ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE KIBDELONES

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Dedication

For Rosie

Acknowledgements

Obtaining a doctoral degree requires that one be focused, passionate, and somewhat intelligent. For my time at UT Southwestern the emotional and intellectual support of my friends, colleagues and mentors were the most important part of a successful journey through graduate school. Professor Joseph Ready was my primary mentor who led me to success in the lab. For his tutelage on everything from technique to chemistry problem solving I will be eternally grateful. I am also extremely fortunate that Joe is so attentive to the way his students present themselves in writing and to an audience. My skills in these very important and often overlooked areas have benefitted greatly from his guidance. I hope that our relationship continues and that I can continue to learn from Joe as my career progresses.

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These are just some of the people that I have been lucky enough to be surrounded by during my time at UT Southwestern; there are many other people whose social and scientific support I am thankful for. Events during grad school represent the best and some of the lowest parts of my life so far and I wouldn't trade the relationships that got me through it for anything.

ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE KIBDELONES

by

JOHN R. BUTLER

DISSERTATION

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Abstract

ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE KIBDELONES

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The kibdelones are a family of aromatic polyketides reported in 2006 by Capon and co-workers. These compounds possess potent antibiotic and cytotoxic activities and operate via an unknown and potentially unique mode of action. In order to fully investigate these properties the kibdelones were targeted for total synthesis. Novel methods for heterocycle synthesis and biaryl bond formation were also targeted as part of the synthesis. The kibdelones contain a chlorinated isoquinolinone and stereogenically rich tetrahydroxanthone heterocycles, which make them challenging synthetic targets. To synthesize these compounds a convergent strategy has been developed that splits the molecule into two fragments of similar size. The isoquinolinone moiety was synthesized from amino acid and

benzoic acid fragments using a Pomeranz-Fritsch reaction. Our approach to synthesize the tetrahydroxanthone fragment took advantage of an element of latent C_2 symmetry present in the kibdelones. Using the Shi-epoxidation this fragment was synthesized in an enantioselective fashion from resorcinol. After joining these fragments with sequential Sonogashira reactions a demanding late stage C-H arylation reaction was used to forge the final C-C bond of the natural product. Importantly, this biaryl bond formation was enabled by the serendipitous discovery of a selective copper-catalyzed iodination reaction. All of these efforts led to the successful 20-step synthesis of (-)-kibdelone C, setting the stage for further biological enquiry of these exciting natural products.

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List of Definitions

Ac	acetyl
acac	acetylacetonyl
AD	asymmetric dihydroxylation
anhyd.	anhydrous
APCI	atmospheric pressure chemical ionization
aq.	Aqueous
Ar	aryl (substituted aromatic ring)
BBN (9-BBN)	9-borabicyclo[3.3.1]nonane (9-BBN)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
t-Bu	*tert*-butyl
BuLi	butyl lithium
Bz	benzoyl
calc'd	calculated
cat.	Catalytic
ca	cerca (approximately)
°C	degrees Celsius
conc.	concentrated
Cp	cyclopentadienide
Cp^*	pentamethyl cyclopentadienide
Cy	cyclohexyl
δ	chemical shift downfield from $(CH_3)_4Si$
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCM	dichloromethane
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMDO	dimethyldioxirane
DMAP	*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMS	dimethylsulfide
DMP	Dess-Martin periodinane
dr	diastereomeric ratio
dt	doublet of triplets
E^+	electrophile
	(denotes any electrophile in general
ee	enantiomeric excess
eq.	equation
equiv	equivalent
ES+	electrospray, positive ionization mode
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
E-X	electrophile
	(denotes any electrophile in general
FT-IR	Fourier transform infrared
g	gram
GC	gas chromatography
h	hour

[H]	reductant
Hg mm	millimeter of mercury (760 Hg mm = 1 atm = 760 Torr)
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
hν	light
Hz	hertz
IPA	isopropyl alcohol
i-Pr	isopropyl
IR	infrared
J	coupling constant
L	ligand
LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
liq.	liquid
LTBP	lithium *tert*-butyl peroxide
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet or medium
[M]	metal
MAO	methylaluminoxane
m-CPBA	*m*-chloroperoxybenzoic acid
MDR	multiple drug resistance
Me	methyl
MeCN	acetonitrile

Mes	mesityl
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
MOM	methoxymethyl
m/z	mass / charge
Ms	methane sulfonyl
MS	molecular sieves
N	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
n-Pr	propyl
Nu	nucleophile
o-	ortho
[O]	oxidant
OAc	acetate
OMs	mesylate
OTf	triflate
p-	para
Ph	phenyl
PCC	pyridinium chlorochromate
PhH	benzene
PhMe	toluene
PMBTCA	PMB-acetimidate
PPh_3	triphenylphosphine

ppm	part per million
PPTS	pyridinium *p*-toluenesulfonate
pyr	pyridine
q	quartet
rac	racemic
R_f	retention factor in chromatography
rt	room temperature
SAR	Structure Activity Relationship
s	singlet or strong
t	triplet
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylenediamine
TMS	trimethylsilyl
tol	toluene
T_r	retention time
p-TsOH	*p*-toluenesulfonic acid
Ts	toluenesulfonyl
UV	ultraviolet
w	weak
y	yield
Δ or ↑↓	heat at reflux

Chapter 1 The Kibdelones and Related Natural Products

1.1 Introduction

The kibdelones are a family of biologically active aromatic polyketide natural products with interesting biological properties and intriguing structural motifs (Figure 1-1). This chapter will outline the biological properties of the kibdelones as well as other members of the polycyclic xanthone class of natural products. Synthetic efforts toward the kibdelones and structurally related compounds from other laboratories from the 1980's to the present will also be reviewed.

1.2 The Kibdelones

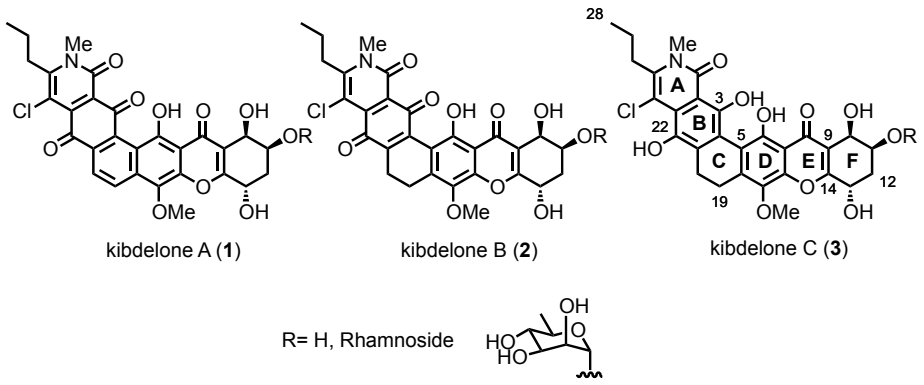


Figure 1-1: The Kibdelones

Isolation

The kibdelones were reported by Capon and co-workers in 2006.[1] The research team purified several compounds from fermentations of a rare soil actinomycete, *Kibdelosporangium* sp., isolated from a soil sample collected from the floor of a sheep sheering shed near Port Augusta, Australia in 1996. Solid fermentation (barley) and extraction with MeOH gave the highest yield of kibdelone metabolites. The hexacyclic, poly-aromatic structures are denoted via A-F lettering (as shown for kibdelone C, Figure 1-1) and were elucidated using extensive 1-D and

2-D NMR experiments. The absolute configuration of these compounds was established by total synthesis (see 1.4 and Chapter 2).

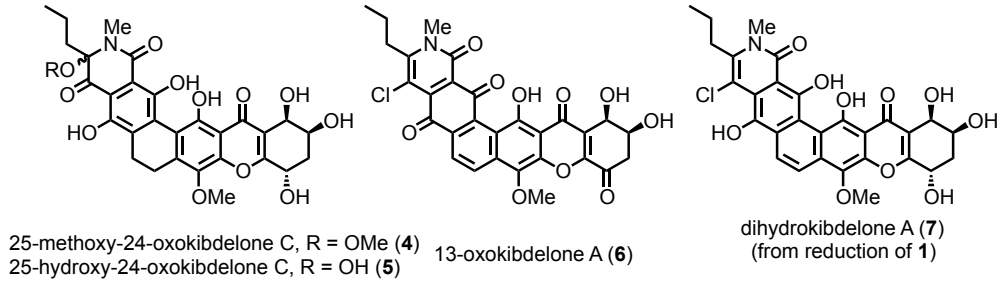
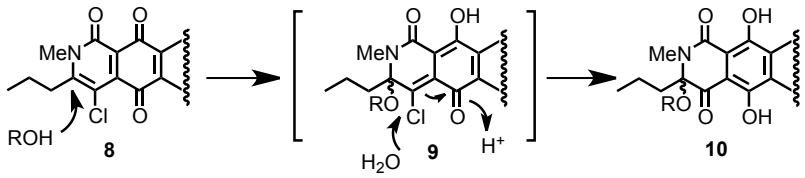


Figure 1-2: Additional Kibdelone Co-Metabolites

Along with kibdelones A-C, the corresponding rhamnosides were isolated (R = rhamnose, Figure 1-1) as well as three additional kibdelone-derived compounds.[1]



Scheme 1-1: Formation of Isolation Artifacts 4 and 5

Methoxy- and hydroxy-oxokibdelone C (Figure 1-2) are thought to arise from either methanol or water addition to kibdelone B followed by quinone tautomerization (Scheme 1-1); however, these derivatives are thought to be artifacts of the isolation procedure and were minor constituents of the extracts of *Kibdelosporangium*. Dihydrokibdelone A was generated by chemical reduction ($Na_2S_2O_4$) of kibdelone A.

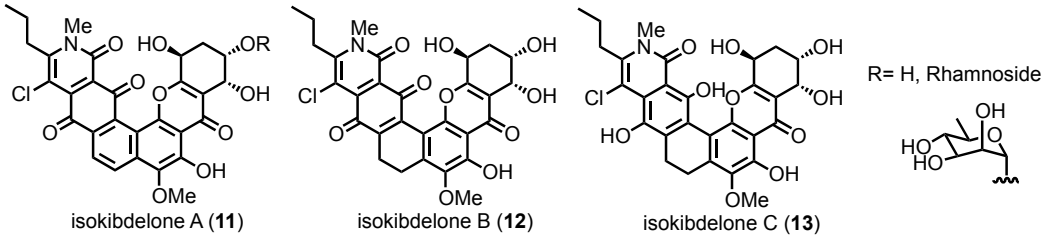
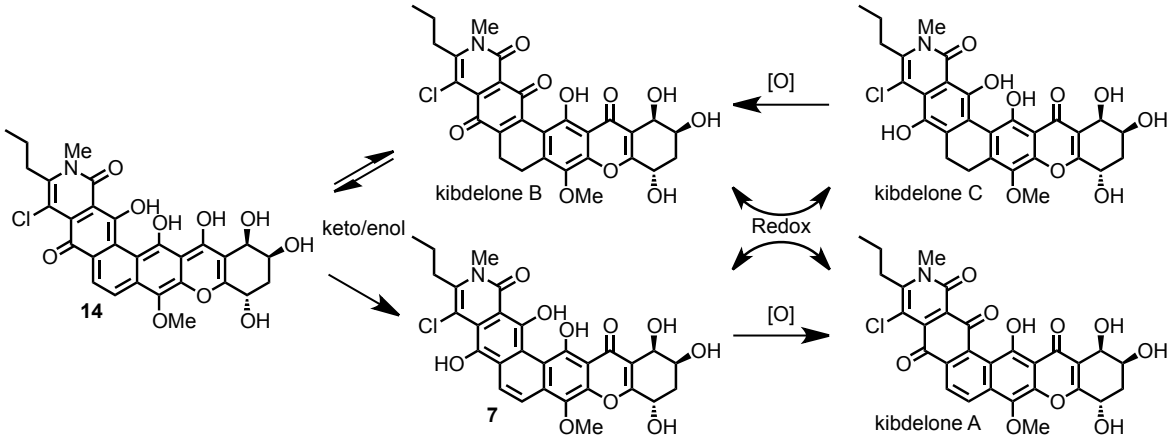


Figure 1-3: The Isokibdelones

Another group of related natural products, the isokibdelones, were isolated from the same bacteria and reported separately in 2006.[2] These compounds are 10-

200 times less potent than the kibdelones against cancer cell lines. More recent experiments from the Capon group revealed that while these compounds are not cytotoxic, they may work synergistically with the kibdelones by blocking active transporters for removal of the kibdelones from cells.[3]



Scheme 1-2: Redox Tautomerization of the Kibdelones

Both the kibdelones and isokibdelones were reported to equilibrate upon standing in methanol via a series of redox-tautomerizations, which could account for similar activities amongst the groups of compounds. The mechanism for this interconversion, as postulated by Capon, *et al.* is shown in Scheme 1-2 and involves redox equilibration via ortho-quinone methide intermediate **14**. This intermediate can convert to either kibdelone B or compound **7** via keto/enol tautomerization. Kibdelone A is stable in methanol and does not interconvert, while kibdelones B and C give an equilibrium mixture of all three compounds. This interesting property would undoubtedly affect synthesis of these compounds and this will be discussed in Chapter 2.

Biological Activity

	Assay ([nM] LD_{99})		
kib.	*H. Contortus (nematode)*	*B. Subtilis (Gram +ve)*	*E. Coli (Gram–ve)*
A	0.67	0.084	2.7
B	2.2	0.13	-
C	8.5	0.13	-

Table 1-1: Anti-Infective Activity of Kibdelones A-C

The kibdelones are potent cytotoxic agents against Gram-positive bacteria, nematodes, and human cancer cell lines. The impressive cytotoxic activity is outlined in Table 1-2 and shows potency against a wide range of cancer cell lines. All three kibdelones have similar potency most likely due to interconversion in cell culture (Scheme 1-2). Some SAR is provided by the additional kibdelone-related metabolites that were isolated: Glycosylation of the kibdelones at C_{11} (R = rhamnose, Figure 1-1) leads to reduced potency, suggesting the stereogenically rich F-ring is important for the activity of these molecules. The biological activity of the compounds in Figure 1-2 was not reported. The kibdelones were also evaluated in the NCI60 cancer cell line panel and COMPARE analysis showed that activity profiles were not statistically similar to any of the 40,000 cytotoxic agents[4] tested by the NCI, which leads to the conclusion that the kibdelones operate by a novel mode of action (see 1.3).

Human tumor Cell Line ([nM] GI_{50})									
kib.	Leukemia (SR)	Nonsmall cell lung (NCI-H322M)	Colon (HCC-2998)	CNS (SF-539)	Melanoma (SK-MEL-5)	Ovarian (SK-OV-3)	Renal (SN12C)	Prostate (DU145)	Breast (MCF7)
A	1.2	1.3	3	1.4	1.7	3.2	<1.0	3.1	5
B	1.7	2.3	<1.0	3.2	3.1	3.6	3.6	3	3.5
C	<1.0	<1.0	<1.0	3	<1.0	<1.0	<1.0	1.4	<1.0

Table 1-2: Cytotoxic Activity of the Kibdelones Against Human Cancer Cell Lines

1.3 Natural Product Drugs and the NCI COMPARE Analysis

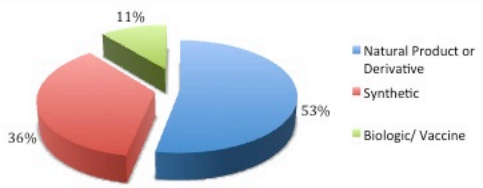


Figure 1-4: Source of Anti-Cancer Drugs

Natural products are the most successful class of compounds for the treatment of cancer. A recent analysis of the source of all 175 approved therapeutics for cancer revealed that 53% were natural products or derived from a natural

product (Figure 1-4).[5] The National Cancer Institute has contributed to the development of natural products as therapeutics in several capacities; one recent effort involves the development of an in-vitro screening program in the late 1980s that utilizes 60 different cancer cell lines, which is known appropriately as the NCI60. The NCI60 was developed to shift screening of novel chemicals from in-vivo mouse models, which focused on leukemia, to more broad in-vitro methods that emphasized solid tumors.[6] A timeline of activity of the NCI60 up to 2006 is shown in Figure 1-5 (from ref. 6). As researchers developed screening protocols they soon found that compounds that functioned in a similar manner produced similar patterns of activity in the 60-cell line panel. They developed this tool into the COMPARE algorithm in an attempt to classify compounds based on their mechanism of action.

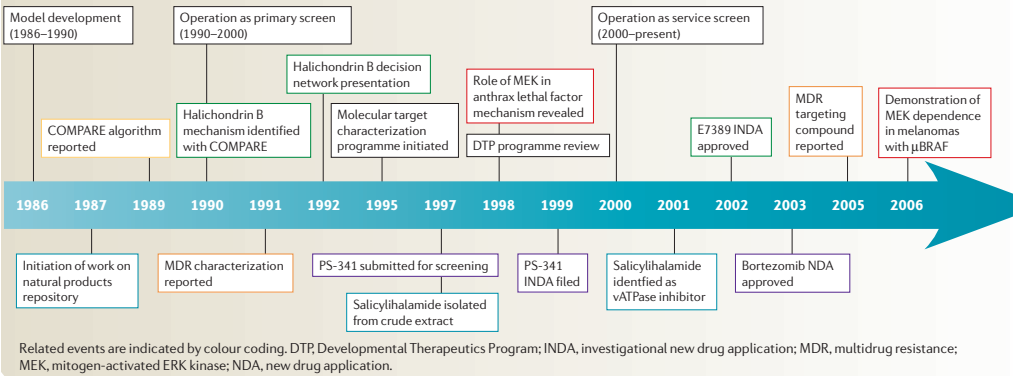


Figure 1-5: Major Events in the Development, Implementation and Use of the NCI60 (ref 6)

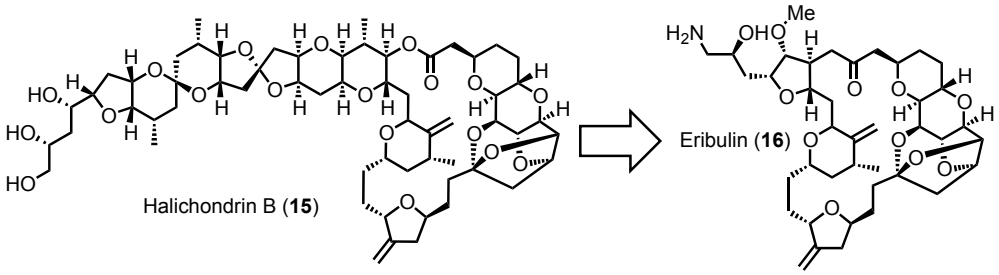
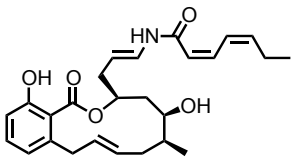


Figure 1-6: Minimal Pharmacophore of Halichondrin B

This screening method has been successful at identifying both natural product and synthetic compounds as cancer drug leads. In the early 90's the

COMPARE analysis was validated by identifying Halichondrin B as an inhibitor of microtubule polymerization.[7] Further pre-clinical development at the NCI and total synthesis enabled identification of a minimal pharmacophore by Yoshito Kishi and coworkers, allowing Eisai pharmaceuticals to gain approval of Eribulin in 2010.[8,9] Another example in which COMPARE analysis predicted a compound to have a novel mode of action was the discovery of the Salicylihalamides as inhibitors of mammalian vacuolar ATPase.[10] Total synthesis by De Brabander and co-workers[11] enabled further analysis of this activity and found the mechanism to be distinct from other ATPase inhibitors.[12] These two examples not only show how NCI60 data can be used to predict compounds of interest, but also how the total synthesis of these leads can be used to produce analogs that can have effects on the treatment of disease and the understanding of biological processes. Considering the historical success of these natural products coupled with NCI60 data, the kibdelones become enticing targets for total synthesis.



Salicyclihalamide A (**17**)

1.4 Polycyclic Xanthone Natural Products

Introduction

Aromatic polyketides comprise a diverse array of complex natural products with numerous biological activities. Within this broader class resides the polycyclic xanthones, of which the kibdelones are a member. Their biosynthesis takes place via the enzymatic machinery of massive polyketide synthase (PKS) complexes. In the lab, chemists have developed several inventive and elegant syntheses of members of this class of natural products. This section will present an overview of the biology of selected polycyclic xanthones and some syntheses that are relevant to the kibdelones.

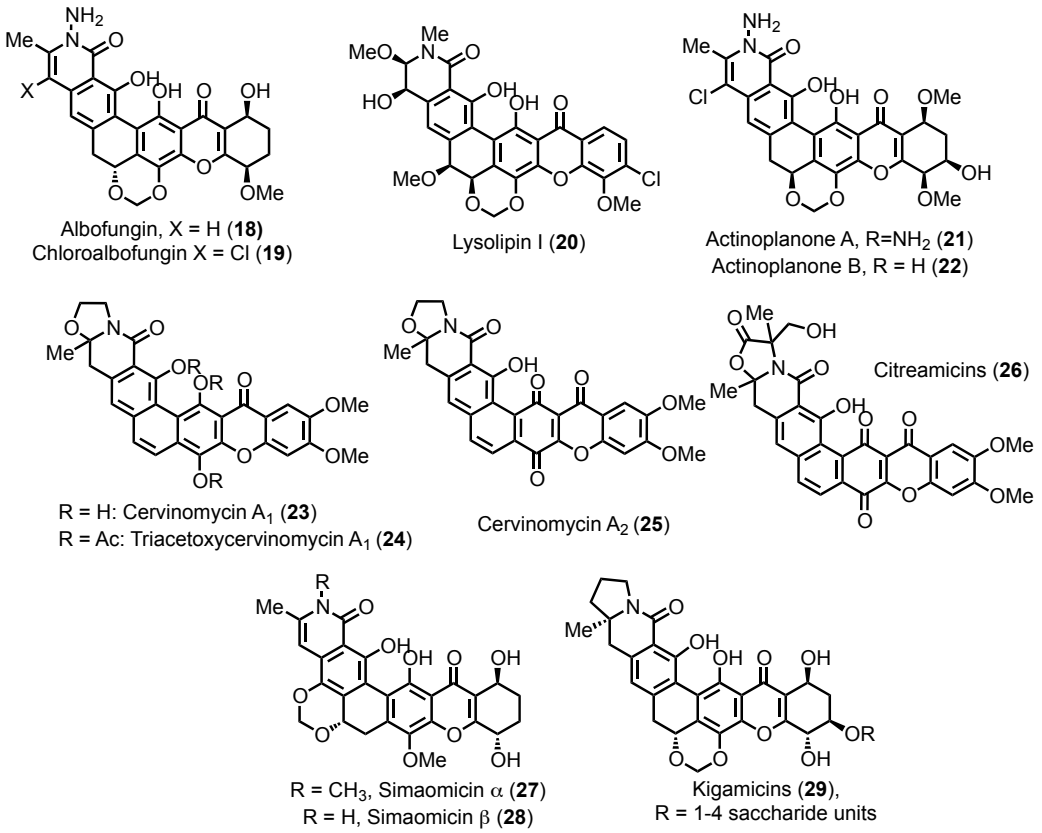
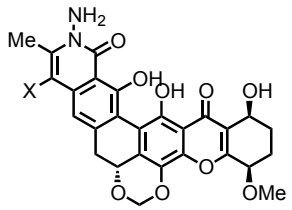


Figure 1-7: Selected Polycyclic Xanthone Natural Products

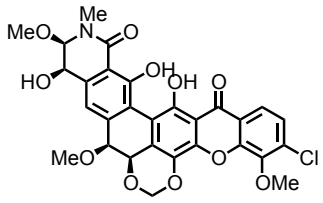
Related Polycyclic Xanthone Natural Products

The class of compounds known as polycyclic xanthones has steadily grown since the first member was isolated in the 1960's. The compounds from this class have a wide range of biological activities and most are potent antibacterial agents against Gram-positive microorganisms. No general structure activity relationship work has been performed and little is known about the mode of action of these compounds. This lack of data is unfortunate because of the quite remarkable amount of structural variation within the class that includes: variations in oxygenation, the presence of acetal rings, additional rings as part of the amide moiety, and the presence of hydrazide functional groups.



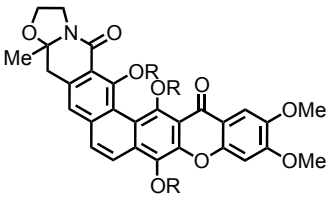
Albofungin, X = H (**18**)
Chloroalbofungin X = Cl (**19**)

Albofungin is one of the earliest reported polycylic xanthone natural products initially reported in 1959.[13] The structure was not elucidated for another 13 years[14] and required correction in 1978 to the structure shown.[15] Studies in Russia during the 1970s found albofungin to have potent Gram-positive antibacterial activity.[16] In yeast albofungin was observed to inhibit RNA synthesis. This activity was associated with the antibacterial activity and thought to be due to inhibition of DNA-dependent RNA synthesis.

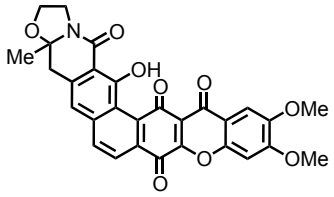


Lysolipin I (**20**)

Lysolipin is another natural product whose structure was obtained after the report of the compound's biological evaluation. The structure of this compound contains oxygenation and sites of unsaturation that are unique among the polycyclic xanthone natural products.[17] Lysolipin has potent antibacterial activity against Gram-positive bacteria and some Gram-negative bacteria (potent against both types after membrane permeation). One hypothesis is that lysolipin can inhibit cell wall synthesis by preventing access to cell wall components through interaction with carrier lipids.[18] Lysolipin was pursued synthetically in the 1980s,[19,20] but no synthesis has been reported to date.



R = H: Cervinomycin A_1 (**23**)
R = Ac: Triacetoxycervinomycin A_1 (**24**)

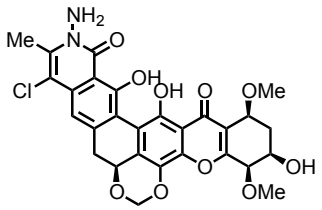


Cervinomycin A_2 (**25**)

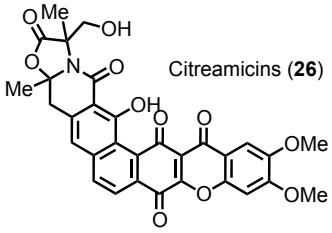
In 1988 the structure of cervinomycin,[21] another member of this class of natural products, was reported after isolation in 1982.[22] While the parent compounds (A_1 & A_2) are sparingly soluble, the tri-acetate derivative had improved

properties as an antibiotic and was pursued as a treatment for anaerobic bacterial infection. At the time only three other polycyclic xanthone natural products existed. This fact, coupled with the promising antibiotic activity, lead to the pursuit of the total synthesis of these molecules by several synthetic chemistry groups (see 1.4.4). In the late 1980's, Omura and coworkers carried out additional research into the mode of action of tri-acetyl cervinomycin against *S. aureus*.[23] They found that the compound had potent bacteriostatic properties but was not bactericidal, even at increased concentrations. Triacetoxycervinomycin also inhibited the incorporation of labeled precursors into macromolecules and caused "leakage" of cellular metabolites at high concentrations (>1 g/mL). This activity could be partially rescued by the addition of phospholipids, which led the team to conclude that the compound interferes with the plasma membrane, and active transporters.

The actinoplanones were also reported in 1988 and contain structural features that are reminiscent of the kibdelones but with differences in stereo- and regio-chemistry. Oxygenation on the C-ring is incorporated into a methylene acetal as shown.[24] These compounds boast potent cytotoxicity against HeLa cells but nothing is known about their mode of action.



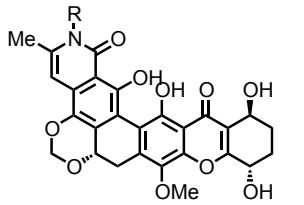
Actinoplanone A, R=NH_2 (**21**)
Actinoplanone B, R = H (**22**)



Citreamicins (**26**)

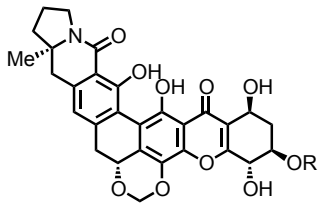
A number of polycyclic xanthones were discovered and characterized by Lederle Laboratories in the late 80's and early 90's. At the time Lederle was a subsidiary of American Cyanimid Corp., but was acquired by Wyeth in 1994. In 1990 they reported the citreamicins,[25] which are structurally very similar to the cervinomycins. Large-scale fermentation (3000 L) enabled isolation of 5 compounds (α-η, variations in catechol oxygenation) of which citreamicin η (shown) was the most active against several strains of Gram-positive bacteria (MIC <0.015 μg/mL). In a later patent from BioMar[26] the in-vitro cytotoxicity of citreamicin α was reported for three cell lines (3-4 nM). Almost two decades later, researchers at

AMRI screening for antibiotics against multi-drug resistant *Staphylococcus aureus* (ATCC 43300) isolated two new citreamicins (δ and ε) from bacteria found along the Sabine River in Texas.[27] While potent against a range of resistant Gram-positive pathogens (MIC 0.1-1 μg/mL), the compounds showed toxicity against cancer cells and normal human dermal fibroblasts (NHDF) with IC_{90}'s of 1-2 and 0.1-0.2 μg/mL, respectively.



R = CH_3, Simaomicin α (**27**)
R = H, Simaomicin β (**28**)

Lederle researchers also reported the structure of the simaomicins in 1989 and coined it "the most effective naturally occuring anticoccidial agent known."[28,29] This statement was based on the finding of an optimal dose of 1 g/ton in the feed of chickens to prevent parasitic infection. More recently, simaomicin α was found to be a potent disruptor of the cell cycle of cultured *Plasmodium falciparum,*[30] and to inhibit the G_2 checkpoint of human T-cell leukemia cells in the presence of bleomycin.[31] The ability to inhibit the G_2 checkpoint in cancer cells is a promising cancer treatment because this activity enhances the sensitivity of cells to DNA-damaging agents (bleomycin, doxorubicin, etc.), allowing their use at lower levels with potentially reduced side effects. Later studies showed that simaomicin α and cervinomycin A_2 both cause G_1 cell cycle arrest and that simaomicin α induces apoptosis.[32] It was also found that simaomicin α does not inhibit known kinases required for the G_2 checkpoint, leaving open the possibility that simaomicin α and other polycyclic xanthones may have a novel cellular target(s).



Kigamicins (**29**),
R = 1-4 saccharide units

Another family of heptacyclic compounds similar to cervinomycin, the kigamicins, were reported recently by a Japanese group screening for compounds that kill cancer cells in nutrient deprived media.[33,34] They term this an "anti-austerity" strategy for cancer drug development and rationalize this approach based on the ability of cancer cells to thrive in tumor microenvironments low in nutrients and oxygen. Several kigamicins were isolated with varying degrees of glycosylation

(OR = 1-7 sugar moieties). Kigamicin D was found to be the most active against pancreatic cancer cells in nutrient poor media[35] and was shown to block the activation of Akt in-vitro and in mice. Akt is a member of an important family of kinases involved in metabolic regulation and is associated with tumor cell survival. For this reason several Akt inhibitors are in clinical trials.[36]

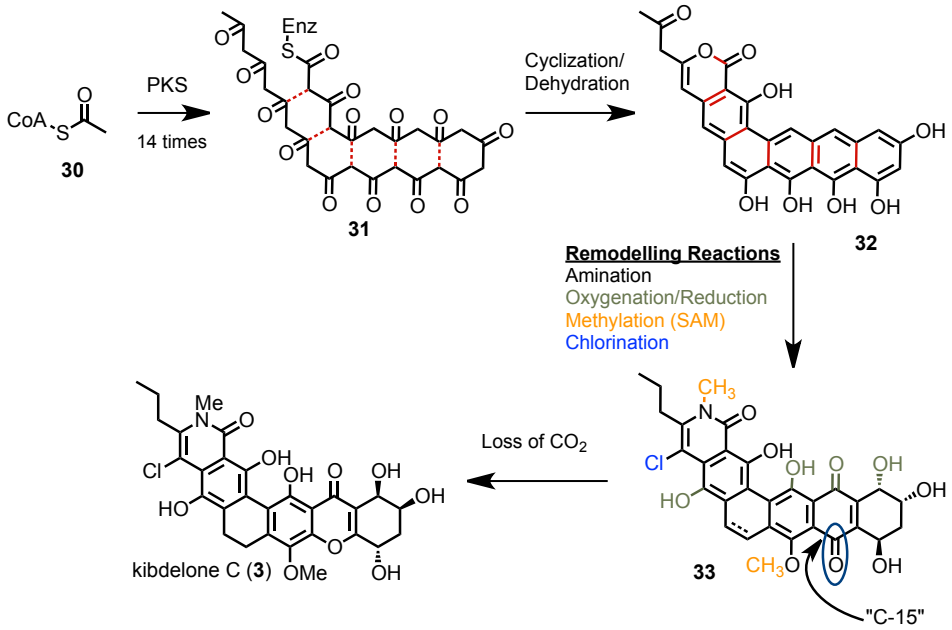
Compound Class	Antibacterial	Antifungal	Nematocidal	Anticancer
kibdelones	X		X	X
citreamicins	X			X
kigamicins	X			X
simaomicins	X			X
albofungins	X	X	X	
actinoplanones	X	X		X
Sch56036[37]		X		
cervinomycins	X			
lysolipins				X
TMC-66[38]				
fredericamycin[39]	X	X		X

Table 1-3: Summary of Biological Activity of Kibdelone-Related Natural Products

This short overview of polycyclic xanthone natural products covers the major members of this class and, while other members of this family are known, they have only minor changes in structure to those presented. All members of this family are potent Gram-positive antibiotics and have varying levels of cytotoxicity against human cancer cells (Table 1-3). Only one study discussed probed the mode of action of tri-acetyl cervinomycin and no general study of this class has been undertaken making comparisons in terms of SAR difficult. Every isolation group ran different assays with each natural product making quantitative comparisons of potency difficult. Based on antibacterial and cytotoxic activity the kibdelones are very potent members of this class of natural products. This data along with the NCI COMPARE analysis makes a convincing case for the further biological evaluation of the kibdelones. Total synthesis would be an excellent way to access these materials as well as simplified derivatives to establish additional SAR and a molecular target.

Biosynthesis of Aromatic Polyketides

The biosynthesis of all polyketides begins by the elongation of an acyl starter unit, normally acetyl- or malonyl-CoA, through a series of decarboxylative Claisen condensations to give a polyketide chain (**31**, Scheme 1-3).[40] In the case of aromatic polyketides this chain undergoes a series of cyclization and dehydration reactions. Secondary remodeling reactions then take place in which diverse enzymatic reactions introduce additional functionality. This process is outlined for kibdelone C in Scheme 1-3.

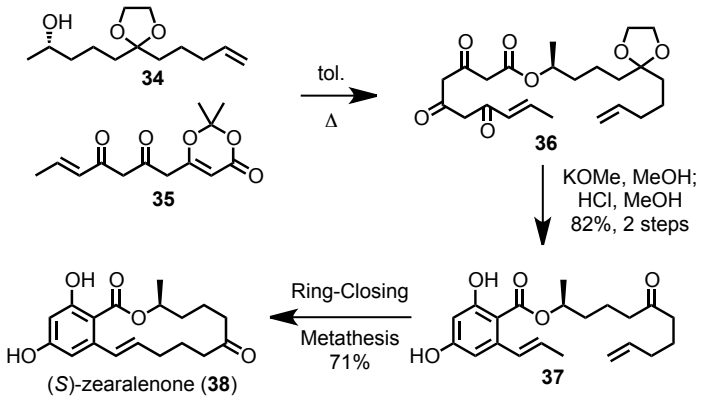


Scheme 1-3: Biosynthesis of the Kibdelones

The biosynthesis of the xanthone ring of natural products like the kibdelones could result from one polyketide chain (**31**), or the combination of two chains. This possibility was assessed by researchers from Lederle labs through feeding experiments with ^{13}C-acetate and analysis of incorporation into the framework of simaomicin α by NMR.[41] They found that every ring-carbon is derived from acetate and that the level of incorporation between carbons was uncoupled for only one carbon corresponding to C-15 of the kibdelones, which is consistent with

the oxidative expulsion of half of this acetate unit as CO_2. Loss of carbon dioxide is thought to take place via a quinone intermediate similar to **33**.

As shown the biosynthesis of these types of aromatic polyketides is highly linear and involves several stages. While instructive in terms of reactivity, these processes are very difficult to replicate without the enzymatic machinery that performs them. The Barrett lab has been able to apply a biomimetic strategy to the synthesis of several resorcylate natural products. Recently they reported the rapid synthesis of several resorcylate natural products including *S*-(−)-zearalenone from dioxinones similar to **35** (Scheme 1-4).[42] Efforts to utilize β-polyketide chains in the biomimetic synthesis of aromatic polyketides have always involved the synthesis of one to two aromatic rings. To make more complex structures such as the kibdelones in the lab, chemists have had to developed inventive and efficient multi-step synthetic sequences.

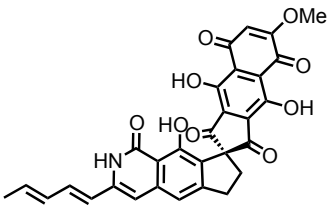


Scheme 1-4: Barrett Synthesis of Zearalenone

1.5 Synthetic Efforts Toward Related Natural Products

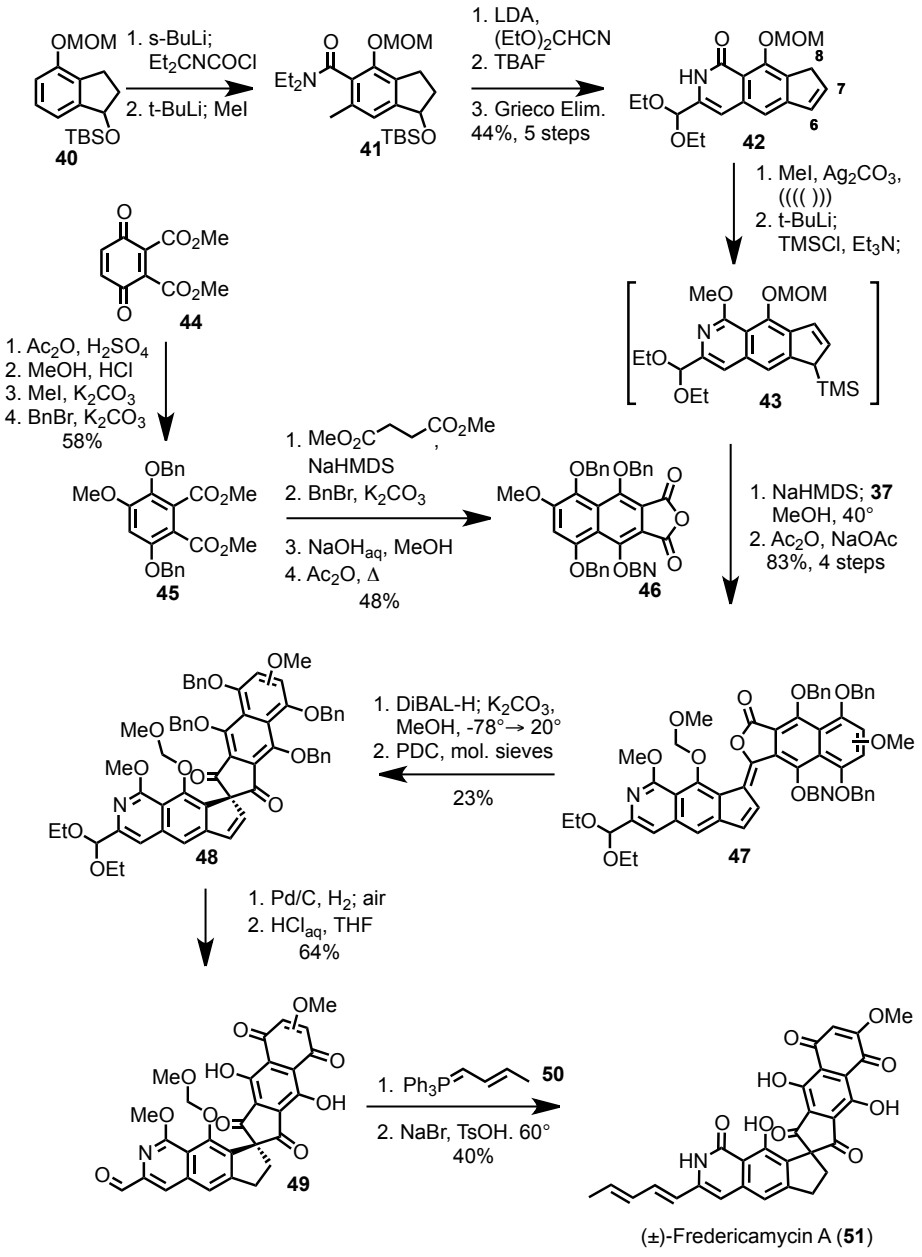
Several syntheses are instructive in planning a synthesis of the kibdelones and, in fact, another synthesis of kibdelone C was reported simultaneously with the efforts from the Ready group. These historical efforts and an overview of the complementary synthesis from the Porco Laboratory will be presented in this section.

Fredericamycin A



Fredericamycin A (**39**)

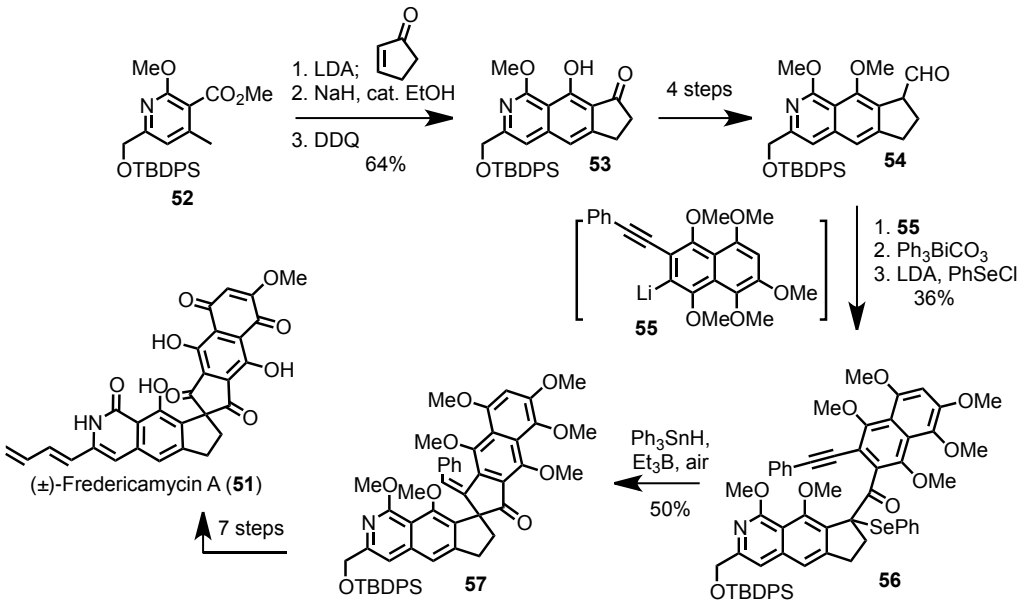
Fredericamycin A is an isoquinolinone-containing natural product that unlike the other natural products discussed up to this point, does not contain a xanthone heterocycle. Reported in the early 1980's, it garnered interest for potent cytotoxic activity and the ability to inhibit protein synthesis in leukemia cells. Fredericamycin also attracted considerable interest from the synthetic community, often under the guise that structural modifications could improve the molecule's poor physical properties. More likely, the reason for the large amount of efforts toward the synthesis of this natural product is the novel spirocyclic skeleton of the fredericamycins. To date, there are seven reported total syntheses of the fredericamycins and more than a dozen papers chronicling efforts toward the molecule.



Scheme 1-5: Kelly Synthesis of Fredericamycin A

The Laboratory of T. Ross Kelly was the first to report the total synthesis of Fredericamycin A in 1986.[43,44] The synthesis is shown in Scheme 1-5, and relies on the sequential metalation of compound **40** for the synthesis of the isoquinolinone.

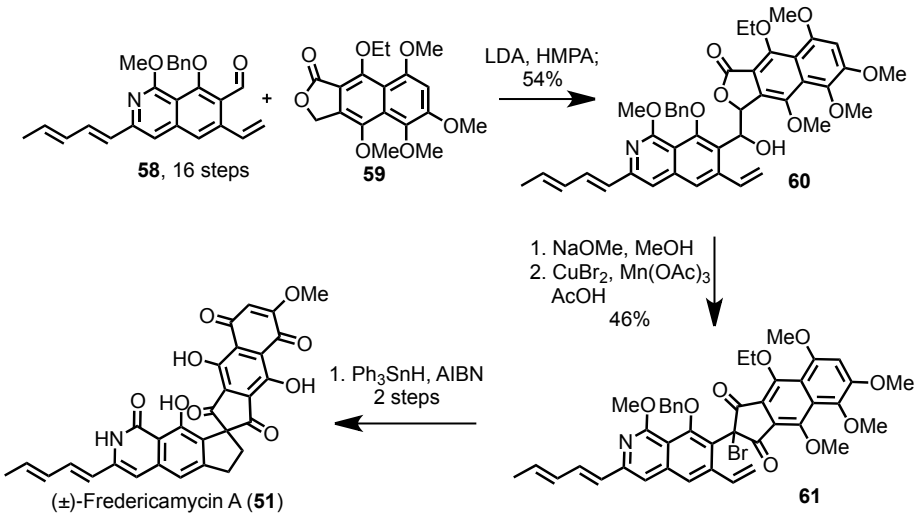
Through optimization, the Kelly group made a key observation that methoxy-isoquinoline **43** performed much better in additions to anhydride **46** than the parent isoquinolinone (**42**). Several groups would target an isoquinoline or methoxy-pyridine directly in the future. For the nucleophilic addition, they also had to overcome the preference of the initial allylic anion derived from **42** to trap exclusively on carbon 6 (Scheme 1-5). In order to switch this regio-preference they trapped the initial anion to form allylsilane **43.** Without isolation of this compound, they deprotonated again and added the anhydride to generate compound **47** exclusively after dehydration. Formation of the spirocycle was then achieved via a fairly inefficient reduction and intramolecular aldol sequence. Wittig installation of the diene and deprotection afforded the natural product. Though at times inefficient, this synthesis established metalation approaches for the isoquinolinone and that the sterically encumbered spirocycle could be accessed via aldol reaction.



Scheme 1-6: Clive Synthesis of Fredericamycin A

Clive and co-workers reported the next total synthesis of Fredericamycin A in1992.[45,46] They devised a radical spiro-cyclization strategy that required the synthesis of α-selenide **56**. To form the isoquinoline fragment they employed directed ortho-metalation, but instead of an indanol derivative like Kelly, they used

methoxy-pyridine **52** and cyclopentanone. This quickly formed the tricyclic isoquinoline fragment in three steps. A further 4 steps were required for the one carbon homologation and oxidation to give an appropriate electrophile for aryl-metal addition. The modest yielding spirocyclization was followed by oxidative cleavage, diene installation, and protecting group adjustments to yield fredericamycin A.

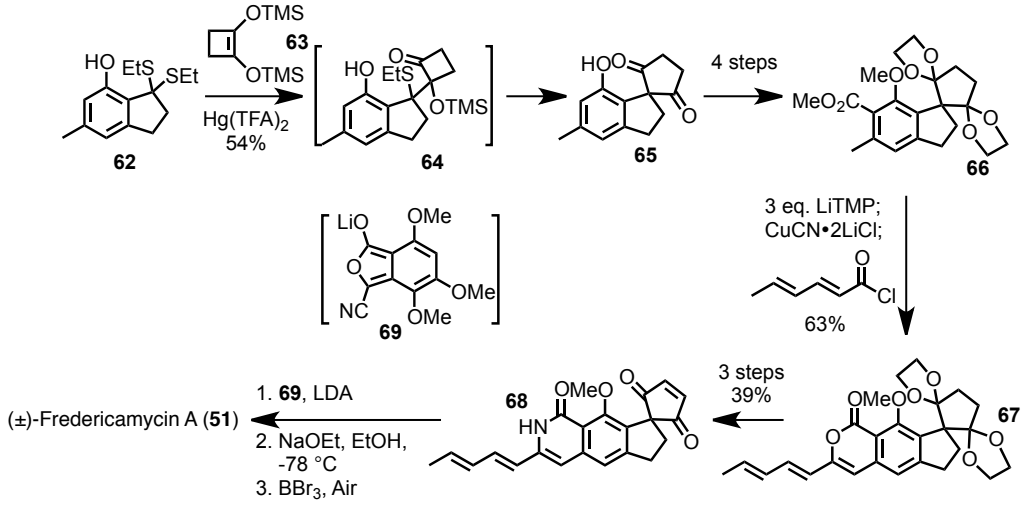


Scheme 1-7: Rao Synthesis of Fredericamycin A

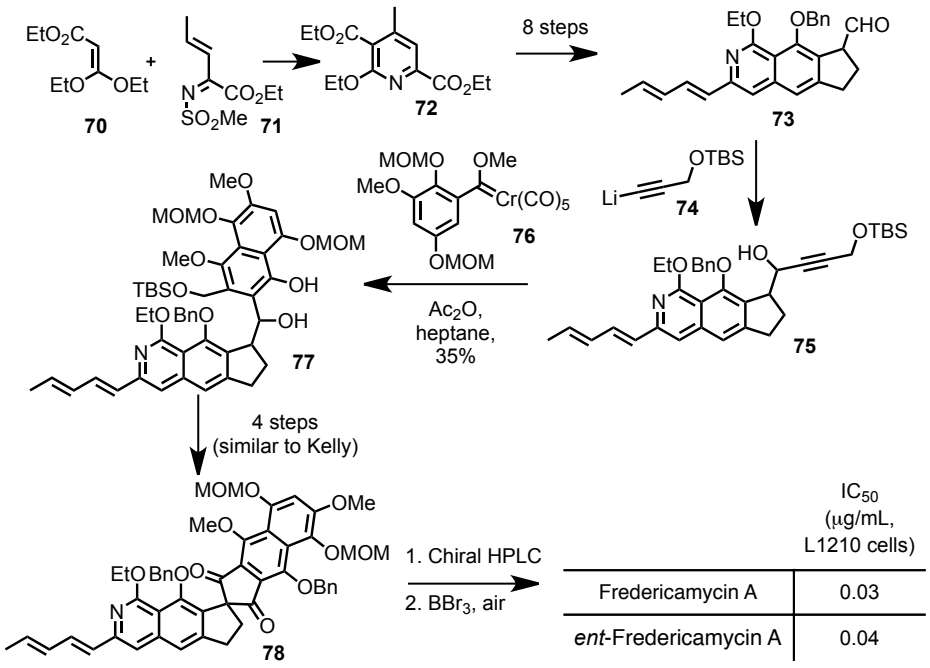
Rao and coworkers used a radical process as well to access the desired spirocycle. Instead of using an alkyne in an exo-cyclization like the Clive Lab, they initiated 5-*endo* ring-closure with bromo-styrene derivative **61** (Scheme 1-7). The use of a styrene with this mode of cyclization obviated the need for oxidative cleavage but introduced a reductive dehalogenation step. Fortunately, to the authors delight, this could be performed in one pot.[47] After a lengthy synthesis of isoquinoline **58** that proceeded through the parent isocoumarin, nucleophilic addition of lactone **59** provided benzylic alcohol **60**. This compound underwent an interesting, and not-commented on, rearrangement with NaOMe to generate a benzphthalide, which was then halogenated to yield **61**. Radical cyclization and deprotections then afforded fredericamycin A. Rao was the first to install the

pentadienyl side chain before fragment coupling, which increases convergency slightly.

The Bach Laboratory used a novel spirocyclization strategy that involved addition of bis(trimethylsiloxy)cyclobutene to thioacetal **62** (Scheme 1-6). Cyclobutane ring opening and acyl migration then gave the requisite dione (**65**), which had to be protected for the remainder of the isoquinolinone synthesis. Ortho-metalation of ester **66** followed by trapping with sorboyl chloride gave the desired isocoumarin **67**. Direct incorporation of the diene at this stage prevented the need for additional functional group manipulations later in the synthesis. Transformation of the isoquinolinone into enedione **68** allowed stepwise cycloaddition to furan **69**, which was generated in-situ. Subsequent deprotection completed a rapid synthesis of fredericamycin A (13 steps LLS from the keto-precursor of **62**).



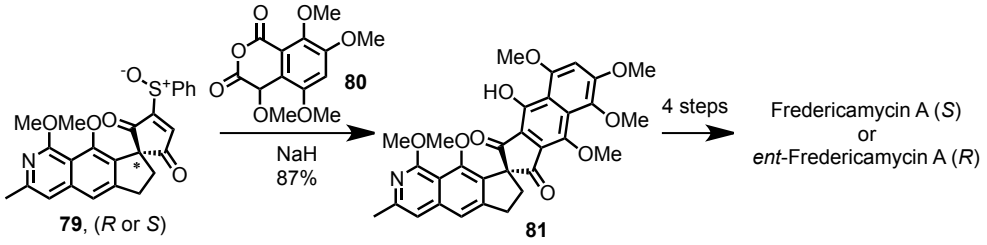
Scheme 1-8: Bach Synthesis of Fredericamycin A



Scheme 1-9: Boger Synthesis of (+) and (-)-Fredericamycin A

To assess the biological importance of the spirocyclic stereocenter of Fredericamycin A the Boger lab utilized chiral chromatography to separate the enantiomers of a late-stage intermediate.[48] Surprisingly, they found that both enantiomers have similar biological activity but in the process they developed an efficient synthesis that is worth presenting (Scheme 1-9). Similar to Clive's synthesis, Boger targeted a substituted pyridine as a precursor to the isoquinolinone fragment. To quickly access this molecule they developed a novel hetero Diels-Alder reaction. Of greater significance, the Boger lab was able to use the Dötz reaction for synthesis of the B ring of the natural product at a late stage. Accordingly, reaction of chromium carbene **76** with alkyne **75** provided all the carbons of Fredericamycin. Oxidative adjustment and then aldol spirocyclization, akin to Kelly's synthesis, provided globally protected Fredericamycin, which was resolved before deprotection. The authors note that their choice of labile protecting groups allowed them to perform clean deprotection reactions without loss of the methyl ether of the natural product.

Fifteen years after the first synthesis of Fredericamycin A was reported, Kita disclosed an enantioselective synthesis of Fredericamycin that utilized chiral sulfoxide **79** in a Hauser annulation[49] with homophthalic anhydride **80**.[50] They were able to synthesize both antipodes of **79** and also established the absolute configuration of fredericamycin A.

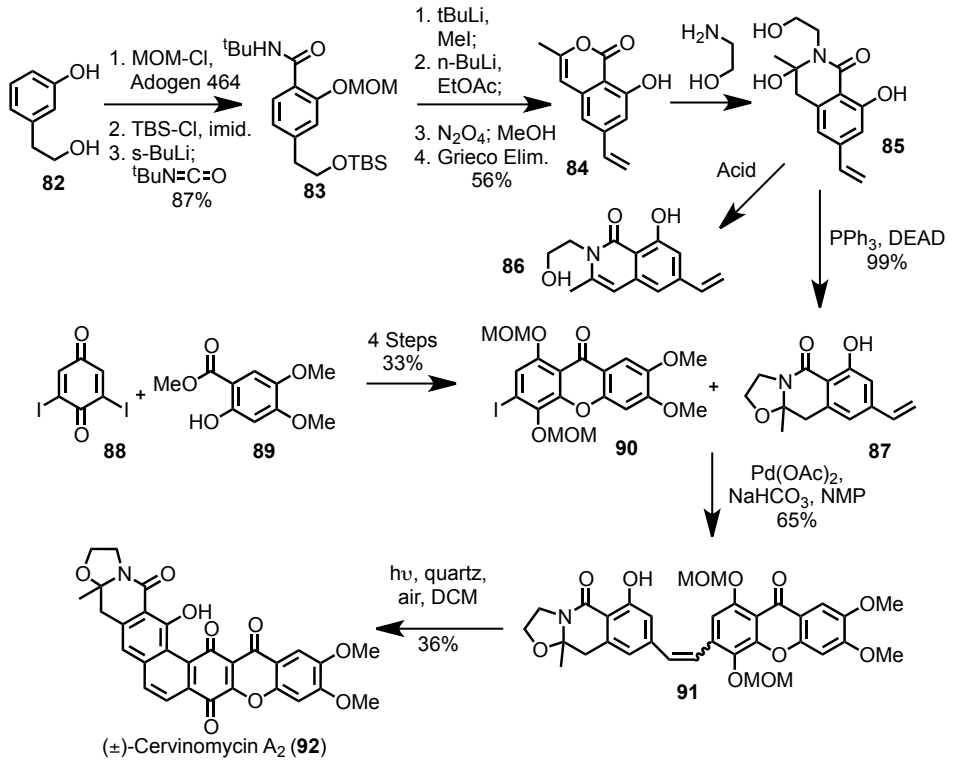


Scheme 1-10: Kita Enantioselective Synthesis of Fredericamycin A

These syntheses of the Fredericamycins display the utility of directed ortho-metalation for isoquinolinone synthesis. In addition, several strategies for increasing the convergency of the synthesis of polycyclic aromatic systems were highlighted in the context of this spirocyclic natural product. The strategies of many of the research groups the potential sensitivity of these heterocycles to reaction conditions, requiring protection as the isoquinoline..

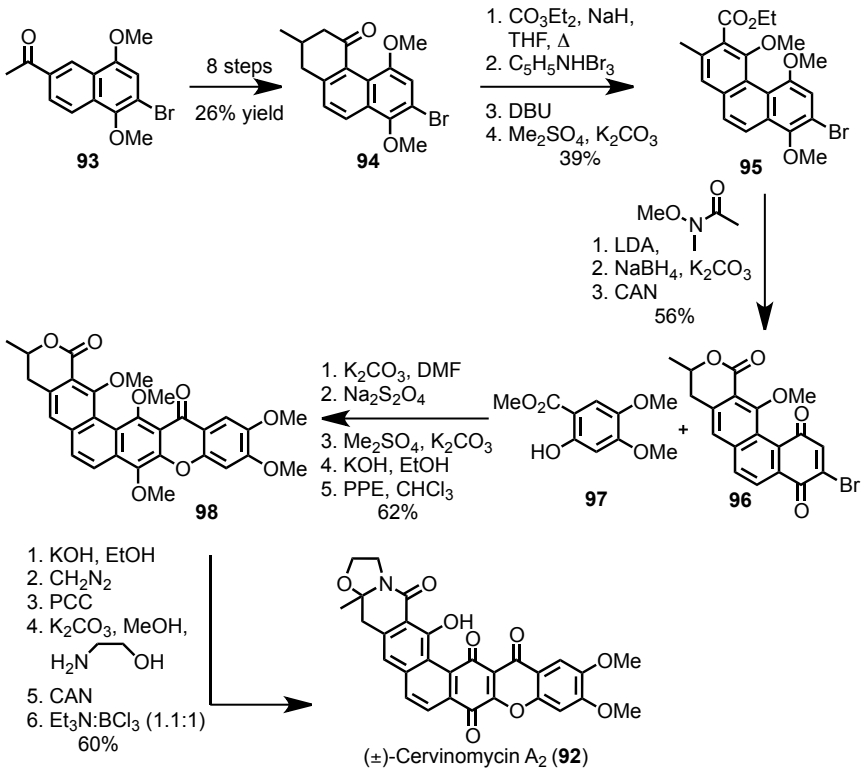
Cervinomycins

Several groups have pursued the synthesis of the cervinomycins due to their medicinal potential. In 1989 the Kelly group was again the first to synthesize this compound.[51] The strategy for isoquinolinone synthesis was similar to that used for Fredericamycin. Their approach to the xanthone would be used by other groups attempting to synthesize these molecules and is useful for the synthesis of additional members of this class of compounds.



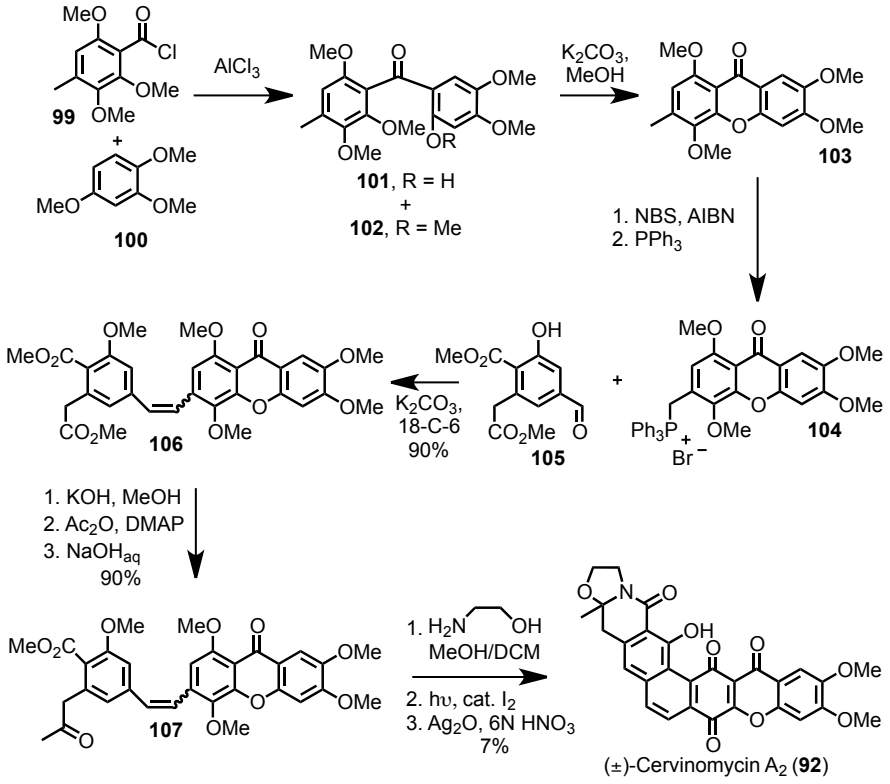
Scheme 1-11: Kelly Synthesis of Cervinomycin A_2

The synthesis commenced with selective protections of diol **82**, the primary alcohol of which represents a latent styrene unit. Kelly's trademark use of sequential ortho-metalations provides the isocoumarin precursor **84** in a three-step process. Styrene formation, ethanolamine treatment and Mitsunobu reaction then formed the oxazolidine (**87**). Xanthone formation is initiated by oxy-Michael addition of phenol **89** to di-iodide **88**. Reduction of the quinone and Friedel-Crafts acylation then provides the xanthone. MOM protection of the hydroquinone provides a substrate for Heck cross-coupling with the styrene containing isoquinolinone fragment. Stilbene **91** is obtained as an inconsequential mixture of isomers as likely equilibration occurs under the ensuing photo-cyclization conditions. The last step of the synthesis forms the final C-C bond of the molecule and also results in MOM deprotection and oxidation to yield cervinomycin A_2.



Scheme 1-12: Rao Synthesis of Cervinomycin A_2

An alternative, more linear, strategy to synthesize the cervinomycins was devised by Rao and co-workers. Their route began with compound **93**, on which they built in two directions to form both heterocycles of the natural product. Compound **94** was used to form a precursor to the isoquinolinone via carboxylation, aromatization, and methylation to provide **95**. In similar fashion to Kelly, the toluyl group of this compound was metalated, trapped with Weinreb acetamide, and reduced to form lactone **96**. Reduction was performed at this stage to prevent isocoumarin formation and allowed the installation of the oxazolidine later in the synthesis via ester amidation instead of a Mitsunobu reaction. Next, as in Kelly's synthesis, oxy-Michael addition and Friedel-Crafts acylation were used to form the xanthone. Hydrolysis of the lactone and oxidation of the resulting homo-benzylic alcohol set the stage for oxazolidine formation with ethanolamine. This was then followed by a two-step demethylation to provide cervinomycin A_2.



Scheme 1-13: Mehta Synthesis of Cervinomycin

Mehta and co-workers published the completion of cervinomycins A_1 and A_2 in 1994.[52,53] Their approach draws many similarities to Kelly's synthesis and is shown in Scheme 1-13. One of the key differences from Kelly's route is the choice of Wittig reaction to form the key stilbene derivative (**106**) for photo-cyclization. Unfortunately, this strategy prevented the use of a fully functionalized isoquinolinone fragment because of incompatibility with the Wittig reaction conditions. The synthesis of the xanthone fragment, which would serve as the ylide component of the Wittig coupling, began with Friedel-Crafts reaction to yield a mixture of phenol **101** and methyl ether **102**. This mixture was treated with potassium carbonate to provide another mixture of the xanthone **103** and unreacted **102** that could now be easily separated. Surprisingly, this S_NAr reaction generates a single regioisomer in excellent yield, but the authors do not comment on this selectivity. As in Rao's synthesis, oxazolidine coupling is performed on keto-

ester **107.** The resulting stilbene is then photolyzed in the presence of catalytic iodine. The photo-cyclization is inefficient but they are able to obtain Cervinomycin A_2 after deprotection.

All of the efforts discussed for the Cervinomycins employ relatively harsh reaction conditions for xanthone formation and multistep routes for isoquinolinone synthesis that utilize metalation or enolate alkylation. These sequences are possible because of the stability of aromatic xanthones. This stability contrasts sharply with the behavior of the corresponding tetrahydroxanthone unit that is present in natural products such as the kibdelones.

Pradimicinone, and FD-594 Aglycones

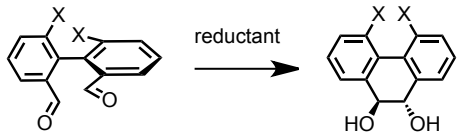
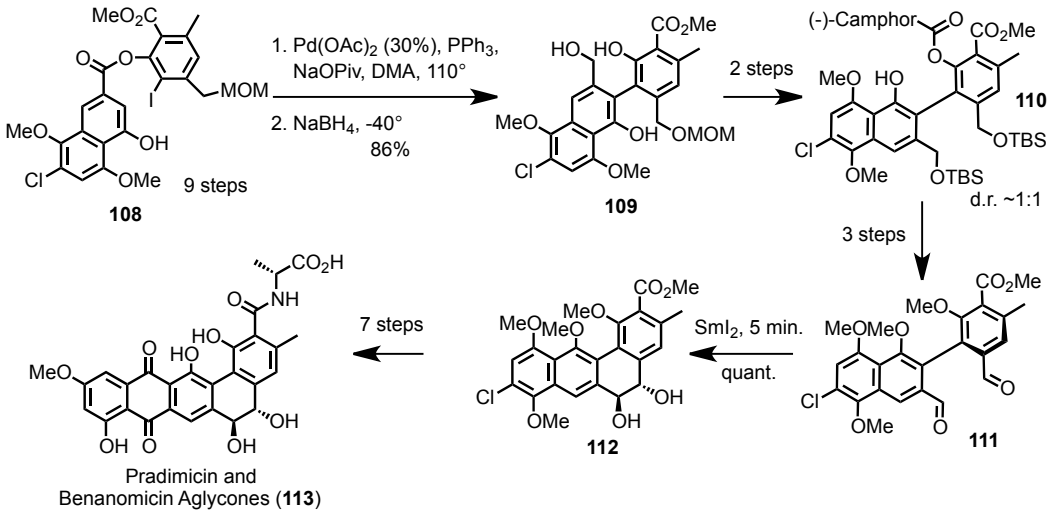
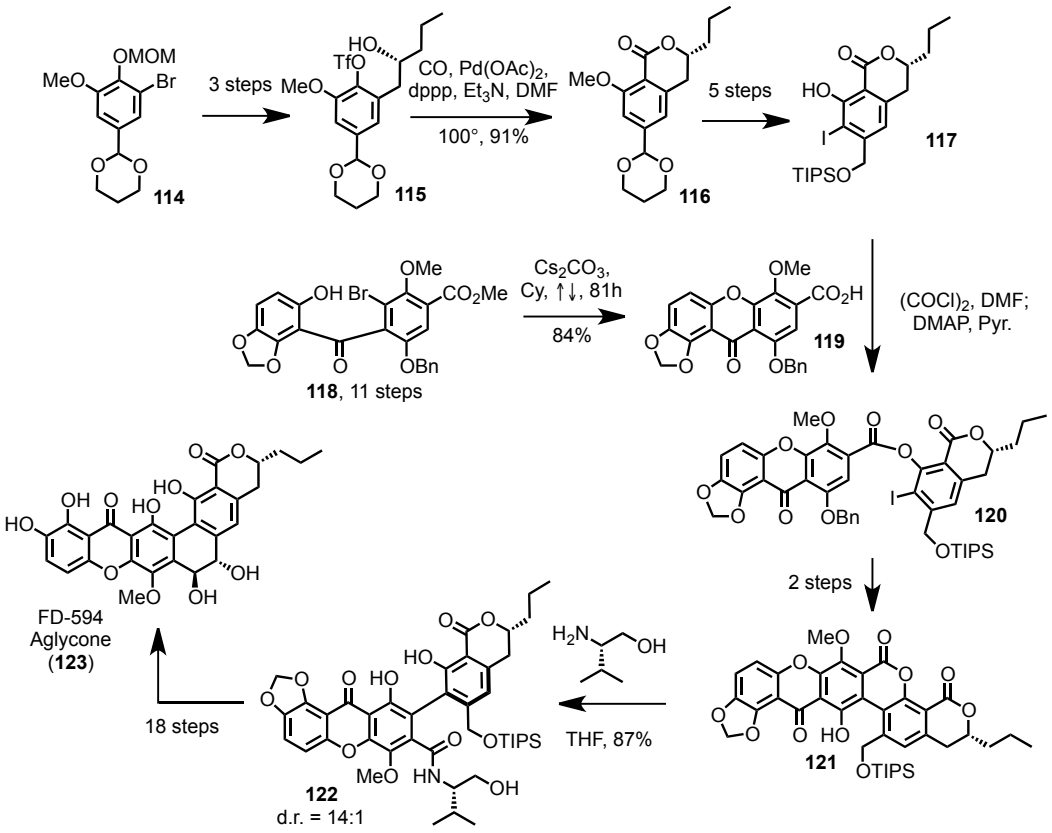


Figure 1-8: Axial to Central Chirality Transfer via Pinacol Coupling

In the late 1990's the Suzuki group developed technology for the transfer of axial chirality to central chirality for the synthesis of optically active trans-diols via pinacol coupling (Figure 1-8).[54] To generate a chiral biaryl for the synthesis of the pradimicin and benanomicin aglycones[55] they resolved phenolic camphor esters (Scheme 1-14, **110**). To access the biaryl substrates for resolution they employed intramolecular C-H arylation with phenolic iodide **108**. This type of arylation is part of a strategy utilized in several of the Suzuki lab's syntheses of these types of natural products**.** In later syntheses of enanomicin[56] and FD-594 aglycone[57] the camphor resolution strategy was replaced by the more efficient method pioneered by Bringmann that involves ring opening of biaryl lactones (i.e. **121**) with chiral nucleophiles.[58]



Scheme 1-14: Suzuki Synthesis of Pradimicin and Benanomicin Aglycones

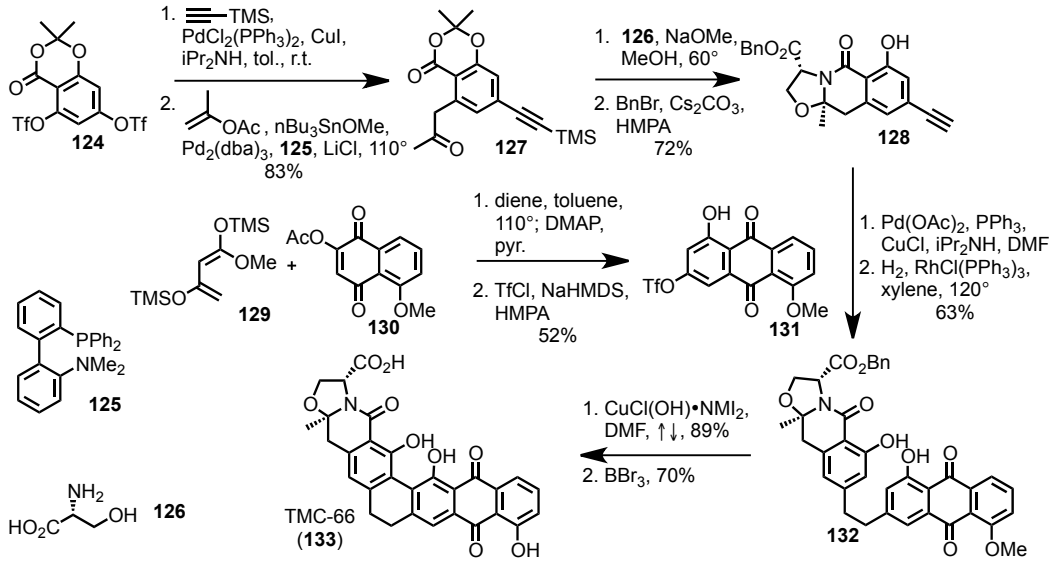


Scheme 1-15: Suzuki Synthesis of FD-594 Aglycone

FD-594 aglycone is similar to Pradimicin and Benanomicin with the addition of dihydro-isocoumarin and xanthone heterocycles, both of which are related to the heterocycles found in the kibdelones. The dihydro-isocoumarin (**117**, Scheme 1-15) was synthesized in optically active form via aryl lithium opening of a chiral epoxide and carbonylation to form the heterocycle. The xanthone coupling partner (**119**) was synthesized under fairly harsh S_NAr reaction conditions. After forming ester **120** it was found that the benzyl group of this substrate had to be removed in order for biaryl bond formation to occur. Selective ring opening was then performed with (*S*)-valinol to give the desired biaryl **122** as a mixture of diastereomers in 14:1 ratio. A further eighteen steps in a similar manner to earlier syntheses was then needed to complete FD-594 aglycone.

Central to all of these syntheses from the Suzuki Laboratory is a C-H arylation reaction with esters of complex aryl halides (i.e. **120 ➔ 121**). Applying this type of reaction to biaryl connections without esters turns out to be much more challenging and will be discussed in Chapter 2.

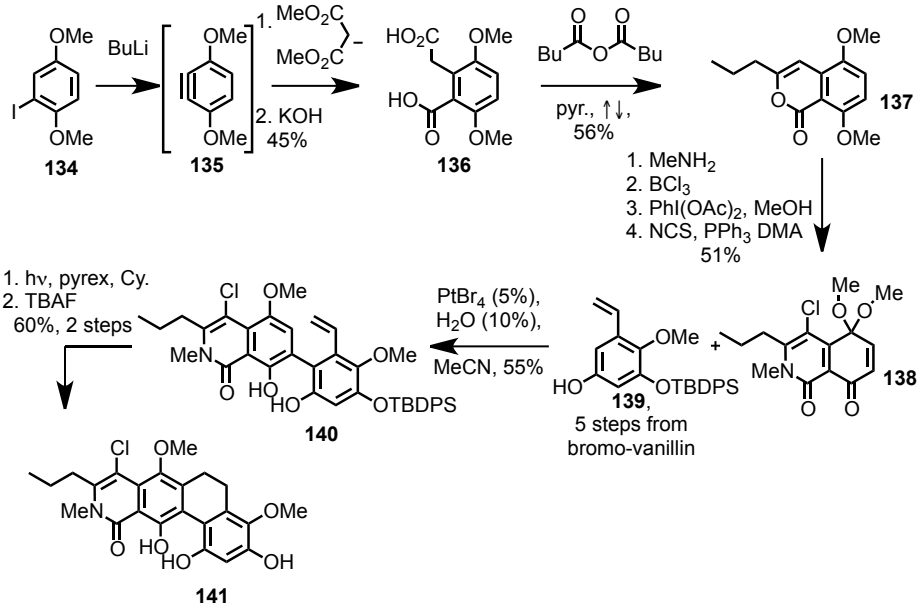
TMC-66



Scheme 1-16: Hosokawa Synthesis of TMC-66

In 2007 Hosokawa and co-workers reported the asymmetric synthesis of TMC-66,[59] an endothelin converting enzyme (ECE) inhibitor discovered in 1999 (Scheme 1-16). They developed a highly convergent synthesis that utilized sequential Sonogashira couplings to bring together two tricyclic fragments. The heterocyclic fragment was prepared from di-triflate **124** via a regioselective Sonogashira reaction and enolate cross coupling in excellent yield. Reaction with D-serine and NaOMe provided the heterocycle. The other half of the molecule was prepared via cycloaddition with quinone **130**; selective triflation then provided the electrophile for the second Sonogashira reaction. After combining the two fragments, phenolic coupling was used to form the final C-C bond of the natural product (**132 → 133**). A Cu^{II}-(*N*-methylimidazole) complex was employed at high temperature (150 °C) to obtain an excellent yield of the desired biaryl in a highly regioselective manner. In this regard, the stability of the molecule under these reaction conditions is noteworthy. Deprotection with BBr_3 provided the natural product in a very efficient 9 steps (LLS).

Kibdelone C



Scheme 1-17: Porco Synthesis of the Isoquinolinone Fragment of Kibdelone C

The Porco group at Boston University published two papers in 2011 on the synthesis of kibdelone C. Their strategy employed a novel Pt-catalyzed arylation reaction to form the tetra-cyclic isoquinolinone fragment and a selective iodo-Michael cyclization to form the F-ring.

To synthesize the isoquinolinone fragment[60] the group first made the parent isocoumarin using a method developed by Kita for the synthesis of homophthalic anhydrides. This method utilizes an aryne intermediate to form the diacaid **136** (Scheme 1-17). Rather than synthesize the anhydride from this compound, the group alkylated **136** with butyric anhydride under conditions that caused both decarboxylation and cyclization to isocoumarin **137**. This isocoumarin could further be functionalized to the *p*-quinone monoketal **138** in four steps. After significant optimization they were able to develop a novel reaction to form the biaryl bond with phenolic styrene **139** that utilized catalysis with Pt^{IV}-aqua complexes. The authors envision activation of the monoketal to take place through one of the two possible intermediates shown in Figure 1-9 leading to either ketal activation (**142**) or dual alkene coordination and ketal activation (**143**). The bulky TBDPS protecting group provides regioselectivity in the addition of phenol **139**.

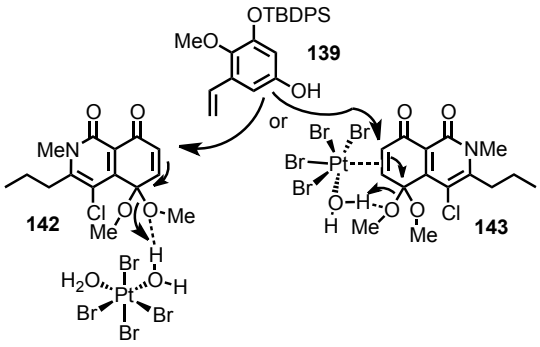


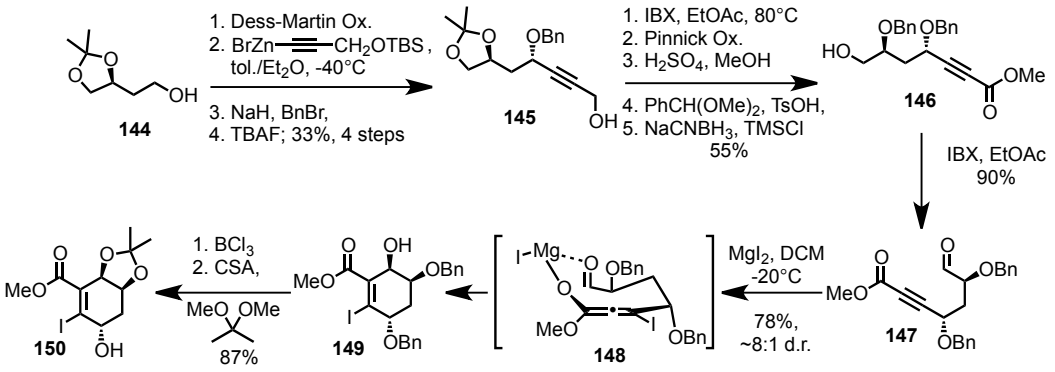
Figure 1-9: Mechanism of Pt-Catalyzed Arylation

The biaryl bond formation was then followed by a photocyclization reaction to form the C ring of the natural product. This two-step sequence represents a formal [4+2] cycloaddition that convergently and regioselectively forms the C ring of the kibdelones. It is noteworthy that photocyclization of 2-vinyl biphenyl such as

140 is much more efficient than cyclization of the related stilbene substrates synthesized by Kelly and others for the Cervinomycins.

Biological evaluation showed this tetracyclic compound to be much less active than the kibdelones.[60] This result reiterates the importance of the xanthone and F ring moieties of these molecules for biological activity as established by the isolation group through the low activity of kibdelone rhamnosides. The Porco group continued their pursuit of these molecules and chose to further functionalize the tetracyclic compound (**141**) via oxy-Michael addition to β-iodoenone **150**.[61]

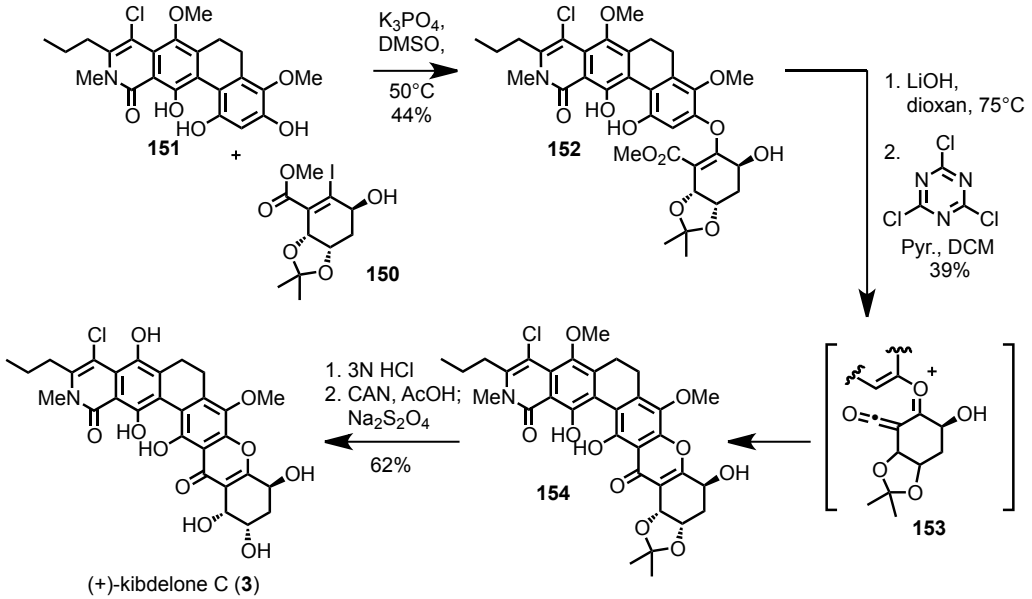
Compound **150** was synthesized from commercially available alcohol **144** (Scheme 1-18) in a 13-step sequence as follows. Oxidation of **144** and selective zinc acetylide addition provided propargylic alcohol **145** after protecting group adjustment. Oxidation to the methyl ester and three additional protecting group manipulations provided primary alcohol **146**, which was further oxidized to yield the substrate for iodo-Michael aldol cyclization. The authors propose this reaction proceeds through transition state **148** to furnish the iodoenone in 8:1 selectivity. The mild conditions used in this cyclization are notable, especially when compared to similar efforts by the Ready Laboratory (see Chapter 2). Two additional protecting group adjustments of **149** were required for optimal yields in the coupling with phenol **139** (Scheme 1-19).



Scheme 1-18: Porco Synthesis of the F-Ring Fragment of Kibdelone C

Oxy-Michael addition of these two fragments (**139** + **150**) required extensive optimization, with all traditional bases failing to provide any product. The

authors attempted to perform a Cu-catalyzed etherification with some success. Through optimization they found that copper was not required for the reaction and that K_3PO_4 in DMSO followed by a careful quench with dilute $KHSO_4$ was optimal. The acid sensitive nature of vinylogous carbonate **152** was problematic because normal reagents used for Friedel-Crafts reaction are acidic. This issue was circumvented through mild acid chloride formation with cyanuric chloride. The authors propose that this acid chloride rearranges to ketene intermediate **153**, which can then do an electrocyclization. This hypothesis is based on the fact that Lewis acids are not required for C-C bond formation. The low yield for this two-step sequence is evidence of the instability of compound **152**. After acetonide only oxidative demethylation of the B ring remained to complete the synthesis. For this purpose, CAN with AcOH as a crucial additive was employed. Under optimized conditions 5:1 selectivity was obtained for the mono-demethylated product, providing kibdelone C after reductive workup. The optical rotation of this compound was identical to the isolation report and co-established the absolute stereochemistry of the natural product.



Scheme 1-19: Porco Synthesis of (+)-Kibdelone C

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Chapter 2 Enantioselective Synthesis of the Kibdelones

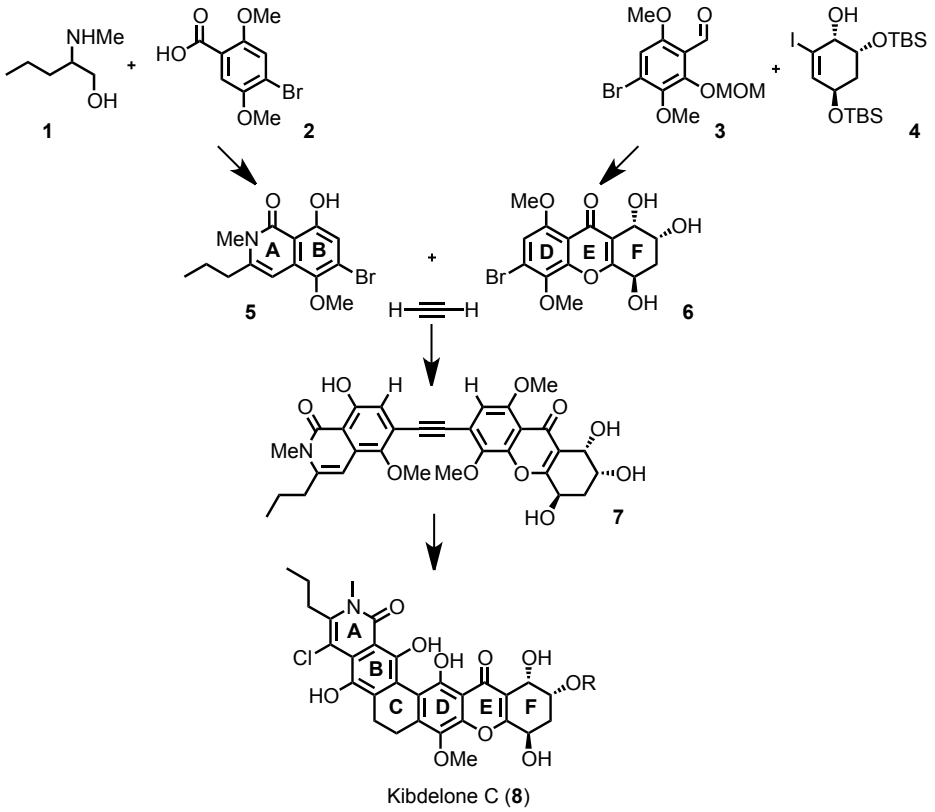
The previous chapter reviewed efforts toward the synthesis of natural products related to the kibdelones and culminated with efforts from the Porco Group for the recent synthesis of kibdelone C. The convergent synthetic strategy outlined below required the development of the synthesis of two heterocyclic fragments representing both the isoquinolinone and xanthone moieties of these molecules. A crucial step in bringing these two fragments together was the forging of a biaryl bond in an intramolecular fashion. This step required substantial optimization and the discovery of novel reaction conditions for successful implementation. To complete the synthesis, substantial trial and error was required to find a sequence of events to allow the isolation of (-)-kibdelone C because of the unstable nature of these compounds. All of these synthetic efforts along with initial biological assay data will be presented in this chapter.

2.1 Ready Lab Strategy for the Kibdelones

Throughout all planning phases the Ready Laboratory has sought a convergent strategy for the synthesis of the kibdelones (Scheme 2-1). The success of this strategy is supported by past efforts in the field on related molecules in which convergent strategies led to the efficient synthesis of poly aromatic structures. Additionally, simple arithmetic dictates higher synthetic efficiencies for linearly short sequences. From a biological standpoint, ease of access to highly functionalized intermediates could also prove advantageous for future studies on the mode of action of these compounds.

To carry out our convergent strategy we planned to split the kibdelones into two heterocyclic fragments representing the AB and DEF rings, **5** and **6** respectively. These fragments would also be made from a pair of simpler molecules. Norvaline-derived amino alcohol **1** and benzoic acid **2** would be coupled and cyclized in a Pomeranz-Fritsch type reaction to form the isoquinolinone of the AB fragment (see 2.2). To synthesize the DEF fragment, several strategies were investigated before

arriving at the convergent route shown in Scheme 2-1. For this convergent strategy the stereogenically rich F-ring (**4**) was synthesized as a separate entity and was coupled with benzaldehyde **3** in preparation for a $HClO_4$-promoted cyclization to form the xanthone ring. This was not the initial strategy; only through the work of several researchers and examination of several routes was success obtained. Throughout these routes the overall goal of convergency was maintained.



Scheme 2-1: Ready Lab Retrosynthetic Strategy for the Kibdelones

The plan to combine the two heterocyclic fragments in such a manner was enabled by the discovery of a dehydrogenative coupling reaction to forge the final C-C of the kibdelones (see Ch. 3). This allowed us to target the biaryl alkyne **7** as the product of sequential Sonogashira reactions. This alkyne could be reduced to give a substrate for the key arylation. Hosokawa's successful synthesis of TMC-66 provided an encouraging precedent for our approach (see 1.4, pg 26); however, the sensitivity of the kibdelone intermediates required quite different chemistry to

accomplish biaryl bond formation. Additionally, as with all well laid plans, the initial idea for biaryl bond formation required significant modification to allow arylation to be successful.

After completing the carbocyclic structure of the kibdelones, chlorination and protecting group modifications would complete the synthesis. At this point it is important to note that this modular strategy lends itself well to the synthesis of other polycyclic xanthone natural products. This was not by accident, as the kibdelones represent the initial foray of an ongoing research program in the Ready Lab. While this was a factor during synthetic development, details of these studies are outside the scope of this dissertation and will be reported elsewhere.

2.2 The Isoquinolinone AB Fragment

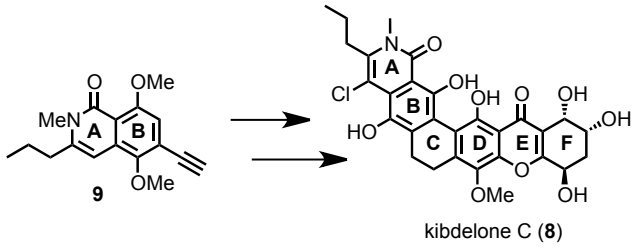
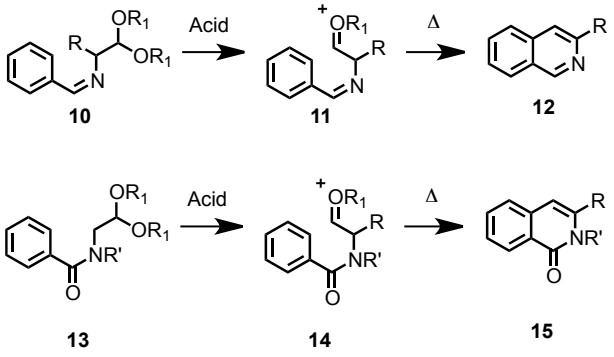


Figure 2-1: AB Fragment of the Kibdelones

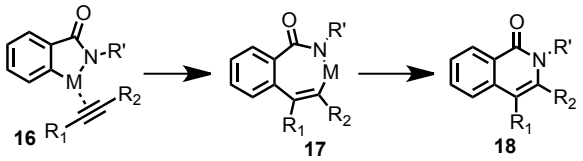
Background



Scheme 2-2: Pomeranz-Fritsch Quinoline and Isoquinolinone Syntheses

Several retrosynthetic disconnections are known in the literature for the synthesis of isoquinolinones (**15**, Scheme 2-2). Ortho-metalation strategies typically

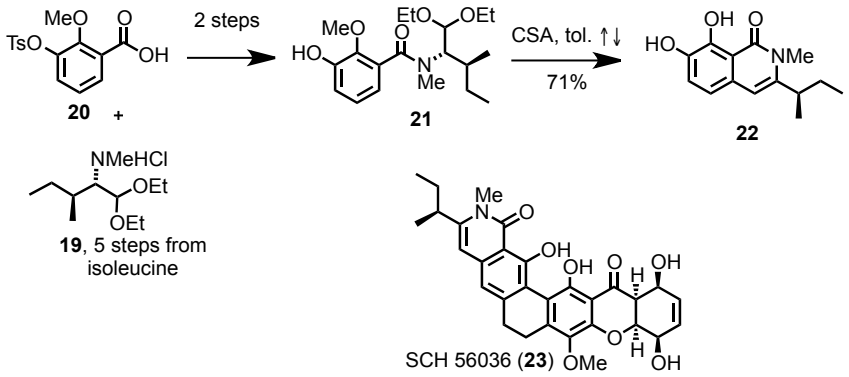
have been used for the synthesis of isoquinolinone-containing natural products (see 1.4). Classical methods for isoquinoline synthesis, such as the Pomeranz-Fritsch reaction, can be applied to isoquinolinones via benzamide starting materials (**13**, Scheme 2-2). In addition to these methods, more recent methodologies to synthesize isoquinolinones have used C-H activation of benzamides with various transition metals followed by insertion of alkynes to form the heterocycle (Scheme 2-3). This method was not considered for the synthesis of the AB fragment of the kibdelones because it was only recently that this type of reaction could be performed in a regioselective manner with terminal alkynes.[1] This type of reaction is related to ongoing research in the Ready Lab that is focused on more efficient syntheses of isoquinolinones from metalated benzamides which will be reported in due course.[2]



Scheme 2-3: Transition Metal Mediated Isoquinolinone Synthesis

The Pomeranz-Fritsch reaction was discovered in 1893[3,4] and has become a versatile method for the synthesis of isoquinolines from benzalaminoacetals (**10**, Scheme 2-2). The reaction utilizes either Lewis or Brønsted acids and sometimes requires fairly harsh conditions.[5] In 2005 the Barrett research group described an approach to the synthesis of the isoquinolinone fragment of the natural product SCH 56036 (**23**, Scheme 2-4).[6] They synthesized the isoleucine acetal **19** in five steps and, after amide formation, performed a Pomeranz-Fritsch cyclization. After screening catalysts for the cyclization reaction they found that camphorsulfonic acid at elevated temperatures provided the best yields. The high temperature of the reaction also caused *O*-demethylation, but it is unclear if this demethylation is a requirement for activation of the aromatic ring prior to substitution. High reaction temperatures were also likely required to overcome the deactivating nature of the electron withdrawing carbonyl group found in **21**. Indeed, this example from the Barrett Lab is the only example of this type of reaction in the literature prior to

efforts from the Ready Lab indicating the difficulty of this variant of the Pomeranz-Fritsch reaction.

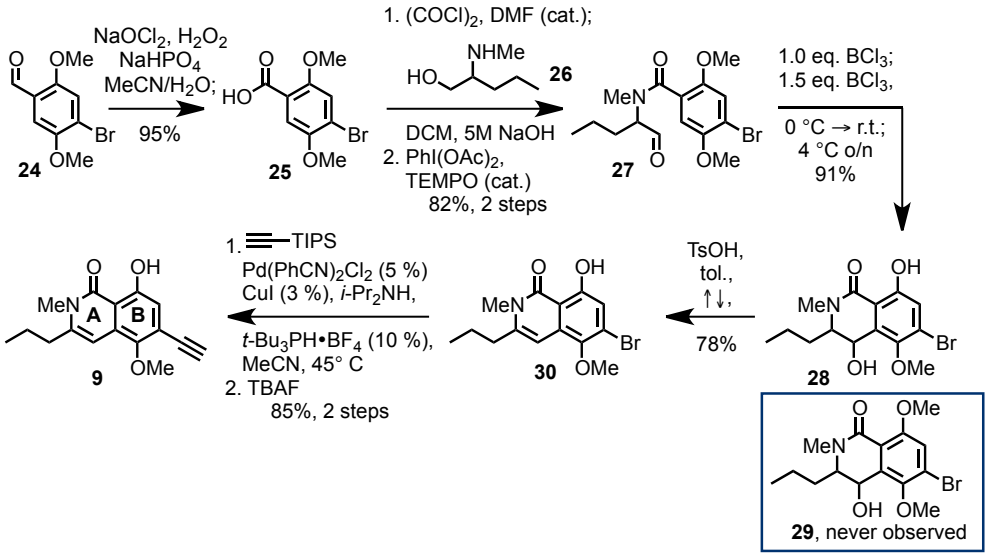


Scheme 2-4: Barrett Approach to the Isoquinolinone of SCH 56036

Synthesis of the kibdelone Isoquinolinone

The Pomeranz-Fritsch approach to the isoquinolinone of the kibdelones is attractive because of the ease of synthesis of the precursors and the relatively short synthetic route that such a disconnection provides. Amino alcohol **26** (Scheme 2-5) is a known compound that can be synthesized in two steps from Norvaline.[7] Benzoic acid **25** is also a known compound that has been synthesized in the literature by mono-magnesiation of the corresponding dibromide and trapping with CO_2.[8] We chose to synthesize **25** by Pinnick oxidation of the known benzaldehyde (**24**)[9] because of higher yields and ease of synthesis on larger scale. **24** is easily made by bromination of commercially available 2,5-dimethoxybenzaldehyde. These two compounds can be coupled using anhydrous conditions or Schotten-Baumann biphasic conditions in similar yield; however, the Schotten-Baumann reaction time is much shorter. With the amide in hand, TEMPO oxidation provided a substrate for cyclization (**27**). After screening many (>15) catalysts it was found that treatment of **27** with excess BCl_3 and heating gave a mixture of the benzylic alcohol (**28**) and isoquinolinone (**30**) products. Remarkably, only boron Lewis acids were found to promote the cyclization and concomitant demethylation was always observed. The alcohol **28** could be converted to the isoquinolinone by treatment with *p*-TsOH in

refluxing toluene to give yields of 50-55% for the isoquinolinone. Initial efforts to optimize this reaction further were unsuccessful.



Scheme 2-5: Synthesis of the AB Isoquinolinone Fragment of the Kibdelones

The cyclization substrate **27** exists as a mixture of 3 major compounds by NMR (fig). The working hypothesis was that this compound existed as a mixture of diastereoisomers that resulted from amide bond rotomers and atropisomers that did not interconvert on the NMR timescale. All efforts to thermally equilibrate these species in the NMR were unsuccessful. Whether or not the efficiency of the cyclization reaction was effected by the apparent inability of these compounds to interconvert was not known until a talented member of the Ready Lab, Dr. Chao Wang, began working on this problem.

Dr. Wang performed a cyclization reaction in an NMR tube and found that after the addition of 1.0 equivalent of BCl3 the complex mixture of compounds converted to a single compound (B, Figure 2-2). When additional BCl_3 is added demethylation occurred and a mixture of cyclized product appeared. The order of these events is unknown, but it is thought that demethylation is required for cyclization; no cyclized product with the O-Me intact (**29**) has ever been isolated. The identity of the compound formed upon initial treatment with BCl_3 is thought be

either chlorohydrin **31** or oxazolidinium acetal **32** (Figure 2-2) based on ^{1}H NMR data and the fact that the intermediate converts back to a mixture of aldehydes upon quenching. Presumably, addition of another equivalent of BCl_3 causes demethylation and disrupts either the boron chelate of **31** or the cyclic acetal of **32** so that cyclization can occur. This process can be performed in a flask by adding 1.0 equivalent of BCl_3, stirring for 30 minutes, adding an additional 1.5 equivalents of the Lewis acid at 0 °C, and then warming to room temperature to provided high yields (90%) of benzylic alcohol **28** (Scheme 2-5). Dehydration of **28** with TsOH as before then furnished the desired isoquinolinone (**29**). Efficient alkynylation of **29** was then performed using the Sonogashira procedure developed by Buchwald and Fu[10] with substitution of the air stable *t*-Bu_3P-HBF_4 salt for *t*-Bu_3P.[11] Desilylation with TBAF revealed the terminal alkyne and provided the AB fragment (**9**) in 6 steps from easily obtained starting materials.

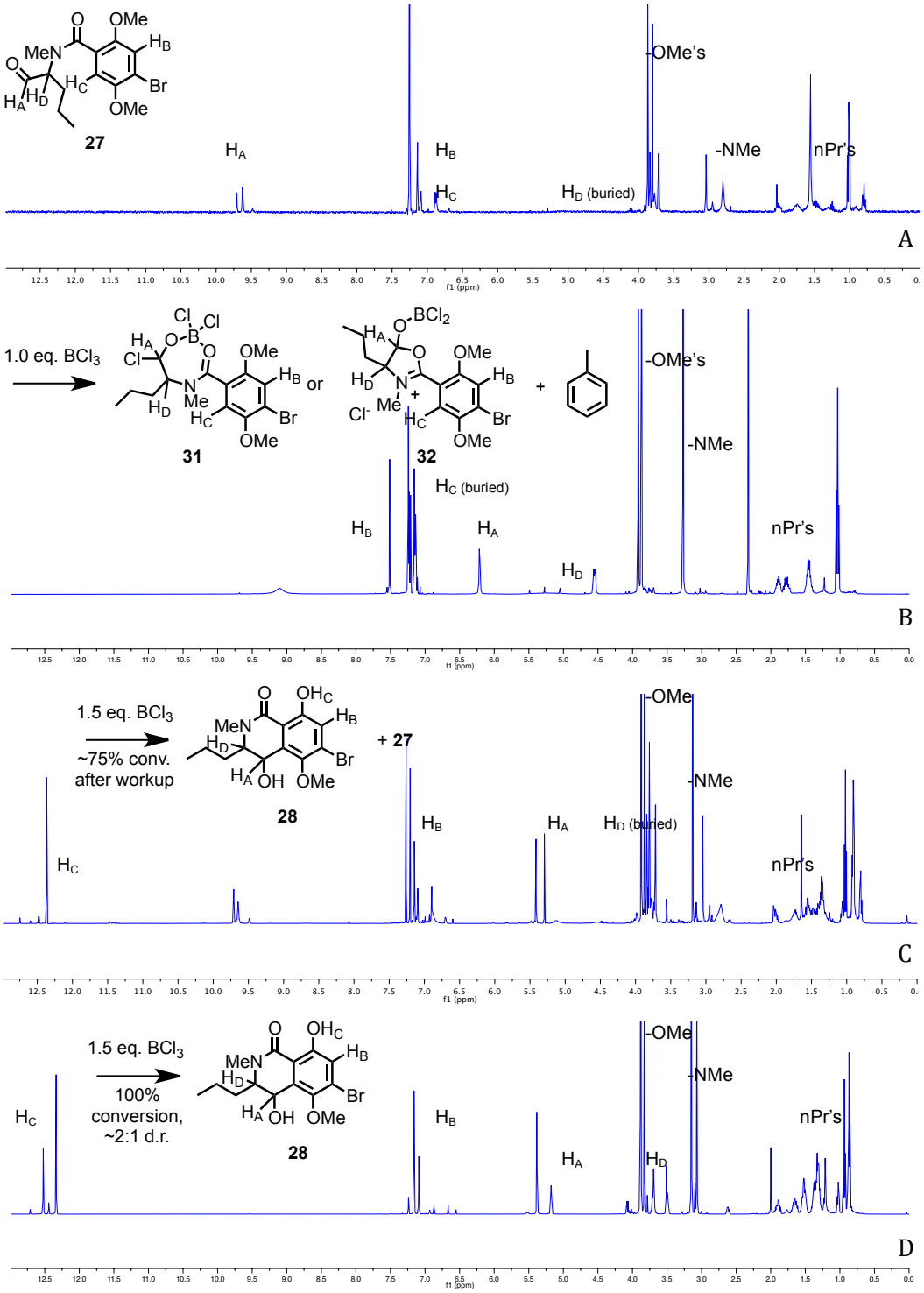


Figure 2-2: NMR Study of BCl_3 Cyclization

2.3 The Tetrahydroxanthone DEF Fragment

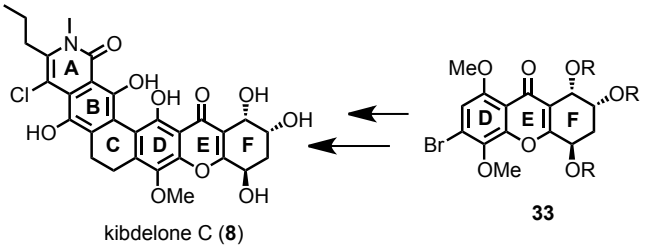
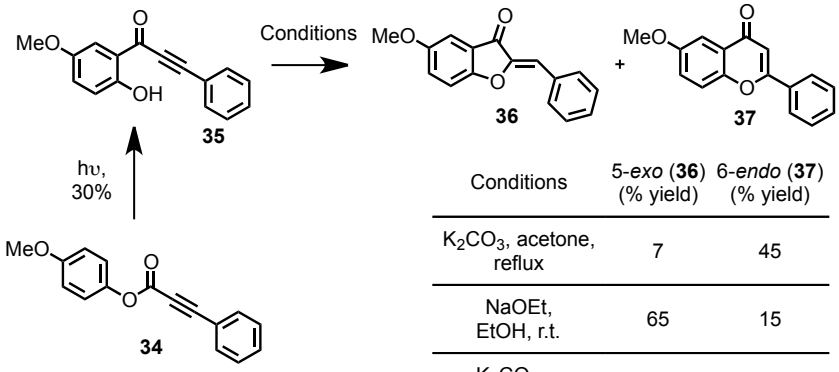


Figure 2-3: The DEF Fragment of the Kibdelones

Background

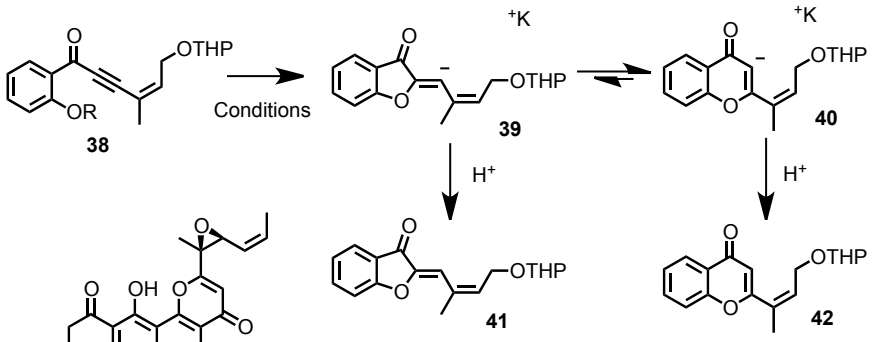


Conditions	5-*exo* (**36**) (% yield)	6-*endo* (**37**) (% yield)
K_2CO_3, acetone, reflux	7	45
NaOEt, EtOH, r.t.	65	15
K_2CO_3, EtOH, r.t.	54	11

Scheme 2-6: Study of 5-*exo* Vs. 6-*endo* Cyclization to Form Chromones (28)

The development of modern methods for the synthesis of tetrahydroxanthones has been closely associated with the total synthesis of natural products. Chromones (**37**, Scheme 2-6) have a pyranone ring in common with tetrahydroxanthones and can be accessed by the base promoted intramolecular addition of phenols to ynones. Miranda *et al.* synthesized phenolic ynones (**35**) via photo-Fries rearrangement of the corresponding esters (Scheme 2-6). They found that 6-*endo* cyclization to give the chromone (**37**) could be favored with moderate selectivity by choice of base.[12] The Saito Lab utilized this mode of cyclization to target natural products like kapurimycin and pluramycin (Scheme 2-7). They optimized conditions for the 6-*endo*, chromone product through treatment of the silyl-protected ynone **38** with KF and 18-crown-6 in anhydrous DMF. These

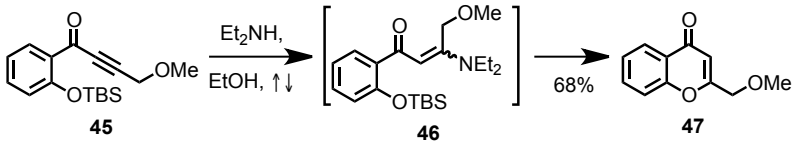
conditions led to exclusive 6-membered ring formation.[13] They hypothesized that the anion derived from 6-*endo* cyclization (**40**) was more stable than the 5-*exo* intermediate, resulting in the selectivity observed.[14] To investigate this hypothesis aliquots were taken from a reaction performed at -20 °C with **38** (R = TBS) in anhydrous DMF, with KF, and 18-crown-6 at different time points, quenched, and analyzed by ^{1}H NMR. Initially a mixture of **38** (R = H):**41**:**42** of 2:5:3 was obtained but as the reaction proceeded over the course of an hour this changed to a 0:2:8 ratio of **38** (R = H):**41**:**42**. Upon warming the reaction to 0 °C and quenching only **42** was isolated. Furthermore, **41** or **42** were recovered unchanged after resubmission to the reaction conditions.



R	Conditions	5-*exo* (**41**) (% yield)	6-*endo* (**42**) (% yield)
H	K_2CO_3, EtOH, reflux	57	16
TBS	KF, 18-C-6, DMF, r.t.	0	97
TBS	KF, 18-C-6, DMF/MeOH, r.t.	66	13
H	KF, 18-C-6, DMF, r.t.	9	83

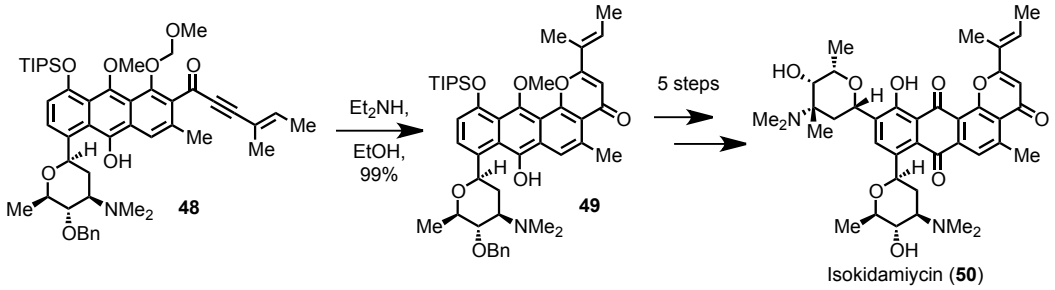
Scheme 2-7: Saito Optimization of Chromone Formation

In the context of developing combinatorial libraries, Brueggemeier and coworkers found that the siloxy ynone substrates utilized by Saito could be cyclized with secondary amines in ethanol (Scheme 2-8).[15] This reaction is thought to proceed via enaminoketone intermediate **46**.



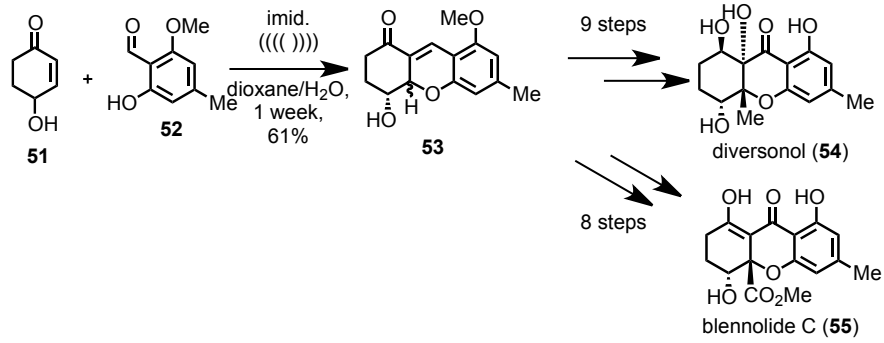
Scheme 2-8: Amine Promoted Chromone Synthesis

The Martin group successfully utilized these conditions (Et_2NH, EtOH) for late stage cyclization in a recent synthesis of isokidamycin (Scheme 2-9).[16] Ynone **48** was synthesized via acetylide addition after failed Pd-catalyzed carbonylative coupling.[17]



Scheme 2-9: Martin Synthesis of Isokidamycin

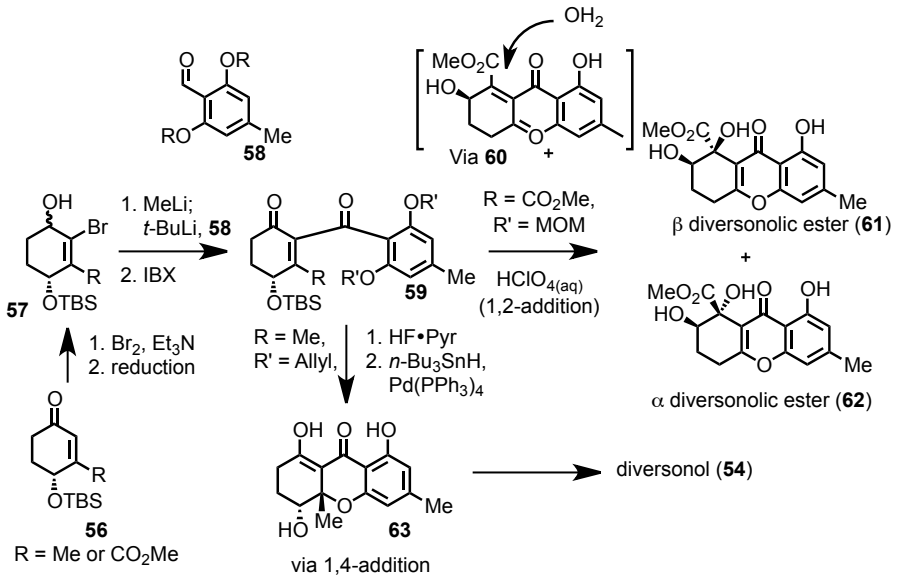
In 2005 the Bräse Laboratory developed a convergent synthesis of tetrahydroxanthenones (**53**, Scheme 2-10) from salicylaldehydes and enones. The tetrahydroxanthenone products were then applied to the synthesis of diversonol and blennolide C (Scheme 2-10) after oxidation and several functional group manipulations.[18,19]



Scheme 2-10: Bräse Synthesis of Diversonol and Blennolide C

The Nicolaou group subsequently reported syntheses of diversonol and blennolide C in 2008 that utilized novel modes of xanthone formation from

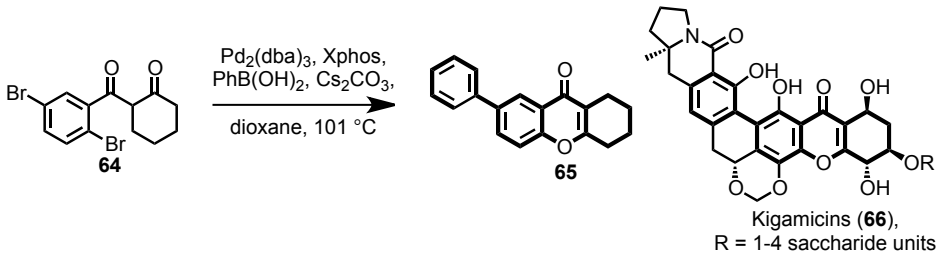
enedione intermediates (**59**, Scheme 2-11).[20] They prepared enediones of type **59** via nucleophilic addition of a cyclohexene dianion to a protected salicylaldehyde followed by oxidation. Treatment of the MOM-protected enedione with acid cleaved the MOM-ether, liberating the phenol and inducing xanthone formation (**61**, **62**) via proposed intermediate **60**. Using a similar enedione intermediate with allyl-protected phenols they were able to effect xanthone formation via 1,4-addition of the phenol during allyl deprotection to provide **63** en route to diversonol. This mode of xanthone formation required deprotection of the allylic alcohol of the cyclohexenone (**59**) prior to cyclization. Porco's synthesis of kibdelone C required a similar deprotection prior to intermolecular oxy-Michael addition (Ch. 1.4).



Scheme 2-11: Nicolaou Synthesis of Diversonol

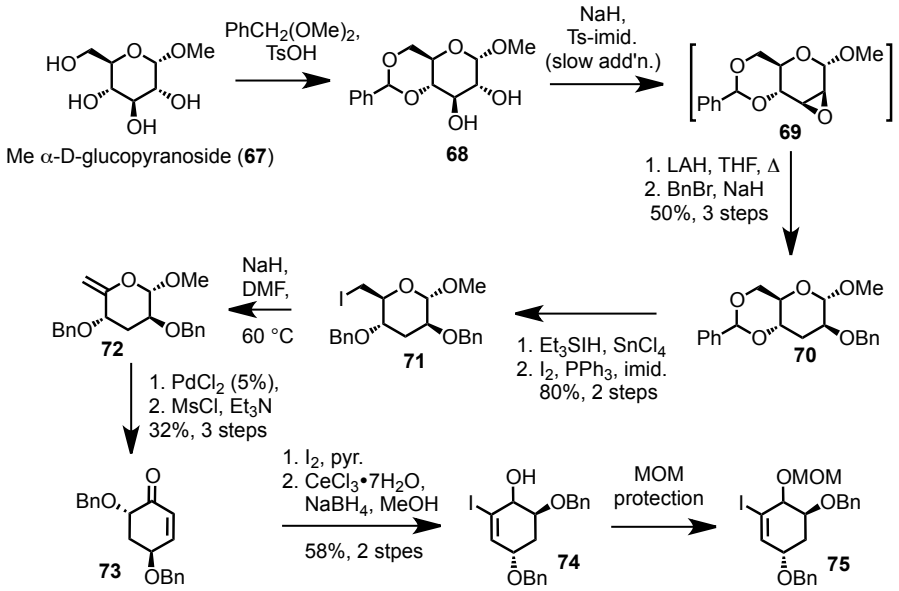
More recently the Shipman group at the University of Warwick reported a method for tetrahydroxanthone synthesis that they applied to a simplified derivative of the kigamicins.[21] This method utilizes the palladium-catalyzed intramolecular cyclization of diones (**64**, Scheme 2-12) with aryl halides to form the aryl C-O bond of the xanthone. When dihalides were used in this reaction, a second cross coupling could be performed in-situ. Using this method they were able to

rapidly access simplified xanthones that maintained activity in "anti-austerity" cytotoxicity assays that were used to identify the kigamicins (Ch. 1.4).



Scheme 2-12: Shipman Method of Tetrahydroxanthone Formation

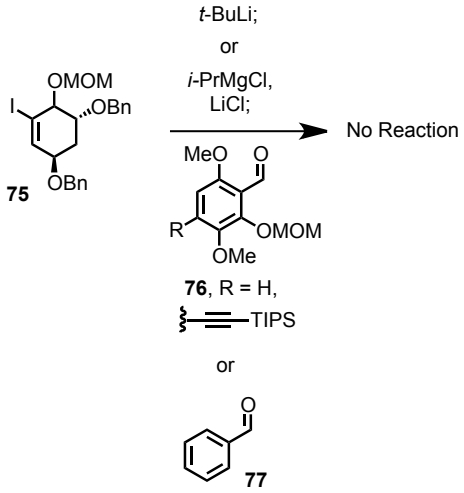
Prior Work Toward the DEF Fragment From the Ready Laboratory



Scheme 2-13: Carbohydrate Based Route to an F-ring Precursor of the Kibdelones

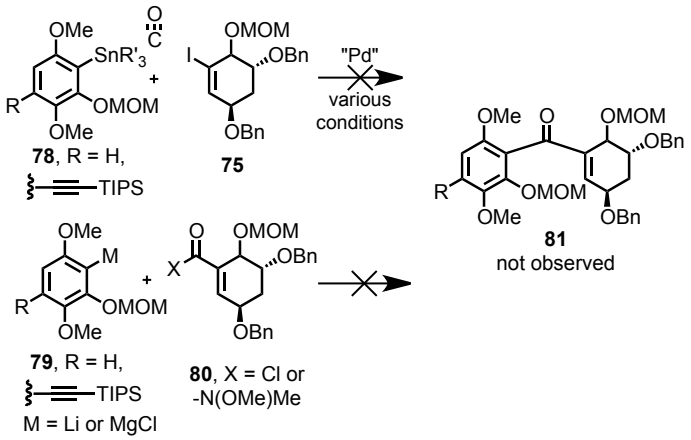
Studies toward the synthesis of the kibdelones began in the Ready Lab in the fall of 2006 and immediately targeted an efficient way to synthesize the tetrahydroxanthone fragment of these molecules (**33**). Using modified literature procedures Dr. Jianwei Bian was able to develop a 13-step route from *D*-glucose for an appropriately oxygenated F-ring precursor of the kibdelones (Scheme 2-13). This route deoxygenated and further functionalized the carbohydrate in lengthy fashion but required minimal chromatography (four columns) and provided the allylic

alcohol **74** in 7% yield. After MOM protection, Dr. Bian attempted to functionalize **75** further. Nucleophilic addition of **75** was attempted by treatment with *t*-BuLi or *i*-PrMgCl and LiCl to effect metal-halogen exchange. The organometallics derived from **75** were then treated with benzaldehydes **76** or without success (Scheme 2-14). Attempts to trap these organometallics with even simple benzaldehyde also met with failure. This led to the conclusion that nucleophiles derived from **75** were not reactive due to steric issues.



Scheme 2-14: Failed Nucleophilic Additions

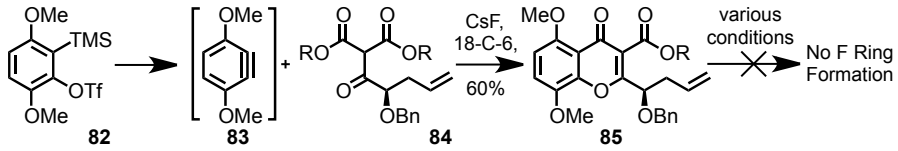
All efforts to utilize aryl organometallic reagents to switch the polarity of coupling of **75** with **76** were also unsuccessful. **75** could be acylated but the addition of organometallics (**79**) or direct carbonylative coupling of **75** with arylstannanes (**78**) never provided the desired product (Scheme 2-15).



Scheme 2-15: Unsuccessful Aryl Metal Reactions

The inability to form a C-C bond in both types of coupling reactions was the result of unproductive combinations of excessive steric hindrance and electronic deactivation of one or both coupling partners. This collection of negative results led to the conclusion that synthesis of the DEF fragment by coupling of arenes and cyclohexene fragments, via nucleophilic or electrophilic means, would not be possible.

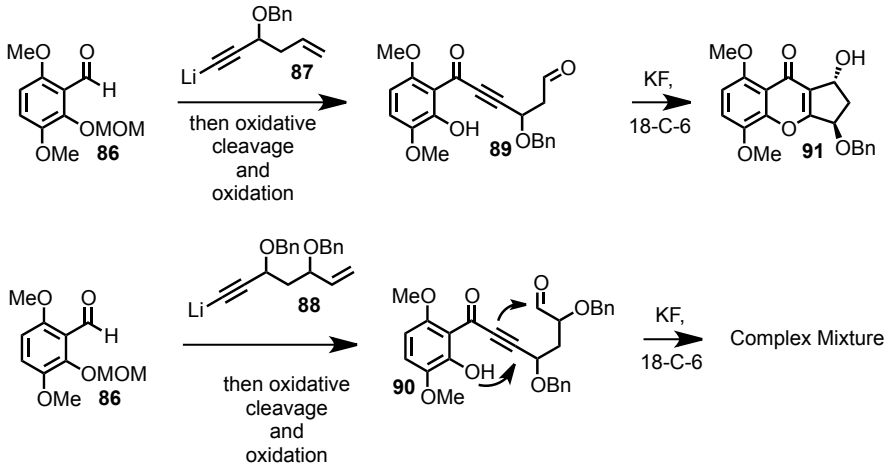
After reconsidering the strategy toward this fragment Dr. Bian investigated alternative methods of xanthone formation. He discovered a novel aryne reaction that utilized β-ketomalonates **84** to form xanthones in one step (Scheme 2-16). While this reactivity was interesting, these products could not be transformed into the desired DEF fragment.



Scheme 2-16: Xanthone Formation From Aryne Intermediates

Looking to overcome the steric and electronic requirements imposed by benzaldehydes such as **76**, Dr. Bian tried to add smaller lithium acetylide nucleophiles (**87** or **88**, Scheme 2-17). This was successful and he was able to make compounds such as **89** after oxidative processing. These products could be treated

with KF and 18-crown-6, in analogy to the method developed by Saito, to effect xanthone cyclization. With aldehyde **89** an additional intramolecular cyclization occurred to form the five membered ring **91** (Scheme 2-17). Unfortunately, when these conditions were applied to substrate **90**, no 6-membered ring formation occurred, and complex mixtures were obtained. At this point Dr. Bian left the Ready Lab and was unable to investigate this reaction further; however, his studies provided excellent reconnaissance for finding a solution for the synthesis of the DEF fragment of the kibdelones.

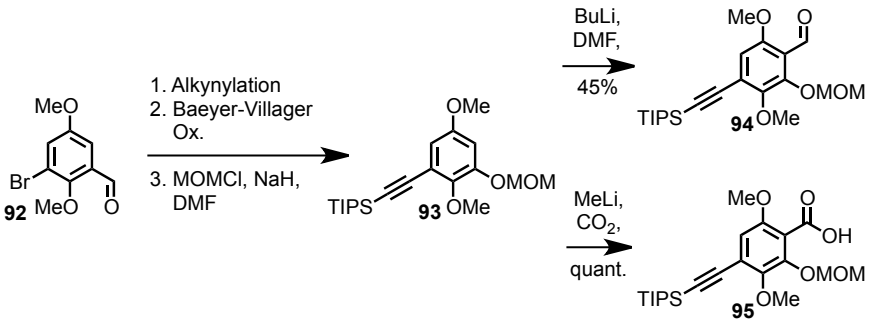


Scheme 2-17: Initial Cascade Cyclization Results

Investigation of Cascade Cyclization for DEF Fragment Formation

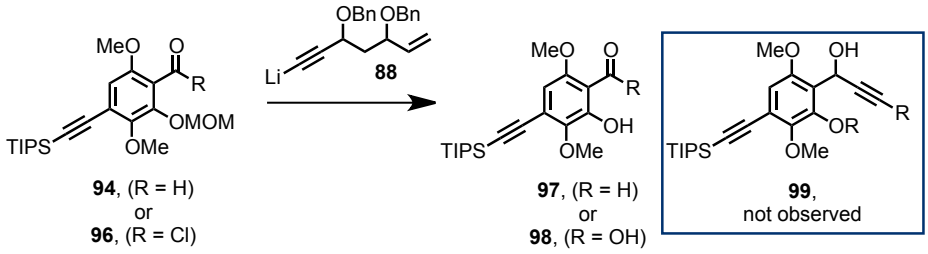
The studies initiated by Jianwei Bian were continued in an attempt to find conditions that would provide the desired 6-membered ring product via cascade cyclization (as in Scheme 2-17). The benzaldehyde (**86**) used in the previous acetylide additions did not contain a handle for later-stage coupling to the AB fragment. Therefore, more functionalized benzaldehydes were prepared. Bromo-benzaldehyde **92** was alkynylated and treated with *m*CPBA to convert the aldehyde into a phenol (Scheme 2-18).[22] This phenol was then protected with an appropriate directing group for ortho-metalation. Lithiation of compound **93** was efficient, as shown by the high yield of carboxylated product **95**, but trapping with DMF to give

benzaldehyde **94** was much lower yielding, indicating the sterically hindered nature of **93**.



Scheme 2-18: Synthesis of Alkynylated D-ring Precursors

Unfortunately, all efforts to add acetylides to benzaldehyde **94** or the acid chloride **96** resulted in recovery of starting materials accompanied by varying amounts of the free phenol **97** or **98** (Scheme 2-19).



Scheme 2-19: Acetylide Addition to Alkynylated Electrophiles

In an attempt to create a more active electrophile for acetylide addition, substantial effort was devoted to formylation of bromophenol **100** (Scheme 2-20) or derivatives thereof. $SnCl_4$ catalyzed formylation[23] of the phenol was moderately successful, but the reaction was found to be difficult to repeat, and low mass balances were often obtained. The reaction appeared fairly clean by crude NMR (Figure 2-4), and after significant attempts at optimization it was concluded that material was polymerizing, most likely via the mechanism shown in Scheme 2-20.

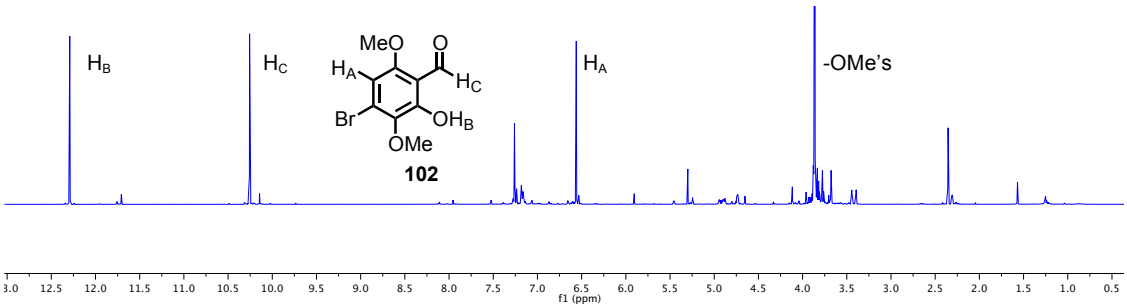
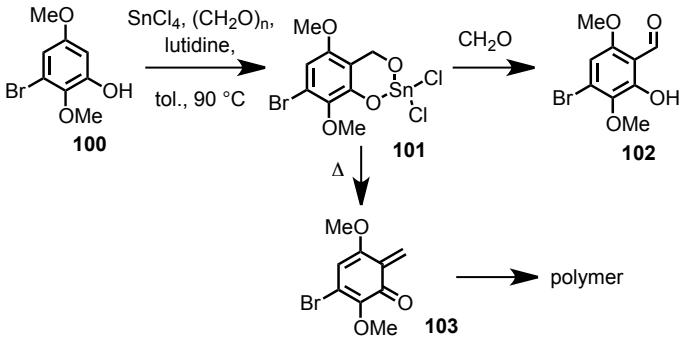
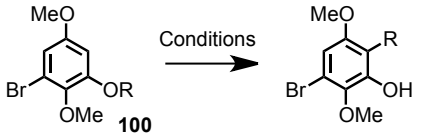


Figure 2-4: Crude ^{1}H NMR of $SnCl_4$ Catalyzed Formylation of 100



Scheme 2-20: Polymerization Pathway in $SnCl_4$ Catalyzed Formylation



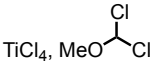
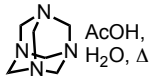
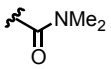
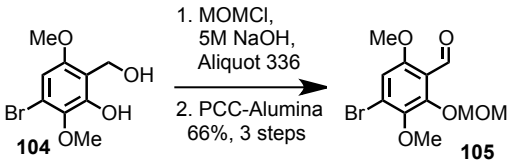
Entry	R	Conditions	Result
1	H	0.5-1.2 eq. $SnCl_4$, $(CH_2O)_n$, lutidine, tol., 90 °C - 165 °C, (μW)	20-55% yield
2	H		2:1 wrong regioisomer
3	H		40% yield
4	MOM	LiTMP; DMF or CO_2	Decomp.
5		LiTMP	N.R.
6	H	Et_2AlCl, $(CH_2O)_n$, 0 °C	91% yield of **104**

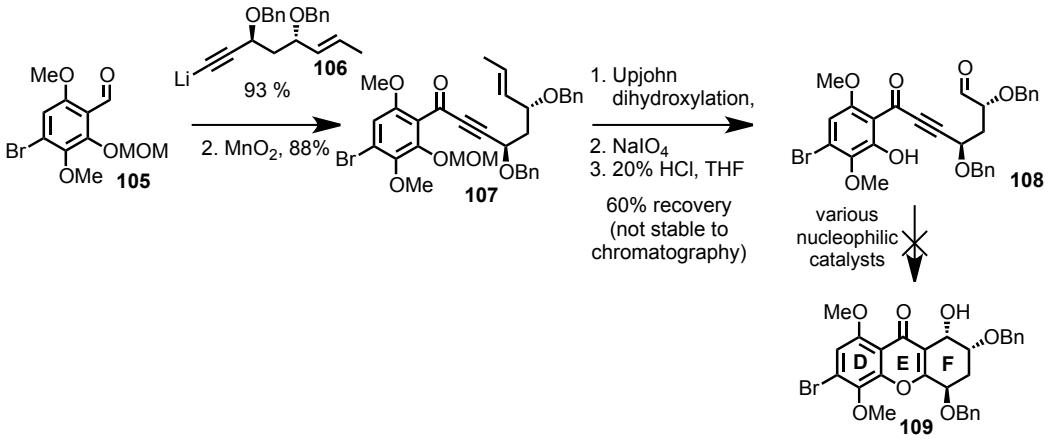
Table 2-1: Formylation Screen

In order to prevent polymerization other methods of formylation were screened that were either milder or did not have benzylic alcohol **104** as an intermediate. Lithiation with alkyl-lithium reagents was not possible because of concerns over lithium-halogen exchange; however, lithium amides were investigated with MOM and carbamate directing groups without any success (Table 2-1, entries 4 and 5). Other methods either suffered from low regioselectivity or yield. Finally, it was found that at lower temperatures, a method for the synthesis of benzylic alcohols worked well (entry 6, Table 2-1).[24] Selective functionalization of the primary alcohol of **104** could be achieved via oxidation with MnO_2, but yields were again low because of mass recovery problems associated with the free phenol. Selective protection of the free phenol was accomplished using Kelly's phase transfer method that was utilized for selective MOM protection in the

synthesis of cervinomycin. Subsequent oxidation with PCC on alumina provided benzaldehyde **105** in excellent yield over 3 steps (Scheme 2-21).

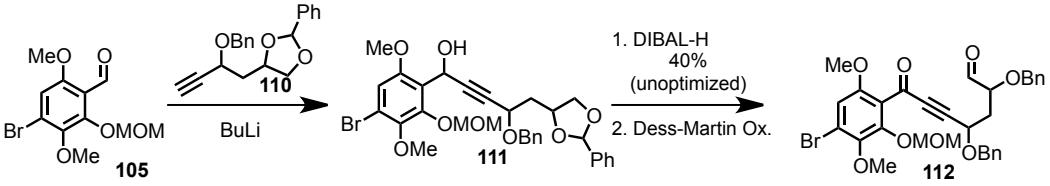


Scheme 2-21: Synthesis of D-Ring Benzaldehyde



Scheme 2-22: Synthesis of Cascade Cyclization Substrates

Benzaldehyde **105** performed much better in acetylide additions, and the corresponding ynones **107** could be obtained in good yield after oxidation (Scheme 2-22). Unfortunately, transformation of the olefin in **107** via oxidative cleavage proved difficult because of instability of the aldehyde product (**108**). Moreover, crude samples of this aldehyde never gave any cyclized products upon treatment with nucleophilic catalysts.

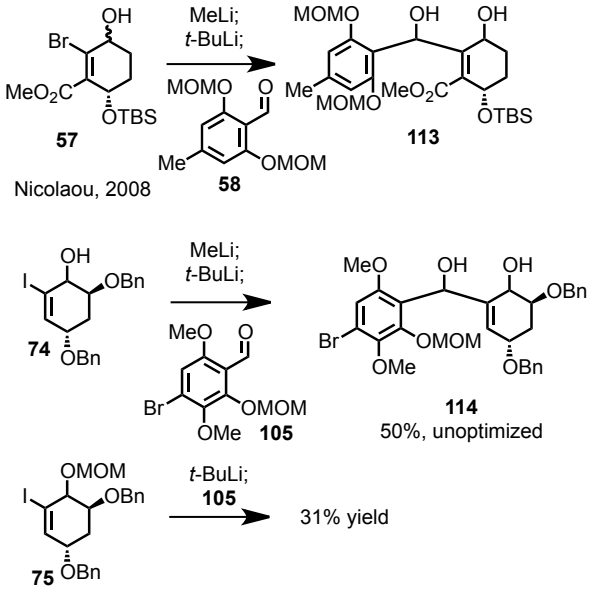


Scheme 2-23: Alternative Cascade Cyclization Substrate Synthesis

To try to overcome the instability of compound **108**, alcohol **111** (Scheme 2-23) was prepared. It was hoped that benzylidene acetal of **111** could be converted

into an alcohol and oxidized in a manner that would provide cleaner material, preventing the need for chromatography, and circumventing the problematic oxidative cleavage.

Before this substrate could be fully assessed in cascade cyclization the Nicolaou group reported their method of xanthone synthesis for diversonol and related natural products (see Background, this section). Key to their synthesis was the ability to add the dianions of cyclohexene derivatives **57** (Scheme 2-24). A similar dianion was accessed by deprotonating **74** with MeLi and adding *t*-BuLi to effect lithium-halogen exchange. Addition of benzaldehyde **105**, gave rise to the benzylic alcohol **114** in moderate yield in the first attempt. The electronics of the benzaldehyde are crucial for this transformation as addition also occurs, albeit in lower yield, with the bulkier MOM protected derivative **75**. This substrate had failed to provide any product with un-brominated benzaldehydes (Scheme 2-14). Successful reaction between **74** and **105** relies on the decreased size of the dianion of **74** and the activated nature of electrophile, **105** relative to the un-brominated benzaldehydes (**76**) tested previously.



Scheme 2-24: Dianion Addition

This result provided a route with a high probability of forming the desired DEF fragment and was pursued with urgency. Immediately two obstacles were apparent: a more efficient synthesis of a suitable F-ring nucleophile was needed and a suitable cyclization to form the xanthone had to be developed.

Dihalocyclopropanation for Synthesis of the F-Ring Precursor

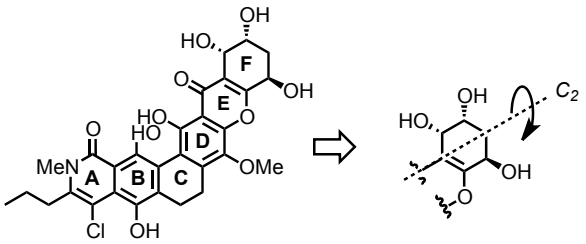
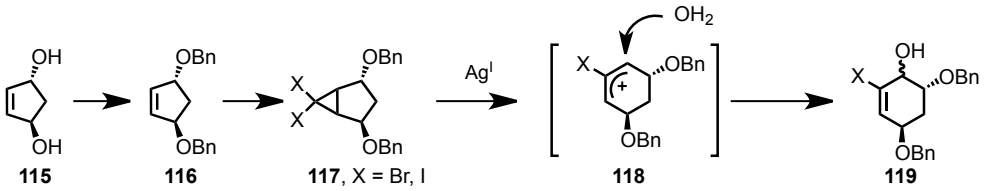


Figure 2-5: Latent C_2 Symmetry in the kibdelones

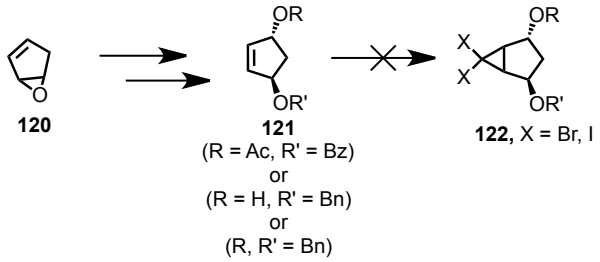
An efficient synthesis of the DEF fragment required facile access to a suitably functionalized F-ring precursor. While considering approaches to the stereogenically rich cyclohexene, it became apparent that an element of latent C_2 symmetry was present in this portion of the kibdelones (Figure 2-5). The construction of complex molecules is often aided at both the planning and execution phases by exploitation of elements of symmetry; therefore, routes that utilize this property were developed.

Dibromocyclopropanes such as **117** (Scheme 2-25) are known to undergo ring opening upon treatment with silver salts, and the allyl-cation formed can then be trapped with nucleophiles.[25] In aqueous reaction mixtures, water acts as the nucleophile, and ring expanded allylic alcohol products (**119**) are formed. Application of this type of reaction to synthesize the F-ring precursor of the kibdelones was advantageous for several reasons. The desired diol starting material (**115**, Scheme 2-25) has been used as a chiral component in natural product synthesis. Additionally, the planned sequence would encompass only 3 steps from diol **115**.

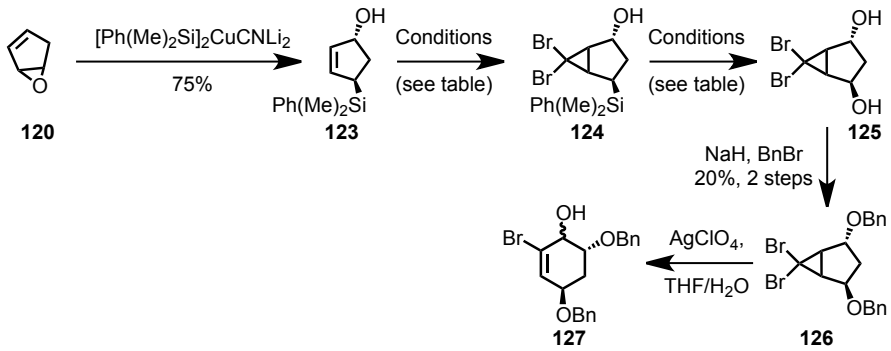


Scheme 2-25: Dibromocyclopropanation Strategy for the F-Ring Fragment

In racemic form, diol **115** can be made from cyclopentadiene epoxide (**120**) in two steps.[26] This efficient synthesis allowed the quick and unfortunate determination that this diol does not undergo dihalocyclopropanation, even with various permutations of protecting groups and reaction conditions.



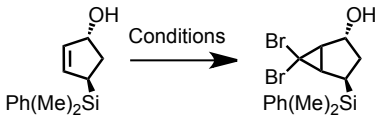
Scheme 2-26: Attempted Dihalocyclopropanation of Diol 121



Scheme 2-27: Dibromocyclopropanation and Subsequent Ring Opening

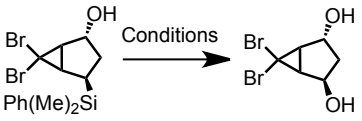
Allylic silanes were targeted as cyclopropanation substrates to increase the electron density of the cyclopentene and improve the reactivity with the electrophilic dihalocarbene.[25] Several methods exist for the synthesis of allylsilanes, but it was envisioned that the most convenient methods for this application would be silyl cuprate reagents such as "[Ph(Me)$_2$Si]$_2$CuCNLi$_2$." Catalytic[27] and

stoichiometric[28] addition of silyl copper reagents to cyclopentadiene epoxide are known in the literature. The method shown in Scheme 2-27 utilizes a preformed silyl cuprate and gave the highest yield for the allylic silane product **123**. After screening multiple dibromocyclopropanation conditions with compound **123**, it was found that phase transfer conditions gave the highest yield (Table 2-2, entry 2). Reaction times were long, and slow addition of base was required to prevent carbene decomposition. Even with this precaution the yield for this reaction was difficult to optimize. Unfortunately, the subsequent Fleming-Tamao oxidation was also difficult to optimize (Table 2-3), presumably because of the sensitive nature of the dibromocyclopropane functionality. Methods that first formed a fluorosilicate followed by treatment with oxidant were found to be the most productive (entries 4 and 5,)



Entry	Conditions	Result
1	50% NaOH, $CHBr_3$, TEBACl	15%
2	50% NaOH, Benzene, $CHBr_3$, TEBACl	34%
3	KOtBu, $CHBr_3$,	N.R.
4	MeLi or tBuMgCl then CBr_4, tBuMgCl	Low conversion, messy
5	Et_2Zn, CCl_4	Decomp.

Table 2-2: Dibromocyclopropanation

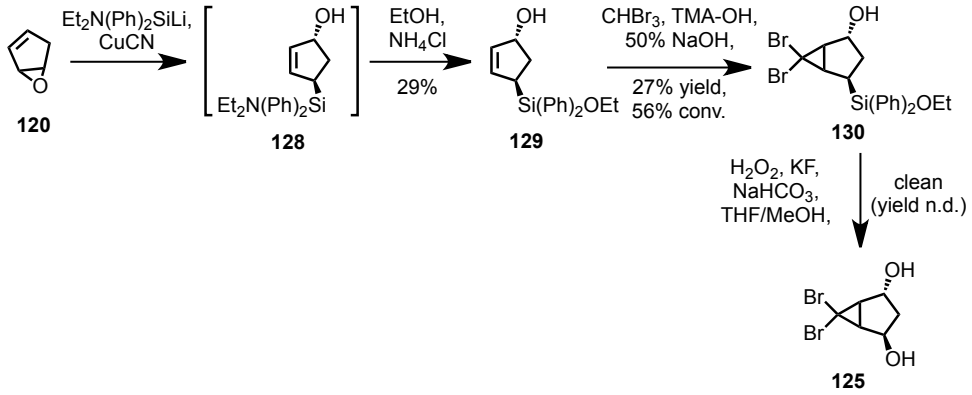


Entry	Conditions	Result
1	$Hg(OAc)_2$ or $Hg(TFA)_2$, AcOOH	messy
2	KBr or Br_2, AcOOH	"
3	Birch reduction, then TBAF, H_2O_2	"
4	HBF_4•OEt_2;KF, H_2O_2, $NaHCO_3$	~20% yield
5	BF_3•$(AcOH)_2$; KF, H_2O_2, $NaHCO_3$	23% yield
6	tBuOOH, KH, TBAF, 60 °C	decomp.

Table 2-3: Fleming-Tamao Oxidation

To try to overcome this incompatibility of the dibromocyclopropane substrate with the conditions for Flemming-Tamao oxidation, focus was shifted to allyl silanes that would be easier to oxidize. In the early 1990's Tamao and coworkers wanted to develop more synthetically useful silyl anions.[29] They were able to use aminosilyl anions in reactions typically performed with trialkyl silyl anions and showed that the siloxane products could be easily oxidized under mild conditions. The siloxanes produced by aminosilyl anion addition (such as **128**, Scheme 2-28) were much less stable than

the corresponding silanes, and it was difficult to obtain a good yield for allylic epoxide opening. This effectively traded the low yielding Flemming-Tamao oxidation for a low yielding synthesis of the allylic siloxane, providing negligible improvements in overall efficiency for the route.



Scheme 2-28: "Functional" Silyl Anion Approach

Shi Epoxidation for Synthesis of the F-Ring Precursor

The latent C_2 symmetry present in the F-ring of the kibdelones can also be exploited in cyclohexane starting materials and synthetic sequences that initiated with a six-member ring were sought. One could imagine that oxidation of cyclohexanone or cyclohexenone derivatives could lead to the desired products. During initial investigations in this regard a report appeared in the literature from the laboratory of Andrew Myers at Harvard University. They reported methodology that utilized the Shi epoxidation to synthesize differentially protected *trans*-diols (Scheme 2-29).[30]

The Shi epoxidation was reported in stoichiometric form in 1996 and the catalytic variant has become a highly useful synthetic procedure for the asymmetric epoxidation of olefins. While developing an organocatalytic method for epoxidation of olefins, Shi and coworkers found that the dioxirane of fructose-derived ketone **131** (Figure 2-6) provided high enantioselectivity in the epoxidation of *trans*-olefins.[31] For the development of the catalytic process they needed to accelerate regeneration of the active dioxirane intermediate (**133**). They reasoned that higher

pH should promote dioxirane formation due to effective deprotonation of intermediate **132**. Slow addition techniques of buffer and oxidant were used to maintain a pH of ~10 and an excess of the base-sensitive terminal oxidant $KHSO_5$ (Oxone, Figure 2-6).[32] High pH also maintains the integrity of the ketone catalyst, which is prone to decomposition at lower pH via Baeyer-Villiger processes. As part of their research to expand the substrate scope of this useful process, the Shi lab also showed that epoxidation of silyl enol ethers could provide optically active α-hydroxy ketones.[33]

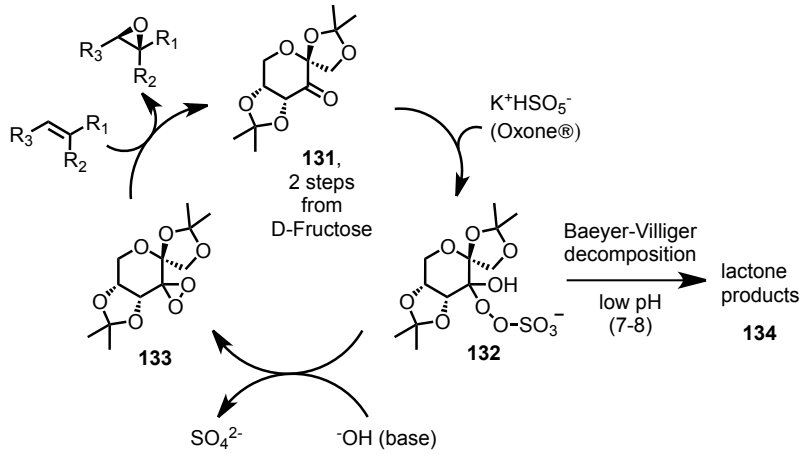
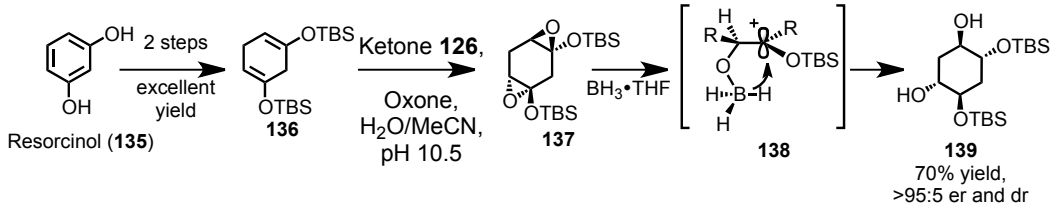


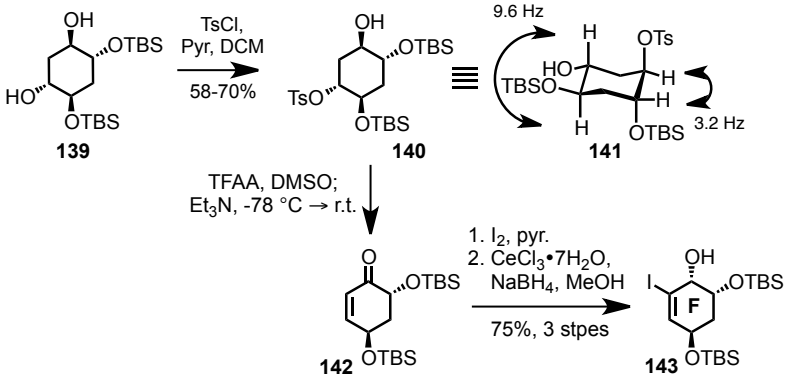
Figure 2-6: Catalytic Cycle of the Shi Epoxidation



Scheme 2-29: Synthesis of Myer's Tetraol 120

Building on the discoveries of the Shi Lab, the 2009 report from the Myers group detailed the reductive opening of silyl enol ether epoxides (**137**, Scheme 2-29) with borane-THF to provide valuable *trans*-diol products that were conveniently differentiated by the silyl group.[30] While they reported several examples, one substrate was immediately apparent as being applicable to the

synthesis of the F-ring of the kibdelones. As detailed in Scheme 2-29, resorcinol can be converted to diene **136** in two steps. This bis-silyl enol ether can be efficiently epoxidized with fructose-derived ketone **126**. The bis-epoxide formed can then be treated with borane-THF to provide the diol **139**. Both the selectivity and yield of this two-step process are excellent, and more importantly for efforts toward the kibdelones, these efficiencies were maintained on multi-gram scale when reproduced in the Ready Lab.

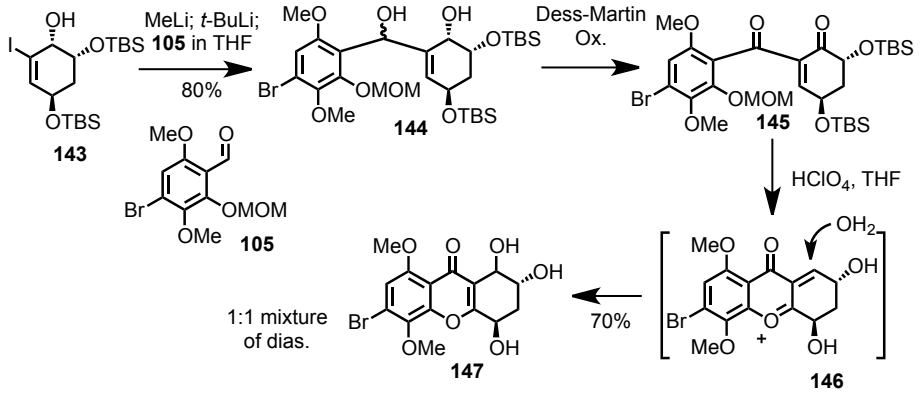


Scheme 2-30: Completion of the Synthesis of the F-Ring Precursor

With an appropriately oxygenated cyclohexane (**120**) in hand, the hurdle of how to further functionalize this molecule into an appropriate nucleophile now needed to be overcome. The most effective way to access enone **142** was surprisingly via monotosylate **140** (Scheme 2-30). Based on NMR coupling constants, we concluded that compound **140** adopts the structure **141**; it is thought that the free equatorial alcohol becomes more hindered, making the second tosylation much slower. Oxidation under Swern conditions brought about ketone formation and tosylate elimination to provide enone **142**.[34] This compound could be processed in a similar fashion to the glucose route (Scheme 2-13) via iodination and Luche reduction. This completes an efficient 8-step synthesis of an appropriate F-ring precursor in 50% yield from commercially available resorcinol. Additionally, this method uses asymmetric catalysis to install all the stereocenters of the kibdelones, which at the time was advantageous since the absolute configuration of the kibdelones was unknown.

Completion of the DEF Fragment of the kibdelones

Concurrent with development of an efficient synthesis of an F-ring precursor, efforts were also focused on devising a strategy to transform the product of nucleophilic addition into the DEF xanthone fragment of the kibdelones. Initial efforts were focused on selective oxidation of the benzylic alcohol (**144**, Scheme 2-31) formed after nucleophilic addition. This would allow xanthone formation to proceed with preservation of the correct *cis*-configuration of the diol on the F-ring. Both selective oxidation and also selective protection (to be followed by oxidation) were attempted without success. Again, drawing on the work of Nicolaou from the synthesis of diversonol, compound **144** was cleanly oxidized to the enedione **145** with Dess-Marin periodinane. Subsequent treatment with $HClO_4$ induced cyclization to provide the xanthone product **147**. This was a fantastic result that provided the desired fragment quickly; however, the need for additional steps to deal with the mixture of diastereoisomers obtained was undesirable.



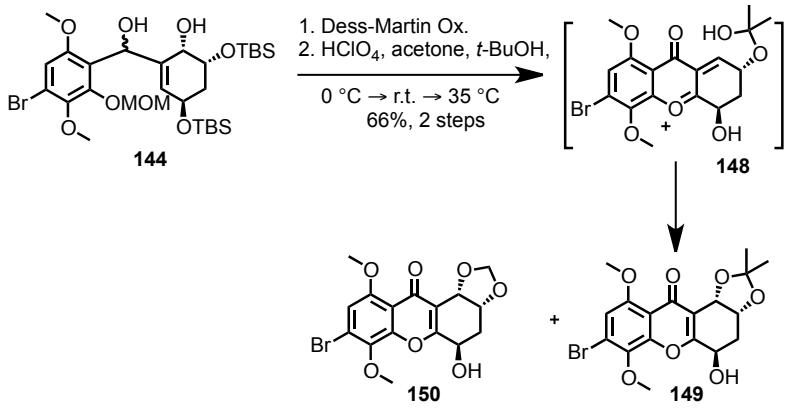
Scheme 2-31: Nucleophilic Addition and Non-Selective Xanthone Formation

While considering a way to improve the selectivity of addition to the extended oxonium ion intermediate **146**, it was reasoned that if the freshly liberated adjacent alcohol could be used to direct intramolecular addition, selectivity for the *cis*-diol product could be obtained. Drawing inspiration from the use of anchimeric assistance in carbohydrate chemistry[35] and the Woodward dihydroxylation,[36] the cyclization reaction was attempted with acetone as the

solvent. Gratifyingly, the extended oxonium ion was now trapped in an intramolecular fashion to yield acetonide **149** (Scheme 2-32), presumably via the acetone adduct **148**. This single operation led to the impressive formation of the xanthone ring, the cleavage of three protecting groups, and the selective formation of the desired *cis*-diol, conveniently protected as an acetonide. Initially the yield for this reaction was moderate because of an unidentified byproduct formed in varying amounts. This byproduct was finally identified as methylene acetal **150** and is thought to be the result of trapping of formaldehyde that is liberated from cleavage of the MOM ether. Addition of *t*-BuOH to the reaction effectively eliminated this byproduct by presumably sequestering formaldehyde (see Table 2-4).

Solvent	Temperature	Time	Result
THF/H_2O	60°	12 hrs.	75% yield 147 (1:1 d.r.)
Acetone	50°	12 hrs.	100% conversion, 1:1 149:150
Acetone	reflux	12 hrs.	40% yield, 2:1 149:150
Acetone, *p*TolSO_2Na	50°	12 hrs.	Decomposition
Acetone/MeOH	reflux	12 hrs.	Methanol addition
Acetone/*t*BuOH	reflux	24 hrs.	1.8:1 -> 3:1 149:150 After Resubmission
Acetone/*t*BuOH	0° -> R.T. -> 35°	48 hrs.	68% yield 149 (2 steps)

Table 2-4: Xanthone Formation Optimization



Scheme 2-32: Selective Formation of the DEF Fragment of the Kibdelones

2.4 Sonogashira Cross Coupling of the AB and DEF Fragments

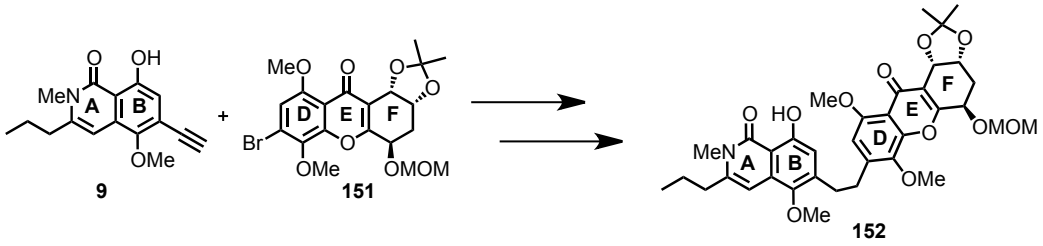
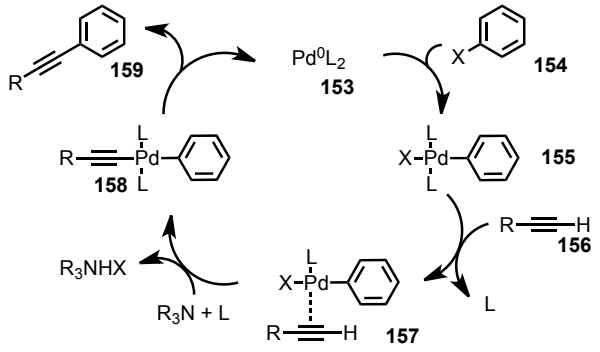


Figure 2-7: Coupling the AB and DEF Fragments

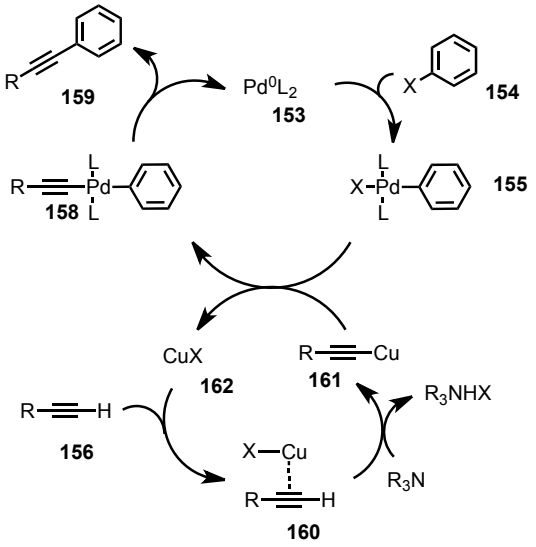
Background



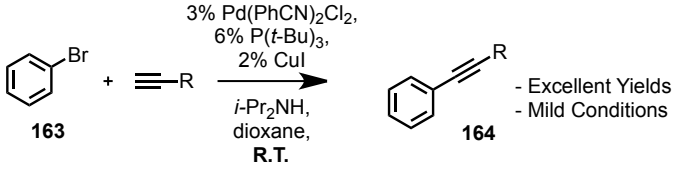
Scheme 2-33: Alkynylation Discovered by Heck and Cassar

The Sonogashira cross coupling is a versatile transition metal-catalyzed reaction that couples terminal alkynes (**156**) with aryl halides or pseudo halides

(**154**) and is well established in organic synthesis. The alkynylation reaction shown in Scheme 2-33 was initially reported independently in 1975 by Heck[37] and Cassar.[38] Later that year the Sonogashira lab reported a similar alkynylation that utilized a copper co-catalyst (Scheme 2-34).[39] This procedure employed milder conditions and became the most frequently used protocol, leading to the name for the reaction being attributed to Sonogashira. The development and application of the reaction has been recently reviewed;[40] however, several recent improvements warrant discussion.



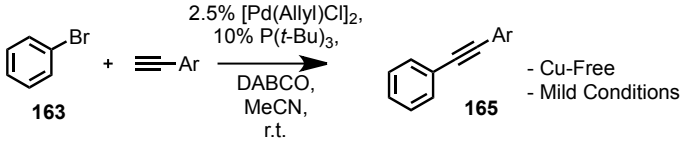
Scheme 2-34: Sonogashira Reaction



Scheme 2-35: Buchwald and Fu Conditions for Sonogashira Reaction

A collaborative effort from the Buchwald and Fu Labs at MIT resulted in the discovery of a highly active system for Sonogashira cross coupling which utilized the bulky *t*-Bu_3P ligand (Scheme 2-35).[10] This ligand created an electron rich Pd-catalyst, a property that is known to result in improved rates of oxidative addition.

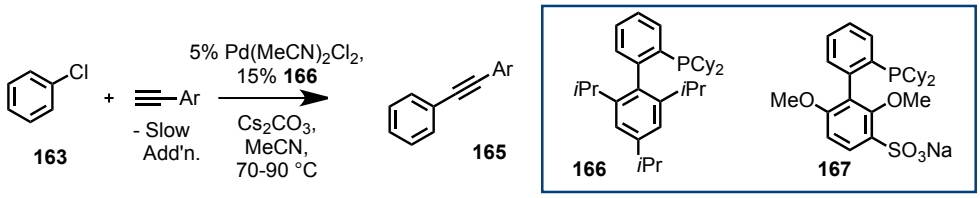
This improved catalytic system allowed reactions with aryl bromides to occur at room temperature.



Scheme 2-36: Mild "Cu-Free" Sonogashira Conditions

One drawback to the Sonogashira reaction is the need to rigorously exclude oxygen from the reaction in order to prevent dimerization of the alkyne component, a side reaction known as Glaser coupling.[41] This issue has led to efforts to improve the Heck and Cassar conditions for so-called "copper-free" Sonogashira reactions. An improved Cu-free procedure was developed by researchers at Merck Process that allowed the room temperature cross coupling of aryl acetylenes with aryl bromides (Scheme 2-36).[42]

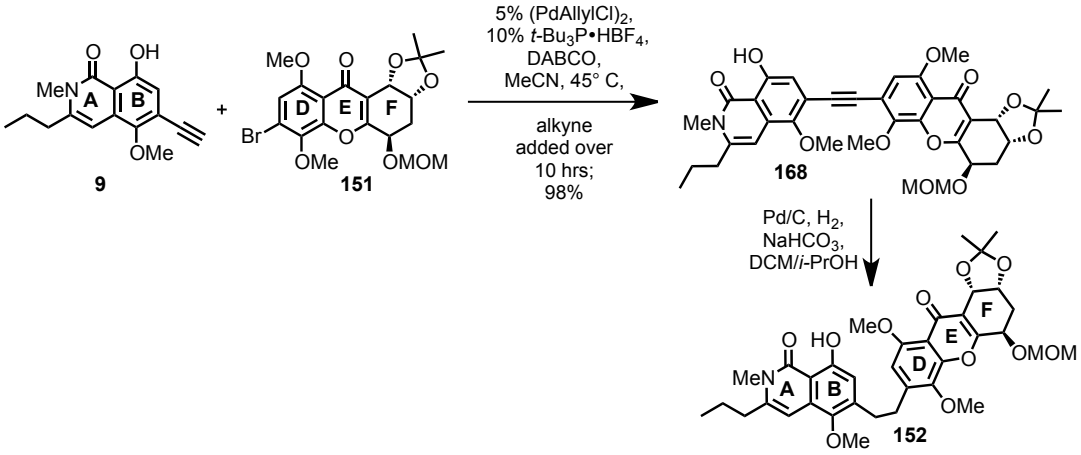
Both of the aforementioned methodologies fail at the cross coupling of aryl chlorides because these substrates are less reactive toward oxidative addition. To address this issue the Buchwald Lab developed a Cu-free procedure that utilized a biaryl phosphine ligand for efficient cross coupling of aryl chlorides (Scheme 2-37).[43] Under the reaction conditions, slow addition of arylacetylenes was necessary to prevent alkyne oligomerization even when precautions were taken to exclude oxygen. The slow addition issue was addressed in a later study that utilized the water-soluble phosphine **167** with biphasic reaction conditions.[44]



Scheme 2-37: Biaryl Phosphine Ligands for the Sonogashira Reaction

Cross Coupling of the AB and DEF Fragments

The reliability and wealth of knowledge about the Sonogashira coupling makes this method ideal for coupling the AB and DEF fragments of the kibdelones. Initially, this reaction was problematic because only dimerization and oligomerization of the alkyne were observed, even when rigorous degassing procedures were employed. When copper-free conditions were employed, some product formation occurred, but the yield was low. Excellent yields could be obtained by employing Cu-free conditions and using a slight excess of the alkyne, added over the course of the reaction (Scheme 2-38).



Scheme 2-38: Sonogashira Crosscoupling of the AB and DEF Fragments

Reduction of diarylalkyne **168** was necessary for subsequent biaryl bond formation. This reduction can be performed with routine hydrogenation conditions; however, when normal solvents were employed (ethyl acetate, MeOH) inconsistent results were obtained. This problem was remedied by using a dichloromethane and *i*-PrOH solvent combination to provide a short reaction time, complete dissolution of the starting material, and full conversion. On several occasions acetonide deprotection occurred during hydrogenation, which was thought to be caused by acid impurities in the bottle of catalyst used. Addition of $NaHCO_3$ as an additive prevented this unwanted side reaction and provided consistent access to pentacyclic compound **152** in good yield.

2.5 Biaryl Bond Formation: Cyclization of the C-Ring of the Kibdelones

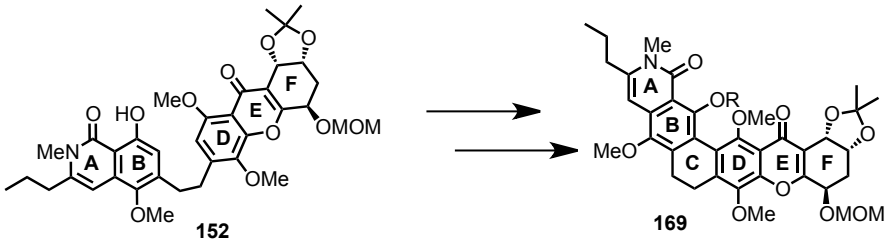
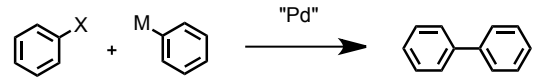


Figure 2-8: Formation of the C-Ring of the kibdelones

Background



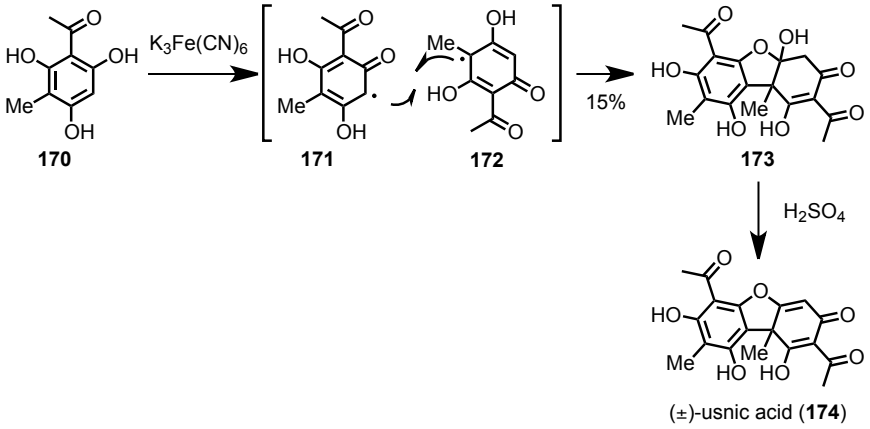
X = halide, OTf, OTs, etc.
M = $B(OH)_2$, SnR_3, MgX, etc.

Figure 2-9: Traditional Palladium-mediated Cross Coupling

The formation of biaryl bonds is a fundamental and widely used reaction in organic synthesis. The prevalence of this bond construction has led to a multitude of methods to synthesize biaryls from diverse starting materials. In modern organic synthesis, the most widely used method for synthesizing such structures involves the transition metal-mediated cross coupling of aryl halides or pseudo-halides with aryl organometallic reagents (Figure 2-9).[45] These type of reactions have been used extensively in the syntheses of natural products.[46] The Chemistry Nobel Prize committee recognized the generality and predictability of such methods by awarding the 2010 prize for "palladium-catalyzed cross couplings in organic synthesis."

Before the discovery of transition metal-catalyzed processes chemists relied on a type of reaction known as oxidative phenolic coupling to form biaryl bonds. This type of bond formation is thought to be involved in the formation of many phenolic natural products and has been used for multiple biomimetic natural product syntheses. In addition to the synthesis of TMC-66 (Scheme 1-16), which is

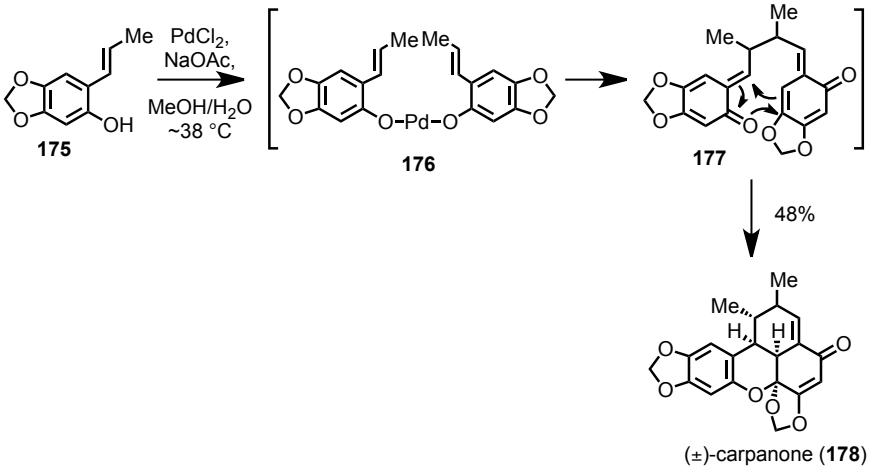
directly related to the kibdelones, there are several historical examples in which phenolic coupling was used for the synthesis of natural products.



170 171 172 173

Scheme 2-39: Robinson Synthesis of Usnic Acid

In 1956 the Barton laboratory utilized a single-electron oxidant, $K_3[Fe(CN)_6]$, to generate radicals (Scheme 2-39). These intermediates can combine to provide dimer **173**. This allowed the two-step synthesis and structure elucidation of usnic acid.[47]

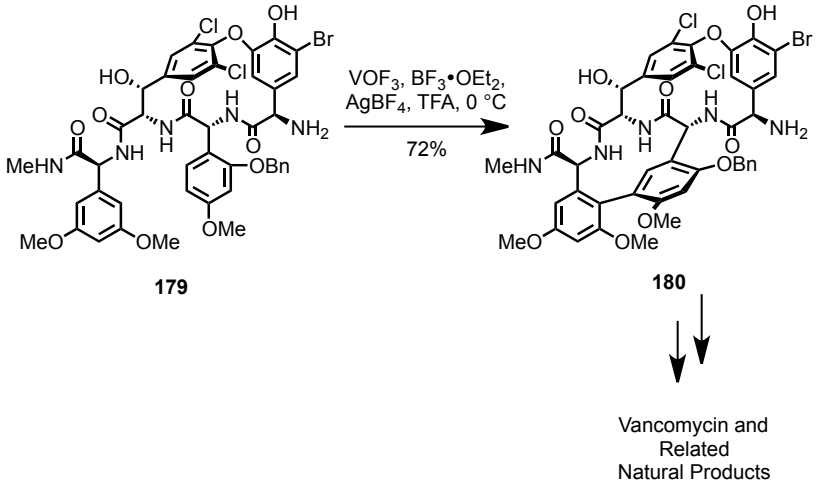


175 176 177

Scheme 2-40: Chapman Synthesis of Carpanone

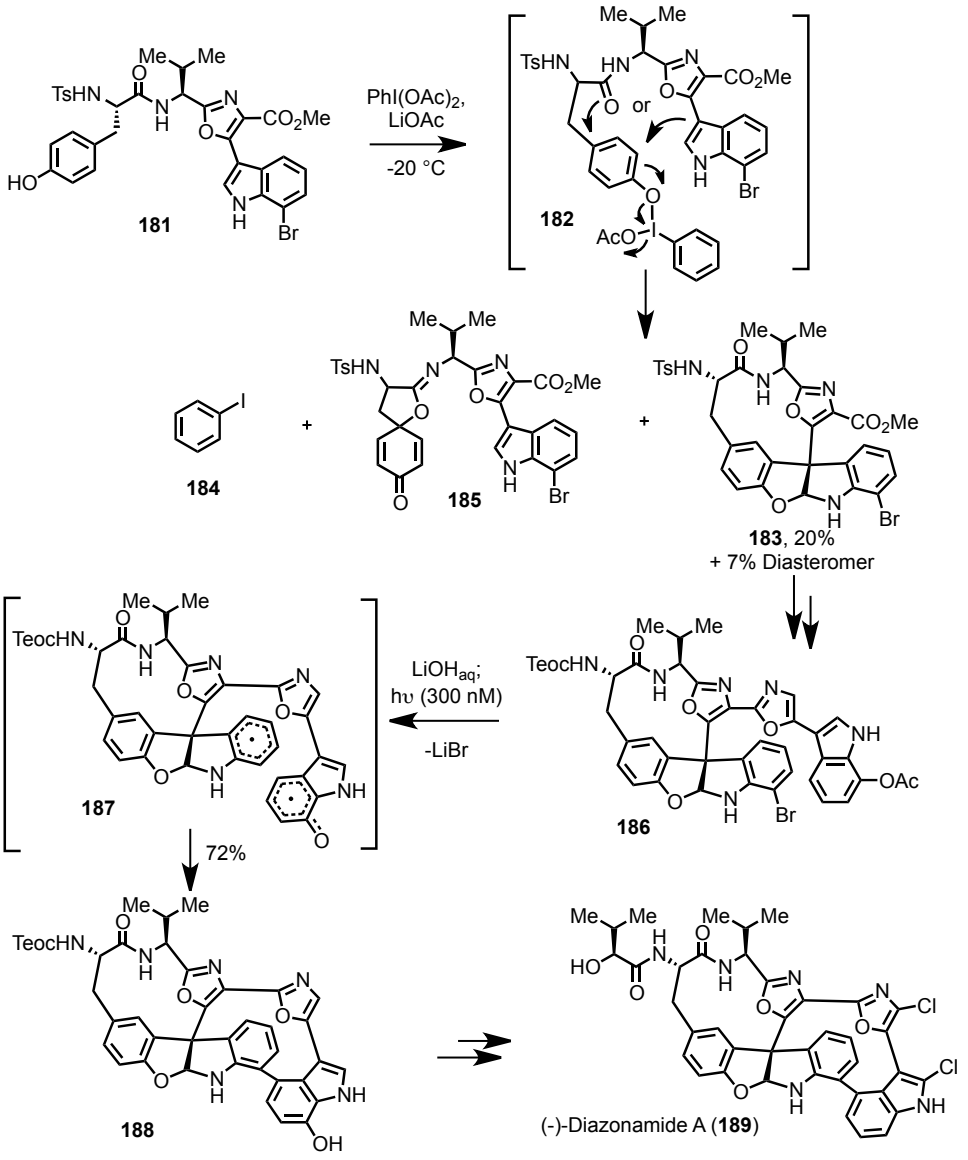
Inspired by the Robinson synthesis, the Chapman Lab at the University of Iowa developed what is now a classical synthesis of carpanone (**178**, Scheme 2-40) using Pd^{II} as a bivalent, two-electron oxidant to dimerize compound **175**.[48] The

dimer subsequently rearranges, and an intramolecular cycloaddition of intermediate **177** takes place to form carpanone. This strategy was employed recently by the Shair group which used $PhI(OAc)_2$ as a substitute for palladium to synthesize a library of carpanone molecules on solid supports.[49]



Scheme 2-41: Evans Approach to Vancomycin and Related Natural Products

The Evans Lab used an oxidative phenolic coupling strategy with non-phenolic substrates (**179**, Scheme 2-41) to form a key biaryl bond in their synthesis of natural products related to the vancomycin antibiotics. A screen of oxidants revealed that VOF_3 with BF_3-OEt_2 provided the key bond formation.



Scheme 2-42: Harran 2nd Generation Synthesis of Diazonamide

Harran and coworkers developed a synthesis of the natural product diazonamide A that contains two biaryl bond formations: first via phenolic coupling with hypervalent iodine followed by a late stage photocyclization to form the final C-C bond of the natural product. Two products resulted from the initial macrocyclization of compound **181** with I^{III}. The quinone product **185** is the result of *para* addition of the amide oxygen, while the mixture of diastereomers of **183**, are

the result of desired *ortho* addition of the indole to the phenol. For the photocycloaddition, **186** was treated with LiOH to form the phenolate and subsequent photolysis then provided **188** in 72% yield. Oxygenation at the 7 position of the indole (**188**) is not present in the natural product but this phenol is much more reactive for the photocyclization.

In addition to the methods already discussed for biaryl bond formation, transition metal catalyzed C-H arylation has found general use in the synthesis of biaryls.[50,51] Although this reaction has been known for many years, it has only recently been developed into a general method for biaryl bond formation. The timeline in Figure 2-10 details the development of this reaction over the last 60 years.

In the early twentieth century it was known that transition metals such as palladium or platinum could dehydrogenate organic molecules to generate unsaturated compouds. Over 50 years ago McNeil capitalized on this reactivity to form biaryl bonds intramolecularly at very high temperatures to generate poly-aromatic hydrocarbon products (**191**).[52] The dehydrogenative ability of palladium was applied to the formation of heterocycles (**193**) in the 1970s with stoichiometric amounts of $Pd(OAc)_2$.[53]

As the understanding of transition metal-catalyzed reactions improved, catalytic methods for C-H arylation were developed that utilized oxidative addition followed by reductive elimination to regenerate the catalyst. Bringmann utilized this in the 1980s for the formation of lactone **196** in the atropisomeric-selective synthesis of (-)-ancistrocladine.[54] The Suzuki Lab also used the intramolecular biaryl bond formation of arene esters in several syntheses that were described in Chapter 1. More than ten years later, the research groups of Rawal and Nomura reported intra- and intermolecular phenol-directed arylation reactions that utilized catalytic palladium acetate.[55,56]

Another seven years would pass before the Fagnou group reported an improved procedure for intramolecular arylation that used the biaryl phosphine DavePhos (**206**) to achieve good yields with a fairly general substrate scope and low

catalyst loadings.[57,58] After a report in 2006 by Echavarren indicating that this type of reaction takes place by a proton abstraction mechanism,[59] the Fagnou group reported the key additive, potassium pivalate, for the intermolecular arylation of aryl halides with benzene.[60] This additive allowed good to excellent yields of biaryls (**205**) to be obtained and the reaction is thought to proceed via transition state **204**. In 2008 the Fagnou Lab reported similar conditions for intramolecular biaryl formation at lower temperatures (50-60 °C) and in excellent yield.[61] The key observation that sterically encumbered carboxylates are important to facilitate a so-called "concerted metalation deprotonation" (CMD) event (**204**)[62] has allowed the expansion over the last five years of this type of reaction to include multiple substrate types. These observations were also instrumental in developing a biaryl bond forming reaction for the synthesis of the kibdelones.

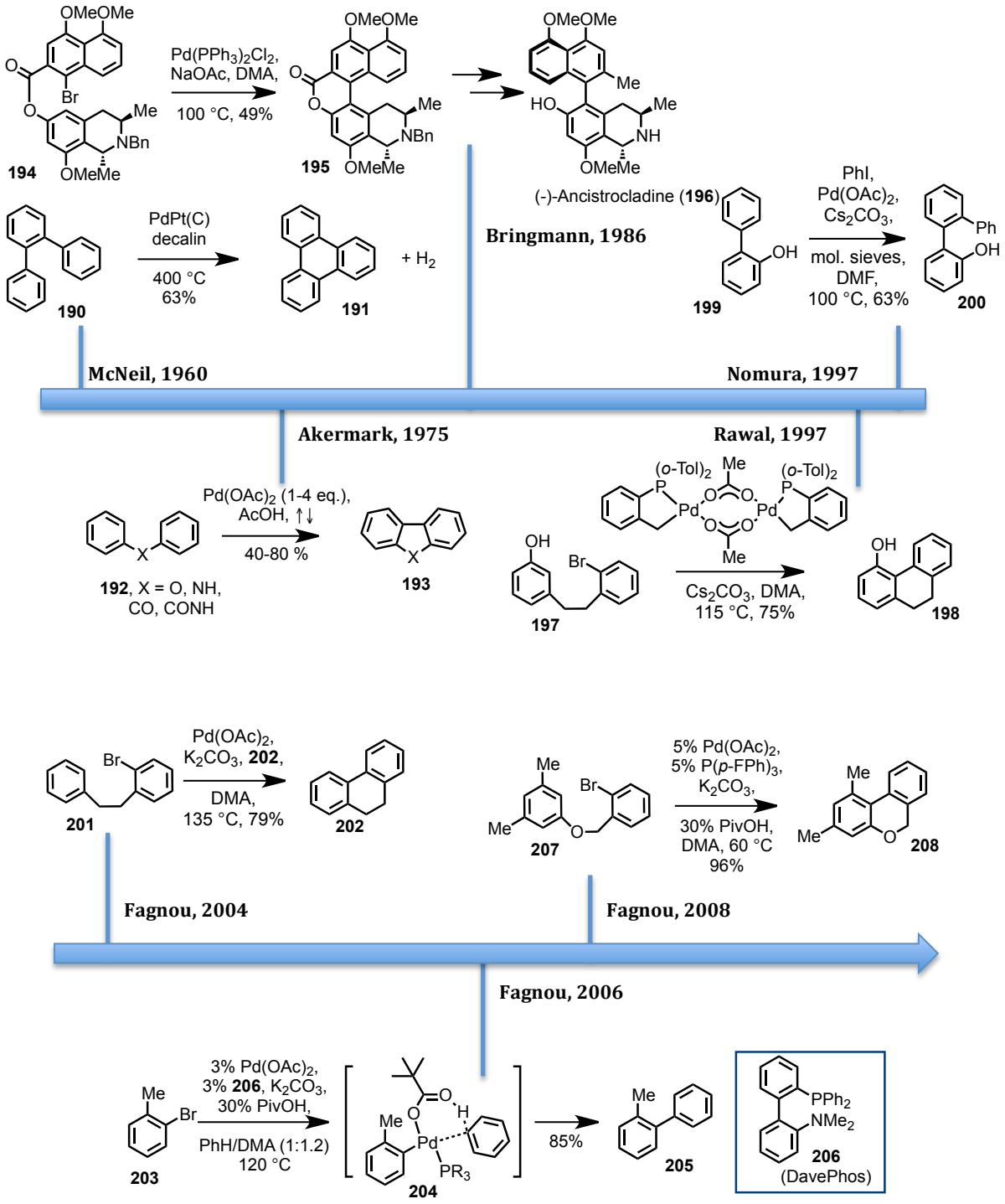


Figure 2-10: Timeline of the Development of C-H Arylation

Prior Work Toward C-Ring Formation from the Ready Lab

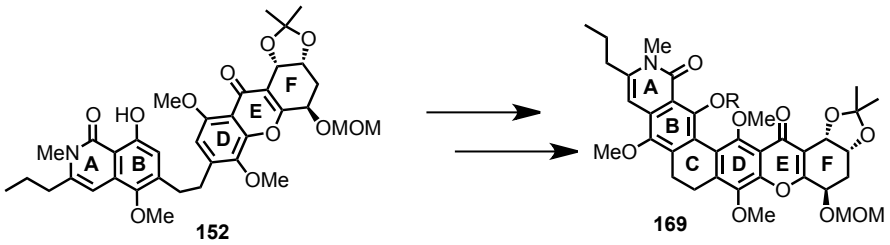
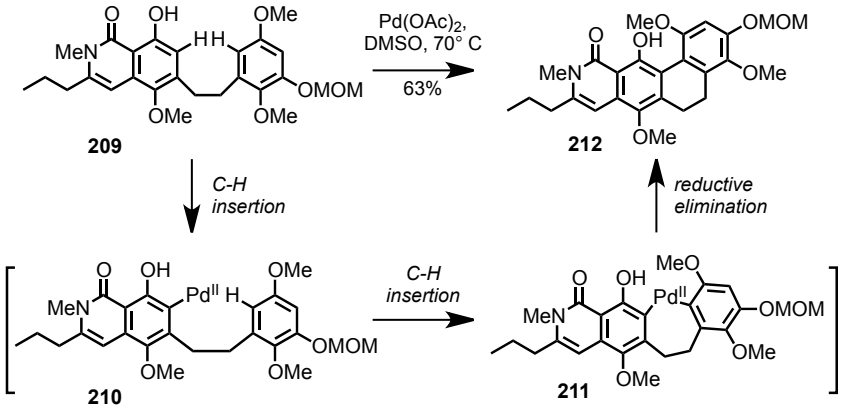


Figure 2-11: Formation of the C-Ring of the Kibdelones

The convergent strategy for the kibdelones relies on the ability to join the AB and DEF fragments through late-stage sequential Sonogashira reactions followed by some form of an arylation reaction to close the C-ring. While the Sonogashira reaction is fairly well studied and reliable, the use of complex substrates such as **152** (Figure 2-11) for arylation is unprecedented. Therefore, early efforts in the Ready Lab were focused on the development of conditions with model systems to effect this bond formation.

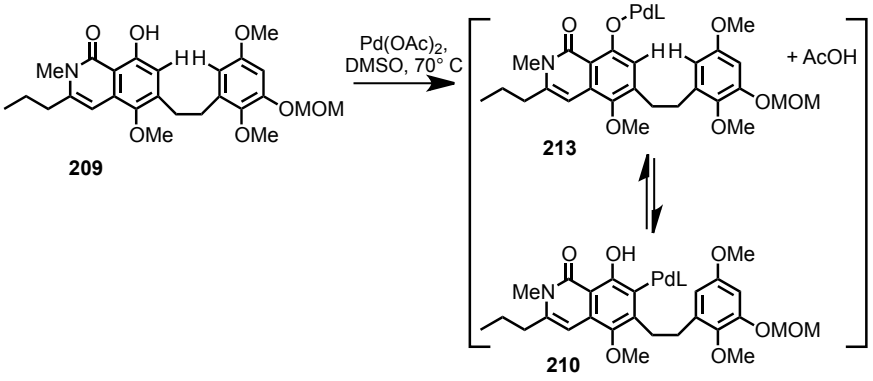


Scheme 2-43: Dehydrogenative Coupling in a Model System

The Ready group began studies on C-ring formation at the outset of the research program to synthesize the kibdelones. Stoichiometric $Pd(OAc)_2$ in DMSO was found to induce biaryl bond formation with substrate **209** in a screen of oxidants for phenolic coupling (Scheme 2-43). This reaction is thought to proceed via sequential C-H insertions leading to palladacycle **211**. Subsequent biaryl bond formation then takes place by way of reductive elimination. This dehydrogenation is

analogous to the heterocycle formations discussed in the preceding section in which electron rich-aromatics were employed.

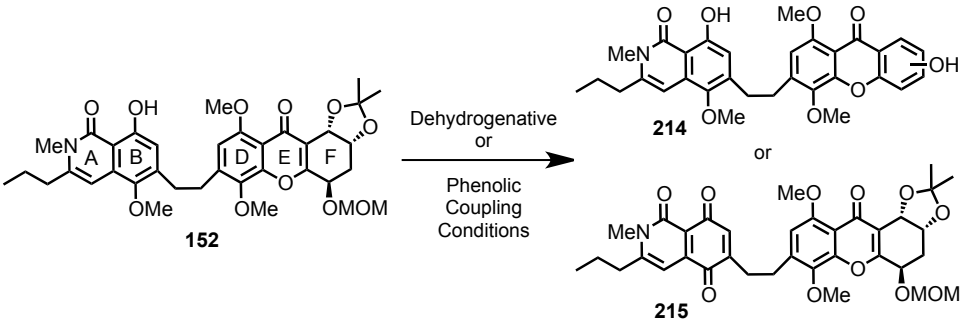
Interestingly, the free phenol is required for this reaction to presumably direct C-H insertion to the ortho position; all substrates with protected phenols failed to give any biaryl product. Pd-phenolate formation is likely the initiating step of this reaction (Scheme 2-44); however, the addition of bases shut the reaction down completely. Acidic additives often accelerate C-H insertion reactions with Pd^{II} so this was not incredibly surprising.[63,64] Additional efforts to find catalytic conditions for this transformation through the incorporation of oxidants failed. This detail was overlooked as a moderate yield of the product was obtained, and prohibitively expensive amounts of $Pd(OAc)_2$ were unlikely to be needed because this reaction would be performed at a very late stage in the synthesis. More complex substrates (i.e. **152**) would not be tested for some time (~2 years) and at this point the sensitivity of this reaction to the electronics of the substrate was not known.



Scheme 2-44: Initiation of Dehydrogenative Coupling

Development of a C-H Arylation Strategy for the Kibdelones

With the development of a dehydrogenative coupling to form the C-ring in the model system above, initial attempts were devoted to using these conditions with substrate **152** (Scheme 2-45).



Scheme 2-45: Failed Biaryl Bond Formation

Surprisingly and unfortunately, all attempts to form the biaryl bond using palladium salts or a myriad of other oxidants in more traditional oxidative phenolic couplings failed. No reaction occurred at the temperatures used for the model system (70 °C) and increased temperatures led to undesired aromatization of the F-ring (**214**) with no observed C-C bond formation. The addition of pivalic acid, which had been shown by Fagnou and others to induce concerted metalation-deprotonation in reactions with aryl halides led to no improvement in this case. When common oxidants were used, quinone **215** was formed, again without any evidence of the desired bond formation. Lewis acids were screened with quinone **215** but no addition to the quinone was ever observed.

These negative results pointed to a distinct difference in the reactivity of the pentacyclic substrate **152** and the compound used in the model study for dehydrogenative coupling (Scheme 2-43). The model compound has a much more electron-rich "D-ring," and it is possible that biaryl bond formation is occurring through an intermediate similar to sigma-complex **216** (Figure 2-12), with palladacycle formation occurring after deprotonation and rearomatization in analogy to aromatic substitution processes. The conditions for C-H arylation developed by the Fagnou Lab are less sensitive to electronics because C-H arylation is thought to take place via concerted metalation deprotonation such as in **218** (Figure 2-12). Attempts to access this type of an intermediate in the dehydrogenative coupling with $Pd(OAc)_2$ and PivOH led to no bond formation; however, Fagnou's conditions employ catalytic palladium salts with phosphines and

aryl halides. Generation of a palladium carboxylate complex under both conditions should yield the same intermediate (**218**, Figure 2-12); hypothetically, phosphine additives might provide stability for the aryl palladium intermediate and improve the subsequent C-H insertion. Additionally, the ability to access an aryl palladium intermediate through oxidative addition could allow alternative conditions to be used in which a more reactive (i.e. cationic) intermediate is formed. To try to access a more stable intermediate that would also be more reactive toward C-H insertion, aryl halides were prepared.

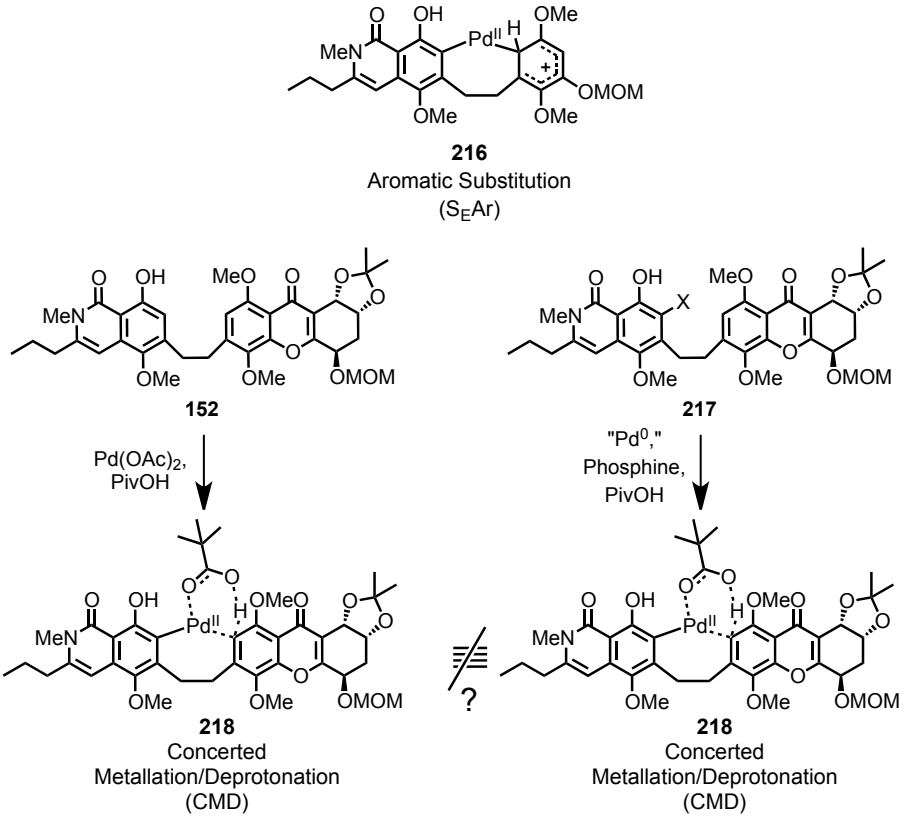
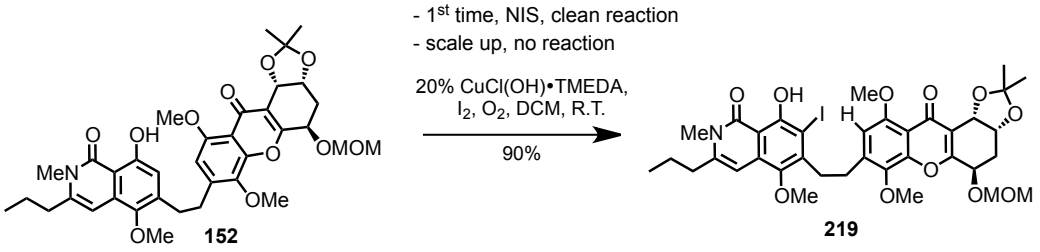


Figure 2-12: Hypothetical Pathways to Palladacycle Formation

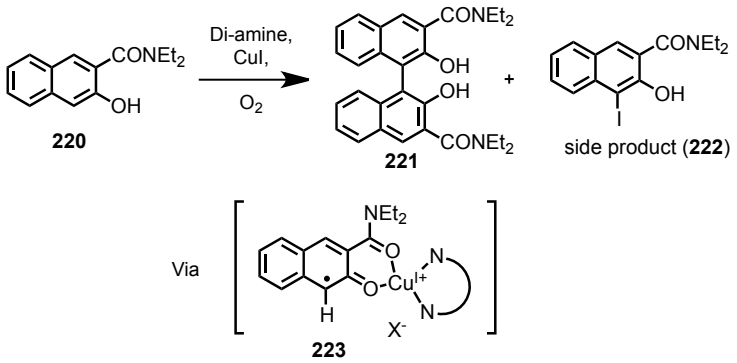
Iodination of compound **152** proceeded cleanly to provide the desired aryl halide on small scale (Scheme 2-46). The inability to reproduce this reaction was initially baffling, but after careful analysis of the initial successful reaction, it was found that the starting material (**152**) had been recovered from a failed oxidative

coupling reaction with stoichiometric amounts of CuCl(OH)-TMEDA complex. Some amount of copper was likely present in the initial iodination reaction allowing for efficient halogenation. After determining which reagents were required for this reaction the catalytic conditions in Scheme 2-46 were found to reproducibly provide the aryl iodide **219** in excellent yield.



Scheme 2-46: Cu-Catalyzed Iodination

A similar reaction was reported by the Kozlowski Lab as a side product in an asymmetric oxidative phenolic coupling reaction to form binaphthols (Scheme 2-47).[65] They proposed intermediate **223** for oxidative coupling, and an analogous intermediate is likely formed in this halogenation reaction. In attempts to broaden the substrate scope of this reaction, it has been found that only phenols with ortho esters or acids provide halogenated products in low to moderate yields. These data with additional substrates supports a chelated intermediate similar to **223** as being operative in this reaction and also highlights the serendipitous nature of the pairing of conditions for halogenation with substrate **152**.



Scheme 2-47: Literature Precedent for Cu-Catalyzed Iodination

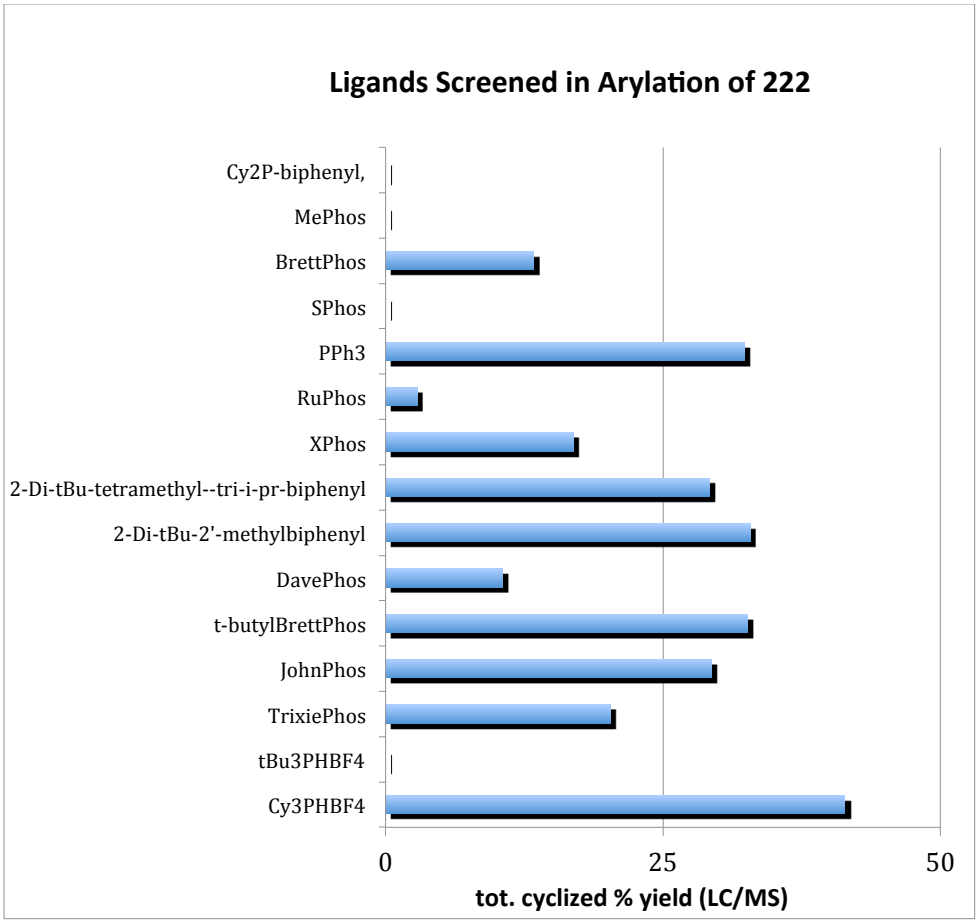


Chart 2-1: Ligands in Arylation of MEM-protected 222 (1.5 eq. Pd, Pd:Ligand 1:2)

With ready access to aryl iodide **219**, the Fagnou results were used as the starting point for screening cyclization conditions. Initially, only decomposition was observed at the high reaction conditions utilized in early studies. At the lower temperatures (50-70 °C) that were reported more recently with pivalate additive only deiodination was observed. The phenol **219** was protected to see if this would lead to stability at higher temperatures. The MOM ether **221** (Scheme 2-48) was prepared but only extensive cleavage occurred under the reaction conditions. A thorough temperature study with the MEM ether **222** found that C-C bond formation indeed occurred at 85 °C. In addition it was found that temperatures higher than 95 °C led to decomposition, and below 85 °C only deiodination was observed. Within this range of temperatures, the desired product was isolated from

clean reaction mixtures in low yield (10-15%) with the remainder of the starting material being converted to a mixture of deiodinated products with or without the MEM ether. A screen of phosphine ligands led to no appreciable gain over the initial Cy_3P-HBF_4 salt that was used (Chart 2-1). A screen of bases revealed that $NaHCO_3$ led to slight improvements (Chart 2-2). Fagnou experienced reduced reactivity with aryl iodides and found that conversions could be improved by employing silver salts.[66] Such additives led to no improvement in this case.

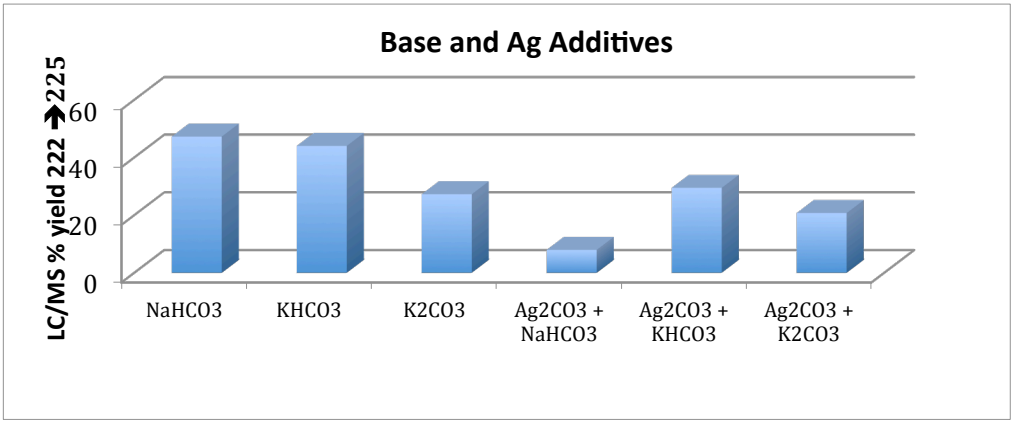
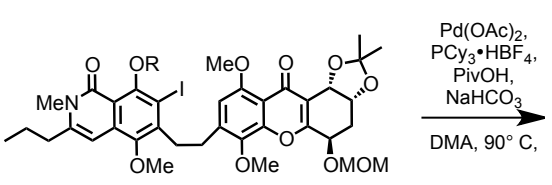
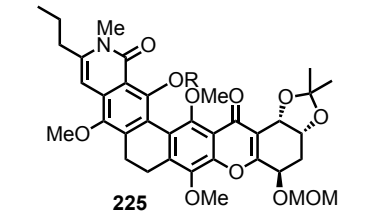


Chart 2-2: Base and Ag Additives in Arylation of 222



Compound	R	Yield of **225**
219	H	0%
220	Me	<5%
221	MOM	0%
222	MEM	15%
223	Ac	0%
224	BOC	55-63%



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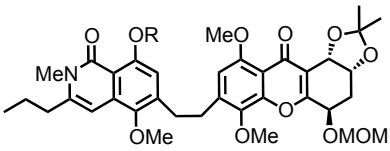
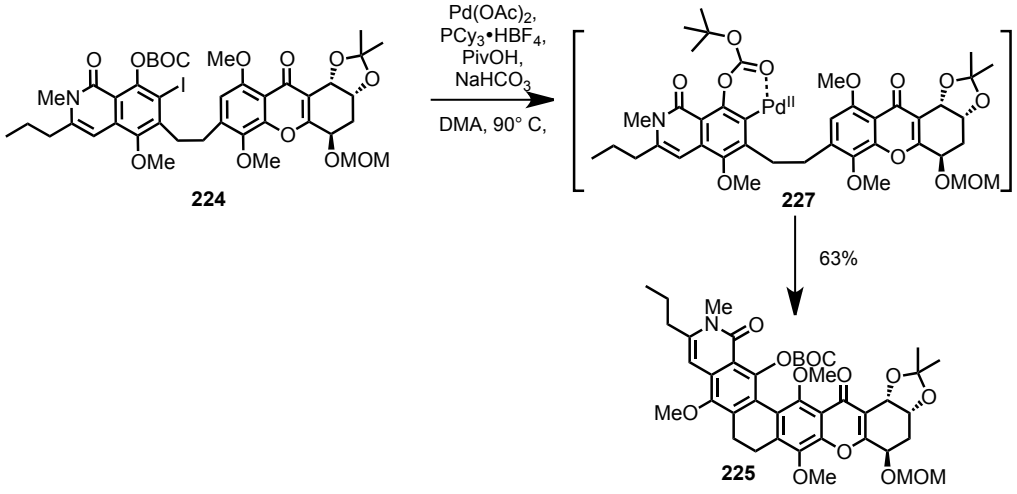


major side product (**226**)

Scheme 2-48: Protecting Group Optimization in the C-H Arylation

A breakthrough in optimization studies came by further varying the protecting group on the phenol (Scheme 2-48). The use of a BOC carbonate (**224**) led to drastically improved conversions. This result was somewhat surprising because esters (**223**) had provided no product; however, this could be due to cleavage under the reaction conditions. Presumably, BOC is stable enough and also provides a chelating group to stabilize the aryl-palladium intermediate **227** (Scheme 2-49). It is thought that this mode of chelation is important because the corresponding methyl ether (**220**) provided very little of the desired product. Further improvements were gained by performing the reaction on increased scale (>100 mg) with the conditions in Scheme 2-49.

With formation of this C-C bond, the carbocyclic core of the kibdelones had been synthesized in moderate yield. This reaction represents one of the most demanding C-H arylations in the literature to date and was enabled by the serendipitous discovery of a novel and selective Cu-catalyzed iodination reaction. The initial hypothesis to use phosphine ligands with an aryl halide to access a more stable aryl palladium complex was inaccurate; instead, aryl halides had enabled the introduction of a chelating group on the phenol that could stabilize the aryl palladium intermediate.

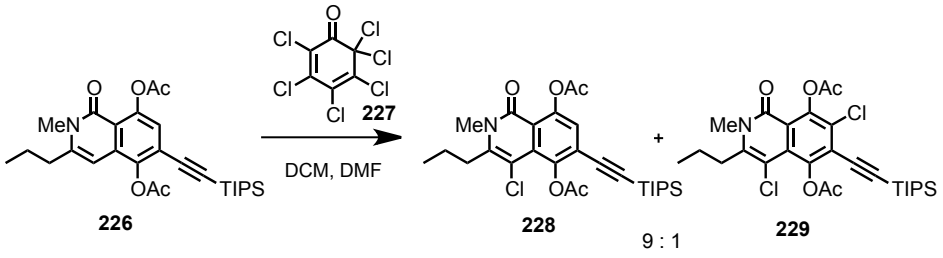


Scheme 2-49: Optimized C-H Arylation

2.6 Completion of the Synthesis of (-)-Kibdelone C

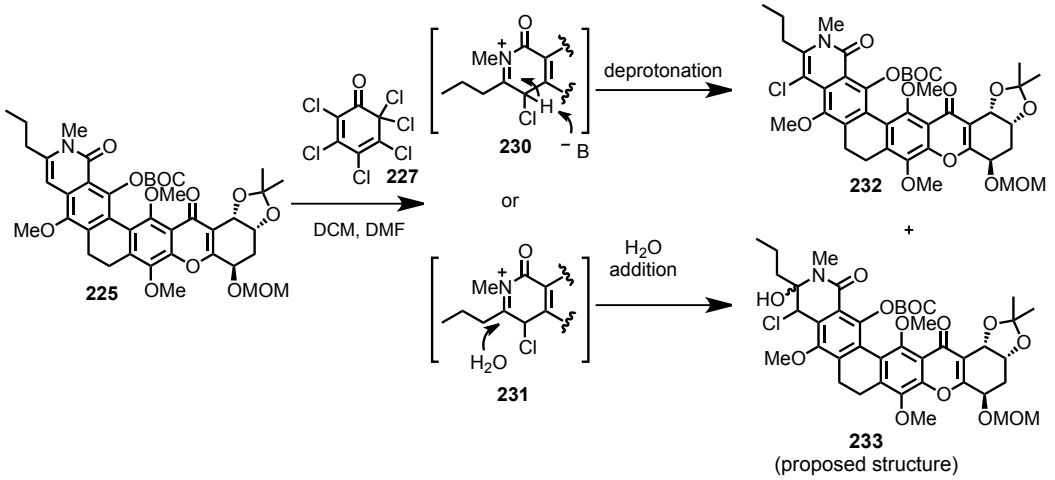
Halogenation and five protecting group manipulations were all that remained to prepare a member of the kibdelones after completion of the carbocyclic core. The fact that this hypothetical three-step sequence appeared to be a "slam dunk" in comparison to the synthetic endeavors that had already been completed bears witness to the amount of optimistic naiveté that existed in the Ready Lab at this time. Significant purification and reaction optimization issues would come to light that were related to the propensity of these compounds to interconvert via redox processes. Only after trial and error was the appropriate identity and order of events established. The ability to adequately troubleshoot the final steps of this synthesis speaks to the efficiency of the synthesis of the carbocyclic core of the kibdelones as well as the phenomenal analytical instrumentation and advice present at UT Southwestern.

Chlorination of the Core of the Kibdelones

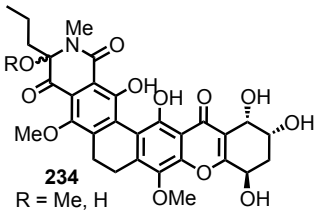


Scheme 2-50: Chlorination of Model Isoquinolinone Substrates

The first task that was tackled was chlorination of the carbocyclic core. Prior work in the Ready Lab had established that cyclohexadienone **227** (Scheme 2-50) provided the desired chlorinated isoquinolinone. The Harran Lab had used this reagent for late stage dichlorination in the synthesis of diazonamide A.[67] As these initial chlorination studies were performed on model substrates, and because of previous issues with model reactions, it was unclear if they would work well for the full kibdelone system.



Scheme 2-51: Chlorination Results in Product Mixtures



Initially it appeared that this skepticism was warranted, as chlorination reactions provided a multitude of products by LC/MS analysis (Figure 2-13). Careful inspection of the mass associated with these peaks revealed that they had the mass of the desired product plus water. To complicate matters the starting material was also a mixture of atropisomers. Additionally, the ^{1}H NMR spectrum of the crude mixture was very difficult to interpret. All of these data led to the idea that water was adding at the isoquinolinone to yield mixtures of diasteromers. As detailed in Chapter 1, the isolation group had observed water or methanol addition to the kibdelones to give α-hydroxy and methoxy ketone products (**234**). The hypothesized structure (**233**) is similar to these compounds with the exception of a different oxidation state at the newly chlorinated carbon. In any event, treatment of the crude mixture with $HClO_4$ caused the multitude of products to converge to a ~1:1 mixture of desired deprotection products **235** (Scheme 2-52), further supporting this hydration hypothesis.

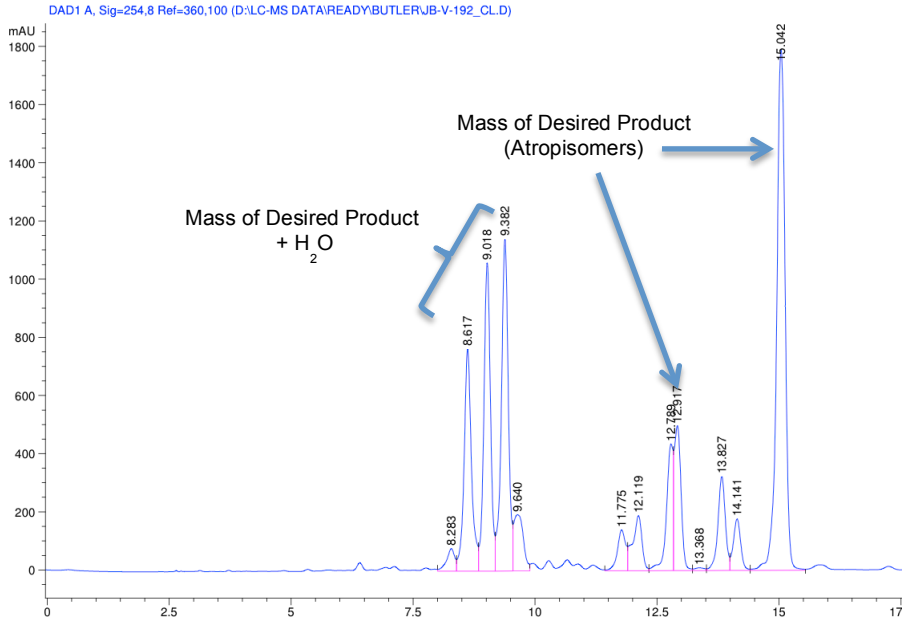
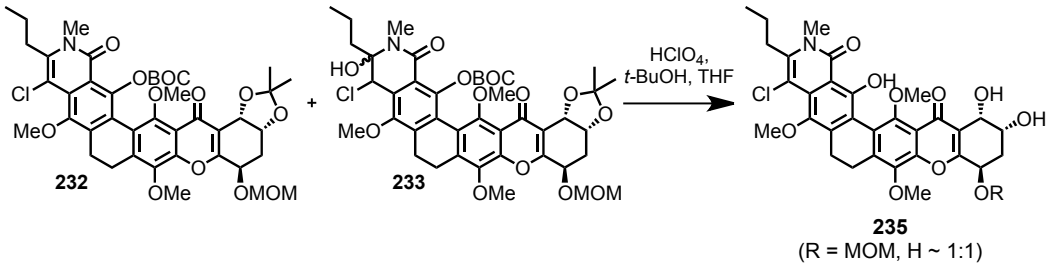


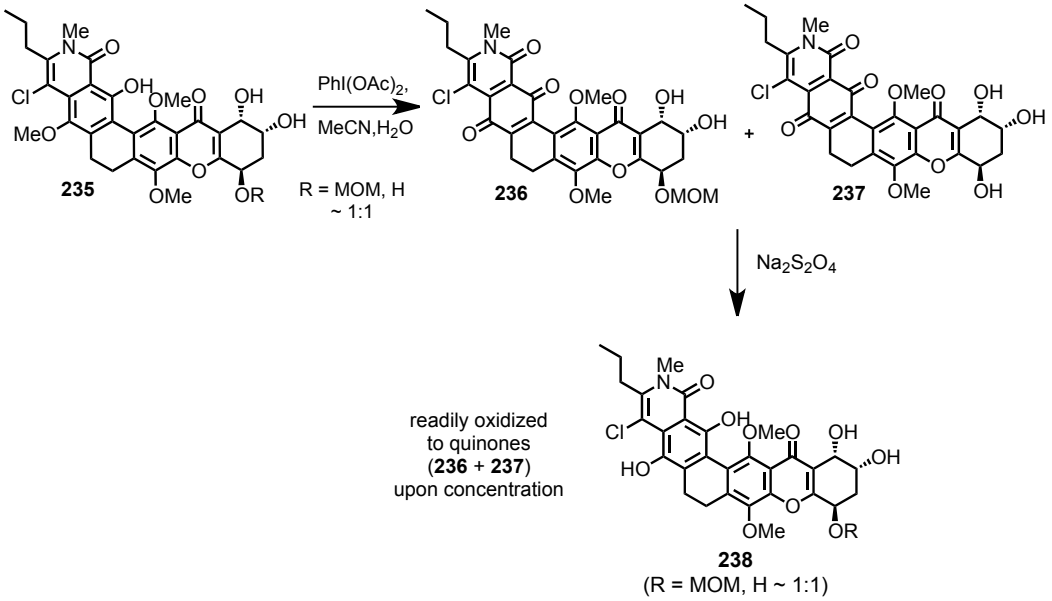
Figure 2-13: LC/MS of the Crude Chlorination Reaction



Scheme 2-52: $HClO_4$ Mediated Deprotection

Complete deprotection of the mixture of **232** and **233** was difficult to achieve under acidic conditions; longer reaction times led to significant decomposition and lower mass recovery. Both compounds (**235**) bear the desired free phenol for oxidative demethylation and could be obtained with good mass balance; therefore, the mixture could be taken forward in the next reaction. Accordingly, oxidative demethylation was performed by treating this mixture with $PhI(OAc)_2$ to cleanly provide a mixture of quinones (**236** and **237**, Scheme 2-53). In theory these quinones can be utilized in the synthesis of kibdelone B, but it was thought that further manipulation of these compounds would be easier at the

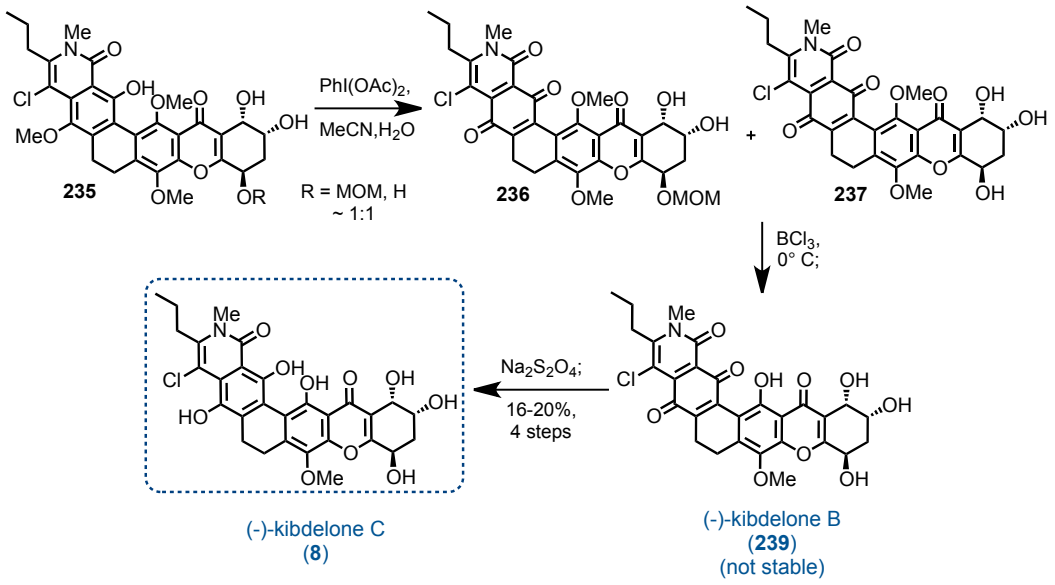
hydroquinone oxidation state (**238**). This conversion was accomplished by reductive workup of the oxidative demethylation reaction with $Na_2S_2O_4$. Unfortunately, attempted purification of the mixture **238** via reverse phase HPLC followed by concentration of the fractions yielded a mixture of hydroquinone and quinone products (i.e. **236-238**), revealing the oxygen sensitivity of these compounds. The reductive workup was thus omitted from the oxidative demethylation reaction with the hope that kibdelone B could be isolated after the final demethylation step.



Scheme 2-53: Late Stage Intermediates are Oxygen Sensitive

Treatment of the mixture of quinones (**236** and **237**) with BCl_3 at low temperature resulted in complete cleavage of any remaining MOM ether and selective demethylation of the D-ring (Scheme 2-54). The crude reaction mixture was fairly clean by LC/MS and NMR but proved difficult to purify. Multiple RP-HPLC purifications led to significant loss of compound without improvements in purity. The kind advice of the lead author of the isolation paper confirmed our suspicions about the stability of kibdelone B.[68] Based on spectra of kibdelone B obtained from Dr. Ratnayake it appeared that the Capon group had been unable to fully purify kibdelone B in their initial report. Fortunately, reductive workup of the BCl_3

demethylation reaction provided kibdelone C. After careful RP-HPLC purification and limited exposure to O_2, samples of kibdelone C could be obtained. Initially, ^1H NMR spectra deemed satisfactory for publication were difficult to collect. Preparation of NMR samples in the glove box after lyophilization of HPLC fractions overnight prevented the incorporation of atmospheric moisture into the sample and allowed the collection of well-resolved spectra. All analytical properties were identical to that reported except for optical rotation which had similar magnitude but opposite sign to that reported for kibdelone C. This establishes the absolute configuration of the natural product as opposite to that represented in Scheme 2-54. The last four steps of the synthesis were best performed in telescope fashion and provided ~5 mg of kibdelone C in pure form on 2 occasions.



Scheme 2-54: Completion of the Synthesis of (-)-Kibdelone C

2.7 Initial Biological Evaluation of (-)-Kibdelone C

Completion of the synthesis of (-)-kibdelone C allowed comparison of the biological activity to that reported for (+)-kibdelone C. Antibacterial assays with *B. subtilis* were performed first due to the ready availability of cultures courtesy of the MacMillan Lab. A disc diffusion assay was done to assess antibacterial activity

qualitatively and growth inhibition was detected quantitatively by measuring the optical density of microtiter plate cultures. Concentration-dependent zones of inhibition were observed in the disc diffusion assay and a MIC of 0.1 μM was calculated from optical density measurements for the p479 strain of *B. subtilis*. This MIC is three orders of magnitude less potent than the natural enantiomer with *B. subtilis*; however, the isolation group used a different strain of bacteria.

Cell Line	IC50 (nM)
HCC44	2.89
HCC366	5.95
H1993	4.84
HCC4017	4.86
HBEC30	5.60

Table 2-5: Cytotoxicity of (-)-Kibdelone C

The HTS core at UT Southwestern performed *in vitro* cytotoxicity assays against several human lung cancer cell lines with (-)-kibdelone C and found that the compound was potent (low nM IC_{50}) against all cell lines tested (Table 2-5). Additionally, (-)-kibdelone C was cytotoxic against a line of immortalized human bronchial epithelial cells (HBEC30) developed at UT Southwestern.[69] All IC_{50} values are slightly lower than the IC_{50} reported for (+)-kibdelone C (<1 nM for a lung cancer cell line). The isolation group did not report data for any of the cell lines tested in Table 2-5, making comparisons difficult.

The fact that cytotoxicity data for the enantiomer of the natural product is so similar to reported data is quite exciting. One could imagine that the two enantiomers present very similar interactions to a macromolecular target because of their flat aromatic structures. As discussed briefly in Chapter 1, the Boger Lab found that both (+)- and (-)-fredericamycin had almost identical activity. If this turned out to be the case for the kibdelones it is possible that the stereo-triad of the F-ring is not necessary for activity and phenols would suffice. Considering the diverse activity of polycyclic xanthone natural products with very similar structures

this may be unlikely. In any event access to both enantiomers of this natural product provides ample opportunity for further biological evaluation.

2.8 Summary and Future Directions

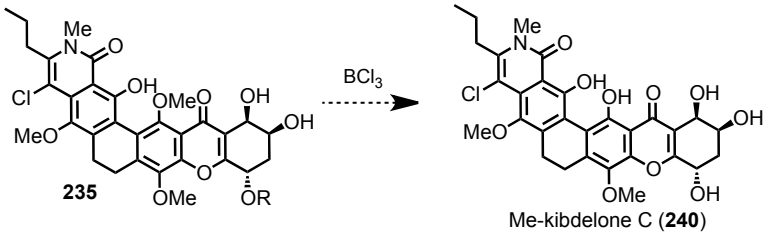
Summary

The isoquinolinone fragment of the kibdelones was synthesized using a Pomeranz-Fritsch cyclization that appears to have an interesting mechanism. The ease of access to the starting materials for this heterocycle allowed synthesis of this fragment in only 6 steps. Asymmetric epoxidation with the Shi catalyst was used to install two of the chiral centers of the F-ring of the kibdelones at an early stage in the synthesis. The method for synthesis of differentiated *trans*-diols developed by the Myers Lab allowed the strategically advantageous utilization of a C_2 symmetric precursor to the F-ring of the natural products. This achievement not only streamlined the synthesis of the kibdelones but also can provide access to the natural enantiomer, (+)-kibdelone C. This provides a unique opportunity to evaluate the biological properties of both enantiomers of kibdelone C. Central to the convergent route for synthesis of the kibdelones was a late stage biaryl bond formation. After much effort this step was achieved by way of a demanding Pd-catalyzed C-H arylation reaction. The ability to perform this reaction was enabled by the serendipitous discovery of a novel Cu-catalyzed iodination. The successful synthesis of (-)-kibdelone C was achieved in 20 steps and 1.4% yield from resorcinol with 34 total synthetic operations from commercially available materials.

Future Work

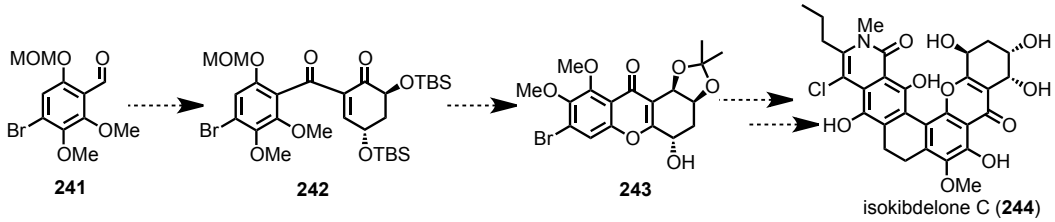
To assess the biological activity of both enantiomers of the natural product in parallel, the immediate goal is to synthesize (+)-kibdelone C. This involves making the F-ring with the enantiomeric Shi catalyst and then repeating the synthesis. To access kibdelone derivatives the final demethylation step with BCl3 can be performed on the penultimate intermediate **235** (Scheme 2-55). This would

yield Me-kibdelone C (**240**), which might be a more stable compound with comparable biological properties.



Scheme 2-55: Proposed Synthesis of Me-Kibdelone C

Synthetic efforts can also be directed toward the synthesis of the isokibdelones. These compounds should be accessible via a route very similar to that developed for the kibdelones by employing regio-isomeric D-ring precursors (Scheme 2-56).



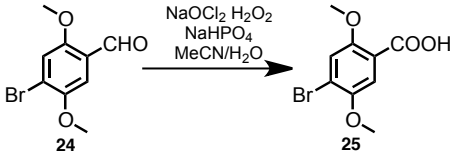
Scheme 2-56: Proposed Synthesis of the Isokibdelones

2.9 Experimental Section

General Experimental:

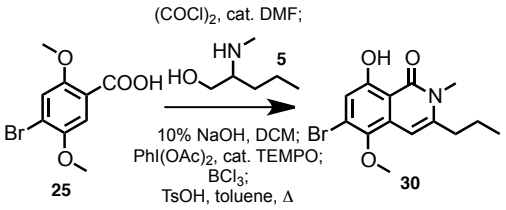
Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly purified solvents. Solvents were purified via passage over alumina columns.[70] All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063 μm) purchased from Sorbent Technologies.[71] ^{1}H and ^{13}C NMR spectra were recorded on Varian Inova-400, Inova-500, or Sedna-600 spectrometers. Chemical shifts are reported relative to internal residual solvent.[72] Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet), p (pentet) sep (septet), and app for apparent. For signals having multiple coupling patterns, the coupling constants are listed in the same order as the pattern (e.g. dt, J = 2.0, 4.0; 2.0 is the coupling constant for the doublet and 4.0 is for the coupling constant for the triplet). Infrared spectra were recorded on a Perkin-Elmer 1000 series FTIR. Low-resolution mass spectra were acquired on an Agilent 1100 LC/MS using acetonitrile and water with 0.1% formic acid mobile phases and ESI or APCI probe. Optical rotations were measured on a Rudolph Research Analytical Autopol® IV Polarimeter. Preparative HPLC was performed with Phenomenex C_{18} columns with $MeCN/H_2O$ mixtures.

Synthetic Procedures



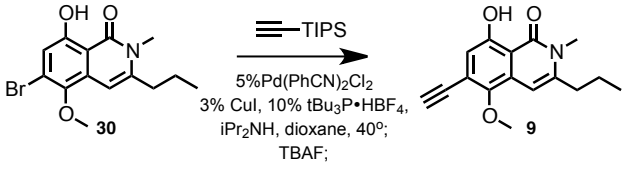
To 4.0 g of 4-bromo-2,5-dimethoxy-benzaldehyde[9] in acetonitrile (40 mL, 0.4 M) was added a solution of $NaHPO_4$ (5.6 g, 2.5 eq.) in water (16 mL), and hydrogen peroxide(30%, 4.6 mL, 2.5 eq.). The flask was stirred vigorously in a room temperature water bath while solid NaOCl (4.4 g, 3 eq.) was added slowly over ~5

min. The product began to precipitate immediately. The reaction was allowed to stir for an additional hour before being diluted with 1 M HCl and extracted with ethyl acetate. The combined extractions were then washed with a saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield benzoic acid **25** (4.06 g, 95% yield) which was used without purification and was identical to that previously reported.[8]



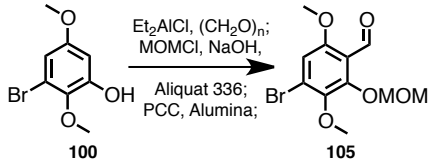
To a solution of benzoic acid **25** (2.3 g, 8.8 mmols) in DCM was added a catalytic amount of DMF (0.03 mL, 5%) followed by slow addition of oxalyl chloride (1.9 mL, 2.5 eq.) at room temperature. Stirring was continued for 1 hour at which time the stir bar was removed from the now homogeneous solution and it was concentrated under reduced pressure. The crude acid chloride was dissolved in DCM (10 mL) and added via cannula to a rapidly stirring solution of amino alcohol **5** (2 steps from norvaline)[7] in freshly prepared 5 M NaOH (130 mL) and DCM (190 mL). After ~2 hours the organic layer was seperated and the aqueous layer was extracted twice with ethyl acetate. The combined extractions were then washed with a saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude amide, which was subjected to oxidation. The crude amide was dissolved in DCM (30 mL, 0.3 M) and TEMPO (0.37 g, 0.1 eq.) was added followed by $PhI(OAc)_2$ (3.7 g, 1.3 eq.). The reaction was stirred for 18 hours, quenched with a saturated solution of $Na_2S_2O_3$, and extracted with DCM. The combined extractions were then washed with saturated $NaHCO_3$, a saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue obtained was then run through a plug of silica gel, washing with ethyl acetate to give a viscous oil. The crude aldehyde was dissolved in DCM (175 mL, 0.05 M), cooled to 0°C and treated in two portions with BCl_3 (1 M in DCM, 1st portion: 1 eq.; 2nd portion:

1.5 eq.) with a 15 minute pause between additions. After stirring for 18 hours at room temperature the reaction was quenched with saturated $NaHCO_3$ and extracted with ethyl acetate. The combined extractions were then washed with a saturated NaCl solution, dried over Na_2SO_4, filtered through a plug of silica gel, and concentrated under reduced pressure. The crude was dissolved in toluene (12 mL, 0.4 M) and TsoH-H_2O (1.3 g, 1.5 eq.) was added. The flask was fitted with a Dean-Stark trap and refluxed for 12-18 hours until no alcohol could be observed by NMR. The reaction was then cooled and saturated $NaHCO_3$ was added. The organic layer was seperated and the aqueous layer was extracted with ethyl acetate. The combined extractions were then washed with a saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography yielded 1.55 g of isoquinolinone **30** as a tan solid (54% yield, 4 steps). 0.4 R_f, 25% ethyl acetate: hexanes. ^{1}H NMR (400 MHz, CDCl3) δ 12.74 (s, 1H), 6.98 (s, 1H), 6.58 (s, 1H), 3.82 (s, 3H), 3.55 (s, 3H), 2.66 (t, *J* = 7.6 Hz, 2H), 1.78 – 1.66 (m, 2H), 1.07 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 166.2, 156.5, 148.1, 143.8, 131.1, 120.5, 114.9, 111.3, 100.9, 83.7, 79.6, 62.0, 35.7, 30.3, 21.6, 13.9. IR (NaCl): 2962, 1652, 1594, 1456, 1427, 1244 $^{-1}$cm. ESI-MS = 325.8, 327.8 [M+H].



Sonogashira cross coupling of aryl bromide **30** was modified from the method reported by Buchwald and Fu.[10] Accordingly, **30** (143 mg, 0.438 mmols) was combined with $Pd(PhCN)_2Cl_2$ (8 mg, 0.05 eq.), CuI (4 mg, 0.02 eq.), and tBu_3PHBF_4 (13 mg, 0.10 eq.) in a vial fitted with an efficient stir bar. These solids were sparged with a stream of nitrogen for ~15 minutes. 1,4-dioxane (0.35 mL, 1.25 M) was then added and the solution was sparged for 10 minutes when diisopropyl amine (0.10 mL, 1.6 eq.) was added while sparging continued. Finally triisopropylsilylacetylene (0.20 mL, 2.0 eq.) was added and sparging was continued for 10 additional minutes. The vial was then heated to 45°C in an aluminum block

with vigorous stirring for 12-18 hours under nitrogen. If not complete after this amount of time additional alkyne was added (0.5-1 eq.). When complete the reaction was filtered through a plug of silica gel, washing with ethyl acetate. The crude alkynylated product was then dissolved in THF (1.10 mL, 0.4 M) and a solution of tetrabutylammonium fluoride (1.0 M, 1.5 eq.) was added at 0°C and allowed to warm to room temperature. Once complete (~2 hours), the reaction was diluted with ethyl acetate and water. The organic phase was separated and the aqueous layer was extracted twice with ethyl acetate. The combined extractions were then washed with a saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was then purified by flash chromatography (0.3 R_f, 25% ethyl acetate: hexanes) to give 100 mg of alkyne **9** (85% over 2 steps). ^{1}H NMR (400 MHz, CDCl3) δ 12.61 (s, 1H), 6.80 (s, 1H), 6.57 (s, 1H), 3.90 (s, 3H), 3.52 (s, 3H), 3.40 (s, 1H), 2.62 (t, *J* = 7.6 Hz, 2H), 1.77 – 1.63 (m, 2H), 1.05 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 166.2, 156.5, 148.1, 143.8, 131.1, 120.5, 114.9, 111.3, 100.9, 83.7, 79.6, 62.0, 35.7, 30.3, 21.6, 13.9. IR (NaCl): 3226, 1657, 1567. 1482, 1243, 1034 $^{-1}$cm. ESI-MS = 272.6 [M+H].

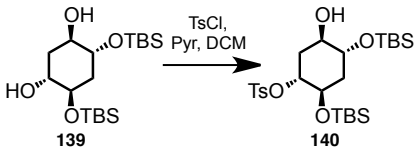


100 **105**

To a round bottom flask containing 5.9 g (25.3 mmol) of phenol **100** (3 steps, from 5-Methoxysalicylaldehyde)[22] and finely powdered paraformaldehyde (3.8g, 5 eq.) was added DCM (0.2 M, 127 mL). This solution was cooled to 0° and Et_2AlCl (1.0 M in DCM, 2.6 eq.) was added over 25 min using an addition funnel.[24] Upon completion of the addition the ice water bath was removed. The reaction was stirred at room temperature until complete by TLC (1 hour, 0.5 R_f, 50% ethyl acetate: hexanes). The reaction was then cooled using an ice water bath and quenched by the *slow* addition of 1M HCl (150 mL). After stirring an additional 15 minutes the organic layer was separated and the aqueous was extracted with DCM (2x). The combined extractions were then washed with a saturated NaCl solution,

dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude diol obtained was dissolved in DCM (84 mL, 0.3 M) and a catalytic amount of Aliquat 336 (1.2 mL, 10 mol%) and freshly prepared aqueous NaOH (5 M, 160 mL, 30 eq.) was added. After stiring vigorously for ~5 minutes MOM-Cl (5.8 mL, 3 eq.) was added dropwise at room temperature. After 1 hour if the reaction was not complete by TLC additional MOM-Cl was added (1-2 eq.) until the starting material was consumed. When the reaction was complete the organic layer was separated and the aqueous layer was extracted 3 times with DCM. The combined extractions were then washed with a saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude benzylic alcohol was then oxidized in DCM with PCC adsorbed on alumina.[73] The resulting solution was stirred for 12-20 hours until oxidation was complete (0.4 R_f, 25% ethyl acetate: hexanes). The reaction was then diluted with Et_2O and filtered using a fritted funnel and celite. The resulting orange oil was purified with flash chromatography (0→25% ethyl acetate:hexanes) to obtain 5.07 g of benzaldehyde **105** (66% over 3 steps). ^{1}H NMR (400 MHz, CDCl3) δ 10.24 (s, 1H), 6.82 (s, 1H), 5.04 (d, *J* = 7.2 Hz, 2H), 3.72 (s, 3H), 3.66 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 188.3, 157.3, 152.5, 144.5, 124.8, 119.1, 111.3, 100.4, 60.8, 57.7, 56.3. IR (NaCl): 2940, 1693, 1579, 1559, 1471, 1377, 1248, 1073 cm^{-1}. ESI-MS = 304.8, 306.8 [M+H].

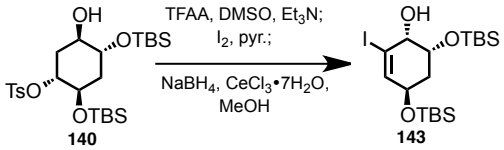
Mono-tosylate (140): Diol **139** was prepared according to the method of Meyers[30] with the exception that metered addition funnels were used for large-scale preparations. This had a minor effect on yield (60-68%, vs. 69% reported) but the material obtained was identical to that reported.



139 **140**

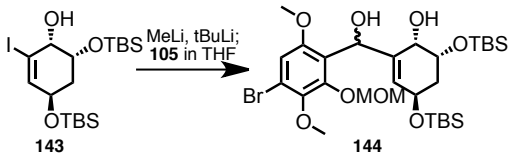
To an oven dried flask was added 0.063 g diol **139** and DCM (0.4 mL, 0.4 M). Pyridine (0.4 mL, 0.4 M) and p-toluenesulfonyl chloride (0.048 g, 1.50 eq.) were added sequentially at room temperature. The reaction was then stirred vigorously

until complete by TLC (2-3 days). Water was then added and the reaction was extracted with ethyl acetate. The combined organic layers were then washed with 1 M HCl, brine, and dried with Na_2SO_4. After concentration, flash chromatography (0→25% ethyl acetate:hexanes) provided mono-tosylate **140** as a white solid (0.063 g, 71%). R_f: 0.25, 25% ethyl acetate in hexanes. ^{1}H NMR (500 MHz, CDCl3) δ 7.80 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 4.39 (d, *J* = 3.2 Hz, 1H), 3.92 (d, *J* = 2.9 Hz, 1H), 3.75 (td, *J* = 9.6, 4.5 Hz, 1H), 3.69 – 3.60 (m, 1H), 2.46 (s, 1H), 2.22 (d, *J* = 31.7 Hz, 1H), 1.99 – 1.68 (m, 2H), 0.90 (s, 4H), 0.85 (s, 4H), 0.08 (s, 1H), 0.07 (s, 1H), 0.02 (s, 1H), -0.02 (s, 1H). ^{13}C NMR (101 MHz, CDCl3) δ 145.0, 133.9, 130.1, 127.9, 80.3, 71.8, 70.6, 68.8, 36.2, 31.7, 25.9, 25.7, 21.8, 18.1, 17.9, -4.3, -4.6, -5.0, -5.1. $[\alpha]_D^{20}$: (-)-10 (c = 1.0, $CHCl_3$). IR (NaCl): 3545, 2858, 1600, 1361, 1254, 1177, 1031 $^{-1}$cm. APCI-MS (negative mode)= 575.2 [M+HCO_2^-].



To a solution of DMSO (0.24 mL, 2 eq.) in DCM (3.1 mL, 1.1 M) at -78°C was added trifluoroacetic anhydride (0.35 mL, 1.5 eq.). After 15 min a -78°C solution of 0.9 g (1.69 mmol) of Mono-tosylate **140** dissolved in DCM (3.4 mL, 0.5 M) was added via cannula. The reaction was stirred for 30 min at -78°C at which time triethylamine was added dropwise (1.2 mL, 5 eq.). The reaction was then allowed to slowly warm to room temperature over 6 hours. It was then quenched by the addition of saturated ammonium chloride solution. The reaction was extracted with ethyl acetate and the organic layer was washed with a saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The enone obtained was dissolved in DCM and pyridine (0.43 mL, 1.2 eq.) and iodine (1.12 g, 2.5 eq.) were added at room temperature. The reaction was stirred until complete by ^{1}H NMR (12-18hrs). The reaction was diluted with ethyl acetate and quenched with a saturated solution of sodium thiosulfate and allowed to stir for ~30 min. The reaction was then diluted with water and extracted with ethyl acetate (3x). The

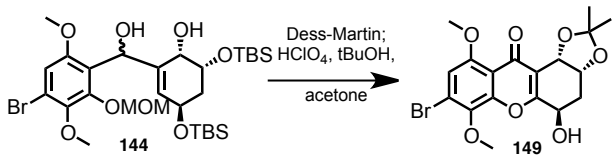
combined organic layers were washed with 1 M HCl, saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude iodo-enone, which was used without purification. The iodo-enone was dissolved in MeOH (18 mL, 0.1 M) and cooled to -78°C. $CeCl_3 \bullet 7H_2O$ (1.31 g, 2 eq.) was added followed by $NaBH_4$ (0.13 g, 2 eq.). Once complete the reaction was quenched by the slow addition of water and after warming, slow addition of 20% citric acid solution. After stiring for 1-2 hours the reaction was extracted with ethyl acetate and the combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (0→25% ethyl acetate:hexanes) provided 0.612 g of vinyl iodide **143** as a single diasteromer. (75% yield over 3 steps). R_f: 0.6, 25% ethyl acetate in hexanes. ^{1}H NMR (400 MHz, CDCl3) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.38 (d, *J* = 3.3 Hz, 1H), 3.90 (d, *J* = 3.3 Hz, 1H), 3.79 – 3.69 (m, 1H), 3.69 – 3.58 (m, 1H), 2.45 (s, 3H), 2.25 (s, 1H), 2.02 – 1.59 (m, 4H), 0.88 (s, 9H), 0.84 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.01 (s, 3H), -0.04 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 142.9, 102.9, 73.8, 68.3, 67.2, 36.6, 25.9, 25.9, 18.2, 18.2, -4.5, -4.5, -4.7, -4.8. $[\alpha]_D^{20}$: (+)-33.4 (c = 1.0, $CHCl_3$). IR (NaCl): 3556, 2930, 2858, 1628, 1471, 1256, 1090, 837 cm^{-1}. APCI-MS (negative mode) = 483.1 [M-H].



143 144

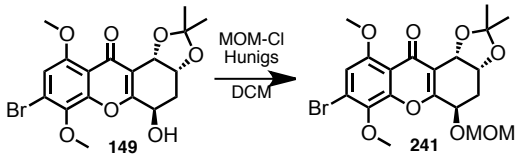
In a round bottom flask vinyl iodide **143** (0.20 g) was dissolved in diethyl ether and cooled to -78°C. A solution of MeLi in diethyl ether (1.6 M, 1.05 eq.) was then added dropwise. The pale yellow solution was allowed to stir at -78°C for 10 minutes before a solution of tBuLi in hexanes (1.7 M, 2.0 eq.) was added dropwise, intensifying the color of the solution. Immediately upon completion of the addition of tBuLi, a -78°C cooled solution of benzaldehyde **105** (0.176 g, 1.4 eq.) in THF (0.8 M) and diethyl ether (0.4 M) was added dropwise via cannula, resulting in a rapid loss of intense color. The reaction was allowed to stir for 2 hours at -78°C when it

was quenched by the addition of a saturated solution of ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the viscous yellow oil by flash chromatography (0→25% ethyl acetate:hexanes) provided diol **144** as an inconsequential 1.1:1 mixture of diastereomers. (0.217 g, 80%) R_f: 0.25, 25% ethyl acetate in hexanes. NMR spectra page S13. IR (NaCl): 3548, 2895, 2857, 1571, 1473, 1254, 1073, 837 $^{-1}$cm. APCI-MS (negative mode) = 661.2, 663.2 [M-H].

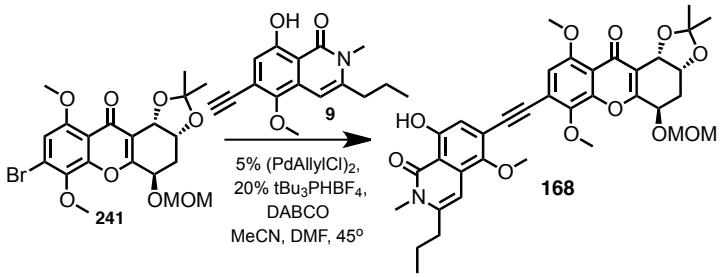


A solution of diol **144** (0.196 g, 0.295 mmol) in DCM (3 mL, 0.1 M) was cooled to 0°C and Dess-Marin periodinane was added (0.375 g, 3.0 eq). After 30 minutes the bath was removed and the reaction was stirred at room temperature until complete, adding more periodinane if not complete after 2 hours. Once complete the reaction was cooled to 0°C and quenched with a 1:1 mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$. After stirring for 45 minutes the reaction was diluted with saturated $NaHCO_3$, extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a yellow oil. The crude ene-dione was dissolved in acetone (30 mL, 0.01 M) and tBuOH (0.3 mL, 10 eq.). The flask was then cooled to 0°C and a 70% solution of $HClO_4$ (0.075 mL, 3.0 eq.) was added dropwise. The reaction was allowed to warm slowly over 20 hours. It was then heated to 35°C for 36 hours at which time the reaction was complete by NMR. The reaction was cooled, quenched with a saturated solution of $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The pale green foam was purified by flash chromatography (0→4% methanol:ethyl acetate) to yield .084 g of acetonide **149**. (66% yield, 2 steps) R_f: 0.4,

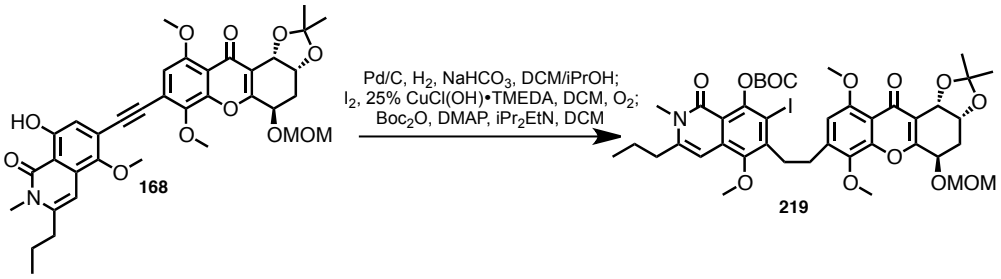
5% methanol in ethyl acetate. ^{1}H NMR (400 MHz, CDCl3) δ 6.93 (s, 1H), 5.32 (d, *J* = 5.8 Hz, 1H), 5.00 (d, *J* = 6.8 Hz, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.85 – 4.80 (m, 1H), 4.64 – 4.58 (m, 1H), 3.91 (s, 6H), 3.50 (s, 3H), 2.50 – 2.40 (m, 1H), 2.14 – 2.05 (m, 1H), 1.44 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 176.3, 162.5, 155.4, 151.2, 139.6, 122.8, 117.5, 114.3, 110.4, 109.1, 70.9, 69.6, 63.1, 61.7, 56.7, 34.4, 27.8, 25.8. $[\alpha]_D^{20}$: (-)-78 (c = 1.0, $CHCl_3$). IR (NaCl): 3407, 2937, 1641, 1567, 1483, 1412, 1040 cm^{-1}. ESI-MS = 426.8, 428.8 [M+H].



Alcohol **149** was dissolved in DCM (2.2 mL, 0.3 M) and cooled to 0°C. Hunigs base (0.23 mL, 2 eq.) was added followed by MOM-Cl (.08 mL, 1.5 eq.) and the reaction was allowed to slowly warm to room temperature over 18 hours. Additional MOM-Cl (1-2 eq.) and base (1-2eq.) were added if necessary. When complete by TLC (R_f: 0.5, 5% methanol in ethyl acetate) the reaction was diluted with a saturated solution of ammonium chloride and ethyl acetate and further extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The pale yellow foam was purified by flash chromatography (0, 50→100% ethyl acetate:hexanes) to yield 0.246 g of MOM ether **241** (79% yield). R_f: 0.5, 5% methanol in ethyl acetate. ^{1}H NMR (400 MHz, CDCl3) δ 6.93 (s, 1H), 5.32 (d, *J* = 5.8 Hz, 1H), 5.00 (d, *J* = 6.8 Hz, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.85 – 4.80 (m, 1H), 4.64 – 4.58 (m, 1H), 3.91 (s, 6H), 3.50 (s, 3H), 2.50 – 2.40 (m, 1H), 2.14 – 2.05 (m, 1H), 1.44 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 175.6, 161.1, 155.3, 151.0, 139.4, 122.4, 117.6, 114.2, 109.9, 109.0, 96.1, 70.4, 68.8, 67.1, 61.2, 56.4, 55.6, 32.5, 27.7, 25.6. $[\alpha]_D^{20}$: (-)-28 (c = 1.0, $CHCl_3$). IR (NaCl): 2937, 1657, 1567, 1482, 1243, 1035 cm^{-1}. ESI-MS = 470.8, 472.8 [M+H].

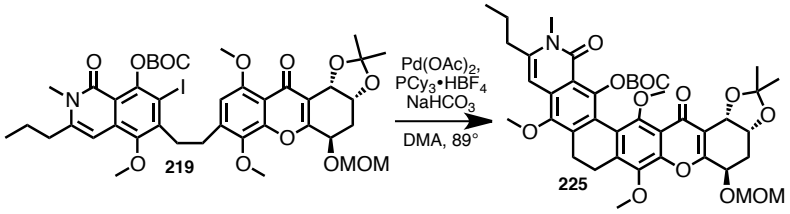


A modified procedure reported by Soheili and co-workers[42] was used for Sonogashira cross-coupling. Accordingly, **241** (0.246 g, 0.522 mmols) was combined with $(PdAllylCl)_2$ (10 mg, 0.05 eq.), DABCO (129 mg, 2.2 eq.), and tBu_3PHBF_4 (30 mg, 0.20 eq.) in a vial fitted with an efficient stir bar under an atmosphere of nitrogen. Acetonitrile (0.52 mL, 1.0 M) was then added and the solution was sparged for 10 minutes. In a separate vial alkyne **9** (0.212 g, 1.5 eq.) was dissolved in degassed DMF (1.57 mL, 0.5 M) and sparged for 10 minutes before being loaded into a syringe. The solution of alkyne was then added via syringe pump over 7 hours at 45°C in an aluminum block with vigorous stirring. Once the addition was finished stirring at this temperature was maintained for an additional 6-10 hours. When complete the reaction was filtered through a plug of silica gel, washing with DCM. The eluent was then concentrated under reduced pressure and purified by flash chromatography (0, 50→100% ethyl acetate:hexanes) to give 0.321 g of alkyne **168** (98% yield) as an orange foam. R_f: 0.2, 75% ethyl acetate: hexanes. ^1H NMR (400 MHz, CDCl3) δ 12.67 (s, 1H), 6.92 (s, 1H), 6.85 (s, 1H), 6.66 (s, 1H), 5.34 (d, *J* = 5.8 Hz, 1H), 5.03 (d, *J* = 6.8 Hz, 1H), 4.88 (d, *J* = 6.8 Hz, 1H), 4.86 – 4.80 (m, 1H), 4.64 – 4.58 (m, 1H), 4.05 (s, 3H), 4.01 (s, 3H), 3.94 (s, 3H), 3.58 (s, 3H), 3.50 (s, 3H), 2.73 – 2.64 (m, 2H), 2.50 – 2.40 (m, 1H), 2.14 – 2.04 (m, 1H), 1.81 – 1.68 (m, 2H), 1.44 (s, 3H), 1.36 (s, 3H), 1.08 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 175.8, 165.8, 161.5, 156.3, 154.7, 150.8, 147.3, 143.8, 143.3, 130.8, 121.4, 120.3, 117.7, 115.2, 113.9, 111.0, 109.0, 108.7, 100.4, 96.2, 92.6, 90.2, 70.5, 68.9, 67.1, 61.9, 61.7, 56.4, 55.7, 35.3, 32.6, 30.0, 27.7, 25.7, 21.2, 13.6. $[\alpha]_D^{20}$: (-)-27 (c = 1.0, $CHCl_3$). IR (NaCl): 2937, 1651, 1603, 1480, 1211, 1035 $^{-1}$cm. ESI-MS = 426.8, 428.8 [M+H].



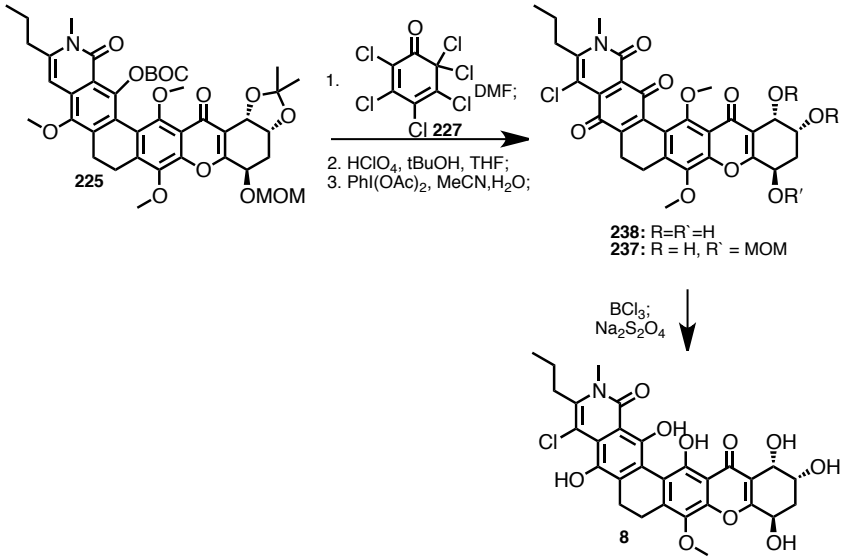
Pd/C (10%, 0.111 g, 0.2 eq.) and $NaHCO_3$ (0.065 g, 1.5 eq.) were added to a vial containing alkyne **168** (0.321 g, 0.52 mmol). DCM and isopropanol (1.3 mL each, 0.2 M) were added, the reaction was sparged with hydrogen for 15 minutes and then stirred under a hydrogen atmosphere for 18 hours. The reaction was then filtered through a pad of celite, washing with DCM and concentrated under reduced pressure. Iodination of the phenol was performed with CuCl(OH)•TMEDA[74] (0.03 g, 0.25 eq.) and iodine (0.132 g, 1.0 eq.) in DCM (1.57 mL, 0.5 M) under an oxygen atmosphere (balloon) over 4-6 hours. Once an NMR aliquot showed complete conversion a 5% $NaHSO_3$ solution was added and allowed to stir for 1 hour. The reaction was then diluted with ethyl acetate, the organic layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The tan foam obtained was dissolved in DCM (2.6 mL, 0.2 M) and DMAP (0.127 g, 2.0 eq.) and Boc_2O (0.6 mL, 5.0 eq.) were added while the reaction was cooled to 0°C. After 10 minutes the bath was removed and the reaction was stirred for 18 hours. The reaction was quenched with a saturated solution of ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The tan foam was purified by flash chromatography (0, 50→100% ethyl acetate:hexanes) to give 0.305 g of aryl iodide **219** (66% yield, 3 steps). R_f: 0.4, 75% ethyl acetate: hexanes. ^{1}H NMR (400 MHz, CDCl3) δ 6.66 (s, 1H), 6.43 (s, 1H), 5.35 (d, *J* = 5.8 Hz, 1H), 5.03 (d, *J* = 6.8 Hz, 1H), 4.88 (d, *J* = 6.8 Hz, 1H), 4.86 – 4.79 (m, 1H), 4.65 – 4.58 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 3.53 (s, 3H), 3.50 (s, 3H), 3.32 – 3.18 (m, 2H), 3.09 – 2.93 (m, 2H),

2.67 – 2.58 (m, 2H), 2.50 – 2.39 (m, 1H), 2.15 – 2.05 (m, 1H), 1.77 – 1.68 (m, 2H), 1.64 (s, 9H), 1.45 (s, 3H), 1.37 (s, 3H), 1.06 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 176.6, 161.3, 160.2, 155.3, 151.2, 150.1, 147.4, 145.6, 140.6, 140.4, 140.0, 132.7, 117.4, 117.2, 113.9, 109.3, 107.5, 98.5, 96.6, 96.6, 83.8, 70.8, 69.8, 68.0, 62.2, 62.0, 56.6, 56.0, 36.5, 36.2, 33.1, 31.0, 30.2, 28.1, 26.1, 21.6, 14.0. $[\alpha]_D^{20}$: (-)-19 (c = 1.0, $CHCl_3$). IR (NaCl): 2936, 1761, 1655, 1620, 1247, 1069 $^{-1}$cm. ESI-MS = 891.7 [M+].



Aryl iodide **219** (0.218 g, 0.24 mmol) and $NaHCO_3$ (0.41 g, 20.0 eq.) was dissolved in degassed dimethylacetamide (24 mL, 0.01 M) and a pre-made solution of $Pd(OAc)_2$ (1.5 eq.), $tBu_3PH•BF_4$ (3.0 eq), and pivalic acid (6.0 eq) in degassed dimethylacetamide (0.2 M, 0.1.8 mL) was added. After evacuating the vessel and backfilling with nitrogen 3 times, the reaction was heated in an aluminum block to 91°C for 18 hrs with vigorous stirring and protection from light (loose foil). The reaction was cooled, poured into a dilute brine solution and extracted with ethyl acetate (4x25 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered over a small silica pad (1") and concentrated under reduced pressure. The green foam was purified by flash chromatography (0, 50→100% ethyl acetate:hexanes) to give 0.115 g of hexacycle **225** as a mixture of atropisomers (63% yield). Rf: 0.3, 75% ethyl acetate:hexanes. ^{1}H NMR (400 MHz, CDCl3) δ 6.55 (s, 1H), 5.44 – 5.29 (m, 1H), 5.16 – 4.97 (m, 1H), 4.97 – 4.79 (m, 2H), 4.71 – 4.56 (m, 1H), 3.93 – 3.74 (app m, 6H), 3.58 – 3.42 (app m, 9H), 3.42 – 3.33 (m, 2H), 2.70 – 2.57 (m, 2H), 2.56 – 2.44 (m, 1H), 2.31 (t, *J* = 12.4 Hz, 1H), 2.25 – 1.96 (m, 2H), 1.77 – 1.68 (m, 2H), 1.66 (s, 9H), 1.46 (s, 3H), 1.37 (s, 3H), 1.07 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 175.4, 171.5, 161.8, 161.7, 161.3, 154.1, 154.0, 151.8, 150.5, 150.4, 147.8, 145.0, 144.4, 140.9, 140.3, 140.2, 136.3, 132.6, 123.0,

122.9, 122.8, 122.7, 117.9, 117.8, 117.5, 117.5, 117.3, 109.4, 109.1, 98.4, 96.6, 96.1, 82.7, 82.6, 71.3, 71.0, 69.6, 69.4, 67.6, 67.3, 64.6, 62.8, 62.1, 62.0, 61.9, 56.2, 56.1, 36.3, 33.6, 33.2, 31.0, 30.9, 29.9, 28.1, 28.1, 27.9, 26.1, 25.9, 23.8, 23.8, 23.6, 23.4, 21.9, 21.3, 19.4, 18.9, 14.1, 14.0. IR (NaCl): 2933, 1764, 1656, 1620, 1467, 1246, 1164, 1036 $^{-1}$cm. ESI-MS = 763.9 [M+H].

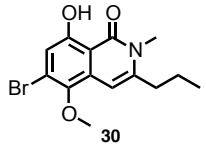


225 (0.030 g, 0.039 mmols) was dissolved in degassed DMF (1.1 mL, 0.05 M) and a solution of dienone **227** in DCM (0.2 M, 1.2 eq.) was added at 0°C and the bath was removed. After 1 hour the reaction was quenched by the addition of excess $Na_2S_2O_4$ and water, while stirring was continued at room temperature for 15 minutes. The reaction was then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was then dissolved in THF (2.8 mL, 0.02 M) and tBuOH (1.1 mL, 0.05 M), cooled to 0°C, and treated with $HClO_4$ (70% solution, 0.05 mL, 10 eq.) for 12 hours at room temperature. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude foam was dissolved in

acetonitrile and water and $PhI(OAc)_2$ (0.036 g, 2.0 eq.) was added. The reaction was stirred for 1 hour and then quenched by the addition of a 1:1 mixture of a saturated solution of $NaHCO_3$ and a saturated solution of $Na_2S_2O_3$ and stirred for 10 minutes. The reaction was then extracted with ethyl acetate (5x3 mL) and the combined organic layers were washed with a saturated solution of $NaHCO_3$, a saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure with a cold water bath. The residue obtained could be purified by semi-preparative RP-HPLC to give Me-Kibdelone B (**238** ~90% purity, ^{1}H NMR of **238** page S19) and compound **237**. ESI-MS 613.8 [M+H], 657.8 [M+H]. However, this crude material was normally used in the next step without purification. Accordingly, crude **237-238** was dissolved in DCM (2.2 mL, 0.01 M), cooled to -78°C, and treated with a solution of BCl_3 (1.0 M in DCM, 6 eq.). After 30 min the reaction was moved to an ice bath and stirred for an additional 1.25 hours. It was then quenched by the addition of a saturated solution of $NaHCO_3$ and stirred for 10 minutes at room temperature. To obtain kibdelone C, the reaction was diluted with acetonitrile (~0.5 mL), treated with excess $Na_2S_2O_4$, stirred for 15 minutes, and then extracted with ethyl acetate. [If $Na_2S_2O_4$ was omitted from the workup kibdelone B could be detected by C_{18} LC/MS (M+H, 583.8: 13.5 min, 30→90% MeCN/H_2O over 20 minutes) and crude NMR; however all efforts to purify kibdelone B resulted in mixtures. Similar observations were made by the isolation group.[68]] The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure with a cold-water bath. This residue was then dissolved in minimal acetonitrile and DMSO/water and a spatual tip of $Na_2S_2O_4$. Purification was performed by RP-HPLC (Phenomenex 250 x 10 mm Luna 5µ C_{18} column, 2 mL/min, 40→90% acetonitrile: water, 13.5 min) and the fractions were lyophilized to yield kibdelone C (**8**) (0.004 g, 16 % yield, 4 steps). ^{1}H NMR (600 MHz, dmso) δ 13.99 (s, 1H), 13.14 (s, 1H), 8.43 (s, 1H), 5.99 (d, J = 6.3 Hz, 1H), 4.97 (s, 1H), 4.74 (d, J = 6.1 Hz, 1H), 4.70 (dd, J = 4.1, 3.8 Hz, 1H), 4.67 (s, 1H), 3.96 – 3.90 (m, 1H), 3.85 (s, 3H), 3.61 (s, 3H), 3.39 (d, J = 13.1 Hz, 1H), 3.30 – 3.26 (m, 1H), 2.98 – 2.94 (m, 2H), 2.24 (ddd, J = 13.0, 12.5, 4.2 Hz, 2H), 2.18 – 2.10 (m, 1H), 1.77 (d, J =

13.1 Hz, 1H), 1.68-1.59 (m, 2H), 1.05 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, dmso) δ 182.4, 165.1, 164.9, 152.6, 152.3, 147.8, 141.3, 140.6, 138.0, 137.4, 135.3, 124.1, 117.9, 116.8, 114.8, 109.5, 108.8, 108.6, 65.1, 64.1, 61.5, 61.4, 33.9, 31.8, 31.7, 23.11, 23.07, 20.3, 13.8. $[\alpha]_D^{20}$: (-)-40 (c = 0.01, $CHCl_3$). ESI-MS = 585.9 [M+].

2.10 Relevant Spectra for the Kibdelones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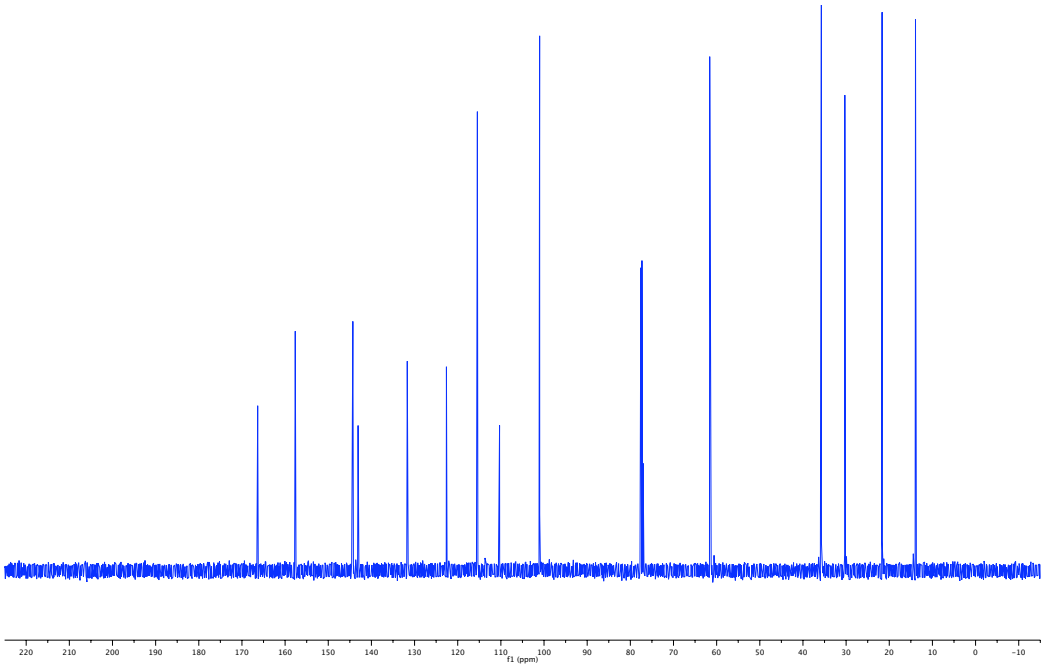
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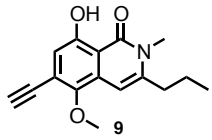
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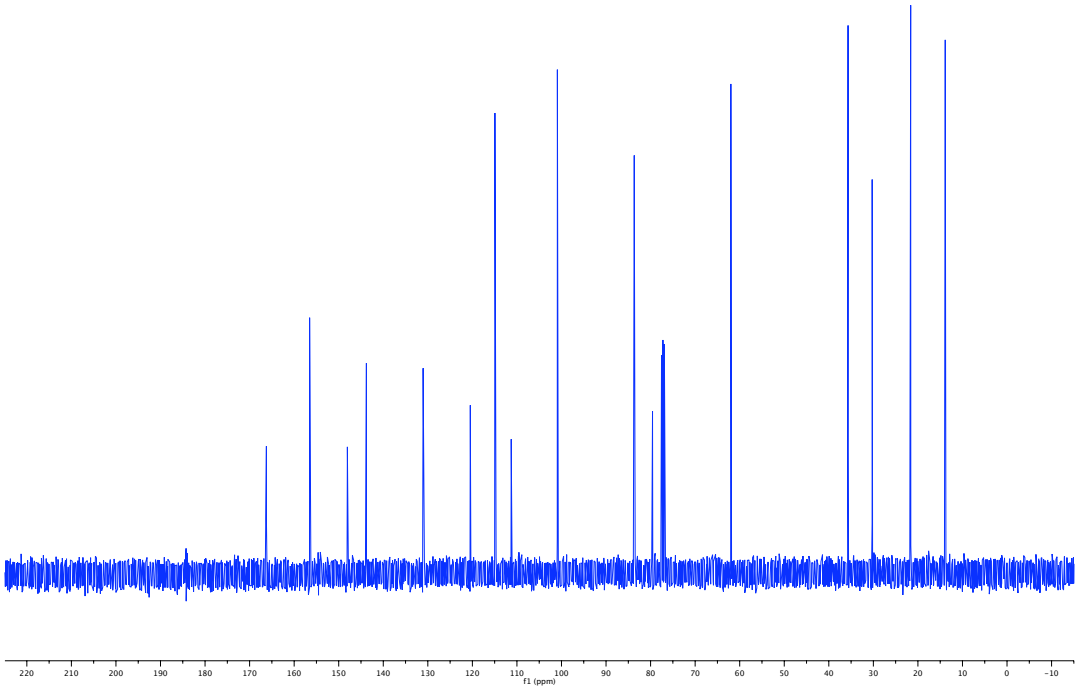
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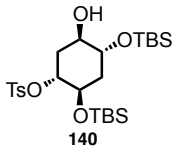
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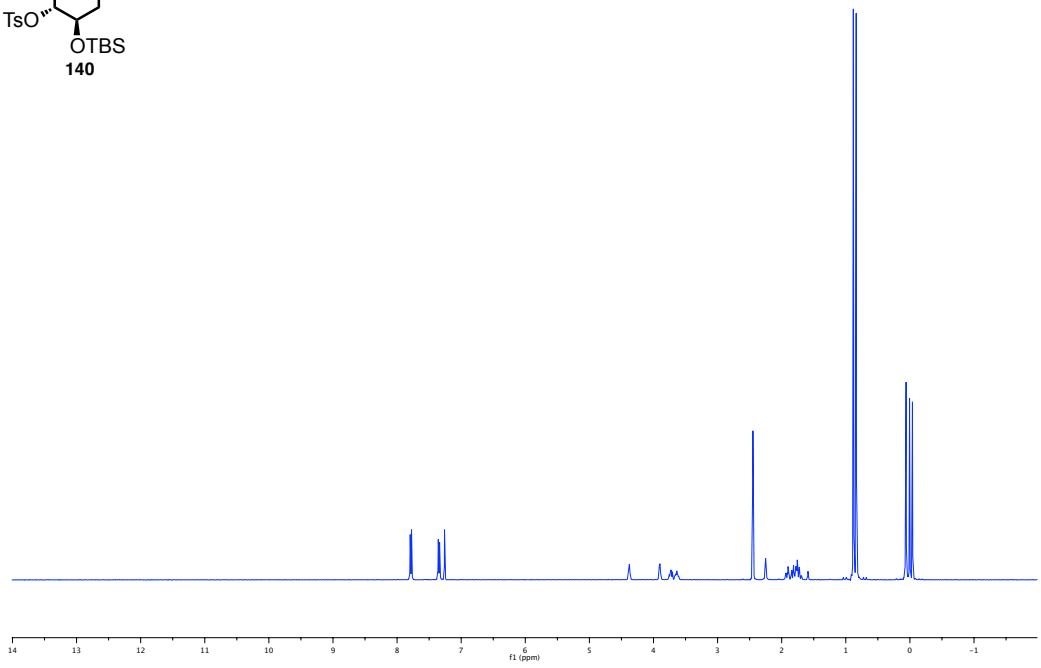
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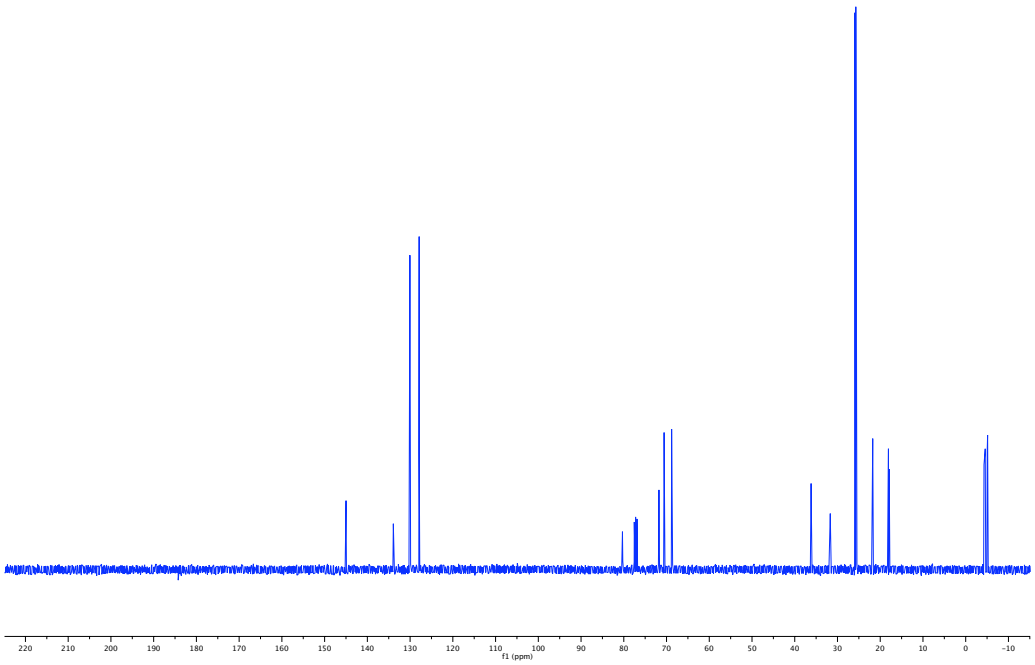
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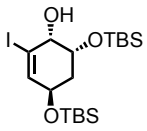
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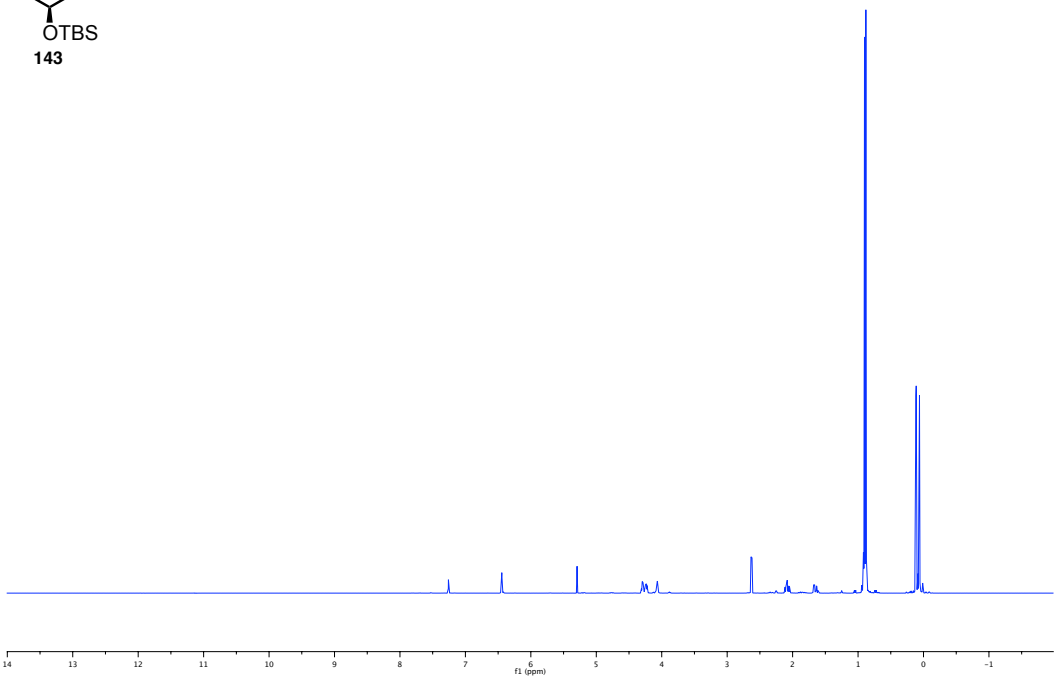
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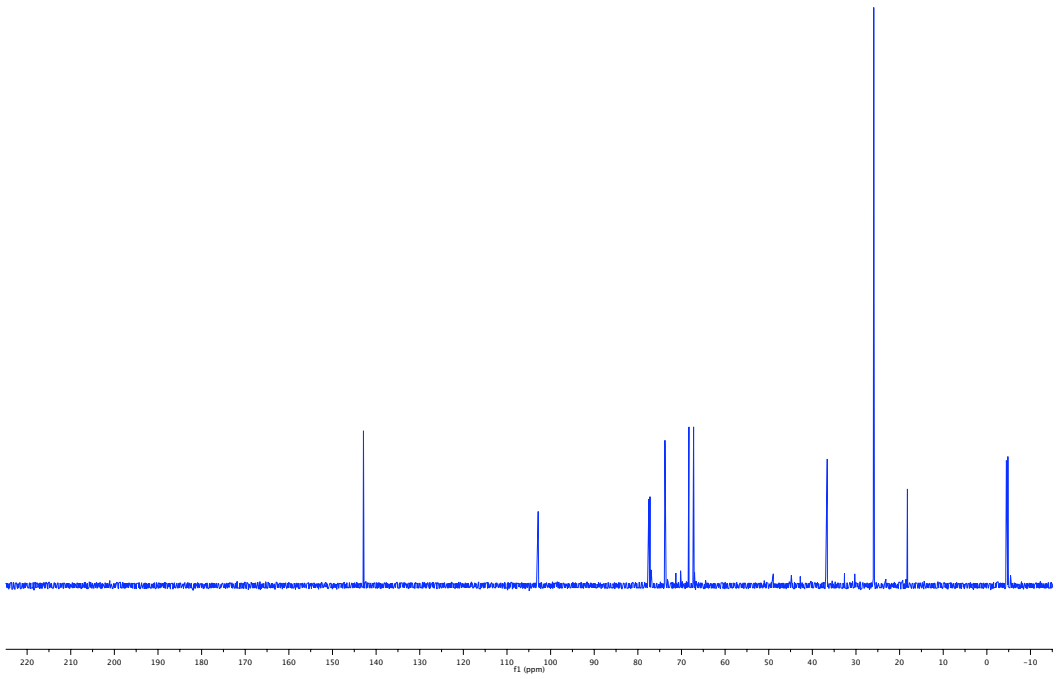
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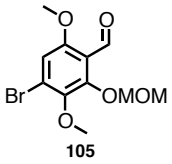
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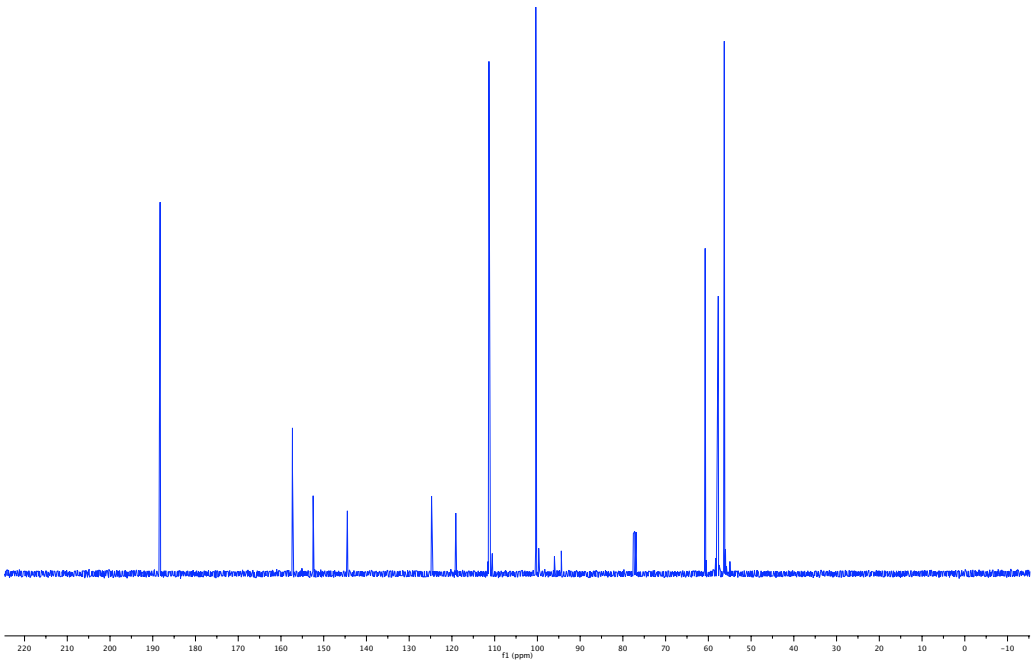
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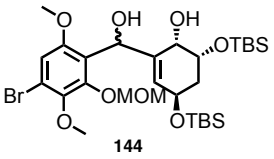
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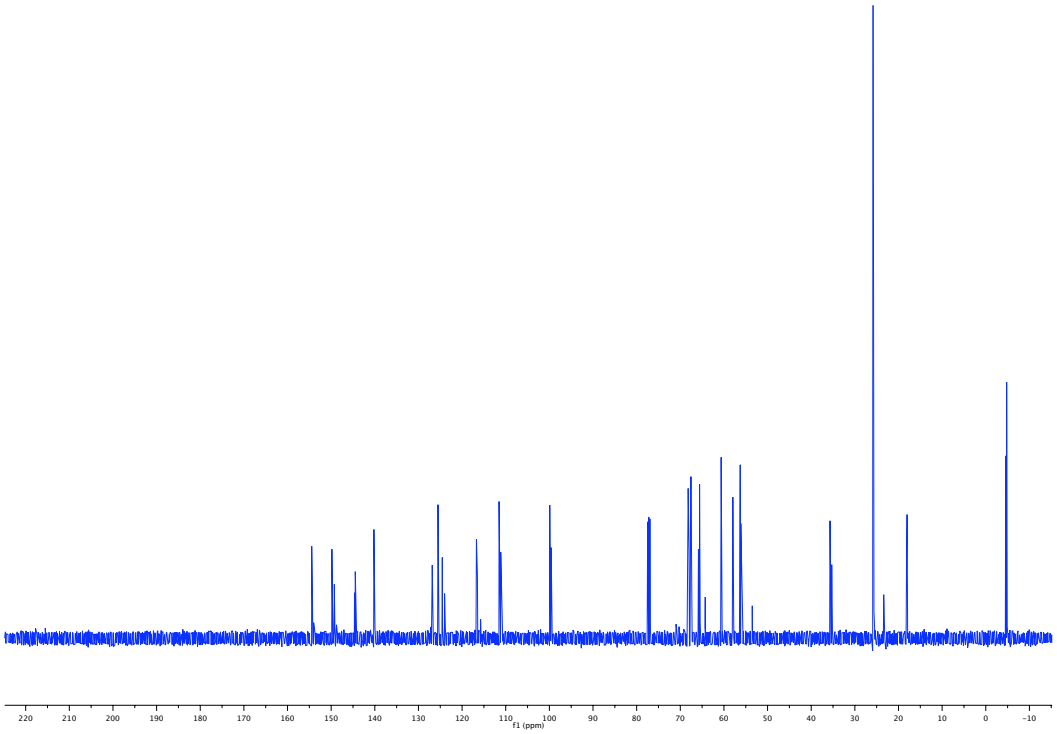
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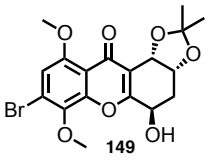
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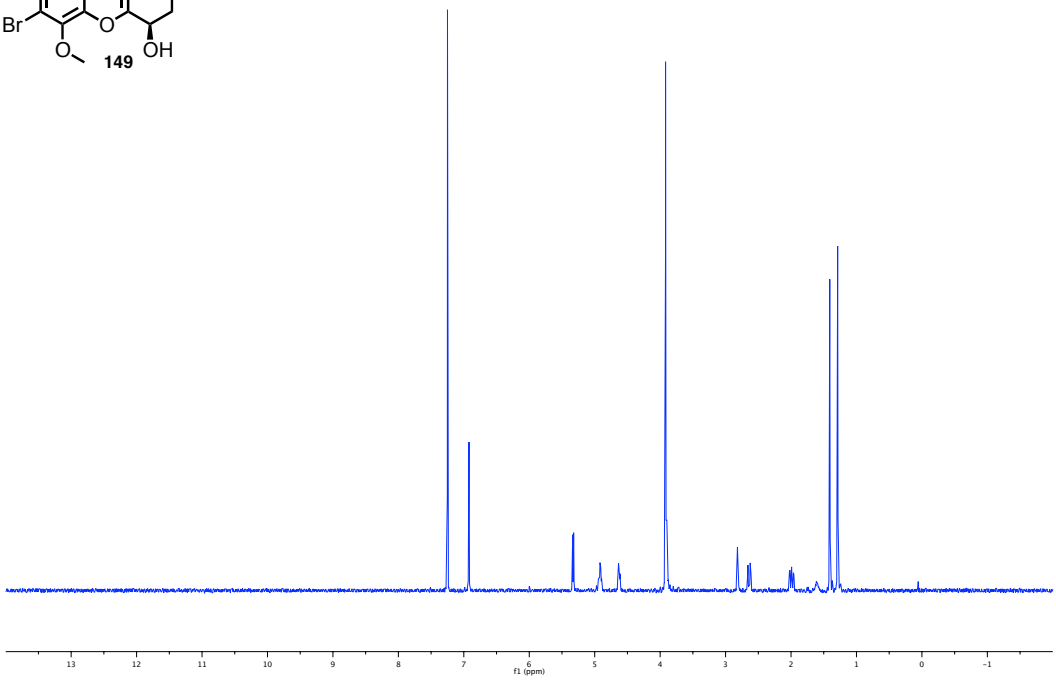
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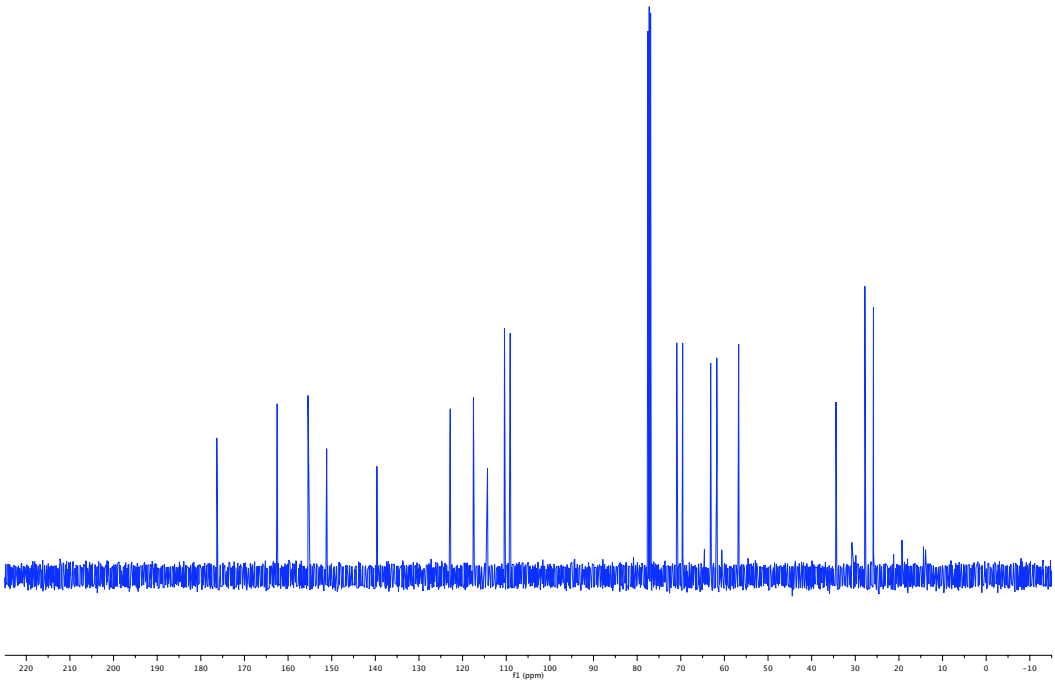
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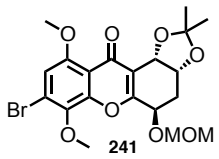
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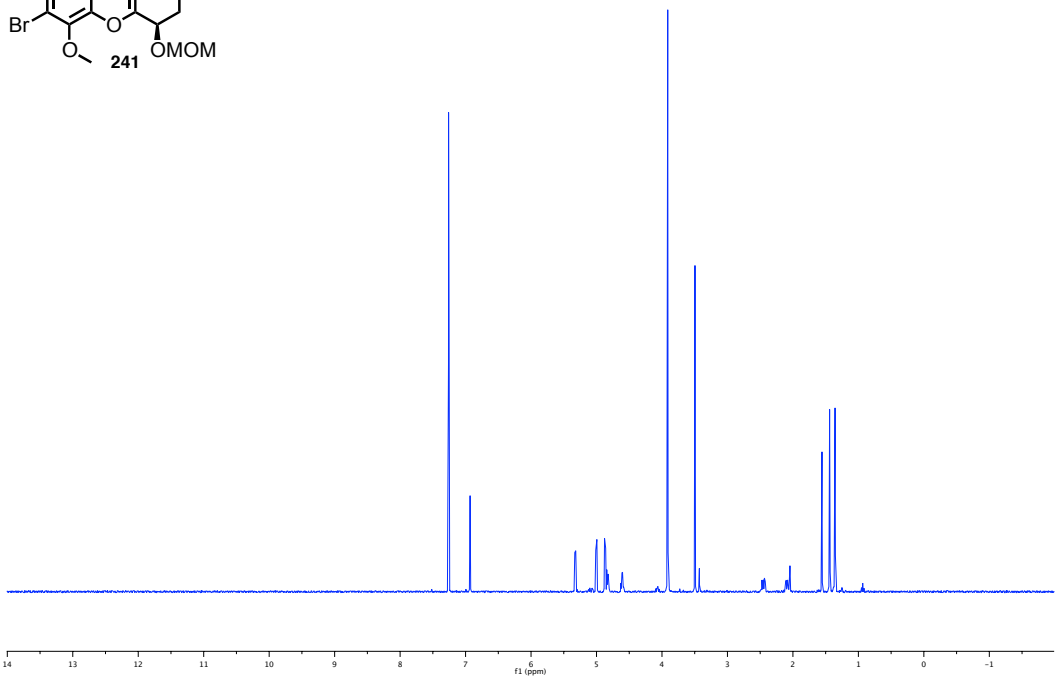
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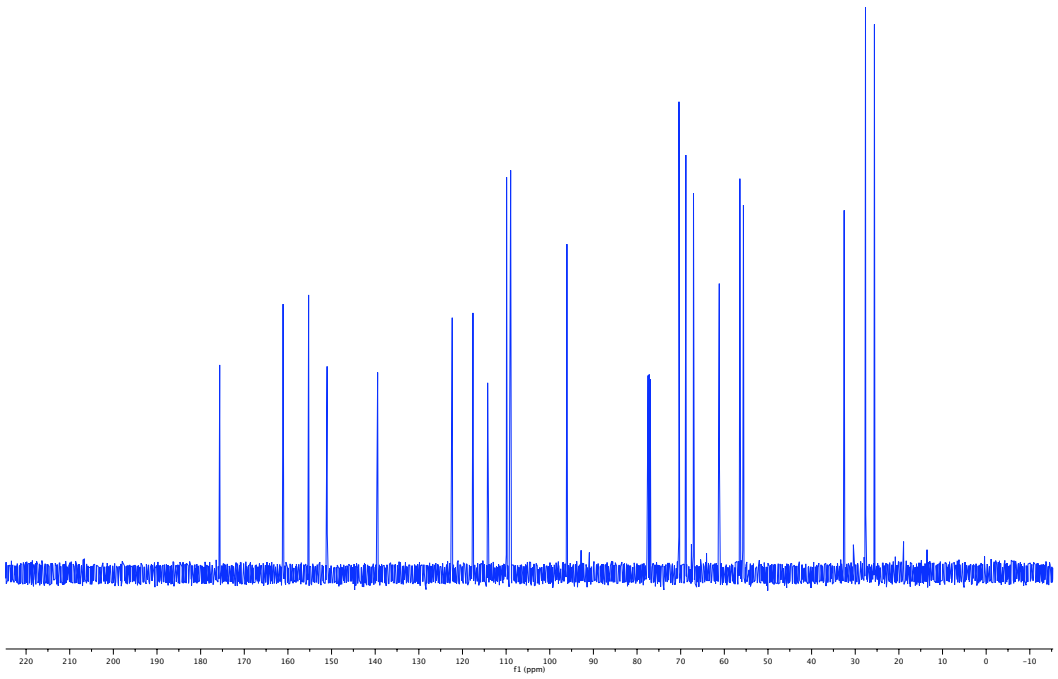
f1 (ppm)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210
200
190
180
170
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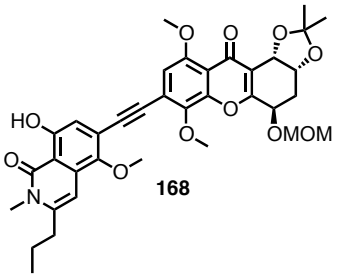
20
10
0
-10
f1 (ppm)


HO
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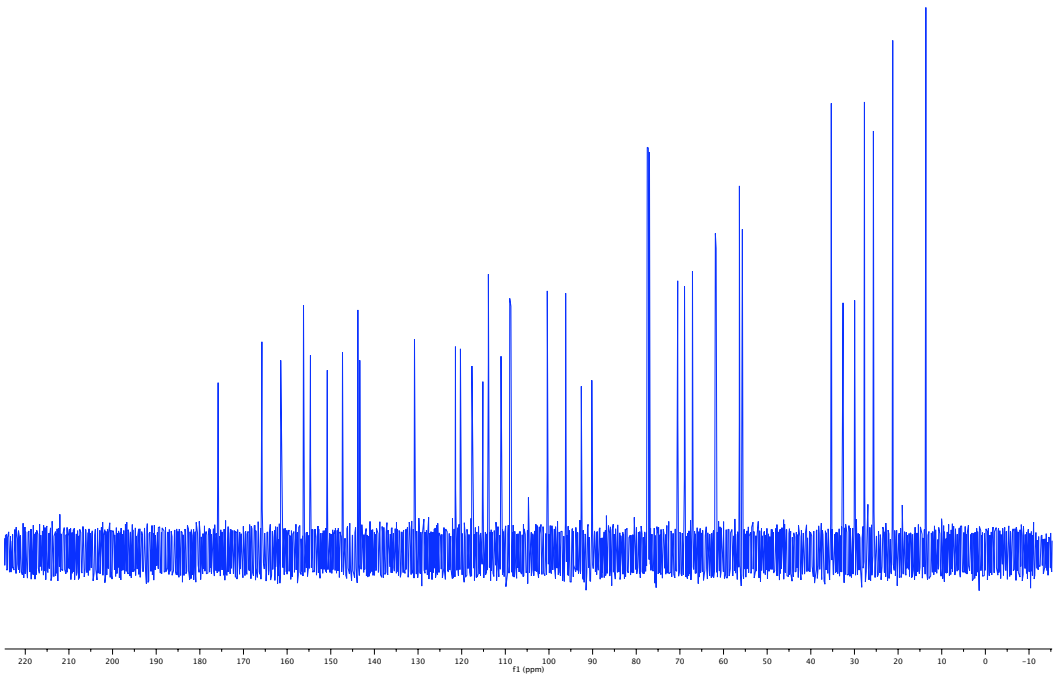
O
O
O
O
O
O
O
OMOM
N

168

15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)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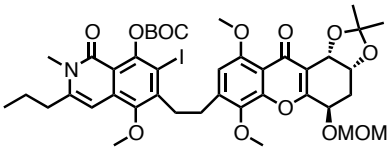
f1 (ppm)


O
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I
N
O
O
O
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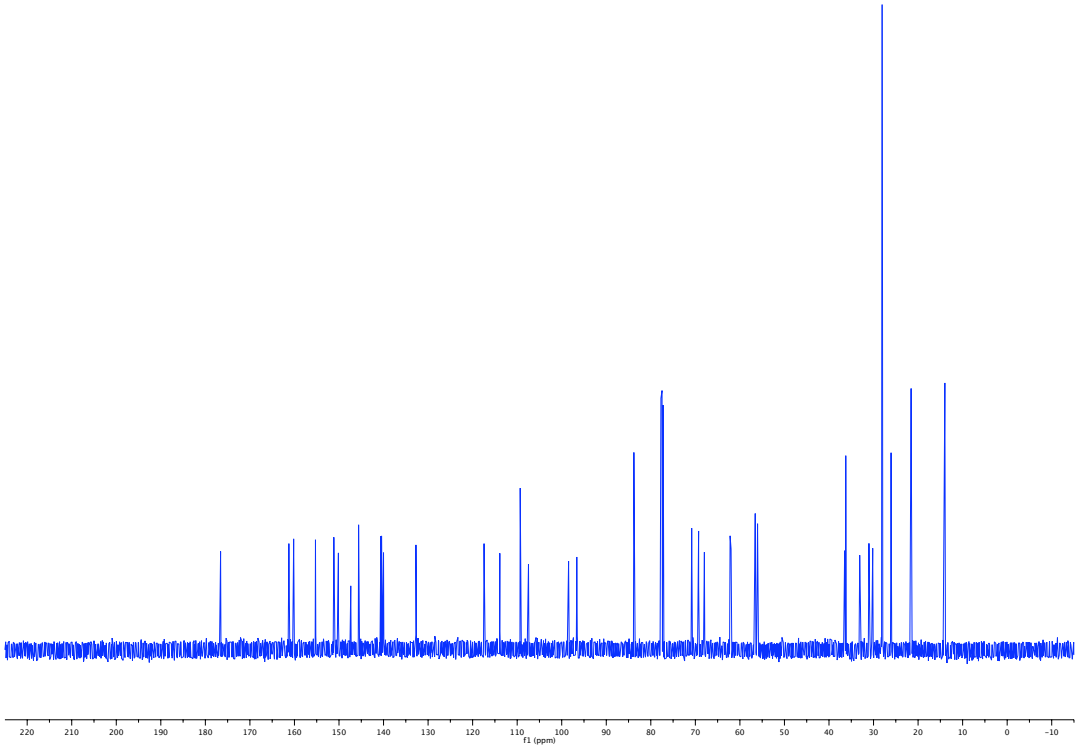
O
O
O
OMOM

219

16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
f1 (ppm)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100
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60
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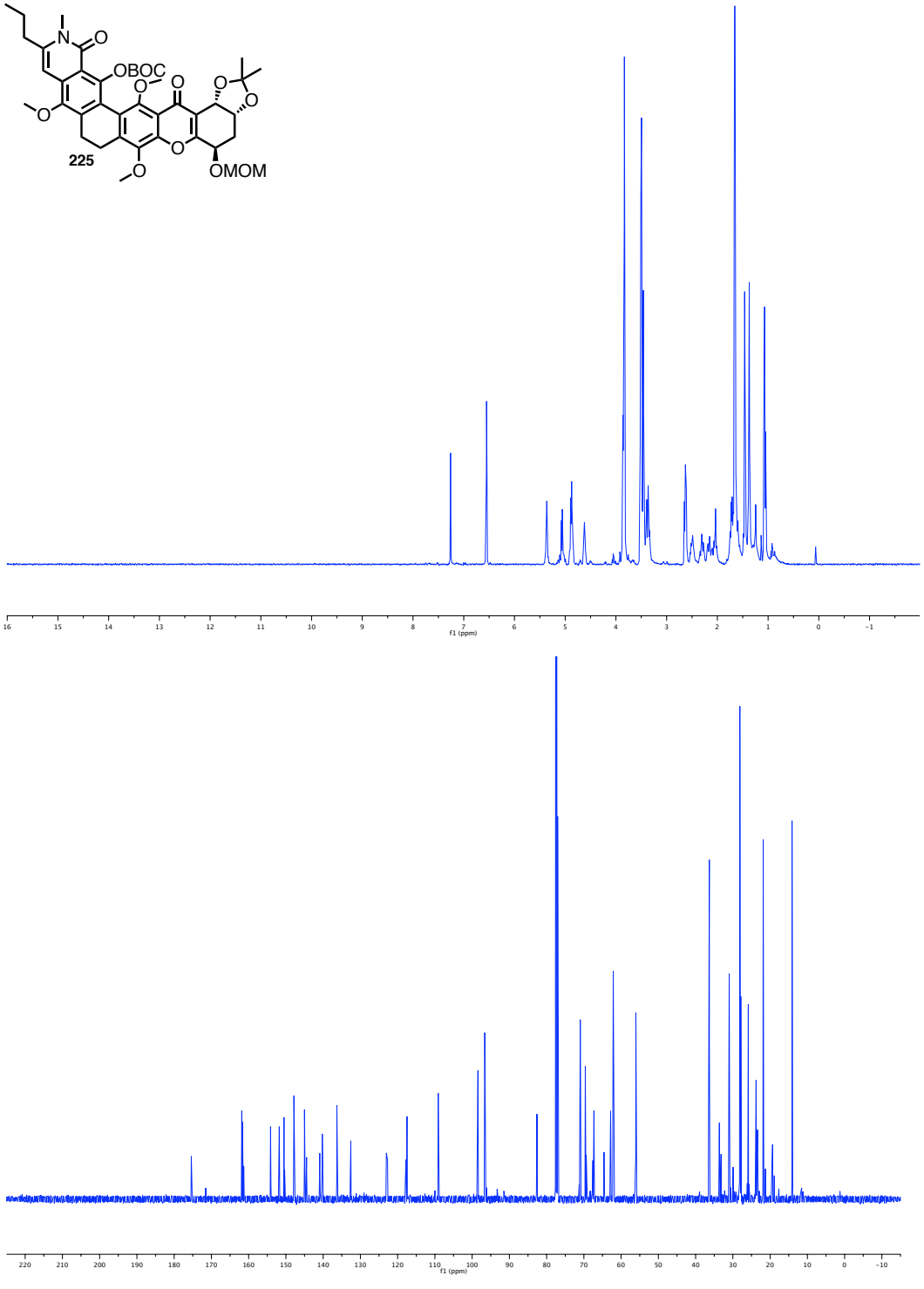
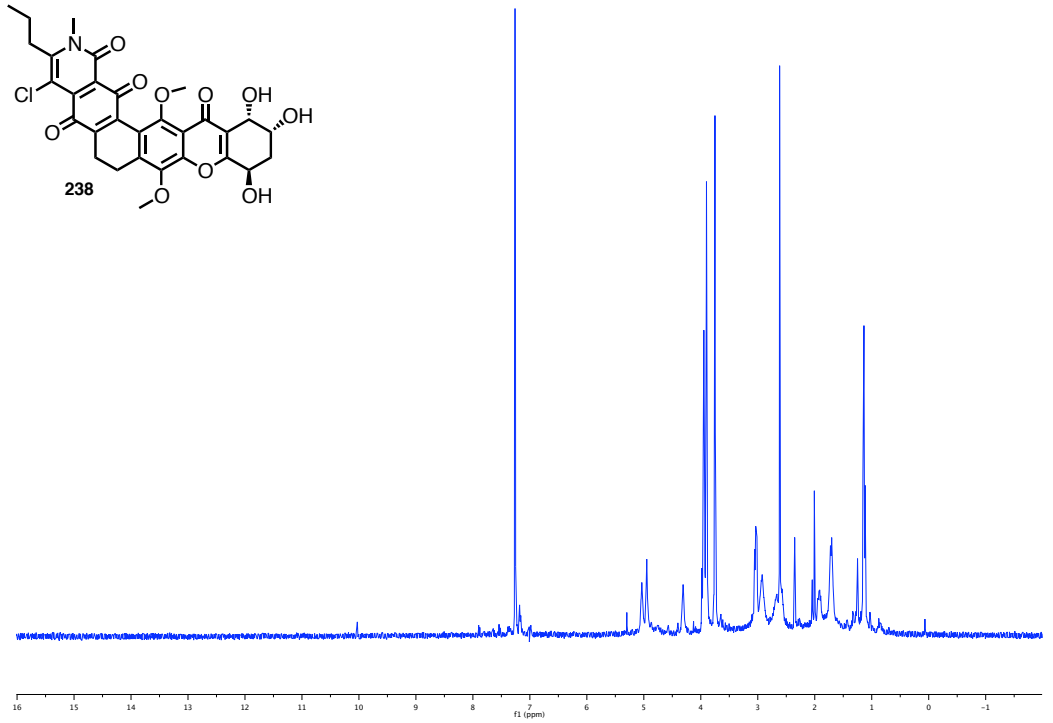
40
30
20
10
0
−10
f1 (ppm)


OBOC
OMOM
225
f1 (ppm)
f1 (ppm)



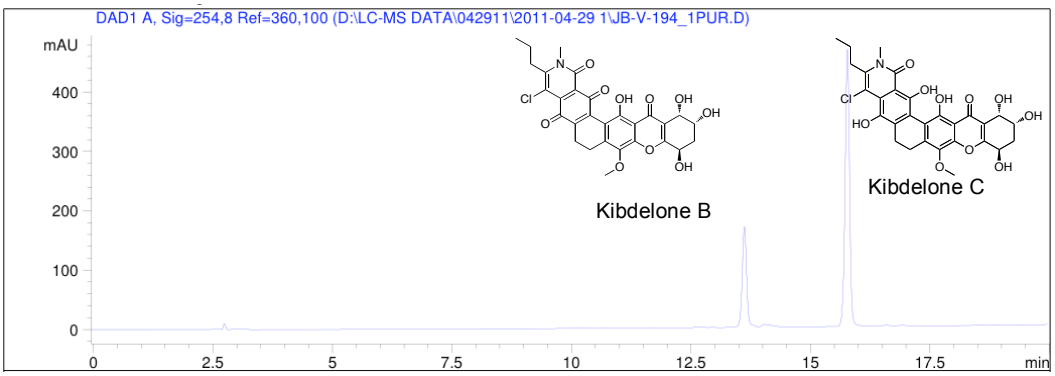
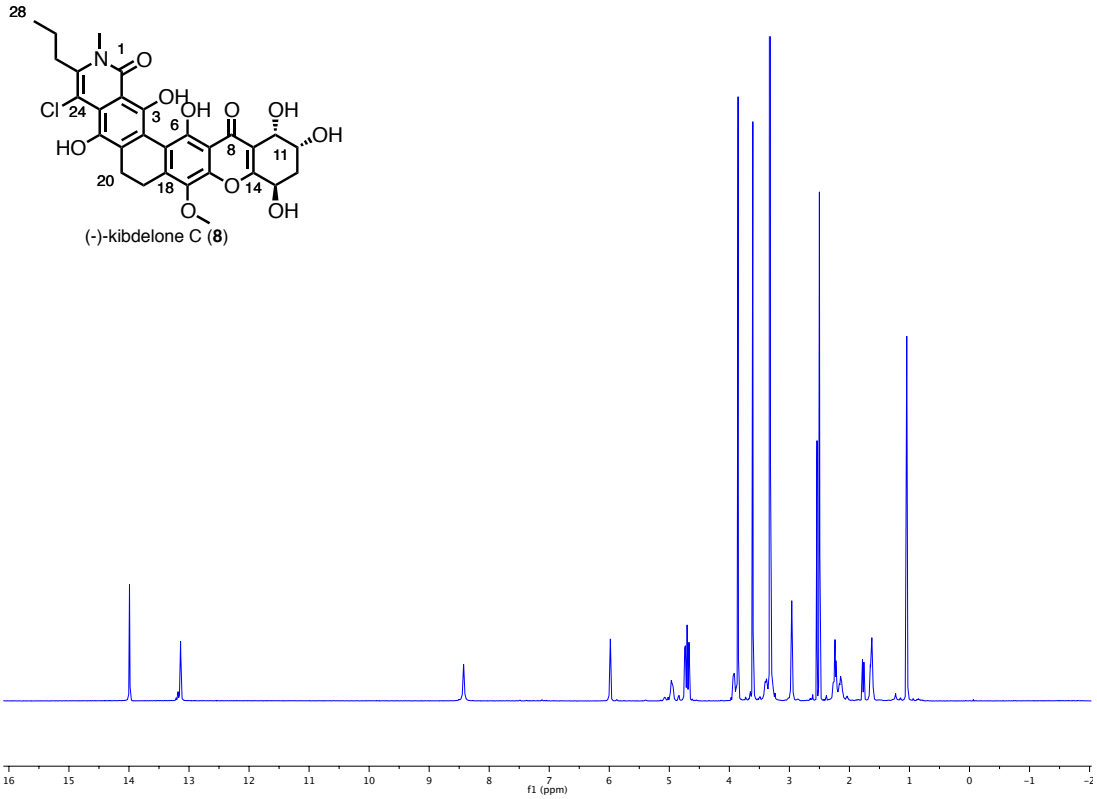


Figure 2-14: RP-HPLC (20-90% MeCN/H_2O) After Demethylation and Attempted Isolation of Kibdelone B



(-)-kibdelone C (**8**)

Comparison of ^{1}H NMR Data for Kibdelone C

No.	^{1}H Synthetic (-)-Kibdelone C	^{1}H Natural (+)-Kibdelone C
10	4.70 (dd, 4.1, 3.8)	4.70 (dd, 4.2, 3.8)
11	3.96 – 3.90 (m)	3.93 (m)
12a	2.24 (ddd, 13.0, 12.5, 4.2) 2 H's	2.24 (ddd, 13.0, 12.5, 4.2)
12b	1.77 (d, 13.0)	1.77 (brd, 13.0)
13	4.69 – 4.64 (m)	4.67 (m)
19a	Underneath (ddd) @ 2.24	2.24 (m)
19b	2.18 – 2.10 (m)	2.14 (m)
20a	3.39 (d, J = 13.1)	3.39 (brd, 13.0)
20b	3.30 – 3.26 m (obscured by water)	3.29 (brd, 13.0)
26	2.98 – 2.94 (m, app t)	2.96 (dd, 8.2, 8.0)
27	1.68-1.59 (m)	1.63 (m)
28	1.05 (t, 7.2)	1.04 (t, 7.2)
17-OMe	3.85 (s)	3.85 (s)
N-Me	3.61 (s)	3.61 (s)
3 OH	13.99 (s)	13.99 (s)
6 OH	13.14 (s)	13.14 (s)
10 OH	4.97 (brs)	4.95 (brs)
11 OH	4.74 (d, 6.1)	4.74 (d, 6.3)
13 OH	5.99 (d, 6.3)	5.99 (d, 6.5)
22 OH	8.43 (s)	8.42 (s)

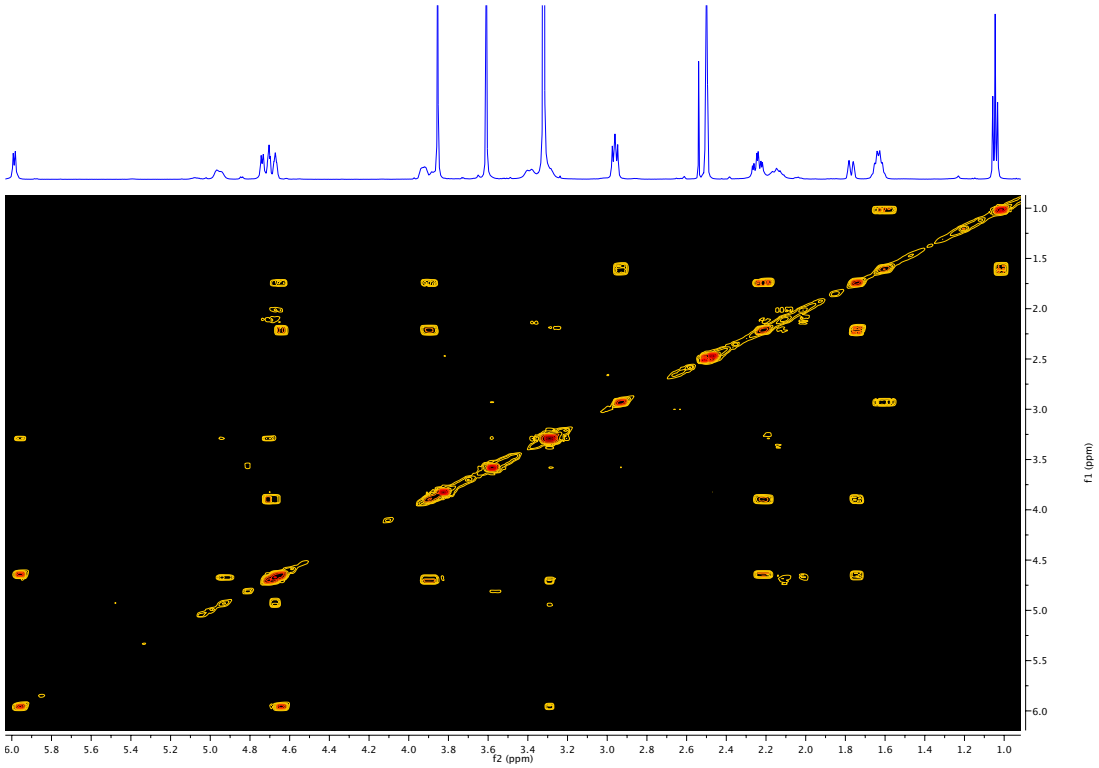
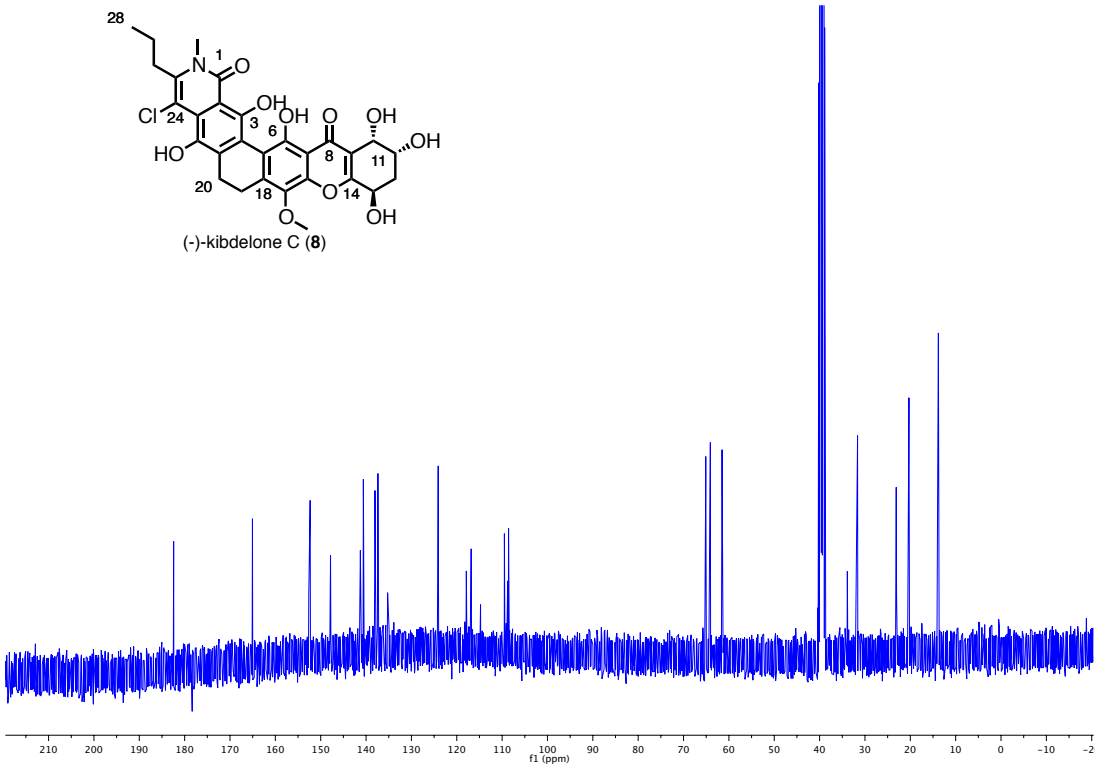


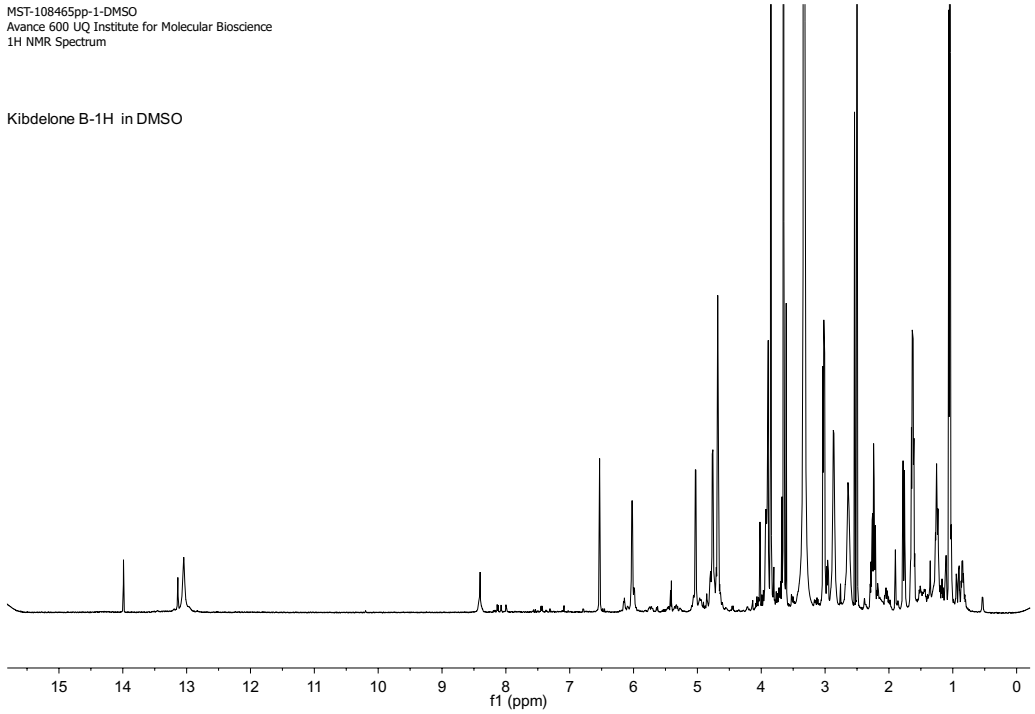
Figure 2-15: GCOSY 1-6 ppm (-)-Kibdelone C (600 MHz, dmso)

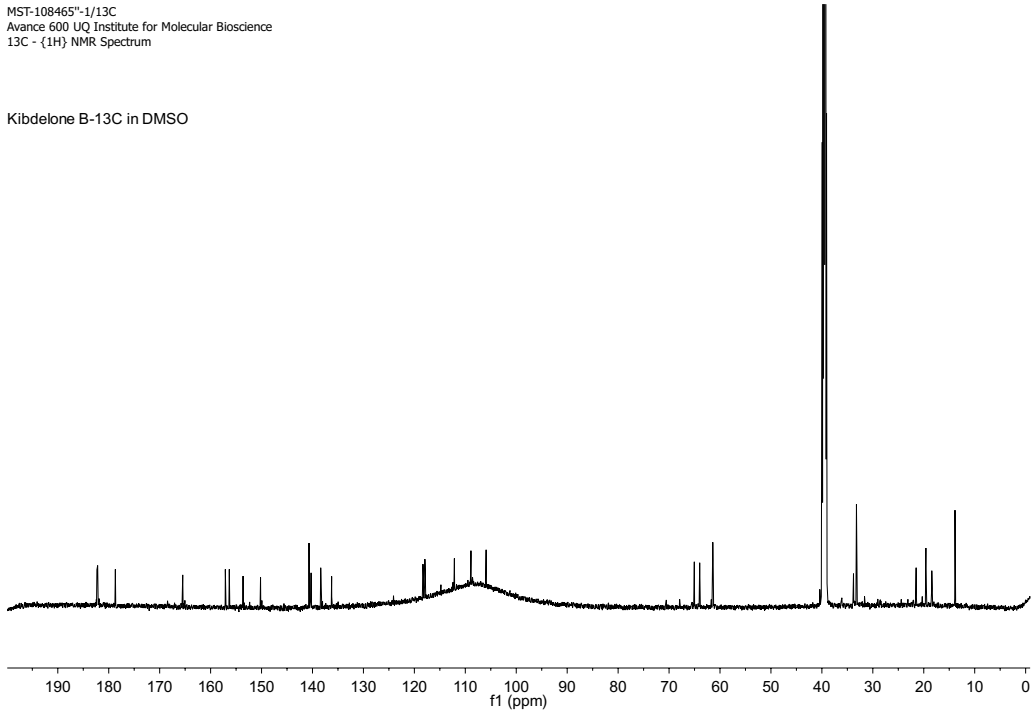

28
N
1
O
OH
Cl
24
3
6
OH
O
OH
OH
HO
8
11
20
18
14
O
O
OH
(-)-kibdelone C (8)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 −2
f1 (ppm)

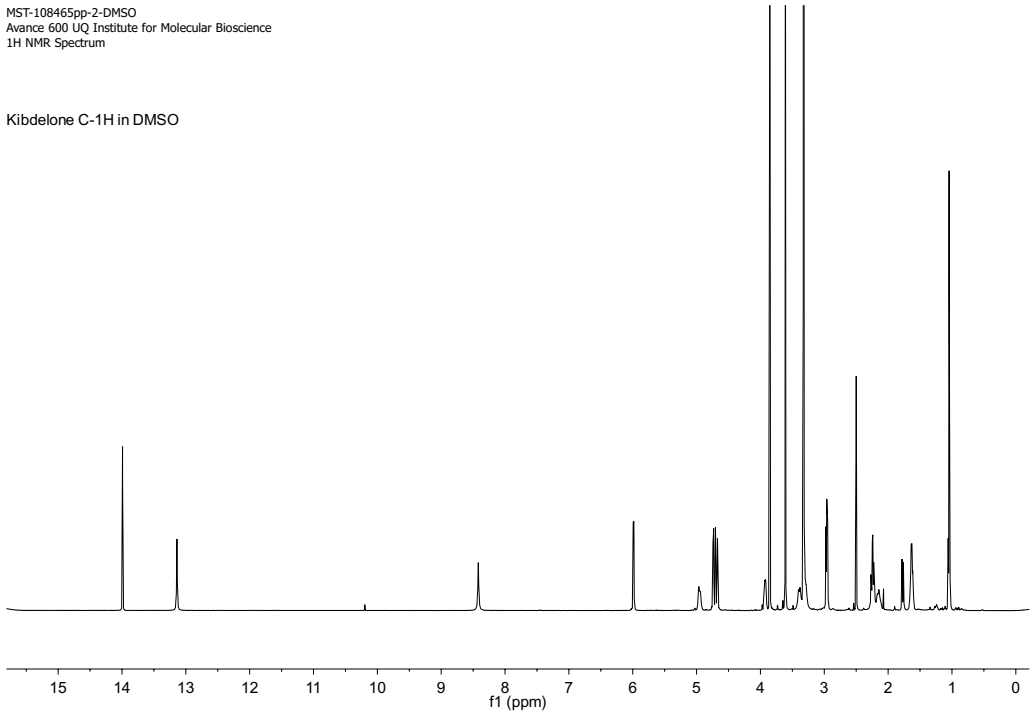
Comparison of ^{13}C NMR Data for Kibdelone C

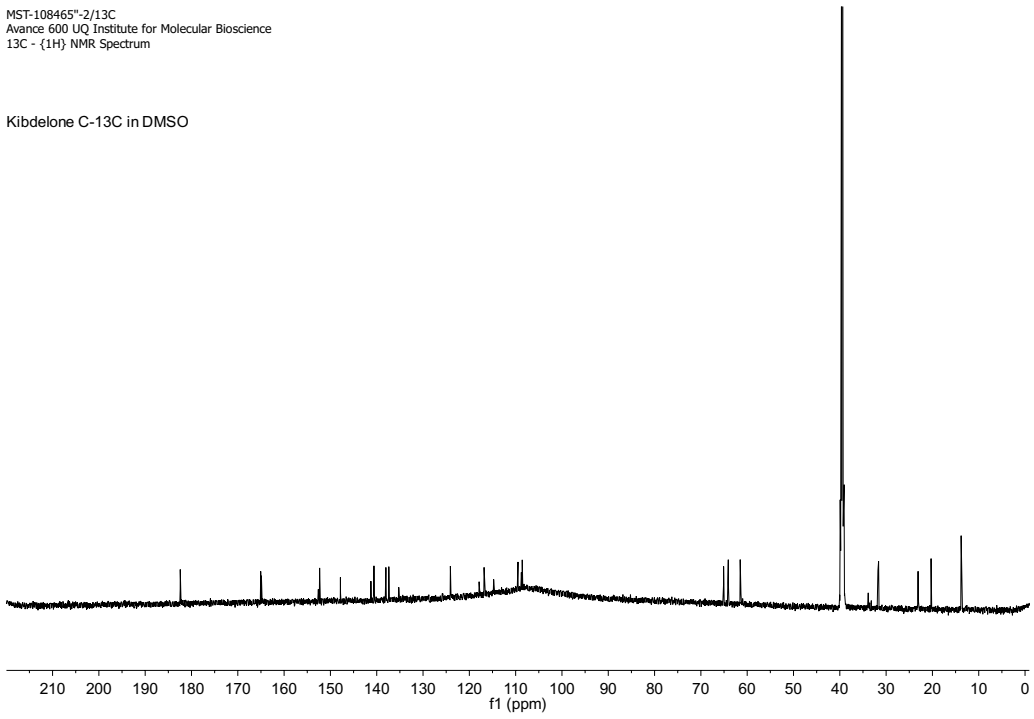
No.	^{13}C Synthetic (-)-Kibdelone C	^{13}C Natural (+)-Kibdelone C
1	165.1	165.0
2	108.8	108.8
3	152.6	152.6
4	116.8	116.8
5	114.7	114.7
6	152.3	152.3
7	108.6	108.6
8	182.4	182.4
9	117.9	117.9
10	61.4	61.4
11	64.1	64.1
12	33.9	33.8
13	65.1	65.1
14	164.9	164.9
16	147.8	147.8
17	135.3	135.2
18	141.3	141.3
19	23.11	23.09
20	23.07	23.05
21	137.4	137.4
22	138.0	138.0
23	124.1	124.1
24	109.5	109.5
25	140.6	140.6
26	31.8	31.8
27	20.3	20.3
28	13.8	13.8
17-OMe	61.5	61.5
N-Me	31.6	31.6

Isolation Spectra From Dr. Ranjala Ratnayake






MST-108465pp-2-DMSO
Avance 600 UQ Institute for Molecular Bioscience
1H NMR Spectrum
Kibdelone C-1H in DMSO
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)


MST-108465"-2/13C
Avance 600 UQ Institute for Molecular Bioscience
13C - {1H} NMR Spectrum
Kibdelone C-13C in DMSO
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Chapter Two Bibliography

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