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Electrolytic Macrocyclizations: Scalable Synthesis of a Diazonamide-Based Drug Development Candidate
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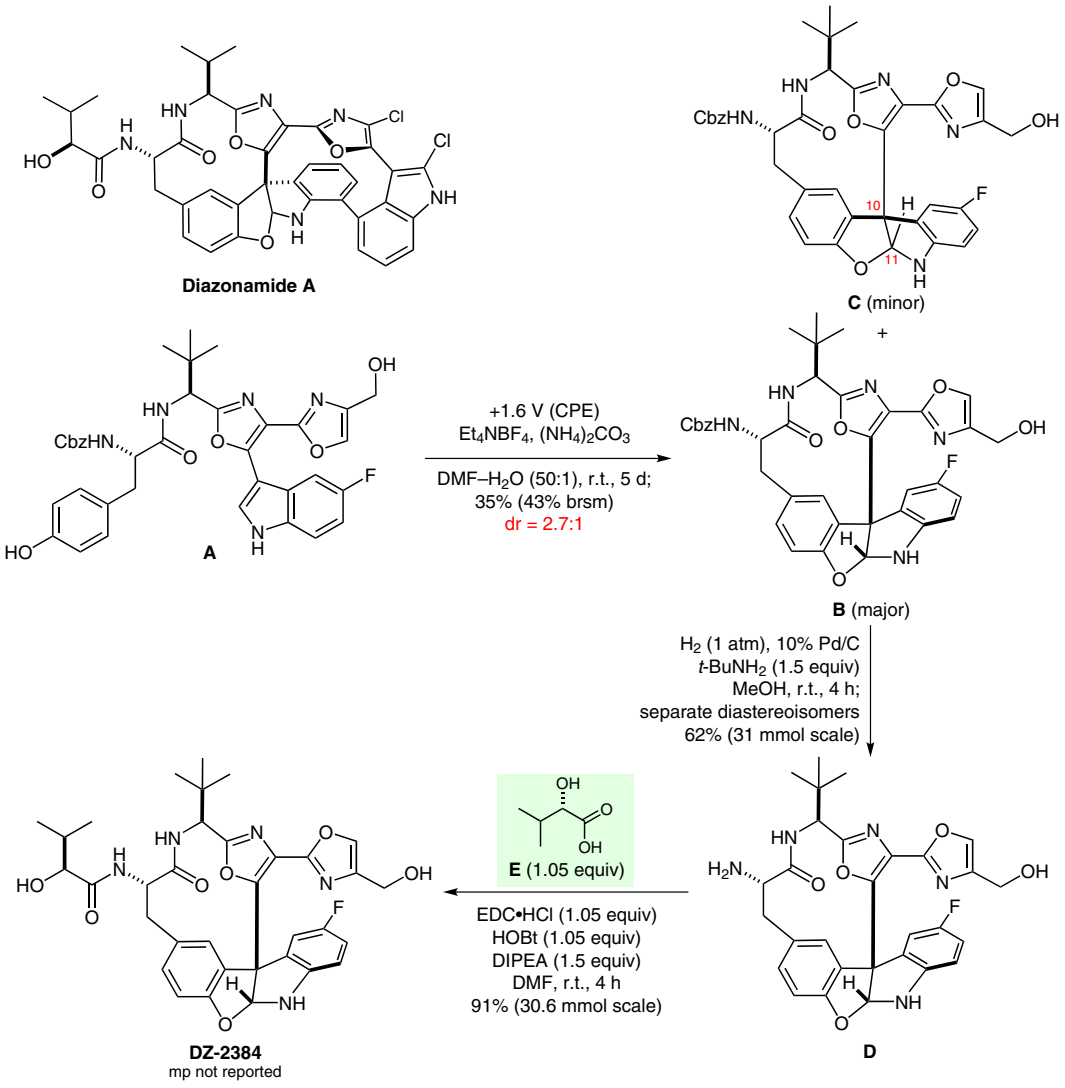
Synthesis of DZ-2384



Significance: Diazonamide A, a metabolite of the ascidian *Diazona angulata*, displays potent in vitro activity against human colon cancer. DZ-2384 is a truncated analogue of diazonamide A that is 10- to 50-fold more efficacious than diazonamide A as an anti-mitotic agent in rodents. The synthesis of DZ-2384 proceeded in 13 total operations and 5.7% overall yield from L-*tert*-leucine.

Comment: The key step of the synthesis depicted is a macrocyclization initiated by an anodic oxidation of **A** at a graphite surface. Anodic oxidation of 60 grams of **A** gave 21 grams of a mixture of **B** (major) and its *epi*-C10,C11 diastereoisomer **C** (minor, dr = 2.7:1), which was separated from unreacted **A** (11.0 g) by silica gel chromatography. Separation of the diastereoisomers was achieved after hydrogenolysis of the Cbz group.

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Category
Synthesis of Natural Products and Potential Drugs

Key words
DZ-2384
diazonamide A
macrocyclization
anodic oxidation