Studies Toward the Total Synthesis of Spiromastixone J

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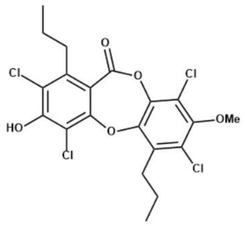
Introduction



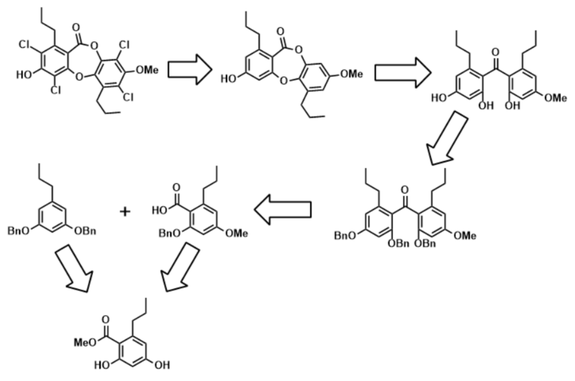
Spiromastixone J

- Depsidone natural product similar to Diploicin, isolated from deep-sea *Spiromastix sp.* fungus collected at 2,869 meter depth by autonomous remotely-operated vehicle[1]
- Isolated in 0.022% yield after three consecutive column chromatography separations performed on 58.4 g of extract after 50 days of fermentation[1]
- Exhibits single digit micromolar IC_{50}s towards multi-drug resistant Gram-Positive Bacteria such as MRSA[1]

Table 1: Reported IC_{50}s of Spiromastixone J

Bacterial Strain		Resistance Phenotype	IC50 (μM)	
			Mastixone J	Levofloxacin
S. aureus	ATCC 33591	MRSA	2	0.25
	15	MSSA	2	0.125
	12-28	MSSA	4	0.25
	12-33	MRSA	4	64

Retrosynthetic Analysis[2]

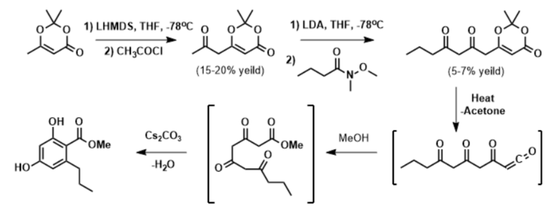


Key Intermediate 1

The above retrosynthetic analysis shows the heavy reliance on a large presence of Key Intermediate 1 (resorcilate).

Experimental Results

Scheme 1: Consecutive Claisen Condensations on Dioxinone[3]



Conclusion: Scheme 1 was too low yielding to be able to produce a sufficient amount of Key Intermediate 1.

Scheme 2: Diels-Alder Cycloaddition[4,5]

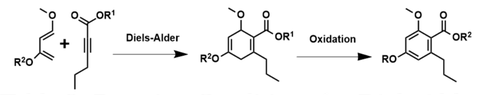
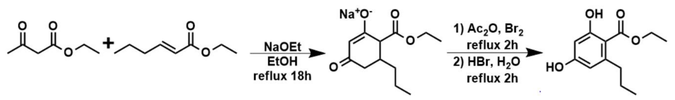


Table 2: Reaction Conditions for Diels Alder

R^1 Group	R^2 Group	Ratio		Solvent	Catalyst	Temperature	Result
		Diene	Dienophile				
Methyl	TBDMS	1	1	None	None	RT	No Reaction
Methyl	TBDMS	1	2	None	None	RT	No Reaction
Methyl	TBDMS	2	1	None	None	RT	No Reaction
Methyl	TBDMS	2	1	None	None	0 C	No Reaction
Methyl	TBDMS	1	2	Toluene	None	80 C	No Reaction
Methyl	TBDMS	1	1	None	$AlCl_3$	0 C	No Reaction
Methyl	TBDMS	1	1	None	$LiClO_4$	RT	No Reaction
Methyl	TBDMS	1	1	Diethyl Ether	$LiClO_4$	RT	No Reaction
Methyl	TBDMS	1	1	Diethyl Ether	$LiClO_4$	60 C	No Reaction
Methyl	TBDMS	1	1	Water	LiCl	RT	No Reaction
Propyl	TBDMS	1	1	None	None	RT	No Reaction
Propyl	TBDMS	1	1	None	None	150 C	No Reaction
Methyl	TMS	1	1	None	None	RT	No Reaction

Extensive diene decomposition was typically observed.
Conclusion: After extensive experimentation, the Diels-Alder approach to Key Intermediate 1 was abandoned.

Scheme 3: Robinson Annulation/Elimination[6,7]

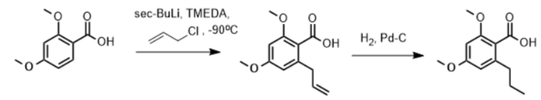


Conclusion: This sequence appears to be the most promising approach to acquire gram-scale quantities of Key Intermediate 1. The second step of Scheme 3 is still low yielding and produces a wide variety of side products. We are currently researching the best method to optimize this reaction.

Future Work

1. Optimization of sequence in Scheme 3. We are currently optimizing the reaction conditions on the shortened and cheaper methyl version (ethyl crotonate).
2. Completion of Spiromastixone J synthesis.
3. Should sequence in Scheme 3 not provide sufficient amounts of desired Key Intermediate 1, an alternative pathway we have considered but not yet explored is the *ortho*-lithiation of the resorcilate seen in the Scheme 4 below.[8]

Scheme 4: Ortho Lithiation[8]



References

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