Total Synthesis of Scholarisine A

Significance: The structural complexity of the akuammiline alkaloid scholarisine A poses considerable synthetic challenges. Snyder and Smith report an elegant and short route to this natural product that relies on a Diels–Alder reaction and radical cyclization to provide rapid access to the target’s core. The indolenine is introduced in an intriguing late-stage C–H arylation step. The architecturally unique alkaloid could thus be prepared in merely 15 steps. It is noteworthy that only one other synthesis of this challenging target has been reported so far (G. L. Adams, P. J. Carroll, A. B. Smith, Ill. J. Am. Chem. Soc. 2012, 134, 4037).

Comment: The lactone of the natural product was introduced early in the synthesis through the Diels–Alder cycloaddition of dienophile A and pyrone B, which afforded C in 83% yield and 3:1 dr. Cleavage of the acetonide followed by displacement of the resulting primary alcohol furnished bromide D. Radical cyclization and subsequent trapping gave key intermediate E in 59% yield as a single diastereomer. An epimerization–lactamization sequence afforded F which was treated with 2-iodoaniline to give imine G. This underwent the challenging tertiary C–H arylation, affording I. A few transformations later the synthesis was completed.