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Scalable Total Synthesis of (–)-Berkelic Acid by Using a Protecting-Group-Free Strategy
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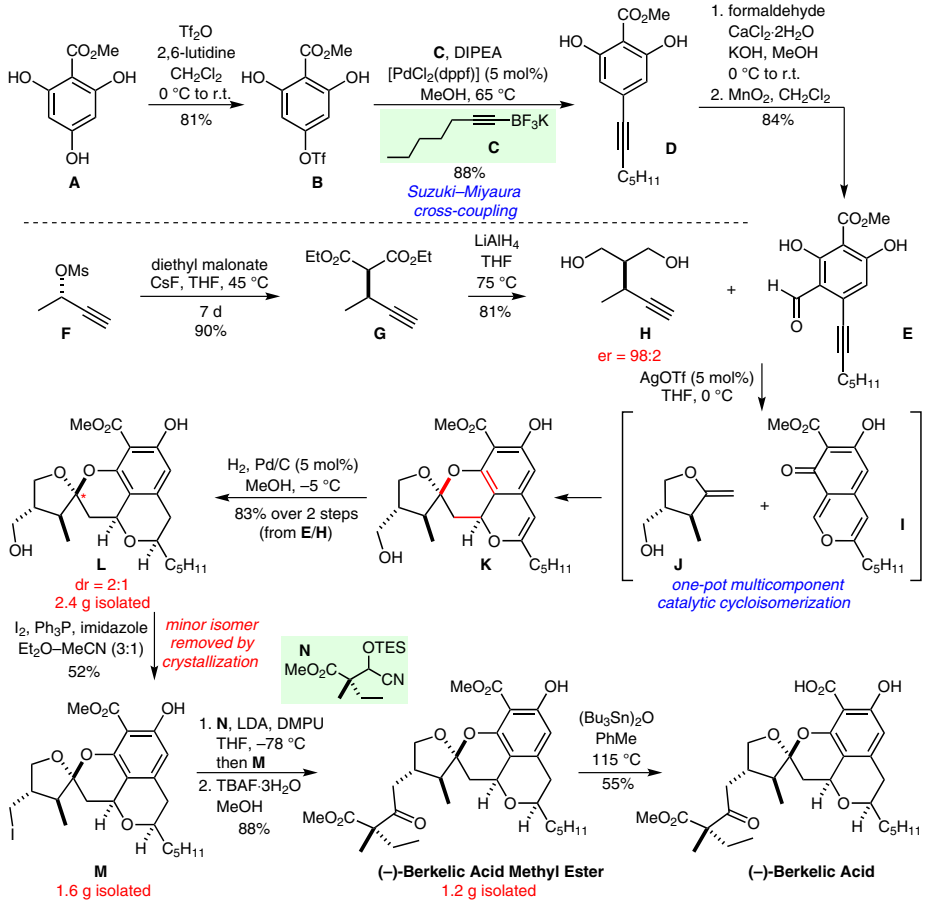
Synthesis of (–)-Berkelic Acid



Significance: (–)-Berkelic acid was isolated from an extremophilic Penicillium species in 2006 by Stierle and co-workers from the surface waters of Berkeley Pit Lake, Butte, Montana, USA. This natural product has been the subject of much interest to the synthetic community due to its unusual structure and diverse range of biological activity. Whilst this is not the first synthesis of this natural product, this route is shown to be highly scalable, with each step leading to the (–)-berkelic acid methyl ester performed on >1 g scale. Due to the reported instability of (–)-berkelic acid, the last step was conducted on a 50 mg scale.

Comment: The key step involved the formation of spiroketal **K** in a one-pot multicomponent cycloisomerization between alkynes **E** and **H** in the presence of catalytic AgOTf. This is thought to proceed via formation of *ortho*-quinonemethide **I** and exocyclic enol ether **J**, which undergo a formal cycloaddition to give product **K**. Subsequent hydrogenation provided **L** as a mixture of only two diastereomers (2:1) in impressive yield in favor of the desired product. This allowed the rapid completion of (–)-berkelic acid in a further four steps.

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Category
Synthesis of Natural Products and Potential Drugs

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Suzuki–Miyaura cross-coupling
π-acid catalysis
multicomponent reaction
(–)-berkelic acid