

The Pennsylvania State University

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Department of Chemistry

**STUDIES TOWARD THE SYNTHESIS OF TMC-95A AND DEVELOPMENT
OF AN ENANTIOSELECTIVE PUMMERER REACTION FOR THE
SYNTHESIS OF 3,3-SPIROCYCLIC OXINDOLES**

A Thesis in

Chemistry

by

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ABSTRACT

Oxidative cyclizations of tryptophan derivatives have seen little use in total synthesis. The use of this methodology in a model system of TMC-95A was explored. This method failed to lead to products for continuation of the synthesis. A new approach to indole C(3) cyclizations was proposed using Pummerer reaction chemistry. This method was found to be successful on both simpler tryptophan derivatives and on the TMC-95A model system, leading to the correct regiochemistry and stereochemistry for TMC-95A.

Further extension of the Pummerer reaction methodology was desired through attempts toward an enantioselective variant with carbon nucleophiles. Results with silyl enol ether nucleophiles showed excellent stereoselectivity.

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Chapter 1

3,3-Spirocyclic Oxindoles – Overview of Synthetic Methods

The search for new methods for the synthesis of 3,3-disubstituted oxindoles is of interest to synthetic organic chemists. Spurring this interest is the large number of 3,3-disubstituted oxindole alkaloid natural products (Figure 1.1).¹ A variety of methods have been developed for accessing these systems.² Unfortunately, several limitations can be identified, with little stereochemical control being the main problem. Additionally, many methods were designed with a specific skeleton as the focus, and have not been shown to be generally applicable.

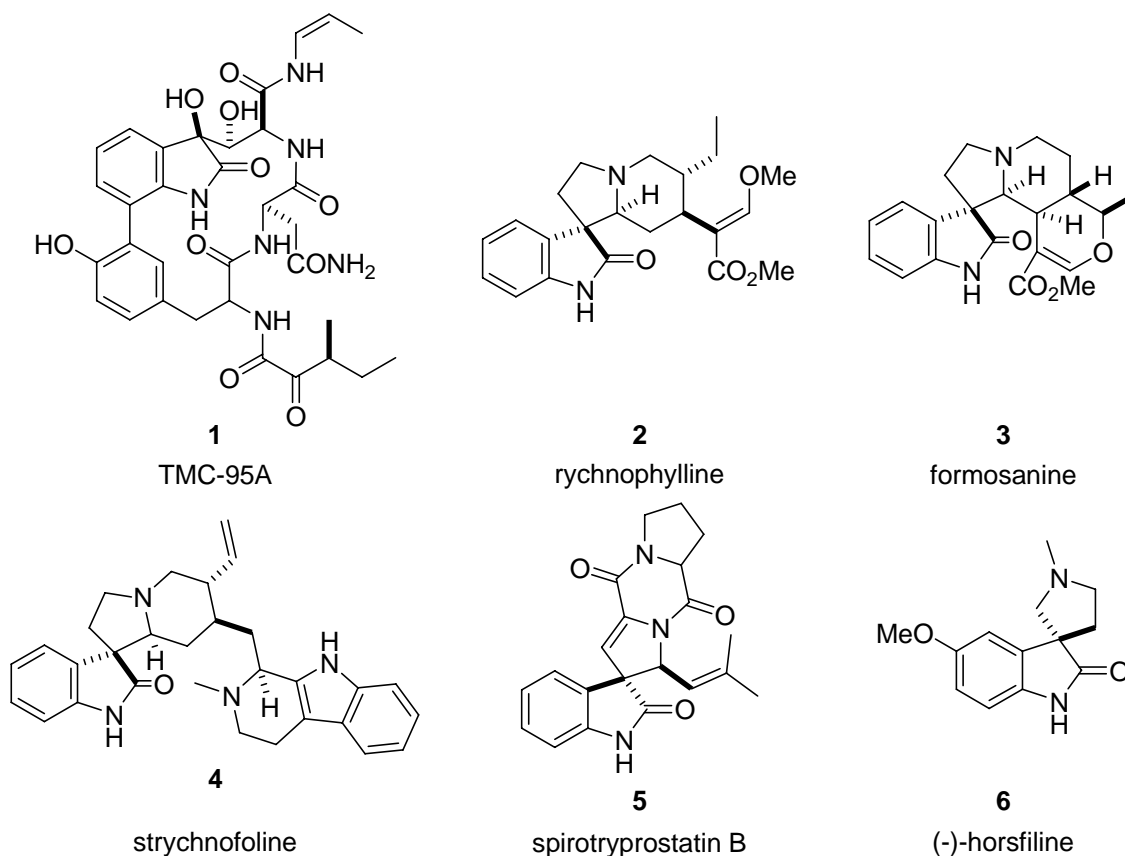


Figure 1.1: 3,3-Disubstituted oxindole containing natural products.

Methods for 3,3-disubstituted oxindole construction vary extensively. One main focus is a biosynthetic-type oxidative rearrangement pathway. Others involve ring

expansion or ring contraction of an already constructed C(3) spirocycle. Another approach uses radicals to close the five-membered ring. 1,3-dipolar cycloadditions have also seen application. There are also examples of Heck coupling, nitroolefination, and Mannich reactions. Some newer methods include photochemistry or a samarium promoted reductive cyclization. These approaches are exemplified below.

1.1 Oxidative Rearrangement

One of the more common methods for formation of 3,3-disubstituted oxindoles follows an oxidative rearrangement strategy. It is postulated that this approach could be a biomimetic route.³ In this mechanism, the N-C(2)-C(3) unit acts as an enamine. An electrophile is added across the C(2)-C(3) double bond of the indole, leading to an imine or iminium ion. Addition of water at C(2) forms an indoline as illustrated in the conversion of **7** into **9**. Subsequent deprotonation of the hydroxyl group initiates a pinacol-type 1,2-shift, resulting in the product oxindole **10**.

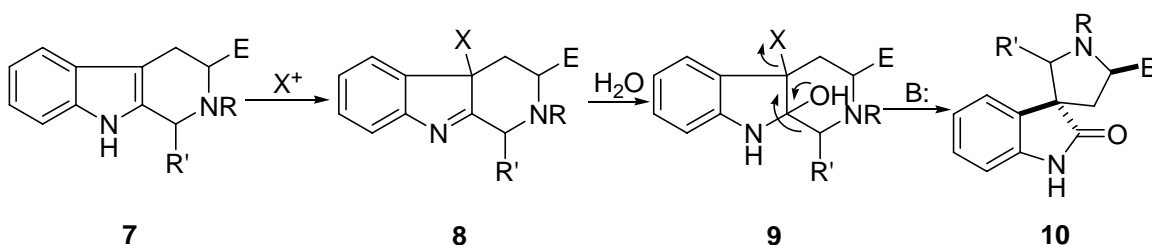


Figure 1.2: Biomimetic type rearrangement.

Several electrophiles have been used successfully in this process. Martin and coworkers⁴ employed this approach in their synthesis of pteropidine (**13**). Indole **11** was treated with *t*-BuOCl leading to chlorination at C(3). Subsequent ring contraction to a 5-membered spirocycle at C(3) set the framework for pteropidine. Reduction of **12** followed by epimerization at C(3) led to the natural product.

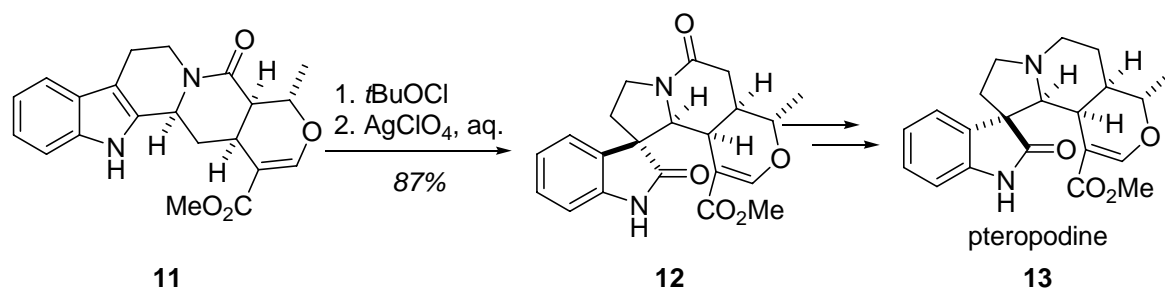


Figure 1.3: Pterodine synthesis key step.

Borschberg and coworkers⁵ used *N*-bromosuccinimide (NBS) in the key step of their synthesis of (-)-horsfiline. Addition of NBS to indole **15** followed by addition of acetic acid formed bromoacetate **15a** en route to spirocycle **16**. This rearrangement completed the skeleton of (-)-horsfiline. It was found that some stereocontrol was possible based on the substitution of the piperidine ring's nitrogen atom.

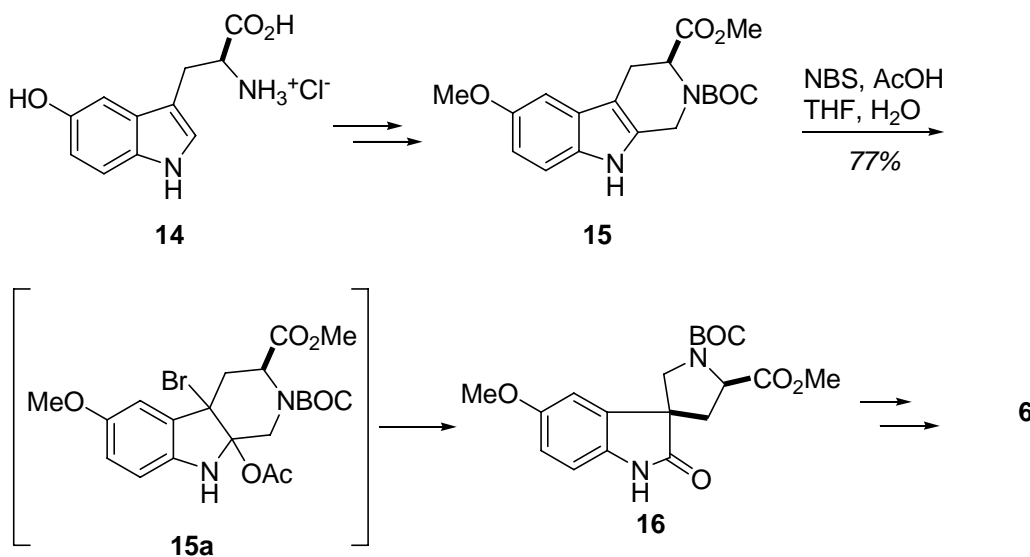


Figure 1.4: Horsfiline synthesis – oxidative rearrangement method.

Two additional electrophiles that have been used are sodium tungstate⁶ and lead tetraacetate.^{1c} Figure 1.5 displays their use in the key steps of the syntheses of racemic

coerulescine and horsfiline. Both electrophiles are proposed to follow the same general mechanism. Osmium tetroxide has also seen some use in this methodology.⁷

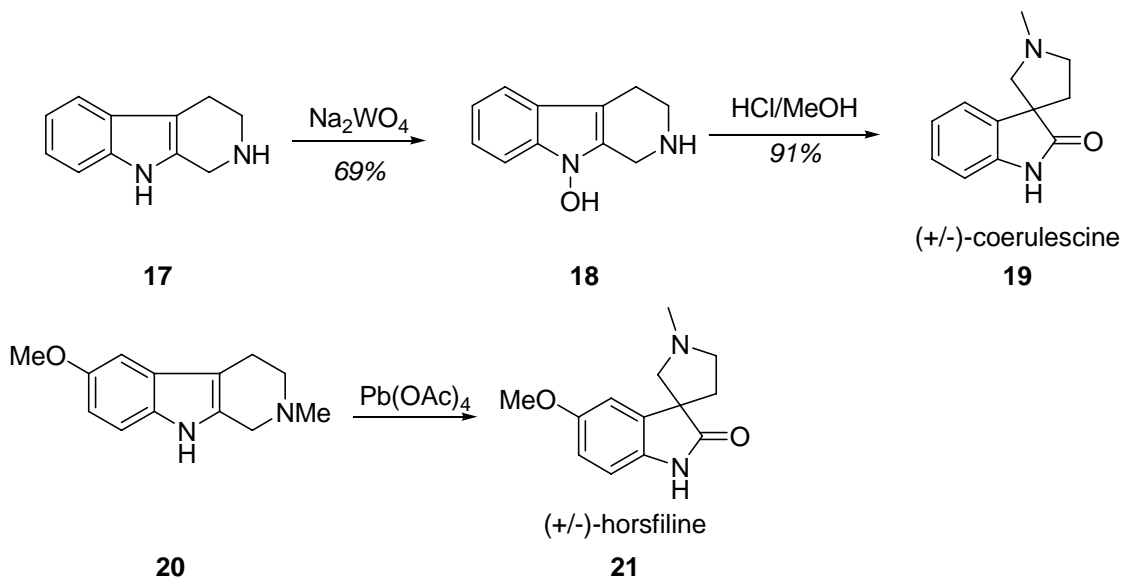


Figure 1.5: Horsfiline and coerulescine syntheses.

1.2 Claisen rearrangement

Another method for the formation of 3,3-disubstituted oxindoles is shown in figure 1.6.⁸ Addition of *N*-chlorosuccinimide (NCS) to indole **22** leads to electrophile addition at C(3). Instead of water, allyl alcohol adds to the imine, resulting in **24**. This compound undergoes a Claisen rearrangement, delivering the oxindole. Spirocycles can be formed from subsequent elaboration if needed.

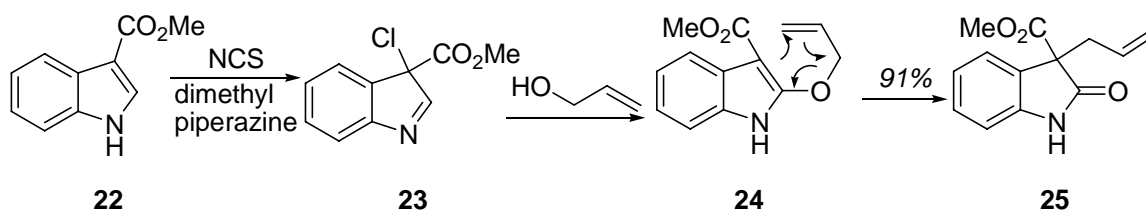


Figure 1.6: Claisen rearrangement to form oxindoles.

Another example is illustrated in figure 1.7. Baldwin and Mao⁹ formed hydroxylamine ester **28** through a DCC coupling of **26** and **27**. A Claisen rearrangement of the enolate derived from **28** yielded acid **29** which was converted to the oxindole upon formation of the anhydride of the acid.

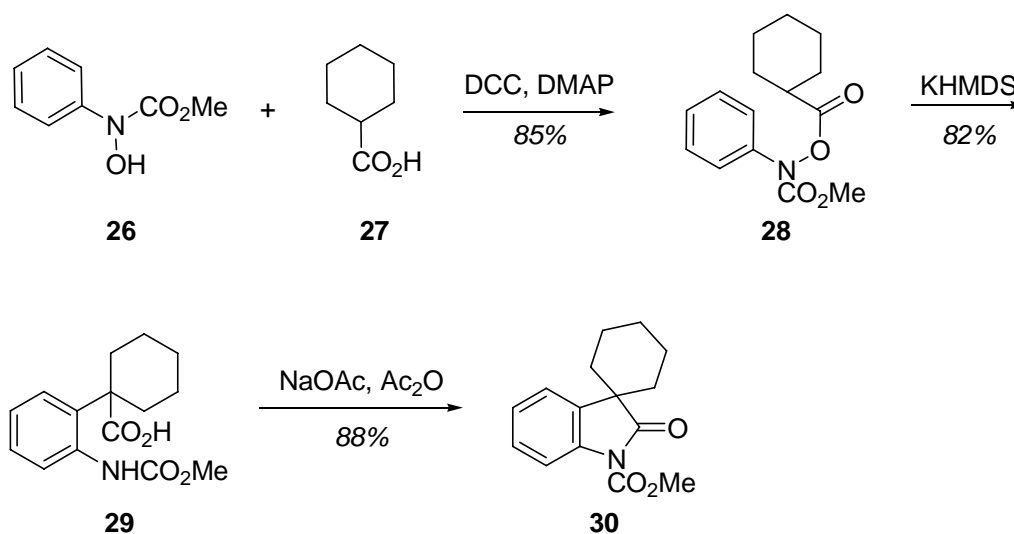


Figure 1.7: Baldwin's oxindole synthesis.

1.3 Oxidative cyclizations of tryptophan derivatives

Another method for 3,3-disubstituted oxindole synthesis is the use of *N*-substituted tryptophan derivatives in electrophile promoted oxidative cyclization reactions to form spirolactones.¹⁰ This method has some mechanistic similarity to the

oxidative rearrangement method. An electrophile is added across the C(2)–C(3) double bond. Nucleophilic addition of the carboxylic acid yields a spirolactone. C(2) is then further oxidized to the oxindole.

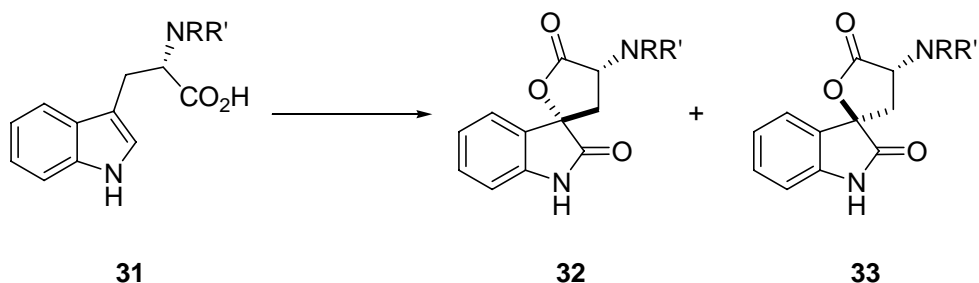


Figure 1.8: Oxidative cyclization results.

R, R'	Conditions	Yield (%)	Ratio 32:33	Ref.
Phthalimide	$\text{CCl}_3\text{SO}_2\text{Cl}/\text{DMSO}$	65	2.5:1	10a
Quinazolinone	$(\text{CH}_3\text{SO}_2)_2/\text{DMSO}$	66	>10:1	10a
Phthalimide	NBS/ NaHCO_3/t -BuOH	89	Not given	10g
Ac, H	<i>t</i> -BuBr/DMSO	67	Not given	10i
Phthalimide	$\text{Tl}(\text{NO}_3)_3$	50	2.1:1	10j
Phthalimide	CrO_3/AcOH	87%	1:1	10d

Table 1.1: Oxidative cyclization results.

This methodology has seen little application in total synthesis. One successful example is Buchi's synthesis of tryptoquivaline **G** (Figure 1.9). In this route, tryptophan derivative **34** was treated with methanesulfonic anhydride in DMSO to yield spirolactone **35** with better than 10:1 diastereoselectivity. None of the other reported examples (Table 1.1) exhibit more than modest stereoselectivity. Also, none of the known examples contain substitution on the carbon adjacent to C(3) of the indole, limiting the scope of the

accessible targets. Additionally, problems exist from overoxidation of the products¹¹ and a lack of control for nucleophilic addition to C(2) versus C(3).¹²

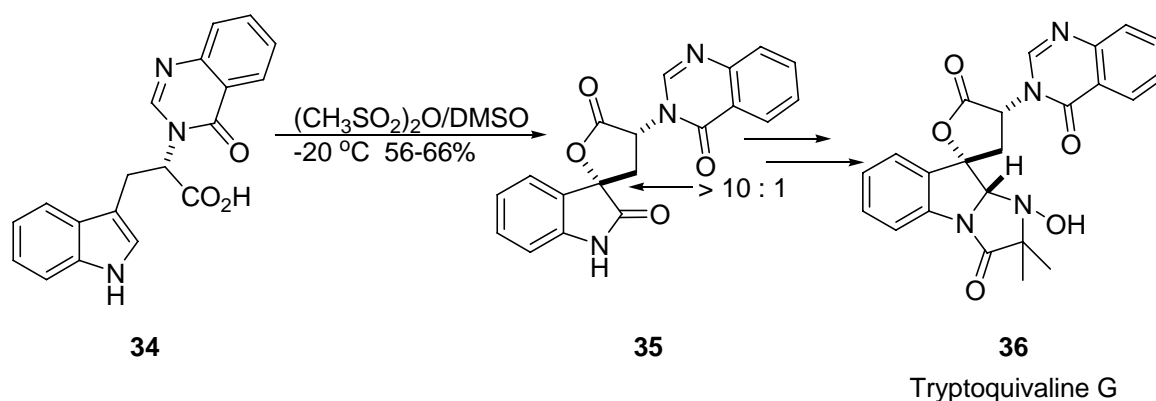


Figure 1.9: Key step in tryptoquivaline G synthesis.

A major problem with this tryptophan-based cyclization lies in the inability to accurately predict its outcome with respect to the site of carboxylate addition (C(2) vs. C(3)). This uncertainty is in part due to a lack of understanding of its mechanism. Three different intermediates have been proposed for this reaction (Figure 1.10).¹⁰ There has been little explanation offered for any stereochemical control observed. Additionally, the lack of natural product targets other than the tryptoquivalines did not spur interest in developing this methodology further.

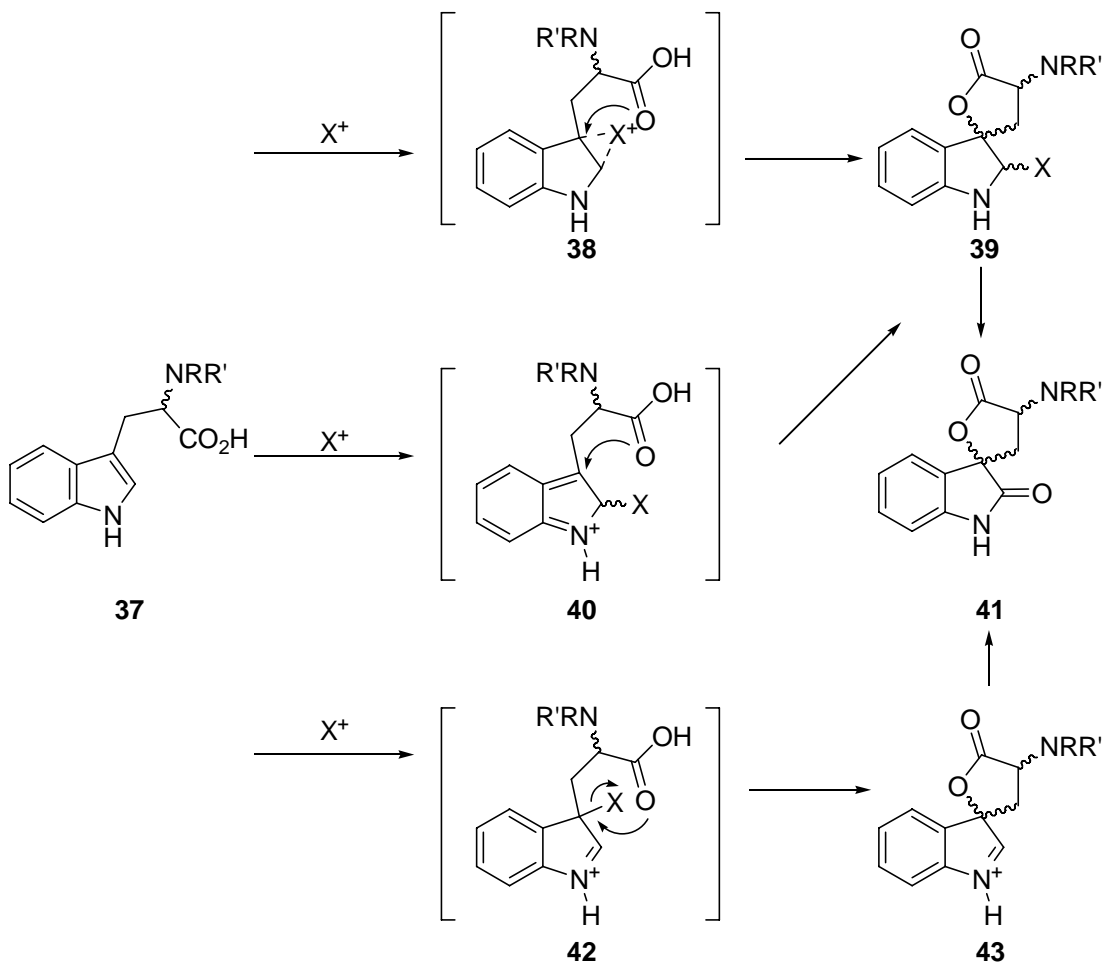


Figure 1.10: Possible mechanisms for the oxidative cyclization.

1.4 Ring expansion reactions

Another method for the preparation of 3,3-disubstituted oxindoles uses ring expansion reactions. Carrier¹³ used this methodology in a synthesis of strychnofoline. A spiro cyclopropane ring at C(3) of oxindole **44** was synthesized. Upon formal [3 + 2] cycloaddition, a single diastereomer, **46**, was obtained. From **46**, the synthesis of strychnofoline was completed in nine additional steps.

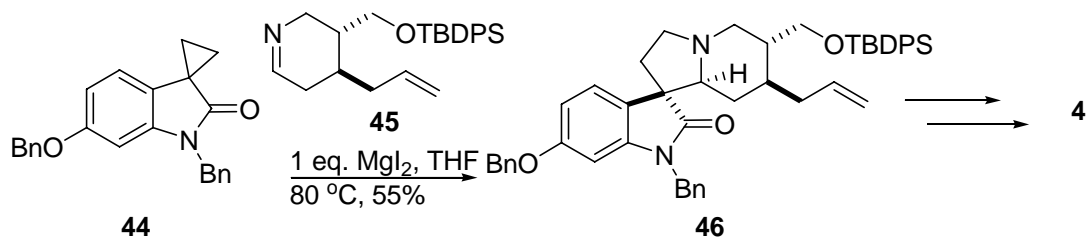


Figure 1.11: Synthesis toward strychnofoline using a ring expansion reaction.

In this methodology, MgI_2 initiates opening of the cyclopropane ring. The key observation was that the charge affinity pattern of the cyclopropane ring was complementary to that of aldimines. Two possible mechanistic pathways have been proposed for this reaction. Both routes lead to the same product although it is unknown whether alkylation of the aldimine occurs prior to, or after, C-C bond formation.

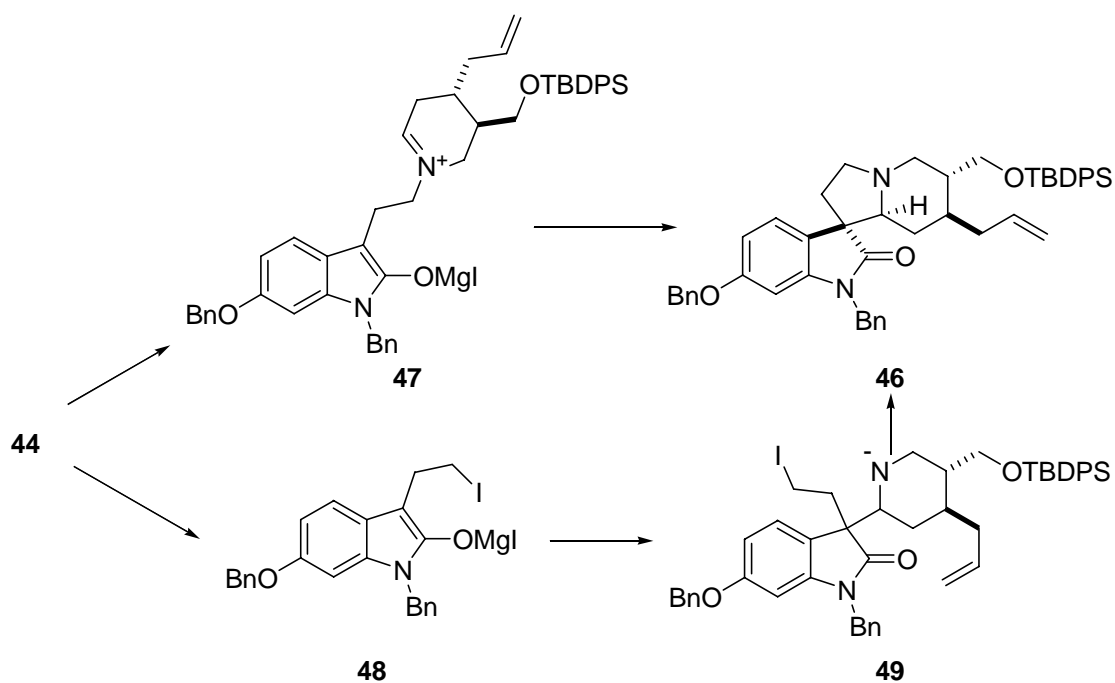


Figure 1.12: Mechanistic possibilities for Carriera's ring expansion reaction.

1.5 Carbene annulation

A new method for spiro lactone formation was recently disclosed by Nair.¹⁴ It is proposed¹⁵ that a homoenolate formed from catalyst **52** and an aldehyde adds into C(3) of an isatin. The resulting alcohol at C(3) cyclizes into the activated carbonyl forming the spiro lactone while simultaneously regenerating the catalyst.

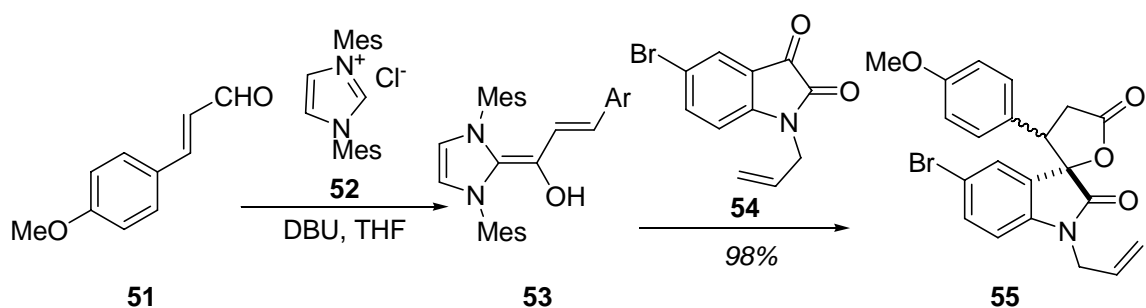


Figure 1.13: Carbene annulation method.

1.6 Radical methods

Several methods that use radical reactions to form 3,3-disubstituted oxindoles are known. Storey and Jones¹⁶ showed that bromoaniline derivatives would undergo radical addition to the α -position of an appended enone, yielding oxindoles upon treatment with tributyltin hydride and AIBN.

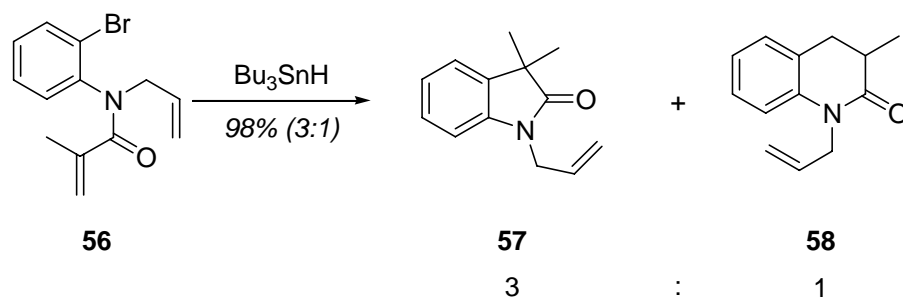


Figure 1.14: Radical addition to enones.

In their total synthesis of gelsemine, Johnson and coworkers¹⁷ found that steric bulk at C(3) caused the failure of other oxindole formation methods. In order to solve this problem, they took advantage of Wender's indole synthesis using benzotriazoles.¹⁸ Photolysis of benzotriazole **59** resulted in a diradical of which two possible resonance forms are **60** and **61**. Ring closure of diradical **61** formed a 2:1 mixture of imino-ethers **62** and **63**. The minor isomer was hydrolyzed to the oxindole and reduced to complete the natural product.

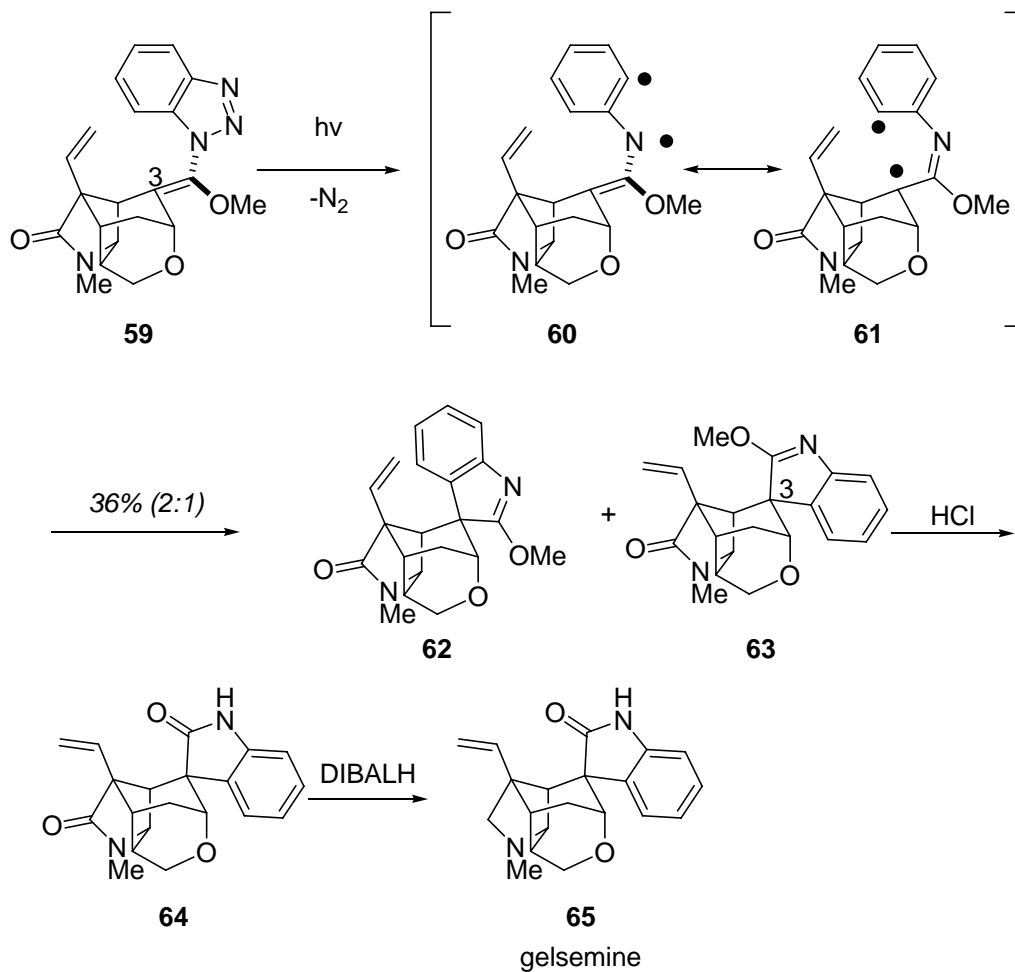


Figure 1.15: Gelsemine synthesis.

Another example of the use of radical reactions in 3,3-disubstituted oxindole formation is provided by Fukuyama and Liu.¹⁹ In this methodology, exposure of isonitrile **66** to benzenethiol and AIBN formed thioimide **67**, which was hydrolyzed to the oxindole.

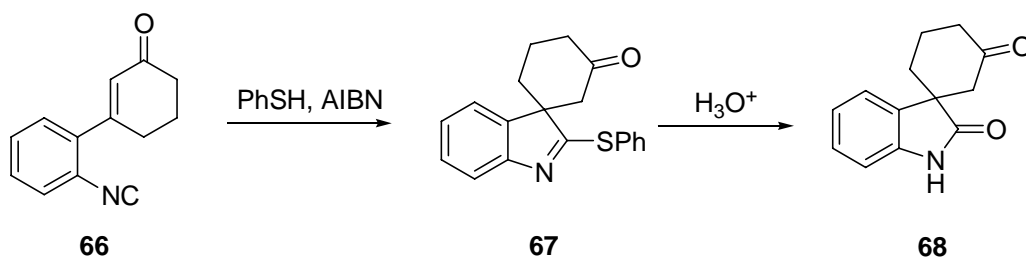


Figure 1.16: Radical route toward oxindoles.

1.7 Mannich Reactions

Oxindole alkaloids are often found to exist as mixtures of C(3) isomers. Wenkert²⁰ and Marion²¹ independently proposed that the isomerization of indole alkaloids in nature could take place through a retro-Mannich/Mannich sequence. Van Tamelen²² used this methodology in the synthesis of a mixture of rychnophylline and isorychnophylline.

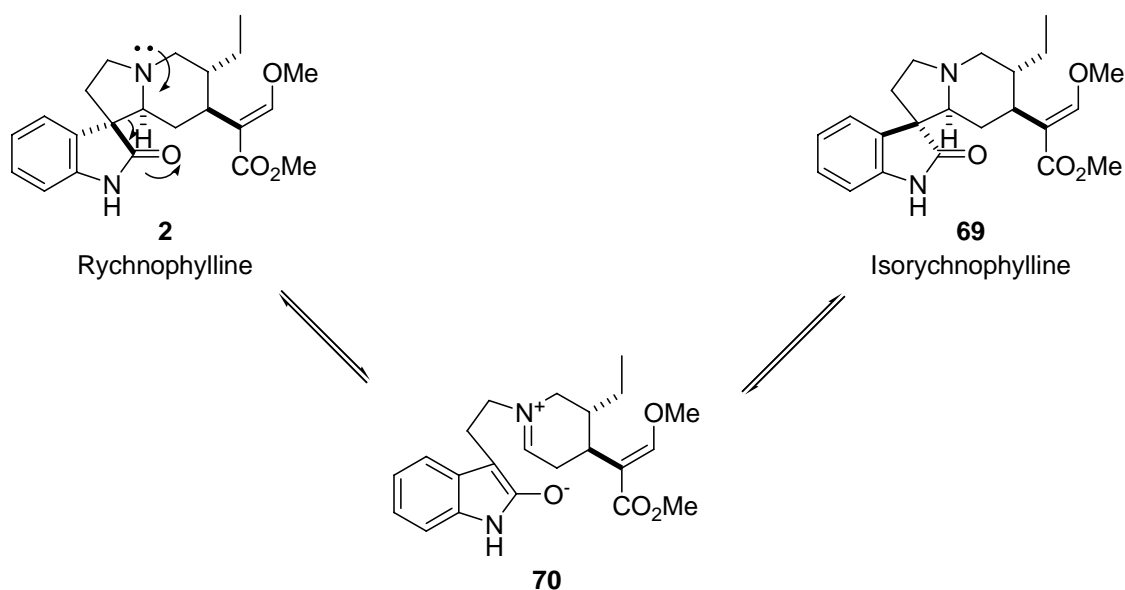


Figure 1.17: Rychnophylline/isorychnophylline isomerization using a Mannich reaction.

In order to further explore the utility of this idea, Laronze²³ employed an intramolecular Mannich reaction with indole **71** and formaldehyde to form racemic horsfiline.

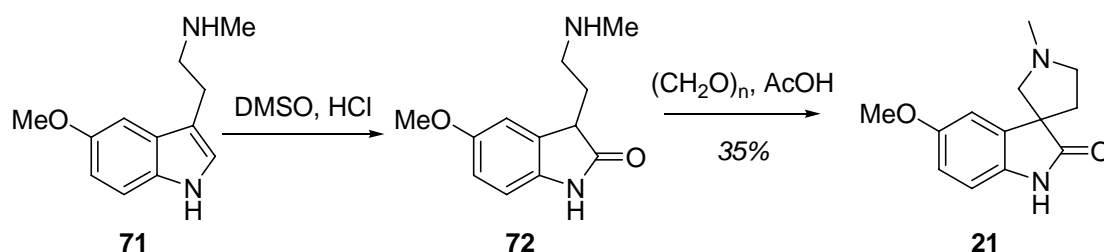


Figure 1.18: Mannich reaction in the synthesis of horsfiline.

Another example in natural product synthesis is Danishefsky's route to spirotryprostatin B.²⁴ A Mannich reaction between oxindole **73** and aldehyde **74** resulted in a nearly equal mixture of all four diastereomers of **75**.

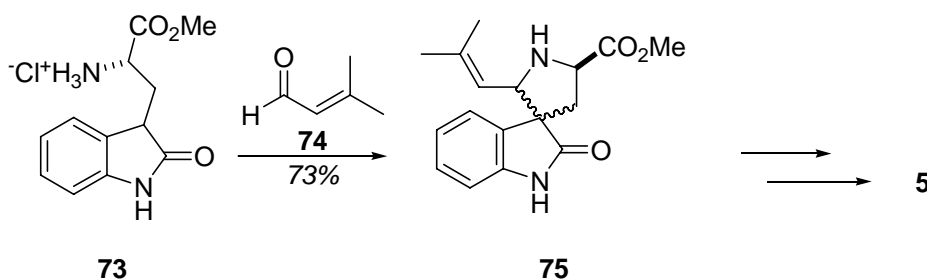


Figure 1.19: Danishefsky's Mannich reaction the route for the spirotryprostatin B synthesis.

1.8 1-3 Dipolar cycloadditions

1,3-Dipolar cycloadditions are another method to access 3,3-disubstituted oxindoles. The first example of this reactivity was demonstrated by Grigg in the use of azomethine ylides with oxindolylidene 3-ylidene acetate.²⁵ More recently, Williams²⁶ used a 1,3 dipolar cycloaddition as the key step in a synthesis of (-)-spirotryprostatin B

(5). The reaction provided a single diastereomeric oxindole, setting four stereocenters in one step. The single diastereomeric product indicated that the reaction proceeds through an E- β -exo transition state.

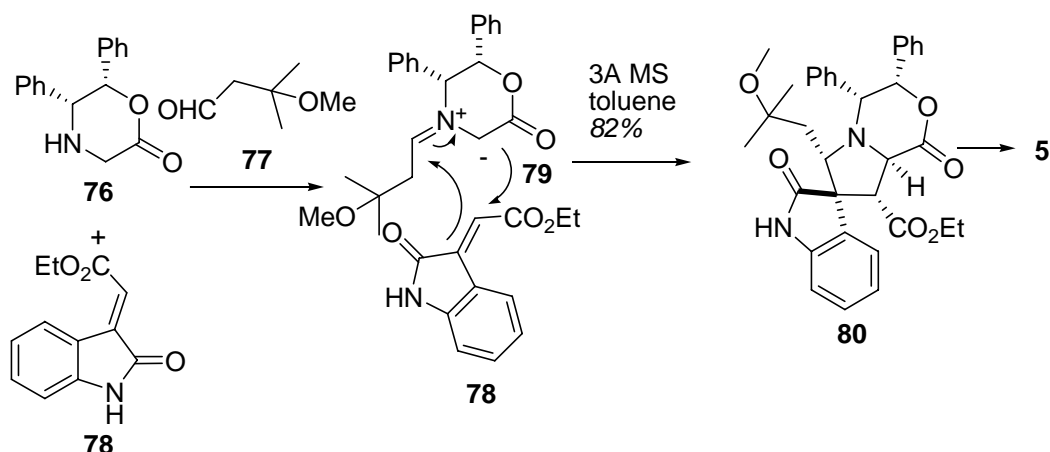


Figure 1.20: Dipolar cycloaddition approach to (-)-spirotryprostatin.

Palmisano used this methodology in a synthesis of (-)-horsfiline.²⁷ Decarboxylation of the iminium ion generated from the reaction of *N*-methylglycine and formaldehyde generated an azomethine ylide **82**. Dipolar cycloaddition of this 4-electron species with **81** yielded the 5-membered ring in **83**. Hydrogenation of the nitro group of **83** simultaneously closed the 5-membered ring of the oxindole to yield (-)-horsfiline. The use of the unusual 2-phenyl-cyclohexyl ester was due to the poor stereoselectivity (< 43%) seen with other esters.

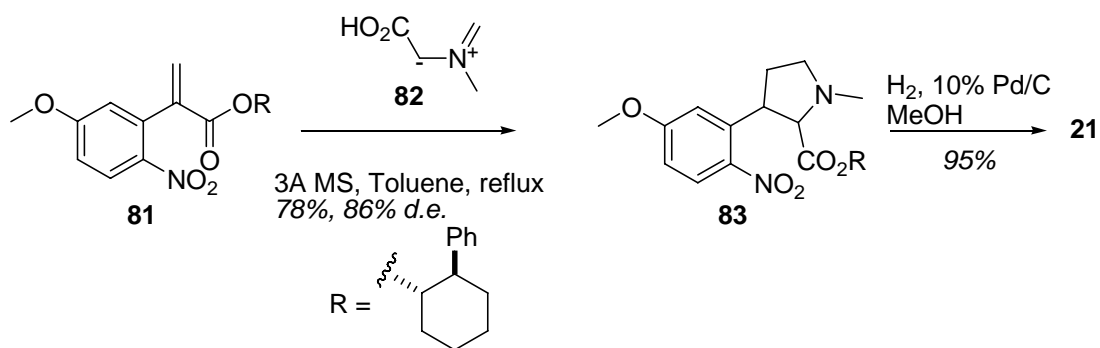


Figure 1.21: Dipolar cycloaddition approach to (-)-horsfiline.

1.9 Transition Metal-Mediated Coupling Reactions

The use of metal coupling reactions constitutes another method for the formation of spirocyclic oxindoles. Overman²⁸ utilized a Heck reaction in a synthesis of gelsemine. It was found that “ligandless” conditions offered high diastereoselectivity for C(3) bond formation (11:1) whereas the use of chiral phosphine ligands gave lower selectivity (< 3:1). As with Johnson’s route (Figure 1.14), C(3) sterics were a concern. In this case, the bond formation involved addition to a tetrasubstituted double bond. They found that the reaction proceeded with high yield and good diastereoselectivity. Unfortunately, the stereochemistry at C(3) was opposite to that found in gelsemine. Epimerization under retro aldol conditions gave the correct stereochemistry and allowed for completion of the synthesis.

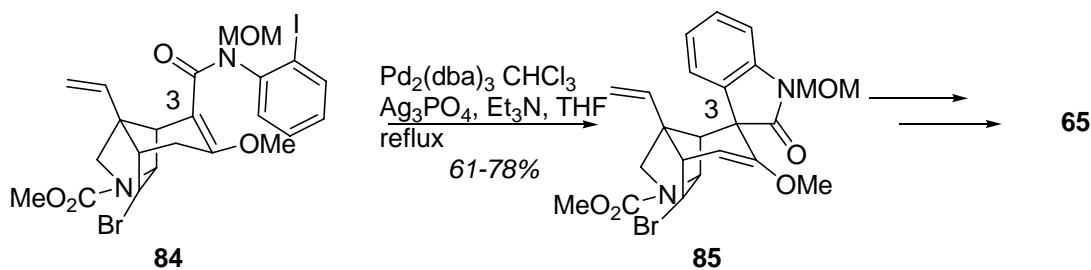


Figure 1.22: Overman’s gelsemine synthesis.

Another example of transition metal-mediated oxindole synthesis can be found in recent work toward perophoramidine by Weinreb.²⁹ In this sequence, a tandem Heck-carbonylation reaction is used to close the oxindole. Also noteworthy is that syn addition of the aryl palladium and carbon monoxide along the olefin led to a single diastereomer of the oxindole product.

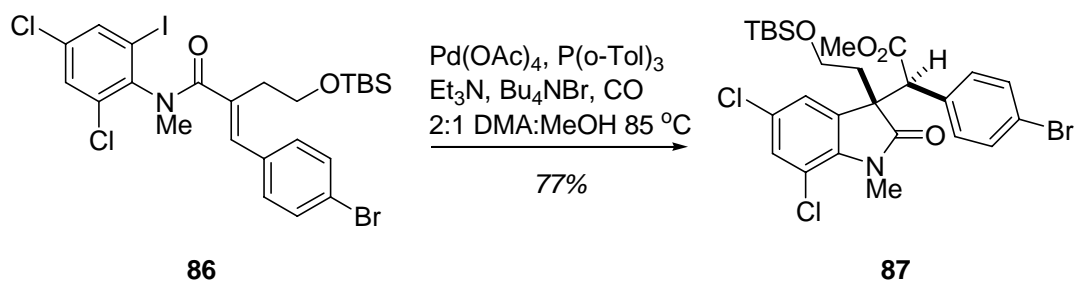


Figure 1.23: Tandem Heck and carbonylation reaction.

1.10 Asymmetric Nitroolefination

Fuji and coworkers demonstrated that asymmetric nitroolefination methodology could be used for formation of the quaternary center at C(3) of oxindoles.³⁰ The enolate generated at C(3) of oxindole **88** is added to chiral nitroenamine **89**. Subsequent elimination of the auxiliary regenerates the nitroolefin with high enantioselectivity. Several additional transformations were used to convert this product to (-)-horsfiline.

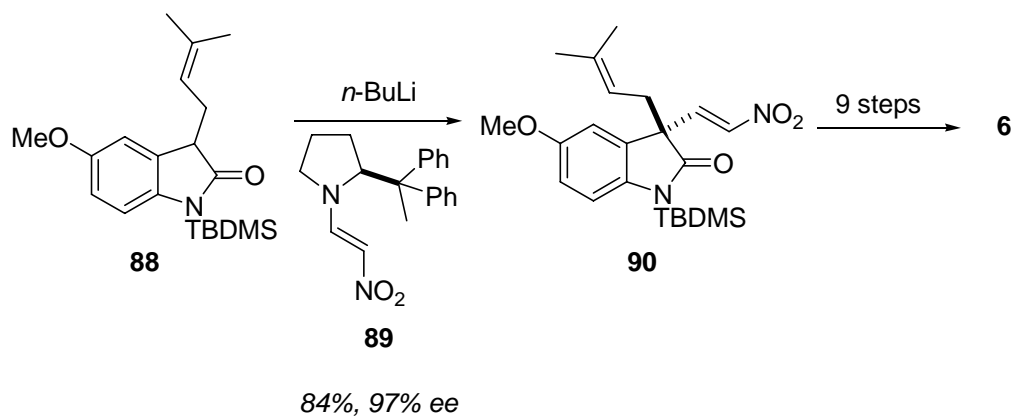


Figure 1.24: Synthesis of (-)-horsfiline using an asymmetric nitroolefination reaction.

1.11 Samarium mediated reductive coupling

A recent report³¹ disclosed a new reductive coupling method for oxindole synthesis. Opening of cyclic carbamate **91** via β -elimination following exposure to phosgene led to formation of intermediate isocyanate **92**. Reductively mediated addition of the cyclobutene double bond to the isocyanate gave oxindole **93** with good stereoselectivity. Eventually, this methodology led to a total synthesis of welwitindolinone A isonitrile.³²

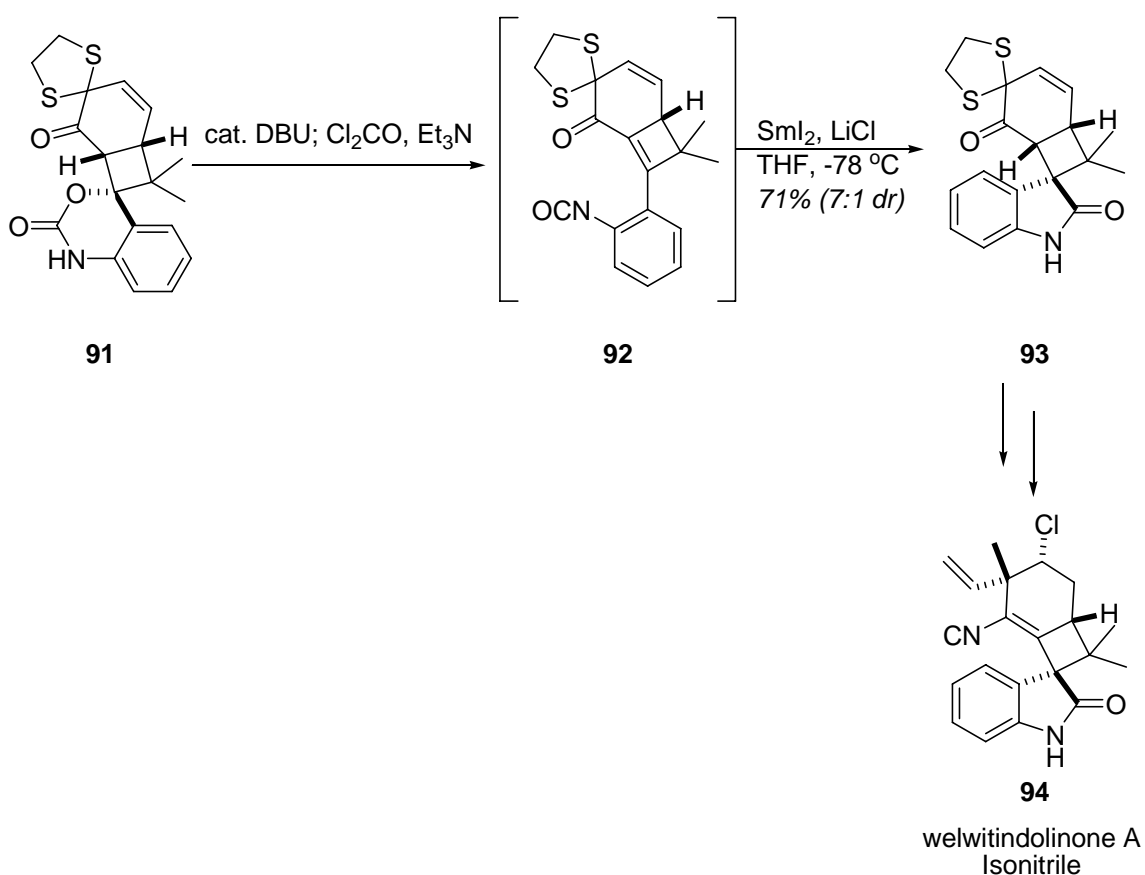


Figure 1.25: Reductive coupling as a strategy for oxindole synthesis.

1.12 Photochemistry

One final method for formation of 3,3-disubstituted oxindoles utilizes a photochemically induced dimerization of *N*-acetyl isatin with an alkyne.³³ This reaction led to a 2:1 mixture of diastereomeric products. This method is unlikely to see much use due to the specific nature of the dimeric products.

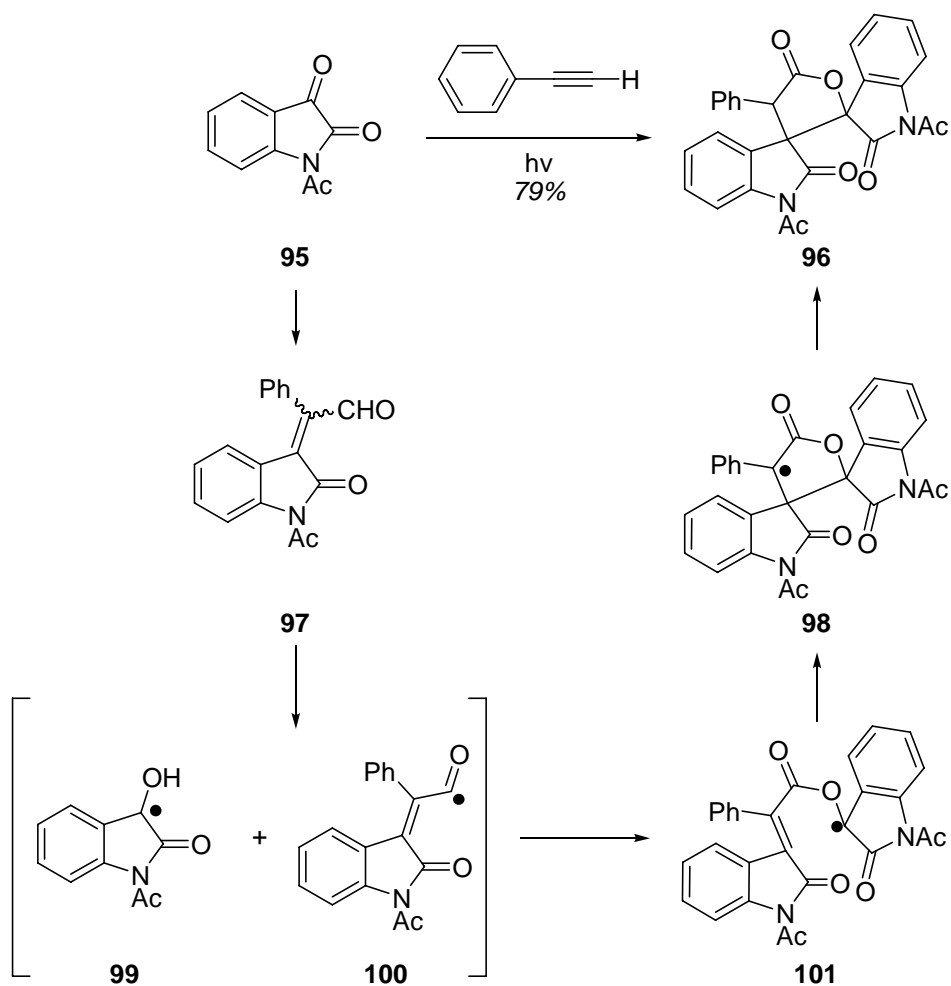


Figure 1.26: Photochemical dimerization to form oxindoles.

1.13 Conclusions

The abundance of natural products containing the 3,3-disubstituted oxindole core has generated interest in methods for their synthesis. Toward this goal, development of efficient routes which allow for regio- and stereochemical control are important. Whereas a number of successful strategies have been developed, many are specific to a limited number of natural product skeletons. The development of methods which are more general and allow for high levels of stereoselectivity in their application would be a valuable addition to this area.

Chapter 2 Pummerer reaction methodology

2.1 Pummerer reaction; history and mechanism.

The chemistry now known as the Pummerer reaction was originally observed by Smythe in 1909 (Figure 2.1).³⁴ However, he had little rationale or explanation for the observed products.

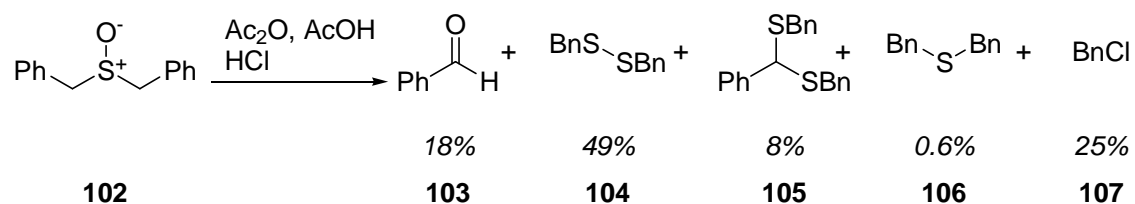


Figure 2.1: Smythe's reaction.

Later that year, Pummerer reported a similar result.³⁵ As an explanation for the formal oxidation at carbon, he proposed sulfonyl chloride **109** as an intermediate. This species was (in his proposal) followed by a 1,2-chloride shift to yield **110**, which was hydrolyzed to glyoxylic acid.

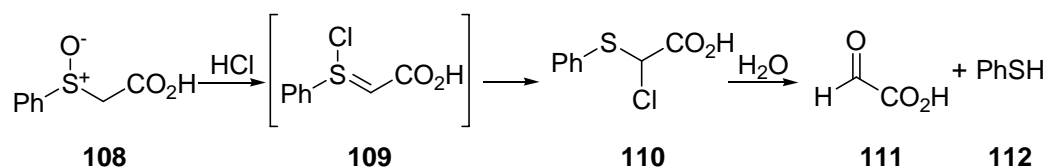


Figure 2.2: Pummerer's first result.

In 1910, he published his only other paper on this topic.³⁶ That report described the first example with conditions similar to modern methods. Sulfoxide **113** was activated with acetic anhydride, and OAc^- functioned as the nucleophile to furnish product **116** (Figure 2.3).

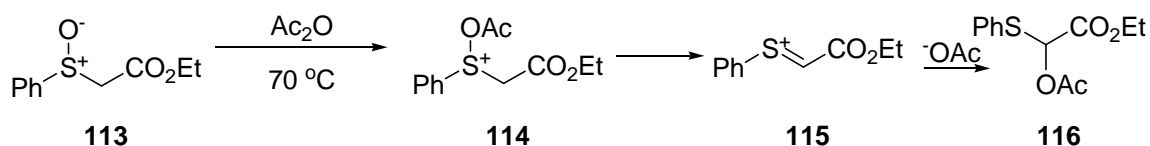


Figure 2.3: Ac₂O activated Pummerer.

The Pummerer reaction is defined as any reaction which follows the general mechanism in figure 2.4. Activation of a sulfoxide can be accomplished with a number of different electrophiles (e.g. Ac₂O, TFAA, Tf₂O, TMSOTf), resulting in sulfonium salts of the type 118. Deprotonation at the α-carbon results in a thionium ion, 119. Nucleophilic addition at this carbon leads to products of the type 120.

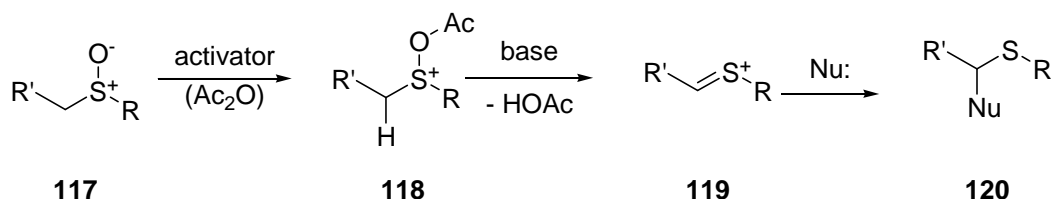


Figure 2.4: General Pummerer reaction mechanism.

2.2 Indole based Pummerer reaction.

The general scheme for an indole based Pummerer reaction is displayed in figure 2.5. This process provides for C(3) activation through the presence of a sulfoxide at C(2). The goal of this methodology is to eliminate two problems in known methods for spirocycle formation at C(3) of the oxindole core. By separating oxidation and cyclization into separate steps, product overoxidation should not be a concern. Problems with C(2) versus C(3) regioselectivity should not be present here (vide infra). Upon activation of the C(2) sulfoxide, attack of an appended nucleophile will form the

spirocycle at C(3). Subsequent hydrolysis of the thioimide product will lead to the oxindole.

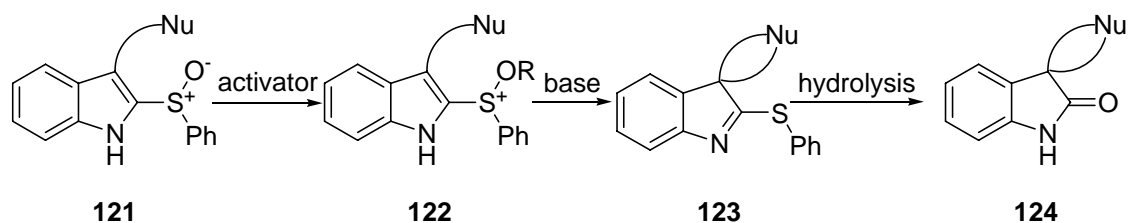


Figure 2.5: General scheme for the indole based Pummerer reaction.

For Pummerer reactions of this type, two mechanistic extremes are possible. These two processes have been termed the *additive* and the *vinyllogous* mechanisms.³⁷

2.2.1 Vinyllogous mechanism

In the vinyllogous mechanism (Figure 2.6), sulfoxide activation is followed by deprotonation of the indole nitrogen atom. From here, similar to the classical Pummerer reaction, this deprotonation triggers elimination of the activated oxygen leaving group to form a sulfonium ion at C(2). Nucleophilic attack theoretically could occur at three positions (C(2), C(3), C(4)). Only C(3) addition is expected to occur. Attack at any of the other positions would be energetically unfavorable. Path **a** would break aromaticity, presumably making it a higher energy process. Nucleophilic attack at C(2) (path **b**) would not restore aromaticity to the indole core. Attack at C(3) (path **c**) will restore aromaticity, providing the most energetically favorable pathway.

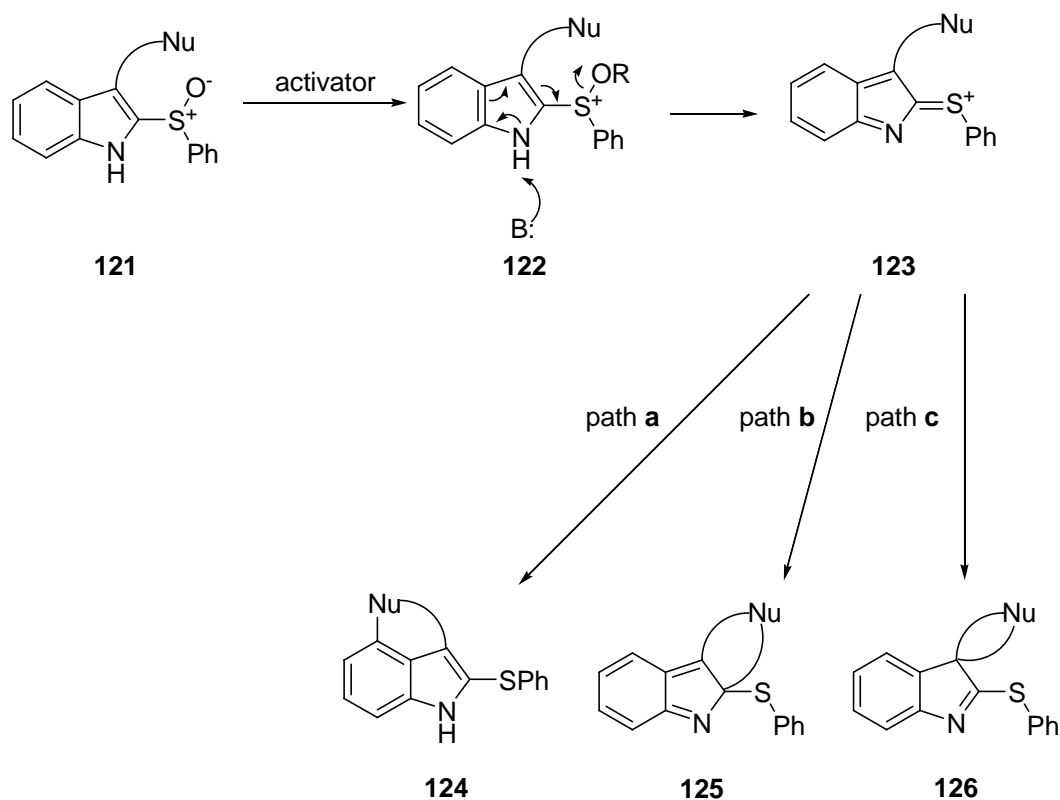


Figure 2.6: Vinylogous indole Pummerer reaction.

2.2.2 Additive mechanism

The second mechanism is termed the additive mechanism. In this mechanism, it is attack of the internal nucleophile itself which leads to formation of the sulfonium ion. Subsequent deprotonation of the indole nitrogen leads to the thioimide product. As in the vinylogous case, C(3) addition is expected to predominate. Attack on either phenyl ring (path **a** or **b**) would break aromaticity. Only through C(3) addition would aromaticity be retained. It is for this reason that exclusive attack at C(3) is expected.

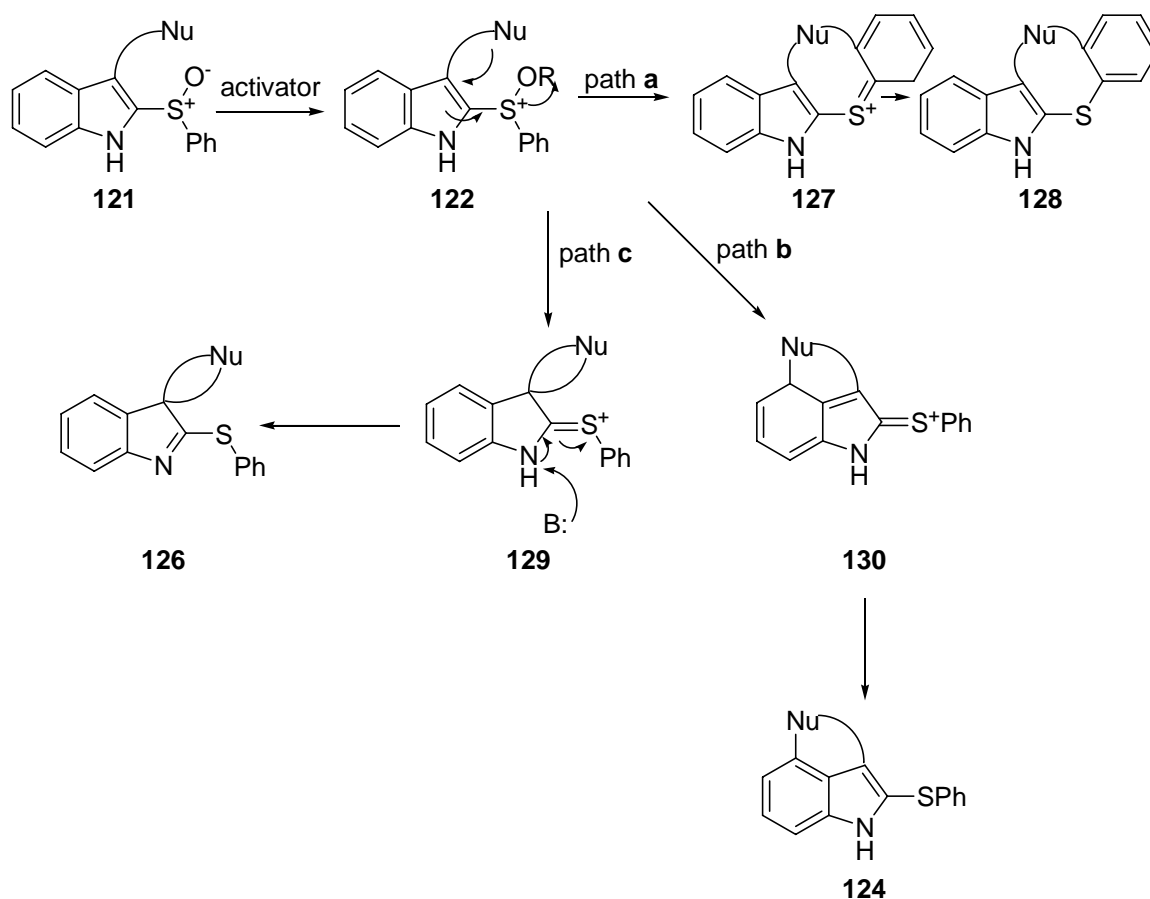


Figure 2.7: Additive indole Pummerer mechanism.

Direct evidence that delineates which mechanism the indole based Pummerer reaction proceeds through is not yet in hand. Some information from work toward an asymmetric version of this transformation may suggest the prevalence of one of the two pathways, as detailed below.

2.3 Asymmetric Pummerer reaction

2.3.1 Background

Earlier results from Penn State³⁸ showed success in this indole functionalization chemistry with carbon based nucleophiles (Figure 2.8). Use of racemic sulfoxides led, of course, to racemic thioimide and oxindole products. There are a limited number of examples of enantioselective Pummerer reactions based on chiral sulfoxides, and so the feasibility of achieving absolute stereocontrol through the use of chiral indole-2-sulfoxides was deemed worthy of investigation.

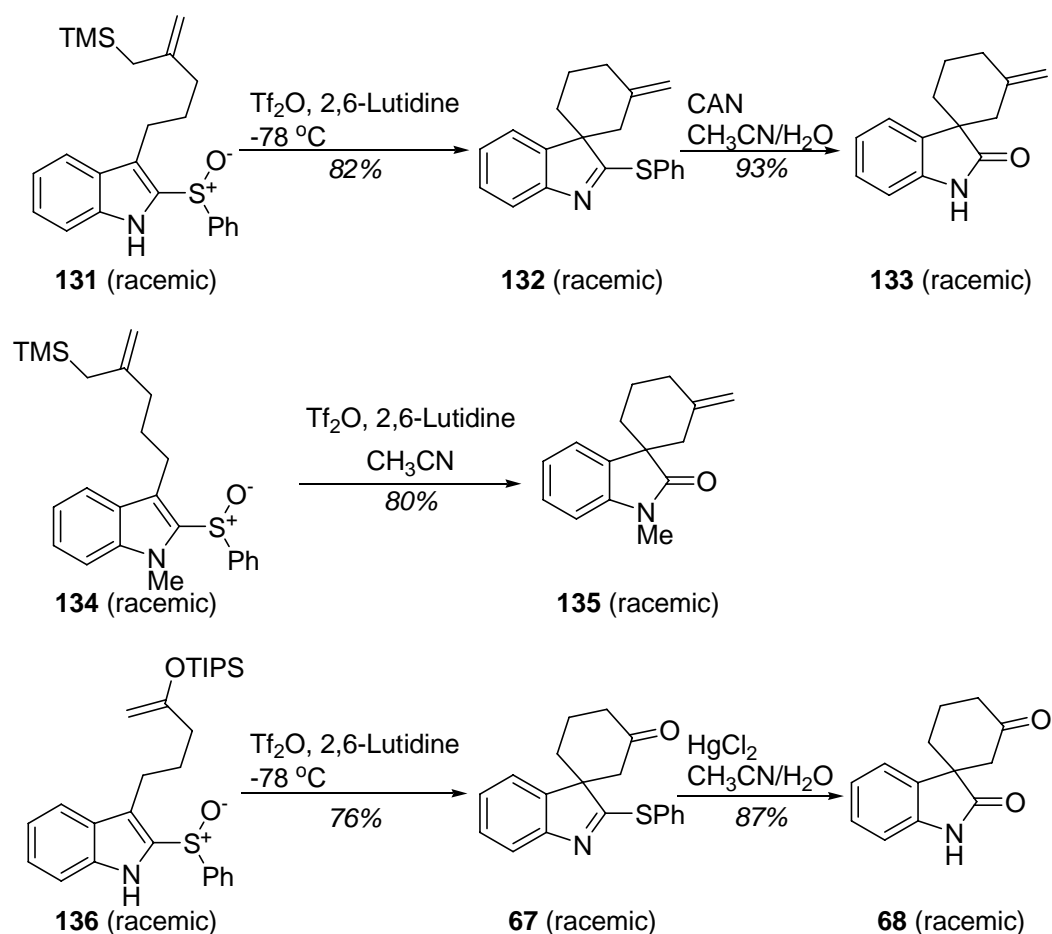


Figure 2.8: Racemic indole based Pummerer reactions using carbon nucleophiles.

The difference in the two mechanistic pathways may play a significant role in the success of this work. The additive mechanism which bears stereochemical information when the new C-C bond is formed seems the most likely route by which asymmetric induction might be achieved. A reaction that follows the vinylogous pathway could proceed through achiral intermediate **123**. Reaction through this intermediate would eliminate any transfer of chirality from the chiral sulfoxide during the cyclization process. On the other hand, a vinylogous mechanism leading to chiral tight ion pairs that retain (planar) stereochemical information may provide a middle ground between these mechanistic extremes. The stereochemical outcome in this instance is uncertain.

In the additive mechanism, it is possible that a substrate with an activated chiral sulfoxide such as **122** would orient itself in a conformation that avoids the steric interaction between the incoming nucleophile and the activated sulfoxide or the phenyl ring. In this scenario, it is expected that there may be some enantioselectivity upon oxindole formation.

More specifically, a proposed transition state analysis for this reaction is given in Figure **2.9**. Orthogonal alignment of the sulfoxide bond with the C(2)-C(3) double bond is expected to be necessary for good orbital overlap.³⁹ Rotamers **139** and **141**, which contain the lowest steric interaction between the incoming nucleophile and the triflate (or phenyl ring), are the most favorable with regard to minimizing steric interactions. Rotation around the S-O bond will likely favor the antiperiplanar position of the lone pairs of the sulfur and oxygen atoms in order to minimize electrostatic repulsion. Taking into account both sterics and electrostatics, **139** should be the lowest energy transition

state. This would result in nucleophilic attack will come from the bottom face, favoring formation of enantiomer **142**.

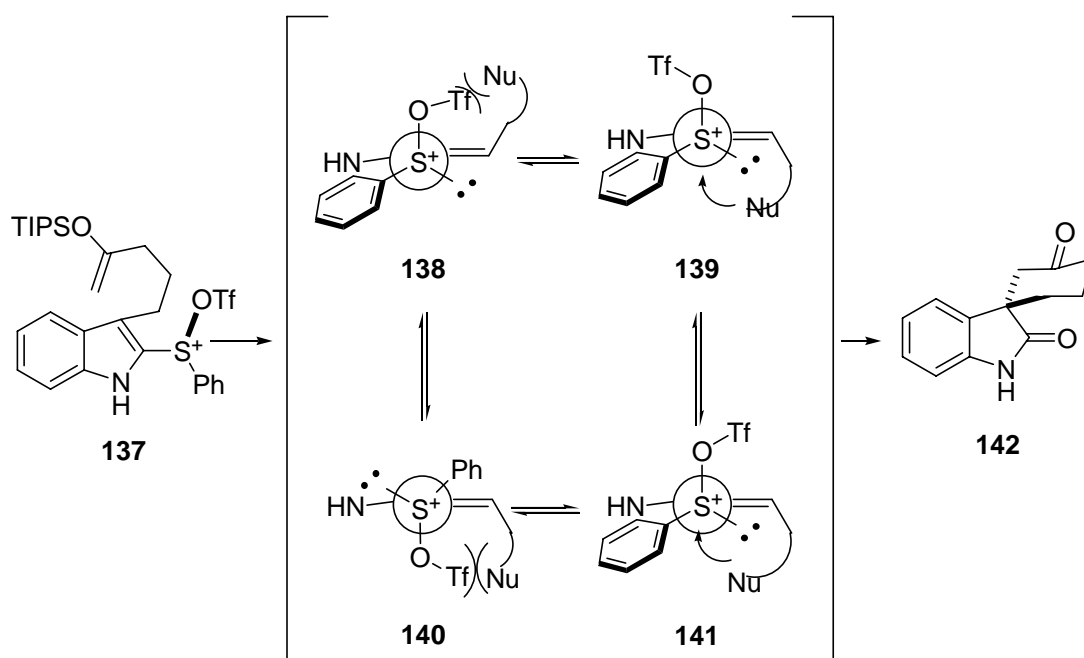


Figure 2.9: A proposal for expecting enantioselectivity in the Pummerer reaction of chiral indole-2-sulfoxides.

An alternative mechanism for obtaining enantioselectivity upon C-C bond formation is a chiral tight ion pair. Through tight ion pair **144** the vinylogous mechanism may exhibit enantioselectivity. If this chiral ion pair can be trapped by the internal nucleophile prior to racemization, similar results to that of the additive mechanism may be seen.

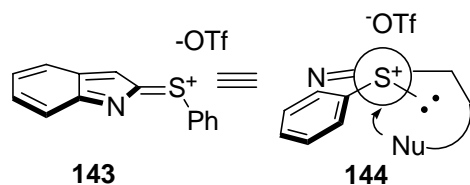


Figure 2.10: Tight ion pair for enantioselectivity in the Pummerer reaction.

Kita⁴⁰ has had success in obtaining high selectivities using chiral sulfoxides and silyl ketene acetals in the presence of zinc (II) iodide (Figure 2.11). Some selectivity is due to the α -carbon substituent, in that it is thought that deprotonation of the α -carbon plays a role in the stereoselectivity. Deprotonation is controlled by the requirement for an *anti*-periplanar orientation of the proton and the S-O bond. The siloxy anion then rearranges on the same face. In systems with an α -methylene unit, decreased selectivities were seen ($\sim 80\%$ *ee*). It is also possible that the selectivity may arise from a tight ion pair of the sulfonium ion with the ^-OTBS . However, the use of chiral sulfoxides using classical Pummerer reaction conditions has not met with great success ($< 30\%$ *ee*).⁴¹

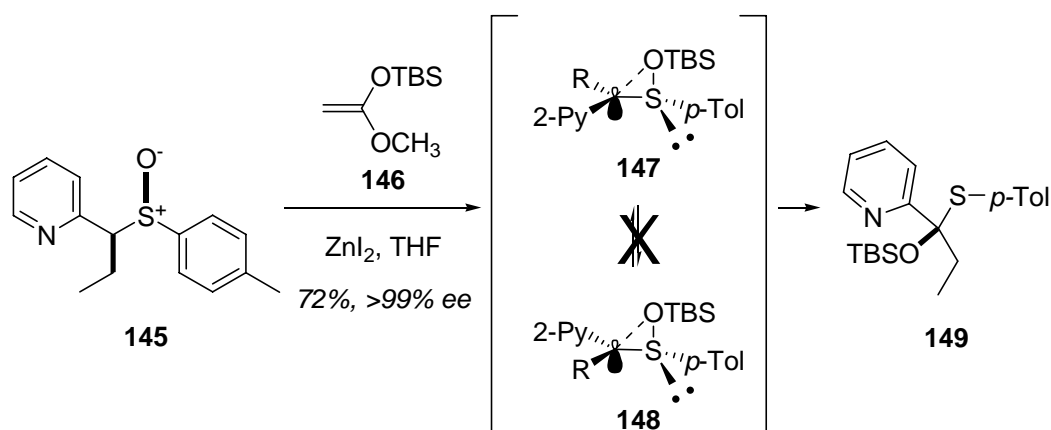


Figure 2.11: Kita's enantioselective Pummerer reaction.

2.3.2 Chiral sulfoxides

While there are a variety of methods to synthesize chiral sulfoxides,⁴² many of them involve asymmetric oxidation of a sulfide. Without a method to assay the absolute configuration at sulfur, these methods alone do not always allow for the unambiguous synthesis of a specific chiral sulfoxide. Work by Evans⁴³ provides a solution to this problem. By addition of the anion of a chiral oxazolidinone to benzenesulfinyl chloride, chiral sulfoxides such as **152** can be obtained in high (>95%) *ee*. The chirality then can be transferred to an appropriate substrate in an S_N2 reaction with inversion of configuration using an appropriate nucleophile.

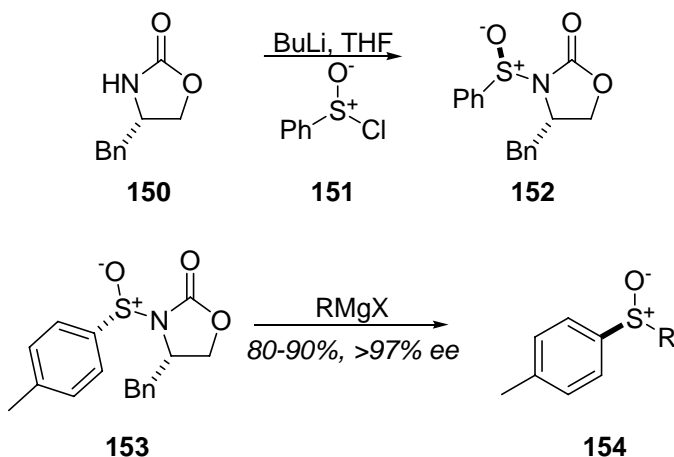


Figure 2.12: Evans' oxazolidinone route to chiral sulfoxides.

Work by Marino⁴⁴ provides a basis for substitution at C(2) of an indole. Ortho-lithiation with an appropriate nitrogen protecting group (BOC, Ts) using *sec*-butyllithium provides the C(2) anion. Quenching that anion with **156** provides virtually enantiomerically pure C(2)-sulfoxide products. The stereochemistry is assigned by assuming complete inversion at the sulfur center.

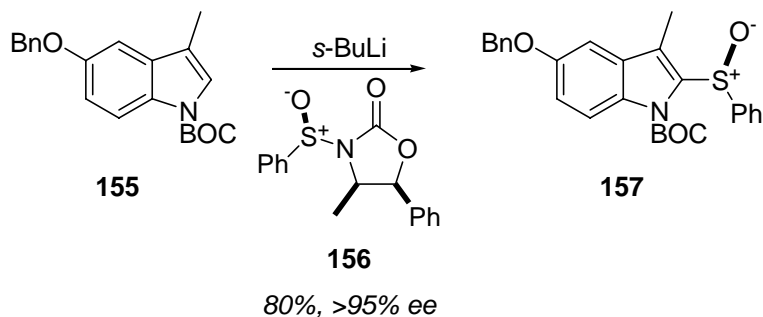


Figure 2.13: Marino's use of Evans reagent.

2.4 Iodonium based Pummerer reaction methodology

One of the disadvantages of the classical Pummerer reaction is the distinct oxidation step. This step can be low yielding due to overoxidation to the sulfone. An alternative method of activation for Pummerer-like processes involves the use of hypervalent iodine species as simultaneous oxidizers and activators. An example of this process is given by Tamura⁴⁵ who showed that concomitant oxidation and activation took place in a single step (Figure 2.4). This alternative to the classical sulfoxide based methods may be useful when traditional methods are unsuccessful or inconvenient. Other hypervalent iodonium sources which have shown utility in this process are $\text{PhI}(\text{OAc})_2$ and $\text{PhI}(\text{CN})\text{OTf}$.⁴⁶

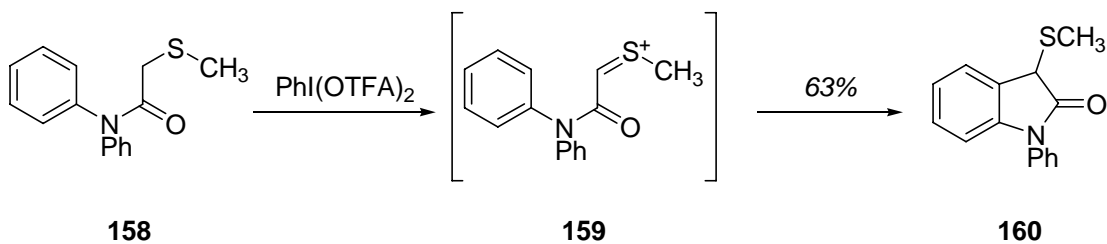


Figure 2.14: Tamura's iodonium based Pummerer reaction.

Similar to the classical Pummerer reaction, the iodonium based chemistry as applied to an indole substrate has two mechanistic possibilities. Initially, the sulfide may add to the iodine of Stang's reagent with loss of triflate. This intermediate, **162**, is similar in structure and reactivity to the activated sulfoxide species. From here, additive and vinylogous mechanisms are analogous to those discussed earlier with the sulfoxide series and they result in thioimide **123**. Of course, this hypervalent iodine initiation only applies to racemic oxindole synthesis.

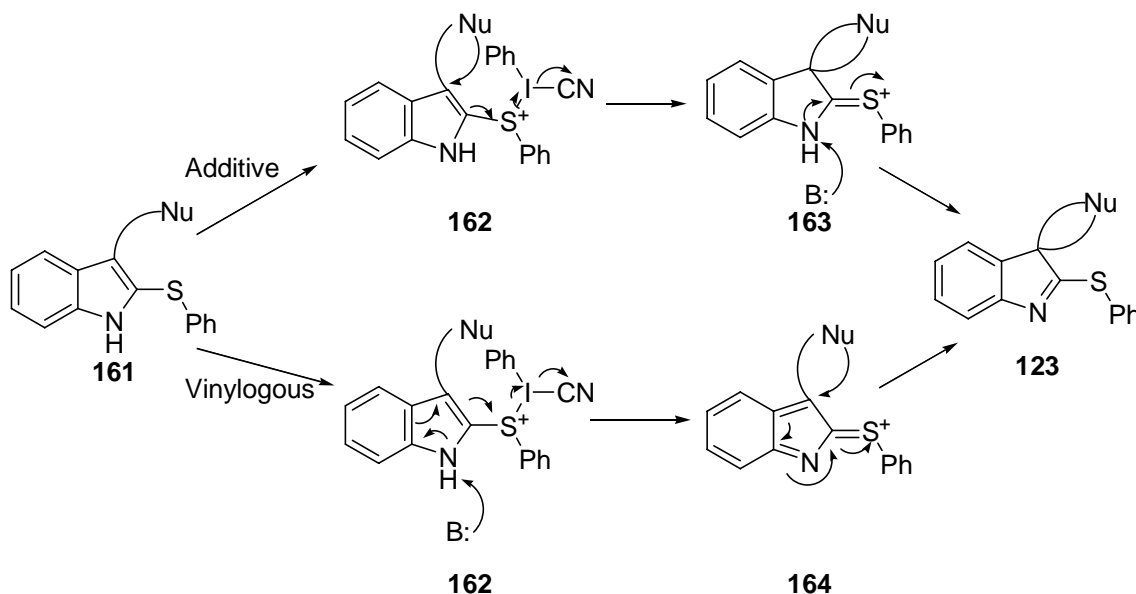


Figure 2.15: Mechanism for the PhI(CN)OTf mediated Pummerer reaction.

Chapter 3

Review of TMC-95A-D background and synthesis

3.1 Isolation and Biological Activity of TMC-95 A – D

TMC-95A – D (**1a-d**) are four novel proteasome inhibitors isolated from the fermentation broth of *Apiospora montagnei* Sacc. TC 1093.^{1a} The four compounds are found to consist of a novel cyclic peptide structure containing L-tyrosine, L-asparagine, and a highly oxidized L-tryptophan unit. The difference in the four structures was found to reside with the stereochemical relationship at C(7) and C(36).

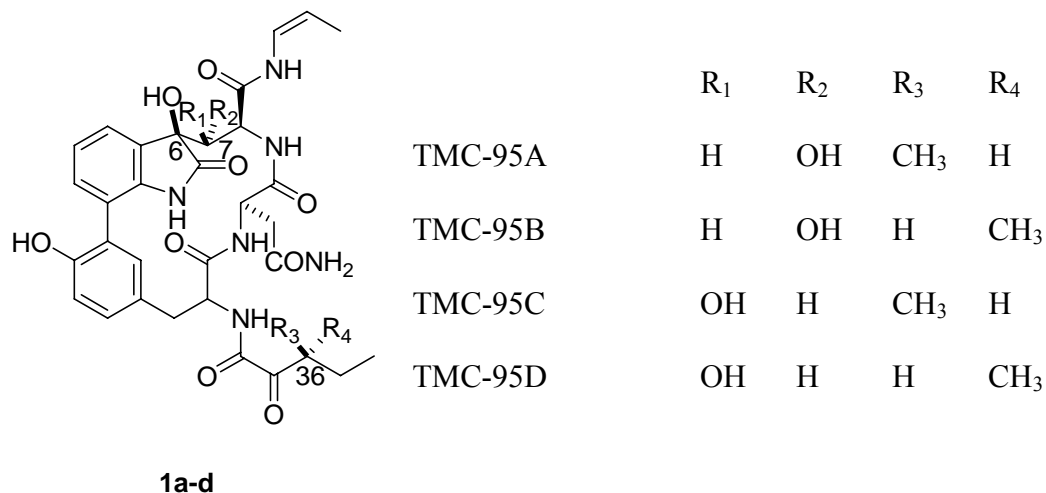


Figure 3.1: TMC-95A-D.

The inhibitory activity of the TMC-95 compounds was tested in chymotrypsin-like (ChT-L), trypsin-like (T-L), and peptidylglutamyl-peptide hydrolyzing (PGPH) activities assays with the 20S proteasome (Table 3.1).⁴⁷ All four compounds showed good inhibition against these 20S proteasome activities, with both TMC-95A and B showing better inhibition than a known proteasome inhibitor, *N*-Acetyl-Leu-Leu-nLeu-CHO (ALLN). The 20S proteasome makes up the catalytic core of the 26S proteasome,

which is responsible for degradation of ubiquitinated proteins in ATP dependent processes. Recent studies indicate that activation of the ubiquitin-proteasome pathway may be a major cause of the muscle destruction seen in cancer, diabetes, and sepsis.⁴⁸ Additionally, TMC-95A showed cytotoxicity against human colon carcinoma cells and human promyelocytic cells with IC_{50} values of 4.4 μ M and 9.8 μ M, respectively.

Compound	ChT-L (IC_{50} , μ M)	T-L (IC_{50} , μ M)	PGPH (IC_{50} , μ M)
TMC-95A	0.0054	0.20	0.060
TMC-95B	0.0087	0.49	0.060
TMC-95C	0.36	14	8.7
TMC-95D	0.27	9.3	3.3
ALLN	6.6	6.0	21

Table 3.1: Inhibitory activities of TMC-95A-D against 20S proteasome activities.

3.2 Synthetic approaches toward TMC-95A

The biological activity of these compounds has led to interest in their total synthesis. At this time, total syntheses of TMC-95A have been completed by Danishefsky⁴⁹ and Hirama.⁵⁰ A formal synthesis has been completed by Williams.⁵¹ Additional synthetic studies toward these compounds have been disclosed by Ma.⁵² Work toward a better understanding of the biological activity, and attempts to improve upon this activity, have been studied through the synthesis of analogues by Moroder,⁵³ Vidal,⁵⁴ and Danishefsky.⁵⁵

A review of the synthetic approaches will be discussed below. The major difference in each route is the synthesis of the oxidized tryptophan portion. All three routes used similar approaches for the southern half.

3.2.1 Danishefsky *et al.*

Danishefsky's retrosynthesis (Figure 3.2) breaks TMC-95A and B into four components. These components consisted of an oxidized tryptophan piece originating from 7-iodooxindole, two amino acid derived pieces originating from L-tyrosine and L-asparagine, and the final piece was derived from (\pm)-3-methyl-2-oxopentanoic acid. The key transformations included (1) setting the stereocenters at C(6) and C(7) using a Sharpless asymmetric dihydroxylation reaction, and (2) formation of the *cis*-enamide functionality using a thermal rearrangement of an α -silylallyl amide.

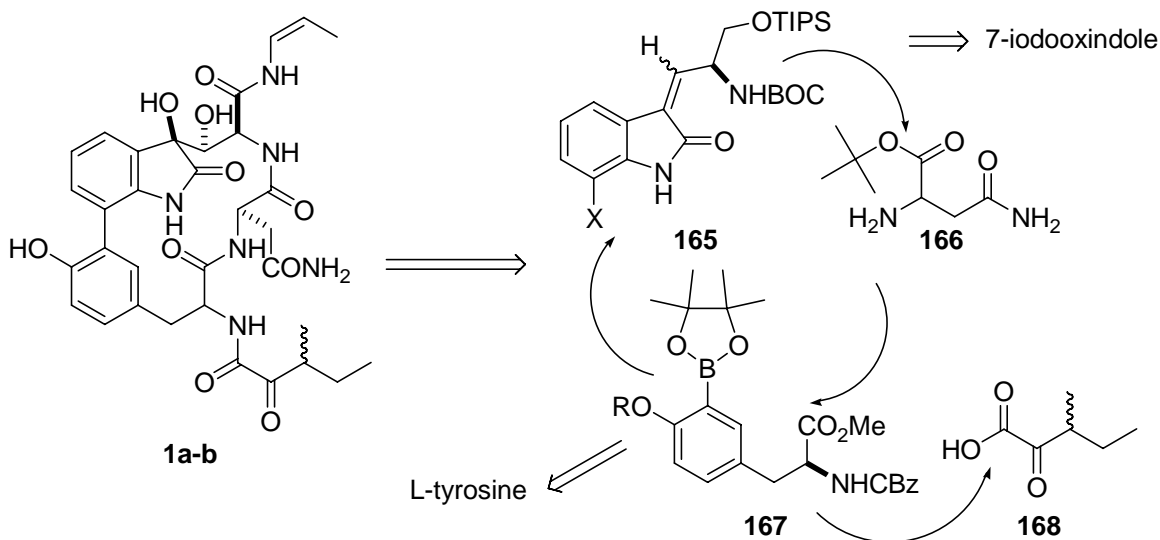


Figure 3.2: Danishefsky's retrosynthetic analysis.

The synthesis commenced with an aldol condensation of oxindole **169** with Garner aldehyde **170**. Elimination of the derived mesylate yielded a 1:1.3 mixture of double bond isomers. An iodine mediated isomerization of the olefin converted the *E*

isomer to the *Z* isomer, setting up oxindole **171** for the biaryl coupling. The partner for the biaryl coupling, **174**, was synthesized in 5 steps from L-tyrosine. From here, **171** and **174** underwent a Suzuki coupling to yield **172**.

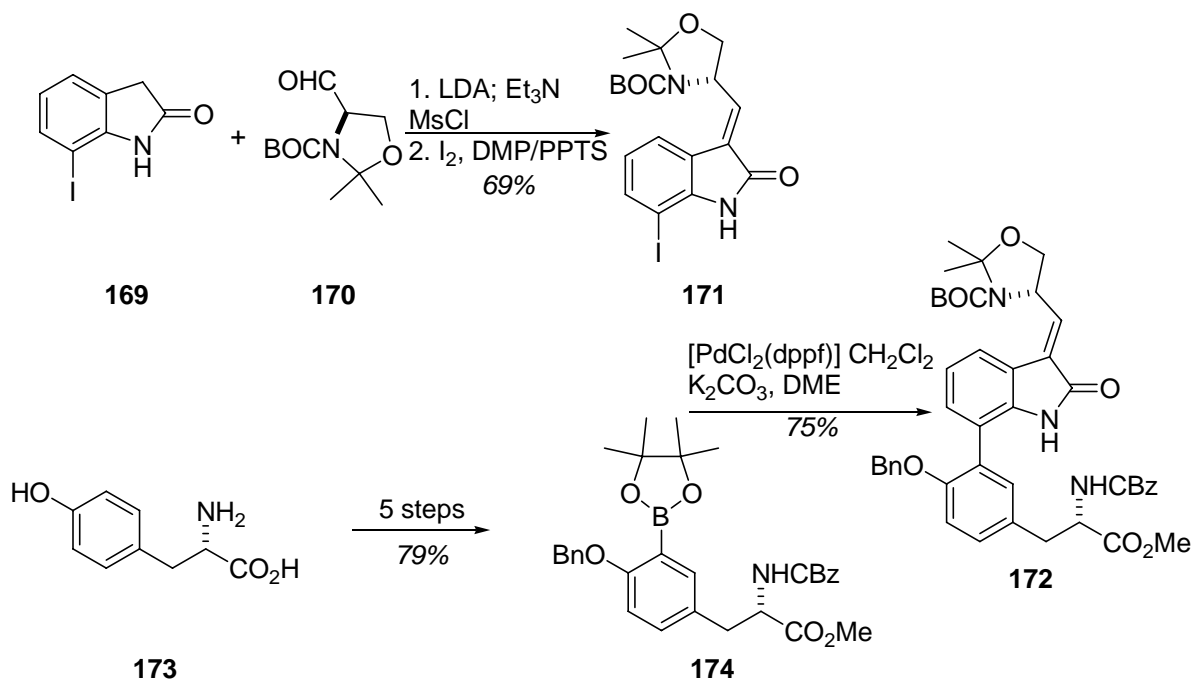


Figure 3.3: Biaryl coupling of the oxindole with the tyrosine piece.

Ester hydrolysis within **172**, followed by EDC coupling of the derived acid with L-asparagine-*t*-butyl ester, afforded **175**. An asymmetric dihydroxylation of the C(6)-C(7) alkene using (DHQD)₂PHAL furnished diol **176** with the correct stereochemistry for TMC-95A and B predominating (5:1).

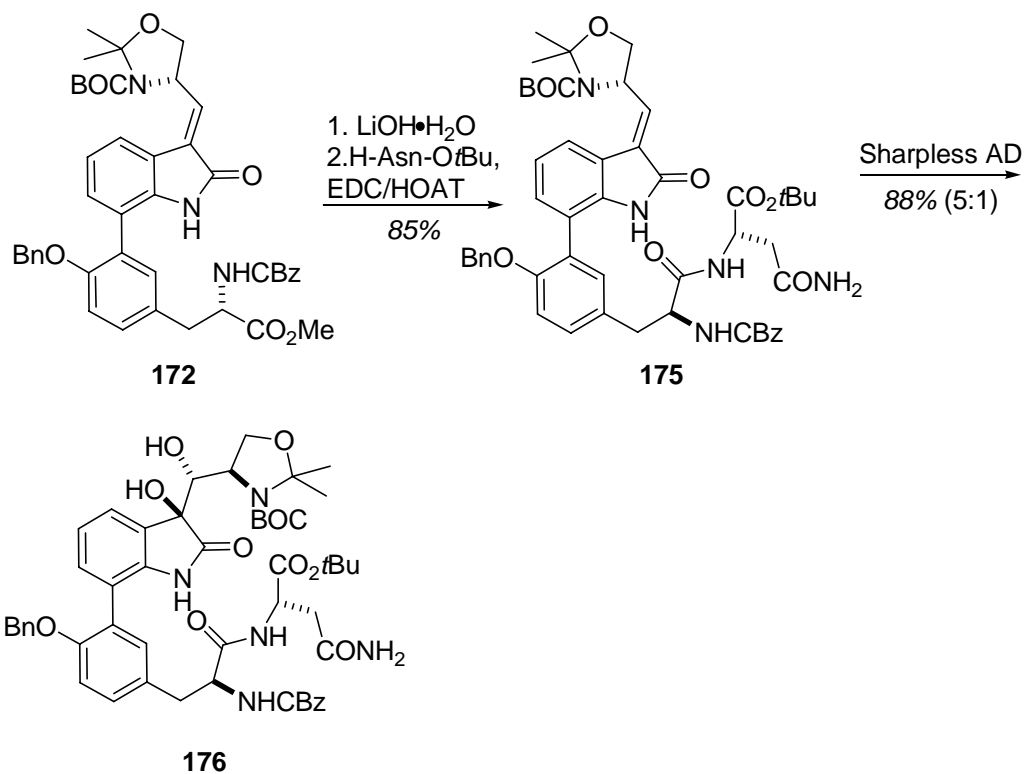


Figure 3.4: Sharpless dihydroxylation to set the stereochemistry at C(6) and C(7).

From **176**, deprotection of the acetonide yielded the triol, and the primary alcohol was selectively protected as its TIPS ether. TFA deprotection of the BOC and *t*-butyl ester groups followed by an EDC mediated coupling of the derived amino acid yielded the macrolactam. A series of transformations led to **179**, the precursor for the rearrangement/hydrolysis sequence that completes the synthesis.

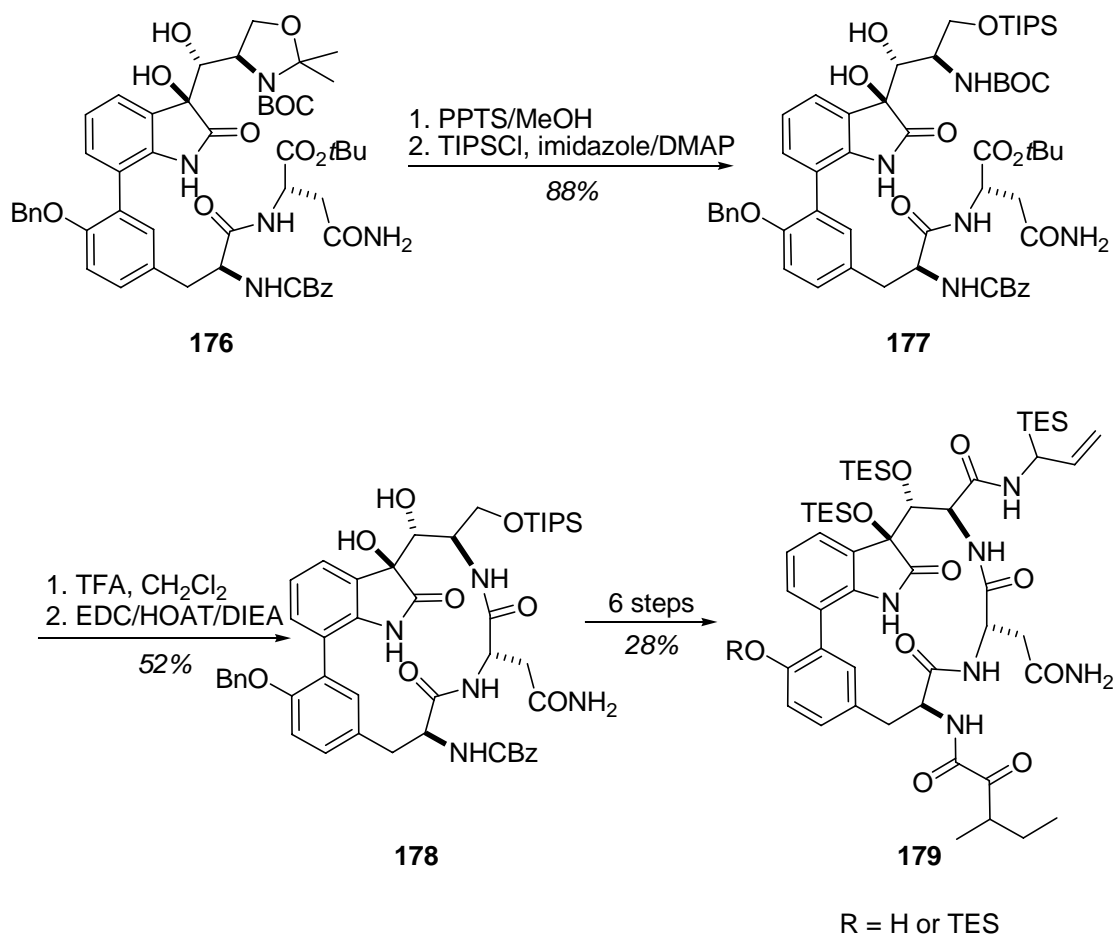


Figure 3.5: Synthesis of the macrolactam.

The *cis*-enamide was formed through rearrangement and hydrolysis of a silyl allyl amide. A thermal rearrangement of **180** forms silyl imidate **181**. Subsequent hydrolysis reveals the *cis*-enamide.

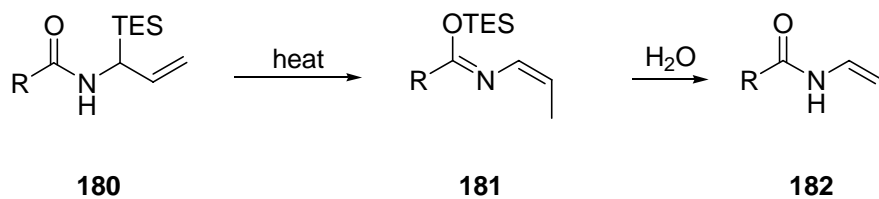


Figure 3.6: Enamide formation.

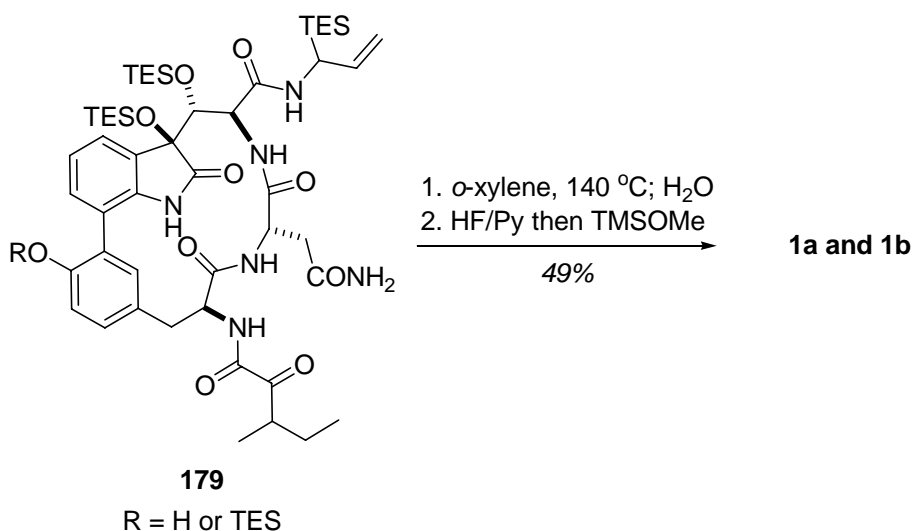


Figure 3.7: Completion of the synthesis.

Global deprotection of the silicon protecting groups led to the isolation of TMC-95A and B. Danishefsky's route led to 2 of the TMC-95 congeners in 21 linear steps, and 23 steps overall. The key transformations were an asymmetric dihydroxylation to set the stereochemistry at C(6) and C(7), and a rearrangement/hydrolysis sequence to yield the sensitive *cis*-enamide functionality.

3.2.2 Hirama *et al.*

Hirama and coworkers used a similar approach for the southern half of the TMC-95 system, but their approach for the northern half differed. A similar retrosynthesis breaks TMC-95A into L-tyrosine, L-asparagine, an oxidized tryptophan piece and L-*allo*-threonine. A stereoselective epoxidation of the C(6)-C(7) double bond led to the correct stereochemistry at both carbons. The *cis*-enamide group was formed through a decarboxylation of L-*allo*-threonine.

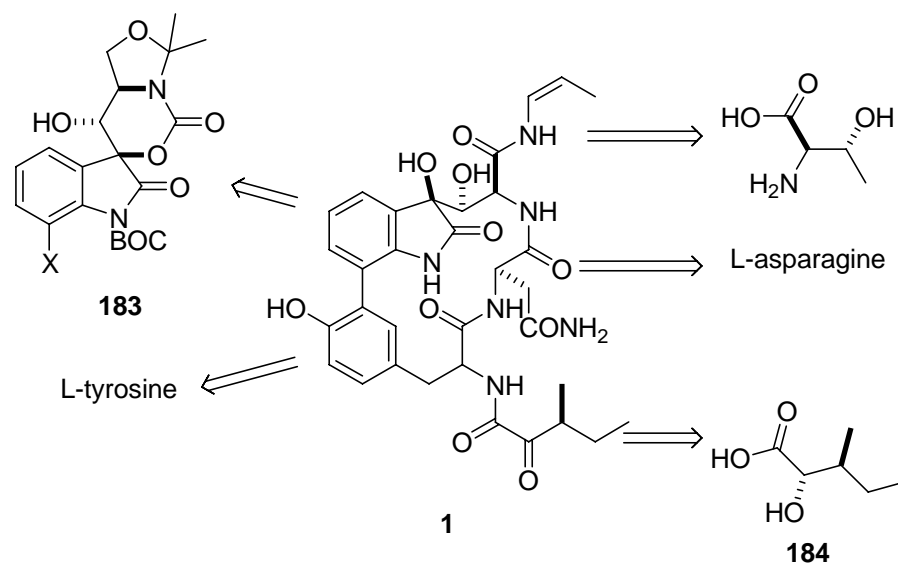


Figure 3.8: Hirama's retrosynthesis.

Hirama's synthesis started with methyl ester **185**. Reduction to the aldehyde followed by a Horner-Emmons reaction formed ester **186**. Amidation of the ester with 2,6-dibromoaniline yielded **187**. A Mizoroki-Heck reaction using "ligandless" conditions yielded oxindole **188**. The C(6)-C(7) double bond was stereoselectively oxidized with dimethyldioxirane, which, upon treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$, afforded cyclic carbamate **190**.

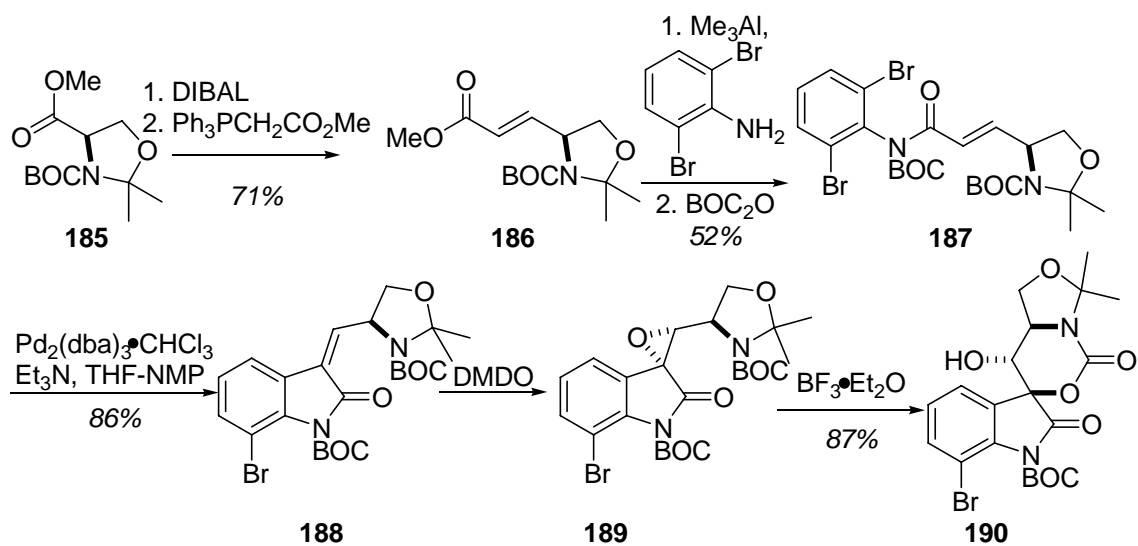


Figure 3.9: Hirama's synthesis of the oxindole portion of TMC-95A.

Oxindole **190** was further elaborated through protecting group manipulation and exchange of bromine for iodine. Using conditions developed by Gassman,⁵⁶ the acetonide and carbamate were cleaved to yield triol **192**. Finally, the amine and two of the alcohols were protected to set the tryptophan piece for further elaboration.

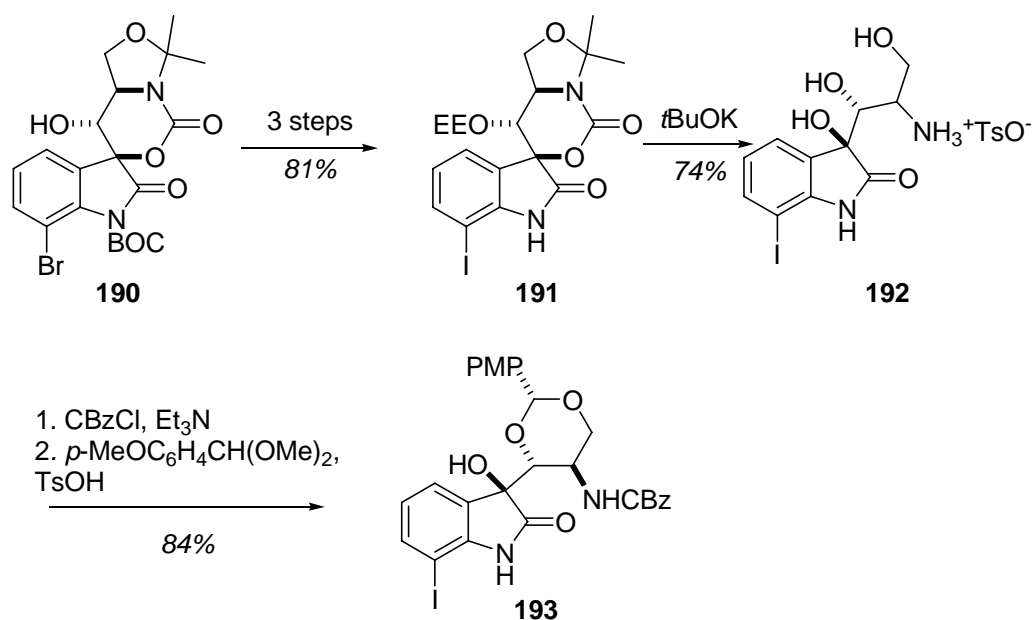


Figure 3.10: Continuing the synthesis of the northern half.

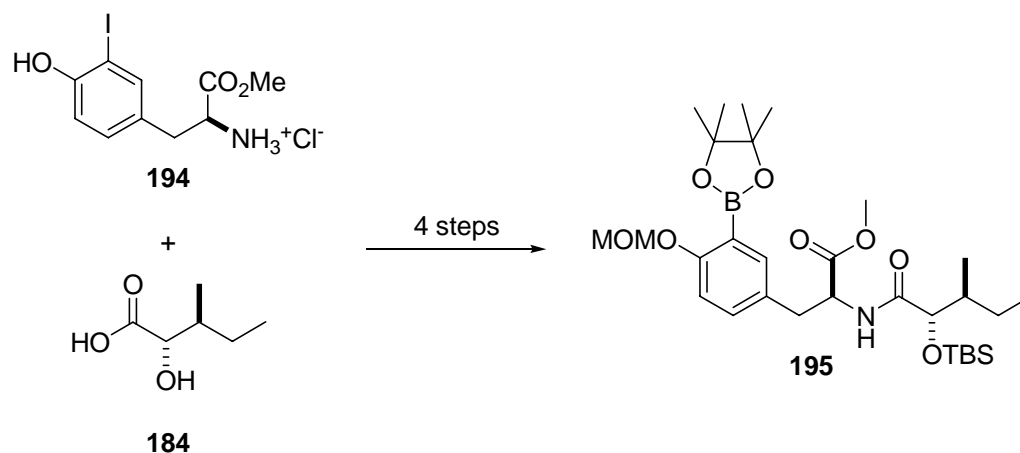


Figure 3.11: Synthesis of the tyrosine derived piece.

Boronic ester **195** was derived from tyrosine and acid **184** in four steps. The completion of the synthesis started with the Suzuki coupling of **190** with **195**. Six additional steps installed the L-asparagine unit, and the macrolactam was closed under standard carbodiimide conditions. The PMP acetal was cleaved to afford triol **198**. Oxidation of the primary alcohol to the acid followed by coupling of this carboxylate to L-*allo*-threonine benzyl ester and finally deprotection of the benzyl ester furnished acid **199**. Treatment of **199** under Mitsunobu-type conditions (PPh₃ and DEAD) favored *anti*-elimination to afford *cis*-enamide **200**. Two deprotections and an oxidation were used to complete the synthesis of TMC-95A.

Hirama's route to TMC-95A utilized chiral acid **184**, leading to only one of the TMC-95 congeners upon completion. Synthesis of the southern portion is similar to Danishefsky's work. The most significant difference is the use of L-*allo*-threonine and its dehydrative decarboxylation to yield the *cis*-enamide. The route is also longer at 29 linear steps and 33 steps overall.

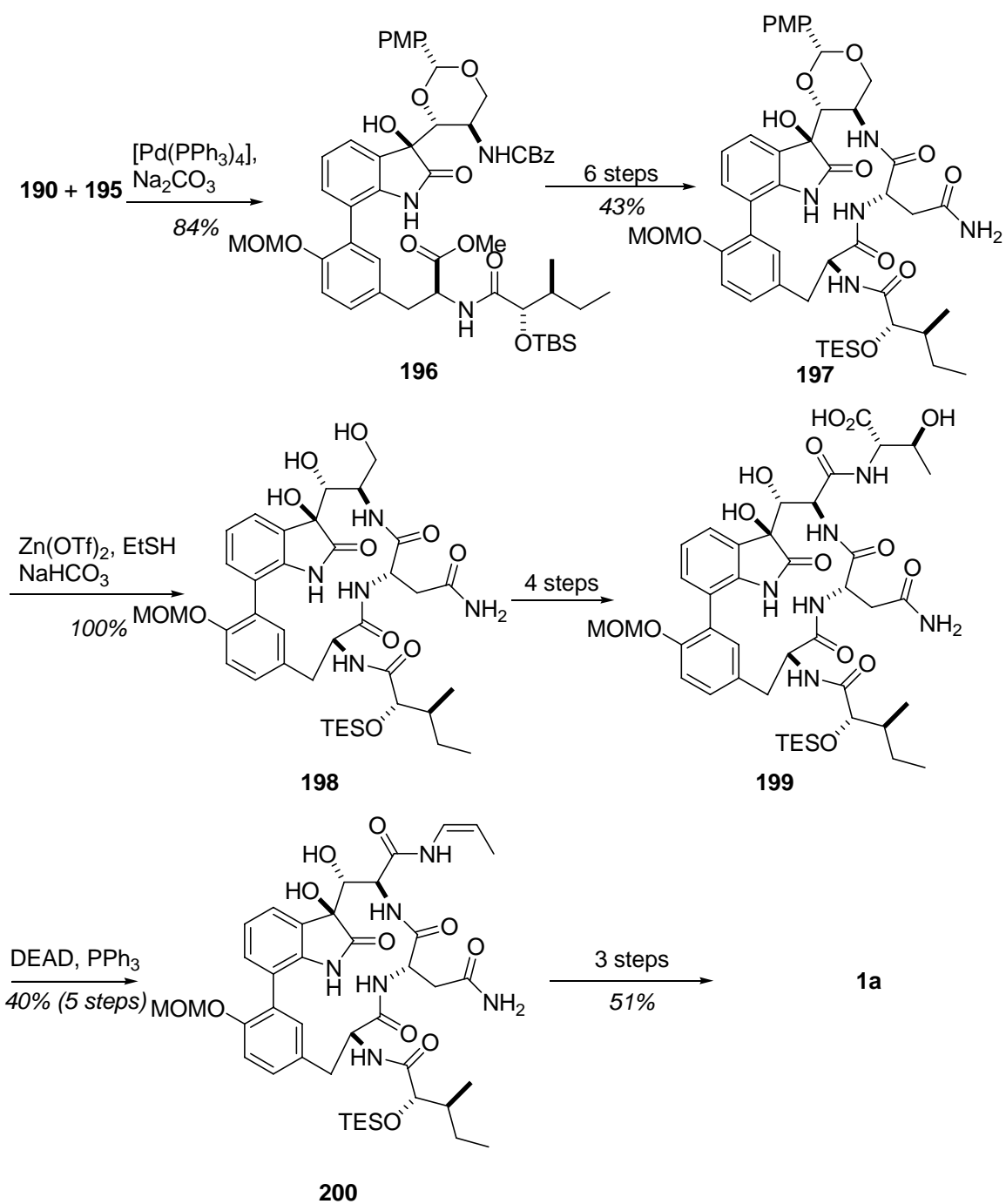


Figure 3.12: Completion of Hirama's synthesis.

3.2.3 Williams *et al.*

Williams and Albrecht completed a formal synthesis of TMC-95A and B. Again, the southern half was derived from L-tyrosine and L-asparagine. The northern half component **201** was synthesized by a Julia olefination between 7-iodoisatin and **202**. Synthesis of the sensitive *cis*-enamide was not explored due to the interception of **213**, one of Danishefsky's advanced intermediates.

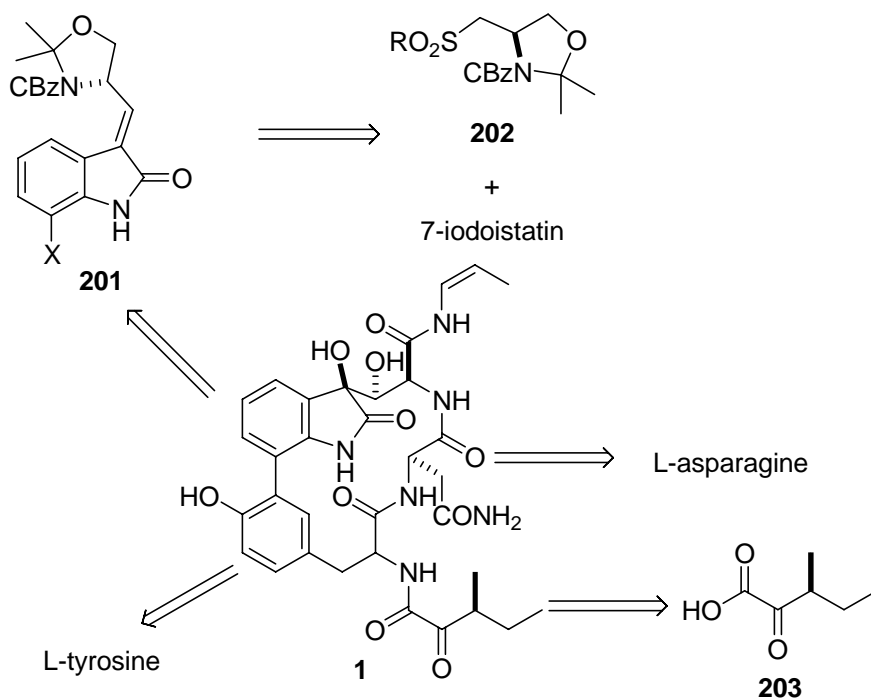


Figure 3.13: Williams' retrosynthesis.

The synthesis started with *N*-Cbz-serine methyl ester, which was converted in four steps to acetonide **205**. A modified Julia coupling with 7-iodoisatin yielded **206** in good yield with a 5:1 preference for the thermodynamic *E*-alkene product.

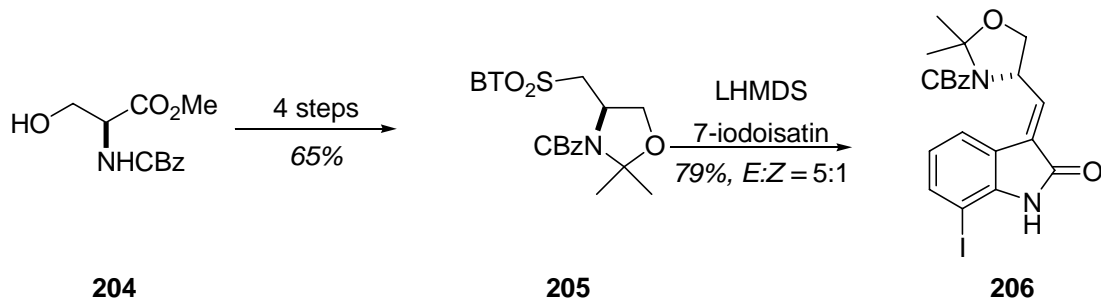


Figure 3.14: Williams' oxindole synthesis.

Protected tyrosine derivative **207** was converted to its boronic ester which underwent a Suzuki coupling with oxindole **206** to yield **209**. Hydrolysis of the methyl ester followed by coupling of the derived acid to L-asparagine benzyl ester led to **210**.

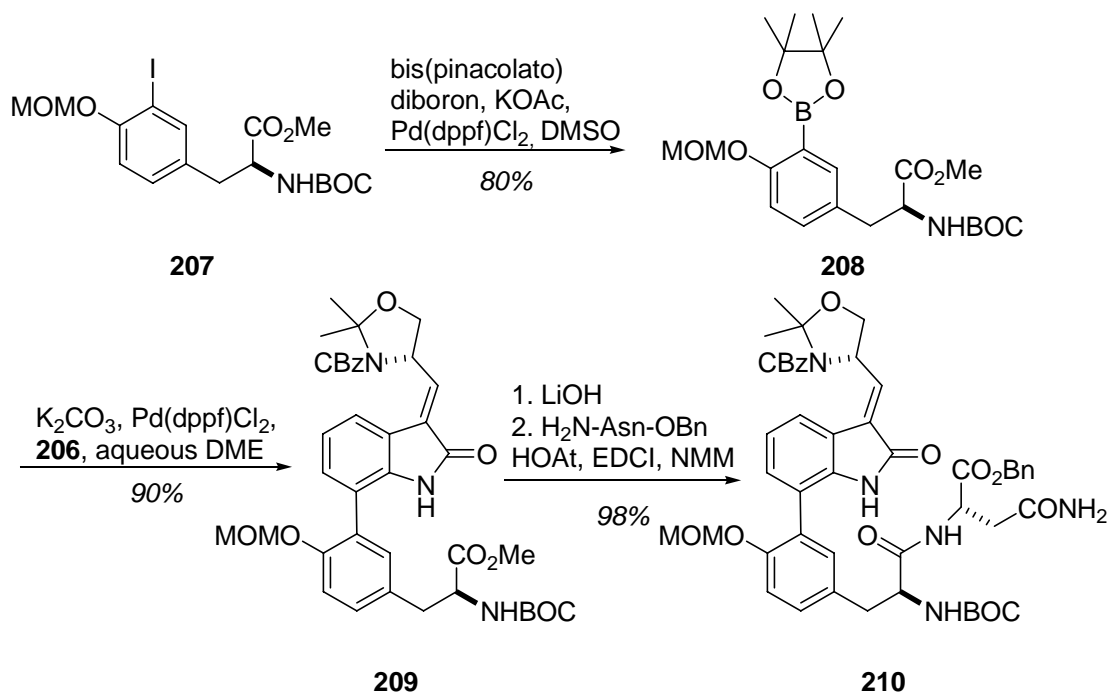


Figure 3.15: Biaryl coupling in the Williams route.

The formal synthesis was completed through dihydroxylation of the C(6)-C(7) olefin, resulting in the correct stereochemistry. A series of transformations revealed the

acid and free amine for macrolactam formation. Finally, conversion of the primary alcohol to its TES ether provided completion of the Williams effort by reaching one of the advanced intermediates from Danishefsky's route.

The formal synthesis of TMC-95A and B was accomplished by Williams and Albrecht in 14 steps. Although the retrosynthesis was similar to Danishefsky's, with the only major difference being the Julia coupling, they were able to synthesize one of Danishefsky's advanced intermediates in fewer steps.

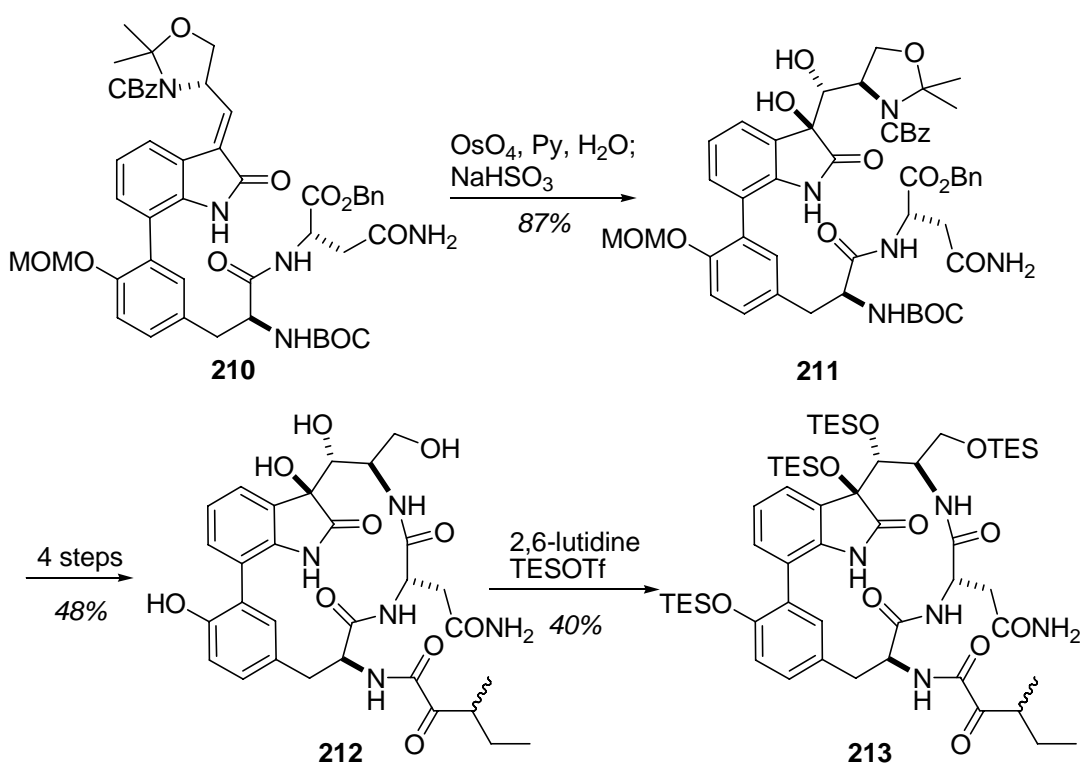


Figure 3.16: Completion of Williams' synthesis.

3.3 Conclusions

At this time, three syntheses (two total and one formal) of the TMC-95 compounds have been achieved. The key transformations are formation of the *cis*-enamide and establishment of the correct stereochemistry at C(6) and C(7). The southern portion is completed in similar fashion in each route.

Chapter 4

Studies toward the oxindole core of TMC-95

4.1 Retrosynthesis

The initial studies toward the TMC-95 compounds followed the retrosynthesis seen in Figure 4.1. The macrocycle would be closed in two steps, a Suzuki coupling followed by macrolactamization. The dipeptide **217** was successfully constructed in 5 steps and 23% overall yield from tyrosine and asparagine.⁵⁷

Interest in TMC-95 focused on the oxidative cyclization methodology. Two main factors had to be addressed in order to ascertain the feasibility of this strategy. Most of the known examples of tryptophan oxidative cyclizations showed either modest stereoselectivity at C(3) of the indole or did not report a ratio. As this reaction would be used to set C(6) relative stereochemistry (TMC-95 numbering), high selectivity was critical. It was also unknown what effect the oxygen substituent at C(7) would have. All known examples were on *N*-substituted tryptophan derivatives, with no other functionality. It was hypothesized that a sufficiently bulky protecting group on the C(7) oxygen might be used to influence the relative stereochemistry of C-O bond formation at C(6) upon oxidative cyclization (**219**→**218**). From spiro lactone **218**, ring opening with *L*-*allo*-threonine and dehydrative decarboxylation would lead to the northern half of TMC-95. The precursors for cyclization would be derived from indole-3-carbaldehyde.

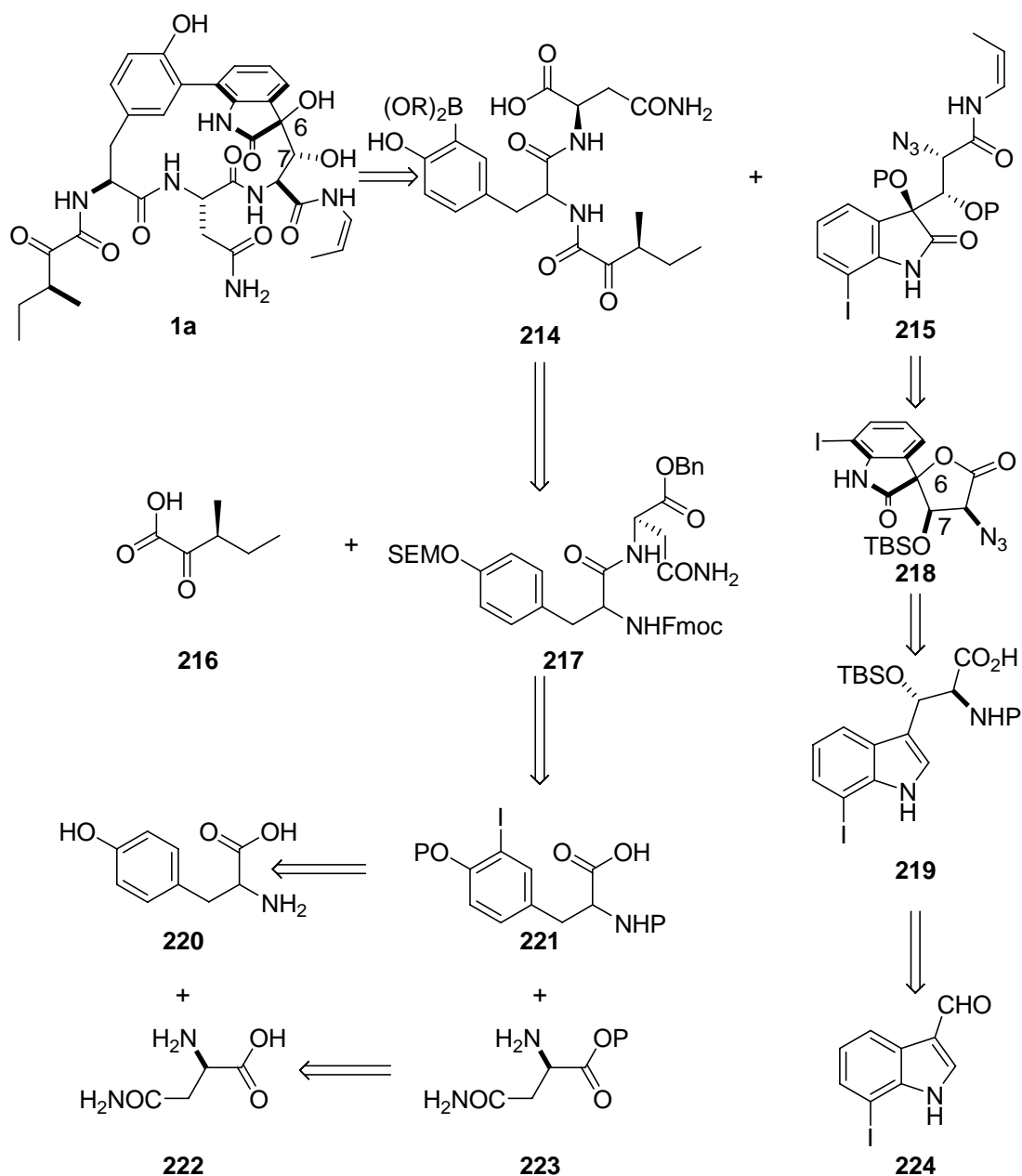


Figure 4.1: Retrosynthesis of TMC-95A.

Two possible transition states for the key **219**→**218** cyclization are presented in Figure 4.2. The expectation that there will be a stereochemical preference at C(6) originates from **227** where a steric interaction would be present between the C(7) oxygen

substituent and the peri-positioned hydrogen. No such steric interaction exists in the alternative transition state **225**.

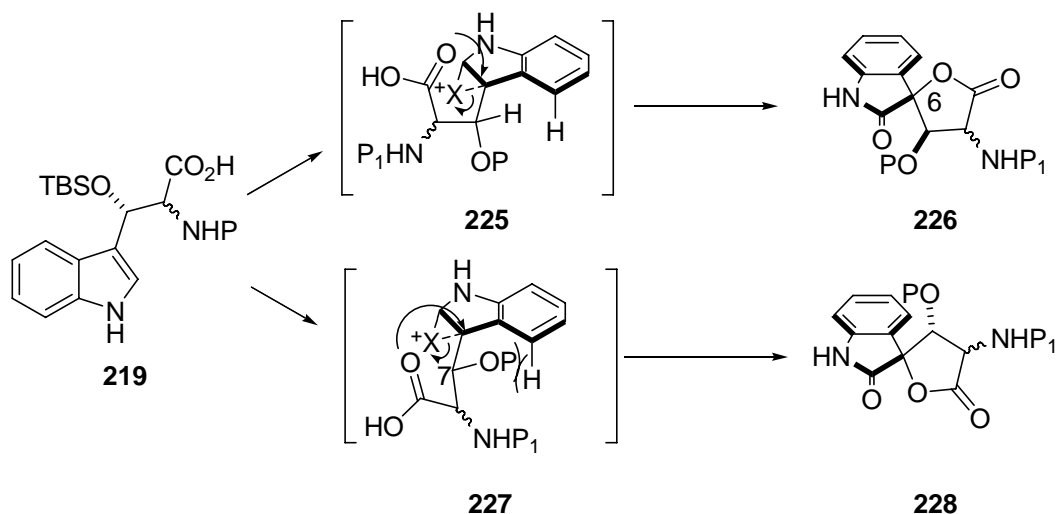


Figure 4.2: Possible cyclization transition states.

4.2 Oxidative cyclization approaches.

Work towards the first model system commenced with the known enoate **229**.⁵⁸ This model has the incorrect relative stereochemistry between C(7) and C(8) (TMC-95 numbering) for TMC-95A and B, but it still has value as a test of the transition state analysis shown in Figure 4.2. Amino alcohol **230** was formed in >99% *ee* (10:1 regiochemical preference) via a Sharpless asymmetric aminohydroxylation reaction.⁵⁹ Protection of the alcohol as its TIPS ether followed by hydrolysis of the ester led to **231**, which was ready for attempts at the key cyclization step. A variety of conditions were screened. Only NBS and sodium bicarbonate led to a cyclized product. A single diastereomeric compound was isolated from this reaction. As anticipated from the

analysis in Figure 4.2, an nOe between the C(7) hydrogen and the peri-positioned hydrogen determined that the stereochemistry was as shown in **232**. While the incorrect stereochemistry for the TMC-95 compounds was obtained as expected, the isolation of a single diastereomer was encouraging, as was the ability to correctly predict the relative C(6)/C(7) stereochemistry of the product based on the stereochemistry of the transition state model **225**.

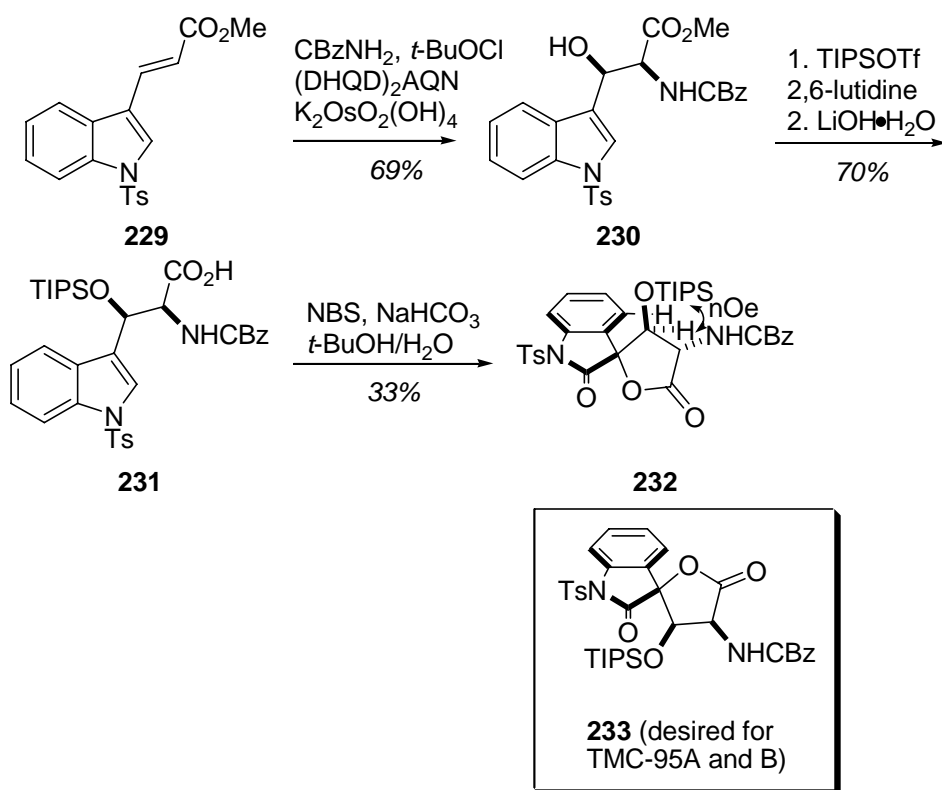


Figure 4.3: Syn amino alcohol model system.

Synthesis of the required anti amido alcohol **236**, which does contain the correct C(7)/C(8) relative and absolute stereochemistry for TMC-95A synthesis started from enoate **229**. A Sharpless asymmetric dihydroxylation⁶⁰ gave the desired diol in >99% *ee*. A sequence developed by Boger⁶¹ was followed to yield protected azido alcohol **235**. The azide was reduced and protected in a one pot procedure.⁶² The yield of this reaction

was not optimized due to the downstream cyclization results. Hydrolysis of the methyl ester led to the cyclization substrate **236**. A similar set of cyclization conditions as before were screened with **236**. Again, NBS/NaHCO₃ was the only reagent combination to lead to a cyclization product. However, the presence of a singlet at 6.62 ppm (and a lower IR shift: 1764 cm⁻¹ for **237** compared to 1810 cm⁻¹ for **232**) suggested valerolactone **237** was formed. Additionally, an HMBC correlation between the proton at C(2) of the indoline and the carbonyl carbon of the lactone provided further evidence for structure **237**. Interestingly, this species was isolated as a single diastereomer, although the ring junction stereochemistry was not assigned

The basis for the formation of **237** instead of **233** may be explained through examination of the transition states. Transition state **238** would lead to the desired 5-membered lactone **233**. However, this assembly contains an unfavorable eclipsing interaction between the OTBS and NHCBz groups. Transition state **239**, which may normally represent a higher energy mode of nucleophilic addition, displays a gauche interaction between OTBS and NHCBz and leads to the observed product **237**. **238** and **239** are the expected transition states in this scenario. Transition states **40** and **42** both require addition of the nitrogen atom's lone pair. The use of an electron withdrawing group on the indole nitrogen makes these transition states unlikely. With undesired C(2) addition in the oxidative cyclization, any new strategy would have to overcome this unfavorable eclipsing interaction to steer the transformation back to the TMC-95 butyrolactone-type product.

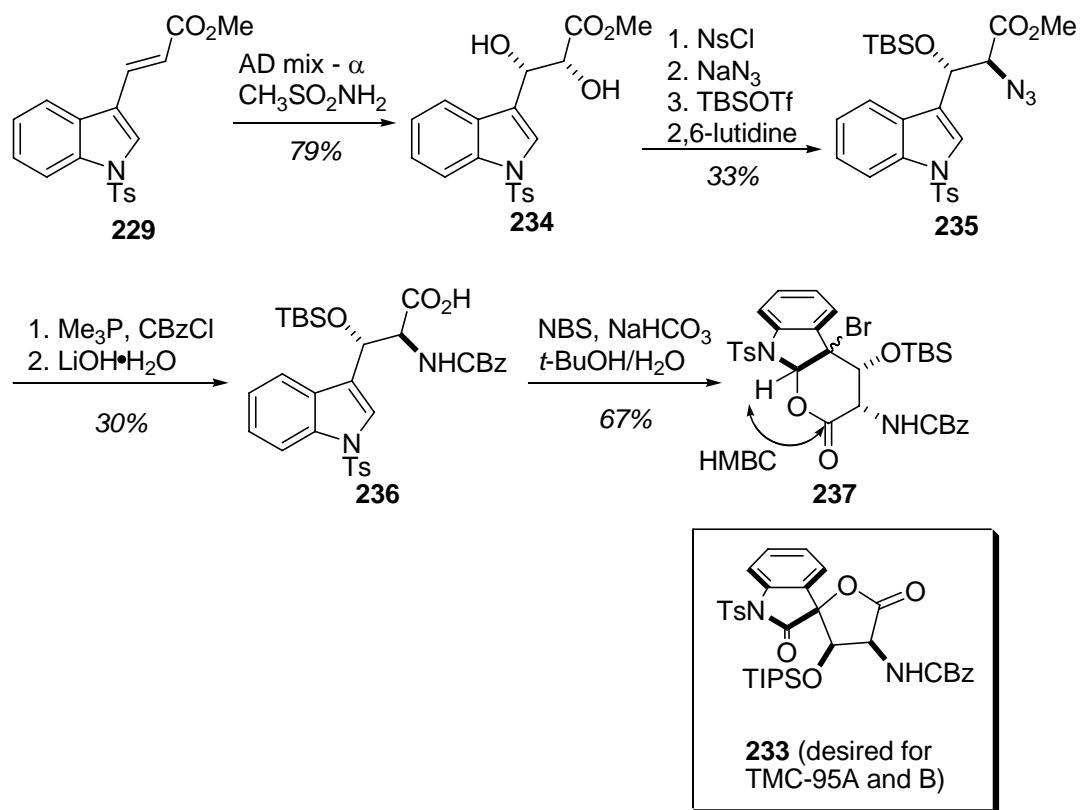


Figure 4.4: Anti amino alcohol model system.

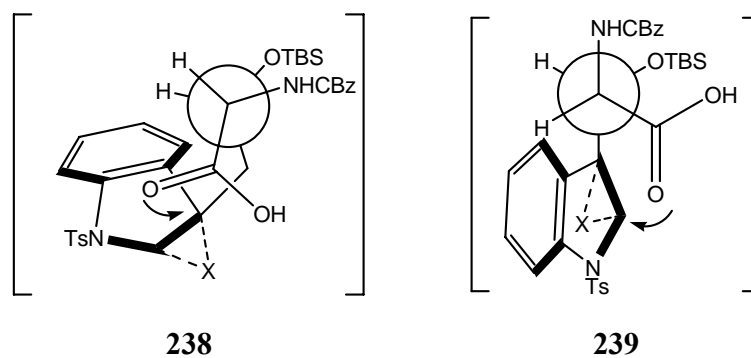


Figure 4.5: Explanation for the observation that a 6-membered alternative is favored.

As an alternative to the *N*-tosyl indole series, screening of an acid with a free *N*-H indole was also desired. Attempts to remove the tosyl group on an intermediate more

advanced than **229** were unsuccessful. Attempts at azide formation on a substrate bearing a free *N*-H encountered problems. A route that avoids both of these issues begins with indole-3-carbaldehyde. Protection of the indole nitrogen followed by a Horner-Emmons reaction gave enoate **241**. The same route used before with **235** led to azide **243**. Here, one-pot reduction of the azide and protection of the derived amine with BOC-ON afforded the protected anti-amino alcohol in good yield. All attempts to hydrolyze the methyl ester led to decomposition of the starting material. Use of distannoxane catalyzed transesterification conditions⁶³ afforded the benzyl ester. Hydrogenation was successful in removing both the benzyl and CBz protecting groups in quantitative yield. A wide variety of electrophilic cyclization conditions were screened (Table **4.1**). Unfortunately, no productive cyclization was seen, with all attempts leading to decomposition of the starting material.

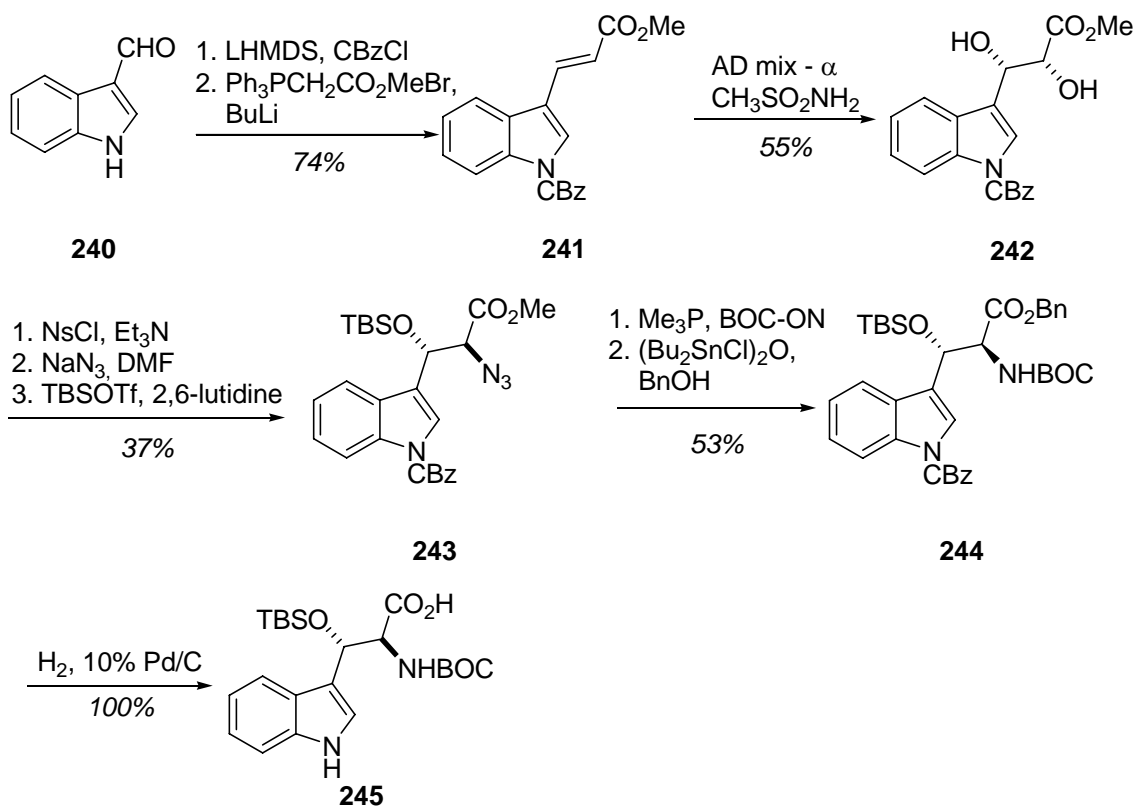


Figure 4.6: Synthesis of the free indole N-H cyclization precursor **245**.

Conditions	Temperature
NBS/NaHCO ₃ t-BuOH/H ₂ O	RT
t-BuBr/DMSO	40 °C
t-BuBr/DMSO/CH ₂ Cl ₂ , sealed tube	45 °C
DMDO	
CrO ₃ /AcOH	40 °C
CCl ₃ SO ₂ Cl/DMSO	-20 °C
(CH ₃ SO ₂) ₂ O/DMSO	-20 °C
NBS/t-BuOH	
mCPBA	
PhI(OAc) ₂	
NBS, DMSO, CH ₂ Cl ₂	
Pb(OAc) ₄ , benzene	
NBS, pyridine, DMSO, CH ₂ Cl ₂	
PhI(O ₂ CCF ₃) ₂	

Table 4.1: Cyclization attempts with deprotected indole **245**.

4.3 Pummerer reaction methodology development

With the failure of these brominative cyclizations to form the desired products, a different approach toward cyclization was needed. Any new strategy would need to overcome the unfavorable eclipsing interaction seen in Figure 4.5. For this purpose, Pummerer methodology was explored. Through either the vinylogous or additive mechanisms, cyclization of a pendant nucleophile at C(3) would be favored (*vide supra*). In the vinylogous mechanism, rearomatization would be the driving force to promote cyclization at C(3). Nucleophilic attack at C(2) would not lead to an intermediate that could regain aromaticity in the 6-membered ring. This energy difference was expected to force the reaction to give only the desired 5-membered ring product. In the additive mechanism, attack at C(2) would not be possible. Regardless of the mechanistic preference, the presence of the silyl ether was expected to generate the desired C(6)-C(7) relative stereochemistry based upon the analysis shown in Figure 4.7.

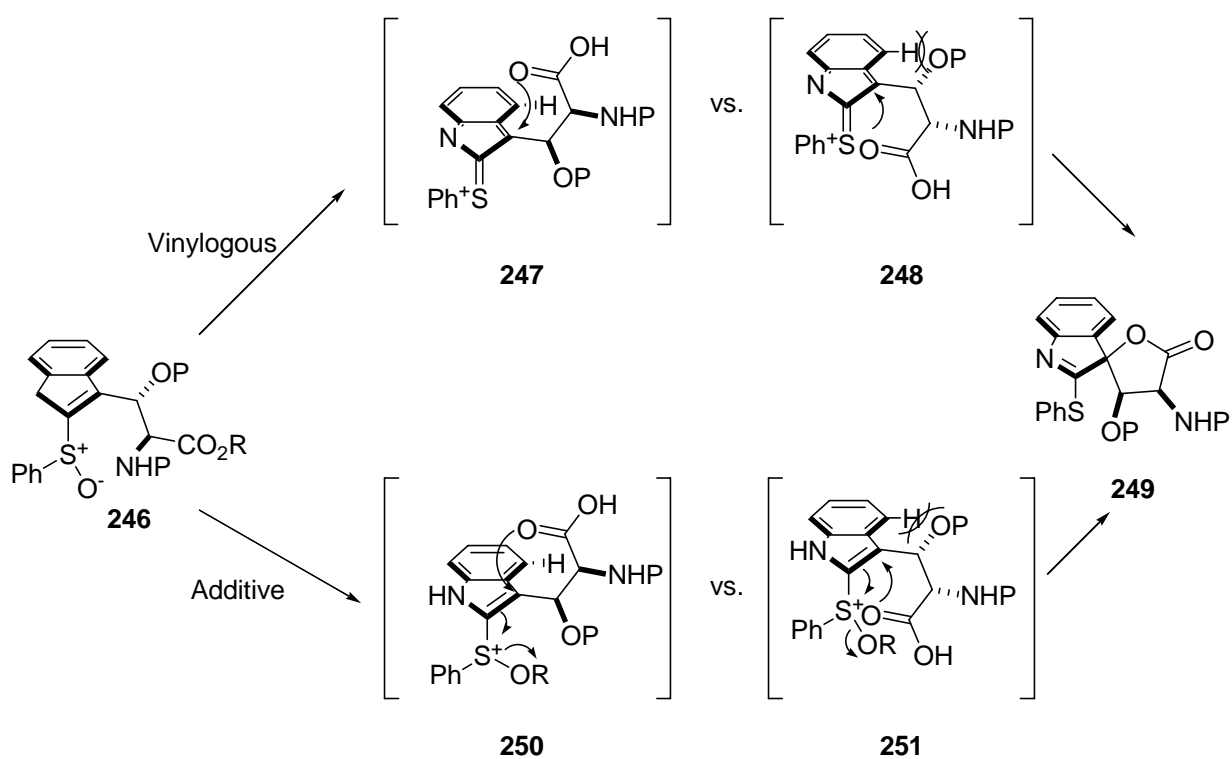


Figure 4.7: Transition states of the Pummerer mediated oxidative cyclization of a tryptophan derivative.

4.3.1 Tryptophan-based model system

In order to test this hypothesis, an initial set of studies with simpler tryptophan derivatives was explored. Starting from N-BOC tryptophan, sulfoxide **255** was formed in two steps.⁶⁴ A variety of conditions were screened with **255**, with none leading to productive cyclization. The first encouraging result with this methodology was seen with sulfoxide **256**. By utilizing a TBS ester in the cyclization substrate, a low yield of the desired 5-membered lactone **254**, as a 1:1 mixture of diastereomers, was observed. Subsequent hydrolysis of the thioimide successfully led to the oxindole **257**. Whereas

the yield was lower than desired, this initial success prompted further exploration for formation of 3,3-spirocyclic oxindoles.⁶⁵ Other conditions (activators and bases) for this reaction were examined, but did not lead to increased yields. Longer reaction times did not lead to improvement, although the initial trial showed a significant amount of starting material present in the crude reaction mixture. Several factors might contribute to the low yield. Foremost is the instability of the TBS ester. It is likely that the yield was low in the sulfide oxidation step, although product instability precluded isolation and therefore yield measurement. Second, the lifetime of the TBS ester group was found even at low temperature to be very short. If the TBS group was cleaved in the reaction, the resulting acid **255** was known to decompose under these reaction conditions. This sensitivity would account for the yield not increasing when the reaction time was lengthened. Future results (*vide infra*) showed that the BOC group could function as a nucleophile in this process and therefore compete with the silyl ester for the C(3) electrophile. While the six membered cyclic carbamate was not recovered from this particular trial, it was seen with other related substrates. Results were improved by use of the hypervalent iodine reagent, PhI(CN)OTf developed by Stang and Zhdankin.⁶⁶ Employing this reagent enabled use of a more readily accessible substrate (acid **253**) than the TBS ester. The success of this reaction raised a question as to why the acid succeeded here when it has failed with the sulfoxide conditions. One possibility in the latter case is formation of a mixed anhydride from trifluoroacetic anhydride and **255**. This mixed anhydride could compete as an activator, resulting in a cyclic intermediate which may not be able to adopt the proper conformation for a Pummerer reaction to occur readily.

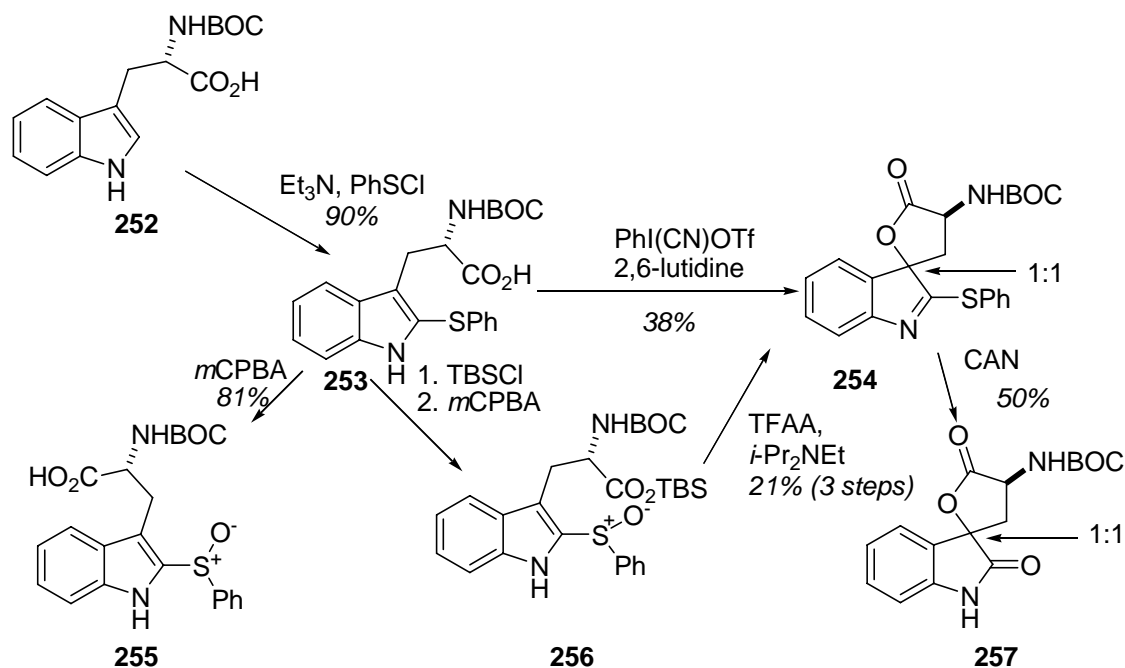


Figure 4.8: Initial Pummerer studies with the indole system.

Further attempts were made to extend this reaction to substrates bearing other ester groups. Attempts to use methyl ester **259**, made in two steps from sulfide **253**, led to a mixture of two products. The desired lactone was isolated in 33% yield. However, an additional 63% yield of **260** was isolated from competitive addition of the trifluoroacetate anion (and hydrolysis upon workup). While the yields were not as high as desired, the strategy appeared to have promise as a method for forming 3,3' spirocyclic oxindoles. At this point, application to the oxindole portion of TMC-95A was investigated.

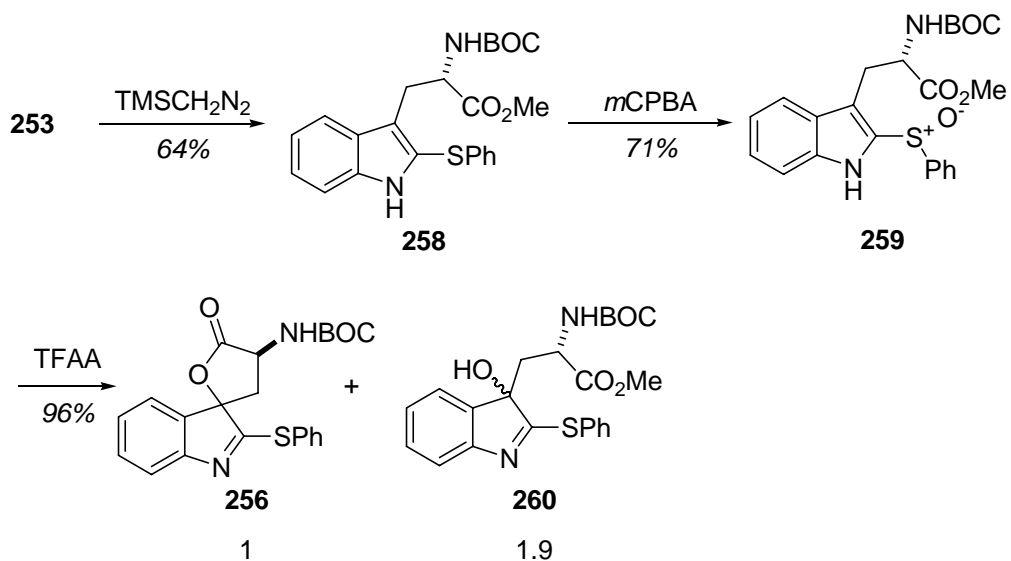


Figure 4.9: Pummerer reaction in the methyl ester series.

4.3.2 Pummerer methodology as applied to TMC-95A

The modified retrosynthesis of the oxindole portion of TMC-95A is seen in Figure 4.10. The spiro lactone **262** would be derived from **263**, which would be made starting from **264**.⁶⁷

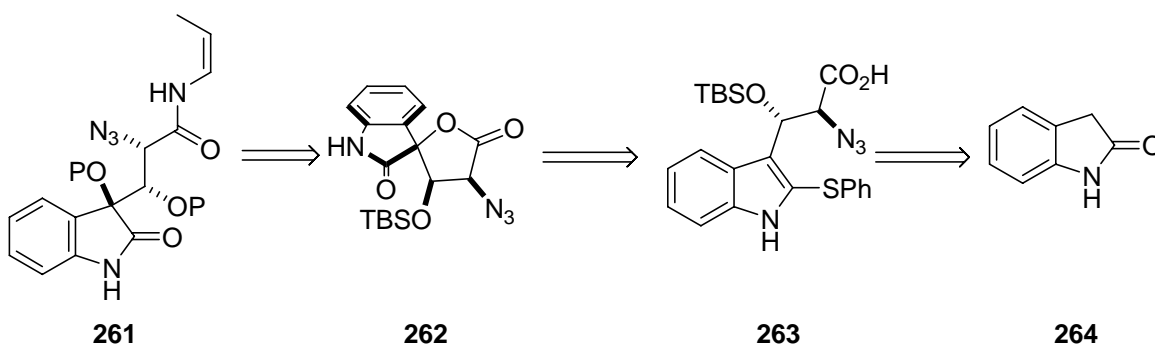


Figure 4.10: New oxindole retrosynthesis for the Pummerer based TMC-95 synthesis.

This route begins with known indole **265**.⁶⁸ Addition of the anion of benzenethiol gave sulfur substitution at C(2).⁶⁹ Additional steps to form the anti azido alcohol were

similar to those used before with **235**, resulting in azide **267** in good yield. The azide functionality was maintained due to other results which showed competition of the amine protecting group (vide infra) in cyclization. Hydrolysis of both protecting groups occurred readily with lithium hydroxide to yield the key precursor for cyclization, **263**.

Successful Pummerer-mediated cyclization of **263** furnished lactone **268** as a single diastereomer and regioisomer. Extensive optimization of the Pummerer methodology was completed (Table 4.2), resulting in 40% as the best yield. Hydrolysis of the thioimidate led to oxindole **262**. The stereochemistry at C(6) was determined to be appropriate for TMC-95A (and B) synthesis. This assignment was based on an nOe observation between the hydrogen at C(7) and the peri positioned hydrogen of **262**.

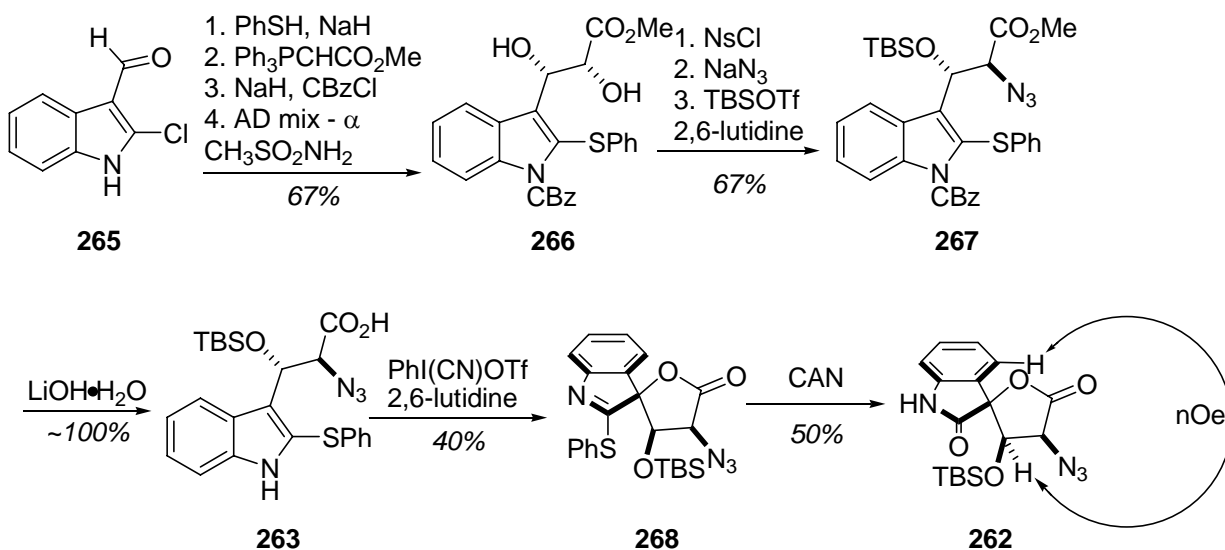


Figure 4.11: TMC-95A Pummerer based route.

Base	Equiv. Base	Solvent	Equiv. Stang	Temperature	Product	Yield
2,6-Lutidine	3	CH ₂ Cl ₂	3.5	-78 °C to RT	Lactone	40%
2,6-Lutidine	3	Ether	3.5	-78 °C to RT	Lactone	40%
2,6-Lutidine	3	Toluene	3.5	-78 °C to RT	Lactone	35%
2,6-Lutidine	3	CF ₃ CH ₂ OH	3.5	-40 °C to RT	Lactone	32%
2,6-ditertbutyl pyridine	3	CH ₂ Cl ₂	3.5	-78 °C to RT	Lactone	20%
2,6-Lutidine	5	CH ₂ Cl ₂	3.5	-78 °C to RT	Lactone	13%
2,6-Lutidine	10	CH ₂ Cl ₂	3.5	-78 °C to RT	Lactone	10%
2,6-Lutidine	3	CH ₂ Cl ₂	3.5	0 °C	Lactone	10%
2,6-Lutidine	3	Hexafluoroisopropanol	3.5	-78 °C to RT	Lactone	<10%
2,6-Lutidine	3	CH ₂ Cl ₂	3.5	-20 °C	Lactone	<10%
2,6-Lutidine	3	CH ₃ CN	3.5	-40 °C to RT	Lactone	<10%
2,6-Lutidine	3	CH ₂ Cl ₂	1	-78 °C to RT	Lactone	<5%
2,6-Lutidine	3	CH ₂ Cl ₂	2	-78 °C to RT	Lactone	<5%
2,6-Lutidine	1	CH ₂ Cl ₂	3.5	-78 °C to RT	Lactone	Trace
2,6-Lutidine	2	CH ₂ Cl ₂	3.5	-78 °C to RT	Lactone	Trace
None	3	CH ₂ Cl ₂	3.5	-78 °C to RT	dec.	
2,6-Lutidine	3	THF	3.5	-78 °C to RT	dec.	
2,6-Lutidine	3	CH ₂ Cl ₂	3.5	RT	dec.	
2,6-Lutidine	3	CH ₂ Cl ₂	3.5	-78 °C	dec.	
Pyridine	3	CH ₂ Cl ₂	3.5	-78 °C to RT	dec.	
K ₂ CO ₃	3	CH ₂ Cl ₂	3.5	-78 °C to RT	dec.	
2,6-Lutidine	3	CH ₂ Cl ₂	3.5	-40 °C	dec.	
2,6-Lutidine	3	CH ₂ Cl ₂	3.5	-78 °C to RT	dec.	
2,6-Lutidine	3	CH ₂ Cl ₂	3.5	-78 °C to RT	dec.	

Table 4.2: Optimization of Stang-initiated Pummerer reaction on **263**.

A series of related substrates were also examined, including a TBS ester containing species. In this case, the unstable TBS ester did not yield any cyclized product, and only the derived acid was recovered. Additionally, the use of a *t*-butyl ester was investigated. Initially, the azide was reduced to the BOC-protected amine. Pummerer reaction attempts with sulfide **270** (Figure 4.12) showed that inclusion of the carbamate protecting group gave rise to an undesired 6-membered cyclic carbamate product (**271**).

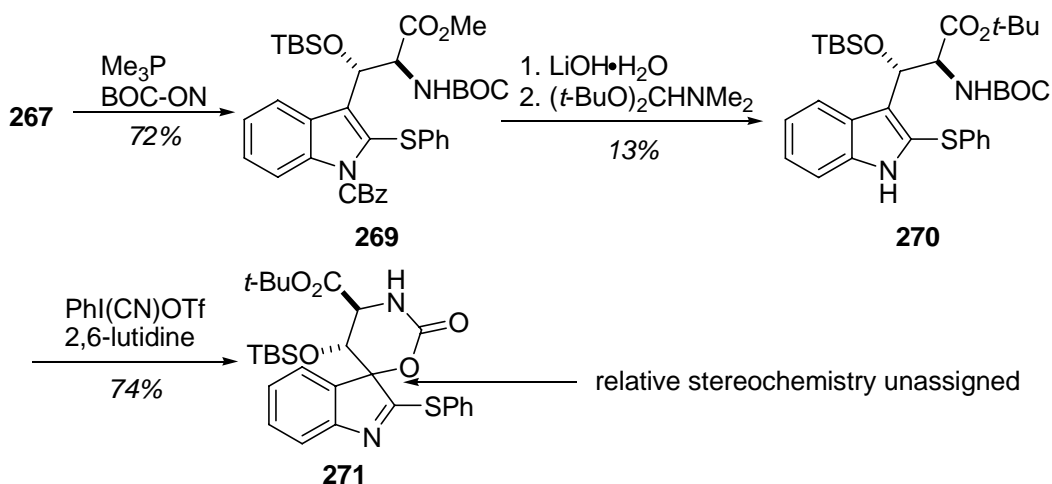


Figure 4.12: Cyclic carbamate.

A Pummerer reaction on *t*-butyl ester substrates that retained the azide was also explored. These substrates were made via formation of the *t*-butyl ester from acid **263** with dimethylformamide di-*tert*-butyl acetal, followed by oxidation to the sulfoxide. Both the sulfide and sulfoxide were exposed to appropriate conditions, and both substrates led to the desired product. However, neither reaction showed an improvement over that realized with acid **263**.

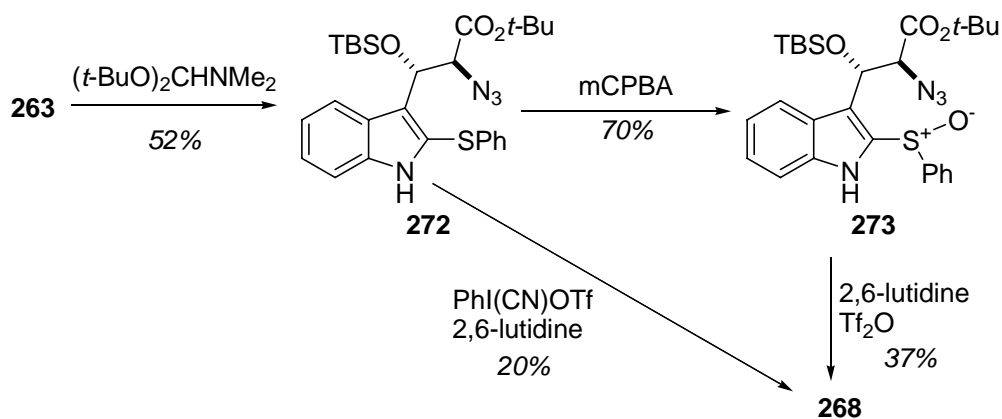


Figure 4.13: *t*-Butyl ester based Pummerer reactions.

4.4 Conclusions

The synthesis of the oxindole portion of the TMC-95 compounds was explored through both an oxidative cyclization approach and through development of new methodology using Pummerer chemistry. The initial chemistry highlighted problems of the oxidative cyclization approach: a lack of access to the desired stereo- and regioisomeric product. Development of the Pummerer methodology removed the possibility of cyclization at C(2) by using aromaticity as the driving force for C(3) attack. Application to the TMC-95A model system yielded spiro lactone oxindole **262** which possessed the correct stereochemistry at C(3). The project was terminated at this point due to the successful synthesis of TMC-95A by Danishefsky, Hiram, and Williams. Since the planned conversion of lactone **262** to TMC-95A closely followed these other routes, there appeared to be little to gain by continuing this work.

Chapter 5

Methods toward an enantioselective Pummerer reaction

Recent results from Penn State have shown that the indole based Pummerer chemistry is a useful method for formation of spiro six membered rings at C(3) of oxindoles using carbon nucleophiles.⁶⁵ The next stage of this work involved the synthesis of chiral versions of these spirocyclic products from enantiopure sulfoxides. Preliminary evidence indicated that there would be some enantioselectivity induced by a chiral sulfoxide.⁷⁰ However, these scouting experiments were performed on sulfoxides with varying *ee*'s. In addition, a method was needed by which enantiopure indole-2-sulfoxides with known configuration could be synthesized. Additional optimization was needed to find the highest obtainable *ee*'s for these reactions. Moreover, the preliminary work had only measured the *ee*'s, but had not defined the absolute stereochemistry at C(3) of the spirocyclic product. Finally, both unsubstituted indoles and 5-methoxyindoles were tested to determine if the electron donating ability of the methoxy group would have an impact on the *ee*.

In order for the chiral sulfoxide to transfer stereochemical information to the forming C-C bond, the reaction must proceed through either an additive mechanism or a vinylogous pathway through a tight ion pair. If the reaction were to proceed through the vinylogous mechanism with formation of an achiral sulfonium ion, all stereochemical information would be lost. This achiral intermediate would lead to racemic products.

Determination of the enantiomeric excesses of the Pummerer products was achieved using ¹H NMR titration with one of the chiral shift reagents (*S*)-(+)-2,2,2-

trifluoro-1-(9-anthryl)ethanol⁷¹ (*S*-(+)-TFAE) or europium [3-(trifluoromethylhydroxymethylene)-(+)-camphorate]⁷² (Eu(tfc)₃).

5.1 Substrate synthesis

Using the previous results as a starting point, the initial goal was the synthesis of the six enantiopure sulfoxides shown in Figure 5.1. Whereas a route was known to racemic material, this chemistry would not be useful here. In order to secure chiral sulfoxides of known absolute stereochemistry, it was necessary to develop new routes to each of these compounds which would utilize C(2) lithiation and reaction with (4*R*,5*S*)-4-methyl-5-phenyl-3-[*p*-phenyl]-2-isooxazolidinone.⁴³ Marino had shown⁴⁴ that this approach is a useful method for the synthesis of chiral sulfoxides at C(2) of indoles.

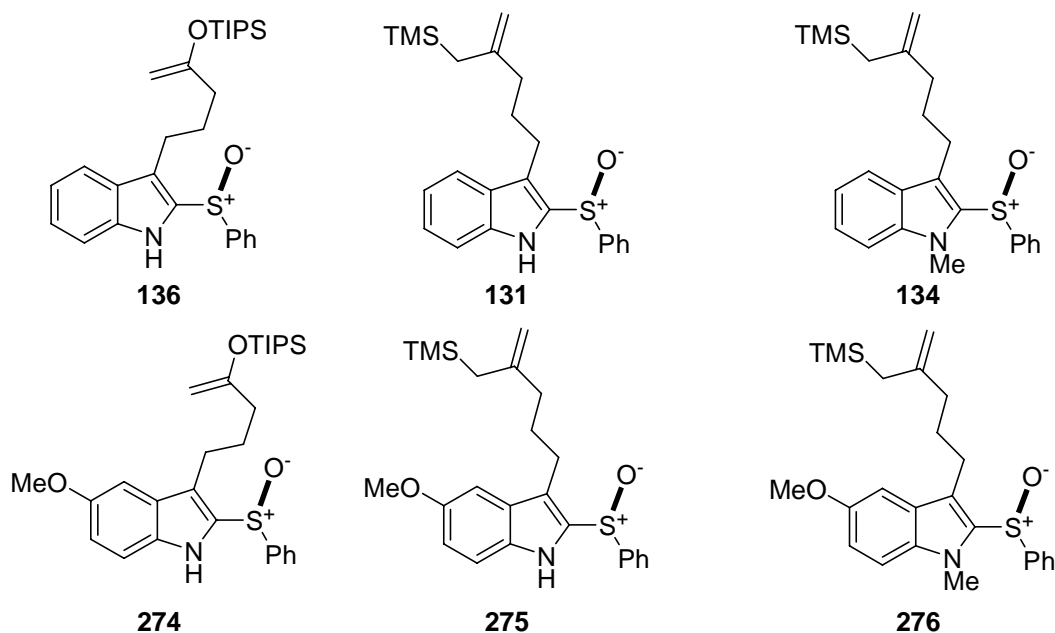


Figure 5.1: Chiral sulfoxides examined in this study.

5.1.1 Allylsilanes

Synthesis of the allylsilane chiral sulfoxides **131**, **134**, **275**, and **276** started with 5-methoxyindole butyric acid (**281**), which was available in four steps from *p*-anisidine (Figure 5.2).⁷³

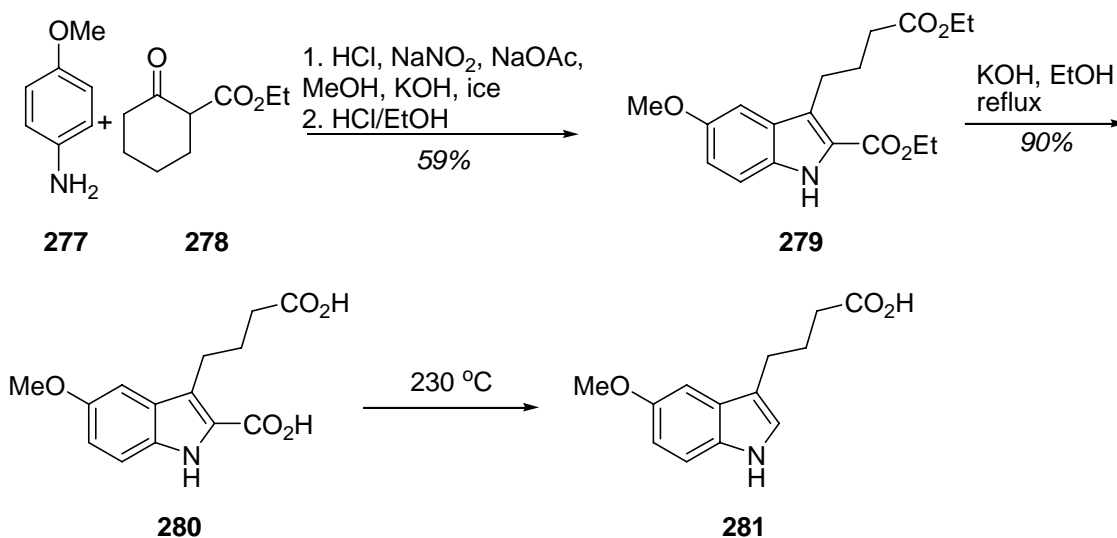


Figure 5.2: Japp-Klingemann synthesis of 5-methoxy indole 3-butyric acid.

The acid was converted to the methyl ester **282** with trimethylsilyl diazomethane. Peterson olefination of **282** by addition of (trimethylsilyl)methyl lithium in the presence of cerium (III) chloride, followed by silica gel assisted elimination, yielded allylsilane **283**. BOC protection of the indole formed precursor **284** for chiral sulfoxide formation at C(2). Ortho lithiation with *s*-butyllithium followed by quenching of the derived C(2) lithiate with (4*R*,5*S*)-4-methyl-5-phenyl-3-*[p*-phenyl]-2-isooxazolidinone (**156**) produced allylsilane **275** in good yield. Unexpectedly, this reaction also led to removal of the indole nitrogen's BOC group. This deprotection was a fortuitous result as removal of this protecting group was planned next. From here, methylation of the indole nitrogen with lithium bis(trimethylsilylamide) and methyl iodide afforded compound **276**, completing

two of the six compounds desired to test the question of asymmetric induction with this methodology.

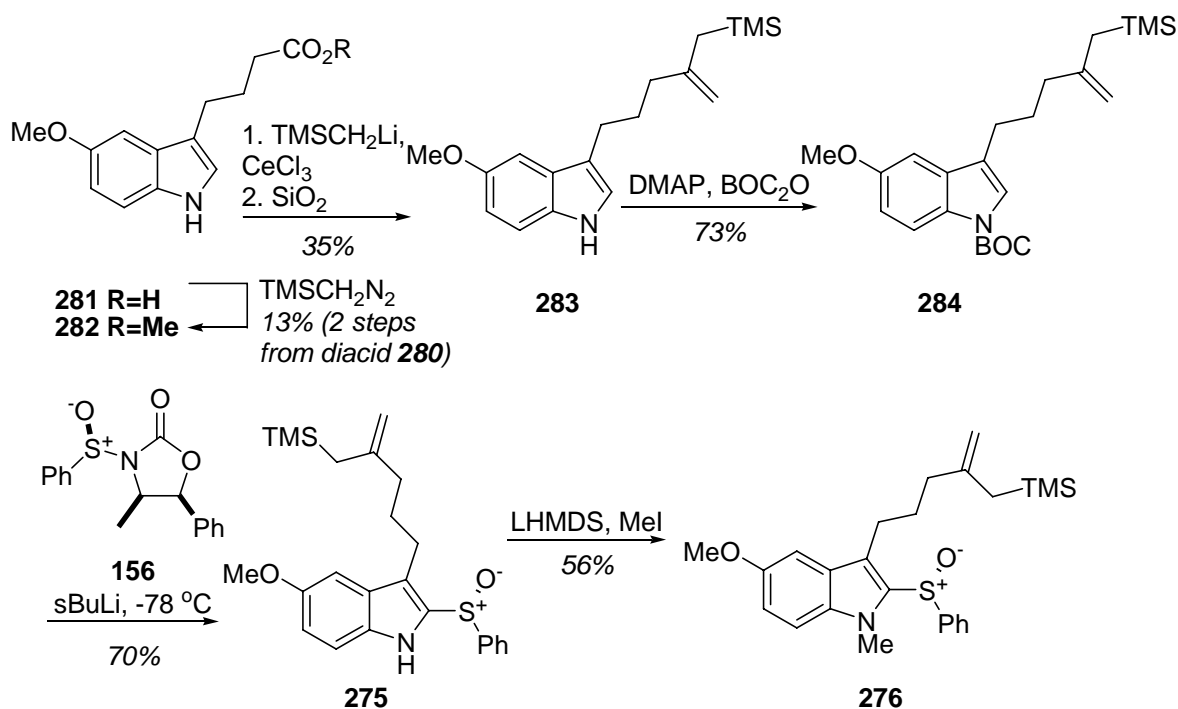


Figure 5.3: 5-Methoxy allylsilane substrate syntheses.

Having established this route, syntheses of the analogous des-methoxy compounds were accomplished following the same strategy (Figure 5.4). The only significant difference in these two routes is the yield of the esterification. This discrepancy can be explained by the origins of the starting materials. Whereas **281** was synthesized in four steps, indole 3-butyric acid is commercially available. The four step procedure for the formation of **281** is seen in figure 5.2. The first three steps were high yielding, but decarboxylation of **280** at high temperature or under microwave conditions was found to give inconsistent yields. In addition, spectral analysis of the decarboxylated material indicated a pure product, but the low yields of the methylation and bromination reaction suggested that this analysis was suspect. Bromination of the crude product **281** with one equivalent of NBS resulted in at least one dibrominated product. When the

reaction was run with addition of small portions of NBS until the process was judged to be complete by TLC analysis, just over 0.5 equivalents were needed, indicating that acid **281** was approximately 50% pure.

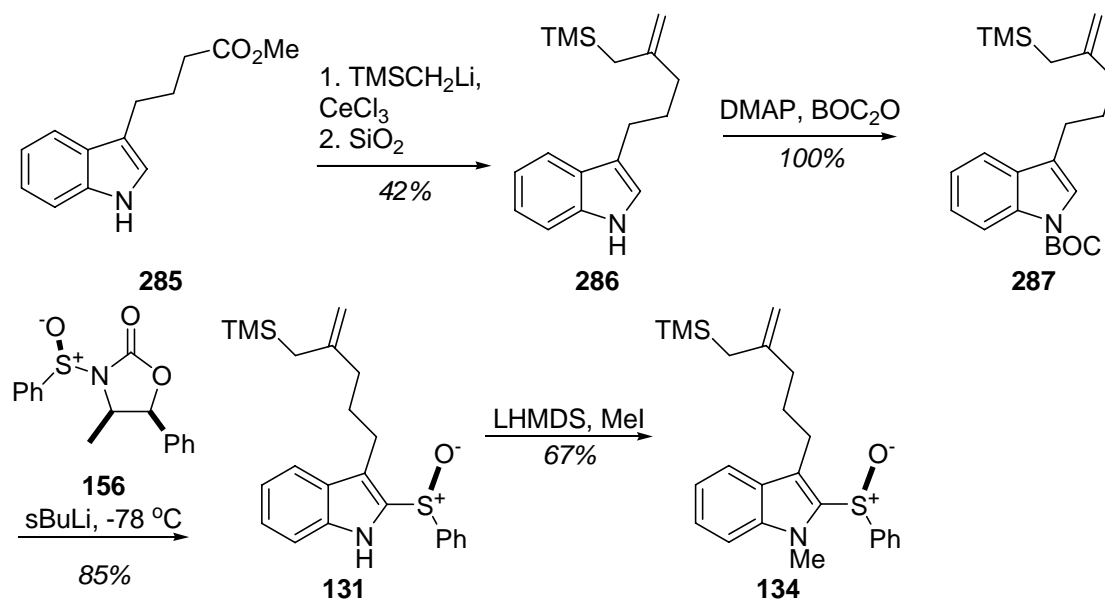


Figure 5.4: Synthesis of allylsilanes **131** and **134**.

5.1.2 Silyl enol ethers

Synthesis of silyl enol ether **274** started with methyl ester **282**. NBS treatment of **282** gave bromination at C(2). Bromination was found to be necessary in this instance because direct metallation of the des-bromo analogue of **288** was unsuccessful. This bromination was followed by protection of the indole nitrogen and then reduction of the methyl ester to the primary alcohol, which was protected as its TBS ether, **288**. *t*-Butyllithium was used to initiate lithium-halogen exchange on **288**.⁷⁴ Quenching of the anion with (4*R*,5*S*)-4-methyl-5-phenyl-3-[*p*-phenyl]-2-isooxazolidinone (**156**) gave sulfoxide **289** in good yield. As with the allylsilane chemistry, the BOC group was

conveniently cleaved in this reaction. Elaboration of **289** was continued with deprotection of the TBS group using TBAF, followed by oxidation of the resulting alcohol with *N*-methyl morpholine *N*-oxide (NMO) and tetrapropylammonium perruthanate (TPAP).⁷⁵ The aldehyde was converted to the ketone through addition of methylmagnesium bromide, resulting in a 1:1 mixture of diastereomeric alcohols which were both oxidized to ketone **293** with TPAP and NMO. Formation of the silyl enol ether **274** was accomplished according to conditions that were previously established.⁶⁵

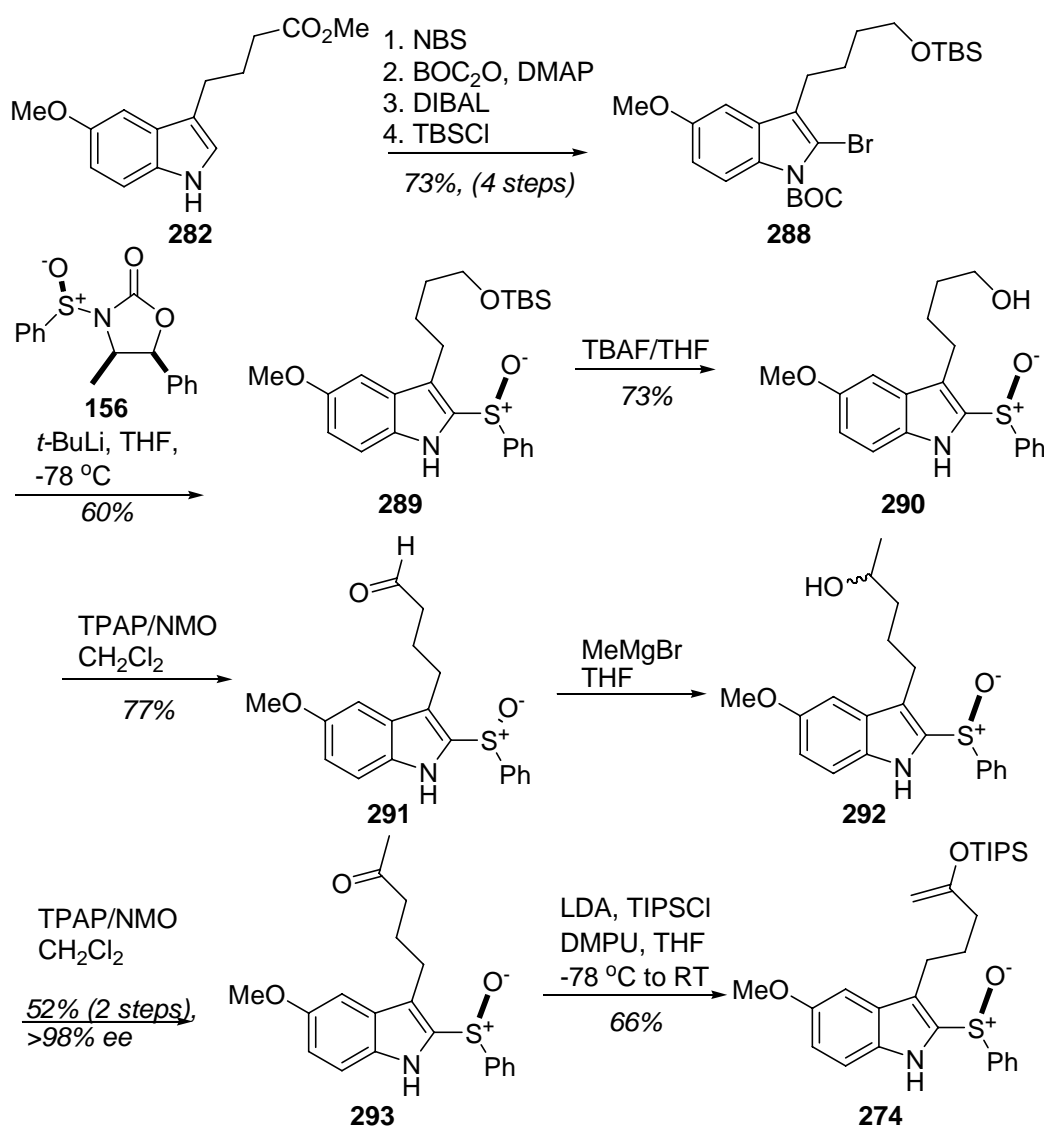


Figure 5.5: 5-Methoxy indole-2-sulfoxide silyl enol ether synthesis.

The final desired substrate, the des-methoxy silyl enol ether **136**, was synthesized using the same route as its 5-methoxy counterpart (Figure 5.6). The yield of the second oxidation was not optimized, as an alternative route was used for synthesis of larger quantities of material, as elaborated in Figure 5.7.

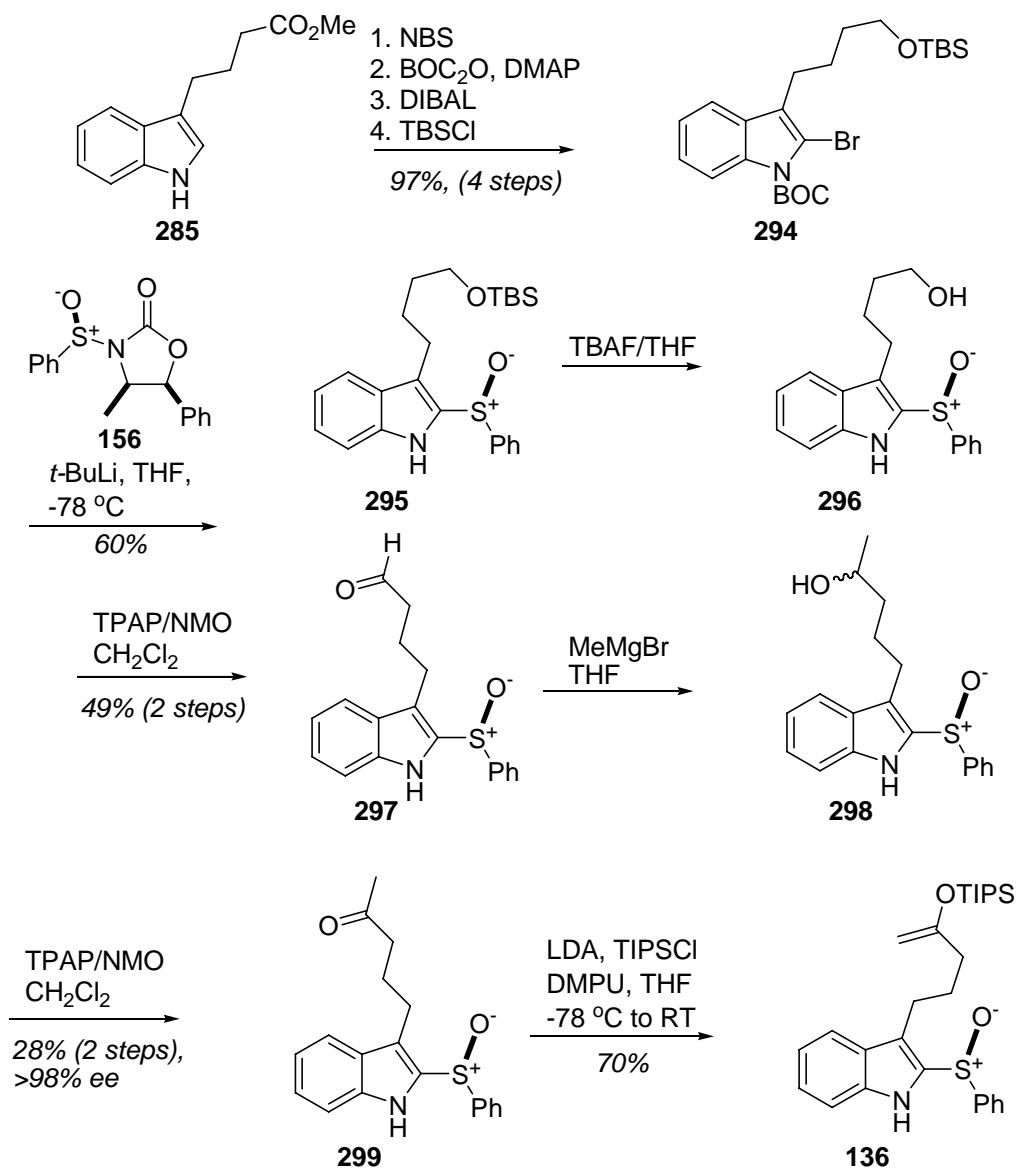


Figure 5.6: 5-H indole-2-sulfoxide silyl enol ether synthesis.

In order to expedite development of this methodology, a shorter, alternative route⁷⁰ was used to access **293** and **299**. This route utilized a chiral oxidation of sulfides **302** and **304**⁷⁶ using oxaziridine **303**, a reagent that was developed by Davis.⁷⁷

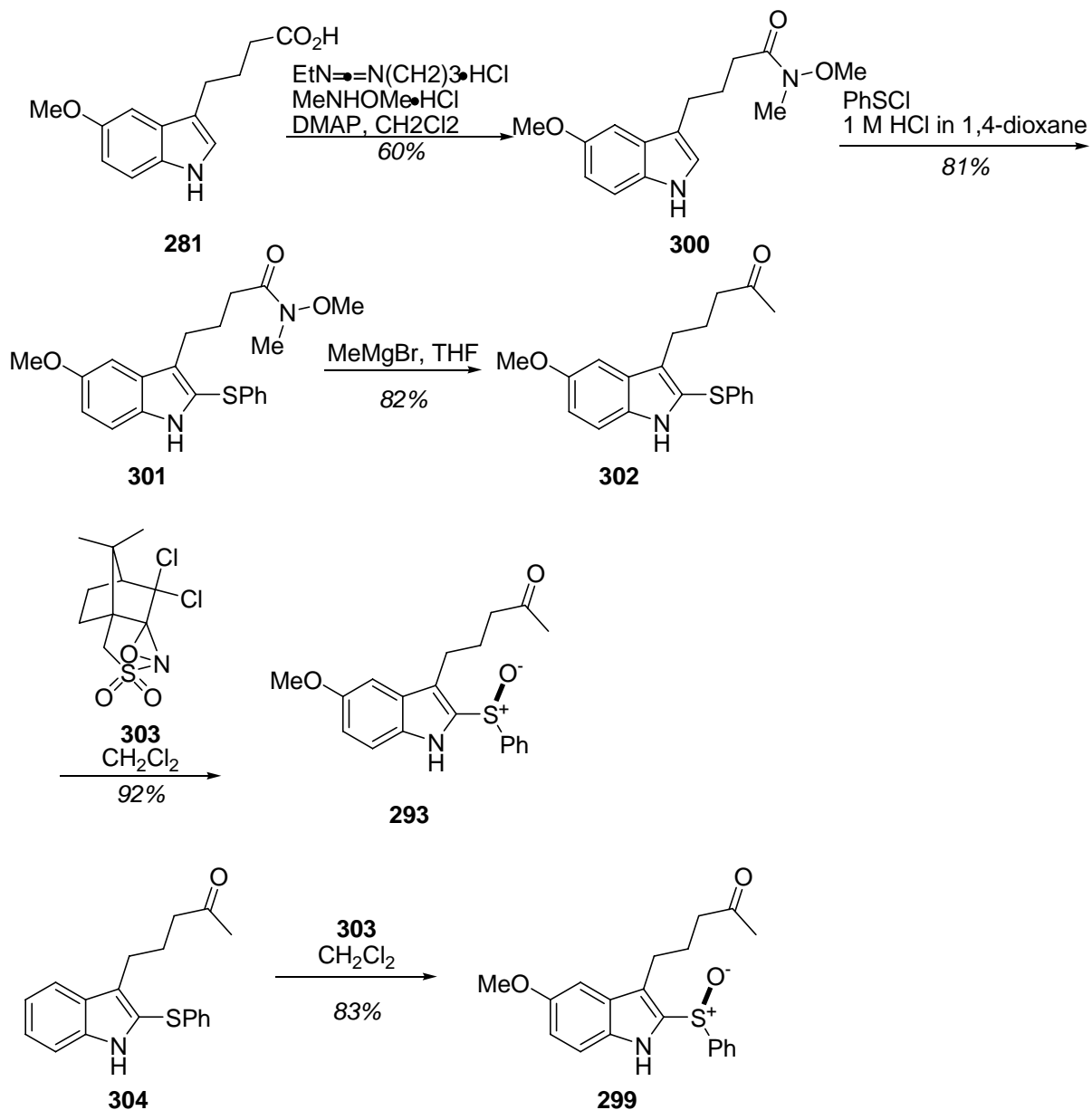


Figure 5.7: Alternative route to **293** and **299**.

5.2 Optimization of Pummerer reaction *ee*'s

With the six substrates in hand, attempts were made to optimize the enantiomeric excess of the key Pummerer cyclization. Toward this goal, several variables which might play a role were considered. The most significant was expected to be solvent. Also of interest was the effect that reaction temperatures would have on the enantiomeric excess. A short exploration of solvent viscosity was carried out to see if increasing the viscosity might be able to preserve any chiral tight ion pair present and hence enhance the *ee*. Finally, the difference between the methoxyindole and the unsubstituted analogue was of interest due to their difference in stabilizing the electron demand generated by the electron deficient transition states. The donating ability of the methoxy group could contribute to a resonance structure (**306**) where a thionium ion intermediate (achiral or chiral tight ion pair) is stabilized. Other factors such as different activators and bases were not investigated due to previous results⁷⁸ which showed that other common activators (TFAA, TMSOTf) were ineffective for this methodology.

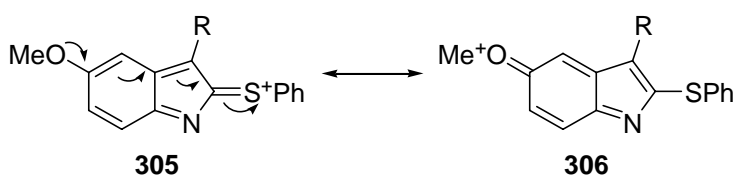


Figure 5.8: Possible resonance effect of the methoxy substituent.

5.2.1 Allylsilanes

The first substrate chosen for optimization was sulfoxide **275**. This system was screened with different solvents. Table 5.1 displays the yields of the three steps used to determine the *ee*'s. It was found that in order to get optimal separation of the ¹H NMR

signals using the shift reagent $\text{Eu}(\text{tfc})_3$, conversion to *N*-methyl oxindole **309** was necessary. However, as neither hydrolysis nor methylation should effect C(3), it was expected that doing so would not affect the ability to accurately measure the *ee* of the initial Pummerer cyclization. Whereas these results did indicate the expected changes with regard to solvent polarity, the use of toluene resulted in the highest *ee*, a disappointing 56%. In order to continue probing the methodology, the next substrate was the des-methoxy sulfoxide, **131**.

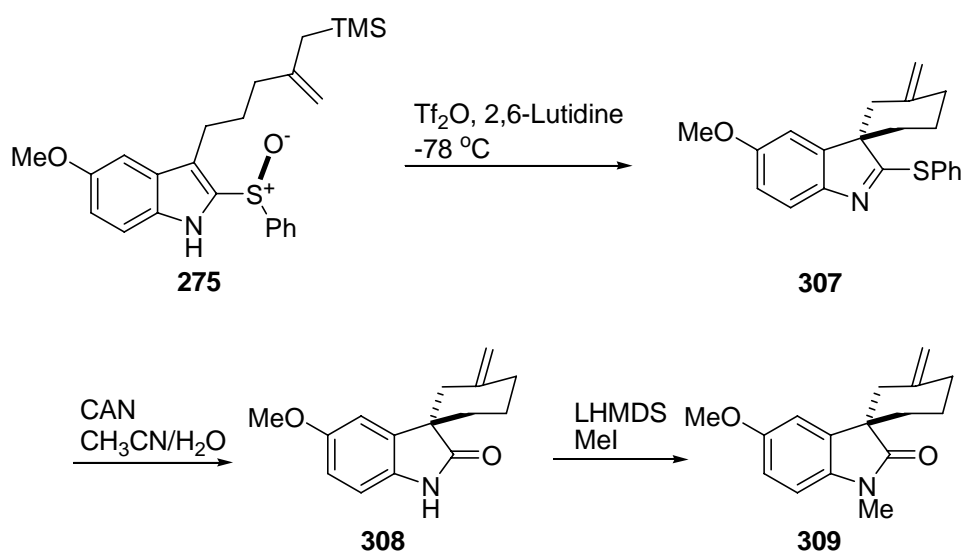


Figure 5.9: 5-Methoxyindole allylsilane Pummerer reactions.

Solvent	Yield 307	Yield 308	Yield 309	<i>ee</i>
Dichloromethane (-78 °C)	47%	50%	44%	10%
Ether (-78 °C)	47%	50%	50%	28%
Toluene (-78 °C)	47%	75%	60%	56%

Table 5.1: Results of the 5-Methoxy allylsilane Pummerer reactions.

The next substrate for investigation was the des-methoxyindole **131**. It was desired to see if the absence of the electron donating methoxy group would impact the *ee*.

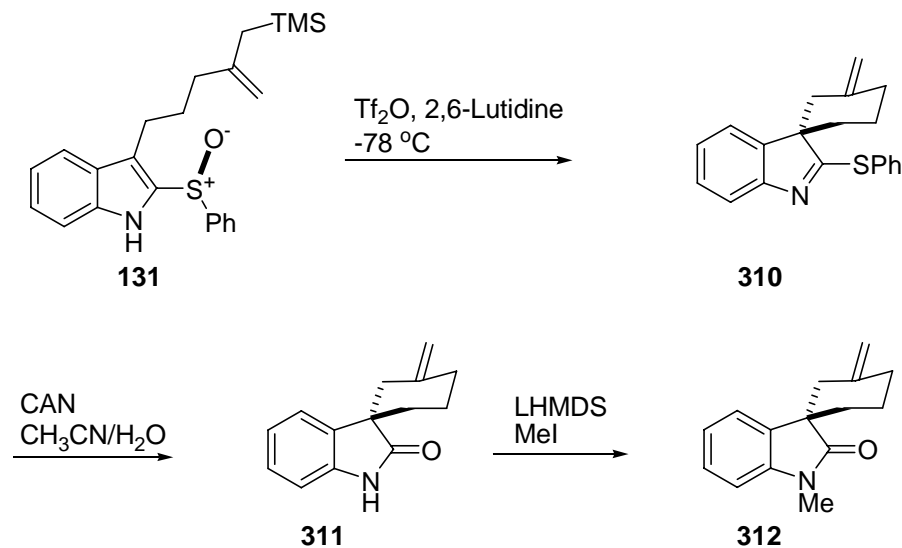


Figure 5.10: 5-H indole allylsilane Pummerer reactions.

A series of solvents were explored with allylsilane **131**. Although some solvents showed improvement over the methoxy series, the *ee* peaked at 58%, similar to the best 5-methoxyindole example. A couple of trends were noted. Enantiomeric excess was directly related to the polarity of the solvent. The best results were seen in the lowest polarity solvent, toluene, while the most polar solvent, trifluoroethanol, gave a racemic mixture. Attempts to use less polar solvents (or mixtures) did not lead to useful results. A mixture of toluene and hexane gave *lower* selectivity than toluene alone. The use of pure hexane as the solvent showed no reactivity, most likely caused by insolubility of the starting sulfoxide. The idea that solvent viscosities⁷⁹ might play a role was also explored. In this scenario, more viscous solvents should favor a tight ion pair over a free thionium ion *if* the vinylogous mechanism were operative. Unfortunately in the search for an appropriate solvent, two trends were observed. Higher viscosity solvents such as tetrachloroethane had higher freezing points and would not allow reaction at the lower temperatures generally employed in this reaction. The use of tetrachloroethane resulted

in a lower *ee* than the most similar solvent previously tried (dichloromethane). This comparison suggested that if the vinylogous mechanism were operative, the increased temperature superseded any possibly beneficial effect that solvent viscosity increase might have on *ee*. The only solvents with higher viscosities that could be cooled to -78 °C were more polar alcohol solvents, and previous results suggested that the *ee* would be low. An attempt with *n*-pentanol confirmed this supposition, resulting in no selectivity. On the other hand, these results are also consistent with reaction through the viscosity invariant additive mechanism. Two further attempts were made at lower temperatures, but likely due to the low nucleophilicity of the allylsilane, no reaction was observed.

Solvent (Temperature)	E _T (30) (kcal/mol) ⁸⁰	Viscosity (mpa s at -25 °C) ⁷⁹	Yield 312 (3 steps)	<i>ee</i>
Trifluoroethanol (-40 °C)	59.8	2.00 (20 °C) ⁸¹	18%	0%
<i>n</i> -pentanol (-78 °C)	49.1	25.4	17%	0%
Tetrachloroethane (-40 °C)	39.4	3.660	17%	26%
Dichloromethane (-78 °C)	40.7	0.727	57%	34%
Ether (-78 °C)	34.5	0.283 (0 °C)	39%	48%
Toluene/hexane (1/1) (-78 °C)	Toluene – 33.9 Hexane – 31.0	Toluene – 1.165 Hexane – 0.405 (0 °C)	18%	48%
Toluene (-78 °C)	33.9	1.165	41%	58%
Toluene (-90 °C)	33.9	1.165	NR	
Ether (-110 °C)	34.5	0.283 (0 °C)	NR	

Table 5.2: Results of the 5-H allylsilane Pummerer reactions.

The next two substrates examined were the *N*-methyl allylsilane sulfoxides **276** and **134**. With the *N*-methylated indoles, it was thought that the reaction may be forced through the additive mechanism, since deprotonation of the indole nitrogen following sulfoxide activation is not available for this substrate and a vinylogous pathway must

result in a presumable high-energy dicationic species **314**. **134** and **276** afforded the lowest enantioselectivity for the allylsilane series. While the absence of the methoxy group on the indole did result in higher *ee*'s, the maximum result was 46% *ee*. The low *ee*'s for this reaction provide some basis for the reaction proceeding through an achiral thionium ion. It is also possible that the transition state analysis in Figure 2.9 may not apply here. The presence of the methylated nitrogen, via an eclipsing interaction with the phenyl ring may lessen the energy difference of the transition states.

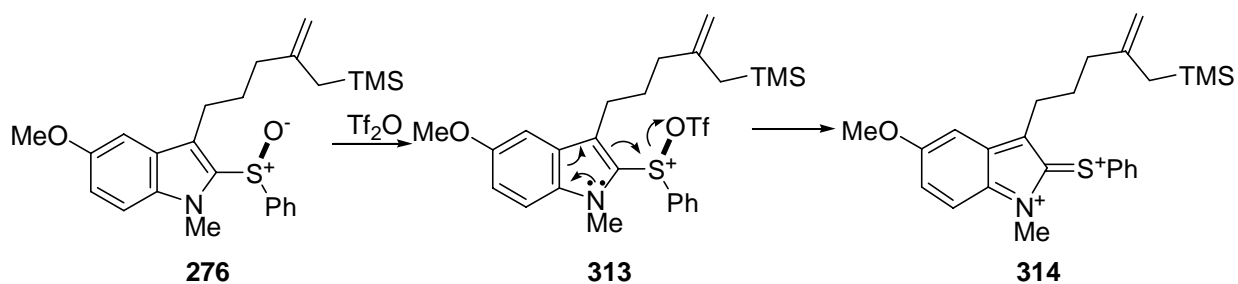


Figure 5.11: Dicationic intermediate for the *N*-methyl based Pummerer reaction.

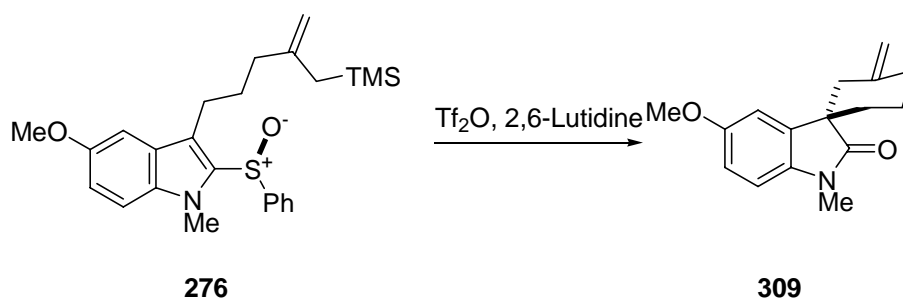


Figure 5.12: *N*-methyl 5-methoxyindole allylsilane Pummerer reaction.

Solvent	Yield 309	<i>ee</i>
Toluene (-78 °C)	41%	20%
Ether (-78 °C)	45%	28%
Acetonitrile (-40 °C)	59%	32%

Table 5.3: *N*-methyl 5-methoxyindole allylsilane Pummerer reaction results.

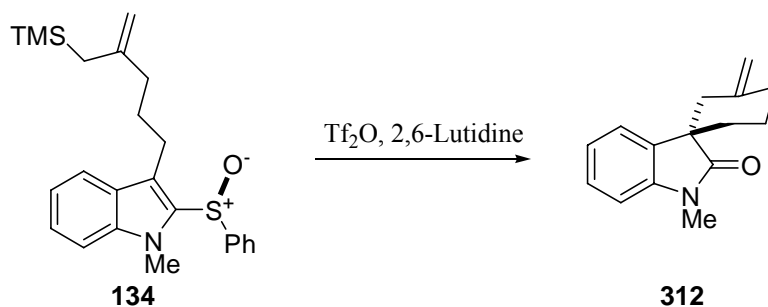


Figure 5.13: *N*-methyl 5-H allylsilane Pummerer reaction.

Solvent	Yield 312	<i>ee</i>
Dichloromethane (-78 °C)	63%	8%
Acetonitrile (-40 °C)	63%	46%

Table 5.4: *N*-methyl 5-H indole allylsilane Pummerer reaction results.

5.2.2 Silyl enol ethers

The final two systems investigated were the silyl enol ethers, **136** and **274**. It was with these compounds that the most encouraging results were seen. Mercury (II) chloride hydrolysis on the crude thioimidates was necessary to obtain a species whose ^1H NMR signals in the presence of (*S*)-TFAE permitted determination of *ee*. Initial attempts with the 5-methoxy series showed poor *ee*'s. These results were immediately improved upon

with the 5(H) series. However, the 68% *ee* was still unsatisfying, and further attempts were made to find better selectivity. Gratifyingly, it was found that by cooling silyl enol ether **136** to -110 °C, and using the standard protocol at this temperature, a single enantiomer of the oxindole product was produced after mercury (II) chloride hydrolysis. Subjecting the methoxy substituted indole **274** to the same conditions led to oxindole **316** in greater than 98% *ee*. These results were in contrast to attempts with the allylsilane (Table **5.2**), which did not react at -110 °C. The most likely explanation is that the lower nucleophilicity of the allylsilane (Mayr N = 1.8)⁸² as compared to the silyl enol ether (Mayr N ~ 5.4)¹⁰ renders it unreactive at the decreased temperature. This may provide some mechanistic elucidation. In the case of a vinylogous mechanism, the starting sulfoxide would not be recovered, unless loss of the leaving group was reversible through a tight ion pair. In the additive mechanism sulfoxide activation would still readily occur, nucleophilic attack would not occur. The starting sulfoxide is recovered presumably upon workup.

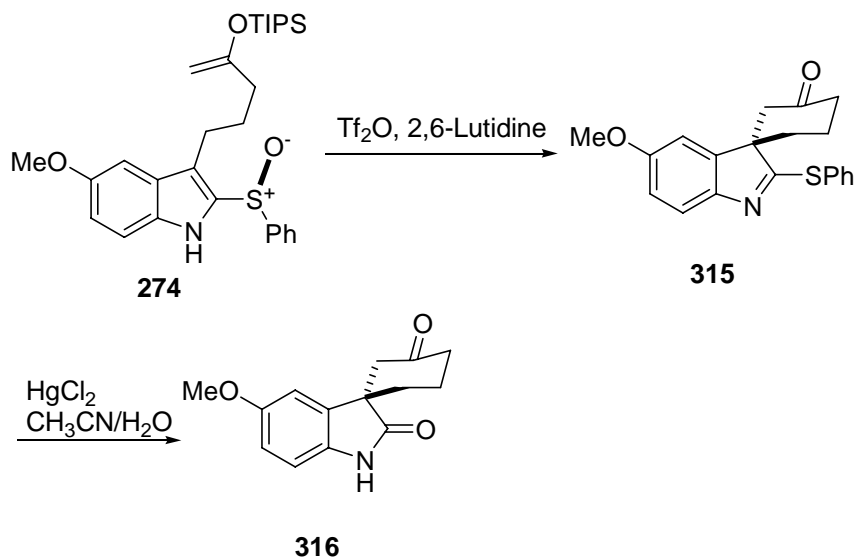


Figure 5.14: 5-methoxyindole silyl enol ether Pummerer reaction.

Solvent	Yield 316 (2 steps)	<i>ee</i>
Dichloromethane (-78 °C)	80%	14%
Ether (-78 °C)	80%	40%
Toluene (-78 °C)	76%	40%
Ether (-110 °C)	32%	>98%

Table 5.5: 5-methoxy silyl enol ether Pummerer reaction.

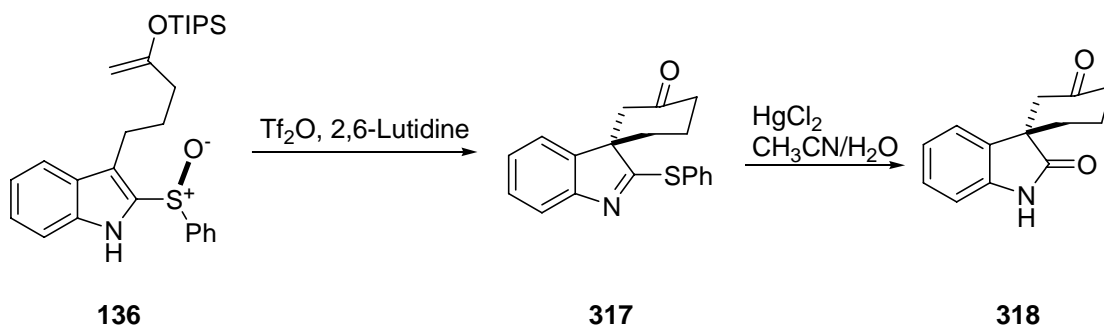


Figure 5.15: 5-H silyl enol ether Pummerer reaction.

Solvent	Yield 318 (2 steps)	<i>ee</i>
Dichloromethane (-78 °C)	33%	42%
Ether (-78 °C)	60%	51%
Toluene (-78 °C)	33%	68%
Ether (-110 °C)	58%	>98%

Table 5.6: 5-H silyl enol ether Pummerer reaction results.

5.3 Absolute stereochemistry determination

Having established that high *ee*'s can be obtained with the silyl enol ether series, attention turned toward methods for determining the absolute stereochemistry of the oxindole product. Following a procedure used on spirobrassinin by Monde and coworkers,⁸³ oxindoles **318** (68% *ee*) and **316** (40% *ee*) were converted to their camphanic acid derivatives. Crude mixtures of the diastereomeric imides were obtained which showed through integration of their ¹H NMR spectra to have retained the same diastereomeric ratio as the enantiomeric ratio in the starting material. Rapid separation of the diastereomers was necessary as exposure of the products to silica gel chromatography for an extended time would cleave the camphanyl moiety.

The major product from each reaction was analyzed through X-ray crystallography using the camphanyl group as an internal standard of known absolute configuration. Crystals suitable for X-ray analysis of oxindole **320** were formed from crystallization with tetrahydrofuran and *n*-hexane. For the des-methoxy oxindole (**322**), crystals suitable for X-ray analysis were obtained via crystallization from dimethoxyethane and *n*-hexane. In both major products, the stereochemistry at the newly

formed spiro center was found to be *S*. This result was consistent with the transition state analysis discussed earlier (Figure 2.9). The origin of the *R* enantiomer in the product mixtures is uncertain, but may be due to (1) reaction through an additive mechanism via higher energy conformer **138**, or (2) reaction through a vinylogous mechanism and an achiral thionium intermediate **123**. The major enantiomer could arise from an additive mechanism as in Figure 2.7, or through a tight ion pair **144** with attack from the thionium ion face opposite of the ⁻OTf unit in a geometry similar to the major additive path transition state **141**.

Further correlation studies were needed to establish the stereochemistry of the allylsilane Pummerer products. It was already established that the *N*-methyl and *N*-H examples resulted in the same stereochemistry, as evidenced by the use of Eu(tfc)₃. Since both reactions showed the same major peak, it suggested that both were the same absolute stereochemistry. Additionally, comparison of the optical rotation of the *N*-methylated oxindole products showed the same sign of rotation for the products derived from the *N*-H allylsilanes and from the *N*-Me allylsilanes. However, in order to compare these species with the secure stereochemistry of **316** determined by X-ray analysis, oxindole **316** was treated with Tebbe's reagent⁸⁴ to yield oxindole **308**. This compound was found to have the same sign of optical rotation as the oxindole species synthesized through the Pummerer reaction/hydrolysis sequence from allylsilane **131**. For the des-methoxy compound, a similar reaction was carried out with methyl triphenylphosphonium bromide. This product was *N*-methylated, and the product was checked with Eu(tfc)₃ and found to have the same major peak as **312**, establishing that both compounds had the same absolute stereochemistry.

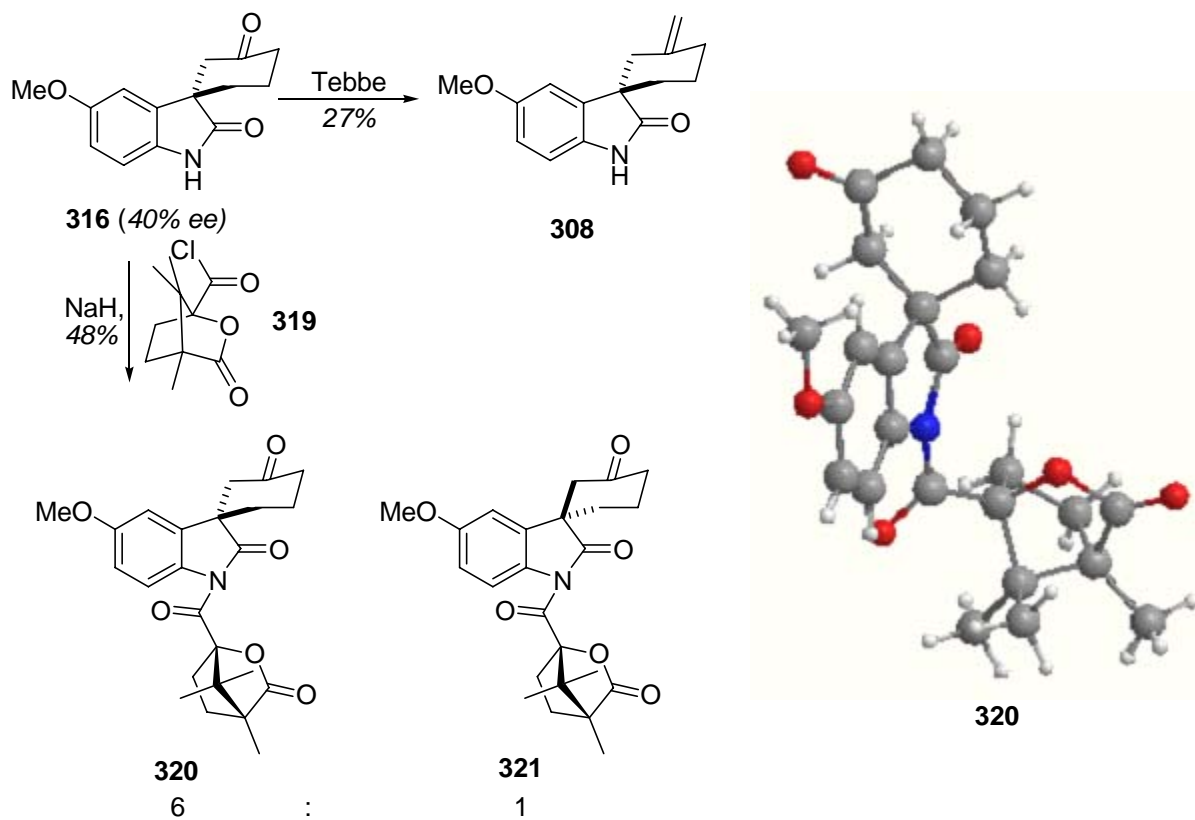


Figure 5.16: Determination of the stereochemistry of the 5-methoxy series.

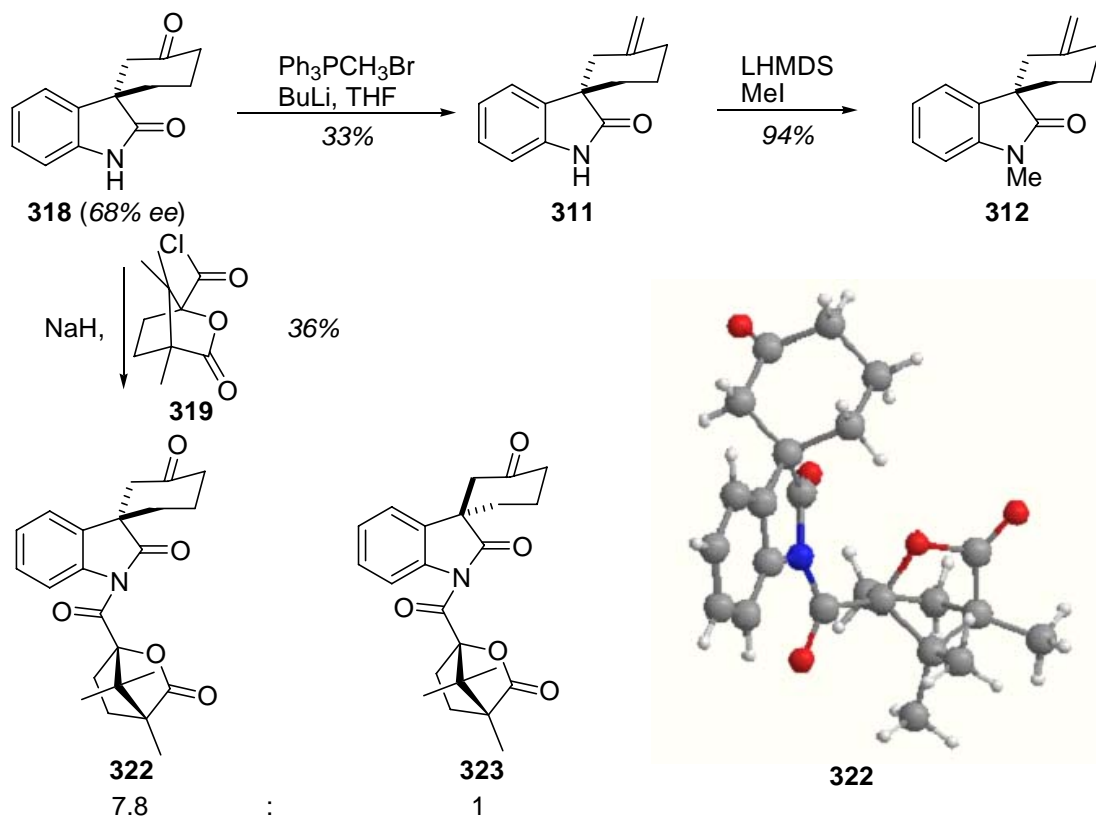


Figure 5.17: Determination of the stereochemistry of the 5H series.

5.4 Conclusions

An extension of the Pummerer methodology previously developed at Penn State has been explored. In order to obtain enantioselectivity in the Pummerer cyclization of chiral sulfoxides, it was necessary to find conditions which would favor the additive mechanism or reaction through a tight ion pair, and not the achiral thionium intermediate present in the vinylogous mechanism. Upon synthesis of enantiopure sulfoxides, optimization of the enantiomeric excess derived from Pummerer-triggered oxidative cyclization of a series of six indole-2-sulfoxide substrates was explored. Through control

of temperature and solvent polarity it was found that at low temperatures (-110 °C), excellent enantioselectivity could be obtained. The success at low temperature was only for the silyl enol ether substrates. It is likely that with the allylsilane sulfoxides, the inherently lower nucleophilicity made them unreactive at lower temperatures. The effects of solvent polarity, solvent viscosity, and the electronics of the indole ring were also explored as possibly influential factors in the selectivity. Solvent polarity exhibited clear trends as the use of alcohol solvents gave no selectivity. In less polar solvents, where a thionium ion might be less stable, and where an additive mechanism or a tight ion pair might be favored, *ee*'s as high as 68% in toluene for the allylsilane series were observed. The ability to achieve high levels of enantioselectivity with the silyl enol ether substrates will serve to further enhance the utility of this methodology.

Chapter 6 Experimental Procedures

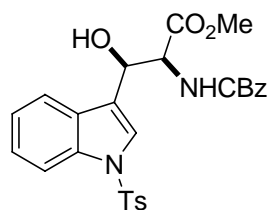
6.1 General

General Experimental. All reactions involving air and moisture sensitive reagents or solvents were performed in flame-dried glassware under an argon or nitrogen atmosphere. Tetrahydrofuran and benzene were distilled from sodium benzophenone ketyl under argon or passed through an activated alumina column immediately before use. Dichloromethane and acetonitrile were distilled from calcium hydride under argon or passed through an activated alumina column immediately before use. Dimethoxyethane was distilled from sodium and fluorenone under argon or passed through an activated alumina column immediately before use. Methanol, toluene, and ether were passed through an activated alumina column immediately before use. All organic reagents were used as purchased. Flash chromatography was performed using 32 – 63 μm silica gel with the indicated solvent systems. All melting points are uncorrected. Low and high-resolution mass spectra were obtained according to the specified technique and were performed at The Huck Institute of the Life Sciences – Proteomics and Mass Spectrometry Core Facility at The Pennsylvania State University, University Park, PA. Combustion analyses were performed by Midwest Microlab, IN.

6.2 Methods toward TMC-95A-D synthesis

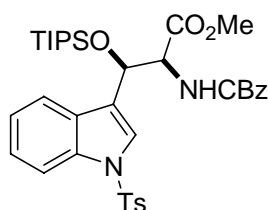
General Procedure for the Pummerer Reaction Promoted by Stang's reagent, $\text{PhI}(\text{CN})\text{OTf}$. The substrate was dissolved in the indicated solvent and cooled to the indicated temperature. 2,6-Lutidine was added followed by $\text{PhI}(\text{CN})\text{OTf}$ in one

portion. The reaction solution was slowly brought to room temperature over 2 h and held there for an additional 15 h. Water was added, the two layers were separated and the aqueous phase was extracted with CH₂Cl₂. The combined organic layers were dried, filtered, and concentrated in vacuo. The crude product was purified via flash chromatography using the indicated solvent system.



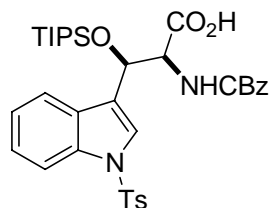
(2*S*,3*R*)-Methyl 2-(Benzyloxycarbonylamino)-3-hydroxy-3-(1-tosyl-1*H*-indol-3-yl)propanoate (230). Freshly prepared *t*-butyl hypochlorite (2.0 mL, 18 mmol) was added to a solution of benzyl carbamate (2.69 g, 17.8 mmol) in 0.4 M sodium hydroxide (35 mL) and *n*-propanol (25 mL) in a flask covered with aluminum foil. This mixture was stirred for 5 min. A solution of (DHQD)₂AQN (150 mg, 0.17 mmol) in *n*-propanol (25 mL), **229** (1.71 g, 4.82 mmol), and a solution of K₂OsO₂(OH)₄ (80 mg, 0.21 mmol) in 0.4 M NaOH (5 mL) were added, and this solution was stirred for 22 h. Sodium bisulfite (2.5 g) was added to the reaction mixture which was then extracted with EtOAc (3 x 30 mL), washed with water and brine, dried over MgSO₄, filtered, and concentrated in vacuo. The product was purified by flash chromatography using 20% EtOAc in hexanes as the eluent to remove excess benzyl carbamate, then 50% EtOAc in hexanes as the eluent to yield 1.72 g (69% > 99% ee⁸⁵) of protected amino alcohol **230** as a white solid. mp 66 – 68 °C; [α]_D²⁵ – 34.6 (c 1 CH₂Cl₂); IR (CDCl₃) 3436, 1712 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, *J* = 9.7 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.68 (s, 1H), 7.57 (d, *J*

= 7.1 Hz, 1H), 7.34 (m, 7H), 7.13 (d, $J = 8.1$ Hz, 2H), 5.86 (d, $J = 8.9$ Hz, 1H), 5.54 (d, $J = 2.2$ Hz, 1H), 5.02 (m, 2H), 4.77 (dd, $J = 8.9, 2.2$ Hz, 1H), 3.73 (s, 3H), 3.37 (s, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ , 171.5, 156.9, 145.4, 136.4, 135.5, 135.4, 130.3, 129.0, 128.9, 128.6, 128.2, 127.2, 125.4, 124.4, 123.9, 122.0, 120.2, 114.1, 68.5, 67.5, 58.9, 53.2, 21.9; ESI m/z (relative intensity) 540.2 ($\text{M} + \text{NH}_4$, 100%), 505.2 ($\text{M} + \text{H} - \text{H}_2\text{O}$, 20%); HRMS calcd for $\text{C}_{27}\text{H}_{26}\text{N}_2\text{O}_7\text{S}$ ($\text{M} + \text{NH}_4$) 540.1804, found 540.1786.



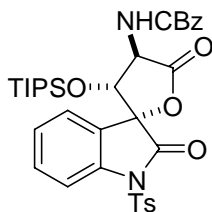
(2*S*,3*R*)-Methyl 2-(Benzyloxycarbonylamino)-3-(1-tosyl-1*H*-indol-3-yl)-3-(triisopropylsilyloxy)propanoate. A solution of protected amino alcohol **230** (1.11 g, 2.1 mmol) and 2,6-lutidine (730 μL , 6.3 mmol) in CH_2Cl_2 (20 mL) were stirred for 5 min. Triisopropylsilyl trifluoromethanesulfonate (750 μL , 2.8 mmol) was added and stirring was continued for 15 h. The reaction mixture was added to water (10 mL), extracted with CH_2Cl_2 (3 x 10 mL), dried over MgSO_4 , filtered, and concentrated in vacuo. The product was purified by flash chromatography using 20% EtOAc in hexanes as the eluent to yield 1.25 g (88%) of the TIPS ether as a colorless oil. IR (CDCl_3) 3442, 1728 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.99 (d, $J = 8.3$ Hz, 1H), 7.75 (d, $J = 7.9$ Hz, 2H), 7.60 (m, 2H), 7.39 (m, 6H), 7.24 (t, $J = 7.1$ Hz, 1H), 7.16 (d, $J = 8.1$ Hz, 2H), 5.67 (d, $J = 3$ Hz, 1H), 5.56 (d, $J = 9.6$ Hz, 1H), 5.08 (d, $J = 12.3$ Hz, 1H), 5.01 (d, $J = 12.3$ Hz, 1H), 4.56 (dd, $J = 9.6, 3$ Hz, 1H), 3.80 (s, 3H), 2.31 (s, 3H), 0.95 (m, 21H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.1, 156.5, 145.4, 136.6, 135.7, 135.5, 130.2, 129.0, 128.8, 128.6, 128.5, 127.1, 125.5, 124.7, 123.9, 123.3, 120.0, 114.3, 69.4, 67.5, 60.0, 52.9, 22.0, 18.3, 12.8; ESI m/z

(relative intensity) 701.2 (M + Na, 100%), 696.3 (M + NH₄, 30%); HRMS calcd for C₃₆H₄₆N₂O₇SSi (M + NH₄) 696.3139, found 696.3190.

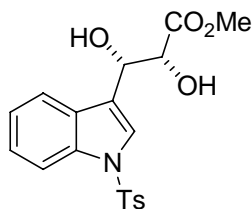


(2*S*,3*R*)-2-(Benzyloxycarbonylamino)-3-(1-tosyl-1*H*-indol-3-yl)-3-

(triisopropylsilyloxy)propanoic Acid (231). The TIPS ether (32 mg, 0.05 mmol) and LiOH•H₂O (7 mg, 0.2 mmol) were stirred for 15 h in THF/H₂O (0.5 mL, 4/1). The reaction solution was acidified with 1 M HCl (2 mL), extracted with CH₂Cl₂ (3 x 5 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 5% MeOH in 1/1 ethyl acetate/hexanes as the eluent to yield to yield 25 mg (80 %) of **231** as a white solid: mp 72 – 75 °C (sublime); IR (CDCl₃) 3419, 3035, 1770, 1719 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.97 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.60 (s, 1H), 7.41 (m, 7H), 7.18 (m, 3H), 5.77 (d, *J* = 3.4 Hz, 1H), 5.42 (d, *J* = 7.6 Hz, 1H), 5.14 (d, *J* = 12 Hz, 1H), 5.06 (d, *J* = 12 Hz, 1H), 4.70 (dd, *J* = 7.3, 3.5 Hz, 1H), 2.31 (s, 3H), 1.05 (m, 21H); ¹³C NMR (125 MHz, CDCl₃) δ 171.1, 156.2, 145.3, 136.1, 135.1, 135.0, 130.1, 129.1, 128.9, 128.5, 128.4, 127.0, 125.3, 124.6, 123.8, 121.5, 119.5, 114.1, 68.0, 67.4, 59.4, 21.8, 18.0, 12.3; ESI *m/z* (relative intensity) 663.3 (M – H, 100%), 507.1 (M – TIPS, 10%); HRMS calcd for C₃₅H₄₄N₂O₇SSi (M - H) 663.2560, found 663.2513; Anal. Calcd for C₃₅H₄₄N₂O₇SSi: C, 63.23; H, 6.67; N, 4.21; S, 4.82; Found: C, 63.31; H, 6.97; N, 4.01; S, 4.79.

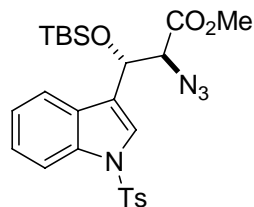


(2*R*,3*R*,4*R*)-4-(2-Oxo-2-phenylethylideneamino)-3-(triisopropylsilyloxy)-3*H*-spiro[furan-2,3'-indoline]-2',5(4*H*)-dione (232). N-bromosuccinimide (16 mg, 0.09 mmol) was added to a solution of **231** (30 mg, 0.045 mmol) and sodium bicarbonate (8 mg, 0.09 mmol) in *t*-BuOH (340 μ L)/H₂O (80 μ L) and stirred for 15 h. The reaction solution was concentrated in vacuo and the residue was purified by flash chromatography using 33% ether in hexanes as the eluent, providing 10 mg (33%) of the **232**, as a white solid. mp 82 – 85 °C (sublime), IR (CDCl₃) 3452, 1810, 1772, 1725 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.97 (m, 3H), 7.53 (m, 2H), 7.42 (m, 1H), 7.36 (m, 7H), 5.50 (d, *J* = 7.4 Hz, 1H), 5.35 (d, *J* = 9 Hz, 1H), 5.22 (d, *J* = 12 Hz, 1H), 5.09 (d, *J* = 12 Hz, 1H), 4.61 (m, 1H), 2.42 (s, 3H), 0.84 (m, 21H); ¹³C NMR (100 MHz, CDCl₃) δ 174.5, 171.7, 156.0, 147.0, 146.6, 141.3, 136.0, 135.0, 132.7, 130.3, 129.0, 128.9, 128.3, 126.1, 125.9, 124.0, 114.3, 83.1, 78.4, 68.0, 57.9, 22.1, 17.9, 12.6; ESI *m/z* (relative intensity) 679.2 (M + H, 35%), 696.3 (M + NH₄, 100%), 701.2 (M + Na, 70%); HRMS calcd for C₃₅H₄₂N₂O₈SSi (M + NH₄) 696.2775, found 696.2778; Anal. Calcd for C₃₅H₄₂N₂O₈SSi: C, 61.92; H, 6.24; N, 4.13; S, 4.72; Found: C, 61.31; H, 6.13; N, 4.01; S, 4.68.



(2R,3S)-Methyl 2,3-Dihydroxy-3-(1-tosyl-1H-indol-3-yl)propanoate (234).

Enoate **229** (2.0 g, 5.6 mmol) was suspended in *t*-BuOH/H₂O (26 mL, 1/1). A modified AD mix- α (potassium ferricyanide (4.40 g), potassium carbonate (1.86 g), (DHQ)₂PHAL (174 mg), and K₂O₅O₂(OH)₄ (18 mg)) and methanesulfonamide (1.28 g, 13.4 mmol) was added in 4 equal portions at 1 h intervals, and stirring was continued for 15 h. Sodium sulfite (8.4 g) was added, and the reaction solution was stirred for 30 min. The reaction solution was extracted with EtOAc (3 x 25 mL), the combined organic fractions were washed with 1 M KOH (25 mL), water, and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 40% EtOAc in hexanes as the eluent, providing 1.72 g (79%, > 99% ee⁸⁶) of diol **234** as a white solid. mp 48 – 51 °C; $[\alpha]_D^{25} + 30.7$ (c 1 CH₂Cl₂); IR (CDCl₃) 3534, 1738, 1598 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.97 (d, *J* = 8.3 Hz, 1H), 7.76 (s, 1H), 7.73 (d, *J* = 5.3 Hz, 2H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 5.25 (d, *J* = 5 Hz, 1H), 4.52 (dd, *J* = 5.1, 2.4 Hz, 1H), 3.78 (s, 3H), 3.50 (d, *J* = 4.9 Hz, 1H), 2.99 (d, *J* = 7.8 Hz, 1H), 2.29 (s, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 173.2, 145.2, 135.3, 135.3, 130.1, 129.2, 127.0, 125.1, 124.5, 123.5, 121.7, 120.1, 113.9, 73.6, 68.6, 43.1, 21.7; APCI *m/z* (relative intensity) 372.2 (M + H – H₂O, 100%); Anal. Calcd for C₁₉H₁₉NO₆S: C, 58.60; H, 4.92; N, 3.60; S, 8.23; Found: C, 58.89; H, 5.30; N, 3.43; S, 7.93.

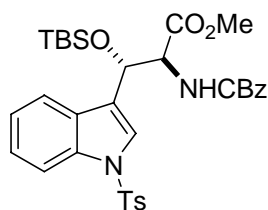


(2*S*,3*S*)-Methyl 2-Azido-3-(*tert*-butyldimethylsilyloxy)-3-(1-tosyl-1*H*-indol-3-yl)propanoate (235). The diol (3.8 g, 9.7 mmol) was dissolved in CH₂Cl₂ (125 mL) and cooled to 0 °C. 4-Nitrobenzenesulfonyl chloride (2.2 g, 10 mmol) and Et₃N (2.85 mL, 20.5 mmol) were added and the reaction solution was stirred at 0 °C for 15 h. The reaction solution was added to 1 M HCl (50 mL), extracted with CH₂Cl₂ (3 x 50 mL), washed with water and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to yield 4.2 g (75%) of a crude yellow-orange solid.

The crude nosylate (4.2 g, 7.4 mmol) was dissolved in DMF (40 mL), and sodium azide (534 mg, 8.2 mmol) was added. The mixture was heated at 45 °C for 15 h. The reaction solution was concentrated in vacuo, and the residue was added to 1 M H₃PO₄ (50 mL), extracted with CH₂Cl₂ (3 x 50 mL), washed with water and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to yield 2.0 g (64%) of the crude azide.

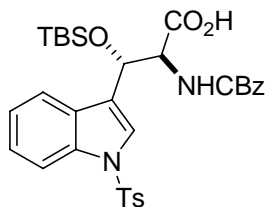
2,6-Lutidine (1.5 mL, 13 mmol) was added to the crude azide (2.0 g, 4.8 mmol) in CH₂Cl₂ (100 mL) and the mixture was stirred for 5 min. *Tert*butyldimethylsilyl trifluoromethanesulfonate (1.5 mL, 6.5 mmol) was added and stirring was continued for 15 h. The reaction solution was added to water (25 mL), extracted with CH₂Cl₂ (3 x 25 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 10% ether in hexanes as the eluent, providing 1.65 g (68%) of the TBS ether as a colorless oil. IR (CDCl₃) 2117, 1748 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.04 (d, *J* = 7.4 Hz, 1H), 7.79 (m, 3H), 7.64 (s, 1H), 7.38 (m, 4H),

5.24 (d, $J = 7.7$ Hz, 1H), 4.25 (d, $J = 7.7$ Hz, 1H), 3.75 (s, 3H), 2.33 (s, 3H), 0.84 (s, 9H), 0.06 (s, 3H), -0.28 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 168.9, 135.6, 135.1, 130.1, 130.0, 128.6, 126.8, 125.2, 125.1, 123.5, 121.7, 120.9, 114.0, 69.9, 66.8, 52.6, 25.6, 21.6, 18.2, -4.9, -5.5; ESI m/z (relative intensity) 551.1 ($\text{M} + \text{Na}$, 100%); HRMS calcd for $\text{C}_{25}\text{H}_{32}\text{N}_4\text{O}_5\text{SSi}$ ($\text{M} + \text{NH}_4$) 546.2206, found 546.2164.

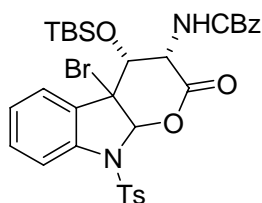


(2*S*,3*S*)-Methyl 2-(Benzyloxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-3-(1-tosyl-1*H*-indol-3-yl)propanoate. Trimethyl phosphine (3.5 mL, 1M in THF, 3.5 mmol) was slowly added to a solution of the TBS ether (1.55 g, 2.9 mmol) in THF (30 mL), and stirring was continued for 45 min. The reaction solution was cooled below -20 $^{\circ}\text{C}$, benzyl chloroformate (440 μL , 3.1 mmol) was added, and the reaction solution was warmed to room temperature and stirred for 15 h. The reaction mixture was added to water (10 mL), extracted with CH_2Cl_2 (3 x 10 mL), washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 20% EtOAc in hexanes as the eluent, providing 650 mg (35%) of the CBz protected amine as a colorless oil. IR (CDCl_3) 3436, 1726 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, $J = 8.2$ Hz, 1H), 7.84 (d, $J = 7.7$ Hz, 1H), 7.71 (m, 2H), 7.44 (s, 1H), 7.37 (m, 7H), 7.18 (d, $J = 8.2$ Hz, 2H), 5.68 (d, $J = 7.7$ Hz, 1H), 5.31 (d, $J = 3$ Hz, 1H), 5.15 (d, $J = 12$ Hz, 1H), 5.11 (d, $J = 12$ Hz, 1H), 4.73 (dd, $J = 7.7, 3$ Hz, 1H), 3.53 (s, 3H), 2.30 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (100 MHz,

CDCl₃) δ 169.5, 155.7, 145.1, 136.3, 135.6, 135.4, 130.1, 130.0, 128.7, 128.4, 128.2, 126.9, 125.1, 124.4, 124.1, 123.0, 120.7, 113.9, 70.5, 67.2, 59.9, 52.1, 25.8, 21.7, 18.3, -4.8, -5.2; ESI m/z (relative intensity) 659.2 (M + Na, 100%), 654.2 (M + NH₄, 35%); HRMS calcd for C₃₃H₄₀N₂O₇SSi (M + NH₄) 654.2669, found 654.2627.

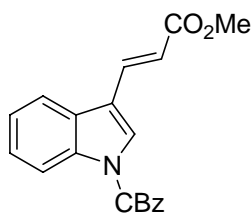


(2S,3S)-2-(Benzyloxycarbonylamino)-3-(tert-butyldimethylsilyloxy)-3-(1-tosyl-1H-indol-3-yl)propanoic Acid (236). The CBz-protected amine (600 mg, 0.94 mmol) and LiOH•H₂O (120 mg, 3.86 mmol) were stirred for 15 h in THF/H₂O (15 mL, 4/1). The reaction mixture was acidified with 1 M HCl (10 mL), extracted with CH₂Cl₂ (3 x 10 mL), washed with water and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo, providing 500 mg (86%) of the product **236** as a white solid. mp 65 – 68 °C; IR (CDCl₃) 3690, 3433, 1716 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.98 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.50 (s, 1H), 7.38 (m, 7H), 7.15 (d, J = 8.2 Hz, 2H), 5.63 (d, J = 7.7 Hz, 1H), 5.35 (d, J = 4.5 Hz, 1H), 5.17 (d, J = 12 Hz, 1H), 5.13 (d, J = 12 Hz, 1H), 4.75 (dd, J = 7.3, 4.5 Hz, 1H), 2.27 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.2, 155.8, 145.2, 136.2, 135.6, 135.2, 130.0, 128.8, 128.6, 128.5, 128.3, 126.9, 125.2, 124.6, 123.8, 122.6, 120.5, 114.0, 70.3, 67.4, 59.7, 25.9, 21.7, 18.4, -4.7, -5.2; APCI m/z (relative intensity) 645.2 (M + Na, 100%); HRMS calcd for C₃₂H₃₈N₂O₇SSi (M + NH₄) 640.2513, found 640.2496.



[4a-Bromo-4-(*tert*-butyl-dimethyl-silyloxy)-2-oxo-9-(toluene-4-sulfonyl)-2,3,4,4a,9,9a-hexahydro-pyrano[2,3-*b*]indol-3-yl]-carbamic Acid Benzyl Ester (237).

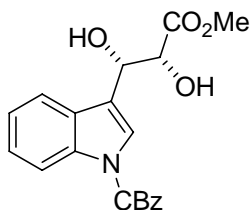
N-bromosuccinimide (250 mg, 1.5 mmol) was added to a solution of **236** (200 mg, 0.32 mmol) and NaHCO₃ (120 mg, 1.4 mmol) in *t*-BuOH (5.5 mL)/H₂O (1.3 mL) and stirred for 15 h. The reaction solution was concentrated in vacuo and purified by flash chromatography using 33% ether in hexanes as the eluent, providing 150 mg (67%) of lactone **237**, as a white solid. mp 92 – 95 °C; IR (CDCl₃) 3426, 1764, 1718 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.93 (d, *J* = 8.3 Hz, 2H), 7.53 (d, 8.3 Hz, 2H), 7.42 (m, 9H), 6.62 (s, 1H), 5.61 (d, *J* = 4.4 Hz, 1H), 5.23 (m, 3H), 4.32 (dd, *J* = 4.4, 1.4 Hz, 1H), 2.40 (s, 3H), 0.95 (s, 9H), 0.27 (s, 3H), 0.09 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 165.4, 155.6, 145.3, 139.9, 135.8, 135.2, 131.9, 130.3, 130.0, 128.8, 128.6, 128.3, 128.1, 125.8, 124.9, 115.2, 98.1, 74.1, 67.5, 63.5, 54.3, 26.1, 21.9, 18.6, -3.5, -4.1; APCIMS *m/z* (relative intensity) 701.1 (M + H, 85%), 703.1 (⁸¹Br, 100%) HRMS calcd for C₃₂H₃₇BrN₂O₇SSi (M + H) 701.1352, found 701.1373; Anal. Calcd for C₃₂H₃₇BrN₂O₇SSi: C, 54.77; H, 5.31; N, 3.99; S, 4.57; Found: C, 54.76; H, 5.30; N, 3.91; S, 4.57.



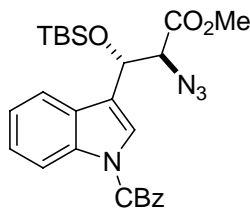
(E)-Benzyl 3-(3-Methoxy-3-oxoprop-1-enyl)-1H-indole-1-carboxylate (241).

Lithium bis(trimethylsilylamide) (1.0 M in THF, 100 mL, 100 mmol) was added to indole-3-carbaldehyde (14.5 g, 100 mmol) in THF (250 mL) and stirred for 90 min at room temperature. Benzyl chloroformate (16.3 mL, 110 mmol) was added and the reaction solution was stirred for 15 h. The reaction solution was added to water (200 mL), extracted with CH₂Cl₂ (3 x 100 mL), dried over MgSO₄, filtered, and concentrated in vacuo to yield 28.3 g (100%) of the crude CBz-protected aldehyde as a yellow solid.

n-Butyllithium (38.5 mL, 2.5 M in hexanes, 96 mmol) was added to (carbomethoxy)methyltriphenylphosphonium bromide (41 g, 100 mmol) in DME (500 mL). To this solution, the protected indole (25.1 g, 90 mmol) was added as a solid in one portion and the reaction solution was stirred for 36 h at room temperature. The reaction solution was added to ice, extracted with CH₂Cl₂ (3 x 200 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was recrystallized from methanol to yield 22.4 g (74%) of alkene **241** as a yellow solid. mp 94 - 96 °C; IR (CDCl₃) 1741, 1707 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.19 (d, *J* = 7.9 Hz, 1H), 7.79 (m, 3H), 7.47 (m, 7H), 6.52 (d, *J* = 16.1 Hz, 1H), 5.41 (s, 2H), 3.79 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 167.8, 150.3, 136.4, 136.3, 136.2, 134.8, 129.1, 129.0, 128.7, 128.2, 127.9, 125.6, 124.0, 120.4, 117.6, 115.7, 69.3, 51.2; ESI *m/z* (relative intensity) 358.1 (M + Na, 100%); HRMS calcd for C₂₀H₁₇NO₄ (M + Na), 358.1043, found 358.1055.



Benzyl 3-((1S,2R)-1,2-Dihydroxy-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate (242). Alkene **241** (280 mg, 0.84 mmol) was added to AD mix- α (1.4 g) and methanesulfonamide (95 mg, 1 mmol) in *t*-BuOH/water (10 mL, 1/1) and stirred for 15 h at room temperature. Sodium sulfite (1.5 g) was added and the reaction solution was stirred for 30 min and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with 1 M KOH (25 mL), water, and brine, dried over MgSO₄, filtered, and concentrated in vacuo. The product was purified by flash chromatography using 40% EtOAc in hexanes as the eluent to yield 170 mg (55%) of the diol as a white solid. mp 104 - 106 °C; $[\alpha]_D^{25} + 11.347$ (c 0.43 CH₂Cl₂); IR (CDCl₃) 3440, 1735, 1644 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.18 (s, 1H)⁸⁷, 7.74 (s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.48 (m, 2H), 7.41 (m, 3H), 7.37 (m, 1H), 7.28 (m, 1H), 5.43 (s, 2H), 5.30 (dd, *J* = 5.8, 1.5 Hz, 1H), 4.54 (dd, *J* = 5.6, 1.5 Hz, 1H), 3.84 (s, 3H), 3.28 (d, *J* = 5.4 Hz, 1H), 2.66 (d, *J* = 8.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 173.3, 150.8, 149.2, 135.8, 135.7, 135.2, 129.0, 128.8, 125.3, 123.6, 123.4, 120.9, 119.5, 115.7, 73.4, 69.0, 68.6, 53.3; ESI *m/z* (relative intensity) 392.1 (M + Na, 100%); HRMS calcd for C₂₀H₁₉NO₆ (M + Na), 392.1110, found 392.1113.

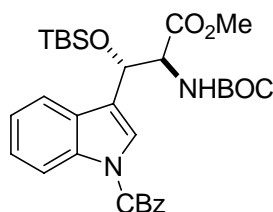


Benzyl 3-((1S,2S)-2-Azido-1-(*tert*-butyldimethylsilyloxy)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate (243). Diol **242** (13.3 g, 36 mmol) was dissolved in CH₂Cl₂ (350 mL) and cooled to 0 °C. Triethylamine (10.2 mL, 73 mmol) and 4-nitrobenzenesulfonyl chloride (7.9 g, 36 mmol) were added and the reaction solution was stirred at 0 °C for 15 h. The reaction solution was added to 1 M HCl (150 mL), extracted with CH₂Cl₂ (3 x 150 mL), washed with water and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to yield 14.4 g (72%) of the crude nosylate as a yellow solid.

Sodium azide (1.87 g, 28.7 mmol) was added to a solution of the nosylate (14.4 g, 25.9) in DMF (130 mL), and the reaction solution was heated for 15 h at 45 °C. The reaction solution was concentrated in vacuo, and the residue was dissolved in CH₂Cl₂ (150 mL), washed with water and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to yield 5.73 g (56%) of the crude azide.

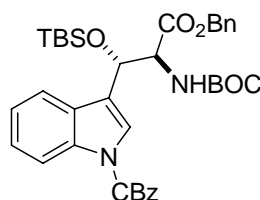
2,6-Lutidine (4.40 mL, 38.1 mmol) was added to the crude azide (5.73 g, 14.5 mmol) in CH₂Cl₂ (250 mL) and stirred for 5 min. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (4.40 mL, 19.1 mmol) was added and stirring was continued for 15 h at room temperature. The reaction solution was added to water (150 mL), extracted with CH₂Cl₂ (3 x 150 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 10% ether in hexanes as the eluent, providing 6.70 g (91%) of the TBS ether as a yellow solid. mp 58 - 60 °C; IR (CDCl₃) 2111, 1743 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.19 (bs, 1H),⁸⁷

7.73 (d, $J = 7.7$ Hz, 1H), 7.66 (s, 1H), 7.50 (m, 2H), 7.44 (m, 3H), 7.33 (m, 1H), 7.26 (m, 1H), 5.49 (d, $J = 12$ Hz, 1H), 5.45 (d, $J = 12$ Hz, 1H), 5.22 (d, $J = 7.7$ Hz, 1H), 4.26 (d, $J = 7.7$ Hz, 1H), 3.75 (s, 3H), 0.84 (s, 9H), 0.06 (s, 3H), -0.21 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.4, 151.1, 149.4, 136.2, 135.4, 129.2, 128.9, 128.6, 125.5, 124.4, 123.5, 120.9, 120.8, 115.9, 70.4, 69.3, 67.3, 52.9, 25.9, 18.4, -4.4, -5.1; ESI m/z (relative intensity) 531.2 (M + Na, 100%); HRMS calcd for $\text{C}_{26}\text{H}_{32}\text{N}_4\text{O}_5\text{Si}$ (M + Na), 531.2040, found 531.2074.



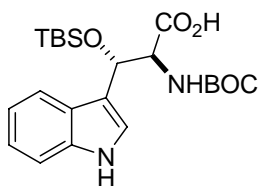
Benzyl 3-((5*S*,6*S*)-6-(Methoxycarbonyl)-2,2,3,3,10,10-hexamethyl-8-oxo-4,9-dioxo-7-aza-3-silaundecan-5-yl)-1*H*-indole-1-carboxylate. Trimethylphosphine (2.7 mL, 1M in THF, 2.7 mmol) was slowly added to a solution of **243** (1.30 g, 2.55 mmol) in THF (25 mL) at room temperature, and stirring was continued for 45 min. The reaction solution was cooled below -20 °C, BOC-ON (680 mg, 2.72 mmol) in THF (10 mL) was added, and the reaction solution was warmed to room temperature and stirred for 15 h. The reaction mixture was added to water (20 mL), extracted with CH_2Cl_2 (3 x 20 mL), washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 10% ether in hexanes as the eluent, providing 1.13 g (76%) of the Boc protected amine as a colorless oil. IR (CDCl_3) 1741 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.16 (bs, 1H),⁸⁷ 7.84 (d, $J = 7.6$ Hz, 1H), 7.52 (s, 1H), 7.49 (m, 2H), 7.42 (m, 3H), 7.33 (m, 2H), 5.49 (d, $J = 11.8$ Hz, 1H), 5.44 (d, $J =$

11.8 Hz, 1H), 5.36 (d, $J = 8.0$ Hz, 1H), 5.28 (d, $J = 3.3$ Hz, 1H), 4.69 (dd, $J = 8.0, 3.6$ Hz, 1H), 3.53 (s, 3H), 1.42 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), -0.10 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.2, 155.0, 150.9, 135.3, 129.2, 129.0 (2 carbons), 128.7, 128.6, 125.0, 123.3, 122.1, 120.8, 115.7, 115.4, 80.1, 70.8, 68.9, 59.7, 52.1, 28.5, 25.9, 18.3, -4.7, -5.1; ESI m/z (relative intensity) 583.3 (M + H, 100%), 605.3 (M + Na, 80%); HRMS calcd for $\text{C}_{31}\text{H}_{42}\text{N}_2\text{O}_7\text{Si}$ (M + H), 583.2840, found 583.2836.

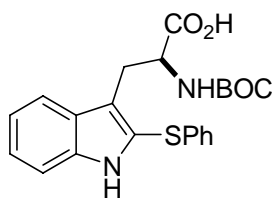


Benzyl 3-((5*S*,6*S*)-6-(Benzyloxycarbonyl)-2,2,3,3,10,10-hexamethyl-8-oxo-4,9-dioxa-7-aza-3-silaundecan-5-yl)-1*H*-indole-1-carboxylate (244**).** The BOC protected amine (4.30 g, 7.4 mmol), benzyl alcohol (7.75 mL, 74 mmol) and bis(dibutylchlorotin) oxide (1.55 g, 28 mmol) in benzene (300 mL) were refluxed for 15 h. Additional bis(dibutylchlorotin) oxide (1.55 g, 28 mmol) was added and refluxing was continued for 24 h. The reaction solution was concentrated in vacuo, and the crude product was purified by flash chromatography using 7% ether in hexanes as the eluent, providing 3.4 g (70%) of benzyl ester **244** as a colorless oil. IR (CDCl_3) 1740, 1710 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.17 (bs, 1H),⁸⁷ 7.90 (d, $J = 7.5$ Hz, 1H), 7.43 (m, 6H), 7.33 (m, 2H), 7.17 (m, 3H), 6.96 (m, 2H), 5.52 (d, $J = 7.7$ Hz, 1H), 5.43 (d, $J = 11.7$ Hz, 1H), 5.34 (m, 2H), 5.00 (d, $J = 12.3$ Hz, 1H), 4.91 (d, $J = 12.3$ Hz, 1H), 4.81 (dd, $J = 7.8, 3.0$ Hz, 1H), 1.45 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), -0.08 (s, 3H) ^{13}C NMR (125 MHz, CDCl_3) δ 169.1, 154.8, 150.5, 135.7, 135.1, 134.9, 128.7, 128.6, 128.3, 128.3, 128.2, 128.1, 128.0, 124.8, 123.2, 123.1, 122.0, 120.4, 115.2, 79.8, 70.7, 68.5, 66.8, 59.3, 28.4, 25.7, 18.1, -

4.9, -5.2; ESI m/z (relative intensity) 681.3 (M + Na, 100%); HRMS calcd for $C_{37}H_{46}N_2O_7Si$ (M + Na), 681.2972, found 681.3019.

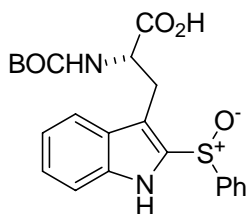


(2*S*,3*S*)-2-(*tert*-Butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-3-(1*H*-indol-3-yl)propanoic Acid (245). Benzyl ester **244** (60 mg, 0.09 mmol) and 10 % palladium-on-carbon were freeze-pump-thaw degassed in THF (3 mL) and stirred under H_2 for 1 h at room temperature. The reaction solution was filtered through Celite and concentrated in vacuo to yield 40 mg (100%) of the crude acid as a white solid which was found to be unstable to silica gel. IR ($CDCl_3$) 3306, 1716 cm^{-1} ; 1H NMR (300 MHz, d^6 -acetone) δ 8.23 (d, $J = 7.9$ Hz, 1H), 8.01 (d, $J = 7.4$ Hz, 1H), 7.73 (s, 1H), 7.46 (m, 2H), 7.23 (m, 1H), 5.96 (d, $J = 8.5$ Hz, 1H), 5.45 (d, $J = 5$ Hz, 1H), 4.74 (dd, $J = 8.5, 5.0$ Hz, 1H), 1.43 (s, 9H), 0.92 (s, 9H), 0.14 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (75 MHz, d^6 -acetone) δ 172.9, 156.3, 138.3, 127.3, 124.8, 122.7, 121.3, 120.1, 116.3, 112.7, 79.7, 71.8, 61.4, 28.9, 26.5, 19.2, -4.2, -4.7; APCI m/z (relative intensity) 457.1 (M + Na, 100%); HRMS calcd for $C_{22}H_{34}N_2O_5Si$ (M + Na), 457.2135, found 457.2123.



(*S*)-2-(*tert*-Butoxycarbonylamino)-3-(2-(phenylthio)-1*H*-indol-3-yl)propanoic Acid (253). A solution of phenylsulfenyl chloride (1.25 mL, 8.7 mmol) in CH_2Cl_2 (30 mL) was added to a solution of *N*-tertbutoxycarbonyl-L-tryptophan (2.5 g, 8.2 mmol) and

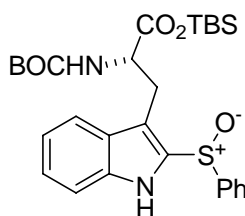
triethylamine (1.25 mL, 9.0 mmol) in CH₂Cl₂ (30 mL) and stirred for 90 min. The reaction solution was concentrated and the residue was purified by flash chromatography using 5% MeOH in 1/1 EtOAc/hexanes as the eluent to yield 3.04 g (90%) of the 2-substituted indole as a white solid. mp 76 – 78 °C; IR (CDCl₃) 3459, 1756, 1711 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.67 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.28 (m, 2H), 7.18 (m, 5H), 5.84 (d, *J* = 7.7 Hz, 1H), 4.54 (m, 1H), 3.50 (dd, *J* = 14, 6 Hz, 1H), 3.34 (dd, *J* = 14, 6 Hz, 1H), 1.30 (s, 9H); ¹³C NMR (75 MHz, d⁶-acetone) δ 173.5, 155.9, 138.4, 137.9, 129.9, 128.8, 127.6, 126.6, 124.0, 123.8, 120.2, 120.1, 119.0, 114.9, 79.0, 55.2, 28.3, 15.5; APCI *m/z* (relative intensity) 413.3 (M + H, 100%); HRMS calcd for C₂₂H₂₄N₂O₄S (M + H) 413.1535, found 413.1520.



3-(2-Benzenesulfinyl-1H-indol-3-yl)-2-tert-butoxycarbonylamino propionic

Acid (255). *m*-Chloroperbenzoic acid (100 mg, 0.58 mmol) was added to a solution of **253** (250 mg, 0.61 mmol) in CH₂Cl₂ (15 mL) at 0 °C and stirred at 0 °C for 1 h, followed by concentration in vacuo. The crude product was purified by flash chromatography using 10% methanol in ethyl acetate as the eluent to yield 200 mg (81%) of **255** as a white solid (1:1 mixture of diastereomers). IR (CDCl₃) 3434, 3259, 1699 cm⁻¹; ¹H NMR (360 MHz, CD₃OD, 1:1 mixture of diastereomers) δ 7.96 (m, 1H), 7.93 (m, 1H), 7.77 (m, 6H), 7.57 (m, 6H), 7.44 (m, 1H), 7.30 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.10 (t, *J* = 7.1 Hz, 2H), 4.56 (m, 1H), 4.49 (m, 1H), 3.71 (td, *J* = 16.8, 5.3 Hz, 2H), 3.51 (dd, *J* = 8.5, 7.9

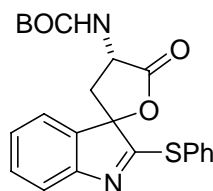
Hz, 2H), 1.29 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD , 1:1 mixture of diastereomers) δ 178.2, 177.2, 156.1, 141.3, 141.2, 138.7, 132.5, 131.0, 129.4, 127.6, 126.9, 125.4, 125.2, 125.1, 121.5, 121.3, 121.1, 120.1, 120.0, 112.1, 80.5, 79.3, 57.0, 56.8, 27.7, 27.0, 21.9; ESI m/z (relative intensity) 427.2 (M - H, 100%); HRMS calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$ (M - H) 427.1328, found 427.1313.



(2S)-tert-butyl dimethylsilyl 2-(tert-butoxycarbonylamino)-3-(2-(phenylsulfinyl)-1H-indol-3-yl)propanoate (256). Acid **253** (2.83 g, 6.9 mmol) was cooled to 0 °C in EtOAc (65 mL). Triethylamine (965 μL , 6.9 mmol) followed by TBSCl (1.08 g, 7.1 mmol) were added and the reaction mixture was stirred at 0 °C for 2 h. The reaction solution was filtered to remove triethylamine hydrochloride and concentrated to yield 3.43 g of the TBS protected ester as a highly unstable beige solid.

The TBS ester (3.43 g, 6.5 mmol) was dissolved in CH_2Cl_2 (120 mL) and cooled to 0 °C. *m*-Chloroperbenzoic acid (1.08 g, 6.3 mmol) was added and the reaction solution was stirred at 0 °C for 3 h. The reaction solution was added to saturated NaHCO_3 (10 mL), extracted with CH_2Cl_2 (3 x 20 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo to yield 3.4 g (100%, 2 steps) of **256** as a highly unstable light brown solid (mixture of diastereomers). IR (CDCl_3) 3442, 1716 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.71 (m, 4H), 7.59 (m, 2H), 7.39 (m, 6H), 7.30 (m, 2H), 7.19 (m, 2H), 7.06 (m, 4H), 5.35 (d, $J = 8$ Hz, 1H), 5.29 (d, $J = 8$ Hz, 1H), 4.60 (m, 2H), 3.61 (m, 1H),

3.43 (m, 3H), 1.33 (s, 9H), 1.31 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H), 0.19 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.6, 172.4, 155.7, 155.5, 143.5, 143.4, 138.3, 138.2, 133.9, 133.7, 131.4, 129.8, 129.6, 127.4, 127.0, 126.2, 125.8, 125.6, 125.4, 120.8, 120.7, 120.6, 120.5, 117.2, 116.7, 112.3, 80.2, 80.2, 55.8, 28.8, 28.6, 26.2, 26.1, 25.9, 25.8, 18.5, 18.0, -3.1, -4.4; APCI m/z (relative intensity) 543.2 (M + H, 100%), 443.1 (M – Boc, 45%); HRMS calcd for $\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_5\text{SSi}$ (M + H) 543.2349, found 543.2341.

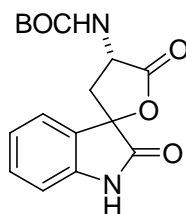


***tert*-Butyl (4*S*)-5-oxo-2'-(phenylthio)-4,5-dihydro-3*H*-spiro[furan-2,3'-indole]-4-ylcarbamate (254).** A solution of trifluoroacetic anhydride (175 μL , 1.24 mmol) in CH_2Cl_2 (20 mL) at -78 $^\circ\text{C}$ was added to a solution of **256** (500 mg, 0.93 mmol) and Hunig's base (400 μL , 2.30 mmol) in CH_2Cl_2 (20 mL) at -78 $^\circ\text{C}$, and the solution was stirred at -78 $^\circ\text{C}$ for 2 h. The reaction solution was warmed to room temperature and added to saturated NaHCO_3 (5 mL), extracted with CH_2Cl_2 (3 x 10 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 80 mg (21%) of **254** as a white solid (1:1 mixture of diastereomers). From this mixture, a small amount (30 mg) of the less polar diastereomer was isolated by flash chromatography using 50% ether in hexanes as the eluent as a white solid. IR (CDCl_3) 3434, 1798, 1714, 1525 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.69 (m, 2H), 7.54 (m, 4H), 7.36 (m, 2H), 7.23 (m, 1H), 5.32 (d, J = 7.1 Hz, 1H), 4.93 (m, 1H), 3.06 (dd, J = 13.7, 9.5 Hz, 1H), 2.83 (m, 1H), 1.52 (s, 9H);

^{13}C NMR (100 MHz, CDCl_3) δ 179.9, 173.8, 155.1, 153.6, 134.5, 131.2, 129.9, 129.6, 126.1, 126.0, 123.4, 119.8, 112.9, 90.4, 81.1, 50.6, 36.9, 28.3.

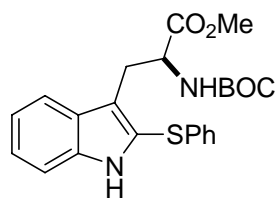
For the mixture: ESI m/z (relative intensity) 411.1 ($M + H$, 100%); HRMS calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$ ($M + H$) 411.1379, found 411.1351; Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$: C, 64.37; H, 5.40; N, 6.82; S, 7.81; Found: C, 64.49; H, 5.75; N, 6.50; S, 7.70.

Lactone 254 from Sulfide 253. **253** (500 mg, 1.21 mmol) was cooled to $-78\text{ }^\circ\text{C}$ in CH_2Cl_2 (40 mL). 2, 6-Lutidine (400 μL , 3.46 mmol) was added followed by $\text{PhI}(\text{CN})\text{OTf}$ (1.12 g, 2.96 mmol). The reaction solution was slowly warmed to room temperature and stirred there for 15 h. The reaction solution was added to water (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 33% ether in hexanes as the eluent to yield 190 mg (38%) of **254** as a white solid (1:1 mixture of diastereomers).



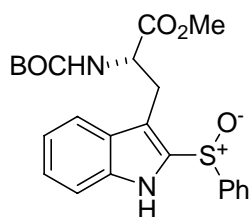
***tert*-Butyl (4*S*)-2',5-dioxo-4,5-dihydro-3*H*-spiro[furan-2,3'-indoline]-4-yl carbamate (257).** Cerium (IV) ammonium nitrate (868 mg, 1.58 mmol) was added to a solution of **254** (550 mg, 1.34 mmol) in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (60 mL, 5/1) and stirred for 15 h. The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic

layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 25% hexanes in Et₂O as the eluent to yield 370 mg (87%) of **257**, as a white solid (1:1 mixture of diastereomers). IR (CDCl₃) 3434, 1793, 1747, 1715 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.13 (s, 2H), 7.49 (d, *J* = 6.5 Hz, 1H), 7.38 (m, 3H), 7.16 (t, *J* = 7.6 Hz, 2H), 6.95 (t, *J* = 8.6 Hz, 2H), 5.88 (d, *J* = 9 Hz, 1H), 5.30 (d, *J* = 9 Hz, 1H), 5.08 (m, 2H), 2.99 (m, 1H), 2.85 (dd, *J* = 9.3, 4.2 Hz, 1H), 2.73 (t, *J* = 12.2 Hz, 1H), 2.51 (dd, *J* = 13.7, 5.6 Hz, 1H), 1.48 (s, 18H); ¹³C NMR (75 MHz, d⁸-THF) δ 176.7, 174.2, 156.2, 143.7, 143.1, 131.8, 131.7, 128.6, 128.0, 125.8, 125.4, 123.6, 123.5, 111.2, 111.0, 81.2, 80.5, 79.8, 50.9, 50.3, 37.9, 37.2, 28.6; APCI *m/z* (relative intensity) 336.0 (M + NH₄, 100%), 262.9 (M + H - *t*-Bu, 40%); HRMS calcd for C₁₅H₁₁N₄O₄S (M + NH₄) 336.1559, found 336.1526.



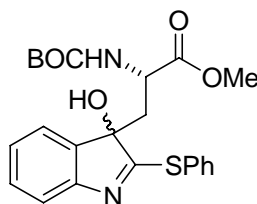
Methyl 3-(2-Benzenesulfinyl-1H-indol-3-yl)-2-tert-butoxycarbonylamino propionate (258). Trimethylsilyldiazomethane (808 μL, 2M in hexanes 1.62 mmol) was added to acid **253** (500 mg, 1.21 mmol) in benzene (5 mL) and methanol (5 mL). The reaction solution was stirred for 45 min and then concentrated in vacuo. The crude product was purified by flash chromatography using 33% ether in hexanes as the eluent to yield 330 mg (64%) of the methyl ester as a white solid. mp 104 - 106 °C; IR (CDCl₃) 3458, 1741, 1710 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.53 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.33 (m, 8H), 5.15 (d, *J* = 8.0 Hz, 1H), 4.66 (m, 1H), 3.61 (s, 3H), 3.44 (dd,

$J = 14.3, 5.5$ Hz, 1H), 3.31 (dd, $J = 14.3, 6.3$ Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (90 MHz, CDCl_3) δ 172.8, 155.3, 137.2, 136.6, 129.4, 128.1, 127.1, 126.3, 123.9, 123.8, 120.3, 119.5, 117.7, 111.2, 79.9, 54.3, 52.5, 28.4, 14.3; ESI m/z (relative intensity) 449.1 (M + Na, 100%); HRMS calcd for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$ 449.1511 (M + Na), found 449.1502.



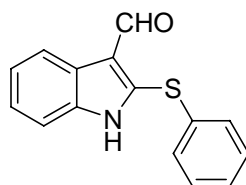
(2S)-methyl 2-(tert-butoxycarbonylamino)-3-(2-(phenylsulfinyl)-1H-indol-3-yl)propanoate (259). The methyl ester (330 mg, 0.77 mmol) was cooled to 0 °C in CH_2Cl_2 (15 mL). *m*-Chloroperbenzoic acid (132 mg, 0.76 mmol) was added and the reaction solution was stirred at 0 °C for 90 min. The reaction solution was added to NaHCO_3 (10 mL), extracted with CH_2Cl_2 (3 x 10 mL), washed with water and brine, and dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 20% hexanes in ether as the eluent to yield 240 mg (71%) of **259** as a white solid (1:1 mixture of diastereomers). IR (CDCl_3) 3439, 1741, 1708 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3 , 1:1 mixture of diastereomers) δ 8.58 (s, 1H), 8.53 (s, 1H), 7.72 (m, 4H), 7.64 (m, 2H), 7.52 (m, 6H), 7.29 (m, 4H), 7.16 (m, 2H), 5.35 (d, $J = 8.2$ Hz, 1H), 5.24 (d, $J = 8.0$ Hz, 1H), 4.73 (m, 2H), 3.74 (s, 3H), 3.64 (s, 3H), 3.59 (d, $J = 5.9$ Hz, 1H), 3.50 (m, 3H), 1.46 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3 , 1:1 mixture of diastereomers) δ 173.2, 172.2, 155.3, 155.1, 143.3, 143.2, 137.8, 137.7, 134, 133.7, 131.2, 129.6, 129.5, 127.3, 127.2, 125.5, 125.2, 120.7, 120.6, 120.3, 120.2, 116.3, 115.8, 112.7, 112.6, 80.2, 80.1, 54.3, 54.2, 52.7, 52.6, 28.5, 28.4, 14.3; ESI m/z (relative

intensity) 465.1 (M + Na, 100%); HRMS calcd for C₂₃H₂₆N₂O₅S 465.1460 (M + Na), found 465.1465.

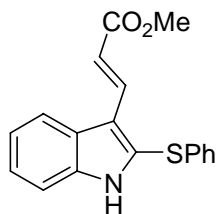


Methyl 2-tert-Butoxycarbonylamino-3-(3-hydroxy-2-phenylsulfonyl-3H-indol-3-yl) propionate (260) and (256) from 259. Diisopropylethylamine (86 μ L, 0.49 mmol) was added to a solution of **259** (88 mg, 0.20 mmol) in CH₂Cl₂ (8 mL) at -78 °C and stirred for 5 min. Trifluoroacetic anhydride (36 μ L, 0.26 mmol) was added and the reaction solution was slowly warmed to room temperature over 3 h and stirred there for 15 h. Additional diisopropylethylamine (86 μ L, 0.49 mmol) and then trifluoroacetic anhydride (36 μ L, 0.26 mmol) were added and the reaction solution was stirred for 48 h. The reaction solution was added to water (10 mL), extracted with CH₂Cl₂ (3 x 5 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 52 mg (63%) of **260** as a white solid (1:1 mixture of diastereomers) and 29 mg (33%) of **256** as a white solid (1:1 mixture of diastereomers). **260**: IR (CDCl₃) 1745, 1714 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 1:1 mixture of diastereomers) δ 8.00 (d, J = 12.2 Hz, 1H), 7.72 (m, 4H), 7.46 (m, 7H), 7.33 (m, 4H), 7.17 (m, 2H), 5.35 (bs, 1H), 5.09 (bs, 1H), 4.57 (bs, 1H), 4.25 (bs, 1H), 3.68 (s, 3H), 3.65 (s, 3H), 2.71 (dd J = 14.4, 5 Hz, 1H), 2.56 (dd, J = 14.6, 9.4 Hz, 1H), 2.34 (dd J = 14.4, 9.0 Hz, 1H), 2.26 (dd, J = 14.7 Hz, 3.6 Hz, 1H), 1.44 (s, 9H), 1.39 (s, 9H); ¹³C NMR (75 MHz, CDCl₃, 1:1 mixture of diastereomers) δ 184.8, 172.4, 154.0, 153.9, 138.6, 134.8, 134.7 130.7, 130.5, 129.7, 129.6, 125.5, 125.3,

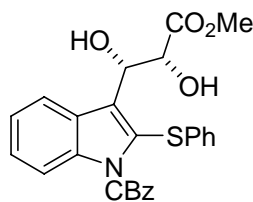
123.5, 123.0, 120.3, 86.6, 86.3, 80.8, 77.4, 52.8, 28.5 (2 carbons), 23.8; ESI m/z (relative intensity) 443.1 (M + H, 85%), 465.1 (M + Na, 100%); HRMS calcd for $C_{23}H_{26}N_2O_5S$ 443.1641 (M + H), found 443.1644.



2-Phenylsulfanyl-1H-indole-3-carbaldehyde. Sodium hydride (1.88 g, 60% dispersion in mineral oil, 47.0 mmol) was added in small portions to a solution of benzenethiol (5.50 mL, 53.5 mmol) in dimethylacetamide (180 mL). Chloride **265** (8.50 g, 47.5 mmol) was added and the reaction solution was heated at 90 °C for 2.5 h. The reaction solution was added to ice, extracted with EtOAc (3 x 40 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 9.95 g (83%) of the 2-substituted indole as a white solid: mp 166 – 169 °C; IR ($CDCl_3$) 3439, 1655 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 10.3 (s, 1H), 8.41 (s, 1H), 8.29 (m, 1H), 7.46 (m, 2H), 7.39 (m, 3H), 7.29 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.6, 140.7, 136.5, 131.9, 131.6, 130.2, 128.9, 126.1, 124.7, 123.4, 121.3, 118.8, 111.1; ESI m/z (relative intensity) 254.0 (M + H, 100%); HRMS calcd for $C_{15}H_{11}N_4O_4S$ (M + H) 254.0640, found 254.0631; Anal. Calcd for $C_{15}H_{11}N_4O_4S$: C, 71.12; H, 4.38; N, 5.53; S, 12.66; Found: C, 71.12; H, 4.42; N, 5.54; S, 12.89.



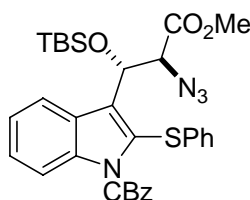
2-Azido-3-(*tert*-butyl-dimethyl-silanyloxy)-3-(2-phenylsulfanyl-1*H*-indol-3-yl)-propionic Acid. *n*-Butyllithium (9.1 mL, 2.3 M in hexanes, 21 mmol) was added to (carbomethoxy)methyltriphenylphosphonium bromide (8.8 g, 21 mmol) in DME (100 mL). To this solution, the aldehyde (4.89 g, 19.3 mmol) in DME (100 mL) was added and the reaction solution was brought to reflux and held there for 40 h. The reaction solution was added to ice, extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 33% ether in hexanes as the eluent to yield 4.84 g (81%) of the alkene as a white solid. mp 161 - 162 °C; IR (CDCl₃) 3450, 1698, 1627 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.18 (d, *J* = 16.1 Hz, 1H), 7.93 (m, 1H), 7.73 (m, 2H), 7.46 (m, 1H), 7.36 (m, 1H), 7.26 (m, 5H), 6.65 (d, *J* = 16.1 Hz, 1H), 3.79 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 168.5, 137.3, 134.8, 132.0, 131.3, 129.4, 128.6, 126.9, 125.8, 124.1, 121.7, 120.4, 117.3, 115.0, 111.6, 51.5; APCI *m/z* (relative intensity) 310.2 (M + H, 100%); HRMS calcd for C₁₈H₁₅NO₂S (M + H) 310.0902, found 310.0892



Benzyl 3-((1S,2R)-1,2-Dihydroxy-3-methoxy-3-oxopropyl)-2-(phenylthio)-1H-indole-1-carboxylate (266). Sodium hydride (702 mg, 60% dispersion in mineral oil, 17.6 mmol) was added to a solution of the alkene (5.0 g, 16 mmol) in THF (100 mL) and stirred for 2 h. Benzyl chloroformate (2.56 mL, 17.9 mmol) was added and stirring was continued for 15 h. The reaction solution was added to ice, extracted with CH₂Cl₂ (3 x 25 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to yield 7.4 g crude of the CBz-protected indole.

The crude CBz-protected indole (7.4 g) was suspended in *t*-BuOH/H₂O (90 mL, 1/1). A modified AD mix- α (potassium ferricyanide (15.80 g), potassium carbonate (6.67 g), (DHQ)₂PHAL (625 mg), and K₂O₅O₂(OH)₄ (63 mg)) and methanesulfonamide (4.61 g, 48.5 mmol) was added in 4 equal portions at 1 h intervals, and stirring was continued for 15 h. Sodium sulfite (25 g) was added, and the reaction solution was stirred for 30 min. The reaction mixture was then extracted with EtOAc (3 x 25 mL), and the combined organic fractions were washed with 1 M KOH (25 mL), water, and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 40% EtOAc in hexanes as the eluent to yield 6.45 g (85%, 2 steps, > 99% ee⁸⁸) of the diol as a white solid. mp 142 – 144 °C; $[\alpha]_D^{25} + 7.8$ (c 1 CH₂Cl₂); IR (CDCl₃) 3531, 1737 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.16 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.34 (m, 7H), 7.18 (m, 3H), 7.03 (m, 2H), 5.60 (dd, *J*

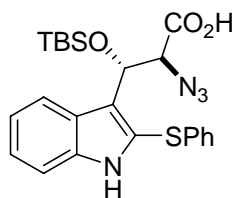
= 6, 4 Hz, 1H), 5.27 (d, $J = 12$ Hz, 1H), 5.22 (d, $J = 12$ Hz, 1H), 4.39 (dd, $J = 6, 4$ Hz, 1H), 3.75 (s, 3H), 3.60 (d, $J = 6$ Hz, 1H), 3.31 (d, $J = 6$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ , 173.0, 150.9, 138.0, 136.8, 134.8, 130.3, 129.9, 129.3, 128.9, 128.8, 127.3, 126.7, 126.6, 126.2, 124.5, 123.6, 121.0, 116.1, 74.5, 70.9, 69.2, 53.3; ESI m/z (relative intensity) 460.2 ($\text{M} + \text{H} - \text{H}_2\text{O}$, 100%); Anal. Calcd for $\text{C}_{26}\text{H}_{23}\text{NO}_6\text{S}$: C, 65.39; H, 4.85; N, 2.93; S, 6.71; Found: C, 65.11; H, 4.90; N, 3.00; S, 6.53.



Benzyl 3-((1S,2S)-2-Azido-1-(*tert*-butyldimethylsilyloxy)-3-methoxy-3-oxopropyl)-2-(phenylthio)-1H-indole-1-carboxylate (267). The diol (1.6 g, 3.4 mmol) was dissolved in CH_2Cl_2 (60 mL) and cooled to 0 °C. Triethylamine (966 μL , 6.9 mmol) and 4-nitrobenzenesulfonyl chloride (772 mg, 3.5 mmol) were added and the reaction solution was stirred at 0 °C for 15 h. The reaction solution was added to 1 M HCl (20 mL), extracted with CH_2Cl_2 (3 x 20 mL), washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo to yield 2.4 g of the crude nosylate as a yellow solid.

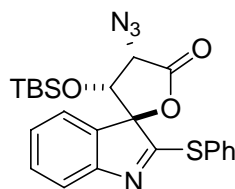
Sodium azide (450 mg, 6.9 mmol) was added to a solution of the nosylate (2.4 g, crude) in acetone/water (50 mL, 1/1), and the reaction solution was heated for 15 h at 60 °C. The acetone was removed in vacuo, and the resulting water layer was extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo to yield 1.78 g of the crude azide.

2,6-Lutidine (1.08 mL, 9.4 mmol) was added to the crude azide (1.78 g) in CH₂Cl₂ (60 mL) and stirred for 5 min. Tertbutyldimethylsilyl trifluoromethanesulfonate (1.08 mL, 4.7 mmol) was added and stirring was continued for 15 h. The reaction solution was added to water (30 mL), extracted with CH₂Cl₂ (3 x 30 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 33% ether in hexanes as the eluent, providing 1.40 g (67% over 3 steps) of the TBS ether as a yellow oil. IR (CDCl₃) 2116, 1739 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.23 (m, 2H), 7.45 (m, 7H), 7.21 (m, 3H), 7.03 (m, 2H), 6.03 (d, *J* = 3 Hz, 1H), 5.36 (d, *J* = 12 Hz, 1H), 5.29 (d, *J* = 12 Hz, 1H), 3.80 (s, 3H), 3.72 (d, *J* = 3 Hz, 1H), 0.90 (s, 9H), -0.02 (s, 3H), -0.28 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 168.7, 150.8, 137.6, 136.9, 134.5, 131.0, 129.2, 128.7, 128.6, 128.0, 126.2, 126.1, 126.0, 125.8, 123.2, 122.2, 121.9, 115.5, 72.7, 69.1, 67.5, 52.7, 25.5, 18.0, -4.8, -6.0; ESI *m/z* (relative intensity) 639.2 (*M* + Na, 100%); HRMS calcd for C₃₂H₃₆N₄O₅SSi (*M* + NH₄) 634.2519, found 634.2558.

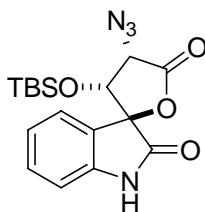


(2*S*,3*S*)-2-Azido-3-(*tert*-butyldimethylsilyloxy)-3-(2-(phenylthio)-1*H*-indol-3-yl)propanoic Acid (263). The TBS ether (835 mg, 1.35 mmol) and LiOH•H₂O (192 mg, 4.57 mmol) were stirred for 15 h in THF/H₂O (25 mL, 4/1). The reaction solution was acidified with 1 M HCl (10 mL), extracted with CH₂Cl₂ (3 x 10 mL), dried over Na₂SO₄, and concentrated in vacuo, to yield 950 mg crude product of **263**, which was found to be unstable to chromatography, as a dark brown oil. IR (CDCl₃) 3455, 3063, 2116, 1722

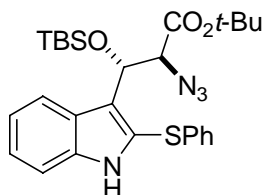
cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 9.83 (s, 1H), 8.18 (s, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.29 (m, 8H), 5.86 (d, *J* = 3.6 Hz, 1H), 3.70 (d, *J* = 3.6 Hz, 1H), 0.85 (s, 9H), -0.01 (s, 3H), -0.30 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.6, 136.8, 135.8, 129.4, 127.8, 127.1, 126.6, 123.6, 122.2, 121.5, 120.8, 120.4, 110.9, 72.1, 67.7, 25.6, 18.1, -4.9, -5.8; ESI *m/z* (relative intensity) 467.1 (M – H, 100%), 503.1 (M + Cl, 10%); HRMS calcd for C₂₃H₂₈N₄O₃SSi (M - H) 467.1573, found 467.1570.



(3*R*,4*S*)-4-Azido-3-(*tert*-butyldimethylsilyloxy)-2'-(phenylthio)-3*H*-spiro[furan-2,3'-indol]-5(4*H*)-one (268). A solution of **263** (20 mg, 0.043 mmol) in CH₂Cl₂ (1 mL) was cooled to -78 °C. 2, 6-Lutidine (15 μL, 0.13 mmol) followed by PhI(CN)OTf (41 mg, 0.11 mmol) were added and the reaction solution was slowly warmed to room temperature over 45 min and stirred there for 15 h. The reaction solution was added to water (3 mL), extracted with CH₂Cl₂ (3 x 5 mL), washed with water and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 20% Et₂O in hexanes as the eluent to yield 8 mg (40%) of **268** as an orange oil. IR (CDCl₃) 2116, 1803, 1524 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.68 (m, 2H), 7.49 (m, 3H), 7.34 (m, 2H), 7.22 (m, 2H), 5.03 (d, *J* = 9.5 Hz, 1H), 4.56 (d, *J* = 9.5 Hz, 1H), 0.79 (s, 9H), 0.00 (s, 3H), -0.48 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 178.0, 169.8, 154.7, 134.5, 134.0, 132.0, 129.9, 129.6, 126.9, 125.7, 122.8, 120.2, 93.2, 79.2, 63.6, 25.3, 17.7, -5.2, -5.9; ESI *m/z* (relative intensity) 467.1 (M + H, 100%); HRMS calcd for C₂₃H₂₆N₄O₃SSi (M + H) 467.1573, found 467.1591.

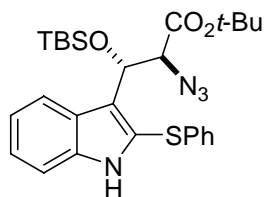


(3R,4S)-4-Azido-3-(tert-butyldimethylsilyloxy)-3H-spiro[furan-2,3'-indoline]-2',5(4H)-dione (262). Cerium (IV) ammonium nitrate (42 mg, 0.077 mmol) was added to a solution of **268** (30 mg, 0.06 mmol) in CH₃CN/H₂O (4.5 mL, 5/1) and stirred for 15 h. The reaction solution was extracted with EtOAc (3 x 5 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 12 mg (50%) of **262**, as a white solid: mp 128 – 130 °C; IR (CDCl₃) 3432, 2117, 1807, 1752 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.50 (m, 2H), 7.41 (m, 1H), 7.15 (m, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 4.93 (d, *J* = 5.1 Hz, 1H), 4.51 (d, *J* = 5.1 Hz), 0.87 (s, 9H), -0.06 (s, 3H), -0.36 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.4, 170.1, 142.4, 132.1, 125.2, 123.9, 123.6, 110.8, 83.1, 79.9, 62.7, 25.4, 17.8, 0.2, -5.5; ESI *m/z* (relative intensity) 392.2 (M + NH₄, 100%) 375.2 (M + H, 16%); HRMS calcd for C₁₇H₂₂N₄O₄Si (M + H) 375.1489, found 375.1454; Anal. Calcd for C₁₇H₂₂N₄O₄Si: C, 54.53; H, 5.92; N, 14.96; Found: C, 54.32; H, 5.94; N, 14.73.



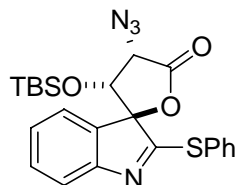
tert-Butyl 2-Azido-3-(tert-butyl-dimethylsilyloxy)-3-(2-phenylsulfanyl-1H-indol-3-yl) propionate (272). *N, N*-Dimethylformamide di-*tert*-butyl acetal (232 μL,

0.97 mmol) was added to a solution of acid **263** (87 mg, 0.19 mmol) in toluene (3 mL). The reaction solution was brought to 55 °C and held there for 15 h. The reaction solution was added to water (5 mL), extracted with ethyl acetate (3 x 5 mL), washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 17% ether in hexanes as the eluent to yield 50 mg (52%) of **272** as a colorless oil. IR (CDCl₃) 3458, 2115, 1733 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.25 (s, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.34 (m, 8H), 5.83 (d, *J* = 4.4 Hz, 1H), 3.70 (m, 1H), 1.40 (s, 9H), 0.94 (s, 9H), 0.09 (s, 3H), -0.29 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 168.9, 137.2, 136.2, 129.8, 129.0, 127.6, 127.1, 124.0, 123.1, 121.9, 121.5, 121.0, 111.2, 83.1, 71.9, 69.0, 28.6, 26.2, 18.5, -4.3, -5.2; ESI *m/z* (relative intensity) 547.1 (M + Na, 100%); HRMS calcd for C₂₇H₃₆N₄O₃SSi 547.2175 (M + Na), found 547.2162.



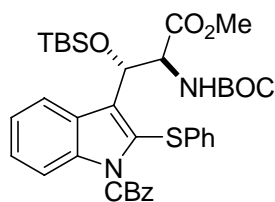
***tert*-Butyl 2-Azido-3-(2-benzenesulfinyl-1H-indol-3-yl)-3-(*tert*-butyl-dimethylsilanyloxy) propionate (273).** Sulfide **272** (153 mg, 0.29 mmol) was cooled to 0 °C in CH₂Cl₂ (9 mL). *m*-Chloroperbenzoic acid (49 mg, 0.28 mmol) was added and the reaction solution was stirred at 0 °C for 20 min. The reaction solution was added to sat. NaHCO₃ (10 mL), extracted with CH₂Cl₂ (3 x 10 mL), washed with water and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 33% hexanes in ether as the eluent to yield 107 mg (70

% of **273** as a white solid (1:1 mixture of diastereomers) and 45 mg of recovered **272** (30 %). IR (CDCl₃) 3430, 2115, 1737 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 1:1 mixture of diastereomers) δ 7.94 (d, *J* = 8.0 Hz, 1H), 7.84 (m, 4H), 7.49 (m, 3H), 7.44 (m, 3H), 7.41 (m, 3H), 7.34 (m, 2H), 7.23 (m, 2H), 7.14 (m, 2H), 5.84 (d, *J* = 3.6 Hz, 1H), 5.74 (d, *J* = 4.4 Hz, 1H), 3.57 (bs, 1H), 3.46 (bs, 1H), 1.43 (s, 18H), 0.94 (s, 9H), 0.86 (s, 9H), 0.17 (s, 3H), 0.07 (s, 3H), -0.01 (s, 3H), -0.33 (s, 3H); ¹³C NMR (100 MHz, CDCl₃, 1:1 mixture of diastereomers) δ 167.6, 167.4, 143.8, 143.3, 137.6, 137.0, 136.8, 134.1, 132.4, 132.0, 131.8, 131.7, 129.7, 129.7, 128.8, 128.8, 126.6, 126.3, 126.3, 125.6, 125.2, 125.1, 121.1, 120.9, 119.4, 112.5, 83.5, 83.4, 70.3, 70.2, 68.7, 68.3, 28.1, 28.1, 18.4, 18.3, 0.2, -4.6, -5.2, -5.3; ESI *m/z* (relative intensity) 563.2 (M + Na, 100%); HRMS calcd for C₂₇H₃₆N₄O₄SSi 563.2124 (M + Na), found 563.2133.



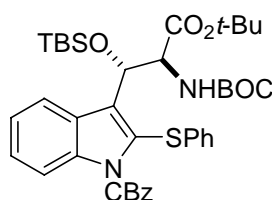
Lactone 268 from 272. A solution of **272** (45 mg, 0.086 mmol) in CH₂Cl₂ (2.5 mL) was cooled to -78 °C. 2, 6-Lutidine (37 μL, 0.32 mmol) followed by PhI(CN)OTf (51 mg, 0.13 mmol) were added and the reaction solution was slowly warmed to room temperature over 45 min and stirred there for 15 h. The reaction solution was added to water (3 mL), extracted with ethyl acetate (3 x 5 mL), washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 10% Et₂O in hexanes as the eluent to yield 8 mg (20%) of **268** as an orange oil.

Lactone 268 from 273. 2,6-Lutidine (17 μ L, 0.15 mmol) was added to **273** (22 mg, 0.041 mmol) in CH_3CN (1 mL) and cooled to -40°C . A solution of Tf_2O (17 μ L, 0.10 mmol) in CH_3CN (1 mL) was added and the reaction solution was slowly warmed to room temperature and stirred for 36 h. The reaction solution was added to sat. NaHCO_3 (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 20% ether in hexanes as the eluent to yield 7 mg (37%) of **268** as an orange oil.



tert-Butyl 2-tert-butoxycarbonylamino-3-(tert-butyl-dimethylsilyloxy)-3-(2-phenylsulfanyl-1H-indol-3-yl) propionate (269). Trimethylphosphine (0.95 mL, 1M in THF, 0.95 mmol) was slowly added to a solution of **267** (200 mg, 0.32 mmol) in THF (4 mL), and stirring was continued for 45 min. The reaction solution was cooled below -20°C , BOC-ON (230 mg, 0.93 mmol) in THF (1 mL) was added, and the reaction solution was warmed to room temperature and stirred for 15 h. The reaction mixture was added to water (10 mL), extracted with CH_2Cl_2 (3 x 10 mL), washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 20% ether in hexanes as the eluent, providing 160 mg (72%) of the BOC protected amine as a colorless oil. IR (CDCl_3) 3550, 1743, 1710 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.21 (d, $J = 8.3$ Hz, 1H), 8.02 (d, $J = 7.8$ Hz, 1H), 7.84 (m, 2H), 7.51 (m, 4H), 7.38 (m, 6H), 5.94 (d, $J = 2.6$ Hz, 1H), 5.72 (d, $J = 9.8$ Hz, 1H), 5.26

(s, 2H), 4.72 (dd, $J = 9.8, 2.3$ Hz, 1H), 3.76 (s, 3H) 1.14 (s, 9H), 0.86 (s, 9H), -0.07 (s, 3H), -0.29 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.1, 155.5, 151.2, 138.1, 137.3, 134.7, 133.3, 131.2, 129.6, 129.2 (2 carbons), 128.9, 128.7, 128.5, 126.4, 126.1, 125.7, 123.0, 115.7, 80.5, 72.1, 69.2, 66.4, 52.7, 28.1, 25.8, 15.2, -3.5, -4.7; ESI m/z (relative intensity) 713.2 (M + Na, 90%); HRMS calcd for $\text{C}_{37}\text{H}_{46}\text{N}_2\text{O}_7\text{SiS}$ 713.2693 (M + Na), found 713.2673.



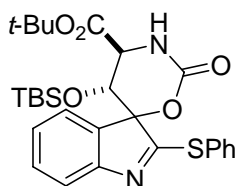
(2*R*,3*S*)-*tert*-Butyl

2-(*tert*-Butoxycarbonylamino)-3-(*tert*-

butyldimethylsilyloxy)-3-(2-(phenylthio)-1*H*-indol-3-yl)propanoate (270). The BOC-protected amine (160 mg, 0.23 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (33 mg, 0.79 mmol) were stirred for 15 h in THF/ H_2O (15 mL, 4/1). The reaction mixture was acidified with 1 M HCl (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent, providing 31 mg (25%) of the acid as a yellow solid.

N,N-Dimethylformamide di-*tert*-butyl acetal (72 μL , 0.30 mmol) was added to a solution of the acid from above (31 mg, 0.057 mmol) in toluene (2 mL). The reaction solution was brought to 55 $^\circ\text{C}$ and held there for 15 h. The reaction solution was added to water (5 mL), extracted with ethyl acetate (3 x 5 mL), washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash

chromatography using 17% ether in hexanes as the eluent to yield 50 mg (52%) of **270** as a colorless oil. IR (CDCl₃) 3692, 3458, 1712 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.07 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.23 (m, 7H), 7.10 (m, 1H), 5.66 (d, *J* = 3.1 Hz, 1H), 5.52 (d, *J* = 10 Hz, 1H), 4.44 (dd, *J* = 9.7, 3.1 Hz, 1H), 1.38 (s, 9H), 1.19 (s, 9H), 0.85 (s, 9H), -0.08 (s, 3H), -0.40 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.8, 155.2, 136.9, 131.2, 131.0, 129.2, 129.0, 127.9, 127.0, 126.4, 126.3, 123.1, 119.9, 110.5, 81.6, 79.2, 70.8, 61.0, 28.3, 28.1, 25.8, 18.0, -4.7, -5.7; ESI *m/z* (relative intensity) 621.2 (M + Na, 100%); HRMS calcd for C₃₂H₄₆N₂O₅SiS 621.2794 (M + Na), found 621.2795.



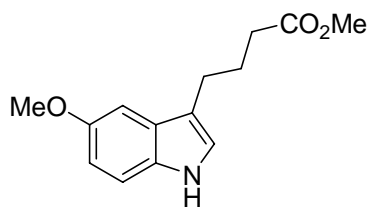
(4'S,5'R)-tert-Butyl 5'-(tert-Butyldimethylsilyloxy)-2'-oxo-2-(phenylthio)spiro[indole-3,6'-[1,3]oxazinane]-4'-carboxylate (271). A solution of **270** (3 mg, 0.005 mmol) in CH₂Cl₂ (1 mL) was cooled to -78 °C. 2, 6-Lutidine (2 μL, 0.017 mmol) followed by PhI(CN)OTf (3 mg, 0.008 mmol) were added and the reaction solution was slowly warmed to room temperature over 45 min and stirred there for 15 h. The reaction solution was added to water (3 mL), extracted with ethyl acetate (3 x 5 mL), washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% Et₂O in hexanes as the eluent to yield 2 mg (74%) of **271** as a colorless oil. IR (CDCl₃) 3691, 1737 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.73 (m, 2H), 7.54 (m, 3H), 7.39 (m, 3H), 7.12 (td *J* = 7.1, 1.6 Hz, 1H), 5.93 (s, 1H), 4.71 (m, 1H), 4.68 (d, *J* = 2.6 Hz, 1H), 1.60 (s, 9H), 0.80 (s, 9H), 0.00 (s,

3H), -0.69 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.4, 166.2, 154.2, 152.4, 135.8, 135.0, 131.1, 130.3, 129.9, 127.6, 127.0, 125.6, 120.2, 85.5, 77.6, 69.5, 58.3, 30.1, 26.3, 18.5, -4.0, -4.6; ESI m/z (relative intensity) 604.1 (M + Na); HRMS calcd for $\text{C}_{28}\text{H}_{36}\text{N}_2\text{O}_5\text{SiS}$ 563.2012 (M + Na), found 563.2018.

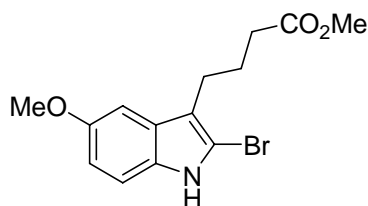
6.3 Enantioselective Pummerer reaction development

General Procedure for the Pummerer Rearrangement. 2,6-Lutidine and then trifluoromethanesulfonic anhydride were added to a solution of the indicated sulfoxide in the specified solvent at the temperature listed. TLC analysis generally showed consumption of the sulfoxide within 20 min. Water was added and the cooling bath was removed, allowing the reaction solution to warm to room temperature. The two layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was used without purification unless otherwise indicated.

General Procedure for Determination of the Enantiomeric Excess of Samples. The enantiomeric excess of the samples was established using ^1H NMR and the chiral shift reagents (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) and europium(III) tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato] ((+)-Eu(tfc) $_3$). The indicated shift reagent was gradually added to the sample to achieve optimal peak separation of the two enantiomers.

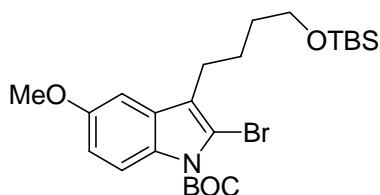


Methyl 4-(5-Methoxy-1H-indol-3-yl)butanoate (282). TMSCH₂N₂ (25 mL, 2.0 M in hexanes, 50 mmol) was added slowly to crude 5-methoxyindole 3-butyric acid (30.39 g, 130 mmol) in benzene (150 mL) and methanol (150 mL). The reaction solution was concentrated in vacuo, and the crude product was purified by flash chromatography using 25% ethyl acetate in hexanes as the eluent to yield 4.21 g (13%, 2 steps – known decarboxylation step included) of **282** as a yellow solid. mp 136 - 138 °C; IR (CDCl₃) 3490, 1740 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, *J* = 8.8 Hz, 1H), 7.06 (d, *J* = 2.3 Hz, 1H), 6.97 (s, 1H), 6.85 (dd, *J* = 8.8, 2.3 Hz, 1H), 3.86 (s, 3H), 3.67 (s, 3H), 2.80 (t, *J* = 7.4 Hz, 2H), 2.43 (t, *J* = 7.4 Hz, 2H), 2.08 (m, 2H); ¹³C NMR (75 MHz, CD₂Cl₂) δ 174.5, 154.1, 131.1, 128.1, 122.9, 115.4, 114.1, 112.1, 100.8, 56.0, 51.7, 33.9, 25.6, 24.8; ESI *m/z* (relative intensity) 248.1 (M + H, 100%); HRMS calcd for C₁₄H₁₈NO₃ (M + H), 248.1287, found 248.1282.



Methyl 4-(2-Bromo-5-methoxy-1H-indol-3-yl)butanoate. Methyl ester **282** (3.44 g, 13.9 mmol) was dissolved in CH₂Cl₂ (140 mL). *N*-bromosuccinimide (1.36 g, 8.5 mmol) was added and the reaction solution was stirred for 20 min at room temperature. One additional portion of *N*-bromosuccinimide (0.15 g, 0.84 mmol) was

added and stirring was continued for 15 min at room temperature. The reaction solution was concentrated in vacuo, and the crude product was purified by flash chromatography using 25% ethyl acetate in hexanes as the eluent to yield 2.94 g (100%) of the bromide as a yellow solid. mp 54 - 56 °C; IR (CDCl₃) 3476, 1741 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.44 (s, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.87 (s, 3H), 3.68 (s, 3H), 2.79 (t, *J* = 7.3 Hz, 2H), 2.42 (t, *J* = 7.3 Hz, 2H), 2.09 (m, 2H); ¹³C NMR (75 MHz, CD₂Cl₂) δ 174.5, 154.1, 131.1, 128.1, 122.9, 115.4, 114.1, 112.1, 100.8, 56.0, 51.7, 33.9, 25.6, 24.8; ESI *m/z* (relative intensity) 326.0 (M + H, 100%), 328.0 (⁸¹Br, 95%); HRMS calcd for C₁₄H₁₇BrNO₃ (M + H), 326.0392, found 326.0387.

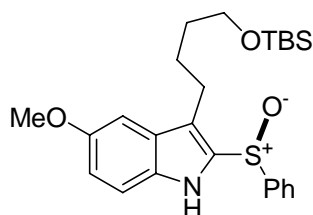


***tert*-Butyl 2-Bromo-3-(4-(*tert*-butyldimethylsilyloxy)butyl)-5-methoxy-1H-indole-1-carboxylate (298).** The bromide (2.66 g, 8.26 mmol) was dissolved in CH₂Cl₂ (100 mL). DMAP (1.40 g, 11.5 mmol) and BOC₂O (2.41 g, 11.1 mmol) were added and the reaction solution was stirred for 70 min at room temperature. The reaction solution was added to water (100 mL), extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to yield 3.44 g (98%) of the BOC-protected indole as a colorless oil.

DIBAL (25.4 mL, 1.0 M in hexanes, 25.4 mmol) was added to a solution of the crude BOC-protected indole (3.07 g, 8.84 mmol) in CH₂Cl₂ (60 mL) and THF (60 mL) at

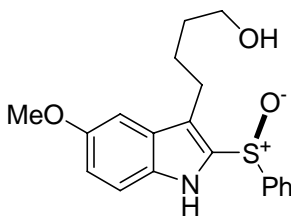
-78 °C. The reaction solution was warmed to room temperature and stirred for 15 h at room temperature. The reaction solution was added to sat. NH₄Cl (300 mL), and filtered to remove the aluminum salts. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to yield the alcohol which was used without purification.

The crude alcohol was dissolved in CH₂Cl₂ (115 mL). Imidazole (1.28 g, 17.3 mmol) and TBSCl (1.47 g, 9.8 mmol) were added and the reaction solution was stirred for 15 h. The reaction solution was added to water (100 mL), extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% benzene in hexanes as the eluent to yield 2.33 g (74%, 2 steps) of **288** as colorless oil. IR (CDCl₃) 1724 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.93 (d, *J* = 9.1 Hz, 1H), 6.87 (m, 2H), 3.81 (s, 3H), 3.62 (t, *J* = 6.2 Hz, 2H), 2.69 (m, 2H), 1.64 (m, 11H), 1.58 (m, 2H), 0.84 (s, 9H), 0.00 (s, 6H); ¹³C NMR (90 MHz, CDCl₃) δ 156.1, 149.4, 131.4, 130.0, 123.4, 116.4, 112.7, 109.3, 101.3, 84.6, 63.1, 55.8, 32.7, 28.4, 26.1, 25.3, 25.2, 18.5, -5.1; ESI *m/z* (relative intensity) 534.1 (M + Na, 100%), 536.1 (⁸¹Br, 95%); HRMS calcd for C₂₄H₃₈NO₄BrSi (M + Na), 534.1651, found 534.1461.



(*S*)-3-(4-(*tert*-butyldimethylsilyloxy)butyl)-5-methoxy-2-(phenylsulfinyl)-1*H*-indole (**289**). Bromide **288** (550 mg, 1.10 mmol) was dissolved in THF (30 mL), and

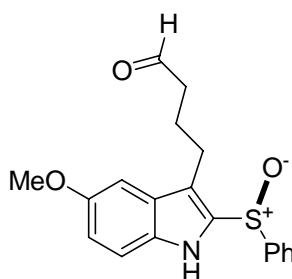
cooled to $-78\text{ }^{\circ}\text{C}$. *t*-BuLi (3.64 mL, 1.7 M in pentane, 6.2 mmol) was added and the reaction solution was stirred for 5 min. A solution of (4*R*,5*S*, *S_R*)-4-methyl-5-phenyl-3-*[p*-phenyl]-2-isooxazolidinone (967 mg, 3.2 mmol) in THF (60 mL) was added and the reaction solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h, warmed to room temperature, and stirred for 36 h. The reaction solution was added to sat. NH_4Cl (50 mL), extracted with CH_2Cl_2 (3 x 50 mL), washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 303 mg (60%) of **289** as a white solid. mp $122 - 124\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} - 60.2$ (c 1 CH_2Cl_2); IR (CDCl_3) 3446 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.49 (s, 1H), 7.59 (m, 2H), 7.43 (m, 3H), 7.13 (d, $J = 8.9\text{ Hz}$, 1H), 6.92 (d, $J = 2.4\text{ Hz}$, 1H), 6.87 (dd, $J = 8.8, 2.4\text{ Hz}$, 1H), 3.77 (s, 3H), 3.65 (m, 2H), 2.95 (m, 2H), 1.82 (m, 2H), 1.68 (m, 2H), 0.82 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.3, 142.6, 131.8, 131.4, 129.9, 128.4, 126.4, 123.8, 121.5, 115.0, 112.0, 100.2, 61.8, 54.8, 31.8, 26.3, 24.9, 23.2, 17.3, -6.3; ESI m/z (relative intensity) 480.1 (M + Na, 100%); HRMS calcd for $\text{C}_{25}\text{H}_{35}\text{NO}_3\text{SiS}$ (M + Na), 480.2005, found 480.2007.



(*S_S*)-4-(5-methoxy-2-(phenylsulfinyl)-1*H*-indol-3-yl)butan-1-ol (290).

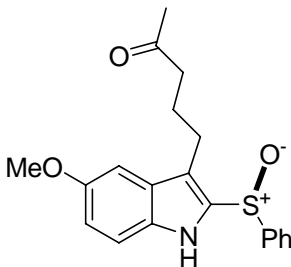
Sulfoxide **289** (303 mg, 0.66 mmol) was dissolved in THF (20 mL). TBAF (994 μL , 1M in THF, 0.99 mmol) was added, and the reaction solution was stirred for 15 h at room temperature. The reaction solution was added to water (10 mL), extracted with CH_2Cl_2

(3 x 10 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using ether and then 2% methanol in ether as the eluent to yield 165 mg (73%) of **290** as a white solid. mp 105 – 106 °C; [α]_D²⁵ - 54.1 (c 0.14 CH₂Cl₂); IR (CDCl₃) 3248 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 9.20 (s, 1H), 7.65 (m, 2H), 7.55 (m, 3H), 7.21 (d, *J* = 8.9 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.84 (s, 3H), 3.70 (t, *J* = 6.4 Hz, 2H), 3.01 (t, *J* = 7.3 Hz, 2H), 2.01 (s, 1H), 1.89 (m, 2H), 1.72 (m, 2H); ¹³C NMR (90 MHz, CDCl₃) δ 154.4, 143.4, 132.7, 132.6, 131.0, 129.4, 127.4, 124.8, 122.2, 116.1, 113.0, 101.3, 62.6, 55.9, 32.5, 27.0, 24.0; ESI *m/z* (relative intensity) 344.1 (M + H, 55%), 366.1 (M + Na, 100%); HRMS calcd for C₁₉H₂₂NO₃S (M + H), 344.1320, found 344.1301.



(*S*)-4-(5-Methoxy-2-(phenylsulfinyl)-1*H*-indol-3-yl)butanal (291). Alcohol **290** (295 mg, 0.86 mmol) was dissolved in CH₂Cl₂ (25 mL). Tetrapropylammonium perruthanate (124 mg, 0.35 mmol) and *N*-methyl morpholine *N*-oxide (352 mg, 3.00 mmol) were added and the mixture was stirred for 1 h at room temperature. The reaction solution was filtered through a plug of silica gel and concentrated in vacuo. The crude product was purified by flash chromatography using ether as the eluent to yield 226 mg (77%) of **291** as a pale yellow oil. IR (CDCl₃) 3441, 1728 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.78 (s, 1H), 8.66 (s, 1H), 7.95 (m, 2H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.53 (m, 2H),

7.33 (d, $J = 9.8$ Hz, 1H), 7.05 (m, 2H), 3.85 (s, 3H), 2.99 (m, 2H), 2.53 (m, 2H), 1.99 (m, 2H); ^{13}C NMR (90 MHz, CDCl_3) δ 202.2, 154.5, 143.5, 133.2, 132.6, 131.2, 129.6, 127.3, 125.1, 121.1, 116.4, 113.5, 101.0, 56.0, 43.4, 23.6, 23.2; APCI m/z (relative intensity) 343.1 (M + H, 100%); HRMS calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_3\text{S}$ (M + H), 342.1164, found 342.1174.

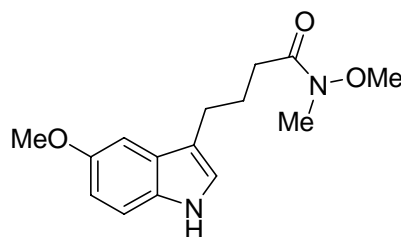


(*S*)-5-(5-Methoxy-2-(phenylsulfinyl)-1*H*-indol-3-yl)pentan-2-one (293).

Aldehyde **291** (55 mg, 0.16 mmol) was dissolved in THF (4 mL). Methyl magnesium bromide (77 μL , 3.0 M in ether, 1.4 mmol) was added and stirred for 45 min at room temperature. The reaction solution was added to sat. NH_4Cl (5 mL), extracted with ethyl acetate (3 x 5 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo to yield 54 mg (95%) of the crude alcohol.

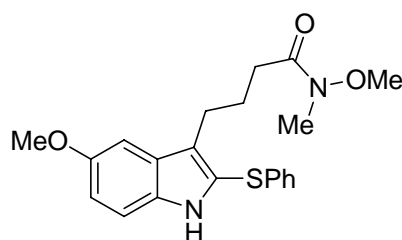
The crude alcohol (54 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (4 mL). Tetrapropylammonium perruthanate (11 mg, 0.031 mmol) and *N*-methyl morpholine *N*-oxide (32 mg, 0.27 mmol) were added and the mixture was stirred for 1 h at room temperature. The reaction solution was filtered through a plug of silica gel and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ethyl acetate in hexanes as the eluent to yield 28 mg (52%) of **293** as a white solid. The enantiomeric purity of the sample was found to be $> 98\%$ *ee* using (*S*)-(+)-2, 2, 2-trifluoro-1-(9-anthryl)ethanol as an ^1H NMR shift reagent. mp 154 – 156 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{25}$ -

139.8 (c 0.7 CH₂Cl₂); IR (CDCl₃) 3444, 1712 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.92 (s, 1H), 7.66 (m, 2H), 7.48 (m, 3H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.04 (d, *J* = 2.1 Hz, 1H), 6.94 (dd, *J* = 7.9, 2.4 Hz, 1H), 3.85 (s, 3H), 3.02 (m, 2H), 2.54 (m, 2H), 2.14 (s, 3H), 2.04 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 208.8, 154.6, 143.6, 133.0, 132.8, 131.2, 129.6, 127.5, 125.0, 121.6, 116.5, 113.3, 101.2, 56.0, 42.9, 30.3, 24.6, 23.6; ESI *m/z* (relative intensity) 356.1 (M + H, 100%); HRMS calcd for C₂₀H₂₂NO₃S (M + H), 356.1320, found 356.1315.



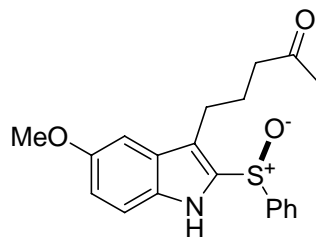
***N*-Methoxy-4-(5-methoxy-1*H*-indol-3-yl)-*N*-methylbutanamide (300).** 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (761 mg, 4.90 mmol) was added in small portions over 3 h to a solution of *N,O*-dimethyl hydroxyl amine hydrochloride (388 mg, 4.00 mmol), DMAP (490 mg, 4.02 mmol), and 5-methoxy-3-indolebutyric acid (880 mg, 3.61 mmol) in CH₂Cl₂ (36 mL). The reaction solution was stirred for 15 h at room temperature. The reaction solution was added to water (30 mL), extracted with CH₂Cl₂ (3 x 30 mL), washed with sat. NaHCO₃ (25 mL) and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 33% ethyl acetate in hexanes as the eluent to yield 603 mg (60%) of **300** as a brown oil. IR (thin film) 3410, 1641 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.46 (s, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.91 (d, *J* = 1.9 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.83 (s, 3H), 3.60 (s, 3H), 3.16 (s, 3H), 2.85 (t, *J*

= 6.8 Hz, 2H), 2.60 (m, 2H), 2.09 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.9, 131.7, 128.0, 127.8, 122.5, 115.7, 112.1, 112.0, 100.9, 61.3, 56.1, 53.6, 31.7, 24.9, 24.8; ESI m/z (relative intensity) 299.1 (M + H, 100%); HRMS calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_3$ (M + Na), 299.1372, found 299.1378.



***N*-Methoxy-4-(5-methoxy-2-(phenylthio)-1*H*-indol-3-yl)-*N*-**

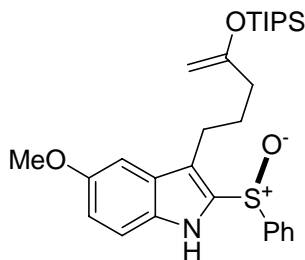
methylbutanamide (301). Phenylsulfenyl chloride (2.86 mL, 24.7 mmol) was added to a solution of **300** (5.85 g, 21.2 mmol) in 1.0 M HCl in 1,4-dioxane (100 mL). The reaction solution was stirred for 30 min at room temperature. The reaction solution was added to 1 M KOH (150 mL) and extracted with EtOAc (3 x 100 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 6.56 g (81%) of **300** as a yellow oil. IR (thin film) 3426, 1638 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.93 (s, 1H), 7.33 (m, 5H), 7.22 (d, $J = 1.4$ Hz, 1H), 7.16 (d, $J = 7.3$ Hz, 1H), 7.09 (dd, $J = 7.9, 1.5$ Hz, 1H), 3.91 (s, 3H), 3.57 (s, 3H), 3.17 (s, 3H), 2.99 (t, $J = 7.4$ Hz, 2H), 2.51 (t, $J = 7.0$ Hz, 2H), 2.09 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.3, 137.7, 132.5, 129.1, 128.1, 127.0, 126.4, 125.6, 123.1, 122.0, 114.1, 112.0, 100.1, 61.1, 60.5, 55.9, 31.0, 25.2, 24.5; ESI m/z (relative intensity) 407.1 (M + Na, 100%); HRMS calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$ (M + Na), 407.1405, found 407.1427.



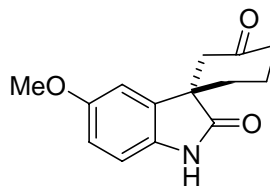
(*S_S*)-5-(5-Methoxy-2-(phenylsulfinyl)-1*H*-indol-3-yl)pentan-2-one (293).

Methyl magnesium bromide (17 mL, 3.0 M in ether, 51 mmol) was added to a solution of **301** (5.56 g, 17.1 mmol) in THF (150 mL) and the reaction solution was stirred at room temperature for 1 h. The reaction solution was added to sat. NH₄Cl (100 mL), extracted with ethyl acetate (3 x 100 mL), dried over Na₂SO₄, and concentrated to yield 4.732 g (82%) of **302** as a yellow solid.

8,8-Dichlorocamphorsulfonyloxaziridine (2.50 g, 8.4 mmol) was added to a solution of **302** (3.71 g, 10.9 mmol) in CH₂Cl₂ (150 mL), and the reaction solution was stirred at room temperature for 15 h. The reaction solution was concentrated, and the crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 2.727 g (92%) of **293** as a white solid. The enantiomeric purity of the sample was found to be > 98% *ee* using (*S*)-(+)-2, 2, 2-trifluoro-1-(9-anthryl)ethanol as an ¹H NMR shift reagent. The spectral data from **293** matched those described earlier for **293**, prepared by the route detailed in Figure 5.5. $[\alpha]_{\text{D}}^{25} - 139.8$ (c 0.7 CH₂Cl₂).



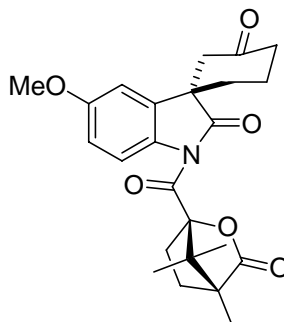
(*S_S*)-5-Methoxy-2-(phenylsulfinyl)-3-(4-(triisopropylsilyloxy)pent-4-enyl)-1*H*-indole (274). Diisopropylamine (3.45 mL, 24.6 mmol) was dissolved in THF (60 mL) and cooled in an ice bath. *n*-Butyllithium (3.32 mL, 1.93 M in hexanes, 25.0 mmol) was added, and the mixture was warmed to room temperature and stirred for 30 min. The solution of lithium diisopropylamide was added to a solution of ketone **293** (2.0 g, 5.6 mmol) in THF (60 mL) at -78 °C, and stirred at -78 °C for 1 h. 1,3-Dimethyl-3, 4, 5, 6-tetrahydro-2(1*H*)-pyrimidinone (15 mL) was added, followed by TIPSCl (3.32 mL, 15.5 mmol) after 10 min. The reaction solution was slowly warmed to room temperature over 2.5 h, and then was added to sat. NH₄Cl (60 mL), extracted with CH₂Cl₂ (3 x 60 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ethyl acetate in hexanes as the eluent to yield 1.91 g (66%) of silyl enol ether **274** as a yellow oil. $[\alpha]_D^{25}$ -47.7 (c 0.77 CH₂Cl₂); IR (CDCl₃) 3457, 1624 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.09 (s, 1H), 7.67 (m, 2H), 7.43 (m, 3H), 7.24 (d, *J* = 8.9 Hz, 1H), 6.96 (d, *J* = 2.2 Hz, 1H), 6.90 (dd, *J* = 8.9, 2.4 Hz, 1H), 4.11 (m, 1H), 4.09 (m, 1H), 3.82 (s, 3H), 3.05 (m, 2H), 2.25 (m, 2H), 2.05 (m, 2H), 1.11 (m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 159.0, 154.1, 143.7, 133.5, 131.8, 130.8, 129.3, 127.0, 125.0, 122.5, 116.1, 113.5, 100.9, 89.6, 55.8, 36.9, 28.7, 24.1, 18.2, 12.7; ESI *m/z* (relative intensity) 534.2 (M + Na, 100%); HRMS calcd for C₂₉H₄₁NO₃SSi (M + Na), 534.2474, found 534.2461.



(S)-5'-Methoxyspiro[cyclohexane-1,3'-indoline]-2',3-dione (316). Silyl enol ether **274** (39 mg, 0.076 mmol) was cooled to $-110\text{ }^{\circ}\text{C}$ in ether (18 mL). 2,6-Lutidine (26 μL , 0.19 mmol) followed by trifluoromethanesulfonic anhydride (26 μL , 0.15 mmol) were added and the reaction solution was stirred at $-110\text{ }^{\circ}\text{C}$ for 1 h. Water (20 mL) was added to the reaction solution, and the mixture was warmed to room temperature. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The thioimide was recovered as a yellowish-orange residue which was used immediately.

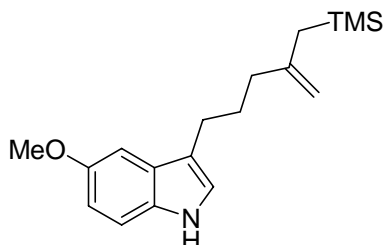
The crude thioimide and mercury (II) chloride (32 mg, 0.12 mmol) were stirred for 16 h at room temperature in acetonitrile/water (4 mL, 1/1). Water (5 mL) was added to the reaction solution, the layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 5 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using ether as the eluent to yield 6.0 mg (33%, 2 steps) of **316** as a tan solid. The enantiomeric purity of the sample was found to be $> 98\%$ *ee* using (*S*)-(+)-2, 2, 2-trifluoro-1-(9-anthryl)ethanol as an ^1H NMR shift reagent. mp $178 - 180\text{ }^{\circ}\text{C}$; $[\alpha]_D^{25} -30.873$ (c 0.30 CH_2Cl_2); IR (CDCl_3) 3438, 1720 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 9.17 (s, 1H), 6.86 (d, $J = 8.2$ Hz, 1H), 6.75 (m, 2H), 3.75 (s, 3H), 2.71 (d, $J = 14.4$ Hz, 1H), 2.59 (m, 2H), 2.39 (m, 2H), 2.13 (m, 2H), 1.88 (d, $J = 9.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.2, 181.1, 155.9, 134.4, 133.5, 112.7,

111.4, 110.9, 56.0, 51.9, 46.4, 40.7, 32.8, 21.7; ESI m/z (relative intensity) 246.1 (M + H, 100%); HRMS calcd for C₁₄H₁₅NO₃ (M + H), 246.1130, found 246.1120.



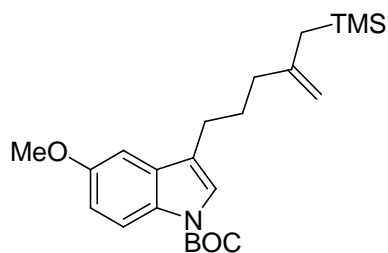
(1S)-5'-methoxy-1'-(4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyl)spiro[cyclohexane-1,3'-indoline]-2',3-dione (320). Sodium hydride (60% dispersion on mineral oil, 18 mg, 0.45 mmol) was added to oxindole **316** (50 mg, 0.20 mmol, 40% ee) in THF (6 mL), and stirred for 90 min at room temperature. (1S,4R)-(-)-camphanoyl chloride (69 mg, 0.33 mmol) was added and the reaction solution was stirred for 15 h at room temperature. The reaction solution was added to water (10 mL), extracted with CH₂Cl₂ (3 x 10 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude products were purified by flash chromatography using 40% ethyl acetate in cyclohexane as the eluent to yield 24 mg (28%) of the major diastereomer and 17 mg (20%) of a mixture of diastereomers (2:1 major:minor). Crystals of major diastereomer **320** that were suitable for X-ray crystallographic analysis were obtained by vapor diffusion crystallization with THF and hexane. mp 74 °C; [α]_D²⁵ - 99.7 (c 0.25 CH₂Cl₂); IR (CDCl₃) 1790, 1716 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, J = 8.9 Hz, 1H), 6.84 (dd, J = 8.9, 2.6 Hz, 1H), 6.75 (d, J = 2.6 Hz, 1H), 3.81 (s, 3H), 2.93 (m, 1H), 2.7 – 2.5 (m, 4H), 2.2 – 1.7 (m, 7H), 1.29 (s, 3H), 1.10 (s, 3H), 0.93 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 208.0, 178.0, 177.9, 170.9, 157.6, 133.6, 131.5, 115.5, 113.2,

110.2, 57.3, 56.0, 54.7, 51.6, 45.8, 40.4, 34.4, 30.9, 29.8, 28.5, 21.2, 17.9, 16.8, 9.9; ESI m/z (relative intensity) 448.2 (M + Na, 100%); HRMS calcd for C₂₄H₂₇NO₆ (M + Na) 448.1736, found 448.1721.

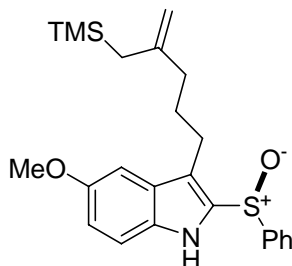


5-Methoxy-3-(4-((trimethylsilyl)methyl)pent-4-enyl)-1H-indole (283). Cerium (III) chloride (12.43 g, 50.7 mmol) was stirred for 15 h in THF (50 mL). The mixture was cooled to -78 °C, and (trimethylsilylmethyl)lithium (53.5 mL, 1.0 M in pentane, 53.5 mmol) was added and stirring was continued at -78 °C for 1 h. Ester **282** (2.4 g, 9.7 mmol) in THF (100 mL) was added, the reaction solution was slowly warmed to room temperature, and held there with stirring for 15 h. The reaction solution was then added to water (100 mL), extracted with ethyl acetate (3 x 75 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. A colorless oil was recovered which was dissolved in CH₂Cl₂ (400 mL). Silica gel was added and stirring was continued for 2 h. The reaction solution was concentrated in vacuo and the residue purified by flash chromatography using 40% ether in hexanes as the eluent to yield 1.00 g (35%) of the allylsilane as a yellow oil. IR (CDCl₃) 3482, 1630 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.81 (s, 1H), 7.19 (d, *J* = 6.7 Hz, 1H), 7.04 (d, *J* = 2.2 Hz, 1H), 6.91 (d, *J* = 1.4 Hz, 1H), 6.85 (dd, *J* = 6.8, 2.3 Hz, 1H), 4.63 (s, 1H), 4.54 (s, 1H), 3.85 (s, 3H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.09 (t, *J* = 7.4 Hz, 2H), 1.88 (m, 2H), 1.55 (s, 2H), 0.00 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 153.9, 147.8, 131.7, 128.1, 122.2, 116.7, 112.1, 111.9, 107.2, 101.1, 56.1, 38.3, 28.3, 27.0, 25.0,

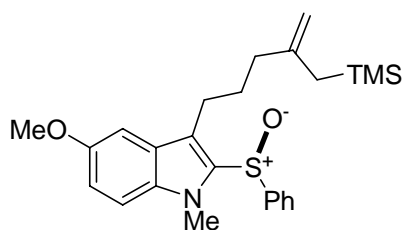
-1.1; ESI m/z (relative intensity) 324.2 (M + Na, 10%); HRMS calcd for C₁₈H₂₇NOSi (M + Na) 324.1760, found 324.1769.



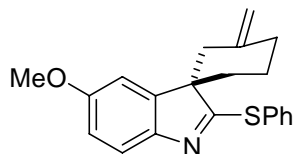
tert-Butyl 5-Methoxy-3-(4-((trimethylsilyl)methyl)pent-4-enyl)-1H-indole-1-carboxylate (284). Indole **283** (333 mg, 1.11 mmol) was dissolved in CH₂Cl₂ (25 mL). BOC₂O (325 mg, 1.5 mmol) and DMAP (183 mg, 1.5 mmol) were added and the reaction solution was stirred for 70 min at room temperature. The reaction solution was added to water (25 mL), extracted with CH₂Cl₂ (3 x 25 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 20% ether in hexanes as the eluent to yield 326 mg (73%) of **284** as a colorless oil. IR (CDCl₃) 1721, 1601 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.01 (s, 1H), 7.34 (s, 1H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.65 (s, 1H), 4.58 (s, 1H), 3.88 (s, 3H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.12 (t, *J* = 6.7 Hz, 2H), 1.91 (m, 2H), 1.67 (s, 9H), 1.57 (s, 2H), 0.03 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.9, 150.0, 147.4, 131.8, 123.2, 121.2, 116.1, 115.8, 112.8, 107.5, 102.2, 83.2, 55.9, 38.1, 28.4, 27.3, 27.0, 24.7, -1.1; ESI m/z (relative intensity) 424.2 (M + Na, 100%); HRMS calcd for C₂₃H₃₅NO₃Si (M + Na) 424.2284, found 424.2250.



(*S,S*)-5-Methoxy-2-(phenylsulfinyl)-3-(4-((trimethylsilyl)methyl)pent-4-enyl)-1*H*-indole (275). Allylsilane **284** (880 mg, 2.19 mmol) was cooled to $-78\text{ }^{\circ}\text{C}$ in THF (60 mL). *s*-BuLi (3.5 mL, 1.4 M in cyclohexane, 4.9 mmol) was added and the stirred for 5 min. A solution of (4*R*,5*S*, *S**R*)-4-methyl-5-phenyl-3-[*p*-phenyl]-2-isooxazolidinone (2.88 g, 9.6 mmol) in THF (120 mL) was added, the solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h, warmed to room temperature, and stirring was continued for 15 h. The reaction solution was added to sat. NH_4Cl (100 mL), extracted with CH_2Cl_2 (3 x 100 mL), washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 650 mg (70%) of **275** as a white solid. mp $102 - 103\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} - 54.8$ (c 0.17 CH_2Cl_2); IR (CDCl_3) $3447, 1764\text{ cm}^{-1}$; ^1H NMR (300 MHz, CDCl_3) δ 8.79 (s, 1H), 7.67 (m, 2H), 7.49 (m, 3H), 7.22 (d, $J = 8.9\text{ Hz}$, 1H), 7.00 (d, $J = 2.3\text{ Hz}$, 1H), 6.94 (dd, $J = 8.9, 2.3\text{ Hz}$, 1H), 4.65 (d, $J = 1.8\text{ Hz}$, 1H), 4.58 (m, 1H), 3.84 (s, 3H), 2.99 (t, $J = 8.3\text{ Hz}$, 2H), 2.12 (t, $J = 7.6\text{ Hz}$, 2H), 1.99 (m, 2H), 1.55 (s, 2H), 0.01 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 154.5, 147.1, 131.1, 129.9, 129.6, 128.9, 126.1, 126.1, 125.3, 125.0, 116.2, 113.2, 107.6, 101.4, 56.0, 38.2, 29.3, 27.1, 24.2, -1.1; ESI m/z (relative intensity) 448.2 (M + Na, 100%); HRMS calcd for $\text{C}_{24}\text{H}_{31}\text{NO}_2\text{SSi}$ (M + Na) 448.1742, found 448.1735.

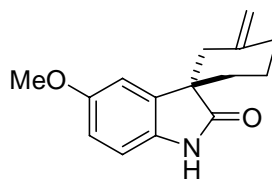


(*S_S*)-5-Methoxy-1-methyl-2-(phenylsulfinyl)-3-(4-(trimethylsilyl)methyl)pent-4-enyl-1*H*-indole (276). Allylsilane **275** (26 mg, 0.064 mmol) was cooled in an ice bath in THF (2 mL). Lithium bis(trimethylsilylamide) (63 μ L, 1.0 M in THF, 0.063 mmol) was added, and the reaction solution was stirred at 0 °C for 30 min. Methyl iodide (18 μ L, 0.29 mmol) was added and the reaction solution was warmed to room temperature and stirred for 3 h. The reaction solution was then added to water (2 mL) and extracted with CH₂Cl₂ (3 x 3 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 15 mg (56%) of **276** as a colorless oil. $[\alpha]_D^{25}$ - 60.9 (c 0.38 CH₂Cl₂); IR 1721 (CDCl₃) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.51 (m, 5H), 7.14 (d, *J* = 8.9 Hz, 1H), 7.07 (d, *J* = 2.3 Hz, 1H), 7.03 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.67 (s, 1H), 4.59 (s, 1H), 3.87 (s, 3H), 3.47 (s, 3H), 3.08 (t, *J* = 7.9 Hz, 2H), 2.16 (t, *J* = 7.4 Hz, 2H), 1.98 (m, 2H), 1.56 (s, 2H), 0.01 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 154.4, 147.2, 145.5, 143.7, 135.0, 130.2, 129.4, 126.2, 125.2, 125.1, 116.7, 110.8, 107.7, 101.6, 56.1, 38.3, 31.0, 30.1, 27.1, 24.3, -1.1; ESI *m/z* (relative intensity) 462.2 (M + Na, 100%); HRMS calcd for C₂₅H₃₃NO₂SSi (M + Na) 462.1899, found 462.1891.



(S)-5'-Methoxy-3-methylene-2'-(phenylthio)spiro[cyclohexane-1,3'-indole]

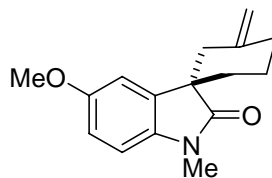
(307). Allylsilane **275** (70 mg, 0.16 mmol) was cooled to $-78\text{ }^{\circ}\text{C}$ in toluene (20 mL). 2,6-Lutidine (58 μL , 0.49 mmol) followed by trifluoromethanesulfonic anhydride (58 μL , 0.34 mmol) were added and the reaction solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. Water (10 mL) was added to the reaction solution, and warmed to room temperature. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 10% ether in hexanes as the eluent to yield 23 mg (42%) of **307** as a colorless oil. $[\alpha]_D^{25} -33.6$ (c 1 CH_2Cl_2); IR (CDCl_3) 1591 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.67 (m, 2H), 7.45 (m, 3H), 7.33 (d, $J = 8.6\text{ Hz}$, 1H), 7.08 (d, $J = 2.5\text{ Hz}$, 1H), 6.80 (dd, $J = 8.5, 2.5\text{ Hz}$, 1H), 4.96 (s, 1H), 4.69 (s, 1H), 3.78 (s, 3H), 2.71 (d, $J = 13.2\text{ Hz}$, 1H), 2.57 (m, 1H), 2.32 (m, 1H), 2.11 (m, 1H), 2.04 (m, 1H), 1.96 (m, 1H), 1.52 (m, 1H), 1.26 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 183.3, 156.4, 148.4, 145.4, 143.7, 134.5, 129.5, 129.1, 129.0, 119.8, 112.0, 111.8, 111.7, 60.3, 55.9, 41.6, 34.2, 33.9, 22.8; m/z (relative intensity) 336.1 (M + H, 100%); HRMS calcd for $\text{C}_{21}\text{H}_{21}\text{NOS}$ (M + H) 336.1422, found 336.1396.



(S)-5'-Methoxy-3-methylenespiro[cyclohexane-1,3'-indolin]-2'-one (308).

From oxindole **316**. Tebbe's reagent (800 μ L, 0.5 M in toluene, 0.4 mmol) was added to oxindole **316** (33 mg, 0.13 mmol) at -78 °C in THF (3 mL), and stirred at -78 °C for 1 h. The reaction solution was warmed to 0 °C and stirred at that temperature for 45 min. 1 M NaOH was added slowly until gas evolution ceased and the remaining mixture was stirred for 90 min and then filtered over Celite. The aqueous layer was removed, and the organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 9 mg (27%) of **308** as colorless oil. $[\alpha]_D^{25}$ - 29.8 (c 0.45 CH₂Cl₂); IR (thin film) 3414, 1705 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.63 (s, 1H), 7.06 (d, *J* = 2.5 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.76 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.92 (d, *J* = 1.7 Hz, 1H), 4.69 (d, *J* = 1.5 Hz, 1H), 3.77 (s, 3H), 2.66 (d, *J* = 13.5 Hz, 1H), 2.53 (m, 1H), 2.29 (m, 1H), 2.27 (m, 1H), 2.05 (m, 3H), 1.82 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 181.7, 155.3, 144.3, 136.0, 133.2, 131.1, 129.1, 111.4, 109.7, 56.0, 50.1, 40.6, 34.2, 33.1, 22.6; ESI *m/z* (relative intensity) 266.1 (M + Na, 100%); HRMS calcd for C₁₅H₁₇NO₂ (M + Na) 266.1157, found 266.1180.

From thioimide **307**. Thioimide **307** (23 mg, 0.069 mmol) and ceric ammonium nitrate (38 mg, 0.069 mmol) were stirred for 15 h in acetonitrile/water (4 mL, 5/1) at room temperature. Water (5 mL) was added to the reaction solution, the layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 14 mg (82%) of **307** as colorless oil. $[\alpha]_D^{25}$ - 10.4 (c 0.74 CH₂Cl₂).

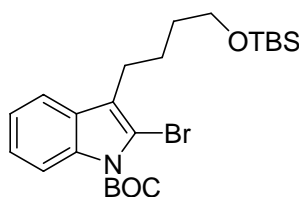


**(S)-5'-Methoxy-1'-methyl-3-methylenespiro[cyclohexane-1,3'-indolin]-2'-one
(309).**

From oxindole **308**: Oxindole **308** (14 mg, 0.058 mmol) was cooled in an ice bath in THF (3 mL). Lithium bis(trimethylsilylamide) (56 μ L, 1.0 M in THF, 0.056 mmol) was added, and the reaction solution was stirred at 0 °C for 30 min. Methyl iodide (18 μ L, 0.29 mmol) was added, the reaction solution was warmed to room temperature and stirred for 3 h. The reaction solution was added to water (2 mL) and extracted with CH₂Cl₂ (3 x 3 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes as the eluent to yield 9 mg (60%) of **309** as a colorless oil. The *ee* was determined to be 56% using (+)-Eu(tfc)₃. $[\alpha]_D^{25}$ -35.2 (c 0.07 CH₂Cl₂); IR (thin film) 1708 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.09 (d, *J* = 2.4 Hz, 1H), 6.82 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.91 (d, *J* = 1.5 Hz, 1H), 4.67 (d, *J* = 1.5 Hz, 1H), 3.78 (s, 3H), 3.20 (s, 3H), 2.67 (m, 1H), 2.51 (m, 1H), 2.33 (m, 1H), 2.10 (m, 1H), 2.02 (m, 1H), 1.93 (m, 2H), 1.50 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 179.7, 155.4, 144.5, 136.6, 135.6, 113.4, 111.3, 111.2, 108.0, 56.0, 49.7, 40.7, 34.2, 33.0, 29.6, 22.7; ESI *m/z* (relative intensity) 280.1 (M + Na, 100%); HRMS calcd for C₁₆H₁₉NO₂ (M + Na) 280.1313, found 280.1287.

From sulfoxide **276**: Allylsilane **276** (38 mg, 0.085 mmol) was cooled to -78 °C in acetonitrile (9 mL). 2,6-Lutidine (30 μ L, 0.26 mmol) followed by trifluoromethanesulfonic anhydride (30 μ L, 0.18 mmol) were added and the reaction

solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. Water (5 mL) was added to the reaction solution and the mixture was warmed to room temperature. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes as the eluent to yield 13 mg (59%) of **292** as a colorless oil. The *ee* was determined to be 32% using (+)-Eu(tfc)₃. $[\alpha]_{\text{D}}^{25} - 4.3$ (c 0.24 CH_2Cl_2)



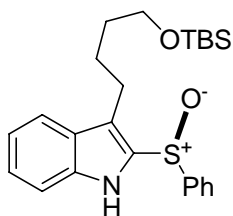
tert-Butyl 2-Bromo-3-(4-(tert-butyldimethylsilyloxy)butyl)-1H-indole-1-carboxylate (294). Methyl ester **275** (15 g, 69 mmol) and *N*-bromosuccinimide (12.3 g, 69 mmol) were stirred in CH_2Cl_2 (300 mL) for 45 min at room temperature and the reaction mixture was concentrated.

The crude 2-bromoindole, DMAP (10.7 g, 88 mmol), and BOC_2O (18.46 g, 85 mmol) were stirred in CH_2Cl_2 (500 mL) for 70 min at room temperature. The reaction solution was added to water (200 mL), extracted with CH_2Cl_2 (3 x 200 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo to give the BOC-protected indole as a brown oil.

DIBAL (280 mL, 1.0 M in hexanes, 280 mmol) was added to a solution of the crude BOC-protected indole in CH_2Cl_2 (300 mL) and THF (300 mL) at $-78\text{ }^{\circ}\text{C}$. The reaction solution was warmed to room temperature and held there with stirring for 15 h.

The reaction solution was added to sat. NH_4Cl (600 mL) and filtered to remove the aluminum salts. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo to yield the alcohol (24.73 g) as an orange oil which was used without purification.

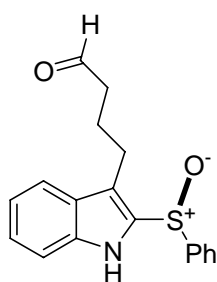
The crude alcohol (24.73 g) was dissolved in CH_2Cl_2 (600 mL). Imidazole (10.89 g, 147.3 mmol) and TBSCl (12.44 g, 82 mmol) were added and the reaction solution was stirred for 15 h at room temperature. The reaction solution was added to water (300 mL), extracted with CH_2Cl_2 (3 x 250 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 10% ether in hexanes as the eluent to yield 23.08 g of **294** (72%, 4 steps) as a reddish-orange oil. IR (CDCl_3) 1738 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.12 (m, 1H), 7.52 (m, 1H), 7.35 (m, 2H), 3.69 (t, $J = 6.1$ Hz, 2H), 2.80 (t, $J = 7.1$ Hz, 2H), 1.72 (m, 11H), 1.68 (m, 2H), 0.92 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 149.3, 136.8, 129.2, 124.4, 123.7, 122.9, 118.5, 115.5, 108.9, 84.7, 63.0, 32.7, 28.4, 26.2, 25.4, 25.2, 18.5, -5.1; ESI m/z (relative intensity) 504.2 (M + Na, 100%), 506.2 (^{81}Br , 95%); HRMS calcd for $\text{C}_{23}\text{H}_{36}\text{BrNO}_3\text{Si}$ (M + Na) 504.1546, found 504.1539.



(*S*)-3-(4-(*tert*-Butyldimethylsilyloxy)butyl)-2-(phenylsulfinyl)-1*H*-indole

(295). Bromide **294** (3.19 g, 6.6 mmol) was dissolved in THF (20 mL), and cooled to –

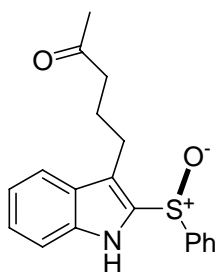
78 °C. *t*-BuLi (9.14 mL, 1.6 M in pentane, 15 mmol) was added and the reaction solution was stirred for 5 min at that temperature. A solution of (4*R*,5*S*, *S_R*)-4-methyl-5-phenyl-3-[*p*-phenyl]-2-isooxazolidinone (2.95 g, 9.8 mmol) in THF (400 mL) was added and the mixture was stirred at - 78 °C for 2 h, warmed to room temperature, and stirred for an additional 15 h. The reaction solution was added to sat. NH₄Cl (150 mL), extracted with CH₂Cl₂ (3 x 150 mL), washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 1.68 g (60%) of **295** as a white solid. mp 92 - 94 °C; [α]²⁵_D - 30.6 (c 0.465 CH₂Cl₂); IR (thin film) 3446 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.25 (s, 1H), 7.71 (m, 2H), 7.64 (m, 1H), 7.44 (m, 4H), 7.23 (m, 1H), 7.14 (m, 1H), 3.74 (m, 2H), 3.10 (m, 2H), 1.88 (m, 2H), 1.73 (m, 2H), 0.95 (s, 9H), 0.10 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 143.5, 138.0, 131.3, 130.7, 129.2, 128.6, 126.7, 124.9, 122.6, 120.1, 119.7, 112.4, 62.7, 32.7, 27.5, 25.9, 24.2, 18.2, -5.3; ESI *m/z* (relative intensity) 450.2 (M + Na, 100%); HRMS calcd for C₂₄H₃₃NO₂SiS (M + Na) 450.1899, found 450.1907.



(*S_S*)-4-(2-(Phenylsulfinyl)-1*H*-indol-3-yl)butanal (**297**). Silyl ether **295** (1.68 g, 3.9 mmol) was dissolved in THF (200 mL). TBAF (4.5 mL, 1.0 M in THF, 4.5 mmol) was added and the reaction solution was stirred for 15 h at room temperature. The

reaction solution was added to water (50 mL), extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo.

The crude alcohol from above was dissolved in CH₂Cl₂ (250 mL). Tetrapropylammonium perruthenate (281 mg, 0.80 mmol) and *N*-methyl morpholine *N*-oxide (402 mg, 3.4 mmol) were added and the mixture was stirred for 1 h. The reaction solution was filtered through a plug of silica gel and concentrated in vacuo. The crude product was purified by flash chromatography using ether as the eluent to yield 590 mg (49%, 2 steps) of **297** as a pale yellow oil. IR (thin film) 3215, 1719 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.83 (s, 1H), 9.75 (m, 1H), 7.66 (m, 3H), 7.43 (m, 3H), 7.33 (m, 1H), 7.25 (m, 1H), 7.10 (m, 1H), 3.07 (m, 2H), 2.54 (m, 2H), 2.09 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 202.1, 143.4, 137.9, 132.3, 131.2, 129.6, 127.0, 125.2, 125.1, 121.4, 120.4, 120.3, 112.6, 43.4, 23.7, 23.4; ESI *m/z* (relative intensity) 334.1 (M + Na, 100%); HRMS calcd for C₁₈H₁₇NO₂S (M + Na) 334.0877, found 334.0878.

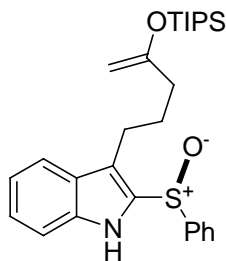


(*S*)-5-(2-(Phenylsulfinyl)-1*H*-indol-3-yl)pentan-2-one (299).

From aldehyde **297**: Aldehyde **297** (590 mg, 1.9 mmol) was dissolved in THF (45 mL). Methyl magnesium bromide (910 μL, 3.0 M in ether, 2.7 mmol) was added and the mixture was stirred for 1 h at room temperature. The reaction solution was added to sat. NH₄Cl (15 mL), extracted with ethyl acetate (3 x 15 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo.

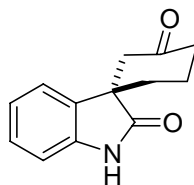
The crude alcohol was dissolved in CH_2Cl_2 (100 mL). Tetrapropylammonium perruthenate (135 mg, 0.39 mmol) and *N*-methyl morpholine *N*-oxide (193 mg, 1.65 mmol) were added and the mixture was stirred for 1 h. The reaction solution was filtered through a plug of silica gel and concentrated in vacuo. The crude product was purified by flash chromatography using ether as the eluent to yield 173 mg (28%, 2 steps) of **299** as a white solid. Spectral data matched those for the racemic mixture.⁶⁵ The enantiomeric purity of the sample was found to be > 98% *ee* using (*S*)-(+)-2, 2, 2-trifluoro-1-(9-anthryl)ethanol as an ¹H NMR shift reagent. $[\alpha]_{\text{D}}^{25} - 127.3$ (c 1.16 CH_2Cl_2)

From ketone **304**: 8,8-Dichlorocamphorsulfonyloxaziridine (4.18 g, 13.5 mmol) was added to a solution of the known ketone **304**⁶⁵ (4.83 g, 16.2 mmol) in CH_2Cl_2 (180 mL), and the reaction solution was stirred at room temperature for 15 h. The reaction solution was concentrated, and the crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 3.64 g (83%) of **299** as a white solid. The enantiomeric purity of the sample was found to be > 98% *ee* using (*S*)-(+)-2, 2, 2-trifluoro-1-(9-anthryl)ethanol as an ¹H NMR shift reagent. Spectral data matched those for the racemic mixture.⁶⁵ $[\alpha]_{\text{D}}^{25} - 128.0$ (c 1.0 CHCl_3)⁷⁰



(*S_s*)-2-(Phenylsulfinyl)-3-(4-(triisopropylsilyloxy)pent-4-enyl)-1*H*-indole

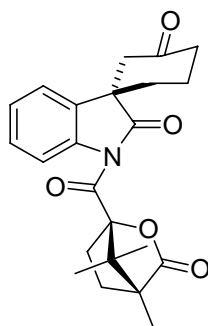
(136). Diisopropylamine (5.68 mL, 40.5 mmol) was dissolved in THF (100 mL) and cooled in an ice bath. *n*-Butyllithium (23.0 mL, 1.8 M in hexanes, 41.4 mmol) was added and the solution was warmed to room temperature and stirred for 30 min. This solution of lithium diisopropylamide was added to a solution of ketone **299** (3.0 g, 9.2 mmol) in THF (100 mL) at -78 °C, and stirred at -78 °C for 1 h. 1,3-Dimethyl-3, 4, 5, 6-tetrahydro-2(1*H*)-pyrimidinone (25 mL) was added, followed by TIPSCl (5.47 mL, 25.6 mmol) after 10 min. The reaction solution was slowly warmed to room temperature over 2.5 h. The reaction solution was added to sat. NH₄Cl (100 mL), extracted with CH₂Cl₂ (3 x 100 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ethyl acetate in hexanes as the eluent to yield 3.1 g (70%) of silyl enol ether **136** as a yellow oil. Spectral data matched those for the racemic mixture.⁶⁵ $[\alpha]_D^{25} - 13.9$ (c 0.77 CH₂Cl₂);



(*S*)-Spiro[cyclohexane-1,3'-indoline]-2',3-dione (318). Silyl enol ether **136** (43 mg, 0.089 mmol) was cooled to -110 °C in ether (21 mL). 2,6-Lutidine (31 μL, 0.27 mmol) followed by trifluoromethanesulfonic anhydride (31 μL, 0.18 mmol) were added

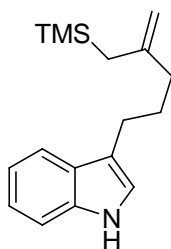
and the reaction solution was stirred at $-110\text{ }^{\circ}\text{C}$ for 2 h. Water (10 mL) was added to the reaction solution and the mixture was warmed to room temperature. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The thioimide was recovered as a yellowish-orange residue which was used immediately.

The crude thioimide and mercury (II) chloride (36 mg, 0.13 mmol) were stirred for 72 h in acetonitrile/water (2 mL, 1/1) at room temperature. Water (2 mL) was added to the reaction solution, the layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 5 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using ether as the eluent to yield 11 mg (58%) of **318** as a white solid. The enantiomeric purity of the sample was found to be $> 98\%$ *ee* using (*S*)-(+)-2, 2, 2-trifluoro-1-(9-anthryl)ethanol. Spectral data matched those for the racemic mixture.⁶⁵ $[\alpha]_{\text{D}}^{25} -43.6$ (c 0.105 CH_2Cl_2).



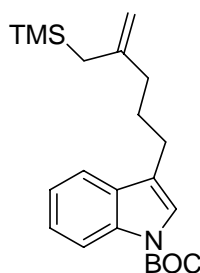
(1*S*)-1'-(4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyl)spiro[cyclohexane-1,3'-indoline]-2',3-dione (322). Sodium hydride (60% dispersion in mineral oil, 20 mg, 0.5 mmol) was added to oxindole **318** (47 mg, 0.19 mmol, 68% *ee*) in THF (7 mL), and stirred for 30 min. (*1*S*,4*R**)-(-)-camphanoyl chloride (75 mg, 0.35 mmol) was added and the reaction solution was stirred for 15 h. The

reaction solution was added to water (10 mL), extracted with CH₂Cl₂ (3 x 10 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude products were purified by flash chromatography using 25% ethyl acetate in cyclohexane as the eluent to yield 27 mg (36%) of the major diastereomer, and 10 mg (13%) of a mixture of diastereomers (4:3 major: minor). Crystals of the major diastereomer suitable for X-ray crystallographic analysis were obtained by vapor diffusion crystallization with dimethoxyethane and hexane. mp 82 - 84 °C; $[\alpha]_D^{25}$ -73.2 (c 0.11 CH₂Cl₂); IR (KBr) 1792, 1717 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.73 (d, *J* = 8.3 Hz, 1H), 7.35, (td *J* = 7.9, 2.6 Hz, 1H), 7.21 (m, 2H), 2.94 (m, 1H), 2.71 (d, *J* = 14.6 Hz, 1H), 2.55 (m, 2H), 2.39 (m, 2H), 2.24 (m, 1H), 2.14 (m, 1H), 2.06 (dd, *J* = 9.6, 3.8 Hz, 1H), 1.98 (m, 2H), 1.82 (m, 1H), 1.29 (s, 3H), 1.10 (s, 3H), 0.93 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 208.2, 178.2, 177.8, 171.6, 138.0, 132.2, 129.0, 125.5, 123.5, 114.2, 93.2, 57.5, 54.8, 51.4, 45.8, 40.5, 34.3, 31.0, 29.8, 21.2, 17.9, 16.8, 9.9; ESI *m/z* (relative intensity) 418.2 (M + Na, 100%); HRMS calcd for C₂₃H₂₅NO₆ (M + Na) 418.1630, found 418.1660.



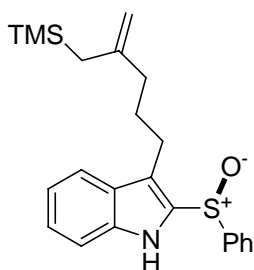
3-(4-((Trimethylsilyl)methyl)pent-4-enyl)-1H-indole (286). Cerium (III) chloride (32.7 g, 133 mmol) was stirred for 15 h in THF (450 mL) at room temperature. This mixture was cooled to -78 °C, and (trimethylsilylmethyl)lithium (138 mL, 1.0 M in pentane, 138 mmol) was added and the solution was stirred for 1 h. Ester **285** (5.36 g, 24.7 mmol) in THF (200 mL) was added and the reaction solution was warmed to room

temperature and held there with stirring for 15 h. The reaction solution was added to water (200 mL), extracted with ethyl acetate (3 x 100 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. A colorless oil was recovered which was dissolved in CH₂Cl₂ (500 mL). Silica gel was added and this mixture was stirred for 2 h, concentrated in vacuo, and purified by flash chromatography using 40% ether in hexanes as the eluent to yield 2.79 g (42%) of the allylsilane as a yellow oil. IR (thin film) 3482, 1602 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.85 (s, 1H), 7.62 (m, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.34 (m, 2H), 6.95 (s, 1H), 4.63 (m, 1H), 4.54 (m, 1H), 2.77 (m, 2H), 2.07 (m, 2H), 1.88 (m, 2H), 1.55 (s, 2H), -0.02 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 147.7, 136.4, 127.7, 121.9, 121.3, 119.2, 119.1, 116.8, 111.3, 107.3, 38.3, 28.4, 27.0, 25.0, -1.1; ESI *m/z* (relative intensity) 272.1 (M + H, 100%); HRMS calcd for C₁₇H₂₅NSi (M + H) 272.1835, found 272.1831.



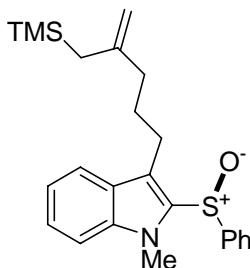
***tert*-Butyl -3-(4-((Trimethylsilyl)methyl)pent-4-enyl)-1*H*-indole-1-carboxylate (287).** Indole **286** (2.79 g, 10.3 mmol) was dissolved in CH₂Cl₂ (125 mL). BOC₂O (3.0 g, 13.8 mmol) and DMAP (1.70 mg, 13.9 mmol) were added and the reaction solution was stirred for 70 min at room temperature. The reaction solution was added to water (50 mL), extracted with CH₂Cl₂ (3 x 50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 10% ether in hexanes as the eluent to yield 3.97 g (100%) of **287** as a colorless oil. IR (thin film)

1719, 1602 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.11 (bs, 1H),⁸³ 7.51 (m, 1H), 7.35 (s, 1H), 7.31 (m, 1H), 7.23 (m, 1H), 4.63 (m, 1H), 4.55 (m, 1H), 2.69 (t, $J = 8.0$ Hz, 2H), 2.09 (t, $J = 7.4$ Hz, 2H), 1.90 (m, 2H), 1.64 (s, 9H), 1.53 (s, 2H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 149.9, 147.1, 136.3, 131.2, 124.6, 122.6, 122.6, 121.3, 119.3, 115.8, 107.8, 82.7, 38.3, 28.1, 27.7, 26.9, 24.8, -1.2; ESI m/z (relative intensity) 394.2 (M + Na, 30%); HRMS calcd for $\text{C}_{22}\text{H}_{33}\text{NO}_2\text{Si}$ (M + Na) 394.2178, found 394.2184.

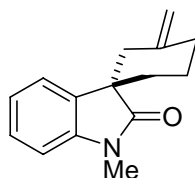


(*S_S*)-2-(Phenylsulfinyl)-3-(4-((trimethylsilyl)methyl)pent-4-enyl)-1H-indole

(131). Allylsilane **287** (1.30 g, 3.5 mmol) was cooled to -78 °C in THF (100 mL). *s*-BuLi (5.6 mL, 1.3 M in cyclohexane, 7.3 mmol) was added and the solution was stirred for 5 min. A solution of (4*R*,5*S*, *S_R*)-4-methyl-5-phenyl-3-[*p*-phenyl]-2-isooxazolidinone (2.30 g, 7.6 mmol) in THF (200 mL) was added and the mixture was stirred at -78 °C for 2 h, warmed to room temperature, and stirred for an additional 15 h. The reaction solution was added to sat. NH_4Cl (100 mL), extracted with CH_2Cl_2 (3 x 100 mL), washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 1.177 g (85%) of **131** as a white solid. Spectral data matched those for the racemic mixture.⁶⁵ $[\alpha]_{\text{D}}^{25} - 29.9$ (c 0.37 CH_2Cl_2).



(*S*)-1-Methyl-2-(phenylsulfinyl)-3-(4-((trimethylsilyl)methyl)pent-4-enyl)-1*H*-indole (134). Allylsilane **131** (287 mg, 0.75 mmol) was cooled in an ice bath in THF (22 mL). Lithium bis(trimethylsilylamide) (1.31 mL, 1.0 M in THF, 1.31 mmol) was added, and the reaction solution was stirred at 0 °C for 30 min. Methyl iodide (340 μ L, 5.5 mmol) was added, the reaction solution was warmed to room temperature and held there with stirring for 15 h. The reaction solution was added to water (20 mL) and extracted with CH₂Cl₂ (3 x 30 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 205 mg (67%) of **134** as a white solid. Spectral data matched those for the racemic mixture.⁶⁵ $[\alpha]_D^{25}$ - 103.2 (c 1.36 CH₂Cl₂)



(*S*)-1'-methyl-3-methylenespiro[cyclohexane-1,3'-indolin]-2'-one (312).

From allylsilane **131**: Allylsilane **131** (40 mg, 0.10 mmol) was cooled to -78 °C in toluene (10 mL). 2,6-Lutidine (36 μ L, 0.30 mmol) followed by trifluoromethanesulfonic anhydride (34 μ L, 0.20 mmol) were added and the reaction solution was stirred at -78 °C for 30 min. Water (10 mL) was added to the reaction

solution, and the mixture was warmed to room temperature. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo.

The crude thioimide **310** and ceric ammonium nitrate (55 mg, 0.10 mmol) were stirred in acetonitrile/water (4.2 mL, 6/1) for 15 h at room temperature. Water (5 mL) was added to the reaction solution, the layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 10 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo.

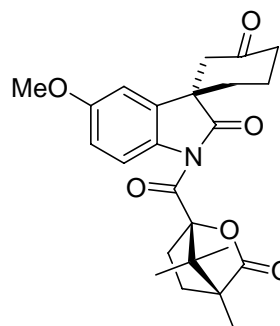
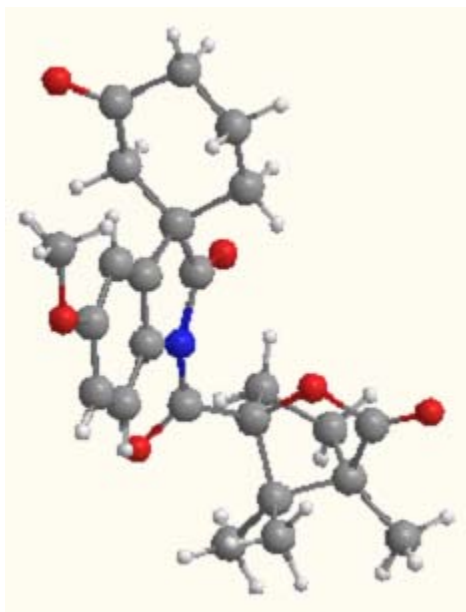
The crude oxindole **311** (8 mg, 0.038 mmol) was cooled in an ice bath in THF (1 mL). Lithium bis(trimethylsilylamide) (40 μL, 1.0 M in THF, 0.040 mmol) was added and the reaction solution was stirred at 0 °C for 30 min. Methyl iodide (10 μL, 0.16 mmol) was added and the reaction solution was warmed to room temperature and held at that temperature with stirring for 3 h. The reaction solution was added to water (2 mL) and extracted with CH₂Cl₂ (3 x 3 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes as the eluent to yield 3.5 mg (18%, 3 steps) of **312** as a colorless oil. The *ee* was determined to be 58% using (+)-Eu(tfc)₃. Spectral data matched those for the racemic mixture.⁶⁵ $[\alpha]_D^{25} - 19.9$ (c 0.17 CH₂Cl₂)

From oxindole **318**. n-Butyllithium (36 μL, 2.4 M in hexanes, 0.086 mmol) was added to methyltriphenylphosphonium bromide (29 mg, 0.081 mmol) in THF (1 mL) and the solution was stirred for 5 min. Oxindole **318** (18 mg, 0.073 mmol) in THF (1 mL) was added and stirred for 24 h, and then the solution was brought to reflux and held there for 24 h. The reaction solution was added to water (5 mL), extracted with CH₂Cl₂

(3 x 5 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent to yield 6 mg (33%) of **311** as a white solid.

Oxindole **311** (6 mg, 0.028 mmol, 68% *ee*) was cooled in an ice bath in THF (1 mL). Lithium bis(trimethylsilylamide) (31 μ L, 1.0 M in THF, 0.031 mmol) was added and the reaction solution was stirred at 0 °C for 30 min. Methyl iodide (8 μ L, 0.12 mmol) was added and the reaction solution was warmed to room temperature and stirred for 90 min. The reaction solution was added to water (2 mL) and extracted with CH₂Cl₂ (3 x 3 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to yield 6 mg (94%) of **312** as a colorless oil. The *ee* was determined to be 68% using (+)-Eu(tfc)₃.

From allylsilane **134**: Allylsilane **134** (34 mg, 0.083 mmol) was cooled to -78 °C in acetonitrile (8 mL). 2,6-Lutidine (29 μ L, 0.25 mmol) followed by trifluoromethanesulfonic anhydride (29 μ L, 0.17 mmol) were added and the reaction solution was stirred at -78 °C for 30 min. Water (5 mL) was added to the reaction solution and the mixture was warmed to room temperature. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 5 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes as the eluent to yield 12 mg (63%) of **312** as a colorless oil. The *ee* was determined to be 46% using (+)-Eu(tfc)₃.

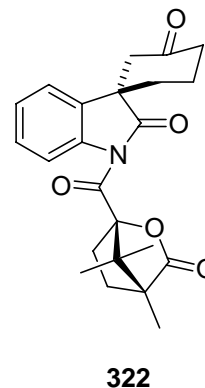
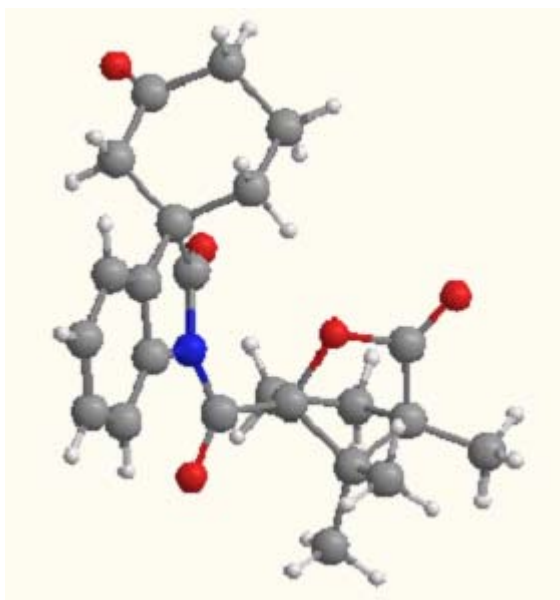
**320**

A colourless brick shaped crystal of agk1 (C₂₄ H₂₇ N O₆) with approximate dimensions 0.10 x 0.30 x 0.35 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 142(2) K, cooled by Rigaku-MSX X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoK α fine-focus sealed tube ($\lambda = 0.71073\text{\AA}$) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3° in ω and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Orthorhombic unit cell yielded a total of 11198 reflections to a maximum θ angle of 28.38° (0.90 Å resolution), of which

4800 were independent, completeness = 94.9%, $R_{\text{int}} = 0.0877$, $R_{\text{sig}} = 0.1219$ and 3270 were greater than $2\sigma(I)$. The final cell constants: $a = 6.986(7)\text{\AA}$, $b = 11.755(11)\text{\AA}$, $c = 25.40(2)\text{\AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, volume = $2086(3)\text{\AA}^3$, are based upon the refinement of the XYZ-centroids of 3576 reflections above $20\sigma(I)$ with $2.361^\circ < \theta < 28.074^\circ$. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.290.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group $P2(1)2(1)2(1)$, with $Z = 4$ for the formula unit, $C_{24}H_{27}NO_6$. The final anisotropic full-matrix least-squares refinement on F^2 with 284 variables converged at $R1 = 9.81\%$, for the observed data and $wR2 = 27.82\%$ for all data. The goodness-of-fit was 1.053. The largest peak on the final difference map was $0.686\text{ e}^-/\text{\AA}^3$ and the largest hole was $-0.460\text{ e}^-/\text{\AA}^3$. Based on the final model, the calculated density of the crystal is 1.355 g/cm^3 and $F(000)$ amounts to 904 electrons.



A colorless block shaped crystal of agk2 (C₂₆ H₂₉ N O₅) with approximate dimensions 0.19 x 0.21 x 0.41 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 123(2) K, cooled by Rigaku-MSX X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoK α fine-focus sealed tube ($\lambda = 0.71073\text{\AA}$) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3° in ω and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Trigonal unit cell yielded a total of 23637 reflections to a maximum θ angle of 28.32° (0.90 Å resolution), of which 5756 were independent, completeness = 100.0 %, $R_{\text{int}} = 0.0310$, $R_{\text{sig}} = 0.0230$ and 5419 were

greater than $2\sigma(I)$. The final cell constants: $a = 12.794(3)\text{\AA}$, $b = 12.794(3)\text{\AA}$, $c = 24.424(7)\text{\AA}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 120^\circ$, volume = $3462.2(13)\text{\AA}^3$, are based upon the refinement of the XYZ-centroids of 5435 reflections above $20\sigma(I)$ with $2.481^\circ < \theta < 28.275^\circ$. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.799.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group $P3(2)21$, with $Z = 6$ for the formula unit, $C_{26}H_{29}NO_5$. The final anisotropic full-matrix least-squares refinement on F^2 with 292 variables converged at $R1 = 5.62\%$, for the observed data and $wR2 = 16.26\%$ for all data. The goodness-of-fit was 1.057. The largest peak on the final difference map was $1.329\text{ e}^-/\text{\AA}^3$ and the largest hole was $-0.417\text{ e}^-/\text{\AA}^3$. Based on the final model, the calculated density of the crystal is 1.253 g/cm^3 and $F(000)$ amounts to 1392 electrons.

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85. The enantiomeric excess was determined by HPLC using an OJ-H column. The retention times using 93:7 hexanes: isopropylalcohol as the eluent: were 228.7 min for the (2R, 3S) enantiomer and 303.3 min for the (2S, 3R enantiomer).

- 86.** The enantiomeric excess was determined by HPLC using an OJ-H column. The retention times using 93:7 hexanes:isopropylalcohol as the eluent: were 133.1 min for the (2S, 3S) enantiomer and 172.9 min for the (2R, 3R enantiomer).
- 87.** The C(7) proton of the indole appears as a broad singlet due to hindered rotation caused by the nitrogen protecting group. A similar substrate was exposed to low temperature ^1H NMR spectroscopy and this peak was found to resolve into two doublets.
- 88.** The enantiomeric excess was determined by HPLC using an OJ-H column. The retention times using 96:4 hexanes:isopropylalcohol as the eluent: were 303.6 min for the (2S, 3S) enantiomer and 349.6 min for the (2R, 3R) enantiomer.

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PUBLICATIONS

“Extending Pummerer Reaction Chemistry. Application to the Oxidative Cyclization of Tryptophan Derivatives,” K. S. Feldman and A. G. Karatjas. *Organic Letters*, 2004, 6, pages 2849-2852.

“Extending Pummerer Reaction Chemistry. Development of a Strategy for the Regio- and Stereoselective Oxidative Cyclization of 3-(ω -Nucleophile)-Tethered Indoles,” K. S. Feldman, D. B. Vidulova, and A. G. Karatjas. *Journal of Organic Chemistry*, 2005, 70, pages 6429-6440.

PRESENTATIONS

“Synthesis of the Oxindole Core of TMC-95,” K. S. Feldman and A. G. Karatjas. 223rd American Chemical Society National Meeting, Orlando, FL, April 11, 2002 (Oral Presentation).