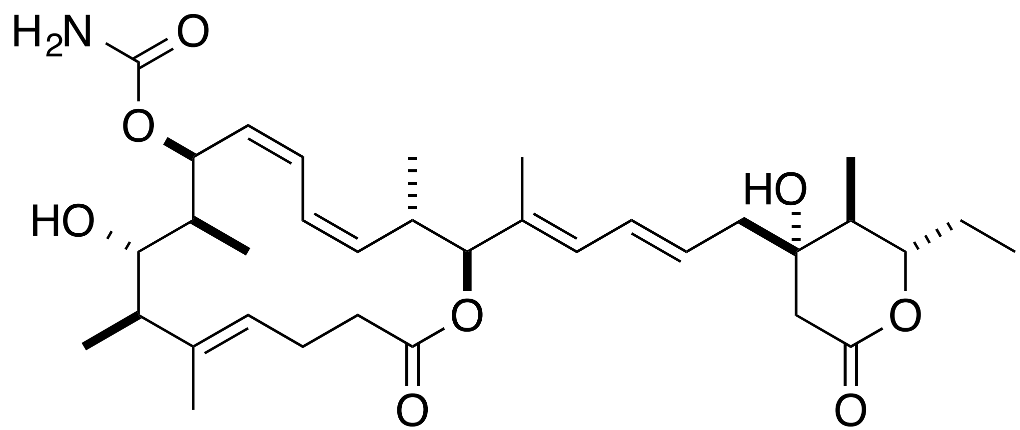
Journal Club

Nick Tappin
Renaud Group
21 May 2015

Total Synthesis of the Antimitotic Marine Macrolide (–)-Leiodermatolide

ACIE **2014**, *53*, 2692–2695

Ian Paterson*, K. K.-H. Ng, S. Williams, D. C. Millican, and S. M. Dally



(–)-leiodermatolide

23 steps, 3.2% yield

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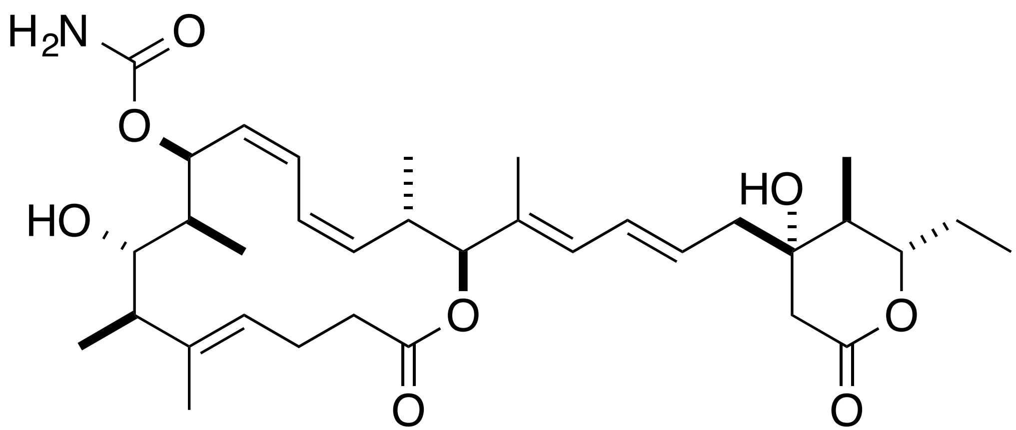


(–)-leiodermatolide

23 steps, 3.2% yield

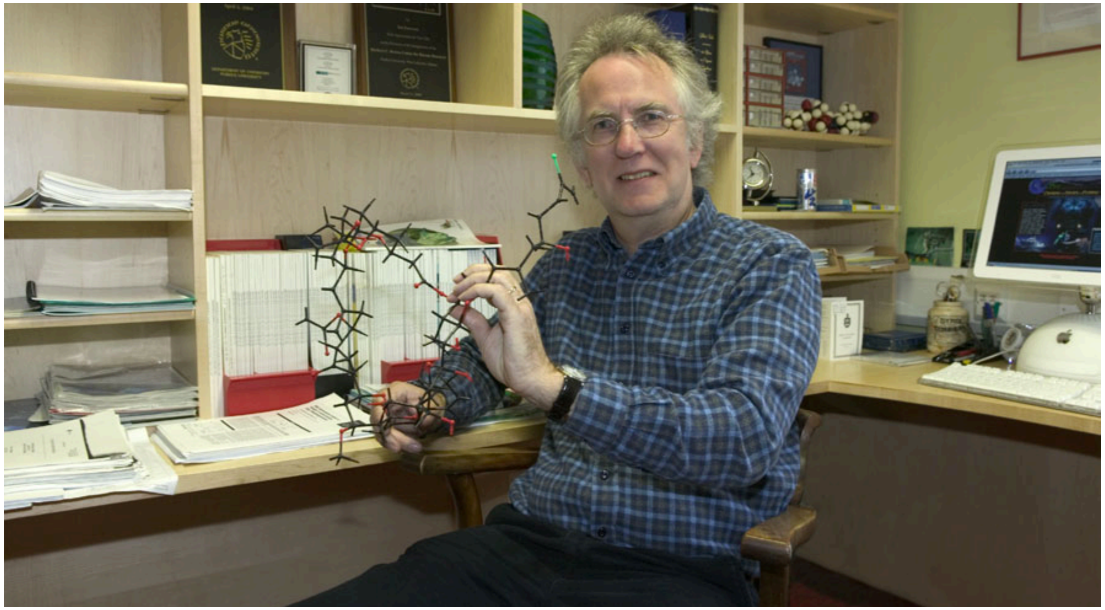
$0.86^{23} = 0.031$*

*if linear; this synthesis is actually convergent (see summary)

Overview

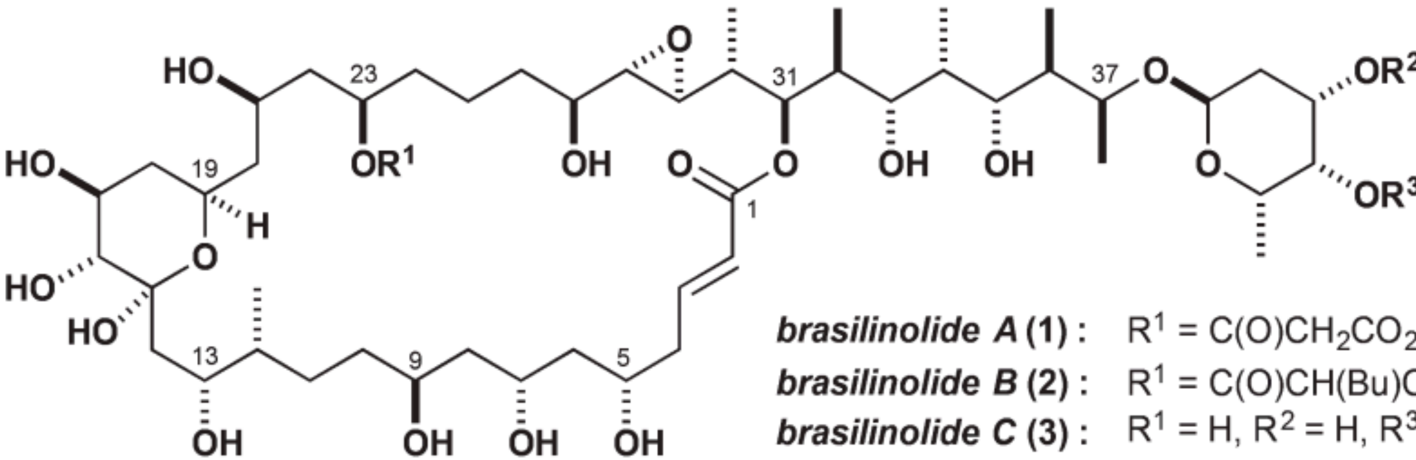
I. Preamble
   i. Paterson Group
   ii. Isolation, Toxicity, Mode of Action, Justification
II. Retrosynthetic Analysis
   i. Structural Features
   ii. Fürstner's Approach
   iii. Maier's Approach
   iv. Paterson's Approach
III. Forward Synthesis
   i. Western Fragment
   ii. Eastern Fragment
   iii. Endgame
IV. Conclusions and Outlook

Paterson Group



- Total synthesis of biologically active natural products
- New synthetic methodologies, asymmetric
- Famous for
  - asymmetric aldol reaction from geometrically defined boron enolate
  - structural assignments based on NMR studies and synthesis
  - As well as synthesizing ‘hot’ molecules (polyols). PKS.
- Fellow of Jesus College, FRSE FRS
- PhD (Fleming), PostDoc (Stork),

Paterson: ‘flavour’ of his work



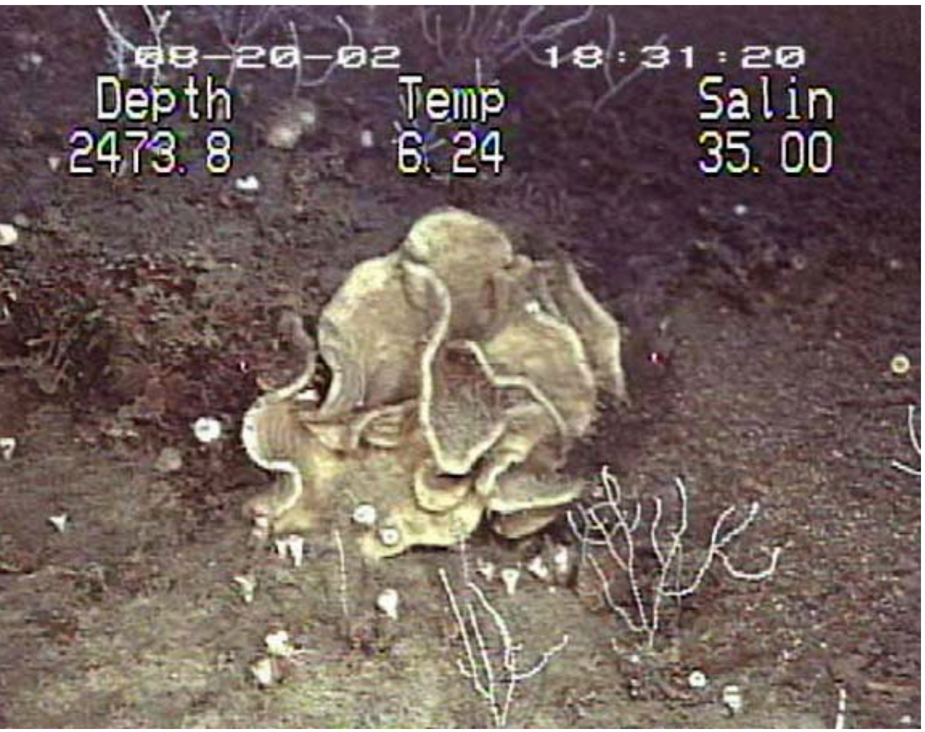
***brasilinolide A* (1) :** $R^1 = C(O)CH_2CO_2H$, $R^2 = C(O)Bu$, $R^3 = H$

***brasilinolide B* (2) :** $R^1 = C(O)CH(Bu)CO_2Me$, $R^2 = Me$, $R^3 = Me$

***brasilinolide C* (3) :** $R^1 = H$, $R^2 = H$, $R^3 = H$

Org. Biomol. Chem. **2015**, *13*, 5716-5733

Isolation



- Wright group 2008
- Submersible near Florida (410m not 2.5km)
- Antiproliferative activity against human cancer cell lines inc. IC_{50}=3.3nM for lung and 5.0nM for PANC-1
- Acting through disruption of tubulin (mitosis stage) dynamics but in distinct way from other tubulin-targeting drugs
- Vinca alkaloids, Taxol, etc.
- Most chemotherapy drugs target tubulin
- This could be a new lead for anticancer agents

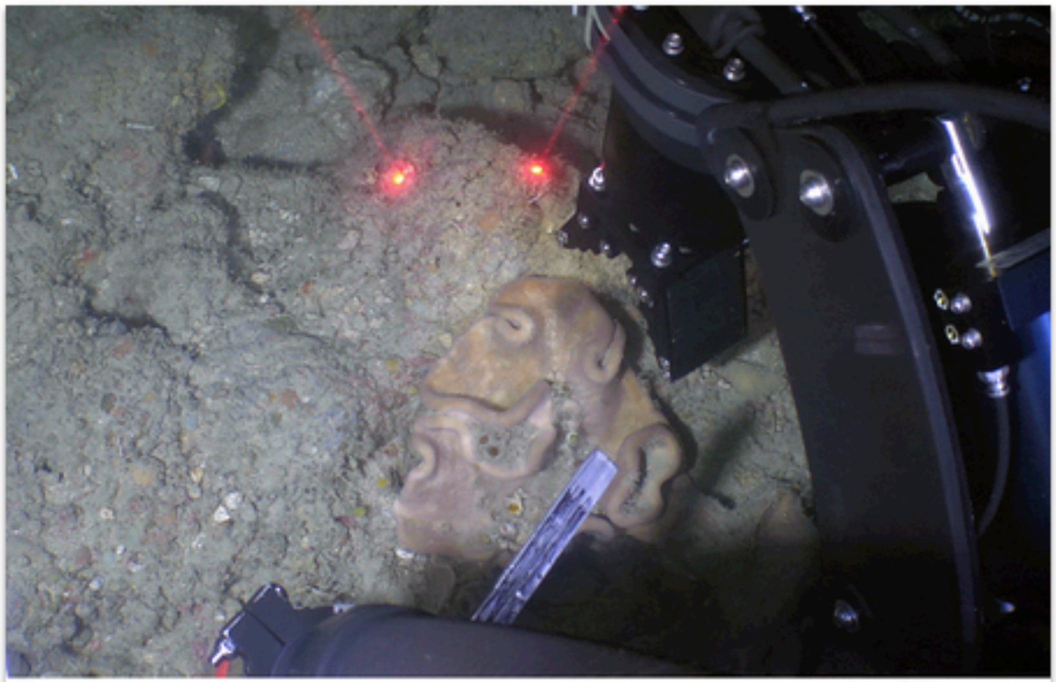
Leiodermatium sp., a deepwater sponge. Image courtesy of Islands in the Sea 2002, NOAA/OER.
U.S. Pat. Appl. Publ. (USA), US2008033035, 14pp**, 2008**

May 15, 2015 Dispatch

Leiodermatium and the Path to a Treatment for Pancreatic Cancer

Amy Wright
Research Professor & Director
Center of Excellence in Biomedical & Marine Biotechnology
FAU Harbor Branch

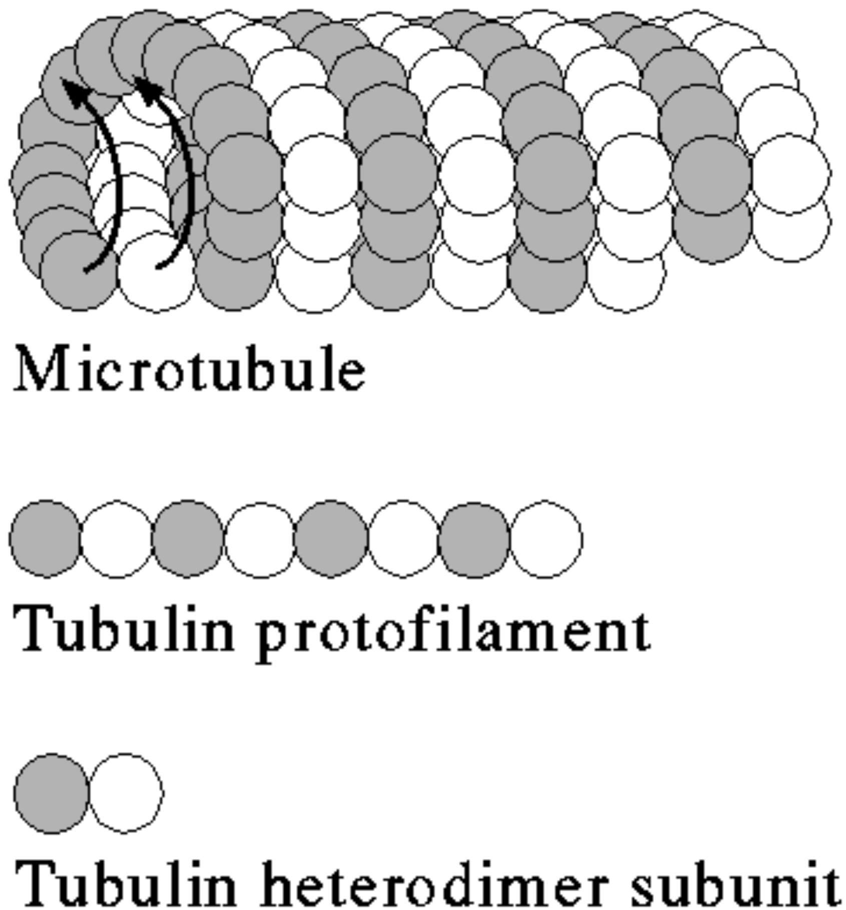
One of the sponges we have observed and collected during three of our deeper dives is a demosponge called *Leiodermatium* sp. It's a "lithistid" sponge because it's rock-like: it has siliceous spicules (microscopic skeletal elements) that interlock to form a rigid skeleton. Our team at Harbor Branch has discovered a chemical in this sponge that has potent activity against pancreatic cancer. The chemical is called "leoidermatolide". We often give common names to these chemicals based on the scientific name organism – in this case, a sponge – from which the chemical was derived.



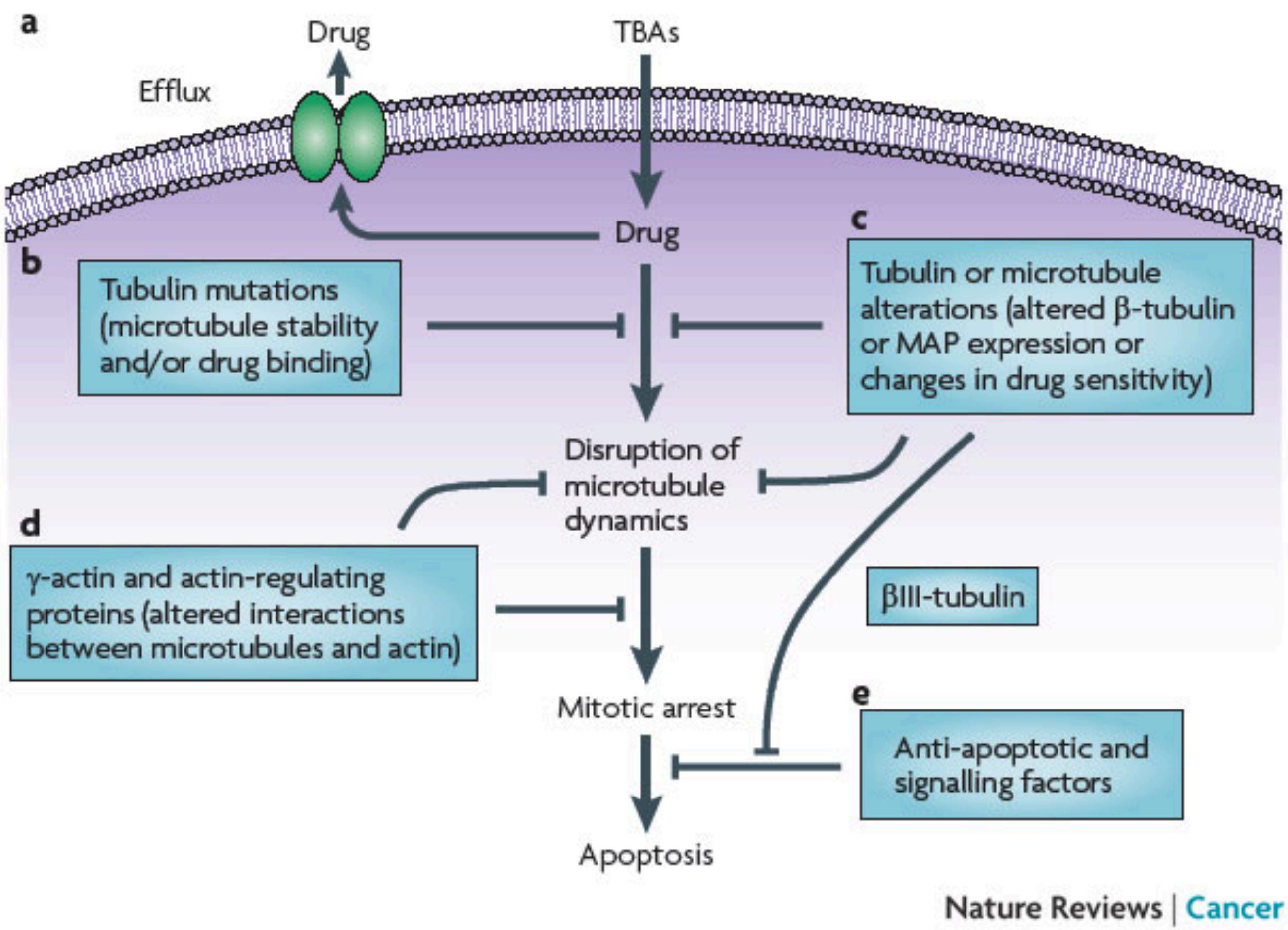
This *Leiodermatium* sp. sponge is about to be collected by the Mohawk ROV.

http://www.fau.edu/hboi/cioert/cioert_at_sea.php

Tubulin

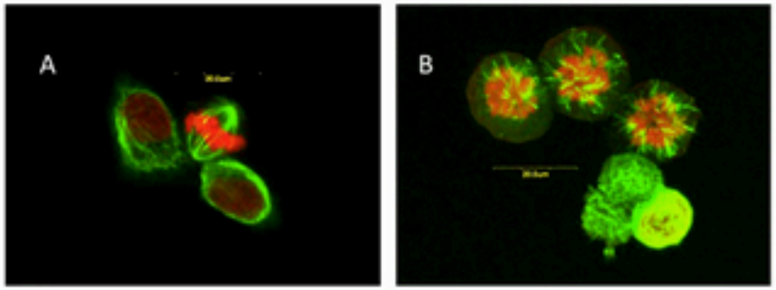

Microtubule
Tubulin protofilament
Tubulin heterodimer subunit

Mode of action: tubulin disruption



Nature Reviews Cancer **2010**, *10*, 194-204

Pancreatic cancer cells actively undergoing mitosis



Control: no leiodermatolide

10nM leiodermatolide

- Green: Tubulin – shows the spindles/microtubules in the cell
- Red: DNA stained with propidium iodide –shows chromosomes in the nucleus

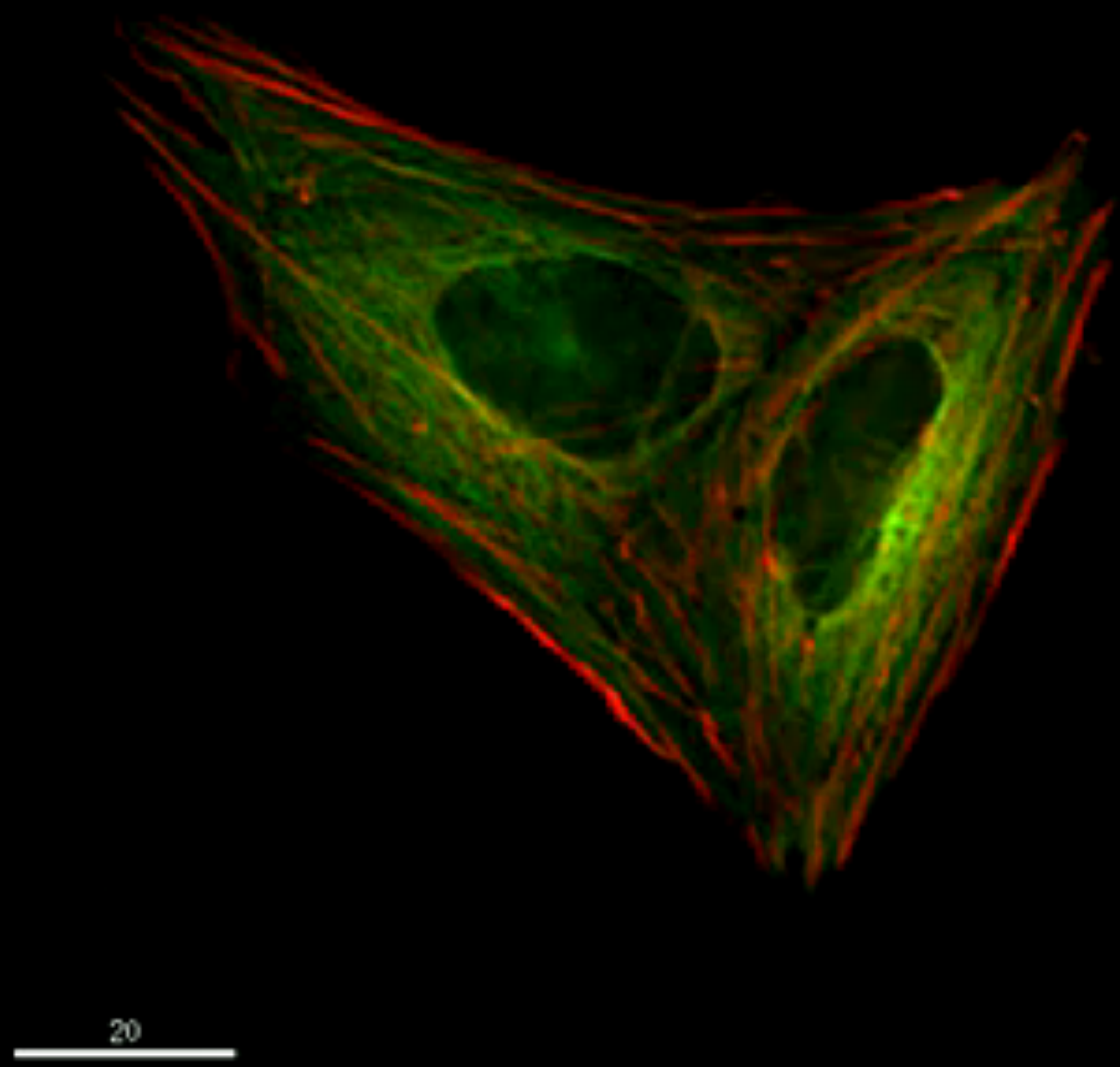
HBOI FAU

These microscope images show the effect of leiodermatolide on pancreatic cancer cells. The photo on the left shows pancreatic cancer cells dividing: the green color is tubulin and shows normal mitotic spindle formation. The red are the chromosomes aligning for cell division. On the right are pancreatic cancer cells treated with leiodermatolide. The green color shows tubulin; no spindles are forming. The red shows that the chromosomes are not aligning for cell division. Leiodermatolide-treated cells cannot divide and will die.

A hallmark of cancer is uncontrolled cell division, and many cancer chemotherapeutics (Taxol™, Vincristine™, Halaven™) function through blocking cell division. These compounds are called anti-mitotic agents. Leiodermatolide is in a class of chemicals called polyketide-derived macrolides. It is a very potent anti-mitotic agent that kills tumor cells at very low doses (nanomolar, or nM) and is highly selective for dividing cells. Leiodermatolide differs from clinically useful drugs that block cell division, but we're still trying to determine exactly how it works. It appears to block spindle formation (required for cells to divide), but without interacting with tubulin. This is unique.

We are very excited about the potential for leiodermatolide to be developed into a drug to treat pancreatic cancer. This is a long process: our team identifies and collects unusual deepwater organisms (usually sponges), and then tests the chemicals derived from these organisms to determine if they have potent, selective activity. If they do, we conduct further research to determine exactly what the chemical is, as well as how it works (its "mechanism of action"). We then patent our discovery and license it to a pharmaceutical company for further development. The process can take many years – but leiodermatolide is ready now for licensing!

http://www.fau.edu/hboi/cioert/cioert_at_sea.php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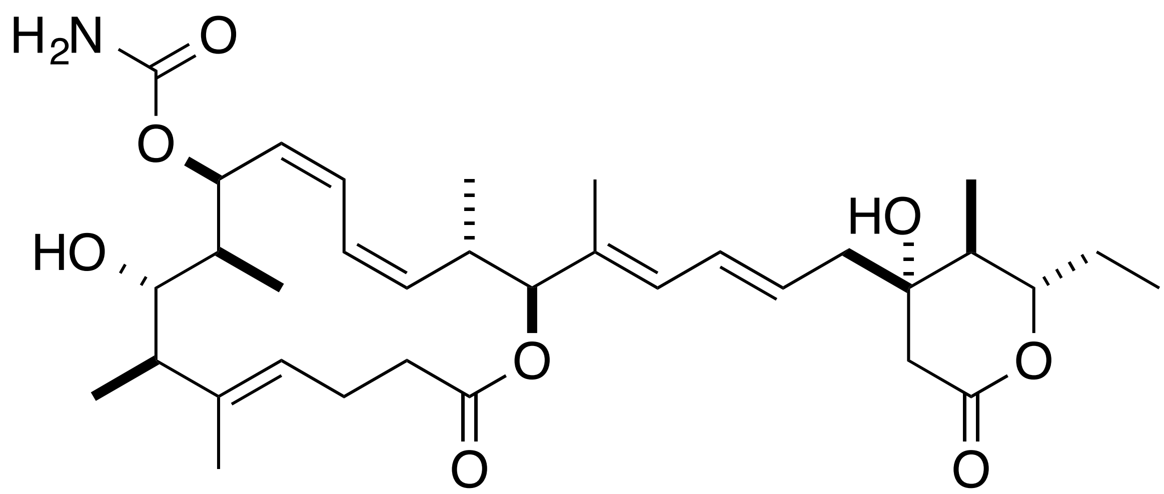
Structural features

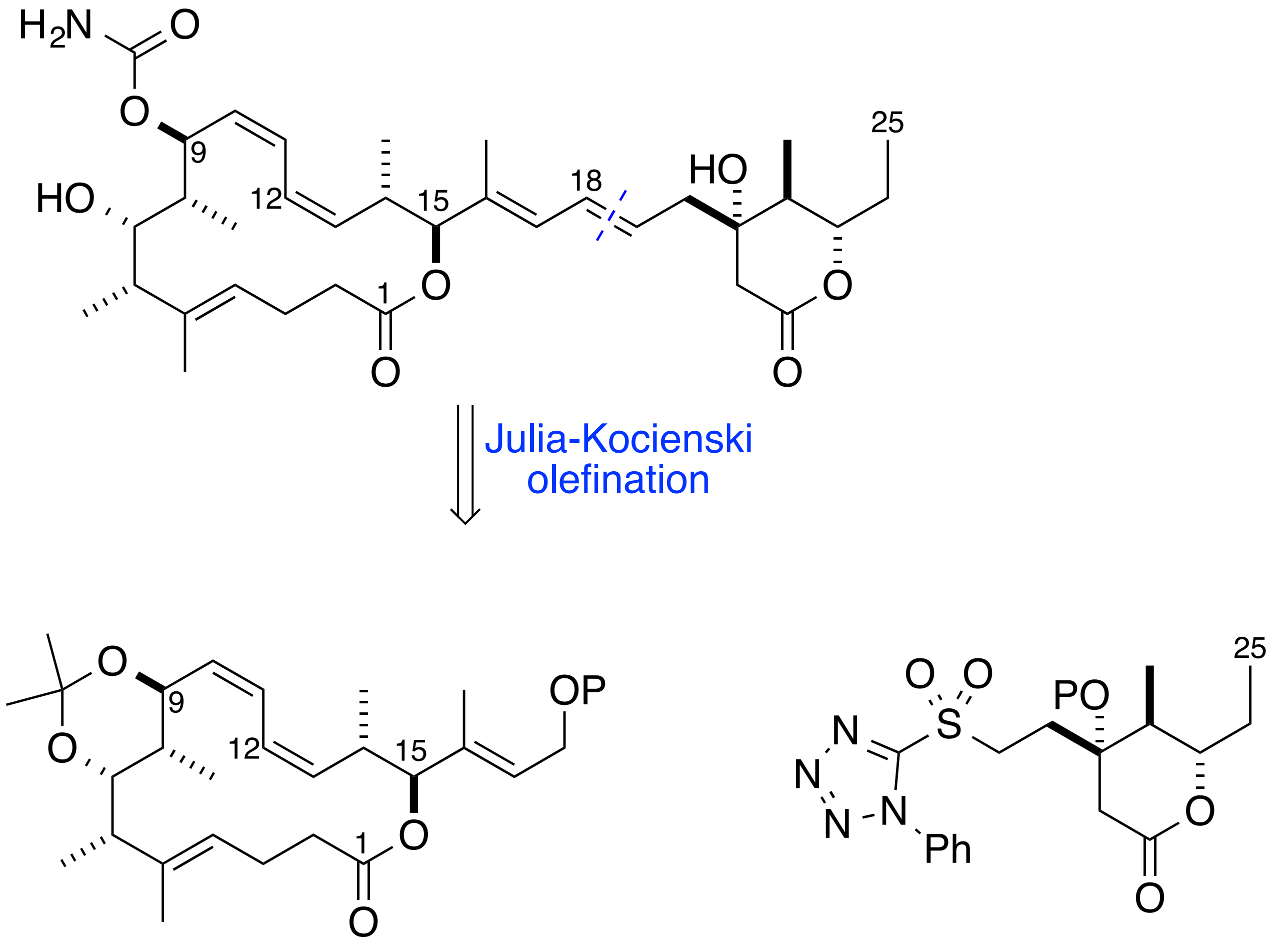


- 16-membered (plateau), triply-unsaturated macrolactone
- *(E-E)*-diene in macrolactone, (*Z-Z*)-diene in side chain
- Terminating d-lactone
- Synthesis needed to determine full configuration of certain stereoclusters
- 5 alkenes and 9 stereocentres
- Question: Propose disconnections….?

Confirmation of relative stereo in macrolactone core: OL **2011**, *13*, 4398-4401 and Maier's work

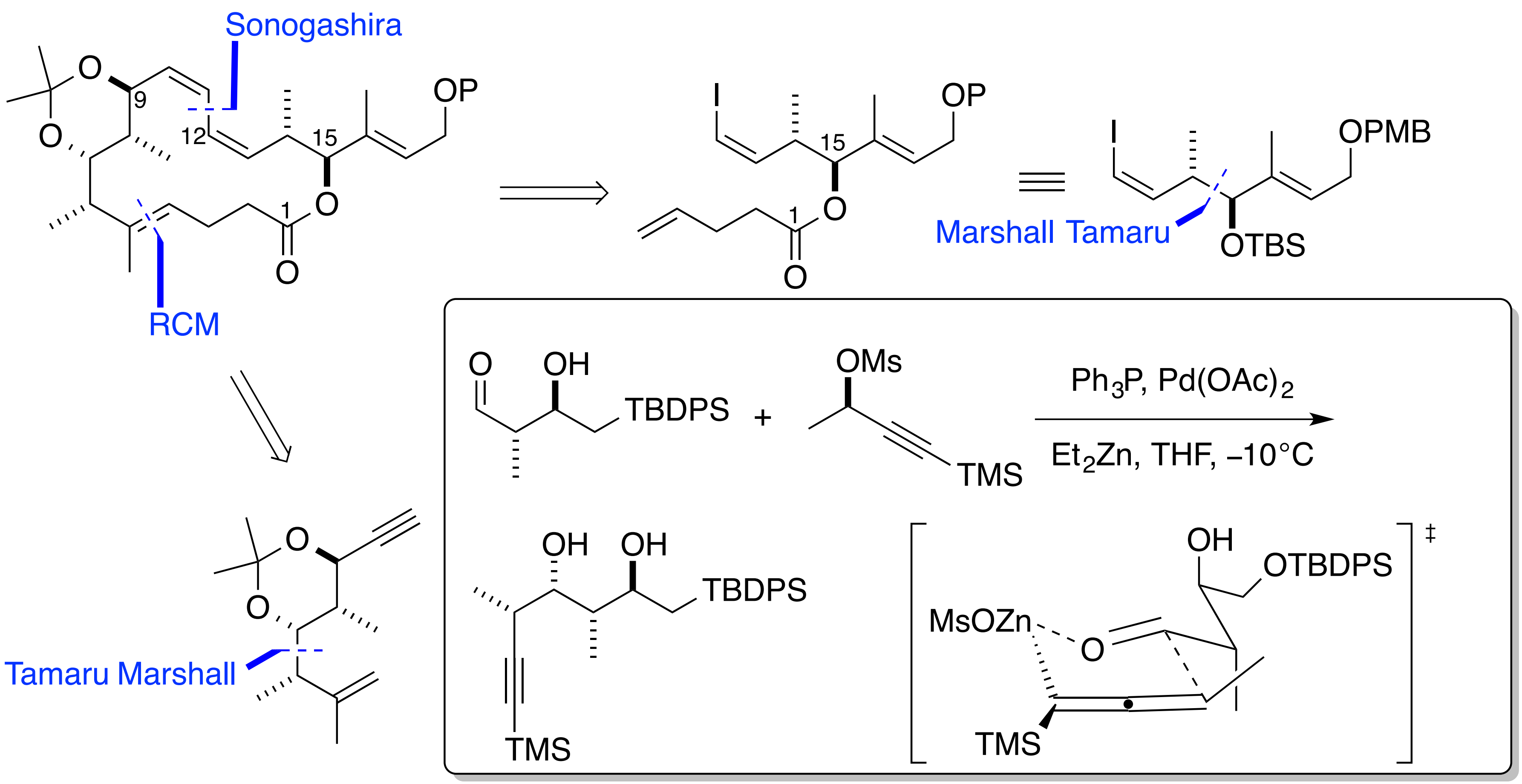
Relative structural assignment: ACIE **2011**, *50*, 3291-3223

Retrosynthesis: Maier



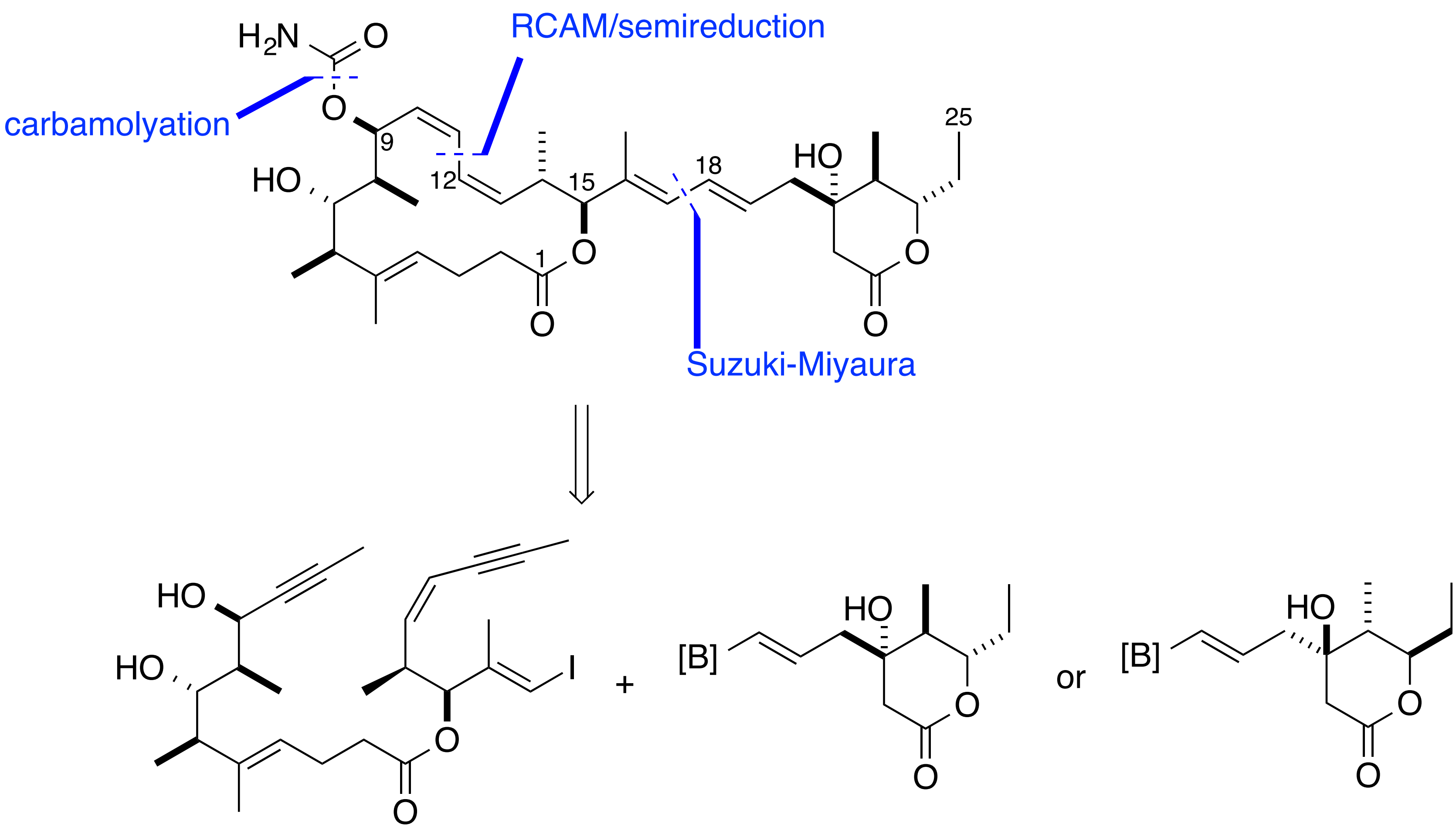
OL **2011**, *13*, 2334-2337 and Maier's work
Synlett **2011**, 191-194

Retrosynthesis: Maier



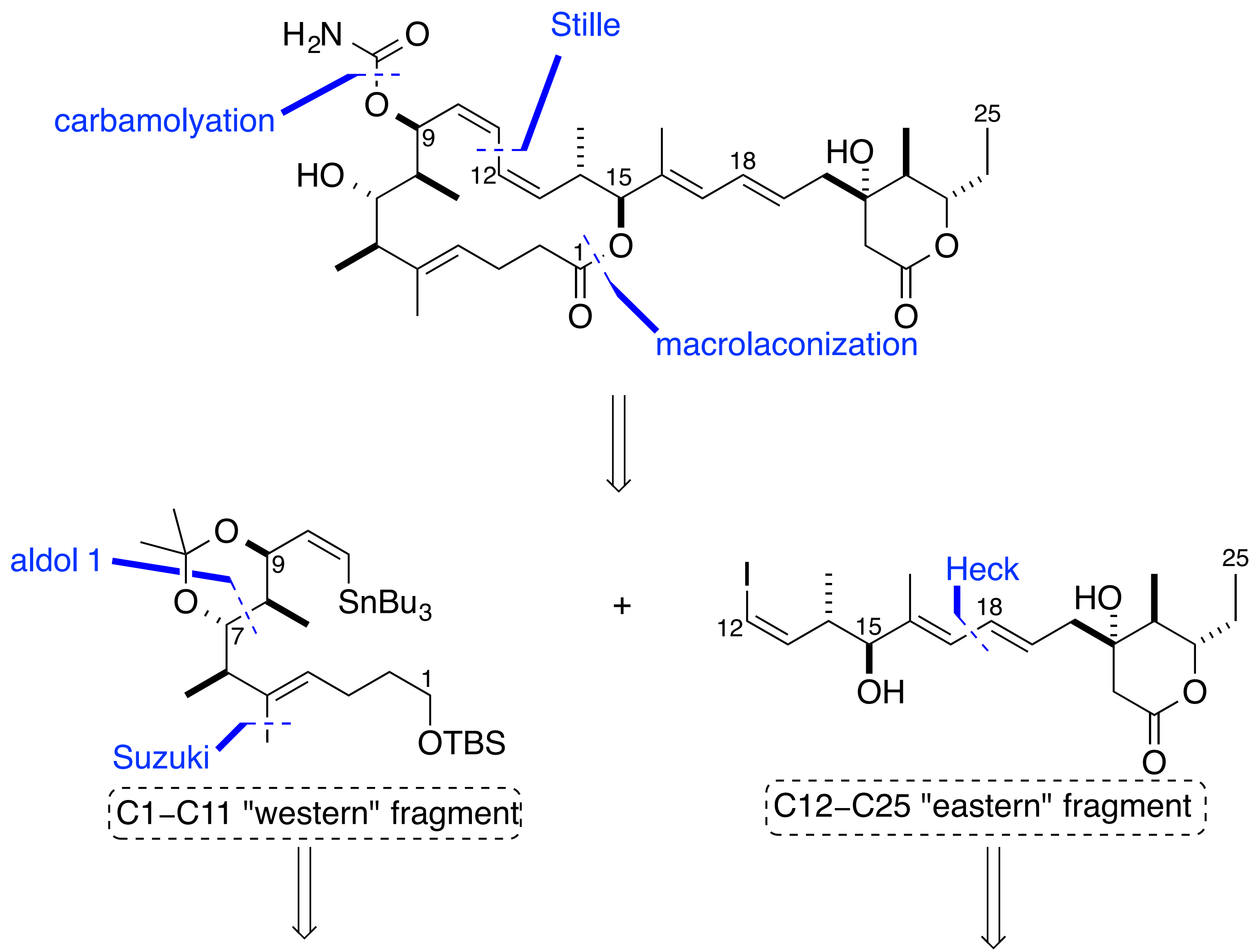
Chem. Rev. **2011**, *100*, 3172-3174 (pp 3163-3185)
Marshall-Tamaru, chiral mesylates: JOC **2011**, *63*, 3813

Retrosynthesis: Furstner

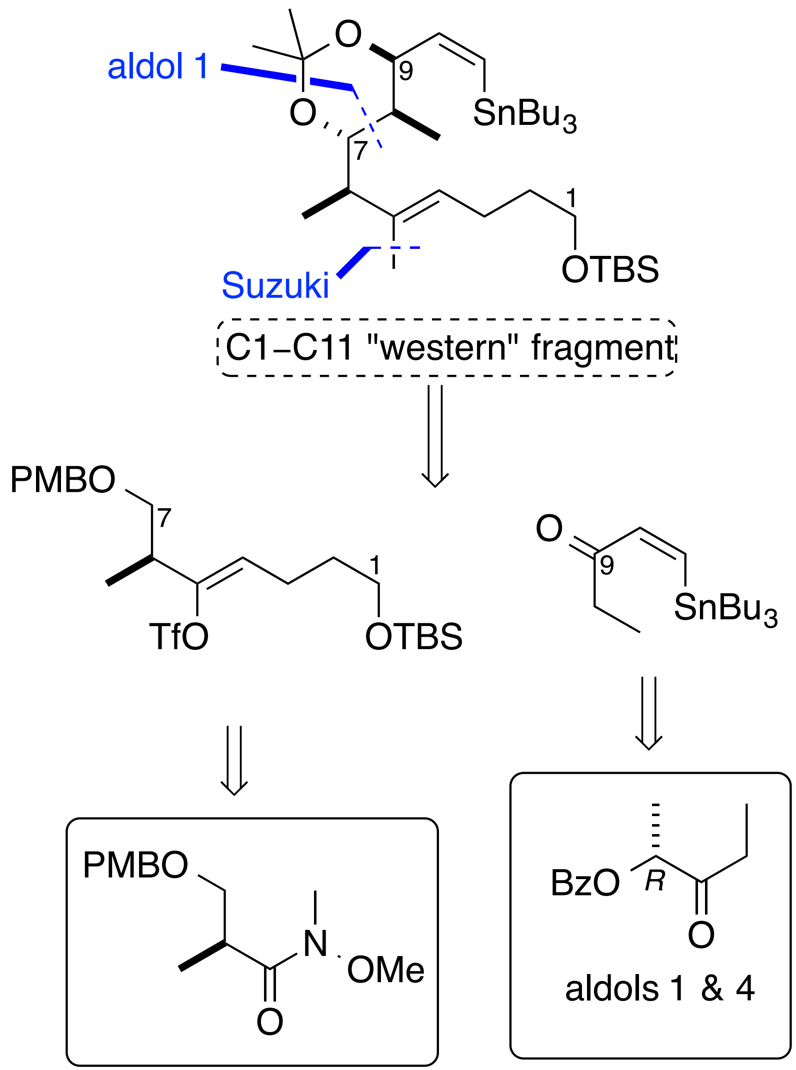


ACIE **2012**, *51*, 12041
AC **2012**, *124*, 12207

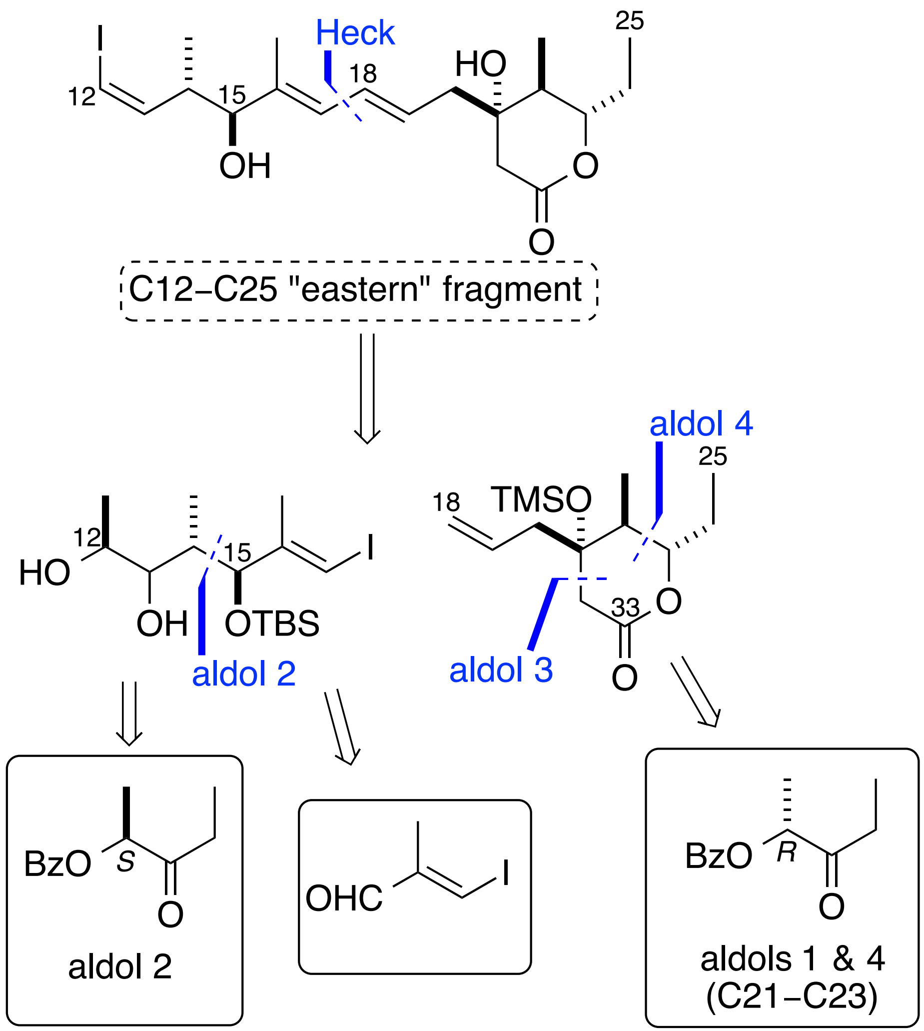
Retrosynthetic Analysis: Paterson



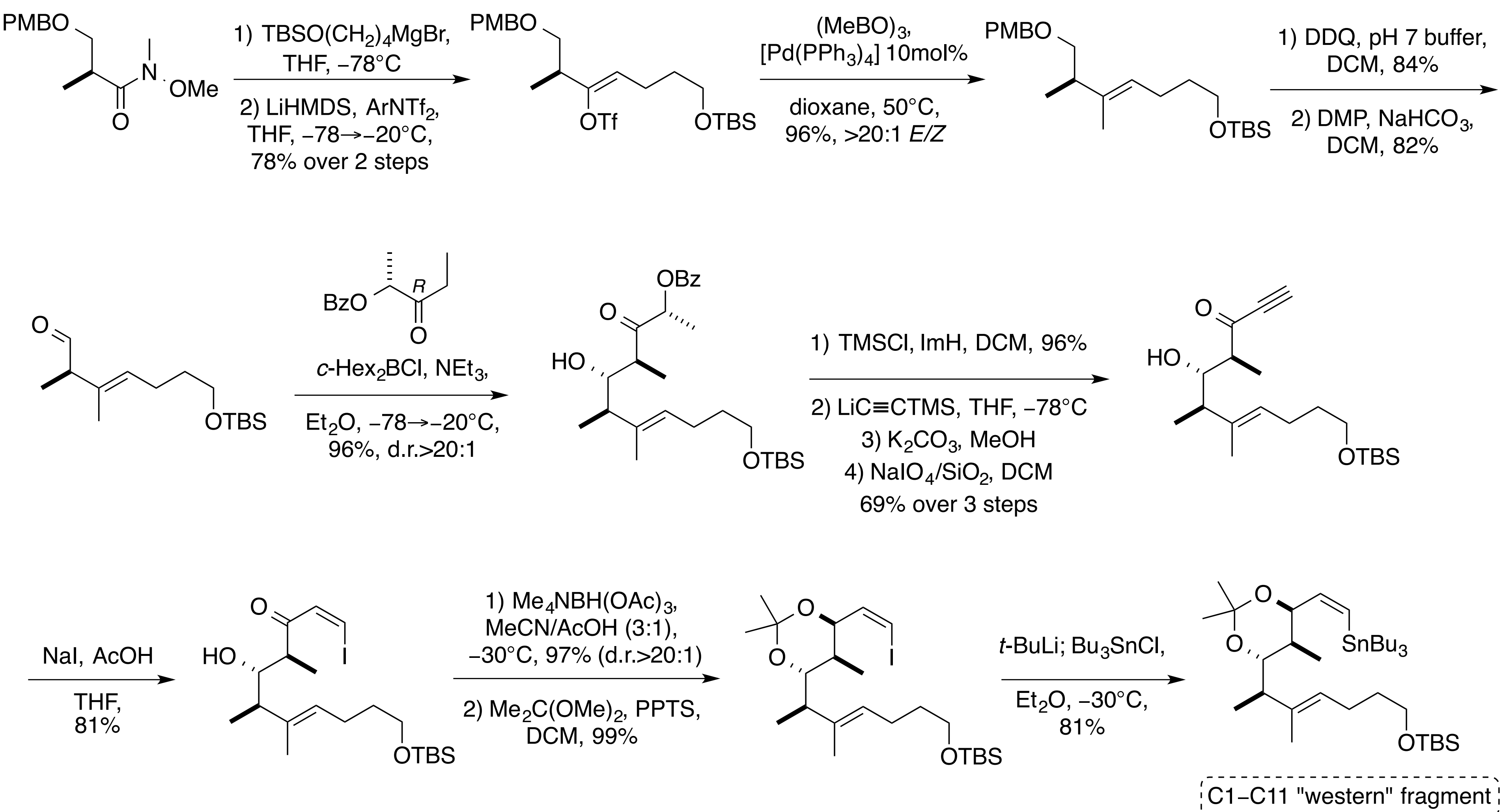
Retrosynthetic Analysis: Paterson



Retrosynthetic Analysis: Paterson

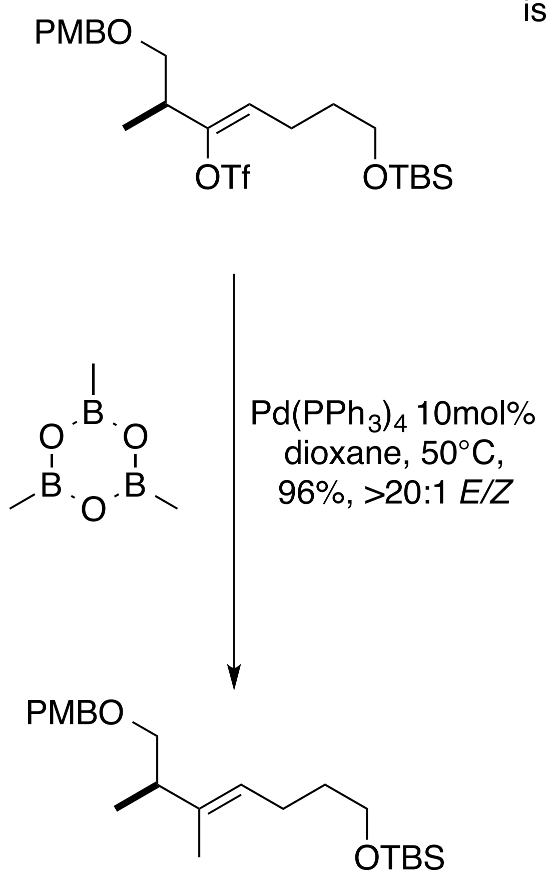


Forward Synthesis: Western

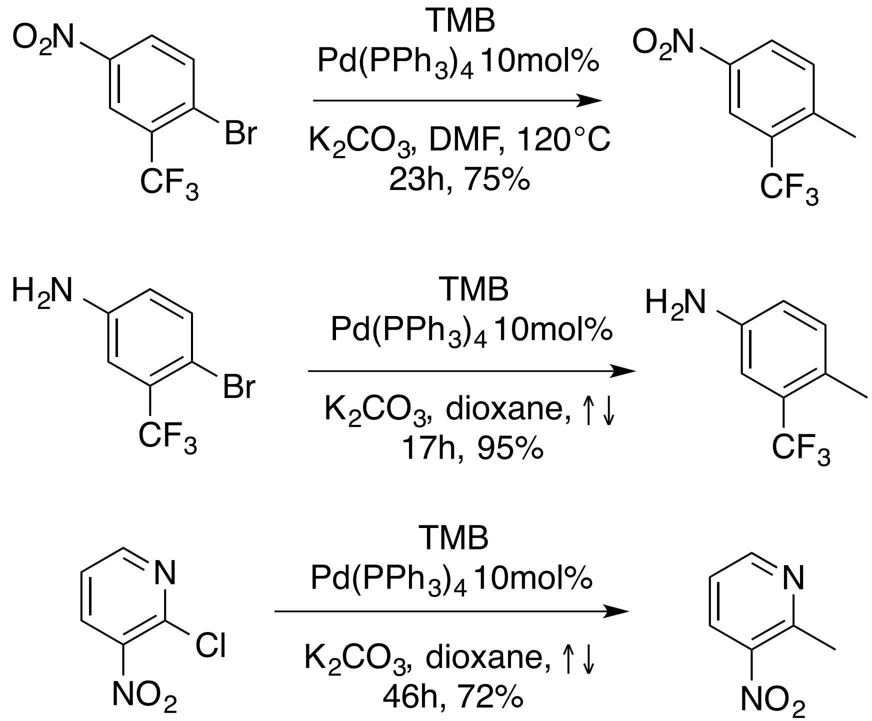


TMB

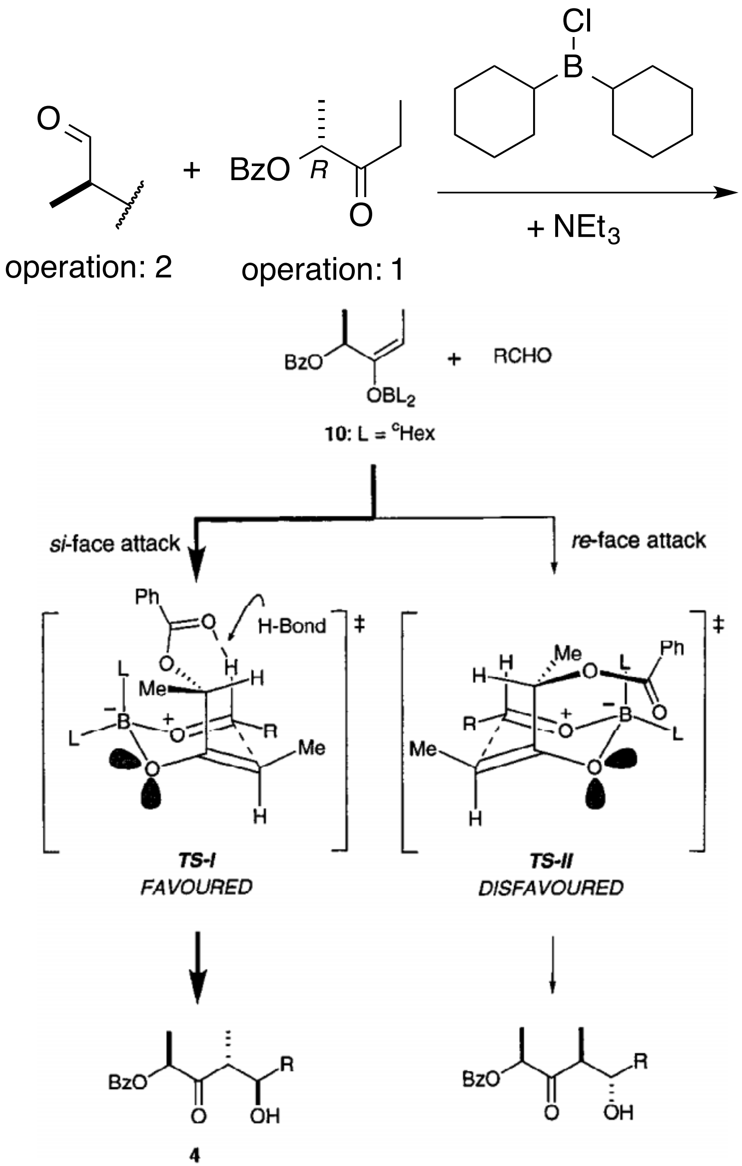
$(MeBO)_3$, TMB, trimethylboroxine, or the anyhdride of methylboronic acid is a cheaper Suzuki-Miyaura coupling partner than methylboronic acid, MBA

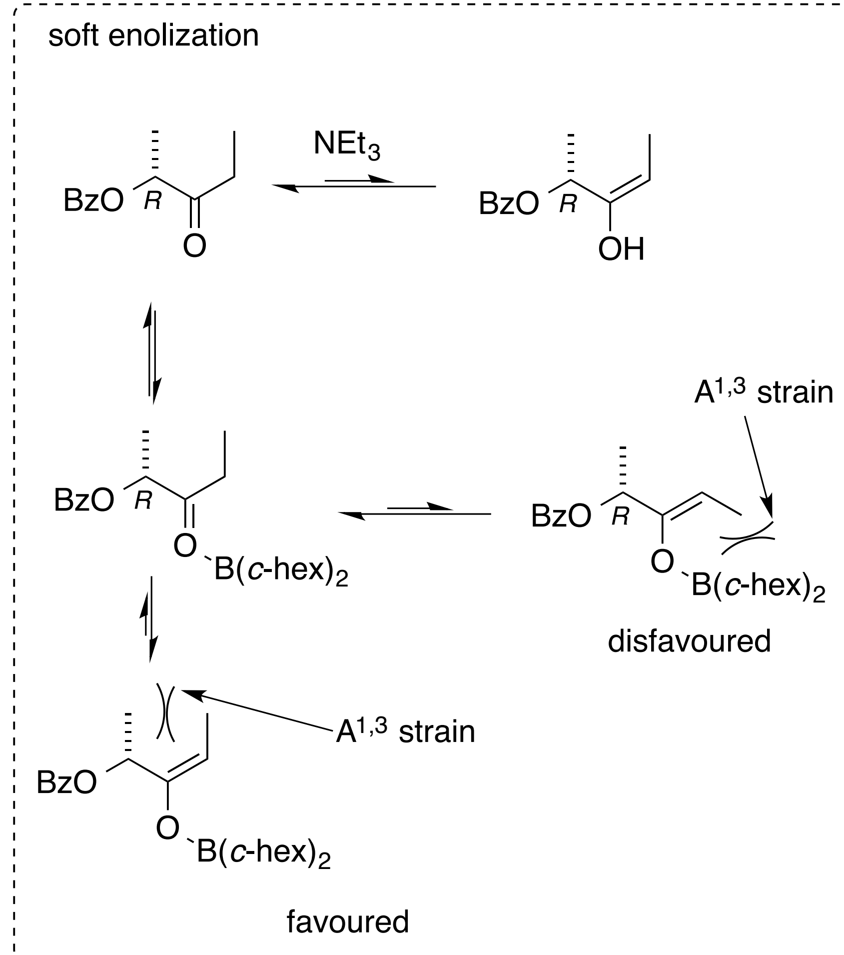


Gray, M.; Andrews, I. P.; Hook, D. F.; Kitteringham, J.; Voyle, M. *Tetrahedron Lett.* **2000**, *41*, 6237–6240.



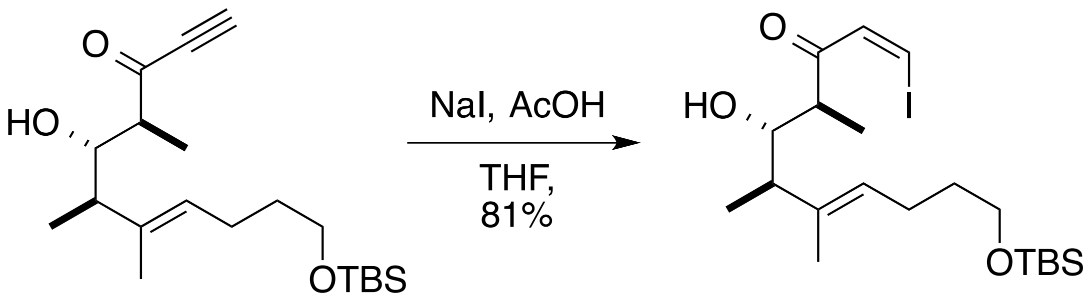
Anti-aldol



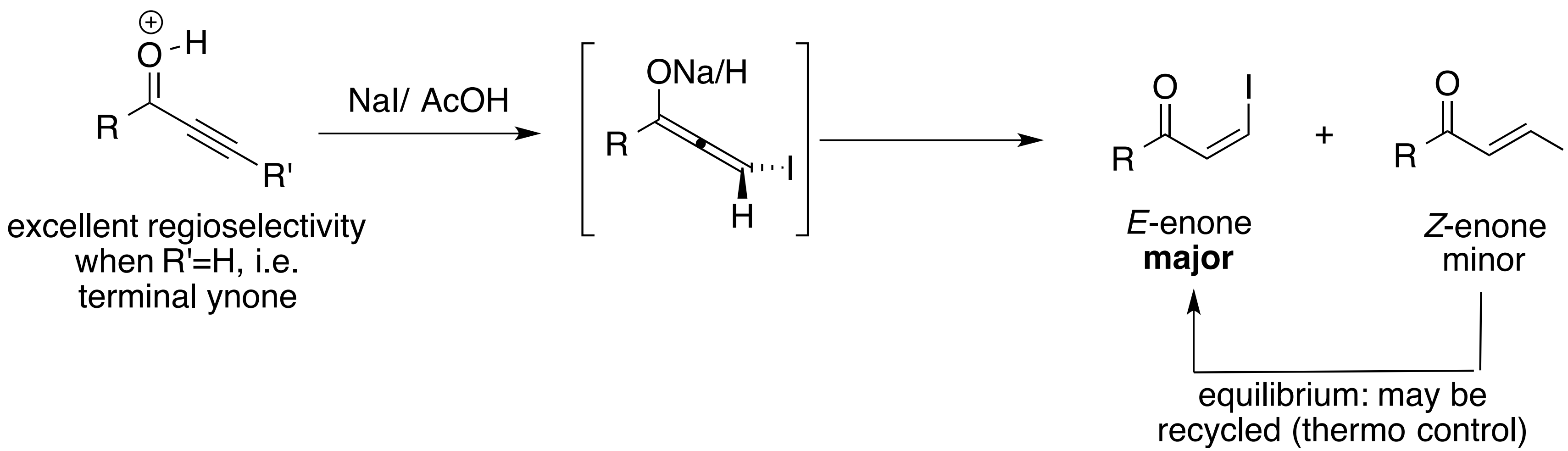


Review: Org. React. **1997**, *51*, 1
NEt_3/ *c*-hexBCl: TL **1994**, *35*, 9083 & 9087
Synthesis **1998**, 639

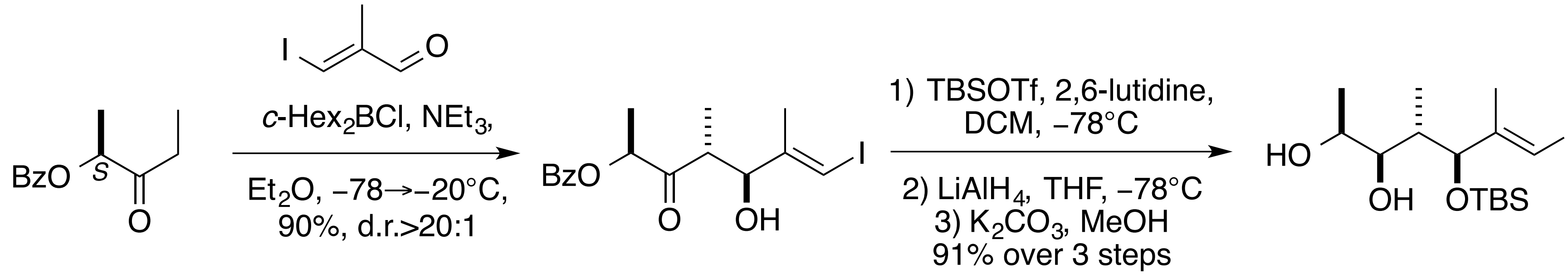
NaI/ AcOH addition to ynone

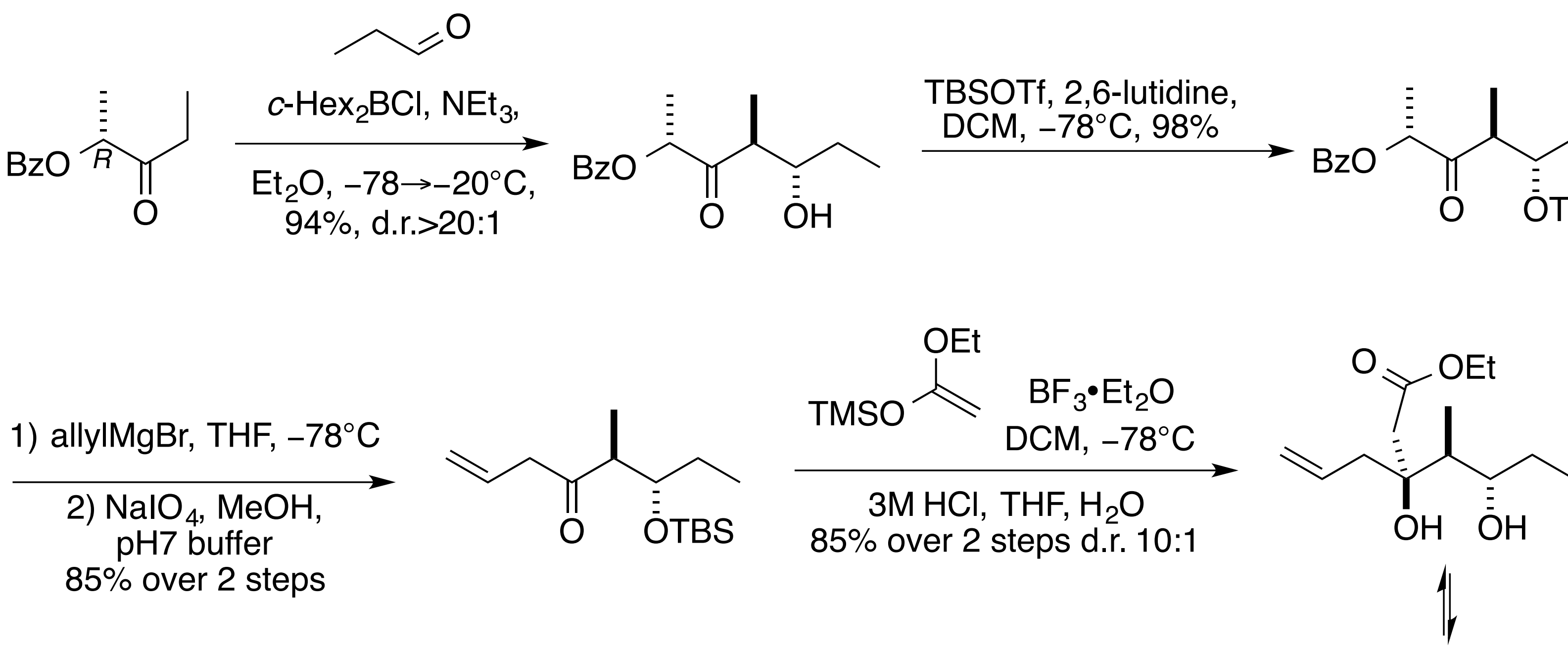


Taniguchi, TL **1986**, *27*, 4763-4766

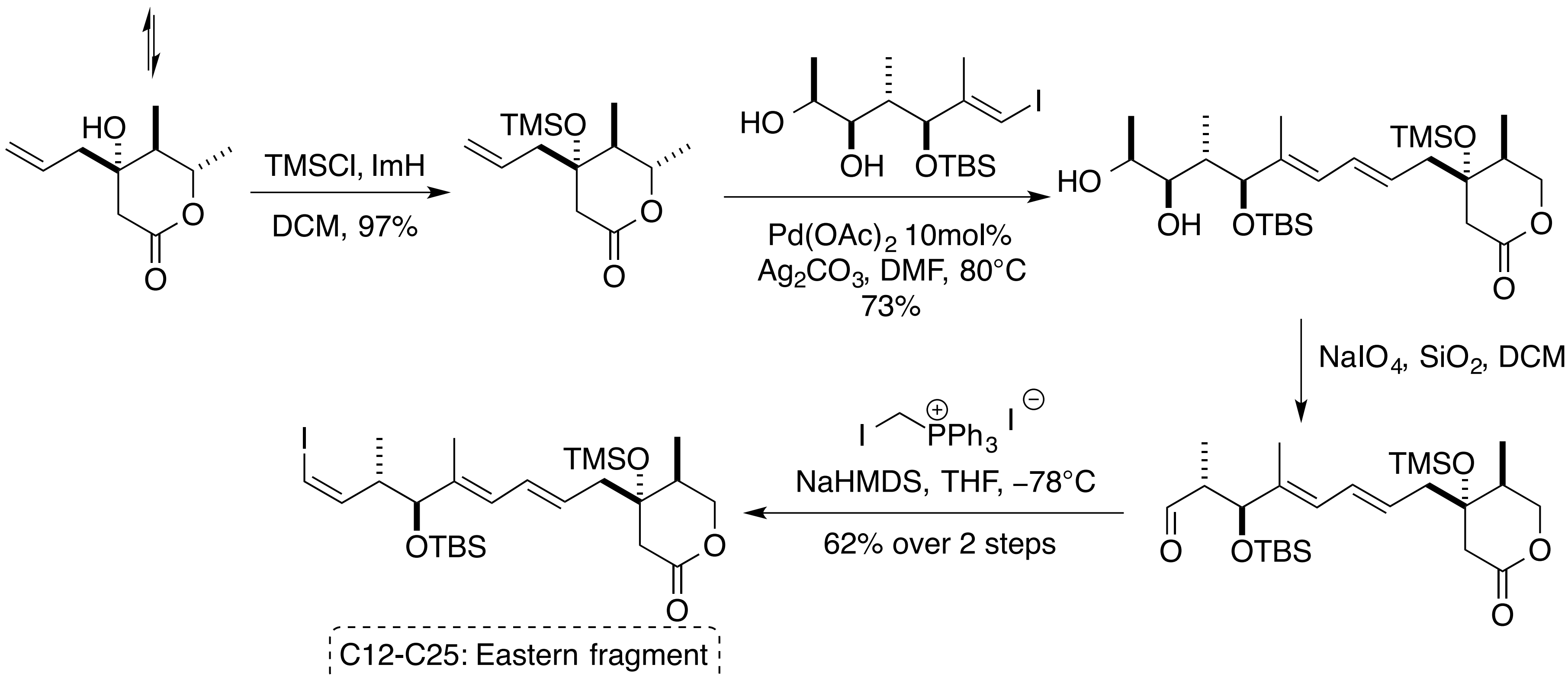


Forward Synthesis: Eastern

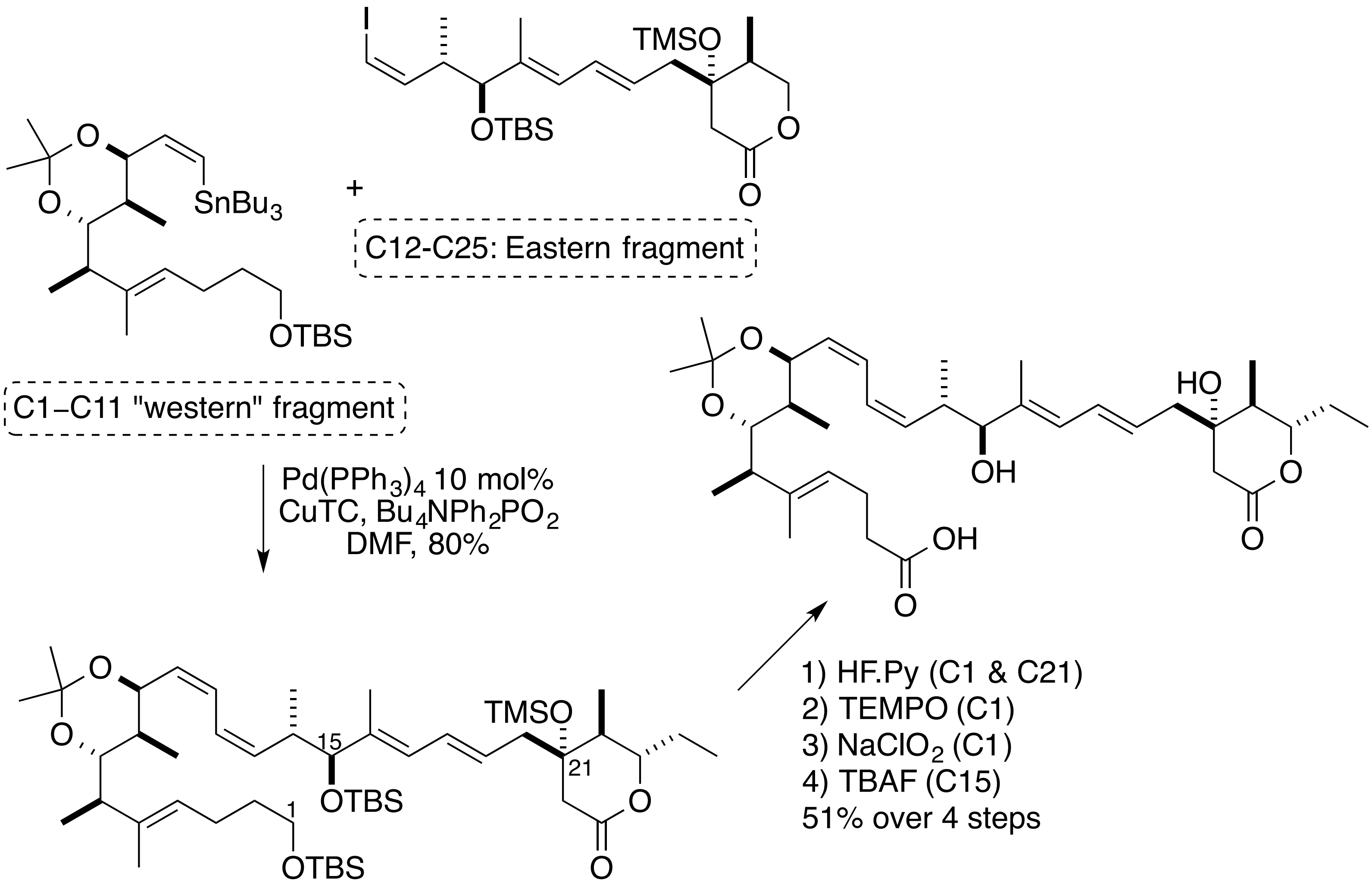




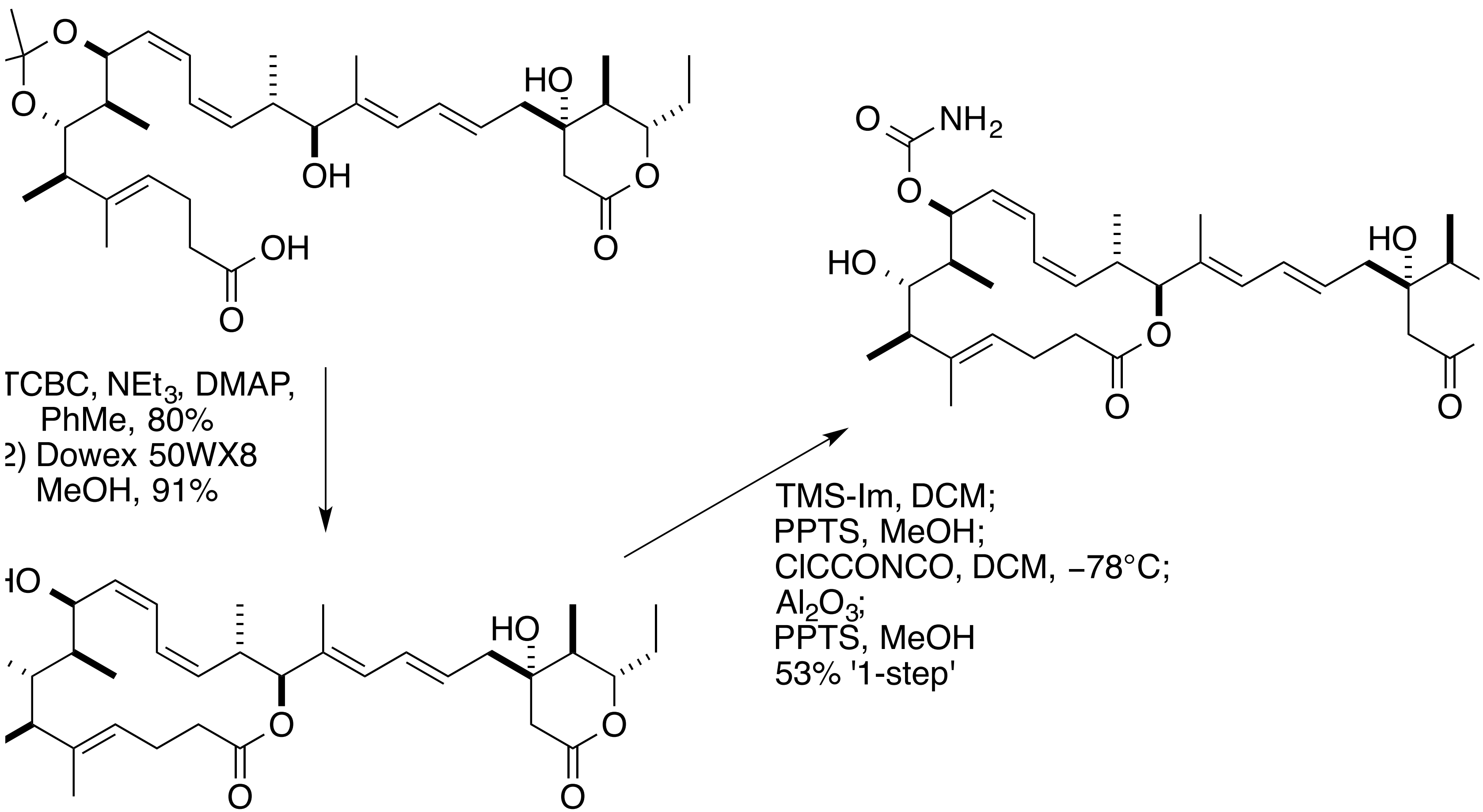
Forward Synthesis: Eastern



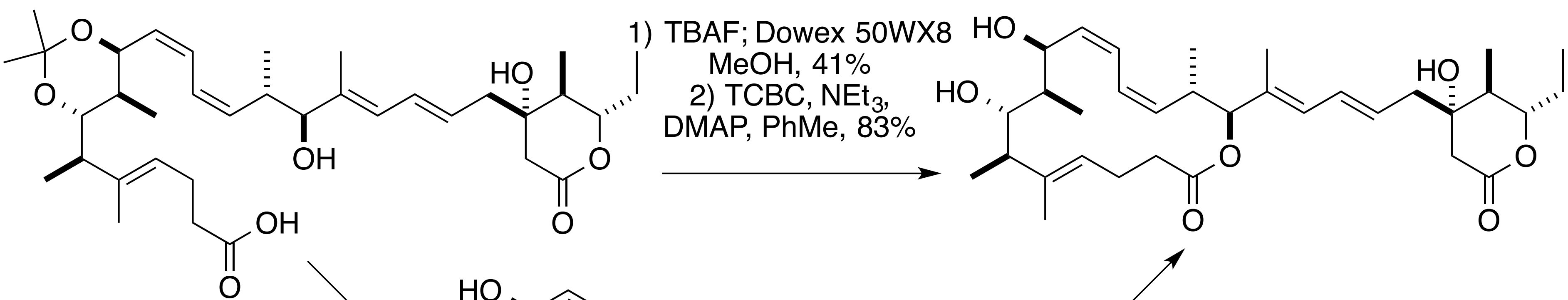
Forward Synthesis: Endgame

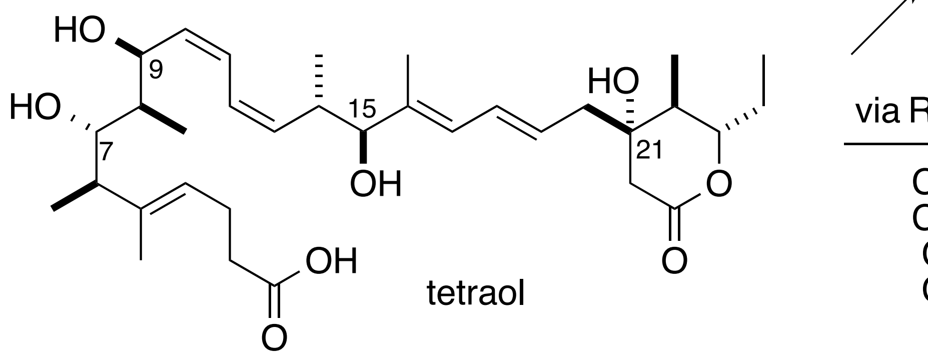


Forward Synthesis: Champagne time



Reverse deprotect/ Yamaguchi

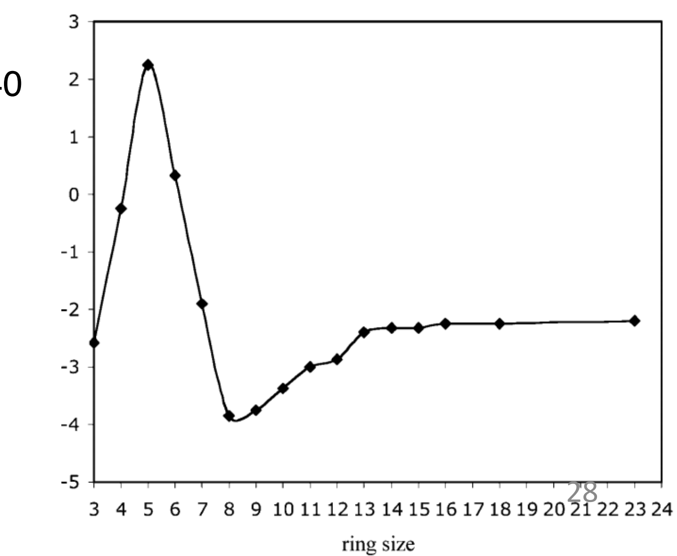




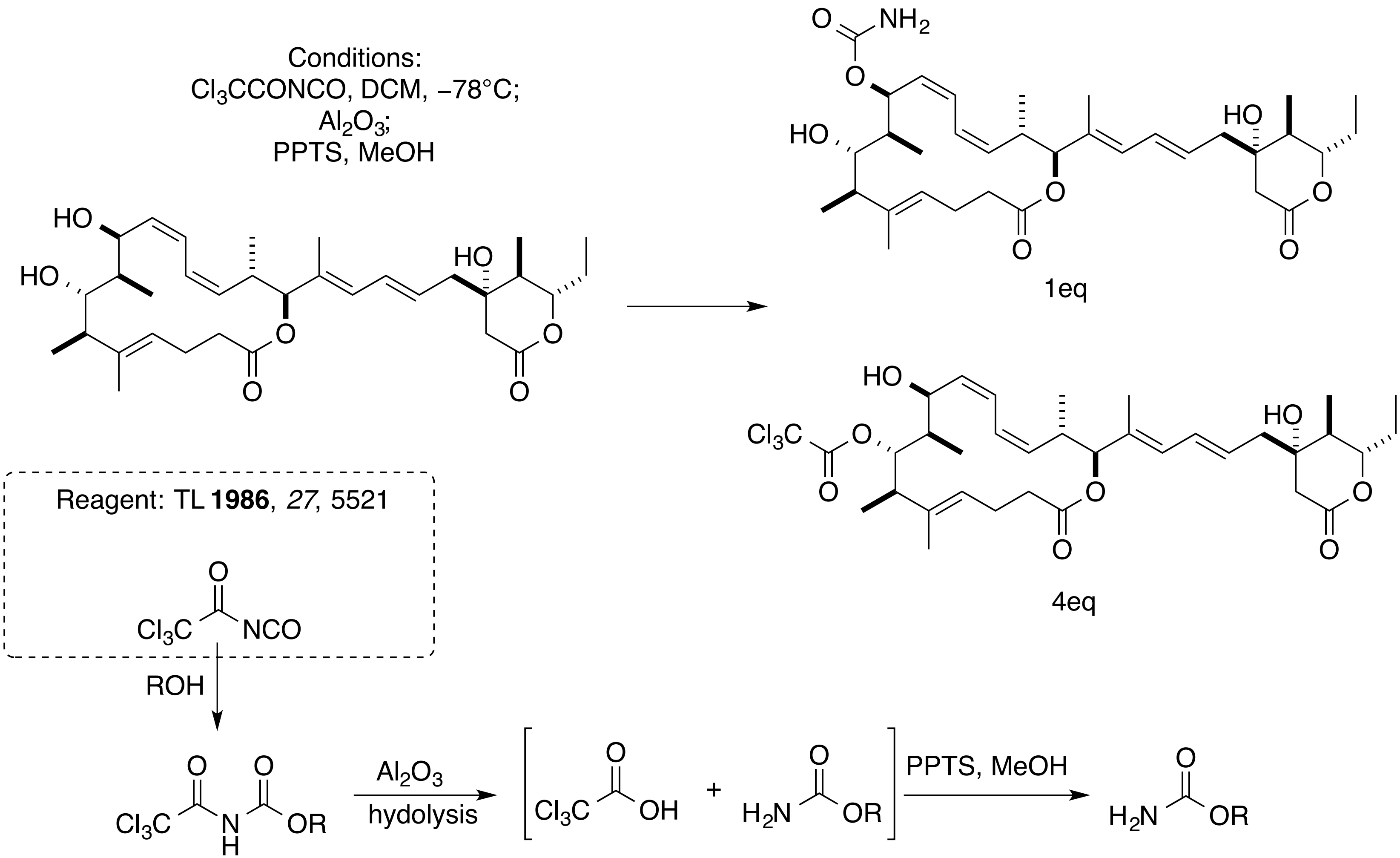
via ROH @	Ring size	comment
C21	22	tertiary
C15	16	good (allylic)
C9	9	v. poor
C7	7	good, but 3 alkenes

Reviews
Macrolactonization: Chem. Rev. (**2006**, *106*, 911-939) **2013**, *113*, PR1-PR40
Ring size: Acc. Chem. Res. **1981**, *14*, 95

Yamaguchi macrolactonization: Bull. Chem Soc. Jpn. **1979**, *52*, 1989-1993
TCBC = 2,4,6-trichlorobenzoyl chloride

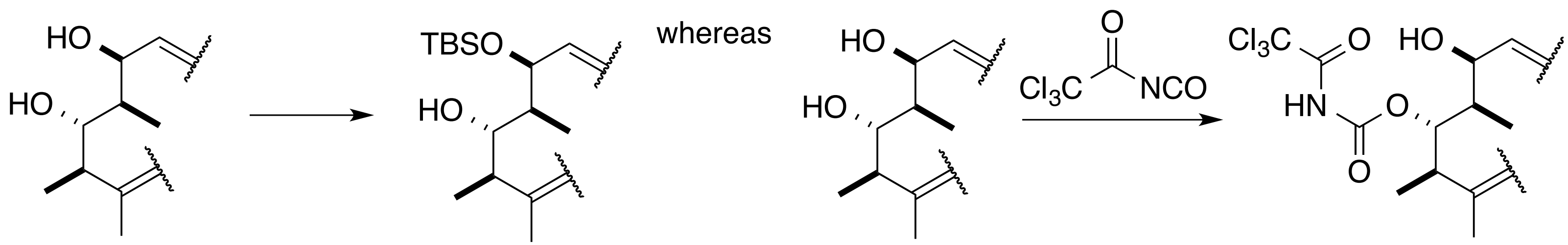


Carbamate formation

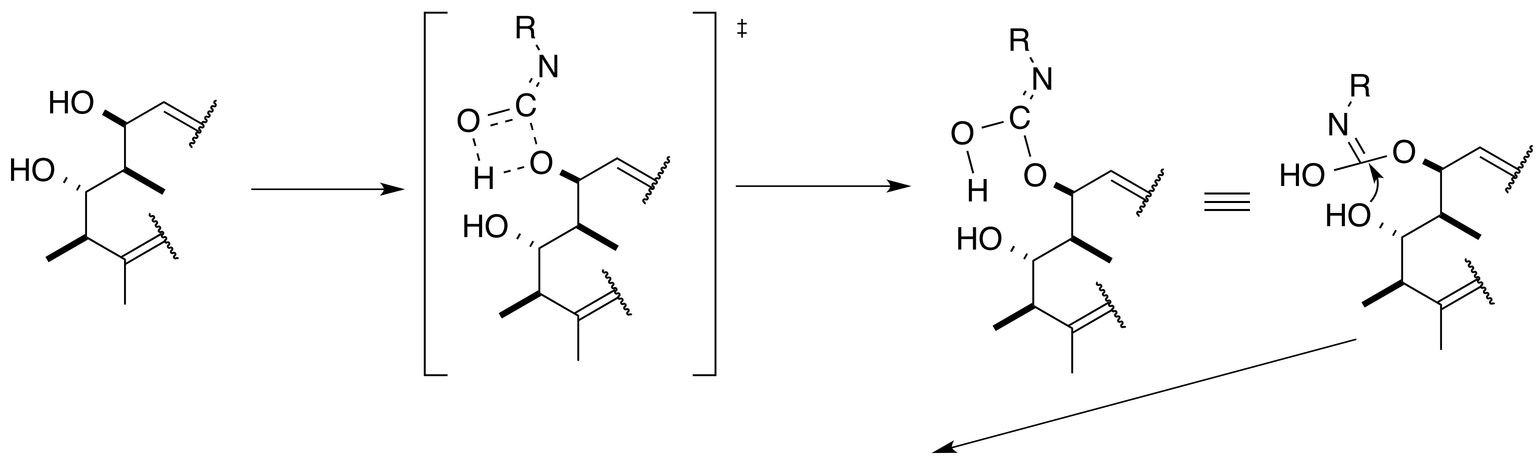


Carbamate formation

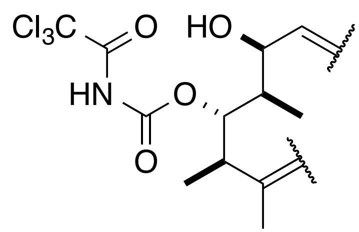
But why does silylation occur exclusively at more accessible C9? Think about mechanism...



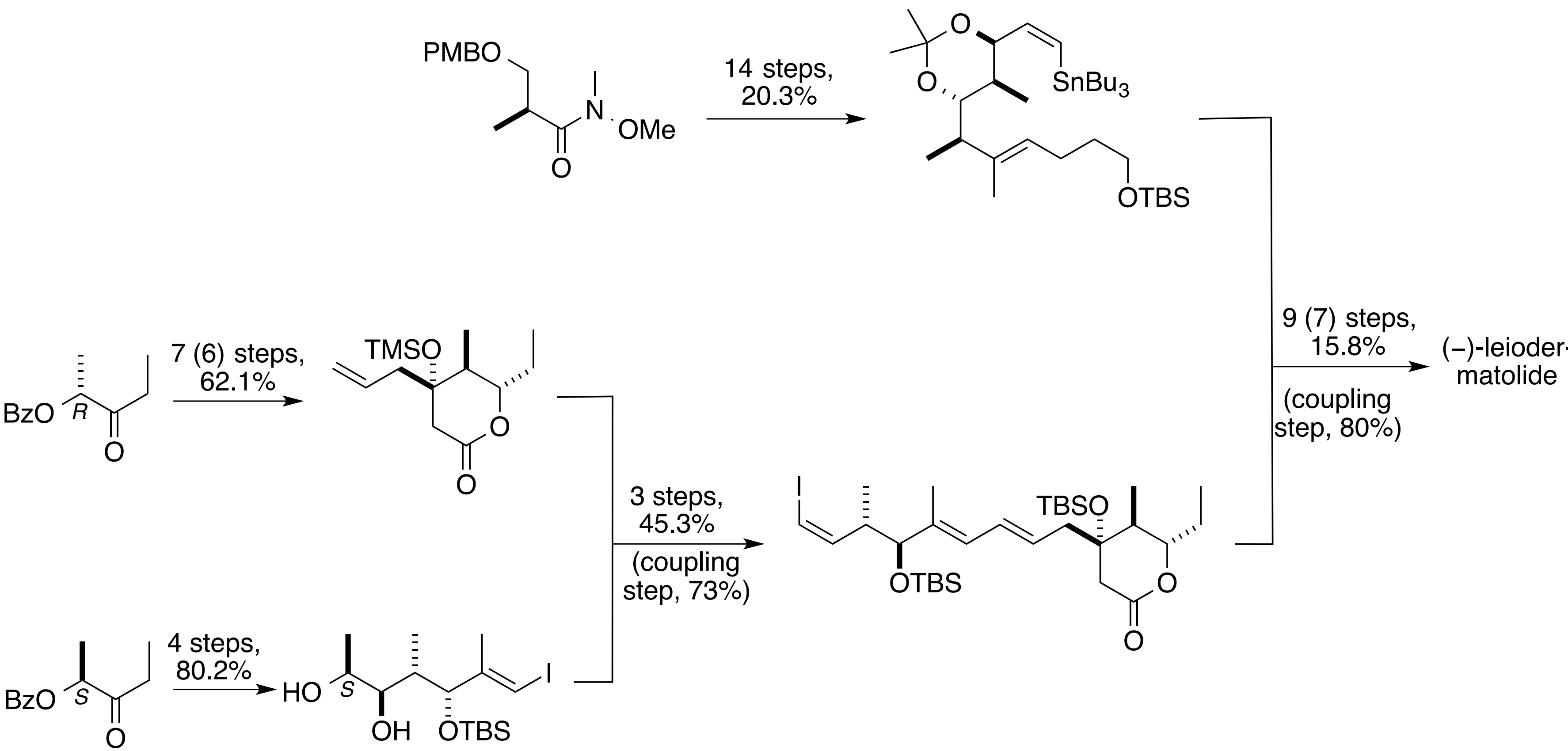
Unusual mechanism has been suggested: JOC **1998**, *63*, 6878



observed major product



Summary



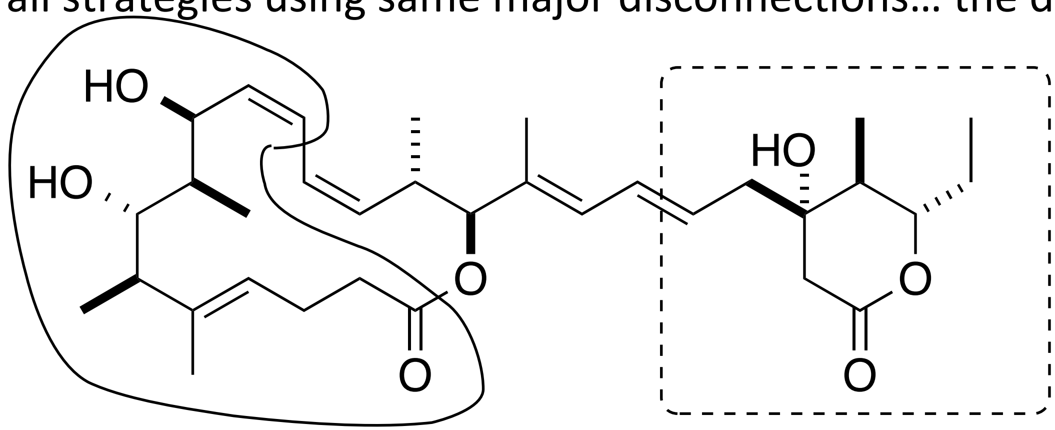
longest linear sequence = (21 or) 23 steps; 0.158*0.203 = 3.2%

real overall yield = (((((0.802+0.621)/2)*0.453)+0.203)/2)*0.158 = 4.2%

$(((((Y_{av}^4 + Y_{av}^7)/2)*Y_{av}^3) + Y_{av}^{14})/2)*Y_{av}^9 = 4.2\%$; solve, $Y_{av} = 82.4\%$

3 synthetic approaches

- Style of synthesis: what is the point? Reliability, efficiency, control, cost, structure determination (dynamic/ modifiable route), POC, or even being there first…?
- *Maier* had more unknowns (influence disconnections)
- Found had epimers of natural prod
- Clever use of Marshall Tamaru 'aldol alternative' (point-axial-point)
- *Furstner* first but racemic, keeping unknown stereocentres at least harmful stage
- *Paterson* **strategic** first disconnections gives two fragments with 14 steps and 4 stereocentres, and 14 steps (but convergent) and 5 stereocentres
- Oxidative glycol cleavage removes many stereocentres and material: Control at the cost of atom economy (but good SMs – synthesized one enantiomer!)
- In the end all strategies using same major disconnections… the devil is in the detail



Marshall-Tamaru

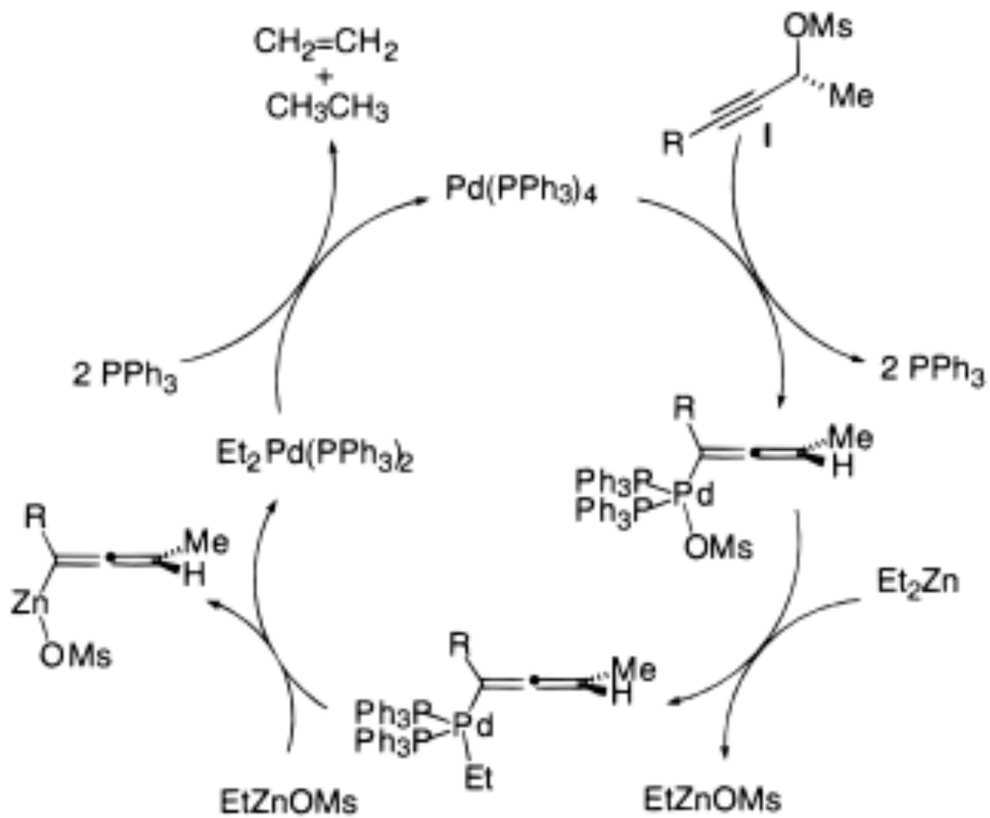


Figure 5. Catalytic cycle for the formation of chiral allenylzinc reagents.