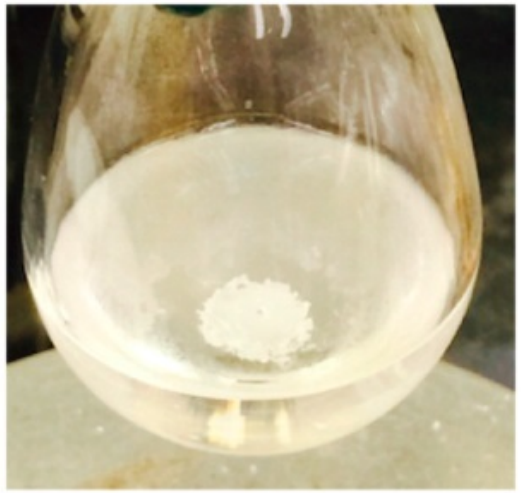
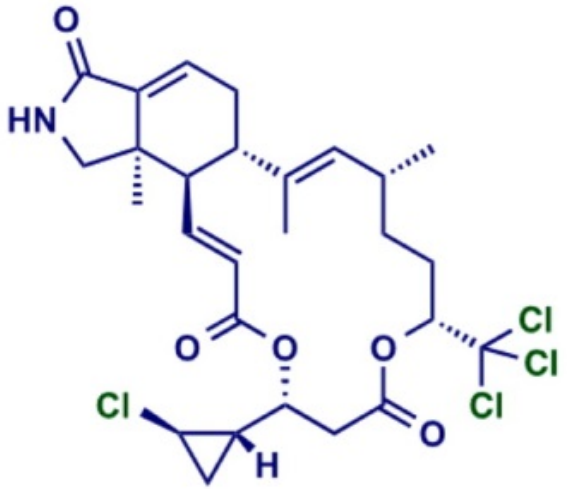
Total Synthesis and Structural Revision of (+)-Muironolide A

Qing Xiao , Kyle Young , and Armen Zakarian.
J. Am. Chem. Soc., **2015**, *137* (18), pp 5907–5910

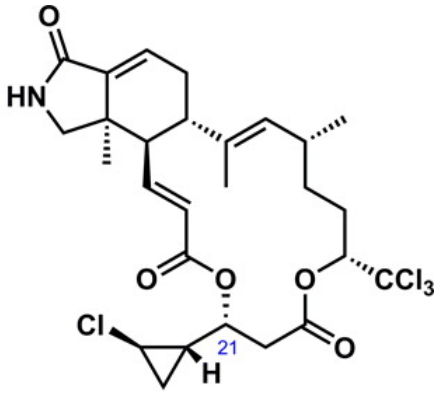




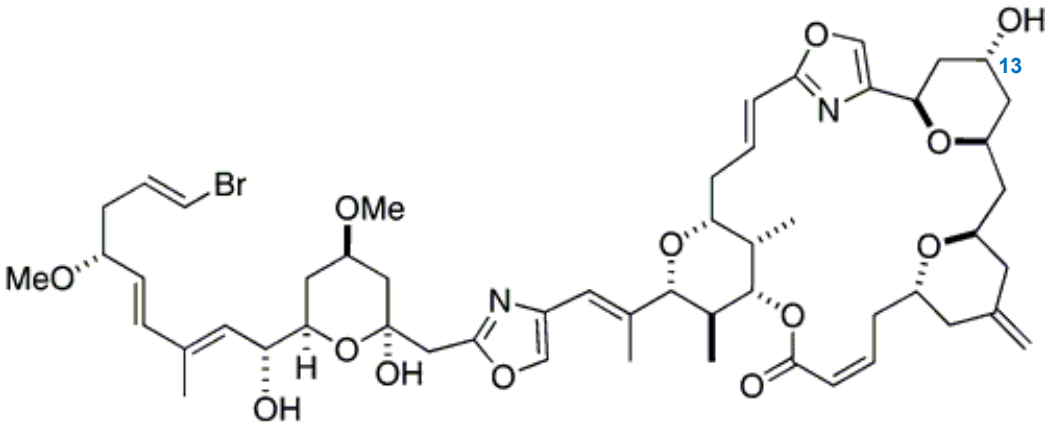
Liming Cao
Wipf Group Current Literature
5/30/2015

Phorbas species

- Marine sponges (the most primitive multicellular animals) descend from ancestral lines predate the Cambrian explosion.
- Sponges are structured by associated complex microbial communities, and have been a rich source of marine natural products, which are speculated to arise from heterogeneous microbial associations.
- Muironolide A was isolated from the sponge of the *Phorbas* species that earlier provided phorboxazoles A and B.



(+)-muironolide A



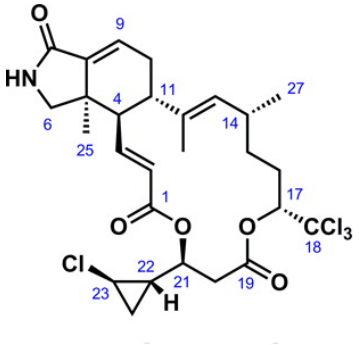
phorboxazole A
phorboxazole B: C13 epimer

J. Am. Chem. Soc. **2009**, 131,7552
J. Am. Chem. Soc. **2015**, 137, 5907
J. Am. Chem. Soc. **1995**, 117, 8126
J. Am. Chem. Soc. **1996**,118, 9422
Tetrahedron Lett. **1996**, 37,7879

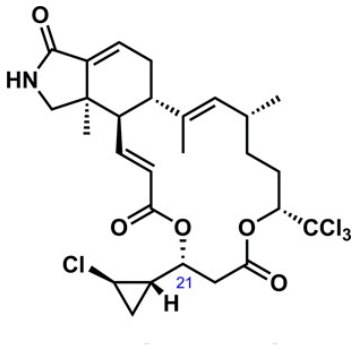
(+)-Muironolide A

- Muironolide A was obtained by Molinski and coworkers from marine sponge *Phorbas* species by repeated HPLC (phenylhexyl column).
- Its elucidation was achieved using the entire sample (90 μg, 152 nmole) by microcryoprobe NMR spectroscopy, FTMS, circular dichroism (CD), and chemical degradation-LCMS.
- Its contains carbon skeleton bearing a hexahydro-1*H*-isoindolone-triketide ring and a trichlorocarbinol ester.
- Its bioactivity includes cytotoxicity against the HCT-116 solid colon tumor cell line (IC_{50} 96.5 μg/mL) and antifungal activity against Cryptococcus neoformans (MIC 16 μg/mL).

- Neither NOESY nor *J*-based methods could unequivocally relay the configuration of the *trans*-2-chlorocyclopropyl ketide (CCK) element to the other macrolide ring stereocenters.



C21-*epi*-muironolide A (**1**)
(original assignment)



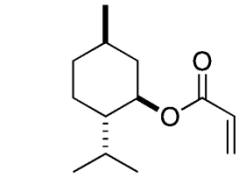
(+)-muironolide A (**3**)
revised structure

J. Am. Chem. Soc. **2009**, 131,7552
J. Am. Chem. Soc. **2015**, 137, 5907
J. Am. Chem. Soc. **1995**, 117, 8126

Chemical Degradation-LCMS

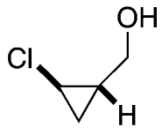
Molinski and coworkers:

Muironolide A → (1. LiOH, THF–H_2O; 2. R-Br) → *trans*-2-chlorocyclopropyl ketide ester



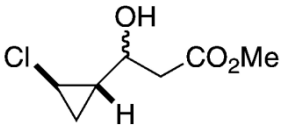
(–)-*O*-menthyl acrylate

→ (steps)

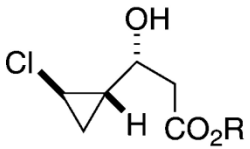


86% ee

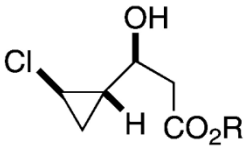
→ (1. PCC, Celite; 2. $BrCH_2CO_2Me$, Zn°, THF; 36% (2 steps))



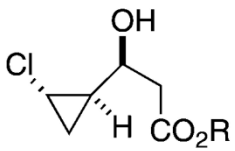
→ (1.LiOH, THF–H_2O; 2. R-Br; 3. HPLC, Chiralpak AD (3:7 *i*PrOH/hexane))



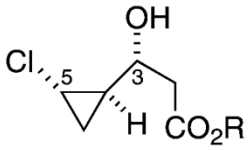
(3*R*, 4*S*, 5*R*)



(3*S*, 4*S*, 5*R*)

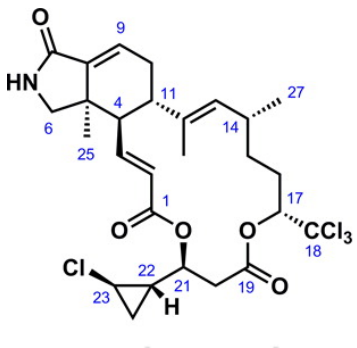


(3*S*, 4*R*, 5*S*)

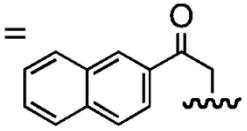


(3*R*, 4*R*, 5*S*)

- Chemical degradation product of Muironolide A coeluted with (3*S*, 4*S*, 5*R*) diastereomer in Chiral LCMS (Chiralpak AD-RH (1:9 H_2O-CH_3CN, 0.1% HCO_2H).



C21-*epi*-muironolide A (**1**)
(original assignment)

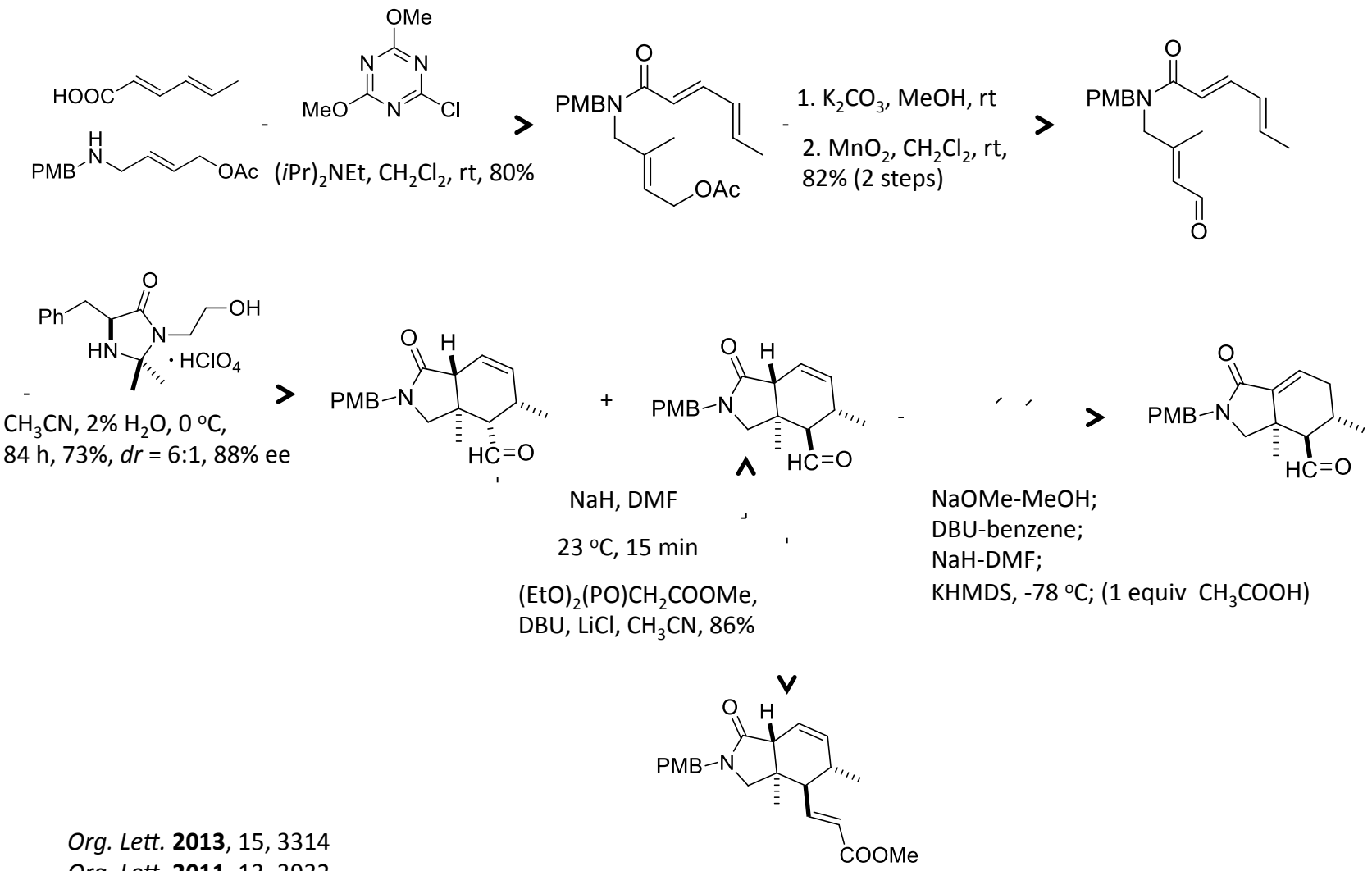
R = 

α-bromo-2-acetylnaphthalene derivatization

J. Am. Chem. Soc. **2009**, 131,7552
J. Org. Chem. **2005**, *70*, 4162

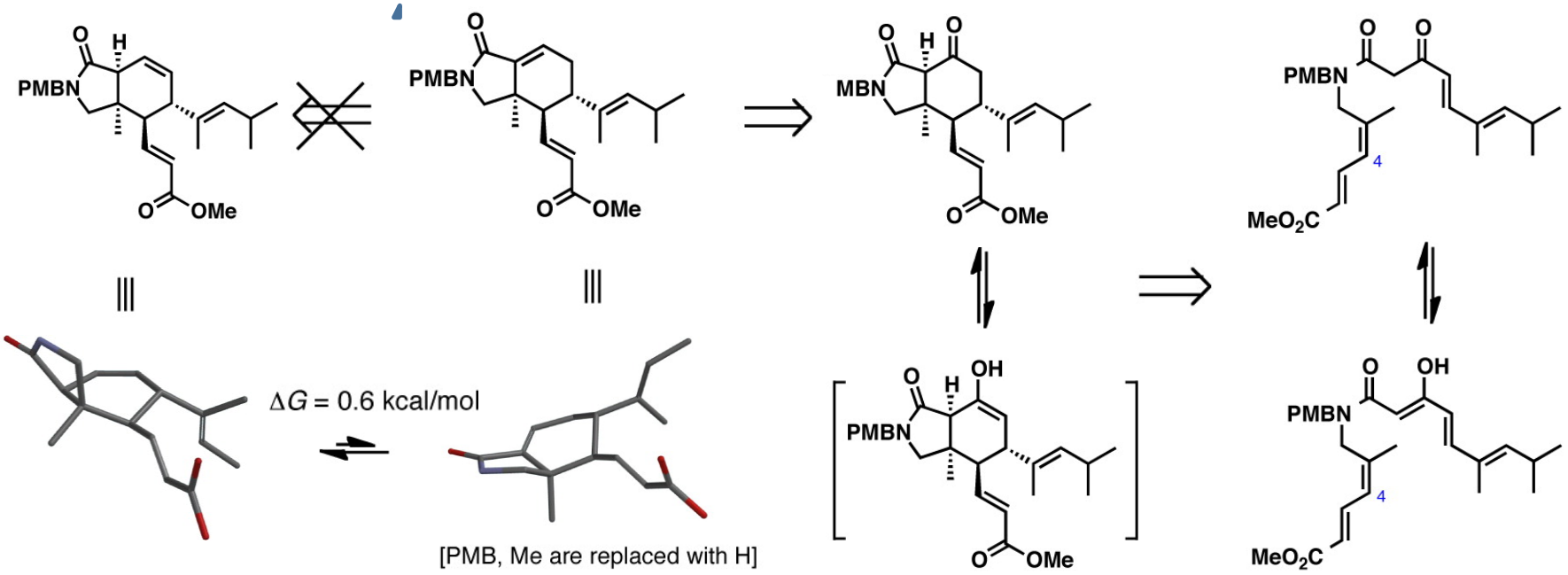
Assembly of the Isoindolinone Core

Molinski and coworkers:



Org. Lett. **2013**, 15, 3314
Org. Lett. **2011**, 13, 3932

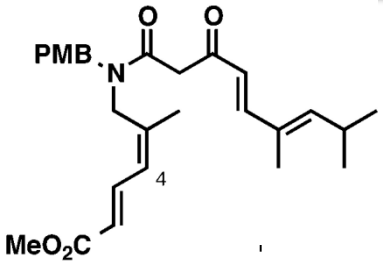
Conformational Analysis of the Bicyclic Ring System



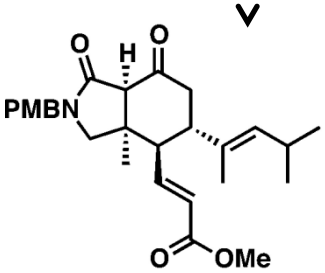
- substitution pattern: strained conformation in the ground state
- double bond isomer: less strained half-chair conformation; thermodynamically unfavorable for isomerization to double bond conjugation
- β-keto amide as the precursor

Org. Lett. **2013**, 15, 3314

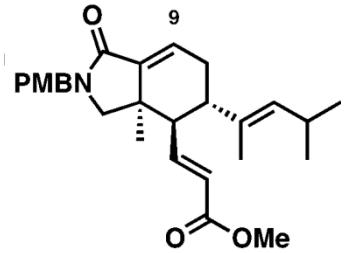
Model System Studies



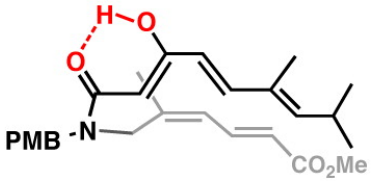
Toluene,
110 °C,
60%,
dr >30:1



1. $NaBH_4$, $CeCl_3$, MeOH
2. CH_3SO_2Cl, Et_3N, CH_2Cl_2, 23 °C
3. DBU, PhMe, 85 °C, 6 h, 64% (3 steps)



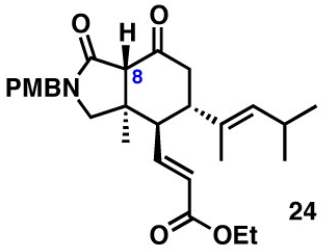
transition structures for the *Z*-isomer



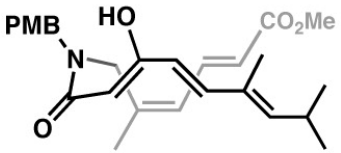
4*E-exo* TS

H-bonding stabilization

major



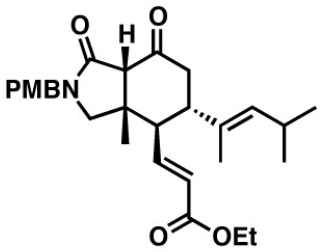
24



4*E-endo* TS

no H-bonding stabilization

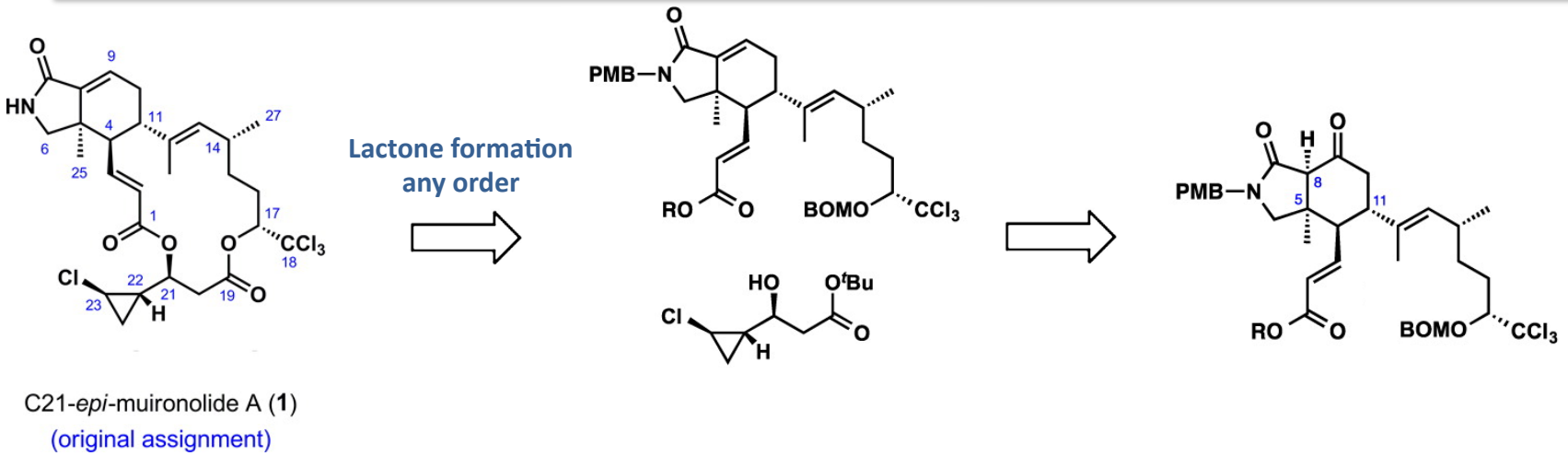
minor



- smooth intramolecular cycloaddition
- *exo*-cyclization favored with high diastereocontrol
- significance: ring system with the correct stereochemistry
- 3 steps to access fully assembled isoindolinone ring system

Org. Lett. **2013**, 15, 3314

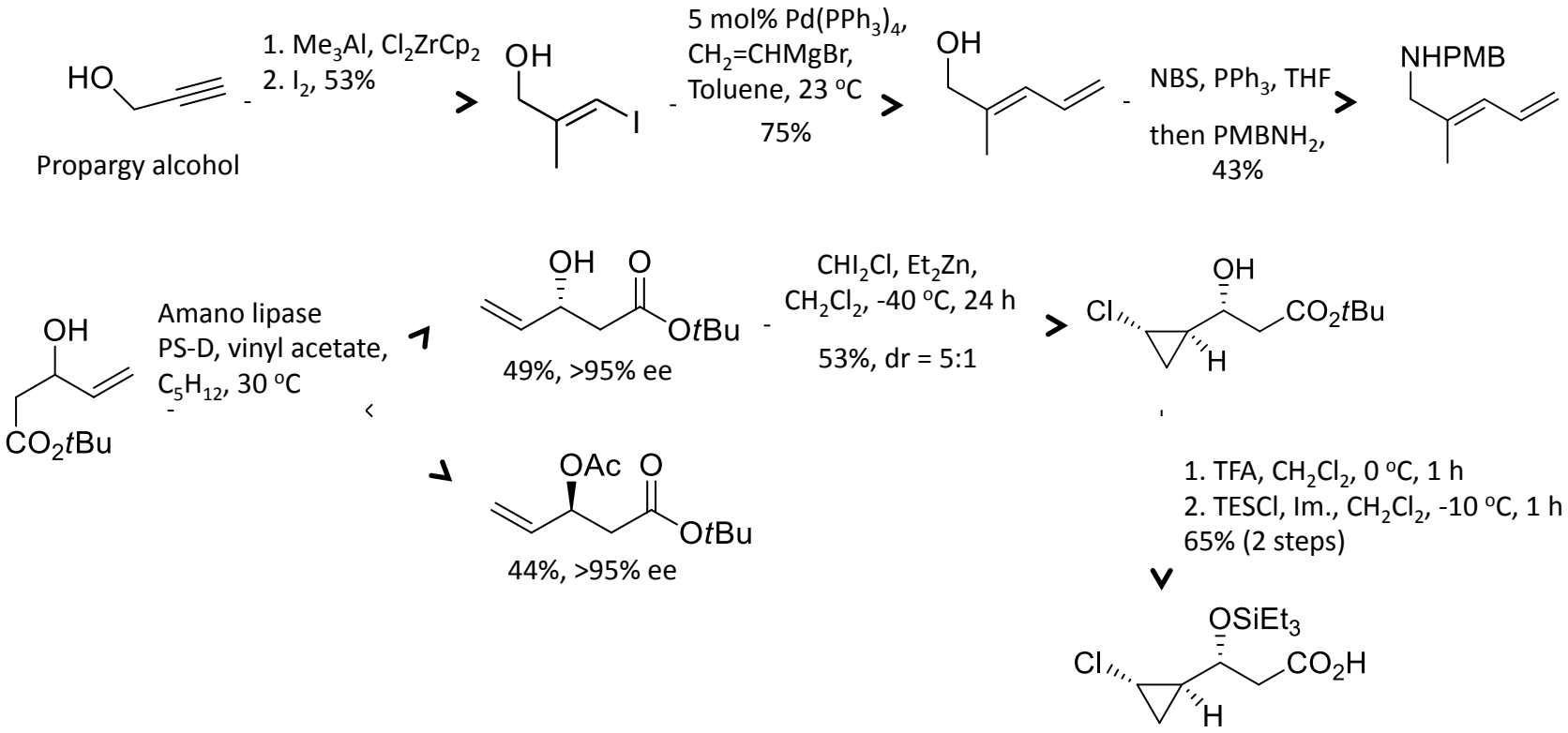
Retrosynthetic Analysis



- Order of esterification: flexible
- Key transformation: exo-selective lanthanide-catalyzed intramolecular Diels–Alder reaction for the construction of the hexahydro-1Hisoindolone subunit

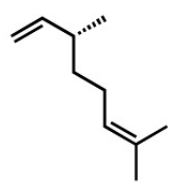
J. Am. Chem. Soc. **2015**, 137, 5907
Org. Lett. **2013**, 15, 3314
Org. Lett. **2011**, 13, 3932
Synlett **2013**, 24, 1861

Synthesis of Starting Material



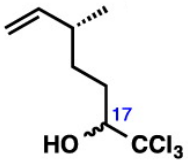
J. Org. Chem. **1997**, 62, 8591
Org. Lett. **2013**, 15, 3314
J. Am. Chem. Soc. **2011**, *133*, 10499
Org. Lett. **2007**, 9, 3161.

Total synthesis of (+)-Muironolide A



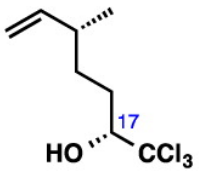
(+)-β-citronellene

1. O_3, CH_2Cl_2, -78 °C, 3 h; then Me_2S, -30 °C, 1 h, 85%
2. $TMSCCl_3$, HCOONa DMF, 23 °C, 1 h, 94%



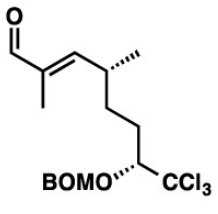
4

1. $(CF_3CO)_2O$, DMSO, *i*-Pr_2NEt, CH_2Cl_2, -78 °C, then 23 °C, 1.5 h, 80%
2. $[RuCl_2(cymene)]_2$ (2.5 mol%), (*R*,*R*)-TsDPEN (5 mol%), HCOOH, Et_3N, DMF, TBME, 23 °C, 2 h, 96%, 10:1 dr

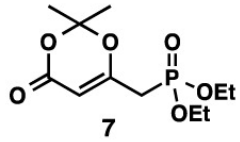


5

1. BOMCl, *i*-Pr_2NEt, TBAI, CH_2Cl_2, 0 °C, then 45 °C, 12 h, 92%
2. CH_2=C(Me)CHO, HG (II) 3 mol%, CHCl3, 65 °C, 62% (+20% SM), *E*:*Z* =10:1

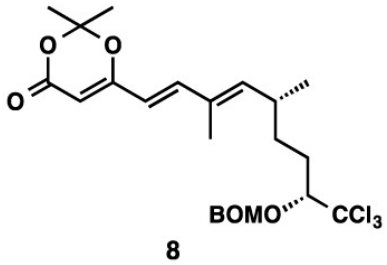


6

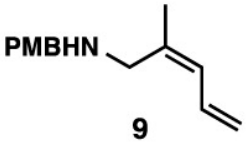


7

NaH, THF, -78 °C, then 23 °C, 12 h, 79%, *E*:*Z* >20:1

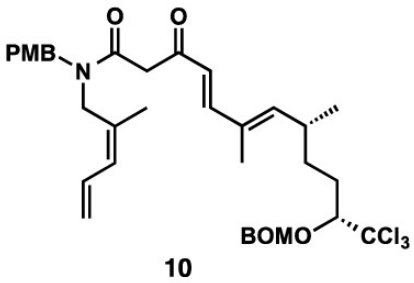


8



9

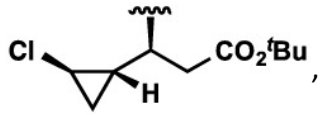
PPTS, toluene, 110 °C, 4 h, 93%

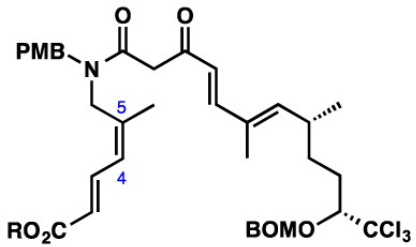


10

CH_2=$CHCO_2R$, HG (II) 3 mol%, CH_2Cl_2, 45 °C, 12 h

3a: R = Me, 89%, *E*:*Z* >20:1

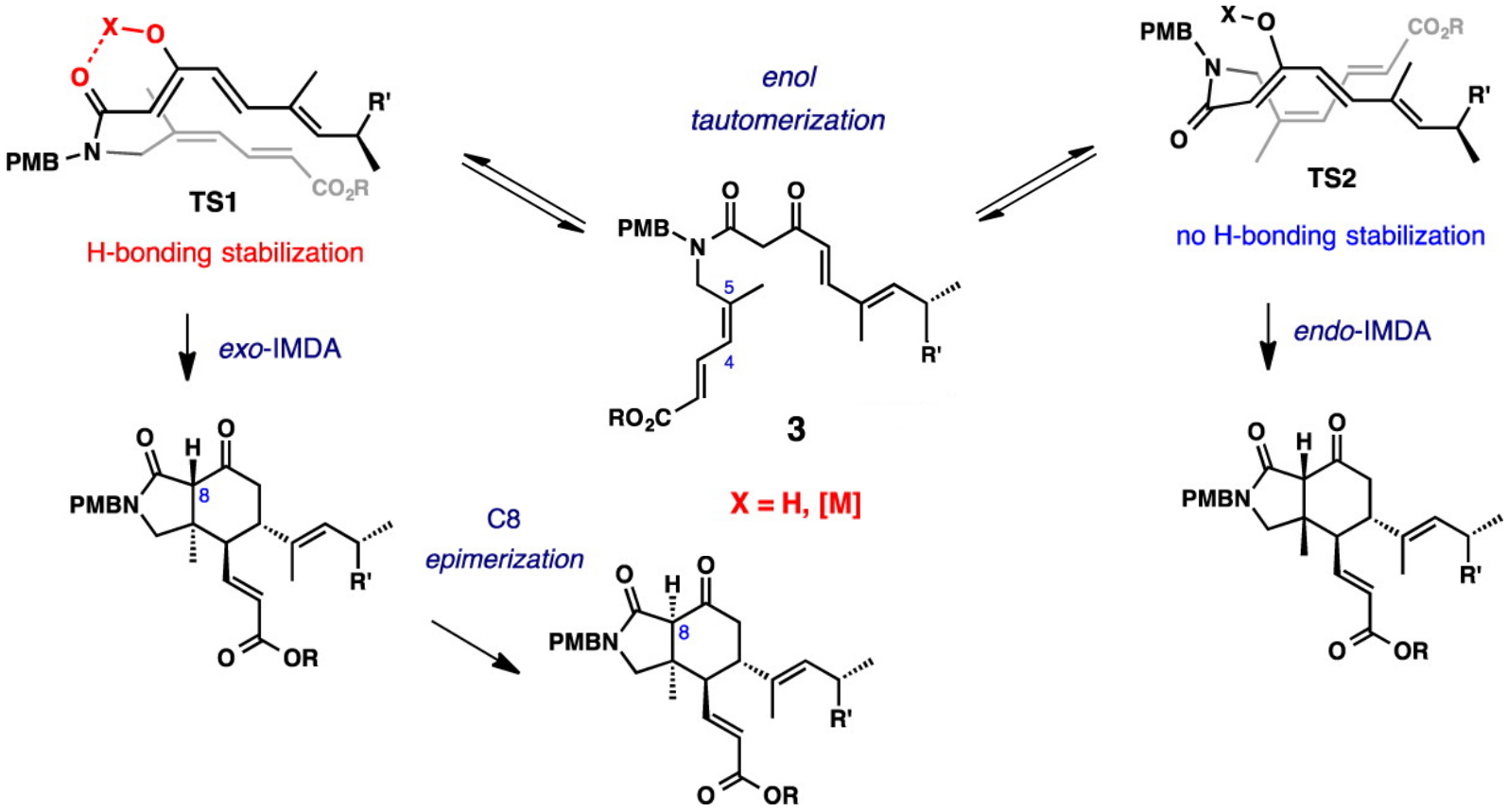
3b: R =  , 64%, *E*:*Z* >20:1



3a or **3b**

J. Am. Chem. Soc. **2015**, 137, 5907

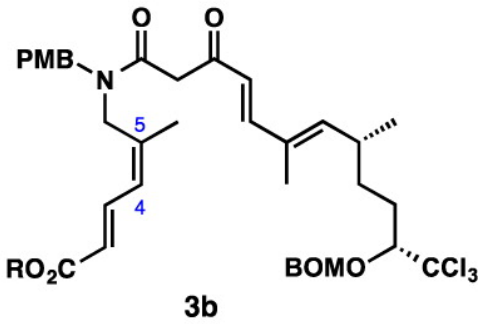
Analysis of Intramolecular Diels–Alder Reaction



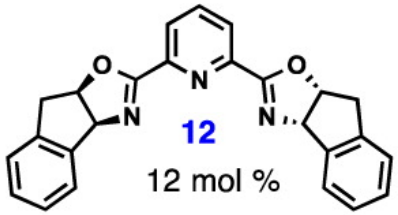
- hydroxy diene accessed from β-keto amide through ketone–enol tautomerization
- exo-IMDA pathway favored due to H-bonding stablization in the TS1
- chelated metal enolate increasing electron density, raising HOMO, and activating diene for IMDA
- soft enolization with lanthanide triflates or nitrates

J. Am. Chem. Soc. **2015**, 137, 5907

Total synthesis of (+)-Muironolide A



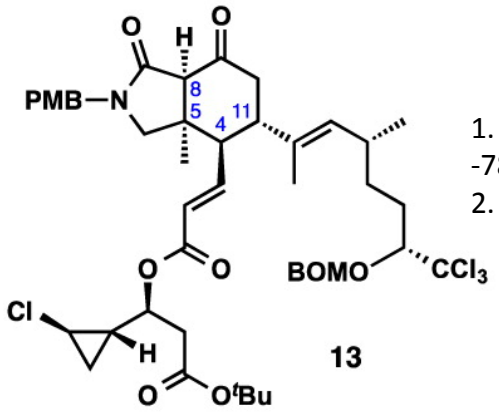
3b



12

12 mol %

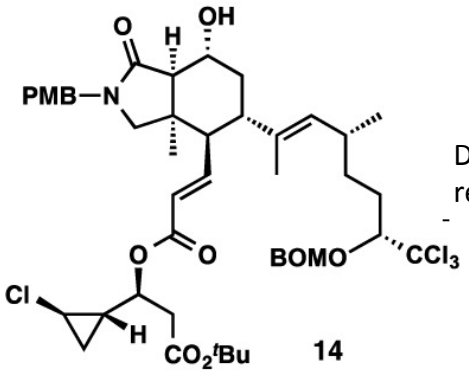
10 mol% $La(OTf)_3$, Et_3N, EtOAc,
45 °C, 24 h, 61%, dr = 3:1



13

1. $NaBH_4$, THF-MeOH (1:1)
-78 °C, 30 min
2. Seperation by HPLC

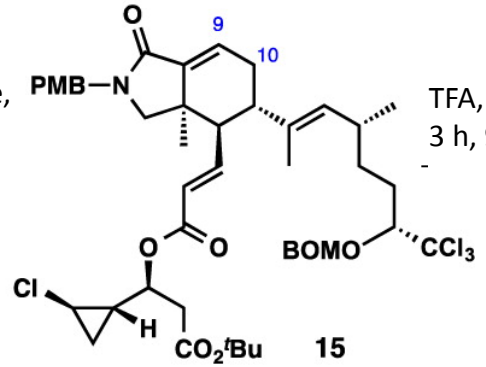
70% (+ 25% diastereomer)



14

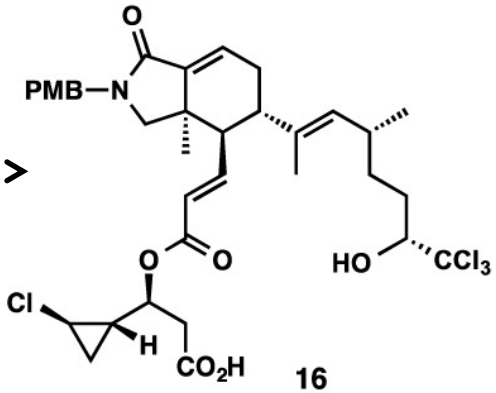
structure supported by X-ray crystallography

DCC, CuCl, toluene,
reflux, 1 h, 80%

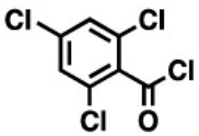


15

TFA, CH_2Cl_2, 23 °C,
3 h, 95%

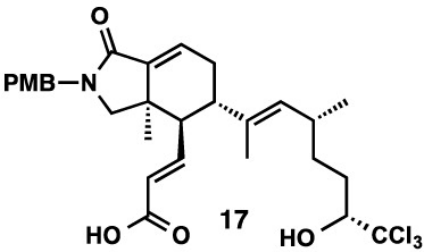


16



Pyr, DMAP, Toluene,
0 °C, then 23 °C, 12 h,
55%

β-elimination

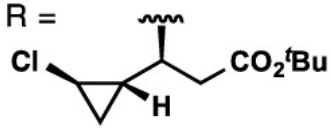


17

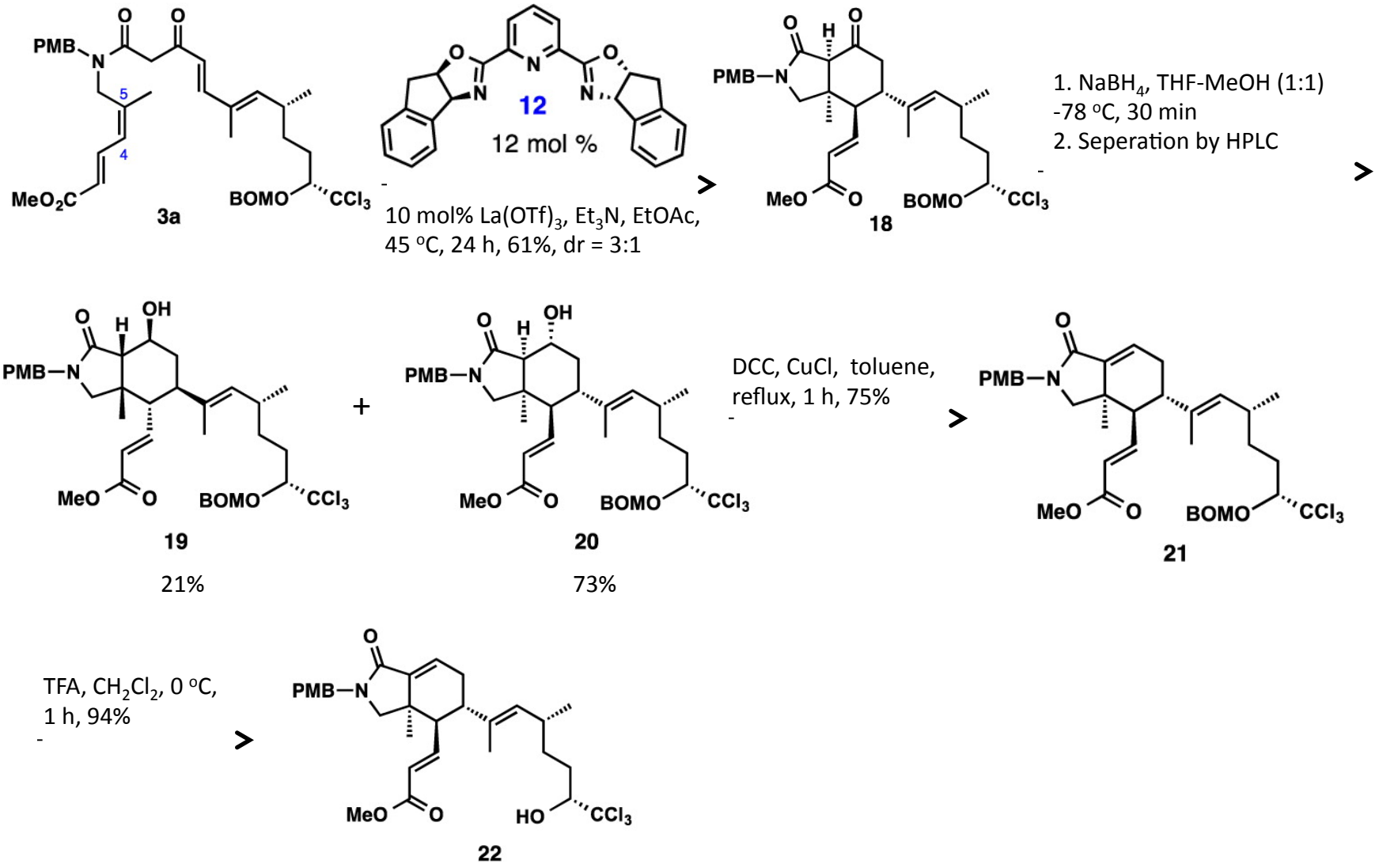
~30-50 %

and higher order macrolactonization products

J. Am. Chem. Soc. **2015**, 137, 5907

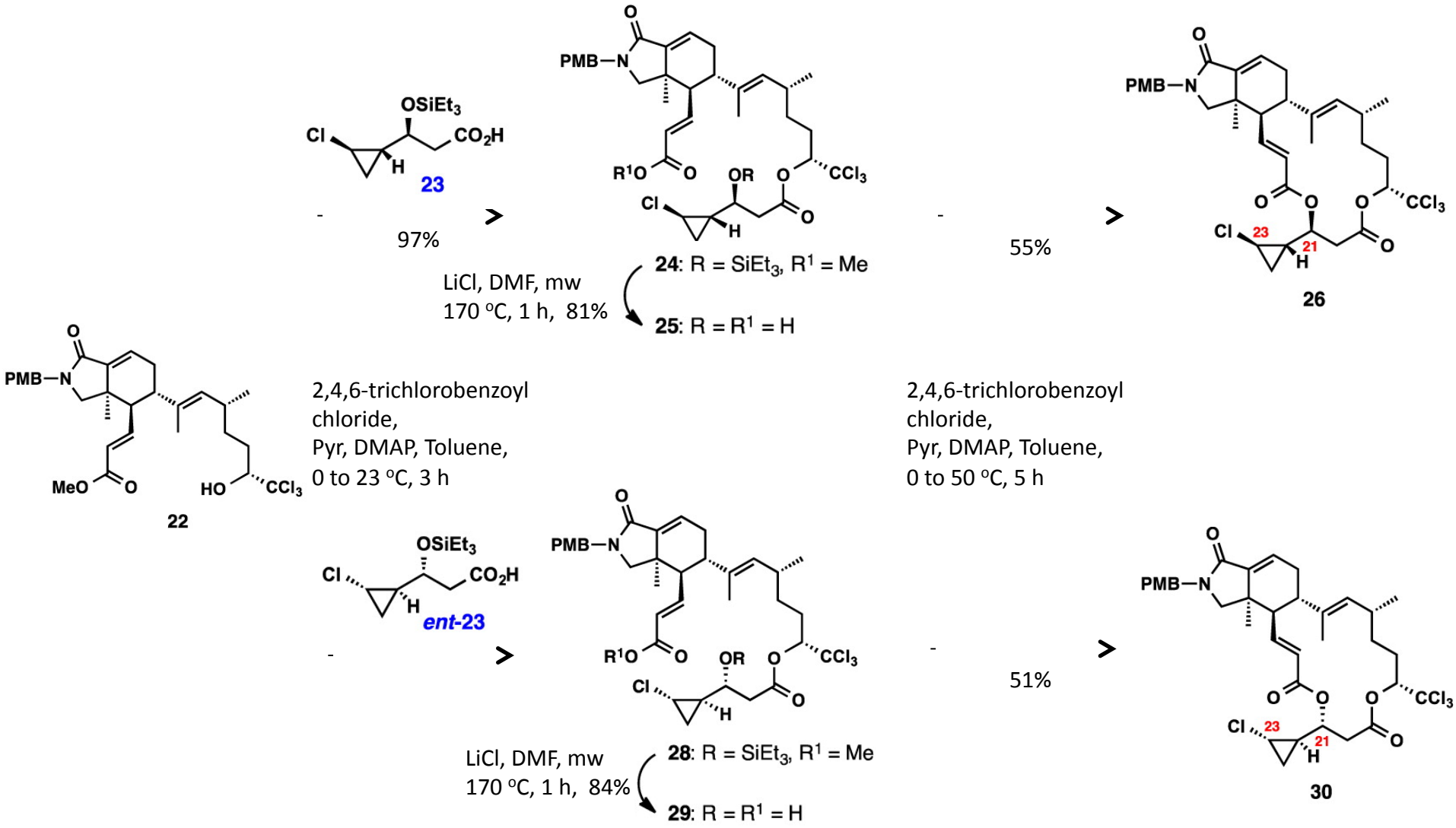


Total synthesis of (+)-Muironolide A



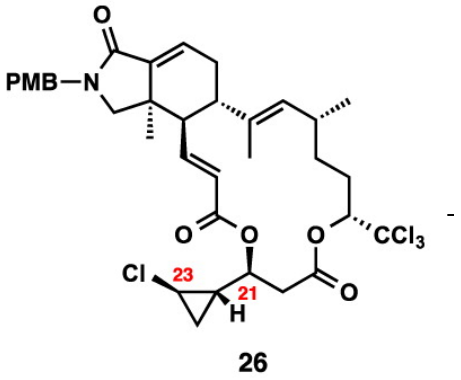
J. Am. Chem. Soc. **2015**, 137, 5907

Total synthesis of (+)-Muironolide A



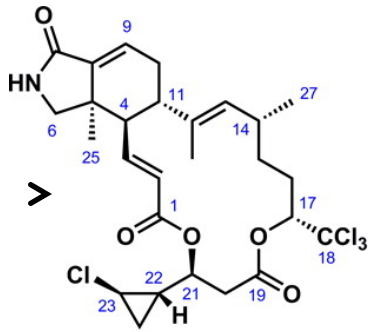
J. Am. Chem. Soc. **2015**, 137, 5907

Total synthesis of (+)-Muironolide A

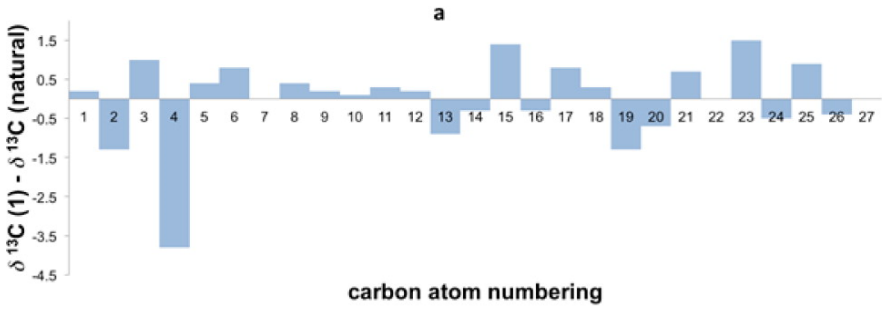


26

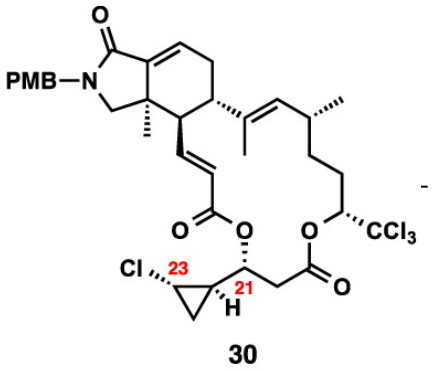
90%



C21-*epi*-muironolide A (**1**)
(original assignment)

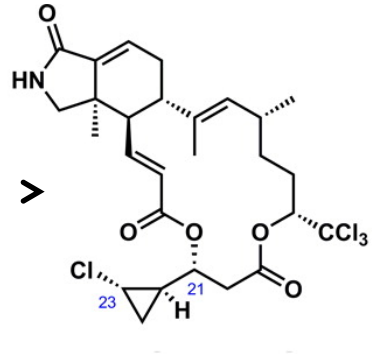


DDQ, H_2O (0.09% or 5 eq.),
dioxane, 100 °C, 8 h

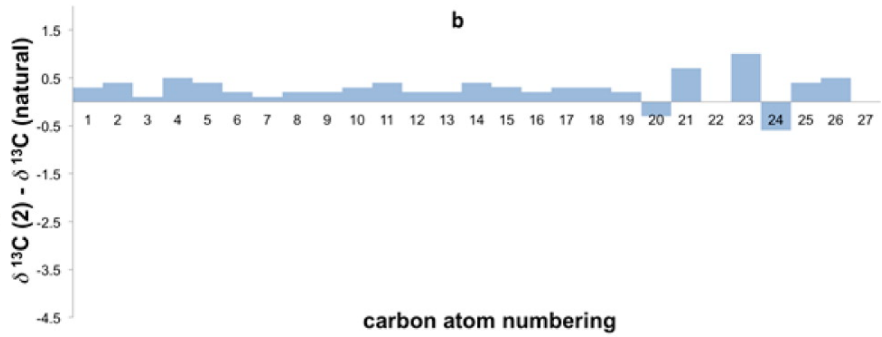


30

90%



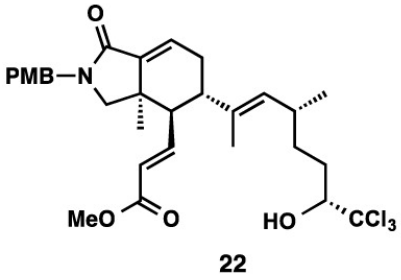
C22,C23-*epi*-muironolide A (**2**)



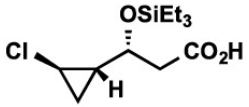
The major differences are confined mostly to the *trans*-chlorocyclopropyl ketide (CCK) unit.

J. Am. Chem. Soc. **2015**, 137, 5907

Total synthesis of (+)-Muironolide A



22



24

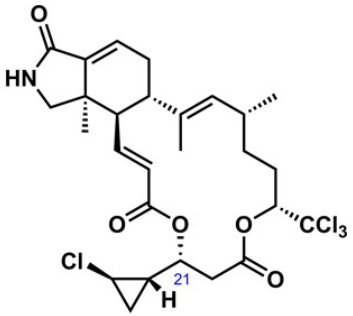
1. 2,4,6-trichlorobenzoyl chloride, Pyr, DMAP, Toluene, 0 to 23 °C, 3 h, 94%

2. LiCl, DMF, mw, 170 °C, 1 h, 61%

3. 2,4,6-trichlorobenzoyl chloride, Pyr, DMAP, Toluene, 0 to 50 °C, 5 h, 50%

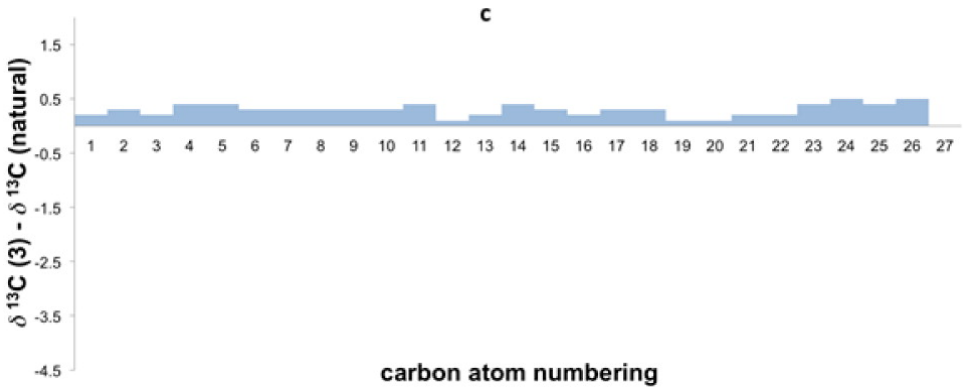
4. DDQ, H_2O (0.09%) dioxane, 100 °C, 8 h, 81%

>



(+)-muironolide A (**3**)
revised structure

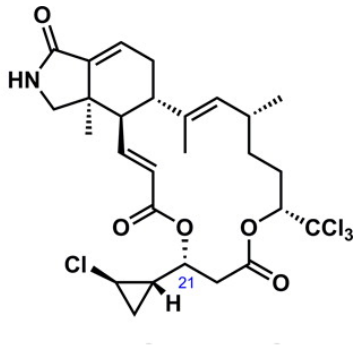
- The physical data were in full agreement with those reported for natural muironolide A.
- Circular dichroism (CD) spectroscopy demonstrated that it is enantiomeric to the natural sample,10 thus establishing its absolute configuration as opposite to that of natural muironolide A.



J. Am. Chem. Soc. **2015**, 137, 5907

Conclusion

- The enantioselective total synthesis of (+)-muironolide A resulted in the adjustment of configuration at C21 and reassignment of the absolute configuration of the natural product.
- 25 mg of the natural product paves the way for a more systematic evaluation of the biological profile of muironolide A.
- This work combines nanoscale NMR analysis with total synthesis for uncovering the full potential of “nearly extinct”, exceedingly rare components of natural product extracts.



(+)-muironolide A (**3**)
revised structure