Phorboxazole compounds as potent anti-tumor agents

Total synthesis of (+)-phorboxazole A, analogs, and derivatives for medicinal chemistry

Inventors
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Problem
Phorboxazoles are naturally occurring compounds that have been isolated from the marine sponge Phorbas, endemic to the western coast of Australia. Previous screens of phorboxazoles against the National Cancer Institute human cell line panel indicated the most potent cytotoxicity assayed. While the mechanism of action in vivo is unknown, phorboxazole arrests the cell cycle at S phase without interfering with microtubule stability. Because of the antimitotic bioactivity, structural complexity, and extreme natural scarcity of the compound, efforts have been underway for the total synthesis of this natural product.

Solution
Researchers in the Smith lab in the Department of Chemistry have completed the total synthesis of phorboxazole compounds and derivatives. The Petasis-Ferrier rearrangement was utilized to construct two tetrahydropyran rings in the phorboxazole macrolide ring, along with an extension of the Julia olefination and application of a novel bifunctional oxazole linchpin. This sequence gave an overall yield of 3-6% in a stereocontrolled, highly convergent Stille coupling to unite the macrocycle with the sidechain. Structure-activity relationship studies on phorboxazole analogs and initial biological screening in leukemia, breast cancer, and brain tumor cell lines have demonstrated extremely potent anticancer activity.

Advantages
• Anti-proliferative activity
• Antifungal and antibiotic activity
• Synthetic scheme does not rely on use of restricted marine sponge
• High yield and stereoselectivity compared to previously demonstrated synthesis of phorboxazoles

Applications
• Potential pharmaceuticals and therapeutics for cancer, inhibiting cancer cell division or inducing apoptosis in malignant cells