Unified approach to prenylated indole alkaloids: total syntheses of \((-\)-17-hydroxy-citrinalin B, \((+)-\text{stephacidin A, and } (+)-\text{notoamide I}\)^†

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A unified strategy for the synthesis of congeners of the prenylated indole alkaloids is presented. This strategy has yielded the first synthesis of the natural product \((-\)-17-hydroxy-citrinalin B as well as syntheses of \((+)-\text{stephacidin A and } (+)-\text{notoamide I. An enolate addition to an } in\text{ situ } generated\text{ isocyanate was utilized in forging a key bicyclo[2.2.2]diazaoctane moiety, and in this way connected the two structural classes of the prenylated indole alkaloids through synthesis.}

**Introduction**

Historically, the undertaking of total syntheses of natural products has focused on ‘target-oriented’ syntheses whereby a single compound is targeted for synthesis to investigate its biological relevance or aspects of its structure.\(^1\) This practice has inspired many new synthesis developments. Recently, however, exercises in complex molecule total synthesis are placing a growing emphasis on the preparation of diverse molecular skeletons from a common intermediate.\(^2\) This practice, which mirrors the biological production of many secondary metabolites but does not necessarily follow along biosynthetic lines, maximizes the opportunities for, and efficiency of, accessing molecular diversity to facilitate structure–activity relationship studies. Over the last 30 years, this concept has led to remarkable unified strategies for the syntheses of various families of natural products.\(^3\) Here, we present the extension of this idea to the syntheses of congeners in the prenylated indole alkaloid family which features a powerful Dieckmann-type cyclization to forge a key \([2.2.2]\)bicycle.

The prenylated indole alkaloids include some of the most structurally diverse secondary metabolites isolated to date (see Fig. 1 for selected examples). Many congeners such as stephacidin A (1), notoamide I (2), mangroavamide A (3) and parapherquamide A (4) contain a bicyclo[2.2.2]diazaoctane structural moiety.\(^4\) Over the last decade however, additional members of the family that lack the bicyclo[2.2.2]diazaoctane core have begun to emerge. This includes the citralins (e.g., 5), citrinadins (e.g., 9) and the cyclopamines (e.g., 8 – albeit isolated in 1979).\(^3\) While myriad bioactivity has been discovered for various prenylated indole alkaloids (especially anthelmintic activity),\(^4\) the recent emergence of the citralins and related compounds\(^5\) that lack the bicyclo[2.2.2]diazaoctane structural motif as potent anti-tumor compounds has heightened interest in the whole family of secondary metabolites.

**Results and discussion**

From our perspective, a unified synthetic approach that affords prenylated indole alkaloid congeners bearing the bicyclo[2.2.2] diazaoctane core as well as those lacking this structural moiety would provide the most strategically efficient approach to these natural products. However, to date, such an approach has not been reported. All the existing syntheses of this family of molecules have targeted either the subset that contains the \([2.2.2]\) diazaoctane bicycle or those molecules that lack this...
structural feature. In this manuscript, we present our studies toward identifying a common intermediate that can be advanced to natural products representative of both prenylated indole alkaloid structural motifs. These studies have led to the identification of 10 (Scheme 1) as such a common intermediate, which now provides the first total synthesis of (−)-17-hydroxy-citralin B (7) as well as a synthesis of (+)-stephacidin A (1) and (+)-notoamide I (2). Our synthetic strategy to these two natural products, which rests on ‘network analysis’ considerations, diverges only at a late stage. Thus, strategic bond disconnection of the maximally bridging ring in, for example, 1 (i.e., the 2,5-diketopiperazine ring) leads back to carbamate 10, where a bond can be formed at a late stage between C16 and the carbamate carbonyl group. In this way, the two sub-families of the prenylated indole alkaloids (e.g., 1 and 7) can be connected by a synthesis sequence characterized by a progressive increase in structural complexity, which distinguishes this approach from prior syntheses of related prenylated indole alkaloids. Hexacycle 10 can in turn arise from tricycle 11 using an indole annulation reaction, which would provide opportunities to prepare other natural products such as paraherquamide A (4) that differ in their indole substitution pattern.

A general strategy for the synthesis of the prenylated indole alkaloids that encompasses the two main structural types (of which 1 and 7 are representative) has not been explored before. In all of the previous syntheses of the bicyclo[2.2.2]diazaoctane bearing congeners, the tetrasubstituted center at C4 – stephacidin numbering – in 1) is constructed at an early stage or through C4–C5 bond formation, which would necessitate its late-stage cleavage (in a complexity minimizing manipulation) in order to form compounds such as 7 from 1. In this latter scenario, an amide hydrolysis of the bicyclo[2.2.2]diazaoctane, decarboxylation, and a diastereoselective protonation at the ring junction (the diastereoselectivity of which is not certain outside of an enzyme pocket) would be required for a conversion of 1 to the sub-family that lacks the diazaoctane structural motif. Our approach to this collection of molecules is complementary.

Synthesis of divergent intermediate 23

Our studies commenced with the preparation of 11 (Scheme 2), which is available in 6 steps from known enantioenriched alcohol 12. Analogous to our previously established sequence, oxidation of the alcohol group of 12 and alkynylation-homologation of the resulting aldehyde using the Ohira–Bestmann reagent (13) affords an alkyne, which upon Boc cleavage and acylation with α-cyano acetyl chloride gives alkyne 14. A formal cycloisomerization of 14, presumably proceeding by anti-Markovnikov hydration of the terminal alkyne followed by Knoevenagel condensation of the incipient aldehyde, was effected using the Grotjahn complex (15) to yield bicycle 16. Diels–Alder cycloaddition of 16 with diene 17, facilitated by SnCl4, gives enone 11 upon basic workup. Even though we had previously accomplished the analogous synthesis of a tricycle lacking the benzyloxy group at C17 (see numbering in 11), it was unclear what influence this added substituent would exert on the diastereoselectivity of the cycloaddition step and so we were gratified to obtain diastereomer 11 in good yield. The structure of 11 is supported by the X-ray structure of keto-alcohol 18 (see 42[C]view in Scheme 2), which we obtained following hydroge- nation and BBr3-mediated cleavage of the benzyl group of 11.

A Johnson iodination of 11 (Scheme 3), followed by hydration of the nitrile group using the Ghaffar–Parkins complex (19) and subsequent Hofmann rearrangement of the resulting carboxamide using phenylidodos trifluoromethyl acetate (PIFA) in the presence of methanol provided carbamate 20. Following the precedent of Myers and Herzon, Suzuki cross-coupling of iodide 20 with pinacol boronic ester 21 followed by reductive cyclization yielded indole annulated hexacycle 22. At this stage, Wacker oxidation of the chromene moiety and treatment of the resulting chromanone with dimethyl sulfide in the presence of methane sulfonic acid unveiled the amine and hydroxyl groups to provide 23, which would serve as the common intermediate to access both 17-hydroxy-citralin B as well as stephacidin A. Of note, while the synthesis of 17-hydroxy-citralin B would serve as the common intermediate to access both 17-hydroxy-citralin B as well as stephacidin A, we lacked the benzyloxy group at C17 (see numbering in 11), it was unclear what influence this added substituent would exert on the diastereoselectivity of the cycloaddition step.

Scheme 2 Preparation of 11. (a) DMP (1.1 equiv.), NaHCO3, CH3Cl2, 0 °C to rt, 2.5 h, >87%; (b) 13 (1.5 equiv.), NaOMe (5.0 equiv.), THF, –78 °C to –50 °C, 2 h, 91%; (c) 4 N HCl/dioxane (4.0 equiv.), 0 °C to rt, 30 min; concentrate; then cyanoacetyl chloride (2.5 equiv.), Et3N (2.5 equiv.), 0 °C to rt, 3 h, 75%; (d) 15 (8 mol%), acetone/H2O, 70 °C, 24 h, 92%; (e) 17 (2.66 equiv.), SnCl4 (1.2 equiv.), CH3Cl2, –78 °C to –42 °C, 30 min, then rt, 30 min, 75%. DMP = Dess–Martin periodinane; Bn = benzyl.
chemoselectivity in the endgame. The success of this route is a testament to the robustness of our synthetic plan, which proceeded without event (especially in the endgame) even in the presence of a free hydroxyl group at C17 from intermediate 23 onwards.

**Synthesis of (±)-stephacidin A (1) and (±)-notoamide I (2) from 23**

In an initial demonstration of the utility of 23 as an intermediate for the synthesis of prenylated indole alkaloid congeners possessing the bicyclo[2.2.2]diazaoctane structural motif, we have completed a synthesis of (±)-stephacidin A and (±)-notoamide I as outlined in Scheme 5. Thus chemoselective carbamoylation of the primary amine of 23 was achieved in high yield in the presence of the secondary hydroxyl to afford phenyl carbamate 25. At this point, oxidation of the hydroxy group and treatment of the resulting ketone with K₂CO₃ forges the bicyclo[2.2.2]diazaoctane framework of stephacidin A, presumably through a Dieckmann condensation via isocyanate/enolate intermediate 26. These exceedingly simple conditions effectively accomplish the task of synthetically connecting the two major sub-families of the prenylated indole alkaloids. From our perspective, polycycle 27 represents a versatile framework that may be advanced to myriad prenylated indole alkaloids including mangrovamide A (3) and paraherquamide A (4). To complete the synthesis of (±)-stephacidin A, removal of the ketone group in the pyrrolidine ring using a Wolff-Kishner protocol followed by reduction of the chromanone carbonyl group and elimination of the resulting hydroxyl gave (±)-stephacidin A (1) in 40% yield over the two steps. Analytical data for synthetic stephacidin A prepared by us matched

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**Scheme 4** Completion of the synthesis of 17-hydroxy-citrinalin B (7) from 23.

(a) Iodine (3.0 equiv.), DMAP (3.0 equiv.), pyridine/CCL₃ (60 °C, 22 h, 77%); (b) 19 (30 mol%), EtOH/H₂O, rt, 4 days, 82%; (c) PIFA (1.1 equiv.), MeOH, 0 °C to rt, 16 h, 89%; (d) 21 (1.5 equiv.), dppfPdCl₂ (10 mol%), K₂PO₄ (3.75 equiv.), DMF, 40 °C, 16 h, 94%; (e) Zn (excess), NaCNBH₃ (5.0 equiv.), sat. aq. NH₄Cl, MeOH, rt, 2 h, 71%; (f) Pd(OAc)₂ (0.40 equiv.), benzoquinone/C₁₄MsOH, 40 °C, Bn-phino)ferrocene; DMF following an adaptation of a procedure groups that are susceptible to reduction) was accomplished in respectable yield to give (–)-17-hydroxy-citrinalin B.

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**Scheme 5** Completion of the synthesis of (±)-stephacidin A (1) and (±)-notoamide I (2).

(a) CICO₂Ph (excess), K₂CO₃, acetone, rt, 16 h, 90%; (b) 20 min; (c) K₂CO₃, acetone, 50 °C, 2 h, 42% over two steps; (d) NH₂NH₂, K₂CO₃, acetone, rt, 16 h, 57%; (e) Vinyl acetate, CH₂Cl₂, rt, 2 h, 71%; (f) MnO₂ (excess), ETOAc, rt, 30 min, 32%. DMP = Dess–Martin periodinane; THF = tetrahydrofuran.
perfectly previously reported spectra.\textsuperscript{26} Furthermore, our X-ray analysis of a single crystal of 1 provided unambiguous support for the structure of the natural isolate (see CYLview in Scheme 5). Stephacidin A is a versatile starting point for the preparation of other prenylated indole alkaloids. For example, 1 was easily converted to (+)-notoamide I (2) upon treatment with MnO\textsubscript{2} in EtOAc (32% yield). Our synthesis of 1 also constitutes formal syntheses of (+)-notoamide B, (+)-avrinvillamide and (+)-stephacidin B.\textsuperscript{26}

**Conclusions**

In conclusion, we have achieved the first unified approach to the two sub-families of the prenylated indole alkaloids (i.e., that either lack or possess the bicyclo[2.2.2]diazaoctane structural motif). Our strategy has been exemplified with the first preparation of the natural product (−)-17-hydroxy-citrinalin B and of (+)-stephacidin A. Key to the success of the approach was the identification of a late-stage common intermediate (23), which could be advanced to either subclass of the prenylated indole alkaloids using a remarkably diastereoselective spiro-oxindole formation attended by a chemoselective oxidation of an amino group to a nitro group. Our synthesis of stephacidin A also featured a complexity building isocyanate capture to forge a [2.2.2]bicycle. Our studies now set the stage for the broad-ranging syntheses of congeners of the prenylated indole alkaloid family to facilitate in-depth studies on their biosynthesis and biological activity.

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**Notes and references**


10 For a Dieckmann cyclization route to form 2,5-diketopiperazines see: (a) C. L. Aboysauff and D. L. Clive, *J. Org. Chem.*, 2012, 77, 5125. For a review on the
11 These sequence of events is the proposed biosynthetic origin of congeners that lack the bicyclo[2.2.2]diazaoctane ring, see ref. 5b and 8d.


15 See ESI† for details.


22 We also isolated the methyl ether (7b) as a minor product in 19% yield, see the ESI† for more details.

23 Our preliminary attempts to effect direct oxygenation of 6 at C17 to give 7 have been unsuccessful.


26 (−)-Notoamide B is accessible in one step from 1 according to the procedure of Williams, et al (ref. 7e). (+)-Avrainvillamide and (−)-stephacidin B are available (as an equilibrium mixture) in two steps from 1 according to the procedure of Baran et al. (ref. 7b).