CONVENIENT ETHERIFICATION USING TRICHLOROACETIMIDATES AND SYNTHESIS OF AMINOSTEROID SHIP INHIBITORS

Kyle Timothy Howard
Syracuse University

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Abstract

Alcohols are a common form of functionality in organic chemistry, and are often present in biologically active molecules. The protection of hydroxy groups is crucial in long multi-step synthetic routes, as the unprotected alcohol is typically not compatible with many reagents. Alcohols are often protected as corresponding benzyl ether, which can then be removed when desired to reveal the alcohol functional group. Classic methodology for protection of alcohols as benzyl ethers requires harsh conditions utilizing strong acids and bases, which functions well for simple substrates. In more complex multifunctional molecules this can lead to degradation and side products. Therefore, there is a need for the development of milder conditions for the protection of alcohols.

Recently a number of reagents have been developed to form benzyl ethers under mild, neutral conditions that and do not disturb the sensitive functionality in complex molecules. Many of these reagents have been based on imidate-type systems. The most common imidate system, the trichloroacetimidate, is often utilized for the installation of ethers under Lewis acid catalyzed conditions. Given their ready availability, a reevaluation of the reactivity of alcohols and trichloroacetimidates has been undertaken. In many cases, simply heating the imidate with an alcohol in refluxing toluene without an exogenous acid or base is an effective method for the formation of the desired ether. This operationally simple procedure is most effective for trichloroacetimidates that are precursors to highly stabilized cations (i.e. the 4-methoxybenzyl and diphenylmethyl group). The use of this new procedure with a number of acid and base sensitive substrates, which are protected in excellent yield without disturbing the delicate functionality present in these molecules, is presented.
Cancer is a group of disorders that are all defined by abnormal cell growth in an organism. This is a very broad set of diseases that can affect multiple organs. While classic cancer treatments have focused on killing all cells that divide quickly, more modern treatments attempt to selectively stop cancer progression by influencing cell signaling pathways. There are many studies about how cancer cells coopt cell signaling pathways and use these systems, which control cell growth in normal cells, to facilitate their own uncontrolled progression. One of the major cell signaling pathways implicated in tumor development is the PI3K pathway, which is governed by the kinase PI3K and the phosphatases PTEN and SHIP.

SHIP1 is an SH2-containing inositol 5’-phosphatase found in blood cells that is responsible for the hydrolysis of phosphatidylinositol-3,4,5-trisphosphate to phosphatidylinositol-4,5-bisphosphate. This enzyme is part of a major cellular signaling pathway (the PI3K pathway) that controls many important cellular events such as proliferation, differentiation and adhesion. SHIP1 inhibition has been found to increase blood cell production and slow the growth of blood cancer cells. Certain aminosteroids show selectivity as SHIP1 inhibitors and therefore may have therapeutic applications. In this study, syntheses of a number of aminosteroid derivatives were performed and these compounds are evaluated for their potential as SHIP1 inhibitors.
CONVENIENT ETHERIFICATION USING TRICHLOROACETIMIDATES AND
SYNTHESIS OF AMINOSTEROID SHIP INHIBITORS

By

Kyle T. Howard

Bachelor of Science in Chemistry, York College of Pennsylvania, York, PA, 2010

Master of Philosophy in Chemistry, Syracuse University, Syracuse, NY, 2012

DISSERTATION

Submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Chemistry

Syracuse University

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Pursuing my graduate degree at Syracuse University has been a challenging experience full of learning, growth, and self-discovery. I consider myself very fortunate to have had this experience. Along this journey I have met many people whom made me a better person. Graduate school would have been extremely difficult without new friends and the support of loved ones at home. To all these people, I owe immense gratitude.

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## ABBREVIATIONS AND ACRONYMS

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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>[α]</td>
<td>Specific rotation</td>
</tr>
<tr>
<td>3AC</td>
<td>3α–aminooxystane</td>
</tr>
<tr>
<td>Akt</td>
<td>Protein kinase B</td>
</tr>
<tr>
<td>Akt1</td>
<td>Protein kinase B 1</td>
</tr>
<tr>
<td>Akt2</td>
<td>Protein kinase B 2</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>AML</td>
<td>Acute myelogenous leukemia</td>
</tr>
<tr>
<td>Anal.</td>
<td>Combustion elemental analysis</td>
</tr>
<tr>
<td>anhyd</td>
<td>Anhydrous</td>
</tr>
<tr>
<td>ATG</td>
<td>Autophagy–related</td>
</tr>
<tr>
<td>BAECs</td>
<td>Bovine aortic endothelial cells</td>
</tr>
<tr>
<td>bFGF</td>
<td>Basic fibroblast growth factor</td>
</tr>
<tr>
<td>BHT</td>
<td>Butylated hydroxytoluene</td>
</tr>
<tr>
<td>BM</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>BMMC</td>
<td>Bone marrow mast cell</td>
</tr>
<tr>
<td>bs</td>
<td>Broad singlet</td>
</tr>
<tr>
<td>Btk</td>
<td>Bruton’s tyrosine kinase</td>
</tr>
<tr>
<td>calcld</td>
<td>Calculated</td>
</tr>
<tr>
<td>CD</td>
<td>Crohn’s Disease</td>
</tr>
<tr>
<td>CF</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical ionization</td>
</tr>
<tr>
<td>CLogP</td>
<td>Calculated partition coefficient</td>
</tr>
<tr>
<td>cod</td>
<td>1,5–Cyclooctadiene</td>
</tr>
<tr>
<td>compd</td>
<td>Compound</td>
</tr>
<tr>
<td>concd</td>
<td>Concentrated</td>
</tr>
<tr>
<td>COSMIC</td>
<td>College of Science Major Instrumentation</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphorsulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift in part per million</td>
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<tr>
<td>DCB</td>
<td>1,4–Dichlorobenzene</td>
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<tr>
<td>DCE</td>
<td>1,2–Dichloreothane</td>
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<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<td>DBU</td>
<td>1,8–Diazabicyclo[5.4.0]undec–7–ene</td>
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<td>DEPT</td>
<td>Distortionless enhancement by polarization transfer</td>
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<td>DIAD</td>
<td>Diisopropyl azodicarboxylate</td>
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<td>DIBAL</td>
<td>Diisobutyaluminum hydride</td>
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<tr>
<td>DMAP</td>
<td>4–Dimethyl aminopyridine</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
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<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
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<td>DMP</td>
<td>Dess–Martin periodinane</td>
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<td>DMPU</td>
<td>1,3–dimethyl–3,4,5,6–tetrahydro–2(1H)–pyrimidinone</td>
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<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
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<tr>
<td>DPM</td>
<td>Diphenyl methyl</td>
</tr>
<tr>
<td>EGF</td>
<td>Epidermal growth factor</td>
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</table>
EGFR  Epidermal growth factor receptor
ERK  Extracellular regulated kinase
ES  Embryonic stem
ESI  Electrospray ionization
FP  Fluorescence polarization
FT  Fourier transform
Gab  Grb2–associated binding
Glut4  Glucose transporter type 4
Grp1  General receptor for phosphoinositides 1
GSK3β  Glycogen synthase kinase 3β
GTP  Guanosine triphosphate
GvHD  Graft vs. Host disease
H&E  Hematoxylin and Eosin
HGF  Hepatocyte growth factor
HIV  Human immunodeficiency virus
HMBC  Heteronuclear multiple bond correlation
HRMS  High–resolution mass spectroscopy
HSC  Hematopoietic stem cells
HTS  High–throughput screening
HWE  Horner–Wadsworth–Emmons
IBD  Inflammatory bowel disease
IC50  Half maximal inhibitory concentration
I–1,3,4,5–P4  Inositol–1,3,4,5–tetrakisphosphate
IL–1β  Interleukin–1β
IP  Inositol phospholipid
IP4  Inositol–1,2,4,5–tetrakisphosphate
JNK  c–Jun N–terminal kinases
Kd  Equilibrium dissociation constant
LAH  Lithium aluminum hydride
LDA  Lithium diisopropylamine
lit.  Literature value
LN  Lymph node
MAP  Mitogen–activated protein
MAPK  Mitogen–activated protein kinases
m–CPBA  meta–Chloroperoxybenzoic acid
MEF  Mouse embryonic fibroblasts
Mes  2,4,6–Trimethylphenyl (mesityl)
MDCK  Madin–Darby canine kidney
MG  Malachite Green
MIR  Myeloid immunoregulatory
MM  Multiple myeloma
MOM  Methoxymethyl
Ms  Methylsulfonyl (mesyl)
MS  Molecular sieves
MySCs  Myeloid suppressor cells
NCI  National Cancer Institute
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>NHK</td>
<td>Nozaki–Hiyama–Kishi</td>
</tr>
<tr>
<td>NK</td>
<td>Natural killer</td>
</tr>
<tr>
<td>NMO</td>
<td>N–Methylmorpholine N–oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>NO</td>
<td>Nitrite</td>
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<tr>
<td>NOESY</td>
<td>Nuclear Overhauser effect spectroscopy</td>
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<td>PCC</td>
<td>Pyridinium chlorochromate</td>
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<td>PDC</td>
<td>Pyridinium dichlorochromane</td>
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<td>PDK1</td>
<td>Phosphatidylinositide kinase 1</td>
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<tr>
<td>PH</td>
<td>Pleckstrin homology</td>
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<td>PI3K</td>
<td>Phosphatidylinositol–3–kinase</td>
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<td>Phosphatidylinositol–3,4,5–trisphosphate</td>
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<td>PIPn</td>
<td>Phosphoinositides</td>
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<td>Pivalate</td>
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<td>PKB</td>
<td>Protein kinase B</td>
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<td>PLC–γ</td>
<td>Phospholipase C–γ</td>
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<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>PMP</td>
<td>para-Methoxyphenyl</td>
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<tr>
<td>PPTS</td>
<td>Pyridinium para–toluenesulfonate</td>
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<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homolog</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
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<tr>
<td>p–TsCl</td>
<td>para–Toluene sulfonate chloride</td>
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<td>Ras</td>
<td>Receptor tyrosine kinases</td>
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<td>RBC</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
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<td>SAR</td>
<td>Structure–activity relationship</td>
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<td>Shc</td>
<td>Src homology 2–containing</td>
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<td>SH2</td>
<td>Src homology 2 containing</td>
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<td>SHIP</td>
<td>Src homology 2 domain–containing inositol 5′–phosphatase</td>
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<tr>
<td>SHIP1</td>
<td>Src homology 2 domain–containing inositol 5′–phosphatase 1</td>
</tr>
<tr>
<td>SNPs</td>
<td>Single–nucleotide polymorphisms</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
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<tr>
<td>TBS</td>
<td>tert–Butyldimethylsilyl</td>
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<tr>
<td>TBDPS</td>
<td>tert–Butyldiphenylsilyl</td>
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<td>TEMPO</td>
<td>2,2,6,6–Tetramethylpiperidin–1–oxyl</td>
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<td>TES</td>
<td>Triethylsilyl</td>
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<td>TFA</td>
<td>Trifluoroacetic acid</td>
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<td>TFAA</td>
<td>Trifluoroacetic anhydride</td>
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<td>TFP</td>
<td>Tri–2–furylphosphine</td>
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<td>THP</td>
<td>Tetrahydropyran–2–yl</td>
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<td>TMEDA</td>
<td>N,N,N,N–Tetramethylmethylenediamine</td>
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<td>TMS</td>
<td>Tetramethylsilane</td>
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<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
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<td>TIPS</td>
<td>Triisopropyl</td>
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<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
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<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>TMS</td>
<td>Tetramethylsilane</td>
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<tr>
<td>Tf</td>
<td>Trifluoromethanesulfonyl (triflyl)</td>
</tr>
<tr>
<td>Ts</td>
<td>para–Toluenesulfonyl (tosyl)</td>
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<tr>
<td>V–ATPases</td>
<td>Vacuolar (H⁺)–ATPases</td>
</tr>
<tr>
<td>Yphos</td>
<td>Tyrosine phosphorylated</td>
</tr>
</tbody>
</table>
DEDICATION

For my family, Dad, Mom, Katelyn,

Grandpa Ed, Grandma Doris, Grandpa Frank and Grandma Ida.

“True wealth is having a healthy mind, body, and spirit. True wealth is having the knowledge to maneuver and navigate the mental obstacles that inhibit your ability to soar. Remember to love yourself, because if you can’t love yourself, how in the hell are you gonna love somebody else?”

-RuPaul
Chapter 1: Formation of Ethers Under Mild Conditions

Abstract:

Alcohols are common in organic molecules, and are often present in biologically active natural products. The protection of hydroxy groups is critical in long multi-step synthetic routes, as the unprotected alcohol is typically not compatible with many reagents. Alcohols are often protected as benzyl ethers or substituted benzyl ethers, which can then be removed under a variety of conditions when desired. Classic protection methods for alcohols as benzyl ethers requires harsh conditions utilizing strong acids and bases, which functions well for simple substrates. In more complex polyfunctional molecules this can lead to degradation and side products. Therefore, there is a need for the development of milder conditions for the protection of alcohols. Recently a number of reagents have been developed to form benzyl ethers under mild, neutral conditions that and do not disturb sensitive functionality. This chapter provides details of many of these reagents and summarizes the conditions needed to install the ethers utilizing these new methods.

Introduction:

Ethers are of great value in organic synthesis since they can act as protecting groups for sensitive alcohols.\textsuperscript{1,2} Simple and mild conditions are often desired to protect and deprotect alcohol substrates as to minimize degradation of a multistep synthesis. There are many known procedures to make ethers with the Williamson ether synthesis being a popular method. Another classical method for ether synthesis is the Koenigs-Knorr reaction for glycoside formation. Both methods employ the use of basic alkali metal alkoxides with alkyl halides. Alternatively ethers may be formed from alcohols under acidic conditions. These methods can be problematic in the
protection of alcohols in complex molecules. For example, carbohydrates can undergo base
catalyzed migration of esters and silyl ethers. Silyl ethers and acetal linkages could also be
disturbed by acid catalyzed cleavage. Metal catalysts have also been employed for the formation
of ethers, however, they are usually expensive.\textsuperscript{3,4} Therefore, development of milder conditions
for the protection of complex alcohols so that other sensitive functionality is not disturbed in
complex molecules is an ongoing area of research.

Recently several different reagents have been advanced for the protection of alcohols in
complex molecules without disturbing delicate functionality. One often cited method is to use
the trichloroacetimidate to form the ether in the presence of a Brønsted or Lewis acid. This
methodology is especially useful for the introduction of benzyl, allyl, and 4-methoxybenzyl
ethers.\textsuperscript{5,6,7} Other benzylic ethers have also been formed under these conditions. For example, the
formation of DPM ethers have been reported with the use of trichloroacetimidates and Lewis
acids (Figure 1.1).\textsuperscript{8,9} Diphenylmethyl trichloroacetimidate can be easily prepared with
diphenylmethanol and trichloroacetonitrile and is stable at room temperature over long periods of
time. The facile formation of DPM ethers with DPM imidate in the presence of TMSOTf
worked well on various primary and secondary alcohols. This methodology was showcased in
the creation of glycosidic bonds. Because the diphenylmethyl group on an \( \alpha \)-alcohol at the 2-\( O \)
position sterically hinders \( \alpha \) bond formation, it facilitates stereoselective \( \beta \)-glucopyranoside
formation.
Schmidt and Michel have demonstrated a use for trichloroacetimidates in glycosidic bond formation. Facile conversion of the glucopyranose to the corresponding imidate is done with base and trichloroacetonitrile or aryl-substituted ketenimines. Then the isolated imidate can be used for an acid catalyzed reaction with another glucopyranose to form a glycosidic bond (Figure 1.2). This methodology avoids using heavy metal salts such as silver salts which were previously utilized for glycoside synthesis.

Trifluoroacetimidates have also been utilized in the benzylation of alcohols. These imidates can be prepared from a one pot reaction of benzyl alcohols via perfluoro nitriles from an amide dehydration. Perfluoro nitriles can be difficult to use since they are extremely volatile and toxic. In a related study, Pohl investigated a number of N-aryl trifluoroacetimidates for the installation of benzyl and allyl protecting groups on carbohydrates (Figure 1.3). These trifluoroacetimidates are prepared from N-aryl trifluoroacetimidoyl chlorides, benzyl or allyl alcohol and base. Employing an electron withdrawing phenyl group on the nitrogen of the
imidate allows for a more stable imidate but still provides reactivity as a leaving group. The perfluoroacetimidates are stable at room temperature for several days. These imidates have been reported to alkylate alcohols in one hour at room temperature. However, the alkylation employs the use of an acid catalyst such as TfOH or TMSOTf.

*Figure 1.3: Alkylation with Trifluoroacetimidate*

Kunishima also established a method for preparing benzyl ethers at room temperature with triazinlammonium salts (Figure 1.4). 4-(4,6-Diphenoxy-1,3,5-triazin-2-yl)-4-benzylmorpholinium trifluoromethanesulfonate (DPT-BM) is prepared from 4,6-diphenoxy-2-trifluoromethanesulfonyloxy-1,3,5-triazine and 4-benzylmorpholine. This triazinlammonium salt is a non-hygroscopic, stable solid and can be stored at cold temperatures for long periods of time. This reagent was used to benzylate primary, secondary and tertiary alcohols in high yields. This alkylation also performed well on acid and base sensitive substrates such as acetoxy, β-hydroxyester, and silyl groups. The major caveat with this reaction is that it uses MgO as an acid scavenger and dehydrating reagent, which introduces another variable into the reaction and could lead to degradation of sensitive molecules. Kunishima has also reported alkylation of alcohols with benzyl or p-methoxybenzyl groups using 2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT) and 2,4,6-tris(p-methoxybenzyl)oxy)-1,3,5-triazine (TriBOT-PM), respectively. However, this method also uses catalytic acid to make the corresponding ethers.
Phosphinimidates have also been explored for their use in the alkylation of alcohols (Figure 1.5) under mild conditions. These stable imidates are made from alkyl diphenylphosphinites and methanesulfonyl azide. The ether formation worked well when a strong electron withdrawing group was bonded to the nitrogen of the phosphinimide. The alkylation was also quite general, and performed well on primary, secondary and tertiary alcohols as well as carbohydrates. One drawback to using phosphinimidates as alkylating agents is that they need catalytic amount of TMSOTf for the transformations to occur.

Dudley has reported the protection of alcohols as benzyl and p-methoxybenzyl groups using 2-benzyloxy-1-methylpyridinium triflate (Bn-OPT) and 2-((4-methoxybenzyloxy)-4-methylquinoline, respectively, in refluxing α,α,α-trifluorotoluene (Figure 1.6). Bn-OPT is a
novel benzylation reagent for alcohols, stable solid, and preactivated. It is prepared by treating 2-benzyloxypyridine with methyl triflate and can be made in situ in the presence of alcohol. The benzylation works well with primary, secondary, and tertiary alcohols. This etherification also worked with β-hydroxyesters and trimethylsilyl ethanol. However, reaction with cinnamyl alcohol only provided trace amounts of product. Additionally in order to prepare this reagent, the toxic and carcinogenic methyl triflate must be prepared and used. Alkylation with 2-(4-methoxybenzoyloxy)-4-methylquinoline also worked on primary, secondary, and tertiary alcohols. This method created by Dudley use additives such as MgO which is a mild base and desiccant to scavenge acid or water. Therefore, this etherification could prove difficult with base sensitive functionality.

*Figure 1.6: Etherification with Pyridinium Salts*

While many reagents have been created to address the problem of protecting alcohols under mild conditions in sensitive systems, work towards a general, inexpensive and nontoxic solution which does not require a strong acid catalyst is still ongoing. In the next chapter we will discuss investigations into utilizing trichloroacetimidates for these transformations without the addition of an acid promoter, providing an alternative solution for the formation of some esters and ethers under mild conditions.
References


Chapter 2: Formation of Esters, Thioethers and Ethers with Trichloroacetimidate

Electrophiles under Catalyst-Free Conditions

Abstract:

Many reagents have been developed to form benzyl ethers and esters under mild, neutral conditions that and do not disturb the sensitive functionality in complex molecules. Most of these reagents are based on acetimidate-type systems, as the rearrangement of these systems to the corresponding acetamide provides a secondary thermodynamic driving force for the ether formation. Trichloroacetimidates are effective at alkylating carboxylic acids, thiols, and alcohols under Lewis acid catalyzed conditions, but little attention has been given to their reactivity under catalyst free conditions. Given their ready availability, a reevaluation of the reactivity of alcohols and trichloroacetimidates has been undertaken. In many cases, simply heating the trichloroacetimidate with an alcohol in refluxing toluene without an exogenous acid or base is an effective method for the formation of the desired ether. This operationally simple procedure is most effective for trichloroacetimidates that are precursors to highly stabilized cations (i.e. the 4-methoxybenzyl and diphenylmethyl group). Esters, thioethers and ethers were formed without the use of an acid or base catalyst. Thermal etherification was performed under neutral conditions with both the DPM and PMB trichloroacetimidate. The use of this new procedure with a number of acid and base sensitive substrates, which are protected in excellent yield without disturbing the delicate functionality present in these molecules, is presented.

1. Catalyst-Free Protection of Esters with Trichloroacetimidates

Carboxylic acids are often protected as esters in multistep organic synthesis. Popular ester protecting groups for carboxylic acids include the 4-methoxybenzyl (PMB) and diphenylmethyl (DPM) esters.1,2 These protecting groups are often used due to their ease of removal via treatment
with acid or by hydrogenation (they may also be removed by saponification).\textsuperscript{1-7} Carboxylic acids are typically protected with a PMB group through alkylation reactions with the corresponding halide and a strong base. DPM esters can be installed with acid catalysis using diphenylmethanol as the electrophile or by treating the carboxylic acid with diphenyldiazomethane.\textsuperscript{8,9,10} The problem with most of these protecting group installations is that they do not tolerate complex substrates with sensitive functionality or they incorporate environmentally hazardous reagents.\textsuperscript{9} Trichloroacetimidates have been used for ester formation through their reaction with carboxylic acids in the presence of an acid catalyst.\textsuperscript{11} There have been scattered reports of ester formation with trichloroacetimidates without the addition of a catalyst, however. For example, Hayashi and co-workers have reported the formation of a PMB ester without a catalyst using 4-methoxybenzyl-2,2,2-trichloroacetimidate directly.\textsuperscript{3,4} Two other examples of catalyst free esterification are also present in the literature, with glycosyl imidates and 2-phenylisopropyl trichloroacetimidate undergoing these reactions.\textsuperscript{12,13} In the examples where a catalyst is not needed for esterification, the imidate may be protonated by the carboxylic acid and then ionize to form a carbocation, which is then trapped by the carboxylate anion. All of these examples of ester formation with trichloroacetimidates use imidates that are precursors to stable carbocations. Loss of the imidate and formation of trichloroacetamide thermodynamically facilitates the alkylation reaction. Given that little was known about the scope of these reactions, an investigation using PMB and DPM trichloroacetimidates to form their respective esters of carboxylic acids without an acid catalyst was initiated.

The formation of esters from trichloroacetimidates may occur by either an $S_N1$ or an $S_N2$ mechanism (Figure 2.1 shows the possible mechanisms for the reaction of a carboxylic acid with PMB trichloroacetimidate \textit{2.1}). For $S_N1$ addition, the carboxylic acid substrate promotes the
reaction by protonating the basic imidate nitrogen. After acetamide 2.3 is formed, the carboxylate anion can add to the PMB cation. In $S_N2$ addition, the carboxylic acid adds to the benzylic position of the PMB imidate causing the acetamide anion to form. The acetamide anion then removes the hydrogen from the protonated acid, forming the PMB ester. A concerted $S_N2$ mechanism involving a 6-membered transition state between the carboxylic acid and the PMB imidate is also a possibility.

Figure 2.1: Proposed Mechanisms of PMB esterification
Ester formation without the presence of an acid catalyst using PMB imidate 2.1 was initially explored. PMB imidate 2.1 is commercially available and may also be easily prepared from PMB alcohol and trichloroacetonitrile using DBU or NaH as a catalyst. Several carboxylic acids were successfully treated with PMB imidate 2.1 to form their corresponding esters without an added acid catalyst (Table 2.1). This simple reaction is carried out at room temperature in dichloromethane. Diverse substrates tolerated the esterification such as alkanes, alkenes, alkynes, and electron rich and electron poor benzoic acids. Under these conditions, carboxylic acids are selectively protected over other functional groups such as alcohols.

Table 2.1: Esterification with PMB Imidate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="2.5" alt="Image" /></td>
<td>43%</td>
</tr>
<tr>
<td>2</td>
<td><img src="2.6" alt="Image" /></td>
<td>60%</td>
</tr>
<tr>
<td>3</td>
<td><img src="2.7" alt="Image" /></td>
<td>54%</td>
</tr>
<tr>
<td>4</td>
<td><img src="2.8" alt="Image" /></td>
<td>64%</td>
</tr>
</tbody>
</table>
Ester formation was successful for the compounds in Table 2.1, resulting in moderate to high yields. Esterification of acetylsalicylic acid gave the highest yield of 80%. The isobutyl ester in entry 1 provided a low yield most likely due to steric effects from the isobutyl group on the acid. Entries 2 and 7 demonstrate that ortho substituents are tolerated on benzoic acid derivatives for this methodology, so some tolerance of sterically demanding substrates was demonstrated. No isomerization was observed for the alkene in entry 3. Entries 4, 5 and 6 provided moderate yields most likely due to sterics from the bulky R groups next to the
carboxylic acids. The highly strained cyclopropyl carboxylic acid provided the respective PMB ester in 51% yield (entry 8), but no opening of the cyclopropane was observed. Entries 9 and 10 again gave lower yields due to sterics of the corresponding carboxylic acids. This study provides evidence that PMB esters can be formed under mild reaction conditions using the trichloroacetimidate, and provides a mild method which may be useful for forming PMB esters in complex multifunctional substrates.\textsuperscript{15} Sterically hindered carboxylic acids may provide lower yields due to sterics, however.

Building on the success with PMB trichloroacetimidate, diphenyl methyl trichloroacetimidate was evaluated as an esterification reagent under catalyst-free conditions (Figure 2.2). Diphenylmethyl trichloroacetimidate was postulated to be an effective alkylating agent because it can lead to a stabilized carbocation, facilitating the S\textsubscript{N}1 substitution pathway with a carboxylic acid. Also, it is a easy to handle white solid that is stable in cold storage for long periods of time and can be easily prepared from the inexpensive diphenylmethanol in high yield.\textsuperscript{16} Ester formation was successful for both \textit{tert}-butylacetic acid \textsuperscript{2.15} and adamantane-1-carboxylic acid \textsuperscript{2.18} with DPM imidate \textsuperscript{2.16} under neutral conditions. Esterification of \textit{tert}-butylacetic acid gave a high yield of 92% while adamantane-1-carboxylic acid was not as reactive which is most likely because of sterics. This study provides evidence that DPM esters such as \textsuperscript{2.17} and \textsuperscript{2.19} may also be formed under mild reaction conditions using the trichloroacetimidates.\textsuperscript{17}
2. Thioethers

Building on the esterification work, the alkylation of thiols was then attempted under catalyst-free conditions. Thiols are less acidic than alcohols, but more acidic than alcohols, so their alkylation was explored next. Sulfides are commonly present in molecules used for pharmaceuticals, enzyme cofactors, and pesticides.\textsuperscript{18,19,20} Sulfides are often synthesized from the alkylation of thiols with alkyl halides or alcohols.\textsuperscript{21} However, these classic methods employ the use of an acid or base catalyst, which may provide problems in complex molecules.\textsuperscript{22}

Trichloroacetimidates were effective in the alkylation of thiols to form thioethers without the addition of an acid, base or metal catalyst (Figure 2.3). This new method for sulfide formation involves simply refluxing the thiol and imidate in THF. Both alkyl and aromatic thiols can be used with this method. Also, a variety of trichloroacetimidates including alkyl, allylic, propargylic and benzylic imidates performed well in the alkylation reaction.\textsuperscript{23}
Figure 2.4 shows two mechanistic possibilities for this thiol alkylation. Depending on the electrophile, this reaction can proceed through either a $S_N1$ or $S_N2$ pathway. The first step for both mechanisms is the imidate gets protonated by the thiol, creating a thiolate anion. Should the electrophile be suitable for $S_N2$ conditions, the sulfur anion will attack with the $R'$ group from the protonated imidate and the acetamide 2.3 is formed directly. A concerted $S_N2$ process as shown in Figure 2.1 may also be possible with a thiol. For the $S_N1$ pathway, the protonated imidate forms the acetamide and an $R'$ cation. Then the thiolate will then attack the $R'$ cation to give the thioether.
Thiol displacement of methyl trichloroacetimidate under these conditions to form a methyl thioether supported the $S_N2$ mechanism. Furthermore, thiol reaction with chiral imidate supports an $S_N2$ mechanism (Figure 2.5). The reaction proceeded with inversion forming sulfide 2.28, with none of the retention product being observed by $^1H$ NMR (the retention product was independently synthesized for comparison).

**Figure 2.5: Thiol reaction with chiral imidate**

3. Ethers

After formation of sulfides with trichloroacetimidates under catalyst free conditions, attention was turned to the etherification of alcohols. Trichloroacetimidates have been routinely used to protect alcohols as ethers at room temperature in the presence of a Brønsted or Lewis acid catalyst$^{24-29}$ Schmidt and co-workers have employed diphenylmethyl trichloroacetimidate 2.16 to make diphenylmethyl (DPM) ethers with a catalytic amount of TMSOTf in excellent
yields. The use of an acid catalyst for this reaction limits the substrates which can participate in the etherification. An example of a problematic acid sensitive substrate would be β-trimethylsilylethanol, which has been reported to be subjected to a Peterson elimination under acidic conditions with a trichloroacetimidate. Other reagents similar to trichloroacetimidates have also been developed for the synthesis of benzyl and PMB ethers. Additionally, trifluoroacetimidate and phosphinimidate type reagents have been introduced for etherification, however these systems still require the use of an acid catalyst.

Diphenylmethyl (DPM) ethers are frequently used as protecting groups for alcohols in organic synthesis. They can easily be removed through hydrogenation or with acidic conditions making the DPM group useful in complex molecules where more than one protecting group is in place. DPM ethers have also proven beneficial for enantioselective reactions since the steric bulk of the group can show increased selectivity in some substrates. The DPM group is also commonly used in medicinal chemistry since the phenyl rings add large hydrophobic groups which increase the lipophilicity of biologically active molecules.

Trichloroacetimidates have been utilized in the Chisholm laboratory to explore ester and sulfide formation. Given the high reactivity of the PMB and DPM trichloroacetimidates with carboxylic acids and thiols, these substrates were chosen for initial exploration as etherification reagents under catalyst-free conditions. PMB and DPM ethers are also commonly used protecting groups, so these methods should have some utility in the synthetic organic community. Studies with DPM imidate have shown that the rearrangement of the imidate to the corresponding acetamide occurs when the imidate is refluxed in toluene. This type of rearrangement is similar to reports of benzylic imidates undergoing rearrangement through a cationic pathway in the presence of a strong acid. We hypothesized that under thermal
conditions a similar process occurs and the DPM imidate ionizes to form a DPM cation and trichloroacetamide anion. The cation could be intercepted by an external nucleophile such as an alcohol. This hypothesis would allow for the formation of DPM ethers under thermal conditions without the use of an acid or base additive. Conditions have now been developed for ether formation under neutral conditions without a catalyst, which typically proceed in moderate to high yields with DPM and PMB imidates.\(^{40}\)

Diphenylmethyl (DPM) imidate was synthesized from benzophenone (Figure 2.6). Reduction of benzophenone to diphenylmethanol is easily done with sodium borohydride in methanol. The treatment of the diphenylmethanol with trichloroacetonitrile (TCAN) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided DPM imidate 2.16. Alfa-Aesar quotes diphenylmethanol at $25.97/mol, TCAN at $36.94/mol and $38.06/mol, allowing for a very cost effective synthesis of DPM imidate. The DPM imidate 2.16 showed stability for long periods of time when stored cold in a refrigerator and is very easy to handle since its physical form is a white powder.

*Figure 2.6: Synthesis of DPM Imidate*

Earlier studies with DPM imidate 2.16 demonstrated that the imidate would rearrange to the corresponding trichloroacetamide when refluxed in toluene (Figure 2.7). Rearrangements of allylic trichloroacetimidates are known and usually occur through a concerted [3,3]-sigmatropic rearrangement (the Overman rearrangement, Figure 2.8).\(^{41}\) However, this rearrangement is less favorable for the DPM imidate. Instead, the rearrangement is believed to occur through a
cationic pathway, where the imidate ionizes under thermal conditions due to the stability of the diphenylmethyl cation. This allows cation 2.32 and trichloroacetamide anion 2.31 to form. The trichloroacetamide anion is a weak base and poor nucleophile with a pKa of approximately 11. An added external nucleophile, such as an alcohol, may therefore intercept the cation 2.32 and form the corresponding DPM ether.

*Figure 2.7: Intercepting the DPM cation*

![Diagram showing the interception of the DPM cation by an external nucleophile](image)

*Figure 2.8: The Overman rearrangement*

![Diagram showing the Overman rearrangement](image)

Our thermal etherification studies began with an exploration of reaction conditions. A solvent screen with 1-octadecanol 2.34 and DPM imidate 2.16 showed that performing the reaction in toluene at reflux gave the best isolated yield of the corresponding DPM ether product (Table 2.2, entry 1). Lower temperatures in toluene provided a lower yield of the desired ether.
product (entry 2), which was attributed to a slower reaction. Nonpolar solvents appeared to be superior for the etherification reaction, with acetonitrile and DMF providing the lowest yields (entries 8 and 9 respectively).

*Table 2.2: Solvent Screen of Etherification with DPM Imidate*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>111</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>50</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>Trifluorotoluene</td>
<td>102</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>1,2-Dichloroethane</td>
<td>83</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>Dichloromethane</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>Tetrahydrofuran</td>
<td>66</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>1,4-Dioxane</td>
<td>101</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>Acetonitrile</td>
<td>82</td>
<td>28</td>
</tr>
<tr>
<td>9</td>
<td>Dimethylformamide</td>
<td>110</td>
<td>33</td>
</tr>
</tbody>
</table>

This catalyst-free etherification was then evaluated with a variety of alcohols to determine the scope of the reaction (Table 2.3). The reaction provided very high yields with benzyl alcohols in entries 1, 2, 3, and 4. Entries 5, 6, 7, 8 show allylic alcohols and phenol derivatives also participate in this reaction. Propargyl alcohol (entry 12) also proved to be an excellent reactant in the transformation, providing a 97% yield of propargyl ether product. The etherification of secondary and tertiary alcohols (entries 9, 10, 11) also proceeded in high yields. This is notable, as many other catalyst-free etherification conditions do not provide high yields with tertiary alcohols. Entries 13, 14, and 15 demonstrate that more complex alcohols can be protected with this methodology. Acid and base sensitive alcohols may also be protected with
this procedure as shown in entries 16-18. The protection of 2-trimethylsilyl ethanol to form ether 2.53 is particularly notable, as this substrate decomposes under acidic and basic conditions, yet is effectively protected under the new thermal conditions. Diols may also be mono protected with this methodology (entries 21-24), although the yields are moderate. In the case of mono protection only one equivalent of DPM imidate was used for the ether formation. Small amounts of diprotected ether were observed for the symmetrical diols. Entries 23 and 24 gave low yields because of the difficult separation of the mixture of mono protected alcohols. These reactions demonstrate that DPM ethers can be formed with neutral conditions using trichloroacetimidates. The ability to monoprotect alcohols preferentially may be explained by the greater acidity of the diol when the two alcohols form an intramolecular hydrogen bond, this was further explored with PMB trichloroacetimidate and is discussed later in this chapter.

*Table 2.3: Etherification with DPM Imidate*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>% Yield</th>
</tr>
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<tbody>
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</tr>
<tr>
<td>2</td>
<td><img src="2.37" alt="Image" /></td>
<td>71%</td>
</tr>
<tr>
<td>3</td>
<td><img src="2.38" alt="Image" /></td>
<td>92%</td>
</tr>
<tr>
<td>4</td>
<td><img src="2.39" alt="Image" /></td>
<td>88%</td>
</tr>
</tbody>
</table>
No racemization was observed in the formation of chiral ethers 2.54 and 2.55 through chiral HPLC analysis (Figure 2.8). Chiral and racemic serine protected ethers were prepared for comparison on chiral HPLC. The chiral HPLC traces show that no racemization occurs under the thermal etherification conditions. The same was observed for chiral ethyl lactate 2.54 (Figure 2.9).
Since ether formation from alcohols performed well with DPM imidate, a study was initiated with 4-methoxybenzyl (PMB) imidate. Both the PMB and DPM imidates have been shown to react with carboxylic acids to form esters without the need for an acid catalyst, so the PMB ether may also be reactive enough to form ethers under thermal conditions. PMB ethers are more common protecting groups for alcohols and can be easily removed under mild oxidation conditions.\textsuperscript{1,2} Since the PMB imidate is an oil, PMB protection under solvent free conditions
was initially explored (Figure 2.10). These neat reactions were performed with either 1-octadecanol or cinnamyl alcohol and 3 equivalents of PMB imidate at 110 °C overnight. This resulted in a good yield for 1-octadecanol, but only a 17% yield of the cinnamyl ether was obtained under these conditions. The addition of 10 mol% trichloroacetamide was also explored to see if the acetamide was catalyzing the reaction. The yield improved slightly for cinnamyl alcohol with the addition of trichloroacetamide but had little effect in the case with 1-octadecanol. As these conditions were not general and yields were moderate, a solvent screen was performed for the PMB etherifications (Table 2.4).

*Figure 2.10: Neat PMB Ether Reactions*
Table 2.4: PMB Ether Solvent Screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>111</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>80</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>50</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>Trifluorotoluene</td>
<td>102</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>1,2-Dichloroethane</td>
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<td>74</td>
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<td>Dichloromethane</td>
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<td>7</td>
<td>Dichloromethane</td>
<td>r.t.</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>Tetrahydrofuran</td>
<td>66</td>
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<td>1,4-Dioxane</td>
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<td>10</td>
<td>Acetonitrile</td>
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</tr>
<tr>
<td>11</td>
<td>Dimethylformamide</td>
<td>110</td>
<td>11</td>
</tr>
</tbody>
</table>

*0.25 M concentration

The solvent screen showed dichloroethane at reflux giving the best yield of PMB ether 2.60. α,α,α-Trifluorotoluene and toluene gave good yields when used at reflux. More polar solvents did not give good yields, as the imidate decomposed rapidly under these conditions. Less polar solvents at lower temperatures typically returned starting material, leading to the conclusion that a temperature in excess of 80 °C was required for the etherification. Alcohol protection with PMB imidate was therefore initially explored in DCE at reflux. However, PMB protection with DCE gave low yields on most substrates. Toluene was then tested as the solvent in hopes that heating the reaction to a higher temperature would improve reaction yields. Figure 2.11 shows PMB etherification of 1-octadecanol (2.34) at concentrations of 0.25 M, 0.5 M, and 1.0 M. Both reactions at concentrations of 0.5 M and 1.0 M gave high yields. PMB etherifications were then performed in toluene at 1.0 M.
Cinnamyl alcohol is an interesting substrate because it is an allylic alcohol. Protection of allylic alcohols have been previously reported in low yields with some PMB etherification reagents, so they were chosen as a test of the methodology. Figure 2.12 shows a study of the PMB etherification of cinnamyl alcohol under various conditions. The etherifications were carried out at 1 M concentration and went for 24 hours unless otherwise noted. PMB protection of cinnamyl alcohol in toluene only yielded 28% of the ether product. One possibility for the low yield is that adventitious water was hydrolyzing the imidate, which led to the low yield. Therefore, a series of drying reagents were tested in the PMB etherification. Molecular sieves, barium oxide and magnesium oxide all led to decreased yield for the etherification. Trichloroacetamide was also tested as a possible catalyst for the etherification but these conditions gave comparable yield of PMB protected cinnamyl alcohol as observed with the neat conditions.
Since PMB protection of cinnamyl alcohol in toluene with various additives gave poor results, a new solvent was tested. Toluene may be destroying the imidate through a Friedel-Crafts process (although these products were never observed directly by $^1$H NMR), so a more electron deficient solvent that was less likely to undergo Friedel-Crafts alkylation was utilized. Therefore, α,α,α-trifluorotoluene was explored as the solvent (Figure 2.13). The etherification in α,α,α-trifluorotoluene gave a 52% yield of the PMB protected cinnamyl alcohol. The etherification was allowed to proceed for two days in hopes of a higher product yield but the yield decreased to 32%. This may mean that shorter reaction times should be explored as a means to increase the reaction yield, but first a number of other alcohol substrates were evaluated at the 24 h time point (Table 2.5).
Since α,α,α-trifluorotoluene provided the PMB protected cinnamyl alcohol in moderate yield, α,α,α-trifluorotoluene was chosen as the solvent for substrate testing. The results of PMB etherification in α,α,α-trifluorotoluene are shown in Table 2.5. Entries 1-4 demonstrate that the methodology performs well with electron rich and electron poor benzyl alcohols. Propargyl alcohol gave an 85% yield of its PMB ether; however, the tertiary propargyl alcohol yielded no reaction product (entries 5-6). Other tertiary alcohols, like adamantyl alcohol, did provide some product although the yields were more moderate than observed for the DPM imidate. Entry 8 demonstrates PMB etherification of an electron poor phenol works with a 76% yield. The dihydrocholesterol derivative, a secondary alcohol, in entry 11 provided a 55% yield, which again is lower than was observed for secondary alcohols in the case of the DPM imidate. Entries 9-10 and 12-16 are more complex examples that are acid and base sensitive. These examples gave moderate to low yields demonstrating the PMB imidate is significantly less reactive than the DPM imidate. Further studies on the reaction conditions or the use of a more reactive imidate (like 2,4-dimethoxybenzyl or 2,6-dimethoxybenzyl) may be required to access a more general system for the benzyl protection of alcohols.
Table 2.5: PMB Etherifications in α,α,α-Trifluorotoluene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><a href="image">Image of product</a></td>
<td>81%</td>
</tr>
<tr>
<td>2</td>
<td><a href="image">Image of product</a></td>
<td>78%</td>
</tr>
<tr>
<td>3</td>
<td><a href="image">Image of product</a></td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td><a href="image">Image of product</a></td>
<td>67%</td>
</tr>
<tr>
<td>5</td>
<td><a href="image">Image of product</a></td>
<td>85%</td>
</tr>
<tr>
<td>6</td>
<td><a href="image">Image of product</a></td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td><a href="image">Image of product</a></td>
<td>40%</td>
</tr>
<tr>
<td>8</td>
<td><a href="image">Image of product</a></td>
<td>76%</td>
</tr>
<tr>
<td>9</td>
<td><a href="image">Image of product</a></td>
<td>33%</td>
</tr>
</tbody>
</table>
PMB etherification was also performed on a number of diols (Table 2.6). The lower reactivity of the PMB imidate may be beneficial in these cases, as higher selectivity may be accessed for these systems. Entry 1 shows the mono PMB protected 1,4-butanediol in 59% yield. This yield is expected since in the presence of one equivalent of imidate a 2:1:1 mixture of mono product: dialkylated product: starting material is predicted. Entry 2 is the dialkylated product of 1,4-butanediol and was obtained in only a 41% yield. Primary alcohols can selectively be protected in the presence of secondary and tertiary alcohols (entries 3, 4). Some
diols undergo monoprotection in much higher yields than could be anticipated a priori, for example entries 5 and 6 were obtained in 80% and 79% yield respectively.

*Table 2.6: PMB Etherification of Diols*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO-\text{OPMB} _\text{2.79}</td>
<td>59%\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>PMBO-\text{OPMB} _\text{2.80}</td>
<td>41%\textsuperscript{b}</td>
</tr>
<tr>
<td>3</td>
<td>OH-\text{OPMB} _\text{2.81}</td>
<td>34%\textsuperscript{a}</td>
</tr>
<tr>
<td>4</td>
<td>OH-\text{OPMB} _\text{2.82}</td>
<td>68%\textsuperscript{a}</td>
</tr>
<tr>
<td>5</td>
<td>HO-\text{OPMB} _\text{2.83}</td>
<td>80%\textsuperscript{a}</td>
</tr>
<tr>
<td>6</td>
<td>HO-\text{OPMB} _\text{2.84}</td>
<td>79%\textsuperscript{a}</td>
</tr>
<tr>
<td>7</td>
<td>HO-\text{OPMB} _\text{2.85}</td>
<td>36%\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 1 eq. of PMB imidate was used.
\textsuperscript{b} 3.3 eq. of PMB imidate were used.

The yield of the monoprotected product in these reactions is significantly higher than one would predict based on statistical reactivity of the diols. The ability of these systems to form 5
and 6 membered hydrogen bonds (Figure 2.14) may explain this reactivity. One of the hydrogens becomes more acidic when the diol is participating in this hydrogen bonding, leading to the selective formation of the monoprotected ether. This intramolecular H-bonding is not possible after monoprotection. The alkyne in entry 7 restricts that capability for hydrogen bonding and therefore gave a lower yield of the monoprotected product (36%), further supporting the role of hydrogen bonding in these systems.

*Figure 2.14: Hydrogen bonding in diols*

A one-pot PMB etherification from 4-methoxybenzyl alcohol was also attempted (Figure 2.15). In this procedure, the PMB imidate is generated *in situ* and not isolated. After the PMB imidate is observed by TLC, 4-nitrobenzyl alcohol was added. This alcohol was chosen because of its high reactivity in the PMB etherification. These experiments were performed in both toluene and α,α,α-trifluorotoluene. The reaction in toluene only gave 15% yield of PMB protected product while the reaction in α,α,α-trifluorotoluene gave 34% yield of product. These poor yields may be due to the imidate forming in low yield in these solvents, as typically the imidate formation is performed in diethyl ether.
Conclusions and Future Work

Thermal etherification was successful with both DPM and PMB imidate. Neutral, thermal conditions do not require an acid or base catalyst for etherification. The DPM imidate was found to be more reactive under these conditions, and therefore the method was more general with regard to the alcohol substrates. This novel methodology allows for alcohol protection on sensitive substrates. Chirality centers are also undisturbed when subjected to the reaction conditions. Trichloroacetimidates were used to alkylate carboxylic acids and thiols as well. Etherification using trichloroacetimidates under mild conditions will continue to be explored. Further investigation using different substrates will be conducted. Etherification of alcohols with other imidates will also be studied using similar, neutral conditions. Imidates with more electron rich groups, such as 2,4- or 2,6-dimethoxybenzylimidate, will be tested to see if reaction conditions and yields improve as compared to the 4-methoxybenzyl trichloroacetimidate.
Experimental Procedures

**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. DCM and THF were dried by passage through an alumina column by the method of Grubbs.¹ 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. Elemental analyses were performed on an elemental analyzer with a thermal conductivity detector and 2 meter GC column maintained at 50 °C.

**Identity.** Proton (¹H NMR) and carbon (¹³C 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 (CDCl₃), with residual chloroform (δ 7.26 ppm for ¹H NMR, δ 77.23 ppm for ¹³C NMR) or tetramethylsilane (δ 0.00 for ¹H NMR, δ 0.00 for ¹³C 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.

4-methoxybenzyl 3,3-dimethylbutanoate 2.5

In a flame dried 50 mL round bottom flask, tert-butylacetic acid (400 mg, 3.44 mmol) was dissolved in dry dichloromethane (14 mL). 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.934 g, 3.44 mmol) was added. The reaction was stirred at room temperature for 24 hours. The reaction was taken up in ethyl acetate, washed with sat. aq. sodium bicarbonate three times, dried with sodium sulfate and concentrated. Purification was done with flash column chromatography (10% ether/hexane) to give a clear oil (346 mg, 43%). TLC $R_f$ = 0.58 (15% ethyl acetate/hexanes); IR (neat) 2957, 2836, 1731, 1515 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.30 (d, $J = 9.0$ Hz, 2H), 6.89 (d, $J = 8.6$, 2H), 5.04 (s, 2H), 3.81 (s, 3H), 2.22 (s, 2H), 1.01 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 172.3, 159.7, 130.2, 128.5, 114.0, 65.8, 55.3, 48.1, 30.9, 29.8. Anal calcd for C$_{14}$H$_{20}$O$_3$: C, 71.16; H, 8.53. Found: C, 71.37; H, 8.37.
4-methoxybenzyl 2-methoxybenzoate 2.6

In a flame dried 50 mL round bottom flask, o-anisic acid (400 mg, 2.63 mmol) was dissolved in dry dichloromethane (11 mL). 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.486 g, 5.26 mmol) was added. The reaction was stirred at room temperature for 24 hours. The reaction was taken up in ethyl acetate, washed with sat. aq. sodium bicarbonate three times, dried with sodium sulfate and concentrated. Purification was done with flash column chromatography (10% ethyl acetate/hexanes) to give a clear oil (433 mg, 60%). TLC R<sub>f</sub> = 0.56 (25% ethyl acetate/hexanes); IR (neat) 2956, 2837, 1724, 1514, 1245 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.81 (d, <i>J</i> = 9.8 Hz, 1H), 7.37-7.41 (m, 3H), 6.89-6.97 (m, 4H), 5.29 (s, 2H), 3.88 (s, 3H), 3.79 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.0, 159.6, 159.4, 133.6, 131.7, 130.0, 128.4, 120.1, 113.9, 112.1, 66.4, 56.0, 55.3.

(E)-4-methoxybenzyl but-2-enoate 2.7


In a flame dried 50 mL round bottom flask, crotonic acid (400 mg, 4.65 mmol) was dissolved in dry dichloromethane (19 mL). 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.972 g, 6.98 mmol) was added. The reaction was stirred at room temperature for 24 hours. The reaction was taken up in ethyl acetate, washed with sat. aq. sodium bicarbonate three times, dried with sodium sulfate and concentrated. Purification was done with flash column chromatography (10% ethyl acetate/hexanes) to give a clear oil (515 mg, 54%). TLC R<sub>f</sub> = 0.25 (15% ethyl acetate/hexanes);
IR (neat) 3001, 2955, 2837, 1716, 1613, 1515, 1249 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.31 (d, \(J = 8.7\) Hz, 2H), 6.93-7.06 (m, 1H), 6.89 (d, \(J = 8.7\) Hz, 2H), 5.87 (d, \(J = 15.0\) Hz, 1H), 5.10 (s, 2H), 3.80 (s, 3H), 1.86 (d, \(J = 6.0\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 166.4, 159.7, 145.0, 130.1, 128.4, 122.7, 114.0, 65.8, 55.3, 18.0.

\[
\begin{align*}
\text{4-methoxybenzyl-1-adamantanoate 2.8} \\
\text{Lit. Ref.: Rolfe, A.; Loh, J. K.; Maity, P. K.; Hanson, P. R. Org. Lett. 2011, 13, 4-7.}
\end{align*}
\]

In a flame dried 50 mL round bottom flask, 1-adamantanecarboxylic acid (400 mg, 2.22 mmol) was dissolved in dry dichloromethane (9 mL). 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.255 g, 4.44 mmol) was added. The reaction was stirred at room temperature for 24 hours. The reaction was taken up in ethyl acetate, washed with sat. aq. sodium bicarbonate three times, dried with sodium sulfate and concentrated. Purification was done with flash column chromatography (10% ether/hexanes) to give a clear oil (426 mg, 64%). TLC \(R_f = 0.65\) (25% ethyl acetate/hexanes); IR (neat) 2999, 2906, 2851, 1724, 1514, 1229 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.27 (d, \(J = 8.6\) Hz, 2H), 6.88 (d, \(J = 8.7\) Hz, 2H), 5.03 (s, 2H), 3.81 (s, 3H), 1.71-2.00 (m, 15H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 177.6, 159.5, 129.6, 128.8, 113.9, 65.7, 55.3, 40.8, 38.9, 36.6, 28.1.
(S)-4-methoxybenzyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 2.9


In a flame dried 10 mL round bottom flask, (S)-(-)-α-(trifluoromethyl)phenylactic acid (50 mg, 0.214 mmol) was dissolved in dry dichloromethane (1 mL). 4-methoxybenzyl 2,2,2-trichloroacetimidate (12 mg, 0.428 mmol) was added. The reaction was stirred at room temperature overnight. The reaction was taken up in ethyl acetate, washed with sat. aq. sodium bicarbonate three times, dried with sodium sulfate and concentrated. Purification was done with flash column chromatography (10% ether/hexanes) to give a clear oil (38 mg, 50%). TLC _R_f = 0.36 (25% ethyl acetate/hexanes); IR (neat) 2954, 2841, 1747, 1516, 1248, 1174 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.26-7.46 (m, 6H), 6.88 (d, \(J = 8.7\) Hz, 2H), 5.29 (q, \(J = 11.8\) Hz, 2H), 3.81 (s, 3H), 3.51 (s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 166.5, 160.0, 132.3, 130.5, 129.6, 128.4, 127.3, 126.8, 125.2, 121.4, 114.0, 67.9, 55.5, 55.3.

4-methoxybenzyl 2,2-diphenylacetate 2.10

In a flame dried 50 mL round bottom flask, diphenylacetic acid (400 mg, 1.88 mmol) was dissolved in dry dichloromethane (8 mL). 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.062 g,
3.76 mmol) was added. The reaction was stirred at room temperature for 24 hours. The reaction was taken up in ethyl acetate, washed with sat. aq. sodium bicarbonate three times, dried with sodium sulfate and concentrated. Purification was done with flash column chromatography (10% ethyl acetate/hexanes) to give an orange solid (394 mg, 63%). TLC $R_t = 0.35$ (25% ethyl acetate/hexanes); IR (KBr) 3028, 2956, 2836, 1734, 1612, 1514, 1250, 1145 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26-7.34 (m, 11H), 6.90 (d, $J = 8.6$ Hz, 2H), 5.17 (s, 2H), 5.09 (s, 1H), 3.84 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.5, 159.8, 138.8, 130.2, 128.8, 128.7, 127.9, 127.4, 114.0, 66.9, 57.2, 55.4.

**4-methoxybenzyl 2-acetoxybenzoate 2.11**

In a flame dried 50 mL round bottom flask, acetylsalicylic acid (400 mg, 2.22 mmol) was dissolved in dry dichloromethane (9 mL). 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.255 g, 4.44 mmol) was added. The reaction was stirred at room temperature for 24 hours. The reaction was taken up in ethyl acetate, washed with sat. aq. sodium bicarbonate three times, dried with sodium sulfate and concentrated. Purification was done with flash column chromatography (10% ethyl acetate/hexanes) to give a clear oil (534 mg, 80%). TLC $R_t = 0.69$ (25% ethyl acetate/hexanes); IR (neat) 2957, 2837, 1769, 1720, 1610, 1515, 1248 1195 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.04 (d, $J = 1.7$ Hz, 1H), 7.54 (t, $J = 9.0$ Hz, 1H), 7.29-7.38 (m, 3H), 7.09 (d, $J = 9.0$ Hz, 1H), 6.92 (d, $J = 8.7$ Hz, 2H), 5.24 (s, 2H), 3.81 (s, 3H), 2.13 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.8, 164.6, 159.9, 150.7, 133.2, 132.1, 130.5, 127.7, 126.1, 123.9, 123.5, 114.3, 67.0, 55.4, 20.8. Anal calcd for C$_{17}$H$_{16}$O$_5$: C, 67.99; H, 5.37. Found: C, 67.60; H, 5.17.
4-methoxybenzyl cyclopropanecarboxylate 2.12

In a flame dried 50 mL round bottom flask, cyclopropane carboxylic acid (400 mg, 4.65 mmol) was dissolved in dry dichloromethane (19 mL). 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.600 g, 5.66 mmol) was added. The reaction was stirred at room temperature for 24 hours. The reaction was taken up in ethyl acetate, washed with sat. aq. sodium bicarbonate three times, dried with sodium sulfate and concentrated. Purification was done with flash column chromatography (10% ethyl acetate/hexanes) to give a clear oil (493 mg, 51%). TLC R<sub>f</sub> = 0.53 (25% ethyl acetate/hexanes); IR (neat) 3011, 2956, 2836, 1724, 1613, 1515, 1249, 1166 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.30 (d, J= 8.6 Hz, 2H), 6.88 (d, J= 8.7 Hz, 2H), 5.05 (s, 2H), 3.78 (s, 3H), 1.59-1.67 (m, 1H), 0.94-1.08 (m, 2H), 0.78-0.91 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 174.7, 159.6, 130.1, 128.3, 113.9, 66.1, 55.2, 13.0, 8.5.

4-methoxybenzyl 3-(2,4-dichlorobenzyloxy)thiophene-2-carboxylate 2.13

In a flame dried 50 mL round bottom flask, 3-(2,4-dichlorobenzyloxy)thiophene-2-carboxylic acid (400 mg, 1.32 mmol) was dissolved in dry dichloromethane (3 mL). 4-methoxybenzyl 2,2,2-trichloroacetimidate (746 mg, 2.64 mmol) was dissolved in dry dichloromethane (3 mL) and added to the round bottom flask. The reaction was stirred at room temperature for 24 hours.
The reaction was taken up in ethyl acetate, washed with sat. aq. sodium bicarbonate three times, dried with sodium sulfate and concentrated. Purification was done with flash column chromatography (10% ethyl acetate/hexanes) to give a white solid (153 mg, 27%). mp = ; TLC Rf = 0.58 (25% ethyl acetate/hexanes); IR (neat) 2954, 1682, 1588, 1544, 1384, 1248 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.53 (d, J = 8.4 Hz, 1H), 7.34-7.43 (m, 3H), 7.15 (d, J = 6.0 Hz, 1H), 6.89-6.92 (m, 3H), 5.30 (s, 2H), 5.71 (s, 2H), 3.81 (s, 3H).

4-methoxybenzyl 2-(diphenylphosphino)benzoate 2.14

In a flame dried 50 mL round bottom flask, 2-(diphenylphosphino)benzoic acid (400 mg, 1.31 mmol) was dissolved in dry dichloromethane (2.5 mL). 4-methoxybenzyl 2,2,2-trichloroacetimidate (746 mg, 2.64 mmol) was dissolved in dry dichloromethane (2.5 mL) and added to the round bottom flask. The reaction was stirred at room temperature for 24 hours. The reaction was taken up in ethyl acetate, washed with sat. aq. sodium bicarbonate three times, dried with sodium sulfate and concentrated. Purification was done with flash column chromatography (1:1 ethyl acetate/hexanes) to give a clear oil (139 mg, 25%). TLC Rf = 0.26 (60% ethyl acetate/hexanes); IR (neat) 3056, 1727, 1612, 1514, 1248, 1118 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.86-7.90 (m, 1H), 7.39-7.68 (m, 13H), 7.07 (d, J = 14.2 Hz, 2H), 6.78 (d, J = 9.0, 2H), 4.90 (s, 2H), 3.78 (s, 3H).
benzhydryl 3,3-dimethylbutanoate 2.17

In a flame dried 50 mL round bottom flask, tert-butylacetic acid (0.33 mL, 2.58 mmol) was dissolved in dry dichloromethane (10 mL). Benzhydryl 2,2,2-trichloroacetimidate (1.101 g, 3.35 mmol) was added. The reaction was stirred at room temperature for 24 hours. The reaction was concentrated. Purification was done with flash column chromatography (1% ethyl acetate/hexanes) to give a clear oil (0.669 g, 92%). TLC $R_f = 0.79$ (10% ethyl acetate/hexanes); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.26-7.37 (m, 9H), 6.89 (s, 1H), 2.32 (s, 2H), 0.99 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 171.4, 140.6, 128.6, 127.9, 127.4, 76.7, 48.2, 31.1, 29.8. Anal. Calcd for C$_{19}$H$_{22}$O$_2$: C, 80.82; H, 7.85. Found: C, 81.11; H, 8.03.

benzhydryl-1-adamantanoate 2.19

In a flame dried 25 mL round bottom flask, adamantane-1-carboxylic acid (0.300 g, 1.66 mmol) was dissolved in dry dichloromethane (7 mL). Benzhydryl 2,2,2-trichloroacetimidate (0.710 g, 2.16 mmol) was added. The reaction was stirred at room temperature for 24 hours. The reaction was concentrated. Purification was done with flash column chromatography (1% ethyl acetate/hexanes) to give an orange solid (0.177 g, 31%). TLC $R_f = 0.64$ (10% ethyl acetate/hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.23-7.36 (m, 16H), 6.83 (s, 1H), 2.03 (bs, 4H),
1.96 (bs, 9H), 1.73 (bs, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 176.5, 142.4, 140.9, 128.6, 128.5, 127.9, 127.6, 127.4, 127.1, 80.1, 76.3, 40.9, 39.0, 36.7, 28.1. Anal. Calcd for C$_{24}$H$_{26}$O$_2$: C, 83.20; H, 7.56. Found: C, 83.17; H, 7.85.

**General Procedure for Forming Sulfides from Trichloroacetimidates:**

The thiol was placed in a dry round bottom flask and dissolved in anhydrous THF (or toluene) to a concentration of 0.2 M. The trichloroacetimidate (1.2 equiv) was then added and the reaction was warmed to reflux. After 18 hours the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was then pre-adsorbed on silica gel and purified by column chromatography. Alternatively, the residue can be dissolved in ethyl acetate, washed with 2M aq. NaOH (3x), dried (Na$_2$SO$_4$) and concentrated (this workup removes the trichloroacetamide byproduct). For some sulfides this workup provided analytically pure material, in others the residue is purified by silica gel chromatography to provide the pure sulfide product.

![Chemical Structure](image)

**5-[(3-Methyl-2-buteryl)thio]-1-phenyl-1H-tetrazole 2.21.**

Cream colored solid (0.250 g, 98%). mp =38.6-39.9°C; TLC R$_f$ = 0.72 (30% ethyl acetate /70% hexanes); IR (neat) 3062, 3015, 2981, 2928, 2895 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.61-7.55 (m, 5H), 5.44-7.37 (m, 1H), 4.04 (d, J = 8.0 Hz, 2H), 1.73 (s, 6H). Anal calcd for C$_{12}$H$_{14}$N$_4$S: C, 58.51; H, 5.73, N, 22.74. Found: C, 58.29; H, 5.54; N, 22.39.
1-Phenyl-5-[(2E)-3-phenyl-2-propen-1-yl]thio]-1H-tetrazole 2.22.


Yellow oil (0.264 g, 95%). TLC *R*$_f$ = 0.63 (30% ethyl acetate /70% hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.61-7.55 (m, 5H), 7.39-7.27 (m, 5H), 6.72 (d, *J* = 15.6 Hz, 1H), 6.41-6.31 (m, 1H), 4.23 (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 153.9, 136.2, 135.4, 133.8, 130.3, 130.0, 128.8, 128.3, 126.7, 124.0, 122.6, 36.1.

5-(Isopropylthio)-1-phenyl-1H-tetrazole 2.23.


Yellow oil (0.689 g, 38%). TLC *R*$_f$ = 0.64 (35% DCM /65% hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.58-7.52 (m, 5H), 3.42 (heptet, *J* = 6.5 Hz, 1H), 1.51 (d, *J* = 6.5 Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 154.1, 133.7, 130.1, 129.7, 124.0, 39.8, 23.3.

**General Procedure for the Formation of DPM Ethers from Alcohols under Thermal Conditions:**

The alcohol was placed in a 25 mL flame dried round bottom flask and dissolved in anhydrous toluene to a concentration of 0.25 M. The trichloroacetimidate (1.2 equiv) was added and the reaction warmed to reflux. After 18 hours, the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was pre-adsorbed on silica gel and purified by silica gel column chromatography. The residue can be dissolved in ethyl acetate, washed with 2M aq. NaOH (3x), dried (Na$_2$SO$_4$) and concentrated (this workup removes the trichloroacetamide byproduct).
Octadecyloxydiphenylmethane 2.35.

White solid (0.273 g, 85%). mp = 47-48 °C; TLC Rf = 0.80 (10% ethyl acetate/hexanes); IR (solid film from CH$_2$Cl$_2$) 3027, 2923, 2852, 1493, 1453, 1097 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.21-7.37 (m, 10H), 5.33 (s, 1H), 3.44 (t, $J = 6.6$ Hz, 2H), 1.60-1.67 (m, 2H), 1.26 (m, 30H), 0.88 (t, $J = 6.3$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 142.9, 128.5, 127.5, 127.2, 83.8, 69.4, 32.2, 30.1, 29.94, 29.91, 29.87, 29.85, 29.7, 29.6, 26.5, 22.9, 14.3 (several signals in the aliphatic region were not resolved). Anal calcd for C$_{31}$H$_{48}$O: C, 85.26; H, 11.08. Found: C, 85.18; H, 11.13.

Benzyloxydiphenylmethane 2.36.


Clear oil (0.238 g, 94%). TLC Rf = 0.92 (25% ethyl acetate/hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.24-7.42 (m, 15H), 5.46 (s, 1H), 4.56 (s, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 142.4, 138.6, 128.6, 128.6, 127.9, 127.72, 127.65, 127.3, 82.7, 70.7.
(4-Methoxybenzyl)oxy)diphenylmethane 2.37.


Clear oil (0.314 g, 71%). TLC Rf = 0.50 (10% ethyl acetate/hexanes); 1H NMR (300 MHz, CDCl3) \( \delta 7.24-7.41 \) (m, 12H), \( \delta 6.91 \) (d, \( J = 8.7 \) Hz, 2H), \( \delta 5.45 \) (s, 1H), \( \delta 4.50 \) (s, 2H), \( \delta 3.83 \) (s, 3H); 13C NMR (100 MHz, CDCl3) \( \delta 159.3 \), 142.4, 130.6, 129.5, 128.5, 127.6, 127.3, 113.9, 82.2, 70.3, 55.4.

\[
\begin{array}{c}
\text{O}_2\text{N} \\
\text{Ph} \\
\text{Ph} \\
\end{array}
\]

((4-Nitrobenzyl)oxy)methylene)dibenzene 2.39.

Off-white solid (0.460 g, 88%). mp = 62-64 °C (DCM); TLC Rf = 0.59 (40% DCM/60% hexanes); IR (solid film from CH2Cl2) 3062, 3028, 2922, 2857, 1493, 1347, 1288 cm\(^{-1}\); 1H NMR (300 MHz, CDCl3) \( \delta 8.19 \) (d, \( J = 8.7 \) Hz, 2H), \( \delta 7.52 \) (d, \( J = 8.1 \) Hz, 2H), \( \delta 7.25-7.40 \) (m, 10H), \( \delta 5.46 \) (s, 1H), \( \delta 4.62 \) (s, 2H); 13C NMR (75 MHz, CDCl3) \( \delta 147.4 \), 146.1, 141.6, 128.6, 127.8, 127.7, 127.0, 123.6, 83.5, 69.5. Anal calcd for C\(_{20}\)H\(_{17}\)NO\(_3\): C, 77.22; H, 5.37; N, 3.49. Found: C, 77.20; H, 5.31; N, 3.44.

\[
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\end{array}
\]

Cinnamyloxydiphenylmethane 2.43.

White solid (0.395 g, 88%). mp = 55-57 °C; TLC Rf = 0.58 (25% ethyl acetate/hexanes); 1H NMR (300 MHz, CDCl3) δ 7.23-7.42 (m, 15H), 6.63 (d, J = 15.9 Hz, 1H), 6.32-6.41 (m, 1H), 5.51 (s, 1H), 4.20 (dd, J = 6.0, 1.5 Hz, 2H); 13C NMR (75 MHz, CDCl3) δ 142.3, 136.9, 132.3, 128.6, 128.5, 127.7, 127.5, 127.1, 126.6, 126.3, 82.8, 69.4.

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Ph} &
\end{align*}
\]

**Diphenyl(prop-2-ynyloxy)methane 2.47.**


Yellow oil (0.384 g, 97%). TLC Rf = 0.86 (10% ethyl acetate/hexanes); 1H NMR (300 MHz, CDCl3) δ 7.24-7.40 (m, 10H), 5.68 (s, 1H), 4.17 (d, J = 2.4 Hz, 2H), 2.46 (t, J = 2.4 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 141.3, 128.6, 127.9, 127.5, 81.8, 79.9, 74.8, 56.0.

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Ph} &
\end{align*}
\]

**((Cyclohexyloxy)methylene)dibenzene 2.44.**


Clear oil (0.494 g, 93%). TLC Rf = 0.68 (10% ethyl acetate/hexanes); 1H NMR (300 MHz, CDCl3) δ 7.24-7.40 (m, 10H), 5.58 (s, 1H), 3.35-3.44 (m, 1H), 1.93 (dd, J = 9.0, 6.0 Hz, 2H), 1.76-1.82
(m, 2H), 1.41-1.58 (m, 3H), 1.26 (q, \( J = 8.3 \) Hz, 3H); \(^{13}\)C NMR (75MHz, CDCl\(_3\)) \( \delta \)143.3, 128.4, 127.31, 127.26, 80.1, 75.1, 32.5, 26.0, 24.2.

((1-Phenylethoxy)methylene)dibenzene 2.38.


Clear oil (0.434 g, 92%). TLC \( R_f = 0.85 \) (10% acetone/hexanes); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.20-7.41 (m, 15H), 5.31 (s, 1H), 4.51 (q, \( J = 6.6 \) Hz, 1H), 1.53 (d, \( J = 6.3 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 143.9, 143.0, 142.2, 128.7, 128.4, 128.3, 127.73, 127.70, 127.67, 127.3, 127.1, 126.7, 80.2, 75.1, 24.5.

((tert-Pentyloxy)methylene)dibenzene 2.45.


Clear oil (0.489 g, 85%). TLC \( R_f = 0.92 \) (10% ethyl acetate/hexanes); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.41 (d, \( J = 6.9 \) Hz, 4H), 7.33 (t, \( J = 7.2 \) Hz, 4H), 7.20-7.26 (m, 2H), 5.60 (s, 1H), 1.62 (q, \( J = 7.5 \) Hz, 2H), 1.17 (s, 6H), 0.91 (t, \( J = 7.5 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 145.6, 128.3, 127.0, 126.9, 76.9, 75.6, 34.8, 26.1, 8.9.
1-(Benzhydryloxy)adamantane 2.46.

Orange solid (0.383 g, 92%). mp = 64-66 °C; TLC Rf = 0.71 (10% ethyl acetate/hexanes); IR (solid film from CH2Cl2) 3025, 2905, 2850, 1492, 1451, 1354, 1082 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 7.20-7.39 (m, 10H), 5.80 (s, 1H), 2.14 (s, 3H), 1.83 (bs, 6H), 1.62 (bs, 6H); ¹³C NMR (100 MHz, CDCl3) δ 145.3, 128.2, 127.2, 126.9, 74.4, 73.8, 43.0, 36.6, 30.8. Anal calcd for C23H26O: C, 86.75; H, 8.23. Found: C, 86.72; H, 8.18.

2-((Benzhydryloxy)methyl)-3-phenyloxirane 2.51.


Clear oil (0.255 g, 65%) TLC Rf = 0.50 (10% ethyl acetate/hexanes); ¹H NMR (300 MHz, CDCl3) δ 7.25-7.44 (m, 15H), 5.53 (s, 1H), 3.86 (dd, J = 11.5, 3.1 Hz, 1H), 3.80 (d, J = 2.0 Hz, 1H) 3.66 (dd, J = 5.3, 11.5 Hz, 1H), 3.29-3.32 (m, 1H). ¹³C NMR (100 MHz, CDCl3) δ 141.99, 141.94, 137.1, 128.7, 128.6, 128.4, 127.8, 127.77, 127.5, 127.3, 127.2, 125.9, 84.1, 68.9, 61.4, 56.1.
(2-(Benzhydryloxy)ethyl)trimethylsilane 2.53.

Pale yellow oil (0.368 g, 79%). TLC $R_f = 0.56$ (15% DCM/5% triethylamine/80% hexanes); IR (solid film from CH$_2$Cl$_2$) 3087, 3063, 3029, 2953, 2892, 1452, 1317, 1249 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36 (dd, $J = 6.3, 1.2$ Hz, 4H), 7.30 (t, $J = 6.6$ Hz, 4H), 7.22-7.25 (m, 2H), 5.35 (s, 1H), 3.56 (t, $J = 6.0$ Hz, 2H), 1.03 (t, $J = 6.0$ Hz, 2H), 0.00 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.0, 129.6, 128.5, 128.2, 84.6, 67.6, 19.7, 0.0; Anal calcd for C$_{18}$H$_{24}$OSi: C, 76.00; H, 8.50; Found: C, 75.77; H, 8.62.

2-(Benzhydryloxy)isoindoline-1,3-dione 2.49.


Yellow solid (0.323 g, 80%). mp = 160-162 °C; TLC $R_f = 0.29$ (10% acetone/hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.66-7.76 (m, 4H), 7.52-7.56 (m, 4H), 7.29-7.39 (m, 6H), 6.53 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.8, 137.9, 134.4, 128.9, 128.8, 128.5, 128.4, 123.4, 89.7.
(S)-Benzyl 3-(benzhydryloxy)-2-(((benzyloxy)carbonyl)amino)propanoate 2.55.

Clear oil (0.273 g, 91%). \([\alpha]^{21.6}_D\) -12.5 (c 1.26, CHCl₃); TLC R_f = 0.18 (10% ethyl acetate/hexanes); IR (solid film from CH₂Cl₂) 3434, 3341, 3062, 3030, 2949, 2876, 1722, 1498, 1339, 1197, 1067 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) δ 7.07-7.30 (m, 20H), 5.63 (d, J = 12.0 Hz, 1H), 5.19 (s, 1H), 5.12 (d, J = 4.0 Hz, 2H), 5.04 (s, 2H), 4.49 (dt, J = 2.8 Hz, 1H), 3.84 (dd, J = 9.4, 2.8 Hz, 1H), 3.60 (dd, J = 9.4, 3.1 Hz, 1H); ^13C NMR (75 MHz, CDCl₃) δ170.3, 156.1, 141.6, 141.4, 136.4, 135.4, 128.7, 128.65, 128.6, 128.5, 128.4, 128.3, 128.2, 127.7, 127.0, 126.9, 84.2, 69.0, 67.4, 67.2, 54.8. (note: two signals in the aromatic region were not resolved.) Anal calcd for C₃₁H₂₉NO₅: C, 75.13; H, 5.90; N, 2.83. Found: C, 74.94; H, 5.97; N, 3.00. Chiral HPLC analysis: Chiralcel OD (heptane/2-PrOH = 90/10, 1.0 mL/min, 254 nm, 25 °C): t(S enantiomer) = 16.7 min, t(R enantiomer) = 23.9 min.

Methyl 2,3,4-Tri-O-benzyl-6-O-diphenylmethyl-α-D-glucopyranoside 2.52.


Clear colored oil (0.750 g, 73%). TLC R_f = 0.43 (15% ethyl acetate/85% hexanes); ^1H NMR (300 MHz, CDCl₃) δ 7.55-7.18 (m, 25 H), 5.50 (s, 1H), 5.13 (d, J = 10.8 Hz, 1H), 4.98 (t, J = 11.1 Hz,
2H), 4.93 (d, J = 12.0 Hz, 1H), 4.82 (d, J = 11.7 Hz, 1H), 4.80 (d, J = 3.6 Hz, 1H), 4.68 (d, J = 11.1 Hz, 1H), 4.16 (t, J = 9.3 Hz, 1H), 3.89-3.99 (m, 1H), 3.77-3.84 (m, 3H), 3.72 (dd, J = 3.6, 9.6 Hz, 1H), 3.49 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 142.2, 142.1, 138.8, 138.3, 138.2, 128.5, 128.4, 128.36, 128.1, 127.9, 127.8, 127.5, 127.4, 127.2, 126.9, 98.1, 84.1, 82.3, 80.1, 78.0, 75.9, 75.1, 73.4, 70.3, 67.9, 55.1.


White solid (0.374 g, 87%). $[\alpha]^{21.6}_D +12.4$ (c 1.04, CHCl$_3$); mp = 127-129 °C; TLC $R_f = 0.74$ (10% ethyl acetate/hexanes); IR (solid film from CH$_2$Cl$_2$) 3027, 2930, 2865, 1493, 1452, 1381, 1062 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.16-7.34 (m, 10H), 5.54 (s, 1H), 3.28-3.38 (m, 1H), 0.63-1.92 (m, 46H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 143.3, 128.4, 127.4, 127.3, 80.3, 76.5, 56.7, 56.5, 54.6, 45.0, 42.8, 40.3, 39.7, 37.2, 36.4, 36.0, 35.95, 35.7, 35.3, 32.3, 29.1, 28.7, 28.5, 28.2, 24.4, 24.0, 23.0, 22.8, 21.4, 18.9, 12.5, 12.3. Anal calcd for C$_{40}$H$_{58}$O: C, 86.58; H, 10.54. Found: C, 86.59; H, 10.68.
Ethyl 3-(benzhydryloxy)-3-phenylpropanoate 2.50.

White solid (0.178 g, 96%). mp = 73-74 °C; TLC R_f = 0.53 (10% ethyl acetate/hexanes); IR (solid film from CH_2Cl_2) 3061, 3028, 2980, 1736, 1493, 1453, 1268, 1172, 1052 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl_3) δ 7.19-7.40 (m, 15H), 5.24 (s, 1H), 4.81 (ddd, J = 1.3, 4.9, 9.0 Hz, 1H), 4.00-4.23 (m, 2H), 2.96 (ddd, J = 1.4, 9.0, 14.7 Hz, 1H), 2.65 (ddd, J = 1.2, 4.9, 14.7 Hz, 1H), 1.21 (td, J = 1.1, 7.1 Hz, 3H); \(^1^3\)C NMR (100 MHz, CDCl_3) δ 170.8, 142.8, 141.3, 140.7, 128.8, 128.6, 128.3, 128.2, 128.0, 127.9, 127.24, 127.16 126.7, 80.11, 75.7, 60.6, 44.0, 14.3. Anal calcd for C\(_{24}\)H\(_{24}\)O\(_3\): C, 79.97; H, 6.71. Found: C, 79.96; H, 6.88.

\(\text{(R)}\)-Ethyl 2-(benzhydryloxy)propanoate 2.54.


Clear oil (0.434 g, 90%). [\(\alpha\)]\(^{21.6}\)_D = -103.8 (c 1.04, DCM); TLC R_f = 0.57 (10% ethyl acetate/hexanes); \(^1\)H NMR (300 MHz, CDCl_3) δ 7.26-7.41 (m, 10H), 5.57 (s, 1H), 4.16-4.28 (m, 2H), 4.08 (q, J = 6.0 Hz, 1H), 1.49 (d, J = 9.0 Hz, 3H), 1.30 (t, J = 9.0 Hz, 3H); \(^1^3\)C NMR (100 MHz, CDCl_3) δ 173.6, 142.1, 141.1, 128.7, 128.4, 128.0, 127.7, 127.6, 127.5, 82.8, 72.7, 61.0,
19.0, 14.4. Chiral HPLC analysis: Chiralcel OD (heptane/2-PrOH = 99/1, 1.0 mL/min, 254 nm, 25 °C): t_{R\text{ enantiomer}} = 5.3 min, t_{S\text{ enantiomer}} = 5.8 min.

((4-Methoxyphenoxy)methylene)dibenzene 2.40.


Orange solid (0.424 g, 91%). mp = 84-85 °C; TLC Rf = 0.42 (10% acetone/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.26-7.43 (m, 10H), 6.88 (d, J = 9.1 Hz, 2H), 6.75 (d, J = 9.2 Hz, 2H), 6.11 (s, 1H), 3.73 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 154.2, 152.4, 141.7, 128.7, 127.8, 127.1, 117.4, 114.7, 82.8, 55.7.

((4-Nitrophenoxy)methylene)dibenzene 2.41.


Pale yellow colored solid (0.310 g, 61%). mp = 157-158 °C; TLC Rf = 0.36 (10% ethyl acetate/90% hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.13 (d, J = 9.0 Hz, 2H), 7.28-7.42 (m, 10H), 7.02 (d, J = 9.3 Hz, 2H), 6.31 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 162.9, 141.6, 139.8, 128.8, 128.3, 126.7, 125.8, 115.9, 82.5.
Methyl 3-(benzhydryloxy)thiophene-2-carboxylate 2.42.

White solid, (0.280 g, 53%). mp = 105-106 °C; TLC Rf = 0.3 (10% ethyl acetate/90% hexanes);
IR (solid film from CH2Cl2) 3061, 3028, 2948, 1711, 1538, 1228, 1062 cm\(^{-1}\); \(^1\)H NMR (400 MHz,
CDCl3) δ 7.53 (d, \(J = 7.6\) Hz, 4H), 7.35 (t, \(J = 7.2\) Hz, 4H), 7.25–7.28 (m, 3H), 6.74 (d, \(J = 5.6\) Hz,
1H), 6.27 (s, 1H), 3.90 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl3) δ 162.4, 160.1, 141.2, 130.4, 128.9,
128.1, 126.7, 118.7, 111.6, 85.0, 51.8. Anal calcd for C\(_{19}\)H\(_{16}\)O\(_3\)S: C, 70.35; H, 4.97; Found: C, 70.26; H, 5.02.

1-methoxy-4-((1-phenylethoxy)methyl)benzene 2.66


In a 10 mL flame dried round bottom flask, 1-phenylethanol (0.366 g, 3.0 mmol) was dissolved
in anhydrous trifluorotoluene (3 mL). PMB imidate (1.690g, 6.0 mmol) was added to the flask.
The reaction refluxed for 20 hours. The reaction was concentrated. Purification was done using
column chromatography (10% ethyl acetate/hexanes) followed by column chromatography (50%
CH\(_2\)Cl\(_2\)) to give product as a clear colorless oil (0.477 g, 67%).

TLC Rf = 0.52 (10% ethyl acetate/90% hexanes); \(^1\)H NMR (300 MHz, CDCl3) δ 7.35-7.20 (m,
6H), 6.85 (d, \(J = 8.7\) Hz, 2H), 4.46 (q, \(J = 6.6\) Hz, 1H), 4.23 (dd, \(J = 11.4, 46.8\) Hz, 2H), 3.75 (s,
3H), 1.45 (d, \(J = 6.3\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl3) δ 159.2, 143.9, 130.8, 129.4, 128.6,
127.5, 126.4, 113.9, 77.0, 55.3, 24.3;
4-methoxybenzyl benzyl ether 2.63.


81% yield, clear colored oil. TLC $R_f = 0.54$ (20% ethyl acetate/80% hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34-7.23 (m, 7 H), 6.87 (d, $J = 8.4$ Hz, 2 H), 4.51 (s, 2 H), 4.48 (s, 2 H), 3.77 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.1, 138.3, 130.3, 129.3, 128.3, 127.7, 127.5, 113.7, 71.6, 55.2.

![4-methoxybenzyl benzyl ether](image)

bis(4-methoxybenzyl)ether 2.64.


78% yield, clear colored oil. TLC $R_f = 0.50$ (20% acetone/80% hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.27 (d, $J = 8.8$ Hz, 4 H), 6.87 (d, $J = 8.8$ Hz, 4 H), 4.50 (s, 4 H), 3.78 (s, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.1, 130.4, 129.3, 113.7, 71.4, 55.2.

![bis(4-methoxybenzyl)ether](image)

1-methoxy-4-(4-nitro-benzylxoxymethyl)-benzene 2.65.

85% yield, dark yellow colored oil. TLC $R_f = 0.45$ (10% acetone/90% hexanes); IR (neat) 3109, 3076, 3003, 2935, 2838, 1561, 1342, 1302, 1246; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.21 (d, $J = 2$ Hz, 2 H), 7.51 (d, $J = 8.8$ Hz, 2 H), 7.26 (d, $J = 2$ Hz, 2 H), 6.90 (d, $J = 8.8$ Hz, 2 H), 4.61 (s, 2 H), 4.55 (s, 2 H), 3.81 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.5, 147.3, 146.1, 129.6,
129.5, 129.3, 127.8, 123.6, 114.4, 113.9, 72.5, 70.5, 55.3, 44.9; Anal. Calcd for C_{15}H_{15}NO_4: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.80, H, 5.41, N, 5.00.

N-(4-methoxybenzyloxy)phthalimide.

Lit. Ref.: Ramsay, S. L.; Freeman, C.; Grace, P. B.; Redmond, J. W.; MacLeod, J. K.

Carbohydrate Research. 333. 59-71.

58% yield, white colored solid. mp = 134.9-136.3°C (ethyl acetate); TLC \( R_f = 0.28, 0.57 \) (20% ethyl acetate/80% hexanes); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.82-7.71 (m, 4 H) 7.45 (d, \( J = 8.4 \) Hz, 2 H), 6.88 (d, \( J = 8.4 \) Hz, 2 H), 5.15 (s, 2 H), 3.80 (s, 3 H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 163.5, 160.4, 134.3, 131.6, 128.8, 125.8, 123.4, 113.9, 79.4, 55.2.

(4-Methoxyphenyl)methyl propargyl ether 2.67.


82% yield, Clear oil. TLC \( R_f = 0.41 \) (10% Ethyl acetate/90% hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.32 (d, \( J = 8.4 \) Hz, 2 H), 6.93 (d, \( J = 1.8 \) Hz, 2 H), 4.57 (s, 2 H), 4.17 (d, \( J = 2.4 \) Hz, 2 H), 3.82 (s, 3 H), 4.55 (s, 2 H), 2.52 (d, \( J = 2.4 \) Hz, 1 H).

1-((4-methoxybenzyl)oxy)-2-nitrobenzene 2.70.
76% yield, yellow oil. TLC $R_f = 0.30$ (10% ethyl acetate/90% hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.83 (dd, $J = 1.6$, 8.1 Hz, 1H), 7.49 (ddd, $J = 1.7$, 7.5, 8.4 Hz, 1H), 7.38 (d, $J = 8.6$ Hz, 2H), 7.14 (dd, $J = 1.0$, 8.5 Hz, 1H), 7.02 (td, $J = 0.9$, 7.6 Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 2H), 5.16 (s, 2H), 3.81 (s, 3H).

(2-((4-methoxybenzyl)oxy)ethyl)trimethylsilane 2.74.

68% yield, red oil. TLC $R_f = 0.76$ (10% ethyl acetate/90% hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.25 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.1$ Hz, 1H), 4.40 (s, 2H), 3.78 (s, 3H), 3.54 (td, $J = 0.9$, 8.1 Hz, 2H), 0.97 (td, $J = 0.9$, 8.1 Hz, 2H), 0.00 (s, 9H).

(E)-1-((cinnamyoxy)methyl)-4-methoxybenzene 2.62.


52% yield, yellow oil. TLC $R_f = 0.70$ (25% ethyl acetate/75% hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40 (d, $J = 7.2$ Hz, 2H), 7.34-7.30 (m, 4H), 7.25 (d, $J = 6.3$ Hz, 1H), 6.90 (d, $J = 8.6$ Hz, 2H), 6.63 (d, $J = 16.0$ Hz, 1H), 6.33 (dt, $J = 6.0$, 15.9 Hz, 1H), 4.52 (s, 2H), 4.18 (dd, $J = 1.4$, 6.0 Hz, 2H), 3.82 (s, 3H).

1-methoxy-4-((octadecyloxy)methyl)benzene 2.60.

96 % yield, white solid. mp = 45.6-46.5°C (dichloromethane). TLC Rf = 0.82 (10% ethyl acetate/90% hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.26\) (d, \(J = 8.8\) Hz, 2H), 6.87 (d, \(J = 8.7\) Hz, 2H), 4.42 (s, 2H), 3.79 (s, 3H), 3.43 (t, \(J = 6.7\) Hz, 2H), 1.63-1.56 (m, 2H), 1.36-1.25 (m, 34H), 0.88 (t, \(J = 6.6\) Hz, 3H).

\[
\begin{align*}
&\text{ethyl 3-((4-methoxybenzyl)oxy)-3-phenylpropanoate 2.77.} \\
&61\% \text{ yield, clear oil. TLC } R_f = 0.47 (10\% \text{ ethyl acetate/90}\% \text{ hexanes}); \quad \text{\(^1\)H NMR (300 MHz, CDCl\(_3\)) } \delta 7.39-7.29 \text{ (m, 5H), 7.19 (d, } J = 8.7 \text{ Hz, 2H), 6.85 (d, } J = 8.7 \text{ Hz, 2H), 4.83 (q, } J = 5.1 \text{ Hz, 1H), 4.38 (d, } J = 11.4 \text{ Hz, 1H), 4.23 (d, } J = 11.1 \text{ Hz, 1H), 4.17-4.06 \text{ (m, 2H), 3.80 (s, 3H),} \\
&\quad 2.85 (dd, } J = 9.0, 15.0 \text{ Hz, 1H), 2.59 (dd, } J = 4.8, 15.3 \text{ Hz, 1H), 1.20 (t, } J = 7.2 \text{ Hz, 3H).}
\end{align*}
\]

\[
\begin{align*}
&\text{3-[(4-Methoxybenzyl)oxy]propan-1-ol 2.84.} \\
&79\% \text{ yield, pale yellow oil. TLC } R_f = 0.43 (50 \% \text{ ethyl acetate}/50 \% \text{ hexanes}); \quad \text{\(^1\)H NMR (300 MHz, CDCl\(_3\)) } \delta 7.28 \text{ (d, } J = 8.7 \text{ Hz, 2H), 6.91 (d, } J = 8.7 \text{ Hz, 2H), 4.48 (s, 2H), 3.84 (s, 3H),} \\
&\quad 3.80 \text{ (t, } J = 5.5 \text{ Hz, 2H), 3.67 (t, } J = 5.8 \text{ Hz, 2H), 2.17 (bs, 1 H), 1.88 (q, } J = 5.7 \text{ Hz, 2H).}
\end{align*}
\]

\[
\begin{align*}
&\text{2-(4-Methoxybenzylxyloxy)ethanol 2.83.}
\end{align*}
\]

80% yield, yellow oil. TLC $R_f = 0.32$ (50% ethyl acetate/50% hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.30 (d, $J = 7.8$ Hz, 2 H), 6.92 (d, $J = 11.6$ Hz, 2 H), 4.53 (s, 2 H), 3.84 (s, 3 H), 3.78 (t, $J = 4.7$ Hz, 2 H), 3.61 (t, $J = 4.8$ Hz, 2 H), 1.85 (bs, 1 H).

![Chemical structure](image)

**4-[(4-Methoxyphenyl)methoxy]-2-butyn-1-ol 2.85.**


36% yield, yellow oil. TLC $R_f = 0.52$ (50% ethyl acetate/50% hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.30 (d, $J = 6.6$ Hz, 2 H), 6.91 (d, $J = 11.6$ Hz, 2 H), 4.56 (s, 2 H), 4.36 (t, $J = 1.8$ Hz, 2 H), 4.21 (t, $J = 2.1$ Hz, 2 H), 3.84 (s, 3 H).
Appendix A. $^1$H AND $^{13}$C NMR SPECTRA SUPPLEMENT TO CHAPTER 2

4-methoxybenzyl 3,3-dimethylbutanoate
4-methoxybenzyl 3,3-dimethylbutanoate

4-methoxybenzyl 2-methoxybenzoate

4-methoxybenzyl 2-methoxybenzoate
4-methoxybenzyl 2-methoxybenzoate

(E)-4-methoxybenzyl 2-enoate

but-2-enoate
(E)-4-methoxybenzyl but-2-enoate

(3r,5r,7r)-4-methoxybenzyl adamantane-1-carboxylate
(S)-4-methoxybenzyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate

4-methoxybenzyl 2,2-diphenylacetate

4-methoxybenzyl 2,2-diphenylacetate
4-methoxybenzyl 2,2-diphenylacetate

4-methoxybenzyl 2-acetoxybenzoate
4-methoxybenzyl cyclopropanecarboxylate

4-methoxybenzyl 3-((2,4-dichlorobenzyl)oxy)thiophene-2-carboxylate
4-methoxybenzyl 2-(diphenylphosphino)benzoate

[Chemical structure diagram]

ppm
(3r,5r,7r)-benzhydryl adamantane-1-carboxylate

2.19
Octadecyloxydiphenylmethane
Benzyloxydiphenylmethane

ODPM
11
(4-Methoxybenzyl) diphenylmethane
Cinnamyl oxydiphenylmethane

\[
\text{ODPM} \quad 14
\]
Cinnamylloxydiphenylmethane
Diphenyl(prop-2-ynyloxy)ethane

ODPM
15
ODPM
16

{(Cyclohexyl)oxymethylene}dibenzene
((1-Phenylethoxy)methylene)dibenzene

ODPM

17
(tertiary-Phenyl)methylenedibenzene
((tert-Pentyloxy)methylene)dibenzene
2-{{Benzhydroxyloxy}methyl}-3-phenyloxirane
2-{[Benzyloxy]methyl}-3-phenyloxirane
DPMO \( \overset{\text{21}}{\text{SiMe}}_3 \)

RCD-II-66 C13
2-(Benzhydryloxy)isoindoline-1,3-dione

N
O
DPMO
22
2-(Benzhydryloxy)isoindoline-1,3-dicarboxylic Acid

[Image of a chemical structure and an NMR spectrum]
(3S,5S,9S,10S,13R,14S,17R)-9-(Benzhydryloxy)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)hexadecahydro-1H-cycloptenta[a]phenanthrene
(3S,5S,6R,8S,9S,10S,13R,14S,17R)-3-((Benzydryloxy)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthrene
Ethyl 3-(benzhydroxy)-3-phenylpropanoate
Ethyl 3-\{benzhydryloxy\}-3-phenylpropanoate
(R)-Ethyl 2-(benzhydryloxy)propanoate

[Diagram of molecular structure and NMR spectrum]

ppm
(3S)-Benzy l 3-(benzydrox y)-2-{{(benzyle oxy) carbonyl} amino}butanoate

\[
\begin{align*}
\text{Cbz} & \quad \text{O} \\
\text{DPMO} & \quad 28 \\
\end{align*}
\]
((4-Methoxyphenoxy)methylene) dibenzene
((4-Methoxyphenoxy)methylene)dibenzene

DPMO

129
DPMO - \( \text{NO}_2 \)

ppm

2.00 3.84 10.34 2.05 1.00
Methyl 3-(benzydryloxy)thiophene-2-carboxylate
Methyl 3-(benzhydryloxy)thiophene-2-carboxylate

![Chemical Structure](image)
2-[(Benzzyldioxyl)napthalene]
10% 2-Propanol/Hexane

Chiracel OD

![Chart with peaks](image)

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10% 2-Propanol/Hexane

Chiracel OD

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100.0000
1% 2-Propanol/Hexane

Chiracel OD

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1% 2-Propanol/Hexane

Chiracel OD

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References


Chapter 3: Modulation of SHIP for Therapeutic Purposes

Abstract:

The SH2-containing inositol 5’-phosphatase-1 (SHIP1) is an enzyme found in blood cells that is responsible for the hydrolysis of phosphatidylinositol-3,4,5-trisphosphate to phosphatidylinositol-4,5-bisphosphate. This enzyme is part of a major cell signaling pathway (the PI3K pathway) that affects many important cellular functions such as proliferation, differentiation and adhesion. SHIP1 inhibition has been found to increase blood cell production and slow the growth of blood cancer cells, and therefore SHIP1 inhibition with small molecules is being explored. High throughput screening small molecule libraries identified several SHIP1 inhibitors including 3α-aminocholestane (3AC). 3AC and certain other aminosteroids show selectivity as SHIP1 inhibitors and therefore may have therapeutic applications. Further synthetic studies have been undertaken to determine which portions of the aminosteroid SHIP1 inhibitor are important for biological activity. In addition, modifications to the molecule which improve solubility and potency have also been pursued in order to facilitate the evaluation of these inhibitors in other biological settings. In this chapter the syntheses of a number of aminosteroid derivatives and the evaluation of these compounds for their potential as SHIP1 inhibitors is described.

PI3K Signaling Pathway

When eukaryotic cells shuttle information about changes in the extracellular environment to the nucleus the signals must cross the cell membrane. Enzymes on the interior of the cell membrane are integral to this process, as they initiate signaling cascades inside the cell that involves a complex system made up of both enzymes and second messengers such as
phosphatidylinositols. Phosphatidylinositols play a prominent role in cell signaling. These lipids are intercalated on the interior of the cell membrane and are used to assist in the transduction of signals across the plasma membrane from the external environment to the nucleus. Phosphatidylinositol signaling has a major influence in cell division and survival.\(^1,2\) This signaling also plays a role in cell differentiation and adhesion.\(^1,2\)

One of the best known phosphatidylinositol signaling pathways is mediated by phosphatidylinositol-3-kinase, PI3K. PI3K is responsible for phosphorylating phosphatidylinositol-4,5-bisphosphate, PI(4,5)P\(_2\), to form phosphatidylinositol-3,4,5-trisphosphate, PI(3,4,5)P\(_3\) (Figure 3.1). When activated, PI3K can rapidly synthesize PI(3,4,5)P\(_3\), which then activates a number of protein kinases resulting in an accelerating signal cascade through the cytoplasm to the nucleus. Aberrant activation of PI3K is known to lead to cancer.\(^3,4\)

The phosphatase and tensin homolog protein, PTEN, also regulates this pathway. The PTEN protein exerts its influence on the pathway by acting as a 3’ inositol phosphatase, reversing the PI3K reaction by hydrolyzing PI(3,4,5)P\(_3\) back to PI(4,5)P\(_2\). This function of PTEN is crucial, as PTEN knockout mice quickly develop terminal cancer.\(^5,6\) Other inositol phosphatases hydrolyze PI(3,4,5)P\(_3\) to PI(3,4)P\(_2\), a second, but distinct inositol bisphosphate. In blood cells (and other cells related to the hematopoietic system), SH2-containing inositol 5’-phosphatase or SHIP1, is the inositol phosphatase that hydrolyzes PI(3,4,5)P\(_3\) to PI(3,4)P\(_2\).\(^2,7\) Unlike PTEN, SHIP1 knockout mice are viable and do not develop terminal cancer, although their immune system is modified.\(^8,9\)
Many other signaling enzymes are involved in the transmission of the PI3K signal in order for it to reach the nucleus and exert its effects on cellular metabolism (Figure 3.2). After PI(3,4,5)P$_3$ is formed from PI3K, it binds with the protein kinase PDK1. PDK1 then phosphorylates a second protein kinase AKT, which is activated and begins to phosphorylate a number of other protein kinases.$^{10}$ Both PI(3,4,5)P$_3$ and PI(3,4)P$_2$ are required in the signaling pathway in order to fully activate AKT.$^{11,12}$ Once activated, AKT controls the activation and inhibition of different functions relating to cellular survival and proliferation. One kinase that AKT activates is mTOR, which controls regulatory cell growth pathways. Inhibition at the start of the PI3K signaling pathway would cut off the branching of signals and may restore normal control of cell growth.
SHIP plays a significant role in regulation of the PI3K signaling pathway. By hydrolyzing PI(3,4,5)P₃ to PI(3,4)P₂, SHIP modulates the intensity of the signal and influences immune response and cellular division.¹⁴,¹⁵,¹⁶ There are three major paralogs of the SHIP enzyme: SHIP1, SHIP2, and sSHIP. The expression of SHIP1 occurs primarily in blood and bone marrow cells. SHIP2 is expressed in a wide variety of cells throughout the rest of the body. The sSHIP enzyme is only expressed in stem cells. A genetic study of SHIP1 determined that the enzyme plays a role in blood cell biology and immunology.¹⁴,¹⁵,¹⁶ Most importantly for this study, it was found that SHIP1 inhibition induces apoptosis in blood cancer cells.⁹ This implicates the development of SHIP1 inhibitors as a possible treatment for hematopoietic neoplasms.
Attempts at crystallizing the whole SHIP enzyme have not been successful. Potter and coworkers were able to obtain a crystal structure of a portion of the SHIP2 enzyme containing the active site (Figure 3.3). The crystal structure was obtained when a biphenyl 2,3',4,5',6-pentakisphosphate (BiPh(2,3',4,5',6)P₅) synthetic ligand was bound to the catalytic site of the SHIP2 protein. The biphenyl phosphate ligand bonds to the polar residues in the SHIP2 active site through hydrogen bond interactions in the binding pocket. The 5' phosphate of BiPh(2,3',4,5',6)P₅ mimics the 5'-phosphatase of PI(3,4,5)P₃. This phosphate shows hydrogen bonds to Arg682, Tyr661 and Arg611. The hydrogen-bonding network forces the phosphate into a conformation where hydrolysis is facilitated. Molecular modeling studies have implicated that a loop of the enzyme (the PI4M loop) near the active site folds over the (BiPh(2,3',4,5',6)P₅) ligand and encloses it after it binds to SHIP2. Analysis of SHIP2 binding to the small molecule is an excellent starting point for the development of small molecule inhibitors.

Figure 3.3: Crystal Structure of SHIP2
**Rationale for SHIP Antagonist or Agonist**

Control of PI(3,4,5)P₃ production plays a critical role in signal transduction in the PI3K pathway. A possible way to govern PIP₃ production is manipulation of the phosphatase enzyme SHIP. Inhibition of the SHIP enzyme would stop PI(3,4,5)P₃ from hydrolyzing to PI(3,4)P₂ while upregulating SHIP would convert all PI(3,4,5)P₃ to PI(3,4)P₂. As both PI(3,4,5)P₃ and PI(3,4)P₂ are required for full activation of AKT, both inhibition and upregulation of SHIP may significantly affect the PI3K signaling pathway and could lead to blood cancer cell apoptosis depending on the molecular pathology of the neoplasm. There are many possible uses for SHIP inhibitors including cancer, bone marrow transplantation, stem cell mobilization and transplantation, blood cell production, and obesity.

**Cancer**

The PI3K-AKT-mTOR pathway is intimately involved in cell survival and therefore has become a focus for cancer treatment.¹⁸,¹⁹,²⁰ SHIP1, SHIP2 and PTEN are the enzymes predominantly responsible for controlling the AKT-mTOR signaling, which influences the survival of cancer cells and tumors. Since SHIP1 is primarily expressed in hematopoietic cells, SHIP1 inhibition may be used for therapeutic treatment regarding human blood cell cancers such as leukemia and multiple myeloma.⁸

Modulation of the other paralogs of SHIP may also be a useful strategy in the treatment of other types of cancer. SHIP2 overexpression has been implicated in the development of breast cancer, for example.⁷ SHIP2 causes an increase in EGF-induced signaling for various breast cancers which is atypical. High levels of EGF-induced signaling can lead to an increase of cellular proliferation for the cancer cells.²¹ Various breast cancer cells lines overexpress SHIP2 such as MDA-MB-231, SKBR-3, MDA-468, MDA-436, MCF-7 and ZR-75. SHIP2 inhibition
for the MDA-MB-231 breast cancer cell line showed a dramatic decrease in cell proliferation demonstrating SHIP2’s potential for therapeutic cancer treatment of breast cancer.

**Bone Marrow Transplantation**

Small molecule SHIP1 inhibitors could also be effective at minimizing complications for bone marrow transplant recipients and the management of myelodysplastic syndromes.\(^{22,23}\) SHIP1 inhibitors show potential for therapeutic possibilities in treating Graft vs Host disease (GvHD) caused by bone marrow transplants.\(^{24}\) Bone marrow transplants play a considerable role in organ transplants, as well as treatment of cancer and genetic disorders.\(^{23}\) However, these transplants are risky due to the occurrence of GvHD which can cause rejection of the transplant and ultimately death. Experiments have shown that transplants of mismatched bone marrow grafts are well tolerated in SHIP1 knockout mice, as these mice possess a modified immune system which tolerates the grafts. These mice do well with bone marrow transplants because they do not develop GvHD due to an increased expression of human T regulatory cell numbers. Even multiple kinds of mismatched bone marrow grafts are successful in SHIP1 knockout mice.\(^{25}\) SHIP1 inhibitors therefore have therapeutic potential in the area of organ transplants and engraftments.

**Stem Cell Mobilization and Transplantation**

The proliferation of hematopoietic STEM cells (HSCs) is increased in SHIP1 knockout mice.\(^{26}\) Significantly more HSCs are found in the plasma of SHIP1 knockout mice instead of typically being found in the bone marrow.\(^{8}\) This suggests the use of a SHIP1 inhibitor could be used to mobilize STEM cells from the bone marrow to the bloodstream. Once in the
bloodstream, the HSCs are much easier to harvest so they can then be used in HSC transplantation.

**Blood Cell Production**

SHIP1 inhibitors may be effective as a means to boost or protect blood cell production in cancer patients, helping prevent disease or infection as a result of neutropenia.\(^{22,23,26}\) SHIP1 inhibition in the PI3K signaling pathway leads to an increase of PI(3,4,5)P\(_3\) which causes an increase in cell division specific to blood cells. A small molecule SHIP1 inhibitor could be taken orally and used in cancer treatment where chemotherapy and radiation kill healthy hematopoietic cells. Typically protein based growth factors are now used for this purpose, but because of their peptidic nature these drugs must be given intravenously. *In vivo* studies with mice indicated an increase of blood cell production after the mice were administered a SHIP1 inhibitor.\(^8\) These *in vivo* mice studies demonstrate the therapeutic potential of SHIP1 inhibitors for blood cell production after chemotherapy or radiation poisoning.\(^{27,28}\)

**Obesity**

SHIP1 inhibition may be used to treat inflammatory pathways that can lead to obesity. By inhibiting SHIP1, expression of immunoregulatory cells is increased and can promote a lean-body state. Studies using mice that were fed a high fat diet showed a loss of body weight and fat content when treated with a SHIP1 inhibitor. Use of a SHIP1 inhibitor in adult aged mice diminished inflammation in the visceral adipose tissue (VAT) which can cause obesity. These mice lost body fat and also gained lean muscle mass, despite being on a high calorie diet. Thus the use of a SHIP1 inhibitor could be a successful treatment for diet-associated obesity.\(^{29}\)
Structure Activity Relationships

High throughput screening with small molecule libraries discovered four types of SHIP inhibitors\(^8,35\) have been discovered and they fall into the categories of aminosteroids (3.4), quinoline aminoalcohols (3.5), tryptamines (3.6) and thiophenes (3.7). An example of each can be seen in Figure 3.4. The aminosteroid 3AC (3.4) demonstrated selectivity for SHIP1 over other inositol phosphatases unlike 3.5 and 3.6, which are unselective SHIP1/SHIP2 inhibitors, and thiophenes (like 3.7) which are selective small molecule SHIP2 inhibitors. The parent compound, 3AC (3.4), was unfortunately found to have very poor water solubility.

Figure 3.4: SHIP Inhibitors

To address the poor water solubility, a number of analogs were synthesized.\(^30\) Androsterone derivative 3.9, (Figure 3.5), is more soluble in water and has a higher potency as a SHIP1 inhibitor. Compound 3.9 is not a selective SHIP1 inhibitor, however, as it shows equal inhibition of SHIP1 and SHIP2. Acylation or alkylation of the amine significantly reduced inhibitory activity. Moreover, the inclusion of polar functional groups on the D ring was shown to decrease activity vs. SHIP1, like in the case of compound 3.13.
From these structure activity studies, a general impression of the binding pocket for the aminosteroids can be proposed. This model indicates that polar functionality is tolerated on the A ring while only hydrophobic groups are allowed on ring D (Figure 3.6).\(^8\)

**Figure 3.6: Structure Activity Relationship of the Aminosteroid SHIP inhibitors**

The known crystal structure of SHIP2 led to our own molecular modeling of the SHIP1 active site.\(^{17}\) Using the SHIP2 x-ray structure as a guide, a model of the SHIP1 active site was constructed *in silico*. Figure 3.7 shows this proposed model of the active site of SHIP1 and a
model with aminosteroid 3AC docked in the active site. The model for SHIP1 is based on the crystal structure of the SHIP2 active site, but many of the residues near the active site have been changed as they are different than those found in SHIP2. The largest changes are seen in the PI4M loop region (Figure 3.7). In the model of 3.4 binding to SHIP1, the C17 sidechain on the D ring of the aminosteroid is in the PI4M loop region. In the crystal structure for SHIP2 there is a threonine in the PI4M loop region, however, in SHIP1 there is a more lipophilic tyrosine. This difference in amino acids may explain the selectivity of the inhibition for SHIP1 when we have a sidechain at C17.

Figure 3.7: Proposed model of active site for SHIP1

Figure 3.8 shows the % inhibition of aminosteroid inhibitors 3.4 (3AC), 3.9 (K185), and 3.14 (K118) in the malachite green assay for phosphatase activity. 3AC showed selective inhibition for SHIP1, where as K185 and K118 showed inhibition for both SHIP1 and SHIP2.
Since androsterone derivative 3.9 (K185) showed improved solubility and an increased activity as a SHIP1 inhibitor from 3.4 (3AC), aminosteroids without or with a smaller carbon chain on the D ring were synthesized (Figure 3.9). Based on the molecular modeling studies, it was thought that an aminosteroid with a smaller carbon chain on the D ring would maintain selectivity for SHIP1 while maintaining the improved water solubility. The aminosteroid 3.9 was not only synthesized on large scale but the β form of the aminosteroid (K118) was synthesized as well. In addition, two aminosteroid derivatives with alkenes on the D ring of the
steroid were synthesized. Finally, an aminosteroid with a methyl group on the D ring was prepared.

Figure 3.9: SHIP1 Inhibitors and Potential Analogues

![Compound Structures]

Androsterone derivatives

For the synthesis of analogue 3.9, a supply of steroid 3.19 was needed as the starting material. Reduction of androsterone 3.18 through a Yamamura-Clemmensen reduction was explored for this purpose as an alternative to the Wolff-Kishner (Figure 3.10), which was providing irreproducible yields.\(^{31}\)

Figure 3.10: Clemmensen Reduction of Trans-Androsterone

The Clemmensen reduction was thought to be a more attractive methodology because the reaction is faster and proceeds at a lower temperature than the Wolff-Kishner reduction.\(^{31}\) The reaction was optimized by varying the amounts of zinc metal and TMSCl used, as well as the reaction time and concentration. Eventually an 85% yield of the desired product was obtained.
However, when the reaction scale was increased to two grams, only 56% yield was obtained (Table 3.1). Also, $^1$H NMR spectra showed an unidentified minor impurity in the product that could not be removed. This impurity did not appear in the product when a Wolff-Kishner reduction was used.

*Table 3.1: Clemmensen Reduction of Trans-Androsterone*

<table>
<thead>
<tr>
<th>Entry</th>
<th>mmol Zn/TMSCl</th>
<th>Equivalents Zn/TMSCl</th>
<th>Concentration (M)</th>
<th>Time</th>
<th>Percent yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20/20</td>
<td>100/100</td>
<td>0.01</td>
<td>1 hour</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>20/20</td>
<td>100/100</td>
<td>0.01</td>
<td>24 hours</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>5/5</td>
<td>25/25</td>
<td>0.01</td>
<td>1 hour</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>20/20</td>
<td>100/100</td>
<td>0.04</td>
<td>1 hour</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>2/2</td>
<td>10/10</td>
<td>0.1</td>
<td>1 hour</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>4/4</td>
<td>20/20</td>
<td>0.1</td>
<td>1 hour</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>4/4</td>
<td>20/20</td>
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<td>54</td>
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<tr>
<td>8</td>
<td>8/8</td>
<td>40/40</td>
<td>0.04</td>
<td>1 hour</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>20/5</td>
<td>100/25</td>
<td>0.04</td>
<td>5 hours</td>
<td>85</td>
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<tr>
<td>10</td>
<td>20/5</td>
<td>100/25</td>
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<td>80</td>
</tr>
<tr>
<td>11</td>
<td>723/181</td>
<td>100/25</td>
<td>0.04</td>
<td>1 hour</td>
<td>56$^a$</td>
</tr>
</tbody>
</table>

$^a$ 2 gram scale (7.23 mmol)

To circumvent the Clemmensen and Wolff-Kishner reactions, hydrazone 3.20 was prepared (Table 3.2). This hydrazone may then be reduced with a number of reducing agents. Though the proposed synthetic route will introduce more steps to the original synthesis, producing steroid 3.19 under mild conditions in high yield on large scale was key to our efforts. Ketone 3.18 was converted to the hydrazone 3.20 by refluxing with hydrazine in ethanol. Crude hydrazone 3.20 was then exposed to different reduction conditions (Table 3.2), including
exposure to either potassium tert-butoxide or potassium bis(trimethylsilyl) amide. The reaction was also performed at room temperature in DMSO or refluxed in toluene. However, none of the reaction conditions gave a high yield of the product.

Table 3.2: Reduction of Hydrazone 3.20

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOC(CH₃)₃</td>
<td>Toluene</td>
<td>110°C</td>
<td>5 hours</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>KOC(CH₃)₃</td>
<td>DMSO</td>
<td>rt</td>
<td>16 hours</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>KOC(CH₃)₃</td>
<td>DMSO</td>
<td>rt</td>
<td>8 hours</td>
<td>9%</td>
</tr>
<tr>
<td>4</td>
<td>KOC(CH₃)₃</td>
<td>DMSO</td>
<td>rt</td>
<td>24 hours</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>KHMDSD</td>
<td>DMSO</td>
<td>rt</td>
<td>22 hours</td>
<td>6%</td>
</tr>
<tr>
<td>6</td>
<td>KOC(CH₃)₃</td>
<td>Toluene</td>
<td>110°C</td>
<td>24 hours</td>
<td>2%</td>
</tr>
</tbody>
</table>

Because of the low yield observed in the preparation of 3.19 through hydrazone removal of 3.20, the Wolff-Kishner reaction was re-explored. A modified Wolff-Kishner reaction was employed for the ketone reduction of the androsterone where diethylene glycol was used to conduct the reaction in a much higher temperature. In addition, a brine solution was used in the workup and methyl tert-butyl ether was used in the extraction in place of HCl and DCM, which facilitated the isolation of the reaction product. The extraction with brine and MTBE was very clean and contained no precipitates. When DCM and HCl were employed the extraction was messy and contained insoluble salts making the extraction difficult. The cleaner extraction conditions with MTBE and brine allowed for a higher yield of product. These conditions allowed for the large scale reduction of ketone 3.18 with a 69% yield. Later it was found that water generated by the formation of the hydrazide was lowering the boiling point of the reaction.
mixture in the Wolff-Kishner reaction, which was the cause for the more moderate yields on large scale. Simply distilling off approximately half the diethylene glycol removed the water and led to consistently high yields of the desired product.

A large scale synthesis of aminosteroid 3.9 (K185) was needed by our collaborators for biological testing. Using the modified Wolff-Kishner conditions, androsterone was reduced to alcohol 3.19. A Mitsunobu reaction was performed on alcohol 3.19 to convert it to phthalimide 3.21. Phthalimide was used for the installation of the nitrogen because of its easy reduction to an amine. The phthalimide group was then removed with hydrazine to give amine 3.22. HCl (g) was used to form the aminosteroid salt 3.9 (Figure 3.11).

*Figure 3.11: Synthesis of Aminosteroid K185*

The aminosteroid K118 (3.14) was synthesized on large scale, as this molecule also shows significant activity as a SHIP inhibitor and good water solubility properties. Alcohol 3.19 was subjected to a Mitsunobu reaction with iodomethane to provide iodide 3.23. Iodide 3.23 was displaced with sodium azide to give β azide 3.24. Initially, a lithium aluminum hydride reduction was used to reduce the azide 3.24 to amine 3.25. However, the aluminum salt
impurities from the hydride reduction proved difficult to remove. Instead, Staudinger conditions were used to reduce azide $3.24$ to amine $3.25$. Amine salt $3.14$ was then formed utilizing the reaction of hydrogen chloride (HCl) gas with amine $3.25$ (Figure 3.12).

*Figure 3.12: Synthesis of Aminosteroid K118*

![Chemical Diagram]

For the synthesis of aminosteroid K179 ($3.15$), *trans*-androsterone was used as the starting material. The ketone on the D ring first needed to be converted to an internal alkene. In order to accomplish this transformation, a Shapiro reaction was investigated. Androsterone $3.18$ was initially converted to tosylhydrazone $3.26$. A Shapiro reaction using methyl lithium was used to transform the tosylhydrazone to alkene $3.27$. Mitsunobu reaction with DPPA was then used to introduce the azide in steroid $3.28$. Azide $3.28$ was reduced to amine $3.29$ using lithium aluminum hydride, and aminosteroid salt $3.15$ (K179) was formed using a solution of HCl in ether and amine $3.29$ (Figure 3.13).
In addition, the synthesis of aminosteroid 3.16 was performed in a similar manner to the synthesis of alkene 3.15. A Wittig reaction was performed on trans-androsterone 3.18 which allowed for the installation of external alkene on the D ring of the steroid. Initially, sodium hydride was used for the Wittig reaction but no product was observed, perhaps because the sodium hydride had degraded over time. The use of n-butyl lithium instead of sodium hydride gave a product yield of 79% for this Wittig reaction. The alcohol 3.30 was then converted to phthalimide 3.31 through a Mitsunobu reaction. Aminosteroid salt 3.16 was made from alkene 3.32 using HCl in methanol/ethyl acetate (which was conveniently formed by the addition of acetyl chloride to methanol, followed by the addition of ethyl acetate) to provide the amine salt.
Figure 3.14: Synthesis of Alkene 3.16

The synthesis of amine hydrochloride salt 3.17 was then attempted starting with the reduction of alkene 3.30. The reduction of the alkene on the D ring of 3.30 was performed using a palladium catalyzed hydrogenation. This reaction allowed for the installation of a methyl group on the D ring of the steroid nucleus. The stereochemistry of the methyl group is assumed to be controlled by the nearby axial methyl group, which precludes axial attack and leads selectively to the product shown. The alcohol 3.33 was then subjected to a Mitsunobu reaction to provide phthalimide 3.34. Removal of the phthalimide group with hydrazine then gave amine 3.35. Aminosteroid salt 3.17 was formed utilizing HCl (g) and amine 3.35 (Figure 3.15).
After the proposed SHIP inhibitors were synthesized, they were tested for inhibition of both SHIP1 and SHIP2 utilizing the malachite green assay. The results are shown in Figure 3.16. K185 (3.9) and K118 (3.14) were also included for comparison since they show inhibition of SHIP1 and SHIP2. However, K185 demonstrated higher toxicity in mice studies than K118. An exploration of β-isomers may lead to a less toxic SHIP inhibitor. K179 (3.15) was active for inhibition of both SHIP1 and SHIP2. The biological activity of aminosteroids 3.16 and 3.17 is still being explored. These studies demonstrate that a longer alkyl C-17 chain on the D ring of the steroid maybe necessary for selective SHIP1 inhibition. Additionally a C16-C17 alkene is tolerated in the binding pocket, opening the way for the preparation of other analogs with substitution at C17 and unsaturation at C16-C17.
Conclusions

A number of aminosteroid derivatives were synthesized and tested for their ability to inhibit SHIP. Removal of the C-17 carbon chain on the D-ring of the steroid was explored. The steroids 3.9 (K185), 3.14 (K118), and 3.15 (K179) showed high potency but lost selectivity for SHIP1 inhibition. Molecular modeling predicted a need for a long carbon chain at C-17 for selective binding to SHIP1 over SHIP2. Aminosteroids with alkenes on the C-17 carbon were synthesized and showed activity as SHIP inhibitors. Installing alkenes allows for functionalization of the D ring of the steroid, with the goal being installation of the shortest
carbon chain that maintains SHIP1 selectivity but also provides a compound with good water solubility so it may be used in animal studies. Further studies of the aminosteroid with smaller carbon chains on the D-ring are now being conducted. These aminosteroids show activity for the treatment of blood cancer cells and may have uses in the treatment of obesity.

Experimental Procedures

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. DCM and THF were dried by passage through an alumina column. 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. Elemental analyses were performed on an elemental analyzer with a thermal conductivity detector and 2 meter GC column maintained at 50 °C.

Identity. Proton (¹H NMR) and carbon (¹³C 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 (CDCl₃), with residual chloroform (δ 7.26 ppm for ¹H NMR, δ 77.23 ppm for ¹³C NMR) or tetramethylsilane (δ 0.00 for ¹H NMR, δ 0.00 for ¹³C 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 CH₂Cl₂ followed by evaporation or as KBr pellets.

\[
\text{N_2H_4, KOH, (HOCH}_2\text{CH}_2\text{O) N_2H_4, KOH, (HOCH}_2\text{CH}_2\text{O)} N_2H_4, KOH, (HOCH}_2\text{CH}_2\text{O)} N_2H_4, KOH, (HOCH}_2\text{CH}_2\text{O)} N_2H_4, KOH, (HOCH}_2\text{CH}_2\text{O)} \]

244 °C, 24 h, 69%

\[
\text{N_2H_4, KOH, (HOCH}_2\text{CH}_2\text{O) N_2H_4, KOH, (HOCH}_2\text{CH}_2\text{O)} N_2H_4, KOH, (HOCH}_2\text{CH}_2\text{O)} N_2H_4, KOH, (HOCH}_2\text{CH}_2\text{O)} N_2H_4, KOH, (HOCH}_2\text{CH}_2\text{O)} \]

5α-Androstan-3β-ol (3.19)


In a flame-dried flask, potassium hydroxide (4.764 g, 84.9 mmol) was dissolved in diethylene glycol (41 mL) by heating. The solution was cooled to rt before adding \textit{trans}-androsterone (6 g, 20.7 mmol) and hydrazine hydrate (3 mL, 62.1 mmol). The solution was heated to reflux. After 24 h, the solution was cooled to rt and the reaction mixture was quenched by adding brine (600 mL). The mixture was extracted with MTBE (3 x 200 mL). The organic layers were collected, combined, dried over magnesium sulfate, filtered, and concd under reduced pressure. Purification was done with column chromatography (20% ethyl acetate/hexanes) to give 3.19 as a white solid (3.946 g, 69%). 3.19. mp = 149.3–150.7 °C (DCM) (Lit: 151–152 °C); TLC Rf = 0.33 (ethyl acetate:hexane, 1:4); IR (KBr) 3350, 2930, 2845, 1447, 1377, 1133 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.58 (hept, J = 4.9 Hz, 1H), 1.76–1.82 (m, 1H), 1.70–1.75 (m, 2H), 1.65–1.69 (m, 2H), 1.61–1.63 (m, 1H).
1H), 1.57–1.60 (m, 1H), 1.52–1.57 (m, 2H), 1.47–1.50 (m, 1H), 1.40–1.45 (m, 1H), 1.33–1.39 (m, 1H), 1.29–1.30 (m, 1H), 1.22–1.28 (m, 4H), 1.04–1.17 (m, 4H), 0.9–1.02 (m, 1H), 0.85–0.93 (m, 2H), 0.80 (s, 3H), 0.68 (s, 3H) 0.60–0.65 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 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.

3α–Phthalimido–5α–androstane (3.21)

In a 100 mL round bottom flask, 5α–androstane–3β–ol 3.19 (1.0 g, 3.62 mmol) was dissolved in dry THF (36 mL). Triphenylphosphine (1.138 g, 4.34 mmol) was added into the solution followed by diisopropyl azodicarboxylate (DIAD) (0.86 mL, 4.34 mmol). The resulting yellow solution was stirred continuously at rt for 10 min before adding phthalimide (639 mg, 4.34 mmol). The solution was stirred continuously at rt. After 24 h, the reaction mixture was concd and the residue was purified with column chromatography (hexanes) to give 3.21 as a white solid (0.927 g, 63%). 3.21. TLC $R_f$ = 0.39 (10% ethyl acetate/hexane); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.78–7.83 (m, 2H), 7.67–7.74 (m, 2H), 4.49–4.51 (m, 1H), 0.81–2.12 (m, 33H), 0.73 (s, 3H).

3α–amino–5α–androstane (3.22)
In a 250 mL round bottom flask 3α–Phthalimido–5α–androstanone 3.21 (1.413 g, 3.48 mmol) was suspended in 70 ml MeOH. Hydrazine (13 mL, 271 mmol) was added and the reaction refluxed for one hour. The solvent was evaporated and the residue was dissolved in DCM (20 mL). The solution was extracted with NaOH (20 mL, 1M) 5 times. The organic layers were collected, combined, dried with sodium sulfate, filtered and concentrated. Purification was done with column chromatography (90:9:1 DCM:MeOH:NH₄OH) to give 3.22 as a clear oil (724 mg, 75%). 3.22. IR (KBr) 2926, 2855, 1472, 1378, 1124, 753 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.18 (bs, 1H), 1.71–1.73 (m, 2H), 1.65–1.69 (m, 3H), 1.61–1.63 (m, 1H), 1.59–1.60 (m, 1H), 1.55–1.57 (m, 2H), 1.50–1.53 (m, 1H), 1.40–1.45 (m, 3H), 1.30–1.32 (m, 1H), 1.23–1.29 (m, 3H), 1.18–1.21 (m, 3H), 1.14–1.18 (m, 2H), 1.07–1.10 (m, 2H), 0.89–1.99 (m, 2H), 0.78 (s, 3H), 0.69 (s, 3H).

3α–Amino–5α–androstane hydrochloride (3.9)

The α–amine 3.22 (1.135 g, 4.12 mmol) was dissolved in diethyl ether (5 mL). Hydrogen chloride (g), resulting from sulfuric acid being added to sodium chloride, was bubbled into the diethyl ether which resulted in precipitate formation. The suspension was filtered. The precipitate was collected and dried under vacuum to afford amine salt 3.9 (1.139 g, 89%) as a white solid. 3.9. mp = 252.2 °C (diethyl ether) (dec.); IR (KBr) 3320, 2945, 1619, 1495, 1443, 1379 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ...
CDCl$_3$ δ 8.45 (bs, 3H), 3.60 (bs, 1H), 1.84 (bs, 2H), 1.62–1.69 (m, 8H), 1.51–1.58 (m, 4H), 1.37–1.44 (m, 1H), 1.23–1.29 (m, 2H), 1.09–1.20 (m, 4H), 0.92–1.07 (m, 3H), 0.79 (s, 3H), 0.69 (s, 3H); $^{13}$C NMR (75 MHz, CD$_3$OD) δ 54.2, 53.3, 48.0, 41.0, 40.6, 38.9, 38.8, 36.3, 36.0, 32.3, 31.6, 28.6, 25.6, 25.0, 20.9, 20.7, 17.8, 11.6. Anal calcd for C$_{19}$H$_{34}$ClN: C, 73.16; H, 10.99; N, 4.49. Found: C, 73.56; H, 11.19; N, 4.50.

(3R,5S,8S,9S,10S,13S,14S)–3–iodo–10,13–dimethylhexadecahydro–1H–cyclopenta[a]phenanthrene (3.23)

In a flame dried round bottom flask, $\beta$–alcohol 3.19 (1.00 g, 3.62 mmol) and triphenylphosphine (1.138 g, 4.34 mmol) were dissolved in dry benzene (20 mL). A solution of DIAD (0.86 mL, 4.34 mmol) in dry benzene (8 mL) was added dropwise over several minutes followed by a solution of iodomethane (0.27 mL, 4.34 mmol) in dry benzene (8 mL). The resulting milky yellow solution was stirred continuously at rt. After approximately 24 h, the reaction mixture was concd and the residue was purified through flash column chromatography eluting with hexane which afforded 3.23 (1.194 g, 85%) as a white solid. 3.23. $^1$H NMR (300 MHz, CDCl$_3$) δ 4.94 (quint, $J = 2.6$ Hz, 1H), 1.91 (pt, $J = 15.4$, 3.3 Hz, 1H), 1.70–1.76 (m, 1H), 1.66–1.69 (m, 2H), 1.59–1.64 (m, 3H), 1.56–1.58 (m, 1H), 1.52–1.54 (m, 1H), 1.49 (t, $J = 3.3$ Hz, 1H), 1.45 (t, $J = 2.2$ Hz, 1H), 1.39–1.43 (m, 1H), 1.30–1.36 (m, 1H), 1.28 (d, $J = 4.0$ Hz, 1H), 1.22–1.26 (m, 2H), 1.18–1.21 (m, 1H), 1.13–1.17 (m, 2H), 1.07–1.11 (m, 1H), 0.97–1.04 (m, 1H), 0.89–0.95 (m, 1H), 0.83–0.87 (m, 1H), 0.79 (s, 3H), 0.69 (s, 3H).

In a flame dried–round bottom flask, iodide 3.23 (1.483 g, 3.84 mmol) and sodium azide (2.496 g, 38.4 mmol) were suspended in dry DMF (20 mL). The suspension was heated to 80 °C. After 5 hours, the solution was cooled at rt before quenching the reaction by adding water (200 mL). The quenched reaction mixture was extracted with diethyl ether (3 x 200 mL). The organic layers were collected, combined, dried over magnesium sulfate, filtered, and concd under reduced pressure. Purification using flash column chromatography with hexane was done to afford azide 3.24 (0.859 g, 74%) as white solid. 3.24. TLC Rf = 0.38 (hexanes); 1H NMR (300 MHz, CDCl3) δ 3.25 (dt, J = 12.9, 4.5 Hz, 1H), 1.78–1.86 (m, 1H), 1.72–1.76 (m, 1H), 1.64–1.71 (m, 2H), 1.58–1.63 (m, 2H), 1.52–1.57 (m, 2H), 1.48–1.51 (m, 1H), 1.44–1.47 (m, 1H), 1.40–1.43 (m, 1H), 1.33–1.39 (m, 1H), 1.20–1.31 (m, 4H), 1.02–1.19 (m, 4H), 0.83–0.99 (m, 3H), 0.80 (s, 3H), 0.68 (s, 3H), 0.61–0.70 (m, 1H).

3β–Amino–5α–androstane (3.25)
In a flame dried flask, azide 3.24 (1.694 g, 5.62 mmol) and triphenylphosphine (2.938 g, 11.2 mmol) was dissolved in dry THF (26 mL). The solution was stirred continuously at rt. After approximately 2 hours, water (7 mL) was added and the solution was heated to reflux overnight. The solution was cooled at rt. The organic layer was collected, dried over sodium sulfate, and concd under reduced pressure. Purification was done with column chromatography (90:9:1 DCM: MeOH: NH₄OH) to give 3.25 as a clear oil (1.456 g, 94%). 3.25. ¹H NMR (300 MHz, CDCl₃) δ 2.59-2.74 (m, 1H), 1.99 (bs, 2H), 0.61-1.73 (m, 35H).

3β–Amino–5α–androstan hydrochloride (3.14)


The β–amine 3.25 (1.456 g, 5.29 mmol) was dissolved in diethyl ether (10 mL). Hydrogen chloride (g), resulting from sulfuric acid being added to sodium chloride, was bubbled into the diethyl ether solution which resulted in precipitate formation. The suspension was filtered. The precipitate was collected and dried under vacuum to afford amine salt 3.14 (1.589 g, 96%) as a white solid. 3.14. mp = 276.2 °C (diethyl ether) (dec.); IR (KBr) 3449, 2928, 2361, 1984, 1451, 1377 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.29 (bs, 3H), 3.13 (bs, 1H), 1.99 (app d, 1H), 1.55–1.580 (m, 10H), 1.38–1.48 (m, 2H), 1.23–1.35 (m, 4H), 1.06–1.19 (m, 4H), 0.89–1.02 (m, 3H), 0.84 (s, 3H), 0.68 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 54.7, 54.5, 51.5, 45.3, 41.0, 40.6, 39.0, 36.9, 35.9, 35.7, 33.3,
32.4, 28.5, 27.1, 25.7, 21.3, 20.7, 17.8, 12.5. Anal calcd for C_{19}H_{34}ClN: C, 73.16; H, 10.99; N, 4.49. Found: C, 72.96; H, 10.80; N, 4.31.

(3S,5S,8S,9S,10S,13S,14S)-10,13-Dimethyl-hexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (3.19).


In a round bottom flask, *trans*-androsterone (58 mg, 0.20 mmol) was dissolved in 3:1 methanol/dichloromethane (5 mL) and cooled to 0°C. Zinc (1.308 g, 20 mmol) was added to the solution followed by chlorotrimethylsilane (0.635 mL, 5 mmol) dropwise at 0°C. The reaction was stirred for 1 hour. Solid sodium bicarbonate (2.016 g, 24 mmol) was added to quench the reaction. The mixture was filtered and the filtrate was concentrated. The residue was diluted with saturated aqueous ammonium chloride and extracted with dichloromethane. The organic layer was dried using sodium sulfate, filtered and concentrated. Purification was done with flash column chromatography (25% ethyl acetate/hexanes) to give solid 3.19 (44 mg, 80%). 3.19. *mp* = 149-150°C (CDCl_3); TLC *R_f* = 0.33 (25% ethyl acetate/hexanes); IR (neat) 3349, 2930, 2844 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl_3) \(\delta\) 3.59 (m, 1H), 0.59-1.82 (m, 34H).


In a 50 mL round bottom flask, trans-androsterone (2.00 g, 6.89 mmol), *p*-toluene sulfonyl hydrazide (1.42 g, 7.62 mmol), and *p*-toluene sulfonic acid monohydrate (20 mg, 0.1 mmol) were dissolved in ethanol (10 mL). The reaction refluxed overnight. The next day additional *p*-toluene sulfonyl hydrazide (700 mg) and *p*-toluene sulfonic acid monohydrate (20 mg) were added. The reaction refluxed for another 5 hours. The solvent was evaporated under reduced pressure. Purification was done with flash column chromatography (1:1 ethyl acetate/hexanes) to give KTH-1-123 as white solid (4.006 g, 63%). mp = 161-186°C (1:1 ethyl acetate/hexanes); TLC *R*$_f$ = 0.08 (25% ethyl acetate/hexanes); IR (neat) 3400, 3200, 2926, 1597, 1333, 1165 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.82 (d, $J$ = 8.4 Hz, 2H), 7.29 (d, $J$ = 7.8 Hz, 2H), 3.50-3.58 (m, 1H), 2.42 (s, 3H), 0.77-2.22 (m, 28H).
In a flame dried 50 mL round bottom flask, 3.26 was dissolved in dry THF (11 mL) and cooled to 0°C. Methyl lithium (3 M in diethoxymethane, 2.4 mL, 7.19 mmol) was added dropwise over 5 minutes. A precipitate formed and redissolved as methyl lithium addition continued. The red solution was stirred at room temperature for 24 hours. Methyl lithium (3 M in diethoxymethane, 1.2 mL, 3.6 mmol) was added to the flask and the reaction stirred for 6 hours. The reaction was quenched with slow addition of water, then diethyl ether was added. The mixture was acidified with 2 M hydrochloric acid. The organic layer was separated, washed with water twice then brine once, dried with sodium sulfate and concentrated. Purification was done using column chromatography (15% ethyl acetate/hexanes) to give 3.27 as a white solid (248 mg, 41%). 3.27. mp = 114-118°C (15% ethyl acetate/hexanes); TLC Rf = 0.40 (25% ethyl acetate/hexanes); IR (neat) 3246, 3044, 2934, 2846, 1449, 1042 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.83 (d, J = 9.3 Hz, 1H), 5.66-5.70 (m, 1H), 3.53-3.64 (m, 1H), 0.75-2.13 (m, 28H).

In a 50 mL round bottom flask, alcohol 3.27 (0.24 g, 0.875 mmol) was dissolved in dry THF (9 mL). Triphenylphosphine (0.23 g, 0.875 mmol) was added into the solution followed by diisopropyl azodicarboxylate (DIAD) (0.17 mL, 0.875 mmol). The resulting yellow solution was stirred continuously at rt for 10 min before adding diphenylphosphoryl azide (0.23 mL, 1.05 mmol). The solution was stirred continuously at rt. After 24 h, the reaction mixture was concd and the residue was purified with column chromatography to give 3.28 as a white solid (0.193 g, 74%).

3.28. TLC Rf = 0.33 (Hexanes); 1H NMR (300 MHz, CDCl3) δ 5.81-5.83 (m, 1H), 5.69-5.70 (m, 1H), 3.87-3.89 (m, 1H), 0.75-1.89 (m, 28H).

(3R,5S,8R,9S,10S,13R,14S)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-3-amine (3.29)

In a flame dried round bottom flask, LAH (0.085 g, 2.13 mmol, 95%) was suspended in dry THF (2.5 mL). The suspension was cooled at 0 °C using ice/water cold bath before adding the solution of α–azide 3.28 (0.193 g, 0.645 mmol) in dry THF (2.5 mL). The solution was warmed to rt and then refluxed for 5 hours. The reaction was then cooled to rt before diluting the solution with THF (5 mL). The diluted reaction mixture was cooled at 0 °C and quenched using a Fieser method. The reaction mixture was stirred continuously until it turned into a milky white suspension. The suspension was then filtered through celite and washed with THF. The filtrate was dried over sodium sulfate and concd under reduced pressure. Purification was done with column chromatography (90:9:1 DCM: MeOH: NH₄OH) to afford α–amine 3.29 (0.113 g, 64%).
3.29. TLC Rf = 0.23 (90:9:1 DCM: MeOH: NH₄OH); H NMR (300 MHz, CDCl₃) δ 5.79-5.82 (m, 1H), 5.67-5.68 (m, 1H), 3.16 (s, 1H), 0.73-1.87 (m, 28H).

(3R,5S,8R,9S,10S,13R,14S)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-3-amine hydrochloride (3.15)

The α–amine 3.29 (0.100 g, 0.366 mmol) was dissolved in diethyl ether (5 mL). A solution of hydrogen chloride in diethyl ether (0.37 mL, 2 M) was added dropwise which resulted in precipitate formation. The suspension was filtered and the precipitate was collected, washed with diethyl ether, and dried under vacuum to afford amine salt 3.15 (0.106 g, 94%) as a white solid. H NMR (300 MHz, DMSO-d₆) δ 7.98 (bs, 3H), 5.84 (bs, 1H), 5.68 (bs, 1H), 3.34 (bs, 1H), 0.72-2.03 (m, 34H). Anal calcd for C₁₉H₃₂ClN: C, 73.63; H, 10.41; N, 4.52. Found: C, 73.31; H, 10.15; N, 4.73.

(3S,5S,8R,9S,10S,13S,14S)-10,13-dimethyl-17-methylene-hexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (3.30)

[Ph₃PMe]Br (6.144 g, 17.2 mmol) was suspended in dry THF (24 mL). The suspension was cooled to 0°C and n-butyl lithium was added slowly (6.88 mL, 17.2 mmol, 2.5 M in hexanes). A solution of 3.18 (1.0 g, 3.44 mmol) in dry THF (33 mL) was added dropwise, and the resulting mixture was stirred at reflux for 20 hours. After cooling to room temperature, some water was added dropwise, and then the mixture was diluted with water (200 mL) and diethyl ether (200 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 X 150 mL). The combined organic layers were dried MgSO₄, filtered, and concentrated. Purification was done with column chromatography (1:1 Et₂O: hexanes) to yield 3.30 (0.782 g, 79% as a white solid. 3.30. TLC Rₓ = 0.57 (2:1 Et₂O:hexanes); ¹H NMR (300 MHz, CDCl₃) δ 4.61 (s, 1H), 4.59 (s, 1H), 3.49-3.67 (m, 1H), 2.50-2.63 (m, 1H), 2.12-2.31 (m, 1H), 0.65-1.82 (m, 30H).

In a 100 mL round bottom flask, 5α–androstan–3β–ol 3.30 (0.782 g, 2.71 mmol) was dissolved in dry THF (27 mL). Triphenylphosphine (0.852 g, 3.25 mmol) was added into the solution followed by diisopropryl azodicarboxylate (DIAD) (0.64 mL, 3.25 mmol). The resulting yellow solution was stirred continuously at rt for 10 min before adding phthalimide (478 mg, 3.25 mmol). The solution was stirred continuously at rt. After 24 h, the reaction mixture was concd and the residue was purified with column chromatography (5% ethyl acetate/hexanes) to give 3.31 as a white solid (0.639 g, 56%). 3.31. TLC Rₓ = 0.53 (10% ethyl acetate/hexanes); ¹H NMR
(300 MHz, CDCl$_3$) $\delta$ 7.79-7.82 (m, 2H), 7.68-7.71 (m, 2H), 4.62 (s, 1H), 4.61 (s, 1H), 4.49-4.51 (m, 1H), 2.40-2.59 (m, 1H), 0.78-2.31 (m, 32H).

(3R,5S,8R,9S,10S,13S,14S)-10,13-dimethyl-17-methylene-hexadecahydro-1H-cyclopenta[a]phenanthren-3-amine (3.32)

In a 250 mL round bottom flask, steroid 3.31 (0.639 g, 1.53 mmol) was suspended in 77 ml MeOH. Hydrazine (5.8 mL, 119 mmol) was added and the reaction refluxed for one hour. The solvent was evaporated and the residue was dissolved in DCM (150 mL). The mixture was extracted with a NaOH solution (150 mL, 1M) 5 times. The organic layers were collected, combined, dried with sodium sulfate, filtered and concentrated. Purification was done with column chromatography (90:9:1 DCM:MeOH:NH$_4$OH) to give 3.32 as a clear oil (384 mg, 87%). 3.32. TLC $R_f$ = 0.09 (90:9:1 DCM:MeOH:NH$_4$OH); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.61 (s, 1H), 4.59 (s, 1H), 3.22 (bs, 1H), 2.41-2.71 (m, 3H), 2.20-2.26 (m, 1H), 0.73-1.80 (m, 34H).

(3R,5S,8R,9S,10S,13S,14S)-10,13-dimethyl-17-methylene-hexadecahydro-1H-cyclopenta[a]phenanthren-3-amine hydrochloride (3.16)

In a flame dried 50 mL round bottom flask, MeOH (0.11 mL, 2.61 mmol) was suspended in ethyl acetate (5 mL) and cooled to 0°C. Acetyl chloride (0.19 mL, 2.61 mmol) was added slowly
and the reaction stirred for 10 minutes. Amine 3.32 was dissolved in a small amount of ethyl acetate and added to the flask. A white solution formed. The mixture stirred for 30 minutes. The product was filtered and dried under vacuum to give 3.16 as a white solid (0.067 g, 40%). 3.16

$^1$H NMR (300 MHz, CD$_3$OD) $\delta$ 4.59 (s, 1H), 4.57 (s, 1H), 3.49 (bs, 1H), 2.42-2.59 (m, 1H), 2.10-2.29 (m, 1H), 0.73-2.01 (m, 52H).

Anal calcd for C$_{20}$H$_{34}$ClN: C, 74.16; H, 10.58; N, 4.32. Found: C, 74.17; H, 10.47; N, 4.42.

(3S,5S,8S,9S,10S,13R,14S,17S)-10,13,17-trimethyl-hexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (3.33)


In a flame dried 100 mL round bottom flask, steroid 3.30 (0.69 g, 2.4 mmol) was dissolved in isopropanol (24 mL). Palladium on carbon was added to the flask (0.077 g, 0.72 mmol) and the mixture was put under vacuum. Hydrogen gas was added after the vacuum was removed and the mixture stirred at 65°C for 17 hours. The mixture was filtered through silica (ether) and concentrated to give 3.33 as a white solid (0.629 g, 90%). 3.33. TLC $R_f = 0.53$ (25% ethyl acetate/hexanes) $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.53-3.62 (m, 1H), 0.72-1.89 (m, 37H), 0.52 (s, 3H).
2-((3R,5S,8S,9S,10S,13R,14S,17S)-10,13,17-trimethyl-hexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)isoindoline-1,3-dione (3.34)

In a flame dried 100 mL round bottom flask, alcohol 3.33 (0.629 g, 2.17 mmol) was dissolved in dry THF (22 mL). Triphenylphosphine (0.682 g, 2.6 mmol) was added into the solution followed by diisopropryl azodicarboxylate (DIAD) (0.52 mL, 2.6 mmol). The resulting yellow solution was stirred continuously at rt for 10 min before adding phthalimide (0.383 g, 2.6 mmol). The solution was stirred continuously at rt. After 24 h, the reaction mixture was concd and the residue was purified with column chromatography (hexanes) to give 3.34 as a white solid (0.445 g, 49%). 3.34 ¹H NMR (300 MHz, CDCl₃) δ 7.79-7.82 (m, 2H), 7.68-7.70 (m, 2H), 4.47-4.52 (m, 1H), 0.73-2.1 (m, 36H), 0.54 (s, 3H).

(3R,5S,8S,9S,10S,13R,14S,17S)-10,13,17-trimethyl-hexadecahydro-1H-cyclopenta[a]phenanthren-3-ylamine (3.35)

In a 50 mL round bottom flask, steroid 3.34 (0.445 g, 1.06 mmol) was suspended in 11 ml MeOH. Hydrazine (4 mL, 82.7 mmol) was added and the reaction refluxed for one hour. The solvent was evaporated and the residue was dissolved in DCM (20 mL). The mixture was extracted with a NaOH solution (20 mL, 1M) 5 times. The organic layers were collected,
combined, dried with sodium sulfate, filtered and concentrated. Purification was done with column chromatography (90:9:1 DCM:MeOH:NH₄OH) to give 3.35 as a clear oil (215 mg, 70%). 3.35 ¹H NMR (300 MHz, CDCl₃) δ 3.18 (bs, 1H), 0.71-1.75 (m, 38H), 0.53 (s, 3H).

(3R,5S,8S,9S,10S,13R,14S,17S)-10,13,17-trimethyl-hexadecahydro-1H-cyclopenta[a]phenanthren-3-amine hydrochloride (3.17)

Amine 3.35 (0.215 g, 0.743 mmol) was dissolved in diethyl ether (10 mL). Hydrogen chloride (g), resulting from sulfuric acid being added to calcium chloride, was bubbled into the diethyl ether solution which resulted in precipitate formation. The suspension was filtered. The precipitate was collected and dried under vacuum to afford amine salt 3.17 (0.184 g, 76%) as a white solid. 3.17 ¹H NMR (300 MHz, CDCl₃) δ 8.45 (bs, 3H), 3.60 (bs, 1H) 0.73-1.82 (m, 35H), 0.53 (s, 3H). Anal calcd for C₂₀H₃₆ClN: C, 73.69; H, 11.13; N, 4.30. Found: C, 73.73; H, 10.81; N, 4.26.
Appendix B. $^1$H AND $^{13}$C NMR SPECTRA SUPPLEMENT TO
CHAPTER 3

(3S,5S,8S,9S,10S,13S,14S)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol

3.19
2-[[3R,5S,7S,10S,13S,14S]-10,13-dimethylhexadecahydro-1H-cyclopenta[d]phenanthren-3-yl]isoxindole-1,3-dione
(3R,5S,8S,10S,13S,14S)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-amine

(3R,5S,8S,16S,13S,14S)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-aminium chloride
(3R,5S,8S,10S,13S,14S)-3-iodo-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene

3.23

(3S,5S,8S,10S,13S,14S)-3-azido-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene

3.24
(3S,5S,8S,9S,10S,13S,14S)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-amine

H3NCl 3.14
(3S,5S,8S,9S,10S,13S,14S)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-aminium chloride
$N^\prime\{3,5,5,8,9,9,13,13,14,14\}-3$-hydroxy-10,13-dimethyl-dodecahydro-1H-cyclopenta[a]phenanthren-17(2H,4H,14H)-ylidyne)-4-methylbenzenesulfonohydrazide

(3S,5S,8R,9S,10S,13R,14S)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol

$N^\prime\{3,5,5,8,9,9,13,13,14,14\}-3$-hydroxy-10,13-dimethyl-dodecahydro-1H-cyclopenta[a]phenanthren-17(2H,4H,14H)-ylidyne)-4-methylbenzenesulfonohydrazide

(3S,5S,8R,9S,10S,13R,14S)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol
(3R,5S,6R,9S,10S,13R,14S)-3-azido-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthrene

3.00 ppm: 3.22, 0.99 ppm: 0.92, 0.83 ppm: 0.71, 0.70 ppm: 0.70

(3R,5S,6R,9S,10S,13R,14S)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-3-amine

3.00 ppm: 3.22, 0.99 ppm: 0.92, 0.83 ppm: 0.71, 0.70 ppm: 0.70

(3R,5S,6R,9S,10S,13R,14S)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-3-amine

3.00 ppm: 3.22, 0.99 ppm: 0.92, 0.83 ppm: 0.71, 0.70 ppm: 0.70
(3R,5S,8R,9S,10S,13R,14S)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[α]phenanthren-3-aminium chloride

3.15

(3S,5S,8R,9S,10S,13S,14S)-10,13-dimethyl-17-methylenehexadecahydro-1H-cyclopenta[α]phenanthren-3-ol

3.30
(3R,5S,8R,9S,10S,13S,14S)-10,13-dimethyl-17-methylenehexadecahydro-1H-cyclopenta[α]phenanthren-3-yl)isoindoline-1,3-dione

(3R,5S,8R,9S,10S,13S,14S)-10,13-dimethyl-17-methylenehexadecahydro-1H-cyclopenta[α]phenanthren-3-amine
(3R,5S,8S,10S,13S,14S)-10,13-dimethyl-17-methylenehexadecahydro-1H-cyclopenta[a]phenanthren-3-aminium chloride

(3S,5S,8S,10S,13R,14S,17S)-10,13,17-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol
2-(3R,5R,8S,9S,10S,13R,14S,17S)-10,13,17-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ylisoindoline-1,3-dione
References


Kyle Timothy Howard
Department of Chemistry  kthoward@syr.edu
1-014 Center for Science and Technology  717-318-8885
Syracuse, NY 13244-4100

Education

M.Phil. Chemistry, Advisor: Prof John D. Chisholm, Syracuse University. May 2012.
B.S. Chemistry (major) and Mathematics (minor), York College of Pennsylvania. May 2010.

Honors

William D. Johnson Award for Outstanding Graduate Teaching (2015)

Publications


**Presentations**


**Research Experience**

**Research Areas:** Organic synthesis and medicinal chemistry, synthesis and structure activity relationship studies of SHIP inhibitors, formation of PMB and DPM ethers using trichloroacetimidates using thermal conditions.

**Lab Techniques:** Characterization of novel organic compounds utilizing Nuclear Magnetic Resonance (NMR) Spectroscopy ($^1$H, $^{13}$C), Infrared (IR) Spectroscopy, High Resolution Mass Spectroscopy (HRMS), Polarimetry, combustion analysis, Liquid Chromatography–Mass Spectrometry (LC–MS) and high pressure liquid chromatography, thin layer chromatography.

**Undergraduate Mentoring:** Syracuse University undergraduate students and summer Research Experience for Undergraduates (REU) participants.

**Teaching Experience**

**Graduate Teaching Assistant for Organic Chemistry I & II Recitations**
- Guest lectured for Organic Chemistry lecture when Professor was unavailable.
• Designed worksheets, practice exams, and their corresponding answer keys for students.
• Facilitated discussion relevant to organic chemistry topics discussed in the lecture.
• Assisted in proctoring and grading exams.
• Held weekly office hours for students to provide extra help.

Graduate Teaching Assistant for Organic Chemistry I & II Laboratory
• Conducts lectures relevant to the experiments to be performed.
• Develop students’ knowledge in chemistry including laboratory techniques essential in handling glassware, reagents, and equipment.

References

1. Professor John D. Chisholm, Department of Chemistry, Syracuse University. E-mail: jdchisho@syr.edu; Phone: (315) 443–6894.

2. Professor James Kallmerten, Department of Chemistry, Syracuse University. E-mail: jkallmer@syr.edu; (315) 443-2854.

3. Professor Kathleen Halligan, Department of Chemistry, York College of Pennsylvania. E-mail: khalliga@ycp.edu; (717) 815-6872.