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Enantioselective Synthesis of N1999A2
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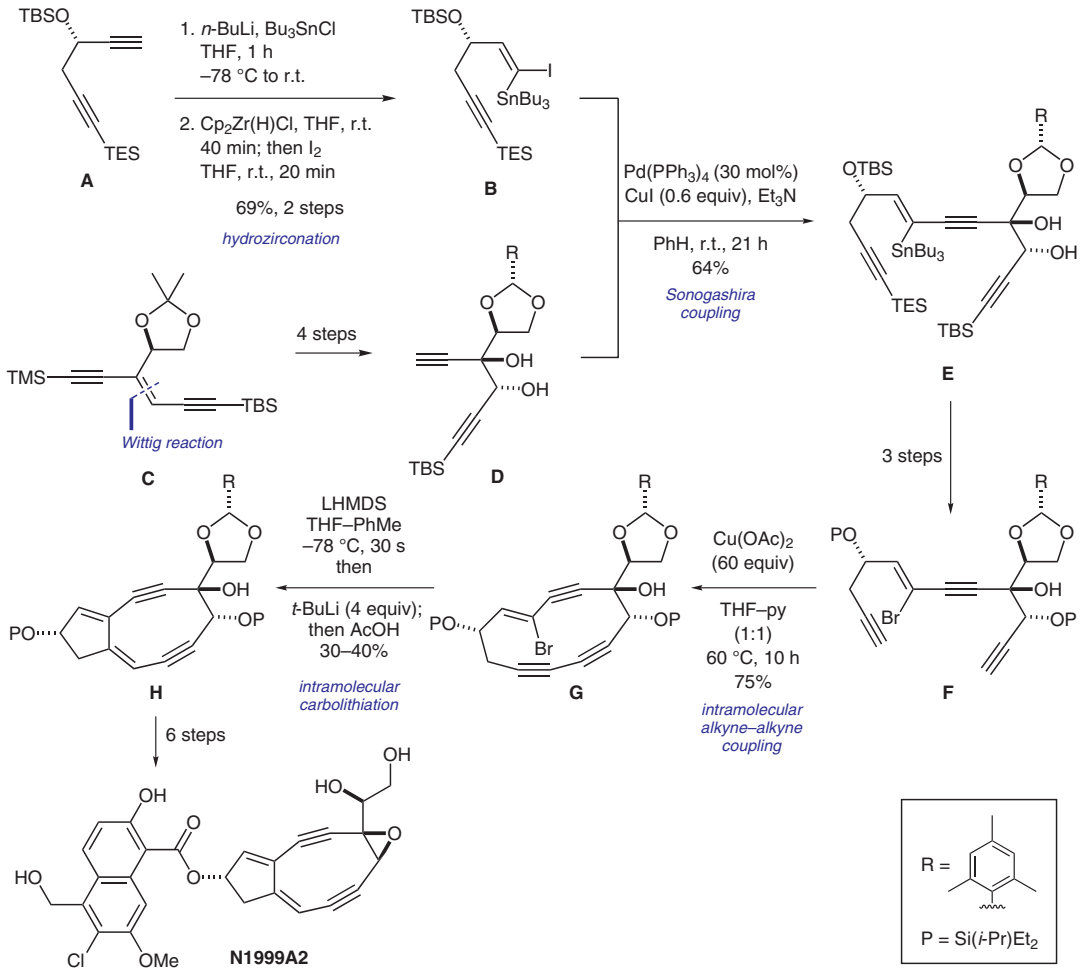
Synthesis of N1999A2



Significance: N1999A2 is an enediyne antibiotic that damages DNA by radical means. Noteworthy in this synthesis is the deft use of mild organometallic processes and a carefully wrought protecting group strategy to accomplish construction of the very sensitive target.

Review: *Chemistry and Biology of the Enediyne Anticancer Antibiotics* K. C. Nicolaou, W.-M. Dai *Angew. Chem. Int. Ed.* **1991**, *30*, 1387–1530.

Comment: Treatment of bisalkyne **F** with $Cu(OAc)_2$ gave **G** via intramolecular alkyne–alkyne coupling. Addition of LHMDS followed by *t*-BuLi gave **H** via lithium–bromine exchange followed by intramolecular carbolithiation. This step suffered from poor scalability and all subsequent intermediates (including **K**) were unstable in neat form. Despite such adversity, N1999A2 was accessed in six further steps.

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Category
Synthesis of Natural Products and Potential Drugs

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hydrozirconation
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alkyne–alkyne coupling
carbolithiation