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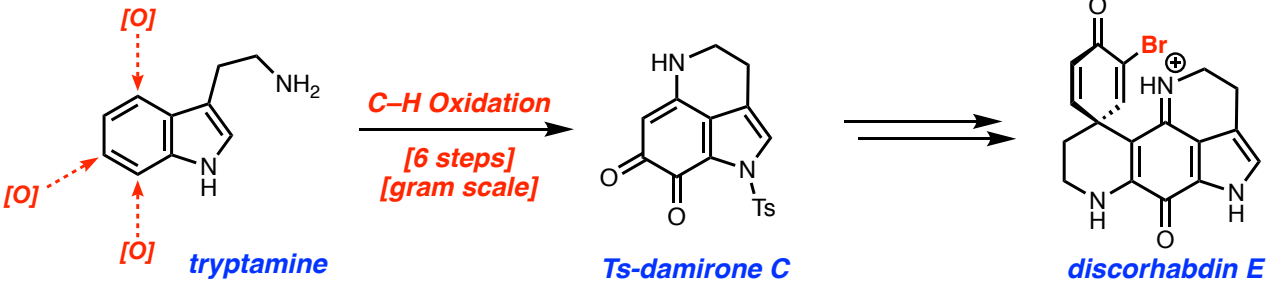
Graphical Abstract:



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A Convenient C–H Functionalization Platform for Pyrroloiminoquinone Alkaloid Synthesis

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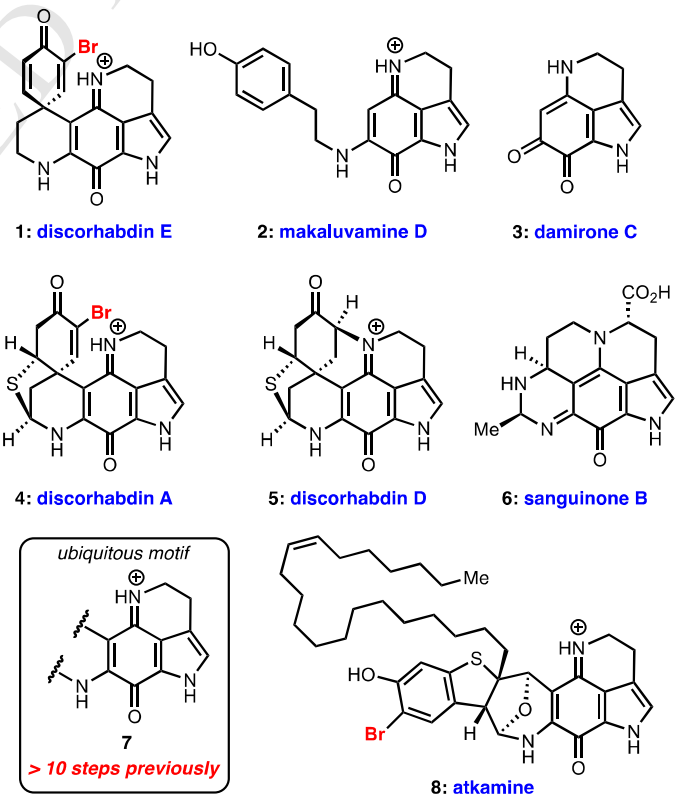
Abstract: Pyrroloiminoquinone alkaloids represent a structurally intriguing class of natural products that display an array of useful biological properties. Here, we present a versatile and scalable platform for the synthesis of this diverse family – and in particular the antitumor discorhabdins – built upon sequential selective C–H functionalization of tryptamine. The utility of this strategy is showcased through short formal syntheses of damirones A–C, makaluvamines D and I, and discorhadbin E. Additionally, we describe efforts to develop the first catalytic asymmetric entry to the discorhabdin subclass.

Alkaloids have long captured the imagination of synthetic chemists and medical practitioners alike due to the challenge their intricate structures present and the wide array of useful biological properties often encoded therein.[1] Among this large collection of natural products, the pyrroloiminoquinone alkaloids represent a unique subset of structural complexity. These compounds are typically isolated from marine sources and encompass many diverse classes, such as the discorhabdins, makaluvamines, and damirones (Figure 1), displaying antitumor, antimalarial, antiviral, antifeedant and antibacterial properties.[2] Within this larger group of alkaloids, arguably the most complex and interesting biologically are the discorhabdins, a family of over 50 members isolated from various species of marine sponge.[3] The discorhabdins display noteworthy anticancer activities, with nanomolar cytotoxicity (IC_{50} often <50 nM) being observed *in vitro* against a range of cancer cell lines; however, *in vivo* studies have proven less promising, either due to compound instability or nonspecific cytotoxicity.[3,4,5] For this reason, a flexible de novo synthetic entry to the family would be desirable for detailed SAR studies,[5] ideally allowing their selectivity profile to be fine-tuned while also providing access to related pyrroloiminoquinone targets.

Figure 1. Representative pyrroloiminoquinone alkaloids.

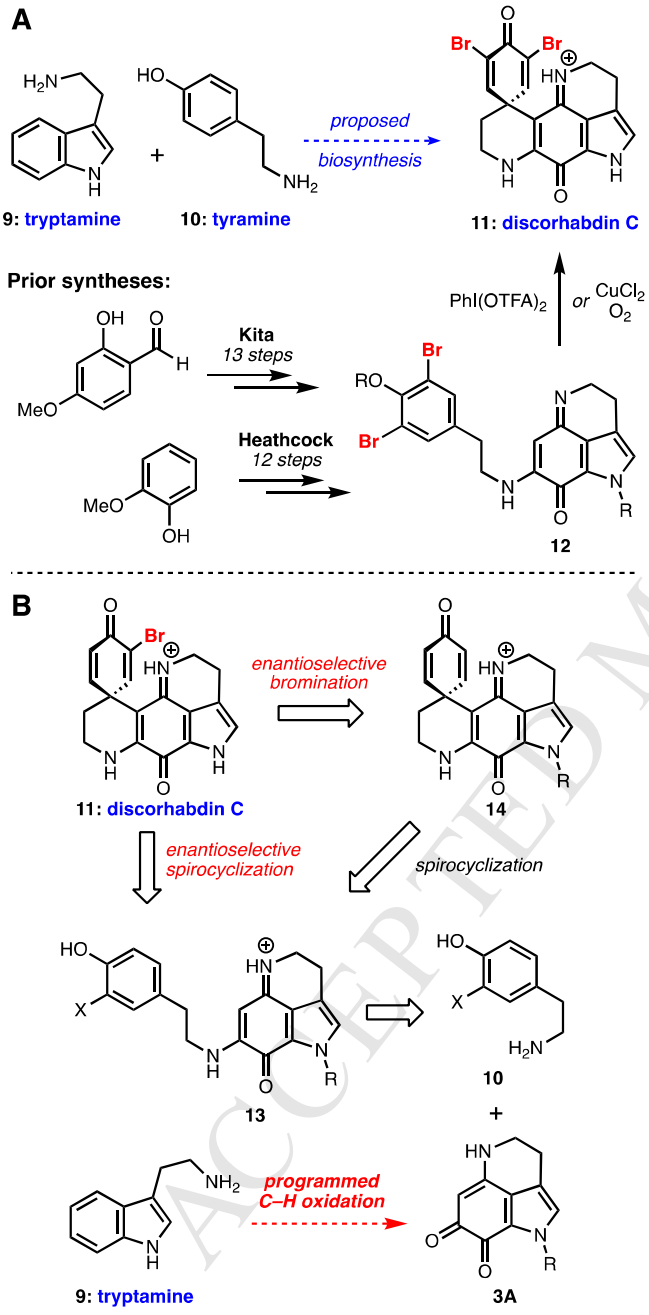


Structurally, the discorhabdins contain a unique polycyclic framework, comprising a tricyclic pyrroloiminoquinone ring system fused to a spirodienone fragment via a quaternary stereogenic spirocenter, as exemplified in discorhabdin E[6] (**1**, Figure 1). More complex members feature additional ring systems (e.g., **4**, **5**) and the class as a whole contains an impressive array of heteroatoms, with nitrogen, sulfur, bromine and oxygen substituents all commonly found within the same molecule. Of note is the particularly challenging arrangement of *N*-atoms in the pyrroloiminoquinone portion of the molecules, which results in a highly basic doubly vinylogous guanidinine (i.e. **7**); in fact, such substructures have typically required more than 10 steps to construct.[3]

Biosynthetically, these natural products are postulated to arise from the combination of two amino acid-derived fragments: tryptamine (**9**) and tyramine (**10**), which

form makaluvamine-type structures (e.g., **2**, Figure 1) that are in turn spirocyclized to the discorhabins (e.g., discorhabdin C **11**, Scheme 1A).[3] Indeed, while there have been many creative approaches to these molecules,[7] the majority of successful synthetic efforts have followed this biomimetic blueprint. For example, notable work from the Kita and Heathcock groups involved synthesizing makaluvamine-type structures **12** from simple aromatic building blocks which are then oxidatively spirocyclized under hypervalent iodine(III) or aerobic copper-mediated conditions en route to discorhabdins C (**11**),[8,9,10] E (**1**),[10] and A (**4**)[11] (Scheme 1A).

Scheme 1. (**A**) Proposed biosynthetic origins, notable prior art, (**B**) our approach to the discorhabdins.

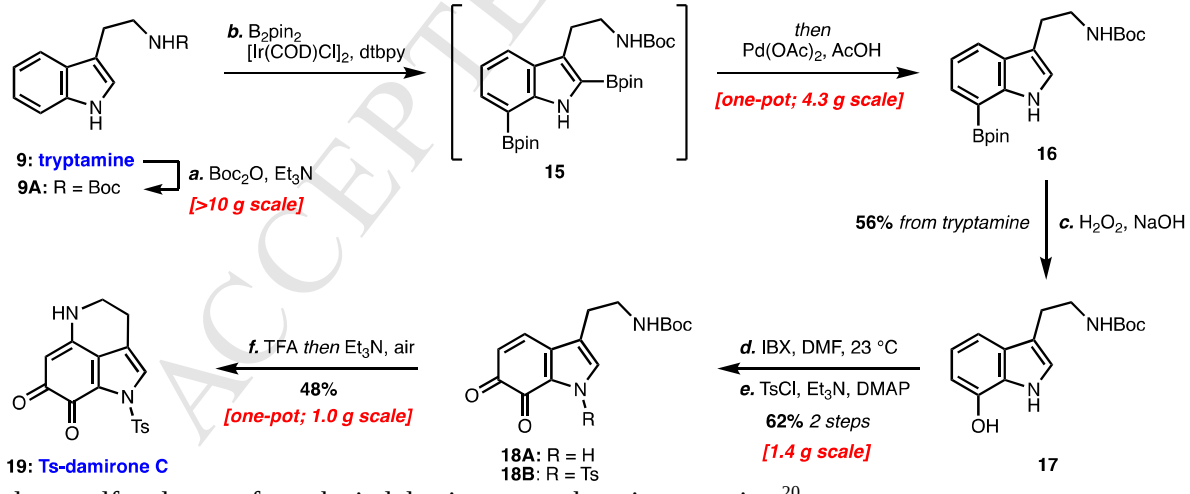


In planning our own bioinspired approach to these important targets, we noted two key areas in these prior studies where significant improvement might be possible: first, while highly effective in their sequential transformation of oxidized tryptamine fragments to makaluvamine-type intermediates to spirocyclic compounds, these routes invested the majority of their synthetic effort in preparation of such tryptamine frameworks, typically via lengthy de novo sequences from simple aromatics (Scheme 1A).[8-11] Second, no enantioselective approach to the family has been described to date,[12] meaning that a catalytic asymmetric entry to the class could prove especially enabling. Given our lab's interest in both catalytic asymmetric halofunctionalization transformations[13] and novel synthetic strategies enabled by C–H functionalization,[14] we formulated a plan towards one of the prototypical chiral members of the discorhabdin family, discorhabdin E (**1**). As outlined in Scheme 1B, we hoped to set the chirality of its lone stereocenter through the development of either an asymmetric spirocyclization of a brominated makaluvamine-type precursor **13** (X = Br) or via a brominative desymmetrization of achiral spirodienone **14**, also available from a similar precursor (**13**, X = H). We postulated that **13** could be formed through a condensation reaction between an appropriate tyramine partner **10A** and an orthoquinone tricycle **3A**, encompassing the framework of the natural product damirone C[15] (**3**). In contrast to the relatively lengthy prior syntheses of tricycles of type **3A**,[16] we sought to streamline our preparation of this key fragment by beginning with the readily available, unsubstituted tryptamine scaffold, and simply installing the necessary carbon–heteroatom bonds through selective C–H oxidations. Importantly, **3A** could also serve as a versatile intermediate for accessing other classes of pyrroloiminoquinone alkaloids (see Figure 1). Herein, we

report the execution of this plan, resulting in convenient, scalable access to such an intermediate, along with our efforts to develop the first catalytic asymmetric entry to the discorhabdins as a prelude to optimizing their antitumor properties.

Our route began with the quantitative *N*-Boc-protection of tryptamine (**9**), followed by the application of a modified one-pot C–H diborylation/monodeborylation procedure under Ir- and Pd-catalysis, developed by Movassaghi and co-workers (Scheme 2).[17] This process proceeds via diborylated intermediate **15** and achieves the net installation of a C-7 Bpin substituent, which could be easily transformed to the corresponding phenol through treatment with alkaline H_2O_2 to deliver **17** in 56% overall yield from tryptamine. This sequence proved highly scalable and was reliably conducted on decagram quantities of **17** with little variation in yield. With a C-7 phenol in place, selective oxidation to the corresponding orthoquinone **18A** with IBX proceeded effectively,[18] with this being the first demonstration of this process in an indole setting to the best of our knowledge. Although precedent exists for cyclization of tryptamine orthoquinones similar to **18A** under basic aerobic conditions,[16b-d,f] our efforts to cyclize the corresponding amine salts (available from acidic *N*-Boc deprotection), routinely resulted in extensive decomposition, with no damirone C (**3**) being isolated. We found, however, that protection of the indole nitrogen of **18A** with a tosyl group (62% over two steps from phenol **17**) gave a material (**18B**) that could be cleanly converted to tricycle **19** in 48% yield by treatment with TFA, evaporation of the volatiles, and exposure to Et_3N in MeOH under air.[19] This protocol can reliably be conducted on gram scale, and to date we have prepared over 2.5 g of **19**. Indeed, the synthesis of **19** in 6 steps and 15% overall yield from tryptamine represents the shortest preparation of this material to date (15 steps previously),[16a] and also constitutes the formal synthesis of several pyrroloiminoquinone alkaloids including damirones A–C and makaluvamines D and I.[16] Furthermore, we found that **19** could be condensed with tyramine fragments **10** and **10A** under mild conditions to give makaluvamine-type compounds **2A** and **20** in 71 and 29% yield, respectively (Scheme 3). In these reactions, careful control of reaction time and purification was important for maximizing material throughput; even so, achieving high conversions in the brominated series proved unexpectedly challenging. We observed that longer reaction times led to competitive degradation of both **20** and its condensation product. One such identified pathway was transfer of the

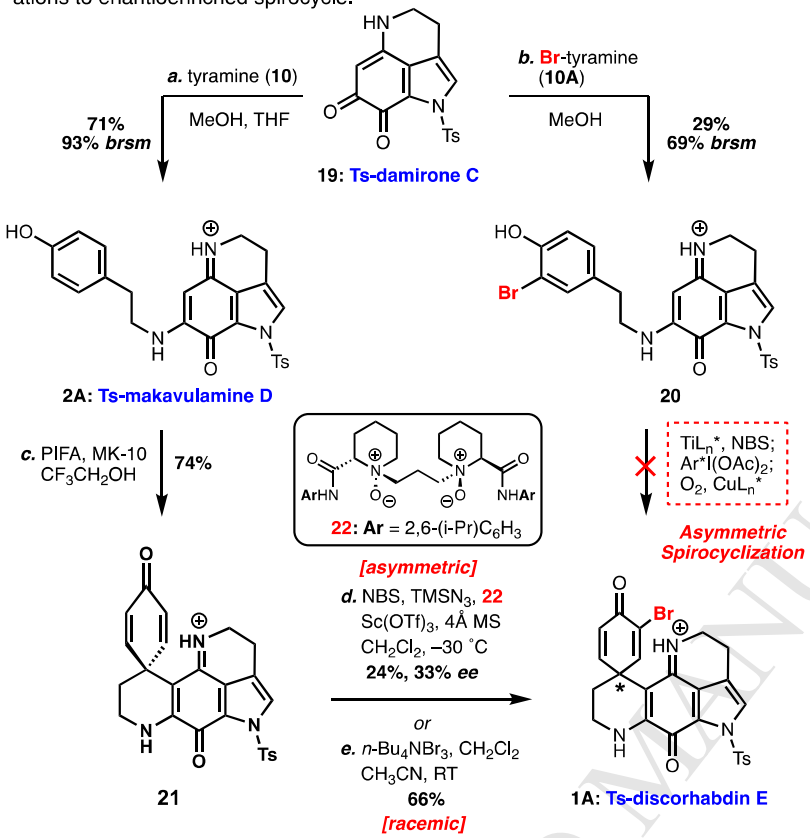
Scheme 2. Synthesis of Ts-damirone C via sequential C–H functionalization of tryptamine.



toluenesulfonyl group from the indole nitrogen to the primary amine.[20]

While the preparation of **20** constituted a racemic formal synthesis of discorhabdin E (**1**),[10] we aimed to provide an asymmetric entry to the family. It should be noted, however, that the properties of compounds post condensation rendered the development of such a process challenging, with the basic and heteroatom-rich scaffolds limiting the choice of strategies or, in the case of polar salt forms of **20** (and

Scheme 3. Preparation of makaluvamine-type materials and attempted transformations to enantioenriched spirocycle.



21), solvents. While our initial efforts focusing on an asymmetric spirocyclization of **2A** and **20** were largely unfruitful, explorations of a brominative desymmetrization approach on spirodienone **21** proved more rewarding. This material was reliably prepared in 74% yield by treatment of **2A** under conditions of Kita et al. employing PIFA and Montmorillonite K-10 clay in 2,2,2-trifluoroethanol.[11] Although the aerobic Cu-based conditions[10] of Heathcock and Aubart provided high yields of **21** on small scale (<50 mg of **2A**), in our hands their method proved much less effective on scale-up. Initial attempts at effecting the desired bromination of **21** showed that this could be readily accomplished in a racemic sense using *n*-Bu_4NBr_3 (66% yield of *rac*-**1A**). In contrast, achieving an analogous enantioselective transformation proved challenging. For example, while explorations in a model system showed organocatalytic methods to be viable, the complications inherent to the structure of **21** (either as its TFA salt or free base) led to no productive reactivity. Efforts to condense chiral auxiliaries such as (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) onto the ketone were unfortunately unsuccessful. Similarly, attempted bromination of chiral salt forms of **21** (formed from **21** and an equivalent amount of chiral phosphoric acid) delivered the desired product in poor yield and with no enantioselectivity.

Given these failures, we then proceeded to explore Baylis–Hillman-type brominations with an appropriate combination of nucleophile and brominating reagent. Inspired by a recent report by Feng and co-workers on the asymmetric haloazidation of acyclic enones,[21] we found in initial trials that the combination of TMS azide and NBS as nucleophile and bromonium source, respectively, in the presence of a catalytic amount of $Sc(OTf)_3$ delivered *rac*-**1A** directly (34%, 43% **21** recovered) without isolation of the intermediate bromoazide. We then proceeded to test various combinations of Lewis acidic metals and chiral ligands (see SI for details) in this process. Among the many systems screened, we ultimately found that treatment of **21** with TMS azide and NBS in the presence of a combination of $Sc(OTf)_3$ and chiral *N*,*N*'-dioxide ligand **22**[22] (30 mol% of each) in CH_2Cl_2 at –30 °C with 4Å MS provided the desired bromoenone **1A** in 23% yield and 33% ee. The use of other Br^+ sources (e.g. NBA, DBDMH, TBCHD, BsNMeBr; for a complete list, see Supporting Information), nucleophiles ($TsNH_2$, *p*-$NsNH_2$)[23] and various solvents did not improve the enantioinduction (see SI for full details). While the selectivity achieved to date is admittedly moderate, it is important to note that this nevertheless represents the first catalytic asymmetric inroad towards the discorhabdin family, hinting at the challenge posed by their unique scaffolds.

In summary, we have described a short and scalable entry to the pyrroloiminoquinone alkaloids via a key tricyclic intermediate, available through a series of selective C–H functionalization reactions on the parent tryptamine framework. Through this synthetic platform we have achieved concise formal syntheses of damirones A–C, makaluvamines D and I, and discorhadbin E. Finally, we have disclosed our preliminary efforts toward a catalytic asymmetric solution to the discorhabdin alkaloids, providing the key spirocycle of discorhadbin E with moderate enantioselectivity. It is our hope that the tools and strategies presented herein will prove useful in future synthetic endeavors toward this broad class of bioactive alkaloids.

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19. Some loss of material was observed when compound **17** was subjected to silica gel chromatography, with crude yields of **17** (pure by ^{1}H NMR) after work-up at □70–75%. However, we observed that chromatogaphed **17** performed better in the subsequent condensation reactions.
20. It is possible in this case that the more acidic brominated phenol results in a greater amount of a zwitterionic form of bromotyramine **10A**, rendering it less nucleophilic. Efforts to employ basic additives or the *O*-TBS variant of **10A** led to little improvement, however.
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