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).

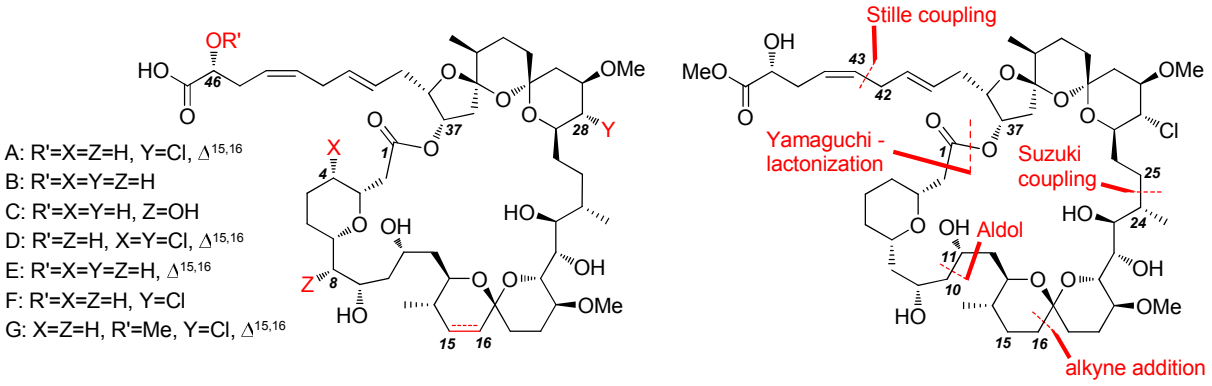

Figure 1: Spirastrellolides A – G (left); Retrosynthetic analysis of Spirastrellolide F Methyl Ester (right).

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 π-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 built 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.

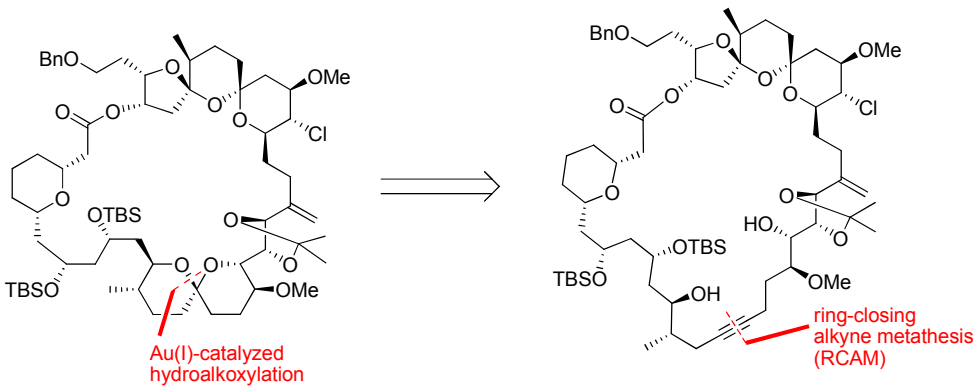

Figure 2: Second retrosynthetic analysis of Spirastrellolide F Methyl Ester.

References:

[1] D. E. Williams, M. Roberge, R. Van Soest, R. J. Andersen, *J. Am. Chem. Soc*. **2003**, *125*, 5296 – 5297.

[2] a) K. Warabi, D. E. Williams, B. O. Patrick, M. Roberge, R. J. Andersen, *J. Am. Chem. Soc*. **2007**, *129*, 508 – 509; b) D. E. Williams, R. A. Keyzers, K. Warabi, K. Desjardine, J. L. Riffell, M. Roberge, R. J. Andersen, *J. Org. Chem*. **2007**, 72, 9842 – 9845.

[3] a) G. W. O'Neil, J. Ceccon, S. Benson, M.-P. Collin, B. Fasching, A. Fürstner, *Angew. Chem. Int. Ed.* **2009**, 48, 9940 – 9945; b) S. Benson, M.-P. Collin, G. W. O'Neil, J. Ceccon, B. Fasching, M. D. B. Fenster, C. Godbout, K. Radkowski, R. Goddard, A. Fürstner, *Angew. Chem. Int. Ed.* **2009**, 48, 9946 – 9950.