ACCOUNTS
of chemical research

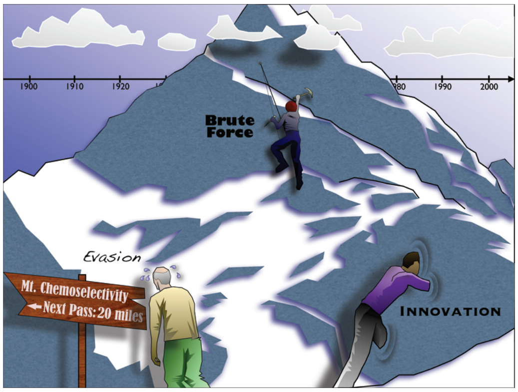
Chemoselectivity: The Mother of Invention in Total Synthesis

RYAN A. SHENVI, DANIEL P. O'MALLEY, AND PHIL S. BARAN*
Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

RECEIVED ON AUGUST 23, 2008

CONSPECTUS

The true creator is necessity, who is the mother of our invention. — Plato



IUPAC defines chemoselectivity as "the preferential reaction of a chemical reagent with one of two or more different functional groups", a definition that describes in rather understated terms the single greatest obstacle to complex molecule synthesis. Indeed, efforts to synthesize natural products often become case studies in the art and science of chemoselective control, a skill that nature has practiced deftly for billions of years but man has yet to master. Confrontation of one or perhaps a collection of functional groups that are either promiscuously reactive or stubbornly inert has the potential to unravel an entire strategic design. One could argue that the degree to which chemists can control chemoselectivity pales in comparison to the state of the art in stereocontrol. In this Account, we hope to illustrate how the combination of necessity and tenacity leads to the invention of chemoselective chemistry for the construction of complex molecules.

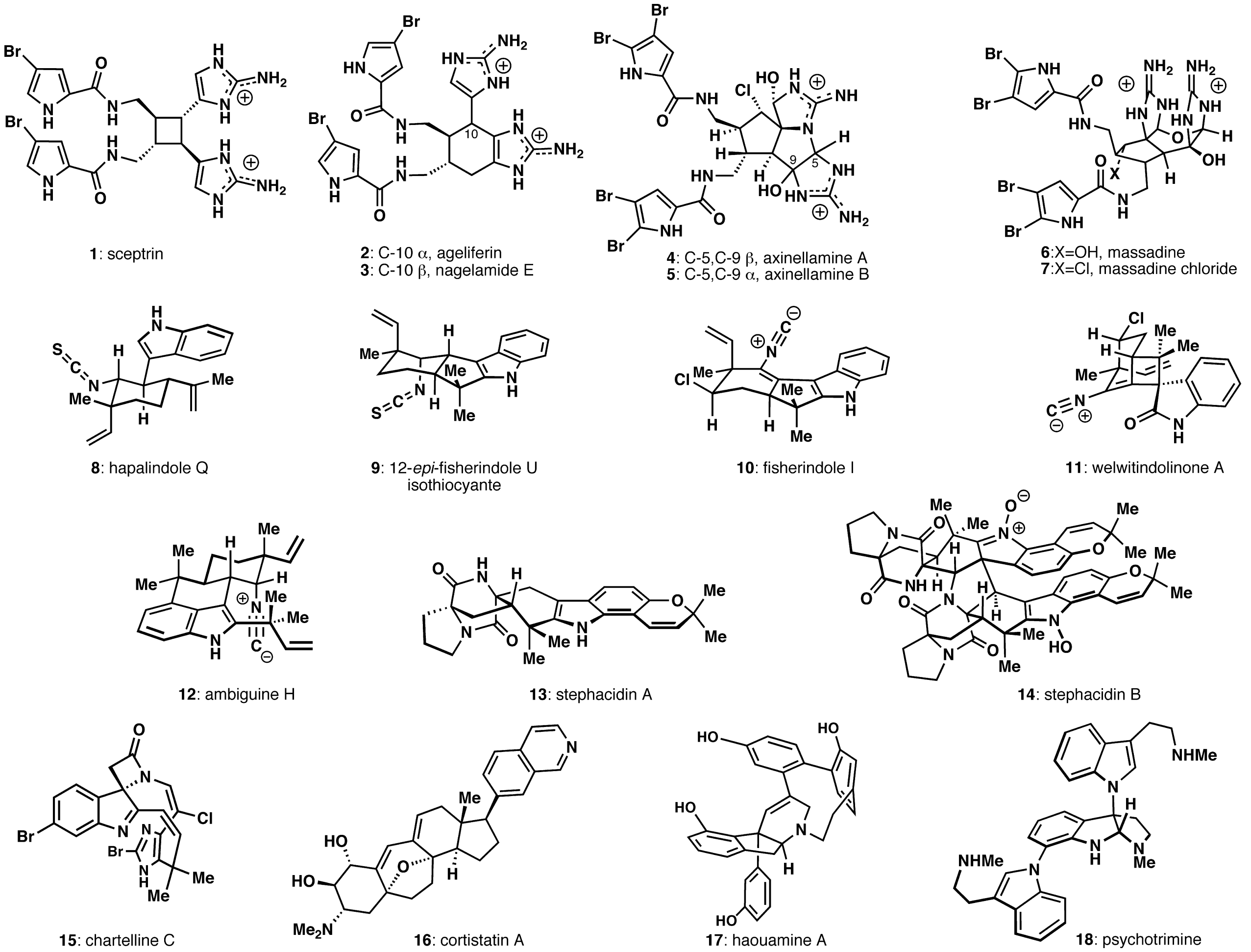
In our laboratory, a premium is placed upon selecting targets that would be difficult or impossible to synthesize using traditional techniques. The successful total synthesis of such molecules demands a high degree of innovation, which in turn enables the discovery of new reactivity and principles for controlling chemoselectivity. In devising an approach to a difficult target, we choose bond disconnections that primarily maximize skeletal simplification, especially when the proposed chemistry is poorly precedented or completely unknown. By choosing such a strategy—rather than adapting an approach to fit known reactions—innovation and invention become the primary goal of the total synthesis. Delivery of the target molecule in a concise and convergent manner is the natural consequence of such endeavors, and invention becomes a prerequisite for success.

Introduction

The instinctual desire of organic chemists to take up the challenge of synthesizing the most daunting natural products has traditionally proven to be a major driving force for innovation in synthetic chemistry. New techniques developed during the pursuit of one target then find application in completely unrelated problems, enabling the synthesis of other previously inaccessible natural products. History is replete with examples of synthetic methods inspired by a single target or class of targets that have become standard selections in a chemist's repertoire.[1]

In the course of planning and executing the syntheses described in this Account (Figure 1), we have found that there are several guidelines that are particularly useful in devising viable synthetic approaches to target molecules: (1) redox reactions that do not form carbon−carbon or carbon−heteroatom bonds should be minimized; (2) the percentage of C−C bond-forming and strategic C−C bond-breaking events relative to the total number of steps in a synthesis should be

10.1021/ar800182r CCC: $71.50



1: sceptrin

2: C-10 α, ageliferin
3: C-10 β, nagelamide E

4: C-5,C-9 β, axinellamine A
5: C-5,C-9 α, axinellamine B

6:X=OH, massadine
7:X=Cl, massadine chloride

8: hapalindole Q

9: 12-*epi*-fisherindole U isothiocyante

10: fisherindole I

11: welwitindolinone A

12: ambiguine H

13: stephacidin A

14: stephacidin B

15: chartelline C

16: cortistatin A

17: haouamine A

18: psychotrimine

FIGURE 1. Representative natural products synthesized in the Baran research group (2003–2008).

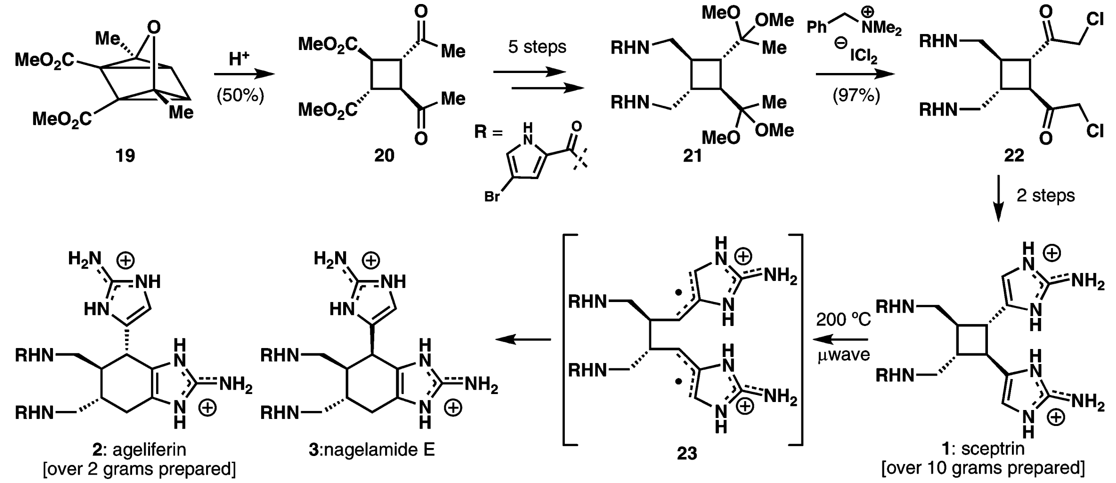
maximized; (3) disconnections should be chosen to maximize convergency; (4) the oxidation state of intermediates should fluctuate as little as possible during the synthesis (Redox-Economy); (5) where possible, cascade or tandem reactions should be designed and incorporated to maximize structural change per step; (6) the innate reactivity of functional groups should be exploited to reduce the number of (or perhaps even eliminate) protecting groups; (7) effort should be spent on the invention of new methodology to facilitate the aforementioned criteria and to uncover new aspects of chemical reactivity; (8) if the target molecule is of natural origin, known or proposed biosynthetic pathways should only be incorporated to the extent that they aid the above considerations.[2] Each of these principles, some to a greater extent than others, require one to address the ever present issue of chemoselectivity.[3] With regards to the issue of protecting groups, we would submit that these artificial agents, while often enabling in the synthesis of certain classes of molecules, are the direct offspring of chemists' inability to control chemoselectivity.

The degree to which these guidelines apply to a given synthesis, of course, varies considerably with the structure of target. Deviations from the ideal implementation of these guidelines may also be necessitated by experimental difficulties encountered during the course of the synthesis. In the examples discussed in this Account, we seek to illustrate how the application of these guidelines has allowed for considerable innovation during the synthesis of complex natural products.

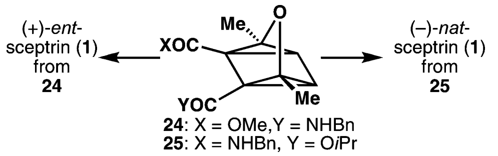
Pyrrole–Imidazole Alkaloids

The pyrrole–imidazole alkaloids are a series of natural products derived from marine sponges that share hymenidin as a common biosynthetic precursor.[4] Within this class of alkaloids, sceptrin (**1**) was selected as the initial target because of its presumed role as a biosynthetic precursor to other members of the class. Although sceptrin appears to be a [2 + 2] dimer of hymenidin, the isolation chemists reported their inability to dimerize hymenidin under a variety of conditions. Consequently, a strategy centered upon the initial formation of the

SCHEME 1. An Oxaquadricyclane Fragmentation Leads to the First Total Synthesis of Sceptrin (**1**) and an Unusual Cyclobutane Fragmentation Delivers the Cyclohexyl Pyrrole–Imidazole Alkaloids Ageliferin (**2**) and Nagelamide E (**3**)



SCHEME 2. Enantioselective Access to Sceptrin and Ageliferin



molecule's cyclobutane core was selected. This was accomplished by fragmentation of oxaquadricyclane **19** (Scheme 1), which was obtained from 2,5-dimethyl furan and dimethyl acetylenedicarboxylate. Standard functional group manipulations then led to intermediate **21**, which lacked only the 2-aminoimidazole units of sceptrin. The installation of these heterocycles required halogenation of the methyl ketones, a seemingly straightforward task complicated by the propensity of the bromopyrroles to react with electrophilic halogenating reagents. The potential for halogenation at the methine carbons α to the ketones and for multiple halogenation of the methyl groups posed further selectivity challenges. This obstacle was eventually surmounted by the use of benzyltrimethylammonium dichloroiodate to chlorinate ketal **21**.

While the fragmentation of oxaquadricyclane **19** provided a facile means to acquire cyclobutane **20** in racemic form, the ill-defined mechanism of this reaction rendered prospects of an enantioselective synthesis uncertain. Nonetheless, attempts were made to effect an enantioselective synthesis by differentiating the enolization energies of the two carbonyl groups. The use of an enzymatic desymmetrization allowed access to oxaquadricyclanes **24** and **25**. After some modification of the fragmentation conditions, **25** was elaborated to the natural enantiomer of sceptrin and **24** to the unnatural enantiomer (Scheme 2), culminating in an approach that solved a problem of enantioselectivity by addressing chemoselectivity.[5]

The widely held belief that ageliferin (**2**, Scheme 1) was the product of a [4 + 2] dimerization of hymenidin notwithstanding, we proposed an alternative biosynthesis in which sceptrin served as a direct biosynthetic precursor to ageliferin via a [1,3] rearrangement and tautomerization. By heating sceptrin acetate to 195–200 °C in water using a microwave reactor, we obtained ageliferin in 50% yield, along with 28% of its epimer **3**, which was at a later date identified as a natural product and named nagelamide E, and 12% recovered sceptrin.[6] Computational studies indicated that this rearrangement likely proceeds by a radical scission of the cyclobutane, followed by 6-*endo* recombination of the diradical (**23**) and tautomerization to form ageliferin.[6]

Not surprisingly, sceptrin also served as a synthetic precursor to oxysceptrin and nakamuric acid (Figure 2).[7] These presumably biomimetic transformations relied on the ability to chemoselectively oxidize the aminoimidazole in preference to the bromopyrrole. These studies have led to a robust route that delivers **1** and **2** in multigram quantities using a single protecting group and one chromatographic separation.[7]

Having completed sceptrin, ageliferin, and their derivatives, our attention turned to the most complicated alkaloids in this class, typified by the axinellamines and massadines (**4**–**7**). These challenging alkaloids are centered around a hexasub-

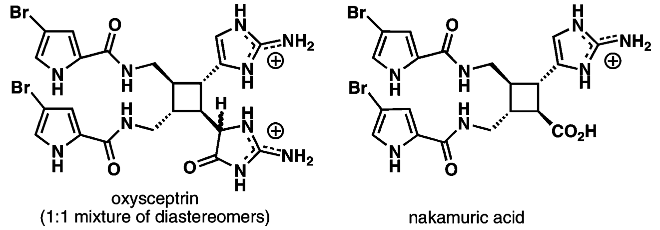
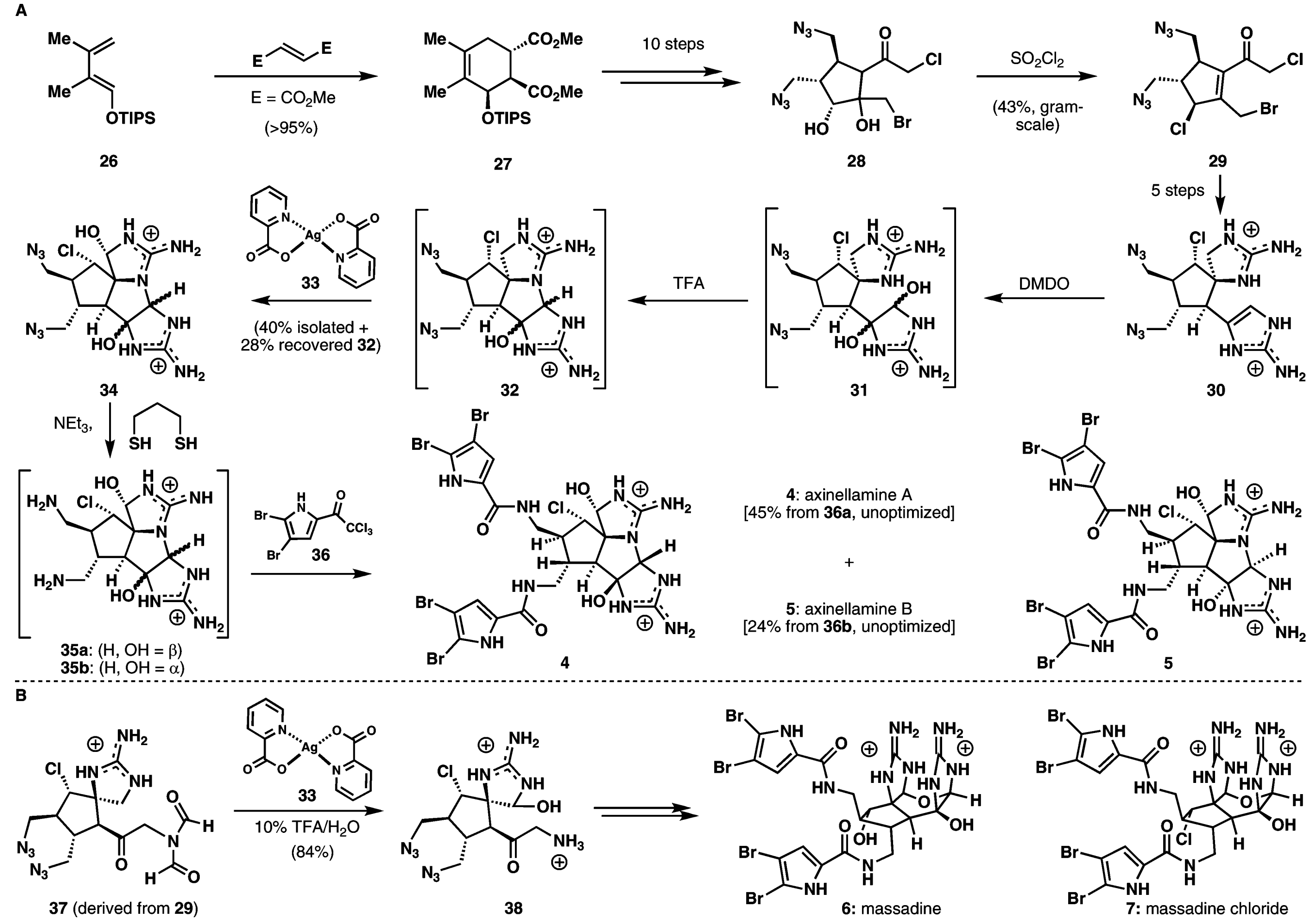


FIGURE 2. Oxysceptrin and nakamuric acid: natural products obtained by chemoselective oxidation of sceptrin (**1**).

SCHEME 3. Incorporation of a Strategically Simplifying Late-Stage Chemoselective Intermolecular Oxidation Facilitates the Total Synthesis of Axinellamines A (**4**) and B (**5**), Massadine (**6**), and Massadine Chloride (**7**)



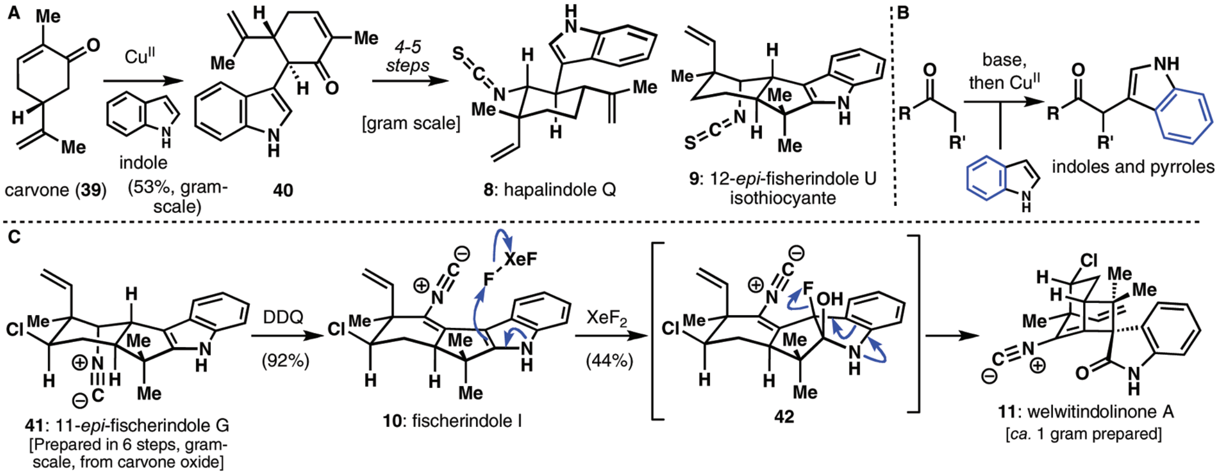
stituted cyclopentane core that possesses five of the molecule's eight total contiguous stereocenters. In addition, the ten nitrogen atoms present in these molecules render them highly polar and complicate seemingly routine reactions and purifications.

This synthesis began with a Diels–Alder reaction between siloxy diene **26** (Scheme 3A) and dimethyl fumarate to give cyclohexene **27**.[8] The configuration of these three stereocenters would be used to set the configuration of the five remaining stereocenters in the molecule. After some functional group manipulations, dehydration of the tertiary alcohol of **28** or similar intermediates proved unexpectedly difficult, as did conversion of the secondary alcohol to the requisite chloride. A cascade reaction was therefore developed to solve both of these problems simultaneously; upon treatment with sulfuryl chloride, diol **28** gave chloro enone **29** in 43% yield on a multigram scale. Elaboration of **29** installed the 2-aminoimidazole and spiro guanidine units. The 2-aminoimidazole of **30** was then oxidized with dimethyldioxirane (to give **31**), and the axinellamine core was closed by exposure to trifluoracetic acid (forming **32** as a mixture of two diastereomers).

At this point, the most crucial transformation remaining was the oxidation of the spiro methylene unit to the aminal oxidation state. This would require late-stage intermolecular chemoselective oxidation next to only one of the six guanidine nitrogens in the molecule. Although there were a number of reports describing the oxidation of amines to imines, there was no precedent for oxidizing a guanidine to an aminal of this type. After considerable experimentation, silver(II) picolinate (**33**) was found to be the optimum reagent for the oxidation of **32**, giving a 40% yield of **34** as a 3:1 mixture of diastereomers (which correspond to axinellamines A and B) and 28% of recovered **32**. The diastereomers of **34** were separated by the use of preparative HPLC.

The reduction of the azides in **34** to the amines proved difficult, but a solution was found by using 1,3-propanedithiol and triethylamine. Completion of the axinellamines then required acylation of the two newly formed primary amines of

SCHEME 4. Another Strategically Simplifying Transformation, Indole−Enolate Oxidative Coupling, Provides an Entry into the Hapalindole and Fisherindole Alkaloids, Including Welwitindolinone A (**11**)



35a/b in the presence of the six unprotected guanidine nitrogens. The use of trichloroketone **36** and Hünig's base in DMF allowed us to capitalize on the difference in nucleophilicity between primary amines and guanidines and gave axinellamine A in 45% yield from the major diastereomer of **35a**. Use of the minor diastereomer (**35b**) gave 24% axinellamine B under identical conditions. The synthesis of massadine (**6**, Scheme 3B) relied upon the chemoselective silver-mediated oxidation, which was dramatically improved by conducting the reaction in a TFA/water solution. Indeed, the yield of the oxidation of **32** to **34** could be improved to 77%. This robust, reliable, and scalable procedure allowed the evaluation of multiple routes to the massadines. Ultimately, **37** (derived from **29**) was oxidized to afford **38** in 84% isolated yield. This intermediate could then be elaborated into massadine (**6**) and massadine chloride (**7**).[9] The ability to manipulate and chemoselectively react intermediates containing six or more unprotected nitrogen atoms proved key in completing the first total synthesis of the axinellamines and massadines.[10]

Indole Alkaloids from Cyanobacteria

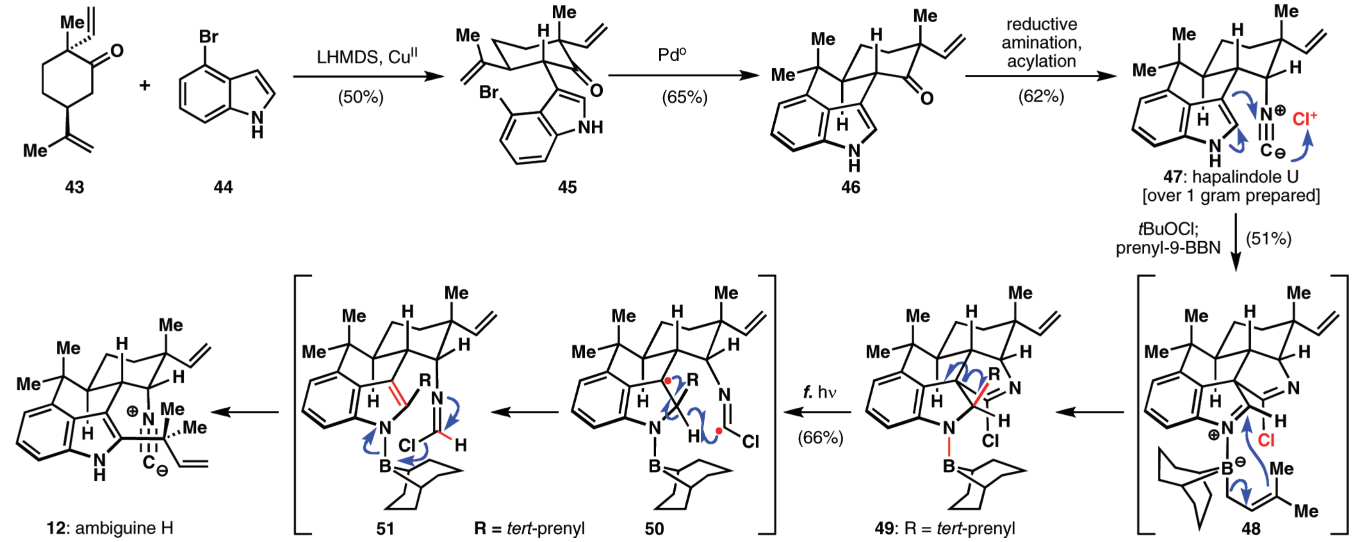
The Stigonematacae family of cyanobacteria has produced over 60 members of an architecturally complex family of indole alkaloids that includes the hapalindoles, fischerindoles, welwitindolinones, and ambiguines. These alkaloids consist of an indole attached to a terpene-derived carbocyclic unit. The members of these families vary in the degree and position of functionalization and cyclization, with the ambiguines also bearing an additional terpene unit.

Given the large number of known members of this family, the retrosynthetic plan was heavily influenced by presumed biosynthetic relationships. The simplest members of the family were targeted first, with the intention of using them as synthetic precursors of more complex members. Hapalindole Q (**8**)[11] was therefore selected as the initial target. Noting the similarity of the terpene-derived fragment to the readily available carvone (**39**, Scheme 4A), it was quickly recognized that the most direct approach to this alkaloid would involve the coupling of indole to a carvone-derived fragment. Unfortunately, the functional group arrangement of the targets did not readily lend itself to the use of traditional methods, such as palladium-catalyzed coupling. Although a suitable substrate likely could have been found, this would have required multiple functional group manipulations. A chemoselective method was therefore sought to effect the direct coupling of indole and carvone.

Drawing inspiration from the oxidative coupling of enolates, indole and carvone were deprotonated using lithium hexamethyldisilazide (LHMDS) and then exposed to a variety of oxidants. Copper(II)-2-ethylhexanoate proved to be the optimum reagent for this transformation, giving a 53% yield of coupled product **40** on a multigram scale. This compound could then be elaborated to the natural products hapalindole Q (**10**) and 12-*epi*-fisherindole U isothiocyanate (**11**) in four and five steps, respectively.[12] In addition to allowing access to these natural products in remarkably concise and practical fashion, this powerful reaction proved applicable to a wide variety of substrates, including ketones, amides, esters, and pyrroles (Scheme 4B).[13,14] This interesting type of reactivity has also been extended to allow for the first practical intermolecular enolate heterocouplings (see next section).[15]

Having established the viability of the oxidative indole−carbonyl coupling, welwitindolinone A (**11**, Scheme 4C)[16] was selected as the next target in this family. We hypothesized that welwitindolinone A (**11**) arises biosynthetically by an oxida-

SCHEME 5. A Peculiar Fifth Ring (**49**) Is Found To Undergo Norrish Fragmentation, Delivering the Sterically Crowded Indole Alkaloid, Ambiguine H (**12**), Which Was Synthesized without Recourse to Protecting Groups



tive ring contraction of fisherindole I (**10**), so this natural product was prepared in a manner similar to **9**, using a terpene portion derived from carvone oxide.[17] After arriving at 11-epi-fischerindole G (**41**) in six steps (gram scale), benzylic oxidation took place readily with DDQ to afford fischerindole I (**10**). Considerable experimentation led to the finding that XeF_2 can chemoselectively fluorohydroxylate **10** to give **11** as a single diastereomer in 44% yield presumably via **42**. It should be noted that other sorts of oxidants such as those based on electrophilic sources of Br, Cl, and I led to considerably lower yields and were not scalable due to competing reaction with the sensitive isonitrile moiety. In contrast, use of XeF_2 has enabled the procurement of ca. 1 g of enantiopure welwitindolinone A (**11**).[18]

Ambiguine H (**12**, Scheme 5) was selected as the next target in this series of alkaloids. It was anticipated that this natural product could be accessed by prenylation of hapalindole U (**47**). This natural product was conveniently accessed by an oxidative coupling of 4-bromoindole (**44**) and a terpene-derived ketone unit (**43**), followed by a Heck cyclization to install the central cyclohexane ring yielding tetracycle **46**. Stereoselective reductive amination and isonitrile formation led cleanly to over 1 g of hapalindole U (**47**). Attempted prenylation of **47** under Danishefsky's conditions (*t*BuOCl followed by 9-BBN) rather unexpectedly produced pentacyclic compound **49**. While there was a pressing desire to change course and pursue alternative strategies that would circumnavigate this reactivity, instead the unique structure was embraced. As a result, a cascade reaction was uncovered whereby UV irradiation initiated a chemoselective C—C bond fragmentation (via intermediates **50** and **51**) and removed the undesired chlorine atom and 9-BBN unit to give ambiguine H (**12**). This transformation illustrates an interesting case where a strategy is diverted through unanticipated reactivity, only to be restored by a subsequent chemoselective reaction.

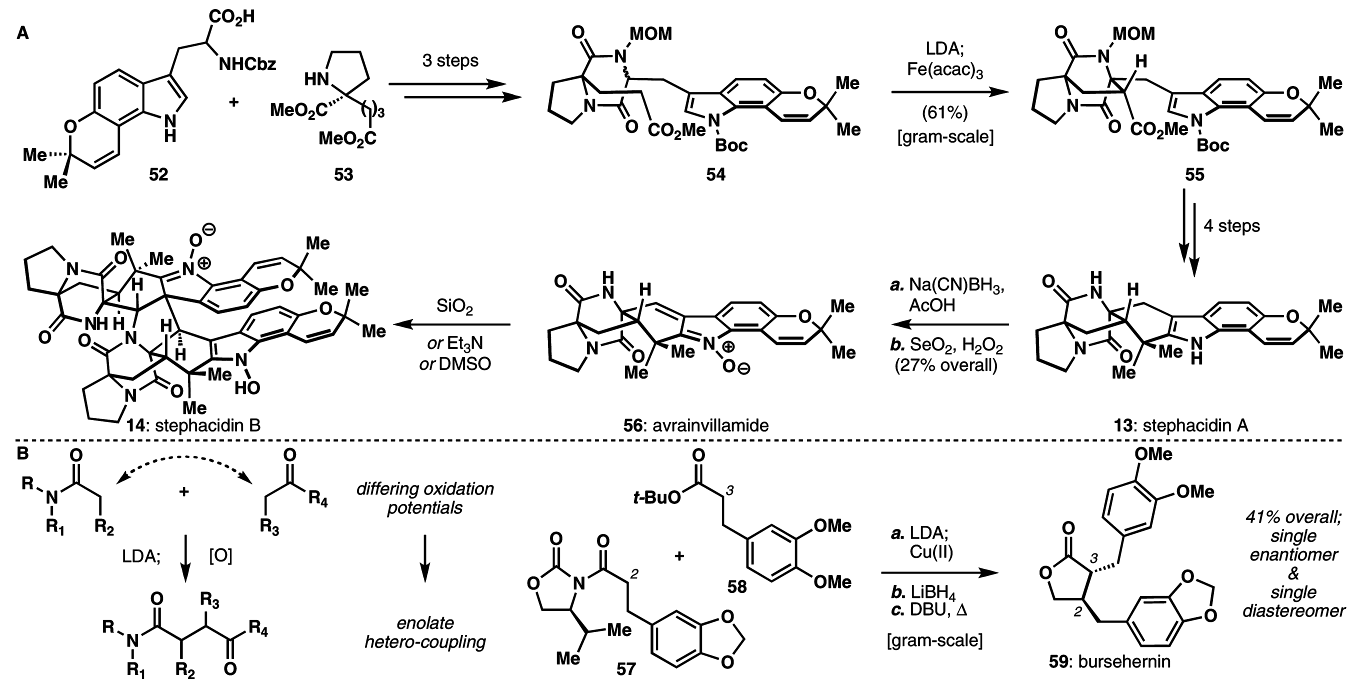
These syntheses are also notable for both their brevity and complete avoidance of protecting group chemistry. This is a direct result of the decision to explore unknown chemistry in order to make the most direct retrosynthetic disconnection and the use of highly chemoselective reactions to differentiate similarly reactive functionality. Other approaches relying on previously proven methods would likely have been possible; however they almost certainly would have required significantly longer routes and the use of multiple protecting groups. In addition, gram quantities of many of these alkaloids are now readily available.

Stephacidins, Avrainvillamide, and Bursehernin

The structural complexity of known marine alkaloids took an astonishing leap forward in 2002 with the isolation of stephacidin B (**14**, Scheme 6A) a dimeric, prenylated tryptophan—proline metabolite isolated by scientists at Bristol-Myers Squibb (BMS),[19a] and a clear relative of avrainvillamide (**56**), isolated independently by both the Fenical research group and Pfizer.[19b,c] Stephacidin A (**13**), also isolated by BMS, presented itself as an ideal initial target; its role as a biosynthetic precursor to **56** and **14** seemed probable, and its structure provided ample opportunity for invention-oriented synthesis design.[20,21]

Central to our synthesis planning was the idea that two different enolates might undergo oxidative heterocoupling both

SCHEME 6. Intra- and Intermolecular Enolate Heterocoupling in Total Synthesis: The Stephacidin Alkaloids and Bursehernin



stereo- and chemoselectively (**54** → **55**) and this coupling might be predictable based on enolate oxidation potentials and well-defined transition state geometries. In fact, subsequent to the stephacidin synthesis, these features were indeed fully explored in an intermolecular sense (Scheme 6B), ultimately resulting in an enantioselective synthesis of the unsymmetric lignan bursehernin (**59**).[15]

For the synthesis of **13**, **14**, and **56**, the amino acid derivatives **52** and **53** were first subjected to peptide coupling and elaborated to diketopiperazine **54**. Then, in a noteworthy example of the power of enolate heterocoupling, the ester and amide enolates derived from **54** coupled stereo- and chemoselectively to yield the characteristic bicyclo[2.2.2]-diazaoctane **55** embedded in the stephacidins. While this intermediate could be converted in short fashion to stephacidin A (**13**), oxidation to the unique α,β-unsaturated benzonitrone avrainvillamide (**56**) proved more difficult. Eventually, it was found that initial Gribble reduction of **13** was necessary for generation of the correct oxidation state (**56**), which could be achieved with selenium dioxide and hydrogen peroxide. Quite unexpectedly, dimerization occurred spontaneously,[21a] but reversibly, under a variety of passive conditions, producing stephacidin B (**14**) as the unnatural enantiomer.

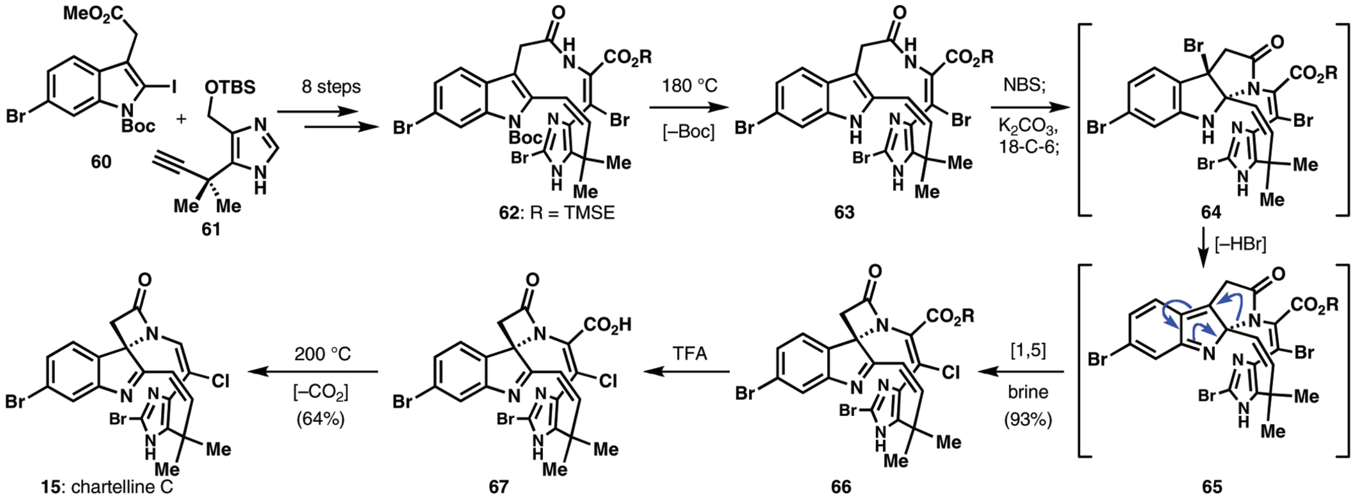
Chartelline Alkaloids

Investigations into the chartelline alkaloids,[22] the first reported members of the "halohistophan"[23] family, precipitated two different, but related, inquiries. First, we sought to approach the syntheses of these compounds as sheer chemical challenges, and to do so with the brevity implied by the guidelines in the Introduction. This was a sizable task, because several approaches to the alkaloids had previously been described: although elegant and concise, these efforts nevertheless fell short of their targets.[24] Second, we hoped to learn something of the innate chemical properties of the chartelline skeleton: how it behaved and what implications this behavior might hold for a biosynthetic hypothesis we had formulated, recognizing the securines as putative biosynthetic precursors to the chartellines via oxidative ring contraction.[25]

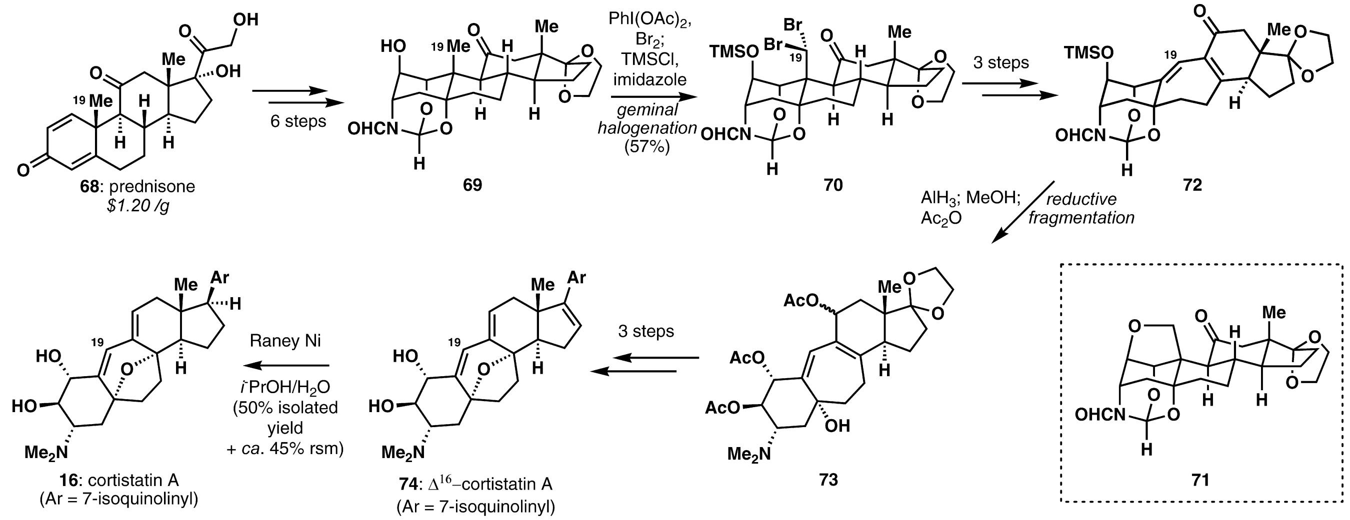
These two goals exhibited a synergistic effect on one another. Ultimately, an efficient synthesis of the general "halohistophan" macrocycle (**60** + **61** → **62**, Scheme 7) enabled inquiry into the properties of this structure, confirming its ability to serve as a viable precursor to the chartelline skeleton. Reciprocally, application of this newly discovered and potentially biomimetic reactivity (**63** → **64** → **65**) enabled an efficient synthesis of the natural product core containing the chartellines' hallmark β-lactam (**66**).[26] The intermediacy of dearomatized pyrrolo-2*H*-indole **65** was implicated in the key transformation; this high-energy intermediate likely provides the driving force for forming various strained ring systems.[18]

Two further reactions are worth comment. First, the facile bromine → chlorine exchange (**65** → **66**) that took place underscores the role of bromonium in the halohistophans' biosyntheses, while chlorine is likely incorporated solely as its anion.[27] The *in vitro* halide metathesis exemplifies a chemose-

SCHEME 7. Inquiry into a Revised Chartelline Biosynthesis Leads to the Discovery of a Remarkable [1,5]-Sigmatropic Rearrangement (**65** → **66**) and an Unusual, Noncatalyzed Decarboxylation (**67** → **15**)



SCHEME 8. The Discovery of an Alcohol-Directed *gem*-Dihalogenation, Strategic Masking of Functionality in a Unique Orthoamide Steroid Skeleton, And Late-Stage Chemoselective Reduction Enable the Synthesis of Cortistatin A (**16**)



lective mimicry of nature, which is simply a consequence of the innate reactivity of the carbon scaffold. Second, and quite unexpectedly, a reagent-free thermal decarboxylation (**67** → **15**) was uncovered as a feasible means to chemoselectively excise the superfluous alkenylcarboxylate functionality, delivering the natural product, chartelline C, as a racemate.

Cortistatins

Cortistatin A (**16**)[28] represented an excellent opportunity to develop new chemoselective reactions. A semisynthetic route to these marine steroids was deemed an acceptable strategy due to the economy of using prednisone, which is synthesized annually on multiton scale, as well as the dominance of semisynthetic steroids on the rigorous U.S. pharmaceuticals market, constituting 10% of the top 200 brand name drugs. The most significant innovation in our synthesis occurred as a result of difficulties encountered during attempted oxidation of the angular C19 methyl group. Instructive failures guided the evolution of a synthesis strategy, finally resulting in the first alcohol-directed, hydrocarbon geminal dihalogenation (**69** → **70**), which established the correct methine oxidation state of the skeletal 19-carbon (Scheme 8). The reaction proceeds by the standard mechanism for hypohalite radical halogenation,[29] but in an iterative sense, wherein etherification (to **71**) is suppressed by low temperatures. Interestingly, the selectivity for dibromination (57%) over mono- or tribromination well surpasses what would be expected with only the governance of statistics (a maximum yield of 27%).[30]

Elaboration of intermediate **70** to the unsaturated cycloheptyl ketone **72** allowed for the reductive fragmentation of an aza-dioxa-heteroadamantane (**72** → **73**), which was demonstrated to provide access to the fully functionalized A-ring of cortistatin A. While borane had performed admirably on a model system bearing no alkenes, the significantly less carbophilic aluminum reagent, alane, allowed for this highly chemoselective transformation to be performed in the presence of the crucial diene moiety.

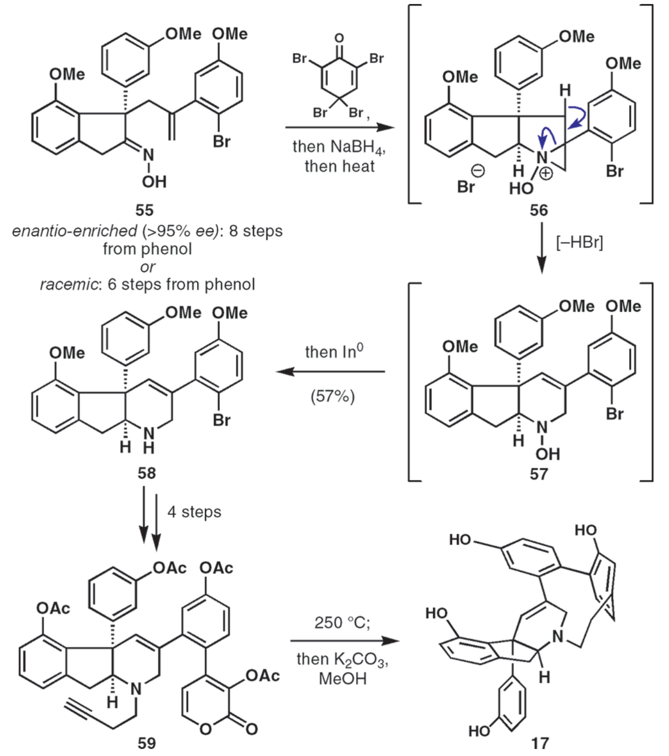
Finally, just as the synthesis of axinellamines A and B demonstrated the value of a strategic late-stage chemoselective oxidation, cortistatin necessitated a late-stage differentiating reduction event in the presence of several reductively labile functional groups. Nevertheless, as a result of this high-risk strategy, amine **74** could be elaborated to the natural product (**16**) in short order, largely owing to a chemoselective, Raney nickel-mediated hydrogenation of the 16,17-olefin (**74** → **16**) in preference to reduction of the diene, deoxygenation of the alcohols, or partial reduction of the isoquinoline.[31,32]

Haouamine A

Haouamine A (**17**), an unusual tunicate metabolite isolated from *Aplidium haouarianum*,[33] stimulated a spate of activity among chemists shortly after its isolation in 2003.[34] This widespread interest was prompted by a variety of challenges, including (1) synthesis of the unique indeno-tetrahydropyridine core, (2) synthesis of a remarkable "bent" aromatic ring embedded in a biarylparacyclophane, (3) control of potential atropisomerism[35] around this unusual biphenyl linkage, and (4) inquiry into the biosynthetic origins of this structurally unprecedented alkaloid.[36]

Oxime **75**, which contains the key chiral quaternary carbon of the haouamine skeleton, was synthesized in a short fashion either racemically[35] or enantioselectively[36] (6 vs 8 steps, respectively; Scheme 9). This intermediate could be converted to the haouamine core **78** in a one-pot cascade sequence, including position-selective aziridinium fragmentation (**76** → **77**) followed by chemoselective reduction (**77** → **78**). Further elaboration provided tetraacetate **79**, whose alkyne and pyrone subunits reacted upon heating, extruding carbon dioxide to form haouamine tetraacetate, which could be solvolyzed to give the natural product (**17**). Notably, this macrocyclization proceeded with high atropselectivity to deliver the desired isomer in a 10:1 ratio to the undesired isomer.[35] While investigating the tetrahydropyridine core, evidence was accumulated against a Chichibaban-like phenylacetaldehyde tetramerization as a likely biosynthetic pathway to these compounds.[36,37] Instead, the absolute stereochemistry of haouamine A, which was determined by these studies, implicated a natural amino acid to be a metabolic precursor to the haouamines.

SCHEME 9. A Unique Cascade Sequence for Forming the Heterocyclic Core and a Pyrone Diels−Alder Macrocyclization Lead to a Short Synthesis of Haouamine A (**17**)

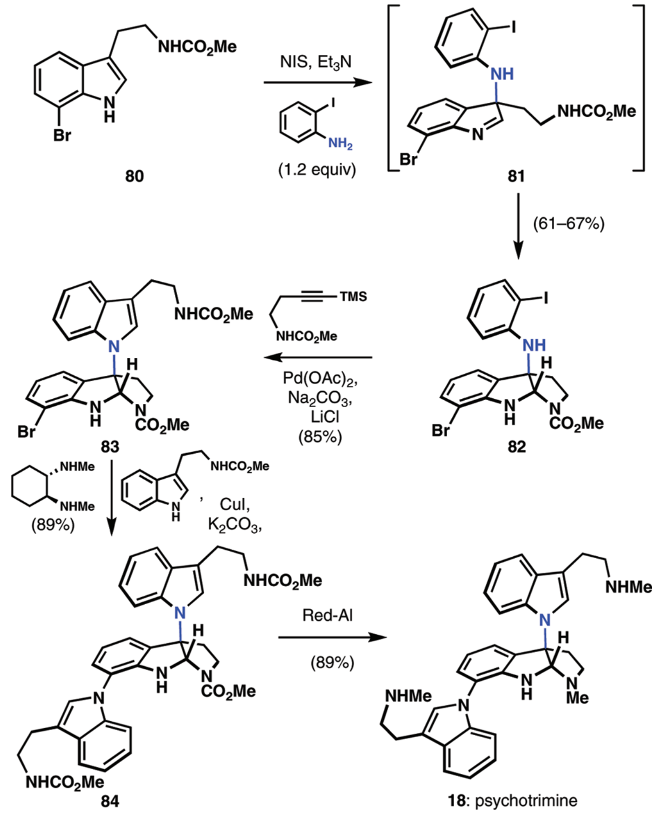


Psychotrimine

Psychotrimine (**18**)[38] represents a nearly unassailable class of N1−C3 indole dimers whose syntheses had evaded chemists for decades.[39] Constitutionally isomeric C3−C3 (indole numbering system) dimers have seen extensive investigation,[40] reflecting the inherent preference for oxidative indole or tryptamine dimerization to favor C−C bond construction.[41] Not surprisingly then, the structural novelty imposed by a C3−N1 linkage propelled the invention of a powerfully simple chemoselective method for C−N bond construction, specifically the formation of an indole C-3 quaternary linkage to an aniline nitrogen.[42] The sequence that results from this simplifying transformation minimizes oxidation state fluctuations, functional group interconversions, and protecting group chemistry, which are all otherwise aspects of an *inability* to control chemoselectivity, thus streamlining the total synthesis of **18** (Scheme 10) to a mere four steps (from **80**, which is readily available in one step from commercial material).

The route began with tryptamine **80**, which when treated with 2-iodoaniline and *N*-iodosuccinimide underwent smooth oxidative C−N bond formation, initially forming **81**, the chain tautomer of pyrroloindoline **82**. The reaction appears to proceed via the intermediacy of an initial *N*-io-

SCHEME 10. A New Method for Oxidative C−N Bond Formation between Indoles and Anilines (**80** → **82**) Enables a Four-Step Synthesis of Psychotrimine (**18**)



18: psychotrimine
[over 2 grams prepared]

doaniline, which is intercepted by the electron rich-indole, though more detailed mechanistic studies are necessary. Larock indole synthesis (**82** → **83**) provided the N1−C3 dimeric indole core, which could be subjected to a remarkably chemoselective Buchwald−Goldberg−Ullmann coupling to furnish the trimeric psychotrimine skeleton **84**. Indeed, despite the presense of no less than four N−H bonds with somewhat similar pK_a, only the desired N−C bond was formed in 89% isolated yield. Interestingly, palladium-mediated N−C bond formation was completely nonselective in this coupling. Conversion of the carbamate groups to methyl groups using Red-Al produced the natural product (**18**) in an overall yield of 41−45% in four steps. It is noteworthy that to date over 2 g of this natural product have been synthesized.

Conclusion and Outlook

Nature's cache of medicinally relevant or structurally captivating molecules is tremendous and has propelled chemical knowledge a vast distance, even in the past decade. While this propulsion is fueled by Nature's persistent ability to surprise and amaze, the spark that ignites innovation can only be provided by human ingenuity in the face of opposition. In total synthesis endeavors, that opposition almost always manifests itself as a problem of *chemoselectivity*. The brilliant insights penned by Trost over 25 years ago still ring true today:[3] "Considering that lack of chemoselectivity frequently accounts for as many as 40 percent of the steps of a complex synthesis, much remains to be done for enhanced synthetic efficiency". The introduction to this Account detailed a conceptual framework through which our laboratory approaches new undertakings. However, it cannot be overemphasized that the greatest challenges in synthesis are most often the least expected, and therefore also the most fruitful, since they provoke the chemist into dramatic action. In such circumstances, one should not bemoan the inability of existing chemistry to accomplish a desired transformation but rather rejoice at opportunity to discover its answer! Ultimately, the only real failure is recourse to tried and true methods. The selectivity challenges encountered and finally overcome in total synthesis open a window into the future: while simply reading the literature demonstrates how far we've come, it is only repeated defeat and frustration that reveals how far we still have to go.

Funding for this research was provided by the National Institutes of Health, the National Science Foundation, The Scripps Research Institute, Amgen, AstraZeneca, the Beckman Foundation, Bristol-Myers Squibb, DuPont, Eli Lilly, GlaxoSmithKline, Merck, Pfizer, Roche, the Searle Scholarship Fund, and the Sloan Foundation.

BIOGRAPHICAL INFORMATION

Ryan A. Shenvi received his B.S. degree in chemistry from Penn State University, performing research in the laboratories of Professors John R. Desjarlais and Raymond L. Funk. His doctoral research was conducted under the guidance of Professor Phil S. Baran at the Scripps Research Institute, from which he earned a Ph.D. in 2008. He is currently an NIH Ruth L. Kirschstein postdoctoral fellow in the laboratories of Professor E. J. Corey at Harvard University.

Daniel P. O'Malley received a B.S. degree in Chemistry from Rice University in 2003. He completed his Ph.D. in 2008 under the guidance of Professor Phil S. Baran at the Scripps Research Institute. He is presently an Alexander von Humboldt postdoctoral fellow in the laboratory of Professor Alois Fürstner at the Max Planck Institut für Kohlenforschung in Mülheim an der Ruhr, Germany.

Phil S. Baran was born in New Jersey in 1977 and received his undergraduate education from NYU with Professor David I. Schuster in 1997. After earning his Ph.D. with Professor K. C. Nicolaou at Scripps in 2001, he pursued postdoctoral studies with Professor E. J. Corey at Harvard until 2003, at which point he began his independent career at Scripps, rising to the rank of Professor in 2008. His laboratory is dedicated to the study of fundamental organic chemistry through the auspices of natural product total synthesis.

FOOTNOTES

*pbaran@scripps.edu

REFERENCES

1 Nicolaou, K. C.; Snyder, S. A. The Essence of Total Synthesis. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11929–11936.

2 Baran, P. S.; Maimone, T. J.; Richter, J. M. Total Synthesis of Marine Natural Products Without Using Protecting Groups. *Nature* **2007**, *446*, 404–408.

3 The word "chemoselectivity" and the challenges in designing reactions that are chemoselective were first pointed out by Trost in 1973, see: Trost, B. M.; Salzmann, T. N. New Synthetic Reactions. Sulfenylation—Dehydrosulfenylation as a Method for Introduction of Unsaturation. *J. Am. Chem. Soc.* **1973**, *95*, 6840–6842. For a detailed discussion, see: Trost, B. M. Selectivity: A Key to Synthetic Efficiency. *Science* **1983**, *219*, 245–250.

4 For a review on the isolation, biosynthesis, and synthetic studies of dimeric pyrrole—imidazole alkaloids, see: Kock, M.; Grube, A.; Seiple, I.; Baran, P. S. The Pursuit of Palau'amine. *Angew. Chem., Int. Ed.* **2007**, *46*, 6586–6594, and references therein.

5 Baran, P. S.; Li, K.; O'Malley, D. P.; Mitsos, C. Short, Enantioselective Total Synthesis of Sceptrin and Ageliferin by Programmed Oxaquadricyclane Fragmentation. *Angew. Chem., Int. Ed.* **2006**, *45*, 249–252.

6 Northrop, B. H.; O'Malley, D. P.; Zografos, A. L.; Baran, P. S.; Houk, K. N. Mechanism of the Vinylcyclobutane Rearrangement of Sceptrin to Ageliferin and Nagelamide E. *Angew. Chem., Int. Ed.* **2006**, *45*, 4126–4130.

7 O'Malley, D. P.; Li, K.; Maue, M.; Zografos, A. L.; Baran, P. S. Total Synthesis of Dimeric Pyrrole-Imidazole Alkaloids: Sceptrin, Ageliferin, Nagelamide E, Oxysceptrin, Nakamuric Acid, and the Axinellamine Carbon Skeleton. *J. Am. Chem. Soc.* **2007**, *129*, 4762–4775.

8 (a) O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. Total Synthesis of (±)-Axinellamines A and B. *Angew. Chem. Int. Ed.* **2008**, *47*, 3637–3639. (b) Yamaguchi, J.; Seiple, I. B.; Young, I. S.; O'Malley, D. P.; Maue, M.; Baran, P. S. Synthesis of 1,9-Dideoxy-pre-axinellamine. *Angew. Chem. Int. Ed.* **2008**, *47*, 3634–3636.

9 Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. Total Syntheses of (±)-Massadine and Massadine Chloride. *J. Am. Chem. Soc.* **2008**, *130*, 16490–16491.

10 Arndt, H.-D.; Riedrich, M. Synthesis of Marine Alkaloids from the Oroidin Family. *Angew. Chem., Int. Ed.* **2008**, *47*, 4785–4788.

11 Moore, R. E.; Cheuk, C.; Yang, X.-Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. Hapalindoles, Antibacterial and Antimycotic Alkaloids from the Cyanophyte *Hapalosiphon fontinalis*. *J. Org. Chem.* **1987**, *52*, 1036–1043.

12 Baran, P. S.; Richter, J. M. Direct Coupling of Indoles with Carbonyl Compounds: Short, Enantioselective, Gram-Scale Synthetic Entry into the Hapalindole and Fischerindole Alkaloid Families. *J. Am. Chem. Soc.* **2004**, *126*, 7450–7451.

13 Baran, P. S.; Richter, J. M.; Lin, D. W. Direct Coupling of Pyrroles with Carbonyl Compounds: Short, Enantioselective Synthesis of (*S*)-Ketorolac. *Angew. Chem., Int. Ed.* **2005**, *44*, 609–612.

14 Richter, J. M.; Whitefield, B., W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. Scope and Mechanism of Direct Indole and Pyrrole Couplings Adjacent to Carbonyl Compounds: Total Synthesis of Acremoauxin A and Oxazinin 3. *J. Am. Chem. Soc.* **2007**, *129*, 12858–12869.

15 (a) Baran, P. S.; DeMartino, M. P. Intermolecular Oxidative Enolate Heterocoupling. *Angew. Chem., Int. Ed.* **2006**, *45*, 7083–7086. (b) DeMartino, M. P.; Chen, K.; Baran, P. S. Intermolecular Enolate Heterocoupling: Scope, Mechanism, and Application. *J. Am. Chem. Soc.* **2008**, *130*, 11546–11560.

16 Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. Welwitindolinones, Unusual Alkaloids from the Blue-Green-Algae Hapalosiphon-Welwitschii and Westiella-Intricata - Relationship to Fischerindoles and Hapalindoles. *J. Am. Chem. Soc.* **1994**, *116*, 9935–9942.

17 Baran, P. S.; Richter, J. M. Enantioselective Total Syntheses of Welwitindolinone A and Fischerindoles I and G. *J. Am. Chem. Soc.* **2005**, *127*, 15394–15396.

18 Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. Enantiospecific Total Synthesis of the Hapalindoles, Fischerindoles, and Welwitindolinones via a Redox Economic Approach. *J. Am. Chem. Soc.* **2008**, *130*, 17938–17954.

19 (a) Qian-Cutrone, J.; Huang, S.; Shu, Y.-Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klohr, S. E.; Gao, Q. Stephacidin A and B: Two Structurally Novel, Selective Inhibitors of the Testosterone-Dependent Prostate LNCaP Cells. *J. Am. Chem. Soc.* **2002**, *124*, 14556–14557. (b) Fenical, W.; Jensen, P. R.; Cheng, X. C. Avrainvillamide, a Cytotoxic Marine Natural Product, and Derivatives thereof. U.S. Patent 6,066,635, 2000. (c) Sugie, Y.; Hirai, H.; Inagaki, T.; Ishiguro, M.; Kim, Y.-S.; Kojima, Y.; Sakakibara, T.; Sakemi, S.; Sugiura, A.; Suzuki, Y.; Brennan, L.; Duignan, J.; Huang, L. H.; Sutcliffe, J.; Kojima, N. A New Antibiotic CJ-17,665 from Aspergillus ochraceus. *J. Antibiot.* **2001**, *54*, 911–916.

20 (a) Baran, P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. D. Short, Enantioselective Total Synthesis of Stephacidin A. *Angew. Chem., Int. Ed.* **2005**, *44*, 606–609. (b) Baran, P. S.; Guerrero, C. A.; Hafensteiner, B. D.; Ambhaikar, N. B. Total Synthesis of Avrainvillamide (CJ-17,665) and Stephacidin B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3892–3895. (c) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. Enantioselective Total Synthesis of Avrainvillamide and the Stephacidins. *J. Am. Chem. Soc.* **2006**, *128*, 8678–8693.

21 For elegant total syntheses of the stephacidins from the Myers and Williams groups, see: (a) Herzon, S. B.; Myers, A. G. Enantioselective Synthesis of Stephacidin B. *J. Am. Chem. Soc.* **2005**, *127*, 5342–5345. (b) Artman, G. D., III; Grubbs, A. W.; Williams, R. M. Concise, Asymmetric, Stereocontrolled Total Synthesis of Stephacidins A, B, and Notoamide B. *J. Am. Chem. Soc.* **2007**, *129*, 6336–6342.

22 Rahback, L.; Christophersen, C. Marine Alkaloids. 19. Three New Alkaloids, Securamines E-G, from the Marine Bryozoan Securiflustra Securifrons. *J. Nat. Prod.* **1997**, *60*, 175–177, and references therein.

23 Named for the presumed origins of the securamine; securamine, chartelline, and chartellamide alkaloids as all derived from halogenated histidine-tryptophan metabolites.

24 For studies towards the chartellines and related alkaloids, see refs 25–27, and (a) Sun, C.; Lin, X.; Weinreb, S. M. Explorations on the Total Synthesis of the Unusual Marine Alkaloid Chartelline A. *J. Org. Chem.* **2006**, *71*, 3159–3166. (b) Sun, C.; Camp, J. E.; Weinreb, S. M. Construction of Beta-Haloenamides Via Direct Copper-Promoted Coupling of Lactams with 2-Chloro and 2-Bromo Vinyliodides. *Org. Lett.* **2006**, *8*, 1779–1781. (c) Kajii, S.; Nishikawa, T.; Isobe, M. Synthetic Studies and Biosynthetic Speculation on Marine Alkaloid Chartelline. *Chem. Commun.* **2008**, 3121–3123.

25 Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. A Remarkable Ring Contraction En Route to the Chartelline Alkaloids. *Angew. Chem., Int. Ed.* **2005**, *44*, 3714–3717.

26 Baran, P. S.; Shenvi, R. A. Total Synthesis of (±)-Chartelline C. *J. Am. Chem. Soc.* **2006**, *128*, 14028–14029.

27 For a more detailed discussion, see: (a) Shenvi, R. A. Ph.D. Thesis, The Scripps Research Institute, 2008. For a contrary view, see: (b) Black, P. J.; Hecker, E. A.; Magnus, P.; Magnus, P. Studies Towards the Synthesis of the Marine Alkaloid Chartelline C. *Tetrahedron Lett.* **2007**, *48*, 6364–6367.

28 Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. Cortistatins A, B, C, and D, Anti-Angiogenic Steroidal Alkaloids, from the Marine Sponge Corticium Simplex. *J. Am. Chem. Soc.* **2006**, *128*, 3148–3149.

29 Cekovic, Z. Reactions of Delta-Carbon Radicals Generated by 1,5-Hydrogen Transfer to Alkoxyl Radicals. *Tetrahedron* **2003**, *59*, 8073–8090.

30 McQuarrie, D. A.; Simon, J. D. *Physical Chemistry: A Molecular Approach*; University Science Books: Sausolito, CA, 1997.

31 Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. Synthesis of (+)-Cortistatin A. *J. Am. Chem. Soc.* **2008**, *130*, 7241–7243.

32 For two beautiful syntheses of cortistatin A from Hajos—Parrish ketone, see: (a) Nicolaou, K. C.; Sun, Y.-P.; Peng, X.-S.; Polet, D.; Chen, D.Y.-K. Total Synthesis of (+)-Cortistatin A. *Angew. Chem., Int. Ed.* **2008**, *47*, 7310–7313. (b) Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. Enantioselective Synthesis of (+)-Cortistatin A, a Potent and Selective Inhibitor of Endothelial Cell Proliferation. *J. Am. Chem. Soc.* **2008**, *130*, 16864–16866. For studies towards the cortistatins, see: (c) Dai, M.; Danishefsky, S. J. An Oxidative Dearomatization Cyclization Model for Cortistatin A. *Heterocycles*, **2008**, DOI: COM-08-S(F)6. (d) Yamashita, S.; Iso, K.; Hirama, M. A Concise Synthesis of the Pentacyclic Framework of Cortistatins. *Org. Lett.* **2008**, *10*, 3413–3415. (e) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. Rapid Construction of the Cortistatin Pentacyclic Core. *Angew. Chem., Int. Ed.* **2008**, *47*, 6650–6653. (f) Craft, D. T.; Gung, B. W. The First Transannular [4 + 3] cycloaddition reaction: Synthesis of the ABCD Ring Structure of Cortistatins. *Tetrahedron Lett.* **2008**, *49*, 5931–5934. (g) Dai, M.; Danishefsky, S. J. A Concise Synthesis of the Cortistatin Core. *Tetrahedron Lett.* **2008**, *49*, 6610–6612. (h) Dai, M.; Wang, Z.; Danishefsky, S. J. A Novel α,β-Unsaturated Nitrone-Aryne [3 + 2] Cycloaddition and its Application in the Synthesis of the Cortistatin Core. *Tetrahedron Lett.* **2008**, *49*, 6613–6616. (i) Kürti, L.; Czakó, B.; Corey, E. J. A

Short, Scalable Synthesis of the Carbocyclic Core of the Anti-Angiogenic Cortistatins from (+)-Estrone by B-Ring Expansion. *Org. Lett.* **2008**, *10*, 5247–5250.

33 Garrido, L.; Zubía, E.; Ortega, M. J.; Salva, J. Haouamines A and B: A New Class of Alkaloids from the Ascidian *Aplidium haouarianum*. *J. Org. Chem.* **2003**, *68*, 293–299.

34 (a) Smith, N. D.; Hayashida, J.; Rawal, V. H. Facile Synthesis of the Indeno-Tetrahydropyridine Core of Haouamine A. *Org. Lett.* **2005**, *7*, 4309–4312. (b) Grundl, M. A.; Trauner, D. Synthetic Studies toward the Haouamines. *Org. Lett.* **2006**, *8*, 23–25. (c) Wipf, P.; Furegati, M. Synthesis of the 3-Aza-[7]-Paracyclophane Core of Haouamine A and B. *Org. Lett.* **2006**, *8*, 1901–1904. (d) Jeong, J. H.; Weinreb, S. M. Formal Total Synthesis of the Cytotoxic Marine Ascidian Alkaloid Haouamine A. *Org. Lett.* **2006**, *8*, 2309–2312. (e) Fürstner, A.; Ackerstaff, J. Formal Total Synthesis of (−)-Haouamine A. *Chem. Commun.* **2008**, 2870–2872.

35 Baran, P. S.; Burns, N. Z. Total Synthesis of (±)-Haouamine A. *J. Am. Chem. Soc.* **2006**, *128*, 3908–3909.

36 Burns, N. Z.; Baran, P. S. On the Origin of the Haouamine Alkaloids. *Angew. Chem., Int. Ed.* **2007**, *47*, 205–208.

37 Gravel, E.; Poupon, E.; Hocquemiller, R. Biogenetic Hypothesis and First Steps Towards a Biomimetic Synthesis of Haouamines. *Chem. Commun.* **2007**, 719–721.

38 Takayama, H.; Mori, I.; Kitajima, M.; Aimi, N.; Lajis, N. H. New Type of Pentameric Indole Alkaloids from *Psychotria rostrata*. *Org. Lett.* **2004**, *6*, 2945–2948. A synthesis of **16** was recently reported: Matsuda, Y.; Kitajima, M.; Takayama, H. First Total Synthesis of Trimeric Indole Alkaloid Psychotrimine. *Org. Lett.* **2008**, *10*, 125–128.

39 For the first report of an N1−C3 linked indole dimer natural product, see: (a) McInnes, A. G.; Taylor, A.; Walter., J. A. The Structure of Chetomin. *J. Am. Chem. Soc.* **1976**, *98*, 6741. For an alternative approach to N1−C3 bond formation, appearing subsequent to our own work, see: (b) Espejo, V. R.; Rainier., J. D. An Expeditious Synthesis of C(3)−N(1′) Heterodimeric Indolines. *J. Am. Chem. Soc.* **2008**, *130*, 12894–12895.

40 Steven, A.; Overman, L. E. Total Synthesis of Complex Cyclotryptamine Alkaloids: Stereocontrolled Construction of Quaternary Carbon Stereocenters. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488–5508.

41 For example, see: Ishikawa, H.; Takayama, H.; Aimi, N. Dimerization of Indole Derivatives with Hypervalent Iodines(III): A New Entry for the Concise Total Synthesis of rac- and meso-Chimonanthines. *Tetrahedron Lett.* **2002**, *43*, 5637–5639.

42 Newhouse, T. J.; Baran, P. S. Total Synthesis of (±)-Psychotrimine. *J. Am. Chem. Soc.* **2008**, *130*, 10886–10887.