Literature Report
2013-11-12

Dehydrogenative Coupling to Enable the Enantioselective Total Synthesis of (-)-Simaomicin

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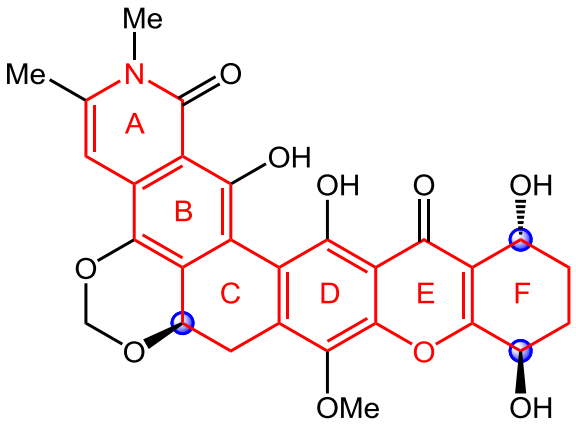
Checker Wu, B.

Ready, J. M. *et al*
Angew. Chem. Int. Ed. **2013**, *52*, 10796-10799.

UT Southwestern
Medical Center

Contents

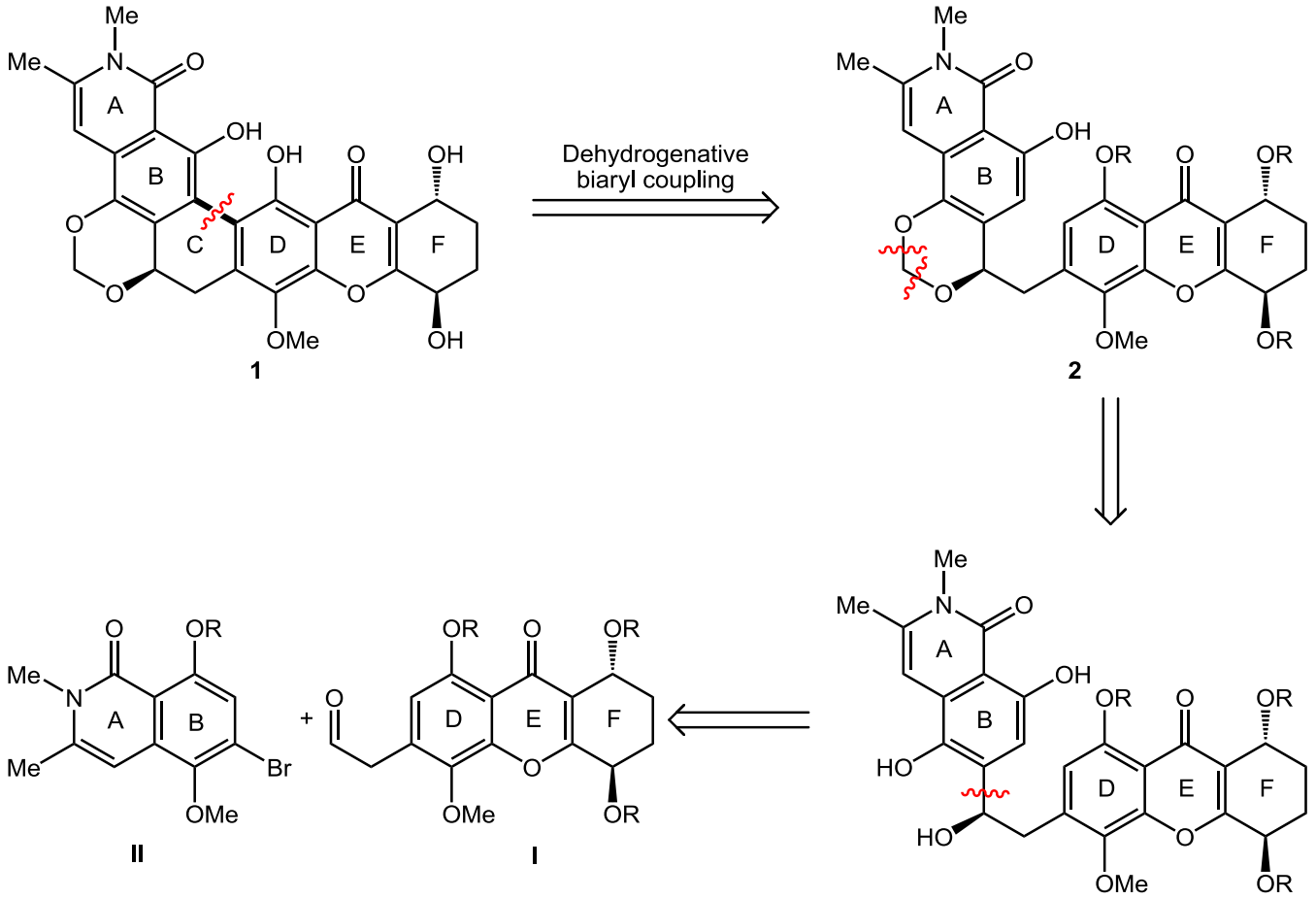
1 Introduction



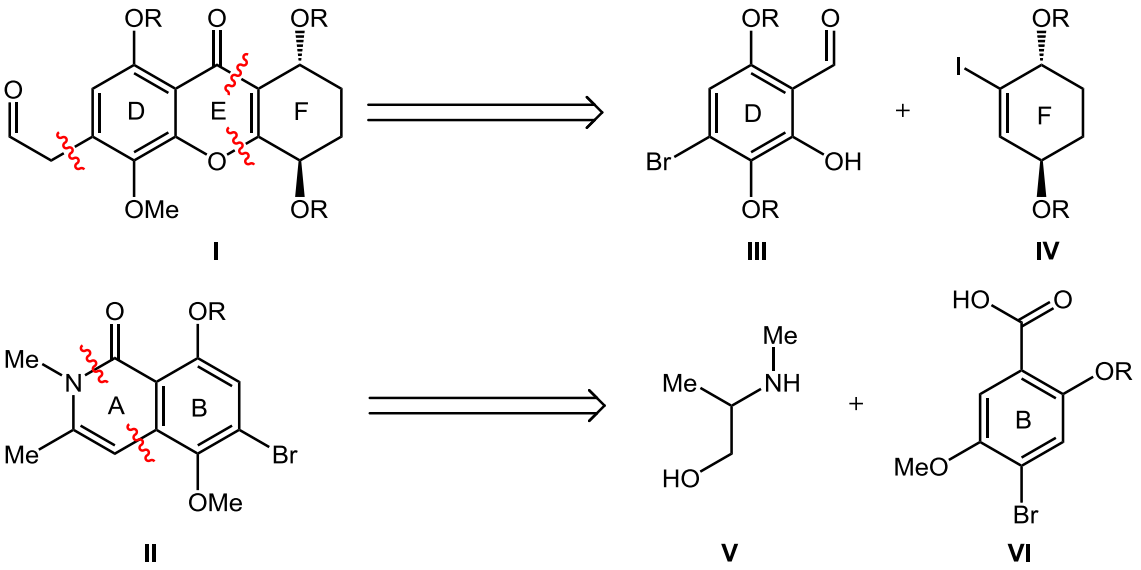
Simaomicin

- Isolated from the culture broth of an actinomycete in 1989
- Polycyclic xanthone natural product, 3 stereo-centers
- The most potent natural-occurring anticoccidial agent reported
- Anti-parasitic activity, Antitumor activity

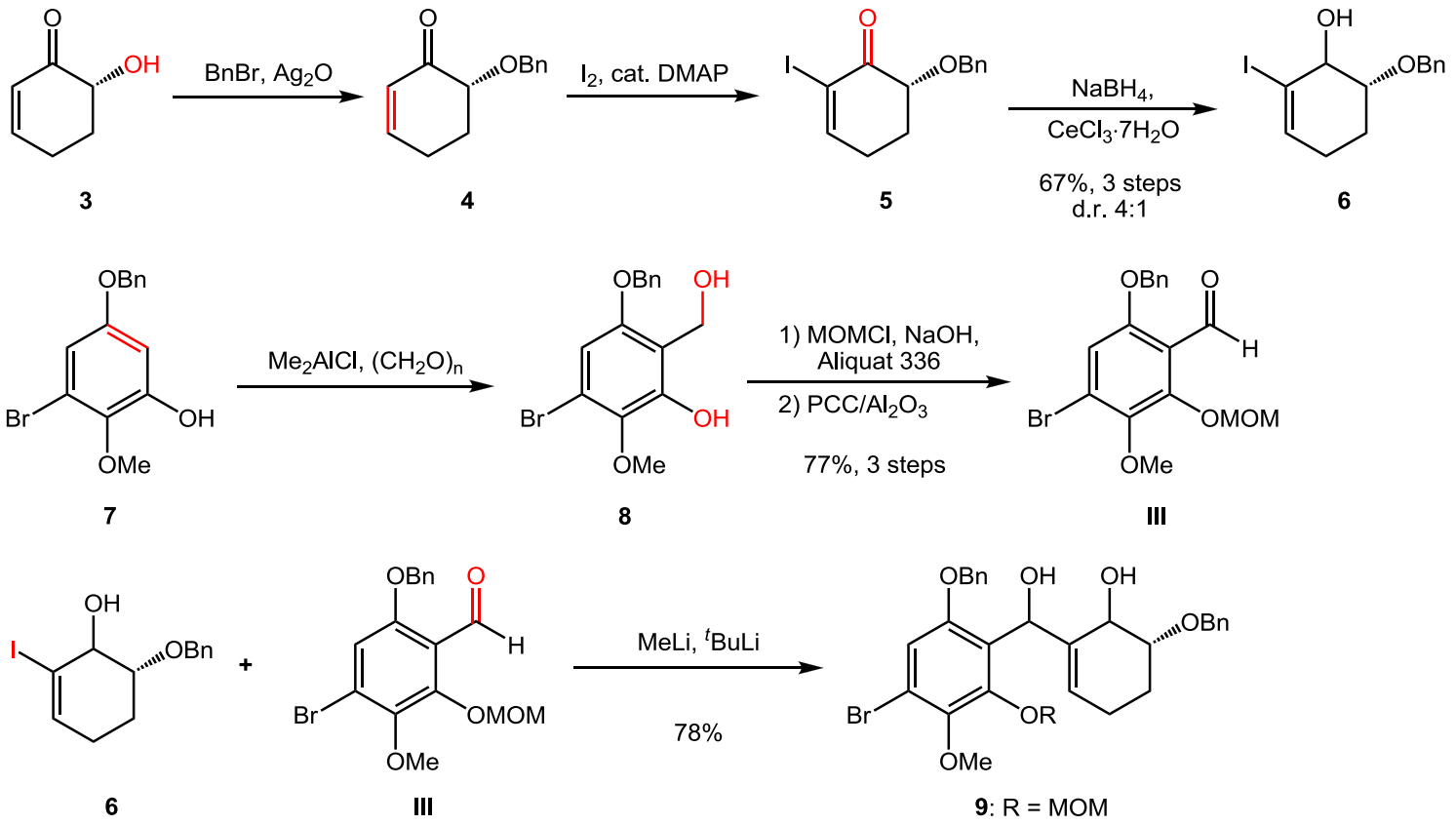
2 Retrosynthesis of Simaomicin



2 Retrosynthesis of Simaomicin

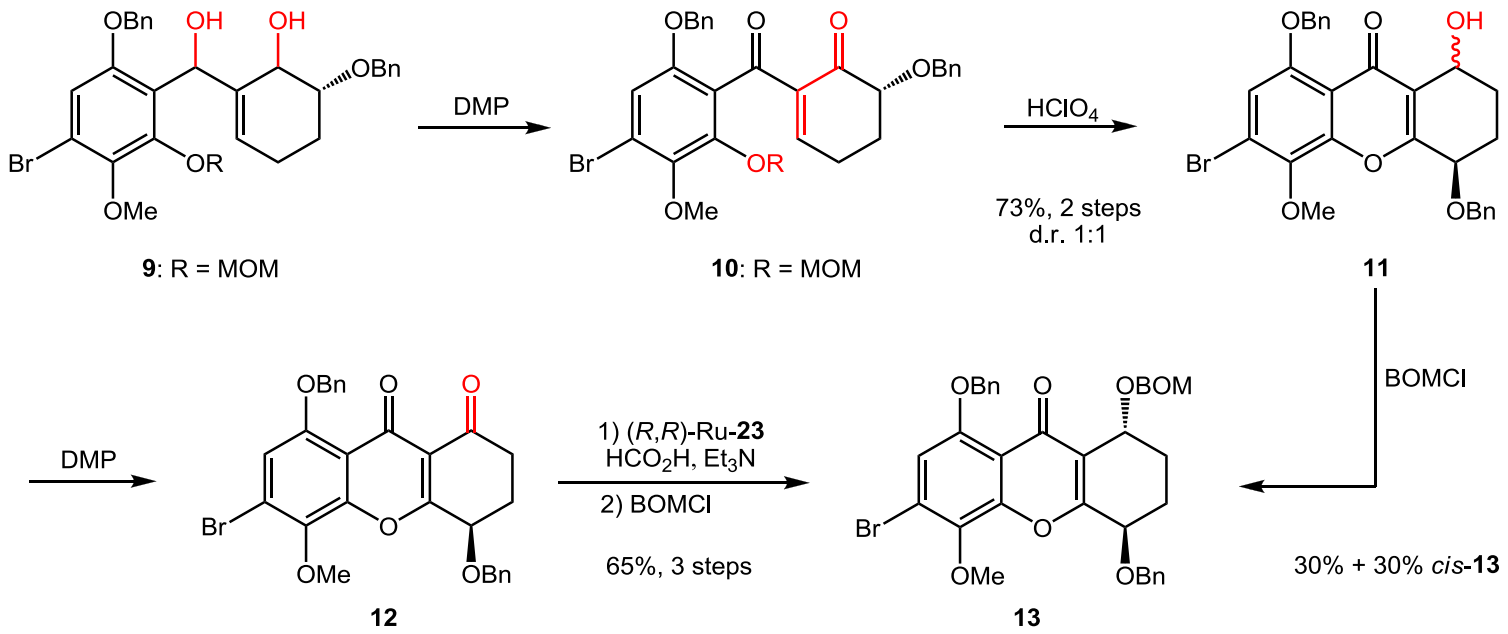


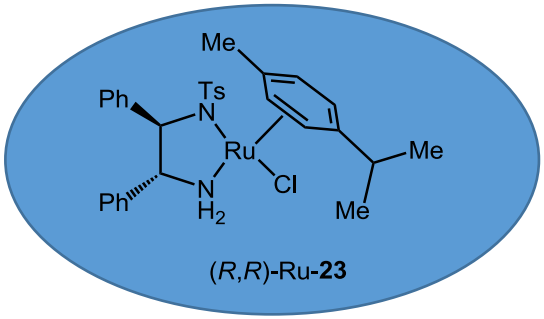
3 Synthesis of Simaomicin



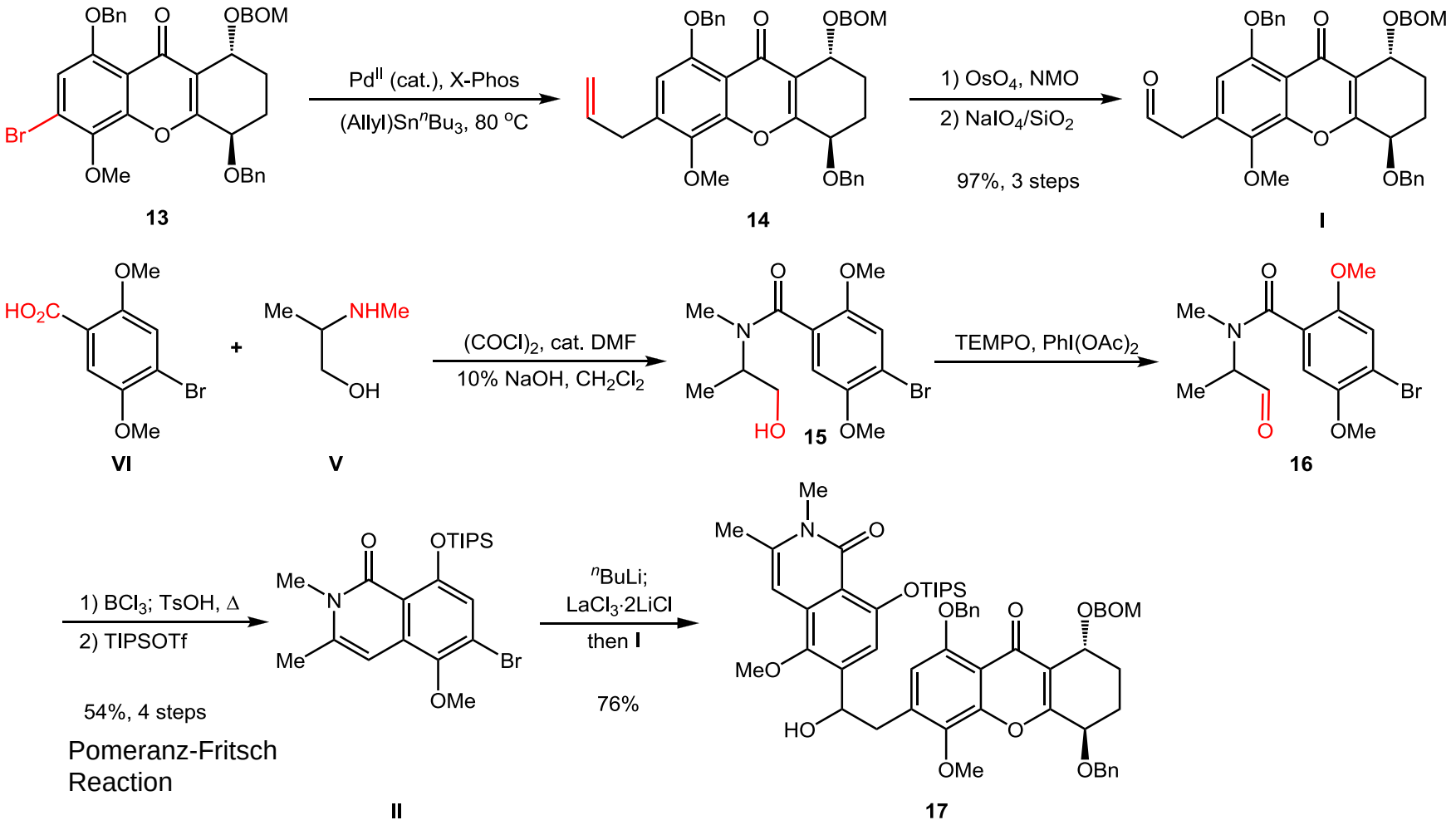
Aliquat 336: methyl trioctyl ammonium chloride

3 Synthesis of Simaomicin



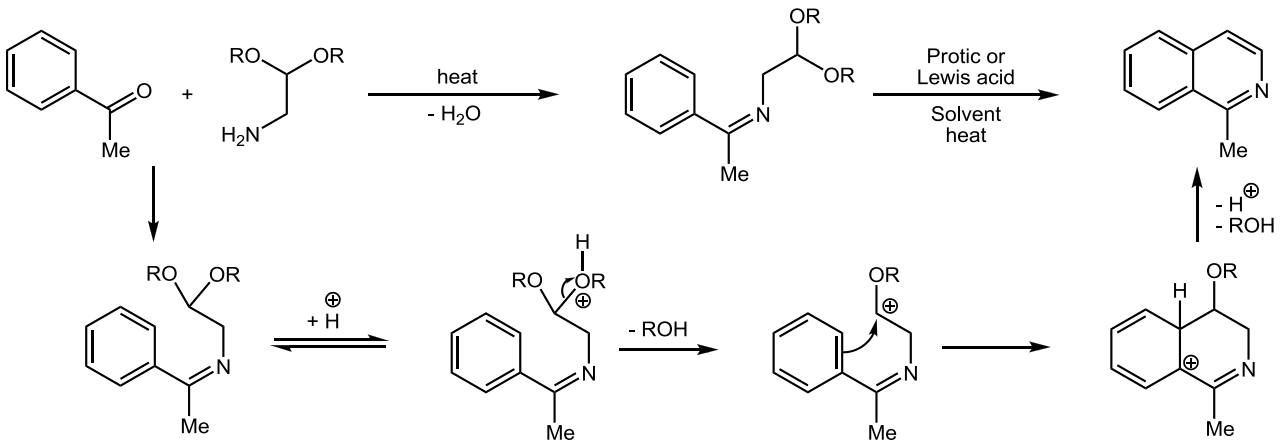


3 Synthesis of Simaomicin

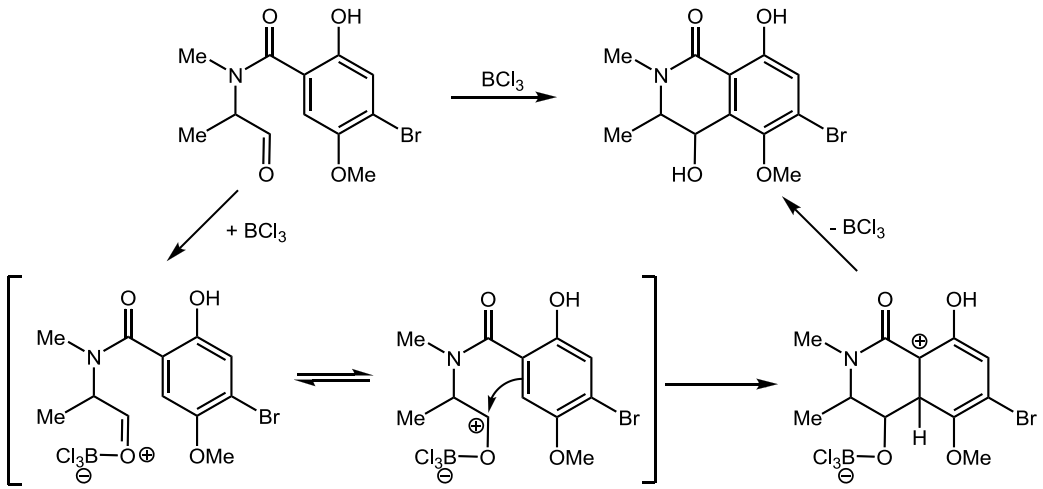


3 Synthesis of Simaomicin

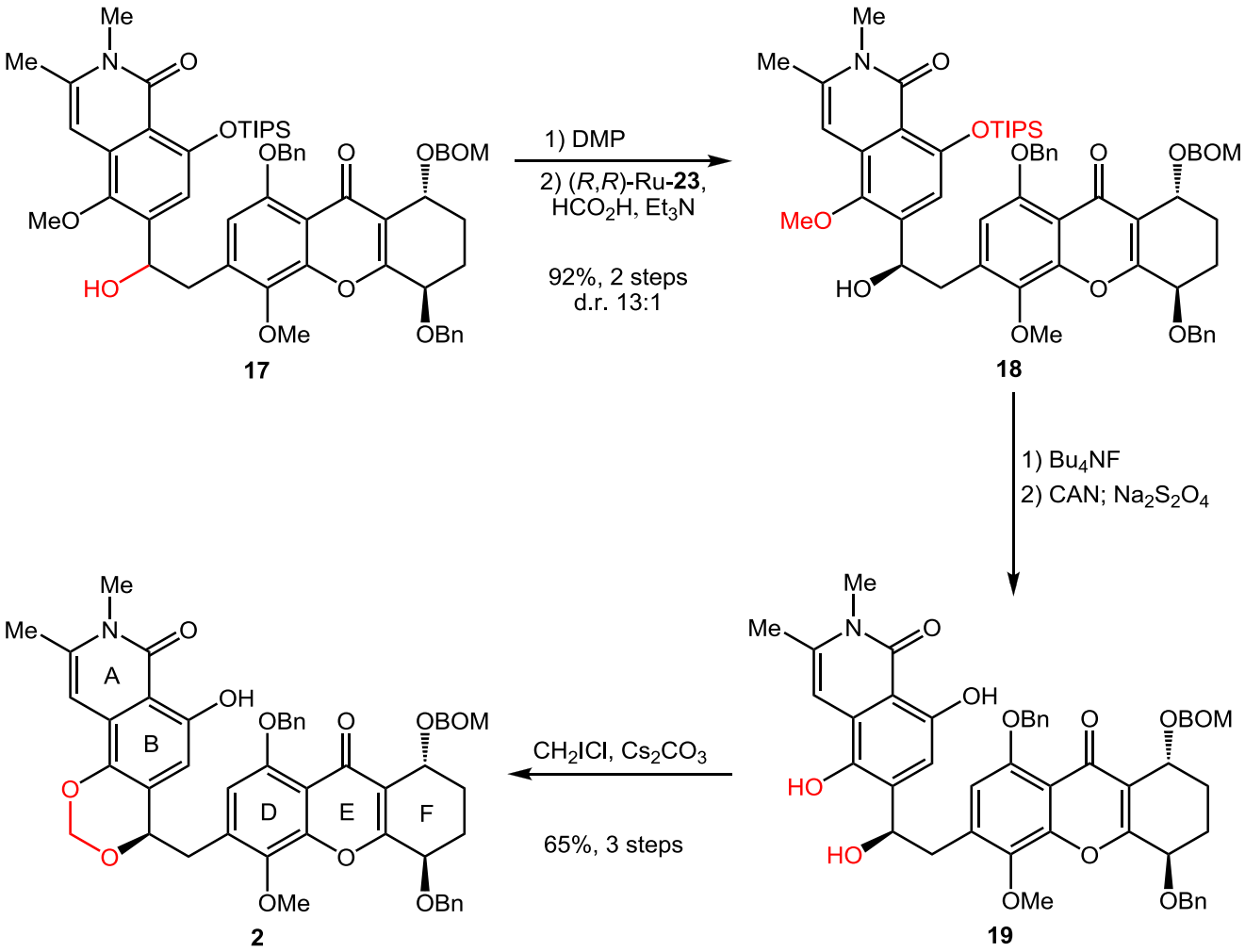
Pomeranz-Fritsch Reaction



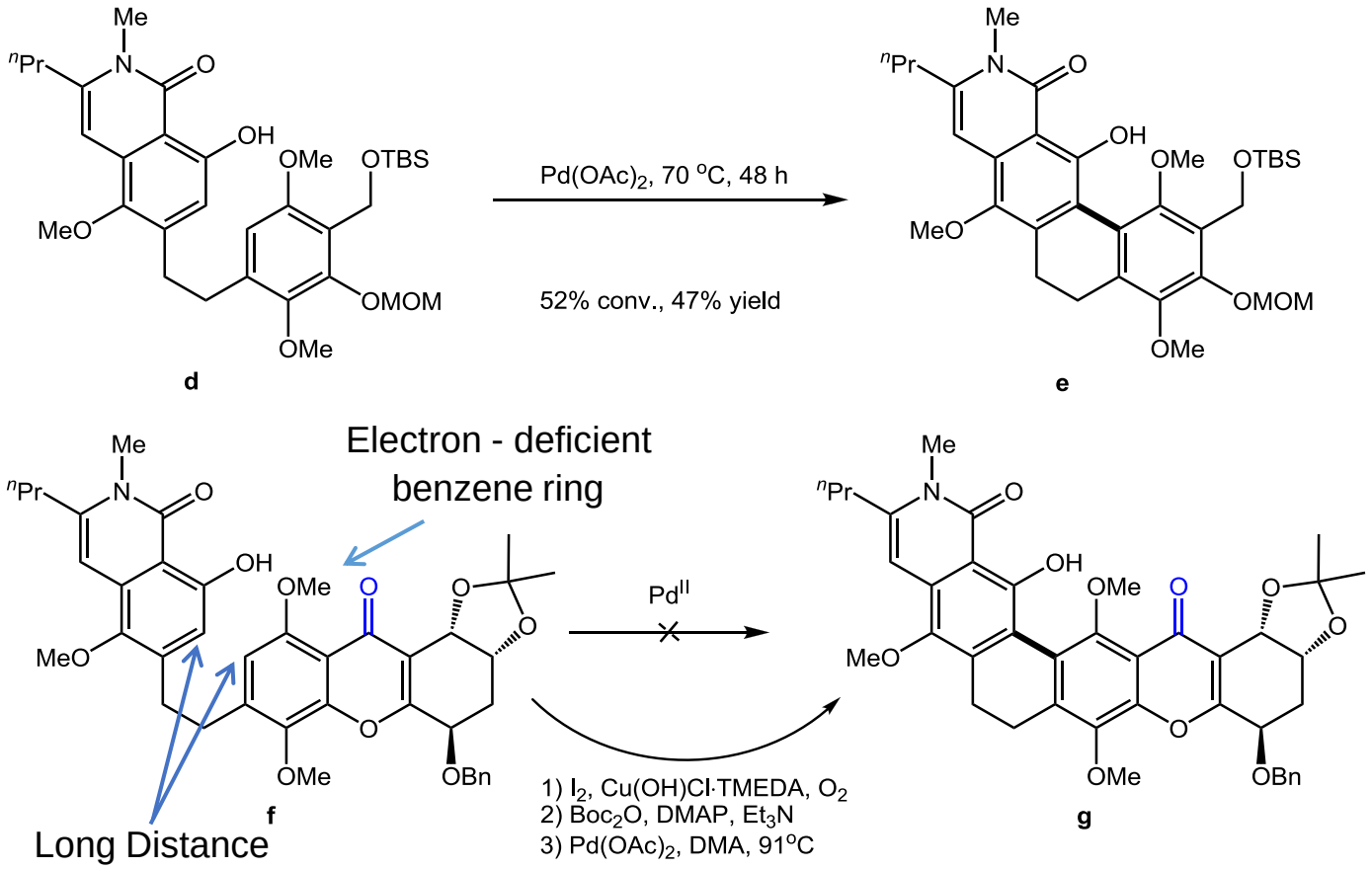
Plausible Mechanism



3 Synthesis of Simaomicin

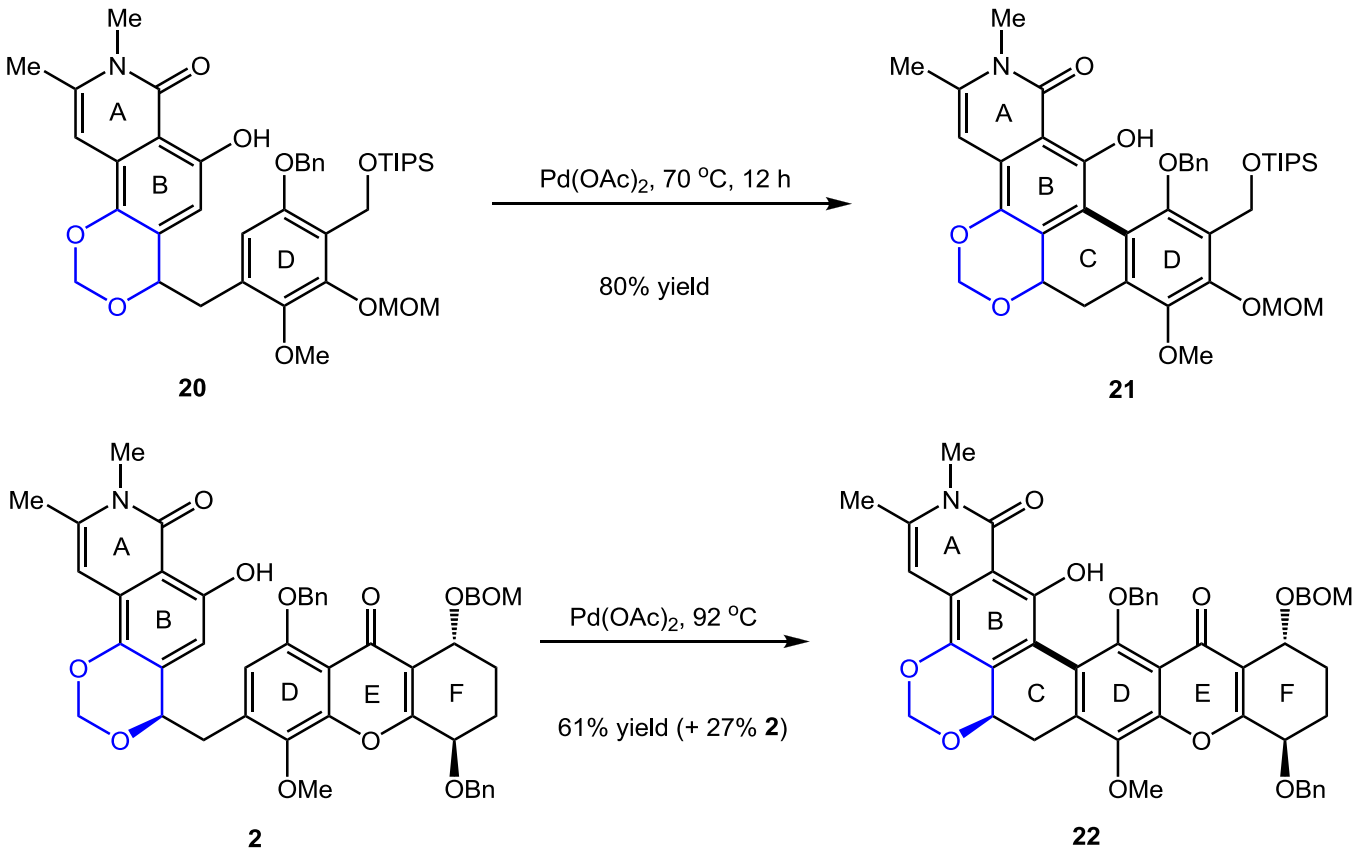


3 Synthesis of Simaomicin

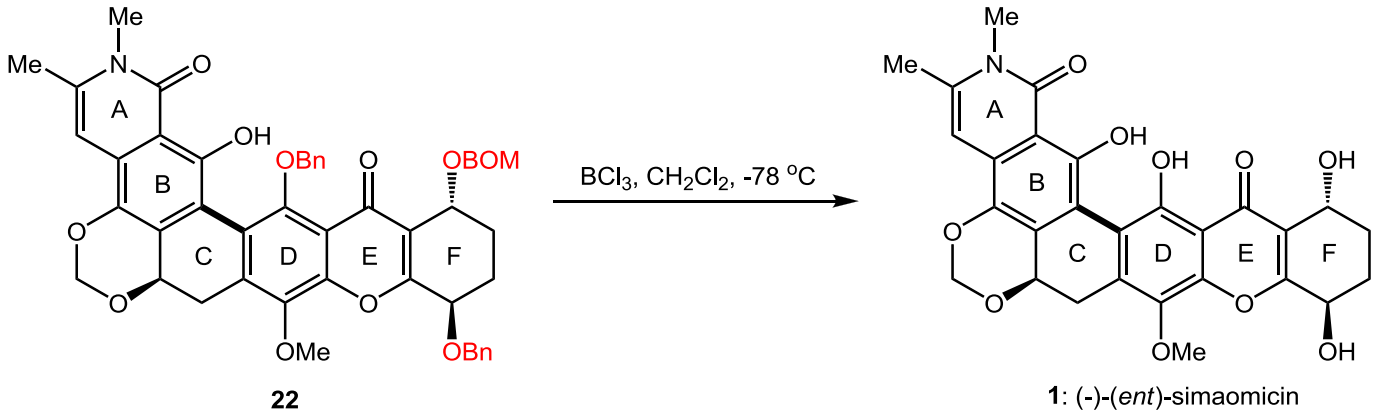


Ready, J. M. *et al J. Am. Chem. Soc*. **2011**, *133*, 9956-9959.

3 Synthesis of Simaomicin



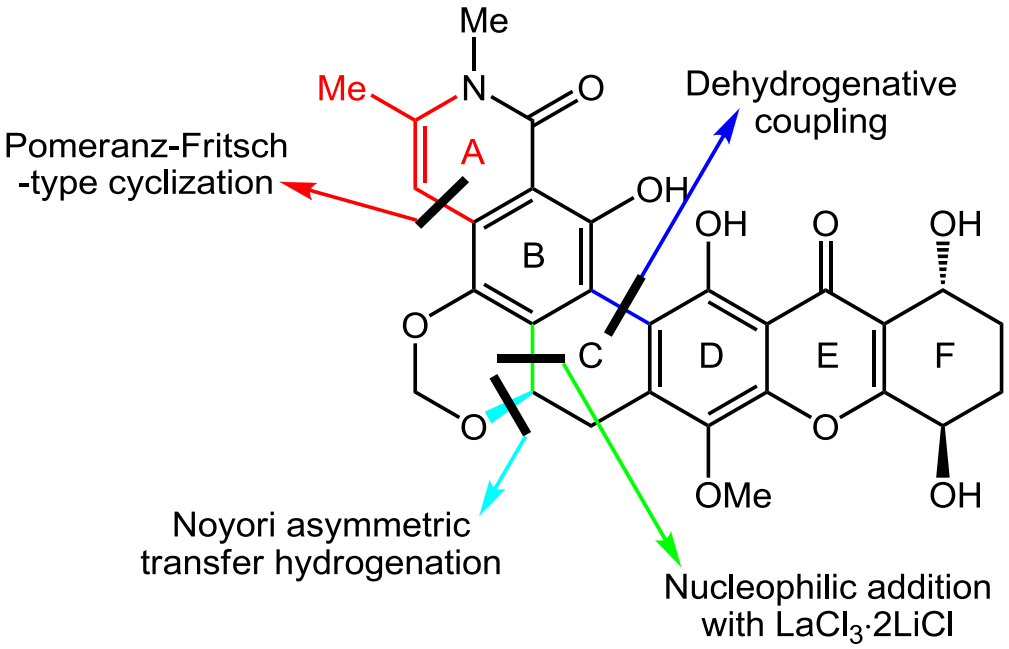
3 Synthesis of Simaomicin



The longest linear steps: 20 steps

Total yields: 5.8%

4 Summary


Me
Me
N
O
A
Pomeranz-Fritsch
-type cyclization
Dehydrogenative
coupling
OH
OH
O
OH
B
O
C
D
E
F
O
O
OMe
OH
Noyori asymmetric
transfer hydrogenation
Nucleophilic addition
with $LaCl_3 \cdot 2LiCl$

Simaomicin is a polycyclic xanthone natural product with remarkable biological properties. It was isolated by scientists from American Cyanamid Company from the culture broth of an actinomycete, and its structure and relative stereochemistry were established by NMR spectroscopy and X-ray crystallography. Simaomicin originally garnered attention for its ability to prevent coccidiosis infection in chickens that were fed meal containing 1 mg drug/kg feed. The isolation group noted that it was “the most potent natural-occurring anticoccidial agent reported”. Fifteen years after its structure and anti-parasitic activity was reported, Tomoda and co-workers revealed that simaomicin had little effect on Jurkat cells as a single agent at low concentration, but that it synergized with the DNA damaging agent bleomycin.

Thus, while bleomycin caused G2-arrest, the combination of bleomycin and simaomicin was cytotoxic against this T-lymphocyte cell line. Provocatively, even much higher concentrations of simaomicin had little effect on a normal HUVEC cell line. The molecular underpinnings for these effects are unknown, but the checkpoint regulators Chk1, Chk2, ATM, ATR, and Wee1 are not inhibited. The natural product was found to suppress phosphorylation of retinoblastoma protein, but a molecular target has not been identified. The therapeutic implication of these observations is that co-administration of a DNA damaging agent with a cell-cycle inhibitor could be more efficacious than treatment with a single agent.

In conclusion, we report the first total synthesis of simaomicin, and establish its absolute stereochemistry. Noteworthy features of the synthesis include its convergent nature, the use of $LaCl_3 \cdot 2LiCl$ in a late-stage fragment union, and a direct dehydrogenative coupling to complete the carbon skeleton of the natural product. Initial biological profiling revealed that (+)- and (-)-simaomicin display similar biological activity. Ongoing experiments aim to identify a binding partner for this natural product and understand its mode of toxicity.

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