STUDIES DIRECTED TOWARD
THE TOTAL SYNTHESIS OF DRAGMACIDIN E

A Dissertation in
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by
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ABSTRACT

Dragmacidin E is the only member in the dragmacidin family that contains a 7-membered 3,4-bridged indole. In addition, it is the only member in the family that has not succumbed to synthesis. In our model studies, we have synthesized the core of dragmacidin E, which contains all the rings, in 17 steps (0.95% overall yield) from tryptophan methyl ester. Our strategy to construct the required 7-membered ring involved a Witkop photocyclization and a reductive Dieckmann cyclization. Following our model studies, we have been able to prepare the bridged indole moiety of dragmacidin E containing all of the required functionality to complete the synthesis of the natural product. Efforts to accomplish this goal are currently underway.
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Chapter 1

Dragmacidins and Related Natural Products

1.1 Overview

Interest in marine natural products has grown over the past decade because of their novel molecular structures and promising biological properties. Dragmacidin (1) was first isolated from the deep water marine sponge Dramicidon sp. by McConnell and coworkers in 1988. Since then, several members of the dragmacidin family (Figure 1-1) have been isolated from marine sponges of the genera Halicortex, Hexadella, Spongosorites and the tunicate Didemnum candidum. These natural products contain two functionalized indole rings linked by a piperazine or pyrazinone ring. Biosynthetically, they are formed from the condensation of two tryptamine derivatives in a head-to-tail orientation. It has been reported that this class of compounds exhibits a wide range of biological and pharmacological effects, including cytotoxic, antitumor, antiviral and antifungal activity. All of these natural products, except for dragmacidin E, have been synthesized. This chapter briefly discusses how each molecule was synthesized and how each synthetic strategy might relate to the synthesis of dragmacidin E. In addition, syntheses of structurally related natural products in the hamacanthin family will be discussed.
1. R¹ = H, R² = Me, R³ = OH, R⁴ = Br : Dragmacidin
2. R² = Me, R¹ = R³ = R⁴ = H : Dragmacidin A
3. R¹ = R² = Me, R³ = R⁴ = H : Dragmacidin B
4. R¹ = R² = R³ = R⁴ = H : Dragmacidin C

Figure 1-1: Structures of dragmacidins.

1.2 Total syntheses of dragmacidin B

Dragmacidin B (3) is one of the simpler members of the dragmacidin family. The structure of dragmacidin B contains two identical indole moieties linked by a dimethylpiperazine ring in a symmetrical fashion. Due to the simplicity of this molecule, the synthesis of dragmacidin B was the first in the family to be reported. In 1994, Cava and Whitlock reported a 3-step synthesis of dragmacidin B starting from 1,4-dimethylpiperazine-2,5-dione (8) and 6-bromoindole (10) (Figure 1-2).³ In this synthesis, the piperazinedione 8 was brominated to give the intermediate 9, which was subsequently treated with 6-bromoindole in DMF to give bisindolyl piperazinedione 11 in 57% overall
yield. Reduction of the carbonyl groups in 11 with borane then furnished dragmacidin B (3) in 25% yield.

Figure 1-2: Cava’s total synthesis of dragmacidin B.

Another synthesis of dragmacidin B was reported by Horne and coworkers in 2000. Their strategy involved constructing the central ring by condensing two α-aminoketones to form the pyrazine ring, followed by reduction of this pyrazine to form a piperazine. In this synthesis (Figure 1-3), the required α-aminoketone 15 was prepared in 2 steps from indolyl acyl cyanide 12: 1) catalytic hydrogenation of the acyl cyanide in 12 to oxotryptamine 13, and 2) bromination at C(6) of the indole nucleus to give the required precursor 15. It should be noted that the latter reaction also produced the undesired 5-bromoindole analogue 14 as a major product in an approximate ratio of 2:1 to the desired product. Dimerization of 15 under thermal conditions in a sealed tube under an atmosphere of argon, followed by exposure to air, resulted in pyrazine 16. Reductive
methylation of the pyrazine with NaBH₃CN in formic acid afforded only the desired thermodynamically more stable *trans* diequatorial species dragmacidin B (3).

![Chemical Reaction Diagram](image)

**Figure 1-3**: Horne’s total synthesis of dragmacidin B.

Although both of these syntheses appear to be simple, applying their strategies to more complex molecules such as dragmacidin and dragmacidin A could be problematic as these more complex target molecules lack symmetry; both molecules have only one methylated piperazine nitrogen, and dragmacidin contains two different functionalized indole moieties. All possible pairs of bisindole products would be obtained if either
method was employed to synthesize more complex dragmacidins. Synthesis of dragmacidin A by the latter method, however, is possible via a desymmetrization sequence, as discussed in Section 1.4.

1.3 Total synthesis of dragmacidin

Not long after the first success in synthesis of dragmacidin B, Wuonola and coworkers reported the synthesis of dragmacidin (1).\(^5\) In this synthesis, two different functionalized indole moieties were brought together by a simple coupling reaction to form an amide bond and then cyclized to construct the piperazinedione linker. This strategy allows coupling of two different indole moieties with total control of regioselectivity. The two functionalized indoles were prepared as follows (Figure 1-4):

The indolyl amine precursor \(18\) was prepared from 6-bromoindole (10) by a Vilsmeier-Haack reaction to give aldehyde \(17\) followed by a modified Strecker reaction to give the amine \(18\). The indolyloxoyacetyl chloride \(20\) was prepared in one step from a reaction of dibromoindole \(19\) and oxalyl chloride. The two indoles were brought together by acylation of aminonitrile \(18\) with acid chloride \(20\) to form cyanoamide \(21\) (91% yield). It is important to note that this coupling reaction is carried out before hydrolysis of the cyano group as aminonitrile \(18\) was unstable and readily reverted back to the starting aldehyde upon aqueous workup. It should also be noted that aminonitrile \(18\) could only be isolated as its carbamate derivative after treatment with ethyl chloroformate, for example, and all attempts to hydrolyze the nitrile function within this carbamate to the corresponding acid resulted in decomposition. Hydrolysis of the cyano group in \(21\) generated amide \(22\) (92% yield). Intramolecular cyclization of the newly formed amide with one of the carbonyl groups resulted in bisindolyl piperazinedione \(23\) (62% yield) as
the sole product. As in the previous synthesis, reduction of the piperazinedione 23 with BH₃ gave trans-piperazine 24 (37% yield) and the cis-isomer (9% yield) in a 4:1 ratio. Removal of the methyl ether of trans-piperazine 24 with BBr₃ furnished dragmacidin (86% yield).
Figure 1-4: Wuonola’s total synthesis of dragmacidin.
1.4 Total syntheses of dragmacidin A

The first total synthesis of dragmacidin A was reported by Kawasaki and coworkers. Their strategy was very similar to Wuonola’s dragmacidin work. This route involved condensation of two indolylglycines, one containing a carboxylic acid group and the other a free amino group, to form an amide bond, followed by cyclization to form a piperazinedione ring. Instead of attempting to hydrolyze the cyano group of the carbamate derivative of aminonitrile like in the previous synthesis, Kawasaki installed an ester and an azide function on an indolinone. Both of the groups could easily be transformed to the required carboxylic acid and amine functionalities without reverting back to the indolinone precursor.

In this synthesis (Figure 1-5), methyl indolylglycine ester was prepared in 3 steps from 6-bromoindolin-3-one by 1) Wittig olefination of to form 3-alkylideneindoline, 2) elimination of methanol to form electrophilic intermediate followed by azide addition to generate indolyl azidoacetate, and 3) reduction of the azide with triphenylphosphine in the presence of water to produce indolylglycine. The second indolylglycine was prepared from in 7 steps involving protection/deprotection, methylation of the amino group and hydrolysis. It should be noted that deacetylation of the indole also took place unintentionally during hydrolysis, and this problem contributed to a dead end in this first attempt at dragmacidin A synthesis. Condensation of indolylglycines and yielded bisindole. Attempts to remove the Boc group to give intermediate were problematic, and a complex mixture was observed. Deamination, which was facilitated by the lone pair of the unprotected indole nitrogen, was observed in some
cases. As a result, protection of this indole with an electron withdrawing group such as acetyl was needed, but numerous attempts to effect this step only led to failure.

Figure 1-5: Kawasaki’s strategy to form a bisindole in the synthesis of dragmacidin A.

Instead of reintroducing an acetyl group to the free indole, preserving the original indole-\(N\)-protecting group was pursued. The plan was to use a different carboxyl-protecting group that could be removed without hydrolysis. As a result, allyl indolylglycine ester 34 was synthesized in a similar manner as in the previous route.
The desired N-Ac-indolylglycine 35 was obtained when the allyl ester of 34 was removed with RhCl(PPh₃)₃ in EtOH-H₂O at 70 °C. Condensation of indolylglycines 35 and 29 gave the desired bisindole 36 in 67% yield along with its diastereomer in 21% yield. Removal of the Boc group and cyclization of the resulting amino ester to form piperazinedione 37 was achieved by successive treatment of 36 with HCO₂H at room temperature and then NH₃ at 0 °C. Reduction of the piperazinedione with borane afforded dragmacidin A (2). Kawasaki and coworkers later applied this methodology to synthesize dragmacidins B and C, and dihydrohamacanthin A.⁷

**Figure 1-6:** Kawasaki’s total synthesis of dragmacidin A.

A more concise synthesis of dragmacidin A, reported by Nelson and Anstiss,⁸ used desymmetrization of bisindole pyrazine 16 as the key step (Figure 1-7). This
pyrazine was previously prepared by Horne in the synthesis of dragmacidin B. In Nelson’s synthesis, the indole nitrogens were protected with SEMCl and the pyrazine ring was reduced by NaBH₃CN to a piperazine ring (38). Desymmetrization of this ring occurred to give bisindolyl-N-formylpiperazine 40 (66% yield, 48% ee) when bisindolyl piperazine 38 was treated with chiral acylating agent 39 in dioxane. Removal of the SEM groups with TBAF and reduction of the formamide moiety with borane furnished the natural product.

Figure 1-7: Nelson’s total synthesis of dragmacidin A.
1.5 Total synthesis of dragmacidin D

An attempt toward the synthesis of dragmacidin D was first reported by Jiang and coworkers in early 2002. In the first report (Figure 1-8), Jiang demonstrated the construction of the bisindolyl pyrazinone core of dragmacidin D by 1) a coupling reaction of Weinreb amide 41 and indolyl glycine 42 to form dipeptide 43, 2) selective reduction of the Weinreb amide in 43, and removal of the Boc group to yield aldehyde-amine 44, and 3) cyclization of 44 to furnish bisindolyl pyrazinone 45.

![Chemical Structures](image)

Figure 1-8: Jiang’s synthesis of 3,6-bis(3′-indolyl)-2(1H)-pyrazinone.

In a subsequent paper, Jiang et al. reported an enantioselective synthesis of the aminomidazole segment of dragmacidin D (Figure 1-9). It was envisioned that the free aminimidazole moiety of dragmacidin D could be derived from imidazolyl acetamide 55 by hydrolysis to remove the acetyl group. In addition, acetamide 55 could be derived
from the condensation of $N$-acetylguanidine (54) and $\alpha$-bromoketone 53. In this synthesis, opening of enantiomerically pure epoxide 47 with a lithiated derivative of 4-bromoindole 46 regio- and stereoselectively gave indolyl alcohol 48. Swern oxidation of the secondary alcohol in 48 resulted in undesired 3-functionalized indoles 49 and 50. These unwanted additions were a result of the electron-donating property of the TBS group, which increased the nucleophilicity of the indole at C(3). Therefore, the TBS group was removed by TBAF and replaced with an electron-withdrawing Ts group to generate indolyl alcohol 51. Swern oxidation of the hydroxyl group in 51 with oxalyl chloride, DMSO and Et$_3$N at -40 ºC, followed by removal of the Tr group upon chromatography on SiO$_2$, gave $\alpha$-hydroxy ketone 52. The hydroxyl group in 52 was converted to an OMs group and displaced by a bromide to generate $\alpha$-bromoketone 53. The desired aminoimidazole 55 was obtained when 53 was treated with $N$-acetylguanidine (54) in DMF for 4 days. Jiang and coworkers published another paper describing a method to install two indole moieties on a methoxypyrazine ring using Suzuki and Stille cross-coupling reactions,$^{10}$ but they never finished the synthesis of dragmacidin D after it was completed by another research group.
Figure 1-9: Jiang’s synthesis of the aminoimidazole segment of dragmacidin D.

In 2002, Stoltz and coworkers achieved the first total synthesis of dragmacidin D. Their strategy involved selective Suzuki couplings to sequentially install two different functionalized indole moieties on the methoxypyrazine ring, and then construction of an aminoimidazole at a late stage in the synthesis. The initial attempt to construct a pyrazinone ring in simple model studies showed that pyrazinone 45 could be formed from the cyclocondensation of ketoaldehyde 56 and aminoamide 57 (Figure 1-10). However, this type of reaction produced none of the dragmacidin framework 60 when the more complex substrates 58a-c were employed.
Figure 1-10: Stoltz's attempts to construct bisindolyl pyrazinones via cyclocondensation.

The cyclocondensation approach was therefore abandoned and the focus was shifted to a palladium-mediated coupling (Figure 1-11). In this approach, sequential installation of 6-bromoindole 62 and 7-OBn indole 64 on a pyrazine ring was possible since the pyrazine ring 61 contained different halogen groups, which allowed sequential oxidative additions into the carbon-halogen bonds with Pd (0). Oxidative addition of the weaker C-I bond took place first in a Suzuki coupling with bromoindole 62 to give indolyl pyrazine 63. Subsequent Suzuki coupling of 63 with 7-OBn indole 64 at 50 °C generated bisindolyl pyrazine 65. Temperature control was necessary in this step as the
C-Br bond of the bromoindole unit would compete with the desired mode of coupling at higher temperatures.

$$\text{61} + \text{62} \rightarrow \text{63} +$$

Figure 1-11: Stoltz’s sequential selective Suzuki couplings.

To complete the synthesis, transformation of the OTBS group to the requisite aminimidazole unit and removal of all the protecting groups was required. Stoltz’s initial attempt first targeted the aminimidazole ring and then involved removal of the protecting groups to form the natural product as illustrated in Figure 1-12. However, this strategy failed as all attempts to remove the protecting groups resulted in undesired cleavage of the aminimidazole moiety. In this approach, the TBS group of 65 was removed with HF·pyridine, and the resulting hydroxyl group was oxidized under Dess-Martin conditions, followed by further oxidized with NaClO₄/NaH₂PO₄, to generate carboxylic acid 66. Homologation of 66 to α-bromoketone 67 was achieved by treatment of 66 with oxalyl chloride, diazomethane and HBr, respectively. Following Jiang’s chemistry to construct an aminimidazole ring, α-bromoketone 67 was treated with
acetylguanidine in order to form aminoimidazole 68. However, only substitution of the Br took place to yield the undesired \( \alpha \)-acetoxy ketone 69. To get around this problem, \( \alpha \)-bromoketone 67 was converted to an \( \alpha \)-aminoketone intermediate with \( \text{NH}_3/\text{MeOH} \), which cyclized to form guanidine 70 upon exposure to cyanamide in EtOH.

Figure 1-12: Stoltz’s failed attempts on the synthesis of dragmacidin D.
As a result of these difficulties, the Stoltz group developed a new strategy based on first removing all the protecting groups and then forming the sensitive aminoimidazole functionality. In this approach (Figure 1-13), the TBS moiety of 65 was removed with HF·pyridine, and the resulting hydroxyl group was oxidized to aldehyde 71 using Dess-Martin periodinane. Addition of nitromethane anion to the aldehyde and subsequent oxidation of the resulting hydroxyl group gave nitroketone 72. This nitroketone group was not as sensitive as the aminoimidazole group under basic conditions, which allowed removal of the Ts and SEM groups by the action of KOH and LiBF₄ followed by NaOH, respectively, to yield N-unprotected bisindole 73. The nitro group of 73 was reduced with stannous chloride to give an amine intermediate, and subsequent removal of the benzyl and methyl ethers with TMSI afforded the fully deprotected α-aminoketone 74. In this step, deprotection by TMSI instead of catalytic hydrogenation was necessary as debromination of one of the indole moieties occurred in the latter case. Dragmacidin D was successfully obtained upon exposure of 74 to cyanamide followed by treatment with TFA to furnish the TFA salt of the natural product.
1.6 Total synthesis of (+)-dragmacidin F

Stoltz and coworkers also applied their strategy of sequential installation of indole moieties onto a pyrazine ring to the synthesis of dragmacidin F (Figure 1-14). In this
synthesis, a Suzuki coupling reaction of optically active pyrroloboronic ester 76, which was prepared from (-)-quinic acid (75), and dibromide 63 generated pyrrolyl indolyl pyrazine 77. Similar to the synthesis of dragmacidin D, the TBS group was removed with LiBF₄ and the resulting alcohol was oxidized with Dess-Martin periodinane to give ketone 78. The next step required installation of an amino group at the α position of the ketone, but most known approaches failed. With limited options, a 5-step synthesis via an O-tosyloxime intermediate 79 and a Neber rearrangement was carried out to give the desired aminoketone 80 with concomitant loss of both the Ts and SEM groups in overall excellent yield. Removal of both the methyl ethers of 80 with TMSI, followed by treatment of the resulting intermediate with cyanamide and aqueous NaOH, furnished (+)-dragmacidin F (7) with a specific rotation of +146° (c 0.45, CH₃OH). However, the natural product has a negative specific rotation (-159° (c 0.40, CH₃OH)). Therefore, the absolute configuration of natural dragmacidin F is (4″S, 6″S, 6‴S). Since dragmacidins D, E and F are likely to be biosynthetically related, it is logical to assume that they all possess the same absolute configuration. Based on this assumption, the absolute configuration of natural dragmacidins D and F would be (6‴S) and (5‴R, 6‴S), respectively (as shown in Figure 1-1).

Stoltz and coworkers later applied a similar strategy to the total synthesis of natural dragmacidin F starting from the same (-)-quinic acid. They also applied their strategy featuring Suzuki coupling to generate a bisindolyl pyrazine for the formal total synthesis of dragmacidin B, trans-dragmacidin C, and cis- and trans-dihydrohamacanthins A.
1.7 Funk’s attempt toward the total synthesis of dragmacidin E

Dragmacidin E (6) was isolated from a marine sponge (Spongosorites sp.), collected in deep water near the southern coast of Australia. The aqueous ethanol extract of the sponge was reported to exhibit some biological properties including the
potent inhibition of serine-threonine protein phosphatases (PP1 and PP2A) and antimicrobial activity against the bacterium *Escherichia coli* and fungus *Candida albicans*. However, it was later reported that the potency of dragmacidin E as a protein phosphatase inhibitor was quite low. Further studies also revealed that this biological activity was not due to dragmacidin E.

Funk and Huntley have reported a strategy for the construction of the core ring system of dragmacidin E (Figure 1-15). Their strategy of functionalization of a pyrazine ring involved 1) addition of a metalated pyrazine to an aldehyde followed by an intramolecular Heck reaction to close the 7-membered ring that is attached to the pyrazine ring, and 2) a Stille coupling reaction to install an indole moiety. In this synthesis, pyrazine 61 was metalated with LDA and the resulting lithiated pyrazine intermediate was added to 5-hexenal (81) to give an alcohol intermediate, which was subsequently protected as TIPS ether 82. A Stille coupling reaction of 82 with stannane 83 afforded indolyl pyrazine 84, and an intramolecular Heck reaction of 84 furnished cycloheptannelated indolyl pyrazine 85. Next, an indole synthesis was carried out to complete the core ring system of dragmacidin E. Cycloheptenone 86 was obtained from oxidative cleavage of alkene 85 followed by dehydrogenation of the resulting ketone by the Saegusa protocol. Treatment of 86 with iodine in the presence of pyridine resulted in formation of 2-iodoenone 87, which was subjected to another Stille coupling with dienylstannane 88 to afford trienecarbamate 89, a precursor for a 6π-electrocyclic ring closure. This ring closure was achieved thermally in refluxing toluene, and the resulting cyclohexadiene product was oxidized by DDQ to give benzoxazolidine 90. To complete the synthesis of the indole, both the Boc and *N,O*-acetal groups were removed to give
hydroxyaniline intermediate, which was subsequently protected as benzyl ether \(^91\). Alkylation of methyl iodoacetate (92) with aniline \(^91\) followed by hydrolysis of the methyl ester afforded anilinoacetic acid \(^93\). Acid \(^93\) was treated with \(\text{Et}_3\text{N}\) in acetic anhydride to furnish the core ring system \(^94\) via condensation, decarboxylation, and acylation. Work is currently in progress to complete the synthesis of dragmacidin E.
Figure 1-15: Funk’s attempt toward the total synthesis of dragmacidin E.
1.8 Hamacanthin A and hamacanthin B

Hamacanthin A (95) and hamacanthin B (96) (Figure 1-16) are two bioactive alkaloids isolated from a deep-water marine sponge, Hamacantha sp. Both hamacanths have been reported to show significant antimicrobial activity against Candida albicans, Cryptococcus neoformans, and Bacillus subtilis. The structures of the hamacanthins contain two indole moieties, similar to members of the dragmacidin family. The major difference here is the linker between the two indole units. While members of the dragmacidin family have either a piperazine or pyrazinone ring as a linker, hamacanthins have a dihydropyrazinone as a linker. In addition, hamacanthin B differs from hamacanthin A in the position of attachment of the second bromoindole moiety to the linker; hamacanthin A has the two indole moieties attached at C(3) and C(6) whereas hamacanthin B has them attached at C(3) and C(5) of the dihydropyrazinone ring.

Figure 1-16: Structures of hamacanthin A and hamacanthin B.

1.8.1 Total syntheses of hamacanthin A

An enantioselective synthesis of (-)-hamacanthin A was first reported in 2001 by Jiang and coworkers (Figure 1-17). Similar to Wuonola’s work on dragmacin, Jiang’s strategy involved a coupling reaction of two indole moieties followed by an intramolecular aza-Wittig-type cyclization. In this synthesis, the required amine precursor was prepared from 6-bromoindole-3-carboxaldehyde (17). Protection of the
indole nitrogen of 17 with TsCl yielded $N$-protected indolecarboxaldehyde 97. A Wittig olefination of the aldehyde formed vinyl indole 98. Since the absolute configuration of hamacanthin A had not been assigned, the arbitrarily chosen (S) configuration of indolyl-1,2-ethanediol 99 was synthesized by asymmetric dihydroxylation with AD-mix-$\alpha$. Both of the hydroxyl groups in 99 would ultimately be converted to amino groups via azide intermediates. Jiang chose to convert the secondary alcohol first as the primary alcohol could be selectively protected with TBSCI to yield O-TBS alcohol 100. Displacement of the remaining alcohol by azide was achieved by a Mitsunobu reaction to form azide 101. The primary alcohol was deprotected by treating 101 with TBAF to generate alcohol 102. Reduction of the azido group of 102 with LiAlH$_4$, followed by protection of the newly formed amino group with (Boc)$_2$O, and tosylation of the primary hydroxyl group, gave 6-bromoindolyl aminooethanol 103 in 56% yield. The debromo analogue of 103 was also obtained in 14% yield as a result of reductive debromination by LiAlH$_4$. The primary tosylate group could now be displaced by sodium azide to yield indolyl azidoethylamine 104. The free azidoamine, which was obtained by treating 104 with TFA, was coupled with indolyloxoacetyl chloride 105 in the presence of Et$_3$N to afford bisindole 106. A Staudinger-aza-Wittig sequence through iminophosphorane intermediate 107 resulted in formation of the dihydropyrazinone ring in bisindole 108. Removal of the tosyl group on the indole nitrogen with refluxing, basic methanol furnished hamacanthin A with a specific rotation of $-79^\circ$ ($c$ 0.20, CH$_3$OH). However, the natural product has a positive specific rotation of $+84^\circ$ ($c$ 0.10, CH$_3$OH). Therefore, natural hamacanthin A has an $S$-configuration as shown in the above structure.
Figure 1-17: Jiang’s enantioselective synthesis of (-)-hamacanthin A.
Jiang also applied this methodology to the synthesis of dihydrohamacanthin A and dragmacidin A. The dihydropyrazinone ring of 108 was reduced with NaBH₄ to give a piperazinone ring in the former synthesis, and further reduced with BH₃ to give a piperazine ring in the latter synthesis.

Similar methodology also was utilized by Denis and coworkers in the synthesis of hamacanthin A (Figure 1-18). Instead of having an azido group in the coupling precursor, Denis chose to use a protected amino group, which cyclized to form the dihydropyrazinone ring upon deprotection. In this synthesis, the amine coupling precursor was prepared from indolyl N-hydroxylamine 109 as follows: Oxidation of the hydroxylamine 109 with manganese dioxide gave nitrone 110. Hydroxyaminolysis of nitrone 110 yielded primary N-hydroxylamine 111, which was reduced with titanium trichloride to give the desired amine. Coupling of amine 112 with indolyloxoacetyl chloride 105 furnished bisindole 113. Removal of the Boc group with formic acid gave the amine intermediate, which cyclized to give hamacanthin A.
Kawasaki and coworkers also reported an approach similar to Denis’s starting from indolylglycine intermediate 30 to arrive at bisindole 115 (Figure 1-19).\(^{21}\) Interestingly, Kawasaki found that the Boc group could be removed with formic acid at room temperature followed by heating in dichloroethane to give hamacanthin B precursor 120 as the major product in 63% yield along with hamacanthin A precursor 119 in 31% yield. This hamacanthin B precursor presumably was formed through transamidation of amine 116 to its regioisomer 118 via intermediate 117. Surprisingly, when dichloroethane was replaced by ethanol, the reaction proceeded regioselectively to afford
only 119 in 74% yield. Deacylation of 119 and 120 with ammonium hydroxide furnished hamacanthins A (95) and B (96), respectively. Kawasaki later reported an enantioselective synthesis of these natural products using the same strategy with a chiral 114 as the starting material.\textsuperscript{22}

Figure 1-19: Kawasaki’s total synthesis of hamacanthins A and B.
1.8.2 Total synthesis of hamacanthin B

Using the same methodology as in the synthesis of hamacanthin A, Jiang and coworkers also successfully synthesized hamacanthin B by changing the position of the reacting amino group of the indolyl amine precursor in the coupling reaction (Figure 1-20). In this synthesis, (R)-indolyl-1,2-ethanediol 121 was obtained by asymmetric dihydroxylation of vinyl indole 98 with AD-mix-β since hamacanthin B was expected to have the same (S)-configuration as hamacanthin A. Unlike in the hamacanthin A synthesis, the primary hydroxyl group of 121 was selectively tosylated and displaced with sodium azide to yield azido indole 122. Reduction of this azide with tin (II) chloride dihydrate followed by protection of the resulting amine with (Boc)₂O furnished hydroxy tryptamine 123. The secondary hydroxyl group was then converted to an azido group by a Mitsunobu reaction to give azido indole 124. Similar to the synthesis of hamacanthin A, the free azidoamine, which was obtained by removal of the Boc group of 124 with TFA, was coupled with indolyloxoacetyl chloride 105 to afford bisindole 125. An intramolecular Staudinger-aza-Wittig cyclization resulted in a formation of a bisindolyl dihydropyrazinone intermediate. Removal of the tosyl group of the indole with L-Selectride in refluxing THF furnished hamacanthin B (96) with a specific rotation of +183° (c 0.1, CH₃OH). This value is consistent with the natural product, which has a positive specific rotation (+176° (c 0.10, CH₃OH)). Therefore, natural hamacanthin B has an S-configuration as shown in the structure below.
1.8.3 Total syntheses of the dihydrohamacanthins

A concise and direct synthesis of a pyrazinone ring was reported by Horne and coworkers in the synthesis of the dihydrohamacanthins. In the synthesis of dihydrohamacanthins A (Figure 1-21), the pyrazinone ring of 127 was formed in one step from condensation of the amine salt of indolyl α-aminoketone 13 with indolyl ketoamide 126. Reduction of the pyrazinone ring in 127 with NaBH₃CN then gave a 1:1 mixture of cis and trans-debromodihydrohamacanthins (128a and 128b). In the synthesis of dihydrohamacanthin B (Figure 1-22), indolyl α-ketoamine 129 was first coupled with α-ketoacid chloride 130 to generate α-ketoamide 131. Condensation of 131 with aqueous
ammonia yielded bisindolyl pyrazinone 132. Reduction of the pyrazinone ring in 132 with NaBH₃CN gave dihydrohamacanthin B (133).

Figure 1-21: Horne’s total synthesis of dihydrohamacanthins A.

Figure 1-22: Horne’s total synthesis of 6′-debromo-cis-3,4-dihydrohamacanthin B.
1.9 Conclusion

In summary, natural products of the dragmacidin and hamacanthin families have drawn considerable interest from synthetic organic chemists over the past two decades. With the exception of dragmacidin E, all of these natural products have been synthesized. Most methodologies to synthesize hamacanthin and the simpler dragmacidin targets have involved an amide-forming coupling reaction, followed by a cyclization to join two indole moieties. For more complex molecules including dragmacidins D, E and F, a pyrazine ring and indole (or pre-indole) moieties were typically joined by palladium-mediated couplings such as Suzuki, Stille and Heck reactions. These strategies took advantage of the fact that halogenated pyrazines are highly reactive, compared to simple non-heterocyclic aromatic halides, toward palladium-mediated coupling reactions with metalated indole substrates.26
Chapter 2

Witkop Photocyclization

2.1 Overview

Natural products containing 3,4-bridged indoles are enduring targets in organic synthesis. Some examples of these natural products are dragmacidin E (6),\textsuperscript{2c} indolactam V (134),\textsuperscript{27} serotobenine (135),\textsuperscript{28} and hapalindole J (136)\textsuperscript{29} (Figure 2-1). Constructing a 3,4-bridged indole is challenging and only a few examples of reactions that achieve this goal have been reported. Chapter 2 discusses how this framework can be synthesized via a diradical intermediate as discovered by Witkop and coworkers.\textsuperscript{30} Further developments of this transformation by other chemists, which include a detailed mechanism and applications of this cyclization in natural product synthesis, will also be discussed.

![Figure 2-1: Natural products containing 3,4-bridged indoles.](attachment:image.png)
2.2 Construction of 3,4-bridged indoles

There are only a few examples reported in the literature to construct directly a bridge across C(3) and C(4) of the indole nucleus. These cases include (1) Fridel-Crafts-type cyclization of indolylpropionyl chloride 137 in the presence of AlCl₃ to form

![Chemical structures and reactions]

Figure 2.2: Various methods of constructing 3,4-bridged indoles.
bridged lactone 138,\textsuperscript{31} (2) cyclization of an iminium ion, generated from indolylamine 140 and 4-methoxybenzaldehyde, to form bridged amine 141,\textsuperscript{32} and (3) Heck-type palladium-mediated coupling of 4-bromoindolylamine 143 to form bridged amine 144\textsuperscript{33} (Figure 2-2). In addition, the total synthesis of hapalindole J (136), in which the 3,4-bridged indole 136 was formed by an intramolecular cyclization of ketone 145 in the presence of boron trifluoride etherate (>57% yield), has been reported. Cyclization at C(5) of the indole also took place to give a small amount (~5% yield) of the by-product 147.\textsuperscript{34} One common problem associated with all of these methods is a competing side reaction where cyclization can occur at an undesired position of the indole nucleus. The Witkop photocyclization also suffers from this side reaction, but in some cases, cyclization occurs only at the C(4) of the indole as will be discussed later in this chapter.

\textbf{2.3 Early discovery and mechanism}

In 1966, Witkop, Yonemitsu and Cerutti discovered a photocyclization to construct an 8-membered ring containing 3,4-bridged indole from a tryptophan derivative.\textsuperscript{30} They found that when a 10.0 mM aqueous, neutral solution of \textit{N}-chloroacetyl-L-tryptophan (148) was irradiated at 254 nm (Hanovia light source with a Vycor filter), the 8-membered lactam 149a was generated; its crystalline methyl ester 149b was obtained by the action of diazomethane in 40% overall yield (Figure 2-3).
The reaction also worked well with substituted indoles. For example, \(N\)-chloroacetyl-5-methoxytryptamine (150) was irradiated with the same light source in aqueous THF (11.5 mM) buffered with NaOAc to afford lactam 161 in 46% yield (Figure 2-4).\(^{35}\)

Witkop and coworkers initially proposed a mechanistic picture featuring photolytic homolysis of the C-Cl bond followed by intramolecular aromatic substitution of the free radical at C(4) of the indole nucleus to form intermediate 153 (Figure 2-5).\(^{30}\) Homolysis of the C-H bond at C(4) and rearomatization then would form lactam 149a. Alternatively, a concerted intramolecular cyclization with the extrusion of chloride ion from intermediate 154 might also be a possibility.
Figure 2-5: Initial proposed mechanisms of the Witkop photocyclization by Witkop and coworkers.

Further studies utilizing fluorescence quenching, solvent effects and flash photolysis led to a revised mechanism, which is now generally accepted. In this mechanism, intramolecular single electron transfer (SET) from the excited singlet state of an aromatic chromophore to the chlorocarbonyl moiety takes place initially (Figure 2-6). This electron transfer leads to heterolytic cleavage of the C-Cl bond, and the resulting acetamido radical subsequently couples with the aromatic radical cation. Finally, loss of a proton leads to the desired product.
2.4 Further developments

Most of the development of this reaction in the early 90’s was a result of work by Moody et al. When attempting to perform the original Witkop cyclization (Figure 2-7), Moody found that $149_b$ was obtained in poor yield over numerous runs (10-25% yield). One factor that caused this poor yield was the formation of the 2,3-fused by-product $149_c$, which was not originally reported by Witkop. This finding of cyclization at C(2) of the indole nucleus was in agreement with the work reported by Yonemitsu and Naruto. It was earlier reported by these workers that $N$-chloroacetyl derivatives ($155$) of different indolylethylamines underwent photocyclization at the ortho and peri positions to give the corresponding azepinoindole and azocinoindole derivatives ($156$) (Figure 2-8). The relative reactivity of each position of the indole ring was found to be in the order $3 > 6,4$
> 7.2 > 5 > 1, which approximately correlates with the SOMO-ED (singly occupied molecular orbital-electron density) values of the indole-1-radical \((R = H)\) (157) or 1-methylindole radical cation \((R = \text{Me})\) (158) (Figure 2-9).

Figure 2-7: Moody and coworkers’ attempts on the original Witkop cyclization.

Figure 2-8: Photocyclization of \(N\)-chloroacetyl derivatives of indoleethylamines.

Figure 2-9: Frontier electron densities of indole-1-radical and 1-methylindole radical cation.

Moody found that the Witkop photocyclization produced a better yield of the desired 3,4-bridged indole (34% yield) when the methyl ester analogue 159 was
irradiated at 254 nm in anhydrous acetonitrile instead of aqueous solution (Figure 2-10). Replacing chlorine with bromine or iodine led to a similar result for bromine and a complex mixture of unidentified products for iodine. In addition, irradiation of 159 at 350 nm produced no reaction. It also was found that when dichloroacetyl tryptophan derivatives were irradiated in anhydrous acetonitrile, yields of the desired 3,4-bridged indole were much improved and no cyclization at C(2) of the indole was observed. These higher yields might be favored by the presence of the second chlorine atom, which might help to facilitate radical formation by stabilizing the radical intermediate. This stabilization is a result of hyperconjugation of the singly filled $p$ orbital of the radical and the filled $p$ orbital of the chlorine atom. For example, irradiation of dichloroamide 160 at 254 nm followed by aqueous workup produced the $trans$-adduct 161 in 58% yield. The hydroxyl group is exclusively $trans$ to the ester group, a result that can be explained as follows (Figure 2-11): Irradiation of 160 generated both the $trans$-chloride 162 and $cis$-chloride 163. Internal $S_N2$ displacement of the $trans$-chloride by the ester carbonyl gave the bridged indole 164, whereas the $cis$-chloride 163 could not undergo such displacement. Nucleophilic attack of water on either 163 or 164 then generated the $trans$-alcohol 161.
Figure 2-10: Improved conditions for the Witkop cyclization by Moody and co-workers.

Figure 2-11: Group-assisted and direct displacement of a chloride.

When substrate 160 was modified with an alkyl group at the α-carbon of the amide, elimination of HCl can occur to give an exocyclic alkene as the product. For
example, irradiation of dichloroamide 165 in anhydrous acetonitrile at 254 nm generated alkene 166 in 43% yield (Figure 2-12). Presumably, the unobserved intermediate 166a underwent another photochemical reaction (SET and elimination of Cl) to generate cation intermediate 166b during the course of the reaction. On the other hand, bridged indole 167 was obtained as a major product (46% yield) when this reaction was carried out in 20% H2O/CH3CN. In this case, water presumably added to intermediate 166b at a rate faster than the formation of a double bond, subsequent lactonization then afforded 167. Therefore, it is important that this reaction be carried out under anhydrous conditions if an exocyclic alkene like 166 is the desired product.

Figure 2-12: Photocyclization of a (dichloroacetyl)tryptophan derivative under anhydrous and aqueous conditions.
Attempts to prepare higher homologous lactams were also successful in a few cases, although no success on smaller ring analogues has been reported. Endo and coworkers attempted to construct 10-membered lactams from vinylogous chloroamides such as 168 (Figure 2-13).\textsuperscript{43} However, the expected 10-membered lactam was not observed, but instead an 8-membered lactam bridged across C(3) and C(4) of the indole 169 was obtained along with the 2,3-bridged byproduct 170. This product mixture presumably was a result of an allyl radical intermediate which could couple at either the $\alpha$- or $\gamma$- positions of the amide with C(4) of the indole. By removing the double bond conjugated to the amide, the radical has only one site to combine with C(4) of the indole nucleus. Thus, formation of a 10-membered lactam is possible as reported by Bosch and coworkers in the synthesis of lactam 172.\textsuperscript{44} A 9-membered lactam (174) was also successfully synthesized by Mascal and coworkers.\textsuperscript{45}
Studies on the effects of indole substituents on the yield of Witkop photocyclization were investigated by Bremner and coworkers (Figure 2-14). These studies were carried out to form 1,7-bridged systems rather than 3,4-bridged systems, but a similar effect was expected since both types of cyclization proceed via the same mechanism. Bremner found that when 175a-c were irradiated with UV light, 175b reacted significantly faster than 175a, which also reacted significantly faster than 175c (4 h, 8 h and > 16 h, respectively) to give a mixture of 176-178, respectively. The combined yield of products in the methoxy series was slightly higher than the yield of the parent compound (R = H) because of the stabilizing effect of the electron donating methoxy
group on the radical cation intermediate. The fluoride atom has the opposite effect and the combined yield was somewhat poorer.

![Chemical structures and yields]

**Figure 2-14**: Effect of substituents on photocyclization.

### 2.5 Applications

Moody and coworkers have applied the Witkop photocyclization to construct a 3,4-bridged indole in the synthesis of (-)-indolelactam V (134). This compound was isolated from *Streptoverticillium blastmyceticum* NA34-17, and has the core structure common to the teleocidin family of tumor promoters. The metabolite contains a 9-membered lactam bridged across C(3) and C(4) of the indole. Although yields of many of the reactions used in this synthesis, including the Witkop photocyclization, were moderate, the synthesis was relatively short (only 5 steps from the photochemical
precursor, 1.5% overall yield). In comparison, a previous synthesis of (-)-indolactam V by Kogan et al. required 10 steps from L-tryptophan methyl ester and proceeded in 17.1% overall yield. The synthesis by Moody was carried out as follows (Figure 2-15): Photocyclization of $\alpha,\alpha$-dichloroamide 179 in aqueous acetonitrile generated alcohol 180 along with the 2,3-fused byproduct 181. The hydroxyl group of 180 was replaced by azide to generate 182. Irradiation of azide 182 then gave the ring-expanded imine 183. Reduction of imine 183 with NaBH$_3$CN to amine 184 followed by N-methylation furnished the desired natural product.

Moody et al. have also applied the Witkop photocyclization to prepare a tryptophan-derived azamacrocycle 186, which is tightly wound into the form of a left-handed double helix through strong transannular hydrogen bonding interactions (Figure 2-16). This species was synthesized in 3 steps from ($\alpha,\alpha$-dichloroacetyl)tryptophan methyl ester (160) as follows: Irradiation of 160 followed by workup in the presence of sodium azide generated azidopyrrolobenzazocine 185. Tetraazacyclooctadecane 187 was then obtained via intermediate 186 by the exposure of 185 to either heat or UV light.
Figure 2-15: Total synthesis of (-)-indolactam V via the Witkop photocyclization.
2.6 Conclusion

The Witkop photocyclization is a powerful method to construct a 3,4-bridged indole from a tryptophan precursor. This substrate contains an N-unprotected indole electron donor and a carbonyl electron acceptor in close proximity. When this substrate is irradiated with UV light, single electron transfer occurs from the donor to the acceptor. Yields of the 3,4-bridged indoles are moderate in most cases, and improvements in these yields can be achieved with (dichloroacetyl)tryptophan derivatives or substrates with electron donating substituents on the indole core. This methodology has been applied in the syntheses of indolactam V and an unnatural double-helical macrocycle. Our attempts to synthesize dragmacidin E will use this reaction to construct the 3,4-fused indole core of the natural product.
3.1 Retrosynthesis of dragmacidin E

It was originally envisioned that the core structure of dragmacidin E (6) could be derived from a cyclocondensation of $\alpha$-aminoketone 188 and ketoamide 189 (Figure 3-1). This type of reaction was documented by Horne in the synthesis of dihydrohamacanthin A (Section 1.8.3). Ketoamide 189 could be prepared from 6-bromoindole (10). The urea unit of 188 could be derived from the carbonyl group of ketone 190 via a Strecker reaction. The desired stereochemistry at C(5'') and C(6'') of 188 might be achieved if addition of a cyano group to the imine intermediate derived from ketone 190 occurs away from an $\alpha$-methyl group. The 7-membered ketone 190 could be generated from bridged amide 191 via hydrolysis followed by decarboxylation. The bridged amide 191 could be formed via a Dieckmann cyclization of enolate intermediate 192, which could be generated from conjugate hydride addition to 8-membered lactam 193. This compound (193) was an obvious target for the Witkop photocyclization. Finally, the photocyclization precursor, dichloroamide 194, could be derived from simple 7-hydroxyindole (195).
3.2 Model studies

3.2.1 Witkop photocyclization

We began to explore the Witkop photocyclization with model substrate chloroamide 198 (Figure 3-2), which was easily prepared in one step (98%) by acylation of commercially available L-tryptophan methyl ester hydrochloride (196) with 2-
chloropropionyl chloride (197). Following the reaction conditions employed by Moody (Section 2.4), a solution of chloroamide 198 in CH₃CN was irradiated at 254 nm to give a diastereomeric mixture of 199a and 199b (~3:1) in 43% yield. The stereochemical assignment of these compounds is based on NOE analysis of the carbamate derivative of 199b (Figure 3-4). We envisioned that lactams 199a and 199b could serve as precursors for the Dieckmann cyclization. However, both the amide and indole nitrogens required protection during this cyclization step since deprotonation of both nitrogens would likely occur in the presence of base. Therefore, we attempted to protect lactams 199a and 199b with Boc₂O to generate bis-Boc lactam 200. Unfortunately, only monoBoc lactam 201 was observed.

Figure 3-2: Witkop photocyclization of N-(2-chloropropionyl)tryptophan methyl ester.
Since we were unable to protect the amide nitrogen of lactams 199a and 199b, we instead attempted to install a protecting group on the photocyclization precursor 198 (Figure 3-3). Treatment of 198 with Boc₂O and DMAP generated bis-Boc chloroamide 202 in 83% yield. Unfortunately, irradiation of 202 at 254 nm resulted in a mixture of unidentified products.

![Figure 3-3: Attempt at the Witkop photocyclization of bis-Boc chloroamide 202.](image)

Since the indole nucleus acted as an electron donor in the Witkop photocyclization, we speculated that the electron withdrawing Boc group on the indole nitrogen might be responsible for the failure to form 200. Therefore, we attempted to selectively protect the amide nitrogen to form monoBoc chloroamide 205 (Figure 3-4). However, an initial attempt to treat chloroamide 198 with 1 equivalent of Boc₂O only resulted in protection of the indole nitrogen. As a result, the indole nitrogen of 198 was first protected as its benzylcarbamate, 203. Subsequent protection of the amide nitrogen of 203 with Boc₂O, followed by removal of the Cbz group by catalytic hydrogenation resulted in the desired monoBoc compound 205. When a solution of 205 in CH₃CN was irradiated at 254 nm, a single diastereomer of lactam 206 was obtained in a very low yield (6%). Irradiation of 205 at 300 nm gave the desired product in a comparable yield (8%). The yield was slightly increased (up to 13%) when the light source was switched from the Rayonet to the Hanovia. When lactam 206 was treated with Boc₂O and DMAP,
a diastereomeric mixture of bis-Boc lactams 200a (26%) and 200b (35%) was obtained. This mixture of diastereomeric compounds was a result of epimerization at C(5'') in the presence of DMAP. The relative stereochemistry of 200b was tentatively assigned by NOE analysis as shown. Removal of the Boc groups of 200a with SiO₂ at 40 °C under vacuum resulted in a single diastereomer whose NMR data was consistent with that of 199a.

We started to explore an alternative substrate since chloroamide 205 underwent the Witkop photocyclization to give the desired lactam 206 in very low yield. Dichloroamide 208 was chosen and prepared by acylation of tryptophan methyl ester 196 with 2,2-dichloropropionyl chloride (207) (Figure 3-5). Irradiation of dichloroamide 208
at 254 nm resulted in the desired 8-membered lactam 209 in 53% yield. Interestingly, the 2,3-bridged isomer 210 was also generated (209:210 ~ 5:1 by 1H NMR) although it was previously reported by Moody that these types of dichloroamide substrates only cyclize at C(4) of the indole nucleus (Figure 2-10).

![Chemical Structures](image)

Figure 3-5: Witkop photocyclization of N-(2,2-dichloropropionyl)tryptophan methyl ester.

### 3.2.2 Construction of a tetracyclic model system for dragmacidin E

With the 8-membered lactam in hand, the next operation in the synthesis is a ring contraction. Both the indole and lactam nitrogens of 209 were first protected with (Boc)₂O to give 211 in 77% yield (Figure 3.6). Catalytic hydrogenation of the double bond in 211 generated a diastereomeric mixture of α-methyl lactams 200a and 200b in 62% and 10% yields, respectively. Dieckmann cyclization occurred when a mixture of
200a and 200b was treated with TMS$_2$NLi, which deprotonated the $\alpha$-carbon of the lactam to form the unobserved enolate intermediate 212. This intermediate cyclized to form bridged amide 213 in 69% yield along with the fully protected analogue 214 in 15% yield. A better alternative route was later realized when 211 was treated with a hydride reagent (N-Selectride), which presumably generated the same enolate intermediate 212, to afford 213 in 76% yield. The lactam protecting group was then reinstalled on 213 to generate 214 in quantitative yield.

Figure 3-6: Dieckmann cyclization to form a bridged amide.

We now had a 7-membered ring ketone, which was ready for imidazolone introduction. The first step of this transformation involved generation of a diamine via 1) a Strecker reaction, and 2) subsequent reduction of the resulting cyano group. For the Strecker reaction, benzylamine was first selected since it resulted in the formation of a
relatively stable and easy-to-handle benzylimine. When ketone 213 was treated with benzylamine in the presence of a mild acid such as TsOH in refluxing benzene, imine 215a was formed with 100% conversion (Figure 3-7). The crude imine was stable and could be stored at room temperature for days without reverting to the parent substrates. Addition of TMSCN to this imine afforded a single diastereomer of benzylaminonitrile 216a whose stereochemistry was not assigned. Attempts to reduce the cyano group in 216a to form diamine 218 with various reducing reagents (BH₃-SMe₂, BH₃-THF, NaBH₄/CoCl₂, DIBAL, LiAlH₄, SnCl₂, H₂ (Pd/C, Pd(OH)₂/C, Raney Ni, Rh(PPh₃)₃Cl)) only led to the starting imine 215a and/or aminonitrile 216a and, in some cases, reduction of the imine. To prevent the retro-Strecker reaction from taking place, an electron withdrawing group on the amine nitrogen of 216a was necessary. Attempts to protect the amino group of 216a (regardless of whether the amide nitrogen would get acylated or not) with (Boc)₂O, TFAA or methyl chloroformate (MocCl) failed. It has been reported that the nitrogen of benzylaminonitrile could be protected as its formamide derivative in excellent yield using in situ generated acetic formic anhydride under solvent free conditions. For example, aminonitrile 219 was protected as formamide 220 (97% yield) under these reaction conditions (Figure 3-8). However, attempts to protect the amino group in 216a or 216b under these conditions failed.
We speculated that protection of the amine function would occur easily if this chemistry was performed on a primary amine. Therefore, we attempted to generate an aminonitrile from NH₃ instead of BnNH₂. Following the reaction conditions employed by Postel, treatment of ketone 213 with saturated NH₃ in MeOH in the presence of titanium isopropoxide followed by addition of TMSCN resulted in aminonitrile 221 in 62% yield (Figure 3-9). This compound was quite polar and not very soluble in most organic solvents. Therefore, we used the fully protected amide 214 to generate aminonitrile 222, a species that was less polar than 221 and had no solubility problems. The stereochemical assignment of 222 is based on analysis of its protected derivative 223. Protection of the amino group in 222 with methyl chloroformate (MocCl) in the...
presence of K$_2$CO$_3$ in refluxing THF resulted in N-Moc aminonitrile 223 in good yield (78%). An NOE signal between the $\alpha$-positioned proton on C(8") and the NH of 223 indicated the relative stereochemistry of this compound as shown. To complete the construction of the imidazolone ring, the cyano group in 223 was reduced by catalytic hydrogenation (1500 psi) to afford amine 224. This compound was then treated with LiOH in refluxing aqueous THF with the expectation that the lactam bridge will be opened and the imidazolone ring would form in one step. However, only the formation of the imidazolone ring took place to give pentacycle 225. In fact, we were unable to cleave the lactam bridge using various nucleophiles (KOH/DMSO, Cs$_2$CO$_3$/THF/H$_2$O, H$_2$SO$_4$/H$_2$O, LiAlH$_4$, LiEt$_3$BH, NaBH$_4$, NaBH$_3$NMe$_2$, LiBH$_3$NH$_2$, NH$_2$NH$_2$). Only recovered starting material and/or partial/full removal of the Boc groups was observed.
Figure 3-9: Attempts to cleave the lactam bridge of pentacycle 225.

It seemed plausible that the difficulty with this lactam cleavage was a result of steric effects from subsituents surrounding the bridged imide unit. Therefore, we examined the less hindered compound 214 (Figure 3-10), and found that the lactam bridge in this species was cleaved easily by aqueous LiOH/THF to generate, presumably, an amino carboxylate intermediate. This unobserved species underwent decarboxylation to give a ~2:1 diastereomeric mixture of ketones 227a and 227b in excellent yield (98%).
The relatively stereochemistries of both compounds were assigned by NOE analysis as shown. It appeared that the diastereomer ratio was a result of thermodynamic equilibration (favoring the β-isomer as shown for 227a) upon formation of the ketones as resubjection of either 227a or 227b to the basic reaction conditions led to the same ~2:1 product ratio (227a: 227b).

![Chemical structures and reactions](image)

Figure 3-10: Attempts to form an aminonitrile from a 7-membered ring ketone.

Although the decarboxylation product was not obtained as a single diastereomer in this step, it was possible to generate a single diastereomer in the next step using a Stecker reaction since epimerization of the methyl group at C(5'''') could also take place. We believed that formation of the desired epimer might be achieved if there was an energetic preference for one of the corresponding imine configurations over the other. In
fact, molecular mechanics calculations (Macromodel 9.0) showed that there would be a preference for the $\alpha$-isomer versus the $\beta$-isomer imine by as much as 3.0 kcal/mol (Figure 3-11). This preference could be the result of $\Lambda^{1,3}$ strain in the $\beta$-isomer. Further examination of this model led us to believe that the trajectory of cyanide addition to the imine would occur away from the pseudoaxial methyl group. However, when ketone 227 was subjected to the imine-forming conditions previously implemented successfully with 213 or 214, no reaction took place.
Macromodel 9.0 calculations (MMFF parameter set)

10000-step directed Monte Carlo search about all rotatable bonds. Each minima shown was found over 450 times.

Figure 3-11: Macromodel calculations of the imine intermediates 228. \(^{53}\)
With this failure, we explored an alternative strategy for forming the desired spiromidazolone. We speculated that this functionality could be derived from the reduction of a spirohydantoin,\textsuperscript{54} which could be formed in one step from a ketone under Bucherer-Bergs reaction conditions.\textsuperscript{55} For example (Figure 3-12), treatment of ketones \textit{230}\textsuperscript{56} and \textit{232}\textsuperscript{57} with (NH\textsubscript{4})\textsubscript{2}CO\textsubscript{3} and KCN in a mixture of EtOH and H\textsubscript{2}O at elevated temperatures resulted in spirohydantoins \textit{231a/231b}, and \textit{233}, respectively, in good yields. Presumably, this reaction proceeded via carbamate anion \textit{233a} and \(\alpha\)-carboxamidoisocyanate intermediate \textit{233b}.\textsuperscript{58} Unfortunately, we have never been able to form hydantoin \textit{234} after numerous attempts (Figure 3-13).

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{EtO}_2\text{C} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\textit{230} \quad \text{(NH}_4\text{)}_2\text{CO}_3, \text{KCN} \quad \text{EtOH, H}_2\text{O, 35 °C} \quad \text{73%} \\
\text{EtO}_2\text{C} & \quad \text{EtO}_2\text{C} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\textit{231a} \quad \textit{87:13} \\
\textit{231b}

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{C}_2\text{H}_5 & \quad \text{C}_2\text{H}_5 \\
\end{align*}
\]

\textit{232} \quad (\text{NH}_4\text{)}_2\text{CO}_3, \text{KCN} \quad \text{NH}_4\text{Cl, EtOH, H}_2\text{O, 60 °C, 80%} \\
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{C}_2\text{H}_5 & \quad \text{C}_2\text{H}_5 \\
\end{align*}
\]

\textit{233a} \quad \text{233b} \quad \text{233}

Figure 3-12: Hydantoin formation in the presence of (NH\textsubscript{4})\textsubscript{2}CO\textsubscript{3} and KCN.
With limited options, we were forced to return to the aminonitrile route. Fortunately, we were able to generate a single diastereomer of aminonitrile 229 under forcing Strecker conditions (85 °C in a sealed tube) (Figure 3-14). The relative stereochemistry of 229, which is in agreement with our prediction (Figure 3-11), is assigned based on NOE analysis of its derivative 236. Although only a single diastereomer was obtained in this reaction, examination of the product by polarimetry revealed the loss of optical activity. Thus, epimerization took place at both C(5′′′) and C(7′′′) under the harsh conditions employed, resulting in racemic product. In fact, recovered starting material from this reaction carried out at room temperature also showed minimal optical activity, which implied that epimerization at C(7′′′) was unavoidable under these reaction conditions. Protection of the amino group in 229 with methyl chloroformate (MocCl) resulted in N-Moc aminonitrile 235. Subsequent attempted catalytic hydrogenation of the cyano group of 235 surprisingly resulted in either recovered starting material or a complex mixture. However, success was realized when 235 was treated with NaBH₄ in the presence of CoCl₂ to generate amine 236. NOE analysis of 236 confirmed the desired relative stereochemistry to be as shown. When 236 was treated with 2 equivalents of LiOH in refluxing aqueous THF for 6 h, it
was converted to bis-Boc imidazolone 238 in 54% (over steps) along with a trace amount of monoBoc imidazolone 237. However, attempts to oxidize C(8\textsuperscript{\textprime\textprime\prime}) in 238 with DDQ in aqueous THF led to no reaction. This failure could be a result of the depleted electron density of the indole nucleus as a consequence of the Boc group on the indole nitrogen. To obtain more 237 instead of 238, increased equivalents of LiOH and longer reaction times were needed (it took 4 days and 5 equivalents of LiOH to generate 237: 238 = 69:31). Due to the low solubility of LiOH in aqueous THF, CsOH was used instead. After treating 236 with 30 equivalents of CsOH at reflux for 5 days, a ratio of 237: 238 = 74:26 was obtained. Only 237 was obtained after 7 days of heating. However, extensive decomposition also took place when the reaction was heated for a long period of time. Shorter reaction times could be achieved (down to 1 hour) when the reaction was carried out in a microwave reactor. However, this procedure only could be used for small scale reactions (< 30 mg) and was not always reproducible. Fortunately, by changing the solvent to EtOH and using LiOH, the reaction went to completion in 4 hours to generate 237 in 63% (over 2 steps) along with a trace amount of 238. Oxidation of 237 with DDQ in aqueous THF went smoothly to afford ketone 239 in 73% yield. Selective protection of the indole nitrogen with 1 equivalent of (Boc)\textsubscript{2}O furnished the tetracyclic system 240 in excellent yield (94%).
3.2.3 Attempts toward the synthesis of the central pyrazinone ring

3.2.3.1 Condensation approach

With protected amines 237 and 238 in hand, we envisioned that the derived primary amine species 241 would condense with ketoamide 242 to join the two indole moieties. Therefore, bis-Boc compound 238 was deprotected with TFA to give amine 241 (77% yield). Unfortunately, attempts toward the condensation of amine 241 with
ketoamide 242 in the presence of titanium isoproxide to give bisindole 243 failed (Figure 3-15). We speculated that the electrophilicity of the carbonyl group in 242 was attenuated because it is a vinylogous amide. Therefore, it appeared that an electron withdrawing group was needed on the indole nitrogen. However, attempts to selectively protect the indole nitrogen of ketoamide 242 failed, and as a result methyl (indol-3-yl)-oxo-acetate was used instead. This compound was protected with CbzCl to give protected ketoester 244 (80% yield). Unfortunately, attempts to condense 241 with 244 only led to deprotection of 244. As in our original retrosynthesis, condensation of α-aminoketone 246, which was prepared in 93% yield by deprotection of 239 with TFA, and ketoamide 242 also was attempted as a means to form bisindolyl pyrazinone 247 in one step (Figure 3-16). However, this reaction led to a complex mixture of uncharacterized products.
Figure 3-15: Attempts toward condensation of amine 241 with ketoamides or ketoester.

Figure 3-16: Attempts toward the condensation of α-aminoketone and ketoamide to form bisindolyl pyrazinone 247 in one step.

With the failure of electrophiles 242 and 244 to participate in imine-forming condensation reactions, we then employed ethyl glyoxylate (248) as a potentially more
reactive alternative. This substrate is very receptive toward nucleophilic addition, and imine formation takes place easily in refluxing toluene or in the presence of drying agents such as Na$_2$SO$_4$, MgSO$_4$ or molecular sieves.$^{60}$ Subsequent addition of indole C(3) to this glyoxal imine also was reported.$^{61}$ Our attempts toward the condensation of amine \textbf{241} with ethyl glyoxylate led to a complex mixture of unidentified products (Figure 3-17). Since we were not able to determine whether imine \textbf{249} formed, the reaction was carried on by adding 6-bromoindole (\textbf{10}) with the expectation that bisindole \textbf{250} would be obtained. Unfortunately, no desired product was observed. In addition, the addition of amine \textbf{241} to diazo compound \textbf{251} was examined (Figure 3-18). In the presence of TFA,$^{62}$ the reaction led to a complex mixture. Whereas, in the presence of Rh$_2$(OAc)$_4$,$^{63}$ no reaction took place.

![Chemical structures](image)

Figure 3-17: Attempts to condense amine \textbf{241} with ethyl glyoxylate.
3.2.3.2 Strecker reaction approach

It was envisioned that amine 241 could undergo a Strecker reaction with indole-3-carboxaldehyde (253) to generate aminonitrile 254 (Figure 3-19). Hydrolysis of the cyano group in 254 followed by conversion of the intermediate amide to an ester and DDQ oxidation of the indole methylene could result in keto ester 255, a species that could cyclize to form heptacyclic 256 when treated with NH₄OAc under reflux.

Figure 3-18: Attempts to add amine 241 to diazo compound 251.

Figure 3-19: Proposed synthesis of a pyrazinone ring via a Strecker reaction.
To test the feasibility of this approach, we used tryptamine (257) as a model (Figure 3-20). It was found that imine 258 was formed easily when a solution of tryptamine and indole-3-carboxaldehyde (253) was heated to reflux or treated with titanium isopropoxide at room temperature. Subsequent addition of TMSCN to 258 resulted in 87-91% conversion of the imine to aminonitrile 259.

![Figure 3-20: Tryptamine model for the formation of aminonitrile.](image)

With this exciting result, we then turned to our tetracyclic system (Figure 3-21). Treatment of 241 with aldehyde 253 in the presence of titanium isopropoxide in refluxing methanol resulted in 100% conversion of the free amine to imine 260a. Isolation of this imine became problematic as most of it reverted back to starting materials upon column chromatography on silica gel. As a result, a mixture of aldehyde 253 and imine 260 was
usually obtained. Subsequent addition of TMSCN or KCN to 260 \textit{in situ} or stepwise only yielded the recovered imine. An attempt to add nitromethane anion to 260 to produce 261 was explored, but no reaction took place. We speculated that the electrophilicity of the imine might increase if the nitrogen of the indole carboxaldehyde was protected with an electron withdrawing group. Therefore, we protected the aldehyde nitrogen with either electron-withdrawing Ts or Boc groups to give protected aldehydes 262 or 263, respectively (Figure 3-22). We were pleased to see that both aldehydes 262 and 263 were very reactive toward amine 241 in the presence of titanium isopropoxide at room temperature. However, subsequent addition of TMSCN to these amines resulted in a complex mixture from which any 264/265, if formed, could not be identified.

![Chemical structures](image)

Figure 3-21: Attempts to form an aminonitrile of the model tetracyclic system.
Figure 3-22: Attempts to form aminonitriles of the model tetracyclic system with protected indole-3-carboxaldehydes.

With these frustrating results, we speculated that perhaps we needed a stronger electron withdrawing group to protect the indole nitrogen. As a result, a triflate group was chosen as it had been used by Overman to deactivate the indole nitrogen. Protection of the indole was accomplished by treating aldehyde 253 with Tf₂O in the presence of Et₃N to provide protected aldehyde 266 (52% yield) (Figure 3-23). We initially examined condensation of aldehyde 266 with tryptamine, and we found that the formation of the imine occurred rapidly at room temperature in the absence of any catalysts. Subsequent addition of TMSCN to the imine afforded aminonitrile 267 in 64% yield.

We then turned to investigate our model tetracyclic system, and found that the imine intermediate 268 was highly reactive. Addition of the proximate imidazolone nitrogen to the imine intermediate 268 took place to give heptacyclic species 269, as confirmed by X-ray analysis (Figure 3-24). Subsequent addition of TMSCN to 269 in situ or stepwise only resulted in the recovery of starting material. To avoid this problem,
selective protection of the imidazolone moiety would be necessary and would add protection/deprotection steps to the synthesis. In addition, we had never been able to hydrolyze any aminonitriles using this approach. Another protecting group perhaps would be needed to protect the amino group of these compounds to prevent them from converting back to the parent substrates. To circumvent this hydrolysis problem, we also attempted to form imine 272 (Figure 3-25) from amine 241 and N-Tf indolyl keto ester 271 in the expectation that the triflate protecting group would dramatically increase the electrophilicity of the ketone carbonyl. Unfortunately, decomposition took place. Because of these complications, this approach eventually was abandoned.
Figure 3-23: Attempts to from an aminonitrile from N-Tf indole-3-carboxaldehyde.
3.2.3.3 Imine approach

We envisioned that we could generate another nucleophilic group, such as an imine, at C(8''') instead of having an amino group at C(7'''') act as a nucleophile to condense with a carbonyl group. This imine might be prepared in one step from indolyl ketone 239, and could couple with highly reactive α-ketoacid chloride 130 to provide...
bisindole 274 (Figure 3-26). Numerous attempts (NH$_3$/MeOH, NH$_4$Cl, 70-80 °C; NH$_3$/MeOH, Ti(OiPr)$_4$; NH$_4$OAc, MeOH, Δ) to generate imine 273 were examined. Due to the fact that we could not determine whether the desired imine was formed, acid chloride 130 was added to the crude reaction mixture. Unfortunately, the protocol produced a mixture of uncharacterized products.

![Figure 3-26: Attempts to form bisindole 274 via the imine approach.](image_url)

In order to determine whether the imine 273 was formed, reductive amination was carried out to form amine 275, but all attempts at this transformation also failed (Figure 3-27). We speculated that the N-benzylimine or oxime of 239 should be more stable than 273, and we might be able to isolate and/or identify these species. Numerous attempts to
form benzylimine 276 or oxime 277 employing various reaction conditions were carried out, but no reaction took place. With these frustrating results, we then employed N-protected indolyl ketone 240 with the expectation that it would be more reactive toward nucleophilic addition (Figure 3-28). However, all attempts were fruitless as deprotection of the indole easily took place to give 239 under basic or acidic conditions.

![Reaction Diagram]

Figure 3-27: Attempts to form an amine, benzylimine or oxime from ketone 239.
Figure 3-28: Attempts to form an imine from N-Boc indolyl ketone 240.

3.2.3.4 Coupling reaction and cyclization approach

It has been reported that oxidation of the benzylic position of aromatic compounds with DDQ results in an azide product when water is replaced by TMSN₃ (Figure 3-29). For example, when alkyl methoxybenzene 279 was treated under these conditions, azide 280 was obtained in excellent yield. Encouraged by this precedent, we envisioned that instead of obtaining ketone 239, azide 281 could be formed from oxidation of 237 with DDQ in the presence of TMSN₃ (Figure 3-30). Inspired by Jiang’s chemistry, reduction of this azide would give an amine intermediate, which could couple with indolyl acid chloride 130 to form bisindole 282. Deprotection and cyclization of 282 followed by oxidation of the resulting dihydropyrazinone ring would give the desired pyrazinone product 247.
Figure 3-29: Selective conversion of a benzylic C-H bond to an azide function by oxidative nucleophilic substitution.

We first tested the feasibility of this strategy with N-Boc tryptamine (283) (Figure 3-31), which was prepared by treating tryptamine with (Boc)$_2$O in the presence of Et$_3$N. We were pleased to see that the oxidative nucleophilic substitution reaction went smoothly to give azide 285 in 81% yield, presumably via the iminium ion intermediate 284. Azide 285 was then reduced via catalytic hydrogenation and the resulting amine
was acylated with indolyl acid chloride 130 to afford bisindole 286 in 74% yield over 2 steps. Deprotection and cyclization of bisindole 286 has been accomplished by Denis, as discussed earlier on a similar substrate, to give dihydropyrazionone 287 (Section 1.8.1).20 Although this methodology looked promising, we were not able to obtain azide 281 from indole 237. When 237 was treated with DDQ and TMSN3 in either THF or CHCl3 at various temperatures (-40 °C to room temperature), no desired product was observed. At temperatures below 0 °C, most of the starting material was recovered, and at temperatures higher than 0 °C, decomposition occurred.

Figure 3-31: Synthesis of bisindole via an azide intermediate.
Another approach to add an azido group might utilize substitution of a suitably activated hydroxyl group. The alcohol substrate could come from the reduction of the ketone that was generated by DDQ oxidation. To test the feasibility of this approach, we began our studies with our tryptamine model (Figure 3-32). Indolyl ketone 288 was synthesized in 2 steps from tryptamine (257) following Nicolaou’s method. Reduction of ketone 288 with NaBH₄ only resulted in recovered starting material. To increase the electrophilicity of the carbonyl group, we protected the indole nitrogen in 288 with Boc₂O to give N-protected indole 289 in 82% yield over 2 steps. As we expected, reduction of ketone 289 with NaBH₄ went smoothly to give alcohol 290 in quantitative yield. Substitution of the hydroxyl group was carried out by treating alcohol 290 with DPPA in the presence of DBU to generate azido indole 291 in 85% yield. Reduction of the azide group in 291 and subsequent coupling between the resulting amine and indolyl oxoacetyl chloride 130 afforded bisindole 292 in 75% yield over 2 steps. Bisindole 292 could be deprotected with either TFA or formic acid. TFA-mediated deprotection benefited a shorter reaction time (< 1 h) but proceeded in slightly lower yield (66%), whereas formic acid required a much longer reaction time (48 h) but afforded a slightly higher yield (75%). Dihydropyrazine 287 was then oxidized with DDQ in refluxing benzene to furnish the pyrazinone product 45 in 37% yield. Alternatively, the last 2 steps could be consolidated by heating bisindole 292 in air. Not only did deprotection of the Boc groups and cyclization occur, but also oxidation took place to furnish pyrazinone 45 when bisindole 292 was heated at 180 °C with exposure to air. Yields of 45 for both reactions were relatively low due to its insolubility in most organic solvents, which led to problems with column chromatography.
Figure 3-32: Successful route to construct model bisindolyl pyrazinone 45 from tryptamine.

With this success, we then turned to our tetracyclic system (Figure 3-33). Reduction of ketone 240 resulted in a ~ 1:1 mixture of alcohols 293a and 293b. This
crude mixture was carried on to generate a diastereomeric mixture of azides $281a$ (see Chapter 4 for NOE signals) and $281b$ (47% and 17% yields, respectively, over 2 steps) along with the recovery of a single diastereomer of the starting material, presumably $293b$ (15% yield). Although a diastereomeric mixture was obtained in these two steps, it would not present a problem at the end of the synthesis as aromatization would convert this stereogenic $sp^3$ carbon to an $sp^2$ carbon. However, formation of alcohol $293a$ was favored as it would all be converted to azide $281a$. It is possible that alcohol $293b$ was less reactive toward nucleophilic substitution because the bulky N-Boc group hindered nucleophile attack from the top face of the substrate. To test for the stereoselectivity of ketone reduction, we employed bulkier reducing reagents (i.e. LiAl(OtBu)$_3$H, L-Selectride, LiBEt$_3$H, DIBAL, and Al(OiPr)$_3$) with the expectation that the Boc group would block these reagents from attacking from the top face, and more $293a$ would be obtained. However, all attempts only led to the recovery of the starting ketone or deprotection of the indole.

We then attempted to reduce azides $281a$ and $281b$ with catalytic hydrogenation (Pd/C) as in our tryptamine model. However, this reaction led only to a complex mixture of uncharacterized products. Fortunately, when the azides were treated with NaBH$_4$ in the presence of NiCl$_2$·6H$_2$O, the desired amines were obtained. Subsequent treatment of this amine mixture with indolyl oxoacetyl chloride $130$ in the presence of Et$_3$N afforded bisindole $294$ in 65% yield over 2 steps. Removal of the Boc groups in $294$ with refluxing formic acid/1,2-dichloroethane only resulted in a complex mixture. Treatment of $294$ with TFA led to promising products, but reproducibility and isolation of the desired products became our biggest problems as decomposition often took place and we
could not obtain good NMR spectra of these compounds. When the deprotected derivatives of 294 were carried on and treated with DDQ in refluxing benzene, decomposition took place. Fortunately, the desired pyrazinone 247 was obtained in one step in 32% yield when 294 was heated at 180 °C in air for 1 h. Extensive decomposition also took place at this temperature and optimization using lower temperatures or shorter reaction times will be needed to obtain a better yield of 247.
Figure 3-33: Synthesis of dragmacidin E analogue.
3.3 Attempts toward the synthesis of dragmacidin E

3.3.1 Witkop photocyclization

We started with the synthesis of a 7-hydroxy indole derivative following Bartoli’s indole synthesis in order to synthesize a precursor for the Witkop photocyclization.67 It was reported by Gilmore that when 1-benzyloxy-2-nitrobenzene (296a) was treated with vinylmagnesium bromide under Bartoli’s general conditions, only 13% yield of 7-benzyloxy indole (297a) was obtained (Figure 3-34).68 The yield could be improved by replacing the benzyl group with bulkier substituents, and Gilmore discovered that the benzhydryl group gave the highest yield of 7-hydroxy indole derivative 297b (57% yield). As a result, we chose to alkylate 2-nitrophenol (298) with benzhydryl bromide (299), instead of benzyl bromide as we originally intended, to give 2-benzhydryloxy nitrobenzene (296b) in 93% yield (Figure 3-35). When the protected nitrophenol 296b was treated with vinylmagnesium bromide in acetonitrile (-40 ºC to rt), the desired indole 297b was obtained in 55% yield, which was comparable to the results obtained by Gilmore. This indole then was treated with phosphorus (V) oxychloride in DMF according to the standard conditions of the Vilsmeir-Haack reaction69 to give aldehyde 300 in 93% yield.
It was reported by Schmidt and Wild that indolyl alkene 303 could be generated as a Z/E > 50 mixture from the reaction of phosphonate 302 and aldehyde 301 (Figure 3-36). Based on this example, we planned to carry out the olefination of our aldehyde with a phosphonate ester under similar conditions. It also was reported by Kozikowski and Greco that olefination of indolecarboxaldehyde 304 took place to generate indolyl alkene 306 without the need to protect the indole. Therefore, we planned to form our
alkene using \( N \)-unprotected indolcarboxaldehyde 300. With 300 in hand, we needed to synthesize an appropriate phosphonate ester, which was prepared as follows (Figure 3-37): Acylation of glycine methyl ester (307) with 2,2-dichloropropionyl chloride (207) gave dichloroacetamide 308 (80\% yield), which was brominated with NBS to generate bromoamide 309. The Michalis-Arbuzov reaction of bromoamide 309 with trimethyl phosphite afforded the desired phosphonate 310 as a crude white solid in quantitative yield, which was carried on without purification.

Figure 3-36: Schmidt and Kozikowski’s olefin syntheses.
However, attempts to perform a Horner-Wadsworth-Emmons reaction with 310 and aldehyde 300 to generate alkene 313 only resulted in recovered starting material (Figure 3-38). This failure could be a result of deprotonation of the indole NH by the ylide intermediate (or unconsumed NaH). Therefore, we protected indolyl aldehyde 300 with 4-nitrophenyl 2-(trimethylsilyl)ethyl carbonate (311) to generate N-TEOC indolecarboxaldehyde 312 (92% yield). When 312 was treated with the phosphorus ylide, generated in situ from phosphonate 310 and DBU, the desired alkene 314 was obtained in good yield (84%). In this olefination, only the Z isomer was obtained and none of the E isomer was observed. Attempts also were made to protect 300 with CbzCl, as this protecting group could be simultaneously removed during catalytic hydrogenation of the double bond. When 311 was replaced by CbzCl, the reaction gave a very low yield of N-Cbz-7-benzhydryloxy-indole-3-carboxaldehyde (15%) and deprotection of the benzhydryl ether occurred.
Figure 3-38: Olefination of indolecarboxaldehyde 312.

Catalytic hydrogenation of alkene 314 might be accomplished asymmetrically using chiral catalysts such as Rh(COD)$_2$BF$_4$/DIPAMP or BMMP as was reported on similar substrates. However, since the chirality of the aminonitrile formed in the Strecker reaction in our model studies was lost, it was not necessary to generate a chiral product from this asymmetric hydrogenation. Therefore, achiral Wilkinson’s catalyst was selected. This rhodium-containing catalyst was chosen over palladium catalysts because we were concerned that undesired dechlorination of the substrate would take place in the presence of palladium. When we attempted to hydrogenate 314 in toluene at room temperature, the double bond was fully reduced and the benzhydryl ether was left untouched to generate methyl 7-benzhydrylindolyl propionate 315 in 76% yield (Figure 3-39). Concomitant O-benzhydryl removal occurred when the reaction was carried out in
a 1:1 mixture of toluene and methanol at 45 °C to afford methyl 7-hydroxyindole propionate 316 in 98% yield. It was important that the reaction temperature was kept around 45 °C since lower temperatures resulted in longer reaction times or recovered starting material due to the low solubility of 314 in MeOH at low temperatures. Higher temperatures (> 60 °C) resulted in a complex mixture of products including those with demono and dedichlorination and/or decomposition. Removal of the silyl groups of 315 and 316 with TBAF led to dichloroamides 317 and 318 as the precursors for photocyclization in 95% and 96% yields, respectively.

Figure 3-39: Hydrogenation and deprotection of the Witkop photocyclization precursors.
When dichloroamide \textbf{317} was irradiated at 254 nm, a complex mixture was obtained (Figure 3-40). This complication could be a result of the bulky benzhydryl protecting group, which contains two aromatic rings capable of becoming involved in a radical process during photocyclization. We speculated that a smaller protecting group such as a benzyl group might reduce the chance of being involved in a radical process. Therefore, the benzyl ether analogue of \textbf{317} was synthesized in a similar manner. Irradiation of this substrate also produced a complex mixture. As a result, we turned to our hydroxyindole substrate \textbf{318}, which was not our first choice since we would have to introduce a protecting group selectively on to this hydroxyl group later in the synthesis. Surprisingly, photocyclization of \textbf{318} furnished the desired 3,4-bridged indole \textbf{320} in 66% yield. The yield was slightly higher than in our model studies, perhaps as a consequence of the stabilizing effect of the hydroxyl group on the radical cation (Section 2.3). In fact, the isolated yield of \textbf{320} should have been higher since the crude $^1$H NMR spectrum showed almost exclusively the desired product with a trace amount of another alkene isomer, presumably the 2,3-bridged indole \textbf{321}. This low isolated yield might be a result of the product’s insolubility and instability. In addition, decomposition of \textbf{320} seemed to take place even during chromatography; exposure of this compound to air for days led to extensive decomposition. It also should be noted that the starting material \textbf{318} itself is not stable, and turned from white to brown on exposure to air overnight and black after a few days. Storing this compound in a freezer slowed down the decomposition process, but complete decomposition did occur after a few months. As a result, deprotection of \textbf{316} to provide \textbf{318} was carried out immediately before the compound was used.
3.3.2 Construction of a tetracyclic ring system

The phenolic hydroxyl group of the cyclized product (320) was protected with BnBr (81% yield) and following our model studies, both of the NH groups then were protected with (Boc)$_2$O to furnish 322 (69% yield) (Figure 3-41). Reductive Dieckmann cyclization of alkene 322 followed by Boc protection of the intermediate amide gave the bridged imide 323 in 90% yield. Hydrolysis of the imide in 323 led to a ~2:1 diastereomeric mixture of ketones 324a and 324b in 89% yield. When a mixture of ketones 324a and 324b was treated under the Strecker conditions used in our model studies, the desired aminonitrile 325b was obtained in only 38% yield along with the undesired diastereomer 325a (see Chapter 4 for NOE signals) in 19% yield. It should be noted that the yield of this reaction was not always reproducible as decomposition easily occurred when the reaction was carried out at high temperatures (> 70 ºC) or when the
reaction was performed on a small scale (< 500 mg). We also found that saturated NH₃ in MeOH had to be freshly prepared to get a reasonable yield although this requirement was not a problem at all with our model studies. We speculated that this low yield might be a result of an electronic effect of the benzyl ether since a steric effect seemed to be impossible due to the great distance between the benzyl and the carbonyl groups. With the presence of the electron donating benzyl ether on the indole, the electrophilicity of the carbonyl group might be attenuated. Therefore, the benzyl group was replaced with an electron-withdrawing Boc group as we expected that this modification would increase the electrophilicity of the ketone carbonyl. However, this switch resulted in no improvement of the yield of the desired product (< 18% yield). A different cyanide reagent (TBSCN) was also employed in place of TMSCN as the bulkier TBS group was expected to result in greater facial selectivity. However, this change produced no significant improvement.

With the desired aminonitrile in hand, we protected the newly formed amine with methyl chloroformate to give carbamate 326 (see Chapter 4 for NOE signals) in 89% yield. Reduction of the cyano group of 326, and subsequent formation of the cyclic imidazolone under basic conditions, gave imidazolone 327 in 43% yield over 2 steps. Oxidation of indole 327 with DDQ (68% yield), and protection of the indole with (Boc)₂O (55% yield) furnished the desired ketone 328.
Figure 3-41: Construction of a tetracyclic ring system of dragmacidin E.

3.4 Future work

Future work on this problem will involve optimization of the Strecker reaction of ketone 324a and 324b. The ketone substrates will be modified with various protecting groups such as TBS, TIPS and Ts on the phenol in order to test how these protecting
groups affect the yield of the desired product. In addition, ketone 328 will be carried on to complete the synthesis of dragmacidin E following the chemistry developed in our model studies (Figure 3-42). Specifically, the required sequence includes 1) formation of azide 329, 2) reduction of the azide and acylation of the resulting amine to form bisindole 330, and 3) deprotection, cyclization and oxidation to afford pyrazinone 331. To complete the synthesis, we will follow Stoltz’s strategy by removing the protecting group before forming the guanidine unit. The benzyl ether of 331 will be removed by TMSI as in the case of dragmacidin D synthesis. Treatment of the resulting unprotected substrate with Lawesson’s reagent would result in thiourea 332. Nucleophilic displacement of the thiocarbonyl with ammonia would convert it into a guanidine moiety. Following the example of dragmacidin D synthesis, this guanidine would be treated with TFA to obtain the natural product as a TFA salt.

There are a few precedents supporting the selective conversion of the urea carbonyl to the corresponding thiocarbonyl. For example, hydantoin 333 was converted into thiourea 334 in good yield without interference by the amide carbonyl (Figure 3-43).73 Similarly, urea 335 was transformed into thiourea 336 in comparable yield.74 There are numerous examples of how to transform a thiourea to a guanidine with NH₃ in the presence of a base such as diisopropylethylamine,75 so this transformation might not present a problem in our synthesis.
Figure 3-42: Proposed plan to complete the synthesis of dragmacidin E.

Figure 3-43: Precedents for the conversion of a urea carbonyl to a thiocarbonyl.
If the thiourea $\rightarrow$ guanidine transform is problematic, an alternative strategy would be explored. Following a procedure developed by Jacobi, treatment of the unprotected analogue of 331 with Meerwein’s salt would afford ethoxyamidine 337 (Figure 3-44). Heating 337 in the presence of ammonium propionate would furnish the desired guanidine. This chemistry has been successfully applied to the synthesis of dibromophakellin in our research group. Alternatively, we might be able to hydrolyze the urea under harsh basic or acid conditions to form diamine 338. The reaction is well preceded, but only on simple molecules such as cyclic ureas 339 and 341 (Figure 3-45). If we have success in this transformation, the resulting diamine would be treated with cyanogen bromide (NCBr) to provide the desired guanidine. It should also be noted that reintroduction of a protecting group on the hydroxyl group might be needed. If this protection is required in this case, (Boc)$_2$O will be used as this carbonate could be removed by TFA at the end of the synthesis.
3.5 Conclusion

We have been able to synthesize the dragmacidin E core 247 in a model system in 17 steps (0.95% overall yield) from tryptophan methyl ester. Construction of the 7-membered bridge at C(3) and C(4) of the indole nucleus was accomplished by employing
a Witkop photocyclization and a reductive Dieckmann cyclization. The two indole moieties were brought together by acylation followed by deprotection, cyclization and aromatization to furnish the desired product. Unfortunately, racemization occurred during an intermediate Strecker reaction. Thus far, all attempts to circumvent this problem have failed. Toward the synthesis of dragmacidin E, a tetracyclic indolyl ketone 328 has been prepared. Following our model studies, we should be able to synthesize the dragmacidin E core 331. As a future plan, the amidazolone unit would be converted to a guanidine and removal of the benzyl ether would reveal the natural product.
Chapter 4

Experimentals

**Material and Methods.** Unless stated otherwise, moisture and oxygen sensitive reactions were carried out in flame-dried glassware under a nitrogen or argon atmosphere using anhydrous, deoxygenated solvents. Tetrahydrofuran was dried by passage through an activated alumina column under a nitrogen atmosphere or distillation from sodium benzophenone ketyl under an argon atmosphere. Dichloromethane and acetonitrile were dried by passage through an activated alumina column under a nitrogen atmosphere or distillation from calcium hydride under an argon atmosphere. HPLC grade acetonitrile was used as received for large scale photochemical reactions and it did not significantly lower the yield of the product. Methanol was dried by passage through an activated alumina column under a nitrogen atmosphere or distillation from magnesium under a nitrogen or argon atmosphere. Absolute ethanol was used as received. All other solvents were dried by passage through an activated alumina column under a nitrogen atmosphere. All other commercially obtained reagents were used as received. Flash chromatography was performed on 32-63 µm silica gel. Melting points were taken with a Melt-Temp apparatus and are uncorrected. Chemical shifts of $^1$H NMR spectra are reported relative to Me$_4$Si ($\delta$ 0.00), DMSO-d6 ($\delta$ 2.49) or acetone-d6 ($\delta$ 2.04) if the former was absent. $^{13}$C NMR spectra are reported relative to Me$_4$Si ($\delta$ 0.0), CDCl$_3$ ($\delta$ 77.0), DMSO-d6 ($\delta$ 39.5) or acetone-d6 ($\delta$ 29.8) if the former was absent.
Methyl 2-(2,2-Dichloropropionylamino)-3-(1H-indol-3-yl)propionate (208).

To a solution of 2,2-dichloropropionic acid (90%, 6.7 mL, 59 mmol) in CH₂Cl₂ (50 mL) was added 2 drops of DMF followed by oxalyl chloride (10.0 mL, 119 mmol). The reaction mixture was stirred for 2.5 h until bubbling stopped. The resulting yellow acid chloride solution was concentrated under reduced pressure and then redissolved in CH₂Cl₂ (40 mL). The acid chloride solution was cannulated to an ice-cooled solution of L-tryptophan methyl ester hydrochloride (10.01 g, 39 mmol) and dimethylaminopyridine (DMAP) (10.05 g, 82 mmol) in CH₂Cl₂ (60 mL). The resulting red solution was stirred in an ice bath for 3 h and then at room temperature for 12 h. The reaction mixture was poured into ice water (50 mL) and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc) to afford the dichloroamide 208 as a light brown solid (13.13 g, 97%). mp 143-144 °C; [α]₂⁰° +51° (c 1.00, CHCl₃); IR (film) 3368, 3315, 1728, 1678 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.26 (br s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.29 (br s, 1H), 7.19 (ddd, J = 8.0, 7.0, 1.3 Hz, 1H), 7.11 (ddd, J = 7.8, 7.0, 1.1 Hz, 1H), 7.02 (d, J = 2.1 Hz, 1H), 4.86 (ddd, J = 7.7, 5.3, 5.3 Hz, 1H), 3.69 (s, 3H), 3.42 (dd, J = 18.5, 5.2 Hz, 1H), 3.37 (dd, J =
18.9, 5.1 Hz, 1H), 2.25 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.4, 165.9, 136.1, 127.3, 123.0, 122.3, 119.7, 118.5, 111.3, 109.2, 82.1, 53.8, 52.6, 33.9, 27.2; LRMS(ESI) m/z (relative intensity) 365.0 (100%, M+Na$^+$); HRMS (ESI) m/z calcd for [C$_{15}$H$_{16}$N$_2$O$_3$Cl$_2$Na]$^+$: 365.0436, found 365.0426.

Methyl 7-Methylene-6-oxo-1,3,4,5,6,7-hexahydroazocino[4,5,6-cd]indole-4-carboxylate (209). A solution of dichloroamide 208 (150 mg, 0.44 mmol) in CH$_3$CN (87.5 mL) in a quartz vessel was degassed by passage of dry nitrogen for 30 min prior to, and during, irradiation. This solution was irradiated at 254 nm in a Rayonet photochemical reactor for 30 min. The resulting light brown solution was concentrated under reduced pressure. The $^1$H NMR spectrum of the crude residue showed 209:210 ~ 5:1. This residue was purified by flash chromatography on silica gel (1:3 hexanes/EtOAc) to afford the bridged indoles 209 (63 mg, 53%) and 210 (9 mg, 8%) as yellow solids. Major Product (209): mp 194-195 °C; [$\alpha$]$^2$$_D$ -347° (c 0.60, CHCl$_3$); IR (film) 3305, 1741, 1653 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.42 (br s, 1H), 7.35 (ddd, $J$ = 8.2, 4.5, 3.5 Hz, 1H), 7.20-7.15 (m, 2H), 7.07 (dd, $J$ = 1.3, 1.2 Hz, 1H), 6.33 (d, $J$ = 9 Hz, 1H), 5.60 (d, $J$ = 0.9 Hz, 1H), 5.50 (d, $J$ = 0.7 Hz, 1H), 5.07 (ddd, $J$ = 11.8, 9.0, 2.8 Hz, 1H), 3.84 (s, 3H), 3.56 (ddd, $J$ = 16.3, 3.0, 0.9 Hz, 1H), 3.29 (ddd, $J$ = 16.3, 11.8, 0.9 Hz, 1H), 3.09 (s, 3H), 2.95 (s, 3H), 2.51 (s, 3H), 2.37 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.8, 165.9, 134.1, 127.4, 123.0, 122.4, 119.0, 118.5, 111.3, 109.2, 82.1, 52.5, 33.8, 27.2; LRMS(ESI) m/z (relative intensity) 357.0 (100%, M+Na$^+$); HRMS (ESI) m/z calcd for [C$_{15}$H$_{16}$N$_2$O$_3$Cl$_2$Na]$^+$: 357.0436, found 357.0426.
$^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.7, 171.7, 147.8, 136.6, 129.8, 124.2, 122.9, 122.0, 121.7, 116.6, 112.2, 110.4, 55.7, 52.9, 33.1; LRMS(ESI) $m/z$ (relative intensity) 293.1 (97%, M+Na$^+$); HRMS (ESI) $m/z$ calcd for [C$_{15}$H$_{14}$N$_2$O$_3$Na]$^+$: 293.0896, found 293.0902. Anal. Calcd for C$_{15}$H$_{14}$N$_2$O$_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.75; H, 5.32; N, 10.20.

Minor Product (210): mp 118-120 °C; IR (film) 3307, 1740, 1658 cm$^{-1}$; $^1$H NMR (300 MHz, acetone-d6) δ 10.28 (br s, 1H), 7.49 (d, $J = 7.9$ Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.19 (br s, 1H), 7.15 (dt, $J = 7.0$, 1.1 Hz, 1H), 7.03 (dt, $J = 7.5$, 1.0 Hz, 1H), 6.07 (s, 1H), 6.00 (s, 1H), 4.59 (ddd, $J = 9.3$, 6.0, 2.8 Hz, 1H), 3.74 (s, 3H), 3.40 (dd, $J = 16.7$, 2.8 Hz, 1H), 3.22 (dd, $J = 16.7$, 9.4 Hz, 1H); $^{13}$C NMR (75 MHz, acetone-d6) δ 171.8, 169.6, 137.5, 129.3, 129.2, 124.0, 121.5, 120.1, 119.4, 112.0, 111.8, 54.6, 53.1, 30.1, missing one $sp^2$ C; LRMS(ESI) $m/z$ (relative intensity) 271.1 (100%, M+H$^+$); HRMS (ESI) $m/z$ calcd for [C$_{15}$H$_{15}$N$_2$O$_3$]$^+$: 271.1083, found 271.1096.

![211](image)

1,5-Di-tert-butyl 4-Methyl-7-methylene-6-oxo-3,4,6,7-tetrahydroazocino[4,5,6-cd]indole-1,4,5-tricarboxylate (211). A solution of di-tert-butyldicarbonate (Boc$_2$O) (1.13 g, 5.18 mmol) in CH$_3$CN (6 mL) was cannulated into a suspension of indole 209 (335 mg, 1.24 mmol) and DMAP (34 mg, 0.28 mmol) in CH$_3$CN (6 mL). After the
addition was complete, the indole 209 slowly became soluble and it all went into solution in less than 10 min. The reaction mixture was stirred at room temperature for 2 h. The resulting dark brown solution was poured into ice water (20 mL) and extracted with ether (3 x 20 mL). The organic extracts were combined, washed with brine solution (20 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3:2 hexanes/ether) to afford the desired protected product 211 as a white solid (446 mg, 77%). mp 118-120 °C; [α]°D +61° (c 1.00, CHCl₃); IR (film) 1734, 1693 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.30 (d, J = 6.5 Hz, 1H), 7.53 (s, 1H), 7.38-7.29 (m, 2H) 6.47 (d, J = 1.0 Hz, 1H), 6.05 (d, J = 1.0 Hz, 1H), 4.77 (dd, J = 12.7, 4.3 Hz, 1H), 3.85 (s, 3H), 3.30 (dd, J = 15.3, 4.3 Hz, 1H), 3.11 (ddd, J = 15.2, 12.8, 1.2 Hz, 1H), 1.67 (s, 9H), 1.08 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 174.3, 170.7, 151.4, 149.0, 144.6, 136.6, 129.5, 129.4, 127.2, 125.7, 124.3, 124.0, 116.1, 115.7, 83.9, 82.9, 57.4, 52.6, 28.1, 27.4, 26.7; LRMS(ESI) m/z (relative intensity) 493.2 (100%, M+Na⁺); HRMS (ESI) m/z calcd for [C₂₅H₃₀N₂O₇Na]⁺: 493.1951, found 493.1944. Anal. Calcd for C₂₅H₃₀N₂O₇: C, 63.82; H, 6.43; N, 5.95. Found: C, 63.83; H, 6.47; N, 5.83.
1,5-Di-tert-butyl 4-Methyl-7-methyl-6-oxo-3,4,6,7-tetrahydroazocino[4,5,6-cd]indole-1,4,5-tricarboxylate (200a and 200b). To a solution of indole 211 (483 mg, 1.03 mmol) in MeOH (15 mL) was added 10% w/w Pd/C (22 mg, 0.02 mmol). The reaction mixture was stirred under a H₂ atmosphere (1 atm) for 2 days. The resulting black suspension was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether) to afford both the trans-methyl imide 200a as a white solid (309 mg, 62%) and the cis-methyl imide 200b as a white solid (49 mg, 10%). Major product: mp 167-168°C; [α]²⁰D -296° (c 1.00, CHCl₃); IR (film) 1734 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.07 (d, J = 8.1 Hz, 1H), 7.44 (s, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 5.59 (t, J = 9.5 Hz, 1H), 4.48 (q, J = 6.6 Hz, 1H), 3.84 (s, 3H), 3.57 (d, J = 9.5 Hz, 2H), 1.67 (d, J = 6.8 Hz, 3H), 1.65 (s, 9H), 1.00 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 175.9, 172.0, 153.3, 149.3, 135.6, 130.9, 129.0, 125.0, 124.5, 119.6, 114.9, 114.4, 83.8, 82.3, 56.0, 52.9, 43.9, 29.6, 28.1, 27.2, 12.2; LRMS(ESI) m/z (relative intensity) 495.1 (30%, M+Na⁺); HRMS (ESI) m/z calcld for [C₂₅H₃₂N₂O₇Na]⁺: 495.2107, found 495.2111.

Minor product: mp 96-98°C; [α]²⁰D +216° (c 0.33, CHCl₃); IR (film) 1737, 1700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.21 (d, J = 8.2 Hz, 1H), 7.50 (s, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.07 (d, J = 7.2 Hz, 1H), 4.74 (br d, J ~ 8.7 Hz, 1H), 4.54 (br q, J ~ 5.6 Hz, 1H),
3.82 (s, 3H), 3.32 (dd, \(J = 15.4, 4.5\) Hz, 1H), 3.06 (dd, \(J = 14.7, 12.5\) Hz, 1H), 1.66 (s, 9H), 1.50 (d, \(J = 7.3\) Hz, 3H), 1.16 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 183.5, 170.9, 151.5, 149.1, 137.5, 135.4, 126.8, 125.7, 125.6, 124.3, 115.4, 114.3, 83.8, 83.2, 56.8, 52.6, 49.5, 28.2, 27.9, 27.6, 21.4; LRMS(ESI) \(m/z\) (relative intensity) 495.1 (72%, M+Na\(^+\)); HRMS (ESI) \(m/z\) calcd for \([C_{25}H_{32}N_2O_7Na]^+\): 495.2107, found 495.2101.

**Oxoamide 213** and **Oximide 214.** **Method A:** To an ice-cooled solution of \textit{trans-200a} (339 mg, 0.72 mmol) in THF (10 mL) was added slowly a 1 M lithium hexamethyldisilazide (LHMDS) solution in THF (800 \(\mu\)L, 0.80 mmol). The reaction mixture was stirred at room temperature for 15 h. The resulting yellow solution was poured into a 1 M aq. H\(_3\)PO\(_4\) solution (10 mL) and extracted with ether (3 x 20 mL). The combined organic extracts were dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3:2 hexanes/ether and 1:4 hexanes/\(\text{EtOAc}\), respectively) to afford the bridged amide 213 as a white solid (169 mg, 69%) and its \(N\)-protected analogue 214 as a light yellow solid (46 mg, 15%).

**Method B1:** A solution of indole 211 (604 mg, 1.28 mmol) in THF (15 mL) was cooled to -78 °C and a 1 M solution of \(N\)-Selectride in THF (1.42 mL, 1.42 mmol) was added slowly. The reaction mixture was stirred at -78 °C for 1 h and then at room
temperature for 4 h. The resulting red solution was poured into ice water (15 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:3 hexanes/EtOAc and 100% EtOAc, respectively) to afford the bridged amide 213 as a light yellow solid (333 mg, 76%).

**Method B2:** A solution of Boc₂O (1.92 g, 8.80 mmol) in CH₃CN (20 mL) was cannulated into a suspension of amide 213 (1.49 g, 4.38 mmol) and DMAP (54 mg, 0.44 mmol) in CH₃CN (20 mL). After the addition was complete, the indole 213 slowly became soluble and it all went into solution in less than 10 min. The reaction mixture was stirred at room temperature for 1 h. The resulting slightly yellow solution was poured into ice water (30 mL) and extracted with ether (3 x 30 mL). The organic extracts were combined, washed with brine solution (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3:2 hexanes/ether) to afford the desired protected product 214 as a white solid (1.93 g, quantitative). **Oxoamide 213:** mp 206-208 °C; [α]²⁰ D +24° (c 0.52, CHCl₃); IR (film) 3241, 1774, 1733, 1704 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.17 (d, J = 8.2 Hz, 1H), 7.48 (s, 1H), 7.46 (br s, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.24 (dd, J = 7.7, 0.9 Hz, 1H), 4.46 (ddd, J = 4.1, 3.0, 1.3 Hz, 1H), 3.27 (ddd, J = 17.0, 4.0, 1.0 Hz, 1H), 1.73 (s, 3H), 1.62 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 209.8, 175.1, 149.0, 135.8, 128.8, 126.5, 124.9, 124.7, 118.9, 115.3, 113.8, 84.1, 60.9, 56.2, 29.3, 28.1, 12.8; LRMS(ESI) m/z (relative intensity) 363.1 (68%, M+Na⁺); HRMS (ESI) m/z calcd for [C₁₉H₂₀N₂O₄Na]⁺: 363.1321, found 363.1317.
Oximide 214: mp 122-124 °C; [α]$_D^{20}$ +10° (c 1.00, CHCl$_3$); IR (film) 1799, 1764, 1742 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.20 (d, $J = 8.2$ Hz, 1H), 7.55 (s, 1H), 7.35 (t, $J = 8.0$ Hz, 1H), 7.25 (dd, $J = 7.6$, 0.9 Hz, 1H), 4.89 (dd, $J = 4.2$, 2.9 Hz, 1H), 3.70 (ddd, $J = 17.1$, 4.3, 0.9 Hz, 1H), 3.16 (ddd, $J = 17.1$, 2.8, 2.0 Hz, 1H), 1.78 (s, 3H), 1.65 (s, 9H), 1.52 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 207.6, 170.6, 149.3, 149.0, 135.8, 127.6, 126.3, 124.9, 124.7, 118.8, 115.5, 113.2, 84.4, 84.2, 64.8, 59.1, 28.1, 27.9, 26.9, 13.4; LRMS(ESI) $m/z$ (relative intensity) 463.2 (65%, M+Na$^+$); HRMS (ESI) $m/z$ calcd for [C$_{24}$H$_{28}$N$_2$O$_6$Na]$^+$: 463.1845, found 463.1841.

Aminonitrile 222. To a suspension of amide 214 (1.00 g, 2.28 mmol) in MeOH (23 mL) was added saturated NH$_3$/MeOH (3.4 mL) followed by titanium isopropoxide (810 µL, 2.74 mmol). The reaction mixture was stirred at room temperature for 1 h, and then trimethylsilylcyanide (TMSCN) (1.20 mL, 9.00 mmol) was added. The reaction mixture was stirred for an additional 4 h. The resulting yellow solution was poured into ice water (25 mL) and extracted with CH$_2$Cl$_2$ (3 x 75 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:2 hexanes/ether) to afford the aminonitrile 222 as a white solid (736 mg, 69%). mp 154-156 °C; [α]$_D^{20}$ +56° (c 0.80, CHCl$_3$); IR (film) 3381, 3320, 2254, 1785, 1736 cm$^{-1}$; $^1$H NMR (300 MHz,
CDCl$_3$) δ 8.22 (dd, $J = 6.4$, 2.6 Hz, 1H), 7.53 (s, 1H), 7.38-7.31 (m, 2H), 4.96 (dd, $J = 3.7$, 3.0 Hz, 1H), 3.69 (ddd, $J = 17.8$, 3.9, 0.9 Hz, 1H), 3.24 (ddd, $J = 17.8$, 2.6, 2.1 Hz, 1H), 2.05 (s, 3H), 1.74 (s, 2H), 1.65 (s, 9H), 1.52 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.8, 149.4, 149.0, 135.6, 127.6, 127.1, 125.0, 124.8, 122.3, 121.6, 116.2, 113.9, 84.4, 84.2, 62.9, 60.5, 56.7, 28.2, 27.9, 25.1, 18.9; LRMS(ESI) m/z (relative intensity) 489.1 (88%, M+Na$^+$); HRMS (ESI) m/z calcd for [C$_{25}$H$_{30}$N$_4$O$_5$Na]$^+$: 489.2114, found 489.2110.

$\text{N-Moc Aminonitrile 223}$. To a mixture of aminonitrile 222 (602 mg, 1.29 mmol) and K$_2$CO$_3$ (357 mg, 2.58 mmol) was added THF (13 mL) followed by methylchloroformate (MocCl) (220 µL, 2.61 mmol). The reaction mixture was heated to reflux for 20 h. The resulting yellow solution was allowed to cool to room temperature, poured into ice water (15 mL), and extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:2 hexanes/ether) to afford the desired protected amine 223 as a white solid (527 mg, 78%). mp 164-166 °C; [$\alpha$]$^{20}_D$ +43° (c 0.76, CHCl$_3$); IR (film) 3301, 2256, 1790, 1732 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.24 (app.t, $J = 4.3$ Hz, 1H), 7.51 (s, 1H), 7.38-7.28 (m, 2H), 5.38 (br s, 1H), 5.19 (br s, 1H), 3.65 (d, $J = 18.8$ Hz, 1H), 3.60 (s, 3H), 2.98 (d, $J = 17.9$...
Hz, 1H), 2.08 (s, 3H), 1.65 (s, 9H), 1.49 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.2, 155.1, 148.8, 148.7, 135.5, 127.4, 125.5, 124.8, 124.6, 122.5, 118.0, 116.6, 113.8, 84.3, 84.1, 61.9, 60.4, 55.4, 52.8, 27.8, 27.6, 24.9, 19.1; LRMS(ESI) $m/z$ (relative intensity) 547.2 (60%, M+Na$^+$); HRMS (ESI) $m/z$ calcd for [C$_{27}$H$_{32}$N$_4$O$_7$Na]$^+$: 547.2169, found 547.2165.

![Image of chemical structure]

**N-Moc Amine 224.** To a solution of aminonitrile 223 (669 mg, 1.28 mmol) in a 1:1 mixture of MeOH and EtOH (40 mL) was added PtO$_2$ (145 mg, 0.64 mmol) followed by a 10% solution of HCl in MeOH (1.05 mL, 1.27 mmol). The reaction mixture was placed in a sealable metal container equipped with a gas inlet and pressure gauge and pressurized with H$_2$ at 1500 psi for 17 h. The resulting clear and colorless solution with settled black particles was filtered through a Celite pad and the filtrate was poured into ice water (20 mL) and extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure to give the crude residue as a white solid (674 mg). The crude residue was carried on to the next step without purification. IR (film) 3401, 1782, 1731 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.20 (d, $J = 7.9$ Hz, 1H), 7.47 (s, 1H), 7.34-7.27 (m, 2H), 4.83 (br s, 1H), 4.77 (s, 1H), 3.76 (d, $J = 13.7$ Hz, 1H), 3.61 (dd, $J = 18.1$, 3.3 Hz, 1H), 3.48 (s, 3H), 3.24 (d, $J = 13.7$ Hz, 1H), 3.03 (d, $J = 17.9$ Hz, 1H), 1.81 (s, 3H), 1.65 (s, 9H), 1.49 (s, 9H), 1.32 (br s,
2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.6, 155.9, 149.7, 149.0, 135.6, 129.4, 128.2, 124.3, 124.1, 121.9, 115.7, 115.6, 83.7, 83.2, 62.7, 61.2, 56.9, 51.9, 46.2, 27.9, 27.8, 25.8, 16.2; LRMS(ESI) $m/z$ (relative intensity) 529.2 (72%, M+H$^+$); HRMS (ESI) $m/z$ calcd for [C$_{27}$H$_{37}$N$_4$O$_7$]$^+$: 529.2662, found 529.2656.

Spirocyclic Imidazolone 225. To a solution of amine 224 (674 mg, 1.28 mmol) in THF (25 mL) was added a deoxygenated 1 M aq. LiOH solution (5.1 mL, 5.1 mmol). The reaction mixture was heated to reflux for 17 h. The resulting slightly yellow solution was allowed to cool to room temperature and then poured into ice water and extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure to give a yellow solid (600 mg). Cold ether (10 mL) was added to the resulting yellow solid to dissolve impurities and the desired cyclic urea 225 was collected by filtration (394 mg, 62% over 2 steps). mp 248 $^\circ$C (dec.); [\(\alpha\)]$_D$ $^{20}$ +88$^\circ$ (c 1.00, DMSO); IR (film) 3344, 1782, 1730, 1687 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 8.45 (s, 1H), 8.08 (d, $J$ = 8.2 Hz, 1H), 7.82 (s, 1H), 7.73 (s, 1H), 7.58 (d, $J$ = 7.9, 1H), 7.30 (t, $J$ = 8.1 Hz, 1H), 4.27 (dd, $J$ = 12.4, 3.1 Hz, 1H), 3.83 (dd, $J$ = 16.1, 2.9 Hz, 1H), 3.60 (d, $J$ = 10.4 Hz, 1H), 3.34 (s, 3H), 3.21 (d, $J$ = 8.9 Hz, 1H), 2.86 (t, $J$ = 13.5 Hz, 1H), 1.60 (s, 9H), 1.46 (s, 9H), 1.43 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-d6) $\delta$ 175.6, 153.7, 150.9, 148.7, 135.4, 132.5, 127.4, 124.4, 124.2, 123.8, 114.3, 113.6,
83.8 81.7, 65.9, 55.1, 53.7, 48.6, 27.8, 27.7, 26.4, 19.4; LRMS (ESI) m/z (relative intensity) 519.2 (52%, M+Na⁺); HRMS (ESI) m/z calcd for [C₂₆H₃₂N₄O₆Na]⁺: 519.2220, found 519.2227.

**tert-Butyl 8-tert-Butoxycarbonylamino-6-methyl-7-oxo-6,7,8,9-tetrahydro-2-azabenzo[cd]azulene-2-carboxylate (227a and 227b).** To an ice-cooled solution of amide 214 (1.029 g, 2.34 mmol) in THF (47 mL) was added a deoxygenated 1 M aq. LiOH solution (4.7 mL, 4.7 mmol). The reaction mixture was stirred in an ice bath for 1 h and then at room temperature for 14 h. The resulting slightly yellow solution was poured into ice water (30 mL) and extracted with ether (3 × 40 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3:2 hexanes/ether) to afford a ~ 2:1 diastereomeric mixture of ketones 227a and 227b as a white solid (951 mg, 98%). Major product (227a): mp 163-164 °C; [α]²⁰_D +29° (c 1.00, CHCl₃); IR (film) 3416, 1729 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, J = 8.1 Hz, 1H), 7.43 (s, 1H), 7.26 (t, J = 7.9 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 5.42 (br s, 1 H), 4.74 (br dd, J = 9.2, 4.6 Hz, 1H), 4.62 (q, J = 6.8 Hz, 1H), 3.60 (dd, J = 15.7, 4.6 Hz, 1H), 3.17
(dd, \( J = 15.8, 4.2 \) Hz, 1H), 1.65 (s, 9H), 1.65 (d, \( J = 6.9 \) Hz, 3H), 1.45 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 206.1, 155.5, 149.2, 135.1, 130.7, 128.3, 125.0, 123.0, 118.7, 116.1, 114.1, 83.5, 79.5, 61.4, 45.7, 28.2, 28.0, 27.6, 14.4; LRMS(ESI) \( m/z \) (relative intensity) 437.2 (100%, M+Na\(^{+}\)); HRMS (ESI) \( m/z \) calcd for [C\(_{23}H_{30}N_{2}O_{5}Na\]^+: 437.2052, found 457.2042. Anal. Calcd for C\(_{23}H_{30}N_{2}O_{5}\): C, 66.65; H, 7.30; N, 6.76. Found: C, 66.59; H, 7.32; N, 6.76.

Minor product (227b): mp 170-171 °C; [\( \alpha \)]\(_{20}^{20}\D +90° \) (c 1.00, CHCl\(_3\)) ; IR (film) 3385, 1720 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.06 (d, \( J = 8.1 \) Hz, 1H), 7.48 (s, 1H), 7.30 (t, \( J = 7.9 \) Hz, 1H), 7.08 (d, \( J = 7.6 \) Hz, 1H), 5.52 (br s, 1 H), 4.50 (q, \( J = 7.0 \) Hz, 1H), 4.43 (br dd, \( J \approx 11.9, 5.7 \) Hz, 1H), 3.29 (dd, \( J = 14.7, 2.7 \) Hz, 1H), 3.19 (ddd, \( J = 15.2, 10.2, 1.4 \) Hz, 1H), 1.66 (s, 9H), 1.64 (d, \( J = 7.0 \) Hz, 3H), 1.45 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 208.8, 154.4, 149.4, 135.6, 130.7, 128.0, 124.9, 123.1, 120.1, 116.1, 113.9, 83.7, 80.0, 58.9, 49.0, 29.3, 28.3, 28.1, 16.4; LRMS(ESI) \( m/z \) (relative intensity) 437.2 (100%, M+Na\(^{+}\)); HRMS (ESI) \( m/z \) calcd for [C\(_{23}H_{30}N_{2}O_{5}Na\]^+: 437.2052, found 437.2060.

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(\(\pm\))-\textit{tert}-Butyl 7-Amino-8-\textit{tert}-butoxycarbonylamino-7-cyano-6-methyl-6,7,8,9-tetrahydro-2-azabenzo[cd]azulene-2-carboxylate (229). A solution of the
diastereomeric mixture of ketones 227a and 227b (645 mg, 1.56 mmol) and NH₄Cl (166 mg, 3.10 mmol) in saturated NH₃/MeOH (15 mL) in a sealed tube was heated to 85 °C for 4 h. The reaction mixture was allowed to cool to room temperature and TMSCN (830 µL, 6.22 mmol) was added. The reaction mixture was stirred in a sealed tube at room temperature for 14 h. The resulting yellow suspension was diluted with CH₂Cl₂ (25 mL) and then poured into ice water (20 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc and 100% EtOAc, respectively) to afford the aminonitrile 229 as a light yellow solid (494 mg, 72%). mp 152-154 °C; [α]D²⁰⁻0.8° (c 1.00, CHCl₃); IR (film) 3326, 2252, 1727 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.00 (d, J = 8.0 Hz, 1H), 7.40 (s, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 5.16 (br d, J = 9.9 Hz, 1H), 4.0 (td, J = 9.8, 2.8 Hz, 1H), 3.70 (q, J = 7.1 Hz, 1H), 3.24 (dd, J = 15.5, 9.5 Hz, 1H), 3.05 (dd, J = 15.7, 2.4 Hz, 1H), 2.05 (br s, 2H), 1.66 (s, 9H), 1.62 (d, J = 7.2 Hz, 3H), 1.45 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.7, 149.5, 135.4, 132.0, 129.1, 124.9, 122.7, 122.3, 121.8, 116.7, 114.5, 83.7, 80.7, 65.2, 57.6, 43.6, 30.4, 28.3, 28.2, 15.6; LRMS(ESI) m/z (relative intensity) 441.2 (35%, M+H⁺); HRMS (ESI) m/z calced for [C₂₄H₃₃N₄O₄]⁺: 441.2502, found 441.2497.
(±)-tert-Butyl 8-tert-Butoxycarbonylamino-7-cyano-7-methoxycarbonylamino-6-methyl-6,7,8,9-tetrahydro-2-azabenzo[cd]azulene-2-carboxylate (235). To a mixture of aminonitrile 229 (84 mg, 0.19 mmol) and K$_2$CO$_3$ (53 mg, 0.38 mmol) was added THF (4 mL) followed by methylchloroformate (MocCl) (100 µL, 1.19 mmol). The reaction mixture was heated to reflux and held there for 20 h. The resulting yellow solution was allowed to cool to room temperature, poured into ice water (10 mL), and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:2 hexanes/ether) to afford the desired product 235 as a white solid (77 mg, 81%). mp 138-140 °C; [α]$^\text{D}$ +0.2° (c 1.00, CHCl$_3$); IR (film) 3328, 2254, 1731, 1689 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.02 (d, $J$ = 8.0 Hz, 1H), 7.42 (s, 1H), 7.27 (t, $J$ = 7.9 Hz, 1H), 7.10 (d, $J$ = 7.3 Hz, 1H), 6.50 (br s, 1H), 5.40 (br d, $J$ = 9.1 Hz, 1H), 4.43 (td, $J$ = 8.5, 5.5 Hz, 1H), 4.42 (q, $J$ = 7.3 Hz, 1H), 3.73 (s, 3H), 3.42 (dd, $J$ = 16.9, 5.1 Hz, 1H), 3.16 (dd, $J$ = 17.1, 7.8 Hz, 1H), 1.65 (s, 9H), 1.47 (s, 9H), 1.44 (d, $J$ = 7.4, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 156.8, 155.1, 149.3, 135.6, 133.1, 127.9, 124.9, 123.2, 123.1, 117.4, 114.4, 141.4, 83.7, 81.4, 65.0, 53.0, 52.4, 43.7, 30.4, 28.08, 28.06, 17.5; LRMS(ESI) $m/z$ (relative intensity) 521.2 (100%, M+Na$^+$);
HRMS (ESI) \( m/z \) calcd for \([C_{26}H_{34}N_4O_6Na]^+\): 521.2376, found 521.2361. Anal. Calcd for \(C_{26}H_{34}N_4O_6\): C, 62.63; H, 6.87; N, 11.24. Found: C, 62.37; H, 6.97; N, 10.99.

(±)-tert-Butyl 7-Aminomethyl-8-tert-butoxycarbonylamino-7-methoxycarbonylamino-6-methyl-6,7,8,9-tetrahydro-2-azabenz\[cd\]azulene-2-carboxylate (236)

To a solution of aminonitrile 235 (358 mg, 0.72 mmol) in MeOH (30 mL) was added cobalt (II) chloride (2.33 g, 17.9 mmol). The resulting dark blue solution was cooled in an ice bath and sodium borohydride (679 mg, 17.9 mmol) was added in portions. The resulting black suspension was stirred at room temperature for 3 h. It was then recooled in an ice bath and additional sodium borohydride (679 mg, 17.9 mmol) was added in portions. The reaction mixture was stirred at room temperature for 38 h. The resulting black suspension was diluted with MeOH (30 mL) and acidified with 1 M \(H_3PO_4\) solution (30 mL). The acidic solution was stirred vigorously for 1 h until it turned pink and clear. The pink solution was diluted with \(CH_2Cl_2\) (30 mL) and made alkaline by the addition of saturated NaHCO₃ (30 mL). The resulting purple precipitate was filtered off and washed with \(CH_2Cl_2\) (30 mL). The organic layer of the filtrate was separated and the aqueous layer was extracted with \(CH_2Cl_2\) (2 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product
was carried on without purification. For characterization purpose, a portion was purified by flash chromatography on silica gel (3:2 hexanes/ether, 3% and 5% saturated NH$_3$/MeOH in CH$_2$Cl$_2$, respectively) to afford the desired amine 236 as a white solid. mp 124-126 °C; [$\alpha$]$^\circ_{20}$D -0.2° (c 1.00, CHCl$_3$); IR (film) 3325, 1729 cm$^{-1}$; $^1$H NMR (300 MHz, C$_6$D$_6$) δ 8.33 (d, $J$ = 7.2 Hz, 1H), 7.23 (s, 1H), 7.11 (t, $J$ = 7.8 Hz, 1H), 6.96 (d, $J$ = 9.5 Hz, 1H), 6.90 (d, $J$ = 6.8 Hz, 1H), 5.78 (s, 1H), 4.73 (td, $J$ = 10.7, 4.6 Hz, 1H), 4.30 (q, $J$ = 7.1 Hz, 1H), 3.76 (d, $J$ = 13.3 Hz, 1H), 3.47 (s, 3H), 3.29 (dd, $J$ = 16.9, 4.6 Hz, 1H), 2.78 (ddd, $J$ = 16.6, 12.1, 1.7 Hz, 1H), 2.64 (dd, $J$ = 13.2 Hz, 1H), 1.52 (s, 9H), 1.39 (s, 9H), 1.24 (d, $J$ = 7.2 Hz, 3H), 0.59 (br s, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 156.4, 155.1, 149.5, 136.4, 135.8, 127.1, 124.5, 123.7, 123.0, 115.6, 113.1, 83.5, 79.8, 62.8, 51.7, 51.3, 43.8, 43.2, 30.2, 28.5, 28.2, 20.5; LRMS(ESI) $m/z$ (relative intensity) 503.2 (100%, M+H$^+$); HRMS (ESI) $m/z$ calcd for [C$_{26}$H$_{39}$N$_4$O$_6$]$^+$: 503.2870, found 503.2874.

(±)-Spirocyclic Imidazolone 237. To a solution of the amine 236 in EtOH (10 ml) was added a 1 M LiOH solution (10 mL). The reaction mixture was heated to ~95 °C for 4 h. The resulting black suspension was diluted with CH$_2$Cl$_2$ (100 mL), and poured into ice water (30 mL) and brine (30 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 50 mL). The organic extracts were
combined, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3% and 5% saturated NH$_3$/MeOH in CH$_2$Cl$_2$) to afford the desired product 237 as a yellow solid (510 mg, 63% over 2 steps). mp 176-178 °C IR (film) 3416, 1687 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.19 (br s, 1H), 7.23 (dd, $J = 8.2$, 0.9 Hz, 1H), 7.13 (t, $J = 7.6$ Hz, 1H), 7.02 (s, 1H), 6.93 (d, $J = 7.1$ Hz, 1H), 5.42 (br s, 1 H), 4.98 (br d, $J = 8.6$ Hz, 1H), 4.58 (m, 1H), 4.43 (br s, 1H), 3.69 (q, $J = 7.1$ Hz, 1H), 3.49-3.21 (m, 2H), 3.19 (d, $J = 9.7$ Hz, 1H), 2.84 (dd, $J = 15.4$, 11.7 Hz, 1H), 1.48 (s, 9H), 1.40 (d, $J = 7.2$ Hz, 3H); $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 161.6, 155.9, 136.4, 135.2, 123.3, 122.5, 121.1, 119.1, 109.3, 109.2, 77.9, 65.6, 49.3, 49.1, 44.6, 28.4, 28.2, 19.4; LRMS(ESI) $m/z$ (relative intensity) 371.2 (100%, M+H$^+$); HRMS (ESI) $m/z$ calcd for [C$_{20}$H$_{26}$N$_4$O$_3$Na]$^+$: 393.1903, found 393.1898.

(±)-Spirocyclic Imidazolone 239. To an ice-cooled solution of the cyclic imidazolone 237 (507 mg, 1.37 mmol) in a mixture of THF (13 mL) and H$_2$O (2.6 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (932 mg, 4.11 mmol). The reaction mixture was stirred in an ice bath for 20 min. The resulting dark yellow solution was diluted with EtOAc (50 mL) and washed with saturated NaHCO$_3$ solution (3 x 50 mL). The aqueous layer was extracted with EtOAc (50 mL). The organic extracts
were combined, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3% and 5% saturated NH$_3$/MeOH in CH$_2$Cl$_2$) to afford the desired product 239 as a yellow solid (382 mg, 73%). mp 276 °C (dec.); IR (film) 3408, 1691, 1634 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 12.32 (s, 1H), 8.19 (s, 1H), 7.37 (dd, $J$ = 7.2, 0.9 Hz, 1H), 7.20 (t, $J$ = 7.6 Hz, 1H), 7.11 (d, $J$ = 6.9 Hz, 1H), 6.95 (d, $J$ = 8.6 Hz, 1H), 6.44 (s, 1H), 6.02 (s, 1H), 4.89 (d, $J$ = 8.6 Hz, 1H), 3.53 (q, $J$ = 7.2 Hz, 1H), 3.11 (d, $J$ = 8.6 Hz, 1H), 2.76 (d, $J$ = 9.1 Hz, 1H), 1.45 (s, 9H), 1.40 (d, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 188.7, 161.5, 156.9, 136.7, 134.7, 133.2, 123.1, 122.6, 121.2, 114.2, 110.7, 78.4, 62.4, 61.4, 49.3, 46.8, 28.4, 19.9; LRMS(ESI) m/z (relative intensity) 407.2 (100%, M+Na$^+$); HRMS (ESI) m/z calcd for [C$_{20}$H$_{24}$N$_4$O$_4$Na]$^+$: 407.1696, found 407.1699.

(±)-$N$-Boc Ketoindole 240. A solution of Boc$_2$O (256 mg, 1.17 mmol) in CH$_3$CN (1 mL) was slowly added to a suspension of the keto indole 239 (410 mg, 1.07 mmol) and DMAP (13 mg, 0.11 mmol) in CH$_3$CN (20 mL). The reaction mixture immediately turned yellow and clear. It was stirred at room temperature for 10 min, concentrated under reduced pressure to reduce the volume down to ~10 mL and then diluted with CH$_2$Cl$_2$ (60 mL). The mixture was poured into ice water (10 mL) and brine (10 mL).
The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether, 3% and 5% saturated NH₃/MeOH in CH₂Cl₂) to afford the desired protected product 240 as a yellow solid (484 mg, 94%). mp 270 °C (dec.); IR (film) 3392, 3241, 1751, 1715, 1666 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.47 (s, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 6.14 (d, J = 5.8 Hz, 1H), 5.87 (s, 1H), 5.67 (s, 1H), 5.12 (d, J = 5.8 Hz, 1H), 3.75 (q, J = 6.9 Hz, 1H), 3.14 (d, J = 10.4 Hz, 1H), 3.10 (d, J = 9.9 Hz, 1H), 1.70 (s, 9H), 1.59 (d, J = 7.1 Hz, 3H), 1.48 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 189.4, 162.3, 157.6, 148.4, 136.0, 134.6, 132.8, 125.8, 125.7, 122.2, 117.2, 113.7, 85.8, 80.5, 63.9, 61.5, 49.3, 47.8, 28.2, 27.9, 20.4; LRMS(ESI) m/z (relative intensity) 507.2 (100%, M+Na⁺); HRMS (ESI) m/z calcd for [C₂₅H₃₃N₄O₆]⁺: 485.2400, found 485.2390.

**N-Tf Indole-3-carboxaldehyde (266).** To an ice-cooled suspension of indole-3-carboxaldehyde (253) (301 mg, 2.07 mmol) in CH₂Cl₂ (15 mL) was added Et₃N (720 µL, 5.17 mmol) followed Tf₂O (870 µL, 5.17 mmol). The reaction mixture was stirred for 2 h (0 °C to room temperature). The resulting dark brown solution was poured into ice
water (20 mL) and extracted with EtOAc (3 x 30 mL). The organic extracts were combined, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3:1 hexanes/ether) to afford the desired product 266 as a white solid (299 mg, 52%). mp 102-103 °C; IR (film) 1681 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 10.16 (s, 1H), 8.34 (m, 1H), 8.05 (s, 1H), 7.90 (m, 1H), 7.50 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 185.4, 136.4, 136.3, 127.8, 126.8, 126.6, 125.1, 123.5, 119.72 (q, $J$ = 324 Hz), 113.9; LRMS (ESI) $m$/z (relative intensity) 292.1 (100%, M-H$_2$O+MeOH+H$^+$); HRMS (ESI) $m$/z calcd for [C$_{11}$H$_9$F$_3$NO$_3$S]$^+$: 292.0255, found 292.0251.

Bisindole 269. To an ice-cooled suspension of diBoc indolyl imidazolone 238 in CH$_2$Cl$_2$ (1 mL) was added TFA (1 ml). The reaction mixture was stirred for 2 h at room temperature. The resulting yellow-orange solution was diluted with CH$_2$Cl$_2$ (5 mL) and hexanes (5 mL), and concentrated to dryness under reduced pressure. The crude residue was dissolved in saturated NH$_3$/MeOH (5 mL) and then purified by flash chromatography on silica gel (5%, 10% and 20% saturated NH$_3$/MeOH in CH$_2$Cl$_2$) to afford the free amine 241 as a yellow solid (111 mg, 77%). This compound (73 mg, 0.27 mmol) was
dissolved in MeOH (4 mL). Indolecarboxaldehyde 266 (94 mg, 0.34 mmol) was added followed by titanium isopropoxide (5 drops). The reaction mixture was stirred at room temperature for 5 h. A portion (5%) of the reaction mixture was removed and concentrated to dryness under reduced pressure. The crude residue was purified by flash chromatography on silica gel (5% and 10% saturated NH₃/MeOH in CH₂Cl₂) to afford the bisindole 269 as a white solid (3.9 mg, 55%). To the rest of the reaction, TMSCN (200 µL, 1.50 mmol) was added and the reaction was stirred at room temperature for 14 h. It was concentrated to dryness under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford the bisindole 269 as a white solid (28.3 mg, 21%). mp 248-249 °C; IR (film) 3294, 1694 cm⁻¹; ¹H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.42 (m, 1H), 7.73 (m, 1H), 7.45-7.42 (m, 3H), 7.14 (s, 1H), 7.10 (d, J = 7.4 Hz, 1H), 6.90 (s, 1H), 6.87 (t, J = 7.6 Hz, 1H), 6.72 (d, J = 6.9 Hz, 1H), 5.72 (d, J = 3.7 Hz, 1H), 4.12 (br s, 1H), 3.92 (br t, J ~ 8 Hz, 1H), 3.51-3.42 (m, 3H), 2.78 (t, J = 13.5 Hz, 1H), 2.63 (d, J = 8.8 Hz, 1H), 0.47 (d, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, DMSO-d6) δ 166.4, 137.0, 135.6, 135.0, 130.0, 127.9, 126.4, 125.2, 123.2, 122.9, 122.5, 122.2, 120.7, 120.5, 119.1 (q, J = 325 Hz), 113.0, 109.3, 108.8, 72.9, 71.6, 56.9, 46.8, 46.5, 24.8, 18.3; LRMS(ESI) m/z (relative intensity) 530.2 (100%, M+H⁺); HRMS (ESI) m/z calcd for [C₂₅H₂₃N₅O₃SF₃]⁺: 530.1474, found 530.1503.
A colorless brick shaped crystal of **269** (C25 H22 F3 N5 O3 S, C6 H6) with approximate dimensions 0.15 x 0.18 x 0.20 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 298(2) K, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoKα fine-focus sealed tube (λ = 0.71073Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3° in ω and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Monoclinic unit cell yielded a total of 23708 reflections to a maximum θ angle of 28.61° (0.90 Å resolution), of which 7711 were independent, completeness = 96.7%, R_int = 0.0513, R_sig = 0.0759 and 3152 were greater than 2σ(I). The final cell constants: a = 18.134(4) Å, b = 12.530(3) Å, c = 28.556(6) Å, α = 90°, β = 106.320(4)°, γ = 90°, volume = 6227(2)Å³, are
based upon the refinement of the XYZ-centroids of 4143 reflections above 20σ(I) with 2.298° < θ < 28.314°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.8342.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) software package using the space group C2/c, with Z = 8 for the formula unit, C31 H28 F3 N5 O3 S. The final anisotropic full-matrix least-squares refinement on F² with 390 variables converged at R1 = 9.03%, for the observed data and wR2 = 27.38% for all data. The goodness-of-fit was 1.008. The largest peak on the final difference map was 0.367 e⁻/Å³ and the largest hole was -0.202 e⁻/Å³. Based on the final model, the calculated density of the crystal is 1.299 g/cm³ and F(000) amounts to 2528 electrons.

Azido Indole 285. To a yellow suspension of tryptamine (1.00 g, 6.24 mmol) in 1,4-dioxane (5 mL) was added Et₃N (1.80 mL, 12.9 mmol). A solution of (Boc)₂O (1.50 g, 6.87 mmol) in 1,4-dioxane (5 mL) was then cannulated into the reaction mixture. This mixture was stirred for 1 h and the resulting yellow solution was concentrated to dryness under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:2 hexanes/ether) to give the desired N-Boc amine intermediate 283 as an
amorphous white solid (1.62 g, quantitative yield). This compound (200 mg, 0.77 mmol) was dissolved in THF (4 mL) and cooled to 0 °C. TMSN₃ (210 µL, 1.57 mmol) was added followed by a solution of DDQ (227 mg, 1.00 mmol) in THF (4 mL). The reaction mixture was stirred for 16 h (0 °C to room temperature). The resulting yellow solution was diluted with EtOAc (30 mL) and washed with saturated NaHCO₃ solution (3 x 30 mL). The aqueous layer was extracted with EtOAc (30 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:2 hexanes/ether) to afford the desired product 285 as a yellow solid (189 mg, 81%). mp 64-66 °C; IR (film) 3411, 3323, 2104, 1694 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.92 (br s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.3 Hz, 1H), 7.10 (t, J = 7.3 Hz, 1H), 6.98 (s, 1H), 5.09 (br t, J ~ 5.5 Hz, 1H), 4.89 (dd, J = 8.2, 5.1 Hz, 1H), 3.52 (m, 2H), 1.46 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 156.0, 136.4, 125.4, 123.0, 122.4, 119.9, 119.0, 111.6, 111.1, 79.8, 59.5, 44.7, 28.3; LRMS(ESI) m/z (relative intensity) 259.2 (20%, M-N₃⁻), 313.2 (100%, M-N₃⁻+MeO⁺+Na⁺); HRMS (ESI) m/z calcd for [C₁₅H₁₉N₂O₂]⁺: 259.1447, found 259.1447.
**Bisindole 286.** To a solution of azido indole 285 (189 mg, 0.63 mmol) in MeOH (6 mL) was added 10% Pd/C (7 mg, 7 µmol). The reaction mixture was stirred under an H₂ atmosphere (1 atm) for 12 h. The resulting black suspension was filtered through a pad of Celite and washed with EtOAc (40 mL). The filtrate was concentrated to dryness under reduced pressure. The crude residue was dissolved in CH₂Cl₂ (6 mL) and cooled to 0 °C. Indol-3-yloxy-acetyl chloride (130) (143 mg, 0.0.69 mmol) was added followed by Et₃N (180 µL, 1.29 mmol). The reaction mixture was stirred for 1 h (0 °C to rt), and the unreacted acid chloride was filtered off and washed with CH₂Cl₂ (15 mL). The filtrate was poured into ice water (15 mL) and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 15 mL). The extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Ether (10 mL) was added to the crude residue to dissolve impurities and the desired bisindole 286 was collected by filtration as a light yellow solid (254 mg, 75% yield). NMR data were consistent with those reported in the literature.²⁰
Protected Oxtroptamine 289. To a solution of \( N \)-Boc tryptamine 288 (1.00 g, 3.84 mmol) in a mixture of THF (40 mL) and water (4 mL) was added DDQ (1.75 g, 7.71 mmol) at 0 °C. The resulting deep red solution was stirred for 1 h (0 °C to rt), and then diluted with EtOAc (60 mL) and washed with saturated aqueous NaHCO\(_3\) solution (3 x 60 mL) and brine (30 mL). The aqueous phase was extracted with EtOAc (30 mL). The organic extracts were combined, dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure to give the desired ketone intermediate as a yellow solid. This compound was then suspended in CH\(_3\)CN (30 mL), and DMAP (47 mg, 0.38 mmol) was added followed by slow addition of a solution of (Boc)\(_2\)O (754 mg, 3.46 mmol) in CH\(_3\)CN (9 mL) over 10 min until TLC showed the disappearance of the starting material. The resulting dark brown and clear solution was concentrated to dryness under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether) to give the protected oxotryptamine 289 as a white solid (1.18 g, 82% yield over 2 steps). mp 150-151 °C; IR (film) 3432, 1750, 1712, 1672 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.27 (m, 1H), 8.22 (s, 1H), 8.14 (d, \( J = 7.6 \) Hz, 1H), 7.38-7.33 (m, 2H), 5.62 (br s, 1H), 4.52 (d, \( J = 4.6 \) Hz, 2H), 1.77 (s, 9H), 1.49 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 190.2, 155.7, 148.6, 135.3, 131.5, 126.9, 125.5, 124.4, 122.1, 117.4, 114.9, 85.4, 79.6, 47.6, 28.2, 28.0; LRMS(ESI) \( m/z \) (relative intensity) 375.2 (75%, M+H\(^{+}\)); HRMS (ESI) \( m/z \) calcd for [C\(_{20}\)H\(_{27}\)N\(_2\)O\(_3\)]\(^{+}\): 375.1920, found 375.1925.
Hydroxy Indole 290. To an ice-cooled suspension of ketone 289 (1.63 g, 4.35 mmol) in MeOH (40 mL) was added NaBH₄ (825 mg, 21.8 mmol) in portions. The reaction mixture was stirred at room temperature for 30 min. The volume of the resulting clear and colorless solution was reduced by concentrating under reduced pressure to ~10 mL. The resulting mixture was poured into ice water (25 mL) and extracted with EtOAc (3 x 25 mL). The organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/EtOAc) to give the desired alcohol 290 as a foamy white solid (1.64 g, quantitative yield). mp 62-64 °C; IR (film) 3400, 1734, 1708, 1690 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.15 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.59 (s, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.23 (d, J = 7.4 Hz, 1H), 5.10 (br t, J = 3.3 Hz, 1H), 5.02 (br s, 1H), 3.67 (ddd, J = 14.0, 6.6, 3.6 Hz, 1H), 3.42 (dt, J = 13.6, 6.8 Hz, 1H), 3.15 (br s, 1H), 1.66 (s, 9H), 1.45 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 156.9, 149.5, 135.7, 128.3, 124.5, 122.8, 122.6, 121.4, 119.5, 115.2, 83.6, 79.7, 67.9, 46.8, 28.3, 28.1; LRMS(ESI) m/z 399.3 (relative intensity) (100%, M+Na⁺); HRMS (ESI) m/z calcd for [C₂₀H₂₈N₂O₅Na]⁺: 399.1896, found 399.1893.
Azido Indole 291. To a solution of alcohol 290 (735 mg, 1.95 mmol) in toluene (20 mL) was added diphenyl phosphorylazide (DPPA) (560 µL, 2.59 mmol) followed by DBU (390 µL, 2.61 mmol). The reaction mixture was stirred at room temperature for 18 h. iPrOH (5 mL) and a 1 M NaOH solution (5 mL) were added to the reaction mixture, and stirring was continued for 1 h to consume excess DPPA. The resulting slightly yellow solution was poured into ice water (20 mL) and extracted with ether (3 x 20 mL). The extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether) to give the desired azide 291 as a white solid (668 mg, 85% yield). mp 64-66 °C; IR (film) 3366, 2103, 1736, 1713 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.18 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.63 (s, 1H), 7.34 (dd, J = 7.4, 1.1 Hz, 1H), 7.25 (dd, J = 7.5, 1.0 Hz, 1H), 5.18 (br t, J = 5.7 Hz, 1H), 4.96 (br dd, J = 8.1, 4.8 Hz, 1H), 3.64 (dt, J = 13.9, 6.0 Hz, 1H), 3.40 (ddd, J = 14.1, 8.6, 5.8 Hz, 1H), 1.66 (s, 9H), 1.44 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.7, 149.2, 135.6, 128.0, 124.8, 123.8, 122.8, 119.4, 116.5, 115.3, 83.9, 79.5, 58.8, 44.6, 28.2, 27.9; LRMS(ESI) m/z (relative intensity) 424.2 (100%, M+Na⁺); HRMS (ESI) m/z calcd for [C₂₀H₂₇N₅O₄Na]⁺: 424.1961, found 424.1975.
Bisindole 292. To a solution of azido indole 291 (250 mg, 0.62 mmol) in MeOH (6 mL) was added 10% Pd/C (7 mg, 7 µmol). The reaction mixture was stirred under an H₂ atmosphere (1 atm) for 12 h. The resulting black suspension was filtered through a pad of Celite and washed with EtOAc (40 mL). The filtrate was concentrated to dryness under reduced pressure. The crude residue was dissolved in CH₂Cl₂ (6 mL) and cooled to 0 °C. Indol-3-yl-oxo-acetyl chloride (130) (155 mg, 0.75 mmol) was added followed by Et₃N (180 µL, 1.29 mmol). The reaction mixture was stirred for 1 h (0 °C to rt), and the unreacted acid chloride was filtered off and washed with CH₂Cl₂ (15 mL). The filtrate was poured into ice water (15 mL) and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 15 mL). The extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Ether (10 mL) was added to the crude residue to dissolve impurities and the desired bisindole 292 was collected by filtration as a light yellow solid (254 mg, 75% yield). mp 201-202 °C; IR (film) 3362, 3311, 1732, 1673 cm⁻¹; ¹H NMR (300 MHz, DMSO-d6) δ 12.29 (s, 1H), 9.14 (d, J = 9.1 Hz, 1H), 8.71 (s, 1H), 8.23 (t, J = 4.1 Hz, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 7.4 Hz, 1H), 7.71 (s, 1H), 7.53 (t, J = 4.2 Hz, 1H), 7.36-7.24 (m, 4H), 7.12 (t, J = 5.7 Hz, 1H), 5.43 (q, J = 7.2 Hz, 1H), 3.56 (dt, J = 13.7, 7.4 Hz, 1H), 3.40 (dt, J = 13.1, 7.2 Hz,
1H), 1.61 (s, 9H), 1.33 (s, 9H); $^{13}$C NMR (75 MHz, DMSO-d6) \( \delta \) 182.0, 163.3, 155.9, 149.0, 138.4, 136.3, 134.7, 129.2, 126.2, 124.5, 123.4, 123.3, 122.65, 122.57, 121.2, 119.9, 119.5, 114.8, 112.6, 112.2, 83.7, 77.8, 45.2, 43.5, 28.1, 27.7; LRMS(ESI) \( m/z \) (relative intensity) 569.2 (100%, M+Na$^+$); HRMS (ESI) \( m/z \) calcd for \([\text{C}_{30}\text{H}_{35}\text{N}_4\text{O}_6]\)^+: 547.2557, found 547.2552.

**Bisindolyl Dihydropyrazinone 287. Method A:** TFA (2 mL) was added to a solution of bisindole 292 (300 mg, 0.55 mmol) in CH$_2$Cl$_2$ at 0 °C. The reaction mixture was stirred for 1 h (0 °C to rt). The resulting orange-yellow solution was diluted with CH$_2$Cl$_2$ (10 mL) and hexanes (10 mL) and concentrated to dryness under reduced pressure. The crude residue was dissolved in EtOAc (30 mL) and poured into cold saturated NaHCO$_3$ solution (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The organic extracts were combined, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:3 hexanes/EtOAc) to give the desired product 287 as a yellow solid (119 mg, 66% yield).
**Method B:** Formic acid (1.1 mL) was added to a solution of bisindole 292 (40 mg, 0.073 mmol) in 1,2-dichloroethane (3.0 mL). The reaction mixture was heated to reflux for 48 h. The resulting orange solution was allowed to cool to room temperature, diluted with EtOAc (20 mL), and poured into cold saturated NaHCO₃ solution (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:3 hexanes/EtOAc) to give the desired product 287 as a yellow solid (18 mg, 75% yield). mp 250 °C (dec.); IR (film) 3385, 1655 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 11.52 (d, J = 1.8 Hz, 1H), 11.04 (s, 1H), 8.78 (s, 1H), 8.43 (d, J = 2.8 Hz, 1H), 8.39 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 2.3 Hz, 1H), 7.18-7.02 (m, 4H), 5.00 (t, J = 5.7 Hz, 1H), 4.12 (m, 2H); ¹³C NMR (75 MHz, DMSO-d₆) δ 157.9, 157.7, 136.7, 136.1, 131.9, 126.0, 125.6, 123.5, 122.6, 122.1, 121.4, 120.4, 119.0, 118.8, 112.9, 111.7, 111.6, 111.1, 53.7, 46.5; LRMS(ESI) m/z (relative intensity) 329.1 (100%, M+H⁺); HRMS (ESI) m/z calcd for [C₂₀H₁₇N₄O]⁺: 329.1402, found 329.1409.
Bisindolyl Pyrazinone 45. Method A: To a suspension of bisindolyl dihydropyrazinone 287 (6 mg, 0.02 mmol) in benzene (1 mL) was added DDQ (9 mg, 0.04 mmol). The resulting deep red solution was heated to reflux for 3 h, and then allowed to cool to room temperature and diluted with EtOAc (10 mL). The mixture was washed with saturated NaHCO₃ solution (3 x 10 mL). The aqueous layer was extracted with EtOAc (10 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:3 hexanes/EtOAc and 100% EtOAc) to give the desired pyrazinone 45 as an orange solid (2.2 mg, 37% yield).

Method B: Bisindole 292 (30 mg, 0.055 mmol) in a round-bottomed flask was heated in a sand bath to 180 °C with exposure to air for 2 h. The resulting black solid was purified by flash chromatography on silica gel (1:3 hexanes/EtOAc and 100% EtOAc) to give the desired pyrazinone 45 as an orange solid (6.0 mg, 34% yield). NMR data were consistent with those reported in the literature.¹¹
(±)-Azido Indoles 281a and 281b. To an ice-cooled solution of keto indole 240 (222 mg, 0.46 mmol) in MeOH (5 mL) was added NaBH₄ (87 mg, 2.3 mmol). The reaction mixture immediately turned from bright yellow to colorless. It was stirred for 1 h (0 °C to room temperature) with TLC monitoring. Then the reaction mixture was cooled back to 0 °C. Additional NaBH₄ (87 mg, 2.3 mmol) was added and the reaction mixture was stirred for an additional 2 h (0 °C to room temperature). It was poured into ice water (20 mL) and extracted with EtOAc (3 x 20 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was dissolved in a mixture of toluene (4 mL) and DMF (0.46 mL) and DPPA (500 µL, 2.31 mmol) was added followed by DBU (410 µL, 2.74 mmol). The reaction mixture was stirred at room temperature for 24 h. The resulting dark brown solution was poured into ice water (30 mL) and extracted with EtOAc (3 x 30 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/EtOAc, 3% and 5% saturated NH₃/MeOH in CH₂Cl₂) and repurified by preparative TLC (5% saturated NH₃/MeOH in CH₂Cl₂) to afford the desired azides 281a (109 mg, 47%) and 281b (40 mg, 17%), and unconsumed alcohol 293b (33 mg, 15%) as
off-white solids. Major product (281a): mp 170-172 °C; IR (film) 3257, 2096, 1693 cm⁻¹; ¹H NMR (300 MHz, acetone-d6) δ 8.07 (dd, J = 8.3, 0.9 Hz, 1H), 7.86 (s, 1H), 7.33 (t, \( J = 7.9 \) Hz, 1H), 7.19 (dd, J = 7.4, 0.9 Hz, 1H), 6.78 (br d, J = 9.9 Hz, 1H), 5.64 (br s, 1H), 5.38 (br s, 1H), 5.02 (d, J = 10.0 Hz, 1H), 4.55 (t, J = 9.2 Hz, 1H), 3.60 (q, J = 7.2 Hz, 1H), 3.52 (dd, J = 9.6 Hz, 1.2 Hz, 1H), 2.96 (d, J = 9.7 Hz, 1H), 1.68 (s, 9H), 1.46 (d, \( J = 7.2 \) Hz, 3H), 1.45 (s, 9H); ¹³C NMR (75 MHz, CD₃OD) δ 164.8, 158.8, 150.5, 137.1, 136.2, 127.2, 126.3, 125.8, 125.0, 117.0, 114.6, 85.7, 80.9, 66.8, 62.5, 58.2, 51.1, 47.3, 28.8, 28.3, 19.1; LRMS(ESI) m/z (relative intensity) 534.3 (100%, M+Na⁺); HRMS (ESI) m/z calcd for [C₂₅H₃₃N₇O₅Na⁺]: 534.2441, found 534.2442.

Minor product (281b): mp 170-172 °C; IR (film) 3260, 2099, 1733, 1693 cm⁻¹; ¹H NMR (300 MHz, acetone-d6) δ 8.05 (d, J = 8.1 Hz, 1H), 7.92 (s, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 6.44 (br d, J = 10.2 Hz, 1H), 5.61 (br s, 1H), 5.43 (br s, 1H), 5.33 (dd, J = 2.4 Hz, 1H), 4.32 (d, J = 8.8 Hz, 1H), 3.99 (dd, J = 10.2, 1.6 Hz, 1H), 3.59 (q, J = 7.0 Hz, 1H), 3.27 (d, J = 10.4 Hz, 1H), 1.68 (s, 9H), 1.44 (d, J = 7.0 Hz, 3H), 1.38 (s, 9H); ¹³C NMR (75 MHz, acetone-d6) δ 162.5, 156.9, 150.0, 136.4, 135.9, 128.1, 126.3, 126.1, 123.8, 117.4, 114.4, 85.0, 79.6, 67.1, 61.8, 57.7, 48.6, 46.7, 28.5, 28.1, 16.4; LRMS(ESI) m/z (relative intensity) 534.2 (100%, M+Na⁺); HRMS (ESI) m/z calcd for [C₂₅H₃₄N₇O₅]⁺: 512.2621, found 512.2626.
Bisindole 294. To a solution of a mixture of azido indoles 281a and 281b (10 mg, 0.020 mmol) in MeOH (2 mL) was added cobalt (II) chloride hexahydrate (40 mg, 1.06 mmol). The resulting light green solution was cooled in an ice bath and NaBH₄ (20 mg, 0.084 mmol) was added in portions. The resulting black suspension was stirred for 12 h (0 °C to room temperature). The reaction mixture was filtered through a Celite pad and washed with EtOAc (50 mL). The organic filtrate was washed with 0.01 M EDTA (2 x 10 mL) and brine solution (10 ml), dried over anhydrous Na₂SO₄ and concentrated to dryness under reduced pressure. The residue was then dissolved in CH₂Cl₂ (1 mL) and cooled to 0 °C. Indol-3-yl-oxo-acetyl chloride (130) (5 mg, 0.024 mmol) was added followed by Et₃N (6 µL, 0.043 mmol). The reaction mixture was stirred for 1 h (0 °C to room temperature), and then diluted with EtOAc (20 mL) and poured into ice water. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3% and 5% saturated NH₃/MeOH in CH₂Cl₂, respectively) to afford the desired bisindole 294 as a white solid (8.3 mg, 65%). Major diastereomer (as shown): mp 250 °C (dec.); IR (film) 3306, 1703 cm⁻¹; ¹H NMR (300 MHz, acetone-d6) δ 11.47 (br s, 1H), 9.07 (d, J = 3.2 Hz, 1H), 8.71 (br d, J = 8.6 Hz, 1H), 8.36 (m, 1H),
8.05 (d, $J = 7.9$ Hz, 1H), 7.65 (d, $J = 1.7$ Hz, 1H), 7.58 (m, 1H), 7.34-7.24 (m, 3H), 7.18 (d, $J = 7.3$ Hz, 1H), 6.24 (br d, $J = 9.1$ Hz, 1H), 5.88 (s, 1H), 5.65 (s, 1H), 5.46 (dt, $J = 9.9$, 1.5 Hz, 1H), 4.69 (t, $J = 9.5$ Hz, 1H), 3.81 (d, $J = 9.3$ Hz, 1H), 3.65 (q, $J = 7.0$ Hz, 1H), 3.22 (d, $J = 9.4$ Hz, 1H), 1.62 (s, 9H), 1.50 (d, $J = 7.1$ Hz, 3H), 1.24 (s, 9H); $^{13}$C NMR (75 MHz, acetone-d6) δ 181.7, 164.3, 163.0, 158.0, 150.0, 139.6, 137.4, 136.5, 136.4, 127.7, 126.3, 125.6, 125.1, 124.5, 124.3, 123.5, 122.7, 119.7, 114.1, 113.8, 113.1, 84.8, 79.6, 65.8, 57.4, 49.7, 49.0, 46.8, 28.5, 28.1, 18.9; LRMS(ESI) $m/z$ (relative intensity) 557.2 (100%, M+H$^+$); HRMS (ESI) $m/z$ calcd for [C$_{35}$H$_{41}$N$_6$O$_7$]$^+$: 657.3037, found 657.3038. Due to limited material, the minor isomer could not be isolated for characterization.

**Bisindolyl Pyrazinone 247.** Bisindole 294 (10 mg, 0.018 mmol) in a round-bottomed flask was heated in a sand bath to 180 °C with exposure to air. The resulting dark yellow-brown solid was purified by preparative TLC (10% saturated NH$_3$/MeOH in CH$_2$Cl$_2$) to afford the desired bisindolyl pyrazinone 247 as a bright yellow solid (2.1 mg, 32%). mp 250 °C (dec.); IR (film) 3234, 1685 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d6) δ 12.24 (br s, 1H), 11.97 (br s, 1H), 11.52 (br s, 1H), 8.80 (d, $J = 8.4$ Hz, 1H), 8.76 (s, 1H), 8.32 (s, 1H), 7.43 (d, $J = 7.8$ Hz, 1H), 7.37 (d, $J = 8.1$ Hz, 1H), 7.3 (m, 1H), 7.17 (t, $J =$
7.4 Hz, 1H), 7.11 (t, J = 6.2 Hz, 1H), 7.03 (d, J = 6.9 Hz, 1H), 2.96 (d, J = 9.2 Hz, 1H), 2.79 (d, J = 8.8 Hz, 1H), 1.02 (d, J = 7.0 Hz, 3H), missing (q, J = 7.0 Hz, 1H) at ~3.4 ppm due to overlap with the water peak; LRMS(ESI) m/z (relative intensity) 437.2 (100%, M+H+); HRMS (ESI) m/z calcd for [C_{25}H_{21}N_{6}O_{2}]^+: 437.1726, found 437.1738.

7-Benzhydryloxyindole-3-carboxaldehyde (300). Phosphorus(V) oxychloride (50 µL, 0.42 mmol) was added slowly to DMF (0.5 mL) at 0 ºC. The reaction mixture was stirred at this temperature for 20 min and a solution of 7-benzhydrylindole (297b) in DMF (2 mL) was added via cannula. The resulting dark brown solution was heated to 40 ºC for 12 h followed by cooling to room temperature and then in an ice bath. Ice (~1 g) was added to the reaction mixture followed by slow addition of a 1 M NaOH solution (1 mL). The mixture was heated to 95 ºC for 1 h and again allowed to cool to room temperature and then cooled in an ice bath. The liquid phase was slowly decanted off to leave a black syrup. This residue dissolved in CH₂Cl₂ (10 mL). The black organic phase was poured into ice water (10 mL) and the organic phase was separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/EtOAc) to give
the desired aldehyde 300 as a yellow solid (127 mg, 93% yield). mp 158-160 °C (recrystallized from EtOAc); IR (film) 3107, 1659 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.03 (br s, 1H), 9.84 (s, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 3.1 Hz, 1H), 7.38 (d, J = 6.7 Hz, 4H), 7.18-7.28 (m, 6 H), 7.02 (t, J = 5.3 Hz, 1H), 6.66 (d, J = 7.9 Hz, 1 H), 6.35 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 185.7, 144.4, 140.6, 135.6, 128.6, 127.9, 127.7, 126.9, 125.9, 123.5, 119.5, 114.4, 107.4, 82.1; LRMS(ESI) m/z (relative intensity) 328.1 (100%, M+H⁺); HRMS (ESI) m/z calcd for [C₂₂H₁₈NO₂]⁺: 328.1338, found 328.1328.

Methyl (2,2-Dichloropropionylamino)-acetate (308). To a solution of 2,2-dichloropropionic acid (90%, 13.6 mL, 119 mmol) in CH₂Cl₂ (100 mL) was added 2 drops of DMF followed by oxalyl chloride (20.8 mL, 238 mmol). The reaction mixture was stirred for 7.5 h until bubbling stopped. The resulting yellow acid chloride solution was concentrated under reduced pressure and then redissolved in CH₂Cl₂ (50 mL). The acid chloride solution was cannulated to an ice-cooled solution of glycine methyl ester hydrochloride (10.00 g, 79.64 mmol) and DMAP (20.43 g, 167.2 mmol) in CH₂Cl₂ (150 mL). The resulting red solution was stirred for 12 h (0 °C → room temperature) and it turned dark brown. The reaction mixture was poured into ice water (100 mL) and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under
reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether) to afford the dichloroamide 308 as a light yellow syrup (13.63 g, 80%). IR (film) 3368, 1753, 1686 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.43 (br s, 1H), 4.11 (d, $J$ = 5.3 Hz, 2H), 3.80 (s, 3H), 2.31 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.3, 166.6, 81.7, 52.5, 41.9, 33.8; LRMS(ESI) m/z (relative intensity) 214.0 (100%, M+H$^+$); HRMS (ESI) m/z calcd for [C$_6$H$_{10}$NO$_3$Cl$_2$]$^+$: 214.0038, found 214.0040.

![Phosphonate](image)

**Methyl (2,2-Dichloropropionylamino)-(dimethoxyphosphoryl)-acetate (310).**

To a solution of dichloroamide 308 (10.71 g, 50.04 mmol) in CCl$_4$ (100 mL) was added $N$-bromosuccinimide (NBS) (9.51 g, 53.4 mmol). The reaction mixture was heated to reflux under sunlamp irradiation for 3 h. The precipitate was filtered off and washed with CCl$_4$ (20 mL). The filtrate was concentrated under reduced pressure to give a yellow liquid. This liquid was dissolved in CH$_2$Cl$_2$ (100 mL) and trimethyl phosphite (P(OMe)$_3$) (6.52 g, 52.6 mmol) was added. The reaction mixture was stirred at room temperature for 13 h. It was concentrated to dryness under reduced pressure to give the desired product as an off-white solid (16.12 g, 100% crude). This phosphonate was carried on to the next step without purification. For characterization purpose, a portion was recrystallized from EtOAc to give the desired phosphonate 310 as a white solid. mp 93-94 °C; IR (film) 3206, 1756, 1696 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.54 (br d, $J$ = 7.5 Hz, 1H), 5.12
(dd, $J = 21.6, 8.7$ Hz, 1H), 3.88 (s, 3H), 3.88 (d, $J = 11.3$ Hz, 3H), 3.85 (d, $J = 11.3$ Hz, 3H), 2.31 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.0, 165.7 (d, $J = 5.1$ Hz), 81.3, 54.2 (d, $J = 6.3$ Hz), 53.9 (d, $J = 6.9$ Hz), 53.4, 51.0 (d, $J = 147.2$ Hz), 33.6; LRMS(ESI) m/z (relative intensity) 322.1 (100%, M+H$^+$); HRMS (ESI) m/z calcd for [C$_8$H$_{15}$NO$_6$Cl$_2$P]$^+$: 322.0014, found 322.0014.

![Chemical Structure](image)

$N$-[(Trimethylsilylethoxy)carbonyl]-7-benzhydroxyindole-3-carboxaldehyde (312). To an ice-cooled suspension of NaH (60% dispersion in mineral oil, 2.75 g, 68.75 mmol) in THF (30 mL) was added a solution of aldehyde 300 (15.03 g, 45.91 mmol) in THF (130 mL) via cannula. The suspension was stirred at 0 °C for 30 min and then a solution of 4-nitrophenyl-2-(trimethylsilyl)ethyl carbonate (14.31 g, 50.50 mmol) in THF (70 mL) was added via cannula. The reaction mixture was stirred at room temperature for 18 h. The resulting orange suspension was poured into ice water (200 mL) and extracted with ether (3 x 100 mL). The organic extracts were combined, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (2:1 hexanes/ether) to give the desired protected aldehyde 312 as a yellow solid (19.81 g, 92% yield). mp 101-102 °C (recrystallized from ether); IR (film) 1767, 1676 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$
9.98 (s, 1H), 8.09 (s, 1H), 7.90 (d, \( J = 7.9 \) Hz, 1H), 7.48 (d, \( J = 7.4 \) Hz, 4H), 7.31-7.16 (m, 6H), 7.09 (t, 5.3 Hz, 1H), 6.75 (d, \( J = 8.2 \) Hz, 1H), 6.28 (s, 1H), 4.30 (m, 2H), 1.02 (m, 2H), 0.00 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl3) \( \delta \) 189.3, 149.9, 145.8, 141.0, 138.4, 128.7, 128.5, 127.7, 126.7, 125.7, 125.5, 121.3, 114.4, 110.7, 82.3, 67.2, 17.4, -1.7; LRMS(ESI) \( m/z \) (relative intensity) 494.2 (70%, M+Na\(^+\)); HRMS (ESI) \( m/z \) calcd for [C\(_{28}\)H\(_{29}\)NO\(_4\)NaSi\(^+\)]: 494.1764, found 494.1748.

**Methyl-2-(2,2-dichloropropionylamino)-3-(N[trimethylsilylethoxy]carbonyl)-7-benzhydroxyindol-3-yl)-acrylate (314).** To an ice-cooled suspension of dimethylphosphoryl amide 310 (12.50 g, 38.8 mmol) in CH\(_2\)Cl\(_2\) (100 mL) was added DBU (5.80 mL g, 38.8 mmol). The reaction mixture was stirred at 0 °C for 20 min and then aldehyde 312 (12.20 g, 25.9 mmol) in CH\(_2\)Cl\(_2\) (100 mL) was added via cannula. The reaction mixture was stirred at room temperature for 12 h. The resulting dark brown solution was poured into a mixture of ice water (100 mL) and brine (50 mL), and the organic layer was separated. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 x 50 mL). The organic extracts were combined, dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether) to give the desired alkene 314 as a white solid (14.58 g,
84% yield). mp 140-142 °C (recrystallized from hexanes/ether); IR (film) 3306, 1760, 1721, 1706 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.12 (s, 1H), 7.94 (s, 1H), 7.70 (s, 1H), 7.51 (d, $J = 7.1$ Hz, 4H), 7.30-7.16 (m, 7H), 7.01 (t, 8.0 Hz, 1H), 6.70 (d, $J = 7.9$ Hz, 1H), 6.26 (s, 1H), 4.28 (m, 2H), 3.77 (s, 3H), 2.32 (s, 3H), 1.00 (m, 2H), 0.00 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 164.6, 163.7, 150.0, 146.2, 141.2, 132.2, 130.2, 128.5, 127.6, 126.7, 125.5, 124.43, 124.39, 121.5, 113.3, 111.0, 109.9, 82.17, 82.06, 66.6, 52.6, 33.5, 17.5, -1.7; LRMS(ESI) $m/z$ (relative intensity) 689.2 (100%, M+Na$^+$); HRMS (ESI) $m/z$ calcd for [C$_{34}$H$_{36}$N$_2$O$_6$NaSiCl$_2$]$^+$: 689.1617, found 689.1621.

Methyl-2-(2,2-dichloropropionylamino)-3-(N[(trimethylsilylethoxy)carbonyl]-7-benzhydryloxyindol-3-yl)-propionate (315). To a solution of the alkene 314 (50 mg, 0.075 mmol) in toluene (5 mL) was added Rh(PPh$_3$)$_3$Cl (1 mg, 0.001 mmol) under an N$_2$ atmosphere. The reaction mixture was placed in a sealable metal container equipped with a gas inlet and pressure gauge and pressurized with H$_2$ at 850 psi for 40 h. The resulting light brown solution was concentrated to dryness under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether) to give the desired dichloroamide 315 as a white foamy solid (29 mg, 76% yield). mp 56-58 °C; IR (film) 3407, 1751, 1696 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.52 (d, $J = 7.0$ Hz, 4H),
7.38 (s, 1H), 7.30-7.17 (m, 7H), 7.03-6.96 (m, 2H), 6.68 (dd, J = 6.6, 2.4 Hz, 1H), 6.26 (s, 1H), 4.80 (dt, J = 7.6, 5.4 Hz, 1H), 4.27 (m, 2H), 3.64 (s, 3H), 3.24 (d, J = 5.4 Hz, 2H), 2.22 (s, 3H), 1.00 (m, 2H), 0.00 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 171.0, 165.8, 150.5, 146.4, 141.5, 133.2, 128.5, 127.6, 126.84, 126.75, 125.1, 123.7, 113.9, 111.3, 109.6, 82.2, 82.0, 65.9, 53.3, 52.7, 33.9, 26.9, 17.5, -1.6; LRMS(ESI) m/z (relative intensity) 669.3 (55%, M+H⁺), 686.3 (100%, M+NH₄⁺); HRMS (ESI) m/z calcd for [C₃₄H₃₉N₂O₆SiCl₂]+: 669.1954, found 669.1981.

![Methyl-2-(2,2-dichloropropionylamino)-3-(N[(trimethylsilyl)ethoxy]carbonyl)-7-hydroxyindol-3-yl)-propionate (316)](image)

Methyl-2-(2,2-dichloropropionylamino)-3-(N[(trimethylsilyl)ethoxy]carbonyl)-7-hydroxyindol-3-yl)-propionate (316). To a solution of the alkene 314 (10.40 g, 15.6 mmol) in a 1:1 mixture of MeOH and toluene (100 mL) was added Rh(PPh₃)₃Cl (145 mg, 0.64 mmol) under an N₂ atmosphere. The reaction mixture was placed in a sealable metal container equipped with a gas inlet pressure gauge, and this vessel was pressurized with H₂ at 1250 psi with heating to 45 °C for 50 h. The resulting dark brown solution was concentrated to dryness under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether) to give the desired dichloroamide 316 as a white solid (7.68 g, 98% yield). mp 96-97 °C (recrystallized from ether); IR (film) 3406, 1746, 1695 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.65 (s, 1H), 7.32 (br d, J
= 7.5 Hz, 1H), 7.31 (s, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 4.80 (ddd, J = 7.5, 5.6, 5.5 Hz, 1H) 4.45 (m, 2H), 3.67 (s, 3H), 3.24 (dd, J = 14.9, 5.5 Hz, 1H), 3.18 (dd, J = 14.9, 5.6 Hz, 1H), 2.24 (s, 3H), 1.13 (m, 2H), 0.08 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 170.8, 165.7, 153.2, 144.7, 144.7, 132.9, 125.4, 124.0, 123.2, 116.5, 113.2, 109.7, 81.9, 67.5, 52.9, 52.7, 33.7, 26.7, 17.5, -1.6; LRMS(ESI) m/z (relative intensity) 503.1 (100%, M+H+); HRMS (ESI) m/z calcd for [C21H29N2O6SiCl2]+: 503.1172, found 503.1200.

Methyl 2-(2,2-Dichloropropionylamino)-3-(7-benzhydryloxyindol-3-yl)-pro-pionate (317). To a solution of N-TEOC indolyl dichloroamide 315 (56 mg, 0.084 mmol) in THF (1 mL) was added 1 M tetrabutylammonium fluoride (TBAF) (100 µL, 0.10 mmol). The reaction mixture was stirred at room temperature for 1 h and then was poured into ice water and extracted with CH2Cl2 (3 x 10 mL). The organic extracts were combined, dried over anhydrous Na2SO4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether) to give the unprotected indole 317 as a yellow foamy solid (42 mg, 95% yield). mp 114-116 °C; IR (film) 3404, 1743, 1690 cm−1; 1H NMR (300 MHz, CDCl3) δ 8.36 (br s, 1H), 7.39 (dd, J = 7.0, 1.0 Hz, 4H), 7.33-7.20 (m, 7H), 7.08 (d, J = 7.9 Hz, 1H), 6.95 (s, 1H),
6.84 (t, $J = 7.9$ Hz, 1H), 6.52 (d, $J = 7.7$ Hz, 1H), 6.31 (s, 1H), 4.80 (dt, $J = 7.7$, 5.2 Hz, 1H), 3.64 (s, 3H), 3.35 (dd, $J = 15.0$, 5.2 Hz, 1H), 3.29 (dd, $J = 15.0$, 5.2 Hz, 1H), 2.21 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.3, 165.8, 144.6, 141.1, 128.8, 128.6, 127.8, 127.2, 126.9, 122.6, 120.1, 111.6, 109.7, 105.5, 82.1 (2C), 53.8, 52.6, 33.9, 27.2; LRMS (ESI) m/z (relative intensity) 542.2 (100%, M+NH$_4^+$); HRMS (ESI) m/z calcd for [C$_{28}$H$_{30}$N$_3$O$_4$Cl$_2$]$^+$: 542.1613, found 542.1635.

Methyl 2-(2,2-Dichloropropionylamino)-3-(7-hydroxyindol-3-yl)-propionate (318). To a solution of N-TEOC indolyl dichloroamide 316 (7.54 g, 15.0 mmol) in THF (70 mL) was added 1 M TBAF (15.0 mL, 15.0 mmol). The reaction mixture was stirred at room temperature for 1 h and then poured into ice water and extracted with EtOAc (3 x 70 mL). The organic extracts were combined, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/EtOAc) to give the unprotected indole 318 as a white foamy solid (5.19 g, 96% yield). mp 55-57 °C; IR (film) 3396, 1738, 1679 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d6) $\delta$ 10.65 (s, 1H), 9.46 (s, 1H), 8.70 (d, $J = 7.7$ Hz, 1H), 7.07 (d, $J = 2.4$ Hz, 1H), 6.97 (d, $J = 7.9$ Hz, 1H), 6.79 (t, $J = 7.8$ Hz, 1H), 6.50 (d, $J = 7.5$ Hz, 1H), 4.51 (dt, $J = 8.0$, 5.9 Hz, 1H), 3.65 (s, 3H), 3.24 (m, 2H), 2.16 (s, 3H); $^{13}$C
NMR (75 MHz, DMSO-d6) δ 171.5, 165.6, 143.6, 129.1, 126.2, 123.4, 119.3, 109.7, 109.2, 105.5, 82.9, 54.3, 52.2, 34.2, 26.2; LRMS(ESI) m/z (relative intensity) 359.1 (75%, M+H\(^+\)), 381.0 (100%, M+Na\(^+\)); HRMS (ESI) m/z calcd for [C\(_{15}\)H\(_{17}\)N\(_2\)O\(_4\)Cl\(_2\)]\(^+\): 359.0565, found 359.0543.

Methyl 10-Hydroxy-7-methylene-6-oxo-1,3,4,5,6,7-hexahydroazocino[4,5,6-cd]indole-4-carboxylate (320). A solution of dichloroamide 318 (157 mg, 0.44 mmol) in CH\(_3\)CN (87.5 mL) in a quartz vessel was degassed by passage of dry nitrogen for 30 min prior to, and during, irradiation. This solution was irradiated at 254 nm in a Rayonet photochemical reactor for 30 min. The resulting light brown solution was concentrated under reduced pressure and purified by flash chromatography on silica gel (1:4 hexanes/EtOAc and 100% EtOAc, respectively) to afford the bridged indole 320 as a yellow solid (83 mg, 66%). mp 232-234 °C; IR (film) 3320, 1736, 1635 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.80 (s, 1H), 7.99 (d, \(J = 7.2\) Hz, 1H), 7.18 (s, 1H), 6.76 (dd, \(J = 7.7, 1.6\) Hz, 1H), 6.50 (dd, \(J = 7.7, 1.9\) Hz, 1H), 5.32 (s, 1H), 5.12 (s, 1H), 4.86 (app br s, 1H), 3.73 (s, 3H), 3.42 (d, \(J = 15.6\) Hz, 1H), 3.21 (dd, \(J = 15.1, 13.2\) Hz, 1H); \(^1\)C NMR (75 MHz, DMSO-d6) δ 172.1, 171.5, 148.7, 144.3, 126.5, 124.8, 124.6, 121.4, 121.2, 112.6, 110.4, 104.9, 55.4, 52.4, 32.1; LRMS(Cl) m/z (relative
intensity) 287.1 (97%, M+H⁺); HRMS (ESI) m/z calcd for [C_{15}H_{15}N_{2}O_{4}]⁺: 287.1032, found 287.1048.

Methyl 10-Benzyloxy-7-methylene-6-oxo-1,3,4,5,6,7-hexahydroazocino[4,5,6-cd]indole-4-carboxylate (SM1). To a solution of hydroxy indole 320 (1.16 g, 4.05 mmol) in DMF (20 mL) was added K₂CO₃ (646 mg, 4.67 mmol) followed by benzylbromide (560 µL, 4.68 mmol). The reaction mixture for stirred at room temperature for 16 h and then poured into ice water and extracted with EtOAc (3 x 40 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1:3 hexanes/EtOAc) to afford the protected product SM1 as a yellow solid (1.24 g, 81%). mp 216-217 °C (recrystallized from EtOAc/MeOH); IR (film) 3333, 1742, 1652 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 11.39 (d, J = 2.1 Hz, 1H), 8.05 (br d, J = 9.0 Hz, 1H), 7.54 (d, J = 7.0 Hz, 2H), 7.42-7.32 (m, 3H), 7.23 (d, J = 2.5 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 5.35 (s, 1H), 5.27 (s, 2H), 5.16 (s, 1H), 4.86 (br t, J ~ 10 Hz, 1H), 3.73 (s, 3H), 3.44 (dd, J = 16.7, 2.6 Hz, 1H), 3.21 (dd, J = 16.3, 12.4 Hz, 1H); ¹³C NMR (75 MHz, DMSO-d₆) δ 171.8, 171.4, 148.3, 145.4, 137.2, 128.4, 127.8, 127.5, 126.6, 125.0, 124.3, 123.2, 120.8, 113.2, 110.5, 102.5, 69.1, 55.3, 52.4, 31.1; LRMS(ESI)
$m/z$ (relative intensity) 377.2 (100%, $M^+$); HRMS (ESI) $m/z$ calcd for $[C_{22}H_{21}N_2O_4]^+$: 377.1501, found 377.1514.

1,5-Di-tert-butyl 4-Methyl-10-benzyloxy-7-methylene-6-oxo-3,4,6,7-tetrahydroazocino[4,5,6-cd]indole-1,4,5-tricarboxylate (322). A solution of (Boc)$_2$O (1.72 g, 7.87 mmol) in CH$_3$CN (10 mL) was cannulated into a suspension of benzhydryl indole SM1 (1.22 g, 3.24 mmol) and DMAP (40 mg, 0.33 mmol) in CH$_3$CN (20 mL). The reaction mixture was stirred at room temperature for 20 min. The resulting dark brown solution was poured into ice water (30 mL) and extracted with ether (3 x 30 mL). The organic extracts were combined, dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether) to afford the desired protected product 322 as a white solid (1.29 g, 69%). mp 179-180 °C (recrystallized from ether); IR (film) 1732, 1692 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J = 6.9$ Hz, 2H), 7.41 (s, 1H), 7.37-7.26 (m, 4H), 6.88 (d, $J = 8.4$ Hz, 1H), 6.35 (s, 1H), 5.92 (s, 1H), 5.21 (s, 2H), 4.77 (dd, $J = 12.6$, 4.1 Hz, 1H), 3.83 (s, 3H), 3.28 (dd, $J = 15.3$, 4.2 Hz, 1H), 3.09 (dd, $J = 14.5$, 12.9 Hz, 1H), 1.54 (s, 9H), 1.07 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.6, 170.8, 151.3, 148.3, 148.1, 144.4, 136.7, 129.9, 128.3, 128.2, 128.0, 127.7, 127.2, 126.0, 125.3, 122.7, 115.2, 108.1, 83.5,
82.6, 70.8, 57.5, 52.5, 27.7, 27.4, 26.5; LRMS(AP+) m/z (relative intensity) 577.2 (95%, M+H⁺); HRMS (AP+) m/z calcd for [C₃₂H₃₇N₂O₈]⁺: 577.2250, found 577.2600.

**Oxoimide 323.** A solution of imide 322 (2.26 g, 3.92 mmol) in THF (39 mL) was cooled to -78 °C and a 1 M solution of N-selectride in THF (4.30 mL, 4.30 mmol) was added slowly. The reaction mixture was stirred for 24 h (-78 °C to room temperature). The resulting red solution was poured into ice water (30 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, passed through a SiO₂ pad, and concentrated under reduced pressure. The crude residue was suspended in CH₃CN (25 mL) and DMAP (48 mg, 0.39 mmol) was added followed by a solution of Boc₂O (1.72 g, 7.88 mmol) in CH₃CN (10 mL). The reaction mixture was stirred at room temperature for 20 min, then additional DMAP (48 mg, 0.39 mmol) was added. The reaction mixture was stirred for another 20 min. The resulting brown solution was poured into ice water (30 mL) and extracted with ether (3 x 40 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether) to afford the bridged amide 323 as a white solid (1.92 g, 90%). mp 96-98 °C (recrystallized from ether/hexanes); IR (film) 1798, 1763, 1744, 1721 cm⁻¹; ¹H
NMR (300 MHz, CDCl₃) δ 7.47 (dd, J = 8.2, 1.7 Hz, 2H), 7.42 (s, 1H), 7.37-7.25 (m, 3H), 7.15 (d, J = 8.5 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 5.17 (s, 2H), 4.86 (dd, J = 4.2, 2.9 Hz, 1H), 3.68 (ddd, J = 17.0, 4.3, 0.6 Hz, 1H), 3.14 (ddd, J = 16.9, 2.8, 2.0 Hz, 1H), 1.52 (s, 3H), 1.48 (s, 9H), 1.07 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 207.9, 170.9, 149.4, 148.6, 147.8, 136.7, 128.9, 128.3, 127.8, 127.5, 127.4, 125.4, 120.2, 119.9, 112.5, 107.8, 84.3, 83.8, 70.8, 64.7, 58.3, 27.9, 27.7, 27.0, 13.5; LRMS(ESI) m/z (relative intensity) 569.2 (100%, M+Na⁺); HRMS (ESI) m/z calcd for [C₃₁H₃₄N₂O₇Na]⁺: 569.2264, found 569.2280.

(±)-tert-Butyl 3-Benzyloxy-8-tert-butoxycarbonylamino-6-methyl-7-oxo-6,7,8,9-tetrahydro-2-azabenzo[cd]azulene-2-carboxylate (324a and 324b). To an ice-cooled solution of imide 323 (746 mg, 1.36 mmol) in THF (27 mL) was added a deoxygenated 1 M aq. LiOH solution (2.7 mL, 2.7 mmol). The reaction mixture was stirred for 14 h (0 °C to room temperature). The resulting slightly yellow solution was poured into ice water (30 mL) and extracted with ether (3 x 30 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether) to afford a
~ 2:1 mixture of diastereomeric ketones 324a and 324b as a white solid (633 mg, 89%).

Major product (324a): mp 156-157 °C (recrystallized from ether); IR (film) 3417, 1756, 1710 cm⁻¹; ¹H NMR (300 MHz, C₆D₆) δ 7.44 (d, J = 6.9 Hz, 2H), 7.26 (s, 1H), 7.23-7.11 (m, 3H), 6.75 (dd, J = 8.2, 1.0 Hz, 1H), 6.59 (d, J = 8.3 Hz, 1H), 5.40 (br d, J = 5.9 Hz, 1H), 4.91 (s, 2H), 4.64 (br dd, J ~ 4.0, 3.0 Hz, 1H), 4.11 (q, J = 6.7 Hz, 1H), 3.24 (dd, J = 15.9, 4.0 Hz, 1H), 3.11 (dd, J = 15.9, 3.0 Hz, 1H), 1.40 (s, 9H), 1.38 (d, J = 6.6 Hz, 3H), 1.32 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 206.4, 155.6, 148.7, 146.6, 137.0, 131.1, 128.2, 127.6, 127.2, 125.8, 124.9, 123.4, 119.7, 115.6, 109.1, 83.2, 79.6, 70.9, 61.4, 44.9, 28.2, 27.7, 27.6, 14.2; LRMS(ESI) m/z (relative intensity) 543.2 (100%, M+Na⁺); HRMS (ESI) m/z calcd for [C₃₀H₃₆N₂O₆Na]⁺: 543.2471, found 543.2467.

Minor product (324b): mp 161-162 °C (recrystallized from ether); IR (film) 3385, 1755, 1717 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.50 (d, J = 6.9 Hz, 2H), 7.40-7.26 (m, 4H), 6.97 (d, J = 8.2 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 5.50 (br s, 1 H), 5.19 (s, 2H), 4.48 (q, J = 6.8 Hz, 1H), 4.31 (br q, J = 6.4 Hz, 1H), 3.26 (app d, J = 7.0 Hz, 2H), 1.59 (d, J = 6.9 Hz, 3H), 1.53 (s, 9H), 1.45 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 208.7, 155.5, 148.8, 146.6, 137.1, 131.1, 128.3, 127.7, 127.4, 125.8, 125.2, 123.3, 121.2, 116.0, 109.2, 83.4, 80.0, 71.1, 59.4, 47.8, 29.2, 28.3, 27.8, 15.8; LRMS(ESI) m/z (relative intensity) 543.3 (78%, M+Na⁺); HRMS (ESI) m/z calcd for [C₃₀H₃₆N₂O₆Na]⁺: 543.2471, found 543.2484.
(±)-tert-Butyl 7-Amino-3-benzyloxy-8-tert-butoxycarbonylamino-7-cyano-6-methyl-6,7,8,9-tetrahydro-2-azabenzo[cd]azulene-2-carboxylate (325a and 325b). A solution of the diastereomeric mixture of ketones 324a and 324b (736 mg, 1.41 mmol) and NH₄Cl (151 mg, 2.82 mmol) in saturated NH₃/MeOH (14 mL) in a sealed tube was heated to 70 °C for 4 h. The reaction mixture was allowed to cool to room temperature and TMSCN (750 µL, 5.62 mmol) was added. The reaction mixture was stirred in a sealed tube at room temperature for 15 h. The resulting yellow suspension was diluted with CH₂Cl₂ (25 mL) and then poured into ice water (20 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (2:1 and 1:1 hexanes/EtOAc, respectively) to afford the aminonitriles 325a (146 mg, 19%) and 325b (297 mg, 38%) as light yellow solids. Minor product (325a): mp 149-150 °C (recrystallized from ether); IR (film) 3379, 1754, 1715 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.49 (d, J = 7.0 Hz, 2H), 7.38-7.25 (m, 4H), 6.97 (d, J = 8.2 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 5.55 (br d, J ~ 8.8 Hz, 1H), 5.16 (s, 2H), 4.43 (br t, J ~ 9.3 Hz, 1H), 3.48 (q, J = 6.9 Hz, 1H), 3.11 (dd, J = 14.9, 10.5 Hz, 1H), 2.97 (dd, J = 15.9, 3.0 Hz, 1H), 1.92 (br s,
2H), 1.55 (d, \( J = 7.1 \) Hz, 3H), 1.51 (s, 9H), 1.46 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 154.9, 148.8, 146.8, 137.0, 131.0, 128.2, 127.6, 127.3, 125.7, 125.2, 124.5, 123.7, 121.9, 115.5, 108.7, 83.3, 80.0, 70.9, 62.5, 52.9, 46.3, 28.4, 28.3, 27.7, 19.0; LRMS(ESI) \( m/z \) (relative intensity) 547.3 (100%, M+H\(^{+}\)); HRMS (ESI) \( m/z \) calcd for [C\(_{31}\)H\(_{39}\)N\(_4\)O\(_5\)]\(^{+}\): 547.2920, found 547.2940.

Major product (325b): mp 143-144 °C (recrystallized from ether); IR (film) 3318, 2222, 1755, 1714 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.49 (d, \( J = 7.0 \) Hz, 2H), 7.38-7.25 (m, 4H), 6.96 (d, \( J = 8.2 \) Hz, 1H), 6.79 (d, \( J = 8.2 \) Hz, 1H), 5.22 (br d, \( J = 9.4 \) Hz, 1H), 5.17 (s, 2H), 3.95 (t, \( J = 9.3 \) Hz, 1H), 3.68 (q, \( J = 7.0 \) Hz, 1H), 3.26 (dd, \( J = 15.4, 9.9 \) Hz, 1H), 2.92 (d, \( J = 14.3 \) Hz, 1H), 2.01 (br s, 2H), 1.60 (d, \( J = 7.1 \) Hz, 3H), 1.52 (s, 9H), 1.45 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 155.7, 148.9, 147.0, 137.1, 132.2, 128.3, 127.6, 127.3, 125.1, 124.9, 124.0, 122.7, 122.3, 116.7, 108.9, 83.3, 80.5, 71.0, 65.7, 58.5, 42.0, 30.0, 28.2, 27.8, 15.2; LRMS(AP+) \( m/z \) (relative intensity) 547.3 (100%, M+H\(^{+}\)); HRMS (AP+) \( m/z \) calcd for [C\(_{31}\)H\(_{39}\)N\(_4\)O\(_5\)]\(^{+}\): 547.2920, found 547.2881.

(±)-\textit{tert}-Butyl 3-Benzoxyl-8-\textit{tert}-butoxycarbonylamino-7-cyano-7-methoxy-carbonylamino-6-methyl-6,7,8,9-tetrahydro-2-azabeno[cd]azulene-2-carboxylate
(326). To a mixture of aminonitrile 325b (294 mg, 0.54 mmol) and K₂CO₃ (149 mg, 1.08 mmol) was added THF (6 mL) followed by methylchloroformate (MocCl) (540 µL, 6.42 mmol). The reaction mixture was heated to reflux and held there for 24 h. The resulting yellow solution was allowed to cool to room temperature, poured into ice water (15 mL), and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:2 hexanes/ether) to afford the desired product 326 as a white solid (289 mg, 89%). mp 120-122 °C; IR (film) 3323, 2237, 1755, 1730, 1684 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.49 (d, J = 6.8 Hz, 2H), 7.37-7.25 (m, 4H), 7.00 (d, J = 8.2 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.27 (br s, 1H), 5.40 (br d, J = 9.3 Hz, 1H), 5.17 (s, 2H), 4.33 (ddd, J = 8.9, 7.9, 5.1 Hz, 1H), 4.15 (q, J = 7.0 Hz, 1H), 3.70 (s, 3H), 3.31 (dd, J = 16.5, 4.8 Hz, 1H), 3.17 (dd, J = 15.9, 7.6 Hz, 1H), 1.50 (s, 9H), 1.46 (s, 9H), 1.44 (d, J = 7.0, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 156.6, 155.2, 148.7, 146.9, 137.0, 131.1, 128.2, 127.6, 127.3, 125.7, 125.2, 125.0, 123.9, 117.6, 114.1, 108.9, 83.3, 81.2, 70.9, 65.5, 54.1, 52.3, 42.7, 30.1, 28.1, 27.7, 17.1; LRMS(ESI) m/z (relative intensity) 622.3 (55%, M+NH₄⁺); HRMS (ESI) m/z calcd for [C₃₅H₄₆N₅O₇]⁺: 622.3241, found 622.3260.
(±)-Spiroyclic Imidazolone 327. To a solution of aminonitrile 326 (44 mg, 0.073 mmol) in MeOH (4 mL) was added cobalt (II) chloride (236 mg, 7.82 mmol). The resulting dark blue solution was cooled in an ice bath and sodium borohydride (69 mg, 1.8 mmol) was added in portions. The resulting black suspension was stirred at 0 °C for 30 min. Then additional sodium borohydride (69 mg, 1.8 mmol) was added in portions. The reaction mixture was stirred for 14 h (0 °C to room temperature). The resulting black suspension was diluted with CH₂Cl₂ (4 mL) and acidified with 1 M HCl solution (6 mL). The acidic solution was stirred vigorously for 1 h until it turned fuchsia and clear. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was dissolved in EtOH (1 ml) and a 1 M LiOH solution (1 mL) was added. The reaction mixture was heated to ~95 °C for 6 h. The resulting black suspension was diluted with CH₂Cl₂ (10 mL), and poured into ice water (5 mL) and brine (5 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3% and 5% saturated NH₃/MeOH in
CH₂Cl₂) to afford the desired product 327 as a yellow solid (15 mg, 43%). mp 222-224 °C IR (film) 3260, 1701 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.59 (br s, 1H), 7.47-7.35 (m, 5H), 6.94 (s, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.64 (d, J = 7.9 Hz, 1H), 5.43 (br s, 1H), 5.24 (br d, J = 9.0 Hz, 1H), 5.15 (s, 2H), 4.96 (s, 1H), 4.55 (br m, 1H), 3.58 (q, J = 7.0 Hz, 1H), 3.38 (m, 2H), 3.13 (d, J = 9.5 Hz, 1H), 2.81 (dd, J = 15.9, 12.0 Hz, 1H), 1.46 (s, 9H), 1.36 (d, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, DMSO-d₆) δ 161.6, 155.9, 143.5, 137.5, 128.3, 127.8, 127.7, 127.5, 126.3, 125.0, 122.3, 119.1, 109.9, 102.9, 77.9, 69.1, 65.7, 49.6, 48.4, 44.6, 28.3, 28.2, 19.4; LRMS(ESI) m/z (relative intensity) 477.2 (100%, M+H⁺); HRMS (ESI) m/z calcd for [C₂₇H₃₃N₄O₄]⁺: 477.2502, found 477.2505.

(±)-Spirocyclic Imidazolone SM2. To an ice-cooled solution of the cyclic imidazolone 327 (7.5 mg, 0.016 mmol) in a mixture of THF (0.5 mL) and H₂O (0.1 mL) was added DDQ (11 mg, 0.048 mmol). The reaction mixture was stirred for 2 h (0 °C to room temperature). The resulting dark yellow solution was diluted with EtOAc (5 mL) and washed with saturated NaHCO₃ solution (3 x 5 mL). The aqueous layer was extracted with EtOAc (5 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was
purified by flash chromatography on silica gel (3% and 5% saturated NH₃/MeOH in CH₂Cl₂) to afford the desired product SM2 as a yellow solid (5.2 mg, 68%). mp 240 °C (dec.); IR (film) 3368, 1704, 1641 cm⁻¹; ¹H NMR (300 MHz, acetone-d₆) δ 11.76 (br s, 1H), 8.14 (d, J = 3.1 Hz, 1H), 7.56 (d, J = 6.8 Hz, 2H), 7.44-7.34 (m, 3H), 7.10 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.36 (d, J = 6.1 Hz, 1H), 5.75 (s, 1H), 5.42 (s, 1H), 5.28 (s, 2H), 5.08 (d, J = 6.3 Hz, 1H), 3.61 (q, J = 7.1 Hz, 1H), 3.16 (d, J = 9.3 Hz, 1H), 3.05 (d, J = 9.7 Hz, 1H), 1.54 (d, J = 7.1 Hz, 3H), 1.46 (s, 9H); ¹³C NMR (75 MHz, acetone-d₆) δ 189.2, 162.6, 158.7, 145.3, 138.1, 132.8, 129.3, 128.8, 128.6, 128.0, 127.7, 124.5, 123.9, 116.1, 106.0, 80.1, 70.8, 64.5, 62.4, 50.3, 48.7, 28.5, 20.9; LRMS(ESI) m/z (relative intensity) 491.1 (100%, M+H⁺); HRMS (ESI) m/z calcd for [C₂₇H₃₁N₄O₅]⁺: 491.2294, found 491.2278.

(±)-N-Boc Ketoindole 328. A solution of Boc₂O (15 mg, 0.069 mmol) in CH₃CN (0.1 mL) was slowly added to a suspension of the keto indole SM2 (18 mg, 0.037 mmol) and DMAP (0.5 mg, 0.004 mmol) in CH₃CN (0.5 mL). The reaction mixture immediately turned yellow and clear. It was stirred at room temperature for 20 min, and then diluted with CH₂Cl₂ (10 mL). The mixture was poured into ice water (5 mL) and brine (5 mL).
The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL). The organic extracts were combined, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% saturated NH$_3$/MeOH in CH$_2$Cl$_2$) to afford the desired Boc-protected product 328 as a white solid (12 mg, 55%). mp 250 °C (dec.); IR (film) 3384, 1768, 1711, 1659 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.30 (s, 1H), 7.50 (d, $J$ = 7.3 Hz, 2H), 7.40-7.2 (m, 3H), 7.14 (d, $J$ = 8.3 Hz, 1H), 6.95 (d, $J$ = 8.3 Hz, 1H), 6.13 (d, $J$ = 5.8 Hz, 1H), 5.79 (s, 1H), 5.25 (d, $J$ = 19.7 Hz, 1H), 5.18 (d, $J$ = 11.7 Hz, 1H), 5.13 (d, $J$ = 5.7 Hz, 1H), 4.54 (s, 1H), 3.69 (q, $J$ = 7.0 Hz, 1H), 3.13 (app s, 2H), 1.62 (d, $J$ = 7.1 Hz, 3H), 1.53 (s, 9H), 1.50 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 189.4, 161.9, 157.9, 147.8, 146.0, 136.5, 135.1, 128.4, 128.0, 127.6, 126.8, 126.7, 125.3, 124.8, 116.9, 109.3, 85.7, 80.7, 71.1, 64.2, 64.5, 48.8, 47.7, 28.3, 27.6, 20.8; LRMS(ESI) m/z (relative intensity) 591.3 (100%, M+H$^+$); HRMS (ESI) m/z calcd for [C$_{32}$H$_{39}$N$_4$O$_7$]$^+$: 591.2819, found 591.2872.
Bibliography


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