Synthesis of Sarpagine Alkaloids

Significance: The authors report the enantioselective total synthesis of three sarpagine indole alkaloids which were isolated from the plant family Apocynaceae. The route relies on a common intermediate G, which is impressively accessed using key features such as a [5+2] oxidopyridinium cycloaddition and a ring expansion. The three natural products were synthesized in only eight steps starting from known materials (12 steps from commercially available compounds).

Comment: The synthesis commenced with a [5+2] cycloaddition between oxidopyridinium salt A and Aggarwal’s chiral ketene equivalent B, thus yielding the desired regioisomer C in a 2:1 ratio. Next, ketone G was accessed through an intramolecular palladium-catalyzed enolate coupling of D, followed by Wittig reaction, deprotection of the dithiolane, and ring expansion. The indole was introduced in the last step by a Fischer indole synthesis using phenylhydrazines with different substitution patterns to afford the three targets.