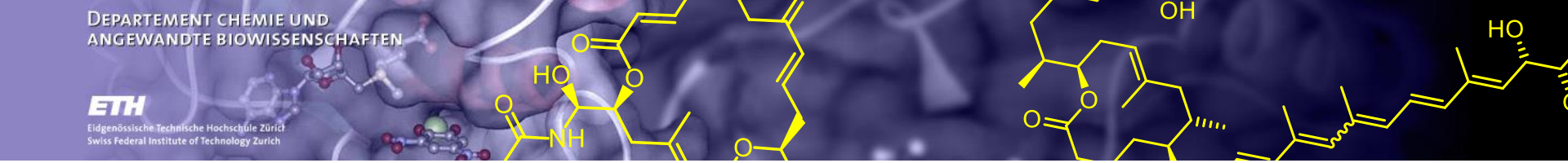
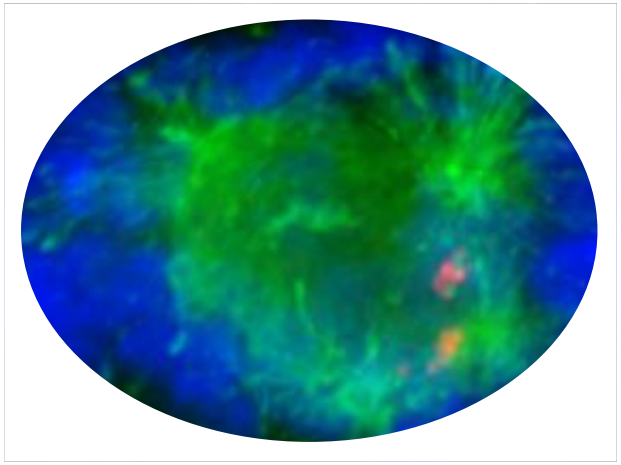


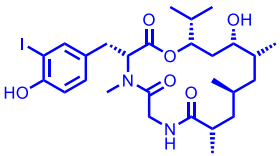
The Chemistry and Biology of the Marine Macrolides Zampanolide and Dactylolide



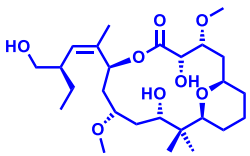
Karl-Heinz Altmann
ETH Zürich

EFMC-YSN MedChemBioOnline
May 26, 2020

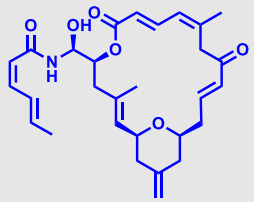
Bioactive Natural Products: Targets



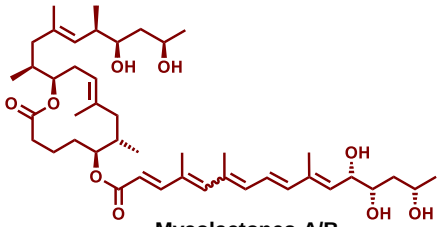
Doliculide
Tao 2015



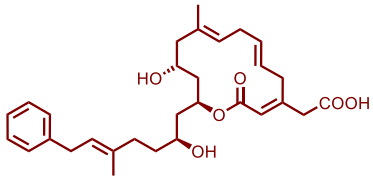
Peloruside (analog)
Wullschleger 2013



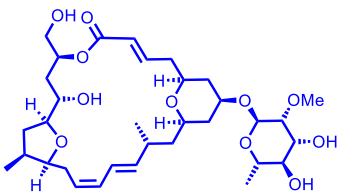
Zampanolide
Zurwerra 2012



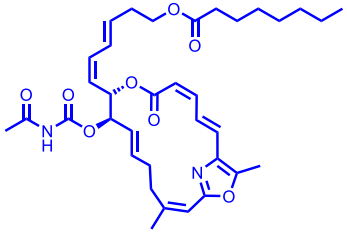
Mycolactones A/B
Gersbach 2011



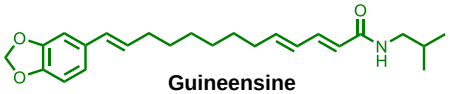
Ripostatin B
Glaus 2012



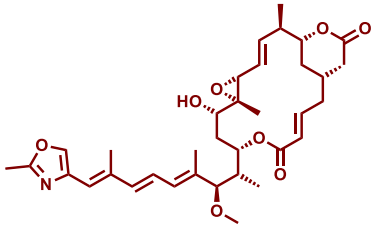
Mandelalide A
Brütsch 2016



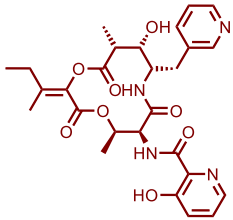
Salarin C (analog)
Schroff 2018



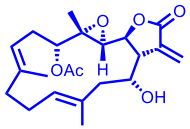
Guineensine
Bartholomäus, 2019



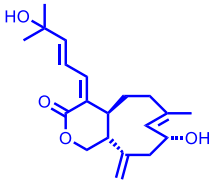
Rhizoxin F
Neuhaus, Liniger 2013



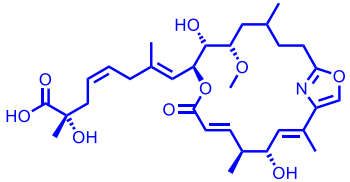
Pyridomycin (analogs)
Horlacher 2013



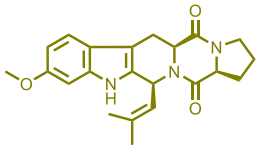
Michaolide F
Schiess, unpublished



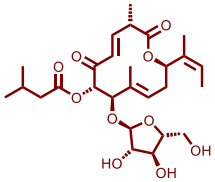
Isoxeniolide A
Betschart, unpublished



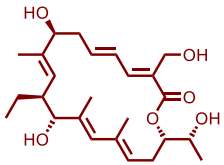
(Nominal) Leiodolide A
Edenharter, unpublished



Fumitremorgin C
Zechner, unpublished

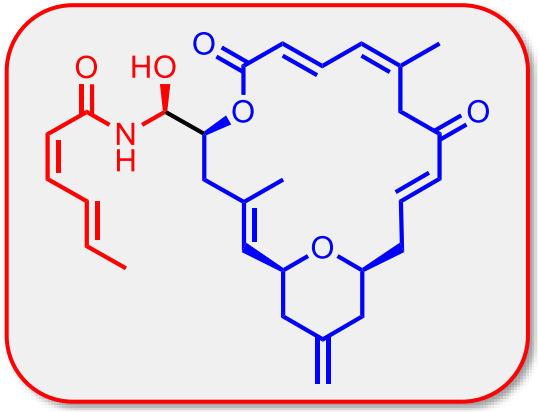


Disciformycin B
Waser, unpublished

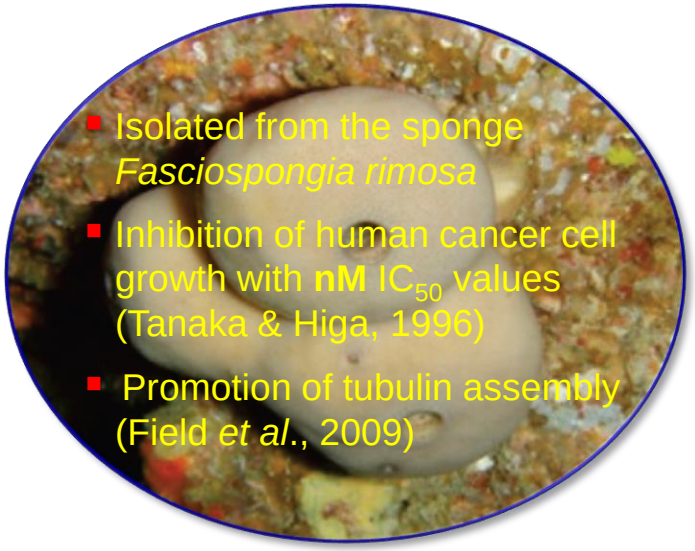


Tiacumycin B Aglycone
Glaus 2015

(–)-Zampanolide: A Marine Macrolide with a Unique Structure

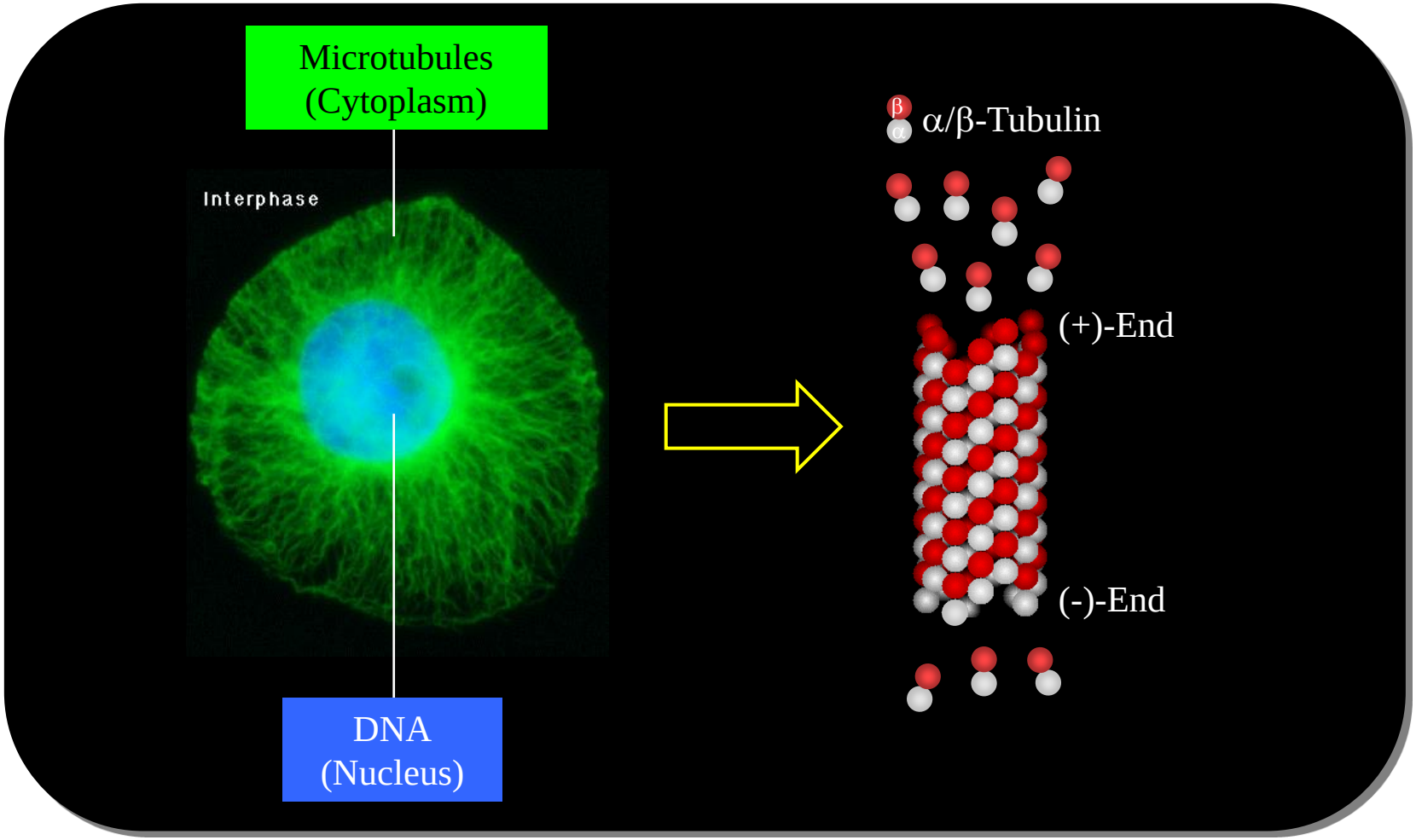


(-)-Zampanolide

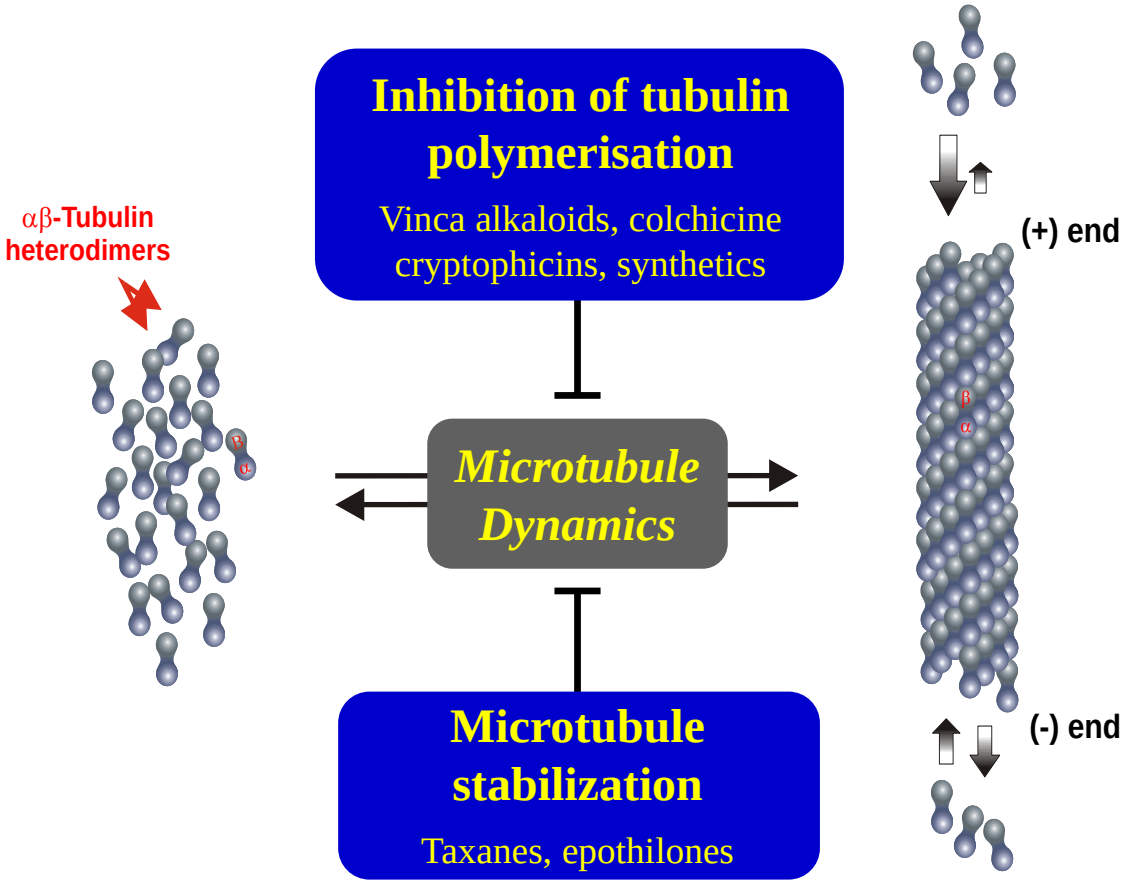


- Isolated from the sponge *Fasciospongia rimosa*
- Inhibition of human cancer cell growth with **nM** IC_{50} values (Tanaka & Higa, 1996)
- Promotion of tubulin assembly (Field *et al*., 2009)

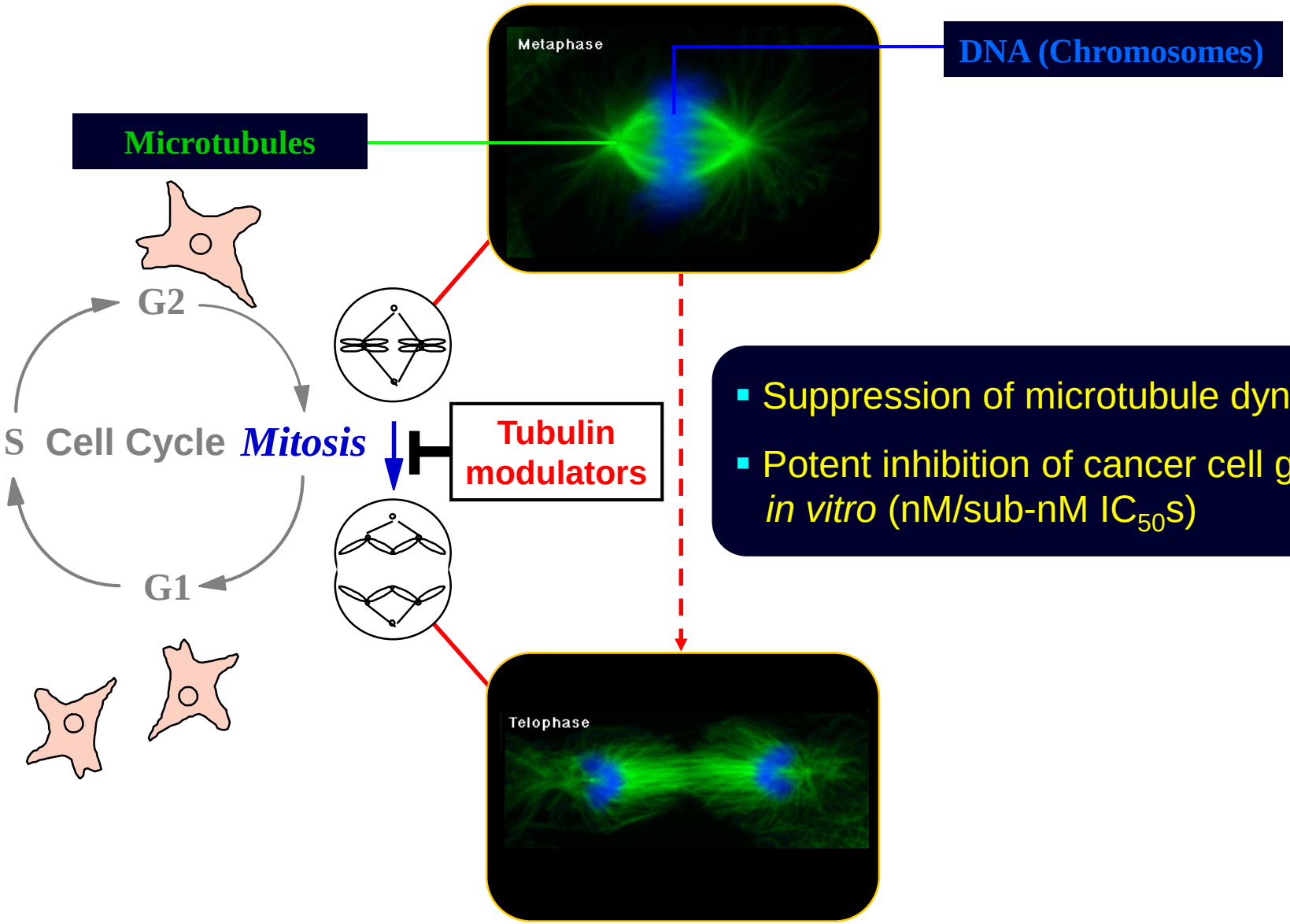
Microtubule Structure and Dynamic Instability



Tubulin Polymerization Inhibitors and MSA

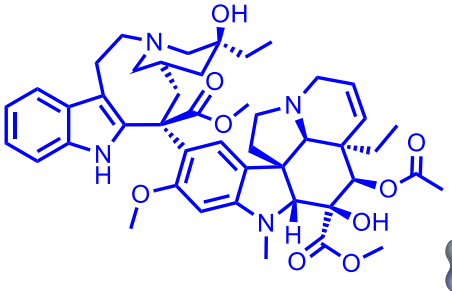


Tubulin Modulators: G2/M Arrest and Apoptosis

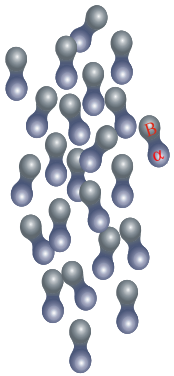


- Suppression of microtubule dynamics
- Potent inhibition of cancer cell growth *in vitro* (nM/sub-nM IC_{50}s)

Tubulin Polymerization Inhibitors and MSA



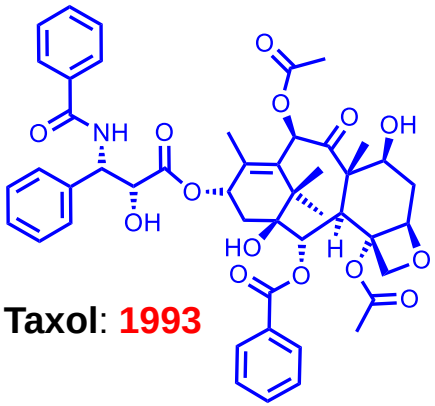
Vinblastine: **1963**



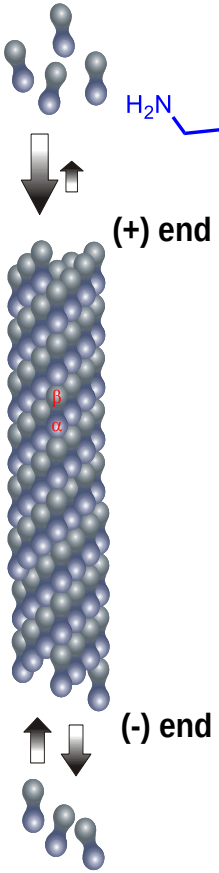
Inhibition of tubulin polymerisation

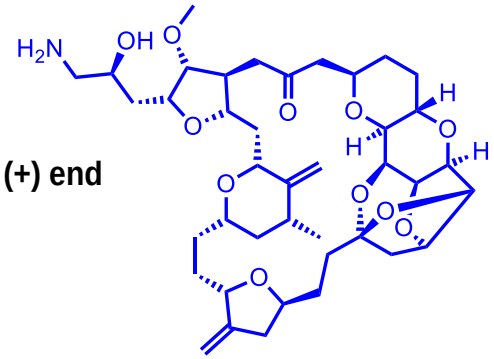
Microtubule Dynamics

Microtubule stabilization



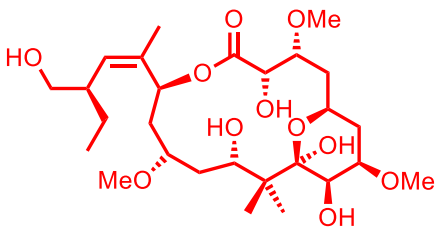
Taxol: **1993**



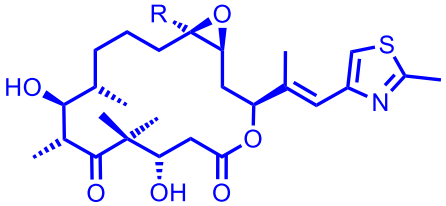


Eribulin: **2010**

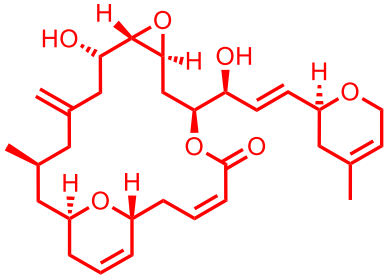
Non-Taxane Natural Product Microtubule Stabilizers



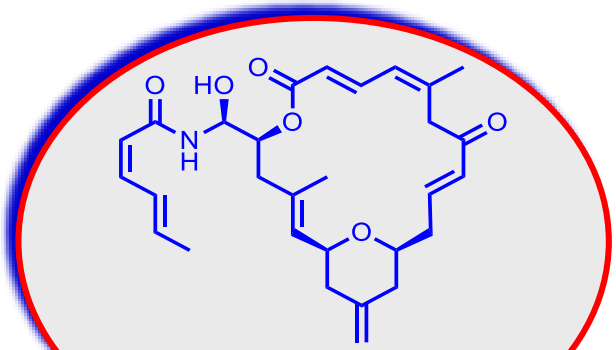
Peloruside A
(**Sponge**)



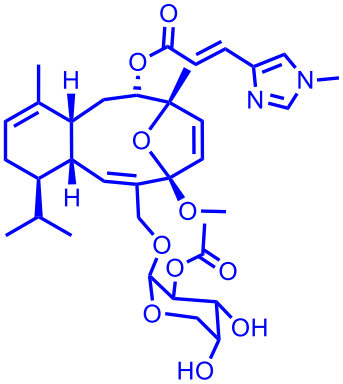
Epothilones A/B
(**Myxobacteria**)



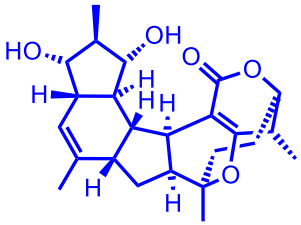
Laulimalide
(**Sponge**)



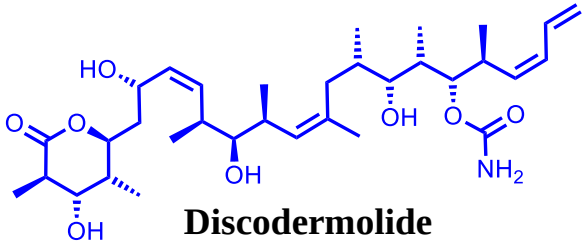
Zampanolide
(**Sponge**)



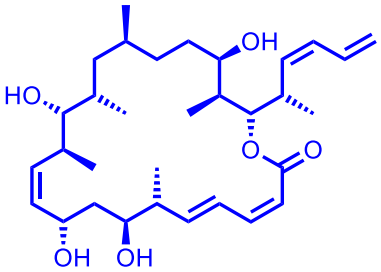
Eleutherobin
(**Soft coral**)



Cyclostreptin
(**Streptomyces**)

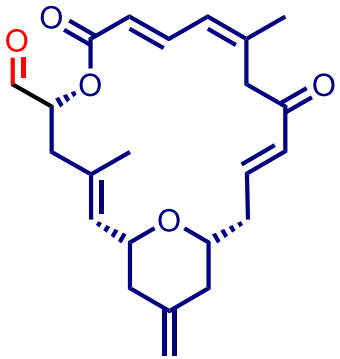


Discodermolide
(**Sponge**)

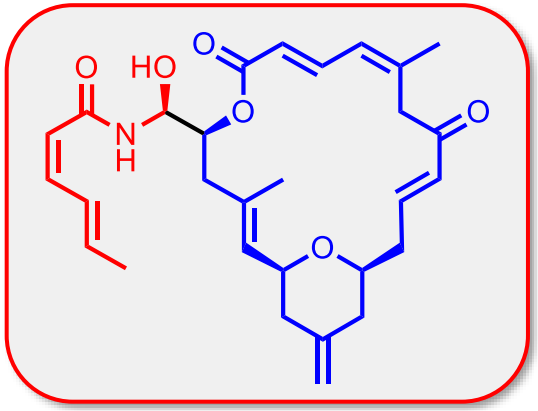


Dictyostatin
(**Sponge**)

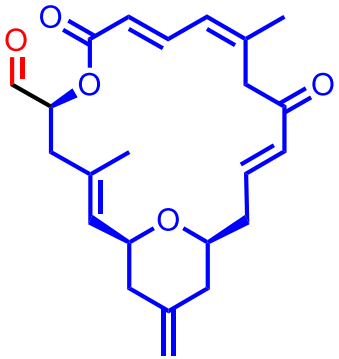
(–)-Zampanolide and (+)-Dactylolide: Stereochemical Divergence in NP Biosynthesis



(+)-Dactylolide



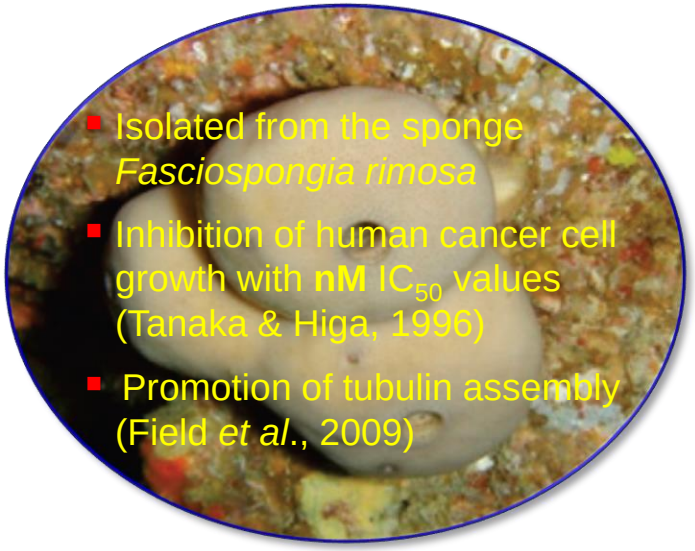
(-)-Zampanolide



(-)-Dactylolide

- Isolated from a sponge of the genus *Dactylospongia*
- Inhibition of human cancer cell growth with **μM** IC_{50} values

(Cutignano *et al*., 2001)



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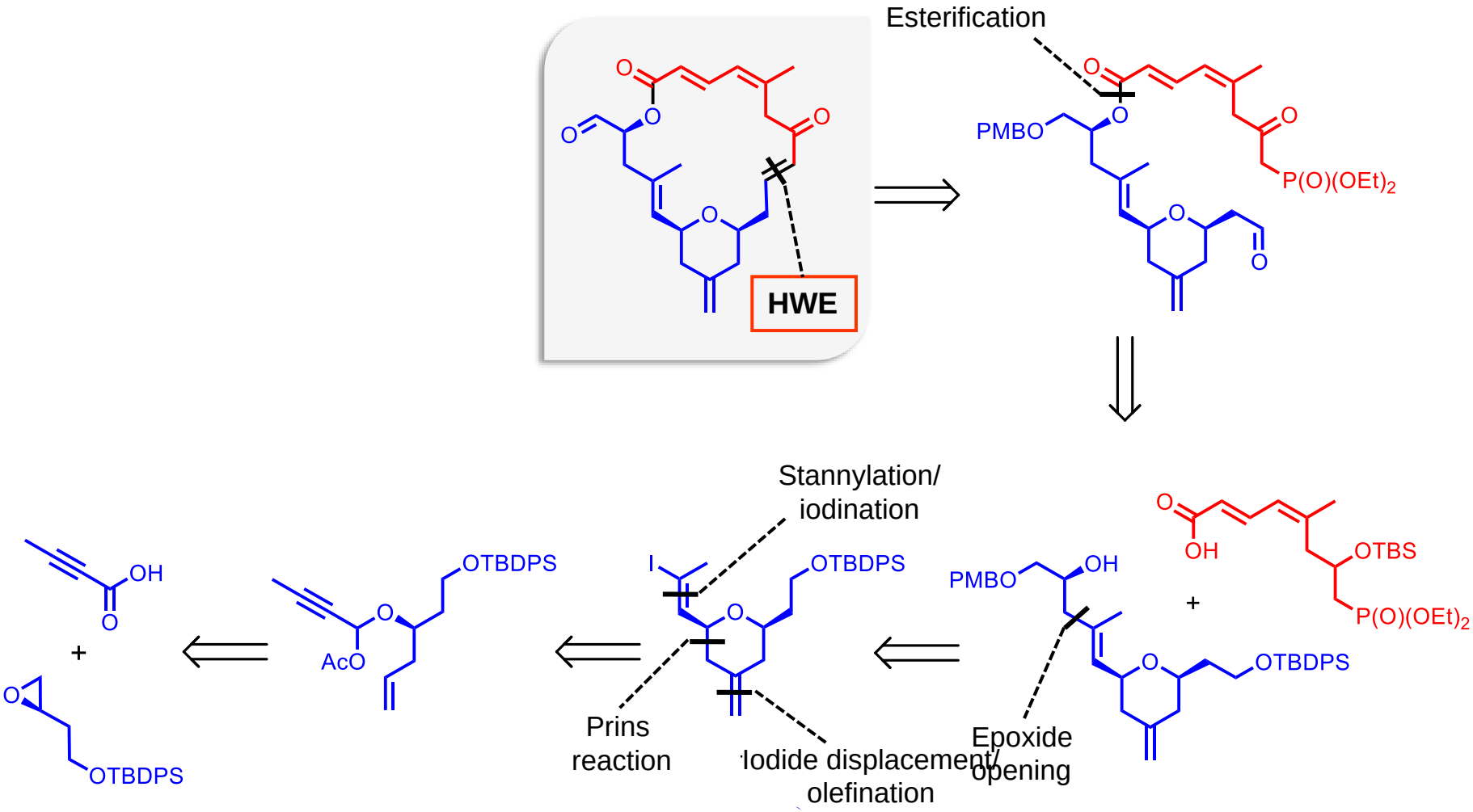
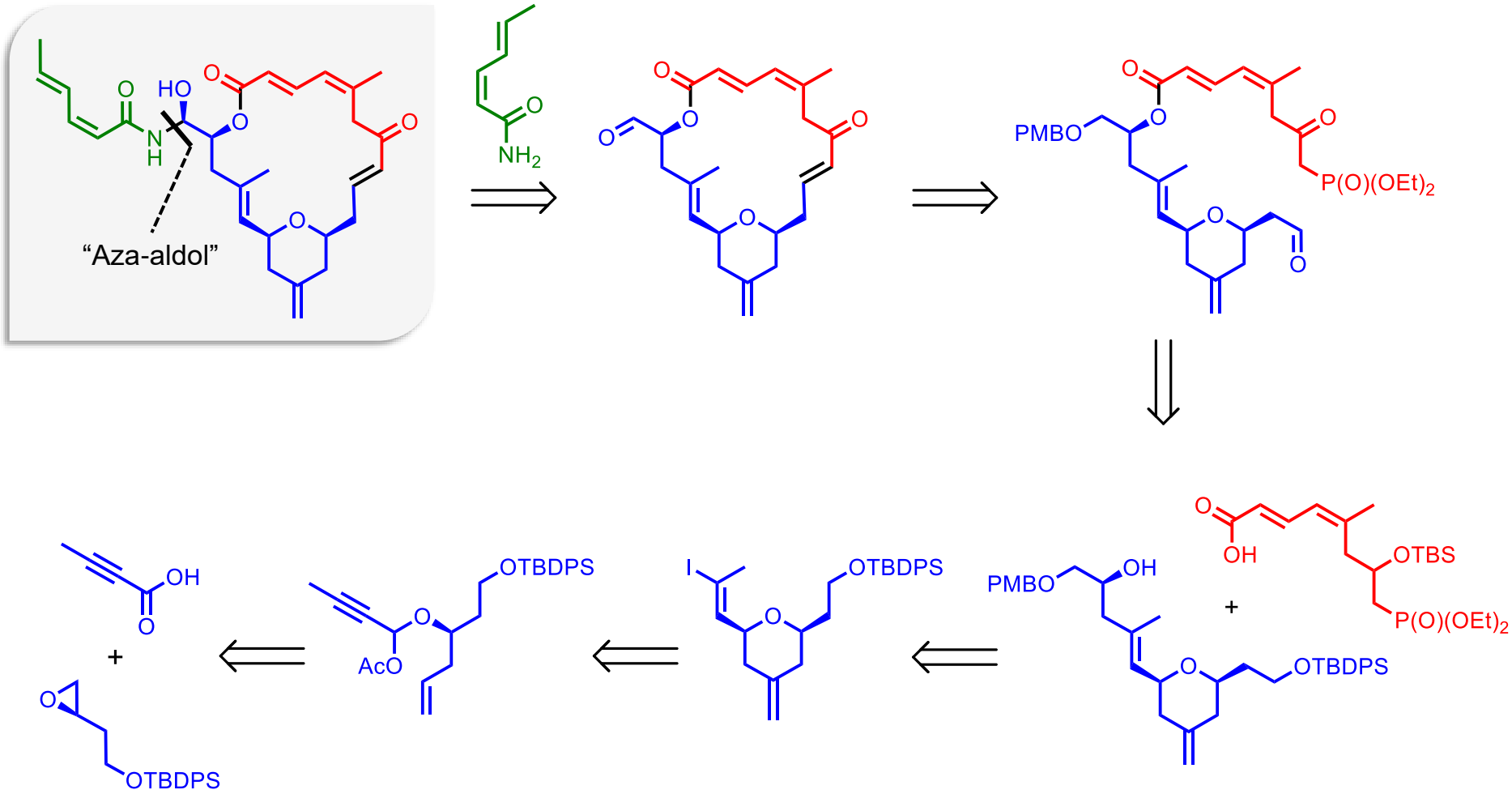
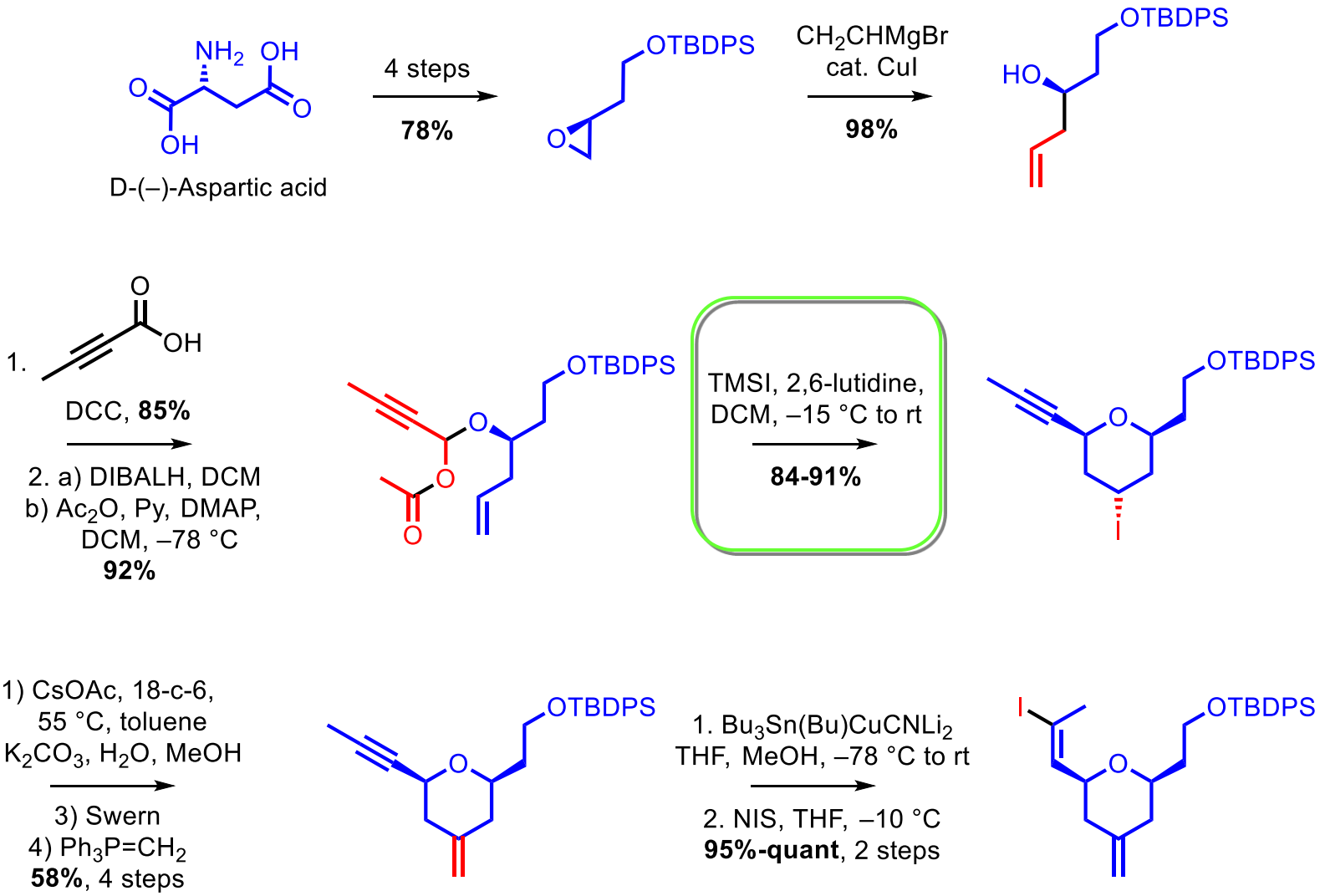
(–)-Dactylolide: Retrosynthesis



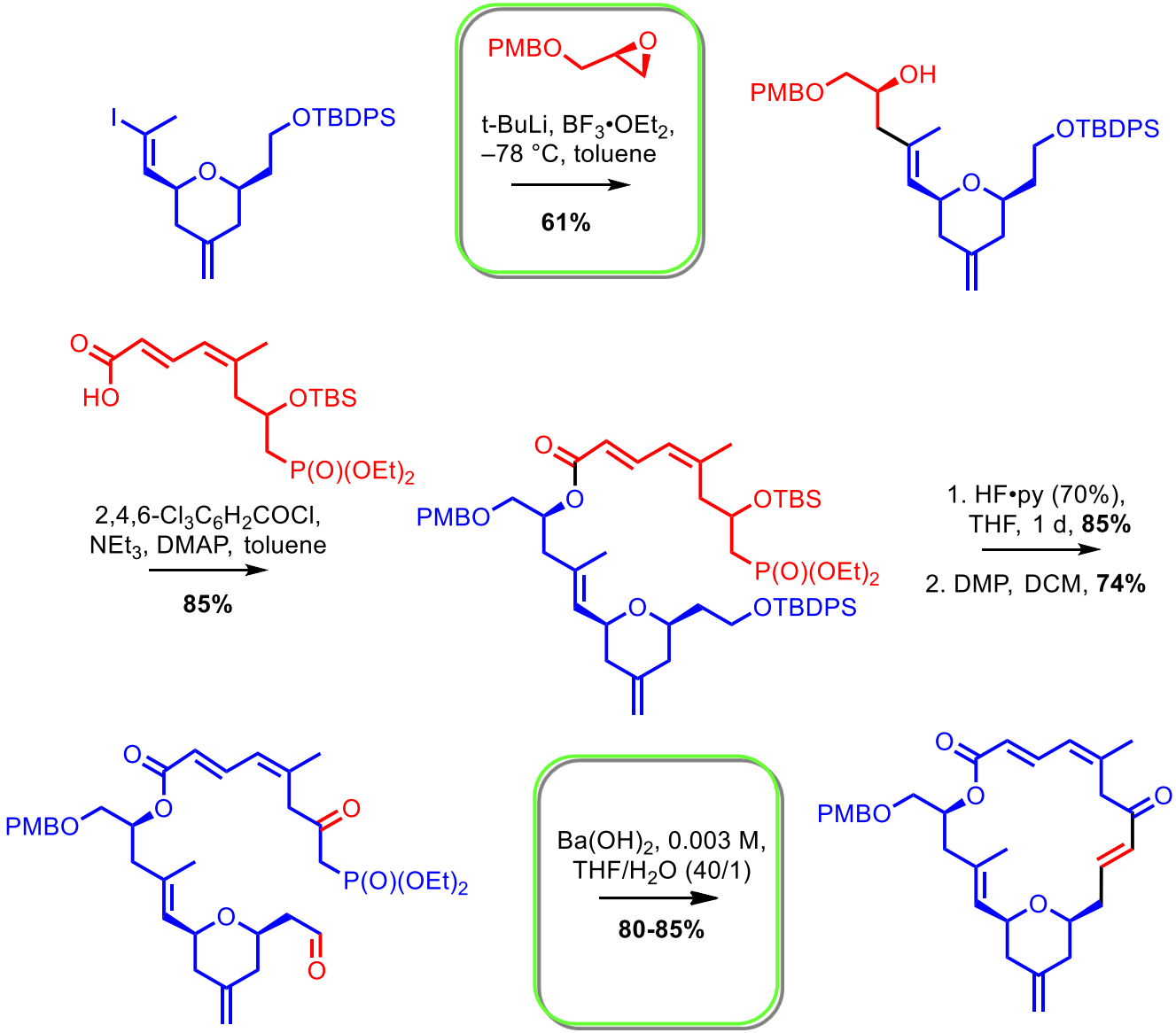
(–)-Zampanolide: Retrosynthesis



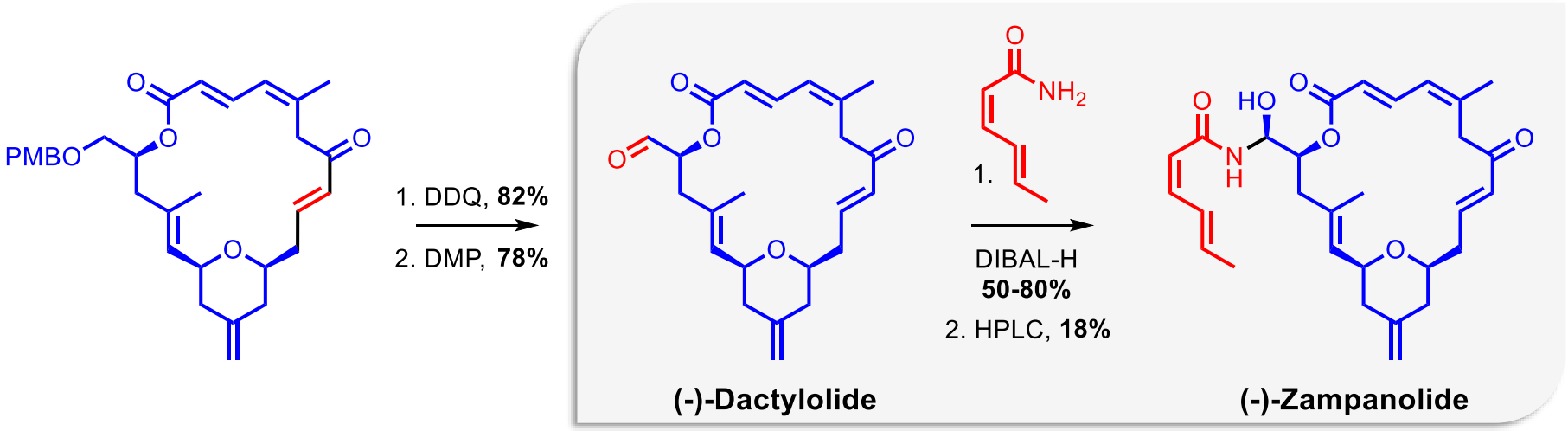
THP Ring Construction



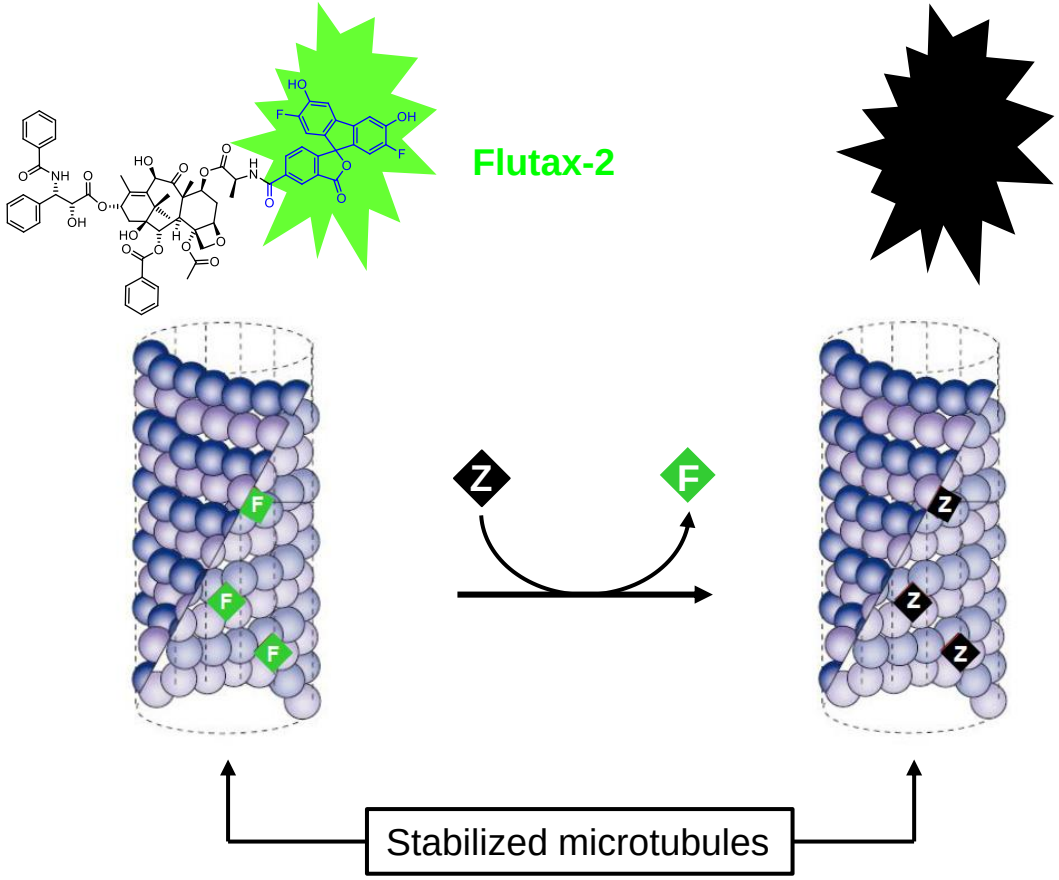
Fragment Assembly and Ring Closure



Total Synthesis of (–)-Dactylolide and (–)-Zampanolide



(–)-Dactylolide and (–)-Zampanolide: Binding to Microtubules

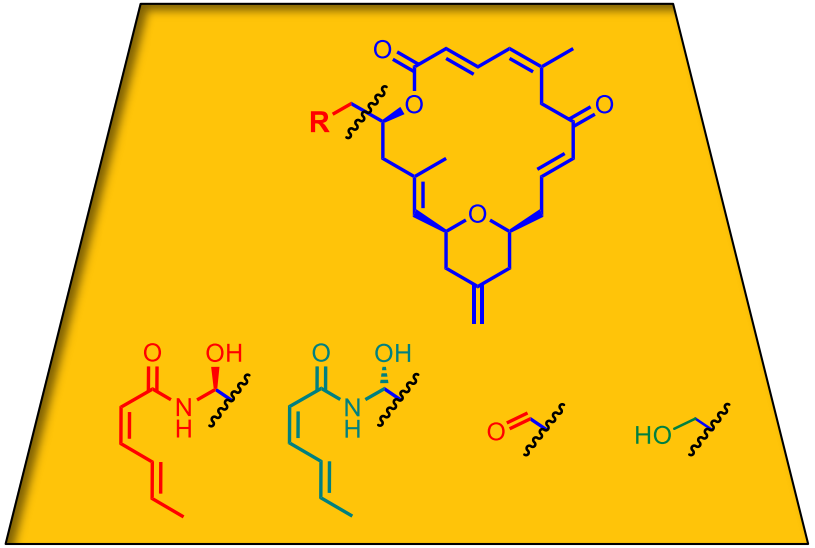


	K_b (37 °C) (M)
(-)-Zampanolide	25.8×10^7
(-)-Dactylolide	0.14×10^7
Taxol	1.07×10^7

J. J. Field, *et al*. *Chem. Biol.* **2012**, *19*, 686.

(-)-Dactylolide/(-)-Zampanolide: Inhibition of Cancer Cell Proliferation

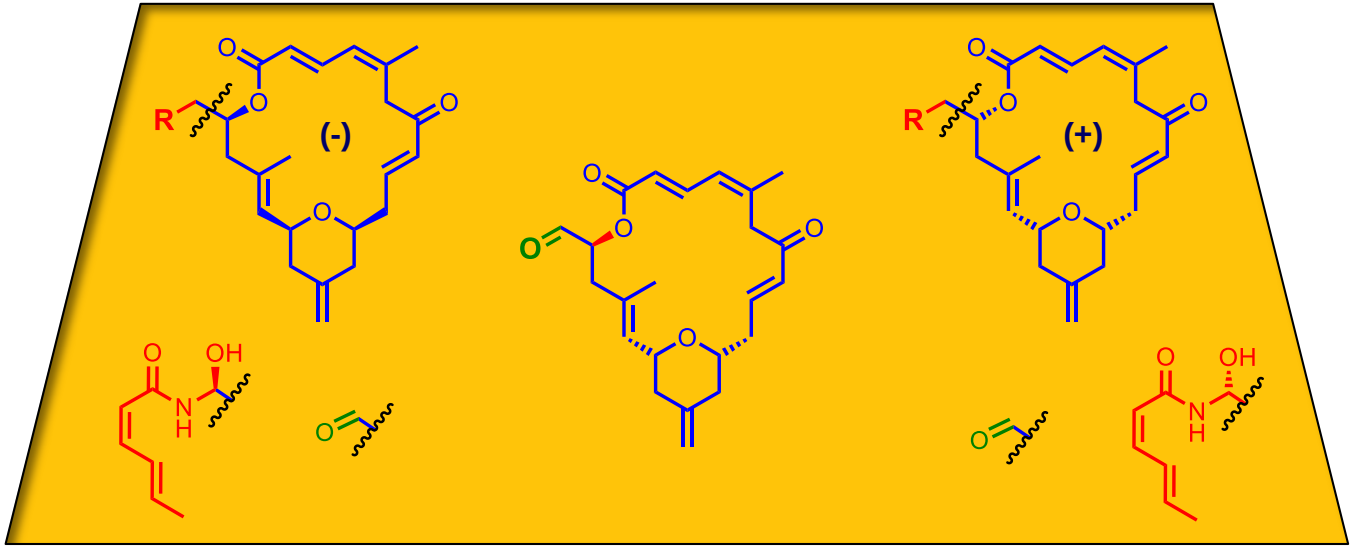
IC_{50} [nM]



Cell line				
A549	3.2	53	302	149
MCF-7	6.5	42	248	68
HCT116	7.2	88	210	249
A2780	3.0	-	1'252	-

Data generated by J. Gertsch, F. Diaz, I. Barasoain

Dactylolide and Zampanolide: Inhibition of Cancer Cell Proliferation

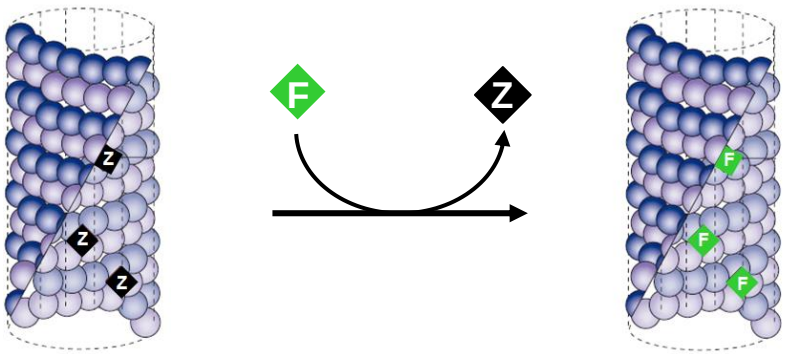


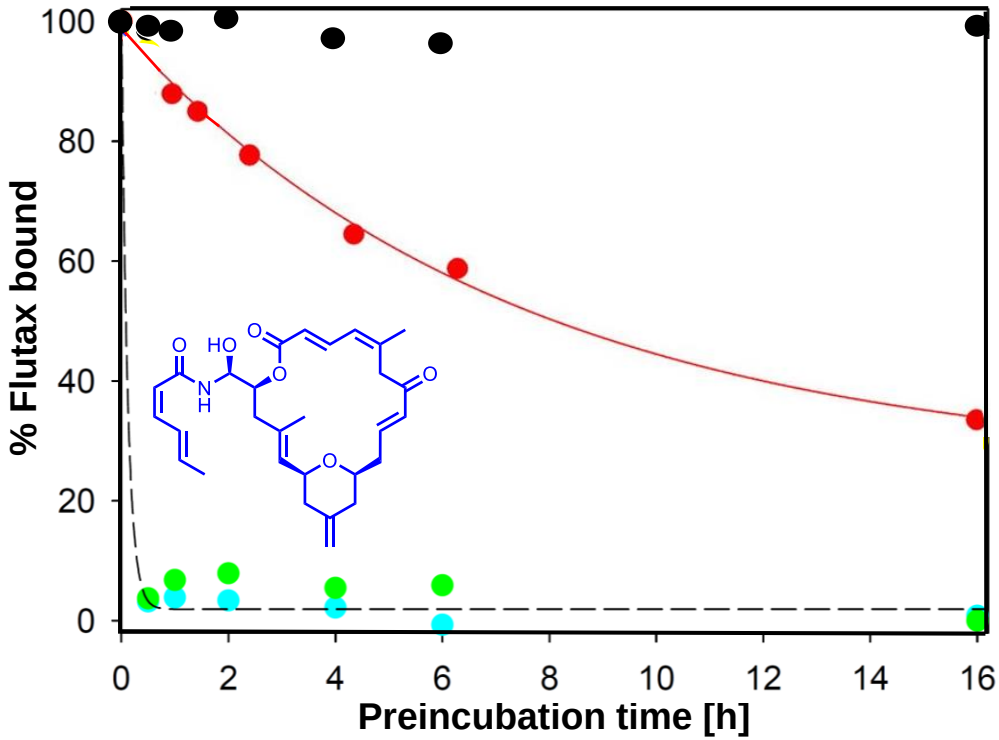
IC_{50} [nM]

Cell line					
A2780	0.81	1'254	15'382	9'488	10'500
A2780AD	2.68	1'252	11'299	12'848	12'445

Data generated by J. Gertsch, F. Diaz, I. Barasoain

(-)-Zampanolide: Irreversible Binding to Microtubules

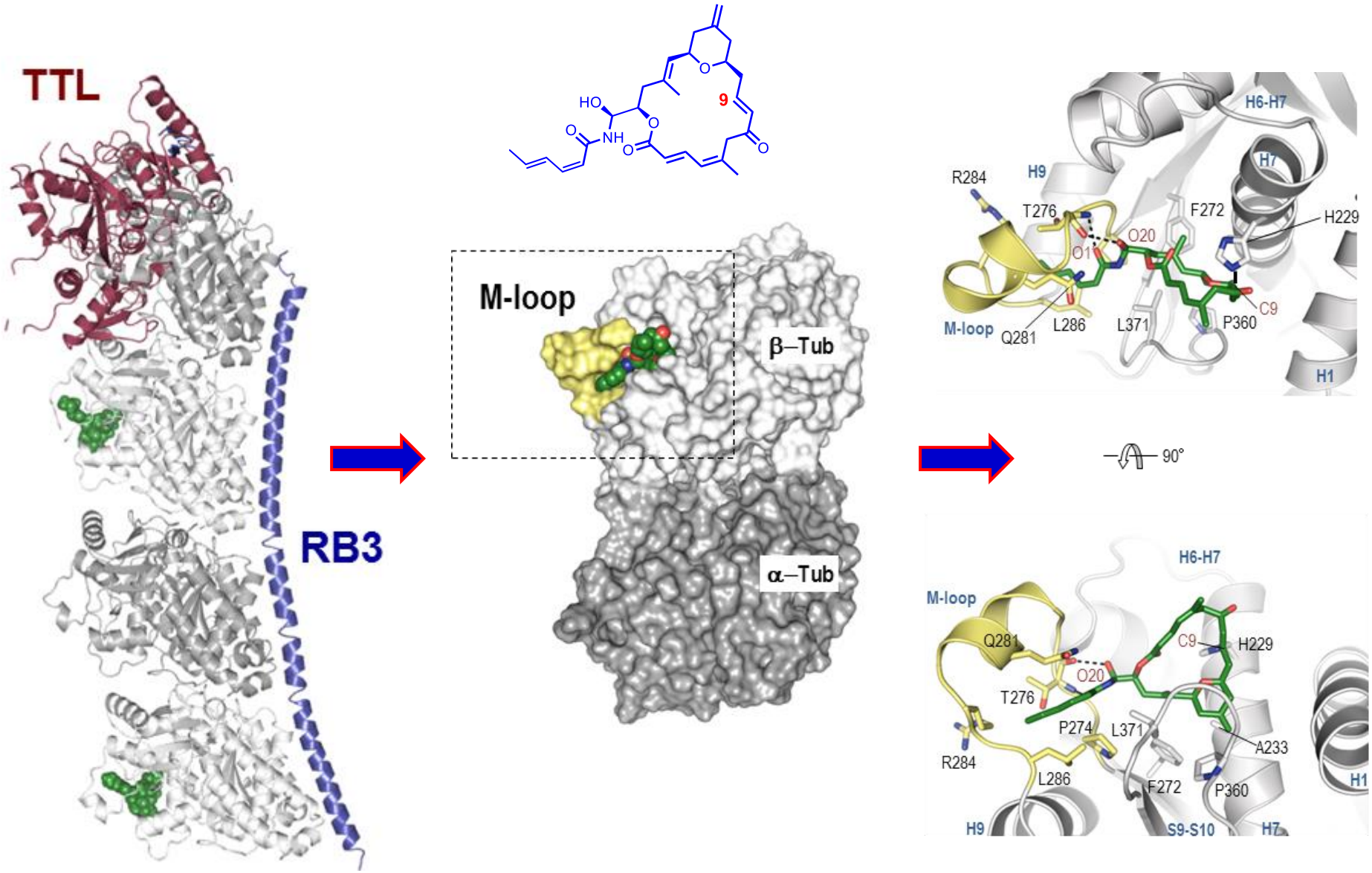




- Control (DMSO)
- (-)-Zampanolide (syn)
- (-)-Zampanolide (nat)
- (-)-Dactylolide

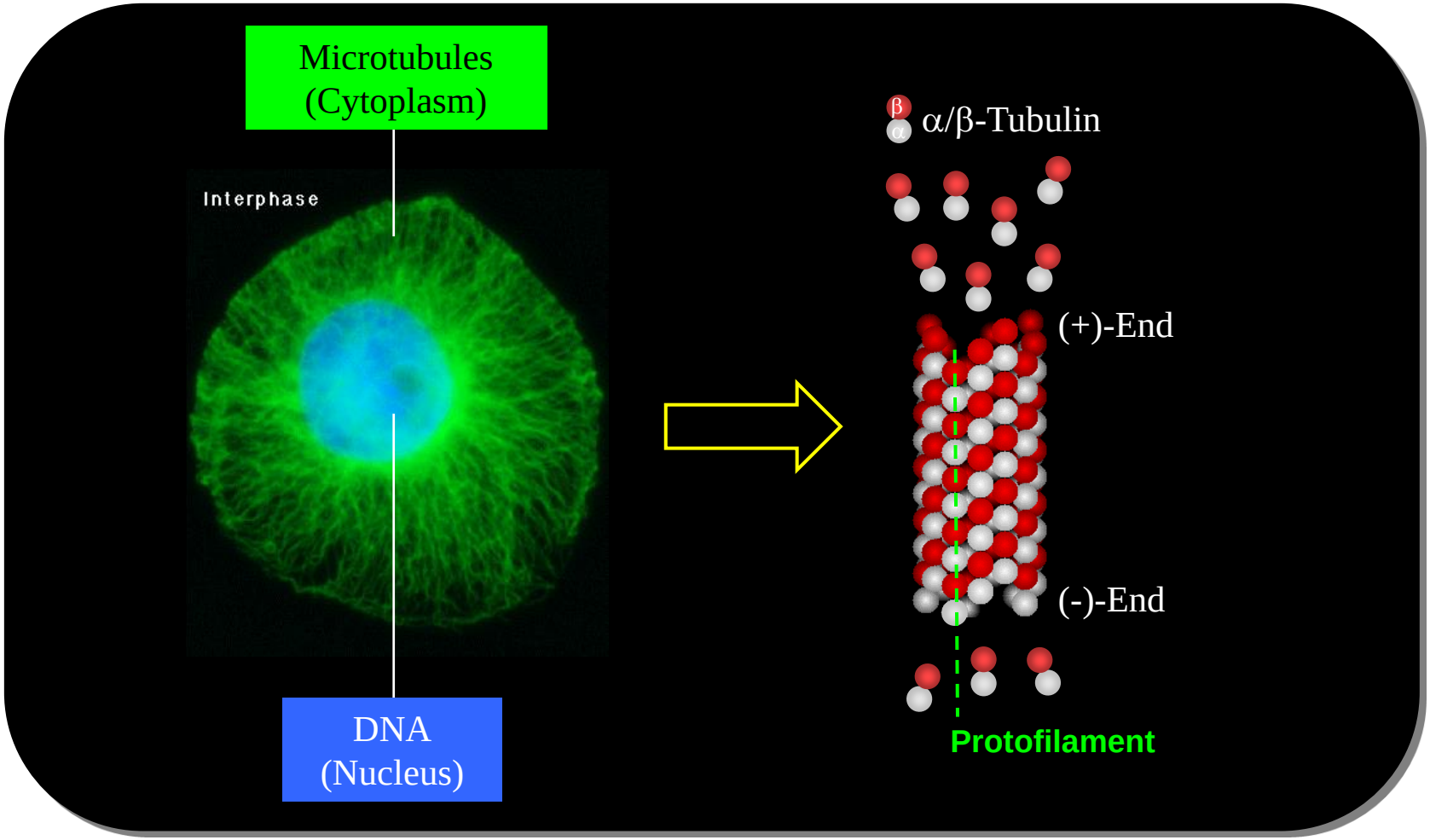
J. J. Field, *et al*. *Chem. Biol.* **2012**, *19*, 686.

Tubulin-Zampanolide Complex at 1.8 Å Resolution

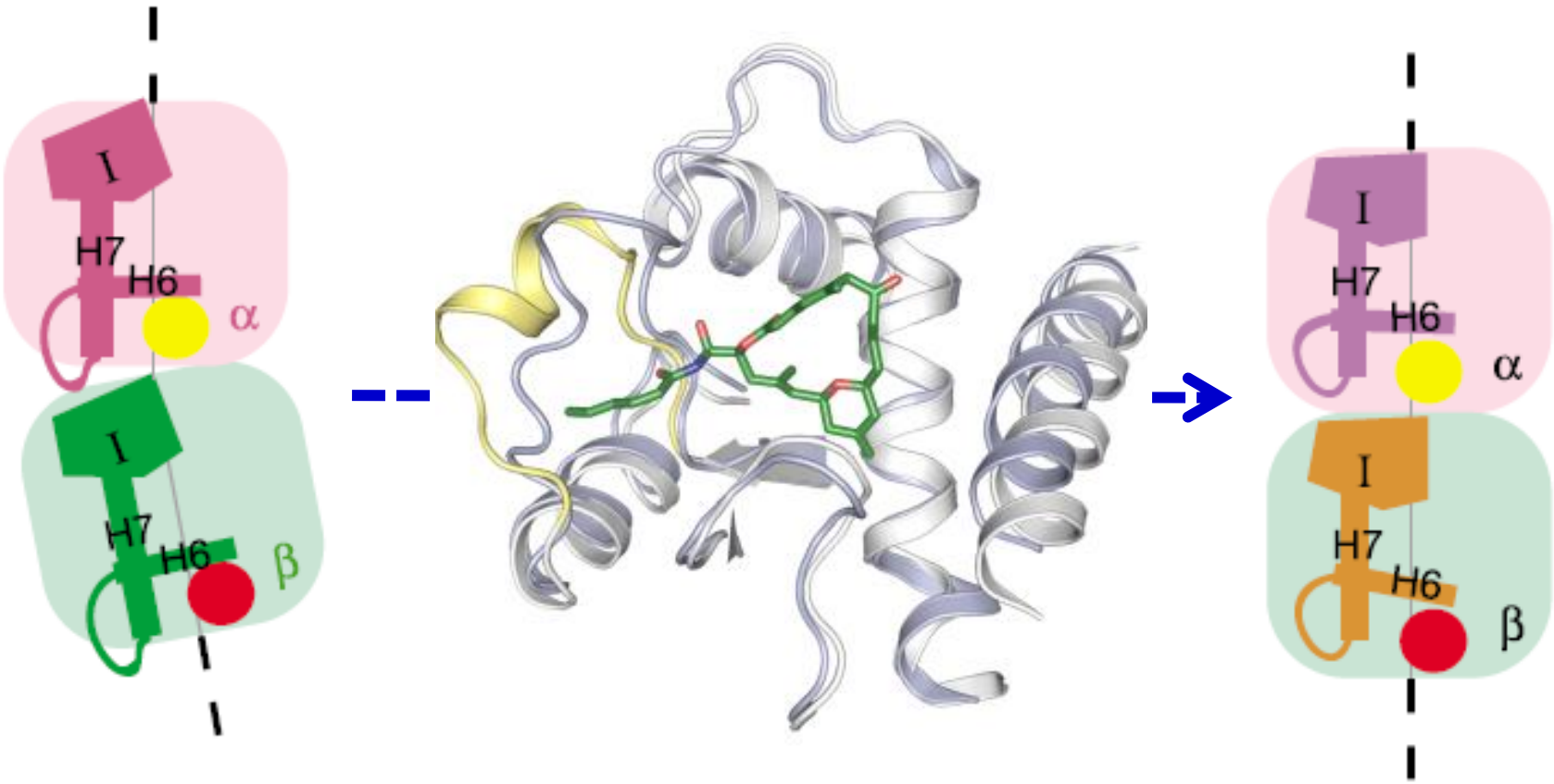


A. Prota, M. Steinmetz, K.-H. Altmann, *et al*. *Science* **2013**, *339*, 587.

Microtubule Structure and Dynamic Instability



M-Loop Structuring as the Trigger for Microtubule Assembly?



Curved

Straight
(Protofilament)

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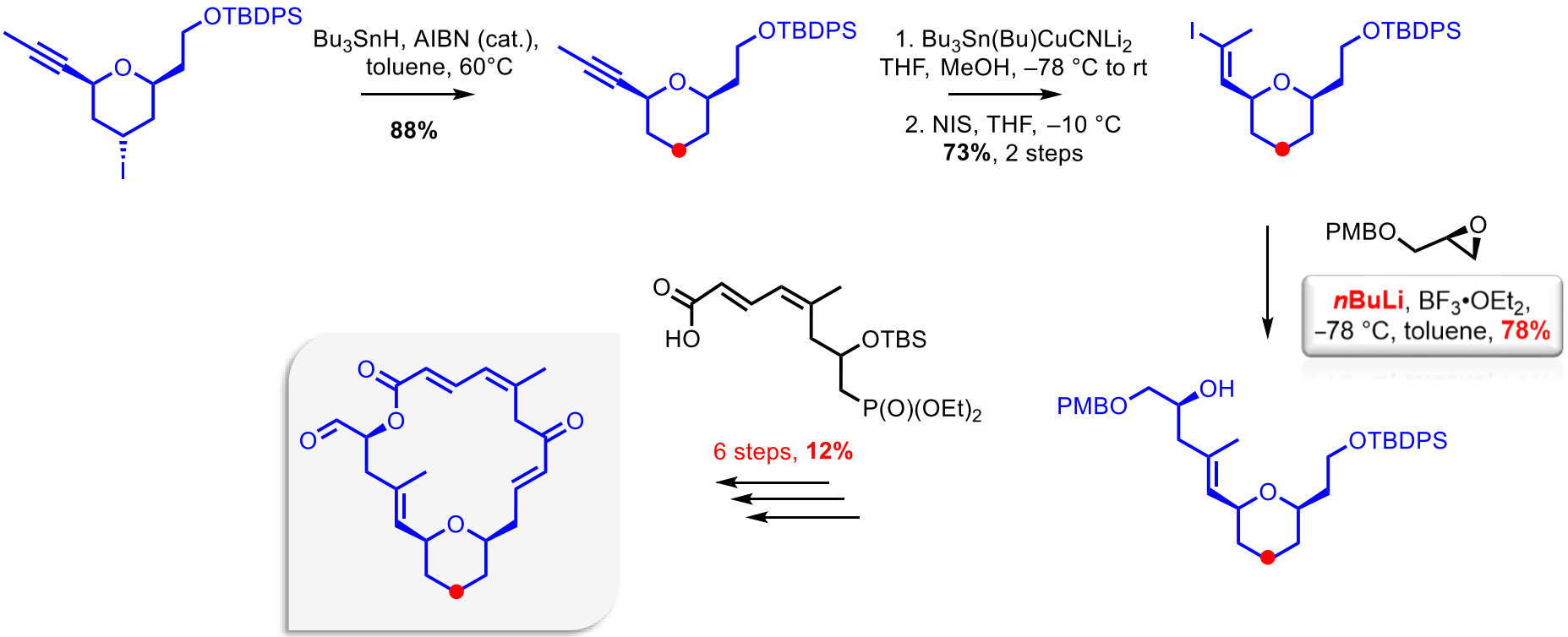
13-Desmethylene-(-)-Dactylolide/(-)-Zampanolide



Tubulin Inhibitors in Drug Discovery: The Future ?

REVIEWS

Microtubule-binding agents: a dynamic field of cancer therapeutics

Charles Dumontet and Mary Ann Jordan‡*

NATURE REVIEWS | DRUG DISCOVERY VOLUME 9 | OCTOBER 2010 | 791

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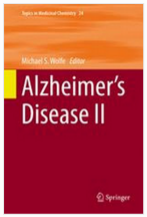
The antibody-drug conjugate: an enabling modality for natural product-based cancer therapeutics

Cite this: *Nat. Prod. Rep.*, 2013, **30**, 625

Hans-Peter Gerber,[a] Frank E. Koehn[b] and Robert T. Abraham*[c]



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