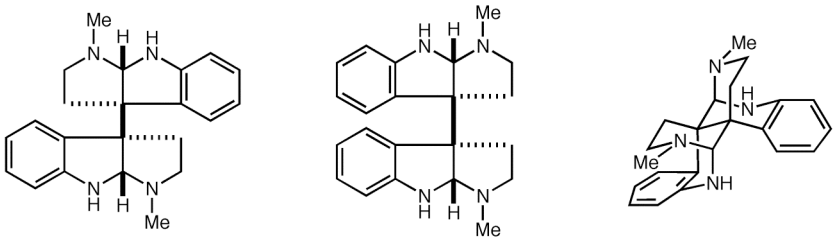
C h a p t e r 3

Synthetic Studies Towards Bis-Quaternary Carbon Containing Pyrroloindolines

Introduction

The Calycanthaceous alkaloids contain a challenging bis-quaternary carbon stereogenic architectural motif that has been the inspiration for numerous elegant synthetic studies. The structural elucidation of the parent compounds, chimonanthine and calycanthine represent a hallmark in structural elucidation by degradation.[1-4]

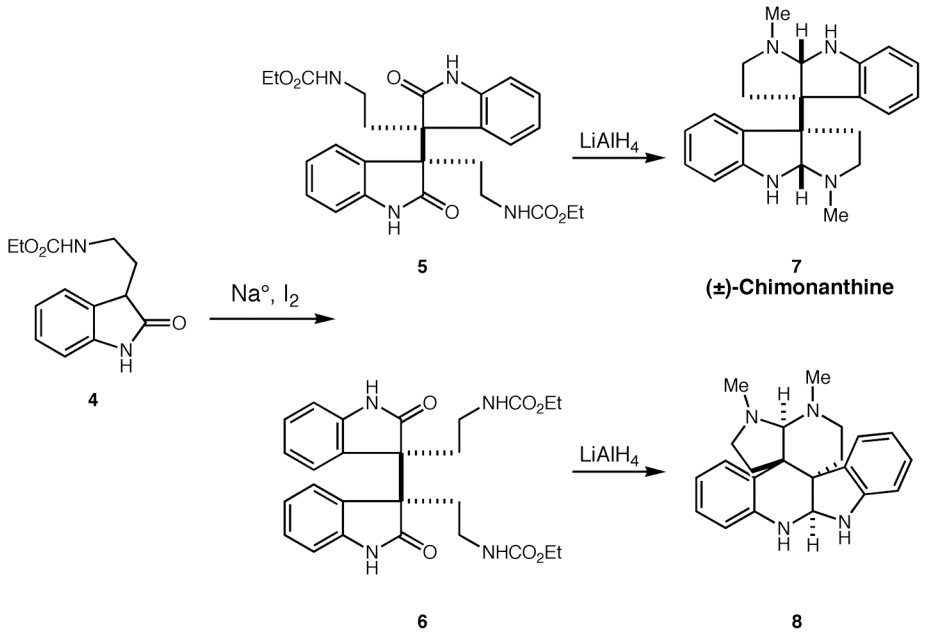
Figure 1. Structurally Related Cyclotryptamine Alkaloids Natural Isolates



(–)-Chimonanthine **1** | ***meso*-Chimonanthine** **2** | **(+)-Calycanthine** **3**

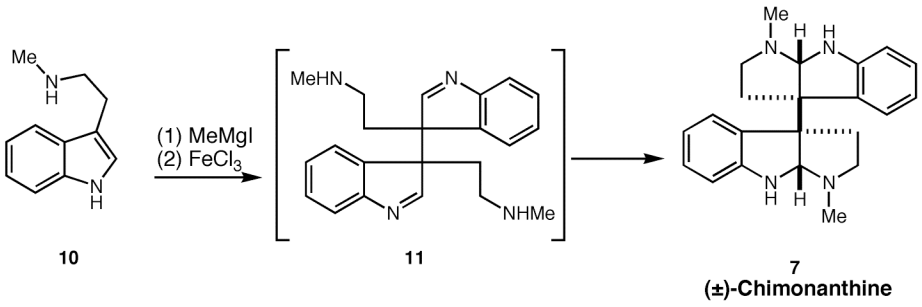
These structurally related natural isolates (Figure 1) are all thought to be biosynthetically related to tryptamine *via* an oxidative dimerization. The groups of Hendrickson[5,6] and Scott[7] employed two notable dimerization strategies in their syntheses. Hendrickson, as shown in Figure 2, dimerized the sodium salt of oxotryptamine **4** in the presence of iodine to produce a racemic and diastereotopic mixture of bis-oxindoles **5** and **6**. Reduction of the C_2 symmetric diastereomer with lithium aluminum hydride produced racemic chimonanthine **7**. Interestingly, reduction of the *meso*-diastereomer produced geometrically rearranged product **8**.

Figure 2. Hendrickson Oxidative Dimerization of Oxotryptamine 4



As shown in Figure 3, Scott found that the Grignard derivative of N-methyltryptamine **10** was oxidized by ferric chloride to directly produce racemic chimonanthine in 20% yield. A small amount of *meso*-chimonanthine was also observed. From this work the presence of intermediate bis-indolenine **11** was postulated.

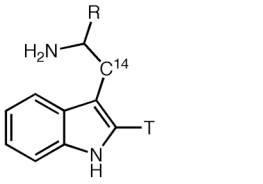
Figure 3. Scott's Oxidative Dimerization of Tryptamine 10



Though these two complementary approaches both provide the desired hexacyclic natural products, they proceed in low yields and are not diastereoselective. With respect to the biosynthesis of the Calycanthaceous alkaloids, it was unclear as to whether an oxindole (such as **5** or **6**) or bis-indolenine intermediate (such as **11**) was present. To

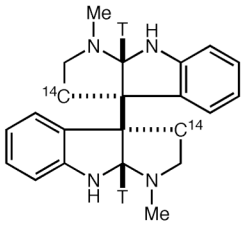
answer this question, Kirby converted doubly labeled tryptamine and tryptophan to chimonanthine by feeding the precursors to leaf bearing shoots of *Chimonanthus fragrans*.[8] As shown in Figure 4, good incorporation of [β-^{14}C, 2-^{3}H]-tryptamine (11.1%) and (±)-[β-^{14}C, 2-^{3}H]-tryptophan (3.6%) into chimonanthine was observed. These labeling experiments demonstrated that the biosynthetic pathway does not involve the oxidative coupling of an oxindole intermediate. Due to the incorporation of the radiolabels, a bis-indolenine intermediate (such as **11**) has become the accepted core structure for the biosynthesis of this architecture.

Figure 4. Kirby's Feeding Experiment Establishes Pathway



12 R= H, Tryptamine

13 R=CO_2H, Tryptophan



7

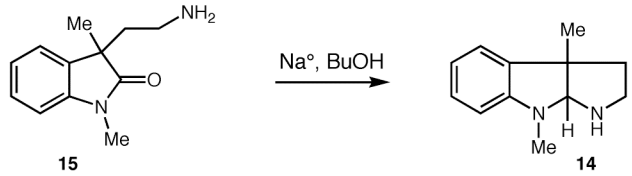
Labelled (±)-Chimonanthene

Shoots grown for 7 days in aqueous solution of **12** or **13**. Then extracted.

Kirby thus established that there is not an oxindole intermediate in the biosynthesis of the Calycanthaceous alkaloids. Though oxindoles are not intermediates in the synthesis of the Calycanthaceous alkaloids, these structures have been widely studied as precursors for pyrroloindolines.[9]

Julian first succeeded in synthesizing the pyrroloindoline core **14** by using the Ladenburg reduction on a 3,3-disubstituted oxindole ethylamine **15** (Figure 5).[10] Since Julian's work, many synthetic efforts on the pyrroloindoline architecture have focused on oxindole intermediates. [9]

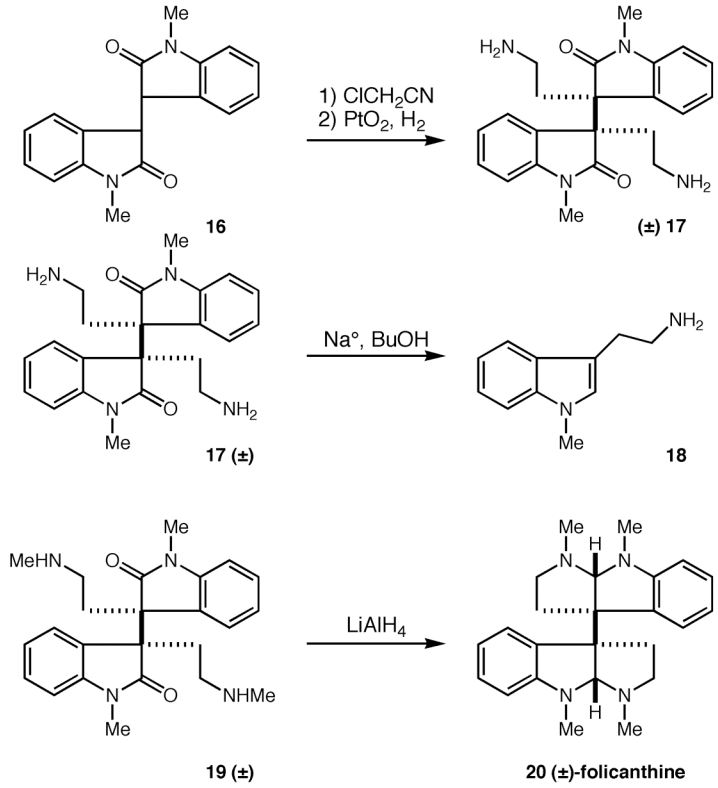
Figure 5. Julian's Reductive Cyclizations onto Oxindoles Produced Pyrroloindolines



15 **14**

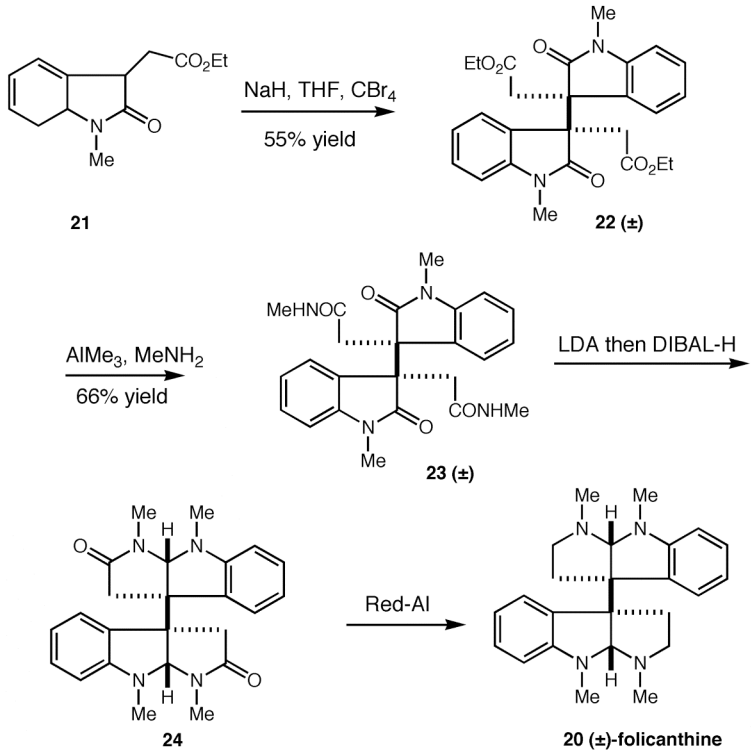
In a series of monographs,[11-13] Hino demonstrated in 1961 and 1963 that bis-oxindole ethylamine **17** could be synthesized from bis-oxindole **16** via successive alkylations with chloroacrylonitrile (Figure 6). Hino also disclosed that the Ladenburg reduction causes cleavage of the corresponding bis-quaternary system **17** to N-methyltryptamine **18** (Figure 6) whereas the lithium aluminum hydride reduction of **17** provided only starting material. Shortly after Hendrickson disclosed his synthesis of chimonanthine in 1962, Hino demonstrated that the lithium aluminum hydride reduction of **19** proceeds to racemic folicanthine **20** (yield not given, Figure 6).[14]

Figure 6. Hino Prepares bis-quaternary Carbons via Alkylation of Indigo Derivative 16



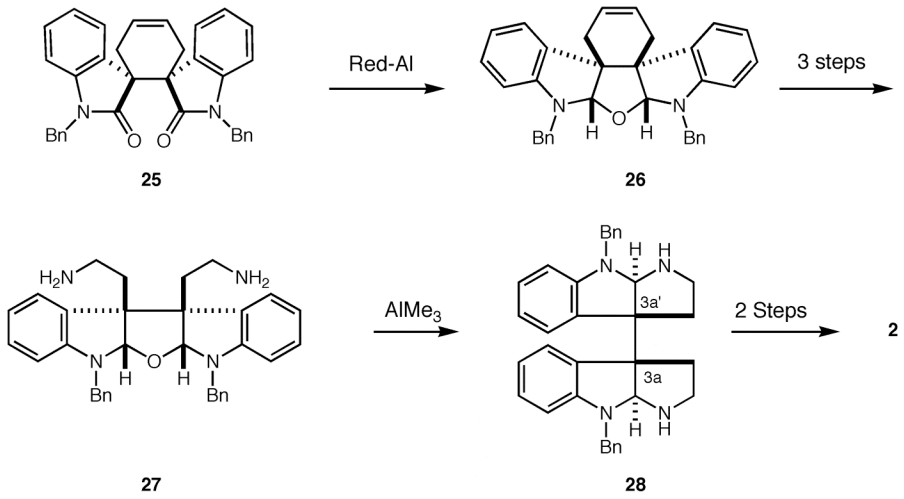
Rodrigo has also synthesized racemic folicanthine through an oxindole intermediate (Figure 7).[15] Though longer in chemical steps, Rodrigo's radical anion chain dimerization of **21** proceeds with much higher chemical efficiency than the previously mentioned dimerizations to produce the bis-quaternary oxindole **22**. Bis-amide **23**, prepared from **22**, was reduced to 24 by a process in which the lithium salt of the secondary amide was preformed with lithium diisopropylamide in THF followed by reduction with DIBAL-H. Reduced compound **24** could be converted to (±)-folicanthine by the action of Red-Al.

Figure 7. Rodrigo Finds Improved Reaction Conditions for Dimerization



As mentioned in Chapter 2, elegant work by the Overman group has produced concise syntheses of (+), (–), and *meso*—chimonanthine, (+), (–), and *meso*—calycanthine,[16-18] idiospermuline,[19] quadrigemine C, psycholeine,[20] hodgkinsine, hodgkinsine B,[21] ditryptophenaline and *ent*—WIN 64821.[22] Like the previous synthetic efforts of Hendrickson, Hino, and Rodrigo, Overman proceeds through oxindole intermediates. Since Overman's synthetic sequence to produce the bis-quaternary structure has been dealt with in Chapter 2 of this thesis, only the key NCN bond forming steps will be discussed in more detail here. In the stereocontrolled synthesis of *meso*-chimonanthine **2**, cyclohexene **25** was converted to hexacycle **26** by the action of Red-Al (Figure 8). Elaboration to bis-ethylamine intermediate **27** is followed by reductive cyclization to forge the desired hexacycle **28**. Subsequent elaboration of **28** provided **2**.

Figure 8. Overman Utilizes a di-aminol as a Synthetic Intermediate



Direct Pyrroloindoline Formation Route

With the exception of Scott's synthesis, all of the syntheses discussed to this point have utilized bis-oxindole intermediates. As discussed above, Hendrickson and Hino both found interesting behavior associated with bis-oxindole intermediates. In particular, Hino notes that they have a propensity to fragment about the 3-3a quaternary carbon juncture. There is also evidence that this fragmentation occurs in the syntheses from the Rodrigo and Overman groups.

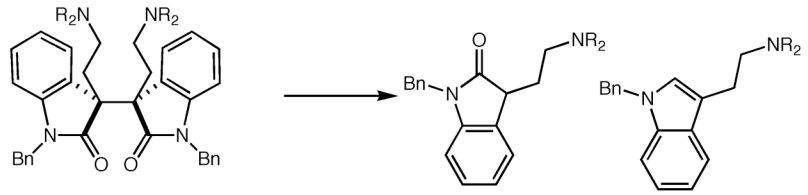
Rodrigo found it difficult to transform bis-amide **23** (from figure 7) to folicanthine and states (numbering changed for consistency and clarity) that…

"Treatment with various reducing agents (lithium aluminum hydride, lithium triethyl borohydride, various borane derivatives, sodium borohydride with methanesulfonic acid in DMSO) under many conditions in different solvents resulted in complex mixtures of products or no reaction at all; borane reduction of **23** produced a low yield of N1,N-dimethyltryptamine resulting from cleavage of the long (1.58Å in **22**) C3-C3' bond of **23**."

This is consistent with Hino's observations concerning bis-reductions of di-amines onto bis-oxindoles.

Interestingly, as shown in Figure 9, Link and Overman[18] state that *meso*-symmetric compound **29** can be synthesized from **25** but that treatment with reducing agents typically lead to a ~1:1 mixture of oxindole and indole fragments **30** and **31**. This result is in keeping with the known propensity of these compounds to fragment that has been observed by Hino and Rodrigo.

Figure 9. Overman Observes Fragmentation to 30 and 31



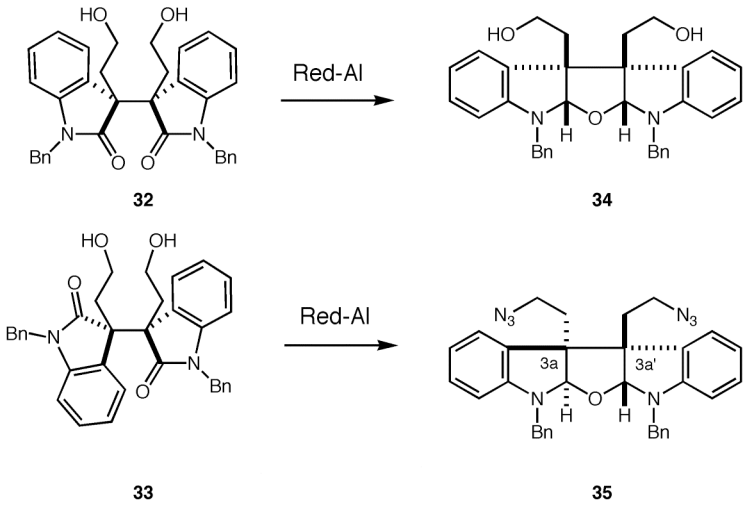
29 **30** **31**

R=alkyl or H and CO_2R'

Later work by Overman[17] showed that both the acyclic meso and D/L diastereomers of diols **32** and **33** can be converted to pentacycles **34** and **35** respectively (Figure 10). These diol pentacycles were then converted the desired hexacyclic alkaloids. Subsequently the Overman group has disclosed numerous elegant syntheses of pyrroloindoline containing alkaloids.[23-25]

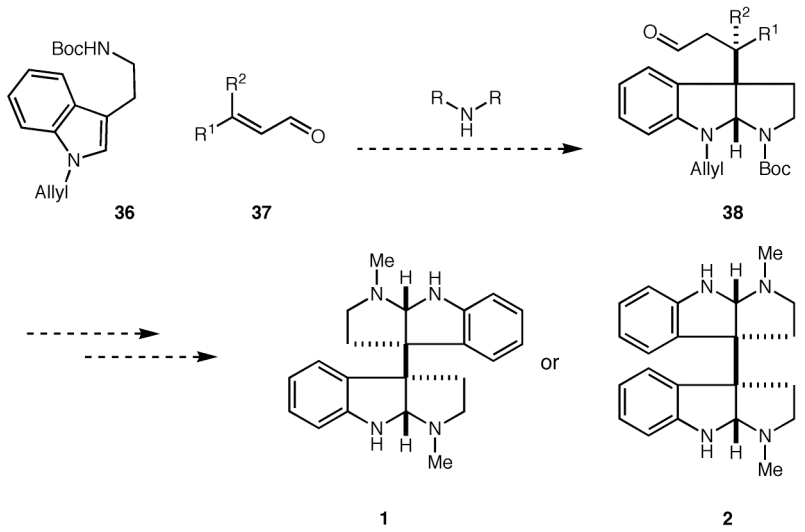
Mindful of the elegant work on this class of natural products, we sought to extend our direct pyrroloindoline construction to molecules bearing vicinal quaternary stereogenicity. We anticipated that if successful, this technique may serve as a complementary approach to the work of Overman and others.

Figure 10. Later Overman Work Circumvents Fragmentation



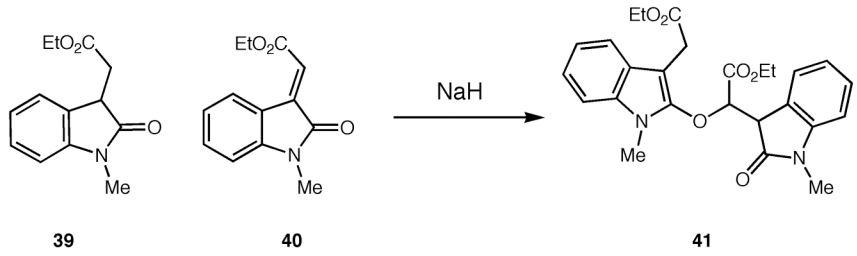
With the desire to access the bis-quaternary carbon architecture of the Calycanthaceous alkaloids we sought to extend the direct pyrroloindoline construction reaction to an appropriate β,β-disubstituted enal (Figure 11, union of **36** and **37** to produce **38**).[26] It was anticipated that if the direct pyrroloindoline construction were feasible and stereoselective that our synthesis would more closely model the biomimetic synthesis than previous syntheses have. We further anticipated that avoiding a bis-oxindole intermediate would obviate some of the known issues associated with the synthesis of these molecules. In close collaboration with Dr. Gérald Lélais, synthetic studies to achieve this objective were undertaken.

Figure 11. Desired Synthesis to Mimic Biomimetic Pathway



In Rodrigo's synthesis of folicanthine, an interesting, yet unsuccessful, approach to the bis-quaternary architecture was noted (figure 12). Rodrigo states (numbering changed for consistency and clarity) that "A Michael addition of the oxindole enolate generated from **39** with sodium hydride, to the unsaturated ester only gave **41**, the dimmer formed by addition of the enolate oxygen to the double bond of **40**." It was speculated that a structure similar to **40** could be utilized as our enal in conjunction with out direct pyrroloindoline formation reaction.

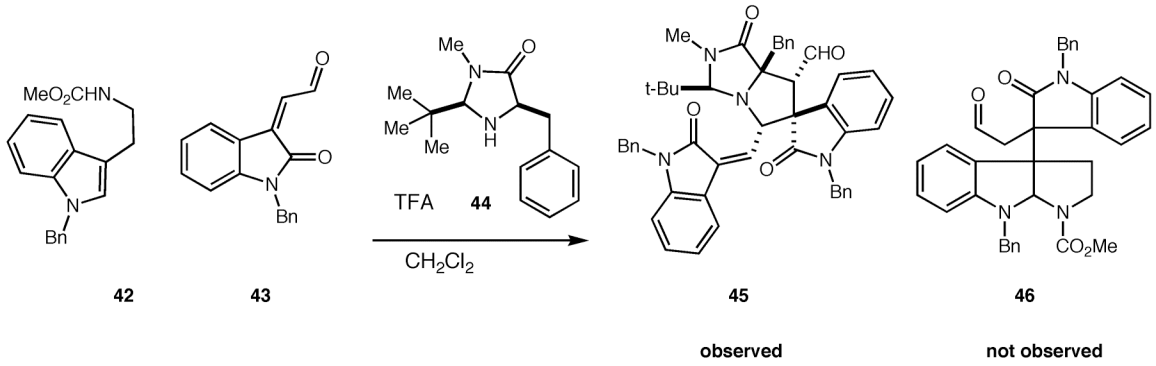
Figure 12. Literature Precedent for Michael Addition Approach



The organocatalytic union of tryptamine **42** with known conjugated isatin **43** in the presence of catalyst **44** (Equation 1) was attempted. The product formed from this

reaction, as well as the reaction with other tryptamines, is catalyst incorporated adduct **45**. None of the desired conjugate addition adduct **46** could be identified from any of the reactions attempted. The relative stereochemistry of structure **45** was assigned by correlations in the HMBC as well as ROESY spectra

Equation 1. Undesired Formation of Catalyst Incorporated Product

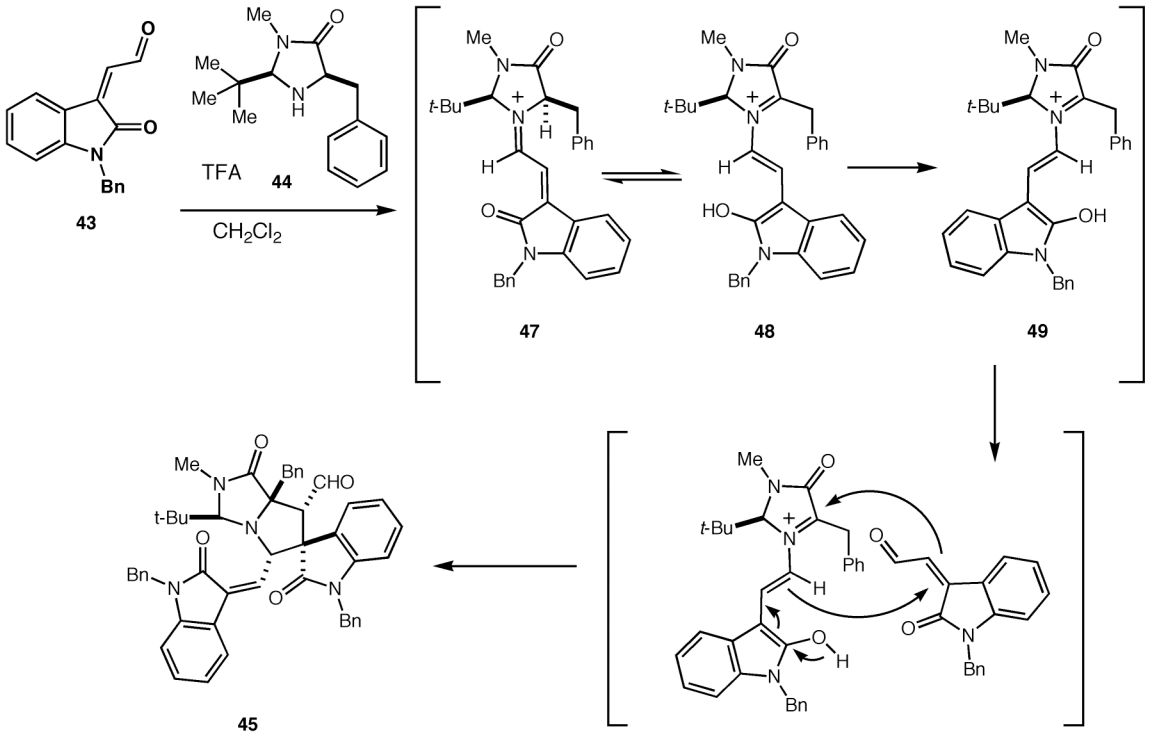


42 **43** **45** **46**

observed **not observed**

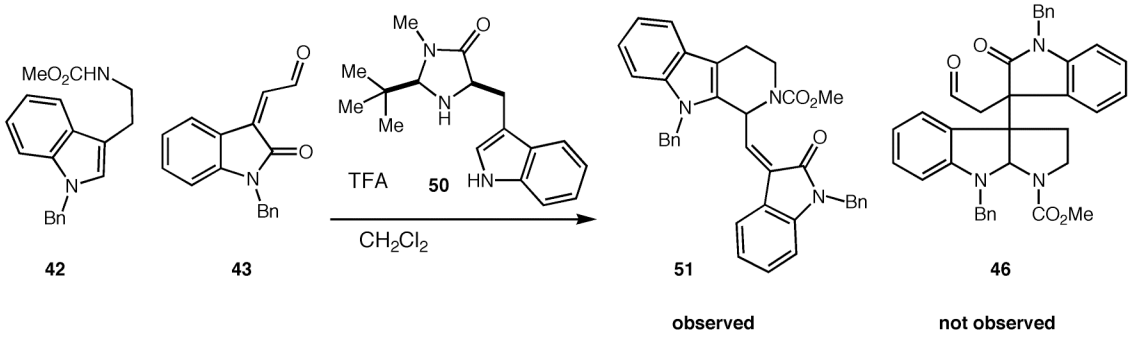
Catalyst incorporated adduct **45** is thought to arise from deprotonation of the catalyst iminium species **47** to produce dipolarophile **48** which equilibrates to dipolarophile **49**. Cycloaddition of dipolarophile **49** with another equivalent of **43** produces the catalyst-bound adduct (Figure 13).

Figure 13. Proposed Mechanism for the Formation of Catalyst Incorporated Adduct 45



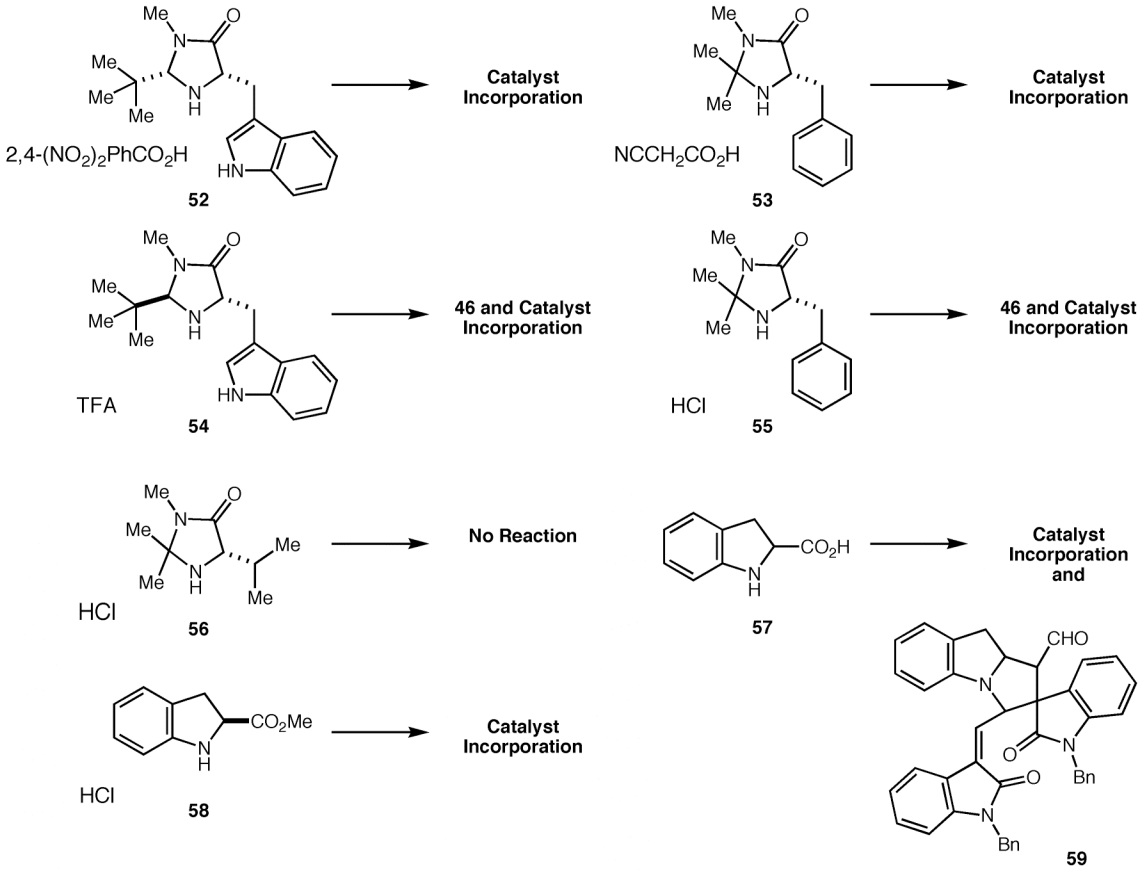
Exploration of this reaction with the tryptophan-derived catalyst **50** (Equation 2) was found to cleanly produce Pictet-Spengler adduct **51** in quantitative yield when the TFA salt of the catalyst is used. It has also been found that **51** can be synthesized by the action of TFA in the absence of amine catalyst. None of the desired conjugate addition adduct **46** could be identified from any of the reactions attempted.

Equation 2. Pictet-Spengler by-product 51 Formed in Preference to 46



Due to the nature of the catalyst-incorporated adduct **45** as well as the rapid synthesis of Pictet-Spengler adduct **51**, it was hypothesized that alternate catalyst structures, as well as alternate acidities of counter ion may affect the formation of desired adduct in preference to these byproducts. As shown in Figure 14 other reaction conditions failed to yield the desired bis-quaternary adduct. The only products that were formed were a mixture of the analogous catalyst-incorporated adducts and the Pictet-Spengler product **51**. Reaction with catalysts **52** and **53** were meant to test the hypothesis that modulation of the cocatalyst acidity would bias the reaction toward conjugate addition. Unfortunately that outcome did not occur. Reaction with catalysts **54**, **55** and **56** were meant to test the hypothesis that the catalyst-iminium complex would react with tryptamine **42** instead of isatin **43** if the steric environment was modulated to hinder formation of dipolarophiles such as **49**. Unfortunately that outcome did not occur. Reaction with catalysts **57** and **58** were meant to test the hypothesis that an indoline catalyst (as opposed to an imidazolidinone) may bias the reaction toward conjugate addition.[27] Of note is the reaction catalyzed by indoline catalyst **58**. In this reaction a third by-product, that of the decarboxylated catalyst incorporated adduct **59**, was formed. Again, none of the desired conjugate addition adduct **46** could be identified from any of these reactions.

Figure 14. Other Catalysts Likewise do not Produce Desired Conjugate Addition Adduct 46

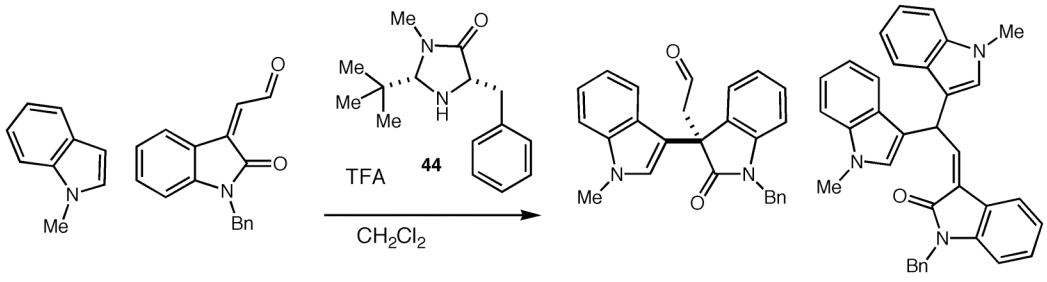


Examination of Isatin Derived Aldehyde 43

It is well precedented that β,β-disubstituted enals are significantly less reactive in organocatalyzed processes than the corresponding mono-substituted analogues.[28] To understand the issues associated with the failure to produce **46**, investigation of isatin-derived enal **43** was begun. To assay the viability of utilizing **43** as a substrate for the direct construction of vicinal quaternary stereocenters, a model study with N-methylindole **60** was undertaken. It was found that this alkylation, Equation 3, progressed to afford two different compounds in variable yields. Compound **61** is the product of N-methylindole undergoing a Friedel-Crafts alkylation at the β position of the enal whereas **62** is the product of N-methylindole undergoing successive Friedel-Crafts

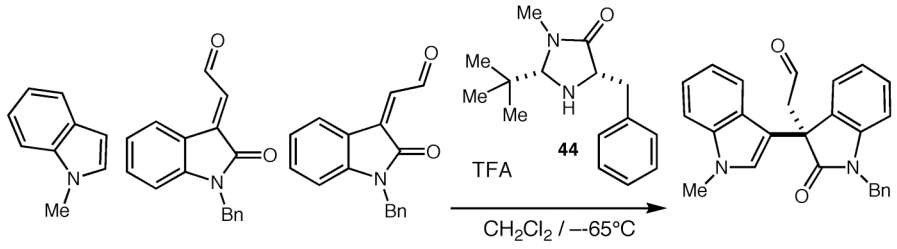
alkylations at the α position of the enal. Though undesirable, it was found that the amount of **62** produced was dependent on the temperature of the reaction and that cold temperatures (–65°C) eliminated its production.

Equation 3. Isatin Model Study with N-methylindole



A preliminary survey of reaction conditions showed that production of **61** could be made moderately enantioselective. Additionally, it was shown that the olefin geometry of enal **43** is important. Reaction of **60** with the ***Z*-43** geometry produced a facile reaction whereas reaction with the ***E*-43** was sluggish and proceeded with the same sense of enantioinduction. This indicated to us that the *E*-isomer slowly equilibrates to the *Z* under reaction conditions as shown in Table 1. At this point we decided to not pursue the optimization of the enantioselectivity of **61** further.

Table 1. Isatin Enal can be Utilized Successfully for a More Reactive System



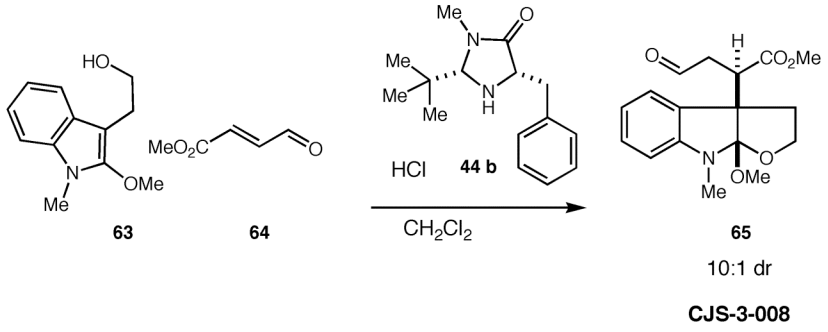
Ratio		ee	Relative Rate
E **- 40**	**Z - 40**	**61**	
>50	1	71.7	Very Slow
1.9	1	74	Slow
1	1.5	74	Slow
1	>50	75	Fast

Interest in Friedel-crafts adduct **61** led us to believe that a viable route could still be found for the organocatalytic construction of a desired bis-quaternary adduct. Since it was apparent that the tryptamines (such as **42**) would not react with **43** to provide the desired bis-quaternary adduct this route was abandoned. As such, the identification of a more reactive tryptamine that would produce the requisite bis-quaternary architecture was sought.

Initial Investigation of Oxindole Alkylation

As part of his studies on the direct furanoindoline construction, Dr. Christopher Sinz determined that methoxyindole **63** reacted with conjugated glyoxal **64** to form methoxyl furanoindoline **65** (Equation 4).

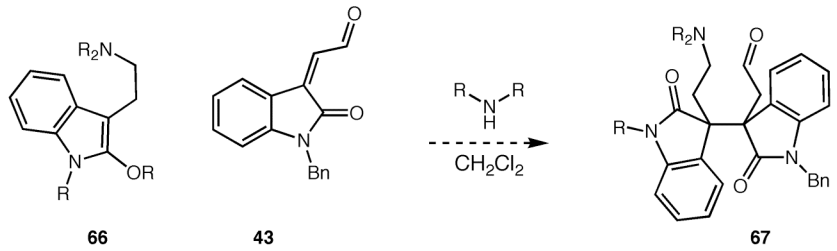
Equation 4. Oxindole Alkylation by Dr. Christopher Sinz



Having noted the preponderance of bis-oxindoles as intermediates in the previous syntheses of the Calycanthaceous alkaloids, and the higher nucleophilicity of oxindoles than indoles, we sought to extend this reaction to prepare 3,3a-bis-oxindoles. It was anticipated that an oxindole alkylation with **43** could provide a framework for elaboration to the hexacyclic core of the Calycanthaceous alkaloids. With this in mind we anticipated that reaction of protected oxotryptamine **66** with **43** would furnish a bis-

oxindole adduct **67** (Figure 15). It was further anticipated that **67** may serve as a valuable structure for the synthesis of bis-quaternary oxindole compounds

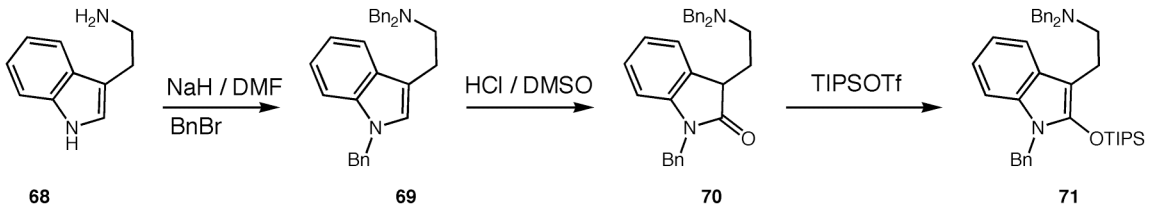
Figure 15. Proposed bis-oxindole Construction



Path to Bis-Oxindole Diethylamine

Tryptamine (**68**) was subjected to sodium hydride in dimethylformamide and tribenzylated with three equivalents of benzyl bromide to provide **69** in good yield (Figure 16). Dissolving **69** in DMSO and exposing this solution to concentrated hydrochloric acid achieved its conversion to **70**. This reaction proceeds with the loss of dimethyl sulfide as a byproduct in a presumed Swern-like mechanism. The yields of this reaction are variable depending on the vigor with which the DMSO solution is stirred. Caking of crude product on the side of the flask can occur which results in non-specific product degradation. Upon purification, **70** can be converted to siloxytryptamine **71** in near quantitative yield.

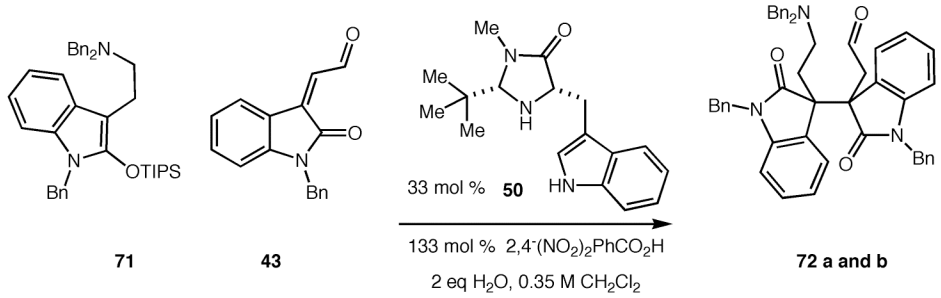
Figure 16. Synthesis of Siloxytryptamine Precursor



After much work, it was found that the reaction of **71** with **43** (Equation 5) was greatly affected by the quantity of water and the strength of the acid cocatalyst in the

reaction. Notably, the reaction does not proceed in the absence of water and facile hydrolysis of **71** to oxindole **70** is observed when large (>15% by volume) quantities of water are used. Likewise, it was found that in order for the reaction to proceed an extra equivalent of acid is required to protonate the ethylamine moiety of **71**. Strong acids such as TFA though were found to facilitate rapid hydrolysis of **71** to **70**. Weak acids such as 2,4-dinitrobenzoic acid, though, were found to promote the union of the reactive partners. Surprisingly, reaction of **71** with **43** in the presence of catalyst **50** produces a small quantity of the aforementioned catalyst incorporated product along with a ~1:1 diastereomeric mixture of fragile aldehydes **72a** and **72b**. Utilization of salts of catalyst **44** provided significantly lower amounts of **72a**, **72b**, catalyst incorporated adduct **45** and two inseparable compounds whose identity remains a mystery. [29] Supercritical fluid chromatography was utilized to separate **72a** and **72b** into their enantiomeric pairs. It was found that this reaction is poorly enantioselective providing **72a** in 33% ee and **72b** in 40% ee. The low observed diastereo- and enantiocontrol in this reaction is in stark contrast with that observed for the direct pyrroloindoline construction. This perhaps lends credence to the stereochemical models given in chapter 2. Namely, a β,β-disubstituted enal would contain three more or less equally encumbered quadrants and a 2-substituted tryptamine would change the S group to roughly the same size as the M group. These occurrences would perhaps combine to provide a reaction environment less amenable to high selectivity.

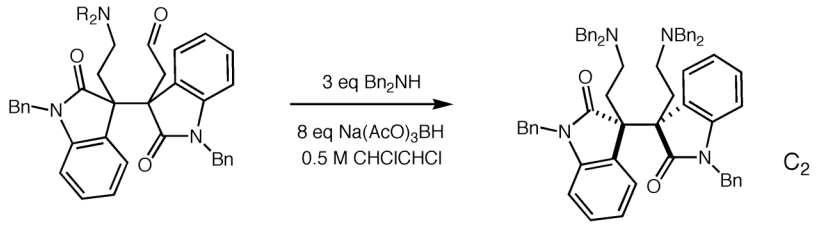
Equation 5. Successful Union to Synthesize bis-quaternary Dioxindole



71 **43** **72 a and b**

Good yield can be attained for bis-oxindole ethylamines **73** and **74** (Equations 6 and 7) under reductive amination conditions. Compound **73** was found to be the C_2 symmetric diastereomer via correlation to intermediates from Overman's work. Likewise, **74** was found to be the *meso*-diastereomer.

Equation 6: Reductive amination of 72 a provides C_2 symmetric core



72 a **73**

Equation 7: Reductive amination of 72 b provides *meso* symmetric core

72 b **74**

Optimization of the enantioselectivity of this organocatalyzed construction of bis-quaternary dioxindoles is currently an ongoing project in the MacMillan lab and the results of these studies will be reported elsewhere.

Limitations And Considerations

The lack of reactivity of tryptamines such as **42** with **43** prohibits the direct construction of bis-quaternary pyrroloindolines via the method described in Chapter 2 of this thesis. It is conceivable that alternate α, β-unsaturated aldehydes can be discovered that will circumvent this problem. Currently, the oxindole alkylation of **71** with **43** is not selective. Further work exploring the isatin and oxotryptamine protecting groups may circumvent this problem.

Conclusions

We have successfully devised a system for the direct construction of vicinal quaternary stereocenters using organocatalysis. Though poorly selective, equation 5 is the first example of this construction using our iminium catalysis concept. Future extension of this work will focus improving the selectivity of this new process.

Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[2] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by $KMnO_4$ stain.

^{1}H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Irvine Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using either a Chiralcel ODH column (25

[1]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

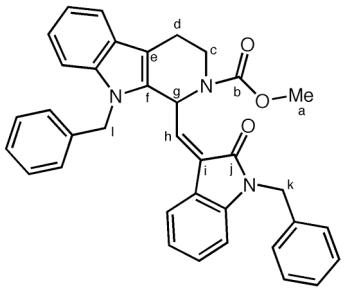
[2]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

cm) and OD guard (5 cm) or a Chiralcel AD column (25 cm) and AD guard (5 cm) as noted.

Catalyst incorporated adduct **(45)**. General procedure for generating catalyst incorporated isatin adducts: A 2-dram vial equipped with a magnetic stir bar and containing the Triflouroacetic acid salt of (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (0.323 mmol) was charged with methylene chloride (2.75 mL), water (35 μL) and placed in a bath at –20°C. The solution was stirred for 5 min before addition of isatin derived aldehyde ***E*-43** (765mg, 2.91 mmol). The resulting suspension was stirred at constant temperature for 4 days. The reaction mixture was exposed to pH 7.0 buffer (2 mL) and extracted with methylene chloride. The organic solution was then transferred through a silica gel plug into a flask and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography in a gradient from 10-60% EtOAc / Hexanes to afford the title compound as an orange solid. IR (film) 3064, 3030, 2958, 2923, 2863, 1707, 1611, 1482, 1468, 1454, 1390, 1362, 1345, 1297, 1250, 1175, 1101, 749, 697, 553 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.0 (s, 1H, ao), 7.76 (d, 2H, ae), 7.60 (t, 2H, ab), 7.51 (t, H, x), 7.26 (m, 4H, n, w, z), 7.18 (m, 6H, s, v, aa, ad), 7.05 (d, 2H, u), 6.95 (q, 2H, p, y), 6.80 (d, 1H, ac), 6.74 (t, 1H, r), 6.54 (d, 1H, m), 6.39 (d, 1H, l), 6.27 (d, 1H, q), 6.04 (d, 1H, h), 5.2 (d, 1H, e), 4.9 (s, 1H, k), 4.8 (s, 2H, d), 4.7 (d, 1H, e), 3.65(s, 1H, i), 3.6 (d, 1H, f), 3.4 (d, 1H, f), 3.2 (s, 3H, b), 1.1 (s, 9H, a); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.19 (ao),

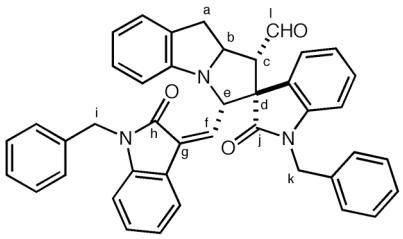
176.82 (an), 175.09 (am), 165.61 (al), 143.28 (ak), 142.17 (aj), 136.53 (ai), 136.12 (ah), 135.90 (ag), 132.82 (af), 131.33 (ae), 130.54 (ad), 129.71 (ac), 129.46 (ab), 129.06 (aa), 128.93 (z), 128.38 (y), 127.99 (x), 127.73 (w), 127.42 (v), 127.14 (u), 126.87 (t), 126.82 (s), 122.66 (r), 122.60 (q), 122.26 (p), 121.92 (o), 120.18 (n), 109.32 (m), 109.25 (l), 84.6 (k), 77.8 (j), 66.9 (i), (64.37 (h), 59.9 (g), 43.97 (f), 43.91 (e), 43.26 (d) 38.15 (c), 33.02 (b), 27.06 (a); HRMS (CI) exact mass calcd for ($C_{49}H_{47}N_4O_4$) requires *m/z* 755.3597, found *m/z* 755.3629.

Pictet-Spengler adduct (51). A 2-dram vial equipped with a magnetic stir bar and containing the Triflouroacetic acid salt of (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (0.0571 mmol) was charged with methylene chloride (0.300 mL), water (25 μL) and stirred at room temperature. To this solution was added N-10-methylcarbamate-1-benzyltryptamine (50 mg, 0.162 mmol), the solution was stirred for 5 min before addition of isatin derived aldehyde ***E*-43** (128 mg, 0.487 mmol). The resulting suspension was stirred at constant temperature for 8 h. The reaction mixture was exposed to pH 7.0 buffer (2 mL) and extracted with methylene chloride. The organic solution was then transferred through a silica gel plug into a flask and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography in 15% EtOAc / Hexanes to afford the title compound as an off yellow solid (85 mg, 0.153 mmol). IR (film) 3029, 2921, 1698, 1650, 1611, 1495, 1483, 1468, 1444, 1403, 1385, 1361, 1249, 1307, 1269, 1256, 1240, 1196, 1170, 1113, 1029, 1001, 912, 862, 788, 767, 732, 696, 656, 617, 662



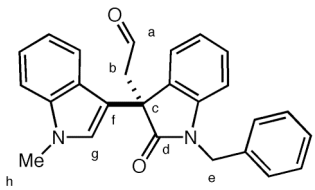
cm^{-1}; ^1H NMR (500 MHz, 80°C, CD_3SOCD_3) δ 7.7 (d, 1H, g), 7.56 (m, 1H, Ar-H), 7.40 (d, 1H, Ar-H), 7.2-7.3 (m, 6H, Ar-H), 7.15-7 (m, 4H, n, Ar-H), 6.96 (d, 1H, h) 6.9-6.7 (m, 6H, Ar-H), 5.40 (dd, 2H, l), 4.90 (s, 2H, k), 4.33 (m, 1H, c), 3.70 (m, 1H, c), 3.61 (s, 3H, a), 2.90 (m, 2H, d); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.95, (j), 156.19 (b), 142.27, 138.51 (f), 138.17, 137.13, 134.07 (h), 133.50, 130.07, 129.20, 128.56, 128.01, 127.97, 127.62, 127.40, 126.92, 126.26, 122.84, 122.53, 122.38, 121.05, 119.99, 118.92, 110.80, 109.74 (e), 109.46, 53.09 (a), 46.90 (l), 46.43 (g), 43.49 (k), 38.50 (c) 21.44 (d); HRMS (CI) exact mass calcd for ($C_{36}H_{32}N_3O_3$) requires *m/z* 554.2444, found *m/z* 554.2436.

Descarboxyl catalyst incorporated adduct (59) A 2-dram vial equipped with a magnetic stir bar and containing the indoline-2-carboxylic acid (7 mg, 0.0433 mmol) was charged with methylene chloride (0.260 mL), water (20 μL) and stirred at –4°C. To this solution was added N-10-methylcarbamate-1-benzyltryptamine (40 mg, 0.130 mmol), the solution was stirred for 5 min before addition of isatin derived aldehyde ***E*-43** (68 mg, 0.260 mmol). The resulting suspension was stirred at constant temperature for 24 h. The reaction mixture was exposed to pH 7.0 buffer (1 mL) and extracted with methylene chloride. The organic solution was then transferred through a silica gel plug into a flask and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography in 15% EtOAc / hexanes to afford the title compound as an off-yellow solid (10 mg) as well as the corresponding non-decarboxylated catalyst incorporated adduct (9 mg). IR (film) 3421, 3059, 3030, 2923, 2852, 1718, 1653, 1610, 1481, 1467,



1437, 1383, 1363, 1264, 1227, 1175, 1133, 1102, 1028, 1006, 946, 906, 860, 789, 748, 697, 668, 638, 552 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.2 (s, 1H, l), 7.42 (d, 1H, Ar-H), 7.30 (m, 5H, Ar-H), 7.0-7.2 (m, 14H, Ar-H), 6.9 (m, 3H, Ar-H), 6.72 (2d, 2H, f, Ar-H), 6.6-6.66 (2d, 2H, Ar-H), 6.3 (d, 1H, e), 5.08 (td, 2H, b), 4.95 (d, 1H, k), 4.87 (s, 2H, i), 4.76 (d, 1H, k), 3.65(s, 1H, i), 3.73 (d, 1H, c), 3.5 (dd, 1H, a), 3.28 (dd, 1H, a); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.998 (l), 176.308 (j), 166.246 (h), 152.674, 143.202, 142.332, 138.734 (f), 136.308, 135.671, 129.801, 129.517, 129.295 (g), 128.927, 128.865, 128.457, 127.940, 127.765, 127.725, 127.572, 127.237, 125.766, 125.708, 125.409, 122.732, 122.241, 121.713, 119.972, 112.401, 110.205, 109.109, 67.321 (e), 65.792 (b), 64.685 (c), 61.866 (d), 46.659 (k), 43.541 (i), 34.601 (a); HRMS (CI) exact mass calcd for ($C_{42}H_{34}N_3O_3$) requires *m/z* 628.2600, found *m/z* 628.2610.

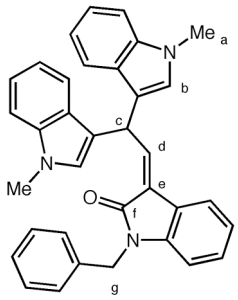
2-((*R*)-1-benzyl-3-(1-methyl-1*H*-indol-3-yl)-2-oxoindolin-3-yl)acetaldehyde. (61). A 2-



dram vial equipped with a magnetic stir bar and containing the Triflouroacetic acid salt of (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (8mg, 0.0234 mmol) was charged with methylene chloride (0.250 mL), and stirred at –70°C. To this solution was added N-methylindole (16 μL mg, 0.123 mmol), the solution was stirred for 5 min before addition of isatin derived aldehyde ***E*-43** (29.4 mg, 0.112 mmol). The resulting suspension was stirred at constant temperature for 24 h. The reaction mixture was exposed to pH 7.0 buffer (1 mL) and extracted with methylene chloride. The organic solution was then transferred through a silica gel plug into a flask and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography in 25% EtOAc /

Hexanes to afford the title compound as a white solid (24.7 mg, 0.0627 mmol, 56% yield, 70% ee). IR (film) 3056, 2930, 2826, 2736, 1713, 1610, 1487, 1466, 1349, 1172, 910, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H, a), 7.2-7.4 (d, 9H, Ar-H), 7.08 (td, 1H, Ar-H), 7.00 (td, 1H, Ar-H), 6.95 (s, 1H, g), 5.05 (d, 2H, e), 3.76 (s, 3H, h), 3.68 (dd, 1H, C**H**$_2$CO); 3.52 (dd, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.34 (a), 177.82 (d), 142.987, 137.82, 135.852, 131.639, 128.811, 128.696, 127.715, 127.621, 125.518, 124.289, 122.905, 122.132, 120.715, 119.959, 112.424, 109.669, 109.642, 49.456 (c), 49.167 (b), 44.350 (e), 32.908 (h); HRMS (CI) exact mass calcd for ($C_{26}H_{23}N_2O_2$) requires *m/z* 395.1760, found *m/z* 395.1775. $[\alpha]_D$ = –47.1 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel ODH and OD guard column (15% Ethanol / hexanes, 1 mL/min); *S* isomer t_r = 17.11 min and *R* isomer t_r = 24 min.

(*Z*)-3-(2,2-bis(1-methyl-1*H*-indol-3-yl)ethylidene)-1-benzylindolin-2-one (62). A 2-dram vial equipped with a magnetic stir bar and containing the Triflouroacetic acid salt of (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (27mg, 0.076 mmol) was charged with methylene chloride (0.760 mL), and stirred at –40°C. To this solution was added N-methylindole (50 μL mg, 0.380 mmol), the solution was stirred for 5 min before addition of isatin derived aldehyde ***E*-43** (130.2 mg, 0.495 mmol). The resulting suspension was stirred at constant temperature for 24 h. The reaction mixture was exposed to pH 7.0 buffer (1 mL) and extracted with methylene chloride. The organic solution was then transferred through a silica gel plug into a flask



and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography in 20% EtOAc / Hexanes to afford the title compound as a yellow solid (64.6 mg, 0.127 mmol, 33% yield) as well as conjugate addition adduct **61** as a white solid (54.1 mg). IR (film) 3056, 2929, 1737, 1694, 1644, 1612, 1484, 1469, 1360, 1330, 1172, 909, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, 2H, Ar-H), 7.3-7.5 (m, 12H, Ar-H), 7.17 (m, 3H, Ar-H), 7.101 (s, sH, b), 7.0 (t, 1H, Ar-H), 6.7 (d, 1H, Ar-H), 5.10 (s, 2H, g), 3.80 (s, 6H, a); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.604 (f), 143.041, 141.395, 137.471, 136.403, 129.120, 128.837, 128.609, 127.561, 127.507, 127.427, 127.185, 124,336, 123.336, 123.489, 121.857, 121.722, 120.607, 119.425, 119.055, 115.870, 109.313, 108.876, 43.449 (g), 32.820 (a), 31.557 (c); HRMS (CI) exact mass calcd for ($C_{35}H_{29}N_3O$) requires *m/z* 507.2311, found *m/z* 507.2303.

***N*,*N*-dibenzyl-2-(1-benzyl-1*H*-indol-3-yl)ethanamine (69)**. Tryptamine (10g, 62.5 mmol) was dissolved in 500 ml of DMF. To this solution was added NaH (40% dispersion in mineral oil, 8.0g, 200 mmol of NaH). After stirring for 30 minutes, the system was charged with Benzyl Bromide (24ml, 200 mmol) and allowed to stir until judged complete by TLC (12 h). This reaction was then quenched by the following method: Addition to a separatory funnel containing 1L H_2O and ½ L of EtOAc. The system was extracted 3X with EtOAc. The combined organic layers were washed with 0.5 L charges of H_2O 3X. Removal of solvent *in vacou*, followed by silica gel chromatography in 15% EA/Hex provided the title compound as an oily yellow solid (26.47g, 98% yield, r.f. 0.5 on TLC plate in 15% EA/Hex). IR (film) 3060, 3027, 2923, 2796, 1737, 1603, 1494, 1466, 1453, 1358, 1331, 1246, 1175, 1129, 1074, 1027, 970, 913, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (m, 5 Ar-H), 7.30 (m, 10 Ar-H), 7.18 (t, *J* = 6.9 Hz, 1H, Ar-H), 7.2 (m, 2H, Ar-H), 7.06 (t, *J* = 6.9 Hz, 1H, Ar-H), 6.87 (s, 1H, NCHC), 5.32 (s, 2H, NC$\mathbf{H_2}$Ph), 3.83 (s, 4H, N(C$\mathbf{H}_2$Ph)$_2$), 3.14 (t, *J* = 6.8 Hz, 2H, C$\mathbf{H}_2$NBn$_2$), 2.98 (t, *J* = 8.2 Hz, 2H, ArC$\mathbf{H}_2$CH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4,

138.2, 136.9, 129.2, 129.1, 128.7, 128.6, 127.9, 127.2, 127.1, 126.1, 121.9, 119.5, 119.2, 114.1, 109.9, 58.8, 54.4, 50.1, 23.5; HRMS (CI) exact mass calcd for ($C_{31}H_{31}N_2$) requires *m/z* 431.2487, found *m/z* 431.2467.

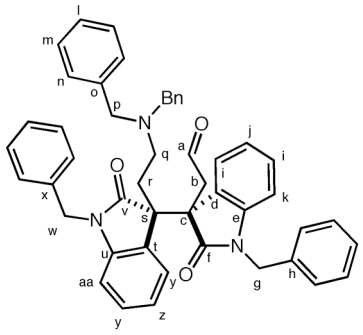
1-Benzyl-3-(2-(dibenzylamino)ethyl)indolin-2-one (70). *N*,*N*-dibenzyl-2-(1-benzyl-1*H*-indol-3-yl)ethanamine (18.93g, 44 mmol) was dissolved in DMSO (108 ml) and brought to a vigorous stir. Concentrated HCl (216 ml) was added dropwise to this solution via a buret. Upon final addition of the HCl, the solution was allowed to stir for 10 minutes, after which the system was added to a solution of 1L EtOAc, 500ml EtOH, and 1L of 1N Aqueous NaOH. The aqueous layer was further basified until a neutral pH was attained. The system was cooled to 0°C via an ice bath. This solution was then extracted 3X with EtOAc. The combined organics were washed with brine and dried over Na_2SO_4. IR (film) 3454, 3085, 3061, 3029, 2928, 2801, 1950, 1887, 1809, 1710, 1613, 1488, 1456, 1453, 1360, 1196, 1168, 1129, 1077, 1013, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.38 (m, 5 Ar-H), 7.36-7.25 (m, 10 Ar-H), 7.13 (t, *J* = 7.9 Hz, 1H, Ar-H), 6.85 (td, *J* = 0.8, 7.4 Hz, 1H, Ar-H), 6.71 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.67 (d, *J* = 7.4 Hz, 1H, NCHC), 4.92 (abq, *J* = 15.7, 8.5 Hz, 2H, NC**H**$_2$Ph), 3.83 (d, *J* = 13.6 Hz, 2H, N(C**H**$_2$Ph)$_2$), 3.71 (dd, *J* = 4.9, 7.9 Hz, 1H, C**H**CH$_2$), 3.54 (d, *J* = 13.6 Hz, 2H, N(C**H**$_2$Ph)$_2$), 2.76 (m, 2H, C**H**$_2$NBn$_2$), 2.43 (m, 1H, CHC**H**$_2$CH$_2$), 1.98 (m, 1H, CHC**H**$_2$CH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.20, 143.25, 139.45, 136.11, 129.34, 129.16, 128.78, 128.56, 128.32, 127.58, 127.37, 126.99, 124.06, 122.22, 108.84, 65.28, 58.28, 50.08, 43.70, 43.13, 29.04; HRMS (CI) exact mass calcd for ($C_{31}H_{31}N_2O$) requires *m/z* 447.2436, found *m/z* 447.2431.

***N*,*N*-dibenzyl-[2-(1-benzyl-20-triisopropylsilanyloxy-1*H*-indol-3-yl)ethyl]-amine (71).** 1-Benzyl-3-(2-(dibenzylamino)ethyl)indolin-2-one (1g, 2.2 mmol) was dissolved in CH_2Cl_2 (14ml). To this was added Et_3N (0.936 ml, 0.68 mmol) and TIPSOTf (1.2 ml, 4.4 mmol). The reaction was stirred for 2 h. At completion, a saturated solution of aqueous $NaHCO_3$ (5 ml) was added and the system was extracted with CH_2Cl_2 3X. The combined organics were dried over Na_2SO_4. The solvent was removed and the crude compound was passed through a plug of Davisil silica with 10%

EA / Hex. The compound was attained as an off yellow viscous liquid (1.295g, 97% yield). IR (film) 3464, 3062, 3029, 2945, 2867, 1721, 1701, 1620, 1583, 1475, 1413, 1369, 1261, 1009, 883, 737, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.5-7.56 (d, *J* = 6.9 Hz, 4H, Ar-H), 7.4 (t, *J* = 7.4 Hz, 4H, Ar-H), 7.26-7.34 (m, 5H, Ar-H), 7.20-7.18 (m, 1H, Ar-H), 7.14-7.10 (m, 2H, Ar-H), 7.08-7.00 (m, 3H, Ar-H), 5.28 (s, 2H, $ArNCH_2Ph$), 3.80 (s, 4H, NCH_2Ph), 3.02 (ddd, *J* = 1.9, 6.6, 13.0, $C\mathbf{H}_2NBn_2$), 2.92 (ddd, *J* = 1.9, 6.6, 13.0, Hz, 2H, $ArC\mathbf{H}_2CH_2$); 1.43-1.28 (m, 3H, $C\mathbf{H}(CH_3)_2$); 1.16 (m, 18H, $CH(C\mathbf{H_3})_2$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.48, 145.07, 140.26, 137.94, 131.59, 128.85, 128.55, 128.27, 127.62, 127.05, 126.85, 126.35, 119.46, 119.18, 117.75, 108.95, 91.65, 58.72, 54.06, 45.08, 22.68, 18.17, 18.01, 17.87, 13.90, 12.41; HRMS (CI) exact mass calcd for M + H ($C_{40}H_{51}N_2OSi$) requires *m/z* 603.3771, found *m/z* 603.3744.

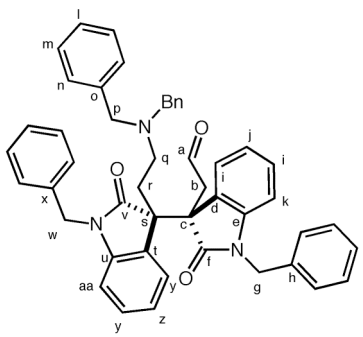
Method for generation of 72a and 72 b: A 2-dram vial equipped with a magnetic stir bar and containing isatin derived aldehyde ***E*-43** (500 mg, 1.90 mmol) was charged with methylene chloride (0.90 mL), water (23 μL), and stirred at –20°C. To this solution, *N*,*N*-dibenzyl-[2-(1-benzyl-20-triisopropylsilanyloxy-1*H*-indol-3-yl)ethyl]-amine (381 mg, 0.634 mmol) was added as a solution in 0.9 mL of methylene chloride (0.5 mL solution followed by 0.4 mL of methylene chloride as a rinse of vial and needle). To this solution was added the free base of (2*S*, 5*S*)- 2-*tert*-butyl-5-(1*H*-indol-3-ylmethyl)3-methyl-imidazolidin-4-one (60.2mg, 0.211 mmol) and 2,4-dinitrobenzoic acid (179 mg, 0.845 mmol). The resulting suspension was stirred at constant temperature for 10 days. The reaction mixture was exposed to pH 7.0 buffer (2 mL) and extracted with methylene chloride. The organic solution was then transferred into a flask to which 1 spoonful of celite had been added, and concentrated *in vacuo*. The resulting slurry was purified by silica gel chromatography in a series of columns: Column #1 eluent 10% EtOAc / Toluene. This cleans most of the ***E*-43** from the desired products. On the lower collection of spots, run column #2. Column #2: Gradient from 10-100% EtOAc / Hexanes. Compounds **72a** (64 mg, 0.0902 mmol, 14.2% yield) and **72b** (110 mg, 0.155 mmol, 24.1% yield) can be isolated with the additional compound being located with an Rf on the TLC plate of 0.235 in 25% EtOAc / hexanes.

Bis-oxindole aldehyde (72a) Following the above method, compound **72a** has an Rf on the TLC plate of 0.32 in 25% EtOAc / hexanes (64 mg, 0.0902 mmol, 14.2% yield). IR



(film) 3053, 3025, 2924, 2813, 1710, 1608, 1488, 1465, 1364, 1174, 1078, 1027, 736, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (d, 1H, a), 7.35 (m, 4, Ar-H), 7.29 (m, 10H, Ar-H and m), 7.25 (m, 4H, n), 7.08 (dd, 2H, l), 6.92 (m, 2H, i), 6.85 (m, 2H, y), 6.60 (t, 1H, j), 6.58 (t, 1H, z), 6.32 (d, 1H, k), 6.26 (d, 1H, aa), 5.18 (d, 1H, g), 4.96 (d, 1H, w), 4.49 (d, 1H, g), 4.35 (dd, 1H, b), 4.33 (d, 1H, w), 3.59 (s, 1H, b), 3.54 (s, 4H, p), 3.16 (td, 1H, r), 2.55 (td, 1H, r), 1.98 (td, 1H, q), 1.82 (td, 1H, q); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.340 (a), 177.012 (f), 176.755 (v), 143.063 (u), 142.499 (e), 139.202 (o), 135.410 (h), 135.359 (x), 128.776, 128.673, 128.640, 128.402, 128.223, 128.098, 127.662, 127.582, 127.534, 127.475, 126.746 (n), 126.629, 123.783, 122.819, 121.947 (j), 121.830, 108.668 (k), 108.451 (aa), 57.732 (p), 54.460 (s), 51.640 (c), 48.218 (q), 44.218(g), 43.884 (w,b), 25.443 (r); HRMS (CI) exact mass calcd for ($C_{48}H_{44}N_3O_3$) requires *m/z* 710.3383, found *m/z* 710.3375.

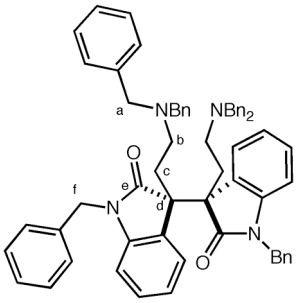
Bis-oxindole aldehyde (72b) Following the above method, compound **72b** has an Rf on



the TLC plate of 0.147 in 25% EtOAc / hexanes (110 mg, 0.155 mmol, 24.1% yield). IR (film) 3404, 3059, 3029, 2955, 2926, 2868, 1794, 1710, 1609, 1487, 1466, 1454, 1435, 1381, 1362, 1298, 1266, 1203, 1175, 1123, 1078, 1028, 917, 853, 789, 748, 735, 698, 552 cm^{-1}; ^{1}H NMR

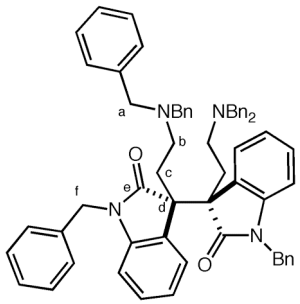
(500 MHz, $CDCl_3$) δ 9.40 (d, 1H, a), 7.1-7.3 (m, 22H, Ar-H), 7.03 (m, 1H, Ar-H), 6.96 (t, 1H, Ar-H), 6.7-6.9 (m, 2H, Ar-H), 6.52 (d, 2H, Ar-H), 4.9 (d, 1H, g), 4.80 (dd, 2H, w), 4.5 (d, 1H, b), 4.45 (d, 1H, g), 3,55 (d, 2H, p), 3.43 (d, 2H, p), 3.35 (d, 1H, b), 2.7 (m, 1H, r), 2.2 (m, 2H, r and q), 1.7 (m, 1H, q); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.283 (a), 176.482 (v), 176.391 (f), 144.706, 143.664, 139.682 (o), 136.119, 135.795, 129.302, 128.943, 128.848, 128.772, 128.406, 127.681, 127.589, 127.326, 127.173, 127.089, 124.312, 123.881, 122.161, 109.637, 109.366, 59.161 (p), 54.019 (c), 53.344 (s), 49.651 (q), 45.062 (b), 44.444 (w,g), 25.443 (r); HRMS (CI) exact mass calcd for ($C_{48}H_{44}N_3O_3$) requires *m/z* 710.3383, found *m/z* 710.3410.

C2-symmetric bis-oxindole diethylamine (73) A 2-dram vial equipped with a magnetic stir bar and compound **72a** (9.4 mg, 0.0133 mmol) was charged with freshly distilled Dichloroethene (53 μL). To this solution was added freshly distilled dibenzylamine (19.1 μL). The solution was allowed to stir for 5 minutes at which time $Na(AcO)_3BH$ (8.9 mg) was added and the slurry was allowed to stir for 24 h and monitored by TLC. Upon completion, the reaction was quenched with water and extracted with dichloromethane twice. The organic solution was then transferred through a silica gel plug into a flask and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography in 25% EtOAc / Hexanes to afford the title compound as a white solid (10.5 mg, 0.0118 mmol, 89% yield). IR (film) 3060, 3027, 2923, 2802, 1703, 1609, 1487, 1465, 1453, 1363, 1219, 1177, 1155, 1117, 1077, 1028, 981, 910, 748, 734, 697, 668, 552 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25-



7.31 (m, 17H, Ar-H), 7.18-7.25 (m, 9H, Ar-H), 7.09 (d, *J* = 6.4 Hz, 4H, Ar-H), 6.8 (t, *J* = 7.3 Hz, 4H, Ar-H), 6.54 (t, *J* = 7.3 Hz, 2H, Ar-H), 6.24 (d, *J* = 7.8 Hz, 2H, Ar-H), 4.95 (d, *J* = 15.1 Hz, 2H, f), 4.32 (d, *J* = 15.6 Hz, 2H, f), 3.55 (s, 8H, a), 3.16 (td, *J* = 4.4, 12.2 Hz, 2H, b), 2.64 (td, *J* = 4.4,12.2 Hz, 2H, b), 1.97 (td, *J* = 3.9,12.2 Hz, 2H, c), 1.80 (td, *J* = 4.4,12.2 Hz, 2H, c); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.455 (e), 142.761, 139.684, 135.890, 129.062, 128.858, 128.304, 128.202, 128.057, 127.925, 127.711, 126.895, 123.905, 122.037, 108.457, 58.072 (a), 55.060 (d), 49.004 (b), 44.062 (f), 25.767 (c); HRMS (CI) exact mass calcd for ($C_{62}H_{59}N_4O_2$) requires *m/z* 891.4638, found *m/z* 891.4622.

Meso-symmetric bis-oxindole diethylamine (74) A 2-dram vial equipped with a magnetic stir bar and compound **72a** (10 mg, 0.0141 mmol) was charged with freshly distilled Dichloroethene (53 μL). To this solution was added freshly distilled dibenzylamine (19.1 μL). The solution was allowed to stir for 5 minutes at which time $Na(AcO)_3BH$ (8.9 mg) was added and the slurry was allowed to stir for 24 h and monitored by TLC. Upon completion, the reaction was quenched with water and extracted with dichloromethane twice. The organic solution was then transferred through a silica gel plug into a flask and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography in 25% EtOAc / Hexanes to afford the title compound as a white solid (8 mg, 0.00897 mmol, 64% yield). IR (film) 3027, 2924, 1711, 1608, 1486, 1465, 1453, 1360, 1178, 1077, 1027, 982, 911, 734, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.27 (m, 16H, Ar-H), 7.18-7.22 (m, 4H, Ar-H),



7.13-7.17 (m, 4H, Ar-H), 7.05 (t, *J* = 7.8 Hz, 2H, Ar-H), 6.89 (mound, 3H, Ar-H), 6.67 (mound, 2H, Ar-H), 6.44 (d, *J* = 6.8 Hz, 2H, Ar-H), 6.25 (mound, 1H, Ar-H), 4.61 (mound, 4H, f), 3.57 (d, *J* = 13.7 Hz, 4H, a), 3.79 (d, *J* = 13.7 Hz, 4H, a), 3.06 (mound, 2H, b), 2.22 (td, *J* = 3.5, 11.8 Hz, 2H, c), 2.13 (td, *J* = 4.4, 12.2 Hz, 2H, b), 1.74 (td, *J* = 3.5, 12.2 Hz, 2H, c); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.610 (e), 143.865, 139.779, 136.134, 129.018, 128.752, 128.694, 128.519, 128.311, 127.430, 127.357, 126.928, 124.306, 122.070, 109.054, 58.629 (a), 55.464 (d), 49.452 (b), 44.088 (f), 29.944 (c); HRMS (CI) exact mass calcd for ($C_{62}H_{59}N_4O_2$) requires *m/z* 891.4638, found *m/z* 891.4668.

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(28) It is well precedented in the MacMillan lab that with the sole exception of conjugate hydride delivery, disubstituted enals do not readily participate in iminium catalysis.

(29) Mass spectral analysis of this mixture shows that both of these compounds have the same mass as the desired adducts 72a and 72b. The NMR spectra of this mixture bears a striking resemblance to the spectra of 72a and 72b with the exception that the aldehyde peak is not present in the H or C13 spectra.