanthones in the quality control of small centaury (*Centaurium erythraea*) flowering tops. *J. Agric. Food Chem*., **2002,** *50*, 460.

28. Jankovic, T.; Krstic, D.; Savinkin-Fodulovic, K.; Menkovic, N.; Menkovic, N.; Grubisic, D. Xanthones and secoiridoids from hairy root cultures of *Centaurium erythraea* and *C-pulchellum*. *Planta Med*., **2002,** *68*, 944.

29. Krstic, D.; Jankovic, T.; Savinkin-Fodulovic, K.; Menkovic, N.; Grubisic, A. Secoiridoids and xanthones in the shoots and roots of *Centaurium pulchellum* cultured *in vitro*. *In Vitro Cell. Dev. Biol. – Plant*, **2003,** *39*, 203.

30. Morel, C.; Séraphin, D.; Oger, J.-M.; Litaudon, M.; Sévenet, T.; Richomme, P.; Bruneton, J. New xanthones from *Calophyllum caledonicum*. *J. Nat. Prod*., **2000,** *63*, 1471.

31. Hay, A.-E.; Guilet, D.; Morel, C.; Larcher, G.; Macherel, D.; Le Ray, A.-M.; Litaudon, M.; Richomme, P. Antifungal chromans inhibiting the mitochondrial respiratory chain of pea seeds and new xanthones from *Calophyllum caledonicum*. *Planta Med*., **2003,** *69*, 1130.

32. Pinheiro, L; Cortez, D.A.G.; Vidotti, G.J.; Young, MC.M.; Ferreira, A.G. Phytochemical study and evaluation of the molluscicdal activity of *Kielineyera voriabilis* MART. (*Clusiaceae). Quim. Nov*, **2003,** *26*, 157.

33. Ishiguro, K.; Nagata, S.; Oku, H.; Yamaki, M. Bisxanthones from *Hypericum japonicum*: inhibitors of PAF-induced hypotension. *Planta Med*. **2002,** *68* 258.

34. Elix, J.A., Bennett, S.A. 6-*O*-Methylarthothelin and 1,3,5-tri-*O*-methylarthothelin, 2 new xanthones from a *Dimelaena lichen*. *Aust. J. Chem*. **1990,** *43*, 1587.

35. Elix, J.A., Bennett, S.A., Jiang, H. 2,5-Dichloro-6-methylnorlichexanthone and 4,5-dichloro-6-*O*-methylnorlichexanthone, 2 new xanthones from an Australian *Dimelaena lichen*. *Aust. J. Chem*. **1991,** *43*, 1157.

36. Fujita, M.; Inoue, T. Biosynthesis of mangiferin in *Anemarrhena asphodeloides* bunge. I. The origin of the xanthone nucleus. *Chem. Pharm Bull*. **1980,** *28*, 2476.

37. Locksley, H.D., Murray, I.G. Extractives from *Guttiferae*. 16. Biogenetic-type synthesis of xanthones from their benzophenone precursors. *J. Chem Soc. (C)*. **1970,** *2*, 392.

38. Gupta, P.; Lewis, J.R. Biogenesis of xanthones in *Gentiana lutea*. *J. Chem. Soc. (C)*. **1971,** *4*, 629.

39. McMaster, W.J.; Scott, A.I.; Trippett, S. Metabolic Products of *Penicillum patulum*. *J. Chem Soc*. **1960,** 4628.

40. Birch A.J.; Baldas, J.; Hlubucek, J.R.; Simpson T.J., Westerman, P.W. Biosynthesis of fungal xanthone ravenelin. *J. Chem. Soc. Perkin Tran. I*. **1976,** *8*, 898.

41. Carpenter, I.; Locksey, H.; Scheinman, F. Xanthones in higher plants: Biogenetic proposals and a chemotaxonomic survey. *Phytochemistry*, **1969,** *8*, 2013.

42. Lewis, J.R. Oxidative coupling. 6. Synthesis of xanthones. *J. Chem. Soc*. **1964,** 5074.

43. Atkinson, J.E.; Gupta, P.; Lewis, J.R. Benzophenone participation in xanthone biosynthesis (*Gentianaceae*). *Chem. Commun*. **1968,** 1386.

44. Ellis, R.C.; Whalley, W.B.; Ball, K. Biogenetic-type synthesis of xanthones. *Chem. Commun*. **1967,** 803.

45. Markham, K.R. Gentian pigements. 2. Xanthones from *Gentiana bellidifolia*. *Tetrahedron*, **1965,** *21*, 1449.

46. Gottlieb, O.R. Biogenetic proposals regarding aucuparinas and xanthones. *Phytochemistry*, **1968,** *7*, 411.

47. Pinto, M.; Sousa, E.; Nascimento, M.S.J. Xanthone Derivatives: New Insights in Biological Activities. *Curr. Med. Chem*. **2005,** *12*, 2517.

48. Sousa, M.E.; Pinto, M.M.M. Synthesis of Xanthones: An Overview. *Curr. Med. Chem*. **2005,** *12*, 2447.

49. Michael, A. *Ann. Chem. J*., **1883,** *5*, 81.

50. Kostanecki, S. *Ber*., **1891,** *24*, 1898.

51. Grover, P.K.; Shah, G.D.; Shah, R.C. Xanthones. 4. A new synthesis of hydroxyxanthones and hydroxybenzophenones. *J. Chem. Soc*. **1955,** 3982.

52. Muller, P.; Venakis, T.; Eugster, C.H. Activated quinones—*O*-addition versus *C*-addition of phenols—new regiospecific syntheses of xanthones, thioxanthones and *N*-methyl-9-acridones. *Helv. Chim. Acta*. **1985,** *68*, 2359.

53. Scheinmann, F.; Quillinan, A.J. Studies in xanthone series. 12. General synthesis of polyoxygenated xanthones from benzophenone precursors. *J. Chem. Soc. Perkin Trans. I* **1973,** *2*, 1329.

54. Dean, M.F.; Goodchild, J.; Houghton, L.E.; Martin, J.A.; Morton, R.B.; Parton, B.; Price, A.W.; Somvichien, N. Boron trichloride as a selective demethylating agent. *Tetrahedron Letters*, **1966,** 4153.

55. Iikubo, K.; Ishikawa, Y.; Ando, N.; Umezawa, K.; Nishiyama, S. The first direct synthesis of α-mangostin, a potent inhibitor of the acidic sphingomyelinase. *Tetrahedron Letters*, **2002,** *43*, 291.

56. Finnegan, R.A.; Merkel, K.E. Synthesis of 2,5-dihydroxyxanthone and 4,5-dihydroxyxanthone. *J. Org. Chem*. **1972,** *37*, 2986.

57. Zhou, C.; Larock, R.C. Synthesis of aryl ketones or ketimins by palladium-catalyzed arene C-H addition to nitriles. *J. Org. Chem*. **2006,** *71*, 3551.

58. Moroz, A.A.; Shvartsberg, M.S. The Ullmann ether condensation. *Russ. Chem. Rev.* **1974,** *43*, 697.

59. Davies, J.S.H.; Lamb; F.; Suschitzky, H. Studies in the xanthone series. 2. Preparation and reaction of 1-formyl-2-hydroxyxanthone. *J. Chem. Soc.* **1958,** 1790.

60. Jackson, W.T.; Boyd, R.J.; Froelich, L.L.; Gapinski, D.M.; Mallett, B.E.; Sawyer, .S. Design, synthesis, and pharmacological evaluation of potent xanthone dicarboxylic-acid leukotriene-B4 receptor antagonists. *J. Med. Chem.* **1993,** *36*, 1726.

61. Elix, J.A.; Gaul, K.L.; Jiang, H. The structure and synthesis of some minor xanthones from the lichen *Rinodina thiomela*. *Aust. J. Chem.* **1993,** *46,* 95.

62. Familoni, O.B.; Ionica, I.; Bower, J.F.; Snieckus, V. Intramolecular anionic Friedel-Crafts equivalents. A general regiospecific route to substituted and naturally occurring xanthen-9-ones. *Synlett,* **1997,** 1081.

63. Sousa, E.P.; Silva, A.M.S.; Pinto, M.M.M.; Pedro, M.M.; Cerqueira, A.M. Isomeric kielcorins and dihydroxyxanthones: Synthesis, structure elucidation, and inhibitory activities of growth of human cancer cell lines and on the proliferation of human lymphocytes *in vitro*. *Helv. Chim. Acta*. **2002,** *85*, 2862.

64. Kolokythas, G.; Kostakis, I.K.; Pouli, N.; Marakos, P.; Kletsas, D.; Pratsinis, H. Synthesis and cytotoxic activity of some new azapyranoxanthenone aminoderivatives. *Bioorg. Med. Chem.*, **2003,** *11*, 4591.

65. Reisch, J.; Mester, I.; El-Moghazy Aly, S.M. Synthesis of acronycine isosters. *J. Chem. Soc., Perkin Trans 1*. **1983,** 219.

66. Hauser, F.M.; Dorsch, W.A. A new regiospecific preparation of xanthones. *Org. Lett*. **2003,** *5*, 3753.

67. Liebeskind, L.S.; Sun, L. Novel construction of highly-substituted xanthones. *J. Am. Chem. Soc*. **1996,** *118*, 12473.

68. Himeshima, Y.; Sonoda, T.; Kobayashi, H. Fluoride-induced 1,2-elimination of *ortho*-trimethylsilylphenyl triflate to benzyne under mild conditions. *Chem. Lett*. **1983,** 1211.

69. Zhao, J.; Larock, R.C. One-pot synthesis of xanthones and thioxanthones by the tandem coupling—Cyclization of arynes and salicylates. *Org. Lett*. **2005,** *7*, 4273.

70. Dubrovskiy, A.V.; Larock, R.C. Intermolecular C—O addition of carboxylic acids to arynes. *Org. Lett.* **2010,** *12*, 3117.

71. Santos, L.C.; Piacente, S.; De Riccardis F.; Eletto, A.M.; Pizza, C.; Vilegas, W. Xanthones and flavonoids from *Leiothrix curvifolia* and *Leiothrix flavescens*. *Phytochemistry*, **2001,** *56*, 853.

72. Mulholland, D.A.; Koorbanally, C.; Crouch, N.R.; Sandor, P. Xanthones from *Drimiopsis maculata*. *J. Nat. Prod.*, **2004,** *67*, 1726.

73. Rezanka, T.; Jachymova, J.; Dembitsky V.M. Prenylated xanthone glucosides from Ural's lichen *Umbilicaria proboscidea*. *Phytochemistry*, **2002,** *62*, 607.

74. Andreu, G.L.P.; Maurmann, N.; Reolon, G.K.; de Farias, C.B.; Schwartsmann, G.; Delgado, R.; Roesier, R. Mangiferin, a naturally occurring glucoxilxanthone improves long-term memory recognition in rats. *Eur. J. Pharmacol.* **2010,** *635*, 124.

75. Dang, A.-T.; Miller, D.O., Dawe, L.N.; Bodwell, G.J. Electron-Deficient Dienes. 5. An Inverse-Electron-Demand Diels—Alder Approach to 2-Substituted 4-Methoxyxanthones and 3,4-Dimethoxyxanthones. *Org. Lett.* **2008,** *10*, 233.

76. Nguyen, H.T.; Lallemand, M.-C.; Boutefnouchet, S.; Michel, S.; Tillequin, F. Antitumor *Psoropermum* Xanthones and *Sarcomelicope* Acridones: Privileged Structures Implied in DNA Alkylation. *J. Nat. Prod.* **2009,** *72*, 527.

77. Leet, J.E.; Liu, X.; Drexler, D.M.; Cantone, J.L.; Huang, S.; Mamber, S.W.; Fairchild, C.R.; Hussain, R.; Newman, D.J.; Kingston, D.G.I. Cytotoxic Xanthones from *Psorospermum molluscum* from the Madagascar Rain Forest. *J. Nat. Prod.* **2008,** *71*, 460.

78. Kupchan, S.M.; Streelman, D.R.; Sneden, A.T. Psorospermin, a New antileukemic xanthone from *Psorospermum febrifugum*. *J. Nat. Prod.* **1980,** *43*, 296.

79. Bressler, R. Herb-drug interactions. St. John's wort and prescription medications. *Geriatrics*, **2005,** *60*, 21.

80. Kraus, G.A.; Bae, J.; Schuster, J. The First Synthesis of a Diyone from *Echinacea pallida*. *Synthesis*, **2005,** 3502.

81. Naidu, M.; Kuan, C.-Y.K; Lo, W.-L.; Raza, M.; Tolkovska, A.; Mak, N.-K.; Wong, R.N.-S.; Keynes, R. Analysis of the action of Euxanthone, a Plant-

Derived Compound that Stimulates Neurite Outgrowth. *Neuroscience,* **2007,** *148(4)*, 915.

82. Llikhitwitayawuid, K.; Chanmahasathien, W.; Ruangrungsi, N.; Krungkrai, J. Xanthones with Antimalarial Activity from *Garcinia dulcis*. *Planta Medica*, **1998,** *64(3)*, 281.

83. Reutrakul, V.; Chanakul, W.; Pohmakotr, M.; Jaipetch, T.; Yoosook, C.; Kasisit, J.; Napaswat, C.; Santisuk, T.; Prabpai, S.; Kongsaeree, P.; Tuchinda, P. Anti-HIV-1 Constituents from Leaves and Twigs of *Cratoxylum arborescens*. *Planta Medica*, **2006,** 72(15), 1433.

84. Lin, L.-L.; Huang, F.; Chen, S.-B.; Yang, D.-J.; Chen, S.-L.; Yang, J.-S.; Xiao, P.-G. Xanthones from the Roots of *Polygala caudate* and their Antioxidation and Vasodilation Activities *in vitro*. *Planta Medica*, **2005,** *71*, 32.

85. Patel, G.N.; Trivedi, K.N. A Convenient Synthesis of Naturally Occuring Xanthones. *Synthetic Commun*., **1989,** *19*, 1641.

86. (a) Kraus, G.A.; Kirihara, M., Quinone photochemistry. A general synthesis of acylhydrochinones, *J. Org. Chem*. **1992,** *57*, 3256.; (b) Kraus, G.A. and Liu, P., Benzophenone-mediated conjugated additions of aromatic aldehydes to quinones, *Tetrahedron Lett*. **1994,** *35*, 7723.; (c) Kraus, G.A., Kirihara, M., and Wu, Y., A photochemical alternative to certain Friedel-Crafts reactions, in *Benign by Design. Alternative Synthetic Design for Pollution Prevention*, Anastas, P.T. and Farris, C.A., Eds., ACS Symposium Series 577, American Chemical Society, Washington D.C., 76-83, 1994; (d) Kraus, G.A., Maeda, H., Lui, P., Melekhov, A., and Lu, Y., A photochemical alternative to certain Friedel-Crafts reactions, in Green Chemistry: *Frontiers in Benign Chemical Syntheses and Processes,* Anastas, P.T. and Williamson, T.C., Eds., Oxford University Press, Oxford, 1998, chap. 4. 72-86; (e) Pacut, R., Grimm, M.L., Kraus, G.A., and Tanko, J.M., Photochemistry in supercritical carbon dioxide. The benzophenone-mediated addition of aldehydes to α,β-unsaturated carbonyl compounds, *Tetrahedron Lett*. **2001,** *42* 1415.

87. Schiel, C., Oelgemöller, M., Ortner, J., and Mattay, J., Green photochemistry: the solar-chemical photo-Friedel-Crafts acylation of quinones, *Green Chem*., *3*, 224-228, 2001.

88. Snieckus, V., Cuevas, J.C., Sloan, C.P., Liu, H., and Curran, D.P. Intramolecular α-Amidoyl to Aryl 1,5-Hydrogen Atom Transfer Reactions. Heteroannulation and α-Nitrogen Functionalization by Radical Translocation. *J. Am. Chem. Soc*. **1990,** *112*, 896.

89. Kobayashi, K., Suzuki, M., Takeuchi, H., Konishi, H.S., Suginome, H. Photoinduced Molecular Transformations. Part 147. Photoacylation and Photoalkylation of 2-Arylamino- and 2-Alkylamino-1,4-napthoquinones. *J. Chem. Soc., Perkin Trans. 1*, **1994,** 1099.

90. M. Oelgemöller and J. Mattay, The photochemical Friedel-Crafts acylation of quinones—From the beginnings of organic photochemisty to modern solarchemical applications, in *Handbook of Organic Photochemistry and Photobiology*, ed. W. Horspool and F. Lenci, CRC press, Boca Raton, 2nd edn, 2003, 88/1–88/45.

91. Mondal, M.; Puranik, V.G.; Argade, N.P. Facile Syntheis of 1,3,7-Trihydroxyxanthone and Its Regioselective Coupling Reactions with Prenal: Simple and Efficient Access to Osajaxanthone and Nigrolineaxanthone F. *J. Org. Chem.* **2006,** *71*, 4992.

92. Likhitwitayawuid, K.; Chanmahasathien, W.; Ruangrungsi, N.; Krungkrai, J. Xanthones with Antimalarial Activity from *Garcinia dulcis*. *Planta Medica* **1998,** *64*, 281.

93. Kraus, G.A.; Fulton, B.S. Tandem Claisen-Diels-Alder Reactions in Synthesis. A Facile Approach to Anthracyclines. *J. Org. Chem.* **1985,** *50*, 1782.

94. Bruce, J.M.; Roshan-Ali, Y. Claisen Rerrangement of Meta-Substituted Allyl Phenyl Ethers. J. *Chem. Soc., Perkin Trans. 1*. **1981,** 2677.

95. Hassfeld, J.; Eggert, U.; Kalesse. Synthesis of the C1—C7 Macrolactone of Tedanolide. *Synthesis*, **2005,** *7*, 1183.

96. Baktharaman, S.; Afagh, N.; Vandersteen, A.; Yudin A. K. Unprotected Vinyl Aziridines: Facile Synthesis and Cascade Transformations. *Org. Lett.* **2010,** *12*, 240.

97. Robiette, R.; Richardson, J.; Aggarwal, V.K.; Harvey, J.N. On the Origin of High *E* Selectivity in the Wittig Reaction of Stabilized Ylides: Importance of Dipole—Dipole Interaction. *J. Am. Chem. Soc.* **2005,** *127*, 13468.

98. Ritter, Tobias; Hejl, A. Wenzel, A.G.; Funk, T.W; Grubbs, R.H. A Standard System of Characterization for Olefin Metathesis Catalysts. *Organometallics*, **2006,** *25*, 5740.

99. Habib, A.M.; Ko, D.K.; Masuda, S.; McCloud, T.; Reddy, K.S.; Aboushoer, M.; McKenzie, A.; Byrn, S.R.; Chang, C.-J.; Cassady, J.M. Structure and Stereochemistry of Psorospermin and Related Cytotoxic Dihydrofuranoxanthones from *Psorospermum febrifugum*. *J. Org. Chem.* **1987,** *52*, 412.

100. Ho, D.K.; McKenzie, A.T.; Byrn, S.R.; Cassady, J.M. $O^5$-Methyl-(±)-(2´*R*,3´*R*)-psorospermin. *J. Org. Chem.* **1987,** *52*, 342.

101. Schwaebe, M.K.; Moran, T.J.; Whitten, J.P. Total synthesis of psorospermin. *Tetrahedron Letters*. **2005,** *46*, 827.

102. Still, W.C.; Gennari, C. Direct Synthesis of *Z*-Unsaturated Esters. A Useful Modification of the Horner-Emmons Olefination. *Tetrahedron Letters*. **1983,** *41*, 4405.

103. Katsuki, T.; Sharpless, K.B. The first practical method for asymmetric epoxidation. *J. Am. Chem. Soc*. **1980,** *102*, 5974.

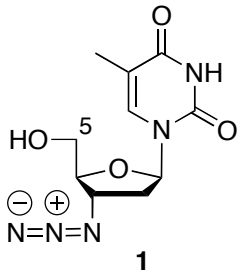
104. Wenkui, L.; Chan, C.-L.; Leung, H.-W.; Yeung, H.-W.; Xiao, P. Xanthones from *Polygala caudata*. *Phytochemistry* **1999**, *51*, 953.

105. Locksley, H.D.; Moore, I.; Scheinmann, F. Extractives from *Guttiferae*. Part II. The isolation and structure of four polyhydroxyxanthones in *Symphonia globulifera* L. *J. Chem. Soc. C*. **1966**, 430.

# CHAPTER 3: SYNTHESIS OF CHROMAN ALDEHYDES THAT INHIBIT HIV

## INTRODUCTION

Since 1983 the Human Immunodeficiency Virus (HIV) / AIDS has been a worldwide health problem.[1] At the end of 2009, an estimated 33.3 million people were living with HIV, a retrovirus in the lentivirus subfamily. HIV-1 is the more pathogenic of the two known HIV types.[2] Before the first anti-HIV drug—zidovudine[3] (AZT) (Figure 1)—was brought to market in 1987, infection with HIV quickly led to AIDS and then death. Now there are 25[3] approved drugs belonging to seven different classes of antiviral drugs that are used in combination therapy known as highly active antiretroviral therapy (HAART).[4] With this therapy, HIV is now a chronic infection that can be controlled for years. However, there is still no vaccine that prevents the infection or therapy that cures the disease and eliminates all infectious particles despite substantial research.[2] A keyword search of "HIV" in the ISI Web of Knowledge[SM] covering 2009-2011 resulted in 40,916 published papers.




**1**

**Figure 1.** Zidovudine, the first drug against HIV

Discovering and developing drugs for HIV is based on knowledge of the viral life cycle, which is divided into roughly ten different steps: virus-cell adsorption, virus-cell fusion, uncoating, reverse transcription, integration, DNA replication, transcription,

translation, budding (assembly/release), and maturation.[2,4] The 25 anti-HIV drugs are categorized into seven groups (Table 1) based on the effects the drugs have on the viral life cycle. These groups are (i) nucleoside reverse transcriptase inhibitors (NRTIs); (ii) nucleotide reverse transcriptase ininhibitors (NtRTIs); (iii) non-nucleoside reverse transcriptase inhibitors (NNRTIs); (iv) protease inhibitors (PIs); (v) fusion inhibitors (FIs); (vi) co-receptor inhibitors (CRIs); and (vii) integrase inhibitors.[4]

**Table 1**[2]: Approved antiretroviral drugs

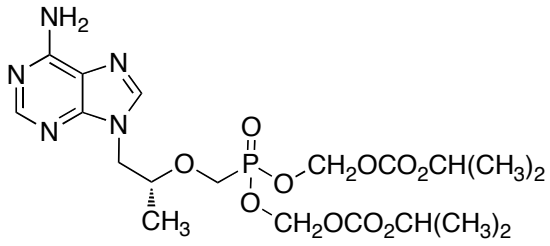
| | Approval date |
|---|---|
| **Co-receptor inhibitors (CRIs)** | |
| Maraviroc (UK-427,857, Selzentry®) | 06 August 2007 |
| **Fusion inhibitors (FIs)** | |
| Enfuvirtide (T20, Fuzeon®) | 13 March 2003 |
| **Integrase inhibitors** | |
| Raltegravir (MK-0518, Isentress®) | 12 October 2007 |
| **Reverse transcriptase inhibitors** | |
| **Nucleoside/nucleotide analogues (NRTIs/NtRTIs)** | |
| Abacavir (ABC, Ziagen®) | 17 December 1998 |
| Didanonise (ddI, Videx®) | 09 October 1991 |
| Emtricitabine (FTC, Emtriva®) | 02 July 2003 |
| Stavudine (d4T, Zerit®) | 24 June 1994 |
| Lamivudine (3TC, Epivir®) | 17 November 1995 |
| Tenofovir (DF, Viread®) | 26 October 2001 |

| | |
|---|---|
| Zalcitabine (ddc, Hivid®) | 19 June 1992 |
| Zidovudine (AZT, Retrovir®) | 19 March 1987 |
| **Non-nucleoside inhibitors (NNRTIs)** | |
| Delavirdine (DLV, Rescriptor®) | 4 April 1997 |
| Efavirenz (EFV, Sustiva®) | 17 September 1998 |
| Etravirine (TMC125, Intelence®) | 18 January 2008 |
| Nevirapine (NVP, Viramune®) | 21 June 1996 |
| **Protease inhibitors (PIs)** | |
| Amprenavir (AMP, Agenerase®) | 15 April 1999 |
| Atazanavir (ATZ, Reyataz®) | 20 June 2003 |
| Darunavir (TMC-114, Prezista®) | 23 June 2006 |
| Fosamprenavir (GW-433908, Lexiva®) | 20 October 2003 |
| Indinavir (IDV, Crixivan®) | 13 March 1996 |
| Lopinavir (ABT-378, Kaletra® (trade name in combination with RTV)) | 15 September 2000 |
| Nelfinair (NFV, Viracept®) | 14 March 1997 |
| Ritonavir (RTV, Norvir®) | 01 March 1996 |
| Saquinavir (SQV, Fortovase®, Invirase®) | 07 November 1997 |
| Tipranavir (TPV, Aptivus®) | 22 June 2005 |

Nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine (**1**) and nucleotide reverse transcriptase ininhibitors (NtRTIs) target HIV reverse transcriptase at the catalytic substrate (dNTP) binding site and an allosteric site. NRTIs are converted to

their activate forms in the cell by kinases, which phosphorylate the 5´-hydroxy group three times. The resulting triphosphosphates are competitive inhibitors or alternative substrates during chain elongation, which is terminated by NRTIs.[4]

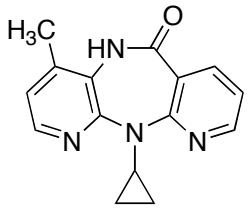
Tenofovir (**2**) (Figure 2) is the only approved nucleotide reverse transcriptase inhibitor (NtRTI). The compound contains a phosphonate group that is analogous to a phosphate group, so **2** requires only two phosphorylation steps before is converted to the active metabolite. Also, the phosphonate cannot be cleaved by esterases as is the case with phosphates. Like NRTIs, **2** acts as a competitive inhibitor or an alternative substrate.[4]




**2**

**Figure 2.** Tenofovir, a NtRTI

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as Nevirapine (**3**) (Figure 3) interact with an allosteric binding site on HIV-1 reverse transcriptase, which blocks the activity of the enzyme. NNRTIs are integral to the HAART therapies for patients new to treatment because the drugs are potent, safe and easy to dose. However, they become ineffective as reverse transcriptase readily undergoes mutations in the sequence of amino acids near the allosteric binding site.[4]




**3**

**Figure 3.** Nevirapine, a NNRTI

During the HIV life cycle, viral proteases cleave viral precursor polyproteins to afford mature functional or structural viral proteins. HIV protease inhibitors (PIs) are peptidomimetics that contain a key hydroxyethylene group, which is structurally similar to the peptide linkage(s) in the polyprotein precursor (Figure 4). The PIs bind the active site of the of the HIV protease, blocking protease activity since the hydroxyethylene bond cannot be cleaved. Nelfinavir (**4**) is a PI (Figure 5).[4]

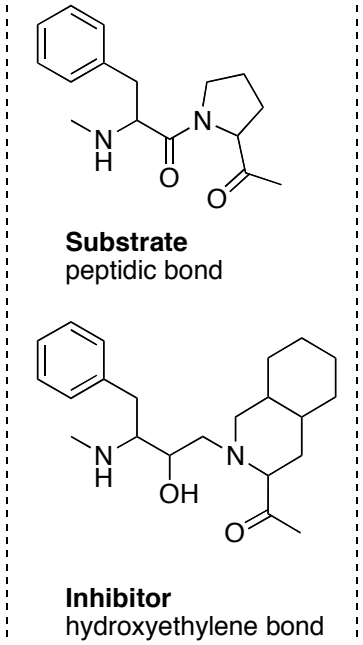
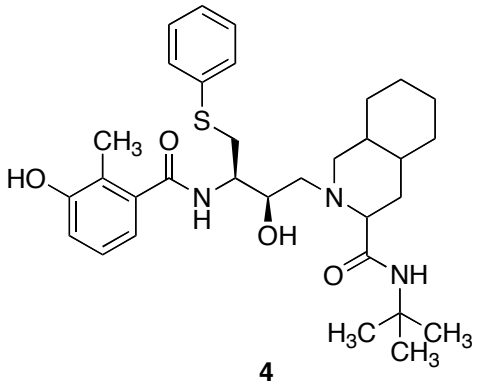



**Figure 4.** The hydroxyethylene group of PIs mimics the peptide bond

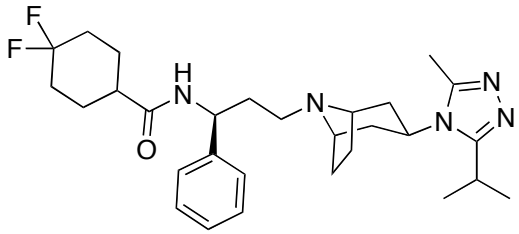



4

**Figure 5.** Nelfinavir, a protease inhibitor

Fusion inhibitors (FIs) and co-receptor inhibitors (CRIs) inhibit viral entry into cells. Enfuvirtide is the only approved HIV FI. It is a peptide with the same sequence of amino acids as the residues 643-678 in the HIV-1 envelope precursor glycoprotein gp160. Cellular serine proteases cleave gp160 to gp120—gp41 heterodimer. Fusion of the viral envelope with the cell membrane is facilitated by gp41. Enfuvirtide inhibits that process. This is the only anti-HIV drug that has to be subcutaneously injected.[4]

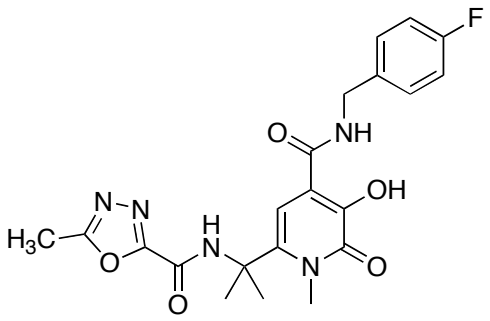
During viral entry into cells, the HIV envelope gp120 interacts with human chemokine receptors CCR5 and CXCR4. This changes the conformation of gp120, exposing co-receptor binding sites, which are able to bind co-receptors. This is followed by a conformation change in HIV gp41 and insertion of the fusion peptide into the human cell. Co-receptor inhibitors (CRIs) prevent the conformation change in gp41 and subsequently the insertion of the fusion peptide. Maraviroc (**5**) (Figure 6) is currently the only approved CRI.[4]




5

**Figure 6**. Maraviroc, a co-receptor inhibitor

HIV integrase inhibitors inhibit the integration of viral DNA in to host DNA.[2] This process is important for the maintenance of the viral genome, viral gene expression and replication. Raltegravir (**6**) (Figure 7) is currently the only approved integrase inhibitor.[4]

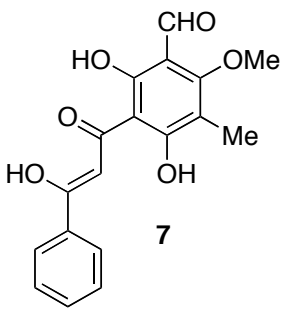



**6**

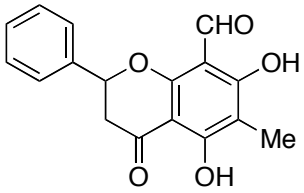
**Figure 7.** Raltegravir, an integrase inhibitor

New antiviral drugs that act by mechanisms other than those of the 25 approved drugs are needed because of rapidly developing drug-resistance in HIV and drug toxicity.[2] The development of most of the approved antiretrovirals was guided by well-characterized compounds with an expected interaction within the viral lifecycle such as the nucleoside analogues.[6] However, many HIV patients who were administered these synthetic drugs developed various side effects such as anemia from AZT (**1**).[7] Plant based traditional medicines have attracted interest since they are known to be non-toxic by long practical experience.[6,7] As a result of a concerted effort to identify natural products that inhibit HIV, many useful natural product leads have been reported.[8] Several small molecular weight natural products have been discovered that inhibit viruses.[9]

Lawinal (**8**) (Figure 8) is a flavonoid antiviral containing an aldehyde. It was isolated from the roots of *Desmos* spp., which are native to southern Asian countries and used as folk medicines in China.[10] Lawinal was evaluated for inhibition of HIV replication in H9 lymphocyte cells, and demonstrated potent anti-HIV activity with an ability to inhibit 50% of HIV replication ($EC_{50}$) value at 2.30 μg/mL and a therapeutic index (TI) of 45.2. Also isolated and evaluated was the related chalcone 2-methoxy-3-methyl-4,6-dihydroxy-5-(3´-hydroxy)-cinnamoylbenzaldehyde (**7**).[10] Remarkably, its anti-HIV activity was highly potent with the $EC_{50}$ value at 0.022 μg/mL and a large TI (489). Compound **7** is an excellent lead compound for further anti-HIV drug development.[10] As part of an effort to identify useful antiviral agents,[11,12] we synthesized chroman aldehydes related to **7** and **8**. Compound **9** (Figure 9) is an example of a synthetic analogue of **7**.

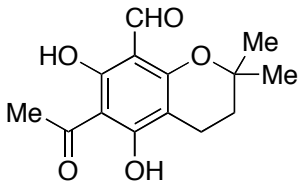



**7**




**8**

**Figure 8.** Structures of small molecule antiviral agents from *Desmos* spp.




**9**

**Figure 9.** A synthetic analogue of **7**

The structure of chalcone **7** is interesting since the ketone group is able to chelate to each of the three hydroxy groups in turn, which gives stability to the enol form and makes the conceivable diketo form **7a** (Figure 10) or the cyclic hemiketal forms **7b** and **7c** less favorable.[9]

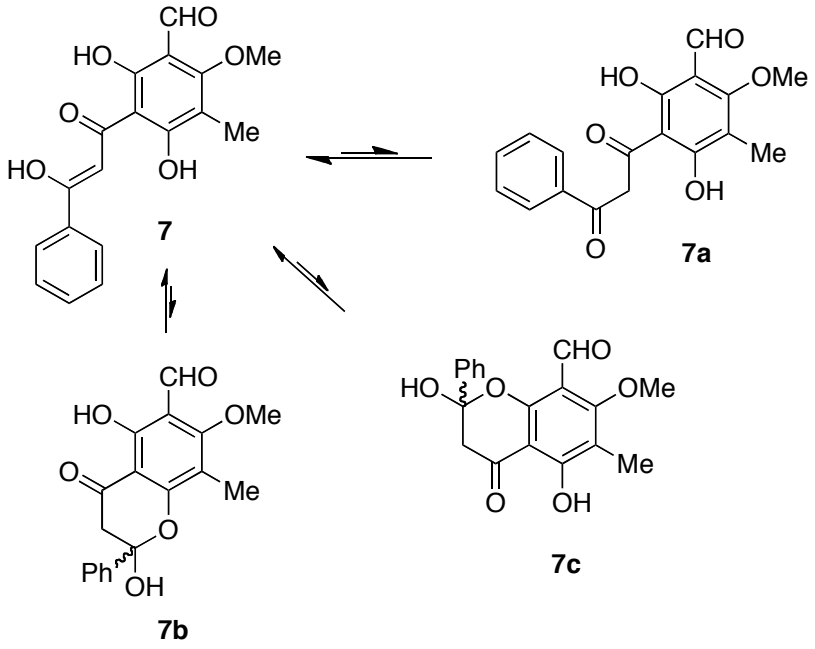
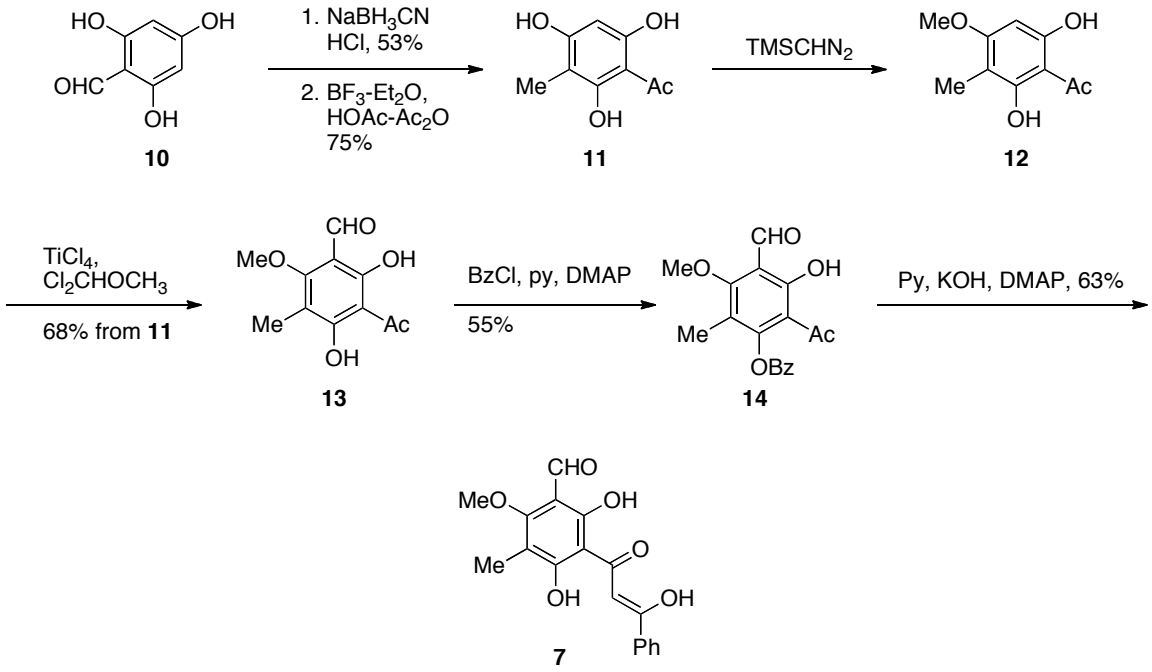



**Figure 10.**

Nakagawa-Goto and Lee synthesized **7** from commercially available 2,4,6-trihydroxybenzaldehyde in six steps without using protecting groups (Scheme 1).[13] Aldehyde **10** was reduced with sodium cyanoborohydride ($NaBH_3CN$) under acidic conditions to 2,4,6-trihydroxytoluene, followed by Friedel-Crafts acylation with $Ac_2O$ in the presence of $BF_3{\cdot}Et_2O$ to obtain ketone **11**. Trimethylsilyldiazomethane ($TMSCHN_2$) was used to effect monomethylation to give **12**, which was formylated with dichloromethyl methyl ether ($Cl_2CHOCH_3$) in the presence of $TiCl_4$ to yield **13**. Monobenzoate **14** resulted from treatment of **13** with benzoyl chloride, pyridine and

DMAP. The Baker—Venkataraman rearrangement of **14** was accomplished with KOH in pyridine.




**Scheme 1.** Total synthesis of an anti-HIV chalcone from genus *Desmos*

A structural unit that is common in natural products is the 2,2-dimethylbenzopyran motif, which is considered a privileged structure.[5,14] The term *privileged structure* was first proposed by Evans to describe special structural types that bind to multiple, unrelated classes of protein receptors as high affinity ligands.[14,15] Typical of privileged structures, the dimethylpyran units are rigid, polycylic heteroatomic systems that are able to hold various substituents in a well-defined three-dimensional space.[14,16] The analogue, compound **9**, contains a dimethylpyran unit.

Three examples of anti-viral natural products that contain the 2,2-dimethylbenzopyran unit are shown in Figure 11. (+)-Calanolide A (**15**), a phloroglucinol derivative, was isolated from *Calophyllum lanigerum*, a tropical rainforest tree, through a

screening program by the U.S. National Cancer Institute (NCI).[17] The compound is classified as an NNRTI, but its HIV sensitivity/resistance profile is different from the approved NNRTIs.[2] Mallotochromene (**16**), another phloroglucinol derivative, was isolated from the pericarps of *Mallotus japonicus* and shows strong anti-reverse transcriptase activity.[6] Fuscin (**17**) was isolated from the soil fungus *Oidiodendron griseum*.[18] It showed competitive inhibition of the binding of macrophage inflammatory protein (MIP)-1α to human CCR5 with an $IC_{50}$ value of 21 μM in the scintillation proximity binding assay.[19,18]

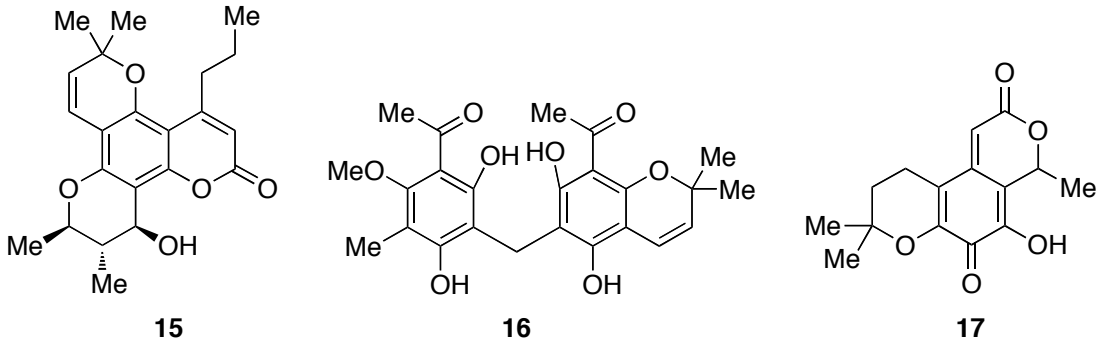
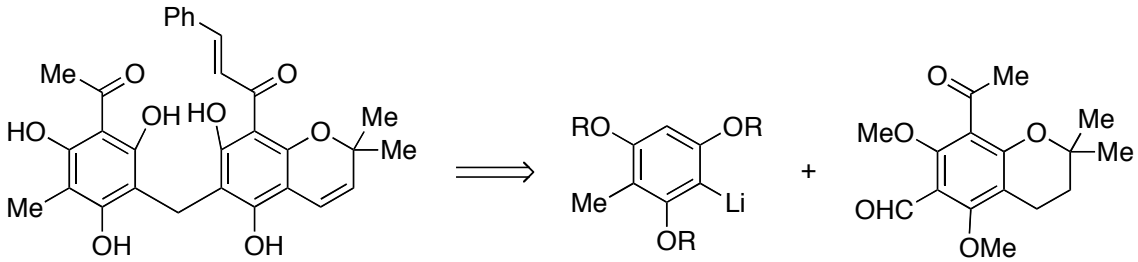



**Figure 11.** The 2,2-dimethylbenzopyran motif in anti-HIV-1 natural products

We synthesized chroman analogues of anti-HIV compound **7** during the course of a collaborative project with Iowa State University Veterinary Medicine researchers. They were interested in rottlerin (**18**) (Scheme 11) and synthetic derivatives of **18** for structure-activity relationship (SAR) studies since it was a lead compound for the treatment of Parkinson's Disease. Rottlerin has been isolated from *Mallotus philippensis* (Kamala Tree).[20] The compound is a chalcone and tetrahydroxy derivative of **16**.

A planned route to **18** involved the disconnection shown in Scheme 11. The methylene bridged phloroglucinol dimer could come from the 1,2-addition of the anion of tris-*O*-protected 2,4,6-trihydroxytoluene (**19**) with chroman aldehyde **20**. This route was

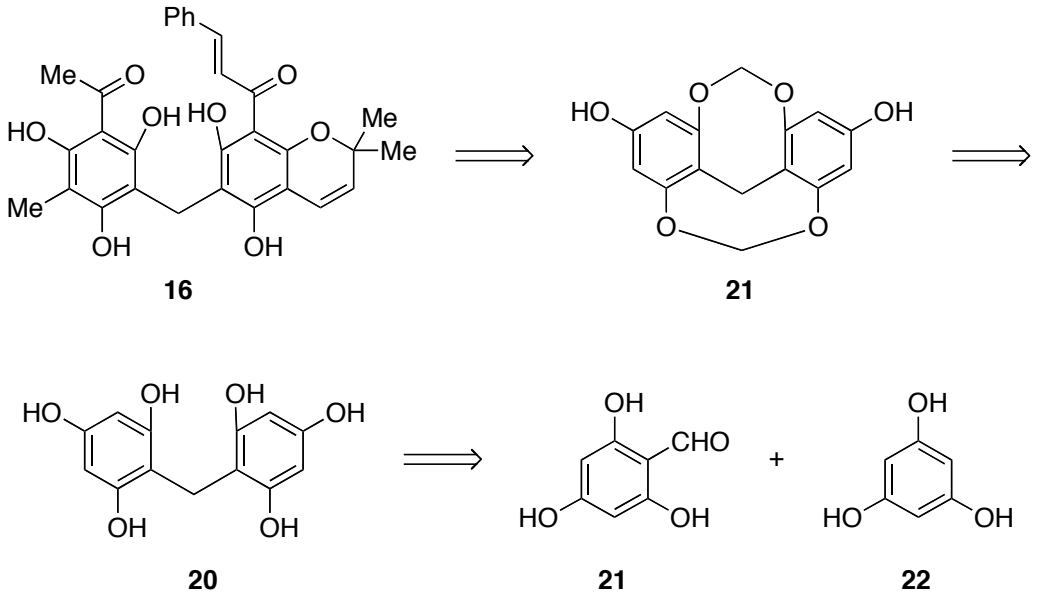
unsuccessful. However, our efforts resulted in the synthesis of antiviral chroman aldehydes related to **7** and **8**.



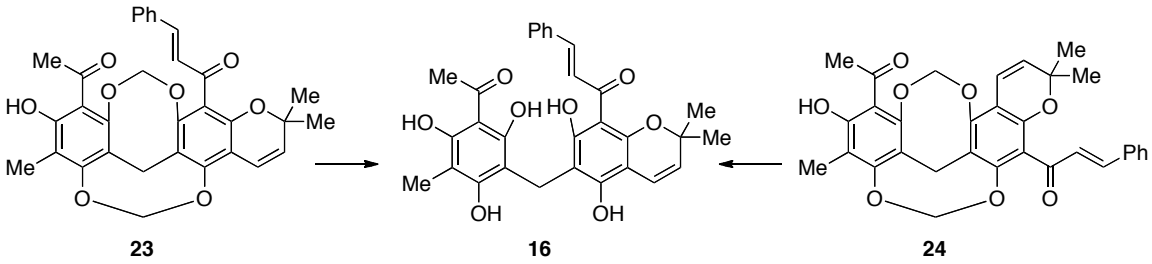

**Scheme 2**. A retrosynthesis of rottlerin (**18**)

## RESULTS AND DISCUSSION

Our initial synthetic plan for rottlerin was based on the tetracyclic, symmetrical intermediate **21** (Scheme 3), which could be derived from the known phloroglucinol dimer (**20**),[21] which was made from 2,4,6-trihydroxybenzaldehyde (**21**) and phloroglucinol (**22**). Two sequential Friedel-Crafts acylations of **21** were expected to occur, one on each aromatic ring. Sequential alkylations would then produce fully substituted aromatic rings. Mixtures of compounds with different substitution patterns were expected. However, after removing the acetal carbons, the number of compounds in the mixture would diminish because of the symmetrical nature of the phloroglucinol dimer core. For example, isomers **23** and **24** (Scheme 4) can both be transformed into rottlerin after cleavage of the acetal bridges. Other isomers—those having the wrong pairing of acyl group and alkyl group on the same ring—would also form, which would have been acceptable and even desirable for the SAR studies.




**Scheme 3.** The original synthetic plan for rottlerin

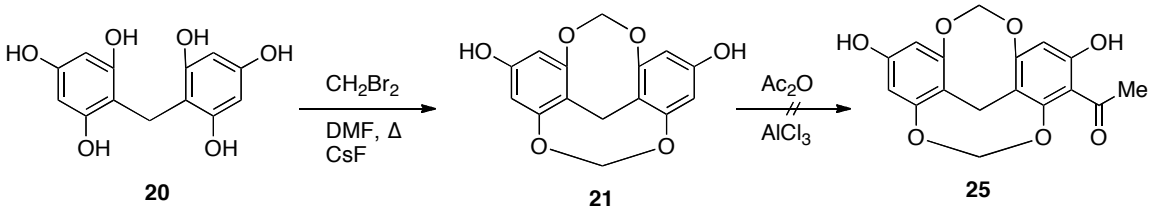



**Scheme 4.** The symmetrical core simplifies the mixture after ring cleavage

The key intermediate (**21**) was made by treating compound **20** with CsF and dibromomethane in boiling DMF for three hours. The best yield was 31%. Diminishing yields resulted when more than 900 milligrams of **20** were used. Compound **21** decomposed under Friedel-Crafts conditions. The aromatic rings could be brominated and the phenols could be acetylated, but we could not make carbon-carbon bonds to the phloroglucinol core.

After the initial plan failed, the disconnection shown in Scheme 2 was examined. The 2,2-dimethylbenzopyran aldehyde **20** was required. Methods to prepare benzopyrans

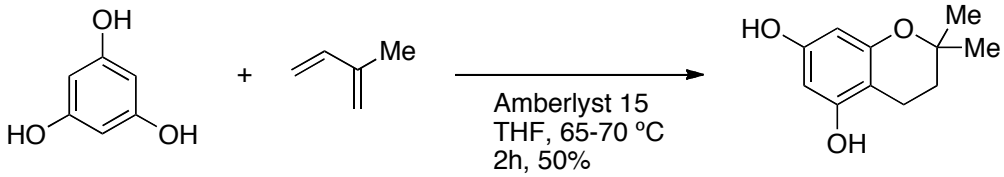
include Clemmensen reduction of 2,2-dimethylchromanones,[22] addition of methyl magnesium iodide to dihydrocoumarins,[23] and condensation of phenols with 2-methylbut-3-en-2-ol in an aqueous citric acid solution.[24] The starting materials used in the first two methods must be prepared.[25] The third method uses commercially available starting materials and mild conditions, but the condensation between the five-carbon alcohol and phloroglucinol gave only 18.5% yield.[24]




**20** **21** **25**

**Scheme 4.** Synthesis of the key intermediate

Banerji developed a convenient one-step synthesis of 2,2-dimethylchromans from the nuclear isoprenylation of phenols with isoprene (**26**) (Scheme 5)[26]. The reaction with phloroglucinol (**22**) gave 2,2-dimethylchroman-5,7-diol (**27**) in 50% yield. The reaction is catalyzed by Amberlyst 15®, a macroreticular sulfonic acid cation exchange resin. Concerning the procedure, to a boiling slurry of Amberlyst 15 and **22** in THF, **26** in heptane was added over 2 hours, heated for 30 minutes and then cooled, filtered and purified. When performed in this manner, starting material was returned.




**22** **26** **27**

**Scheme 5.** Amberlyst 15 catalyzed prenylation of phloroglucinol

Ahluwalia's[25] conditions employed a catalytic amount of orthophosphoric acid and he obtained a 70% yield of three products: **27**, **28**, and **29** in the ratio of 5 : 4 : 5, respectively (Figure 12). In this procedure, to an acidic slurry of **22** and orthophosphoric acid in light petroleum at 30-35 ºC, was added **26** in light petroleum over 2 hours, stirred for two hours, then worked up and purified. When performed in this manner, starting material was returned. By switching the solvent to THF and boiling for 12 hours, the yield of **27** was 30%. Compounds **28** and **29** were not observed.

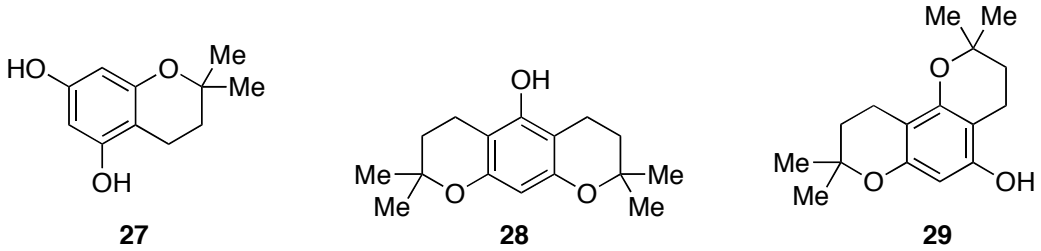
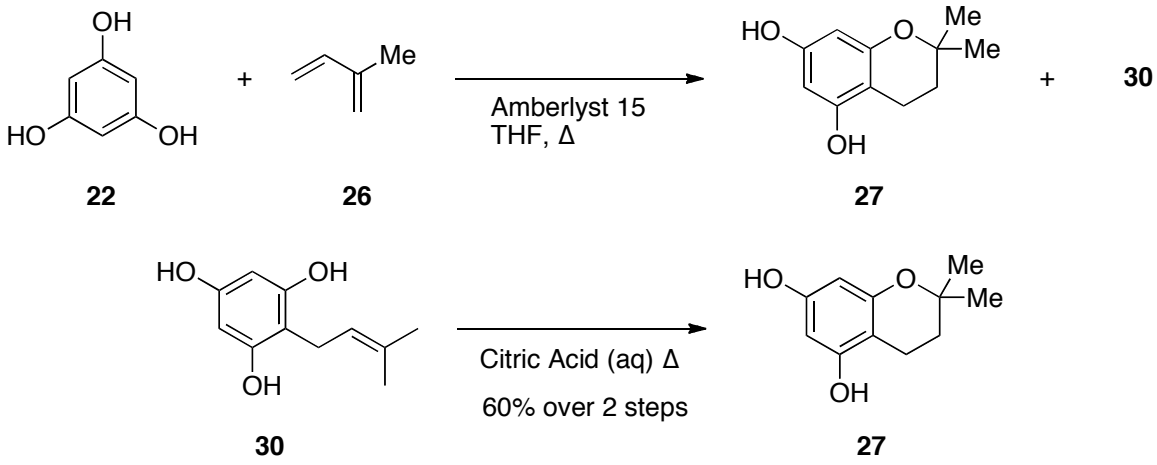



**Figure 12.** Products from the orthophosphoric acid catalyzed isoprenylation of **22**

Modifying Banerji's conditions (Scheme 6) by adding three equivalents of isoprene all at once and then boiling for 12 hours, a mixture of **27** and **30** formed. Filtering off the Amberlyst 15 and then treating the mixture with 5% citric acid in boiling water[24] produced **27** in a 60% yield over two steps. Switching the solvent to 1,4-dioxane and boiling for 17 hours resulted in a one-pot reaction that produced **27**, **28**, and **29** in 69%, 4.8%, and 5% yields, respectively. The reaction was successful on a multi-gram scale.

As shown in Scheme 7, acetylation of **27** with acetic anhydride afforded a mixture of **31**, **32** and **33**[27] in 86% yield. Chromatography yielded a mixture of **31** and **32** in 82% yield and diketone **33** in 4% yield. In early formylation experiments, the mixture of **31** and **32** was treated with $TiCl_4$ and dichloromethyl methyl ether.[13,28] Separation of the keto

aldehydes **35** and **36** could be accomplished by careful chromatography. Later, ketone **32** could be readily separated from **31** by recrystallization. Formylation of **32** with produced keto aldehyde **36** in 56% yield.




**Scheme 6.** Two-step process for synthesizing **27**

Concluding our examination of the disconnection in Scheme 2, treatment of **36** with potassium *tert*-butoxide and methyl iodide produced dimethoxy keto aldehyde **20** in 10% yield. Byproducts of this reaction were the two mono-*O*-methylated isomers and compounds alkylated at the α carbon. Fortunately, compound **20** could be separated from this complex mixture. Unfortunately, the reaction of **20** with phenyllithium did not give benzhydrol **37** (Scheme 8).

However, at this juncture our efforts were already directed towards synthesizing analogues of **7**. While searching the literature for methods of formylating acetophenones, the Nakagawa-Goto and Lee total synthesis of **7**[13] (Scheme 1) came to our attention. Noticing the similarities between **7** and **35** (Figure 13), we were thankful to have a use for what was once an unproductive byproduct of the rottlerin synthesis.

To better understand the effects of structure on activity, we prepared dialdehyde **34** from **27**. As shown in Scheme 9, oxidation of **35** with DDQ[29] in benzene produced chromene **38**. Benzoylation followed by rearrangement to a β-diketone generated **39**.

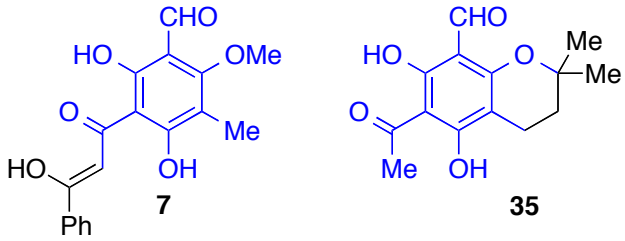
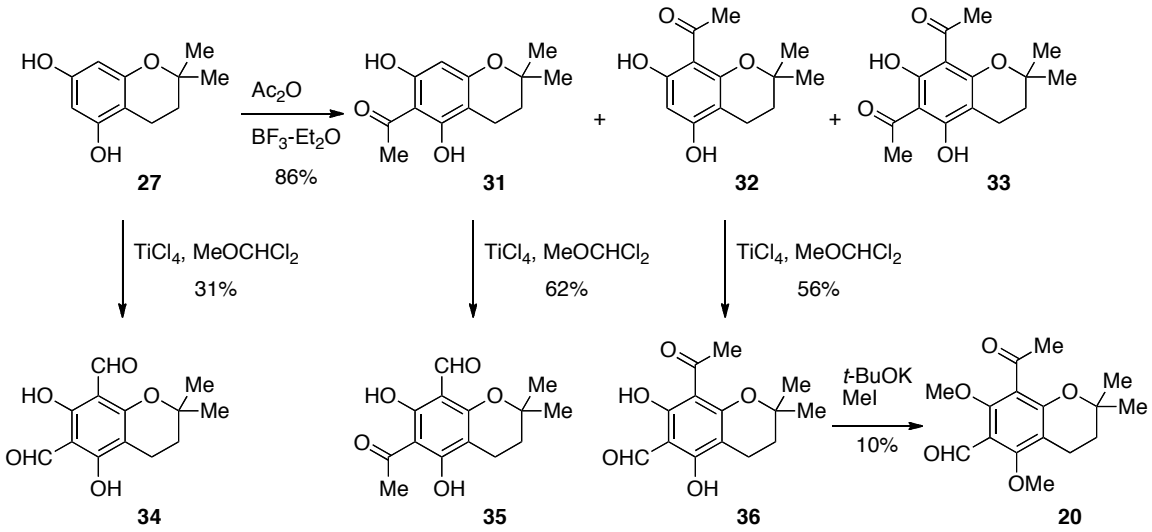
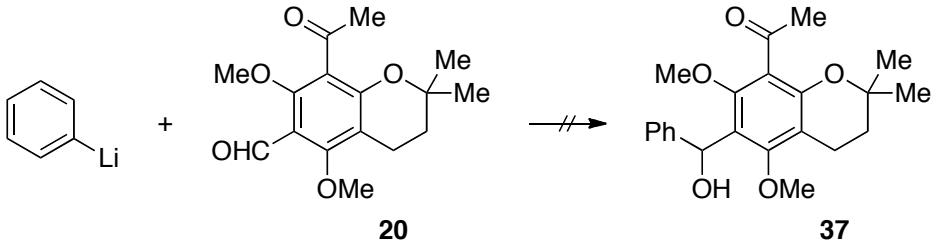


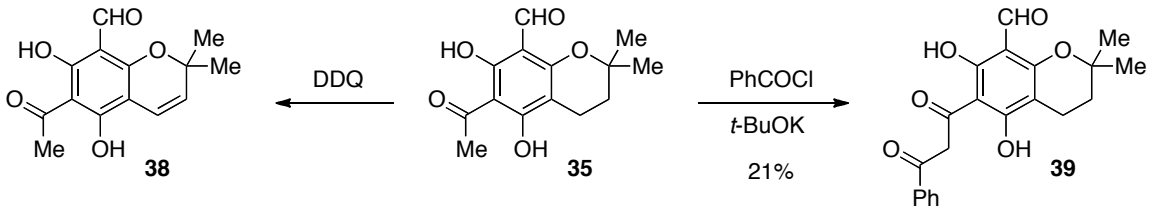

**Figure 13**. Similarities between **7** and **35**




**Scheme 7.** Synthesis of analogs




**Scheme 8.** Unsuccessful approach to rottlerin




**Scheme 9.** Derivatives of aldehyde **7**

Our collaborators in the Department of Microbiology, University of Iowa, evaluated compounds **20**, **33**-**36**, **38** and **39** for their ability to inhibit HIV infectivity in HeLa37 cells as previously described.[30] The concentration of compounds that inhibited 50% and 90% of HIV infectivity ($IC_{50}$ and $IC_{90}$) are shown in Table 2. The cytotoxicity of each compound was tested at the same concentrations. Compound **39** was the most cytotoxic. All the compounds had inhibitory activity against HIV. Compounds **35**, **36** and **38** gave the lowest $IC_{50}$ values between 30 and 40 μM.

**Table 2.**
Anti-HIV activity and cytotoxicity of synthesized phloroglucinols

| Compound | Cytotoxicity (μM) | | HIV-1 Infection (μM) | |
|---|---|---|---|---|
| | $LC_{50}$ | $LC_{90}$ | $IC_{50}$ | $IC_{90}$ |
| **20** | >100 | N/D | 55.3 | >100 |
| **33** | >100 | N/D | >100 | >100 |
| **34** | >100 | N/D | 77.3 | >100 |
| **35** | 145 | 258 | 30.2 | 85 |
| **36** | >100 | N/D | 39.8 | 85.6 |
| **38** | >100 | N/D | 34.6 | 98.2 |
| **39** | 82.4 | N/D | 40.7 | 86.6 |

Compound **35** has a TI of about 5, which was significantly smaller than that reported for Wu for compound **7**,[10] due to apparently reduced antiviral activity of compound **35**. Diketone **33** was the least active, indicating that an aldehyde moiety is necessary for good activity. The *O*-methylated compound **20** showed good activity. The

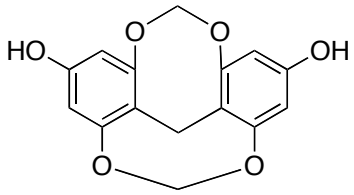
closest analogue to **7**, diketone **39**, exhibited good activity but had the highest cytotoxicity.

## CONCLUSION

We improved a method for synthesizing 2,2-dimethylbenzopyrans, a privileged structure in natural products. We synthesized a series of chroman aldehydes that are related to naturally derived aldehydes **7** and **8**. The analogues showed anti-HIV activity, but none showed an $IC_{50}$ value or therapeutic index comparable to compound **7**.

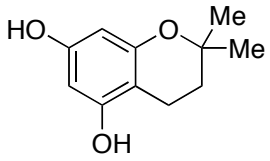
## EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Dichloromethane, benzene and diisopropyl amine were distilled over calcium hydride. All experiments were performed under an argon atmosphere unless otherwise noted. Organic extracts were dried over anhydrous magnesium sulfate. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Varian 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for $^1H$ and 77.23 ppm for $^{13}C$), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.

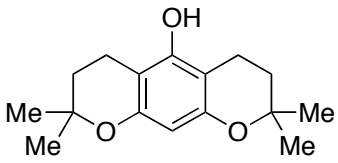


**21**

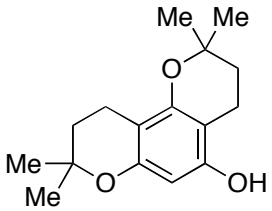
*Key intermediate* **21**: An oven dried 50 mL round bottom flask was fitted with a stir bar and charged with the phloroglucinol dimer **20** (900 mg, 3.41 mmol), anhydrous DMF (12 mL), anhydrous CsF (3.23 g, 21.25 mmol), and dibromomethane (592 μL, 7.16 mmol). The flask was fitted with a heat exchanger and heated for 3 h. The dark brown residue in the flask was diluted with ethyl acetate and water then transferred to a separatory funnel. It was extracted with ethyl acetate (2x), washed with water (3x), dried over $MgSO_4$, and concentrated. The product was purified on a column of silica gel with a 30% solution of ethyl acetate in hexanes to afford **21** (305 mg, 1.09 mmol, 32% yield) as a pale pink solid, $^1$H NMR (400 MHz, acetone-$d_6$) δ 8.49 (s, 2H), 6.31 (s, 4H), 5.82 (d, $J$ = 7.6 Hz, 2H), 4.53 (d, $J$ = 7.6 Hz, 2H), 3.91 (s, 2H).



**27**



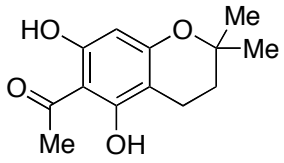
**28**



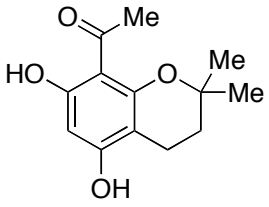
**29**

*2,2-Dimethyl-5,7-dihydroxychroman* (**27**): A 100-mL round bottom flask equipped with a stir bar was charged with phloroglucinol dihydrate (500.9 mg, 3.97 mmol) followed by 1,4-dioxane (10 mL) and Amberlyst 15 (1.5 g). The resulting mixture was coled to 0 ºC, and then isoprene (600 mL, 6.0 mmol) was added over 5 min. The reaction vessel was next equipped with a reflux condenser and boiled. After 17 h, the reaction mixture was

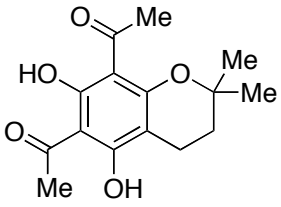
cooled to rt, filtered through Celite, and the catalyst was washed with hot acetone. The filtrate was concentrated in vacuo to afford a light yellow solid, which was purified by column chromatography (hexanes:ethyl acetate = 9:1 to 1:1) to first give a mixture of **28** and **29**, which were separated on a silica gel column eluted with toluene. The first fraction gave **29** (54 mg). The second fraction gave **28** (50 mg). The spectral data matched the lit.[25] The title compound (**27**) was isolated (536 mg, 69%) as colorless needles from benzene, mp 163-164 ºC (lit.,[12] 163-164 ºC). The final fraction contained recovered phloroglucinol (85.6 mg).




**31**



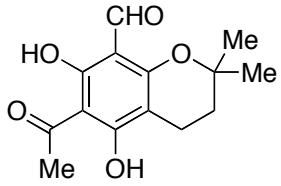

**32**




**33**

*Synthesis of* **31**, **32** and **33** *by the acetylation of* **27**: A 50-mL round bottom flask with a stir bar was charged with **3** (1.70 g, 8.77 mmol) followed by AcOH (18.4 mL) and $Ac_2O$ (0.91 mL, 9.65 mmol). The resulting mixture was stirred vigorously and warmed to 40 ºC until it was homogeneous, and then $BF_3{\cdot}OEt_2$ (1.17 mL, 9.21 mmol) was added over 1 min. The resulting red mixture was warmed to 100 ºC. After 10 h at that temperatue, the mixture was cooled to 0 ºC, quenched with water (10 mL) and pured into a separatory funnel containing ethyl acetate (25 mL). The phases were separated and the aqueous phase as extracted with ethyl acetate (3 x 25 mL) and five percent MeOH in ethyl acetate (5 x 20 mL). The combined organic fractions were washed with water (2 x 25 mL) and brine (1 x 25 mL), dried over $MgSO_4$, filtered and concentrated. The pale orange solid was purified by chromatography. Elution with hexanes:ethyl acetate (50:1) gave 6,8-

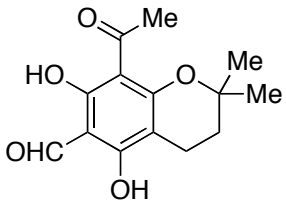
diacetyl-2,2-dimethylchroman-5,7-diol (**33**) (97.6 mg, 4% yield) as pale yellow needles, mp 129-130 ºC (lit.[27] 131-132.5 ºC); $^1$NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 3H), 2.60 (t, $J$ = 6.8 Hz, 2H), 1.42 (s, 3H). Elution with hexanes:ethyl acetate (5:1) gave a 1:1 mixture (by $^1$H NMR) of 6-acetyl-2,2-dimethylchroman-5,7-diol (**31**) and 8-acetyl-2,2-dimethylchroman (**32**) (1.68 g, 81.4%). Crystallization from benzene first gave **31** as a yellow solid, mp 230-230.5 ºC (lit.,[27] 230 ºC); $^1$HMR (400 MHz, acetone-$d_6$) δ 5.87 (s, 1H), 2.61 (s, 3H), 2.53 (t, $J$ = 6.8 Hz, 2H), 1.78 (t, $J$ = 6.8 Hz, 2H), 1.30 (s, 6H). The mother liquor was concentrated and the yellow residue afforded **32** as a yellow solid from benzene, mp 150-151 ºC (lit.,[27] 150 ºC); $^1$H NMR (400 MHz, acetone-$d_6$) δ 5.94 (s, 1H), 2.57 (t, partially obscured, $J$ = 6.8 Hz, 2H), 2.55 (s, 3H), 1.76 (t, $J$ = 6.8 Hz, 2H), 1.37 (s, 6H).




**35**

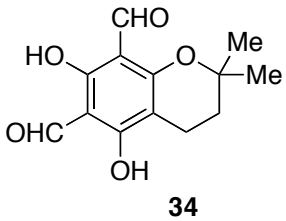
*6-Acetyl-2,2-dimethyl-8-formylchroman-5,7-diol* (**35**): A 100-mL round bottom flask equipped with a stir bar was charged with **31** (620.9 mg, 2.63 mmol) followed by anhydrous $CH_2Cl_2$ (50 mL). The resulting mixture was cooled to –78 ºC and then $TiCl_4$ (1.5 mL, 13.4 mmol) was added. This mixture was treated with $Cl_2CHOMe$ (2.26 mL, 25 mmol). The resulting red solution was spontaneously warmed to rt and then stirred for 10 h. Then it was cooled to 0 ºC, slowly quenched with ice-cold water (10 mL), stirred for 1 and poured into a separatory funnel. The organic phase was washed with water (3 x 25 mL) and brine (1 x 25 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The

residue was purified by column chromatography. Elution with two percent ethyl acetate and 98% hexanes gave **35** (427.2 mg, 62%) as yellow prisms, mp 102-104 ºC. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 2.69 (s, 3H), 2,56 (t, *J* = 6.8 Hz, 2H), 1.82 (t, *J* = 6.8 Hz, 2H), 1.39 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 203.7, 191.8, 171.0, 168.3, 161.8, 103.9, 103.4, 100.3, 77.8, 32.6, 31.5, 26.6, 15.5. HRMS, Calcd for $C_{14}H_{16}O_5$: 264.0998, Found: 264.1004.




**36**

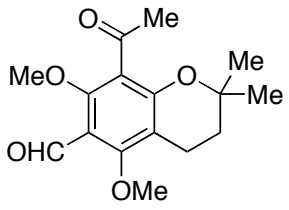
*8-Acetyl-5,7-dihydroxy-2,2-dimethylchroman-6-carboxaldehyde* (**36**): The reaction of **32** under conditions identical to those used for the formylation of **31** provided compound **36** as pale yellow needles, mp 131-134 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 13.23 (s, 1H), 10.18 (s, 1H), 3.63 (s, 3H), 2.60 (t, partially obscured, *J* = 6.8 Hz, 2H), 1.83 (t, *J* = 6.8 Hz, 2H), 1.44 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 203.4, 192.3, 169.7, 167.3, 163.0, 104.4, 104.2, 99.6, 78.4, 33.2, 31.1, 26.9, 15.3.




**34**

*5,7-Dihydroxy-2,2-dimethylchroman-6,8-dicarbaldehyde* (**34**): A 100-mL round bottom flask equipped with a stir bar was charged with **27** (57 mg, 0.295 mmol) followed by anhydrous $CH_2Cl_2$ (10 mL). The mixture was gently warmed and vigorously stirred to

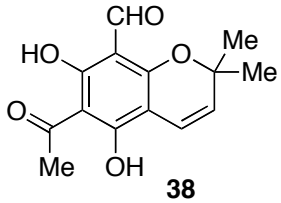
fully dissolve the starting material. Next, $Cl_2CHOMe$ (160 $\mu$L, 1.77 mmol) was added to the reaction mixture at rt. After cooling to –78 ºC, $TiCl_4$ (98 $\mu$L, 0.885 mmol) was added in drops over 5 min. The resulting red solution was spontaneously warmed to rt and then stirred for 10 h. It was then cooled to 0 ºC, slowly quenched with ic-cold water (5 mL), and stirred for 1 h. The $CH_2Cl_2$ was then distilled off using a rotary evaporator. The purplish slurry was dissolved in ethyl acetate (20 mL) and pured into a separatory funnel. The organic phase was washed with water (3 x 20 mL) and brine (1 x 20 mL) then dried over $MgSO_4$, filtered and concentrated to give a dark purplish-brown residue. It was purified by column chromatography (ethyl aceate, hexanes) to give **34** (23 mg, 31% yield) as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 10.16 (s, 1H), 10.04, (s, 1H), 3.59 (t, $J$ = 6.4 Hz, 2H), 1.82 (t, $J$ = 6.4 Hz, 2H), 1.42 (s, 6H). $^{13}$C (100 MHz, $CDCl_3$) δ 192.1 (overlap of 2 Cs), 168.9, 168.1, 163.3, 104.1, 103.7, 100.0, 78.3, 31.4, 26.7, 12.1. HRMS, Calcd for $C_{13}H_{14}O_5$: 250.08412, Found 250.08458.




**20**

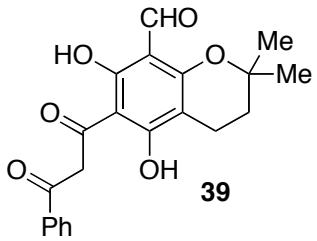
*8-Acetyl-5,7-dimethoxy-2,2-dimethylchroman-6-carbaldehyde* (**10**): A 50-mL round bottom flask equipped with a stir bar was charged with **36** (55.3 mg, 0.209 mmol) followed by THF (2 mL) and *t*-BuOH (0.5 mL). The resulting mixture was cooled to 0 °C and then *t*-BuOK (56.4 mg, 0.502 mmol) was added all at once. MeI (65 µL, 1.05 mmol) was added in drops over 1 min. The ice bath was removed to allow the resulting yellow slurry to warm to rt; then it was warmed to 40 °C for 2 h. After cooling to rt, the mixture

was quenched with water and acidified with 1 N HCl. The mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on $SiO_2$ (ethyl acetate-hexanes) to obtain **20** (6.3 mg, 10%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.23 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.73 (t, $J$ = 6.4 Hz, 2H), 1.82 (t, $J$ = 6.4 Hz, 2H), 1.36 (s, 6H).




**38**

*6-Acetyl-2,2-dimethyl-8-formylchromen-5,7-diol* (**38**): A slurry of **7** (75.9 mg, 0.287 mmol) and DDQ (71.7 mg, 0.316 mmol) in benzene (3 mL) was heated at 100 ºC in a sealed tube for 20 h. Then the mixture was filtered through Celite. Benzene was used to rinse the reaction flask and wash the filterpad. The filtrate was concentrated, and then the residue was purified by column chromatography on $SiO_2$ to obtain **38** (1.6 mg, 2%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.15 (s, 1H), 10.20 (s, 1H), 6.61 (d, $J$ = 10 Hz, 1H), 5.51 (d, $J$ = 10 Hz, 1H), 2.68 (s, 3H), 1.55 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 203.6, 192.7, 178.3, 170.9, 164.6, 124.8, 115.4, 104.8, 104.3, 101.1, 80.7, 33.2, 28.8. HRMS Calcd for $C_{14}H_{14}O_5$: 262.0841, Found 262.0846.




**39**

*6-(1,3-Dioxo-3-phenylpropyl)-2,2-dimethyl-8-formylchroman-5,7-diol* (**39**): Potassium *tert*-butoxide (100 mg, 0.82 mmol) was suspended in *t*-BuOH (1.5 mL) and anhydrous THF (5 mL), and then cooled to –10 ºC. A solution of **35** (58.1 mg, 0.22 mmol) in anhydrous THF (5 mL) was added. After stirring at –10 ºC for 15 min, benzoyl chloride (0.512 mL, 0.44 mmol) was added. The ice bath was removed, and the mixture warmed to rt. Then the mixture was heated at reflux for 5 h. After cooling to rt, the mixture was quenched with water and acidified with 1 N HCl. The mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatograpy on $SiO_2$ (ethyl acetate:hexanes = 1:19) to obtain **39** (17 mg, 21% yield) as a mixture of tautomers. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.03 (s, 1H, C*H*O, for enol form), 9.95 (s, 0.73H, C*H*O, for 1,3-diketo form), 7.97-7.92 (m, Ar*H*, for both forms), 7.65 (s, olefin for enol form), 1.40 (s, 6H, 2 x C$H_3$, for enol form) 1.39 (s, 6H, 2 x C$H_3$, for 1,3-diketo form); HRMS Calcd for $C_{21}H_{20}O_6$: 368.126, Found 368.126.

**REFERENCES**


1. *AIDS Epidemic Update 2010*, UNAIDS, Geneva, Switzerland, 2010.

2. Cos, P.; Maes, L.; Vlietinck, A.; Pieters, L. Plant-Derived Leading Compounds for Chemotherapy of Human Immunodefiency Virus (HIV) Infection—An Update (1998-1997). *Planta Med*. **2008,** *74*, 1323.

3. Green, W.C.; Debyser, Z.; Ikeda, Y.; Freed, E.O.; Stephens, E.; Yonemoto, W.; Buckheit, R.W.; Esté, J.A.; Cihlar, T. Novel targets for HIV therapy. *Antiviral Research*. **2008,** *80*, 251.

4. De Clercq, E. The design of drugs for HIV and HCV. *Nat. Rev. Drug Discov*. **2007,** *6*, 1001.

5. Nguyen, H.T.; Lallemand, M.-C.; Boutefnouchet, S.; Michel, S.; Tillequin, F. Antitumor *Psoropermum* Xanthones and *Sarcomelicope* Acridones: Privileged Structures Implied in DNA Alkylation. *J. Nat. Prod.* **2009,** *72*, 527.

6. Nakane, H.; Arisawa, M.; Fujita, A.; Koshimura, S.; Ono, K. Inhibition of HIV-reverse transcriptase activity by some phloroglucinol derivatives. *FEBS Lett.* **1991,** *286*, 83.

7. Richman, D.D.; Fischl, M.A.; Grieco, M.H.; Gottlieb, M.S.; Volberding, P.A.; Laskin, O.L.; Leedom, J.M.; Groopman, J.E.; Mildvan, D.; Hirsch, M.S.; Jackson, G.G.; Durack, D.T.; Phil, D.; Nusinoff-Lehrman, S. The Toxicity of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex—A Double-Blind, Placebo-Controlled Trial. *New Engl. J. Med.* **1988,** *317*, 192.

8. Gambari, R.; Lampronti, I. In *Advances in Phytomedicine; Lead Molecules from Natural Products;* Hassan Khan, M.T., Ahter, A., Eds.; Elsevier, 2006; Vol. 2, p 299.

9. Liu, T.; Li, A.X.; Miao, Y.P.; Wu, K.Z.; Ma, Y. Screening of new non-nucleoside reverse transcriptase inhibitors of HIV-1 based on traditional Chinese medicines database. *Chin. Chem. Lett.* **2009,** *20*(11), 1386.

10. Wu, J.-H.; Wang, X.-H.; Yi, Y.-H.; Lee, K.-H. Anti-AIDS Agents 54. A Potent Anti-HIV Chalcone and Flavonoids from Genus *Desmos*. *Bioorg. Med. Chem. Lett.* **2003,** *13*(10), 1813.

11. Maury, W.; Price, J.P.; Brindley, M.A.; Oh, C.S.; Neighbors, J.D.; Wiemer, D.F.; Willis, N.; Carpenter, S.; Hauck, C.; Murphy, P.; Widrlechner, M.P.; Delate, K.; Kumar, G.; Kraus, G.A.; Rizshsky, L.; Nikolau, B. Identification of light-independent inhibition of human immunodeficiency virus-1 infection through bioguided fractionation of *Hypericum perforatum*. *Virol J.* **2009,** *6*, 101.

12. Kraus, G.A.; Yuan, Y.; Kempena, A. A Convenient Synthesis of Type A Procyanidins. *Molecules*. **2009,** *14*, 807.

13. Nakagawan-Goto, K.; Lee, K.-H. Anti-AIDS agents 68. The first total synthesis of a uniquie potent anti-HIV chalcone from genus *Desmos*. *Tetrahedron Letters*, **2006,** *47*, 8263.

14. Nicolaou, K.C.; Pferrerkorn, J.A.; Roecker, A.J.; Cao, G.-Q.; Barluenga, S.; Mitchel, H.J. Natural Product-like Combinatorial Libraries Based on Privileged Structures. 1. Gener Principles and Solid-Phase Synthesis of Benzopyrans. *J. Am. Chem. Soc.* **2000,** *122*, 9939.

15. Evans, B.E.; Rittle, K.E.; Bock, M.G.; DiPardo R.M.; Freidinger, R.M.; Whitter, W.L.; Lundell, G.F.; Veber, D.F.; Anderson, P.S.; Chang, R.S.L.; Lotti, V.J.; Cerino, D.J.; Chen, T.B.; Kling, P.J.; Kunkel, K.A.; Springer, J.P.; Hirshfield, J. Methods for Drug Discover: Development of Potent, Selective, Orally Effective Cholecystokinin Antagonists. *J. Med. Chem.* **1988,** *31*, 2235.

16. Mason, J.S.; Morize, I.; Menard, P.R.; Cheney, D.L.; Hulme, C.; Labaudiniere, R.F. New 4-Point Pharmacophore Method for Molecular Similarity and Diversity Applications: Overview of the Method and Applications, Including a Novel Approach to the Design of Combinatorial Libraries Containing Privileged Substructures. *J. Med. Chem.* **1999,** *42,* 3251.

17. Kashman, Y.; Gustafson, K.R.; Fuller, R.W.; Cardellina, J.H.; McMahon, J.B.; Currens, M.J. et al. The calanolides, a novel HIV-inhibitory class of coumarin derivatives from the tropical rainforest tree, *Calophyllum lanigerum*. *J. Med. Chem*. **1992,** *35*, 2735.

*18*. Yoganathan, K.; Rossant, C.; Ng, S.; Huang, Y.; Buttler, M.S.; Buss, A.D. 10-Methoxydihydrofuscin, Fuscinarin, and Fuscin, Novel Antagonists of the Human CCR5 Receptor from *Oidioddendron Griseum*. *J. Nat. Prod*. **2003,** *66*, 1116.

*19*. Singh, I.P.; Bodiwala, H.S. Recent advances in anti-HIV natural products. *Nat. Prod. Rep*. **2010,** *27*, 1781.

*20*. Furusawa, M.; Ido, Y.; Tanaka, T.; Ito, T.; Nakaya, K.; Ibrahim, I.; Ohyama, M.; Iinuma, M.; Shiratka, Y.; Takahashi, Y. Novel, Complex Flavonoids from *Mallotus philippensis* (Kamala Tree). *Helvetica Chimica Acta*, **2005,** *88*, 1048.

*21*. Boyer, F.-D.; Ducrot, P.-H. Hydrogenation of substituted aromatic aldehydes: nucleophillic trapping of the reaction intermediate, application to the efficient synthesis of methylene linked flavonol dimers. *Tetrahedron Letters*, **2005,** *46*, 5177.

22. Bhat, H.B.; Venkataraman, K. Synthetical Experiments in the Chromone Group—XXV. Synthesis of Dihydrojacareubin and a New General Method for the Synthesis of 2,2-Dimethylchromanones. *Tetrahedron*, **1963,** *19*, 77.

23. Adams, R.; Cain, C.K.; Loewe, S. Tetrahydrocannabinol Analogs with Marihuana Activity. *J. Am. Chem. Soc*. **1941,** *63*, 1977.

24. Molyneux, R.J.; Jurd, L. Isoprenylation of Polyphenols in Aqueous Acid Solutions. *Tetrahedron,* **1970,** *26*, 4743.

25. Ahluwalia, V.K.; Arora, K.K.; Jolly, R.S. Acid-catalysed Condensation of Isoprene with Phenols. Formation of 2,2-Dimethylchromans. *J. Chem. Soc. Perkin Trans 1*. **1982,** 335.

26. Kalena, G.P.; Jain, A.; Banerji. Amberlyst 15 Catalyzed Prenylation of Phenols: One-Step Synthesis of Benzopyrans. *Molecules*. **1997,** *2*, 100.

27. Donnelly, W.J.; Shannon, P.V.R. Synthetic Approaches to the Deoxyhumulones; Some New 2,2-Dimethylchromens from *Phloracetophenone*. *J. Chem. Soc., Perkin Trans. 1* **1972,** 25.

28. Cresp, T.M.; Sargent, M.V.; Elix, J.A.; Murphy, D.P.H. Formylation and Bromination *ortho* to the Hydroxy-group of 2-Carbonyl-substituted Phenols in the Presence of Titanium(IV) Chloride. *J. Chem Soc., Perkin Trans 1* **1973,** 340.

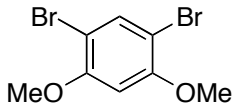
29. Ahluwalia, V.K.; Jolly, R.S. Reaction of 2,2-Dimethylchromans with 2,3-Dichloro-5,6-Dicyanobenzoquinone (DDQ). *Synlett* **1982,** 74.

30. Platt, E.J.; Wehrly, K.; Kuhmann, S.E.; Chesebro, B.; Kabat, D. Effects of CCR5 and CD4 Cell Surface Concentrations on Infections of Macrophagetropic Isolates of Human Immunodeficiency Virus Type 1. *J. Virol*. **1998,** *72*, 2855.

# CHAPTER 4: SELECTIVE METALATION OF 4,6-DIBROMORESCORINOL DIMETHYL ETHER WITH LiTMP

## INTRODUCTION

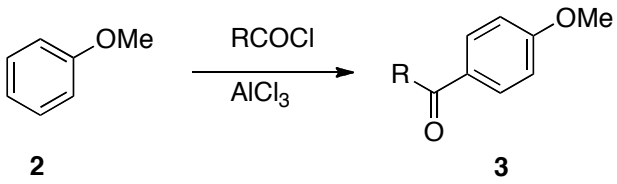
In Wyatt and Warren's 2007 textbook,[1] they begin the chapter by covering the *ortho* strategy for aromatic compounds with a look at traditional methods: the Friedel-Crafts reaction, the Fries rearrangement and the Claisen rearrangement. Most of the chapter is dedicated to *ortho*-lithiation—a powerful synthetic technique. The introduction herein is organized similarly, leading up to the unexpected selectivity in the *ortho*-lithiation of 4,6-dibromoresorcinol dimethyl ether (**1**) with lithium tetramethylpiperidide (LiTMP).




**1**

### Traditional methods of *ortho* substitution

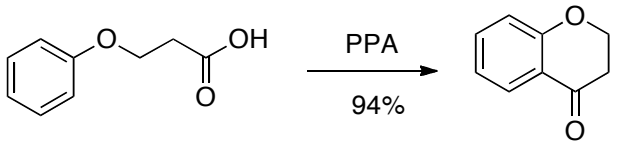
Making carbon-carbon bonds to aromatic rings by electrophilic substitution reactions using *ortho* and *para* or *meta* directing groups is taught to organic chemists early in their training.[1,2] When working with activated aromatic rings, mixtures of *ortho* and *para* substituted products are formed. This is acceptable at an early stage in a synthetic route since large scales can be used, separation is usually trivial and uses can be found for the unwanted isomer. A large activating group can direct substitution to the *para* position. However, making high yields of *ortho* compounds is difficult.




**2** **3**

**Scheme 1.** Acylation of anisole

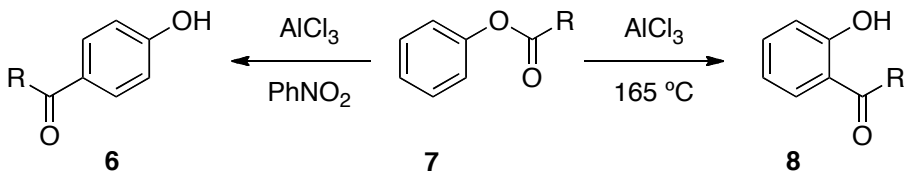
Friedel-Crafts acylation of simple aromatic ethers such as anisole (**2**, Scheme 1) predominately gives the *para* ketone **3**.[3] Compound **4** must give the *ortho* product **5** (Scheme 2) since the electrophile is tethered to the aromatic ring.[4]




**4** **5**

**Scheme 2.** An *ortho* product from the Friedel-Crafts acylation

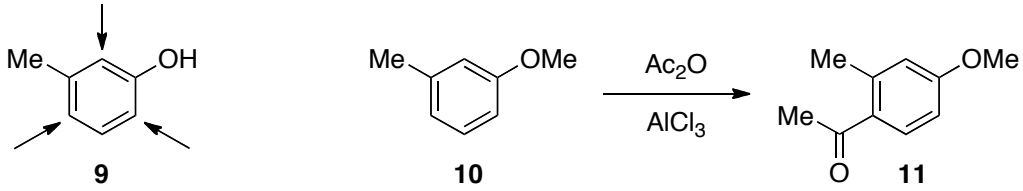
The Fries reaction[5] converts phenol esters **7**, Scheme 3, to *ortho*- or *para*-hyroxy ketones upon treatment with aluminum chloride. In polar solvents such as nitrobenzene ($PhNO_2$), the major product is *para*-substituted **6**. However, the *ortho*-products (**8**) are obtained selectively when **7** is heated to high temperatures either neat or in non-polar solvents. During the process,[1] the Lewis acid catalyzes the cleavage of the ester bond to form an ion pair consisting of an acylium ion and a metal complex of the phenol. Electrostatic interactions hold the pair close together when the reaction is performed without solvent or with a non-polar solvent, which leads to *ortho*-substitution. The pair separates in polar solvents, leading to normal Friedel-Crafts selectivity.



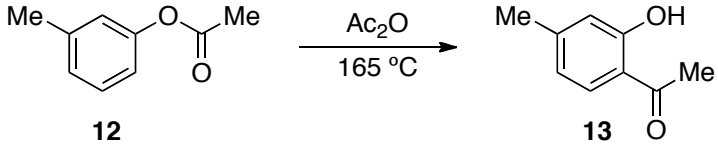

**6** **7** **8**

**Scheme 3.** Fries rearrangement

Three positions in *m*-cresol (**9**) Scheme 4 are activated. Friedel-Crafts acylation of methyl ether **10** produced ketone **11** almost exclusively.[1] The Fries reaction of the simple *meta*-substituted phenol ester **12** (Scheme 5) resulted in a 95% yield of compound **13**.[6]

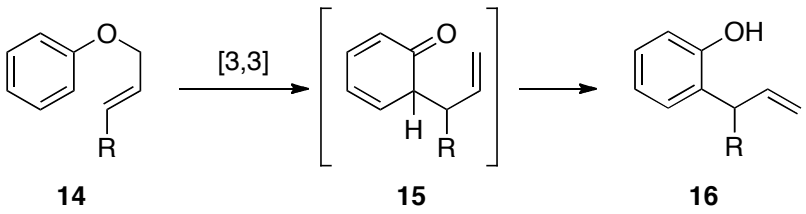



**Scheme 4**. Acylation of *m*-cresol methyl ether

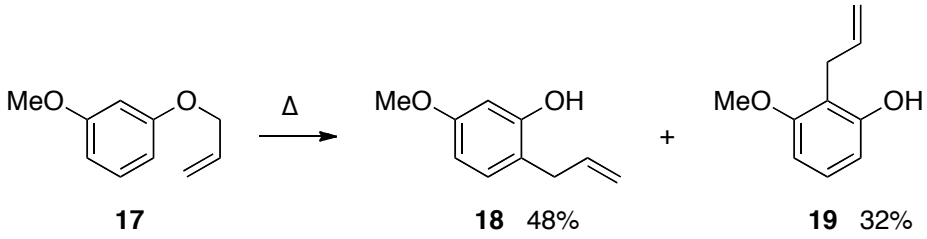



**Scheme 5.** Fries reaction of a *meta*-substituted phenol ester

The Claisen rearrangement (CR)[7] produces *ortho*-substituted phenols (Scheme 6) through a [3,3] sigmatropic rearrangement of allyl aryl ethers **14** to give intermediates (**15**) that are the "keto form" of new phenols **16**. The reactions are regiospecific in the allyl portion. However, the CR of resorcinol derivatives **17** (Scheme 7) gives mixtures of isomers **18** and **19**.[8]



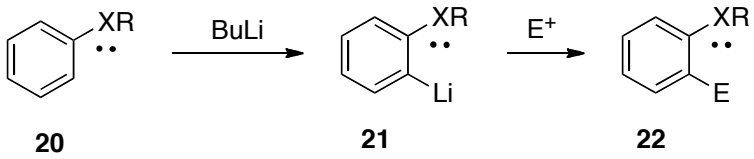

**Scheme 6.** The Claisen rearrangement




**Scheme 7.** The CR of **17** gave a mixture[8]

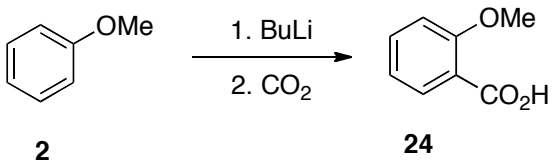
***Ortho*-lithiation**

Lithium is introduced *ortho* to a ring substituent that is already present, Scheme 8,[1] and the process is called *ortho*- or directed lithiation. It has taken over classical electrophilic aromatic substitution as the primary way of making regiospecifically substituted aromatic rings.[9]




**Scheme 8.** General *ortho*-lithiation reaction

Gilman[10] and Wittig[11] conducted the first lithiations in 1939 and 1940, respectively. Gilman treated anisole (Scheme 9) with *n*-butyllithium in ether for twenty hours followed addition of powdered carbon dioxide to yield **24** in 19% yield. The methoxy group is the *ortho* directing group and is called the '*ortho*-director.'[1] The lone pair on the oxygen atom coordinates to the organolithium reagent.




**Scheme 9.** *Ortho*-lithiation of anisole

The Fries and Claisen rearrangements require an oxygen atom *ortho* to the site where substitutions will occur. On the other hand, *ortho*-lithiation works well not only with oxygen atoms, but also with a variety of other directing groups. This makes the reaction much more versatile than the traditional methods.[1]

Gschwend and Rodriguez reviewed the lithiation reaction in 1979.[12] In their discussion of the mechanism, they note the importance of distinguishing between the *two* types of metalating agents, lithium alkyls or aryls and lithium dialkylamides. The first type, lithium alkyls and lithium aryls, are oligomers in solution and they are Lewis acids that can coordinate with Lewis bases such as amines and ethers. Coordination depolymerizes the alkyl lithiums, which makes them kinetically more basic. Therefore, tetrahydrofuran is the most used solvent since it generates the active lithiating species by coordination and depolymerization of the oligomers.

The second type of lithiating agent—lithium dialkylamides—has less Lewis-acid character than the first type. Lithium dialkylamides are also thermodynamically less basic than alkyl or aryl lithiums as the $pK_a$ of secondary amines is ~30 and the $pK_a$ of *n*-butane is 45-50.

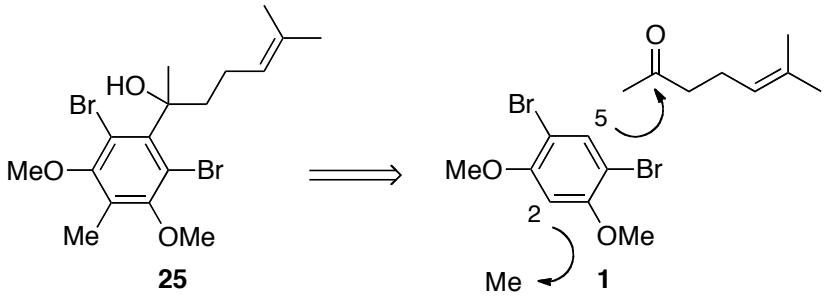
When alkyl or aromatic lithiums are used, the first step in the reaction is coordination of the Lewis-acidic metal with the lone pair in the substrate heteroatom.[12] The next step is abstraction of the *ortho* hydrogen atom by the carbanionic portion of the lithiating agent, which generates the lithiated product. Other factors such as inductive effects of heteroatoms or substituents are also important in these reactions. Therefore, Gschwend and Rodriguez proposed that the process occurs by *two* limiting mechanisms:

1. "coordination only" mechanism

2. "acid-base" mechanism

In the *ortho*-lithiation of anisole (Scheme 9), both effects contribute. Fluorine is unable to coordinate alkyl lithiums, yet it is an excellent *ortho* director.[1] Therefore, only the acid-base mechanism is operational when fluorobenzene is the substrate. All of the aryl halides are good *ortho* directors. Lithium dialkylamides are used to lithiate bromo- or iodobenzenes because metal-halogen exchange occurs instead when alkyl lithiums are used. Since halogens are non-coordinating and lithium diallkylamides are not Lewis acidic, the acid-base mechanism is operational during the *ortho*-lithiation of the halobenzenes.

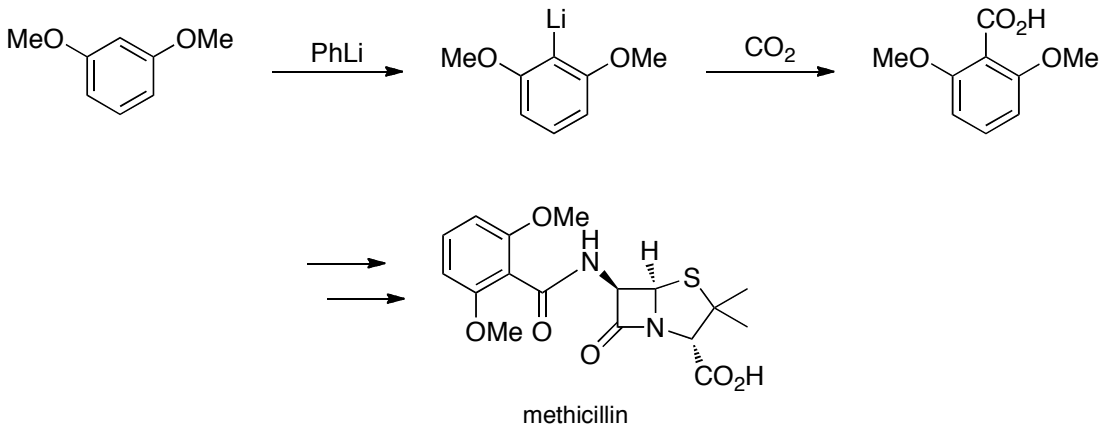
As an intermediate towards a natural product total synthesis, compound **25** was a target in our lab (Scheme 10). The planned route required 4,6-dibromoresorcinol dimethyl ether (**1**), which was prepared by brominating commercially available 1,3-dimethoxybenzene.[13] The next step was to employ directed *ortho*-lithiation to deprotonate and then alkylate **1** first at position 2—methyl ether is a strong *ortho*-directing group—and then at postion 5—bromine is an *ortho*-directing group weaker than methyl ether.[9]




**Scheme 10**

As previous studies had shown, 1,3-dimethoxybenzene is synthetically useful because of the combined effects of the *O*-methyl groups to direct lithiation to the 2-position. [14,15] For example, trapping 2,6-dimethoxyphenyllithium with $CO_2$ is a key step

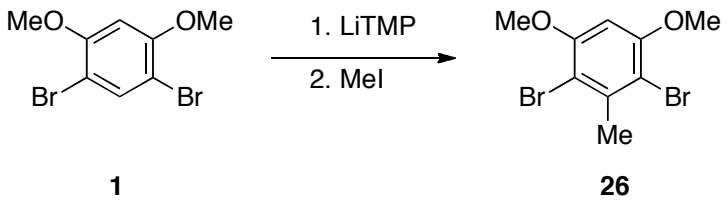
in the synthesis of methicillin (Scheme 11).[16] On the other hand, there are fewer examples of the metalation of 1,3-dibromobenzenes.[17,18]




**Scheme 11.** Metalation of 1,3-dimethoxybenzene used in a total synthesis

## RESULTS AND DISCUSSION

At –78 °C in tetrahydrofuran (THF), lithium tetramethylpiperidide (LiTMP) selectively deprotonated **1** at the position adjacent to the halogens. Trapping the intermediate with methyl iodide afforded derivative **26** in 96% yield (Scheme 12). A strong NOE correlation between the aromatic ring hydrogen and the *O*-methyl groups supported the structure of **26**. Further support of **26** came from dibrominating 2,6-dimethoxytoluene, which gave a compound with a different proton NMR spectrum than **26**.



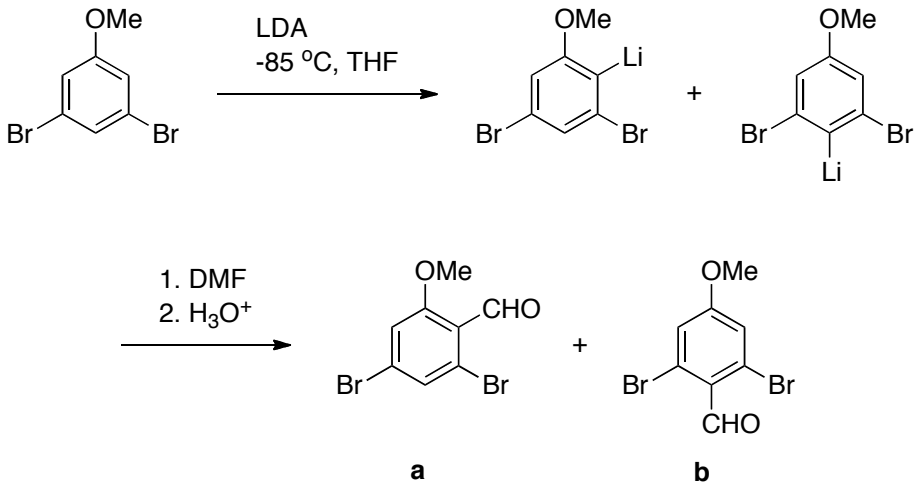

**1** **26**

**Scheme 12.** Metalation and alkylation of **1**

The reason why the bromines were the more powerful *ortho*-directing groups is not

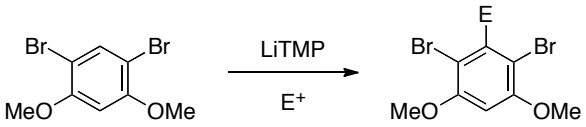
clear. Serwatowski and co-workers[19] studied the metalation of 2,5- and 3,5-dibromoanisole with lithium diisopropylamide at –85 °C. They observed a mixture of metalation products with a product ratio that was time dependent—**a** and **b** were formed in a ratio of 85:15 when litiation of 3,5-dibromoanisole was carried out for 15 minutes prior to quenching with DMF, the ratio changed to 70:30 when lithiation was carried out for 2 hours (Scheme 13).

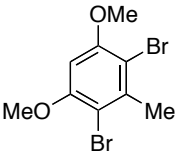
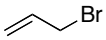
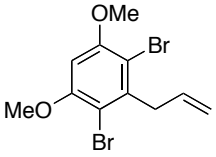
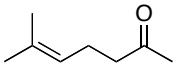
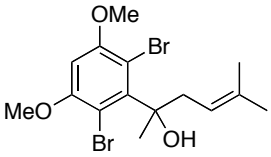
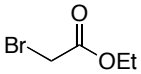
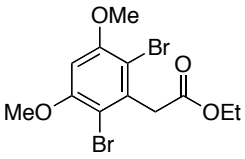
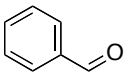
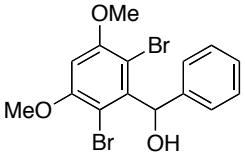
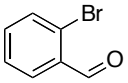
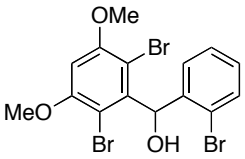
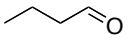
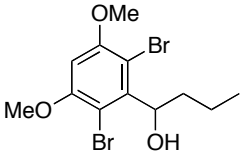
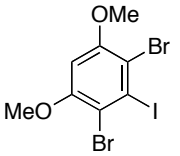
At temperatures greater than –70 °C, they observed benzyne formation. Hickey and co-workers also observed benzyne formation—this could be minimized by carefully controlling the reaction temperature—when they studied the metalation of 3-bromochlorobenzene on an industrial scale.[20]




**Scheme 13.** LDA-mediated metalation of 3,5-dibromoanisole

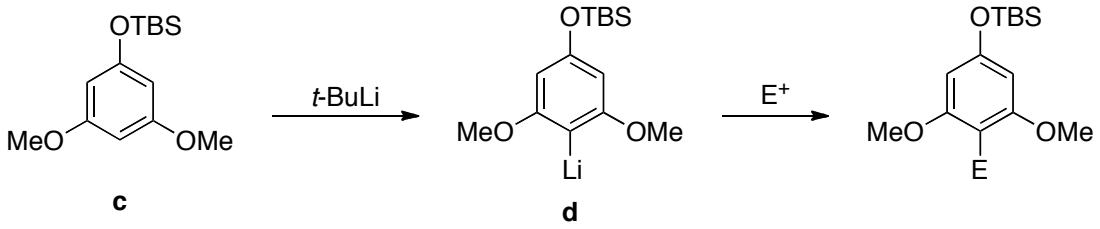
**Table 1**. Reaction of the anion of **1**with representative electrophiles




| Entry | Electrophile | Product | | Yield, % |
|---|---|---|---|---|
| 1 | Methyl Iodide |  | **26** | 96 |
| 2 |  |  | **27** | 98 |
| 3 |  |  | | 0 |
| 4 |  |  | | 0 |
| 5 |  |  | **28** | 72 |
| 6 |  |  | **29** | 55 |
| 7 |  |  | **30** | 53 |
| 8 | Iodine |  | **31** | 75 |

The metalation of **1** did not lead to the desired product. However, the reaction was regioselective. Therefore, we reacted the anion of **1** with representative electrophiles. This work is described in Table 1. As the results illustrate, some compounds with acidic α-protons—6-methyl-5-hepten-2-one (entry 3) and ethyl bromoacetate (entry 4)—did not afford the desired products, presumably due to anion exchange. Steric hindrance between the electrophile and the bromine atoms of the anion of **1** likely leads to this exchange rather than nucleophilic addition to the carbonyl group. Fortunately, the anion of **1** reacts effectively with iodine, alkyl halides, and both aliphatic and aromatic aldehydes.

Trost and Saulnier[21] showed that the steric demand of the *t*-butyldimethylsilyl group in **c** (Scheme 14) directs metalation away from the positions *ortho* to the phenolic oxygen bearing the protecting group. The reaction of **c** with *t*-BuLi selectively gives the 4-lithio anion **d** that reacts effectively with electrophiles.

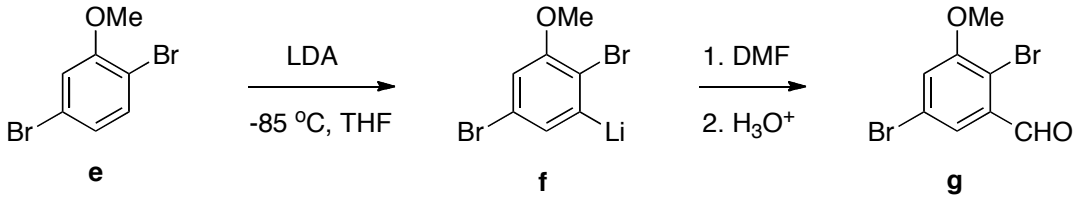



**c** **d**

**Scheme 14.**

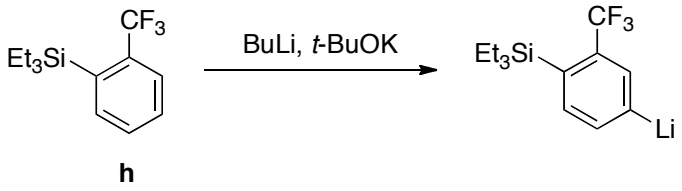
Serwatowski and co-workers[19] found that with 2,5-dibromoanisole (**e**) (Scheme 15) the regiochemistry of metalation is controlled by the bromine at position 2. Treatment of **e** with LDA generated the 3-lithio species **f** that was quenched with DMF to afford aldehyde **g** in a 47% yield. They rationalized that deprotionation occurred at the 3-position due to the long-range inductive effect of the methoxy group, and they believed

sterics between the bromine and the methoxy group forced the methoxy group into the *anti*-oriented conformer with respect to the adjacent bromine. This hindered metalation at the position *ortho* to the methoxy group.




**Scheme 15.**

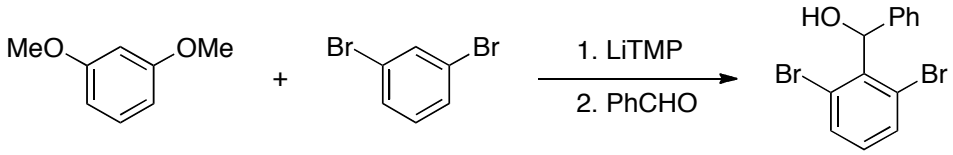
Schlosser and co-workers invoked an effect termed 'steric buttressing' to rationalize the novel metalation reaction shown in Scheme 16.[22] The superbasic LiC-KOR mixture of stoichiometric amounts of butyllithium and potassium *tert*-butoxide metalates benzotrifluoride only at the *ortho* position. However, triethyl[(2-trifluoromethyl)phenyl]silane (**h)** was metalated only at the 4-position.




**Scheme 16.** Schlosser's evidence of steric buttressing

Since we found no reports of the reaction of 1,3-dimethoxybenzene with LiTMP, a possible explanation for the observed result is that LiTMP does not readily deprotonate 1,3-dimethoxybenzene at low temperatures. Treatment of 1,3-dimethoxybenzene with LiTMP under the conditions used to deprotonate **1**, followed by addition of benzaldehyde, afforded a 40% yield of the benzhydrol. Significantly, a competition experiment using one equivalent of 1,3-dimethoxybenzene and one equivalent of 1,3-

dibromobenzene with one equivalent of LiTMP, using conditions employed to deprotonate **1** followed by quenching with benzaldehyde, produced *only* the adduct with 1,3-dibromobenzene (Scheme 17). In view of this experiment, it is unlikely that steric buttressing plays a large role in the observed selectivity with **2**.




**Scheme 17.** Competition experiment

## CONCLUSION

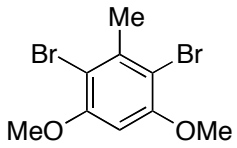
The metalation of **1** is regioselective. The anion is stable enough at –78 °C to react with a variety of electrophiles. Regardless of the origin of the regioselectivity, this selective deprotonation will likely find a number of applications in the synthesis of resorcinol-based natural products.

## EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Dichloromethane, benzene and diisopropyl amine were distilled over calcium hydride. All experiments were performed under an argon atmosphere unless otherwise noted. Organic extracts were dried over anhydrous magnesium sulfate. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Varian 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for $^1H$ and 77.23 ppm for $^{13}C$), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High

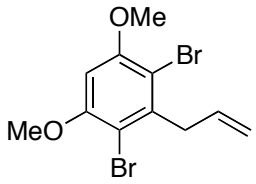
resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.

**Representative experimental procedure.** To a solution of tetramethylpiperidide (326 mg, 0.392 mL, 2.3 mmol) in THF (5 mL) at 0 °C was added *n*-BuLi (2.5 M in hexane, 0.843 mL, 2.1 mmol). After stirring for 20 min, the flask was cooled to –78 °C. Quickly, the flask was opened, solid 4,6-dibromoresorcinol dimethyl ether (**1**; 297 mg, 1.0 mmol) was added all at once, and the flask was resealed. Compound **1** dissolved to give a homogeneous mixture, which became a white slurry about 30 min after the addition. After stirring at –78 °C for a total time of 3 h, a room temperature solution of allyl bromide (607 mg, 0.424 mL, 5.0 mmol) in THF (1 mL) was added over 1 min. The resulting mixture was stirred at –78 °C for 30 min and then the ice bath was removed. After warming to r.t., the reaction mixture was poured into saturated $NH_4Cl$ solution and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried (brine and $MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (EtOAc—hexane, 1:99) to give **27** (329 mg, 98%) as a white solid.

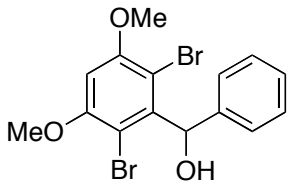



**1,3-Dibromo-2-methyl-4,6-dimethoxybenzene (26):** Purification by column chromatography on silica gel (EtOAc–hexane, 1:20) gave the title compound **26** in 96% yield, which crystallized from benzene–hexane (3:1) as white needles; mp 168–169 °C (Lit.[18] 168–169 °C). $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.42 (s, 1 H), 3.91 (s, 6 H), 2.62 (s,

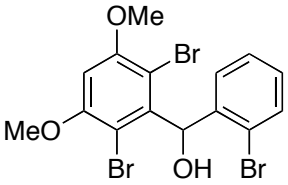
3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 155.7, 139.2, 105.7, 94.8, 56.5, 24.2. HRMS (EI): *m/z* calcd for $C_9H_{10}Br_2O_2$: 309.9027; found: 309.9032. Anal. Calcd for $C_9H_{10}Br_2O_2$: C, 34.87; H, 3.25. Found: C, 34.85; H, 3.20.



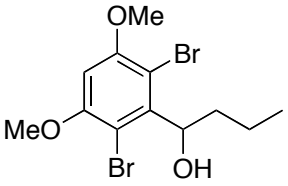

**2-Allyl-1,3-dibromo-4,6-dimethoxybenzene (27):** Purification by column chromatography on silica gel (EtOAc–hexane, 1:99) gave the title compound **27** in 98% yield, which crystallized from hexane as white plates; mp 67–68 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.45 (s, 1 H), 5.96–5.86 (m, 1 H), 5.12–5.07 (m, 2 H), 3.92 (s, 6 H), 3.87 (d, *J* = 8.00 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 155.9, 140.2, 133.1, 116.5, 105.8, 95.3, 56.5, 40.9. HRMS (EI): *m/z* calcd for $C_{11}H_{12}Br_2O_2$: 335.9184; found: 335.9189.



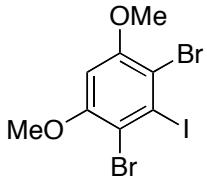

**(2,6-Dibromo-3,5-dimethoxyphenyl)(phenyl)methanol (28):** Purification by column chromatography on silica gel (EtOAc–hexane, 1:9) gave the title compound **28** in 72% yield, which crystallized from benzene–hexane (1:3) as white prisms; mp 147–148 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5 H), 6.80 (d, *J* = 11.2 Hz, 1 H), 6.55 (s, 1 H), 3.94 (s, 6 H), 3.87 (d, *J* = 11.2 Hz, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 156.2, 141.5, 141.4, 128.1, 126.9, 125.4, 96.3, 96.3, 76.5, 56.6. HRMS (EI): *m/z* calcd $C_{15}H_{14}Br_2O_3$: 401.9289; found: 401.9294.




**(2-Bromophenyl)(2,6-dibromo-3,5-dimethoxy- phenyl)methanol (29):** Purification by column chromatography on silica gel (EtOAc–hexane, 1:9) gave the title compound **29** in 55% yield, which crystallized from benzene–hexanes (3:1) as a white powder; mp 190–191 °C. $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.22 (t, *J* = 8.0 Hz, 1 H), 7.14 (t, *J* = 8.0 Hz, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.54 (s, 1 H), 3.93 (s, 6 H), 3.50 (d, *J* = 8.0 Hz, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 156.2, 139.8, 139.2, 133.4, 129.8, 129.3, 126.8, 123.7, 105.8, 96.5, 77.2, 56.7. HRMS (EI): *m/z* calcd for $C_{15}H_{13}Br_3O_3$: 367.9446; found: 367.9450.




**1-(2,6-Dibromo-3,5-dimethoxyphenyl)butan-1-ol (30):** Purification by column chromatography on silica gel (EtOAc–hexane, 1:9) gave the title compound **30** in 53% yield as a pale-yellow viscous liquid which solidified upon drying in vacuo; mp 73–74 °C. $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 6.44 (s, 1 H), 5.54–5.48 (m, 1 H), 3.89 (s, 6 H), 3.27 (d, J = 8.0 Hz, 1 H), 2.12–2.03 (m, 1 H), 1.87–1.78 (m, 1 H), 1.65–1.53 (m, 1 H), 1.41–1.28 (m, 1 H). $^{13}$C NMR (100 MHz, CDCl3): δ = 155.9, 141.9, 95.7, 75.9, 56.6, 37.2, 19.2, 13.9. HRMS (EI): *m/z* calcd for $C_{12}H_{16}Br_2O_3$: 367.9446; found: 367.9450.




**2,6-Dibromo-1-iodo-3,5-dimethoxybenzene (31):** Purification by column chromatography on silica gel (EtOAc–hexane, 1:9) gave the title compound **31** in 75% yield, which crystallized from hexanes as white needles; mp 181–182 °C. $^{1}$H NMR (400 MHz, CDCl3): δ = 6.57 (s, 1 H), 3.91 (s, 6 H). $_{13}$C NMR (100 MHz, $CDCl_3$): δ = 156.3, 112.2, 111.5, 96.9, 56.9. HRMS (EI): *m/z* calcd for $C_8H_7Br_2IO_2$: 421.7837; found: 421.7845.

## REFERENCES

1. Wyatt, P.; Warren, S. *Organic Synthesis: Strategy and Control*; John Wiley & Sons: London; 2007, p 90-112.

2. Jenks, W. *Electrophilic Aromatic Substitution: Ch 16* [PDF document]. Retrieved from Lecture Notes Online Web site: http://avogadro.chem.iastate.edu/CHEM332A/documents/lecturenotes/Notes016.pdf

3. Gore, P.H.; Aromatic Ketone Synthesis. In *Friedel—Crafts and Related Reactions*; Olah, G.A. Eds.; Vol. III, Part 1; Interscience Publishers: New York; 1964, p. 1-382.

4. Barlow, J.W.; Walsh, J.J. Synthesis and evaluation of dimeric 1,2,3,4-tetrahydro-naphthalenylamine and Indan-1-ylamine derivatives with mast cell-stabilising and anti-allergic activity. *Eur. J. Med. Chem.* **2010,** *45*, 25.

5. Blatt, A.H. The Fries Reaction. *Chem. Rev.* **1940,** *27*, 413.

6. Baltzly, R.; Ide, W.S.; Phillips, A.P. The Mechanisms of the Fries Reaction. *J. Am. Chem. Soc.* **1955,** *77*, 2523.

7. Rhoads, S.J.; Raulins, N.R. Claisen and Cope rearrangements. *Org. React.* **1975,** *22*, 1.

8. Ito, F.; Fusegi, K.; Kumamoto, T.; Ishikawa, T. Boron Trichloride Mediated Regioselective Claisen Rearrangements of Resorcinol Derivatives: Application to Resorcinol Carvonyl Ethers. *Synthesis*, **2007,** *12*, 1785.

9. Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press; Oxford: 2002. p. 28-73.

10. Gilman, H.; Bebb, R.L. Relative reactivities of organometallic compounds. XX. Metalation. *J. Am. Chem. Soc.* **1939,** *61*, 109.

11. Wittig, G.; Fuhrman, G. On the performance of halogenized anisole towards phenyl-lithium (V Announcement on the reaction measure of phenyl-lithium). *Chem. Ber.* **1940,** *73*, 1197.

12. Gschwend, H.W.; Rodriguez, H.R. *Org. Reac.* **1979,** *26*, 1.

13. Majetich, G.; Hicks, R.; Reister, S. Electrophilic aromatic bromination using bromodimethylsulfonium bromide generated *in situ*. *J. Org. Chem.* **1997,** *62*, 4321.

14. Shirley, D.A.; Johnson, J.R.; Hendrix, J.P. The product distribution in metalation of some aromatic substrates with *n*-butyllithium. *J. Organomet. Chem.* **1968,** *11*, 209.

15. Shirley, D.A.; Hendrix, J.P. Steric effects in metalation of some aromatic substrates with alkyllithium reagents. *J. Organomet. Chem.* **1968,** *11*, 217.

16. Totter, F.; Rittmeyer, P. In *Organometallics in Synthesis*; Schlosser, M. Ed.; Wiley: NewYork, 1994; pp. 169-194.

17. (a) Leroux, F.; Schlosser, M. The "aryne" route to biaryls featuring uncommon substitution patterns. *Angew. Chem. Int. Ed.* **2002,** *41*, 4272. (b) Mongin, F.; Schlosser, M. The acidifying effects of chlorine and bronmine: Little difference. *Tetrahedron Lett.* **1997,** *38*, 1559.

18. Smith, C.F.; Moore, G.J.; Tamborski, C. Improved synthesis of pentabromophenylmagnesium brominde and 1,2,4,5-tetrabromophenylbis(magnesium bromide). *J. Organomet. Chem.* **1971,** *33*, C21.

19. Dabrowski, M.; Kubicka, J.; Lulinski, S.; Serwatowski, J. A study on the metalation of alkoxydibromobenzenes. *Tetrahedron Lett.* **2005,** *46*, 4175.

20. Hickey, M.R.; Allwein, S.P.; Nelson, T.D.; Kress, M.H.; Sudah, O.S.; Moment, A.J.; Rodgers, S.D.; Kaba, M.; Fernandez, P. Process development and pilot plant

synthesis of methyl 2-bromo-6-chlorobenzoate. *Org. Process Res. Dev.* **2005,** *9*, 764.

21. Trost, B.M.; Saulnier, M.G. Regioselectivity in lithiation of tert-butyldimethylsiloxy-3,5-dimethoxybenzene—a synthesis of the trimethyl ether of sophoraflavanone-A. *Tetrahedron Lett.* **1985,** *26*, 123.

22. Schlosser, M.; Heiss, C.; Leroux, F. Trifluoromethyl-substituted phenylsilanes: The regiochemical course of their metalation dictated by buttressing effects. *Eur. J. Org. Chem.* **2006,** 735.

# CHAPTER 5. GENERAL CONCLUSIONS

Chapter 2 describes the efficient syntheses of simple oxygenated xanthones using an environmentally benign methodology. It is shown that the xanthone nucleus can be regioselectivly elaborated into an intermediate that is key to the synthesis of psoroxanthin, a cytotoxic compound. Progress towards the total synthesis of psoroxanthin is ongoing in our labs.

Chapter 3 describes the syntheses of analogues of an anti-HIV natural product. In structure activity relationship studies, it was shown that the aldehyde functional group is important to the anti-HIV properties. An imporoved procedure for the synthesis of the 2,2-dimethylbenzopyran unit was also developed.

Chapter 4 describes the unexpected regioselectivity in the metaltion of 4,6-dibromorescorinol dimethyl ether with LiTMP. It occurred between the bromines.

## ACKNOWLEDGMENTS

Thank you, Dr. Kraus, for everything. Your clear thinking and reliable guidance inspire confidence in me.

Thank you Drs. Phillips, Schmidt-Rohr, Winter, and Zhao, my program of study committee. Thank you also Dr. Larock for serving on the POSC for my preliminary oral exam.

Thank you fellow Kraus group members, past and present. I am proud to be in your number.

Thank you to everyone in the office of the Department of Chemistry at Iowa State University—especially Renee Harris, Beverly Nutt, Lynette Edsall, and Patti Boone—for all of your help and caring.

Thank you to my brothers and Mom and Dad, for your constant support, encouragement, love and sacrifice. And thank you to my grandmother, Rosemary Vogel. Memories of you inspire me today.