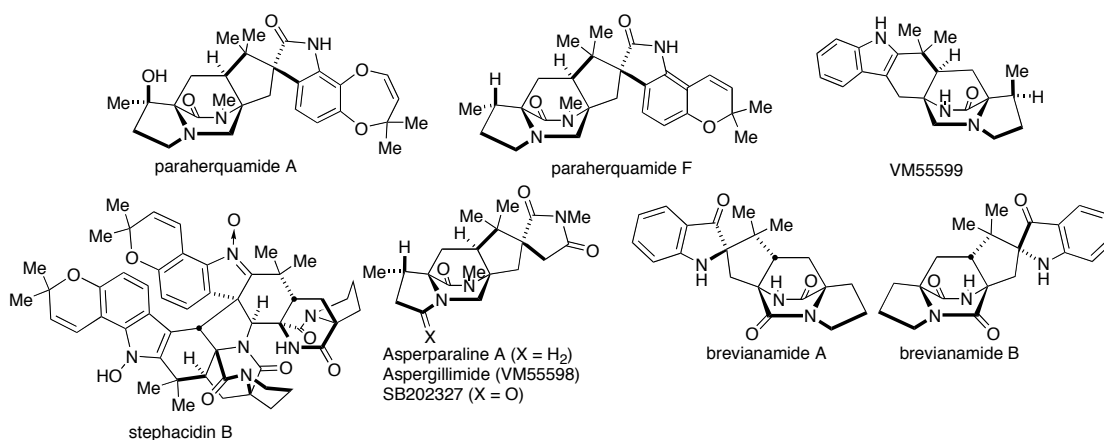


II. TOTAL SYNTHESIS AND BIOSYNTHESIS OF NATURAL PRODUCTS

The biosynthesis of complex, biologically active natural products is being pursued with the ultimate objectives of probing, understanding and manipulating the genetic machinery of complex, secondary metabolite construction in bacteria, fungi, and plants. In this area, we have targeted several biosynthetic pathways that have unusual intrigue and potential commercial importance. Extensive use of natural product total synthesis, stable and radioisotope synthesis of biosynthetic intermediates and biological methods are being employed to map and probe secondary metabolic pathways in detail.

(a) Paraherquamides/Brevianamides/Asperparaline: Total Synthesis and Biosynthesis

The paraherquamide family of alkaloids, produced by various *Penicillium* sp. and *Aspergillus* sp. molds, display a range of interesting biological activities including anti-parasitic and insecticidal properties. These substances are the result of "mixed" biosynthetic pathways conscripting proteinogenic α -amino acids and isoprene units as primary building blocks. We have completed the total synthesis of several members of the brevianamide/paraherquamide class of alkaloids. We are presently engaged in completing the total syntheses of other paraherquamides, asperparaline and a related metabolite, VM55599.



Major Accomplishments:

1. Asymmetric total syntheses of (-)-Brevianamide B (1988) and (+)-paraherquamide B (1993) plus several biosynthetic intermediates have been completed; (see: *J. Am. Chem. Soc.*, **1996**, *118*, 557~579).
2. The asymmetric stereocontrolled total synthesis of paraherquamide A has been completed (see: *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 2540~2544).
3. The biomimetic total synthesis of *d,l*-VM55599 has been completed (see: *J. Am. Chem. Soc.*, **2000**, *122*, 1675~1683) and an asymmetric synthesis of (-)-VM55599 has recently been completed (see: *J. Am. Chem. Soc.* **2002**, *124*, 2556~2559).
4. A ligand-assisted method to control the facial selectivity of the intramolecular S_N2' cyclization was devised to construct the bicyclo[2.2.2]ring system; (see: *J. Am. Chem. Soc.*, **1990**, *112*, 808~821 & *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 2540~2544.).
5. Biogenetic implications: In search of a Diels-Alderase. (*J. Am. Chem. Soc.* **1989**, *111*, 3064). Extensive use of the total syntheses to prepare isotopically labeled biosynthetic intermediates to establish biosynthetic pathway metabolites and isolate the Diels-Alderases are under study; (see: *J. Am. Chem. Soc.*, **1993**, *115*, 347~348).
6. Studies on the biosynthesis of paraherquamide A have revealed that the biosynthetic building block of the β -hydroxy- β -methylproline ring is L-isoleucine; (see: *J. Am. Chem. Soc.*, **1996**, *118*, 7008-7009).
7. The mechanism of reverse prenylation of the indole ring in the biosynthesis of these alkaloids has been studied and a facially indiscriminate S_N2' prenyl transfer has been implicated (see: *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 786~789).

