Abstract Ph.D. Thesis
Total Synthesis of Spirastrellolide F Methyl Ester
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In 2003, extracts from the Caribbean marine sponge *Spirastrella coccinea* collected by ANDERSEN and coworkers were screened in a cell-based assay that detects mitotic arrest. The major antimitotic component of the extract was the novel polyketide spirastrellolide A.\(^1\) Ongoing examination of the *S. coccinea* extract has since identified six additional spirastrellolides, B – G, differing by substitution at C\(_4\), C\(_8\), C\(_{28}\) and C\(_{46}\) and the presence or absence of unsaturation between C\(_{15}\)-C\(_{16}\) (Figure 1, left).\(^2\) Unique among antimitotic macrolides, the spirastrellolide methyl esters do not affect tubulin polymerization *in vitro* but are shown to be very potent (IC\(_{50}\) = 1 nM) and selective inhibitors of protein phosphatase 2A (PP2A).

The major disconnections for the synthesis of spirastrellolide F methyl ester are outlined in Figure 1 (right). Specifically, a palladium-catalyzed sp\(^3\)-sp\(^2\) SUZUKI cross-coupling at C\(_{24}\)-C\(_{25}\) and a YAMAGUCHI-lactonization are utilized to form the macrolactone core. Additionally, the construction of the southern fragment involves a 1,3–anti MUKAIYAMA aldol reaction to set the C\(_{11}\) stereogenic center, as well as, an alkyne addition at C\(_{17}\). The linkage of the side chain and thereby synthesis of the skipped-diene is achieved via a palladium \(\pi\)-alkyl STILLE cross-coupling. All necessary fragments have been synthesized and coupled to complete the total synthesis of spirastrellolide F methyl ester.\(^3\)
A second synthetic approach towards spirastrellolide F methyl ester involves a ring-closing alkyne metathesis (RCAM) to build the macrocyclic core, followed by hydroalkoxylation via carbophilic activation of the triple bond with a Au(I)-catalyst (Figure 2). Consequently, the isolated enolether is transformed into the desired 6,6-spirocycle thus completing the formal total synthesis of the corresponding macrolactone of spirastrellolide F methyl ester.

![Figure 2: Second retrosynthetic analysis of Spirastrellolide F Methyl Ester.](image)

References:

