

# Total Synthesis of (+)-Muironolide A

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JACS **2015**, 137, 5907-5910

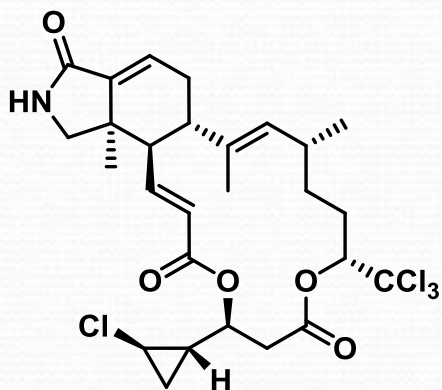
DOI: 10.1021/jacs.5b03531



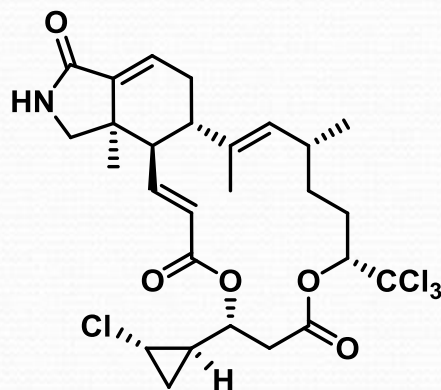
*Phorbac amaranthus*

Current literature  
Andrey Kuzovlev  
13.08.2015

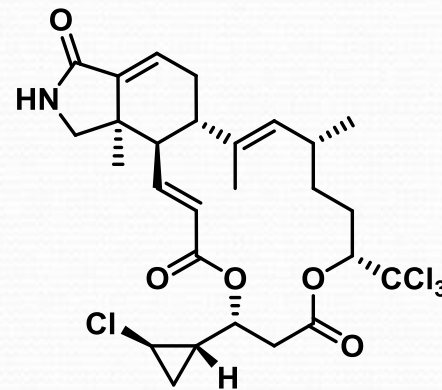
# Introduction



C21-*epi*-muironolide A  
(original assignment)



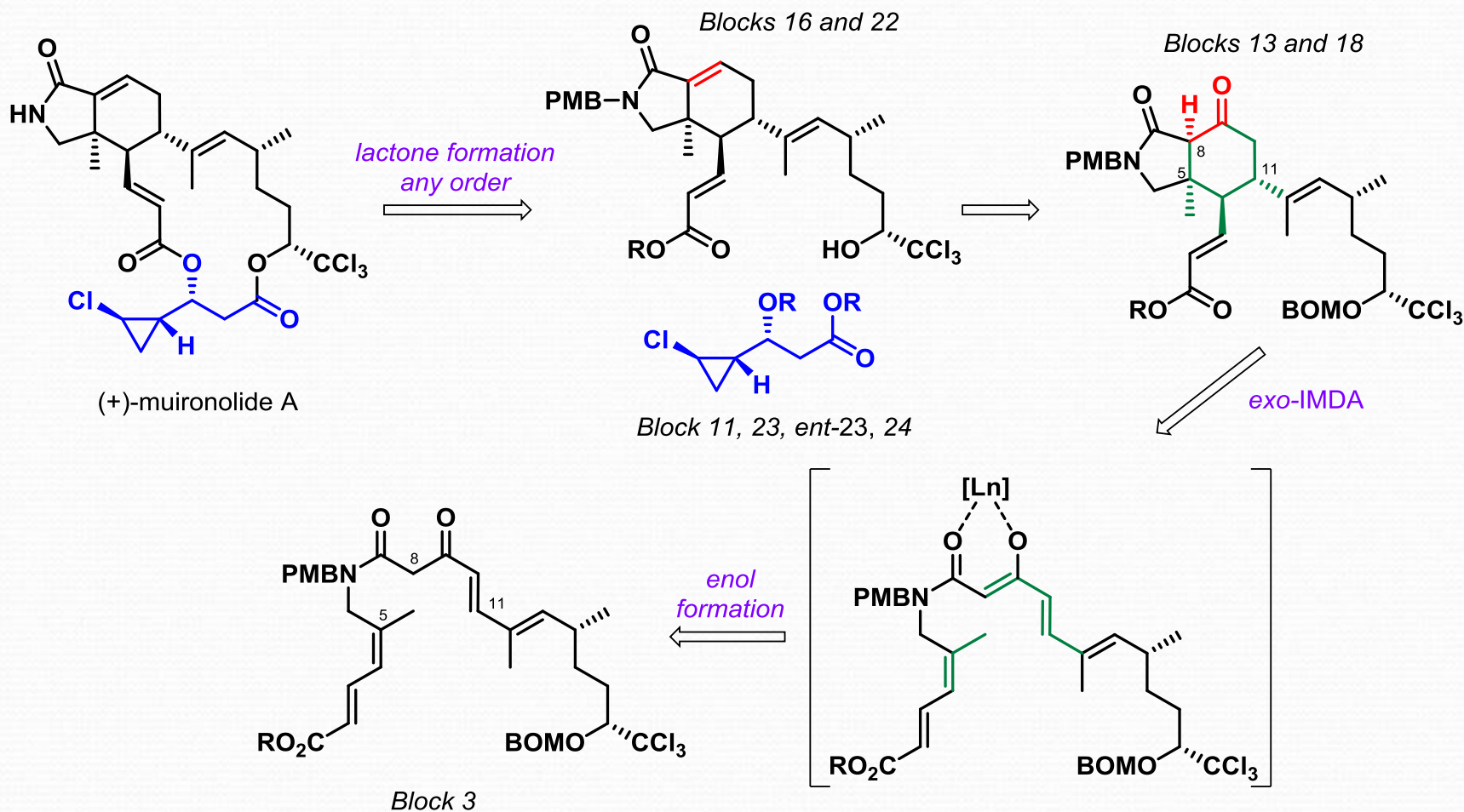
C22,C23-*epi*-muironolide A



(+)-muironolide A  
(revised structure)

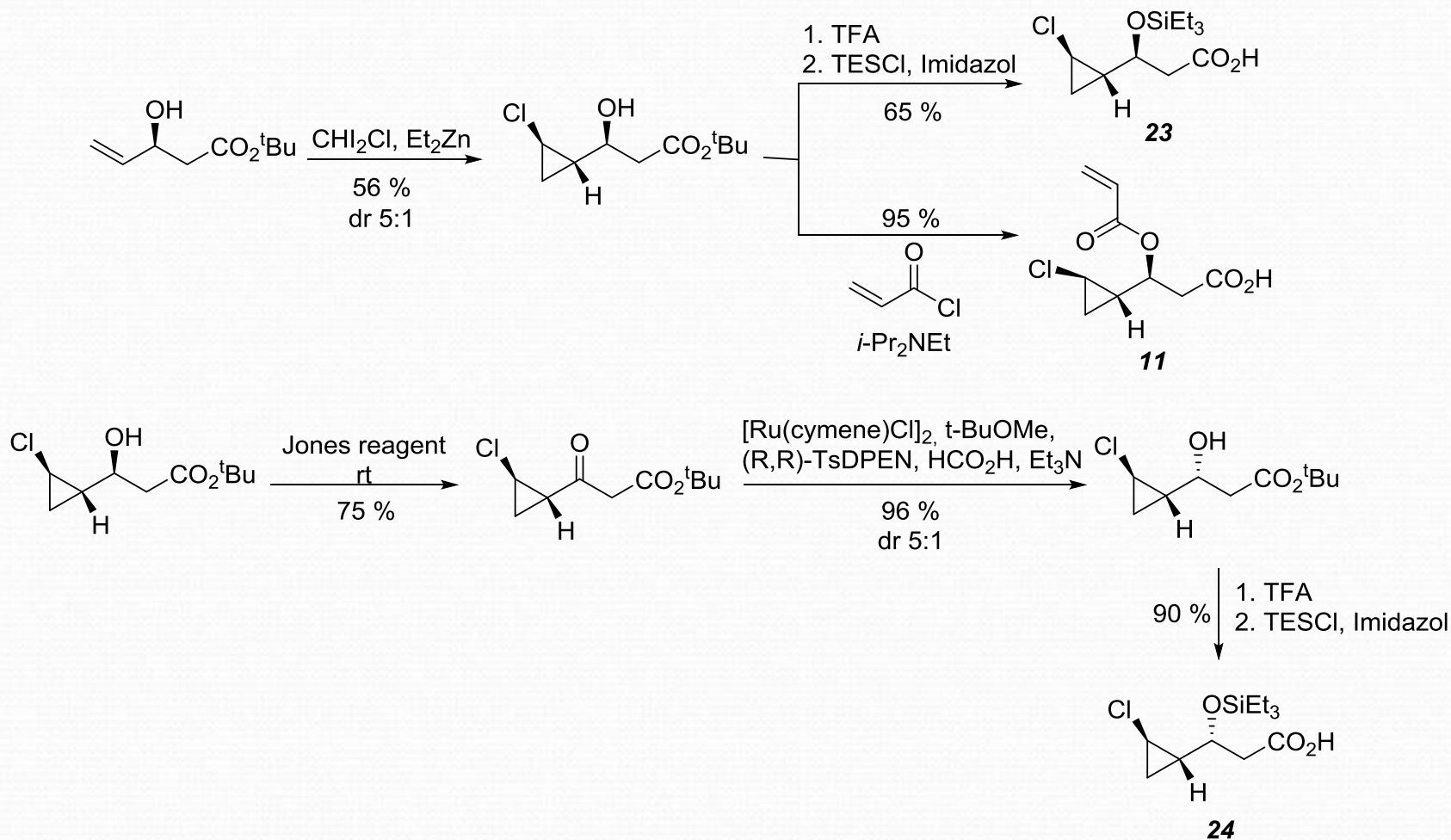
- Muironolide A was isolated by Molinski and co-workers from the Western Australian sponge *Phorbis* in 1993.
- Structure of muironolide A from minor HPLC fraction (90 µg) was determined by NMR in the same group in 2008.
- Antifungal activity against *Cryptococcus neoformans*.
- Cytotoxic activity against some colon tumor cell.

# Retrosynthetic Analysis of (+)-Muironolide A



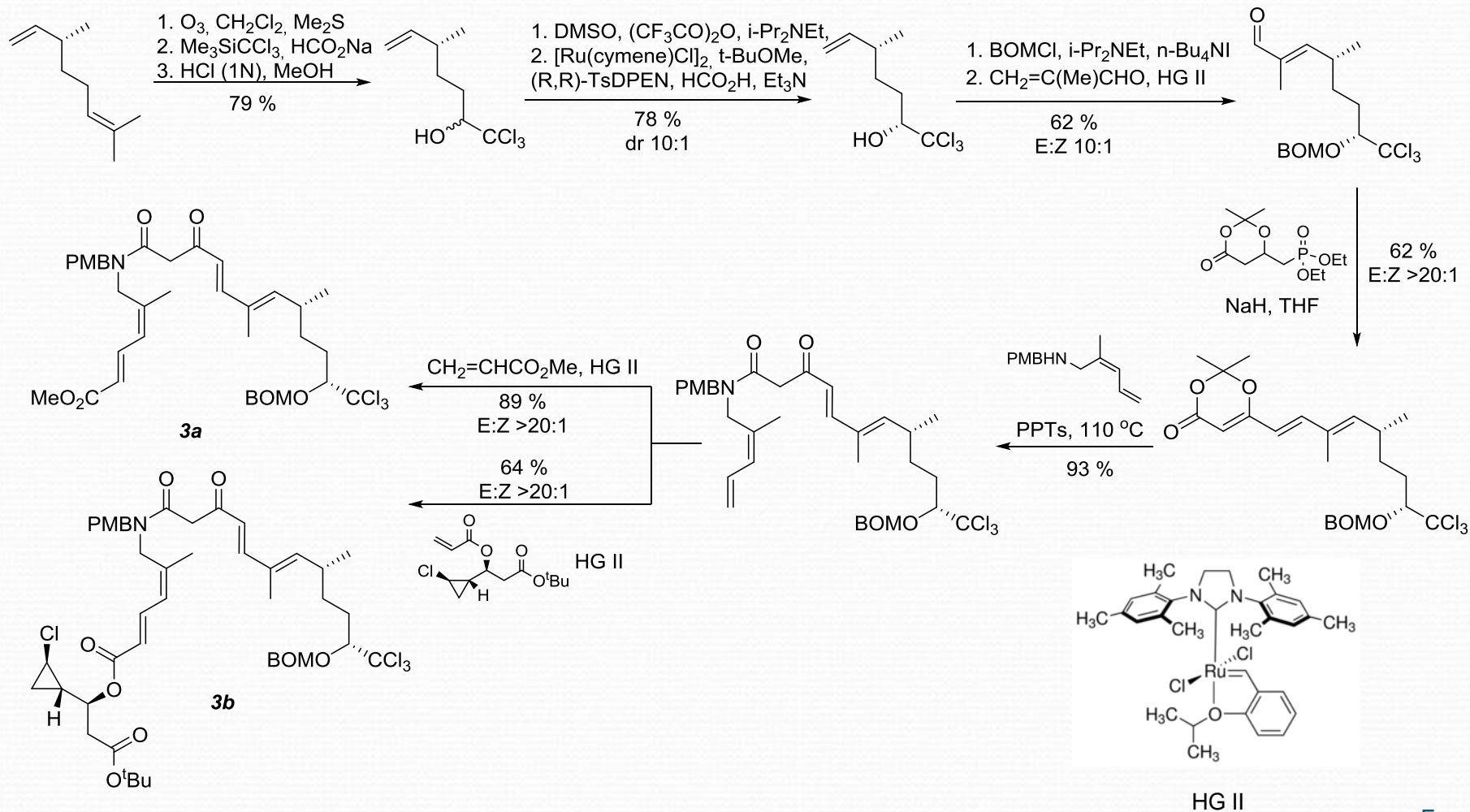


# Synthesis of Building Block 11, 23, 24



# Synthesis of Building Block 3a and 3b

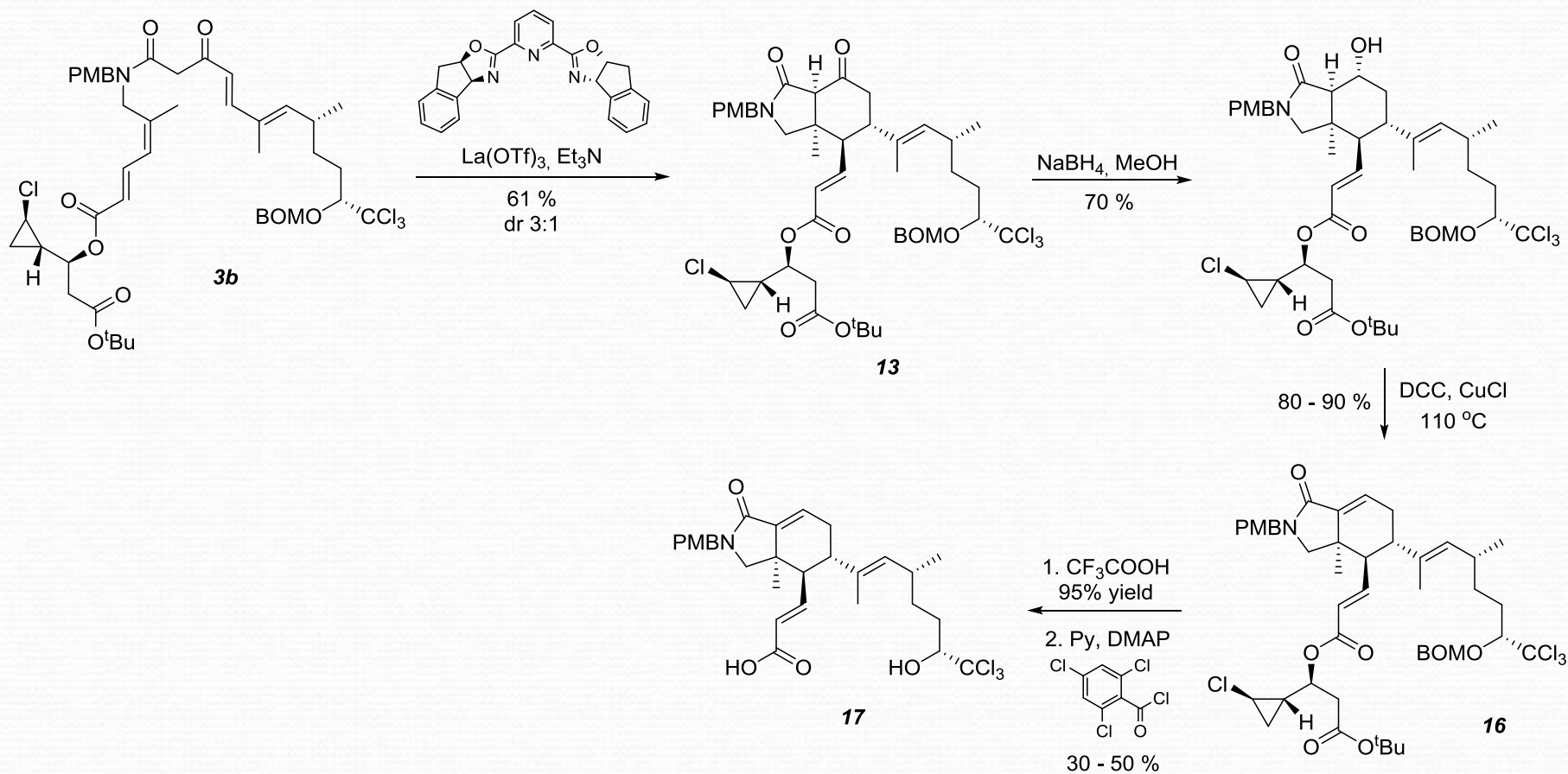
2



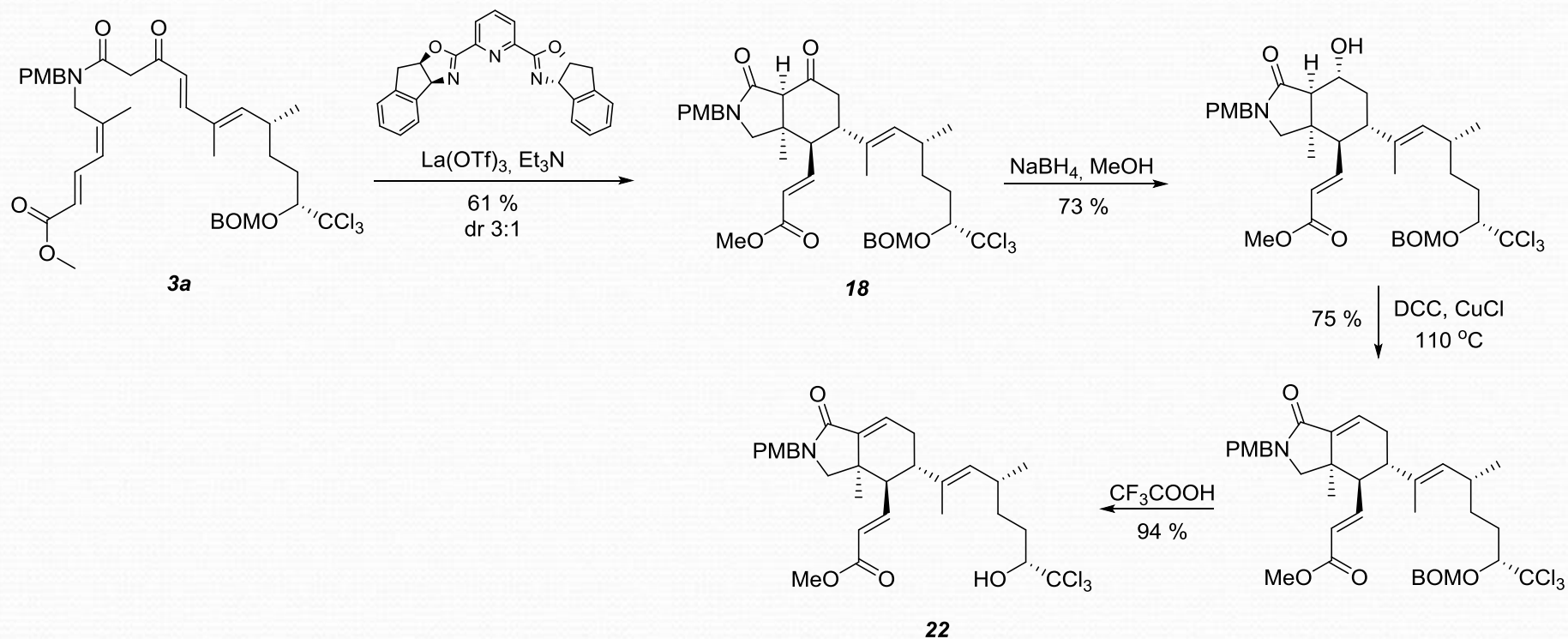
5

# Attempt of Synthesis (+)-Muironolide A via Blocks 3b, 13 and 16

1

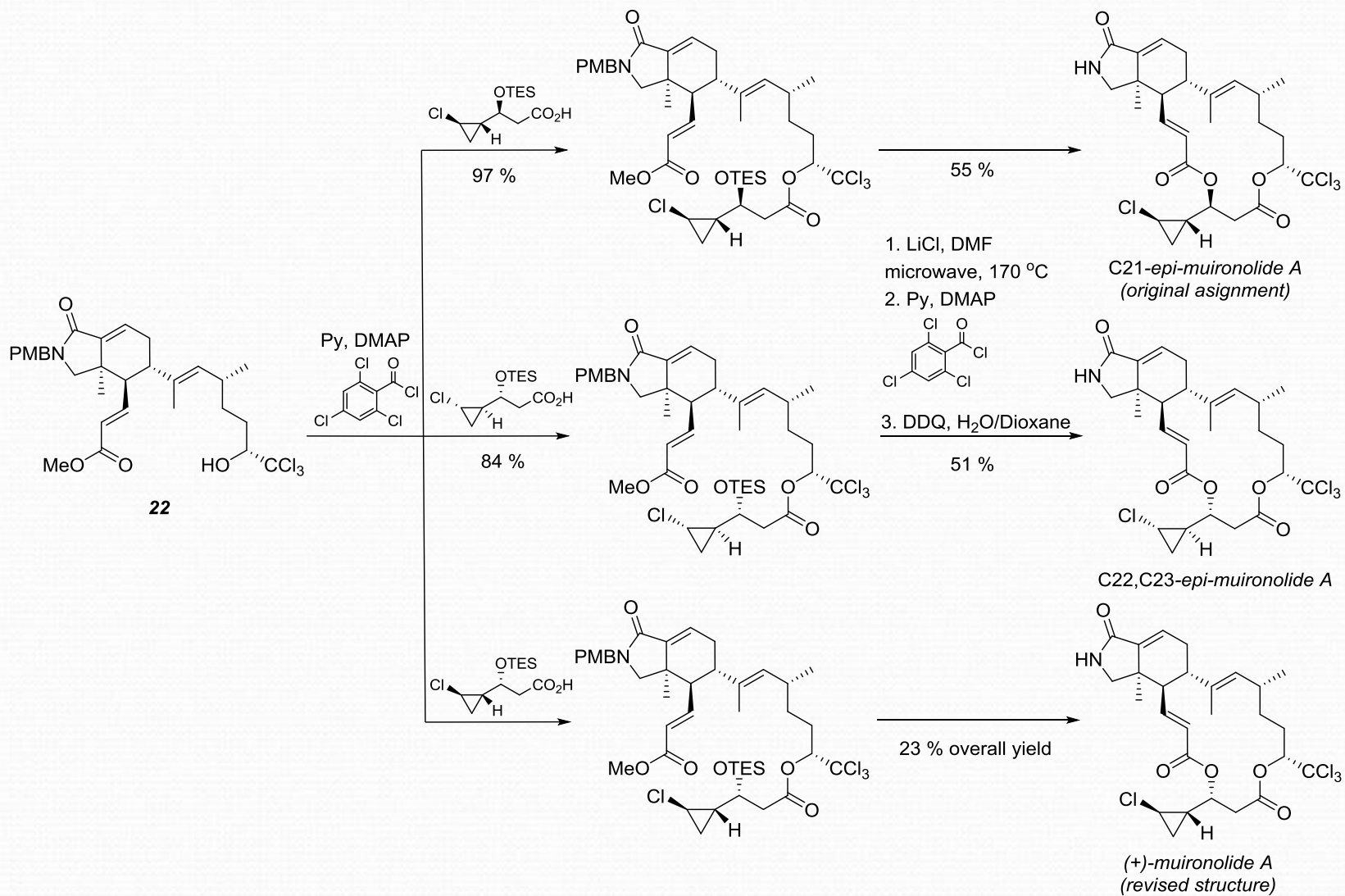


# Synthesis of Building Block 22 via Blocks 3a and 18



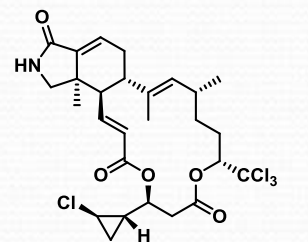
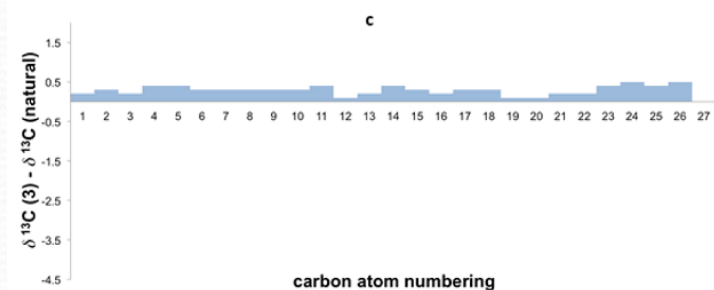
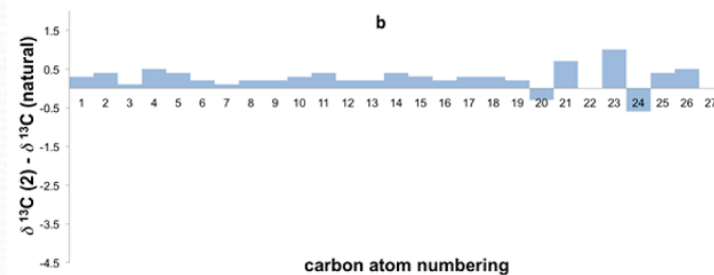
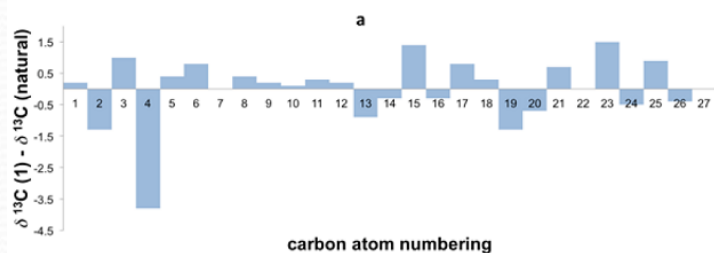


# Completion of the Total Synthesis

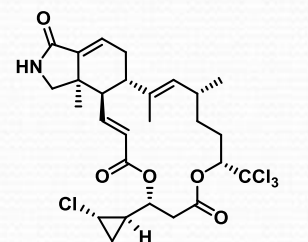




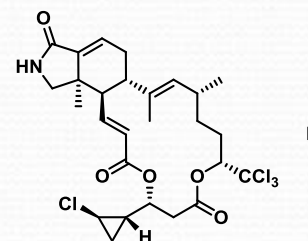
# Differences in the $^{13}\text{C}$ NMR Chemical Shift between I, II, III and Natural Muironolide A



C21-epi-muironolide A  
(original assignment)



C22,C23-epi-muironolide A

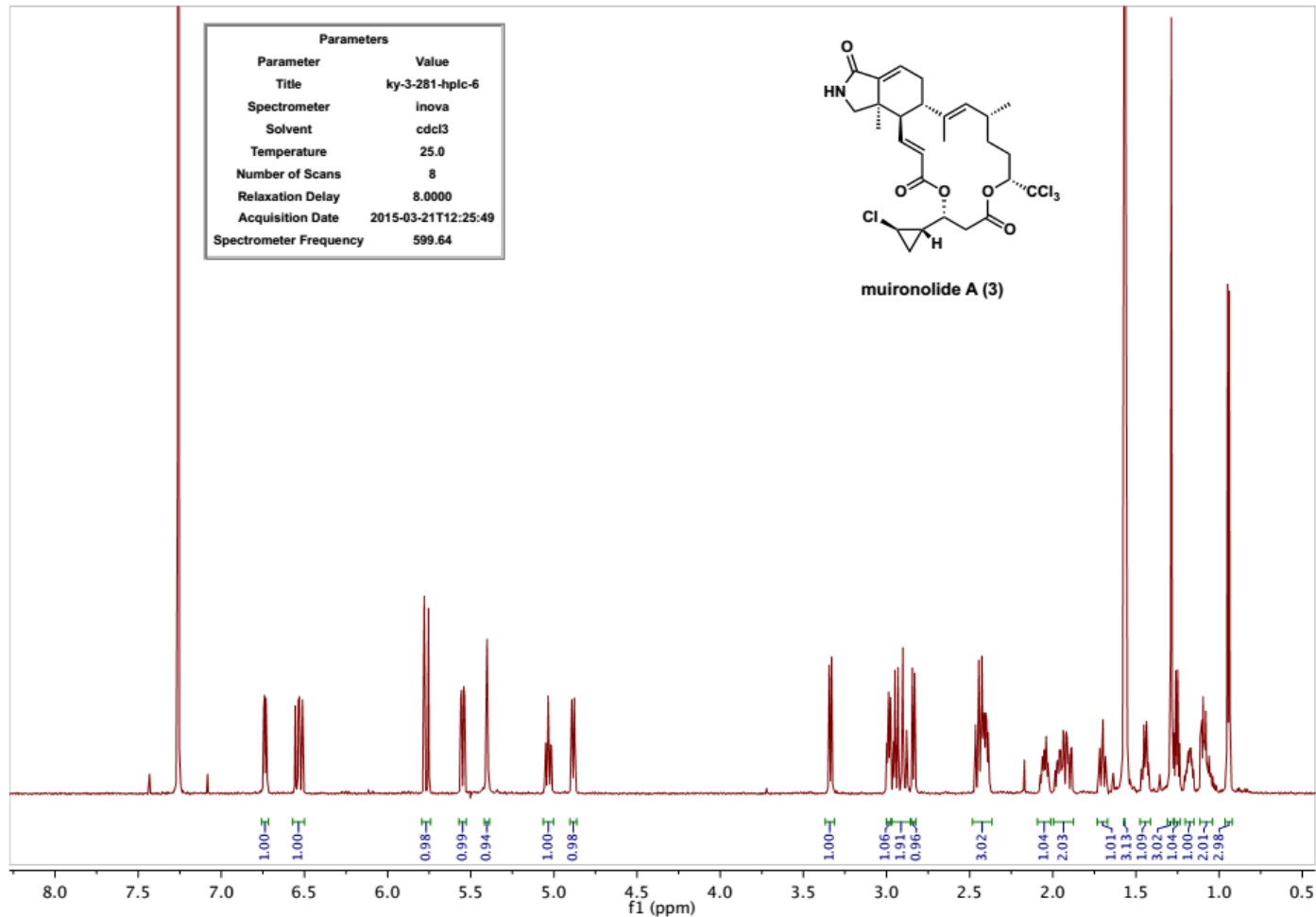


(+)-muironolide A  
(revised structure)

## Conclusions

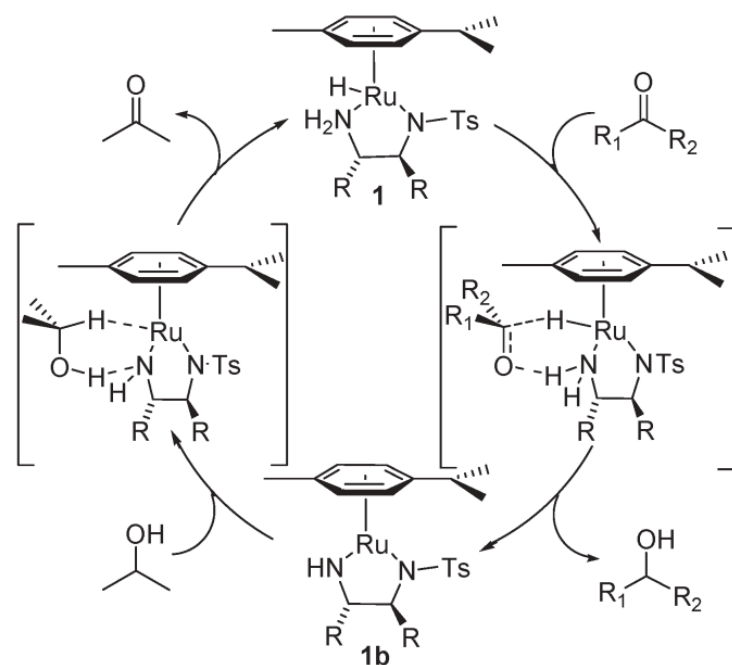
- First total synthesis of (+)-Muironolide A
- Delivered 25 mg of the compound paves the way for systematic evaluation of biological activity
- Reassignment of the absolute configuration of the natural product
- Key-steps of the synthesis:
  - macrolactone formation by Yamaguchi reagent
  - *exo*-selective lanthanide-catalyzed IMDA
  - thermolysis of dioxinone phosphonate with protected amine
  - ruthenium-catalyzed reduction

# *Thank you for your attention!*

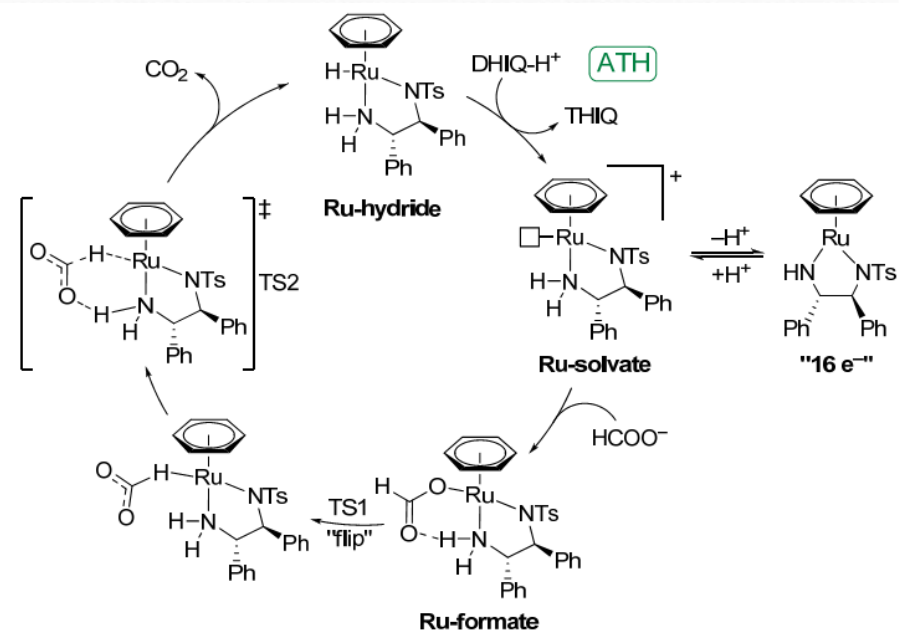




# Asymmetric Transfer Hydrogenation by Chiral Ruthenium(II) Complex and HCOOH/Et<sub>3</sub>N



**Scheme 7** Catalytic cycle of catalyst **1** via a concerted six-membered transition state.

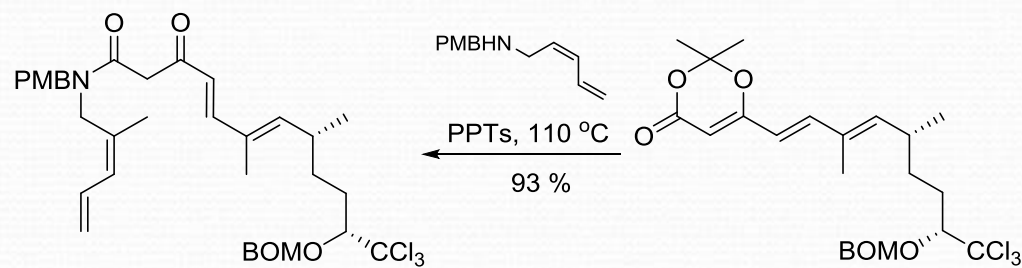
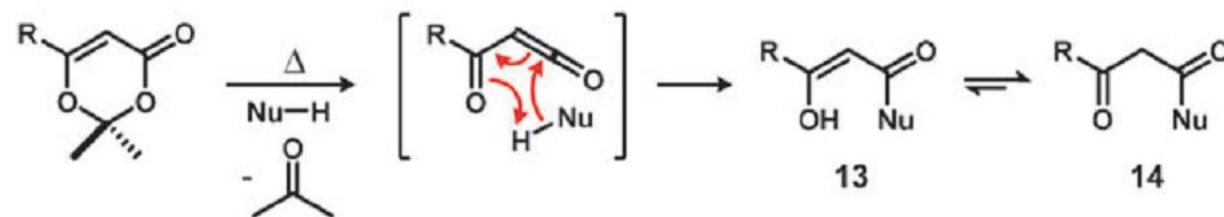


J. Samec, J. Backvall, P. Andersson, P. Brandt *Chem. Soc. Rev.* **2006**, *35*, 237-248

J. Vaclavik, P. Sot, P. Vilhanova, J. Pechacek, M. Kuzma and P. Kacer *Molecules* **2013**, *18*, 6804-6828

# Thermolysis of dioxinone phosphonate with nucleophiles

1



K. Reber, S. Tilley, E. Sorensen *Chem. Soc. Rev.* **2009**, 38, 3022-3034

# Intramolecular Diels-Alder reaction

