Synthesis of Potent Anti-Inflammatory Fungal Macrolactones

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The secondary metabolite 14-deoxyoxacyclododecindione, isolated from *Exserohilum rostratum*, exhibits highly potent anti-inflammatory activity in the nanomolar range and may serve as a lead structure for new therapeutics for the treatment of chronic inflammatory and/or fibrotic diseases. While various synthetic approaches to the 12-membered skeleton like an attempted carbonylative ring closure (pathway A) or a ring-closing metathesis/double-bond isomerisation sequence (pathway B) were unsuccessful, a ring-closing metathesis/hydrogenation/unsaturation sequence (pathway C) furnished a highly potent analogue. Ultimately, an intramolecular Friedel-Crafts-acylation (pathway D) permitted the total synthesis of the natural product. The unknown relative stereochemistry was elucidated and initial structure-activity relationships were established for the oxacyclododecindione-type macrolactones.