The Thesis Committee for Eric J. Moorhead
certifies that this is the approved version of the following thesis:

Synthesis of (±)-Methyl Rocaglate Using an Unprecedented Acetyl Bromide Mediated Nazarov Reaction

APPROVED BY
SUPERVISING COMMITTEE:

Supervisor:

Philip D. Magnus

Eric V. Anslyn

Synthesis of (±)-Methyl Rocaglate Using an Unprecedented Acetyl Bromide Mediated Nazarov Reaction

by

Eric J. Moorhead, B.A.

Thesis

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Master of Arts

The University of Texas at Austin

May 2012

Dedication

To my partner, Patrick, who gave me the love and support I needed to pursue my passion.

Acknowledgements

I would like to thank Professor Philip Magnus for all his guidance and support during my graduate career. I would also like to thank the members, past and present, of the Magnus group, especially Bahman Ghavimi, for helpful discussions and insight.

Abstract

Synthesis of (±)-Methyl Rocaglate Using an Unprecedented Acetyl Bromide Mediated Nazarov Reaction

Eric J. Moorhead, M.A.

The University of Texas at Austin, 2012

Supervisor: Philip D. Magnus

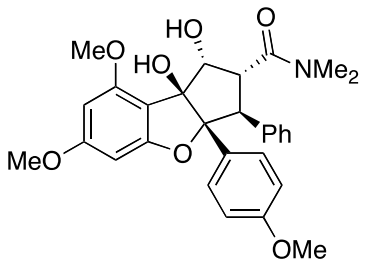
To date, the Nazarov cyclization of a pentadienone has not been a proven methodology towards the construction of the core of the rocaglate natural products. It has been found that this conversion can be achieved using acetylbromide in excellent yield. This represents the first time acetylbromide has been employed in this manner. This methadology provides a very effective and direct route to the core structures of this class of molecules.

Table of Contents

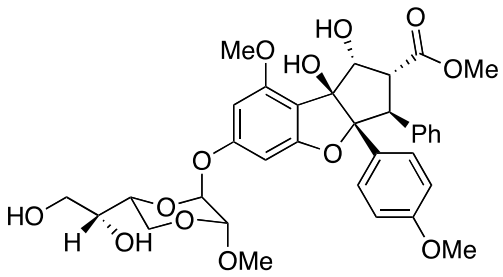
Chapter 1: The Rocaglamide Family of Natural Products and Efforts in Synthesis

1.1 Introduction

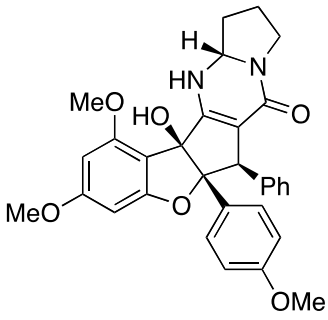
The rocaglamides, isolated from the genus *Aglaia*, represent a unique group of natural products consisting of a cyclopenta[*b*]tetrahydrobenzofuran skeleton (Figure 1.1).[1] This class of natural products derives their name from the parent compound, rocaglamide **1.1.1**, first isolated in 1982.[2]



Rocaglamide 1.1.1



Silvestrol 1.1.2



Aglaiastatin 1.1.3

Figure 1.1 Representative members of the rocaglamide family

This class of molecules has received much attention due to their broad range of biological activities. Almost all members of this family display potent insecticidal activity.[3] However, greater interest lies in the anti-tumor properties of the rocaglamides.[4]

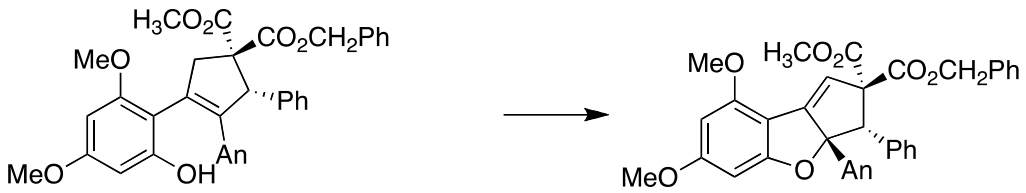
In concentrations of 1-10 ng/mL, rocaglamide **1.1.1** has been shown to operate via a cytostatic mechanism.[5] Higher concentrations of 25 ng/mL have been shown to trigger apoptosis in leukemia cells.[6] This activity, combined with a low toxicity towards normal cells, makes members of the rocaglamide family promising targets in cancer therapy.

1.2 Previous Syntheses

Due to the biological activity of rocaglamide, as well its interesting structure, several research groups have undertaken its total synthesis. Enantioselective syntheses have been reported by Trost[7] and Porco.[8] Racemic syntheses have been reported by Taylor[9], and Frontier.[10] These syntheses tend to suffer from issues of reproducibility, formation of the desired *cis*-aryl geometry, as well as low yielding reactions.

1.2.1 Trost's Enantioselective Synthesis

Trost reported the first total synthesis of rocaglamide.[7] This synthesis established the absolute stereochemistry of (-)-rocaglamide. The key step of this synthesis was the oxidative cyclization of **1.2.1**, via an allylic cation, to form the tricyclic core **1.2.2** (Scheme 1.2.1).



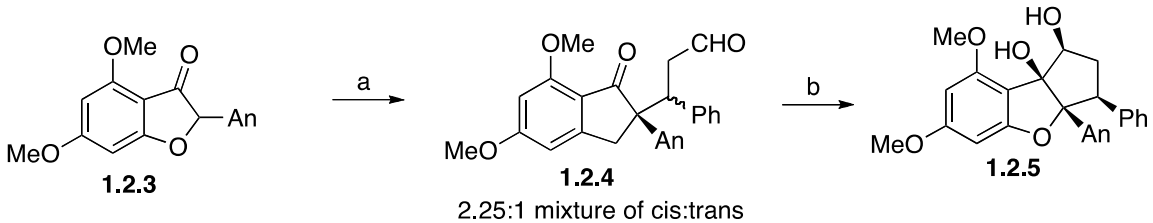
Conditions: DDQ, THF, 75%

Scheme 1.2.1 Formation of tricyclic core

Unfortunately, the approach of the phenolic oxygen was from the same face as the phenolic substituent, thus resulting in the undesired *trans*-aryl geometry. This meant that further steps were needed to establish the desired *cis*-aryl geometry.

1.2.2 Taylor's Synthesis

Taylor's synthesis of rocaglamide is based on the conguate addition of benzofuran **1.2.3** to *E*-cinnamaldehyde. [9] A pinacolic coupling of **1.2.4** will furnish the tricyclic core of rocaglamide (Scheme 1.2.2).



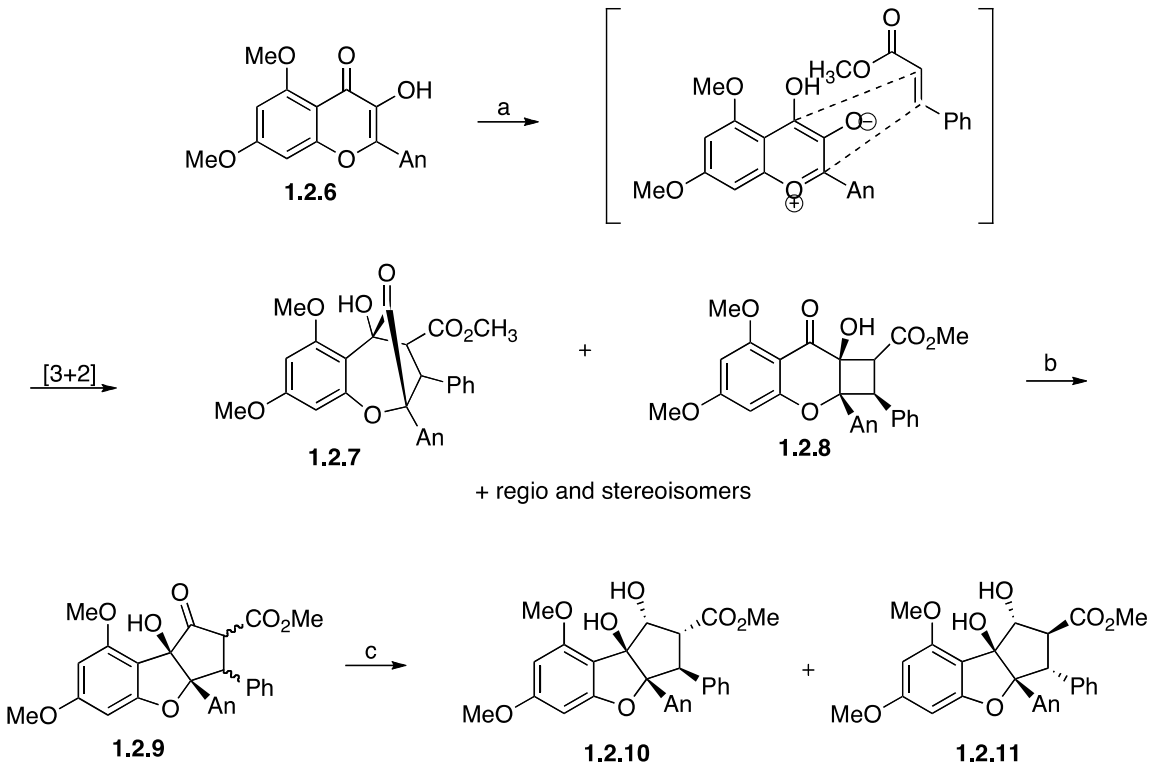
Conditions: (a) *E*-cinnamaldehyde, Triton B, ^{t}BuOH, 69%; (b) SmI_2, THF, 58%.

Scheme 1.2.2 Taylor's formation of the tricyclic core

Taylor's synthesis, while shorter than that of Trost, required separation of diastereomers to afford the correct stereochemistry in the natural product. Also, the SmI_2 promoted pinacolic coupling was not reproducible.

1.2.3 Porco's [3+2] Strategy

Porco's synthesis was based on the proposed biosynthesis of Proksch.[11] It was proven that exposure of hydroxyflavone **1.2.6** in the presence of methyl cinnamate would yield aglain **1.2.7** in 33% yield and benzo[*b*]cyclobutapyran-8-one **1.2.8** in 17% yield (Scheme 1.2.3).[8]



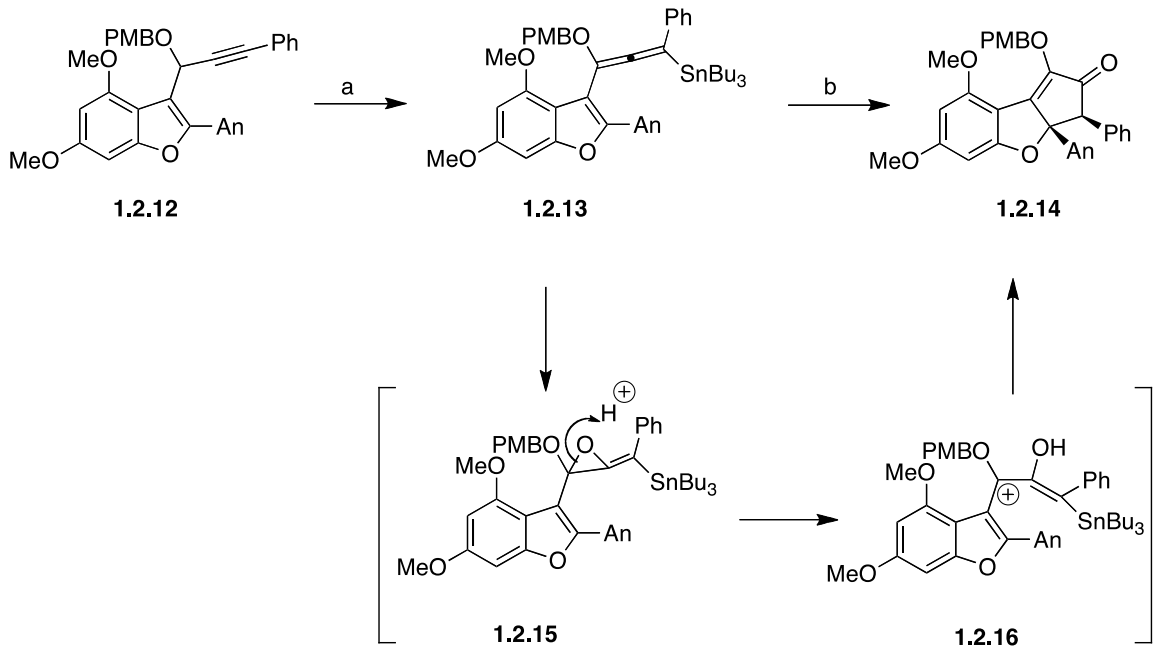
Conditions: (a) methyl cinnamate, *hv* (350 nm), MeOH, **1.2.7** (33%) **1.2.8** (17%); (b) NaOMe, MeOH, 95%; (c) $Me_4NBH(OAc)_3$, MeCN, AcOH, **1.2.10** (51%), **1.2.11** (27%)

Scheme 1.2.3 Porco's Synthesis of the rocaglamide core

However, the photocyclization is neither region- nor stereoselective, requiring the separation of multiple products. Following separation of regioisomers, **1.2.7** and **1.2.8** were treated under basic conditions to induce the alpha-ketol rearrangement to **1.2.9** as a mixture of compounds. Templated reduction yielded both trans-diols **1.2.10** and **1.2.11**. Although this is the shortest route to the rocaglamides, it suffers from a lack of regio- and stereo-selectivity, requiring the separation of products at multiple stages.

1.2.4 Frontier's Synthesis

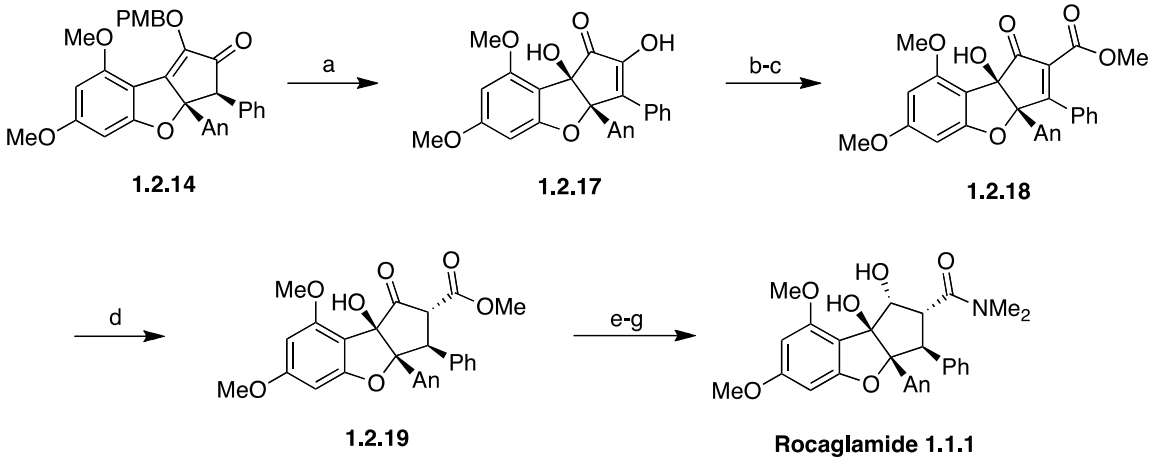
Frontier's synthesis involves the construction of ring C using an epoxide-opening induced Nazarov cyclization. While this did result in the formation of ring C, it was low yielding.[10] Treatment of **1.2.12** with *t*-butyl lithium and subsequent trapping of the allenyl anion with tri-*n*-butylin chloride yielded stannyl alkoxyallene **1.2.13**. Upon treatment of **1.2.13** with excess *m*-CPBA, cyclopentenone **1.2.14** was formed as a single diastereomer. This reaction is presumed to proceed *via* epoxidation of the allenyl ether to give **1.2.15**. This epoxide can open under acidic conditions to yield the pentadienyl cation **1.2.16** which will cyclize to **1.2.14** (Scheme 1.2.4).



Conditions: (a) *t*-BuLi, BuSnCl, Et_2O; (b) *m*-CPBA, DMF, <40% (over 2 steps)

Scheme 1.2.4 Peracid initiated Nazarov cyclization

To complete the synthesis, **1.2.14** was treated with DDQ, cleaving the PMB group, followed by oxidation of the benzylic position to afford **1.2.17**. Palladium catalyzed carbonylative conditions yielded methyl ester **1.2.18**. Trost's hydrogenation conditions[7] afforded cyclopentanone **1.2.19** as a single diastereomer. Templated reduction, saponification and amide formation completed the synthesis of (±)-rocaglamide (Scheme 1.2.5).



1.2.14 **1.2.17** **1.2.18**

1.2.19 **Rocaglamide 1.1.1**

Conditions: (a) DDQ, CH_2Cl_2/H_20, 71%; (b) KHMDS, $PhNTf_2$, THF, 83%; (c) $Pd(PPH_3)_4$, CO, MeOH, *i*PrEtN, THF (83%); (d) PtO_2, H_2, EtOH, 65%; (e) $NaHB(OAc)_3$, MeCN/AcOH, 56%; (f) LiOH, THF/H_2O, 82%; (g) $Me_2NH•HCl$, DCC, DMAP, 60%.

Scheme 1.2.5 Completion of (±)-rocaglamide

1.3 References

(1) Bacher, M.; Hofer, O.; Brader, G.; Vajrodya, S.; Gregor, H. Thapsakins: possible biogenetic intermediates towards insecticidal cyclopenta[*b*]benzofurans from *Aglaia edulis*. *Phytochemistry* **1999**, *52*, 253-263.

(2) King, M. L.; Chiang, C.-C.; Ling, H.-C.; Fujita, E.; Ochiai, M.; McPhail. A. T. X-ray Crystal Structure of Rocaglamide, a Novel Antileukemic 1*H*-Cyclopenta[*b*]benzofuran from *Aglaia elliptifolia*. *J. Chem. Soc., Chem. Commun.* **1982**, 1150-1151.

(3) Bacher, M.; Hofer, O.; Brader, G.; Vajrodya, S.; Gregor, H. Thapsakins: possible biogenetic intermediates towards insecticidal cyclopenta[*b*]benzofurans from *Aglaia edulis*. *Phytochemistry* **1999**, *52*, 253-263.

(4) Cui, B.; Chai, H.; Santisuk, T.; Reutrakul, V.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Kinghorn, A. D. Novel Cytotoxic 1*H*-Cyclopenta[*b*]benzofuran Lignans from *Aglaia elliptica*. *Tetrahedron* **1997**, *53*, 17625-17632.

(5) Lee, S. K.; Cui, B.; Mehta, R. R.; Kinghorn, A. D.; Pezzuto, J. M. Cytostatic mechanism and antitumor potential of novel 1*H*-cyclopenta[*b*]benzofuran lignans isolated from *Aglaia elliptica*. *Chem. Biol. Interact.* **1998**, *115*, 215-228.

(6) Zhu, J. Y.; Lavrik, I. N.; Mahlknecht, U.; Giaisi, M.; Proksch, P.; Krammer, P. H.; Li-Weber, M. The traditional Chinese herbal compound rocaglamide preferentially induces apoptosis in leukemia cells by modulation of mitogen-activated protein kinase activities. *Int. J. Cancer* **2007**, *121*, 1839-1846.

(7) Trost, B. M.; Greenspan, P. D.; Yang, B. V.; Saulnier, M. G. An Unusual Oxidative Cyclization. A Synthesis and Absolute Stereochemical Assignment of (-)-Rocaglamide. *J. Am. Chem. Soc.* **1990**, *112*, 9022-9024.

(8) Davey, A. E.; Taylor, R. J. K. A Novel 1,3-Dithiane-base Cyclopenta-annellation Procedure: Synthesis of the Rocaglamide Skeleton. *J. Chem. Soc., Chem. Commun.* **1987**, 25-27.

(9) Gerard, B.; Jones, II, G.; Porco, J. A. A Biomimetic Approach to the Rocaglamides Employing Photogeneration of Oxidopyryliums Derived from 3-Hydroxyflavones. *J. Am. Chem. Soc.* **2004**, *126*, 13620-13621.

(10) Malona, J. A.; Cariou, K.; Frontier, A. J. Nazarov Cyclization Initiated by Peracid Oxidation: The Total Synthesis of (±)-Rocaglamide. *J. Am. Chem. Soc.* **2009**, *131*, 7560-7561.

(11) Proksch, P; Edrada, R.; Ebel, R.; Bohnenstengel, F. I.; Nugroho, B.W. Chemistry and Biological Activity of Rocaglamide Derivatives and Related Compound in *Aglaia* Species (Meliaceae). *Curr. Org. Chem.* **2001**, *5*, 923-938

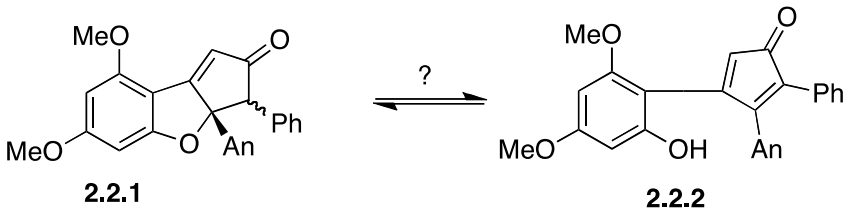
Chapter 2: Previous Work in the Magnus Group

2.1 Introduction

The synthetic challenges of rocaglamide have been of great interest to the Magnus research group over the past several years. In particular, the formation of the desired *cis*-aryl geometry was a focal point of research efforts.

2.2 Synthesis of 1,2-anhydro methyl rocaglate

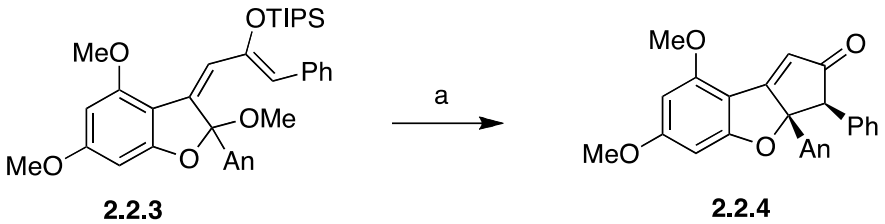
The first methodology explored in the Magnus group centered around whether enone **2.2.1** would equilibrate (*via* beta-hydride elimination), either under acidic or basic conditions, to triarylcyclone **2.2.2** (Scheme 2.2.1). If such an equilibrium existed, would there be a preference for *cis*-or-*trans* aryl geometry?[1]



2.2.1 **2.2.2**

Scheme 2.2.1 Hypothesized equilibration

In order to test this hypothesis, TIPS enol ether **2.2.3** was constructed and subsequently treated with $SnCl_4$ to give the cyclization product **2.2.4** (Scheme 2.2.2).

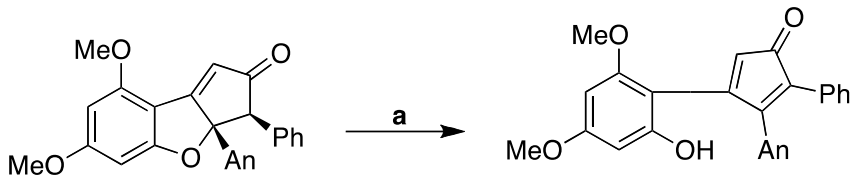


2.2.3 **2.2.4**

Conditions: (a) $SnCl_4$, CH_2Cl_2, 50%

Scheme 2.2.2 Nazarov or Mukaiyama condensation

With enone **2.2.4** in hand, the beta-hydride-elimination hypothesis could be tested. Upon exposure of enone **2.2.4** to basic conditions, the deep crimson color characteristic of cyclone **2.2.5** was observed (Scheme 2.2.3).

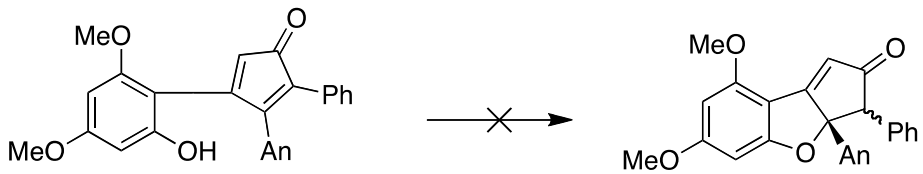


2.2.4 **2.2.2**

Conditions: (a) KO*t*Bu/*t*BuOH

Scheme 2.2.3 Formation of triarylcyclone

However, cyclization of the phenol oxygens back onto the enone could not be induced under a variety of conditions (Scheme 2.2.4).

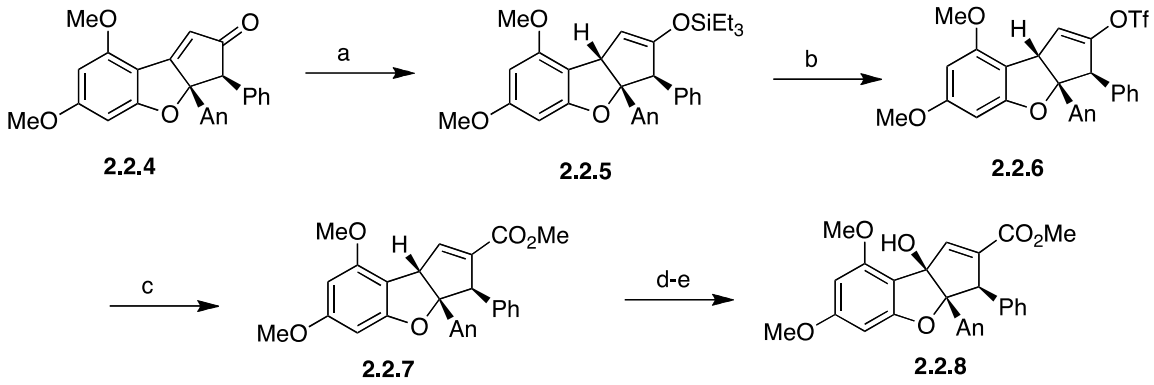


2.2.2 **2.2.1**

Scheme 2.2.4 Attempt to cyclize

Unfortunately, the initial hypothesis had been proven incorrect. However, **2.2.4** was further functionalized to **2.2.5** *via* hydrosilylation. Desilylation followed by an enolate trapping afforded enol triflate **2.2.6**. Palladium catalyzed carbonylation of **2.2.6**

afforded the ester moiety in **2.2.7**. Benzylic oxidation to the peroxide, followed by reduction, yieled 1,2-anhydro methyl rocaglate **1.2.8** (Scheme 2.2.5).[1]



Conditions: (a) Et_3SiH, $RhCl(PPh_3)_3$, benzene, 88%; (b) $BnMe_3NF$, $PhNTf_2$, 4**Å** MS, THF, 74%; (c) CO (G), $Pd(OAc)_2$, PPh_3, Et_3N, MeOH, DMF, 82%; (d) *t*-BuOOH, DARCO, K_2CO_3, benzene, (e) Al(Hg), THF, 36% (2 steps).

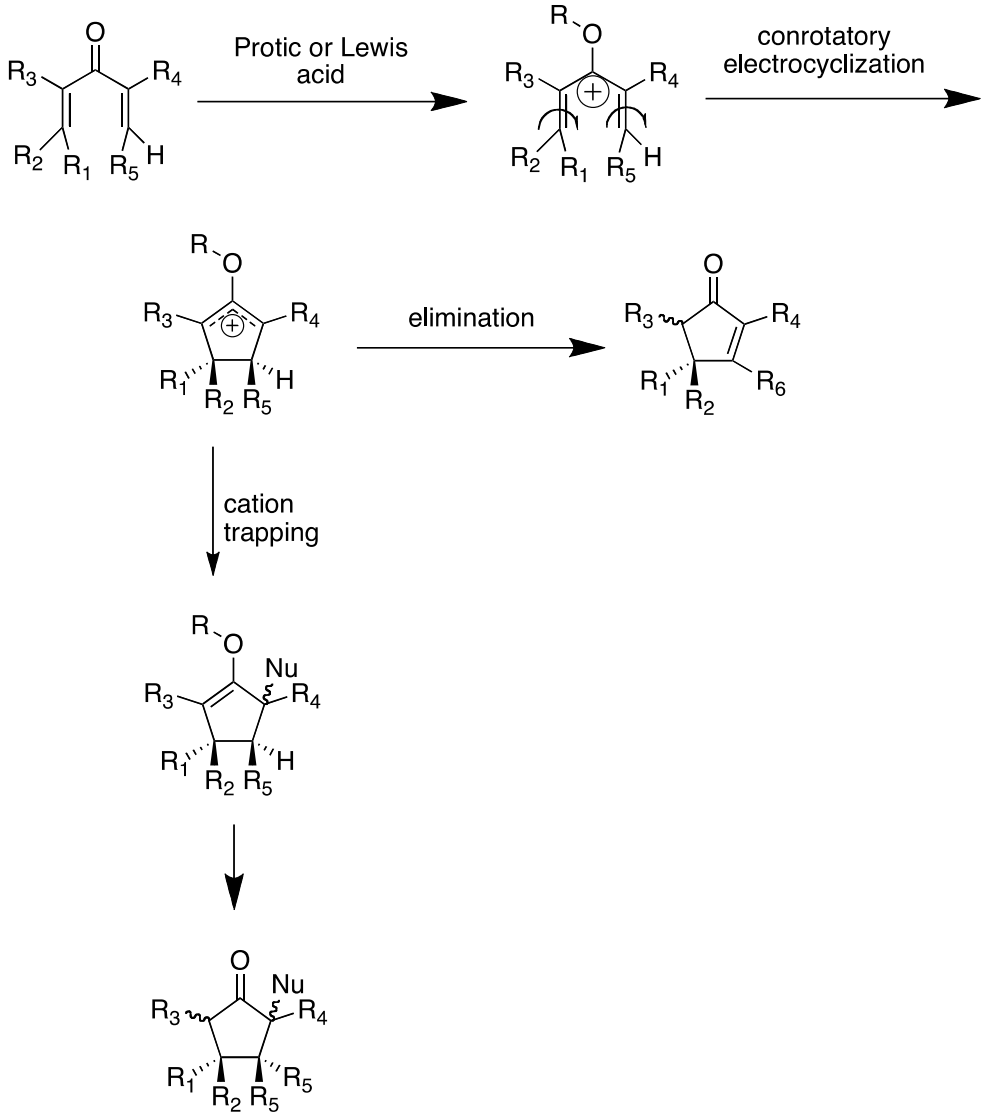
Scheme 2.2.5. Formation of 1,2-anhydro methyl rocaglate

Unfortunately, this synthetic route toward rocaglamide was abandoned as sufficient amounts of alcohol **2.2.8** could not be procured.

2.3 Studies of the Nazarov Cyclization

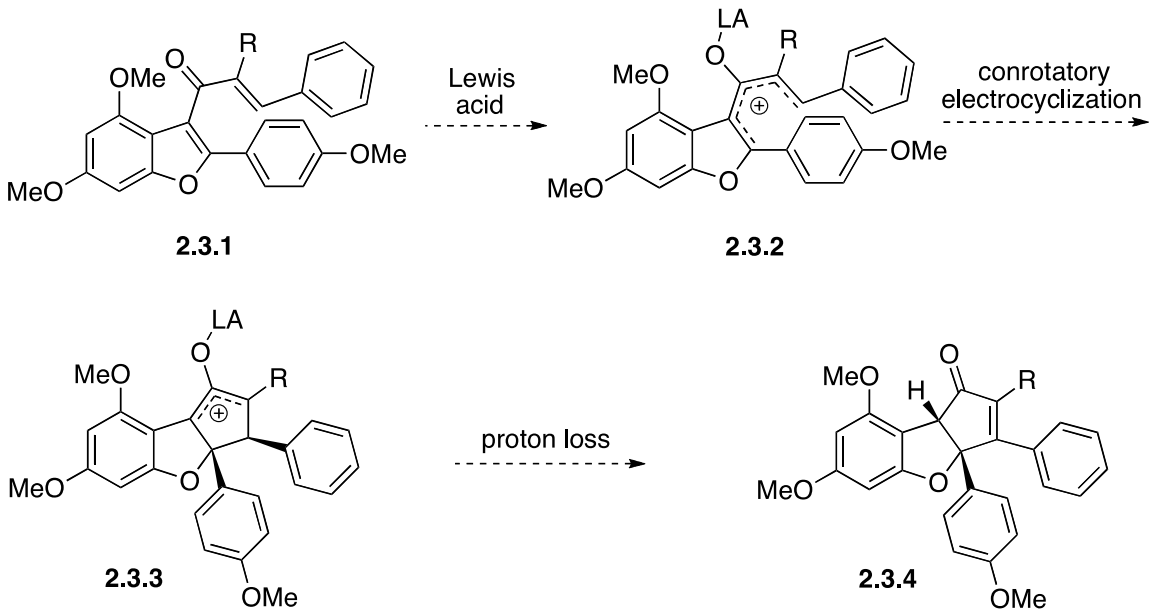
In keeping with the theme of diastereoselective synthesis of ring C, alternative routes were explored in the Magnus group. The Nazarov cyclization represents an attractive methodology for the formation of the desired *cis*-aryl geometry. Through coordination with either a Lewis or protic acid, a pentadienyl cation can form, which will then undergo a 4π-conrotatory[2] cyclization, forming an allylic cation. This cation, in turn, can either be trapped by a nucleophile or undergo proton loss to become an alkene

(Scheme 2.3.1).[3]



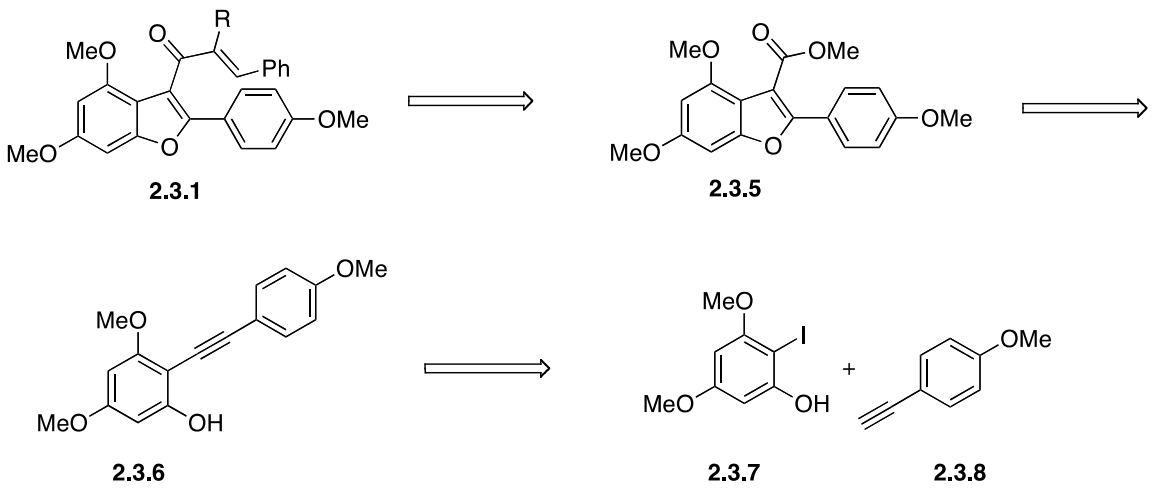
Scheme 2.3.1 Mechanism of Nazarov Cyclization

Upon applying the Nazarov cyclization of a dienone to the synthesis of ring C of rocaglamide, a model system involving a general dienone **2.3.1** was envisioned, by where Lewis acidic conditions could promote a conrotatory electrocyclization (Scheme 2.3.2).



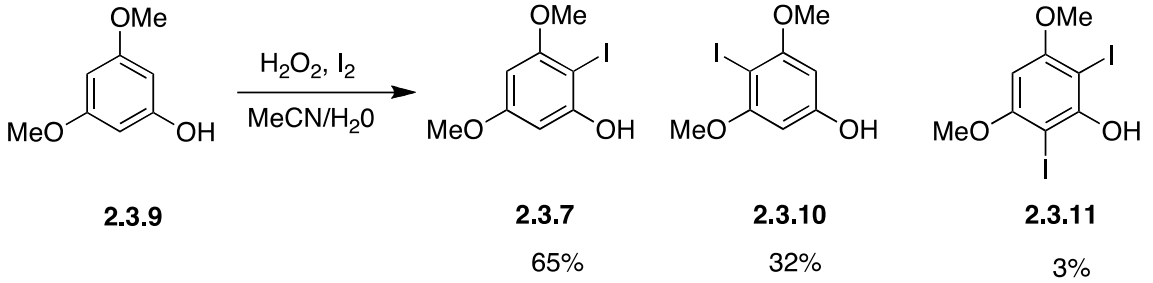
Scheme 2.3.2 Nazarov cyclization to form ring C

General dienone **2.3.1** represents an attractive target for cyclization for many reasons. First, assuming a proton loss mechanism, two stereocenters are formed convergently. Second, the electronics of the cyclization can be tuned using various moieties at the α-position. Thirdly, the synthesis of a variety of dienones of this nature can all be constructed via Horner-Wadsworth-Emmons olefination of the same parent benzofuran **2.3.5**, which is easily constructed from inexpensive, commercially available substrates. Construction of benzo[*b*]carboxylate **2.3.5** could be constructed via Pd(II)-catalyzed carbonylative cyclization of phenolic acetylene **2.3.6**, which is accessible via Kumada coupling of iodophenol **2.3.7** and acetylene **2.3.8** (Scheme 2.3.3).



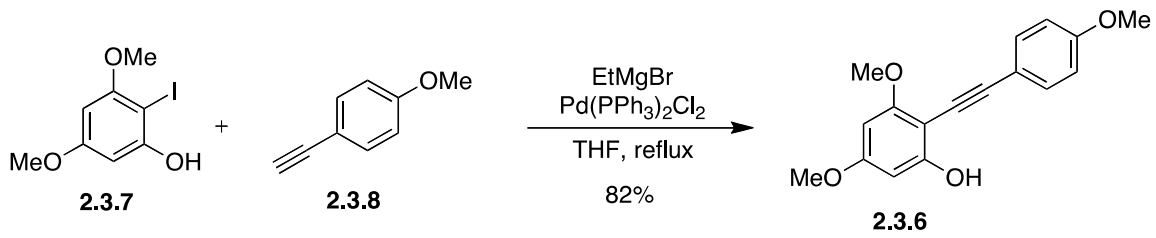
Scheme 2.3.3 Retrosynthesis of dienone 2.3.1

Ortho-iodophenol **2.3.7** is prepared in a 7:3 ratio of the undesired *para*-iodophenol **2.3.10** from 3,5-dimethoxyphenol (Scheme 2.3.4).[4] The two major products are easily separated using column chromatography. Small amounts of the di-iodophenol **2.3.11** can subsequently removed via recrystallization. Furthermore, the undesired *para*-iodophenol can be recycled under acidic conditions to give larger amounts of the *ortho*-iodo compound.



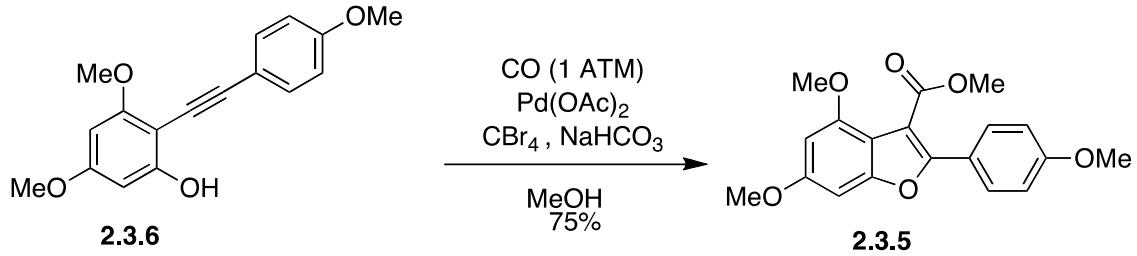
Scheme 2.3.4. Iodination of 3,5-dimethoxyphenol

Acetylene **2.3.6** can be constructed via Kumada[5] cross coupling of iodophenol **2.3.7** and acetylene **2.3.8** in 82% yield (Scheme 2.3.5).[6]



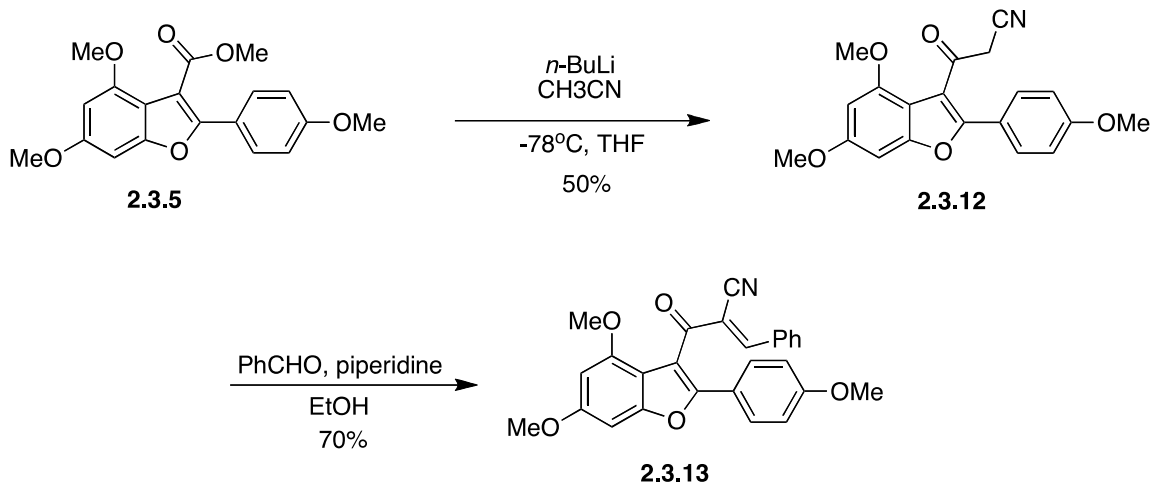
Scheme 2.3.5. Kumada cross coupling

Subsequently, using Palladium(II)-catalyzed carbonylative cyclization, the desired carbonylated benzofuran **2.3.5** can be synthesized. Optimized conditions employing CBr_4 as an oxidant and $NaHCO_3$ as the base produced benzofuran **2.3.5** in 81% yield.[7]



Scheme 2.3.6 Carbonylative cyclization

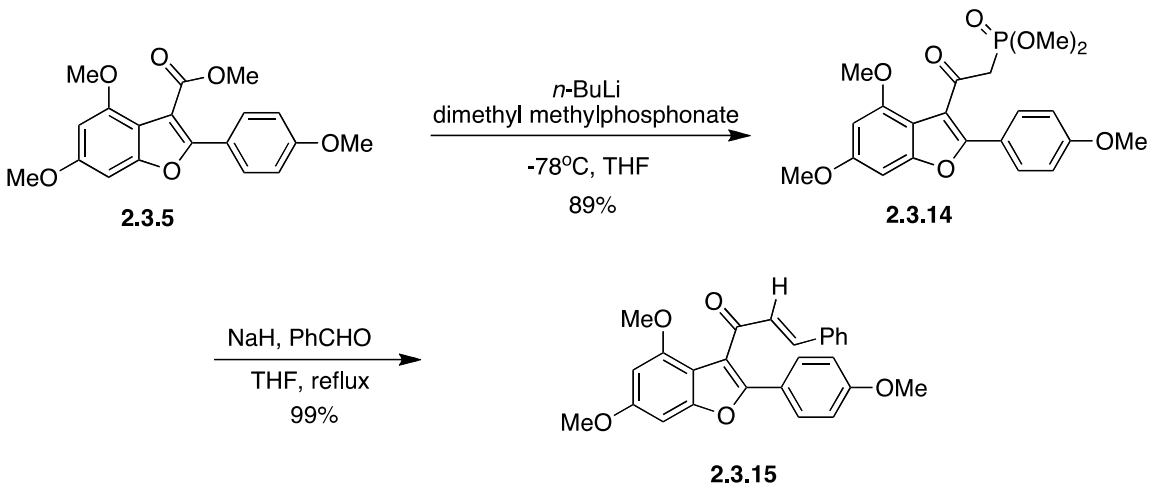
With parent benzofuran in hand, a series of dienones were constructed. The first dienone constructed was the α-cyano dienone **2.3.13**. Treatment of benzofuran **2.3.6** with lithiated acetonitrile formed the α-cyano ketone **2.3.12** in 50% yield. Dienone **2.3.13** was then formed via Knoevenagel condensation with benzaldehye in 70% yield (scheme 2.3.7).[7]



Scheme 2.3.7. Formation of α-cyano dienone

Unfortunately, dienone **2.3.13** was resistant to cyclization under many conditions. Weak Lewis acids such as $Cu(OTf)_2$ returned starting material, while harsher conditions, including Lewis acids $TiCl_4$, $Sc(OTf)_3$, $SnCl_4$, $FeCl_3$ and protic acids H_2SO_4 and HCl all resulted in intractable mixtures. Correspondence with Alison Frontier at the University of Rochester revealed that similar dienones with electron-withdrawing groups at the α-position effectively shut down cyclization.[8] Thus, a new dienone, one with an α-hydrogen, was envisioned.

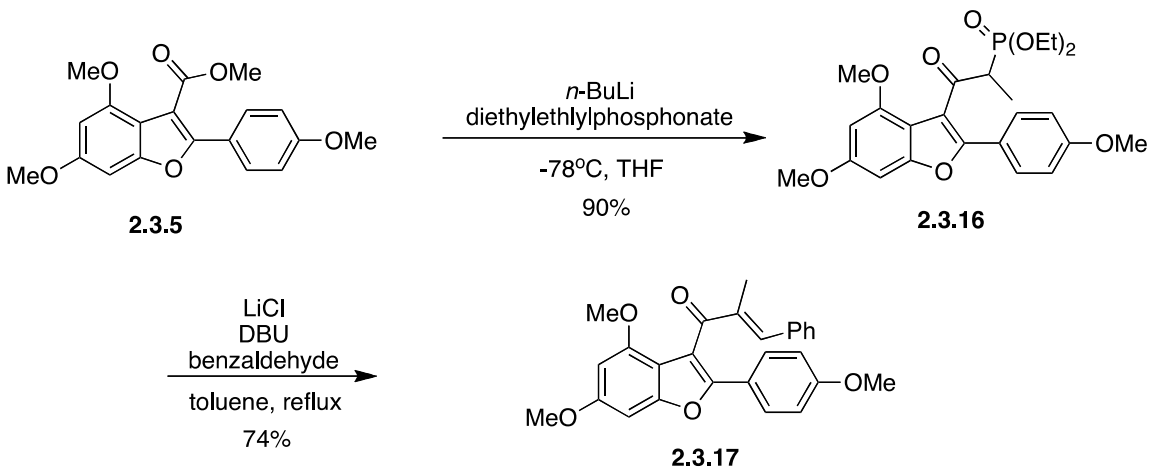
Construction of the α-protio dienone was amenable with parent benzofuran. This dienone, lacking the electron-withdrawing substituent, was thought to be a better substrate for cyclization. In a two step procedure, **2.3.5** was reacted with lithiated dimethyl methylphosphonate providing ß-keto phosphonate **2.3.14** in good yield. Horner-Wadsworth-Emmons olefination with benzaldehyde furnished dienone **2.3.15** in excellent yield (Scheme 2.5).[7]



Scheme 2.3.8 Synthesis of α-protio dienone

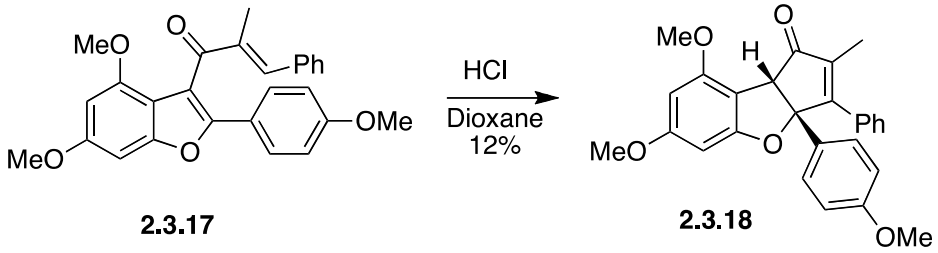
The cyclization of **2.3.15** was screened with many reagents and various conditions. Lewis acids, such as $AlCl_3$and $Se(OTf)_3$, resulted in the retro Friedel-Crafts product. Protic acids such as H_2SO_4 and HCl also furnished a retro Friedel-Crafts product. Interestingly, treatment of **2.3.15** with HCl in dioxane yielded no reaction. It was conjectured that a delocalized cation was being formed under the reaction conditions via the observation of a dark-purple color. If it were possible to stabilize this cation, it was hypothesized that one could shift the equilibrium of the pentadienyl cation and the allylic cation towards the latter. In order to provide stability of the delocalized cation, an α-methyl dienone was constructed.

Treatment of **2.3.5** with lithiated diethyl ethylphosphonate yielded beta-ketophosphonate **2.3.16** in 90% yield. Horner-Wadsworth-Emmons olefination using Masamune-Roush conditions yielded dienone **2.3.17** in 74% yield (Scheme 2.6).[7]



Scheme 2.3.9 Construction of α-methyl dienone

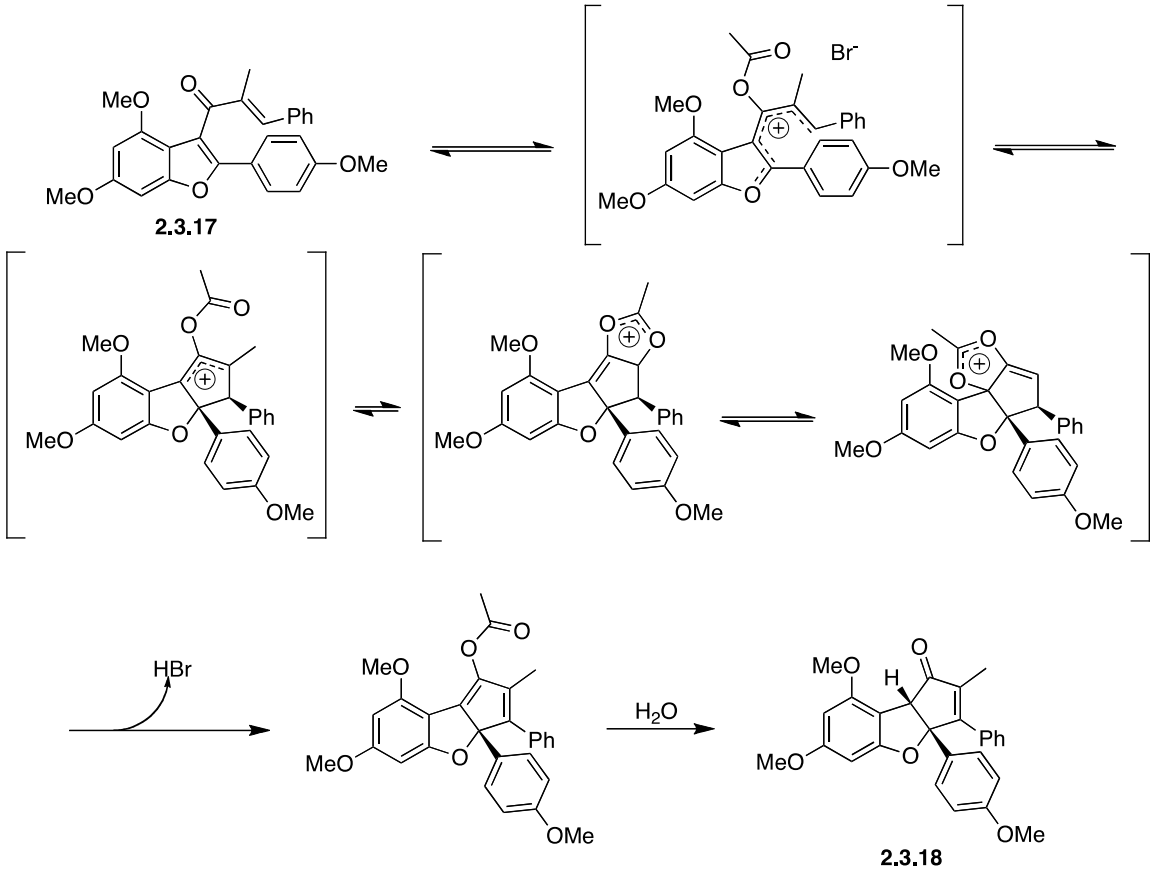
Various conditions were screened for the cyclization of α-methyl dienone **2.3.17**. Lewis acids resulted in fragmentation of the molecule in a retro Friedel-Crafts fashion. However, upon treatment with HCl in dioxane, the cyclized product **2.3.18** was isolated in 12% yield.[7]



Scheme 2.3.10 Nazarov cyclization of α-methyl dienone

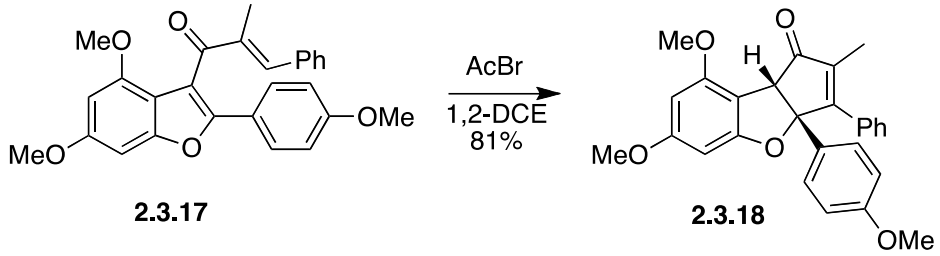
This result substantiated the hypothesis that stabilization of the allylic cation would lead to formation of ring C. In contrasting this reagent with others tried, it was hypothesized that the Lewis-basic oxygens of dioxane could further stabilize the allylic cation in an intermolecular fashion. Expanding from this, one could imagine even further cation stabilization if there were a Lewis basic neighboring group. Acylation of the carbonyl with highly reactive acetly bromide would stabilize the allylic cation through

the neighboring group participation of the acetate. Aqueous workup would then furnish the desired enone **2.3.18** (Scheme 2.3.11).



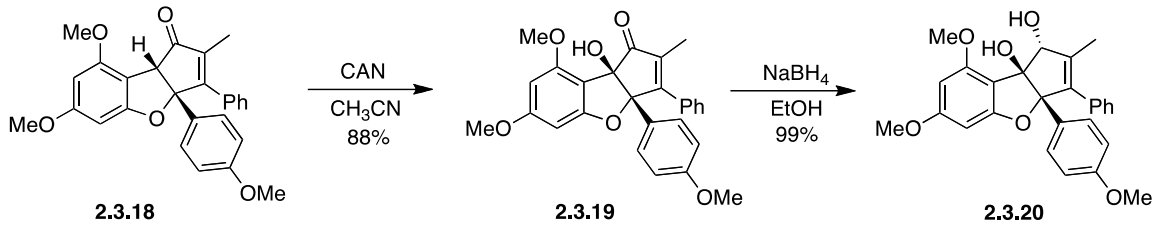
Scheme 2.3.11 Hypothesized mechanism of cyclization.

Pleasingly, when acetyl bromide was employed, the yield of the reaction improved almost seven-fold (Scheme 2.3.12).[9]



Scheme 2.3.12 Nazarov cyclization using acetly bromide

With the cyclized product obtained in good yield, the further functionalization of ring C could be explored. CAN oxidation yielded **2.3.19** in good yield and with the proper stereochemistry, as confirmed via X-ray crystallography. Templated reduction of the ketone yielded the trans-diol **2.3.20** in quantitative yield (Scheme 2.3.13).[7]



Scheme 2.3.13 Further functionalization of ring C

Various reagents to oxidize the allylic methyl group were screened on compounds **2.3.18**, **2.3.19** and **2.3.20**. Selenium dioxide and Pd(II) conditions tended to return starting material. Chromium trioxide/3,5-dimethylpyridine and DDQ conditions destroyed the product. Bromination attempts using NBS/AIBN systems resulted in undesired aromatic bromination of ring A. Unfortunately, no conditions were found to advance these late-stage intermediates to the natural product. It was at this stage in the project that Dr. Wes Freund defended his dissertation.[7]

2.4 References

(1) Magnus, P.; Stent. M. A. H. Stereospecific Synthesis of (±)-1,2-Anhydro Methyl Rocaglate. *Org. Lett.* **2005**, *7*, 3853-3855.

(2) Woodward, R. B.; Hoffmann, R. Stereochemistry of Electrocyclic Reactions. *J. Am. Chem. Soc.* **1965**, *87*, 395-397.

(3) Santelli-Rouvier, C.; Santelli, M. The Nazarov Cyclisation. *Synthesis* **1983**, 429-442.

(4) Jereb, M.; Zupan, M.; Stavber, S. Effective and selective iodofunctionalisation of organic molecules in water using the iodine-hydrogen peroxide tandem. *Chem. Commun*. **2004**, 2614-2615.

(5) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. Alkyl group isomerization in the cross-coupling reaction of secondary alkyl Grignard reagents with organic halides in the presence of nickel-phosphine complexes as catalysts. *J. Am. Chem. Soc.* **1972**, *94*, 9268-9269.

(6) Dr. Trevor Rainey, Ph. D., unpublished results. Studies directed towards the synthesis of irroratin A and studies directed towards the synthesis of rocaglamide and silverstrol. The University of Texas at Austin, **2006**.

(7) Dr. Wes A. Freund, Ph. D., unpublished results. Studies on the Total Synthesis of (±)-Rocaglamide. The University of Texas at Austin, **2006**.

(8) Malona, J. A.; Cariou, K.; Frontier, A. J. Nazarov Cyclization Initiated by Peracid Oxidation: The Total Synthesis of (±)-Rocaglamide. *J. Am. Chem. Soc.* **2009**, *131*, 7560-7561.

(9) Magnus, P.; Freund, W. A.; Moorhead, E. J.; Rainery, T. J. Synthesis of (±)-Methyl Rocaglate Using and Unprecedented Acetyl Bromide Mediated Nazarov Reaction. *J. Am. Chem. Soc.* **2009**, *134*, 6140-6142.

Chapter 3: Completion of the Formal Synthesis of Rocaglamide

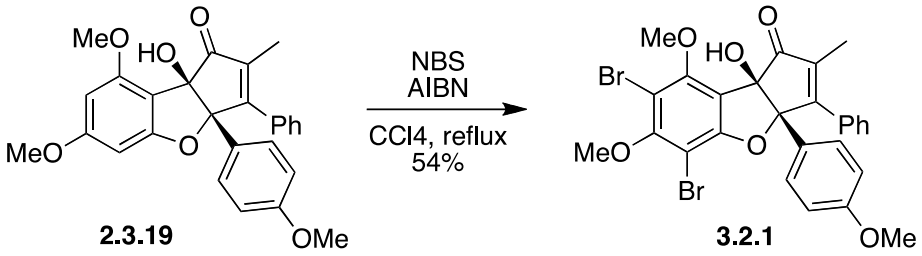
3.1 Introduction

The formation of the tricyclic core using a novel acetyl bromide initiated Nazarov cyclization represented a great advancement in the synthesis of the rocaglamide core. It was determined that the continued exploration of this route was deserved of new attention and continued research effort.

3.2 Exploration of Halogenation

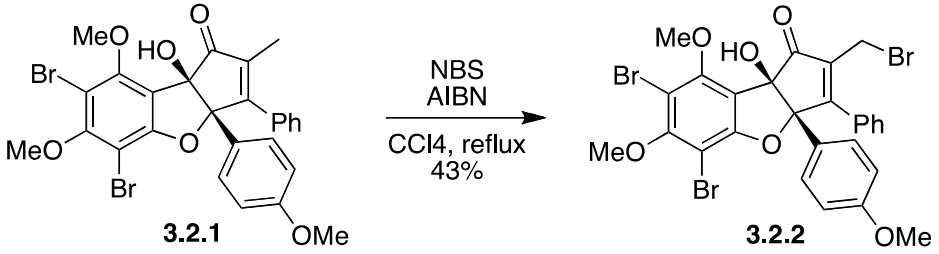
Upon reinvestigation of the problematic oxidation of the allylic methyl group, radical halogenation was revisited. Previous research deomstrated that bromination occurs first on the A-ring. However, it was hypothesized that once the two aryl positions adjacent to the methoxy groups were bromiated, the subsequent bromination would occur at the allyilc methyl position, ideally in a one-pot procedure. The inactivated phenyl would not be brominated and the *ortho* positions on the anisol ring would be too sterically encumbered by the adjacent phenyl ring. Once a functional handle has been installed on the methyl group, subsequent synthetic manipulations could furnish the desired moeity and the aryl bromides could be removed *via* hydrogenation chemistry.

It was upon reaction of **2.3.19** with a large excess of NBS in CCl_4 that the dibrominated product **3.2.1** was isolated rather than the tribrominated product (Scheme 3.2.1).



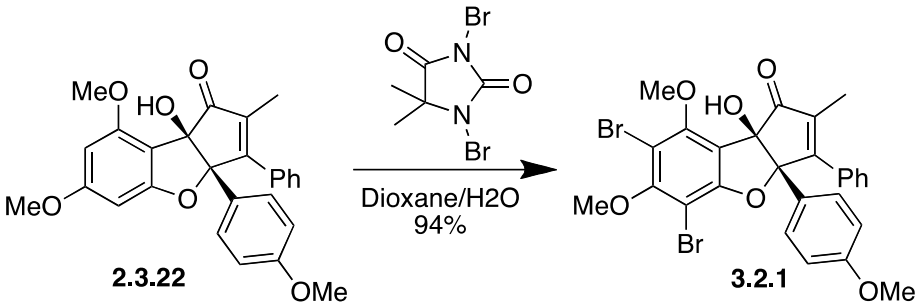
Scheme 3.2.1 Dibromination of ring A

While isolation of the dibrominated product was not ideal, further bromination of **3.2.1** could occur upon treatment with NBS in refluxing CCl_4 to yield **3.2.2** (Scheme 3.2.2).



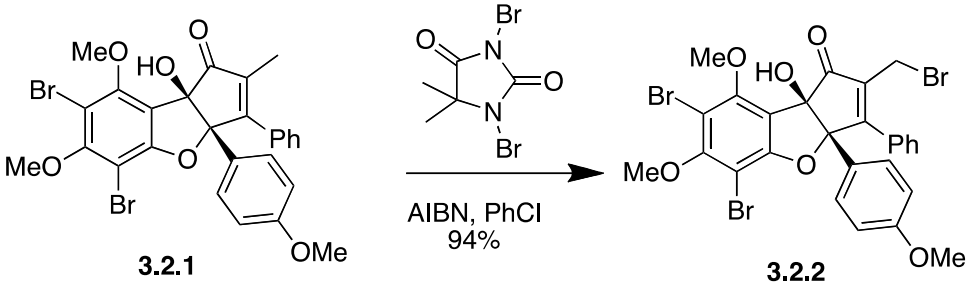
Scheme 3.2.2 Formation of tri-brominated moiety

Although the yields were modest with these conditions, and reaction times were several days, it was established that the allylic methyl group could be oxidized under radical halogenation conditions. New methods of aromatic halogenation were explored, resulting in the optimized treatment of **2.3.19** with 1,3-Dibromo-5,5-dimethylhydantoin in wet dioxane. This provided **3.2.1** in near quantitative yield (Scheme 3.2.3).



Scheme 3.2.3. Optimized aromatic halogenation

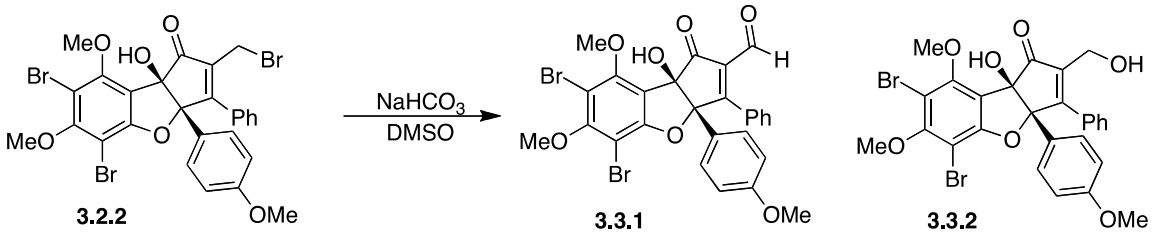
Furthermore, a simple aqueous workup yielded the desired product in spectroscopically pure sample. Optimizing the bromination of the allylic methy group was examined next. It was hypothesized that using a high temperature boiling solvent would reduce reaction time. The first solvent screened was 1,2-dichlorobenze, with a boiling point of 181^{o}C, compared to that of CCl_4, 77^{o}C. 1,2-dichlorobenzene resulted in faster consumption of starting material, but yields were modest, due to the possible decomposition of starting material. Chlorobenzene, with a boiling point of 131^{o}C,between that of CCl_4 and 1,2-dichlorobenzene, was found to be the ideal solvent. Clean conversion to **3.2.2** occurred in a matter of hours, and a simple aqueous workup resulted in pure sample (Scheme 3.2.4).



Scheme 3.2.4 Optimized synthesis of 3.2.2

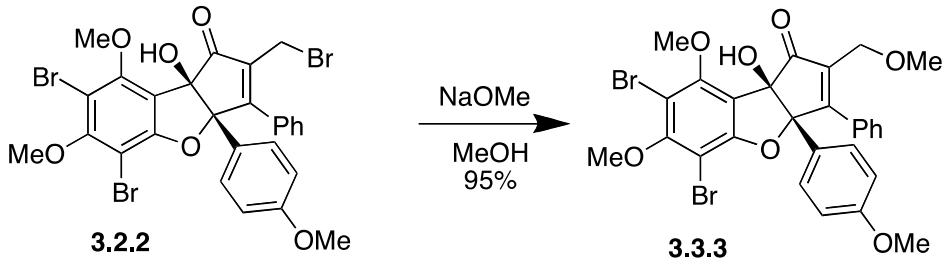
3.3 Further Oxidation Studies

With a scalable and reliable route to **3.2.2**, further oxidation methods were attempted. Upon exposure of **3.2.2** to Kornblum conditions, aldehyde **3.3.1** and **3.2.2** were identified *via* ^{1}H-NMR (Scheme 3.3.1).



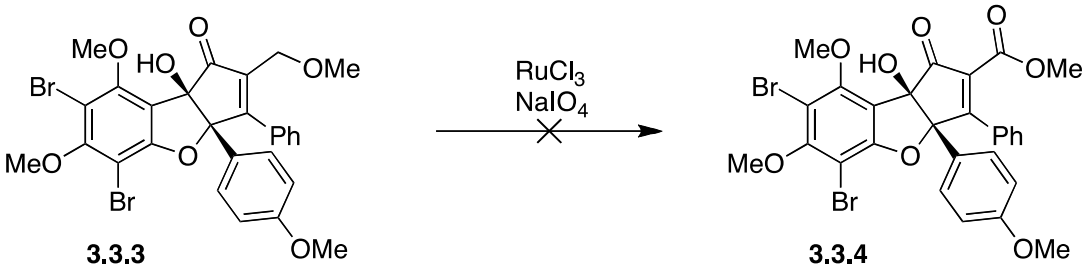
Scheme 3.3.1 Kornblum Oxidation

Unfortunately, both aldehyde **3.3.1** and **3.3.2** proved to be unstable to flash chromatography. It was conjectured that a methyl ether, instead of an aldehyde or an alcohol, would be more robust and amenable to isolation and purification. Pleasingly, treatment of **3.2.2** with freshly prepared $NaOCH_3$/MeOH solution resulted in clean conversion to methyl ester **3.3.3** in excellent yield (Scheme 3.3.2).



Scheme 3.3.2 Conversion to methyl ether

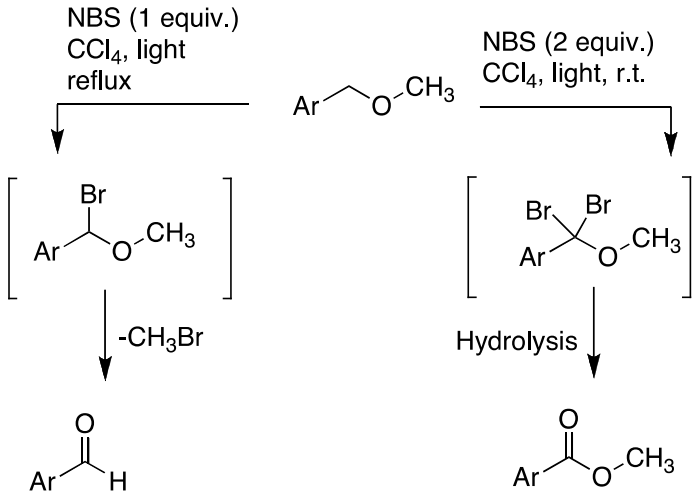
With **3.3.3** in hand, various methods of oxidation were screened for the conversion to **3.3.4** (Scheme 3.3.3).



3.3.3 **3.3.4**

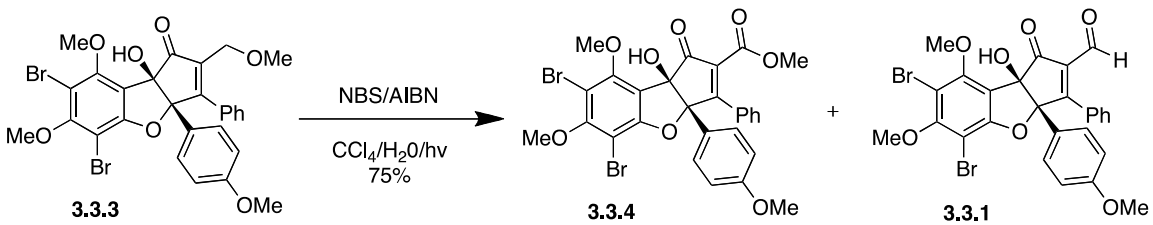
Scheme 3.3.3 Attempted oxidation of 3.3.3

Unfortunately, no adequate conditions were found using Ruthenium based systems. Upon further literature investigation, the oxidation of benzylic methyl ethers to methyl esters was shown to proceed smoothly using 2 equivalents of NBS.[1] If only one equivalent of NBS was used, the aldehyde was isolated (Scheme 3.3.4).



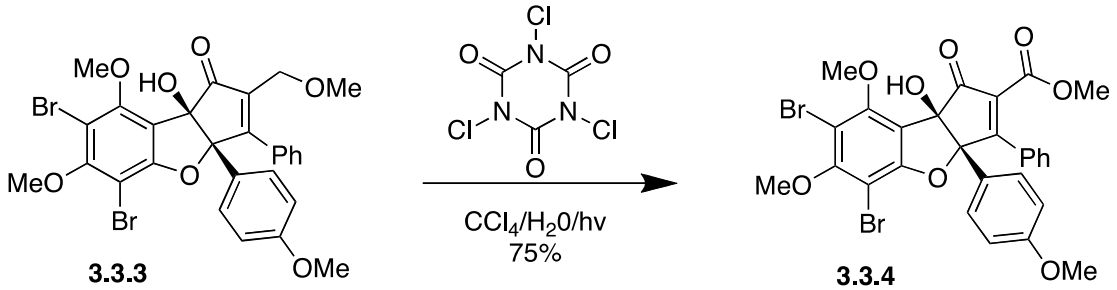
Scheme 3.3.4 Benzylic Oxidation

Upon treatment of **3.3.3** with 2 equivalents of NBS, methyl ester **3.3.4** was observed, as well as aldehyde **3.3.1** (Scheme 3.3.5).



Scheme 3.3.5 NBS mediated oxidation

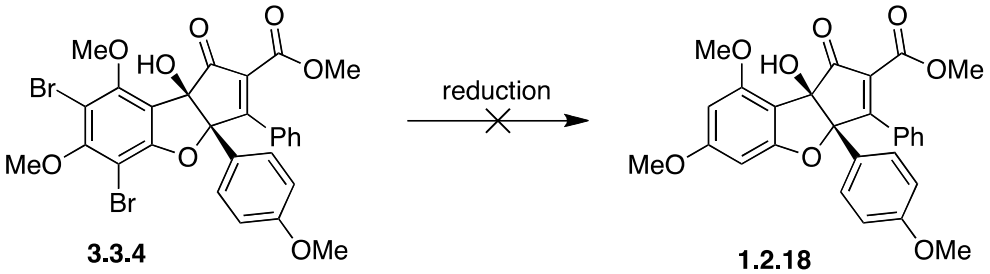
Various other radical halogen sources were screened with a variety of equivalents. It was eventually discovered that treatment of **3.3.3** with an excess of trichloroisocyanuric acid would result in the exclusive formation of **3.3.4** (Scheme 3.3.6).



Scheme 3.3.6 Formation of methyl ester

3.4 Completion of (±)-Methyl Rocaglate

With methyl ester **3.3.4** in hand, various reduction techniques were attempted to remove the aryl bromines to form known advanced intermediate **1.2.18** (Scheme 3.4.1).[2]



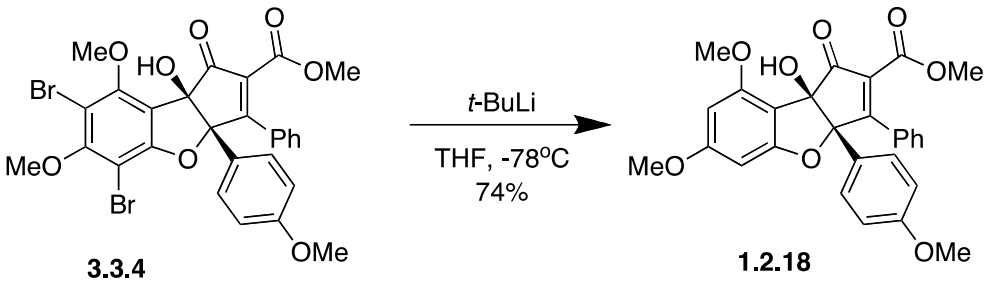
Scheme 3.4.1 Reduction of 3.3.4

A series of transition metal hydride sources were attempted. There was speculation that too strong of a hydride donor would result in the reduction of the α/β-unsaturated ketone or other undesired side reactions. Milder transition metal complexes were screened and unfortunately none resulted in the removal of the aromatic bromines. This data is summarized in the table below.

Reagents and Conditions	**Outcome**
Pd(C), H_2(g), EtOH, r.t.	no reaction
Pd(C), H_2(g), MeOH, r.t.	no reaction
Pd(C), H_2(g), MeOH, 60^oC	decomposition
Raney Nickel, H_2(g), MeOH, r.t.	no reaction
Raney Nickel, H_2(g), MeOH, 60^oC	decomposition
Zn, NH_4HCO_3, MeOH, r.t.	no reaction
Zn, NH_4HCO_3, MeOH, 60^oC	decomposition
Pd(C), $(NH_2)_2HCO_3$, MeOH, r.t.	no reaction
Pd(C), $(NH_2)_2HCO_3$, MeOH, 60^oC	decomposition

Table 3.4 Attempts at Reduction

With no leads using this method, it was envisioned that lithium-halogen exchange with compound **3.3.4**, followed a quench with water, could produce **1.2.18**. Treatment of **3.3.4** with *n*-butyl lithium resulted in a complex mixture of products. It was believed that *n*-butyl lithium could both displace the ester and well as add into the α/β- unsaturated ketone. It was hypothesized that *t*-butyl lithium, due to its steric bulk, would be less prone to addition. Pleasingly, treatment of **3.3.4** with a large excess of *t*-BuLi resulted in **1.2.18** in good yield (Scheme 3.4.2).



Purification via column chromatography completed the synthesis of (±) methyl rocaglate.[3] The concise route to the rocaglamide core, 6 steps in this method, represents a very direct and inexpensive method to access this class of natural products.

3.5 References

(1) Mayhoub, A.S.; Talukdar, A.; Cushman, M. An Oxidation of Benzyl Methyl Ethers with NBS that Selectively Affords Aldehydes or Aromatic Methyl Esters. *J. Org. Chem.* **2010**, *75*, 3507-3510.

(2) Malona, J. A.; Cariou, K.; Frontier, A. J. Nazarov Cyclization Initiated by Peracid Oxidation: The Total Synthesis of (±)-Rocaglamide. *J. Am. Chem. Soc.* **2009**, *131*, 7560-7561.

(3) Magnus, P.; Freund, W. A.; Moorhead, E. J.; Rainey, T. J. Synthesis of (±)-Methyl Rocaglate Using and Unprecedented Acetyl Bromide Mediated Nazarov Reaction. *J. Am. Chem. Soc.* **2009**, *134*, 6140-6142.

Chapter 4: Experimental Conditions and Compound Data

4.1 General Information

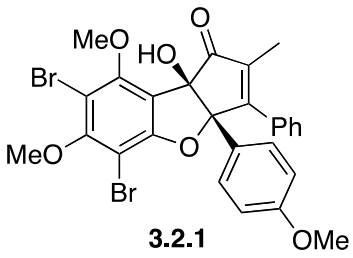
Melting points were measured on a Thomas-Hoover capillary tube apparatus and are uncorrected. Infrared spectra were recorded with a Nicolet FT-IR spectrophotometer as thin films on a NaCl disc. ^{1}H NMR spectra were recorded on a Varian Mercury 400 MHz instrument as solutions in the indicated solvents and are reported in parts per million (ppm) relative to tetramethylsilane and referenced internally to protonated residual solvent. ^{13}C spectra were recorded at 75 MHz on a General Electric QE-300 spectrometer as well as on a Varian Inova 500 MHz instrument and a Varian Inova 600 MHz instrument and are referenced internally to the indicated solvent. Mass spectra were obtained on either a VG ZAB2E or a Finnegan TSQ70 spectrometer using CI.

All reactions requiring anhydrous conditions were performed in oven-dried (110^{o} C for >30 min.) or flame-dried glassware under an atmosphere of argon. Anhydrous solvents were distilled under dry nitrogen as follows: CH_2Cl_2 and 1,2-DCE from CaH_2; THF and Et_2O from sodium benzophenone ketyl. Reactions were monitored using thin-layer chromatography on glass-backed plates coated with silica gel containing a fluorescent indicator (25 μm Silica Gel 60, F_{254}) and were visualized using standard techniques: UV fluorescence (254 or 365 nm); phosphomolybdic acid stain. Flash

column chromatography was preformed on silica gel (Kieselgel 60, 40-60 μm), with the indicated eluent.

4.2 Experimental Conditions and Compound Data

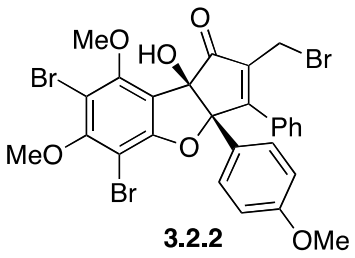
Cyclopentenone 3.2.1



3.2.1

Cyclopentenone **2.3.19** (0.86g, 1.93 mmol) was dissolved in wet dioxane (40mL dioxane, 8 mL H_2O). The flask was cooled to 0 °C and wrapped in aluminum foil. To this mixture was added 5,5-Dimethyl-1,3-dibromohydantoin (2.21g, 7.73 mmol). The solution was stirred at 0 °C for 2 h at which time the starting material had been consumed. The solution was diluted with 50mL H_2O and extracted with EtOAc (3 x 50mL). The organic layer was washed with H_2O (1 x 25mL), brine (1 x 25mL) and subsequently dried ($MgSO_4$) and isolated *en vacuo* to give **20** as light yellow solid (1.09g, 94%). R_f = 0.45 (30% EtOAc in hexane). Mp. 184-186 °C. IR (thin film) 3300, 2979, 2932, 2868, 1721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.40-7.39 (2H, m), 7.34-7.33 (3H, m), 7.25 (2H, d, *J*= 8.0 Hz), 6.88 (2H, d, *J*= 8.8 Hz), 3.96 (3H, s), 3.90 (3H, s), 3.81 (3H, s), 2.08 (3H, s). ^{13}C NMR (600 MHz, $CDCl_3$) 201.1, 160.7, 159.7, 157.6, 156.6, 155.3, 138.8, 132.4, 129.5, 129.4, 128.3, 127.6, 125.7, 117.9, 113.9, 105.7, 99.3, 95.8, 86.6, 62.2, 60.8, 55.2, 10.5. HRMS calculated for $C_{27}H_{22}O_6Br_2$ $(M)^+$ 601.9763. Found 601.9756.

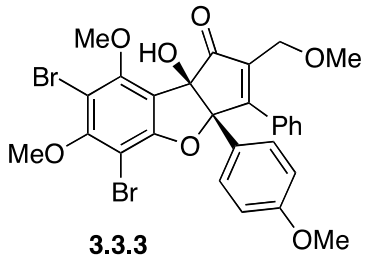
Cyclopentenone 3.2.3



3.2.2

To a solution of brominated cyclopentenone **3.2.1** (0.25g, 0.42mmol) and 5,5-dimethyl-1,3- dibromohydantoin (0.12g, 0.42 mmol) dissolved in chlorobenzene (15mL) was added AIBN (3.4 mg, 0.021 mmol). The solution was heated to reflux for 3h. The solvent was removed *in vacuo* to yield a light brown solid. This residue was taken up in EtOAc (25 mL) and washed with H_2O (3 x 10mL), brine (1 x 10mL) and subsequently dried ($MgSO_4$) and evaporated *in vacuo* to give **21** as light yellow solid (0.27g, 94%). R_f = 0.52 (30% EtOAc in hexane). Mp. 176-178 °C. IR (thin film) 3257, 2983, 2936, 1722, 1514 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.50-7.38 (5H, m), 7.27 (2H, d, *J*= 6.8 Hz), 6.91 (2H, d, *J*= 8.8 Hz), 4.23 (1H, d, *J*= 14 Hz), 4.14 (1H, *J*= 14 Hz), 3.97 (3H, s), 3.91 (3H, s), 3.80 (3H, s). ^{13}C NMR (600 MHz, $CDCl_3$) 198.6, 177.5, 163.2, 160.0, 157.8, 156.6, 155.4, 137.9, 131.2, 130.5, 129.1, 128.7, 127.5, 125.0, 117.4, 114.2, 106.0, 99.0, 95.3, 87.1, 62.3, 60.9, 55.2. HRMS calculated for $C_{27}H_{21}O_6Br_3Na$ $(M+Na)^+$ 700.8781. Found 700.8784.

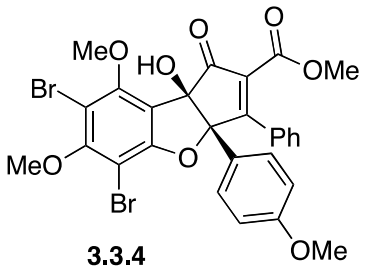
Methyl Ether 3.2.3



3.3.3

The bromide **3.2.2** (0.27g, 0.39mmol) at room temperature under argon was treated with 20mL of freshly prepared 0.1N $NaOCH_3$ in methanol. The reaction was stirred at room temperature for an hour at which time the starting material had been consumed. The solvent was evaporated *in vacuo* to yield a light yellow solid. The residue was taken up in EtOAc (25 mL) and washed with H_2O (3 x 10mL), brine (1 x 10mL) and subsequently dried ($MgSO_4$) and evaporated *in vacuo* to give **22** as light yellow solid (0.24g, 95%). R_f = 0.35 (30% EtOAc in hexane). Mp. 160-162 °C. IR (thin film) 3327, 3017, 2940, 1722, 1593 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.57-7.55 (2H, m), 7.36-7.34 (3H, m), 7.26 (2H, d, *J*= 8.0 Hz), 6.89 (2H, d, *J*= 8.8 Hz), 4.26 (1H, d, *J*= 14.0 Hz),4.16 (1H, d, *J*= 14 Hz), 3.94 (3H, s), 3.90 (3H, s), 3.78 (3H, s), 3.40 (3H, s). ^{13}C NMR (600 MHz, $CDCl_3$) 218.1, 154.5, 153.1,153.0, 152.9, 141.7, 134.0, 116.7, 110.0, 107.2, 106.5, 105.9, 104.0, 103.9, 103.6, 103.4, 87.5, 87.3, 86.6, 52.4, 52.3, 48.2, 40.2, 32.6. HRMS calculated for $C_{28}H_{24}O_7Br_2Na$ $(M+Na)^+$ 652.9781. Found 652.9781.

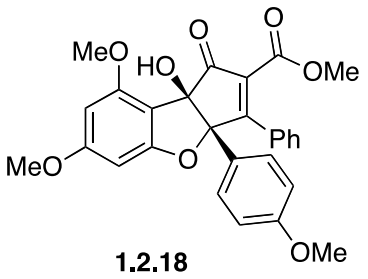
Methyl Ester 3.2.4



3.3.4

To methyl ether **3.3.3** (56mg, 0.098 mmol) in CCl_4 (5 mL) was added trichloroisocyanuric acid (65mg, 0.18 mmol). A 50 watt bulb was placed approximately 10 cm from the flask. The reaction was illuminated for 4 hours at which time the starting material had been consumed. Then was added 5mL of 0.1N KOH solution (50% H_2O, 50% acetonitrile) and the reaction was stirred for 15 min. The reaction was diluted with 15 mL H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The organic layer was washed with H_2O (1 x 15 mL) and brine (1 x 15mL) and dried ($MgSO_4$) and evaporated i*n vacuo* to give a light yellow solid. The solid was taken up in EtOAc and filtered over a plug of silica to give **23** as a slight yellow solid (43mg, 75%). R_f = 0.30 (30% EtOAc in hexane). Mp. 155-157 °C. IR (thin film) 3430, 3015, 2940, 2852, 2362, 1733, 1609 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.43-7.31 (7H, m) 6.93 (2H, d, *J*= 9.2 Hz), 3.94 (3H, s), 3.90 (3H, s), 3.82 (3H, s), 3.80 (3H, s). ^{13}C NMR (600 MHz, $CDCl_3$) 195.6, 166.1, 163.6, 160.2, 158.0, 156.8, 155.4, 133.4, 131.4, 130.6, 129.6, 128.5, 127.5, 124.6, 117.2, 114.3, 106.2, 98.8, 95.9, 87.7, 62.4, 60.9, 55.3, 52.8. HRMS calculated for $C_{28}H_{22}O_8Br_2Na$ $(M+Na)^+$ 668.9556. Found 668.9587.

(±)-Methyl Rocaglate 1.2.18



1.2.18

To a solution of methyl ester **3.3.4** (43 mg, 0.067 mmol) in THF at -78 °C was added *t*-butyl lithium (0.4 mL of 1.6M solution in pentane, 0.67 mmol). The reaction was stirred at -78 °C for 30 min, at which point the reaction was quenched with 1.0 mL H_2O. The reaction mixture was diluted with 10mL H_2O and the aqueous layer was extracted with EtOAc (2 x 10mL). The organic layer was washed with H_2O (1 x 10mL) and brine (1 x 10mL), dried (MgSO4) and evaporated *in vacuo* to give a light yellow solid. This solid was purified via flash chromatography (10-50% EtOAc/Hexanes) to yield **24** as a white solid Mp. 188-192 °C (24 mg, 74%). R_f= 0.09 (30% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) 7.43-7.31 (7H, m) 6.93 (2H, d, *J*= 8.8 Hz), 6.11 (1H, d, *J*= 2.0 Hz), 6.06 (1H, d, *J*= 2.0 Hz) 3.94 (3H, s), 3.90 (3H, s), 3.82 (3H, s), 3.80 (3H, s). ^{13}C NMR (600 MHz, $CDCl_3$) 196.3, 165.1, 164.7, 164.2, 161.1, 159.9, 158.5, 132.3, 129.9, 129.8, 129.5, 128.4, 127.5, 125.5, 114.1, 105.9, 98.7, 92.8, 88.8, 87.0, 55.7, 55.6, 55.2, 52.6. HRMS calculated for $C_{28}H_{24}O_8Na$ $(M+Na)^+$ 511.1363. Found 511.1364.

Chapter 5: Bibliography

(1) Bacher, M.; Hofer, O.; Brader, G.; Vajrodya, S.; Gregor, H. Thapsakins: possible biogenetic intermediates towards insecticidal cyclopenta[*b*]benzofurans from *Aglaia edulis*. *Phytochemistry* **1999**, *52*, 253-263.

(2) King, M. L.; Chiang, C.-C.; Ling, H.-C.; Fujita, E.; Ochiai, M.; McPhail. A. T. X-ray Crystal Structure of Rocaglamide, a Novel Antileukemic 1*H*-Cyclopenta[*b*]benzofuran from *Aglaia elliptifolia*. *J. Chem. Soc., Chem. Commun.* **1982**, 1150-1151.

(3) Bacher, M.; Hofer, O.; Brader, G.; Vajrodya, S.; Gregor, H. Thapsakins: possible biogenetic intermediates towards insecticidal cyclopenta[*b*]benzofurans from *Aglaia edulis*. *Phytochemistry* **1999**, *52*, 253-263.

(4) Cui, B.; Chai, H.; Santisuk, T.; Reutrakul, V.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Kinghorn, A. D. Novel Cytotoxic 1*H*-Cyclopenta[*b*]benzofuran Lignans from *Aglaia elliptica*. *Tetrahedron* **1997**, *53*, 17625-17632.

(5) Lee, S. K.; Cui, B.; Mehta, R. R.; Kinghorn, A. D.; Pezzuto, J. M. Cytostatic mechanism and antitumor potential of novel 1*H*-cyclopenta[*b*]benzofuran lignans isolated from *Aglaia elliptica*. *Chem. Biol. Interact.* **1998**, *115*, 215-228.

(6) Zhu, J. Y.; Lavrik, I. N.; Mahlknecht, U.; Giaisi, M.; Proksch, P.; Krammer, P. H.; Li-Weber, M. The traditional Chinese herbal compound rocaglamide preferentially induces apoptosis in leukemia cells by modulation of mitogen-activated protein kinase activities. *Int. J. Cancer* **2007**, *121*, 1839-1846.

(7) Trost, B. M.; Greenspan, P. D.; Yang, B. V.; Saulnier, M. G. An Unusual Oxidative Cyclization. A Synthesis and Absolute Stereochemical Assignment of (-)-Rocaglamide. *J. Am. Chem. Soc.* **1990**, *112*, 9022-9024.

(8) Davey, A. E.; Taylor, R. J. K. A Novel 1,3-Dithiane-base Cyclopenta-annellation Procedure: Synthesis of the Rocaglamide Skeleton. *J. Chem. Soc., Chem. Commun.* **1987**, 25-27.

(9) Gerard, B.; Jones, II, G.; Porco, J. A. A Biomimetic Approach to the Rocaglamides Employing Photogeneration of Oxidopyryliums Derived from 3-Hydroxyflavones. *J. Am. Chem. Soc.* **2004**, *126*, 13620-13621.

(10) Malona, J. A.; Cariou, K.; Frontier, A. J. Nazarov Cyclization Initiated by Peracid Oxidation: The Total Synthesis of (±)-Rocaglamide. *J. Am. Chem. Soc.* **2009**, *131*, 7560-7561.

(11) Proksch, P; Edrada, R.; Ebel, R.; Bohnenstengel, F. I.; Nugroho, B.W. Chemistry and Biological Activity of Rocaglamide Derivatives and Related Compound in *Aglaia* Species (Meliaceae). *Curr. Org. Chem.* **2001**, *5*, 923-938

(12) Magnus, P.; Stent. M. A. H. Stereospecific Synthesis of (±)-1,2-Anhydro Methyl Rocaglate. *Org. Lett.* **2005**, *7*, 3853-3855.

(13) Woodward, R. B.; Hoffmann, R. Stereochemistry of Electrocyclic Reactions. *J. Am. Chem. Soc.* **1965**, *87*, 395-397.

(14) Santelli-Rouvier, C.; Santelli, M. The Nazarov Cyclisation. *Synthesis* **1983**, 429-442.

(15) Jereb, M.; Zupan, M.; Stavber, S. Effective and selective iodofunctionalisation of organic molecules in water using the iodine-hydrogen peroxide tandem. *Chem. Commun*. **2004**, 2614-2615.

(16) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. Alkyl group isomerization in the cross-coupling reaction of secondary alkyl Grignard reagents with organic halides in the presence of nickel-phosphine complexes as catalysts. *J. Am. Chem. Soc.* **1972**, *94*, 9268-9269.

(17) Dr. Trevor Rainey, Ph. D., unpublished results. Studies directed towards the synthesis of irroratin A and studies directed towards the synthesis of rocaglamide and silverstrol. The University of Texas at Austin, **2006**.

(18) Dr. Wes A. Freund, Ph. D., unpublished results. Studies on the Total Synthesis of (±)-Rocaglamide. The University of Texas at Austin, **2006**.

(19) Malona, J. A.; Cariou, K.; Frontier, A. J. Nazarov Cyclization Initiated by Peracid Oxidation: The Total Synthesis of (±)-Rocaglamide. *J. Am. Chem. Soc.* **2009**, *131*, 7560-7561.

(20) Magnus, P.; Freund, W. A.; Moorhead, E. J.; Rainery, T. J. Synthesis of (±)-Methyl Rocaglate Using and Unprecedented Acetyl Bromide Mediated Nazarov Reaction. *J. Am. Chem. Soc.* **2009**, *134*, 6140-6142.

(21) Mayhoub, A.S.; Talukdar, A.; Cushman, M. An Oxidation of Benzyl Methyl Ethers with NBS that Selectively Affords Aldehydes or Aromatic Methyl Esters. *J. Org. Chem*. **2010**, *75*, 3507-3510.

(22) Malona, J. A.; Cariou, K.; Frontier, A. J. Nazarov Cyclization Initiated by Peracid Oxidation: The Total Synthesis of (±)-Rocaglamide. *J. Am. Chem. Soc.* **2009**, *131*, 7560-7561.

(23) Magnus, P.; Freund, W. A.; Moorhead, E. J.; Rainey, T. J. Synthesis of (±)-Methyl Rocaglate Using and Unprecedented Acetyl Bromide Mediated Nazarov Reaction. *J. Am. Chem. Soc.* **2009**, *134*, 6140-6142.