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Concise syntheses of the 1,7-dihydropyrano[2,3-*g*]indole ring system of the stephacidins, aspergamides and norgeamides

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Abstract—Three approaches towards the synthesis of the 1,7-dihydropyrano[2,3-*g*]indole ring system of the stephacidins, paraherquamides and norgeamides have been investigated. The first involves a tandem nitrene insertion/aromatic Claisen rearrangement. The second consists of a more conventional approach from commercially available 6-benzyloxyindole. The third approach is a revised synthesis of the 2-prenylated pyrano indole necessary for a biomimetic Diels–Alder approach towards the stephacidins, aspergamides and the norgeamides.

Fungi continue to be a rich source of complex and unprecedented indole alkaloids with a wide range of biological activity. As is often the case, the indole ring is oxidized to produce a variety of functionalized heterocyclic ring systems. In particular, the 1,7-dihydropyrano[2,3-*g*]indole ring system has recently been observed in several novel alkaloids. For example, the aspergamides A (**1**) and B (**2**) were isolated from *Aspergillus ochraceus* by Zeek and co-workers, who elucidated their structures using NMR experiments (Fig. 1).[1] Both were characterized by a bicyclo[2.2.2]diazaoctane bridged bicycle and a 1,7-dihydropyrano-[2,3-*g*]indole ring system. Furthermore, aspergamide A (**1**) exhibits a unique α-hydroxy nitrone moiety, whereas aspergamide B (**2**) is the dehydrated imine congener. Structurally related to the aspergamides, avrainvillamide (CJ-17,665, **3**) also contains a [2.2.2] bridged bicycle and the pyrano indole ring system, in addition to an unprecedented vinyl nitrone moiety, which had previously not been observed in this family.[2]

In addition to the aspergamides and avrainvillamide, a German institute cultivated four alkaloids containing the aforementioned indole ring system from a marine fungus growing in the North Sea.[3] The norgeamides A-D (**4**–**7**) are unique, in that they do not contain the bridged diazaoctane observed in related alkaloids. Instead, norgeamides A (**4**) and B (**5**) are comprised of a pyrano 2-oxindole moiety bearing a reverse prenyl group at C3, one of the two quaternary centers present in these compounds. An oxidized diketopiperazine (DKP) unit harbors the remaining quaternary center at C17. Alternatively, norgeamides C (**6**) and D (**7**) find the reverse prenyl group at C2 of a pyrroloindole ring system and a hydroxyl group at C3. Preliminary biological assays of the norgeamides reveal that norgeamide A (**4**) to be the most cytotoxic against several carcinoma cell lines.[3]

However, the most intriguing alkaloid recently isolated containing the pyrano indole ring system is stephacidin B (**9**). Isolated by Bristol-Meyers Squibb (BMS) from the fungus *A. ochraceus* WC76466,[4] the stephacidins A (**8**) and B (**9**) both displayed in vitro cytotoxicity against a panel of carcinoma cell lines with **9** being five- to thirty-fold more cytotoxic than **8** possessing a high affinity for testosterone-dependent prostate LNCaP cancer cells. However, the cytotoxicity of stephacidin B (**9**) is eclipsed by its unprecedented structure, which was determined using NMR experiments and X-ray crystallography. Stephacidin B contains fifteen rings, nine stereogenic centers and two pyrano indole rings and was proposed to be a dimer of **3**.[5] The unique structure, cytotoxicity and biosynthetic relationships between

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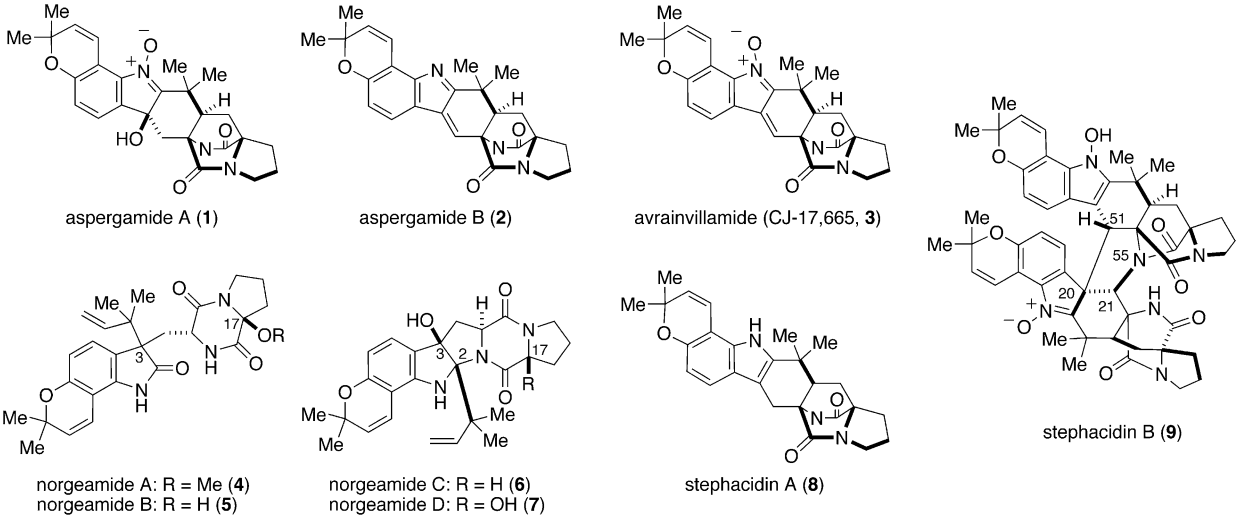
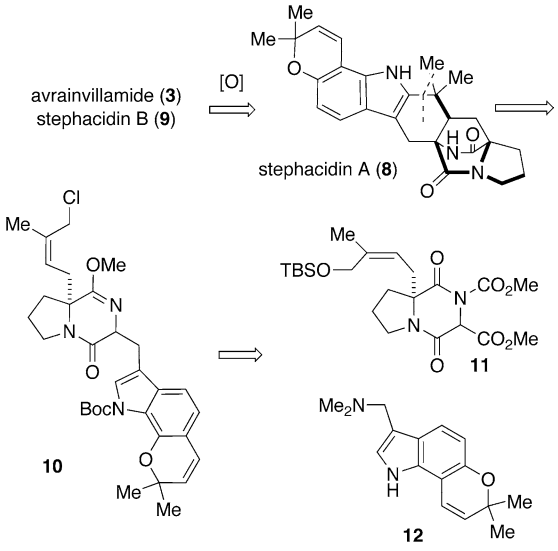


Figure 1. Recently isolated alkaloids containing a 1,7-dihydropyrano[2,3-*g*]indole ring system.

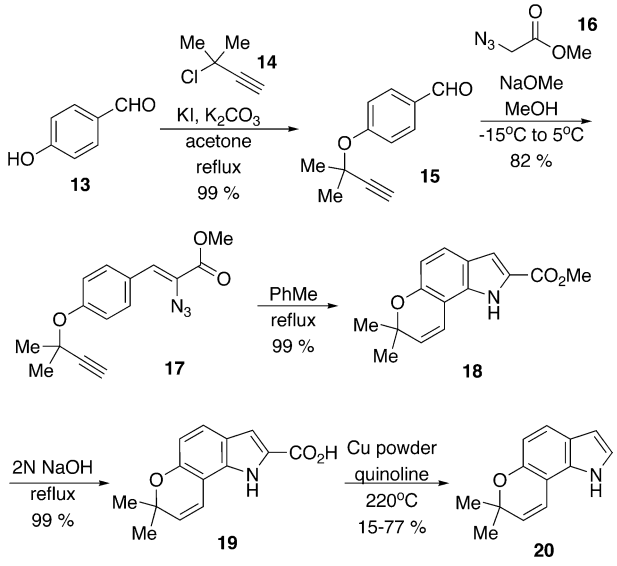
these alkaloids have recently resulted in intense synthetic interest including the first total synthesis of avrainvillamide (**3**) and stephacidin B (**9**) by Myers,[6] and more recently, Baran's revised total synthesis of stephacidin A (**8**) en route to stephacidin B (**9**).[7]

Our laboratory has a rich history with respect to similar alkaloids containing many of the structural features highlighted in Figure 1.[8] We developed the first intramolecular S_N2' approach for the preparation of the [2.2.2]diazaoctane ring system found in these alkaloids that was employed in asymmetric total syntheses of brevianamide B, paraherquamide B and paraherquamide A.[8] Retrosynthetically, we envisioned that stephacidin A (**8**) could be oxidized[7] to afford avrainvillamide (**3**) and stephacidin B (**9**, Scheme 1). In turn, **4** would be accessed from lactim ether **10** via displacement of the allylic chloride in an S_N2' fashion to produce the bridged bicycle and subsequent cyclization at C2 of the indole would produce the cyclohexyl ring of **8**. It was envisioned that the lactim ether **10** can be accessed from a coupling of the known diketopiperazine **11** and previously unknown gramine **12**.

Since we were endeavoring to access two alkaloids from a common intermediate, it was necessary to develop a concise, high yielding synthesis of gramine **12** for the S_N2' approach. To this end, we were drawn to the elegant nitrene insertion/Claisen rearrangement chemistry developed by Moody for the synthesis of allyl substituted indoles.[9,10] Thus, 4-hydroxybenzaldehyde (**13**) was alkylated with 3-chloro-3-methyl-1-butyne (**14**) using KI and K_2CO_3 in refluxing acetone affording the ether aldehyde **15** in excellent yield (Scheme 2).[11] Condensation of the aldehyde **15** with methyl azidoacetate[9,10] (**16**) cleanly afforded the conjugated azide **17** in good yield. Generation of the nitrene from **17** in refluxing toluene facilitated formation of the indole formation via CH insertion and, additionally, the pyran ring was formed



Scheme 1. An S_N2' retrosynthetic approach towards the stephacidins.



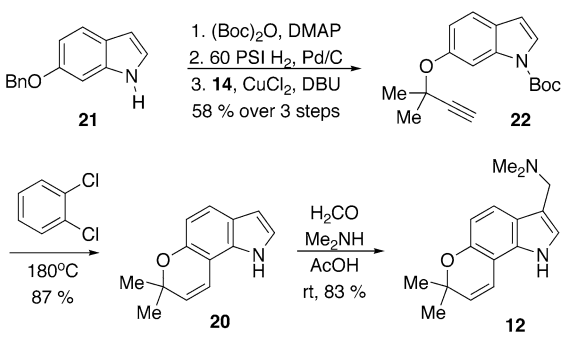
Scheme 2. Synthesis of indole **20** via a Claisen/nitrene insertion.

under these conditions through a Claisen cyclization[12] to produce compound **18** in excellent yield and as a single regioisomer. Subsequent saponification of methyl ester **18** to acid **19** was uneventful. However, decarboxylation of **19** proved to be capricious with yields of the desired indole **20** ranging from 15% to 77%. Unfortunately, an exhaustive effort with various forms of copper, additives and solvents failed to provide consistency to this key transformation.

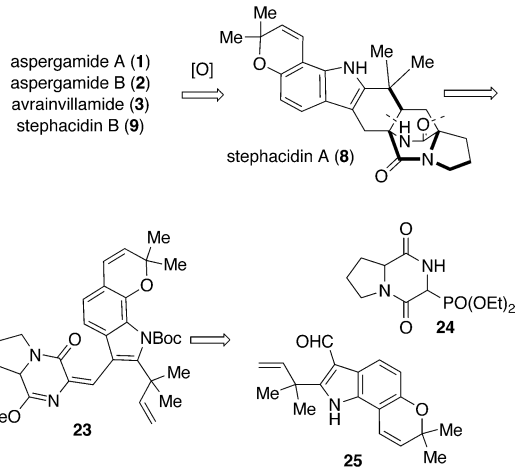
Alternatively, a more direct approach to gramine **12** was realized from commercially available 6-benzyloxyindole (**21**, Scheme 3).[13] Protection of the indole nitrogen of **21** with $(Boc)_2O$, followed by debenzylation and alkylation of the resulting crude phenol with the previously employed chloride **14** afforded aryl ether **22** in 58% over the three steps on a multigram scale.[12b] Finally, heating of alkyne **22** in *o*-dichlorobenzene cleanly effected the aromatic Claisen cyclization as well as Boc cleavage to afford the desired pyrano indole **20** in 87% yield. Finally, conversion of indole **20** to the desired gramine **12** was accomplished using standard conditions in 83% yield.

More recently, our laboratory has reported the synthesis of isotopically labelled putative biosynthetic intermediates in this family of alkaloids and feeding experiments describing the biosynthetic pathway towards these bridged bicycle alkaloids.[8,14–16] A substantial body of evidence suggests that the biosynthetic formation of the bicyclo[2.2.2]diazaoctane core is accomplished via a Diels–Alder reaction. To this end, we have developed a secondary, biomimetic approach towards these alkaloids (Scheme 4). In the case of the stephacidins, the bridged diazaoctane of stephacidin A (**8**) can be disconnected retrosynthetically to afford **23**. Further disconnection of the Diels–Alder precursor **23** generates the DKP **24** and the prenylated indole **25.**

We recently reported the synthesis of prenylated indole **25** via a Fisher indole strategy.[12b] Unfortunately, the key Fisher ring formation step exhibited poor regioselectivity generating a ~1:1 mixture of the 4- and 6-methoxyindoles, thereby limiting the throughput of material for further manipulation. In order to overcome the deficiencies of the Fisher route, we were drawn to a report by Tatsuta in which 3-chloroindoles can be reverse prenylated at C2 of indole with prenyl 9-BBN.[17] To this end, the hydroxyl group of commercially available 6-



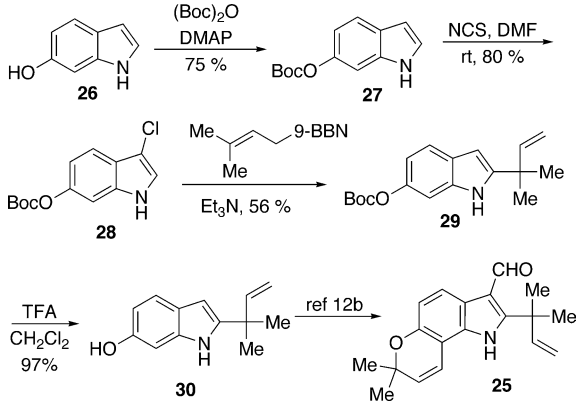
Scheme 3. Synthesis of gramine 12 from 6-benzyloxyindole (**21**).



Scheme 4. A Diels–Alder approach towards the stephacidins.

hydroxyindole[18] (**26**) was protected as its Boc carbonate to form indole **27** in 75% yield (Scheme 5). Indole **27** was then chlorinated using NCS to afford the 3-chloroindole **28** in good yield. Pleasingly, compound **28** readily reacted with prenyl-9-BBN[19] to afford 2-prenylated indole **29** in 56% yield. We believe that the electron-withdrawing nature of the carbonate is vital for the success of this reaction in that electron-rich protected variants of **28** (i.e., silyl ethers and alkyl ethers) failed to produce any of the desired prenylated indole. Finally, removal of the Boc carbonate of **29** with TFA produced the previously synthesized 6-hydroxy-2-prenyl indole **30** obtained by the Fisher indole approach. Indole **30** was converted to the pyrano indole **25** according to our previous report[12b] in three steps, thereby providing the necessary indole for our biomimetic approach in a more concise and regioselective manner.

In conclusion, we have described the synthesis of our key gramine **12** by two different strategies. The first route proved to be capricious and failed to afford the desired indole precursor in high yield. The second route produced the desired gramine **12** in only five steps and in 41% overall yield. Furthermore, we have revised our synthesis of the prenylated indole **25** via a boron-mediated reverse prenylation reaction, thereby providing multigram quantities of **25**, regioselectively. These



Scheme 5. Synthesis of 2-reverse prenylated indole **25**.

substances should find broad utility in the preparation of the stephacidins, aspergamides and norgeamides as well as for the preparation of isotopically labelled biosynthetic intermediates for biosynthetic studies, which are currently being pursued in our laboratories.

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Supplementary data

The supplementary data is available with the paper at ScienceDirect. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.112.

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