

Institute of Organic Chemistry

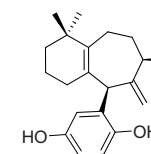
University of Zurich

Late Transition Metals in Natural Product Synthesis:
a (sometimes) successful story

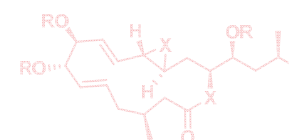
Prof. Cristina Nevado
nevado@oci.uzh.ch

Outlook

1. Total Synthesis of Frondosin A via Au-chemistry

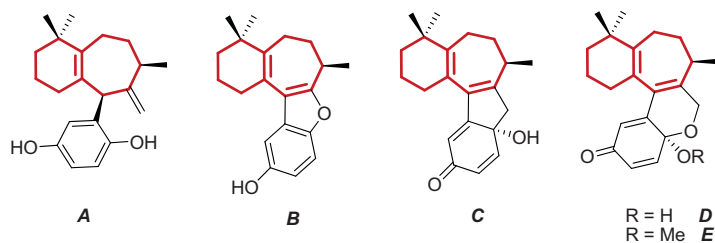


2. Natural Products as Chemical Probes: Iriomoteolide-3a



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Frondosin A-D



Both enantiomers [(+) and (-)] are **biologically active**

Frondosin A: the most **potent** compound

Mode of action: **inhibit the binding of interleukin-8 (IL-8)** in low μM range

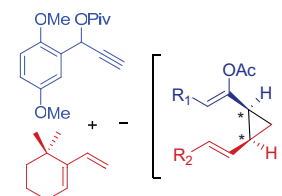
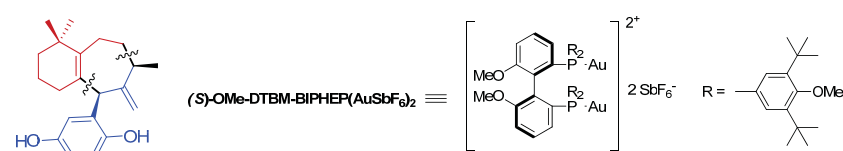
IL-8 : chemokine produced by fibroblasts, epithelial and endothelial cells triggers an **anti-inflammatory cascade** and can be induced during an immune response to promote cells of the immune system to a site of infection



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Enantioselective Synthesis of Frondosin A-D

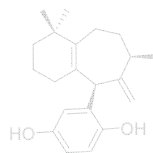
FRONDOSIN A



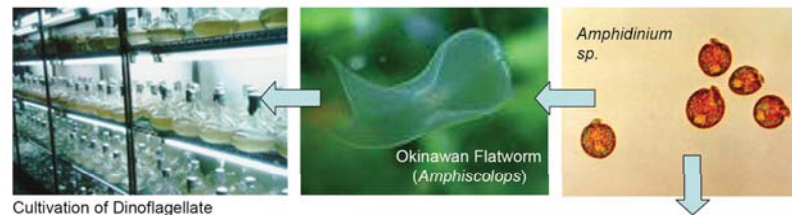
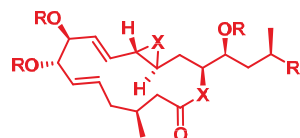
Previous enantioselective total synthesis: 21 steps, 3% yield: Trost, B. M. et al. *JACS* **2007**, 11781

Outlook

1. Total Synthesis of Frondosin A via Au-chemistry



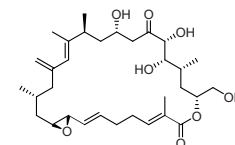
2. Natural Products as Chemical Probes: Iriomoteolide-3a



Cultivation of Dinoflagellate

Okinawan Flatworm
(Amphiscolops)

Amphidinium
sp.

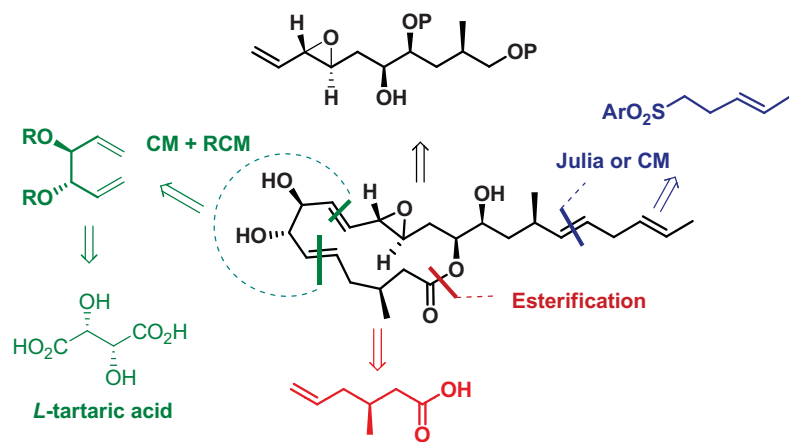


AMPHIDINOLIDES A-Y
Nat. Prod. Rep., 2004, 21, 77

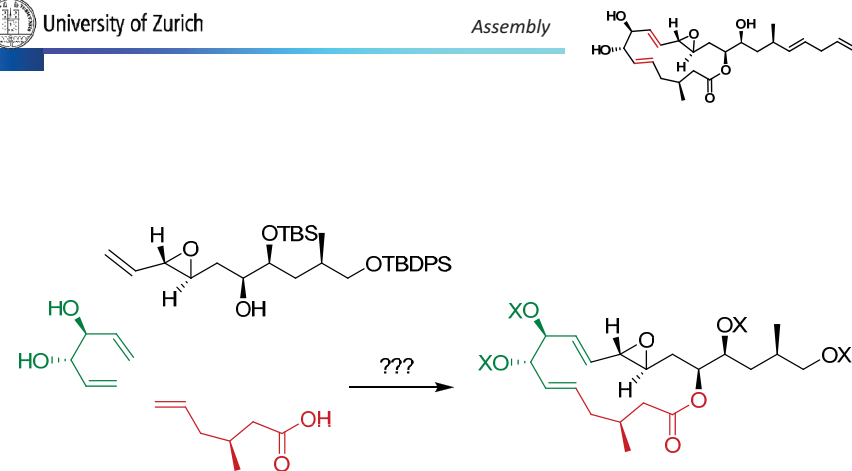
AMPHIDINOLIDES and IRIOMOTEOLIDES SHARE CYTOTOXIC ACTIVITY

COMMON ORIGIN = RELATED STRUCTURES = SAME CELLULAR TARGETS?

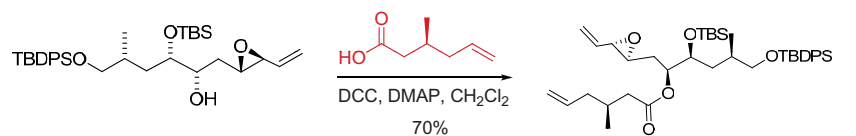
Total Synthesis of Iriomoteolide 3a



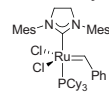
Total Synthesis of Iriomoteolide 3a



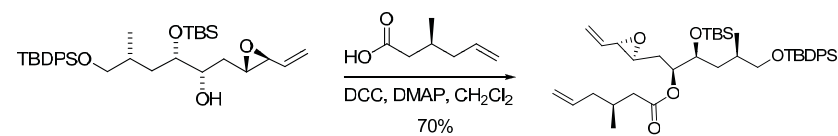
Cribiú, Jäger, Nevado, Angew. Chem. Int. Ed. 2009, 8780



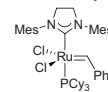
Grubbs' catalyst (II)



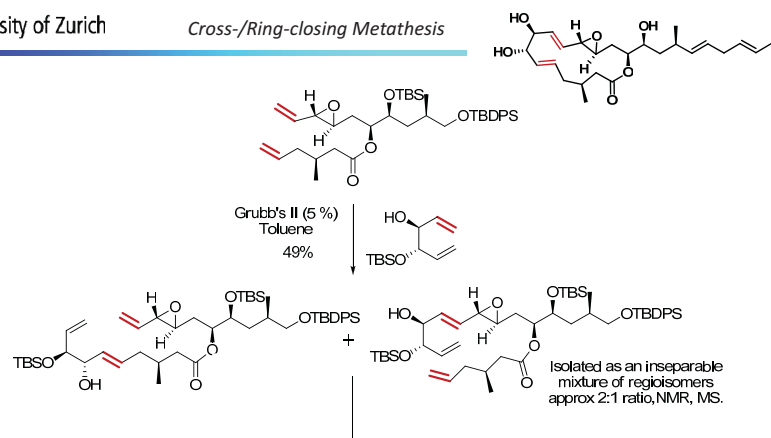
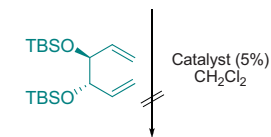
Cribiú, Jäger, Nevado, *Angew. Chem. Int. Ed.* **2009**, 8780



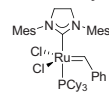
Grubbs' catalyst (II)



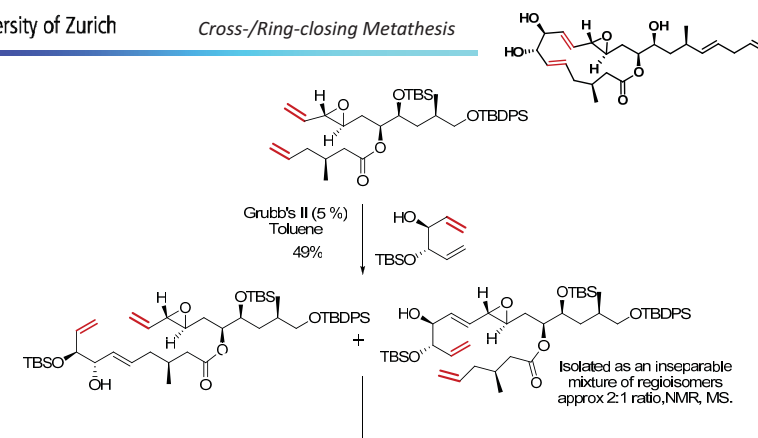
Cribiú, Jäger, Nevado, *Angew. Chem. Int. Ed.* **2009**, 8780



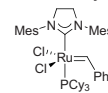
Grubbs' catalyst (II)



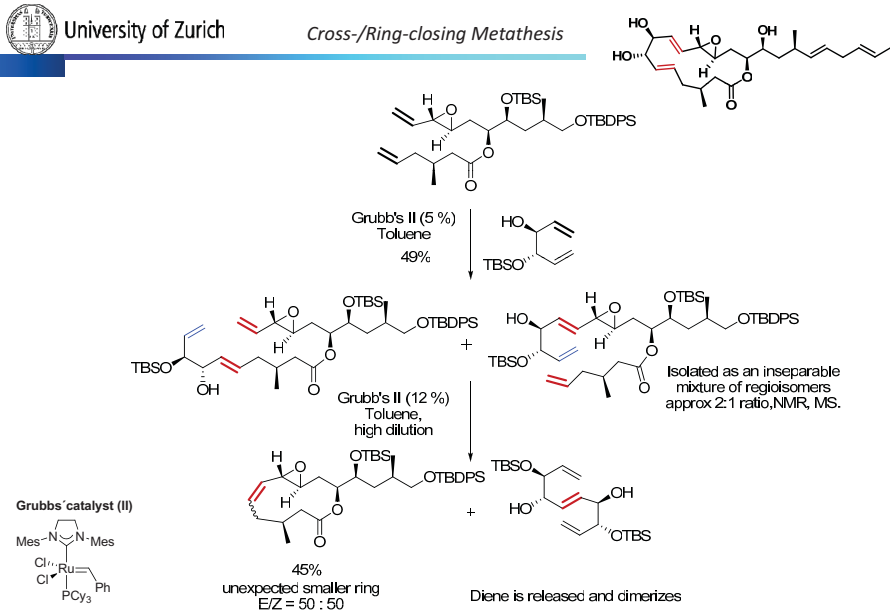
Cribiú, Jäger, Nevado, *Angew. Chem. Int. Ed.* **2009**, 8780



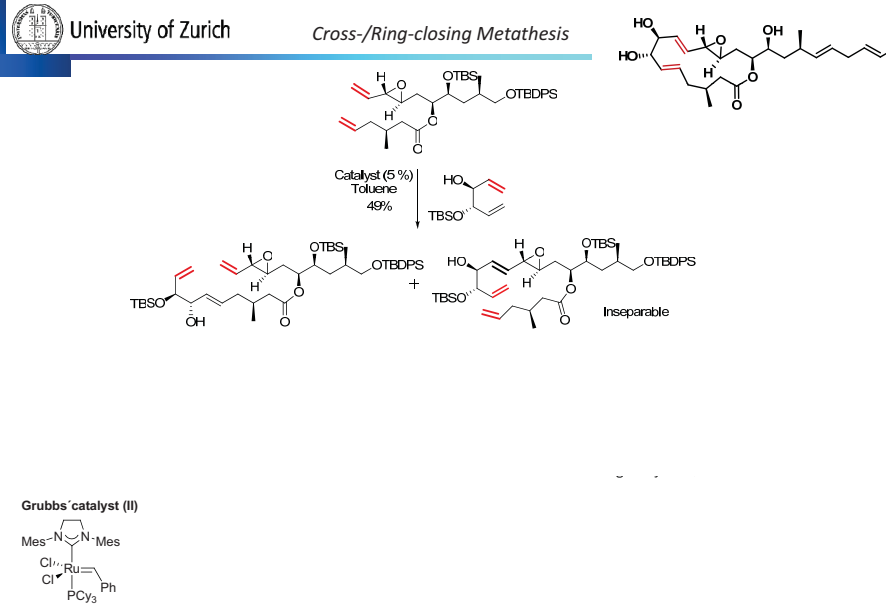
Grubbs' catalyst (II)



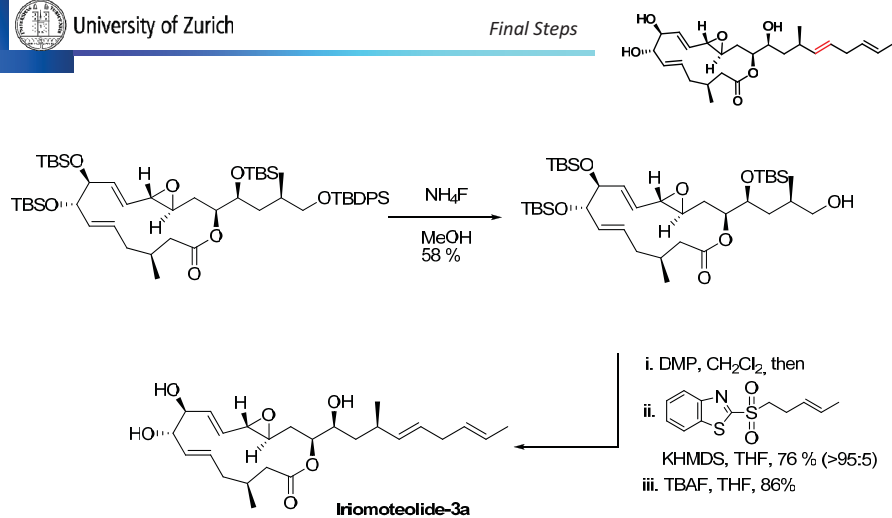
Cribiú, Jäger, Nevado, *Angew. Chem. Int. Ed.* **2009**, 8780



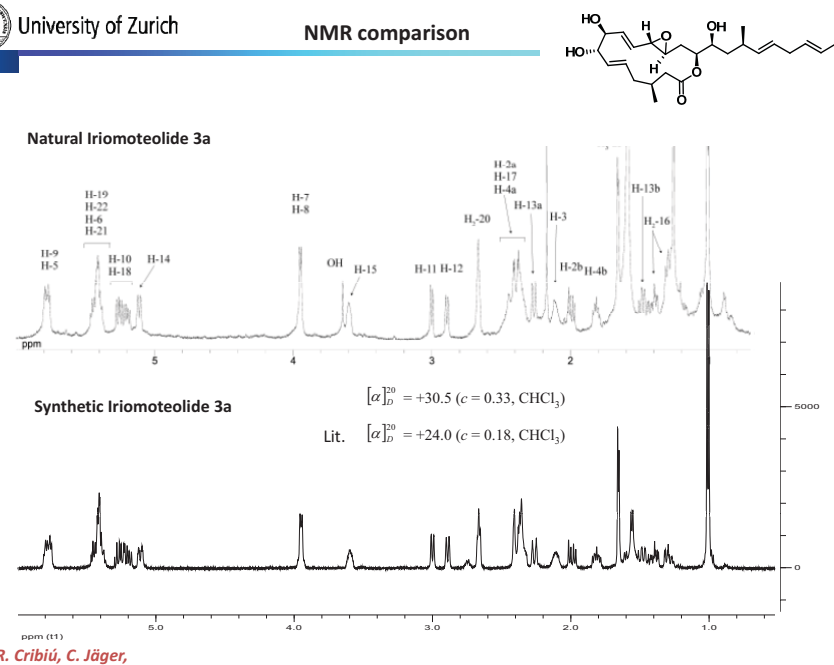
Cribiú, Jäger, Nevado, *Angew. Chem. Int. Ed.* **2009**, 8780



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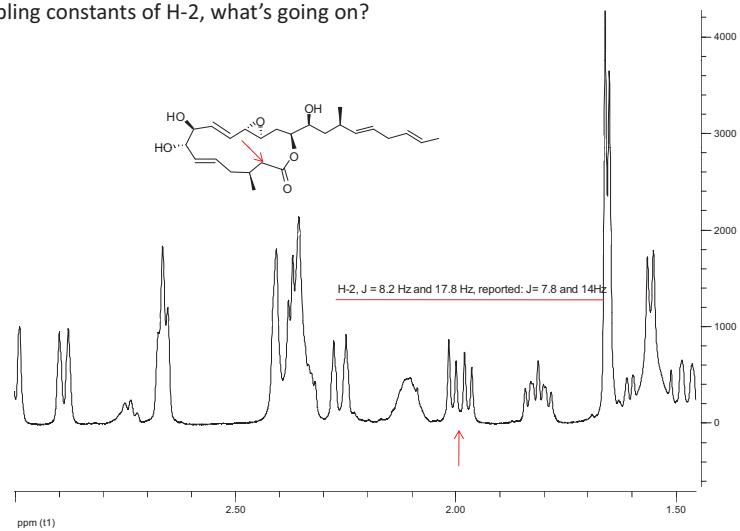


Cribiú, Jäger, Nevado, *Angew. Chem. Int. Ed.* **2009**, 8780

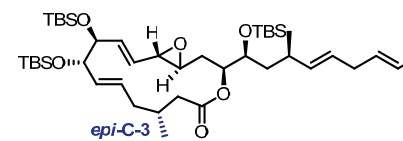




All the chemical shifts of ^1H and ^{13}C , and coupling constants fitted well, except Coupling constants of H-2, what's going on?

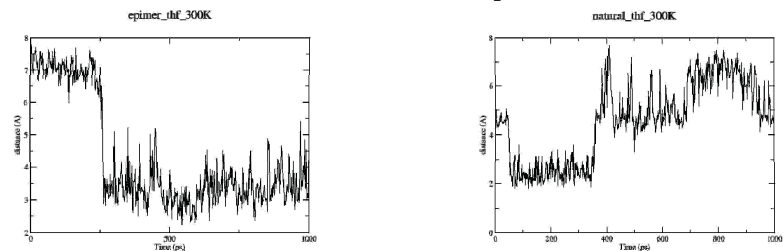


R. Cribiú, C. Jäger,



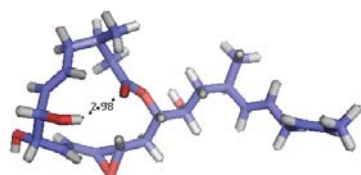
R. Cribiú, C. Jäger,

Unpublished Results

MD simulations: THF/H₂O

Epimer

Natural



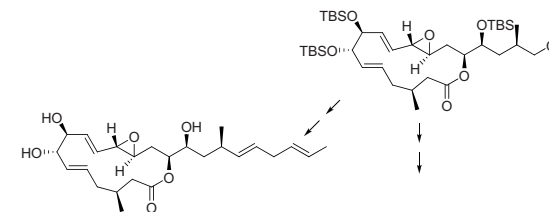
Most stable conformer
-894579 kcal/mol



Most stable conformer
-894583 kcal/mol

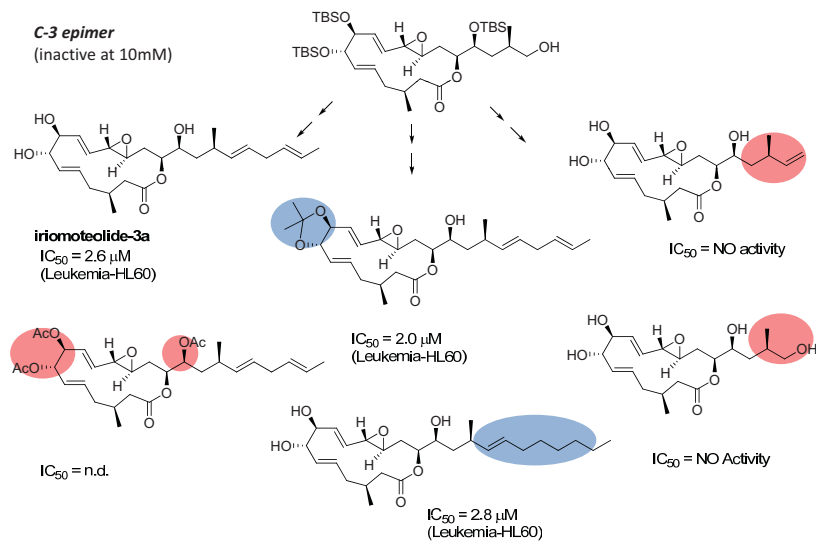


Irio-3a : Synthetic Collection



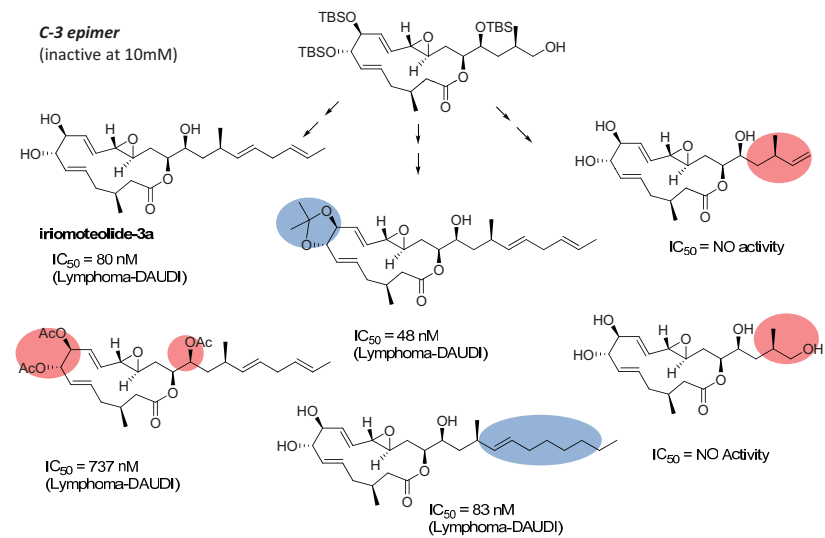
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