This Dissertation Committee for Matthew W. Leighty certifies that this is the approved version of the following dissertation:

Vinylogous Esters and Amides: Useful Synthons for Diversity-Oriented and Natural Product Synthesis

Dissertation Committee:

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Abstract:

Vinylogous Esters and Amides: Useful Synthons for Diversity-Oriented and Natural Product Synthesis

Matthew W. Leighty

The University of Kansas, 2009

The first total synthesis of boehmeriasin A was achieved in seven steps from readily available materials with an overall yield of 29%. The absolute stereochemistry of the natural product was determined to be of the (*R*)-configuration. (-)-(*R*)-Boehmeriasin A demonstrated potent cytotoxicity in several cancer cell lines including drug resistant cancer cells where paclitaxel is inactive.

An efficient and mild method for the construction if chromones was developed that requires only a single purification step at the end of the sequence and results in moderate to good yields of the isolated chromones. This method was applied toward the synthesis of 5-hydroxy-2-(2-phenylethyl)chromone, a neuroprotective chromone.

The reduction of tertiary amides using $Cp_2Zr(H)Cl$ to the corresponding aldehydes on a preparatory scale results in good isolated yields of the products. Through a modified workup procedure, issues not previously observed were overcome to afford good isolated yields of the corresponding aldehydes.

Acknowledgements

Through the peaks and valleys that come with being a graduate student there have been many individuals who have offered support and here I would to like to extend a formal expression of gratitude. First and foremost, I need to thank my parents for their unconditional love and support. I am also sincerely grateful to Dr. Gunda Georg for her insightful advice and allowing me the creative freedom to work on a wide array of topics in a very multidisciniplary group.

I would like to thank all of the faculty members of the Medicinal Chemistry and Chemistry Departments of the University of Kansas for making KU such an enjoyable place to learn and grow. In addition, I appreciate the University of Minnesota being such a gracious host over the last portion of my career. I need to extend a great deal of gratitude to my dissertation committee, Dr. Apurba Dutta, Dr. Gary Grunewald, Dr. Paul Hanson, and Dr. Helena Malinakova. All members greatly facilitated my understanding of synthetic medicinal chemistry.

I owe thanks to Dr. Victor Young for X-Ray analysis and Dr. Defeng Tian for conducting the cytotoxicity assays. I also want to specifically thank several current and former graduate students of the Medicinal Chemistry Department at The University of Kansas. These individuals made life at the bench and outside of Malott Hall and the ITDD much more enjoyable. I know many will be lifelong friends and colleagues. I would like to extend a great deal of thanks to Dr. Jared Spletstoser, Dr. Brandon Turunen, Micah Niphakis, and Chris Schneider for many useful chemistry

discussions. Andrea Knickerbocker has been a tremendous friend over the course of my stay in the Georg group and I owe her a tremendous amount of gratitude.

This dissertation is dedicated to my parents, Marilyn and Leighton,

for their unconditional love and support….

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List of Abbreviations

AcOH – acetic acid

ATP – adenosine-5'-triphosphate

BBN – 9-borabicyclo[3.3.1]nonane

Boc – *tert*-butoxycarbonyl

br – broad

calc'd – calculated

cat. – catalytic

CNS – central nervous system

conc. – concentrated

d – doublet

DIEA – *N*,*N*-diisopropylethylamine

DMF – *N*,*N*-dimethylformamide

DMSO – dimethyl sulfoxide

DOPA – 3,4-dihydroxy-L-phenylalanine

dppf – 1,1′-bis(diphenylphosphino)ferrocene

EDCI – *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride

Et – ethyl

Et_2O – diethyl ether

EtOAc – ethyl acetate

FT – fourier transform

g – gram

GI – growth inhibitory concentration

h – hour

HPLC – high pressure liquid chromatography

HRMS – high resolution mass spectrometry

Hz – hertz

*i*Pr – isopropyl

IR – infrared

LAH – lithium aluminum hydride

LDA – lithium diisopropylamide

M – molar

m – multiplet

Me – methyl

MeCN – acetonitrile

MeOH – methanol

mg – milligram

MHz – megahertz

min – minute

μL – microliter

mL – milliliter

mM – millimolar

mmol – millimole

MOM-Cl – chloromethyl methyl ether

MPLC – medium pressure liquid chromatography

*n*BuLi – lithium-1-butanide

NCS – *N*-chlorosuccinimide

nm – nanometer

nM – nanomolar

NMM – *N*-methylmorpholine

NMR – nuclear magnetic resonance

PCC – pyridinium chlorochromate

PDC – pyridinium dichromate

Ph – phenyl

PIFA – [bis(trifluoroacetoxy)iodo]benzene

q – quartet

rt – room temperature

s – singlet

t – triplet

TBS – *tert*-butyldimethylsilyl

*t*BuOH – *tert*-butanol

Tf – triflate

TFA – trifluoroacetic acid

THF – tetrahydrofuran

TLC – thin layer chromatography

TMEDA – *N*,*N*,*N*′,*N*′-tetramethylethylenediamine

TMS – trimethylsilyl

UPLC – ultra high-pressure liquid chromatography

UV – ultraviolet

Chapter 1

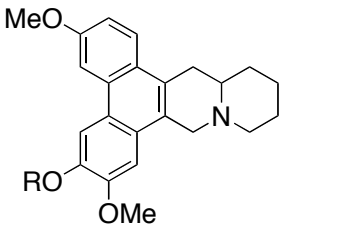
Total Synthesis, Absolute Stereochemistry Determination, and Initial Biological Evaluation of Boehmeriasin A

1.1 Background

Natural products continue to be valuable sources of biologically active molecules that can serve as lead compounds for further development.[1] Examples of anticancer natural products that have inspired compounds on the market include the epothilones, taxanes, and *Vinca* alkaloids.[2] Phenanthroindolizidine and the less prevalent phenanthroquinolizidine alkaloids also have prominent anticancer profiles.[3-23] These alkaloids demonstrate other pharmacological activities including antiinflammmatory,[24-29] antimicrobial,[16] and antiviral activities[28,29] as well. Since the isolation of the first phenanthroindolizidine tylophorine in 1935,[30] this class of natural products has attracted the attention of the synthetic community due to their unique architecture and impressive biological activity that has culminated in several total syntheses of these alkaloids.[12]

Boehmeriasin A and B were recently isolated from the aqueous ethanolic extract of *Boehmeria siamensis* Craib (Utricaceae) through a bioassay-guided fractionation investigation (Figure 1).[13] The structures of these phenanthroquinolizidine alkaloids were determined through spectral evidence. However, the absolute stereochemistry of either alkaloid was not determined. Both alkaloids were evaluated against a panel of twelve different cancer cell lines for

cytotoxic activity that included leukemia and cancers of the lung, colon, breast, prostate, and kidney. Boehmeriasin A was found to be more potent than paclitaxel and boehmeriasin B in most cell lines evaluated with GI_{50} values ranging from 0.80 to 265 nM. Boehmeriasin A potently inhibits the proliferation of breast cancer cell line MDA-MB-231 through G1 cell cycle arrest and differentiation induction.[31] The natural product caused decreased expression levels of cyclin D1 and cyclin E1, changes in cell morphology, increased lipid droplet accumulation, and elevated expression of adipocyte differentiation-related protein in these cells. This may be of clinical relevance as cyclin D1 is amplified and/or overexpressed in many different types of cancer[32] and is associated with poor prognosis and chemoresistance.[33] Interestingly, very few apoptotic cells were detected when the cells were treated with this natural product. However, boehmeriasin A's molecular target(s) responsible for its cytotoxicity have not been elucidated. The reported biological activity combined with the Georg group's previous interest in this class of natural products[34] made boehmeriasin A an attractive target for a total synthesis. Herein, the first total synthesis of this natural product, determination of its absolute stereochemistry, and initial anticancer activity is reported.

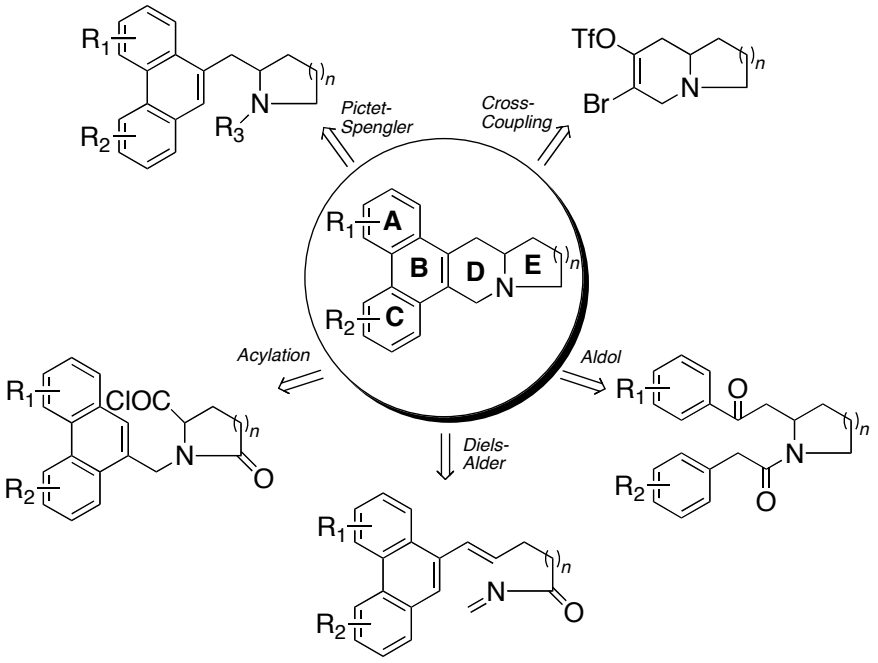


R = Me; boehmeriasin A (**1**)
R = H; boehmeriasin B (**2**)

Figure 1. Structures of Boehmeriasin A and B.

Since the last comprehensive review of the phenanthroindolizidine and phenanthroquinolizidine alkaloids, more than twenty new phenanthroindolizidine and phenanthroquinolizidine alkaloids have been isolated and several total syntheses of these natural products have appeared in the literature.[12] Although these synthetic endeavors employed novel reactions during the course of the synthesis, typical construction of the alkaloids follows two general strategies. The first strategy involves assembly of the phenanthrene portion of the molecule first followed by synthesis of the aliphatic section of the molecule. The second commonly employed strategy assembles of the indolizidine or quinolizidine prior to construction of the aromatic ring system. Of these two general methods, five common synthetic approaches in their respective syntheses of the alkaloids have been used (Scheme 1). Where assembly of the phenanthrene core is carried out first the aliphatic core is commonly prepared through a Pictect-Spengler reaction, Friedel-Crafts acylation, or Diels-Alder reaction. When the indolizidine or quinolizidine scaffold was prepared prior to the phenanthrene moiety, an aldol reaction to assemble ring D followed by an intramolecular bi-aryl coupling reaction has been used. Alternatively, upon successful construction of the aliphatic core, palladium-mediated cross-coupling reactions have been used to install rings A and C followed by an oxidative coupling to afford the desired natural products.

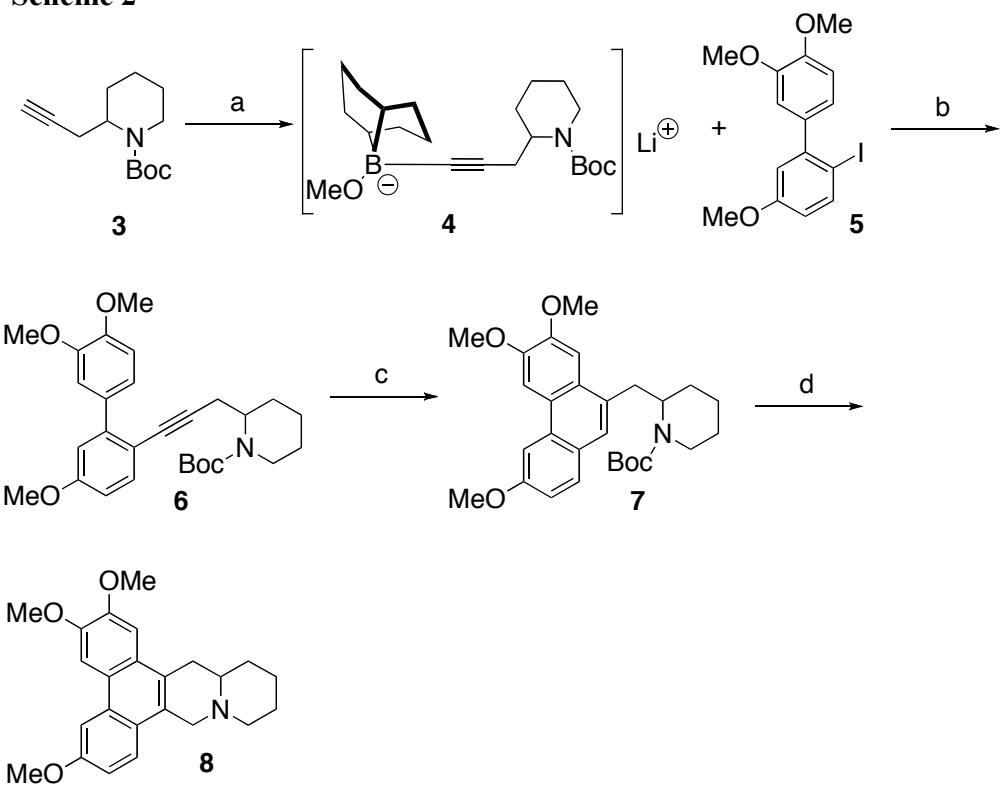
Scheme 1



A frequently used strategy involves synthesizing the phenanthrene ring (rings A-C) with the required substitution pattern for the alkaloid of interest and then forming the indolizidine or quinolizidine portion through a Pictet-Spengler reaction. This approach is exemplified by a synthetic route developed by Fürstner and co-workers (Scheme 2).[35] As an example of this approach, the synthesis of (±)-cryptopleurine (**8**) is shown in Scheme 2. Using conditions developed in the same laboratories, alkyne **3** was treated with *n*BuLi and 9-MeO-9-BBN to afford intermediate **4** that was subsequently coupled with aryliodide **5** to give the key bi-aryl intermediate **6**. Compound **6** next underwent a $PtCl_2$-catalyzed cycloisomerization to afford the desired phenanthrene **7** in 97% yield. The synthesis of (±)-cryptopleurine (**8**) was accomplished under a tandem deprotection/Pictect-Spengler reaction sequence to afford the natural product in good yield. The same authors also applied

this route to the asymmetric synthesis of the indolizidine alkaloids (-)-antofine, (-)-tylophorine, and (-)-ficuseptine C, respectively, utilizing D-*N*-Boc-prolinol as the starting material.[35]

Scheme 2

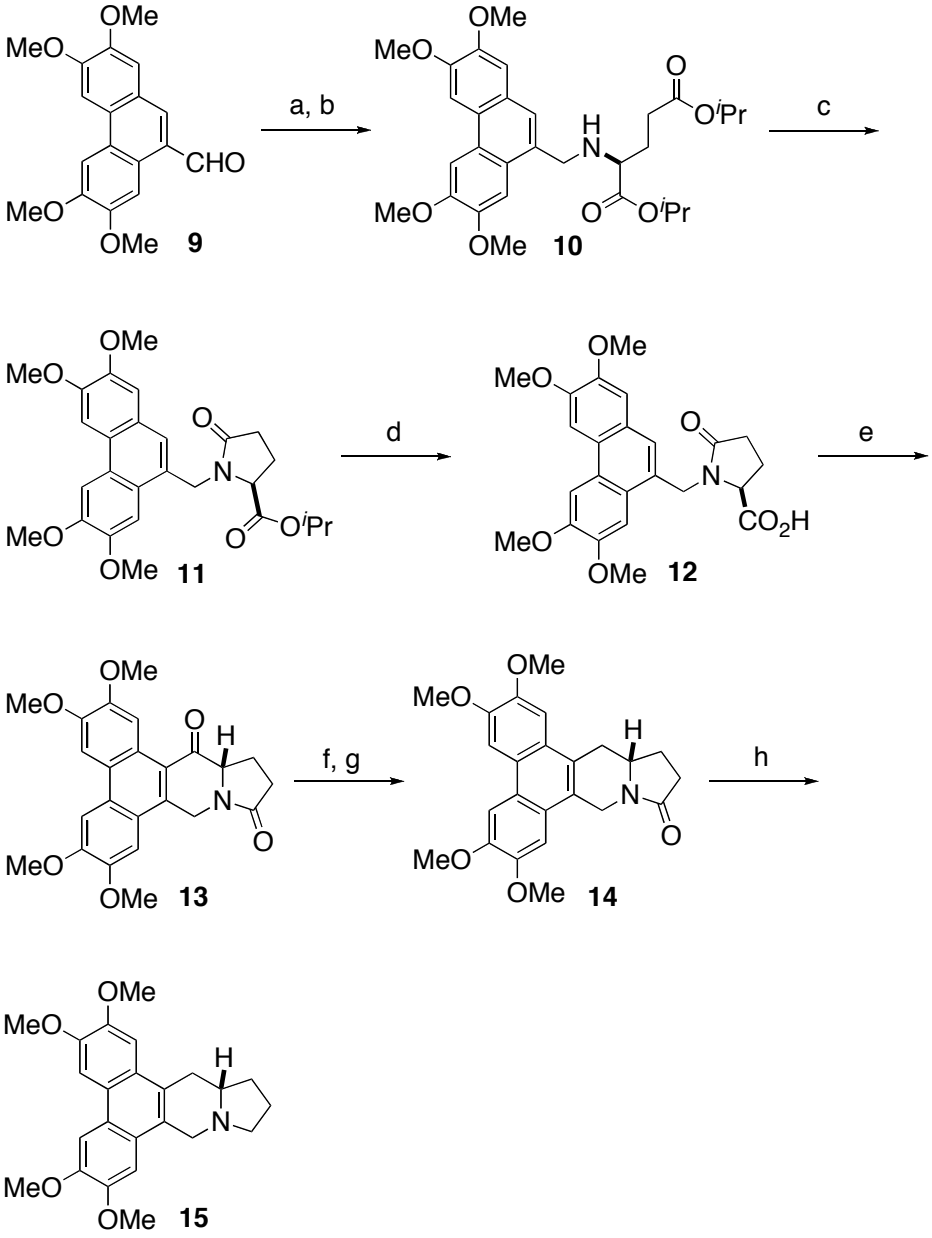


a. *n*BuLi, THF, -40 °C; then 9-MeO-9-BBN; b. [(dppf)$PdCl_2$], THF, reflux, 82%; c. $PtCl_2$ (20 mol %), toluene (0.05 M), 60 °C, 3 h, 97%; d. aq. HCHO, HCl/EtOH, 80 °C, 67%.

Another common strategy used to construct phenanthrene-type alkaloids is that of an intramolecular Friedel-Crafts acylation reaction. The synthesis of (+)-tylophorine (**15**) by Rapoport and coworkers serves as a prototypical example of this approach (Scheme 3).[36] Using a chiral-pool approach, aldehyde **9** was transformed into glutamate derivative **10** via a reductive amination reaction. This intermediate was cyclized under acidic conditions and treated with MeOH and KOH to afford

pyroglutamate derivative **12**. Acid **12** underwent the key Friedel-Crafts acylation reaction by converting the acid to the acid chloride and that was followed by treatment with $SnCl_4$ afforded the desired lactam **13** in good yield. Ketone **13** was reduced in a two-step fashion by treatment with either Adam's catalyst or L-Selectride to give the corresponding alcohol followed by treatment with $SOCl_2$ followed by hydrogenation that yielded intermediate **14**. A final reduction with LAH gave the desired natural product, (+)-tylophorine (**15**), in excellent yield.

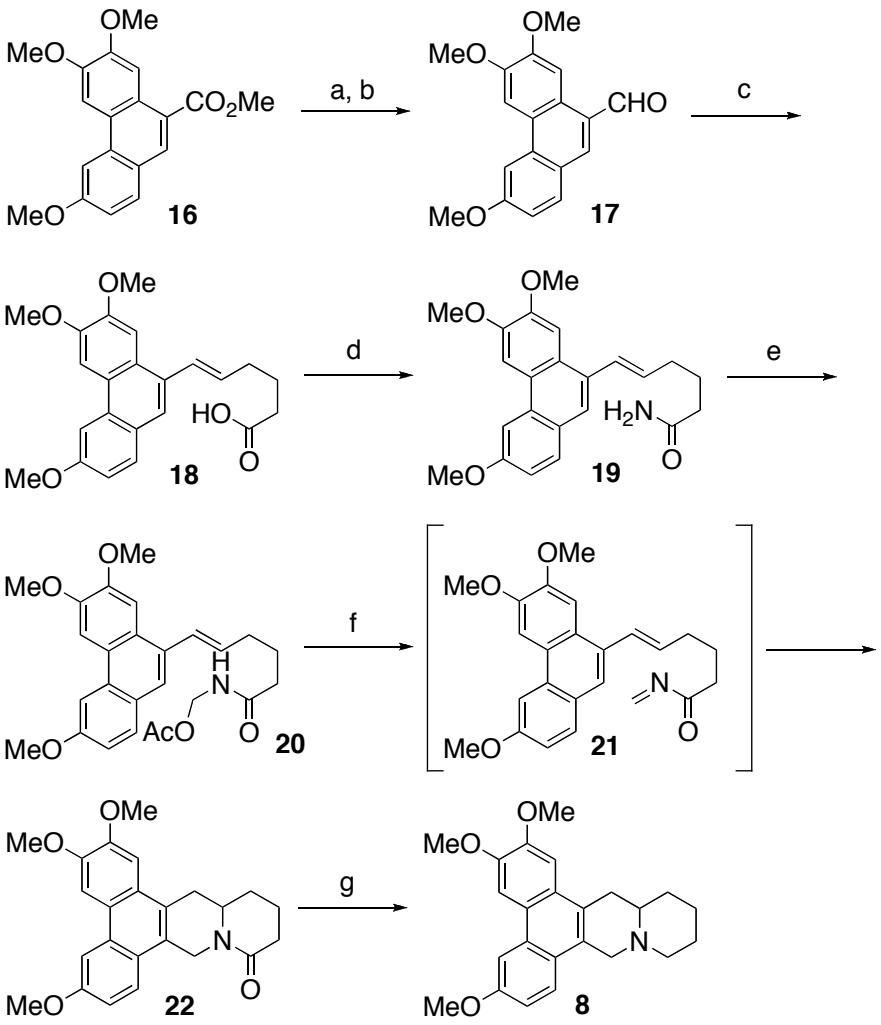
Scheme 3



a. (*S*)-diisopropylglutamate, CH_2Cl_2, HOAc, reflux; b. $NaCNBH_3$, isopropanol, HOAc; c. MeOH/AcOH (2:1), 45 °C, 3 h; d. KOH, MeOH, dioxane, 88% (from **9**); e. $(COCl)_2$, DMF, CH_2Cl_2, then $SnCl_4$, reflux, 94%; f. H_2/$Pd(OH)_2$-C, dioxane, 95% (α/β = 4:96) or L-Selectride, THF, 95%, (α/β = 97:3); g. $SOCl_2$, CH_2Cl_2, then H_2/10% Pd-C, EtOH, 88% (2 steps); h. LAH, THF, reflux, 96%.

The use of an intramolecular Diels-Alder reaction to assemble the non-aromatic portion of the molecule is another commonly employed strategy used in the syntheses of these natural products. This synthetic strategy was first used by Weinreb and coworkers and later by Grieco *et al*. in their respective syntheses of (±)-cryptopleurine (**8**, Scheme 4).[37-39] In the Weinreb route, ester **16** is initially transformed to aldehyde **17** that then undergoes a Wittig reaction to give acid **18** in moderate yield and selectivity. The acid is transformed to amide **19** and upon treatment with paraformaldehyde followed by the addition of acetic anhydride affords the desired intramolecular Diels-Alder substrate **20**. Upon heating in 1,2-dichlorobenzene, amide **20** is first converted to acyl imine **21** *in situ* that undergoes the key intramolecular Diels-Alder reaction to afford lactam **22**. A subsequent reduction with LAH gives the desired phenanthroquinolizidine alkaloid **8**.

Scheme 4

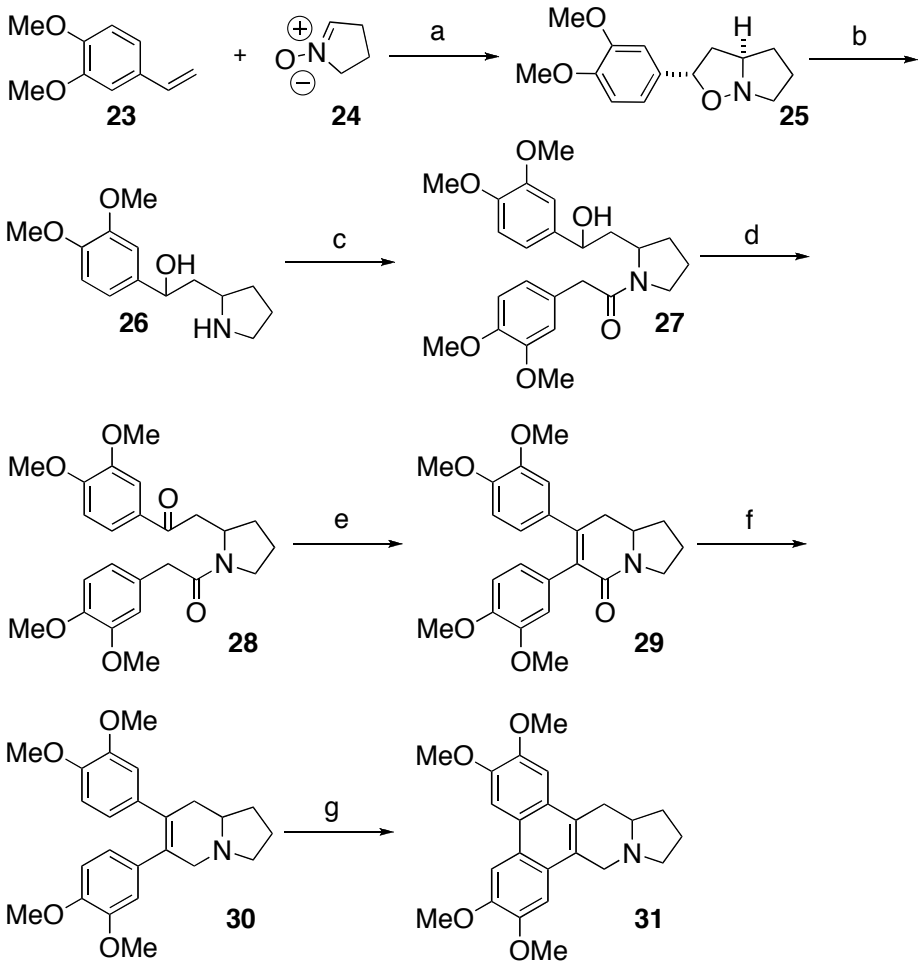


a. LAH, THF, 80%; b. PCC, CH_2Cl_2, 98%; c. $Ph_3^+(CH_2)_4CO_2HBr^-$, TMEDA, LDA, THF, 60% (E/Z = ~3:1); d. $ClCO_2Et$, pyridine, THF, conc. NH_4OH, 89%; e. $(CHO)_x$, Ce_2CO_3, THF, then Ac_2O, cat. pyridine, 52%; f. 1,2-$Cl_2C_6H_4$, 210-212 °C, 70 min, 66%; g. LAH, THF, 53%.

Assembling the indolizidine or quinolizidine nucleus (rings D and E) prior to the phenanthrene portion has been utilized. In these cases, ring C is assembled through a bi-aryl coupling reaction. Kibayashi and coworkers implemented this strategy through the use of an intramolecular aldol approach in the synthesis of (±)-tylophorine (**31**, Scheme 5).[40] A regioselective 1,3-dipolar cycloaddition with styrene

derivative **23** and pyrroline oxide **24** was used to afford isoxazole **25** as an inseparable diastereomeric mixture. This was inconsequential, as an oxidation later in the synthetic route would remove one asymmetric center. Hydrogenation followed by acylation gave amide **27** in good yield that was subsequently oxidized to yield ketone **28**. Intermediate **28** was subjected to an ethanolic KOH solution to afford the desired intramolecular aldol product **29** in excellent yield. Reduction with LAH afforded (±)-septicine (**30**) and further treatment with I_2 under photochemical irradiation afforded the natural product (±)-tylophorine (**31**). This synthetic strategy has also been used for the synthesis of (±)-cryptopleurine (**8**).[41,42]

Scheme 5

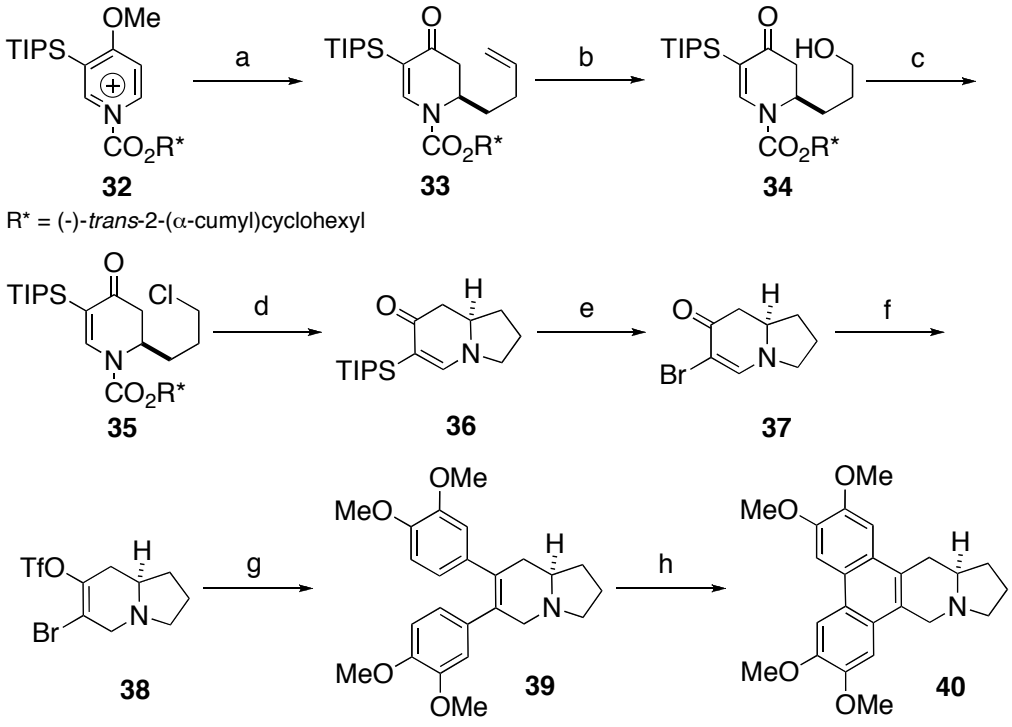


a. toluene, reflux, 3 h, 88% (*cis*:*trans* = 5:2); b. H_2, 10% Pd-C, MeOH, rt, 86%; c. 3,4-dimethoxyphenylacetyl chloride, K_2CO_3, CH_2Cl_2, 70%; d. CrO_3, CH_2Cl_2, 86%; e. 5% KOH, EtOH, reflux, 90 min, 95%; f. LAH/$AlCl_3$ (3:1), Et_2O/THF, 88%; g. I_2, CH_2Cl_2, hν, 43%.

Comins and coworkers have used *N*-acyldihydropyridone chemistry developed in their laboratories for the construction of several members of this class of alkaloids.[43,44] The synthesis of (-)-tylophorine serves as a model of this synthetic strategy (Scheme 6). First treating pyridinium **32** with but-3-enylmagnesium bromide followed by an acidic workup furnishes enaminone **33** in good yield. Conversion of the terminal alkene to the primary alcohol **34** occurs in excellent yield over a two-step

protocol. The alcohol is converted to the corresponding chloride **35** that upon treatment with sodium methoxide initially removes the chiral auxiliary and an ensuing intramolecular cyclization affords the enaminone **36** in excellent overall yield. Conversion of the triispropyl moiety to the bromide derivative proceeded smoothly; this intermediate underwent treatment with L-Selectride and the resultant enolate was trapped with 2-$(Tf)_2$N-5-Cl-pyridine, a reagent developed in the Comins group,[45] to afford the desired triflate **38**. A subsequent double Negishi cross-coupling reaction afforded enantiopure (-)-septicine (**39**) in good yield. An oxidative bi-aryl coupling reaction was then utilized to afford (-)-tylophorine (**40**).

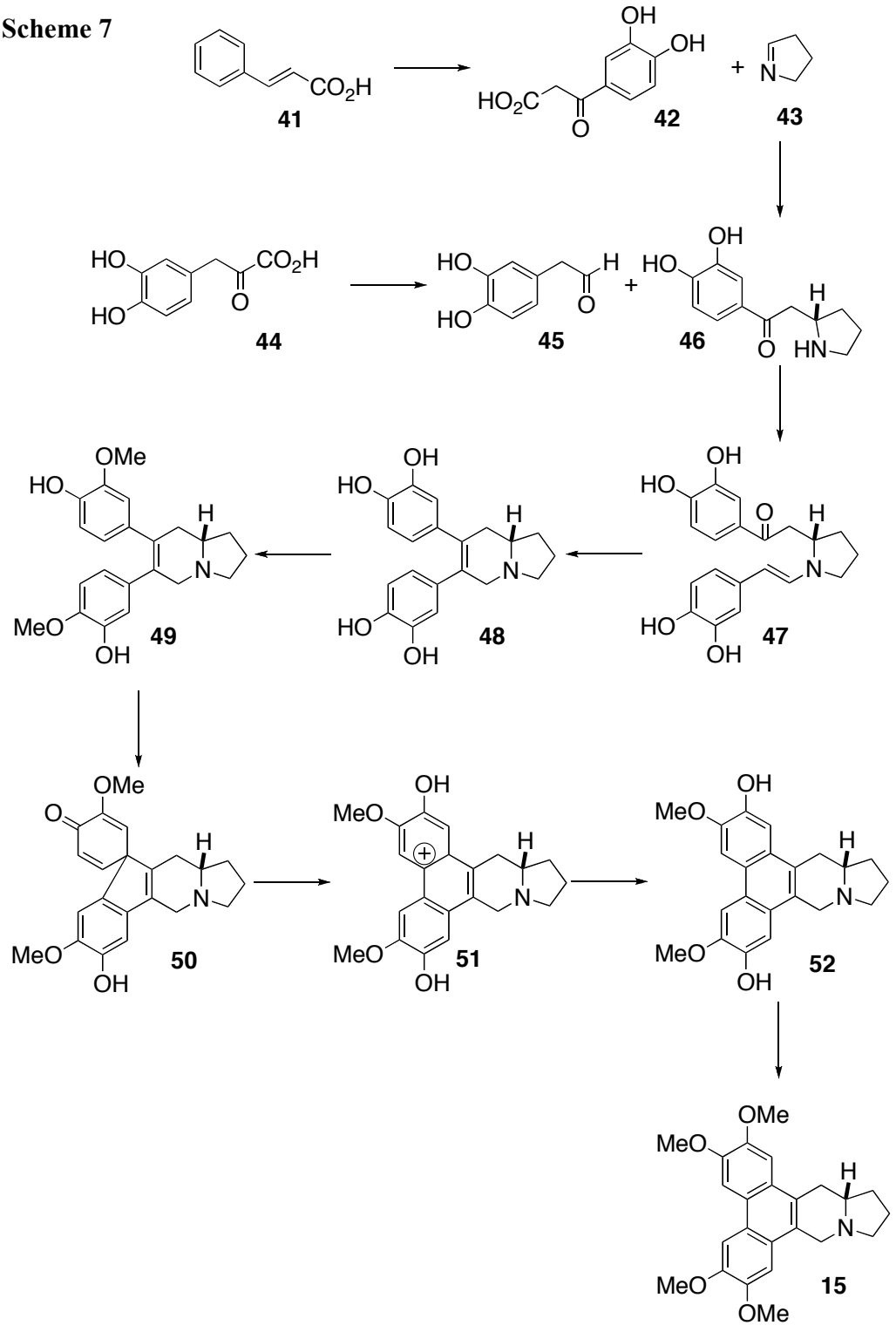
Scheme 6



a. i. $CH_2CH(CH_2)_2MgBr$, THF, ii. H_3O^+, 91%; b. i. OsO_4, cat. $NaIO_4$, ii. L-Selectride, 81%; c. PPh_3, NCS, CH_2Cl_2, 96%; d. NaOMe, MeOH, 91%; e. pyr•HBr_3, CH_2Cl_2, $LiCO_3$, 95%; f. i. L-Selectride, THF, -78 °C, ii. 2-$(Tf)_2$N-5-Cl-pyridine, 71%; g. 3,4-$(MeO)_2C_6H_3$-ZnBr, $Pd(PPh_3)_4$, THF, 60 °C, 67%; h. VOF_3, TFA, 68%, >98% ee.

The biosynthesis of these alkaloids, namely tylophorine and tylophorinine, has been investigated. Through the use of feeding experiments with labeled precursors using *Tylophora asthmatica*, the biosynthetic pathway for this class of natural products has been deduced (Scheme 7).[46-52] Initially, phenylalanine is converted to cinnamic acid (**41**) and subsequently into acid **42**. This intermediate reacts with Δ^1-pyrroline **43**, derived from ornithine, to afford phenacylpyrrolidine **46** that reacts with aldehyde **45**, which originates from either DOPA or tyrosine, to give enamine **47**. An intramolecular condensation reaction ensues to give indolizidine **48**. After two catecholic methylations, bis-methoxy indolizine **49** undergoes an intramolecular bi-aryl oxidation reaction to afford intermediate **50** that rearranges to cation **51**. This transient species is transformed into (+)-tylophorine (**15**) after an aromatization and bis-methylation. Presumably cryptopleurine is biosynthesized in a similar manner via the Δ^1-piperidine instead of the Δ^1-pyrroline.[51]

Scheme 7



Although the phenanthrene-type alkaloids have been known for some time, only tylocrebrine, due to its antileukemia activity,[53] has advanced into clinical trials but was discontinued due to neurological toxicity.[54] The Georg group has hypothesized that this toxicity may be due to tylocrebrine's similarity to dopamine (Figure 2A). The natural product may be acting like a dopamine mimic in the CNS and thus causing the observed unwanted side-effects. Also, these natural products are known to readily undergo oxidation to the pyridinium species in the laboratory and this could occur presumably by monoamine oxidase B *in vivo*. Therefore the untoward effects may be related to the Parkinson-like symptoms analogous to those caused by MPP^+ (Figure 2B).[55] However, the actual mechanism(s) for the neurological side-effects caused by the natural product still remain unclear.

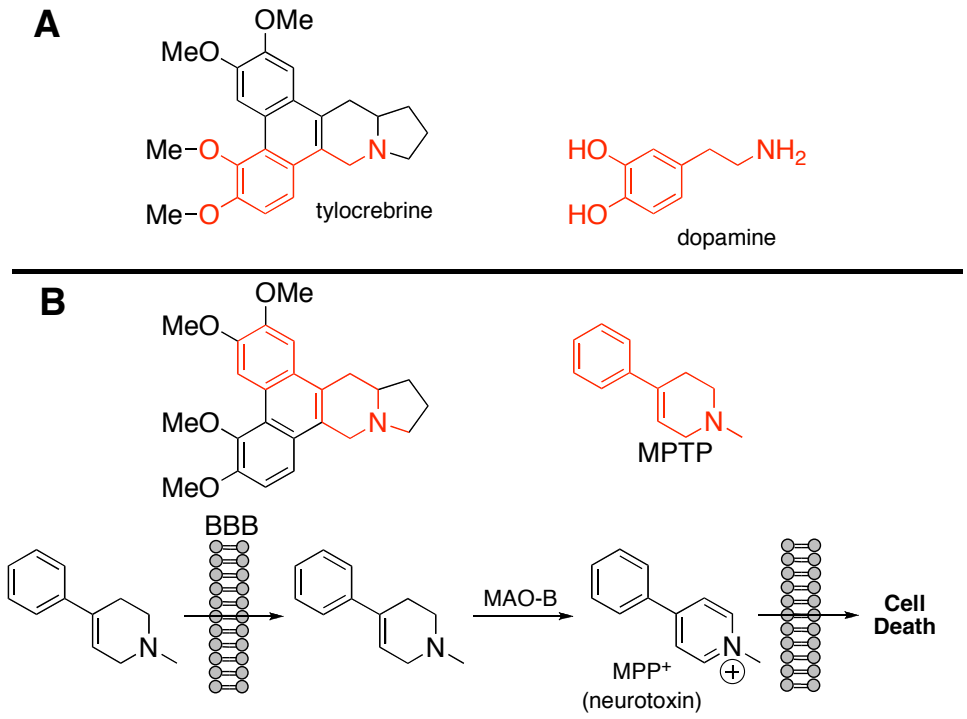


Figure 2. Hypothesized CNS neurological toxicity mechanisms of tylocrebrine.

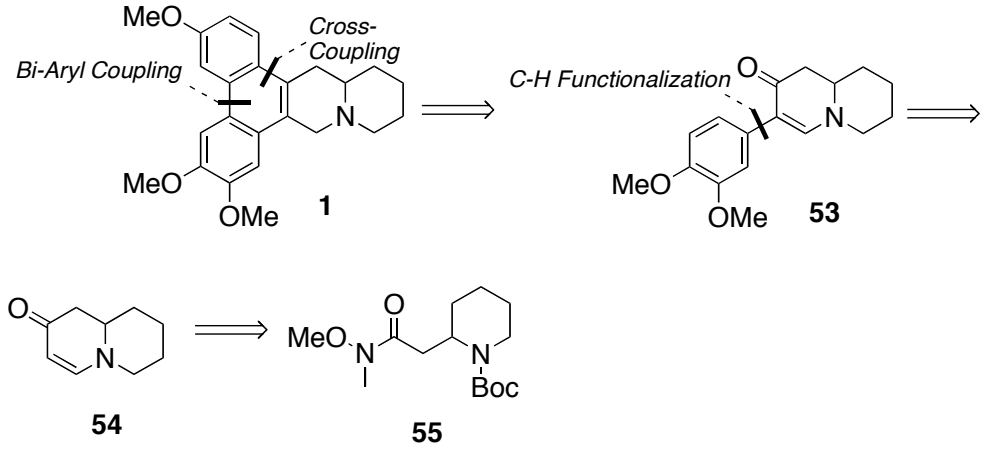
In recent years, these alkaloids and their analogues have reemerged as potential anticancer agents in part due to the recent advances in chemical and molecular biology. In particular, simplified and hydrophilic analogues of the parent phenanthroindolizidines and phenanthroquinolizidines have been prepared in order to overcome the unwanted neurological side effects seen with tylocrebrine.[20,21] These analogues, although generally not as potent as the parent molecules, have retained cytotoxic activity, but interestingly, some analogues demonstrate a differing mechanism-of-action compared to the parent compound or even analogues within the same series of compounds.[7] In addition, no general structure-activity relationship (SAR) has emerged from these analogues and the SAR of each series appears to be target and/or tissue specific.

1.2 Retrosynthesis

In an antithetic sense, boehmeriasin A (**1**) was to be synthesized using the general *N*-acyldihydropyridone strategy discussed above (Scheme 8). Only the racemic natural product is shown for clarity; however, the same synthetic strategy for both the racemic and enantiopure syntheses was to be used. The natural product was envisioned to be derived from an intramolecular bi-aryl coupling of the *seco*-natural product which itself was to be accessed from a palladium-mediated cross-coupling reaction. The triflate coupling partner for the cross-coupling was to be obtained using a literature procedure for the conversion of cyclic enaminones to triflates in a one-pot synthetic operation that was to occur on arylated enaminone **53**. This advanced intermediate was envisioned to arise from a novel, palladium(II)-catalyzed

C-H functionalization utilizing organotrifluoroborates. The enaminone coupling partner for this transformation would be attained from Weinreb amide **55** through methods developed in the Georg laboratories.

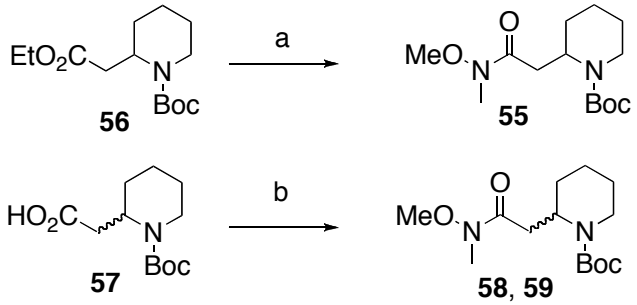
Scheme 8



1.3 Synthesis of α-Arylated Enaminones

Weinreb amides **55**, **58**, and **59** were prepared from either known ester **56**[35] or the corresponding commercially available (*S*)- or (*R*)-acids **57**, respectively (Scheme 9).[56] Each of the amides was treated with ethynylmagnesium bromide to afford the corresponding ynones **60-62** in excellent yields (Scheme 10).[57] These compounds were subjected to a one-pot, two-step protocol for the cyclization of Boc-ynones to enaminones using conditions developed in the Georg laboratories.[56,58] In this protocol, the ynone is treated with formic acid and NaI to give the corresponding vinyl iodide that is subjected to a methanolic K_2CO_3 solution to afford the enaminones **54**, **63** and **64** in excellent yields.[58] This modification of the reported procedure was developed to minimize racemization that was found to occur in the original report (Scheme 11). Mechanistically, treatment of the ynone with formic acid

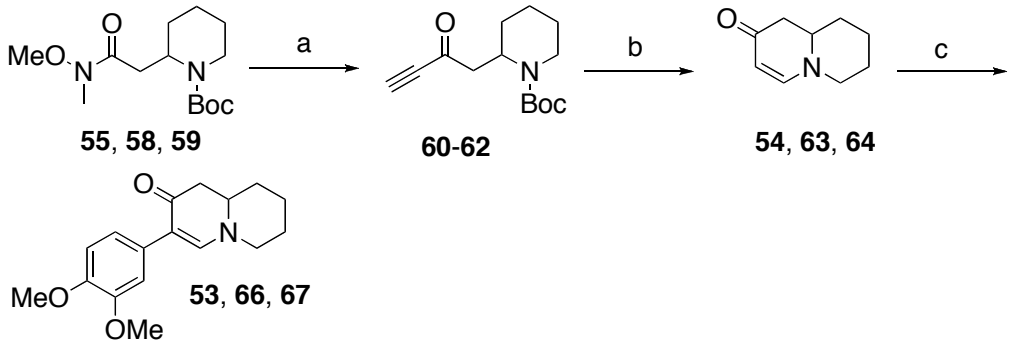
Scheme 9



a. HN(OMe)Me•HCl, *i*PrMgCl, THF, ≤-5 °C; (±)-**55**, 94%;
b. HN(OMe)Me•HCl, EDCI, NMM, CH_2Cl_2, 0 °C to rt; (*S*)-**58**, 96%; (*R*)-**59**, 98%.

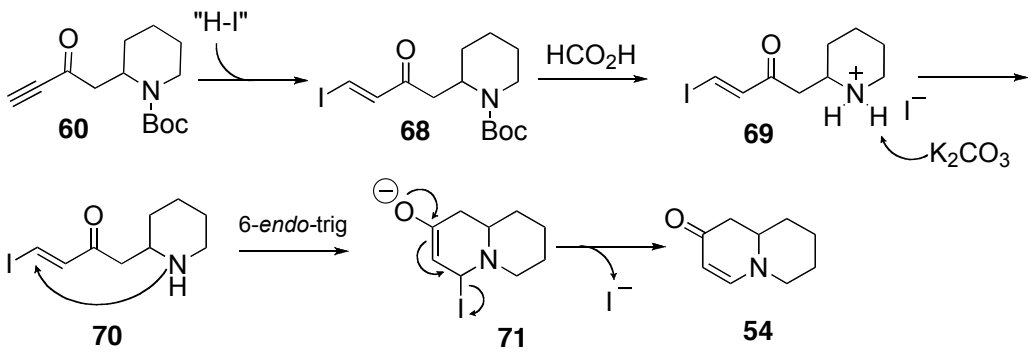
and NaI adds an equivalent of HI across the ynone to generate the vinyl iodide species **68** and eventually intermediate **69** is formed after Boc removal. Upon treatment with a methanolic K_2CO_3 solution, the protonated amine is first deprotonated, which attacks the vinyl iodide to give transient species **71** in a 6-*endo*-trig manner. A subsequent elimination of the iodide affords the desired enaminone **54**.

Scheme 10



a. ethynylmagnesium bromide, THF, -78 °C to rt; (±)-**60**, 93%; (*S*)-**61**, 90%; (*R*)-**62**, 91%; b. formic acid, NaI; then K_2CO_3, MeOH; (±)-**54**, 94%; (*S*)-**63**, 87%; (*R*)-**64**, 91%; c. potassium 3,4-dimethoxyphenyltrifluoroborate (**65**), $Pd(OAc)_2$, $Cu(OAc)_2$, K_2CO_3, *t*BuOH/AcOH/DMSO (20:5:1), acetone/H_2O (2:1); (±)-**53**, 84%; (*S*)-**66**, 77%; (*R*)-**67**, 76%.

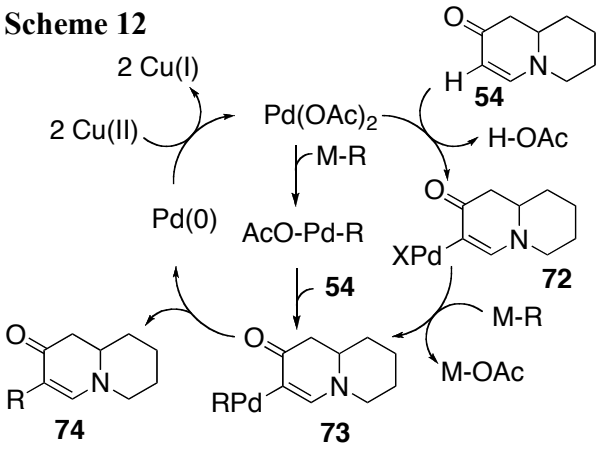
Scheme 11



With rapid access to the desired enaminones established, a novel palladium(II)-catalyzed C-H functionalization using enaminones and potassium organotrifluoroborates was employed.[59] The proposed mechanism for this transformation is depicted in Scheme 12. Palladation of the enaminone **54** occurs first via electrophilic attack of $Pd(OAc)_2$ on the enaminone followed by deprotonation to yield intermediate **72**. Transmetallation ensues and a subsequent reductive elimination occurs to give the desired coupled product **74**. However, an alternative mechanism may also be operational. Transmetalation may occur prior to palladation of the enaminone giving rise to homocoupled products that are observed reaction products.[59] This method represents a powerful means of accessing these products, as previous methods required an initial prefunctionalization of the enaminone to the appropriate α-halogenated derivative followed by Suzuki coupling.[60] This protocol obviates this requirement and thus allows for a more facile means of accessing these compounds. Gratifyingly, using a slight modification of the reported procedure for scale-up purposes employing the coupling partner potassium

3,4-dimethoxyphenyltrifluoroborate (**65**), prepared according to a known procedure,[61] afforded good yields of the desired coupled products **53**, **66**, **67** (Scheme 10).

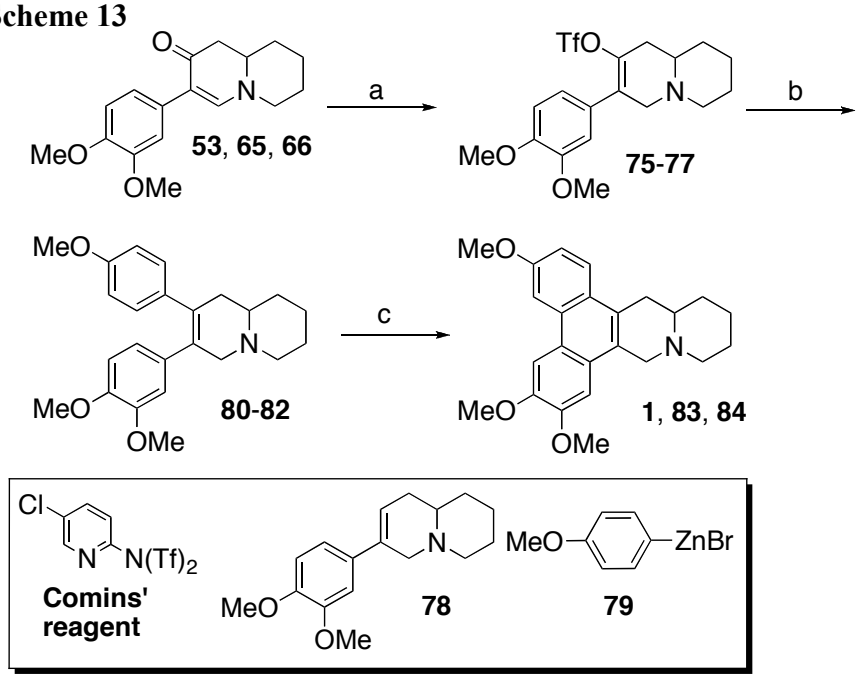
Scheme 12



1.4 Completion of Synthesis

With a route to the envisioned α-arylated products now in place, the final synthetic sequence was undertaken (Scheme 13). Utilizing a procedure developed by Comins and coworkers, enaminones **53**, **66**, and **67** were treated with L-Selectride and the resultant enolates were trapped with Comins' reagent to arrive at the desired triflates **75**-**77** in good yields.[43] The intermediates were initially subjected to a Suzuki coupling using commercially available potassium 4-methoxyphenyltrifluoroborate with conditions developed by Buchwald *et al*.[62] However, during the course of this reaction a side-product was generated that was difficult to remove completely from the product by all chromatographic means attempted. Additionally, in some reaction attempts variable amounts of the reduced product **78** were produced. To overcome this problem, a Negishi cross-coupling reaction was implemented which furnished easily purified products and near quantitative yields of the desired *seco*-natural products.[43]

Scheme 13



a. L-Selectride, THF, -78 °C to rt, then Comins' reagent; (±)-**75**, 85%; (*S*)-**76**, 77%; (*R*)-**77**, 68%; b. **79**, $Pd(PPh_3)$, THF, 60 °C, 1 h; (±)-**80**, 97%; (*S*)-**81**, 99%; (*R*)-**82**, 92%; c. VOF_3, CH_2Cl_2/EtOAc/TFA, -78 °C to rt, 1 h; (±)-**1**, 89%; (*S*)-**83**, 83%, >98:2 er; (*R*)-**84**, 74%, 97.5:2.5 er.

The synthesis was completed with a VOF_3-mediated bi-aryl ring closure to afford (±)-boehmeriasin A (**1**), (*S*)-boehmeriasin A (**83**), and (*R*)- boehmeriasin A (**84**) in good yields.[37] These conditions proved optimal because the use of other oxidants (e.g. PIFA[63] or $FeCl_3$[64]) resulted in a difficult to remove side-product, which is believed to be the regioisomeric product. The formation of this side product is completely suppressed through the use of VOF_3 in acidic media at low temperature. The final products were crystallized from CH_2Cl_2/MeOH and the crystal structure for the (*R*)-antipode is shown in Figure 3. The spectral data of the synthetic natural product was consistent with those reported for the isolated natural product. In addition, the specific rotation of the (*R*)-enantiomer gave a matching sign and

magnitude with those found in the literature (lit. -80, MeOH, c = 0.10; obs. -86, MeOH, c = 0.10)[13] and thus establishing the absolute stereochemistry of the natural product.

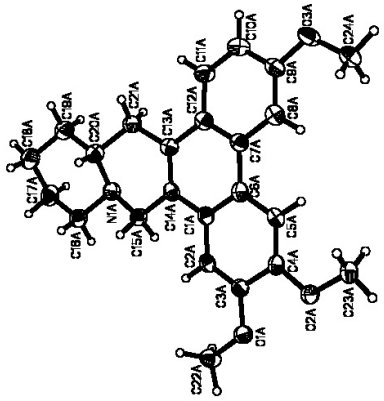


Figure 3. Crystal structure of (-)-(*R*)-boehmeriasin A.

1.5 Biological Evaluation

The natural products and synthetic intermediates were subjected to cytotoxicity assays to confirm the reported biological activity and establish an initial SAR for boehmeriasin A in breast (MCF7), ovarian drug-resistant (NCI-ADR-RES), and colon (COLO-205) cancer cell lines (Table 1). Enaminone **54** and arylated enaminone **53** did not display any cytotoxic activity in any of these cell lines. Compound **78** and *seco*-boehmeriasin A **80** were also void of any cytotoxic activity in the cell lines evaluated. However, racemic boehmeriasin A (**1**) did show potent cytotoxic activity. This indicates that a full phenanthrene ring system is required for potent cytotoxic activity. This is in accord with other studies of synthetic analogues of this class of natural products.[20] (-)-Boehmeriasin A (**84**) was much more potent than its antipode, (+)-**83**, in all of the cell lines evaluated. Important to note is that all

of the natural product derivatives showed activity in the drug resistant cancer cells, NCI-ADR-RES, where paclitaxel is inactive. Additionally, the hydrochloride salt of (±)-boehmeriasin A also demonstrates potent cytotoxic activity in these cell lines.

Table 1. Biological evaluation of boehmeriasin A and synthetic intermediates.

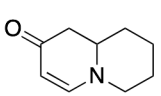
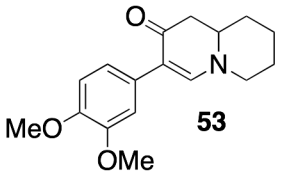
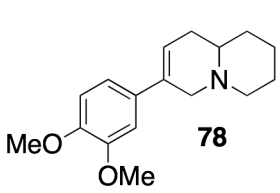
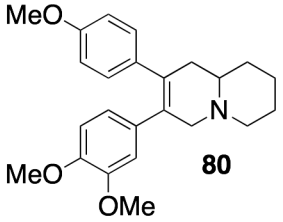
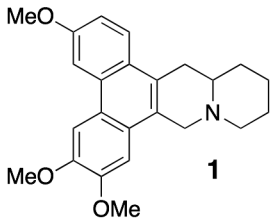
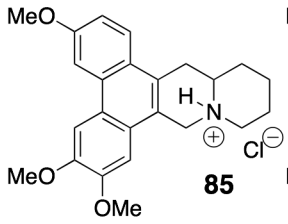
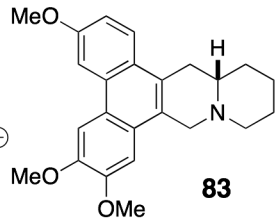
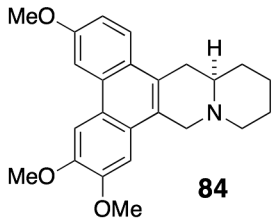
Compound	paclitaxel	colchicine	 **54**	 **53**	 **78**	 **80**
Cancer Cell Line						
MCF7 (nM)	1.49		> 50,000	> 50,000	> 50,000	> 50,000
NCI-ADR-RES (nM)	> 50,000	1570	> 50,000	> 50,000	> 50,000	> 50,000
COLO-205 (nM)	2.31		> 50,000	> 50,000	> 50,000	> 50,000

Table 1. Biological evaluation of boehmeriasin A and synthetic intermediates (cont.).

Compound	paclitaxel	colchicine	 **1**	 **85**	 **83**	 **84**
Cancer Cell Line						
MCF7 (nM)	1.49		<50	<50	103	<12.5
NCI-ADR-RES (nM)	> 50,000	1570	<200	<50	548	62
COLO-205 (nM)	2.31		<50	<3	162	<3

1.6 Conclusions

In conclusion, the first total synthesis of (-)-(*R*)-boehmeriasin A was accomplished in seven steps from commercially available material with an overall yield of 29% and the absolute stereochemistry of the natural product was determined to be of the (*R*)-configuration. The synthetic route deserves several comments. Boehmeriasin A is the first phenanthroquinolizidine alkaloid to be prepared using novel enaminone chemistry developed in the Georg group laboratories. In addition, this research for the first time utilizes a palladium(II)-mediated C-H functionalization of a quinolizinone in a total synthesis. When evaluated for cytotoxic activity, (-)-(*R*)-boehmeriasin A demonstrates potent cytotoxicity in several different cancer cell lines. From the analogues evaluated, some initial SAR could be deduced. First, a full phenanthrene is required for cytotoxic activity because synthetic intermediates lacking any portion of this ring system were void of anticancer activity. Also, it was found that the (*R*)-enantiomer is more potent compared to its antipode in all cell lines evaluated and the hydrochloride salt of (±)-boehmeriasin A also demonstrates potent cytotoxic activity. In addition, these compounds display potent cytotoxic activity in drug resistant cancer cells where paclitaxel is inactive.

Chapter 2

Development of a Sequential, One-Pot Synthesis of Chromones

2.1 Background

The chromone motif and its derivatives are privileged structures that demonstrate a wide range of biological activities (Figure 4).[65] These secondary metabolites are produced by polyketide synthases encoded in the chromosomes of a variety of organisms, typically of plant origin.[66,67] The isolated natural products frequently consist of highly oxygenated chromones that act as free radical scavengers or as defenses against external stressors for the producing organism.[67] Of the wide array of biological activity displayed by chromones, they are known primarily for their antioxidant activity.[68-70] Additional pharmacological activities displayed by these compounds include antiinflammatory, antitumor, and antimutagenic properties.[71,72] It has been postulated that their impressive biological activity results from the ability of chromones to act as ATP mimics in various biological targets.[73] Due to their broad biological profiles, these natural products have often been used as lead compounds in medicinal chemistry programs. Several chromone compounds, namely flavones, have been recently introduced into clinical trials for the treatment of ulcerative colitis and angiogenesis inhibition.[2] As a continuation of the Georg group's interest in chromones as biological probes,[74] efforts towards a general method for the construction of chromones via a sequential, one-pot synthetic route are presented.

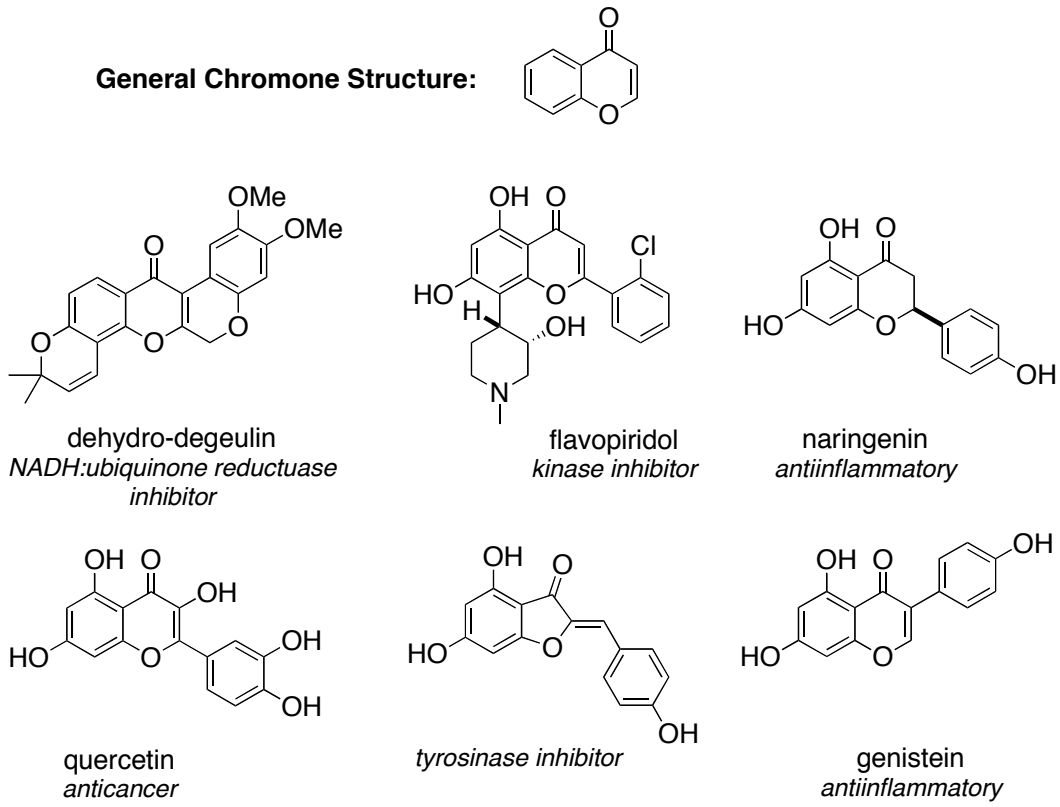


Figure 4. Representative chromone natural products.

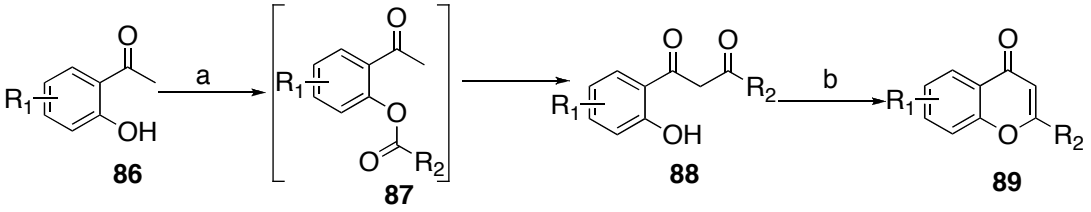
2.2 Previous Routes to Chromones

The most popular method for the construction of chromones is the Baker-Venkataraman rearrangement (Scheme 14).[75,76] In this reaction substituted 2-hydroxy acetophenones **86** are converted to esters **87**, which rearrange under basic conditions to afford diketones **88**. These intermediates cyclize to chromones **89** under rather harsh conditions, for example, by treatment with concentrated sulfuric acid or heating with glacial acetic acid. However, variants that use milder reagents have been developed.[77] Another common method to access these compounds involves the intramolecular Michael addition of 2-hydroxyphenyl ynones **90** into the

corresponding 1,4-benzopyrones **89** (Scheme 14).[78] This strategy generally affords good yields of the desired chromone. Until recently, however, synthesis of the cyclization precursors (i.e. ynones) have relied upon toxic reagents (e.g. $HgCl_2$, PDC, or 18-crown-6) and/or suffered from poor yields.[79-82] In addition, the one-step synthesis of chromones has been reported but mixtures of flavones and aurones were produced in modest yields.[83] A similar approach was used for the synthesis of flavones and quinolones that required the use of high temperatures and resulted in modest to good yields of the desired products.[84]

Scheme 14

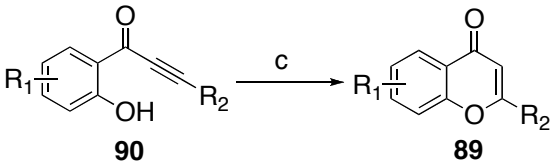
Baker-Venkataraman Rearrangement



86 **87** **88** **89**

a. R_2COCl, pyridine, KOH; b. H^+.

Intramolecular Michael Addition



90 **89**

c. K_2CO_3, MeOH or acetone, reflux.

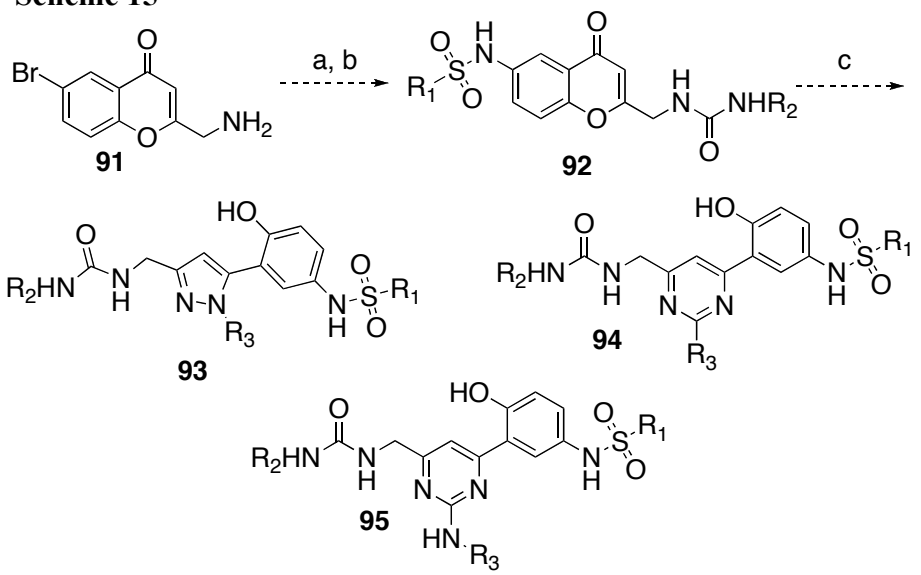
2.3 Diversity-Oriented Synthesis Approach to Chromones

Ideally a mild and highly efficient synthesis of the chromone core, which does not require the use of large quantities of toxic chromium or mercury reagents, could

be employed to construct a variety of these compounds for use in diversity-oriented synthesis (DOS).[85-87] The underlying tenet of DOS is to efficiently prepare collections of skeletally diverse small molecules intended to mimic natural product scaffolds. Natural product-like compounds are desired as foundations for lead entities as these entities have been selected over time to contain motifs (i.e. privileged structures) that elicit biological activity.[88] Accordingly, the privileged nature of the chromone motif makes it an excellent starting point for the generation of DOS-based libraries. Not surprisingly, libraries based on the chromone scaffold have been reported.[89-98] In addition, these scaffolds have inspired the development of new polymer-bound reagents for use in their construction.[99-101] Although these methods afforded libraries of chromone derivatives, they were limited in substrate scope. Therefore, a more general method allowing access to a diverse set of chromones for use in DOS was desired. A library of unique chromones, located in relatively unpopulated chemical space, would add value to any high-throughput screening set due to their privileged nature.

A hypothetical library of unique chromones was envisioned upon development of a new route to these compounds (Scheme 15). Chromone **91** would first be treated with isocyanates and the resulting ureas would undergo an amidation reaction to afford a library of chromones **92**. These intermediates can be further transformed into subsequent libraries of pyrazoles **93**, pyrimidines **94**, or amino pyrimidines **95** via treatment with hydrazines, amidines, or guanidines, respectively, via reaction of the latent 1,3-dicarbonyl.[94,95]

Scheme 15



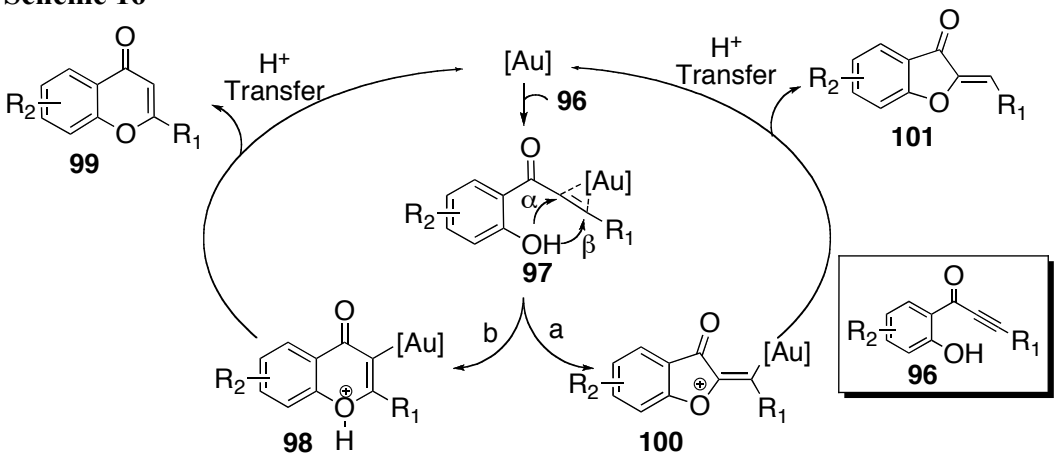
a. R_2NCO; b. Pd(0), $R_1SO_2NH_2$; c. R_3-NH-NH_2 or $R_3C(NH)NH_2$ or $R_3NHC(NH)NH_2$.

2.4 Chromone Synthesis via Gold Catalysis

Gold catalysts are well known for their unique ability to coordinate to alkynes. This coordination renders the alkyne electrophilic and prone to nucleophilic attack or rearrangement to afford unique skeletons.[102,103] These catalysts assist in the efficient construction of diverse molecular structures, in particular carbocycles and heterocycles, with great synthetic efficiency that would be difficult to prepare by other methods. As ynones are useful synthons[56] and no previous reports utilizing gold catalysis with these substrates were known, the feasibility of preparing chromone derivatives via intramolecular cyclization using gold catalysis was undertaken. The reaction pathway envisioned for this process is depicted in Scheme 16. Initial coordination of the catalyst to the ynone **96** gives complex **97** that can be cyclized in either a 6-*endo*-dig or 5-*exo*-dig fashion. Attack at the β-position produces

intermediate **98** followed by a proton transfer giving chromone **99**. However, nucleophilic attack at the α-position yields gold complex **100** that is subsequently converted into aurone **101**. In order to test the viability of this reaction pathway, an efficient synthetic route to the requisite phenolic ynones was developed.

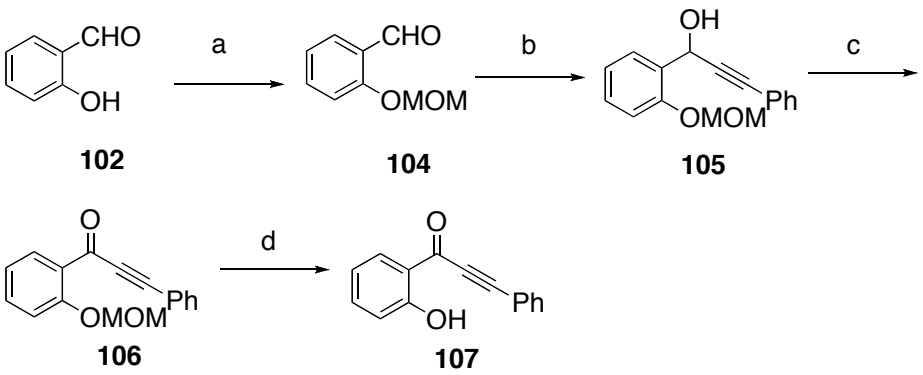
Scheme 16



2.5 Synthesis of Phenolic Ynones

As an initial model system to test these synthons as cyclization substrates, ynone **107** was synthesized in a sequential, one-pot fashion through a modification of a literature procedure (Scheme 17).[97] Protection of aldehyde **102** with MOM-Cl, followed by treatment with lithiated phenyl acetylene, oxidation with MnO_2, and deprotection with TFA gave ynone **107** in good overall yield and required only a single chromatographic purification at the end of the synthesis. This route was chosen over previous methods as this would allow synthetic intermediates at be utilized for subsequent DOS-based libraries. With an efficient route to the cyclization substrate in place, investigation into the gold-mediated cyclization was explored.

Scheme 17



102 **104** **105** **106** **107**

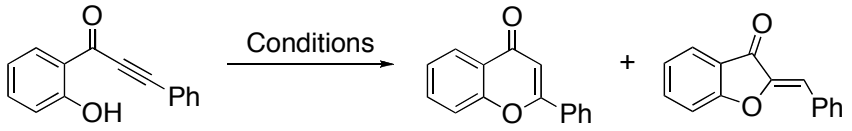
a. MOM-Cl, DIEA, CH_2Cl_2; b. *n*BuLi, HCCPh (**103**), THF then aldehyde, 0 ºC to rt; c. MnO_2, 1,2-dichloroethane, reflux; d. TFA, CH_2Cl_2; 74% (4 steps).

2.6 Optimization of Ynone Cyclization

Screening several commercially available gold catalysts in acetonitrile and several temperatures resulted in very slow reactions producing only trace quantities of flavone (**108**) (Table 2, Entries 1-4). Presumably this is a consequence of the electron-deficient nature of the ynone reducing its ability to coordinate to the catalyst. In an attempt to increase the reaction rates, K_2CO_3 was added to increase the nucleophilicity of the phenolic moiety for attack of the ynone (Entry 5). Complete consumption of starting material was observed at room temperature resulting in a mixture of the corresponding flavone and aurone (85:15). However, carrying out the reaction without the gold catalyst resulted in only the flavone being isolated (Entry 6). Thus, a gold catalyst was not required for the cyclization to occur which is in agreement with previous reports.[79-81] However, these examples utilized refluxing in either MeOH or acetone whereas stirring in acetonitrile at room temperature is sufficient for cyclization to occur. An analogous cyclization was recently reported utilizing AuCl and propargyl alcohols followed by an oxidation to access the

corresponding aurones.[104] This report corroborated our results that prolonged reaction times produce low yields of flavones when utilizing only the gold catalyst in conjunction with ynones. In addition, treating ynones similar to compound **107** with other transition metals (e.g. Pd or Ag) also results in aurone formation.[105,106] Deprotection with 4 M HCl in dioxane and cyclization and K_2CO_3 in MeOH which were previously used to construct enaminones from Boc-ynones were also examined.[56] These conditions resulted in the formation of an undetermined side-product. Therefore, deprotection with TFA and cyclization with K_2CO_3 in acetonitrile at ambient temperature were deemed to be the optimal conditions to access the chromones.

Table 2. Optimization of cyclization conditions.



107 **108** **109**

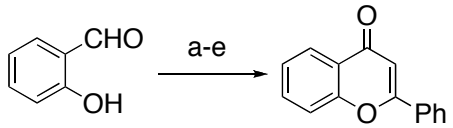
Entry	Catalyst	Solvent	Base	Temp	Time	Flavone	Aurone
1	$AuCl_3$	MeCN	none	80	12	Trace	--
2	AuCl	MeCN	none	80	12	no	--
3	$(PPh_3)AuCl$	wet	none	rt	12	Trace	--
4	$AuCl_3$	wet	none	rt	12	no	--
5	$AuCl_3$	wet	K_2CO_3	rt	2	85	15
6	none	wet	K_2CO_3	rt	4	>95%	--

2.7 Development of a Sequential, One-Pot Synthesis of Chromones

An investigation to determine if the above synthetic steps would be amenable to a sequential, one-pot endeavor starting with aldehyde **102** was next evaluated

(Scheme 18). An analogous route has been reported but resulted in a moderate overall yield utilizing large excesses of toxic chromium and mercury reagents.[77] Additionally, purifications were performed after each reaction in the sequence. When salicylaldehyde (**102**) was subjected to the optimized procedure, flavone (**108**) was obtained in excellent yield over the five-step sequence. A single chromatographic step at the end of the series proved to be an acceptable means to access chromone **108**. Thus, conditions for a high-yielding, operationally mild, one-pot protocol for the synthesis of chromones were established.

Scheme 18



102 **108**

a. MOM-Cl, DIEA, CH_2Cl_2; b. *n*BuLi, HCCPh (**103**), THF then aldehyde, 0 ºC to rt; c. MnO_2, 1,2-dichloroethane, reflux; d. TFA, CH_2Cl_2; e. K_2CO_3, MeCN, 77 %, (5 Steps).

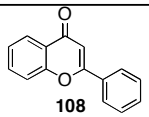
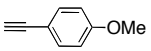
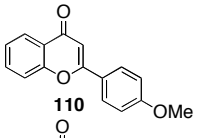
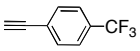
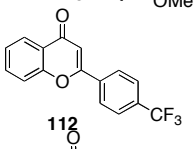
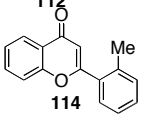
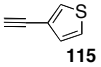
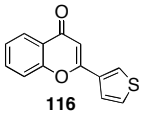
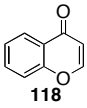
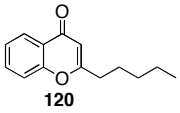
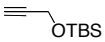
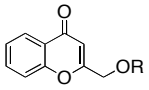
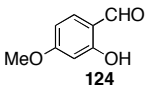
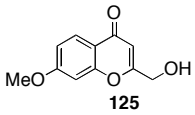
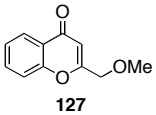
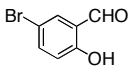
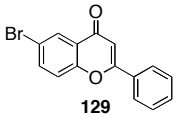
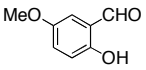
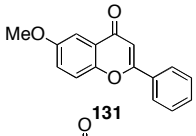
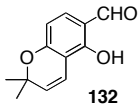
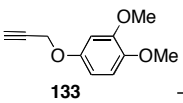
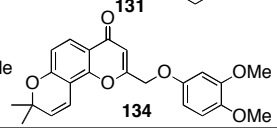
2.8 Exploration of Scope of Optimized Route

With the optimized five-step sequence in place, a series of flavone derivatives was prepared to explore the scope of the reaction sequence (Table 3). The electronic nature of the ynone was evaluated and all variants (e.g. electron-neutral, electron-rich, and electron-poor ynones) underwent cyclization resulting in synthetically useful yields of the corresponding flavones (Entries 1-3). Altering the electronic nature of the aromatic rings does slightly lower the overall isolated yield. Previous reports suggest that the reaction occurs through a vinylic carbanion.[78] Therefore modifying the electronic nature of the ynone substituent renders a less stable carbanion at the α-

position, resulting in lower chromone product formation. Small amounts of the corresponding aurone were detected in these cases. The aurones and chromones can be easily distinguished from one another through several different methods. Chromatographically, the aurones are generally less polar on TLC (silica gel) compared to flavones. In addition, the vinyl proton of aurones is commonly shifted more downfield (i.e. >6.8 ppm) when compared to the analogous proton in flavone systems (i.e. <6.8 ppm). Sterically demanding aryl moieties also provide good yields of the corresponding chromones; however, significant amounts of the corresponding aurones are also produced (Entry 4). This suggests that steric hindrance in proximity to the ynone plays a greater role in the regioselective outcome than the electronic character of the ynone using this protocol. Heteroaromatic rings are also suitable reaction substrates (Entry 5). TMS-protected and alkyl ynones furnished the desired chromone in excellent overall yields (Entries 6 and 7). The low isolated yields of the chromones **122**, **123**, and **125** were unexpected (Entries 8 and 9). The lower yields observed in these cases are hypothesized to result from an intermolecular attack of the free alcohol once the chromone has been generated. Accordingly, protection of the free hydroxyl moiety as a methyl ether results in a significantly increased overall yield compared to the free hydroxyl case (Entry 10). The electronic character of the aldehyde partner was also evaluated and both electron-poor and electron-rich functional groups afford good yields of the desired products (Entries 11 and 12). Preparation of a natural product-like compound (e.g. rotenone) was also explored and gratifyingly the synthetic route was able to afford moderate yields for this example

(Entry 13). Notable features of this synthetic route are that only a single purification step is necessary and the reaction sequence can tolerate a wide range of functionality, which is ideal for library synthesis.

Table 3. Scope of the sequential, one-pot chromone synthesis.

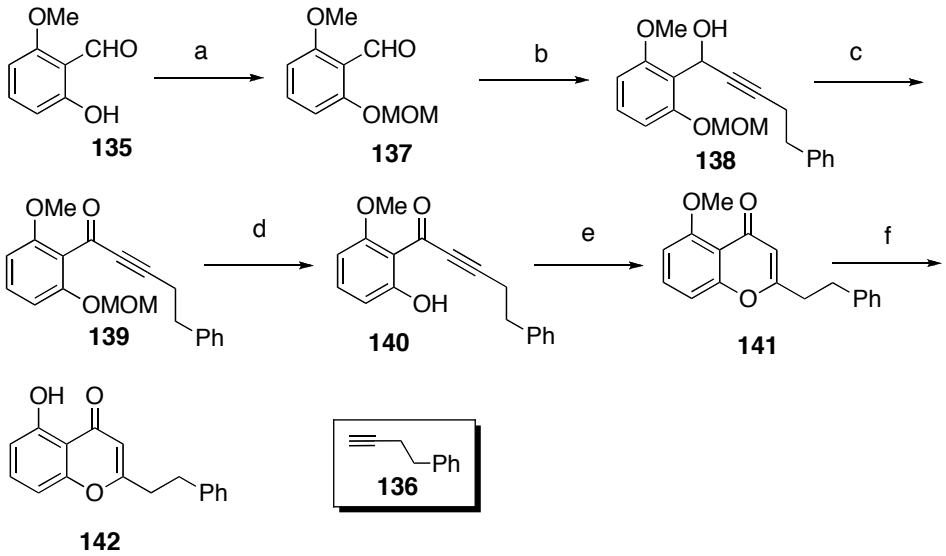
Entry	Aldehyde	Alkyne	Flavone	Yield (%)
1	 **102**	 **103**	 **108**	77
2	**102**	 **109**	 **110**	59[a]
3	**102**	 **111**	 **112**	56[b]
4	**102**	 **113**	 **114**	72[c]
5	**102**	 **115**	 **116**	74
6	**102**	 **117**	 **118**	58
7	**102**	 **119**	 **120**	91
8	**102**	 **121**		**122**, R = H; 14% **123**, R = TBS; 13%
9	 **124**	**121**	 **125**	7
10	**102**	 **126**	 **127**	38
11	 **128**	**103**	 **129**	65
12	 **130**	**103**	 **131**	50
13	 **132**	 **133**	 **134**	37

a. Trace aurone, b. 5% aurone, c. 28% aurone

2.9 Extension to Natural Product Synthesis

To further extend the scope of this method, the synthesis of the natural product, hydroxy-2-(2-phenylethyl)chromone (**142**), was undertaken (Scheme 19). This compound was isolated from the methanolic extract of the rhizomes of *Imperata cylindrica* Beauv. (Gramine) through a bioactivity-guided fractionation screen for neuroprotective compounds.[107] Chromone **142** was found to significantly protect primary cultures of rat cortical cells from glutamate-induced neurotoxicity at 10 μM. The synthesis commenced by treating aldehyde **135** with MOM-Cl, lithiated alkyne **136**, and MnO_2 to afford the corresponding ynone **139**. This intermediate was deprotected and cyclized to afford the penultimate product **141** in 15% overall yield from aldehyde **135**. The synthesis was completed by treating chromone **141** with BBr_3 to afford the natural product **142** in good yield. The spectral data of the synthetic material were consistent with those reported in the literature for the isolated natural product.[107]

Scheme 19



a. MOM-Cl, DIEA, CH_2Cl_2; b. *n*BuLi, **136**, THF then aldehyde, 0 ºC to rt; c. MnO_2, 1,2-dichloroethane, reflux; d. TFA, CH_2Cl_2; e. K_2CO_3, MeCN, 15% (5 steps); f. BBr_3, CH_2Cl_2; 66%.

2.10 Conclusions

A five-step, one-pot procedure for the synthesis of chromone derivatives has been developed. This protocol displays high functional group compatibility, mild reaction conditions, high yields, and requires a single chromatographic step after the completion of the synthesis. In addition, this method generally affords excellent selectivity of the desired chromone over the aurone products. During this investigation a high-yielding synthesis of ynones, which are excellent substrates for constructing DOS libraries, has also been developed. The above protocol was applied to the first total synthesis of 5-hydroxy-2-(2-phenylethyl)chromone (**142**), a neuroprotective chromone isolated from *Imperata cylindrica*.

Chapter 3

A Preparative Scale Procedure for the Reduction of Tertiary Amides with $Cp_2Zr(H)Cl$

3.1 Background

Amides are prevalent structural units throughout Nature and are inert to many chemical transformations.[108] However, synthetic methods do exist to convert this moiety into the corresponding alcohols, aldehydes, and amines. Many of these methods are rather harsh and can affect other functional groups within the same molecule, although milder methods have been developed.[109] In particular, the reduction of amides into the corresponding aldehydes has proven to be a difficult synthetic challenge. Most examples have demonstrated high substrate specificity and are commonly affected by the substituents on the nitrogen atom.[110,111] In addition, conditions used to perform this transformation usually require highly activated aluminum or boron reagents that commonly result in over reduction products and low levels of chemoselectivity en route to the desired aldehydes.

Schwartz's reagent ($Cp_2Zr(H)Cl$), first reported by Wailes and Weigold, is a 16-electron, d^0 complex with the zirconium at an oxidation state of (+4).[112,113] The remaining valence for the metal renders the molecule Lewis acidic while the absence of a valence-shell filled nonbonding orbital leaves the reagent with low nucleophilic aptitude. This empty orbital allows for complexation of the metal to an array of

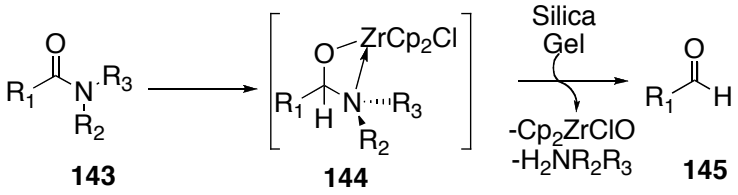
functional groups with nonbonding electron pairs, e.g. π-bonds/electrons and in some cases σ-bonds/electrons.[114]

The most commonly used synthetic application for this reagent is that of hydrozirconation due to its predictable ability to add stereo- and regioselectively across π-bonds.[115,116] These reactive intermediates can react with a range of electrophiles or undergo carbonylation or halogenation. Alternatively, the vinyl zirconium species can undergo transmetallation to participate in various cross-coupling reactions. Additionally, heteroaromatic moieties can be reduced via hydrozirconation.[117-121]

The Georg group recently reported a general method to convert amides into aldehydes using Schwartz's reagent with excellent chemoselectivity.[122-124] Mechanistically, the reduction of amides with $Cp_2Zr(H)Cl$ proceeds through an 18-electron zirconacycle intermediate that is subsequently hydrolyzed to afford the corresponding aldehydes (Scheme 20). This method is generally tolerant of many functional groups, high yielding, and operational under mild reaction conditions in very short reaction times. This procedure is able to reduce aromatic, heteroaromatic, and aliphatic amides in excellent yields. Furthermore, this protocol has been extended to afford deuterated aldehydes in excellent yields which are useful substrates to study enzymatic reactions.[122] In addition, primary, secondary, and Weinreb amides can all be reduced to the corresponding aldehyde in good to excellent yields. This method has also been applied to the removal of amide-based chiral auxiliaries although the resulting yields of the produced aldehydes were

substrate specific. Although amides containing an alkene or alkyne moiety can be reduced with this procedure, the corresponding yields are generally reduced compared to the previously mentioned examples. This presumably is a consequence of side-reactions with the unsaturated bonds present within these substrates. An investigation of sterically hindered amides revealed that this procedure is somewhat sensitive to congestion around the amide unit and the corresponding yield is substrate specific. However, Rawal and coworkers developed conditions to circumvent this limitation using three equivalents of $Cp_2Zr(H)Cl$ in CH_2Cl_2.[125] Although a very thorough investigation of the scope and mechanism has been reported on a laboratory scale, previously no examination of this procedure on a preparative scale (i.e. >1 g scale) has been conducted. Herein development of a preparatory scale reduction of tertiary amides is presented.

Scheme 20

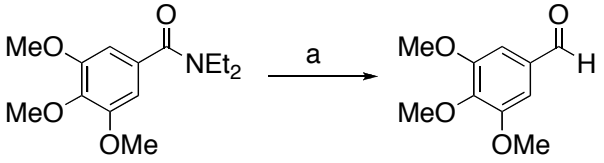


3.2 Preparatory Scale Reduction of Tertiary Amides with $Cp_2Zr(H)Cl$

Amide **146**, prepared from the corresponding acid chloride, was chosen as a model substrate to test the feasibility of a preparatory procedure for the reduction of tertiary amides to the corresponding aldehyde using the Schwartz reagent (Scheme 21). In this protocol the readily available $Cp_2Zr(H)Cl$ is suspended in anhydrous THF under a nitrogen atmosphere and amide **146** in THF is then added to the suspension

(Scheme 21). The reaction is complete within minutes in very good isolated yield on multigram quantities. Although this procedure generally afforded good yields of the corresponding aldehyde **147**, two problems were encountered that needed to be addressed upon scale up, which included (1) side-product formation after quenching the reaction with silica gel and (2) overcoming the quality of different lots of $Cp_2Zr(H)Cl$ from commercial vendors.

Scheme 21



146 **147**

a. $Cp_2Zr(H)Cl$, THF; 99%.

The first issue to be addressed when conducting the reactions was a problematic side reaction that resulted in intractable reaction mixtures. In some reactions a bright yellow/orange by-product was observed that was not noticed on smaller scale reaction (i.e. <100 mg) and was difficult to separate from the aldehyde. This impurity was not observed during the course of the reaction but only appeared after quenching the reaction with silica gel. Identifying the isolated impurity was unsuccessful; however, its presence seemed temperature and concentration dependent in the presence of silica gel. Generally by-product formation was noticed during evaporation of the solvent from the crude reaction mixture and increased amounts were observed when heating the flask containing the crude reaction/silica gel mixture above 30 ºC during this time. The resulting impurity was observed as a change in color of the silica gel from a pale yellow to orange-red. In addition, exposing the

crude aldehyde to silica gel for more than 30 minutes under high-vacuum conditions also led to increased amount of this by-product. Not surprisingly, increased amounts of the impurity led to a decreased amount of the isolated aldehyde and difficult to purify reaction mixtures. Varying the amount of silica gel or alternatively using celite or neutral alumina as a replacement for the silica gel were attempted but side-product formation was also observed in these cases. It was hypothesized that prolonged exposure to the solid medium needed to be minimized but long enough to sequester the zirconium by-products in order to obtain the desired aldehyde without side-product contamination. As such, upon complete consumption of amide, silica gel was added to the reaction and stirred for five minutes under ambient conditions. The heterogeneous mixture was filtered and washed with diethyl ether. The filtrate was concentrated and purified under standard chromatographic conditions. This did greatly reduce the observed by-product formation. However, some zirconium oxide by-products were not always completely sequestered and leached through into the filtrate and occasionally resulted in observable by-product formation. Thus, an additional workup step was implemented. After filtration, the filtrate was subjected to an aqueous workup to remove any remaining zirconium by-products from the crude mixture. This procedure was effective in providing the desired reaction product without observable by-product formation. Important to note is that the order of steps is crucial because conducting an aqueous workup of the reaction mixture (i.e. without a silica gel quench) results in difficult to break emulsions.

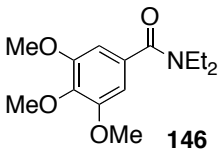
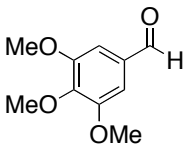
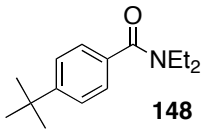
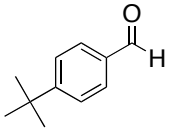
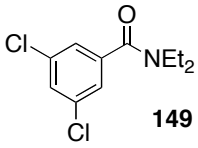
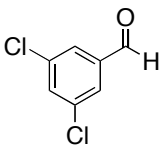
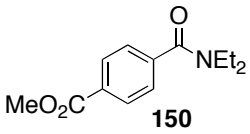
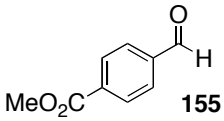
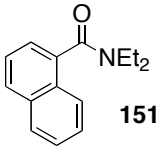
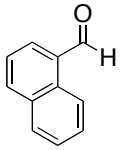
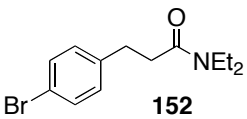
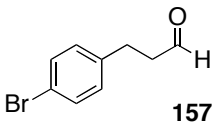
A second matter to address when conducting these reactions on a preparatory scale was the quality of the Schwartz reagent itself. The yields of the isolated aldehyde were highly dependent on the source and lot of the reagent used. Although this reagent can be prepared from Cp_2ZrCl_2,[126] most commonly this reagent was purchased from commercial vendors, due to ease of access and availability, and generally successful reactions were observed. However, inconsistencies in the quality of the commercial reagent were observed here and also recently in a procedure for the directed hydrozirconation of homopropargylic alcohols.[127] Early experiments required only 1.2 equivalents of $Cp_2Zr(H)Cl$ for the reaction to go to completion. However, in subsequent experiments, using a different lot of the commercial reagent, more $Cp_2Zr(H)Cl$ was needed for complete consumption of the starting amide. The use of 2 equivalents was enough to overcome this discrepancy in quality from lot-to-lot and afforded complete reactions in very short reaction times. Thus, the best conditions for preparatory reductions of amides with $Cp_2Zr(H)Cl$ involve the use of 2 equivalents of the Schwartz reagent and upon complete consumption of starting material, quenching the reaction with silica gel, filtering, and subjecting the filtrate to an aqueous workup. Important to note is that the amount of Schwartz's reagent used when reducing tertiary amides might be amenable to less than 2 equivalents depending on the particular substrate of interest to provide a more economical reaction.

3.3 Scope of Reduction of Amides with Schwartz's Reagent

With an optimized preparatory procedure now in place, this procedure was tested on a representative set of tertiary amides to examine functional group

compatibility on a preparatory scale (Table 4). Both neutral and electron-deficient aromatic amides are readily reduced affording the corresponding aldehydes in good yields (Entries 1 and 2). Demonstrated in Entry 3, *selective* amide reduction occurs in the presence of an ester in good yield. In addition, bulky amides and non-aromatic amides can be reduced to the corresponding aldehydes in excellent yields (Entries 4 and 5).

Table 4. Scope of Optimized Prepatory Scale Procedure.

Entry	Amide	Aldehyde	Time (min)	Scale (mmol)	Yield (%)
	 **146**	 **147**	15	60	99
1	 **148**	 **153**	10	20	90
2	 **149**	 **154**	15	11	92
3	 **150**	 **155**	15	12	85
4	 **151**	 **156**	15	7	95
5	 **152**	 **157**	15	2.4	85

3.4 Conclusions

In conclusion, a mild and operationally simple method for the selective reduction of tertiary amides to aldehydes using $Cp_2Zr(H)Cl$ on a preparatory scale is presented, employing a modified workup procedure. It is well known that conditions used on a laboratory scale sometimes need revision on preparatory scale and that was found here. Through a modified workup procedure, by-product formation that was not previously observed on a laboratory scale was suppressed. This method offers an alternative to known methods that are either substrate selective or can result in over-reduction products. In addition, this reaction can be conducted in the presence of esters and results in *selective* reduction of the amide to afford the corresponding aldehyde. Therefore, this procedure is a significant improvement over known amide reduction methods due to its mild and selective nature.

Chapter 4

Experimental

4.1 Materials and Methods

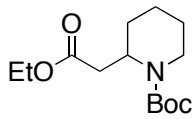
Melting points were determined using a melting point apparatus and are uncorrected. Infrared spectra were obtained as thin films on NaCl plates using an FT-IR instrument. NMR experiments were performed on a 400 MHz instrument using the residual solvent peak as internal standard unless otherwise indicated. Samples obtained in $CDCl_3$ were referenced to 7.26 ppm for ^1H and 77.16 for ^{13}C and samples obtained in d_6-DMSO were referenced to 2.50 for ^1H and 39.52 for ^{13}C.[128] All chemical shifts were recorded in parts per million (ppm) and coupling constants (*J*) are in Hz and assigned according to the procedure of Hoye and coworkers.[129] The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Specific rotations were obtained using a polarimeter at 25.0 ºC. High-resolution mass spectra were obtained utilizing the electrospray ionization technique.

All reactions were performed under an atmosphere of nitrogen in flame-dried glassware unless otherwise indicated. THF, CH_2Cl_2, and DMF were dried and deoxygenated by passing the nitrogen-purged solvents through activated alumina columns on a solvent purification system. All other reagents and solvents were used as purchased. Reaction progress was monitored by thin layer chromatography (TLC, silica gel, 10 × 20 cm, 250 micron) visualizing with UV light (254 nm) or developing the plates with either ninhydrin or phosphomolybdic acid/$Ce(SO_4)_2$ stains. All

compounds were purified using either MPLC, using either silica gel (60 Å, 230-400 mesh), neutral alumina (58 Å, ~150 mesh), or standard flash chromatography techniques utilizing the indicated conditions. All compounds were concentrated using standard rotary evaporator and high-vacuum techniques. HPLC analysis was conducted on an HPLC system equipped with a photodiode array detector. UPLC-MS analysis was used to determine product purities. All compounds were purified to >95% homogeneity prior to biological evaluation.

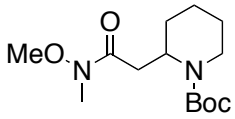
4.2 Experimental Procedures

4.2.1 Chapter 1



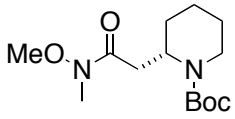
***tert*-Butyl-2-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (56).** Ethyl 2-(pyridin-2-yl)acetate (16.5 g, 100 mmol) and Boc_2O (48.10 g, 220 mmol) in ethanol (1 L) was placed in a flow hydrogenator equipped with a 10% Pd-C cartridge. The reaction was allowed to react at 0.5 mL/min at 70 °C with 30 bar H_2 pressure in a closed-loop fashion until TLC analysis (50% ethyl acetate in hexanes) indicated complete consumption of starting material (~7 d). The resulting clear solution was concentrated and purified my MPLC (0-50% acetone in hexanes, 210 nm, 50 min) to give 25.49 g of a pale yellow oil (89%). The spectral data are consistent with those reported in the literature.[35] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t, J = 7.1 Hz), 1.45 (9H, s), 1.49-1.70 (6H, m), 2.52 (1H, dd, J = 4.6, 10.7 Hz), 2.49-2.59 (1H, m), 2.77 (1H, t, J = 12.7 Hz), 3.98 (1H, d, J = 12.2 Hz), 4.11 (2H, q, J = 2.1 Hz), 4.70

(1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.32, 19.01, 25.45, 28.32, 28.54, 35.47, 60.60, 79.64, 154.87, 171.55.



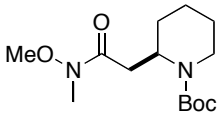
(±)-*tert*-Butyl-2-(2-(methoxy(methyl)amino)-2-oxoethyl)piperidine-1-carboxylate (55). Ester **56** (27.5 g, 101 mmol) was dissolved in THF (200 mL) and cooled to an internal temperature of -20 ºC. HN(OMe)Me•HCl (15.8 g, 162 mmol) was added to the stirring solution resulting in a slurry that was maintained at an internal temperature of -20 ºC. A 2.0 M *i*PrMgCl solution (152 mL, 304 mmol) was added to the slurry over 30 min via syringe pump addition while maintaining the internal temperature ≤ -5 ºC during the addition. Upon complete consumption of starting material as determined by TLC (50% EtOAc in hexanes), the reaction was transferred to a separatory funnel containing saturated aq. NH_4Cl and EtOAc. The layers were separated and the aqueous layer was extracted twice more with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and purified by MPLC on silica gel (0-50% acetone in hexanes, 50 min, 210 nm) to give 23.3 g of the title compound as a yellow oil (80%). The spectral data are consistent with those reported in the literature.[56] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (9H, s), 1.43-1.48 (1H, m), 1.49-1.61 (5H, m), 2.56 (1H, dd, *J* = 6.7, 13.9 Hz), 2.64 (1H, dd, *J* = 8.2, 14.0 Hz), 2.77 (1H, t, *J* = 12.9 Hz), 3.11 (3H, s), 3.65 (3H, s), 3.94 (1H, d, *J* = 11.92 Hz), 4.68 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.02, 25.38, 28.43, 32.12, 32.83, 39.38, 47.70, 61.30, 79.32, 154.81, 172.26. IR (neat, NaCl):

2935, 1689, 1665, 1411, 1365, 1164 cm^{-1}. HRMS (ESI^+): *m/z* calc'd for $C_{14}H_{26}N_2NaO_4$, 309.1790; found, 309.1794.

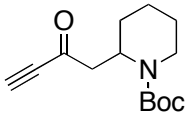


(*S*)-*tert*-Butyl-2-(2-(methoxy(methyl)amino)-2-oxoethyl)piperidine-1-carboxylate (58). To a stirring solution of commercially available (*S*)-2-(1-(*tert*-butoxycarbonyl)piperidin-2-yl)acetic acid (4.00 g, 16.5 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C were added HN(OMe)Me•HCl (1.82 g, 18.2 mmol), NMM (2.00 mL, 18.2 mmol), and EDCI (3.52 g, 18.2 mmol) in sequence and the reaction was allowed to warm to room temperature overnight. The reaction mixture was transferred to a separatory funnel containing 10% aq. HCl and CH_2Cl_2. The layers were separated and the aqueous layer was extracted twice more with CH_2Cl_2. The combined organic layers were washed with saturated aq. $NaHCO_3$; the layers were separated and the aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and purified by MPLC on silica gel (0-50% acetone in hexanes, 50 min, 210 nm) to give 4.53 g of the title compound as a yellow oil (96%). The spectral data are consistent with those reported in the literature.[56] ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (9H, s), 1.47-1.52 (1H, m), 1.52-1.65 (5H, m), 2.61 (1H, dd, *J* = 6.6, 13.8 Hz), 2.69 (1H, dd, *J* = 8.3, 14.0 Hz), 2.82 (1H, t, *J* = 12.9 Hz), 3.15 (3H, s), 3.69 (3H, s), 3.98 (1H, d, *J* = 11.9 Hz), 4.72 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.13, 25.49, 28.55, 32.25, 32.95, 39.51, 47.88, 61.41, 79.47, 154.94, 172.43. IR (neat, NaCl): 2936, 1690, 1666, 1411, 1365, 1164 cm^{-1}. $[\alpha]_D^{25}$ = -5.61 (*c* = 1.31,

$CHCl_3$). HRMS (ESI^+): *m/z* calc'd for $C_{14}H_{26}N_2NaO_4$, 309.1790; found, 309.1789.

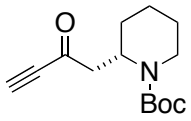


(*R*)-*tert*-Butyl-2-(2-(methoxy(methyl)amino)-2-oxoethyl)piperidine-1-carboxylate (59). The identical procedure for the synthesis of amide **58** was used employing the following amounts; (*R*)-2-(1-(*tert*-butoxycarbonyl)piperidin-2-yl)acetic acid (4.00 g, 16.5 mmol), CH_2Cl_2 (30 mL), HN(OMe)Me•HCl (1.82 g, 18.2 mmol), NMM (2.00 mL, 18.2 mmol), and EDCI (3.52 g, 18.2 mmol), to afford 4.62 g of the title compound as a yellow oil (98%). The spectral data are consistent with those reported in the literature.[56] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (9H, s), 1.42-1.51 (1H, m), 1.54-1.60 (5H, m), 2.56 (1H, dd, *J* = 6.80, 13.89 Hz), 2.62 (1H, dd, *J* = 8.24, 14.01 Hz), 2.77 (1H, t, *J* = 12.86 Hz), 3.00 (3H, s), 3.64 (3H, s), 3.93 (1H, d, *J* = 12.00 Hz), 4.67 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.00, 25.37, 38.42, 32.11, 32.82, 39.37, 47.74, 61.29, 79.32, 154.81, 172.27. IR (neat, NaCl) 2936, 1689, 1665, 1410, 1365, 1164. $[\alpha]_D^{25}$ = 7.54 (*c* = 1.14, $CHCl_3$). HRMS (ESI^+): *m/z* calc'd for $C_{14}H_{26}N_2NaO_4$, 309.1790; found, 309.1786.



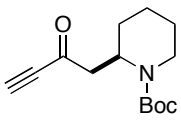
(±)-*tert*-Butyl-2-(2-oxobut-3-ynyl)piperidine-1-carboxylate (60). To a stirring solution of amide **55** (23.3 g, 81.2 mmol) in THF (15 mL) cooled to -78 °C was added ethynylmagnesium bromide (0.5 M, 650 mL, 325 mmol) over 30 min. Thirty minutes after complete addition, the reaction mixture was warmed to room

temperature. Following complete consumption of starting material as determined by TLC (50% EtOAc in hexanes), the reaction mixture was transferred to a flask containing 1 M aq. $NaHSO_4$ (1 L) cooled to 0 °C and stirred for 1 h. The solution was transferred to a separatory funnel and extracted twice with EtOAc. The combined organic layers were washed with aq. saturated $NaHCO_3$, brine, dried over Na_2SO_4, concentrated, and purified by MPLC on silica gel (0-50% acetone in hexanes, 50 min, 210 nm) to give 16.4 g of the title compound as a white solid (80%). The spectral data are consistent with those reported in the literature.[56] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.47-1.55 (2H, m), 1.59-1.72 (4H, m), 2.74-2.81 (2H, m), 2.86 (1H, dd, J = 7.1, 14.4 Hz), 3.25 (1H, s), 4.00 (1H, d, J = 10.7 Hz), 4.83 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.00, 25.32, 28.50, 28.62, 39.33, 46.02, 47.61, 78.98, 80.04, 81.71, 154.73, 185.21. IR (neat, NaCl): 3212, 2936, 2090, 1679, 1411, 1366, 1165 cm^{-1}. MP = 60-62 °C. HRMS (ESI$^+$): *m/z* calc'd for $C_{14}H_{21}NNaO_3$, 274.1419; found 274.1416.

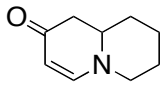


(*S*)-*tert*-Butyl-2-(2-oxobut-3-ynyl)piperidine-1-carboxylate (61). The identical procedure for the synthesis of ynone **58** was used employing the following amounts; amide **58** (4.43 g, 15.5 mmol), THF (40 mL), ethynylmagnesium bromide (0.5 M, 124 mL, 62.0 mmol), 1 M aq. $NaHSO_4$ (500 mL) to give 3.52 g of the title compound as a white solid (91%). The spectral data are consistent with those reported in the literature.[56] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.46-1.55 (2H, m), 1.59-1.72

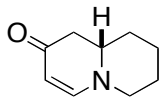
(4H, m), 2.74-2.81 (2H, m), 2.86 (1H, dd, J = 7.0, 14.3 Hz), 3.25 (1H, s), 4.00 (1H, d, J = 11.0 Hz), 4.83 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.00, 25.32, 28.49, 28.63, 39.46, 46.02, 47.57, 78.99, 80.04, 81.71, 154.73, 185.22. IR (neat, NaCl): 3212, 2937, 2091, 1681, 1412, 1366, 1166 cm^{-1}. MP = 71-73 °C. $[\alpha]_D^{25}$ = +45.6 (c = 0.563, $CHCl_3$). HRMS (ESI$^+$): *m/z* calc'd for $C_{14}H_{21}NNaO_3$, 274.1419; found 274.1417.



(*R*)-*tert*-Butyl-2-(2-oxobut-3-ynyl)piperidine-1-carboxylate (62). The identical procedure for the synthesis of ynone **61** was used employing the following amounts; amide **59** (4.36 g, 15.2 mmol), THF (45 mL), ethynylmagnesium bromide (122 mL, 60.9 mmol), 1 M aq. $NaHSO_4$ (500 mL) to give 3.43 g of the title compound as a white solid (90%). The spectral data are consistent with those reported in the literature.[56] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.46-1.55 (2H, m), 1.58-1.71 (4H, m), 1.64-1.72 (2H, m), 2.73-2.77 (1H, m), 2.77-2.80 (1H, m), 2.85 (1H, dd, J = 7.1, 14.4 Hz), 3.26 (1H, s), 4.00 (1H, d, J = 10.88 Hz), 4.82 (1H, br s). ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.99, 25.31, 28.48, 28.61, 39.33, 46.01, 47.52, 79.00, 80.03, 81.70, 154.72, 185.20. IR (neat, NaCl): 2937, 2091, 1682, 1412, 1366, 1166. MP = 71-73 °C. $[\alpha]_D^{25}$ = -44.2 (c = 0.740, $CHCl_3$). HRMS (ESI$^+$): *m/z* calc'd for $C_{14}H_{21}NNaO_3$, 274.1419; found 274.1414.

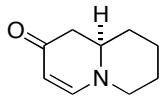


(±)-7,8,9,9a-Tetrahydro-1*H*-quinolizin-2(6*H*)-one (54). To a round-bottomed flask containing ynone **60** (13.3 g, 52.8 mmol) and NaI (23.7 g, 158 mmol) was added formic acid (500 mL) and the reaction was stirred under an ambient atmosphere overnight. The resulting reaction mixture was concentrated to dryness and methanol (820 mL) and K_2CO_3 (3.43 g, 24.6 mmol) were added in sequence to the flask and the reaction mixture was stirred overnight at ambient temperature. The resulting solution was concentrated, dry-loaded onto silica gel, and purified by MPLC on silica gel (15-65% acetone in hexanes, 50 min, 210 nm) to give 6.02 g of the title compound as a yellow solid (92%). The spectral data are consistent with those reported in the literature.[56] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (1H, dddd, *J* = 3.2, 6.5, 12.5, 15.9 Hz), 1.45-1.54 (1H, m), 1.55-1.64 (1H, m), 1.71-1.79 (2H, m), 1.82-1.89 (1H, m), 2.36 (1H, dd, *J* = 13.1, 16.4), 2.47 (1H, dd, *J* = 5.6, 16.4 Hz), 2.98 (1H, dt, *J* = 3.0, 12.6 Hz), 3.26-3.34 (1H, m), 3.36-3.40 (1H, m), 4.98 (1H, d, *J* = 7.0 Hz), 6.86 (1H, d, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.33, 25.77, 31.85, 43.40, 53.15, 57.33, 99.62, 154.97, 192.55. IR (neat, NaCl): 2938, 1634, 1587, 1446, 1389, 1324, 1237, 1143 cm^{-1}. MP = 67-69 °C. HRMS (ESI$^+$): *m/z* calc'd for $C_9H_{13}NNaO$, 174.0895; found 174.0893.



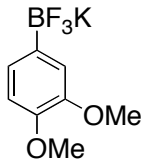
(*S*)-7,8,9,9a-Tetrahydro-1*H*-quinolizin-2(6*H*)-one (63). The identical procedure for the synthesis of enaminone **54** was used employing the following amounts; ynone **61**

(1.99 g, 7.96 mmol), NaI (3.60 g, 23.9 mmol), formic acid (40 mL); MeOH (800 mL) and K_2CO_3 (3.30 g, 23.9 mmol) to give 1.13 g of the title compound as a white solid (94%). The spectral data are consistent with those reported in the literature.[56] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (1H, dddd, *J* = 3.0, 6.4, 12.4, 15.8 Hz), 1.43-1.50 (1H, m), 1.52-1.61 (1H, m), 1.70-1.76 (2H, m), 1.79-1.86 (1H, m), 2.32 (1H, dd, *J* = 13.1, 16.4 Hz), 2.44 (1H, dd, *J* = 5.6, 16.4 Hz), 2.95 (1H, dt, *J* = 3.0, 12.7 Hz), 3.23-3.31 (1H, m), 3.34-3.38 (1H, m), 4.94 (1H, d, *J* = 7.6 Hz), 6.84 (1H, d, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.24, 25.69, 31.76, 43.30, 53.06, 57.22, 99.45, 154.93, 192.44. IR (neat, NaCl): 2940, 1631, 1581, 1239, 1143 cm^{-1}. MP = 47-49 °C. $[\alpha]_D^{25}$ = +145 (*c* = 1.15, $CHCl_3$), HRMS (ESI^+): *m/z* calc'd for $C_9H_{13}NNaO$, 174.0895; found 174.0884.

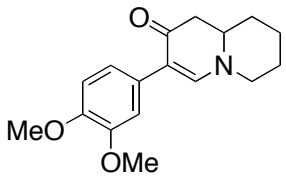


(*R*)-7,8,9,9a-Tetrahydro-1*H*-quinolizin-2(6*H*)-one (64). The identical procedure for the synthesis of enaminone **54** was used employing the following amounts; ynone **62** (2.02 g, 7.96 mmol), NaI (3.63 g, 23.9 mmol), formic acid (40 mL); MeOH (800 mL) and K_2CO_3 (3.3 g, 23.9 mmol) to give 1.08 g of the title compound as a white solid (90 %). The spectral data are consistent with those reported in the literature.[56] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (1H, dddd, *J* = 3.1. 6.4, 12.4, 15.9 Hz), 1.44-1.52 (1H, m), 1.58 (1H, dddd, *J* = 4.2, 7.9, 12.8, 26.0 Hz), 1.70-1.78 (2H, m), 1.81-1.88 (1H, m), 2.34 (1H, dd, *J* = 13.1, 16.4 Hz), 2.46 (1H, dd, *J* = 5.6, 16.4 Hz), 2.97 (1H, dt, *J* = 3.0, 12.6 Hz), 3.24-3.32 (1H, m), 3.35-3.39 (1H, m), 4.96 (1H, d, *J* = 7.6 Hz),

6.85 (1H, d, J = 7.6 Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.29, 25.73, 31.81, 43.33, 53.11, 57.27, 99.51, 154.98, 192.52. IR (neat, NaCl): 3449 (br), 2938, 1637, 1588, 1444, 1237. MP = 47-49 °C. $[\alpha]_D^{25}$ = -140 (c = 1.20, $CHCl_3$). HRMS (ESI^+): *m/z* calc'd for $C_9H_{13}NNaO$, 174.0895; found 174.0893.

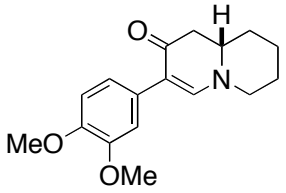


Potassium 3,4-Dimethoxyphenyltrifluoroborate (65). 3,4-Dimethoxyphenylboronic acid (2.00 g, 11.0 mmol) and KHF_2 (2.00 g, 25.3 mmol) were combined in a MeOH/H_2O (60 mL) solution in a polypropylene screw-top vessel and placed on an orbital shaker overnight at room temperature. The resulting slurry was concentrated to dryness and subsequently dissolved in hot acetone and filtered. The filtrate was concentrated until the trifluoroborate was sparingly soluble. The solution was gently heated and Et_2O was added resulting in a white precipitate that was cooled to 4 °C overnight. The heterogeneous solution was filtered and the resulting solid was washed with Et_2O and dried to afford 2.56 g of the title compound as a white solid (96%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.66 (3H, s), 3.67 (3H, s), 6.69 (1H, d, J = 7.8 Hz), 6.83 (1H, d, J = 7.8 Hz), 6.87 (1H, s). ^{13}C NMR (100 MHz, d_6-DMSO) δ 55.11, 55.41, 110.91, 115.10 (1C, d, J = 1.2 Hz), 123.51 (d, 1C, J = 1.3 Hz), 146.69, 147.46. ^{19}F NMR (376.4 MHz, d_6-DMSO, $CFCl_3$ internal std) δ -137.89. CHN: calc'd for $C_8H_9BF_3KO_2$, C, 39.37; H, 3.72; found: C, 38.98; H, 3.89.



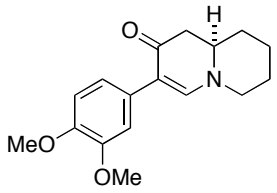
(±)-3-(3,4-Dimethoxyphenyl)-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one (53). Enaminone **54** (749 mg, 4.95 mmol), $[Pd(OAc)_2]_3$ (334 mg, 0.50 mmol), anhydrous $Cu(OAc)_2$ (2.74 g, 14.9 mmol), and K_2CO_3 (1.37 g, 9.90 mmol) were combined in a *t*BuOH/AcOH/DMSO solution (20:5:1, 50 mL) and stirred for 5 min. The reaction mixture was heated to 60 °C and potassium 3,4-dimethoxyphenyltrifluoroborate (2.42 g, 9.90 mmol) in acetone/H_2O (2:1, 20 mL) was added to the reaction mixture over 1 h. An additional portion of $[Pd(OAc)_2]_3$ (168 mg, 0.25 mmol) was added to the stirring mixture and the remaining potassium 3,4-dimethoxyphenyltrifluoroborate (2.42 g, 9.90 mmol) in acetone/H_2O (2:1, 20 mL) was added to the reaction mixture over 1 h. The reaction mixture was cooled room temperature and K_2CO_3 was added to the dark reaction medium until gas evolution ceased. The basic solution was filtered through a celite plug eluting with EtOAc, concentrated, and purified by MPLC on silica gel (15-65% acetone in hexanes, 50 min, 210 nm) to give 1.19 g of the title compound as a white solid (83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (1H, dddd, *J* = 3.0, 6.2, 12.3, 19.2 Hz), 1.48-1.60 (1H, m), 1.61-1.70 (1H, m), 1.77-1.86 (2H, m), 1.87-1.92 (1H, m), 2.51 (1H, dd, *J* = 13.3, 16.2 Hz), 2.61 (1H, dd, *J* = 5.4, 16.2 Hz), 3.06 (1H, dt, *J* = 3.0, 12.7 Hz), 3.34-3.42 (1H, m), 3.44-3.48 (1H, m), 3.86 (3H, s), 3.88 (3H, s), 6.82 (1H, d, *J* = 8.3 Hz), 6.85 (1H, dd, *J* = 1.8, 8.3 Hz), 7.02 (1H, d, *J* = 1.8 Hz), 7.10 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.26, 25.82, 31.83,

44.07, 53.31, 56.00, 56.10, 57.39, 111.29, 112.05, 112.27, 119.72, 129.20, 147.48, 148.66, 153.72, 189.90. IR (neat, NaCl): 2936, 1634, 1595, 1515, 1251, 1028 cm^{-1}. MP = 123-125 °C. HRMS (ESI^+): *m/z* calc'd for $C_{17}H_{22}NO_3$, 288.1600; found 288.1598.

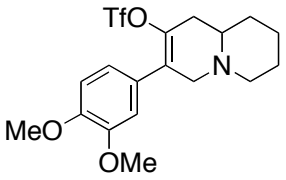


(*S*)-3-(3,4-Dimethoxyphenyl)-7,8,9,9a-tetrahydro-1*H*-quinolizin-2(6*H*)-one (66). The identical procedure for the synthesis of quinolizidone **53** was used employing the following amounts; enaminone **63** (301 mg, 1.98 mmol), $[Pd(OAc)_2]_3$ (133 mg, 0.20 mmol and 67 mg, 0.1 mmol), anhydrous $Cu(OAc)_2$ (1.08 g, 5.94 mmol), K_2CO_3 (551 mg, 3.96 mmol), *t*BuOH/AcOH/DMSO (20:5:1, 18 mL), two portions of potassium 3,4-dimethoxyphenyltrifluoroborate (1.0 g, 4.1 mmol) in acetone/H_2O (2:1, 7.5 mL) to give 415 mg of the title compound as a white solid (73%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (1H, dddd, *J* = 2.9, 6.1, 12.3, 19.0 Hz), 1.48-1.58 (1H, m), 1.59-1.69 (1H, m), 1.77-1.85 (2H, m), 1.86-1.90 (1H, m), 2.51 (1H, dd, *J* = 13.3, 16.1 Hz), 2.61 (1H, dd, *J* = 5.4, 16.2 Hz), 3.05 (1H, dt, *J* = 3.0, 12.7 Hz), 3.34-3.42 (1H, m), 3.44-3.48 (1H, m), 3.85 (3H, s), 3.88 (3H, s), 6.81 (1H, d, *J* = 8.3 Hz), 6.86 (1H, dd, *J* = 1.8, 8.3 Hz), 7.02 (1H, d, *J* = 1.7 Hz), 7.08 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.23, 25.79, 31.81, 44.03, 53.28, 55.97, 56.08, 57.35, 111.27, 112.03, 112.21, 119.70, 129.18, 147.44, 148.62, 153.73, 189.89. IR (neat, NaCl): 3468 (br), 2935,

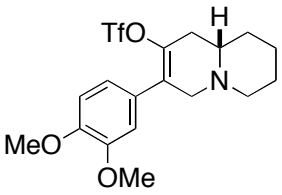
1634, 1595, 1515, 1251, 1027 cm^{-1}. MP = 112-114 °C. $[\alpha]_D^{25}$ = +5.96 (*c* = 1.14, $CHCl_3$). HRMS (ESI^+): *m/z* calc'd for $C_{17}H_{22}NO_3$, 288.1600; found 288.1592.



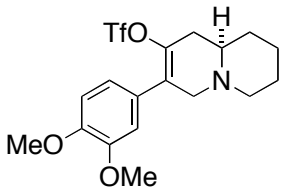
(*R*)-3-(3,4-Dimethoxyphenyl)-7,8,9,9a-tetrahydro-1*H*-quinolizin-2(6*H*)-one (67). The identical procedure for the synthesis of quinolizidone **53** was used employing the following amounts; enaminone **64** (366 mg, 2.42 mmol), $[Pd(OAc)_2]_3$ (163 mg, 0.24 mmol and 81 mg, 0.12), anhydrous $Cu(OAc)_2$ (1.22 g, 6.72 mmol), K_2CO_3 (670 g, 4.84 mmol), *t*BuOH/AcOH/DMSO (20:5:1, 15 mL), two portions of potassium 3,4-dimethoxyphenyltrifluoroborate (1.18 g, 4.85 mmol) in acetone/H_2O (2:1, 8 mL). to give 526 mg of the title compound as a white solid (75%).^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (1H, dddd, *J* = 2.9, 6.2, 12.2, 19.1 Hz), 1.48-1.57 (1H, m), 1.57-1.67 (1H, m), 1.76-1.85 (2H, m), 1.86-1.91 (1H, m), 2.50 (1H, dd, *J* = 13.3, 16.2 Hz), 2.60 (1H, dd, *J* = 5.4, 16.2 Hz), 3.05 (1H, dt, *J* = 2.99, 12.69 Hz), 3.33-3.41 (1H, m), 3.44-3.48 (1H, m), 3.85 (3H, s), 3.88 (3H, s), 6.81 (1H, d, *J* = 8.3 Hz), 6.85 (1H, dd, *J* = 1.8, 8.3 Hz), 7.02 (1H, d, *J* = 1.76 Hz), 7.08 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ. 23.22, 25.78, 31.80, 44.03, 53.28, 55.97, 56.07, 57.34, 111.26, 112.02, 112.20, 119.69, 129.18, 147.71, 148.62, 153.71, 189.86. IR (neat, NaCl): 2936, 1595, 1514, 1250, 1027. MP = 112-114 °C. $[\alpha]_D^{25}$ = -6.60 (c = 0.773, $CHCl_3$). HRMS (ESI^+): *m/z* calc'd for $C_{17}H_{22}NO_3$, 288.1600; found 288.1590.



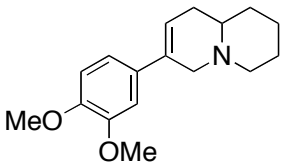
(±)-3-(3,4-Dimethoxyphenyl)-4,6,7,8,9,9a-hexahydro-1*H*-quinolizin-2-yl Trifluoromethanesulfonate (75). Quinolizidone **53** (300 mg, 1.04 mmol) was dissolved in THF (3 mL) and cooled to -78 °C. L-Selectride (1.0 M, 1.04 mL, 1.04 mmol) was added dropwise to the stirring solution and the reaction was maintained at -78 °C for 30 min at which time the solution was warmed to room temperature. Comins' reagent (**74**, 494 mg, 1.25 mmol) was subsequently added to the reaction mixture and allowed to stir at room temperature overnight. The resulting solution was quenched with saturated aq. $NaHCO_3$ (1.0 mL), diluted with CH_2Cl_2 (3.0 mL), dried with K_2CO_3, and filtered through celite. The resulting filtrate was concentrated and purified by MPLC on silica gel (15-55% EtOAc in hexanes with 1% TEA, 40 min, 254 nm) to afford the title compound as a red-brown oil (81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28-1.32 (1H, m), 1.34-1.45 (1H, m), 1.60-1.73 (2H, m), 1.78-1.81 (1H, m), 1.84-1.87 (1H, m), 2.10 (1H, dt, *J* = 3.2, 11.7 Hz), 2.35-2.44 (1H, m), 2.47-2.54 (2H, m), 3.03-3.06 (1H, m), 3.11 (1H, td, *J* = 3.3, 16.4 Hz), 3.56 (1H, d, *J* = 16.4 Hz), 3.86 (3H, s), 3.88 (3H, s), 6.81-6.85 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.71, 25.68, 33.05, 35.73, 54.94, 55.97, 56.02, 57.83, 59.17, 111.07, 111.73, 118.22 (1C, q, *J* = 320.0 Hz), 120.72, 126.59, 128.00, 140.39, 148.86, 149.16. IR (neat, NaCl): 2936, 1519, 1414, 1211, 1141, 1031 cm^{-1}. HRMS (ESI$^+$): *m/z* calc'd for $C_{18}H_{23}F_3NO_5S_3$, 422.1249; found 422.1248.



(*S*)-3-(3,4-Dimethoxyphenyl)-4,6,7,8,9,9a-hexahydro-1*H*-quinolizin-2-yl Trifluoromethanesulfonate (76). The identical procedure for the synthesis of triflate **75** was used employing the following amounts; quinolizidone **65** (312 mg, 1.10 mmol), THF (5 mL), L-Selectride (1.0 M, 1.1 mL, 1.1 mmol), Comins' reagent (514 mg, 1.3 mmol) to yield 333 mg of the title compound as a red-brown oil (72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24-1.27 (1H, m), 1.29-1.32 (1H, m), 1.58-1.68 (2H, m), 1.72-1.75 (1H, m), 1.78-1.81 (1H, m), 2.05 (1H, dt, *J* = 2.9, 11.6 Hz), 2.33-2.37 (1H, m), 2.42-2.49 (2H, m), 2.98-3.00 (1H, m), 3.04-3.08 (1H, m), 3.54 (1H, d, *J* = 16.4 Hz), 3.80 (3H, br s), 3.81 (3H, br s), 6.77-6.82 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.70, 25.68, 33.06, 35.74, 54.91, 55.93, 55.98, 57.79, 59.17, 111.04, 111.70, 118.19 (1C, q, *J* = 320 Hz), 120.68, 126.60, 128.00, 140.39, 148.82, 149.12. IR (neat, NaCl): 2936, 1519, 1415, 1210, 1141, 1030 cm^{-1}. $[\alpha]_D^{25}$ = +57 (*c* = 0.60, $CHCl_3$). HRMS (ESI^+): *m/z* calc'd for $C_{18}H_{23}F_3NO_5S_3$, 422.1249; found 422.1262.

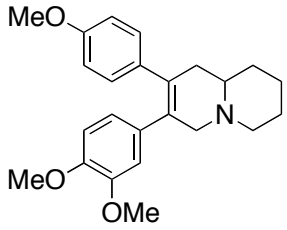


(*R*)-3-(3,4-Dimethoxyphenyl)-4,6,7,8,9,9a-hexahydro-1*H*-quinolizin-2-yl Trifluoromethanesulfonate (77). The identical procedure for the synthesis of triflate **75** was used employing the following amounts; quinolizidone **66** (526 mg, 1.83 mmol), THF (12 mL), L-Selectride (1.0 M, 1.9 mL, 1.88 mmol), Comins' reagent (935 mg, 2.38 mmol) to yield 591 mg of the title compound as a red-brown oil (77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23-1.28 (1H, m), 1.30-1.36 (1H, m), 1.59-1.70 (2H, m), 1.73-1.76 (1H, m), 1.80-1.82 (1H, m), 2.05 (1H, dt, *J* = 2.9, 11.6 Hz), 2.33-2.36 (1H, m), 2.40-2.50 (2H, m), 2.98-3.01 (1H, m), 3.05-3.09 (1H, m), 3.54 (1H, d, *J* = 16.4 Hz), 3.82 (3H, br s), 3.83 (3H, br s), 6.80-6.83 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.72, 25.70, 33.08, 35.76, 54.94, 55.96, 56.01, 57.81, 59.20, 111.06, 111.72, 118.21 (1C, q, J = 320 Hz), 120.70, 126.62, 128.01, 140.41, 148.84, 149.14. IR (neat, NaCl): 2936, 1519, 1415, 1210, 1141, 1030 cm^{-1}. $[\alpha]_D^{25}$ = -49 (*c* = 0.97, $CHCl_3$). HRMS (ESI$^+$): *m/z* calc'd for $C_{18}H_{23}F_3NO_5S_3$, 422.1249; found 422.1239.



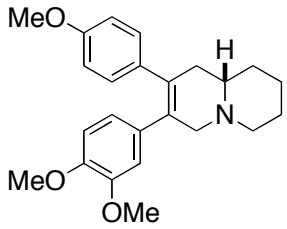
(±)-7-(3,4-Dimethoxyphenyl)-2,3,4,6,9,9a-hexahydro-1*H*-quinolizine (78). Typical experimental procedure used for Suzuki coupling: Triflate **75** (1 equiv), $Pd(OAc)_2$ (10 mol%), S-Phos (20 mol%), potassium 4-methoxyphenyltrifluoroborate

(1.5 equiv), K_2CO_3 were dissolved in degassed HPLC grade MeOH and heated to 60 °C overnight. The resulting reaction mixture was immediately purified by MPLC to give the side-product **77** in variable yields as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28-1.36 (2H, m), 1.68-1.72 (2H, m), 1.78-1.81 (2H, m), 2.12-2.28 (4H, m), 3.02-3.10 (2H, m), 3.62-3.65 (1H, m), 3.86 (3H, s), 3.88 (3H, s), 5.94-5.95 (1H, m), 6.79-6.81 (1H, m), 6.85-6.88 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.47, 25.95, 33.43, 34.09, 55.96, 56.01, 56.21, 56.93, 57.20, 108.77, 111.01, 117.50, 120.79, 133.28, 134.40, 148.37, 148.82. IR (neat, NaCl): 2926, 1600, 1581, 1519, 1166, 1147, 1028, 805 cm^{-1}. MP = 114-116 °C. HRMS (ESI$^+$): *m/z* calc'd for $C_{17}H_{24}NO_2$, 274.1801; found 274.1807.



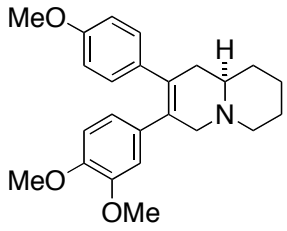
(±)-7-(3,4-Dimethoxyphenyl)-8-(4-methoxyphenyl)-2,3,4,6,9,9a-hexahydro-1*H*-quinolizine (80). A reaction vessel containing $ZnBr_2$ (297 mg, 1.32 mmol) was flame-dried under vacuum and upon reaching room temperature it was released from vacuum and fitted immediately with a septum and placed under a nitrogen atmosphere. THF (4 mL) was added to the purged reaction vessel and once homogeneity was achieved, 4-methoxyphenylmagnesium bromide (0.5 M in THF, 2.2 mL, 1.11 mmol) was added, resulting in a white slurry that was stirred for 10 min. This solution was transferred to a reaction vessel containing triflate **75** (155 mg, 0.37 mmol) and $Pd(PPh_3)_4$ (48 mg, 0.04 mmol) and the reaction mixture was heated to 60

°C. Monitoring by TLC (50% EtOAc in hexanes with 1% TEA) showed complete consumption of starting material within 1 h. The reaction was allowed to cool to room temperature and immediately purified by MPLC on silica gel (25-75% EtOAc in hexanes with 1% TEA, 50 min, 254 nm) to give 135 mg of the title compound as a tan foam (97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31-1.39 (2H, m), 1.66-1.74 (2H, m), 1.79-1.85 (2H, m), 2.08-2.14 (1H, m), 2.30-2.32 (1H, m), 2.34-2.42 (1H, m), 2.49-2.53 (1H, m), 3.02-3.11 (2H, m), 3.56 (3H, s), 3.63 (1H, d, J = 16.5 Hz), 3.71 (3H, s), 3.80 (3H, s), 6.47 (1H, m), 6.62-6.64 (4H, m), 6.92 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.36, 25.90, 33.32, 39.82, 55.09, 55.51, 55.60, 55.67, 57.90, 60.11, 110.52, 113.19, 113.24, 120.86, 129.80, 131.23, 131.41, 133.26, 134.37, 147.34, 148.04, 157.84. IR (neat, NaCl): 2930, 1606, 1511, 1246, 1030, 755 cm^{-1}. HRMS (ESI^+): *m/z* calc'd for $C_{24}H_{29}NO_3$, 380.2232; found 380.2226.



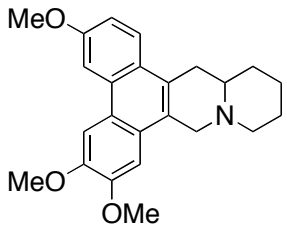
(*S*)-7-(3,4-Dimethoxyphenyl)-8-(4-methoxyphenyl)-2,3,4,6,9,9a-hexahydro-1*H*-quinolizine (81). The identical procedure for the synthesis of quinolizine **80** was used employing the following amounts; $ZnBr_2$ (160 mg, 0.71 mmol), 4-methoxyphenylmagnesium bromide (0.5 M in THF, 1.2 mL, 0.60 mmol), THF (2 mL), triflate **76** (84 mg, 0.20 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) to give 70 mg of the title compound as a tan foam (92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31-

1.39 (2H, m), 1.70-1.73 (2H, m), 1.80-1.86 (2H, m), 2.08-2.15 (1H, m), 2.30-2.32 (1H, m), 2.35-2.41 (1H, m), 2.48-2.54 (1H, m), 3.02-3.11 (2H, m), 3.56 (3H, s), 3.63 (1H, d, J = 16.6 Hz), 3.72 (3H, s), 3.81 (3H, s), 6.49 (1H, m), 6.64-6.69 (4H, m), 6.92-6.97 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.51, 26.05, 33.46, 39.96, 55.27, 55.67, 55.76, 55.83, 58.06, 60.27, 110.65, 113.32, 113.39, 121.00, 129.95, 131.38, 131.57, 133.42, 134.53, 147.48, 148.18, 157.97. IR (neat, NaCl): 2930, 1606, 1511, 1245, 1030, 755 cm^{-1}. $[\alpha]_D^{25}$ = 160 (c = 0.98, $CHCl_3$). HRMS (ESI$^+$): *m/z* calc'd for $C_{24}H_{29}NO_3$, 380.2226; found 380.2229.



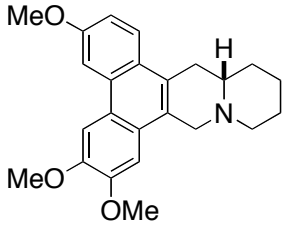
(*R*)-7-(3,4-Dimethoxyphenyl)-8-(4-methoxyphenyl)-2,3,4,6,9,9a-hexahydro-1*H*-quinolizine (82). The identical procedure for the synthesis of quinolizine **80** was used employing the following amounts; $ZnBr_2$ (365 mg, 1.6 mmol), 4-methoxyphenylmagnesium bromide (0.5 M in THF, 2.8 mL, 1.4 mmol), THF (5 mL), triflate **77** (195 mg, 0.46 mmol), and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) to give 176 mg of the title compound as a tan foam (99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-1.38 (2H, m), 1.67-1.76 (2H, m), 1.79-1.85 (2H, m), 2.08-2.15 (1H, m), 2.30-2.32 (1H, m), 2.35-2.41 (1H, m), 2.49-2.53 (1H, m), 3.03-3.11 (2H, m), 3.56 (3H, s), 3.63 (1H, d, J = 16.5 Hz), 3.71 (3H, s), 3.80 (3H, s), 6.49 (1H, s), 6.65-6.67 (4H, m), 6.93-6.95 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.36, 25.90, 33.32, 39.82, 55.09, 55.51, 55.60,

55.67, 57.90, 60.11, 110.52, 113.19, 113.24, 120.86, 129.80, 131.23, 131.41, 133.26, 134.37, 147.34, 148.04, 157.84. IR (neat, NaCl): 2930, 1606, 1511, 1246, 1030, 756 cm^{-1}. $[\alpha]_D^{25}$ = -160 (*c* = 0.89, $CHCl_3$). HRMS (ESI^+): *m/z* calc'd for $C_{24}H_{29}NO_3$, 380.2226; found. 380.2233.



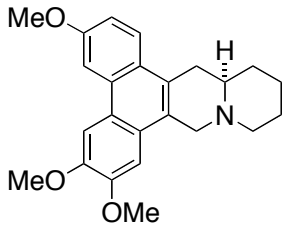
(±)-Boehmeriasin A (1). Quinolizine **80** (105 mg, 0.28 mmol) in CH_2Cl_2 (25 mL) was cooled to -78 °C under a nitrogen atmosphere. VOF_3 (73 mg, 0.59 mmol) in a solution of TFA/CH_2Cl_2/EtOAc (1:1:1, 6 mL) was subsequently added to the stirring solution in one portion at -78 °C. The reaction was monitored by TLC (50% EtOAc in hexanes with 1% TEA) and complete consumption of starting material was observed within 1 h. The reaction was quenched with 10% aq. NaOH (10 mL) and the solution was warmed to room temperature. The layers were separated and the aqueous phase was extracted CH_2Cl_2 (2×). The combined organic extracts were dried with Na_2SO_4, concentrated, and purified by MPLC on silica gel (35-85% EtOAc in hexanes with 1% TEA, 50 min, 254 nm) to give 101 mg of the title compound as a white solid (97%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.39-1.45 (1H, m), 1.48-1.55 (1H, m), 1.71-1.80 (2H, m), 1.86 (1H, m), 1.96-2.00 (1H, m), 2.23-2.27 (1H, m), 2.29-2.32 (1H, m), 2.85-2.91 (1H, m), 3.11 (1H, dd, *J* = 2.9 Hz), 3.26 (1H, d, *J* = 11.0 Hz), 3.51 (1H, d, *J* = 15.2 Hz), 3.99 (3H, s), 4.03 (3H, s), 4.08 (3H, s), 4.29 (1H, d, *J* =15.2 Hz),

7.08 (1H, s), 7.18 (1H, dd, J = 2.5 Hz, 9.0 Hz), 7.85-7.87 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.53, 26.16, 33.95, 34.87, 55.66, 56.11, 56.14, 56.36, 56.54, 57.68, 103.21, 104.17, 104.77, 114.89, 123.40, 124.44, 125.16, 125.35, 126.10, 130.40, 148.32, 149.53, 157.67. IR (neat, NaCl): 2928, 2253, 1611, 1511, 1470, 1256, 1204, 1140, 1040 cm^{-1}. MP = decomp. >214 °C. HRMS (ESI^+): *m/z* calc'd for $C_{24}H_{29}NO_3$, 378.2069; found 378.2067.



(*S*)-Boehmeriasin A (83). The identical procedure for the synthesis of (±)-boehmeriasin A (**1**) was used employing the following amounts; quinolizine **81** (76 mg, 0.20 mmol), CH_2Cl_2 (17 mL), VOF_3 (55 mg, 0.44 mmol),TFA/CH_2Cl_2/EtOAc (1:1:1, 3 mL) to give 56 mg of the title compound as a white solid (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39-1.45 (1H, m), 1.48-1.55 (1H, m), 1.71-1.80 (2H, m), 1.86 (1H, m), 1.96-2.00 (1H, m), 2.23-2.27 (1H, m), 2.29-2.31 (1H, m), 2.84-2.91 (1H, m), 3.09 (1H, dd, J = 2.9 Hz), 3.25 (1H, d, J = 11.0 Hz), 3.50 (1H, d, J = 15.2 Hz), 3.98 (3H, s), 4.03 (3H, s), 4.07 (3H, s), 4.28 (1H, d, J = 15.2 Hz), 7.07 (1H, s), 7.17 (1H, dd, J = 2.3, 9.0 Hz), 7.84-7.86 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.52, 26.16, 33.94, 34.85, 55.65, 56.10, 56.12, 56.33, 56.53, 57.64, 103.19, 104.14, 104.74, 114.87, 123.39, 124.41, 125.14, 125.34, 126.07, 130.39, 148.30, 149.51, 157.66. IR (neat, NaCl): 2932, 2252, 1612, 1513, 1470, 1256, 1204, 1141, 1041, 730 cm^{-1}.

$[\alpha]_D^{25}$ = +73 (*c* = 0.14, MeOH) (Note: compound is sparingly soluble in MeOH). MP = decomp. >214 °C. HRMS (ESI^+): *m/z* calc'd for $C_{24}H_{29}NO_3$, 378.2069; found 378.2070. Chiral HPLC analysis (Chiralpak AD-H (250 mm x 4.6 mm), 35-80% isopropanol in *n*-heptane, 45 min, 0.5 mL/min, 254 nm, (*S*)-isomer, t_R = 24.2 min, (*R*)-isomer, t_R = 32.6 min, er = 97:3).



(*R*)-Boehmeriasin A (84). The identical procedure for the synthesis of (±)-boehmeriasin A (**1**) was used employing the following amounts; quinolizine **82** (40 mg, 0.11 mmol), CH_2Cl_2 (9 mL), VOF_3 (30 mg, 0.22 mmol), TFA/CH_2Cl_2/EtOAc (1:1:1, 3 mL) to give 31.2 mg of the title compound as a white solid (83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.47 (1H, m), 1.49-1.56 (1H, m), 1.72-1.80 (2H, m), 1.86 (1H, m), 1.97-2.00 (1H, m), 2.25-2.29 (1H, m), 2.31-2.35 (1H, m), 2.87-2.93 (1H, m), 3.09 (1H, dd, *J* = 2.9 Hz), 3.27 (1H, d, *J* = 11.0 Hz), 3.53 (1H, d, *J* = 15.2 Hz), 3.99 (3H, s), 4.03 (3H, s), 4.08 (3H, s), 4.31 (1H, d, *J* = 15.2 Hz), 7.09 (1H, s), 7.18 (1H, dd, *J* = 2.5, 9.0 Hz), 7.85-7.87 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.53, 26.16, 33.95, 34.87, 55.66, 56.11, 56.14, 56.36, 56.54, 57.68, 103.21, 104.17, 104.77, 114.88, 123.40, 124.44, 125.16, 125.35, 126.10, 130.40, 148.32, 149.53, 157.66. IR (neat, NaCl): 2932, 2253, 1612, 1513, 1470, 1256, 1204, 1140, 1041, 731 cm^{-1}. $[\alpha]_D^{25}$ = -93 (*c* = 0.15, $CHCl_3$); $[\alpha]_D^{25}$ = -86 (*c* = 0.10, MeOH) (Note: compound is

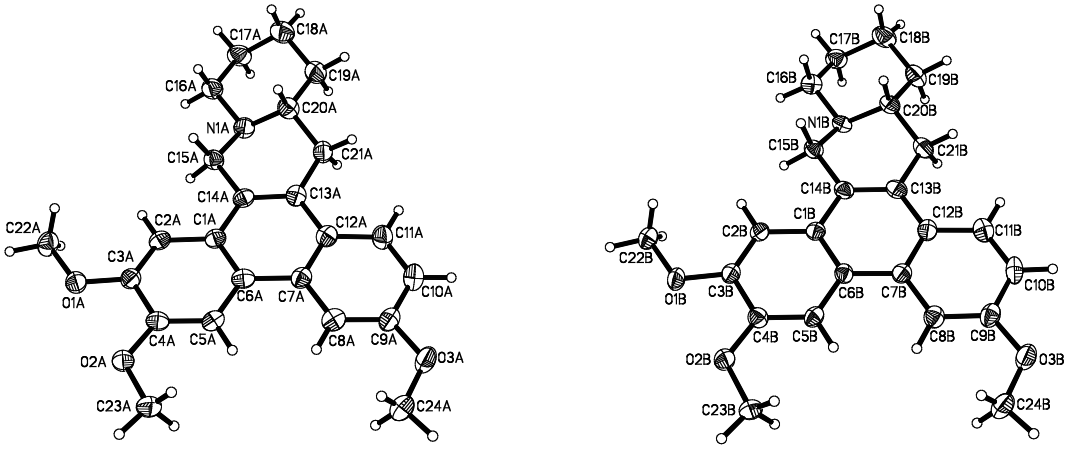
sparingly soluble in MeOH). MP = decomp. >214 °C. HRMS (ESI^+): *m/z* calc'd for $C_{24}H_{29}NO_3$, 378.2069; found 378.2057. Chiral HPLC analysis (Chiralpak AD-H (250 mm x 4.6 mm), 35-80% isopropanol in *n*-heptane, 45 min, 0.5 mL/min, 254 nm, (*S*)-isomer, t_R = 24.2 min, (*R*)-isomer, t_R = 32.6 min, er = 97:3).

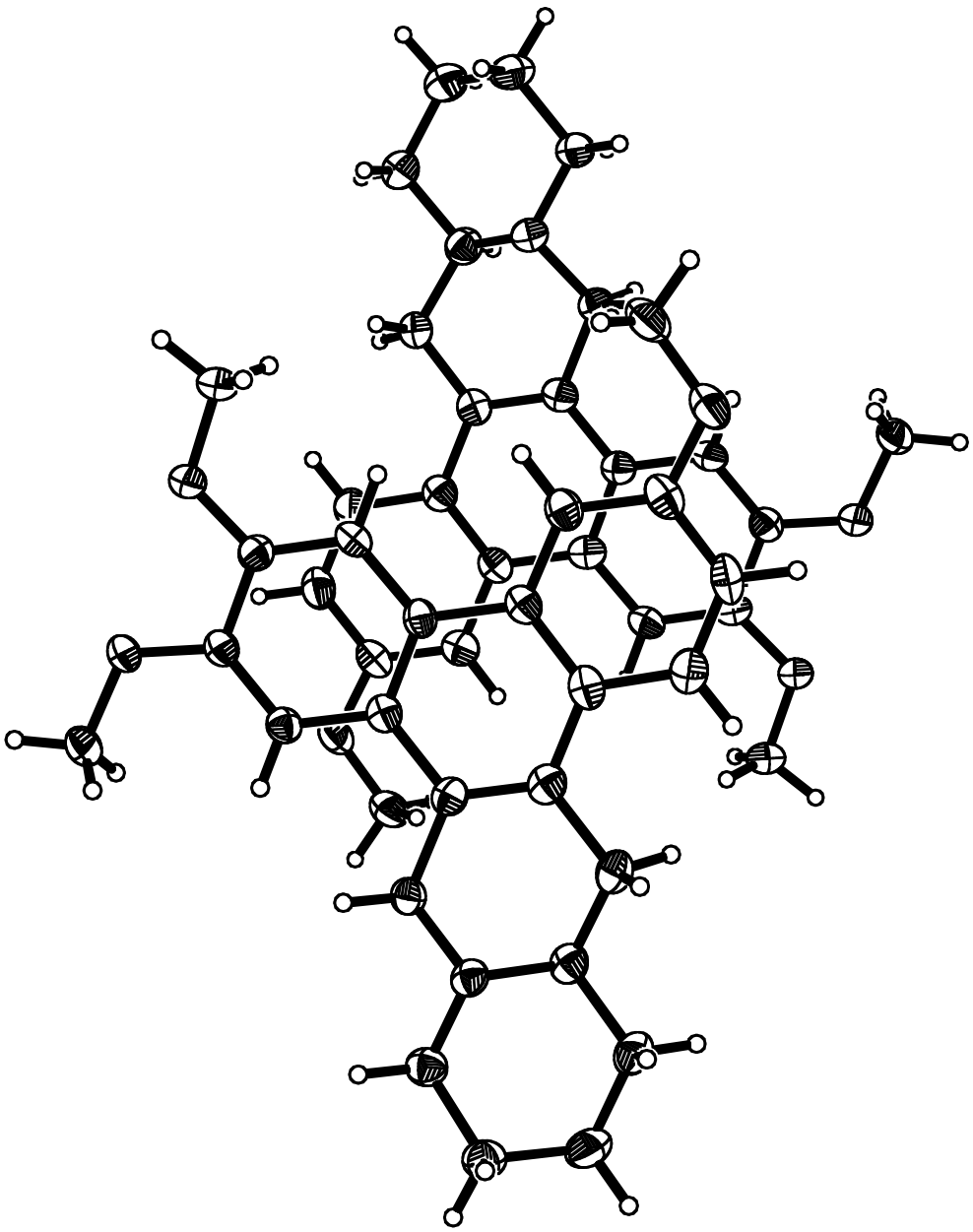
4.2.2 Biological Evaluation

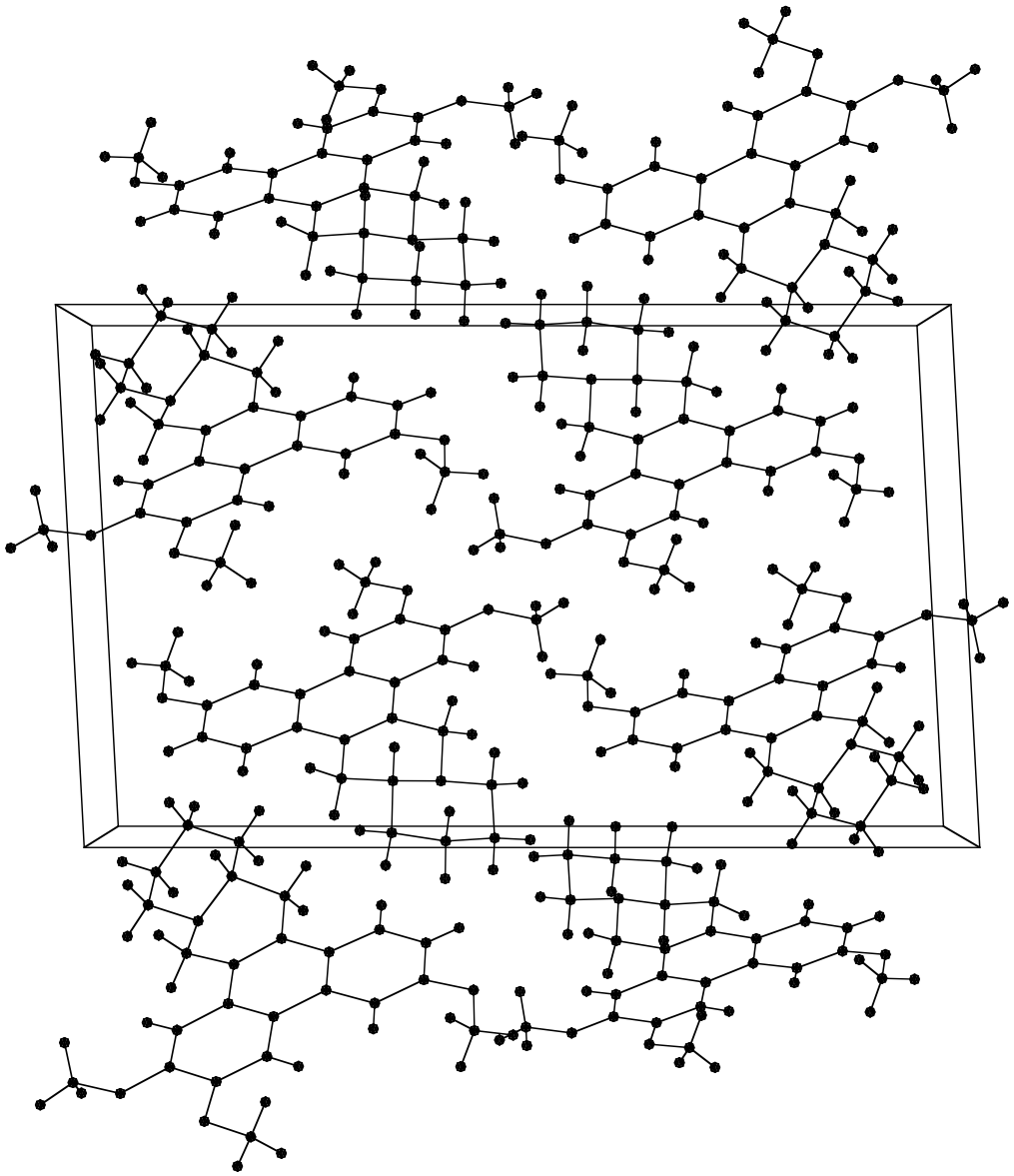
Cytotoxicity Assay.[130,131] The human cancer cell lines MCF7, NCI-ADR-RES (NCI), and COLO-205 (ATCC CCL-222) were grown in normal RPMI 1640 culture medium containing 10% fetal bovine serum. The cells, in exponential-phase maintenance culture, were dissociated with 0.25% trypsin and harvested at 125×g for 5 min. Trypsin was removed and the cells were resuspended in new culture medium. The cell density was adjusted to 1 x 10^5 and dispensed in triplicate on 96-well plates in 50 μL volumes. After incubation overnight at 37 °C under 5% CO_2, 50 μL of culture medium containing various concentrations of the test compounds was added. Paclitaxel and colchicine were used as positive controls. After 48 h incubation, the relative cell viability in each well was determined by using the AlamarBlue Assay Kit. The IC_{50} of each compound was determined by fitting the relative viability of the cells to the drug concentration using a dose-response model.

CRYSTAL STRUCTURE REPORT

$C_{24}\ H_{27}\ N\ O_3$







Data collection

A crystal (approximate dimensions 0.45x 0.23 x 0.12mm^3) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a CCD area detector diffractometer for a data collection at173(2) K.[1] A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 110 reflections. The data collection was carried out using MoKa radiation (graphite monochromator) with a frame time of 30 seconds and a detector distance of 4.9 cm. A randomly oriented region of reciprocal space was surveyed to the extent of one sphere and to a resolution of 0.80 Å. Four major sections of frames were collected with 0.30º steps in w at four different f settings and a detector position of -28º in2q. The intensity data were corrected for absorption and decay (SADABS).[2] Final cell constants were calculated from 2932 strong reflections from the actual data collection after integration (SAINT).[3] Please refer to Table 1 for additional crystal and refinement information.

Structure solution and refinement

The structure was solved using Bruker SHELXTL[4] and refined using Bruker SHELXTL.[4] The space group $P2_1$ was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least squares / difference Fourier

cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to $R1 = 0.0428$ and $wR2 = 0.1185$ (F^2, all data).

Structure description

The structure is the one suggested. This is isostructural to the 09035 structure completed on the racemic material in space group $P2_1/c$ with similar cell constants. In that structure the site was occupied with both enantiomers in a 0.69:0.31 ratio. It is no surprise that this 97 ee material crystallizes in a similar unit cell lacking the true inversion symmetry. One of the two unique molecules does exhibit a few small difference Fourier peaks in the region of the chiral center, indicating a possibility of some small contamination of the S-isomer, but this cannot modeled in the ~5% range.

Data collection and structure solution were conducted at the X-Ray Crystallographic Laboratory, 192 Kolthoff Hall, Department of Chemistry, University of Minnesota. All calculations were performed using Pentium computers using the current SHELXTL suite of programs. All publications arising from this report MUST either 1) include Victor G. Young, Jr. as a coauthor or 2) acknowledge Victor G. Young, Jr. and the X-Ray Crystallographic Laboratory.

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[1] SMART V5.054, Bruker Analytical X-ray Systems, Madison, WI (2001).

[2] An empirical correction for absorption anisotropy, R. Blessing, *Acta Cryst.* **A51**, 33-38(1995).

[3] SAINT+ V6.45, Bruker Analytical X-Ray Systems, Madison, WI (2003).

[4] SHELXTL V6.14, Bruker Analytical X-Ray Systems, Madison, WI (2000).

[5] A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna. Sir97: a new tool for crystal structure determination andrefinement. *J. Appl. Cryst.* **32**, 115-119(1998).

[6] M. C. Burla, M. Camalli, B. Carrozzini, G. L. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna. Sir2002: a new Direct Methods program for automatic solution and refinement of crystal structures. *J. Appl. Cryst.* (2003), in preparation.

[7] A. L. Spek, *Acta. Cryst.***A46**, C34 (1990). PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands, A. L.Spek (2000).

Some equations of interest:

$$R_{int} = S|F_o^2 - \langle F_o^2 \rangle| / S|F_o^2|$$

$$R_1 = S||F_o| - |F_c|| / S|F_o|$$

$$wR2 = [S[w(F_o^2 - F_c^2)^2] / S[w(F_o^2)^2]]^{1/2}$$

where $w = q / [s^2(F_o^2) + (a*P)^2 + b*P + d + e*\sin(q)]$

$$GooF = S = [S[w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$$

Table 1. Crystal data and structure refinement for 09047b.

Identification code	09047b	
Empirical formula	C_{24} H_{27} N O_3	
Formula weight	377.47	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	*a* = 13.378(3) Å	a = 90°
	b = 6.5197(12) Å	b = 93.028(3)°
	c = 22.033(4) Å	g = 90°
Volume	1919.1(6) $Å^3$	
Z	4	
Density (calculated)	1.306 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	808	
Crystal color, morphology	Colorless, Plate	
Crystal size	0.45 x 0.23 x 0.12 mm^3	
Theta range for data collection	0.93 to 26.39°	
Index ranges	-16 £*h* £ 16,0 £*k* £ 8,0 £*l* £ 27	
Reflections collected	18876	

Independent reflections	4281 [R(int) = 0.0383]
Observed reflections	3380
Completeness to theta = 26.39°	99.7%
Absorption correction	Multi-scan
Max. and min. transmission	0.9898 and 0.9626
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4281 / 1 / 511
Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0428, wR2 = 0.1058
R indices (all data)	R1 = 0.0617, wR2 = 0.1185
Absolute structure parameter	1.3(16)
Largest diff. peak and hole	0.321 and -0.186 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for 09047b. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
O1A	5728(2)	13185(4)	386(1)	34(1)
O2A	5402(2)	15208(4)	1348(1)	35(1)
O3A	7473(2)	11505(4)	4272(1)	38(1)
N1A	8368(2)	4846(4)	1062(1)	32(1)
C1A	7114(2)	9850(5)	1511(1)	26(1)
C2A	6675(2)	10553(5)	947(1)	27(1)
C3A	6136(2)	12326(5)	906(1)	27(1)
C4A	5963(2)	13466(5)	1442(1)	27(1)
C5A	6364(2)	12804(6)	1990(1)	29(1)
C6A	6956(2)	10997(5)	2040(1)	27(1)
C7A	7392(2)	10297(6)	2622(1)	28(1)
C8A	7223(2)	11339(6)	3172(1)	31(1)
C9A	7602(2)	10598(6)	3720(1)	31(1)
C10A	8173(2)	8787(6)	3746(2)	37(1)
C11A	8365(2)	7780(6)	3216(1)	34(1)
C12A	7986(2)	8505(5)	2643(1)	29(1)

C13A	8178(2)	7423(5)	2086(1)	28(1)
C14A	7727(2)	8035(5)	1545(1)	27(1)
C15A	7865(2)	6827(5)	972(1)	28(1)
C16A	8638(2)	4107(6)	462(1)	35(1)
C17A	9178(2)	2054(6)	501(2)	41(1)
C18A	10105(3)	2218(7)	917(2)	46(1)
C19A	9815(3)	3001(7)	1537(2)	40(1)
C20A	9237(2)	5029(5)	1488(1)	34(1)
C21A	8885(2)	5627(6)	2107(1)	33(1)
C22A	5837(2)	12114(6)	-171(1)	35(1)
C23A	5235(2)	16425(6)	1869(1)	34(1)
C24A	6864(2)	13307(7)	4270(2)	39(1)
O1B	4341(2)	2045(4)	4630(1)	32(1)
O2B	4714(2)	110(4)	3655(1)	32(1)
O3B	2634(2)	3803(4)	746(1)	37(1)
N1B	1213(2)	9582(4)	4018(1)	26(1)
C1B	2962(2)	5401(5)	3508(1)	23(1)
C2B	3382(2)	4671(5)	4072(1)	24(1)
C3B	3949(2)	2921(5)	4106(1)	25(1)
C4B	4149(2)	1826(5)	3569(1)	26(1)
C5B	3767(2)	2539(5)	3019(1)	25(1)
C6B	3161(2)	4319(5)	2971(1)	24(1)

C7B	2732(2)	5039(5)	2394(1)	24(1)
C8B	2893(2)	3986(6)	1843(1)	29(1)
C9B	2510(2)	4726(6)	1295(1)	31(1)
C10B	1945(2)	6542(6)	1277(1)	35(1)
C11B	1762(2)	7547(6)	1802(1)	34(1)
C12B	2140(2)	6843(5)	2377(1)	28(1)
C13B	1933(2)	7902(5)	2934(1)	27(1)
C14B	2319(2)	7197(5)	3478(1)	25(1)
C15B	2100(2)	8283(5)	4062(1)	26(1)
C16B	1180(2)	10734(6)	4588(1)	31(1)
C17B	260(2)	12103(5)	4595(1)	35(1)
C18B	267(3)	13627(6)	4069(2)	41(1)
C19B	371(2)	12474(6)	3475(2)	37(1)
C20B	1261(2)	10991(5)	3498(1)	28(1)
C21B	1266(2)	9772(5)	2910(1)	32(1)
C22B	4151(2)	3026(6)	5192(1)	35(1)
C23B	4875(2)	-1120(6)	3134(1)	32(1)
C24B	3227(3)	1984(7)	743(2)	41(1)

Table 3. Bond lengths [Å] and angles [°] for 09047b.

O(1A)-C(3A)	1.364(4)	C(7A)-C(8A)	1.417(4)
O(1A)-C(22A)	1.426(4)	C(8A)-C(9A)	1.373(4)
O(2A)-C(4A)	1.371(4)	C(8A)-H(8AA)	0.9500
O(2A)-C(23A)	1.422(4)	C(9A)-C(10A)	1.406(5)
O(3A)-C(9A)	1.371(4)	C(10A)-C(11A)	1.375(5)
O(3A)-C(24A)	1.429(5)	C(10A)-H(10A)	0.9500
N(1A)-C(20A)	1.461(4)	C(11A)-C(12A)	1.417(4)
N(1A)-C(15A)	1.465(4)	C(11A)-H(11A)	0.9500
N(1A)-C(16A)	1.469(4)	C(12A)-C(13A)	1.450(4)
C(1A)-C(6A)	1.411(4)	C(13A)-C(14A)	1.367(4)
C(1A)-C(2A)	1.422(4)	C(13A)-C(21A)	1.505(5)
C(1A)-C(14A)	1.439(5)	C(14A)-C(15A)	1.507(4)
C(2A)-C(3A)	1.363(5)	C(15A)-H(15A)	0.9900
C(2A)-H(2AA)	0.9500	C(15A)-H(15B)	0.9900
C(3A)-C(4A)	1.424(4)	C(16A)-C(17A)	1.521(5)
C(4A)-C(5A)	1.365(4)	C(16A)-H(16A)	0.9900
C(5A)-C(6A)	1.421(5)	C(16A)-H(16B)	0.9900
C(5A)-H(5AA)	0.9500	C(17A)-C(18A)	1.506(5)
C(6A)-C(7A)	1.455(4)	C(17A)-H(17A)	0.9900
C(7A)-C(12A)	1.412(5)	C(17A)-H(17B)	0.9900

C(18A)-C(19A)	1.527(5)	O(2B)-C(23B)	1.426(4)
C(18A)-H(18A)	0.9900	O(3B)-C(9B)	1.369(4)
C(18A)-H(18B)	0.9900	O(3B)-C(24B)	1.427(5)
C(19A)-C(20A)	1.532(5)	N(1B)-C(15B)	1.457(4)
C(19A)-H(19A)	0.9900	N(1B)-C(16B)	1.465(4)
C(19A)-H(19B)	0.9900	N(1B)-C(20B)	1.474(4)
C(20A)-C(21A)	1.515(4)	C(1B)-C(6B)	1.415(4)
C(20A)-H(20A)	1.0000	C(1B)-C(2B)	1.419(4)
C(21A)-H(21A)	0.9900	C(1B)-C(14B)	1.453(4)
C(21A)-H(21B)	0.9900	C(2B)-C(3B)	1.370(5)
C(22A)-H(22D)	0.9800	C(2B)-H(2BA)	0.9500
C(22A)-H(22E)	0.9800	C(3B)-C(4B)	1.419(4)
C(22A)-H(22F)	0.9800	C(4B)-C(5B)	1.371(4)
C(23A)-H(23D)	0.9800	C(5B)-C(6B)	1.417(4)
C(23A)-H(23E)	0.9800	C(5B)-H(5BA)	0.9500
C(23A)-H(23F)	0.9800	C(6B)-C(7B)	1.446(4)
C(24A)-H(24D)	0.9800	C(7B)-C(12B)	1.417(5)
C(24A)-H(24E)	0.9800	C(7B)-C(8B)	1.421(4)
C(24A)-H(24F)	0.9800	C(8B)-C(9B)	1.374(4)
O(1B)-C(3B)	1.367(3)	C(8B)-H(8BA)	0.9500
O(1B)-C(22B)	1.429(4)	C(9B)-C(10B)	1.404(5)
O(2B)-C(4B)	1.358(4)	C(10B)-C(11B)	1.363(5)

C(10B)-H(10B)	0.9500	C(18B)-H(18D)	0.9900
C(11B)-C(12B)	1.416(4)	C(19B)-C(20B)	1.532(4)
C(11B)-H(11B)	0.9500	C(19B)-H(19C)	0.9900
C(12B)-C(13B)	1.447(4)	C(19B)-H(19D)	0.9900
C(13B)-C(14B)	1.360(4)	C(20B)-C(21B)	1.521(4)
C(13B)-C(21B)	1.510(5)	C(20B)-H(20B)	1.0000
C(14B)-C(15B)	1.512(4)	C(21B)-H(21C)	0.9900
C(15B)-H(15C)	0.9900	C(21B)-H(21D)	0.9900
C(15B)-H(15D)	0.9900	C(22B)-H(22A)	0.9800
C(16B)-C(17B)	1.521(4)	C(22B)-H(22B)	0.9800
C(16B)-H(16C)	0.9900	C(22B)-H(22C)	0.9800
C(16B)-H(16D)	0.9900	C(23B)-H(23A)	0.9800
C(17B)-C(18B)	1.528(5)	C(23B)-H(23B)	0.9800
C(17B)-H(17C)	0.9900	C(23B)-H(23C)	0.9800
C(17B)-H(17D)	0.9900	C(24B)-H(24A)	0.9800
C(18B)-C(19B)	1.522(5)	C(24B)-H(24B)	0.9800
C(18B)-H(18C)	0.9900	C(24B)-H(24C)	0.9800

C(3A)-O(1A)-C(22A)	117.9(3)	C(20A)-N(1A)-C(16A)	112.4(2)
C(4A)-O(2A)-C(23A)	116.7(2)	C(15A)-N(1A)-C(16A)	107.6(2)
C(9A)-O(3A)-C(24A)	116.7(3)	C(6A)-C(1A)-C(2A)	118.6(3)
C(20A)-N(1A)-C(15A)	111.1(2)	C(6A)-C(1A)-C(14A)	120.1(3)

C(2A)-C(1A)-C(14A)	121.3(3)	O(3A)-C(9A)-C(8A)	124.8(3)
C(3A)-C(2A)-C(1A)	121.6(3)	O(3A)-C(9A)-C(10A)	114.9(3)
C(3A)-C(2A)-H(2AA)	119.2	C(8A)-C(9A)-C(10A)	120.3(3)
C(1A)-C(2A)-H(2AA)	119.2	C(11A)-C(10A)-C(9A)	119.5(3)
C(2A)-C(3A)-O(1A)	126.2(3)	C(11A)-C(10A)-H(10A)	120.2
C(2A)-C(3A)-C(4A)	119.8(3)	C(9A)-C(10A)-H(10A)	120.2
O(1A)-C(3A)-C(4A)	114.1(3)	C(10A)-C(11A)-C(12A)	121.5(3)
C(5A)-C(4A)-O(2A)	125.6(3)	C(10A)-C(11A)-H(11A)	119.2
C(5A)-C(4A)-C(3A)	119.6(3)	C(12A)-C(11A)-H(11A)	119.2
O(2A)-C(4A)-C(3A)	114.8(3)	C(7A)-C(12A)-C(11A)	118.6(3)
C(4A)-C(5A)-C(6A)	121.5(3)	C(7A)-C(12A)-C(13A)	120.0(3)
C(4A)-C(5A)-H(5AA)	119.2	C(11A)-C(12A)-C(13A)	121.4(3)
C(6A)-C(5A)-H(5AA)	119.2	C(14A)-C(13A)-C(12A)	120.4(3)
C(1A)-C(6A)-C(5A)	118.8(3)	C(14A)-C(13A)-C(21A)	120.1(3)
C(1A)-C(6A)-C(7A)	119.5(3)	C(12A)-C(13A)-C(21A)	119.5(3)
C(5A)-C(6A)-C(7A)	121.7(3)	C(13A)-C(14A)-C(1A)	120.7(3)
C(12A)-C(7A)-C(8A)	119.0(3)	C(13A)-C(14A)-C(15A)	120.7(3)
C(12A)-C(7A)-C(6A)	119.1(3)	C(1A)-C(14A)-C(15A)	118.6(3)
C(8A)-C(7A)-C(6A)	121.9(3)	N(1A)-C(15A)-C(14A)	115.1(3)
C(9A)-C(8A)-C(7A)	121.0(3)	N(1A)-C(15A)-H(15A)	108.5
C(9A)-C(8A)-H(8AA)	119.5	C(14A)-C(15A)-H(15A)	108.5
C(7A)-C(8A)-H(8AA)	119.5	N(1A)-C(15A)-H(15B)	108.5

C(14A)-C(15A)-H(15B)	108.5	C(20A)-C(19A)-H(19A)	109.2
H(15A)-C(15A)-H(15B)	107.5	C(18A)-C(19A)-H(19B)	109.2
N(1A)-C(16A)-C(17A)	112.2(3)	C(20A)-C(19A)-H(19B)	109.2
N(1A)-C(16A)-H(16A)	109.2	H(19A)-C(19A)-H(19B)	107.9
C(17A)-C(16A)-H(16A)	109.2	N(1A)-C(20A)-C(21A)	109.0(2)
N(1A)-C(16A)-H(16B)	109.2	N(1A)-C(20A)-C(19A)	110.8(3)
C(17A)-C(16A)-H(16B)	109.2	C(21A)-C(20A)-C(19A)	109.8(3)
H(16A)-C(16A)-H(16B)	107.9	N(1A)-C(20A)-H(20A)	109.1
C(18A)-C(17A)-C(16A)	110.2(3)	C(21A)-C(20A)-H(20A)	109.1
C(18A)-C(17A)-H(17A)	109.6	C(19A)-C(20A)-H(20A)	109.1
C(16A)-C(17A)-H(17A)	109.6	C(13A)-C(21A)-C(20A)	113.5(3)
C(18A)-C(17A)-H(17B)	109.6	C(13A)-C(21A)-H(21A)	108.9
C(16A)-C(17A)-H(17B)	109.6	C(20A)-C(21A)-H(21A)	108.9
H(17A)-C(17A)-H(17B)	108.1	C(13A)-C(21A)-H(21B)	108.9
C(17A)-C(18A)-C(19A)	109.2(3)	C(20A)-C(21A)-H(21B)	108.9
C(17A)-C(18A)-H(18A)	109.8	H(21A)-C(21A)-H(21B)	107.7
C(19A)-C(18A)-H(18A)	109.8	O(1A)-C(22A)-H(22D)	109.5
C(17A)-C(18A)-H(18B)	109.8	O(1A)-C(22A)-H(22E)	109.5
C(19A)-C(18A)-H(18B)	109.8	H(22D)-C(22A)-H(22E)	109.5
H(18A)-C(18A)-H(18B)	108.3	O(1A)-C(22A)-H(22F)	109.5
C(18A)-C(19A)-C(20A)	112.2(3)	H(22D)-C(22A)-H(22F)	109.5
C(18A)-C(19A)-H(19A)	109.2	H(22E)-C(22A)-H(22F)	109.5

O(2A)-C(23A)-H(23D)	109.5	C(3B)-C(2B)-H(2BA)	119.4
O(2A)-C(23A)-H(23E)	109.5	C(1B)-C(2B)-H(2BA)	119.4
H(23D)-C(23A)-H(23E)	109.5	O(1B)-C(3B)-C(2B)	125.4(3)
O(2A)-C(23A)-H(23F)	109.5	O(1B)-C(3B)-C(4B)	114.4(3)
H(23D)-C(23A)-H(23F)	109.5	C(2B)-C(3B)-C(4B)	120.2(3)
H(23E)-C(23A)-H(23F)	109.5	O(2B)-C(4B)-C(5B)	125.6(3)
O(3A)-C(24A)-H(24D)	109.5	O(2B)-C(4B)-C(3B)	115.2(3)
O(3A)-C(24A)-H(24E)	109.5	C(5B)-C(4B)-C(3B)	119.2(3)
H(24D)-C(24A)-H(24E)	109.5	C(4B)-C(5B)-C(6B)	121.9(3)
O(3A)-C(24A)-H(24F)	109.5	C(4B)-C(5B)-H(5BA)	119.0
H(24D)-C(24A)-H(24F)	109.5	C(6B)-C(5B)-H(5BA)	119.0
H(24E)-C(24A)-H(24F)	109.5	C(1B)-C(6B)-C(5B)	118.6(3)
C(3B)-O(1B)-C(22B)	117.9(3)	C(1B)-C(6B)-C(7B)	119.4(3)
C(4B)-O(2B)-C(23B)	117.3(2)	C(5B)-C(6B)-C(7B)	122.0(3)
C(9B)-O(3B)-C(24B)	117.6(3)	C(12B)-C(7B)-C(8B)	119.3(3)
C(15B)-N(1B)-C(16B)	107.6(2)	C(12B)-C(7B)-C(6B)	119.2(3)
C(15B)-N(1B)-C(20B)	110.2(2)	C(8B)-C(7B)-C(6B)	121.6(3)
C(16B)-N(1B)-C(20B)	110.6(2)	C(9B)-C(8B)-C(7B)	121.0(3)
C(6B)-C(1B)-C(2B)	118.8(3)	C(9B)-C(8B)-H(8BA)	119.5
C(6B)-C(1B)-C(14B)	120.0(3)	C(7B)-C(8B)-H(8BA)	119.5
C(2B)-C(1B)-C(14B)	121.2(3)	O(3B)-C(9B)-C(8B)	124.4(3)
C(3B)-C(2B)-C(1B)	121.3(3)	O(3B)-C(9B)-C(10B)	115.8(3)

C(8B)-C(9B)-C(10B)	119.7(3)	N(1B)-C(16B)-C(17B)	111.7(2)
C(11B)-C(10B)-C(9B)	120.1(3)	N(1B)-C(16B)-H(16C)	109.3
C(11B)-C(10B)-H(10B)	119.9	C(17B)-C(16B)-H(16C)	109.3
C(9B)-C(10B)-H(10B)	119.9	N(1B)-C(16B)-H(16D)	109.3
C(10B)-C(11B)-C(12B)	122.2(3)	C(17B)-C(16B)-H(16D)	109.3
C(10B)-C(11B)-H(11B)	118.9	H(16C)-C(16B)-H(16D)	107.9
C(12B)-C(11B)-H(11B)	118.9	C(16B)-C(17B)-C(18B)	109.6(2)
C(11B)-C(12B)-C(7B)	117.7(3)	C(16B)-C(17B)-H(17C)	109.7
C(11B)-C(12B)-C(13B)	122.0(3)	C(18B)-C(17B)-H(17C)	109.7
C(7B)-C(12B)-C(13B)	120.4(3)	C(16B)-C(17B)-H(17D)	109.7
C(14B)-C(13B)-C(12B)	120.3(3)	C(18B)-C(17B)-H(17D)	109.7
C(14B)-C(13B)-C(21B)	120.0(3)	H(17C)-C(17B)-H(17D)	108.2
C(12B)-C(13B)-C(21B)	119.6(3)	C(19B)-C(18B)-C(17B)	109.6(3)
C(13B)-C(14B)-C(1B)	120.7(3)	C(19B)-C(18B)-H(18C)	109.7
C(13B)-C(14B)-C(15B)	120.7(3)	C(17B)-C(18B)-H(18C)	109.7
C(1B)-C(14B)-C(15B)	118.6(3)	C(19B)-C(18B)-H(18D)	109.7
N(1B)-C(15B)-C(14B)	114.2(2)	C(17B)-C(18B)-H(18D)	109.7
N(1B)-C(15B)-H(15C)	108.7	H(18C)-C(18B)-H(18D)	108.2
C(14B)-C(15B)-H(15C)	108.7	C(18B)-C(19B)-C(20B)	112.9(3)
N(1B)-C(15B)-H(15D)	108.7	C(18B)-C(19B)-H(19C)	109.0
C(14B)-C(15B)-H(15D)	108.7	C(20B)-C(19B)-H(19C)	109.0
H(15C)-C(15B)-H(15D)	107.6	C(18B)-C(19B)-H(19D)	109.0

C(20B)-C(19B)-H(19D)	109.0	H(22A)-C(22B)-H(22B)	109.5
H(19C)-C(19B)-H(19D)	107.8	O(1B)-C(22B)-H(22C)	109.5
N(1B)-C(20B)-C(21B)	109.9(3)	H(22A)-C(22B)-H(22C)	109.5
N(1B)-C(20B)-C(19B)	110.7(2)	H(22B)-C(22B)-H(22C)	109.5
C(21B)-C(20B)-C(19B)	109.9(3)	O(2B)-C(23B)-H(23A)	109.5
N(1B)-C(20B)-H(20B)	108.8	O(2B)-C(23B)-H(23B)	109.5
C(21B)-C(20B)-H(20B)	108.8	H(23A)-C(23B)-H(23B)	109.5
C(19B)-C(20B)-H(20B)	108.8	O(2B)-C(23B)-H(23C)	109.5
C(13B)-C(21B)-C(20B)	114.9(3)	H(23A)-C(23B)-H(23C)	109.5
C(13B)-C(21B)-H(21C)	108.5	H(23B)-C(23B)-H(23C)	109.5
C(20B)-C(21B)-H(21C)	108.5	O(3B)-C(24B)-H(24A)	109.5
C(13B)-C(21B)-H(21D)	108.5	O(3B)-C(24B)-H(24B)	109.5
C(20B)-C(21B)-H(21D)	108.5	H(24A)-C(24B)-H(24B)	109.5
H(21C)-C(21B)-H(21D)	107.5	O(3B)-C(24B)-H(24C)	109.5
O(1B)-C(22B)-H(22A)	109.5	H(24A)-C(24B)-H(24C)	109.5
O(1B)-C(22B)-H(22B)	109.5	H(24B)-C(24B)-H(24C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 09047b. The anisotropic

displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1A	43(1)	34(1)	26(1)	-4(1)	0(1)	12(1)
O2A	43(1)	34(1)	27(1)	-3(1)	2(1)	14(1)
O3A	49(1)	42(2)	22(1)	-3(1)	0(1)	0(1)
N1A	36(1)	27(1)	32(1)	-2(1)	2(1)	3(1)
C1A	26(1)	25(2)	27(2)	0(2)	5(1)	-3(1)
C2A	30(2)	25(2)	25(2)	-5(2)	5(1)	-1(1)
C3A	27(1)	30(2)	25(2)	0(2)	2(1)	-1(1)
C4A	27(2)	24(2)	31(2)	-4(2)	4(1)	2(1)
C5A	31(2)	31(2)	25(2)	-2(2)	7(1)	-2(2)
C6A	23(1)	25(2)	33(2)	-2(1)	6(1)	-5(1)
C7A	26(1)	31(2)	25(2)	0(2)	2(1)	-5(1)
C8A	32(2)	28(2)	32(2)	-2(2)	5(1)	-5(2)
C9A	31(2)	38(2)	23(2)	-1(2)	2(1)	-8(2)
C10A	43(2)	38(2)	29(2)	4(2)	-4(1)	-2(2)
C11A	39(2)	33(2)	31(2)	3(2)	-2(1)	2(2)

C12A	30(2)	28(2)	30(2)	2(2)	4(1)	-5(2)
C13A	28(2)	29(2)	28(2)	0(2)	0(1)	-4(1)
C14A	25(1)	28(2)	28(2)	0(2)	6(1)	-4(1)
C15A	30(2)	25(2)	30(2)	-1(2)	1(1)	2(1)
C16A	36(2)	34(2)	34(2)	-5(2)	1(1)	6(2)
C17A	41(2)	36(2)	45(2)	-8(2)	5(2)	7(2)
C18A	45(2)	47(2)	47(2)	-3(2)	3(2)	15(2)
C19A	41(2)	40(2)	38(2)	1(2)	0(1)	9(2)
C20A	33(2)	34(2)	36(2)	0(2)	1(1)	2(2)
C21A	36(2)	33(2)	28(2)	1(2)	-1(1)	5(2)
C22A	47(2)	30(2)	27(2)	-4(2)	-1(1)	1(2)
C23A	37(2)	33(2)	33(2)	-4(2)	7(1)	7(2)
C24A	45(2)	44(2)	28(2)	-7(2)	2(1)	1(2)
O1B	40(1)	36(1)	18(1)	-1(1)	-2(1)	9(1)
O2B	41(1)	33(1)	23(1)	-3(1)	1(1)	11(1)
O3B	46(1)	43(2)	23(1)	-1(1)	0(1)	-3(1)
N1B	28(1)	19(1)	30(1)	2(1)	3(1)	-1(1)
C1B	24(1)	22(2)	24(2)	1(1)	1(1)	-6(1)
C2B	27(1)	24(2)	22(2)	-2(1)	0(1)	-2(1)
C3B	26(1)	26(2)	21(2)	-1(2)	0(1)	-2(1)
C4B	26(1)	25(2)	26(2)	1(2)	2(1)	2(1)
C5B	28(1)	29(2)	19(2)	-2(1)	3(1)	-1(1)

C6B	24(1)	24(2)	23(2)	3(1)	0(1)	-4(1)
C7B	26(1)	24(2)	23(2)	1(1)	3(1)	-7(1)
C8B	29(2)	30(2)	26(2)	2(2)	2(1)	-4(1)
C9B	33(2)	36(2)	23(2)	1(2)	1(1)	-9(2)
C10B	36(2)	44(2)	24(2)	11(2)	-4(1)	-2(2)
C11B	33(2)	35(2)	33(2)	5(2)	-1(1)	1(2)
C12B	28(1)	29(2)	26(2)	4(2)	-1(1)	-8(1)
C13B	28(2)	21(2)	32(2)	3(2)	3(1)	-5(1)
C14B	26(1)	20(2)	29(2)	2(2)	1(1)	-3(1)
C15B	31(2)	23(2)	26(2)	2(1)	4(1)	-1(1)
C16B	31(2)	31(2)	32(2)	-1(1)	5(1)	-1(1)
C17B	38(2)	31(2)	36(2)	-3(2)	6(1)	3(2)
C18B	45(2)	31(2)	48(2)	0(2)	8(2)	12(2)
C19B	40(2)	31(2)	40(2)	8(2)	4(1)	8(2)
C20B	29(2)	23(2)	33(2)	3(1)	3(1)	-3(1)
C21B	35(2)	26(2)	35(2)	6(2)	1(1)	1(2)
C22B	46(2)	36(2)	21(2)	-2(2)	-2(1)	4(2)
C23B	39(2)	30(2)	26(2)	-7(2)	4(1)	6(2)
C24B	56(2)	43(2)	24(2)	-6(2)	2(2)	-3(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3)

for 09047b.

	x	y	z	U(eq)
H2AA	6760	9769	590	32
H5AA	6245	13570	2346	34
H8AA	6842	12569	3161	37
H10A	8425	8264	4126	44
H11A	8761	6570	3235	41
H15A	7198	6586	768	34
H15B	8256	7670	696	34
H16A	9074	5132	276	42
H16B	8023	3964	195	42
H17A	8727	996	657	49
H17B	9365	1632	90	49
H18A	10587	3175	741	55
H18B	10429	857	962	55
H19A	10429	3198	1801	48
H19B	9397	1957	1729	48

H20A	9690	6124	1343	41
H21A	8548	4434	2284	39
H21B	9476	5968	2377	39
H22D	5499	12880	-505	52
H22E	5536	10748	-145	52
H22F	6549	11978	-246	52
H23D	4835	17630	1747	52
H23E	5879	16871	2057	52
H23F	4876	15614	2162	52
H24D	6818	13805	4687	59
H24E	6193	12980	4098	59
H24F	7165	14370	4023	59
H2BA	3268	5410	4434	29
H5BA	3912	1817	2660	30
H8BA	3270	2751	1853	34
H10B	1690	7071	898	42
H11B	1368	8759	1781	40
H15C	2014	7242	4383	32
H15D	2685	9138	4191	32
H16C	1790	11590	4642	37
H16D	1175	9760	4933	37
H17C	259	12855	4986	42

H17D	-353	11253	4557	42
H18C	-363	14428	4048	50
H18D	833	14594	4135	50
H19C	452	13477	3144	44
H19D	-252	11692	3378	44
H20B	1894	11804	3544	34
H21C	573	9330	2798	38
H21D	1483	10688	2583	38
H22A	4472	2245	5529	52
H22B	3428	3084	5241	52
H22C	4423	4421	5193	52
H23A	5281	-2318	3256	47
H23B	5226	-312	2837	47
H23C	4229	-1577	2952	47
H24A	3278	1509	324	62
H24B	2912	917	981	62
H24C	3898	2278	922	62

Table 6. Torsion angles [°] for 09047b.

C6A-C1A-C2A-C3A	2.0(4)	C1A-C6A-C7A-C12A	1.4(4)
C14A-C1A-C2A-C3A	-176.7(3)	C5A-C6A-C7A-C12A	-179.1(3)
C1A-C2A-C3A-O1A	176.5(3)	C1A-C6A-C7A-C8A	-177.3(3)
C1A-C2A-C3A-C4A	-3.0(4)	C5A-C6A-C7A-C8A	2.2(5)
C22A-O1A-C3A-C2A	2.5(4)	C12A-C7A-C8A-C9A	-1.9(5)
C22A-O1A-C3A-C4A	-178.0(3)	C6A-C7A-C8A-C9A	176.8(3)
C23A-O2A-C4A-C5A	0.5(4)	C24A-O3A-C9A-C8A	2.6(5)
C23A-O2A-C4A-C3A	-178.3(3)	C24A-O3A-C9A-C10A	-177.7(3)
C2A-C3A-C4A-C5A	1.9(5)	C7A-C8A-C9A-O3A	-179.9(3)
O1A-C3A-C4A-C5A	-177.6(3)	C7A-C8A-C9A-C10A	0.4(5)
C2A-C3A-C4A-O2A	-179.3(3)	O3A-C9A-C10A-C11A	-178.7(3)
O1A-C3A-C4A-O2A	1.2(4)	C8A-C9A-C10A-C11A	1.0(5)
O2A-C4A-C5A-C6A	-178.6(3)	C9A-C10A-C11A-C12A	-1.0(5)
C3A-C4A-C5A-C6A	0.1(5)	C8A-C7A-C12A-C11A	1.9(4)
C2A-C1A-C6A-C5A	0.1(4)	C6A-C7A-C12A-C11A	-176.8(3)
C14A-C1A-C6A-C5A	178.7(3)	C8A-C7A-C12A-C13A	-179.4(3)
C2A-C1A-C6A-C7A	179.6(3)	C6A-C7A-C12A-C13A	1.8(4)
C14A-C1A-C6A-C7A	-1.8(4)	C10A-C11A-C12A-C7A	-0.5(5)
C4A-C5A-C6A-C1A	-1.1(4)	C10A-C11A-C12A-C13A	-179.1(3)
C4A-C5A-C6A-C7A	179.4(3)	C7A-C12A-C13A-C14A	-4.9(5)

C11A-C12A-C13A-C14A173.7(3)

C7A-C12A-C13A-C21A 174.5(3)

C11A-C12A-C13A-C21A-6.8(5)

C12A-C13A-C14A-C1A 4.6(5)

C21A-C13A-C14A-C1A-174.8(3)

C12A-C13A-C14A-C15A-175.6(3)

C21A-C13A-C14A-C15A 5.0(5)

C6A-C1A-C14A-C13A -1.3(4)

C2A-C1A-C14A-C13A 177.3(3)

C6A-C1A-C14A-C15A 178.9(3)

C2A-C1A-C14A-C15A -2.5(4)

C20A-N1A-C15A-C14A -44.2(3)

C16A-N1A-C15A-C14A-167.5(3)

C13A-C14A-C15A-N1A 9.1(4)

C1A-C14A-C15A-N1A -171.1(2)

C20A-N1A-C16A-C17A 56.9(4)

C15A-N1A-C16A-C17A 179.4(3)

N1A-C16A-C17A-C18A -57.5(4)

C16A-C17A-C18A-C19A55.7(4)

C17A-C18A-C19A-C20A-55.1(4)

C15A-N1A-C20A-C21A 64.1(3)

C16A-N1A-C20A-C21A-175.4(3)

C15A-N1A-C20A-C19A-174.9(3)

C16A-N1A-C20A-C19A -54.4(4)

C18A-C19A-C20A-N1A 54.2(4)

C18A-C19A-C20A-C21A174.7(3)

C14A-C13A-C21A-C20A15.6(4)

C12A-C13A-C21A-C20A-163.9(3)

N1A-C20A-C21A-C13A -49.5(4)

C19A-C20A-C21A-C13A-171.1(3)

C6B-C1B-C2B-C3B -1.8(4)

C14B-C1B-C2B-C3B 176.8(3)

C22B-O1B-C3B-C2B -0.3(4)

C22B-O1B-C3B-C4B -178.4(3)

C1B-C2B-C3B-O1B -176.5(3)

C1B-C2B-C3B-C4B 1.6(4)

C23B-O2B-C4B-C5B -3.8(4)

C23B-O2B-C4B-C3B 175.6(3)

O1B-C3B-C4B-O2B -1.4(4)

C2B-C3B-C4B-O2B -179.7(3)

O1B-C3B-C4B-C5B 178.1(3)

C2B-C3B-C4B-C5B -0.1(4)

O2B-C4B-C5B-C6B 178.3(3)

C3B-C4B-C5B-C6B -1.2(4)

C2B-C1B-C6B-C5B	0.5(4)	C6B-C7B-C12B-C11B	177.7(3)
C14B-C1B-C6B-C5B	-178.1(3)	C8B-C7B-C12B-C13B	177.7(3)
C2B-C1B-C6B-C7B	179.6(3)	C6B-C7B-C12B-C13B	-2.6(4)
C14B-C1B-C6B-C7B	1.0(4)	C11B-C12B-C13B-C14B	-179.2(3)
C4B-C5B-C6B-C1B	1.0(4)	C7B-C12B-C13B-C14B	1.2(4)
C4B-C5B-C6B-C7B	-178.1(3)	C11B-C12B-C13B-C21B	2.2(4)
C1B-C6B-C7B-C12B	1.5(4)	C7B-C12B-C13B-C21B	-177.5(3)
C5B-C6B-C7B-C12B	-179.4(3)	C12B-C13B-C14B-C1B	1.4(4)
C1B-C6B-C7B-C8B	-178.8(3)	C21B-C13B-C14B-C1B	-180.0(3)
C5B-C6B-C7B-C8B	0.3(4)	C12B-C13B-C14B-C15B	-179.5(3)
C12B-C7B-C8B-C9B	2.1(4)	C21B-C13B-C14B-C15B	-0.9(4)
C6B-C7B-C8B-C9B	-177.6(3)	C6B-C1B-C14B-C13B	-2.5(4)
C24B-O3B-C9B-C8B	-2.0(4)	C2B-C1B-C14B-C13B	178.9(3)
C24B-O3B-C9B-C10B	178.3(3)	C6B-C1B-C14B-C15B	178.4(3)
C7B-C8B-C9B-O3B	179.9(3)	C2B-C1B-C14B-C15B	-0.2(4)
C7B-C8B-C9B-C10B	-0.5(5)	C16B-N1B-C15B-C14B	-172.3(3)
O3B-C9B-C10B-C11B	178.5(3)	C20B-N1B-C15B-C14B	-51.7(3)
C8B-C9B-C10B-C11B	-1.1(5)	C13B-C14B-C15B-N1B	20.6(4)
C9B-C10B-C11B-C12B	1.1(5)	C1B-C14B-C15B-N1B	-160.3(3)
C10B-C11B-C12B-C7B	0.4(5)	C15B-N1B-C16B-C17B	-178.4(3)
C10B-C11B-C12B-C13B	-179.2(3)	C20B-N1B-C16B-C17B	61.2(3)
C8B-C7B-C12B-C11B	-2.0(4)	N1B-C16B-C17B-C18B	-59.5(4)

C16B-C17B-C18B-C19B 53.9(4)

C17B-C18B-C19B-C20B-52.3(4)

C15B-N1B-C20B-C21B 62.7(3)

C16B-N1B-C20B-C21B -178.5(2)

C15B-N1B-C20B-C19B -175.8(3)

C16B-N1B-C20B-C19B -57.0(3)

C18B-C19B-C20B-N1B 53.9(4)

C18B-C19B-C20B-C21B175.4(3)

C14B-C13B-C21B-C20B 12.6(4)

C12B-C13B-C21B-C20B-168.8(3)

N1B-C20B-C21B-C13B -43.0(3)

C19B-C20B-C21B-C13B-165.0(3)

4.2.2 Chapter 2

General procedure of sequential, one-pot synthesis of flavones and chromones

Step 1. DIEA (2.5 mL, 14.3 mmol) was added to the appropriate salicylaldehyde derivative (4.8 mmol) in CH_2Cl_2 (10 mL) and stirred for 5 min at room temperature before MOM-Cl (0.5 mL, 6.2 mmol) was added to the reaction medium and the resulting reaction mixture was stirred overnight at this temperature. The reaction was quenched with saturated aq. $NaHCO_3$, transferred to a separatory funnel, and the layers were separated. The aqueous phase was extracted twice more with CH_2Cl_2 and the combined organic layers were concentrated, and used without further purification.

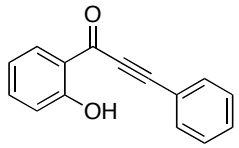
Step 2. To a stirred solution of the appropriate terminal alkyne (7.2 mmol) in THF (10 mL) at 0 ºC was added *n*BuLi (2.5 M in hexanes, 2.8 mL, 7.2 mmol) dropwise and warmed to room temperature after 30 min. The generated lithiated alkyne was added to the crude aldehyde in THF (10 mL) at 0 ºC. The flask containing the alkyne was washed with THF (5 mL) and transferred to the aldehyde containing flask. The resulting reaction was monitored by TLC (EtOAc in hexanes) and after complete consumption of starting material (30-60 min) the reaction medium was transferred to a separatory funnel containing saturated aq. NH_4Cl and EtOAc. The layers were separated and the aqueous phase was extracted twice more with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, concentrated, and used without further purification.

Step 3. The crude propargyl alcohol and MnO_2 (2.1 g, 24 mmol) were combined in 1,2-dichloroethane (40 mL) and refluxed overnight. (Note: In most cases the

reactions demonstrated complete conversion by TLC analysis; however, electron-deficient ynones required additional MnO_2 and longer reaction times to drive the reaction to completion). The reaction mixture was cooled to room temperature, filtered through a celite plug, and concentrated to afford the crude ynone that was used in the next reaction without purification.

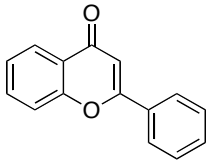
Step 4. Trifluoroacetic acid (2 mL) was added to the crude ynone in CH_2Cl_2 (18 mL) under an ambient atmosphere and stirred for 30 min at room temperature. The reaction was concentrated to dryness and used immediately in the next step without purification.

Step 5. The resulting crude ynone was dissolved in MeCN (480 mL) and K_2CO_3 (2.0 g, 14.3 mmol) was added to the stirring solution and stirred at ambient atmosphere overnight. Silica gel (~45g) was added to the reaction and was concentrated to dryness and purified by MPLC on silica gel (0-60% EtOAc in hexanes, 60 min, 254 nm) to afford the corresponding flavones.

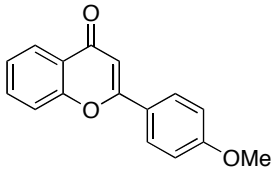


1-(2-Hydroxyphenyl)-3-phenylprop-2-yn-1-one (107). Steps 1-4 of the general procedure was used to afford 5.07 g of the title compound as a yellow solid (74%). The spectral data are consistent with those reported in the literature.[104] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98-7.02 (2H, m), 7.42-7.46 (2H, m), 7.50-7.55 (2H, m), 7.68-7.71 (2H, m), 8.12-8.14 (1H, m), 11.76 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.79,

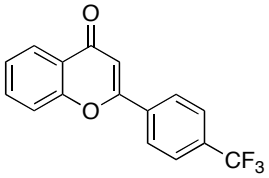
96.15, 118.25, 119.53, 119.78, 120.88, 128.89, 131.31, 133.14, 133.25, 137.28, 162.91, 182.38.



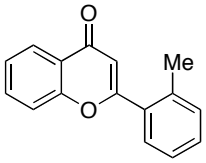
Flavone (108). The general procedure was used to afford 800 mg of the title compound as a white solid (77%). The spectral data are consistent with those reported in the literature.[132] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (1H, s), 7.39 (1H, t, *J* = 7.52 Hz), 7.47-7.55 (4H, m), 7.65-7.69 (1H, m), 7.88-7.90 (2H, m), 8.21 (1H, dd, *J* = 1.56, 7.92 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.62, 118.14, 124.01, 125.27, 125.73, 126.32, 129.09, 131.66, 131.80, 133.82, 156.29, 163.40, 178.45.



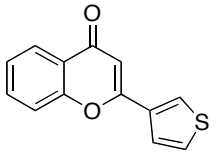
2-(4-Methoxyphenyl)-4*H*-chromen-4-one (110). The general procedure was used to afford 713 mg of the title compound as a yellow solid (59%). The spectral data are consistent with those reported in the literature.[133] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, s), 6.75 (1H, s), 7.01 (1H, dd, *J* = 2.1, 5.0 Hz), 7.04 (1H, dd, *J* = 2.9, 5.0 Hz), 7.39-7.43 (1H, m), 7.55 (1H, dd, *J* = 0.7, 8.4 Hz), 7.68 (1H, ddd, *J* = 1.7, 7.1, 8.6 Hz), 7.87 (1H, dd, *J* = 2.1, 5.0 Hz), 7.90 (1H, dd, *J* = 2.9, 5.0 Hz), 8.22 (1H, dd, *J* = 1.6, 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.65, 106.35, 114.61, 118.10, 124.10, 124.40, 125.21, 125.81, 128.15, 133.69, 156.33, 162.55, 163.54, 178.51.



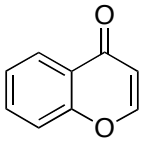
2-(4-(Trifluoromethyl)phenyl)-4*H*-chromen-4-one (112). The general procedure was used to afford 752 mg of the title compound as a yellow solid (38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (1H, s), 7.47 (1H, d, 8.9 Hz), 7.50-7.56 (3H, m), 7.77 (1H, dd, *J* = 2.5, 8.9 Hz), 7.89-7.92 (2H, m), 8.35 (1H, d, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.72, 113.08, 121.35, 123.97, 123.98 (1C, q, *J* = 272.2 Hz), 124.93, 125.80 (1C, q, *J* = 3.7 Hz), 130.58, 130.90, 131.23, 131.50, 135.80 (1C, d, *J* = 1.2 Hz), 147.83, 166.34, 184.72. IR (neat, NaCl): 2924, 1645, 1470, 1325, 1117 cm^{-1}. MP = 137-139 ºC. HRMS (ESI^+): *m/z* calc'd for $C_{16}H_{10}F_3O_2$, 291.0634; found 291.0633.



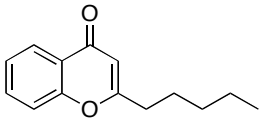
2-*o*-Tolyl-4*H*-chromen-4-one (114). The general procedure was used to afford 518 mg of the title compound as a yellow solid (44%). The spectral data are consistent with those reported in the literature.[134] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (3H, s), 6.49 (1H, s), 7.30-7.33 (2H, s), 7.39-7.45 (2H, m), 7.49 (1H, d, *J* = 8.2 Hz), 7.51-7.54 (1H, m), 7.68 (1H, ddd, *J* = 1.7, 7.2, 8.6 Hz), 8.26 (1H, dd, *J* = 1.6, 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.64, 112.05, 118.14, 123.90, 125.33, 125.83, 126.30, 129.29, 130.82, 131.36, 132.72, 133.86, 156.56, 166.16, 178.36.



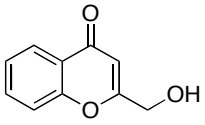
2-(Thiophen-3-yl)-4*H*-chromen-4-one (116). The general procedure was used to afford 793 mg of the title compound as a tan solid (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (1H, s), 7.35-7.39 (1H, s), 7.42 (1H, dd, *J* = 3.0, 5.2 Hz), 7.45 (1H, dd, *J* = 1.32, 5.2 Hz), 7.48-7.50 (1H, m), 7.65 (1H, ddd, *J* = 1.7, 7.2, 8.6 Hz), 7.99 (1H, dd, *J* = 1.3, 3.0 Hz), 8.19 (1H, dd, *J* = 1.6, 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.30, 118.08, 124.12, 125.17, 125.27, 125.80, 126.95, 127.50, 133.83, 134.34, 156.18, 159.66, 178.54. IR (neat, NaCl): 3084, 1640, 1572, 1465, 1358, 1128 cm^{-1}. MP = 113-115 °C. HRMS (ESI^+): *m/z* calc'd for $C_{13}H_8NaO_2S$, 251.0143; found 251.0139.



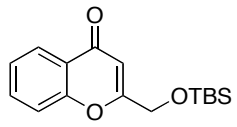
4*H*-Chromen-4-one (118). The general procedure was used to afford 405 mg of the title compound as a white solid (58%). The spectral data are consistent with those reported in the literature.[132] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (1H, d, *J* = 6.0 Hz), 7.36-7.40 (1H, m), 7.43 (1H, dd, *J* = 0.6, 8.6 Hz), 7.65 (1H, ddd, *J* = 1.7, 7.2, 8.6 Hz), 7.83 (1H, d, *J* = 6.0 Hz), 8.18 (1H, dd, *J* = 1.62, 7.98 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.09, 118.27, 124.99, 125.33, 125.89, 133.85, 155.40, 156.60, 177.69.



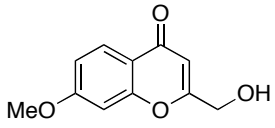
2-Pentyl-4*H*-chromen-4-one (120). The general procedure was used to afford 918 mg of the title compound as an oily solid (91%). The spectral data are consistent with those reported in the literature.[84] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-0.93 (3H, m), 1.34-1.41 (4H, m), 1.71-1.76 (2H, m), 2.61 (2H, t, *J* = 7.6 Hz), 6.17 (1H, s), 7.35-7.39 (1H, m), 7.42 (1H, d, *J* = 8.44 Hz), 7.64 (1H, ddd, *J* = 1.7, 7.2, 8.6 Hz), 8.18 (1H, dd, *J* = 1.58, 7.94 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.04, 22.47, 26.61, 31.26, 34.34, 109.96, 117.98, 123.89, 125.01, 125.81, 133.52, 156.66, 169.96, 178.54.



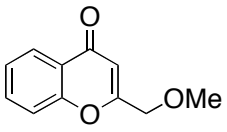
2-(Hydroxymethyl)-4*H*-chromen-4-one (122). The general procedure was used to afford 630 mg of the title compound as a yellow solid (14%). The spectral data are consistent with those reported in the literature.[135] ^{1}H NMR (400 MHz, d_6-DMSO) δ 4.49 (2H, dd, *J* = 0.8, 6.1 Hz), 5.84 (1H, t, *J* = 6.1 Hz), 6.38 (1H, s), 7.49-7.53 (1H, m), 7.64-7.66 (1H, m), 7.83 (1H, ddd, *J* = 1.7, 7.1, 8.6 Hz), 8.07 (1H, dd, *J* = 1.6, 8.0 Hz). ^{13}C NMR (100 MHz, d_6-DMSO) δ 59.80, 107.27, 118.21, 123.43, 124.93, 125.34, 134.18, 155.67, 169.78, 176.79.



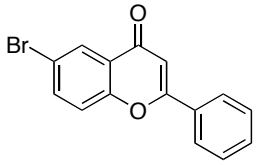
2-((*tert*-Butyldimethylsilyloxy)methyl)-4*H*-chromen-4-one (123). The general procedure was used to afford 961 mg of the title compound as a tan solid (13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (6H, s), 0.95 (9H, s), 4.58 (2H, d, 1.0 Hz), 6.47 (1H, t, 1.0 Hz), 7.35-7.40 (2H, m), 7.63 (1H, ddd, *J* = 1.7, 7.1, 10.1 Hz), 8.19 (1H, dd, *J* = 1.4, 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.30, 18.44, 25.91, 61.79, 108.11, 117.90, 124.27, 125.16, 125.98, 133.70, 156.23, 168.27, 178.41. IR (neat, NaCl): 1639, 1596, 1466, 1355, 1095 cm^{-1}. MP = 159-161 °C. HRMS (ESI^{+}): *m/z* calc'd for $C_{16}H_{23}O_3Si$, 291.1416; found 291.1402.



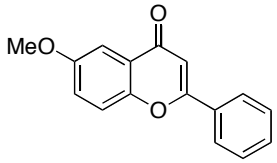
2-(Hydroxymethyl)-7-methoxy-4*H*-chromen-4-one (125). The general procedure was used to afford 68 mg of the title compound as a white solid (7%). The spectral data are consistent with those reported in the literature.[136] ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.92 (3H, s), 4.45 (2H, dd, *J* = 0.9, 6.1 Hz), 5.80 (1H, t, 6.1 Hz), 6.29 (1H, s), 7.08 (1H, dd, *J* = 2.42, 8.82 Hz), 7.14 (1H, d, *J* = 2.4 Hz), 7.96 (1H, d, *J* = 8.84 Hz). ^{13}C NMR (100 MHz, d_6-DMSO) δ 56.06, 59.74, 100.69, 107.19, 114.41, 117.17, 126.33, 157.48, 163.74, 169.11, 176.16.



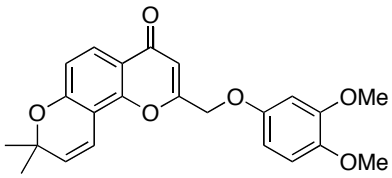
2-(Methoxymethyl)-4*H*-chromen-4-one (127). The general procedure was used to afford 348 mg of the title compound as an oily solid (38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (3H, s), 4.36 (2H, s), 6.40 (1H, s), 7.39 (1H, t, *J* = 7.5 Hz), 7.44 (1H, d, *J* = 8.4 Hz), 7.63-7.67 (1H, m), 8.18 (1H, d, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.34, 70.87, 109.74, 118.10, 124.15, 125.30, 125.89, 133.86, 156.40, 164.96, 178.21. IR (neat, NaCl): 2933, 1656, 1466, 1349, 1123, 758 cm^{-1}. HRMS (ESI^+): *m/z* calc'd for $C_{11}H_{11}O_3$, 191.0708; found 191.0706.



6-Bromo-2-phenyl-4*H*-chromen-4-one (129). The general procedure was used to afford 1.02 g of the title compound as a tan solid (72%). The spectral data are consistent with those reported in the literature.[90] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, s), 7.48 (1H, d, *J* = 8.84 Hz), 7.52-7.57 (3H, m), 7.79 (1H, dd, *J* = 2.5, 8.8 Hz), 7.91-7.93 (2H, m), 8.37 (1H, d, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.62, 118.77, 120.16, 125.35, 126.41, 128.45, 129.22, 131.43, 131.99, 136.82, 155.07, 163.75, 177.10.

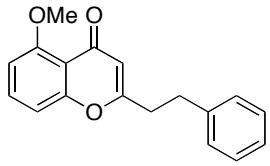


6-Methoxy-2-phenyl-4*H*-chromen-4-one (131). The general procedure was used to afford 601 mg of the title compound as a yellow solid (50%). The spectral data are consistent with those reported in the literature.[137,138] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (3H, s), 6.82 (1H, s), 7.29 (1H, dd, *J* = 3.1, 9.1 Hz), 7.49-7.54 (4H, m), 7.60 (1H, d, *J* = 3.1 Hz), 7.90-7.94 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.09, 104.98, 107.00, 119.65, 123.96, 124.72, 126.38, 129.17, 131.17, 132.04, 151.24, 157.15, 163.31, 178.45.

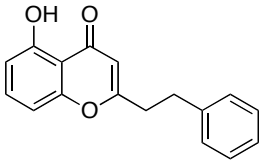


2',2'-Dimethyl-2-(3,4-dimethoxyphenyloxy)methylpyrano[2,3-*f*]-chromen-4-one (134). The general procedure was used to afford 2.13 g of the title compound as a tan solid (37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (6H, s), 3.85 (3H, s), 3.88 (3H, s), 4.92 (2H, d, *J* = 0.7 Hz), 5.71 (1H, d, *J* = 10.0 Hz), 6.44 (1H, m), 6.47 (1H, dd, *J* = 2.9, 8.8 Hz), 6.61 (1H, d, *J* = 2.8 Hz), 6.75 (1H, dd, *J* = 0.5, 10.0 Hz), 6.75-6.80 (1H, m), 6.84 (1H, dd, *J* = 0.5, 8.7 Hz) 7.95 (1H, d, J = 8.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.23 (2C), 56.02, 56.47, 66.85, 77.82, 101.40, 104.20, 109.32, 109.91, 111.65, 114.99, 115.29, 117.90, 126.19, 130.49, 144.49, 150.09, 152.37, 152.39, 157.61, 162.94, 177.46. IR (neat, NaCl): 2974, 1685, 1599, 1513, 1231, 1122 cm^{-1}.

MP = 107-109 °C. HRMS (ESI^+): *m/z* calc'd for $C_{23}H_{22}NaO_6$, 417.1314; found 417.1318.



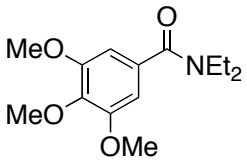
5-Methoxy-2-(2-phenylethyl)chromone (141). The general procedure was used to afford 267 mg of the title compound as a brown oily solid (15%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.84-2.88 (2H, m), 3.01-3.05 (2H, m), 3.97 (3H, s), 6.05 (1H, s), 6.79 (1H, d, *J* = 8.0 Hz), 6.98 (1H, dd, *J* = 0.88, 8.44 Hz), 7.19-7.23 (3H, m), 7.27-7.31 (2H, m), 7.52 (1H, t, *J* = 8.36 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.95, 35.62, 56.59, 106.37, 110.10, 111.91, 114.55, 126.66, 128.45, 128.77, 133.62, 139.97, 158.69, 159.92, 166.01, 178.33. IR (neat, NaCl): 2932, 1657, 1604, 1475, 1386, 1265, 1083 cm^{-1}. MP = 107-109 °C. HRMS (ESI^+): *m/z* calc'd for $C_{18}H_{17}O_3$, 281.1178; found 281.1182.



5-Hydroxy-2-(2-phenylethyl)chromone (142). A BBr_3 solution (1.0 M in CH_2Cl_2, 200 μL, 0.20 mmol) was added dropwise into a solution of chromone **66** (42 mg, 0.15 mmol) in CH_2Cl_2 (6 mL) at -78 ºC. The mixture was allowed to warm to room temperature. MeOH (1.0 mL) was added into the reaction flask to quench the reaction and the mixture was partitioned between H_2O and CH_2Cl_2. The organic phase was washed with H_2O several times, dried over Na_2SO_4, and concentrated. The residue

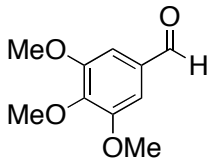
was purified by flash chromatography (30% EtOAc in hexanes) as brown solid (26 mg, 66%). The spectral data are consistent with those reported in the literature.[107] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (2H, dd, *J* = 7.2, 8.1 Hz), 3.06 (2H, dd, *J* = 7.2, 8.1 Hz), 6.07 (1H, s), 6.78 (1H, d, *J* = 8.2 Hz), 6.87 (1H, d, *J* = 8.36 Hz), 7.19-7.24 (3H, m), 7.30 (2H, dd, *J* = 7.2, 7.4 Hz), 7.50 (1H, t, *J* = 8.32 Hz), 12.52 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.00, 36.21, 106.97, 108.98, 110.73, 111.38, 126.80, 128.38, 128.84, 135.29, 139.56, 156.86, 160.93, 169.94, 183.63. IR (neat, NaCl): 2925, 1655, 1618, 1474, 1409, 1256, 847, 802 cm^{-1}. MP = 71-73 °C. HRMS (ESI^{+}): *m/z* calc'd for $C_{17}H_{15}O_3$, 267.1021; found 267.1021.

4.2.3 Chapter 3

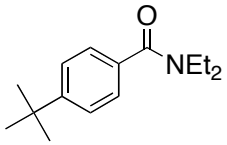


***N,N*-Diethyl-3,4,5-trimethoxybenzamide (146)**. A round bottom flask was charged with 3,4,5-trimethoxybenzoyl chloride (20 g, 86.7 mmol, 1 equiv) under ambient atmosphere and subsequently fitted with a rubber septum. The acid chloride was dissolved in 170 mL anhydrous CH_2Cl_2 and cooled with an ice-water bath. Diethylamine (18 mL, 173.4 mmol) was added over 10 min to the cooled solution and the reaction was warmed to room temperature overnight. The reaction was checked by TLC (20% hexanes in EtOAc) and indicated the absence of acid chloride. The reaction mixture was diluted with 10% aq. HCl (50 mL) and transferred to a separatory funnel containing CH_2Cl_2 (150 mL) and 10% aq. HCl (150 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic layers were washed with saturated $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The residue was dissolved with a minimal amount of hot diethyl ether and allowed to stand at room temperature overnight. The resulting crystals were collected via suction filtration and washed with ice-cold diethyl ether and transferred to a round-bottomed flask and dried overnight to afford 13.4 g of pure amide as a white solid (57%). The spectral data are consistent with those reported in the literature.[139] ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 1.14

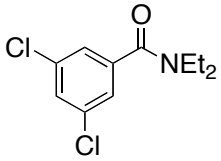
(6H, t, J = 7.0 Hz), 3.36 (4H, br s), 3.80 (3H, s), 3.81 (6H, s), 6.55 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 12.88, 14.31, 39.33, 43.33, 56.15, 60.81, 103.56, 132.64, 138.63, 153.21, 170.90.



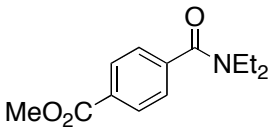
3,4,5-Trimethoxybenzaldehyde (147). A round bottom flask was charged with $Cp_2Zr(H)Cl$ (15.5 g, 60 mmol) under a nitrogen atmosphere and THF (60 mL) was added resulting in a cloudy, white suspension. Amide **146** (8 g, 30 mmol) in 30 mL THF was added dropwise to the suspension over 10 min via syringe pump. Upon complete addition of amide, the slurry was allowed to stir for 15 minutes at room temperature. The reaction was monitored by TLC (EtOAc) and demonstrated the absence of the amide **146**. Silica gel (60 g) was added in one portion and the mixture was allowed to stir 5 min open to the atmosphere. The heterogeneous solution was filtered eluting with Et_2O. The filtrate was poured into a separatory funnel containing H_2O and Et_2O. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated. The crude aldehyde was purified by MPLC using silica gel (0-40% ethyl acetate in hexanes, 40 minutes, 254 nm) to give 5.81 g of pure aldehyde **147** as a white solid in 99% yield. The spectral data are consistent with those reported in the literature.[139] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (6H, s), 3.93 (3H, s), 7.12 (2H, s), 9.86 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) 56.25, 60.99, 106.66, 131.72, 143.52, 153.63, 191.10.



4-*tert*-Butyl-*N*,*N*-diethylbenzamide (148). The same procedure for the synthesis of amide **146** was used to afford 10.54 g of the title compound as a white solid (82%). The spectral data are consistent with those reported in the literature.[140] ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 1.16 (6H, m), 1.31 (9H, s), 3.40 (4H, br s), 7.27-7.30 (2H, m), 7.36-7.39 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 12.88, 14.31, 39.33, 43.33, 56.14, 60.81, 103.56, 132.64, 138.63, 153.21, 170.90.

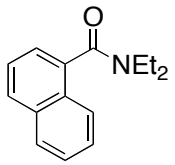


3,5-Dichloro-*N*,*N*-diethylbenzamide (149). The same procedure for the synthesis of amide **146** was used to afford 4.35 g of the title compound as a white solid (90%).[141] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, br s), 1.17 (3H, br s), 3.18 (1H, m), 3.46 (1H, m), 7.19 (2H, d, J = 1.9 Hz), 7.32 (1H, t, J = 1.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.76, 14.14, 39.47, 43.31, 124.80, 129.17, 135.21, 139.91, 168.09.

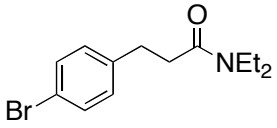


Methyl 4-(Diethylcarbamoyl)benzoate (150). The same procedure for the synthesis of amide **146** was used to afford 5.88 g of the title compound as a colorless oil (99%). The spectral data are consistent with those reported in the literature.[142] ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 1.13 (6H, br s), 3.20 (2H, br s), 3.47 (2H, br s), 3.87 (3H, s),

7.38 (2H, d, J = 8.5 Hz), 8.01 (2H, d, J = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 12.86, 14.17, 39.32, 43.23, 52.25, 126.27, 129.77, 130.63, 141.57, 166.41, 170.23.

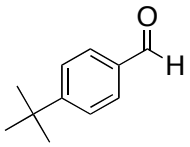


***N*,*N*-Diethyl-1-naphthamide (151)**. The same procedure for the synthesis of amide **146** was used to afford 16.10 g of the title compound as a yellow oil (90%). The spectral data are consistent with those reported in the literature.[143] ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 0.98 (3H, t, J = 7.1 Hz), 1.37 (3H, t, J = 7.1 Hz), 3.09 (2H, q, J = 6.86 Hz), 3.69 (2H, br s), 7.37-7.39 (1H, m), 7.43-7.52 (3H, m), 7.81-7.86 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 13.13, 14.31, 39.06, 43.14, 123.22, 124.80, 125.17, 126.38, 126.89, 128.37, 128.77, 129.66, 133.51, 135.24, 170.31.

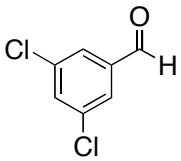


3-(4-Bromophenyl)-*N*,*N*-diethylpropanamide (152). To a stirring solution of commercially available 3-(4-bromophenyl)propanoic acid (4.51 g, 19.6 mmol) in CH_2Cl_2 (40 mL) cooled to 0 °C were EDCI (4.12 g, 21.6 mmol), and added diethylamine (4.50 mL, 43.2 mmol) in sequence and the reaction was allowed to warm to room temperature overnight. The reaction mixture was transferred to a separatory funnel containing 10% aq. HCl and CH_2Cl_2. The layers were separated and the aqueous layer was extracted twice more with CH_2Cl_2. The combined organic

layers were washed with saturated aq. $NaHCO_3$; the layers were separated and the aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and purified by MPLC on silica gel (0-50% ethyl acetate in hexanes, 50 min, 254 nm) to give 2.64 g of the title compound as a white solid (47%). The spectral data are consistent with those reported in the literature.[144] ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (6H, t, *J* = 7.1 Hz), 2.54-2.58 (2H, m), 2.91-2.95 (2H, m), 3.22 (2H, q, *J* = 7.1 Hz), 3.37 (2H, q, *J* = 7.1 Hz), 7.01 (2H, m), 7.38-7.40 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$,) δ 13.23, 14.43, 31.05, 34.87, 40.39, 42.02, 119.94, 130.43 (2C), 131.60 (2C), 140.73, 170.95).

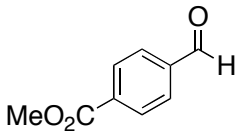


4-*tert*-Butylbenzaldehyde (153). The same procedure for the synthesis of aldehyde **147** was used to afford 2.92 g of the title compounds as a colorless oil (90%). The spectral data are consistent with those reported in the literature.[145] ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 1.31 (9H, m), 7.50-.52 (2H, m), 7.76 (2H, m), 9.94 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$, rotamers) 31.01, 35.27, 125.93, 129.63, 134.09, 158.31, 191.84.

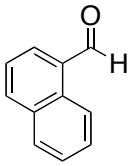


3,5-Dichlorobenzaldehyde (154). The same procedure for the synthesis of aldehyde **147** was used to afford 1.75 g of the title compounds as a yellow solid (92%). The

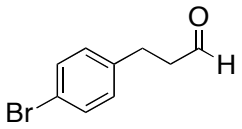
spectral data are consistent with those reported in the literature.[145] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, t, *J* = 1.9 Hz), 7.72 (2H, d, *J* =1.9 Hz), 9.91 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) 127.88, 134.15, 136.26, 138.58, 189.44.



Methyl 4-Formylbenzoate (155). The same procedure for the synthesis of aldehyde **147** was used to afford 1.83 g of the title compounds as a yellow solid (93%). The spectral data are consistent with those reported in the literature.[145] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, s), 7.87-7.89 (2H, m), 8.11 (2H, d, *J* = 8.2 Hz), 10.03 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) 52.54, 129.47, 130.13, 134.99, 139.09, 165.97, 191.65.



1-Naphthaldehyde (156). The same procedure for the synthesis of aldehyde **147** was used to afford 1.10 g of the title compounds as yellow oil (97%). The spectral data are consistent with those reported in the literature.[132] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.66 (2H, m), 7.68-7.72 (1H, m), 7.93 (1H, d, *J* = 8.2 Hz), 8.00 (1H, d, *J* = 7.0 Hz), 8.11 (1H, d, *J* = 8.2 Hz), 9.26 (1H, d, *J* = 8.6 Hz), 10.41 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) 125.03 (2C), 127.12, 128.62, 129.23, 130.67, 131.54, 133.86, 135.46, 136.87, 193.73.



3-(4-Bromophenyl)propanal (157). The same procedure for the synthesis of aldehyde **147** was used to afford 449 mg of the title compounds as colorless oil (85%). The spectral data are consistent with those reported in the literature.[146] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67-2.71 (2H, m), 2.82-2.85 (2H, t, *J* = 7.4 Hz), 7.01-7.03 (2H, m), 7.32-7.35 (2H, m), 9.71-9.72 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) 27.23, 44.71, 119.76, 129.99 (2C), 131.37 (2C), 139.34, 200.80.

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