Total Synthesis of Indoxamycins A, C, and F

Significance: In 2009, a Japanese research group reported the isolation of a novel class of natural products, the indoxamycins. These marine-derived polyketides are characterized by a highly substituted tricyclic core, bearing six contiguous stereogenic centers, three of which are quaternary. This work describes not only the total synthesis of indoxamycin A, C, and F, but also a stereochemical revision. This finding is in agreement with the total synthesis and the resulting structural reassignment of another member of the family, indoxamycin B (O. F. Jeker, E. M. Carreira Angew. Chem. Int. Ed. 2012, 51, 3474; Synfacts 2012, 8, 593).

Comment: A salient feature of the presented synthesis is a highly selective palladium-catalyzed reductive 1,6-enyne cyclization to access bicycle B in excellent yield. After four more steps, a tandem 1,2-Grignard addition–oxa-Michael–methenyl migration (C→H) followed by double-bond isomerization provides rapid entry to common intermediate I. From this branching point, all three target molecules could be synthesized in a few transformations (3–4 steps) and high overall yield. The spectra of all three natural products matched the reported isolation data, therefore confirming the hypothesis of a stereochemical misassignment at C2 and of the double-bond geometry.