Trichloroacetimidates as Alkylating Reagents in C-N Bond Formation and Synthesis of Aminosteroid and Quinoline Inhibitors of Src Homology 2 Domain-Containing Inositol Phosphatase (SHIP)

Daniel Ryan Wallach
Syracuse University

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Abstract

Trichloroacetimidates have frequently been used in the formation of glycosidic bonds and other ethers, which is especially useful for the introduction of ether protecting groups. Trichloroacetimidates have also been used as electrophiles in Friedel-Crafts alkylation reactions. The formation of C-N bonds has also been accomplished utilizing trichloroacetimidates. Most frequently C-N bond formation with trichloroacetimidates is associated with sigmatropic rearrangement of an allylic trichloroacetimdate to an allylic trichloroacetamide. This reaction can proceed thermally or through the use of Lewis acid or transition metal catalysts. Recently, the direct substitution of trichloroacetimidates using nitrogen nucleophiles has been accomplished utilizing transition metal catalysts, which indicates that trichloroacetimidates may be suitable alkylation partners for certain nitrogen nucleophiles.

Trichloroacetimidates are now shown to be effective alkylating reagents for the monosubstitution of anilines using the Brønsted acid catalyst (±)-camphorsulfonic acid. The reaction is especially efficient for electron deficient anilines while electron rich anilines provided lower yields due to competing Friedel-Crafts reactions. A one-pot procedure for generating the trichloroacetimdate in situ followed by displacement with the aniline is also described, and the yields for this one-step process are similar to the two-step protocol. The displacement of a chiral imidate by 4-chloroaniline led to significant racemization which indicates that the reaction may proceed through a carbocation intermediate.

The alkylation of sulfonamides with trichloroacetimidates under thermal conditions is also described. Primary and secondary trichloroacetimidates are found to be suitable electrophiles under these conditions, while tertiary trichloroacetimidates provide reduced yields. Aryl and alkyl sulfonamides with varying electronic properties were well tolerated under the
reaction conditions. A bioactive analog of the analgesic ketoprofen is synthesized using the described methodology. Complete racemization of a chiral trichloroacetimidate is observed under these reaction conditions which is evidence that the reaction proceeds through an $S_{N}1$ type mechanism.

Pyrroloindoline trichloroacetimidates may react with amine nucleophiles in the presence of catalytic BF$_3$·OEt$_2$ to generate pyrroloindoline systems decorated with amines at the C3a position. The natural product kapakahine C is a complex heterocyclic compound containing a substituted pyrroloindoline-pyridoindoline core that may be accessed using this method. A route to the synthesis of the substituted pyridoindoline core of kapakahine C was investigated. Optimization of key reactions in this sequence, including a peptide coupling reaction and oxidative cyclization, was performed. Investigation into completing the synthesis of kapakahine C is ongoing.

The inhibition of the SH2-containing inositol 5\' -phosphatase (SHIP) can modulate the dephosphorylation of phosphoinositols. These molecules act as second messengers in a signal transduction cascade, with the placement of phosphorylation on the inositol acting to convey information in the transmission of signals from the cell membrane to the cell nucleus. The concentration of these phosphates has an effect on cellular function such as cell proliferation, survival, and differentiation.

The synthesis of six aminosteroid SHIP inhibitors is described. Optimization of the key steps in the synthetic sequence was conducted. The synthesis of two quinoline based SHIP inhibitors, which were identified in a high-throughput screening conducted by the National Cancer Institute (NCI), was also completed. Studies were conducted to synthesize these
molecules on multi-gram scale. The synthesized compounds were tested for inhibitory activity in a Malachite Green assay.
Trichloroacetimidates as Alkylating Reagents in C-N Bond Formation and Synthesis of Aminosteroid and Quinoline Inhibitors of Src Homology 2 Domain-Containing Inositol Phosphatase (SHIP)

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MPhil, Syracuse University, 2013

DISSERTATION

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Syracuse University
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As I near the end of this long journey and pour over the research I have done since arriving at Syracuse University it becomes apparent how much of the work was accomplished with the help of others. It would be wrong to present this work without acknowledging all those who helped me get to this point.

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<td>[α]</td>
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<tr>
<td>Hz</td>
<td>hertz</td>
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<td>coupling constant</td>
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<tr>
<td>LAH</td>
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<tr>
<td>LD₅₀</td>
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<td>LDA</td>
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<td>LHMDS</td>
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GC gas chromatography
h hour(s)
MAP mitogen activated protein
MAPK mitogen activated protein kinases
max maximum
Me methyl
MEM (2-methoxyethoxy)methyl
Mes 2,4,6-trimethylphenyl
MHC major histocompatibility complex
MHz megahertz
min minute(s), minimum
mM millimolar
MO molecular orbital
mol mole(s); molecular
MOM methoxymethyl
mp melting point
Ms methylsulfonyl (mesyl)
MS mass spectrometry
MTBE methyl tert-butyl ether
MW mol wt molecular weight
m/z mass-to-charge ratio
N normal
NBS N-bromosuccinimide
NCI National Cancer Institute
NCS N-chlorosuccinimide
m multiplet
M molar
nm nanometers
NMO N-methylmorpholine-N-oxide
NMP N-methylpyrrolidone
NMR nuclear magnetic resonance
NOE nuclear Overhauser effect
NOESY nuclear Overhauser effect spectroscopy
NRT natural resonance theory
Nu nucleophile
OD optical density
ORD optical rotary dispersion
PCC pyridinium chlorochromate
PDC pyridinium dichromate
PDK1 phosphoinositide-dependent kinase 1
PE petroleum ether
Ph phenyl
PI-3,4,5-P3 inositol trisphosphate,
phosphatidylinositol (3,4,5)-trisphosphate
PI3K phosphatidylinositol-4,5-bisphosphate
3-kinase
piv pivaloyl
pKa acid dissociation constant
pm picometer(s)
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</tr>
<tr>
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<td>pyridinium p-toluenesulfonate</td>
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<tr>
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<td>PTC</td>
<td>phase-transfer catalysis</td>
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<td>volume per unit volume</td>
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xxi
T absolute temperature in kelvins (K)  
w/w weight per unit weight

TBS tert-butyldimethylsilyl
Chapter 1

Trichloroacetimidates as Alkylating Reagents in C-N Bond Formation and Related Transformations

Abstract: Trichloroacetimidates are often used in the formation of ethers in the synthesis of glycosidic bonds or in the introduction of ether protecting groups. Most often these groups are benzyl or 4-methoxybenzyl ethers, although a number of other ethers have also been formed with trichloroacetimidates. Trichloroacetimidates have been shown to be competent electrophiles in Friedel-Crafts reactions. Trichloroacetimidates are also commonly used for the formation of C-N bonds. Most often this entails the rearrangement of allylic trichloroacetimidates to form allylic amines, but more recent studies have shown that imidates may be used to efficiently alkylate amines. In this chapter a brief overview of the common reactivity of trichloroacetimidates is provided as background to place the results in the next three chapters in context.

Carboximidates, often referred to generally as imidates, are organic functional groups characterized by a R'-N=C(OR'')R linkage (Figure 1.1). Trichloroacetimidates are a subset of the imidate functional group which are characterized by an N-H bond and trichloromethyl group at the R' and R positions respectively. The first reported synthesis of a trichloroacetimidate was published by Steinkopf and Malinowski, as part of their studies on the reactivity of trichloroacetonitrile.\(^1\)\(^2\) The use of trichloroacetimidates was then expanded by Cramer who reported the use of benzylic imidates as leaving groups in substitution reactions.\(^3\)\(^4\) Initially, trichloroacetimidates were synthesized by the addition of trichloroacetonitrile to an alkoxide ion. In later years milder conditions utilizing DBU as a base were discovered by Bernet which avoided the use of metal hydride reagents.\(^5\) Classically, trichloroacetimidates have been utilized
for C-O and C-N bond forming reactions such as glycosidic bond formation, the synthesis of allylic amines (the Overman rearrangement), and in the formation of alcohol and carboxylic acid protecting groups.

![Figure 1.1: General Structures of Carboximidates and Trichloroacetimidates](image)

**Figure 1.1: General Structures of Carboximidates and Trichloroacetimidates**

**Glycosidic Bond Formation**

The use of trichloroacetimidates as alkylating reagents in glycosidic bond formation was first demonstrated by Schmidt and coworkers in the early 1980s.$^6$–$^9$ Schmidt showed that α and β glycosyl imidates could be conveniently prepared from the reaction of both benzyl and acetyl protected glucopyranose with trichloroacetonitrile in the presence of a catalytic amount of NaH. The imidates could then be displaced with alcohols to afford the corresponding ether utilizing a Lewis acid like trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst (Scheme 1.1).

![Scheme 1.1](image)

Since Schmidt's initial discovery additional advances have been made to glycosidic bond formation with trichloroacetimidates including the use of other Lewis acid catalysts such as BF$_3$·OEt$_2$,$^{10}$ and phenylboron difluoride.$^{11}$ Glycosylation using trichloroacetimidates is valuable
as the α and β anomers of the protected carbohydrate products can be obtained predictably and selectively. This chemistry has now been utilized in much more complex systems, with the trichloroacetimidate donor being competent even in the introduction of a trisaccharide unit of the immunological adjuvant QS-21A 2.9 (Scheme 1.2).^12

**Scheme 1.2**

Schmidt's research into glycosidic bond formation using trichloroacetimidates led to similar research into the formation of other C-O ether bonds using trichloroacetimidates. This research has been especially useful in the installment of protecting groups in complex organic
molecules. Trichloroacetimidates have been used for the formation of benzyl ethers\textsuperscript{13-15} in a number of complex systems. This method has become especially popular in systems that are sensitive to base, like the $\beta$-hydroxy ester 1.9 (Scheme 1.3). Under basic conditions compound 1.9 undergoes a facile retroaldol reaction, which complicates formation of the corresponding ether under Williamson type conditions (NaH, BnBr). Alternatively, exposure of the alcohol to benzyl trichloroacetimidate in the presence of triflic acid provides the desired benzyl ether product in 79% yield. More recently it was shown that diphenylmethyl ethers\textsuperscript{16} may be installed under thermal conditions (refluxing toluene) without the need for an exogenous acid catalyst, which should further extend the utility of trichloroacetimidates in ether synthesis, as under thermal conditions both acid and base sensitive alcohols may be etherified in good yield.

Scheme 1.3

The formation of ethers using trichloroacetimidates also provides an opportunity for asymmetric catalysis. For example, conditions for substituting $\alpha$-allylic imidates utilizing carboxylic acids to form the corresponding esters were investigated by Overman (Scheme 1.4).\textsuperscript{17} This reaction utilized the palladium catalyst cobalt oxazoline palladacyclic complex (COP) to form the corresponding allylic esters with good yields and selectivity. These reactions were used to synthesize bioactive molecules such as (+)-cloriolide,\textsuperscript{19} and (+)-polyrhactide B.\textsuperscript{20} Methods for the formation of allylic phenolic ethers were also investigated, and their formation was achieved with similar yields and selectivities.\textsuperscript{21-23} A number of systems which employ chiral
acids as organocatalysts have also been employed in etherification reactions\textsuperscript{24, 25} using imidates as starting materials. The use of trichloroacetimidates for the formation of ethers demonstrates their synthetic utility as reagents for oxygen alkylation, which may be used to install protecting groups rapidly and efficiently under mild conditions.

**Scheme 1.4**

Trichloroacetimidates have also been used for the introduction of ester protecting groups of carboxylic acids.\textsuperscript{26, 27} Spontaneous esterification has been reported with glycosyl imidates,\textsuperscript{10} 4-methoxy-benzyl trichloroacetimidate,\textsuperscript{29, 30} and 2-phenylisopropyl trichloroacetimidate.\textsuperscript{31, 32} The formation of diphenylmethyl and esters using the corresponding imidate without the use of exogenous acid has also been reported.\textsuperscript{33} Similarly, thermal formation of 4-methoxy benzyl (PMB) esters has been accomplished using PMB imidate and various carboxylic acids.\textsuperscript{34} Both the PMB and DPM protecting groups may be removed via hydrogenation to regenerate the
corresponding carboxylic acid, or can be removed under acidic conditions, making these groups flexible protecting groups for the carboxylate.

**Friedel-Crafts Reactions**

Carbon-carbon bond forming reactions utilizing trichloroacetimidates are also known. The Friedel-Crafts reaction of trichloroacetimidates and arenes is among the most useful and versatile reaction of this type. Classically alkyl and acyl halides have been used as leaving groups in Friedel-Crafts alkylation and acylation,\textsuperscript{35,36} however research performed by Schmidt showed that trichloroacetimidates were also suitable alkylating agents for Friedel-Crafts reactions with electron-rich arenes (Scheme 1.5).\textsuperscript{37} Trichloroacetimidates may provide advantages over alkyl halides as substrates in these reactions, as even electron poor benzylic trichloroacetimidates undergo these alkylation reactions. This high degree of reactivity may be due to the rearrangement of the imidate to the acetamide byproduct, which adds a secondary thermodynamic driving force to the alkylation reaction.

**Scheme 1.5**

\[\text{1.18} + \text{1.19} \rightarrow \text{1.20} \quad \text{TMSOTf (0.2 equiv)} \]

Friedel-Crafts reactions utilizing trichloroacetimidates have been used in the synthesis of biologically interesting compounds. Given the use of trichloroacetimidates in carbohydrate chemistry, it is perhaps unsurprising that this chemistry has found use in the formation of C-glycosides. A number of targets such as analogs of the aryl-C glycoside visnagin such as 1.24
(Scheme 1.6), and the flavone-C glycosides vitexin, isovitexin and isoembigenin have been accessed using trichloroacetimidate alkylation chemistry.

**Scheme 1.6**

The Friedel-Crafts alkylation employing trichloroacetimidates has also been utilized in the synthesis of complex natural products. For example, Fukuyama utilized this chemistry in the synthesis of the dictyodendrins. These compounds were the first marine alkaloids which possess inhibitory activity against telomerase, and enzyme that is a new potential target for cancer chemotherapy. The imidate alkylation allowed for the modular addition of benzyl groups to a highly functionalized indole core (Scheme 1.7).
Scheme 1.7

Rearrangement of Allylic Trichloroacetimidates for the Synthesis of Allylic Amines
(Overman Rearrangement)

The incorporation of nitrogen into organic molecules is an important synthetic challenge for organic chemists due to the prevalence of nitrogen-containing pharmaceuticals, natural products and bioactive compounds. Of particular interest is the displacement of alcohols for nitrogen atoms, as alcohols are common inexpensive starting materials. One method of introducing nitrogen from an allylic alcohol utilizing an imidate intermediate is an aza-Claisen rearrangement known as the Overman rearrangement\textsuperscript{41,42} which involves a [3,3]-sigmatropic rearrangement of a trichloroacetimidate to a trichloroacetamide (Scheme 1.8). The development of this rearrangement is important as it allows for the synthesis of allylic amines from easily accessible allylic alcohols.\textsuperscript{43} Formation of the necessary imidate requires only the base-catalyzed formation of the imidate from an allylic alcohol and trichloroacetonitrile. The base can
be varied depending on the required reaction conditions, for example 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is often employed as a base for primary and secondary alcohols, whereas the stronger alkoxide-forming base KH is frequently used to generate tertiary trichloroacetimidates.\textsuperscript{44, 45} Overman found that the trichloroacetimidate can then be treated with catalytic amounts of mercury (II) salts to catalyze the rearrangement of the trichloroacetimidate to the corresponding acetamide.\textsuperscript{42} Thermal rearrangements of the trichloroacetimidates could also be accomplished using a solvent with a high boiling point such as xylene and heating the reaction to 140°C.\textsuperscript{41, 46} The variety of relatively mild conditions available for the Overman rearrangement as well as the power of selectively converting a readily attainable allylic alcohol into an allylic amine led to the widespread use of this reaction.

**Scheme 1.8**

Mechanistically, there are two possible pathways for the Overman rearrangement. With no catalyst, the reaction is thought to proceed through a concerted sigmatropic pathway (Scheme 1.9).
With a transition metal catalyst, a two-step reaction pathway is proposed (Scheme 1.10). The first step involves the transition metal catalyst adding across the olefin to form a mercurinium ion (in the case of mercury catalyzed Overman rearrangement) or its equivalent. The intermediate 1.33 can then suffers breakage of the C-O bond and rearranges to form amide 1.32. Overman provides evidence for this mechanism by noting that rearrangement is successful for imidates which contain nucleophilic promoting R groups, such as alkyl substituents, and fails for substrates in which substitution at C-2 is favored such as cyclohex-2-en-1-yl 2,2,2-trichloroacetimidate. Overall, the mechanistic pathway of the Overman rearrangement resembles that of the aza-Claisen rearrangement.

**Scheme 1.10**

![Scheme 1.10 Diagram]

Since its initial discovery many investigations to improve the Overman rearrangement have been undertaken. The use of palladium as a catalyst rather than mercury offers several advantages. First, palladium is considerably less toxic than mercury. Second, the palladium-catalyzed rearrangement has high transfer of chirality and provide trans alkenes selectively. For these reasons palladium has become the transition metal of choice for catalysis of the Overman rearrangement. Since the use of palladium as a transition metal catalyst for Overman rearrangements became more widespread other improvements and modifications for Overman rearrangement have been reported. In particular, it was found that chiral palladium catalysts such as 1.35 may be employed in palladium catalyzed enantioselective rearrangement reactions. (Scheme 1.11). Chiral palladium complexes containing chiral oxazoline, chiral diamine
ligands,$^{52}$ neutral ferrocenyl palladacycles$^{50,53}$ and chiral cobalt palladacycles$^{54,55}$ have been developed. These palladium complexes have been used to catalyze enantioselective rearrangements of trichloroacetimidates, which convert allylic imidates to their corresponding chiral amides.

**Scheme 1.11**

The palladium-catalyzed rearrangement occurs via a cyclization-induced rearrangement (CIR) mechanism. The rearrangement proceeds via a pi-allyl complex where palladium coordinates to the alkene 1.37 leading to the formation of the pi-allyl complex 1.40.$^{56}$ Addition of the nucleophile 1.39 leads to the product 1.42.
Enantioselective Overman rearrangements have enjoyed use in the synthesis of bioactive compounds. The GABA aminotransaminase inhibitor (S)-vigabatrin 1.46 (Figure 1.2) was synthesized using this chemistry. The palladium catalyst cobalt oxazoline palladacyclic complex 1.16 used in this transformation was capable of catalyzing the rearrangement of \( \alpha \)-allyl trichloroacetimidates. This interesting development led to further investigation of Overman rearrangements of \( \alpha \)-allyl trichloroacetimidates. Overman found that subjecting \( \alpha \)-allyl imidate 1.43 to intramolecular aminopalladation led to a 1:1 mixture of the 4-vinyl oxazoline 1.44 and the diacetate 1.45 (Scheme 1.13).\(^{57}\) This research led to the discovery of reactions for synthesizing vinyloxazolidinones from \( \alpha \)-allylic trichloroacetimidates. Although the COP-palladium catalyst was unsuccessful in catalyzing \( \alpha \)-allylic Overman rearrangements, the resulting chiral esterification and etherifications that resulted from this research proved synthetically useful.\(^{57,58}\)
Alternative Trichloroacetimidate-Based Formation of C-N Bonds

Despite numerous improvements to the Overman rearrangement relatively few alternative methods for using trichloroacetimidates for forming C-N bonds are known. One such reaction is the rearrangement of benzylic trichloroacetimidates to trichloroacetamides discovered by Cramer.\(^4\) This reaction is notable as it is the first reaction that demonstrates the displacement of trichloroacetimidates by nitrogen at the ipso carbon. This reaction was also observed for methyl imidate as well as more highly substituted benzyl imidates. For more substituted imidates formation of a carbocation intermediate facilitates rearrangement to the corresponding trichloroacetamide (Scheme 1.14).\(^4\) Methyl imidate can rearrange to the corresponding acetamide through a concerted mechanism (Scheme 1.15). Other similar rearrangements of trichloroacetimidates have been utilized for the synthesis of β-xylosidases inhibitor conduramine B,\(^59\) and for the synthesis of the multifunctional synthon 2-trichloromethyl-4-vinylloxazoline.\(^60\)
The use of trichloroacetimidates for rearrangement reactions such as the Overman rearrangement and for alkylation chemistry offers several advantages over other methods. Firstly, trichloroacetimidates are easily prepared via the reaction of alcohols with inexpensive trichloroacetonitrile\(^3\) and a catalytic amount of base. Trichloroacetimidates are also quite stable, for example the electron rich benzyl imidate 1.53 can be stored without significant decomposition for years at low temperature (-20°C). Further the reaction is driven not only by the displacement, but also by the rearrangement of the trichloroacetimidate to the more stable trichloroacetamide. This additional driving force helps facilitate trichloroacetimidate rearrangements and displacements so that they can occur under milder conditions. For displacement reactions the trichloroacetamide side product that is generated is far less acidic than comparable acidic byproducts in related displacement reactions such as HBr, HOMs, and HOTs, leading to fewer side reactions in reactions where no stoichiometric base is added. The trichloroacetamide byproduct may also be removed from the reaction mixture by successive
washing with aqueous 2M NaOH solution. These advantages have led to the investigation of the synthetic utility of trichloroacetimidates in direct alkylation reactions.

![Figure 1.3: Electron Rich Trichloroacetimidate](image)

A small number of direct alkylations of nitrogen nucleophiles utilizing trichloroacetimidate electrophiles have been reported. For example, the direct alkylation of trichloroacetimidates with nitrogen based heterocycles has been reported. In these reactions the alkylation is facilitated by the use of a strong acid such as TMSOTf. The bulky imidate 2,2,2-tert-butyl trichloroacetimidate has also been used to form C-N bonds with anilines, requiring the use of BF$_3$·OEt$_2$ to proceed to completion. Intriguingly, Piemontesi discovered certain nitrogen nucleophiles including indole, aniline, and morpholine could be alkylated in situ with 3-hydroxyoxindoles through an imidate intermediate (Scheme 1.16). The reaction was catalyzed by (PhO)$_2$PO$_2$H and though the scope tested was limited, these reactions provide strong evidence that Brønsted acid catalyzed alkylations of trichloroacetimidates with nitrogen nucleophiles is a viable synthetic strategy.

**Scheme 1.16**
Transition metals have also been used to enact these transformations. For example, rhodium catalyzed alkylations of N-methyl anilines with secondary allylic trichloroacetimidates have been reported (Scheme 1.17). These alkylations are noteworthy as they occur without significant formation of the linear product and also do not require the use of the common Lewis acids used in trichloroacetimidate alkylation such as BF$_3$·OEt$_2$ and TMSOTf. A number of improvements have been made to this methodology including a broadening of scope to include tertiary trichloroacetimidates, asymmetric aminations of tertiary trichloroacetimidates using a chiral rhodium catalyst, asymmetric aminations of secondary trichloroacetimidates using a chiral rhodium catalyst, and a study of asymmetric aminations of secondary and tertiary trichloroacetimidates with a chiral rhodium catalyst capable of alkylating anilines that lacked a chelating functional group at the β-position. This chemistry has also been utilized for the enantioselective synthesis of seven-membered nitrogen heterocycles. Apart from rhodium, palladium based transition metal catalysts have also been used to synthesize amine-linked pseudodisaccharides using trichloroacetimidates.

Scheme 1.17

Conclusion

Trichloroacetimidates have been used for both C-O and C-N bond forming reactions. Etherifications and esterifications utilizing trichloroacetimidates typically employ the use of strong Lewis acid catalysts such as BF$_3$·OEt$_2$ and TMSOTf, although in some cases the reactions
proceed with no catalyst or promoter. The Overman rearrangement has been widely used to form allylic amines from allylic alcohols. Direct alkylation of trichloroacetimidates with nitrogen nucleophiles has been accomplished with the use of rhodium catalysts and in some cases strong Brønsted acid catalysts. Due to the precedence of using trichloroacetimidates with oxygen and nitrogen nucleophiles, we hypothesized that trichloroacetimidates may be suitable partners for thermal and Brønsted acid catalyzed alkylation of anilines and sulfonamides.

References


Chapter 2

Brønsted-Acid Catalyzed Monoalkylation of Anilines with Trichloroacetimidates

Abstract

Trichloroacetimidates are shown to be synthetically useful alkylating agents for the monosubstitution of anilines using a Brønsted acid catalyst to facilitate the reaction. Electron poor anilines provided superior yields under these conditions while electron rich aniline substitutions provided lower yields due to competing Friedel-Crafts alkylation. A one-pot procedure involving the displacement of the reactive imidate intermediate formed from the alcohol in situ is also demonstrated, and the yields for this convenient process are comparable to the two-step protocol. The displacement of a chiral trichloroacetimidate using this chemistry was found to led to significant racemization, which favors a mechanism that proceeds through a carbocation intermediate.

Introduction

Substituted anilines are a common functional group found in many natural products and bioactive compounds (Figure 2.1). For example, a substituted aniline comprises the core of the tyrosine kinase inhibitor lavendustin A (2.4), the analgesic fentanyl (2.5), and the topoisomerase inhibitor 5,6-dihydrobicolorine (2.6). Substituted anilines are also found in compounds such as the cholesterol lowering drug ezetimibe (2.7), the lipoxygenase inhibitor onosmin B (2.8), and the antifolate drug methotrexate (2.9). Other anilines are used frequently in molecules with sensor applications and in synthetic receptors. Due to the prevalence of substituted anilines in bioactive and pharmacologically interesting molecules, methodologies for
their formation are of great interest. This led to the study described below, where anilines are alkylated with trichloroacetimidates. The conversion of carboxylic acids to esters and thiols to thioethers via alkylation with trichloroacetimidates has previously been observed,\textsuperscript{10-12} and therefore it was hypothesized that anilines could be alkylated with trichloroacetimidates in a similar manner employing a Brønsted acid catalyst.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2_1.png}
\caption{Some Aniline-Based Bioactive Compounds and Pharmaceuticals}
\end{figure}

Some alkylation reactions of anilines using trichloroacetimidates are known. A search of the literature revealed that anilines are typically alkylated with imidates using the strong Lewis acid catalyst BF\textsubscript{3}ˑOEt\textsubscript{2}.\textsuperscript{13-17} The alkylation has also been accomplished using copper (II) triflate in nitromethane, which resulted in improved yields of the desired N-alkyl product with tert-butyl- 2,2,2-trichloroacetimidate.\textsuperscript{18} Allylic trichloroacetimidates have been used to alkylate anilines with transition metal catalysts. Typically, these reactions\textsuperscript{19} employ catalyst systems based on rhodium,\textsuperscript{20-25} iridium\textsuperscript{26} or palladium.\textsuperscript{27,28} Less is known about the use of protic acids for catalyzing these N-alkylation reactions, however, Piemontesi and co-workers recently were able to use amine nucleophiles in substitution reactions with an oxindole based...
trichloroacetimidate and the protic acid catalyst (PhO)$_2$PO$_2$H.\textsuperscript{29} More recently the Chisholm group has shown that O- and S- alkylation reaction may occur under thermal conditions without the addition of a catalyst.\textsuperscript{12,30} There was therefore interest in evaluating the reaction of amines with trichloroacetimidates with and without the presence of a Brønsted acid catalyst, as this could provide a new method for the formation of these valuable systems.

**Results and Discussion**

Research into this transformation begun by optimizing conditions for the alkylation of 2,5-dichloroaniline \textbf{2.2} with 1-phenethyltrichloroacetimidate \textbf{2.1} (Table \textbf{2.1}). Aniline \textbf{2.2} was chosen because it is readily available, inexpensive and easy to handle. Imidate \textbf{2.1}\textsuperscript{31} was used as it is prepared from the readily available 1-phenethylalcohol. No reaction between the aniline and the imidate was observed in control reactions without the use of an acid catalyst (entries 1 and 2). The use of BF$_3$ˑOEt$_2$ as a Lewis acid catalyst resulted in the formation of desired product \textbf{2.3} in 33\% yield (entry 3). In this case, the low yield of the product was likely the result of the formation of a number of side products including the N-dialkylation product. The imidate was used as the limiting reagent in an attempt to improve the reactions yield (entry 4). Although the yield improved to 68\%, a number of side products including the dialkylation product were observed in a $^1$H NMR spectrum of the crude material and purification by silica gel chromatography was difficult. The observed polyalkylation may be especially problematic for less encumbered trichloroacetimidates. In order to favor monoalkylation, it was hypothesized that greater selectivity may be achieved using a weaker Brønsted acid as a catalyst, which may minimize dialkylation as the protonated alkylaniline should be less acidic than the protonated unsubstituted aniline. Use of diphenylphosphoric acid as a catalyst was therefore explored, producing the desired monoalkylation product with 31\% yield (entry 5). Although the yield was
low, we were pleased to note that only the desired product 2.3 and unreacted starting material appeared to remain in the reaction mixture, with no dialkylation product being observed. A number of other Brønsted acid catalysts were evaluated to build on this result. Dibenzyl phosphate failed to produce any of the desired product (entry 6). The acids PPTS and DNBSA provided yields of 91% and 90% respectively (entries 7 and 8). Racemic camphorsulfonic acid (CSA) was also used and the desired product was isolated with an excellent yield of 97% (entry 9). When 2.5 mol% of the catalyst CSA was used the yield was reduced to 22% (entry 10). The amount of imidate was also increased to see if the dialkylation product could be obtained selectively. Interestingly, no dialkylation product was observed by $^1$H NMR and 82% yield of the desired product was recovered with 2.4 equiv of imidate and (±)-CSA (entry 11). Overall, the reaction conditions from entry 9 gave us the best result so these conditions were used in further studies.
Table 2.1

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\(^{a}\) Reaction was refluxed in toluene

With conditions for the monoalkylation of anilines using trichloroacetimidates in hand, the focus shifted to testing the scope of the reaction with various anilines (Table 2.2). Aniline was monosubstituted with imidate 2.1 with a yield of 76% (entry 1). Aryl halides were well tolerated under the reaction conditions with many aryl halide-containing anilines being successfully alkylated (entries 2-3, 5-8, 10-11). Electron poor anilines performed best under the tested conditions with yields ranging from 94%-99% (entries 8-12). This is notable and useful because electron deficient anilines are often poorly reactive substrates for reductive amination as formation of the key imine intermediate is slow.\(^{32,33}\) More moderate yields were obtained with electron rich anilines providing yields of 70% and 74% (entries 13-14). Some reactions which worked poorly were improved upon heating in refluxing toluene (entries 3-4). Sulfides and nitro...
containing compounds (entries 9 and 13) were tolerated under the reaction conditions. N-
Substituted anilines participated in the reaction readily with N-methyl aniline and indoline
providing the corresponding tri-substituted anilines 2.23 and 2.22 in yields of 84% and 74%
respectively (entries 14, 15). Sterics also appeared to play a role in the reaction as the presence
of two ortho bromides effectively stopped the reaction (entry 17). On the other hand,
incorporation of a single ortho substituent was well tolerated with the reaction (entries 5-11).
Due to the success of anilines we attempted to expand the scope of the reaction by using the
amine morpholine as a nucleophile (entry 16) however no reaction occurred under these
conditions. Even heating the reaction in toluene at reflux with (±)-CSA as a catalyst resulted in
no formation of the desired substituted morpholine. This result may be due to the less acidic
ammonium salt formed from the morpholine, which is not acidic enough to activate the imidate
by protonation, resulting in no reaction. In any case, alkylation of various anilines using imidate
2.1 proceeded well for a number of electron rich and electron deficient anilines.
Table 2.2

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\(^a\)Reaction performed in toluene at reflux

There was also interest in evaluating the scope of the reaction with respect to the imidate and a study was undertaken to investigate this aspect of the substrate scope (Table 2.3). This
investigation found that unhindered benzylic imidates were effective and well tolerated electrophiles in these N-alkylation reactions (entries 1-4). The electron-poor 4-cyanobenzyl imidate 2.28 was the only benzylic imidate to give poor conversion (entry 4). In this case heating the reaction to reflux was necessary and provided the desired product 2.33 with a yield of (43%), as no product could be observed at room temperature. Likewise secondary benzylic imidates provided good yields and were well tolerated (entries 5-7, 9). Allylic imidates were also successfully employed as alkylating reagents under the reaction conditions providing the corresponding monoalkylated anilines in yields of 77-79% (entries 8-9). The tertiary imidate 2.42 provided the corresponding product 2.43 in low yield of 42% (entry 10). The lower yield in this case was attributed to steric effects. Similarly, the tert-butyl-2,2,2-trichloroacetimidate 2.44 gave a lower yield of the corresponding monosubstituted tert-butyl aniline 2.45. Apparently, the Brønsted acid catalyzed conditions are more mild than the Lewis acid conditions which have been employed by other groups for less sterically hindered aniline alkylation with tertiary trichloroacetimidates.\textsuperscript{14-17, 34} Furthermore, most reactions between anilines and tert-butyl-2,2,2-trichloroacetimidate 2.44 require a large excess of imidate (2-5 equivalents). The observed results are consistent with research done by Cran and coworkers that utilized the copper triflate as a catalyst for the alkylation of anilines with excess tert-butyl-2,2,2-trichloroacetimidate in warm nitromethane solvent.\textsuperscript{18} These conditions were highly optimized to obtain high yields with this imidate. The primary imidate 2.46 was also evaluated, and none of the desired product 2.47 could be detected during the reaction even in refluxing toluene (entry 12). Alternatively, the phthalimidomethyl imidate 2.48 was used successfully as an alkylating agent and provided the corresponding product 2.49 in excellent yield (74%, entry 13). During this investigation it was also noted that these reactions seemed to favor substitution over elimination. This property
might be synthetically useful for alkylation of anilines with electrophiles that are normally prone to elimination. To further investigate this preference for substitution, the homopropargyl imidate 2.50 was synthesized and subjected to the optimized reaction conditions. Homopropargyl imidate 2.50 is known to be problematic with regards to elimination when the corresponding sulfonate ester is subjected to nucleophiles, as the electron withdrawing alkyne makes the β-proton more acidic. Alkylation of 2,5-dichloroaniline using homopropargyl imidate 2.50 resulted in an impressive 63% yield of the desired substitution product. Although some elimination products were observed in the crude ¹H NMR, the peaks corresponding to these products were contaminated with other minor impurities which made determination of the relevant ratios difficult. These impurities could not be isolated due to their extremely nonpolar nature.
Given the success of the imidate N-alkylation methodology, the extension to a one-pot Brønsted acid catalyzed protocol for monoalkylating anilines starting from the alcohol using the
trichloroacetimidate as an intermediate was attempted. This protocol would avoid having to isolate and purify the imidate intermediate, and allow for the direct substitution of alcohols with anilines. Typically, the direct alkylation of anilines using alcohols requires the use of transition metal catalysts and high temperatures.\textsuperscript{35-42} A direct procedure utilizing an imidate intermediate could avoid these harsh conditions. Experiments began by taking 1-phenethyl alcohol and treating with trichloroacetonitrile (TCAN) and 10 mol % DBU catalyst followed by addition of N-methylaniline and 20 mol % of (±)-CSA. This method proved to be successful and several substituted anilines were synthesized using this method (Table 2.4). In several cases the yields for the single-pot procedure were higher than the two-step protocol. N-Substituted anilines (compound 2.23), electron poor anilines (compounds 2.20, 2.3, 2.35, 2.27, 2.8), and benzyl imidates (entries 2.27, 2.52) were all tolerated under these reaction conditions. Along with the synthesis of several substituted anilines, the lipoxygenase inhibitor onosmin B 2.8 was also synthesized in 85% yield using this methodology.\textsuperscript{5} Similarly the piperonal derivative 2.52 was prepared using this methodology in 81% yield. This reaction represents a formal synthesis of 5,6-dihydrobicoline (Figure 2.1), as this system has been cyclized previously to the natural product in a single step.\textsuperscript{43, 44}
With conditions for the one-pot alkylation of anilines with trichloroacetimidates demonstrated, work began on investigating the mechanism of the N-substitution reaction. The propensity of aniline substitution to displace the enantiomerically enriched trichloroacetimidate R-(2.1) (Scheme 2.1) was investigated. Direct alkylation of a chiral imidate resulting in a chiral aniline with either retained or inverted chemistry would be synthetically useful as the chiral amine products are quite valuable. Alternatively, racemization during the substitution may implicate a cation as an intermediate in the substitution reaction. Relevant to this experiment, the substitution of enantiomerically pure imidates using oxygen nucleophiles frequently provides enantiomeric mixtures as products. Reaction of imidate (R)-2.1 with 4-chloroaniline using (±)-CSA as an acid catalyst provided the desired substituted aniline 2.11 in 85% yield. Analysis of
the product by chiral HPLC revealed that the product was a 35:65 mixture of enantiomers. Comparison to a known literature example showed that a majority of the S stereoisomer was recovered. The significant racemization observed is likely due to the formation of a carbocation intermediate. The lack of complete racemization may be attributed to ion pairing occurring during the substitution reaction. As one of the ions (the camphorsulfonate) is chiral, it is interesting to speculate on the role of the chirality on the outcome of this transformation, as a chiral ion pair may lead to chiral induction in the reaction product. The use of chiral CSA would be unlikely to control the enantiomeric ratio of product, however, because the chirality of CSA is far from the sulfonate which takes part in the ion pairing near the forming chirality center in the transition state. In the future, the use of chiral CSA and other chiral acids to catalyze the alkylation of anilines using chiral imidates may be investigated to determine if any significant change in enantioselectivity is observed, or if the enantioselectivity of the reaction can be controlled by these effects.

Scheme 2.1

The results of the chiral HPLC analysis combined with the method's failure when ethyl trichloroacetimidate is employed are consistent with an S_{N}1 type mechanism that proceeds through a carbocation intermediate. Although some degree of stereocontrol was observed it should be noted that scalemic mixtures can be formed from cationic processes through ion-pairing. A proposed mechanism for the reaction is show in figure 2.2. Protonation of the aniline and imidate are possible through a reversible process, as the pKa of the aniline and the
imidate are likely similar. Loss of the trichloroacetamide from the protonated imidate can lead to a carbocation intermediate which is then trapped by the aniline. This process also results in the formation of the trichloroacetamide byproduct which is always observed in the crude reaction mixture. A final proton transfer produces the product and regenerates the protonated aniline to complete turnover of the catalytic cycle. The ammonium salts of the more basic amine substrates such as morpholine may not be strong enough to protonate the trichloroacetimidate, which may explain the low reactivity of these compounds.

![Proposed Mechanism of Aniline Substitution](image)

**Figure 2.2: Proposed Mechanism of Aniline Substitution**

**Conclusion**

A procedure for monosubstitution of anilines using the Brønsted acid catalyst (±)-CSA and trichloroacetimidate electrophiles is described. The alkylation is successful in a variety of anilines and is most effective with electron deficient anilines. Electron rich anilines are more troublesome substrates for this reaction as Friedal-Crafts side products are occasionally
observed. Basic alkyl amines such as morpholine fail to react and are not compatible under the
described conditions. Primary and secondary benzyl and allylic imidates were found to be
reactive and a variety of substituted anilines are synthesized using these imidates. A one step
procedure where the imidate is formed in situ and displaced by the aniline was also developed.
The protocol's usefulness was demonstrated through the synthesis of lipoxygenase inhibitor
onosmin B and a formal synthesis of 5,6-dihydrobicolorine. Mechanistic studies appear to
implicate a cationic pathway for the alkylation reaction.

Experimental Section

General Information. All anhydrous reactions were run under a positive pressure of argon or
nitrogen. All syringes, needles, and reaction flasks required for anhydrous reactions were dried in
an oven and cooled under an N₂ atmosphere or in a desiccator. Dichloromethane and THF were
dried by passage through an alumina column following the method of Grubbs (Pangborn, A. B.;
Triethylamine was distilled from CaH₂. All other reagents and solvents were purchased from
commercial sources and used without further purification.

Analysis and Purification. Analytical thin layer chromatography (TLC) was performed on
precoated glass backed plates (silica gel 60 F₂₅₄; 0.25 mm thickness). The TLC plates were
visualized by UV illumination and by staining. Solvents for chromatography are listed as
volume:volume ratios. Flash column chromatography was carried out on silica gel (40-63 μm).
Melting points were recorded using an electrothermal melting point apparatus and are
uncorrected. Optical rotations were measured at the sodium D line (589 nm) on a digital polarimeter and reported in reagent grade solvent. Enantiopurity was determined using chiral phase HPLC with an OD-H (0.46 × 25 cm) column. Elemental analyses were performed on an elemental analyzer with a thermal conductivity detector and 2 meter GC column maintained at 50 °C.

**Identity.** Proton (\(^1\)H NMR) and carbon (\(^{13}\)C NMR) nuclear magnetic resonance spectra were recorded at 300 or 400 MHz and 75 or 100 MHz respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Coupling constants are reported in hertz (Hz). The spectra were recorded in solutions of deuterated chloroform (CDCl\(_3\)), with residual chloroform (d 7.26 ppm for \(^1\)H NMR, δ 77.23 ppm for \(^{13}\)C NMR) as the internal reference. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; sep = septet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets; tt = triplet of triplets; qd = quartet of doublets; ddd = doublet of doublet of doublets; br s = broad singlet). Where applicable, the number of protons attached to the corresponding carbon atom was determined by DEPT 135 NMR. Infrared (IR) spectra were obtained as thin films on NaCl plates by dissolving the compound in CH\(_2\)Cl\(_2\) followed by evaporation or as KBr pellets.

**Representative Procedure A: Reaction of Imidate 5 with 2,5-Dichloroaniline 2.3.**

1-Phenethyl imidate 2.1 (0.30 g, 1.13 mmol) and 2,5-dichloroaniline 2.2 (0.15 g, 0.94 mmol) were added to a flame dried round bottom flask under argon. Dry dichloromethane (4 mL) was added followed by racemic camphorsulfonic acid (0.03 g, 0.11 mmol). The reaction was stirred at room temperature for 24h. After triethylamine (0.5 mL) was added, the reaction mixture was
preadsorbed on silica gel and purified by silica gel chromatography using 19% dichloromethane/80% hexanes/1% triethylamine to give 0.24 g (97%) of substituted aniline 2.3 as a yellow oil.

**Representative Procedure B: Single Flask Synthesis of Monosubstituted Aniline 2.3.**

1-Phenethyl alcohol (0.33 g, 2.73 mmol) and trichloroacetonitrile (0.33 mL, 3.27 mmol) were added to a flame dried round bottom flask under argon. Dry dichloromethane (4 mL) was added followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.04 g, 0.27 mmol). The reaction was stirred at room temperature and monitored for disappearance of the alcohol by TLC (4 hours). 2,5-Dichloroaniline 2.2 (0.37 g, 2.28 mmol) was added followed by camphorsulfonic acid (0.13 g, 0.54 mmol). The reaction was allowed to stir at room temperature for 24 h. Triethylamine (0.5 mL) was then added, the reaction mixture was preadsorbed on silica gel and purified by silica gel chromatography using 19% dichloromethane/80% hexanes/1% triethylamine to provide 0.55 g (90%) of substituted aniline 2.3 as a yellow oil.

2,5-Dichloro-N-(1-phenylethyl)aniline (2.3)


Prepared using procedure A (0.24 g, 97%) from 2,5-dichloroaniline 6 and the known imidate 2.1 or procedure B (0.55 g, 90%) from 1-phenethyl alcohol, purified using silica gel chromatography (4% ethyl acetate/ 95% hexanes/1% triethylamine).
2.3. Yellow oil (0.24 g, 97%); TLC Rf = 0.71 (19% dichloromethane/80% hexanes/1% triethylamine); 1H NMR (300 MHz, CDCl3) δ 7.35-7.25 (m, 5H), 7.14 (d, J = 8.4 Hz, 1H), 6.54 (dd, J = 8.4, 2.4 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 4.49 (q, J = 6.6 Hz, 1H), 1.57 (d, J = 6.6 Hz, 3H); 13C NMR (300 MHz, CDCl3) δ 144.0, 133.6, 129.8, 129.1, 128.5, 127.6, 125.9, 117.3, 117.2, 112.4, 53.5, 25.1.

N-(1-Phenylethyl)aniline (2.10)


Prepared using procedure A from aniline and the known imidate 2.1,31 purified using silica gel chromatography (95% hexanes/4% ethyl acetate/1% triethylamine).

2.10. Yellow oil (0.14 g, 76%); TLC Rf = 0.59 (95% hexanes/4% ethyl acetate/1% triethylamine); 1H NMR (300 MHz, CDCl3) δ 7.38-7.28 (m, 4H), 7.25-7.24 (m, 1H), 7.12-7.06 (m, 2H), 6.66 (t, J = 7.8 Hz, 1H), 6.54 (d, J = 7.5Hz, 2H), 4.48 (q, J = 6.9 Hz, 1H), 1.53 (d, J = 6.9 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ 147.5, 145.4, 129.4, 128.9, 127.1, 126.1, 117.5, 113.6, 53.7, 25.3.

4-Chloro-N-(1-phenylethyl)aniline (2.11)

Prepared using procedure A from 4-chloroaniline and the known imidate 2.1, purified using silica gel chromatography (4% ethyl acetate/95% hexanes/1% triethylamine).

2.11. Reddish crystals (0.19 g, 89%); mp = 58-60 °C; TLC R_f = 0.43 (5% ethyl acetate/95% hexanes); ^1^H NMR (300 MHz, CDCl_3) δ 7.33-7.19 (m, 5H), 7.00 (dt, J = 9.9, 3.0 Hz, 2H), 6.40 (dt, J = 10.2, 3.3 Hz, 2H), 4.42 (q, J = 6.9 Hz, 1H), 4.04 (br s, 1H), 1.49 (d, J = 6.6 Hz, 3H); ^13^C NMR (75 MHz, CDCl_3) δ 145.8, 144.7, 128.9, 128.7, 127.1, 125.8, 121.9, 114.4, 53.6, 25.0.

When (R)-5 (>98:2 er) was used an 85% yield (0.061 g) of reddish crystals was obtained as a 35:65 ratio of R:S enantiomers. Chiral HPLC analysis: Chiralcel OD (heptane/i-PrOH = 95/5, 1.0 mL/min, 254 nm, 25 °C): t_minor = 7.52 min, t_major = 9.75 min, 35:65 ratio, 30% ee.

4-Bromo-N-(1-phenylethyl)aniline (2.12)


Prepared using procedure A from 4-bromoaniline and the known imidate 2.1, purified using silica gel chromatography (49% dichloromethane/50% hexanes/1% triethylamine).

2.12. Off-white solid (0.18 g, 70%); mp = 68-71 °C; TLC R_f = 0.71 (49% dichloromethane/50% hexanes/1% triethylamine); ^1^H NMR (400 MHz, CDCl_3) δ 7.33-7.28 (m, 4H), 7.24-7.21 (m, 1H), 7.14 (dt, J = 9.6, 3.2 Hz, 2H), 6.36 (dt, J = 10.0, 2.4 Hz, 2H), 4.43 (q, J = 6.8 Hz, 1H), 4.06 (br s, 1H) 1.50 (d, J = 6.4 Hz, 3H); ^13^C NMR (75 MHz, CDCl_3) δ 146.3, 144.7, 132.0, 128.9, 127.2, 125.9, 115.0, 109.0, 53.6, 25.1.
2-Bromo-N-(1-phenylethyl)aniline (2.16)


Prepared using procedure *A* from 2-bromoaniline and the known imidate 2.1,31 purified using silica gel (19% dichloromethane/80% hexanes/1% triethylamine).

**2.16.** Clear colorless oil (0.18 g, 70%); TLC R_f = 0.50 (19% dichloromethane/80% hexanes/1% triethylamine); {\textsuperscript{1}H} NMR (400 MHz, CDCl\textsubscript{3}) δ 7.50 (dd, J = 8.0, 1.6 Hz, 1H), 7.44-7.38 (m, 4H), 7.33-7.29 (m, 1H), 7.07 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H), 6.58 (ddd, J = 7.6, 7.2, 1.6 Hz, 1H), 6.48 (dd, J = 8.4, 1.2 Hz, 1H), 4.81 (br d, J = 3.6 Hz, 1H), 4.60 (p, J = 6.8 Hz, 1H), 1.65 (d, J = 6.8 Hz, 3H); {\textsuperscript{13}C} NMR (100 MHz, CDCl\textsubscript{3}) δ 144.6, 144.1, 132.3, 128.9, 128.4, 127.1, 125.8, 117.9, 112.8, 109.7, 53.6, 25.3.

N-(1-Phenylethyl)-3,5-bis(trifluoromethyl)aniline (2.20)


Prepared using procedure *A* (0.29 g, 98%) from 3,5-bis(trifluoromethyl)aniline and the known imidate 2.1,31 or procedure *B* (0.75 g, 99%) from 1-phenethyl alcohol, purified using silica gel chromatography (19% dichloromethane/80% hexanes/1% triethylamine).
2.20. White solid (0.29 g, 98%); mp = 56-57 °C; TLC Rf = 0.47 (19% dichloromethane/80% hexanes/1% triethylamine); 1H NMR (400 MHz, CDCl3) δ 7.39-7.37 (m, 4H), 7.32-7.29 (m, 1H), 7.15 (s, 1H), 6.91 (s, 2H), 4.57 (q, J = 6.8 Hz, 1H), 4.51 (br s, 1H), 1.59 (d, J = 6.8 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ 147.9, 143.6, 132.2 (q, J = 33.0 Hz), 129.2, 127.7, 125.6, 123.8 (q, J = 271.0 Hz), 112.6 (q, J = 3.0 Hz), 110.2 (sep, J = 3.0 Hz), 53.6, 24.6.

2-Nitro-N-(1-phenylethyl)aniline (2.18)

Prepared using procedure A from 2-nitroaniline and the known imidate 2.1, 31 purified using silica gel chromatography (49% dichloromethane/50% hexanes/1% triethylamine).

2.18. Yellow oil (0.24 g, 94%); TLC Rf = 0.31 (50% dichloromethane/50% hexanes); IR (thin film) 3380, 3086, 3029, 2972, 2929, 2873, 1618 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 8.41 (br s, 1H), 8.17 (dd, J = 8.4, 1.5 Hz, 1H), 7.35-7.25 (m, 6H), 6.64-6.57 (m, 2H), 4.69 (p, J = 6.6 Hz, 1H), 1.65 (d, J = 6.9 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ 144.6, 143.7, 136.1, 132.3, 129.1, 127.5, 126.8, 125.7, 115.7, 115.3, 53.3, 25.1. Anal. Calcd for C14H14N2O2: C, 69.41.; H, 5.82; N, 11.56. Found: C, 69.15; H, 5.90; N, 11.16.

4-(Methylthio)-N-(1-phenylethyl)aniline (2.21)

Prepared using procedure A from 4-(methylthio)aniline and the known imidate 2.1,31 purified using silica gel chromatography (5% ethyl acetate/94% hexanes/1% triethylamine).

2.21. Orange oil (0.17g, 70%); TLC Rf = 0.31 (5% ethyl acetate/94% hexanes/1% triethylamine); IR (thin film) 3411, 3082, 3061, 3026, 2979, 2919, 2867, 1598 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.29 (m, 4H), 7.24-7.23 (m, 1H), 7.12 (d, J = 8.4 Hz, 2H), 6.46 (br d, J = 7.6 Hz, 2H), 4.46 (q, J = 6.8 Hz, 1H), 2.36 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 146.2, 145.0, 131.4, 128.8, 127.1, 125.9, 124.2, 114.0, 53.6, 25.0, 19.1.

4-Ethyl-N-(1-phenylethyl)aniline (2.13)


Prepared using procedure A from 4-ethylaniline and the known imidate 2.1,31 purified using silica gel chromatography (1% dichloromethane/98% hexanes/1% triethylamine).

2.13. Orange oil (0.10 g, 47%); TLC Rf = 0.74 (1% dichloromethane/98% hexanes/1% triethylamine); ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.22 (m, 5H), 6.94-6.92 (m, 2H), 6.47 (dt, J = 9.0, 2.4 Hz, 2H), 4.45 (q, J = 6.9 Hz, 1H), 2.49 (q, J = 7.5 Hz, 2H), 1.51 (d, J = 6.6 Hz, 3H), 1.15 (t, J = 7.5, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 145.7, 145.5, 133.3, 128.9, 128.7, 127.1, 126.1, 113.6, 54.0, 28.1, 25.3, 16.2.

2-Fluoro-4-methyl-N-(1-phenylethyl)aniline (2.14)
Prepared using procedure A from 2-fluoro-4-methylaniline and the known imidate 2.1, purified using silica gel chromatography (5% ethyl acetate/94% hexanes/1% triethylamine).

2.14. Clear colorless oil (0.17 g, 80%); TLC \( R_f = 0.59 \) (5% ethyl acetate/94% hexanes/1% triethylamine); IR (thin film) 3431, 3061, 3031, 2968, 2925, 1658 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.38-7.28 (m, 4H), 7.25-7.19 (m, 1H), 6.79 (dd, \( J = 12.3, 1.5 \) Hz, 1H), 6.64-6.61 (m, 1H), 6.40 (br s, 1H), 4.48 (q, \( J = 6.6 \) Hz, 1H), 2.18 (s, 3H), 1.57 (d, \( J = 6.6 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 151.6 (d, \( J = 236.6 \) Hz), 145.2, 133.4 (d, \( J = 11.8 \) Hz), 128.9, 127.2, 126.7 (d, \( J = 6.6 \) Hz), 126.0, 124.9 (d, \( J = 3.1 \) Hz), 115.3 (d, \( J = 18.2 \) Hz), 113.5 (d, \( J = 3.4 \) Hz), 53.8, 25.3, 20.6 (d, \( J = 1.1 \) Hz). Anal. Calcd for C\(_{15}\)H\(_{16}\)FN: C, 78.57; H, 7.03; N, 6.11. Found: C, 78.31; H, 7.27; N, 5.76.

2-Chloro-N-(1-phenylethyl)-5-(trifluoromethyl)aniline (2.19)

Prepared using procedure A from 2-chloro-5-(trifluoromethyl)aniline and the known imidate 2.1, purified using silica gel chromatography (5% ethyl acetate/94% hexanes/1% triethylamine).

2.19. Yellow oil (0.28 g, 98%); TLC \( R_f = 0.57 \) (5% ethyl acetate/94% hexanes/1% triethylamine); IR (thin film) 3428, 3087, 3066, 3031, 2974, 2930, 2873, 1603 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.34-7.25 (m, 6H), 6.80 (ddd, \( J = 8.1, 2.1, 0.6 \) Hz, 1H), 6.64 (d, \( J = 1.8 \) Hz, 1H), 4.55 (q, \( J = 6.6 \) Hz, 1H), 1.60 (d, \( J = 6.6 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 143.6, 143.3, 130.1 (q, \( J = 32.0 \) Hz), 129.3, 129.0, 127.5, 125.7, 124.0 (q, \( J = 271.0 \) Hz), 122.2, 113.7 (q, \( J = 4.0 \) Hz), 108.8 (q, \( J = 4.0 \) Hz), 53.4, 24.7. Anal. Calcd for C\(_{15}\)H\(_{13}\)ClF\(_3\)N: C, 60.11; H, 4.37; N, 4.67. Found: C, 60.27; H, 4.36; N, 4.55.
2-Chloro-4-fluoro-N-(1-phenylethyl)aniline (2.17)

Prepared using procedure A from 2-chloro-4-fluoroaniline and the known imidate 2.1,\textsuperscript{31} purified using silica gel chromatography (19% dichloromethane/80% hexanes/1% triethylamine).

2.17. Dark oil (0.27 g, 99%); TLC $R_f = 0.52$ (19% dichloromethane/80% hexanes/1% triethylamine); IR (thin film) 3424, 3064, 3029, 2971, 2929, 2871, 1599 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.33-7.28 (m, 4H), 7.25-7.22 (m, 1H), 7.03 (dd, $J$ = 8.4, 3.0 Hz, 1H), 6.69 (ddd, $J$ = 9.0, 8.1, 2.7 Hz, 1H), 6.32 (dd, $J$ = 9.0, 5.7 Hz, 1H), 4.52 (br s, 1H), 4.47 (q, $J$ = 6.9 Hz, 1H), 1.57 (d, $J$ = 6.9 Hz, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) $\delta$ 154.4 (d, $J$ = 236.4 Hz) 144.5, 139.9 (d, $J$ = 2.2 Hz), 128.9, 127.2, 125.8, 118.8 (d, $J$ = 10.3 Hz), 116.3 (d, $J$ = 25.8 Hz), 114.3 (d, $J$ = 21.5 Hz), 112.8 (d, $J$ = 8.0 Hz), 53.9, 25.3. Anal. Calcd for C\textsubscript{14}H\textsubscript{13}ClFN: C, 67.34; H, 5.25; N, 5.61. Found: C, 67.39; H, 4.97; N, 5.53.

2-Chloro-4-methyl-N-(1-phenylethyl)aniline (2.15)


Prepared using procedure A from 2-chloro-4-methylaniline and the known imidate 2.15,\textsuperscript{31} purified using silica gel chromatography (5% dichloromethane/94% hexanes/1% triethylamine).

2.15. Yellow oil (0.22 g, 94%); TLC $R_f = 0.56$ (5% dichloromethane/94% hexanes/1% triethylamine); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.35-7.19 (m, 5H), 7.07 (dd, $J$ = 2.1, 0.9 Hz, 1H), 6.76 (dd, $J$ = 8.1, 1.8, 0.6 Hz, 1H), 6.35 (d, $J$ = 8.1 Hz, 1H), 4.51 (q, $J$ = 6.6 Hz, 1H), 2.16 (s,
3H), 1.58 (d, J = 6.6 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 145.0, 140.8, 129.6, 128.9, 128.4, 127.2, 127.0, 126.0, 119.0, 112.9, 53.8, 25.4, 20.3.

N-Methyl-N-(1-phenylethyl)aniline (2.23)


Prepared using procedure A (0.17 g, 84%) from N-methylaniline and the known imidate 2.1, or procedure B (0.36 g, 82%) from 1-phenethyl alcohol, purified using silica gel chromatography (4% ethyl acetate/95% hexanes /1% triethylamine).

2.23. Yellow oil (0.17 g, 84%); TLC $R_f = 0.32$ (2% ethyl acetate/97% hexane /1% triethylamine); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.34-7.22 (m, 7H), 6.84 (d, J = 8.1 Hz, 2H), 6.73 (t, J = 7.2 Hz, 1H), 5.13 (q, J = 6.9 Hz, 1H), 2.68 (s, 3H), 1.55 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 150.4, 143.0, 129.4, 128.6, 127.1, 127.0, 116.9, 113.3, 56.7, 32.0, 16.5.

1-(1-Phenylethyl)indoline (2.22)


Prepared using procedure A from indoline the known imidate 2.1, purified using silica gel chromatography (5% ethyl acetate/94% hexanes/1% triethylamine).

2.22. Dark oil (0.18 g, 74%); TLC $R_f = 0.52$ (5% ethyl acetate/94% hexanes/1% triethylamine); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.42-7.22 (m, 5H), 7.05 (dd, J = 7.2, 0.9 Hz, 1H), 6.98 (t, J = 7.5
Hz, 1H), 6.60 (t, J = 6.9 Hz, 1H), 6.35 (d, J = 7.5 Hz, 1H), 4.71 (q, J = 7.2 Hz, 1H), 3.44-3.28 (m, 2H), 2.94 (t, J = 8.7 Hz, 2H), 1.53 (d, J = 6.9 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ 151.7, 143.2, 130.5, 128.7, 127.5, 127.4, 127.2, 124.7, 117.3, 107.6, 54.9, 48.3, 28.5, 16.9.

N-Benzyl-2,5-dichloroaniline (2.27)

Prepared using procedure A (0.23 g, 92%) from 2,5-dichloroaniline 2.2 and the commercially available benzyl-2,2,2-trichloroacetimidate 2.26 or procedure B (0.37 g, 64%) from benzyl alcohol, purified using silica gel chromatography (19% dichloromethane/80% hexanes/1% triethylamine).

2.27. Clear colorless oil (0.23 g, 92%); TLC Rf = 0.50 (20% dichloromethane/80% hexanes); IR (thin film) 3422, 3064, 3030, 2852, 1595 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 7.39-7.29 (m, 5H), 7.18-7.15 (m, 1H), 6.62-6.59 (m, 2H), 4.76 (br s, 1H), 4.36 (s, 2H); 13C NMR (75 MHz, CDCl3) δ 144.8, 138.1, 133.8, 129.9, 129.1, 127.8, 127.6, 117.5, 117.4, 111.5, 48.0. Anal. Calcd for C13H11Cl2N: C, 61.93; H, 4.40; N, 5.56. Found: C, 62.26; H, 4.26; N, 5.51.

2,5-Dichloro-N-(4-methoxybenzyl)aniline (2.29)

Prepared using procedure A from 2,5-dichloroaniline 2.2 and the commercially available 4-methoxybenzyl-2,2,2-trichloroacetimidate 2.28, purified with silica gel chromatography (5% ethyl acetate/94% hexanes/1% triethylamine).
2.29. Yellow oil (0.22 g, 91%); TLC R<sub>f</sub> = 0.42 (2% ethyl acetate/97% hexanes/1% triethylamine); IR (thin film) 3422, 3071, 3003, 2958, 2836, 1595 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.26 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.62-6.58 (m, 2H), 4.66 (br s, 1H), 4.27 (s, 2H), 3.80 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 159.3, 144.9, 133.8, 130.1, 129.9, 128.9, 117.4, 117.2, 114.4, 111.5, 55.5, 47.5. Anal. Calcd for C<sub>14</sub>H<sub>13</sub>Cl<sub>2</sub>NO: C, 59.59; H, 4.64; N, 4.96. Found: C, 59.61; H, 4.94; N, 4.84.

2.31. Yellow oil (0.20 g, 80%); TLC R<sub>f</sub> = 0.29 (20% dichloromethane/80% hexanes); IR (thin film) 3436, 3107, 3078, 3010, 2915, 1593 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ 7.17 (d, J = 8.4 Hz, 1H), 7.04 (s, 1H), 6.82 (s, 1H), 6.62 (dd, J = 8.4, 2.4 Hz, 1H), 6.51 (d, J = 2.1 Hz, 1H), 5.97 (s, 2H), 4.84 (t, J = 5.4 Hz, 1H), 4.33 (d, J = 5.7Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), δ 147.82, 147.76, 144.2, 133.7, 130.0, 129.8, 117.5, 117.4, 113.5, 113.0, 111.4, 108.7, 101.9, 47.8. Anal. Calcd for C<sub>14</sub>H<sub>10</sub>ONBrCl<sub>2</sub>: C, 44.83; H, 2.69; N, 3.73. Found: C, 45.10; H, 2.74; N, 3.94.

N-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-2,5-dichloroaniline (2.31)

Prepared using procedure A from 2,5-dichloroaniline 2.2 and the known imidate 2.30,<sup>48</sup> purified using silica gel chromatography (19% dichloromethane/80% hexanes/1% triethylamine).

2.33. Prepared using procedure A in refluxing toluene from 2,5-dichloroaniline 6 and the known imidate 2.32,<sup>49</sup> purified using silica gel chromatography (9% ethyl acetate/90% hexanes/1% triethylamine).
**2.33.** White solid (0.11 g, 43%); mp = 114-115 °C; TLC Rₖ = 0.59 (50% dichloromethane/ 50% hexanes); IR (thin film) 3409, 2916, 2224, 1595, 1567 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, J = 6.4, 1.6 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.8 Hz, 1H), 6.63 (dd, J = 8.4, 2.0 Hz, 1H), 6.45 (d, J = 2.0 Hz, 1H), 4.92 (t, J = 5.6 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 144.0, 143.7, 133.7, 132.7, 130.0, 127.6, 118.7, 117.8, 117.5, 111.4, 111.3, 47.2. Anal. Calcd for C₁₄H₁₀Cl₂N₂: C, 60.67; H, 3.64; N, 10.11. Found: C, 60.32; H, 3.58; N, 9.80.

![Structure of White solid](image)

**N-Benzhydryl-2,5-dichloroaniline (2.35)**

Prepared using procedure A (0.28 g, 87%) from 2,5-dichloroaniline 2.2 and the known imidate 2.34 and procedure B (0.39 g, 88%) from diphenylmethanol, purified using silica gel chromatography (10% dichloromethane/89% hexanes/1% triethylamine).

**2.35.** Clear colorless oil (0.28 g, 87%); TLC Rₖ = 0.59 (10% dichloromethane/89% hexanes/1% triethylamine); IR (thin film) 3417, 3031, 2925, 1656, 1596 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.25 (m, 10H), 7.16 (d, J = 8.4 Hz, 1H), 6.59 (dd J = 8.4, 2.4 Hz, 1H), 6.44 (d, J = 2.1 Hz, 1H), 5.52 (s, 1H), 4.95 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 144.1, 141.9, 133.7, 129.9, 129.2, 128.7, 128.0, 127.6 117.7, 112.7, 62.7. Anal. Calcd for C₁₉H₁₅Cl₂N: C, 69.52; H, 4.61; N, 4.27. Found: C, 69.75; H, 4.62; N, 4.60.

![Structure of N-Benzhydryl-2,5-dichloroaniline](image)

**2,5-Dichloro-N-(1-(p-tolyl)ethyl)aniline (2.37)**
Prepared using procedure A from 2,5-dichloroaniline 2.2 and the known imidate 2.36, purified using silica gel chromatography (5% ethyl acetate/94% hexanes/1% triethylamine).

2.37. Clear colorless oil (0.17 g, 68%); TLC R\_f = 0.81 (5% ethyl acetate/95% hexanes); IR (thin film) 3422, 2968, 2923, 2867, 1594 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.23-7.20 (m, 2H), 7.16-7.12 (m, 3H), 6.53 (dd, J = 8.4, 2.4 Hz, 1H), 6.40 (d, J = 2.1 Hz, 1H), 4.72 (br s, 1H), 4.46 (q, J = 6.6 Hz, 1H), 2.33 (s, 3H), 1.55 (d, J = 6.6 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 143.9, 140.8, 136.9, 133.4, 129.6, 125.6, 117.1, 116.9, 112.2, 53.0, 24.9, 21.1 (One signal in the aromatic region was not resolved). Anal. Calcd for C\(_{15}\)H\(_{15}\)Cl\(_2\)N: C, 64.30; H, 5.40; N, 5.00. Found: C, 64.52; H, 5.20; N, 4.74.

![N-Allyl-2,5-dichloroaniline (2.39)](image)

Prepared using procedure A from 2,5-dichloroaniline 2.2 and the commercially available O-allyl 2,2,2-trichloroacetimidate 2.38, purified using silica gel chromatography (4% dichloromethane/94% hexanes/1% triethylamine).

2.39. Clear colorless oil (0.19 g, 77%); TLC R\_f = 0.24 (5% dichloromethane/95% hexanes); IR (thin film) 3426, 3086, 3013, 2985, 2926, 2850, 1645, 1595 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 7.16-7.13 (m, 1H), 6.61-6.58 (m, 2H), 5.94-5.87 (m, 1H), 5.32-5.20 (m, 2H), 4.52 (br s, 1H), 3.82 (d, J = 8.4 Hz, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ 144.6, 134.0, 133.6, 129.7, 117.3, 117.0, 116.8, 111.3, 45.9; Anal. Calcd for C\(_9\)H\(_9\)Cl\(_2\)N: C, 53.49; H, 4.49; N, 6.69. Found: C, 53.40; H, 4.89; N, 6.69.
2.5-Dichloro-N-(cyclohex-2-en-1-yl)aniline (2.41)

Prepared using procedure A from 2,5-dichloroaniline 2.2 and the known imidate 2.40,\(^5\) purified using silica gel chromatography (2% ethyl acetate/97% hexanes/1% triethylamine).

2.41. Orange oil (0.19 g, 79%); TLC \(R_f = 0.60\) (5% ethyl acetate/95% hexanes); IR (thin film) 3418, 3026, 2938, 2862, 1593 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.14\) (d, \(J = 8.4\) Hz, 1H), 6.66 (d, \(J = 2.4\) Hz, 1H), 6.57 (dd, \(J = 8.4, 2.4\) Hz, 1H), 5.94-5.88 (m, 1H), 5.75-5.70 (m, 1H), 4.36 (br d, \(J = 7.8\) Hz, 1H), 3.98 (br s, 1H), 2.09-2.05 (m, 2H), 1.96-1.89 (m, 1H), 1.77-1.63 (m, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 143.8, 133.6, 131.2, 129.9, 127.4, 117.3, 116.5, 111.3, 47.7, 28.6, 25.1, 19.5\); Anal. Calcd for C\(_{12}\)H\(_{13}\)Cl\(_2\)N: C, 59.52; H, 5.41; N, 5.78. Found: C, 59.38; H, 5.27; N, 5.45.

\[\text{Cl} \quad \text{HN} \quad \text{Cl} \]

2,5-Dichloro-N-(2-phenylpropan-2-yl)aniline (2.43)

Prepared using procedure A from 2,5-dichloroaniline 2.2 and the known imidate 2.42,\(^5\) purified using silica gel chromatography (9% dichloromethane/90% hexanes/1% triethylamine).

2.43. Clear colorless oil (0.22 g, 42%); TLC \(R_f = 0.58\) (10% dichloromethane/90% hexanes); IR (thin film) 3419, 3042, 3011, 2857, 1578 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.45-7.42\) (m, 2H), 7.34 (tt, \(J = 6.8, 1.6\) Hz, 2H), 7.25 (tt, \(J = 6.8, 1.6\) Hz, 1H), 7.12 (d, \(J = 8.4\) Hz, 1H), 6.48 (dd, \(J = 8.0, 2.4\) Hz, 1H), 6.06 (d, \(J = 2.4\) Hz, 1H), 4.84 (br s, 1H), 1.68 (s, 6H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 145.9, 142.7, 132.7, 129.6, 128.9, 126.9, 125.4, 118.0, 116.8, 114.4, 56.1, 30.5\); Anal. Calcd for C\(_{15}\)H\(_{15}\)Cl\(_2\)N: C, 64.30; H, 5.40; N, 5.00. Found: C, 63.95; H, 5.71; N, 4.70.

\[\text{Cl} \quad \text{HN} \quad \text{Cl} \]
N-(tert-Butyl)-2,5-dichloroaniline (2.45)
Prepared using procedure A from 2,5-dichloroaniline 2.2 and the commercially available tert-butyl 2,2,2-trichloroacetimidate 2.44 with 10 mol% BF₃·OEt₂, purified using silica gel chromatography (19% dichloromethane/80% hexanes/1% triethylamine).

2.45. Clear colorless oil (0.01 g, 5%); TLC Rᵣ = 0.45 (20% dichloromethane/80% hexanes); IR (thin film) 3416, 3086, 3060, 2981, 1504 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.14 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.56 (dd, J = 8.4, 2.4 Hz, 1H), 4.38 (br s, 1H), 1.40 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 143.6, 132.9, 131.8, 129.8, 118.6, 116.6, 113.8, 51.4, 29.6. Anal. Calcd for C₁₀H₁₃Cl₂N: C, 55.06; H, 6.01; N, 6.42. Found: C, 55.13; H, 6.35; N, 6.13.

2-((2,5-Dichlorophenyl)amino)methyl)isoindoline-1,3-dione (2.49)
Prepared using procedure A from 2,5-dichloroaniline 2.2 and the known imidate 2.48, purified using silica gel chromatography (20% ethyl acetate/79% hexanes/1% triethylamine).

2.49. White powder (0.24 g, 74%); mp = 200-201 °C; TLC Rᵣ = 0.83 (20% ethyl acetate/79% hexanes/1% triethylamine); IR (KBr) 3397, 3067, 1718, 1657 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.88-7.86 (m, 2H), 7.74-7.72 (m, 2H), 7.26 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.66 (dd, J = 8.4, 2.4 Hz, 1H), 5.47 (t, J = 7.6 Hz, 1H), 5.19 (d, J = 7.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 168.2, 142.0, 134.4, 133.8, 131.8, 130.1, 123.7, 119.0, 118.0, 112.4, 46.6. Anal. Calcd for C₁₅H₁₀Cl₂N₂O₂: C, 56.10; H, 3.14; N, 8.72. Found: C, 56.06; H, 3.33; N, 8.51.
2,5-Dichloro-N-(1,4-diphenylbut-3-yn-1-yl)aniline (2.51)

Prepared using procedure A from 2,5-dichloroaniline 2.2 and the known imidate 2.50,55 purified using silica gel chromatography (4% dichloromethane/ 95% hexanes/1% triethylamine).

2.51. Yellow solid (50 mg, 63%); mp = 86-88 °C; TLC Rf = 0.54 (10% ethyl acetate/90% hexanes); IR (KBr) 3380, 3114, 2989, 1594, 1504 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.27 (m, 10H), 7.15 (d, J = 8.4 Hz, 1H), 6.57 (dd, J = 8.4, 2.4 Hz, 1H), 6.40 (d, J = 2.0 Hz, 1H), 5.33 (d, J = 5.2 Hz, 1H), 4.61 (q, J = 5.6 Hz, 1H), 3.05 (dd, J = 16.8, 5.2 Hz, 1H), 2.91 (dd, J = 16.8, 6.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 143.8, 141.1, 133.4, 131.6, 129.7, 128.9, 128.3, 128.1, 127.9, 126.2, 123.0, 117.7, 117.5, 112.6, 84.8, 84.2, 56.5, 29.3. Anal. Calcd for C₂₂H₁₇Cl₂N: C, 72.14; H, 4.68; N, 3.82. Found: C, 72.35; H, 4.63; N, 3.82.

N-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-N-methylaniline (2.52)

Prepared using procedure B from the known 6-bromo-1,3-benzodioxole-5-methanol56 and N-methylaniline, purified using silica gel chromatography (49% dichloromethane/50% hexanes/1% triethylamine).

2.52 Yellow solid (0.81 g, 81%); mp = 72-74°C; TLC Rf = 0.37 (50% dichloromethane/50% hexanes); IR (KBr) 3436, 3093, 3064, 2893, 2827, 2565, 1597 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.24-7.20 (m, 2H), 7.04 (s, 1H), 6.73 (dt, J = 7.2, 0.8 Hz, 1H), 6.73-6.65 (m, 3H), 5.93 (s, 2H), 4.44 (s, 2H), 3.07 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 149.2, 147.8, 147.3, 131.0, 129.3, 116.8, 113.0, 112.6, 112.1, 108.0, 101.7, 57.4, 38.8. Anal. Calcd for C₁₅H₁₄O₂NBr: C, 56.27; H, 4.41; N, 4.37. Found: C, 56.43; H, 4.28; N, 4.36.
Onosmin B (2.8)


Prepared using procedure B with 4-methylbenzyl alcohol and 2-aminomethylbenzoate, purified using silica gel chromatography (29% dichloromethane/70% hexanes/1% triethylamine).

2.8. Clear colorless oil (0.26 g, 85%); TLC R<sub>f</sub> = 0.55 (10% ethyl acetate/90% hexanes); IR (thin film) 3368, 3078, 3020, 2949, 2921, 2847, 1681 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.14 (br s, 1H), 7.92 (dd, <i>J</i> = 8.0, 1.6 Hz, 1H), 7.29 (ddd, <i>J</i> = 8.5, 7.2, 1.6 Hz, 1H), 7.26-7.23 (m, 2H), 7.14 (d, <i>J</i> = 7.6 Hz, 2H), 6.65 (dd, <i>J</i> = 8.0, 0.8 Hz, 1H), 6.59 (ddd, <i>J</i> = 8.0, 7.2, 1.2 Hz, 1H), 4.41 (s, 2H), 3.86, (s, 3H), 2.33 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 169.1, 150.9, 136.8, 135.7, 134.6, 131.6, 129.4, 127.1, 114.8, 111.7, 110.2, 51.5, 46.8, 21.1. Anal. Calcd for C<sub>16</sub>H<sub>17</sub>O<sub>2</sub>N: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.54; H, 6.67; N, 5.83.

References


Chapter 3

Alkylation of Sulfonamides with Trichloroacetimidates Under Thermal Conditions

Abstract
The intermolecular alkylation of sulfonamides with trichloroacetimidates using thermal conditions is reported herein. Allylic and benzylic imidates were found to be effective alkylating agents under the reported reaction conditions. Secondary imidates were found to provide the higher yields than primary and tertiary trichloroacetimidates. Aryl and alkyl sulfonamides were both alkylated effectively with yields ranging from 55%-98%. A bioactive ketoprofen analog was efficiently synthesized using the described methodology. An \( S_N1 \) type mechanism for the reported reaction is proposed and evidence supporting this hypothesis is provided via the alkylation of a chiral trichloroacetimidate, which proceeded with complete racemization.

Introduction
The sulfonamide functional group plays an important role in many bioactive and pharmaceutically interesting compounds. Several interesting medicinally relevant sulfonamides have been described in the literature, such as the HMG-CoA reductase inhibitor rosuvastatin\(^1\) (3.4) and the cardiac rhythmicity regulator efsevin\(^2\) (3.5). Other bioactive sulfonamides such as the inhibitor of delayed-rectifier k\(^+\) chromanol 293B\(^3\) (3.6), the selective EP(2) receptor agonist taprenepag isopropyl\(^4\) (3.7) and the ketoprofen analog 3.8 are shown in Figure 3.1.\(^5\) Examination of the use of sulfonamides in pharmaceuticals shows that sulfonamides are a well represented functional group in medicinal chemistry and drug design.\(^6,7\) The synthesis of new
sulfonamide-containing structures continues to be a popular avenue for drug discovery.\textsuperscript{8} Sulfonamides have also been used for insecticidal and agricultural applications.\textsuperscript{9,10} Overall, the varied biological activity of sulfonamides defines their use as valuable synthetic targets with a variety of uses.

\begin{figure}[ht]
\centering
\includegraphics[width=\textwidth]{sulfonamide Structures.png}
\caption{Bioactive and Pharmacologically Interesting N-Substituted Sulfonamides}
\end{figure}

In addition, sulfonamides serve an important purpose in synthetic organic chemistry as they facilitate the introduction of nitrogen into organic molecules. Sulfonamides often function as protecting groups to conceal the reactive amine moiety during functional group manipulation. Initially, the use of sulfonamides as protecting groups was limited due to the harsh conditions required for cleavage.\textsuperscript{11,12} However, this has changed as more mild conditions for the deprotection of sulfonamides have now been developed. In particular, the discovery of the 2-(trimethylsilyl)-ethanesulfonamide (SES-NH\textsubscript{2}) by Weinreb\textsuperscript{13} and the utilization of the 2- and 4-nitrobenzene sulfonamides by Fukuyama\textsuperscript{14} have expanded the potential of this chemistry. These developments have lead to increased use of sulfonamides in synthetic organic chemistry.
Due to the numerous uses for substituted sulfonamides in medicinal chemistry and synthetic chemistry, effective methods for the formation of substituted sulfonamides are highly desired. Most commonly, substituted sulfonamides are formed from amines and sulfonyl chlorides.\textsuperscript{15, 16} Direct alkylation of sulfonamides with alkyl halides\textsuperscript{17, 18} and reductive amination\textsuperscript{19, 20} methods are also popular. The Mitsunobu reaction can also be employed to convert an alcohol into a substituted sulfonamide.\textsuperscript{13, 14, 21} The high level of interest in synthetic methods for preparing substituted sulfonamides has led to newer, more atom-economical methods for their formation. These include transition-metal catalyzed methods such as the hydroaminations of alkenes,\textsuperscript{22-30} C-H activation methods,\textsuperscript{31-36} metal catalyzed additions to N-sulfonyl imines,\textsuperscript{11, 37-41} alkylation via \( \pi \)-allyl metal complexes,\textsuperscript{42-44} and alkylation of alcohols with borrowing hydrogen methods.\textsuperscript{45-48} The direct alkylation of allylic and benzylic alcohols have also been explored although these methods typically require the use of strong acid catalysts.\textsuperscript{49, 50} As the thermal alkylations of thiols and alcohols with trichloroacetimidates have been observed to proceed without a catalyst or promoter,\textsuperscript{51, 52} it was hypothesized that sulfonamide alkylation could be accomplished thermally through the use of trichloroacetimidates without the use of exogenous acid.

\textbf{Results and Discussion}

The research began with the optimization of the reaction of 1-phenylethyl imidate 3.9 and toluene sulfonamide 3.10. Imidate 3.9 was chosen as it is easily prepared from inexpensive and commercially available 1-phenylethyl alcohol, while toluene sulfonamide 3.10 was chosen because it is inexpensive and relatively soluble in a variety of organic solvents. At first Lewis acid catalysts were evaluated to promote this transformation. The reaction of imidate 3.9 with sulfonamide 3.10 in toluene with 10 mol\% BF\textsubscript{3} OEt\textsubscript{2} as a catalyst provided the substitution
product in 29% yield (entry 1). Along with the desired product, a significant side product, the rearranged trichloroacetamide, was also observed in the crude $^1\text{H}$ NMR of the reaction mixture. The formation of this undesirable side product from the rearrangement of the trichloroacetimidate has been reported previously.\textsuperscript{53} Switching the Lewis acid catalyst from BF$_3$OEt$_2$ to TMSOTf failed to provide the desired product and again primarily trichloroacetamide was recovered from the reaction mixture (entry 2). As the rearrangement of benzylic trichloroacetimidates to acetamides using Lewis acids has been reported in the literature, it was considered that perhaps stronger Brønsted acid catalysts may catalyze the reaction and reduce the amount of rearranged acetamide. The substitution was therefore evaluated with 2,4-dinitrobenzenesulfonic acid (DNBSA) as an acid catalyst and the result was an encouraging 71% yield of the desired product 3.11 (entry 3). PPTS provided similar results albeit at a reduced yield of 51% (entry 4). Although these results were encouraging, we were intrigued by the possibility of a substitution reaction that could be performed without the use of exogenous acid catalysts. The search for such conditions was initiated by heating toluene sulfonamide 3.10 and imidate 3.9 in toluene at 86° C (entry 5). No reaction was observed under these conditions, however, and switching the solvent to refluxing THF resulted in the formation of a complex mixture (entry 6). Treating imidate 3.9 with toluenesulfonamide 3.10 in refluxing toluene (111 °C boiling point) provided the desired product 3.11 in 76% yield (entry 7). Shorter reaction times were not as effective as conversion to the substituted sulfonamide 3.11 was not complete and so isolated yields were more moderate (24%, entry 8). At this point it was noted that toluene sulfonamide 3.10 was only slightly soluble in toluene, while the substituted sulfonamide 3.11 and the trichloroacetamide byproduct were completely soluble. This differential solubility may account for some loss of yield, as the soluble trichloroacetamide may
compete with the poorly soluble sulfonamide for the benzylic electrophile. A protocol where the imidate was added in portions was therefore devised, as less trichloroacetamide would be in the reaction mixture to compete with toluene sulfonamide as a nucleophile, leading to more sulfonamide substitution product and less of the undesired acetamide byproduct. Adding the trichloroacetimidate in portions provided an improved yield of 86% (entry 9). Although the amount of imidate used in the reaction was increased, a similar reaction without the stepwise addition of trichloroacetimidate 3.9 did not result in an increased yield (entry 10). As the conditions used in entry 9 provided the best yield, this protocol was chosen to test the robustness of the thermal substitution reaction.

**Table 3.1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>eq. imidate</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>10 mol % BF$_3$-OEt$_2$, rt, 18h</td>
<td>toluene</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>10 mol % TMSOTf, rt, 18h</td>
<td>toluene</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>10 mol %ONBSA, rt, 18h</td>
<td>toluene</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>10 mol % PPTS, rt</td>
<td>toluene</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>85°C, 18h</td>
<td>toluene</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>reflux, 18h</td>
<td>THF</td>
<td>0</td>
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<tr>
<td>7</td>
<td>1.2</td>
<td>reflux, 18h</td>
<td>toluene</td>
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</tr>
<tr>
<td>8</td>
<td>1.2</td>
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<td>toluene</td>
<td>24</td>
</tr>
<tr>
<td>9$^a$</td>
<td>1.5</td>
<td>reflux</td>
<td>toluene</td>
<td>86</td>
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<tr>
<td>10</td>
<td>1.5</td>
<td>reflux, 18h</td>
<td>toluene</td>
<td>74</td>
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</table>

$^a$ The imidate added in 6 portions (one every 30 min) over 2.5 h, then the reaction mixture was heated at reflux for another 16 h.
The scope of the thermal substitution reaction with respect to the sulfonamide was then investigated (Table 3.2). The reaction of a number of different benzenesulfonamides with the phenethyl trichloroacetimidate 3.9 provided the desired alkylation product, with 4-methoxybenzenesulfonamide, benzenesulfonamide and 4-chlorobenzenesulfonamide providing yields of 75%, 74% and 84% respectively (entries 1-3). Similarly, alkyl sulfonamides were tolerated well, with methane sulfonamide and ethane sulfonamide providing yields of 79% and 76% respectively (entries 6-7). To our delight 2-(trimethylsilyl)-ethanesulfonamide provided the desired product 3.20 with a yield of 70% (entry 8). This is notable as this sulfonamide can be cleaved to the corresponding amine through the use of cesium fluoride in DMF. The artificial sweetener saccharin was found to be an exceptional reagent for this reaction and provided 98% yield of the desired substitution product (entry 9). Saccharin has been used in the Gabriel synthesis as a surrogate for phthalimide, so this substitution provides an alternative for this popular route to primary amines. N-Substituted sulfonamides were less reactive under these reaction conditions. N-Methyl toluenesulfonamide gave just 27% of the desired product (entry 10) while N-benzyltoluene sulfonamide failed to react altogether (entry 11). Under the thermal conditions, 2-nitrobenzenesulfonamide provided a poor yield of only 13% (entry 5). This result was particularly disappointing as nitrobenzenesulfonamides have been used by Fukuyama as reagents for installing amines.
Due to the utility of 2-nitrobenzenesulfonamide and 4-nitrobenzenesulfonamide in organic synthesis, expanding the scope of the imidate substitution to include these substrates was further investigated (Table 3.3). First, it was noted that although the reaction of 1-phenethyl imidate 3.9 with 2-nitrobenzenesulfonamide was poor, the more reactive imidate diphenylmethyl imidate 3.25 was capable of alkylation under these original conditions with a yield of 80% (entry 1). Although this was result was encouraging, expanding the scope to less reactive imidates was necessary. Adding the strong acid DNBSA as a catalyst in CH$_2$Cl$_2$ resulted in a yield of 17% (entry 3). The more mild acid PPTS was incapable of catalyzing this
reaction and the starting materials were recovered unchanged (entry 4). Heating 2-nitrobenzensulfonamide and phenethyl imidate 3.9 in THF at reflux without an acid catalyst resulted in the formation of a complex mixture of products (entry 5). Performing the reaction in refluxing dichloroethane (DCE) without the addition of an acid catalyst resulted in a yield of 14% while refluxing conditions in dimethoxyethane (DME) resulted in 12% yield of the desired substituted sulfonamide (entries 6-7). Utilizing BF$_3$·OEt$_2$ as a Lewis acid catalyst in DCM, the substituted sulfonamide 3.17 was isolated in 12% yield. Although the yield for this reaction was low it was noted that the reaction was completed quickly, requiring just 1 hour to proceed to completion. These low yields may be due to 2-nitrobenzenesulfonamide being exceptionally insoluble in most of these solvents. Therefore slow addition of imidate 3.9 to the sulfonamide while utilizing BF$_3$·OEt$_2$ as a promoter was investigated, as this procedure would maximize the concentration of the sulfonamide nucleophile relative to the concentration of the electrophile, minimizing the risk of decomposition of the imidate by rearrangement. The slow addition of the imidate would allow enough time for the sparingly soluble 2-nitrobenzenesulfonamide to be converted into the more soluble substituted sulfonamide 3.17. Slow addition of imidate 3.9 with a syringe pump resulted in a drastically increased yield of 44% for compound 3.17 (entry 9).
Encouraged by this increase in yield with slow addition of imidate 3.9, a slow addition procedure with syringe pump was applied in a number of other variations to improve the yield of the 2-nitrobenzene sulfonamide alkylation. Lewis acid catalyzed addition of imidate 3.9 to the sulfonamide in DCM with the Lewis acid catalyst BF$_3$·OEt$_2$ at room temperature provided the desired product 3.17 (60%, Table 3.4, entry 1) with an improved yield. Heating this reaction to reflux provided a yield of 59% (entry 2). Although the yield was similar, it was noted that a significantly better ratio of desired product 3.17 to the rearranged product 3.27 was realized as indicated by $^1$H NMR. Increasing the amount of sulfonamide to 1.3 equivalents provided product 3.17 with an increased yield of 70% (entry 3). No further substantial increase in yield was obtained by further increasing the equivalents of imidate (entry 4). Several other solvents were also evaluated, but performing the substitution in acetonitrile provided no product (entry 5) whereas changing the solvent to nitromethane provided a more moderate yield of 53% (entry 6).
Encouragingly no rearrangement of imidate was observed in this reaction. Unfortunately a number of unidentifiable side products made purification by column chromatography difficult and therefore the isolated yield was lower than observed with DCM. Performing the substitution in nitromethane at 50°C resulted in an improved yield of 61% (entry 7), but this was still lower than that obtained with DCM. At this elevated temperature some of the rearrangement product 3.27 could again be observed in the crude $^1$H NMR. Addition of the imidate slowly over 10h with a syringe pump was also evaluated. Unfortunately, this method provided a poor yield of 3.17 (12%, entry 8) and was found to be comparable to yields acquired from mixing the imidate and sulfonamide in toluene at reflux (Table 3.3, entry 2). Using the Lewis acid CuSO$_4$ as a catalyst resulted in no observed reaction (entry 9) and using DNBSA resulted in the isolation of only 4% of product 3.17 (entry 10). The possibility of using 2-nitrobenzene sulfonamide as the limiting reagent was also evaluated. Entries 11-14 represent the highest yields obtained using the trichloroacetimidate as the limiting reagent. Unfortunately even using a large excess of sulfonamide (entry 14) resulted in an isolation of just 58% of the desired product 3.17. All yields are listed with respect to the limiting reagent. Overall, the conditions from entry 3 were found to be the most efficient, so these conditions were used to alkylate 2-nitrobenzenesulfonamide.
Table 3.4

The scope of the imidate alkylation was now investigated with respect to the imidate alkylation partner. Secondary benzylic imidates were tolerated well with yields ranging from 44% to 94% (entries 1-9) (Table 3.5). Primary benzylic imidates provided lower yields (55%-68%, entries 10-11) while benzyl imidate failed to produce any of the desired product 3.38 (entry 12). The highly reactive diphenylmethyl imidate provided the desired product 3.34 in excellent yield.
yield (89%) with no formation of the rearranged trichloroacetamide product observed (entry 8). The diphenylmethyl group has been used as a protecting group for sulfonamides, so this represents a new method for its' introduction. Ethers and aryl halides were also tolerated under the reaction conditions the substituted sulfonamide 3.32 was synthesized with a yield of 89% (entry 6). Esters were also caused no issues under the reaction conditions, and substituted sulfonamide 3.35 was formed cleanly with a yield of 67% (entry 9). The substituted sulfonamides 3.29 and 3.30 were both formed with yields of 79% for both compounds (entries 3-4). The sterically hindered substituted sulfonamide 3.31 was formed with good yield of 94% (entry 5). Similarly the o-bromobenzylcylcimidate provided the desired substitution product 3.32 with a yield of 88% (entry 6). The highly reactive furfuryl imidate was found to provide the corresponding substituted sulfonamide 3.33 with a more moderate yield of 44%. This reagent may be rearranging to the trichloroacetamide quickly under the reaction conditions, and hydrolysis of this imidate has also been noted to be quite facile. Allyl imidates were tolerated under the reaction conditions which was exciting due to the proclivity of allyl imidates towards the competing Overman rearrangement. Allyl imidates provided the corresponding substituted sulfonamides 3.39 and 3.40 with yields of 60% and 28% respectively (entries 13-14). Unsurprisingly, the more stable secondary allyl imidate gave higher yields in the substitution reaction. Methyl imidate was found to be slightly reactive under the reaction conditions and N-methylsulfonamide 3.41 was recovered in 5% yield (entry 15). tert-Butyl imidate was found to be totally unreactive under the reaction conditions (entry 16).
The mechanism for the thermal substitution reaction was investigated next. As noted in table 3.5, trichloroacetimidates that formed more stable carbocations typically provided higher

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Result</th>
<th>Entry</th>
<th>Product</th>
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</table>
yields. In table 3.4, there was no obvious difference between highly nucleophilic and weakly nucleophilic sulfonamides that could not be explained by solubility problems. These results led us to hypothesize that an $S_N^1$ mechanism was operative in this transformation (Scheme 3.2). To provide further evidence for this mechanism chiral (R)-3.9 was treated with toluenesulfonamide 3.10 in toluene resulting in an 81% yield of product 3.11 (Scheme 3.1). Analysis of the product 3.11 using chiral HPLC showed that the product was racemic. This result provided further evidence that the reaction is proceeding via an $S_N^1$ pathway, as a cationic intermediate is expected to lead to significant racemization.

The sulfonamide alkylation was then applied to the synthesis of the ketoprofen analog 3.8 which was first synthesized by Sakurai and coworkers (Scheme 3.3). Sulfonamide 3.8 has
shown a variety of interesting pharmacological properties including LTD₄ antagonistic activity, TXA₂ antagonistic activity, and TXA₂ synthase inhibitory activity. ⁶₀-⁶² The previously described synthesis of ketoprofen analog ³.⁸ required two steps: formation of the diphenylmethylazide from the corresponding alcohol and then an additional step to reduce the azide to the corresponding amine. A more rapid route could be realized using the new thermal alkylation conditions. The synthesis was initiated by preparing alcohol ³.⁴⁸ via the method described by Sakurai and coworkers. Formation of trichloroacetimidate ³.⁴⁹ proceeded without difficulty and the desired product ³.⁴⁹ was isolated following column chromatography in excellent yield (99%). Thermal alkylation of 4-chlorobenzene sulfonamide with trichloroacetimidate ³.⁴⁹ provided substituted sulfonamide ³.⁵⁰ in high yield (88%). This completed a formal synthesis of ketoprofen analog ³.⁸ as saponification of ³.⁵⁰ leads directly to ³.⁸. The desired target could then be accessed through a known saponification reaction with NaOH in one fewer step than the published synthesis.

**Scheme 3.3**
Conclusion

The development of thermal conditions for the alkylation of sulfonamides with trichloroacetimidates has been completed. The scope of the reaction has been tested with respect to both sulfonamides and trichloroacetimidates. Monosubstitution was found to occur with primary sulfonamides, whereas monosubstituted sulfonamides were alkylated less effectively using the described conditions. Conditions for alkylating the useful reagent 2-nitrobenzene sulfonamide were also optimized. The substitution of imidate (R)-3.9 with toluene sulfonamide resulted in racemic product which provided strong evidence that the process is most likely an $S_N$1 pathway. A formal synthesis of the ketoprofen analog 3.8 was then completed using the described chemistry in one less step than the previously published synthesis.

Experimental Section

Representative Sulfonamide Substitution Procedure A: To a flame dried round bottom flask under an atmosphere of argon was added $p$-toluene sulfonamide 3.10 (0.13 g, 0.77 mmol) and toluene (4 mL). Phenethyl imidate 3.9 (51 mg, 0.19 mmol) was added and the reaction mixture was heated to reflux. Phenethyl imidate 3.9 (0.05 g, 0.19 mmol) was added to the refluxing reaction mixture every 30 minutes until 1.14 mmol (1.5 equiv) of phenethyl imidate 3.9 was added. After stirring at reflux overnight, the reaction mixture was allowed to cool to room temperature, preadsorbed on silica gel and purified by silica gel chromatography (30% ethyl acetate/70% hexanes) to give 0.180 g (86%) of substituted sulfonamide 3.11 as a white solid.

![Chemical Structure](image)

4-Methyl-N-(1-phenylethyl)benzenesulfonamide (3.11)

Prepared using procedure \textbf{A} (0.180 g, 86\%) using the known imidate\textsuperscript{63} and purified using silica gel chromatography (30\% ethyl acetate/70\% hexanes).

\textbf{3.11}. White solid (0.18 g, 86\%); mp = 74-78 °C; TLC $R_f = 0.43$ (20\% ethyl acetate/80\% hexanes); $^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 7.61 (dt, $J = 8.7$, 2.1 Hz, 2H), 7.21-7.17 (m, 5H), 7.11-7.08 (m, 2H), 4.76 (d, $J = 6.8$ Hz, 1H), 4.47 (p, $J = 6.9$ Hz, 1H), 2.39 (s, 3H), 1.42 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl\textsubscript{3}) $\delta$ 143.1, 142.0, 137.7, 129.4, 128.5, 127.5, 127.1, 126.1, 53.6, 23.5, 21.5. Chiral HPLC analysis: Chiralcel OD (heptane/i-PrOH = 90/10, 1.0 mL/min, 254 nm, 25 °C): $t = 10.6$, 12.8 min.

\begin{figure}
\centering
\includegraphics[width=0.3\textwidth]{chemical_structure.png}
\caption{4-Methoxy-N-(1-phenylethyl)benzenesulfonamide (3.14)}
\end{figure}


Prepared using procedure \textbf{A} (0.17 g, 75\%) using the known imidate\textsuperscript{63} and purified by silica gel chromatography (100\% DCM).

\textbf{3.14}. Waxy off-white solid (0.17 g, 75\%); mp = 94-96 °C; TLC $R_f = 0.25$ (100\% DCM); $^1$H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 7.65 (dt, $J = 9.2$, 2.8 Hz, 2H), 7.21-7.15 (m, 3H), 7.11-7.09 (m, 2H), 6.82 (dt, $J = 9.6$, 2.8 Hz, 2H), 5.35 (d, $J = 7.2$ Hz, 1H), 4.43 (p, $J = 7.2$ Hz, 1H), 3.82 (s, 3H), 1.40 (d, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl\textsubscript{3}) $\delta$ 162.6, 142.2, 132.2, 129.2, 128.5, 127.4, 126.2, 114.0, 55.6, 53.7, 23.6.
N-(1-Phenylethyl)benzenesulfonamide (3.15)


Prepared using procedure A (0.14 g, 72%) using the known imidate and purified using silica gel chromatography (30% ethyl acetate/70% hexanes).

3.15. White solid (0.14 g, 74%); mp = 87-91 °C; TLC Rf = 0.44 (30% ethyl acetate/70% hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.74-7.71 (m, 2H), 7.44 (td, J = 6.4, 1.2 Hz, 1H), 7.36-7.31 (m, 2H), 7.14-7.07 (m, 5H), 5.65 (d, J = 7.2 Hz, 1H), 4.48 (p, J = 6.8 Hz, 1H), 1.40 (d, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 142.0, 140.7, 132.3, 128.8, 128.5, 127.4, 127.0, 126.1, 53.8, 23.6.

4-Chloro-N-(1-phenylethyl)benzenesulfonamide (3.16)


Prepared using procedure A (0.19 g, 83%) using the known imidate and purified using silica gel chromatography (10% ethyl acetate/90% hexanes).

3.16. White amorphous solid (0.15 g, 85%); mp = 71-75 °C; TLC Rf = 0.21 (10% ethyl acetate/90% hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.8
Hz, 3H), 7.19-7.17 (m, 2H), 7.08-7.05 (m, 2H), 5.14 (d, $J = 7.2$ Hz, 1H), 4.50 (p, $J = 6.8$ Hz, 1H), 1.44 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 141.6, 139.2, 138.7, 129.0, 128.6, 128.5, 127.6, 126.1, 53.9, 23.6.

2-Nitro-N-(1-phenylethyl)benzenesulfonamide (3.17)


2-Nitrobenzenesulfonamide (0.18 g, 0.87 mmol) and BF$_3$•OEt$_2$ (0.02 g, 0.09 mmol) were suspended in DCM (4 mL). The suspension was heated to reflux. A 0.1 M solution of 1-phenethyl trichloroacetimidate 3.9$^{63}$ (0.30 g, 1.13 mmol) in DCM was added to the suspension using a syringe pump over the course of one hour. The reaction was refluxed for 18h. After cooling to room temperature, the reaction was poured into saturated aq. NaHCO$_3$ and extracted with DCM (3x). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was purified via silica gel chromatography (100% DCM) providing 3.17 (0.18 g, 70%) as a white solid. The sulfonamide 3.17 was also prepared using procedure A (0.04 g, 13%).

3.17. White solid (0.18 g, 70%); mp = 89-91 °C; TLC $R_f = 0.58$ (100% DCM); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.67 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.54 (td, $J = 7.6$, 1.2 Hz, 1H), 7.40 (td, $J = 8.0$, 1.6 Hz, 1H), 7.12-7.06 (m, 5H), 5.77 (d, $J = 8.4$ Hz, 1H), 4.69 (p, $J = 6.8$ Hz, 1H), 1.52 (d, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 147.3, 141.2, 134.5, 132.9, 132.5, 130.8, 128.5, 127.7, 126.1, 124.9, 55.0, 23.7.
N-(1-Phenylethyl)methanesulfonamide (3.18)


Prepared using procedure A (0.12 g, 79%) using the known imidate and purified using silica gel chromatography (30% ethyl acetate/70% hexanes).

3.18. Yellow oil (0.12 g, 79%); TLC R$_f$ = 0.35 (30% ethyl acetate/70% hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39-7.26 (m, 5H), 5.16 (d, $J = 7.2$ Hz, 1H); 4.64 (p, $J = 7.2$ Hz, 1H), 2.61 (s, 3H), 1.53 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 142.4, 129.0, 128.0, 126.2, 53.8, 41.8, 24.0.

N-(1-Phenylethyl)ethanesulfonamide (3.19)


Prepared using procedure A (0.15 g, 76%) using the known imidate and purified using silica gel chromatography (100% DCM flushed with 30% ethyl acetate/70% hexanes).

3.19. White solid (0.15 g, 76%); mp = 89-91 °C; TLC R$_f$ = 0.34 (30% ethyl acetate/70% hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36-7.26 (m, 5H), 5.16 (br d, $J = 7.1$ Hz, 1H), 4.62 (p, $J = 7.1$ Hz, 1H), 2.76 (h, $J = 7.4$ Hz, 1H), 2.61 (h, $J = 7.4$ Hz, 1H), 1.54 (d, $J = 6.9$ Hz, 3H), 1.17 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 142.8, 128.8, 127.9, 126.2, 53.7, 47.9, 24.2, 8.0.
N-(1-Phenylethyl)-2-(trimethylsilyl)ethanesulfonamide (3.20)


Prepared using procedure A (0.13 g, 70%) using the known imidate\textsuperscript{63} and purified by silica gel chromatography (30% ethyl acetate/80% hexanes).

**3.20.** White crystals (0.13 g, 70%); mp = 61-64 °C; TLC $R_f = 0.58$ (20% ethyl acetate/80% hexanes); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 7.38-7.27 (m, 5H), 4.73 (d, $J = 6.9$ Hz, 1H), 4.62 (p, $J = 6.9$ Hz, 1H), 2.61 (td, $J = 14.0$, 3.9 Hz, 1H), 2.47 (td, $J = 13.9$, 4.4 Hz, 1H), 1.54 (d, $J = 6.9$ Hz, 3H), 0.86 (td, $J = 13.8$, 4.0, 1H), 0.74 (td, $J = 14.0$, 4.3 Hz, 1H), -0.13 (s, 9H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) $\delta$ 143.0, 129.1, 128.2, 126.4, 53.9, 50.0, 24.3, 10.5, -2.0.

![Chemical Structure](image)

3-Oxo-N-(1-phenylethyl)benzo[d]isothiazole-2(3H)-sulfonamide 1,1-dioxide (3.21)


Prepared using procedure A using the known imidate\textsuperscript{63} and purified by silica gel chromatography (20% ethyl acetate/80% hexanes). The crude product was then taken up in ethyl acetate (30 mL) and washed with 2M NaOH (5 x 20 mL). The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo* to provide 3.21 as a clear colorless oil (0.22 g, 98%).

**3.21.** Clear colorless oil (0.22 g, 98%); TLC $R_f = 0.37$ (20% ethyl acetate, 80% hexanes); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 7.98-7.95 (m, 1H), 7.90-7.88 (m, 1H), 7.82 (td, $J = 7.4$, 1.2 Hz, 1H),
7.77 (td, J = 7.2, 1.4 Hz, 1H), 7.60-7.57 (m, 2H), 7.36 (tt, J = 6.8, 1.2 Hz, 2H), 7.29 (tt, J = 6.2, 1.3 Hz, 1H), 5.45 (q, J = 7.3 Hz, 1H), 2.03 (d, J = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 158.5, 138.6, 137.8, 134.6, 134.2, 128.5, 128.2, 127.7, 127.3, 125.0, 120.7, 53.0, 17.7.

4-Methyl-N-(1-phenylethyl)benzenesulfonamide (3.22)


Prepared using procedure A (0.06 g, 27%) using the known imidate$^{53}$ and purified using silica gel chromatography (100% DCM).

**3.22.** White powder (0.06 g, 27%); mp = 60-62 °C; TLC R$_f$ = 0.52 (100% DCM); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.74 (dt, J = 8.4, 1.8 Hz, 2H), 7.32-7.24 (m, 7H), 5.29 (q, J = 7.0 Hz, 1H), 2.57 (s, 3H), 2.43 (s, 3H), 1.29 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 143.1, 139.9, 137.3, 129.7, 128.4, 127.5, 127.3, 127.1, 54.8, 28.4, 21.5, 15.2.

1-(p-Tolyl)ethyl 2,2,2-trichloroacetimidate (S3.28)

To a round bottom flask under argon was added 1-(p-tolyl)ethanol (0.51 g, 3.74 mmol), trichloroacetonitrile (0.48 mL, 4.86 mmol) and DCM (7 mL). DBU (0.06 mL, 0.37 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. Triethylamine (1 mL) was added to the reaction mixture and the solvent was removed *in vacuo*. Purification of the
residue by silica gel chromatography (1% triethylamine/9% ethyl acetate/90% hexanes) provided imidate S3.28 as white crystals (0.81 g, 77%).

**S3.28.** White crystals (0.81 g, 77%); mp = 41-42 °C; TLC $R_f = 0.50$ (10% ethyl acetate/90% hexanes); IR (KBr) 3344, 2982, 2931, 2868, 1663, 1285 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.27 (br s, 1H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.17 (d, $J = 7.8$ Hz, 2H), 5.94 (q, $J = 6.6$ Hz, 1H), 2.34 (s, 3H), 1.63 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.7, 138.4, 137.6, 129.2, 125.8, 91.8, 77.2, 22.2, 21.2. Anal. Calcd for C$_{11}$H$_{12}$Cl$_3$NO: C, 47.09; H, 4.31; N, 4.99. Found: C, 46.75; H, 4.05; N, 4.80.

4-Methyl-N-(1-(p-tolyl)ethyl)benzenesulfonamide (3.28)


Prepared using procedure A (0.19 g, 89%) using imidate S3.28 and purified using silica gel chromatography (30% ethyl acetate/70% hexanes).

**3.28.** White powder (0.19 g, 89%); mp = 118-119 °C; TLC $R_f = 0.65$ (30% ethyl acetate/70% hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62 (dt, $J = 8.3$, 1.0 Hz, 2H), 7.17 (dd, $J = 8.5$, 0.6 Hz, 2H), 6.98 (app s, 4H), 5.04 (d, $J = 7.0$ Hz, 1H), 4.40 (p, $J = 6.9$ Hz, 1H), 2.38 (s, 3H), 2.27 (s, 3H) 1.39 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.0, 139.1, 137.8, 137.1, 129.4, 129.2, 127.1, 126.1, 53.4, 23.5, 21.5, 21.0.
1,2,3,4-Tetrahydronaphthalen-1-yl 2,2,2-trichloroacetimidate (S3.29)

To a round bottom flask under argon was added 1,2,3,4-tetrahydronaphthalen-1-ol (1.00 g, 6.75 mmol), DBU (0.10 mL, 0.67 mmol) and DCM (23 mL). The reaction mixture was stirred at room temperature for 15 minutes and then cooled to 0°C in an ice/water bath. Trichloroacetonitrile (0.88 mL, 8.77 mmol) was added and the reaction mixture was warmed to room temperature and stirred overnight. The solvent was then removed in vacuo. Triethylamine (1 mL) was added and the residue was purified by silica gel chromatography (2% triethylamine/10% ethyl acetate/88% hexanes) to provide S3.29 as a clear colorless oil (1.68 g, 94%).

S3.29. Clear colorless oil (1.68 g, 94%); TLC R_f = dec. (10% ethyl acetate/90% hexanes); IR (thin film) 3341, 3064, 3024, 2940, 2869, 1657 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.39 (br s, 1H), 7.39-7.37 (m, 1H), 7.27-7.14 (m, 3H), 6.10 (t, J = 4.8 Hz, 1H), 2.93-2.74 (m, 2H), 2.22-1.96 (m, 3H), 1.89-1.81 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 162.5, 138.1, 134.2, 129.6, 129.1, 128.3, 126.1, 92.1, 75.5, 29.1, 27.9, 19.1. Anal. Calcd for C₁₂H₁₂Cl₃NO: C, 49.26; H, 3.82; N, 4.75. Found: C, 48.92; H, 4.44; N, 4.92.

4-Methyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzenesulfonamide (3.29)

Prepared using procedure A (0.18 g, 79%) using imidate S3.29 and purified using silica gel chromatography (30% ethyl acetate/70% hexanes).

**S3.29.** Beige solid (0.18 g, 79%); mp = 115-118 °C; TLC Rf = 0.62 (30% ethyl acetate/70% hexanes); 1H NMR (400 MHz, CDCl3) δ 7.75 (td, J = 8.4, 1.9 Hz, 2H), 7.26 (d, J = 7.9 Hz, 2H), 7.05 (td, J = 7.3, 1.2 Hz, 1H), 7.00-6.94 (m, 2H), 6.87 (d, J = 7.6 Hz, 1H), 4.67 (br d, J = 7.8 Hz, 1H), 4.37 (p, J = 5.2 Hz, 1H), 2.71-2.54 (m, 2H), 2.38 (s, 3H), 1.79-1.71 (m, 3H), 1.66-1.62 (m, 1H); 13C NMR (100 MHz, CDCl3) δ 143.4, 138.2, 137.6, 135.6, 129.8, 129.2, 128.8, 127.6, 127.2, 126.3, 51.9, 30.8, 28.9, 21.6, 19.2.

![Structure](image)

1-(Naphthalen-1-yl)ethyl 2,2,2-trichloroacetimidate (S3.30)

To a round bottom flask under argon was added 1-(naphthalen-1-yl)ethanol (0.85 g, 4.92 mmol), trichloroacetonitrile (0.59 mL, 5.90 mmol) and DCM (12 mL). DBU (0.08 mL, 0.49 mmol) was added to the reaction mixture and the reaction mixture was stirred at room temperature for 18h. Triethylamine (1 mL) was added to the reaction mixture and the reaction mixture was purified by silica gel chromatography (2% triethylamine/8% ethyl acetate/90% hexanes) to provide S3.30 as a clear colorless oil (1.32 g, 85%).

**S3.30.** Clear colorless oil (1.32 g, 85%); TLC Rf = 0.80 (10% ethyl acetate/90% hexanes); IR (DCM) 3339, 3052, 2983, 2933, 2870, 1661, 1598 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 8.36 (br s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.89-7.87 (m, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 7.1 Hz, 1H), 7.56-7.47 (m, 3H), 6.74 (q, J = 6.6 Hz, 1H), 1.81 (d, J = 6.6 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 161.7, 137.1, 133.8, 130.2, 128.9, 128.5, 126.3, 125.7, 125.4, 123.2, 123.0, 91.8, 74.6,
21.34. Anal. Calcd for C\textsubscript{14}H\textsubscript{12}Cl\textsubscript{3}NO: C, 53.11; H, 3.82; N, 4.42. Found: C, 53.47; H, 3.62; N, 4.75.

4-Methyl-N-(1-(naphthalen-1-yl)ethyl)benzenesulfonamide (3.30)


Prepared using procedure A (0.20 g, 79%) using imidate 3.30 and purified using silica gel chromatography (30% ethyl acetate/70% hexanes).

3.30 Orange oil (0.20 g, 79%); TLC R\textsubscript{f} = 0.43 (30% ethyl acetate/70% hexanes); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.89-7.87 (m, 1H), 7.80-7.78 (m, 1H), 7.67 (d, \(J = 8.1\) Hz, 1H), 7.56 (dt, \(J = 8.3, 1.7\) Hz, 2H), 7.47-7.40 (m, 2H), 7.36 (dd, \(J = 7.2, 1.0\) Hz, 1H), 7.31-7.27 (m, 1H), 7.04 (d, \(J = 7.9\) Hz, 2H), 5.28 (p, \(J = 6.8\) Hz, 1H), 5.15 (d, \(J = 6.8\) Hz, 1H), 2.31 (s, 3H), 1.58 (d, \(J = 6.8\) Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 143.1, 137.7, 137.5, 133.8, 130.1, 129.3, 128.8, 128.1, 127.1, 126.3, 125.6, 125.3, 123.4, 122.6, 49.8, 23.2, 21.4.

1-(o-Toly)ethyl 2,2,2-trichloroacetimide (S3.31)

To a round bottom flask under argon was added 1-(o-toly)ethanol (1.08 g, 8.89 mmol), trichloroacetonitrile (1.16 mL, 11.56 mmol) and DCM (17 mL). DBU (0.13 mL, 0.89 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The solvent was then removed in vacuo. Triethylamine (1 mL) was added and the residue was purified by silica gel
chromatography (1% triethylamine/9% ethyl acetate/90% hexanes) to provide **S3.31** as white crystals (1.82 g, 73%).

**S3.31.** Clear colorless oil (1.82 g, 73%); TLC R<sub>f</sub> = 0.68 (10% ethyl acetate/90% hexanes); IR (KBr) 3342, 3025, 2980, 2931, 1662, 1288 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.27 (br s, 1H), 7.51-7.48 (m, 1H), 7.25-7.14 (m, 3H), 6.14 (q, J = 6.5 Hz, 1H), 2.42 (s, 3H), 1.61 (d, J = 6.6 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 161.5, 139.7, 134.7, 130.3, 127.7, 126.3, 125.1, 91.8, 74.3, 21.0, 19.0. Anal. Calcd for C<sub>11</sub>H<sub>12</sub>Cl<sub>3</sub>NO: C, 47.09; H, 4.31; N, 4.99. Found: C, 46.88; H, 4.06; N, 4.81.

![Structure](image)

**4-Methyl-N-(1-(o-tolyl)ethyl)benzenesulfonamide (3.31)**


Prepared using procedure A (0.21 g, 94%) using imidate **S3.31** and purified using silica gel chromatography (30% ethyl acetate/70% hexanes).

**3.31** Off-white solid (0.31 g, 94%); mp = 87-89 °C; TLC R<sub>f</sub> = 0.56 (30% ethyl acetate/70% hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.50 (dt, J = 8.3, 1.7 Hz, 2H), 7.06-7.01 (m, 3H), 6.95-6.87 (m, 3H), 5.60 (d, J = 7.2 Hz, 1H), 4.62 (p, J = 6.9 Hz, 1H), 2.24 (s, 3H), 2.10 (s, 3H), 1.23 (d, J = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 143.0, 140.5, 137.7, 134.3, 130.3, 129.4, 127.1, 127.0, 126.4, 125.5, 49.8, 23.1 21.5, 19.0.
1-(6-Bromobenzo[d][1,3]dioxol-5-yl)ethyl 2,2,2-trichloroacetimidate (S3.32)

To a round bottom flask under argon was added 1-(6-bromobenzo[d][1,3]dioxol-5-yl)ethanol (2.90 g, 11.83 mmol), DBU (0.18 mL, 1.18 mmol) and DCM (39 mL). The reaction mixture was stirred at room temperature for 15 min. and then cooled to 0°C in an ice/water bath. Trichloroacetonitrile (1.53 mL, 15.38 mmol) was added to the reaction mixture and the reaction mixture was warmed to room temperature and stirred overnight. The solvent was then removed in vacuo. Triethylamine (1 mL) was added and the residue was purified by silica gel chromatography (1% triethylamine/50% ethyl acetate/49% hexanes) to provide S3.32 as a clear colorless oil (3.80 g, 83%).

**S3.32.** Clear colorless oil (3.80 g, 83%); TLC *R*<sub>f</sub> = 0.69 (30% ethyl acetate/70% hexanes); IR (thin film) 3339, 3080, 2983, 2930, 2897, 1667 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.37 (br s, 1H), 7.03 (s, 1H), 6.98 (s, 1H), 6.17 (q, *J* = 6.4 Hz, 1H), 5.96 (q, *J* = 1.2 Hz, 2H), 1.58 (d, *J* = 6.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 161.1, 147.81, 147.80, 134.2, 112.6, 112.0, 106.2, 101.8, 91.5, 76.3, 21.0. Anal. Calcd for C<sub>11</sub>H<sub>9</sub>BrCl<sub>3</sub>N<sub>3</sub>O<sub>3</sub>: C, 33.92; H, 2.33; N, 3.60. Found: C, 33.88; H, 2.49; N, 3.48.

N-(1-(6-Bromobenzo[d][1,3]dioxol-5-yl)ethyl)-4-methylbenzenesulfonamide (3.32)

Prepared using procedure A (0.29 g, 88%) using imidate S3.32 and purified by silica gel chromatography (30% ethyl acetate, 70% hexanes).
3.32. Yellow powder (0.29 g, 88%); mp = 106 °C (dec); TLC Rf = 0.53 (30% ethyl acetate/70% hexanes); IR (KBr) 3272, 2986, 1714, 1478, 1326 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.64 (dt, J = 8.5, 1.9 Hz, 2H), 7.18 (dd, J = 8.4, 0.5 Hz, 2H), 6.82 (s, 1H), 6.69 (s, 1H), 5.89 (dd, J = 6.9, 1.4 Hz, 2H), 5.46 (d, J = 6.6 Hz, 1H), 4.79 (p, J = 6.8 Hz, 1H), 2.38 (s, 3H), 1.32 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.6, 147.4, 143.2, 137.0, 134.6, 129.4, 127.2, 112.37, 112.36, 107.4, 101.8, 52.9, 22.9, 21.5. Anal. Calcd for C₁₆H₁₆BrNO₄S: C, 48.25; H, 4.05; N, 3.52. Found: C, 48.07; H, 4.06; N, 3.30.

\[ \text{1-(Furan-2-yl)pentyl 2,2,2-trichloroacetimidate (S3.33)} \]

To a round bottom flask containing 1-(furan-2-yl)pentan-1-ol⁶⁵ (0.52 g, 3.37 mmol) dissolved in DCM (33 mL) was added trichloroacetonitrile (0.58 g, 4.04 mmol) and DBU (0.05 g, 0.34 mmol). The reaction mixture was stirred at room temperature for 1 hour. The solvent was then removed in vacuo. Triethylamine (1 mL) was added and the residue was purified by silica gel chromatography (1% triethylamine/19% ethyl acetate/80% hexanes) to provide S3.33 as a yellow oil (0.32 g, 33%).

S3.33. Yellow oil (0.32 g, 33%); TLC Rf = 0.62 (20% ethyl acetate/80% hexanes); IR (KBr) 3346, 2960, 2873, 1656, 1501 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 7.40 (dd, J = 1.8, 0.8 Hz, 1H), 6.39 (d, J = 3.12 Hz, 1H), 6.34 (dd, J = 3.2, 1.8 Hz, 1H), 5.96 (t, J = 6.6 Hz, 1H), 2.18-2.08 (m, 1H), 2.07-1.98 (m, 1H), 1.47-1.26 (m, 4H), 0.91 (t, J = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 162.0, 152.3, 142.4, 110.2, 108.5, 91.7, 73.9, 32.4, 27.4, 22.3, 13.9. Anal. Calcd for C₁₁H₁₄Cl₃NO₂: C, 44.25; H, 4.73; N, 4.69. Found: C, 44.49; H, 4.45; N, 4.79.
**N-(1-(Furan-2-yl)pentyl)-4-methylbenzenesulfonamide (3.33)**


Prepared using procedure A (0.09 g, 44%) with imidate S3.33 and purified using silica gel chromatography (20% ethyl acetate/80% hexanes).

**3.33.** Reddish solid (0.09 g, 44%); mp = 54-56 °C; TLC Rf = 0.38 (20% ethyl acetate.80% hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61 (dt, $J = 8.5$, 1.9Hz, 2H), 7.18 (dd, $J = 8.5$, 0.6 Hz, 2H), 7.12 (dd, $J = 1.8$, 0.8 Hz, 1H), 6.09 (dd, $J = 3.2$, 1.8 Hz, 1H), 5.89 (d, $J = 3.2$ Hz, 1H), 5.1 (d, $J = 8.7$ Hz, 1H), 4.38 (q, $J = 7.3$ Hz, 1H), 2.37 (s, 3H), 1.78-1.73 (m, 2H), 1.28-1.20 (m, 3H), 1.18-1.11 (m, 1H), 0.82 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 153.2, 142.9, 141.7, 137.8, 129.3, 127.0, 109.9, 106.7, 51.7, 34.7, 27.7, 22.1, 21.4, 13.8.

**N-Benzhydryl-4-methylbenzenesulfonamide (3.35)**


Prepared using procedure A (0.23 g, 89%) using the known imidate$^{66}$ and purified using silica gel chromatography (20% ethyl acetate/80% hexanes).
**3.35.** White powder (0.23 g, 89%); mp = 122-124 °C; TLC R_f = 0.42 (20% ethyl acetate/80% hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.56 (dt, J = 8.5, 2.0 Hz, 2H), 7.23-7.19 (m, 6H), 7.15-7.08 (m, 6H), 5.56 (d, J = 6.8 Hz, 1H), 5.01 (d, J = 6.8 Hz, 1H), 2.38 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 143.2, 140.6, 137.4, 129.4, 128.5, 127.5, 127.2, 61.4, 21.5.

![](image)

**N-benzhydryl-2-nitroaniline (3.26)**


Prepare using procedure A (0.22 g, 80%) using the known imidate and purified using silica gel chromatography (80% dichloromethane/20% hexanes).

**3.26.** White solid (0.22 g, 80%); mp = 165-166°C; TLC R_f = 0.48 (80% dichloromethane/20% hexanes); ¹H NMR (400 MHz CDCl₃), δ 7.69 (dd, J = 3.8, 1.2 Hz, 1H), 7.67 (dd, J = 3.9, 1.3 Hz, 1H), 7.52 (td, J = 7.6, 1.4 Hz, 1H), 7.38 (td, J = 7.8, 1.3 Hz, 1H), 7.18-7.16 (m, 10H), 6.18 (d, J = 9.0 Hz, 1H), 5.81 (d, J = 9.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃), δ 147.2, 139.4, 134.4, 133.0, 132.5, 130.8, 128.6, 127.9, 127.5, 124.9, 62.3.

![](image)

**Methyl 4-(4-(phenyl(2,2,2-trichloro-1-iminoethoxy)methyl)phenyl)butanoate (S3.35)**

To a round bottom flask containing the known alcohol (0.09 g, 0.31 mmol) was added DCM (1 mL) followed by trichloroacetonitrile (0.06 g, 0.38 mmol) and DBU (0.01 g, 0.03 mmol). The reaction mixture was stirred at room temperature for 4 hours. The solvent was then removed *in
Triethylamine (1 mL) was added to the residue and the reaction mixture was purified by silica gel chromatography (1% triethylamine/29% ethyl acetate/70% hexanes) to provide S3.35 as a pale yellow oil (0.130 g, 99%).

S3.35. Pale yellow oil (0.13 g, 99%); TLC R<sub>f</sub> = 0.22 (30% ethyl acetate/70% hexanes); IR (KBr) 3651, 3279, 1731, 1495 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz CDCl<sub>3</sub>) δ 8.40 (br s, 1H), 7.43-7.41 (m, 2H), 7.35-7.33 (m, 4H), 7.29-7.28 (m, 1H), 7.15 (d, <i>J</i> = 8.2 Hz, 2H), 6.92 (s, 1H), 3.63 (s, 3H), 2.62 (t, <i>J</i> = 7.4 Hz, 2H), 2.32 (t, <i>J</i> = 7.4 Hz, 2H), 1.93 (p, <i>J</i> = 7.6 Hz, 2H); <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>) δ 173.8, 161.4, 143.0, 140.8, 140.7, 138.3, 137.4, 129.3, 128.6, 128.5, 127.4, 127.3, 127.2, 61.1, 51.7, 34.6, 33.3.

Methyl 4-(4-(4-methylphenylsulfonamido)(phenyl)methyl)phenyl)butanoate (3.50).

Prepared following procedure A (0.23 g, 67%) with imidate S3.35 and purified using silica gel chromatography (30% ethyl acetate/70% hexanes) followed by a second purification using silica gel chromatography (100% DCM).

3.50. Clear colorless oil (0.23 g, 67%); TLC R<sub>f</sub> = 0.45 (30% ethyl acetate/70% hexanes); IR (DCM) 3328, 3227, 3062, 2950, 2864, 1731, 1599 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz CDCl<sub>3</sub>) δ 7.55 (dt, <i>J</i> = 6.6, 1.6 Hz, 2H), 7.20-7.17 (m, 3H), 7.12-7.09 (m, 4H), 7.00 (d, <i>J</i> = 1.6 Hz, 4H), 5.53 (d, <i>J</i> = 6.9 Hz, 1H), 5.32 (d, <i>J</i> = 7.2 Hz, 1H), 3.65 (s, 3H), 2.56 (t, <i>J</i> = 7.4 Hz, 2H), 2.36 (s, 3H), 2.29 (t, <i>J</i> = 7.4 Hz, 2H), 1.88 (p, <i>J</i> = 7.6 Hz, 2H); <sup>13</sup>C NMR (100 MHz CDCl<sub>3</sub>) δ 174.0, 143.0, 140.8, 140.7, 138.3, 137.4, 129.3, 128.6, 128.5, 127.4, 127.3, 127.2, 61.1, 51.7, 34.6, 33.3.

\[ \text{N-(4-Methoxybenzyl)-4-methylbenzenesulfonamide (3.36)} \]


Prepared using procedure A (0.17 g, 75%) using the commercially available imidate and purified using silica gel chromatography (100% DCM) followed by recrystallization from methanol.

**3.36.** White solid (0.17 g, 68%); mp = 122-123 °C; TLC R$_f$ = 0.61 (40% acetone/60% hexanes);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.75 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.10 (d $J = 8.7$ Hz, 2H), 6.79 (d, $J = 8.7$ Hz, 2H), 4.59 (t, $J = 5.8$ Hz, 1H), 4.05 (d, $J = 6.0$ Hz, 2H), 3.78 (s, 3H), 2.44 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.3, 143.5, 136.9, 129.7, 128.3, 129.3, 127.2, 114.1, 55.3, 46.8, 21.5.

\[ \text{4-Methyl-N-(2-methylbenzyl)benzenesulfonamide (3.37)} \]


Prepared using procedure A (0.12 g, 55%) using the known imidate$^{69}$ and purified using silica gel chromatography (30% ethyl acetate/70% hexanes).
3.37. White solid (0.12 g, 55%); mp = 107-109 °C; TLC R<sub>f</sub> = 0.31 (30% ethyl acetate/70% hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.76 (dt, <i>J</i> = 8.5, 2.0 Hz, 2H), 7.31 (dd, <i>J</i> = 8.5, 0.6 Hz, 2H), 7.20-7.10 (m, 4H), 4.45 (t, <i>J</i> = 5.8 Hz, 1H), 4.09 (d, <i>J</i> = 6.0 Hz, 2H), 2.44 (s, 3H), 2.24 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 143.6, 136.7, 136.6, 133.9, 130.6, 129.7, 128.9, 128.3, 127.2, 126.2, 45.4, 21.6, 18.8.

N-(Cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide (3.39)


Prepared using procedure A (0.12 g, 60%) using the known imidate<sup>70</sup> and purified using silica gel chromatography (30% ethyl acetate/70% hexanes).

3.39. Colorless crystals (0.12 g, 60%); mp = 99-100 °C; TLC R<sub>f</sub> = 0.45 (30% ethyl acetate/70% hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.77 (dt, <i>J</i> = 8.5, 2.0 Hz, 2H), 7.30 (dd, <i>J</i> = 8.5, 0.6 Hz, 2H), 5.79-5.74 (m, 1H), 5.37-5.32 (m, 1H), 4.44 (d, <i>J</i> = 8.6 Hz, 1H), 3.84-3.79 (m, 1H), 2.43 (s, 3H), 2.00-1.87 (m, 2H), 1.79-1.73 (m, 1H), 1.64-1.50 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 143.2, 138.4, 131.5, 129.7, 127.1, 127.0, 49.0, 30.2, 24.5, 21.5, 19.3.

N-Allyl-4-methylbenzenesulfonamide (3.40)

Prepared using procedure A (0.05 g, 28%) using the commercially available imidate and purified using silica gel chromatography (30% ethyl acetate/70% hexanes).

**3.40.** Off-white solid (0.05 g, 28%); mp = 53-56 °C; TLC R<sub>f</sub> = 0.42 (30% ethyl acetate/70% hexanes); $^1$H NMR (400 MHz CDCl<sub>3</sub>) δ 7.76 (dt, $J = 8.5, 2.0$ Hz, 2H), 7.31 (dd, $J = 8.5, 0.6$ Hz, 2H), 5.77-5.68 (m, 1H), 5.19-5.08 (m, 2H), 4.51 (t, $J = 4.50$ Hz, 1H), 3.59 (tt, $J = 6.1, 1.5$ Hz, 2H), 2.43 (s, 3H); $^{13}$C NMR (100 MHz, CDCl<sub>3</sub>) δ 143.5, 137.0, 133.0, 129.7, 127.2, 117.7, 45.8, 21.5.

![Structure](image)

**N,4-Dimethylbenzenesulfonamide (3.41)**


Prepared using procedure A (0.01 g, 5%) using the commercially available imidate and purified using silica gel chromatography (30% ethyl acetate/70% hexanes).

**3.41.** Off-white solid (0.01 g, 5%); mp = 69-71 °C; TLC R<sub>f</sub> = 0.33 (30% ethyl acetate/70% hexanes); $^1$H NMR (400 MHz CDCl<sub>3</sub>) δ 7.68 (dt, $J = 8.3$ Hz, 2H), 7.25 (dd, $J = 8.4, 0.5$ Hz, 2H), 4.22 (d, $J = 4.7$ Hz, 1H), 2.58 (d, $J = 5.4$ Hz, 3H), 2.37 (s, 3H); $^{13}$C NMR (100 MHz, CDCl<sub>3</sub>) δ 143.5, 135.8, 129.7, 127.3, 29.4, 21.5.
Methyl-4-((4-chlorophenylsulfonamido)(phenyl)methyl)phenyl)butanoate (3.50)


Prepared using procedure A (0.08 g, 88%) and purified using silica gel chromatography (30% ethyl acetate/70% hexanes).

3.50. Clear colorless oil (0.08 g, 88%); TLC $R_f = 0.40$ (30% ethyl acetate/70% hexanes); IR (KBr) 3153, 2986, 2920, 1730, 1586 cm$^{-1}$; $^1$H NMR (400 MHz CDCl$_3$) $\delta$ 7.53 (dt, $J = 9.2$, 2.5 Hz, 2H), 7.25-7.18 (m, 5H), 7.12-7.09 (m, 2H), 7.00 (br s, 4H), 5.58 (d, $J = 7.6$ Hz, 1H), 5.53 (d, $J = 7.6$ Hz, 1H), 3.65 (s, 3H), 2.57 (t, $J = 7.4$ Hz, 2H), 2.30 (t, $J = 7.4$ Hz, 2H), 1.89 (p, $J = 7.6$ Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.9, 141.1, 140.2, 139.0, 138.7, 137.7, 128.9, 128.7, 128.59, 128.57, 127.7, 127.4, 127.3, 61.3, 51.6, 34.6, 33.4, 26.4. Anal. Calcd for C$_{24}$H$_{24}$ClNO$_4$S: C, 62.94; H, 5.28; N, 3.06. Found: C, 63.17; H, 5.35; N, 3.22.

References


Chapter 4

Studies Towards the Synthesis of Kapakahine C

Abstract

Kapakahine C is a complex heterocyclic natural product isolated from the marine sponge *cribrochalina olemda* which contains a unique fused pyrroloindoline-pyridoindoline core decorated with a cyclic pentapeptide. The molecule may be divided retro synthetically into three fragments: the pyrroloindoline, the pyridoindoline and the pentapeptide sections. A route to kapakahine C utilizing a trichloroacetimidate electrophile and a pyrroloindoline nucleophile was investigated. The synthesis of the pyrroloindoline and the pentapeptide sections were completed. Optimization of the key oxidative cyclization step in the formation of the pyridoindoline section of kapakahine C was undertaken and research to improve this reaction is ongoing.

Introduction

Recently, the development of mild and effective methods for the derivatization of nitrogen containing heterocycles has attracted significant synthetic interest. One attractive target for such derivatization is the pyrroloindoline heterocycle, which is typically composed of a hydrogenated pyrrole ring fused to indoline. The pyrroloindoline functional group is prevalent in many bioactive molecules such as (-)-physostigmine (4.1),^1^ flustramine B (4.2),^2^ (+)-chimonanthine (4.3),^3^ psychotrimine (4.4),^4^ chaetocochin A (4.5),^5^ and kapakahine C (4.6).^6^ Some of these molecules have enjoyed success as pharmaceuticals. For example, physostigmine 4.1 has been used to treat conditions such as Alzheimer's disease and glaucoma. ^7^ The alkaloid hodgkinsine B (4.8) has been shown to possess analgesic properties. ^8^ Other pyrroloindolines have attracted academic interest due to their varied biological activity and complex architectures.
For example, psychotrimine was found to inhibit the growth of various bacteria including staphylococcus aureus 8325 and staphylococcus epidermidis RP62A at concentrations of 64μg/mL and 32μg/mL respectively.\(^9\) Amauromine (4.7) was revealed to have vasodilating activity as well as potent activity in studies that measure the reversal of multiple drug resistance\(^10,11,12\). The alkaloid neoxaline (4.9) has shown interesting activity as a tumor suppressor.\(^13\) Given the varied and complex bioactivity associated with this structural class of alkaloids, selective and mild methods for the derivatization of these compounds are desirable with a number of approaches to this system under development.
Unsurprisingly, many strategies for the formation and alkylation of the pyrroloindoline core structure have already been investigated. Common starting materials for synthesizing pyrroloindolines include functionalized indoles and tryptamines. Of particular interest to our group was functionalization of the pyrroloindoline core at the C3a position. This position is a point of diversity within pyrroloindoline alkaloids, with systems containing oxygen, nitrogen, sp² and sp³ hybridized carbon atoms at the C3a position being well-known. Methods for the rapid incorporation of carbon and heteroatom nucleophiles at this position would facilitate
derivatization of a common pyrroloindoline intermediate, which allows for the synthesis of most pyrroloindoline based natural products. In addition these methods may provide a means to rapidly evaluate the biological activity of a library of pyrroloindolines, that can be rapidly prepared. Most common methods for the incorporation of diverse functionality at the C3a position of a pyrroloindoline scaffold involve either alkylation of a C3a-bromide (like compound 4.10) using a stoichiometric silver salt as a promoter or the stoichiometric use of a strong base such as KOTBu (Scheme 4.1). For instance, Zinzallay and coworkers synthesized C3a substituted pyrroloindolines via nucleophilic substitution at the C3a position using nitrogen, oxygen, sulfur and carbon based nucleophiles although this reaction required the use of stoichiometric silver nitrate and phase transfer agent. Numerous other alkylation examples that employ stoichiometric silver salts or strong base are known. The use of a strong base is limited to systems which have an ester at the C2-position, as these reactions have been shown to proceed through an azetidine intermediate. These preparations represent the most commonly used procedures for the rapid functionalization of pyrroloindolines at the C3a position.

Scheme 4.1

Although methods for the formation and derivatization of pyrroloindolines and indoles have been researched heavily in recent years, common approaches to pyrroloindoline synthesis suffer from some drawbacks. The use of silver salts can cause alkylations to become expensive, as these reagents must be used in stoichiometric amounts and the price of silver has
been increasing. Some pyrroloindoline compounds may be unstable in the presence of bases such as KOTBu. Given these drawbacks a mild method for the functionalization of pyrroloindolines at the C3a position is desirable, preferable one that is dependent on catalytic reagents. An alkylation of pyrroloindolines with a trichloroacetimidate at the C3a position may alleviate some of the issues of pyrroloindoline derivatization at the C3a position and meet the criteria of a system that may be alkylated under catalytic conditions.

Alkylation with different types of nucleophiles (including carboxylic acids, thiols, alcohols, sulfonamides and anilines) using trichloroacetimidates has been investigated by our laboratory and by other researchers. In many cases the trichloroacetimidate is reactive enough to alkylate these functional groups without the need for any additional catalyst or promoter. The use of trichloroacetimidates to alkylate pyrroloindolines offers several advantages over traditional methods. First, trichloroacetimidate alkylations typically proceed with use of catalytic amounts of acid rather than the expensive stoichiometric silver salts used in traditional methods. Secondly trichloroacetimidates are easily prepared from alcohols and inexpensive trichloroacetonitrile (~$240/ kg) and may be generated in situ. Furthermore trichloroacetimidates are quite stable and resistant to decomposition when stored properly. For example, highly reactive 3,4-dimethoxybenzyl 2,2,2-trichloroacetimidate was found to be stable for more than 3 years while stored in a sealed vial at -20° C (Figure 4.2). Displacement of trichloroacetimidates can proceed under mild conditions as substitutions are exothermic and driven not only by the formation of the new C-X bond but also by the rearrangement of the imidate to the trichloroacetamide. For this reason, even electron-deficient trichloroacetimidates may be used as alkylating agents. Additionally, the trichloroacetamide byproduct generated from these reactions is a mild, rather than strong, acid that can be removed.
through either column chromatography or by washing with aqueous 2M NaOH solution. For these reasons we hypothesized that alkylations of pyrroloindolines may be improved through the use of trichloroacetimidates.

![Structure of 3,4-Dimethoxybenzyl 2,2,2-trichloroacetimidate 4.12](image)

**Figure 4.2: Structure of 3,4-Dimethoxybenzyl 2,2,2-trichloroacetimidate 4.12**

In order to test our hypothesis a pyrroloindoline system with a trichloroacetimidate at the C3a position was synthesized. Known pyrroloindoline 4.13, which was synthesized from tryptamine, was treated with trichloroacetonitrile and DBU to form the corresponding imidate 4.14. This imidate was found to be a competent electrophile with a number of carbon, nitrogen and oxygen nucleophiles. While these substitution reactions did not occur under thermal conditions, catalytic amounts of BF₃•OEt₂ was all that was necessary to promote these reactions. Many of these reactions were quite rapid as well (depending on the nucleophile), with most being complete in just 10 min at room temperature.

**Scheme 4.2**

Given the prevalence of bioactive pyrroloindoline containing systems in pharmaceuticals and our hypothesis that we could improve the alkylation of pyrroloindolines, we sought to
demonstrate the utility of this new alkylation method in the total synthesis of a complex natural product. The synthesis of kapakahine C, a cyclic peptide that was isolated from the marine sponge *cribrochalina olemda* along with several other members of the kapakahine family, became a focus of the next step in this project. Kapakahine C makes an attractive synthetic target for several reasons. First, kapakahine C has shown cytotoxic activity against P388 murine leukemia cells at an IC$_{50}$ value of 5.0 µg/mL. Second, it was isolated from a marine sponge which makes the isolation of large quantities of kapakahine C from natural sources practically difficult. Third, kapakahine C is the most complex member of the kapakahine family and although kapakahines B, E and F have been synthesized, no synthesis of kapakahine C has ever been reported. Additionally the structure of kapakahine C is unique in that it is comprised of a polycyclic core whose structure is that of a pyrroloindoline bound by the indole nitrogen to a pyridoindoline. The existence of such a linkage makes kapakahine C an intriguing target for elaboration using the newly developed pyrroloindoline alkylation chemistry.

**Retrosynthetic Analysis**

Retrosynthetic analysis of kapakahine C revealed that the target molecule could be divided into three fragments A, B, and C (Scheme 4.3). Fragment A, a protected polypeptide chain may be easily be constructed through peptide coupling reactions of commercially available amino acids. The desired pyrroloindoline, fragment B, was envisioned to come from tryptophan. The key step in forming this fragment would be the oxidative cyclization of protected tryptophan 4.19. This chemistry is known, and though the product is obtained as a 1:1 mixture of diastereomers, the brevity of the planned scheme is synthetically desirable. The final piece, fragment C, could be prepared from an oxidative cyclization from the protected dipeptide 4.20, analogously to the work of Evano which utilized a similar approach in his synthesis of
Compound 4.20 was thought to be available from a precursor derived from the inexpensive and readily available amino acids, tryptophan and tyrosine.

Synthesis of Kapakahine C

With good routes in hand to access fragments A and B, work became focused on the synthesis of fragment C. First the known protected tyrosine 4.22 was prepared from commercially available L-tyrosine (Scheme 4.4). Fischer esterification of L-tyrosine in methanol with thionyl chloride provided the corresponding methyl ester 4.24. Subsequent Boc
protection of the amine then gave intermediate 4.25 which was benzylated on the phenol to provide benzyl ether 4.26. Deprotection of the Boc group was accomplished using trifluoroacetic acid in DCM to provide protected tyrosine 4.22 in 85% yield over 4 steps. This route proved to be an efficient method for preparing protected tyrosine 4.22 as it required only two chromatographic purifications and was scaled from 5 grams of L-tyrosine to 15 grams of L-tyrosine without complication.

Scheme 4.4

With protected L-tyrosine 4.22 in hand we shifted our focus to preparing the coupled peptide 4.20. Initially, L-tryptophan was protected using phthalic anhydride and TEA in refluxing toluene which provided phthalimide 4.21 in 96% yield (Scheme 4.5). Again column
chromatography was not required for purification of this product and the reaction was easily scaled to 15 g of L-tryptophan.

Scheme 4.5

Subsequent coupling of protected tyrosine 4.22 and protected tryptophan 4.21 proceeded with some difficulty (Table 4.1). The coupling proceeded with low yields with HATU when left for a period of 18h hours (entries 1-3). This was likely due to epimerization of the α proton next to the electron-withdrawing phthalimide, which gave a mixture of diastereomers that was difficult to separate by chromatography. To combat this problem the more hindered base diisopropylethylamine (DIPEA) was used (entry 4). Although the reaction now proceeded without formation of the undesired epimer, the rate of the transformation was depressed and low yields still resulted. Switching the base back to TEA and reducing the reaction time to 4 hours served the desired purpose of increasing the yield to 65% (entry 5). No epimerized product was isolated from this reaction after shortening the reaction time, evidently the racemization occurred significantly more slowly than the coupling.
Table 4.1

<table>
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<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
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<tr>
<td>1</td>
<td>HATU, TEA, CH₂Cl₂, 0°C to rt, 18h</td>
<td>42%</td>
</tr>
<tr>
<td>2</td>
<td>HATU, TEA, CH₂Cl₂, 0°C to rt, 18h</td>
<td>48%</td>
</tr>
<tr>
<td>3</td>
<td>HATU, TEA, CH₂Cl₂, 0°C to rt, 18h</td>
<td>43%</td>
</tr>
<tr>
<td>4</td>
<td>HATU, DIPEA, CH₂Cl₂, 0°C to rt, 18h</td>
<td>58%</td>
</tr>
<tr>
<td>5</td>
<td>HATU, TEA, CH₂Cl₂, 0°C to rt, 4h</td>
<td>65%</td>
</tr>
</tbody>
</table>

With coupled product 4.20 in hand we sought to perform an oxidative cyclization to provide the corresponding alcohol 4.29 (Table 4.2). A number of different conditions were evaluated to affect the cyclization. Generation of DMDO in situ using oxone in acetone/DCM failed to provide any product and starting material was recovered (entry 1). MCPBA was used to try to close the ring through an epoxide intermediate but no product could be recovered from the crude reaction mixture (entry 2). The use of CuCl₂ and TEMPO, a procedure reported by Deng and coworkers, similarly resulted in a complex mixture from which the product could not be isolated (entry 3). The use of 2.0 equiv NCS and O₂ to cyclize the indole to the desired pyridinoindoline according to the procedure of Evano resulted in the formation of the desired product 4.29 and the unoxidized indole product 4.30 in yields of 25% and 37% respectively. Although the yield of the desired alcohol was low, we were able to oxidize the indole 4.30 to the corresponding alcohol 4.29 in 50% yield (Scheme 4.6). Further optimization of this reaction was then initiated in order to access enough material to continue the synthesis. The presence of
unidentifiable side products in the reaction mixture led us to believe that epimerization of the α amino stereocenter may be causing complications. We attempted to alleviate these problems by reducing the temperature of the reaction to -78 °C and switching the base to DIPEA (entries 5, 6). Unfortunately both of these reactions failed to generate product and starting material was recovered. The halo-succinimides NBS and NIS were also evaluated in this cyclization, but these reagents failed to produce product (entries 7, 8). Surprisingly, increasing the reaction temperature to reflux increased to reaction yield of the desired alcohol to 36%. Presumably, this is because a greater portion of the indole is converted to the corresponding pyridinoindoline alcohol at high temperatures. Increasing the reaction time to 1h further increased the yield to 60% (entry 17). Unfortunately when this reaction was scaled up from 50 mg to 500 mg the yield dropped down to 32% (entry 18) and more effort was required to optimize the reaction at larger scale. Extending the reaction time further to 18h gave the desired product with a yield to 33% (entry 10). Switching the solvent to dichloroethane so the reaction could be heated at a higher temperature resulted in a yield of 20% (entry 11). Likewise, performing the transformation in a pressure tube to access a higher temperature in DCM solvent also resulted in a 20% yield (entry 12). The amount of NCS was also adjusted, but neither raising nor lowering the amount of NCS resulted in a higher yield (entries 13-14). These results may be due to the requirement of more oxygen to oxidize the indole on a larger scale. A moderate improvement in yield was observed (38%) by bubbling oxygen through the dichloromethane during the reaction (entry 20). Interestingly, a diastereomer of 4.29 containing the (S) alcohol could be isolated during this reactions. Evidently, either diastereomer may be formed under these harsh conditions. Work to further increase the efficiency of this reaction on a large scale is still ongoing.
Table 4.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oxone, acetone, CH₂Cl₂, NaHCO₃, rt, 18h</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>2 eq. MCPBA, 8 eq. TFA, CH₂Cl₂, -40°C, 1h</td>
<td>crude mixture</td>
</tr>
<tr>
<td>3</td>
<td>DBU, CuCl₂, TEMPO, CH₃CN, rt, 24h</td>
<td>crude mixture</td>
</tr>
<tr>
<td>4</td>
<td>NCS, CH₂Cl₂, TEA, O₂, 0°C to rt, 4h&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25% A, 37% B</td>
</tr>
<tr>
<td>5</td>
<td>NCS, CH₂Cl₂, DIPEA, O₂, 0°C to rt, 4h</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>NCS, CH₂Cl₂, TEA, O₂, -78°C to rt, 2h</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>NBS, CH₂Cl₂, TEA, O₂, 0°C to rt, 40 min</td>
<td>NR</td>
</tr>
<tr>
<td>8</td>
<td>NIS, CH₂Cl₂, TEA, O₂, 0°C to rt, 40 min</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>NCS, CH₂Cl₂, TEA, rt to reflux, 0.5h</td>
<td>36% A: 49% B</td>
</tr>
<tr>
<td>10</td>
<td>NCS, CH₂Cl₂, TEA, reflux, 18h</td>
<td>33% A: 24% B</td>
</tr>
<tr>
<td>11</td>
<td>NCS, DCE, TEA, O₂, rt to reflux, 1h</td>
<td>A: 20% B: 30%</td>
</tr>
<tr>
<td>12</td>
<td>NCS, CH₂Cl₂, TEA, O₂, pressure tube</td>
<td>A: 20% B 23%</td>
</tr>
<tr>
<td>13</td>
<td>3.0 equiv. NCS, CH₂Cl₂, TEA, rt to reflux, 1h</td>
<td>20% A: - B</td>
</tr>
<tr>
<td>14</td>
<td>1.0 equiv. NCS, CH₂Cl₂, TEA, rt to reflux, 1h</td>
<td>6% A: 12% B</td>
</tr>
<tr>
<td>15</td>
<td>NCS, CH₂Cl₂, TEA, reflux, 5h</td>
<td>35% A: 50% B</td>
</tr>
<tr>
<td>16</td>
<td>NCS, CH₂Cl₂, TEA, rt to reflux, 18h</td>
<td>20% A: &gt;30% B</td>
</tr>
<tr>
<td>17</td>
<td>NCS, CH₂Cl₂, TEA, rt to reflux, 1h</td>
<td>60% A: &gt;30% B</td>
</tr>
<tr>
<td>18</td>
<td>NCS, CH₂Cl₂, TEA, rt to reflux, 1h (500 mg 4.20)</td>
<td>32% A: 44% B</td>
</tr>
<tr>
<td>19</td>
<td>NCS, CH₂Cl₂, TEA, O₂, rt to reflux, 1h (500 mg 4.20)</td>
<td>16% A: 50% B</td>
</tr>
<tr>
<td>20</td>
<td>NCS, CH₂Cl₂, TEA, O₂, rt, 2h</td>
<td>38% A: 27% B&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> 24% recovery of (S) alcohol diastereomer of 4.29
After optimization of the oxidative cyclization is complete the pyridoindoline 4.30 will be reduced with NaBH$_3$CN (Scheme 4.7). Cyclization of the resulting amine to the corresponding lactam should readily occur as evidenced by the work of Evano.$^{46}$ Formation of the desired trichloroacetimidate with TCAN and DBU in dichloromethane will then be accomplished. Finally reaction of imidate 4.32 with fragment 4.17 will be evaluated to form the "western" portion of kapakahine C.
Conclusion

Kapakahine C precursor 4.29 was synthesized in a yield of 33% over 6 linear steps. Coupling precursors 4.21 and 4.22 were synthesized on large scale. Conditions for the coupling of fragments 4.21, and 4.22 were investigated and optimized. Optimization of the oxidative cyclization of 4.20 to pyridinoindoline 4.29 was undertaken and conditions were found to affect the transformation resulting in 60% yield of the desired product. Future work will involve further optimization of the oxidative cyclization and the use of this compound in an imidate coupling reaction to form the western portion of kapakahine C. Attempts will then be made to attach and cyclize the peptide section of the molecule to complete the synthesis of the natural product.

Experimental Section

(S)-2-(1,3-Dioxoisindolin-2-yl)-3-(1H-indol-3-yl)propanoic acid (4.21)


To a flame dried round bottom flask at room temperature was added L-tryptophan (5.0 g, 24.5 mmol), phthalic anhydride (3.6 g, 24.5 mmol) and toluene (75 mL). Triethylamine was added (0.4 mL, 5.4 mmol) and the reaction mixture was heated to reflux for 24 h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo. Water (100 mL)
was added and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was dissolved in MeOH (50 mL) and concentrated under reduced pressure to provide 7.9 g (96%) of product 4.21 as a yellow foam.

4.21. mp = 88-92 °C; TLC R_f = 0.26 (10% MeOH/90% Dichloromethane); ^1H NMR (400 MHz, CDCl_3) δ 7.98 (br d, J = 1.4 Hz, 1H), 7.69-7.55 (m, 2H), 7.48-7.45 (m, 2H), 7.19-7.08 (m, 2H), 6.99 (td, J = 7.1, 1.1 Hz, 1H), 6.92 (td, J = 8.0, 1.0 Hz, 1H), 6.85 (d, J = 2.2 Hz), 5.13 (dd, J = 10.9, 5.08 Hz, 1H), 3.67-3.52 (m, 2H).

(S)-Methyl 3-((4-(benzyloxy)phenyl)-2-((S)-2-(1,3-dioxoisooindolin-2-yl)-3-(1H-indol-3-yl)propanamido)propanoate (4.20)

To a flame dried round bottom flask kept at 0°C in an ice/water bath was added protected tyrosine^47 4.22 (1.0 g, 3.51 mmol) and CH_2Cl_2 (35 mL). HATU (2.0 g, 5.21 mmol) and triethylamine (1.97 mL, 14.02 mmol) were then added. In a separate flask protected tryptophan 4.21 (1.41 g, 4.21 mmol) was dissolved in CH_2Cl_2 (42 mL), and this solution was added dropwise to the first solution at 0°C. The reaction mixture was stirred at 0.5 h at 0 °C and then allowed to warm to room temperature. The reaction was stirred at room temperature for 4 h. H_2O (30 mL) was added and the organic and aqueous layers were separated. The organic layer
was washed with saturated NaHCO (3 x 20 mL) and brine (1 x 20 mL), dried over Na₂SO₄, filtered and concentrated. Purification of the resulting crude residue by silica gel column chromatography (50% ethyl acetate/50% hexanes) resulted in the isolation of 0.59 g (59%) of product 4.20 as a yellow foam.

4.20. mp = 76-77 °C; TLC Rf = 0.52 (50% ethyl acetate/50% hexanes); IR (KBr) 3359, 3060, 2952, 1776, 1714, 1513 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.93 (s, 1H), 7.77 (dd, J = 5.5, 3.0 Hz, 2H), 7.66 (dd, J = 5.5, 3.0 Hz, 2H), 7.63 (d, J = 7.6 Hz, 1H), 7.42-7.30 (m, 5H), 7.27-7.26 (m, 1H), 7.16 (dt, J = 7.0, 1.1 Hz, 1H), 7.10 (dt, J = 7.2, 1.2 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.79 (dt, J = 9.5, 2.8 Hz, 2H), 6.63 (dt, J = 9.5, 2.8 Hz, 2H), 6.55 (d, J = 7.7 Hz, 1H), 5.24 (t, J = 7.9 Hz, 1H), 4.94 (s, 2H), 4.85-4.50 (s, 1H), 3.76 (dd, J = 15.2, 7.4 Hz, 1H), 3.68 (s, 3H), 3.56 (ddd, J = 15.0, 8.1, 0.5 Hz, 1H), 3.00 (dd, J = 14.0, 5.5 Hz, 1H), 2.93 (dd, J = 14.0, 6.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 171.6, 168.2, 167.9, 157.7, 137.0, 136.3, 134.1, 131.7, 130.1, 128.6, 128.0, 127.4, 126.8, 123.4, 122.9, 122.4, 119.8, 118.7, 114.8, 111.2, 111.1, 69.9, 54.0, 53.5, 52.3, 36.8, 25.5. Anal. Calcd for C₃₆H₃₁N₃O₆: C, 71.87; H, 5.19; N, 6.98. Found: C,71.48; H, 5.38; N, 7.38.

(S)-Methyl 3-(4-(benzylloxy)phenyl)-2-((S)-3-(1,3-dioxoisoindolin-2-yl)-2-oxo-2,3,4,9-tetrahydro-1H-pyrido[2,3-b]indol-1-yl)propanoate (4.30)
To a flame dried round bottom flask was added protected peptide 4.20 (0.10 g, 1.67 mmol) and CH$_2$Cl$_2$ (3 mL) at room temperature. N-Chlorosuccinimide (0.04 g, 0.33 mmol) and triethylamine (0.7 mL, 0.50 mmol) were then added. Oxygen was bubbled through the resulting solution and the mixture was stirred at room temperature for 2 h. The progress of the transformation was carefully monitored and CH$_2$Cl$_2$ was added as needed to keep the level of solvent at approximately 3 mL. After 2 h the solvent was removed in $\textit{in vacuo}$. Purification of the crude residue by silica gel column chromatography (50% ethyl acetate/50% hexanes) resulted in the isolation of 0.03 g (27%) of indole 4.30 as a yellow foam.

**4.30.** mp = 116-117 °C; TLC $R_f$ = 0.51 (50% ethyl acetate/50% hexanes); IR 3415, 2984, 1715, 1585 (KBr) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.05 (br s, 1H), 7.88 (dd, $J$ = 5.5, 3.04 Hz, 2H), 7.74 (dd, $J$ = 5.4, 3.1 Hz, 2H), 7.43-7.22 (m, 9H), 7.16 (d, $J$ = 8.6 Hz, 2H), 7.13-7.06 (m, 2H), 6.79 (d, $J$ = 8.7 Hz, 2H), 5.20 (t, $J$ = 7.6 Hz, 1H), 5.11 (dd, $J$ = 13.7, 7.9 Hz, 1H), 4.88 (s, 3H), 3.72 (s, 3H), 3.61 (t, $J$ = 14.2 Hz, 1H), 3.47-3.35 (m, 2H), 3.06 (dd, $J$ = 14.6, 7.9 Hz, 1H);

HRMS (ESI$^+$) m/z Calc’d for C$_{36}$H$_{29}$N$_3$O$_6$ [M + Na$^+$] 622.1949, found 622.1949

![Chemical structure](image)

(S)-Methyl 3-(4-(benzyloxy)phenyl)-2-((3S,4aR)-3-(1,3-dioxoisooindolin-2-yl)-4a-hydroxy-2-oxo-2,3,4,4a-tetrahydro-1H-pyrido[2,3-b]indol-1-yl)propanoate (4.29)
To a flame dried round bottom flask was added protected peptide **4.20** (0.05 g, 0.08 mmol) and CH$_2$Cl$_2$ (1.5 mL) at room temperature. N-Chlorosuccinimide (0.02 g, 0.17 mmol) and triethylamine (0.04 mL, 0.25 mmol) were then added. The solution was heated to reflux and stirred for 1 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed *in vacuo*. Purification by silica gel column chromatography (50% ethyl acetate/50% hexanes) resulted in the isolation of 0.03 g (60%) of cyclized alcohol **4.29** as a yellow foam.

**4.29.** mp = 95-97 °C; TLC $R_f = 0.67$ (50% ethyl acetate/50% hexanes); IR (CH$_2$Cl$_2$) 3061, 3034, 2950, 1781, 1617, 1580 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.92-7.91 (m, 1H), 7.82-7.81 (m, 1H), 7.48 (d, $J = 7.5$ Hz, 1H), 7.43-7.28 (m, 8H), 7.23-7.13 (m, 2H), 6.86 (dd, $J = 6.8$, 1.9 Hz, 2H), 5.69 (dd, $J = 9.6$, 5.7 Hz, 1H ), 5.49 (dd, $J = 10.3$, 7.4 Hz, 1H), 5.01 (s, 2H), 3.78 (s, 3H), 3.63-3.42 (m, 2H), 2.85-2.87 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.4, 167.3, 167.0, 166.9, 166.4, 157.6, 152.2, 137.2, 136.0, 134.5, 131.8, 131.6, 131.1, 130.4, 130.3, 129.4, 128.5, 127.9, 127.5, 125.7, 123.9, 123.7, 122.2, 120.7, 114.8, 70.0, 64.9, 56.9, 46.9, 33.3, 32.7. HRMS (ESI$^+$) m/z Calc’d for C$_{36}$H$_{29}$N$_3$O$_7$ [M + Na$^+$] 638.1898, found 638.1897

![Chemical Structure](image)

(S)-Methyl 3-(4-(benzylxoy)phenyl)-2-((3S,4aS)-3-(1,3-dioxoisindolin-2-yl)-4a-hydroxy-2-oxo-2,3,4,4a-tetrahydro-1H-pyrido[2,3-b]indol-1-yl)propanoate ((S)-4.29)
To a flame dried round bottom flask was added protected peptide 4.20 (0.10 g, 1.67 mmol) and CH₂Cl₂ (3 mL) at room temperature. N-Chlorosuccinimide (0.04 g, 0.33 mmol) and triethylamine (0.7 mL, 0.50 mmol) were then added. The solution was heated to reflux and oxygen was bubbled through the reaction mixture with stirring at reflux for 1 h. The progress of the transformation was carefully monitored and CH₂Cl₂ was added as needed to keep the level of solvent at approximately 3 mL. The reaction mixture was allowed to cool to rt and solvent was removed in *in vacuo*. Purification of the crude residue by silica gel column chromatography (50% ethyl acetate/50% hexanes) resulted in the isolation of 0.02 g (24%) of cyclized alcohol (S)-4.29 as a yellow foam.

**(S)-4.29.** **mp = 112-114 °C; TLC Rₙ = 0.54 (50% ethyl acetate/50% hexanes); IR (KBr) 3410, 2933, 1721, 1617, 1512 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.93-7.91 (m, 2H), 7.83-7.81 (m, 2H), 7.76-7.73 (m, 2H), 7.48 (d, J = 7.4 Hz, 1H), 7.44-7.29 (m, 7H), 7.23-7.16 (m, 3H), 6.87-6.83 (m, 2H), 5.69 (dd, J = 9.6, 6.0 Hz, 1H), 5.52-5.48 (m, 1H), 5.00 (s, 2H), 3.78 (s, 3H), 3.63-3.58 (m, 1H), 3.49-3.42 (m, 1H), 2.86-2.83 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.7, 169.3, 167.5, 157.7, 153.3, 137.0, 136.0, 134.3, 130.9, 130.3, 129.7, 128.5, 127.9, 127.5, 125.2, 123.8, 123.6, 122.3, 120.4, 114.8, 70.0, 60.4, 56.3, 52.7, 46.4, 32.8, 32.1. Anal. Calcd for C₃₆H₂₉N₃O₇: C, 70.23; H, 4.75; N, 6.83. Found: C,70.08; H, 5.02; N, 6.46.

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Chapter 5
Synthesis of Aminosteroid and Quinoline SHIP Inhibitors

Abstract

Recent research has shown that inhibition of the SH2-containing inositol phosphatase SHIP can modulate the dephosphorylation of phosphoinositols, which are intercalated in the cell membrane. The molecules act as second messengers in a signal transduction cascade, with the phosphorylation pattern on the inositol acting as a key recognition element in the transmission of signals through the cell membrane. The concentration of these second messenger phosphates has a profound effect on cellular function such as cell differentiation, survival, and proliferation. Inhibition of the phosphatase activity of SHIP can be accomplished through the use of small molecule inhibitors such as aminosteroids and quinolines. The work herein describes the synthesis of six aminosteroid analogs of a well studied SHIP inhibitor 3AC. Research was conducted to improve the efficiency of the synthesis of these molecules. The synthesized aminosteroids were tested for SHIP inhibitory potency in a Malachite Green assay.

Also described is the synthesis of two quinoline SHIP inhibitors NSC13480 and NSC305787. Research was conducted to efficiently synthesize these molecules on multi-gram scale. The synthesized quinolines were tested for their inhibitory activity in a Malachite Green assay. The structure activity studies show that a basic near the 4-position of the quinoline and the heterocycle are both required for SHIP inhibition.

Introduction
Phospholipids are a common component of the cell membrane in eukaryotes. One class of phospholipids are comprised of fatty acid chains that are connected to an inositol ring which are further decorated with phosphate groups, often called phosphoinositols. Although phosphoinositols make up only a small part of the cell membrane, these molecules play an important role in cell differentiation, survival, proliferation and effector function. Intracellular enzymes called kinases add phosphates to these inositol rings, while phosphatases remove these phosphates. The phosphorylation pattern on the inositol plays a key role in cellular signaling, as signals are transmitted through these molecules with the phosphorylation pattern acting as a control element for other signaling enzymes. These other signaling enzymes include mitogen activated protein kinases (MAPK), and extracellular-regulated kinases (ERK), whose roles have been studied extensively utilizing small-molecule kinase inhibitors.

The phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) signaling pathway is a major signaling pathway with roles in cellular functions such as cell growth, differentiation, cell motility, and survival. PI3K, once activated by an external stimuli, rapidly synthesizes its target inositol triphosphate, phosphatidylinositol (3,4,5)-trisphosphate (PI-3,4,5-P₃). The PI3K pathway is also regulated by the Src homology 2-containing inositol 5’-phosphatase SHIP which dephosphorylates the second messenger phosphatidylinositol (3,4,5)-trisphosphate (PI-3,4,5-P₃), to form phosphatidylinositol (3,4)-bisphosphate (Figure 5.1). A second phosphatase protein, phosphatase and tensin homolog (PTEN), hydrolyses (PI-3,4,5-P₃) to form phosphatidylinositol (4,5)-bisphosphate. Association of (PI-3,4,5-P₃) with the protein serine-threonine kinase Akt, (sometimes called protein kinase B), and phosphoinositide-dependant kinase 1 (PDK1) at the plasma membrane leads to the phosphorylation and activation of Akt by PDK1, initiating a cascade of protein phosphorylation events that transfers signals from the membrane to the cell.
The concentration of phosphoinositol phosphates regulate downstream effector cascades by controlling the phosphorylation of a host of other proteins downstream in the PI3K signaling pathway.²

**Figure 5.1: PI3K Modification of Inositol at the Cell Membrane**

Two paralogs of SHIP exist in eukaryotic cells, SHIP1 and SHIP2. SHIP1, a 145 kDa enzyme,¹⁰ is found primarily in blood and bone marrow cells, but it can also be found in embryonic stem cells and mesenchymal stem cells.¹¹-¹⁴ In contrast SHIP2 is found ubiquitously throughout the other tissues in the body. SHIP2 is especially prevalent in skeletal muscles, the heart, and placenta.¹⁵ Despite sharing a high rate of amino acid conversion, SHIP1 and SHIP2 each play unique roles in *in vivo* functions such as cellular expression and receptor recruitment.¹⁶ Specifically, SHIP1 is a negative regulator of cell growth and mediates the inhibitory activity of mast cells and B cells.¹⁷-¹⁹ SHIP1 has also been shown to be an inducer of cellular apoptosis,²⁰ and as a negative controller in hematopoietic cell proliferation/survival.²¹ Alternatively, SHIP2 has a role as an inhibitor for the insulin pathway, and mediates insulin resistance.²² The various biological effects regulated independently by SHIP1 and SHIP2 makes
the inhibition and upregulation of SHIP1 and SHIP2 a desirable objective for the treatment of a number of disease states.

Control of the PI3K pathway through inhibition and upregulation of SHIP1 and/or SHIP2 may have applications for the treatment of several human diseases, including cancer. One application of PI3K pathway regulation is the treatment of leukemia. Furthermore, breast cancer tumors and hematological malignancies such as the plasma cell disorder multiple myeloma may be suppressed by regulation of inositol phosphatases in the PI3K pathway. Modulation of PTEN could in theory be used to control PI3K signaling, however, due to PTEN’s role as a tumor suppressor, PTEN inhibition has little hope for therapeutic potential. The inhibition of the PI3K enzyme is also under investigation as an approach in cancer treatment, although inhibition of this enzyme has been troubled by the need for isoform specific inhibitors. As PTEN and PI3K have been shown to be problematic targets, control of PI-3,4,5-P3 through modulation of SHIP1 and SHIP2 has become a passionately researched objective.

Besides cancer, SHIP inhibition has shown promising results in the treatment of several other diseases. For instance, SHIP has been shown to be a repressor of mast cell hyperplasia, cytokine production, and allergic inflammation in vivo. This activity against anaphylactic events in allergy sufferers has led to the development of AQX-1125 which is a candidate for the treatment of allergic asthma (Figure 5.2). Due to the role of SHIP2 as a controller of insulin signaling, SHIP2 inhibition may have potential in the treatment of diabetes as increased activation of SHIP2 results in decreased activation of insulin-stimulated mitogen activated protein (MAP) and decreased insulin-stimulated thymidine incorporation. SHIP inhibition has also shown potential to facilitate bone marrow transplantation and ameliorate Graft vs. Host
Overexpression of an MHC independent-ligand in SHIP knockout mice further provides evidence for inhibition of SHIP as a treatment in Graft Vs. Host disease.\(^{39}\) SHIP knockout mice were also shown to develop a severe inflammatory condition in their lower intestine that appears related to Crohn's disease in humans.\(^{40}\) SHIP1 may also be a genetic determinant to Crohn's Disease susceptibility in humans as single nucleotide polymorphisms found at the same loci as SHIP1 are highly enriched in Crohn's disease patients.\(^{41}\) SHIP1 has also been implicated as playing a role in cystic fibrosis.\(^{42}\) Regulation of osteoclast formation and function is also accomplished by SHIP1.\(^{43}\) Furthermore, inhibition of the SHIP1 enzyme has been shown to lead to an increase in blood cell production in \textit{in vivo} studies with mice.\(^{44}\) Finally, SHIP inhibition should theoretically be a useful treatment in patients with AIDS. This is because patients with AIDS show a reduction in reduced natural killer (NK) cells. SHIP1 has been shown to regulate NK cells.\(^{38,45}\) Therefore the decrease in NK cells may be partially attributed to an increased levels of SHIP1.\(^{46}\) Due to the therapeutic potential of SHIP regulation in ailments such as cancer, diabetes, Graft Vs. Host disease, Crohn's disease, AIDS, and the potential of SHIP1 inhibition to result in increased blood cell production, modulation of the SHIP enzyme utilizing small molecules is a valuable research goal.

\[ \text{Figure 5.2: Structure of AQX-1125} \]

Our investigations have focused on several types of SHIP inhibitors, including aminosteroids (5.5), quinoline aminoalcohols (5.6), tryptamines (5.7) and thiophenes (5.8)
Of these four classes, my research projects have been focused on synthetic efforts towards the aminosteroids and quinoline classes of SHIP inhibitors.

![Figure 5.3: Some Common SHIP Inhibitors](image)

**Aminosteroids**

Utilizing high throughput screening, the parent aminosteroid 3α-aminocholestane 5.5 (3AC) was identified as a selective inhibitor of the SHIP1 enzyme. In the Malachite Green phosphate assay, a biological assay used to follow phosphate release and adapted to for use in determining the activity of the SHIP enzyme, 3AC shows a detectable level of selective SHIP1 inhibition at 2mM and 50% inhibition at 10 mM. Further testing of 3AC in mice revealed that treatment with the molecule expands the myeloid immunoregulatory cell pool and increases the production of red blood cells in myelosuppressed hosts. Treatment with 3AC was also found to significantly increase the number of MIR cells in the spleen and lymph nodes of treated mice with no comparable change observed in the controls. Although 3AC is a selective SHIP1 inhibitor it is not very soluble in water and not potent enough to be a promising drug candidate.
For these reasons we sought to develop aminosteroids that are more potent than 3AC, while also focusing on target molecules that are more polar and water soluble to improve bioavailability and facilitate dosing in animal models.

A number of analogs of 3AC have been prepared in the Chisholm laboratory for both in vitro testing and in vivo trials in mice. Structure-activity studies on these compounds have revealed some useful trends that have guided us toward new synthetic targets. In particular, nonpolar groups on the D ring of the steroid skeleton seem to improve selectivity for SHIP1 inhibition and lower inhibitory activity against SHIP2 (Figure 5.4). These groups may help the aminosteroid fit into a nonpolar section of the binding pocket of SHIP1. Conversely, it was found that polar groups on the D ring of the steroid substructure significantly reduce the SHIP inhibitory activity of these compounds. Based on these observations a tentative model for the binding pocket of SHIP may be proposed (Figure 5.5). The synthesis of our aminosteroid SHIP inhibitors were planned around this model.

Figure 5.4: Steroid Ring System and Numbering

Figure 5.5: Structure Activity Relationships of Aminosteroids
In order to synthesize more potent selective SHIP1 inhibitors an analog with a long chain hydrocarbon tail at the C17 position seems necessary. To improve potency, another polar functional group on the A ring of the steroid was incorporated. The A ring is thought to bind to the phosphatase active site, which is made up of primarily polar amino acids, so it may be possible to form a second contact with a polar group in this area of the enzyme. In addition, a second polar group on the steroid A ring would increase water solubility. To test this hypothesis four molecules based on our previously synthesized molecules were designed to be synthesized (Figure 5.6). The synthesis of aminosteroids K111 and K141 was also planned on larger scale in order to test the compounds in vivo in mice.

![Proposed 3AC Analogs to be Synthesized](image)

**Figure 5.6: Proposed 3AC Analogs to be Synthesized**

**Quinolines**

The high-throughput screening using the National Cancer Institute's (NCI) diversity set also identified a pair of potential quinoline based SHIP inhibitors, NSC 305787 5.15 and
NSC13480  \textbf{5.16}. \textsuperscript{50} Both quinolines were designed as antimalarial agents by chemists at the Walter Reed Army Institute of Research.\textsuperscript{51} The program developed analogs of quinine \textbf{5.17} which is structurally similar to quinidine \textbf{5.18}. This work culminated in the development of mefloquinone \textbf{5.19} which is marketed as Larium and used as a prophylactic and to treat malaria. Recently, mefloquinone \textbf{5.19} was shown to possess anticancer properties at high concentrations, which may be attributed to SHIP inhibition, as our studies have shown that mefloquine does inhibit SHIP at similar concentrations.\textsuperscript{52} Additionally, several similar quinoline amino alcohols have shown activity as antibacterials,\textsuperscript{53} as biofilm formation inhibitors,\textsuperscript{54} and as inducers of vacuolization and cell death in glioblastoma cells.\textsuperscript{55} Because the SHIP gene is not present in bacteria it is unlikely that SHIP inhibition plays a role in these mefloquine's biofilm inhibition or antimicrobial microbial properties, but the quinoline aminoalcohol scaffold may be modified into a selective SHIP inhibitor once structure activity studies reveal the necessary functionality for SHIP inhibition. SHIP inhibition has been shown to be cytotoxic to a number of human cancer cell types both \textit{in vitro} and \textit{in vivo}.\textsuperscript{56-58, 59} Due to our interest in designing and producing effective inhibitors of the SHIP1 and SHIP2 enzymes, we sought to synthesize the quinoline-based SHIP inhibitors \textbf{5.15}-HCl and \textbf{5.16}-HCl, verify their structures and test their activity against SHIP. In addition, the role of the aminoalcohol would be probed with these studies to determine if the chirality centers in the parent molecules are necessary for SHIP inhibition.
Results and Discussion

Initially a synthetic route to the desired aminosteroids 5.13 and 5.14 was developed. The steroid diamines would be derived from the α-bromoketone 5.20 (Scheme 5.1), as this compound is readily formed from a bromination reaction with the corresponding ketone. This ketone is readily available from commercially available 3β, 5α-dihydrocholesterol 5.21.

Scheme 5.1

The synthesis of 5.13 began with an oxidation of commercially available 5-α-cholestan-β-3-ol 5.21 with pyridinium chlorochromate in DCM (Scheme 5.2). The reaction proceeded smoothly providing the corresponding ketone 5.22 in 99% yield. The ketone 5.22 was then brominated at the α position using pyridinium tribromide to provide ketobromide 5.20 in 72%
yield. The interesting regio and stereo selectivity of this reaction warrants some additional discussion. Examination of the possible enol intermediates show that enol 5.26 is the most thermodynamically stable (Figure 5.8). Studies performed by Velluz and coworkers show that enol 5.27 is disfavored. This is due to the steric strain imposed by the axial C-10 methyl group is greater for a decalin with a 3,4 alkene (5.27) than a 2,3 alkene (5.26). Additionally, the enolization shown in figure 5.8 causes planarization of the α hydrogen leading to steric strain between the α hydrogen and the C-6 equatorial hydrogen. The stereochemistry of the bromide is always obtained as the shown equatorial isomer. This is because epimerization of the bromide will lead to the equatorial alcohol to relieve 1,3 diaxial strain between the bromide and the C-10 axial methyl group. This epimerization may be rapid under the reaction conditions, as enolization of the ketone is facilitated by the acetic acid media. Indeed, examination of the crude reaction via 1H NMR shows no product with axial bromides (Figure 5.9). Evidently, other ketobromides are formed in this reaction but the desired ketobromide 5.20 is less soluble in the polar solvent and precipitates from the reaction, allowing for its isolation by filtration. This allowed for rapid isolation of ketobromide 5.20 which was obtained following α bromination in 72% yield.
Scheme 5.2

Figure 5.8: Possible Enol Intermediates
After formation of ketobromide 5.20, S
\textsubscript{N}2 displacement of the bromide with NaN\textsubscript{3} resulted in the formation of the corresponding ketoazide 5.23 with good yield (75%). Epimerization of the azide moiety resulted in the formation of the less strained equatorial azide. Again the axial methyl group at the C-10 position controls the observed stereochemistry, as it induces rapid equilibration of the azide to the equatorial isomer to avoid the 1,3-diaxial interaction. Chemoselective reduction of the ketone functional group with sodium borohydride then resulted in the formation of diastereomers 5.24 and 5.25 which could be isolated using column chromatography resulting in yields of 38% of 5.24 and 24% of 5.25. Difficulty was encountered in separating the cis-azido alcohol from unidentifiable impurities, which is almost certainly the cause of the uneven yields. After this point the synthesis of compounds 5.24 and 5.25 diverged and the alcohols were treated separately. Lithium aluminum hydride reduction of azidoalcohol 5.24 provided the corresponding amine, which was taken on without purification.
The amine was then treated with HCl (g) to generate the amine hydrochloride salt 5.11 with a yield of 28% over 2 steps.

**Scheme 5.3**

With the synthesis of 5.11 completed, we set our sights on the synthesis of the related diastereomer 5.12. The azido alcohol 5.25 was reduced via a Staudinger reduction to generate aminoalcohol 5.30 with excellent yield (98%). Treatment of amine 5.30 with HCl gas generated amine hydrochloride 5.12 with a 95% yield.

**Scheme 5.4**

The synthesis of the diamine 5.13 was envisioned to occur from alcohol 5.24 (Scheme 5.5). The alcohol was mesylated using MsCl and pyridine and the corresponding mesylate 5.31 was carried on to the next step without purification. The mesylate was displaced with sodium azide to provide the corresponding diazide steroid 5.31 with a yield of 68% over 2 steps. The SN2 displacement resulted in an inversion of stereochemistry at the C3 position, as was clear.
from the coupling constants in the $^1$H NMR. With pure diazide 5.31 in hand lithium aluminum hydride reduction to provide the diamine 5.32 was attempted. Unfortunately, the reaction resulted in a complex mixture from which the desired product could not be isolated. A Staudinger reduction was also evaluated, and again the result was a complex mixture that did not provide the desired product. Finally, hydrogenation conditions were used and the reaction proceeded smoothly providing the corresponding diamine. The diamine was acidified using gaseous HCl to provide diamine hydrochloride 5.13 in 24% yield over 2 steps.

Scheme 5.5

With the synthesis of 5.13 complete we set our focus on the synthesis of diastereomer 5.14. The azidoalcohol 5.25 was converted to the corresponding mesylate using methanesulfonyl chloride and pyridine (Scheme 5.6). The resulting crude mesylate was converted to the diazide following and $S_{N2}$ displacement with sodium azide providing diazide 5.33 with a yield of 37% over 2 steps. The $S_{N2}$ attack resulted in an inversion of stereochemistry.
at the C3 position as determined by $^1$H NMR. Again, the diazide 5.33 was subjected to reduction conditions with LiAlH$_4$ and again we were disappointed to find the reaction provided only a crude mixture. Subjecting diazide 5.33 to hydrogenation conditions, however, provided the desired diamine with little trouble. Acidification of this diamine with HCl gas provided the corresponding diamine chloride 5.14 in 20% yield over 2 steps. With the syntheses of steroid 5.11-5.14 completed the compounds were given to our collaborators at SUNY Upstate for testing in a malachite green assay, and these results will be disclosed in due course.

**Scheme 5.6**

In addition to the synthesis of the aminoalcohols and diamines, the synthesis of two other aminosteroid analogs (K111 and K141) was scaled up so that the compounds could undergo further biological testing. The synthesis of aminosteroid SHIP inhibitor K111 began with a Wolff-Kishner reduction of commercially available pregnenolone 5.35. Although it was expected that this reaction would run smoothly due to the lack of complicating functional groups
present in pregnenolone, the reaction was more challenging than anticipated and many conditions had to be evaluated to reach the eventual yield of 85%. Initial attempts to reduce the ketone to the corresponding alkane via Wolff-Kishner reduction failed and no product was recovered (Table 5.1, entry 1). A second attempt using HCl and DCM for the extraction also failed as an emulsion formed which made separation difficult (entry 2). At this point, it was noted that despite the reaction being heated to refluxing conditions, the drip rate from the reflux condenser was very slow. It was hypothesized that the reaction may not be going to completion because the sand bath was not heating the reaction to a hot enough temperature. To our delight, changing to a different sand bath which was smaller, improving contact with the reaction flask and therefore gave better heat delivery provided significantly improved results and the desired steroid 5.36 was obtained in good yield (63%-65%, entries 3-4). In addition MTBE was utilized for the extractive workup and although separation with the solvent was easy, many extractions were required to fully remove the steroid from the aqueous layer. Changing the extraction solvent to ethyl acetate provided cleaner workup conditions and provided our desired steroid 5.36 in excellent yield (85%, entry 5). A Mitsunobu reaction of the C3 alcohol using diisopropyl azodicarboxylate (DIAD) and diphenylphosphoryl azide then provided the corresponding azide 5.37 in good yield (84%) with inverted stereochemistry relative to the starting alcohol. Lithium aluminum hydride reduction of azide 5.37 proceeded smoothly and resulted in the isolation of amine 5.38 in 46% yield. The synthesis was completed by treatment of amine 5.38 with gaseous HCl which afforded the hydrochloride salt in 68% yield. Synthesis of K111 was completed and resulted in the formation of K111 in 22% overall yield over 4 steps.
The synthesis of aminosteroid K141 was then undertaken (Scheme 5.8). Again, a Wolff-Kishner reduction was the first step of the reaction. Here, as previously discussed, high temperatures were key to getting the reaction to proceed to completion (Table 5.2). The larger sand bath again provided none of the desired product 5.40 (entries 1-2). After switching to the smaller sand bath, the use of MTBE in the extraction was key to achieving higher isolated yields.
of the desired steroid product 5.40. The C3 alcohol of compound 5.40 was then oxidized with pyridinium chlorochromate (PCC) and purified through a short plug of silica gel, providing the corresponding ketone product 5.41. Bromination of ketone 5.41 was accomplished using pyridinium tribromide in acetic acid. Filtration of crude reaction mixture resulted in the isolation of ketobromide 5.42 in good yield (68%). Presumably, the regioselectivity and stereoselectivity of this reaction is governed by the same forces which provided ketobromide 5.20 (see Scheme 5.2). Displacement of the secondary bromide via substitution with sodium azide resulted in the isolation of ketoazide 5.43 in 56% yield. In this case displacement of the bromide was followed by epimerization which provided the more thermodynamically stable equatorial azide as the sole observed substitution product. Chemoselective reduction of the ketone over the azide was accomplished by use of the bulky reducing agent L-selectride, resulting in the formation of the azido alcohol 5.44 in 70% yield. The bulky reducing reagent prefers to deliver the hydride from the equatorial face, which leads to the selective formation of the axial alcohol. Reduction of the azide to the corresponding amine was followed by formation of the hydrochloride salt with gaseous HCl in diethyl ether. This provided synthetic target K141 in 40% yield over 2 steps. The overall yield for the reaction sequence was 9% over 7 steps. Approximately 1 g of K111 and K141 were prepared using these routes, and these materials were then provided to co-workers at SUNY Upstate Medical University for further evaluation.
Scheme 5.8

Table 5.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scale (mmol)</th>
<th>Extraction conditions</th>
<th>Sand bath diameter (cm)</th>
<th>Yield (%)</th>
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<td>26</td>
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<tr>
<td>6</td>
<td>20.6</td>
<td>a</td>
<td>16</td>
<td>83</td>
</tr>
</tbody>
</table>

Extraction conditions: a) Extracted with MTBE 7 x 200 mL, organic layers washed with brine  
b) Quenched with HCl (30 mL) extracted w/ CH₂Cl₂ (7 x 100 mL), washed with brine
Synthesis of Quinoline SHIP Inhibitors

The quinolines NSC13480 and NSC305787 have been reported to have activity as SHIP inhibitors. The development of a synthesis amenable to accessing these compounds on a gram scale was investigated to the molecules could undergo further biological evaluation. Retrosynthetically the route used to access these molecules would follow the general path outlined in Scheme 5.9. The aminoalcohol portion of the molecule would derive from an epoxide like 5.46, which can be opened upon deprotection of the amine to form the piperidine ring. The epoxide will come from the corresponding E-alkene, which may be accessed by Horner-Wittig chemistry.

Scheme 5.9

The new synthetic route to dichloroquinoline 5.15·HCl began with a chlorination of isatin 5.50 using trichloroisocyanuric acid (TCCA) and sulfuric acid as a solvent. This reaction initially posed a throughput problem as the transformation is highly exothermic, with large scale attempts heating uncontrollably. Furthermore, some low yielding steps later in the synthesis to form the desired quinoline meant that large quantities of dichloroisatin 5.51 would need to be synthesized in order to achieve the desired throughput. This reaction overheating issue was solved by beginning the reaction at -78°C and allowing the reaction mixture to slowly and safely warm to room temperature. Using this technique up to 100 mmol of isatin could be produced in
a single batch, with the yield being virtually quantitative. Following the chlorination reaction, dichloroisatin 5.51 was subjected to a Pfitzinger reaction which provided the desired carboxylic acid 5.52 in 17% yield over 2 steps. Although the yield for this reaction was low the product could be easily isolated from crude side products through recrystallization which was desirable when performing the reaction on large scale. Reduction of carboxylic acid 5.52 with BH₃ in THF resulted in the formation of the desired alcohol 5.53. Alcohol 5.53 was the converted to the corresponding chloride 5.54 using thionyl chloride in DCM. Despite the apparent simplicity of this reaction numerous conditions had to be tried to affect the desired transformation (Table 5.3). The Appel reaction was initially evaluated (entries 1-2), but the reaction provided a complex mixture of compounds that was difficult to purify so the reaction was not pursued. Other chlorinating agents such as oxalyl chloride (entry 3) and TCCA (entry 4) were found to consume the starting material, however no desired chloride product could be isolated from the reaction mixture. Treating alcohol 5.53 with SOCl₂ in pyridine gave the product 5.54 along with a side product that appears to be formed from displacement of the resulting chloride 5.54 with another nucleophile, perhaps some type of chlorosulfonate (entry 5). The chlorinating agent methanesulfonyl chloride was also evaluated but consumption of starting material was not observed, and these conditions were not further optimized (entry 6). Eventually, it was determined that SOCl₂ in DCM in the absence of pyridine provided the best and most consistent results for the formation of chloride 5.54 (entry 7). Chloride 5.54 was obtained in 44% yield over 2 steps from carboxylic acid 5.52 (entry 8). An Arbuzov reaction with chloride 5.54 resulted in the isolation of the corresponding phosphonate 5.55 in 75% yield. This product was isolated following silica gel chromatography and taken forward in the synthesis of 5.15 HCl.
Scheme 5.10

With the synthesis of phosphonate precursor complete, the intermediate phosphonate 5.55 was provided to other co-workers for completion of the synthesis. A Horner-Wadsworth-Emmons
reaction was performed with the phosphonate precursor 5.55 and aldehyde intermediate 5.49 and the desired E alkene was obtained with good selectivity (>20:1 by \(^1\)H NMR) and yield (74%). The E alkene 5.56 was then epoxidized using meta-chloroperoxybenzoic acid (m-CPBA) to provide the corresponding epoxide 5.57. Deprotection of the phthalimide moiety of 5.57 with hydrazine resulted in the spontaneous cyclization of the newly formed amine and opening of the epoxide to provide desired product 5.15. Finally, treatment of amine 5.15 with HCl resulted in the formation of amine hydrochloride salt 5.15·HCl in 60% yield.

**Scheme 5.11**

With the synthesis of quinoline SHIP inhibitor 5.15·HCl completed work began on the synthesis of the second quinoline 5.16·HCl. This synthesis began with a Doebner condensation of 1-naphthylamine 5.58, benzaldehyde and pyruvic acid in ethanol. The reaction resulted in the
isolation of carboxylic acid 5.59 in 25% yield. Although the yield for this reaction was low, the reaction required only 3.5 hours of reaction time and just a simple filtration for purification. Furthermore the reaction was easily scaled up to use 100 mmol of 1-naphthylamine without difficulty. The carboxylic acid 5.59 was then reduced to alcohol 5.60 using NaBH₄ and I₂ to form borane in situ. This reaction allowed us to avoid using the more expensive reducing agent BH₃•THF. Alcohol 5.60 was converted to chloride 5.61 in 44% yield over 2 steps without difficulty using thionyl chloride. An Arbuzov reaction of chloride 5.61 provided the corresponding phosphonate compound 5.62 in 42% yield. Overall, the synthesis of this portion of the molecule was operationally simple despite some yields being low.

Scheme 5.12

With synthesis of the phosphonate 5.62 completed, work began on the finishing the synthesis of aminoalcohol 5.16·HCl. The aldehyde condensation partner 5.49 was synthesized in two steps from commercially available amino alcohol 5.63 in 86% yield over two steps. Subsequent Horner-Wadsworth-Emmons⁶¹ reaction of phosphonate 5.62 and aldehyde 5.49 resulted in the formation of the corresponding E alkene 5.64 in 68%. The E alkene was formed preferentially over the Z alkene in greater than 20:1 ratio (as determined by ¹H NMR analysis). Epoxidation of alkene 5.64 with meta-chloroperoxybenzoic acid (m-CPBA) provided the desired epoxide 5.65 in 61% yield. Removal of the phthalimide protecting group with hydrazine led to a
cyclization reaction of the resulting amine on the epoxide, providing the desired aminoalcohol product \( \text{5.16} \) in 62% yield. Formation of the hydrochloride salt with HCl in ether provided the synthetic target \( \text{5.16-HCl} \) in 60% yield.

**Scheme 5.13**

With the synthesis of quinoline SHIP inhibitors \( \text{5.15-HCl} \) and \( \text{5.16-HCl} \) completed, these compounds were turned over to our collaborators at SUNY Upstate in order to test their inhibition of SHIP1 and SHIP2 (Table 5.4). When these compounds were initially synthesized, their inhibition was tested using a Fluorescence Polarization assay for phosphatase activity. Unfortunately, this assay was expensive and great care had to be taken with fluorescent compounds such as quinolines to assure accurate and repeatable results, as the fluorescence of the quinoline often interfered with the results of the assay. For this reason our collaborators employed the colorimetric Malachite Green assay in order to evaluate the compounds’ SHIP inhibitory activity. The quinoline \( \text{5.16-HCl} \) was found to precipitate in the conditions used in the
Malachite Green assay and so the more soluble citrate salt of this compound was prepared and evaluated (entries 1-2). The inhibitory activity of 5.16-citrate was found to be moderate with the compound providing 38% and 17% inhibition for SHIP1 and SHIP2 respectively. Interestingly, 5.15-HCl provided significantly stronger inhibition results with 38% and 73% inhibition for SHIP1 and SHIP2 respectively (entry 3). The high SHIP2 inhibition is particularly notable.

Mefloquine hydrochloride provided inhibition of 54% against both SHIP paralogs (entry 4). The previously reported antitumor activity possessed by mefloquine may be explained by this SHIP inhibitor activity. The quinine and quinidine sulfates 5.17 and 5.18 both showed comparatively little SHIP inhibition (entries 5-6). The role of the aminoalcohol core in the SHIP inhibitory activity was also probed. Carboxylic acids 5.59 and 5.52 were tested as well as alcohols x and x and no significant inhibition of SHIP was observed except for some moderate SHIP1 inhibitory activity displayed by carboxylic acid 5.52 (entries 7-10). From these results we hypothesized that the amine portion of the molecule may be more important to SHIP inhibitory activity. The lack of activity of (1R,2S)-(−)- ephedrine 5.66 and (1R,2S)-(+) pseudoephedrine 5.67 in the Malachite Green assay also supported that the quinoline and amine may both be necessary for SHIP inhibition. To test this hypothesis the quinoline 5.68 was synthesized from alcohol 5.60 using classical Gabriel conditions. Quinoline 5.68 was found to exhibit significant activity in the Malachite Green assay with 41% inhibition against the SHIP1 paralog and 66% inhibition against the SHIP2 paralog. The result confirms the importance of both the amine and quinoline moieties for SHIP inhibition and provides a blueprint for future development of quinoline SHIP inhibitors.
Table 5.4

<table>
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<tr>
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<td>N/A⁵</td>
<td>N/A⁵</td>
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<tr>
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<td>5.16·citrate</td>
<td>38</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>5.15·HCl</td>
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<tr>
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<tr>
<td>5</td>
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</tr>
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<tr>
<td>13</td>
<td>5.68</td>
<td>41</td>
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</table>

³ Results from the Malachite Green assay performed at 1 mM concentration
⁴ Compound precipitated during testing
⁵ Evaluated at 500 μM

Conclusion

A viable synthetic route to the aminosteroid analogs of selective SHIP1 inhibitor 3AC 5.11, 5.12, 5.13, 5.14, K111, and K141 has been developed. Optimization of Wolff-Kishner reactions for compounds 5.35, and 5.39 led to a more efficient syntheses of these compounds. Similarly, optimization of the azide reducing conditions for compounds 5.31, and 5.33, was also conducted. The aminosteroids are now being tested for SHIP1 and SHIP2 inhibitory activity by our collaborators at SUNY upstate.

Quinoline SHIP inhibitors 5.15·HCl and 5.16·HCl were synthesized with overall yields of 1.0% and 0.7% respectively. Optimization of the synthetic routes used to prepare these
compounds allowed for their preparation on multi-gram scale. Structure activity relationships conducted on the intermediates for these compounds show that both quinoline and amine are necessary for SHIP inhibition. The synthesis of similar aminosteroid and quinoline SHIP1 selective, SHIP2 selective, and pan-SHIP inhibitors will be used to probe the biological effects of SHIP inhibition.

**Experimental Section**

(5S,8R,9S,10S,13R,14S,17R)-10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)tetradecahydro-1H-cyclopenta[a]phenanthren-3(2H)-one (5.22)


To pyridinium chlorochromate (3.30 g, 15.44 mmol), dissolved in dichloromethane (40 mL) was added 5α-cholestan-3-β-ol (3.00 g, 7.78 mmol) followed by silica gel (3.30 g). The reaction mixture was stirred at rt overnight. The resulting suspension was filtered through a plug of silica gel with 10% ethyl acetate/90% hexanes until no more product was observed in the filtrate by TLC. The solvent was removed *in vacuo* resulting in the isolation of 2.97 g (99%) of ketone 5.22 as a white powder.

5.22. White powder (2.97 g, 99%); mp = 129-131°C; TLC R<sub>f</sub> = 0.36 (10% ethyl acetate/90% hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ 2.42-2.23 (m, 3H), 2.10-1.93 (m, 3H), 1.87-1.78 (m, 1H), 1.72-1.67 (m, 1H), 1.60-1.48 (m, 8H), 1.42-1.29 (m, 7H), 1.26-1.23 (m, 1H), 1.18-1.05 (m, 7H), 1.01-0.94 (m, 4H), 0.91-0.85 (m, 9H), 0.76-0.70 (m, 1H), 0.68 (s, 3H).
((2R,5S,8R,9S,10S,13R,14S,17R)-2-Bromo-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)tetradecahydro-1H-cyclopenta[a]phenanthren-3(2H)-one (5.20)


Ketone 5.22 (0.99 g, 2.62 mmol) was dissolved in acetic acid (2.62 mL). The solution was warmed to 50 °C in an oil bath and pyridinium tribromide (0.84 g, 2.62 mmol) was added. The reaction was stirred at 50 °C for 10 minutes until a precipitate formed. The reaction mixture was allowed to cool to room temperature and the precipitate was collected by filtration and dried under reduced pressure resulting in the isolation of 0.88 g (72%) of ketobromide 5.20 as an off-white solid.

5.20. Off white solid (1.57 g, 68%); mp = 157-158 °C; TLC Rf = 0.49 (10% ethyl acetate/90% hexanes); 1H NMR (400 MHz, CDCl3), δ 4.74 (dd, J = 13.6, 6.0 Hz, 1H), 2.63 (dd, J = 12.8, 6.0 Hz, 1H), 2.42-2.39 (m, 2H), 1.99 (dt, J = 12.8, 3.4 Hz, 1H), 1.88-1.78 (m, 2H), 1.72-1.68 (m, 1H), 1.55 (app s, 9H), 1.40-1.32 (m, 7H), 1.17-1.08 (m, 8H), 1.03-0.97 (m, 2H), 0.91-0.85 (m, 8H), 0.81-0.75 (m, 1H), 0.60 (s, 3H).
(2R,5S,8R,9S,10S,13R,14S,17R)-2-Azido-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)tetradecahydro-1H-cyclopenta[a]phenanthren-3(2H)-one (5.23)


Ketobromide **5.20** (0.50 g, 1.07 mmol) was dissolved in dimethylformamide (20 mL). NaN₃ (0.08 g, 1.29 mmol) was added and the solution was stirred at room temperature for 4 hours. The solution was then poured over crushed ice and allowed to warm to room temperature. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with cold water (2 x 20 mL), and brine (1 x 20 mL). The organic extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Silica gel chromatography (10% ethyl acetate/90% hexanes) was performed, resulting in the isolation of 0.35 g (75%) of **5.23** as a white solid.

**5.23.** White solid (0.35 g, 75%); mp 118-121 °C; TLC _R_f = 0.46 (10% ethyl acetate/90% hexanes); ¹H NMR (400 MHz, CDCl₃), δ 3.98 (dd, _J_ = 12.8, 6.4 Hz, 1H), 2.40-2.11 (m, 3H), 2.00 (dt, _J_ = 12.6, 3.4 Hz, 1H), 1.86-1.78 (m, 1H), 1.74-1.68 (m, 1H), 1.60-1.48 (m, 4H), 1.41-1.30 (m, 8H), 1.29-1.23 (m, 2H), 1.18-1.10 (m, 5H), 1.08 (s, 3H), 1.05-0.96 (m, 3H), 0.91-0.85 (m, 9H), 0.81-0.74 (m, 1H), 0.67 (s, 3H).
Reduction of \((2R,5S,8R,9S,10S,13R,14S,17R)-2\text{-Azido-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)tetradecahydro-1H-cyclopenta[a]phenanthren-3(2H)-one}\)


A solution of azidoketone 5.23 (2.87 g, 1.66 mmol) in diethyl ether (25 mL) was added to a suspension of sodium borohydride (0.37 g, 2.48 mmol) in ether:methanol (250 mL, 4:1). The reaction mixture was stirred continuously at room temperature. After approximately 2 h, the reaction mixture was quenched by adding saturated sodium bicarbonate solution (25 mL). The reaction mixture was extracted with ether (3 x 25 mL). The organic layers were collected, dried over magnesium sulfate, and concentrated under reduced pressure. The concentrate was purified using silica gel chromatography (5% ethyl acetate/95% hexane) to afford 5.24 (1.08 g, 38%) as a white foam and 5.25 (0.67 g, 24%) as a clear colorless oil.

**5.24.** White foam (1.08 g, 38%); mp = 95-100°C; TLC \(R_f = 0.18\) (5% ethyl acetate/95% hexanes); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)), \(\delta\) 3.46-3.32 (m, 2H), 2.16 (d, \(J = 2.9\) Hz, 1H), 2.03-1.96 (m, 2H), 1.88-1.78 (m, 1H), 1.74-1.68 (m, 2H), 1.53-1.47 (m, 3H), 1.36-1.24 (m, 9H), 1.16-1.00 (m, 9H), 0.91-0.85 (m, 14H), 0.73-0.67 (m, 1H), 0.65 (s, 3H).
5.25. Clear colorless oil (0.67 g, 24%); TLC R<sub>f</sub> = 0.27 (5% ethyl acetate/95% hexanes); H<br>NMR (400 MHz, CDCl<sub>3</sub>), δ 3.97 (br s, 1H), 3.56-3.51 (m, 1H), 2.00-1.95 (m, 2H), 1.86-1.75 (m, 2H), 1.69-1.45 (m, 8H), 1.40-1.21 (m, 8H), 1.18-0.98 (m, 9H), 0.91-0.85 (m, 10H), 0.82 (s, 3H), 0.65 (s, 3H).

**Diagram**


A suspension of LiAlH<sub>4</sub> (0.05 g, 1.29 mmol) in THF (3 mL) was cooled at 0 °C using an ice/water bath. A solution of azidoalcohol 5.24 (0.17 g, 0.39 mmol) in THF (3 mL) was added dropwise to the cooled suspension. After approximately 10 min, the reaction mixture was allowed to warm to room temperature after which it was heated to reflux. After 4h, the reaction mixture was cooled to room temperature and diluted with THF (6 mL). The reaction mixture was then cooled to 0 °C and quenched using the Fieser method. The quenched reaction mixture was filtered through celite, dried over magnesium sulfate, and concentrated under reduced pressure. Purification by column chromatography (1% NH₄OH/9% MeOH/90% dichloromethane) resulted in the isolation of free amine. The free amine was dissolved in diethyl ether and dry hydrogen chloride, produced from reacting sodium chloride with concentrated sulfuric acid, was purged into the solution resulting in the formation of a precipitate. The solution was filtered through celite and the precipitate was collected, washed with diethyl ether, and dried under reduced pressure to afford 0.05 g (28% over 2 steps) of amine salt x as a white solid.
5.11. White solid (0.05 g, 28%); mp = 202 °C (dec); IR (KBr) 3418, 2932, 1655, 1501, 1459 cm⁻¹; ¹H NMR (400 MHz, MeOD), δ 3.46 (td, J = 10.6, 5.0 Hz, 1H), 3.31 (br s, 2H), 3.08-3.02 (m, 1H), 2.05-2.02 (m, 2H), 1.87-1.81 (m, 1H), 1.73-1.68 (m, 2H), 1.59-1.50 (m, 3H), 1.39-1.25 (m, 10H), 1.19-1.02 (m, 10H), 0.94-0.87 (m, 13H), 0.81-0.74 (m, 1H), 0.71 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ 56.3, 56.2, 54.0, 53.6, 44.4, 42.3, 40.9, 39.8, 39.3, 36.6, 36.2, 35.9, 34.9, 31.5, 27.9, 27.7, 27.6, 23.8, 23.5, 21.7, 21.5, 21.1, 17.8, 11.8, 11.1. Anal. Calcd for C₂₇H₅₀ClNO: C, 73.68; H, 11.45; N, 3.18. Found: C, 73.86; H, 11.70; N, 2.95.

![Chemical structure](https://via.placeholder.com/150)


To a flame dried round bottom flash was added azidoalcohol 5.25 (0.06, 0.13 mmol) and PPh₃ (0.07 g, 0.26 mmol). Dry THF was added (1 mL) and the reaction mixture was stirred at room temperature for 2h. Water was added (5 mL) and the reaction mixture was refluxed overnight. The reaction mixture was cooled to room temperature and the organic layer was collected, dried over magnesium sulfate and concentrated under reduced pressure. The resulting material was dissolved in THF and silica gel (0.5 g) was added. The mixture was stirred at 40 °C for 1h and concentrated *in vacuo*. Purification by column chromatography (1% NH₄OH/9% MeOH/90% dichloromethane) resulted in the isolation of free amine 5.30 (0.05 g, 98%).
**5.30.** White solid (0.05g, 98%); mp = 198-202 °C; TLC R<sub>f</sub> = 0.47 (10% MeOH/ 90% CH<sub>2</sub>Cl<sub>2</sub>);

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ 3.72 (br s, 1H), 3.00 (dt, J = 12.0, 4.0 Hz, 1H), 1.95 (dt, J = 12.3, 4.0 Hz, 2H), 1.83-1.76 (m, 3H), 1.67-1.63 (m, 1H), 1.60-1.45 (m, 7H), 1.34-1.23 (m, 7H), 1.12-1.06 (m, 7H), 1.02-0.97 (m, 3H), 0.91-0.85 (m, 10H), 0.80 (s, 3H), 0.78-0.71 (m, 1H), 0.64 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), δ 56.4, 56.22, 54.19, 42.6, 41.0, 40.0, 39.5, 38.1, 36.4, 36.2, 35.8, 35.1, 34.1, 31.9, 29.7, 28.23, 28.21, 28.0, 27.9, 24.2, 23.8, 22.8, 22.6, 20.9, 18.7, 12.5, 12.1.


Free amine 5.30 was dissolved in diethyl ether (25 mL). Dry hydrogen chloride gas, produced from reacting sodium chloride with concentrated sulfuric acid, was purged into the solution resulting in the formation of a precipitate. The solution was filtered through celite and the precipitate was collected, washed with diethyl ether, and dried under reduced pressure to afford 0.05 g (95%) of amine salt 5.12 as a white solid.

**5.12.** White solid (0.05 g, 95%); mp = 207°C (dec): IR (KBr) 3438, 2829, 1656, 1451 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD), δ 4.01 (s, 1H), 3.33-3.32 (m, 4H), 2.06-2.03 (m, 1H), 1.89-1.83 (m, 1H), 1.76-1.72 (m, 2H), 1.65-1.53 (m, 6H), 1.45-1.31 (m, 10H), 1.21-1.12 (m, 5H), 1.08-1.02 (m, 3H), 0.96-0.88 (m, 12 H), 0.87-0.80 (m, 1H), 0.72 (s, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD), δ 64.8, 56.4, 56.2, 54.1 50.1, 42.3, 39.8, 39.3, 37.8, 36.6, 36.3, 35.9, 35.7, 35.0, 34.8, 31.6, 27.9,
27.7, 27.4, 23.5, 21.8, 21.5, 20.6, 17.8, 11.1, 10.9. Anal. Calcd for C$_{27}$H$_{50}$ClNO: C, 73.68; H, 11.45; N, 3.18. Found: C, 74.08; H, 11.70; N, 2.95.

(2R,3S,5S,8R,9S,10S,13R,14S,17R)-2,3-Diazido-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthrene (5.31)

Azidoalcohol 5.24 (0.21 g, 0.48 mmol) was dissolved in pyridine (2 mL). Methanesulfonyl chloride (0.07 mL, 0.82 mmol) was added dropwise and the reaction mixture was stirred for 24 h. Water (5 mL) was added and the quenched reaction mixture was extracted with DCM (20 mL). The organic layers were collected, washed with hydrochloric acid (2 x 10 mL, 6 M) followed by sat. sodium bicarbonate (2 x 10 mL) and water (2 x 10 mL). The solution was dried over sodium sulfate and concentrated under reduced pressure to afford the corresponding crude azidomesylate. The azidomesylate was dissolved in DMF (2 mL) and sodium azide (0.53 g, 0.82 mmol) was added. The reaction mixture was stirred for 20h at 100 °C. The reaction mixture was cooled and poured over crushed ice. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with H$_2$O, (1 x 10 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. Purification by column chromatography (10% ethyl acetate/90% hexanes) resulted in the isolation of 0.30 g (68% over two steps) of the product 5.31 as a white solid.

5.31. White solid (0.23 g, 68%); mp = 98-100 °C; IR (KBr) 2938, 2870, 2851, 2080, 1460 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$), $\delta$ 3.91-3.90 (m, 1H), 3.49 (dt, $J = 12.5, 4.0$ Hz, 1H), 1.98 (dt, $J =$ 171
12.3, 3.0 Hz, 1H), 1.84-1.77 (m, 2H), 1.69-1.65 (m, 1H), 1.58-0.80 (m, 37H), 0.65 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$), $\delta$ 61.8, 58.8, 56.3, 36.2, 54.0, 42.6, 39.8, 39.5, 39.1, 37.4, 36.8, 36.2, 35.8, 34.9, 32.5, 31.6, 28.2, 28.0, 27.5, 24.2, 23.8, 22.8, 22.6, 20.9, 18.7, 12.6, 12.1. Anal. Calcd for C$_{27}$H$_{46}$N$_6$: C, 71.32; H, 10.20; N, 18.48. Found: C, 71.60; H, 10.43; N, 18.69.


To a flame dried round bottom flask was added diazide 5.31 (0.08 g, 0.2 mmol) and 10% Pd/C (0.02 g, 0.02 mmol). A balloon filled with hydrogen gas was added to the reaction vessel and MeOH (5 mL) was added carefully. The reaction mixture was stirred at room temperature for 90 min. The reaction mixture was filtered through celite and washed through with methanol. The filtrate was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting powder was dissolved in diethyl ether (20 mL). Dry hydrogen chloride gas, produced from reacting sodium chloride with concentrated sulfuric acid, was purged into the solution resulting in the formation of a precipitate. The solution was filtered through celite and the precipitate was collected, washed with diethyl ether, and dried under reduced pressure to afford 0.06 g (24% over two steps) of amine salt 5.13 as a white solid.

5.13. White solid (0.06 g, 24%); mp = 183 °C (dec); IR (KBr) 3429, 2932, 1657, 1459, 1251 cm$^{-1}$; $^1$H NMR (300 MHz, MeOD), $\delta$ 3.70 (br s, 1H), 3.61-3.57 (m, 1H), 1.97-1.87 (m, 2H), 1.67-0.90 (m, 27H), 0.85-0.83 (m, 8H), 0.79-0.77 (m, 10H), 0.61 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ 56.24, 56.16, 53.2, 49.3, 42.3, 39.7, 39.2, 38.0, 36.8, 36.0, 35.9, 35.7, 34.8, 31.2, 30.7, 27.8,
27.7, 26.9, 23.7, 23.5, 21.8, 21.5, 20.6, 17.8, 11.2, 11.1. Anal. Calcd for C_{27}H_{52}Cl_{2}N_{2}: C, 68.18; H, 11.02; N, 5.89. Found: C, 68.58; H, 10.64; N, 5.86.


In a round bottom flask, azidoalcohol 5.25 (1.08 g, 2.45 mmol) was dissolved in pyridine (10 mL). Methanesulfonyl chloride (0.34 mL, 4.17 mmol) was added dropwise and the reaction mixture was stirred for 24h. Water (10 mL) was added and the quenched reaction mixture was extracted with DCM (20 mL). The organic layers were collected, washed with hydrochloric acid (2 x 20 mL, 6 M) followed by sat. sodium bicarbonate (2 x 10 mL) and water (2 x 10 mL). The solution was dried over sodium sulfate and concentrated under reduced pressure to afford the corresponding crude azidomesylate. The azidomesylate was dissolved in DMF (10 mL) and sodium azide (0.26 g, 3.98 mmol) was added. The reaction mixture was stirred for 20h at 100°C. The reaction mixture was cooled and poured over crushed ice. The resulting mixture was extracted with ethyl acetate (5 x 10 mL). The organic layer was washed with H_{2}O, (1 x 10 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. Purification by column chromatography (10% ethyl acetate/90% hexanes) resulted in the isolation of the diazide 5.33 (0.42 g, 37% over two steps) as a white solid.

5.33. White solid (0.42 g, 37%); mp 80-81 °C; IR (KBr) 2930, 2853, 2097, 1257 cm^{-1}; ^1H NMR (300 MHz, MeOD), δ 3.39-3.30 (m, 1H), 3.21 (td, J = 11.5, 5.1 Hz, 1H), 2.05 (dd, J = 12.9, 4.5 Hz, 1H), 1.98 (dt, J = 12.7, 3.3 Hz, 1H), 1.84-1.66 (m, 3H), 1.56-1.41 (m, 5H), 1.33-0.99 (m,
16H), 0.91-0.83 (m, 14H), 0.73-0.67 (m, 1H), 0.65 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$), δ 44.5, 43.0, 42.6, 39.8, 39.5, 36.7, 36.2, 35.8, 34.9, 33.2, 31.7, 28.2, 28.0, 27.8, 24.2, 23.8, 22.8, 22.6, 21.2, 18.7, 12.9, 12.1. Anal. Calcd for C$_{27}$H$_{46}$N$_6$: C, 71.32; H, 10.20; N, 18.48. Found: C, 71.73; H, 10.9; N, 18.33.


To a flame dried round bottom flask was added diazide 5.33 (0.20 g, 0.44 mmol) and 10% Pd/C (0.47 g, 0.04 mmol). A balloon filled with hydrogen gas was added to the reaction vessel and MeOH (5 mL) was added carefully. The reaction mixture was stirred at room temperature for 90 min. The reaction mixture was filtered through celite and washed through with methanol. The filtrate was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting powder was dissolved in diethyl ether (30 mL). Dry hydrogen chloride gas, produced from reacting sodium chloride with concentrated sulfuric acid, was purged into the solution resulting in the formation of a precipitate. The solution was filtered through celite and the precipitate was collected, washed with diethyl ether, and dried under reduced pressure to afford 0.04 g (20% over two steps) of amine salt 5.14 as a white solid.

5.14. White solid (0.05g 20%); mp = 211 °C (dec); IR (KBr) 3423, 2951, 1656, 1491 cm$^{-1}$; $^1$H NMR (300 MHz, CD$_3$OD), δ 3.43-3.36 (m, 1H), 3.27-3.23 (m, 1H), 2.06 (dd, J = 12.5, 3.0 Hz, 1H), 1.94 (dt, J = 12.6, 4.0 Hz, 1H), 1.78-1.69 (m, 2H), 1.67-1.62 (m, 1H), 1.58-1.48 (m, 2H), 1.30-1.14 (m, 12H), 1.09-0.67 (m, 22H), 0.61 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$), δ 56.22,
56.19, 53.5, 52.4, 49.8, 43.8, 42.3, 41.4, 39.7, 39.3, 36.1, 35.9, 35.7, 34.8, 31.6, 31.2, 27.8, 27.7, 27.1, 23.7, 23.5, 21.7, 21.5, 20.9, 17.7, 11.3, 11.0. Anal. Calcd for C_{27}H_{52}Cl_{2}N_{2}: C, 68.18; H, 11.02; N, 5.89. Found: C, 68.52; H, 10.75; N, 5.53.

\[(3S,8S,9S,10R,13R,14S,17S)-17-\text{Ethyl}-2,3,4,7,8,9,10,11,12,13,14,15,16,17-\text{tetradecahydro}-10,13-\text{dimethyl}-1\text{H}-\text{cyclopenta}[a]phenanthren}-3\text{-ol (5.36)}\]


KOH (1.59 g, 28.39 mmol) was suspended in ethylene glycol (15 mL) and the reaction mixture was warmed to reflux until the KOH dissolved. The solution was allowed to cool to room temperature, and pregnenolone 5.35 (3.00 g, 9.49 mmol) was added followed by hydrazine monohydrate (1.23 mL, 21.03 mmol). The reaction mixture was heated to reflux and stirred overnight. The mixture was then allowed to cool to room temperature and brine (600 mL) was added. The suspension was then extracted with ethyl acetate (7 x 100 mL). The organic layers were collected, combined, dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% ethyl acetate/80% hexanes) resulting in the isolation of 2.44 g (85%) of 5.36 as a white powder.

5.36. mp 126-128 °C (chloroform); [\(\alpha\)]\(_{D}\) - 4.88 (c 11.5, CH\(_2\)Cl\(_2\)); TLC \(R_f\) = 0.29 (20% ethyl acetate/80% hexanes); IR (CHCl\(_3\)) 3497, 2942, 1638 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.36-
5.35 (m, 1H), 3.58-3.48 (m, 1H), 2.34-2.18 (m, 2H), 2.04-1.72 (m, 5H), 1.66-1.35 (m, 9H), 1.22-1.04 (m, 5H), 1.01 (s, 4H), 0.90-0.82 (m, 4H), 0.58 (s, 3H).

\[(3R,8S,9S,10R,13R,14S,17S)\]-3-Azido-17-ethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-10,13-dimethyl-1H-cyclopenta[a]phenanthrene (5.37)


To a flame dried round bottom flask under argon was added 5.36 (0.30 g, 1.00 mmol), PPh\(_3\) (0.39 g, 1.49 mmol) and benzene (4 mL). DIAD (0.19 mL, 1.00 mmol) and (PhO)\(_2\)PON\(_3\) (0.22 mL, 1.00 mmol) were then added to the solution. The reaction mixture was stirred at room temperature for 24 h. Additional PPh\(_3\) (0.39 g, 1.49 mmol), DIAD (0.19 mL, 1.00 mmol), and (PhO)\(_2\)PON\(_3\) (0.22 mL, 1.00 mmol) were added after TLC showed that starting material remained. The reaction mixture was allowed to stir at room temperature for 2 h, until TLC showed that all starting alcohol 5.36 was consumed. The solution was concentrated *in vacuo,* and the residue was purified by silica gel chromatography (10% ethyl acetate/90% hexanes) resulting in the isolation of 0.28 g (84%) of azide 5.37 as a white powder.

5.37. mp 121-122 °C (chloroform); \([\alpha]_D \text{ - 0.11 (c 8.0, CH}_2\text{Cl}_2\text{); TLC } R_f \text{ = 0.53 (3% ethyl acetate/97% hexanes); IR (CHCl}_3\text{) 2943, 2111, 2082, 1651 cm}^{-1}; \text{ }^1\text{H NMR (300 MHz, CDCl}_3\text{) } \delta
5.42-5.39 (m, 1H), 3.89 (t, J = 2.9 Hz, 1H), 2.57-2.49 (m, 1H), 2.19 (dt, J = 15.0, 2.8 Hz, 1H),
2.05-1.94 (m, 1H), 1.89-1.83 (m, 1H) 1.80-1.72 (m, 2H), 1.70-1.34 (m, 8H), 1.25-1.03 (m, 6H),
1.01 (s, 3H), 0.96-0.83 (m, 5H), 0.58 (s, 3H).

(3R,8S,9S,10R,13R,14S,17S)-17-Ethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-
10,13-dimethyl-1H-cyclopenta[a]phenanthren-3-amine (5.38)

Lit. Ref: Cave, A.; Jarreau, F. X.; Khuong Huu, Q.; Leboeuf, M.; Serban, N.; Goutarel, R.,
Steroid alkaloids. LVIII. Influence of the nature of aprotic polar solvents on the stereochemistry
and the mechanism of azidolysis of 3β-tosyloxy-Δ5 steroids. Application to a synthesis of 3α-

To a flame dried flask purged with argon was added 5.37 (2.00 g, 6.11 mmol) followed by THF
(200 mL). The reaction mixture was cooled to 0°C in an ice bath and solid LiAlH₄ (2.31 g, 61.11
mmol) was added slowly. The reaction mixture was removed from the ice bath and allowed to
stir for 24 h. The solution was then cooled to 0 °C in an ice bath and quenched with H₂O (10
mL) and 15% NaOH (10 mL). More H₂O (15 mL) was then added until the solution turned to a
cloudy white suspension. The reaction mixture was vacuum filtered and extracted with ethyl
acetate (5 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried
with MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified using
silica gel chromatography (95% CH₂Cl₂/4% MeOH/1% NH₄OH) providing 0.85 g (46 %) of
5.38 as an off white solid.
5.39. mp 86-88 °C (chloroform); [α]D - 7.50 (c 9.5, CH2Cl2); TLC Rf = 0.83 (95% CH2Cl2/4% MeOH/1% NH4OH); IR (CHCl3) 3375, 2934, 2854, 1584 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 5.36-5.35 (m, 1H), 0.54-0.34 (m, 1H) 3.15 (br, s, 1H), 2.60-2.55 (m, 1H), 2.01-1.33 (m, 15H), 1.22-1.03 (m, 5H), 1.00 (s, 4H) 0.89-0.74 (m, 4H), 0.57 (s, 3H).

(3R,8S,9S,10R,13R,14S,17S)-17-Ethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-10,13-dimethyl-1H-cyclopenta[a]phenanthren-3-aminium chloride (K111)

The β–amine 5.38 (1.05 g, 3.49mmol) was dissolved in diethyl ether (50 mL). Dry hydrogen chloride gas, produced from reacting sodium chloride with concentrated sulfuric acid, was purged into the solution resulting in the formation of a precipitate. The solution was filtered and the precipitate was collected, washed with diethyl ether, and dried under vacuum to afford 0.79 g (69%) of amine salt K111 as a tan powder.

K111. mp 283-285 °C (diethyl ether); [α]D - 3.25 (c 10.5, DMSO); IR (CH3OH) 3431, 2944, 2519, 2238, 2075, 1643 cm⁻¹; ¹H NMR (300 MHz, CD3OD) δ 7.69 (br s, 3H), 5.36-5.35 (m, 1H), 3.39-3.34 (m, 1H), 2.61-2.56 (m, 1H), 2.08-1.02 (m, 21H), 0.95 (s, 3H), 0.84 (t, J = 7.4 Hz, 3H), 0.54 (s, 3H); ¹³C NMR (75 MHz, CDCl3) δ 135.8, 125.6, 56.3, 53.2, 50.2, 41.9, 37.8, 37.2, 34.9, 32.2, 31.9, 31.8, 28.0, 24.4, 22.9, 20.4, 18.0, 12.5, 11.9, 11.6. Anal calcd for C21H36ClN: C, 74.63; H, 10.74; N, 4.14. Found: C, 74.44; H, 10.87, N, 4.55.
KOH (4.76 g, 84.58 mmol) was suspended in ethylene glycol (30 mL) and the reaction mixture was warmed to reflux until the KOH dissolved. The solution was allowed to cool to room temperature, and epiandrosterone 5.39 (6.00 g, 20.63 mmol) was added followed by hydrazine monohydrate (3.10 mL, 61.89 mmol). The reaction mixture was heated back to reflux and stirred overnight. The resulting solution was allowed to cool to room temperature and brine (600 mL) was added. The layers were then separated, and the aqueous layer was extracted with methyl tert-butyl ether (7 x 200 mL). The organic layers were collected, combined, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% ethyl acetate/80% hexanes) providing 4.78 g (83%) of 5.40 as a white solid.

**5.40.** mp = 149-151 °C (CH₂Cl₂); TLC Rf = 0.33 (ethyl acetate 20%/hexane 80%); IR (KBr) 3350, 2930, 2845, 1447, 1377, 1133 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.59 (hept, J = 4.9 Hz, 1H), 1.84–1.76 (m, 1H), 1.75–1.71 (m, 2H), 1.70–1.65 (m, 2H), 1.64–1.62 (m, 1H), 1.60–1.58 (m, 1H), 1.57–1.55 (m, 1H), 1.52–1.50 (m, 1H), 1.48–1.47 (m, 1H), 1.46–1.44 (m, 1H), 1.43–1.37 (m, 2H), 1.36–1.32 (m, 1H), 1.29–1.22(m, 4H), 1.17–1.10 (m, 4H), 0.98-0.83 (m, 3H), 0.80 (s, 3H), 0.69 (s, 3H), 0.66–0.60 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 71.6, 54.8, 54.7, 45.1, 41.0, 40.6, 39.1, 38.4, 37.3, 36.1, 35.8, 32.7, 31.7, 29.0, 25.7, 21.5, 20.7, 17.7, 12.6.
(5S,8S,9S,10S,13S,14S)-10,13-Dimethyltetradecahydro-1H-cyclopenta[a]phenanthren-3(2H)-one (5.41)


To pyridinium chlorochromate (7.48 g, 34.79 mmol) dissolved in dichloromethane (30 mL) was added 5.40 (4.78 g, 17.32 mmol) followed by silica gel (7.48 g). The reaction mixture was stirred at room temperature overnight. The resulting suspension was filtered through a plug of silica gel with dichloromethane until no more product was observed in the filtrate by TLC. The solvent was removed *in vacuo* resulting in the isolation of 4.70 g (99%) of 5.41 as a white powder.

5.41. TLC R<sub>f</sub> = 0.39 (20% ethyl acetate/80% hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.40–2.22 (m, 3H), 2.11–1.98 (m, 2H), 1.77–1.69 (m, 2H), 1.67–1.61 (m, 2H), 1.60–1.50 (m, 3H), 1.49–1.38 (m, 2H), 1.38–1.30 (m, 4H), 1.21–1.08 (m, 3H), 1.01 (s, 3H), 0.99–0.87 (m, 2H), 0.75 (dd, J = 10.7, 4.2 Hz, 1H), 0.72 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 210.7, 54.0, 53.8, 46.4, 44.3, 40.5, 40.1, 38.5, 38.3, 37.8, 35.4, 35.4, 31.8, 28.7, 25.2, 21.2, 20.2, 17.2.
Ketone 5.41 (0.82 g, 3.00 mmol) was dissolved in acetic acid (30 mL) The solution was warmed to 50 °C in an oil bath and pyridinium tribromide (0.96 g, 3.00 mmol) was added. The reaction was stirred at 50 °C for 30 minutes until a precipitate formed. The reaction mixture was allowed to cool to room temperature and the precipitate was collected by filtration and dried under reduced pressure resulting in the isolation of 0.72 g (68%) of ketobromide 5.42 as an off-white solid.

5.42. mp = 198-204 °C (CHCl₃); TLC Rₗ = 0.92 (10% ethyl acetate/90% hexanes); IR (KBr) 2924, 2865, 2846, 1716, 1656, 1311 cm⁻¹; [α]ᵣ°D = +29.2 (c 1.13, DCM); ¹H NMR (300 MHz, CDCl₃) δ 4.75 (dd, J = 13.4, 6.3 Hz, 1H), 2.65 (dd, J = 12.6, 6.3 Hz, 1H), 2.43–2.40 (m, 2H), 1.84 (d, J = 13.4 Hz, 1H), 1.78–1.76 (m, 1H), 1.73–1.71 (m, 1H), 1.67–1.53 (m, 6H), 1.48–1.41 (m, 2H), 1.39–1.33 (m, 2H), 1.31–1.28 (m, 1H), 1.19–1.13 (m, 2H), 1.09 (s, 3H), 1.02–0.86 (m, 2H), 0.84–0.77 (m, 1H), 0.72 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 201.5, 54.9, 54.4, 54.1, 52.1, 47.7, 44.2, 41.1, 40.5, 39.4, 38.8, 35.5, 32.1, 28.7, 25.7, 21.8, 20.7, 17.8, 12.4.

Ketobromide 5.42 (0.36 g, 1.01 mmol) was dissolved in dimethylformamide (20 mL). NaN₃ (0.08 g, 1.20 mmol) was added and the solution was stirred at room temperature for 4 h. The solution was poured over crushed ice and allowed to warm to room temperature. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with cold water (2 x 20 mL), and brine (1 x 20 mL). The organic extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Silica gel chromatography (10% ethyl acetate/90% hexanes) was performed, resulting in the isolation of 0.17 g (56%) of 5.43 as a white powder.

5.43. mp = 131-132 °C (ethyl alcohol); TLC Rf = 0.63 (20% ethyl acetate/80% hexanes); IR (KBr) 2928, 2833, 2105, 1714, 1282, 1156 cm⁻¹; [α]D²¹⁴ = +54.8 (c 1.00, DCM); ¹H NMR (300 MHz, CDCl₃) δ 3.98 (dd, J = 13.1, 6.4 Hz, 1H), 2.42–2.21 (m, 3H), 1.77–1.70 (m, 2H), 167–1.55 (m, 6H), 1.47–1.25 (m, 6H), 1.19–1.13 (m, 2H), 1.09 (s, 3H), 1.01–1.87 (m, 2H), 0.84–0.76 (m, 1H), 0.71 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 205.5, 64.2, 54.4, 54.2, 47.9, 45.8, 44.0, 41.1, 40.5, 38.8, 37.3, 35.4, 32.1, 28.7, 25.7, 21.8, 20.7, 17.7, 12.8.

To a flame dried round bottom flask was added, ketoazide 5.43 (0.12 g, 0.39 mmol) and tetrahydrofuran (8 mL). The reaction mixture was cooled to -78 °C in a dry ice/acetone bath and 1 M L-selectride in THF (0.60 mL, 0.60 mmol) was added dropwise. The mixture was stirred at -78 °C for 2 h. The reaction mixture was then transferred to an ice/water bath and quenched with sat. aq. NH₄Cl (8 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL), and the combined organic extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Silica gel chromatography (10% ethyl acetate/90% hexanes) provided 88 mg (70%) of 5.44 as an off-white solid.

5.44. mp = 76–81 °C (CH₂Cl₂); TLC Rₖ = 0.69 (20% ethyl acetate/80% hexanes); IR (KBr) 3435, 2927, 2099, 1451, 1248, 1038 cm⁻¹; [α]D²⁰ = −60.7 (c 10.94, DCM); ¹H NMR (300 MHz, CDCl₃) δ 3.97–3.95 (br s, 1H), 3.53 (ddd, J = 12.5, 4.6, 3.0, Hz, 1H), 1.95 (br s, 1H), 1.81–1.73 (m, 3H), 1.63–1.53 (m, 5H), 1.51–1.38 (m, 3H), 1.32–1.22 (m, 3H), 1.21–1.07 (m, 4H), 1.02–0.85 (m, 3H), 0.82 (s, 3H), 0.69 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 68.2, 61.2, 54.6, 54.6, 41.0, 40.6, 38.9, 38.3, 37.2, 37.1, 35.6, 34.5, 32.4, 27.9, 25.7, 21.2, 20.7, 17.8, 12.5.
(2R,3S,5S,8S,9S,10S,13S,14S)–3–Hydroxy–10,13–dimethylhexadecahydro–1H–cyclopenta[a]phenanthren–2–aminium chloride (K141)

A suspension of lithium aluminum hydride (0.55 g, 14.42 mmol) in tetrahydrofuran (31 mL) in a round bottom flask was cooled to 0 °C using an ice/water bath. A solution of azide 5.44 (1.37 g, 4.34 mmol) in tetrahydrofuran (31 mL) was added slowly. The solution was stirred at 0 °C for 10 min and then warmed slowly to reflux. The mixture was stirred at reflux for 4 h and allowed to cool to room temperature. The reaction mixture was then diluted with tetrahydrofuran (62 mL) and cooled to 0 °C in an ice/water bath. H₂O (3 mL), and 15% NaOH (3 mL) were added followed by additional H₂O (9 mL). The reaction mixture was filtered through celite and the salts were washed with diethyl ether (40 mL). The filtrate was concentrated under reduced pressure, and the organic residue was dissolved in a mixture of ether (30 mL) and chloroform (30 mL). The mixture was filtered through celite to remove any undissolved solids. The filtrate was concentrated under reduced pressure and the resulting solid was dissolved in ether (100 mL). Dry hydrogen chloride gas, produced from reacting sodium chloride with concentrated sulfuric acid, was purged into the solution resulting in the formation of a precipitate. The solution was filtered through celite and the precipitate was collected, washed with diethyl ether, and dried under reduced pressure to afford 0.58 g (40% over 2 steps) of amine salt K141 as a pale yellow powder.

**K141.** mp = 235 °C (diethyl ether) (dec.); IR (KBr) 3399, 3043, 2926, 1970, 1600, 1085 cm⁻¹; 

\[ \alpha \]D²²⁸ = +17.4 (c 0.33, methanol); ¹H NMR (300 MHz, CD₃OD) δ 4.59 (bs, 1H), 3.98 (s, 1H),
1.77–1.74 (m, 3H), 1.67–1.64 (m, 2H), 1.62–1.51 (m, 5H), 1.48–1.33 (m, 5H), 1.29–1.27 (m, 2H), 1.19–1.14 (m, 2H), 1.02–0.92 (m, 2H), 1.02-0.92 (m, 2H), 0.88 (s, 3H), 0.84-0.79 (m, 1H), 0.73 (s, 3H); $^{13}$C NMR (75 MHz, CD$_3$OD) δ 66.3, 51.6, 42.1, 41.6, 40.1, 39.4, 38.2, 38.0, 36.9, 36.4, 33.6, 29.0, 26.6, 22.2, 21.5, 18.1, 12.5. Anal calcd for C$_{19}$H$_{34}$OClN: C, 69.59; H, 10.45; N, 4.27. Found: C, 69.85; H, 10.20, N, 4.21.

2-(Hydroxy(2-phenylbenzo[h]quinolin-4-yl)methyl)piperidin-1-ium chloride (5.16•HCl)


Amine 5.16 (1.37 g, 3.72 mmol) was suspended in 100 mL diethyl ether and anhydrous hydrogen chloride (2M in diethyl ether, 4.0 mL, 8.0 mmol) was added. The resulting precipitate was collected by vacuum filtration, suspended in 100 mL ethanol, and filtered again to provide 900 mg (60%) amine hydrochloride salt 5.16•HCl as a white solid.

5.16•HCl. mp = 258 °C (dec.); IR (KBr) 3280, 2936, 2854, 2710, 1589, 1377, 1106, 832, 698 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$) δ 9.65 (d, $J = 12.8$ Hz, 1H), 9.43-9.37 (m, 1H), 8.39 (d, $J = 10.4$ Hz, 3H), 8.32 (s, 1H), 8.24 (d, $J = 9.6$ Hz, 1H), 8.10-8.06 (m, 1H), 8.03 (d, $J = 12.8$ Hz, 1H), 7.84-7.75 (m, 2H), 7.65-7.58 (m, 2H), 7.57-7.50 (m, 1H), 6.60 (d, $J = 4.2$ Hz, 1H), 5.90 (s, 1H), 3.52-3.39 (m, 1H), 3.09-2.94 (m, 1H), 1.79-1.52 (m, 4H), 1.37-1.19 (m, 2H); $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 153.8, 147.3, 145.2, 138.7, 132.9, 131.0, 129.5, 128.9, 128.4, 127.8, 127.6,

(2-Phenylbenzo[h]quinolin-4-yl)(piperidin-2-yl)methanol (5.16)

Epoxide 5.65 (3.00 g, 6.00 mmol) was dissolved in a mixture of 30 mL ethanol and 30 mL THF. Hydrazine hydrate (600 µL, 12.4 mmol) was added and the reaction was refluxed for 2 hours. The reaction was concentrated under vacuum to provide a crude mixture of product and byproducts. Silica gel chromatography (90% dichloromethane / 9% methanol / 1% NH₄OH) provided the free amine as a brown solid with some orange colored impurities. The mixture was suspended in 30 mL methanol and filtered to provide amine 5.16 (1.37 g, 62%) as a tan solid.

5.16. mp = 175 °C (dec.); TLC Rᵣ = 0.20 (90% dichloromethane / 9% methanol / 1% NH₄OH); IR (KBr) 3286, 3060, 2932, 2851, 2744, 1590, 1443, 1382, 1107, 1048, 885, 700 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 9.42-9.38 (m, 1H), 8.41-8.38 (m, 2H), 8.30 (s, 1H), 8.16 (d, J = 9.3 Hz, 1H), 8.06-8.03 (m, 1H), 7.95 (d, J = 9.2 Hz, 1H), 7.82-7.73 (m, 2H), 7.65-7.59 (m, 2H), 7.56-7.50 (m, 1H), 5.73 (br s, 1H), 5.34 (br s, 1H), 2.96-2.86 (m, 2H), 2.54-2.40 (m, 1H), 1.74-1.66 (m, 1H), 1.59-1.51 (m, 1H), 1.48-1.40 (m, 1H), 1.34-1.14 (m, 3H); ¹³C NMR (100 MHz, DMSO-d₆) δ 153.8, 150.3, 145.3, 139.0, 133.0, 131.3, 129.4, 129.0, 128.3, 127.8, 127.0, 126.9, 124.5, 122.8, 121.6, 116.9, 72.2, 61.4, 46.5, 26.7, 26.0, 24.1 (One signal in the aromatic region was not resolved). Anal. Calcd for C₂₅H₂₄N₂O: C, 81.49; H, 6.57; N, 7.60. Found: C, 81.16; H, 6.24; N, 7.83.
2-((2-(Adamantan-1-yl)-6,8-dichloroquinolin-4-yl)(hydroxy)methyl)piperidin-1-ium chloride (5.15·HCl)


Amine 5.15 (678 mg, 1.52 mmol) was suspended in diethyl ether and anhydrous hydrogen chloride (2M in diethyl ether, 1.6 mL, 3.2 mmol) was added. The resulting precipitate was collected by vacuum filtration, re-suspended in 25 mL diethyl ether with 25 mL of ethanol added and filtered again to provide 440 mg (60%) of 5.15·HCl as a white solid.

5.15·HCl. mp = 202 °C (dec.); IR (film) 3271, 2904, 2847, 1595, 1451, 1130 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 10.15 (d, J = 9.5 Hz, 1H), 8.52 (d, J = 2.1 Hz, 1H), 8.46-8.35 (m, 1H), 8.05 (d, J = 2.1 Hz, 1H), 7.85 (s, 1H), 6.57 (d, J = 4.5 Hz, 1H), 5.85 (s, 1H), 3.31-3.20 (m, 2H), 2.94 (q, J = 11.5 Hz, 1H), 2.12 (br s, 3H), 2.06 (br s, 6H), 1.78 (br s, 6H), 1.72-1.53 (m, 4H), 1.33-1.12 (m, 2H); ¹³C NMR (100 MHz, DMSO-d₆) δ 168.8, 146.4, 141.6, 134.6, 130.4, 129.4, 125.2, 121.9, 117.5, 67.6, 58.4, 44.1, 41.1, 39.8, 36.2, 28.0, 21.7, 21.0, 20.7. Anal. Calcd for C₂₅H₃₁C₁₃N₂O: C, 62.31; H, 6.48; N, 5.81. Found: C, 62.03 H, 6.36; N, 6.22.
(2-(Adamantan-1-yl)-6,8-dichloroquinolin-4-yl)(piperidin-2-yl)methanol (5.15)

Epoxide 5.57 (2.50 g, 4.34 mmol) was dissolved in 15 mL ethanol. Hydrazine hydrate (632 µL, 13.0 mmol) was added and the mixture was refluxed for 3 hours. After cooling to room temperature, the mixture was concentrated under vacuum and purified by silica gel chromatography (90% dichloromethane / 9% methanol / 1% NH₄OH) to provide 983 mg of amine 5.15 (51%) as a beige solid.

5.15. mp = 180 °C (dec.); TLC Rf = 0.29 (90% dichloromethane / 9% methanol / 1% NH₄OH); IR (KBr) 3309, 3068, 2906, 2849, 2675, 1597, 1482, 1309, 1116, 869 cm⁻¹; \(^1\)H NMR (300 MHz, DMSO-d₆) δ 8.25 (d, J = 2.1 Hz, 1H), 7.99 (d, J = 2.1, 1H), 7.78 (s, 1H), 5.66 (s, 1H), 5.08 (s, 1H), 2.88 (d, J = 14.4 Hz, 1H), 2.71-2.63 (m, 1H), 2.44-2.30 (m, 1H), 2.11 (br s, 3H), 2.05 (br s, 6H), 1.78 (br s, 6H), 1.73-1.64 (m, 1H), 1.48-1.38 (m, 2H), 1.28-1.11 (m, 3H); \(^1^3\)C NMR (100 MHz, DMSO-d₆) δ 168.8, 149.1, 141.6, 134.5, 129.3, 128.9, 126.1, 122.4, 117.7, 72.4, 61.1, 46.3, 41.2, 41.1, 36.2, 28.0, 26.2, 25.8, 23.9. Anal. Calcd for C₂₅H₃₈Cl₂N₂O: C, 67.41; H, 6.79; N, 6.29. Found: C, 67.55; H, 6.96; N, 6.26.
2-(5-Hydroxypentyl)isoindoline-1,3-dione (5.63s)


5-Amino-1-pentanol (18.7 g, 181 mmol) and phthalic anhydride (26.8 g, 181 mmol) were heated to reflux in 181 mL toluene with a Dean-Stark condenser attached for 24 h. The mixture was cooled to room temperature, transferred to a separatory funnel using ethyl acetate, washed once with brine, dried with sodium sulfate, and concentrated under vacuum to provide 39.2 g (93%) 2-(5-hydroxypentyl)isoindoline-1,3-dione 5.63s as a white solid.

5.63s. mp = 43-48 °C; TLC R₆ = 0.29 (60% ethyl acetate / 40% hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.87-7.80 (m, 2H), 7.74-7.67 (m, 2H), 3.70 (t, J = 7.1 Hz, 2H), 3.64 (t, J = 6.3 Hz, 2H), 1.77-1.56 (m, 4H), 1.48-1.36 (m, 2H)

5-(1,3-Dioxoisooindolin-2-yl)pentanal (5.49)


2-(5-hydroxypentyl)isoindoline-1,3-dione 5.63s (932 mg, 4.00 mmol) was dissolved in 13 mL anhydrous dichloromethane and cooled to 0 °C while under argon. Trichloroisocyanuric acid
(974 mg, 4.20 mmol) and TEMPO (6 mg, 0.04 mmol) were then added. The mixture was stirred at room temperature for 20 min and then filtered through celite. The resulting solution was washed with saturated sodium bicarbonate, 1M HCl, and brine, dried with sodium sulfate, and concentrated under vacuum to provide 850 mg (92%) aldehyde 5.49 as a yellow oil.

**5.49.** TLC Rf = 0.70 (100% diethyl ether); ¹H NMR (300 MHz, CDCl₃) δ 9.76 (t, J = 1.6 Hz, 1H), 7.88-7.81 (m, 2H), 7.75-7.68 (m, 2H), 3.71 (t, J = 6.8 Hz, 2H), 2.51 (td, J = 7.4, 1.5 Hz, 2H), 1.80-1.61 (m, 4H).

![Chemical Structure](image)

**2-Phenylbenzo[h]quinoline-4-carboxylic acid (5.59)**


1-Naphthylamine **5.58** (25.0 g, 175 mmol) was dissolved in 100 mL of ethanol. Benzaldehyde (17.8 mL, 18.6 g, 175 mmol) and pyruvic acid (12.2 mL, 15.4 g, 175 mmol) were added sequentially to the 1-naphthylamine solution at room temperature. The reaction was then refluxed open to air for 3 h. After cooling to room temperature, the mixture was vacuum filtered. The resulting solid was thoroughly washed with ethanol and dried under vacuum to yield 13.7 g (26%) of carboxylic acid **5.59** as a yellow solid.

**5.59.** mp = 294-297 °C; TLC Rf = 0.11 (20% ethyl acetate / 80% hexanes); IR (KBr) 3061, 2623, 1704, 1256, 868, 742, 687 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 9.42-9.39 (m, 1H), 8.58 (s, 1H), 8.54 (d, J = 9.3 Hz, 1H), 8.48-8.44 (m, 2H), 8.11-8.04 (m, 2H), 7.87-7.79 (m, 2H), 7.66-
7.53 (m, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 167.9, 154.4, 146.3, 138.1, 138.0, 133.1, 130.8, 129.9, 129.1, 128.9, 128.7, 128.0, 127.5, 127.2, 124.5, 122.3, 121.9, 118.9. Anal. Calcd for C$_{20}$H$_{13}$NO$_2$: C, 80.25; H, 4.38; N, 4.68; Found: C, 80.04; H, 4.39; N, 4.96.

![Chemical Structure](image)

(2-Phenylbenzo[h]quinolin-4-yl)methanol (5.60)

Carboxylic acid 5.59 (5.00 g, 16.7 mmol) was suspended in 17 mL anhydrous THF under argon. After cooling the mixture to 0 °C, borane-tetrahydrofuran complex (1M in THF, 34.0 mL, 34.0 mmol) was slowly added to the well-stirred mixture. After hydrogen gas evolution ceased, the reaction was allowed to warm to room temperature and stirred for 6 h. The mixture was then cooled to 0 °C and aqueous NaOH (3 M, 17 mL) was slowly added. The mixture was stirred at room temperature for 12 h, after which the THF was removed in vacuo. The resulting mixture was then extracted with ethyl acetate. The combined organic extracts were dried with MgSO$_4$, filtered, and evaporated to an oil, which was diluted with 50 mL of methanol. The methanol was then removed under vacuum to yield 3.81 g (80%) of alcohol 5.60 as a white solid.

5.60. mp = 140-144 °C; TLC R$_f$ = 0.32 (20% ethyl acetate / 80% hexanes); IR (KBr) 3343, 3061, 2899, 1591, 1377, 1020, 756, 693 cm$^{-1}$; 1 H NMR (300 MHz, DMSO-$d_6$) δ 9.41-9.38 (m, 1H), 8.44-8.40 (m, 2H), 8.32 (s, 1H), 8.03-8.07 (m, 1H), 8.00-7.94 (m, 2H), 7.83-7.74 (m, 2H), 7.65-7.59 (m, 2H), 7.56-7.50 (m, 1H), 5.72 (t, $J$ = 5.5 Hz, 1H), 5.16 (d, $J$ = 5.5 Hz, 2H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 154.4, 149.0, 145.0, 139.1, 133.2, 131.3, 129.5, 129.0, 128.3, 128.0, 127.13,
127.09, 127.05, 124.4, 122.5, 121.1, 116.0, 60.3. Anal. Calcd. for C_{20}H_{15}NO: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.06; H, 4.97; N, 5.09.

![Chemical structure](image)

**4-(Chloromethyl)-2-phenylbenzo[h]quinoline (5.61)**

Alcohol **5.60** (13.5 g, 47.4 mmol) was dissolved in 95 mL anhydrous dichloromethane. Neat thionyl chloride (4.82 mL, 7.90 g, 66.4 mmol) was slowly added to the solution at room temperature. The reaction was stirred at room temperature for 18 h and then carefully quenched with saturated aqueous NaHCO₃. The reaction was diluted with an equal volume of water and vigorously stirred until all solids dissolved. The organic layer was separated, washed with brine, dried with Na₂SO₄, filtered, and evaporated under vacuum to yield 10.3 g (72%) of chloride **5.61** as a tan solid.

**5.61.** mp = 145-153 °C; TLC R_f = 0.80 (20% ethyl acetate / 80% hexanes); IR (KBr) 3062, 2942, 1588, 1053, 752, 689 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.53-9.50 (m, 1H), 8.36-8.34 (m, 2H), 8.06 (s, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.95-7.88 (m, 2H), 7.79-7.70 (m, 2H), 7.60-7.55 (m, 2H), 7.52-7.48 (m, 1H), 5.10 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 155.4, 146.8, 142.5, 139.4, 133.7, 132.2, 129.6, 129.0, 128.6, 128.3, 127.9, 127.6, 127.3, 125.3, 123.0, 120.4, 119.1, 43.1. Anal. Calcd. for C_{20}H_{14}ClN: C, 79.07; H, 4.65; N, 4.61. Found: C, 78.96; H, 4.50; N 4.83.
Dimethyl ((2-phenylbenzo[h]quinolin-4-yl)methyl)phosphonate (5.62)

Chloride 5.61 (1.97 g, 6.50 mmol) and trimethyl phosphite (13.7 g, 13.0 mL, 110 mmol) were combined in a flask with 6.5 mL of toluene. The mixture was refluxed for 3 d. After cooling to room temperature, the mixture was concentrated under vacuum to a brown oil which was trititated with diethyl ether. The resulting precipitate was vacuum filtered and washed with cold diethyl ether to yield 2.12 g (87%) of phosphonate 5.62 as a white solid.

5.62. mp = 136-137 °C; TLC Rf = 0.43 (20% acetone / 80% dichloromethane); IR (KBr) 3061, 2953, 1587, 1252, 1053, 804 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.54-9.51 (m, 1H), 8.37-8.34 (m, 2H), 8.02-7.84 (m, 4H), 7.79-7.68 (m, 2H), 7.60-7.54 (m, 2H), 7.52-7.46 (m, 1H), 3.75 (d, J = 22.5 Hz, 2H), 3.66 (d, J = 10.8 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 154.9 (d, J = 3.6 Hz), 146.8 (d, J = 2.5 Hz), 139.5, 138.4 (d, J = 9.3 Hz), 133.7, 132.2, 129.5, 129.0, 128.5, 127.79, 127.78, 127.6, 127.2, 125.3, 124.2 (d, J = 5.1 Hz), 121.2 (d, J = 1.5 Hz), 121.0 (d, J = 6.5 Hz), 53.3 (d, J = 6.7 Hz), 30.3 (d, J = 138.2 Hz). Anal. Calcd for C₂₂H₂₀NO₃P: C, 70.02; H, 5.34; N, 3.71. Found C, 69.69; H, 5.42; N, 3.88.
(E)-2-(6-(2-Phenylbenzo[h]quinolin-4-yl)hex-5-en-1-yl)isoindoline-1,3-dione (5.64)

Phosphonate 5.62 (377 mg, 1.00 mmol) and lithium chloride (63 mg, 1.50 mmol) were combined in a flask under argon and 5 mL of anhydrous THF was added followed by DBU (228 mg, 224 µL, 1.50 mmol). Aldehyde 5.49 (347 mg, 1.50 mmol) was dissolved in 5 mL anhydrous THF under argon. The aldehyde solution was then transferred to the stirred phosphonate solution dropwise at room temperature. After stirring for 24 h, the reaction was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried with MgSO₄, filtered, and concentrated under vacuum. Purification by silica gel chromatography (20% ethyl acetate / 80% hexanes) provided 330 mg (68%) of olefin 5.64 as a yellow solid.

5.64. mp = 135-144 °C; TLC Rₛ = 0.67 (30% ethyl acetate / 70% hexanes); IR (KBr) 3059, 2934, 2872, 1705, 1581, 1398, 1368, 1036, 721 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.52-9.50 (m, 1H), 8.37-8.35 (m, 2H), 8.02 (s, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.86-7.82 (m, 2H), 7.80 (d, J = 9.1 Hz, 1H), 7.76-7.67 (m, 4H), 7.59-7.54 (m, 2H), 7.50-7.46 (m, 1H), 7.19 (d, J = 15.7 Hz, 1H), 6.53 (dt, J = 15.7, 6.9 Hz, 1H), 3.79 (t, J = 7.3 Hz, 2H), 2.47 (q, J = 7.1 Hz, 2H), 1.85 (p, J = 7.5 Hz, 2H), 1.67 (p, J = 7.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 168.6, 155.1, 146.6, 144.0, 140.1, 137.1, 134.0, 133.7, 132.21, 132.19, 129.2, 128.9, 128.1, 127.7, 127.6, 127.1, 126.9, 126.1, 125.3, 123.3, 122.9, 121.2, 115.6, 37.9, 33.1, 28.3, 26.4. Anal. Calcd for C₃₃H₂₆N₂O₂: C, 82.13; H, 5.43; N, 5.81; Found: C, 82.44; H, 5.13; N, 5.84.
2-(4-(3-(2-Phenylbenzo[h]quinolin-4-yl)oxiran-2-yl)butyl)isoindoline-1,3-dione (5.65)

Olefin 5.64 (4.76 g, 9.86 mmol) was dissolved in 62 mL of CHCl₃. To this solution was added 3-chloroperbenzoic acid (approx. 70%, 5.11 g, approx. 29.6 mmol). The mixture was heated to reflux for 18 h. The reaction was then allowed to cool to rt, and the excess peracid was consumed by vigorously stirring the solution with 10% aq. Na₂SO₃. The mixture was poured into sat. aq. NaHCO₃ and extracted with DCM. The combined organic extracts were washed once with brine, dried with Na₂SO₄, and concentrated under vacuum. The crude solid was triturated with methanol and filtered to provide 3.00 g of epoxide 5.65 (61%) as a tan solid.

5.65. mp = 55-69 °C; TLC Rₓ = 0.61 (30% ethyl acetate / 70% hexanes); IR (KBr) 3059, 2933, 2858, 1710, 1590, 1466, 720 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.51 (dd, J = 7.9, 0.8 Hz, 1H), 8.37-8.34 (m, 2H), 7.93-7.89 (m, 2H), 7.88-7.83 (m, 2H), 7.80 (d, J = 9.0 Hz, 1H), 7.78-7.69 (m, 4H), 7.50-7.45 (m, 1H), 4.36 (d, J = 1.9 Hz, 1H), 3.78 (t, J = 7.2 Hz, 2H), 3.04-3.01 (m, 1H), 2.07-1.98 (m, 1H), 1.95-1.80 (m, 3H), 1.75-1.62 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 168.6, 155.7, 146.0, 144.0, 139.7, 134.2, 133.6, 132.3, 132.2, 129.5, 129.0, 128.4, 127.93, 127.90, 127.7, 127.3, 125.4, 123.4, 123.2, 120.0, 114.2, 62.9, 55.9, 37.8, 32.1, 28.6, 23.5. Anal. Calcd for C₃₃H₂₆N₂O₃: C, 79.50; H, 5.26; N, 5.62. Found: C, 79.46; H, 5.28; N, 5.65.
**5,7-Dichloroindoline-2,3-dione (5.51)**


Isatin **5.50** (14.7 g, 100 mmol) and trichloroisocyanuric acid (23.2 g, 100 mmol) were combined in a flask and cooled to -78 °C with a dry ice-acetone bath. Concentrated sulfuric acid (75 mL) was added dropwise to the mixture via an addition funnel. The mixture was allowed to slowly warm to room temperature. After stirring for 3 days, the mixture was poured over ice and stirred until all the ice had melted. The precipitate was collected by vacuum filtration and washed twice with water. The orange-red solid was then washed with acetone until only a white solid (isocyanuric acid) remained. The filtrate was concentrated under vacuum to yield 19.8 g (92%) of dichloroisatin **5.51** as an orange-red solid.

**5.51.** mp = 211-217 °C; TLC *R*$_f$ = 0.65 (50% ethyl acetate / 50% hexanes); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.59 (br s, 1H), 7.85 (d, *J* = 2.0 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H).
1-(Adamantan-1-yl)ethanone (5.51s)


1-Adamantanecarboxylic acid (7.20 g, 40.0 mmol) was dissolved in 40 mL of diethyl ether under argon. The mixture was maintained at approximately -5 °C with a NaCl-ice bath while methyl lithium (1.6M in diethyl ether, 52.5 mL, 84.0 mmol) was added dropwise with vigorous stirring. After complete addition, the cooling bath was removed and the slurry was allowed to stir for one hour at room temperature. The reaction was quenched and diluted by the addition of water and extracted with diethyl ether. The combined organic extracts were dried with MgSO₄, filtered, concentrated under vacuum, and purified by silica gel chromatography (10% ethyl acetate / 90% hexanes) to yield 5.70 g (80%) of ketone 5.51s as a white solid.

5.51s. mp = 52-54 °C; TLC R<sub>f</sub> = 0.43 (10% ethyl acetate / 90% hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.09 (s, 3H), 2.04 (br s, 3H), 1.82-1.64 (m, 12H).
2-(Adamantan-1-yl)-6,8-dichloroquinoline-4-carboxylic acid (5.52)


Dichloroisatin 5.51 (33.8 g, 157 mmol, 2.0 equiv), ketone 5.51s (14.0 g, 78.7 mmol, 1.0 equiv), and potassium hydroxide (28.6 g, 501 mmol, 6.4 mmol) were combined with 78 mL ethanol and 26 mL H₂O and heated to reflux for 48 h. The mixture was then allowed to cool to room temperature and concentrated under vacuum to leave a brown paste, which was taken up in H₂O and diethyl ether. The organic layer was discarded and the aqueous layer was washed once more with diethyl ether. The aqueous layer was then acidified (pH 4 to 5) by the dropwise addition of concentrated HCl. The resulting precipitate was isolated by vacuum filtration and recrystallized from ethanol to provide 12.7 g (43%) of carboxylic acid 5.52 as a tan solid.

5.52. mp = 152-157 °C; TLC Rₕ = 0.15 (30% ethyl acetate / 70% hexanes); IR (KBr) 3462, 2902, 2848, 2651, 1703, 1591, 1268, 1193 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 8.71 (s, 1H), 8.16-8.12 (m, 2H), 2.68 (br s, 6H), 2.11 (br s, 3H), 1.79 (br s, 6H); ¹³C NMR (100 MHz, DMSO-d₆) δ 169.4, 166.9, 142.2, 136.1, 134.5, 131.1, 129.7, 124.6, 123.6, 120.8, 40.9, 36.0, 28.0 (One signal in the aliphatic region was not resolved). Anal. Calcd for C₂₀H₁₉Cl₂NO₂: C, 63.84; H, 5.09; N, 3.72. Found: C, 64.18; H, 5.03; N, 3.87.
2-(Adamantan-1-yl)-6,8-dichloroquinolin-4-yl)methanol (5.53)

Carboxylic acid 5.52 (3.48 g, 9.26 mmol) was dissolved in 10 mL of anhydrous THF under argon. After cooling the mixture to 0 °C, borane-tetrahydrofuran complex (1 M in THF, 18.5 mL, 18.5 mmol) was slowly added to the mixture. After hydrogen gas evolution ceased, the cooling bath was removed and the mixture was allowed to stir at room temperature overnight. The mixture was again cooled to 0 °C and quenched with 20 mL 3M NaOH. The cooling bath was removed and, after stirring at room temperature for 6 h, the mixture was extracted with diethyl ether. The combined organic extracts were dried with MgSO₄, filtered, concentrated under vacuum, and purified by silica gel chromatography (30% ethyl acetate / 70% hexanes) to yield 2.00 g (60%) of alcohol 5.53 as a beige solid.

5.52. mp = 190-198 °C; TLC Rᵣ = 0.56 (30% ethyl acetate / 70% hexanes); IR (KBr) 3278, 2899, 2845, 1596, 1448, 1081, 1060 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.83 (d, J = 2.3 Hz, 1H), 7.77 (d, J = 2.2 Hz, 1H), 7.68 (s, 1H), 5.13 (dd, J = 5.7, 0.9 Hz, 2H), 2.16 (br s, 3H), 2.13 (br s, 6H), 1.91 (t, J = 5.8 Hz, 1H), 1.83 (br s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 170.1, 145.1, 142.5, 135.9, 130.9, 129.7, 126.0, 121.1, 117.0, 62.3, 41.9, 40.6, 37.0, 28.9. Anal. Calcd. for C₂₀H₂₁Cl₂NO: C, 66.30; H, 5.84; N, 3.87. Found: C, 66.44; H, 5.59; N, 3.69.
Alcohol 5.53 (8.36 g, 23.1 mmol) was dissolved in DCM (250 mL). Thionyl chloride (2.52 mL, 34.66 mmol) was then added. The mixture was stirred at 0 °C for 1 h and then quenched with sat. aq. NaHCO₃. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic extracts were dried over sodium sulfate, filtered, concentrated under vacuum, and purified by silica gel chromatography (1% ether / 99% hexanes) to provide 4.40 g (50%) of chloride 5.54 as a white solid.

**5.54.** mp = 155-158 °C; TLC Rₜ = 0.34 (100% hexanes); IR (KBr) 2900, 2847, 1672, 1597, 1450, 721 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.94 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.58 (s, 1H), 4.91 (s, 2H), 2.17 (br s, 3H), 2.12 (br s, 6H), 1.83 (br s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 170.0, 142.9, 141.5, 136.2, 131.4, 130.1, 126.1, 121.3, 119.9, 42.8, 41.8, 40.6, 36.9 28.8. Anal. Calcd. for C₂₀H₂₀Cl₃N: C, 63.09; H, 5.29; N, 3.68. Found: C, 63.28; H, 5.63; N, 3.57.

**5.55.** mp = 155-158 °C; TLC Rₜ = 0.34 (100% hexanes); IR (KBr) 2900, 2847, 1672, 1597, 1450, 721 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.94 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.58 (s, 1H), 4.91 (s, 2H), 2.17 (br s, 3H), 2.12 (br s, 6H), 1.83 (br s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 170.0, 142.9, 141.5, 136.2, 131.4, 130.1, 126.1, 121.3, 119.9, 42.8, 41.8, 40.6, 36.9 28.8. Anal. Calcd. for C₂₀H₂₀Cl₃N: C, 63.09; H, 5.29; N, 3.68. Found: C, 63.28; H, 5.63; N, 3.57.
concentrated under vacuum, and purified by silica gel chromatography (40% ethyl acetate / 60% hexanes) to provide 1.06 g (74%) phosphonate 5.55 as a white solid.

**5.55.** mp = 152-153 °C; TLC R_f = 0.33 (60% ethyl acetate / 40% hexanes); IR (KBr) 2952, 2902, 2847, 1772, 1711, 1594, 1398, 1239, 1075, 1031, 856, 830 cm⁻¹;¹H NMR (300 MHz, CDCl₃) δ 7.91 (d, J = 2.1 Hz, 1H), 7.78 (d, J = 2.1 Hz, 1H), 7.54 (d, J = 3.6 Hz, 1H), 3.66 (d, J = 11.1 Hz, 6H), 3.55 (d, J = 22.5 Hz, 2H), 2.16 (br s, 3H), 2.11 (br s, 6H), 1.82 (br s, 6H);¹³C NMR (75 MHz, CDCl₃) δ 169.4 (d, J = 3.9 Hz), 142.9 (d, J = 2.3 Hz), 137.5 (d, J = 9.2 Hz), 135.9, 131.0, 129.8, 127.4 (d, J = 4.7 Hz), 122.0 (d, J = 1.3 Hz), 121.7 (d, J = 7.0 Hz), 53.3 (d, J = 6.9 Hz), 41.8, 40.4, 36.9, 30.1 (d, J = 139.1 Hz), 28.8. Anal. Calcd. for C₂₂H₂₆Cl₂NO₃P: C, 58.16; H, 5.77; N, 3.08. Found: C, 57.97; H, 5.57; N, 2.94.

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\text{NHPhth}\quad\text{Cl}\quad\text{N}\quad\text{Cl}\quad\text{Cl}
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**2-((E)-6-(2-(Adamantan-1-yl)-6,8-dichloroquinolin-4-yl)hex-5-en-1-yl)isoindoline-1,3-dione (5.56)**

Phosphonate 5.55 (454 mg, 1.00 mmol) and lithium chloride (63 mg, 1.50 mmol) were combined in a flask under argon. Anhydrous THF (5 mL) was then added followed by DBU (152 mg, 149 µL, 1.00 mmol). Aldehyde 5.49 (347 mg, 1.50 mmol) was dissolved in 5 mL anhydrous THF under argon in a separate flask. The aldehyde solution was then transferred to the stirred phosphonate solution dropwise at room temperature. After stirring for 24 hours, the reaction was diluted with H₂O and extracted with ethyl acetate. The combined organic extracts were dried
with MgSO$_4$, filtered, and concentrated under vacuum. Purification by silica gel chromatography (10 % ethyl acetate / 90% hexanes) provided 402 mg of olefin 5.56 (68 %) as a white foam.

**5.56.** mp = 63-69 °C; TLC R$_f$ = 0.29 (5% ethyl acetate / 95% hexanes); IR (film) 2903, 2848, 1771, 1712, 1396, 719 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.92 (d, $J = 2.1$ Hz, 1H), 7.86-7.83 (m, 2H), 7.74-7.69 (m, 3H), 7.53 (s, 1H), 6.95 (d, $J = 15.6$ Hz, 1H), 6.40 (dt, $J = 6.9$, 15.6 Hz, 1H), 3.77 (t, $J = 6.9$ Hz, 2H), 2.42 (q, $J = 6.9$ Hz, 2H), 2.19-2.10 (m, 9H), 1.86-1.76 (m, 8H), 1.68- 1.56 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.7, 168.6, 143.1, 142.8, 137.8, 135.6, 134.1, 132.2, 130.3, 129.5, 126.4, 125.4, 123.4, 121.8, 115.8, 41.9, 40.4, 37.8, 37.0, 33.1, 28.9, 28.3, 26.4. Anal. Calcd for C$_{33}$H$_{32}$Cl$_2$N$_2$O$_2$: C, 70.84; H, 5.76; N, 5.01. Found: C, 70.57; H, 5.90; N, 5.03.

![Chemical Structure](image)

**2-(4-(3-(2-(Adamantan-1-yl)-6,8-dichloroquinolin-4-yl)oxiran-2-yl)butyl)isoindoline-1,3-dione (5.57)**

Olefin 5.56 (3.27 g, 5.84 mmol) and 3-chloroperbenzoic acid (approx. 70%, 3.03 g, approx. 17.5 mmol) were dissolved in 34 mL of chloroform. The mixture was refluxed for 15 h. After cooling to room temperature, the reaction was quenched with 10% aqueous Na$_2$SO$_3$, diluted with DCM, and then washed with saturated sodium bicarbonate and brine. The organic layer was dried with sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (10% ethyl acetate / 90% hexanes) to provide 2.52 g (75%) epoxide 5.57 as a white foam.
5.57. TLC Rf = 0.26 (30% ethyl acetate / 70% hexanes); IR (KBr) 2904, 2849, 1772, 1713, 1596, 1397, 720 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.87-7.83 (m, 3H), 7.77 (d, J = 2.1 Hz, 1H), 7.74-7.70 (m, 2H), 7.48 (s, 1H), 4.14 (d, J = 1.8 Hz, 1H), 3.76 (t, J = 7.1 Hz, 2H), 2.93-2.88 (m, 1H), 2.14 (br s, 3H), 2.10-1.96 (m, 8H), 1.88-1.76 (m, 8H), 1.70-1.58 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 170.3, 168.6, 142.9, 142.2, 136.1, 134.1, 132.2, 131.0, 129.7, 126.4, 123.4, 120.6, 114.9, 62.9, 55.5, 41.8, 40.6, 37.7, 36.9, 31.9, 28.9, 28.5, 23.4.\) Anal. Calcd for C\(_{33}\)H\(_{32}\)Cl\(_2\)N\(_2\)O\(_3\): C, 68.87; H, 5.60; N, 4.87. Found: C, 68.98; H, 5.84; N, 4.92.

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\begin{align*}
\text{(2-Phenylbenzo[h]quinolin-4-yl)methanaminium chloride (5.68).}
\end{align*}
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Chloride 5.61 (304 mg, 1.00 mmol), phthalimide (177 mg, 1.20 mmol), and potassium carbonate (276 mg, 2.00 mmol) were suspended in 10 mL DMF and heated to 80 °C for 24 h. The mixture was cooled to rt and decanted to remove inorganic solids. The organic portion was diluted with 40 mL methanol to produce a precipitate, which was filtered, washed with methanol, and dried to provide 344 mg (83%) of quinolyl phthalimide 5.61A as a tan solid.
**5.61A.** mp = 215-218 °C; TLC R<sub>f</sub> = 0.26 (20% ethyl acetate / 80% hexanes); IR (KBr) 2922, 2851, 1714, 1642, 1391, 1105 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.52-9.50 (m, 1H), 8.31-8.25 (m, 3H), 8.07 (s, 1H), 7.93-7.85 (m, 4H), 7.78-7.68 (m, 4H), 7.56-7.51 (m, 2H), 7.48-7.44 (m, 1H), 5.42 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.2, 155.5, 146.9, 141.6, 139.8, 134.5, 133.7, 132.3, 132.1, 129.5, 129.0, 128.5, 128.2, 127.9, 127.8, 127.2, 125.4, 123.8, 123.3, 120.7, 119.6, 39.1. Anal. Calcd for C<sub>28</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: C, 81.14; H, 4.38; N, 6.76. Found: C, 80.79; H, 4.57; N, 6.76.

The quinolyl phthalimide 5.61A (300 mg, 0.72 mmol) was suspended in 4 mL ethanol. Hydrazine hydrate (175 µL, 3.6 mmol) was added and the mixture was heated to reflux for 3 hours. The reaction was then cooled to room temperature and vacuum filtered. The resulting precipitate was washed with methanol and the combined filtrates were concentrated and purified by silica gel chromatography (5% methanol / 90% dichloromethane) to provide 184 mg of quinolyl amine 5.61B (90%) as a white solid.

**5.61B.** mp = 121-123 °C; TLC R<sub>f</sub> = 0.19 (5% methanol / 95% dichloromethane); IR (KBr) 3446, 3058, 1625, 1591, 1553, 1499, 1381 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.53 (d, J = 8.2 Hz, 1H), 8.39-8.36 (m, 2H), 8.10 (s, 1H), 7.94-7.91 (m, 2H), 7.84 (d, J = 9.1 Hz, 1H), 7.78-7.68 (m, 2H), 7.59-7.55 (m, 2H), 7.52-7.46 (m, 1H), 4.48 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 155.6, 148.7, 146.4, 140.1, 133.7, 132.4, 129.4, 129.0, 128.3, 127.9, 127.7, 127.1, 125.4, 123.3, 120.4, 116.8, 43.4 (One signal in the aromatic region was not resolved). Anal. Calcd for C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.44; H, 5.54; N, 9.61.

The quinolyl amine 5.61B (128 mg, 0.45 mmol) was dissolved in 3 mL methanol and HCl in diethyl ether (2 M, 270 µL, 0.54 mmol) was added. The mixture was stirred for 5 minutes and
concentrated in vacuo. The resulting oil was triturated with diethyl ether until a yellow precipitate formed. This was collected by vacuum filtration, washed with diethyl ether, and dried to provide 133 mg (92%) amine hydrochloride 5.68 as a yellow solid.

5.68. mp = 178 °C (dec.); IR (KBr) 3429, 3080, 2911, 1625, 1513, 1377 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 9.42-9.38 (m, 1H), 8.80 (br s, 3H), 8.48-8.45 (m, 3H), 8.12-8.03 (m, 3H), 7.90-7.76 (m, 2H), 7.66-7.52 (m, 3H), 4.74 (q, J = 5.7 Hz, 2H); ¹³C NMR (100 MHz, DMSO-d₆) δ 154.2, 145.3, 140.9, 138.6, 133.2, 131.0, 129.8, 129.0, 128.6, 128.0, 127.8, 127.4, 127.2, 124.4, 122.6, 120.9, 118.4, 38.7. Anal. Calcd for C₂₀H₁₇ClN₂: C, 74.88; H, 5.34; N, 8.73. Found: C, 74.49; H, 5.40; N, 8.61.

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Phosphatase 2 Results in Negative Regulation of Insulin-Induced Metabolic Actions in 3T3-L1

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Crohn's disease-like ileitis. *Gut* 2011, 60, 177-188.

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Schumm, L. P.; Steinhart, A. H.; Targan, S. R.; Xavier, R. J.; Libioulle, C.; Sandor, C.; Lathrop,
M.; Belaiche, J.; Dewit, O.; Gut, I.; Heath, S.; Laukens, D.; Mni, M.; Rutgeerts, P.; Van Gossum,
R.; Anderson, C. A.; Drummond, H.; Nimmo, E.; Ahmad, T.; Prescott, N. J.; Onnie, C. M.;
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1% iPrOH/heptane, Chiralcel OJ column

![Diagram](image)

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1% iPrOH/heptane, Chiralcel OJ column
5% iPrOH/heptane, Chiralcel OD column

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5% iPrOH/heptane, Chiralcel OD column

1% iPrOH/heptane, 1mL/min, Chiralcel OJ column

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<th>Peak No</th>
<th>Ret. Time (min)</th>
<th>Area (counts)</th>
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<th>Width 1/2 (sec)</th>
<th>Result (Area%)</th>
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10% iPrOH/heptane, 1mL/min, Chiralcel OJ column

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10% iPrOH/heptane, 1mL/min, Chiralcel OD column
For assignment of which enantiomer represents which HPLC signal, see Mikhailine, A. A.; Maishan, M. I.; Morris, R. H. Org. Lett. 2012, 14, 4638-4641.
NSC305787 (5,15+HCl) obtained from the NCI
Daniel Wallach
Syracuse, NY 13203
drwallac@syr.edu / (516)316-0231

Academic Track Record

Syracuse University
GPA: 3.92/4.0
Chemistry
PhD, Aug. 2011-Dec. 2016 (expected)

Syracuse University
Chemistry
M. Phil., May 2013

Binghamton University
Chemistry
GPA: 3.69/4.0; Magna Cum Laude
B.S., Aug. 2007-May 2011

Publications


Selected Conference Presentations

Underlined: Presenter


Research Experience

Alkylation of Sulfonamides and Anilines with Trichloroacetimidates
Dec 2012 - present
Advisor: John Chisholm
- Explored reactivity of various trichloroacetimidates with electron rich and poor anilines and sulfonamides
- Total synthesis of lipoxygenase inhibitor Onosmin B and formal synthesis of natural product 5,6-bicolorine completed

*Synthesis of Aminosteroid and Quinoline SHIP Inhibitors* Dec 2012 - present
Advisor: John Chisholm; Collaborators: William Kerr (Microbiology, SUNY Upstate Medical University)
- Successfully synthesized multiple quinoline based inhibitors of the SH2 containing inositol 5'-phosphatase (SHIP)
- Several aminosteroids have been synthesized in our lab and sent to collaborators at SUNY upstate for *in vitro* studies on various cell lines

*Synthesis and Measurement of Platinum Alloy Nanoparticles* Sept 2010 - May 2011
Advisor: C.J. Zhong; Mentor: Rameshwori Loukrakpam
- Prepared platinum alloy nanoparticles and introduced capping agents to maintain uniform spacing
- Tested platinum alloy nanoparticles via hydrolysis to determine catalytic capabilities

**Teaching Experience**

*Undergraduate Mentor*, Syracuse University May 2013 - present
- Mentored undergraduate and REU students in organic chemistry laboratory techniques
- Advisor: Dr. J. Chisholm

*Teaching Assistant*, Syracuse University Aug 2011 - present
- Instructed students in a laboratory and recitation setting. Created original lesson plans, led weekly classes and evaluated sections of 30 students.
- Advisors: Dr. D. Clark, Dr. N. Totah, Dr. J. Chisholm, Dr. Y. Luk, Dr. M. Sponsler, Dr. J. Kallmerten

*Private Tutor*, Binghamton University Jan 2011-May 2011
- Scheduled and led individual tutoring sessions for undergraduates enrolled in general chemistry

**Awards and Honors**
- *Syracuse University Summer Fellowship*, Syracuse University, May 2014
  Awarded to Syracuse students for full time study for a graduate degree
- *Walter E. Kaskan Award in Physical Chemistry*, Binghamton University, May 2011
  Awarded for outstanding academic achievement in the field of physical chemistry.
- *Undergraduate Award for Research and Creative Work*, Binghamton University, March 2010, November 2010, March 2011
  Awarded to support expenses for students’ independent research or creative work