



Strategies and Tactics in Organic Synthesis: Chapter 11. Total Synthesis of Aspergillide C

Joseph D. Panarese, Stephen P. Waters

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In 2008, (+)-aspergillide C, a structurally novel marine metabolite bearing a 14-membered macrolactone around a 2,6-dihydropyran core, was isolated from a marine-derived fungus, *Aspergillus ostianus*. In a biological assay, (+)-aspergillide C displayed promising anticancer activity ($LD_{50}=2.0\mu\text{g/ml}$) against mouse lymphocytic leukemia cells (L1210). Due to its notable biological activity and interesting architecture, we viewed aspergillide C as an attractive synthetic target. Moreover, the aspergillide scaffold could lend itself to diverse structural modifications in projected syntheses of biologically active congeners. In this account, we describe our enantioselective approach to aspergillide C from (S)-(-)-glyceraldehyde acetone and the Danishefsky–Kitahara diene. Strategic transformations include a heterocyclocondensation reaction, a Ferrier-type addition, and a palladium-catalyzed oxidative lactonization to set key stereocenters within the dihydropyran core, followed by fragment coupling through an (E)-selective Julia–Kocienski olefination.

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