INTERMOLECULAR CONJUGATE ADDITION OF CARBON NUCLEOPHILES TO NITROSOALKENES AND STUDIES TOWARD A TOTAL SYNTHESIS OF ANGUSTILODINE, ALSTILOBANINE A, AND ALSTILOBANINE E

A Dissertation in

Chemistry

by

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Abstract

An efficient procedure for the alkylation of nitrosoalkenes has been developed in which an array of potassium ester enolates were found to add in Michael fashion to various nitrosoalkenes generated via the Denmark protocol from α-chloro-O-TBS ketoximes and α-chloro-O-TBS aldoximes. Using this methodology, a number of different α-alkylated oxime constructs were synthesized including systems which contain vicinal quaternary centers.

A total synthesis of the structurally unique monoterpane indole alkaloids angustilodine (167), alstilobanine A (169), and alstilobanine E (168) has been initiated. Initial exploratory studies identified indole-2-acetate ester enolates as suitable nucleophiles for conjugate additions to 3-piperidone derived nitrosoalkenes. The Michael adduct 266, which contains the indole-piperidine substructure found in alkaloids 167-169, was prepared from the conjugate addition of the monoanion of indole-2-acetate 218 to the 3-piperidone derived nitrosoalkene 265. However, subsequent functionalization of the indole C-3 was found to be difficult.

A more convergent and highly efficient reaction was developed, which employed the conjugate addition of the dianion derived from 2,3-disubstituted indole 286, containing an oxoacetate moiety at the indole C-3, to nitrosoalkene 265 to prepare Michael adduct 315 in nearly quantitative yield. Additionally, an efficient stepwise deoxygenation sequence was developed to reduce the ketone in 3-oxoacetate 315 after all attempts to directly reduce this moiety in the related system 291 failed.

Attempted conversion of the indole containing oxime 325 to ketone 326 using standard deoximation reactions led to low yields and/or product degradation. Therefore, a mild protocol for the reductive deoximation of ketoxime pivalates was developed and was found to be
compatible with the indole containing ketoxime pivalates 354 and 359 as well as various other model ketoxime pivalates. Ketone 360 was subsequently converted to the key keto-acid 361 which was subjected to Romo’s intramolecular aldol lactonization conditions to stereoselectively form pentacyclic \( \beta \)-lactone 362 which contains the \( cis \)-azadecalin ring system found within the alkaloids 167-169.

Numerous strategies have been examined for installing a C-17 hydroxymethyl group and completing the total synthesis of alkaloids 167-169. It was discovered that intermolecular alkylation of the enolate derived from indole ester 374 with formaldehyde produces the hydroxymethyl compound 393 containing the undesired stereochemistry at C-17. On the other hand, the C-17 carbon could be installed with the proper stereochemistry via a silicon-tethered intramolecular ester enolate alkylation to provide the cyclic siloxane 408. However, numerous attempts to oxidize siloxane 408 and its derivatives to a hydroxymethyl compound under standard Fleming-Tamao conditions failed. Preliminary experiments using the Woerpel modification to the Fleming-Tamao oxidation on cyclic siloxane 449 have identified this reaction to be potentially useful for generation of the C-17 hydroxymethyl unit. Future optimization and implementation of this procedure will provide the late stage intermediate triol 463, which will be used to complete the total synthesis of angustilodine (167) and alstilobanine E (168). A Barton-McCombie deoxygenation of the primary alcohol in cyclic siloxane 449 will produce siloxane 469, which should undergo a similar oxidation en route to a total synthesis of alstilobanine A (169).
# TABLE OF CONTENTS

List of Figures ........................................................................................................... viii
List of Tables ............................................................................................................. ix
Acknowledgements ................................................................................................... x

Chapter 1. Background and Introduction on Nitrosoalkenes ........................................ 1
1.1 – General Information on Nitrosoalkenes ............................................................ 1
1.2 – Methods for Generation of Nitrosoalkenes ....................................................... 1
  1.2.1 – Base Promoted 1,4-Elimination from α-Heteroatom-functionalized Free Oximes .... 1
  1.2.2 – Fluoride Promoted 1,4-Elimination from α-Halo-O-silyloximes ....................... 2
  1.2.3 – Miscellaneous Addition and Elimination Methods ........................................... 3
1.3 – Reactions of Nitrosoalkenes .............................................................................. 8
  1.3.1 – Tautomerization ........................................................................................... 8
  1.3.2 – Intramolecular Cyclizations .......................................................................... 9
  1.3.3 – Cycloadditions ......................................................................................... 10
    1.3.3.1 – [4+2] Cycloadditions with Nitrosoalkenes as the 4π-Component ............... 11
    1.3.3.2 – [4+2] Cycloadditions with Nitrosoalkenes as the 2π-Component ............... 15
    1.3.3.3 – [3+2] Cycloadditions of Nitrosoalkenes ............................................... 16
  1.3.4 – Aromatic Substitutions .............................................................................. 16
  1.3.5 – Conjugate Additions to Nitrosoalkenes ...................................................... 18
    1.3.5.1 – Conventional Procedure for Conjugate Addition to Nitrosoalkenes .......... 19
    1.3.5.2 – Conjugate Addition to Nitrosoalkenes Generated via the Denmark Protocol .... 19
1.4 – Previous Weinreb Group Studies on Conjugate Addition of Nucleophiles to Nitrosoalkenes
.................................................................................................................................................. 21

Chapter 2 - Investigation of the Conjugate Addition of Carbon Nucleophiles to Nitrosoalkenes
Generated via the Denmark Protocol .................................................................................................. 26
2.1 – Results and Discussion .................................................................................................................. 26

Chapter 3 – Studies Toward a Total Synthesis of Angustilodine, Alstilobanine A, and
Alstilobanine E .................................................................................................................................. 32
3.1 – General Background on Monoterpenes Indole Alkaloids ............................................................ 32
3.2 – Apparicine and Angustilodine-Type Alkaloids of the Aspidospermatan Subclass ................. 33
3.3 – Biosynthesis of Apparicine- and Angustilodine-Type Alkaloids ............................................... 37
3.4 – Previous Synthetic Studies on Apparicine-Type Alkaloids ....................................................... 39
3.5 – A Unified Strategy for Synthesis of Apparicine- and Angustilodine-Type Alkaloids .... 41
3.6 – First Generation Retrosynthetic Plan for the Synthesis of the Angustilodine Alkaloids .... 42
3.7 – Background on the Key Romo Aldol-Lactonization Methodology ......................................... 43
3.8 – Model Studies on the Conjugate Addition of Indole-2-acetate Enolates to Cyclic
Nitrosoalkenes ................................................................................................................................... 47
3.9 – Revision to Retrosynthesis ......................................................................................................... 53
3.10 – Synthesis of the 3-Piperidone Nitrosoalkene Precursor ............................................................. 54
3.11 – Conjugate Addition of Indole-2-acetate Methyl Esters to Nitrosoalkenes Derived from 3-
Piperidone .......................................................................................................................................... 62
3.12 – Attempted Installation of a C-3 Acetic Acid Unit on Michael Adduct 270 ......................... 65
LIST OF FIGURES

Figure 1. Nitrosoalkene Structure ................................................................. 1
Figure 2. Structure of 1,1-Bis-(t-butyl)-2-nitrosoethene ........................................ 9
Figure 3. Skeletal Subtypes of the Aspidospermatan Subclass of Monoterpene Alkaloids ...... 34
Figure 4. Selected Apparicine-Type Alkaloids .......................................................... 35
Figure 5. Angustilodine-Type Alkaloids ................................................................. 36
Figure 6. Conformations of Alstilobanine A (169) and Major 1,3-Diol 364 ..................... 98
Figure 7. ORTEP and Wireframe Structure of Compound 381 ................................. 105
Figure 8. A1,3-Strain in N-Cbz Indole Enolate 385 ............................................... 107
Figure 9. ORTEP Structure of O-TBS Ether 411 .................................................. 114
Figure 10. ORTEP and Wireframe Structure of Z-357 ........................................... 186
LIST OF TABLES

Table 1. Intermolecular Michael Additions of Carbon Nucleophiles to Cyclic Nitrosoalkenes . 28
Table 2. Intermolecular Michael Additions of Carbon Nucleophiles to Nitrosoalkenes Derived from Aldoximes................................................................. 29
Table 3. Intermolecular Michael Additions of Carbon Nucleophiles to Terminal Nitrosoalkenes .............................................................................................................. 30
Table 4. Examples of β-Lactones Produced via Nucleophile-Catalyzed Aldol Lactonization ... 45
Table 5. Examples of Enantioselective Nucleophile-Catalyzed Aldol Lactonizations ............ 46
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Chapter 1 – Background and Introduction on Nitrosoalkenes

1.1 – General Information on Nitrosoalkenes

In the late 19th century, nitrosoalkenes 1 were first postulated by Mathaipoulos as transient intermediates in the reaction of α-halooximes with nucleophilic bases (Figure 1). Since then, the nitrosoalkene moiety has been revealed to be a highly reactive, typically unstable functional group which usually has a lifetime on the order of seconds. The presence of a nitrosoalkene may be validated in situ by spectroscopy, although, in general, indirect evidence for the existence of nitrosoalkene intermediates has been gained by trapping as a Diels-Alder or Michael-type adduct (vide infra). Additionally, some kinetic experiments have been conducted which suggest the intermediacy of nitrosoalkenes in conjugate addition reactions. In very rare cases, nitrosoalkenes which contain a bulky aryl, t-alkyl, or halo substituent at the β-carbon may be isolated.

![Nitrosoalkene Structure](image-url)

Figure 1. Nitrosoalkene Structure

1.2 – Methods for Generation of Nitrosoalkenes

1.2.1 – Base Promoted 1,4-Elimination from α-Heteroatom-functionalized Oximes

Over the last 100 years, a number of different methods have been developed for the generation of nitrosoalkenes from a variety of synthetic precursors. However, base promoted
1,4-elimination of α-functionalized free oximes such as 2, where X is a suitable leaving group, is the simplest and most frequently employed method (Scheme 1). In principle, the leaving group component may be any heteroatom-based functional group which stabilizes a negative charge, although in the vast majority of cases, a halogen (usually chlorine) is employed. Some other rare examples of leaving groups include sulfonates, phenylsulfinites, nitrite, sulfoxides, and oxirane oxygens.

Scheme 1

A variety of bases may be used to effect nitrosoalkene formation. However, the type of base employed can have a dramatic impact on the outcome of the reaction. For instance, sparingly soluble inorganic bases, such as metal carbonates and hydroxides, are often used to generate nitrosoalkenes in a slow and controlled manner in order to minimize side reactions such as polymerization. On the other hand, soluble organic bases such as amines or alkoxides may be employed for rapid generation of the nitrosoalkene. In many instances involving nucleophilic addition to nitrosoalkenes, the nucleophilic component may also act as the base (vide infra).

1.2.2 – Fluoride Promoted 1,4-Elimination from α-Halo-\textit{O}-silyloximes

Denmark and coworkers have developed a useful alternative to the conventional base promoted generation of nitrosoalkenes which involves 1,4-elimination of α-chloro-silyloximes 3
by fluoride (Scheme 2). One notable advantage of this protocol is that the nitrosoalkene can be generated at a specific point in a reaction upon addition of the fluoride source, typically tetrabutylammonium fluoride (TBAF) or cesium fluoride. Interestingly, Denmark found that nitrosoalkenes derived from t-butylcyclohexanone generated via this protocol are very reactive and have approximately 3-5 times shorter half-lives than those generated from the corresponding free $\alpha$-chlorooximes and triethylamine. Consequently, reactions employing this method of nitrosoalkene generation should proceed at a considerably faster rate. Denmark also discovered that the stereochemical orientation of the chlorine and/or oxime geometry have little to no effect on the efficiency of nitrosoalkene generation when employing either the classical or fluoride-promoted method. This observation is significant since it allows for maximum flexibility in preparation of the nitrosoalkene precursors.

Scheme 2

1.2.3 – Miscellaneous Addition and Elimination Methods

Although most nitrosoalkenes used in organic synthesis have been generated via elimination of $\alpha$-chlorooximes and $\alpha$-chloro-$O$-silyloximes, a number of alternative methods exist, but are rather limited in their scope. Combination of vinyl radicals with nitric oxide is a direct, albeit usually inefficient way to form a nitrosoalkene. This method was employed by Griffin and Haszeldine to produce the very first isolable nitrosoalkene, 1,1,2-
trifluoronitrosoethylene (5) (Scheme 3) by irradiating 1,1,2-trifluoroiodoethylene (4) in the presence of nitric oxide.

Scheme 3

One of the oldest known methods for preparation of α-chlorooximes, the most common precursor to nitrosoalkenes, is to treat olefins with nitrosyl chloride (Scheme 4). 19 The initially formed nitroso-chloroalkane 7, which typically tautomerizes to form α-chlorooxime 8, may also dimerize to yield appreciable amounts of diazene dioxide 9. As with the α-chlorooxime 8, the nitrosochloride dimers 9 may be treated with nucleophilic bases to generate a common nitrosoalkene intermediates 10 and Michael adducts 11. 20

Scheme 4

Appropriately substituted silyl nitronates can be converted to nitrosoalkenes by elimination of trialkysiloxide (Scheme 5). For example, silyl nitronates such as 12 are
converted to nitrosoalkenes such as 13 upon treatment with alkyllithium bases (Scheme 5a).\textsuperscript{21} Generally, excess alkyllithium reagent adds to the nitrosoalkene intermediate in a Michael fashion. More recently, it was discovered that treatment of β-nitroesters such as 15 with $N$, $O$-bis(trimethylsilyl)acetamide (BSA) provides silyl nitronate intermediates 16 which undergo spontaneous elimination to the corresponding nitrosoalkenes such as 17 (Scheme 5b).\textsuperscript{22} This type of nitrosoalkene generation protocol has been used in hetero-Diels-Alder cycloadditions with enol ethers to yield cycloadducts such as 18 (\textit{vide infra}).

Scheme 5

Interestingly, the addition of the sulfoxonium ylide 19 to aryl nitrile oxides such as 20 can produce nitrosoalkene intermediates 21 following the expulsion of dimethyl sulfoxide (Scheme 6). Typically, in this type of reaction the intermediate nitrosoalkene 21 will react with excess ylide 19 to ultimately produce adducts such as 22 and 23.\textsuperscript{23}
In certain cases, ring fragmentations can lead to nitrosoalkene intermediates. Abramovitch\textsuperscript{24} and others\textsuperscript{25} have observed both the thermal and photochemical decomposition of 2-azidopyridine N-oxides such as 24 to form oxazines 26 and nitrones 27 (Scheme 7). It is most likely that these products are generated from a dienylnitroso intermediate like 25.

Another, ring opening reaction to generate nitrosoalkenes is by reaction of α-bromo-oxazinones with hydroxide (Scheme 8).\textsuperscript{26} For example, reaction of 28 with sodium hydroxide leads to the nitrosoalkene tautomer 30 in high yield. In the few substrates examined, nitrosoalkene formation appears to occur with good efficiency. However, no examples of using intermediates like 29 in either Michael additions or cycloadditions have been reported.
Retro-Michael reactions\textsuperscript{27} and retro-Diels-Alder reactions,\textsuperscript{28} especially those that undergoing cleavage to produce more stable systems (i.e. aromatic rings) have been postulated to proceed via nitrosoalkene intermediates (Scheme 9). However, it appears that the reversibility of these types of reactions affects the overall ability to generate the nitrosoalkene intermediate stoichiometrically. For example, Gilchrist and coworkers showed that thermal fragmentation of indolinoxazine 31 generates methyl 2-nitrosoacrylate (33) which can be trapped with indole or \textit{n}-pentanol to produce adducts 34 or 35, respectively.

\textbf{Scheme 9}

\[\text{\begin{tikzpicture}
\node (m1) at (0,0) {31};
\node (m2) at (3,0) {32};
\node (m3) at (6,0) {33};
\node (n1) at (9,0) {34};
\node (n2) at (9,1.5) {35};
\draw[->,thick] (m1) -- (m2);
\draw[->,thick] (m2) -- (m3);
\draw[->,thick] (m3) -- (n1);
\draw[->,thick] (m3) -- (n2);
\end{tikzpicture}}\]

Very recently, Hsieh and Dong have developed a novel Pd-catalyzed reduction of 2,2-bis(aryl)-1-nitroalkenes to nitrosoalkenes \textit{en route} to the synthesis of 3-arylindoles (Scheme 10). Mechanistically, this reaction most likely proceeds via the palladium bound nitrosoalkene 38, a product of decarboxylation from the initially formed palladacycle 37. Further cyclization and a proton shift leads to the \textit{N}-hydroxyindole 40, which is reduced further to indole 41 by the Pd-catalyst and a second equivalent of CO.
1.3 – Reactions of Nitrosoalkenes

1.3.1 - Tautomerization

Probably the most common degradation pathway for nitrosoalkenes which bear an allylic hydrogen is tautomerization. For example, Kisan and Prtizkow found that treatment of either $\alpha$-chlorooxime 42 or $\alpha$-sulfatooxime 43 with triethylamine (TEA) produces a blue-colored solution ($\lambda_{\text{max}} = 740$ nm) corresponding to formation of nitrosoalkene 44. In the absence of nucleophiles, this solution fades to colorless within 15-30 min, which most likely is due to a conversion of nitrosoalkene 44 to tautomers 45 and 46.
Nitrosoalkene systems without allylic hydrogens tend to be more stable since tautomerization is not possible. For example, nitrosoalkene 47, which lacks allylic hydrogens exists as an isolable blue solid with a melting point of 38 °C (Figure 2).\(^8\)

![Scheme 11](image)

**Figure 2. Structure of 1,1-Bis-(\(t\)-butyl)-2-nitrosoethene**

### 1.3.2 – Intramolecular Cyclizations

Another unimolecular mode of decomposition that may be observed for nitrosoalkenes is an intramolecular 4\(\pi\)-electrocyclization to form oxazetes 48 (Scheme 12). Typically, these highly strained intermediates undergo fragmentation to produce the corresponding nitriles 50 and carbonyl compounds 49. For example, treatment of \(\alpha\)-chlorooximes 51 and 53 with NaHCO\(_3\) yields benzonitrile and benzophenone, respectively (Scheme 12b,c).\(^3\)
Another noteworthy unimolecular reaction involving intramolecular cyclizations of dienynitroso compounds to form oxazines and nitrones was previously discussed (cf. Scheme 7).

### 1.3.3 – Cycloadditions

Cycloadditions are one of the most synthetically useful reactions involving nitrosoalkenes and therefore much attention has been directed to this area. In the majority of cases, nitrosoalkenes tend to participate as the $4\pi$ component in inverse electron demand hetero-Diels-Alder cycloadditions (Scheme 13, path A). However, several instances where the N-O $\pi$-bond acts as the dienophile have also been documented (path B). Although the C-C double bond of nitrosoalkenes could theoretically participate as a dienophile, there are no known examples of products arising from path C. However, such products, if formed, may undergo a facile [3,3] sigmatropic rearrangement to form the products of a path A type cycloaddition. Products of [3+2] cycloadditions (path D) have only been isolated as side products in Diels-Alder reactions.
However, recent developments have uncovered favorable pathways for synthesizing nitrones via formal [3+2] cycloadditions (vide infra).

Scheme 13

1.3.3.1 - [4+2] Cycloadditions with Nitrosoalkenes as the 4π-Component

Over the years, both inter- and intramolecular hetero-Diels-Alder cycloadditions in which a nitrosoalkene is the 4π-component have developed into a versatile set of reactions for the construction of highly functionalized 1,2-oxazines. A number of different electron rich olefins can be utilized with a variety of electrophilic nitrosoalkenes in inverse electron demand [4+2]-cycloadditions.\textsuperscript{15,30} Suitable dienophiles for this reaction include, among others, enol ethers, enamines, allyl silanes, allenes, and even fullerenes.\textsuperscript{31} In a representative example, Reissig and coworkers demonstrated the highly electrophilic 1-nitroso-1-trifluoromethylethylene (56) undergoes hetero-Diels-Alder cycloadditions with allyl trimethylsilane, 3,4-dihydro-2H-pyran,
and methoxyallene to give the corresponding cycloadducts in modest to good overall yield (Scheme 14).\(^{32}\)

### Scheme 14

In some instances, the [4+2]-cycloadducts obtained in these reactions may actually be formed via stepwise pathways. For example, Gilchrist has shown that furans and enamines add efficiently to \(\alpha\)-nitrosostyrene to give the products of a formal [4+2]-cycloaddition (Scheme 15). Since a number of other dienophiles failed in this reaction (i.e. cyclopentene, anthracene, 1,3-diphenylisobenzofuran, and dimethyl acetylenedicarboxylate), Gilchrist postulated that formation of a normal electron demand Diels-Alder adduct \(61\) occurs initially and subsequent [3,3] sigmatropic rearrangement produces \(62.\)\(^{33}\) In seminal work, Gilchrist also demonstrated that enamines react particularly well with nitrosoalkenes to give formal Diels-Alder adducts. However, such reactions most likely proceed via an initial Michael addition to produce an oximate-iminium ion species \(63\) which undergoes further cyclization to produce the formal [4+2]-cycloadduct \(64.\) Recent theoretical calculations on these types of reactions by Domingo et al. further reinforce this hypothesis.\(^{34}\)
Despite the potential synthetic utility of 1,2-oxazines in complex molecule synthesis, surprisingly few examples of hetero-Diels-Alder reactions with nitrosoalkenes to construct natural products or other complex systems are found in the literature. However, Gallos et al. have recently synthesized the cytotoxic alkaloid (±)-crispine (69) utilizing a nitrosoalkene hetero-Diels-Alder cycloaddition as the key step. Thus, a mixture of α-bromooxime 66 and Na₂CO₃ was stirred in neat ethyl vinyl ether to provide cycloadduct 67, which contains all atoms necessary for completion of the natural product. Next, a reductive cyclization of the C=N bond in 67 provided the tricyclic product 68 which was converted to the natural product in two additional reductive transformations.
Denmark has explored the utility of intramolecular [4+2]-cycloadditions of nitrosoalkenes. It was found that α-chloro-O-silyloximes tethered to a methylenol ether such as 70 are capable of undergoing efficient cycloadditions to produce tricyclic oxazine compounds such as 72 and 73 with good levels of diastereoselectivity (Scheme 17). Use of the sparingly soluble cesium fluoride was critical for successful reactions to occur since rapid generation of the nitrosoalkene with TBAF led to inferior results. Interestingly, use of Z-enol ethers led to considerably lower yields, which may be due to a preference for the methoxy group in transition state 71 to be endo to the nitrosoalkene.
1.3.3.2 – [4+2]-Cycloadditions with Nitrosoalkenes as the 2π-Component

Diels-Alder cycloadditions in which the nitrosoalkene is the dienophilic component are relatively rare. In all known examples, the participating nitrosoalkene contains at least one vinylic halogen, usually at the β-position. The cycloadducts of these reactions are generally unstable and undergo rearrangement. For example, β-dichloronitrosoethylene (74) reacts with cyclopentadiene to give the Diels-Alder adduct 75 which isomerizes to epoxyepimine 76 upon warming to room temperature (Scheme 18). The intermediacy of the initial Diels-Alder adduct 75 has been affirmed by low-temperature NMR experiments.
1.3.3.3 – [3+2]-Cycloadditions of Nitrosoalkenes

Until recently, the only instances of nitrosoalkenes participating in [3+2]-cycloadditions were as minor side reactions during hetero-Diels-Alder reactions. In 2009, Palacios and coworkers revealed that α-phosphinyl- and α-phosphonyl-nitrosoalkenes such as 77 have a unique propensity to undergo [3+2]-cycloadditions with enamines 78 (Scheme 19). This process appears to be general for the phosphorus-bearing nitrosoalkenes, leading selectively to N-hydroxypyrrole derivatives 81 in good yield. However, a stepwise mechanism involving formation of iminium oxamate 79 and subsequent cyclization to 80, rather than a concerted cycloaddition, is probably operational.

![Scheme 19](image)

1.3.4 – Aromatic Substitutions

Electron rich aromatics and heteroaromatics can react with electrophilic nitrosoalkenes to yield the corresponding aromatic substitution products in good yield. Typically, the nitrosoalkenes that participate in aromatic substitution contain an α-carbonyl group that
enhances the electrophilicity of the nitrosoalkene. For example, the electron rich 1,3-dimethoxybenzene (82) was found to add to the nitrosoalkene generated from α-chlorooxime 83 to give the regioisomeric products 84 and 85 (Scheme 20a). Similarly, electron rich heteroaromatics such as furans, benzofurans, pyrroles, and indoles will add efficiently to pyruvate-derived nitrosoalkenes. In many of these cases, it is likely that an initial [4+2]-cycloaddition takes place followed by a rearrangement to give the expected substitution products. For example, reaction of 2-methylindole (86) with 4-chloro-3-butan-2-one oxime (83) and base gives the expected substitution product 87 (Scheme 20b). However, under the same set of conditions, use of 3-methylindole (88) leads to isolation of the cycloadduct 89 (Scheme 20c).

Scheme 20
1.3.5 – Conjugate Additions to Nitrosoalkenes

Conjugate addition of nucleophiles to nitrosoalkene intermediates provides a useful but underutilized means for the synthesis of α-functionalized carbonyls (Scheme 21). In this manner, the nitrosoalkene 1 can act as an enolonium ion surrogate (92), allowing for the umpolung construction of α-functionalized carbonyls 91 as compared to standard enolate chemistry. Although several direct S_N2 displacements of α-haloketones, and to a lesser extent α-haloaldehydes, have been documented, this method is not general since many nucleophiles preferentially add to the electrophilic C-O π-bond. Furthermore, treatment of α-haloketones with malonates and other nucleophilic bases can induce undesirable Favorskii rearrangements.

Scheme 21

A wide array of hetero- and carbon-based nucleophiles have been shown to add in a Michael fashion to nitrosoalkenes. Heteroatom nucleophiles found to participate in this reaction include alcohols, acetates, amines, azides, nitrites, and thiols. Carbon nucleophiles include ester and ketone enolates, β-dicarbonyls, malononitrile, acetyliides, sulfoxonium ylides (cf. scheme 6) and alkyl or aryl Grignard reagents. As mentioned above, carbon nucleophiles such as enamines and enol ethers, which give formal [4+2]-cycloadducts, most likely react through a stepwise conjugate addition/cyclization pathway (cf. Scheme 15).
1.3.5.1 – Conventional Procedure for Conjugate Addition to Nitrosoalkenes

In the vast majority of cases, two or more equivalents of the nucleophile is added to a free \(\alpha\)-halooxime since the first equivalent effects a 1,4-elimination to generate the nitrosoalkene. For example, in seminal studies on nucleophilic additions to \(\alpha\)-chlorocycloalkanone oximes, Ohno et al. showed that subjection of oxime 93 to a large excess of either morpholine, sodium azide, sodium nitrite, phenylacetylenemagnesium bromide, or diethyl malonate sodium salt produced the corresponding Michael adducts 94 in good yields (Scheme 22).\(^5\)

**Scheme 22**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>R</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>morpholine, EtOH, rt</td>
<td>N-morpholino</td>
<td>71</td>
</tr>
<tr>
<td>NaN(_3), MeCN, reflux</td>
<td>(\text{N}_3)</td>
<td>80</td>
</tr>
<tr>
<td>AgNO(_2), ether, rt</td>
<td>(\text{NO}_2)</td>
<td>80</td>
</tr>
<tr>
<td>NaHCO(_3)(CO(_2)Et)(_2), ether</td>
<td>(Et(_2)O)(_2)C</td>
<td>96</td>
</tr>
<tr>
<td>PhC(_\equiv)CMgBr, THF, rt</td>
<td>PhC(_\equiv)C</td>
<td>60</td>
</tr>
</tbody>
</table>

1.3.5.2 – Conjugate Addition to Nitrosoalkenes Generated via the Denmark Protocol

Despite the propensity of nitrosoalkenes to participate in Michael additions with a large variety of nucleophiles, nitrosoalkene methodology has found surprisingly little use in organic synthesis. This may be due in part to the fact that the classical procedure for nitrosoalkene generation, which generally requires two or more equivalents of nucleophile, is inefficient,
particularly if the nucleophile is valuable. However, this problem can be overcome by generating nitrosoalkenes via the Denmark protocol in which only 1 equivalent of nucleophile is required. For example, Barrett and coworkers demonstrated that a single equivalent of the valuable anomeric alcohol 95 adds to one equivalent of the nitrosoalkene generated from $\alpha$-chloro-$O$-TBS-oxime 96 to yield glycoside 97 (Scheme 23a).44 Surprisingly, this type of strategy has found only sporadic use in related Michael additions (vide infra).45 While the majority of these examples involve addition of oxygen, nitrogen, or sulfur nucleophiles, only a few instances involving the addition of a carbon nucleophile have been documented. In one such case, Hassner and coworkers showed that the sodium salt of allyl malonate 98 adds to 1-nitrosobutene, generated in situ from $\alpha$-bromo-$O$-TMS-oxime 99 and TBAF, to give adduct 100 in good yield (Scheme 23b).45e However, since 3 equivalents of the malonate nucleophile were employed in this case, little efficiency was demonstrated in this particular alkylation.

Scheme 23
1.4 – Previous Weinreb Group Studies on Conjugate Addition of Nucleophiles to Nitrosoalkenes

In recent years, the Weinreb group has begun to systematically investigate Michael additions to nitrosoalkenes in order to explore their potential as enolonium ion equivalents. The preliminary investigations were aimed at developing the first intramolecular conjugate additions of tethered nucleophiles to nitrosoalkenes to form fused and bridged ring systems. To access the requisite substrates for this process, two reactions developed in the Weinreb group were relied upon, namely, the ring closing metathesis of vinyl chlorides and the regioselective oxidation of vinyl chlorides to \( \alpha \)-chloroketones. Thus, diene 101 was converted to cyclic vinyl chloride 102 using Grubb’s 2nd generation catalyst (Scheme 24). Next, treatment of 102 with sodium hypochlorite and acetic acid in acetone produced \( \alpha \)-chloroketone 103 and subsequent oximation with \( O \)-TBS-hydroxylamine provided \( \alpha \)-chloro-\( O \)-TBS-oxime 104 as an inconsequential mixture of diastereomers and geometric isomers. Since nitrosoalkenes have very short lifetimes, deprotonation of the tethered malonate with NaHMDS was performed first, followed by addition of TBAF to unveil the nitrosoalkene functionality. After warming the reaction mixture to 0 °C, the [2.2.2]-bicyclic product 105 was produced in 74% yield.
Examples of other ring systems produced by this methodology are shown in Scheme 25. Through this method, various bridged and ring systems can be constructed in good yields. Interestingly, other types of soft carbanions have been shown to participate in these additions (Scheme 25, entries c,d). In general, use of NaHMDS or KHMDS for formation of the carbanions led to superior results than with LiHMDS. Additionally, a sulfonamide nucleophile was used for construction of an azabicyclic ring system (Scheme 25, entry e).\(^49\)
Our group is also studying the scope of intermolecular conjugate additions to nitrosoalkenes (*vide infra*), and we became interested in exploring factors which might control stereoselectivity in these reactions. The first study was focused on examining diastereoselectivity in the addition of nucleophiles to γ-chiral acyclic nitrosoalkenes derived from...
aldoximes (Scheme 26). It was found that conjugate addition of malonate nucleophiles derived from 117 to the nitrosoalkene 118 derived from 116 led to exclusive formation of anti adducts 119. Assuming that the nitrosoalkene reacts via the presumably lower energy E-configuration, formation of the anti products would arise from Burgi-Dunitz attack of the nucleophile on the preferred Felkin-Ahn-type conformation 118b where the phenyl group is perpendicular to the alkene and the methyl group is “inside”. To firmly establish the relative stereochemistry of 119a, a thermal intramolecular 1,3-dipolar cycloaddition was effected to provide the cis-fused isoxazolidine 120. Conversion of the free amine to the tosylate then provided the crystalline compound 121, whose stereochemistry was elucidated using X-ray diffraction.

Scheme 26

Several additional systems related to 188 were examined and shown also to undergo diastereoselective conjugate additions with various nucleophiles. For example, addition of the potassium salt of diethyl α-allylmalonate (117a) to the β-alkoxy nitrosoalkene derived from 122 led exclusively to anti product 123, again via a similar Felkin-Ahn-type process (Scheme 27a).
This result rules out a polar Felkin-Ahn mechanism in which the alkoxy substituent would be perpendicular to the alkene instead of the phenyl group (cf. Scheme 26). To examine whether a chelation effect could be observed in the methoxy series, the corresponding lithium salt of $\alpha$-allyl diethyl malonate was used in this reaction. However, the adduct 123 was again produced exclusively with the same anti-stereochemistry but in a somewhat lower yield. Similarly, it was discovered that $N$-methyltoluensulfonamide potassium salt adds to the nitrosoalkene derived from 124 to also yield the corresponding anti product 125 (Scheme 27b).

**Scheme 27**
Chapter 2 – Results and Discussion

2.1 – Investigation of the Conjugate Addition of Carbon Nucleophiles to Nitrosoalkenes

Generated via the Denmark Protocol

As part of our ongoing studies on utilizing nitrosoalkenes as enolonium ion equivalents in organic synthesis (see Section 1.4), we became interested in systematically exploring the alkylation of nitrosoalkenes produced via the Denmark protocol. Since only a few examples of this strategy have been documented in the literature, and since this strategy would be well suited for use with valuable nucleophiles (such as in a total synthesis project), we were prompted to explore a range of carbon nucleophiles and nitrosoalkenes that could participate in this reaction.

Since conjugate additions to nitrosocycloalkenes are relatively rare, we decided to conduct our initial optimization experiments using nitrosocyclohexene derived from the \( \alpha \)-chloro-\( O \)-TBS-oxime 127 (Scheme 28). We first tested the enolate of methyl phenylacetate (126) as the nucleophilic component in these reactions. Thus, deprotonation of methyl phenylacetate (126) (1.2 equiv) with KHMDS at -78 °C followed by sequential addition of \( \alpha \)-chloro-\( O \)-TBS-oxime 127 (1.0 equiv) and TBAF (1.2 equiv) and warming to 0 °C provided the Michael adduct 128 in 79% yield. It should be noted that allowing the reaction mixture to warm to room temperature prior to aqueous workup leads to formation of oxazanone 129 and various decomposition byproducts.
We next sought to examine these general reaction conditions (Scheme 29) using various ester-containing nucleophiles and nitrosoalkene precursors. This work was performed in collaboration with Puhui Li and Jason Witek of our group. Using nitrosocyclohexene, several additional nucleophiles were found to participate effectively in the Michael addition (Table 1). Use of malonates in the Michael reaction gave adducts in reasonable to excellent yields (entries 1-3). Additionally, a β-ketoester, α-sulfonyl ester, and an α-nitroester were all identified as compatible nucleophiles (entries 4-6). Nitrosocyclopentene also performed well in these reactions, albeit in slightly lower yields compared to the cyclohexanone-derived nitrosoalkenes (entries 7-12). In certain cases, the type of base employed affects the outcome of the reaction. For example, the potassium salt of ethyl nitroacetate was found to react with nitrosocyclohexene to yield the corresponding Michael adduct in 57% yield (entry 4). However, when KHMDS was replaced with either LiHMDS or NaHMDS, none of the desired Michael adduct was produced. In contrast, use of LiHMDS or NaHMDS as the base with diethyl malonate and nitrosocyclohexene provided the Michael adduct in nearly the same yields as with KHMDS (91% and 94%, respectively, entry 1).
Scheme 29

Table 1. Intermolecular Michael Additions of Carbon Nucleophiles to Cyclic Nitrosoalkenes

<table>
<thead>
<tr>
<th>entry</th>
<th>ester derivative</th>
<th>nitrosoalkene precursor</th>
<th>product</th>
<th>yield</th>
<th>entry</th>
<th>ester derivative</th>
<th>nitrosoalkene precursor</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO₂C₂O₂EtClN</td>
<td>OTBS</td>
<td>EtO₂C₂O₂EtOH</td>
<td>95%</td>
<td>7</td>
<td>MeO₂C₂PhN</td>
<td>OTBS</td>
<td>MeO₂C₂PhOH</td>
<td>79%</td>
</tr>
<tr>
<td>2</td>
<td>EtO₂C₂O₂EtMeN</td>
<td>OTBS</td>
<td>EtO₂C₂O₂EtOH</td>
<td>84%</td>
<td>8</td>
<td>EtO₂C₂O₂EtN</td>
<td>OTBS</td>
<td>EtO₂C₂O₂EtOH</td>
<td>85%</td>
</tr>
<tr>
<td>3</td>
<td>EtO₂C₂O₂EtEtN</td>
<td>OTBS</td>
<td>EtO₂C₂O₂EtOH</td>
<td>69%</td>
<td>9</td>
<td>EtO₂C₂O₂EtN</td>
<td>OTBS</td>
<td>EtO₂C₂O₂EtOH</td>
<td>72%</td>
</tr>
<tr>
<td>4</td>
<td>EtO₂C₂O₂NO₂N</td>
<td>OTBS</td>
<td>EtO₂C₂O₂EtOH</td>
<td>57%</td>
<td>10</td>
<td>EtO₂C₂O₂EtN</td>
<td>OTBS</td>
<td>EtO₂C₂O₂EtOH</td>
<td>73%</td>
</tr>
<tr>
<td>5</td>
<td>EtO₂C₂O₂MeN</td>
<td>OTBS</td>
<td>EtO₂C₂O₂EtOH</td>
<td>71%</td>
<td>11</td>
<td>MeO₂C₂SO₂PhN</td>
<td>OTBS</td>
<td>PhO₂SMeOH</td>
<td>82%</td>
</tr>
<tr>
<td>6</td>
<td>MeO₂C₂SO₂PhN</td>
<td>OTBS</td>
<td>MeO₂C₂MeOH</td>
<td>95%</td>
<td>12</td>
<td>MeO₂C₂PhN</td>
<td>OTBS</td>
<td>MeO₂C₂PhOH</td>
<td>55%</td>
</tr>
</tbody>
</table>

* Use of LiHMDS and NaHMDS gave yields of 91% and 94%, respectively. † No desired product was formed when using LiHMDS or NaHMDS. ‡ An accurate stereochemical assignment could not be made since the products exist as a complex mixture of E/Z-isomers and/or diastereomers which were not separable by column chromatography. ‡‡ 2 eq of LiHMDS and 2 eq of ester derivative were used. ‡§ The deprotonation step was performed at 0°C to prevent freezing of the reaction mixture.
We also examined the use of nitrosoalkenes derived from aldoximes since conjugate additions to such species are not well studied\textsuperscript{45} and also because the direct $\alpha$-alkylation of aldehydes by conventional enolate chemistry is inherently difficult.\textsuperscript{52} It was found that $\alpha$-chloro hydrocinnamaldehyde-derived nitrosoalkenes react efficiently with malonates and methyl phenylacetate anions (Table 2, entries 1-5). Similarly, addition of malonate and methyl phenylacetate enolates to the exocyclic nitrosoalkene derived from cyclohexane carboxaldehyde proceeded in good yields (entries 6-9). To our delight, we discovered that use of $\alpha$-alkyl malonates in this reaction produces vicinal quaternary centers in good yields (entries 7-8).

**Table 2. Intermolecular Michael Additions of Carbon Nucleophiles to Nitrosoalkenes**

*Derived from Aldoximes*

<table>
<thead>
<tr>
<th>entry</th>
<th>ester derivative</th>
<th>nitrosoalkene precursor</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO$_2$C$_2$CO$_2$Et</td>
<td>N\textsuperscript{N}OTBS \textsuperscript{a}</td>
<td>OH</td>
<td>51%\textsuperscript{e}</td>
</tr>
<tr>
<td>2</td>
<td>EtO$_2$C$_2$CO$_2$Et</td>
<td>N\textsuperscript{N}OTBS \textsuperscript{a}</td>
<td>Me</td>
<td>69%</td>
</tr>
<tr>
<td>3</td>
<td>EtO$_2$C$_2$CO$_2$Et</td>
<td>N\textsuperscript{N}OTBS \textsuperscript{a}</td>
<td>Et</td>
<td>66%\textsuperscript{a}</td>
</tr>
<tr>
<td>4</td>
<td>MeO$<em>2$C$</em>\text{Ph}$$\text{N}^\text{N}$OTBS</td>
<td>OH</td>
<td>75%\textsuperscript{d}</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>EtO$<em>2$C$</em>\text{CO}_2$Et</td>
<td>N\textsuperscript{N}OTBS \textsuperscript{a}</td>
<td>Cl</td>
<td>67%\textsuperscript{d}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>entry</th>
<th>ester derivative</th>
<th>nitrosoalkene precursor</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>EtO$_2$C$_2$CO$_2$Et</td>
<td>N\textsuperscript{N}OTBS \textsuperscript{a}</td>
<td>Cl</td>
<td>64%\textsuperscript{o}</td>
</tr>
<tr>
<td>7</td>
<td>EtO$_2$C$_2$CO$_2$Et</td>
<td>N\textsuperscript{N}OTBS \textsuperscript{a}</td>
<td>Me</td>
<td>74%</td>
</tr>
<tr>
<td>8</td>
<td>EtO$_2$C$_2$CO$_2$Et</td>
<td>N\textsuperscript{N}OTBS \textsuperscript{a}</td>
<td>Et</td>
<td>66%\textsuperscript{a}</td>
</tr>
<tr>
<td>9</td>
<td>MeO$<em>2$C$</em>\text{Ph}$$\text{N}^\text{N}$OTBS</td>
<td>OH</td>
<td>63%</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} An accurate stereochemical assignment could not be made since the products exist as a complex mixture of E/Z-isomers and/or diastereomers which were not separable by column chromatography. \textsuperscript{b} 2 eq of HNMDS and 2 eq of ester derivative were used. \textsuperscript{c} The deprotonation step was performed at 0 °C to prevent freezing of the reaction mixture. \textsuperscript{d} Use of LiHMDS and NaHMDS gave 34% and 31%, respectively. \textsuperscript{e} E/Z ratio could not be determined.
Terminal nitrosoalkenes, such as those derived from chloromethyl ketones, are typically employed as heterodienes in Diels-Alder cycloadditions.\(^2\) Since only a few reactions involving conjugate addition to terminal nitrosoalkenes have been reported, we wished to extend our methodology to these systems. In this instance, both malonate and methyl phenyl acetate enolates added efficiently to produce the corresponding Michael adducts in good overall yield (Table 3, entries 1-3).

**Table 3. Intermolecular Michael Additions of Carbon Nucleophiles to Terminal Nitrosoalkenes**

<table>
<thead>
<tr>
<th>entry</th>
<th>ester derivative</th>
<th>nitrosoalkene precursor</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO₂C₂CO₂Et</td>
<td>ClN₂TBS</td>
<td>EtO₂C₂N¹OHPh</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>EtO₂C₂CO₂Et</td>
<td>ClN₂TBS</td>
<td>EtO₂C₂N¹OHPh</td>
<td>71%</td>
</tr>
<tr>
<td>3</td>
<td>MeO₂C₂Ph</td>
<td>ClN₂TBS</td>
<td>MeO₂C₂N¹OHPh</td>
<td>73%</td>
</tr>
</tbody>
</table>

When phenylsulfonyl acetonitrile (133) and \(\alpha\)-chloro-\(O\)-TBS-oxime 127 were subjected to the above standard conditions only the unstable adduct 135 was isolated, which results from an intramolecular cyclization of the intermediate oxime anion onto the cyano group of 134.\(^53\) Although the reaction appears to occur cleanly on analysis by thin layer chromatography, the moderate yield is likely due to the chromatographic instability of 135.
While the above methodology worked well for soft ester containing nucleophiles, it was somewhat surprising that simple ester or ketone enolates such as those prepared from \( t \)-butyl acetate or acetophenone did not participate in the Michael addition despite ample precedent that such nucleophiles add efficiently to nitrosoalkenes generated under classical conditions from \( \alpha \)-chlorooximes.\(^2\) We had also attempted to use nitrosoalkene systems derived from \( \alpha \)-chloro-\( O \)-TBS-oxime \( \text{136} \) as a means to form \( \alpha \)-quaternary centers. However, in all cases examined no Michael addition could be effected and only the nitrosoalkene tautomer \( \text{137} \) was isolated. This is probably due to the fact that nitrosoalkene \( \text{44} \) undergoes relatively fast tautomerization (cf. Scheme 11),\(^{29a} \) and also since nitrosoalkenes generated via the Denmark protocol tend to have shorter lifetimes relative to those generated from \( \alpha \)-chlorooximes.\(^{13b} \)
Chapter 3. Studies Toward a Total Synthesis of Angustilodine, Alstilobanine A, and
Alstilobanine E

3.1 – General Background on Monoterpene Indole Alkaloids

Monoterpene indole alkaloids, which are usually comprised of a 3-(2-aminoethyl)indole (tryptamine) appended to a single C\textsubscript{9}- or C\textsubscript{10}-terpene unit, constitute one of the largest classes of natural products known.\textsuperscript{54} Considering the vast range of structural diversity found within this class of alkaloids, it is rather remarkable that all members arise biogenetically from strictosidine (140), which itself is a condensation product of tryptamine (138) and secologanin (139) (Scheme 31).\textsuperscript{55}

Scheme 31

![Scheme 31 diagram](image)

Scheme 32 depicts the biogenetic interrelationship of the ten main skeletal types of monoterpene indole alkaloids from strictosidine as the biosynthetic origin. It is worth noting that the tryptamine fragment of these alkaloids generally shows little or no modification. Most of the observed modifications typically include oxygenation of the indole nucleus whereas the tryptamine bridge is less often affected (\textit{vide infra}). The C\textsubscript{9}- or C\textsubscript{10}-monoterpene moiety adds significant structural diversity to this class of indole alkaloids since the terpene skeleton can undergo a myriad of oxidations, rearrangements, and cyclizations to produce a wide array of
different skeletal types. Thus, the large structural diversity displayed by monoterpenoid indole alkaloids can be primarily attributed to variation in the monoterpenoid unit.

Scheme 32

3.2 – Apparicine and Angustilodine-Type Alkaloids of the Aspidospermatan Subclass

The aspidospermatan subclass of monoterpenoid indole alkaloids currently includes about 20 unique skeletal subtypes that have all been isolated from the Apocynaceae family of plants (Figure 3). Most of the structural subtypes found within this class are derived from stemmadenine, which itself is grouped under the aspidospermatan subclass despite the fact that it
is a biogenetic precursor of aspidospermatans. Interestingly, a number of subtypes within the aspidospermatan class lack one or both carbons of the usual two carbon tryptamine bridge, which is an exceptionally rare feature among tryptamine-derived alkaloids (i.e. 147-153, 155, and 157-160). These natural products are often referred to as “apparicine-type” alkaloids after the simplest member of the group (cf. 147).

![Skeletal Subtypes](image)

Figure 3. Skeletal Subtypes of the Aspidospermatan Subclass of Monoterpene Alkaloids
Several interesting members of the apparicine subclass are shown in Figure 4. The characteristic 1-azabicyclo[4.2.2]decane ring system of apparicine (161) is conserved among some members of this group (i.e. 162-164). Additionally, higher degrees of oxidation are found in congeners such as (E)-vallesamine (162), in addition to alstonamine (163) and angustilobine A (164) which contain an additional ring. Some seco- and seco-nor derivatives such as nor-6,7-secoangustilobine A (165) and 6,7-seco-19,20-α-epoxyangustilobine B (166) have also been isolated. Over 20 additional alkaloids related to this subtype are found in a number of different flowering plants of the Apocynaceae family. Many of these alkaloids are biologically active and exhibit a broad pharmacological profile.

![Apparicine and congeners](image1)

**Figure 4. Selected Apparicine-Type Alkaloids**

In 2004, Kam and Choo isolated a new alkaloid, angustilodine (167), which contains a unique skeletal type, from the leaves of the Malayan plant Alstonia angustiloba (Figure 5). The structure of angustilodine was determined by spectroscopic analysis to include an indole appended to a cis-azadecalin ring system interfused with a 7-membered ring bridging ether.
More recently, Morita and coworkers discovered the \( N \)-demethyl derivative of alstilobanine E (168) as well as alstilobanine A (169), which lacks the bridging oxepane ring found in 167 and 168.\(^{59}\) The alstilobanines were found to possess modest vasorelaxant activity. For clarity, compounds 167-169 will be referred to “angustilodine-type” alkaloids.

![Figure 5. Angustilodine-Type Alkaloids](image)

Interestingly, the Morita group determined through \(^{1}\text{H}-^{1}\text{H} \) NOESY correlations in CD\(_3\)OD solution that the piperidine ring in alstilobanine E (168) exists in a boat conformation. On the other hand, Kam and Choo draw the piperidine ring in angustilodine (167) in the chair form. However, it is unclear if this chair conformation is only assumed, since no \(^{1}\text{H}-^{1}\text{H} \) NOESY correlations within the piperidine ring were reported and there is no discussion of this point. It is quite possible that the piperidine ring in angustilodine (167) actually exists in a similar boat
conformation as alstilobanine E (168). The piperidine ring of alstilobanine A (169), on the other hand, was determined by $^1$H-$^1$H NOESY experiments to exist in a chair form.

### 3.3 – Biosynthesis of Apparicine- and Angustilodine-Type Alkaloids

Both apparicine and angustilodine-type alkaloids probably originate biogenetically from stemmadenine (170) (Scheme 33). As illustrated in the transformation of stemmadenine (170) to (E)-vallesamine (162), an initial oxidation of 170 to the corresponding N-oxide 171 is followed by Potier-Polonovski fragmentation to the azafulvene iminium intermediate 172. Excision of the iminium carbon would produce amino azafulvene 173 which undergoes an intramolecular Mannich addition to afford (E)-vallesamine (162). Additional decarboxylations, dehydrations, and/or oxidative ring closures can be invoked in the biosynthesis of the related apparicine alkaloids (cf. Figure 4). For example, a concerted decarboxylative-dehydration of (E)-vallesamine (162) produces apparicine (161). It should also be noted that partial synthesis of both apparicine (from pericine) and vallesamine (from stemmadenine) have been achieved, further supporting the feasibility of this biosynthetic hypothesis. Additionally, it was demonstrated by feeding experiments that radio-labeled stemmadenine (170) and (E)-vallesamine (162) are both converted into apparicine (161).
Similarly, the biogenesis of angustilodine-type alkaloids is believed to also proceed from the fragmentation of stemmadenine (Scheme 34). In this case, the Potier-Polonovski fragmentation product 172 (cf. Scheme 33) may undergo nucleophilic addition to the azafulvene to generate indole 174. To produce the alstilobanine E skeleton, an isomerization/epoxidation of the olefinic moiety in 175 and rearomatization of the indole first produces intermediate 176. Intramolecular attack of the nucleophilic indole C-3 carbon onto the epoxide of 174 would generate alstilobanine A (169). The angustilodine skeleton may be generated from 175 following cyclization of the primary alcohol onto the alkene to give the 7-membered ring ether 176. A similar intramolecular epoxide addition of indole 178 would lead to angustilodine (167) and alstilobanine A (168).
3.4 – Previous Synthetic Studies on Apparicine Type Alkaloids

To date, very little synthetic work has been directed towards the synthesis of apparicine and related alkaloids. In 1977, Joule showed that the 1-azabicyclo[4.2.2]decane framework of apparicine could be obtained from indoleamine 179 via an intramolecular Mannich reaction (Scheme 35). However, application of this reaction in substituted systems more closely related to the natural product was not successful.
It was not until 2009 that the Bennesar group reported the first synthesis of apparicine, which is the only member of this class of alkaloids to have been prepared to date. The successful route featured a ring-closing metathesis of diene 181 to provide the tricyclic compound 182 (Scheme 36). Next, alkene isomerization to produce 183, followed by Boc-removal and alkylation of the resulting free amine with tosylate 184 provided the indole 185. Finally, formation of the azabicyclic core via an intramolecular Heck reaction gave apparicine (161) but in only 15% yield.
More recently, Joule et al. reported a formal synthesis of apparicine based on the Bennesar route. The key step of this synthesis was a high dilution intramolecular Mannich reaction of 186 to form the eight-membered ring structure 187, which was converted to the Bennesar intermediate 185 in one additional step (Scheme 37).

Scheme 37

3.5 – A Unified Strategy for Synthesis of Apparicine- and Angustilodine-Type Alkaloids

Our interest in the apparicine and angustilodine-type alkaloids was inspired by our recent work on the conjugate addition of carbon nucleophiles to vinylnitroso compounds (cf. Chapter 2). We recognized that the indole-piperidine substructure embedded within the framework of the apparicine and angustilodine alkaloids could be forged via an intermolecular conjugate addition of an indole-2-acetate enolate like 188 to the 3-piperidone-derived nitrosoalkene 189 (Scheme 38). The Michael adduct 190 of this pivotal conjugate addition reaction could then, in principle, be further elaborated to various members of the apparicine/angustilodine group of alkaloids, for example 160, 161, or 165 (see also Figure 4). Our group has already initiated synthetic efforts toward some of the more interesting alkaloids in this class. However, this thesis focuses on efforts toward the total synthesis of indole alkaloids of the angustilodine skeletal type (vide infra).
3.6 – First Generation Retrosynthetic Plan for the Synthesis of the Angustilodine Alkaloids

At the onset of our study, we planned to access all three angustilodine alkaloids 167-169 through the common late stage intermediate 192 (Scheme 39). Thus, regioselective cyclodehydration of 192 via the natural product-like conformation shown would form the bridging seven membered ring ether found in angustilodine (167) and alstilobanine E (168). Alternatively, a selective Barton-McCombie deoxygenation of the C-18 alcohol in 192 would provide the alstilobanine A (169) structure. In order to access triol 192, a selective lactonization of the diester 194 would provide lactone 193, which in turn would be chemoselectively reduced to afford 192. The 1,3-diol 194 would be produced directly from β-lactone 195. In a key reaction, the keto-acid 197 would be converted to the cis-azadecalin β-lactone 195 via ammonium-enolate 196 using Romo’s aldol lactonization methodology (vide infra). Finally, construction of the indole-piperidine substructure in keto-acid 197 would be accomplished via conjugate addition of an indole-2-malonate 198 to a nitrosoalkene generated from α-chlorooxime 199 using our methodology.
3.7 - Background on the Key Romo Aldol-Lactonization Methodology

Many of the recent developments in the efficient construction of β-lactones have undoubtedly been driven by their importance as reactive synthetic intermediates\(^{65}\) and potent pharmacophores in bioactive compounds.\(^{66}\) Of the available methods for synthesizing β-lactones directly from simple starting materials, the intramolecular nucleophile-catalyzed aldol lactonization (NCAL) developed by Romo and coworkers stands out as one of the more useful variants (Scheme 40).\(^{65d}\) In this method, simple keto-acid and aldehyde-acid substrates can be
converted to β-lactones in one-pot in the presence of a carboxylic acid activator and a nucleophilic amine catalyst. Mechanistically, the process begins with activation of the carboxylic acid 200 and subsequent transacylation by the nucleophilic catalyst to produce an acyl ammonium species 202. Enolization to ammonium enolate 203 and subsequent attack of this enolate on the carbonyl group produces diastereomeric products 204 and 205, the former of which cannot cyclize to a β-lactone due to ring strain. However, a retro aldol of 204 regenerates ammonium enolate 203. Lactonization of intermediate 205, however, leads to the β-lactone 207 and regenerates the nucleophilic amine catalyst.

**Scheme 40**

![Scheme 40 Diagram](image)

Initially, this process was only applicable to substrates containing electrophilic aldehydes. However, the Romo group discovered that use of a modified Mukaiyama salt for carboxylic acid activation enabled participation of less electrophilic aliphatic ketones (Table 4). For example, using the combination of 2-bromo-N-propylpyridinium triflate and 4-pyrrolidinopyridine (PPY), bicyclic and tricyclic fused β-lactones can be constructed with high diastereoselectivity (Table 4, entries 1-4). It should be noted that a cis-decalin containing the same relative stereochemistry as found in the angustilodine cis-azadecalin substructure can be
produced, with no detectable amounts of the corresponding trans-decalin, from a racemic ketoacid (entry 4). Additionally, a complex amide containing substrate, which was utilized in the total synthesis of (-)-salinosporamide A, could be employed to produce highly substituted β-lactone (entry 5). 68g

Table 4. Examples of β-Lactones Produced via Nucleophile-Catalyzed Aldol Lactonization

<table>
<thead>
<tr>
<th>entry</th>
<th>keto-acid</th>
<th>β-lactone</th>
<th>dr</th>
<th>%yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>&gt;19:1</td>
<td>67%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>&gt;19:1</td>
<td>40%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>&gt;19:1</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td>&gt;19:1</td>
<td>57%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td>2-3:1</td>
<td>25-35%</td>
</tr>
</tbody>
</table>

Since the Romo NCAL process proceeds via an ammonium enolate intermediate (cf. Scheme 40), it is possible to induce asymmetry in this type of reaction. Very recently, the Romo group was able to exploit this feature of the NCAL reaction by employing a chiral cyclic
isothiourea derivative as the nucleophilic catalyst. Thus, using TsCl as the activating agent, (S)-HBTM as the nucleophilic catalyst, and 1 equivalent of LiCl to accelerate the rate of the reaction, various keto-acids were converted to their corresponding \( \beta \)-lactones with good enantioselectivity (Table 5). Omission of LiCl in this reaction improves the enantioselectivity slightly but the overall yields of the \( \beta \)-lactone products are significantly diminished.

Table 5. Examples of Enantioselective Nucleophile-Catalyzed Aldol Lactonizations

\[
\begin{align*}
\text{entry} & \quad \text{keto-acid} & \quad \beta\text{-lactone} & \quad \%\text{ee} & \quad \%\text{yield} \\
1 & \quad \begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array} & \quad \begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array} & \quad 90 & \quad 93 \\
2 & \quad \begin{array}{c}
\begin{array}{c}
\text{Ph}
\end{array}
\end{array} & \quad \begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array} & \quad 87 & \quad 70 \\
3 & \quad \begin{array}{c}
\begin{array}{c}
\text{MeO}_2\text{C}
\end{array}
\end{array} & \quad \begin{array}{c}
\begin{array}{c}
\text{MeO}_2\text{C}
\end{array}
\end{array} & \quad 98 & \quad 85 \\
4 & \quad \begin{array}{c}
\begin{array}{c}
\text{MeO}_2\text{C}
\end{array}
\end{array} & \quad \begin{array}{c}
\begin{array}{c}
\text{MeO}_2\text{C}
\end{array}
\end{array} & \quad >98 & \quad 71 \\
\end{align*}
\]

3.8 – Model Studies on the Conjugate Addition of Indole-2-acetate Enolates to Cyclic Nitrosoalkenes

At the onset of our work we sought to identify a suitable indole containing nucleophile to participate in the proposed nitrosoalkene Michael addition (cf. Scheme 39). Since we expected
that preparation of the requisite 4-chloro-3-piperidone oxime 199 might be challenging, we opted to use the α-chlorooxime derived from cyclohexanone as a model system. Ideally, it was hoped that a fully substituted indole such as 210, containing the required C-3 acetic acid functionality would prove to be compatible with the conjugate addition methodology (Scheme 41). Thus, synthesis of 210 was accomplished via treatment of the known indole 20870 with t-butyl hypochlorite to form a 3-chloroindolenine intermediate71 followed by addition of thallium malonate 209.72 Unfortunately, deprotonation of indole malonate 210 using either K2CO3 or LiHMDS (1 equiv) followed by addition of α-chlorooxime 211 (1 equiv) failed to produce the desired Michael adduct 212 and only the starting indole was recovered.

We reasoned that the failure to alkylate the fully functionalized indole 210 may be due, in part, to the competitive deprotonation of the indole NH. To avoid this issue, we attempted a number of different methods to protect the indole with alkyl or sulfonyl groups. However, this protection proved to be less straightforward than anticipated. For example, attempted methylation of the indole nitrogen with dimethyl sulfate led to exclusive methylation at the malonate active methine (Scheme 42). Additionally, deprotonation of indole 210 with a variety of bases followed by the addition of benzenesulfonyl chloride or TsCl gave no reaction.
A second potential issue with using an indole nucleophile such as 210 is the presence of acidic $\alpha$-protons on the C-3 acetate. To see whether removal of the C-3 acetate would facilitate the Michael reaction, dimethyl indole-2-malonate (214)\textsuperscript{73} was prepared and employed as the nucleophile in the model conjugate addition reaction (Scheme 43). Unfortunately, formation of the monoanion of 214 (2 equiv), followed by addition of $\alpha$-chlorooxime 211 (1 equiv), led exclusively to the C-3 alkylated indole 215. Once again, we met with the same difficulty protecting the indole nitrogen of 214 via alkylation or sulfonylation (cf. Scheme 42). In this system, it was found that the indole nitrogen could be protected as a Boc-carbamate 216, but this process is accompanied with concomitant acylation of the malonate group to yield 217 as the major product.\textsuperscript{74}
At this point, it became clear that use of an indole-2-malonate nucleophile in the conjugate addition reaction was problematic. We reasoned that indole-2-acetic acid methyl ester (218) might act as a better partner in these Michael additions since the derived ester enolate would be more nucleophilic than a malonate enolate. However, in order to effect a conjugate addition using this substrate, it was anticipated that formation of the dianion would be necessary since deprotonation at the presumably more acidic NH of the indole would occur first. It was also unclear at this point whether, under classical conditions, a single equivalent of the dianion of 218 could serve as the base to deprotonate the α-chlorooxime and the nucleophile to form a Michael adduct with the resulting nitrosoalkene. To examine this possibility, the indole 218 (1 equiv) was treated with n-BuLi (2 equiv) at -78 °C to produce the corresponding dianion (Scheme 44). Next, 1 equivalent of α-chlorooxime 211 was added dropwise and the resulting mixture was stirred at -78 °C for 1 h. Gratifyingly, the desired Michael adduct 219 was isolated from the reaction, albeit in only 20% unoptimized yield.

Scheme 44
While attempting to optimize the reaction utilizing the dianion of 218, we serendipitously discovered due to an error in calculating stoichiometry that reacting 2 equivalents of the monoanion (instead of the intended 1 equivalent of the dianion) with 1 equivalent of α-chlorooxime 211 led to clean production of the Michael adduct in 78% yield and with almost complete recovery of the excess starting indole ester 218. This fortunate observation suggested that the indole monoanion probably exists as an equilibrating mixture of the initially formed and presumably more stable anion 220a and the more nucleophilic enolate anion 220b (Scheme 45). While either anion could deprotonate α-chlorooxime 211 to form the transient nitrosoalkene 221, only 220b adds to nitrosoalkene 221 in a Michael fashion to produce C-alkylation product 219 exclusively. It should also be noted that Michael adduct 219 was determined by ¹H and ¹³C NMR analysis to be a single diastereomer but an E/Z-mixture of oxime isomers. The relative stereochemistry of the two stereocenters in 219 could not be determined. However, this stereochemistry is inconsequential to the total synthesis (vide infra).

Scheme 45
Because the monoanion of 218 could be employed, we found that it was also possible to use the Denmark procedure to generate nitrosoalkene 221. Thus, addition of α-chloro-O-TBS-oxime 127 (1 equiv) to a -78 °C solution of the monoanion derived from 218 (1 equiv) followed by the addition of TBAF and warming to 0 °C led to formation of Michael adduct 219 in 42% unoptimized yield (Scheme 46).

Scheme 46

After successfully synthesizing the model indole-cyclohexanone oxime system, our next goal was to identify a set of mild conditions by which the oxime functionality of 219 could be converted to the corresponding ketone. While this operation could, in principle, be performed at various stages in the synthesis, our main concern was that the majority of known deoximation protocols, which are either hydrolytic or oxidative, might be incompatible with the sensitive indole and amino groups (vide infra). Therefore, we opted to utilize a mild, reductive procedure involving low-valent titanium (Scheme 47). Thus, when oxime 219 was treated with TiCl3 all of the starting oxime was converted to ketone 222 as observed by TLC analysis.
However, subjecting the crude product to flash column chromatography on silica gel provided the ketone 222 in 63% yield and a cyclocondensation product 223 in 13% yield. Furthermore, when the purified ketone 222 was dissolved in CDCl₃, complete conversion to the tetracyclic pyrrole 223 was observed (presumably due to a trace of HCl).

Scheme 47

In light of this result, we decided to determine if it was possible to use an N-protected indole in the nitrosoalkene conjugate addition. As noted before, attempts at N-alkylation and N-sulfonylation of earlier indole systems proved to be fruitless (cf. Schemes 42 and 43). Similar to these previous results, we found that it was also very difficult to protect the indole nitrogen with alkyl and sulfonyl groups. For example, attempted N-methylation of indole 218 with NaH (1 equiv.) and MeI only produced a mixture of C-alkylated products 224 and 225 along with N,C-dimethylated product 226 (Scheme 48). Similar reactivity was observed using other electrophiles (i.e. BOM-Cl, PMB-Cl, etc). This problem is most likely due to equilibration of the initially formed indole nitrogen anion with the more reactive C-2 enolate (cf. Scheme 45).

Scheme 48
On the other hand, we were pleased to find that Boc-protection in this system proceeds cleanly to give Boc-indole 227 in high yield (Scheme 48). Alkylation of the monoanion derived from indole 227 (1.2 equiv) with 1.0 equivalent of the nitrosoalkene derived from α-chloro-O-TBS-oxime 127 via the Denmark protocol led to clean production of adduct 228. Furthermore, reductive cleavage of the oxime in 228 with TiCl₃ proceeded without incident to give ketone 229 in an unoptimized 48% yield.

3.9 – Revision to Retrosynthesis

After identifying indole-2-acetate enolates as viable nucleophiles for the key conjugate addition reaction, our retrosynthetic plan required some revision. Thus, conjugate addition of the monoanion derived from indole ester 234 with the nitrosoalkene derived from 235 would produce adduct 233 (Scheme 49). At this point, the acetic acid unit would be introduced via alkylation at the nucleophilic indole C-3 of indole 233. Finally, the C-17 hydroxymethyl unit of
would be introduced at a late stage via combining the ester enolate of indole ester 230 with formaldehyde.

Scheme 49

3.10 – Synthesis of the 3-Piperidone Nitrosoalkene Precursor

With a potential route toward the angustilodine alkaloids developed, we turned our attention toward the synthesis of the requisite α-chlorooxime 241 derived from a N-protected 3-piperidone. It should be noted that although multiple approaches for the regioselective formation of α-chlorooxime 241 could be envisioned, earlier studies by Joshua Sacher in our group on the synthesis of 4-chloro-3-piperidones revealed several important limitations for synthesizing compounds related to 240. First, regioselective chlorination of β-ketoesters\(^{76}\) such as 236 followed by decarboxylation of 237 to the desired α-chloroketone 240 could not be realized since the latter step of this sequence only produced complex mixtures. Secondly, formation of
α-chloroketones utilizing our previously disclosed strategy\(^\text{47,48}\) was not possible since oxidation of vinyl chlorides such as \(\text{239}\) with sodium hypochlorite under various conditions failed to provide \(\text{240}\). Finally, it was observed that 3-piperidones containing a basic nitrogen (i.e. \(P = \text{alkyl}\)) tended to be unstable and thus could not be converted to an \(\alpha\)-chlorooxime \(\text{240}\). A survey of the literature provided additional examples of the instability of enolizable \(\alpha\)-aminoketones containing a basic nitrogen.\(^{77}\)

**Scheme 50**

![Scheme 50](image)

Given the above information, it seemed prudent to install the chlorine atom at the latest possible stage so as to avoid subjecting any labile chlorinated compounds to multiple synthetic steps. Initially, we wished to utilize an enol ether derived from a 3-piperidone in an electrophilic chlorination to provide the \(\alpha\)-chloroketone regioselectively. Engler and Wanner have shown that methyl enol ethers \(\text{244}\) can be formed with modest to good regioselectivity from 3-piperidones \(\text{242}\) in a two step procedure (Scheme 51a).\(^{78}\) Thus, conversion of 3-piperidones \(\text{242}\) to ketalts \(\text{243}\) and subsequent elimination of methanol with \(\text{AlCl}_3\) and TEA provided methyl enol ethers \(\text{244}\) as the major regioisomers. It was reported that the nature of the \(N\)-sulfonyl group affects the regioselectivity of the elimination step and use of the \(N\)-benzylsulfonyl group gave the best results.\(^{78}\) Thus, we synthesized methyl enol ether \(\text{244c}\) by this method, but as a 3:1
mixture of regioisomers. Unfortunately, treatment of 244c with NCS under standard conditions\textsuperscript{79} did not provide the desired $\alpha$-chloroketone 245 and only a complex mixture was obtained.

**Scheme 51**

Next, we attempted to synthesize the TMS-enol ether 247 from $N$-tosyl-3-piperidone\textsuperscript{80} (246) by trapping the corresponding kinetic enolate\textsuperscript{80,81} with TMS-Cl. However, only a complex mixture of products was isolated which contained a significant amount of toluenesulfinic acid (251). This decomposition pathway is likely the result of equilibration of the initially formed kinetic enolate 249a with the thermodynamic enolate 249b, which eliminates toluenesulfinic acid to produce imine 250.\textsuperscript{80} Additionally, direct addition of $N$-chlorosuccinimide to the enolate solution did not yield any of the desired $\alpha$-chloroketone 248.
While a variety of methods have been developed for the $\alpha$-halogenation of ketones, the majority of these procedures focus on symmetrical ketones or aryl ketones where only one chlorinated product can form. On the other hand, relatively few reports exist on the regioselective $\alpha$-halogenation of unsymmetrical ketones. In order to probe the regioselectivity of halogenation in the 3-piperidone system, ketone 242c was treated with a stoichiometric amount of bromine in chloroform to produce a 3:1 mixture of mono-brominated regioisomers favoring the desired $\alpha$-bromoketone 252a (Scheme 53). Although we were pleased to observe this regioselectivity, when the $\alpha$-bromoketone 252a was condensed with $O$-TBS-hydroxylamine, the desired oxime 253 could be obtained but not without contamination by substitution and elimination products 254 and 255, respectively.
Encouraged by the $\alpha$-bromination of ketone 242c, we sought to develop an analogous protocol for $\alpha$-chlorination of $N$-sulfonyl-protected 3-piperidones. However, a process which avoided the use of chlorine gas was highly preferable. Early studies by Masilamani and Rogic have showed that sulfuryl chloride is an effective reagent for the mono-chlorination of symmetrical cyclohexanones and displays reactivity similar to elemental chlorine.82 Fortunately, treatment of $N$-tosyl-3-piperidone (246) with sulfuryl chloride produced a mixture of $\alpha$-chloroketones 256a and 256b with good regioselectivity (~5-7:1 by analysis of the crude product) and the desired $\alpha$-chloroketone regioisomer 256a could be separated from 256b by column chromatography (Scheme 54). It should also be noted that when using fresh bottles of sulfuryl chloride, only 1 equivalent of the chlorinating reagent was required. Since sulfuryl chloride gradually decomposes to sulfur dioxide and chlorine upon standing, additional equivalents of this reagent must be used from older bottles. However, we have found that as many as 8 equivalents could be used if older reagents (~1 year stored at room temperature) were employed with no apparent effect on the outcome of the reaction.
Since removal of tosyl protecting groups from amines is often a difficult process, we were prompted to examine the compatibility of other electron withdrawing protecting groups on the 3-piperidone nitrogen that might be easier to remove. Thus, \textit{N}-SES-3-piperidone (258) was synthesized by selective \textit{N}-sufonylation of 3-hydroxypiperidine (256) with SES-Cl\textsuperscript{83} and subsequent Jones oxidation (Scheme 55). Additionally, \textit{N}-Boc-3-piperidone (259), \textit{N}-(2-nitrophenyl)-3-piperidone (260) and \textit{N}-(2-nitrophenyl)-3-piperidone (261) were prepared according to literature procedures.\textsuperscript{84,78}

Piperidones 258-261 were treated with fresh sulfuryl chloride (1 equiv) and the crude product was examined by \textsuperscript{1}H NMR to obtain the ratio of regioisomeric $\alpha$-chloroketones (yields
were not determined). Interestingly, chlorination of \textit{N}-Boc-3-piperidone (259) led to exclusive formation of the undesired regioisomer \textit{B} (Scheme 56). Treatment of all three \textit{N}-sulfonyl-3-piperidones 258, 260, and 261 with sulfuryl chloride produced the desired 4-chloro-3-piperidone \textit{A} as the major regioisomer but in somewhat a lower \textit{A}:/\textit{B} ratios than with \textit{N}-tosyl-3-piperidone (cf. Scheme 54).

\begin{center}
\textbf{Scheme 56}
\end{center}

\begin{center}
\begin{tabular}{c|c}
\hline
Protecting group (P) & Ratio (\textit{A}:\textit{B}) \\
\hline
\textit{Boc} & only \textit{B} \\
2-\textit{NO}_2\textit{C}_6\textit{H}_4\textit{SO}_2 & \sim5:1 \\
4-\textit{NO}_2\textit{C}_6\textit{H}_4\textit{SO}_2 & \sim3:1 \\
SES & \sim4:1 \\
\hline
\end{tabular}
\end{center}

At a later time, an alternative protocol for the regioselective chlorination of ketone 246 was developed by Pradeep Chauhan in our group. By this method, \textit{\alpha}-chloroketone 248a could be produced exclusively from 3-piperidone 246 by treatment with NCS and Amberlyst-15 in \textit{EtOAc} (Scheme 57).\textsuperscript{85} In this case, direct isolation of the product by filtration of the reaction mixture through a pad of Celite yields a mixture of primarily enol tautomer 262 and some of the desired ketone 248a as observed by \textit{\textit{^1H}} NMR of the crude product. However, subjecting this mixture to subsequent oximation reactions led to poor results. In order to obtain the keto-form 248a exclusively, silica gel was added to the reaction mixture after complete consumption of the ketone 246 and the resulting mixture was stirred for 2 h prior to workup.
Our next objective was to find suitable conditions for oximation of ketone 248a. Formation of O-TBS-oxime 263 from 3-piperidone 248a was accomplished in high yield by treatment of 248a with O-TBS-hydroxylamine and PPTS (Scheme 58). Conversion of α-chloroketone 248a to the corresponding α-chlorooxime 264 using the standard basic conditions was not possible because of the base lability of the α-chlorooxime. However, oximation of 248a under acidic conditions provided the desired α-chlorooxime 264 in good yield. Unfortunately, purification of 264 via silica gel chromatography led to some degradation of the product. Although, the crude oxime 264 could be used in subsequent conjugate addition reactions (vide infra), some residual acetic acid in the crude material affected the overall yield. Furthermore, washing the crude product from this oximation reaction with aqueous sodium bicarbonate led to product degradation presumably via formation of the corresponding nitrosoalkene. Because of these problems, we developed a neutral protocol in which α-chloroketone 248a (1.0 equiv) and hydroxylamine hydrochloride (1.1 equiv) are dissolved in DMSO and stirred at room temperature to yield α-chlorooxime 264 in high purity which can be used without further purification.
3.11 – Conjugate Addition of Indole-2-acetate Methyl Esters to Nitrosoalkenes Derived from 3-Piperidone

With oxime derivatives 263 and 264 in hand, our efforts were now directed at finding a suitable indole ester nucleophile in the key conjugate addition. Thus, the monoanion of indole 218 (1.2 equiv) was generated at -78 °C and then α-chloro-O-TBS-oxime 263 (1.0 equiv) was added followed by TBAF to generate the nitrosoalkene 265 (Scheme 59). After warming the reaction mixture to 0 °C and stirring for 2 h, the desired Michael addition of ester enolate 220b to nitrosoalkene 265 occurred to provide adduct 266, albeit in only 12% yield. Surprisingly, addition of the enolate derived from N-Boc indole 227, which fared well in the model alkylation (cf. Scheme 48), to the nitrosoalkene 265 derived from 263 via the Denmark protocol did not produce any of the Michael adduct 267.
We reasoned that the problems with the above reactions may be related to the relatively short lifetime and high reactivity of the nitrosoalkene 265 generated from 263 under the Denmark conditions. Therefore, we examined the reaction of the ester enolates of indoles 218 and 227 with α-chlorooxime 264. Under classical conditions, α-chlorooxime 264 (1 equiv) was added dropwise to a solution of the monoanion of the free indole 218 (2 equiv) at -78 °C (Scheme 60a). Gratifyingly, production of the Michael adduct 266 occurred quickly at this temperature and this product could be isolated in an acceptable 59% yield with the remainder of the unreacted starting indole recovered. As was observed in the model alkylation, Michael adduct 266 was isolated as a single diastereomer but as a mixture of oxime isomers. However,
the relative chemistry of the two stereocenters in 266 was not determined. Next, α-chlorooxime 264 (1 equiv) was added to a solution of the monoanion of N-Boc indole 227 (2 equiv). However, very little of the desired Michael adduct 267 was produced at -78 °C or upon warming the reaction mixture to 0 °C (Scheme 60b).

Scheme 60

Before moving forward with our revised plan (cf. Scheme 49), we wanted to see if a deoximation of the 3-piperidone oxime was possible in this system. Once again, however, unmasking of the carbonyl functionality of 266 via titanium (III)-mediated deoximation led to a mixture of the desired ketone 268 and cyclocondensation product 269 (Scheme 61). Selective protection of the indole as a Boc-carbamat e was not possible at this stage since O-acylation of the oxime occurred preferentially. For example, treatment of 266 with 2 equivalents of Boc₂O and TEA produced a 1:1 mixture of O-Boc oxime 270 and bis-Boc compound 271. Use of 1
equivalent of Boc₂O in this reaction led to exclusive formation of the O-Boc oxime 270 in modest yield.

Scheme 61

3.12 – Attempted Installation of a C-3 Acetic Acid Unit on Michael Adduct 270

To move forward in the synthesis, installation of an acetic acid substituent onto C-3 of the indole was required. Nucleophilic addition of the electron rich C-3 of indole in 270 to an α-haloacetate derivative appeared to be the most straightforward approach (Scheme 62). Following this step and subsequent indole nitrogen protection, we hoped to simultaneously hydrolyze the ester and oxime functionalities to give the key keto-acid 273. Unfortunately, treatment of indole 270 with a variety of bases (LDA, NaH, K₂CO₃, etc.) followed by addition of t-butyl bromoacetate produced no desired C-3 alkylation product 272. Usually, only
decomposition of the starting indole 270 was observed. It is possible that an enolate equilibration of the indoyl anion with the ester enolate complicates the reaction (cf. Scheme 45). As an alternative, we turned to Qin’s indole cyclopropanation/ring opening strategy to functionalize C-3 of the indole 270. However, indole 270 was found to be unreactive toward both Cu$^{86}$ and Rh$^{87}$-carbenoids generated from t-butyl diazoacetate. Instead, rapid dimerization of the metal-carbenoids led to production of $E$- and $Z$-di-$t$-butyl fumarate.

Scheme 62

At the same time that we were examining the above strategy, we explored another C-3 alkylation process utilizing allylic electrophiles (Scheme 63). In this case, it was hoped that after C-3 allylation and indole protection, oxidative cleavage of both the alkene and the oxime in 274 using KMnO$_4$ under acidic conditions would provide keto-acid 273 in a single operation. However, as before, no alkylation product 274 was observed when 270 was treated with a variety of bases followed by addition of allyl bromide. Additionally, application of Tamaru’s method for indole C-3 alkylation using a $\pi$-allyl palladium species failed to provide 274.$^{88}$
Since installation of a 2-carbon unit at C-3 was proving to be difficult, we turned our attention to 1-carbon homologations. Toward this end, we found that subjection of indole 270 to a Vilsmaier-Haack formylation provided 275 in good yield (Scheme 64). We had hoped that Wittig homologation of 275 using ylide 276 would afford the methylenol ether 277 and a subsequent one-pot deoximation/oxidation would produce the key keto-acid 273. However, the aldehyde moiety of 275 was unreactive toward phosphonium ylide 276. This failure to react may be due to the fact that aldehyde 275 is actually a vinylogous amide which may be deprotonated by ylide 276.
Alternatively, we found that treatment of indole 270 with dimethylamine hydrochloride and formalin under acidic conditions led to a clean conversion to the gramine derivative 278 which was used crude in the following step due to its instability. Quaternization of the gramine 278 with MeI in the presence of KCN produced the desired nitrile product 279 in low yield along with the corresponding deacylated oxime 280. Because it would be necessary to reprotect the oxime before subsequent operations, this route was abandoned.

**Scheme 65**

3.13 – Conjugate Addition of 2,3-Disubstituted Indoles to Nitrosoalkenes Revisited

Since we were unable to develop an effective route for installation of a C-3 acetic acid unit into indole 270, we decided to explore the potential of a different convergent approach utilizing a 2,3-disubstituted indole nucleophile in the key nitrosoalkene conjugate addition step. Thus, placement of an oxoacetate moiety at C-3 of the indole nucleophile would be accomplished by reacting indole 218 with oxalyl chloride and treating the resulting adduct with an appropriate alcohol to form an oxoacetate ester 283 (Scheme 66). Next, a conjugate
addition of the ester enolate of indole derivative 283 to the nitrosoalkene derived from α-chlorooxime 282 would provide adduct 281. Following reductive removal of the oxoacetate ketone oxygen, hydrolysis of the ester to a carboxylic acid, and conversion of an oxime to a ketone to provide keto ester 232, the synthesis would proceed as previously planned (cf. Scheme 49). It is also worth noting that indoyl C-3 ketones similar to 281 have previously been reduced to the corresponding methylene compounds in one step.94

Scheme 66

First, for maximum flexibility in the synthesis, we attempted to prepare several indoles of type 283 with differentially protected carboxylic acids. Thus, indole 218 was treated with oxalyl chloride to cleanly provide adduct 284, which was not isolated but reacted in situ with either t-BuOH, BnOH, or 2-trimethylsilylethanol. Whereas both BnOH and 2-trimethylsilylethanol (TMSE-OH) added efficiently to acid chloride 284 to provide the corresponding esters 285 and 286 respectively in good yields, the sterically hindered t-BuOH gave a complex mixture of products. Using acid chloride 284 with t-BuOK and heating did not improve the outcome of the esterification.
Additionally, indole malonate 214 was converted to the benzyl oxoacetate 288 in an analogous manner (Scheme 68). Unfortunately, addition of the model α-chlorooxime 211 (1 equiv) to either the monoanion (2 equiv) or dianion (1 equiv) of indole malonate 288 did not produce any adduct 289 and most of the starting indole was recovered in both cases.

Due to the high cost of 2-trimethylsilylethanol, our initial experiments using the indole-3-oxoacetate system were carried out using the benzyl ester 285. Additionally, we decided to use the N-Ns-piperidone-oxime 290 (Ns = 2-nitrophenylsulfonyl) since these types of sulfonamides are, in general, easier to cleave than other aryl sulfonamides.92 At this point, we were unsure if
the presence of the C-3 oxoacetate moiety would change the equilibrium behavior of the corresponding monoanion as observed in earlier systems (cf. Scheme 45). Previously, it was noted that using 2 equivalents of an indole ester monoanion 218 gave a higher yielding and cleaner reaction in the alkylation of nitrosocyclohexene than with 1 equivalent of the corresponding dianion (cf. Scheme 44). In this case, we were pleased to find that reacting the dianion of 285 (1 equiv) with \( \alpha \)-chlorooxime 290 (1 equiv) provided adduct 291 in 81% yield (Scheme 69). Using 2 equivalents of the monoanion derived from indole 285 in the conjugate addition reaction provided adduct 291 in approximately the same yield. Once again, these results indicate a monoanion equilibration similar to that observed in the earlier system (cf. Scheme 45).

In the present case, we believe the dianion 293a first deprotonates the oxime 290 providing nitrosoalkene 294 and an equilibrium mixture of the anion 293b and the presumably more nucleophilic anion 293c. The latter anion 293c then reacts with the nitrosoalkene 294 to produce Michael adduct 291 as a single diastereomer and a 1:1 mixture of oxime geometric isomers. Based on the results of a closely related conjugate addition reaction, the relative stereochemistry of 291 has been assigned as shown (\textit{vide infra}). Silyl oxime 292 was subsequently prepared in nearly quantitative yield by treatment of oxime 291 with TBSCI and imidazole.
During the study of the above conjugate addition (cf. Scheme 69), we also examined the use of $N$-protected indole ester monoanions in this key reaction. However, use of the $N$-protected indole substrates in the key conjugate addition reaction had a deleterious effect on the outcome of the reaction. For example, when the model $\alpha$-chlorooxime 211 was added to 2 equivalents of the monoanion of Boc-protected indole ester 295, two products were formed (Scheme 70). The desired adduct 296 and the minor adduct 297, resulting from double alkylation, was isolated as a $\sim$4:1 mixture.
We also examined the effect of an electron donating alkyl protecting group on the indole nitrogen. Not surprisingly, it was difficult to directly alkylate the indole nitrogen (Scheme 71). For example, treatment of indole ester 286 with sodium hydride in DMF followed by addition of PMB-Cl only led to $\alpha$-alkylation of the ester (entry a). Similarly, deprotonation of indole ester 285 with a weaker base and addition of PMB-Cl provided a similar $\alpha$-ester alkylation product 299 (entry b).
Since direct alkylation of the indole nitrogen was problematic, \( N \)-methyl protected indole 301, which we previously attempted to prepare (cf. Scheme 48), was synthesized from \( N \)-methylindole (300) in 4 steps following a literature procedure (Scheme 72).\(^{93} \) The indole 301 was treated with oxaly chloride followed by BnOH to provide the C-3 oxoacetate 302. However, addition of the monoanion of \( N \)-methyl protected indole 302 (2 equiv) to the nitrosoalkene derived from \( \alpha \)-chlorooxime 290 (1 equiv) provided the desired impure adduct 303 in only 14% impure yield along with double alkylation product 304 in 8% yield.

Scheme 72

3.14 – Ketone Reduction of Indole-3-oxoacetates with Hydride Reagents

After identifying an efficient conjugate addition reaction using 2,3-disubstituted indole 285 and \( \alpha \)-chlorooxime 290 (cf. Scheme 69), we turned our attention to removing the ketone oxygen of the 3-oxoacetate functionality in indole-3-oxoacetate 292. In order to do this, we envisioned that an initial reduction of the ketone in 292 with a metal hydride would provide
alkoxide 305 (Scheme 73). We believed that this intermediate would spontaneously eliminate to yield azafulvene 306, which would be reduced by a second equivalent of hydride to provide 307.

Scheme 73

A number of indole-2- and 3-oxoacetates have been deoxygenated using triethylsilane and TFA and we first examined these conditions in our system. However, when oxoacetate 292 was subjected to TFA and triethylsilane, the desired product 307 was not observed, but rather tetracycle 309 was isolated in moderate yield and as a single diastereomer of unknown configuration (Scheme 74). This product is likely the result of an acidic cleavage of the oxime moiety and a concomitant reduction of both the ketone and indole functionalities to give indoline ketone intermediate 308. Cyclocondensation of the ketone onto the indoline nitrogen leads to tetracycle 309. Running the reaction at lower temperatures had little effect on the outcome of this reaction.
We had hoped that placement of a protecting group on the indole nitrogen would serve the dual purpose of preventing both the reduction at the indole and the cyclocondensation of the newly generated ketone. Thus, NH-indole 292 was converted to the methyl carbamate 310. However, treatment of 310 with TFA and triethylsilane did not generate any of the desired reduced product and only the free oxime 311 was isolated (Scheme 75).
We also examined several alternative hydride reduction methods to effect the deoxygenation of oxoacetate 292. For example, it was discovered that treatment of 292 with NaBH₄ (1 equiv) provided alcohol 312, which was quite stable and could be chromatographed. In order to effect complete reduction to the methylene compound 307, an excess of NaBH₄ was added to oxoacetate 292. However this led to a complex mixture of products, one of which was identified as the aldehyde 313. Addition of Lewis⁹⁵ or protic⁹¹b acids to the reaction medium in order to facilitate formation of an azafulvene did not improve the outcome. Several attempts were made to mesylate the alcohol moiety of 312 in the presence of NaBH₄ in order to expedite generation of an azafulvene intermediate, but this method also failed. Finally, some attempted reductions of the alcohol 312 using P₂I₄,⁹⁶ Ph₃P/I₂,⁹⁷ or a Barton-McCombie sequence⁹⁸ failed to provide any of the desired product 307.

Scheme 76

It was discovered that deoxygenation of the oxoacetate 292 could be achieved, albeit in low yield and with concomitant indole reduction, by treating 292 with NaBH₃CN/ZnI₂ in
refluxing 1,2-dichloroethane, followed by refluxing the crude material in MeOH to break up the resulting amine borane complex (Scheme 77). Reoxidation of indoline 314 to indole 307 was attempted using DDQ but was unsuccessful.

Scheme 77

3.15 – Stepwise Deoxygenation of the Indole-3-oxoacetates

Since deoxygenation of the oxoacetate functionality in 292 using hydride reagents proved to be unsuccessful, and since the presence of the benzyl ester of the oxoacetate and nitrophenylsulfonamide functionalities in 292 precluded the use of catalytic hydrogenation, we turned to the modified substrate 315 with which we could explore the latter process. Thus, using the methodology previously developed, addition of the dianion of indole 286 to the nitrosoalkene generated from α-chlorooxime 264 provided Michael adduct 315 as a single diastereomer and a 1:1 mixture of oxime isomers in excellent yield (Scheme 78). The relative stereochemistry of 315 was subsequently established by X-ray analysis on a derivative (vide infra).
The stereochemical outcome of the above Michael addition may be rationalized by invoking transition state 316a, where a metal complexed ester enolate is oriented in such a way as to minimize steric interactions between the indole and the bulky tosyl group of the nitrosoalkene component (Scheme 79). Such an orientation avoids the significant steric interactions which are present when the tosyl group is syn to the indole as depicted in transition state 316b.
Prior to the deoxygenation sequence, oxime 315 was converted to OTBS ether 317 in good yield (Scheme 80). Next, treatment of oxoacetate 317 with NaBH₄ (1 equiv) cleanly provided the alcohol 318 in nearly quantitative yield. However no reduction occurred when either ketone 315 or alcohol 317 was subjected to standard hydrogenation conditions (H₂ (1 atm), Pd/C, EtOH).¹⁰¹,⁹³ On the other hand, in a reductive hydrogenation of a similar system, Hlasta and coworkers had found that converting the alcohol to an acetate and then subjecting this compound to hydrogenation with Pd/C in a 1:9 TEA/EtOH solution was necessary for reduction to occur (presumably via an azafulvene). Therefore, alcohol 318 was acetylated in high yield to provide the acetate 319. Gratifyingly, treatment of the activated compound 319 under Hlasta’s hydrogenation conditions⁹³ provided the desired reduction product 320, albeit with some minor impurities which co-eluted with 320 during purification by column chromatography. We suspected from ¹H NMR analysis of the products that the impurities may be a side product resulting from the addition of EtOH to the azafulvene intermediate.

Scheme 80
To investigate the nature of these side products, indoles \( E-319 \) and \( Z-319 \) were individually treated with a 1:9 TEA/EtOH mixture in the absence of \( \text{H}_2 \) and Pd/C (Scheme 81) leading to adducts \( E-321 \) and \( Z-321 \) which result from the attack of EtOH on to the azafulvene intermediate. Indeed, EtOH adducts \( E-321 \) and \( Z-321 \) were confirmed to be the side products of the above hydrogenation by comparison of \(^1\text{H}\) NMR spectra. It was also discovered that in all of the TLC mobile phases examined, the ethanol adducts \( E-321 \) and \( Z-321 \) had identical \( R_f \) values as the reduction products \( E-320 \) and \( Z-320 \), respectively. Thus, we were unable to separate the side products \( 321 \) from the desired deoxygenation products \( 320 \).

**Scheme 81**

Since the contamination of deoxygenation products \( 320 \) with ethanol adducts \( 321 \) compromised the efficiency of later steps in the synthesis, we needed to develop an alternative hydrogenation protocol. To determine if an alcohol solvent was necessary for the hydrogenation of acetate \( 319 \), the EtOH was replaced with EtOAc, but no reaction occurred during several hours (Scheme 82). However, if EtOH was then added to the hydrogenation reaction medium, the product \( 320 \) began to form. Additionally, the acetate \( 319 \) was not reduced when the
TEA/EtOH solvent mixture was replaced with AcOH. Interestingly, attempted hydrogenation of acetate 319 using the more reactive Pearlman’s catalyst in EtOH, with or without TEA, failed to produce any of the desired compound 320. Therefore, it became apparent that an alcohol solvent was necessary for the hydrogenolysis to occur. In order to minimize formation of an alcohol-indole adduct, we treated acetate 319 with various TEA/alcohol mixtures and discovered that no substitution occurs when 319 is stirred in a 1:9 TEA/t-BuOH solution for 24 h.

Gratifyingly, when acetate 319 was subjected to the modified hydrogenation conditions using t-BuOH instead of EtOH, the deoxygenation product 320 was produced in nearly quantitative yield (Scheme 83) with no detectable side products. However, the reduction occurred at a significantly slower pace in t-BuOH (~5 days) as compared to EtOH (~1 day).
Before moving forward in the synthesis, we decided to investigate toluenesulfonamide 320 as a model substrate for probing the eventual removal of the N-Ts protecting group. Since removal of this protecting group would be one of the final steps in our synthesis, we needed to find a deprotection method that would be compatible with the indole and ester functionalities that are present in the natural product (cf. Scheme 49). We were pleased to find that treatment of indole 320 with sodium naphthalenide produced the free amine 323 in 55% unoptimized yield (Scheme 84).

3.16 - Development and Application of a New Reductive Deoximation Protocol

Based on our previous observations (cf. Schemes 47 and 61), it was evident that protection of the indole nitrogen of 320 was required before converting the oxime to a ketone in
order to avoid cyclocondensation between the ketone and nitrogen of the indole. Furthermore, since we were unable to install $N$-sulfonyl or a $N$-alkyl protecting groups in a related system (cf. Schemes 48), we opted to protect the indole as a Boc-carbamate. Thus, indole 320 was converted to $N$-Boc indole 324 in good yield (Scheme 85). Next, treatment of $O$-TBS oxime 324 with TBAF for 1 minute at 0 °C led to loss of the TBS group and produced free oxime 325 in 93% yield. Stirring the reaction mixture for longer time periods led to degradation of the product, presumably due to side reactions of basic TBAF with the Boc-carbamate\textsuperscript{102} and/or TMSE groups. For example, when the same desilylation reaction was run for 15 min, oxime 325 was isolated in only 18% yield.

Scheme 84

Previously using model oximes, we had identified TiCl$_3$ as a suitable reagent for deoximations in the presence of the sensitive indole functionality (cf. Schemes 47, 48 and 61). Unfortunately, when the more complex oxime 325 was subjected to the same conditions the desired ketone 326 was isolated in only 26% yield (Scheme 86). Several other deoximation protocols were tested but were largely ineffective. For example, oxidative cleavage of the oxime
with Dess Martin periodinane\textsuperscript{103} produced the ketone \textbf{326} in low yield along with multiple side products. Similarly, use of KMnO\textsubscript{4}\textsuperscript{104} to cleave the oxime led to a complex mixture of products with only a small amount ketone observed by thin layer chromatography. Finally, an acidic hydrolysis of the oxime with acetic acid was attempted\textsuperscript{105a}. However, only slow formation of the ketone product \textbf{326} was observed at room temperature and heating of the reaction mixture generated a complex mixture of products.

\textbf{Scheme 86}

Based on the above difficulty in converting oxime \textbf{325} to ketone \textbf{326}, we were prompted to develop new deoximation methodology that might be applicable to sensitive alkaloid systems such as \textbf{325}. The majority of existing deoximation protocols,\textsuperscript{105} which are generally run under hydrolytic or oxidative conditions, are often incompatible with indole and/or amine functionality found in many alkaloids. Therefore, we sought to develop a mild, reductive deoximation protocol that would be compatible with such systems.
In this regard, we were inspired by Burke’s methodology for reductive conversion of oximes to enamides with iron powder and acetic anhydride in hot toluene (Scheme 87). For example, when propiophenone oxime (327) was heated in a mixture of Fe, Ac₂O, AcOH, and PhMe at 75 °C, the enamide 328 was isolated in high purity as a mixture of geometric isomers (no yield was reported). Interestingly, in the absence of added AcOH, the reductive amidation occurs at a slower rate.

Scheme 87

This method was later improved by Zhang, who found that the Fe(0)-mediated reductive amidation could be effected at room temperature in DMF when a catalytic amount of TMSCl was added to the reaction mixture (Scheme 88a). For example, α-oxygenated aryl ketoximes 329 were converted under these mild conditions to the corresponding enamides 330 in good yields. More recently, our group expanded the scope of this reaction by employing acid chlorides and chloroformates of various types to produce enamides and enecarbamates (Scheme 88b). For example, in the presence of benzoyl chloride, α-tetralone oxime 331 was converted to enamide 332 in good yield. Alternatively, when ethyl chloroformate was used as the acylating agent enecarbamate 333 was generated in good yield. Additionally, non-conjugated enamides and enecarbamates can be prepared by this methodology. However, these compounds were found to be quite unstable toward hydrolysis and chromatography and were generally used without purification in subsequent reactions (vide infra).
Mechanistically, it is most likely that these types of reactions involve two single electron reductions (Scheme 89). Thus, following formation of the O-acyl oxime 336, a single electron reduction produces the iminyl radical 337. Subsequent single electron reduction of iminyl radical 337 generates the iminyl anion 338 which is then protonated to yield the imine 339. Capture of the acylating agent 335 by the enamine tautomer 340 leads to the N-acyl enamine product 341.
Deoximation reactions which are promoted by Fe(0) have been previously reported.\textsuperscript{110,111} However, these methods are generally run under harsh conditions (i.e. Fe and conc. HCl in refluxing MeOH). It occurred to us that a modification of the above Burke/Zhang oxime reduction procedures (Cf. Schemes 87-89), in which the acylating reagent is omitted, may produce an imine intermediate such as 339 which would be easily hydrolyzed to the corresponding carbonyl compound upon aqueous work-up.

To explore the feasibility of this idea, we treated the model 3-piperidone oxime 342 with Fe powder and a catalytic amount of TMSCl in MeOH, THF, or PhMe (Scheme 90). However, no ketone 246 was produced at room temperature or at reflux for several hours and only E/Z isomerization of the oxime was observed.

Scheme 90

In the earlier study, we had observed that the enamides and enecarbamates derived from aliphatic ketoximes were very susceptible to hydrolysis.\textsuperscript{108} Since we needed to obtain the corresponding ketone 246 from oxime 342, we turned our attention to forming the enamide \textit{in situ} and then purposely hydrolyzing this intermediate to the corresponding ketone (Scheme 91a). Thus, when Ac₂O and a catalytic amount of TMSCl was added to a solution of the model oxime 342 and Fe powder (10 equiv) in THF, complete consumption of the starting material occurred at
room temperature within 30 min to presumably generate enamide 345. After an acidic work-up with 1 M HCl, ketone 246 and some oxime acetate 343 were isolated. However, the overall yield of ketone 246 was highly variable (37-70%). Unfortunately, application of this procedure to our synthetic substrate 325 also led to variable yields of ketone 326 (Scheme 91b).

Scheme 86

Since acetylation of the oxime most likely occurs prior to reductive imine formation as depicted in Scheme 91a, we hoped that preformation of the oxime acetate 343 would boost the overall efficiency of the reaction. Additionally, by omitting Ac₂O from the reaction, the sole product of the reduction should be imine 344 which should be quite prone to hydrolysis. Indeed, when oxime acetate 343 was subjected to the previously developed conditions, but without acetic anhydride, complete consumption of the oxime acetate was observed within 30 min and
production of ketone 246 was observed by TLC analysis (via *in situ* hydrolysis of the intermediate imine 344). Aqueous work-up led to isolation of the ketone 246 in moderate yields (~60-70%) as well as some of the free oxime 342. Surprisingly, however, this reaction was irreproducible and in several runs very little of the oxime acetate 343 was converted to ketone 246. After some investigation, it was discovered that the successful reactions had been run in flasks which had previously been soaked in concentrated nitric acid and then thoroughly rinsed with water to remove the iron oxide residues of previous runs. Thus, we realized that a trace amount of acid was catalyzing the conversion of 343 to 246. Indeed, addition of a catalytic amount of various acids (nitric acid, trifluoroacetic acid, and *p*-toluenesulfonic acid) increased the amount of ketone produced. However use of a small amount of glacial acetic acid gave the best results. When these new conditions were applied to the complex indole oxime acetate 346, available in high yield from acetylation of oxime 325, the ketone was produced in a reasonable 57% yield along with some deacetylated oxime 325.

**Scheme 92**
Since we observed some deacetylation of the ketoxime acetate 346 in this reaction to form the unreactive free oxime 325, we decided to explore the use of other less labile O-acyl-groups in this reaction that might circumvent this problem. This phase of the study was conducted by Jason Witek of our group. Initially, 4-phenylcyclohexanone oxime was O-acylated with several different groups that we hoped would expedite imine formation and/or inhibit deacylation to the unreactive free oxime (Scheme 93). Once again, the oxime acetate 347 was converted to ketone 351 in reasonable yield but with formation of some free oxime by-product. Use of benzoate 348 and ethyl carbonate 349 in the deoximation procedure led to lower yields of ketone 351. On the other hand, use of the pivalate 350 provided ketone 351 in 88% isolated yield and with no detectable amount of the free oxime.

Scheme 93

<table>
<thead>
<tr>
<th>Acyl Group (R)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>347 (Ac)</td>
<td>68%</td>
</tr>
<tr>
<td>348 (Bz)</td>
<td>27%</td>
</tr>
<tr>
<td>349 (CO₂Et)</td>
<td>44%</td>
</tr>
<tr>
<td>350 (Piv)</td>
<td>88%</td>
</tr>
</tbody>
</table>

Based on the above optimization studies, a general procedure for deoximation was developed (Scheme 94). Thus, a catalytic amount of glacial AcOH (1 drop) and TMSCl (1 drop) are sequentially added to a mixture of oxime pivalate 352 (1 eq) and Fe powder (10 eq) at room temperature. The mixture is stirred for 30 min, diluted with water, stirred for an additional 15 min and then worked up to provide the ketone 353. These general conditions were applied to several types of ketoxime pivalates shown in Table 5. It should be noted that aldoxime pivalates
were found to be poor substrates under the general deoximation conditions since formation of nitriles was favored over production of the corresponding aldehydes.

**Scheme 94**

![Scheme 94](image)

**Table 5. Conversion of Ketoxime Pivalates to the Corresponding Ketones**

<table>
<thead>
<tr>
<th>entry</th>
<th>oxime pivalate</th>
<th>carbonyl product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>( \text{PivO} \text{N} \text{Ts} )</td>
<td>( \text{O} \text{N} \text{Ts} )</td>
<td>81%</td>
</tr>
<tr>
<td>B</td>
<td>( \text{EtOC} \text{C} \text{N} \text{Ts} )</td>
<td>( \text{EtOC} \text{C} \text{O} )</td>
<td>54%</td>
</tr>
<tr>
<td>C</td>
<td>( \text{N} \text{OPiv} )</td>
<td>( \text{C} \text{O} )</td>
<td>71%</td>
</tr>
<tr>
<td>D</td>
<td>( \text{N} \text{OPiv} )</td>
<td>( \text{O} \text{C} )</td>
<td>95%</td>
</tr>
<tr>
<td>E</td>
<td>( \text{N} \text{OPiv} )</td>
<td>( \text{O} )</td>
<td>91%</td>
</tr>
</tbody>
</table>

Gratifyingly, subjecting the indole oxime pivalate 354 to the general deoximation conditions provided ketone 326 in 84% yield (Scheme 89).
3.17 – Synthesis of Keto Acid 361 and Subsequent Application of Romo’s Aldol Lactonization

With an efficient route to ketone 326 now developed, all that remained to access the key keto acid substrate for the Romo aldol lactonization was to selectively cleave the 2-trimethylsilylthethyl ester to the corresponding carboxylic acid. However, attempted removal of the 2-trimethylsilylthethyl ester in 326 using several fluoride-based methods only led to decomposition of the starting material, perhaps due to the presence of the Boc-carbamate which is sensitive to fluoride.102 Alternatively, it was found that treatment of 326 with TFA led to the desired cleavage of the 2-trimethylsilylthethyl ester.113 However, concomitant loss of the Boc protecting group was unavoidable and only cyclodehydration product 356 was isolated from the reaction (Scheme 96). Therefore, a more acid stable protecting group for the indole nitrogen was required.
At this stage of the synthesis, the oxime isomers of NH indole 320 were separated and individually subjected to Cbz-protection conditions to provide N-Cbz indoles $E$- and $Z$-357 in identical 89% yields (Scheme 97). This separation was required because in these acylation reactions, some unreacted NH indole remains and the chromatographic polarity of NH indole $Z$-320 is approximately the same as N-Cbz indole $E$-357, which makes purification difficult. Slow evaporation of an EtOAc solution of $Z$-357 provided crystals that were suitable for X-ray analysis$^{141}$ (see Experimental Section for ORTEP of $Z$-357 (pg. 186)) and the relative stereochemistry of the compound was determined to be as shown (cf. Scheme 79).
Moving forward, the recombined mixture of O-TBS-oximes 357 was treated with TBAF buffered with AcOH to prevent side reactions resulting from the basic fluoride to give the free oximes 358 (cf. Scheme 85). Subsequent conversion of oximes 358 to the oxime pivalates 359 and reductive deoximation using our Fe-mediated protocol provided ketone 360 in good yield. Finally, 2-trimethylsilylethyl ester 360 was smoothly converted to the pivotal keto acid 361 in 92% yield by treatment with TFA.112
With keto acid 361 in hand, we were now ready to attempt the key Romo aldol lactonization. Thus, slow addition of the keto acid 361 to a mixture 2-bromo-N-propylpyridinium triflate, Hunig’s base, and PPY in dichloromethane led to smooth conversion to the pentacyclic β-lactones which were isolated as a chromatographically inseparable 8:1 mixture of the desired cis-azadecaline 362 and the trans-azadecalin 363 (Scheme 92). This diastereomeric β-lactone mixture was treated with DIBAL-H to provide a 7.5:1 mixture of 1,3-diols 364 and 365 which were now separable by column chromatography.
Extensive 2D-NMR analysis (HMBC, HMQC, COSY, and NOESY) was conducted in order to determine the structure and conformation of the cis-azadecalin 1,3-diol 364. It should be noted that 1,3-diol 364 is similar in structure to alstilobanine A (169), which in solution has the piperidine ring in a chair conformation (169a) and where the C-19 tertiary hydroxyl group is axial relative to that ring (Figure 6). However, azadecalin 364 is in the opposite conformation in which the C-20 alcohol is equatorial to the piperidine ring. The difference in ring conformations between 364 and 169 may be due to the presence of the C-16 hydroxy methyl group in alstilobanine A. This substituent may cause the piperidine ring of alstilobanine A to exist as the cis-azadecalin conformer 169a, rather than a conformation like 169b in which the C-20 hydroxyl group has an energetically penalizing 1,3-diaxial interaction with the C-16 hydroxymethyl group. Conversely, the piperidine ring in 1,3-diol 364a may exist in the opposite conformer relative to alstilobanine A to avoid torsional strain between the C-16-C/C-22 and C-14/C-15 bonds that
would exist in a conformation like 364b. The structure of the trans-azadecalin system was later established by X-ray analysis (*vide infra*).

![Conformations of Alstitialobanine A (169) and Major 1,3-Diol 364](image_url)

**Figure 6. Conformations of Alstitialobanine A (169) and Major 1,3-Diol 364**

3.18 – Attempted Intermolecular Ester Enolate Alkylations to Install the C-17 Hydroxymethyl Unit

Our plan at this stage of the synthesis was to add formaldehyde (or an equivalent) to the upper face of an enolate derived from 366 which could exist in conformations 367a or 367b (Scheme 100). It was our anticipation that the electrophile might add from the top, least congested face of either enolate, although such attack would be more likely from the natural product-like conformation 367b, where the C20-O bond is in the equatorial position.
Conversely, addition of electrophiles to the top face of conformation 367a may be hindered by a developing 1,3-diaxial interaction between the C20-O bond and the incoming electrophile.

**Scheme 100**

Initial attempts were made to directly install the C-17 hydroxymethyl group into 1,3-diol 364. Unfortunately, only starting material was recovered upon treatment of 364 with potassium carbonate and formalin. Treatment of 364 with NaH (3 equiv) and paraformaldehyde in DMF only led to decomposition. Therefore, we opted to protect the 1,3-diol of 364 at this stage. Treatment of 364 with the di-tert-butyldisilyl bis(triflate)\(^{114}\) and 2,6-lutidine only led to silylation of the primary alcohol to yield silanol 369 (Scheme 101a). However, subjecting 364 to a mixture of 2,2-dimethoxypropane and acetone under acidic conditions provided acetonide 370 in low yield (Scheme 101b). Unfortunately, we were unable to optimize this reaction. Alternatively, reacting 1,3-diol 364 with triphosgene\(^{115}\) produced the cyclic carbonate 371 in high yield (Scheme 101c). The protected 1,3-diols 370 and 371 are assumed to maintain the unnatural cis-azadecaln
conformation shown. However, no 2D NMR studies were conducted in order to confirm this supposition.

Scheme 101

Unfortunately, treatment of indole ester 371 with LDA and monomeric formaldehyde at -78 °C gave no condensation product, and warming of the reaction mixture led to loss of the carbonate protecting group (Scheme 102a). Similarly, treatment of indole ester 370 with LDA and monomeric formaldehyde did not produce any condensation product 373 and only starting material was recovered (Scheme 102b).
We reasoned that converting 1,3-diol 364 to acetonide 370 was low yielding since the product contained a 1,3-diaxial interaction between the axial methyl group on the acetonide ring and the C-21 methylene of the piperidine ring (cf. Scheme 101b). To circumvent this problem, 1,3-diol 364 was stirred in refluxing dimethoxyethane containing a catalytic amount of p-toluenesulfonic acid to yield the corresponding acetal 374 as a single diastereomer (Scheme 103). The methyl group of the acetal was determined to be in an equatorial position based on $^1$H-$^1$H-NOESY analysis of a later intermediate (vide infra). Once again, however, treatment of the indole ester 374 with a variety of bases (LDA, NaH, KHMDS, etc.) followed by addition of monomeric formaldehyde failed to produce any of the condensation product 375 and starting material was recovered in all cases.
Since we thought that it might be possible that the highly reactive monomeric formaldehyde was polymerizing at a faster rate than it was reacting with the ester enolate derived from 374, the alkylation was attempted using various halomethyl ethers that could later be converted to a hydroxymethyl group (i.e. BOM-Cl, PMB-Cl, MOM-Cl) (Scheme 104). Unfortunately, all alkylation attempts failed with these electrophiles and starting material was recovered in the majority of cases.
3.19 – Intramolecular Alkylation Strategy to Form a 7-Membered Ring Ether

Since we were having difficulty installing the C-17 hydroxymethyl group via intermolecular additions, we were prompted to see whether we could construct the 7-membered bridging ether through an intramolecular alkylation strategy (Scheme 105). For example, intramolecular attack of the enolate derived from indole ester 378 onto the tethered halomethyl ether would directly form the bridging ether 377. In turn, the halomethyl ether of 378 could be generated directly from the methylthiomethyl (MTM) ether 379 by a number of known methods.

Scheme 105

To explore conversion of the primary alcohol in diol 364 to a methylthiomethyl ether, a Pummerer alkylation using DMSO/Ac₂O was first tested. However, these attempts predominately led to oxidation of the primary alcohol to give the corresponding aldehyde. On the other hand, the method of Kyler, which utilizes benzoyl peroxide and dimethyl sulfide, produced MTM-ether 380 in reasonable yield (Scheme 106). Subsequent TBS-protection of the tertiary
alcohol provided the crystalline compound 381, which was unambiguously shown to exist in the unnatural azadecalin conformation by X-ray crystallography (Figure 7). \(^{141}\)

**Scheme 106**

![Scheme 106](image-url)

104
Figure 7. ORTEP and Wireframe Structure of Compound 381
Initial attempts to convert the methyl thiomethyl ether 381 to an iodomethyl ether using Mel\textsuperscript{118d} failed, and in all cases loss of the MTM group to yield primary alcohol 384 was observed (Scheme 107). However, treatment of MTM-ether 381 with sulfuryl chloride\textsuperscript{119} cleanly produced the chloromethyl ether 382. This compound proved to be quite sensitive and could not be chromatographed or even dissolved in CDCl\textsubscript{3} without conversion to primary alcohol 384 (presumably due to traces of HCl and H\textsubscript{2}O). However, concentration of the reaction mixture in \textit{vacuo} gave essentially pure chloromethyl ether 382 as determined by \textsuperscript{1}H NMR analysis of the crude material in C\textsubscript{6}D\textsubscript{6}. Unfortunately, all attempts to effect an intramolecular alkylation of 382 failed and primary alcohol 384 was usually the only product obtained from the reaction.

\textbf{Scheme 107}

\begin{center}
\includegraphics[width=\textwidth]{scheme107.png}
\end{center}

conditions tried:
LiHMDS, THF, -78 °C to rt
NaH, THF, 0 to 50 °C
LDA, THF, -78 °C to rt
LDA, HMPA, THF, -78 °C to rt
3.20 – Intermolecular Ester Enolate Alkylation Revisited

When planning our synthesis, we had anticipated that formation of the requisite C-17 hydroxymethyl system at this stage would be challenging. However, we were surprised to find that absolutely no C-17 alkylation products were observed in any of the above reactions. In light of these failures, we reasoned that the main problem may lie in formation of the ester enolate itself. Inspection of molecular models suggested that the ester enolate of 385 might be unstable due to A1,3 strain121 with the adjacent Cbz-carbamate (Figure 8). Although we had considered this potential problem earlier, it seemed reasonable that the enolate could perhaps assume a conformation in which A1,3 strain would be minimized.

![Figure 8. A1,3-Strain in N-Cbz Indole Enolate 385](image)

In order to test this hypothesis, the Cbz-carbamate moiety of 374 was removed via hydrogenolysis to yield NH indole 389 in 96% yield (Scheme 108). Indeed, treatment of the free indole 389 with LiHMDS (3.5 eq) followed by addition of monomeric formaldehyde produced several alkylation products. Two of these products were identified as hemiaminal 390 and cyclic aminal 391 which also contained a hydroxymethyl group of unknown configuration. It should be noted that Overman and coworkers have successfully α-hydroxymethylated a similar indole ester by this procedure.73 When indole ester 389 was treated with 1.0 equivalent of LiHMDS at -78
°C followed by addition of BOM-Cl and warming to rt, a complex mixture of products was produced, one of which was identified as the N-alkylated compound 392.

**Scheme 108**

While we were examining the alkylation of the enolate derived from NH indole ester 389, we discovered that when N-Cbz indole 374 was treated with an excess of sodium hydride and paraformaldehyde in DMF, the alkylation product 393 containing a free indole was obtained in good yield (Scheme 109). In this case, it is most likely that cleavage of the Cbz-carbamate in 374 by adventitious sodium hydroxide occurs prior to the formation of dianion 394 and subsequent alkylation. Unfortunately, the alkylation product was isolated exclusively as the undesired C-17 diastereomer which was proven by observation of a strong nuclear Overhauser effect between the methyl ester and acetal methyl protons. The stereochemical outcome of the reaction may be explained by examining the initially formed enolate 394a. In this intermediate,
attack by the enolate on the electrophile from the desired top face is hindered by a 1,3-diaxial interaction between the incoming electrophile and the C20-O bond. Furthermore, conformational inversion of the azadecalin system to an alstilobane A-type conformation 394b may be prevented by A1,3-strain between the enolate and the C14/C15 bond of the adjacent piperidine ring.

**Scheme 109**

![Scheme 109](image)

### 3.21 – A Silicon-Tethered Intramolecular Ester Enolate Alkylation to Install C-17

Given the above result, it was unlikely that we could install the C-17 hydroxymethyl substituent with the requisite configuration via an intermolecular alkylation. However, since all derivatives of the 1,3-diol 364 presumably exist in the unnatural cis-azadecalin conformation (cf. Figure 6), we reasoned that the C-17 hydroxymethyl group could be installed using an intramolecular alkylation of a halomethylsilane like 397 (Scheme 110).122 The cyclic siloxane
produced by this process could then undergo a Fleming-Tamao oxidation\textsuperscript{123} to generate the C-17 hydroxymethyl moiety with the proper stereochemistry.

\textbf{Scheme 110}

To investigate this strategy, the tertiary alcohol moiety of \textbf{380} was smoothly converted to the chloromethyl(dimethyl)silyl protected derivative \textbf{398} by treatment with an excess of chloromethyl(dimethyl)silyl triflate and 2,6-lutidine in refluxing CH\textsubscript{2}Cl\textsubscript{2} (Scheme 111).\textsuperscript{124} Next, a Finkelstein reaction converted chloride \textbf{398} to the iodide \textbf{399}. However, Cbz-removal via catalytic hydrogenation was not possible on any of the synthetic intermediates which contained the catalyst poisoning sulfide. Use of Bennesar’s procedure\textsuperscript{125} involving tributyltin radical mediated Cbz-cleavage appeared to provide some of the desired deprotected product derived from \textbf{380}. However, this material contained several impurities and could not be used in subsequent reactions. Similarly, base catalyzed methanolysis\textsuperscript{126} of the N-Cbz indole \textbf{380} failed to provide the desired NH indole. With N-Cbz indole \textbf{399} in hand, we attempted to effect the desired intramolecular ester enolate alkylation, but unsurprisingly, based on the results discussed above, no reaction occurred and only the starting indole was recovered.
Scheme 111

One of our strategies for synthesizing alstilobanine A (169), which lacks the 7-membered bridging ether, was to deoxygenate the C-18 primary alcohol using a Barton-McCombie sequence. Toward this end, xanthate ester 401 was prepared in acceptable yield using standard conditions (Scheme 112). However subjecting 401 to radical deoxygenation in refluxing toluene only led to formation of the oxetane 403 in low yield, presumably via an S_N2-pathway. Alternatively, we attempted to employ Myers protocol for the selective deoxygenation of primary alcohols in the presence of secondary and tertiary alcohols, but unfortunately this reaction failed in our system.\textsuperscript{127}
Fortunately, selective protection of the primary alcohol in 364 could be achieved with TBSOTf and 2,6-lutidine to provide OTBS ether 404 (Scheme 113). Next, removal of the Cbz-protecting group via hydrogenolysis occurred cleanly to give NH indole 405 and subsequent silylation of the tertiary alcohol with chloromethyl(dimethyl)silyl triflate produced chloromethylsilane 406. Refluxing 406 in a solution of NaI and acetone provided iodide 407 in nearly quantitative yield. To our delight, treatment of the indole ester 407 with KHMDS (3 equiv) effected cyclization at C-16 to produce the silyl ether 408 in excellent yield.
At the same time that we were developing the above route for the synthesis of siloxane 408, we were also testing an alternative one-pot strategy for eventual introduction of the two silyl groups into intermediate 364 to make 406. For this study, we used the minor trans-azadecalin 1,3-diol 365 as a model system. Thus, the N-Cbz-protecting group in 365 was removed via hydrogenolysis and the crude NH indole 409 was treated with TBSOTf and 2,6-lutidine (Scheme 114). After complete consumption of the starting indole 409 as monitored by TLC, chloromethyl(dimethyl)silyl triflate and additional 2,6-lutidine was added to the reaction mixture to ultimately provide the differentially bis-O-silylated product 411 in 90% yield over 2 steps. In one of the runs of this reaction, not all of the monosilylated intermediate 410 was converted to disilylated product 414. Compound 410 was isolated and found to be crystalline and analysis of this derivative by X-ray diffraction\(^\text{141}\) confirmed the structure of a trans-azadecalin ring system in 365 (Figure 9).
Scheme 114

![Scheme 114](image)

Figure 9. ORTEP Structure of O-TBS Ether 411
3.22 – Attempted Fleming-Tamao Oxidation of Cyclic Silyl Ethers

After successfully forming the challenging C-16/C-17 bond using a silicon tethered intramolecular alkylation, the next step was to convert the siloxane into the corresponding hydroxymethyl compound. While numerous methods exist for this transformation, we decided to focus on oxidations run in basic media since we reasoned that the peroxide anion would be less likely to oxidize the nucleophilic indole than under neutral or acidic conditions. For easier monitoring of the reaction, the TBS group was first removed from 408 by treatment with TBAF to provide primary alcohol 412 (Scheme 115). Unfortunately, when silane 412 was subjected to the standard Tamao conditions, no reaction occurred at room temperature or upon refluxing the reaction mixture (entries A and B). However, when KF was replaced with TBAF, the 1,3-diol 414 was isolated as the sole product (entry C). Thus, it is likely that the oxidation occurs to initially generate the triol 413, but under the basic conditions a retro-aldol reaction takes place to ultimately produce 1,3-diol ester 414. In order to examine whether more neutral conditions would provide the triol, 412 was treated with KHF₂ and H₂O₂ in hot DMF, but only a complex mixture was obtained (entry D). Interestingly, subjecting the OTBS protected substrate 408 to the same conditions as entry C led to no reaction (entry E). In a parallel reaction, the same substrate was treated under similar conditions but without TBAF (entry F). Initially, no reaction occurred at room temperature, but when a large excess of hydrogen peroxide was added, and the reaction mixture was refluxed for 2 days, two new products were formed in low yield which were tentatively assigned as hydroxymethyl compounds 415 and 416 resulting from over-oxidation and/or elimination.
One of the drawbacks of the Fleming-Tamao oxidation is that sterically hindered siloxanes, such as in our system, are often difficult to oxidize.\textsuperscript{123c} In order to enhance the reactivity of our system, some attempts were made to open the cyclic silyl ether \textbf{412} to the more reactive silanol \textbf{418} or silyl fluoride \textbf{417} (Scheme 116). Unfortunately, treatment of \textbf{412} with excess TBAF at room temperature produced no reaction after several days and heating the reaction mixture led to complete decomposition (entries A and B).\textsuperscript{128} Treatment of the silane
with silica gel failed to produce the desired silanol 418 (entry C). Additionally, the siloxane was found to be stable under basic conditions for several days (entry D). Finally, acidic hydrolysis of the Si-O bond in 412 was attempted, but 412 was stable in AcOH (entry E) and treatment with TFA only produced the trifluoroacetate 419 (entry F).

Scheme 116

As seen above, the cyclic silyl ether 412 was very stable under a variety of conditions. Since siloxanes derived from tertiary alcohols tend to be less reactive toward hydrolysis and oxidation than the corresponding siloxanes derived from secondary and primary alcohols, we decided to move the silicon tether to the primary alcohol. In this case, the silyl group should be more prone to both hydrolysis and oxidation compared to the sterically hindered siloxane 412. Thus, the primary alcohol of 414 was silylated with a chloromethyl(dimethyl)silyl group to yield
chloromethylsiloxane 420 (Scheme 117). This compound, which was very acid sensitive, was immediately treated with TMSOTf and 2,6-lutidine to give the desired disilyl compound 421 as well as some of the bis-OTMS product 422. When compound 421, was treated with KHMDS, a mixture of several products was obtained which included the intramolecular alkylation products 423 and 424, as well as the ring-opened product 425 in an overall low yield. Unfortunately, we were unable to optimize this reaction to produce any of the cycloalkylation products 423-425 in higher yield.

Scheme 117

To improve the acid stability of the silicon tether, we decided at this point to use a chloromethyl(diphenyl)silyl group instead. Thus, the 1,3-diol 414 was selectively silylated with
chloromethyl(diphenyl)silyl chloride to give 426, which was considerably more stable than 420 (Scheme 118). After trimethylsilyl protection of the tertiary alcohol 426, indole ester 427 was treated with KHMDS to effect an intramolecular alkylation. Surprisingly, only a trace amount of what is presumably the cycloalkylation product 428 was observed via mass spectrometry but very little material could be isolated (<10% of the mass balance).

Scheme 118

Since we had already developed an efficient route to form the cyclic dimethylsilyl ether 408 (cf. Scheme 113), we decided to prepare the analogous diphenylsilyl ether since, in general, diphenylsiloxanes are more prone to undergo a Fleming-Tamao oxidation than the corresponding dialkylsiloxanes.131 Moreover, a protodesilylation of one or both of the phenyl groups could, in principle, be effected to produce even more reactive silyl intermediates for the oxidation.123c

In order to install the chloromethyl(diphenyl)silyl group onto the tertiary alcohol of 405, it was necessary to synthesize diphenylsilyl triflate 430, which to the best of our knowledge was
previously unknown. Thus, treatment of chloromethyl triphenylsilane (429) with TfOH in refluxing 1,2-dichloroethane produced the desired triflate in an unoptimized 50% yield (Scheme 119).

Scheme 119

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \quad \text{Cl} \quad \text{Si} \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \quad \text{OTf} \\
\text{reflux} & \quad 50\% \\
\end{align*}
\]

Silylation of tertiary alcohol 405 with chloromethyl(diphenyl)silyl triflate and subsequent conversion of the chloride to the corresponding iodide provided iodomethylsilane 432 in good yield (Scheme 120). However, we were surprised to find that treatment of 432 with KHMDS led to only a very small amount of the desired product 433 and, once again, very little material was isolable (<15% of the mass balance).

Scheme 120
3.23 – Reprotection of the Indole Nitrogen to Prevent a Retro Aldol Reaction

As discussed above, we had discovered an oxidation/retro-aldol sequence involving cyclic silyl ether 412 (cf. Scheme 115). However, based on our previous observations, we reasoned that it might be possible to prevent the retro-aldol process from occurring if the indole nitrogen is acylated during the Fleming-Tamao oxidation since formation of an enolate intermediate would be disfavored due to A^1,3 strain (cf. Figure 7). Toward this end, the Cbz-protecting group was reintroduced onto the indole nitrogen of 408, albeit in low yield (Scheme 121a). However, Boc-protection of the indole 408 was achieved in high yield to provide N-Boc indole 446 (Scheme 121b). In addition, since we were concerned that the Cbz- and Boc-protecting groups may too labile under the required basic conditions of the Fleming-Tamao oxidation, a N-benzyl protected analogue 448 was also prepared from indole 408 (Scheme 121c). Additionally, the primary OTBS groups of 444, 446, and 448, were removed with TBAF to yield the corresponding primary alcohols 445, 447, and 449, respectively.
When removing the O-TBS-protecting group from the N-Boc indole 446, we observed formation of a significant amount of the NH-indole as a side product. Therefore, due to the sensitivity of the Boc-carbamate to fluoride, N-Boc indole 447 was subjected to buffered Fleming-Tamao oxidation conditions (Scheme 122), but unfortunately no reaction occurred at room temperature or at reflux (entries A and B). We also examined the use of stronger oxidants with the N-Boc indole 447. However, when 447 was treated with m-CPBA and KF in DMF
only starting material was recovered (entry C). On the other hand, treatment of 447 with peracetic acid (formed \textit{in situ} from 30\% \text{H}_2\text{O}_2 \text{ and Ac}_2\text{O}) led to a small amount of the overoxidized product assumed to be diol 451 (entry D). \textit{N}-Cbz indole 444 was heated in a mixture of \text{H}_2\text{O}_2, \text{KF}, \text{and DMF} but no reaction occurred (entry E). Finally, \textit{N}-Bn indole 449 was subjected to the same conditions that promoted an oxidation/retro-aldol of the corresponding NH indole 412 (cf. Scheme 115), but no reaction occurred at room temperature or on heating the reaction mixture.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Entry} & \textbf{Indole} & \textbf{Oxidation Conditions} & \textbf{Result} \\
\hline
A & 447 & TBAF, 30\% \text{H}_2\text{O}_2, \text{MeOH/THF, pH = 7 buffer, rt} & no reaction \\
B & 447 & TBAF, 30\% \text{H}_2\text{O}_2, \text{MeOH/THF, pH = 7 buffer, reflux} & no reaction \\
C & 446 & \\textit{m}-CPBA, \text{KF, DMF} & no reaction \\
D & 446 & \text{Ac}_2\text{O}, 30\% \text{H}_2\text{O}_2, \text{KF, DMF, 50 \textdegree C} & 451 (~5\%) \\
E & 444 & \text{KF, 30\% \text{H}_2\text{O}_2, DMF, 80 \textdegree C} & no reaction \\
F & 449 & \text{KHCO}_3, \text{TBAF, 30\% \text{H}_2\text{O}_2, MeOH/THF, rt-40 \textdegree C} & no reaction \\
\hline
\end{tabular}
\end{table}
3.24 – Use of the Woerpel Modification of the Fleming-Tamao Oxidation

Woerpel has developed a useful modification for the oxidation of sterically hindered siloxanes. For example, when the oxasilacyclopentane 452 was treated under standard conditions (aqueous H₂O₂, KHCO₃, and KF) only starting material was recovered (Scheme 123). Additionally, none of the other usual modifications to the Fleming-Tamao oxidation were successful with this substrate. However, it was found that when oxasilacyclopentane 452 was added to a mixture of t-BuOOH (14 equiv) and CsOH·H₂O (12 equiv) in DMF at room temperature, an oxidation occurred to produce dioxasilacyclohexane 453, which could be isolated from the reaction mixture. However, to complete the transformation, TBAF (5 equiv) was added to 453 and the resulting reaction mixture was stirred for 8 h at 75 °C to provide 1,3-diol 454. It should be noted that in the absence of TBAF or when less than 5 equivalents of the fluoride source is used, not all of the dioxasilacyclohexane 453 was converted to the 1,3-diol 454. Notably, this protocol has been used in the successful oxidations of generally unreactive substrates such as alkoxysilanes derived from tertiary alcohols and even silanes bearing four alkyl substituents.

Scheme 123

Although this method has been demonstrated to be effective in simple systems, we had initially avoided using these highly basic conditions with our substrates which contained base
sensitive ester and carbamate functionalities. However, with \(N\)-Bn protected indole 449 in hand, we were prompted to examine Woerpel’s conditions even though we expected that the methyl ester would likely be converted to the acid. When siloxane 449 was subjected to Woerpel’s standard conditions, all of the starting material was consumed and a crude mixture containing primarily the retro-aldol product 455 was obtained. For full characterization, this material was converted to the methyl ester 456 using TMSCHN\(_2\) in MeOH (Scheme 124).\(^{135}\) This result is somewhat surprising since we expected that the presence of the \(N\)-benzyl group should slow the retro-aldol pathway due to the \(A^{1,3}\) strain present in intermediate enolate 457.

**Scheme 124**

\[\text{t-BuOOH (70\% in H}_2\text{O)} \quad \text{CsOH H}_2\text{O, DMF} \quad 10 \text{ min.}\]

\[\text{then, TBAF} \quad 75 \text{ °C, 6.5 h}\]

\[449 \quad \xrightarrow{\text{R} = \text{H}} \quad 455 \quad \xrightarrow{\text{TMSCHN}_2} \quad 456 \quad \text{MeOH, Et}_2\text{O} \quad 37\% (2 \text{ steps})\]

It was evident that modification of the Woerpel conditions would be necessary in order to avoid the undesired retro-aldol pathway following the initial Fleming-Tamao oxidation. As we were studying the above \(N\)-Bn indole system, we decided to also examine \(N\)-Boc indole 447, which we had in hand, under Woerpel’s conditions. We anticipated that hydrolysis of the Boc-protecting group and methyl ester would occur, but we were curious to see if the retro-aldol
reaction would take place if we ran the oxidation at room temperature. In the initial test reaction, 5 mg of the N-Boc indole 447 was subjected to the Woerpel conditions at room temperature and the reaction was stirred for 2.5 h. Analysis of the crude product mixture by mass spectrometry suggested that only a small amount of the desired triol 457 (X = OH) was present. However, we were surprised to find that the primary molecular ion peak in the spectrum corresponded to a product resulting from dehydration of the triol 457. For characterization purposes, the crude mixture was treated with TMSCHN₂ and MeOH to provide 2 mg of the corresponding methyl ester of the dehydration product. Based on the ¹H NMR spectrum of this product, it appears that the major product is a cyclic ether, which could be the result of an intramolecular etherification via an intermediate like 457a or 457b. However, due to lack of material, it has not been determined whether the ether is the desired 7-membered ring 458 or the undesired 5-membered ring 459. Unfortunately, running this reaction on a larger scale using 30 mg of the starting siloxane 447 was less efficient, and once again only a very small amount of the apparent dehydration product was obtained.
Using what was learned from the oxidation of N-Boc indole 447, we subjected N-Bn indole to the Woerpel conditions at room temperature. Thus, when siloxane 449 was added to a solution of t-BuOOH, CsOH, and DMF at room temperature and the mixture was stirred for 10 minutes, complete consumption of the starting material was observed. Mass spectral analysis of an aliquot suggested that the oxidation product 462 was formed (Scheme 126). It should be noted again that Woerpel has also observed the formation of similar oxidation products in the absence of TBAF (cf. Scheme 123). Addition of TBAF produced a crude mixture of carboxylic acid products which was re-esterified to produce the corresponding methyl esters. Unfortunately, the transformation was low yielding overall and we were unable to fully
characterize the products beyond obtaining mass spectra. In this experiment, two components were obtained by preparative thin layer chromatography which both had the same molecular weight corresponding to the isomeric cyclodehydration products 464 and 465. However, the structure of these products could not be confirmed since not enough material was produced for $^1$H NMR analysis. Additionally, a peak with the molecular weight for the acid triol 463 was observed in the mass spectrum of the crude product mixture from the oxidation reaction. Unfortunately, none of the corresponding methyl ester triol 466 was isolated from the esterification reaction which is probably due to its high polarity.

Scheme 126
3.25 – Summary of Current Synthetic Route

Scheme 127

![Chemical Reaction Diagram]

- **246** to **248a** to **264**
- **218** to **286** to **315**
- **319** to **320** to **360**
- **357** to **358**
- **361** to **362** to **363**
3.26 - Future Work

Since subjecting N-Bn indole 449 to Woerpel’s conditions without the TBAF cleanly produced what may be the desired oxidized product 462 (cf. Scheme 117), we will try to obtain this product or the corresponding triol 466 (Scheme 118). The highly polar product(s) of this
oxidation will be purified by preparative HPLC (MeCN/H₂O gradient + 1% TFA) which will likely furnish only triol 463 due to the presumed acid lability of the dimethyldioxysilane group in 462. Following esterification of the carboxylic acid, a cyclodehydration\(^{136}\) of the triol 466, which should exist in the alstilobanine A conformation (cf. Figure 6), will be performed to furnish a 7-membered cyclic ether. Removal of the Ts- and Bn-protecting groups from this compound with Na/naphthalenide will provide alstilobanine E (168). It should be noted that removal of the Ts-protecting group on an earlier intermediate 320 was accomplished using Na/naphthalenide (cf. Scheme 84). A selective N-methylation of 168 will produce angustilodine (167). To access alstilobanine A (169), a Barton-McCombie deoxygenation of primary alcohol 449 will be performed. Finally, an oxidation/esterification sequence and deprotection will provide alstilobanine A (169).

**Scheme 118**
Chapter 4 – Experimental Section

**General Methods.** All reactions were carried out under an argon atmosphere in flame-dried glassware using standard Schlenk techniques unless otherwise noted. Anhydrous tetrahydrofuran, diethyl ether, dichloromethane, and toluene were obtained from a solvent dispensing system equipped with alumina drying columns. Additional solvents and reagents were used as obtained from commercial sources without further purification. Flash column chromatography was performed using EM Science silica gel 60 (230-400 mesh). Preparative thin layer chromatography was performed using 0.5 or 1.0 mm EM Science silica gel 60 PF\textsubscript{254} plates. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were obtained on a Bruker CDPX-300, DPX-300, AMX-360, or DRX-400 MHz spectrometer. Infrared spectra were obtained on a Perkin-Elmer 1600 FTIR. Nominal mass spectra were obtained on an Applied Biosystems 150EX. High resolution mass spectra were obtained on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. X-Ray data was collected on a Bruker SMART APEX CCD area detector system.

![Conversion of \(\alpha\)-Chloroketones to \(\alpha\)-Chloro-\(O\)-TBS-oximes.](attachment:image.png)

**General Procedure for Conversion of \(\alpha\)-Chloroketones to \(\alpha\)-Chloro-\(O\)-TBS-oximes.**

To a stirred solution of the \(\alpha\)-chloroketone (1.0 eq) in \(\text{CH}_2\text{Cl}_2\) (ca. 0.5 M) was added PPTS (0.05 equiv.), 4Å powdered molecular sieves (~15 mg per mmol of \(\alpha\)-chloro ketone), followed by \(O\)-TBS-hydroxylamine (1.1-2.0 equiv.). The resulting mixture was stirred until complete
consumption of the starting $\alpha$-chloroketone was observed (typically 1-2 days) and then filtered through a Celite pad washing with CH$_2$Cl$_2$. The filtrate was concentrated *in vacuo* to give a residue which was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexanes to give the $\alpha$-chloro-O-TBS-oxime.

\[
\text{2-Chlorocyclohexanone } O-(\text{tert-Butyldimethylsilyl}) \text{ Oxime (127). } \alpha\text{-Chloro-O-TBS-oxime 127 was obtained using the above general experimental procedure with the following quantities: } \alpha\text{-chlorocyclohexanone (1.0 mL, 8.19 mmol), CH}_2\text{Cl}_2 \text{ (15 mL), PPTS (105 mg, 0.41 mmol), 4Å powdered molecular sieves (} \sim100 \text{ mg), and } O\text{-TBS-hydroxylamine (2.54 g, 16.4 mmol). 2.18 g, 100%, } \sim2:1 \text{ mixture of oxime isomers. } ^1\text{H NMR (400 MHz, CDCl}_3) \delta 5.69 \text{ (s, 0.33H), 4.77 (s, 0.67H), 3.27 (d, } J = 14.6 \text{ Hz, 0.67H), 2.56 (td, } J = 13.9, 4.7, 0.33\text{H), 2.35 (d, } J = 14.2 \text{ Hz, 0.33H) 2.22-1.81 (m, 4.67 H), 1.66-1.63 (m, 1H), 1.43-1.32 (m, 1H), 1.09-0.95 (m, 9H), 0.18 (s, 6H). }
\]

\[
\text{2-Chlorocyclopentanone } O-(\text{tert-Butyldimethylsilyl}) \text{ Oxime. } \text{The title compound was obtained using the above general experimental procedure with the following quantities: } \alpha\text{-chlorocyclopentanone (100 mg, 0.77 mmol), CH}_2\text{Cl}_2 \text{ (1.5 mL), PPTS (10 mg, 0.04 mmol), 4Å}
\]
powdered molecular sieves (~12 mg), and O-TBS-hydroxylamine (147 mg, 0.95 mmol). 172 mg, 81%, ~2:1 mixture of oxime isomers. $^1$H NMR (300 MHz, CDCl$_3$) δ 4.82 (dd, $J = 2.6, 0.8$ Hz, 0.33H), 4.59 (dd, $J = 4.6, 2.8$ Hz, 0.67H), 2.51-2.45 (m, 1H), 2.26-2.15 (m, 1H), 1.93-1.88 (m, 3H), 1.70-1.67 (m, 1H), 0.79-0.76 (m, 9H), 0.00-0.02 (m, 6H); LRMS-ES+ m/z (relative intensity) 248 (MH$^+$, 30).

2-Chloro-3-phenylpropanal O-(tert-Butyldimethylsilyl) Oxime. The title compound was obtained using the above general experimental procedure with the following quantities: 2-chloro-3-phenylpropanal$^{137}$ (1.0 g, 5.93 mmol), CH$_2$Cl$_2$ (10 mL), PPTS (76 mg, 0.30 mmol), 4Å powdered molecular sieves (~70 mg), and O-TBS-hydroxylamine (1.0 g, 6.52 mmol). 1.24 g, 70%, ~2:1 mixture of oxime isomers. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.20-7.08 (m, 6H), 5.30 (m, 0.33H), 4.59 (q, $J = 7.2$ Hz, 0.67H), 3.12-3.02 (m, 2H), 0.77-0.75 (m, 9H), 0.05-0.00 (m, 6H).

(E)-1-Chlorocyclohexanecarboxaldehyde O-(tert-Butyldimethylsilyl) Oxime. The title compound was obtained using the above general experimental procedure with the following quantities: 1-chlorocyclohexanecarbaldehyde$^{138}$ (120 mg, 0.82 mmol), CH$_2$Cl$_2$ (1.5 mL), PPTS (10 mg, 0.04 mmol), 4Å powdered molecular sieves (~10 mg), and O-TBS-hydroxylamine (140
mg, 0.90 mmol). 136 mg, 60%. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36 (s, 1H), 1.85-1.40 (m, 10H), 0.77 (s, 9H), -0.01 (s, 6H); LRMS-ES $m/z$ (relative intensity) 276 (MH$^+$, 15).

1-Chloro-4-phenylbutan-2-one O-(tert-Butyldimethylsilyl) Oxime. The title compound was obtained using the above general experimental procedure with the following quantities: 1-chloro-4-phenylbutan-2-one (86 mL, 0.47 mmol), CH$_2$Cl$_2$ (1 mL), PPTS (6 mg, 0.02 mmol), 4Å powdered molecular sieves (~6 mg), and O-TBS-hydroxylamine (81 mg, 0.52 mmol). 81 mg, 55%, ~2:1 mixture of oxime isomers. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.17-7.02 (m, 5H), 4.12 (s, 1.3H), 3.83 (s, 0.7H), 2.77-2.54 (m, 4H), 0.81 (s, 3H), 0.77 (s, 6H), 0.04 (s, 2H), -0.01 (s, 4H); LRMS-ES $m/z$ (relative intensity) 312 (MH$^+$, 25).

General Procedure for Intermolecular Michael Additions of Carbon Nucleophiles to Nitrosoalkenes. To a -78 °C solution of ester derivative 130 (0.46 mmol) in THF (1 mL) was added KHMDS (917 $\mu$L, 0.5 M in PhMe, 0.46 mmol). The resulting solution was then stirred for 45 min at that temperature. The O-TBS-oxime 131 dissolved in THF (0.38 mmol in 0.3 mL of THF) was added slowly over 1 min, followed by the dropwise addition of TBAF (458 $\mu$L, 1.0
M in THF, 0.46 mmol) over 3 min. The resulting solution was immediately transferred to a 0 °C ice bath and stirred for an additional 2 h. The reaction mixture was diluted with conc. aqueous NH₄Cl and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue, which was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate and hexanes. Isolated yields of conjugate addition products 132 are shown in Scheme 132 and Tables 1-3.

\[
\begin{align*}
\text{(E) and (Z)-Methyl 2-(2-(Hydroxyimino)cyclohexyl)-2-phenylacetate (128).} \\
\text{\textsuperscript{1}H NMR (300 MHz, CDCl₃, \textasciitilde3:1 mixture of oxime isomers) \text{\(\delta\)} 8.09 (br s, 1H), 7.40-7.26 (m, 5H), 4.09 (d, J = 10.6 Hz, 0.25H), 3.78 (d, J = 11.3 Hz, 0.75H), 3.68 (s, 1H), 3.59 (s, 2H), 3.30 (dt, J = 12.4, 3.0 Hz, 0.75H), 3.16-3.09 (m, 0.25H), 3.00 (td, J = 11.1, 4.0 Hz, 0.75H), 2.62-2.57 (m, 0.25H), 1.99-1.39 (m, 7H); \text{\textsuperscript{13}C NMR (75 MHz, CDCl₃) \text{\(\delta\)} 174.4, 173.8, 161.9, 160.1, 137.6, 137.3, 129.2, 129.1, 129.0, 128.9, 128.7, 128.0, 127.8, 52.5, 52.2, 45.8, 45.1, 31.5, 30.9, 26.7, 26.5, 25.4, 25.0, 23.4, 23.2; LRMS-ES+ m/z (relative intensity) 262 (MH\textsuperscript{+}, 80).}
\end{align*}
\]
(E)-Ethyl 2-(2-(Hydroxyimino)cyclohexyl)-2-(ethylester)acetate (Table 1, entry 1).  
$^1$H NMR (300 MHz, CDCl$_3$) δ 8.09 (br s, 1H), 4.22-4.11 (m, 4H), 3.69 (d, J = 10.2 Hz, 1H), 3.20-3.16 (m, 1H), 3.01 (td, J = 10.6, 4.0 Hz, 1H), 1.93-1.78 (m, 4H), 1.60-1.42 (m, 3H), 1.28-1.20 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.1, 168.7, 160.4, 61.83, 61.82, 53.8, 42.6, 31.2, 26.3, 25.2, 24.7, 14.5, 14.1; LRMS-ES$^+$ m/z (relative intensity) 272 (MH$^+$, 100).

(E)-Ethyl 2-(2-(Hydroxyimino)cyclohexyl)-2-(ethylester)-2-methylacetate (Table 1, entry 2).  $^1$H NMR (300 MHz, CDCl$_3$) δ 7.54 (br s, 1H), 4.13-4.00 (m, 4H), 3.30-3.25 (m, 1H), 3.09-3.01 (m, 1H), 1.85-1.72 (m 3H), 1.59-1.26 (m, 7H), 1.18-1.08 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.9, 171.8, 158.9, 61.8. 61.7, 56.1, 47.5, 30.2, 26.4, 26.3, 25.1, 17.0, 14.4, 14.3; LRMS-ES$^+$ m/z (relative intensity) 286 (MH$^+$, 80).

(E)-Ethyl 2-(2-(Hydroxyimino)cyclohexyl)-2-(ethylester)-2-ethylacetate (Table 1, entry 3).  $^1$H NMR (300 MHz, CDCl$_3$) δ 7.71 (br s, 1H), 4.12-3.99 (m, 4H), 3.20 (dt, J = 13.5,
4.0 Hz, 1H), 2.74 (dd, J = 11.4, 3.9 Hz, 1H), 2.16-2.07 (m, 1H), 1.95-1.30 (m, 8H), 1.19-1.13 (m, 6H), 0.84 (t, J = 7.5 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.8, 171.7, 159.0, 61.3, 61.1, 59.5, 48.6, 31.4, 28.1, 26.70, 26.69, 25.4, 14.44, 14.35, 10.3; LRMS-ES+ m/z (relative intensity) 300 (MH$^+$, 50).

![Image 1]

(E) and (Z)-Ethyl 2-(2-(Hydroxyimino)cyclohexyl)-2-nitroacetate (Table 1, entry 4).

$^1$H NMR (300 MHz, CDCl$_3$, ~1:1 mixture of oxime isomers) δ 7.00 (br s, 1H), 5.38 (d, J = 9.9 Hz, 0.5H), 5.34 (d, J = 9.8, 0.5H), 4.30-4.15 (m, 2H), 3.31-3.13 (m, 2H), 1.86-1.71 (m, 4H), 1.48-1.17 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 164.7, 163.7, 159.0, 158.4, 90.0, 88.0, 63.4, 63.3, 43.3, 43.1, 29.6, 29.2, 25.94, 25.88, 25.4, 25.1, 24.7, 14.2; LRMS-ES+ m/z (relative intensity) 245 (MH$^+$, 75).

![Image 2]

Ethyl 2-(2-(Hydroxyimino)cyclohexyl)-3-oxobutanoate (Table 1, entry 5). $^1$H NMR (300 MHz, CDCl$_3$, complex mixture of diastereomers and/or oxime isomers) δ 4.58-4.25 (m, 2H), 3.00-2.71 (m, 3H), 2.45-2.03 (m, 4H), 1.82-1.31 (m, 9H); LRMS-ES+ m/z (relative intensity) 242 (MH$^+$, 75).
(E)-Methyl 2-(Phenylsulfonyl)-2-(2-(hydroxyimino)cyclohexyl)acetate (Table 1, entry 6). \( ^1H \) NMR (300 MHz, CDCl\(_3\), ~2:1 mixture of oxime isomers) \( \delta \) 8.00 (br s, 1H), 7.95-7.85 (m, 2H), 7.69-7.64 (m, 1H), 7.57-7.51 (m, 2H), 4.62 (d, \( J = 6.5 \) Hz, 0.33H), 4.29 (d, \( J = 11.0 \) Hz, 0.67H), 3.60 (s, 1H), 3.27 (s, 2H), 3.23-3.11 (m, 2H), 2.85-2.63 (m, 1H), 2.20-2.15 (m, 1H), 1.89-1.49 (m, 5H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\), \( \delta \) 167.0, 165.9, 160.3, 159.2, 138.8, 138.4, 134.7, 134.6, 129.53, 129.51, 129.41, 129.38, 72.7, 70.1, 53.1, 53.0, 42.5, 41.1, 32.2, 30.5, 26.4, 26.1, 25.1, 25.0, 24.4, 23.8; LRMS-ES+ \( m/z \) (relative intensity) 326 (MH\(^+\), 50).

(E)-Ethyl 2-(2-(Hydroxyimino)cyclopentyl)-2-(ethylester)acetate (Table 1, entry 8). \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.15 (br s, 1H), 4.18-4.01 (m, 4H), 3.53 (d, \( J = 8.0 \) Hz, 1H), 3.15-3.09 (m, 1H), 2.55-2.50 (m, 1H), 2.34-2.28 (m, 1H), 1.95-1.79 (m, 2H), 1.64-1.55 (m, 2H), 1.20-1.14 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 168.8, 168.5, 166.2, 62.0, 61.8, 53.8, 42.7, 29.5, 27.5, 22.7, 14.44, 14.37; LRMS-ES+ \( m/z \) (relative intensity) 258 (MH\(^+\), 90).
(E)-Ethyl 2-(2-(Hydroxyimino)cyclopentyl)-2-(ethylester)-2-methylacetate (Table 1, entry 9). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.95 (br s, 1H), 4.13-4.00 (m, 4H), 3.29-3.22 (m, 1H), 2.65-2.55 (m, 1H), 2.23-2.14 (m, 1H), 1.93-1.85 (m, 1H), 1.79-1.73 (m, 1H), 1.54-1.42 (m, 2H), 1.34 (s, 3H), 1.15-1.05 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.7, 171.5, 165.4, 61.9, 61.8, 56.2, 47.5, 28.9, 28.4, 22.6, 17.6, 14.4, 14.3; LRMS-ES+ $m/z$ (relative intensity) 272 (MH$^+$, 90).

(E)-Ethyl 2-(2-(Hydroxyimino)cyclopentyl)-2-(ethylester)-2-ethylacetate (Table 1, entry 10). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.04 (br s, 1H), 4.13-3.99 (m, 4H), 3.10-3.05 (m, 1H), 2.62 (dd, $J = 18.5$, 8.1 Hz, 1H), 2.20-2.14 (m, 1H), 2.00-1.88 (m, 3H), 1.74-1.64 (m, 2H), 1.50-1.38 (m, 1H), 1.17-1.12 (m, 6H), 0.86 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.23, 171.15, 61.5, 61.4, 60.7, 47.2, 29.1, 28.5, 28.3, 22.7, 14.4, 10.2; LRMS-ES+ $m/z$ (relative intensity) 286 (MH$^+$, 70).

(E) and (Z)-Methyl 2-(2-(Hydroxyimino)cyclopentyl)-2-(phenylsulfonyl) acetate (Table 1, entry 11). $^1$H NMR (300 MHz, CDCl$_3$, ~1:1 mixture of oxime isomers) $\delta$ 7.88-7.45
(E) and (Z)-Methyl 2-(2-(Hydroxyimino)cyclopentyl)-2-phenylacetate (Table 1, entry 12). $^1$H NMR (300 MHz, CDCl$_3$, ~2:1 mixture of oxime isomers) $\delta$ 8.05 (br s, 1H), 7.24-7.14 (m, 5H), 3.88 (d, $J = 7.4$ Hz, 0.33H), 3.57 (s, 2H), 3.56 (s, 1H), 3.47 (d, $J = 10.4$ Hz, 0.67H), 3.45-3.27 (m, 0.67 H), 3.05-2.95 (m, 0.33H), 2.56-2.47 (m, 1H), 2.40-2.30 (m, 1H), 1.81-1.60 (m, 2H), 1.50-1.44 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.2, 173.4, 167.2, 167.1, 137.84, 137.81, 129.1, 129.0, 128.7, 127.9, 127.7, 54.3, 52.8, 52.6, 52.4, 46.8, 46.3, 30.6, 29.6, 27.9, 27.6, 22.6, 22.4; LRMS-ES$^+$ m/z (relative intensity) 248 (MH$^+$, 50).

(E)-Diethyl 2-(1-(Hydroxyimino)-3-phenylpropan-2-yl)malonate (Table 2, entry 1). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.91 (br s, 1H), 7.54-7.51 (m, 1H), 7.34-7.18 (m, 5H), 4.26-4.19 (m, 4H), 3.59 (d, $J = 7.1$ Hz, 1H), 3.40-3.35 (m, 1H), 2.93-2.89 (m, 2H), 1.32-1.26 (m, 6H); $^{13}$C
NMR (90 MHz, CDCl₃) δ 168.1, 167.8, 151.4, 137.9, 129.3, 129.2, 128.62, 128.56
126.74, 126.70, 61.8, 61.7, 53.7, 41.2, 36.7, 14.1.

\(\text{(E)-Diethyl 2-(1-(Hydroxyimino)-3-phenylpropan-2-yl)-2-methylmalonate (Table 2, entry 2).}\) \(^1\)H NMR (300 MHz, CDCl₃) δ 7.76 (br s, 1H), 7.24-7.04 (m, 6H), 4.15-3.99 (m, 4H),
3.14 (ddd, \(J = 10.9, 7.9, 3.0\) Hz, 1H), 2.85-2.62 (m, 2H), 1.40 (s, 3H), 1.19-1.01 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl₃) δ 171.3, 171.2, 150.9, 139.5, 129.6, 129.0, 128.8, 126.8, 126.7, 62.14,
62.10, 57.2, 47.1, 35.4, 18.6, 14.5, 14.4; LRMS-ES+ \(m/z\) (relative intensity) 322 (MH⁺, 60).

\(\text{(E)-Diethyl 2-(1-(Hydroxyimino)-3-phenylpropan-2-yl)-2-ethylmalonate (Table 2, entry 3).}\) \(^1\)H NMR (300 MHz, CDCl₃) δ 7.67 (br s, 1H), 7.29-7.09 (m, 6H), 4.25-4.16 (m, 4H),
3.14-3.03 (m, 2H), 2.55-2.46 (m, 1H), 2.02-1.84 (m, 2H), 1.32-1.17 (m, 6H), 0.83 (t, \(J = 7.4\) Hz,
3H); \(^{13}\)C NMR (75 MHz, CDCl₃) δ 170.9, 170.8, 151.0, 139.7, 129.7, 129.0, 128.8, 126.7, 61.8,
61.1, 45.6, 36.1, 27.9, 14.6, 9.0; LRMS-ES+ \(m/z\) (relative intensity) 336 (MH⁺, 40).
(E) and (Z)-Methyl 3-Benzyl-4-(hydroxyimino)-2-phenylbutanoate (Table 2, entry 4). \[ \text{1H NMR (300 MHz, CDCl}_3\text{, ~2:1 mixture of oxime isomers) } \delta 7.91 \text{ (br s, 0.66H), 7.65 (br s 0.33H), 7.25-6.84 (m, 11H), 3.60-3.55 (m, 1H), 3.49 (s, 1H), 3.43 (s, 2H), 3.25-3.16 (m, 1H), 2.71-2.49 (m, 2H), 2.36-2.24 (m, 1H); LRMS-ES+ } m/z \text{ (relative intensity) 298 (MH}^+, 75). \]

(E)-Diethyl 2-Allyl-2-(1-(hydroxyimino)-3-phenylpropan-2-yl)malonate (Table 2, entry 5). \[ \text{1H NMR (360 MHz, CDCl}_3\text{) } \delta 7.81 \text{ (s, 1H), 7.38 (d, } J = 8.4, \text{ 1H), 7.30-7.17 (m, 5H), 5.86-5.77 (m, 1H), 5.17-5.12 (m, 2H), 4.31-4.24 (m, 4H), 3.23-3.12 (m, 2H), 2.81-2.63 (m, 3H), 1.36-1.22 (m, 6H); } 13\text{C NMR (75 MHz, CDCl}_3\text{) } \delta 170.4, 170.3, 151.0, 139.6, 132.7, 129.7, 128.8, 126.8, 119.6, 62.0, 60.8, 46.0, 39.0, 35.9, 14.6. \]

(E)-Diethyl 2-(1-((Hydroxyimino)methyl)cyclohexyl)malonate (Table 2, entry 6). \[ \text{1H NMR (300 MHz, CDCl}_3\text{) } \delta 8.01 \text{ (br s, 1H), 7.63 (s, 1H), 4.15-4.07 (m, 4H), 3.51 (s, 1H), 1.99-} \]
1.82 (m, 2H), 1.58-1.40 (m, 8H), 1.19 (t, $J = 7.1$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 167.7, 155.8, 61.7, 60.6, 42.1, 33.2, 26.0, 22.3, 14.5; LRMS-ES+ m/z (relative intensity) 286 (MH$^+$, 60).

(E)-Diethyl 2-(1-((Hydroxyimino)methyl)cyclohexyl)-2-methylmalonate (Table 2, entry 7). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.92 (s, 1H), 7.43 (s, 1H), 4.07 (q, $J = 7.1$ Hz, 4H), 1.99 (d, $J = 12.4$ Hz, 2H), 1.53-1.44 (m, 6H), 1.34-1.23 (m, 5H), 1.13 (t, $J = 7.1$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.3, 158.5, 61.8, 61.6, 45.4, 30.1, 26.1, 22.9, 18.7, 14.4; LRMS-ES+ m/z (relative intensity) 300 (MH$^+$, 60).

(E) and (Z)-Diethyl 2-(1-((Hydroxyimino)methyl)cyclohexyl)-2-ethylmalonate (Table 2, entry 8). $^1$H NMR (300 MHz, CDCl$_3$, ~3:1 mixture of oxime isomers) $\delta$ 7.78 (s, 0.75H), 7.72 (s, 0.25H), 7.37 (s, 0.75H), 7.17 (s, 0.25H), 4.18-4.06 (m, 4H), 1.96-1.80 (m, 4H), 1.57-1.38 (m, 8H), 1.21-1.17 (m, 6H), 0.82-0.76 (m, 3H); LRMS-ES+ m/z (relative intensity) 314 (MH$^+$, 60).
(E)-Methyl 2-(1-((Hydroxyimino)methyl)cyclohexyl)-2-phenylacetate (Table 2, entry 9). \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 7.99 (s, 1H), 7.42 (s, 1H), 7.24-7.13 (m, 5H), 3.59 (s, 1H), 3.55 (s, 3H), 1.80-1.20 (m, 10H); \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 170.9, 153.5, 132.7, 128.6, 126.4, 126.1, 59.7, 50.3, 41.5, 32.2, 30.7, 24.2, 20.8, 20.3; LRMS-ES\(^+\) \(m/z\) (relative intensity) 276 (MH\(^+\), 40).

(E)-5,5-Bis(ethyl ester)-1-phenylhexan-3-one Oxime (Table 3, entry 1). \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 8.81 (br s, 1H), 7.19-7.05 (m, 5H), 4.17-3.94 (m, 4H), 2.73-2.62 (m, 4H), 2.46 (dd, \(J = 8.8, 5.6\) Hz, 2H), 1.35 (s, 3H), 1.16-1.08 (m, 6H); \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 172.3, 157.1, 141.6, 128.8, 128.7, 126.5, 62.1, 61.9, 52.7, 39.6, 31.8, 31.2, 25.1, 20.5, 14.4; LRMS-ES\(^+\) \(m/z\) (relative intensity) 336 (MH\(^+\), 75).

(E)-5,5-Bis(ethyl ester)-1-phenylheptan-3-one Oxime (Table 3, entry 2). \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 8.01 (br s, 1H), 7.21-7.07 (m, 5H), 4.10-4.01 (m, 4H), 2.78-2.70 (m, 4H), 2.47 (dd, \(J = 8.7, 5.5\) Hz, 2H), 1.95 (q, \(J = 7.6\) Hz, 2H), 1.16-1.10 (m, 6H), 0.70 (t, \(J = 7.6\) Hz, 3H); LRMS-ES\(^+\) \(m/z\) (relative intensity) 380 (MH\(^+\), 15).
3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.6, 157.3, 141.6, 128.9, 128.7, 126.5, 61.8, 57.0, 36.1, 31.9, 31.4, 31.1, 25.8, 14.6, 14.4, 9.1; LRMS-ES $m/z$ (relative intensity) 350 (MH$^+$, 80).

(E)-Methyl 4-(Hydroxyimino)-2,6-diphenylhexanoate (Table 3, entry 3). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.20 (br s, 1H), 7.22-7.09 (m, 10H), 3.88 (dd, $J = 10.2$, 4.8 Hz, 1H), 3.55 (s, 3H), 2.95 (dd, $J = 16.6$, 10.2, 1H), 2.72 (dd, $J = 10.6$, 6.8, 2H), 2.52 (dd, $J = 9.2$, 5.9, 2H), 2.36 (dd, $J = 16.6$, 4.8 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 174.2, 159.1, 141.6, 139.0, 129.2, 128.9, 128.7, 128.2, 128.0, 126.6, 52.7, 48.3, 38.6, 31.8, 31.1; LRMS-ES $m/z$ (relative intensity) 312 (MH$^+$, 50).

4-(Phenylsulfonyl)-5,6,7,8-tetrahydro-4a$H$-benzo[c][1,2]oxazin-3-amine (135). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.90-7.83 (m, 2H), 7.55-7.43 (m, 3H), 4.90 (br s, 2H), 2.41-2.06 (m, 4H), 1.67-1.59 (m, 5H); LRMS-ES $m/z$ (relative intensity) 293 (MH$^+$, 60).
Dimethyl 2-(3-(2-(tert-Butoxy)-2-oxoethyl)-1H-indol-2-yl)malonate (210). To a stirred solution of indole 20870 (100 mg, 0.43 mmol), TEA (72 μL, 0.51 mmol), and THF (15 mL) at -78 °C was added tert-butyl hypochlorite (60 μL, 0.51 mmol). The resulting solution was stirred for 30 min at -78 °C and then dimethyl malonate thallium salt72 was added (209 mg, 0.62 mmol). The resulting solution was stirred for 7 h at rt and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to afford indole-2-malonate 210 (99 mg, 63%). 1H NMR (300 MHz, CDCl3) δ 9.17 (s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.25-7.15 (m, 2H), 5.22 (s, 1H), 3.80 (s, 6H), 3.72 (s, 2H), 1.44 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 170.9, 168.0, 136.2, 127.9, 126.3, 123.1, 120.2, 119.4, 111.7, 108.8, 81.3, 53.6, 49.5, 32.0, 28.4; LRMS-ES+ m/z (relative intensity) 379 (M+NH4+, 30).

Dimethyl 2-(3-(2-(tert-Butoxy)-2-oxoethyl)-1H-indol-2-yl)-2-methylmalonate (213). To a stirred solution of indole 210 (24.5 mg, 0.07 mmol), potassium carbonate (14 mg, 0.10 mmol), and acetone (1 mL) was added dimethyl sulfate (9 μL, 0.09 mmol). The resulting mixture was stirred at rt for 20 h and then diluted with water and EtOAc. The organic layer was dried over MgSO4 and concentrated in vacuo to give a residue, which was purified by
preparative thin layer chromatography (25% EtOAc/hexanes, eluted three times for complete separation) to give methyl malonate 213 (14 mg, 55%) and recovered starting indole 210 (11 mg, 45%). $^1$H NMR (300 MHz, CDCl$_3$) δ 9.77 (s, 1H), 7.57 (d, $J = 7.9$ Hz, 1H), 7.39 (d, $J = 8.0$ Hz, 1H), 7.21 (t, $J = 7.0$, 1H), 7.13 (t, $J = 7.0$ Hz, 1H), 3.83 (s, 6H), 3.64 (s, 2H), 1.99 (s, 3H), 1.45 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.7, 171.0, 134.8, 131.5, 129.0, 122.7, 120.1, 119.3, 111.6, 106.7, 81.1, 54.0, 53.7, 32.0, 28.5, 24.5; LRMS-ES+ m/z (relative intensity) 398 (M+Na$^+$, 75).

Dimethyl 2-(3-(2-(Hydroxyimino)cyclohexyl)-1H-indol-2-yl)malonate (215). Method A. To a -78 °C solution of indole malonate 214 (100.0 mg, 0.404 mmol) in THF (1 mL) was added LiHMDS (1.0 M in THF, 404 μL, 0.404 mmol) and the resulting solution was stirred for 30 min. A solution of oxime 211 (30 mg, 0.202 mmol) in THF (0.5 mL) was added dropwise over 3 min and the reaction mixture was stirred for 1.5 h at -78 °C and then 1 h at 0 °C. The reaction mixture was diluted with NH$_4$Cl$_{(aq)}$, the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo to give a residue which was purified by preparative thin layer chromatography (30% EtOAc/hexanes) to afford Michael adduct 215 (less polar oxime isomer - 29.4 mg, 40%; more polar oxime isomer - 33.2 mg, 46%). Less polar oxime isomer: $^1$H NMR (300 MHz, CDCl$_3$) δ 11.34 (s, 1H), 7.71 (s, 1H), 7.57-7.46 (m, 1H), 7.23-6.93 (m, 1H), 5.23-4.93 (m, 3H), 5.59 (s,
1H), 3.81-3.72 (m, 6H), 3.47-3.42 (m, 1H), 2.61 (dd, \( J = 12.7, 3.0 \) Hz, 1H), 2.05-1.95 (m, 1H), 1.80-1.19 (m, 6H). More polar oxime isomer: \(^1\text{H NMR} (300 \text{ MHz, CDCl}_3) \delta 9.03 \text{ (s, 1H)}, 7.54 \text{ (d, } J = 7.9 \text{ Hz, 1H)}, 7.37 \text{ (d, } J = 7.4 \text{ Hz, 1H)}, 7.18 \text{ (d, } J = 7.1 \text{ Hz, 1H)}, 7.07 \text{ (d, } J = 7.0 \text{ Hz, 1H)}, 5.02 \text{ (s, 1H)}, 3.77 \text{ (s, 3H)}, 3.74 \text{ (s, 3H)}, 3.66 \text{ (dd, } J = 12.5, 7.7 \text{ Hz, 1H)}, 3.48 \text{ (d, } J = 14.5 \text{ Hz, 1H)}, 2.12-1.58 \text{ (m, 8H)}. Mixture of oxime isomers: LRMS-ES\(^+\) \text{m/z (relative intensity) } 359 (\text{MH}^+, 100).

Method B. To a stirred solution of indole malonate 214 (50 mg, 0.20 mmol) in THF (1 mL) at -78 °C was added \( n-\text{BuLi} \) (2.0 M in hexanes, 100 μL, 0.20 mmol). The resulting solution was stirred for 45 min and a solution of oxime 127 (46 mg, 0.18 mmol, in 0.5 mL THF) was added followed by dropwise addition of TBAF (1.0 M in THF, 210 μL, 0.21 mmol). After stirring for 25 min at -78 °C, the reaction mixture was transferred to a 0 °C ice bath and stirred for an additional 2 h. The reaction mixture was quenched with \( \text{NH}_4\text{Cl}_\text{(aq)} \), the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO\(_4\) and concentrated \textit{in vacuo} to afford a residue which was purified by flash chromatography on silica gel (25% EtOAc/hexanes) to give Michael adduct 215 (19 mg, 26%) as a mixture of oxime isomers.

### Dimethyl 2-(1-(\textit{tert}-Butoxycarbonyl)-1\(H\)-indol-2-yl)malonate (216) and \textit{1-tert-}Butyl 1,1-Dimethyl (1-(\textit{tert}-Butoxycarbonyl)-1\(H\)-indol-2-yl)methanetricarboxylate (217).

To a stirred solution of indole malonate 214\(^73\) (100 mg, 0.40 mmol), Boc\(_2\)O (135 mg, 0.61 mmol), and
CH₂Cl₂ (1.5 mL) at 0 °C was added TEA (96 μL, 0.69 mmol) followed by DMAP (5 mg, 0.04 mmol). The resulting solution was stirred at rt for 90 min and then diluted with NaHCO₃(aq). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give a residue which was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to yield N-Boc indole 216 (18 mg, 13%) and bis-Boc indole 217 (133 mg, 74%).

**N-Boc indole 216:** ¹H NMR (300 MHz, CDCl₃, ~5:1 mixture of Boc-rotamers) δ 8.09-8.06 (m, 1H), 7.56-7.53 (m, 1H), 7.36-7.25 (m, 2H), 6.57 (t, J = 0.9 Hz, 1H), 5.53 (d, J = 0.9 Hz, 1H), 3.85 (s, 6H), 1.70 (s, 9H). Bis-Boc indole 217: ¹H NMR (300 MHz, CDCl₃) δ 8.19-8.16 (m, 1H), 8.08-8.05 (m, 1H), 7.40-7.26 (m, 2H), 6.82 (s, 1H), 3.77 (s, 6H), 1.68 (s, 9H), 1.64 (s, 9H).

![N-Boc indole](image)

**Methyl 2-(2-(Hydroxyimino)cyclohexyl)-2-(1H-indol-2-yl)acetate (219). Method A.**

To a stirred solution of indole ester 218 ¹⁴⁰ (40 mg, 0.21 mmol) in THF (0.75 mL) at -78 °C was added n-BuLi (2.15 M in hexanes, 90 μL, 0.20 mmol). The resulting solution was stirred for 45 min and a solution of α-chlorooxime 211 (16.4 mg, 0.11 mmol, in 0.25 mL THF) was added dropwise over 20 min. After stirring for an additional 45 min at -78 °C, the reaction mixture was quenched with NH₄Cl(aq), the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to produce a residue which was purified by flash chromatography on silica gel (25%
EtOAc/hexanes) to give Michael adduct 219 (26 mg, 78% based on starting oxime 211) as ~9:1 mixture of oxime isomers and recovered starting indole (23 mg, 58% based on starting indole 218). $^1$H NMR (300 MHz, CDCl$_3$) Major oxime isomer: $\delta$ 8.56 (s, 1H), 7.57 (d, $J$ = 7.8 Hz, 1H), 7.35 (d, $J$ = 8.0 Hz, 1H), 7.17 (t, $J$ = 8.1 Hz, 1H), 7.11 (t, $J$ = 7.5 Hz, 1H), 6.42 (s, 1H) 4.10 (d, $J$ = 10.7 Hz, 1H), 3.70 (s, 3H), 3.15-3.10 (m, 1H), 3.01 (td, $J$ = 10.4, 4.3 Hz, 1H), 2.10-2.04 (m, 1H), 1.80-1.41 (m, 5H), 1.28-1.22 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.9, 161.6, 136.7, 133.6, 128.2, 122.5, 120.7, 120.2, 111.3, 103.3, 52.9, 47.1, 45.2, 31.7, 26.4, 24.8, 24.4; LRMS-ES+ $m/z$ (relative intensity) 301 (MH$^+$, 50).

**Method B.** To a stirred solution of indole ester 218$^{140}$ (50 mg, 0.26 mmol) in THF (0.75 mL) at -78 °C was added $n$-BuLi (2.15 M in hexanes, 123 $\mu$L, 0.26 mmol). The resulting solution was stirred for 45 min and a solution of $\alpha$-chlorooxime 127 (69 mg, 0.26 mmol, in 0.25 mL THF) was added followed by dropwise addition of TBAF (1.0 M in THF, 260 $\mu$L, 0.26 mmol). The reaction mixture was stirred for 1 h at -78 °C and then quenched with NH$_4$Cl(aq). The organic layer was separated, the aqueous layer was extracted with EtOAc, and the combined organic layers were dried over MgSO$_4$ and concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (25% EtOAc/hexanes) to yield Michael adduct 219 (44 mg, 55%) as a mixture of E and Z-oxime isomers and recovered starting indole (21 mg, 42%).
Methyl 2-(1H-Indol-2-yl)-2-(2-oxocyclohexyl)acetate (222) and Methyl 2,3,4,10-Tetrahydro-1H-indolo[1,2-a]indole-11-carboxylate (223). To a stirred solution of oxime 219 (40.0 mg, 0.13 mmol), ammonium acetate (126 mg, 1.63 mmol), water (4 mL), and THF (4 mL) was added TiCl₃ solution (Aldrich, 10 wt% TiCl₃, 20-30 wt% HCl, 422 μL, 0.33 mmol). The resulting solution was stirred for 18 h and then extracted with ether. The combined organic layers were washed with NaHCO₃(aq), dried over MgSO₄, and then concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (15-25% EtOAc/hexanes) to afford ketone 222 (24 mg, 63%) and tetracyclic pyrrole 223 (4.5 mg, 13%). Ketone 222: ¹H NMR (300 MHz, CDCl₃) δ 8.43 (s, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.37-7.34 (m, 2H), 7.22-7.10 (m, 2H), 6.41-6.40 (m, 1H), 4.02 (d, J = 9.6 Hz, 1H), 3.75 (s, 3H), 3.23-3.15 (m, 1H), 3.00-2.95 (m, 1H), 2.86 (tt, J = 8.1, 1.6 Hz, 1H), 2.50-2.41 (m, 2H), 1.96-1.60 (m, 3H); ¹³C NMR (75 MHz, THF-D₈) δ 209.5, 172.6, 137.2, 134.2, 129.0, 121.2, 119.9, 119.4, 111.0, 101.3, 53.1, 51.5, 46.0, 42.1, 32.0, 28.5, 25.6; LRMS-ES+ m/z (relative intensity) 286 (MH⁺, 40). Pyrrole 223: ¹H NMR (300 MHz, CDCl₃) δ 7.49-7.46 (m, 1H), 7.40-7.30 (m, 2H), 7.15 (td, J = 7.4, 1.3 Hz, 1H), 4.04 (s, 2H), 3.87 (s, 3H), 2.97 (t, J = 6.2 Hz, 2H), 2.85 (tt, J = 6.12, 1.7 Hz, 2H), 1.96-1.90 (m, 2H), 1.87-1.81 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 166.4, 141.7, 141.2, 135.2, 127.9, 126.4, 123.84, 123.76, 123.5, 111.5, 106.9, 51.1, 31.4, 23.8, 23.5, 23.3, 23.1; LRMS-ES+ m/z (relative intensity) 268 (MH⁺, 100).
**tert-Butyl 2-(2-Methoxy-2-oxoethyl)-1H-indole-1-carboxylate (227).** To a stirred solution of indole ester 218\textsuperscript{140} (100 mg, 0.53 mmol), Boc\textsubscript{2}O (177 mg, 0.79 mmol), and CH\textsubscript{2}Cl\textsubscript{2} (2 mL) was added TEA (125 \(\mu\)L, 0.90 mmol) followed by DMAP (6.5 mg, 0.05 mmol). The resulting solution was stirred for 70 min at rt and then diluted with NaHCO\textsubscript{3(aq)}. The organic layer was separated and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layers were dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo} to yield a residue which was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to give N-Boc indole 227 (126 mg, 82%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 8.15-8.12 (m, 1H), 7.54-7.51 (m, 1H), 7.35-7.21 (m, 2H), 6.51 (s, 1H), 4.08 (s, 2H), 3.75 (s, 3H), 1.70 (s, 9H).

**tert-Butyl 2-(1-(2-(Hydroxyimino)cyclohexyl)-2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (228).** To a stirred solution of indole ester 227 (63.0 mg, 0.22 mmol) in THF (1 mL) at -78 °C was added LHMDS (1.0 M in THF, 220 \(\mu\)L, 0.22 mmol). The resulting solution was stirred for 35 min and a solution of \(\alpha\)-chlorooxime 127 (48 mg, 0.18 mmol, in 0.5 mL THF) was added followed by dropwise addition of TBAF (1.0 M in THF, 220 \(\mu\)L, 0.22 mmol). The reaction mixture was transferred to a 0 °C ice bath and stirred for an additional 1 h and 45 min and then quenched with NH\textsubscript{4}Cl\textsubscript{(aq)}. The organic layer was separated and the aqueous layer was
extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated \textit{in vacuo} to yield a residue, which was purified by flash chromatography (15-25\% EtOAc/hexanes) to give Michael adduct \textbf{228} (57.7 mg, 79\%) as a ~2:1 mixture of oxime isomers. $^1$H NMR (300 MHz, CDCl₃) $\delta$ 8.12-8.06 (m, 1H), 7.54-7.49 (m, 1H), 7.33-7.19 (m, 2H), 6.68 (s, 0.66H), 6.63 (s, 0.33H), 5.29 (d, $J = 10.9$ Hz, 0.66 H), 5.24 (d, $J = 8.2$ Hz, 0.33H), 3.71 (s, 1H), 3.66 (s, 2H), 3.25-3.19 (m, 0.66H), 3.11-3.04 (m, 1H), 2.95-2.90 (m, 0.33H), 2.19-1.99 (m, 1H), 1.90-1.63 (m, 12H), 1.57-1.38 (m, 3H); $^{13}$C NMR (75 MHz, CDCl₃) $\delta$ 173.5, 173.0, 161.6, 160.5, 150.9, 150.8, 137.9, 137.1, 136.9, 129.3, 129.3, 124.4, 124.3, 123.3, 123.1, 120.84, 120.77, 116.2, 116.0, 110.3, 109.3, 85.1, 84.8, 60.9, 52.7, 52.5, 46.8, 44.8, 44.5, 31.0, 30.6, 28.7, 28.6, 26.6, 26.4, 25.4, 24.7, 24.2; LRMS-ES+ \textit{m/z} (relative intensity) 401 (MH⁺, 100).

\textit{tert-Butyl 2-(2-Methoxy-2-oxo-1-(2-oxocyclohexyl)ethyl)-1H-indole-1-carboxylate} (\textbf{229}). To a stirred solution of oxime \textbf{228} (25.0 mg, 0.062 mmol), ammonium acetate (59 mg, 0.77 mmol), water (2.5 mL), and THF (2.5 mL) was added TiCl₃ solution (Aldrich, 10 wt\% TiCl₃, 20-30 wt\% HCl, 200 μL, 0.15 mmol). The resulting solution was stirred for 17 h and then extracted with ether. The organic layers were washed with NaHCO₃(aq), dried over MgSO₄, and concentrated \textit{in vacuo} to give a residue, which was purified by flash chromatography on silica gel (10-15\% EtOAc/hexanes) to afford ketone \textbf{229} (11.5 mg, 48\%) as a ~4:1 mixture of diastereomers or Boc-rotamers. $^1$H NMR (300 MHz, CDCl₃) Only the major peaks are reported: $\delta$ 8.06 (d, $J = 8.3$ Hz, 1H), 7.52-7.50 (m, 1H), 7.31-7.22 (m, 2H), 6.56 (s, 1H), 5.13 (d, $J = 9.6$ Hz, 1H), 2.19-1.99 (m, 12H), 1.57-1.38 (m, 3H); $^{13}$C NMR (75 MHz, CDCl₃) $\delta$ 173.5, 173.0, 161.6, 160.5, 150.9, 150.8, 137.9, 137.1, 136.9, 129.3, 129.3, 124.4, 124.3, 123.3, 123.1, 120.84, 120.77, 116.2, 116.0, 110.3, 109.3, 85.1, 84.8, 60.9, 52.7, 52.5, 46.8, 44.8, 44.5, 31.0, 30.6, 28.7, 28.6, 26.6, 26.4, 25.4, 24.7, 24.2; LRMS-ES+ \textit{m/z} (relative intensity) 401 (MH⁺, 100).
4-Chloro-1-tosylpiperidin-3-one (248a). **Method A.** To a stirred solution of readily prepared 1-tosylpiperidin-3-one (246)<sup>80</sup> (2.00 g, 7.90 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at 0 °C was added sulfuryl chloride (2.0 mL, 23.7 mmol) and the solution was stirred for 17 h gradually warming to rt. An aqueous solution of NaHCO<sub>3</sub> was added to the reaction and the mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with water and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give a solid which was purified by flash chromatography on silica gel (1:1:1 hexanes/CH<sub>2</sub>Cl<sub>2</sub>/EtOAc) to yield α-chloroketone 248a (1.77 g, 78%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.69 (d, <i>J</i> = 8.2 Hz, 2H), 7.39 (d, <i>J</i> = 8.0 Hz, 2H), 4.35 (t, <i>J</i> = 5.0 Hz, 1H), 3.84 (s, 2H), 3.53-3.50 (m, 1H), 3.42-3.38 (m, 1H), 2.53-2.48 (m, 4H), 2.27-2.22 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 195.1, 145.0, 132.9, 130.5, 128.1, 58.6, 53.5, 42.3, 34.0, 22.0; LRMS-ES+ <i>m/z</i> (relative intensity) 288 (MH<sup>+</sup>, 100); HRMS-ES+ (C<sub>12</sub>H<sub>18</sub>ClN<sub>2</sub>O<sub>3</sub>S) calcd 305.0729 (M+NH<sub>4</sub><sup>+</sup>), found 305.0727.

**Method B.** To a stirred solution of piperidone 246 (4.00 g, 31.6 mmol) in EtOAc (250 mL) was added Amberlyst-15 (19.5 g) followed by NCS (3.88 g, 56.9 mmol) and the resulting mixture was stirred at rt for 20 h. Silica gel (~3 g) was added and the resulting mixture was stirred for an additional 2 h, filtered, and concentrated *in vacuo* to give a residue, which was
purified by flash column chromatography on silica gel (2:2:1-1:1:1 hexanes/CH₂Cl₂/EtOAc) to afford the α-chloroketone \textbf{248a} (2.71 g, 59%).

\[ \text{Cl} \]
\[ \text{O} \]
\[ \text{N}_{\text{Ns}} \]

**4-Chloro-1-nosylpiperidin-3-one (Scheme 56, entry b).** To a stirred solution of 1-nosylpiperidin-3-one (260) \textsuperscript{78} (609 mg, 2.14 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added sulfuryl chloride (650 μL, 7.50 mmol) and the solution was stirred for 18 h gradually warming to rt. An aqueous solution of NaHCO₃ was added and the mixture was stirred vigorously for 5 min. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with water and brine, dried over MgSO₄, and concentrated \textit{in vacuo} to give a solid which was purified by flash chromatography on silica gel (1:1:1 hexanes/CH₂Cl₂/EtOAc) to afford the title compound (437 mg, 64%) as a mixture of keto and enol tautomers. \textsuperscript{1}H NMR (300 MHz, CDCl₃, + 1 drop of trifluoroacetic acid to generate the ketone exclusively) δ 8.14-8.04 (m, 1H), 7.86-7.71 (m, 3H), 4.57-4.51 (m, 1H), 4.33-4.02 (m, 2H), 3.85-3.74 (m, 2H), 2.65-2.58 (m, 1H), 2.38-2.31 (m, 1H); LRMS-ES+ \textit{m/z} (relative intensity) 319 (MH⁺, 50).
4-Chloro-1-tosylpiperidin-3-one O-(tert-Butyldimethylsilyl) Oxime (263). To a stirred solution of α-chloroketone 248a (110 mg, 0.38 mmol) in CH₂Cl₂ (3 mL) was added PPTS (5 mg, 0.02 mmol), 4Å powdered molecular sieves (25 mg), and then O-TBS-hydroxylamine (59 mg, 0.38 mmol). The resulting mixture was stirred for 14 h at rt and then filtered through a Celite plug washing with CH₂Cl₂. The filtrate was concentrated in vacuo to give a residue which was purified by flash column chromatography on silica gel (5% EtOAc/hexanes) to yield the α-chloro-O-TBS-oxime 263 (67 mg, 42%) as a ~8:1 mixture of oxime isomers. ¹H NMR (300 MHz, CDCl₃) Only the major oxime isomer peaks are reported: δ 7.71 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 5.22 (d, J = 14.4 Hz, 1H), 4.79 (s, 1H), 3.82 (d, J = 12.6 Hz, 1H), 3.18-3.06 (m, 2H), 2.46 (s, 3H), 2.20-2.01 (m, 2H), 0.95 (s, 9H), 0.20 (s, 6H); LRMS-ES⁺ m/z (relative intensity) 418 (MH⁺, 90).

4-Chloro-1-tosylpiperidin-3-one Oxime (290). To a stirred solution of N-Ns-4-chloropiperdone oxime (129 mg, 0.41 mmol) in DMSO (1 mL) was added H₂NOHHCl (34 mg, 0.49 mmol) and the resulting solution was stirred for 18 h at rt. The reaction mixture was diluted with water (5 mL) and extracted repeatedly with CHCl₃. The combined organic layers were washed with water and brine and dried over MgSO₄. Removal of the solvent in vacuo provided...
α-chlorooxime 290 (119 mg, 88%) as a ~2:1 mixture of oxime isomers. This material was used in subsequent reactions without further purification. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.29 (s, 0.33H), 8.21 (s, 0.67H), 8.11-8.05 (m, 1H), 7.80-7.67 (m, 3H), 5.61 (s, 0.33H), 5.19 (d, $J = 15.3$ Hz, 0.67H), 4.85 (t, $J = 3.1$ Hz, 0.67H), 4.30 (d, $J = 15.0$ Hz, 0.33H), 3.99-3.90 (m, 1.33 H), 3.70 (d, $J = 15.4$ Hz, 0.67H), 3.59-3.54 (m, 1H), 2.34-2.17 (m, 2H).

4-Chloro-1-tosylpiperidin-3-one Oxime (264). To a stirred solution of α-chloroketone 248a (5.40 g, 18.8 mmol) in DMSO (50 mL) was added H$_2$NOH$\cdot$HCl (1.46 g, 20.6 mmol) and the resulting solution was stirred at rt for 18 h. The reaction mixture was diluted with water (300 mL) and extracted repeatedly with CH$_2$Cl$_2$. The combined organic layers were then washed with water, brine, and then dried over MgSO$_4$. Removal of the solvent in vacuo provided pure α-chlorooxime 264 (5.49 g, 97%) as a white solid which was used in the following reaction without further purification. $^1$H NMR (300 MHz, CDCl$_3$, ~2:1 E/Z mixture of oxime isomers) $\delta$ 7.81-7.70 (m, 2H), 7.40-7.38 (d, $J = 8.2$ Hz, 2H), 5.53 (m, 0.33H), 5.15 (d, $J = 14.2$ Hz, 0.67H), 4.77 (t, $J = 3.0$ Hz, 0.67H), 4.30-4.27 (m, 0.33 H), 3.85-3.80 (m, 1H), 3.45 (d, $J = 13.6$ Hz, 0.33H), 3.23 (d, $J = 14.5$ Hz, 0.67H), 3.11 (td, $J = 11.9$ Hz, 3.0 Hz, 0.67H), 2.95 (m, 0.33H), 2.48 (m, 3H), 2.28-2.08 (m, 2H).
Methyl 2-(3-(Hydroxyimino)-1-tosylpiperidin-4-yl)-2-(1H-indol-2-yl)acetate (266).

To a stirred solution of indole ester 218\textsuperscript{140}(691 mg, 3.65 mmol) in THF (11 mL) at -78 °C was added LiHMDS (1.0 M in THF, 3.65 mL, 3.65 mmol). The resulting solution was stirred for 30 min and a solution of α-chlorooxime 264 (553 mg, 1.83 mmol, in 7 mL of THF) was added dropwise over 8 min. After stirring the mixture for an additional 90 min at -78 °C the reaction was quenched with NH\textsubscript{4}Cl\textsubscript{(aq)}. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo} to give a residue which was purified by flash chromatography on silica gel (15-50% EtOAc/hexanes) to afford Michael adduct 266 (491 mg, 59%) as a ~3:1 mixture of oxime isomers and recovered starting indole (454 mg, 66%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, ~3:1 mixture of oxime isomers) \(\delta\) 8.83 (s, 1H), 8.60 (br s, 1H), 7.69-7.09 (m, 8H), 6.36 (s, 0.75 H), 6.29 (s, 0.25 H), 4.89 (d, \(J = 14.8\) Hz, 0.75 H), 4.56 (d, \(J = 15.0\) Hz, 0.25H), 3.98 (d, \(J = 10.3\) Hz, 1 H), 3.69 (s, 0.75 H), 3.67 (s, 2.25 H), 3.60-3.46 (m, 1H), 3.20 (d, \(J = 14.4\) Hz, 1H), 3.02 (td, \(J = 10.7, 4.7\) Hz, 1H), 2.76-2.72 (m, 1H), 2.45-2.41 (m, 4H), 1.63-1.59 (m, 1H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 173.4, 153.4, 144.5, 136.7, 133.2, 132.5, 130.4, 130.3, 128.4, 128.1, 122.6, 120.7, 120.5, 111.5, 46.6, 46.5, 45.3, 42.3, 42.1, 28.1, 22.0; LRMS-ES\textsuperscript{+} \(m/z\) (relative intensity) 456 (MH\textsuperscript{+}, 95); HRMS-ES\textsuperscript{+} (C\textsubscript{23}H\textsubscript{26}N\textsubscript{3}O\textsubscript{5}S) calcd 456.1593 (MH\textsuperscript{+}), found 456.1571.
**tert-Butyl 2-(1-(3-(Hydroxyimino)-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (267).** To a -78 °C solution of N-Boc indole 227 (32.8 mg, 0.113 mmol) in THF (1 mL) was added LiHMDS (113 μL, 0.11 mmol, 1.0 M in THF) and the resulting solution was stirred for 30 min. A solution of α-chlorooxime 264 (17.2 mg, 0.057 mmol) in THF (1 mL) was added dropwise over 8 min. The reaction mixture was transferred to an ice-bath, stirred for 1.5 h, and then quenched with NH₄Cl(aq). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (15-50% EtOAc/hexanes) to afford Michael adduct 267 (4.3 mg, 7%) as a ~2:1 mixture of oxime isomers. ¹H NMR (300 MHz, CDCl₃) δ 8.07-8.00 (m, 1H), 7.74-7.68 (m, 3H), 7.47-7.22 (m, 5H), 6.56 (s, 0.66 H), 6.53 (s, 0.33H), 5.22 (d, J = 10.5 Hz, 0.66H), 5.15 (d, J = 7.1 Hz, 0.33H), 4.99 (d, J = 14.4 Hz, 0.66H), 4.58-4.52 (m, 0.33H), 3.71-3.52 (m, 5H), 3.12-2.89 (m, 2H), 2.48-2.42 (m, 4H), 1.73-1.58 (m, 10H); LRMS-ES⁺ m/z (relative intensity) 556 (MH⁺, 75).

**Methyl 2-(3-(((tert-Butoxycarbonyl)oxy)imino)-1-tosylpiperidin-4-yl)-2-(1H-indol-2-yl)acetate (270).** To a stirred solution of indole 266 (21.0 mg, 0.046 mmol), Boc₂O (10 mg,
0.046 mmol), and CH₂Cl₂ (1 mL) was added TEA (20 μL, 0.14 mmol) followed by DMAP (0.6 mg, 5 μmol). The resulting solution was stirred for 1 h at rt and then diluted with NaHCO₃(aq). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (25-50% EtOAc/hexanes) to yield O-Boc oxime 270 (14.2 mg, 55%) as a single O-Boc oxime isomer assumed to be the less hindered (E)-compound. ¹H NMR (400 MHz, CDCl₃) δ 9.5 (s, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.17 (t, J = 7.1 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 6.28 (s, 1H), 4.87 (d, J = 15.1 Hz, 1H), 4.52 (d, J = 5.2 Hz, 1H), 3.37 (s, 3H), 3.66-3.63 (m, 1H), 3.24 (d, J = 15.2 Hz, 1H), 3.04 (dt, J = 12.2, 5.1 Hz, 1H), 2.83 (td, J = 12.2, 3.6 Hz, 1H), 2.37 (s, 3H), 2.14-2.10 (m, 1H), 1.64 (s, 9H), 1.48-1.40 (m, 1H); LRMS-ES⁺ m/z (relative intensity) 556 (MH⁺, 100).

Methyl 2-(3-(((tert-Butoxycarbonyl)oxy)imino)-1-tosylpiperidin-4-yl)-2-(3-formyl-1H-indol-2-yl)acetate (275). To a stirred solution of indole 270 (73 mg, 0.13 mmol) in DMF (0.5 mL) at 0 °C was added POCl₃ (31 μL, 0.33 mmol). The resulting solution was stirred at rt for 17 h, diluted with EtOAc, and washed with NaHCO₃(aq) followed by brine. The organic layer was dried over MgSO₄ and concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (15-40% EtOAc/hexanes) to afford 3-formylindole 275 (54 mg,
Benzyl 2-(2-(2-Methoxy-2-oxoethyl)-1H-indol-3-yl)-2-oxoacetate (285). To a stirred solution of indole ester 218\textsuperscript{140} (150 mg, 0.79 mmol) in Et\textsubscript{2}O (10 mL) at 0 °C was added oxalyl chloride (350 μL, 4.0 mmol). After stirring the mixture for 30 min, benzyl alcohol (1.6 mL, 15.9 mmol) was added followed by the slow and careful addition of TEA (3.3 mL, 23.8 mmol) over 5 min. The resulting thick slurry was stirred rigorously at rt for 2 h and then quenched with water. The organic layer was separated and the aqueous layer extracted with Et\textsubscript{2}O. The combined organic layers were washed with water and brine, dried over MgSO\textsubscript{4}, and concentrated \textit{in vacuo} to give a viscous oil. This material was purified by flash column chromatography on silica gel (20-40% EtOAc/hexanes) to give indole-3-oxoacetate 285 (196 mg, 71%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 10.43 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.49-7.47 (m, 2H), 7.40-7.38 (m, 4H), 7.24 (t, J = 7.8 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 5.46 (s, 2H), 4.26 (s, 2H), 3.79 (s, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 181.9, 171.1, 166.0, 142.5, 135.3, 134.9, 129.4, 129.2, 129.1, 126.0, 124.0, 135.7, 133.0, 130.3, 128.0, 127.0, 124.1, 119.3, 114.9, 112.5, 85.8, 64.8, 60.9, 53.2, 45.5, 43.8, 43.3, 28.2, 21.9; LRMS-ES\textsuperscript{+} m/z (relative intensity) 584 (MH\textsuperscript{+}, 75).
123.4, 120.2, 112.3, 110.4, 68.2, 60.9, 53.0, 32.9; LRMS-ES+ m/z (relative intensity) 352 (MH⁻, 80).

2-(Trimethylsilyl)ethyl-2-(2-(2-methoxy-2-oxoethyl)-1H-indol-3-yl)-2-oxoacetate (286). To a stirred solution of indole 218(1.00 g, 5.3 mmol) in Et₂O (200 mL) at 0 °C was added oxalyl chloride (1.88 mL, 21.1 mmol). After stirring the mixture for 30 min, 2-trimethylsilyl ethanol (12.4 mL, 84.6 mmol) was added followed by the slow and careful addition of TEA (17.7 mL, 127 mmol) over 5 min. The resulting thick slurry was stirred vigorously at rt for 2 h and then quenched with water. The organic layer was separated and the aqueous layer extracted with Et₂O. The combined organic layers were washed with water and brine, dried over MgSO₄, and concentrated in vacuo to give a viscous red oil. This material was purified by flash chromatography on silica gel (20-40% EtOAc/hexanes) to give indole-3-oxoacetate 286 (1.26 g, 66%). ^1H NMR (300 MHz, CDCl₃) δ 10.50 (s, 1H), 7.83-7.78 (m, 1H), 7.45-7.40 (m, 1H), 7.30-7.23 (m, 2H), 4.56-4.50 (m, 2H), 4.32 (s, 2H), 3.82 (s, 3H), 1.22-1.16 (m, 2H), 0.10 (s, 9H); ^13C NMR (75 MHz, CDCl₃) δ 182.5; 171.3, 166.5, 142.3, 135.4, 126.1, 124.0, 123.4, 120.3, 112.3, 110.5, 65.2, 53.1, 32.9, 17.8, -1.1; LRMS-ES+ m/z (relative intensity) 362 (MH⁻, 80); HRMS-ES+ (C₁₈H₂₄NO₅Si) calcd 362.1424 (MH⁺), found 362.1416.
**Dimethyl 2-(3-(Benzyloxy)-2-oxoacetyl)-1H-indol-2-yl)malonate (288).** To a stirred solution of indole malonate 214\(^{73}\) (77.7 mg, 0.314 mmol) in Et\(_2\)O (5 mL) at 0 °C was added oxalyl chloride (112 \(\mu\)L, 1.26 mmol). After stirring the mixture for 30 min at 0 °C and 1 h at rt, benzyl alcohol (520 \(\mu\)L, 5.03 mmol) was added followed by the slow and careful addition of TEA (1.05 mL, 7.54 mmol) over 5 min. The resulting thick slurry was stirred vigorously at rt for 2 h and then quenched with water. The organic layer was separated and the aqueous layer was extracted with Et\(_2\)O. The combined organic layers were washed with water and brine, dried over MgSO\(_4\), and concentrated \textit{in vacuo} to give a viscous oil. This material was purified by flash column chromatography on silica gel (25-40% EtOAc/hexanes) to give indole-3-oxoacetate 288 (65.5 mg, 51%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 10.25 (s, 1H), 7.54 (d, \(J = 8.1\) Hz, 1H), 7.50-7.39 (m, 6H), 7.29-7.25 (m, 1H), 7.14 (t, \(J = 7.3\) Hz, 1H), 6.11 (s, 1H), 5.48 (s, 2H), 3.81 (s, 6H); LRMS-ES\(^+\) m/z (relative intensity) 410 (MH\(^+\), 90).

**Benzyl 2-(2-(1-(3-(Hydroxyimino)-1-nosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-1H-indol-3-yl)-2-oxoacetate (291).** To a -78 °C solution of indole 285 (110 mg, 0.31 mmol) in THF (2 mL) was added LiHMDS (630 \(\mu\)L, 0.63 mmol, 1.0 M in THF) and the resulting solution was stirred for 50 min. A solution of oxime 290 (104 mg, 0.31 mmol) in THF (1 mL) was then added.
dropwise over 1 min. The reaction mixture was stirred for 2 h at -78 °C and then quenched with 
NH₄Cl(aq). The organic layer was separated and the aqueous layer was extracted with EtOAc. 
The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a 
residue, which was purified by flash chromatography on silica gel (50% EtOAc/hexanes) to yield 
Michael adduct 291 (165 mg, 81%) as a ~1:1 mixture of oxime isomers and recovered starting 
indole 285 (21 mg, 19%). ¹H NMR (300 MHz, CDCl₃) δ 9.95 (s, 0.5H), 0.89 (s, 0.5H), 8.04 (s, 
0.5H), 7.96 (dd, J = 7.5, 1.7 Hz, 0.5H), 7.92-7.88 (m, 1H), 7.65-7.60 (m, 1H), 7.52-7.39 (m, 
8.5H), 7.25-7.20 (m, 1.5H), 7.15-7.10 (m, 1H), 5.50 (d, J = 6.3 Hz, 0.5H), 5.45 (s, 2H), 5.17 (d, J 
= 8.5 Hz, 0.5H), 4.97 (d, J = 16.1 Hz, 0.5H), 4.67 (d, J = 15.8 Hz, 0.5H), 4.11-4.07 (m, 0.5H), 
4.02 (d, J = 15.9 Hz, 0.5H), 3.76-3.68 (m, 4H), 3.45-3.42 (m, 0.5H), 3.32-3.26 (m, 1H), 3.13-3.09 
(m, 0.5H), 2.06-2.02 (0.5H), 1.84-1.60 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 182.8, 
182.4, 172.8, 171.9, 165.8, 165.6, 153.03, 153.00, 148.5, 148.1, 143.13, 143.08, 135.6, 135.5, 
134.84, 134.79, 134.4, 134.2, 132.2, 132.1, 131.9, 131.8, 131.3, 131.2, 129.6, 129.5, 129.4, 
129.3, 129.20, 129.18, 125.8, 125.5, 124.6, 125.5, 124.4, 124.3, 123.5, 123.2, 120.3, 120.0, 
112.6, 112.4, 111.4, 111.2, 68.4, 68.3, 64.9, 53.4, 53.3, 44.8, 44.5, 44.0, 43.5, 43.3, 42.7, 42.2, 
41.7, 31.0, 28.0, 27.8, 19.6; LRMS-ES⁺ m/z (relative intensity) 649 (MH⁺, 100).

Benzyl 2-(2-(1-(3-(((tert-Butyldimethylsilyl)oxy)imino)-1-nosylpiperidin-4-yl)-2-
methoxy-2-oxoethyl)-1H-indol-3-yl)-2-oxoacetate (292). To a stirred solution of oxime 291
(165 mg, 0.25 mmol), imidazole (70 mg, 1.0 mmol), and CH₂Cl₂ (5 mL) was added TBS-Cl (103 mg, 0.66 mmol). The resulting mixture was stirred at rt for 4 h and then diluted with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue. This material was purified by flash chromatography on silica gel (25-50% EtOAc/hexanes) to give O-TBS-oxime 292 (186 mg, 96%) as a ~1:1 mixture of oxime isomers. ¹H NMR (300 MHz, CDCl₃) δ 9.87 (s, 0.5H), 9.84 (s, 0.5H), 7.96-7.89 (m, 1H), 7.67-7.64 (m, 1H), 7.54-7.36 (m, 8.5H), 7.32-7.15 (2.5H), 5.50 (d, J = 7.5 Hz, 0.5H), 5.46 (s, 2H), 5.13-5.07 (m, 1H), 4.92 (d, J = 15.8 Hz, 0.5H), 3.77-3.65 (m, 5H), 3.52-3.48 (m, 0.5H), 3.29-3.12 (m, 1.5H), 2.04-1.98 (m, 0.5H), 1.88-1.70 (m, 1.5H), 0.99 (s, 9H), 0.31 (s, 1.5H), 0.26 (s, 1.5H), 0.23 (s, 1.5H), 0.21 (s, 1.5H); ¹³C NMR (75 MHz, CDCl₃) δ 182.8, 182.3, 172.5, 170.9, 165.8, 165.7, 157.5, 156.8, 148.6, 148.2, 143.9, 143.5, 135.5, 135.4, 134.88, 134.86, 134.4, 134.3, 132.1, 131.9, 131.8, 131.7, 131.2, 131.1, 129.6, 129.5, 129.4, 129.3, 129.21, 129.19, 125.8, 125.6, 124.6, 124.5, 124.4, 124.2, 123.5, 123.2, 120.5, 120.0, 112.4, 112.3, 111.19, 111.17, 68.3, 68.2, 53.2, 53.1, 45.0, 44.9, 44.2, 43.5, 43.4, 43.0, 42.7, 28.3, 27.6, 26.32, 26.25, 18.3, 18.2, -4.2, -4.6, -4.7; LRMS-ES⁺ m/z (relative intensity) 763 (MH⁺, 100).

**tert-Butyl 3-(2-(Benzyloxy)-2-oxoacetyl)-2-(2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (295).** To a stirred solution of indole 285 (26.0 mg, 0.074 mmol), Boc₂O (18 mg, 0.081 mmol), and CH₂Cl₂ (1 mL) was added TEA (21 μL, 0.15 mmol) followed by DMAP (1
mg, 0.007 mmol). The resulting solution was stirred at rt for 13 h and then diluted with NaHCO₃(aq). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (10-30% EtO/hexanes) to afford N-Boc indole 295 (13.6 mg, 41%). ¹H NMR (300 MHz, CDCl₃) δ 8.11 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.46-7.29 (m, 6H), 7.19 (t, J = 7.2 Hz, 1H), 5.44 (s, 2H), 4.55 (s, 2H), 3.71 (s, 3H), 1.69 (s, 9H); LRMS-ES+ m/z (relative intensity) 452 (MH⁺, 50).

**tert-Butyl 3-(2-(Benzyloxy)-2-oxoacetyl)-2-(1-(2-(hydroxyimino)cyclohexyl)-2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (296).** To a -78 °C solution of indole 295 (13.6 mg, 0.030 mmol) in THF (0.5 mL) was added LiHMDS (30 μL, 0.030 mmol, 1.0 M in THF) and the resulting solution was stirred for 30 min. A solution of oxime 211 (2.2 mg, 0.015 mmol) in THF (0.5 mL) was then added dropwise over 1 min. The reaction mixture was stirred for 2 h at -78 °C and then quenched with NH₄Cl(aq). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue. This material was purified by flash chromatography on silica gel (15-25% EtOAc/hexanes) to give Michael adduct 296 (8.0 mg, ~95%) as a ~3:1 mixture of oxime isomers contaminated with a small amount of the bis-alkylation product 297. ¹H NMR (300 MHz, CDCl₃) δ 8.06-7.95 (m, 1H), 7.64 (br s, 0.5H), 7.48-7.27 (m, 7H), 7.20-7.18 (m, 1H), 6.81 (br s, 0.5H), 5.97-5.95 (d, J = 7.8 Hz, 0.5H), 5.54-5.43 (m, 1.5H), 3.61-3.56 (m,
3H), 3.45-3.37 (m, 1H), 1.93-1.63 (m, 14H), 1.43-1.13 (m, 6H); LRMS-ES+ m/z (relative intensity) 563 (MH+, 75) with bis-alkylation product: 674 (MH+, 40).

Methyl 3-(4-Methoxyphenyl)-2-(3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)acetyl)-1H-indol-2-yl)propanoate (298). To a stirred solution of indole 286 (54.4 mg, 0.151 mmol) and DMF (1 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 6.6 mg, 0.17 mmol) and the resulting solution was stirred at rt for 30 min. p-Methoxybenzyl chloride (23 μL, 0.17 mmol) and TBAI (5.6 mg, 0.015 mmol) were added and the reaction was stirred for 5 h at rt before diluting with water and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, then dried over MgSO₄ and concentrated in vacuo to give a residue. This material was purified by preparative thin layer chromatography (50% EtOAc/hexanes) to give alkylation product 298 (29.8 mg, 41%) and recovered starting indole 286 (18.9 mg, 35%). "H NMR (400 MHz, CDCl₃) δ 10.08 (s, 1H), 7.79-7.77 (m, 1H), 7.43-7.41 (m, 1H), 7.31-7.28 (m, 2H), 7.09 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.05 (dd, J = 9.4, 4.6 Hz, 1H), 4.61-4.50 (m, 2H), 3.80 (s, 3H), 3.64 (s, 3H), 3.35 (dd, J = 13.4, 4.5 Hz, 1H), 3.16 (dd, J = 13.3, 9.5 Hz, 1H), 1.28-1.18 (m, 2H), 0.11 (s, 9H); "C NMR (75 MHz, CDCl₃) δ 182.5, 174.6, 166.5, 159.1, 146.4, 135.2, 130.5, 129.5, 126.1, 124.1, 123.4, 120.4, 114.3, 112.3, 109.5, 65.2, 55.6, 52.9, 46.2, 40.9, 17.8, -1.1; LRMS-ES+ m/z (relative intensity) 336 (MH+, 100).
Methyl 2-(3-(2-(Benzyloxy)-2-oxoacetyl)-1H-indol-2-yl)-3-(4-methoxyphenyl) propanoate (298). To a stirred solution of indole 285 (41 mg, 0.12 mmol), K₂CO₃ (24 mg, 0.18 mmol) and MeCN (3 mL) was added p-methoxybenzyl chloride (24 µL, 0.18 mmol) and the resulting solution was stirred at reflux for 6 h. After cooling to rt, the reaction mixture was diluted with water and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue. This material was purified by preparative thin layer chromatography (50% EtOAc/hexanes) to afford alkylation product 299 (26 mg, 47%). ¹H NMR (400 MHz, CDCl₃) δ 10.08 (s, 1H), 7.54-7.49 (m, 3H), 7.41-7.39 (m, 4H), 7.26 (t, J = 7.4 Hz, 1H), 7.14 (t, J = 7.3 Hz, 1H), 7.07 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.50 (ABq, J = 21.2, 12.0 Hz, 2H), 3.80 (s, 3H), 3.63 (s, 3H), 3.34 (dd, J = 13.4, 4.7 Hz, 1H), 3.15 (dd, J = 13.4, 9.4 Hz, 1H).

Benzyl 2-(2-(2-Methoxy-2-oxoethyl)-1-methyl-1H-indol-3-yl)-2-oxoacetate (302). To a stirred solution of indole ester 301 (604 mg, 2.97 mmol) in Et₂O (100 mL) at 0 °C was added oxalyl chloride (1.06 mL, 11.9 mmol). After stirring the mixture for 30 min, benzyl alcohol (4.92 mL, 47.6 mmol) was added followed by the slow and careful addition of TEA (9.94 mL, 71.3 mmol) over 5 min. The resulting thick slurry was stirred vigorously at rt for 2 h and then
quenched with water. The organic layer was separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with water and brine, dried over MgSO₄, and concentrated in vacuo to give a viscous oil which was purified by flash chromatography on silica gel (25% to 50% EtOAc/hexanes) to afford indole-3-oxoacetate 302 (911 mg, 84%). ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, J = 8.0 Hz, 1H), 7.47-7.45 (m, 2H), 7.38-7.35 (m, 3H), 7.24 (d, J = 3.8 Hz, 2H), 7.15-7.10 (m, 1H), 5.42 (s, 2H), 4.16 (s, 2H), 3.66 (s, 3H), 3.54 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 181.6, 169.1, 166.1, 143.3, 137.4, 135.1, 129.4, 129.2, 129.1, 125.7, 123.5, 120.3, 110.7, 110.4, 68.1, 60.8, 52.9, 32.2, 30.4; LRMS-ES⁺ m/z (relative intensity) 366 (MH⁺, 100).

Methyl 6-(2-(Benzyloxy)-2-oxoethyl)-2-nosyl-2,3,4,5,5a,6-hexahydro-1H-pyrido[4',3':4,5]pyrrolo[1,2-a]indole-5-carboxylate (309). To a solution of indole 292 (43.0 mg, 0.056 mmol) in TFA (0.5 mL) was added triethylsilane (18 μL, 0.113 mmol). The resulting solution was stirred for 4 h at rt and then concentrated in vacuo. The resulting residue was dissolved in EtOAc and washed with NaHCO₃(aq). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue which was purified by preparative thin layer
chromatography (60% EtOAc/hexanes) to yield tetracycle 209 (10.4 mg, 31%).  

1H NMR (300 MHz, CDCl3) δ 7.88-7.85 (m, 1H), 7.68-7.52 (m, 4H), 7.35-7.33 (m, 6H), 7.22-7.10 (m, 2H), 5.13 (s, 2H), 4.78 (q, J = 7.4 Hz, 1H), 4.12-4.0 (m, 1H), 3.89-3.60 (m, 5H), 3.45-3.39 (m, 1H), 3.29-3.21 (m, 1H), 3.08 (dd, J = 13.6, 8.0 Hz, 1H), 2.19-1.97 (m, 2H);  

13C NMR (75 MHz, CDCl3) δ 171.9, 171.5, 148.5, 137.2, 136.3, 134.2, 132.5, 132.3, 132.1, 131.2, 129.0, 128.8, 128.7, 124.6, 122.4, 120.3, 119.5, 110.2, 102.3, 67.0, 53.7, 53.0, 46.3, 45.5, 43.5, 42.9, 30.6, 25.8;  

LRMS-ES+ m/z (relative intensity) 604 (MH+, 100).

\[\text{(Z)-Methyl 3-(2-(Benzyloxy)-2-oxoacetyl)-2-(1-(3-((tert-butyldimethylsilyl)-oxy)imino)-1-nosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (310).}\]

To a stirred solution of indole 292 (22.0 mg, 0.029 mmol) and THF (0.5 mL) at -78 °C was added LiHMDS (1.0 M in THF, 29 mL, 0.029 mmol) and the resulting solution was stirred for 30 min. Methyl chloroformate (12 μL, 0.15 mmol) was added and the reaction mixture was stirred for 18 h gradually warming to rt before quenching with water. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO4 and concentrated in vacuo to give a residue which was purified by preparative thin layer chromatography (30-40% EtOAc/hexanes) to afford methyl carbamate 310 (9.0 mg, 38%).  

1H NMR (300 MHz, CDCl3) δ 8.11 (d, J = 8.5 Hz, 1H), 7.89-7.87 (m, 1H), 7.58-7.52 (m, 3H), 7.45-7.42 (m, 5H), 7.34 (t, J = 8.4 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 8.0 Hz,
1H), 5.72 (d, J = 9.7 Hz, 1H), 5.43 (ABq, J = 16.8, 11.9 Hz, 2H), 4.08 (s, 3H), 3.90-3.87 (m, 1H), 3.70-3.68 (m, 1H), 3.63-3.57 (m, 4H), 3.03 (d, J = 14.9 Hz, 1H), 2.58 (d, J = 14.6 Hz, 1H), 2.13-2.07 (m, 1H), 0.98-0.86 (m, 1H) 0.71 (s, 9H), -0.08 (s, 3H), -0.26 (s, 3H); LRMS-ES+ m/z (relative intensity) 821 (MH+, 100).

**Methyl 3-(2-(Benzyloxy)-2-oxoacetyl)-2-(1-(3-(hydroxyimino)-1-nosyl-piperidin-4-y1)-2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (311).** To a stirred solution of indole 310 (9.0 mg, 0.011 mmol) in TFA (0.5 mL) was added triethylsilane (3.5 µL, 0.022 mmol). The resulting solution was stirred for 4 h at rt and then concentrated *in vacuo*. The resulting residue was dissolved in EtOAc and washed with NaHCO₃(aq). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give a residue which was purified by preparative thin layer chromatography (50% EtOAc/hexanes) to yield free oxime 311 (6.7 mg, 86%) as a ~1:1 mixture of diastereomers. ¹H NMR (300 MHz, CDCl₃) δ 8.10-8.07 (m, 1H), 7.91-7.89 (m, 1H), 7.61-7.54 (m, 3H), 7.47-7.37 (m, 6H), 7.29-7.14 (m, 2H), 5.66 (d, J = 9.4 Hz, 1H), 5.44 (s, 2H), 4.82 (d, J = 15.7 Hz, 1H), 4.06 (s, 3H), 3.97-3.85 (m, 1H), 3.64-3.55 (m, 5H), 3.08 (d, J = 15.7 Hz, 1H), 2.49-2.43 (m, 1H), 2.24-2.15 (m, 1H), 1.85-1.70 (m, 1H); LRMS-ES+ m/z (relative intensity) 707 (MH⁺, 50).
Methyl 2-(3-(Hydroxyimino)-1-tosylpiperidin-4-yl)-2-(3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)acetyl)-1H-indol-2-yl)acetate (315).  To a -78 °C solution of indole 286 (5.80 g, 16.1 mmol) in THF (100 mL) was added LiHMDS (1.0 M in THF, 32.1 mL, 32.1 mmol) and the resulting solution was stirred for 30 min.  A solution of oxime 264 (4.86 g, 16.1 mmol) in THF (30 mL) was then added dropwise over 3 min.  The reaction mixture was stirred for 2 h at -78 °C and then quenched with NH₄Cl(aq).  The organic layer was separated and the aqueous layer was extracted with EtOAc.  The combined organic layers were dried over MgSO₄ and concentrated in vacuo to afford a residue which was purified by flash chromatography on silica gel (50% EtOAc/hexanes) to give Michael adduct 315 (10.00 g, 99%).  ¹H NMR (300 MHz, CDCl₃) δ 10.31 (s, 0.5H), 10.23 (s, 0.5H), 8.90 (s, 0.5H), 8.66 (s, 0.5H), 7.79-7.58 (m, 3H), 7.39-7.17 (m, 5H), 5.59 (d, J = 5.9 Hz, 0.5H), 5.13 (d, J = 8.6 Hz, 0.5H), 4.93 (d, J = 14.5 Hz, 0.5H), 4.60-4.50 (m, 2H), 3.69-4.47 (m, 4H) 3.37 (p, J = 5.7 Hz, 0.5H), 3.20 (d, J = 14.6 Hz, 0.5 H); 3.10 (q, J = 7.3 Hz, 0.5H), 2.97-2.85 (m, 1H), 2.44-2.28 (m, 3H), 2.08-2.03 (m, 0.5H), 1.78-1.76 (m, 0.5H), 1.41-1.31 (m, 0.5H), 0.11-0.07 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 183.6, 183.0, 172.6, 171.9, 166.5, 166.5, 152.8, 152.7, 144.61, 144.57, 143.5, 143.4, 135.83, 135.80, 130.4, 130.3, 128.06, 127.96, 125.8, 125.6, 124.4, 124.2, 123.4, 123.2, 120.0, 119.6, 112.9, 112.7, 111.2, 111.1, 65.33, 65.29, 53.3, 53.2, 45.4, 44.9, 44.2, 43.4, 42.9, 42.7, 42.3, 41.9, 27.9, 27.8, 22.0, 21.9, 17.8, 14.6, 14.2, -1.1; LRMS-ES+ m/z (relative intensity) 666 (M+K⁺, 100); HRMS-ES+ (C₃₀H₄₁N₄O₈SSi) calcd 645.2414 (M+NH₄⁺), found 645.2445.
Methyl 2-(3-(((tert-Butyldimethylsilyl)oxy)imino)-1-tosylpiperidin-4-yl)-2-(3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)acetyl)-1H-indol-2-yl)acetate (317). To a solution of oxime 315 (10.00 g, 15.9 mmol), imidazole (4.43 g, 64.4 mmol), and CH₂Cl₂ (600 mL) was added TBS-Cl (6.50 g, 41.8 mmol). The resulting mixture was stirred for 17 h at rt and then diluted with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to yield a residue which was purified by flash chromatography on silica gel (15-30% EtOAc/hexanes) to give O-TBS-oxime 317 (9.88 g, 84%). ¹H NMR (300 MHz, CDCl₃) δ 9.91 (s, 0.5H), 9.79 (s, 0.5H), 7.77-7.61 (m, 3H), 7.41-7.21 (m, 5H) 5.56 (d, J = 5.7 Hz, 0.5H), 5.06-4.97 (m, 1H), 4.84 (d, J = 15.0, 0.5H), 4.54-4.45 (m, 2H), 3.69-3.60 (m, 4H), 3.41 (dt, J = 7.1, 12.6 Hz, 0.5H), 3.30 (d, J = 15.0 Hz, 0.5H), 3.18 (d, J = 14.9 Hz, 0.5H), 3.00-2.92 (m, 1H), 2.85-2.70 (m, 0.5H), 2.42 (s, 1.5H) 2.32 (s, 1.5H), 2.06-1.98 (m, 0.5H), 1.85-1.70 (m, 0.5H), 1.65-1.55 (m, 0.5H), 1.40-1.35 (m, 1H), 1.20-1.13 (m, 2H), 0.99 (m, 9H), 0.31-0.20 (m, 6H), 0.10-0.07 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 183.4, 182.8, 172.6, 171.0, 166.3, 166.1, 157.9, 156.8, 144.40, 144.37, 143.6, 143.4, 135.5, 135.4, 133.9, 133.6, 130.20, 130.15, 128.0, 127.9, 126.0, 125.7, 124.4, 124.2, 123.5, 123.2, 120.6, 120.0, 112.4, 112.2, 111.3, 65.1, 53.2, 53.0, 45.2, 44.1, 43.5, 43.3, 42.9, 28.1, 27.7, 26.34, 26.28, 21.93, 21.85, 18.3, 18.2, 17.79, 17.76, -1.1, -4.2, -4.6, -4.8; LRMS-ES⁺ m/z (relative intensity) 780 (M+K⁺, 100); HRMS-ES⁺ (C₃₆H₅₂N₃O₈SSi₂) calcd 742.3014 (MH⁺), found 742.3005.
Methyl 2-(3-(((tert-Butyldimethylsilyl)oxy)imino)-1-tosylpiperidin-4-yl)-2-(3-(1-hydroxy-2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indol-2-yl)acetate (318). To a stirred solution of indole-3-oxoacetate 317 (6.07 g, 8.18 mmol) in MeOH (70 mL) and THF (70 mL) at 0 °C was added NaBH₄ (378 mg, 9.79 mmol). The resulting solution was stirred for 1 h at 0 °C and then diluted with NH₄Cl(aq). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers washed with water, brine, and then dried over MgSO₄. Removal of the solvent in vacuo provided alcohol 318 (6.05 g, 99%) which was used in the following reaction without further purification. ¹H NMR (300 MHz, CDCl₃) δ 8.99 (s, 0.5H), 8.81-8.78 (m, 0.5H), 7.66-7.60 (m, 3H), 7.33-7.07 (m, 5H), 5.39-5.28 (m, 1H), 5.15-5.0 (m, 0.5H), 4.95-4.85 (m, 0.5H), 5.54-4.50 (m, 0.5H), 4.35-4.11 (m, 2.5H), 3.68-3.25 (m, 6H), 3.20-2.90 (m, 1.5H), 3.70-3.60 (m, 0.5H), 2.45-2.36 (m, 3H), 1.95-1.80 (m, 0.5H), 1.65-1.20 (m, 2H), 1.01-0.87 (m, 11H), 0.27-0.17 (m, 6H), 0.04--0.05 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 174.6, 174.5, 174.3, 173.2, 173.1, 171.8, 157.6, 157.5, 156.9, 156.7, 156.3, 144.3, 136.24, 136.17, 135.7, 134.0, 133.9, 131.4, 130.2, 128.1, 128.0, 126.4, 126.2, 126.1, 123.2, 122.8, 120.8, 120.4, 119.7, 119.6, 119.3, 112.62, 112.56, 112.2, 112.0, 111.6, 66.8, 66.5, 66.2, 65.2, 64.94, 64.89, 53.9, 53.0, 52.9, 52.8, 45.4, 45.3, 44.8, 44.2, 44.2, 43.4, 43.4, 43.3, 43.0, 42.8, 42.6, 42.5, 42.3, 42.1, 28.4, 27.8, 26.4, 26.3, 22.0, 21.9, 18.4, 18.3, 17.8, 17.6, -1.2, -4.5, -4.7, -4.9; LRMS-ES+ m/z (relative intensity) 782 (M+K⁺, 100); HRMS-ES+ (C₃₆H₅₄N₅O₈S₂Si₂) calcd 744.3170 (MH⁺), found 744.3148.
Methyl 2-(3-(1-Acetoxy-2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indol-2-yl)-2-(3-((tert-butyldimethylsilyl)oxy)imino)-1-tosylpiperidin-4-yl)acetate (319). The alcohol 318 (6.05 g, 8.13 mmol) was dissolved in Ac₂O (40 mL) and pyridine (40 mL) and the mixture was stirred at rt for 26 h. The solvent was removed \textit{in vacuo} and the resulting crude product was purified by flash chromatography on silica gel (15-25% EtOAc/hexanes) to give acetate 319 (5.84 g, 91%). For characterization purposes, \textit{E}-319 and \textit{Z}-319 were separated for NMR analysis. \textit{E}-319 (more polar oxime isomer, ~3:1 mixture of acetoxy diastereomers): ¹H NMR (400 MHz, CDCl₃) δ 9.07 (s, 0.75H), 9.03 (s, 0.25H), 7.75-7.71 (m, 1H), 7.64 (d, \(J = 8.2\) Hz, 2H), 7.32-7.13 (m, 5H), 6.21 (s, 0.25H), 6.18 (s, 0.75H), 4.97-4.88 (m, 1H), 4.52 (d, \(J = 5.9\) Hz, 0.25H), 4.48 (d, \(J = 5.5\) Hz, 0.75H), 4.28-4.20 (m, 1H), 4.09-4.02 (m, 1H), 3.67-3.55 (m, 4H), 3.41-3.31 (m, 2H), 3.00-2.93 (m, 1H), 2.39-2.36 (m, 3H), 2.14 (s, 3H), 1.95-1.70 (m, 3H), 1.60-1.40 (m, 2H), 0.98 (s, 9H), 0.29-0.18 (m, 6H), 0.00--0.02 (m, 9H); ¹³C NMR (90 MHz, CDCl₃) δ 171.0, 170.8, 170.6, 170.5, 169.1, 157.3, 144.0, 135.3, 135.2, 133.7, 133.5, 132.2, 131.7, 129.8, 127.6, 126.2, 126.1, 122.7, 120.3, 119.3, 111.2, 108.0, 107.8, 67.7, 64.2, 53.4, 52.5, 44.8, 43.2, 42.9, 42.7, 42.4, 42.1, 28.0, 26.0, 25.9, 21.5, 20.9, 20.7, 17.9, 17.3, -1.56, -1.59, -4.8, -5.1; \textit{Z}-319 (less polar oxime isomer, ~2:1 mixture of acetoxy diastereomers): ¹H NMR (300 MHz, CDCl₃) δ 8.73-8.71 (m, 1H), 7.76 (d, \(J = 7.6\) Hz, 1H), 7.66 (d, \(J = 8.2\) Hz, 1H), 7.35-7.14 (m, 5H), 6.24-6.22 (m, 1H), 5.02 (t, \(J = 7.1\) Hz, 1H), 4.34-4.07 (m, 3H), 3.66-3.53 (m, 4H), 3.15-3.07 (m, 2H), 2.72 (d, \(J = 11.3\) Hz, 1H), 2.45 (s, 3H), 2.20-2.18 (m, 3H), 1.58-1.39 (m, 2H), 1.00-0.89 (m, 12H), 0.26 (s, 3H), 0.20 (s, 3H), 0.02--0.04 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 173.1, 173.0, 170.9, 170.8, 169.3, 169.2, 156.7, 144.4, 136.1, 136.0, 133.8, 133.6, 132.4, 132.2, 130.2, 128.1, 126.7, 123.5, 123.4, 121.1, 120.2, 111.5, 108.54, 108.50, 68.4, 68.0, 64.7, 64.5, 53.9, 53.0, 52.9, 45.4, 44.4, 44.1, 42.8, 42.6, 42.5, 28.5, 28.0, 26.4, 22.0, 21.2, 21.1, 18.4, 17.7, 17.6, -1.2, -4.75, -
4.89, -4.92; mixture of \( E \)- and \( Z \)-319: LRMS-ES+ \( m/z \) (relative intensity) 824 (\( M+K^+ \), 25); HRMS-ES+ (C\(_{38}H_{56}N_3O_9SSi_2\)) calcd 786.3276 (MH\(^+\)), found 786.3286.

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(Z)-\text{Methyl} \quad 2-(3-(((\text{tert-Butyldimethylsilyl})oxy)imino)-1-tosylpiperidin-4-yl)-2-(3-(1-ethoxy-2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1\text{-H-indol-2-yl})acetate (Z-321). \quad \text{Indole} \ Z-319 \ (23.3 \text{ mg}, 0.030 \text{ mmol}) \text{ was dissolved in 10:1 EtOH/TEA (1.1 mL) and the solution was stirred for 22 h at rt. The solution was and concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (30\% EtOAc/hexanes) to give ethanol adduct Z-321 (17.2 mg, 75\%) as a \( \sim \)1:1 mixture of ethoxy-diastereomers. }^1\text{H NMR (300 MHz, CDCl}_3\) \( \delta \) 8.37 (s, 0.5H), 8.33 (s, 0.5H), 7.83-7.80 (m, 1H), 7.68 (d, \( J = 7.8 \text{ Hz}, 2H \)), 7.34 (d, \( J = 8.0 \text{ Hz}, 2H \)), 7.28-7.25 (m, 1H), 7.21-7.11 (m, 2H), 5.12-5.00 (m, 1H), 4.43-4.08 (m, 3H), 3.65-3.58 (m, 4H), 3.52-5.48 (m, 1H), 3.15-3.10 (m, 2H), 2.75-2.65 (m, 1H), 2.45 (s, 3H), 1.62-1.40 (m, 3H), 1.30-1.21 (m, 2H), 1.00-0.93 (m, 12H), 0.25-0.19 (m, 6H), 0.04-0.01 (m, 9H); LRMS-ES+ \( m/z \) (relative intensity) 810 (\( M+K^+ \), 50).

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(E)-\text{Methyl} \quad 2-(3-(((\text{tert-Butyldimethylsilyl})oxy)imino)-1-tosylpiperidin-4-yl)-2-(3-(1-ethoxy-2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1\text{-H-indol-2-yl})acetate (E-321). \quad \text{Using the above procedure with the } E \text{-oxime isomer } E-319 \ (22.0 \text{ mg}, 0.028 \text{ mmol}) \text{ afforded ethanol adduct } E-321 \ (14.5 \text{ mg}, 67\%) \text{ as a } \sim 1:1 \text{ mixture of ethoxy-diastereomers. }^1\text{H NMR (300 MHz, CDCl}_3\) \( \delta \) 9.03 (s, 0.5H), 8.99 (s, 0.5H), 7.73-7.70 (m, 1H), 7.66-7.63 (m, 2H), 7.31-7.25 (m, 3H), 7.21 (t,
$J = 8.0 \text{ Hz, } 1\text{H}$, $7.13 \text{ (t, } J = 7.2 \text{ Hz, } 1\text{H})$, $5.21 \text{ (s, } 0.5\text{H})$, $5.15 \text{ (s, } 0.5\text{H})$, $5.01 \text{ (t, } J = 15.8 \text{ Hz, } 1\text{H})$, $4.82 \text{ (d, } J = 5.6 \text{ Hz, } 0.5\text{H})$, $4.75 \text{ (d, } J = 5.6 \text{ Hz, } 0.5\text{H})$, $4.23-4.16 \text{ (m, } 1\text{H})$, $4.09-3.99 \text{ (m, } 1\text{H})$, $3.67-3.55 \text{ (m, } 4.5\text{H})$, $3.49-3.44 \text{ (m, } 1.5\text{H})$, $3.37-3.32 \text{ (m, } 1.5\text{H})$, $3.24 \text{ (d, } J = 15.9 \text{ Hz, } 0.5\text{H})$, $2.95-2.88 \text{ (m, } 1\text{H})$, $2.37 \text{ (s, } 1.5\text{H})$, $2.36 \text{ (s, } 1.5\text{H})$, $1.97-1.86 \text{ (m, } 1\text{H})$, $1.41-1.28 \text{ (m, } 1\text{H})$, $1.23-1.16 \text{ (m, } 3\text{H})$, $1.00 \text{ (s, } 4.5\text{H})$, $0.99 \text{ (s, } 4.5\text{H})$, $0.96-0.87 \text{ (m, } 2\text{H})$, $0.31 \text{ (s, } 1.5\text{H})$, $0.28 \text{ (s, } 1.5\text{H})$, $0.20 \text{ (s, } 3\text{H})$, $-0.01 \text{ (s, } 9\text{H})$; LRMS-ES+ $m/z$ (relative intensity) 810 (M+K+, 60).

Methyl 2-(3-((tert-Butyldimethylsilyl)oxy)imino)-1-tosylpiperidin-4-yl)-2-(3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indol-2-yl)acetate (320). To a solution of acetate 319 (413 mg, 0.525 mmol) and t-BuOH (12.5 mL) under an argon atmosphere was added Pd/C (10 wt% Pd on carbon, 84 mg, 0.079 mmol). The resulting mixture evacuated and backfilled with H$_2$ from a balloon and then TEA (1.4 mL) was added. The mixture was warmed to 30 °C and stirred for 4 days. An additional portion of TEA (350 μL) was added and the reaction mixture was stirred for another 24 h. The reaction mixture was filtered through a pad of Celite eluting with EtOAc and the filtrate was concentrated in vacuo to afford a residue, which was purified by flash chromatography on silica gel (10-25% EtOAc/hexanes) to give indole $E$-320 (190 mg) and indole $Z$-320 (184 mg, combined 98% yield). $^1$H NMR (300 MHz, CDCl$_3$, ~1:1 mixture of oxime isomers) δ 8.81 (s, 0.5H), 8.43 (s, 0.5H), 7.69-7.61 (m, 3H), 7.36-7.14 (m, 5H), 5.10 (d, $J = 14.3 \text{ Hz, } 0.5\text{H}$), 4.88 (d, $J = 14.9 \text{ Hz, } 0.5\text{H}$), 4.39 (d, $J = 6.0 \text{ Hz, } 0.5\text{H}$), 4.22-4.10 (m, 2.5H),
3.71-3.59 (m, 6.5H), 3.41 (d, J = 15.1 Hz, 0.5H), 3.31 (p, J = 5.9 Hz, 0.5H), 3.12-2.96 (m, 1.5H) 2.48 (s, 1.5H), 2.40 (s, 1.5H), 1.92-1.88 (m, 0.5H), 1.63-1.59 (m, 1.5H), 1.04-0.99 (m, 11H), 0.28-0.20 (m, 6H), 0.08-0.05 (m, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 173.3, 172.0, 171.9, 171.8, 157.5, 156.8, 144.3, 136.1, 135.8, 134.0, 133.7, 130.4, 130.20, 130.16, 128.7, 128.4, 128.2, 128.04, 128.80, 126.0, 123.0, 122.6, 120.5, 120.0, 119.5, 119.2, 111.4, 108.6, 107.9, 65.6, 63.5, 52.9, 52.8, 45.6, 45.0, 44.2, 43.4, 43.0, 42.9, 42.6, 42.3, 34.7, 32.4, 32.2, 30.9, 30.8, 30.1, 29.8, 28.1, 27.9, 26.4, 26.4, 23.2, 22.0, 21.9, 21.7, 18.5, 18.3, 17.84, 17.79, 14.6, -1.1, -4.5, -4.69, -4.74, -4.88; LRMS-ES+ m/z (relative intensity) 766 (M+K$^+$, 75); $^{E}$-320: HRMS-ES+ (C$_{36}$H$_{57}$N$_4$O$_7$SSi$_2$) calcd 745.3487 (M+NH$_4^+$), found 745.3478. $^{Z}$-320: HRMS-ES+ (C$_{36}$H$_{54}$N$_3$O$_7$SSi$_2$) calcd 728.3221 (M+H$^+$), found 728.3224.

Methyl 2-(3-(((tert-Butyldimethylsilyl)oxy)imino)piperidin-4-yl)-2-(3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indol-2-yl)acetate (323). A stock solution of sodium-naphthalenide was prepared by adding Na (39 mg, 1.7 mmol) to a stirred solution of naphthalene (222 mg, 1.72 mmol) and 1,2-dimethoxyethane (2 mL). The resulting solution was stirred for 30 min and then 1 mL of the stock sodium-naphthalenide solution was added dropwise over 10 min to a -78 °C solution of indole 320 (25.0 mg, 0.034 mmol) in 1,2-dimethoxyethane (2 mL). The reaction mixture was quenched with NH$_4$Cl(aq) and then concentrated in vacuo. The resulting residue was taken up in EtOAc and washed with water. The organic layer was dried over
MgSO₄ and concentrated in vacuo to give a residue, which was purified by flash chromatography on silica gel (85% EtOAc/hexanes + 1% TEA) to afford amine 323 (10.8 mg, 55%). ¹H NMR (360 MHz, CDCl₃, ~2:1 mixture of oxime isomers) δ 8.08 (s, 0.33H), 8.37 (s, 0.66H), 7.65-7.60 (m, 1H), 7.35-7.10 (m, 3H), 4.58-4.35 (m, 2H), 4.27-4.08 (m, 3H), 3.75-3.65 (m, 5H), 3.53-3.48 (m, 0.66H), 3.30-3.12 (m, 1.33H), 3.10-2.96 (m, 2H), 2.78-2.68 (m, 1H), 1.93-1.88 (m, 1H), 1.60-1.48 (m, 2H), 1.05-0.98 (m, 9H), 0.30-0.15 (m, 6H), 0.04--0.01 (m, 9H); LRMS-ES⁺ m/z (relative intensity) 574(MH⁺, 100).

 tert-Butyl 2-(1-(3-(((tert-Butyldimethylsilyl)oxy)imino)-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indole-1-carboxylate (324). To a stirred solution of indole 320 (1.00 g, 1.37 mmol), Boc₂O (1.80 g, 8.24 mmol), and CH₂Cl₂ (60 mL) at 0 °C was added TEA (2.90 mL, 20.6 mmol) followed by DMAP (17 mg, 0.14 mmol). The resulting solution was stirred at rt for 16 h and then diluted with NaHCO₃(aq). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to yield a residue which was purified by flash chromatography on silica gel (10-15% EtOAc/hexanes) to give N-Boc indole 324 (1.00 g, 88%) as a ~1:1 mixture of oxime isomers. ²H NMR (300 MHz, CDCl₃, mixture of BOC-rotamers) δ 8.01-7.94 (m, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.57-7.43 (m, 1H), 7.35-7.25 (m, 4H), 5.60-5.22 (m, 2H), 4.15-4.06 (m, 2H), 3.67-3.56 (m, 6H), 3.45-3.38 (m, 1H),
2.90 (d, J = 13.9 Hz, 1H), 2.64 (t, J = 8.7 Hz, 1H), 2.47 (s, 3H), 1.67-1.65 (m, 9H), 1.54-1.15 (m, 4H), 0.98-0.90 (m, 9H), 0.21-0.16 (m, 6H), 0.03 (s, 9H); LRMS-ES+ m/z (relative intensity) 828 (MH+, 80).  

E-324: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.94 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.32-7.20 (m, 2H), 4.18-4.12 (m, 2H), 3.75-3.46 (m, 8H), 3.09-3.01 (m, 1H), 2.55-2.50 (m, 1H), 2.47 (s, 3H), 2.03-1.92 (m, 1H), 1.67 (s, 9H), 1.29-1.25 (m, 1H), 1.01-0.91 (m, 3H), 0.76 (s, 9H), 0.03 (s, 9H), -0.08 (s, 3H), -0.18 (s, 3H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 171.3, 170.6, 150.5, 143.7, 135.4, 133.0, 129.8, 129.4, 127.9, 124.5, 122.7, 118.9, 116.0, 115.0, 84.4, 63.2, 52.0, 42.8, 42.0, 30.7, 28.2, 27.4, 26.3, 25.8, 21.6, 17.9, 17.4, -1.5, -5.5, -5.6; LRMS-ES+ m/z (relative intensity) 828 (MH+, 75); HRMS-ES+ (C$_{41}$H$_{62}$N$_3$O$_9$Si$_2$S) calcd 828.3745 (MH$^+$), found 828.3746.

tert-Butyl 2-(1-(3-(Hydroxyimino)-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indole-1-carboxylate (325). To a stirred solution of O-TBS-oxime 324 (500 mg, 0.604 mmol) and THF (9 mL) at 0 °C was added TBAF (1.0 M in THF, 604 µL, 0.604 mmol). The resulting solution was stirred for 1 min and then immediately diluted with NH$_4$Cl(aq). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo to give a residue which was purified by flash column chromatography on silica gel (30% EtOAc/hexanes) to afford free oxime 325 (401 mg, 93%) as a ~1:1 mixture of oxime isomers. Z-
**325**: $^1$H NMR (400 MHz, CDCl$_3$, mixture of BOC-rotamers) $\delta$ 8.03-7.95 (m, 1H), 7.69 (d, $J$ = 8.0 Hz, 1H), 7.60-7.40 (m, 2H), 7.36-7.25 (m, 4H), 5.69-5.15 (m, 2H), 4.15-4.07 (m, 2H), 3.68-3.58 (m, 5H), 3.37-3.35 (m, 1H), 2.95-2.90 (m, 1H), 2.65-2.63 (m, 1H), 2.47 (s, 3H), 1.67-1.54 (m, 10H), 1.43-1.21 (m, 2H), 1.01-0.87 (m, 3H), 0.04 (s, 9H); LRMS-ES+ m/z (relative intensity) 714 (MH$^+$, 50).

**E-325**: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.94 (d, $J$ = 8.1 Hz, 1H), 7.69 (d, $J$ = 8.1 Hz, 2H), 7.47 (d, $J$ = 7.8 Hz, 1H), 7.35 (d, $J$ = 8.1 Hz, 2H), 7.30-7.21 (m, 2H), 4.17-4.12 (m, 2H), 3.80-3.74 (m, 1H), 3.67-3.55 (m, 5H), 3.50-3.30 (m, 2H), 3.13-3.07 (m, 1H), 2.48-2.45 (m, 4H), 2.35-2.30 (m, 1H), 2.12-2.06 (m, 1H), 1.73-1.57 (m, 10H), 1.05-0.95 (m, 3H), 0.03 (s, 9H); LRMS-ES+ m/z (relative intensity) 714 (MH$^+$, 100); HRMS-ES+ (C$_{35}$H$_{48}$N$_3$O$_9$SiS) calcd 714.2881 (MH$^+$), found 714.2867.

*tert*-Butyl 2-(2-Methoxy-2-oxo-1-(3-((pivaloyloxy)imino)-1-tosylpiperidin-4-yl)ethyl)-3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indole-1-carboxylate (354). Oxime 325 (149 mg, 0.209 mmol) was dissolved in pivalic anhydride (1 mL) and pyridine (2 mL) and the solution was stirred at rt for 36 h. The volatiles were removed *in vacuo* and the resulting crude product was purified by flash chromatography on silica gel (15-25% EtOAc/hexanes) to give oxime pivalate 354 (120 mg, 72%) as a complex mixture of oxime isomers and Boc-rotamers. $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 8.08 (d, $J$ = 7.8 Hz, 0.33H), 7.96-7.91 (m, 0.67H), 7.69-7.65 (m, 2H), 7.59 (d, $J$ = 7.6 Hz, 0.66H), 7.47 (d, $J$ = 7.0 Hz, 0.33H), 7.40-7.25 (m, 4H), 5.72-5.67 (m,
0.5H), 5.47-5.45 (m, 0.5H), 5.10-5.03 (m, 1H), 4.22-4.02 (m, 2.5H), 3.80-3.57 (m, 6H), 3.40-
3.30 (m, 0.5H), 3.15-3.04 (m, 1H), 2.80-2.64 (m, 1H), 2.49 (s, 3H), 1.71-1.66 (m, 10H), 1.55-
1.53 (m, 1H), 1.38-1.35 (m, 9H), 1.01-0.97 (m, 3H), 0.05 (s, 9H).

General Procedure for the Conversion of Ketoxime Pivalates to Ketones. To a
solution of oxime pivalate 352 (0.10 mmol) in THF (1 mL) was added iron powder (55.8 mg, 1.0
mmol) followed by glacial AcOH (1 drop, cat.) and TMSCl (1 drop, cat.). After stirring at rt for
30 min, the reaction mixture was diluted with H2O (1 mL) and stirred for an additional 15 min.
The liquid phase was separated from the remaining Fe powder using a pipette and transferred to
a separatory funnel. The Fe powder was then washed with EtOAc (3 x 2 mL) and the washings
were added to the separatory funnel. The organic layer was separated and the aqueous layer was
extracted with EtOAc. The combined organic layers were dried over MgSO4 and concentrated
in vacuo to give a residue which was purified by flash column chromatography on silica gel eluting
with a mixture of ethyl acetate and hexanes. Known ketones were characterized by comparison
to their reported 1H NMR spectra (cf. Table 5).
**tert-Butyl 2-(2-Methoxy-2-oxo-1-(3-oxo-1-tosylpiperidin-4-yl)ethyl)-3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indole-1-carboxylate (326).** Following the above general experimental procedure at a 0.03 M concentration, ketoxime pivalate 354 (30 mg, 0.038 mmol) was converted to ketone 326 (22 mg, 84%). $^1$H NMR (300 MHz, CDCl$_3$, mixture of Boc-rotamers).$\delta$ 7.97-7.90 (m, 1H), 7.74 (d, $J = 8.1$ Hz, 2H), 7.69-7.64 (m, 1H), 7.38 (d, $J = 8.4$ Hz, 2H), 7.34-7.28 (m, 2H), 4.34-4.05 (m, 3H), 3.66-3.59 (m, 7H), 3.41-3.36 (m, 1H), 2.86 (td, $J = 11.3$, 3.9 Hz, 1H), 2.49 (s, 3H), 1.68-1.46 (m, 11H), 1.04-0.91 (m, 3H), 0.07-0.03 (m, 9H); LRMS-ES+ m/z (relative intensity) 716 (M+NH$_4^+$, 100); HRMS-ES+ (C$_{35}$H$_{50}$N$_3$O$_9$SiS) calcd 716.3037 (M+NH$_4^+$), found 716.3013.

**2-(5-(Methoxycarbonyl)-2-tosyl-2,3,4,6-tetrahydro-1H-pyrido[4',3':4,5]pyrrolo[1,2-a]indol-6-yl)acetic Acid (356).** To a stirred solution of TMSE-ester 326 (21.5 mg, 0.0308 mmol) in CH$_2$Cl$_2$ (2.5 mL) was added TFA (100 μL). The resulting solution was stirred for 1.5 h at rt, an additional portion of TFA (500 μL) was added, and the solution was stirred for an additional 3 h. The solvent was removed in vacuo to give a residue which was purified by flash column chromatography on silica gel (40% EtOAc/hexanes + 1% AcOH) to afford tetracyclic
pyrrole \textbf{356} (9.3 mg, 61%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J = 8.1$ Hz, 2H) 7.54-7.52 (m, 1H), 7.39-7.31 (m, 3H), 7.20-7.17 (m, 2H), 4.60-4.55 (m, 2H), 3.84 (s, 3H), 3.78-3.75 (m, 1H). 3.66-3.59 (m, 1H), 3.48-3.38 (m, 2H), 2.96-2.95 (m, 2H), 2.74 (br s, 1H), 2.44-2.36 (m, 4H); LRMS-ES+ m/z (relative intensity) 481 (MH$^+$, 100).

Benzyl 2-(1-((3-tert-Butyldimethylsilyl)oxy)imino)-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indole-1-carboxylate (357). To a –78 °C stirred solution of indole \textit{Z}-\textbf{320} (830 mg, 1.14 mmol) and THF (20 mL) was added KHMDS (0.5 M in THF, 2.5 mL, 1.25 mmol). The resulting solution was stirred for 45 min and Cbz-Cl (212 $\mu$L, 1.48 mmol) was added. The solution was stirred for 12 h at –78 °C and then quenched with NH$_4$Cl(aq). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO$_4$ and concentrated \textit{in vacuo} to give a residue which was purified by flash column chromatography on silica gel (10-15% EtOAc/hexanes) to yield \textit{N}-Cbz-indole \textit{Z}-\textbf{357} (870 mg, 89%). An identical procedure was followed using indole \textit{E}-\textbf{320} (820 mg, 1.13 mmol) to prepare \textit{N}-Cbz-indole \textit{E}-\textbf{357} (860 mg, 89%). \textit{Z}-\textbf{357}: $^1$H NMR (300 MHz, CDCl$_3$, mixture of Cbz-rotamers) $\delta$ 8.14-8.02 (m, 1H), 7.68-7.13 (m, 12H), 5.72-5.51 (m, 1.6H), 5.33-5.16 (m, 2.4H), 4.18-4.10 (m, 2H), 3.67-3.50 (m, 6H), 3.16-3.11 (m, 1H), 2.72-2.67 (m, 1H), 2.51-2.43 (m, 3H), 2.25-2.15 (m, 1H), 1.15-1.10, 1.04-0.93 (m, 12H), 0.27-0.19 (m, 6H), 0.03 (s, 9H), (m, 1H). \textit{E}-\textbf{357}: $^1$H NMR (300 MHz, CDCl$_3$)
\( \delta \) 8.01-7.98 (m, 1H), 7.68 (d, \( J = 8.3 \) Hz, 2H), 7.49-7.46 (m, 3H), 7.42-7.33 (m, 5H), 7.26-7.16 (m, 2H), 5.41 (s, 2H), 4.17-4.07 (m, 2.5H), 3.80-3.71 (m, 1H), 3.65-3.60 (m, 3H), 3.54-3.37 (m, 4.5H), 3.03-2.95 (m, 1H), 2.50-2.38 (m, 4H), 2.01-1.90 (m, 1H), 0.99-0.87 (m, 3H), 0.77 (s, 9H), 0.02 (s, 9H), -0.03 (s, 3H), -0.17 (s, 3H). Mixture of \( E \)- and \( Z \)-357: LRMS-ES+ \( m/z \) (relative intensity) 862 (MH\(^+\), 90); HRMS-ES+ (C\(_{44}H_{60}N_3O_9SSi_2\)) calcd 862.3589 (MH\(^+\)), found 862.3585. Slow evaporation of a solution of \( Z \)-357 in EtOAc provided crystals which were analyzed by X-ray diffraction (Figure 9).\(^{141}\)

Figure 10. ORTEP and Wireframe Structures of \( Z \)-357
Benzyl 2-(1-(3-(Hydroxyimino)-1-tosylpiperidin-4-yl)-2-methoxy-2-oxoethyl)-3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indole-1-carboxylate (358). To a stirred solution of O-TBS-oxime 357 (685 mg, 0.794 mmol) and THF (37 mL) was added AcOH (370 μL) followed by TBAF (1.0 M in THF, 1.19 mL, 1.19 mmol). The resulting solution was stirred overnight at rt and then diluted with NH₄Cl(aq). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue which was purified by flash column chromatography on silica gel (30% EtOAc/hexanes) to afford free oxime 358 (590 mg, 99%) as a complex mixture of oxime isomers and Cbz-rotamers. ¹H NMR (300 MHz, CDCl₃) δ 8.56-7.29 (m, 13H), 5.74-4.91 (m, 2.7H), 4.23-4.13 (m, 2.4H), 3.70-3.50 (m, 5.7H), 3.25-3.10 (m, 1.4H), 2.52-2.45 (3.6H), 2.28-2.25 (m, 0.5H), 1.95-1.85 (m, 0.5H), 1.60-1.40 (m, 2H), 1.33-1.17 (m, 1H), 1.00-0.90 (m, 3H), 0.10-0.01 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 173.4, 172.2, 172.0, 170.9, 153.3, 151.8, 144.4, 144.3, 136.2, 135.0, 133.4, 132.7, 131.7, 130.3, 130.2, 129.9, 129.8, 129.4, 129.2, 129.03, 128.99, 128.8, 128.3, 128.2, 127.4, 126.0, 125.7, 123.9, 123.1, 120.4, 119.6, 119.5, 117.6, 116.3, 111.4, 108.6, 70.2, 69.3, 69.1, 64.2, 63.9, 63.7, 53.0, 52.6, 46.0, 45.4, 44.3, 44.1, 42.8, 42.4, 42.3, 40.9, 31.4, 30.9, 30.8, 30.4, 28.9, 27.8, 26.4, 26.1, 22.03, 22.00, 18.4, 17.8, 17.7, 1.5, -1.1, -2.5, -3.1; LRMS-ES+ m/z (relative intensity) 748 (MH⁺, 75); HRMS-ES+ (C₃₈H₄₆N₃O₈Si₂) calcd 748.2724 (MH⁺), found 748.2690.
Benzyl 2-(2-Methoxy-2-oxo-1-(3-((pivaloyloxy)imino)-1-tosylpiperidin-4-yl)ethyl)-3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indole-1-carboxylate (359). The oxime 358 (550 mg, 0.735 mmol) was dissolved in Piv$_2$O (6 mL) and pyridine (12 mL) and the mixture was warmed to 60 °C. After stirring the mixture for 12 h at that temperature, the solvent was removed in vacuo using PhMe to azeotropically remove the excess Piv$_2$O. The resulting crude product was purified by flash chromatography on silica gel (15-30% EtOAc/hexanes) to give oxime-pivalate 359 (527 mg, 94%) as a complex mixture of oxime isomers and Cbz-rotamers.

$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.01 (s, 0.3H), 8.13-7.95 (m, 0.5H), 7.67-7.11 (m, 12.2H), 5.69-4.89 (m, 2H), 4.19-4.14 (m, 2H), 3.77-3.50 (m, 6H), 3.35-3.10 (m, 2H), 2.83-2.70 (m, 1H), 2.52-2.43 (m, 3H), 2.30-2.20 (m, 0.5H), 1.85-1.50 (m, 1.5H), 1.38-1.26 (m, 11H), 1.03-0.97 (m, 2H), 0.06-0.00 (m, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.6, 174.1, 171.6, 171.3, 170.8, 161.2, 160.8, 152.1, 151.8, 144.7, 144.6, 135.9, 135.8, 135.3, 135.1, 133.2, 132.5, 132.2, 130.4, 130.2, 129.7, 129.5, 129.4, 129.2, 129.10, 129.08, 128.8, 128.4, 128.2, 127.7, 125.7, 125.5, 123.9, 123.5, 119.8, 119.3, 118.2, 116.5, 116.5, 116.2, 69.7, 69.1, 64.0, 63.9, 52.8, 52.7, 45.8, 44.6, 43.5, 42.2, 40.6, 39.2, 38.9, 31.3, 31.2, 29.0, 27.7, 27.4, 22.0, 17.8, 17.6, 1.5, -1.1; LRMS-ES+ $m/z$ (relative intensity) 849 (M+NH$_4^+$, 25); HRMS-ES+ (C$_{43}$H$_{57}$N$_4$O$_{10}$SSi) calcd 849.3565 (M+NH$_4^+$), found 849.3587.
Benzyl 2-(2-Methoxy-2-oxo-1-(3-oxo-1-tosylpiperidin-4-yl)ethyl)-3-(2-oxo-2-(2-(trimethylsilyl)ethoxy)ethyl)-1H-indole-1-carboxylate (360). To a solution of oxime pivalate 359 (81.0 mg, 0.097 mmol) in THF (2 mL) at 0 °C was added iron powder (54 mg, 0.97 mmol) followed by AcOH (1 drop, cat.) and TMSCl (1 drop, cat.). After stirring for 30 min, the reaction mixture was diluted with H2O (2 mL) and stirred for an additional 15 min. The liquid phase was separated from the remaining Fe powder using a pipette and transferred to a separatory funnel. The Fe powder was then washed with EtOAc and the washings were added to the separatory funnel. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO4 and concentrated in vacuo to give a residue which was purified by flash column chromatography on silica gel (25% EtOAc/hexanes) to afford ketone 360 (64.4 mg, 90%). 1H NMR (300 MHz, CDCl3) δ 8.09 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.58-7.20 (m, 10H), 5.40 (ABq, J = 106.0, 11.8 Hz, 2H), 4.93 (d, J = 6.6 Hz, 1H), 4.18-4.11 (m, 2H), 4.02 (d, J = 13.8 Hz, 1H), 3.71-3.64 (m, 3H), 3.50 (s, 3H), 3.34 (q, J = 9.9 Hz, 1H), 3.21 (d, J = 14.1 Hz, 1H), 2.51-2.43 (m, 4H), 1.55-1.44 (m, 1H), 1.30-1.22 (m, 1H), 1.00-0.94 (m, 2H), 0.04 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 201.9, 171.6, 170.6, 151.9, 144.7, 135.8, 135.0, 132.5, 132.1, 130.3, 129.7, 129.4, 129.2, 128.8, 128.43, 128.35, 127.7, 125.8, 124.0, 119.7, 117.8, 116.3, 69.2, 64.2, 56.4, 52.8, 49.1, 45.6, 40.3, 31.1, 27.9, 27.7, 27.5, 22.0, 17.7, -1.1; LRMS-ES+ m/z (relative intensity) 750 (M+NH4+, 75); HRMS-ES+ (C38H48N3O9SSi) calcd 750.2881 (M+NH4+), found 750.2878.
2-((Benzyloxy)carbonyl)-2-(2-methoxy-2-oxo-1-(3-oxo-1-tosylpiperidin-4-yl)ethyl)-1H-indol-3-yl)acetic Acid (361). To a stirred solution of TMSE-ester 360 (332 mg, 0.453 mmol) in CH₂Cl₂ (12 mL) was added TFA (3 mL). The resulting solution was stirred for 16 h at rt. The solvent was removed *in vacuo* to give a residue which was purified by flash column chromatography on silica gel (40% EtOAc/hexanes + 1% AcOH) to yield carboxylic acid 361 (274 mg, 96%). ¹H NMR (300 MHz, CDCl₃) δ 8.10 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.66-7.17 (m, 10H), 5.41 (ABq, J = 101.7, 11.9 Hz, 2H), 4.91 (d, J = 6.8 Hz, 1H), 4.03 (d, J = 13.8 Hz, 1H), 3.70 (br s, 2H), 3.60-3.49 (m, 4), 3.38 (p, J = 7.2 Hz, 1H), 3.22 (d, J = 13.7 Hz, 1H), 2.50-2.45 (m, 4H), 1.45-1.27 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 202.1, 177.7, 171.6, 151.9, 144.7, 135.7, 134.9, 132.6, 132.4, 130.3, 129.6, 129.5, 129.2, 128.3, 125.9, 124.1, 119.5, 117.0, 116.3, 69.3, 56.3, 52.9, 49.1, 45.5, 40.5, 30.4, 27.9, 22.0, 21.2; LRMS-ES⁺ m/z (relative intensity) 633 (MH⁺, 100); HRMS-ES⁺ (C₃₃H₃₆N₃O₉S) calcd 650.2172 (M+NH₄⁺), found 650.2142.

β-Lactones 362 and 363. To a solution of 2-bromo-N-propylpyridinium triflate⁶₈b (196 mg, 0.503 mmol), PPY (76 mg, 0.503 mmol), and CH₂Cl₂ (9 mL) was added DIPEA (118 μL,
0.670 mmol). To this mixture, a solution of keto-acid 361 (212 mg, 0.335 mmol) in CH$_2$Cl$_2$ (4 mL) was added via syringe-pump over 1 h. The resulting solution was stirred for 20 h and then concentrated in vacuo to give a residue, which was purified by flash column chromatography on silica gel (40% EtOAc/hexanes) to afford β-lactones 362 and 363 (190 mg, 92%) as an ~8:1 mixture of inseparable diastereomers. FTIR (film) 1835 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, ~8:1 mixture of diastereomers (only the major diastereomer 362 peaks are reported)) δ 8.05 (d, $J$ = 5.5 Hz, 1H), 7.68 (d, $J$ = 6.1 Hz, 2H), 7.62 (d, $J$ = 5.9 Hz, 1H), 7.49-7.30 (m, 9H), 5.48 (d, $J$ = 9.0 Hz, 1H), 5.34 (d, $J$ = 9.1 Hz, 1H), 4.78 (s, 1H), 4.43 (d, $J$ = 4.4 Hz, 1H), 3.89 (d, $J$ = 8.9 Hz, 1H), 3.52-3.49 (m, 4H), 2.98 (d, $J$ = 8.9 Hz, 1H), 2.57 (q, $J$ = 5.5 Hz, 1H), 2.51-2.43 (m, 4H) $^{13}$C NMR (75 MHz, CDCl$_3$, ~8:1 mixture of diastereomers (only the major diastereomer 362 peaks are reported)) δ 171.0, 165.8, 152.2, 144.9, 137.0, 134.9, 132.7, 130.4, 130.3, 129.5, 129.22, 129.16, 128.2, 127.2, 126.1, 124.2, 119.1, 115.9, 110.9, 75.9, 69.7, 55.0, 53.5, 52.5, 51.3, 45.2, 43.6, 38.8, 25.6, 25.5, 22.0; LRMS-ES$^+$ m/z (relative intensity) 615 (MH$^+$, 100). HRMS-ES$^+$ (C$_{33}$H$_{34}$N$_3$O$_8$S) calcd 632.2067 (M$^+$NH$_4^+$), found 632.2053.

1,3-Diols 364 and 365. To a 0 °C solution of β-lactones 362 and 363 (62.8 mg, 0.102 mmol) was added DIBAL-H (1.0 M in PhMe, 511 μL, 0.511 mmol). The resulting solution was stirred for 1.5 h, then poured into a stirring solution of NH$_4$Cl$_{aq}$ and the mixture was stirred for an additional 2 h. The organic layer was separated and the aqueous layer was extracted with
EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue which was purified by preparative thin layer chromatography on silica gel (50% EtOAc/hexanes) to afford major diol 364 (41.8 mg, 66%) and minor diol 365 (5.6 mg, 9%).

**Major 1,3-diol 364:** ¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, J = 7.8 Hz, 1H), 7.67-7.64 (m, 3H), 7.49-7.47 (m, 2H), 7.43-7.28 (m, 7H), 5.47 (d, J = 12.0 Hz, 1H), 5.29 (d, J = 12.1 Hz, 1H), 4.80-4.75 (m, 1H), 4.68 (d, J = 4.0 Hz, 1H), 4.50-4.45 (m, 1H), 3.77 (br s, 1H), 3.65 (s, 1H), 3.50 (s, 3H), 2.47 (s, 3H), 2.30-2.22 (m, 2H), 2.15-2.10 (m, 1H), 1.99 (br s, 1H), 1.67 (s, 1H), 1.60-1.54 (m, 1H), 1.30-1.26 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 172.9, 152.0, 144.3, 137.1, 135.1, 133.3, 130.3, 130.2, 129.2, 129.1, 128.5, 128.1, 128.0, 125.2, 123.8, 119.4, 116.4, 114.0, 73.1, 69.3, 60.7, 54.3, 52.1, 46.1, 44.6, 43.6, 36.7, 24.9, 22.0; LRMS-ES+ m/z (relative intensity) 619 (MH⁺, 100); HRMS-ES+ (C₃₃H₃₅N₂O₈S) calcd 619.2114 (MH⁺), found 619.2150.

**Minor 1,3-diol 365:** ¹H NMR (400 MHz, CDCl₃) δ 8.18 (d, J = 7.9 Hz, 1H), 7.67-7.55 (m, 3H), 7.48-7.28 (m, 9H), 5.43 (q, J = 8.4 Hz, 2H), 4.65-4.53 (m, 2H), 4.33-4.30 (m, 1H), 4.10 (br s, 1H), 3.54 (s, 2H), 3.51 (s, 3H), 2.46-2.43 (m, 4H), 2.42-2.38 (m, 2H), 2.36-2.26 (m, 1H), 1.81-1.76 (m, 1H), 1.70-1.65 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 173.6, 151.9, 144.3, 137.0, 135.1, 133.3, 130.3, 129.30, 129.25, 129.2, 128.3, 128.2, 128.0, 125.4, 123.9, 119.5, 116.6, 72.5, 71.1, 69.3, 61.3, 57.5, 54.2, 52.7, 45.4, 25.7, 22.0; LRMS-ES+ m/z (relative intensity) 619 (MH⁺, 100); HRMS-ES+ (C₃₃H₃₅N₂O₈S) calcd 619.2114 (MH⁺), found 619.2138.
Bis-tert-Butylsilanol 369. To a solution of 1,3-diol 364 (16 mg, 0.026 mmol) and 2,6-lutidine (9 μL, 0.078 mmol) in CH₂Cl₂ (1 mL) was added di-t-butylsilyl bis(triflate) (11 μL, 0.034 mmol). The resulting mixture was stirred for 1 h at rt and then washed with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (25% EtOAc/hexanes) to yield silanol 369 (21 mg, 100%). ¹H NMR (400 MHz, CDCl₃) δ 8.18 (d, J = 7.4 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.45-7.31 (m, 10H), 5.42 (s, 1H), 5.39 (ABq, J = 86.1, 12.2 Hz, 2H), 4.96 (dd, J = 11.5, 3.0 Hz, 1H), 4.70 (dd, J = 5.7, 2.2 Hz, 1H), 4.57 (d, J = 10.6 Hz, 1H), 4.18-4.07 (m, 2H), 3.78 (d, J = 11.3 Hz, 1H), 3.66 (br s, 1H), 3.50 (s, 3H), 2.52 (s, 3H), 2.26 (d, J = 10.1 Hz, 1H), 2.12-2.05 (m, 2H), 1.65-1.54 (m, 2H), 1.32-1.22 (m, 1H), 1.00 (s, 9H), 0.44 (s, 9H); LRMS-ES+ m/z (relative intensity) 777 (MH⁺, 100).

Cyclic Acetonide 370. To a stirred solution of 1,3-diol 364 (10.0 mg, 0.016 mmol), 4 Å molecular sieves (10 mg), and acetone (2 mL) was added Amberlyst-15 (10 mg). The resulting
mixture was stirred for 15 h and additional Amberlyst-15 (50 mg) was added. After stirring for an additional 18 h, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo to give a residue. This material was purified by preparative thin layer chromatography on silica gel (25% EtOAc/hexanes) to give acetonide 370 (1.6 mg, 15%) and recovered 1,3-diol 364 (8.0 mg, 80%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.12 (d, $J$ = 7.2 Hz, 1H), 7.70 (d, $J$ = 8.2 Hz, 2H), 7.50-7.38 (m, 8H), 7.32-7.27 (m, 2H), 5.40 (ABq, $J$ = 60.3, 12.3 Hz, 2H), 4.61-4.51 (m, 3H), 4.44-4.39 (m, 1H), 3.79 (d, $J$ = 11.5 Hz, 1H), 3.51-3.48 (m, 4H), 2.49 (s, 3H), 2.25-2.22 (m, 2H), 2.10-2.02 (m, 1H), 1.54 (s, 3H), 1.28-1.17 (m, 2H), 1.15 (s, 3H); LRMS-ES+ m/z (relative intensity) 659 (MH$^+$, 60).

**Cyclic Carbonate 371.** To a stirred solution of 1,3-diol 364 (11.5 mg, 0.0186 mmol) and pyridine (22 μL, 0.26 mmol) in CH$_2$Cl$_2$ (1 mL) at 0 °C was added triphosgene (11 μL, 0.017 mmol). The resulting mixture was stirred for 18 h gradually warming to rt and then quenched with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (30% EtOAc/hexanes) to afford carbonate 371 (10.9 mg, 91%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.14 (d, $J$ = 7.3 Hz, 1H), 7.68 (d, $J$ = 8.3 Hz, 2H), 7.53-7.32 (m, 10H), 5.40 (ABq, $J$ = 39.0, 12.1 Hz, 2H), 5.09 (d, $J$ = 12.0 Hz, 1H), 4.91 (dd, $J$ = 12.0, 2.9 Hz, 1H), 4.63 (dd, $J$ = 6.0, 2.0 Hz, 1H), 4.28 (dd, $J$ = 11.9,
1.4 Hz, 1H), 4.01 (br s, 1H), 3.88-3.84 (m, 1H), 3.50 (s, 3H), 2.49 (s, 3H), 2.46-2.40 (m, 1H),
2.32 (td, \( J = 12.2, 3.1 \) Hz, 1H), 1.71-1.59 (m, 2H), 1.42-1.37 (m, 1H); LRMS-ES+ \( m/z \) (relative
intensity) 662 (M+NH\(_4^+\), 100).

6-Benzyl 5-Methyl 11a-Hydroxy-11-(hydroxymethyl)-2-tosyl-3,4,4a,5,11,11a-
hexahydro-1\(H\)-pyrido[4,3-b]carbazole-5,6(2\(H\))-dicarboxylate (374). To a solution of 1,3-diol
364 (12.0 mg, 0.019 mmol) in MeCH(OMe)\(_2\) (1 mL) was added a catalytic amount of \( p-\)
TsOH.H\(_2\)O (<1 mg) and the resulting mixture was placed in a preheated oil bath at 80 °C. After
stirring for 30 min, the solution was concentrated \textit{in vacuo} to give a residue which was purified
by column chromatography on silica gel (30% EtOAc/hexanes) to yield the acetal 374 (11.6 mg,
93%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.12 (br d, \( J = 6.1 \) Hz, 1H), 7.71 (d, \( J = 8.2 \) Hz, 2H), 7.52-7.48 (m, 3H), 7.46-7.38 (5H), 7.31-7.27 (m, 2H), 5.50 (d, \( J = 12.1 \) Hz, 1H), 5.34 (d, \( J = 10.3 \) Hz,
1H), 5.07 (q, \( J = 5.0 \) Hz, 1H), 4.78-4.66 (m, 3H), 4.36 (dd, \( J = 12.3, 3.0 \) Hz, 1H), 3.84-3.80 (m,
1H), 3.52 (s, 3H), 3.40 (br s, 1H), 2.49 (s, 3H), 2.27 (td, \( J = 12.2, 2.9 \) Hz, 1H), 2.19-2.06 (m,
2H), 1.70-1.55 (m, 1H), 1.31-1.23 (m, 1H), 1.20 (d, \( J = 4.9 \) Hz, 3H); \(^{13}\)C NMR (75 MHz,
CDCl\(_3\)) \( \delta \) 172.9, 152.3, 144.5, 135.4, 133.5, 131.5, 130.4, 129.3, 129.13, 129.06, 128.3, 127.9,
124.8, 123.4, 119.5, 116.5, 116.3, 93.3, 72.5, 69.1, 65.3, 53.9, 52.1, 50.4, 46.2, 44.5, 43.3, 29.7,
23.7, 22.0, 21.6; LRMS-ES+ \( m/z \) (relative intensity) 645 (MH\(^+\), 50).
Methyl Thiomethyl Ether 380. Benzyol peroxide (278 mg, 1.11 mmol) was added portionwise over approximately 20 min to a 0 °C solution of 1,3-diol 364 (86 mg, 0.14 mmol) and dimethyl sulfide (163 μL, 2.22 mmol) in MeCN (6 mL). The resulting solution was stirred for 13 h while maintaining a temperature of 0 to 5 °C. The reaction mixture was diluted with 1:1 Na₂SO₃(aq) and NaHCO₃(aq), the organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue which was purified by flash column chromatography on silica gel (gradient 25-40% EtOAc/hexanes) to afford sulfide 380 (64 mg, 68%). ¹H NMR (400 MHz, CDCl₃) δ 8.15-8.09 (m, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 6.7 Hz, 2H), 7.51-7.48 (m, 2H), 7.43-7.37 (m, 5H), 7.30-7.26 (m, 2H), 5.49 (d, J = 11.7 Hz, 1H), 5.33-5.28 (m, 1H), 4.85 (d, J = 10.6 Hz, 1H), 4.70-4.69 (m, 1H), 4.58 (q, J = 9.5 Hz, 2H), 4.47 (s, 1H), 4.24-4.14 (m, 2H), 3.82-3.80 (m, 2H), 3.51 (s, 3H), 2.48 (s, 3H), 2.27-2.21 (m, 1H), 2.16-2.13 (m, 1H), 1.74 (s, 3H); LRMS-ES+ m/z (relative intensity) 679 (MH⁺, 75); HRMS-ES+ (C₃₅H₃₉N₂O₈S₂) calcd 679.2148 (MH⁺), found 679.2134.
**TBS Ether 381.** A sealed tube was charged with a solution of alcohol 380 (50.9 mg, 0.0750 mmol) and 2,6-lutidine (438 μL, 3.75 mmol) in CH₂Cl₂ (5 mL). TBSOTf (357 μL, 1.87 mmol) was added to the solution and the tube was sealed and heated at 40 °C with stirring for 24 h. After cooling to the mixture to rt, additional 2,6-lutidine (438 μL, 3.75 mmol) and TBSOTf (357 μL, 1.87 mmol) were added and the mixture heated for 24 h at 40 °C. After cooling to rt, the reaction mixture was washed with 1 M HCl, the organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give a residue which was purified by flash chromatography on silica gel (5-20% EtOAc/hexanes) to afford TBS ether 381 (43.8 mg, 74%). ¹H NMR (400 MHz, CDCl₃) δ 8.15 (d, J = 6.7 Hz, 1H), 7.90 (d, J = 6.9 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.45-7.43 (m, 2H), 7.41-7.34 (m, 5H), 7.32-7.37 (m, 2H), 5.51 (d, J = 12.1 Hz, 1H), 5.20 (d, J = 11.3 Hz, 1H), 4.84 (s, 2H), 4.54 (d, J = 3.5 Hz, 1H), 4.49 (d, J = 10.3 Hz, 1H), 4.10 (dd, J = 10.5, 4.2 Hz, 1H), 4.02 (dd, J = 10.5, 6.0 Hz, 1H), 3.77-3.72 (m, 2H), 3.52 (s, 3H), 2.48 (s, 3H), 2.33 (s, 3H), 2.19-2.11 (m, 2H), 2.09-2.03 (m, 1H), 1.53 (qd, J = 13.3, 4.5 Hz, 1H), 1.23-1.20 (m, 1H), 0.78 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.9, 151.9, 144.3, 137.2, 135.2, 133.0, 130.1, 129.1, 129.04, 129.03, 128.8, 128.3, 124.8, 123.3, 120.9, 118.4, 117.9, 115.7, 75.8, 75.2, 69.0, 67.8, 55.3, 52.1, 46.5, 45.9, 43.7, 37.4, 26.2, 24.8, 22.0, 19.0, 14.7, -1.1, -1.4; LRMS-ES⁺ m/z (relative intensity) 810 (MH⁺, 20). Slow evaporation of a solution of TBS ether 381 in 1:1 MeOH/CHCl₃ provide crystals which were analyzed by X-ray diffraction.₁⁴¹
Chloromethyl Ether 382. To a stirred solution of sulfide 381 (13.9 mg, 0.0175 mmol) in CH$_2$Cl$_2$ (1.5 mL) at 0 °C was added sulfuryl chloride (0.1 M in CH$_2$Cl$_2$, 19 μL, 0.019 mmol) and the solution was stirred for 30 min until TLC analysis indicated complete consumption of the starting material. The solution was then concentrated in vacuo to give essentially pure chloromethyl ether 382 which was used immediately in subsequent reactions. $^1$H NMR (400 MHz, C$_6$D$_6$) δ 7.89 (d, $J$ = 9.0 Hz, 1H), 7.76 (d, $J$ = 8.2 Hz, 2H), 7.25-7.10 (m, 8H), 6.91 (d, $J$ = 8.2 Hz, 2H), 5.73 (d, $J$ = 5.7 Hz, 1H), 5.48 (d, $J$ = 5.7 Hz, 1H), 5.32 (d, $J$ = 12.3 Hz, 1H), 4.96 (d, $J$ = 12.1 Hz, 1H), 4.88-4.85 (m, 1H), 4.71 (d, $J$ = 10.6 Hz, 2H), 4.55 (dd, $J$ = 11.0, 3.6 Hz, 1H), 4.40 (dd, $J$ = 11.0, 7.2 Hz, 1H), 4.03 (p, $J$ = 3.2 Hz, 1H), 3.71-3.64 (m, 1H), 2.28-2.24 (m, 2H), 2.00-1.97 (m, 4H), 1.91-1.85 (m, 2H), 0.85 (s, 9H), 0.24 (s, 3H), 0.12 (s, 3H).

Cyclic Acetal Indole 389. To a solution of Cbz-carbamate 374 (11.6 mg, 0.0180 mmol) in MeOH (2 mL) and EtOAc (2 mL) under an argon atmosphere was added Pd/C (10 wt%, 4.1 mg, 0.0039 mmol). The resulting mixture was evacuated and backfilled three times with H$_2$ from a balloon and the resulting suspension was stirred for 2 h. The reaction mixture was then filtered through a pad of Celite with EtOAc and the filtrate was concentrated in vacuo to give a
residue. This material was purified by flash column chromatography on silica gel (30% EtOAc/hexanes) to give NH indole 389 (9.1 mg, 99%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 9.13 (s, 1H), 7.72 (d, \(J = 8.3\) Hz, 2H), 7.54 (d, \(J = 7.9\) Hz, 1H), 7.41-7.38 (m, 3H), 7.20-7.12 (m, 2H), 5.07 (q, \(J = 5.0\) Hz, 1H), 4.82 (d, \(J = 12.2\) Hz, 1H), 4.68 (dd, \(J = 11.3, 1.6\) Hz, 1H), 4.59 (dd, \(J = 4.5, 2.2\) Hz, 1H), 4.34 (dd, \(J = 12.2, 3.2\) Hz, 1H), 3.82-3.77 (m, 4H), 3.39 (br s, 1H), 2.49 (s, 3H), 2.36 (td, \(J = 12.0, 3.2\) Hz, 1H), 2.25-2.18 (m, 2H), 1.60-1.55 (m, 2H), 1.20 (d, \(J = 4.9\) Hz, 3H); LRMS-ES+ m/z (relative intensity) 511 (MH\(^+\), 100).

**Hydroxymethyl Compound 393.** To a stirred suspension of paraformaldehyde (4.3 mg, 0.140 mmol) and ester 374 (6.0 mg, 0.009 mmol) in DMF (0.5 mL) was added NaH (60% dispersion on mineral oil, 1.9 mg, 0.005 mmol) and the resulting mixture was stirred for 2 h at rt. The reaction mixture was diluted with brine and EtOAc. The organic layer was separated and washed with water and then brine. The organic layer was dried over MgSO\(_4\) and concentrated \textit{in vacuo} to give a residue which was purified by flash column chromatography on silica gel (75% EtOAc/hexanes) to give \(\beta\)-hydroxy ester 394 (4.7 mg, 93%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.91 (s, 1H), 7.70 (d, \(J = 6.1\) Hz, 2H), 7.57 (d, \(J = 6.0\) Hz, 1H), 7.40-7.36 (m, 3H), 7.20 (t, \(J = 5.5\) Hz, 1H), 7.12 (t, \(J = 5.8\) Hz, 1H), 5.03 (q, \(J = 3.7\) Hz, 1H), 4.83 (d, \(J = 9.0\) Hz, 1H), 4.67 (d, \(J = 8.1\) Hz, 1H), 4.37 (dd, \(J = 9.1, 2.1\) Hz, 1H), 3.86-3.78 (m, 2H), 3.68 (s, 3H), 3.39-3.37 (m, 1H), 2.49 (s, 3H), 2.39-2.26 (m, 2H), 2.21-2.16 (m, 2H), 1.54-1.41 (m, 2H), 1.10 (d, \(J = 3.7\) Hz, 3H); \(^13\)C
NMR (75 MHz, CDCl$_3$) $\delta$ 175.9, 144.5, 137.3, 133.3, 132.8, 130.3, 128.0, 126.0, 122.3, 119.7, 119.4, 111.8, 108.2, 93.1, 73.6, 68.7, 65.8, 52.8, 50.4, 49.5, 47.7, 46.2, 30.0, 22.7, 22.0, 21.3; LRMS-ES+ m/z (relative intensity) 541 (MH$^+$, 30); HRMS-ES+ (C$_{28}$H$_{36}$N$_3$O$_7$S) calcd 558.2274 (M+NH$_4^+$), found 558.2265.

Chloromethyl(dimethyl)silane 398. To a solution of crude alcohol 380 (4.8 mg, 0.0071 mmol) and 2,6-lutidine (38 mg, 0.35 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added chloromethyl(dimethyl)chlorosilane (35 $\mu$L, 0.18 mmol). The resulting mixture was refluxed for 1 h, cooled to rt, and then washed with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (5-25% EtOAc/hexanes) to afford chloromethylsilane 398 (5.0 mg, 90%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.12 (d, $J = 7.4$ Hz, 1H), 7.84-7.82 (m, 1H), 7.69 (d, $J = 8.2$ Hz, 2H), 7.48-7.46 (m, 2H), 7.42-7.33 (m, 5H), 7.31-7.25 (m, 2H), 5.50 (d, $J = 12.1$ Hz, 1H), 5.26 (d, $J = 12.0$ Hz, 1H), 4.83 (ABq, $J = 12.7$, 11.6 Hz, 2H), 4.53 (d, $J = 10.2$ Hz, 1H), 4.48 (dd, $J = 5.5$, 2.3 Hz, 1H), 4.16 (dd, $J = 3.9$, 10.4, 1H), 3.89 (dd, $J = 10.4$, 7.0 Hz, 1H), 3.81-3.78 (m, 1H), 3.73 (br d, $J = 10.6$ Hz, 1H), 3.51 (s, 3H), 2.74 (s, 2H), 2.48 (s, 3H), 2.31 (s, 3H), 2.23-2.13 (m, 2H), 2.08-2.04 (m, 1H), 1.54 (qd, $J = 13.3$, 4.3 Hz, 1H), 1.27-1.23 (m, 1H), 0.30 (s, 3H), 0.28 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.7, 144.4, 135.3, 132.9, 130.1, 129.12, 129.09, 129.0, 128.8,
Iodomethyl(dimethyl)silane 399. A sealed tube was charged with chloride 388 (9.5 mg, 0.0121 mmol), acetone (1 mL), and then NaI (45 mg, 0.30 mmol). The vessel was sealed and the resulting mixture was heated at reflux and stirred for 14 h. After cooling to rt, the reaction mixture was diluted with ether and the organic phase was washed with water followed by Na2S2O3(aq). The aqueous layers were extracted with ether and the combined organic layers were dried over MgSO4 and concentrated in vacuo to give a residue. This material was purified by flash chromatography on silica gel (30% EtOAc/hexanes) to give iodide 399 (7.8 mg, 74%). 1H NMR (300 MHz, CDCl3) δ 8.13 (br d, J = 7.2, 1H), 7.87-7.84 (m, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.48-7.37 (m, 7H), 7.32-7.23 (m, 2H), 5.51 (d, J = 12.1 Hz, 1H), 5.26 (br d, J = 10.8 Hz, 1H), 4.8 (s, 2H), 4.56-4.53 (m, 2H), 4.19-4.11 (m, 1H), 3.92 (dd, J = 10.3, 6.9 Hz, 1H), 3.83-3.72 (m, 2H), 3.52 (s, 3H), 2.50 (s, 3H), 2.32 (s, 3H), 2.25-2.00 (m, 3H), 1.95 (s, 2H), 1.58 (qd, J = 13.2, 4.8 Hz, 1H), 1.29-1.23 (m, 1H), 0.36 (s, 3H), 0.35 (s, 3H); LRMS-ES+ m/z (relative intensity) 894 (M+NH4+, 30).
**TBS Ether 404.** To a solution of 1,3-diol 364 (39.7 mg, 0.0642 mmol) and 2,6-lutidine (75 μL, 0.64 mmol) in CH₂Cl₂ (3 mL) at 0 °C was added TBSOTf (61 μL, 0.32 mmol). The resulting mixture was stirred for 1 h and then washed with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give a residue which was purified by flash chromatography on silica gel (30% EtOAc/hexanes) to afford O-TBS-ether 404 (45 mg, 96%).

\[ \text{δ} \]

\[ \text{H NMR (300 MHz, CDCl}_3\text{)} \hspace{1em} \text{δ} \]

8.14 (d, \(J = 9.2\) Hz, 1H), 7.70-7.67 (m, 2H), 7.59-7.56 (m, 1H), 7.48-7.34 (m, 7H), 7.30-7.25 (m, 2H), 5.50 (d, \(J = 7.8\) Hz, 1H), 5.29 (d, \(J = 12.2\) Hz, 1H), 4.73-4.69 (m, 2H), 4.51 (ddd, \(J = 11.2, 1.7\) Hz, 1H), 4.15 (d, \(J = 10.2\) Hz, 1H), 3.77 (br d, \(J = 11.6\) Hz, 1H), 3.66-3.64 (m, 1H), 3.50 (s, 3H), 2.47 (s, 3H), 2.22-2.17 (m, 2H), 2.10-2.03 (m, 1H), 1.63-1.53 (m, 2H), 0.60 (s, 9H), 0.04-0.03 (m, 6H);

\[ \text{\textsuperscript{13}C NMR (75 MHz, CDCl}_3\text{)} \hspace{1em} \text{δ} \]

173.1, 152.0, 144.3, 135.4, 130.2, 129.1, 129.0, 128.9, 128.6, 128.0, 124.7, 123.1, 119.9, 116.1, 115.6, 72.8, 69.0, 61.5, 54.7, 52.0, 46.2, 45.1, 43.5, 36.1, 30.1, 26.1, 25.7, 24.7, 22.0, 18.0, 1.4, -5.2, -5.7; LRMS-ES+ \(m/z\) (relative intensity) 733 (MH⁺, 100); HRMS-ES+ (C₃₉H₄₉N₂O₈SSi) calcd 733.2979 (MH⁺), found 733.2961.
Chloromethyl(dimethyl)silane 406. To a solution of N-Cbz-indole 404 (45.0 mg, 0.061 mmol) in MeOH (1.5 mL) and EtOAc (1.5 mL) under an argon atmosphere was added Pd/C (10 wt%, 6.5 mg, 0.006 mmol). The resulting mixture was evacuated and backfilled three times with H₂ from a balloon and the resulting suspension was stirred for 2.5 h. The reaction mixture was then filtered through a pad of Celite with EtOAc and the filtrate was concentrated in vacuo to give NH indole 405, which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 9.14 (s, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 7.8 Hz, 1H), 7.40-7.33 (m, 3H), 7.18 (t, J = 6.2 Hz, 1H), 7.13 (t, J = 8.1 Hz, 1H), 5.70 (s, 1H), 4.64-4.52 (m, 3H), 4.19 (dd, J = 11.4, 1.7 Hz, 1H), 3.80 (s, 3H), 3.77-3.68 (m, 1H), 3.69-3.67 (m, 1H), 2.48 (s, 3H), 2.31-2.18 (m, 3H), 1.54-1.41 (m, 2H), 0.67 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); LRMS-ES⁺ m/z (relative intensity) 599 (MH⁺, 75); HRMS-ES⁺ (C₃₁H₄₃N₂O₆SSi) calcd 599.2611 (MH⁺), found 599.2585.

To a solution of crude alcohol 405 and 2,6-lutidine (270 µL, 1.23 mmol) in CH₂Cl₂ (2.5 mL) was added chloromethyl(dimethyl)silyl triflate (289 µL, 2.47 mmol). The resulting mixture was stirred for 1.5 h at rt and then washed with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to afford a residue, which was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to give chlormethyl(dimethyl)silane 496 (32.9 mg, 76%). ¹H NMR (400 MHz, CDCl₃) δ 9.16 (s, 1H), 7.67-7.62 (m, 3H), 7.40-7.33 (m, 3H), 7.20-7.12 (m, 2H), 4.73 (dd, J = 10.1, 1.5 Hz, 1H), 4.45-4.39 (m, 2H), 3.89 (t, J = 10.1 Hz,
1H), 3.82 (s, 3H), 3.78-3.70 (m, 2H), 2.77 (ABq, $J = 13.8, 5.0$ Hz, 2H), 2.48 (s, 3H), 2.26-2.17 (m, 3H), 1.51-1.42 (m, 1H), 1.37-1.26 (m, 1H). 1.04 (s, 9H), 0.32-0.28 (m, 12H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 173.4, 144.1, 136.8, 133.4, 130.1, 128.7, 128.1, 127.0, 121.9, 119.81, 119.78, 111.8, 108.2, 76.2, 64.0, 60.8, 56.8, 52.9, 47.7, 46.4, 39.8, 31.5, 26.8, 24.2, 22.0, 21.5, 19.2, 14.6, 0.2, -0.1, -4.6, -5.0; LRMS-ES+ m/z (relative intensity) 705 (MH$^+$, 50).

Iodomethyl(dimethyl)silane 407. A sealed tube was charged with chloride 406 (77.4 mg, 0.110 mmol), acetone (5 mL) and then NaI (411 mg, 2.74 mmol). The vessel was sealed and the resulting mixture was heated at reflux and stirred for 15 h. After cooling to rt, the reaction mixture was diluted with ether and the organic phase was washed with water followed by Na$_2$S$_2$O$_3$(aq). The aqueous layers were extracted with ether and the combined organic layers were dried over MgSO$_4$ and concentrated in vacuo to give a residue. This material was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to give iodide 407 (84.4 mg, 97%). $^1$H NMR (300 MHz, CDCl$_3$) δ 9.17 (s, 1H), 7.69-7.64 (m, 3H), 7.40-7.47 (m, 3H), 7.21-7.11 (m, 2H), 4.73 (d, $J = 9.9$ Hz, 1H), 4.48-4.42 (m, 2H), 3.92 (t, $J = 9.8$ Hz, 1H), 3.82 (s, 3H), 3.78-3.70 (m, 2H), 2.48 (s, 3H), 2.28-2.16 (m, 3H), 2.03 (q, $J = 8.7$ Hz, 2H), 1.50-1.28 (m, 3H), 1.05 (s, 9H), 0.38-0.28 (m, 12H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 173.4, 144.1, 136.8, 133.4, 130.1, 128.7, 128.1, 127.0, 121.8, 119.8, 111.7, 108.2, 76.2, 64.0, 56.8, 52.8, 47.8, 46.4, 39.9, 39.8, 26.8, 24.2, 22.0, 19.2, 1.3, 0.7, -4.5, -4.9, -12.4; LRMS-ES+ m/z (relative intensity) 797 (MH$^+$, 40).
Cyclic Silyl Ether 408. To a solution of indole ester 407 (36.9 mg, 0.0463 mmol) at -78 °C was added KHMDS (0.1 M solution in THF, 1.39 mL, 0.139 mmol). The resulting mixture was stirred for 1 h at -78 °C, then transferred to a ice bath and stirred for an additional 15 min. The reaction mixture was diluted with NH₄Cl(aq), the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue, which was purified by flash chromatography on silica gel (25% EtOAc/hexanes) to afford pentacycle 408 (31.0 mg, 97%). 

**1H NMR (300 MHz, CDCl₃) δ**

- 9.00 (s, 1H), 8.06 (d, J = 7.08 Hz, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.39-7.34 (m, 3H), 7.21 (t, J = 7.7 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 4.50 (d, J = 10.7 Hz, 1H), 5.60 (dd, J = 10.4, 4.8 Hz, 1H), 4.17 (dd, J = 10.5, 5.1 Hz, 1H), 3.80-3.72 (m, 5H), 2.47 (s, 3H), 2.34-2.26 (m, 1H), 2.08 (d, J = 11.1 Hz, 1H), 1.91-1.86 (m, 1H), 1.53-1.41 (m, 3H), 1.06 (s, 9H), 0.97-0.85 (m, 2H), 0.29 (s, 3H), 0.27 (s, 3H), 0.10 (s, 6H);

**13C NMR (75 MHz, CDCl₃) δ**

- 176.1, 143.8, 137.8, 133.6, 132.1, 130.0, 128.4, 127.1, 122.4, 121.8, 119.6, 111.5, 110.4, 75.5, 65.6, 55.6, 52.8, 49.9, 46.9, 46.7, 40.5, 30.1, 28.0, 26.7, 25.5, 22.0, 19.1, 2.23, 2.16, -4.8, -4.9; LRMS-ES+ m/z (relative intensity) 669 (MH⁺, 30); HRMS-ES+ (C₃₄H₄₉N₂O₆Si₂) calcd 669.2850 (MH⁺), found 669.2857.
Minor Free Indole O-TBS ether 410. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.18 (s, 1H), 7.67 (d, $J$ = 8.1 Hz, 2H), 7.57 (d, $J$ = 7.8 Hz, 1H), 7.35-7.32 (m, 3H), 7.16 (t, $J$ = 7.1 Hz, 1H), 7.11 (t, $J$ = 7.3 Hz, 1H), 5.67 (s, 1H), 4.56-4.42 (m, 2H), 3.68 (s, 3H), 3.53-3.45 (m, 3H), 2.58 (d, $J$ = 10.4 Hz, 4H), 2.45 (s, 3H), 1.70 (br s, 1H), 1.62-1.59 (m, 1H), 0.69 (s, 9H), 0.06 (s, 3H), -0.17 (s, 3H). Slow evaporation of a solution of TBS ether 410 in 1:1 MeOH/CHCl$_3$ provide crystals which were analyzed by X-ray diffraction (cf. Figure 9).$^{141}$

Primary Alcohol 412. To a stirred solution of O-TBS ether 408 (15.0 mg, 0.022 mmol) and THF (1 mL) at 0 °C was added TBAF (1.0 M in THF, 67 μL, 0.067 mmol). The resulting solution was stirred for 1 h and then diluted with NH$_4$Cl(aq). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo to give a residue which was purified by flash column chromatography on silica gel (25% EtOAc/hexanes) to afford alcohol 412 (11.2 mg, 90%). $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 8.96 (s, 1H), 7.95 (d, $J$ = 7.9 Hz, 1H), 7.73 (d, $J$ = 8.2 Hz, 2H), 7.41-7.37 (m, 3H), 7.24 (t, $J$ = 7.1 Hz, 1H), 7.16 (t, $J$ = 7.2 Hz, 1H), 4.51-4.32 (m, 3H), 3.94-3.91 (m, 1H), 3.82 (s, 3H), 3.78 (t, $J$ = 5.0 Hz, 1H), 2.55-2.49 (m, 4H), 2.33 (t, $J$ = 6.3 Hz, 1H), 2.22 (d, $J$
= 11.2 Hz, 1H), 2.02-1.97 (m, 1H), 1.60-1.50 (m, 2H), 1.37-1.27 (m, 2H), 0.12 (s, 3H), -0.53 (s, 3H); LRMS-ES+ m/z (relative intensity) 555 (MH⁺, 50).

**Trifluoroacetate 419.** To a solution of O-TBS-ether 408 (6.5 mg, 0.0097 mmol) in CH₂Cl₂ (0.75 mL) was added TFA (0.25 mL) and the resulting mixture was stirred for 20 h at rt. Concentration of the crude mixture in vacuo gave a residue which was purified by preparative thin layer chromatography (4:2:1 hexanes/CH₂Cl₂/EtOAc) to give trifluoroacetate 412 (6.0 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ 9.12 (s, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 10.1 Hz, 2H), 7.42 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.25 (t, J = 7.7 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 5.02-4.99 (m, 2H), 4.17-4.07 (m, 2H), 3.85-3.80 (m, 4H), 2.47 (s, 3H), 2.37 (td, J = 11.4, 3.3 Hz, 1H), 2.12 (d, J = 11.7 Hz, 1H), 2.00 (dd, J = 12.0, 4.1 Hz, 1H), 1.56-1.29 (m, 4H), 0.14 (s, 3H), -0.48 (s, 3H); LRMS-ES+ m/z (relative intensity) 651 (MH⁺, 100).

Retro-aldol Product 414. To a stirred solution of cyclic silyl ether 412 (1.0 mg, 0.002 mmol) and KHCO₃ (10 mg, 0.010 mmol) in 1:1 MeOH/THF (250 μL), was added TBAF (1.0 M
in THF, 40 μL, 0.040 mmol) followed by hydrogen peroxide (30 wt% in water, 150 μL). The reaction mixture was stirred for 16 h and then diluted with Na2SO3(aq) and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO4 and concentrated *in vacuo* to give a residue which was purified by preparative thin layer chromatography (50% EtOAc/hexanes) to afford retro-aldol product 414 (0.5 mg, 58%). 1H NMR (300 MHz, CDCl3) δ 9.27 (s, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.26-7.16 (m, 2H), 5.13 (s, 1H), 4.79 (d, J = 12.6 Hz, 1H), 4.56 (dd, J = 4.7, 2.2 Hz, 1H), 4.16 (dd, J = 11.2, 1.8 Hz, 1H), 3.82 (s, 3H), 3.78-3.75 (m, 1H), 3.71-3.68 (m, 1H), 2.47 (s, 3H), 2.32-2.22 (m, 3H), 1.85-1.81 (m, 1H), 1.61-1.47 (m, 3H); 13C NMR (75 MHz, CDCl3) δ 172.4, 144.2, 137.0, 133.5, 131.1, 130.2, 129.0, 128.0, 127.4, 126.4, 122.3, 120.3, 119.0, 112.1, 105.2, 73.5, 60.9, 54.8, 52.8, 46.2, 45.8, 39.9, 37.3, 24.2, 22.0; LRMS-ES+ m/z (relative intensity) 484 (MH+, 100).

**Chloromethyl(dimethyl)silane 420.** To a solution of N-Cbz-indole 364 (102 mg, 0.165 mmol) in MeOH (2 mL) and EtOAc (2 mL) under an argon atmosphere was added Pd/C (10 wt%, 17.5 mg, 0.0165 mmol). The resulting mixture was evacuated and backfilled three times with H2 from a balloon and the resulting suspension was stirred for 2 h. The reaction mixture was filtered through a pad of Celite with EtOAc and the filtrate was concentrated *in vacuo* to afford NH-indole 414, which was used in the next step without further purification. 1H NMR
(300 MHz, CDCl₃) δ 9.27 (s, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.26-7.16 (m, 2H), 5.13 (s, 1H), 4.79 (d, J = 12.6 Hz, 1H), 4.56 (dd, J = 4.7, 2.2 Hz, 1H), 4.16 (dd, J = 11.2, 1.8 Hz, 1H), 3.82 (s, 3H), 3.78-3.75 (m, 1H), 3.71-3.68 (m, 1H), 2.47 (s, 3H), 2.32-2.22 (m, 3H), 1.85-1.81 (m, 1H), 1.61-1.47 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 172.4, 144.2, 137.0, 133.5, 131.1, 130.2, 129.0, 128.0, 127.4, 126.4, 122.3, 120.3, 119.0, 112.1, 105.2, 73.5, 60.9, 54.8, 52.8, 46.2, 45.8, 39.9, 37.3, 24.2, 22.0; LRMS-ES+ m/z (relative intensity) 484 (MH⁺, 100).

To a solution of the above crude 1,3-diol 414 and 2,6-lutidine (19 μL, 0.17 mmol) in CH₂Cl₂ (2.5 mL) was added chloromethyl(dimethyl)chlorosilane (22 μL, 0.17 mmol) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C and then 1 h at rt. The reaction mixture was diluted with NH₄Cl(aq), the organic layer was removed, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (25-75% EtOAc/hexanes) to afford chloromethyl dimethylsilyl ether 420 (95 mg, 98%). ¹H NMR (300 MHz, CDCl₃) δ 8.13 (s, 1H), 7.74-7.60 (m, 3H), 7.38-7.33 (m, 3H), 7.25-7.13 (m, 2H), 4.59-4.50 (m, 3H), 3.79-3.71 (m, 4H), 3.51 (d, J = 3.7 Hz, 2H), 2.73-2.58 (m, 3H), 2.49-2.42 (m, 4H), 1.97-1.91 (m, 1H), 1.69-1.57 (m, 2H), 0.15 (s, 3H), 0.10 (s, 3H); LRMS-ES+ m/z (relative intensity) 591 (MH⁺, 25).
Chloromethyl(dimethyl)silane 421. To a solution of tertiary alcohol 420 (95.0 mg, 0.161 mmol) and 2,6-lutidine (113 μL, 0.966 mmol) in CH₂Cl₂ (2 mL) was added TMSOTf (88 μL, 0.17 mmol) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C and then 1 h at rt. The reaction mixture was filtered through a silica gel plug eluting with 30% EtOAc/hexanes. The filtrate was concentrated in vacuo to give a residue which was dissolved in CH₂Cl₂ and washed with NH₄Cl[aq]. The organic layer was dried over MgSO₄ and concentrated in vacuo to give a residue. This material was purified by flash chromatography on silica gel (30% EtOAc/hexanes) to yield chloromethyl dimethylsilyl ether 421 (37.5 mg, 35%) which was contaminated with a small amount of bis-TMS product 422. ¹H NMR (400 MHz, CDCl₃) δ 9.13 (s, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 7.9 Hz, 2H), 7.23-7.11 (m, 2H), 4.77 (dd, J = 10.3, 1.7 Hz, 1H), 4.49 (dd, J = 10.1, 4.0 Hz, 1H), 4.38-4.34 (m, 1H), 3.99 (t, J = 9.9 Hz, 1H), 3.81 (s, 3H), 3.79-3.70 (m, 2H), 3.03 (ABq, J = 16.7, 13.8 Hz, 2H), 2.48 (s, 3H), 2.26-2.14 (m, 3H), 1.50-1.27 (m, 2H), 0.44 (s, 6H), 0.16 (s, 9H); LRMS-ES+ m/z (relative intensity) 663 (MH⁺, 20).

Bis-TMS product 422. ¹H NMR (300 MHz, CDCl₃) δ 9.12 (s, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.39-7.35 (m, 3H), 7.20-7.09 (m, 2H), 4.84 (dd, J = 10.1, 1.7 Hz, 1H), 4.39-4.24 (m, 2H), 3.87 (t, J = 9.8 Hz, 1H), 3.81 (s, 3H), 3.74-3.70 (m, 2H), 2.48 (s, 3H), 2.28-2.12 (m, 3H), 1.50-1.34 (m, 2H), 0.28 (s, 9H), 0.16 (s, 9H); LRMS-ES+ m/z (relative intensity) 629 (MH⁺, 90).
Chloromethyl(diphenyl)silane 426. To a solution of 1,3-diol 414 (16.0 mg, 0.033 mmol) and imidazole (6.8 mg, 0.099 mmol) in CH$_2$Cl$_2$ (1 mL) was added chloromethyl(diphenyl)chlorosilane$^{142}$ (14 μL, 0.050 mmol). The resulting mixture was stirred for 1 h, diluted with CH$_2$Cl$_2$, and then washed with ice-cold 0.1 M HCl. The organic layer was dried over MgSO$_4$ and concentrated in vacuo to give a residue, which was purified by preparative thin layer chromatography (50% EtOAc/hexanes) to afford chloromethyl diphenylsilylether 426 (16.3 mg, 69%). $^1$H NMR (300 MHz, CDCl$_3$) δ 9.21 (s, 1H), 7.67 (d, $J = 6.5$ Hz, 2H), 7.53-7.34 (m, 13H), 7.18-7.08 (m, 2H), 6.99-6.93 (m, 1H), 4.80 (s, 1H), 4.70 (dd, $J = 11.1$, 3.0 Hz, 1H), 4.60-4.52 (m, 2H), 4.30 (dd, $J = 11.3$, 1.7 Hz, 1H), 3.81 (s, 3H), 3.76-3.74 (m, 2H), 3.12 (ABq, $J = 59.2$, 14.3 Hz, 2H), 2.47 (s, 3H), 2.34-2.21 (m, 3H), 1.53-1.43 (m, 2H); LRMS-ES$^+$ $m/z$ (relative intensity) 715 (MH$^+$, 50).

Chloromethyl(diphenyl)silane 427. To a solution of tertiary alcohol 426 (12.5 mg, 0.0175 mmol) and 2,6-lutidine (20 μL, 0.175 mmol) in CH$_2$Cl$_2$ (1 mL) was added TMSOTf (16 μL, 0.087 mmol). The resulting mixture was stirred for 45 min at rt, diluted with CH$_2$Cl$_2$ and
then washed with ice-cold 0.1 M HCl. The organic layer was dried over MgSO₄ and concentrated in vacuo to give a residue which was purified by preparative thin layer chromatography (30% EtOAc/hexanes) to yield chloromethyl silane 427 (10.9 mg, 79%) and the bis-TMS side product 422 (3.7 mg, 20%). ¹H NMR (400 MHz, CDCl₃) δ 9.09 (s, 1H), 7.92-7.84 (m, 4H), 7.70 (d, J = 8.3 Hz, 2H), 7.59-7.48 (m, 6H), 7.37 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 8.8 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 6.80 (t, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 4.87 (dd, J = 10.3, 1.9 Hz, 1H), 4.42 (dd, J = 10.1, 3.8 Hz, 1H), 4.35 (dd, J = 4.2, 2.0 Hz, 1H), 4.20-4.12 (m, 1H), 3.83-3.77 (m, 5H), 3.62 (ABq, J = 75.9 Hz, 14.0 Hz, 2H), 2.53 (s, 3H), 2.29-2.18 (3H), 1.50-1.29 (m, 2H), 0.15 (s, 9H); LRMS-ES+ m/z (relative intensity) 787 (MH⁺, 25).

Chloromethyl(diphenylsilyl) Trifluoromethanesulfonate (430). Triflic acid (159 μL, 1.76 mmol) was added to a stirred solution of chloromethyl(triphenyl)silane (429)¹³² (670 mg, 1.76 mmol) in 1,2-dichloroethane (4 mL). The resulting solution was refluxed for 30 min and the 1,2-dichloroethane was removed by distillation at atmospheric pressure. The triflate 430 was isolated by vacuum distillation (410 mg, 50%, bp 102-105 °C / 0.25 mmHg). FTIR (film) 1260, 1174, 1037 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.75-7.36 (m, 10H), 3.57 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 135.6, 133.0, 129.1, 126.7, 118.7 (J₁₃,C,F = 316 Hz), 25.5; ¹⁹F NMR (282 MHz, CDCl₃) δ -76.6.
Chloromethyl(diphenyl)silane 431. A sealed tube was charged with tertiary alcohol 405 (27.0 mg, 0.045 mmol) and 2,6-lutidine (105 μL, 0.90 mmol) in CH₂Cl₂ (2 mL). Chloromethyl(diphenyl)silyl triflate (171 mg, 0.45 mmol) was added, the vessel was sealed, and the resulting mixture was heated at 40 °C for 16 h. After cooling to rt, the reaction mixture was washed with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to afford a residue which was purified by flash chromatography on silica gel (40% EtOAc/hexanes) to give chloromethylsilane 431 (23.7 mg, 63%). ¹H NMR (300 MHz, CDCl₃) δ 9.18 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.64-7.30 (m, 15H), 7.28-7.23 (m, 2H), 4.68 (dd, J = 10.1, 1.3 Hz, 1H), 4.54 (dd, J = 10.6, 4.4 Hz, 1H), 4.40 (dd, J = 4.3, 1.9 Hz, 1H), 4.27 (dd, J = 10.5, 8.9 Hz, 1H), 3.84-3.79 (m, 1H), 3.70 (s, 3H), 3.64-3.58 (m, 1H), 3.31 (s, 2H), 2.53 (s, 3H), 2.14 (d, J = 10.2 Hz, 1H), 2.01 (dt, J = 12.6, 4.0 Hz, 1H), 1.88 (td, J = 11.4, 1.9 Hz, 1H), 1.44-1.16 (m, 2H), 1.05 (s, 9H), 0.37 (s, 3H), 0.32 (s, 3H); LRMS-ES+ m/z (relative intensity) 829 (MH⁺, 15).

Iodomethyl(diphenyl)silane 432. A sealed tube was charged with chloride 431 (23.7 mg, 0.0286 mmol), acetone (3 mL) and then NaI (107 mg, 0.714 mmol). The vessel was sealed...
and the resulting mixture was heated at 40 °C and stirred for 17 h. The reaction mixture was cooled to rt, additional NaI (200 mg, 1.33 mmol) was added, and the resulting mixture was stirred for 5 h at 40 °C. After cooling to rt, the reaction mixture was diluted with ether and the organic phase was washed with water followed by Na₂S₂O₃(aq). The aqueous layer was extracted with ether and the combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue. This material was purified by flash column chromatography on silica gel (30% EtOAc/hexanes) to give iodide 432 (25.4 mg, 97%). ᵃH NMR (300 MHz, CDCl₃) δ 9.17 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.63-7.30 (m, 15H), 7.22-7.14 (m, 2H), 4.68 (d, J = 10.1 Hz, 1H), 4.54 (dd, J = 10.6, 4.5 Hz, 1H), 4.39-4.27 (m, 2H), 3.91-3.79 (m, 2H), 3.68 (s, 3H), 3.60-3.56 (m, 1H), 2.53 (s, 3H), 1.95-1.83 (m, 2H), 1.47-1.15 (m, 3H), 1.06 (s, 9H), 0.39 (s, 3H), 0.37 (s, 3H); LRMS-ES⁺ m/z (relative intensity) 921 (MH⁺, 15).

N-Cbz Indole 444. To a stirred solution of indole 408 (10 mg, 0.015 mmol) in THF (300 μL) at −78 °C was added KHMDS (0.1 M in THF, 300 μL, 0.030 mmol). The resulting solution was stirred for 45 min and then Cbz-Cl (11 μL, 0.075 mmol) was added. The solution was stirred for 5 h at −78 °C and then 12 h at rt before diluting with NH₄Cl(aq) and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a residue which was purified by preparative thin layer chromatography (30% EtOAc/hexanes) to afford N-Cbz-indole.
444 (3.4 mg, 28%) and recovered starting indole 408 (6.4 mg, 64%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.20 (d, \(J = 7.4\) Hz, 1H), 8.11 (d, \(J = 7.7\) Hz, 1H), 7.69 (d, \(J = 8.2\) Hz, 2H). 7.52-7.25 (m, 9H), 5.45 (ABq, \(J = 52.0, 12.1\) Hz, 2H), 4.34 (d, \(J = 11.2\) Hz, 1H), 4.21 (dd, \(J = 9.3, 3.9\) Hz, 1H), 4.04 (dd, \(J = 10.9, 4.4\) Hz, 1H), 3.73-3.70 (m, 2H), 3.31 (s, 3H), 2.48 (s, 3H), 2.16-2.01 (m, 2H), 1.81 (s, 2H), 1.72-1.48 (m, 2H), 1.19-1.13 (m, 1H), 1.06 (s, 9H), 0.28 (s, 3H), 0.25 (s, 3H), 0.14 (s, 3H), -0.43 (s, 3H); HRMS-ES\(^{+}\) (C\(_{42}\)H\(_{55}\)N\(_2\)O\(_8\)Si\(_2\)S) calcd 803.3218 (MH\(^+\)), found 803.3223.

**Primary Alcohol N-Boc-Indole 447.** To a stirred solution of indole 408 (15.8 mg, 0.024 mmol) and triethylamine (66 \(\mu\)L, 0.47 mmol) in CH\(_2\)Cl\(_2\) (2 mL) was added Boc\(_2\)O (53 mg, 0.24 mmol) and then DMAP (~0.5 mg, cat.). The resulting mixture was warmed to 35 °C, stirred for 35 h, and then diluted with NaHCO\(_3\)(aq). The organic layer was separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\). The combined organic layers were dried over MgSO\(_4\) and concentrated in vacuo to give a residue, which was used directly in the following step. For characterization purposes a sample was purified by flash chromatography on silica gel (20% EtOAc/hexanes). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.17 (d, \(J = 7.0\) Hz, 1H), 8.05 (d, \(J = 8.2\) Hz, 1H), 7.69 (d, \(J = 8.3\) Hz, 2H), 7.37-7.23 (m, 4H) 4.34 (d, \(J = 9.7\) Hz, 1H), 4.21 (dd, \(J = 10.8, 3.9\) Hz, 1H), 4.05 (dd, \(J = 10.8, 4.3\) Hz, 1H), 3.73-3.68 (m, 2H), 3.56 (s, 3H), 2.47 (s, 3H), 2.20-2.10 (m, 1H), 2.02 (d, \(J = 11.3\) Hz, 1H), 1.85 (ABq, \(J = 16.6, 15.2\) Hz, 2H), 1.68 (s, 9H), 1.61-1.51
(m, 1H), 1.20-1.14 (m, 2H), 1.05 (s, 9H), 0.28 (s, 3H), 0.24 (s, 3H), 0.13 (s, 3H), -0.43 (s, 3H);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.3, 151.0, 143.9, 136.7, 133.6, 133.4, 130.0, 128.8, 128.3, 124.7, 122.7, 121.8, 118.1, 116.1, 84.7, 74.5, 63.6, 55.2, 52.4, 52.0, 48.8, 46.7, 40.8, 30.1, 28.6, 27.8, 26.6, 26.1, 23.5, 22.0, 19.0, 2.3, 2.0, -4.8, -5.2; LRMS-ES+ $m/z$ (relative intensity) 769 (MH$^+$, 80).

To a stirred solution of the above crude $O$-TBS-oxime 446 and THF (2 mL) was added TBAF (1.0 M in THF, 115 $\mu$L, 0.115 mmol). The resulting solution was stirred for 10 h at rt and additional TBAF was added (230 $\mu$L, 0.230 mmol). The solution was stirred for 5 h longer and then diluted with NH$_4$Cl$_{(aq)}$. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo to afford a residue which was purified by flash column chromatography on silica gel (25-40% EtOAc/hexanes) to give primary alcohol 447 (15.0 mg, 97%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.09-8.02 (m, 2H), 7.70 (d, $J = 8.3$ Hz, 2H), 7.40-7.31 (m, 4H), 4.46-4.38 (m, 1H), 4.29-4.21 (m, 2H), 3.94-3.89 (m, 1H), 3.70 (t, $J = 3.4$ Hz, 1H), 3.60 (s, 3H), 2.58 (dd, $J = 7.7$, 6.3 Hz, 1H), 2.49 (s, 3H), 2.45-2.38 (m, 1H), 2.18 (d, $J = 12.1$ Hz, 1H), 1.91-1.80 (m, 3H), 1.70 (s, 9H), 1.31-1.25 (m, 2H), 0.15 (s, 3H), -0.04 (s, 3H); LRMS-ES+ $m/z$ (relative intensity) 655 (MH$^+$, 30).
**N-Benzyl Indole 448.** To a stirred solution of indole 408 (32.6 mg, 0.0487 mmol) in DMF (0.8 mL) and THF (0.5 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 5.6 mg, 0.15 mmol). The resulting mixture was stirred for 30 min and benzyl bromide (53 μL, 0.44 mmol) was added. The reaction mixture was stirred for 20 min at 0 °C and then 20 min at rt. The reaction mixture was diluted with water and Et₂O, the organic layer was separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with water, brine, dried over MgSO₄, and concentrated *in vacuo* to give a residue which was purified by flash column chromatography on silica gel (25% EtOAc/hexanes) to afford N-benzyl indole 448 (25.8 mg, 70%). ¹H NMR (400 MHz, CDCl₃) δ 8.18-8.14 (m, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.27-7.23 (m, 3H), 7.12-7.10 (m, 2H), 6.99-6.97 (m, 3H), 5.12 (ABq, J = 56.0, 17.4 Hz, 2H), 4.52 (dd, J = 11.2, 1.7 Hz, 1H), 4.28 (dd, J = 10.6, 4.8 Hz, 1H), 4.18 (dd, J = 10.6, 4.8 Hz, 1H), 3.83 (t, J = 4.7 Hz, 1H), 3.77-3.74 (m, 1H), 3.40 (s, 3H), 2.47 (s, 3H), 2.24-2.19 (m, 1H), 2.03 (d, J = 11.2 Hz, 1H), 1.77-1.65 (m, 3H), 1.20-1.15 (m, 1H), 1.08-1.06 (s, 10H), 0.29 (s, 3H), 0.27 (s, 3H), 0.07 (s, 3H), -0.54 (s, 3H); LRMS-ES+ m/z (relative intensity) 759 (MH⁺, 30).
**Primary Alcohol 449.** To a stirred solution of O-TBS-oxime 408 (25.8 mg, 0.034 mmol) and THF (2 mL) was added TBAF (1.0 M in THF, 340 μL, 0.340 mmol). The resulting solution was stirred for 15 h and then diluted with NH₄Cl(aq). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give a residue which was purified by flash column chromatography on silica gel (25-40% EtOAc/hexanes) to afford primary alcohol 449 (12.6 mg, 57%). ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 7.29-7.25 (m, 3H), 7.16-7.10 (m, 2H), 7.05-6.95 (m, 3H), 5.15 (ABq, J = 40.2, 17.8 Hz, 2H), 4.56-4.37 (m, 3H), 3.95-3.91 (m, 1H), 3.81-3.79 (m, 1H), 3.40 (s, 3H), 2.47-2.36 (m, 5H), 2.15 (d, J = 11.9 Hz, 1H), 1.81-1.65 (m, 3H), 1.23 (d, J = 14.4 Hz, 1H), 1.00-0.90 (m, 1H), 0.09 (s, 3H), -0.53 (s, 3H); LRMS-ES+ m/z (relative intensity) 645 (MH⁺, 50).

**Retro-aldol Product 456.** To a stirred solution of ³-butyl hydroperoxide (70% in water, 35 μL, 0.25 mmol) in DMF (200 μL) at 0 °C was added cesium hydroxide monohydrate (35 mg, 0.21 mmol). The resulting mixture was stirred at rt for 10 min and then cyclic silyl ether 449 (3 mg, 0.005 mmol) in DMF (200 μL) was added dropwise. After stirring the mixture for 10 min,
TBAF (1.0 M in THF, 88 μL, 0.088 mmol) was added and the resulting mixture was heated at 75 °C and stirred for 6.5 h. After cooling the mixture to rt, solid Na₂S₂O₃ was added and the solvent was removed *in vacuo*. The resulting residue was diluted with EtOAc and water. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water then brine, dried over MgSO₄, and concentrated *in vacuo* to give a residue which was used in subsequent reactions without further purification.

The above crude residue was dissolved in MeOH (500 μL) and cooled to 0 °C. TMS-diazomethane (100 μL) was added and the resulting mixture was stirred for 45 min at 0 °C and 45 min at rt. The volatiles were removed *in vacuo* to give a residue which was purified by preparative thin layer chromatography (50% EtOAc/hexanes) to give the retro-aldol product 456 (1 mg, 37%). ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.31-7.16 (m, 6H), 6.88 (d, J = 7.6 Hz, 2H), 5.30 (ABq, J = 116.6, 17.4 Hz, 2H), 5.05-4.96 (m, 1H), 4.72 (d, J = 13.6 Hz, 1H), 4.39 (t, J = 10.9 Hz, 1H), 3.95-3.86 (m, 1H), 3.75-3.74 (m, 1H), 3.56 (s, 3H), 3.37-3.34 (m, 1H), 2.46-2.34 (m, 6H), 2.11-2.00 (m, 1H), 1.02-0.88 (m, 3H); LRMS-ES+ m/z (relative intensity) 575 (MH⁺, 50).

**Cyclic Ether Product 459 or 461.** To a stirred solution of *t*-butyl hydroperoxide (5.5 M in decane, 19 μL, 0.11 mmol) in DMF (300 μL) at 0 °C was added cesium hydroxide monohydrate (15 mg, 0.092 mmol). The resulting mixture was stirred at room rt for 10 min and
then cyclic silyl ether 447 (5 mg, 0.008 mmol) in DMF (400 μL) was added dropwise. After stirring the mixture for 10 min, TBAF (1.0 M in THF, 38 μL, 0.038 mmol) was added and the resulting mixture was stirred at rt for 2.5 h. Solid Na₂S₂O₃ was added and the solvent was removed in vacuo. The resulting residue was diluted with EtOAc and water. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water then brine, dried over MgSO₄, and concentrated in vacuo to give a residue which was used in the subsequent reaction without further purification.

The above crude residue was dissolved in MeOH (500 μL) and Et₂O (200 μL). TMS-diazomethane (100 μL) was added and the resulting mixture was stirred for 1.5 h at rt. The volatiles were removed in vacuo to give a residue which was purified by preparative thin layer chromatography (50% EtOAc/hexanes) to afford a dehydration product assumed to be cyclic ether 459 or 461 (2 mg, 53%). ¹H NMR (400 MHz, CDCl₃) δ 9.05 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 7.7 Hz, 1H), 7.40-7.36 (m, 3H), 7.23-7.13 (m, 2H), 4.75 (d, J = 10.8 Hz, 1H), 4.41 (tt, J = 8.9, 2.7 Hz, 1H), 4.25-4.20 (m, 4H), 4.02-3.98 (m, 1H). 3.89 (s, 3H), 3.75 (dd, J = 7.0, 3.0 Hz, 1H), 2.50-2.46 (m, 5H), 2.39 (dd, J = 9.4, 3.0 Hz, 1H), 2.32 (dd, J = 12.7, 3.0 Hz, 1H), 1.72-1.55 (m, 2H). Due to the small amount of material, the aliphatic region (1.6-1.2 ppm) was complex due to overlap of water and grease peaks. LRMS-ES+ m/z (relative intensity) 497 (MH⁺, 25).
References and Notes


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Max M. Majireck was born in 1983 and raised in the South Hills of Pittsburgh, PA. After graduating from South Park High School in 2001, he attended Grove City College where he earned his B.S. in biochemistry in 2005. His undergraduate research with Charles E. Kriley focused on the synthesis and characterization of novel transition metal-phosphine coordination complexes. While enrolled at Grove City College, Max also conducted summer research internships at Purdue University with Ian P. Rothwell studying organometallic synthesis and at Consol Energy developing technology for reducing mercury emissions from coal-fired power plants. In the Fall of 2005, he joined the laboratory of Steven M. Weinreb where he worked on the total synthesis of complex alkaloids and developing new methodologies for organic synthesis. Upon completion of his graduate studies, Max will begin a postdoctoral appointment with Stuart L. Schreiber at Harvard University and the Broad Institute of MIT and Harvard.