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Article

Evolution of a Synthetic Strategy for Complex Polypyrrole Alkaloids: Total Syntheses of Curvulamine and Curindolizine

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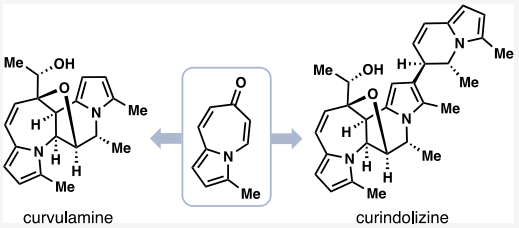
ABSTRACT: Structurally unprecedented antibacterial alkaloids containing multiple electron-rich pyrrole units have recently been isolated from *Curvularia* sp. and *Bipolaris maydis* fungi. This article documents the evolution of a synthetic program aimed at accessing the flagship metabolites curvulamine and curindolizine which are presumably a dimer and trimer of a $C_{10}N$ biosynthetic building block, respectively. Starting with curvulamine, we detail several strategies to merge two simple, bioinspired fragments, which while ultimately unsuccessful, led us toward a pyrroloazepinone building block-based strategy and an improved synthesis of this 10π-aromatic heterocycle. A two-step annulation process was then designed to forge a conserved tetracyclic bis-pyrrole architecture and advanced into a variety of late-stage intermediates; unfortunately, however, a failed decarboxylation thwarted the total synthesis of curvulamine. By tailoring our annulation precursors, success was ultimately found through the use of a cyanohydrin nucleophile which enabled a 10-step total synthesis of curvulamine. Attempts were then made to realize a biomimetic coupling of curvulamine with an additional $C_{10}N$ fragment to arrive at curindolizine, the most complex family member. Although unproductive, we developed a 14-step total synthesis of this alkaloid through an abiotic coupling approach. Throughout this work, effort was made to harness and exploit the innate reactivity of the pyrrole nucleus, an objective which has uncovered many interesting findings in the chemistry of this reactive heterocycle.



INTRODUCTION

Owing to a variety of disparate chemical architectures and often unique chemical reactivity, pyrrole-containing alkaloids have captivated practitioners of total synthesis for many decades.[1] The high acid sensitivity and oxidative fragility inherent to electron-rich pyrroles, however, places many additional constraints on the employable tactics used to access these fascinating natural products.[2] In 2014, Tan and co-workers discovered the unusual, electron-rich bis-pyrrole-containing natural product curvulamine (**1**) from *Curvularia* sp. IFB-Z10 fungus isolated from the intestinal tract of the white croaker fish (Figure 1).[3] The white croaker can feed on dead and decaying prey, suggesting its gut flora may harbor unique antimicrobial producing organisms, and indeed **1** was reported to possess notable antibacterial activity against a small panel of both Gram-positive and negative pathogens including *V. parvula*, *B. Vulgatus*, and *Streptococcus* and *Peptostreptococcus* sp. Serendipitously, when scaling up the fungal fermentation of **1**, a new, even more complex alkaloid, namely curindolizine (**2**), was subsequently isolated.[4] Interestingly, **2** did not possess the antibiotic activity of **1**, but instead demonstrated anti-inflammatory properties in lipopolysaccharide-induced macrophages. More recently, genome mining efforts have culminated in the discovery of additional curvulamine-type secondary metabolites known as bipolamines (see **3**−**10**), all produced by the fungal strain *Bipolaris maydis* (Figure 1).[5]

The chemical structures of **1** and **2** (and **5**−**10**) bear little resemblance to known alkaloids and suggest the involvement of unique biosynthetic machinery. Initial isotopic feeding experiments in *Curvularia* sp. pointed to a mixed polyketide/amino acid origin for **1**, wherein two molecules of alanine and eight acetyl-CoA units serve as building blocks.[3] Recently, Tan and co-workers discovered the biosynthetic gene cluster responsible for the synthesis of $C_{10}N$ fragment **16**, a potential monomeric building block for this family, in *Bipolaris maydis* (Figure 2).[5] A Pyridoxal phosphate (PLP)-dependent enzyme CuaB merges polyketide fragment **11** with alanine/PLP condensation product **12** resulting in intermediate **13** after C−C bond formation. CuaB also possesses oxygenase activity, catalyzing the decarboxylative oxygenation of **13** to **14** and ultimately **15** following cofactor release and hydroperoxide reduction. Aminodiketone **15** then undergoes spontaneous cyclo-condensation to produce isolable vinylogous lactam **16**. Two enzymes, an oxidase CuaD and a reductase CuaC, are then assumed to process this material into hypothetical

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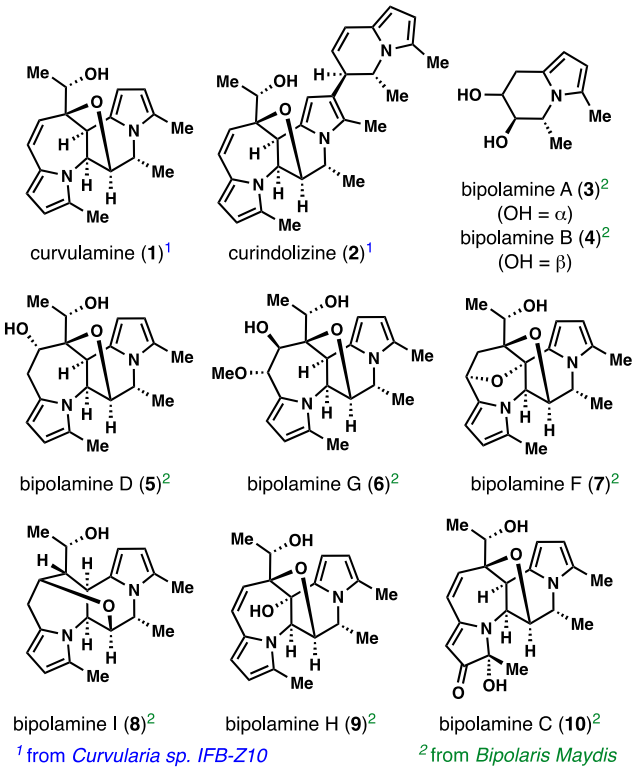

Figure 1. Fungal-derived polypyrrole alkaloids.

indolizidine **17**, via an epoxidation of the polyene (via CuaD) and a postulated C−N bond-forming reductive cyclization which opens the epoxide (via CuaC).[6] The latter step also requires *trans* to *cis* isomerization of the central alkene. While the structural resemblance between **17** and bipolamines A (**3**) and B (**4**) is clear, the enzymology behind the conversion of this $C_{10}N$ unit into higher order $(C_{10}N)_2$- and $(C_{10}N)_3$-containing natural products such as **1**, **2**, and **5**−**10** remains mysterious. Presumably **17** merges with **16** (or an oxidized variant) to produce $(C_{10}N)_2$ metabolites and a further reaction with **17** generates **2**, the lone $(C_{10}N)_3$-level structure.

We recently reported a chemical synthesis of (−)-curvulamine, the first reported synthetic work toward any of these alkaloid natural products.[7] Our successful route to **1**, while concise, required intensive experimentation as we navigated multiple strategic dead-ends and detours, unanticipated chemical reactivity, and unpredictable compound stability. Herein we document the evolution of a synthetic strategy toward (−)-curvulamine as well as the first total synthesis of the most complex family member (+)-curindolizine.

RESULTS AND DISCUSSION

Initial Synthetic Planning. In 2015, we began our synthetic investigations with little information regarding the biosynthesis of these alkaloids, although we found it highly plausible that a building block similar to **17** might merge with a linear $C_{10}N$ fragment to forge the carbocyclic core of **1**. We initially devised a hypothetical annulation between dianion **18** and dication **19** to construct the 7-membered ring present in higher order members (see inset, Scheme 1). In this coupling, which we evaluated in sequential fashion, the innate nucleophilicity of the pyrrole anion and an enolate would be leveraged directly. We also anticipated that dication-like reactivity could be accessible via 2-fold activation of a suitable indolizidine diol intermediate.

We began our bioinspired approach by first developing a robust route to an indolizidine coupling partner (Scheme 1). Enol ether **20** and aldehyde **21** were merged via a diastereoselective magnesium bromide-mediated Mukaiyama aldol reaction generating oxonium ion **22** that was immediately attacked by the pendant electron-rich pyrrole leading to **23** in 40% yield (10:1 *dr*).[8] Diol **24** was obtained after sequential functional group interconversions in which the secondary alcohol was protected (SEMCl, DIPEA), the TIPS group removed (TBAF), and the allyl group cleaved (Pd^0, K_2CO_3, MeOH). As testament to the high reactivity of this pyrrole-containing nucleus, simple diol activation with carbonyldiimidazole (CDI) generated noticeable quantities of imidazole **26**. Presumably, benzylic ionization generated an azafulvene structure which was attacked by imidazole and further rearomatized to **26** via loss of water. This deleterious process could be averted though by first brominating the pyrrole ring (NBS) prior to activation with CDI. Through this sequence cyclic carbonate **25**, whose structure was confirmed

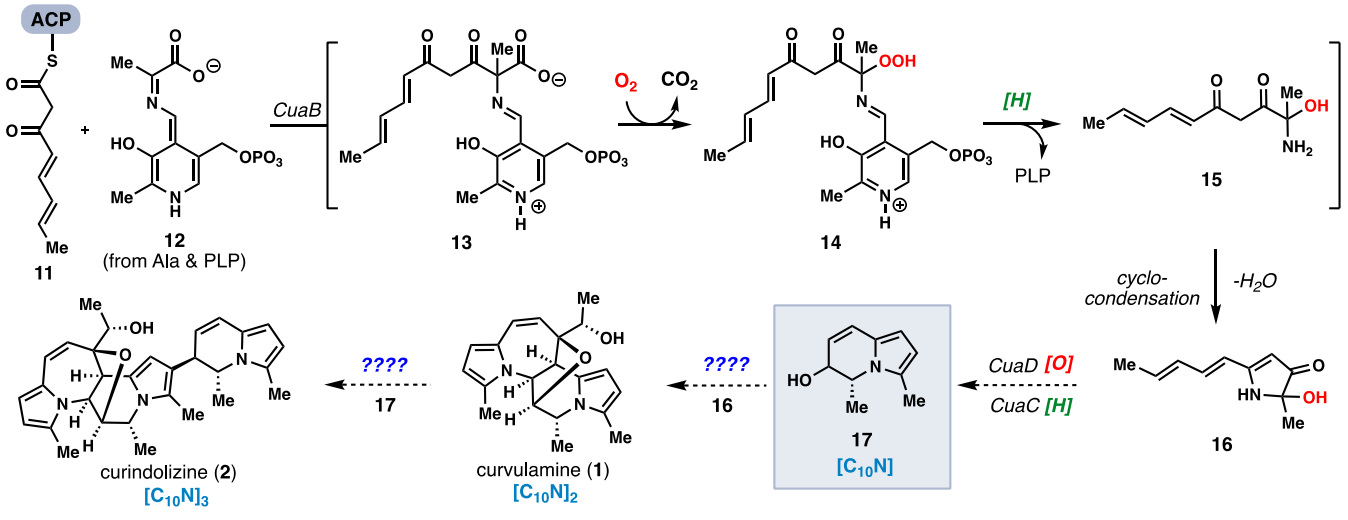

Figure 2. Tan's investigations into the early stages of polypyrrole alkaloid biosynthesis in *Bipolaris maydis*.

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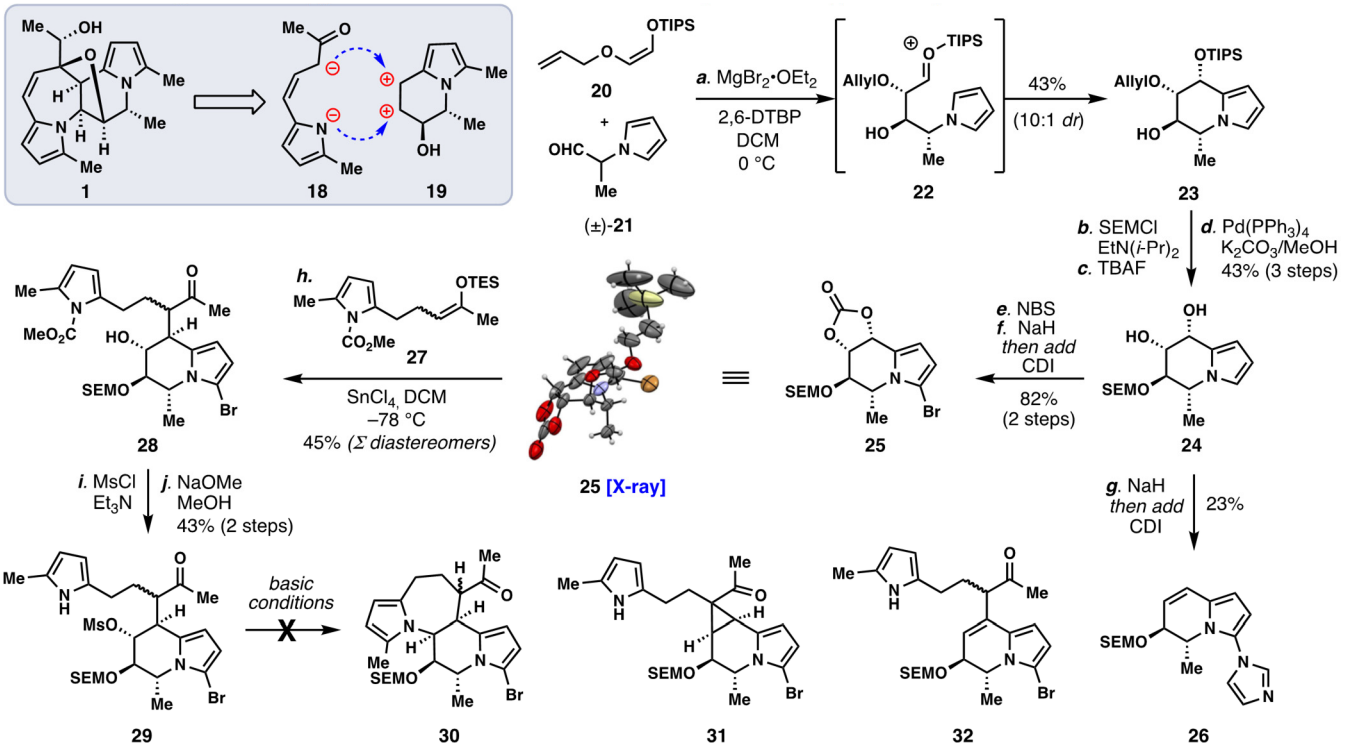
Scheme 1. First-Generation Approach to Curvulamine via the Merger of Bioinspired Fragments[a]



[a]Reagents and conditions: (a) **20** (1.5 equiv), **21** (1.0 equiv), $MgBr_2{\cdot}OEt_2$ (3.0 equiv), 2,6-DTBP (1.1 equiv), DCM, 0 °C, 12 h, 43% (10:1 *dr*); (b) SEMCl (2.0 equiv), EtN(*i*-Pr)$_2$ (4.0 equiv), DCE, 40 °C, 12 h, 91%; (c) TBAF (1.0 M in THF, 1.1 equiv), THF, 50 °C, 12 h, 89%; (d) $Pd(PPh_3)_4$ (0.05 equiv), K_2CO_3 (2.0 equiv), MeOH, 100 °C, 4 h, 53%; (e) NBS (1.05 equiv), DMF, 0 °C, 1 h, *used without purification*; (f) NaH (4.0 equiv), DMF, 0 °C, 5 min, *then add* CDI (3.0 equiv), 25 °C, 30 min, 82% (2 steps); (g) NaH (4.0 equiv), DMF, 0 °C, 30 min *then add* CDI (1.1 equiv), 0 °C, 1 h, 23%; (h) **25** (1.0 equiv), **27** (1.5 equiv), $SnCl_4$ (1.0 equiv), DCM, −78 °C, 3 h, 45% (10.6:3.4:1.5:1.0 *dr*); (i) MsCl (1.1 equiv), Et_3N (1.2 equiv), DCM, 0 °C, 1 h, 81%; (j) NaOMe (5.0 equiv), MeOH, 0 °C, 1 h, 53%. TIPS = triisopropylsilyl, DTBP = di-*tert*-butylpyridine, SEM = 2-(trimethylsilyl)ethoxymethyl, DCE = 1,2-dichloroethane, TBAF = tetrabutylammonium fluoride, NBS = *N*-bromosuccinimide, DMF = dimethylformamide, CDI = 1,1′-carbonyldiimidazole, TES = triethylsilyl.

by X-ray crystallographic analysis, could be obtained in good yield.

With indolizidine **25** in hand, attempts were then made to realize the designed annulation process (Scheme 1). We found that **25** could be coupled with pyrrole-containing silyl enol ether **27** (prepared in 3-steps)[9] via $SnCl_4$-mediated activation of the cyclic carbonate (**25**) which delivered **28** as an inseparable mixture of diastereomers in 55% yield.[10,11] With the first crucial bond formed, effort was directed toward intramolecular C−N bond formation to close the seven-membered ring. While **28**, could be activated (MsCl, Et_3N) and the pyrrole anion unveiled (NaOMe, MeOH), we have never elucidated a productive cyclization transformation to afford **30**. In many instances, unwanted reactivity stemming from the methyl ketone was observed. For instance, treating **29** with TBAF in THF generated cyclopropane **31** and products of *O*-alkylation of the methyl ketone enolate. While this reactivity could be potentially averted by reduction or protection of the carbonyl, attempts to realize seven-membered ring closure of ketone analogs was also unsuccessful. Moreover, the conversion of **29** to alkene **32** also occurred under mild conditions (Cs_2CO_3, MeCN, 0 °C).[12]

A Revised Indolizidine-Based Approach. Our inability to form a carbon−nitrogen bond via intramolecular displacement led us to consider a revised orchestration of events, wherein the C−N bond would be constructed through an intermolecular coupling and the 7-membered ring assembled via a 7-*endo* radical cyclization (see inset, Scheme 2A). We believed the reactivity of hypothetical vinylcation **33** could be replicated by a vinyl triflate (or halide) precursor.

Efforts to realize this revised plan were facilitated by the observation that previously employed diol **24** underwent a facile redox-neutral isomerization to generate ketone **34** under mildly acidic conditions via an ionization/1,2-hydride shift pathway (Scheme 2A). The ketone formed (**34**), could then be converted to vinyl triflate **35** (NaHMDS, $PhNTf_2$) setting up the key pyrrole C−N bond-forming event. While a model pyrrole (i.e 2,5-dimethylpyrrole) successfully coupled with **35** under Pd-catalyzed cross-coupling conditions to generate **36**,[13] we could not extend this transformation to more complex pyrroles featuring extended side chains such as **37**−**39**.[14]

Undeterred by these findings, we retooled our initial aldol-based synthesis of the indolizidine core to incorporate a fragment that already contains a pyrrole C−N bond (Scheme 2B). Deprotonation of pyrrole ester **40** (NaHMDS) followed by addition of aldehyde **41** generated adduct **42** in good yield (82%). Careful DIBAL reduction of this material then furnished an intermediate aldehyde, which underwent cyclization and dehydration to produce **43** when exposed to silica gel. Finally, ruthenium-catalyzed cross metathesis of this material with methyl vinyl ketone generated cyclization precursor **44**.

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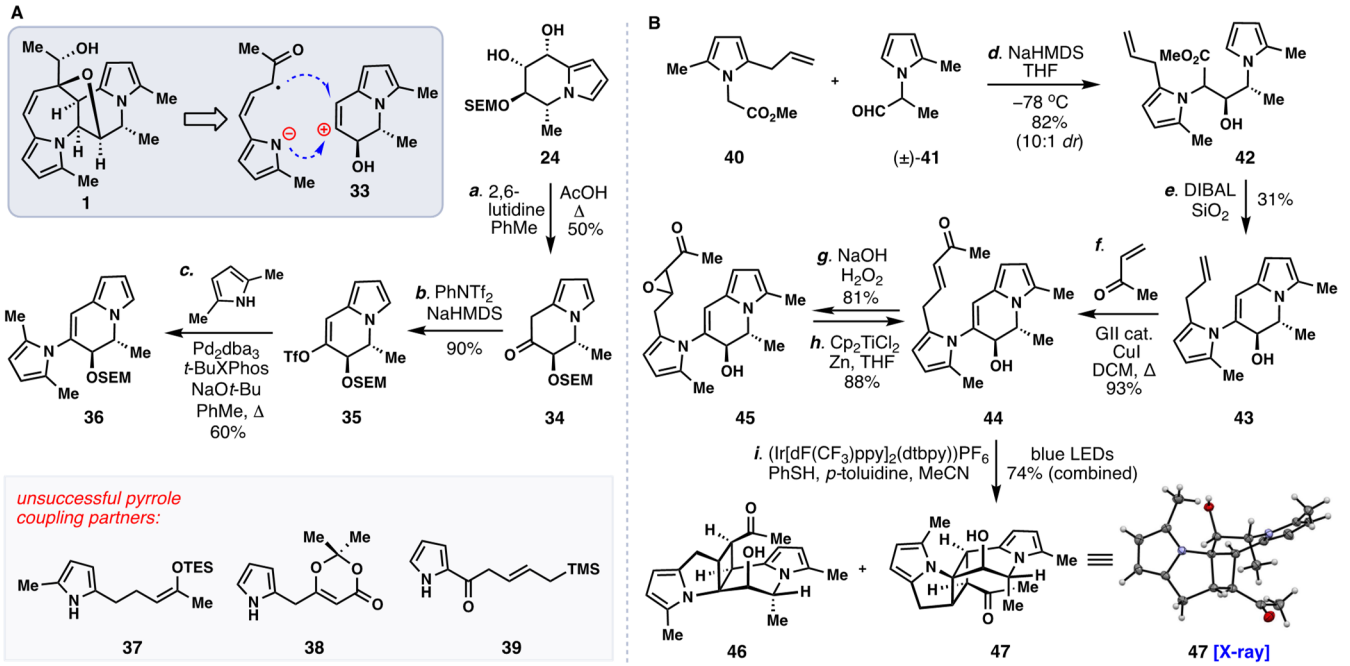
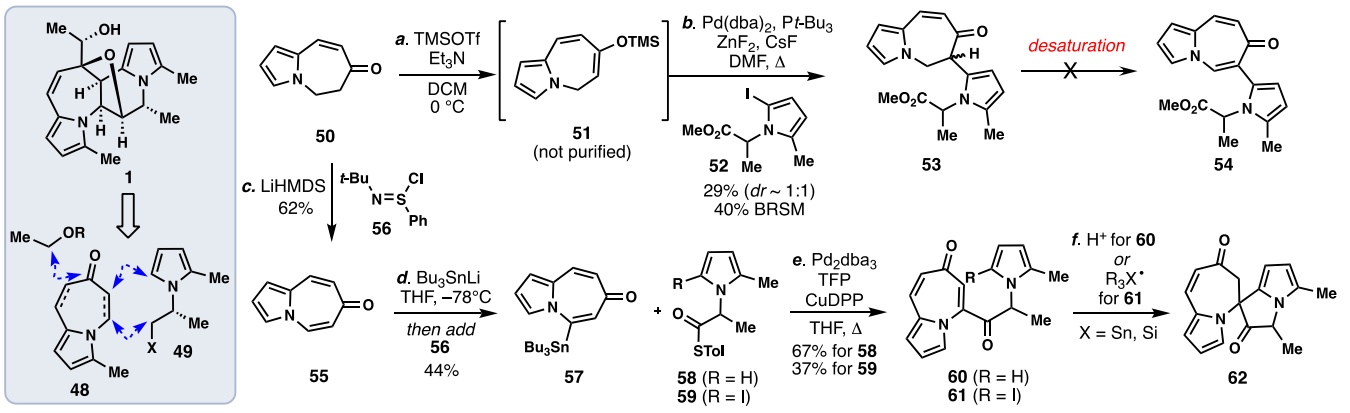
Scheme 2. Revised Indolizidine-Based Route to 1[a]



[a]Reagents and conditions: (a) 2,6-lutidine (1.0 equiv), AcOH (1.0 equiv), PhMe, 150 °C, 15 min, 50%; (b) NaHMDS (2.0 equiv), THF, −78 °C, 30 min, *then add* $PhNTf_2$ (1.2 equiv), −78 °C, 1 h, 90%; (c) 2,6-dimethylpyrrole (1.5 equiv), $Pd_2(dba)_3$ (0.05 equiv), *t*-BuXPhos (0.1 equiv), NaO*t*-Bu (1.4 equiv), PhMe, 60 °C, 12 h, 60%; (d) **40** (1.0 equiv), NaHMDS (1.1 equiv), THF, −78 °C, 30 min, *then add* **41** (1.1 equiv), −78 °C, 1 h, 82%; (e) DIBAL (5.0 equiv), PhMe, −78 °C, 1 h, *then add* SiO_2, DCM, 25 °C, 30 min, 31%; (f) MVK (3.0 equiv), GII (0.01 equiv), CuI (0.02 equiv), DCM, 50 °C, 1 h, 93%; (g) 1 M NaOH (2.0 equiv), 50% H_2O_2 (2.0 equiv), MeOH, 0 to 25 °C, 3 h, 81%; (h) Cp_2TiCl_2 (1.0 equiv), Zn^0 (8.0 equiv), THF, 25 °C, 30 min, 88%; (i) $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (0.01 equiv), PhSH (1.1 equiv), *p*-toluidine (0.5 equiv), MeCN, blue LED irradiation, 25 °C, 3 h, 74% (**46**:**47** ≈ 1:1). Tf = trifluoromethanesulfonyl, NaHMDS = sodium 1,1,1-trimethyl-*N*-(trimethylsilyl)silanaminide, MVK = methyl vinyl ketone, TMS = trimethylsilyl, dba = dibenzylideneacetone, *t*-BuXPhos = 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl, GII cat. = Grubbs second generation catalyst = (1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-(phenylmethylene)(tricyclohexylphosphine)ruthenium, $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ = [4,4′-*Bis*(1,1-dimethylethyl)-2,2′-bipyridine-*N*1,*N*1′] *bis*[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate.

Scheme 3. Towards a Pyrroloazepinone-Based Route to 1[a]



[a]Reagents and conditions: (a) Et_3N (1.5 equiv), TMSOTf (1.1 equiv), DCM, 0 °C, 30 min, *used without purification*; (b) $Pd(dba)_2$ (0.05 equiv), P*t*-Bu_3 (0.1 equiv), ZnF_2 (1.5 equiv), CsF (1.5 equiv), DMF, 70 °C, 5 h, 29% (1:1 *dr*) (40% BRSM); (c) LiHMDS (1.2 equiv), THF, −78 °C, 30 min, *then add* **56** (1.1 equiv), −78 °C, 3 h, 62%; (d) *n*Bu_3SnLi (1.2 equiv), THF, −78 °C, 1 h, *then add* **56** (1.1 equiv), −78 °C, 3 h, 44%; (e) **57** (1.1 equiv), **58** (1.0 equiv), Pd_2dba_3 (0.05 equiv), TFP (0.2 equiv), CuDPP (1.1 equiv), THF, 60 °C, 1.5 h, 67% *or* **57** (1.1 equiv), **59** (1.0 equiv), Pd_2dba_3 (0.05 equiv), TFP (0.2 equiv), CuDPP (1.1 equiv), THF, 60 °C, 1.5 h, 37%; (f) **60** (1.0 equiv), PPTS (0.5 equiv), PhMe, 60 °C, 1.5 h, 91% (4:1 *dr*) *or* **61** (1.0 equiv), $(TMS)_3SiH$ (1.5 equiv), BEt_3 (1.1 equiv), O_2, DCM, −78 °C, 2 h, 43% (6:1 *dr*). LiHMDS = lithium 1,1,1-trimethyl-*N*-(trimethylsilyl)silanaminide, dba = dibenzylideneacetone, TFP = tri(2-furyl)phosphine, DPP = diphenylphosphinate.

With **44** secured, we commenced attempts to construct the key 7-membered ring via radical cyclization.[15] Reductive radical cyclizations initiated at the pendant enone with M/$HSiR_3$ (M = Fe, Co)-based systems led to reduction without cyclization.[16] While an epoxide (see **45**) could be generated from **44** (H_2O_2, NaOH), attempted titanocene-mediated cyclizations only returned enone **44**.[17] The addition of a thiyl radical to initiate radical cyclization was also explored

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under photoredox conditions,[18] but these conditions instead promoted a rather facile, yet unselective, [2 + 2] cycloaddition to generate cyclobutanes **46** and **47** in 74% combined yield.[19]

Initial Forays Into a Pyrroloazepinone Fragment-Based Synthesis. Faced with an inability to form both of the key bonds needed for a successful indolizidine annulation-based approach, we adjusted our retrosynthesis to include a pre-existing 7-membered ring (see inset, Scheme 3). Specifically, we considered the convergence of a 5,7-fused pyrrole-containing synthetic unit (see **48**) with fragment **49**, an alternative retrosynthetic strategy for carbocyclic construction of curvulamine's core, lending to a potentially more facile six-membered ring-forming annulation. Nevertheless, the precise oxidation state of **48** and the reaction types capable of realizing this annulation remained open questions; ultimately, only through significant experimentation and reactivity reconnaissance gathering did a successful route to **1** emerge along these lines.

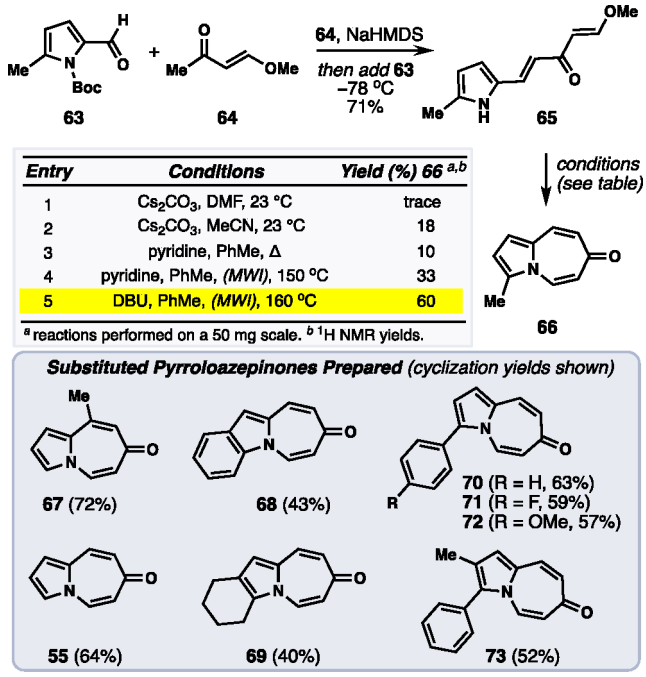
We initiated our investigations using enone **50**, a known Robinson annulation product of 2-formylpyrrole and methyl vinyl ketone.[20] To construct one of the two key C−C bonds in the revised annulation, we turned toward Pd-catalyzed enolate arylation. Enone **50** could be converted to sensitive trimethylsilyl enol ether **51** and merged with pyrrole iodide **52** to generate **53**.[21] However, further manipulation of this material proved challenging; we were unable to produce dienone **54** through Saegusa-Ito or related enolate oxidation processes.

Given these setbacks, we found it prudent to investigate installation of the alternative key C−C bond first (Scheme 3). Unlike **54**, enone **50** could be oxidized to pyrroloazepinone **55** using Mukaiyama's desaturation reagent *N-tert*-Butylbenzenesulfinimidoyl chloride (**56**). Pyrroloazepinones such as **55**—uncommon 10π-aromatic heterocycles—are infrequently used in synthesis and their reactivity is largely unexplored.[22] While we did not know it at the time, this heteroaromatic proved key in the development of a concise route to **1**.

Pyrroloazepinone **55** underwent productive conjugate addition with a variety of nucleophiles (*vide infra*). Initially we found that tributylstannyllithium (LDA, $HSnBu_3$) was readily added and that the resulting enolate could be directly oxidized with **56** to produce stannane **57** (Scheme 3). We envisioned that this fragment could be merged with a pyrrole-containing thioester via Liebeskind-Srogl coupling. Experimentally, we discovered that **56** reacted with thioester **58** and iodo-variant **59** in 67% and 37% yield, respectively.[23] The products formed, namely enediones **60** and **61**, lacked only a single C−C bond for advancement into the tetracyclic scaffold of **1**. However, upon treating dienone **60** with a variety of Lewis acids, we observed exclusive formation spirocycle **62** as a mixture of diastereomers. Attempts to elicit direct, palladium-catalyzed dehydrogenative coupling of **60** were also complicated by this Lewis-acid catalyzed background reaction. Employing iodide **61** and changing the reaction manifold to one based on free radicals (i.e., Bu_3SnH/AIBN or $(TMS)_3SiH/Et_3B/O_2$) did not change the outcome as spirocyclic enone **62** was again generated.

While the two strategies in Scheme 3 were ultimately dead-ends, we were keen to survey additional nucleophilic partners in the coupling with a pyrroloazepinone heterocycle. An initial impediment to such endeavors was the difficulty in preparing large quantities of **55**. Specifically, enone **50** (prepared using a two-step Robinson annulation), was produced in yields ranging from only ∼20−25% and large quantities of reagent **56** was also required to produce **55**.[24]

Given this backdrop, we investigated alternatives routes to this class of heterocycles (Figure 3). Inspired by the work of



Entry	Conditions	Yield (%) 66 [a,b]
1	Cs_2CO_3, DMF, 23 °C	trace
2	Cs_2CO_3, MeCN, 23 °C	18
3	pyridine, PhMe, Δ	10
4	pyridine, PhMe, *(MWI)*, 150 °C	33
5	DBU, PhMe, *(MWI)*, 160 °C	60

[a] reactions performed on a 50 mg scale. [b] ^1H NMR yields.

Figure 3. Two-step synthesis of novel pyrroloazepinones.

Flitsch,[22] we developed a straightforward synthesis using Boc-protected 2-formylpyrroles, ubiquitous Vilsmeier−Haack formylation products, as starting materials (Figure 3). The enolate of vinylogous ester **64** was first added to pyrrole **63** resulting in direct formation of dienone **65** through an aldol addition/Boc-migration/E1cB elimination pathway. With access to dienone **65** we evaluated cyclization conditions to produce the 10π aromatic nucleus (see Table, Figure 3). We sought to avoid flash vacuum pyrolysis and other low-yielding cyclization conditions observed in the cyclization of related vinylogous amides.[22]

Dienone **65** formed pyrroloazepinone **66** under mild conditions (Cs_2CO_3, 25 °C), but the yield of this cyclization was low (<20%, see entries 1−2). Microwave-induced thermal cyclizations employing amine bases proved more efficient, and utilizing DBU we were able to prepare **66** in 60% yield (entry 5)—notably these conditions were also scalable and enabled multigram procurement of this key building block.[25,26]

Next, we surveyed these cyclization conditions for the synthesis of novel, substituted pyrroloazepinones (see **67**−**73**, Figure 3). Previously prepared heteroaromatic **55** was produced in comparable yield to **66** (64% cyclization yield) as was isomeric methyl-containing substrate **67**. Importantly, **67** also demonstrates that ketones, and not just aldehydes, can be used in this methodology. Indole (see **68**) and tetrahydroindole (see **69**) units could also be incorporated although cyclization yields were somewhat diminished (40−43%). Aryl substituents were also tolerated on the pyrrole ring, leading to products **70**−**73**.

Exploring a Dearomative Approach. With a robust synthesis of pyrroloazepinone **66** in hand, we proceeded to evaluate a carbon-based nucleophile in the dearomative

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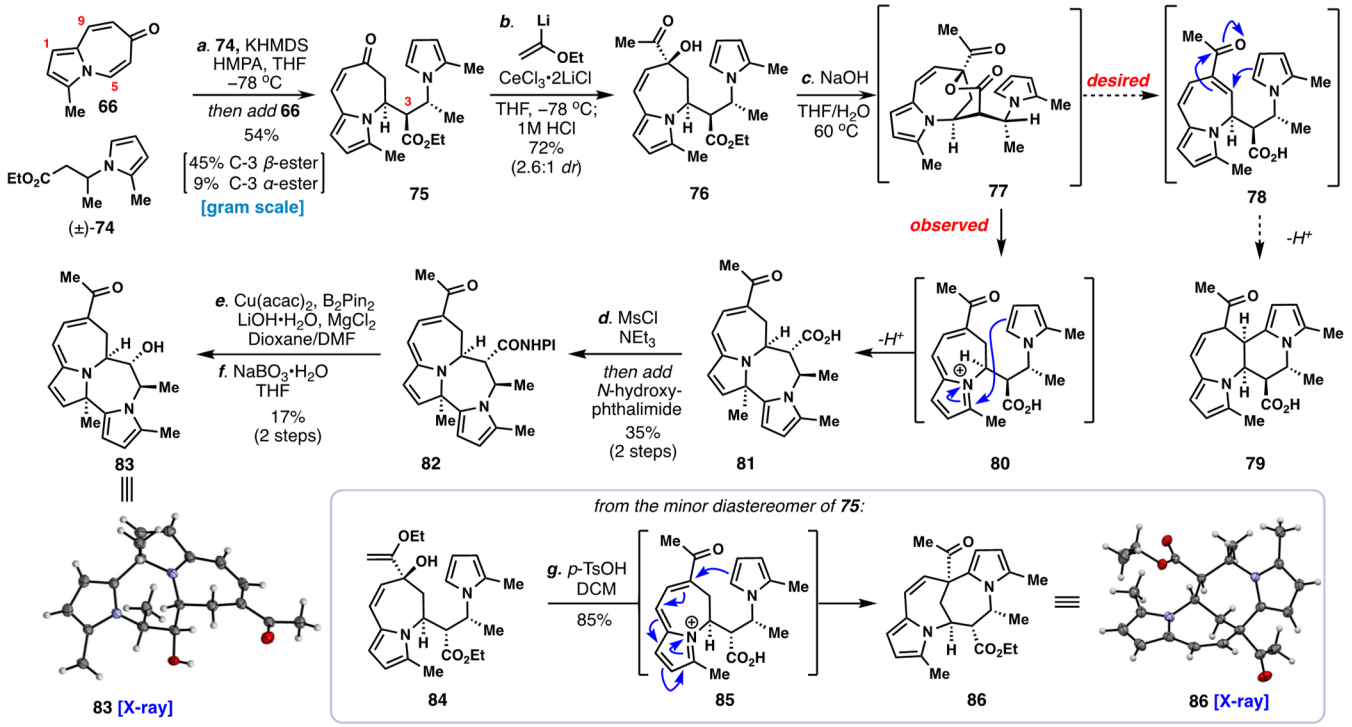
Scheme 4. Successful Dearomative C−C Bond Formation Leads to Unexpected Pyrrole Reactivity



[a]Reagents and conditions: (a) (±)-**74** (1.4 equiv), KHMDS (1.4 equiv), THF, −78 °C, 30 min, *then add* HMPA (5.0 equiv), **66** (1.0 equiv), −78 °C, 2 h, 54% (5:1 *dr*); (b) ethyl vinyl ether (7.5 equiv), *t*-BuLi (7.0 equiv), THF, −78 to 0 °C, 30 min; **75** (1.0 equiv), $CeCl_3$ (1.0 equiv), LiCl (2.0 equiv), 0 °C, 30 min, *then add* lithiated ethyl vinyl ether, −78 °C, 1 h, *then add* 1 M HCl, 25 °C, 30 min, 72% (2.6:1 *dr*); (c) 5 M NaOH (2.0 equiv), THF, 60 °C, 1 h, *used without purification*; (d) MsCl (5.0 equiv), Et_3N (10.0 equiv), DCM, 0 °C, 15 min, *then add N*-hydroxyphthalimide (2.2 equiv), 0 °C, 30 min, 35% (2 steps); (e) $Cu(acac)_2$ (2.0 equiv), B_2Pin_2 (1.5 equiv), $LiOH{\cdot}H_2O$ (15.0 equiv), $MgCl_2$ (1.2 equiv), Dioxane/DMF = 5:1 (*v*:*v*), 25 °C, 2 h, *used without purification*; (f) $NaBO_3{\cdot}H_2O$ (5.0 equiv), THF/H_2O = 1/1, 25 °C, 30 min, 17% for 2 steps; (g) *p*-TsOH (0.5 equiv), DCM, 25 °C, 85%. KHMDS = potassium bis(trimethylsilyl)amide, HMPA = hexamethylphosphoramide, acac = acetylacetonate, B_2Pin_2 = 4,4,4′,4′,5,5,5′,5′-Octamethyl-2,2′-bi-1,3,2-dioxaborolane.

conjugate addition reaction (Scheme 4). Much to our delight, we observed that the potassium enolate of pyrrole-containing ester **74** could be prepared, and in the presence of HMPA, added to **66** to yield coupled product **75** in 54% yield and with 5:1 diastereoselectivity at C-3. While **66** possesses several sites for Michael-type attack (see C1, C9, and C5), under these conditions selectivity for the C5 position was observed.[27] Notably the stereochemical relationship between the methyl group and the stereocenter on the 7-membered ring are correct for advancement to **1** as well. We assumed (albeit incorrectly) that the C-3 ester could be easily removed later in the synthesis by decarboxylative methods (*vide infra*).

Adopting the conditions of Knochel,[28] a cerium-mediated 1,2-addition of lithiated ethyl vinyl ether into enone **75** produced methyl ketone **76** as a mixture of diastereomers (72%, 2.6:1 *dr*) after acidic hydrolysis (aq. HCl) of the enol ether (Scheme 4). We had hoped that treating compound **76** with base would transiently generate lactone **77** which in turn might undergo an E2 elimination, thus generating enone **78**. An intramolecular addition of the pyrrole to this newly generated Michael acceptor would then produce **79**, the key tetracyclic core of all $(C_{10}N)_2$ members. Subjecting **76** to sodium hydroxide at slightly elevated temperature followed by an acidic quench led to a markedly different outcome, however, wherein a rather remarkable dearomatized enamine (**81**) containing a 5,7,5,7-fused ring system was produced. We speculate that **77** was indeed formed, but the electron-rich vinyl pyrrole nucleus expelled the carboxylate leaving group forming an extended azafulvenium ion (**80**). Interestingly, this electrophile was attacked by the second pyrrole at a substituted carbon center leading to pyrrole dearomatization and formation of a quaternary center. While related enamines are highly unstable,[2] conjugation to the electron-withdrawing ketone stabilizes this structure. Conversion of **81** to NHPI ester **82** (MsCl, Et_3N, *N*-Hydroxyphthalimide) then allowed for a copper-mediated decarboxylative borylation and oxidation furnishing alcohol **83** whose structure was confirmed by single crystal X-ray diffraction.[29] While these unoptimized transformations were low-yielding, this work suggested that the extraneous carbon atom added in the dearomative conjugate addition could be removed to yield a hydroxyl group.

We also briefly explored the reactivity of intermediates stemming from the minor diastereomer of **75** (see inset, Scheme 4). Compound **84** could be formed analogously to **76**. Interestingly, treatment of **84** with *para*-toluenesulfonic acid generated putative azafulvenium ion **85** which was also quenched through intermolecular attack from the pendant pyrrole to afford **86**. Fascinatingly, the sole product formed (in 85%) in this cyclization, however, was tetracycle **86** whose notable diazabicyclo[4.4.1]undecane core was confirmed crystallographically.[30]

While neither of these two pathways yielded the desired tetracyclic core of **1**, we felt that the initial conjugate addition reaction with heterocycle **66** was a promising route for further exploration and that a decarboxylation reaction could be employed late-stage. In reality, these assumptions proved

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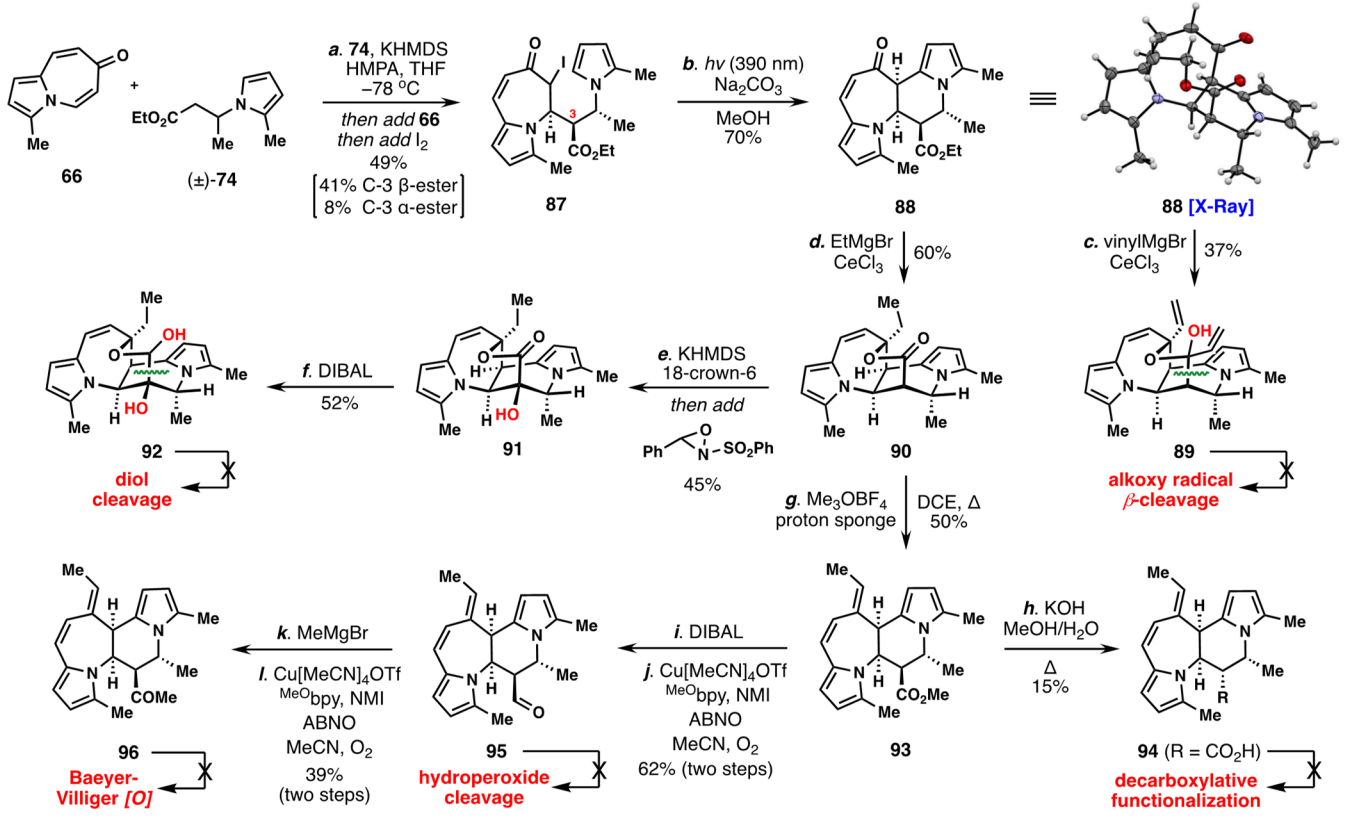
Scheme 5. Successful Synthesis of the Curvulamine Core



[a]Reagents and conditions: a) (±)-**74** (1.4 equiv), KHMDS (1.4 equiv), THF, −78 °C, 30 min *then add* HMPA (5.0 equiv), **66** (1.0 equiv), −78 °C, 2 h, *then add* I_2 (1.1 equiv), −78 °C, 30 min, 49% (5:1 *dr*); (b) Na_2CO_3 (5.0 equiv), MeOH, Kessil Lamp KSPR160 (390 nm, 40 W), 25 °C, 1 h, 70%; (c) **88** (1.0 equiv), $CeCl_3$ (2.0 equiv), THF, 0 °C, 30 min, *then add* vinylMgBr (2.5 equiv), 30 min, −78 °C, 1 h, 37%; (d) **88** (1.0 equiv), $CeCl_3$ (2.0 equiv), THF, 0 °C, 30 min, *then add* EtMgBr (1.05 equiv), −78 °C, 1 h, 60%; (e) KHMDS (2.0 equiv), 18-crown-6 (2.0 equiv), THF, −78 °C, 30 min, *then add* Davis oxaziridine (1.2 equiv), −78 °C, 30 min, 45%; (f) DIBAL (1.2 equiv), DCM, −78 °C, 30 min, 52%; (g) Me_3OBF_4 (1.5 equiv), proton sponge (3.0 equiv), DCE, 90 °C, 12 h, 50%; (h) 1 M KOH (3.0 equiv), MeOH, 90 °C, 12 h, 15%; (i) DIBAL (2.5 equiv), DCM, −78 °C, 30 min, 82%; (j) $Cu[MeCN]_4OTf$ (0.1 equiv), ^{MeO}bpy (0.1 equiv), NMI (0.1 equiv), ABNO (0.05 equiv), O_2, MeCN, 25 °C, 30 min, 75%; (k) MeMgBr (1.1 equiv), THF, −15 °C, 30 min, 71%; (l) $Cu[MeCN]_4OTf$ (0.1 equiv), ^{MeO}bpy (0.1 equiv), NMI (0.1 equiv), ABNO (0.05 equiv), O_2, MeCN, 25 °C, 30 min, 55%. 18-crown-6 = 1,4,7,10,13,16-Hexaoxacyclooctadecane, ^{MeO}bpy = 4−4′-dimethoxy-2−2′-bipyridine, NMI = 1-methylimidazole, ABNO = 9-azabicyclo[3.3.1]nonane *N*-oxyl.

partially correct and significant experimentation remained to clarify a workable pathway forward.

Successful Synthesis of the Curvulamine Core Leads to a Difficult Decarboxylation. Our inability to close the six-membered ring via polar, pyrrole cyclization approaches led us to consider radical-based methods (Scheme 5). Specifically, our dearomative conjugate addition furnished an enolate which we believed could be oxidized to a radical. Unfortunately, the addition of common single-electron oxidants to this coupling reaction did not lead to pyrrole C-2 functionalization despite literature precedent suggesting its feasibility.[31] We could however quench the anionic coupling of **66** and **74** with NIS or I_2 leading to iodide **87** (49% combined yield), thus allowing for a broader survey of reaction conditions to be explored (Scheme 5).[32] While photoredox chemistry was explored with some success,[7] control experiments found that simple irradiation of **87** (390 nm light) forged compound **88** in good yield (70%) thus accomplishing our first successful synthesis of the curvulamine tetracycle. While unknown at the time, substantial challenges awaited.

With tetracyclic enone **88** in hand, a variety of endgames were envisioned all of which required a C−C bond cleavage event to excise the extraneous C-3 carbon atom of the ester (Scheme 5). Initially, we added excess vinyl magnesium bromide to **88** producing double addition product **89**. We had hoped that the array of known methods to generate alkoxy radicals would allow for facile C−C bond *β*-cleavage of the desired bond shown in green and further radical functionalization. Unfortunately, Suárez conditions (PIDA, I_2, *hν*) single-electron oxidants ($FeCl_3$, $AgNO_3/K_2S_2O_8$/NIS), and a variety of other reagents (Ir(III)/*hν*, $CeBr_3/O_2/h\nu$) failed to provide detectable quantities of C−C bond cleaved products—only decomposition was typically observed. Attempts to convert the tertiary alcohol into a hydroperoxide for iron-induced C−C bond cleavage were also unproductive.[33,34]

To promote the C−C cleavage process, we reasoned that introduction of an additional hydroxyl group (thus constructing a 1,2-diol motif) might allow for a wider reactivity window to be explored. Carefully controlled addition of ethylmagnesium bromide mediated by $CeCl_3$ allowed for the conversion of **88** into lactone **90**. Remarkably, this material could be deprotonated (KHMDS, 18-crown-6) at the bridgehead position allowing for hydroxylation with Davis' oxaziridine. The *α*-hydroxylactone formed (**91**) could then be reduced with DIBAL to generate *α*-hydroxy acetal **92**. Much to our dismay, however, standard diol cleavage

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conditions ($NaIO_4$, $Pb(OAc)_4$, H_5IO_6) were all incompatible with this sensitive substrate leading only to intractable mixtures.

We then decided to explore the chemistry of a conformationally distinct ester intermediate, finding that alkylative lactone opening of **90** (Me_3OBF_4, proton sponge, Δ) furnished methyl ester **93** in moderate yield.[35] Given the breadth and renaissance in decarboxylative functionalization chemistry, we first looked toward hydrolysis of methyl ester to prepare carboxylic acid **94**. The hydrolysis of this quite hindered ester proved challenging, resulting in only 15% yield of acid **94** along with extensive decomposition.[36] Nevertheless, we were able to explore several strategies with this limited amount of material. Similar to substrate **89**, direct decarboxylative functionalization of the free acid under radical generating conditions (i.e., Suárez chemistry, Ag^I salts, $Pb(OAc)_4$, photoredox catalysis) did not lead to isolable products. We had hoped that Barton's decarboxylative oxygenation might allow for a peroxidation cascade an analogy to our prior work on terpene scaffolds;[37,38] while a Barton ester could be formed in trace quantities, instant decomposition was observed during its activation in the presence of oxygen. Finally, decarboxylative borylation/oxidation, which had been used to construct **83** in low yield (Scheme 4), was unsuccessful in this setting under a variety of conditions.[29,39]

As a last-ditch effort, we attempted to remove this recalcitrant carbon atom from multiple different carbonyl bearing intermediates (Scheme 5). Ester **93** was reduced cleanly with DIBAL to generate a primary alcohol which could be oxidized to an aldehyde using Stahl's mild copper-catalyzed conditions.[40] Unfortunately, attempts at performing Iwasawa's cobalt salen-catalyzed cleavage reaction of an *in situ* generated hydroperoxide led to extensive decomposition.[41] In our final foray, we turned to the tried-and-true Baeyer–Villiger oxidation. While methyl ketone **96** could be synthesized from aldehyde **95** in two steps, this substrate was not compatible with peracids likely as a result of the vinyl pyrrole nucleus (*vide infra*).

The results in Scheme 5 were both encouraging and frustrating as is often the case during a total synthesis. While a viable strategy to the elusive curvulamine tetracycle had emerged, it was clear that alternative nucleophiles in the conjugate addition would need to be examined if we were to synthesize **1** by this strategy.

Reactivity of Alternative Nucleophiles in the Dearomative Conjugate Addition. We undertook a fairly comprehensive study of various carbanions and their reactivity with our key pyrroloazepinone (see **66** + **97** → **98**, Figure 4). Although we had not succeeded in decarboxylating acid **94**, the extremely low yield in preparing this material from ester **93** compelled us to examine free carboxylic acid **99** in the dearomative coupling (Figure 4). We attempted to generate the dianion of **99** using an excess of strong base (KHMDS) and found that a new product was formed after the addition of **66**. Much to our surprise the structure of the "coupled product" turned out to be dimer **100** whose structure was secured by X-ray crystallography. Excess base apparently deprotonated the acidic methyl group of **66**, forming an anion which added in a conjugate fashion to another molecule of **66** resulting in a formal annulation after a second, intramolecular Michael addition.

A lithiated carbamate strategy was also briefly explored as this would correctly incorporate a masked hydroxyl group at

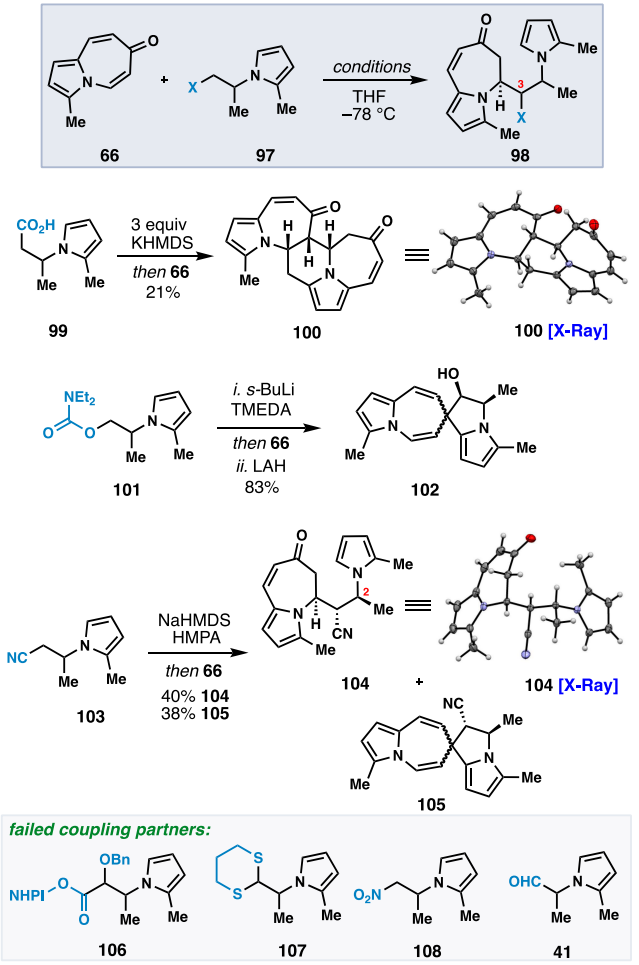

Figure 4. Examination of alternative nucleophiles in the conjugate addition to pyrroloazepinone **66**.

the desired position.[42] Deprotonation of **101** (*s*-BuLi) followed by addition of **66** generated several new products which were most easily analyzed following lithium aluminum hydride reduction of the carbamate. To our surprise we found that tetracycle **102**, formed as a mixture of diastereomeric spirocycles, was the major product. This product ostensibly stems from lithiate 1,2-addition followed by ionization of the highly labile tertiary alcohol to form an aromatic carbocation which is trapped by the electron-rich pyrrole.

Next, we considered the use of a metalated nitrile owing to the possibility for downstream reductive decyanation/functionalization.[43] The anion derived from **103** underwent coupling with **66** to generate coupled product **104** (40%) whose structure was confirmed by X-ray crystallographic analysis. Notably the stereochemical configuration of the methyl group (C2) is opposite to that found in curvulamine and would have to be corrected at some point. In addition to **104**, we also observed substantial amounts (38%) of spirocycle **105** in analogy to **102**. In addition to these "successful" experiments, a number of other pyrrole-containing nucleophiles (see **106**–**108**) were examined but did not lead to C–C bond formation with **66**. In addition, we attempted to generate the ketyl radical of **41** in the presence of **66**, but did not observe any productive coupling.

Total Synthesis of Curvulamine. Given the successful coupling of nitrile **103**, we chose to evaluate one final

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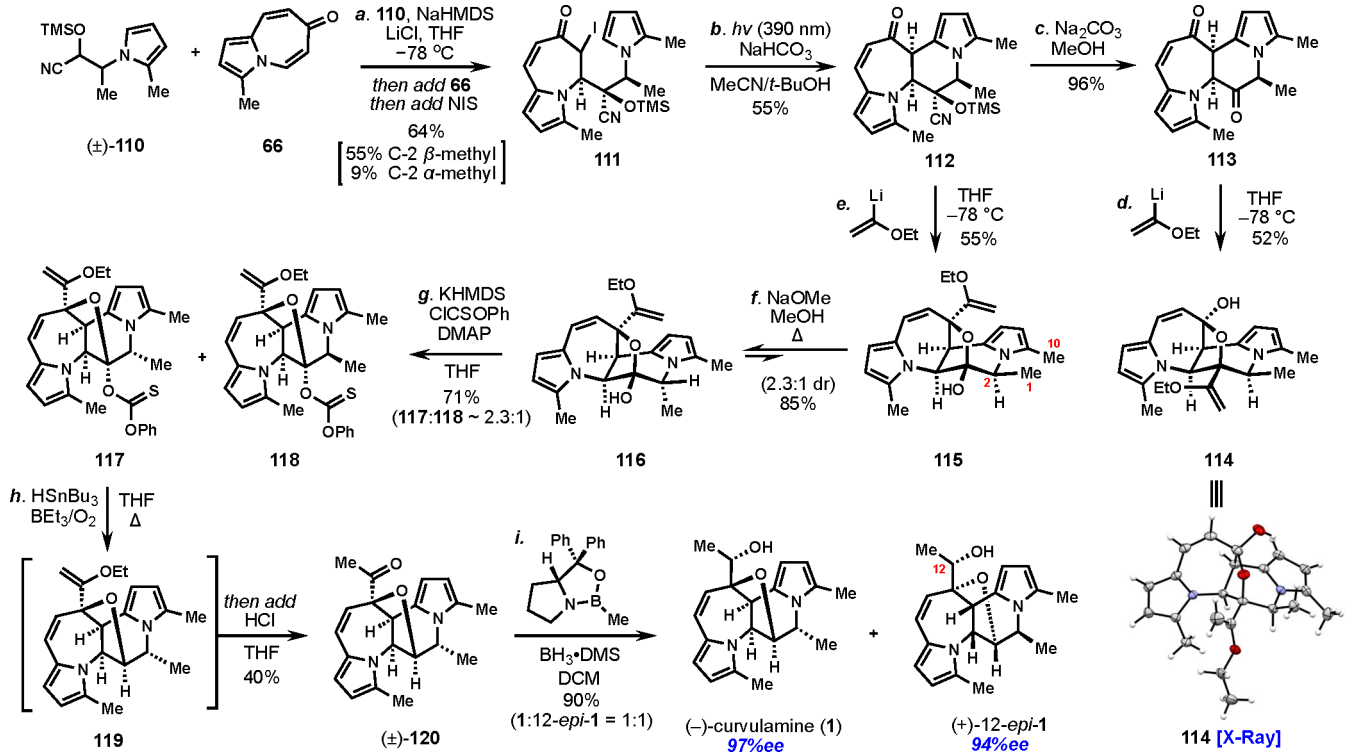
Scheme 6. Total Synthesis of Curvulamine



[a]Reagents and conditions: (a) **110** (1.5 equiv), LiCl (5.0 equiv), NaHMDS (1.6 equiv), THF, −78 °C, 30 min *then add* **66** (1.0 equiv), THF, −78 °C, 1 h *then add* NIS (1.5 equiv), THF, −78 °C, 5 min (64%); (b) $NaHCO_3$ (5.0 equiv), MeCN/*t*-BuOH (4:1), Kessil Lamp KSPR160 (390 nm, 40W), 23 °C, ∼2 h (55%); (c) Na_2CO_3 (2.0 equiv), MeOH, 23 °C, 5 min (96%); (d) ethyl vinyl ether (5.5 equiv), *t*-BuLi (5.0 equiv), THF, −78 °C, 30 min *then add* **113** (1.0 equiv), −78 °C, 1 h (52%); (e) ethyl vinyl ether (5.5 equiv), *t*-BuLi (5.0 equiv), THF, −78 °C, 30 min *then add* **112** (1.0 equiv), −78 °C, 1 h (55%); (f) NaOMe (5.0 equiv), MeOH, 90 °C, 4 h (85%); (g) KHMDS (1.6 equiv), −78 °C, 30 min*; then add* phenyl chlorothionoformate (2.0 equiv), DMAP (2.0 equiv), THF, −78 to 0 °C, 20 min (50% **117** + 21% **118**); (h) $HSnBu_3$ (2.0 equiv), BEt_3 (1.0 equiv), O_2, THF, 45 °C, 1 h *then add aq.* HCl, 0 °C, 5 min (40%); (i) (*R*)-2-methyl-CBS-oxazaborolidine (1.0 equiv), BH_3·DMS (2.0 equiv), DCM, 23 °C, 1 h (45% (−)-**1** + 45% (+)-12-*epi*-**1**; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, NIS = *N*-iodosuccinimide.

nucleophile—a cyanohydrin—which are known to undergo 1,4-addition reactions.[44] Ultimately this decision proved critical in enabling the first total synthesis of curvulamine (Scheme 6).[7] Unlike **74**, deprotonation of cyanohydrin **110** using KHMDS in the presence of HMPA lead to E1cB of the pyrrole anion, producing a variety of undesired products when reacted with **66**.[45] A stable carbanion could be made however using NaHMDS in the presence of LiCl; this species added to **66**, giving a 64% yield of coupled product **111** (∼6:1 *dr*) after quenching with *N*-iodosuccinimide. As noted when forming **104**, the C2 stereocenter was incorrectly set during this process. From **111**, our previously developed photochemical cyclization generated tetracyclic ketone in moderate yield (55%). The cyanohydrin could be easily removed by basic methanolysis to give diketone **113**. Interestingly, this compound reacted with lithiated ethyl vinyl ether to give **114**, the product of nucleophilic addition at the incorrect carbonyl group. Satisfyingly, however, treatment of **112** with an excess of the same nucleophile produced lactol **115** bearing the correct connectivity in 55% isolated yield.

With **115** in hand we proceeded to investigate epimerization of the C2 methyl group. We found it plausible that allylic 1,3-strain minimization between the two methyl groups (C1 and C10) might favor the desired stereochemistry. Gratifyingly, basic treatment of **115** (NaOMe, MeOH, Δ) established a 2.3:1 mixture of lactols favoring the epimerized isomer (**116**) in 85% combined yield.

The next obstacle in the synthesis of curvulamine entailed removal of the bridgehead hydroxyl group comprising the lactol motif. The inseparable, thermodynamic mixture of lactols (**115**/**116**) was activated (KHMDS, pyridine, ClCSOPh) generating a mixture of thiocarbonate epimers **117** and **118** (71% yield) which could be separated chromatographically. Of practical importance, the undesired isomer (i.e., **118**) could be recycled by one-pot, base-mediated methanolysis/epimerization (NaOMe, MeOH, Δ) redelivering the equilibrium mixture of **115** and **116**. Finally, reductive deoxygenation ($HSnBu_3$, BEt_3/O_2) with concomitant enol ether hydrolysis of intermediate **119** during acidic workup (aq. HCl) afforded methyl ketone (±)-**120** in 40%.

To complete the synthesis of racemic **1** we simply needed to reduce (±)-**120** diastereoselectively. A variety of reducing agents (DIBAL, $NaBH_4$, $LiBH(Et)_3$, $LiAlH_4$, and other simple hydrides) afforded primarily the undesired secondary alcohol diastereomer, namely (±)-12-*epi*-**1**. Intrigued by a possible reagent controlled solution, we exposed our methyl ketone to CBS reduction conditions ((*R*)-2-Methyl-CBS-oxazaborolidine, BH_3·DMS, DCM).[46] Interestingly, a near perfect stereodivergent reduction ensued wherein (±)-**120** was converted into an easily separable 1:1 mixture of (−)-(**1**) and (+)-12-*epi*-**1** with 97% and 94% ee respectively (90%

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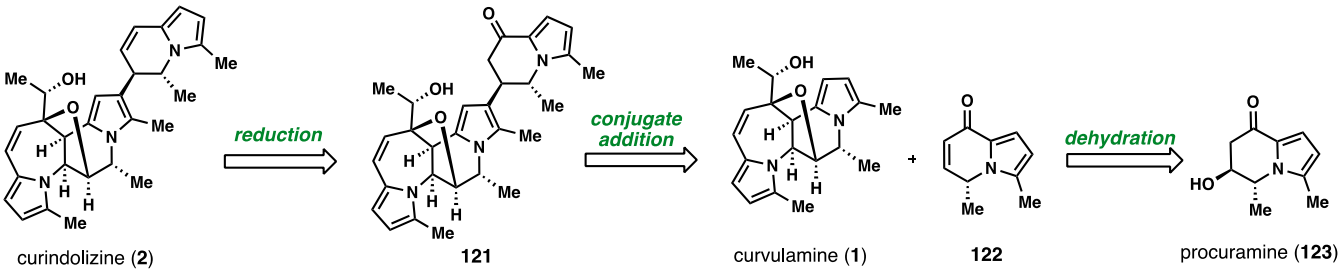

Figure 5. Tan's biosynthetic hypothesis regarding the origins of curindolizine.

overall yield).[47,48] Our journey to **1**, which was filled with numerous roadblocks and unexpected surprises, was finally complete.

TOTAL SYNTHESIS OF CURINDOLIZINE

With a 10-step route to curvulamine in place, we turned our attention toward curindolizine (**2**), the most complex—and only trimeric $(C_{10}N)_3$—member in the family (Figure 5). When scaling up a 300 L fermentation of *Curvularia* sp. IFB-Z10, Tan and co-workers found that **2** was formed in preference to **1**.[4] It was proposed that curindolizine is produced from the Michael addition reaction of **1** and enone **122**, which could be derived from procuramine (**123**), a simple $C_{10}N$ member present in the fermentation broth. Additionally, when **1** and **123** were exposed to cell lysate containing the intracellular protein fractions, **2** could be detected implicating enzymatic assistance in this coupling. The direct coupling of **1** and **123** still requires a reduction step to generate curindolizine and thus it was not clear to us if nature's pathway involves the sequence shown in Figure 5 or one involving allylic alcohol **17**, the previously speculated biosynthetic intermediate from *B. maydis* and a possible Friedel–Crafts (rather than Michael) coupling partner (Figure 6). We developed simple chemistry to

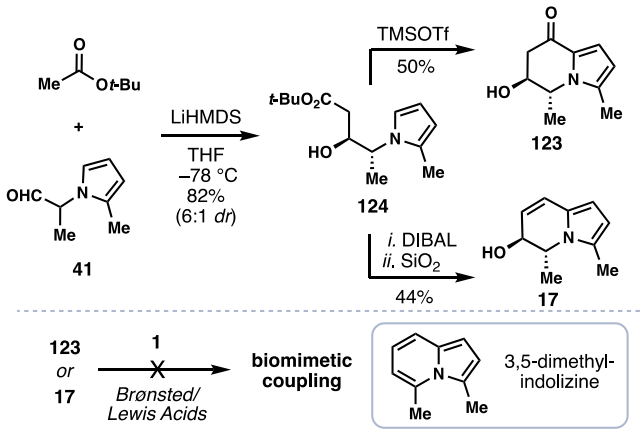

Figure 6. Preparation and reactivity of candidate biosynthetic coupling partners.

access both **17** and **123** based largely on our unsuccessful initial attempts to synthesize **1** via bioinspired strategies. An aldol reaction between methyl *tert*-butyl acetate and aldehyde **41** first generated **124** (82%, 6:1 *dr*). Mild Friedel–Crafts acylation of this material (TMSOTf) then generated procuramine (**123**) in 50% yield. Alternatively, **124** could be reduced with DIBAL generating an aldehyde which cyclized and dehydrated in the presence of silica gel to yield **17** (44%). Unfortunately attempts to merge either **17** or **123** with curvulamine (**1**) under acidic conditions have not yielded coupled products to date (Figure 6). Moreover, reacting **1** with other activated α,β-unsaturated carbonyls such as acylate systems or cyclohexenone has not demonstrated the feasibility of productive Michael addition chemistry at the desired pyrrole position—only recovered starting material or decomposition is observed in the presence of Brønsted or Lewis acids. Similarly, attempts at coupling **17** with **1** have only led to aromatization of **17** forming 3,5-dimethylindolizine. Against this backdrop, we investigated nonbiomimetic strategies to access this complex family member (Scheme 7).

While a logical solution to the coupling problem would be to simply halogenate **1** and explore various C–C bond-forming reactions, the locus of reactivity with electrophilic reagents in this multiheterocyclic system lies at the vinyl pyrrole group.[49] Fortunately, previously prepared tetracycle **112** (prepared in 5 steps on a gram scale) underwent very clean iodination to yield iodide **124** in 88% yield (Scheme 7). Presumably this is the least-hindered position on the more electron-rich pyrrole ring. A Ce(III)-mediated addition of lithiated ethyl vinyl ether to this material then gave **125** after *in situ* silylation (TMSCl). Iodide **125** could be converted into an organozinc reagent (*t*-BuLi *then* $ZnCl_2$) and subjected to Pd-catalyzed Negishi coupling with racemic triflate **126** to yield a separable mixture of diastereomeric products (see **127** and **128**) in 80% combined yield.[50] The desired isomer (**128**) could then be stereoselectively reduced by samarium iodide to generate ester **129** as essentially a single compound. Gratifyingly the relative relationship between this newly formed stereocenter and the adjacent methyl group is as found in **2**.[51] A similar four-step sequence as the one employed in the synthesis of **1**, namely (*i*) thermodynamic equilibration of the methyl-containing stereocenter, (*ii*) thiocarbamate formation, (*iii*) deoxygenation, and (*iv*) CBS reduction proceeded uneventfully in this setting, thereby advancing (±)-**129** into (−)-**130**. In the final step of the synthesis, and in analogy to the preparation of **17**, careful DIBAL reduction of this material generated an aldehyde which cyclized directly to (+)-curindolizine (**2**) in 70% yield, thus completing the first synthesis of this complex trimeric alkaloid in 14 steps.

DISCUSSION

In this article, we have chronicled the evolution of a total synthetic strategy toward complex polypyrrole alkaloids from *Curvularia* sp. fungi resulting in a 10-step total synthesis of curvulamine (**1**) and 14-step route to curindolizine (**2**). Given their unprecedented chemical structures and mysterious biosynthetic origins, a variety of approaches were brought to bear on this synthetic problem. Throughout each planning stage though, effort was made to explore and exploit the innate reactivity of the electron-rich pyrrole nucleus.[52] Indeed, we

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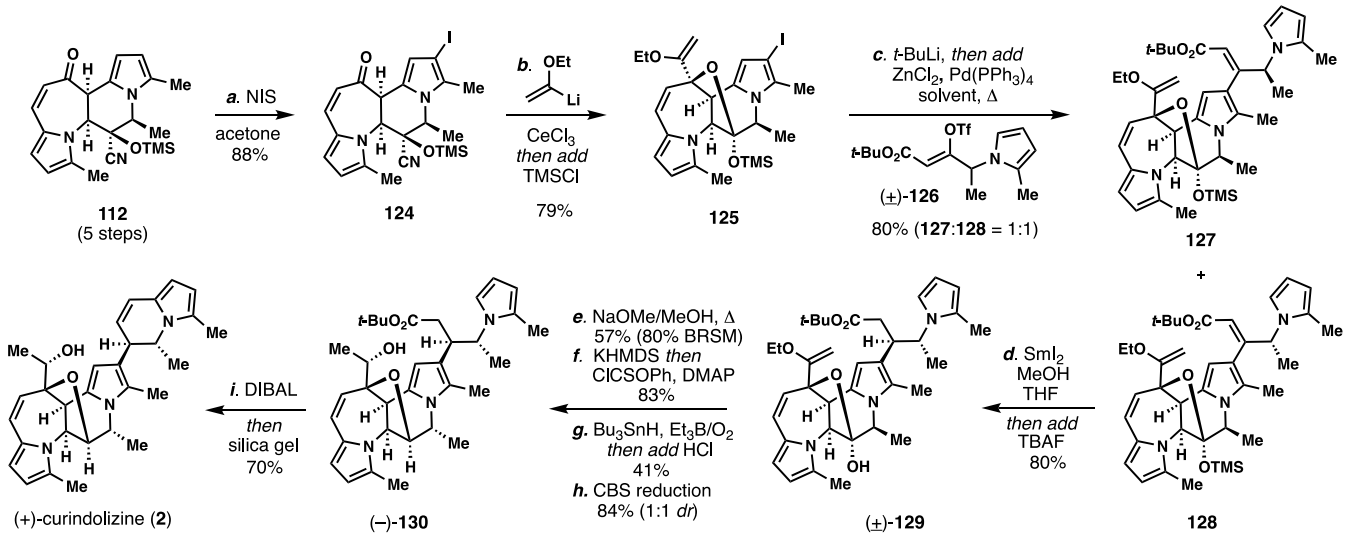
Scheme 7. Total Synthesis of Curindolizine



[a]Reagents and conditions: (a) NIS (1.05 equiv), acetone, 0 °C, 30 min, 88%; (b) ethyl vinyl ether (5.5 equiv), *t*-BuLi (5.0 equiv), THF, −78 to 0 °C, 30 min, *then add* $CeCl_3$ (5.0 equiv), 25 °C, 1 h, *then add* **124**, −78 °C, 1 h, *then add* TMSCl (5.0 equiv), −78 °C, 30 min, 79%; (c) **125** (1.0 equiv), *t*-BuLi (2.5 equiv), THF, −78 °C, 30 min, *then add* $ZnCl_2$ (3.0 equiv), −78 °C, 1 h, *then add* $Pd(PPh_3)_4$ (0.03 equiv), (±)-**126** (2.0 equiv), 25 °C, 6 h, 80% (**127**:**128** = 1:1); (d) SmI_2 (2.0 equiv), THF/MeOH = 9/1, 0 °C, 30 min, *then add* TBAF (2.0 equiv), 25 °C, 30 min, 80%; (e) NaOMe (5.0 equiv), MeOH, 90 °C, 1 h, 57% (80% BRSM); (f) KHMDS (1.2 equiv), −78 °C, 30 min; *then add* DMAP (2.0 equiv), Phenyl chlorothionoformate (2.0 equiv), THF, −78 °C, 1 h, 83%; (g) $HSnBu_3$ (2.0 equiv), BEt_3 (1.0 equiv), O_2, THF, 45 °C, 1 h, *then add aq.* HCl, 0 °C, 30 min, 41%; (h) (*R*)-2-methyl-CBS-oxazaborolidine (1.0 equiv), BH_3·DMS (2.0 equiv), DCM, 23 °C, 1 h, 42% (−)-**130** + 42% (+)-12-*epi*-**130**; (i) DIBAL (5.0 equiv), DCM, −78 °C, 30 min, *then add* silica gel, 5 min, 70%.

have observed the pyrrole as a nucleophile, radical acceptor, and electrophile (as part of several azafulvenium ions encountered) in the course of our studies. While many of the synthetic intermediates described herein proved challenging to work with from a technical perspective (i.e., air and acid sensitivity), we were rewarded by beholding their interesting and unexpected reactivity in a novel chemical architecture. During our studies we also developed an improved synthesis of pyrroloazepinones, which should find broader use in heterocyclic chemistry, as well as expanded the knowledge base surrounding the reactivity of this exotic 10π-electron heteroaromatic. Finally, we developed a route to curindolizine, despite being unable to elicit a direct, biomimetic coupling of $(C_{10}N)_2$ and $C_{10}N$ fragments. While not demonstrated herein, we believe our finding can also enable routes to bipolamine-type metabolites as well as facilitate a greater understanding of the antibacterial properties of these alkaloids. Such investigations are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c13465.

Experimental procedures and spectroscopic data (PDF)

Accession Codes

CCDC 2059551−2059556 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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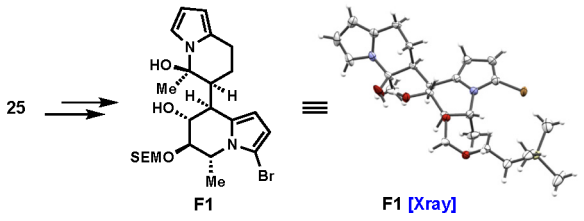
(9) See the Supporting Information for synthetic preparation

(10) These compounds were quite sensitive to silica gel purification and the individual isomers could not be separated by careful chromatography.

(11) For the addition of a silyl ketene thioacetal to an azafulvenium ion, see ref 2b.

(12) In a model study lacking the pyrrole C2 methyl group, we advanced compound **25** along similar lines as **28** (see SI for synthetic details). Upon unveiling the free pyrrole nitrogen, we found the product (see **F1** below) exists as a stable hemiaminal that also thwarted cyclization attempts.



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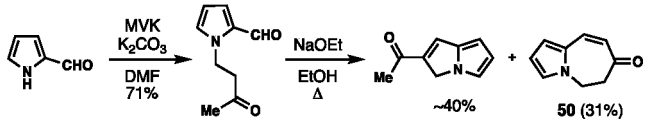
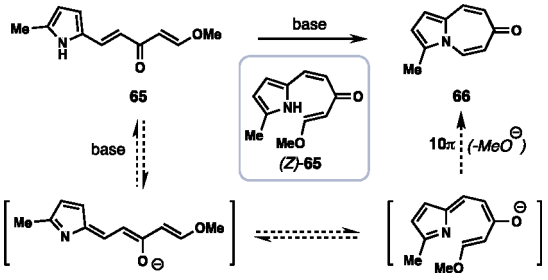
(24) The Robinson annulation favors 5-membered (pyrrolizine) ring formation as shown below:



(25) Several plausible mechanisms can be envisioned for the cyclization of **65** to **66** including conjugate addition/elimination of the pyrrole anion of (*Z*)-**65** or a 10π-electrocyclization as show below. We note that (*Z*)-**65** has been isolated from many of the cyclization reaction mixtures.



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(26) While **63** and **64** could be directly converted into **66** in a single step using NaO*t*-Bu in THF (~30% yield on 0.5 mmol scale), this reaction afforded only ~10% yield on a gram scale.
(27) This selectivity was only observed under conditions employing a weakly bound potassium counterion (KHMDS) and highly polar additive (HMPA). Although somewhat unstable, products tentatively arising from C9 attack were observed in initial experiments using LHMDS as base in THF (without HMPA). C5 selectivity (over C9) cannot be rationalized by the LUMO orbital coefficients of **66**, or steric effects, but the natural charge (and Mulliken charge) of C5 is positive, while the C1 and C9 carbons are negative, suggesting the importance of Coulombic factors in this process.
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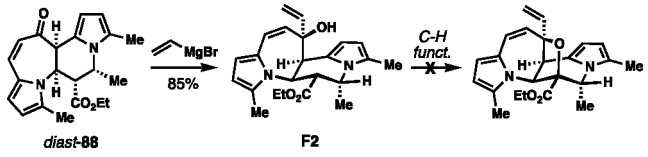

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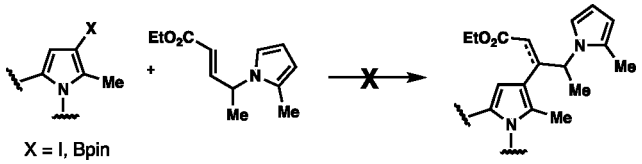
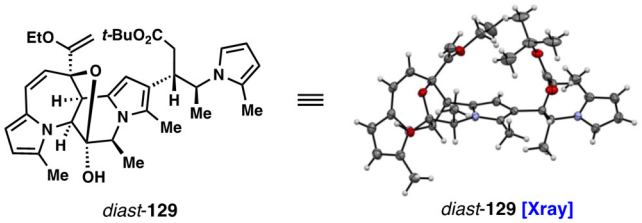
(49) Treating **1** with NBS for example leads to dibromination of the alkene and not bromination of the desired pyrrole. These addition products are also highly unstable and could not be manipulated further.
(50) A number of additional reaction manifolds, including cuprate conjugate addition, Heck reaction, and Hayashi−Miyaura coupling, were explored to couple the fragments below but were uniformly unsuccessful.



(51) In addition to successfully completing the total synthesis of **2**, an X-ray crystal structure of the samarium iodide reduction product of isomer **127** was obtained (see *diast*-**129** below) and allowed us to deduce which isomer to carry forward.



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