# A Convergent Total Synthesis of the Telomerase Inhibitor (±)-γ-Rubromycin

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Reissig, H**.** *et al.*
*Angew. Chem. Int. Ed.* **2014**, *53,* 4332-4336.

柏林自由大学

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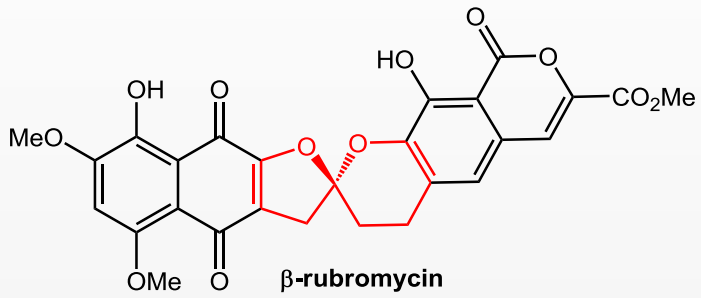
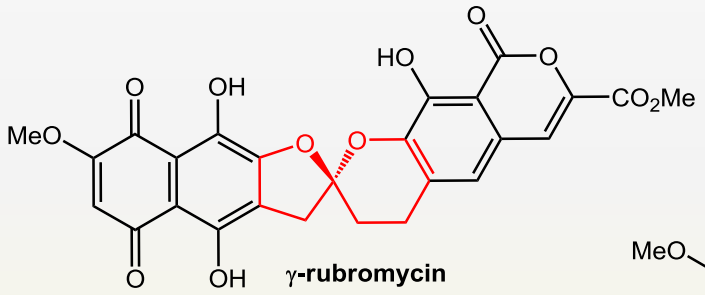
# Introduction

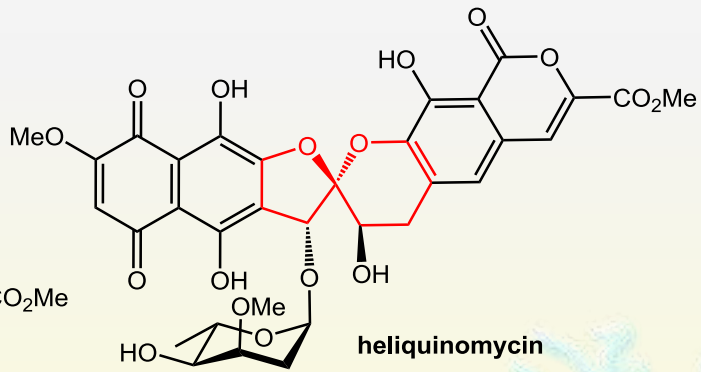



β-rubromycin

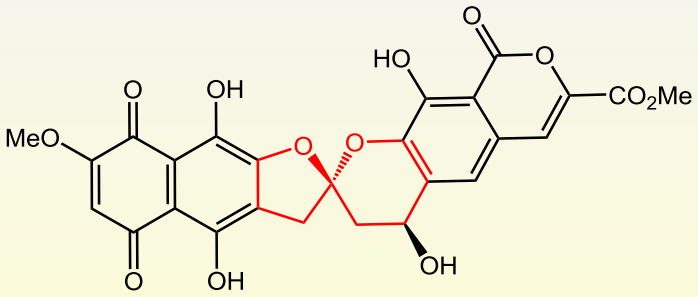
**1953**: Isolated from the mycelia of *Streptomyces collinus* (Brockmann and Renneberg)
**2000**: Revision of structure (Zeeck et al)




γ-rubromycin



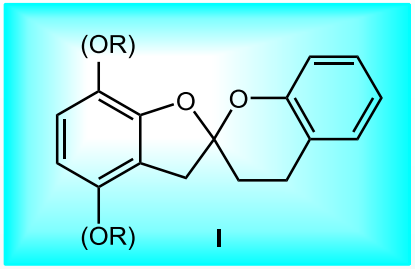

heliquinomycin




purpuromycin

# Kita's work – The first total synthesis of (±)-γ-Rubromycin

## Construction of the core structure of (±)-γ-Rubromycin

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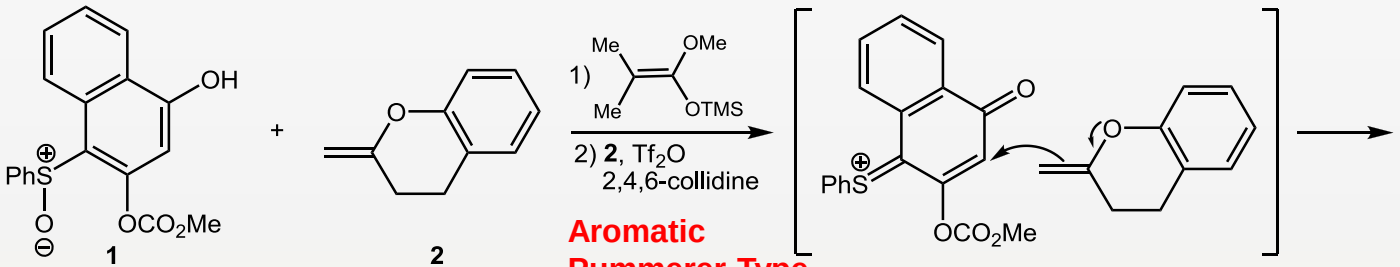
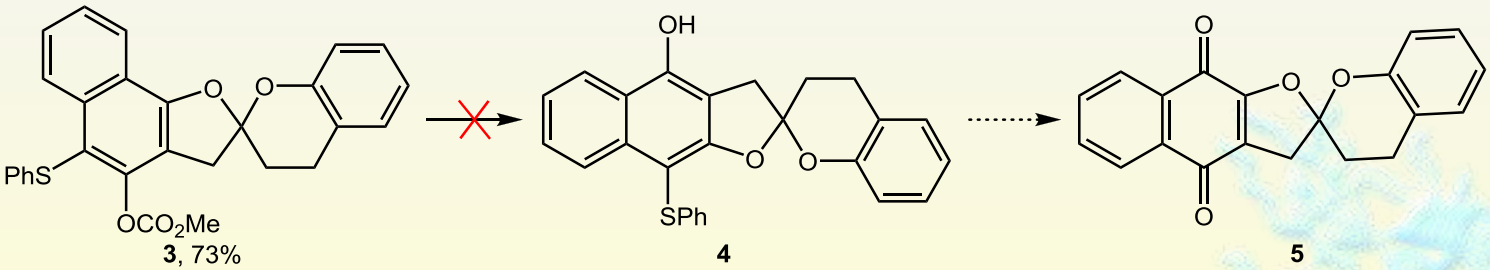
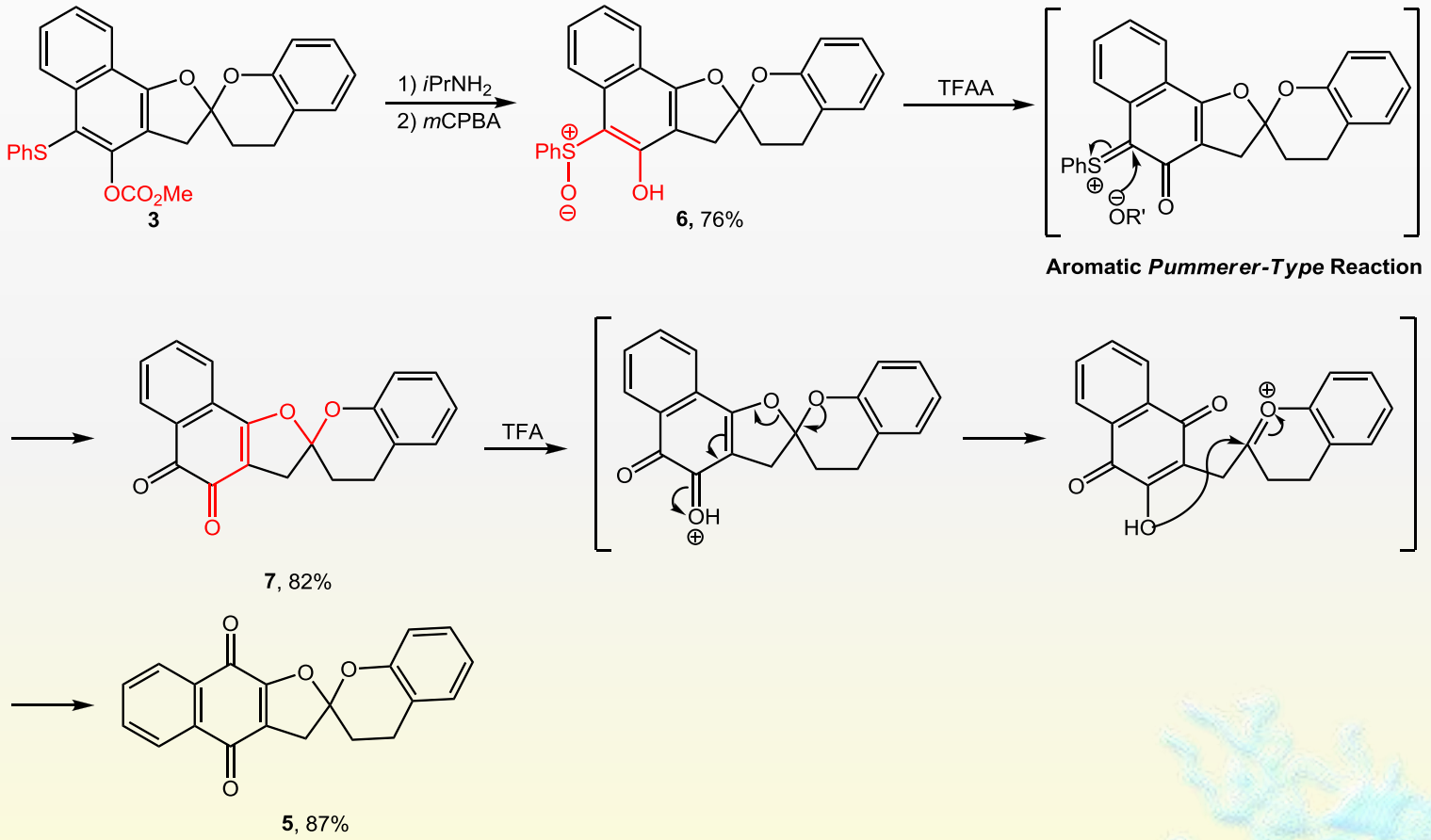



**Aromatic Pummerer-Type Reaction**




Kita, Y. *et al*. *Angew. Chem. Int. Ed.* **2007**, *46*, 7458-7461.

# Kita's work – The first total synthesis of (±)-γ-Rubromycin



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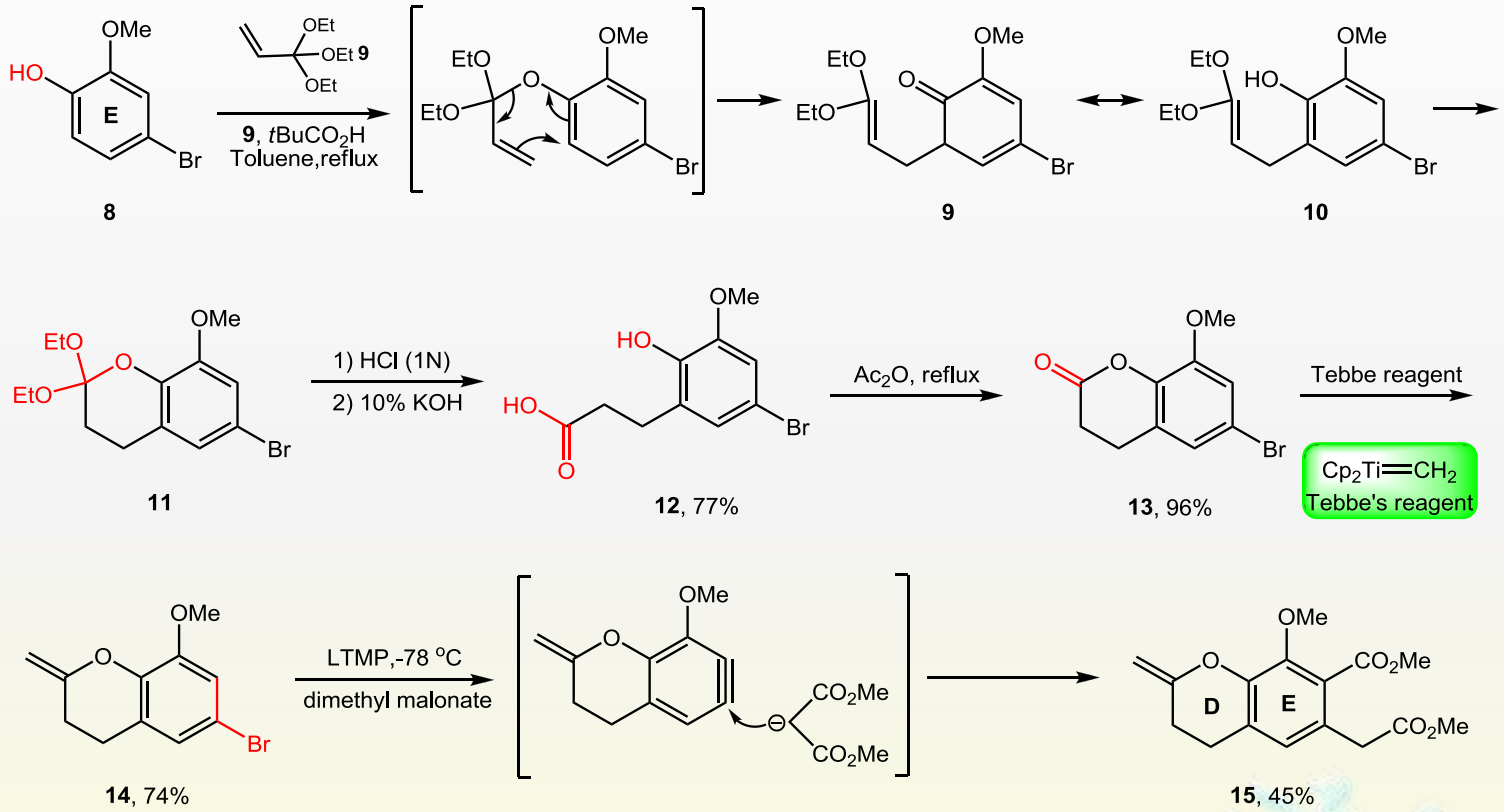
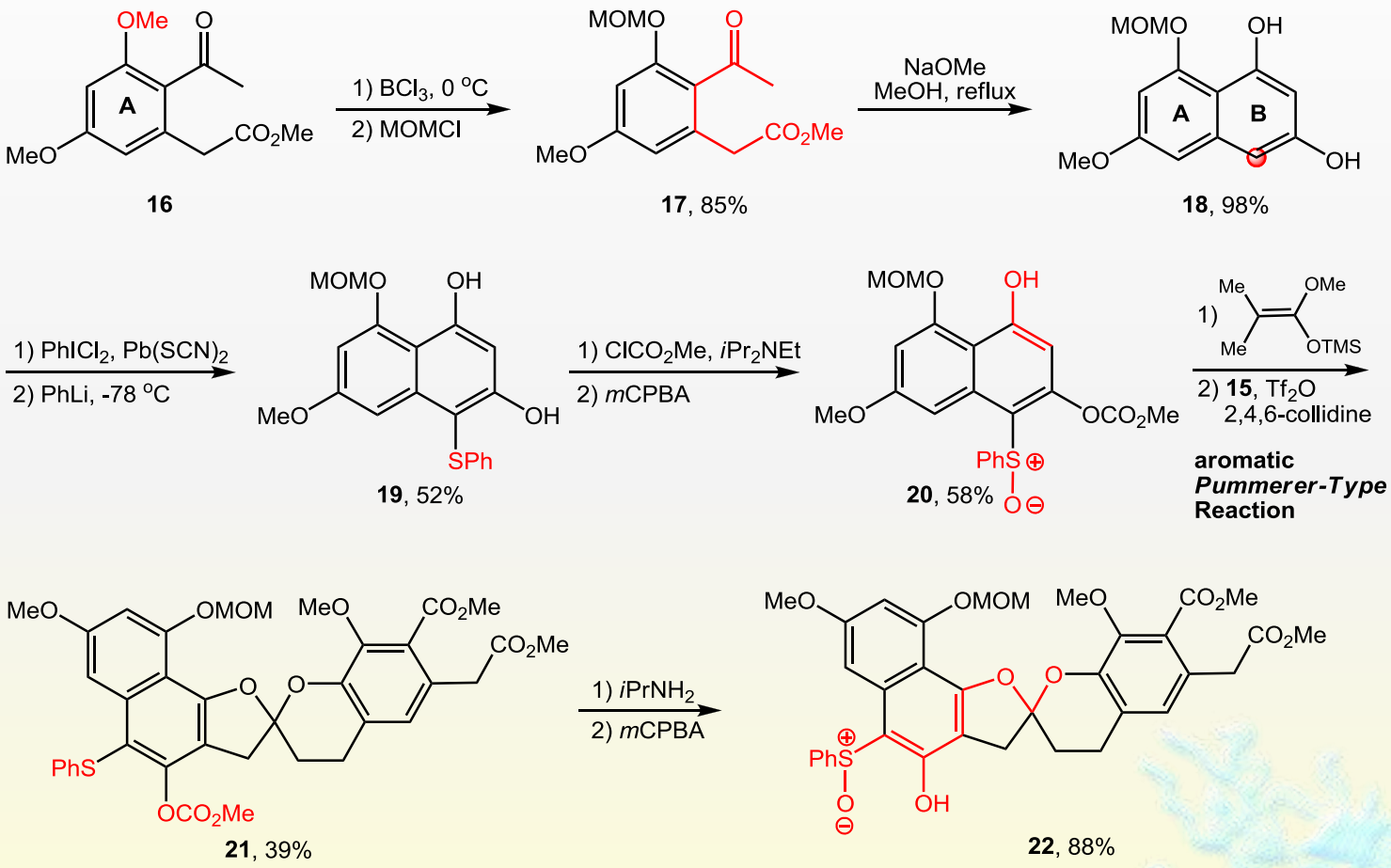
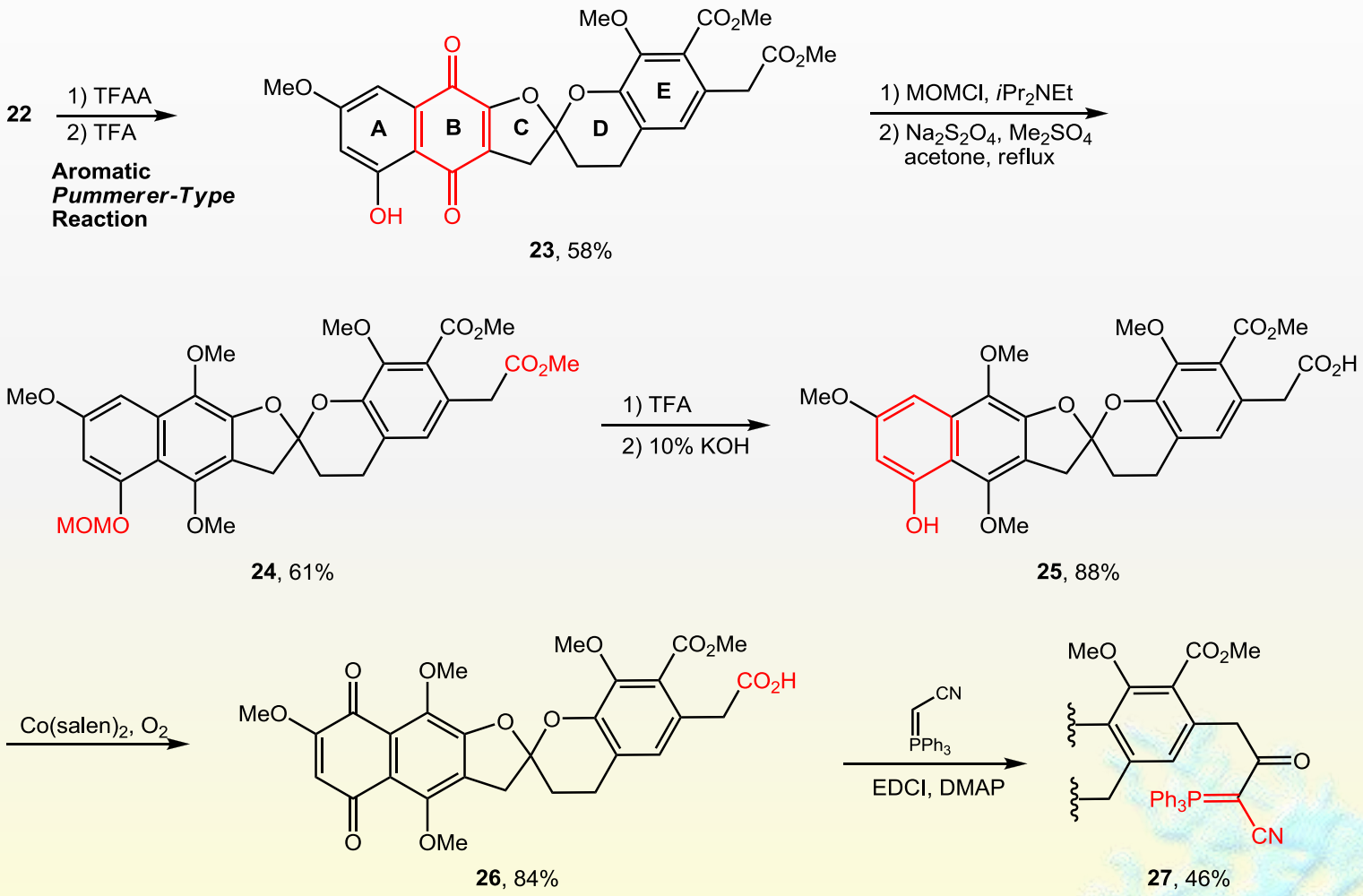


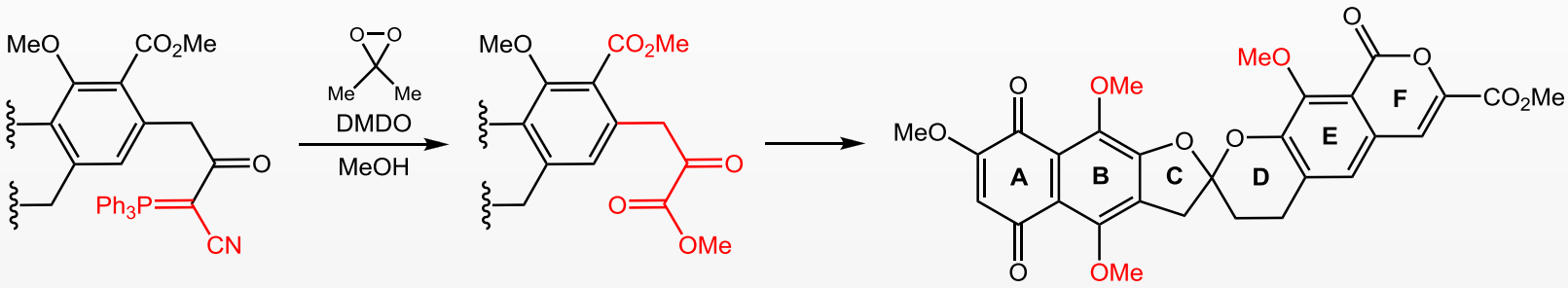
# Kita's work – The first total synthesis of (±)-γ-Rubromycin



# Kita's work – The first total synthesis of (±)-γ-Rubromycin



# Kita's work – The first total synthesis of (±)-γ-Rubromycin

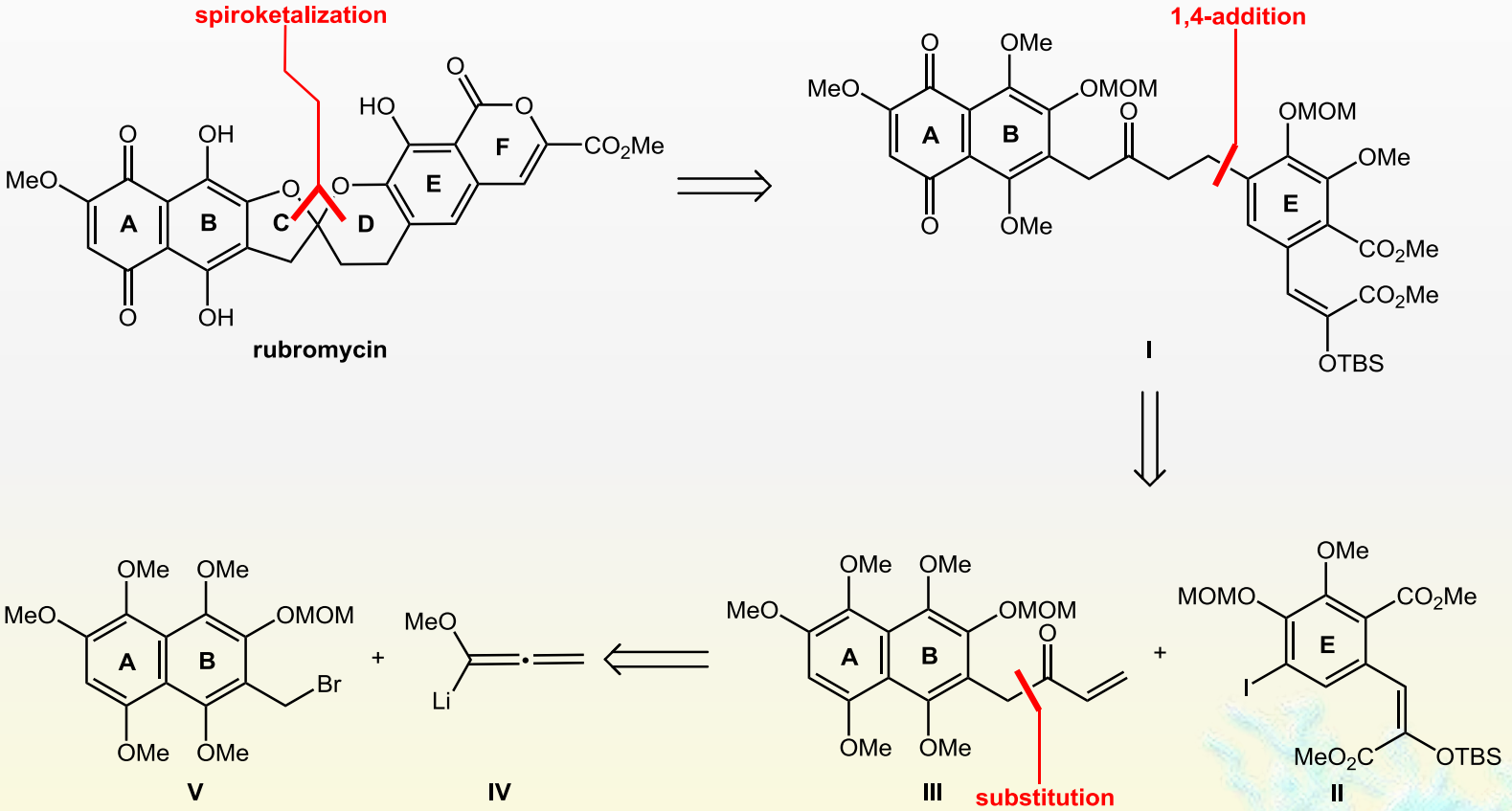



**27** **28** **29**, 56%

**γ-rubromycin**, 65%

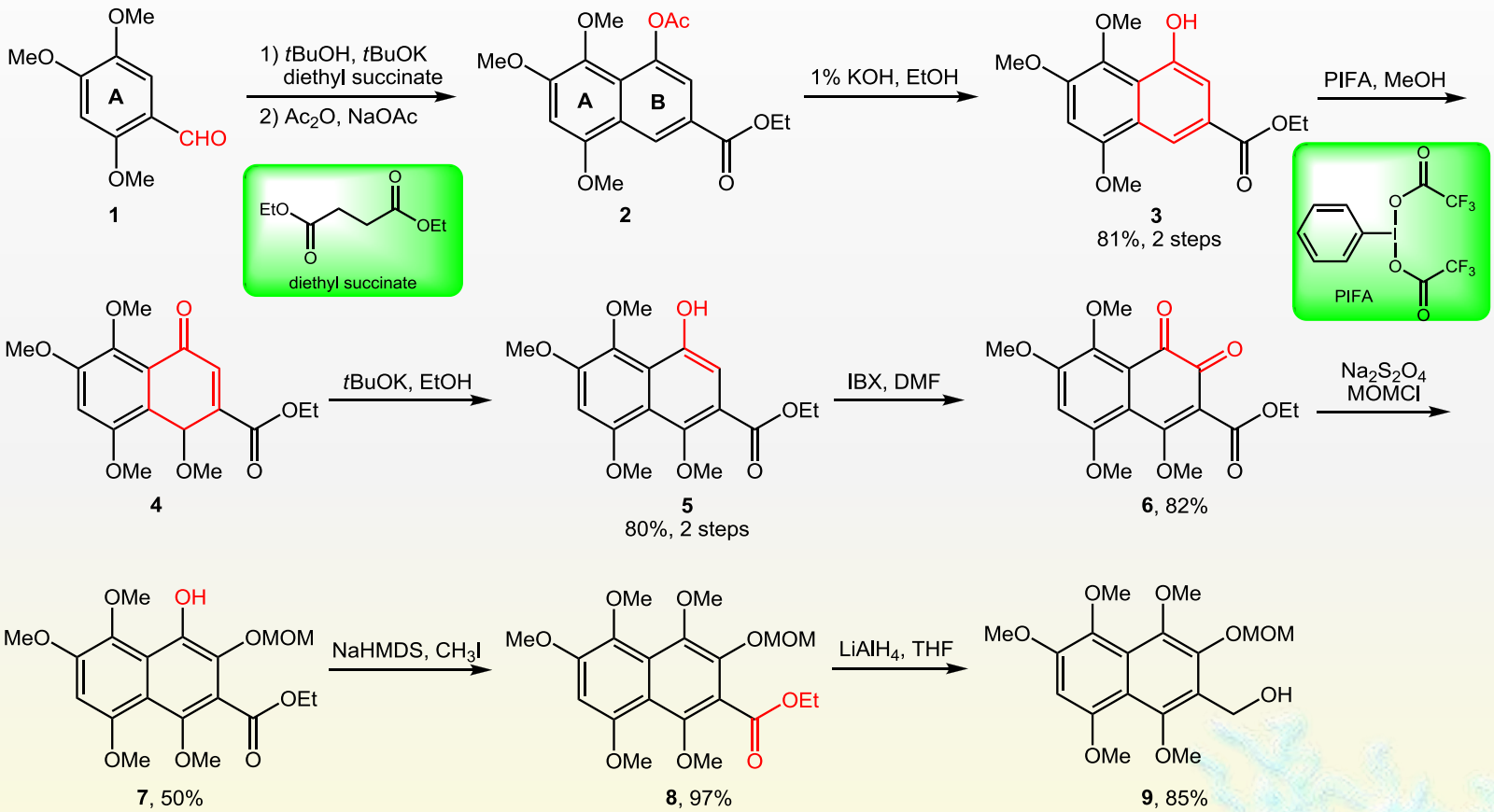
# Reissig's work– A convergent total synthesis

## Retrosynthesis of (±)-γ-Rubromycin

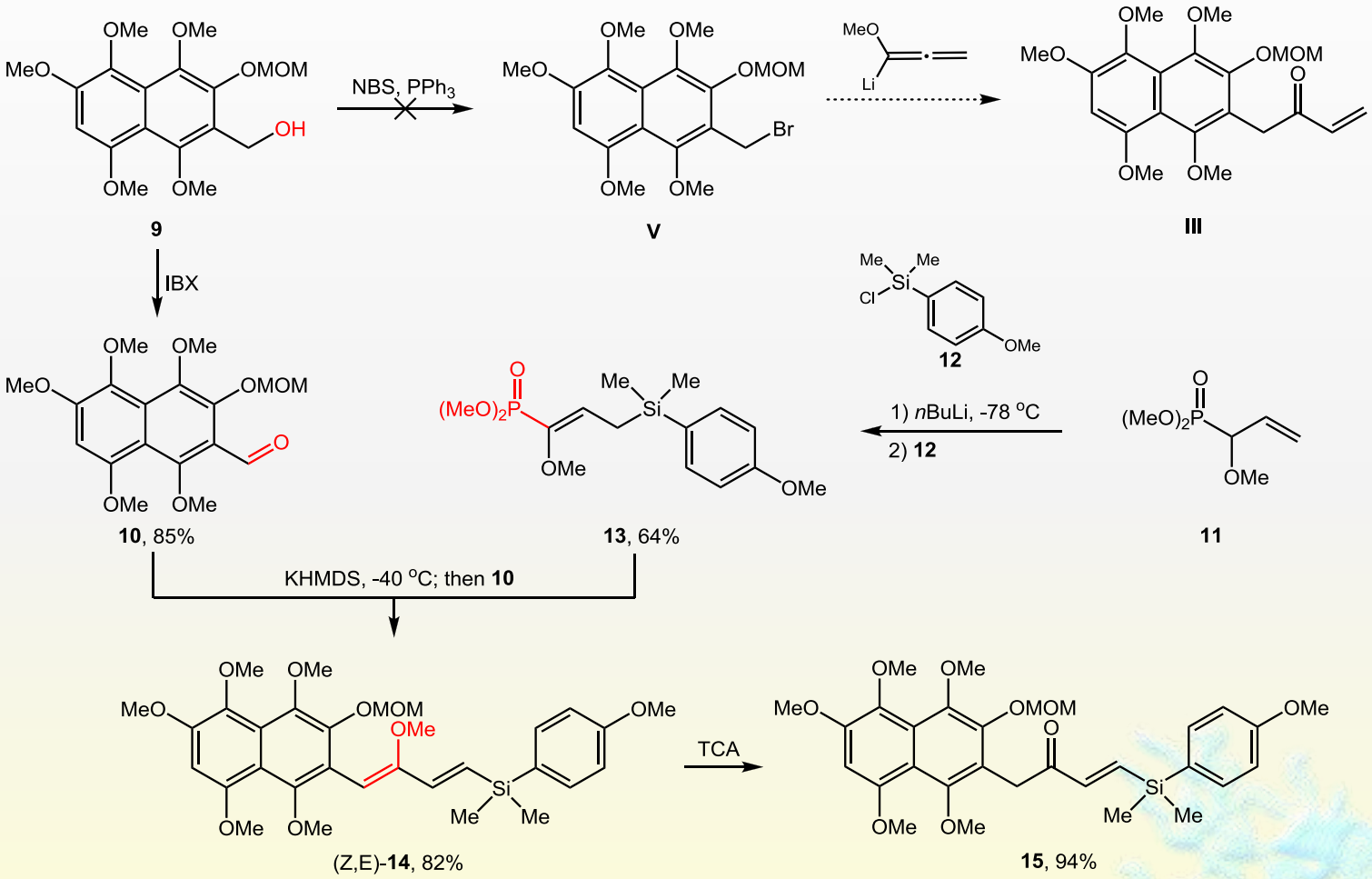



Reissig, H. *et al*. *Angew. Chem. Int. Ed.* **2014**, *53*, 4332-4336.

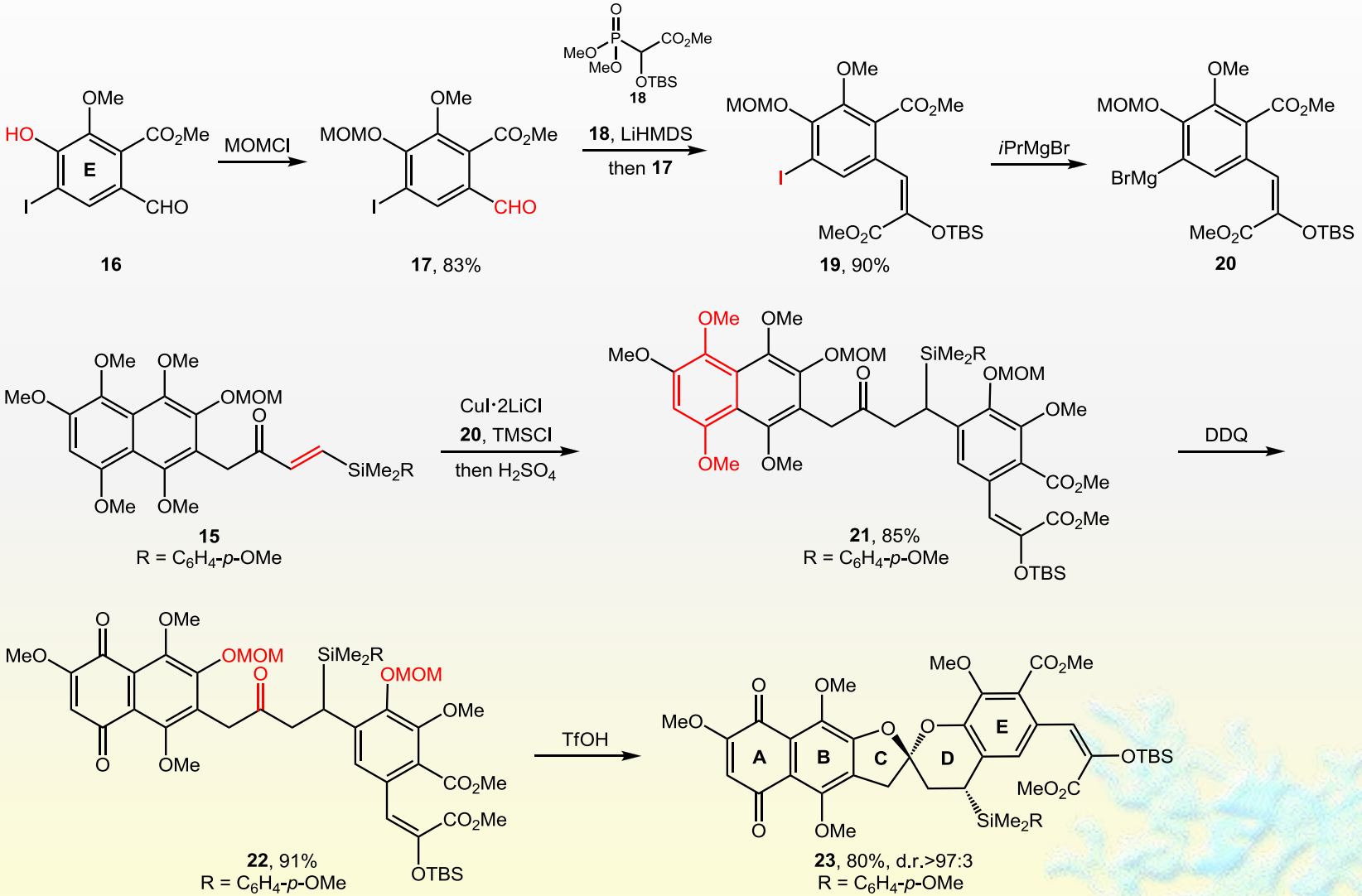
# Reissig's work– A convergent total synthesis



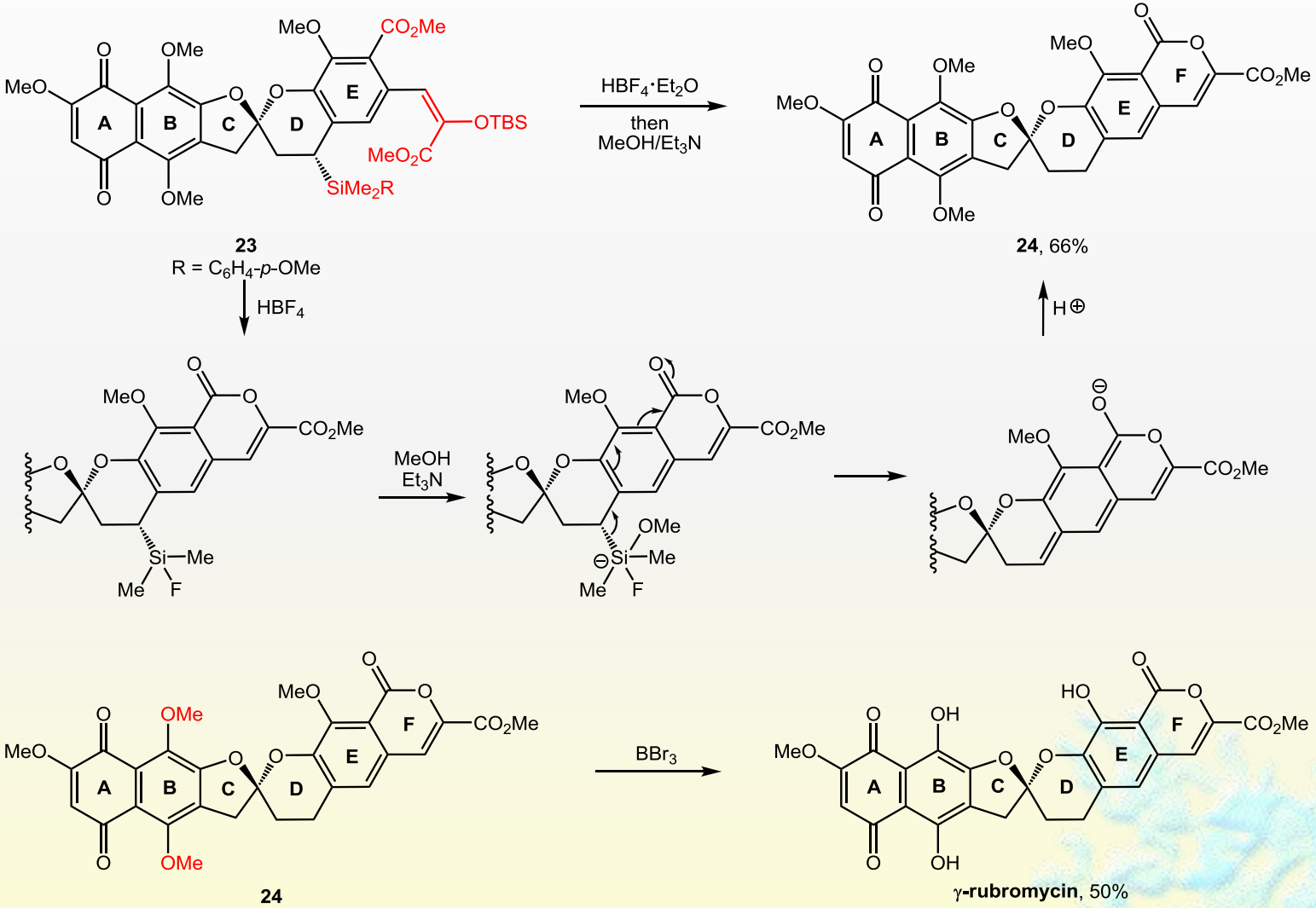
# Reissig's work– A convergent total synthesis



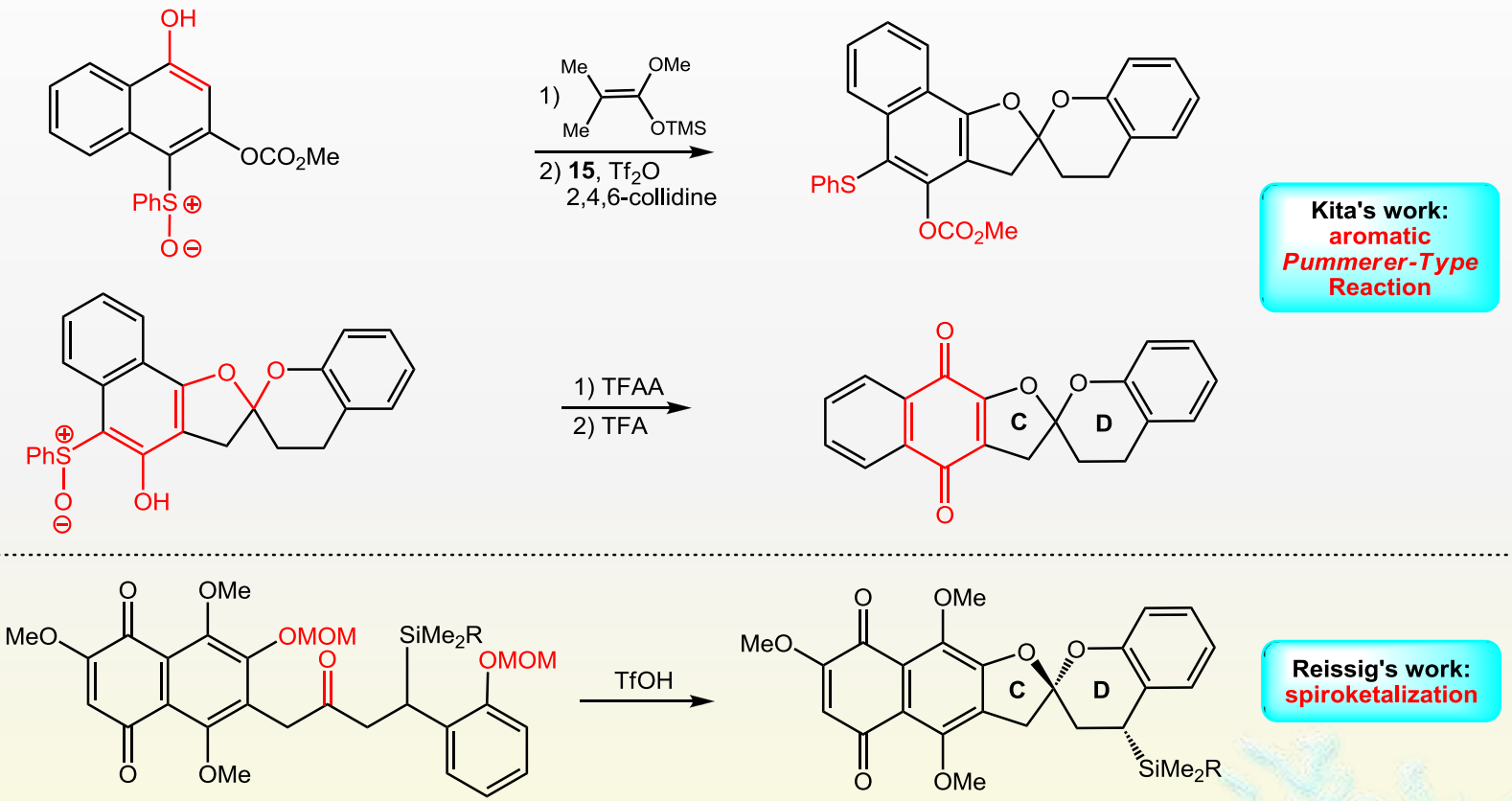
# Reissig's work– A convergent total synthesis



# Reissig's work– A convergent total synthesis



# Summary

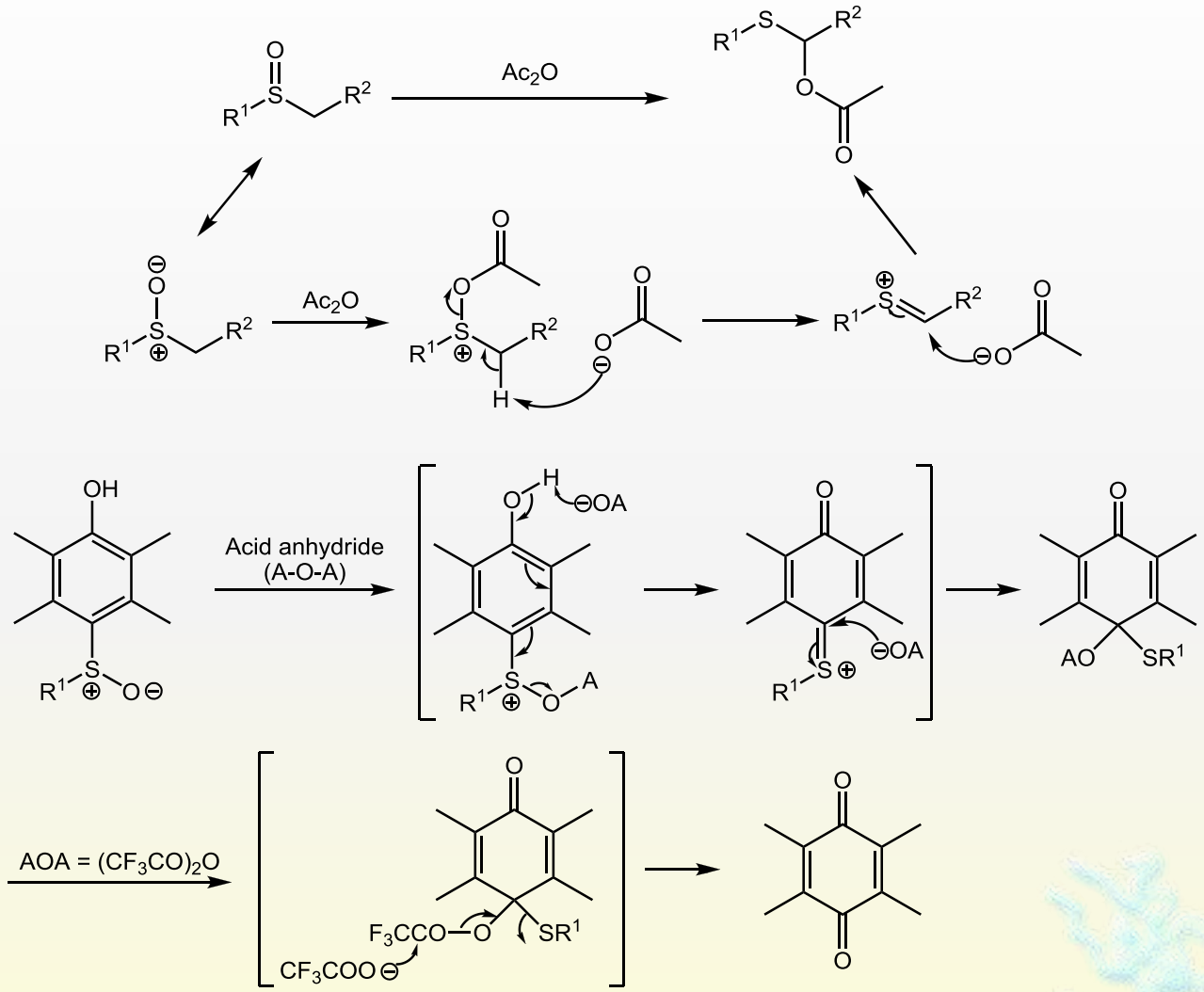

OH
OCO2Me
PhS
O
1)
Me
OMe
Me
OTMS
2) 15, Tf2O
2,4,6-collidine
PhS
OCO2Me
O
O
1) TFAA
2) TFA
C
D
MeO
OMe
OMOM
SiMe2R
TfOH
Kita's work:
aromatic
Pummerer-Type
Reaction
Reissig's work:
spiroketalization

The history of the rubromycins started with the isolation of β-rubromycin from the mycelia of the actinomycetes strain *Streptomyces collinus* by Brockmann and Renneberg in the 1950s. Shortly after, the structure of the isolated natural product was elucidated by chemical derivatizations, degradation experiments, and NMR spectroscopic studies; a first proposal suggested an *ortho*-quinoid structure. However, in 2000 Zeeck and co-workers could unequivocally confirm a *para*-quinoid structure of the naphthoquinone moiety with the aid of modern NMR methods and $^{13}C$-labeling experiments, thus correcting the originally proposed formula.

In addition to β-rubromycin, other representatives of this interesting class of natural products have been described over the years, including the structurally closely related γ-rubromycin, purpuromycin, and heliquinomycin. Biological studies reveal, that - in addition to their role as effective antibiotics and HIV-1-RT inhibitors - the rubromycins display potent activity against human telomerase, and their high biological activity significantly depends on the presence of the [5,6]-bisbenzannulated spiroketal moiety as a central structural motif.

With this route to (±)-γ-rubromycin we have described a new total synthesis of this natural product. The synthesis is convergent and very efficient in its single steps and makes γ-rubromycin accessible in 18 steps (longest linear sequence) with an overall yield of 3.8%. The key steps of this synthesis are: the chemoselective 1,4-addition of highly functionalized Grignard reagent **20** , the efficient ketalization of intermediate **22** to spiroketal **23**, and the subsequent acid-induced protodesilylation with concurrent isocoumarin formation to give γ-rubromycin precursor **24**. The developed protocols are very robust and also feasible on a larger scale and should be suitable for the synthesis of analogues of rubromycin. In addition, our strategy should allow an asymmetric synthesis of γ-rubromycin, since enantioselective 1,4-additions of functionalized aryl Grignard reagents β-silylated enone **15** are known.

# Pummerer重排反应




Kita, Y. *et al*. *J. Chem. Soc., Chem. Commun.* **1995**, 1013-1014.

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