Investigations Into Carbon Nanotube And Natural Product Synthesis.

Geoffrey Giampa

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INVESTIGATIONS INTO CARBON NANOTUBE AND NATURAL PRODUCT SYNTHESIS.

A Dissertation Presented

by

Geoffrey Giampa

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The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
Specializing in Organic Chemistry

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ABSTRACT

This dissertation describes research into the synthesis of carbon nanotubes using traditional organic synthetic methods, as well as work on the fragmentation of β-hydroxy-α-diazoesters with a γ-hetero group and applications of their reactivity towards natural product synthesis.

Carbon nanotubes are unique structures that can exhibit different electronic properties based on their chiral vector, and are a potential future source of semiconductors. Current methods of synthesis are unable to be adapted to commercial synthesis, providing the opportunity for the application of organic synthetic methods to generate them more uniformly and on a larger scale.

The generation of tethered aldehyde ynoates and their utilization in 1,3-dipolar cycloadditions has been well developed by the Brewer group. Traditionally they have been generated from γ-siloxy-β-hydroxy-α-diazoesters, herein we explore utilizing an amino group as the fragmentation initializer. Additionally, application of the tethered aldehyde ynoate towards the synthesis of the natural products Demissidine and Aspidospermine are discussed.
ACKNOWLEDGEMENTS

I would like to thank Professor Thomas Hughes for allowing me to join his group when I first arrived at UVM, and providing me with the opportunity to work independently. Additionally, I would like to thank Dr. Andrew Korich who was a senior group member in the Hughes group who helped to introduce me to working in a lab and providing valuable information on lab techniques and procedures.

I am indebted to Professor Matthias Brewer who accepted me into his research group after I was no longer able to continue research with Professor Hughes. He has provided me guidance into expanding my chemistry knowledge, and the opportunity to work on many interesting and challenging projects.

I would not have made it this far without the insight and support of my fellow Brewer group members, especially Dr. Nikolay Tsvetkov and Dr. Jodi Ogilve. Nikolay provided me with many valuable insights into chemistry and helped to keep my mind sharp with many challenging games. Jodi was best “gal” at my wedding and has been an important part in my life since coming to UVM, taking me under her wing and helping me to acclimatize to VT and UVM. Even more importantly was the emotional support when dealing with chemistry or life issues. I am eternally grateful for all that you and Graham have done for Katie and me.
I would not be here without the love and support of my parents, who may not always understand what I’m doing or talking about, but have always, had the patience to help me achieve my goals. Their sacrifice to get me an education that has allowed me to reach this achievement is invaluable.

A special thanks to my grandfather, Dr. William Stafford, who inspired me to reach for my dreams, and always encouraged me to never stop learning. You will always be in my heart.

Lastly, and most importantly, I want to thank my loving and resourceful wife, Katherine Giampa. Without her strength and support I doubt that I would be completing this work and have no idea where I would be. You are my North Star, my anchor, my everything.
FORWARD

This dissertation is broken into two distinct sections. The first chapter details my research with Dr. Hughes on carbon nantotubes and covers my first years at the University of Vermont. Chapters 2-4 detail my time research with Dr. Brewer on the fragmentation of $\gamma$-siloxy-$\beta$-hydroxy-$\alpha$-diazooesters to tethered aldehyde ynoates and the ability to perform subsequent 1,3-dipolar cycloadditions on them. The change in research topics and principal investigators came about as a result of Dr. Hughes leaving the University of Vermont, and Dr. Brewer providing me the opportunity to complete my studies here.
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<tr>
<td>Ac</td>
<td>Acyl</td>
</tr>
<tr>
<td>Boc</td>
<td>t-Butyl carbonate</td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>Methylene Chloride</td>
</tr>
<tr>
<td>CNT</td>
<td>Carbon nanotube</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicycloundec-7-ene</td>
</tr>
<tr>
<td>DMAD</td>
<td>Dimethyl acetylenedicarboxylate</td>
</tr>
<tr>
<td>DMAP</td>
<td>Dimethylaminopyridine</td>
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<td>DMDO</td>
<td>Dimethyldioxirane</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>GC MS</td>
<td>Gas chromatography mass spectrometry</td>
</tr>
<tr>
<td>GCS</td>
<td>Graphitic carbon sheets</td>
</tr>
<tr>
<td>HBC</td>
<td>Hexabenzo-[bc,ef,hi,kl,no,qr]-coronene</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>LAH</td>
<td>Lithium aluminum hydride</td>
</tr>
<tr>
<td>mCPBA</td>
<td>m-Chloroperoxycarboxylic acid</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>nBu</td>
<td>n-Butyl</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>OSM</td>
<td>Organic synthetic method</td>
</tr>
<tr>
<td>PAH</td>
<td>Polycyclic aromatic hydrocarbons</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>sBu</td>
<td>s-Butyl</td>
</tr>
<tr>
<td>SWNT</td>
<td>Single walled nanotube</td>
</tr>
<tr>
<td>TBAB</td>
<td>Tetrabutylammonium bromide</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>t-Butyldimethylsilyl</td>
</tr>
<tr>
<td>tBu</td>
<td>t-Butyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Trifluoromethanesulfonate</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TM</td>
<td>Transition metal</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-Tetramethyl-1,2-diaminoethane</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TsOH</td>
<td>p-Toluenesulfonic acid</td>
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CHAPTER 1: CARBON NANOTUBE BELTS

1.1. Carbon Nanotubes

1.1.1. Discovery of Carbon Nanotubes

Since the discovery of Buckminsterfullerene (C$_{60}$), in 1985 [1] by H.W. Kroto, J.R. Heath, S.C. O’Brien, R.F. Curl, and R.E. Smalley (of which Kroto, Curl, and Smalley were awarded the 1996 Nobel Prize in Chemistry), there has been an avid interest in generating and elucidating the structure and properties of other fullerenes and graphitic carbon sheets (GCSs). One category of GCSs to attract interest is carbon nanotubes (CNTs), which are graphite sheets that have been rolled into a tube shape. CNTs can come in a variety of different shapes and sizes, and can exist as single walled nanotubes (SWNTs) or multi walled nanotubes, which like Russian nesting dolls are made up of one CNT inside of another CNT.

These CNTs can come in a variety of lengths and diameters and can have three different chiral vectors. The chiral vectors describe how the graphite sheet is wrapped to make its tubular shape, and is determined by the lattice angle of the wrapping. An angle of 0° being an armchair, an angle of 30° being a zig-zag, and any angle in between being a chiral CNT (Figure 1.1). This can also be expressed by mapping the number of unit vectors required to connect two atoms in the planar hexagonal lattice to form a seamless tube. Any tube that is named (m, 0) has a zig-zag pattern, tubes named (m, m) are armchair, and any tube named (m, n) is chiral. The example in Figure 1.1, if rolled at θ = 0° (in blue) would be (10, 0) zig-zag CNT, while if it was rolled at θ = 30° (in green) would be (6, 6) armchair CNT.
1.1.2. Properties of Carbon Nanotubes

Carbon SWNTs have attracted attention for their mechanical and electronic properties for application in nanotechnology. Predictions suggest that SWCNTs should have Young’s modulus values, a measure of the stiffness of an elastic material, to be similar to in-plane graphite, about 1000 GPa, which studies have corroborated [3]. They have several other desirable physical properties due to their sp²-hybridized bonds, including a tensile strength almost ten times greater than Kevlar, a density lighter than aluminum, a thermal conductivity greater than diamond, and a thermal stability exceeding 1000 °C [4]. Furthermore, SWCNTs have a low chemical reactivity, leading to their stability in a variety of organic solvents. Additionally, the electronic properties
of SWCNTs have been predicted and experimentally verified to range from metallic conductor to semiconductor, based on the chiral vector of the nanotube, with armchair tubes behaving as metallic, and zigzag and chiral behaving as semiconductors [5].

The theoretical basis for the armchair CNTs behaving as metallic is in part due to the overlap of bonding and antibonding orbitals creating only a small gap at the Fermi level allowing electrons to flow freely, which is caused by the curvature in the graphene sheet. In comparison zig-zag and chiral will, based on their curvature, have more moderate gaps and more restricted electron flow [6]. The conductance and stability of these molecules (mechanical, thermal, and chemical) allows SWCNTs to be able to carry large current densities, about two to three times greater than pure copper or aluminum, without being destroyed, and makes them ideal for the creation of molecular field transistors. These field transistors could see use as replacements for silicon based circuits in electronic devices [7].

1.2. Methods of Preparation

There are currently three main methods for synthesizing SWCNTs: laser vaporization, arc evaporation, and high pressure carbon monoxide (HiPco) decomposition. SWCNTs are produced as the primary product of these reactions, though they also may contain amorphous carbon, metal catalysts, or other graphene and fullerene side products [8].

While these methods can usually be controlled to create SWCNTs or multi-walled CNTs, it is harder to control length, diameter, and chiral vector. Some processes will produce mostly uniform diameter SWCNTs, but even within this
uniformity, the tubes produced have a limited scope of diameters that will form, precluding some diameters from being an option to produce. Laser vaporization and arc evaporation also produce the SWCNTs as ropelike bundles [9]. All of these methods are able to produce milligram to gram quantities of SWCNTs in a matter of hours, but in order to use SWCNTs in commercial applications, they will need to be produced on a kilogram to ton scale [10].

One complication of their low solubility is the difficulty of purifying samples of mixed chiral vector, length, diameter, and single or multiwalled. This leads to two even larger drawbacks to the traditional methods listed above: difficulty in characterizing the CNTs and their application in electronics, which will require all the material to have uniform properties to perform at peak efficiency. The characterization problem occurs because the ropelike bundles of different tubes become entangled and lead to a mixing of energy states that can be difficult to distinguish. Ropelike bundles can be separated by ultrasonication, but this technique can damage the sidewalls of the CNTs [4]. One area that has shown some success is the use of DNA sequences combined with ion exchange chromatography to purify SWCNTs [11]. Yet, this process suffers from significant problems. The largest hurdle is that only specific DNA sequences interact with specific SWCNTs, and the process has thus far only been done on microgram quantities. Additionally, the purity of samples acquired after purification are 60-90%.
1.3. Chemical Synthetic Approach

1.3.1. Benefits of Organic Synthetic Methods

Traditional organic synthetic methods (OSM) are widely used due to the higher level of control achievable when building molecular structures. In the synthesis of SWCNTs this control would not only allow for the synthesis of tubes with known size and chiral vector, but more importantly enable the formation of only SWCNTs of one set size and chiral vector. If a uniform batch of CNTs could be synthesized, it would greatly increase the ability to determine the exact structure of the CNTs, as well as characterize their distinct chemical and physical properties. These properties could most readily be deduced by forming short narrow tubes.

Another strength of OSMs are the ease with which many diverse structure can be generated from a common feedstock or from derivatives. For example, while initial investigations would benefit from short narrow tubes for ease of deducing structure and properties, later applications will likely require longer length or wider diameter CNTs, depending on the desired application requirements. Additionally, this ease of diversification from a common starting material lends itself to readily incorporating substituents on the CNT. This would allow for easily producing CNTs with different solubilities, conductivity/electronic properties, and other chemical and physical properties.
1.3.2. Precedence

1.3.2.1. Carbon Nanotube Segments and Growth

No group has thus far been able to synthesize a CNT by OSMs, but several groups have synthesized potential precursors or fragments of CNTs. Some groups, such as Gleiter et al., have successfully synthesized carbon nanotube belts that are one aromatic ring in height (Figure 1.2) [12]. Recently, other groups, such as Scott et al., have focused on synthesizing geodesic domes, or the caps of CNTs, which may be used as a template to grow CNTs of a matching diameter and chiral vector (Figure 1.3) [13]. Similarly, Itami et al., have worked on growing tubes from nanorings using ethanol as a feedstock (Figure 1.4) [14].

![Figure 1.2: Carbon Nanotube Belt](image1.png)

![Figure 1.3: Carbon Nanotube Cap Growth](image2.png)
1.3.2.2. Synthesis of Hexabenzocoronene

Klaus Müllen et al. focused on improving on a method of developing polyphenylene dendrimers, which could then readily be transformed into polycyclic arenes via the Scholl oxidative cyclodehydrogenation [15]. One of the remarkable features of these dendrimers is that they are themselves readily prepared by a Diels-Alder cycloaddition between diarylethynes (e.g. 2, Scheme 1.1) and tetraarylcyclopentadienones (e.g. 1, Scheme 1.1), both of which are readily accessible synthetically, followed by cheletropic loss of CO. An example of this work (Figure 1.5) is the synthesis of hexabeno-[bc,ef,hi,kl,no,qr]-coronene (HBC). Müllen has used this process to make several large polycyclic aromatic hydrocarbons (PAHs) in good yields, including a compound with 222 carbons (Scheme 1.2) [16].

1.3.2.2.1. Scholl Reaction

The Scholl reaction, first reported by Roland Scholl in 1910, is a type of dehydrogenative aromatic coupling reaction that results in the formation of a condensed ring system. Later Balaban and Nenitzecu reformulated it as the “the elimination of two aryl-bound hydrogens accompanied by the formation of an aryl-aryl bond under the influence of Friedel-Crafts catalysts” [17].
There is a debate as to whether the Scholl reaction should be considered more generally as an oxidative aromatic coupling reaction, but generally it has been proposed...
that the Scholl reaction is a distinct category and occurs when “non-oxidizing Bronsted or Lewis acids are used to perform the reaction (with the use of an additional oxidant or without).”[18]. Additionally, Scholl reactions tend to occur intramolecularly, while oxidative aromatic coupling reactions tend to be intermolecular in nature. Mechanistically, the difference between these two types of reactions is believed to be that Scholl reactions involve the formation of a σ complex between aromatic compound and the Lewis acid, which leads to the formation of an arenium cation that undergoes electrophilic attack and finally undergoes dehydrogenation. The oxidative aromatic coupling reactions are believed to instead go through a radical cation mechanism, which necessitates electron rich aromatic compounds.

Classically, the Scholl reaction used aluminium trichloride in the industrial synthesis of anthraquinone-derived dyes, often neat and at high temperatures. Additional salt melts (such as AlCl₃/NaCl) or high boiling solvents (such as dichlorobenzene) were also used. In 1961, Kovacic and Kyriakis introduced new conditions, which were later modified by Müllen that resulted in reactions that could be run at 25 °C.

1.3.2.2.2. High Temperature Diels-Alder Dendrimer Synthesis

Müllen et al.’s synthesis of polyphenylene dendrimers was chosen due to the well-known reactivity of tetraphenylcyclopentadienones (e.g. 1, Scheme 1.3) with phenylacetylenes (e.g. 2, Scheme 1.3) to yield hexa- and penta- phenylbenzenes [19]. These Diels-Alder starting materials are also desirable, as mentioned, for their easy synthetic availability. Tetraphenylcyclopentadienones are readily synthesized from the
Knoevenagel condensation of benzils and diarylacetones, and the phenylacetylenes are easily prepared via Sonogashira couplings (Scheme 1.3)

**Scheme 1.3**

1.4. Investigations Toward the Synthesis of Carbon Nanotube Belts

1.4.1. Retrosynthetic Approach

1.4.1.1. Starting Material Considerations

As has been described, SWCNTs can be classified as sheets of graphene that have been rolled into a cylindrical form. The most efficient route to these tubes would be to couple two edges of the same graphene sheet together to form the tube. Unfortunately, unless the SWCNT were to possess a very large diameter, the strain involved in folding the two sides together, in order to get them close enough to react, would be too great to overcome.

An alternative, and more viable, approach should focus on an incremental buildup of strain in the molecule. One approach towards this would incorporate the
ideas of Müllen et al., and apply them to an unstrained polycyclic ring system. Since it is known that phenyl-acetylenes can undergo Diels-Alder cycloadditions with substituted cyclopentadienones, in theory a macrocyclic phenylacetylene ring (II) of sufficient diameter could be synthesized and it could undergo a Diels-Alder cycloaddition with a substituted cyclopentadienone to yield a toric form of Müllen et al.’s PAH, which should then readily undergo Scholl oxidation to produce a carbon nanotube belt (Scheme 1.4).

Scheme 1.4

Cyclenes are rings of atoms containing one or more alkyne units, and typically are trimers consisting of three repeating units (e.g. 11 in Scheme 1.4), but have rarely been made as dimers and tetramers [20]. The trimer in Scheme 1.4 would most likely be too strained for SWCNT synthesis, thus necessitating a larger ring size. Increasing the cyclene ring diameter will require using benzene rings as the link extenders, in order to allow for Scholl oxidative cyclodehydrogenation to yield a nanotube belt.
Additionally, the cyclopentadienone to fit our nanotube belt design would need to be disubstituted instead of tetrasubstituted as in the case of Müllen et al.

1.4.1.2. Project Goal

The goal of my project was to apply a Diels-Alder cycloaddition to a cyclene trimer with a cyclopentadienone and then use Scholl oxidative cyclodehydrogenation to make a nanotube belt (similar to Scheme 1.4).

Scheme 1.5

1.4.1.3. Retrosynthetic Route

With these factors in mind we have proposed that the [9, 0] zigzag nanotube belt 15 could be synthesized from Scholl oxidative cyclodehydrogenation of the nanotube belt precursor 16. The nanotube belt could be prepared from the Diels-Alder cycloaddition between biaryl acetylene trimer 17 and 3,4-diphenylcyclo-pentadienone 18.
18, followed by rearomatization due to loss of carbon monoxide (Scheme 1.5). This method also provides a route by which other [3n, 0] SWCNTs can be synthesized. For example, by changing the cyclene from a trimer to a tetramer, a [12, 0] SWCNT would be synthesized, which may be beneficial as the increased ring size of the tetramer should be relatively strain free, in comparison. Additionally, modification of the cyclene can allow for the creation of CNTs that have chiral vectors that are either armchair, in the case of trimer 19 (Scheme 1.6), or chiral, in the case of 22 (Scheme 1.7).

Scheme 1.6
1.4.2. Synthesis of Proposed Starting Materials

1.4.2.1. Biaryl Cyclene Trimer

The biaryl cyclene trimer 17 was synthesized by Dr. Andrew Korich [21], using a Suzuki and Sonogashira protocol (Scheme 1.8).
Scheme 1.8

1) NaNO₂, HCl, MeCN, H₂O
2) Et₃NH, K₂CO₃, H₂O, 97%

H₂N

24

Et₂N₂

25

B₂O₃

26

PdCl₂(dppe), KOAc, DMSO, 80 °C, 64%

N₂Et₂

28

Cl₂Pd(dppe)₂, K₂PO₃, DME, 80 °C, 95%

N₂Et₂

29

Br

PdCl₂(dppe)₂, Cul, Et₃N/THF, 99%

Br

27

TIPS

29

Br

TIPS

29

N₂Et₂

30

MeI, 120 °C, 98%

N₂Et₂

31

N₂Et₂

32

Cl₂Pd(dppe)₂, Cul, Et₃N, THF, 75%

N₂Et₂

33

MeI, 120 °C, 100%

N₂Et₂

34

Pd(dbk), PPh₃, Cul, Et₃N, 45%

1) MeI, 120 °C, 94%
2) TBAF, THF, 83%
1.4.2.2. Cyclopentadienone

Known compound 38 is a precursor of the cyclopentadienone 18, and is readily prepared by a known Knoevenagel condensation of acetone and benzil (Scheme 1.9) [22]. Compound 38 does not undergo loss of the second hydroxyl group due to the anti-aromatic nature of 18, which is convenient as cyclopentadienones readily dimerize.

Scheme 1.9

1.4.3. Synthesis of [9, 0] Nanotube Fragment

We propose that heating cyclopentadienone precursor 38 with cyclene 17, in the presence of a strong acid or base would result in the formation of cyclopentadienone 18. Subsequent Diels-Alder cycloaddition and cheletropic loss of carbon monoxide would form nanotube precursor 16, which would then be able to undergo Scholl oxidative cyclodehydrogenation to yield the [9,0] carbon nanotube belt 15 (Scheme 1.10).
1.4.4. Synthesis of 1,2,4,5-tetraphenylbenzene

Since the cyclene trimer was not trivial to make, we decided that it would be more appropriate to use a model system to optimize the Diels-Alder reaction. Diphenylacetylene 39 (Scheme 1.12) was chosen as the alkyne substrate because it is commercially available and should be similar in electronics as the individual acetylene groups of 17. Additionally, the reaction of 39 and 38 is a known reaction. Dilthey and Hurtig had previously synthesized 1,2,4,5-tetraphenylbenzene 40 by heating 39 and 38.
neat for 1 hour at 275 °C, which after extraction resulted in colorless crystals of 40 (melting point 262 – 263 °C) with a yield of 6.5% [23].

We hoped to not only increase the yield of the reaction, but also reduce the reaction temperature by utilizing a catalyst. A temperature of less than 200 °C would prevent phenyl shifts from occurring [24], a factor that may be responsible for the lower yields obtained by Dilthey and Hurtig. Furthermore, while we could run the reactions neat, as Hurtig and Dilthey did, we preferred to run the reaction in a solvent due to concerns that the cyclene trimer may undergo one or two Diels-Alder additions and then become so large that it segregates out of the reaction mixture thus inhibiting the process of generating 16.

1.4.4.1. Overall Results

Despite extensive investigations we never obtained a significantly greater yield than Hurtig and Dilthey. The best yield, 21%, was obtained after running the reaction for one week at 181 °C with InCl$_3$ as the catalyst. The next best result was obtained by using Cu$^{II}$(OAc)$_2$$\cdot$H$_2$O as the catalyst for 168 hours at 220-230 °C, which gave a yield of 19%. Below I will detail the adjustment in reaction variables that were attempted, difficulties encountered in the synthesis, and ways that the reaction might be improved in the future.

1.4.4.1. Dimerization Impediment

Regardless of modifications to the procedure, one of the biggest hurdles to overcome for this reaction is the dimerization of the in situ generated 18, resulting in 41 (Scheme 1.11). The dimer 41 could also potentially undergo other side reactions, such
forming a trimer with an additional equivalent of 18 or undergo a phenyl shift and rearomatization process. The production of 41 was confirmed by running a control experiment with just 38, and this material was found to decompose over time. These unwanted side reactions resulted in two major problems, the preferential formation of the byproducts over the desired product and the difficulty of separating the desired product from those byproducts. The most debilitating of these problems was the consumption of 38, which is no longer present for the reaction with 39.

Scheme 1.11

One potential solution would have been to use an excess of the dienophile (39). In the model system this is not a problem, because both of the starting materials are readily accessible. However, in the actual system (Scheme 1.10) the cyclene trimer 17, requires several steps to synthesize, and therefore would not be efficient to be used as the excess reagent. Therefore I wanted to make sure that an excess of 38 in the reaction would not significantly diminish the reaction yield. With this in mind, experiments were run using variable quantities of dienophile and diene. The results showed no significant change in yield through these variations.
Another issue caused by the formation of 41, and other side products, became apparent during purification. Dimer 41 proved to be difficult to separate from the desired product 40. Chromatography proved to be inefficient in the purification of 40, though optimization of the eluent system gave a higher ratio of 40 to 41. Ultimately, recrystallization allowed for the isolation of pure 40.

Through trial and error I determined that the best way to purify 40 was to remove the solvent in vacuo and add hexanes to the crude mixture, solvent removal was not always possible if the solvent was high boiling, which caused the majority of the unreacted 38 and 41 and other side products to crash out of solution. These solids were shown to contain only trace amounts of 40. The filtrate was then concentrated, dissolved in a minimum of methylene chloride, and acetone was added. As the dichloromethane slowly evaporated, white crystals of 40 slowly precipitated.

Repeated chromatography and recrystallization resulted in enough material to verify the formation of 40 by $^1$H nuclear magnetic resonance (NMR), $^{13}$C NMR, and gas chromatography mass spectrometry (GC MS). However, due to the low yields of these reactions it was required to combine several to be able to have enough 40 to precipitate from the hexanes. As such, this was not an appropriate way to determine yield of individual reactions.

1.4.4.3. Calculation of Yield

Yield of individual reactions was ultimately determined by a GC MS calibration curve. The rigorously purified 40 was injected with known quantities of $o$-terphenyl to generate the graph in Figure 1.5. It was necessary to add in the $o$-terphenyl, because,
while the GC MS could provide individual intensities of the compounds detected, they alone were not reliable, but the ratio between the samples’ intensities was unchanging. This was also used before pure 40 was obtained, to gauge the consumption of diphenylacetylene and assumed formation of product.

![GC MS Calibration Curve](image)

**Figure 1.5: Tetraphenylbenzene Calibration Curve**

**1.4.4.4. Optimization Attempts**

The general procedure was as follows: combine 38 and 39 with solvent and a catalyst and heat for a period time (Scheme 1.6). The results of varying these conditions are listed below. Solvent effects were not investigated, and changes to the solvent were only made in order to achieve higher reaction temperatures.

**Scheme 1.12**
Reaction temperature had the largest effect on the yield of the reaction. Temperatures from 110 °C to 260 °C were tested. Reactions below 220 °C were run in an oil bath, while higher temperature reactions required the use of a sand bath. In general, higher temperature reactions produced a better yield than lower temperature reactions. One major difference between the procedure used in high and low temperature reactions was that high temperature reactions were run in sealed tubes, rather than round bottom flasks with condensers.

The high temperature reactions had an issue of consistency, due in large part to the sand baths being used. Temperature within the sand bath was variable, and if the hood sash height was changed, a significant change in temperature could occur. Thus in addition to wanting to run the reaction below 200 °C to prevent phenyl shifts, it is also preferable to run these reactions at such temperatures in order to maintain a consistent temperature. In order to counteract some of these problems, reactions were run in batches within the same sand bath so that they all would be exposed to the same temperature environment.

Without any catalyst it was determined that heating at reflux in dichlorobenzene (180 °C) could produce trace amounts of desired 40. Unless the reaction was run at very high temperatures, unreacted 38 was always recoverable. By running the reaction for almost an hour at 260 °C the uncatalyzed reaction was able to be improved to 14.5 % yield, a slight improvement over Hurtig and Dilthey’s reported yields.

My initial investigations were focused on promoting the formation of the cyclopentadienone from 38, with the belief that this would allow the reaction to be run
at lower temperatures. The first route that we investigated was a modified method developed by Rose and Statham [25], in which 38, 39, and K$_2$PO$_4$ were placed in a flask with a stir bar and heated in an oil bath to 120 °C. Unfortunately, these conditions did not yield any of the desired 40 or the undesired 41. In cases where the reaction was run without solvent, some of the diphenylacetylene sublimated.

Under the impression that base might not be the best route to promote the formation of the cyclopentadienone, I considered the acid catalyzed variant. To start, I adopted conditions that were similar to those reported by Sharpless et al. [26], in which 38 and dimethyl acetylenedicarboxylate (DMAD) were allowed to react in the presence of a catalytic amount of p-toluenesulfonic acid (TsOH) and in refluxing toluene under N$_2$ for 48 hours, at which point an additional catalytic amount of TsOH was added and the reaction was continued for an additional 24 hours.

Compared to the base promoted reactions, trace amounts of desired 40 were detected by GC MS, even when run at 110 °C. In addition to 40, 41, and unreacted starting material, there were also signs of decomposed 38. Ultimately the best conditions using TsOH as the catalyst provided only a 15% yield (entry 8 on Table 1.1).

In addition to using this catalyst at higher temperatures and longer time, the effects of which are detailed below, I varied the quantity of catalyst used. The amount of catalyst was modified from a 5% to greater than one equivalent. As can be seen in Table 1.1, the addition of more or less TsOH had little to no effect on the results.
Table 1.1: Acid Catalyzed Diels-Alder Variable Modifications

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio 39 : 38</th>
<th>Temp °C</th>
<th>Time</th>
<th>Equivalents of Catalyst</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00 : 4.26</td>
<td>181</td>
<td>72 h</td>
<td>1.73</td>
<td>1.64%</td>
</tr>
<tr>
<td>2</td>
<td>1.00 : 4.23</td>
<td>181</td>
<td>72 h</td>
<td>0.174</td>
<td>2.38%</td>
</tr>
<tr>
<td>3</td>
<td>1.00 : 3.63</td>
<td>220-230</td>
<td>24 h</td>
<td>0.144</td>
<td>7.35%</td>
</tr>
<tr>
<td>4</td>
<td>1.00 : 3.63</td>
<td>220-230</td>
<td>24 h</td>
<td>0.297</td>
<td>7.81%</td>
</tr>
<tr>
<td>5</td>
<td>1.00 : 3.00</td>
<td>220-230</td>
<td>24 h</td>
<td>0.101</td>
<td>12.36%</td>
</tr>
<tr>
<td>6</td>
<td>1.00 : 3.01</td>
<td>220-230</td>
<td>24 h</td>
<td>0.0502</td>
<td>8.65%</td>
</tr>
<tr>
<td>7</td>
<td>1.00 : 4.06</td>
<td>220-230</td>
<td>25.5 h</td>
<td>0.0922</td>
<td>8.38%</td>
</tr>
<tr>
<td>8</td>
<td>1.00 : 4.08</td>
<td>220-230</td>
<td>25.5 h</td>
<td>0.582</td>
<td>14.68%</td>
</tr>
</tbody>
</table>

Due to the low yields of the TsOH catalyzed reactions, I investigated using other Lewis acids that would promote the formation of 18 and would hopefully also activate the alkyne towards Diels-Alder cycloaddition. Ultimately, this did result in the best yield obtained overall, when InCl₃ was used. Additionally, in comparison to other catalyst systems, Cu(II)(OAc)₂•H₂O generally performed better. By using Cu(II)(OAc)₂•H₂O, I was able to achieve a yield of 19% in 168 hours when heated to 220-230 °C; however, this was above our temperature goal.

The following transition metals (TM) catalysts were investigated: Pd(OAc)₂, InCl₃, CuI, AgSbF₆, Cu(II)(OAc)₂•H₂O, PdCl₂, CuICl, CuTf₂, InICl, and Rh₂(OAc)₄. The TM catalysts were used on their own or in conjunction with an equimolar catalytic loading of TsOH, to promote the diene formation. Due to its initial enhanced performance, Cu(II)(OAc)₂•H₂O was used to assess catalyst loading effects. Quantity of catalyst was varied from 5-60%, with no significant change in yield.
One feature of the TM catalysts that was noticed at lower temperatures was that they generally produced less of the undesired 41. However, this did not result in a higher yield of the desired 40, in comparison to reactions run with only TsOH as the catalyst. The use of CuI and PdCl2 were the cleanest of the initial reactions investigated.

Next, reaction time and concentration were varied to determine their effect on the yield of desired 40. In general, running for a longer a time and adding more 38 did not produce a significant change in the yield of the reaction, and subsequently most reactions were run for 24 hours. There were not any major changes in yield by running more or less concentrated, until the reaction was made very dilute, in which case the yield was greatly decreased. All of these reactions used CuII(OAc)2•H2O with TsOH as the catalyst system.

1.4.5. Future Directions

One area to investigate in the future would be a modification of the diene to the 2-pyrone 42, which Stille et al. had previously successfully reacted with 39 in a 68% yield (Scheme 1.13) [27]. While the yield of this reaction is significantly greater than that obtained by Dilthey and Hurtig, a direct comparison is not possible since Stille et al. ran their reaction at 300 ºC for 24 hours. However, while the temperature and time were significantly raised, the yield were also significantly raised, and the possibility exists that the yield might be maintained at lower temperatures with the addition of a TM catalyst, as seen in the above experiments.
1.4.5.2. Modifications to Existing Pathway

Due to the low yields of these reactions, further investigation could result in improved yields. Without getting into substrate modifications, there are several areas of potential improvement. One would involve utilizing a microwave reactor, which might result in both more consistently obtaining the desired temperature, in addition to the increased yield that some microwave reactions have produced compared to their traditionally heated counterparts. Another area of focus would involve pressurizing the reactions, a condition known to increase the yields of Diels-Alder reactions. Lastly, investigating the use of other catalysts that would preferentially activate the alkyne, such as gold catalysts [28], over the already reactive diene 18 should lead to significant improvements in yield.

1.5. References


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CHAPTER 2: RING FRAGMENTATIONS

2.1. Types of Fragmentation Reactions

Fragmentation reactions are a class of reactions that can be used to break molecules into smaller components as well as expose masked functional groups. There are a variety of types of fragmentation reactions, but in general they can be defined as any reaction in which a molecule decomposes or breaks into two or more parts. These types of reactions can occur for cyclic or acyclic systems, and typically involve the loss of a leaving group and the generation of an unsaturated bond.

One well known type of fragmentation reaction was established by Grob [1] and involves the breaking of a molecule into three units, a nucleofuge, an unsaturated fragment, and an electrofuge (Scheme 2.1). In this case the electrofugal group 44 is a fragment that leaves without the bonding electron pair, and the nucleofugal group 46 is a fragment that leaves with the bonding electron pair.

Eschenmoser and Tanabe detailed another fragmentation reaction that occurs when $p$-toluenesulfonyl hydrazones are applied to $\alpha,\beta$-epoxy ketones, resulting in tethered ketone acetylenes [2]. One of the main applications of this reaction is the generation of medium to large ring ketones containing an internal acetylene (Scheme 2.2). In addition to making macrocyclic systems, this methodology can be used to generate steroids with acetylenic ketones (Scheme 2.3) [3] or be more Grob like and generate untethered ketones and alkynes (Scheme 2.4) [4].
Similar to the Eschenmoser-Tanabe fragmentation, Dudley et al. developed a route to generate acyclic tethered alkynyl ketones as well as tethered alkynyl aldehydes via nucleophilic addition to vinylogous acyl triflates (Scheme 2.5) [5]. The mechanism of Dudley’s reaction goes through a Grob-type fragmentation after generation of the anionic electrofugal component in the intermediate. The Dudley group tested out several nucleophiles including Grignards and alkyl and aryl lithium reagents.
2.2. Brewer Group

2.2.1. Discovery of Lewis Acid Promoted Fragmentation of γ-Siloxyl-β-Hydroxy-α-Diazo Esters

2.2.1.1. Reaction of α-Diazo Esters

The Brewer group initially investigated the reactivity of α-diazo esters with the goal of generating polycycles containing all carbon quaternary centers via either a rearrangement or nucleophilic trapping (Scheme 2.6). When α-diazo ester 60 was combined with CH₂Cl₂ and chilled to -78 °C, followed by addition of indium (III) triflate (In(OTf)₃) and warming to room temperature, a complex mixture of products was produced, of which ethyl-3-phenylpropiolate (61) was isolated in a 17% yield (Scheme 2.7) [6]. Intrigued by this reactivity the Brewer group was interested to see if this reactivity could be applied to a ring fragmentation reaction. To better explore this reactivity Dr. Draghici synthesized γ-siloxyl-β-hydroxy-α-diazo ester 62 and found that when the same reaction conditions were applied it fragmented to provide tethered aldehyde-ynoate 65 in an 87% yield (Scheme 2.8).

Scheme 2.6

Scheme 2.7
Gratified by the successful fragmentation of 62, Dr. Draghici focused on optimizing the reaction conditions. Several Lewis acids were investigated and it was determined that tin tetrachloride (SnCl\textsubscript{4}) resulted in the best yield of 94%. Additionally, it was determined that gas evolution did not occur until temperatures were raised to -20 °C, and that consistently good results could be obtained when the reaction was run at 0 °C.

2.2.1.2. Reaction Scope

Using the optimized conditions the Brewer group explored the range of substrates the reaction could be applied to [7]. In most of the examples presented in the text below, the formation of the fragmentation precursor from the α-siloxy ketone preferentially formed the cis-diol diastereomer (such as 62). Additionally, in cases where the trans-diol was formed, the yield of the fragmentation was significantly reduced or non-existent.

The Brewer group first explored how ring size effected the fragmentation. It was determined that 6 and 7–membered rings fragmented in similar yields, and that it was possible to fragment 5–membered rings, although the yields were slightly lowered. Additionally, olefins and aryl rings were well tolerated and gave comparable yields. Even a more structurally complex compound such as steroid derivate 65 (Scheme 2.9) was able to be fragmented in 76% yield.
Modifying the $\gamma$ carbon provided details that would help to elucidate the mechanistic pathway, discussed in the next section. Changing from a $t$-butyldimethylsilyl ether (OTBS) to a triethylsilyl ether or benzyl ether had no significant effect on the fragmentation reaction. The use of a tertiary alcohol derivative or an acetal were able to undergo fragmentation to the tethered ketone or ester ynoates, respectively, though in reduced yields. However, changing to an acetoxy or enol ether resulted in a complex product mixture.

The diazo ester moiety was also modified to diazo ketones. Alkyl and aryl ketones were all successfully fragmented in moderate to good yield. Several $\alpha$-diazo ketones derived from N-CBz and N-Boc protected $\alpha$-amino acids were also developed and successfully fragmented. In the case of N-CBz protection the yields ranged from 62-74%. The N-Boc protected $\alpha$-amino ynoes’ yield suffered, presumably due to the instability of the Boc group to the Lewis-acidic reaction conditions.

### 2.2.1.3. Proposed Mechanism of the Fragmentation

An initial reaction mechanism was proposed based upon the known reactivity of $\beta$-hydroxy-$\alpha$-diazo compounds presented by Wenkert and McPherson [8] as well as Padwa et al. [9]. The nuances of the mechanism were then further elucidated by Dr. Jabre (Scheme 2.10). To start, the Lewis acid promoted elimination of the $\beta$-hydroxy
group provides vinyl diazonium intermediate (67), which then undergoes Grob-type fragmentation with subsequent loss of the silyl protecting group. An alternative potential mechanism could involve the loss of nitrogen by 67 to form a vinyl cation prior to fragmentation, such as in the work reported by Padwa.

**Scheme 2.10**

Previously I mentioned that when the *trans*-diol is allowed to react with SnCl₄, the yields suffer dramatically (Scheme 2.11). Based on these observations we have determined that in order for the β-hydroxyl group to be eliminated it must be perpendicular to the plane the diazo and ester group must lie in. This requirement explains why the *trans*-diol (69 in Scheme 2.11) exhibits a significantly lower yield, because it would be expected that significant steric interactions between the diazo and silyloxy group would interfere with the compound assuming the required geometry for fragmentation.
2.2.2. Application Towards Natural Product Synthesis

Tri-cyclic 2,5-dihydrophyrroles are a common structural motif found in many biologically active natural products (a few examples are in Figure 2.1), and therefore make for an attractive synthetic intermediate. Coldham et al. recently utilized a 1,3-dipolar cycloaddition reaction of an azomethine ylide to generate the core of (±) aspidospermine [10]. The Brewer group believed that a wide range of azomethine ylides, for use in synthesizing 2,5-dihydrophyrroles, could be produced from the condensation of tethered aldehyde ynoates, generated by the fragmentation of γ-siloxy-β-hydroxy-α-diazo esters, with an amine capable of being transformed into an azomethine ylide.
To test this theory, the Brewer group warmed 65 and proline in toluene to reflux, which generated the desired tricyclic 2,5-dihydropyrrole 78 in a 30% yield (Scheme 2.12) [11]. Gratified at this positive result, the group worked to optimize the reaction and expand on its scope.

One potential deterrent to the yield of the dipolar cycloaddition was the low solubility of proline. In order to increase the solubility of the amino acid, the Brewer group synthesized silyl ester derivatives, which showed a dramatic increase in yield (Table 2.1). The group found that both pipecolinic ester derivatives and acyclic amino esters were able to undergo the 1,3-diopolar cycloaddition, albeit generally in reduced yields. This methodology was also successful when applied to other tethered aldehyde ynoates in comparable yields.
### Scheme 2.12

![Chemical Scheme](image)

### Table 2.1: 2,5-Dihydropyrroles Prepared From Tethered Aldehyde Ynoate (65)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino Silylester</th>
<th>2,5-dihydro pyrrole</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>46</td>
</tr>
</tbody>
</table>

### 2.3. References


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CHAPTER 3: γ-AMINO FRAGMENTATIONS

3.1. A New Fragmentation Substrate

The fragmentation developed by the Brewer group is centered on the reactivity of γ-siloxy-β-hydroxy-α-diazo esters. Having explored many derivatives of these compounds we wanted to expand the scope of this reaction by changing one of the key functional groups. We theorized that the γ-siloxy group could be replaced by another electron rich group that could act as the electofugal component in the Grob type fragmentation. While it would be interesting to explore many functional groups that might be able to produce the fragmentation, we wanted one that could also be used to generate synthons useful in producing natural products. With this in mind we decided that the most useful group to investigate would be an amino group. Fragmentation of such a substance would lead to an iminium product, and if the amine was chosen carefully, it might be possible for the generation of 2,5-dihydropyrroles, as in our standard method. This process provides a benefit over our standard method, because later stage condensation of the unmasked aldehyde with an amine may not be practical. Additionally, other types of amines might provide iminiums that could be taken advantage of in other types of transformations.

3.2. Project Goals

My goals with this project were to synthesis a library of γ-amino-β-hydroxy-α-diazo esters, which could be subjected to Lewis acid fragmentation methodology. Additionally, this methodology was to be applied to the synthesis of the core of Aspidospermine (72, Figure 2.1), an indole alkaloid with a challenging architecture.
3.3. Synthesis of α-Amino Ketones

The synthesis of α-amino ketones proved to be more challenging than initially anticipated, but ultimately the Amadori reaction proved to be successful for several substrates. Below I will detail the initial routes that we attempted, followed by the successful application of the Amadori reaction.

3.3.1. Attempted Routes

3.3.1.1. Nucleophilic Displacement of α-Halogen Ketone

One of the first routes that we investigated, for the synthesis of α-amino ketones, was the displacement of an α-halogen ketone with a nucleophilic amine. Unfortunately, we found this reaction to be unproductive. I attempted to use a procedure from Tu et al. [1] in which 2-bromocyclohexanone (87) was combined with L-proline and sodium bicarbonate in ethanol and brought to reflux (Scheme 3.1).

![Scheme 3.1](image-url)

When this proved to be unreactive, most likely due to the poor solubility of L-proline, I attempted to use the more soluble L-proline methyl ester hydrochloride salt 89 with α-bromoketone 87. This produced a minor amount of the desired product (90, Scheme 3.2), but the major product observed was the dimer of 89 (91 in Scheme 3.2). To combat the problem of dimerization, I tried changing to L-prolinol, which we theorized could be later oxidized to the α-amino ketone (Scheme 3.3). Regrettably, no desired product was observed.
3.3.1.2. Epoxide Ring Opening

Due to the lack of desired reactivity by the α-halogen ketones I next explored using a procedure developed by Nelson et al. [2] in which an epoxide could be opened with an amine, which then could be oxidized to the α-amino ketone. In my first attempt I combined L-proline with cyclohexene oxide and toluene and refluxed for 24 hours (Scheme 3.4). Unfortunately no reaction was observed.

Assuming that the lack of reactivity was again due to solubility issues, the reaction was repeated using 89 and sodium bicarbonate (Scheme 3.5). This proved to be more soluble, and rather than producing the undesired dimer (as in Scheme 3.2), resulted in lactone 96. We believed that this lactone could still result in the desired amino alcohol by reversing the lactonization. In order to accomplish this, 96 was stirred in methanol with sodium methoxide at room temperature; unfortunately none of
the desired product was generated. I then attempted to oxidize the lactone to the carboxylic acid using a procedure from Steiner and Mailton [3], in which 96 was combined with pyridinium chlorochromate (PCC) and stirred in methylene chloride at room temperature, but without any of the desired product being generated.

Scheme 3.5

To overcome the issue of solubility and lactonization I next focused on again using the Nelson procedure, but this time using L-prolinol (Scheme 3.6). Gratifyingly, while the crude mixture was complex, the desired product 99 was identified by GC MS. The product was taken on directly to the oxidation step, where it was combined with sulfuric acid and potassium permanganate (KMNO₄) at 0 °C and then allowed to warm to room temperature. However, none of the desired α-amino ketone was detected.

Scheme 3.6

3.3.1.3. Reductive Aminations

I next investigated using reductive amination to generate the α-amino ketone. I first investigated using reductive amination with a masked ketone to prevent lactonization. Using a procedure based on work by Yang et al. [4] to a mixture of 2-
(tert-butyldimethylsilyloxy)cyclohex-2-enone 10) and proline 89 in methanol at room temperature was added triethylsilane and indium (III) trichloride (Scheme 3.7). However, after stirring the reaction for 5 days, only starting material was recovered.

**Scheme 3.7**

Next I adapted a procedure from Hoveyda and Snapper et al. [5]. To a round bottom flask charged with palladium on carbon and methanol, was added L-proline and 101. The reaction was allowed to stir under a hydrogen atmosphere (Scheme 3.8). In this case the reductive amination was successful in a quantitative yield; however, not surprisingly the reaction conditions resulted in the product being further reduced from silyl enol ether 102 to silyl ether 103. Despite the conditions preventing an easy conversion to the α-amino ketone, via deprotection and tautomerization of the enol, we felt that it should still be possible to deprotect and then oxidize to the α-amino ketone. Subsequent reactions would use 2-(tert-butyldimethyl-silyloxy)cyclohexanone 105 as the starting material. This was synthesized using a known procedure [6], in which a solution of 2-hydroxy cyclohexanone dimer 104, imidazole, catalytic dimethylaminopyridine (DMAP), and tert-butyldimethylsilyl chloride (TBSCI) in CH$_2$Cl$_2$ were stirred at room temperature (Scheme 3.9).
I first tried deprotecting 103 by dissolving it in tetrahydrofuran (THF) and adding tetrabutylammonium fluoride (TBAF) followed by stirring at 45 °C overnight (Scheme 3.10) [7], but no desired material was isolated after working up the reaction. Suspecting that the desired product 95 was getting trapped in the aqueous layer, I next esterified 103 using known procedures [8-9] in low yield (106 in Scheme 3.10). Attempts to deprotect 106 using TBAF only resulted in the formation of lactone 96 in low yield (Scheme 3.11).

Despite the problems with reductive amination, we were still interested in using reductive amination to install the amine group, and decided to explore utilizing an alternate masked ketone, a ketal. Using known procedures by Whol [10], and Frimmer [11] cyclohexanone could, in two steps, be converted to 2,2-dimethoxycyclohexanone
(110 in Scheme 3.12); later a simpler procedure by and Zacuot et al. [12] was used (Scheme 3.13).

\[ \text{Scheme 3.12} \]

\[ \text{Scheme 3.13} \]

Reductive amination of 110 with L-proline using Hoveyda and Snapper’s procedure was ineffective. However, when the reductant was changed to sodium triacetoxyborohydride, the desired amino acid 113 was formed in moderate yield (Scheme 3.14). I then attempted to deprotect the ketal to give the α-amino ketone by combining it with THF and HCl and allowing it to stir at room temperature; however, nothing was recovered from the aqueous layer. To prevent this from happening, I attempted to convert the amino acid to the ester. To accomplish this, I first combined 113 with methyl iodide, potassium carbonate, and dimethylformamide (DMF), but recovered only starting material (Scheme 3.15). I then attempted to react 113 with trimethylsilyl diazomethane in toluene and methanol, but again only recovered starting material and none of the desired 114 (Scheme 3.15).

\[ \text{Scheme 3.14} \]
3.3.2. Amadori Reaction

The route that ultimately resulted in the successful synthesis of α-amino ketones utilized the Amadori reaction. I started by using a procedure developed by Frankel et al. [13], in which L-proline was combined with 104 and benzene, followed by refluxing for 3 days (Scheme 3.16). When there was no sign of the desired product, the procedure was repeated with a catalytic amount of methanol, to increase the solubility of L-proline, but again none of the desired α-amino ketone 113 was produced. Next I combined L-proline and 104 in dichloromethane and allowed the reaction to stir at room temperature overnight [14], but only starting material was recovered.

Scheme 3.16

Suspecting that the problem, as before, was a matter of solubility of L-proline, the Frankel procedure was repeated using methyl ester 89; however, as before this resulted in a minor formation of the desired product and the majority being dimer 91 (Scheme 3.17). Attempts to prevent the dimerization were made by using L-prolinol, which resulted in ketal 116 (Scheme 3.18). Subsequent attempts to oxidize 116 [15] to α-keto amino acid yielded no desired product.
Frustrated by the repeated issues of solubility, dimerization, and oxidation I changed from the methyl ester to L-proline t-butylerster 117 in the hope that this substrate would have the solubility to be in solution and enough steric bulk to prevent it from dimerizing before reacting with 104. To my delight using the Frankel procedure resulted in a moderate to low yield of the desired α-amino ketone (118). Encouraged by these results I repeated the experiment using Alonso’s lower temperature procedure and running for 16 hours, after which a 94% yield was obtained (Scheme 3.19).

In order to increase the yield, the reaction was run under a nitrogen atmosphere. This was necessary as it became apparent that the α-amino ketones readily oxidized to
enones upon exposure to air or silica gel (Scheme 3.20). In addition to using 117, several other amines were tested by Dr. Tsvetkov and me and the results of these studies are summarized in Table 3.1. The reaction in entries 3-5 (Table 1B*) were conducted by Dr. Tsvetkov, and often required modified procedures.

**Scheme 3.20**

![Scheme 3.20](image)

**Table 3.1: α-Amino Ketones prepared**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>α-Amino Ketone</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="117" /></td>
<td><img src="image" alt="118" /></td>
<td>quantitative</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="119" /></td>
<td><img src="image" alt="120" /> + <img src="image" alt="121" /></td>
<td>a</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="122" /></td>
<td><img src="image" alt="123" /></td>
<td>b</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="124" /></td>
<td><img src="image" alt="125" /></td>
<td>c</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="126" /></td>
<td><img src="image" alt="127" /></td>
<td>80%</td>
</tr>
</tbody>
</table>

a In entry 2 the product was more prone to oxidation and even when precautions were taken the crude product contained the oxidized product 121, though in only 10% yield.  
b This compound was found to be the most stable towards oxidation.  
c This compound proved to be the most prone to oxidation and was only obtained by reduction with Pd/C.
3.4. Synthesis and Fragmentation of γ-Amino-β-Hydroxy-α-Diazo Esters

The conversion of α-amino ketones to γ-amino-β-hydroxy-α-diazo esters was accomplished using the aldol-type addition of lithiated ethyl diazo acetate [16] in moderate to good yields (Table 3.2). This was performed on the crude starting materials immediately after forming, to prevent oxidation. Unsurprisingly, after converting the α-amino ketones to γ-amino-β-hydroxy-α-diazo esters, there was an increase in compound stability and they could be stored for periods of time in a -20 °C freezer.

The fragmentation of the γ-amino-β-hydroxy-α-diazo esters proved to be a more challenging endeavor. Initially I dissolved 130 in CH₂Cl₂ and added a solution of SnCl₄ in CH₂Cl₂ (Scheme 3.21) [17]. However, instead of desired product 135, only the hydrolyzed product 65 was recovered, in trace quantities. The reaction was repeated with Indium (III) triflate as the Lewis acid, but again only a small amount of 135 was isolated. Interestingly when the solvent was changed to acetonitrile and the Lewis acid was changed to boron trifluoride etherate (BF₃•Et₂O), the tethered aldehyde-ynoate was produced as the minor product and the hydrolyzed ring expansion (e.g. 137, Scheme 3.21) was the major product (1: 4), though still in low yield. When Dr. Tsvetkov and I subjected the other substrates from Table 3.2 to the same fragmentation conditions with SnCl₄, the result was a low yield of tethered aldehyde ynoate 65.
Table 3.2: γ-Amino-β-Hydroxy-α-Diazo Esters Prepared

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-Amino Ketone</th>
<th>γ-Amino-β-Hydroxy-α-Diazo Ester</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="118" alt="Image" /></td>
<td><img src="130" alt="Image" /></td>
<td>55 %</td>
</tr>
<tr>
<td>2</td>
<td><img src="120" alt="Image" /></td>
<td><img src="131" alt="Image" /></td>
<td>80 %</td>
</tr>
<tr>
<td>3</td>
<td><img src="123" alt="Image" /></td>
<td><img src="132" alt="Image" /></td>
<td>75 %</td>
</tr>
<tr>
<td>4</td>
<td><img src="125" alt="Image" /></td>
<td><img src="133" alt="Image" /></td>
<td>66 %</td>
</tr>
<tr>
<td>5</td>
<td><img src="127" alt="Image" /></td>
<td><img src="134" alt="Image" /></td>
<td>75 %</td>
</tr>
</tbody>
</table>

Entries 1 & 2 were performed by myself, entries 3-5 were performed by Dr. Tsvetkov.

* As stated before the compound in entry 4 was very prone to oxidation, and was reduced with Pd/C and then immediately carried on to form the γ-amino-β-hydroxy-α-diazo ester.

Scheme 3.21

Reviewing previous work within the group showed that when α-diazo ketones were derived from N-Cbz protected α-amino acids (Scheme 3.22) [17], the fragmentation required at least two equivalents of Lewis acid. It was believed that one
equivalent of the Lewis acid was binding to the amine nitrogen, which could be occurring in these substrates as well. Changing to three equivalents of SnCl₄ resulted in an increased yield of aldehyde ynoate 65, but did not lead to any of the desired 135. 

I next investigated if the hydrolysis was occurring in situ or during workup. An ¹H NMR study verified that all of the starting diazo quickly reacted within 10 minutes to form an intermediate, which even with an extended period of time sitting did not form any of the tethered aldehyde ynoate. As a result we changed our work up from quenching the reaction with a sodium bicarbonate solution to quenching with water. This change did not result in any of the desired 135, but did increase the yield of the aldehyde ynoates to about 20%.

**Scheme 3.22**

![Scheme 3.22](image)

3.4.1. Trapping Fragmentation of γ-Amino-β-Hydroxy-α-Diazo Esters

The lack of the desired iminium products, and what we believed to be an artificially low yield of the hydrolyzed product (Scheme 3.21), led us to investigate trapping the iminium intermediate 140 as amine 141 by in situ hydride reduction (Scheme 3.23).

**Scheme 3.23**

![Scheme 3.23](image)
Initially we followed a procedure used by a former group member, Michael Chapman, in which 130 was first treated with SnCl₄, and then sodium cyanoborohydride (Scheme 3.23). However, upon workup no desired product was isolated. The procedure was repeated using sodium borohydride, but with the same result. Both of these procedures were repeated, with the same results, with the compounds from entries 2-5 of Table 3.2. One possible impediment to the trapping reaction was the solubility of the borohydrides, which tended to clump, greatly reducing the amount of reactant available. Mechanically breaking up these clumps did not result in the desired 141.

Due to the poor solubility of the borohydride, we decided to fragment 131 (entry 4, Table 3.2) with SnCl₄, followed by addition of sodium borohydride and a small amount of methanol, which this time resulted in a homogeneous solution. ¹H NMR showed that none of the tethered aldehyde ynoate was present, but the integration ratio between the ethyl ester peaks and aromatic peaks did not indicate the desired tethered amino ynoate 143 had formed (Scheme 3.24). Despite the lack of the desired 143, the lack of the hydrolysis product indicated to us that we were moving in the right direction. We next tried using sodium triacetoxy borohydride as the reductant, without the addition of methanol, due to its increased solubility in dichloromethane. Unfortunately, the results matched the use of sodium borohydride and methanol. Next we changed to sodium borohydride with diglyme as the co-solvent, and were pleased to find that the tethered amino ynoate was isolated in a 60 % yield. Attempts to repeat these results with 130 were unsuccessful; we believe this is because the α-amino ester
is susceptible to reduction under these conditions. When 132 (entry 3, Table 3.2) was subjected to the fragmentation and trapping with sodium triacetoxy borohydride no aldehyde product or starting material was detected, but by $^1$H NMR the nitrogen methyl protons were not observed.

**Scheme 3.24**

3.4.2. Future of $\gamma$-Amino Fragmentations

Fragmentation of $\gamma$-amino-$\beta$-hydroxy-$\alpha$-diazoesters still has the potential for the generation of useful tethered amino ynoates. However, alternate trapping methods, or ways to utilize the in situ generated iminium ions will need to be developed to enhance the value of this methodology.

3.5. References


(3) Steiner, Joseph P.; Mailton, Gregory S.; Patent US2002/52410 A1, 2002


(9) Gabriel, Tobias; Pech, Michael; Wallbaum, Sabini; US2001/8901 A1, **2001**


(12) Zacuto, Michael J.; Cai, Dongwei; *Tet Lett*, **2005**, 46 (3), 447-450


(15) Kalch, Delpine; De Rycke, Nicolas; Moreau, Xavier; Greck Christine*; *Tet Lett*, **2009**, 50, 492-494.


4: Natural Product Synthesis

4.1. Fragmentation and Dipolar Cycloaddition Approach to Natural Products

As stated before, many natural products contain 2,5-dihydropyrole ring systems and the fragmentation/cycloaddition strategy could provide a route to biologically important or structurally challenging alkaloids. Having demonstrated the synthesis of several 2,5-dihydropyroles; including the steroid derivatives 69 and 70 (Scheme 2.11), we endeavored to synthesize a variety of natural products including demissidine, aspidospermine, (±) cycloclavin, diplodialide C, phoracantholide I, and (±) ibophyllidine. To date the Brewer group has successfully synthesized demissidine and (±) cycloclavin. Below I will discuss my contribution towards the synthesis of demissidine and work towards the synthesis of aspidospermine.

4.2. Demissidine

4.2.1. Prior Synthesis of Demissidine

Demissidine (144, Scheme 4.1) is a Solanum steroidal alkaloid that has been isolated from potatoes, and is a potent potato beetle repellent. It was first prepared by Kuhn et al. [1] in 1952 and later by Sato and Latham [2] in 1956. Both of these synthetic routes were simple oxidation reduction sequences starting from the closely related steroidal alkaloid tomatidine (145, Figure 4.1). In 1963, Adam and Shreiber [3] prepared demissidine from pregnenolone acetate (146, Figure 4.1). During the decade in which these syntheses were conducted the products were only identified by melting point or elemental analysis, which does not guarantee that the correct stereochemical outcome was achieved.
4.2.2. Retrosynthetic Route and Key Disconnect of our Synthesis

Based upon our work with steroids 69 and 70 we believed that the indolizidine framework of demissidine could be generated from the 1,3-dipolar cycloaddition of tethered aldehyde ynoate 147 and amino acid 148. Fragmentation of $\gamma$-siloxy-$\beta$-hydroxy-$\alpha$-diazo ester steroid core 149, which could in turn be produced from epiandrosterone (150), would provide the required aldehyde ynoate 147 (Scheme 4.1).

Scheme 4.1

4.2.3. Amino Acid Challenge

The goal of my project was to prepare a pipecolic acid derivative (e.g. 148, Scheme 4.1) that could be used for the key 1,3-dipolar cycloaddition step in the synthesis of demissidine. While appearing to be a structurally simple molecule, it is
crucial for our synthesis that the stereochemistry of the methyl substituent be installed properly before the dipolar cycloaddition takes place. After several failed synthetic routes were investigated, I was ultimately able to develop a concise and high yielding route to N-Boc-(2R,5S)-5-methylpipecolic (151, Figure 4.2) that started from racemic 3-methylpiperdine.

Figure 4.2: N-Boc-(2R,5S)-5-methylpipecolic acid

4.2.4. Early Attempts

My initial attempts to prepare pipecolic acid 151 focused on the nucleophilic addition of glycine derivatives 152 into an electrophilic source of (2S)-2-methylbutane (153, Scheme 4.2). In many cases the methyl butane source was ditosylate 155, which was prepared, as show in (Scheme 4.3) from itaconic acid. Hydrogenation of itaconic acid gave diacid 157, which was then further reduced to diol 158 with Lithium aluminum hydride (LAH) [4]. Diol 158 was then tosylate using known procedures [5–6] to provide tosylate 155.
My first attempts to alkylate glycine followed a procedure published by Luche et al. [7] in which cyclic amines were formed by reaction of a deprotonated amino acid with a 1,4-haloalkane (Scheme 4.4). For my experiments, I used Boc glycine methyl ester (159, Scheme 4.5), but after purification none of the desired 163 was isolated.

Suspecting that the tosylate might not be an efficient enough leaving group the reaction was repeated with freshly prepared iodobutane (165) as the alkylating agent. This modification also produced no desired product. Concerned that the anion might not be forming correctly, an NMR experiment was run in which the electrophile was replaced with deuterated methanol. This experiment revealed that the ester group was being hydrolyzed during workup, which may be the reason why similar reactions in the literature utilized bulkier esters. With this in mind I tried the Luche procedure with N-
Boc-glycine \( t \)-butyl ester (166) and iodobutane (Scheme 4.6). However, none of the desired 167 was detected, but a minor byproduct, which we believed was the result of a double addition of iodobutane (168, Scheme 4.6) was formed.

**Scheme 4.6**

![Scheme 4.6 diagram](image)

An alternate procedure for generating cyclic amino esters was reported by Corey et al. [8]. In this report \( t \)-butylglycinate benzophenone imine (169) was transformed into \( t \)-butyl pipecolinate (174, Scheme 4.7) under phast transfer conditions using a chiral quaternary salt to set the seterocenter at the \( \alpha \)-position. We hoped that ditosylate 155 could be used as the electrophile and that tetrabutylammonium bromide (TBAB) could serve as the phase transfer catalyst, because in our case, the stereochemistry of the \( \alpha \)-position is unimportant in the final product, since it will be lost during the 1,3-dipolarcycloaddition step.

**Scheme 4.7**

![Scheme 4.7 diagram](image)
To start N-(diphenylmethylene) glycine methyl ester (177) was synthesized in a 75% yield using a procedure developed by O’Donnell [9] (Scheme 4.8). This material was taken on to the next step without purification, as it deteriorated into benzophenone and glycine methyl ester upon exposure to air/silica. For the alkylation reaction (Scheme 4.9), the Corey procedure was used, changing to using glycine 177, TBAB, and ditosylate 155. After purification only benzophenone and 155 were recovered. Reaction temperature was later elevated from -50 °C to rt, but none of the desired product was generated.

**Scheme 4.8**

![Scheme 4.8](image)

**Scheme 4.9**

![Scheme 4.9](image)

I next tried to adapt another O’Donnell method [10], in which N-(diphenylmethylene)glycine ethyl ester was reacted with various alkyl halides using potassium carbonate (K$_2$CO$_3$) as the base (Scheme 4.10). Unfortunately, there was no reaction and only starting materials or decomposed starting materials were recovered. The reaction time was increased, and the K$_2$CO$_3$ was ground to a fine powder, but with no change in reactivity. The electrophile was changed to 1-iodobutane, but again no reaction occurred.
Due to the lack of reactivity, and considering that both of the other methods had used more electron rich amino esters (ethyl and t-butyl), I synthesized t-butylglycinate benzophenone imine (169) in a 98% yield, using the same procedure as for 177. Using the O’Donnell procedure, 169 was combined with 155, but mostly unreacted starting material were recovered with a trace amount of what may have been the desired t-butyl 2-((diphenylmethyl-ene)amino)-5-methyl-6-(tosloxy) hexanoate (181, Scheme 4.11). Similar results were obtained when the electrophile was changed to 1-iodobutane.

### Scheme 4.11

4.2.5. Directed Reduction Approach

Because the alkylation chemistry failed to return product, I change my approach and next investigated the possibility of performing a directed reduction of an external olefin on a pippecolinic acid derivative. Pedregal et al. [11] and Jefford et al. [12] have shown cases where similar cyclic amines with external alkenes were selectively reduced (Figure 4.3 and Figure 4.4, respectively). In the case of Jefford et al.,
4.4) the ratio between heterocycles 186 and 187 could be varied by changing the catalyst and solvent.

Figure 4.3: Pedegral Reduction

Figure 4.4: Jeffords Catalyst Controlled Reduction

5-Keto-L-pipecolic ester 192 was prepared in 5 steps (Scheme 4.12) via a known route [13,14]. The external alkene was generated from ketone 192 in up to 50% yield by a Wittig olefination [12,15]. An alternate procedure utilizing Kt-BuO as base gave the product more consistently in a 50% yield, but these conditions also racemized the product.

Scheme 4.12
A variety of TM catalysts and solvents were assayed for the reduction of the external alkene of 193 (Scheme 4.14). Unfortunately, none gave good diastereoselectivity and the best results gave a 3:1 ratio of diastereomers 195 and 194. The ratio of the products was determined by NMR, based upon work that Lautens et al. [16] had performed on similar substrates.

Initial reductions focused on using PtO₂ as the catalyst, as in the Pedregal example. The use of methanol or ethyl acetate, as solvents, provided only a 1:2 ratio of 195 to 194. Changing to toluene or diethyl ether improved the ratio to 1:3. Next, Crabtree’s catalyst was tested, but a 1:1 mixture of products was obtained. When the catalyst was changed to palladium on carbon (Pd/C), the results showed no improvement over those of PtO₂.

I next investigated reducing amino ester 193. Using a Granberg patent [17], ester 193 was combined with ethanol, water, and lithium hydroxide in a round bottom flask and allowed to stir overnight. Acidic workup provided the amino acid in high yield (Scheme 4.15). I repeated the reduction using both Pd/C and PtO₂ with various solvents, but obtained similar product ratios to the ester reductions.
The reductions described thus far relied on the bulk of the ester to block the approach of the catalyst, resulting in the delivery of the hydrogen trans to the ester group. At this time I decided to investigate the use of a directed reduction. Riera et al. [18] had shown that cyclic amino alcohols 197 and 200 could be reduced to give a cis: trans ratio of 10-16:1 (Scheme 4.16). The Riera group had had similar problems when trying to perform the reduction using an amino ester. Using the Riera method with amino alcohol 203 (Scheme 4.17), will provide the methyl group cis to the alcohol, which would ultimately provide the (5R) diastereomer of pipecolic acid 151 (Figure 4.2), instead of the desired (5S). It should be simple to overcome this problem by changing the synthetic route from starting with (S)-2-aminopentanedioic acid (188, Scheme 4.12) to (R)-2-aminopentanedioic acid.

To test this method, amino ester 193 was reduced (Scheme 4.17) with LAH, to give amino alcohol 203 in a quantitative yield. Hydrogentation using the conditions
used by Riera, gave a single diastereomer of amino alcohol 204. The stereochemistry of the diastereomer that was generated could not be easily determined because the NMR shifts were very different from the starting alkene 193. Although this material could be transformed into the desired pipecolic acid derivative, we were discouraged to note that this route would require a total of 8 steps, and that some of these steps were low yielding. With this in mind, we looked for a new and more efficient route.

4.2.6. Final Route

A new literature search found a series of Glaxo Group patents [19] that described the synthesis of N-Boc protected 2-formyl-5-methylpiperdines (208 a & b) by alkylation of (3S-N-Boc-3-methylpiperidine (207). This material was enantioenriched by resolution via co-crystallization of 3-methyl piperdine with mandelic acid (Scheme 4.18). Gawley et al. [20] used the same procedure to alkylate N-Boc piperdine with a variety of electrophiles.
The Glaxo recrystallization procedure proved to be arduous and the yield and enantiopurity (as determined by HPLC analysis of the Boc protected product), were not reproducible. However, a more robust method for this resolution was detailed in a Synaptic Pharmaceutical Corporation patent [21]. In this method (S)-mandelic acid was heated in ethyl acetate in a flask until it dissolved, and then the solution was treated with 3-methylpiperidine. The mixture was allowed to come to room temperature and precipitate was isolated by filtration and washed with 1:1 EtOAc: Et$_2$O to provide salt 209 in a 60% yield. Combining salt 209 with THF, a 2.5 M solution of sodium hydroxide and Boc anhydride provided 5-methylpiperidine 210 in up to a 90% yield with a 98% or higher ee, which was determined by HPLC analysis (Scheme 4.19).

Scheme 4.19

With piperdine 210 in hand I investigated the possibility of effecting a directed lithiation sequence using carbon dioxide as the electrophile, to generate pipecolic acid 151 (Scheme 4.20). Ultimately the reaction would be a success, providing N-Boc-(2R,5S)-5-methylpipecolic acid (151) as a single diastereomer in up to a 73% yield. In order to achieve these results 210 was combined in a flame dried flask under a nitrogen atmosphere with distilled N,N,N',N'-tetramethyl-1,2-diaminoethane (TMEDA) and diethyl ether and chilled to -78 °C, followed by the dropwise addition of filtered s-BuLi. In all cases, when s-BuLi was used without filtering out the LiH that was present
in the bottle, no reaction would occur. Next anhydrous dry ice, obtained by subliming and re-condensing dry ice, was allowed to sublime through the reaction mixture. Early attempts were made to prevent double addition by cannulating the reaction mixture onto dry ice, but these experiments were found to have a lower yield. After 2 hours the reaction was quenched at -78 °C with methanol. Special care was required to prevent violent off gassing at this point, as the reaction mixture is saturated with dissolved carbon dioxide. An acid-base extraction and concentration in vacuo provided 151 as a white solid.

Scheme 4.20

4.2.7. Synthesis of Demissidine

The synthesis of demissidine [22] was spear headed by Brewer group member Dr. Zhang. This synthesis started with Epiandrosterone (151), which was converted to diazoester 149 in a four steps (Scheme 4.21). Fragmentation using standard conditions provided the tethered aldehyde ynoate 147. The 5-methylpipecolic acid I prepared was deprotected and converted to amino acid silyl ester 148 (Scheme 4.22). The 1,3-dipolar addition of 148 and 147 proceeded smoothly to give the 2,5-dihydropyrole in an 80% yield. An oxidation and selective reduction sequence set the stereocenters in 214, and decarboxylation and deprotection of the alcohol provided demissidine (144, Scheme 4.23).
Scheme 4.21

1) CuBr₂, MeOH reflux, 76% yield
2) i) TBDPSI, imidazole, DMAP, CH₂Cl₂
   ii) NaOH, H₂O
   DMF/CH₂Cl₂
   84% yield

1) TBSCI, imidazole, DMAP, CH₂Cl₂
   92% yield
2) LDA, THF, -78 °C
   66% yield

Scheme 4.22

1) TFA, 81% yield
2) Poly(vinyl) pyridine,
   H₂O
3) Et₂NTMS
   95 °C, 12 h
4.3. Aspidospermine

4.3.1. Background

Aspidospermine (72, Figure 4.5) is an indole alkaloid that was first isolated in the 1800s from *Aspidosperma quebracho blanco*, and later from several other plant sources [23]. It has been a synthetic target since its discovery because of its challenging pentacyclic structure and also for the wide range of biological activity it has exhibited including acting as a diuretic, vasoconstriction, hypertensive, and respiratory stimulant [23]. It has been synthesized both in racemic form as well as in its optically pure form several times, first starting with the landmark work of Stork and
Dolfini in 1963 [24]. In 2003 Shishido et al. were able to successfully synthesize it in just 17 steps with an overall 1.6% yield [25], and in 2006 by Pearson and Aponick completed a formal synthesis and were able to increase the overall yield to 2.0% with 21 total steps [26]. In one of the most recent advances, Boger et al. reported a divergent synthesis of (+)–spegazzine and (-)–aspidospermine, which gave the product in 17 steps with an overall yield of 4.2% [24]. A short and high yielding synthesis was reported by Mac Millian et al., which gave (+)–aspidospermine in 9 steps and 24% overall yield [27].

![Figure 4.5: Aspidospermine](image)

**4.3.2. Brewer Group Key Disconnect and Project Goals**

We believe that the core of aspidospermine can be generated by the fragmentation and 1,3-dipolarcycloaddition sequence (Scheme 4.24). If a model system could generate the core in Scheme 4.24, then work could be done to stereoselectively install the quaternary ethyl group. The aromatic ring and nitrogen ring could be stereoselectively installed either before or after fragmentation. My goal with the project was to generate the aspidospermine core 217 and investigate incorporating the necessary remaining functional groups (or masked ones) that could later allow for the complete synthesis of Aspidospermine.
4.3.3. 8-Hydroxyquinoline Route

Despite the issues we faced fragmenting the simple \(\gamma\)-amino-\(\beta\)-hydroxy-\(\alpha\)-diazooesters, we decided to investigate this approach to the core of aspidospermine 217, because it offered the most concise route. We believed that this could be achieved by the fragmentation and 1,3-dipolar cycloaddition of \(\gamma\)-amino-\(\beta\)-hydroxy-\(\alpha\)-diazooester 216. The fragmentation precursor could be generated from \(\alpha\)-amino ketone 218 using our usual aldol-type addition of lithiated ethyl diazo acetate [27]. The \(\alpha\)-amino ketone should be easily generated from the oxidation of amino alcohol 219, which in turn could be generated from the alkylation of amino alcohol 220. Lastly the required amino alcohol could be generated by the reduction of 8-hydroxyquinoline 221 (Scheme 4.25).
The reduction of 8-hydroxyquionline was accomplished by hydrogenation over rhodium on alumina under 500-800 psi of hydrogen gas for 14 hours [28] (Scheme 4.26), which provided 220 as a mixture of diastereomers. The diastereomeric mixture, based upon Fache et al.’s work [29], are the cis and trans ring junction products (220 a & b are the major diastereomers). Oxidation of the diastereomeric mixture of 220 to give ketone 222 proved to be difficult.

Scheme 4.26

Initial attempts to oxidize 220 using Swern conditions [30,31] gave only enamine 223 in 20% yield. At this time this over oxidation was not desirable, though we noted that it could be very useful in the future to allow for a 1,4-addition and installation of the ethyl group of Aspidospermine (Scheme 4.27). Next I tried to use Jones oxidation [32], in which freshly prepared Jones Reagent was added to a stirred solution of 220 in acetone at 0 °C. After workup and Soxlet extraction a complex product mixture was obtained. For my final attempt I used a Dess-Martin oxidation [33], in which Dess-Martin periodinane was added portionwise to a stirring solution of
220 and CH₂Cl₂. However, this resulted in the formation of over oxidized 224 and other aromatic products.

Scheme 4.27

In order to avoid the requisite reduction step we instead investigated performing the alkylation step first, followed by oxidation, which based upon our previous work would be less likely to oxidize. The N-alkylation of 220 proved to be more difficult and lower yielding than expected. A variety of procedures in which 220 was combined with base and an electrophilic source of (methylene)trimethylsilane [34,35] were assayed. Ultimately a procedure from Lesur et al.[36], was adopted in which 220 was combined with dimethylformamide (DMF) and triethylamine and then heated to 80 ºC. This was followed by the slow addition of (iodomethyl)trimethylsilane, synthesized from a Finkelstein reaction of (chloro-methyl)trimethylsilane in acetone with sodium iodide in a 40% yield of 219 (Scheme 4.28).

Scheme 4.28

An alternative route that ultimately proved too inefficient to arrive at 219 is shown in scheme 4.29. In this route, 220 was Boc protected [37] in 62% yield; attempts to repeat this reaction were less successful due to the generation of dimer 228. The secondary alcohol was than oxidized under Swern conditions to give ketone 229 in
40% yield along with the diastereomer in 10% yield. Boc deprotection [38] provided the desired α-amino ketone salt 230 in 90% yield. Salt 230 was then alkylated using the Lesur procedure but most of the material was lost after aqueous workup and no desired product was detected.

**Scheme 4.29**

Due to the low yield of the N-alkylation step I investigated first protecting the alcohol of 219. TBS protection was accomplished by combining 220 with TBSCl, DMAP, Imidazole, and CH₂Cl₂ [39], which resulted in TBS protection of both the alcohol and the nitrogen (Scheme 4.30). The nitrogen was selectively deprotected by adding TBAF to a stirring solution of silyl protected amine 231 in THF at 0 °C, to give silyl ether 232. However, at this point more promising oxidation methods were pursued.

**Scheme 4.30**
Oxidation of the alkylated amine substrate 219 again proved more difficult than expected. Due to purification problems, the crude material was ultimately taken on to the diazoester addition step (Scheme 4.31) without purification. Chromium based oxidations, PCC [40] and Jones [41], provided poor yields over the two steps, but Swern oxidation followed by our standard diazo ester addition resulted in the desired \( \gamma \)-amnio-\( \beta \)-hydroxy-\( \alpha \)-diazoester 216 in 40% yield over the two steps. Interestingly, 216 was formed as a single diastereomer.

\[ \text{Scheme 4.31} \]

With 216 in hand I subjected it to the standard fragmentation conditions we had devised for \( \gamma \)-amnio-\( \beta \)-hydroxy-\( \alpha \)-diazoesters, but this returned only starting material (Scheme 4.32). Changing the conditions to use BF₃\( \cdot \)Et₂O as the Lewis acid resulted in some recovered starting material, as well as the retro aldol product (ketone 218). It seems likely that the fragmentation fails because this diastereomer is unable to obtain the required geometry. It is possible that enamine 223 could be used to prepare the alternate diastereomer, which might fragment better. However, due to the low yields of the alkylation and oxidation steps it was decided that an alternate pathway to 233 would be more practical.
4.3.4. Traditional Fragmentation Approach

Despite the lack of reactivity of the bicyclic diazo 216, we believed that generating the core from a fragmentation/1,3-dipolar cycloaddition should still be possible. We believe that the rigid bicyclic ring was preventing the proper geometry from being achieved for the fragmentation step to occur and that a monocyclic γ-siloxo-β-hydroxy-α-diazoester with an amino chain at the delta position (i.e. 234, Scheme 4.33) might be successful. After fragmentation, condensation of the amine onto the newly formed aldehyde would give the same iminium product (233, Scheme 4.33). We also thought that this approach would provide an opportunity to install the requisite ethyl group. My efforts to bring this approach to fruition are described in the following sections.
4.3.4.1. 1,2-Addition

My initial work on synthesizing the precursor to γ-siloxy-β-hydroxy-α-diazo 234 focused on the 1,2-addition of an alkyl lithium or Grignard reagent into cyclohexane-1,3-dione or its masked equivalent (Scheme 4.34).

Scheme 4.34

In order to generate the precursor for the carbon nucleophile (238, Scheme 4.34) I synthesized N-Boc-3-bromopropyl amine by a known route in 80% yield [42]. I next attempted to alkylate the amine, as I had previously done with the quinoline derivative, but this led to cyclic amine 243 instead (Scheme 4.35). Suspecting that the bromine might be too effective of a leaving group I prepared the HCl salt of N-Boc-3-chloropropyl amine which I then successfully alkylated with iodomethyltrimethylsilane to give chloropropyl amine 242 in 80% yield over two steps.

Scheme 4.35

With amine 242 in hand I attempted several times to generate the corresponding Grignard reagent (244, Scheme 4.36), but reacting this material with masked diketone 245 [43,44] gave no desired addition products and only chlorinated starting material
was recovered. Attempts to generate [45] the corresponding organo-lithium species (247, Scheme 4.37) also failed.

Scheme 4.36

An alternative strategy to forming this C-C bond would be to generate alkyl zinc reagent 248 (Scheme 4.38) and couple it with a vinyl halide. To accomplish this [46] I charged a flame dried flask with zinc powder, lithium chloride, tetrabutylammonium iodide, and THF, added TMSCl followed by 242 and heated to 60 °C for 18 h. An aliquot of the reaction mixture was quenched with water and appeared to show the dehalogenated product, which would indicate that the desired 248 had formed. Unfortunately, the subsequent Pd-mediated coupling of 248 with prepared 3-bromo- or 3-triflyl cyclohexanone [47,48] failed to give any desired coupling product and instead only returned quenched alkyl zinc 248.
I suspected that the chlorine might not be reactive enough to undergo lithium halogen exchange or insertion by magnesium. To circumvent this problem I subjected 242 to a Finkelstein reaction [48] to generate the iodo product (249, Scheme 4.39), but unfortunately only cyclic amine 243 formed under these conditions. Reducing the reaction temperature circumvented this side reaction, but lead to a mixture of 249 and starting material after purification. I attempted to use this mixture of halo-amines to make Grignard 244 and alkyl lithium 248, but again none of the organometallic species were formed.

4.3.5. Ongoing Work

We envision that tricycle 217 can be transformed into aspidospermine by incorporation of the indoline ring system to give the pentacyclic core 264. Decarboxylation and acylation of this material would provide aspidospermine (72, Scheme 4.46).
To incorporate the indoline ring we envisioned forming enolate 266 (Scheme 4.47) which could then undergo direct alkylation with nitroso benzene 268, or trapping as silyl ketene acetal 267, which could then be reacted with 268 in a Diels Alder reaction pathway.

Initial attempts to form the enolate and then trap it as the silyl ketene acetal 267 or react it directly with nitrosobenzene, were not promising. In one run, we formed β,γ-unsaturated enone 271 (Scheme 4.48), which indicates that the enolate had formed and
then quenched. Because 217 was a fairly precious material, we decided to explore the reaction conditions with a model system.

**Scheme 4.48**

4.3.4.2. Current Route

Due to the problems I had forming the requisite organometallic intermediates, I abandoned that route γ-siloxo-β-hydroxy-α-diazo 234 in favor of a more stepwise, but less risky approach shown in schemes 4.40-4.43. This route took advantage of the known secondary amine 255 (Scheme 4.40), which I prepared from m-anisaldehyde (250), by known procedures [49,50] in four steps in an overall 43% yield. The hydrolysis and rearrangement of 1,4-diene 255 to enone 256 (Scheme 4.41) proved to be slightly more complicated than expected. The best procedure [51] identified involved combining 255 with THF and 10 % HCl, which provided the desired product in a 90% yield (Scheme 4.41). It was necessary to store this product as the HCl salt because the free base quickly decomposed in less than one day, even when stored in a -40 °C freezer.
Protecting amine 256 with Boc to give 257 (Scheme 4.42) was straightforward and this material was stable to long term storage. Copper catalyzed conjugate addition of ethyl magnesium bromide (EtMgBr), and trapping with TMSCl [52] gave 258, which contains the ethyl group at the all carbon quaternary center in 90% yield. The inclusion of Et$_3$N in the reaction was paramount; reactions in which Et$_3$N was not added resulted in none of the enol ether trapping, and provided the ketone instead.
Rubottom oxidation to α-siloxoy ketone 259 was initially accomplished using m-chloroperoxy-benzoic acid (mCPBA), but the yields were only about 30% and two diastereomers were formed. A better procedure involved combining enol ether 258 with CH₂Cl₂ and chilling the reaction to 0 °C followed by the addition of a solution of dimethyldioxirane (DMDO) in acetone. This provided the α-hydroxy ketone as a single diastereomer, which was protected as the α-siloxoy ketone by treatment with TMSCl to give 259 in a 70% yield. Initially we were interested in synthesizing the α-siloxoy ketone as the TBS protected alcohol. Unfortunately, the TBS group could not be installed by either transfer during the Rubottom oxidation or the subsequent protecting step, when using mCPBA or DMDO as oxidant. α-Siloxoy ketone 259 was readily converted, using our standard procedure, to γ-siloxoy-β-hydroxy-α-diazo ester 260 in a 73% yield as a single diastereomer (Scheme 4.43).
Initial attempts to convert fragment diazo 260 proved difficult. The standard conditions with SnCl₄, as Lewis acid, gave a complex mixture; it was clear that the Boc group had cleaved, but no aldehyde was present in the crude mixture. When 260 was added to a mixture of indium (III) triflate and CH₂Cl₂ at -5 °C and stirred for 2 hours (Scheme 4.44), the desired tethered aldehyde ynoate 261 and another minor compound that would later be determined to be iminium salt 262, was generated in a 64% yield. Boc deprotection of 261 was explored using a variety of conditions, but these mostly resulted in the formation of a complex mixture [53]. However, when aldehyde ynoate 261 was combined with 2,6-lutidine and CH₂Cl₂ [54] and this mixture was treated with TBSOTf, a mixture of starting 261 and the desired 262 was obtained in a low yield.

With the discovery that the fragmentation reaction conditions were generating some of the desired condensation product, I experimented with optimizing the reaction conditions to promote the in situ condensation of 261. NMR experiments showed that very little of the desired 262 was forming in the reaction mixture, even when the
reaction time was extended to 24 hours. Based on my experience with the amino fragmentations in chapter 3, I decided to change the work up from quenching with NaHCO$_3$ to water, which resulted in dramatic increase in yield of the iminium 262. The addition of molecular sieves and running the reaction at room temperature further helped to promote the formation of the desired iminium salt, which could be purified by triturating with hexanes and resulted in pure iminium salt 262 in a 70% yield.

I was delighted to find that iminium 262 readily underwent 1,3-dipolar cycloaddition [56] by combining it with cesium fluoride in acetonitrile and allowing the reaction mixture to reflux until all of the starting material was consumed, which provided tricyclic aspidospermine core 217 in 60% yield as a single diastereomer (Scheme 4.45). NMR studies have confirmed that the relative stereochemistry of the proton at the tricyclic junction and the ethyl group are in the desired syn conformation.

Scheme 4.45

4.3.5.1. Model System

Due to the lack of results we decided to conduct further investigations using heterocycle 84 (Scheme 4.49), which has been synthesized in our group previously [56] in a few steps and should exhibit similar reactivity to aspidospermine core 217. I prepared 84, as described previously [56], but in my hands the reaction was lower
yielding (10–40% yield) than what was reported in the past (60%). We are uncertain what caused this drastic reduction in yield.

Scheme 4.49

With sufficient quantities of 84 in hand, I attempted to generate the corresponding silyl ketene acetal, and this proved more difficult than expected. Ultimately the best procedure [56] involved chilling a solution of LDA -78 °C followed by adding HMPA and then a solution of heterocycle 84. After stirring for 1 h, a solution of TBSOTf in THF was added dropwise. After another hour the reaction was quenched cold with a saturated solution of NaHCO₃ to provide 274 in 80% yield (Scheme 4.50). Without the addition of HMPA the only product was C-silylation α to the ester.
With silyl ketene acetal 274 in hand, I attempted the Diels-Alder [57] cycloaddition by combining diene 274 with nitrosobenzene and stirring in a variety of solvents at room temperature in the dark. These reaction conditions only provided a complex product mixture, including the azoxy dimer of nitrosobenzene. I believed the issue of nitroso benzene decomposing could be overcome by using an alternate procedure [58], in which the nitrosobenzene was generated in situ from phenyl hydroxylamine. Unfortunately this modified procedure also gave a complex product mixture.

I also examined the possibility of reacting the enolate directly with nitrosobenzene as well as in situ generated nitrosobenzene. In these studies, LDA was generated at 0 °C and then chilled to -78 °C followed by the dropwise addition of 217, followed by the addition nitrosobenzene and the reaction was allowed to stir in the dark for 1 hour. When allowed to warm to room temperature before quenching, only the azoxy dimer of nitrosobenzene and 280 were detected, and when the reactions were quenched at -78 °C a mixture of the azoxy dimer, 280 and 281 were detected (Scheme 4.51).
Because decomposition of the nitrosobenzene was a consistent problem, we investigated the use of phenylazo carboxylate 284 as an alternative nitrogen electrophile. Azo 284 was made by a known procedure (Scheme 4.52) [59]. There are no known examples of using phenylazo carboxylates in Diels Alder reactions, though other derivatives such as phenylazo carbonitriles are well established as Diels-Alder dienophiles. There are several examples of phenylazo carboxylates undergoing 1,2-addition with Grignards.

Using freshly prepared reagents, I combined phenylazo 284 and diene 274 in a round bottom flask with deuterated chloroform, and allowed the reaction to stir at room temperature for 6h under a nitrogen atmosphere. No reaction occurred under these conditions (Scheme 4.53). The reaction time was extended to 24 hours with no change, and after 72 hours, the diene 274 had degraded. The reaction was repeated using THF and refluxing for first 6 h, then 24 h, and finally 48h with the same results. Changing
the solvent to toluene and heating the reaction in a microwave reactor at 120 °C or 170 °C for 30 minutes, also failed to give any desired product.

Scheme 4.53

In an attempt to increase the reactivity of the dienophile we decided to add a Lewis acid to catalyze the Diels-Alder reaction. Based on a procedure by Casamitjana and Bosch [60], 274 was added to a solution of ZnCl₂ and THF and chilled to 0 °C. A solution of phenylazo 284 in THF was added dropwise and the reaction was allowed to stir overnight. Upon workup large amounts of phenylazo 284 were still present but none of the diene 274 present. If there was any desired product formed, it was only in trace quantities.

I next attempted to directly add the enolate of 84 to azo 284 (Scheme 4.54), but only starting materials were recovered, or oxidized 84. The reaction was repeated with the addition of HMPA, but this led to a complex mixture. At this point, it appears that forming the C-N bond in these strategies will not work, and future work will focus on alternative ways to form this critical bond.
4.3.6. Recent Optimizations

While working on completing the last steps in the synthesis of Aspidospermine, our group developed a shorter route to enone 257 that cuts out 4 steps. In this route N-Boc-allylamine (288) was alkylated with (iodomethyl)trimethylsilane, and the alkylated amine was then subjected to hydroboration with 9-BBN to give the corresponding boronate. This material was used in a subsequent Suzuki coupling with 3-iodocyclohex-2-enone (289) to give enone 257 in 60% yield over the two steps (Scheme 4.55) [61]. This optimization route should make material throughput easier, and will undoubtedly facilitate the eventual synthesis of aspidospermine.

4.3.7. Future Direction

Despite the lack of desired reactivity with aspidospermine core 217 and silyl ketene acetal 267, we believe that aspidospermine can still be synthesized from 217. One of our most promising ideas involves converting the ester of 217 to aryl amide
(290, Scheme 4.56), followed by intramolecular Friedel-Crafts conjugate addition to install the tertiary C-C bond of 291. This could then be followed by transesterification and acylation of the amine, which could then undergo palladium catalyzed amination and decarboxylation to provide aspidospermine 72. Miller et al. [62] and others have shown the application of the Friedel-Crafts conjugate addition in medicinal chemistry, and Glorius et al. [63] have shown the application of the palladium catalyzed amination.

### Scheme 4.56

![Scheme 4.56](image)

4.4. Final Remarks

During my time at the University of Vermont I have been privileged to work in both the Hughes and Brewer groups and afforded the opportunity to work on challenging projects in diverse areas of organic chemistry. Within the Hughes group I was involved in studies to chemically generate discrete carbon nanotube belts, which

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may one day drastically change our world by creating more efficient electronics. The
goal of producing nanotube belts has not yet been achieved, but it is only a matter of
time until the correct approach is developed to allow for their production.

My time with the Brewer group has allowed me to explore the synthesis of
natural products. The goal of these projects was to apply the methodology of
fragmentation and 1,3-dipolar cycloaddition to synthesize a variety of natural products.
We have successfully synthesized demissidine in good yield in a few steps, and we
have generated the tricyclic core of aspidospermine. I believe that through my studies
and through the continued studies of the Brewer group, the goal of synthesizing
aspidospermine and other natural products will be achieved.

The projects I have worked on during my time at the University of Vermont
may appear to be quite disparate, but have always involved a common theme: working
to build complex molecules from simple starting materials. Within the Hughes group
colossal compound were generated from relatively small units. The 42 carbon cyclene
\textbf{17} was generated from \( p \)-iodoaniline and 1-bromo-2-iodoaniline (both of which has
only 6 carbons), and would have been joined with cyclopentadienone \textbf{18} (containing 17
carbons) to generate the 90 carbon nanotube belt \textbf{15}.

My work within the Brewer group focused on creating smaller, but more
structurally complex and functional group diverse compounds. The \( \gamma \)-siloxy-\( \beta \)-
hydroxy-\( \alpha \)-diazoesters and \( \gamma \)-amino-\( \beta \)-hydroxy-\( \alpha \)-diazoesters were both quickly
generated from the corresponding 2-hydroxy- or 2-aminoketones, building up a
structurally complex molecule in two steps, in both cases. This quick buildup of
functional groups played a key role in the synthesis of the natural products demissidine and work towards the core of aspidospermine. Both natural products are structurally complex molecules with multiple stereocenters. The synthesis of demissidine required the small pipecolic acid 151, without which setting the stereochemistry of the piperidine methyl group would have been a daunting and potentially impossible task. The intricate core of aspidospermine has now been generated from N-Boc-allylamine, building a tricyclic structure and quaternary center in 7 steps.

I have continually learned over the course of all of my projects that what may appear to be a minor change in choice of reagent or substituents can drastically change the outcome of a reaction. This has served to remind me that almost nothing can be taken for granted, and only through hard work can we get the solutions we seek.

4.5. References

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CHAPTER 5: EXPERIMENTAL PROCEDURES

5.1. Methods and Materials

All reactions were carried out under an atmosphere of nitrogen using flame-dried glassware unless otherwise noted. A rotary evaporator equipped with a water condenser and attached to a vacuum system was used to concentrate in vacuo. Samples were further dried under reduced pressure on a high-vacuum line. Tetrahydrofuran (THF), dichloromethane (CH₂Cl₂), dimethylformamide (DMF), acetonitrile (MeCN), and toluene (PhMe) were dried via a solvent dispensing system. Commerically available SnCl₄ was distilled twice from P₂O₅ under a nitrogen atmosphere and was stored in a sealed tube as a 1 M solution in CH₂Cl₂ or commercially available 1M solutions of SnCl₄ in CH₂Cl₂ were used as received. Trimethylamine (Et₃N) and diisopropylamine (i-Pr₂NH) were distilled from CaH₂ under a nitrogen atmosphere and used directly. p-Toluenesulfonic acid was dissolved in 25 mL CHCl₃ filtered and then diluted with 125 mL petroleum ether and then filtered again followed by concentration in vacuo. Acetone was stirred with drierite and then distilled under nitrogen and stored in a septum-sealed flask. Thionyl chloride was distilled under a nitrogen atmosphere and stored in a sealed tube. Tetramethylethylenediamine (TMEDA) was heated with n-BuLi in hexanes under a nitrogen atmosphere and distilled and stored in a septum-sealed flask over molecular sieves wrapped in foil. (Iodomethyl)trimethylsilane was prepared by known procedure.

Reactions were cooled to -100 °C to -105 °C via liquid N₂-ethanol bath, -40 °C or -78 °C via dry ice-acetone baths, to -15 °C via ice-salt baths and to 0 °C via ice-water baths. Silica gel flash column chromatography was performed using Merck grade 60
silica gel (230-400 mesh) and TLC analysis was carried out using Merck 60F-254 silica on glass plates. Visualizations of TLC plates was achieved using ultraviolet light, ceric ammonium molybdate, iodine vapors, or potassium permanganate. Microwave experiments were conducted in a CEM Discovery Series microwave reactor in sealed reaction vessels with instrument-based temperature and pressure monitoring.

\(^1\)H and \(^{13}\)C NMR spectra were recorded on Bruker ARX 500 (125 MHz) or a Varian Unity Inova 500 (125 MHz) spectrometer in CDCl\(_3\) at 25 °C unless otherwise noted. \(^1\)H chemical shifts are reported in ppm (δ units) downfield from tetramethylsilane. Solvent peaks were used as internal references for all \(^{13}\)C NMR (chloroform δ 77.16 and dimethylsulfoxide δ 39.51). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet), coupling constants (Hz), and number of protons. IR spectra were recorded on a Thermo Nicolet FT200 FT-IR spectrometer with an attenuated total reflectance (ATR) head. High-resolution mass spectra (HRMS) in CI mode were obtained on a Waters GC-TOF mass spectrometer (GCTPremier) employing a direct insertion probe and methane as the reagent gas. Heptacosa was used as an internal reference. Data analysis was performed in automated fashion using Waters software. For ESI mode, HRMS were obtained on a Waters LC-TOF mass spectrometer (LCT-XE Premier) using electrospray ionization in positive mode.
5.2. Experimental Procedures and Compound Characterization Data

5.2.1. Procedure For Synthesis of α-Amino Ketones:

A solution of 2-hydroxycyclohexanone dimer (1 eq) dichloromethane, and amine (1.2 eq) were stirred at room temperature overnight. The solvent was removed in vacuo and the residue was taken on without further purification.

5.2.2. Procedure For Synthesis of γ-Amino-β-Hydroxy-α-Diazoesters and γ-Siloxy-β-Hydroxy-α-Diazoesters:

To a -78 °C solution of α-amino ketone or α-siloxy ketone (4.61 mmol) and ethyl diazoacetate (0.83 mL, 7.89 mmol) in THF (44 mL) was added a solution of lithium diisopropylamine [prepared by the addition of n-butyllithium in hexanes (4.80 mL of a 1.43 M solution) to a 0 °C solution of diisopropylamine (1.04 mL, 7.42 mmol) in THF (12 mL)] via syringe pump over a period of 30 min. The mixture was maintained at -78 °C until complete conversion was achieved as monitored by TLC (~1 h). A saturated solution of NH₄Cl (50 mL) was added to the cold reaction mixture, and upon reaching room temperature the mixture was diluted further with saturated NH₄Cl solution. The aqueous layer was extracted three times with diethyl ether, the combined organic extracts were washed with brine, dried over MgSO₄, and filtered. The solvents were removed in vacuo and the residue was subjected to flash silica gel chromatography.

5.2.3. Procedures and NMR Data For All Other Compounds:

(2S)-t-butyl 1-(2-oxocyclohexyl)pyrrolidine-2-carboxylate (118):

Generated using procedure for synthesis of α-amino ketones. Provided a quantitative yield of an inseparable mixture the title compound as two
diastereomers. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 3.63 (ddd, $J = 8.7$, 4.3, 1.5 Hz, 1H), 3.56 – 3.48 (m, 2H), 3.46 (ddd, $J = 10.4$, 4.9 Hz, 1H), 3.42 – 3.34 (m, 0H), 3.02 – 2.94 (m, 3H), 2.93 – 2.81 (m, 3H), 2.51 – 2.44 (m, 1H), 2.44 – 2.37 (m, 1H), 2.31 – 2.06 (m, 8H), 1.98 – 1.79 (m, 14H), 1.78 – 1.60 (m, 6H), 1.46 (d, $J = 1.5$ Hz, 1H), 1.41 (d, $J = 1.6$ Hz, 17H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 211.62, 175.13, 174.37, 80.39, 69.18, 68.10, 63.62, 61.95, 51.80, 48.71, 41.94, 41.53, 34.21, 33.87, 30.57, 30.13, 28.26, 28.23, 28.19, 28.09, 28.01, 24.58, 24.22, 24.15, 24.08.

2-(phenylamino)cyclohexanone (120):

Generated using procedure for synthesis of $\alpha$-amino ketones. Provided an 80% yield of an inseparable mixture of the title compound and the oxidized enamine product (10: 1); the NMR shows a mixture of conformational and rotational isomers. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.16 (t, 2H), 6.69 (t, 1H), 6.59 (d, 2H), 4.87 (bs, 1H), 3.97 (dd, $J = 12.3$, 5.8, 1.5 Hz, 1H), 2.65 (m, 1H), 2.56 (m, 1H), 2.39 (tdd, $J = 13.4$, 6.3, 1.5 Hz, 1H), 2.13 (m, 1H), 1.90 (m, 1H), 1.86 – 1.74 (m, 1H), 1.68 (m, 1H), 1.41 (qd, $J = 12.8$, 3.7 Hz, 1H).

Diazooester (130):

Generated using procedure for synthesis of $\gamma$-amino-$\beta$-hydroxy-$\alpha$-diazosteres. Flash silica gel chromatography (EtOAc: Hexanes: Triethylamine = 1: 4: 0.02) to provide 55% yield of an inseparable mixture of diastereomers of the title compound as a yellow oil. $R_f = 0.77$ (EtOAc: Hexanes = 1: 50).


\[ \text{Diazoester (131):} \]

\[
\begin{align*}
\text{Generated using procedure for synthesis of } \gamma\text{-amino-} \beta\text{-hydroxy-} \alpha\text{-di}zoesters. \text{ Flash silica gel chromatography (EtOAc: Hexanes:} \\
\text{Triethylamine = 1: 4: 0.02) to provide 84\% yield of an inseparable mixture of} \\
\text{diastereomers of the title compound as a yellow oil. } R_f = 0.58 \text{ (EtOAc: Hexanes = 1:} \\
\text{4); } ^1H \text{ NMR (500 MHz, Chloroform-}d) \delta 7.21 - 7.15 (m, 3H), 6.75 - 6.69 (m, 2H), \\
6.66 (d, J = 7.5, 2.5, 1.9 Hz, 1H), 6.60 (d, 2H), 4.23 (q, J = 7.1, 5.1, 2.6 Hz, 3H), 3.90 \\
t (1H), 3.39 (dd, 1H), 2.30 - 2.24 (m, 1H), 2.04 - 1.97 (m, 1H), 1.92 - 1.83 (m, 1H), \\
1.82 - 1.75 (m, 2H), 1.75 - 1.72 (m, 1H), 1.70 (t, J = 3.4 Hz, 0.5Hz), 1.68 (t, J = 3.6 Hz, \\
0.5H), 1.63 - 1.56 (m, 2H), 1.54 - 1.42 (m, 1H), 1.41 - 1.33 (m, 1H), 1.29 - 1.24 (m, \\
4H); ^13C \text{ NMR (126 MHz, CDCl}_3) \delta 168.54, 168.20, 147.48, 147.06, 129.56, 129.49, \\
129.44, 118.00, 117.60, 113.80, 113.42, 113.24, 73.13, 72.96, 61.12, 61.00, 55.69, \\
\end{align*}
\]

105
1H NMR (500 MHz, Chloroform-d) δ 4.78 (bs, 1H), 3.59 (d, 1H), 3.21 (d, J = 13.3, 3.7 Hz, 1H), 1.99 (bs, 2H), 1.94 (bs, 1H), 1.63 (bd, J = 13.3, 7.6 Hz, 1H), 1.46 (s, 9H), 1.39 (bd, J = 13.6, 4.3 Hz, 1H), 1.00 (d, J = 7.0 Hz, 3H); 13C NMR (126 MHz, CDCl3) δ 178.4, 157.0, 81.0, 54.5 (br), 47.3 (br), 29.0, 27.7, 27.6, 22.2, 17.3; mass calculated for C_{12}H_{20}NO_{4}–: 242.1, found: 242.1; [α]_{D}^{20} = −9.8, (c 0.235, CH3OH).
(S)-1-t-butyl 2-ethyl 5-oxopiperidine-1,2-dicarboxylate (192):

A solution of 191 (1.0804 g, 3.61 mmol) in benzene (7 mL) was added dropwise to a suspension of Rh$_2$(OAc)$_4$ (16.9 mg, 0.038 mmol) in benzene (45 mL) and then heated to reflux for 2 hours. The reaction mixture was then concentrated in vacuo and the residue was subjected to silica gel flash column chromatography (EtOAc: Hexanes = 1: 5) to provide 0.6878 g (70% yield) of the title compound as a yellow oil. $R_f = 0.21$ (EtOAc: Hexanes = 1: 5); NMR is a mixture of rotamers; $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 4.80 (t, $J = 6.4$ Hz, 0.5H), 4.58 (t, $J = 7.2$ Hz, 0.5H), 4.39 (d, $J = 19.0$ Hz, 0.5H), 4.33 – 4.13 (m, 3H), 3.90 (dd, $J = 28.4$, 18.9 Hz, 1H), 2.57 – 2.27 (m, 3H), 2.27 – 2.15 (m, 0.5H), 2.15 – 2.01 (m, 0.5H), 1.46 (d, $J = 13.2$ Hz, 9H), 1.30 (q, $J = 7.2$ Hz, 3H); $[\alpha]^{20}_D = +5.9^\circ$ (c 1.915, CHCl$_3$).

(S)-1-t-butyl 2-ethyl 5-methyleneepiperidine-1,2-dicarboxylate (193):

To 0 °C a solution of i-Pr$_2$NH (0.56 mL, 3.97 mmol) in THF (5 mL) was added dropwise a 1.59 M solution of n-BuLi in hexanes (2.52 mL, 4.01 mmol). After stirring 10 minutes the solution was added dropwise to a 0 °C solution of methyltriphenylphosphonium bromide (1.3193 g, 3.69 mmol) in THF (4 mL). After stirring 1.5 hours, 192 (0.8337 g, 3.07 mmol) in THF (1 mL) was added dropwise and the reaction was allowed to warm to rt and stirred for an additional 1.5 hours. The reaction was then quenched by the addition of a saturated solution of NH$_4$Cl (5 mL) and the mixture was extracted three times with EtOAc (5 mL), and the combined organic layers were dried over MgSO$_4$ and filtered. The solvents were
removed *in vacuo* and the residue was subjected to silica gel flash column chromatography (EtOAc: Hexanes = 1: 9) to provide 0.48 g (58% yield) of the title compound as a yellow oil. \( R_f = 0.42 \) (EtOAc: Hexanes = 1: 5); NMR is a mixture of rotamers; \(^1\)H NMR (500 MHz Chloroform-\( d \)) \( \delta \) 4.87 (d, \( J = 17.8 \) Hz, 1H), 4.78 (s, 1H), 4.22 (m, 2H), 3.79 – 3.57 (m, 1H), 2.38 – 2.20 (m, 2H), 2.09 (bd, \( J = 14.9 \) Hz, 1H), 1.77 (m, 1H), 1.46 (d, 9H), 1.29 (t, \( J = 7.1 \) Hz, 2H), 1.00 – 0.87 (m, 1H); \([\alpha]_D^{20} = -53.9^o\) (c 0.54, CHCl\(_3\)).

**(S)-t-butyl 2-(hydroxymethyl)-5-methyleneepiperidine-1-carboxylate (203):**

\[
\begin{align*}
\text{N} & \quad \text{OH} \\
\text{Boc} & \quad \text{H}
\end{align*}
\]

A solution of 193 (0.5055g, 1.88 mmol) in THF (3.7 mL) was added to a 0 \(^o\)C solution of lithium aluminum hydride (0.1241 g, 3.27 mmol) in THF (2.3 mL). The Reaction was stirred at 0 \(^o\)C for 2 hours followed by the addition of H\(_2\)O (0.12 mL) then 15% NaOH (0.12 mL), then additional H\(_2\)O (0.36 mL). The mixture was then filtered and concentrated *in vacuo* to provide 0.4201 g (99% yield) of the title compound, which was taken on without further purification. \(^1\)H NMR (500 MHz, Chloroform-\( d \)) \( \delta \) 4.94 – 4.82 (s, 1H), 4.77 (s, \( J = 1.5 \) Hz, 1H), 4.40 – 4.21 (m, 2H), 3.81 (dd, \( J = 11.0, 8.4 \) Hz, 1H), 3.67 (dd, \( J = 11.1, 5.5 \) Hz, 1H), 3.59 (bd, \( J = 14.8 \) Hz, 1H), 2.35 – 2.26 (m, 1H), 2.26 – 2.17 (m, 1H), 1.76 (m, \( J = 16.9, 6.7, 5.2 \) Hz, 2H), 1.47 (s, 9H).

**(2S,5S)-tert-butyl 2-(hydroxymethyl)-5-methylpiperidine-1-carboxylate (204):**

\[
\begin{align*}
\text{N} & \quad \text{OH} \\
\text{Boc} & \quad \text{H}
\end{align*}
\]

A suspension of 203 (0.0167g, 0.0741 mmol) and PtO\(_2\) (7.2mg, 0.0317
mmol) in EtOAc (2.5 mL) was stirred in a round bottom flask under 1 atmosphere of H₂ for 19 h. The reaction mixture was then filtered through Celite and the solvents were removed in vacuo to provide 0.0167g (100% yield) of a [ratio] of diastereomers (unknown which diastereomer is the major) of the title compound. \(^1\)H (500 MHz, Chloroform-\(d\)) \(\delta\) 4.03 – 3.94 (m, 1H), 3.79 (dd, \(J = 11.3, 8.6\) Hz, 1H), 3.64 (dd, \(J = 11.3, 4.9\) Hz, 1H), 3.41 – 3.32 (m, 1H), 3.27 (m, \(J = 13.6, 3.6\) Hz, 1H), 1.78 (m, \(J = 12.6, 10.2, 8.4, 5.3, 3.0\) Hz, 3H), 1.54-1.37 (m, 3H), 1.46 (s, 9H), 1.00 – 0.93 (d, 3H).

**Diazoster (216):**

\[
\begin{align*}
\text{Flash silica gel chromatography (EtOAc: Hexanes: Triethylamine = 1: 4: 0.02) to provide } & 0.5712 \text{ g (35\% yield over two steps from 219) of the title compound as a yellow oil. } \text{R}_f = 0.66 \text{ (EtOAc: Hexanes: Triethylamine = 1: 4: 0.02); } \text{\(^1\)H NMR (500 MHz, Chloroform-\(d\)) } \delta \text{ 4.30 – 4.20 (m, 1H), 4.20 – 4.10 (m, 1H), 3.02 – 2.90 (m, 1H), 2.53 (d, 1H), 2.50 – 2.38 (m, 1H), 2.28 (d, 1H), 2.05 – 1.92 (m, 1H), 1.91 – 1.76 (m, 1H), 1.75 – 1.66 (m, 1H), 1.66 – 1.52 (m, 3H), 1.51 – 1.39 (m, 1H), 1.26 (t, } J = 7.1, 1.0 \text{ Hz, 3H), 1.19 – 1.07 (m, 1H), 1.07 – 0.94 (m, 1H), 0.02 (d, } J = 1.1 \text{ Hz, 9H); } \text{\(^{13}\)C NMR (126 MHz, CDCl}_3\) } & \delta \text{ 166.92, 70.58, 70.01, 60.30, 52.30, 37.76, 32.77, 32.42, 30.49, 21.39, 19.12, 14.70, -1.31.}
\end{align*}
\]

**Aspidospermine core (217):**

A solution of 262 (0.0550 g, 0.113 mmol), MeCN (5 mL), and cesium fluoride (40.1 mg, 0.264 mmol) were heated to reflux for 2 hours, after
which the reaction was chilled to rt and the reaction was poured onto water (5 mL). The aqueous layer was extracted three times with diethyl ether (2.5 mL), the organic layers were combined, dried over MgSO$_4$, and filtered. The solvents were removed *in vacuo*, and the residue was subjected to silica gel flash column chromatography (CH$_2$Cl$_2$: MeOH: Et$_3$N = 95: 5: 0.1) to provide 0.0201 g (68% yield) of the title compound. R$_f$ = 0.34 (CH$_2$Cl$_2$: MeOH: Et$_3$N = 95: 5: 0.1); $^1$H NMR (500 MHz, Chloroform-d) δ 4.21 (q, $J$ = 7.1, 2.0 Hz, 1H), 4.20 (q, $J$ = 7.1, 2.0 Hz, 1H), 3.68 (bdt, $J$ = 14.5 Hz, 1H, C11), 3.49 (bd, $J$ = 17.1 Hz, 1H, C8), 3.41 (d, $J$ = 14.5 Hz, 1H, C11), 3.33 (bs, 1H, C6), 2.72 (bd, $J$ = 10.4 Hz, 1H, C2), 2.44 – 2.16 (m, 2H, C2), 2.13 – 1.85 (m, 2H, C8 & C13), 1.82 – 1.10 (m, 18H), 0.84 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (126 MHz, Chloroform-d) δ 165.30, 155.54, 124.05, 73.36, 60.12, 59.93, 50.22, 35.57, 33.89, 32.28, 26.53, 26.26, 19.99, 18.82, 14.35, 7.44.

**Amino alcohol (219):**

A solution of amino alcohol 220 (1.0274 g, 6.62 mmol), (iodomethyl)-trimethylsilane (2.0 mL, 13.5 mmol), DMF (40 mL), and triethylamine (2.80 mL, 20.1 mmol) was heated to 80 °C for 24 hours. The solvents were removed *in vacuo* and the residue was dissolved in EtOAc (20 mL) and washed with water (20 mL). The organic layer was dried over MgSO$_4$, filtered, and the solvents were removed *in vacuo* to provide an impure 1.2065 g (76% yield) of the title compound, which was taken on without further purification. $^1$H NMR (500 MHz, Chloroform-d) δ 4.57 (s, 1H), 3.64 (ddt, $J$ = 12.0, 4.0, 1.9 Hz, 1H), 3.12 (d, $J$ = 15.8 Hz, 1H), 2.94 – 2.83 (m,
3-(3-methoxyphenyl)-N-((trimethylsilyl)methyl)propan-1-amine (254):

(Iodomethyl)trimethylsilane (90 μL, 0.607 mmol) was added to a refluxing solution of aminoalkylanisole 253 (0.0944g, 0.571 mmol) and acetonitrile (10 mL) over a 2 hour period. The reaction mixture was heated for an additional 22 hours. After cooling to room temperature the solvent was removed in vacuo and the residue was dissolved in CHCl₃ (10 mL) and the organic layers was treated with a 10% sodium hydroxide solution until the aqueous phase was pH 14. The organic layer was separated, dried over MgSO₄, and filtered. The solvent was removed in vacuo and the residue was subjected to silica gel flash column chromatography (EtOAc: Hexanes = 1: 4) to provide 0.1153 g (80% yield) of the title compound. Rₚ = 0.48 (EtOAc: Hexanes = 1: 4); ¹H NMR (500 MHz, Chloroform-d) δ 7.21 (t, J = 7.8 Hz, 1H), 6.80 (ddd, J = 7.5, 1.7, 0.9 Hz, 1H), 6.78 – 6.71 (m, 2H), 3.81 (s, 3H), 2.66 (dt, J = J = 17.0, 7.5 Hz, 4H), 2.08 (s, 2H), 1.89 – 1.77 (p, 2H), 0.06 (s, 9H); [α]D²⁰ = -53.9° (c 0.54, CHCl₃).

3-(5-methoxycyclohexa-1,4-dienyl)-N-((trimethylsilyl)methyl)propan-1-amine (255):
Sodium metal (0.988 g, 43 mmol) was slowly, to avoid bronzing of
the sodium, added to a -78 °C solution of aminoalkylanisole 254
(0.8028 g, 3.19 mmol), EtOH (1.3 mL), THF (16 mL), and ammonia (16 mL). The
reaction mixture was stirred for 5 hours and then excess sodium was quenched by the
addition of EtOH (5 mL) and the ammonia was allowed to evaporate under a stream of
nitrogen while warming to room temperature. A brine solution (20 mL) was then
added to the reaction mixture, which was extracted three times with CHCl₃ (10 mL).
The organic extracts were washed with H₂O (20 mL), dried over MgSO₄, and filtered.
The solvents were removed in vacuo to provide 0.6984 g (86% yield) of the title
compound as an oil and taken on without further purification; ¹H NMR (500 MHz,
Chloroform-d) δ 5.46 – 5.38 (m, 1H), 4.63 (bt, J = 4.5, 3.5, 1.1 Hz, 1H), 3.56 (s, 3H),
2.85 – 2.74 (m, 2H), 2.68 – 2.56 (m, 4H), 2.06 (s, 2H), 2.05 – 1.99 (bt, 2H), 1.67 – 1.59
(m, 2H); [α]D²⁰ = -53.9° (c 0.54, CHCl₃).

3-((3-((trimethylsilyl)methylamino)propyl)cyclohex-2-enone hydrochloride (256):
A solution of 255 (1.9672 g, 7.76 mmol), 10% HCl (7.8 mL), and
THF (80 mL) was stirred at room temperature for 12 h. Then the
solvent was removed in vacuo and the residue was dissolved in CH₂Cl₂, dried over
MgSO₄, and filtered. The solvents were removed in vacuo to provide 2.0590 g (96% yield) of the title compound as a white solid, that was taken on without further
purification; ¹H NMR (500 MHz, Chloroform-d) δ 9.38 (s, 2H), 5.91 (s, J = 1.7 Hz,
1H), 3.06 – 2.88 (m, 2H), 2.46 – 2.29 (m, 8H), 2.25 – 2.10 (m, 2H), 2.08 – 1.95 (m,
2H), 1.82 (bs, 2H), 0.30 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 199.57, 163.94, 126.08, 50.46, 37.49, 37.28, 34.80, 29.53, 22.57, 22.43, 1.56

**Free base of (256):**

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 5.91 (s, $J = 1.4$ Hz, 1H), 2.65 (t, $J = 8.1$, 7.6 Hz, 2H), 2.38 (t, $J = 7.4$, 6.0 Hz, 2H), 2.35 – 2.30 (t, 2H), 2.27 (t, $J = 7.8$ Hz, 2H), 2.07 (s, 2H), 2.05 – 1.97 (m, 2H), 1.77 – 1.66 (p, 2H), 0.07 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 199.52, 166.16, 125.55, 53.69, 40.00, 37.25, 35.63, 29.58, 26.80, 22.65, -2.62.

**t-butyl 3-(3-oxocyclohex-1-enyl)propyl((trimethylsilyl)methyl)carbamate (257):**

Di-$t$-butyl dicarbonate was added in portion to a 0 °C solution of 256 (1.9240g, 6.97), 4-dimethyl-aminopyridine (40 mg, 0.328 mmol), MeCN (25 mL), and trimethylamine (0.98 mL, 7.03 mmol), and the reaction was allowed to warm to rt and stirred for 3 hours. The solvent was removed in vacuo and the residue was subjected to silica gel flash column chromatography (EtOAc: Hexanes = 1: 4) to provide 1.7020 g (72% yield) of the title compound as a yellow-green oil. $R_t = 0.21$ (EtOAc: Hexanes = 1: 4); $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 5.93 – 5.85 (s, 1H), 3.18 (bd, $J = 7.5$ Hz, 2H), 2.71 (s, 2H), 2.36 (t, $J = 6.7$ Hz, 2H), 2.33 – 2.26 (t, 2H), 2.24 – 2.15 (t, 2H), 2.00 (p, $J = 6.4$ Hz, 2H), 1.45 (s, 9H), 0.06 (s, 9H); $^{13}$C shows rotational isomers $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$199.66,
Silyl enol ether (258):

A solution of 257 (0.6154 g, 1.81 mmol) in THF (1 mL) was added to a 0 °C homogeneous solution of THF (8 mL), LiCl (19.0 mg, 0.448 mmol), and CuI (51.8 mg, 0.272 mmol) followed by (CH₃)₃SiCl (0.25 mL, 1.97 mmol) and trimethylamine (0.30 mL, 2.15 mmol). After stirring for 10 minutes, a 3M ethylmagnesium bromide solution in diethyl ether (0.72 mL, 2.16 mmol) was slowly added via syringe. After stirring for 0.5 h, the solution was poured onto a saturated aqueous ammonium chloride solution (10 mL), extracted three times with diethyl ether (5 mL), and the organic layers were combined, dried over MgSO₄, and filtered. The solvent was removed in vacuo and the residue was subjected to silica gel flash column chromatography (EtOAc: Hexanes = 1: 4) to provide 0.7107 g (89% yield) of the title compound as a clear colorless oil. Rf = 0.89 (EtOAc: Hexanes = 1: 4); ¹H NMR (500 MHz, Chloroform-d) δ 4.63 (s, J = 1.3 Hz, 1H), 3.22 – 3.01 (m, 2H), 2.71 (s, 3H), 1.98 – 1.89 (t, 2H), 1.65 (p, J = 6.6 Hz, 3H), 1.52-1.38 (m, 2H), 1.45 (s, J = 3.7 Hz, 11H), 1.31 (m, J = 13.7, 10.6, 7.0 Hz, 3H), 1.20 (m, J = 16.5, 8.5 Hz, 1H), 0.79 (t, J = 7.5 Hz, 3H), 0.18 (s, 9H), 0.06 (d, J = 1.2 Hz, 9H); ¹³C NMR (126 MHz, Chloroform-d) δ 155.44, 149.85, 112.91, 78.87, 78.55, 50.03, 49.20, 38.10, 37.75, 37.04, 36.70, 32.54, 31.88, 31.73, 29.89, 28.50, 22.55, 19.45, 8.31, 2.64, 0.37, -1.48
**α-Silyloxy Ketone (259):**

A freshly prepared 0.05 M solution of dimethyldioxirane in acetone (6.5 mL, 0.520 mmol) was chilled to 0 °C and added dropwise to a 0 °C solution of 258 (0.1781 g, 0.403 mmol) in CH₂Cl₂ (5). After the reaction had gone to completion, monitored by TLC, the volatiles were removed in vacuo, and the residue was dissolved in dry CH₂Cl₂ (5 mL) followed by the addition of imidazole (93.0 mg, 1.37 mmol) and 4-dimethyl-aminopyridine (16.2 mg, 0.132 mmol). Then (CH₃)₃SiCl chloride (0.15 mL, 1.18 mmol) was added and the reaction was stirred overnight. The next day Aqueous ammonium chloride (5 mL) was added, the layers were separated, and the aqueous layer was extracted three times with CH₂Cl₂ (2 mL). The organic layers were combined, dried over MgSO₄, and filtered. The solvents were removed in vacuo, and the residue was subjected to silica gel flash column chromatography (EtOAc: Hexanes = 1: 4) to provide 0.1106 g (65% yield) of the title compound. Rf = 0.79 (EtOAc: Hexanes = 1: 4); ¹H NMR (500 MHz, Chloroform-d) δ 3.91 – 3.75 (m, 1H, C₅), 3.07 (m, J = 19.1 Hz, 2H, C10), 2.81 – 2.65 (m, 2H, C12), 2.54 (m, J = 12.7, 6.2 Hz, 1H, C1), 2.27 – 2.12 (m, 1H, C1), 1.84 – 1.62 (m, 3H), 1.59 – 1.41 (m, 3H), 1.46 (s, 9H)1.37 (m, 1H), 1.27 – 1.12 (m, 1H), 0.81 (dt, J = 47.2, 7.5 Hz, 3H), 0.11 (s, 9H), 0.07 (d, J = 4.0 Hz, 9H); ¹³C NMR (126 MHz, Chloroform-d) δ 211.61, 155.36, 81.17, 78.71, 50.02, 49.47, 45.23, 38.72, 38.25, 29.46, 28.49, 25.97, 24.40, 21.53, 21.25, 20.61, 7.49, 6.97, 0.16, 0.11, -1.49.

**Diazoester (260):**

115
Flash silica gel chromatography (EtOAc: Hexanes = 1: 4) to provide 73% yield of the title compound as a yellow oil. Rf = 0.55 (EtOAc: Hexanes = 1: 9); 1H NMR (500 MHz, Chloroform-d) δ 4.29 – 4.12 (m, 2H), 4.07 (d, J = 4.5 Hz, 1H), 3.36 – 3.19 (m, 1H), 3.19 – 2.92 (m, 1H), 2.89 – 2.61 (m, 2H), 2.14 – 2.00 (m, 1H), 2.00 – 1.86 (m, 1H), 1.81 – 1.59 (m, 2H), 1.57-1.32 (m, 5H), 1.45 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H), 0.87 – 0.76 (m, 3H), 0.13 (d, J = 6.0 Hz, 9H), 0.07 (s, 9H); 13C NMR (126 MHz, CDCl3) δ 165.77, 155.40, 78.96, 72.65, 60.25, 53.39, 41.12, 34.69, 28.51, 16.85, 14.57, 7.78, 0.57, -1.50.

Tethered Aldehyde Ynoate (261):

In(OTf)3 (0.7500g, 1.33 mmol) was added in one portion to a -5 °C solution of CH2Cl2 (25 mL), and 260 (0.6902 g, 1.21 mmol), and the reaction was allowed to stir overnight at -5 °C for 4 h. The reaction was quenched with a saturated solution of NaHCO3 (15 mL), and the aqueous layer was extracted three times with CH2Cl2 (10 mL). The combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. The solvents were removed in vacuo, and the residue was subjected to silica gel flash column chromatography (EtOAc: Hexanes = 1: 4) to provide 0.3614 g (66% yield) of the title compound. Rf = 0.64 (EtOAc: Hexanes = 1: 4); 1H NMR (500 MHz, Chloroform-d) δ 9.43 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.15 (bs, 2H), 2.71 (s, 2H), 2.35 (t, J = 6.9 Hz, 2H), 1.64 – 1.52 (m, 8H), 1.52 – 1.35 (m, 5H), 1.46 (s, 9H), 1.32 (t, J = 7.1 Hz, 3H), 0.82 (t, J = 7.5 Hz, 2H), 0.10 – 0.04 (s, 9H); 13C NMR (126 MHz, Dimethylformaide-d) δ 206.55, 155.16, 153.26, 88.95, 78.29,
Iminium Triflate Salt (262):

In a round bottom flask were combined molecular sieves, CH$_2$Cl$_2$ (12 mL), and 260 (0.4193 g, 0.733 mmol). To this was added in one portion In(OTf)$_3$ (0.4162 g, 0.741 mmol), and the reaction was allowed to stir overnight at room temperature. The reaction was quenched with H$_2$O (2 mL) and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was then triturated with hexanes to provide 0.2901 g (81% yield) of the title compound as a brownish orange oil, which was taken on without further purification. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.45 (s, 0.5H), 4.16 (q, $J$ = 7.1 Hz, 2H), 3.86 – 3.60 (m, 4H), 2.36 (t, $J$ = 6.4 Hz, 2H), 1.97 (h, $J$ = 6.1 Hz, 2H), 1.78 – 1.58 (m, 6H), 1.58 – 1.47 (m, 1H), 1.44 – 1.37 (m, 1H), 1.26 (t, $J$ = 7.1 Hz, 3H), 0.94 (t, $J$ = 7.4 Hz, 3H), 0.22 – 0.12 (s, 9H); $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 179.69, 153.59, 87.77, 73.90, 61.85, 55.43, 42.88, 35.02, 29.27, 25.02, 21.81, 18.70, 18.38, 13.95, 7.85, 1.75, 2.62

3-((t-butyldimethylsilyloxy)(ethoxy)methylene)-1-methyl-2,3,5,6,7,7a-hexahydro-1H-indole (274):

Hexamethylphosphoramide (1.5 mL) was added to a -78 °C solution of LDA [a 1.5 M solution of n-BuLi in hexanes (0.97 mL, 1.46 mmol) was...
added dropwise to a 0 °C solution of diisopropylamine (0.22 mL, 1.56 mmol) an THF (2 mL)], which turned greenish-black. Next a solution of 84 (0.2535 g, 1.21 mmol) in THF (0.5 mL) was added dropwise, and the reaction was stirred at -78 °C for 1 hour, after which freshly distilled t-butyldimethylsilyl triflate (0.40 mL, 1.86 mmol) was added dropwise and the reaction was stirred for an additional hour at -78 °C and then quenched cold with a solution of NaHCO₃ (2 mL). The organic layer was then dried over MgSO₄, filtered, and the solvents were removed in vacuo. The residue was then triturated with pentane and filtered, and the solvent was removed in vacuo to provide 0.2380 g (60% yield) of an inseparable mixture of stereoisomers (E & Z) of the title compound, which was taken on without further purification. ¹H NMR (500 MHz, Chloroform-d) δ 5.85 (s, J = 6.3, 3.2 Hz, 1H), 3.99 – 3.79 (m, 2H), 3.65 (dd, J = 27.0, 11.7 Hz, 1H), 2.84 (d, J = 11.7 Hz, 1H), 2.74 (d, J = 11.6 Hz, 1H), 2.65 (dd, J = 9.3, 1.4 Hz, 5H), 2.53 (m, J = 5.6, 3.2 Hz, 1H), 2.35 (s, J = 1.6 Hz, 3H), 2.26 – 2.00 (m, 3H), 1.85 (m, J = 8.3, 4.3 Hz, 1H), 1.50 (ddq, J = 17.4, 10.3, 4.6, 4.1 Hz, 1H), 1.27 (ddd, J = 17.7, 7.8, 6.5 Hz, 4H), 1.22 – 1.08 (m, 1H), 0.96 (d, J = 7.9 Hz, 11H), 0.92 (t, J = 1.5 Hz, 9H), 0.24 – 0.15 (m, 6H), 0.13 – 0.07 (s, 5H).

5.3. References

CHAPTER 6: COMPREHENSIVE BIBLIOGRAPHY


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Listed in order of appearance are the NMR spectra of:
118, 120, 130, 131, 216, 260, 192, 193, 203, 151, 219, 254, 255, 256, 257, 258, 259,
262, 261, 217, 274
EtO₂C

217

f₁ (ppm)

-10 0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210

7.44 14.35 18.82 19.99 26.26 26.53 32.28 33.89 35.57 50.22 59.93 60.12 73.36 124.05 155.54 165.30 217

-73.36 -60.12 50.22 -35.57 -33.89 -32.28 -26.53 -26.35 -18.82 -14.35 -7.44

f₁ (ppm)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10