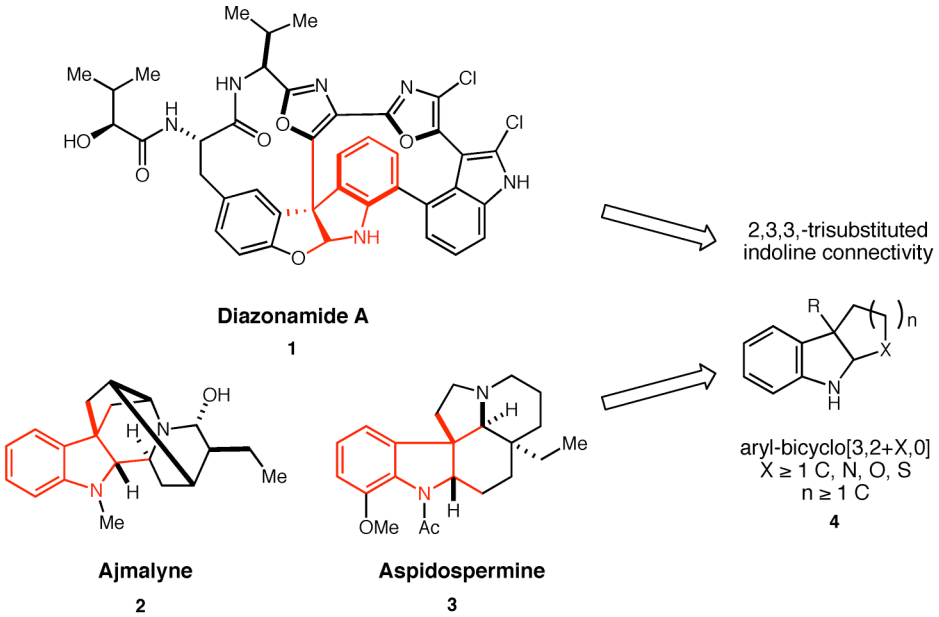
C h a p t e r 2

The Enantioselective Organocatalytic Construction of Pyrroloindolines

Introduction

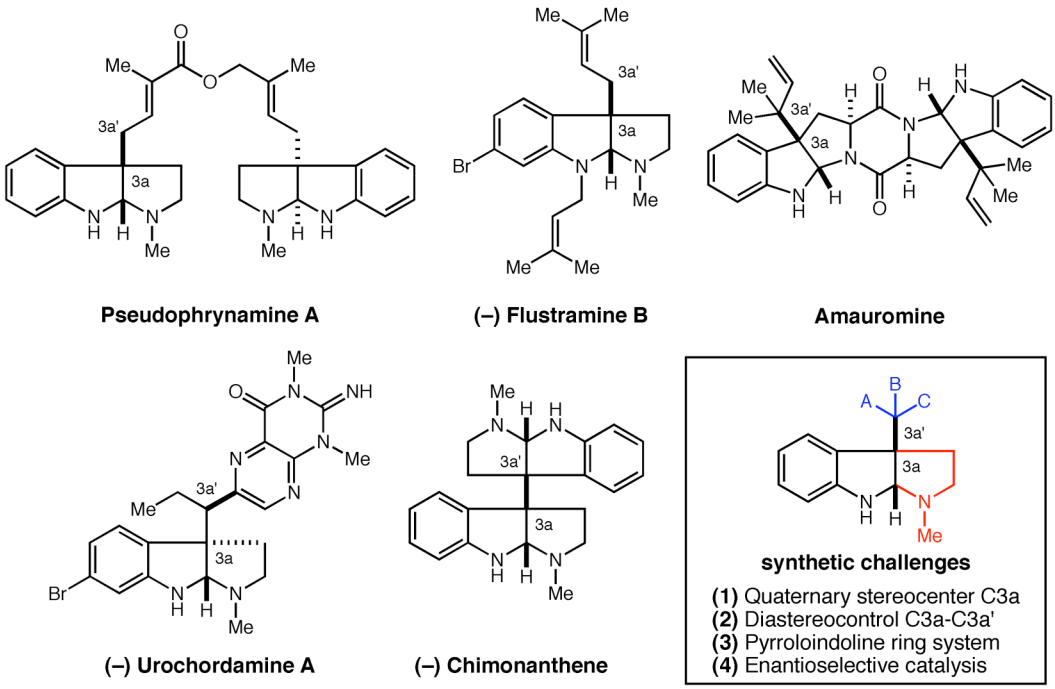
After the successful development of an enantioselective catalytic indole alkylation reaction,[1] attention turned to other common motifs found in indole alkaloids. One such motif is that of the 2,3,3-trisubstitued indoline. Many natural products containing the 2,3,3-trisubstituted indoline motif have been isolated, synthesized, and evaluated for biological activity.[2-4] A representative sampling of natural isolates containing this core motif is presented in Figure 1. Diazonamide A (**1**), ajmalyne (**2**), and aspidospermine (**3**) all contain the common structural motif of an aryl-bicylo[3,2+X,0] ring system with heteroatoms in one or more of the rings (**4**). Compounds containing this motif (such as **1**, **2**, and **3**) have been shown to possess potent biological activities.

Figure 1. Some 2,3,3-Indoline Containing Natural Isolates



One such structure which contains this motif is that of the pyrroloindolines (structure **4**, n=1 X=N). The pyrroloindolines and bis-pyrroloindolines represent a diverse family of structurally complex polyindoline alkaloids that have been isolated from a widespread series of natural sources,[5] including amphibians, plants and marine algae (Figure 2).

Figure 2. Representative Pyrroloindoline Natural Isolates



First described in the late 1930s, this alkaloid family has been found to exhibit remarkable biological properties across a broad spectrum of pharmacological screens. For example, a number of alkaloids isolated from fungal sources that comprise the C(3a)-bispyrroloindoline–diketopiperazine architecture have been shown to be powerful antagonists of cholecystokinin, substance P and neurokinin 1 receptors.[6-8] A related family of alkaloids that incorporates polythioketopiperazines has also been established to exhibit potent anti-cancer activities against lymphocytic leukemia cell lines[9] and cytotoxicity to HeLa cell lines.[10]

Furthermore, McAlpine and co-workers have reported that the pyrroloindoline 5-*N*-acetylardeemin demonstrates the ability to restore vinblastine sensitivity to tumor cell lines that manifest "operational resistance" to cytotoxic agents.[11-13] The hydroxy-pyrroloindoline gypsetin has evoked interest as a potential inhibitor of the enzyme acyl-CoA: cholesterol acyltransferase and as such might find therapeutic use as a cholesterol lowering agent.[14,15] Psycholeine and quadrigemine C have been documented as the first non-peptide antagonists of the somatostatin family of receptors.[16] A number of other polyindolines in this natural product family have also been shown to exhibit significant biological properties.[16-42]

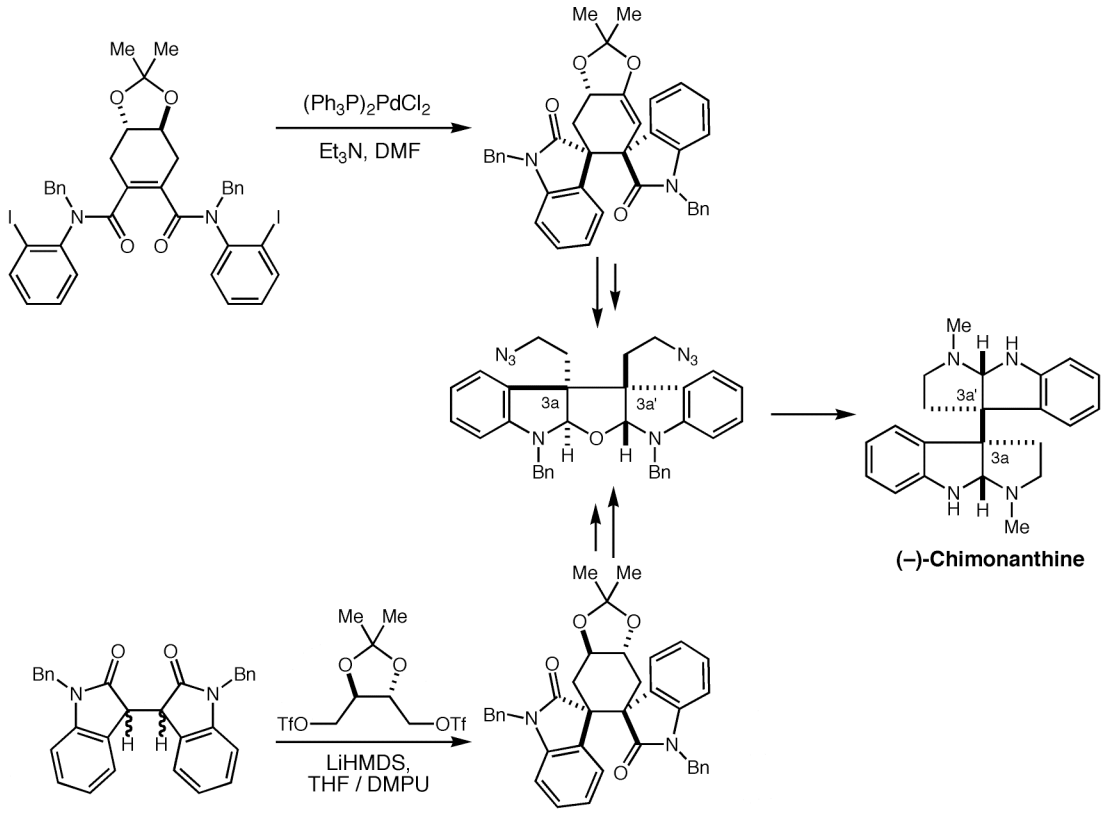
A structural survey of this alkaloid family reveals a central *cis*-fused pyrroloindoline core that in all cases incorporates a quaternary center at the C(3a) site.[43] A challenging structural feature with regard to developing a general strategy, the C(3a') position has been shown to incorporate broad variation in substituents and stereogenicity. For example, while pseudophrynamine A and flustramine B are found to incorporate an unsubstituted methylene at C(3a'), urochordamine A exhibits a tertiary carbon stereocenter at this site, while amauromine and chimonanthine contain vicinal fully substituted carbons between the C(3a)–C(3a') positions. Indeed, chimonanthine presents a formidable synthetic challenge in the form of a vicinal quaternary carbon diastereochemical relationship.

The structural complexity of the pyrroloindolines makes them a particularly elusive and at the same time appealing target for total synthesis efforts. Though many elegant synthetic studies have been performed on this core motif, two are of particular note and deserve attention here. The Overman and Danishefsky groups have made

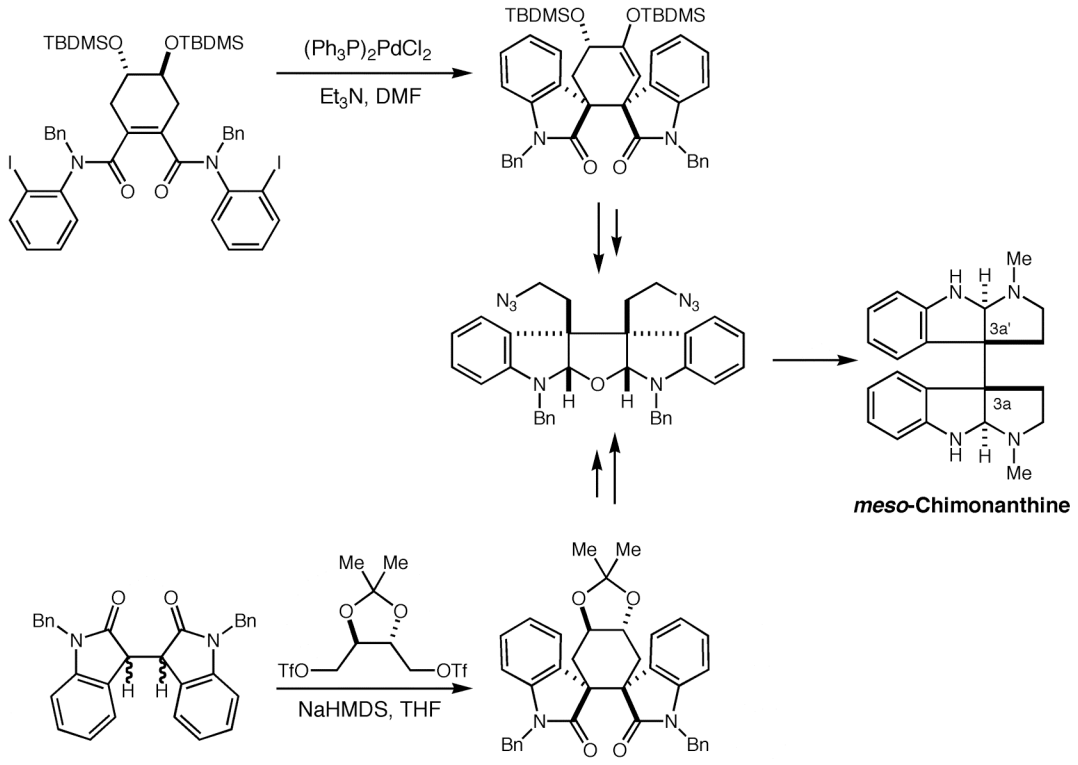
seminal contributions in their design of new reaction methods that have enabled the rapid construction of many of these complex alkaloids. Both of these strategies are elegant, creative and highly effective solutions to the construction of pyrroloindoline architecture.

The Overman group has focused upon the development of bis-Heck[44] as well as bis-oxindole alkylation technologies,[45,46] for the diastereoselective construction of bis-oxindoles that are subsequently converted into the bispyrroloindoline core (Schemes 1 and 2). This bis-Heck technology efficiently utilizes the stereochemical information of a conformationally locked cyclohexene substrate to generate the requisite vicinal C(3a)–C(3a') quaternary carbon relationship. Variation of the cyclohexene protecting groups has been shown to produce both the *meso* and C_2 symmetric cores. Alternatively, the bis-oxindole alkylation strategy utilizes chelate control to produce the *meso* core and non-chelation conditions to produce the C_2 core. Overman has additionally developed asymmetric Heck technology that has been extended to the elegant syntheses of many structurally diverse pyrroloindolines via oxindole intermediates.[47]

Scheme 1. Overman's bis-alkylation and bis-Heck Technologies for (–)-Chimonanthine

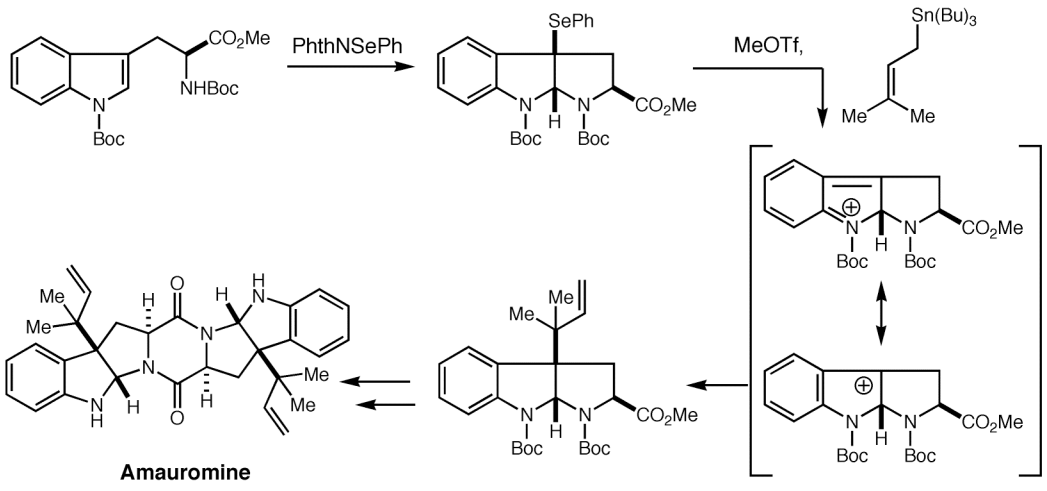


Scheme 2. Overman's bis-alkylation and bis-Heck Technologies for *meso*-Chimonanthine



The Danishefsky group has utilized enantiopure tryptophan-based starting materials for their asymmetric synthesis of amauromine and the ardeemins (Figure 3).[48,49] Their strategy is reliant upon the stereochemical induction from a C3-selenato pyrroloindoline derived from tryptophan in a cascade selenation-ring closing protocol. The selenato functionality is then used in an ingenious radical addition step to introduce the "reverse prenyl" group as exhibited in amauromine. It should be noted that though the selanato adduct is formed as a 16:1 mixture of diastereomers, the corresponding "reverse-prenylation" reaction results in a 9:1 mixture of adducts. Nonetheless, this novel procedure diastereoselectively controls the absolute stereochemistry at the C3 carbon and produces the pyrroloindoline ring system without the need of an oxindole intermediate.

Figure 3. Danishefsky's oxo-selanation Technology for Amauromine

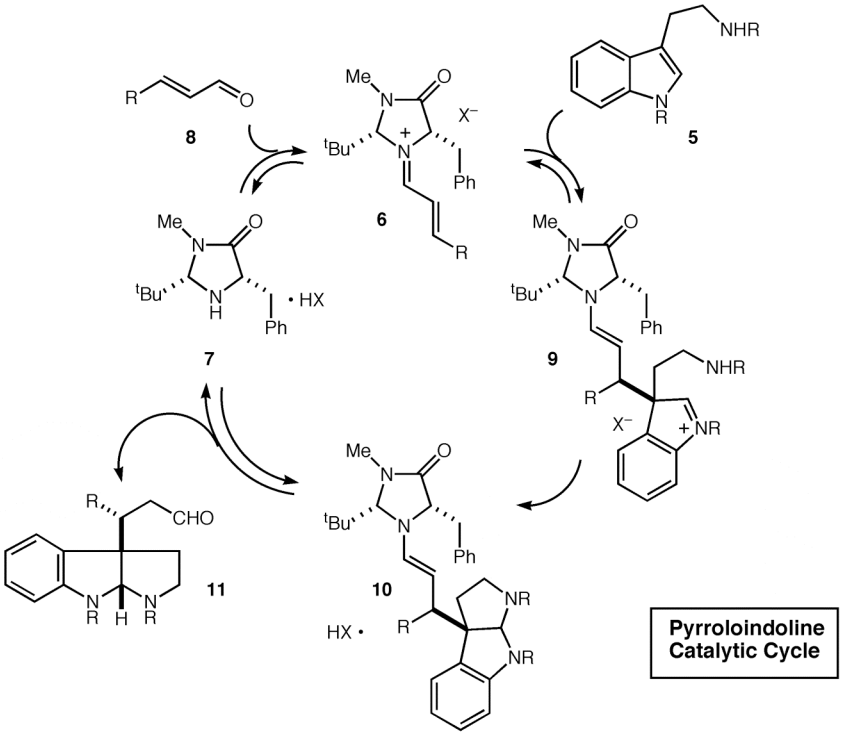


With these elegant approaches in mind, we sought to develop a complementary technology that would allow the enantioselective catalytic construction of pyrroloindoline architecture in one step with concomitant stereocontrolled generation of the requisite C(3a) and vicinal C(3a') stereogenicity.

Reaction Design

Based on a variety of mechanistic considerations, we sought to explore whether the previously discussed indole alkylation pathway might be manipulated to allow the cascade formation of pyrroloindoline architecture in lieu of substituted indole production. As elaborated in Scheme 3, we envisioned that the addition of tryptamine **5** to the activated iminium ion **6** (arising from catalyst **7** and an α,β-unsaturated aldehyde **8**) would generate the C(3)-quaternary carbon substituted indolium ion **9**. As a central design feature, this quaternary carbon bearing indolium cannot undergo rearomatization via proton loss in contrast to the analogous 3-H indole addition pathway. As a result, we expected the prevailing reaction pathway to be partitioned towards a 5-*exo* heterocyclization of the pendant ethylamine thereby generating tricyclic system **10**. Subsequent hydrolysis of the tethered enamine moiety would provide the requisite pyrroloindoline framework **11** and in doing so reconstitute the imidazolidinone catalyst **7**. In terms of molecular complexity development, this cascade sequence should allow the rapid and enantioenriched formation of stereochemically defined pyrroloindoline architecture from tryptamines and simple α,β-unsaturated aldehydes. Moreover, we hoped that the requisite C(3a) quaternary carbon would be forged with high levels of enantio- and diastereocontrol using a simple amine catalyst.

Scheme 3. Organocatalytic Pyrroloindoline Construction



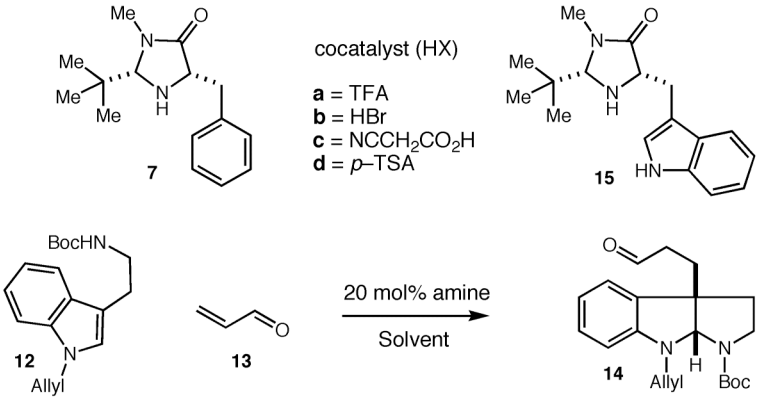
Results With Acrolein

Our enantioselective organocatalytic pyrroloindoline construction was evaluated using *N*(10)-Boc-*N*(1)-allyltryptamine **12** with acrolein **13** and a series of imidazolidinone catalysts (Table 1). In accord with our mechanistic postulate, we were delighted to find that the imidazolidinone catalysts **7a-d** provided the desired pyrroloindoline architecture in good yield (entries 2–8). While useful levels of enantioselectivity could be observed in this addition–cyclization sequence (entry *8*, 84% ee), we were surprised to find large variations in enantioinduction as a function of reaction solvent. As delineated in Table 1, the use of high dielectric media (e.g. MeOH) led to the predominant formation of the (3a*S*)-pyrroloindoline enantiomer (entry 1, (+) 77% ee) while the use of low dielectric solvents provided the (3a*R*)-pyrroloindoline as

the major antipode (entry 8, (–) 84% ee). While reaction media is known to influence a variety of stereoselective processes, this apparent correlation between solvent dielectric and the absolute sense of enantiofacial discrimination is, to our knowledge, without precedent. A stereochemical rationale for these results is given in the section labeled "Stereochemical Rationale for Acrolein."

Interestingly, the tryptophan derived imidazolidinone salt **15a**[50] was found to exhibit the optimal levels of enantioinduction in the addition to acrolein in the presence of CH_2Cl_2-H_2O. This increase in selectivity is postulated to arise from the more efficient stabilization by catalyst **15** of the α,β-unsaturated iminium ion via a favorable cation-π interaction. The superior levels of asymmetric induction and reaction efficiency exhibited by **15a** to afford the pyrroloindoline (3a*S*)-**14** in 89% ee and 85% yield prompted us to select this catalyst for further exploration.

Table 1. Effect of Cocatalyst and Solvent on the Organocatalytic Pyrroloindoline Construction



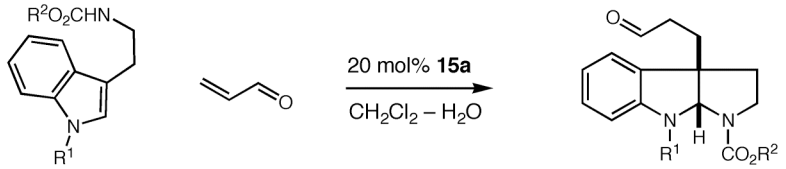
entry	solvent	dielectric	% H_2O	catalyst	temp (°C)	% yield	% ee[a]
1	MeOH	32.6	0	7c	–85	9	77
2	MeOH	32.6	10	7d	–40	64	69
3	Acetone	20.2	10	7d	–40	58	60
4	DME	7.2	10	7d	–40	18	21
5	$CHCl_3$	4.8	10	7d	–40	66	-45
6	Toluene	2.4	10	7d	–40	60	-59
7	Toluene	2.4	2	7b	+4	50	-84
8	CH_2Cl_2	9.1	15	7a	–85	79	70
9	CH_2Cl_2	9.1	15	15a	–85	85	89

[a] Product ratios determined by chiral HPLC.

Results Of Various Protecting Groups With Acrolein

Experiments that probe the scope of the tryptamine N(1) and N(10) substituents are summarized in Table 2. The reaction appears quite tolerant with respect to the steric contribution of the N(10) carbamate substituent (R = Et, allyl, *t*-Bu, entries 1–5, ≥82% yield, 89 to 90% ee). As revealed in entries 2 to 5, the reaction can also accommodate a variety of electron donating N(1)-indole substituents (entry 2, *N*-allyl, 89% ee; entry 3, *N*-prenyl, 89% ee; entry 5, *N*-Bn, 90% ee). To demonstrate the preparative utility, the addition of *N*(10)-Boc-*N*(1)-benzyltryptamine to acrolein was performed on a 25 mmol scale with catalyst **15a** to afford the corresponding pyrroloindoline (entry 5) in 90% ee and 82% yield.

Table 2. Enantioselective Pyrroloindoline Formation with Representative N_1 and N_{10} Substituted Tryptamines



entry	R^1	R^2	time (h)	% yield	% ee[a]
1	Allyl	*t*-Bu	25	85	89
2	Allyl	Et	26	89	89
3	Prenyl	Et	24	89	89
4	Benzyl	Allyl	48	83	89
5	Benzyl	*t*-Bu	30	82	90[b]

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration determined by chemical correlation.

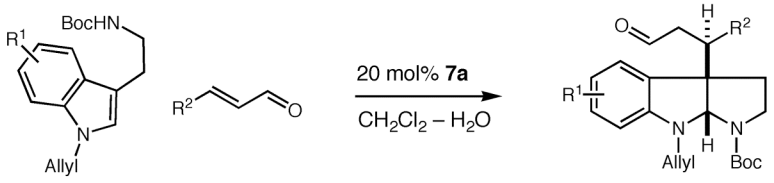
Results With Substituted Acroleins

We next examined the utility of β-substituted-α,β-unsaturated aldehydes in this enantioselective pyrroloindoline formation. The principal issue in this reaction is that of absolute and relative stereocontrol in the construction of the vicinal C(3a)-C(3a') stereocenters. As revealed in Table 3, significant variation in the steric contribution of

the olefin substituent (X = CO_2Me, CH_2OR, COPh, entries 1–3) is possible without loss in yield or enantiocontrol (66–93% yield, 91–94% ee). Importantly from the perspective of pyrroloindoline natural product synthesis, the requisite C(3a)-C(3a') relationship is forged with excellent levels of diastereocontrol (entries 1-7, 13 to 50:1 dr).

This amine catalyzed tryptamine addition-cyclization strategy is also general with respect to indole architecture (Table 3). Incorporation of alkyl and alkoxy substituents at the C(5)–indole position reveals that electronic and steric modification of the indole ring can be accomplished with little influence on reaction selectivity (entries 4 and 5, ≥90% yield, 90 to 92% ee, 10 to 50:1 dr). As revealed in entry 6, we have successfully utilized electron deficient nucleophiles in the context of a 6-bromo substituted tryptamine (86% yield, 97% ee, 31:1 dr). Such halogenated indole adducts should prove to be valuable synthons for use in conjunction with organometallic technologies (e.g., Buchwald–Hartwig[51,52] and Stille couplings[53]). The capacity of 6-bromo tryptamine derivatives to participate in this process has direct implications for the synthesis of 6-bromopyrroloindoline natural products such as flustramine.

Table 3. Enantioselective Pyrroloindoline Formation With Representative Unsaturated Aldehydes and Tryptamines



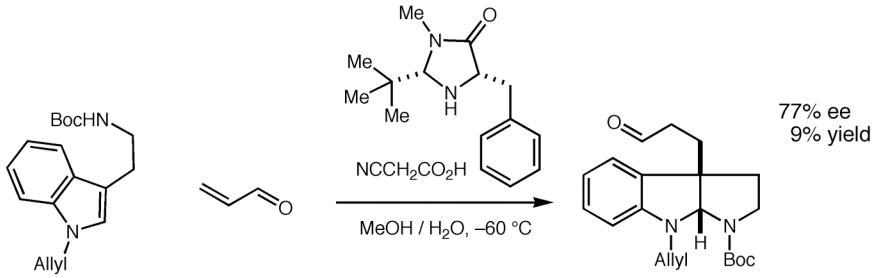
entry	R^1	R^2	time (h)	% yield	% ee[a]	dr
1	H	COPh	64	92	94	13:1
2	H	CH_2OBz	44	66	91	22:1
3	H	CO_2Me	28	93	91	44:1[b]
4	5-Me	CO_2Me	18	94	92	50:1
5	5-MeO	CO_2Me	20	99	90	10:1
6	6-Br	CO_2Me	36	86	97	31:1
7	7-Me	CO_2Me	30	97	99	17:1

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration determined by X-ray crystallography

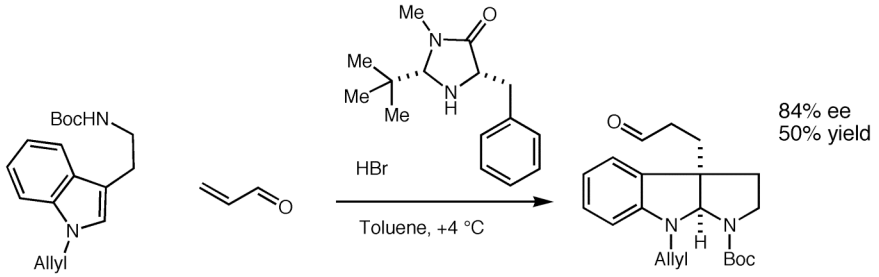
Stereochemical Rationale For Acrolein

As shown in Table 1, the iminium derived from acrolein and imidazolidinone **7** exhibits the ability to differentiate between the prochiral faces of tryptamine. Furthermore, this differentiation is highly dependent upon reaction media. As mentioned earlier, though reaction media is known to influence a variety of stereoselective processes, this apparent correlation between solvent dielectric and the absolute sense of enantiofacial discrimination is, to our knowledge, without precedent. As shown by Equations 1 and 2 (from Table 1, entries 1 and 9), this reversal in stereoselectivity was optimized.

Equation 1. Enantioselective Construction of Pyrroloindole Core in Methanol



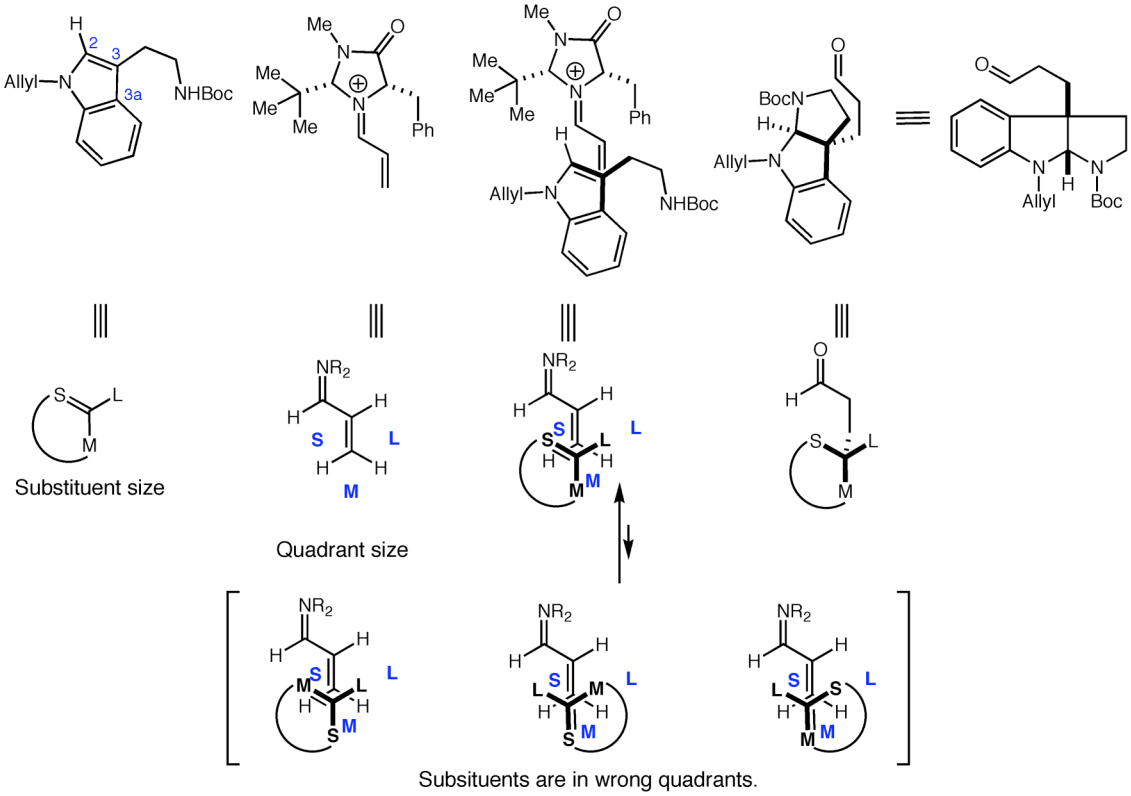
Equation 2. Enantioselective Construction of Pyrroloindole Core in Toluene



It is hypothesized that the low acidity of the acid cocatalyst, high dielectric of the media, relatively high concentration and the cold temperatures of Equation 1 allow for the tryptamine to follow a trajectory as shown in Figure 4. In Figure 4, the substituents about the C3 position of the tryptamine (the ethylamine tether, C3a and C2) are labeled L, M and S (respectively for large, medium and small). The vacant quadrants about the

iminium are likewise labeled as S, M or L. Assuming that the linked region between the M and S substitutents of the tryptamine are required to eclipse one of the β-hydrogens of the iminium, four transition states can be generated. Thus, placement of the largest substituent into the largest vacant quadrant, and so on for the other substituents and quadrants, provides the proposed transition state. It is believed that the tryptamine preferentially undergoes this trajectory based upon predominately steric interactions.

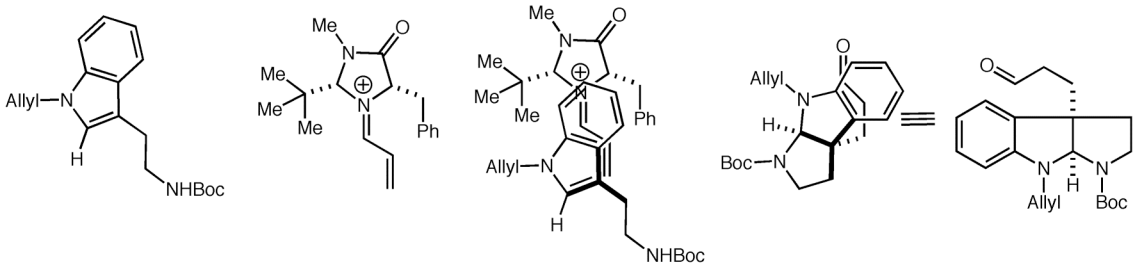
Figure 4. Stereochemical Rationale for Equation 1



It is hypothesized that the high acidity of the acid cocatalyst, low polarity of the solvent, dilute concentration, and relatively warm temperatures of Equation 2 allow for the tryptamine to follow a trajectory as shown in Figure 5. It is believed that the tryptamine preferentially undergoes this trajectory due to beneficial iminium ion stabilization via a cation-π interaction. Since tryptamine is known to be a much better

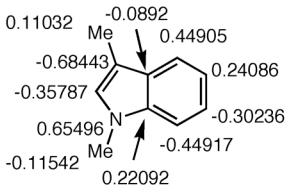
cation-π binder than toluene is, the tryptamine (as opposed to the solvent) places itself in a position to stabilize the iminium. This effective stabilization thus allows the tryptamine to undergo the transition state discussed in Figure 5 in preference to Figure 4 (discussed above). A frontier molecular orbital explanation for the indole facial selectivity in the "cation-π" binding transition state follows.

Figure 5. Stereochemical Rationale for Equation 2

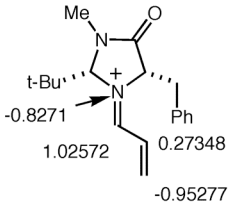


The frontier electron population for indole was originally calculated by Fukui.[54] His calculations showed that the HOMO of indole exhibits high electron density at the C3 position.[55,56] As shown in figure 6 calculation of the HOMO coefficients on 1,3-dimethylindole using Guassian 2004 at the 6-31g++ level of theory with the B3LYP basis set was performed as a model of the HOMO of a differentially substituted tryptamine. Likewise, the LUMO of the iminium ion **6** is provided at the same level of theory.

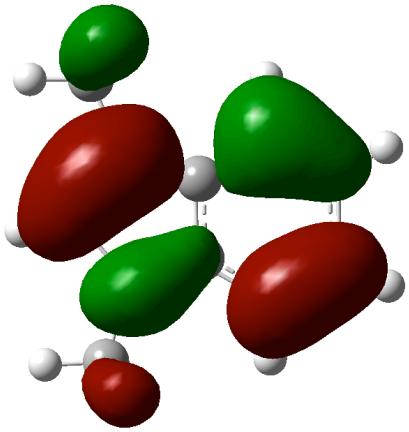
Figure 6. Frontier Molecular Orbital Explanation for Equation 2

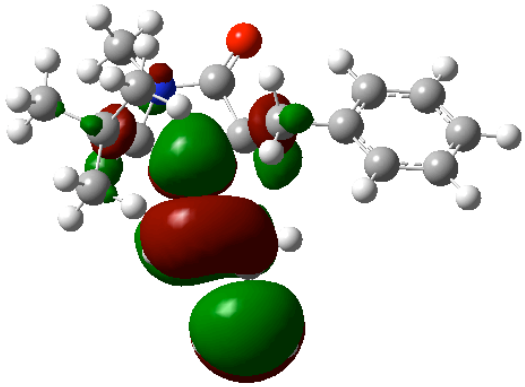


Frontier electron population for 1,3-dimethylindole HOMO



Frontier electron population for iminium LUMO

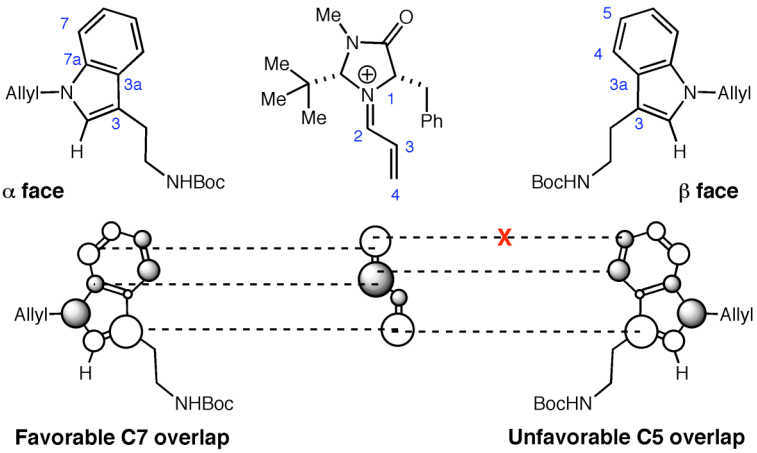




If it is assumed that either of the faces of indole may selectively ligate to the iminium ion in more or less the equivalent steric environment, then a potential explanation for the observed selectivity may be a difference in secondary orbital overlap (figure 7) for the resultant bond forming step. It is proposed that though the α or β face of the tryptamine can undergo the cation-π interaction with the iminium ion, the α face is seen to react in preference to the β due to secondary orbital overlap. If the HOMO of the α face of tryptamine is overlaid onto the LUMO of the iminium ion, then it is seen that orbital alignment can occur. Notably, the C3 and C7 positions of the tryptamine are in geometric and phase alignment with the 1 and 4 positions of the iminium ion. Though the C3a position of the tryptamine is effectively a node, the C7a position of the tryptamine is in phase with the 2 position of the iminium ion. Conversely, if the HOMO

of the β face of tryptamine is overlaid onto the LUMO of the iminium ion, complete orbital alignment does not occur. Notably, though the C3 and C4 positions of the tryptamine can be placed into geometric and phase alignment with the 2 and 4 positions of the iminium ion, the same cannot be said of the C5 position. Though the C3a position of the tryptamine again is an inconsequential node, the C5 position of the tryptamine is out of phase with the 1 position of the iminium ion. Due to the large coefficient of the C5 position, it is assumed that this interaction contributes, to some extent, to the bias toward the α face. In correlation with experimental findings, the impact of this proposed HOMO-LUMO interaction is augmented by the nature of the reaction media.

Figure 7. Tryptamine Facial Selectivity Due to Secondary Orbital Overlap



Thus a possible explanation for the inversion in observed enantioinduction may be related to the ability of the tryptamine to undergo competitive stabilization of the iminium ion with the reaction media. It is thus reasoned that solvent conditions which have a high dipole moment will stabilize the iminium more effectively than the tryptamine and thus lead to a transtition state as shown in Figure 4. The converse, that the tryptamine will stabilize the iminium in a reaction media with a low dipole moment, thus leading to Figure 5, is also reasoned. This is in correlation with Table 1 entries 2-6,

where the sole difference between these reactions is the nature of the major solvent. This line of rationale also successfully predicts the correct enantioface of the tryptamine for the "cation-π" effect as being the opposite face to that given for equation 1.

Stereochemical Rationale for β-Substituted Acroleins

It is hypothesized that placement of a substituent at the β-position of the iminium ion partitions the tryptamine to follow a trajectory as shown in Figure 8. In Figure 8, the substituents about the C3 position of the tryptamine (the ethylamine tether, C3a and C2) are labeled are labeled L, M and S (respectively for large medium and small). Though a substituent is at the β-position, the vacant quadrants about the iminium are once again labeled as S, M or L (the absolute size of the medium and large quadrants of figure 8 are smaller than those of figure 4). The C3 position of the tryptamine and the β-position of the iminium can be aligned in 4 conformations (as shown **16-19**). Two of these transition states (**18** and **19**) can be rejected based upon a presumed deleterious eclipsing interaction of the linked region between the M and S substitutents of the tryptamine and the β carbon of the iminium. Left with 2 transition states (**16** and **17**), placement of the smallest substituent of the tryptamine into the smaller vacant quadrant of the iminium provides the proposed transition state.

Equation 3. Contigous Stereocenter Production

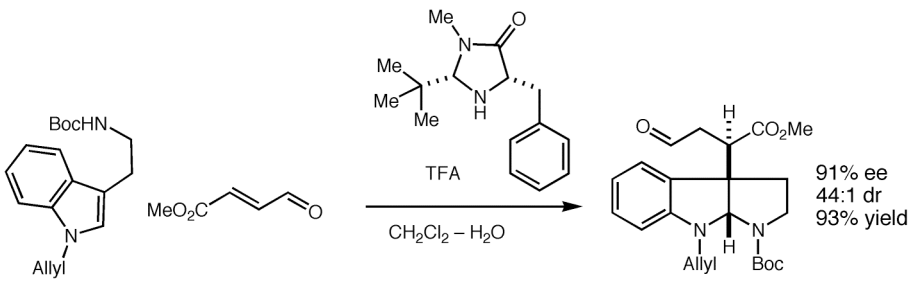
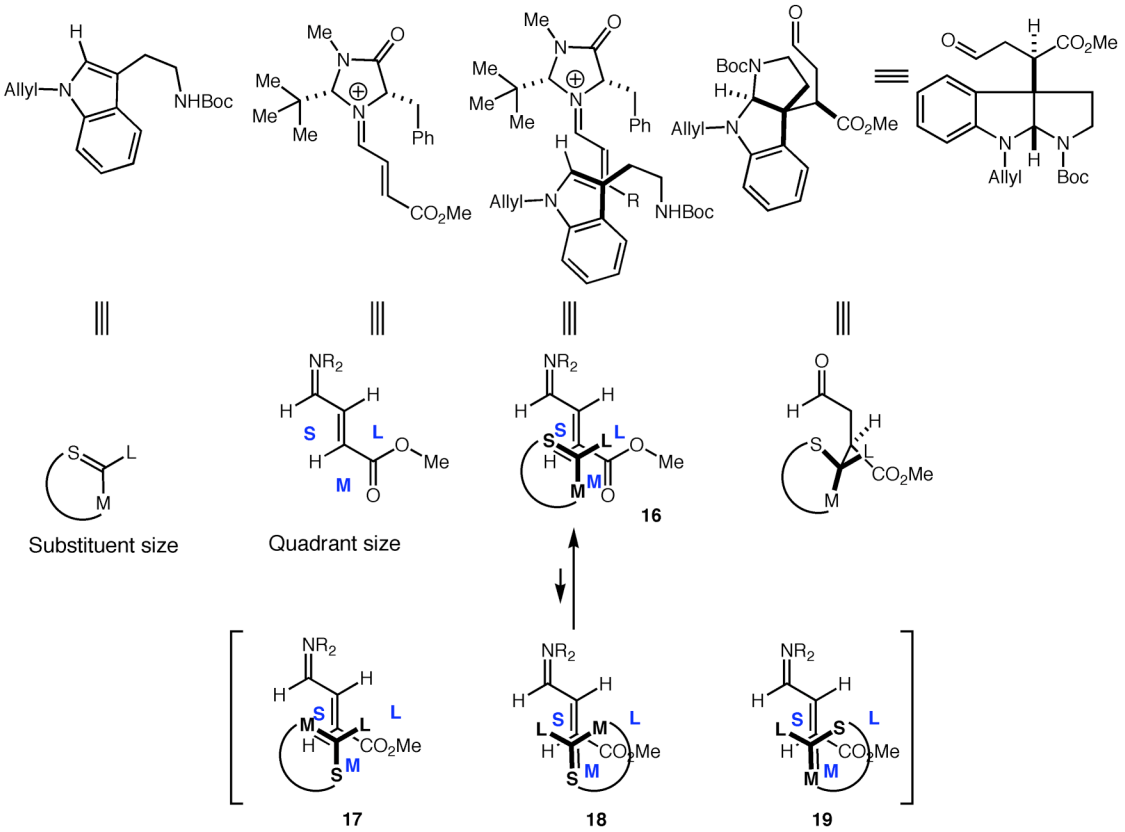


Figure 8. Stereochemical Rationale for Equation 3



Limitations and Considerations

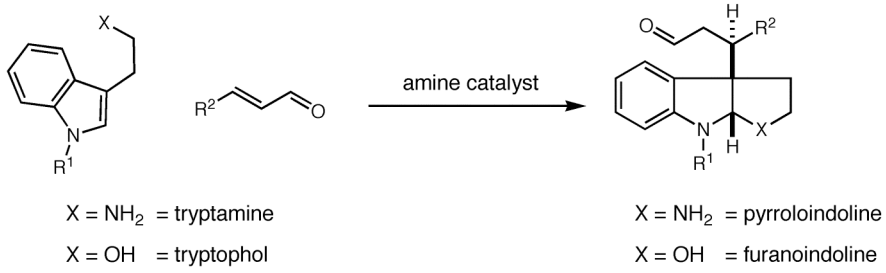
Unfortunately, extension of the cation-π binding trajectory for acrolein to iminium ions with participating β-substituents proved unsuccessful. As such, access to the opposite diastereomer of the pyrroloindoline adducts remains an unresolved issue. Reaction of non-carbamate tryptamines (NH_2, NHMe, NHAc) in this reaction did not prove facile. It is hypothesized that these reactions do not proceed because the ring closure event is not fast relative to elimination of the indolinium ion. This is partially attributed to the higher basicity of the NH_2, NHMe, and NHAc functionalities with respect to that of a carbamate nitrogen. Reaction with β-substituted acroleins, other than ones closely related to those in Table 3, does not proceed. In particular, (*E*)-

crotonaldehye and (*E*)-cinnamaldehyde failed to give any pyrroloindole product. This is assumed to arise from a lack of reactivity of the iminium ion formed. As can be seen from table 3, reaction is seen to occur with the iminium derived from relatively electron deficient α,β-unsaturated aldehydes. Thus reactivity is not seen with α,β-unsaturated aldehydes that are not electron poor. Thus, identification of a catalyst that produces a more reactive iminium ion may provide access to compounds of this type.

Extensions of This Chemistry

Having successfully demonstrated the capacity of iminium catalysis to rapidly build complex pyrroloindoline systems, we sought to advance this enantioselective addition-cyclization technology to the realm of furanoindoline architecture. This oxygen containing tricyclic synthon is also widely represented among natural isolates of biological relevance including: diazonamide A,[57] physovenine,[58] and picrinine.[59] Given their structural similarity to the pyrroloindolines, we envisioned that a wide array of furanoindolines might be rapidly generated in enantioenriched form via the implementation of tryptaphol derivatives in this organocatalytic addition–cyclization sequence (Figure 9).

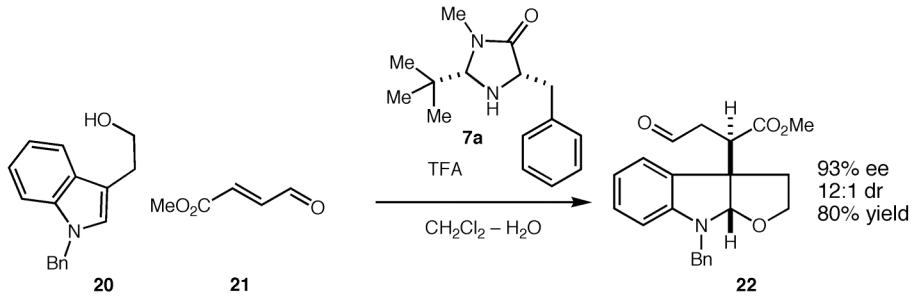
Figure 9. Furoindoline Versus Pyrroloindoline Construction



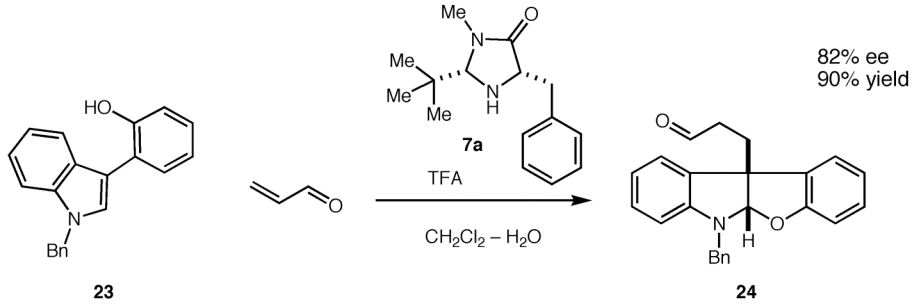
As demonstrated in Equations 4 and 5, preliminary studies by Dr. Christopher Sinz have demonstrated that the catalytic construction of furanoindolines can also be

realized with valuable levels of enantioinduction. Exposure of *N*-Benzyltryptophol **20** to *t*-butyl-4-oxobutenoate **21** in the presence of amine catalyst **7a** results in the production of the desired tricycle **22** in 93% ee and 80% yield (Equation 4). Moreover, the generation of the C(3a)–C(3a') stereochemical relationship is accomplished with high fidelity (12:1 dr), in accord with the analogous pyrroloindoline system. It was also found that 3-phenol substituted indole **23** readily participates in this organocatalytic cascade sequence, thereby providing the basic furanoindoline core **24** of the diazonamide family with excellent enantioselectivity (Equation 5, 90% yield, 82% ee). Work by Dr. Christopher Sinz, Dr. Akio Kayano, Dr. Shojiro Miyazaki, Dr. Simon Blakey, Robert Knowles and Ian Mangion is currently underway in the MacMillan lab toward the total synthesis of diazonamide A.

Equation 4. Enantioselective Construction of Furanoindoline



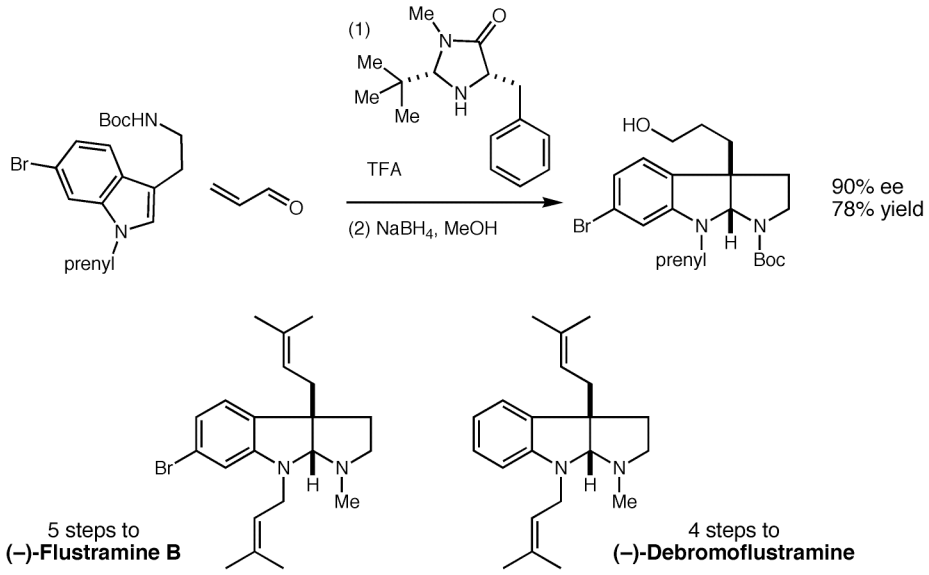
Equation 5. Furanoindoline Construction With Phenol Trap



The flustramines[21,22,60] and flustramides[61] are a small family of marine alkaloids isolated from the Bryozoa *Flusta foliacea* (L.). First described in the late 1970s, this

alkaloid family has yet to undergo broad biological investigation, however, both flustramine A and B, have been shown to block voltage-activated potassium channels[62] as well as exhibit skeletal and smooth muscle relaxant properties.[63] An architectural survey of the flustramine class reveals they are a structurally unique subgroup of the pyrroloindoline isolate class due to the incorporation of a C6-bromine substituent on the indoline ring system. While among the least complex of the pyrroloindoline natural products, the flustramines have not received broad synthetic attention. Indeed, at the present time only two syntheses of flustramine B have been reported,[64,65] both in racemic form. Given that the flustramine skeleton might represent an interesting template for a medicinal or diversity-oriented chemistry evaluation, we were prompted to undertake the enantioselective construction of flustramine B. As a prominent design feature, we sought to enantioselectively construct the central bromo-tricyclic ring system in one chemical step using our organocatalytic pyrroloindoline technology. Dr. Son-Gong Kim and Dr. WenJing Xiao applied the 6-bromopyrroloindoline construction mentioned earlier to the synthesis of (–)-Flustramine B and (–)-Debromoflustramine (Figure 10).

Figure 10. Extension to (–)-Flustramine B and (–)-Debromoflustrame B

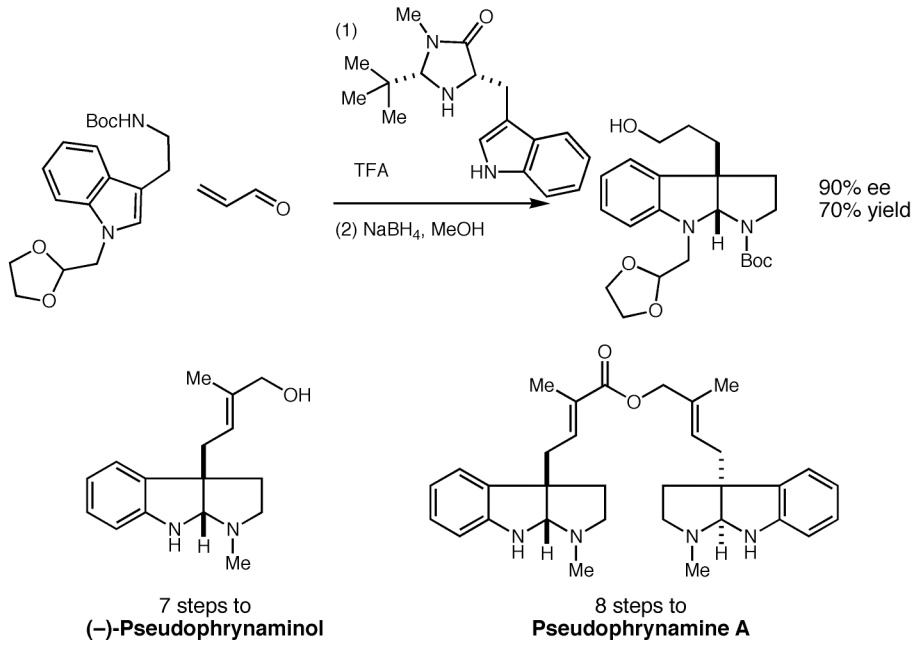


Synthesis by Dr. Sung-Gon Kim and Dr. Wen-Jing Xiao

The psuedophrynamines are a class of pyrroloindolines which contain isoprenoid side chains. These molecules, along with the pumiliotoxins, were discovered from the skin of the Australian myobatrachid frogs of the genus *Psuedophryne*. Unlike the pumiliotoxins though, the psuedophrynamines have not been found in the skin extracts of the related dendrobatid frogs. Studies on captive-raised Australian myobatrachid frogs have recently determined that whereas the pumiliotoxins are sequestered in the skin from a natural source, the psuedophrynamines are synthesized by the animal. This is the first evidence indicating that certain frogs are capable of synthesizing, rather than merely sequestering, complex alkaloids.[66] These compounds possess neurotoxin activity, and are presumed to act as repugnant substances to protect the animals from predation.[67-70] Additionally, pseudophrynaminol has been shown to be a potent and noncompetitive blocker of the nicotinic receptor channels.[71] As such, there has been considerable interest in the synthesis of the pseudophrynamines.[72-76] Given that the pseudophrynamine skeleton might represent an interesting template for a medicinal or diversity-oriented

chemistry evaluation, we were prompted to undertake the enantioselective construction of pseudophrynamine A. Further utilization of the direct pyrroloindoline construction technology, in conjunction with Dr. Shojiro Miyazaki and Dr. Sung-Gon Kim, has culminated in the total syntheses of pseudophrynamine A and pseudophrynaminol (figure 11).

Figure 11. Extension to (–)-Pseudophrynaminol and Pseudophrynamine-A



Syntheses with Dr. Shojiro Miyazaki and Dr.Sung-Gon Kim

Conclusions and Future Directions

In summary, we have further established LUMO-lowering organocatalysis as a broadly useful concept for asymmetric synthesis in the context of pyrroloindoline construction. The rapid construction of this quaternary carbon architecture has potential uses in medicinal chemistry and natural product, as well as diversity-oriented synthesis.

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 using an ice-water bath. 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 anisaldehyde 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 or an ASTEC Chiraldex β-BP (30 m x 0.25 mm) as noted. High

[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.

performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a Chiralcel AD column (25 cm) and AD guard (5 cm) or a Chiralcel OJ column (25 cm) and OJ guard (5 cm) as noted.

General Procedure: An amber 2-dram vial equipped with a magnetic stir bar, containing (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (catalyst 1) or (2*S*, 5*S*)-2-*tert*-butyl-5-(1*H*-indol-3-ylmethyl)3-methyl-imidazolidin-4-one (catalyst 13) acid salt and tryptamine or tryptophol substate was charged with methylene chloride, and water then placed in a bath of the appropriate temperature. The solution was stirred for 5 min before addition of the α,β-unsaturated aldehyde. The resulting suspension was stirred at constant temperature until complete consumption of the indole was observed as determined by TLC. To the reaction mixture was then added pH 7.0 buffer and extracted with diethyl ether and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (solvents noted) to afford the title compounds. The enantioselectivity was determined by subjecting approximately 10 mg of the title compound to an excess of sodium borohydride and 1 mL of absolute ethanol. After 15 min, the remaining sodium borohydride was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The organic layer was separated, filtered through a silica gel plug and subjected to HPLC analysis.

(2*R*,3*R*)-8-Allyl-3a-(3-oxo-propyl)-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-*b*]indole-1-carboxylic acid *tert*-butyl ester (Table 2 entry 1). Prepared according to the general procedure from acrolein (153 μL, 2.43 mmol), N-10-Boc-1-allyltryptamine (166 mg,

0.608 mmol), and (2*R*, 5*R*)-catalyst 2 TFA salt (48 mg, 0.122 mmol) in CH_2Cl_2 (1.63 mL) and water (0.290 mL) at –80 °C for 25 h to provide the title compound as a colorless oil (178 mg, 89% yield, 89% ee) after silica gel chromatography in 25% EtOAc / hexanes. IR (film) 2971, 2932, 2873, 2727, 1725, 1695, 1606, 1491, 1394, 1366, 1220, 1158, 1105, 1080, 936, 888, 743 cm^{-1}; ^1H NMR (300 MHz, VT = 90°C, C_7D_8) δ 9.18 (s, 1H, CHO), 6.96 (d, *J* = 2.8 Hz, 1H, 4-ArH), 6.68 (d, *J* = 7.1 Hz, 1H, 6-ArH), 6.67 (t, *J* = 7.0 Hz, 1H, 5-ArH), 6.29 (d, *J* = 7.7 Hz, 1H, 7-ArH), 5.79 (ddd, *J* = 5, 11, 17 Hz, 1H, $CH_2C\mathbf{H}CH_2$), 5.27 (s, 1H, NCHN), 5.16 (dd, *J* = 1.1, 17 Hz, 1H, $CH_2CHC\mathbf{H}_2$), 5.00 (d, *J* = 1.1, 10 Hz, 1H $CH_2CHC\mathbf{H}_2$), 4.00 (d, *J* = 5 Hz, 2H, $NC\mathbf{H}_2CH$), 3.65 (t, *J* = 8.8 Hz, 1H, $CH_2C\mathbf{H}HN$); 2.83 (dt, *J* = 6.0, 15.4 Hz, 1H, $CH_2CH\mathbf{H}N$); 2.08 (app q, *J* = 2.2 Hz, 1H, $CH_2CH\mathbf{H}CHO$), 1.93-1.46 (m, 5H, $C\mathbf{H}_2CH_2N$, $C\mathbf{H}_2CH\mathbf{H}CHO$), 1.49 (s, 9H, $C(C\mathbf{H}_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 155.0 [153.9], 150.5, 134.5, 130.9, 128.9, 122.9, [117.7] 117.4, 116.0, 106.2, [84.6] 84.1, [80.7] 80.0, [56.9] 55.5, 48.6, 45.6 [45.0], 40.4, 39.0 [38.5], [31.7] 31.3, 28.7; HRMS (CI) exact mass calcd for ($C_{21}H_{28}N_2O_3$) requires *m/z* 356.2100, found *m/z* 356.2112. $[\alpha]_D$ = 449.1 (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 OD–H and OD guard column (4% ethanol / hexanes, 1 mL/min); *R* isomer t_r = 10.7 min and *S* isomer t_r = 12.3 min. The minor counterparts of doubled signals due to Boc rotamers are shown in [ ].

(2*R*,3*R*)-8-allyl-3a-(3-oxo-propyl)-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-*b*]indole-1-carboxylic acid ethyl ester (Table 2 entry 2). Prepared according to the general procedure from acrolein (153 μL, 2.43 mmol), N-10-ethylcarbamate-1-allyltryptamine

(166 mg, 0.608 mmol), and (2*R*, 5*R*)-catalyst 2 TFA salt (48 mg, 0.122 mmol) in CH_2Cl_2 (1.63 mL) and water (0.290 mL) at –80 °C for 26 h to provide the title compound as a colorless oil (178 mg, 89% yield, 89% ee) after silica gel chromatography in 15-25% EtOAc / hexanes. IR (film) 3053, 2979, 2933, 2723, 1698, 1606, 1491, 1464, 1417, 1381, 1343, 1311, 1212, 1165, 1106, 1082, 1031, 936, 891, 744 cm^{-1}; ^1H NMR (300 MHz, VT = 80°C, C_7D_8) δ 9.17 (s, 1H, CHO), 7.01 (d, *J* = 1.2 Hz, 1H, 4-ArH), 6.68 (d, *J* = 7.61 Hz, 1H, 6-ArH), 6.60 (t, *J* = 7.3 Hz, 1H, 5-ArH), 6.31 (d, *J* = 7.9 Hz, 1H, 7-ArH), 5.79 (ddd, *J* = 5.5, 10.7, 22.3 Hz, 1H, $CH_2C\mathbf{H}CH_2$), 5.29 (s, 1H, NCHN), 5.18 (d, *J* = 17 Hz, 1H, $CH_2CHC\mathbf{H}_2$), 5.02 (d, *J* = 1.2, 10 Hz, 1H $CH_2CHC\mathbf{H}_2$), 4.04 (m, 4H, $NC\mathbf{H}_2CH$, $CH_3C\mathbf{H}_2O$), 3.67 (t, *J* = 8.2 Hz, 1H, $CH_2C\mathbf{H}HN$); 2.86 (dt, *J* = 5.8, 16.8 Hz, 1H, $CH_2CH\mathbf{H}N$); 2.10 (app q, *J* = 2.4 Hz, 1H, $CH_2CH\mathbf{H}CHO$), 1.97-1.46 (m, 5H, $C\mathbf{H}_2CH_2N$, $C\mathbf{H}_2CH\mathbf{H}CHO$), 1.09 (t, *J* = 7.0 Hz, 3H, $CH_2C\mathbf{H}_3$); ^{13}C NMR (75 MHz, C_7D_8) δ 199.0, 157.4, 150.4, 134.8, 131.0, 128.8, 122.6, 117.7, 115.9, 106.5, 84.5, 61.1, 48.6, 45.3, 40.1, 38.7, 38.1, 31.2, 14.9; HRMS (CI) exact mass calcd for ($C_{19}H_{24}N_2O_3$) requires *m/z* 328.1787, found *m/z* 328.1792. $[\alpha]_D$ = 308.2 (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 AD and AD guard column (6% ethanol / hexanes, 1 mL/min); *R* isomer t_r = 11.5 min and *S* isomer t_r = 13.6 min.

(2*R*,3*R*)-8-prenyl-3a-(3-oxo-propyl)-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-*b*]indole-1-carboxylic acid ethyl ester (Table 2 entry 3). Prepared according to the general procedure from acrolein (131 μL, 2.08 mmol), N-10-ethylcarbamate-1-prenyltryptamine (171 mg, 0.521 mmol), and (2*R*, 5*R*)-catalyst 2 TFA salt (41 mg, 0.104 mmol) in CH_2Cl_2

(1.43 mL) and water (0.253 mL) at −80 °C for 24 h to provide the title compound as a colorless oil (179 mg, 89% yield, 89% ee) after silica gel chromatography in 15% EtOAc / hexanes. IR (film) 2959, 2927, 2703, 1716, 1695, 1604, 1487, 1444, 1412, 1380, 1348, 1311, 1209, 1161, 1108, 1081, 1017, 932, 895, 772, 745 cm^{-1}; ^1H NMR (300 MHz, VT = 90°C, C_7D_8) δ 9.29 (t, *J* = 1.6 Hz, 1H, CHO), 7.09 (d, *J* = 1.6 Hz, 1H, 4-ArH), 6.78 (dd, *J* = 1.6, 7.7 Hz, 1H, 6-ArH), 6.70 (t, *J* = 8.2 Hz, 1H, 5-ArH), 6.43 (d, *J* = 8.2 Hz, 1H, 7-ArH), 5.39 (m, 2H, $CH_2C\mathbf{H}C(CH_3)_2$, NCHN), 4.29 (dd, *J* = 6.0, 15.9 Hz, 1H, $CH_3CH\mathbf{H}O$), 4.16 (dd, *J* = 7.1, 14.3 Hz, 2H, $NC\mathbf{H}_2CH_,$), 4.05 (dd, *J* = 5.5, 16.5 Hz, 1H, $CH_3C\mathbf{H}HO$), 3.76 (t, *J* = 8.7 Hz, 1H, $CH_2C\mathbf{H}HN$); 2.95 (dt, *J* = 6.0, 14.8 Hz, 1H, $CH_2CH\mathbf{H}N$); 2.17 (app q, *J* = 2.2 Hz, 1H, $CH_2CH\mathbf{H}CHO$), 2.09-1.56 (m, 5H, $C\mathbf{H}_2CH_2N$, $C\mathbf{H}_2CH\mathbf{H}CHO$), 1.77 (s, 3H, $C(C\mathbf{H}_3)_2$), 1.70 (s, 3H, $C(C\mathbf{H}_3)_2$), 1.18 (t, *J* = 7.1 Hz, 3H, $CH_2C\mathbf{H}_3$); ^{13}C NMR (75 MHz, C_7D_8) δ 198.5, 158.4, 150.9, 133.6, 131.5, 128.8, 122.6, 122.1, 117.6, 106.6, 84.8, 60.9, 45.4, 44.2, 43.4, 40.1, 38.5, 31.4, 25.4, 17.9, 14.7; HRMS (CI) exact mass calcd for ($C_{21}H_{28}N_2O_3$) requires *m/z* 356.2100, found *m/z* 356.2093. $[\alpha]_D$ = 265.7 (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 AD and AD guard column (2% ethanol / hexanes, 1 mL/min); *R* isomer t_r = 38.1 min and *S* isomer t_r = 42.6 min.

(2*R*,3*R*)-8-benzyl-3a-(3-oxo-propyl)-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-*b*]indole-1-carboxylic acid allyl ester (Table 2 entry 4). Prepared according to the general procedure from acrolein (133 μL, 2.13 mmol), N-10-allylcarbamate-1-benzyltryptamine (170 mg, 0.532 mmol), and (2*R*, 5*R*)-catalyst 2 TFA salt (42 mg, 0.106 mmol) in CH_2Cl_2

(1.43 mL) and water (0.253 mL) at −80 °C for 24 h to provide the title compound as a colorless oil (166 mg, 83% yield, 89% ee) after silica gel chromatography in 15% EtOAc / hexanes. IR (film) 3063, 3033, 2946, 2887, 2711, 1701, 1603, 1491, 1452, 1408, 1364, 1354, 1330, 1213, 1159, 1105, 1083, 1032, 978, 939, 882, 743, 700 cm^{-1}; ^1H NMR (300 MHz, VT = 90°C, C_7D_8) δ 9.20 (s, 1H, CHO), 7.35 (d, *J* = 7.1 Hz, 1H, BnH), 7.22-6.99 (m, 5H, BnH, 4-ArH), 6.76 (d, *J* = 7.2 Hz, 1H, 6-ArH), 6.67 (t, *J* = 7.1 Hz, 1H, 5-ArH), 6.33 (d, *J* = 8.2 Hz, 1H, 7-ArH), 5.82 (ddd, *J* = 6.0, 11.0, 22.0 Hz, 1H, $CH_2C\mathbf{H}CH_2$), 5.42 (s, 1H, NCHN), 5.16 (d, *J* = 17 Hz, 1H, $CH_2CHC\mathbf{H}_2$), 5.04 (d, *J* = 10.4 Hz, 1H $CH_2CHC\mathbf{H}_2$), 4.74-4.50 (m, 4H, $CH_2C\mathbf{H}_2O$, $NC\mathbf{H}_2Ar$), 3.78 (t, *J* = 8.7 Hz, 1H, $CH_2C\mathbf{H}HN$); 3.00 (dt, *J* = 6.0, 17.0 Hz, 1H, $CH_2CH\mathbf{H}N$); 2.21-2.16 (m, 2H, $CH_2C\mathbf{H}_2CHO$), 1.86-1.77 (m, 2H, $C\mathbf{H}_2CH_2N$), 1.66-1.57 (m, 2H, $C\mathbf{H}_2CH_2CHO$); ^{13}C NMR (75 MHz, C_7D_8) δ 201, 155.5 [154.4], 150.7, 139.2, 133.1 [132.9], 129.3, [128.8] 128.6, 127.6, 127.2 [126.8], 123.1, [118.8] 118.2, 117.9 [117.7], 106.6, 84.3, [66.6] 66.2, [57.0] 55.6, 45.4, 40.2, 39.2 [38.5], [31.7] 31.4; HRMS (CI) exact mass calcd for ($C_{24}H_{26}N_2O_3$) requires *m/z* 390.1943, found *m/z* 390.1945. $[\alpha]_D$ = 247.8 (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 AD and AD guard column (6% isopropanol / hexanes, 1 mL/min); *R* isomer t_r = 31.0 min and *S* isomer t_r = 39.7 min. The minor counterparts of doubled signals due to Boc rotamers are shown in [ ].

(2*S*,3*S*)-8-Bezyl-3a-(3-oxo-propyl)-3,3a,8,8a-tetrahydro-2*H*-pyrrolo[2,3-*b*]indole-1-carboxylic acid *tert*-butyl ester (Table 2 entry 5). Prepared according to the general procedure from acrolein (0.54 mL, 8.0 mmol), N-10-BOC-1-benzyltryptamine (700 mg,

2.0 mmol), and (2*S*, 5*S*)-catalyst 2 TFA (114 mg, 0.40 mmol), and trifluoroacetic acid (31 μL, 0.40 mmol) in CH_2Cl_2 (5.0 mL) and H_2O (1. 0 mL) at –80 ºC was added acrolein). After stirring for 24 h at this temperature, the reaction mixture was purified by column chromatography (silica, 10% EtOAc in hexanes) to afford the title compound (670 mg, 82%) as a colorless, viscous oil; 90% ee; IR (thin film) 2974, 2930, 2719, 1123, 1692, 1604, 1493, 1393, 1365, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.60 (d, *J* = 22.5 Hz, 1H), 7.18-7.34 (m, 5H), 6.95-7.06 (m, 2H), 6.67 (approx d, *J* = 6.6 Hz, 1H), 6.25 (br dd, *J* = 7.2, 31.5 Hz, 1H), 5.40 (d, *J* = 47.4 Hz, 1H), 4.65 (approx s, 2H), 3.86 (br td, *J* = 9.9, 61.8 Hz, 1H), 3.08 (td, *J* = 6.0, 11.4 Hz, 1H), 1.90-2.40 (m, 6H), 1.32 (d, *J* = 29.7 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 154.8, 153.8, 150.8, 130.9, 128.9, 128.8, 128.5, 127.3, 126.9, 126.3, 123.0, 118.0, 117.6, 106.4, 85.3, 84.2, 80.8, 80.1, 57.2, 55.6, 50.8, 50.3, 45.7, 45.2, 40.5, 39.3, 38.4, 32.0, 31.6, 28.7, 28.5; HRMS (CI) exact mass calcd for ($C_{25}H_{30}N_2O_3^+$) requires *m/z* 406.2256, found *m/z*; $[\alpha]_D^{25}$ = –270.1 (c = 1.0, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a by HPLC with a Chiralcel ODH column and ODH guard column (4% EtOH:hexanes, 1 mL/min flow); t_r = 10.5 min and 12.0 min.

(2*S*,3*R*,3a*R*)-8-Allyl-3a-(1-benzoyl-3-oxo-propyl)-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-*b*]indole-1- carboxylic acid *tert*-butyl ester (Table 3 entry 1). Prepared according to the general procedure from methyl 4-oxo-4-phenyl-but-2-enal (131 mg, 0.816 mmol), N-10-BOC-1-allyltryptamine (61 mg, 0.204 mmol), and (2*S*, 5*S*)-catalyst 1 TFA salt (14.7 mg, 0.0408 mmol) in CH_2Cl_2 (410 μL) at –40 °C for 64 h to provide the title compound as a yellow oil (91.9 mg, 92% yield, 94% ee, 12.7:1 dr) after silica gel

chromatography in 25% EtOAc / hexanes. IR (film) 3053, 2968, 2882, 2825, 1717, 1693, 1602, 1493, 1445, 1388, 1369, 1221, 1150, 1097, 973, 935, 883, 773, 745, 692 cm^{-1}; ^1H NMR (300 MHz, VT = 90°C, C_7D_8) δ 8.94 (s, 1H, CHO), 7.95 (d, *J* = 8.2 Hz, 2H, COAr *o*-H), 7.13-6.94 (m, 4H, 4-ArH, COAr *m*-H, COAr *p*-H), 6.77 (d, *J* = 7.7 Hz, 1H, 6-ArH), 6.54 (t, *J* = 7.1 Hz, 1H, 5-ArH), 6.31 (d, *J* = 7.7 Hz, 1H, 7-ArH), 5.96 (s, 1H, NCHN), 5.85 (ddd, *J* = 4.5, 10.4, 22.5 Hz, 1H, $CH_2C\mathbf{H}CH_2$), 5.19 (d, *J* = 17 Hz, 1H, $CH_2CHC\mathbf{H}_2$), 5.02 (d, *J* = 10.4 Hz, 1H $CH_2CHC\mathbf{H}_2$), 4.36 (dd, *J* = 2.7, 9.9 Hz, 2H, $NC\mathbf{H}_2CH$), 3.98 (m, 1H, $CH_2C\mathbf{H}HN$), 3.59 (m, 1H, C**H**COPh), 2.86 (dd, *J* = 9.9, 18.7 Hz, 1H, $CH_2CH\mathbf{H}N$), 2.67 (m, 1H, CHCH**H**CHO), 2.12 (m, 1H, $CH_2CH\mathbf{H}CHO$), 1.76 (m, 2H, $C\mathbf{H_2}CH_2N$), 1.45 (s, 9H, $C(C\mathbf{H}_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 197.6, 150.5, 135.0, 132.5, 130.6, 129.1, 128.9, 128.3, 128.1, 125.3, 124.6, 123.0, 117.5, 115.5, 106.4, 81.9, 79.4, 48.4, 45.0, 44.9, 44.5, 36.5, 28.4, HRMS (CI) exact mass calcd for ($C_{28}H_{33}N_2O_4$) requires *m/z* 461.5738, found *m/z* 461.2440 $[\alpha]_D$ = –247.1 (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 OD-H and OD guard column (5% ethanol / hexanes, 1 mL/min); *Major* isomer t_r = 18.9 min and *Minor* isomer t_r = 26.3 min. The diastereomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel Sil-Rx and (4% ethanol / hexanes, 1 mL/min); *Major* isomer t_r = 10.4 min and *Minor* isomer t_r = 11.3 min.

(2*S*,3*R*,3a*R*)-8-Allyl-3a-(1-benzoyloxymethyl-3-oxo-propyl)-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-*b*]indole-1- carboxylic acid *tert*-butyl ester (Table 3 entry 2). Prepared according to the general procedure from 4-benzyloxy-but-2-enal (155 mg, 0.816 mmol),

N-10-BOC-1-allyltryptamine (61 mg, 0.204 mmol), and (2*S*, 5*S*)-catalyst 1 TFA salt (14.7 mg, 0.0408 mmol) in CH_2Cl_2 (410 μL) at –40 °C for 44 h to provide the title compound as a colorless oil (65.5 mg, 66% yield, 91% ee, 22.4:1 dr) after silica gel chromatography in 20% EtOAc / hexanes. IR (film) 2980, 2872, 1734, 1724, 1689, 1606, 1493, 1389 1365, 1316, 1272, 1218, 1154, 1105, 1065, 1026, 942, 888, 770, 716 cm^{-1}; ^1H NMR (300 MHz, VT = 90°C, C_7D_8) δ 9.37 (s, 1H, CHO), 8.02 (d, *J* = 6.6 Hz, 2H, COAr *o*-H), 7.24-7.03 (m, 4H, 4-ArH, COAr *m*-H, COAr *p*-H), 6.82 (d, *J* = 7.1 Hz, 1H, 6-ArH), 6.66 (t, *J* = 7.1 Hz, 1H, 5-ArH), 6.38 (d, *J* = 8.2 Hz, 1H, 7-ArH), 5.94-5.85 (m, 1H, $CH_2C\mathbf{H}CH_2$), 5.73 (s, 1H, NCHN), 5.27 (d, *J* = 17 Hz, 1H, $CH_2CHC\mathbf{H}_2$), 5.11 (d, *J* = 10.4 Hz, 1H $CH_2CHC\mathbf{H}_2$), 4.52 (dd, *J* = 4.4, 11.5 Hz, 2H, $NC\mathbf{H}_2CH$), 4.11 (m, 1H, CHC**H**HO), 3.96 (dd, *J* = 6.5, 11.5 Hz, 1H, CHCH**H**O), 3.78 (m, 1H, $CH_2C\mathbf{H}HN$), 2.90-2.80 (m, 1H, CHCH**H**CHO), 2.67-2.59 (m, 1H, CHC**H**HCHO), 2.41-2.16 (m, 3H, $CH_2CH\mathbf{H}N$, $C\mathbf{H}HCH_2N$, $C\mathbf{H}CH_2O$), 1.81-1.71 (m, 1H, $CH\mathbf{H}CH_2N$), 1.50 (s, 9H, $C(C\mathbf{H}_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 193.5, 166.5, 150.8, 142.8, 134.5, 133.4, 129.4, 128.7, 125.7, 123.6, 119.3, 117.5, 116.1, 109.8, 106.7, 88.7, 65.7, 59.5, 48.6, 45.6, 43.9, 40.3, 37.2, 28.7, HRMS (CI) exact mass calcd for ($C_{29}H_{35}N_2O_5$) requires *m/z* 491.5998, found *m/z* 491.2546 $[\alpha]_D$ = –148 (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 AD and AD guard column (5% ethanol / hexanes, 1 mL/min); *Major* isomer t_r = 11.7 min and *Minor* isomer t_r = 14.8 min. The diastereomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel Sil column (5% ethanol / hexanes, 1 mL/min); *Minor* isomer t_r = 12.1 min and *Major* isomer t_r = 13.7 min.

(2*S*,3*R*,3a*R*)-8-Allyl-3a-(1-methoxycarbonyl-3-oxo-propyl)-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-*b*]indole-1-carboxylic acid *tert*-butyl ester (Table 3 entry 3). Prepared according to the general procedure from methyl 4-oxo-butenoate (165 mg, 1.45 mmol), N-10-BOC-1-allyltryptamine (109 mg, 0.362 mmol), and (2*S*, 5*S*)-catalyst 1 TFA salt (26.1 mg, 0.0724 mmol) in CH_2Cl_2 (700 μL) at –60 °C for 29 h to provide the title compound as a colorless oil (140 mg, 93% yield, 91% ee, 44:1 dr) after silica gel chromatography in 10-20% EtOAc / hexanes. IR (film) 2973, 2904, 2736, 1730, 1696, 1607, 1493, 1389, 1365, 1217, 1152, 1098, 935, 890, 742 cm^{-1}; ^1H NMR (300 MHz, VT = 90°C, C_7D_8) δ 9.15 (s, 1H, CHO), 7.06 (obs, 1H, 4-ArH), 6.71 (d, *J* = 7.1 Hz, 1H, 6-ArH), 6.64 (t, *J* = 6.6 Hz, 1H, 5-ArH), 6.38 (d, *J* = 7.7 Hz, 1H, 7-ArH), 5.96 (s, 1H, NCHN), 5.96-5.80 (m, 1H, $CH_2C\mathbf{H}CH_2$), 5.28 (d, *J* = 17 Hz, 1H, $CH_2CHC\mathbf{H}_2$), 5.11 (d, *J* = 9.9 Hz, 1H $CH_2CHC\mathbf{H}_2$), 4.08 (s, 2H, $NC\mathbf{H}_2CH$), 3.80 (m, 1H, $CH_2C\mathbf{H}HN$), 3.42 (s, 3H, $CO_2C\mathbf{H_3}$), 3.28 (d, *J* = 11.0 Hz, 1H, $C\mathbf{H}CO_2CH_3$), 2.85 (dd, *J* = 9.9, 16.5 Hz, 1H, $CH_2CH\mathbf{H}N$), 2.70 (dd, *J* = 11.0, 18.1 Hz, 1H, $CH_2CH\mathbf{H}CHO$), 2.20 (m, 1H, $CHCH\mathbf{H}CHO$), 2.11 (t, *J* = 18.2 Hz, 2H, $C\mathbf{H_2}CH_2N$), 1.52 (s, 9H, $C(C\mathbf{H}_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 172.2, 150.6, 135.0, 130.0, 129.0, 125.4, 122.8, 117.7, 115.6, 106.5, 82.4, 79.5, 59.2, 47.4, 45.9, 44.9, 43.6, 38.3, 37.0, 28.5, HRMS (CI) exact mass calcd for ($C_{23}H_{31}N_2O_5$) requires *m/z* 415.2233, found *m/z* 415.2253 $[\alpha]_D$ = –189.9 (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 AD and AD guard column (5% ethanol / hexanes, 1 mL/min); *Major* isomer t_r = 10.0 min and *Minor* isomer t_r = 14.8 min. The diastereomeric ratio was determined by HPLC analysis of the alcohol,

obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel Sil-Rx column and (5% ethanol / hexanes, 1 mL/min); *Minor* isomer t_r = 9.2 min and *Major* isomer t_r = 10.5 min.

(2*S*,3*R*,3a*R*)-8-Allyl-3a-(1-methoxycarbonyl-3-oxo-propyl)-5-methyl-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-*b*]indole-1- carboxylic acid *tert*-butyl ester (Table 3 entry 4). Prepared according to the general procedure from methyl 4-oxo-butenoate (160 mg, 1.4 mmol), N-10-BOC-1-allyl-5-methyltryptamine (110 mg, 0.35 mmol), and (2*S*, 5*S*)-catalyst 1 TFA salt (25.2 mg, 0.07 mmol) in CH_2Cl_2 (700 μL) at –60 °C for 18 h to provide the title compound as a colorless oil (141 mg, 94% yield, 92% ee, >50:1 dr) after silica gel chromatography in 10-20% EtOAc / hexanes. IR (film) 2966, 2871, 2729, 1730, 1694, 1616, 1501, 1395, 1363, 1221, 1154, 1095, 949, 917, 893, 800, 772 cm^{-1}; ^1H NMR (300 MHz, VT = 90°C, C_7D_8) δ 9.15 (s, 1H, CHO), 7.06 (obs, 1H, 4-ArH), 6.62 (s, 1H, 6-ArH), 6.33 (d, *J* = 7.7 Hz, 1H, 7-ArH), 5.95 (s, 1H, NCHN), 5.99-5.90 (m, 1H, $CH_2C\mathbf{H}CH_2$), 5.29 (d, *J* = 17 Hz, 1H, $CH_2CHC\mathbf{H}_2$), 5.13 (d, *J* = 9.9 Hz, 1H $CH_2CHC\mathbf{H}_2$), 4.08 (s, 2H, $NC\mathbf{H}_2CH$), 3.81 (m, 1H, $CH_2C\mathbf{H}HN$), 3.44 (s, 3H, $CO_2C\mathbf{H_3}$), 3.30 (dd, *J* = 10.4, 3.3 Hz, 1H, $C\mathbf{H}CO_2CH_3$), 2.90 (td, *J* = 6.6, 10.4 Hz, 1H, $CH_2CH\mathbf{H}N$), 2.72 (dd, *J* = 10.4, 18.1 Hz, 1H, $CHCH\mathbf{H}CHO$), 2.21 (s, 3H, $ArC\mathbf{H_3}$), 2.26-2.08 (m, 2H, $C\mathbf{H_2}CH_2N$), 1.84 (dd, *J* = 6.0, 12.0, 1H, $CH_2CH\mathbf{H}CHO$), 1.52 (s, 9H, $C(C\mathbf{H}_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 172.2, 148.6, 135.2, 130.4, 129.7, 126.6, 125.4, 123.4, 115.5, 106.5, 82.6, 79.4, 51.2, 48.9, 45.9, 44.9, 43.7, 36.9, 28.5, 20.6 HRMS (CI) exact mass calcd for ($C_{24}H_{32}N_2O_5$) requires *m/z* 428.2311, found *m/z* 428.2327 $[\alpha]_D$ = –164.5 (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 AS and AS guard column (2% ethanol

/ hexanes, 1 mL/min); *Major* isomer t_r = 10.6 min and *Minor* isomer t_r = 12.8 min. The diastereomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AS and AS guard column (7% ethanol / hexanes, 1 mL/min); *Major* isomer t_r = 5.8, 6.2 min and *Minor* isomer t_r = 6.9, 7.3 min.

(2*S*,3*R*,3a*R*)-8-Allyl-3a-(1-methoxycarbonyl-3-oxo-propyl)-5-methoxy-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-*b*]indole-1- carboxylic acid *tert*-butyl ester (Table 3 entry 5). Prepared according to the general procedure from methyl 4-oxo-butenoate (102 mg, 0.9 mmol), N-10-BOC-1-allyl-5-methoxytryptamine (74 mg, 0.23 mmol), and (2*S*, 5*S*)-catalyst 1 TFA salt (16.0 mg, 0.045 mmol) in CH_2Cl_2 (460 μL) at –60 °C for 20 h to provide the title compound as a colorless oil (141 mg, 99% yield, 90% ee, 10:1 dr) after silica gel chromatography in 10-20% EtOAc / hexanes. IR (film) 2976, 2927, 2839, 2721, 1730, 1691, 1496, 1437, 1393, 1364, 1222, 1149, 1041, 987, 943, 909, 889, 806, 772 cm^{-1}; ^1H NMR (300 MHz, VT = 90°C, C_7D_8) δ 9.05 (s, 1H, CHO), 6.55 (dd, *J* = 2.2, 8.2 Hz, 1H, 4-ArH), 6.45 (d, *J* = 1.6 Hz, 1H, 6-ArH), 6.22 (d, *J* = 8.8 Hz, 1H, 7-ArH), 5.82 (s, 1H, NCHN), 5.86 (ddd, *J* = 4.5, 10.4, 22.5 Hz, 1H, $CH_2C\mathbf{H}CH_2$), 5.20 (dd, *J* = 1.6, 17.0 Hz, 1H, $CH_2CHC\mathbf{H}_2$), 5.02 (dd, *J* = 1.6, 11 Hz, 1H $CH_2CHC\mathbf{H}_2$), 3.97 (d, *J* = 4.4 Hz, 2H, $NC\mathbf{H}_2CH$), 3.70 (m, 1H, $CH_2C\mathbf{H}HN$), 3.41 (s, 3H, $CO_2C\mathbf{H_3}$), 3.30 (s, 3H, $ArOC\mathbf{H_3}$), 3.18 (dd, *J* = 10.4, 3.3 Hz, 1H, $C\mathbf{H}CO_2CH_3$), 2.81 (td, *J* = 6.6, 10.4 Hz, 1H, $CH_2CH\mathbf{H}N$), 2.62 (dd, *J* = 10.4, 18.1 Hz, 1H, $CHCH\mathbf{H}CHO$), 2.10-1.90 (m, 2H, $C\mathbf{H_2}CH_2N$), 1.72 (dd, *J* = 6.6, 12.6, 1H, $CH_2CH\mathbf{H}CHO$), 1.42 (s, 9H, $C(C\mathbf{H}_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 171.4, 150.1, 135.4, 128.9, 115.4, 114.2, 110.6, 106.9, 83.0, 79.3, 55.7, 51.0, 49.4, 45.7, 44.9, 43.6, 36.7, 28.4 HRMS (CI) exact mass calcd for

($C_{24}H_{32}N_2O_6$) requires *m/z* 444.2260, found *m/z* 444.2258 $[\alpha]_D$ = –162.5 (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 AS and AS guard column (5% ethanol / hexanes, 1 mL/min); *Major* isomer t_r = 8.6 min and *Minor* isomer t_r = 10.4 min. The diastereomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel Sil-Rx column (5% ethanol / hexanes, 1 mL/min); *Minor* isomer t_r = 20.5 min and *Major* isomer t_r = 22.1 min.

(2*S*,3*R*,3a*R*)-6-Bromo-3a-(1-methoxycarbonyl-3-oxo-propyl)-8-(3-methyl-but-2-enyl)-3,3a,8,8a-tetrahydro-2*H*-pyrrolo[2,3-*b*]indole-1-carboxylic acid *tert*-butyl ester (Table 3 entry 6). Prepared according to the general procedure from methyl 4-oxo-butenoate (597 mg, 5.22 mmol), N-10-Boc-1-Prenyl-6-Bromotryptamine (710 mg, 1.74 mmol), and (2*S*, 5*S*)-catalyst 1 (86 mg, 0.35 mmol), and trifluoroacetic acid (27 μL, 0.35 mmol) in CH_2Cl_2 (43.5 mL) at –40 °C for 24 h to provide the title compound as a colorless oil (778 mg, 86% yield, 97% ee, 31:1 dr) after silica gel chromatography in 20% EtOAc / hexanes as a colorless, viscous oil. IR (thin film) 2971, 2928, 2716, 1728, 1696, 1600, 1490, 1396, 1364, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 6.37 (s, 1H), 5.71 (br s, 1H), 5.09 (br s, 1H), 3.80-4.09 (m, 3H), 3.62 (s, 3H), 3.21 (dd, *J* = 2.7, 11.1 Hz, 1H), 2.80-3.01 (m, 2H), 2.33 (br d, *J* = 17.7 Hz, 1H), 1.91-2.07 (m, 2H), 1.71 (s, 3H), 1.68 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 172.8, 172.5, 154.3, 15.7, 151.6, 134.4, 128.7, 125.6, 124.1, 123.3, 121.3, 120.8, 120.1, 119.8, 109.1, 81.9, 80.9, 80.1, 58.2, 56.9, 52.4, 45.4, 44.7, 43.6, 43.5, 36.6, 36.4, 28.7, 26.0, 18.5; HRMS (CI) exact mass calcd for

($C_{25}H_{33}BrN_2O_5^+$) requires *m/z* 520.1573, found *m/z* 520.1582; $[\alpha]_D^{25}$ = –196.3 (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 OD-H and OD guard column (6% ethanol / hexanes, 1 mL/min); *Major* isomer t_r = 8.4 min and *Minor* isomer t_r = 11.1 min. The diastereomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel Sil-Rx column (3% ethanol / hexanes, 1 mL/min); *Minor* isomer t_r = 18.1 min and *Major* isomer t_r = 19.5 min.

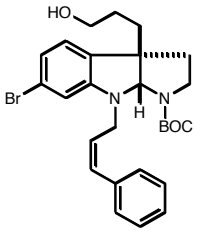
(2*S*,3*R*,3a*R*)-8-Allyl-3a-(1-methoxycarbonyl-3-oxo-propyl)-7-methyl-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-*b*]indole-1- carboxylic acid *tert*-butyl ester (Table 3 entry 7). Prepared according to the general procedure from methyl 4-oxo-butenoate (160 mg, 1.4 mmol), N-10-Boc-1-allyl-7-methyltryptamine (110 mg, 0.35 mmol), and (2*S*, 5*S*)-catalyst 1 TFA salt (25.2 mg, 0.07 mmol) in CH_2Cl_2 (700 μL) at –60 °C for 30 h to provide the title compound as a colorless oil (146 mg, 97% yield, 99% ee, 17:1 dr) after silica gel chromatography in 10-20% EtOAc / hexanes. IR (film) 2976, 2880, 2725, 1738, 1727, 1694, 1601, 1591, 1468, 1402, 1365, 1335, 1250, 1221, 1166, 1136, 937, 911, 881 cm^{-1}; ^1H NMR (300 MHz, VT = 90°C, C_7D_8) δ 9.21 (d, *J* = 4.4 Hz, 1H, CHO), 7.06 (obs, 1H, 4-ArH), 6.83 (d, *J* = 6.6 Hz, 1H, 6-ArH), 6.33 (obs, 1H, 5-ArH), 5.83 (s, 1H, NCHN), 6.05 - 5.87 (m, 1H, $CH_2C\mathbf{H}CH_2$), 5.31 (d, *J* = 17 Hz, 1H, $CH_2CHC\mathbf{H}_2$), 5.11 (d, *J* = 10.4 Hz, 1H $CH_2CHC\mathbf{H}_2$), 4.28 (s, 2H, $NC\mathbf{H}_2CH$), 3.77 (m, 1H, $CH_2C\mathbf{H}HN$), 3.44 (s, 3H, $CO_2C\mathbf{H}_3$), 3.33 (dd, *J* = 7.7, 3.3 Hz, 1H, $C\mathbf{H}CO_2CH_3$), 2.92 (dd, *J* = 10.4, 17.0 Hz, 1H, CHCH**H**CHO), 2.72 (dd, *J* = 10.4, 17.6 Hz, 1H, $CH_2CH\mathbf{H}N$), 2.27 (s, 3H, $Ar\mathbf{CH}_3$),

2.26-2.10 (m, 2H, C**H**$_2$CH$_2$N), 1.89 (m, 1H, CH$_2$CH**H**CHO), 1.54 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 172.3, 148.7, 136.8, 132.4, 128.9, 128.1, 125.3, 120.7, 119.1, 115.5, 83.6, 79.3, 51.3, 51.1, 45.8, 44.5, 44.2, 37.2, 28.4, 21.0, 19.0 HRMS (CI) exact mass calcd for ($C_{24}H_{32}N_2O_5$) requires *m/z* 428.2311, found *m/z* 428.2324 $[\alpha]_D$ = –176.7 (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 AD and AD guard column (5% ethanol / hexanes, 1 mL/min); *Major* isomer t_r = 14.0 min and *Minor* isomer t_r = 16.6 min. The diastereomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel Sil-Rx column (5% ethanol / hexanes, 1 mL/min); *Major* isomer t_r = 10.0 min and *Minor* isomer t_r = 10.7 min.

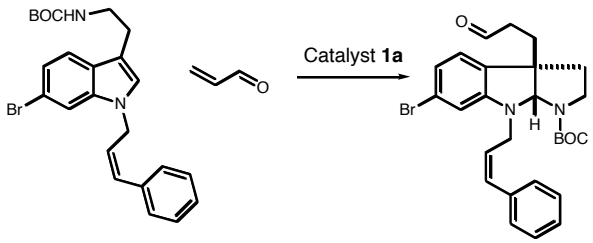
(2*S*,3*R*,3a*R*)-2-(8-Benzyl-2,3,8,8a-tetrahydro-furo[2,3-*b*]indole-3a-yl)-4-oxo-butyric acid *tert*-butyl ester (Equation 6). Prepared according to the general procedure from *t*-butyl 4-oxo-butenoate (622 mg, 4 mmol), N-Benzyltryptophol (334 mg, 1.33 mmol), and (2*S*, 5*S*)-catalyst 1 TFA salt (96 mg, 0.266 mmol) in CH_2Cl_2 (4.80 mL) and IPA (500 μL) at –60 °C for 40 h to provide the title compound as a colorless oil (325 mg, 80% yield, 93% ee, 12:1 dr) after silica gel chromatography in 15% EtOAc / hexanes. IR (film) 2729, 1721, 1601, 1601, 1407, 1446, 1363, 1254, 1217, 1150, 1026, 948, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H, CHO), 7.38-7.23 (m, 5H, CH$_2$ArH), 7.06 (d, *J* = 7.8 Hz, 1H, 4-ArH), 7.02 (d, *J* = 7.2 Hz, 1H, 6-ArH), 6.67 (t, *J* = 7.5 Hz, 1H, 5-ArH), 6.34 (d, *J* = 7.8 Hz, 1H, 7-ArH), 5.64 (s, 1H, NCHO), 4.50 (Abq, *J* =15.9 Hz, Δυ = 18.3, 2H, NCH$_2$Ar), 3.94 (dd, *J* = 7.2, 8.1 Hz, 1H CH$_2$CH**H**O), 3.52-3.44 (m, 1H), 3.25 (dd, *J* =

3.3, 11.7 Hz, 1H), 2.78 (dd, *J* = 11.7, 18.6 Hz, 1H), 2.42-2.25 (m, 2H), 2.14-2.0 (m, 1H), 1.38 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 171, 150., 138.1, 130.0, 128.9, 128.4, 127.4, 127.1, 123.1, 117.8, 105.7, 98.3, 81.7, 66.5, 57.6, 48.9, 46.1, 43.4, 38.5, 28.0, HRMS (CI) exact mass calcd for ($C_{25}H_{28}NO_4$) requires *m/z* 406.2018, found *m/z* 406.2027 $[\alpha]_D$ = -94 (c = 1.25, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AS and AS guard column (2% isopropanol / hexanes, 1 mL/min); *Minor* isomer t_r = 20.7 min and *Major* isomer t_r = 23.5 min. The diastereomeric ratio was determined by NMR analysis.

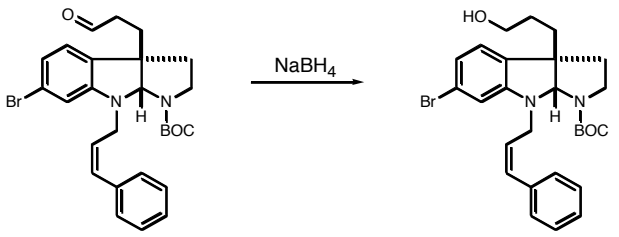
Determination of the absolute stereochemistry of (*S*)-6-Bromo-3a-(3-hydoxy-propyl)-8-(3-phenyl-allyl)-3,3a,8,8a-tetrahydro-2*H*-pyrrolo[2,3-*b*]indole-1-carboxylic acid *tert*-butyl ester by X-ray crystallography.



(*S*)-6-Bromo-3a-(3-hydoxy-propyl)-8-(3-phenyl-allyl)-3,3a,8,8a-tetrahydro-2*H*-pyrrolo[2,3-*b*]indole-1-carboxylic acid *tert*-butyl ester. To a solution of compound N-10- BOC-1-(3-phenyl-allyl)-6-Bromotryptamine (50 mg, 0.11 mmol), (*S,S*)-catalyst **1** (5.4 mg, 0.022 mmol), and trifluoroacetic acid (1.7 μL, 0.022 mmol) in CH_2Cl_2 (0.2 mL) at -60 ºC was



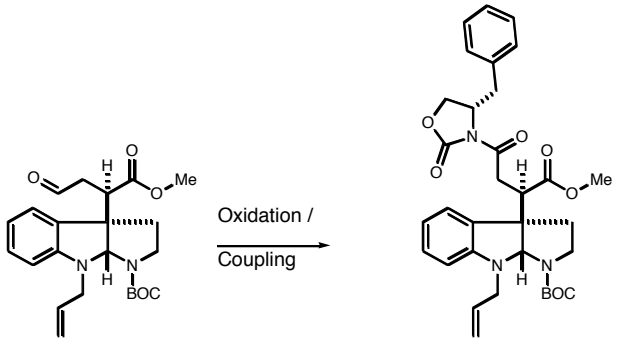
added acrolein (30 μL, 0.44 mmol). After stirring for 36 h at this temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined extract was washed with brine, dried over sodium sulfate, concentrated. The product was used directly in the next reaction without further purification.



To a solution of amine from the reaction above in MeOH (0.2 mL) at 0 °C was added sodium borohydride (25 mg, 0.66 mmol). After stirring for 15 min. at this temperature, the reaction mixture was quenched with 0.5 N HCl solution and extracted with EtOAc. The combined extract was washed with brine, dried over sodium sulfate, concentrated, and purified by column chromatography (silica, 30% EtOAc in hexanes) to afford the title compound (33 mg, 58%) as a colorless, solid; 82% ee; IR (thin film) 3437, 2928, 1690, 1601, 1490, 1398, 1366, 1218, 1156, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.34 (m, 5H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 17.1 Hz, 1H), 6.50 (s, 1H), 6.11-6.22 (m, 1H), 5.37 (d, *J* = 46.5 Hz, 1H), 5.09 (br s, 1H), 3.70-4.23 (m, 3H), 3.54 (br d, *J* = 6.6 Hz, 2H), 2.97-3.11 (m, 1H), 1.21-2.09 (m, 6H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 153.7, 151.7, 1374.2, 131.5, 131.2, 128.8, 128.6, 127.7, 127.5, 126.5, 125.8, 124.1, 122.4, 120.3, 119.9, 109.1, 108.9, 84.9, 84.6, 80.9, 80.2, 63.1, 57.3, 56.0, 45.7, 45.1, 39.0, 38.4, 36.2, 35.9, 28.9, 28.7; HRMS (CI) exact mass calcd for ($C_{27}H_{33}BrN_2O_3$ + H) requires *m/z* 513.1750, found *m/z* 513.1750. $[\alpha]_D^{26}$ = –116.2(c = 3.3, $CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiralcel ODH column and ODH guard column (4% EtOH:hexanes, 1

mL/min flow); t_r = 20.5 min and 22.2 min. This compound was crystallized from evaporation of deuterated chloroform. Coordinates and report are appended as JFA01.

Determination of the absolute stereochemistry of (2*S*,3*R*,3a*R*)-8-Allyl-3a-(1-methoxycarbonyl-3-oxo-propyl)-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-*b*]indole-1-carboxylic acid *tert*-butyl ester by derivatization to (2*S*,3*R*,3a*R*)-8-Allyl-3a-[3-(4-(*S*)-benzyl-2-oxo-oxazolidin-3-yl)-1-methoxycarbonyl-3-oxo-propyl]-3,3a,8,8a-tetrahydro-2*H*-pyrrolo[2,3-*b*]indole-1-carboxylic acid *tert*-butyl ester and subsequent X-ray crystallography.



(2*S*,3*R*,3a*R*)-8-Allyl-3a-[3-(4-(*S*)-benzyl-2-oxo-oxazolidin-3-yl)-1-methoxycarbonyl-3-oxo-propyl]-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-b]indole-1-carboxylic acid tert-butyl ester. (2*S*,3*R*,3a*R*)-8-Allyl-3a-(1-methoxycarbonyl-3-oxo-propyl)-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-b]indole-1- carboxylic acid tert-butyl ester was dissolved in tert-butyl alcohol (4.5 mL) and 2-methyl-2-butene (1.2 mL) and subsequently was stirred for 10 min. To this solution was added an aqueous solution (1.8 mL) of $NaClO_2$ (90.4

mg, 2.23 mmol) and NaH_2PO_4 (138 mg, 1.56 mmol) in one portion. The reaction mixture was stirred at room temperature for 2 h. The organics were removed by concentrating *in vacuo*. The residue was diluted with 5 mL of H_2O, and adjusted to a neutral pH with 1M HCl. Extraction with EtOAc (3x10 mL), drying over Na_2SO_4, and concentration in vacuo provided (2*S*,3*R*,3a*R*)-2-(8-Allyl-1-*tert*-butoxycarbonyl-2,3,8,8a-tetrahydro-1*H*-pyrrolo[2,3-*b*]indol-3a-yl)-succinic acid 1-methyl ester. This isolated residue was dissolved in THF (2ml), TEA (65 μl, 0.468 mmol), and PivCl (27.5 μl, 0.223 mmol) and allowed to stir at room temperature for 15 minutes. To this solution was added LiCl (9.4 mg, 0.223 mmol), and (S)-4-Benzyl-oxazolidin-2-one which was stirred for an additional 8 h. The solution was diluted with 10 mL of H_2O, and adjusted to a neutral pH with 1M HCl. Extraction with Et_2O (3x10 mL), drying over Na_2SO_4, and concentration *in vacuo* provided (2*S*,3*R*,3a*R*)-8-Allyl-3a-[3-(4-(*S*)-benzyl-2-oxo-oxazolidin-3-yl)-1-methoxycarbonyl-3-oxo-propyl]-3,3a,8,8a-tetrahydro-2H-pyrrolo[2,3-b]indole-1-carboxylic acid tert-butyl ester. The resulting solid was crystallized from benzene / hexanes. Coordinates and report are given.

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