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A unified strategy to reverse-prenylated indole alkaloids: total syntheses of preparaherquamide, premalbrancheamide, and (+)-VM-55599†‡

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A full account of our studies toward reverse-prenylated indole alkaloids that contain a bicyclo[2.2.2]core is described. A divergent route is reported which has resulted in the synthesis of preparaherquamide, (+)-VM-55599, and premalbrancheamide. An intramolecular Dieckmann cyclization between an enolate and isocyanate was used to forge the bicyclo[2.2.2]diazaoctane core that is characteristic of these molecules. The pentacyclic indole scaffold was constructed through a one-pot Hofmann rearrangement followed by Fischer indole synthesis. The utilization of our previously reported indole peripheral functionalization strategy also led to natural products including malbrancheamides B, C, stephacidin A, notoamides F, I and R, aspergamide B, and waikialoid A. Ultimately, the divergent route that we devised provided access to a wide range of prenylated indole alkaloids that are differently substituted on the cyclic amine core.

Introduction

Secondary metabolites isolated from fungi of the genera *Penicillium* and *Aspergillus* continue to attract the interest of the chemical synthesis community because of their structural complexity and diverse biological activity. Among these natural products are a series of reverse-prenylated indole alkaloids that exhibit a wide range of bioactivity including, but not limited to, insecticidal, cytotoxic, anthelmintic, and anti-bacterial properties.[1] Representative of this group are the paraherquamides (*e.g.*, **2**, Fig. 1), stephacidins (*e.g.*, **5**), and marcfortines (*e.g.*, **7**), all of which possess a bicyclo[2.2.2]diazaoctane core ring system (highlighted in red in **1**). Structurally, members of this group are comprised of two amino acids, tryptophan (highlighted in blue in **2**) and proline or isoleucine (highlighted in maroon in **3** and **6**, respectively). These core motifs are in turn reverse-prenylated (highlighted in green in **5**).

The different substitution and oxidation patterns present on the core framework of these indole alkaloids, along with their intriguing biogenesis, has spurred numerous synthetic campaigns to prepare them. Prior synthetic strategies can be organized around the construction of the bicyclo[2.2.2]diazaoctane core (Fig. 1B).[2] For example, Williams and co-workers employed a biomimetic intramolecular Diels–Alder reaction to construct the bicyclo ring system en route to (−)-VM5599, *rac*-pre-paraherquamide, *rac*-marcfortine C, and (+) and (−)-versicolamide B (forming C_{22}–C_6 and C_4–C_5, Fig. 1B) and recently, Lawrence and co-workers leveraged a similar bioinspired approach to access (+)-brevianamide A.[2] Notably,

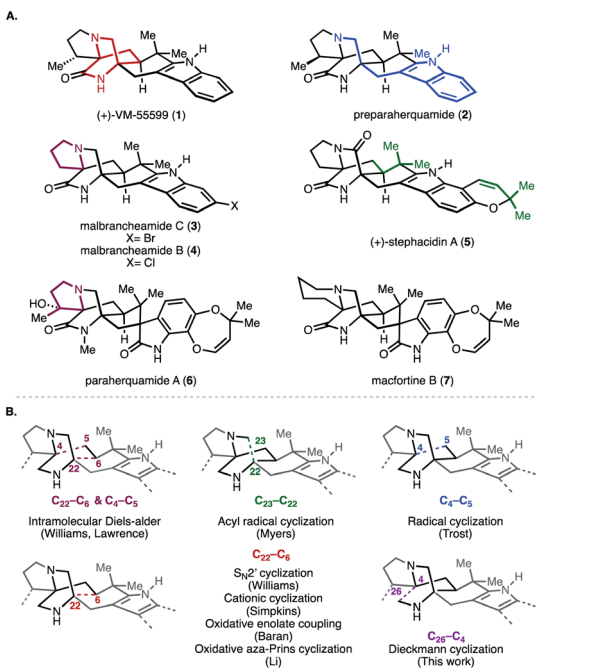

Fig. 1 (A) Selected reverse-prenylated indole alkaloids. (B) Previous approaches to construct the bicyclo[2.2.2]diazaoctane ring system of reverse-prenylated indole alkaloids core. Numbering is based on stephacidin A.

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† Dedicated to the memory of Prof. Robert M. Williams (1953–2020).

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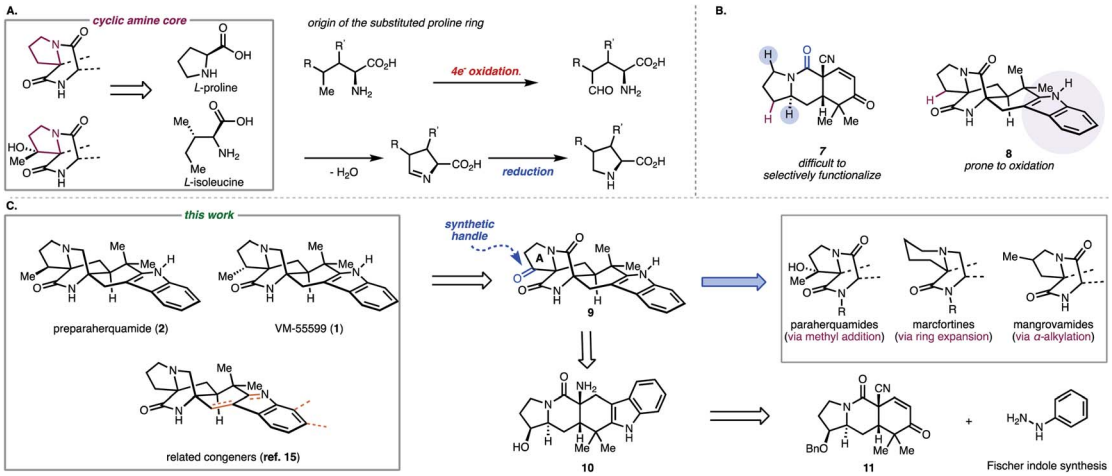


Fig. 2 (A) Origin of cyclic amine core; (B) unsuccessful approaches; (C) retrosynthetic plan for a unified synthesis of reverse prenylated indole alkaloids.

a complementary strategy employed by Williams and co-workers featured an intramolecular S_N2' cyclization in the syntheses of brevianamide B, (−)-paraherquamide A, (+)-paraherquamide B, stephacidins A and B, notoamide B, and avrainvillamide (forming C_{22}–C_6, Fig. 1B).[3] Inspired by the seminal reports of the Mislow and Saegusa laboratories as well as previous work from their own laboratories, Baran and co-workers utilized an oxidative enolate coupling strategy to achieve the first total synthesis of stephacidin A (forming C_{22}–C_6, Fig. 1B).[4] Further oxidative elaboration also resulted in syntheses of avrainvillamide and stephacidin B.[4] Other strategies have relied on cationic, radical, acyl radical, and oxidative aza-Prins cyclizations (Fig. 1B).[5–8]

Despite the existing elegant strategies to access specific congeners within this family of natural products, a unified approach to access prenylated indole alkaloids that either possess or lack additional substituents on the cyclic amine ring (highlighted in maroon in Fig. 2A and labelled ring A in Fig. 2C for clarity) of the hexacyclic framework remained an outstanding challenge.[9] Biosynthetically (Fig. 2A), natural products like paraherquamide A (**6**), which contain a methylproline residue (R′ = Me), are proposed to arise from a 4-electron oxidation of isoleucine to furnish an aldehyde intermediate which undergoes reductive amination.[10,11] Alternatively, congeners like stephacidin A, which feature no substituents on the cyclic amine core, are derived from L-proline. Synthetically, it became evident that adhering to a bioinspired approach would require a series of challenging site selective late-stage oxidations in order to access each member of this reverse-prenylated indole alkaloid family (Fig. 2B).[10,11] For example, issues of chemoselectivity were encountered in our own work with previously reported amide **7** and late-stage oxidation in the presence of the indole moiety proved difficult (**8** in Fig. 2B).[12–14] Given the aforementioned challenges and strategic value of divergent total synthesis for accessing related synthetic targets, a route was designed to leverage a versatile common intermediate (**9**, Fig. 2C) which contains a ketone as a synthetic handle on ring A for diversification. Because ketones engage in a plethora of organic reactions, we envisioned using the diverse reactivity of the carbonyl group to perform either late-stage nucleophilic additions to access members within the paraherquamide family, ring expansion to access macfortine natural products, or leverage enolate chemistry to access the mangrovamides. Another strategic design element embedded in the versatile common intermediate (**9**) is the unsubstituted indole motif, which was selected to maximize access to the diverse indole substitution patterns characteristic of the reverse-prenylated indole alkaloids through late-stage indole C–H functionalization.

From **9**, the bicyclo[2.2.2]diazaoctane structural motif could also be constructed using a similar strategy to our previously reported Dieckmann-type cyclization.[13] Pentacyclic indole **10** was envisioned to arise from our previously reported tricyclic intermediate **11** and phenyl hydrazine by Fischer indole synthesis.[13]

Results and discussion

Our initial approach centered around a one-pot protocol for the construction of the bicyclo[2.2.2]diazaoctane core. It was envisioned that a Hofmann rearrangement performed in the absence of any external nucleophiles would generate isocyanate **13** *in situ*, which could be intercepted by an attendant enol or enolate, through an intramolecular cyclization, to provide the bicyclo[2.2.2]diazaoctane ring (see **9**) in a single-pot transformation.[16] In order to explore the feasibility of this one-pot Hofmann/cyclization event, access to pentacyclic indole **12** was required. We commenced our synthetic studies with enone **11**, which is available in gram-scale quantities (9 steps, 37% overall yield) from commercially available 1-*tert*-butyl 2-ethyl 3-oxopyrrolidine-1,2-dicarboxylate (Fig. 3B; see S1 in the ESI‡).[13] Following hydrogenation of enone **11** using Pd/C, treatment with BBr_3 effected cleavage of the benzyl group to provide ketone **14**.[13] Treatment of ketone **14** with phenyl hydrazine in

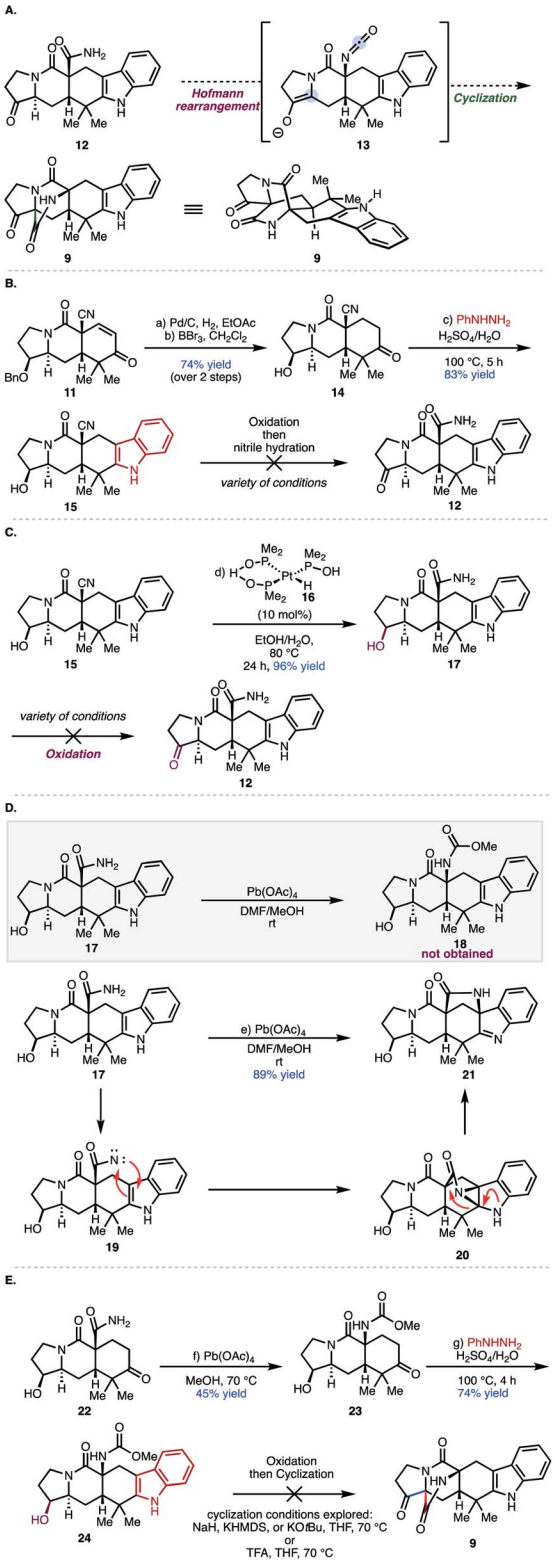
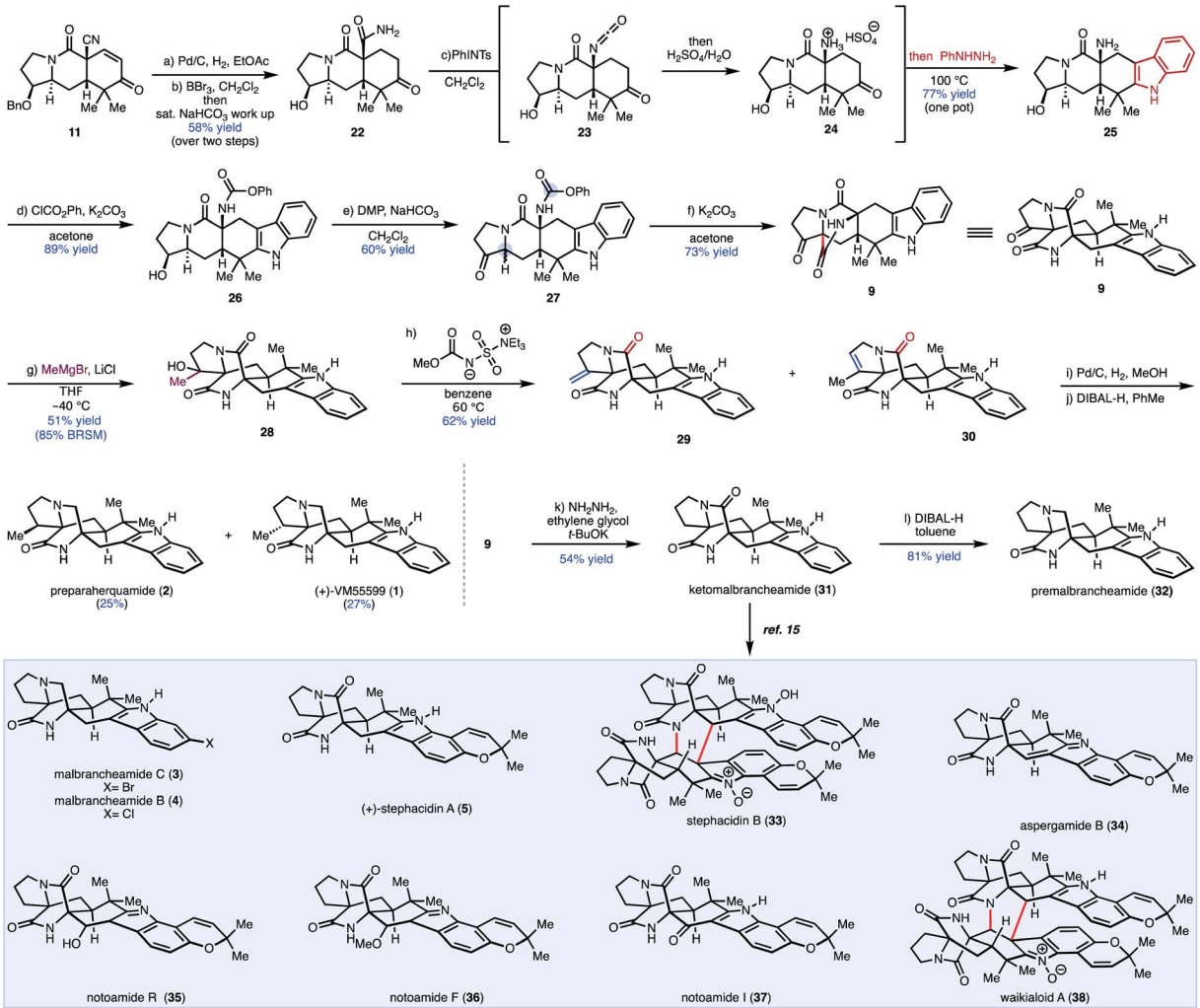


Fig. 3 (A) Proposed one-pot construction of [2.2.2]-diazaoctane core; (B) attempts at synthesizing amide **12**; (C) failed oxidation of **17**; (D) formation of [3.2.1] bicycle **21**. (E) attempted oxidation and cyclization of methyl-carbamate **24**; conditions: (a) Pd/C (10 wt%), H_2, EtOAc, rt, 16 h; (b) BBr_3, (4.6 equiv.), CH_2Cl_2, −78 °C, 15 min, 74% yield over 2 steps; (c) $PhNHNH_2$ (4 equiv.), H_2SO_4/H_2O (5% v/v), 100 °C, 5 h, 83% yield (d) **16** (10 mol%), $EtOH/H_2O$, 24 h, 96% yield (e) $Pb(OAc)_4$ (2 equiv.), DMF/MeOH, 2 h, rt, 89% yield (f) $Pb(OAc)_4$ (5 equiv.), MeOH, 3.5 h, 70 °C, 45% yield (g) $PhNHNH_2$ (4 equiv.), H_2SO_4/H_2O (5% v/v), 100 °C, 4 h, 74% yield.

aqueous sulfuric acid at 100 °C afforded pentacyclic indole **15** in 83% yield. Oxidation of the secondary alcohol group with Dess–Martin periodinane (DMP) gave the desired ketone (not shown) as an inseparable mixture of diastereomers in a 1 : 2 ratio (α : β epimers) that was taken directly to the next reaction because of stability issues. The use of the Ghaffar–Parkins platinum complex failed to provide any desired hydrated product (**12**) and led to a complex product distribution.[17] An alternative procedure for nitrile hydration reported by Lee and co-workers using Wilkinson's catalyst and acetaldoxime in toluene at reflux led only to decomposition of starting material.[18] Presumably, the enol (not shown) can compete for the binding site of the metal center in these cases leading to decomposition pathways. Given the difficulty in performing the nitrile hydration after oxidation of **15**, an alternative sequence was explored. Nitrile **15** was hydrated with the Ghaffar–Parkins complex (**16**) to provide primary amide **17** in 96% yield. At this stage, traditional oxidation methods were explored, which led to either decomposition, low yields, or recovered starting material (Fig. 3B; see the ESI‡ for further details). Presumably, the presence of the nucleophilic primary amide in **17** adversely affected the oxidation of the secondary alcohol group. Because of the issues with functional group incompatibility, Hofmann rearrangement prior to oxidation of the secondary alcohol was explored. With alcohol carboxamide **17** in hand, conditions to effect the Hofmann rearrangement were investigated (see Fig. 3D). Treating **17** with phenyliodoso-trifluoromethyl acetate (PIFA) resulted in decomposition of the starting material. Interestingly, treating carboxamide **17** with $Pb(OAc)_4$ in a mixture of DMF/MeOH at room temperature, resulted in the formation of [3.2.1] bicycle **21** as the sole product of the reaction in 89% yield instead of the expected methyl carbamate (**18**). Presumably, this [3.2.1] bicyclic system arises from an initial oxidation of the primary carboxamide to generate the *N*-acyl nitrene (**19**), which then interacts with the indole C2–C3 double bond forming aziridine **20**. The indole nitrogen then facilitates opening of the aziridine at the C2 position, driven by release of ring strain (as shown by the red arrows). A proton transfer then delivers **21**. Interestingly, while reminiscent of aspeverin,[19] this unique ring system does not translate to any natural product scaffolds that have been reported to date. On the basis of these results, the Hofmann rearrangement would have to be accomplished prior to the installation of the indole moiety in order to avoid the formation of [3.2.1] bicycle **21**.

Following from our prior studies, it was determined that $Pb(OAc)_4$ in the presence of MeOH at room temperature was optimal for mediating the desired transformation to provide the methyl carbamate (**23**, Fig. 3E) accompanied by varying amounts of recovered starting material. After some optimization, it was established that elevated temperatures (70 °C) were required to attain full conversion of the starting material. However, reaction yields dropped dramatically upon scale-up and over 6 equivalents of $Pb(OAc)_4$ were required to achieve complete consumption of the starting material. Nevertheless, methyl carbamate **23** was advanced through the Fischer indole synthesis to provide indole **24** in 74% yield. Subsequent oxidation with Dess–Martin periodinane (DMP) provided the



Scheme 1 Synthesis of preparaherquamide (**2**), (+)-VM-55599 (**1**), ketomalbrancheamide (**31**), premalbrancheamide (**32**) and related congeners. (a) Pd/C (10 wt%), H_2, EtOAc, rt, 16 h; (b) BBr_3, (7.1 equiv.), CH_2Cl_2, −78 °C, 15 min then $NaHCO_3$ (saturated aqueous), 24 h, 58% yield over 2 steps; (d) PhINTs (1.2 equiv.), CH_2Cl_2, rt, 2 h then H_2SO_4/H_2O (5% v/v), 50 °C, 1 h; then $PhNHNH_2$ (4 equiv.), 100 °C, 16 h, 77% yield (over 3 steps; one-pot) (e) $ClCO_2Ph$ (2.4 equiv.), K_2CO_3 (2 equiv.), acetone, rt, 8h, 89% yield. (e) DMP (1.5 equiv.), CH_2Cl_2, rt, 20 min, 60% yield; (f) K_2CO_3 (2 equiv.), acetone, 50 °C, 2 h, 74% yield; (g) MeMgBr (20 equiv.), LiCl (3 equiv.), THF, −40 °C, 2 h, 51% yield (85% BRSM) (h) Burgess reagent (10 equiv.), benzene, 60 °C, 2h, 63% yield (i) Pd/C (10 wt%), H_2 (450 Psi), MeOH, rt, 16 h (j) DIBAL-H (19 equiv.), toluene, 0 °C to rt, 25% yield of **2** and 27% yield of **1**. (k) NH_2NH_2 (1.1 equiv.), ethylene glycol, 70 °C, 17 h, then *t*-BuOK (5.0 equiv.), 170 °C, 2 h, 57% yield. (l) DIBAL-H (20 equiv.), toluene, 0 °C to rt, 81% yield. DMP = Dess–Martin periodinane. BRSM = Based on recovered starting material.

desired ketone precursor (after oxidation of secondary alcohol highlighted in maroon), which was predisposed for the late-stage Dieckmann cyclization to afford the bicyclo[2.2.2]diazaoctane core. Unfortunately, treatment with a variety of bases (NaH, KHMDS, or KO^{t}Bu) or acid (*e.g.*, TFA), were unsuccessful in providing the desired bicyclo[2.2.2] product (**9**). Presumably, the methyl carbamate is not sufficiently electrophilic for the cyclization step and/or the methoxide nucleofuge may subsequently serve as a better nucleophile in an undesired irreversible direction (cleaving the bond highlighted in blue in **9**; Fig. 3E), leading to decomposition. Therefore, the installation of different carbamates was explored; carbamates bearing better leaving groups, such as phenols and polyfluoroalcohols, and thus less nucleophilic nucleofuges, emerged as an attractive option to minimize decomposition pathways.

Ultimately, a one-pot protocol was developed to access pentacyclic indole **25** (Scheme 1). It is worth noting that a modified work up procedure yielded two-step access to primary amide **22** from enone **11** and obviated the need for transition metal-catalyzed nitrile hydration. From **22**, Hofmann rearrangement of the carboxamide was effected under mild conditions using (tosylimino)phenyl-λ^3-iodane (PhINTs).[20] Upon treatment with aqueous acid, the resulting isocyanate (**23**) was converted to the corresponding ammonium intermediate (**24**), which was directly subjected to phenylhydrazine to effect Fischer indolization, providing pentacyclic indole **25** in a single-pot operation from **22**. Chemoselective amine carbamoylation of **25** in the presence of a secondary hydroxy group was achieved in high yield with phenyl chloroformate to afford phenyl carbamate **26**. Oxidation of secondary alcohol **26** provided desired cyclization

precursor **27**. Treatment of **27** with K_2CO_3 in acetone yielded the bicyclo[2.2.2]diazaoctane core, presumably through Dieckmann cyclization of an intermediate enolate (generated from the ketone group) and the isocyanate group (generated *in situ* from the phenyl carbamate under basic conditions).[13,21] Notably, the bicyclo[2.2.2]diazaoctane core was constructed in 5 steps from **11**, which is an improvement over our prior work (10 steps from **11** in that case) and provides access to a wider range of congeners by leveraging the unsubstituted indole motif (*vide infra*).[13]

The syntheses of preparaherquamide and (+)-VM55599 were accomplished through a four-step sequence that installed the requisite functionality on the five-membered ring (Scheme 1). Initial efforts toward olefination of ketone **9** were unsuccessful as Wittig olefinations lead to recovered starting material. A two-step nucleophilic addition followed by alcohol elimination was explored. For example, MeMgBr addition afforded tertiary alcohol **28** in low yields with significant recovered starting material. Presumably, side reactions like alpha deprotonation (enolization) result in low conversion. Re-subjecting the crude mixture to another cycle led to 48% yield of the desired tertiary alcohol (**28**). Efforts to attenuate the basicity of the Grignard reagent were unsuccessful as addition of cerium(III) chloride did not improve conversion and ultimately, it was found that the addition of LiCl led to a 51% yield (85% BRSM) of the desired tertiary alcohol **28**.[22] Treatment of **28** with the Burgess reagent gave a mixture of exocyclic (**29**) and endocyclic (**30**) alkenes in 71% yield (1 : 2 mixture). Hydrogenation of the mixture of alkenes (*i.e.*, **29** and **30**) using Pd/C, followed by chemoselective tertiary amide reduction with DIBAL-H, afforded epimeric natural products preparaherquamide (**2**) and (+)-VM-55599 (**1**) in 25% and 27% yield, respectively.

Having successfully accessed natural products bearing substituents on the pyrrolidine ring (ring A), we turned our efforts toward congeners derived from L-proline to showcase the utility of our unified approach (Scheme 1). Notably, from **9**, indole alkaloids lacking substituents on ring A can be accessed through sequential reduction processes. For example, Wolff–Kishner reduction of the pyrrolidone ketone group in **9** yielded ketopremalbrancheamide (**31**, Scheme 1). From ketopremalbrancheamide, premalbrancheamide (**32**) was synthesized according to the precedent of Williams and co-workers.[23,24] Thus, treating **31** with an excess of DIBAL-H effected chemoselective reduction of the tertiary amide. On the basis of our prior work on indole functionalization, ketomalbrancheamide (**31**) can be elaborated to malbrancheamides B and C, as well as stephacidins A and B, waikialoid A, aspergamide B, and finally notoamides F, I, and R.[15]

Conclusions

In conclusion, a unified approach was developed to access hexacyclic indole alkaloids that either possess or lack substituents on the cyclic amine. Specifically, studies that culminated in the total syntheses of (+)-VM55599 (**1**), preparaherquamide (**2**), and premalbrancheamide (**31**) as well access to ketomalbrancheamide (**32**) which can be elaborated to malbrancheamides B, C, stephacidin A, notoamides F, I and R, aspergamide B, and waikialoid A through our previously reported peripheral indole functionalization strategy is reported. This work serves as a blueprint for a unified approach to the synthesis of reverse-prenylated indole alkaloids possessing a bicyclo[2.2.2]diazaoctane core by addressing a key challenge posed by the diverse range of substitution found on the cyclic amine ring of the core framework. Our modular strategy hinged on leveraging a late-stage intermediate possessing a synthetic handle as well as rapid construction of the pentacyclic indole skeleton through a one-pot Hofmann rearrangement and Fischer indole synthesis.

Conflicts of interest

There are no conflicts to declare.

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