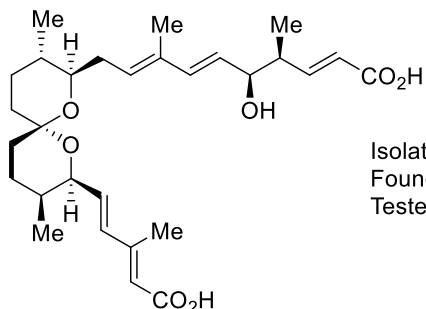


Spirofungin A

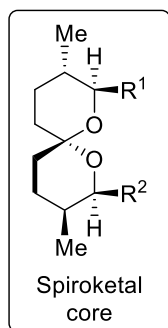
Marjanovic, J.; Kozmin. S. *ACIE* **2007**, *46*, 8854



Isolated from *Streptomyces violaceusniger* Tü 4113
Found to inhibit isoleucyl-tRNA synthetase => Cell antiproliferative activity
Tested against human cancer cell lines (promising at the time of publication)

Conformational analysis of the spiroketal core.

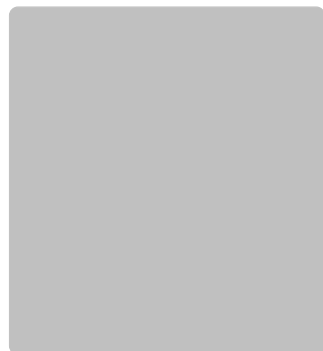
- Which conformation is supposed to be more stable?
- At this stage, do not consider the sterical hindrance of R substituents.
- Now consider the actual sterical hindrance of Rs. Can you figure out the issues that were encountered by the authors when trying to access the desired conformer? (grey box 1)
- Strategy question: Can you imagine the strategic approach that was used by the authors to overcome this problem? Hint: To get the answer, think of one of the research lines of LCSO.
- Draw the molecule (grey box 2)



1



3

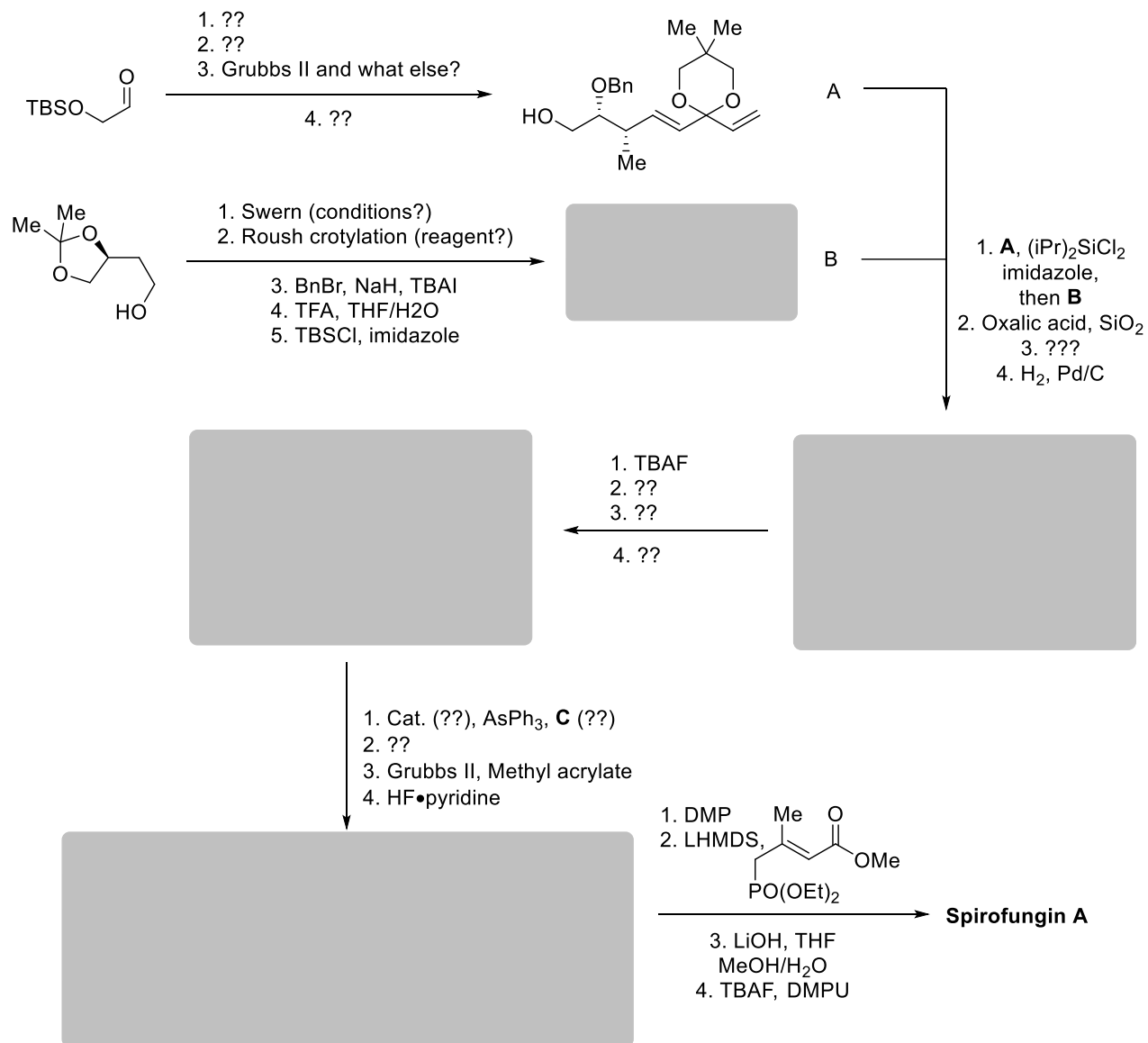


2

(Retro)Synthesis

- Draw the "open" precursor of the spiroketal (when done so, removing the grey box 3 will disclose the actual intermediate).

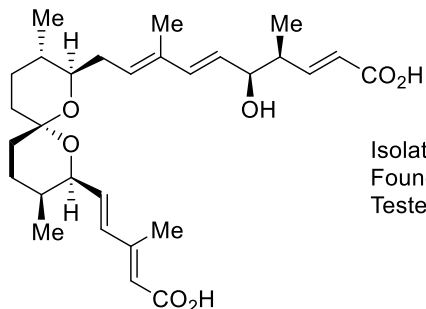
.....



SOLUTION

Spirofungin A

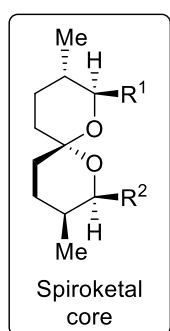
Marjanovic, J.; Kozmin. S. *ACIE* 2007, 46, 8854



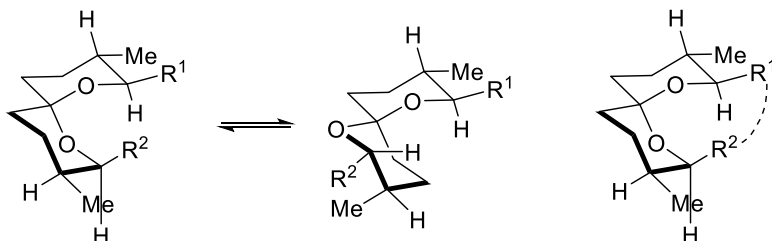
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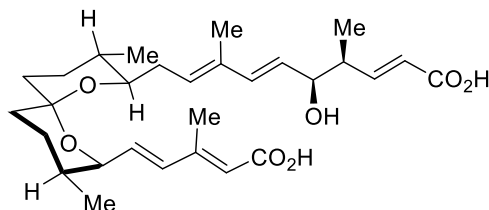
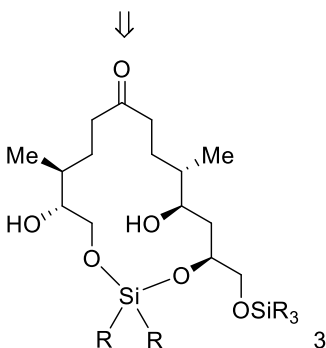


1



Double anomeric stabilization Sterically disfavored Single anomeric stabilization Sterically favored

Problem: Equimolar mixture of the epimers
 Solution: Tethering, to overcome the sterical hindrance issues.



2

(Retro)Synthesis

- Draw the "open" precursor of the spiroketal (when done so, removing the grey box 3 will disclose the actual intermediate).

