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Total Synthesis and Structural Revision of Viridicatumtoxin B
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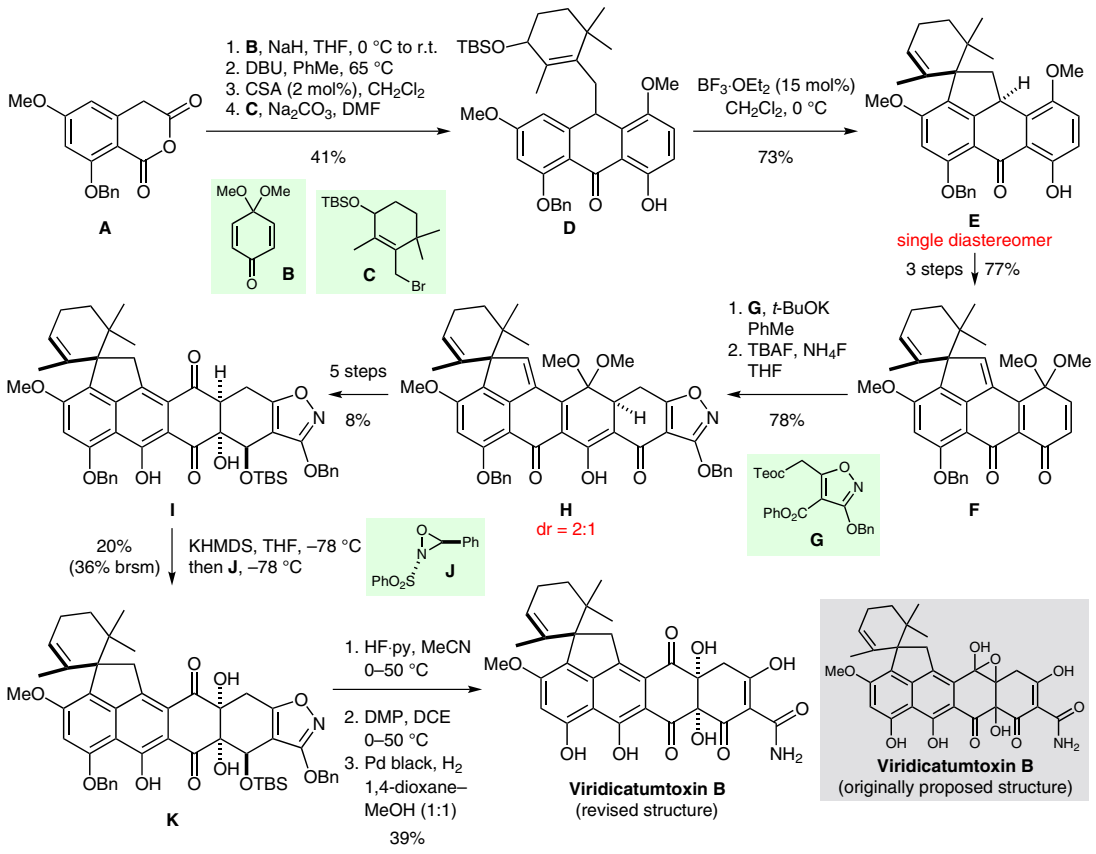
Synthesis of Viridicatumtoxin B



Significance: Structurally related to the tetracycline family of broad-spectrum antibiotics, the viridicatumtoxins feature a densely oxidized tetracyclic carbon skeleton with an appended highly congested spirocycle. The viridicatumtoxins have been shown to exhibit strong antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA), comparable to vancomycin. Nicolaou and co-workers tackled viridicatumtoxin B and accomplished the total synthesis of this impressive target which had previously been incompletely characterized. The synthesis allowed for the revision of the originally proposed structure and the full stereochemical assignment of viridicatumtoxin B.

Comment: Using a highly convergent strategy, the authors constructed the challenging spirocycle **E** by virtue of a Lewis acid catalyzed Friedel–Crafts alkylation. The Michael–Dieckmann annulation of **F** with isoxazole **G** completed the full-carbon skeleton. However, the remaining two hydroxylations proved difficult and were finally achieved by nickel-catalyzed DMDO- and Davis α-hydroxylation, respectively. Critical to the success of these reactions was the choice of oxidation state and protecting-group pattern of the underlying core. Deprotection, oxidation, and hydrogenation of **K** afforded synthetic viridicatumtoxin B, which exists as the hydroxy ketone rather than the originally proposed epoxy hemiacetal.

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