Synthesis of aza-tryptophan derivatives.

Edward Joseph. Brnardic

University of Windsor

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Synthesis of Aza-Tryptophan Derivatives

by

Edward Joseph Brnardic

A thesis submitted to the Faculty of Graduate Studies and Research through the School of Physical Sciences in partial fulfillment of the requirements for the Degree of Master of Science at the University of Windsor

Windsor, Ontario, Canada

September 1998
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Abstract

The preparation of racemic 7-azatryptophan from 7-azaindole has been accomplished. The aldol condensation of 1-tert-butoxycarbonyl-3-formyl-7-azaindole with methyl hippurate installed the carbon framework necessary for the intended product. Subsequent deoxygenation and deprotection of the indole ring, and the amino and acid functional groups yielded racemic 7-azatryptophan.

A variety of attempts to synthesize the enantiomerically pure form of 7-azatryptophan were considered. Of those, Evans' asymmetric glycine enolate aldol condensation, Baldwin's copper catalyzed Grignards for azidine ring opening, and Jackson's coupling reaction with aryl iodides were employed. Unfortunately though, all methods proved unrewarding.
You can’t win!

-Adrian Balboa, Rocky IV
Dedication

To my parents. Without them, this would not have been possible.
Acknowledgments

I would like to start by thanking Dr. James Green for his invaluable help throughout the last couple of years. The improvements that I have made both in a chemistry aspect and on a maturity level is a direct reflection on his leadership and teachings. (Whether he admits it or not!).

A special thanks goes to Dr. Malik Slussi of Allelix Biopharmaceuticals who was my first supervisor. He initially inspired me to pursue a graduate degree in chemistry, and made sure that I did not develop any bad habits. Malik trained me to always be organized, and it has paid dividends.

For their invaluable help I would like to thank Vivi Lazerescu (mass spec.), Mike Fuerth (NMR), Sandra Horton (administrative stuff), Jerry Vriesacker (stockroom and hearts player), and Pat Aroca (T.A. coordinator). Also included in invaluable help are Dr. J. M. McIntosh, and Dr. P. J. Dutton for giving advice whenever needed.

I would also like to thank those with whom I worked with: Richard Guo, Scott Peters, Jeanine Malikoti, Jay Kiser, Anne Charlton, Kevin McKay, Derrick Soong, Justine Taylor and especially Manoj Patel whom I worked with the longest and developed a good friendship.

I have also shared some memorable jokes (usually at their expense) with Dr. Steve Loeb’s group, with whom we shared a lab for a period of time. They consist of Dr. Steve Loeb, James Wisner, Derek Beauchamp, and Dave Tramontozzi. It has certainly been a blast.
Finally there have been two special people with whom I have become good friends with over the last two years. If only I could have the confidence in myself that they have shown in me time and time again.

Francine Salinitri was first a student in a lab that I had T.A.‘ed. From there, we developed a friendship that lasted over the past two years. I was fortunate enough to have Fran work for me this past summer to help complete my project (although I’m still trying to figure out which one of us was the boss). I want to thank her for everything that she has done.

Mike Siwek has also become a very good friend. Over the last two years we have had some good times (usually at each others expense i.e. Hearts, football), and it has certainly been memorable. One of the things that I will miss the most will be the daily conversations with Mike where we talked about everything and nothing.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>nBuLi</td>
<td>normal-butyllithium</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>azo-bis-isobutyronitrile</td>
</tr>
<tr>
<td>Boc</td>
<td>butyloxy carbonyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BPE</td>
<td>1,2-bis(phospholano)ethane</td>
</tr>
<tr>
<td>br s</td>
<td>broad singlet</td>
</tr>
<tr>
<td>Cbz</td>
<td>benzyloxy carbonyl</td>
</tr>
<tr>
<td>COD</td>
<td>1,5-cyclooctadienyl</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in ppm</td>
</tr>
<tr>
<td>DBAD</td>
<td>di-tert-butyl azodicarboxylate</td>
</tr>
<tr>
<td>de</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>DIPAMP</td>
<td>P, P-ethylenebis-[o-methoxyphenyl(phenyl)phosphine]</td>
</tr>
<tr>
<td>DMA</td>
<td>dimethyl acetimide</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DPAMPP</td>
<td>(1S,2R)-N,O-bis(diphenylphosphino)</td>
</tr>
<tr>
<td></td>
<td>-1,2-diphenyl-2-(N-methyl)aminoethanol</td>
</tr>
<tr>
<td>DuPHOS</td>
<td>1,2-bis((2R,5R)-2,5-</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalents</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution MS</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamine</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (NMR)</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>OTf</td>
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<td>o-tol</td>
<td>ortho-tolyl</td>
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<tr>
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<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
</tbody>
</table>
TMSCl  trimethylsilyl chloride
Tr    triphenylmethyl
Ts    para toluenesulfonyl
Synthesis of Aza-Tryptophan Derivatives

Introduction

The amino acid tryptophan is vital to the normal function of all living organisms. It serves a central role in the biosynthesis of proteins, peptides, enzymes, hormones, alkaloids, and other biologically important compounds. Currently there is a considerable amount of interest in the fluorescence of tryptophan as a vehicle for probing the structure and dynamics of proteins and peptides.\(^1\) Unfortunately, studying the fluorescence of tryptophan to monitor protein folding and unfolding becomes difficult if there is overlap in the fluorescence spectrum from other amino acids (i.e. tyrosine). This problem can be circumvented with the use of 7-azatryptophan (Figure 1), due to its unique spectroscopic properties and the fact that it can be substituted for tryptophan in many biological systems. Although 4, 5, and 6-azatryptophan are known,\(^{th}\) they are untested and could possibly possess unique spectroscopic properties as well. 7-Azatryptophan has also drawn additional interest with its effects on nitrogen fixation in certain algae.\(^2\)

![Figure 1: Enantiomers of 7-Azatryptophan](image)
7-Azatryptophan has been synthesized both chemically and enzymatically and is commercially available in racemic form, but efforts to resolve the racemate have thus far proved unrewarding. Of particular interest to our research is the (S)-isomer of 7-azatryptophan for in vitro protein synthesis. Recently, the (R)-isomer of 7-azatryptophan has been chemically synthesized, albeit in low yield (Figure 2). The key step involved the diastereoselective alkylation of the enolate of (1) with 1-(tert-butyloxycarbonyl-3-(iodomethyl)-7-azaindole (2).

![Chemical structures](image)

**Figure 2: Synthesis of (R)-7-Azatryptophan**

Although the alkylation afforded (3) in greater than 98% diastereomeric excess, low temperatures were required and the reaction proceeded very poorly (27% yield). Similar reactions were attempted on the 3-bromomethylindole, but the results were much less
desirable. The recent success of Cavallo\textsuperscript{7} with similar iminoglycinate alkylations on 3-bromomethyl indole derivatives (Figure 3) suggests that the nitrogen in the 7 position is disrupting the alkylation process of the 3-halomethyl-7-azaindole.

![Chemical structures](image)

\textbf{Figure 3: Synthesis of an (R)-Tryptophan Derivative}

There are a variety of synthetic approaches that were considered to be employed to obtain the target molecule, and since the other azaindoles have been synthesized,\textsuperscript{8} an approach that is successful can be applied to form 4, 5, and 6-azatryptophan. In view of the commercial availability of 7-azaindole, the most straightforward strategy for the synthesis of 7-azatryptophan is to selectively functionalize the intact indole system.
Since the C-3 position of 7-azaindole is nucleophilic, and the pseudo-benzylic site at C-3 is electrophilic,9 one can view the key step of the formation of 7-azatryptophan as the coupling of synthons (4) with (5) or (6) with (7) (Figure 4).

![Figure 4: Synthons Leading to 7-Azatryptophan](image)

A tempting approach to (S)-7-azatryptophan is to employ the general strategy of Fallis, but to instead couple the α-bromo indole with Schollkopf's chiral auxiliary (8) to furnish the desired tryptophan unit. The chiral auxiliary is derived from (R)-valine,10 and a major advantage to this reaction sequence is that after removal of the chiral auxiliary, (R)-valine ethyl ester can be isolated and re-used. In an analogous reaction sequence Cook11 was able to enantiospecifically synthesize tryptostatin A using this chiral auxiliary (Figure 5).
The high yields and enantiospecific nature of the reaction appears to be quite tempting, however, with the lack of success of Fallis with the alkylation of the α-bromo azaindole there may not be much success found by employing this strategy.

An appealing alternative to synthons (4) and (5) would be to employ the aldol condensation of the readily available 1-Boc-3-formyl-7-azaindole with a nucleophile. The asymmetric glycine enolate aldol reactions developed by Evans\textsuperscript{12,13} becomes the obvious choice. Evans has used, with great success, oxazolidinone chiral auxiliaries (9) for absolute and relative stereochemical control in aldol reactions with the (S)-acyloxazolidinone, giving the 4-(S) and 4,5-syn diastereomer predominantly. The
isothiocyanate (9) has performed admirably in the desired aldol process as the source of a glycine enolate equivalent when the reaction was mediated by stannous triflate (Figure 6).

![Chemical Structures]

**Figure 6: Asymmetric Glycine Enolate Aldol Reaction**

The high yields and high diastereoselection of this reaction are clear advantages, along with the ability to recover the oxazolidinone chiral auxiliary, but the only known methods to break the thiocarbamate ring may prove to be too harsh for the indole system to survive.
There also exist several specific routes which employ the coupling of synthons (6) and (7) to form 7-azatryptophan. Examples of synthon (7) include the β-lactone (10),\textsuperscript{14} the aziridine (11),\textsuperscript{15} and the 3-iodo-and 3-(tosyloxy) alanine derivatives (12 a and b)\textsuperscript{16} (Figure 7).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure7}
\caption{Approaches to Alanine Synthons}
\end{figure}

Based on the ready C-3 halogenation reaction of 7-azaindole,\textsuperscript{17} it is highly likely that the formation of the corresponding Grignard reagent will be possible. As a result, the employment of Vederas' serine derived β-lactone appears to be a suitable alternative to forming 7-azatryptophan and quite possibly the other azatryptophans. The mono-protected amino β-lactones (10) can be produced readily by cyclization of the corresponding serine derivatives under modified Mitsunobu conditions without loss of optical purity (Figure 8).\textsuperscript{18}
Figure 8: Synthesis of β-Lactones

The copper catalyzed Grignard reagents derived from the halotryptophans are expected to attack 10 at the β-position to afford the N-protected amino acids directly with negligible racemization. The main advantage of this method is the ability to remove all protecting groups in a single reductive step. Nevertheless, the required use of 6 equivalents of the Grignard reagent concerned is a clear disadvantage. An analogous reaction performed by Vederas proceeded in moderate yield (Figure 9).
Another serine-based analogue of synthon (7) that has the potential of undergoing nucleophilic attack is the aziridine (11). In 1989, Sato and Kozikowski\textsuperscript{19} reported that the treatment of protected aziridine carboxylates with indoles will give the corresponding tryptophans (Figure 10). The only Lewis acid found to activate the aziridine to ring opening in the initial work was zinc triflate. Recently Bennani\textsuperscript{21} et al have found that scandium (III) mediates the opening of aziridine carboxylates under milder conditions and gives higher yields. The aziridine of concern could be synthesized from (S)-serine in a number of steps.\textsuperscript{20}

*Yields are based on consumed aziridine*
The aziridine pathway with the most potential appeared to be the one developed by Baldwin\textsuperscript{22}. Baldwin reported that \textit{(S)-tert-}butyl-N-Boc aziridinecarboxylate reacts with copper "catalyzed" Grignard reagents to give protected \(\alpha\)-amino acids in moderate to good yields with negligible racemization (\textbf{Figure 11}). The disadvantages are that the aziridines are thermally unstable and that low temperatures are needed to obtain the highest selectivity of nucleophilic attack on the aziridine (i.e. attack at C-3 vs C-2).

\begin{center}
\begin{tikzpicture}[baseline=(current bounding box.center)]
\node at (0,0) \{\textbf{Figure 11: Aziridine Ring Opening by Copper Catalyzed Grignards}\};
\end{tikzpicture}
\end{center}

A different method of obtaining synthon (7) would be to synthesize \(\beta\)-iodo-\(\textit{(S)}\) alanine as reported by Viallefont\textsuperscript{16}. The reaction of organocuprates with the \(\beta\)-halogen compounds proceeds smoothly enough to retain configuration of the \(\alpha\)-carbon (>80\% ee) (\textbf{Figure 12}). Although the yields were respectable (60-80\%) for most saturated organocuprates, the aromatic cuprates employed by Viallefont gave far less nucleophilic attack product (13) and much more \(\beta\)-elimination product (14).
The problem of synthesizing enantiomerically pure protected β-arylanalines from a β-iodoalanine derivative was solved by Jackson. The protected β-iodoalanine (15) was converted into the organozine reagent (16) and reacted with aryl iodides at 50°C in the presence of catalytic bis(tri-o-tolylphosphine)palladium dichloride to give, in moderate to good yields, enantiomerically pure protected (S)-β-arylanine derivatives (17) (Figure 13).
Figure 13: Synthesis of Enantiomerically Pure Protected β-Aryl Alanines

Other possible methods of synthesizing 7-azatryptophan include methods of introducing the carbon framework onto the indole system and subsequently creating the asymmetric center. One of the most attractive methods of creating this asymmetry involves asymmetric hydrogenation. An excellent example of this approach was performed by Yokoyama,²¹ in which vinylation of an indole derivative with N-Boc dehydroalanine methyl ester (18) in the presence of Pd(OAc)$_2$ gave a dehydrotryptophan, which was later hydrogenated asymmetrically to give the (S)-amino acid enantiomer in high yield and high optical purity (Figure 14). Although the vinylation may be difficult and low yielding, this pathway is very tempting since good optical yields of the final product could be obtained and in a considerably limited number of steps from the starting materials.
A variety of chiral phosphine ligands were investigated in the asymmetric hydrogenation reaction, but only Rh(COD)$_2$BF$_4$/DIPAMP, developed by the Monsanto group, gave satisfactory optical yields (94% ee). However, there is recent work that suggests that a number of chiral phosphine based ligands would be suitable for hydrogenation catalysis. These include DuPHOS,$^{25}$ DPAMPP,$^{26}$ and Me-BPE.$^{27}$ A different method of potentially obtaining a similar vinyl product relates to work done by Schmidt.$^{28}$ The Wadsworth-Horner-Emmons condensation of (19) with (20) gave the corresponding dehydroamino
acid derivative (Figure 15). Enantioselective homogeneous hydrogenation with the \( \text{Rh}^{+1}\)\text{DIPAMP} catalyst lead to the desired product in greater than 98% ee.

![Chemical structure](image)

**Figure 15: Schmidt’s Vinylation and Hydrogenation of an Indole derivative**

One final approach that was worth consideration involved the cobalt mediated propargylation of indoles. Roth\textsuperscript{29} added a cobalt stabilized propargylic cation (21) to indole to give the 3-propargylic indole (Figure 16).
By employing the same methodology to 7-azaindole, followed by the monohydroboration of the resultant 1-alkynyl(trimethylsilane) (22) with dicyclohexylborane, which proceeds in a stereo-and regioselective manner one could in principle obtain the 1-boryl-1-silylalkene (23). The oxidation of (23) with aqueous sodium hydroxide and 5 equivalents of hydrogen peroxide (1 equiv. excess) would afford the desired carboxylic acid (24). With the carbon skeleton of 7-azatryptophan intact, asymmetric amination would be the final critical bond forming step involved in order to synthesize the desired product. Conversion of the aza-indole carboxylic acid to the mixed anhydride (25) followed by the addition of the aza-indole mixed anhydride to the lithiated oxazolidinone (26) (derived from (S)-phenylalanine) would afford the acyl oxazolidinone (27). The reaction of the derived lithium enolates of the acyl oxazolidinones with di-tert-butyl azodicarboxylate (DBAD) has been found to occur instantaneously at -78°C to afford the α-hydrazino derivative in
excellent yield and high diastereoselectivity. Application of this strategy to (27) would give (28): reduction of the N-N bond of the hydrazine and removal of the protecting groups\textsuperscript{32} would afford the desired azatryptophan (Figure 17). Evans also has reported an alternative to this approach which employs the α-azido analogue, prepared either by direct azidation of the enolate or nucleophilic substitution of the α-bromo acyl oxazolidinone\textsuperscript{33}.

![Chemical structures and reactions](image)

Figure 17: Proposed Enantiomeric Amination Leading to 7-Azatryptophan
Results and Discussion

Due to the relatively inexpensive chiral auxiliary and the ability to use one equivalent of each reagent, the Evans' acyl oxazolidinone aldol route was chosen for initial investigation. Prior to attempting this route it was necessary to test whether a simple aldol reaction with a 3-formyl-7-azaindole (31) was possible. Methyl hippurate, which is easily synthesized by the esterification of hippuric acid, was a suitable choice as a nucleophile since it would afford the protected β-hydroxy-7-azatryptophan upon aldol condensation. 3-Formyl-7-azaindole (31) has been synthesized previously by Fallis.\(^6\) Although the pKa of the pyrrole N-H bond is unknown,\(^14\) it was believed to be too acidic for the conditions of the aldol condensation, and therefore it was necessary to protect the pyrrole nitrogen. The first choice as a protecting group to the pyrrole nitrogen was the benzyl group, since in most cases benzyl groups are known to be removed easily by hydrogenation.\(^35\) 1-Benzyl-3-formyl-7-azaindole (32) was then synthesized in 3 steps from 7-azaindole (29) (Figure 18).
The Mannich reaction of 7-azaindole (29) with formaldehyde and dimethylamine afforded 7-azagramine (30) in 87% yield after a modification in the procedure of Fallis. The azagramine was then subjected to the conditions of a Sommelet reaction with hexamethylene tetramine in dilute propionic acid to afford 3-formyl-7-azaindole (31) in a moderate yield of 50%. Subsequent deprotonation of the indole N-H with sodium hydride followed by the addition of benzyl bromide yielded the benzyl protected product (32) in an acceptable yield (61%). It is noteworthy that an excess of sodium hydride could not be used since any sodium hydroxide formed upon quenching would destroy the
indole ring. To minimize this problem, saturated ammonium chloride or dilute hydrochloric acid were used to quench the reaction.

After the preparation of starting materials, the aldol condensation was investigated. Initially, methyl hippurate was deprotonated with 2 equivalents of LDA at -78°C to first remove the more acidic N-H and then the α-C-H. Upon addition of the aldehyde as a solution in THF, preferential attack of the carbanion on the aldehyde afforded protected β-hydroxy-7-azatryptophan (34) in 67% yield, as a mixture of both diastereomers (Figure 19). Attempts to separate the diastereomers proved unrewarding, so the diastereomeric mixture was used in subsequent reactions.

\[
\text{Ph} \quad \begin{array}{c} \text{N} \quad \text{O} \\ \text{OCH}_3 \end{array} \quad \begin{array}{c} \text{N} \quad \text{O} \\ \text{OCH}_3 \end{array} \quad \text{Ph} \quad \text{H} \quad \text{OCH}_3 \quad \text{Ph} \quad \text{H} \quad \text{OCH}_3
\]  

\[
\text{33} \quad \xrightarrow{+2 \text{ LDA}} \quad \text{32} \quad \xrightarrow{-78^\circ \text{C}} \quad \text{34}
\]  

\[
\text{34} \xleftarrow{\text{H}_2\text{O}} \quad \text{34}
\]
Figure 19: Aldol Condensation with Methyl Hippurate

The first attempt at removal of the pseudo-benzyl hydroxy function involved an $S_{N}1$ reaction at the $\beta$-carbon with triethylsilane in trifluoroacetic acid$^{38}$ (Figure 20). Surprisingly though, the product recovered did not come from the reduction of the alcohol but instead from the loss of water, affording the $\alpha$-$\beta$ unsaturated compound (35) in an undetermined stereochemical relationship.

![Chemical Reaction Diagram]

Figure 20: Elimination of Water from Aldol Product

Although this reaction would clearly remove any enantiomeric enrichment introduced at the $\alpha$ carbon in an asymmetric reaction, it affords the possibility of using asymmetric hydrogenation$^{34}$ to yield exclusively the $(S)$-enantiomer. In an attempt to determine if hydrogenation was indeed possible, compound (35) was subjected to palladium (5% on activated carbon) in THF under a hydrogen atmosphere, and after 60 h the reduced product (36) was in fact isolated (Figure 21). It was also interesting to find that hydrogenolysis reaction conditions did not remove the N-benzyl protecting group of the
indole ring: this lead to the use of a Boc group as an alternative protecting group since it has been shown to be more easily removed.\(^6\)

![Chemical structure](image)

**Figure 21: Hydrogenation of the Aldol Product**

Concern was then shifted back to attempting to remove the hydroxy group in a non-racemizing method. Radical reactions have in the past proven to be a method of accomplishing reductions without racemization problems at closely adjacent sites,\(^{39}\) so a variety of conditions were considered. In view of the elimination reaction that had occurred, attention was turned to a reductive method that involved transforming the hydroxy group into a xanthate (37) and then removal of the corresponding xanthate with tributyltin hydride. This reaction was discovered by Barton; the mechanism is radical in character and thus avoids the rearrangements in normal carbocation reactions.\(^{40}\) An attempt to form the xanthate\(^{41}\) by deprotonation of the alcohol with sodium hydride followed by the addition of carbon disulfide and methyl iodide resulted in a retro aldol reaction, giving back the protected 3-formyl-7-azaindole (32) in quantitative yield (Figure 22).
Considering what had occurred, milder conditions for the reduction of the alcohol (34) were investigated. The subsequent choice as a method of reducing the β-hydroxy unit was by hydrogenolysis type conditions. Since it is well known that benzylic alcohols are readily removed by such conditions, a hydrogenolysis reaction was attempted on compound (34). This, however, did not appear to be true of the pseudo-benzylic site of the indole ring as attempts to reduce the alcohol function by hydrogenolysis failed to consume any starting material. In another type of hydrogenolysis reaction, benzylic acetates have been found to be removed by a nickel chloride/sodium borohydride
reaction. The transformation of the alcohol to the acetate is accomplished in a pyridine and acetic anhydride solution, which is much milder than the conditions employed in attempting to form the xanthate. With the inability to remove the indole N-benzyl protecting group, the Boc protecting group was chosen in its place. The aldol condensation of the Boc protected aldehyde with methyl hippurate (33) was then carried out in 60% yield (Figure 23), with an unexpected additional advantage, as the aldol product diastereomers of the alcohol (39) were separable by flash column chromatography on silica gel. Normally, the assignment of syn and anti diastereomers in aldol adducts can be accomplished by observation of the coupling constants (\(J_{AB} = 2-6\) Hz for syn; \(J_{AB} = 7-10\) Hz for anti), although in this case both diastereomers have similar coupling constants (\(J_{AB} = 3.3\) Hz for diastereomer 1; \(J_{AB} = 3.2\) Hz for diastereomer 2). The similarities in coupling constants is probably due to hydrogen bonding of the ester carbonyl to the N-H of the benzamide in the anti isomer which results in a gauche relationship between \(H_A\) and \(H_B\). Another method for inferring the stereochemistry of the aldol product is by the geometry of the enolate. Generally, \(Z\) enolates tend to give \(syn\) aldols and \(E\) enolates tend to give \(anti\) aldols. However, the geometry of the enolate of methyl hippurate has not been reported in literature, and therefore it is difficult to assign the stereochemical nature of the diastereomers. Based on previous work, the lithium enolates of amino esters generally have the \(E\) configuration so it can be inferred that the major diastereomer is the \(anti\) one.
The transformation of the alcohol (39) to the acetate (40) by acetic anhydride in pyridine proceeded smoothly to afford the desired acetate in quantitative yield. Removal of the acetate functional group was then accomplished using anhydrous nickel chloride and sodium borohydride in a dry methanol solution, according to a procedure developed by He et al.\textsuperscript{43} to give the product (40) in 60\% yield. The Boc protecting group was also removed by the excess of sodium borohydride; this has also been observed by Fallis in attempts to reduce compound (38) to the corresponding alcohol.\textsuperscript{6} The removal of the Boc group was of no disadvantage since the azaindole no longer required protection. Subsequent removal of the remaining protecting groups was accomplished by refluxing compound (41) in 6 N HCl to yield racemic 7-azatryptophan (42) (Figure 24).
Figure 24: Synthesis of Racemic 7-Azatryptophan

With the success of this pathway it appeared promising that Evans' asymmetric glycine enolate aldol condensation\(^\text{12}\) could be used to afford the desired azatryptophans. In order to be able to attempt the Evans aldol condensation it first became necessary to synthesize the chiral auxiliary and the Lewis acid stannous triflate. The initial step in the synthesis of the chiral auxiliary featured the reduction of \((S\)-phenylalanine (43) to \((S\)-phenylalaninol (44). The oxazolidinone (45) was then synthesized by carefully heating a solution of \((S\)-phenylalaninol (44) in diethyl carbonate with a catalytic amount of potassium carbonate. The formation of the isothiocyanate (9) was accomplished in 3 steps from the oxazolidinone\(^\text{12}\) (45). (Figure 25).
Stannous triflate (48) was then prepared by the reaction of stannous chloride with trifluoromethanesulfonic acid. This highly air sensitive material required storage in a nitrogen glove box. The only method of testing the purity of stannous triflate that was
available was to attempt an aldol condensation on a small scale and monitor product formation. After aldol condensation of the isothiocyanate with the aldehyde was successful on a small scale, the reaction was repeated on a useful laboratory scale resulting in the formation of (49) in good yield (Figure 26). One problem that was encountered was that the product could not be purified by column chromatography on silica gel. Chromatography resulted in an impurity which was believed to be from the epimerization of one of the new chiral centers, although it could not be separated from the product. An additional problem with purification on silica gel was that a retro aldol reaction was occurring. An attempt to purify the product on basic alumina was also unrewarding as no indole ring was recovered from the column. However, it was fortunate that the reaction would usually proceed in greater than 90% conversion and the residue could usually be recrystallized from ethyl acetate/hexanes to afford (4S)-3-((4\,\text{S}, 5\,\text{R})-5'-\text{t}-\text{Butyloxycarbonyl-7-azaindol-3-yl}-2'\,-\text{thioxazolidinylcarbon-4-yl})-4-\text{phenethyl}-2\,-\text{oxazolidinone (49). The assignment for the chiral centres was based on analogous work by Evans, with similar coupling constants of the hydrogens on the newly formed chiral carbons (Compound (49) J = 5.2, Evans\^{12} J = 4.9).}
Although success was found in carrying out the aldol condensation, all attempts to reduce the C-O bond of the cyclic thiocarbamate proved to be unrewarding. Initially attempts were made to follow the work of Evans\textsuperscript{12} by removing the chiral auxiliary with the methoxide ion derived from methylmagnesium bromide and methanol, but those conditions proved to be harsh on the indole ring. After careful experimentation, some methyl ester (50) could be obtained (approx. 50\%), but it could not be separated from the chiral auxiliary (45) (\textbf{Figure 27}). The ensuing reaction of hydrogen peroxide/lithium hydroxide was attempted on the mixture of the methyl ester (50) and oxazolidinone (45),
but only the oxazolidinone survived these conditions as no indole ring system could be detected in the reaction products.

\[ \text{Figure 27: Removal of the Chiral Auxiliary} \]

Other methods were attempted in reducing the thiocarbamate ring, but there was no improvement in the results. Reactions with triethylsilane/benzoyl peroxide,\textsuperscript{46} tributyltin hydride/AIBN,\textsuperscript{47} nickel chloride/sodium borohydride\textsuperscript{43} and a hydrogenolysis with palladium as a catalyst only yielded starting material, while reactions with sodium cyanoborohydride/zinc iodide,\textsuperscript{48} potassium hydroxide, and hydrogen peroxide/lithium hydroxide\textsuperscript{13} showed no indole system after workup.

With the difficulty encountered in cleaving the thiocarbamate ring an attempt was made to perform a reaction using Evans chiral auxiliary in which a thiocarbamate ring would not be formed at all. This reaction would be possible if the Sn(II) enol-
isothiocyanate could act as a nucleophile and displace a leaving group (in this case the acetate functional group) in an $S_N1$ manner at the pseudo-benzylic site of the indole ring (Figure 28).

![Reactions image]

**Figure 28: Reaction of Isothiocyanate with Indole-Acetate**

A model reaction of this type was investigated with benzyl acetate (51) as the electrophile. Initially the reaction did not occur, and attempts to use boron trifluoride etherate as a stronger Lewis acid as well as higher temperatures (up to room temperature) did not promote nucleophilic attack (Figure 29). Consequently, further work on this approach was abandoned.

![Reactions image]

**Figure 29: Reaction of Evans' Isothiocyanate with Benzyl Acetate**
Attempts were then made to set up the carbon skeleton of the 7-azatryptophan side chain, so that an Evans asymmetric amination\textsuperscript{31} could be attempted. The first approach that was considered was based on the work of Roth.\textsuperscript{29} An attempt to add a cobalt stabilized propargylic cation (21) to 1-benzyl-7-azaindole (52) failed to give similar results to those of Roth when the same propargylic cation was added to indole (Figure 30).\textsuperscript{49}

![Chemical structure](image)

(52) \hspace{1cm} + \hspace{1cm} \text{No Reaction} \hspace{1cm} \text{(21)}

**Figure 30: Cobalt Mediated Propargylation of 7-Azaindole**

An additional approach in an attempt to set up the carbon skeleton was a reaction of 7-azaindole (29) with methyl acrylate (53) in aqueous acetic acid. The reaction was first performed with stirring at room temperature and then heated to \(60^\circ\text{C}\) overnight, but no reaction took place in either case (Figure 31).
At this point, attention was turned towards the use of aziridines. The work by Sato and Kozikowski\(^\text{19}\) appeared to be an appealing candidate towards the synthesis of 7-azatryptophan as they were able to synthesize tryptophan derivatives from indole and Cbz-aziridinecarboxylate methyl ester (58) in the presence of zinc triflate in low yields (40\%) but high optical purity (>95\%). The N-Cbz-aziridinecarboxylate methyl ester (58) was synthesized in 4 steps from serine methyl ester hydrochloride (54) following the procedure of Sato and Kozikowski (Figure 32).\(^\text{19}\) This aziridine was found to be thermally unstable and therefore was synthesized, purified, and stored at low temperatures.
Figure 32: Synthesis of (S)-N-Cbz-Aziridinecarboxylate Methyl Ester

In the subsequent reaction, zinc trflate did mediate the ring opening of the aziridine by 7-aza indole as it did with indole. Unfortunately, this time the ring opening was not by the C-3 position but instead by the pyridine nitrogen, as evidenced by a shift of the indole hydrogen resonances in the $^1$H NMR spectrum, the absence of the indole N-H peak, and the appearance of the CH$_2$ and C*H peaks at approximately 5 ppm (the CH$_2$ peak of 7-azatryptophan appears at 3.4 ppm) (Figure 33).
In an attempt to rectify the regioselectivity problem encountered, three important factors were considered. It was determined that the best way to prevent the attack of the pyridine nitrogen was to actually protect the pyrrole nitrogen. This protection would prevent proton loss to the iso-azaindole in a pyridyl N-attack situation and perhaps therefore favour the C-3 attack. Having established the importance of the protecting group, it became logical to have an electron donating group as the protecting group in an attempt to make the C-3 position more nucleophilic. Finally, the use of a very large protecting group could sterically hinder attack at the pyridine nitrogen. Considering these three factors, the first choice implemented was the use of a trityl group. However, the reaction of 7-azaindole with sodium hydride followed by the addition of trityl chloride was very sluggish and low yielding, so attention was turned to the use of benzyl as a protecting group. The synthesis of 1-benzyl-7-azaindole (52) proceeded rather smoothly, but the zinc mediated reaction with the Cbz-azirdinecarboxylate methyl ester at various temperatures did not occur and the indole derivative was recovered in quantitative yield (Figure 34).
Figure 34: Zinc Mediated Reaction of 1-Benzyl-7-Azaindole with Cbz-Aziridinecarboxylate Methyl Ester

It became quite obvious that the pyridine ring was acting as a very strong electron withdrawing group to the pyrrole ring, so attention was focused on trying to improve the nucleophilic character at the 3-position of the indole ring in reactions with aziridines. The work of Baldwin\textsuperscript{22} appeared to be the next logical focal point as it employs copper catalyzed Grignard reagents to promote ring opening of Boc-aziridinecarboxylate-tert-butyl ester. The synthesis of the Boc-aziridinecarboxylate-tert-butyl ester was accomplished by following a protocol similar to that of the synthesis of the aziridinecarboxylate methyl ester. (S)-Serine (59) was first N-protected with the Cbz group by following the procedure of Moore,\textsuperscript{51} using Schotten-Baumann conditions. The product (60) was then esterified using tert-butanol and N, N-dimethylformamide dineopentyl acetal to give compound (61). Removal of the Cbz group by hydrogenation followed by the protection of the nitrogen with the trityl group gave (62) in high yield (99\%). The N-trityl-serine tert-butyl ester (62) was then O-tosylated (63) by tosyl chloride in pyridine, and subsequent refluxing in THF with triethylamine afforded the N-trityl-aziridinecarboxylate-tert-butyl ester (64), which could be stored for several months at room temperature. Removal of the trityl group with trifluoroacetic acid followed by
reaction of the aziridine salt with triethylamine and di-tert-butyl dicarbonate afforded the thermally unstable Boc-protected aziridinecarboxylate tert-butyl ester (65) (Figure 35).

![Chemical Reaction Diagram]

**Figure 35: Synthesis of (S)-N-Boc-aziridinecarboxylate-tert-butyl ester**

Prior to attempting the copper catalyzed Grignard reaction, an azaindolate reaction of aziridine (65) with the bromomagnesium salt of 7-azaindole (66) (from the reaction of ethyl magnesium bromide with 7-azaindole) was investigated. The result was aziridine ring opening, but again by the pyridine nitrogen (Figure 36). To establish that the bromomagnesium salt was indeed formed, a small aliquot was quenched with D₂O. The
$^1$H NMR showed the product was spectroscopically similar to that of 7-azaindole with the exception of the disappearance of the C-3 hydrogen and the simplification of the splitting pattern of the C-2 proton resonance.

![Chemical Structures](image)

**Figure 36: Reaction of 7-Azaindole with N-Boc-Aziridinecarboxylate-tert-Butyl Ester**

Failing to react the azaindolate with the aziridine, the copper catalyzed Grignard reaction of Baldwin\textsuperscript{22} was investigated. In order to form a stable Grignard reagent, it once again became necessary to protect the pyrrole nitrogen with the benzyl group. Prior to benzylation, 7-azaindole was brominated at the C-3 position to give (67), by a modification to the procedure of Robison and Robison.\textsuperscript{17} Subsequent benzylation
afforded 1-benzyl-3-bromo-7-azaindole (68). Insertion of magnesium was first attempted in a refluxing solution of THF with magnesium turnings. After 1 h the $^1$H NMR of an aliquot showed only starting material so a crystal of iodine was added. After an additional hour the $^1$H NMR still showed only starting material. At this point a drop of 1,2-dibromoethane was added and after an additional hour an $^1$H NMR of a quenched aliquot gave a spectrum identical to that of 1-benzyl-7-azaindole (52), proving that magnesium insertion had indeed taken place (Figure 37).

![Chemical Structures]

**Figure 37: Formation of the Grignard Reagent**

An attempt to perform the aziridine ring opening with the Grignard reagent in a copper catalyzed reaction failed to give any positive results, with the 1-benzyl-7-azaindole (52) being recovered in quantitative yield upon workup, although not all of the aziridine could be recovered. Attempts to promote ring opening by using higher
temperatures only destroyed the thermally unstable aziridine ring, with no trace of product formation (Figure 38).

![Chemical Structure](image)

**Figure 38: Aziridine Ring Opening by Copper Catalyzed Grignard**

As our final chosen route for introducing the amino acid side chain, attention was turned towards the work of Jackson.\(^{23}\) The protected β-iodoalanine (15) was synthesized from (S)-serine in 4 steps.\(^{51}\) Initially (S)-serine was esterified with benzyl alcohol in the presence of benzenesulfonic acid. After purification of the (S)-serine benzyl ester salt (70), Boc protection of the nitrogen was carried out in a solution of 2N NaOH and THF. Subsequent O-tosylation with tosyl chloride in pyridine afforded the N-Boc-O-tosyl-(S)-alanine benzyl ester (72). Displacement of the O-tosyl by sodium iodide in acetone afforded the protected (S)-3-iodoalanine (15) (Figure 39).
Initial attempts to insert zinc into the carbon-iodine bond of compound \( 15 \) using the original protocol of Jackson\textsuperscript{51} by sonication in benzene and DMA with a zinc/copper couple failed completely. The zinc failed to insert at cooler temperatures, although at warmer temperature, zinc did insert but the iodozinc reagent immediately fell apart into...
benzyl acrylate. The addition of a catalytic amount of iodine and copper (I) chloride in separate reactions also failed to promote zinc insertion. A potential solution was the use of Rieke zinc\(^{52}\) which is an extremely reactive source of zinc. Rieke zinc (73) was prepared by the reduction of the zinc salt ZnBr\(_2\) in THF with lithium naphthalanilide. The formation of the radical anion was apparent by the dark green colour streaming off the lithium metal, and after the disappearance of the lithium metal the zinc was ready for use. Attempts to use Rieke zinc did promote zinc insertion into the carbon-halogen bond (16), however the product immediately fell apart to compound (74) as evidenced by \(^1\)H NMR (Figure 40). The reductive elimination of (16) to form (74) could have occurred as a result of residual lithium metal competing for oxidative addition into the aryl-iiodide bond followed by \(\beta\)-hydrogen elimination.

Figure 40: Product Obtained from The Formation of the Organozinc Reagent Using Rieke Zinc

41
With the zinc/copper couple being weakly reactive, and the conditions of Rieke zinc insertion possibly being too reactive, a good compromise was found using the procedure of Knochel.\textsuperscript{51} The procedure called for the use of activation of commercially available zinc dust with 1, 2-dibromoethane and then chlorotrimethylsilane. The \textit{in situ} preparation did finally insert zinc into the carbon-halogen bond with success in a relatively short period of time (1/2 h). It should be noted that Jackson has abandoned his original procedure in favour of Knochel's.\textsuperscript{54} In order to prove that the zinc reagent was in fact formed, it was necessary repeat a literature reaction performed by the Jackson group. The zinc reagent (16) was then reacted with iodobenzene in the presence of a catalytic amount of bis(tri-o-tolyolphosphine) palladium dichloride to form benzyl 2(\textit{S})-[\textit{tert}-butoxycarbonyl]amino]-3-phenyl-propionate\textsuperscript{51} (75) evidenced by NMR of the crude reaction product (Figure 41).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {HN} ;
\node (b) at (0,-1) {CO_2Bn} ;
\node (c) at (0,-2) {Boc} ;
\node (d) at (1,-1) {I} ;
\node (e) at (1,-2) {1. Zn activated with 1. 2-dibromoethane and TMSCl} ;
\node (f) at (2,0) {HN} ;
\node (g) at (2,-1) {CO_2Bn} ;
\node (h) at (2,-2) {Boc} ;
\node (i) at (3,-1) {Ph} ;
\node (j) at (3,-2) {2. Bis(tri-o-tolyolphosphine) palladium dichloride} ;
\node (k) at (4,-1) {15} ;
\node (l) at (5,-1) {75} ;
\node (m) at (4,-2) {3. Iodobenzene} ;
\end{tikzpicture}
\end{center}

\textbf{Figure 41: Jackson’s Reaction of Organo-Zinc with Iodobenzene}

After successful reaction with iodobenzene, the correct aryl iodide had to be synthesized. First 3-iodo-7-azaindole (76) was prepared from 7-azaindole (29) in a modification to the procedure of Herbert and Wibberley.\textsuperscript{55} The reaction only proceeded to a maximum of
30% conversion of 7-azaindole to 3-iodo-7-azaindole, even with varying amounts of iodine present. This, however, did not prove to be a large problem since 7-azaindole could be recovered during purification. It has been reported that organozinc reagents are known to be stable in the presence of a variety of relatively acidic hydrogens (pKa = 18-35). It was believed however, that the N-H of 7-azaindole might present a problem, so the iodoindole was Boc protected before use (Figure 42).

![Reaction Diagram]

**Figure 42: Synthesis of 1-Boc-3-Iodo-7-Azaindole**

The first reaction of the organozinc reagent with 1-Boc-3-iodo-7-azaindole (77) only produced 7-azaindole (29). This most likely came from the insertion of the excess zinc into the azaindole-iodine bond and upon workup, hydrolysis of this bond. Also of note was the fact that the Boc group was also cleaved from the azaindole. This result was
unexpected since Jung\textsuperscript{57} reported that the insertion of zinc into the arylcarbon-iodide bond was much slower than the zinc insertion into the primary iodide. In fact, Jung actually found that an aryl iodide could be added along with the iodoalanine benzyl ester to the activated zinc followed by the addition of the palladium catalyst and still give the coupled product in good yield (71\%). In the case of 1-Boc-3-iodo-7-azaindole, to prevent the electrophile from reacting with the zinc it was necessary to syringe off the supernatant solution from the excess zinc and then add it to the azaindole. This followed a protocol developed by Jackson for reactions where the residual zinc can react unproductively with the electrophile.\textsuperscript{58} With a minimal amount of zinc being transferred, workup of the reaction gave only the starting azaindole with a small amount of 7-azaindole and of course benzyl acrylate from the decomposed organo-zinc reagent.

**Future Work**

With the apparent problems of successfully completing reactions at the C-3 position of the 7-azaindole ring it appears necessary to further explore methods of first inserting the carbon skeleton and then using Evans’ asymmetric amination to introduce the chiral center. The pathway that appears to be most reliable was that developed by Robison and Robison (Figure 43).\textsuperscript{17}
Figure 43: Reactions Leading the Carbon Skeleton of 7-Azatryptophan

Another possible method that should be worthy of consideration is the use of asymmetric hydrogenation. Since many amino acid derivatives are known to be synthesized by asymmetric hydrogenation, and we have discovered that the α, β unsaturation in dehydroazatryptophans can be hydrogenated under mild conditions, this should be a viable pathway. The introduction of the vinyl precursor could possibly be accomplished by analogous reactions of Yokoyama, where Pd(OAc)$_2$ was used to promote the C-3 indole attack on N-Boc-dehydroalanine methyl ester (Figure 44). The protected dehydro-7-azatryptophan could subsequently be asymmetrically hydrogenated to afford the protected 7-azatryptophan.
Figure 44: Proposed Vinylation of a Protected 7-Azaindole
**Experimental**

**General Methods**

All solvents were utilized after drying over the appropriate drying agent. Diethyl ether and tetrahydrofuran were distilled from benzophenone-ketyl immediately prior to use. Dichloromethane, dimethylformamide, pyridine and triethylamine were distilled from calcium hydride.

All column chromatography was performed using Merck Kieselgel 230-400 mesh silica gel while all preparative TLC was done using Uni-plate® 1000 micron silica gel GF plates. Analytical thin layer chromatography was performed using Merck precoated silica gel 60 F<sub>254</sub> aluminium sheets. Flash chromatography was done as described by Still.<sup>41</sup>

Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. Infrared spectra were run on a Bomem Michelson 100. NMR spectra were run on a Bruker Avance 500 Spectrometer at 500 MHz for <sup>1</sup>H and 125 MHz for <sup>13</sup>C, in CDCl<sub>3</sub> solution at 25°C or a Bruker Avance 300 Spectrometer at 300 MHz for <sup>1</sup>H and 75 MHz for <sup>13</sup>C, in CDCl<sub>3</sub> solution at 25°C unless otherwise indicated. Mass spectra were run on a Kratos Profile instrument in electron impact mode.

Melting points were obtained uncorrected from a Thomas Hoover, Uni-Melt® capillary melting point apparatus. Boiling points refer to bulb to bulb distillation unless otherwise stated.
3-(N,N-Dimethylaminomethyl)-7-azaindole (7-azagramine) (30)

Compound (30) was prepared by a modification to the procedure of Fallis. Glacial acetic acid (2.4 g, 39.66 mmol) was added in portions to a stirred solution of 40% aqueous dimethylamine (2.0 g, 18.0 mmol) at 5°C. After stirring for 5 min at 5°C, 37% formaldehyde (1.4 g, 17.0 mmol) was added and the resulting mixture was stirred for 10 min. 7-Azaindole (2.0 g, 17.0 mmol) was then added and the reaction was stirred until a homogeneous solution was obtained. The solution was heated at 60°C for 18 h and neutralized with aqueous NaOH (2.4 g in 16.6 mL of water). Cooling afforded a brown solid. The solid was dissolved in chloroform and the aqueous layer was extracted with chloroform (3 x 50 mL). The combined organic extracts were washed with saturated sodium bicarbonate (1 x 50 mL), water (1 x 50 mL) and then dried over magnesium sulfate and evaporated under reduced pressure to yield a yellow solid. Chromatography [500 mL ethyl acetate (to elute impurities), followed by 500 mL of 5:1 ethyl acetate : triethylamine (to elute product)] afforded the pure product as a yellow solid (2.59 g, 14.78 mmol, 87%): mp = 161-162°C (Lit. 160-162°C). The product was spectroscopically identical to the literature.
3-Formyl-7-azaindole (31)

Compound (31) was prepared by a modification to the procedure of Fallis.⁶ 3-(N,N-Dimethylaminomethyl)-7-azaindole (30) (2.50 g, 14.27 mmol) was dissolved in a solution of hexamethylenetetramine (3.38 g, 24.17 mmol) in 66% aqueous propionic acid (18.3 mL). The resulting mixture was stirred at room temperature for 1 h and then refluxed for 3 h. Cooling the reaction at 5°C for 24 h yielded white crystals (910 mg, 6.23 mmol, 44%): mp = 218-219°C (Lit.⁶ 214-215°C). The product was spectroscopically identical to the literature.

1-Benzyl-3-formyl-7-azaindole (32)

To a mixture of 3-formyl-7-azaindole (31) (900 mg, 6.16 mmol) and sodium hydride (1.1 equiv., 163 mg, 6.78 mmol) (prepared from washing 60% sodium hydride in mineral oil with diethyl ether) was added THF (20 mL) dropwise under a nitrogen atmosphere. After
stirring for 1 h, benzyl bromide (1.1 equiv., 0.67 mL, 6.774 mmol) was added, and the resulting suspension was stirred for 12 h. The reaction was quenched with saturated ammonium chloride (20 mL), and diethyl ether (100 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were washed with saturated sodium bicarbonate (3 x 50 mL) and brine (1 x 50 mL), and then dried over magnesium sulfate and evaporated under reduced pressure to yield a yellow solid. The residue was purified by flash chromatography on silica gel with 1:2 petroleum ether:diethyl ether as the eluent (Rf = 0.3) to afford the product as a yellow solid (880 mg, 3.72 mmol, 61%): mp 68-70°C; IR (CH2Cl2; NaCl) vmax 1667, 1598, 1495, 1484, 1451, and 1432 cm⁻¹; ¹H NMR (300 MHz; CDCl₃) δ: 9.94 (1H, s, CHO), 8.58 (1H, dd. JAB = 2.2 Hz, JAX = 13.0 Hz, C(6)H), 8.47 (1H, dd. JAB = 2.2 Hz, JBX = 8.0 Hz, C(4)H), 7.80 (1H, s, C(2)H), 7.37-7.26 (6H, m, Ph-H and C(5)H), 5.55 (2H, s, CH₂Ph); ¹³C NMR (75 MHz; CDCl₃) δ: 185.0, 149.0, 145.7, 138.2, 136.4, 131.0, 129.5, 128.8, 128.4, 119.5, 118.0, 117.2, 49.0; MS m/e 236 (M+); HRMS m/e for C₁₃H₁₂N₂O calcd. (M⁺) 236.0950, found 236.0948.

\[
\text{O} \\
\text{Ph} \quad \text{N} \quad \text{OCH₃}
\]

**Methyl hippurate (33)**

To a stirred solution of hippuric acid (10.0 g, 55.81 mmol) in methanol (150 mL) was added a catalytic amount of sulfuric acid (1 mL). The resulting solution was refluxed for
20 h. The reaction was cooled to room temperature and the methanol was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (150 mL), washed with saturated sodium bicarbonate (2 x 50 mL), brine (50 mL) and water (50 mL). The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure to yield a white solid. The solid was recrystallized from ethyl acetate/hexanes to afford a white crystalline solid (9.50 g, 51.76 mmol, 93%): mp 81-83°C (Lit. 81-82°C); IR (CH₂Cl₂, NaCl) vₘₓ 3310, 1730, 1632, 1439, 1253, and 701 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ: 7.75 (2H, d, J = 8.7 Hz, ortho protons), 7.56 (1H, br s, NH), 7.38 (1H, t, J = 7.4 Hz, para hydrogen), 7.28 (2H, t, J = 7.7 Hz meta hydrogens), 4.09 (2H, d, J = 5.6 Hz, CH₂), 3.62 (3H, s, CH₃); ¹³C NMR (125 MHz; CDCl₃) δ: 170.2, 167.6, 133.3, 131.4, 128.1, 126.9, 51.9, 41.3.

![Chemical structure](image)

**Methyl 3-(1-benzyl-7-azaindol-3-yl)-3-hydroxy-2-phenylamido-propionate (34)**

To a stirred solution of diisopropyl amine (0.79 mL, 5.58 mmol) in THF (15 mL) at 0°C under nitrogen was added n-butyl lithium (2.41 mL, 2.32 M in hexanes, 5.58 mmol). After stirring for 0.5 h, the mixture was cooled to -78°C, at which point methyl hippurate (33) (540 mg, 2.79 mmol), as a solution in THF (10 mL), was added dropwise. The resulting solution was stirred for 1.5 h and 1-benzyl-3-formyl-7-azaindole (32) (330 mg,
1.40 mmol), as a solution in THF (10 mL), was added dropwise. The mixture was stirred for 3 h, and the reaction was quenched with saturated ammonium chloride (5 mL). The solution was diluted with diethyl ether (150 mL), and the organic layer was washed with saturated sodium bicarbonate (2 x 50 mL) and distilled water (50 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to yield a dark yellow oil. The residue was purified by flash chromatography on silica gel with 3:5 petroleum ether:ethyl acetate as the eluent (Rf = 0.34) to afford the product as a white solid. The solid was recrystallized from ethyl acetate/hexanes to yield a white solid (404 mg, 0.94 mmol, 67%): mp = 122-123°C; IR (CH₂Cl₂, NaCl) v_max 3358, 1740, 1435, 1208, and 773 cm⁻¹. ¹H NMR (300 MHz: CDCl₃) δ: 8.30 (1H, m, C(6)H of both diastereomers), 8.00 (1H, m, C(4)H of both diastereomers), 7.70-7.01 (13H, m, PhH, NH, C(2)H and C(5)H of both diastereomers), 5.65-5.22 (4H, m, CHO, CHNH, and CH₃-Ph of both diastereomers), 4.48 and 4.14 (1H, br s, OH of diastereomer 1 and 2), 3.67 and 3.55 (3H, s, OCH₃ of diastereomer 2 and 1); ¹³C NMR (75 MHz: CDCl₃) δ: 172.1, 171.6, 170.4, 168.9, 144.0, 143.8, 137.3, 137.2, 132.6, 132.3, 129.2, 129.1, 129.0, 128.1, 127.9, 127.6, 127.5, 125.9, 116.4, 114.1, 113.2, 110.0, 71.2, 69.5, 59.5, 57.9, 53.1, 48.2, 30.1, 25.1; MS m/z 411 (M⁺ - H₂O); HRMS m/z for C₂₅H₂₃N₃O₁, calcd. (M⁺ - H₂O) 411.1583, found 411.1591.
Methyl 3-(1-benzyl-7-azaindol-3-yl)-2-phenylamidopropenoate (35)

To a solution of the aldol product (34) (150 mg, 0.35 mmol) in dichloromethane (10 mL) was added triethylsilane (0.06 mL, 0.39 mmol) and trifluoroacetic acid (0.30 mL, 3.84 mmol) under nitrogen. After stirring for 20 h, the reaction was diluted with dichloromethane (40 mL), washed with saturated sodium bicarbonate (20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/hexanes to afford the product as an off-white solid (140 mg, 0.34 mmol, 97%): mp = 140-142°C; IR (CHCl₃, NaCl) νmax 1713, 1644, 1434, 1197, and 773 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ: 8.40 (1H, br s, C(6)H), 8.11 (1H, dd, J₁ = 1.4 Hz, J₂ = 7.9 Hz, C(4)H), 7.88 (1H, s, C(2)H), 7.80-7.16 (12H, m, 10 phenyl hydrogens, C(5)H, C=CH(Indole)), 5.42 (2H, s, CH₂Ph), 3.86 (3H, s, OCH₃), 2.17 (1H, d, J = 2.8 Hz, N-H); ¹³C NMR (75 MHz; CDCl₃) δ: 166.5, 147.9, 144.5, 136.6, 134.2, 132.4, 131.2, 129.2, 128.9, 128.4, 127.9, 127.6, 127.5, 125.7, 120.7, 120.1, 117.6, 116.4, 108.8, 52.9, 48.7; MS m/e 411 (M⁺): HRMS m/e for C₂₅H₂₁N₃O₃ calcd. (M⁺) 411.1583, found 411.1573.
Methyl 3-(1-benzyl-7-azaindol-3-yl)-2-phenylamidopropanoate (36)

To a solution of compound (35) (100 mg, 0.24 mmol) in THF (20 mL) was added palladium (5% on carbon) (50 mg) and the reaction was placed under a hydrogen atmosphere. After stirring for 80 h, the mixture was filtered through a pad of Celite® which was washed with methanol. Evaporation of the solvent under reduced pressure yielded the product as an off-white solid in quantitative yield (100 mg, 0.24 mmol): mp = 126-128°C; IR (CH$_2$Cl$_2$, NaCl) $\nu_{max}$ 1742, 1436, 1179, and 771 cm$^{-1}$; $^1$H NMR (500 MHz; CDCl$_3$) $\delta$: 8.35 (1H, d, $J = 4.0$ Hz, C(6)H), 7.87 (1H, dd, $J = 0.7$ Hz, $J = 7.8$ Hz, C(4)H), 7.66-7.16 (10H, m, PhH), 7.17 (1H, dd, $J = 1.6$ Hz, $J = 7.8$ Hz, C(5)H), 6.96 (1H, s, C(2)H), 5.46 (2H, d, $J = 8.1$ Hz, CH$_2$Ph), 5.12 (1H, m, CH$_2$CH), 3.63 (3H, s, OCH$_3$), 3.42 (2H, m, CH$_2$CH), 2.18 (1H, d, $J = 2.9$ Hz, NH); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$: 172.6, 167.1, 148.2, 143.7, 138.0, 134.1, 132.2, 129.1, 129.0, 128.9, 128.0, 127.8, 127.6, 127.4, 126.8, 116.1, 108.4, 53.8, 52.8, 48.0, 28.4; MS m/e 413 (M$^+$); HRMS m/e for C$_{25}$H$_{23}$N$_3$O$_3$ calcd. (M$^+$) 413.1739, found 413.1730.
1-(\textit{tert}-Butyloxycarbonyl)-3-formyl-7-azaindole (38)

Compound (38) was prepared by a modification of the procedure of Fallis. To a mixture of 3-formyl-7-azaindole (31) (900 mg, 6.16 mmol) and sodium hydride (1.1 equiv., 163 mg, 6.77 mmol) (prepared from washing 60% sodium hydride in mineral oil with diethyl ether) was added THF (20 mL) dropwise under a nitrogen atmosphere. After stirring for 1 h, di-\textit{tert}-butyl dicarbonate (1.4 equiv., 1.88 g, 8.62 mmol) in THF (10 mL) was added, and the resulting suspension was stirred for 12 h. The reaction was quenched with saturated ammonium chloride (20 mL), and diethyl ether (100 mL) was added subsequently. The aqueous layer was extracted with diethyl ether (3 x 50 mL), and the combined organic extracts were washed with saturated sodium bicarbonate (3 x 50 mL), and brine (1 x 50 mL) and then dried over magnesium sulfate and evaporated under reduced pressure to yield a yellow solid. The solid was then recrystallized from hexanes to afford off-white needles (1.09 g, 4.42 mmol, 72%): mp 216-217°C. The product was spectroscopically identical to the literature.
Methyl 3-(1-tert-butyloxycarbonyl)-7-azaindol-3-yl)-3-hydroxy-2-phenylamido-propionate (39)

To a stirred solution of diisopropyl amine (0.72 mL, 5.09 mmol) in THF (15 mL) at 0°C under nitrogen was added n-butyl lithium (2.19 mL, 2.32 M in hexanes, 5.09 mmol). The resulting reaction was stirred for 0.5 h to form LDA. The mixture was cooled to -78°C at which point methyl hippurate (33) (429 mg, 2.54 mmol), as a solution in THF (10 mL), was added dropwise. The resulting solution was stirred for 1.5 h and 1-tert-butyloxycarbonyl-3-formyl-7-azaindole (38) (313 mg, 1.27 mmol), as a solution in THF (10 mL), was added dropwise. The resultant mixture was stirred for an additional 3 h. The reaction was quenched with saturated ammonium chloride (5 mL) at -78°C and after warming to room temperature, the solution was diluted with diethyl ether (150 mL), and the organic layer was washed with saturated sodium bicarbonate (2 x 50 mL) and distilled water (50 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to yield a dark yellow oil. The residue was purified by flash chromatography on silica gel with 5:1 dichloromethane/diethyl ether as the eluent (Rf = 0.25 for diastereomer 1, and 0.22 for diastereomer 2) to afford the product as a white solid. The solid was recrystallized from ethyl acetate/hexanes to yield a white
crystalline solid (diastereomer 1 = 224 mg, diastereomer 2 = 114 mg, total 338 mg, 0.769 mmol, 60%).

**Diastereomer 1**: mp = 143-145°C; IR (CH₂Cl₂, NaCl) v_max 3320, 1744, 1414, 1250, and 775 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ: 8.44 (1H, dd, J = 1.4 Hz, J = 4.8 Hz, C(6)H), 8.02 (1H, dd, J = 1.4 Hz, J = 7.8 Hz, C(4)H), 7.73 (2H, d, J = 7.3 Hz, ortho protons), 7.53, (1H, s, C(2)H), 7.47, (1H, t, J = 7.8 Hz, para proton), 7.35 (2H, t, J = 7.8 Hz, meta protons), 7.25 (1H, d, J = 7.4 Hz, NH), 7.11 (1H, d, J = 7.8 Hz, C(5)H), 5.55 (1H, br s, CH₂OH), 5.23 (1H, dd, J = 3.3, J = 7.4, CHNH), 4.89 (1H, br s, OH), 3.62 (3H, s, OCH₃), 1.59 (9H, s, OC(CH₃)₃); ¹³C NMR (125 MHz; CDCl₃) δ: 169.7, 168.1, 148.1, 147.6, 145.2, 133.0, 132.0, 128.6, 128.5, 127.0, 123.4, 121.3, 118.4, 117.2, 84.2, 69.8, 58.5, 52.5, 27.9; Anal. Calcd. For C₂₃H₂₃N₅O₆: C, 62.80; H, 5.69; N, 9.56. Found: C, 62.53; H, 5.77; N, 9.42.

**Diastereomer 2**: mp = 157-159°C; IR (CH₂Cl₂, NaCl) v_max 3349, 1746, 1416, 1250, and 776 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ: 8.42 (1H, dd, J = 1.2 Hz, J = 4.7 Hz, C(6)H), 7.93 (1H, dd, J = 1.4 Hz, J = 7.8 Hz, C(4)H), 7.70 (2H, d, J = 7.4 Hz, ortho protons), 7.58, (1H, s, C(2)H), 7.47, (1H, t, J = 7.8 Hz, para proton), 7.36 (2H, t, J = 7.6 Hz, meta protons), 7.12 (1H, d, J = 8.6 Hz, NH), 7.10 (1H, m, C(5)H), 5.58 (1H, br s, CH₂OH), 5.18 (1H, dd, J = 3.2, J = 8.6, CHNH), 3.91 (1H, br s, OH), 3.76 (3H, s, CH₃), 1.58 (9H, s, OC(CH₃)₃); ¹³C NMR (125 MHz; CDCl₃) δ: 170.8, 167.7, 148.1, 147.6, 145.3, 133.5,
Calcd. For C_{25}H_{25}N_{5}O_{6}: C, 62.80; H, 5.69; N, 9.56. Found: C, 59.74; H, 5.66; N, 9.12.

![Chemical Structure](image)

**Methyl 3-(1-tert-butylxycarbonyl)-7-azaindol-3-yl)-3-acetoxy-2-phenylamido-propanoate (40)**

To a stirred solution of the aldol product (39) (diastereomer 1: 175 mg, 0.41 mmol; diastereomer 2: 90 mg, 0.20 mmol) in pyridine (2 mL and 1 mL for diastereomers 1 and 2 respectively) under nitrogen was added acetic anhydride (2 mL and 1 mL for diastereomers 1 and 2 respectively). The resulting solution was stirred for 24 h at ambient temperature. The solvents were then removed under reduced pressure to yield the desired acetates in quantitative yield as judged by ^1H NMR spectroscopy. The solid was recrystallized from ethyl acetate/hexanes to yield yellow crystals (diastereomer 1 = 195 mg, 0.41 mmol; diastereomer 2 = 94 mg, 0.20 mmol).

**Diastereomer 1:** mp = 174-176°C; IR (CH₂Cl₂, NaCl) \(\nu_{max}\) 1746, 1665, 1413, and 1249 cm⁻¹; ^1H NMR (500 MHz; CDCl₃) δ: 8.52 (1H, d, J = 4.3 Hz, C(6)H), 8.04 (1H, d, J = 7.7 Hz, C(4)H), 7.72 (2H, d, J = 7.6 Hz, ortho protons), 7.63, (1H, s, C(2)H), 7.59, (1H, t, J = 7.2 Hz, para proton), 7.43 (2H, t, J = 7.4 Hz, meta protons), 7.18 (1H, m, C(5)H), 6.81
(1H, d, J = 7.9 Hz, NH), 6.56 (1H, d, J = 3.5 Hz, CHOAc), 5.54 (1H, dd, J = 3.5, J = 7.9, CHNH), 3.70 (3H, s, OCH₃), 2.15 (3H, s, OCCH₃), 1.66 (9H, t, OC(CH₃)₃); ^{13}C NMR (125 MHz; CDCl₃) δ: 169.9, 169.1, 167.0, 148.1, 147.4, 145.8, 133.3, 132.0, 128.7, 128.6, 127.0, 124.4, 121.1, 118.6, 112.9, 84.6, 70.1, 55.8, 52.7, 28.0, 20.8; Anal. Calcd. For C₂₅H₂₇N₅O₇: C, 62.30; H, 5.61; N, 8.72. Found: C, 61.12; H, 6.09; N, 8.35.

Diastereomer 2: mp = 221-222°C; IR (CH₂Cl₂, NaCl) v_max 1747, 1658, 1413, and 1249 cm⁻¹; ^{1}H NMR (500 MHz; CDCl₃) δ: 8.52 (1H, d, J = 3.9 Hz, C(6)H), 8.02 (1H, d, J = 7.1 Hz, C(4)H), 7.75 - 7.72 (3H, m, ortho protons and C(2)H), 7.54, (1H, t, J = 7.4 Hz, para proton), 7.45 (2H, t, J = 7.6 Hz, meta protons), 7.20 (1H, m, C(5)H), 6.92 (1H, d, J = 9.1 Hz, NH), 6.62 (1H, d, J = 4.8 Hz, CHOH), 5.44 (1H, dd, J = 4.8, J = 9.1, CHNH), 3.72 (3H, s, OCH₃), 2.13 (3H, s, OCCH₃), 1.66 (9H, s, OC(CH₃)₃); ^{13}C NMR (125 MHz; CDCl₃) δ: 169.9, 169.0, 167.2, 148.2, 147.4, 145.9, 133.4, 132.1, 128.7, 128.1, 127.1, 124.9, 121.0, 118.7, 113.3, 84.6, 69.0, 55.8, 52.9, 28.0, 20.8; Anal. Calcd. For C₂₅H₂₇N₅O₇: C, 62.30; H, 5.61; N, 8.72. Found: C, 62.11; H, 6.64; N, 7.61.
Methyl 3-(7-azaindol-3-yl)-2-phenylamidopropanoate (41)

To a stirred solution of acetate (40) (170 mg, 0.35 mmol) in dry methanol (10 mL) under nitrogen was added anhydrous nickel (II) chloride (320 mg, 2.47 mmol). To this solution was added sodium borohydride (187 mg, 4.94 mmol) in portions with stirring. The mixture was stirred at room temperature for 15 min and the methanol was removed subsequently by distillation under reduced pressure. Distilled water (10 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 3:5 petroleum ether:ethyl acetate as the eluent (Rf = 0.25) to afford the product as a yellow solid. The solid was recrystallized from ethyl acetate/hexanes to yield a yellow solid (90 mg, 0.21 mmol, 60%): mp 153-154°C; IR (CH2Cl2, NaCl) νmax 3265, 1738, 1436, and 1248 cm⁻¹. ¹H NMR (500 MHz; CDCl₃) δ: 10.68 (1H, br s. indole NH), 8.29 (1H, br s. C(6)H), 7.87 (1H, d, J = 7.8 Hz, C(4)H), 7.72 (2H, d, J = 7.6 Hz, ortho protons), 7.50 (1H, t, J = 7.3 Hz, para proton), 7.40 (2H, t, J = 7.6 Hz, meta protons), 7.16 (1H, s. C(2)H), 7.03 (1H, m, C(5)H), 6.82 (1H, d, J = 7.3 Hz, NH), 5.17 (1H, m, CHNH), 3.73 (3H, s, OCH₃), 3.50 - 3.41 (2H, m, CH₂); ¹³C NMR (125 MHz; CDCl₃) δ: 172.3, 166.9, 148.7,
142.9, 133.8, 131.8, 128.6, 127.4, 127.0, 123.6, 115.7, 110.6, 108.6, 53.4, 52.5, 27.9: MS m/e 323 (M+); HRMS m/e for C_{18}H_{17}N_{3}O_{3} calcd. (M+) 323.1270, found 323.1267.

![Chemical structure](image)

7-Azatryptophan (42)

Compound (41) was refluxed in 6 N HCl for 48 h. The reaction was cooled and the aqueous layer was washed with chloroform (3 x 10 mL). The aqueous layer was then evaporated under reduced pressure to yield a yellow solid. Addition of ammonium hydroxide afforded, after cooling and recrystallization from water, a solid that was spectroscopically identical to 7-azatryptophan. mp = 256-259°C (Lit.\textsuperscript{6} 261-262°C).

![Chemical structure](image)

(2S)-2-Amino-3-phenylpropanol ((S)-phenylalaninol) (44)

(2S)-2-Amino-3-phenylpropanol (44) was prepared from (S)-phenylalanine in 80% yield according to the procedure of Evans.\textsuperscript{12} mp = 88-90°C (Lit.\textsuperscript{12} 90-92°C). The product was spectroscopically identical to the literature.
(4S)-4-(Phenylmethyl)-2-oxazolidinone (45)

(4S)-4-(Phenylmethyl)-2-oxazolidinone was prepared from compound (44) in 74% yield according to the procedure of Evans.\textsuperscript{12} mp = 87-88°C (Lit.\textsuperscript{12} 87-88.5°C). The product was spectroscopically identical to the literature.

(4S)-3-(Azidoacetyl)-4-(phenylmethyl)-2-oxazolidinone (47)

(4S)-3-(Azidoacetyl)-4-(phenylmethyl)-2-oxazolidinone was prepared from compound (45) in 71% yield according to the procedure of Evans.\textsuperscript{12} mp = 65-67°C (Lit.\textsuperscript{12} 69-70°C). The product was spectroscopically identical to the literature.
(4S)-3-(Isothiocyanatoacyl)-4-(phenylmethyl)-2-oxazolidinone (9)

(4S)-3-(Isothiocyanatoacyl)-4-(phenylmethyl)-2-oxazolidinone was prepared from compound (47) in 71% yield according to the procedure of Evans: Method B.\textsuperscript{12} mp = 98-100°C (Lit.\textsuperscript{12} 101-102°C). The product was spectroscopically identical to the literature.

\[ \text{Sn(OTf)}_2 \]

**Stannous Triflate (48)**

Stannous triflate was prepared from stannous chloride and trifluoromethanesulfonic acid (triflic acid) in 86% yield according to the procedure of Evans.\textsuperscript{12} The purity of the product could only be tested by attempting a small scale aldol reaction.
(4S)-3-((4'S, 5'R)-5'-(1-tert-butyloxycarbonyl-7-azaindol-3-yl)-2'-thiooxazolidinylcarbon-4-yl)-4-(phenylmethyl)-2-oxazolidinone (49)

In a nitrogen dry box stannous triflate (464 mg, 1.11 mmol) was transferred to a flask. The flask was then sealed with a septum and transferred to the Schlenk manifold system and a nitrogen Schlenk line was attached using a needle. THF (4.5 mL) was added and the stirred solution was cooled to -78°C. N-Ethylpiperidine (0.12 mL, 0.84 mmol) was then added, followed by (4S)-3-(isothiocyanatoethyl)-4-(phenylmethyl)-2-oxazolidinone (9) (185 mg, 0.67 mmol) in THF (1 mL). After stirring for 1.5 h at -78°C 1-(tert-butyloxycarbonyl)-3-formyl-7-azaindole (38) (137 mg, 0.56 mmol) in THF (2.5 mL) was added. The reaction was stirred for an additional 5 h at -78°C, and quenched with 1 M pH = 7 phosphate buffer (5 mL). The resultant white suspension was then filtered through Celite®. The filtrate was then diluted with dichloromethane (150 mL), washed with 1 N aqueous sodium bisulfate (2 x 50 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The pure product was obtained by recrystallization of the residue from ethyl acetate/hexanes to yield a white solid (466 mg, 0.89 mmol, 74%); mp 158-160°C; [α]_D^24 +151.2 (c 1 in CH_2Cl_2); IR (CH_2Cl_2, NaCl) ν_max 1782, 1750, 1708, 1492, 1394, and 1252 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ: 8.54 (1H, d, J = 1 Hz, C(6)H), 8.09 (1H, br s, NH), 7.91 (1H, d, J = 8.0 Hz, C(4)H), 7.77 (1H, s, C(2)H), 7.38 -
7.17 (6 H, m, phenyl protons and C(5)H), 6.62 (1H, d, J = 5.2 Hz, CHOCS), 5.27 (1H, d, J = 5.2 Hz, CHNH), 4.77 (1H, m, CHCH₂Ph), 4.33 (2H, m, OCH₂), 3.23 (1H, dd, Jₐₜₜ = 13.6 Hz, Jₐₓ = 3.4 Hz, CH₃HₘPh), 2.96 (1H, dd, Jₐₜₚ = 13.6 Hz, Jₚₓ = 8.7 Hz, CH₃HₘPh), 1.66 (9H, s, OC(CH₃)₃);¹³C NMR (125 MHz, CDCl₃) δ: 188.3, 165.7, 153.7, 148.3, 147.2, 146.1, 133.9, 129.3, 129.2, 128.0, 127.8, 125.4, 119.8, 119.1, 113.5, 85.0, 78.6, 67.7, 63.3, 55.2, 37.5, 28.0; Anal. Calcd. For C₂₅H₂₆N₂O₆S: C, 59.70; H, 4.98; N, 10.72. Found: C, 59.03; H, 4.66; N, 10.27.

Benzyl Acetate (51)

To a stirred solution of benzyl alcohol (5.18 mL, 50 mmol) in pyridine (20.12 mL, 250 mmol) under nitrogen was added acetic anhydride (23.59 mL, 250 mmol). The resulting reaction was stirred for 20 h and then the solvents were removed under reduced pressure. Distillation yielded a colourless liquid, (7.13 g, 47.5 mmol, 95%) bp 206°C:760 torr (Lit.² 213°C/760 torr).
**1-Benzyl-7-azaindole (52)**

To a mixture of 7-azaindole (1.0 g, 8.5 mmol) and sodium hydride (1.1 equiv., 224 mg, 9.35 mmol) (prepared from washing 60% sodium hydride in mineral oil with diethyl ether) was added DMF (20 mL), dropwise under a nitrogen atmosphere. After stirring for 1 h, benzyl bromide (1.2 equiv., 1.38 g, 1.01 mL, 10.2 mmol) was added, and the resulting suspension was stirred for 12 h. The reaction was quenched with saturated ammonium chloride (20 mL), and diethyl ether (100 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 50 mL), and the combined organic extracts were washed with saturated sodium bicarbonate (3 x 50 mL), and brine (1 x 50 mL), dried over magnesium sulfate, and evaporated under reduced pressure to yield an oil. The residue was purified by flash chromatography on silica gel with 5:1 petroleum ether:diethyl ether as the eluent ($R_f = 0.30$) to afford the product as a white solid (1.54 g, 7.40 mmol, 87%).

An analytical sample was obtained by recrystallization from hexanes: mp = 66-68°C; IR (CH$_2$Cl$_2$, NaCl) $\nu_{max}$ 1591, 1511, 1485, 1453, and 1434 cm$^{-1}$; $^1$H NMR (500 MHz; CDCl$_3$) $\delta$: 8.42 (1H, d, $J = 4.6$ Hz, C(6)H), 7.95 (1H, d, $J = 7.7$ Hz, C(4)H), 7.34-7.23 (5H, m, Ph-H), 7.20 (1H, d, $J = 3.4$ Hz, C(2)H), 7.10 (1H, dd, $J_1 = 4.6$ Hz, $J_2 = 7.7$ Hz, C(5)H), 6.52 (1H, d, $J = 3.4$ Hz, C(3)H), 5.53 (2H, s, CH$_2$Ph); $^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$: 147.6, 142.9, 137.7, 128.6, 128.5, 127.8, 127.4, 127.3, 120.3, 115.7, 100.0,
Anal. Calcd. For C_{14}H_{17}N_2: C, 80.67; H, 5.76; N, 13.44. Found: C, 80.99; H, 5.82; N, 13.52.

(S)-N-Triphenylmethyl serine methyl ester (55)

(S)-N-Triphenylmethyl serine methyl ester was prepared from (S)-serine methyl ester hydrochloride (54) in 87% yield according to the procedure of Baldwin.\textsuperscript{20} \( mp = 77-78^\circ C \) (Lit.\textsuperscript{20} 77-78\(^\circ\)C). The product was spectroscopically identical to the literature.

(S)-N-Triphenylmethyl-O-((para)-toluenesulphonyl) serine methyl ester (56)

(S)-N-Triphenylmethyl serine methyl ester was prepared from (S)-N-triphenylmethyl serine methyl ester in 71% yield according to the procedure of Baldwin.\textsuperscript{20} The oil that was obtained solidified upon standing, \( mp = 53-55^\circ C \). The product was spectroscopically identical to that of the literature oil obtained.\textsuperscript{20}
\[ \text{Tr} \]
\[ \text{N} \]
\[ \triangle \text{CO}_2\text{CH}_3 \]

**(S)**-**N**-**Triphenylmethylaziridinecarboxylate methyl ester (57)**

(S)-N-Triphenylmethylaziridinecarboxylate methyl ester was prepared from (S)-N-triphenylmethyl-O-((para)-toluenesulphonyl) serine methyl ester (56) in 67% yield according to the procedure of Baldwin,\textsuperscript{20} mp = 112-114°C (Lit.\textsuperscript{20} 114-116°C). The product was spectroscopically identical to the literature.

\[ \text{Cbz} \]
\[ \text{N} \]
\[ \triangle \text{CO}_2\text{Me} \]

**(S)**-**N**-**Benzylxycarbonylaziridinecarboxylate methyl ester (58)**

(S)-N-Benzylxycarbonylaziridinecarboxylate methyl ester was prepared as a thermally unstable oil from compound (57) in 74% yield according to the procedure of Sato and Kozikowski.\textsuperscript{19} The product was spectroscopically identical to the literature.\textsuperscript{19}
(S)-N-Benzylxycarbonyl serine (60)

(S)-N-Benzylxycarbonyl serine was prepared by a modification of the procedure of Moore. A solution of (S)-serine (8.0 g, 76.1 mmol) in 2 N sodium hydroxide (20 mL) was cooled to 5°C and stirred until no more solid remained. The pH was then adjusted to 9.8 using 2 N sodium hydroxide. Benzyl chloroformate (12 mL, 83.7 mmol) was added slowly over 1.5 h during which time the temperature was kept between 5-8°C and the pH was kept between 9.8-10.0 using 2 N sodium hydroxide with the aid of a pH meter. After the addition of benzyl chloroformate was complete the solution was stirred an additional hour at 10°C in order to hydrolyze any (S)-N,O-biscarbobenzylxylo serine. The basic solution was then extracted with diethyl ether (2 x 150 mL). The aqueous layer was then covered with ethyl acetate (200 mL) and cooled in an ice bath. The solution was then acidified to pH = 3 by the careful addition of 6 N HCl. The layers were then separated and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to yield a white solid. The product was then recrystallized from ethyl acetate to yield a white crystalline solid (13.78 g, 57.60 mmol, 76%): mp 121-122°C (Lit.59 117-119); [α]24° +5.9 (c 6.0, CH₃COOH) (Lit.59 [α] +5.8 c 6, CH₃COOH); IR (CH₂Cl₂, NaCl) νmax 3450, 1746, 1688, 1649, 1537, and 1250 cm⁻¹: ¹H NMR (500 MHz; MeCN-d₃) δ: 12.24 (1H, br s, COOH), 7.29-7.22 (5H, m, Ar H), 5.89 (1H, br s, NH), 5.01 (2H, s,
CH₂Ph). 4.15 (1H, m, C(2)H), 3.78 (1H, dd, J₈₋₋₇ = 11.3 Hz and J₇₋ₓ = 4.4 Hz, C(3)H), 3.70 (1H, dd, J₈₋₋₇ = 11.3 Hz and J₇₋ₓ = 4.0 Hz, C(3)H) 1.89 (1H, br s, CH₂OEt). ¹³C NMR (125 MHz; MeCN-d3) δ: 175.4, 160.2, 141.0, 132.4, 131.9, 131.7, 70.3, 65.8, 59.9; MS m/e 239 (M⁺): HRMS m/e for C₁₁H₁₃NO₅ calcd. (M⁺) 239.0794, found 239.0794. Anal. Calcd. For C₁₁H₁₃NO₅: C, 55.18; H, 5.43; N, 5.85. Found: C, 55.41; H, 5.57; N, 5.75.

(S)-N-Benzzyloxy carbonylserine tert-butyl ester (61)

To a refluxing solution of compound (60) (4.28 g, 17.9 mmol) in a mixture of l-butanol (10 mL) and benzene (20 mL) under a nitrogen atmosphere was added N, N-dimethylformamide dineopentylacetal (4.145 g, 5.0 mL, 17.9 mmol) over 0.5 h. The resulting reaction was refluxed for an additional 3 h and then cooled to room temperature. The benzene was evaporated under reduced pressure and saturated aqueous sodium bicarbonate was added. The aqueous solution was extracted with ethyl acetate (3 x 100 mL), and the combined organic fractions were dried over magnesium sulfate and evaporated under reduced pressure to yield a yellow oil which solidified on standing. The solid was recrystallized from ethyl acetate/hexanes to yield white crystals (2.90 g, 9.8 mmol, 55%): mp 93-94°C; [α]D +2.5 (c 1.0 in CH₂Cl₂); IR (CH₂Cl₂, NaCl) vₘₐₓ 3430, 1724, 1521, 1455, and 1157 cm⁻¹; ¹H NMR (500 MHz; CDCl₃) δ: 7.34-7.30 (5H, m, Ar H), 5.84 (1H, br s, NH), 5.10 (2H, s, CH₂Ph), 4.32 (1H, br s, C(2)H), 3.90 (2H, m,
C(3)H), 2.84 (1H, br s, OH), 1.47 (9 H, s, OC(CH₃)₃). ¹³C NMR (125 MHz; CDCl₃) δ:
169.5, 156.3, 136.1, 128.4, 128.1, 128.0, 82.6, 67.0, 63.4, 56.6, 27.9. Anal. Calcd. For
C₁₅H₂₁NO₂: C. 60.95; H. 7.11; N. 4.74. Found: C. 60.47; H. 7.10; N. 4.78.

(S)-N-Triphenylmethylserine tert-butyl ester (62)

A stirred solution of compound (61) (1.18 g, 4.0 mmol) and palladium (5% on activated
charcoal). (0.5 g) in THF (30 mL) was placed under a hydrogen atmosphere. The
resulting reaction was stirred for 16 h until no starting material remained (as judged by
TLC). The resulting suspension was filtered through a pad of Celite®, and the Celite®
was washed with methanol. The organic solution was evaporated under reduced pressure
and the flask was purged with nitrogen. The residual oil was dissolved in chloroform (25
mL) and cooled to 0°C. Triethylamine (1.05 mL, 7.5 mmol) was then added with stirring
followed after several minutes with the addition of triphenylmethyl chloride (1.04 g, 3.7
mmol) in chloroform (10 mL). After the resulting solution was stirred at 0°C for 24 h,
the solution was washed with 10% citric acid (30 mL), washed with water (30 mL), dried
over magnesium sulfate, and concentrated under reduced pressure to yield a oil which
solidified upon standing. The solid was recrystallized from ethyl acetate/hexanes to yield
a white crystalline solid (1.50 g, 3.72 mmol, 99%): mp 133-134°C; [α]²⁴D -11.7 (c 1 in
CH₂Cl₂); IR (CH₂Cl₂, NaCl) νmax 3450, 1725, 1447, and 1153 cm⁻¹; ¹H NMR (500 MHz;
$\text{CDCl}_3 \delta$: 7.53 (6H, d, J = 7.4 Hz, ortho- Ar H), 7.30-7.22 (9H, m, meta-, para- Ar H), 3.66 (1H, br s, C(2)H), 3.52-3.42 (2H, m, C(3)H), 3.22 (1H, br s, NH), 2.60 (1H, br s, OH), 1.31 (9H, s, OC(CH$_3$)$_3$): $^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$: 172.6, 145.8, 128.7, 127.9, 126.5, 81.3, 71.1, 64.8, 57.9, 27.8; Anal. Calcd. For C$_{26}$H$_{30}$NO$_3$: C, 77.32; H, 7.19; N, 3.47. Found: C, 77.53; H, 7.40; N, 3.28.

(5)-N-Triphenylmethyl-O-tosylserine tert-butyl ester (63)

To a stirring solution of compound (62) (1.48 g, 3.67 mmol) in pyridine (20 mL) at -10°C was added tosyl chloride (1.40 g, 7.34 mmol). The resulting solution was stirred for 1 h at -10°C followed by 30 h at 0°C until no starting material remained (as judged by TLC). The resulting solution was then poured into a beaker of ice-water (100 mL). Continued stirring resulted in the formation of a white solid which was filtered, washed with distilled water and dried under reduced pressure. The solid was recrystallized from ethyl acetate/hexanes to yield a white solid (1.41 g, 2.5 mmol, 69%): mp 133-135°C; [\(\alpha\]$_D$] +1.7 (c 1 in CH$_2$Cl$_2$); IR (CH$_2$Cl$_2$, NaCl) $\nu_{\text{max}}$ 3484, 1741, 1447, 1367, and 1155 cm$^{-1}$; $^1$H NMR (500 MHz; CDCl$_3$) $\delta$: 7.80 (2H, d, J = 8.1 Hz, tosyl ortho protons), 7.40-7.17 (17H, m, Ar H), 4.20 (1H, dd, $J_{AB} = 9.4$ Hz and $J_{AX} = 3.7$ Hz, C(3)H), 3.98 (1H, dd, $J_{AB} = 9.4$ Hz and $J_{BX} = 5.4$ Hz, C(3)H), 3.40 (1H, br s, C(2)H), 2.85 (1H, br s, NH), 2.46 (3H, s, tosyl CH$_3$), 1.18 (9H, s, OC(CH$_3$)$_3$): $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$: 171.3, 145.7, 145.1.
(S)-N-Triphenylmethyaziridinecarboxylate tert-butyl ester (64)

To a stirred solution of compound (63) (1.13 g, 2.02 mmol) in THF (30 mL) under nitrogen was added triethylamine (0.57 mL, 4.0 mmol). The resulting solution was refluxed until no starting material remained (as judged by TLC). The solution was washed with 10% citric acid (30 mL), saturated sodium bicarbonate (30 mL), and water (30 mL), and then dried over magnesium sulfate and concentrated under reduced pressure to yield a yellow solid. The solid was recrystallized from ethyl acetate-hexanes to yield a white crystalline solid (740 mg, 1.91 mmol, 95%); mp 149-151°C; [α]$_D^{24}$ -83.6 (c 1 in CH$_2$Cl$_2$); IR (CH$_2$Cl$_2$, NaCl) $\nu_{max}$ 1736, 1448, and 1150 cm$^{-1}$; $^1$H NMR (500 MHz; CDCl$_3$) $\delta$: 7.52 (6H, d, J = 7.6 Hz, ortho Ar H), 7.30-7.22 (9H, m, meta and para Ar H), 2.22 (1H, br s, C(2)H), 1.80 (1H, dd, $J_{AH} = 6.0$ Hz and $J_{AX} = 2.7$ Hz, C(3)H), 1.34 (1H, d, $J_{AH} = 6.0$ Hz, C(3)H), 1.51 (9H, s, OC(CH$_3$)$_3$); $^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$: 170.7, 143.8, 129.4, 127.5, 126.8, 81.0, 74.2, 32.4, 28.3, 28.0; Anal. Calcd. For C$_{36}$H$_{27}$NO$_2$: C, 80.93; H, 7.00; N, 3.63. Found: C, 80.99; H, 7.03; N, 3.61.
(S)-N-tert-Butyloxy carbonylaziridine carboxylate tert-butyl ester (65)

To a stirred solution of compound (64) (300 mg, 0.78 mmol) in chloroform (3.0 mL) and methanol (2.5 mL) at -10°C was added trifluoroacetic acid (1.5 mL). The resulting solution was stirred under nitrogen at -10°C for 2 h. Removal of the solvent under reduced pressure at 0°C yielded a yellow gum. Triethylamine (8 mL) and di-tert-butyl dicarbonate (1.4 equiv., 237 mg, 1.09 mmol) were added and the resulting reaction was stirred at 0°C for 2 h. Ethyl acetate (50 mL) was then added and the mixture was washed with saturated sodium bicarbonate (20 mL), dried over magnesium sulfate, and evaporated under reduced pressure at temperatures below 20°C. The residue was purified by flash chromatography on silica gel with 7:1 petroleum ether:ethyl acetate as the eluent (Rf = 0.56 - develops under molybdic acid) to provide the product as a thermally unstable oil (161 mg, 0.66 mmol, 85%); IR (CH₂Cl₂, NaCl) νmax 1809, 1738, 1370, and 1144 cm⁻¹; ¹H NMR (300 MHz; CDCl₃) δ: 2.92 (1H, dd, Jₐₕ = 5.1 Hz and Jₐₓ = 3.0 Hz, C(3)H), 2.45 (1H, dd, Jₐₓ = 3.0 Hz and Jₐₓ = 1.2 Hz, C(2)H), 2.30 (1H, dd, Jₐₕ = 5.1 Hz and Jₐₓ = 1.2, C(3)H), 1.48 (9H, s, OC(CH₃)₃), 1.45 (9H, s, OC(CH₃)₃); ¹³C NMR (75 MHz; CDCl₃) δ: 169.5, 159.3, 81.8, 80.5, 34.4, 31.6, 28.0, 27.6; MS m/e 243 (M⁻); HRMS m/e for C₁₂H₂₁NO₃ calcd. (M⁺) 243.1470, found 243.1479.
3-Bromo-7-azaindole (67)

Prepared by a modification of the procedure of Robison and Robison.\textsuperscript{17} To a stirred solution of 7-azaindole (2.36 g, 20 mmol) in chloroform (30 mL) at 0°C was added bromine (3.20 g, 1.04 mL, 20 mmol) in carbon tetrachloride (38 mL). After stirring for 5 min, 2 N HCl (40 mL) was added and the aqueous layer was separated and filtered. Addition of 2 N NaOH slowly until a pH of 7.5 was reached resulted in a dark solution. Cooling of this dark solution at 5°C for 24 h resulted in the formation of a white precipitate. The precipitate was filtered and dried under reduced pressure and purified by flash chromatography on silica gel with 2:1 petroleum ether:ethyl acetate as the eluent ($R_f$ = 0.29) to provide the product as a white solid. The solid was recrystallized from ethyl acetate to afford white crystals (2.311 g, 11.79 mmol, 59%): mp = 188-190°C (Lit.\textsuperscript{17} 188-189°C). IR (CH\textsubscript{2}Cl\textsubscript{2}, NaCl) $\nu_{\text{max}}$ 3335, 1586, 763, and 646 cm$^{-1}$. $^1$H NMR (500 MHz: CDCl$\textsubscript{3}$) $\delta$: 11.18 (1H, br s, NH), 8.46 (1H, br s, C(6)H), 7.94 (1H, d, $J$ = 7.7 Hz, C(4)H), 7.42 (1H, s, C(2)H), 7.21 (1H, dd, $J_1$ = 4.6 Hz, $J_2$ = 7.7 Hz, C(5)H); $^{13}$C NMR (125 MHz: CD$_3$COOD) $\delta$: 147.6, 143.8, 134.6, 130.4, 125.6, 120.2, 93.0.
1-Benzyl-3-bromo-7-azaindole (68)

To a mixture of 3-bromo-7-azaindole (67) (350 mg, 1.80 mmol) and sodium hydride (1.1 equiv., 47 mg, 2.0 mmol) (prepared from washing 60% sodium hydride in mineral oil with diethyl ether) was added DMF (15 mL), dropwise under a nitrogen atmosphere. After stirring for 1 h, benzyl bromide (1.1 equiv., 0.24 mL, 2.0 mmol) was added, and the resulting suspension was stirred for 12 h. The reaction was quenched with saturated ammonium chloride (20 mL), and diethyl ether (100 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 50 mL), and the combined organic extracts were washed with saturated sodium bicarbonate (3 x 50 mL), and brine (1 x 50 mL) and then dried over magnesium sulfate and evaporated under reduced pressure to yield an oil. The residue was purified by flash chromatography on silica gel with 5:1 petroleum ether:diethyl ether as the eluent (Rf = 0.40) to afford the product as a white solid. The solid was recrystallized from ethyl acetate/hexanes to yield white needles (386 mg, 1.34 mmol, 75%): mp = 57-58°C; IR (CH₂Cl₂, NaCl) ν<sub>max</sub> 1595, 1565, 1420, 1321, 766, and 697 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz; CDCl₃) δ: 8.42 (1H, d, J = 4.5 Hz, C(6)H), 7.89 (1H, d, J = 7.9 Hz, C(4)H), 7.34-7.24 (5H, m, Ph-H), 7.20, (1H, s, C(2)H), 7.17 (1H, dd, J<sub>AX</sub> = 4.5 Hz, J<sub>XX</sub> = 7.9 Hz, C(5)H), 5.49 (2H, s, CH₂Ph); <sup>13</sup>C NMR (125 MHz; CDCl₃) δ: 146.6, 144.1, 137.0, 128.7, 127.8, 127.6, 127.4, 126.6, 119.8, 116.4, 88.6, 47.8; Anal. Calcd. For C₁₄H₁₁N₂Br: C, 58.50; H, 3.83; N, 9.75. Found: C, 58.90; H, 3.52; N, 9.56.
1-Benzyl-3-bromomagnesium-7-azaindole (69)

To a stirred solution of 1-benzyl-3-bromo-7-azaindole (68) (144 mg, 0.50 mmol) and magnesium turnings (30 mg) in THF (5 mL) under nitrogen was added 1 crystal of iodine and 1 drop of 1,2-dibromoethane. The resulting solution was refluxed for 1 h to give a 0.1 M solution of the Grignard reagent. To prove the product was formed, an aliquot was removed and quenched with water to give a product which was spectroscopically identical to 1-benzyl-7-azaindole (58).

(S)-Serine benzyl ester benzenesulfonate (70)

(S)-Serine benzyl ester benzenesulfonate was prepared from (S)-serine in 60% yield according to the procedure of Jackson.\textsuperscript{51} mp = 97-98°C (Lit.\textsuperscript{51} 97-98°C). The product was spectroscopically identical to the literature.
**Benzyl 2(S)-[(tert-butoxycarbonyl)amino]-3-hydroxypropionate (71)**

Benzyl 2(S)-[(tert-butoxycarbonyl)amino]-3-hydroxypropionate (71) was prepared from (S)-serine benzyl ester benzenesulfonate (70) in 76% yield according to the procedure of Jackson.\(^{51}\) mp = 69-70°C (Lit.\(^{51}\) 70-71°C). The product was spectroscopically identical to the literature.

**Benzyl 2(S)-[(tert-butoxycarbonyl)amino]-3-p-toluenesulfonyloxypropionate (72)**

Benzyl 2(S)-[(tert-butoxycarbonyl)amino]-3-p-toluenesulfonyloxypropionate (72) was prepared from benzyl 2(S)-[(tert-butoxycarbonyl)amino]-3-hydroxypropionate (71) in 64% yield according to the procedure of Jackson.\(^{51}\) mp = 92-94°C (Lit.\(^{51}\) 95-96°C). The product was spectroscopically identical to the literature.
Benzyl 2(S)-[(tert-butoxycarbonyl)amino]-3-iodopropionate (15)

Benzyl 2(S)-[(tert-butoxycarbonyl)amino]-3-iodopropionate (15) was prepared from benzyl 2(S)-[(tert-butoxycarbonyl)amino]-3-p-toluenesulfonyloxypropionate (72) in 54% yield according to the procedure of Jackson.\textsuperscript{51} mp = 79-80°C (Lit.\textsuperscript{51} 79-80°C). The product was spectroscopically identical to the literature.

Zn*  
**Rieke Zinc (73)**

Rieke zinc was prepared according to the procedure of Rieke.\textsuperscript{52}

Benzyl 2(S)-[(tert-butoxycarbonyl)amino]-3-zinciodopropionate (16)

Benzyl 2(S)-[(tert-butoxycarbonyl)amino]-3-zinciodopropionate (16) was prepared from compound (15) according to the procedure of Knochel.\textsuperscript{53} Product formation was judged by disappearance of starting material on TLC.
**3-Iodo-7-azaindole (76)**

To stirred solution of 7-azaindole (2.36 g, 20 mmol) in chloroform (30 mL) at 0°C was added iodine (4.9 g, 19.4 mmol) in dichloromethane (140 mL). After stirring for 15 min, 2 N HCl (40 mL) was added and the aqueous layer was separated and filtered. Addition of 2 N NaOH slowly until a pH of 7.5 was reached resulted in a dark solution. Cooling of this solution at 5°C for 24 h resulted in the formation of a white precipitate. The precipitate was filtered and dried under reduced pressure and purified by flash chromatography on silica gel with 2:1 petroleum ether:ethyl acetate as the eluent ($R_f = 0.28$) to provide the product as a white solid. The solid was recrystallized from ethyl acetate to afford white crystals (750 mg, 3.07 mmol, 15%): mp = 194-196°C (Lit. $^{55}$ 194-195°C); IR (CH$_2$Cl$_2$, NaCl) $v_{\text{max}}$ 3350, 1581, 764, and 641 cm$^{-1}$. $^1$H NMR (500 MHz: CDCl$_3$) δ: 10.73 (1H, br s, NH), 8.42 (1H, br s, C(6)H), 7.80 (1H, d, J = 7.8 Hz, C(4)H), 7.48, (1H, s, C(2)H), 7.20 (1H, m, C(5)H); $^{13}$C NMR (125 MHz; CD$_3$COOD) δ: 147.7, 143.1, 137.0, 135.9, 129.3, 120.4, 58.4.
**1-(tert-Butyloxycarbonyl)-3-iodo-7-azaindole (77)**

To a mixture of 3-iodo-7-azaindole (76) (270 mg, 1.11 mmol) and sodium hydride (1.2 equiv., 32 mg, 1.33 mmol) (prepared from washing 60% sodium hydride in mineral oil with diethyl ether) was added THF (20 mL), dropwise under a nitrogen atmosphere. After stirring for 1 h, di-tert-butyl dicarbonate (1.3 equiv., 314 mg, 1.44 mmol) in THF (10 mL) was added, and the resulting suspension was stirred for 12 h. The reaction was quenched with saturated ammonium chloride (20 mL), and diethyl ether (100 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 50 mL), and the combined organic extracts were washed with saturated sodium bicarbonate (3 x 50 mL), and brine (1 x 50 mL) and then dried over magnesium sulfate and evaporated under reduced pressure to yield a yellow oil. The oil was covered with a layer of hexanes and cooling afforded off-white crystals (380 mg, 1.10 mmol, 91%): mp 112-114°C; IR (CH₂Cl₂, NaCl) ν<sub>max</sub> 1754, 1568, and 766 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz; CDCl₃) δ: 8.54 (1H, d, J = 4.0 Hz, C(6)H), 7.79 (1H, s, C(2)H), 7.70 (1H, br s, C(4)H), 7.26 (1H, br m, C(5)H), 1.66 (9H, s, OC(CH₃)₃); <sup>13</sup>C NMR (125 MHz; CDCl₃) δ: 147.4, 146.8, 146.2, 130.7, 129.7, 125.2, 119.2, 84.7, 61.8, 28.0: MS m/e 344 (M⁺): HRMS m/e for C₁₂H₁₃N₂O₂I calcd. (M⁺) 344.0022, found 344.0023.
**Procedure for Coupling Reaction**

A suspension of zinc (187 mg, 2.81 mmol) in dry THF (0.2 mL) and 1,2-dibromoethane (0.082 mL, 0.14 mmol) was heated under argon to 60°C for 5 min. After cooling the mixture to 35°C, trimethylsilyl chloride (0.004 mL, 0.03 mmol) was added and the mixture was sonicated for 30 minutes. At this point benzyl 2(S)-[(tert-butoxycarbonyl)amino]-3-iodopropionate (15) (180 mg, 0.44 mmol) in dry THF (0.7 mL) was slowly added and the mixture was stirred for 15-25 min until no starting material remained (as judged by TLC). The solution of the zinc reagent (16) was removed with a syringe and added to 1-(tert-butoxycarbonyl)-3-iodo-7-azaindole (77) (106 mg, 0.31 mmol) in dry THF (0.5 mL) together with bis(tri-o-tolylyphosphate)palladium dichloride (35 mg, 0.04 mmol). The crude reaction product was obtained by evaporation of the solvent under reduced pressure.
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Vita Auctoris

Name: Edward Joseph Brnardic

Place of Birth: Windsor, Ontario, Canada

Year of Birth: 1973

Education:

F. J. Brennan High School, Windsor, Ontario
June 1992

University of Windsor, Windsor, Ontario
May 1996, B. Sc. Honours Chemistry

University of Windsor, Windsor, Ontario
Well maybe I can’t.

-Rocky Balboa, Rocky IV