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Total Synthesis of (±)-Methyl Homosecodaphniphyllate: A Remarkable New Tetracyclization Reaction *J. Am. Chem. Soc.* **1988**, *110*, 8734–8736.

Total Synthesis of (±)-Methyl Homosecodaphniphyllate

Significance: A truly inspiring contribution to the development of tandem cyclization and bioinspired synthesis was made by Heathcock and co-workers in 1988. In this classic communication, the authors provide a striking example of an intramolecular hetero-Diels–Alder reaction and aza–Prins cyclization in the same pot and under mild conditions. The total synthesis proceeds in high yield and selectivity en route to (±)-methyl homosecodaphniphyllate, which ultimately proved accessible in only nine steps and 44% overall yield from simple precursors **A. B.** and **C.**

Comment: The authors commence their elegant route with a tandem Michael addition—enolate alkylation sequence followed by functional group interconversion, thereby obtaining diol **D** in high yield and selectivity. Condensation of the corresponding dialdehyde with ammonia afforded aza-diene **E** in two steps. Hetero-Diels—Alder reaction and aza-Prins cyclization afforded pentacyclic unsaturated amine **I** in a single operation. This advanced intermediate was converted into the target structure in three additional steps.

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Synthesis of Natural Products and Potential Drugs

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hetero-Diels-Alder reaction

aza-Prins reaction

biomimetic synthesis

