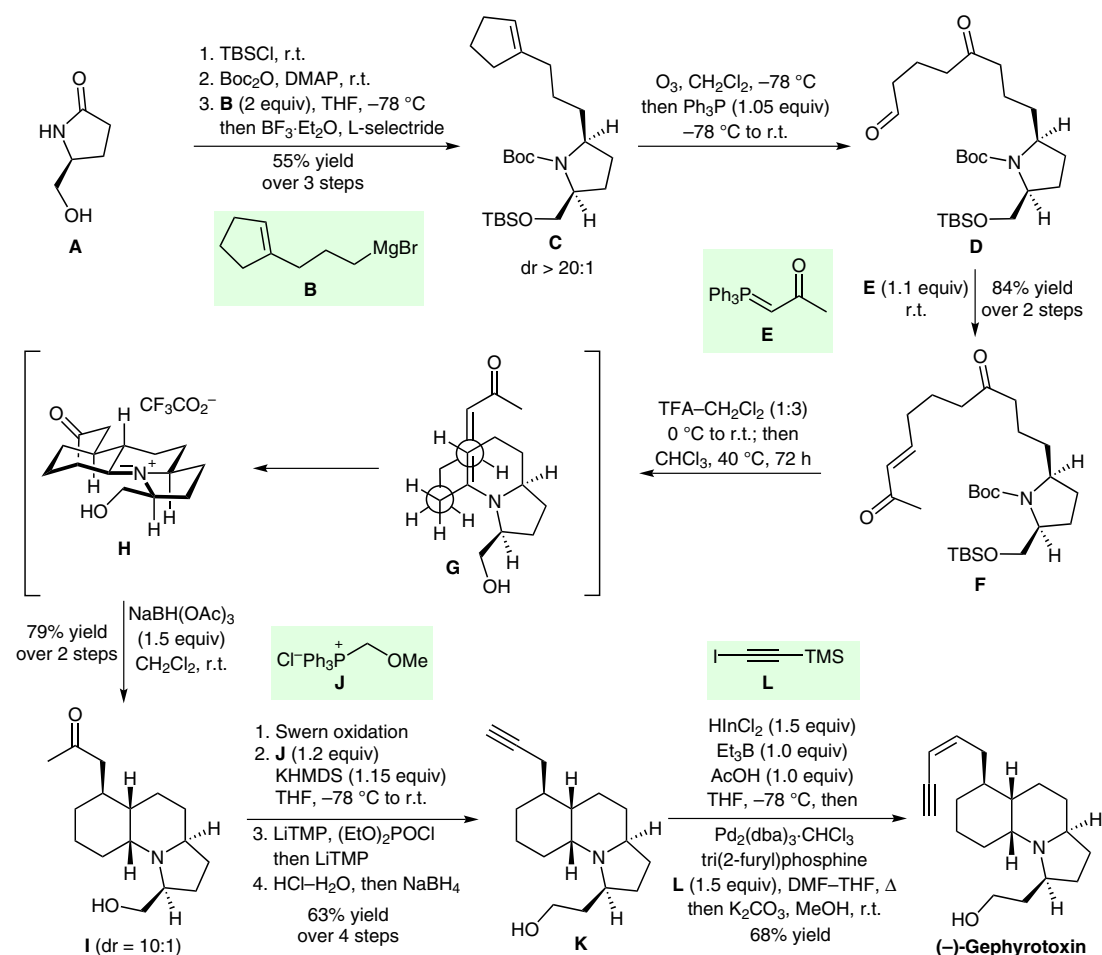


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A Cascade Strategy Enables a Total Synthesis of (-)-Gephyrotoxin

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Total Synthesis of (-)-Gephyrotoxin



Significance: Gephyrotoxin is a relatively non-toxic dendrobatid alkaloid with an unusual neurological profile. Its properties and complex structure have made it the subject of numerous synthetic studies. Total syntheses have been reported by Kishi, Hart, Overman, as well as Sato and Chida, and a number of formal syntheses have been described. Smith and co-workers now report an elegant and concise synthesis of gephyrotoxin that relies on an intramolecular enamine/Michael cascade to access the tricyclic scaffold of the natural product.

Comment: The synthesis commenced with L-pyrroglutaminol (**A**), which was converted into key intermediate **F** in five simple steps. Deprotection of **F** was achieved by treatment with TFA, and warming to 40 °C in chloroform led to formation of iminium salt **H**, which in turn underwent hydroxyl-directed reduction to give **I** in 79% yield. A few functional-group interconversions then led to **K**. Cross-coupling with alkyne **L** followed by deprotection furnished synthetic gephyrotoxin.

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