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TOTAL SYNTHESIS OF RUBROLIDE L, YANGJINHUALINE 'A' AND THE DEVELOPMENT OF CHIRAL MODIFIERS FOR THE ORITO REACTION

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Resumé

Dans la première partie de cette mémoire, nous décrirons notre synthèse convergente du rubrolide L (**32**), un produit naturel isolé d'une ascidie marine provenant de la côte Sud de l'Espagne. Ce produit possède des propriétés antitumorales, antiphosphatases et est surtout un inhibiteur de la réductase de l'aldose humaine (hARL2). Cet enzyme joue un rôle clé dans la transformation de polyols (glucose en sorbitol) avec le coenzyme NADPH. Par conséquent, le rubrolide L est un produit naturel ayant du potentiel pour traiter les complications causées par le diabète de type II. Simultanément à notre synthèse, Z. Wang, B. Ling et al. ont publié leurs résultats quant à l'étude du mécanisme de l'assemblage du rubrolide L, de la réductase de l'aldose humaine et du coenzyme NADPH. Il a été observé que le rubrolide L se lie avec la réductase de l'aldose d'une manière forte et unique par rapport aux autres rubrolides. L'assemblage de la molécule avec l'enzyme ainsi que son activité inhibitrice remarquable font en sorte que la molécule devient très intéressante au niveau de la synthèse. Les étapes clés de la réaction comportent (i) un couplage Suzuki-Miyaura avec un furanone activé en triflate et (ii) une réaction d'aldol dans laquelle la stéréosélectivité est tout à fait contrôlée par l'encombrement stérique du groupement méthoxyphénol adjacent. Après avoir été bromé, le précurseur pour le produit final était vérifié par la spectroscopie NOESY. Plus récemment, une version améliorée de notre synthèse initiale fut effectuée en utilisant un benzaldéhyde bromé. Cela a simplifié la synthèse en éliminant une étape. Finalement, après quatre étapes, nous avons complété la synthèse du rubrolide L avec un rendement de 37% ou 42% après cinq étapes.

Quant à la deuxième partie de cette mémoire, nous avons effectué une synthèse à partir d'un extrait de la plante *Datura metel* L.*,* le produit final étant le yangjinhualine A (**70**). Ce dernier est un exemple d'un furanone substitué en positions 3, 4 et 5. La plante et son extrait sont caractérisés par des propriétés anti-inflammatoires intéressantes. Un couplage de Suzuki semblable ayant été utilisé pour la synthèse du rubrolide L, une synthèse plus rapide vers le yangjinhualine A a été possible après 6 étapes avec un rendement de 33%.

De plus, nous avons investigué, sans succès, un chemin synthétique pour (-)-hygrine (**91**),

(-)-norhygrine (**92**). Ceci, malgré l'échec, nous a fait comprendre les réactions des organolithiens et des réactifs de Grignard sur les nitriles adjacents d'un centre pyrrolidine. Ceci nous a aidé à développer une synthèse vers la (-)-pyrrolsédamine (**93**).

Finalement, puisque ce mémoire se rapporte à la chimie organique, il inclut aussi le développement de différents modificateurs chiraux pour la réduction asymétrique avec le palladium, tel le cinchonidine. Le cinchonidine (CD) est connu comme un alcaloïde encombré stériquement et est également un composé tête-de-série pour la réduction asymétrique, en particulier, celle d'Orito. Nous avons donc synthetisé avec succès le 3-benzyl-1,7,7-triméthylbicyclo[2.2.1]heptan-2-ol (**117**).

Abstract

In first part of this thesis we describe the total synthesis of the Spanish tunicate constituent rubrolide L (**32**), a potent inhibitor of human aldose reductase (hARL2).[19-24] Blocking this enzyme plays a key role in reducing the quantities of sorbitol found in cells that are insulin independent for glucose diffusion such as nerves, kidneys and the retina.[17] Inhibitors of human aldose reductase inhibitors are few and far between with the only example available on the market in Japan. In tests, rubrolide L showed a five-fold increase in inhibitory property compared to Pfizer's widely studied Sorbinil®. These highly sought biological properties make rubrolide L an eminent target for synthesis. Our previous works based on rubrolide C offered a scaffold upon which our synthesis was designed including a Suzuki coupling reaction, followed by utilization of our newly developed method for regio-controlled aldol condensation. Next, the alkylidene was selectively brominated leaving the methoxyphenyl ring untouched (as confirmed by the Nuclear Overhauser Effect Spectroscopy).* Leaving a final deprotection step before the final product was obtained. Recently, a method was observed by our group in which the regio-controlled aldol condensation was made effective by using a brominated substrate with an unprotected phenol, eliminating one step and opening the door to a potential three-step synthesis. The overall yield for our new synthesis of rubrolide L is 42% over 5 steps or 37% over 4 steps.

In the second part of the synthesis, we further build upon our scaffolding from Rubrolide L to examine the synthesis of yangjinhualine A (**70**), a potential anti-inflammatory agent. The optimized conditions for the Suzuki coupling from rubrolide L served as a sturdy starting point of synthesis from the structurally similar triflate. Yangjinhualine A was synthesized in 6 steps with 33% yield.

In the third part we discuss the synthetic route towards (-)-hygrine (**91**), (-)-norhygrine (**92**). Although unsuccessful in this endeavour, we have further understood the

*See 'Annexe'

reactions of alkylhalides on a nitrile moiety adjacent to a pyrrolidine center. In doing so, we have developped a synthesis towards (-)-pyrrolsedamine (**93**).

And finally, the fourth part describes the development of chiral modifiers for the Orito reaction on a Pt(111) surface; the goal of which was to improve upon the widely used cinchonidine (CD). Reported within are the synthesis of 3-benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**117**).

Acknowledgements

I wish to humbly thank my professor Dr. John Boukouvalas to whom I owe all over the last two years for his continual guidance and counsel. The experience I have gained here will stay with me for as long as I can remember. Without the encouragement you have given me, I might not ever have learned what the world of organic chemistry is truly about.

I would like to lovingly thank my parents Jeff and Suzanne for their continued moral support as well as their brilliance for having enrolled me into a French immersion school as a young child. Without them, I surely would not have the education nor the will to continue and excel in academia, especially in another language. Thank you for continuing to remind me the importance of education and without allowing me to forget the necessity of right and left-brain balance. Thank you for supporting me in whatever path I choose.

Thank you, my colleagues: Nicolas Bruneau-Latour, Charles Thibault, Vincent Albert, Raphael Lafleur-Lambert, and more warmly, Richard Loach, with whom I share this degree for without their direction, insight, companionship and *laughs,* this degree would not have been possible. Through all adversity, and challenges you have been there.

I wish to extend my gratitude to Dr. Robert Young from Simon Fraser University that started me on the path of organic chemistry and worked with the utmost patience, kindness and wisdom alongside someone with little experience. I know my path would be much different had I not had a hero in the domain show me the ropes.

Thanks to Professor Peter McBreen and the students of the McBreen group, I have greatly enjoyed working with you and most definitely appreciate the new things I have learned from working in tandem with your team. It has been a rewarding challenge and has helped shaped me as a chemist. Thank you for exposing me to things I would not normally see as a natural product chemist.

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Abbreviations

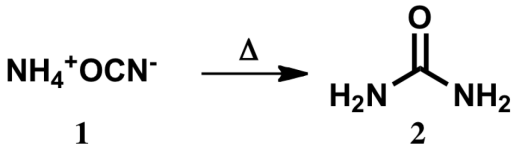
α	observed optical rotation in degrees
[α]	specific rotation
Ac	acetyl
Anhyd	anhydrous
Ar	aryl
Atm	atmosphere
aq	aqueous
av	average
Bn	benzyl
bp	boiling point
br	broad (spectral)
Bu, n-Bu	normal, primary butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
BOC, Boc	*tert*-butoxycarbonyl
Bz	benzoyl (not benzyl)
^{o}C	degrees Celsius
c	concentration
calcd	calculated
CAM	cerium ammonium molybdate
cat	catalytic
calcd	calculated
cb	base catalyzed
cm	centimeter(s)
cm^{-1}	wavenumbers
conc.	concentration
COSY	correlation spectroscopy
Cy	cyclohexyl
δ	chemical shift in parts per million downfield from tetramethylsilane
D	deuterium
d	doublet (spectral), day(s), deci
dd	doublet of doublets (spectral)
dba	trans-dibenzylideneacetone
DBU	l,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
decomp.	decomposition
DEPT	distortionless enhancement by polarization transfer
DIBAL	diisobutylaluminium hydride
DIPEA	N,N-diisopropylethylamine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DOM	directed *ortho* metalation

DNA	deoxyribonucleic acid
dr	diastereomeric ratio
dt	doublet of triplets (spectral)
E1	unimolecular elimination
E2	bimolecular elimination
ED_{50}	dose that is effective in 50% of test subjects
ee	enantiomeric excess
eq	equation
equiv	equivalent
FT	Fourier transformation
GC	gas chromatograhy
Glc	glucose
h	hour(s)
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
hz	hertz
IR	infrared
J	coupling constant (spectral)
L	litre
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
lit.	literature value
LUMO	lowest occupied molecular orbital
μ	micro
M	molar (moles per litre), mega
M^+	molecular parent ion
m	multiplet (spectral)
Me	methyl
min	minute(s), minimum
MHz	megahertz
mM	millimolar (millimoles per litre)
mol	mole(s), molecular (as in mol wt)
mp	melting point
Ms	methylsulfonyl (mesyl)
MS	mass spectroscopy
MTX	maitotoxin
MW, mol wt	molecular weight
m/z	mass-to-charge ratio
N	normal (equivalents per liter)
NAD^+	nicotinamide adenine dinucleotide
NADH	reduced NAD
NBS	N-bromosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy

Ns	*para*-nitrophenylsulfonyl (nosyl)
NSAID	non-steroidal anti-inflammatory drugs
ppm	parts per million
i-Pr	isopropyl
Ph	phenyl
PTC	phase-transfer catalyst
R	any functional group
R_f	retention factor
ROS	reactive oxygen species
rt	room temperature
s	singlet (spectral)
SEM	scanning electron microscopy
SM	starting material
STM	scanning tunneling microscopy
t	triplet (spectral), time, temperature in units of Celsius (^{o}C)
td	triplet of doublets (spectral)
TBS	*tert*-butyldimethylsilyl
temp	temperature
THF	tetrahydrofuran
Tf	trifluromethanesulfonyl (triflyl)
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl, or tetramethylsilane
Ts	*para*-toluenesulfonyl (tosyl)
UHV	ultra-high vacuum
UV	ultraviolet
vis	visible
vol	volume
v/v	volume per unit volume (volume-to-volume ratio)
wt	weight
w/w	weight per unit weight (weight-to-weight ratio)

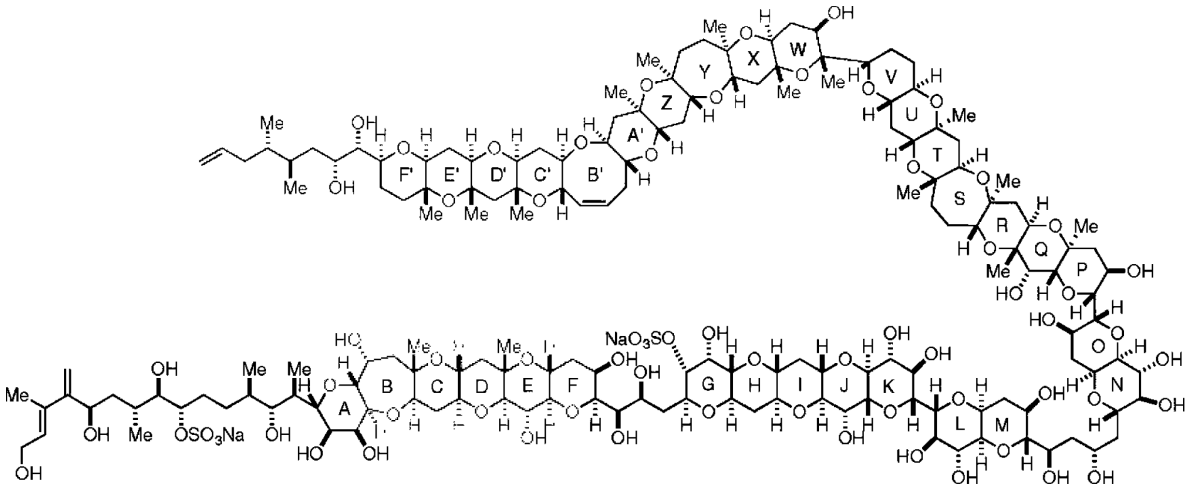
General Introduction

Since the very beginning, early humans have needed to be able to tell the difference between materials in their world to eat and prepare food and care for the ill and injured. In the 18th century scientists began to put shape to their perspective of organic chemistry. It was understood until 19th century that chemists could not create life, as it must contain an immeasurable vital force. It was thought that scientists would never be able to synthesize 'organic' compounds (termed 'organic' coined by Jöns Jakob Berzelius) as they were derived from 'divine conception'. It was groundbreaking for the scientific community when in 1828, Friedrich Wöhler first synthesized[i] urea (**2**), a natural product from ammonium cyanate (**1)**, an inorganic salt. Organic chemistry was born.



Scheme 1 – The first natural product synthesis

This first synthesis in organic chemistry opened the doors of perception for many, which lead to an understanding that in organic chemistry, anything is possible. Today, we have come very far from the suspicions of 19th century science. Currently, the synthesis of the largest to date natural product ever isolated, **3**, is underway. Extremely toxic, **3** was isolated from the dinoflagellate *Gambierdiscus toxicus*, and is the largest natural product (MW = 3422 g/mol) known[2] thus far (with the exception of biopolymers such as proteins or polysaccharides). The complete relative and absolute structure of **3** was determined by two different research groups using 3D NOESY-HMQC.[3] Its total synthesis has been underway since its discovery in 1993. MTX has 32 fused ether rings, 28 hydroxyl groups, 21 methyl groups, 2 sulfates, and 98 chiral centers. Although its physiological role in the dinoflagellate is still unknown, the complex structure presents a magnificent challenge to synthetic chemists.



3, Maitotoxin (MTX)

Recently, biopolymer synthesis has birthed synthetic life by the J. Craig Venter Institute (JCVI), an endeavour that took over a decade to accomplish from start to finish. On May 20th 2010, researchers at JCVI, a genomic research organization, published[4] their results describing the successful construction of the first self-replicating, synthetic bacterial cell. The team synthesized the 1.08 million base pair chromosome of a modified *Mycoplasma mycoides* genome. The cell was able to reproduce its fully-synthetic genome only after the research group was able to overcome hurdles in the chemistry of the its DNA synthesis. Cellular nuclei come with certain fail-safe mechanism to prevent intrusive mistakes in the DNA from being replicated and expressed. One large hurdle the group had to overcome in their project was the methylation of base pairs to pass the cells natural fail-safe tests.

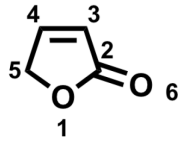
Now, organic chemistry has tools and techniques used specifically for the synthesis, isolation and purification of compounds and various methods for the determination of their properties. Much of the success of a chemist is knowing when and how to use the application of these techniques and tools, the process of which is often quite intricate. A specific branch of this science is dedicated to the creation of natural products (previously generalized as ‘organic’, originating from a vital force). Natural product synthesis is one of the most important and the most challenging sciences as it could never be fully automated or controlled by machines. In many cases, natural product synthesis offers the opportunity to create compounds that may only exist in trace amounts in a rare plant or animal (which

itself could exist in environments not easily accessible), such as marine invertebrates or a inaccessible plant used to cure ailments in ancient Chinese medicine. In addition, creating a synthetic and economic access point to these chemicals, we can further study the effects of these compounds in medicine, without having to go to the source.

Organic chemistry is a science that continually builds upon itself revealing paths to products that would seem untouchable for study in clinical practice or for pharmaceutical use. It is clearly of the utmost importance to further the study of medicine and molecular biology by examining how these new compounds will interact *in vivo* and which, if any, may help us to conquer and control sickness and disease. Interestingly enough, the journey holds just as much importance as the destination. By studying the chemical path we use to obtain access to a desired compound, we can exploit these techniques in analogous products.

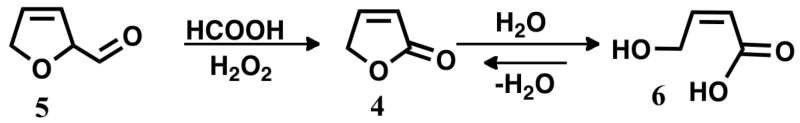
Furanone core

In organic chemistry, **4** is present in many natural products as a scaffold upon which is attached various other chains or cycles bearing functional groups.



4, 2(5*H*)-furanone
(atomic numbering shown)

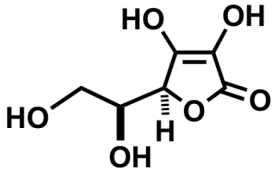
The molecule 2(5*H*)-furanone can be considered as an oxidized derivative of furan. Compounds bearing **4** are also referred to as butenolides (the term butenolide calls for with Greek letter atomic labelling about the ring). In this text, products containing **4** will be named and substituents numbered based on the name 2(5*H*)-furanone. This heterocycle is part of the family of lactones; it is a clear and colourless liquid and quite common in biochemical pathways (especially plants of the genus *Angelica*, hence the name *β-angelica lactone* to which **4** is also referred). Generally, **4** is synthesized by the oxidation of furfural, **5** (**Scheme 2**). It exists in minor amount as the protropic tautomer.



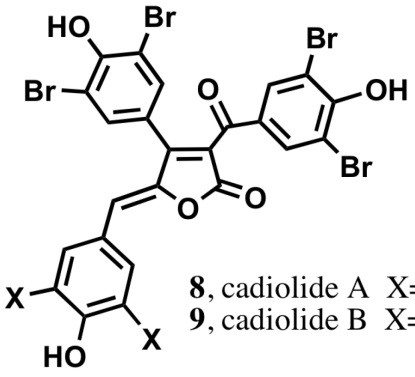
Scheme 2 - Synthesis of 2-(5*H*)-furanone

Certain strategies have been developed for the synthesis of **4**, including the use of 2-trimethylsilyloxyfuran which reacts with electrophiles at furan C_5[5] Additionally, furans with a 2-oxy-boron (or a 2-oxy-tin) substituent react with electrophiles at C_3 *via* chelation control.[6]

Furthermore, many biologically active products, such as **7** and even marine-originating antibiotics such as **8** and **9** contain a furanone ring at its center. The furanone heterocycle has been found at the center in over 13,000 natural products and is one of the most commonly encountered.[7]



7, ascorbic acid



8, cadiolide A X=H
9, cadiolide B X=Br

Figure 1 – Natural products with a furanone center

As an antioxidant, **7** helps to lower the frequency and severity of the common cold,[8] diminish the risk of cataracts,[9] cardiovascular disease (like heart attack and stroke),[10] and lower cholesterol.[11] More recently, **7** has been studied as a pulmonary anti-inflammatory agent to treat asthma.[12] Other groups have looked at treatments for hyperglycaemia by treating the affected with elevated doses of ascorbic acid. It has been reported that **7** can minimize the complication and in some cases prevent diabetes mellitus by reducing glycosylated hemoglobin levels.[13]

Reported by Ireland in 1998,[14] and then later synthesized by Boukouvalas in 2004[15] and 2010 (respectively), **8** and **9** are a pair 3,4,5-trisubstituted furanones obtained from an Indonesian ascidian of the genus *Botryllus.* The cadiolides belong to the family non-nitrogenous marine metabolites that include the antibiotic rubrolides, Rubrolide A (**10**), also isolated from *Botryllus* sp, has been studied for use as an antibiotic. Both, cadiolides and rubrolides share the same 4-aryl-5-arylmethylenefuranone units. These unusual structural features along with the useful biological activities of related lactones make these noteworthy examples of substituted furanones.

1.0 Biological Background

Diabetes

Diabetes mellitus is a disease on the rise that presently affects 3 million Canadians and every year specifically in countries such as China, India and the United States, where there is a devastating increase in new cases. Specifically North America has shown a 23% increase of new diagnosis with over a 46% increase in new cases of diabetes worldwide over the last decade (see **Figure 2**).[17]

The word diabetes comes from the Greek word *dia-baino* that literally means to "pass through". In persons with diabetes mellitus a high blood sugar level is observed causing the bodies cellular nourishment to "pass through" or be excreted. The three main types of diabetes include Types I and II and gestational. All types of diabetes are characterized by an increased by blood glucose level brought on by insufficient insulin secretion from the pancreas or a cellular resistance to the bodies' own glucose, as a result the glucose levels in the blood rise and the compound is excreted through urine. Insulin is a hormone that coordinates with receptors on the outside of cells that permits the diffusion of glucose into cell to be used in cellular respiration to generate adenosine triphosphate or ATP (the body's fuel source). If there is an insufficiency of insulin in the body, blood sugar levels rise as glucose accumulates (hyperglycemia) which leads to many serious complications.[17,18]

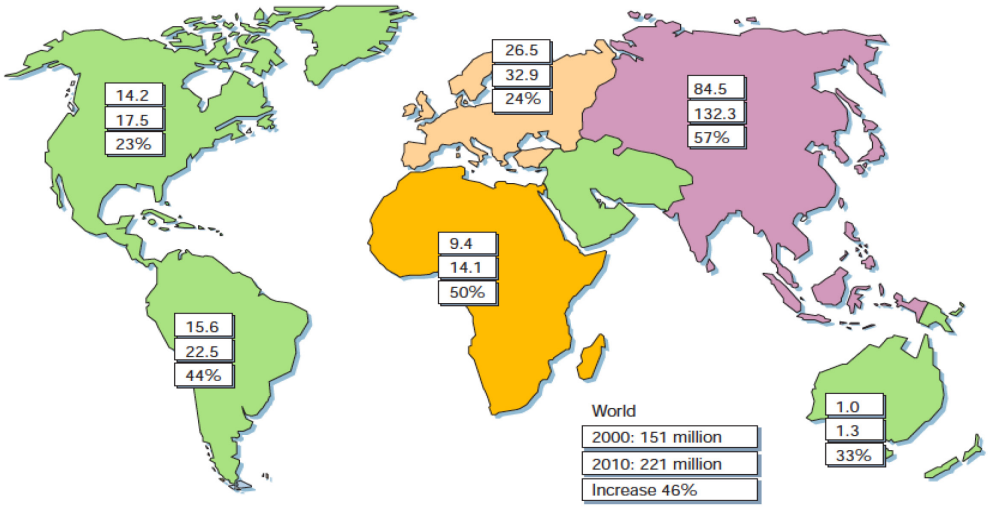


Figure 2 – The increase of new diagnosis of diabetes mellitus worldwide

Type I Diabetes

Type I diabetes is most often seen in young persons and is characterized by an auto-destruction of the islet of Langerhans (or β-cells) of the pancreas which are the cells responsible for insulin production. People with this disease are required to inject a manufactured serum containing insulin into the blood to facilitate the uptake of cellular glucose; failure to do so will result in fatigue and eventual diabetic coma. The amount injected must be carefully monitored, as an overdose will consequently catalyze insulin shock with coma-like symptoms.

Gestational diabetes

Gestational diabetes occurs in 3-4% of women at the onset of pregnancy and, although the symptoms usually disappear after birth, both mother and newborn will have an increased risk of developing other forms of diabetes later on in life.

Type II Diabetes

Among the three main types of diabetes, the most preventable is type II. Type II diabetes is responsible for 90% of all cases worldwide and it is characterized as a hyperglycemia brought on by an insulin resistance or insufficiency. In many cases of insulin resistance, the pancreas will overproduce insulin almost to sheer exhaustion.[17] Persons affected with this type of the disease can be asymptomatic for years, as it progresses and evolves in the body. Most cases of type II are diagnosed when patients seek medical attention for the complications it causes. Long-term side effects include blindness (retina damage caused by neuropathy), cardiovascular disease, chronic renal failure (nephropathy), ulcers and a lack of sensation in the extremities gangrene, amputation, colon cancer, sepsis, coma and in accelerated cases, even death.[16,19]

In the presence of obesity, hypertension (or high blood pressure) and other forms of glucose resistance the disease is then referred to as metabolic syndrome in which patients have a

much higher risk of developing these symptoms as in type II. It has been estimated that up to 75% of people diagnosed with type II diabetes will also develop metabolic syndrome.

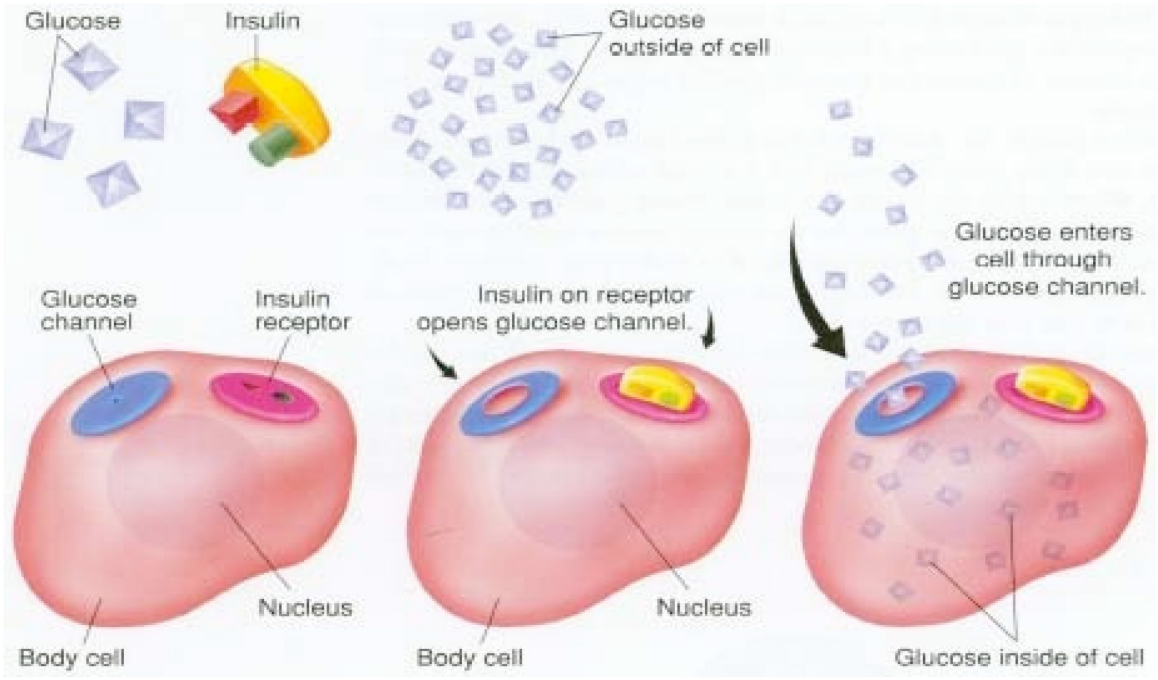


Figure 3 - Insulin-dependent cellular glucose diffusion

Glucose originates from the hydrolysis of dietary carbohydrates like starches or sucrose in the small intestine before being absorbed into the blood. Elevated concentrations of glucose in the blood stimulate the insulin's release from the pancreas. Insulin acts at a cellular level at various target tissues throughout the body stimulating the uptake and consequent metabolism of glucose. In general, insulin catalyses the transformation of glucose into glycogen (the storage form of glucose in the pancreas) *and* facilitates the entry of glucose into muscle, adipose and several other tissues *via* a hexose transporter (GLUT4).[xiii,16]

The body's response to insulin

Like the receptors for other protein hormones, the receptor for insulin is embedded in the plasma membrane. The insulin receptor is composed of two alpha subunits and two beta

subunits linked by disulfide bonds. A tyrosine kinase, whose function is that of an enzyme, transfers phosphate groups from ATP to tyrosine residues on intracellular target proteins. For glucose to enter the muscle cells it requires a receptor on the surface of the plasma membrane to coordinate with insulin before the glucose canal can be activated to facilitate active transport. The binding of insulin to the alpha subunits causes the beta subunits to auto-phosphorylate. This cascading, auto-phosphorylation effect activates the catalytic activity of the receptor generating a biological response. These insulin coordination signals activate the glucose transporter GLUT4. When insulin concentration are low or the receptors have developed a resistance to the bodies' own insulin (that is, the receptors are no longer occupied), the GLUT4 glucose transporters are consequently useless.

Generally, the overall effect of insulin is the decrease of blood glucose levels considering the described mechanism. Insulin and glucose naturally exist in a negative feedback loop, a tandem relationship whose concentrations are directly proportional to one another. That is, as glucose concentrations decrease insulin production also decreases. In the absence of insulin, the bulk of cells are unable to take up glucose and will have to switch to alternate fuels (such as fatty acids) for energy production. However, certain cells (neurons, retinal cells, renal tissues) require a constant supply of glucose. Thus, in these cells, glucose transportation is independent of insulin levels in the blood. In cases in which individual may suffer from hyperglycemia, these tissues inherently receive elevated levels of glucose that diffuse across the cell membrane. Once the cell's energy requirements are met, glucose will be shunted down an ATP-independent process called the polyol pathway (see **Figure 1.5**).[17]

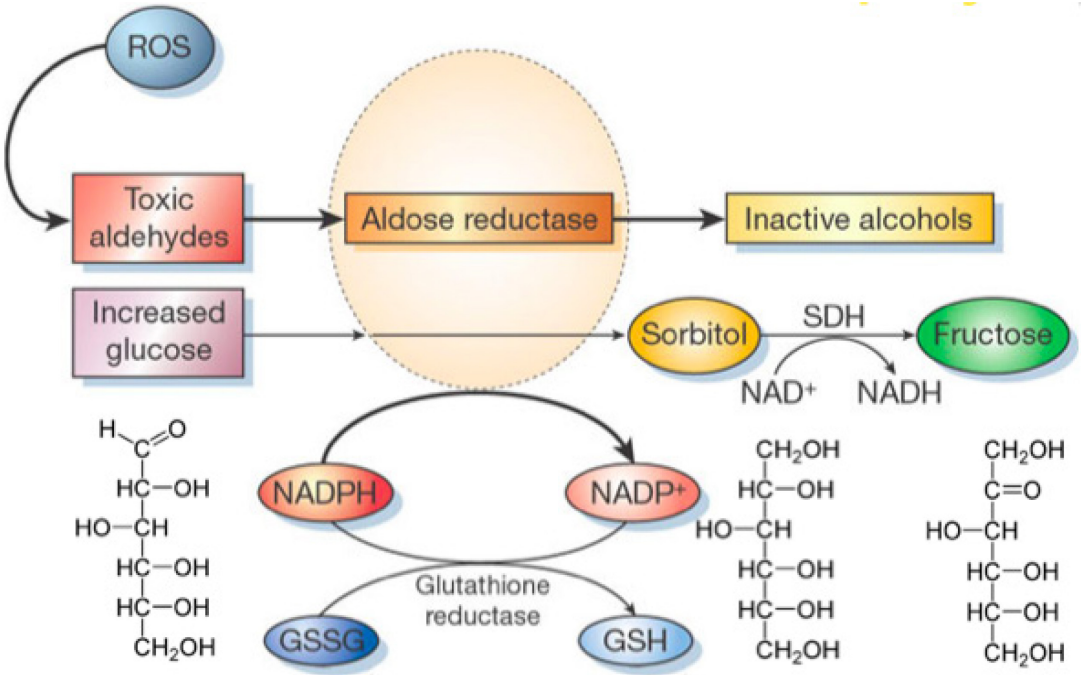


Figure 4 - The production of sorbitol via the polyol pathway

Polyol Pathway

The glucose that enters cells that is not required for energy is reduced via the polyol pathway. In this pathway, reactive oxygen species oxidize toxic aldehydes to an aldose reductase. There is complexation between an intra-cellular enzyme called aldose reductase (ARL2, the first enzyme in the polyol pathway), coenzyme NADPH and the substrate to be reduced, glucose. Glucose's terminal aldehyde is reduced to a primary alcohol (**11**) greatly augmenting the molecules' polarity.[16]

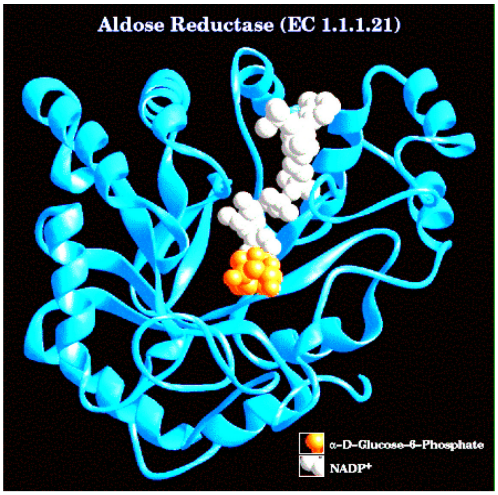
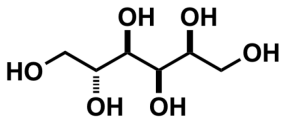


Figure 5 - Aldose reductase complexed with glucose and $NADP^+$ at the active site

The transformation from glucose to sorbitol is the rate-determining step. The second, quicker step of this pathway is sorbitol's oxidation to fructose, catalyzed by sorbitol dehydrogenase. In cases of hyperglycaemia, there is an inevitable rise in cellular sorbitol levels within the cell. Sorbitol, although naturally occurring, can be quite dangerous at high concentrations within the cell. Due to its elevated polarity, sorbitol cannot diffuse out of the cellular membrane and its accumulation causes an exponential increase in the intracellular osmotic pressure within the cell. Finally, the laws of diffusion dictate that across a semi-permeable membrane, water will diffuse to the side of highest solute concentration. The cells become engulfed with extra-cellular fluids and catastrophic lysis occurs destroying tissues and vital organs.[12,13]

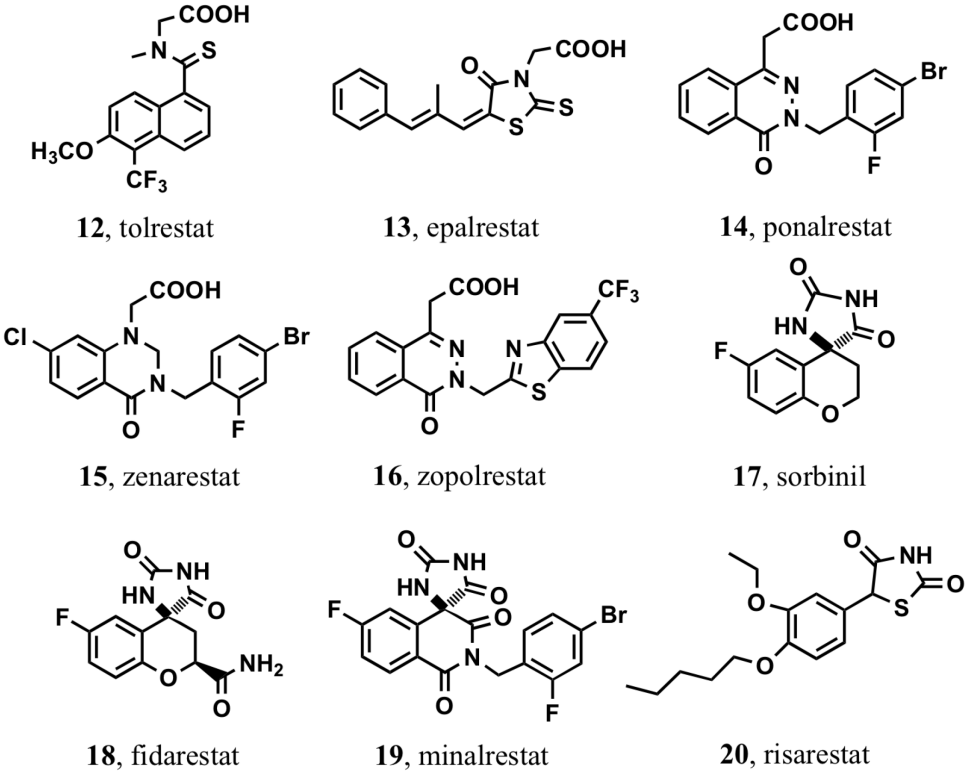


11, sorbitol

As blood glucose levels increase, as does the activity of aldose reductase in sensitive tissues causing a flux of sorbitol and fructose. Sorbitol accumulation in sensitive tissues such as neurons, the retina and kidneys is the main cause of neuropathy, cataracts or blindness and chronic renal failure in the respective tissues. If left untreated, nerves will die causing a lack of sensation or tingling, ulcers and eventually, gangrene.[17]

Aldose Reductase Inhibitors

A new class of drugs called Aldose Reductase Inhibitors (ARIs) are able to block the polyol process by competitive inhibition of aldose reductase (ARL2) when bound with NADPH, consequently arresting the transformation of glucose to sorbitol. Currently, there are no aldose reductase inhibitors available on the market in North America (due to the high FDA standards)[18] and there is only one drug, **13**, available worldwide.[17] Thus, there is great need for other new ARIs.



12, tolrestat **13**, epalrestat **14**, ponalrestat

15, zenarestat **16**, zopolrestat **17**, sorbinil

18, fidarestat **19**, minalrestat **20**, risarestat

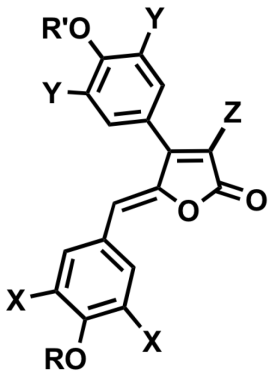
Figure 6 -Various aldose reductase inhibitors[xvii]

To date,[xviii,19] the vast bulk of the products tested for their inhibitive ability on aldose reductase fall into the categories of spiro-hydantoins or carboxylic acids. Spiro-hydantoins (ex. **17**, **18**, **19,** and **20**) diffuse easily across the phospholipid bilayer in cellular membranes. However, studies have shown that these ARI's metabolize in the liver into products with toxic effects. Carboxylic acids (ex. **12**, **13**, **14**, **15**, and **16**) can be easily

metabolized in the liver into non-toxic derivatives, yet their downfall is largely related to their poor diffusion across the cellular membrane resulting in decreased efficacy. As blood pH on average is 7.4, carboxylic acids (pKa ≈ 4-5) are completely ionized. Highly charged or extremely polar products (the case in **11**) diffuse slowly or with great difficulty across a phospholipid bilayer in the cellular membrane. Thus, there is a need for new ARI inhibitors on the market in North America that can easily penetrate cells to get where it is needed to halt sorbitol production and then degrade naturally in the body into non-toxic derivatives.

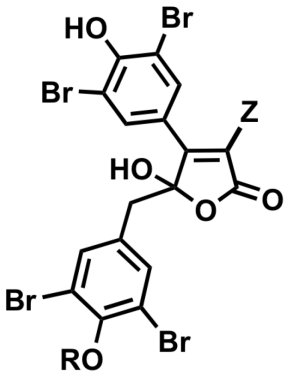
Rubrolides A-N

The first series of rubrolides (A – H) were collected on the coast of the Queen Charlotte Islands, isolated from *Riterella rubra* in 2001.[20] The rubrolide family attracted attention because it was a non-nitrogenous metabolite characterized as having a moderate effect as a phosphatase inhibitor. As part of an ongoing project directed towards the search of pharmacologically active compounds from marine ascidians, the natural products from *Riterella rubra* were screened and were capable of moderate but differential inhibition of protein phosphatases 1 and 2A. With the aid of bioassay guided fractionation, it was shown that this activity was due to rubrolides A – H. The names of which compound were assigned based on the retention on silica after being homogenized from the source. Rubrolides C and E have been synthesized first by Boukouvalas and co-workers.[25]



Compound	Rubrolide	Substituents
21	A	R=R'=Z=H X=Y=Br
22	B	R=R'=H X=Y=Br Z=Cl
23	C	R=R'=Z=Y=H X=Br
24	D	R=R'=Z=X=H Y=Br
25	E	R=R'=X=Y=Z=H
26	F	R=Me R'=X=Y=Z=H

Table 1 - Substituents of Rubrolides A-F (**20**-**26**)



Compound	Rubrolide	Substituents
27	G	R=Z=H
28	H	R=H Z=Cl

Table 2 - Substituents of Rubrolides G (**27**), H (**28**)

The rest of these functionalized furanones that bear the same name (rubrolide I-N) were isolated from the marine tunicate *Synoichum blohmanni* off the south coast of Spain near Tarifa Island by Ortega and co-workers in 2000.[21] The syntheses of rubrolides M and N have been reported by Bellina and co-workers.[22] Rubrolides K, L, M and N (**31** to **34**) attracted the attention of the research group due to the increased cytotoxicity of these compounds against P-388 suspension culture of mouse lymphoid neoplasm, the monolayer cultures of human lung carcinoma (A-549), human colon carcinoma (HT-29) and human melanoma (MEL-28).

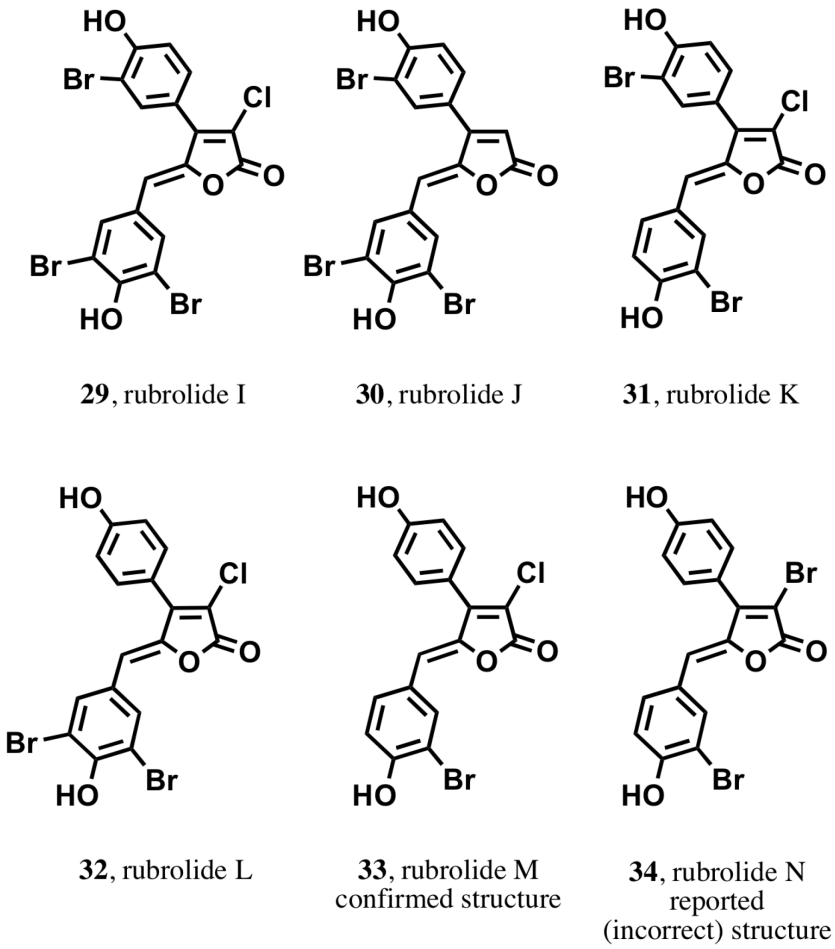


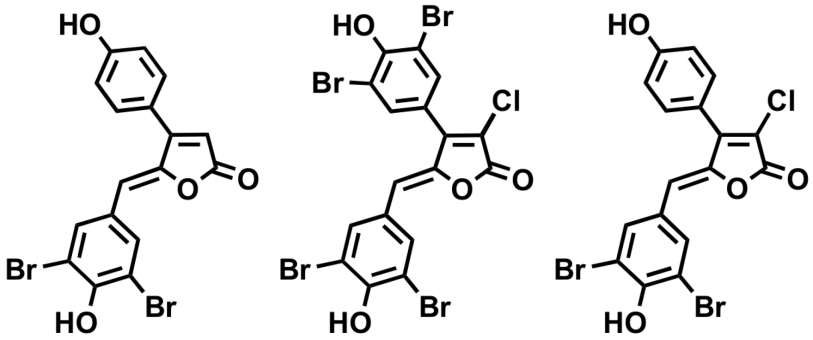
Figure 7 - Rubrolides I - N

An important aspect of total synthesis is the confirmation of structure. Bellina co-workers reported the synthesis of **34** only to find discrepancies in their ^{13}C-NMR compared to the findings of Ortega. The structure of **34** had been elucidated incorrectly, specifically at the C_3 position of the furanone ring bearing a chlorine atom. Bellina and co-workers determined the ^{13}C shifts observed at this position were characteristic of a carbon bearing a bromine atom instead of chlorine. The data proved conclusively the reported structure of **34** was incorrect.

Rubrolide L

Computational docking studies were performed to evaluate the docking capabilities of various rubrolides. Of all the rubrolides evaluated, **32** was found to have the greatest

inhibitory properties amongst the other rubrolides. When compared to Pfizer's sorbinil, **32** outcompeted this ARI's activity by a factor of five-fold.[23] Rubrolide L (**32**) has an elevated inhibitive property with aldose reductase, the enzyme responsible for the conversion of glucose into sorbitol in the polyol pathway. This process, when left unmonitored or unregulated in diabetic patients, risk increasing levels of intra-cellular sorbitol in insulin-independent cell such as the nervous system, kidneys, and the retina of the eye. Compared to the other rubrolides isolated from *Ritella rubra,* rubrolide L not only has an IC_{50} concentration lower than the other rubrolides. Unique, rubrolide L orientates its alkylidene ring such that it is angled to the furanone core, penetrating deeper into the active site pocket compared to the other evaluated rubrolides (see **Figure 5**).



23 IC_{50} = < 57 μM

22 IC_{50} = 18.7 μM

32 IC_{50} = 0.8 μM[23]

Figure 8 – Inhibitory activity of selected rubrolides

Structurally, there are great similarities between **22**, **23** and **32** yet amongst these examples there is exceptional contrast in their relative inhibitive activity. All have the 3,5-dibromo-4-hydroxylbenzilidine group which is important for molecular docking. Both **22** and **32** however have a bulky chlorine atom in the C_3 position of the lactone, which affects its orientation in the active site and clearly increases the bonding strength within the active site over any other factor amongst this class of compounds. One explanation of the reduced activity of **22** compared to **32** is the increased steric hindrance due the 3,5-dibromo groups in **22**, where **32** is substituted with hydrogens. In addition to increased inhibitory activity, **32** maintains hydrogen bonds in the active site regardless of the degree of ionization.[24] The residues that participate in the binding of the inhibitor at the active site include Ser302, His110, and Tyr48. There are at all times at least two and up to four hydrogen bonds

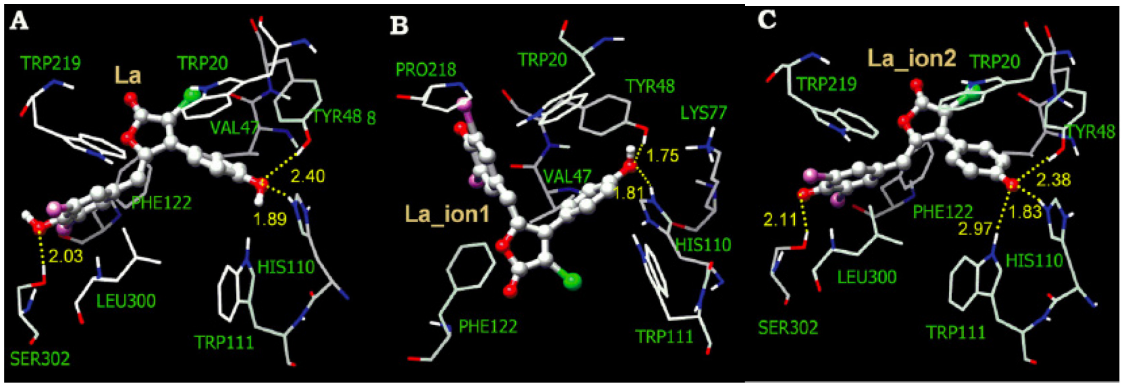


Figure 9 Rubrolide L (**32**) forms hydrogen bonds in the active site of hARL

formed between the hydroxyl groups in **32** at the active site regardless of the degree of molecule ionization. This stabilized docking effect of the active site provides exceptional competitive inhibition with $NADP^+$ thus, effectively shutting down the polyol pathway, encouraging the body to eliminate glucose through urination.

Out of all the inhibitors tested, the interaction between the polar groups (the phenol hydroxyl or the lactone) that interact with the residues at the active site, all are unaltered and the inhibitor ionizes. The inhibitors were classified by their mode of docking. The rubrolides (all but **32**) coordinate to the active residues through their lactone group. Rubrolide L is the only inhibitor tested that bind through the terminal phenolic groups to the active residues.

The structural characteristic is essential to the experimental inhibition activities of inhibitors, which vary a lot under these two binding modes. This is probably because the hydroxyl oxygen (that bears more negative charges than the lactone carbonyl oxygen) can form more stable hydrogen bonds with active residues, which make the hydroxyl binding mode prevail at the binding site. The carbonyl oxygen, which is restricted by the severly hindering aromatic constituents are more encumbered discouraging lactone participation in the assemblage. This, and the free rotating phenol (linked by a single bond to the furanone core), can more effectively bind to the ALR2 active pocket. Thus, the motivation for synthesizing rubrolide L was established: it has strong inhibitive properties of aldose reductase with a unique binding mechanism to the enzyme, it is claimed to have cytotoxic

properties versus various cancer lines and the synthesis of which was not previously reported and finally the structure has not yet been confirmed.

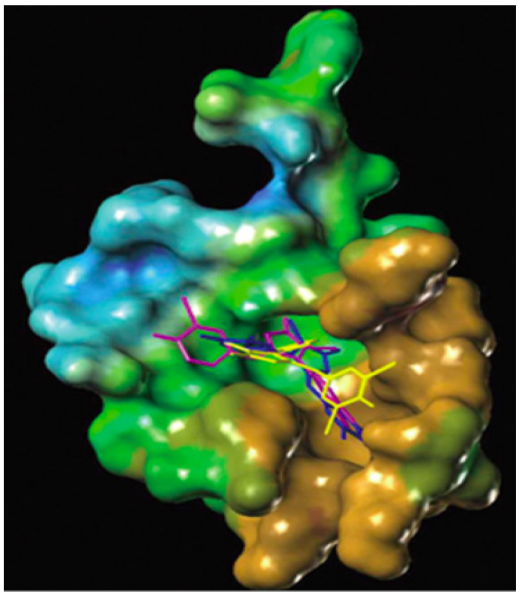


Figure 10 - The confirmation of **32** in the active site of aldose reductase

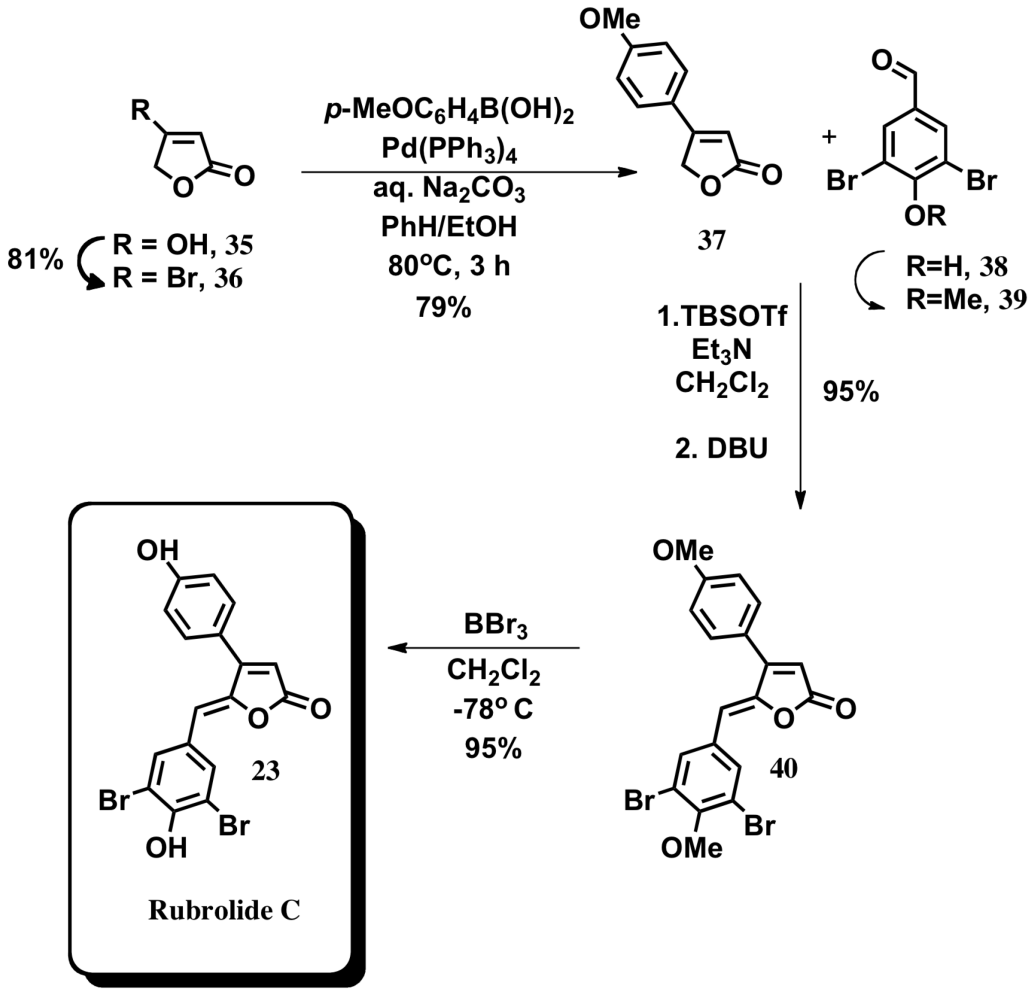
Hurdles in the Synthesis of Rubrolide L

The key-step in the synthesis of these two rubrolides was a two-step, stereocontrolled aldol condensations reactions with E1cB elimination. This reaction appears to be the main reason why rubrolide L has not been synthesized in the past as it may have offered some difficulty in terms of substrate scope. As for rubrolide E, M, and N, (**25**, **33** and **34**) a key step in the synthesis was the condensation of the alkylidene with brominated methoxyphenyl benzaldehyde. In the case of rubrolide C, (**23**) 3,5-dibromo-4-methoxybenzaldehyde underwent stereoselective aldol condensation with 4-(4-methoxyphenyl)-3H-furan-2(5*H*)-one in the presence of TBSOTf with Hünig's base with subsequent elimination with DBU. However, substitute a chlorine atom in position C_3 on the furanone ring and this transformation cannot be effectuated under these same conditions.

Rubrolide C as a guide

The work of our group on the synthesis of rubrolide C served as a reference point[25] for

the synthesis of rubrolide L (see **scheme 3**). The starting material for the synthesis of rubrolide C was 3-tetronic acid, which is converted into the activated 4-bromo-furan-(5*H*)2-one before undergoing a coupling reaction in the presence of palladium catalyst. 3,4-dihydroxyfuran-2(5*H*)-one (**35**) was subjected to Vilsmeier reaction conditions with oxalyl bromide to provide 3-bromo-4-hydroxyfuran-2(5*H*)-one (**36**) in good yield. Then, **36** was subjected to Suzuki-Miyaura cross coupling conditions with 4-methoxyphenylboronic acid in the presence of tetrakistriphenylphosphine palladium to yield 3-methoxyphenylfuran-(5*H*)2-one (**37)** in good yield.



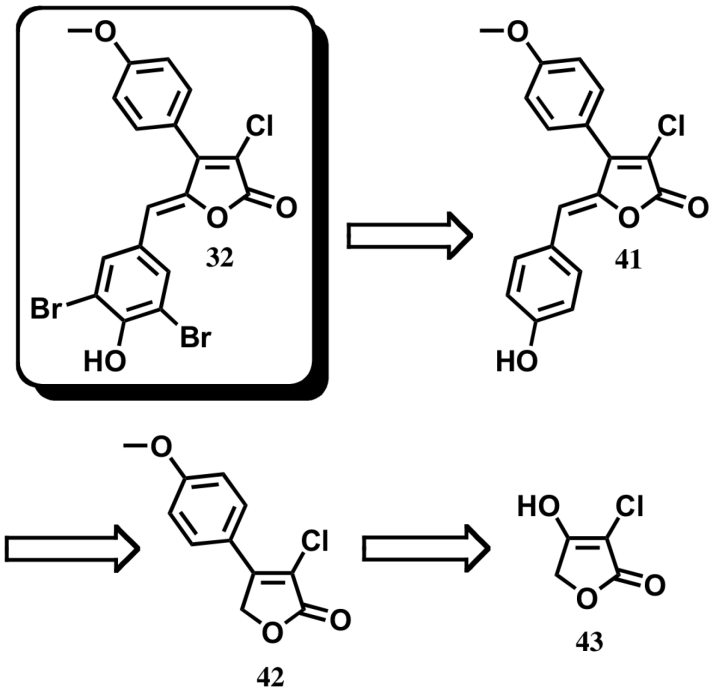
Scheme 3 - Synthesis of Rubrolide C (**23**)

After the cross-coupling, **37** underwent regioselective aldol condensation in the presence of DBU (one-pot). Finally a simple demethoxylation in BBr_3 provides the product in excellent

yield. Over four steps, rubrolide C was synthesized with an overall yield of 61% over 4 steps.

We had developed the following retro-synthetic analysis for **32** based on the previous synthesis of **23**.

Retrosynthetic Analysis of Rubrolide L

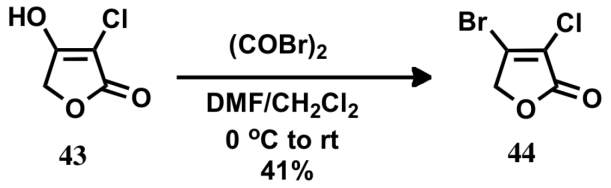


Scheme 4 - Retrosynthesis of rubrolide L (**32**)

To begin, an inexpensive and commercially available adduct of 3-chlorotetronic acid (**43**) would be subjected to Suzuki-Miyaura style cross coupling conditions to stereoselectively control the subsequent aldol condensation. Secondly, a stereocontrolled, aldol condensation would be performed with a subsequent elimination (via an E1cB mechanism) in the presence of DBU to provide exclusively the *Z* isomer. The cross-coupling reaction, due to steric requirements. Following, a selective *meta* bromination of the phenol of the alkylidene ring to provide the alcohol protected precursor. We initially envisioned a selective bromination of the alkylidene moiety (containing a more reactive phenyl group) with two equivalents of molecular bromine. An efficient demethoxylation would then provide the

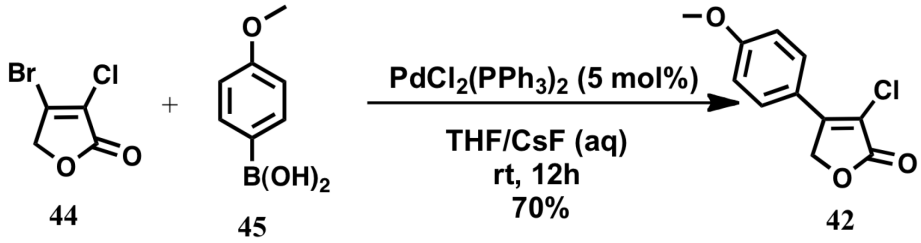
product after 5 steps (see **scheme 4**)

Halogonated Activated Groups for Suzuki-Miyaura Cross-Coupling



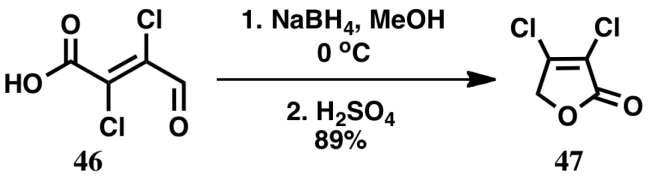
Scheme 5 - Preparation of **44** by Vilsmeier conditions

Exploring different activated groups; our attention was first turned toward the halogens for cross coupling. We examined the cross-coupling behaviour of the 3-chloro-4-bromo-2(5*H*)-furanone. A Vilsmeier reaction (scheme 4) with commercially available 3-chlorotetronic acid afforded the dihalide species, **13** in moderate yield. The product did undergo cross coupling (see **Scheme 5**) to provide **9** in 70% yield, or 29% over two steps.



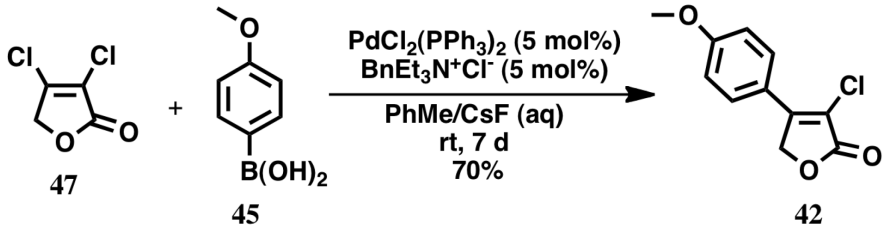
Scheme 6 - Suzuki-Miyaura cross-coupling of **44** and **45**

Bellina and Rossi have reported[26] high yields coupling 3,4-dichloro-2(5*H*)-furanone (after 2 steps from commercially available mucochloric acid). Mucochloric acid is reduced and hydrolysed over two-steps (scheme 6).



Scheme 7 - Reduction of **46** with sodium borohydride to heterocycle **47**

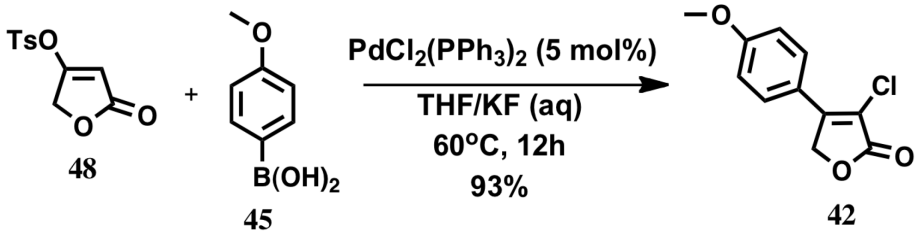
The inexpensive starting material, **46** in **Scheme 7** was treated with using sodium borohydride in methanol over 15 minutes, then sulphuric acid was added. After recrystallization from hot methanol, the now pure, reduced dichloro-adduct (**47**) was coupled at room temperature with the boronic acid **45** over a period of 7 days as reported by Bellina and co-workers.[26] Surprisingly, the reaction outline in **Scheme 7** gave a similar yield with the less reactive dichloro species **47** as it did with **44**.



Scheme 7 – Suzuki-Miyaura cross coupling **45** with **47**

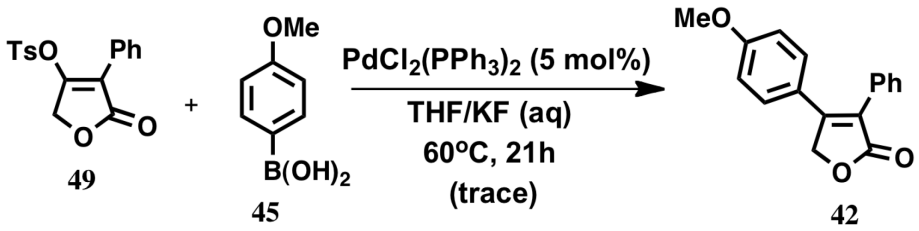
Important for yield in the synthesis of rubrolide L, was the selection of a leaving group for Suzuki-Miyaura style cross coupling. After the evaluation of halogens for Suzuki-Miyaura cross coupling, we decided to turn our attention to pseudo-halides as a coupling partner.

Cross-coupling with pseudohaides



Scheme 8 - Reported Suzuki-Miyaura cross-coupling with **45** and tosylate **48**

Recently, Wu, Yang and co-workers[27] indicated that 3-phenyl-4-tosyloxy-2(5*H*)-furanone, **48** will undergo coupling with **45** in excellent yield when the position C_3 of the furanone ring is occupied by hydrogen (as in **Scheme 8**). In the same study it was indicated that by introducing a greater steric bulk in position C_3 results in reactions furnishing trace amounts of product under similar conditions (see **Scheme 9**).

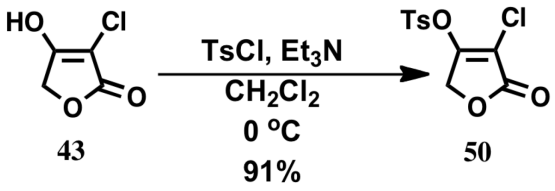


Scheme 9 - Bulkier **49** shows a significant decrease in yield when coupled with **45**

Presumably the steric bulky exhibited by the phenyl group in **49** at the C_3 position would be about that of a chlorine atom. There should be increased activation of a tosylate bearing a chlorine at the C_3 due to the decreased electron density in the C_4 position caused by an inductive effect. This activation should help to counteract the steric hindrance and afford the product in acceptable yields.

Next, we synthesized of the 3-chloro-4-tosyloxy-2(5*H*)-furanone (**10**) from 3-chlorotetronic acid (**50**). The tosylate was evaluated first due to its relative bench-top stability compared to many other groups such as triflates etc. and the success high-yield coupling reactions that have been recently published.[28]

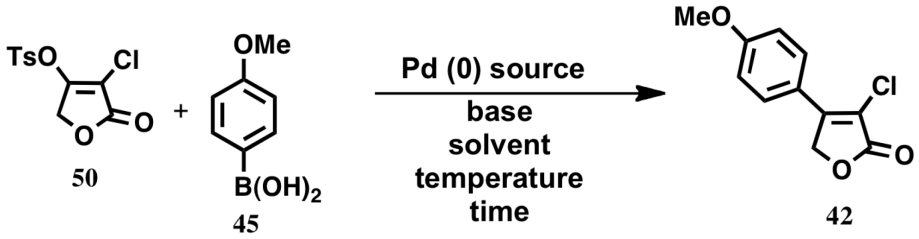
The synthesis of the **50** was achieved in excellent yield by treating **43** with tosyl chloride in dichloromethane under basic conditions using a non-nucleophilic amine. After flash silica chromatography, **50** was carried evaluated as a coupling partner in Suzuki-Miyaura conditions. (see **Scheme 11** and **Table 1**).



Scheme 10 - Synthesis of tosylate 50 from tosyl chloride

The coupling of **50** (refer to **Table 1.1**) provided the higher yields in highly polar solvents

such as methanol and THF. In less polar solvents (ex: DMF and toluene) no trace of product was observed. Gently heating the reaction in less-polar solvent did not increase conversion of **50** relative to those performed at room temperature; all showed no detectable amount of product. The choice of the catalyst also had profound effects on the yield. For this coupling, $Pd(OAc)_2$ outperformed all other sources of palladium(0). The choice of base also had an impact on the yield as seen between entries 6 and 8. Here it is noteworthy that the addition of PCy_3 increased yields in analogous experiments (entries 8 and 9) where product was isolated previously in trials without the addition of the ligand.



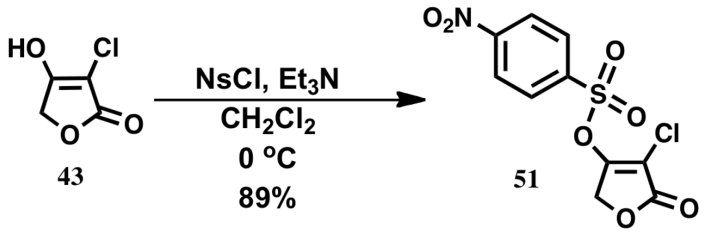
Scheme 11- Optimization of Suzuki-Miyaura conditions with 50

Table 3 - Screening the Suzuki-Miyaura cross-coupling with tosylate **50** and boronic acid **45** (as per **Scheme 11**).

Entry	Catalyst (5% mol)	Solvent(s)	Base	Temp. °C	Time	Ligand (5% mol)	Yield of 9 (%)
1	$PdCl_2(PPh_3)_2$ $BnEt_3N^+Cl^-$	$PhMe/H_2O$	CsF	rt	12 h	-	0
2	$PdCl_2(dppf)$	THF/H_2O	$CsCO_3$	80	24 h	-	trace
3	$PdCl_2(PPh_3)_2$	THF	KF	60	12 h	-	0
4	$Pd(OAc)_2$	DMF	Na_2CO_3	150	24 h	PCy_3	0
5	$Pd(OAc)_2$	THF/H_2O	Na_2CO_3	rt	12 h	PCy_3	0
6	$Pd(OAc)_2$	MeOH	$NaHCO_3$	60	24 h	PCy_3	14
7	$PdCl_2(dppf)$	THF/H_2O	$CsCO_3$	60	24 h	-	18
8	$Pd(OAc)_2$	MeOH	Na_2CO_3	60	24 h	-	25
9	$Pd(OAc)_2$	MeOH	Na_2CO_3	60	24 h	PCy_3	55

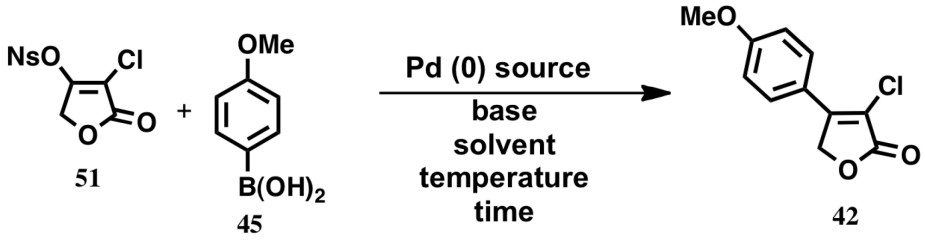
Our investigation was shifted from the tosylate, the p-nitrosulfonate derivative in attempt to improve upon the observed conversions in the Suzuki-Miyauri cross-coupling step in

forming **42**. Nosylate compounds (as in **43**) generally have similar bench-top stability to tosylates yet are more reactive, due to the increased electron donation from the *p*-nitrophenyl group adjacent to the sulfonate. The nosylate (**51**) was prepared in quantitave conversion by treatment of **43** with nosyl chloride in the presence of a non-nucleophilic amine base in dichloromethane at 0°C. After flash silica chromatography 89% of the nosylate **51** was recovered.



Scheme 12 – Synthesis of nosylate **51**

With the nosylate in hand, we subjected the substrate to a few different screenings for coupling with boronic acid (**45**) (see **Table 4**).



Scheme 13 – Coupling optimization of nosylate **51**

Table 4 - The Suzuki-Miyaura cross-coupling results with nosylate **51** and **45** (as per scheme 13).

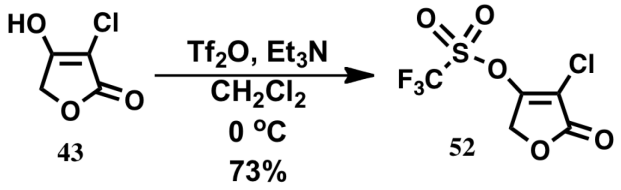
Entry	Catalyst (5% mol)	Solvents	Base	Temp °C	Time	Ligand (5% mol)	Yield of 9 (%)
1	$PdCl_2(dppf)$	THF/H_2O	Na_2CO_3	80	24 h	-	0
2	$PdCl_2(PPh_3)_2$ $BnEt_3N^+Cl^-$	$PhMe/H_2O$	Na_2CO_3	rt	12 h	-	20
3	$Pd(OAc)_2$ $BnEt_3N^+Cl$	$PhMe/H_2O$	Na_2CO_3	rt	12 h	PCy_3	45

Generalized in **Table 4**, the nosylate coupled most efficiently at room temperature in a mixture of toluene and water with a phase-transfer catalyst. This contrasts greatly with the structurally similar tosylate **50**. In the case of **50**, the performance peaked at under 50% yield when coupled in the presence of the Buchwald-Fu ligand, PCy_3. Much to our disappointment, neither the tosylate nor the nosylate provided satisfactory yields when compared to most similar Suzuki-Miyauri cross coupling reactions with similar substrates. We concluded it was in our best interest to sacrifice air and moisture stability for reactivity, as we evaluated other less stable, and consequently, a more reactive pseudo-halide.

Table 5 - Reactivity of various triflating reagents with substrate **45**

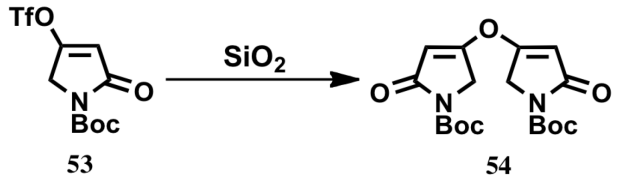
Entry	Triflating reagent	Yield (%)
1	Tf_2O	73
2	$PhNTf_2$	61
3	Comins reagent	33

Prepared from the same starting material as the **50** and **51**, the reactivity of various triflating reagents was evaluated with substrate **45**. The yields varied significantly with various reagents; the details are summarized (see **Table 5**).



Scheme 14 –Synthesis of triflate **52**

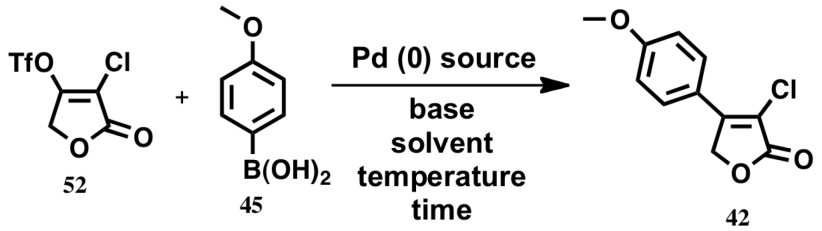
Reacting **43** at 0 ^{o}C in dichloromethane with the anhydride in the presence of triethylamine provided the highest conversion of the triflating reagents evaluated. Purification was performed by distillation under high vacuum due to the sensitivity of **52** on silica chromatography. Other triflating reagents left by-products that easily degraded on silica gel and which also separated less easily during high-vacuum distillation, complicating the purification process even further.



Scheme 12 - Dimerization of 53 on silica

The increased reactivity limited the handling as well as the options of purification of **52**. In **Scheme 12,** one explanation of this poor stability is exemplified by the dimerization of 3-triflic-pyrollidone on silica (**54**). This was supported by the claim of Pelkey and co-workers[29] that had prepared (**53**), which dimerizes on silica and may be representative of the behaviour of **52** under similar conditions. Treating the crude mixture (see **Scheme 14**) directly to Suzuki-Miyauri coupling conditions without further purification was unimpressive in terms of isolable yield (on par with the tosylate and nosylate). After eliminating these alternatives as viable possibilities to acquire **42**, the triflate was distilled using a Kugelrohr distillation apparatus to provide pure product in good yield as a clear and colourless oil, that would begin to darken almost immediately after the product was exposed to air. After distillation, it was essential to use the triflate as soon as possible. It was found that storing the compound under argon at -20 ^{o}C led to its inevitable

decomposition, and it would need be redistilled if stored for longer than 24 h.



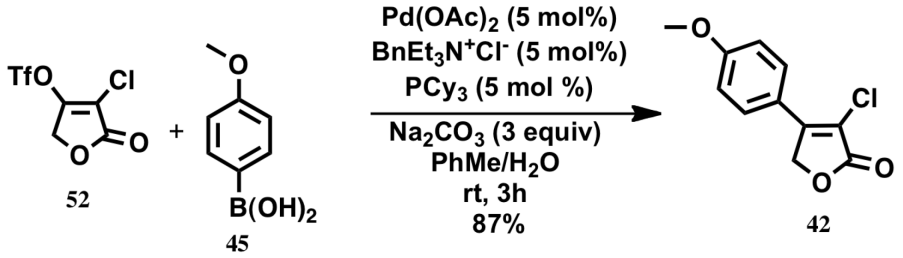
Scheme 13 – General Suzuki-Miyaura coupling scheme with **52**

Carrying forward to the coupling reaction (**Table 2.3**) it was noted that there was a greater effect on yield with regard to choice of solvent than any other criteria. Like nosylate **51, 52** coupled most effectively in oxygen sparged toluene with the aid of a phase transfer catalyst. Heating the reaction to refluxing temperatures impeded the reaction by decomposing the starting materials even as low as 60 ^{o}C. Generally the reaction was very fast; after the initial hour of the reaction the majority of the starting materials had been converted to product. The choice of base was quite significant at times affecting the yield upwards of 80% (entries 12 and 13). Overall Na_2CO_3 had the best performance with these conditions. The investigation solvents effects were significant. Toluene proved most useful especially when exploring the effects of the coupling with an additional ligand, tricyclohexylphosphine. It was reported by Gregory Fu and co-workers that tricyclohexylphosphine (a bulky, electron rich ligand) improves the efficiency of the Suzuki-Miyaura cross-coupling reaction by accelerating the catalytic cycle.[32]

Table 6 - The Suzuki Cross Coupling results with triflate **52** and boronic acid **45** (as per **Scheme 13**)

Entry	Catalyst (5% mol)	Solvent	Base	Temp. °C	Time	Ligand (5% mol)	Yield (%)
1	$PdCl_2(PPh_3)_2$	THF/H_2O	KF	60	12 h	-	9
2	$PdCl_2(PPh_3)_2$	THF/H_2O	CsF	60	12 h	-	trace
3	$PdCl_2(PPh_3)_2$	THF/H_2O	Na_2CO_3	60	12 h	-	13
4	$PdCl_2$(dppf)	THF/H_2O	Na_2CO_3	60	24 h	-	18
5	$PdCl_2(PhCN)_2$	THF/H_2O	Ag_2O	rt	12 h	$AsPh_3$	trace
6	$Pd(OAc)_2$	THF/H_2O	Na_2CO_3	rt	12 h	$P(Cy)_3$	0
7	$PdCl_2(PPh_3)_2$ $BnEt_3N^+Cl$	$PhMe/H_2O$	CsF	rt	7 d	-	65
8	$PdCl_2(PPh_3)_2$ $BnEt_3N^+Cl$	$PhMe/H_2O$	KF	rt	7 d	-	21
9	$PdCl_2(PPh_3)_2$ $BnEt_3N^+Cl$	$PhMe/H_2O$	Cs_2CO_3	80	12 h	-	trace
10	$Pd(OAc)_2$ $BnEt_3N^+Cl$	$PhMe/H_2O$	Na_2CO_3	rt	3 h	-	59
11	$Pd(PPh_3)_4$ $BnEt_3N^+Cl$	$PhMe/H_2O$	Na_2CO_3	80	12 h	-	54
12	$Pd(OAc)_2$ $BnEt_3N^+Cl$	$PhMe/H_2O$	KF	rt	3 h	$P(Cy)_3$	trace
13	$Pd(OAc)_2$ $BnEt_3N^+Cl$	$PhMe/H_2O$	Na_2CO_3	rt	3 h	$P(Cy)_3$	87*

- highlighted in scheme 14



Scheme 14 - Optimized conditions for Suzuki-Miyaura cross-coupling with substrates **52**

and **45**

Other variations of the cross coupling were evaluated such as the Molander[30] boronate (**55**) and 4-methoxyphenylboronic acid MIDA ester (**56**),[31] yet these provided trace amount of product after reacting with **52** under the conditions outlined in **Scheme 14**.

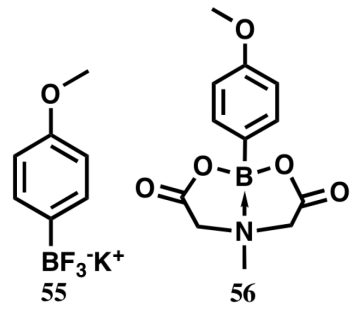


Figure 11 - Molander salt **55** and MIDA ester **56**

PCy_3 and *t*-Bu_3P as a ligand in Suzuki-Miyaura cross coupling reactions

The use of this ligand has been shown by Gregory Fu and co-workers to aid in selectively coupling a particular group particularly when many are present or the group is generally unreactive under normal coupling conditions.[32] Vinyl triflates are a useful class of cross-coupling compounds but due to their lability conditions are critical for efficient coupling of such sensitive substrates.[33a,b] The order of reactivity of activated centers in Suzuki-Miyauri cross-coupling was established as -Br ≥ -OTf > -Cl.

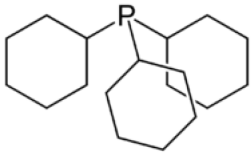


Figure 12 - The steric demonstration of tricyclohexylphosphine molecule

Noteworthy, Fu mentions a complete reversal of selectivity coupling a poly-halide substrate at one center by enforcing a selectivity of halogen partner coupling (as to couple a chloride over a bromide). $P(t\text{-}Bu)_3$ is used in catalytic amount (1:1 relative to the palladium catalyst) with either $Pd(OAc)_2$ or $Pd(dba)_2$, to preferentially couple the chlorine center by selectively

oxidatively inserting at the less sterically hindered, chloride center (i.e. selectivity is as follows in decreasing order of reactivity -Cl ≥ -OTf > -Br). The bulkier ligand, tri-*tert*-butylphosphine (due to the sterically demanding *tert*-butyl groups) allows selectivity in cross coupling reactions. For example: the triflate has a higher steric demand relative to chlorine. The cone angle of tri-*t*-butylphosphine, Tolman cone angle $\theta = 180^{o}$, (formed by the substituents on the phosphine) slows down the oxidative addition for the pseudohalide, oxidatively inserting into the C-Cl bond preferentially (in a hypothetical molecule containing both moieties). A bulky yet electron rich ligand as tri-*t*-butylphosphine hinders oxidative addition with vinyl triflate **52**, and as a result of the electronics of **52** there is no insertion into the C-Cl bond as the C_3 position is strongly deactivated as a result of the adjacent carbonyl of the vinyl chloride.

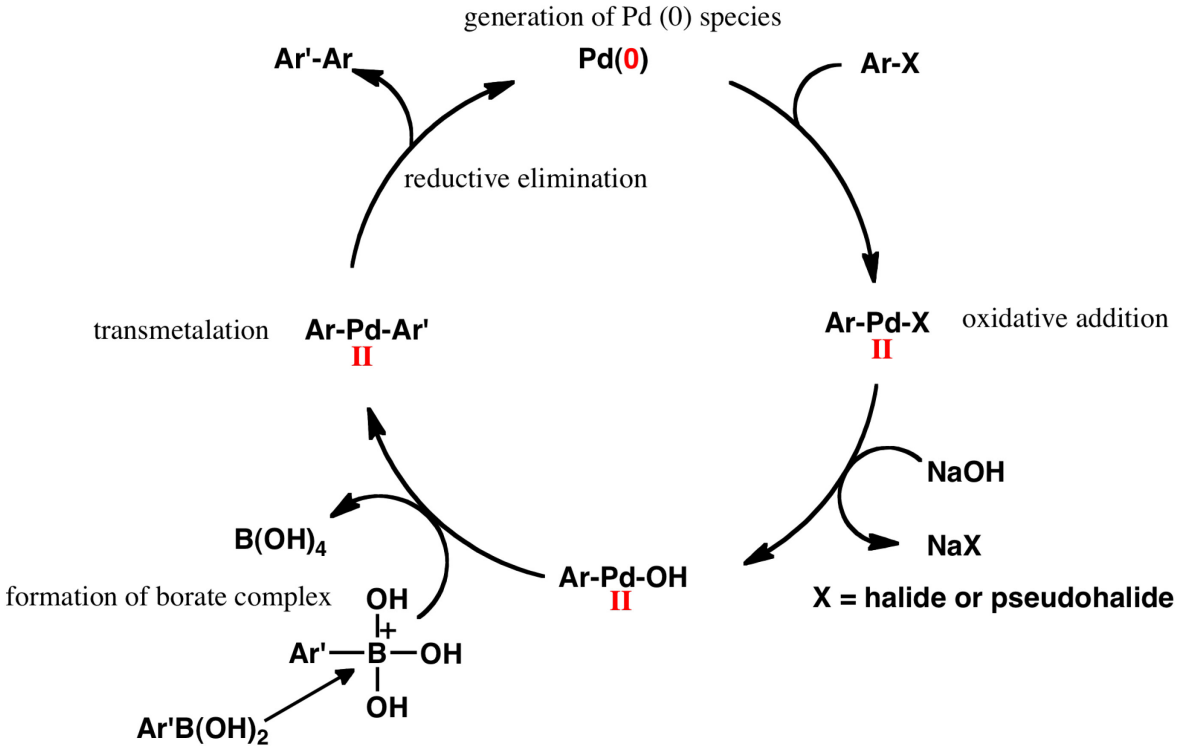


Figure 13 – Proposed catalytic cycle in Suzuki-Miyaura cross coupling

In the case of tricyclohexylphosphine, Tolman cone angle $\theta = 170^{o}$, the difference in angle is such that oxidative addition of the catalytic cycle is accelerated by the electron rich phosphine groups permitting insertion into the C-O bond of triflate **52**. The increased steric bulk on the palladium center consequently increases the rate in which transmetalation and

reductive elimination occur, allowing overall a faster conversion of **52** to **42** before it is degraded under the reaction conditions.

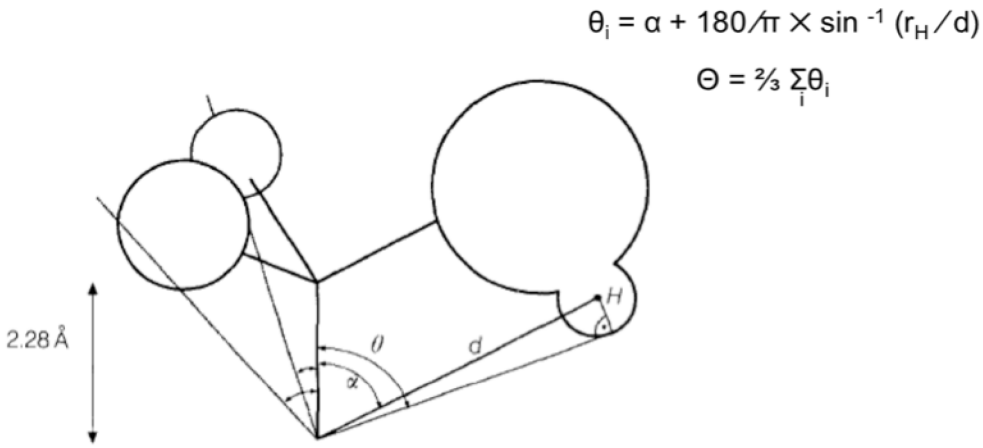
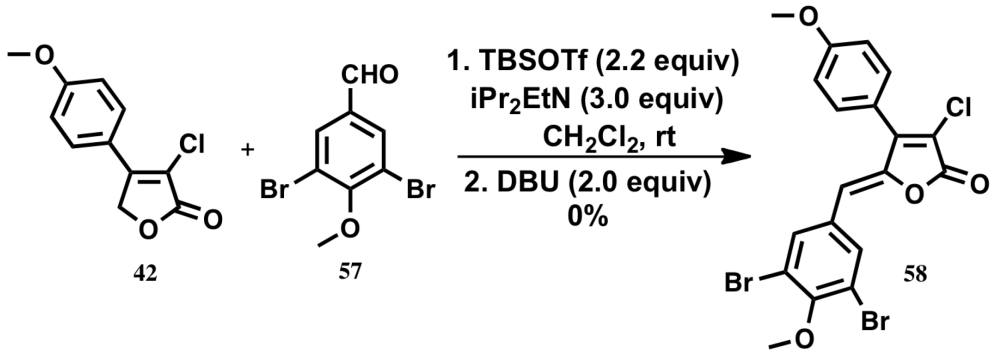


Figure 14 - Calculation of the Tolman cone angle

In the Suzuki-Miyaura cross coupling catalytic cycle, oxidative addition initially forms the *cis* palladium complex, which rapidly isomerizes to the *trans* complex. The steric hindrance of the cyclohexyl groups of the phosphine during reductive elimination helps to accelerate the catalytic cycle favouring the ejection of the transmetalated species.

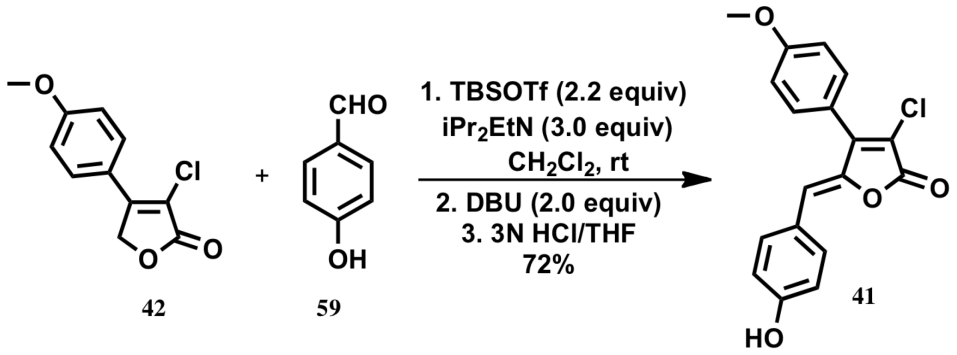
Aldol Condensation

To reiterate, the aldol condensation was key in the synthesis of rubrolide L. A huge hurdle in the synthesis of rubrolide L, the scope of this reaction represents the reason why other groups have not previously carried out its synthesis. Here we have reported a manner to overcome a problem first encountered by Bellina in his work with Rubrolide M (see **Scheme 15**).



Scheme 15 – Aldol condensation representing a precursor for rubrolide L (**32**)

The reaction in **Scheme 15** is analogous to what was performed in the synthesis of rubrolide E.[34] However, due to the electron withdrawing nature of the chlorine at C_3 on the furanone ring and the electron donating potential of a methoxy group *para* to the electrophillic carbonyl, the substrate was highly deactivated and this reaction failed to provide product **58**.



Scheme 16 - Aldol condensation of **42** and **59** to give **41**

We then turned our approach to the aldol reaction with an unbrominated, free-phenol 4-hydroxybenzaldehyde (**59**) with the Suzuki-Miyaura cross coupling product (**42**). In the presence of excess TBSOTf, the free phenol (**41**) is protected by a –TBS moiety prior to the DBU catalysed E1cB. Deprotection of the alkylidene phenol (**41**) was performed *in situ* with 3N HCl dissolved in THF $_{(aq)}$. The effort was fruitful providing one single isomer, *Z*. No *E* isomer was observed.

As illustrated in **Figure 2.3** below, the DIPEA abstracts the proton from the C_5 position, and encourages the electrons to take a stabilizing promenade around the furanone center, momentarily producing a silyloxyfuran *in situ* that exists in equilibrium with a furanone bearing a negative charge in the C_5 position. In the initial deprotonation, the equilibrium is pushed left (i.e. the reaction is disfavoured) because neither N,N-diisopropylethylamine (p*K*a of protonated ammonium $\approx$ 10) nor the hydroxide (pKa_H of conjugate acid $\approx$ 14) is basic enough to remove completely a vinly proton *beta* to a carbonyl (Michael acceptor, p*K*a $\approx$ 25). But, because the elimination of the leaving group is irreversible, only a small

amount of deprotonated alpha, beta unsaturated carbonyl compound is necessary to catalyze this reaction nudging the equilibrium to the right. In this E1cB reaction there is an anion-stabilizing group next to the proton to be removed; it does not stabilize the anion very well but, it makes the proton more acidic, thus, the reaction continues to completion. This negative charge undergoes an S_N2 with the 4-hydroxybenzaldehyde (**59**) creating a free turning benzyl group alpha to an activated OTBS leaving group at C_6. Due to the imposed steric encumberment instigated by the 4-methoxyphenyl at the C_4 position of the ring. This explains the base catalyzed E1, which will only eliminate irreversibly to provide the desired *Z* isomer, none of the *E* isomer is observed.

The negative charge is stabilized by the conjugation with carbonyl groups; a proton adjacent to a carbonyl group is relatively acidic. The proton that is removed in this elimination reaction is conjugated with the carbonyl group, and is therefore also rather acidic (p*K*a ≈ 20). The base abstracts it without the leaving group departing at the same time; the anion that results is stable enough to exist because it can be delocalized onto the carbonyl group. Although the anion is stabilized by the conjugated carbonyl group (to form the aromatic furan), it still prefers to lose the OTBS leaving group and form the alkene. This is the next step in the second row of the mechanism[35] in **Figure 15**.

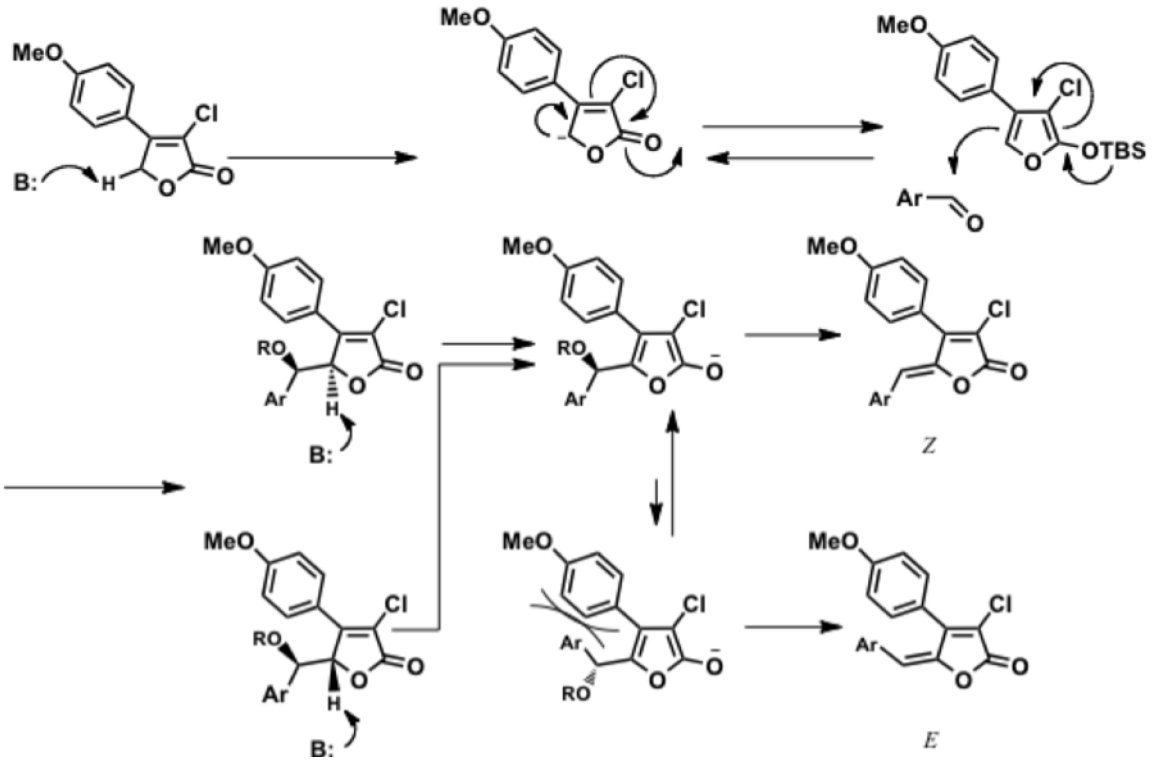
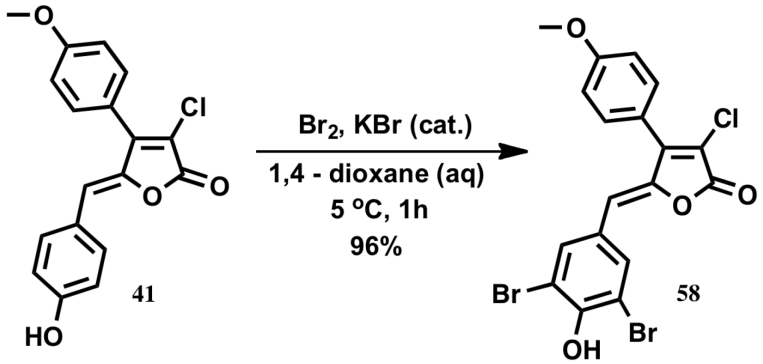


Figure 15 - Mechanism of the one-pot aldol condensation (see **Scheme 16**)

Nearing the final stretch of the synthesis included an exploitive selective bromination of the benzylalkylidene occurred with a slight excess of bromine and a catalytic amount of KBr. Naturally, due to the *ortho/para* directing methoxy group the methoxyphenol was left untouched by bromine, instead the activated *meta* position on the phenol was made brominated exclusively with almost precisely two equivalents added of molecular bromine, using a catalytic amount of potassium bromide.

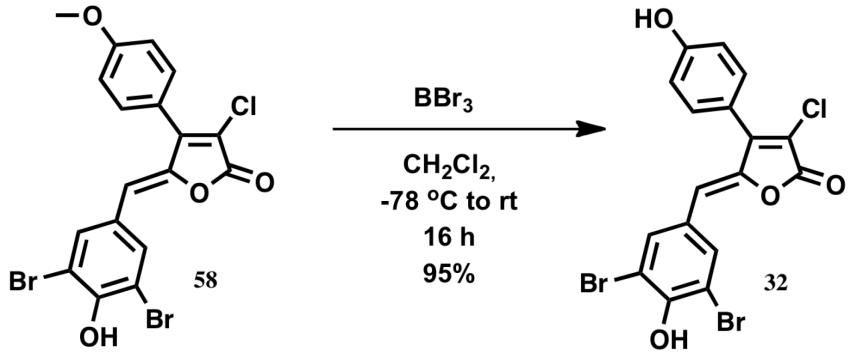


Scheme 20 – The selective bromination of phenol in **41** with Br_2 and KBr (cat.)

On the last stretch of the synthesis, we subjected our synthon to low temperature with

boron tribromide for deprotection to acquire access to the natural product in excellent yield.

Acidic deprotection of the methoxy moiety, gaining access to rubrolide L (32)

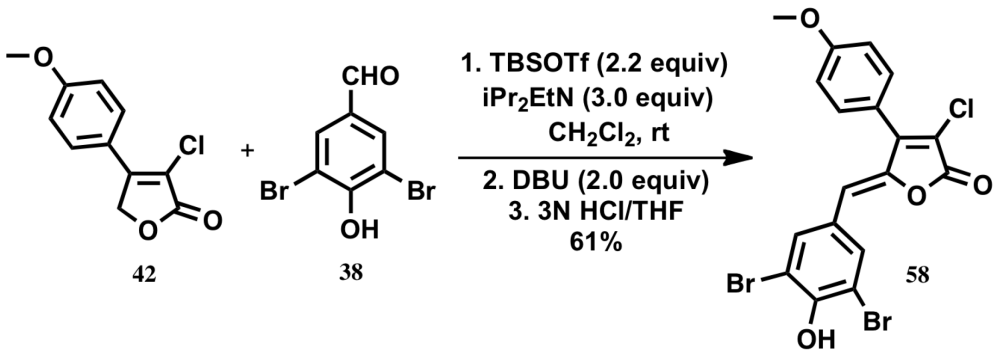


Scheme 17 – Boron tribromide deprotection of methoxy moiety to provide final product **32**

With our synthesis complete, we turned our attention to optimizing its atomical economy. Upon further review, we decided to re-evaluate our synthesis by expanding the scope of the substrates in the aldol condensation.

The first question to ask when evaluating a synthesis is: 'Is a quicker, more efficient synthesis possible?'. In the quest towards to the optimal synthesis (*i.e.* one step, 100% yield), we attempted to eliminate the need for one step of the synthesis by evaluating new substrates in the aldol condensation to create the alkylidene.

Synthesis optimization : the aldol condensation



Scheme 18 - Using **38** directly in the aldol condensation to **58**

To understand the selectivity of the aldol condensation reaction, the 3,5-dibromo-4-hydroxybenzaldehyde (**38**) was subjected to similar conditions as in **Scheme 16** (see **Scheme 18**). The results of this reaction were most surprising as it is unprecedented;[36a,b] there have been no examples of free-phenol condensation of this type to date. Performing the deprotection with BBr_3 (as outlined in **Scheme 17**). For a moderate exchange the isolated yield we have managed to eliminate an unnecessary step in the synthesis of rubrolide L.

We saw previously (see **Scheme 15**) that **57** would not undergo base catalyzed aldol condensation due to the presence of the weakly-activating methoxy groups (relative to hydroxy groups) in *para*. We exploited this principle when selectively brominating the alkylidene ring. The mechanism of activation in presence of TBSOTf can be summarized in **Figure 11**.

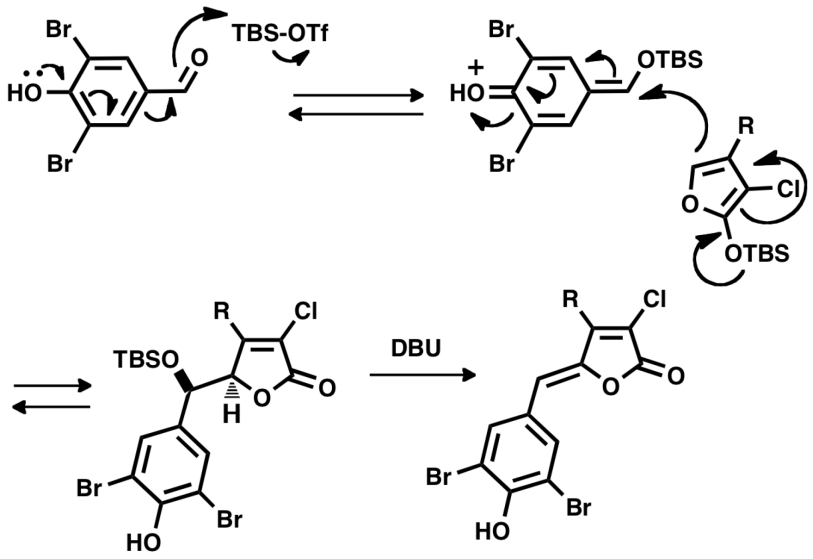
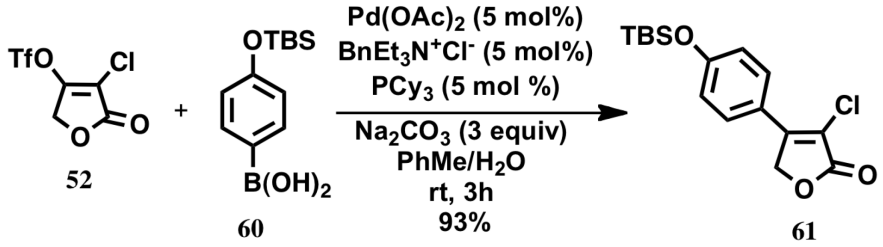


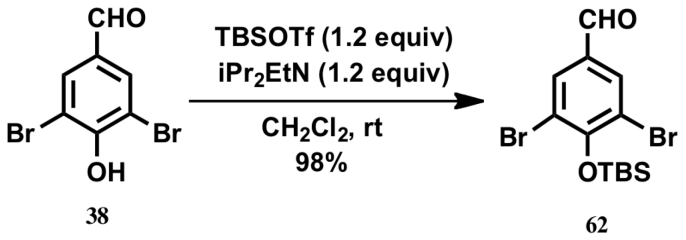
Figure 16 - Activation of the aldehyde group toward electrophilic attack by the Lewis acid.

In a final effort to quicken the synthesis, re-routing was made to couple **52** with 4-TBSO-phenylboronic acid (**60**). The same conditions were used as in **Scheme 14** including the use of the Fu-Buchwald ligand, PCy_3. The isolated yield was 93% which is slightly better than that of **45.**



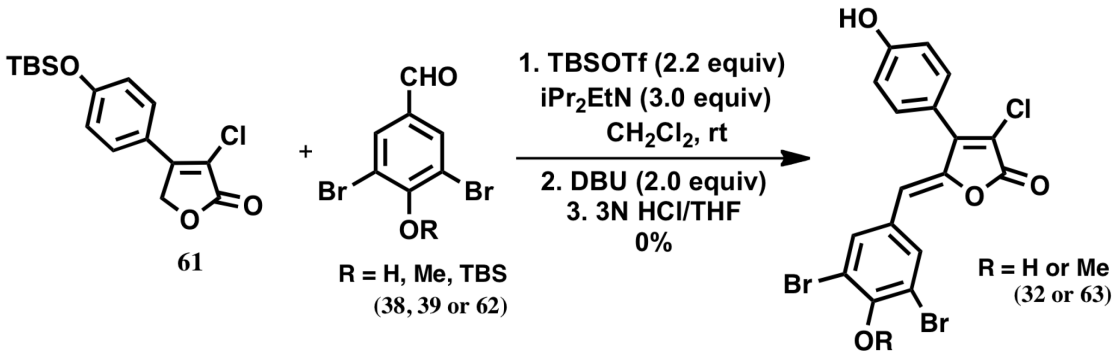
Scheme 19 - Coupling triflate **52** with TBS protected phenol **60**

With **61** in hand (and in excellent yield from the subsequent step) we turned our attention to performing the stereo-controlled aldol reaction with easily assembled synthon (see **Scheme 20**), **62**, which can also be ordered commercially from Sigma-Aldrich.



Scheme 20 – Synthesis of TBS protected 3,5-dibromo-4-hydroxybenzaldehyde, **62**

Unfortunately, the aldol reaction described (see **Scheme 21**) proved to be fruitless with substrate **62.** Condensing other 3,5-dibromobenzaldehydes (**38** and **39**) also gave no conversion and returned starting material. Coupling 3,5-dibromo-4-hydroxybenzaldehyde (as well as other variations such as the TBS protected alcohol group and the methoxy group) provided no product, when reacted with the 3-chloro-4-(4-*tert*-butyldimethylsiloxy)phenyl-2(5*H*)-furanone.



Scheme 21 – Aldol condensation of **61** with various substrates failed to provide product

Future work

Although rubrolide L a potent ARI who activity could be ameliorated by changing its binding mode *in vivo*. Possibly altering the alkylidene ring by substitution of other smaller, more electronegative halogens could potentially increase its binding strength and hence its activity of inhibition for human aldose reductase. Our group is evaluating the synthesis of various analogs of rubrolide L that may change its inhibitive properties. To alter the substituents of the alkylidene ring and study its inhibitive property would thereby lead to a better understanding of the binding mode with human aldose reductase. Thus, we would be examining the role the 3,5-dibromo-4-hydroxyalkylidene moiety plays *in vivo* in hARL2

coordination.

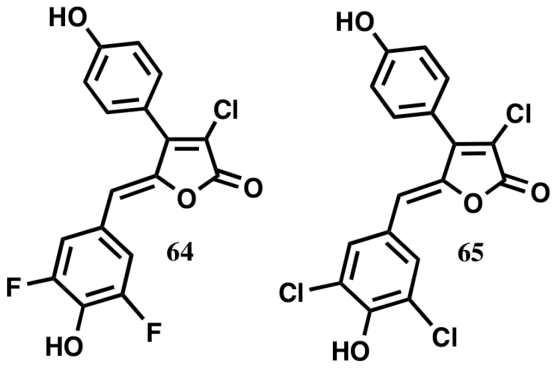
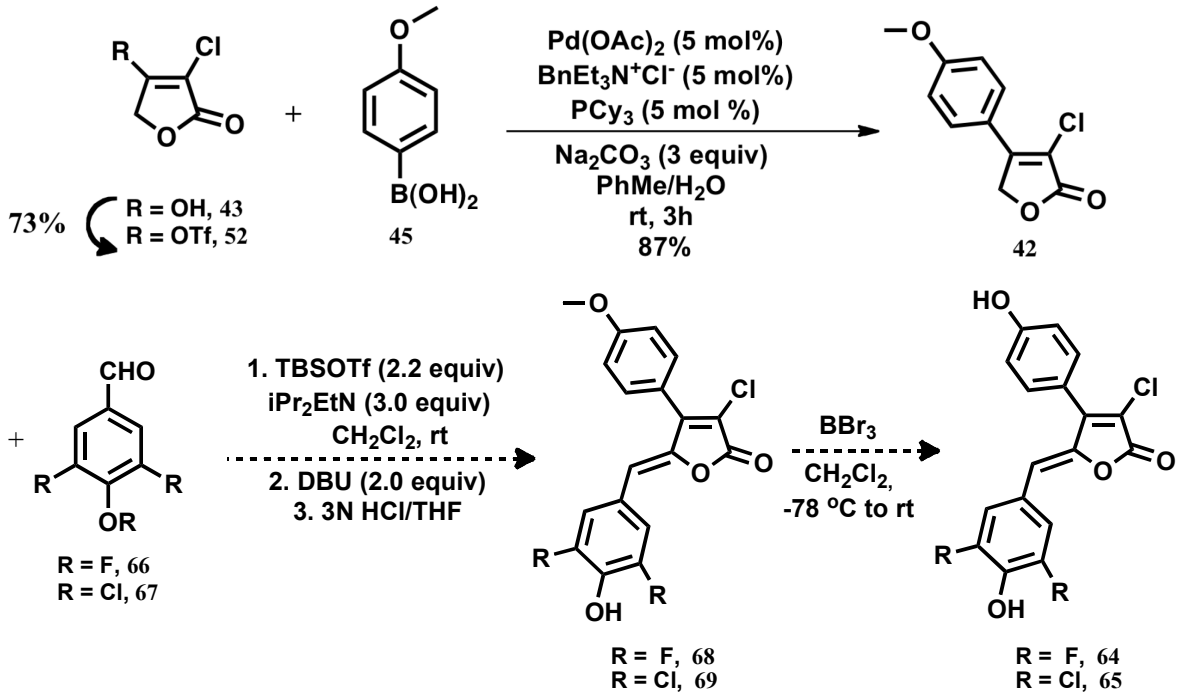


Figure 17 – New analogs of rubrolide L, **64** and **65**

Compounds **64** and **65** are potential candidates as aldose reductase inhibitors. The different halogens, differing in steric bulk and electro-negativities could potentially insert itself differently in the active site of the first enzyme in the polyol pathway, hARL. The synthesis of **64** and **65** would be akin to that of rubrolide L.



Scheme 22 – Planned synthesis of new analogs of rubrolide L (**32**), **64** and **65**.

Using the respective aldehyde, the aldol condensation has been performed for each with yields slightly less than that of **58** from **38** (43% with **66** and 59% with **67**). The subsequent reaction of the aldol-condensation and base catalyzed elimination products would face subsequent phenol deprotection using a similar route as in the original synthetic route of rubrolide L; boron tribromide at low temperature.

Conclusion

There is a great need for new aldose reductase inhibitors as none are available for sale in North America due to the strict FDA regulations. Rubrolide L has showed an elevated, inhibitive property for this enzyme. Relative to the other rubrolides studied,[24] rubrolide L most efficiently binds to aldose reductase, essentially shutting down the production of sorbitol *via* the polyol pathway. The benefits of ARI's have been weighed and assessed as well as their potential for those suffering from the onset of diabetes type II. Finally, rubrolide L has been synthesized in an overall yield of 42% over 5 steps or 37% over 4 steps.

Part Two: Synthesis of Yangjinhualine A

Datura metel L. and ancient Chinese medicine

Flos daturae (baimantuoluo in Chinese) is the dry flower of *Datura metel L*., which belongs to the family of the Solananceae. It is a shrug-like perennial herb with dark green leaves and light white or yellow coloured flowers. Commonly known as angel's trumpet, ingesting large quantities of the plant can have toxic effects on the body including convulsions and coma (due to the tropane alkaloids present in parts of the plant) however, in smaller doses compounds isolated from *Datura metel* L. has been shown to have potential to treat these symptoms. It grows in subtropical climate and is often cultivated for its aesthetic and chemical properties.[37] *Datura* is known for its anti-cholinergic and deliriant properties: *D. metel* is one of the 50 fundamental herbs used in traditional Chinese medicine, where its dried flowers, called *yáng jīn huā* (洋金花) were originally recorded in a Chinese ancient book, *Compendium of Materia Medica*, and also described in the *Chinese Pharmacopoeia*. This herb has a long history as a traditional Chinese medicine and is widely utilized to cure many diseases such as cough, asthma, convulsion, etc., due to its potent and wide-scope of biological activities. It has been reported that the clinical use of *D. metel L*. showed a significant effect on the treatment of psoriasis. However, few reports on its active constituents and pharmacological effects related to the treatment of psoriasis were published. Studies have shown that the non-alkaloid water-soluble part of the flower of *D. metel L*. plays an active role in healing psoriasis.[37-39]

Constituents of *Datura metel* L.

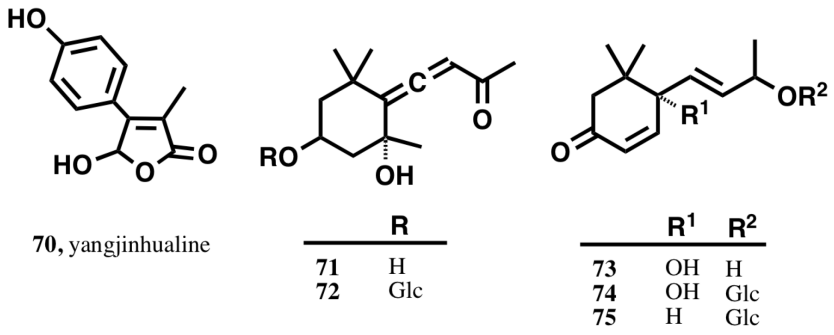


Figure 18 - Some of the non-alkaloidal constituents of *Datura metel* L.

In a handbook for pharmacotherapeutics by Arcangelo and Peterson[16] it was indicated the effective parts of *Flos Daturae* have many pharmacological actions, including anti- asthma, coughs, convulsions and insanity properties. In 2008,[40] Feng and co-workers reported the isolation of a novel component of a polar extraction, named yangjinhualine A (**70**), along with some previously known terpenoids (**71** - **75**) from *Datura metel* L,[3] part of a growing family of naturally occurring α,β–disubstituted γ–hydroxybutenolides.[4,5] Specifically, the non-alkaloidal fractions of yangjinhua have shown to have anti-psoriasis, strong anti-inflammatory and anti-analphylatic properties. The discovery of a new compound and five known megastigmane sesquiterpenes (see **Figure 18**) has prompted further study of the chemical constituents of *D. metel* L. The synthetic community has devoted great attention to various γ-hydroxybutenolides as some examples have known to demonstrate potent anti-tumour,[42] anti-fungal,[xlii] and anti-diabetic properties.[xliii,44] Although the biological activity for **70** has not been reported specifically, we describe the first-ever reported synthesis *D. metel* L.'s the major non-alkaloidal constituent, **70**.

It is worthy of note that γ-hydroxybutenolides exists in equilibrium with their acyclic tautomer.[45] Consequently, they have dual-action functionality (e.g. aldehyde and carboxylic acid groups) that could potentially cause enzyme inhibition through covalent bond formation. For instance, an imine can be formed by condensation of the aldehyde group with a primary amine residue (*cf.* a lysine side-chain) of the enzyme.[46]

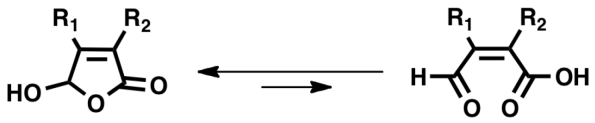


Figure 19 – Open/closed tautomerism of γ–hydroxybutenolides

Non-traditionally and from a pharmaceutical standpoint, the γ-hydroxybutenolide moiety could be considered a bioisostere of the phosphate group.[47] Despite their popularity, regiocontrolled access to unsymmetrically α,β-disubstituted γ-hydroxybutenolides is still a challenge, very few are described in the literature.[48] Most commonly, the use of singlet oxygen, as reported by Faulkner in 1988, involves photooxidation of monosubstituted furans to create ozonides which are deprotected by a hindered base to provide modest yields on small scale synthesis.[49] More recently, Clive and co-workers[50] performed the conversion of furans into γ-hydroxybutenolides using sodium chlorite. Unfortunately, the scope of this technique is limited to γ-hydroxybutenolides with a substituent in the β-position.

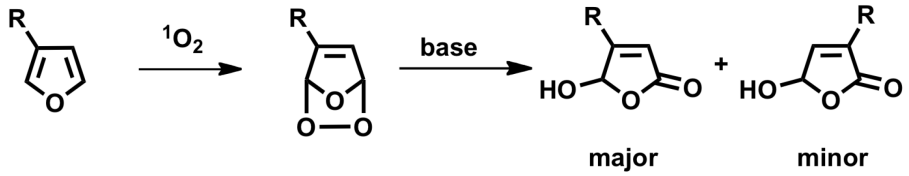
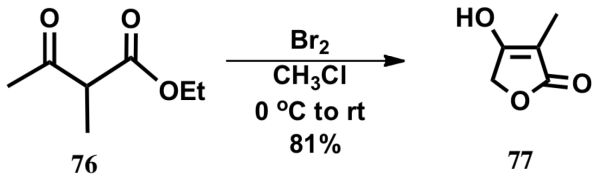


Figure 20 - The use of singlet oxygen to gain access to 5-hydroxy-2(5*H*)-furanones

The synthesis: starting from an acyclic precursor

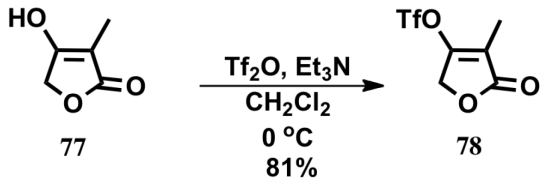
Using the synthesis of rubrolide L as a guide, we first turned our attention to reproducing the conditions for the Suzuki-Miyaura cross coupling from the triflate. It was necessary to begin our synthesis from acyclic precursor (**76**).



Scheme 23 - Formation of alcohol **77**

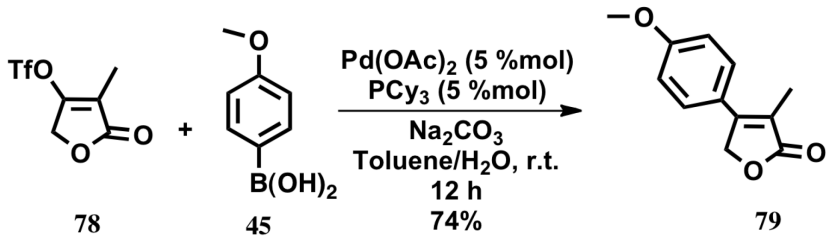
With our 3-methyl-2(5*H*)furanone (**77**) center in place, we were ready to begin the decoration of our heterocyclic anchor.

Suzuki-style cross-coupling revisted



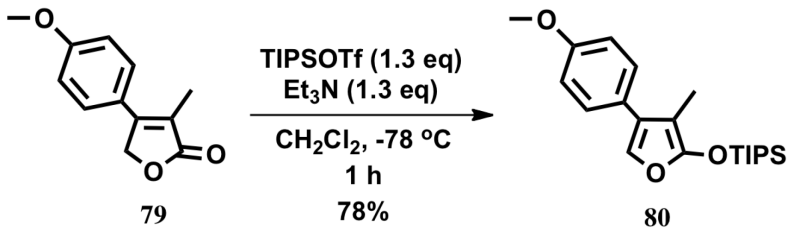
Scheme 24 - Triflate **78** was synthesized from precursor **77**

Initially, we were pleased with the durability of the triflate as it was much more stable than the previously reported **52** despite their structural homology. The yield was higher as a result of the increased stability exuberated by **78** on silica gel. In similar Suzuki-Miyaura cross-coupling screenings, we noted robust **78** coupled much as we would have expected, using a similar substrate (**45**), catalyst, ligand, base, solvent system, time and temperature.



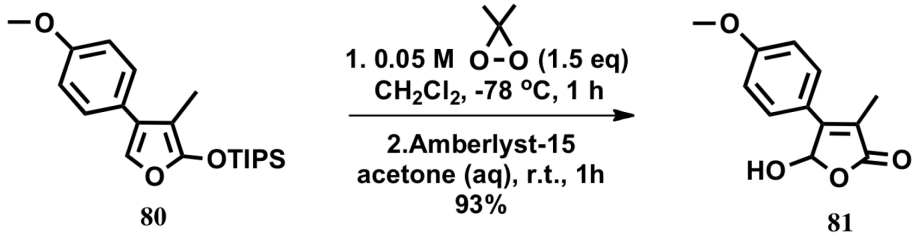
Scheme 25 - Coupling triflate **78** to boronic acid **45**

Next, we create a silyloxyfuran moiety (**80**) using TIPSOTf and triethylamine at low temperature, chromatographed easily on silica gel that has been deactivated with triethylamine and hexanes. Before loading the product, the column was flushed again with hexanes as a preparative measure. The product was loaded and eluted with hexanes.



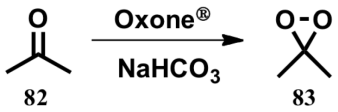
Scheme 26 - Synthesis of silyloxyfuran **80**

Next, a "two-steps, one-pot" procedure was performed; oxidation followed. First, we oxidized **33** with DMDO at low temperature to get the acyclic intermediate and the ring was closed by stirring with amberlyst-15 to acquire the cyclic heterocycle, **80**.



Scheme 27 - Oxidation of **80** with DMDO to **81**

Using dimethyldioxirane as a selective oxidizer



Scheme 28 - Forming DMDO (**83**) from acetone (**82**)

Dimethyldioxirane (DMDO) can be made easily from very inexpensive starting materials (although it must be used immediately and does not store well for periods of time); it can selectively oxidize in the presence of many sensitive functional groups, such as double bonds.[51] Oxone® is $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. The active component potassium monopersulfate ($KHSO_5$, potassium peroxomonosulfate) which is a salt from the Caro's acid, H_2SO_5.

The use of Oxone has increased rapidly throughout the literature.[52] Reasons for this are the stability, the simple handling, the non-toxic nature, the versatility of the reagent and the low costs. This property, along with the excellent yields this reaction provides offers an attractive technique in natural product synthesis.

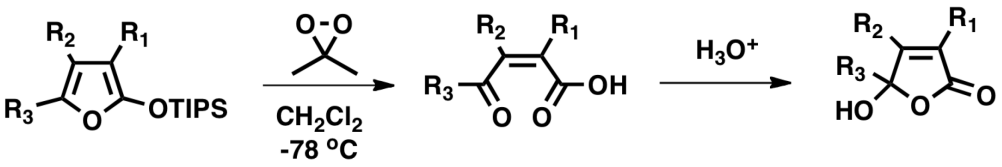


Figure 21 - DMDO oxidation passes through an acyclic precursor

Presently, the mechanism has not been heavily investigated. One possibility for the mechanism is '*butterfly*' mechanism (in which an attack on either side of the silyloxyfuran generates the same product) or an ionic mechanism (see **Figure 3.2**). We can close to a heterocycle and subsequently deprotect the alcohol using dilute hydrochloric acid and tetrahydrofuran to provide the yangjinhualine **2** in excellent yield for this reaction.

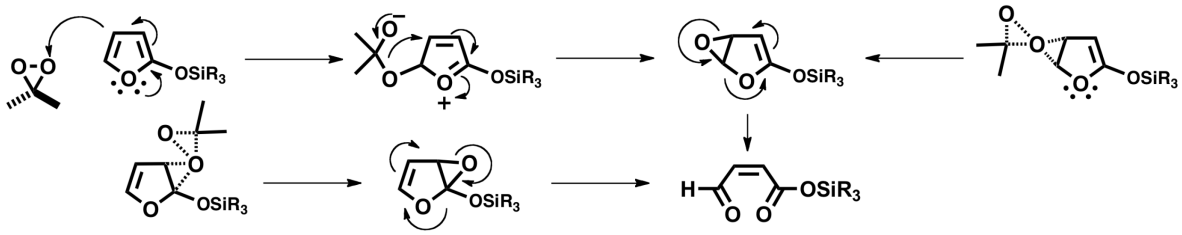
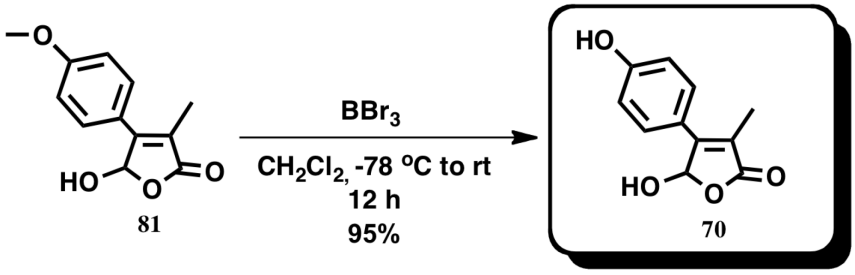


Figure 22 - Probable "Butter-fly" mechanism of DMDO oxidation to 5-hydroxy-2(5*H*)-furanone

With all our functionality in place, we are left with an alcohol deprotection to provide the natural product **70**. Akin to the demethoxylation in the case of rubrolide L, **32** (see **Scheme 17**) we deprotected our phenolic moiety using boron tribromide in dichloromethane at low

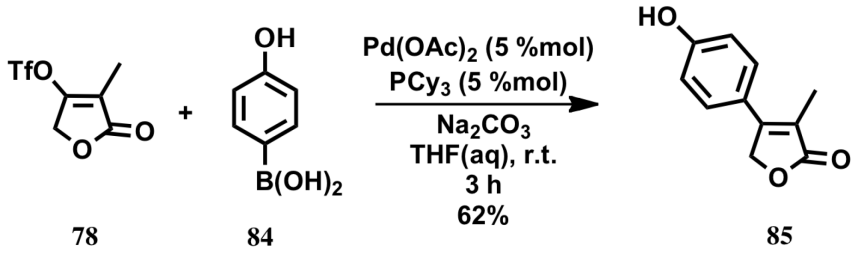


Scheme 29 - Final deprotection of **81** to provide natural product **70**

temperature in excellent yield. This route provided us with **70** with an overall percent yield of 33% over 6 steps.

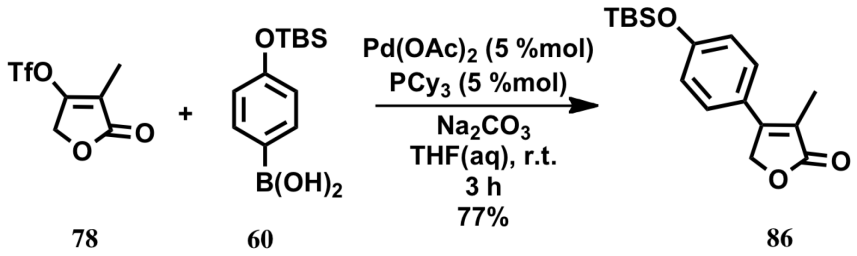
Optimizing the synthesis of yanjinhualine A (70)

The next step to optimize our synthesis be re-evaluating the efficiency of each step. We proposed that cross coupling **78** with an unprotected alcohol version of boronic acid **84** may help to eliminate a step in the



Scheme 30 - Using unprotected boronic acid **84** in Suzuki-Miyaura cross coupling with triflate **70**

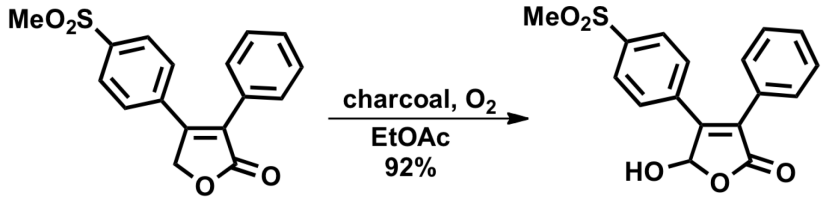
synthesis, yet the yield was less than in expected at 62%. In tandem, **Scheme 31** was also evaluated. Much more satisfied from these results, we pushed forward using an easily deprotected TBS moiety (**85**) in the place of the methoxy group protection of the alcohol. Interestingly enough, both of these cross coupling reactions used the rival solvent system, aqueous tetrahydrofuran. All conditions remained similar, **78** underwent coupling with the 4-OTBS-pheynlboronic acid (**60**) with a slightly better yield of 77%.



78 **60** **86**

Scheme 31 - Boronic acid **60** coupled with **78** to give **87** in very good yield

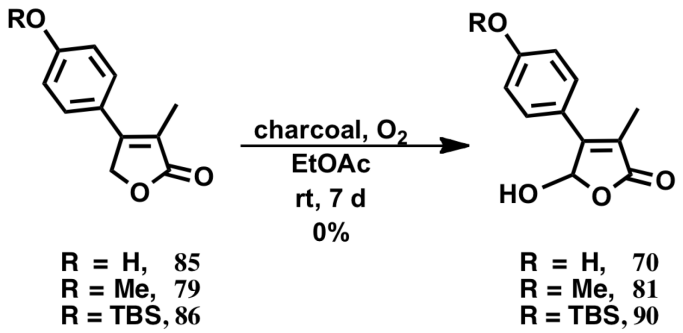
Satisfied, we proceeded to the synthesis of the siloxyfuran **87**, before its oxidation with dimethyldioxirane in scheme 31, in a one-pot method. Unlike using singlet oxygen (see **Figure 20**), our group developed a method to create 5-hydroxy-2(5*H*)-furanones using dimethyldioxirane (reagent in **Figure 21**).



87, Vioxx® **88**

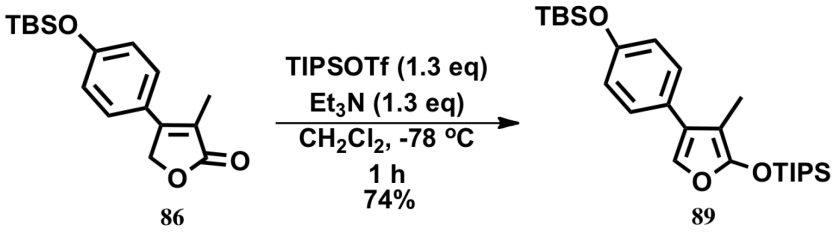
Scheme 32 - Oxidation of Vioxx® (**87**) to alcohol **88** with charcoal and molecular oxygen

Exploring other methods of oxidation, we examined the oxidation of such as the Vioxx® oxidation,[53] (see **Scheme 32)**. Vioxx® is a synthetic drug which belongs to a novel class of non-steroidal anti-inflammatory drugs (NSAID) like **8** and **9**. Using **79, 85** or **86** and an equal mass amount of activated carbon in ethyl acetate (as in **Scheme 32**), the oxidation was attempted of the C_5 atom to produce the hydroxy moiety; if successful this technique would shorten the synthesis one full step.



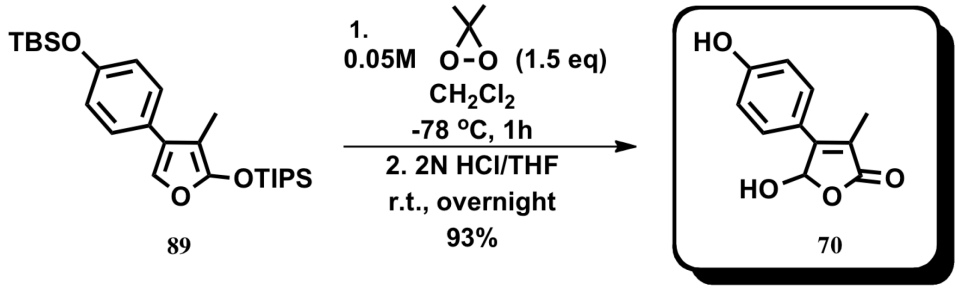
Scheme 33 – Charcoal/O_2 oxidation failed to oxidize **85**, **79** and **86**

Unfortunately, all of the substrates screened (see **Scheme 33**) failed to provide any detectable trace of products **70**, **81** and **90**. We were then forced to continue to use our DMDO method of oxidation and pass to **70** via the silyloxyfuran route as depicted in the synthesis of rubrolide L.



Scheme 34 - Creation of silyloxyfuran **89**

The low isolatable yields of **89** originating from the difficulty in separating it from unreacted **86**, however, with careful silica chromatography (silica deactivated with triethylamine) we were able to isolate **89** in 74% yield.



Scheme 35 – Acquiring access to natural product **70**

With a slight modification in the proton source (see **Scheme 35**) the use of 2N HCl closed our acyclic precursor and deprotected the TBS moiety giving yangjinhualine A in excellent yield.

Conclusion

The effects of yangjihua have been studied since the dawn of ancient Chinese medicine, making compound **70**, a natural occurring component of these dried leaves, an imminent target for synthesis. On the whole, our initial synthetic route over 6 steps provided us with 34% yield. In comparison, using the OTBS moiety and performing its eventual deprotection one-pot (in tandem after the oxidation) we were able to improve the synthesis by eliminating one step by tackling the synthesis with another substrate thereby improving the yield by 2% globally. Unfortunately, oxidation over charcoal in ethyl acetate did not lead to the 5-hydroxy-2(5*H*)furanone from this route, leaving little in the way of optimizing the synthesis with this alternative oxidation technique.

4.0 Attempted Hygrine and Norhygrine Synthesis

Hygrine and norhygrine

Hygrine **(*R*)-(+)-91** is a pyrrolidine alkaloid found mainly in coca leaves (0.2%) and has been detected in many other plants.[54] Unlike its cousin, cocaine (**94**), neither **(*R*)-(+)-91** nor norhygrine **(*R*)-(+)-92** have psychotropic effects. Both **(*R*)-(+)-91** and **(*R*)-(+)-92** (and their respective enantiomers) are useful intermediates for their tropane skeleton in organic synthesis.[55] Carl Liebermann first isolated it **(*R*)-(+)-91** in 1889 (along with a related compound **(*R*)-(+)-92** accompanying **94** in coca and its synthesis was first reported in 1949.[56]

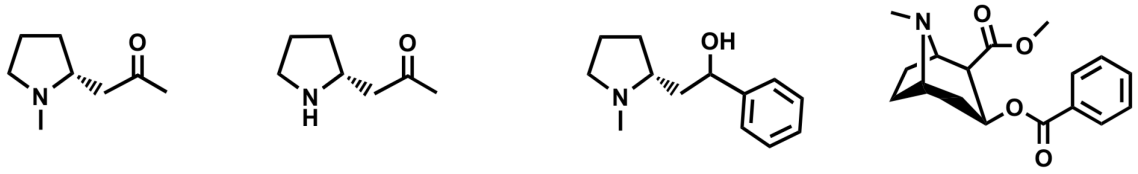
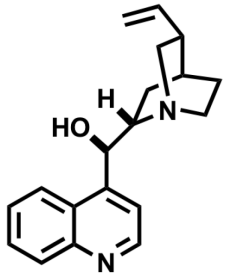


Figure 23 – Naturally occurring pyrrolidines

Pyrrolsedamines, (29)

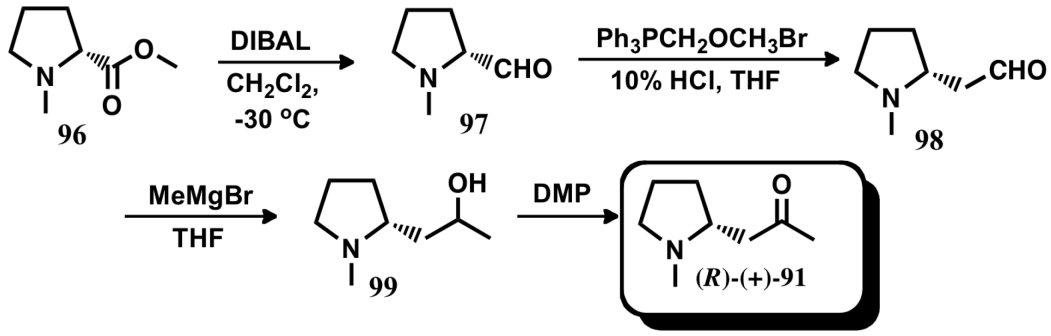
In addition to **(*R*)-(+)-91** and **(*R*)-(+)-92**, pyrrolsedamine and pyrrolallosedamine have been isolated from some *Sedum* species in 1996.[57] These are potential CD mimics (see **Figure 24**) for use in the Orito reaction (asymmetric reduction of pyruvate on Pt(111) surface. The development of new chiral modifiers for asymmetric reduction is often surfaced after the systematic screening of various structures.[58]



95, cinchonidine (CD)

Figure 24 – Cinchonidine or CD is an alkaloid used in asymmetric synthesis

Most syntheses to date start from acyclic precursor, however recently[59] a synthesis of (-)-hygrine, **(*R*)-(+)-91** was performed in 7 steps starting from the inexpensive, commercially available *L*-proline. The key-steps included the functionalization of the side-chain with a

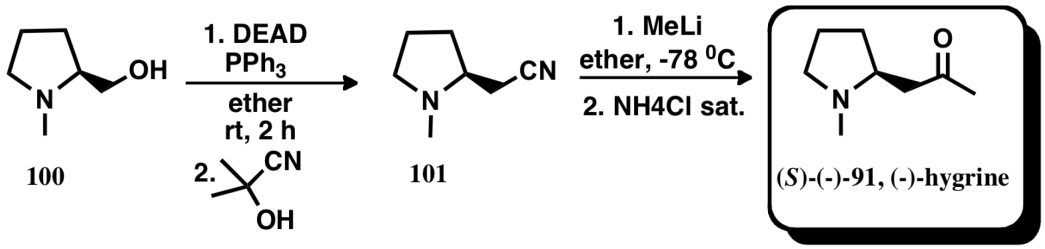


Scheme 36 - Previously reported synthesis of **(*R*)-(+)-91**

Wittig reaction followed by a regioselective Wacker oxidation. Not long before, this was published, a facile approach to (+)-hygrine was published[60] demonstrating a four-step synthesis of **(*R*)-(+)-91** (see **Scheme 36**) with 35% overall yield from commercially available N-methyl-*R*-proline methyl ester (**96**). We have proposed here a two-step synthesis of **(*S*)-(-)-91** (its enatiomer) starting from commercially available N-methyl-*L*-prolinol (**100**).

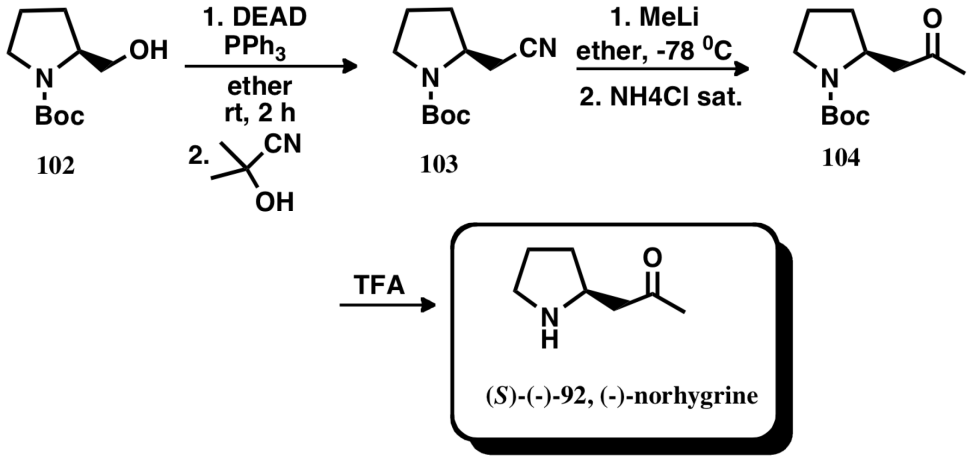
The key-step in this planned two-step synthesis is a one-pot Mitsunobu procedure that converts our starting alcohol (**100**) to nitrile (**101**). From the nitrile, we could then use an

organolithium or a Grignard reagent to get the respective methylketone.



Scheme 37 - Proposed synthesis of **(*S*)-(-)-91**

Using the same logic outlined in **Figure 25**, **(*S*)-(-)-91** has helped us map out a plausible synthesis for its cousin, **(*S*)-(-)-92.**



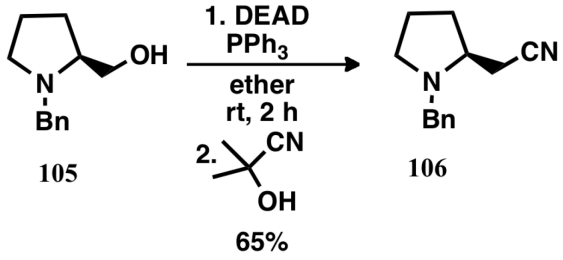
Scheme 38 - Proposed synthesis of **(*S*)-(-)-92**

The Mitsunobu-Wilk reaction

We began our synthesis by evaluating UV-active **105** as we presumed it would be very easy to follow on TLC and is less expensive than **100** and **102**. First we converted the primary alcohol **105** into nitrile **106** using the Mitsunobu-Wilk procedure with diethyl azodicarboxylate and triphenylphosphine in ether (see **Scheme 39**), and later cyanohydrin as a cyano source (which yields acetone as a by-product).

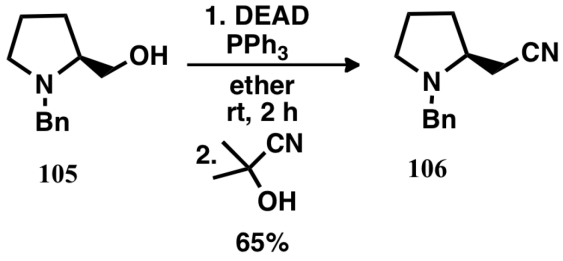
The Mitsunobu-Wilk Reaction allows the conversion of primary and secondary alcohols to

esters, ethers, thioethers and various other compounds.[61] The reaction is well known for efficient inversion of stereogenic centers on sp^3 carbons, which makes the Mitsunobu-Wilk reaction a powerful addition to the chemist's toolbox.



Scheme 39 – The Mitsunobu reaction using **105** to acquire nitrile **106**

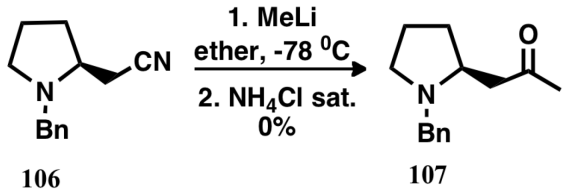
Here, we use this reaction as a two-steps, one-pot transition from a primary alcohol to the respective nitrile. The nucleophile employed is generally acidic, since one of the reagents (DEAD, diethyl azodicarboxylate) must be protonated during the course of the reaction to prevent side reactions. The triphenylphosphine combines with DEAD to generate a phosphonium intermediate that bonds strongly to the alcohol oxygen (creating a good leaving group). Substitution by the cyanide nucleophile (added later in the reaction) completes the process (two steps, one-pot). The alternative to this reaction is to create a good leaving out of the alcohol functional group (such as a tosylate) and after purification of this compound, reflux in DMF with a potassium or sodium cyanide.



Scheme 40 - Benzyl-protected pyrrolidine **105** subjected to Mitsunobu conditions

As outlined (see **Scheme 40**), **105** was stirred in dry ether with triphenylphosphine, with cooling. After five minutes, DEAD was added dropwise to the viscous mixture, which

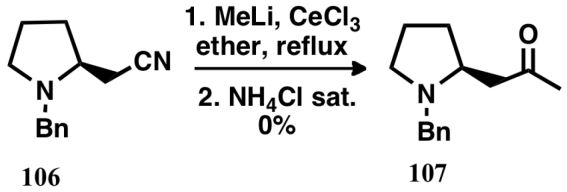
begins to instantly increase the overall viscosity of the solution until stirring ceases. Soon after the addition of DEAD is complete and the cyanohydrin in ethereal solution was added to the mixture and almost immediately the products begin to re-solubilize. . The reaction was left stirring overnight warming to room temperature. The Mitsunobu reaction has also created a name for itself as a "tricky" reaction due to the difficulties it causes in the purification step.[62] Aside from the copious amounts of triphenylphosphine and phosphonium ion, the DEAD and protonated DEAD literally drags its way up a TLC plate or down a silica gel column as it decomposes, making separation of product nearly impossible by these methods. Although there are various versions of polymer bound triphenylphosphine and DEAD reagents that are available from retailers, they are often quite expensive and cannot be reused or even used simultaneously.[63] The crude mixture of **106** was subjected to an acid wash extraction with ether, which was dried on sulfates, evaporated *in vacuo* and was left in the freezer in hexanes for an hour. After filtering through celite most of the remaining triphenylphosphine and triphenylphosphonium salt was removed. The resulting mixture was concentrated again *in vacuo* and distilled. Numerous attempts to chromatograph **106** using flash or slow-drip techniques failed to resolve from the remaining amounts of DEAD and protonated DEAD from the product. The crude mixture was distilled on high-vac (56^{o}C at 1 mm Hg) to afford **36** in 65% yield.



106 **107**

Scheme 41 – Nitrile **106** was subjected to an organolithium reagent at low temperature

We proceeded to the organolithium step as seen in **Scheme 40**. Various conditions with varying the (pre-titrated) methylating agent, time and temperature were attempted. All failed and would, at the best return starting material (see **Scheme 41**).

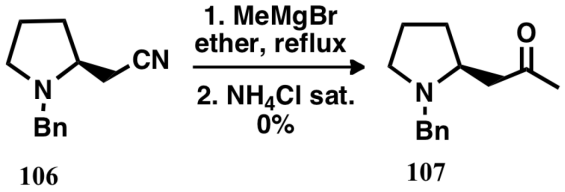


Scheme 42 - $CeCl_3$ as an additive in the organolithium step in transforming **106** to **107**

Many variations of this reaction were attempted such the methylating agent, time, temperature as well as using the Luche method in which dried $CeCl_3$ is added to the organolithium.[lxiii] This method is for the alkylation of ketones, which will form enolates if simple organolithium reagents were to be used. In organolithiums, which are essentially ionically-bonded species, the Li centers bear a substantial ∂^+ charge. By inference, the essential interaction, between the centers of Me and Li^+, is a repulsive/anti-bonding one (unlike in lithium metal where Li^+ species exists with a $1e^-$ pair electron density).[65] The disaggregated methyl group with its considerable ∂- charge is an ideal nucleophile bearing little steric hindrance and no electronic counter-balance. In brief, the reaction has all in its favour to continue to completion except the sterically uninhibited methyl bonded nitrogen, which could deactivate the organolithium though a stabilizing complexation of a Li^+. One could argue that this disaggregation with Li^+ would drive the reaction to completion but based on the observed results, it forms a stable complex awaiting the acidic quenching of Me^- to produce methane and lithium hydroxide.

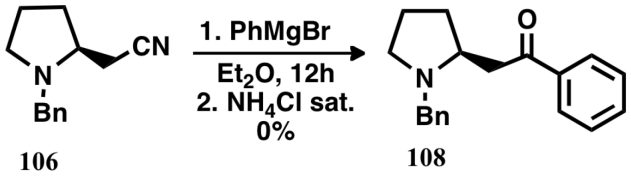
Cerium(III) chloride can be used as a Lewis acid, for example as a catalyst in Friedel-Crafts alkylation reactions. Luche reduction of alpha, beta-unsaturated carbonyl compounds has become a popular method in organic synthesis where $CeCl_3.7H_2O$ is used in conjunction with sodium borohydride. Another important use in organic synthesis is for alkylation of ketones which would otherwise form enolates if simple organolithium reagents were to be used. Yet, as an additive in this addition, the lewis acid (when dried scrupulously) failed to produce **107** in any detectable amount.

Switching ideas, we changed tactics to obtain **47** using Grignard reagents for the addition (see **Scheme 43**).



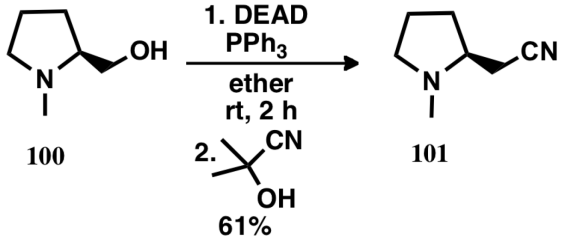
Scheme 43 - Using a Grignard to obtain methyl ketone **107**

However, much to our surprise nitrile **106** seemed resistant to all alkylating methods we evaluated.



Scheme 44 - Using a different, phenyl Grignard reagent to test reactivity of **106**

After various frustrations, we turned to other forms of nucleophilic addition and substitution. In direction of **(*S*)-(-)-93**, **106** was subjected to a Grignard addition with phenylmagnesium bromide and yet, even under refluxing conditions this reaction failed (see **Scheme 44**). This reaction failed to provide change to the starting material (which was recovered).

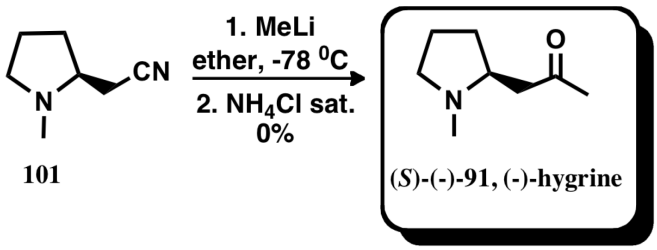


Scheme 45 - Using compound **100** to obtain nitrile **101**

Remaining optimistic, we switched our focus to **100** (inexpensive, relative to its enantiomer), as the precursor for the synthesis of **(S)-(-)-91**. The reaction preceded as well as in outlined in **Scheme 40** yielding 61% of pure **101** after distillation at low pressure (45

^{o}C at 1mm Hg).

(*R*)-(+)-91could not be accessed from **100** by this method, the results observed in scheme 42 were not encouraging.



Scheme 46 - Subjecting **41** to methyl lihtium

On the other hand, if the carbon alpha to the nitrile was depronated to produce the species described below, the consequent workup with NH_4Cl would yield only stating material and consume the organolithium.

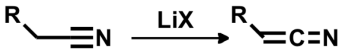
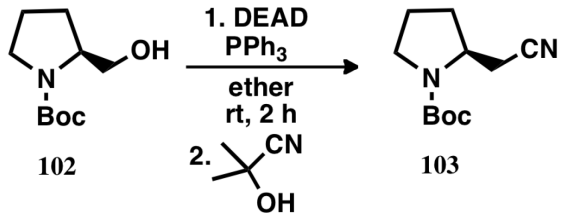


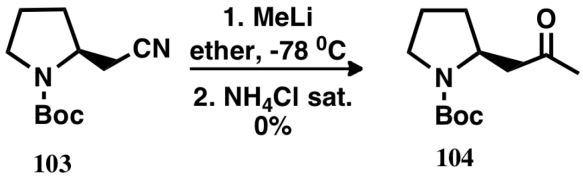
Figure 4.5 Organolithium mediated rearrangment

A less likely scenario would be directed-*ortho* metalation (DOM) leading to an epimerized stereogenic center as in figure 4.5. If the lone-pair of electrons of nitrogen was a factor then adding an electron withdrawing group as a *tert*-butyloxycarbonyl proctecting group would draw the density over more atoms, decreasing the overall electron density around the nitrogen atom.

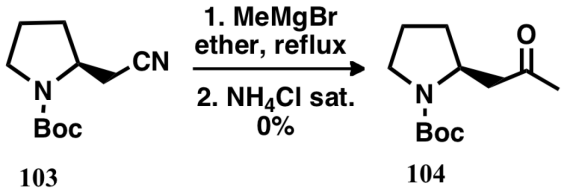


Scheme 47 - Boc-protected pyrrolidine **102** is subjected to Mitsunobu conditions

Nitrile **103** was prepared in good yield *via* an identical route to **106** and **101** and was purified by distillation under reduced pressure. However, following suit, **103** would not react with organolithium or Grignard methylating agents (as per **scheme 47**) This lack of reactivity of nitrile **103** as well as **106** and **101** prevents us from being able to successfully synthesize natural products hygrine or norhygrine from these starting materials.

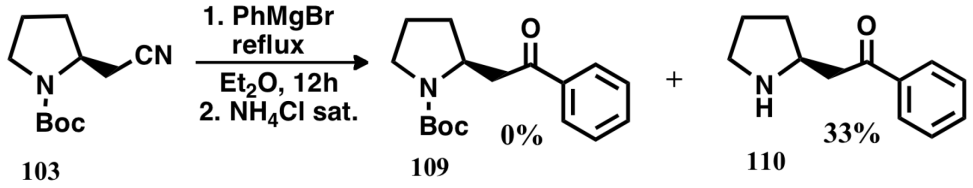


Scheme 48 - Nitrile **103** was unreactive towards methyllithium



Scheme 49 - Nitrile **103** was unreactive towards methyl Grignard reagents

Much to our surprise, when the same nitrile **103** was refluxed in diethyl ether with phenylmagnesium bromide we were able to isolate **110** and none of the protected amine was observed (**109**).



Scheme 50 - Reacting nitrile **50** with phenylating groups provided **110** in low yield

To acquire access to the (-)-pyrrolsedamine and (-)-pyrrolallosedamine, there is a simple two-step procedure that has been explored by other groups for asymmetrically reducing the ketone in **110**.[66]

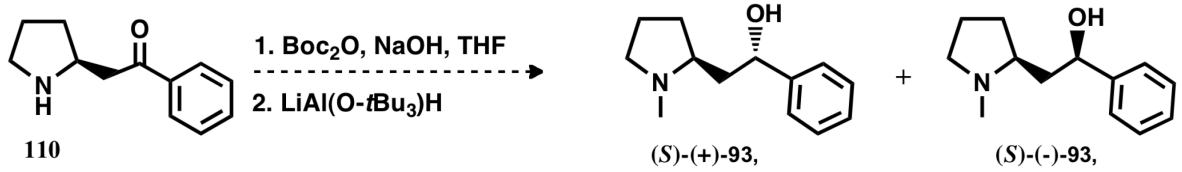
Conclusion

From our studies, we have failed to provide a facile route to (-)-hygrine and (-)-norhygrine using a primary alcohol, converting it to its respective nitrile and then using a methylating agent on those nitrile just three carbons away from the nitrogen in our pyrrolidine center. We have succeeded in reacting one 2-(pyrrolidin-2-yl)acetonitrile with phenylmagenesium bromide in reflux with ether. We have likely done so with the aid of the electron withdrawing Boc group as an amine-protecting group.

Future work

From pyrrolidine **110**, the ketone group could be reduced using using lithium tri-*tert*-butoxyaluminum hydride. This has been shown to provide good *ee* with excellent yields in similar substrate.

First, however, we would need to protect the amine with a Boc protecting group to exploit the route of hydride deprotection. When N-Boc is deprotected with trifluoroacetic acid (or other sources of H^+), we are left with an N-H group. However, deprotection using lithium aluminium hydride (or H^-) we can deprotect the amine leaving a methyl group in its place.



Scheme 51 - Stereoselective hydride reduction of ketone **110**

To re-protect the amine we will take up the amine in tetrahydrofuran, deprotonate using concentrating $NaOH_{(aq)}$ until a pH of 11 is reached. From there, we will add Boc_2O anhydride. After a workup and extraction, we can submit our protected intermediate to a hydride reduction in dry tetrahydrofuran.

5.0 Synthesis of Chiral Auxiliaries for use in Orito Type Reactions

Surface Chemistry

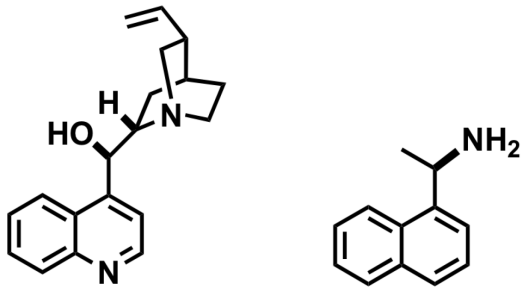
Surface chemistry is a much newer domain of chemistry relative to organic (homogenous) chemistry. However, the potential of surface chemistry in terms of ecology, efficiency, flexibility and financial cost is outstanding. Using solid, insoluble catalysts there is no need for extraction and separation is made facile and timesaving among numerous other advantages. Many different surfaces can be used such as chirally modified metals: Pt, Pd, and Ni. One particular reaction we will pay attention to is the Orito reaction.

The Orito Reaction describes the enantioselective hydrogenation of ketones on chirally modified (cinchonidine) platinum. The demand for asymmetric modifiers is increasing as organic chemistry progresses and understanding the mechanism of this reaction is the most certain way to be able to modify and exploit this niche.

The Orito Reaction

One of the most commonly studied examples is hydrogenation of α-ketoesters, such as ethyl pyruvate, on the surface of alumina-supported platinum catalysts that have been treated with a chiral alkaloid modifier. The most commonly used catalyst is typically cinchonidine. This combination, referred to as the Orito reaction, is the catalytic reduction of ethyl pyruvate to (*R*)-ethyl lactate with an enantiomeric excess of more than 95%.[lxvi] Despite these results, there is little understood on why CD modified Pt is such an efficient chiral catalyst. With hopes of designing or discovering a more efficient catalyst, our group has turned to organic synthesis to help acquire access to new compounds that could meet or exceed the high standard that CD/Pt has set. This will help us to understand the mechanism

of how the substrate, the surface and the catalyst act together.



95 111

Figure 5.1 Cinchonidine (95, CD), and (*R*)-1-(1-napthalyl)ethylamine (111, NEA)

The kinetics of the chiral modifier, the surface and the substrate

To understand how the CD/Pt catalyst works, our group examined bonding interactions between methyl pyruvate and 1-naphthylethylamine (NEA) on a single crystal Pt(111) surface. Since CD is a complex polycyclic molecule the simpler NEA is used in the study. NEA could theoretically be just as efficient a chiral modifier as CD for the Orito reaction. Recently, scanning tunneling microscopy (STM) images of NEA on Pt(111) were recorded.

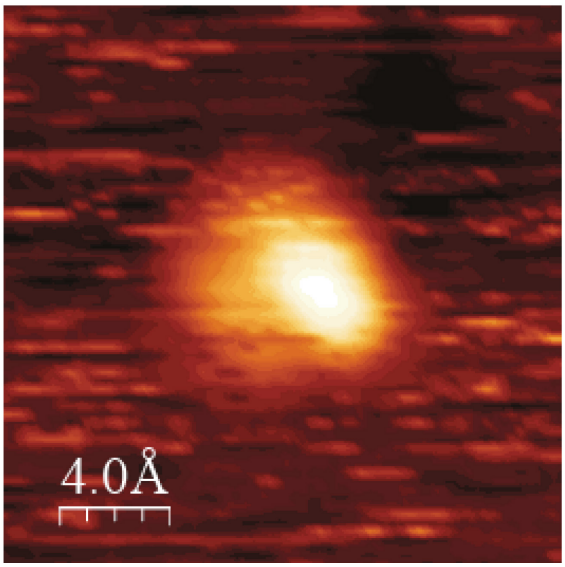
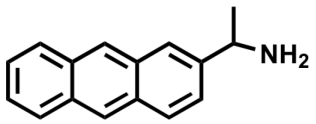


Figure 5.2 STM image of NEA on Pt(111), image shows a bright and darker aura representing the ethylamine group and the aromatic group respectively.

Interpretation of STM images of adsorbed NEA

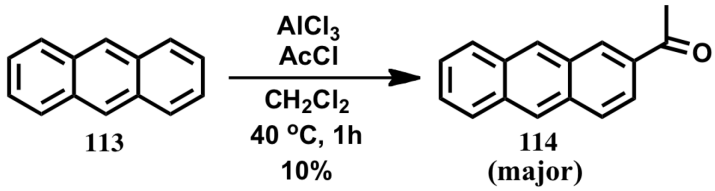
The STM image of NEA on Pt(111) at room temperature shows a bright area and a lighter

region. In order to determine the molecular group that gives the bright area we prepared the larger molecule **112.**



112

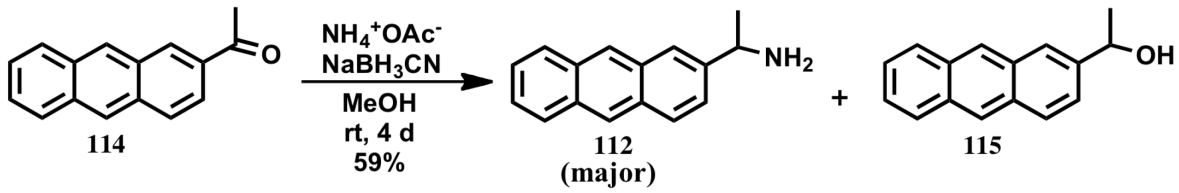
At first, we wanted evaluated 2-acetylanthracene, however it was available only as a rare and impure chemical from Sigma-Aldrich. Next, we turned to synthesizing the 2-substituted isomer, **112**. Synthesizing of **112** was made possible through Freidel-Crafts acylation of inexpensive **113** with $FeCl_3$ in dichloromethane while heating to 40 ^oC.[68] These conditions produced a mixture of 1 (minor), 2 and 9 (major) substituted-acetylanthracene, which were all separable on large scale (~10 g) using column chromatography.



Scheme 52 - Friedel-Crafts acylation of **113** to form ketone **114**

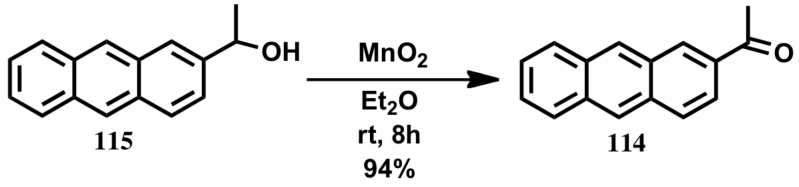
2-Synthesis of 2-ethyalmine anthracene (AEA).

Using 2-acetylanthracene, we can aminate the ketone using ammonium acetate in methanol. A small amount of dichloromethane was used to solubilize **113**. With sodium cyanoborohydride the imminium is reduced to the achiral amine. A chiral version could be made with the Corey-Bakshi-Shibata (CBS) oxazaborolidine reagent; either enantiomer is theoretically obtainable. The CBS oxazaborolidine catalyst has been used in the asymmetric reduction of prochiral ketones.[69]



Scheme 53 – Reductive amination of ketone **113**

The reaction provided two products, **112** (major) and also the reduced ketone **115** (less than 20%), which were both isolated by column chromatography of the crude extract. To regenerate **114**, **115** was oxidized by treatment with MnO_2. The purification of **112** was facilitated through the use of acid-base workup. First forming the hydrochloride salt with 12 N HCl and rinsing with copious amounts of dichloromethane. To generate the free base,



Scheme 54 – Oxidation by manganese dioxide of **115** to generate **112**

the acid was basified to pH 10 with KOH providing pure **112** with 59% yield, and no further purification.

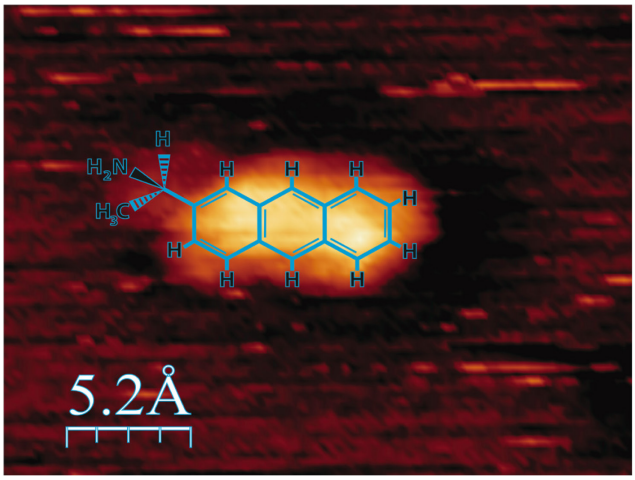
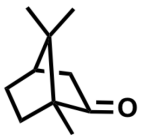


Figure 5.3 STM image of 46a on Pt(111) surface

Systematically searching for new chiral modifiers

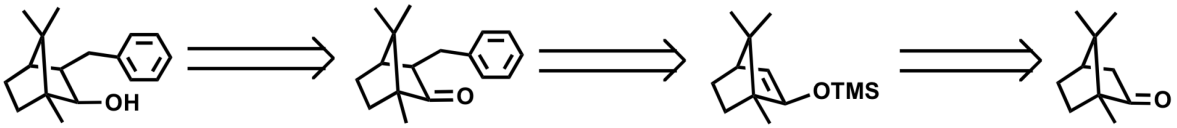
Certain criteria must apply for a chiral modifier to be efficient. First, besides having a stereocenter, it must have two points of contact to link with the substrate on the surface of the platinum. Secondly, it must have a steric hindrance about it such that only one side of the molecule 'sits' on the surface to ensure on one enantiomer is created. To begin our search for a new modifier, we evaluated camphor. Besides being inexpensive, camphor is a bicyclic molecule with bulky methyl groups, which would ensure that it would come into

contact with the platinum surface with one face only.



116

Figure 5.4 the backbone for a new chiral auxiliary, (1*R*)-(+)-camphor.



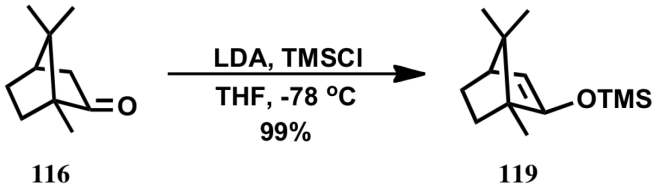
117 **118** **119** **116**

Scheme 55 - Retrosynthesis of **117** from commercially available **116**

Some of the most important characteristics for chiral modifiers for the Orito reaction include a sterically bulky or hindered molecule that will only coordinate with the platinum surface via one face. This makes (1*R*)-(+)-camphor a useful starting material. The other important characteristic is a molecule with two points of contact to provide unique coordination of a pyruvate molecule; bringing these two players together in a unique fashion is essential for asymmetric reduction with a very high ee. There is a recent report of the evaluation of a derivative of camphor as a chiral auxiliary for the highly effective stereoselective hydrocoupling of its cinnamates by electroreduction.[70a,b] This study claims to make the TMS enol siloxy ether using nBuLi at low temperature. However, this is not effective at deprotonating the starting material. It is necessary to use LDA to favour the enolization and obtain the enol siloxy ether. From there, $TiCl_4$ was used despite its undesirable toxicity, at low temperature with a diphenylmethylhalide. From there, a hydride reduction affords the product in what they claim is quantitative yield.

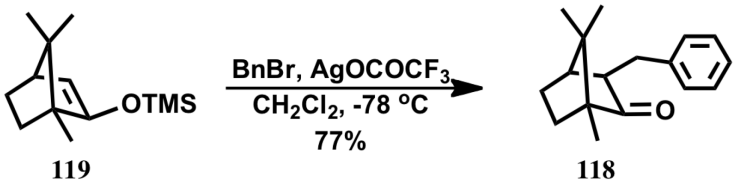
We began our journey from commercially available (+)-(*R)*-camphor, **116**; using LDA (made *in situ* from butyllitium and diisopropylamine in tetrahydrofuran at -78 ^{o}C) we were able to make the siloxy intermediate electrophillic enol trapping. As Bredt's rule dictates: we only deprotonate a non-bridgehead carbon to give uniquely **119.** The crude compound was carried forward to the next reaction without purification, after permitting the reaction

to stir overnight. However, for characterization purposes, the siloxy compound was distilled with a Kugelrohr apparatus at 44 degrees Celsius at 2mm Hg.



Scheme 56 - Treatment of the enol of **116** with TMSCl

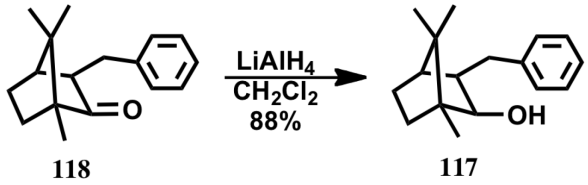
Using a procedure developed by our group, we used $AgOCOCF_3$ in place of the titanium tetrachloride. Titanium tetrachloride is a highly toxic and volatile Lewis acid. Upon contact with moisture in the air it will decompose to form dense clouds of titanium dioxide and hydrogen chloride. It is also extremely reactive and exothermic when exposed to moisture. The use of $AgOCOCF_3$ is preferred to its relative cost, ease of use, robustness in atmospheric conditions and low toxicity. Silver trifluoroacetate, unlike the most frequently used Lewis acids, such as zinc bromide and titanium chloride, activates the alkyl bromide.[71] Due to its nature, it does not greatly damage the acid sensitive enol silyloxyether. The complex is a 'soft' electrophilic alkyl cation, which displaces the enol siloxy ether by desilylation. After the TMS group is displaced, the carbonyl is then re-exposed.



Scheme 57 - Displacing the TMS group of 119 to generate the alpha-substituted ketone **118**

To obtain access to the chiral ligand **117**, we reduced the hindered ketone with lithium aluminium hydride in dry tetrahydrofuran over twelve hours at room temperature. After a standard water and sodium hydroxide workup the product was filtered. The product can be recrystallized from hexanes and ethyl acetate, however we chose to perform column

chromatography to ensure that any traces of **116** and **118** were removed before recrystallization.



118 **117**

Scheme 58 - Asymmetric reduction of **118** with LAH to provide chiral alcohol **117**

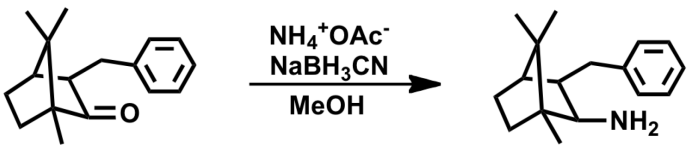
Conclusion

In brief, we have successfully synthesized 2-AEA for STM imaging with 59% yield in one step from the commercially available 2-acetylanthracene.. This has lead the identification of the different coloured spheres seen in the STM images on Pt(111) of NEA. Secondly, we have developed a new synthesis to obtain 3-benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol which will open the door to the synthesis of variations on this modifier from commercially available (1*R*)-(+)-camphor. The yields in this short synthesis were good, 67% over three steps to give a potential CD mimic for use in the Orito reaction.

Future Work

Using the synthesis we have developed for benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol we have opened the door to different possibilities, that is, decorating the C2 and C3 position with various functional groups that might coordinate better with the pyruvate substrate.

As in CD, there are various groups that could help the coordination, the alcohol, the vinyl, the aromatic groups and the amine. It was from this that the idea for **52** was spawned. Using a synthetic route similar to how **51** was obtained, the ketone **50** will be synthesized and a reductive amination will be performed using borohydride and ammonia to yield **52**.



118 **120**

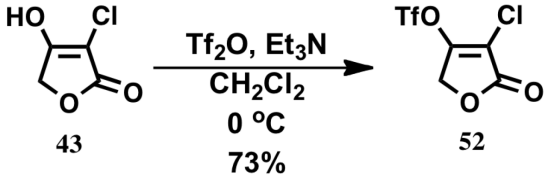
Scheme 59 - Reductive Amination of **118**

From these derivatives of (1*R*)-(+)-camphor it may be possible to discover a chiral modifier offering an *ee* in subsequent hydrogenations greater than that of CD.

Experimental Part

Unless otherwise indicated, all reactions were carried out under an argon atmosphere in flame-dried glassware using freshly distilled, anhydrous solvents. Reactions were monitored by thin layer chromatography on silica gel (0.25 mm thickness) from Silicycle visualised by UV light, cerium ammonium molybdate (CAM) and/or potassium permanganate ($KMnO_4$) as a developing agent. Flash chromatography was performed using silica gel 60 (230-400 mesh) from Silicycle. NMR spectra are recorded using a Varian AS400 or Bruker AM 300 spectrometers. NMR spectra are reported in ppm (parts per million) from tetramethylsilane with the solvent resonances as the internal standard (400 MHz, $CDCl_3$: δ_H 7.26 for ^1H and 100 MHz, $CDCl_3$: δ_C 77.0 for ^{13}C NMR). Fourier transformed infra-red (FTIR) spectra were recorded using a Bomem FT-IR MB Series on NaCl plates (neat), with a KBr pellet or using attenuated total resonance (ATR) on a ZnSe crystal. Optical rotations were measured using a 2 mL cell with a 1 dm length (c = 1 for 10 mg/mL) on a Jasco DIP-360 digital polarimeter with sodium (Na) bulb. High-resolution mass-spectroscopy was recorded using an Agilent LC-MSTOF exact mass spectrometer using electrospray ionisation (70 eV)

3-Chloro-4-triflyloxy-2(5*H*)-furanone, **(52)**



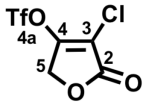
To a stirred solution of 3-chloro-4-hydroxyfuran-2(5*H*)-one **43** (1.04 g, 7.73 mmol) in dry dichloromethane was added dropwise triethylamine (1.29 mL, 9.28 mmol, 1.2 equiv) at 0 ^{o}C. The mixture was left to stir for 10 min under an atmosphere of argon. To the resulting mixture, triflic anhydride (1.56 mL, 9.28 mmol 1.2 equiv) was added dropwise and the solution was left to warm to room temperature with stirring over 2 h. The organic layer was washed with water, (2 x 25 mL), brine (1 x 25 mL), dried on magnesium sulfate and the excess solvent was evaporated under reduced pressure. The crude resin was distilled (72 ^{o}C/0.1 mmHg) to afford pure triflate **52** (1.51 g, 73% yield) as a clear and colourless oil;

Chemical Formula: $C_5H_2ClF_3O_5S$

Molecular Weight: 266.58

R_f = (n/a, degrades on silica)

Numeric sequence:



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 2H) ppm;

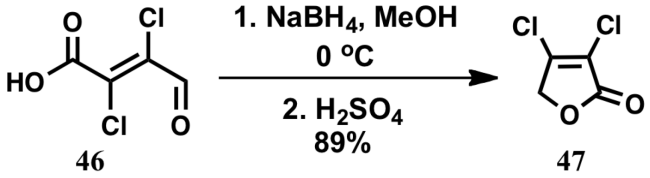
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (C_2), 159.3 (C_4), 118.5 (q, J_{CF} = 321 Hz, C_{4a}), 112.0 (C_3), 67.0 (C_5) ppm;

^{19}F NMR (376 MHz, $CDCl_3$) δ −72.9 ppm;

HRMS (ESI) cald for $C_5H_2O_5F_3SCl$: 265.9264 M^+, found: 265.9274;

IR (neat): ν_{max} 3576, 2958, 1800, 1679, 1443, 1359, 1291, 1232, 1132, 1048, 1024, 999, 805 cm^{-1}

3,4-Dichloro-2(5*H*)-furanone, **(46)**



46 **47**

In a flame dried, 500 mL round bottom flask was cooled a stirred solution of mucochloric acid **46** (18.5 g, 110 mmol) in dry, distilled MeOH (150 mL) with an ice water bath before adding $NaBH_4$ (6.24 g, 165 mmol, 1.6 equiv) portion-wise. The solution was permitted to stir for 35 minutes (at which time TLC indicated the complete consumption of starting material) and a solution of H_2SO_4 (aq) (10.78 g, 101 mmol, 1.0 equiv) in MeOH (60 mL) was added to the resulting mixture. The volatiles were evaporated *in vacuo* and the product was extracted in Et_2O (3 x 100 mL), brine (1 x 25 mL) dried on anhydrous Na_2SO_4 and volatiles evaporated. The crude product was recrystallized from Et_2O/pentane (1:1) to afford pure **47** as long white crystals (13.8 g, 89%)

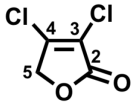
Chemical Formula: $C_4H_2Cl_2O_2$

Molecular Weight: 152.96

R_f = 0.41 (3:1 hexanes/EtOAc), CAM

m.p.: 47-8 °C (lit.[15] 49 °C)

Numeric sequence:



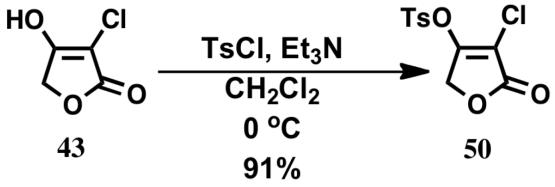
^{1}H NMR (400 MHz, CDCl3) δ 4.88 (s, 2H) ppm;

^{13}C NMR (100 MHz, CDCl3) δ 165.2 (C_2), 149.8 (C_3), 120.8 (C_4), 71.4 (C_5) ppm;

HRMS (ESI) cald for $C_4H_2Cl_2$: 151.9432 $(M+H)^+$, found: 151.943;

IR (KBr): ν_{max} 3526, 3438, 2978, 2943, 2471, 2159, 2036, 1844, 1770, 1721, 1643, 1444, 1245, 1037, 918, 750 cm^{-1}

3-Chloro-5-tosyloxy-2(5*H*)-furanone, **(50)**



To a stirred solution of 3-chloro-4-hydroxyfuran-2(5*H*)-one **43** (1.04 g, 7.73 mmol) in dry distilled CH_2Cl_2 was added dropwise triethylamine (1.29 mL, 1.2 equiv) at 0 ^oC. The mixture was left to stir for 10 min under an atmosphere of argon. To the resulting mixture, *p*-toluenesulfonyl chloride (1.77 g, 9.28 mmol 1.2 equiv) was added dropwise and the solution was left to warm to room temperature with stirring over 2 h. The organic layer was washed with water, (2 x 25 mL), brine (1 x 25 mL), dried on $MgSO_4$ and the excess solvent was evaporated under reduced pressure. The crude resin was purified on SiO_2 (3:1 hexanes/EtOAc) to afford pure tosylate **50** (2.03 g, 91% yield) as a white crystal;

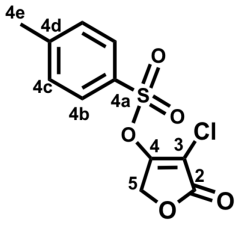
Chemical Formula: $C_{11}H_9ClO_5S$

Molecular Weight: 288.70

R_f = 0.44 (3:1 hexanes/EtOAc), CAM

m.p.: 88-89 ^oC

Numeric sequence:



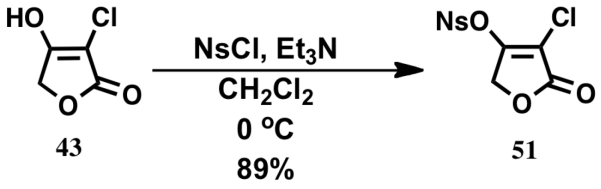
^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 5.06 (s, 2H), 2.52 (s, 3H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 (C_2), 161.0 (C_4), 148.0 (C_{4a}), 131.0 (C_{4d}), 130.6 (C_{4c}), 129.8 (C_{4b}), 108.0 (C_3), 67.3(C_5), 21.8 (C_{4e}) ppm;

HRMS (ESI) cald for $C_{11}H_9ClO_5S$: 287.9859 $(M)^+$, found: 287.9867;

IR (neat): ν_{max} 3331, 3132, 2975, 2901, 2854, 1777, 1664, 1591, 1399, 1362, 1295, 1189, 1173, 1024, 812, 800, 739, 669 cm^{-1}

4-Chloro-5-(*p*-nitrophenylsuflonate)oxy-2(5*H*)-furanone, **(12)**



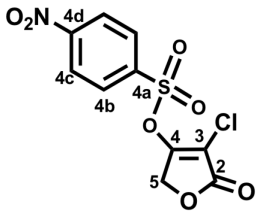
To a stirred solution of 3-chloro-4-hydroxyfuran-2(5H)-one **43** (1.04 g, 7.73 mmol) in dry, distilled CH_2Cl_2 was added dropwise triethylamine (1.29 mL, 1.2 equiv) at 0 ^oC. The mixture was left to stir for 10 min under an atmosphere of argon. To the resulting mixture, *p*-nitrophenylsulfonyl chloride (2.06 g, 9.98 mmol 1.2 equiv) was mixed into the solution and the solution was left to warm to room temperature with stirring over 2 h. The organic layer was washed with water, (2 x 25 mL), brine (1 x 25 mL), dried on $MgSO_4$ and the excess solvent was evaporated under reduced pressure. The crude resin was purified on SiO_2 (3:1 hexanes/EtOAc), all tubes containing the desired product were collected and recrystallized from Et_2O to afford pure product **51** (2.14 g, 89% yield) as a white powder;

Chemical Formula: $C_{10}H_6ClNO_7S$

Molecular Weight: 319.68

R_f = 0.21 (3:1 hexanes/EtOAc), CAM

m.p.: 132-33 ^oC



Numeric sequence:

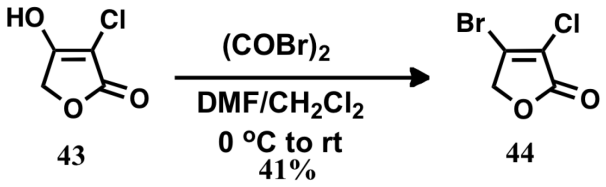
^1H NMR (400 MHz, acetone-d_6) δ 8.57 (d, J = 8 Hz, 2H), 8.46 (d, J = 8 Hz, 2H), 5.02 (s, 2H), ppm;

^{13}C NMR (100 MHz, acetone-d_6) δ 165.5 (C_2), 161.2 (C_4), 152.4 (C_{4a}), 139.6 (C_{4d}), 130.6 (C_{4c}), 125.6 (C_{4b}), 108.9 (C_3), 67.7 (C_5) ppm;

HRMS (ESI) cald for $C_{10}H_6ClNO_7S$: 318.9553 $(M)^+$, found: 318.9576.

IR (KBr): ν_{max} 3172, 3028, 2984, 2762, 1792, 1673, 1405, 1191, 1053, 857, 797 cm^{-1}

3-Chloro-4-bromo-2(5*H*)-furanone, **(13)**



To a solution of 3-chlorotetronic acid **43** (1.04 g, 7.73 mmol) and dimethylformamide (12 mL) in dry, distilled CH_2Cl_2 was added dropwise a solution of oxalyl bromide in dichloromethane (2.0M, 4.64 mL, 9.28 mmol) over a period of one hour at 0 ^oC under argon atmosphere. The mixture was warmed to room temperature over 3 h. The resulting mixture was washed with water (25 mL) and the phases were partitioned. The organic phase was washed with Et_2O (2 x 10 mL). The combined organic layer was washed with saturated $NaHCO_3$ (25 mL), brine (25 mL), dried on $MgSO_4$ and the excess solvent was evaporated under reduced pressure. The crude resin was purified on SiO_2 (5:1 hexanes/EtOAc) to afford pure product **44** (0.63 g, 41% yield) as a beige powder;

Chemical Formula: $C_4H_2BrClO_2$

Molecular Weight: 197.41

m.p.: 63-64 ^oC

R_f = 0.41 (3:1 hexanes/EtOAc), CAM

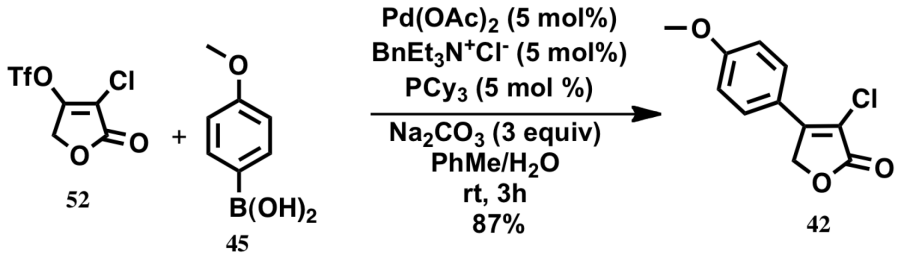
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (s, 2H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3 (C_5), 146.4 (C_3), 122.0 (C_4), 78.3 (C_2) ppm;

HRMS (ESI) cald for $C_4H_2BrClO_2$: 195.8834 $(M)^+$, found: 195.8853;

IR (neat): ν_{max} 3472, 2925, 2850, 1745, 1650, 1430, 1375, 1354, 1293, 1270, 1120, 1080, 995, 667 cm^{-1};

3-Chloro-4-(4-methoxyphenyl)furan-2(5*H*)-one, **(42)**



To a stirred solution of triflate **52** (89.0 mg, 0.33 mmol) in deaerated toluene (6 mL) was added, 4-methoxyphenylboronic acid **45** (75.2 mg, 0.50 mmol, 1.5 equiv), $Pd(OAc)_2$ (3.7 mg, 5% mol), $BnEt_3NCl$ (3.6 mg, 5% mol), PCy_3 (4.6 mg, 5 % mol), Na_2CO_3 (105 mg, 3.0 equiv), deaerated H_2O (0.5 mL) under Ar(g). After stirring at room temperature for 3 h, at which time TLC indicated complete consumption of triflate II, the excess solvent was evaporated *in vacuo* and the subsequent residue was purified by flash silica chromatography (1:1 hexanes/CH_2Cl_2) to afford the desired product **42** (65.3 mg, 87% yield) as a white crystalline powder:

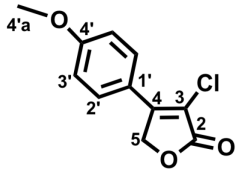
Chemical Formula: $C_{11}H_9ClO_3$

Molecular Weight: 224.64

R_f = 0.45 (CH_2Cl_2), UV

m.p.: 173-175 ^oC (litt[1]: 174-175 ^oC) ;

Numeric sequence:



^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 5.19 (s, 2H), 3.88 (s, 3H) ppm;

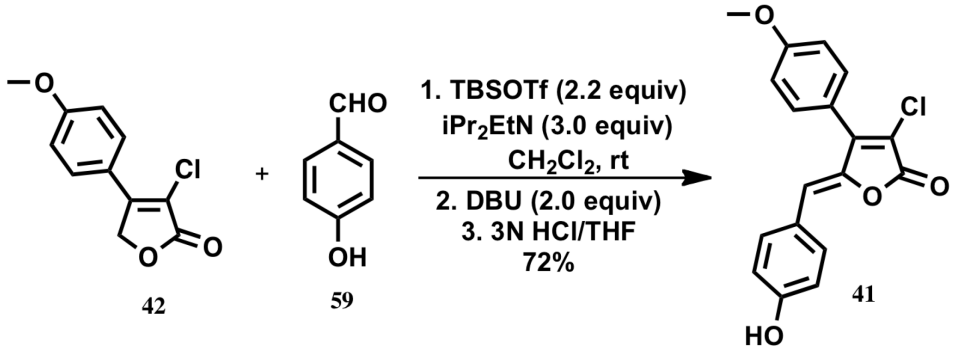
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 (C_2), 162.5 ($C_{4'}$), 151.6 (C_4), 129.3 ($C_{2'}$), 121.5 (C_3), 115.0 ($C_{1'}$) 114.9 ($C_{3'}$), 70.2 (C_5), 55.8 ($C_{4'a}$) ppm;

HRMS (ESI) cald for $C_{11}H_9ClO_3$: 224.0244 $(M)^+$, found: 224.0240.

Elemental Analysis: C, 58.81; H, 4.04; Found: C, 58.52; H, 4.24.

IR (KBr): υ_{max} 3489, 2967, 2933, 2834, 1758, 1605, 1512, 1445, 1333, 1256, 1202, 1186, 1075, 1034, 1023, 829 cm^{-1}

(*Z*)-3-Chloro-5-(4-hydroxybenzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one, **(41)**



42 59 41

To a stirred solution of **42** (36.0 mg, 0.16 mmol) in CH_2Cl_2 (anhydrous) was added TBSOTf (45.0 µL, 0.19 mmol, 2.2 equiv), 4-(*tert*-butyldimethylsiloxy)benzaldehyde, **59** (47.0 µL, 0.19 mmol, 1.2 equiv) followed by N,N-diisopropylethylamine (84.0 µL, 0.48 mmol, 3.0 equiv) in the absence of light. The starting material was consumed after 1 hour (followed by thin layer chromatography) before adding 1,8-diazabicyclo[5.4.0]undec-7-ene (48 µL, 0.32 mmol, 2.0 equiv). To the reaction mixture, which was left stirring under inert atmosphere for 3 h, was added 5 mL of CH_2Cl_2 and then washed with 3N HCl (2 x 25 mL) and brine (1 x 15 mL). TBS deprotection was performed by evaporating the excess solvent *in vacuo* and to the resulting solution was added THF (20 mL) and 3N HCl (4 mL) left to stir overnight in the absence of light. The excess solvent was evaporated *in vacuo* and the subsequent residue was purified by flash silica chromatography (20:1 → 10:1 *v/v* hexanes/EtOAc) and all tubes containing the desired product were collected. Compound **41**was recrystallized from hexanes/EtOAc and then again from hexanes/CH_2Cl_2 to afford the pure, desired product, **41** (37.9 mg, 72 % yield, 2 steps) as a yellow amorphous powder:

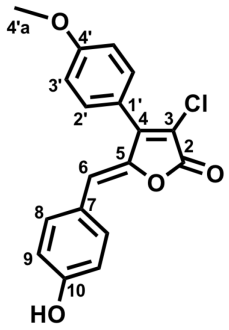
Chemical Formula: $C_{18}H_{13}ClO_4$

Molecular Weight: 328.75

R_f = 0.71 (2:1 hexanes/EtOAc) UV+heat

m.p.: 225 ^oC (decomp.);

Numeric sequence:



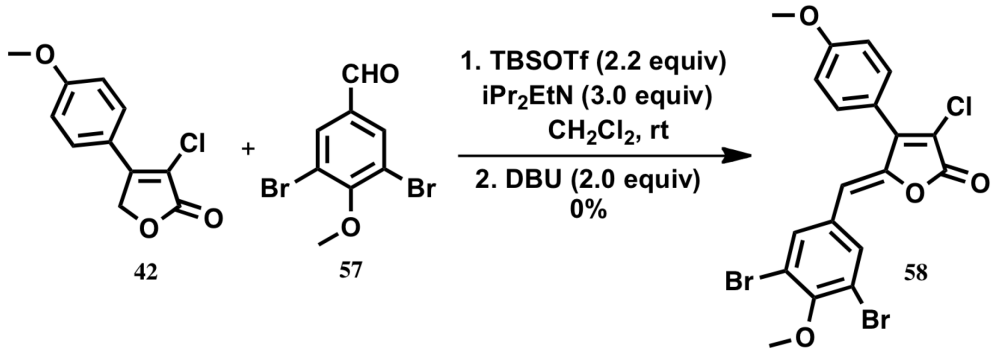
^{1}H NMR (400 MHz, acetone-d_6) δ 8.89 (br s, 1H) 7.70 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.23 (s, 1H), 3.89 (s, 3H);

^{13}C NMR (100 MHz, acetone-d_6) δ 164.9 (C_2), 162.3, 159.8, 151.0, 145.5, 133.7, 131.8, 125.7, 121.2, 116.8, 116.7, 115.4, 115.3, 55.9 ($C_{4'a}$);

HRMS (ESI) cald for $C_{18}H_{13}ClO_4$: 328.0507 $(M)^+$, found: 328.0502;

IR (KBr): υ_{max} 3338, 2929, 2933, 2836, 1744, 1603, 1505, 1442, 1346, 1258, 1170, 1025, 832 cm^{-1}

<u>Attempted Synthesis</u> of:
(*Z*)-3-Chloro-5-(3,5-dibromo-4-methoxybenzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one **(58)**

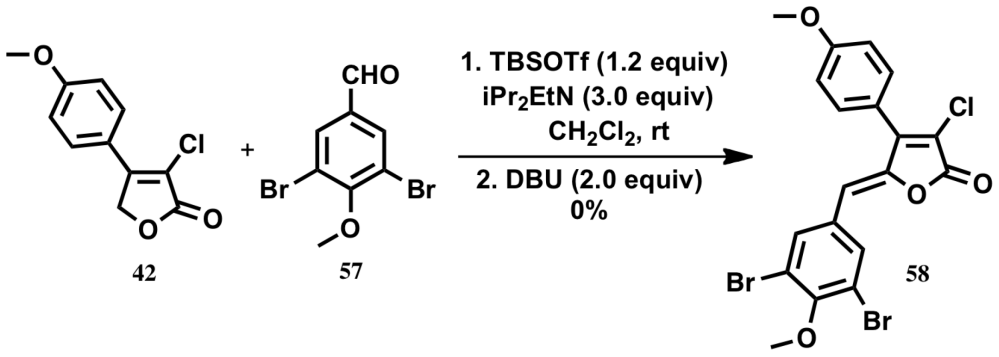


To a stirred solution of **42** (36 mg, 0.16 mmol) in CH_2Cl_2 (anhydrous) in a flame-dried flask under $Ar_{(g)}$, was added TBSOTf (80 µL, 0.35 mmol, 2.2 equiv), 3,5-dibromo-4-methoxybenzaldehyde, **57** (56 mg, 0.19 mmol, 1.2 equiv) followed by N,N-diisopropylethylamine (84 µL, 0.48 mmol, 3.0 equiv) in the absence of light. After stirring at room temperature for 1 h, 1,8-diazabicyclo[5.4.0]undec-7-ene (48 µL, 0.32 mmol, 2.0 equiv) was added to the reaction, which was left stirring under inert atmosphere for another 3 h. Then, 5 mL of CH_2Cl_2 was added to the reaction and the resulting mixture was washed with 3N HCl (2 x 25 mL) and brine (1 x 15 mL) dried (Na_2SO_4) and the volatiles

evaporated *in vacuo*. Reaction failed to provide the desired product, **58** as determined by NMR analysis.

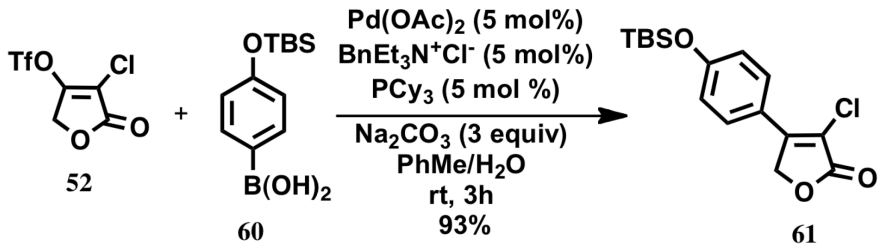
<u>Attempted Synthesis</u> of:

(*Z*)-3-Chloro-5-(3,5-dibromo-4-methoxybenzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one, **(7)**



To a stirred solution of **42** (36 mg, 0.16 mmol) in dry, distilled CH_2Cl_2 in a flame-dried flask under argon atmosphere, was added TBSOTf (40 µL, 0.19 mmol, 1.2 equiv), 3,5-dibromo-4-methoxybenzaldehyde **57** (56 mg, 0.19 mmol, 1.2 equiv) followed by N,N-diisopropylethylamine (82 µL, 0.48 mmol, 3.0 equiv.) in the absence of light at -78 ^{o}C . After stirring at room temperature for 1 h, 1,8-diazabicyclo[5.4.0]undec-7-ene (48 µL, 0.32 mmol, 2.0 equiv) was added to the reaction which was left stirring under inert atmosphere for another 3 h. CH_2Cl_2 was added (5 mL) to the reaction before being washed with 3N HCl (2 x 25 mL) and brine (1 x 15 mL) before the volatiles were removed *in vacuo*. The reaction failed to provide the desired product, **58**, as determined by NMR analysis.

4-(4-(*tert*-Butyldimethylsiloxy)phenyl)-3-chlorofuran-2(5*H*)-one, **(61)**



To a stirred solution of **52** (89 mg, 0.33 mmol, 1.0 equiv) in deaerated toluene (6 mL) was added **60** (101 mg, 0.40 mmol, 1.2 equiv), $Pd(OAc)_2$ (3.7 mg, 5% mol), $BnEt_3NCl$ (5 mg, 5% mol), PCy_3 (4.6 mg, 5 % mol), Na_2CO_3 (105 mg, 3.0 equiv), deaerated H_2O (0.5 mL) under Ar(g). After stirring at room temperature for 3 h, at which time TLC indicated complete consumption of triflate **52**, the excess solvent was evaporated *in vacuo* and the subsequent residue was purified by flash silica chromatography (1:1 hexanes/CH_2Cl_2) to afford the desired product **61** (100 mg, 93% yield) as a white powder:

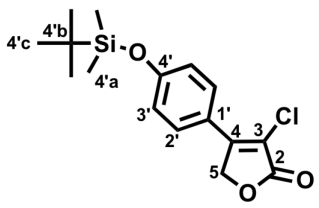
Chemical Formula: $C_{16}H_{21}ClO_3Si$

Molecular Weight: 324.87

R_f = 0.89 (CH_2Cl_2), UV

m.p.: 235 ^oC (decomp.)

Numeric sequence:



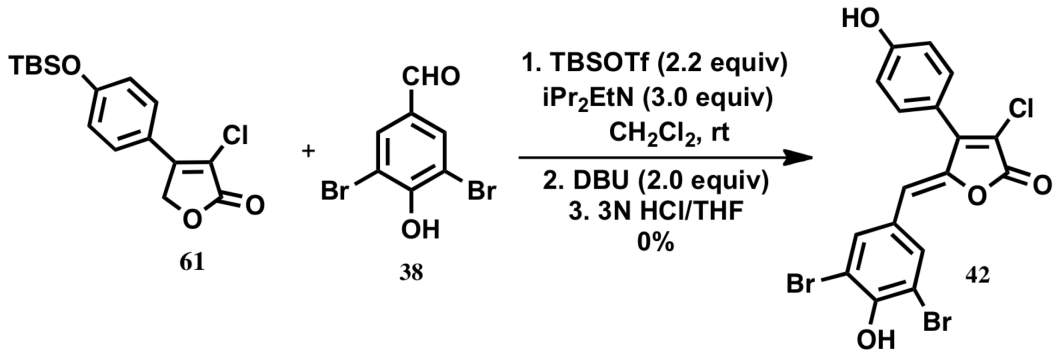
^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 9.0 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 5.20 (s, 1H), 1.00 (s, 9H), 0.25 (s, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (C_2), 159.2 ($C_{4'}$), 151.5 (C_4), 129.3 ($C_{2'}$), 122.1 ($C_{1'}$), 121.0 ($C_{3'}$), 115.2 (C_3), 70.2 (C_5), 25.8 ($C_{4'c}$), 18.5 ($C_{4'b}$), -4.10 ($C_{4'a}$) ppm;

HRMS (ESI) cald for $C_{16}H_{21}ClO_3Si$: 324.0948 $(M)^+$, found: 324.0950

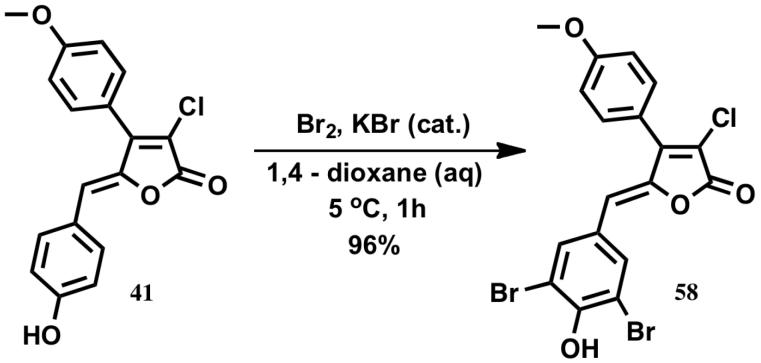
IR (KBr): υ_{max} 3069, 2955, 2927, 2855, 1774, 1603, 1509, 1275, 1176, 1036, 910, 838 cm^{-1}

<u>Attempted Synthesis</u> of: Rubrolide L, (42)



To a stirred solution of **61** (22 mg, 0.07 mmol) in dry, distilled CH_2Cl_2 in a flame-dried flask under argon atmosphere was added TBSOTf (35 µL, 0.15 mmol, 2.2 equiv), 3,5-dibromo-4-hydroxybenzaldehyde, **38** (22 mg, 0.08 mmol, 1.1 equiv) followed by N,N-diisopropylethylamine (37 µL, 0.20 mmol, 3.0 equiv.) in the absence of light at -78 ^{o}C . After stirring at room temperature for 1 h, 1,8-diazabicyclo[5.4.0]undec-7-ene (21 µL, 0.14 mmol, 2.0 equiv) was added to the reaction which was left stirring under inert atmosphere for another 3 h. CH_2Cl_2 was added (5 mL) to the reaction before being washed with 3N HCl (2 x 25 mL) and brine (1 x 15 mL) before the volatiles were removed *in vacuo*. The reaction yielded starting materials **61** and **38** with no detectable trace of the desired product, **42**.

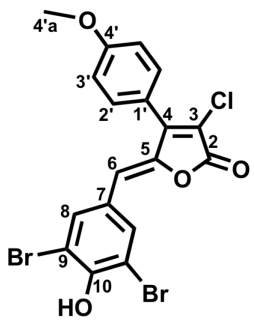
(*Z*)-3-Chloro-5-(3,5-dibromo-4-hydroxybenzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one, **(58)**



To a stirred solution of **41** (12.1 mg, 0.037 mmol) in 1,4-dioxane (0.75 mL) and H_2O (0.15 mL) under argon atmosphere was charged with was added Br_2 (3.9 µL, 0.077 mmol, 2.1 equiv) and KBr (0.5 mg, 0.0004 mmol) in the absence of light at 0 ^{o}C (ice water bath) then

the reaction stirred while warming to 10 ^{o}C. After stirring at room temperature for 1 h, at which time TLC indicated complete consumption of **41** and the resulting mixture was treated with brine (1 x 1 mL), and the organic layer was extracted with EtOAc (2 x 2 mL), washed with $Na_2S_2O_3$ and the excess solvent was dried over $MgSO_4$ evaporated *in vacuo*. The subsequent residue was purified by flash silica chromatography (100:0 → 50:1 → 20:1 *v/v* hexanes/EtOAc) afford the desired product **58** (17.0 mg, 95 % yield) as a light-orange solid:

Chemical Formula: $C_{18}H_{11}Br_2ClO_4$
Molecular Weight: 486.54
m.p.: 228 ^{o}C (decomp.)
R_f = 0.82 (2:1 hexanes/EtOAc), UV
Numeric sequence:



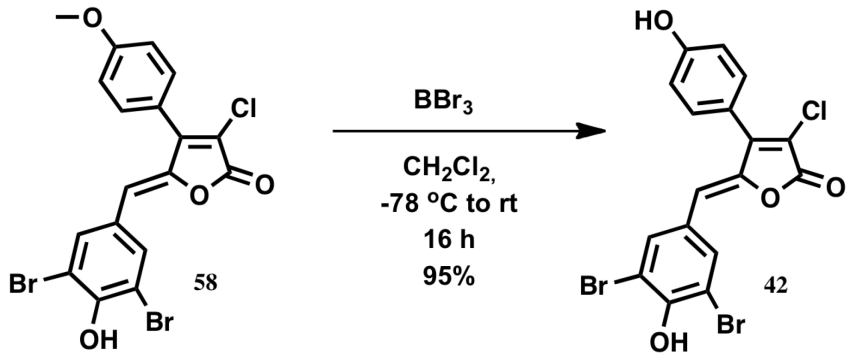
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 2H) 7.48 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.13 (s, 1H), 5.97 (s, 1H), 3.91 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (C_2), 161.7 ($C_{4'}$), 150.4 (C_{10}), 149.6 (C_4), 146.7 (C_5), 134.2 (C_8), 130.9 ($C_{2'}$), 128.0 (C_7), 120.0 ($C_{1'}$), 118.3 (C_3), 114.8 ($C_{3'}$), 111.4 (C_9), 110.6 (C_6), 55.7 ($C_{4'a}$) ppm;

HRMS (ESI) cald for $C_{18}H_{11}Br_2ClO_4$: 483.8713 $(M)^+$, found: 483.8702;

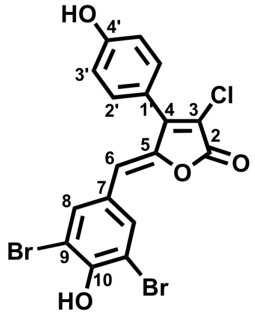
IR (KBr): υ_{max} 3459, 3104, 2971, 2918, 2850, 1775, 1605, 1507, 1479, 1404, 1293, 1259, 1231, 1179, 1144, 1008, 888, 832, 751, 734, 682 cm^{-1}

Rubrolide L, (42)



To a stirred solution of **58** (12.2 mg, 0.025 mmol) in CH_2Cl_2 (4 mL, dry, distilled) a flame-dried, round-bottom flask, was added BBr_3 (1M 75 µL, 0.075 mmol, 3.0 equiv) at -78 ^oC and the reaction was allowed to warm to room temperature overnight, at which time TLC indicated complete consumption of **6**. The resulting mixture was treated with water (2 mL), and the organic layer was extracted with EtOAc (4 x 5 mL), brine (1 x 5 mL) dried over Na_2SO_4 and then concentrated *in vacuo.* The subsequent residue was purified by flash silica chromatography (100:0 → 20:1 → 10:1 *v/v* hexanes/EtOAc) to afford the desired natural product **42** (11.3 mg, 95 % yield) as a reddish-orange solid;

Chemical Formula: $C_{17}H_9Br_2ClO_4$
Molecular Weight: 472.51
R_f = 0.45 (2:1 hexanes/EtOAc), UV
m.p.: 238 ^oC dec; (lit[24]: 238-9 ^oC)
Numeric sequence:



^1H NMR (400 MHz, acetone-d_6) δ 8.05 (s, 2H) 7.52 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 6.28 (s, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (C_2), 159.9 ($C_{4'}$), 151.7 (C_{10}), 150.1 (C_4), 146.7 (C_5), 134.6 (C_8), 131.3 ($C_{2'}$), 128.1 (C_7), 119.0 ($C_{1'}$), 117.1 (C_3), 116.1 ($C_{3'}$), 111.0 (C_9), 110.0 (C_6) ppm;

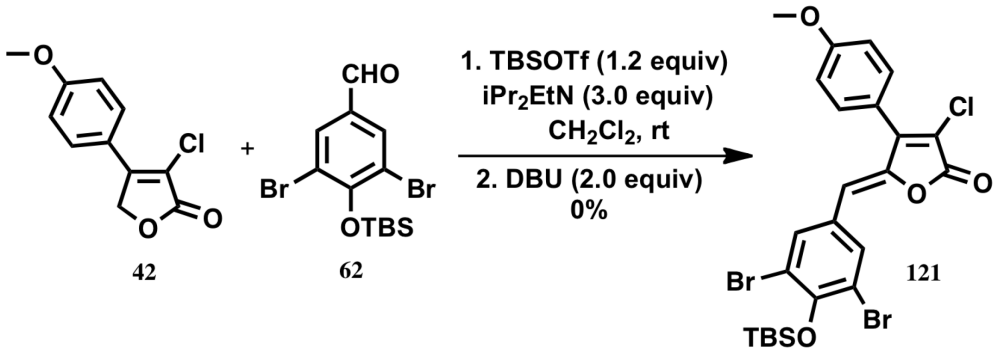
HRMS (ESI) cald for $C_{17}H_9Br_2ClO_4$: 469.8556 $(M)^+$, found: 469.8531;

Elemental Analysis: C, 43.21; H, 1.92; Found C, 43.49; H, 2.30.

IR (KBr): υ_{max} 3479, 3104, 2963, 2924, 2853, 2355, 1751, 1701, 1602, 1508, 1476, 1333, 1281, 1231, 1173, 1080, 1009, 893, 841, 754, 687 cm^{-1};

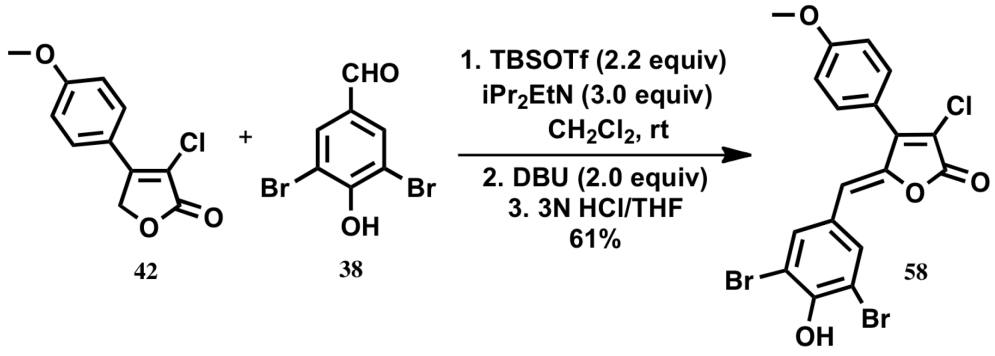
Attempted synthesis of :

(*Z*)-3-Chloro-5-(3,5-dibromo-4-(tert-butyldimethylsilyloxy)benzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one, **(121)**



To a stirred solution of **42** (20.0 mg, 0.09 mmol) in CH_2Cl_2 (anhydrous) was added TBSOTf (25 µL, 0.11 mmol, 1.2 equiv), 3,5-dibromo-4-(tert-butyldimethylsilyloxy)benzaldehyde, **62** (41.9 mg, 0.11 mmol, 1.2 equiv), by N,N-diisopropylethylamine (47 µL, 0.27 mmol, 3.0 equiv) in the absence of light. The starting material was consumed after 1 hour (followed by thin layer chromatography) before adding 1,8-diazabicyclo[5.4.0]undec-7-ene (40 µL, 0.27 mmol, 3.0 equiv). The reaction, which was left stirring under inert atmosphere for 1 h, was added 5 mL of CH_2Cl_2 and then washed with 3N HCl (2 x 25 mL) and brine (1 x 15 mL). The excess solvent was evaporated *in vacuo*. The reaction failed to provide the desired product.

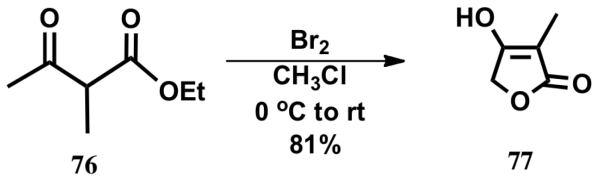
(*Z*)-3-Chloro-5-(4-hydroxybenzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one, **(58)**



To a stirred solution of **42** (23.0 mg, 0.10 mmol) in CH_2Cl_2 (anhydrous) was added

TBSOTf (51 μL, 0.22 mmol, 2.2 equiv), 3,5-dibromo-4-hydroxybenzaldehyde, **38** (33.6 mg, 0.12 mmol, 1.2 equiv), by N,N-diisopropylethylamine (52 μL, 0.30 mmol, 3.0 equiv) in the absence of light. The starting material was consumed after 1 hour (followed by thin layer chromatography) before adding 1,8-diazabicyclo[5.4.0]undec-7-ene (30 μL, 0.20 mmol, 2.0 equiv). The reaction, which was left stirring under inert atmosphere for 1 h, was added 5 mL of CH_2Cl_2 and then washed with 3N HCl (2 x 25 mL) and brine (1 x 15 mL). To the resulting solution were added THF (20 mL) and 3N HCl (4 mL), which was left to stir overnight in the absence of light. The excess solvent was evaporated *in vacuo* before the subsequent residue was purified by flash silica chromatography (20:1 → 10:1 *v/v* hexanes/EtOAc) . All tubes containing the desired product were collected the volatiles were removed *in vacuo* to provide **58**, (30.4 mg, 61 % yield) as a yellow amorphous solid

3-Methyl-4-hydroxy-2(5*H*)furanone, **(77)**



76 77

In a flame dried round bottom flask under inert atmosphere was added dropwise bromine (7.89 mL, 0.15 mmol, 1.1 equiv) to a stirred solution of ethyl α-methylacetoacetate **76** (20.1 g, 0.14 mol, 1.0 equiv) in dry, distilled chloroform (50 ml) at 0 ^{o}C over 20 min. After the addition, the resulting mixture was permitted to stir for 1 h at room temperature. The solvent was then evaporated under reduced pressure to give a dark brown resin which was heated at 130 ^{o}C for 2 h as the mixture darkened significantly in colour. The mixture was let to cool at room temperature before being washed with hexanes. The crude product was slowly recrystallized from hot methanol, filtered and then washed with dichloromethane to give the product, **77** as long white needles (12.9 g, 81% yield).

Chemical Formula: $C_5H_6O_3$
Molecular Weight: 114.10

R_f = 0.23 (EtOAc), CAM+UV

m.p.: 185-6 °C (lit.[9] 189-190 °C)

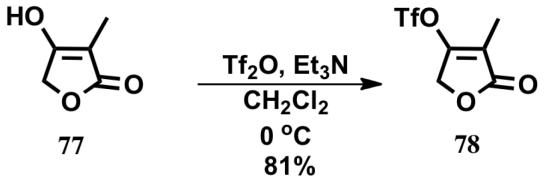
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H, -O*H*), 4.52 (s, 2H, HC_5), 1.52 (s, 3H, HC_6)

^{13}C NMR (100 MHz, DMSO-d_6) δ 175.9 (C_4), 173.6 (C_2), 95.1, (C_3), 67.2 (C_5), 6.7 (C_6);

HRMS (ESI) cald for $C_4H_6O_3$: 102.0317 $(M)^+$, found: 102.0333

IR (KBr): ν_{max} 2939, 2652, 2424, 1683, 1456 cm^{-1};

3-Methyl-4-triflyloxy-2(5*H*)-furanone **(78)**



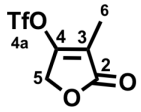
To a stirred solution of 3-methyl-4-hydroxyfuran-2(5H)-one **77** (1.00 g, 8.76 mmol, 1.0 equiv) in dry dichloromethane (10 mL) was added dropwise triethylamine (1.5 mL, 10.5 mmol, 1.2 equiv) at 0 °C. The mixture was left to stir for 10 min under an atmosphere of argon. To the resulting mixture, triflic anhydride (1.78 mL, 10.5 mmol, 1.2 equiv) was added dropwise and the solution was left to warm to room temperature with stirring over 2 h. The organic layer was washed with water, (2 x 25 mL), brine (1 x 25 mL), dried on magnesium sulfate and the excess solvent was evaporated under reduced pressure. The crude resin was purified on silica to afford pure triflate **78** (1.75 g, 81 % yield) as a clear and colourless oil; [72]

Chemical Formula: $C_6H_5F_3O_5S$

Molecular Weight: 246.16

R_f = 0.37 (7:1 hexanes/EtOAc)

Numeric sequence:



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 2H), 1.93 (s, 3H) ppm;

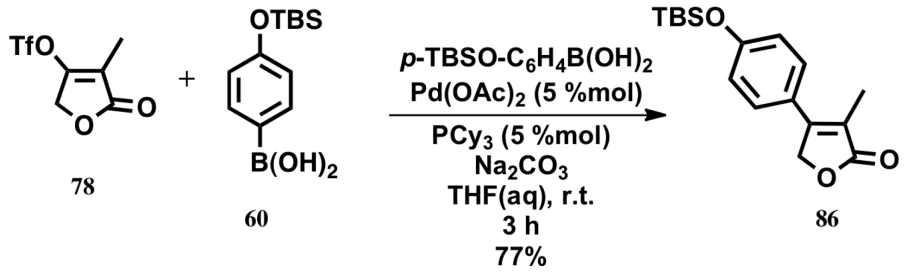
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C_4), 160.5 (C_2), 120.2 (C_3), 117.1 (q, J_{CF} = 321 Hz, C_{4a}), 66.8 (C_5), 7.7 (C_6) ppm;

^{19}F (376 MHz, $CDCl_3$) δ -73.4 ppm;

HRMS (ESI) cald for $C_6H_5O_5F_3S$: 245.9810 $(M)^+$, found: 245.9809;

IR (ATR-ZnSe): ν_{max} 2942, 1783, 1710, 1435 1390, 1308, 1243, 1221, 1099, 917, 814 cm^{-1}

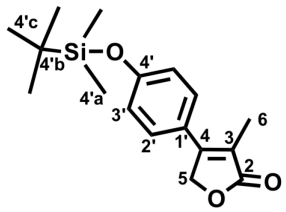
4-(4-(*tert*-Butyldimethylsilyloxy)phenyl)-3-methylfuran-2(5*H*)-one, **(86)**



To a stirred solution of triflate, **78** (500 mg, 2.03 mmol) in deaerated THF (10 mL) was added 4-(tert-butyldimethylsilyloxy)phenylboronic acid **60** (615 mg, 2.44 mmol, 1.2 equiv), $Pd(OAc)_2$ (23 mg, 5% mol), PCy_3 (28 mg, 5 % mol), Na_2CO_3 (645 mg, 3.0 equiv), deaerated nanopure H_2O (0.5 mL) under Ar(g). After stirring at room temperature for 3 h, at which time TLC indicated complete consumption of triflate **10**, the excess solvent was evaporated *in vacuo* and the subsequent residue was purified by flash chromatography (SiO_2 flushed with hexanes/Et_3N before loading product), hexanes, (v/v), 1:1 hexanes/CH_2Cl_2) to afford the desired product **86** (476 mg, 77% yield) as a clear and colourless oil;

Chemical Formula: $C_{17}H_{24}O_3Si$
Molecular Weight: 304.46
R_f = 0.91 (hexanes), CAM or UV
m.p.: 245-6 ^oC (decomp.)

Numeric sequence:



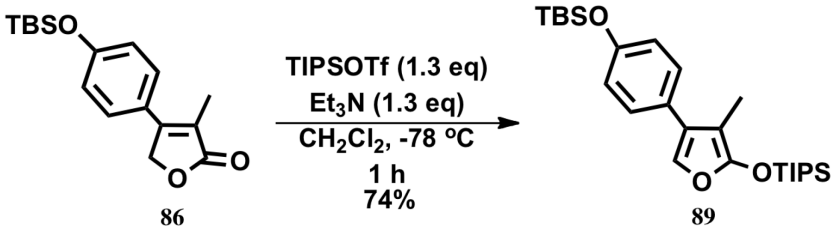
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.03 (dd, *J* = 1.85 Hz, 2H), 2.13 (t, *J* = 1.81 Hz, 3H), 0.99 (s, 9H), 0.24 (s, 6H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1 (C_2), 157.9 ($C_{4'}$), 154.6 (C_4), 129.0 ($C_{2'}$), 124.8 ($C_{1'}$), 121.1 (C_3) 120.9 ($C_{3'}$), 114.8 ($C_{3'}$), 70.6 (C_5), 25.8 ($C_{4'c}$), 18.5 ($C_{4'b}$), 10.7 (C_6), -4.13 ($C_{4'a}$) ppm;

HRMS (ESI) cald for $C_{17}H_{24}O_3Si$: 304.1495, found: 304.1486.

IR (ATR-ZnSe): υ_{max} 3372, 2925, 2854, 2680, 1824, 1723, 1528, 1446, 1341, 1276, 1233, 1126, 1006, 957, 843 cm^{-1};

tert-Butyldimethyl(4-(4-methyl-5-(triisopropylsilyloxy)furan-3-yl)phenoxy)silane, **(89)**



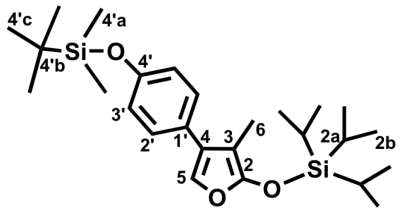
To a stirred solution of **86** (472 mg, 1.55 mmol) at -78 ^oC in dry CH_2Cl_2 (10 mL) was added triethylamine (280 μL, 2.01 mmol, 1.3 equiv), TIPSOTf (540 μL, 2.01 mmol, 1.3 equiv), deaerated nanopure H_2O (0.5 mL) under Ar(g). After stirring for 1 h while warming to room temperature at which time TLC indicated complete consumption of the starting material. The resulting mixture was washed with 10% $NaHCO_3$, dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The subsequent residue was purified by flash silica chromatography (SiO_2 flushed with hexanes/Et_3N, hexanes) using hexanes to elute the desired product **89** (529 mg, 74% yield) as a clear and colourless oil.

Chemical Formula: $C_{26}H_{44}O_3Si_2$

Molecular Weight: 460.80

R*f* = 0.96 (hexanes)

Numeric sequence:



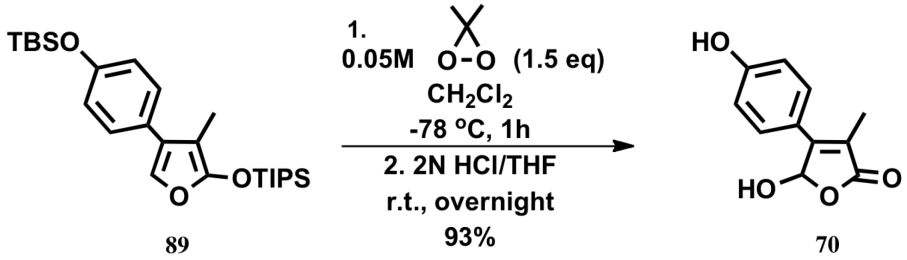
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.8 Hz, 2H), 6.91 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 2.00 (s, 3H), 1.30 (m, 3H), 1.15 (d, 18H), 1.02 (s, 9H), 0.25 (s, 6H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8 ($C_{4'}$), 153.9 (C_5), 128.6 ($C_{2'}$), 128.3 (C_2), 127.3 (C_4), 126.9 ($C_{1'}$), 120.4 ($C_{3'}$), 91.4 (C_3), 26.0 ($C_{4'c}$), 18.5 ($C_{4'b}$), 17.9 (C_{2b}), 12.6 (C_{2a}), 8.44 (C_6), -4.14 ($C_{4'a}$) ppm;

HRMS (ESI) cald for $C_{26}H_{44}O_3\ Si_2$: 460.2829 $(M+H)^+$, found: 460.2837.

IR (KBr): υ_{max} 2946, 2893, 2867, 1649, 1573, 1562, 1503, 1253, 1201, 1102, 994, 882, 812, 780, 673 cm^{-1}

Racemic yangjinhualine A, **(70)**



To a stirred solution of **89** (150 mg, 0.33 mmol) in dry CH_2Cl_2 (10 mL) was added DMDO (10 mL, 0.05 M, 0.50 mmol, 1.5 equiv) at – 78 ^oC under $Ar_{(g)}$. After stirring while warming to room temperature for 1 h, at which time TLC indicated complete consumption of **89**, the excess solvent was evaporated *in vacuo* and to the subsequent residue was added THF (20

mL) and 2N HCl (10 mL) and was left stirring overnight. TLC indicated complete consumption of the starting material and the volatile solvents were again removed *in vacuo* and the aqueous layer was taken up and washed with EtOAc (5 x 15 mL) and brine (1 x 10 mL). The organic layers were collected, dried on Na_2SO_4 and the volatiles were removed in vacuo. The resulting mixture was purified on SiO_2 (CH_2Cl_2/MeOH 100:1 $\rightarrow$ 50:1 $\rightarrow$ 20:1) and then by recrystallization (EtOAc/hexanes) to afford the pure, racemic yangjinhualine A, **70** (62 mg, 93% yield) as a white amorphous solid;

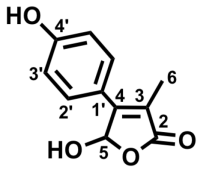
Chemical Formula: $C_{11}H_{10}O_4$

Molecular Weight: 206.19

R*f* = 0.23 (10:1 hexanes/EtOAc) or 0.40 (10:1 CH_2Cl_2/MeOH) $KMnO_4$ or UV

m.p. 210-12 ^oC; (lit.[73] 262-65 ^oC)

Numeric sequence:



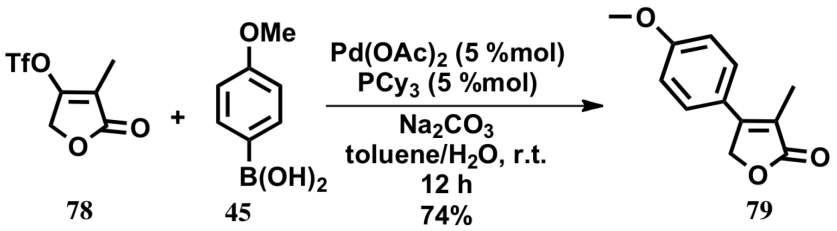
^1H NMR (400 MHz, CD_3OD) δ 7.52 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.38 (d, *J* = 1.04 Hz, 1H), 2.06 (d, *J* = 1.04 Hz 3H) ppm;

^{13}C NMR (100 MHz, CD_3OD) δ 175.5 (C_2), 160.7 ($C_{4'}$), 156.8 (C_4), 131.7 ($C_{2'}$), 123.7 ($C_{1'}$), 122.6 (C_3), 116.7 ($C_{3'}$), 99.1 (C_5), 10.6 (C_6) ppm;

HRMS (ESI) cald for $C_{11}H_{10}O_4$: 206.0579 $(M^*)^+$, found: 206.0579

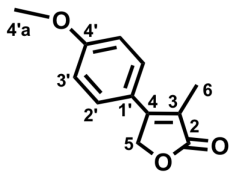
IR (ATR-ZnSe): υ_{max} 3373, 2926, 2855, 2681, 1825, 1723, 1585, 1515, 1447, 1342, 1277, 1234, 1126, 1007, 928, 844, 752 cm^{-1};

4-(4-Methoxyphenyl)-3-methylfuran-2(5*H*)-one, **79**



To a stirred solution of triflate **78** (60 mg, 0.24 mmol) in deaerated toluene (5 mL) was added 4-methoxyphenylboronic acid, **45** (44 mg, 0.29 mmol, 1.2 equiv), $Pd(OAc)_2$ (2.7 mg, 5% mol), PCy_3 (3.4 mg, 5 % mol), Na_2CO_3 (76 mg, 0.72 mmol, 3.0 equiv), deaerated nanopure H_2O (0.5 mL) under $Ar_{(g)}$. After stirring at room temperature for 3 h, at which time TLC indicated complete consumption of starting material, the excess solvent was evaporated *in vacuo* and the subsequent residue was purified by flash silica chromatography (SiO_2 hexanes/CH_2Cl_2 1:1) to afford the desired product **79** (37 mg, 75% yield) as a white crystal;

Chemical Formula: $C_{12}H_{12}O_3$
Molecular Weight: 204.22
R*f* = 0.56 (CH_2Cl_2), UV + CAM
m.p.: 138-139 °C (lit:[22] 140 °C)
Numeric sequence:



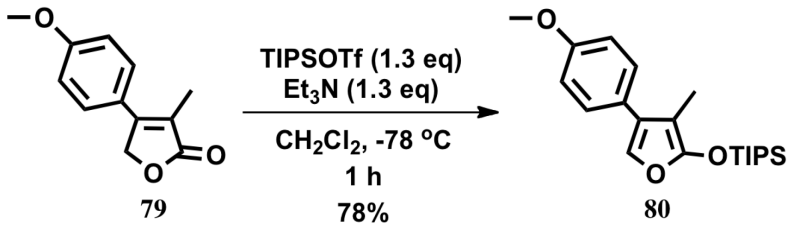
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.02 (s, 2H), 3.85 (s, 3H), 2.11 (s, 3H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1 (C_2), 161.3 ($C_{4'}$), 154.6 (C_4), 129.0 ($C_{2'}$), 124.2 ($C_{1'}$), 120.9 (C_3), 114.8 ($C_{3'}$), 70.6 (C_5), 55.7 ($C_{4'a}$), 10.7 (C_6) ppm;

HRMS (ESI) cald for $C_{12}H_{12}O_3$: 204.0786, found: 204.0797

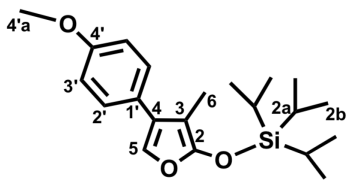
IR (ATR-ZnSe): υ_{max} 3062, 2966, 2835, 1836, 1737, 1650, 1606, 1513, 1442, 1345, 1289, 1257, 1126, 1026, 863, 827, 752, 637 cm^{-1};

(4-(4-Methoxyphenyl-5-(triisopropylsilyloxy)furan-3-yl)phenoxy)silane, **80**



To a stirred solution of **79** (37 mg, 0.18 mmol) at -78 ^{o}C in dry CH_2Cl_2 (10 mL) was added triethylamine (33 μL, 0.23 mmol, 1.3 equiv), TIPSOTf (62 μL, 0.23 mmol, 1.3 equiv), deaerated nanopure H_2O (0.5 mL) under $Ar_{(g)}$. After stirring for 1 h while warming to room temperature at which time TLC indicated complete consumption of the starting material. The resulting mixture was washed with 10% $NaHCO_3$, dried over $MgSO_4$ and the solvent was evaporated *in vacuo.* The subsequent residue was purified by flash silica chromatography (SiO_2 flushed with hexanes/Et_3N, hexanes) using hexanes to afford the desired product **80** (51 mg, 78% yield) as a clear oil.

Chemical Formula: $C_{21}H_{32}O_3Si$
Molecular Weight: 360.56
R*f* = 0.78 (hexanes)
Numeric sequence:



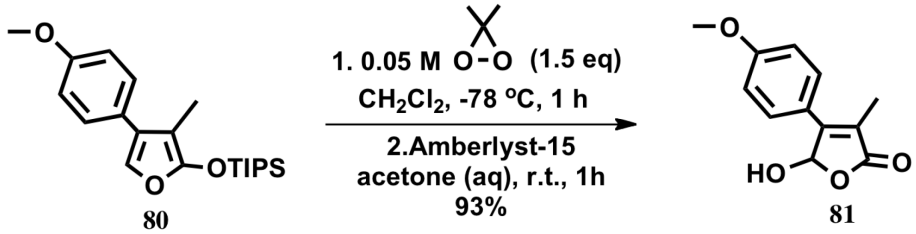
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.89 (s, 1H), 3.83 (s, 3H), 1.96 (s, 3H), 1.27 (m, 3H), 1.07 (d, 18H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 ($C_{4'}$), 153.8 (C_5), 128.7 ($C_{3'}$), 128.2 (C_2), 126.9 ($C_{1'}$), 114.2 ($C_{2'}$), 91.4 (C_3), 55.5 ($C_{4'a}$), 17.9 (C_{2b}), 12.5 (C_{2a}), 8.34 (C_6) ppm;

HRMS (ESI) cald for $C_{21}H_{32}O_3Si$: 360.2121 $(M)^+$, found: 360.XXXX;

IR (ATR-ZnSe): υ_{max} 3472, 2942, 2892, 2866, 2358, 1649, 1649, 1564, 1480, 1248, 882, 831, 801, 659 cm^{-1};

5-Hydroxy-4-(4-methoxyphenyl)-3-methylfuran-2(5*H*)-one, **81**



To a stirred solution of **80** (119 mg, 0.33 mmol) in dry CH_2Cl_2 (10 mL) was added DMDO (10.0 mL, 0.05 M, 0.50 mmol, 1.5 equiv) at – 78 ^oC under $Ar_{(g)}$. After stirring while warming to room temperature for 1 h, at which time TLC indicated complete consumption of **80**, the excess solvent was evaporated *in vacuo* and to the subsequent residue was added Amberlyst-15 (400 mg), acetone (20 mL), nanopure water (1.5 mL) at room temperature under Ar(g). After stirring for 1 h at room temperature, at which time TLC indicated complete consumption of starting material, the residual solvent was filtered through celite, and the volatile solvent was removed *in vacuo*. The resulting mixture was purified by recrystallization to afford **81** (85 mg, 93% yield) as a light-yellow amorphous solid.

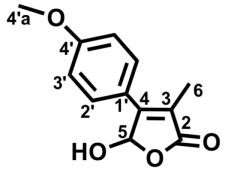
Chemical Formula: $C_{12}H_{12}O_4$

Molecular Weight: 220.22

R*f* = 0.36 (CH_2Cl_2) UV + CAM

m.p.: 155-57 ^oC;

Numeric sequence:



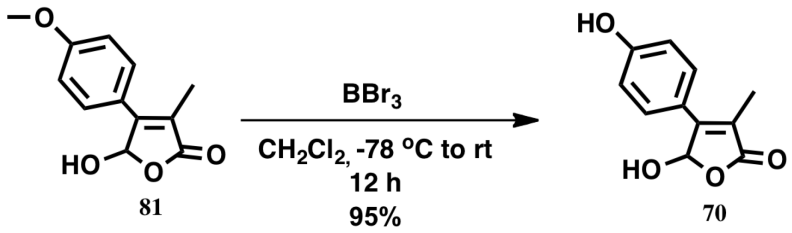
^1H NMR (400 MHz, CD_3OD) δ 7.59 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.40 (s, 1H), 3.87 (s, 3H), 2.13 (s, 3H) ppm;

^{13}C NMR (100 MHz, CD_3OD) 174.0, 161.3, 151.2, 130.3, 124.2, 122.2, 114.0, 97.9, 54.7, 9.2 ppm;

HRMS (ESI) cald for $C_{12}H_{12}O_4$: 205.0886 $(M)^+$, found: 205.0851;

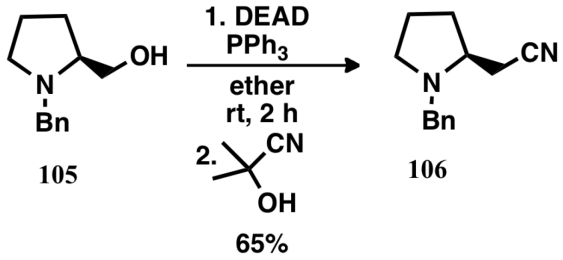
IR (KBr): υ_{max} 3372, 2963, 2948, 2862, 2841, 1759, 1736, 1605, 1515, 1258, 1183, 1032, 956, 837 cm^{-1}.

Yangjinhualine A (racemic), **(70)**



To a stirred solution of **81** (12.2 mg, 0.025 mmol) in CH_2Cl_2 (4 mL, anhydrous) in a sealed, flame-dried flask under $Ar_{(g)}$ was added BBr_3 (1M, 75 μL, 0.075 mmol, 3.0 equiv) at -78 ^oC The reaction was allowed to warm to room temperature overnight, at which time TLC indicated complete consumption of starting material. The resulting mixture was treated with water (2 mL), and the organic layer was extracted with EtOAc (4 x 5 mL), brine (1 x 5 mL) dried over Na_2SO_4 evaporated *in vacuo.* The subsequent residue was purified by flash silica chromatography (100:0 → 20:1 → 10:1 → 1:1 hexanes/EtOAc) afford the desired natural product **70** (10.9 mg, 95 % yield) as a white amorphous solid.

(*S*)-2-(1-Benzylpyrrolidin-2-yl)acetonitrile, **(106)**



To a stirred solution of alcohol, **105** (182 μL, 191 mg, 1.00 mmol) in CH_2Cl_2 (15 mL, anhydrous) in a flame-dried flask under $Ar_{(g)}$ was added PPh_3 (524 mg, 2.00 mmol, 2.0 equiv) at 0 ^oC for 5 minutes at which time DEAD (312 μL, 345 mg, 2.00 mmol, 2.0 equiv) was added to the reaction and was allowed to warm to room temperature over 20 minutes. To the resulting mixture was added cyanohydrin (183 μL, 2.00 mmol, 2.0 equiv) in 1 mL of Et_2O and the reaction was left stirring over night under inert atmosphere, at which time TLC indicated complete consumption of **105**. The resulting mixture was evaporated, diluted with hexanes and cooled to –20 ^oC over 30 minutes, at which time the solution was filtered through sintered glass. The resulting mixture was evaporated under reduced pressure to remove the volatiles and distilled (56 ^oC, 1 mm Hg) to provide the product, **106** as a clear, yellow oil (130 mg, 65 % yield).

Chemical Formula: $C_{13}H_{16}N_2$

Molecular Weight: 200.2795

R*f* =0.55 (1:1 hexanes/EtOAc)

$[\alpha]_D^{25}$= -54.5^o (*c* 1.33, $CHCl_3$)

Numeric Sequence:

^1H NMR (400 MHz, CD_3Cl_3) δ 7.31-7.34 (m, 5H, *H*$C_{2'}$-*H*$C_{5'}$), 3.90 (d, *J*=13.1 Hz, 1H, *H*$C_{1'}$), 3.47 (d, *J*=13.1 Hz, 1H, *H*C_6), 3.00 (m, 1H, *H*C_5), 2.29-2.43 (m, 2H, *H*C_2), 2.16-1.73 (m, 4H, *H*C3-*H*C4) ppm;

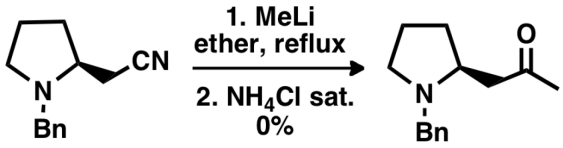
^{13}C NMR (100 MHz, CD_3Cl_3) δ 139.2 ($C_{2'}$), 128.9 ($C_{3'}$), 128.6 ($C_{2'}$), 127.4 ($C_{4'}$), 118.7 (C_7), 60.0 (C_5), 58.9 ($C_{1'}$), 54.7 (C_2), 31.1 (C_4), 23.6 (C_6), 22.8 (C_3), 22.4 (C4) ppm;

HRMS (ESI) cald for $C_{13}H_{16}N_2$: 200.1313 $(M)^+$, found: 200.1320;

IR (ATR): υ_{max} 3028, 2935, 2872, 2802, 1635, 1454, 1253, 1145, 910, 710 cm^{-1}.

Attempted Synthesis of :

(*S*)-1-(1-Benzylpyrrolidin-2-yl)propan-2-one, (**107**)

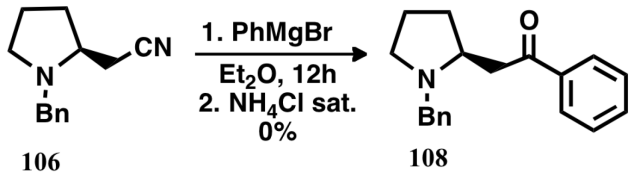


106 **107**

To a stirred solution of nitrile, **106** (182 μL, 191 mg, 1.00 mmol) in a flame-dried flask fitted with a cold-water condenser in dry Et_2O (15 mL) was added MeLi (524 mg, 2.00 mmol, 2.0 equiv) under $Ar_{(g)}$ at -78 ^oC over 5 minutes at which time the reaction was allowed to warm to room temperature over 20 minutes. The reaction was then heated gently to gentle reflux overnight. To the resulting solution was added NH_4Cl $_{(sat.)}$ and the reaction stirred for 15 minutes before the organic layer was partitioned, washed with water (1 x 10 mL), brine, (1 x 10 mL), dried on Na_2SO_4 and the volatiles were removed *in vacuo*. The reaction failed to provide **107** in any detectable quantity and the starting material was consumed as observed through TLC and NMR.

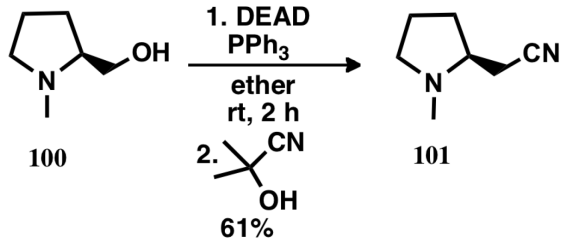
Attempted Synthesis of :

(*S*)-2-(1-Benzylpyrrolidin-2-yl)-1-phenylethanone, (**108**)



To a stirred solution of nitrile, **36** (182 μL, 191 mg, 1.00 mmol) in a flame-dried flask fitted with a cold-water condenser in dry Et_2O (15 mL) was added MeLi (524 mg, 2.00 mmol, 2.0 equiv) under $Ar_{(g)}$ at -78 ^oC over 5 minutes at which time the reaction was allowed to warm to room temperature over 20 minutes. The reaction was then heated gently to gentle reflux overnight. To the resulting solution was added NH_4Cl $_{(sat.)}$ and the reaction stirred for 15 minutes before the organic layer was partitioned, washed with water (1 x 10 mL), brine, (1 x 10 mL), dried on Na_2SO_4 and the volatiles were removed *in vacuo*. The reaction failed to provide **37** in any detectable quantity and the starting material was consumed as observed through TLC and NMR.

(S)-2-(1-Methylpyrrolidin-2-yl)acetonitrile, **(101)**



To a stirred solution of alcohol, **100** (125 μL, 120 mg, 1.0 mmol) in a flame-dried flask stirring in CH_2Cl_2 (4 mL, anhydrous) was added PPh_3 (525 mg, 2.0 mmol, 2.0 equiv) at 0^oC for 5 minutes at which time DEAD (312 μL, 345 mg, 2.0 mmol, 2.0 equiv) reaction was allowed to warm to room temperature over 20 minutes. To the resulting mixture was added cyanohydrin (183 μL, 2.0 mmol) and the reaction was left stirring over night under

inert atmosphere, at which time TLC indicated complete consumption of **100**. The resulting mixture was evaporated, diluted with hexanes and cooled to –20 ^{o}C over 30 minutes, at which time the solution was filtered through sintered glass. The resulting mixture was evaporated under reduced pressure to remove the volatiles and distilled (45 ^{o}C, 1 mm Hg) to provide the product, **101** as a clear, light-yellow oil (75.8 mg, 61% yield)

Chemical Formula: $C_7H_{12}N_2$

Molecular Weight: 124.18

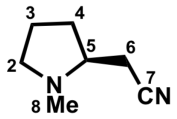
R*f* = 0.58 (100:10:1; CH_2Cl_2, MeOH, Et_3N), $KMnO_4$

b.p. (oil) = 45 ^{o}C, 1 mm Hg

$[\alpha]_D^{25}$= - 35.9 ^{o} (*c* 3.1, $CHCl_3$), -43.0^{o} (c 1.0, MeOH),

Lit:[lxxiii] = $[\alpha]_D^{25}$= - 36.6 ^{o} (*c* 3.0, $CHCl_3$),

Numeric sequence:



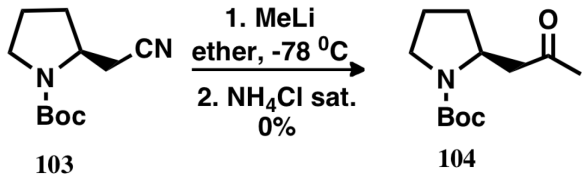
^{1}H NMR (400 MHz, CD_3Cl_3) δ 3.05 (t, 1H, *H*C5), 2.36 (m, 2H, *H*C6), 2.36 (s, 3H, *H*C8), 2.22 (m, 1H, *H*C3), 2.04 (m, 1H, *H*C3), 1.61-1.77 (bm, 4H, *H*C4 and *H*C5) ppm;

^{13}C NMR (100 MHz, CD_3Cl_3) 118.5 δ (C_7), 61.8 (C_2), 57.3 (C_5), 40.6 (C_8), 31.1 (C_6), 22.7 (C_2), 22.4 (C_4) ppm;

HRMS (ESI) cald for $C_7H_{12}N_2$: 124.0997 $(M)^+$, found: 124.1000;

IR (KBr): υ_{max} 3441, 2992, 2941, 2879, 2802, 2241, 2087, 1705, 1369, 1191, 976, 876 cm^{-1}.

<u>Attempted Synthesis of</u> : hygrine, **(104)**



To a stirred solution of nitrile, **103** (100 mg, 0.81 mmol) in a flame-dried flask fitted with a cold-water condenser in dry Et_2O (15 mL) was added MeLi (1M, 161 μL, 161 mmol, 2.0 equiv) under $Ar_{(g)}$ at -78 ^oC over 5 minutes at which time the reaction was allowed to warm to room temperature over 20 minutes. The reaction was then heated gently to gentle reflux overnight. To the resulting solution was added $NH_4Cl_{(sat.)}$ and the reaction stirred for 15 minutes before the organic layer was partitioned, washed with water (1 x 10 mL), brine, (1 x 10 mL), dried on Na_2SO_4 and the volatiles were removed *in vacuo.* The reaction provided starting material with no traces of **104** as determined by NMR analysis.

Chemical Formula: $C_7H_{12}N_2$
Molecular Weight: 124.18

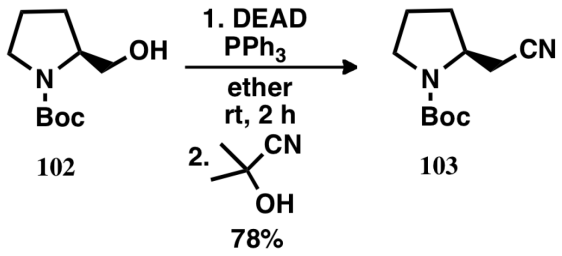
<u>Attempted Synthesis of</u> :
(*S*)-1-(1-Methylpyrrolidin-2-yl)propan-2-one, **(122)**

To a stirred solution of nitrile, **101** (200 mg, 1.62 mmol) in a flame-dried flask fitted with a cold-water condenser in dry Et_2O (10 mL) was added MeLi (1M, 322 μL, 3.22 mmol, 2.0 equiv) under $Ar_{(g)}$ at -78 ^oC over 5 minutes at which time the reaction was allowed to warm to room temperature over 20 minutes. The reaction was then heated gently to gentle reflux overnight. To the resulting solution was added $NH_4Cl_{(sat.)}$ and the reaction stirred for 15 minutes before the organic layer was partitioned, washed with water (1 x 10 mL), brine, (1 x 10 mL), dried on Na_2SO_4 and the volatiles were removed *in vacuo.* The reaction failed to provide **122** in any detectable quantity via NMR and yielded starting material.

Chemical Formula: $C_{13}H_{17}NO$

Molecular Weight: 203.28

(*S*)-tert-Butyl 2-(cyanomethyl)pyrrolidine-1-carboxylate, **(103)**



To a stirred solution of alcohol **102** (500 mg, 2.48 mmol) in a flame-dried flask stirring in CH_2Cl_2 (45 mL, anhydrous) was added PPh_3 (1.30 g, 5.00 mmol, 2.0 equiv) at 0 ^oC for 5 minutes at which time DEAD (100 μL, 5.00 mmol, 2.0 equiv) reaction was allowed to warm to room temperature over 20 minuts. To the resulting mixture was added cyanohydrin (750 μL, 2.00 mmol) in 1 mL of Et_2O and the reaction was left stirring over night under inert atmosphere, at which time TLC indicated complete consumption of **102**. The resulting mixture was evaporated, diluted with hexanes and cooled to –20 ^oC over 30 minutes, at which time the solution was filtered through sintered glass. The resulting mixture was evaporated under reduced pressure to remove the volatiles and distilled (45 ^oC, 1 mm Hg) to provide the product **103** as a clear, light-yellow oil (407 mg, 78% yield)

Chemical Formula: $C_{11}H_{18}N_2O_2$

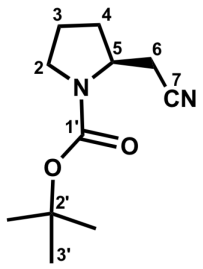
Molecular Weight: 210.27

R*f* = 0.44 (1:1hexanes /EtOAc)

b.p. = 45 ^oC oil

$[\alpha]_D^{25}$= -51.5^o (*c* 1.4, $CHCl_3$)

Numeric Sequence:



^{1}H NMR (400 MHz, CD_3Cl_3) δ 4.18 (m, 1H, *H*C_5), 3.42 (m, 2H, *H*C_6), 2.73-2.69 (m, 3H, *H*C_2), 2.16-1.73 (m, 4H, $HC_{3\text{-}4}$), 1.47 (s, 9H, *H*$C_{3'}$) ppm;

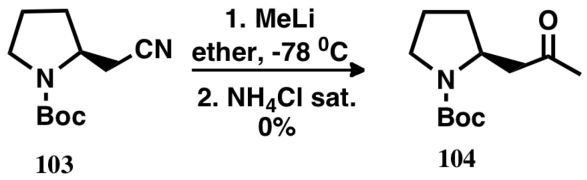
^{13}C NMR (100 MHz, CD_3Cl_3) 157.0 ($C_{1'}$), 123.2 (C_7), 80.5 ($C_{2'}$), 60.1 (C_5), 47.6 (C_2), 30.6 (C_4), 29.5 (C_3), 28.5 ($C_{3'}$), 22.5 (C_6) ppm;

HRMS (ESI) cald for $C_{11}H_{18}N_2O_2$: 210.1368 $(M)^+$, found: 210.1372;

IR (KBr): υ_{max} 3433, 2972, 2930, 2876, 1662, 1410, 1367, 1223, 1128, 935, 786 cm^{-1}.

Attempted Synthesis of :

(*S*)-*tert*-Butyl-2-(2-oxypropyl)pyrrolidine-1-carboxylate, **(104)**

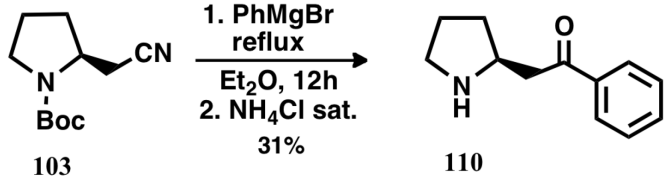


103 **104**

To a stirred solution of nitrile, **103** (200 mg, 0.95 mmol) in a flame-dried flask fitted with a cold-water condenser in dry Et_2O (15 mL) was added MeLi (1M, 190 μL, 1.90 mmol, 2.0 equiv) under $Ar_{(g)}$ at -78 ^oC over 5 minutes at which time the reaction was allowed to warm to room temperature over 20 minutes. The reaction was then heated gently to gentle reflux overnight. To the resulting solution was added NH_4Cl $_{(sat.)}$ and the reaction stirred for 15 minutes before the organic layer was partitioned, washed with water (1 x 10 mL), brine, (1 x 10 mL), dried on Na_2SO_4 and the volatiles were removed *in vacuo*. The reaction failed to provide **104** in any detactable quantity by NMR and yielded starting material.

Chemical Formula: $C_{12}H_{21}NO_3$
Molecular Weight: 227.30

(*S*)-1-(1-Benzylpyrrolidin-2-yl)propan-2-one. **(110)**



103 **110**

To a stirred solution of nitrile, **103** (200 mg, 0.95 mmol) in a flame-dried flask fitted with a cold-water condenser in dry Et_2O (15 mL) was added PhMgBr (1M, 190 μL, 1.90 mmol,

2.0 equiv) under $Ar_{(g)}$ at -78 ^{o}C over 5 minutes at which time the reaction was allowed to warm to room temperature over 20 minutes. The reaction was then heated gently to gentle reflux overnight until complete consumption of the starting material (as indicated by TLC). To the resulting solution was added NH_4Cl $_{(sat.)}$ and the reaction stirred for 15 minutes before the organic layer was partitioned, washed with water (1 x 10 mL), brine, (1 x 10 mL), dried on Na_2SO_4 and the volatiles were removed *in vacuo.* The product was separated by an extractive acid/base workup to provide clear, light yellow oil **110** (56 mg, 31%) .

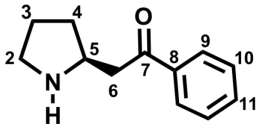
Chemical Formula: $C_{12}H_{15}NO$

Molecular Weight: 189.25

$[\alpha]_D^{25}$= -98.8 (*c* 1.8, $CHCl_3$)

R*f* = 0.33 (100:10:1 CH_2Cl_2/MeOH/Et_3N)

Numeric sequence:



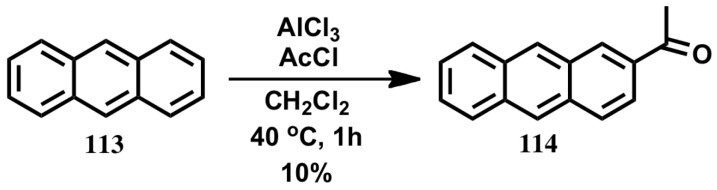
^{1}H NMR (400 MHz, CD_3Cl_3) δ 7.37-7.52 (5H, m), 5.0 (bs, 1H, N-*H*) 4.38 (1H, m), 3.74 (2H, m), 3.49 (m, 2H), 1.61-1.87 (m, 3H), 1.43 (m, 1H) ppm;

^{13}C NMR (100 MHz, CD_3Cl_3) δ 172.5 (C_7), 136.8 (C_8), 128.6 (C_{10}), 127.2 (C_9), 119.8 (C_{11}), 67.5 (C_5), 61.8 (C_2), 51.4 (C_6), 28.8 (C_4), 25.2 (C_3) ppm;

HRMS (ESI) cald for $C_{12}H_{15}NO$ 189.1154 $(M)^+$, found: 189.1172

IR (KBr): υ_{max} 2974, 2877, 2800, 2247, 1731, 1454, 1226, 1110, 740, 700 cm^{-1}.

1-(Anthracen-1-yl)ethanone, **(114)**

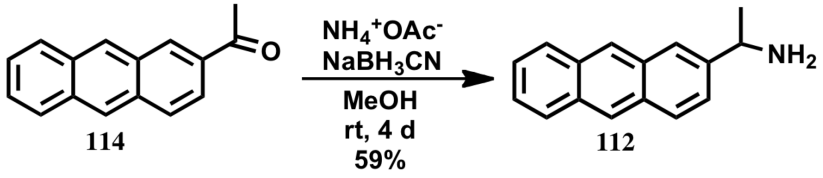


To a solution of anthracene, **113** (500 mg, 2.80 mmol) in dry CH_2Cl_2 (10 mL) was added $AlCl_3$ (374 mg, 2.80 mmol, 1.0 equiv) and acetyl chloride (258 μL, 3.64 mmol, 1.3 equiv). The reaction was permitted to stir at 40 ^oC for 1 h at which time the solution was cooled with an ice bath and water was added slowly to the reaction mixture which was then extracted with CH_2Cl_2 (3 × 15 mL) followed by drying over Na_2SO_4. The resulting mixture was purified on SiO_2 (100:1 to 10:1 Hexanes/EtOAc) to provide **114** as a pure yellow oil (62 mg 10 % yield).

Chemical Formula: $C_{16}H_{12}O$
Molecular Weight: 220.2659
R*f* = 0.89 (10:1 hexanes/EtOAc)

^1H NMR (400 MHz, CD_3Cl_3) δ 8.63 (s, 1H), 8.55 (s, 1H), 8.42 (s, 1H), 7.98-8.05 (m, 3H), 7.52-7.56 (m, 3H), 2.76 (s, 3H) ppm;
^{13}C NMR (100 MHz, CD_3Cl_3) 198.3, 134.2, 133.5, 132.9, 132.3, 131.9, 130.6, 129.2, 129.0, 128.7, 128.5, 126.5, 126.2, 123.0, 122.9 ppm;
HRMS (ESI) cald for 220.0888 $(M)^+$, found: 220.0890
IR (KBr): υ_{max} 3132, 3033, 2921, 1675, 840 cm^{-1}.

1-(Anthracen-2-yl)ethanamine, **(112)**

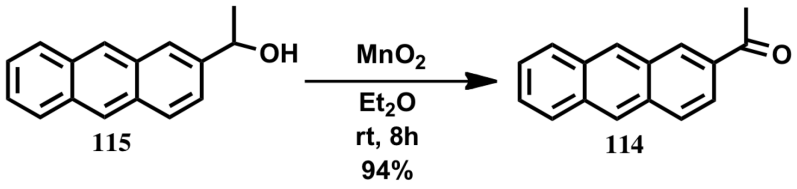


To a solution of 2-(anthracen-1-yl)ethanone **114** (50 mg, 0.23 mmol) in methanol (3 mL) was added NH_4OAc (383 mg). After most of the salt has been dissolved, $NaBH_3CN$ (25 mg) was added and the solution was left to stir at rt for 4 days. The reaction mixture was acidified with 2N HCl (3 mL) and rinsed with Et_2O (2 × 5 mL), the ether was evaporated *in vacuo* to provide crude **112**. To the aqueous solution, 35% aq KOH was added to the clear aqueous phase until the appearance of persistent turbidity and the mixture was then extracted with CH_2Cl_2 (3 × 5 mL) followed by drying of the extract over Na_2SO_4 removal of the volatiles in vacuo afforded pure product, **112** (30 mg, 59% yield)

Chemical Formula: $C_{16}H_{15}N$
Molecular Weight: 221.30
R*f* = 0.19 (10:1 hexanes/EtOAc)
m.p.: 190-3 ^{o}C (decomp.)

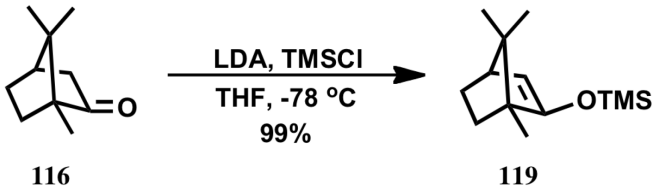
^{1}H NMR (400 MHz, acetone-d_6) δ 8.34 (d, *J*= 7.5 Hz, 2H), 8.02 (m, 4H), 7.50 (dd, J_1= 7.5 Hz, J_2= 15 Hz, 3H), 2.01 (m, 1H), 1.36 (d, *J* = 6.7 Hz, 3H) ppm;
^{13}C NMR (100 MHz, acetone-d_6) δ 132.1, 131.3, 128.3, 128.2, 126.0, 125.5, 125.3, 129.4, 59.3 (*C*NH_2), 24.1 (CH_3-*C*HNH_2), 20.8 (CH-*C*H_3) ppm;
HRMS (ESI) cald for $C_{16}H_{15}N$: 221.1204 $(M)^+$, found: 221.1203
IR (KBr): υ_{max} 3206, 2983, 1675, 1592, 1434, 751 cm^{-1}.

1-(Anthracen-1-yl)ethanone, **(114)**



To a crude solution of 1-(anthracen-1-yl)ethanol **115** (182 mg, 0.82 mmol) in dry Et_2O (10 mL) was added MnO_2 (355 mg, 4.10 mmol, 5.0 equiv) The reaction was permitted to stir at room temperature overnight at which time the solution TLC indicated complete consumption of the starting material and the reaction was filtered with a fritted filter funnel and the volatiles were evaporated *in vacuo* to afford pure product, **114** without purification (170 mg, 94% yield).

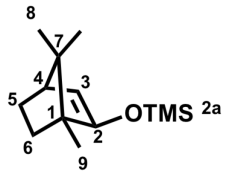
Trimethyl(1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2yloxy)silane, (**47**)



To a stirred solution of diisopropylamine (138 μL, 0.99 mmol, 1.5 equiv) in a flame-dried flask in THF (15 mL, anhydrous) was added slowly n-BuLi (390 μL, 0.98 mmol, 1.5 equiv) at -78 ^oC over 15 minutes. After stirring at the same temperature for an additional 15 minutes, a solution of (1*R*)-(+)-camphor **116** (100 mg, 0.66 mmol, 1.0 equiv) in THF (5 mL, dried and distilled) was added and the resulting solution was permitted to stir for an additional 90 minutes at the same temperature. At which time TMSCl (124 μL, 0.98mmol, 1.5 equiv) was added and the solution was stirred for 90 minutes at -78 ^oC before the solution was permitted to slowly warm to room temperature overnight (at which time TLC indicated complete consumption of the starting material). The solution was poured slowly on $NH_4^+Cl^-$ (sat) and stirred for 15 minutes. The organic layer was washed with water (1 x 10 mL), brine (1 x 10 mL), dried on Na_2SO_4 and the volatiles were removed in vacuo to

provide **119** as a clear, yellow oil (220 mg, 99% yield) which was carried over to the next step without further purification.

Chemical Formula: $C_{13}H_{24}OSi$
Molecular Weight: 224.41
R*f* = 0.95 (10:1hexanes /EtOAc)
b.p. (oil) = 65 ^{o}C (2 mmHg)
$[\alpha]_D^{25}$= 9.2^{o} (*c* 1.8, $CHCl_3$)
Numbering sequence:



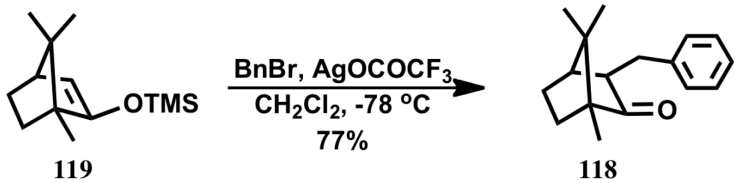
^{1}H NMR (400 MHz, CD_3Cl_3) δ 4.64 (1H, s, HC_3), 2.19 (1H, m, HC_4), 1.84 (m, 2H, HC_5-HC_6), 1.49 (m, 2H, HC_5-HC_6), 0.89 (s, 6H, HC_8), 0.72 (s, 3H, HC_9), 0.19 (s, 9H, HC_{2a}) ppm;

^{13}C NMR (100 MHz, CD_3Cl_3) δ 160.6 (C_2), 103.8 (C_3), 54.9 (C_7), 49.6 (C_4), 31.4 (C_6), 27.5 (C_5), 20.3 (C_8), 20.0 (C_8), 10.2 (C_9), 0.3 (C_{2a}) ppm;

HRMS (ESI) cald for $C_{13}H_{24}OSi$: 224.1596 found: 224.1602;

IR (KBr): υ_{max} 2952, 2871, 1615, 1330, 1251, 1139, 894, 845, 751 cm^{-1}.

3-Benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, **(118)**



119 **118**

Silane **119** (100 mg, 0.45 mmol) was added to a flame-dried flask containing $AgCOOCF_3$ (120 mg, 0.53 mmol, 1.1 equiv) dissolved in CH_2Cl_2 (15 mL, anhydrous) at -78 ^{o}C under an atmosphere of $Ar_{(g)}$. After 10 minutes with stirring, benzyl bromide (65μL, 0.53 mmol, 1.2

equiv) was added to the resulting mixture and the reaction was allowed to warm to room temperature over 1 h. The resulting mixture was filtered through celite and the volatiles were evaporated *in vacuo* to yield **118** as a light yellow oil (84 mg, 77% yield after distillation) which was used in the subsequent reaction without further purification.

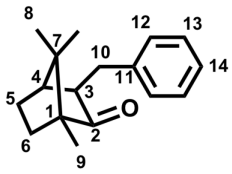
Chemical Formula: $C_{17}H_{22}O$

Molecular Weight: 242.35

Rf = 0.56 (100:1 hexanes /EtOAc)

$[\alpha]_D^{25}$= +201.5 ^{o} (*c* 1.26, $CHCl_3$)

Numeric sequence:



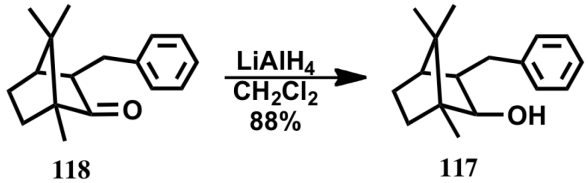
^{1}H NMR (400 MHz, CD_3Cl_3) δ 7.35-7.40 (5H, s, Ar-*H*), 5.35 (2H, m, H_4), 2.36 (dt, J_1= 18.4 Hz, J_2= 4.0 Hz, 1H), 2.08-2.18 (m, 1H) 1.99 (m, 1H), 1.85 (d, *J* =18 Hz, 1H), 1.69 (td, J_1=12.0 Hz, J_2= 3.6 Hz), 1.31-1.44 (m, 3H), 0.96 (s, 3H), 0.92 (s, 3H), 0.84 (s, 3H) ppm;

^{13}C NMR (100 MHz, CD_3Cl_3) δ 220.8 (C_2), 133.4 (C_{11}), 129.1 (C_{13}), 128.7 (C_{12}), 127.3 (C_{14}), 58.1 (C_1), 48.0 (C_7), 47.1 (C_4) 30.2 (C_6) 27.2 (C_5), 20.0 (C_8), 19.4 (C_8), 9.5 (C_9) ppm;

HRMS (ESI) cald for $C_{17}H_{22}O$: 242.1671$(M)^+$, found: 242.1681;

IR (KBr): υ_{max} 3362, 3025, 2952, 2925, 2872, 2853, 1728, 1605, 1582, 1513, 1277, 1066, 836 cm^{-1}.

3-Benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol, (**117**)



118 **117**

To a solution of **118** (100 mg, 0.41 mmol) in dry THF (5 mL) was added LAH (47 mg, 1.23 mmol, 3.0 equiv) at 0 °C. After being stirred for 12 h at room temperature, the mixture was quenched with water (5 mL) and 3N NaOH (5 mL), and extracted with CH_2Cl_2. The product **117** (88 mg, 88%) isolated by column chromatography on silica gel (1:0 → 100:1 → 75:1 → 50:1 *v/v* hexanes/EtOAc).

Chemical Formula: $C_{17}H_{24}O$

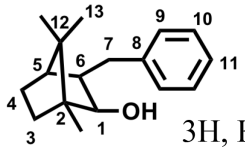
Molecular Weight: 244.37

R*f* = 0.18 (10:1hexanes /EtOAc)

m.p.: 96-97 °C

$[\alpha]_D^{25}$= +261.9^o (*c* 0.99, $CHCl_3$)

Numeric sequence:



^{1}H NMR (400 MHz, CD_3Cl_3) δ 4.64 (1H, s, H_3), 2.19 (1H, m, H_4), 1.84 (m, 2H, H_5-H_6), 1.49 (m, 2H, H_5-H_6), 0.89 (s, 6H, H_8), 0.72 (s, 3H, H_9), 0.19 (s, 9H, H_{2a}) ppm;

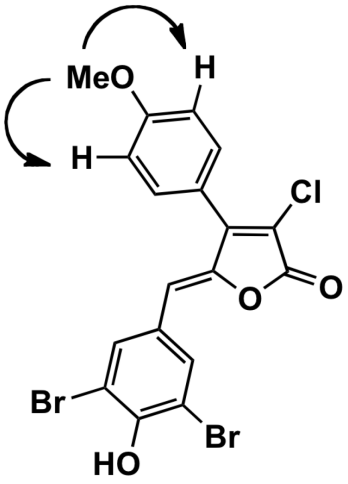
^{13}C NMR (100 MHz, CD_3Cl_3) δ 138.2 (C_8), 128.6 (C_{10}), 128.4 (C_9), 126.6 (C_{11}), 82.1 (C_1), 50.7 (C_5), 49.4 (C_2), 47.6 (C_{12}), 34.1 (C_7), 28.2 (C_3), 25.7 (C_4), 21.4 (C_{13}), 20.0 (C_{13}), 11.3 (C_{14}) ppm;

HRMS (ESI) cald for $C_{17}H_{24}O$: 244.1827 found: 224.1837

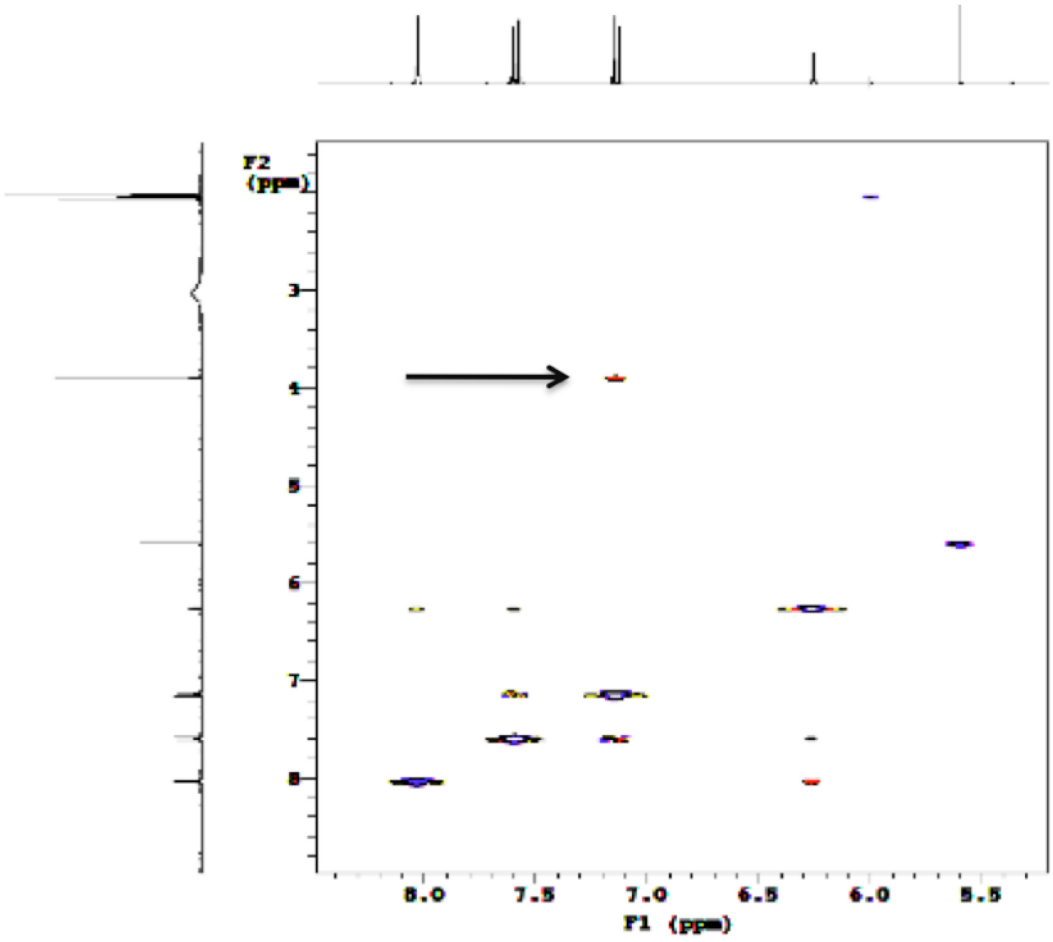
IR (KBr): υ_{max} 3450, 3056, 3024, 2952, 2928, 2873, 2095, 1727, 1604, 1582, 1276, 1066, 695 cm^{-1}.

Annexe

NOESY Spectroscopy - indicated area shows NOE effect between neighbouring protons

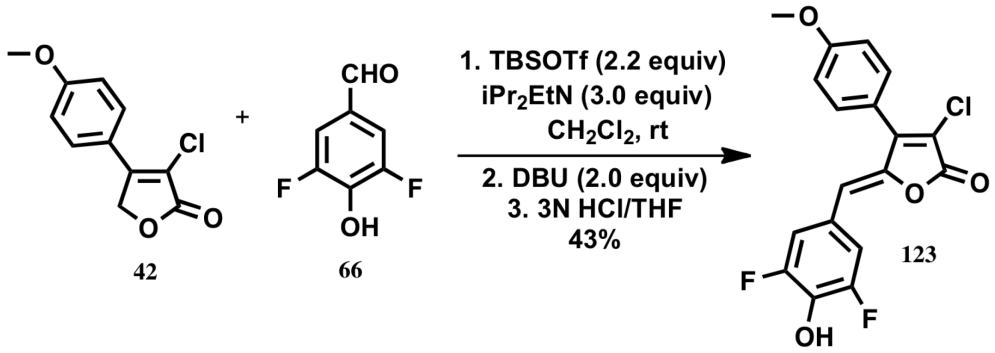


58



Rubrolide L analogs

(*Z*)-3-Chloro-5-(3,5-difluoro-4-hydroxybenzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one, **(123)**



To a stirred solution of **42** (20.0 mg, 0.09 mmol) in CH_2Cl_2 (anhydrous) was added TBSOTf (44 μL, 0.19 mmol, 2.2 equiv), 3,5-fluoro-4-hydroxybenzaldehyde, **66** (20.6 mg, 0.12 mmol, 1.2 equiv), N,N-diisopropylethylamine (48 μL, 0.30 mmol, 3.0 equiv) in the absence of light. The starting material was consumed after 1 hour (followed by thin layer chromatography) before adding 1,8-diazabicyclo[5.4.0]undec-7-ene (30 μL, 0.20 mmol, 2.0 equiv). To the reaction, which was left stirring under inert atmosphere for 1 h, was added 5 mL of CH_2Cl_2 and then washed with 3N HCl (2 x 25 mL) and brine (1 x 15 mL). To the resulting solution were added THF (20 mL) and 3N HCl (4 mL) and was left to stir overnight in the absence of light. The excess solvent was evaporated *in vacuo* before the subsequent residue was purified by flash silica chromatography (20:1 → 10:1 *v/v* hexanes/EtOAc). All tubes containing the desired product were collected and the volatiles were removed *in vacuo* to provide **123** as a light yellow amorphous solid, 14.1 mg 43 % yield

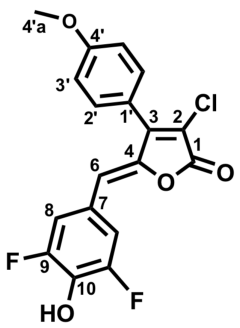
Chemical Formula: $C_{18}H_{11}ClF_2O_4$

Molecular Weight: 364.73

m.p.: 234-35 ^{o}C

R*f*= 0.30 (5:1 hexanes/EtOAc)

Numeric sequence:



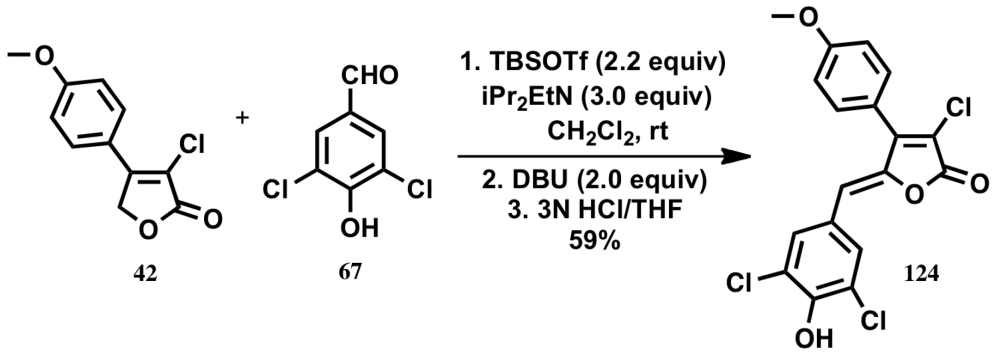
^{1}H NMR (400 MHz, acetone-d_6) δ 8.89 (bs, 1H) 7.70 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 3.89 (s, 3H);

^{13}C NMR (100 MHz, Acetone-d_6) δ 164.9, 162.3, 159.8, 150.9, 145.5, 133.7 (2C), 131.8 (2C), 125.7, 121.2, 116.8 (2C), 115.3 (3C), 55.9;

HRMS (ESI) cald for $C_{19}H_{11}ClF_2O_4$: 328.0507 $(M)^+$, found: 328.0502.

IR (KBr): υ_{max} 3338, 2929, 2933, 2836, 1744, 1603, 1505, 1442, 1346, 1258, 1170, 1025, 832 cm^{-1};

(*Z***)-3-Chloro-5-(3,5-dichloro-4-hydroxybenzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one, (124)**



To a stirred solution of **42** (20.0 mg, 0.09 mmol) in CH_2Cl_2 (anhydrous) was added TBSOTf (51 μL, 0.20 mmol, 2.2 equiv), 3,5-chloro-4-hydroxybenzaldehyde, **67** (20.6 mg, 0.11 mmol, 1.2 equiv), N,N-diisopropylethylamine (47 μL, 0.27 mmol, 3.0 equiv) in the absence of light. The starting material was consumed after 1 hour (followed by thin layer chromatography) before adding 1,8-diazabicyclo[5.4.0]undec-7-ene (27 μL, 0.18 mmol, 2.0 equiv). The reaction, which was left stirring under inert atmosphere for 1 h, was added 5

mL of CH_2Cl_2 and then washed with 3N HCl (2 x 25 mL) and brine (1 x 15 mL). To the resulting solution was added THF (20 mL) and 3N HCl (4 mL) which was left to stir overnight in the absence of light. The excess solvent was evaporated *in vacuo* before the subsequent residue was purified by flash silica chromatography (20:1 → 10:1 *v/v* hexanes/EtOAc). All tubes containing the desired product were collected the volatiles were removed *in vacuo* to provide **124** as a white amorphous solid 21 mg, 59% yield.

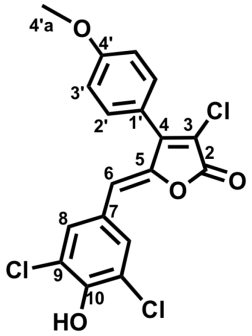
Chemical Formula: $C_{18}H_{11}Cl_3O_4$

Molecular Weight: 397.64

R*f* = 0.40 (5:1 hexanes/EtOAc)

m.p.: 253-54 ^{o}C (decomp.)

Numeric sequence:



^{1}H NMR (400 MHz, acetone-d_6) δ 8.89 (bs, 1H) 7.70 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 3.89 (s, 3H);

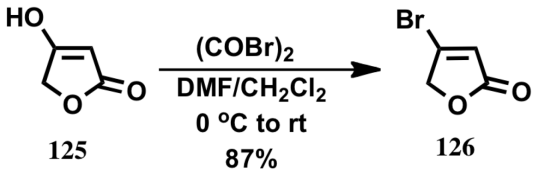
^{13}C NMR (100 MHz, acetone-d_6) δ 164.9 (C_2), 162.3 ($C_{4'}$), 159.8 (C_{10}), 150.9, 145.5, 133.7 ($C_{2'}$), 131.8 ($C_{3'}$), 125.7, 121.2, 116.8 (2C), 115.3 (3C), 55.9 ($C_{4'a}$);

HRMS (ESI) cald for $C_{19}H_{11}Cl_2O_4$: 328.0507 $(M)^+$, found: 328.0502

IR (KBr): υ_{max} 3338, 2929, 2933, 2836, 1744, 1603, 1505, 1442, 1346, 1258, 1170, 1025, 832 cm^{-1};

Attempted Synthesis of Bombardolides A-D

4-Bromo-2(5*H*)-furanone, **(126)**



To a stirred solution of alcohol **125** (200 mg, 0.95 mmol) in a flame-dried flask fitted under $Ar_{(g)}$ in DMF (5 mL), CH_2Cl_2 (10 mL) was added $(COBr)_2$ (1M, 190 μL, 1.90 mmol, 2.0 equiv) at 0 ^oC over 5 minutes at which time the reaction was allowed to warm to room temperature over 2 h until complete consumption of the starting material (as indicated by TLC). To the resulting solution was added NH_4Cl $_{(sat.)}$ and the reaction stirred for 15 minutes before the organic layer was partitioned, washed with water (1 x 10 mL), brine, (1 x 10 mL), dried on Na_2SO_4 and the volatiles were removed *in vacuo.* The resulting crude mixture was purified on Si_2O (hexanes/EtOAc 20:1 $\rightarrow$10:1 $\rightarrow$ 4:1 *v/v)* to provide pure **126** as light beige crystal (182 mg, 87% yield).

Chemical Formula: $C_4H_3BrO_2$
Molecular Weight: 162.9694
R*f* = 0.32 (2:1 hexanes/EtOAc)
m.p.: 77 ^oC (lit[lxxiv] = 77 ^oC)

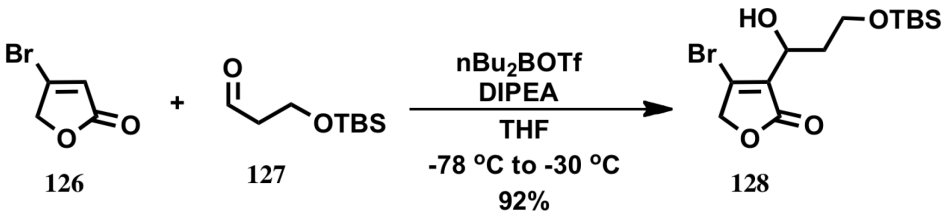
^1H NMR (400 MHz, CD_3Cl_3) δ 6.36 (dd, *J*=2.0 Hz, 1H), 4.87 (s, *J* = 1.8 Hz, 2H) ppm;

^{13}C NMR (100 MHz, CD_3Cl_3) δ 171.1 (C_2), 146.5(C_4), 122.0 (C_3), 75.1 (C_5) ppm;

HRMS (ESI) cald for $C_4H_3BrO_2$: 161.9316 $(M)^+$, found: 161.9325

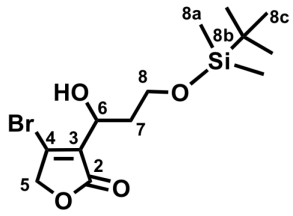
IR (KBr): υ_{max} 2925, 1805, 1762, 1620, 1515, 785, 777 cm^{-1}.

4-Bromo-3-(3-(*tert*-butyldimethylsilyloxy)-1-hydroxypropyl)furan-2(5H)-one, **(128)**



To a solution of 4-bromofuranone **126** (100 mg, 0.66 mmol) in dry THF in a flame-dried round-bottom flask under $Ar_{(g)}$ was added at 0 ^{o}C DIPEA (425 μL, 2.4 mmol, 4.0 eq) and was left to stir for 5 minutes. At which time the solution was cooled to -78 ^{o}C and nBu_2BOTf (2.4 mL, 2.4 mmol, 4.0 equiv) was added dropwise. The resulting solution was permitted to stir 30 h at this temperature, at which time 3-(*tert*-butyldimethylsiloxy)-1-propanal, **127** (123 mg, 0.93 mmol, 1.5 equiv) was added dropwise to the solution and the resulting mixture was permitted to stir another 45 minutes while warming slowly to -30 °C, at which time TLC indicated complete consumption of the starting material. The solution was washed with water (1 x 10 mL) and the organics were extracted with EtOAc (2 x 15 mL), dried on Na_2SO_4 and the volatiles were evaporated *in vacuo.* The resulting mixture was purified on SiO_2 (100:1 to 30:1 to 10:1 hexanes/EtOAc) to provide **128** as a clear, light-yellow oil (204 mg, 92 %).

Chemical Formula: $C_{13}H_{23}BrO_3Si$
Molecular Weight: 351.3088
R*f* = 0.45 (2:1 hexanes/EtOAc)
Numeric Sequence:



^{1}H NMR (400 MHz, CD_3Cl_3) δ 4.77-5.03 (m, 2H, H_2C_5), 3.85-4.44 (m, 3H, HC_6+H_2C_8) 3.25 (br s, 1H, O*H)*, 2.08 (m, 2H, HC_7) 0.89 (s, 9H, HC_{8c}), 0.08 (s, 6H, HC_{8a}) ppm;

^{13}C NMR (100 MHz, CD_3Cl_3) δ 170.2 (C_2), 139.5 (C_3), 132.6 (C_3), 73.3 (C_5), 66.2 (C_8), 60.5

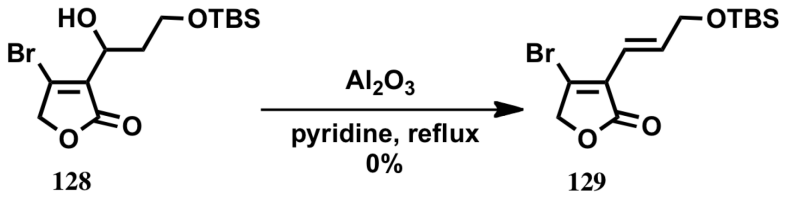
(C_6), 37.2 (C_7), 25.9 (C_{8a}), 18.1 (C_{8b}), -5.49 (C_{8c}) ppm;

HRMS (ESI) cald for $C_{13}H_{23}BrO_4Si$: 351.3088 $(M)^+$, found: 351.3090;

IR (KBr): υ_{max} 2925, 1805, 1762, 1620, 1515, 785, 777 cm^{-1}

Attempted synthesis of :

(E)-4-Bromo-3-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)furan2(5*H)*one, (**49)**



To a solution of **128** (100 mg, 0.66 mmol) in dry pyridine (10 mL) in a flame-dried flask under $Ar_{(g)}$ was added aluminum oxide (100 mg, 0.98 mmol, 1.5 eq) and was left to stir for 5 minutes. At which time the receptacle was sealed with a septum and heated to reflux for 6 h. The solution was left to cool to room temperature. The solution was filtered through sintered glass and added 10 mL of CH_2Cl_2. The mixture was washed with $CuSO_4$ (5 x 15 mL) until it no longer turned purple when mixed with the organic layer. The volatiles were evaporated *in vacuo*. The reaction failed to provide **129**, and **128** was completely consumed, as seen from NMR and TLC.

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