Those Hot Molecules…

A 4 Millenia Story from Capsaicin Human Addiction to Resiniferatoxin Total Synthesis

Damien Mailhol

28/10/10

Outline

- Spices
  - Use
  - History
  - Bio interest
- Resiniferatoxin
  - Retrosynthesis
  - Total synthesis
- Red hot chilli pepper free tasting!

Use

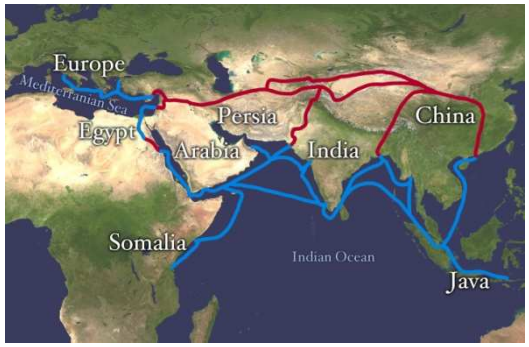
• Spice chemicals often act as defense chemicals to protect the plant from animals, insects and microbes
☛ ideal for food preservation!

• Correlation between the temperature of a country and the amount of spice employed in traditional cuisine:
  • warmer nations (Mexico, India, Thailand) ☛ spicy dishes
  • colder states (England) ☛ much blander menu

• Spices 3 main uses:
  • fragrance
  • medicinal properties
  • food preservation

History

• Ancient Egyptians imported spices from Asia defining the first **spice trade routes**



• Arabs knew sea routes to reach India
☛ Middle East control over the supply of spices to Europe over 4 millennia!

• 1453: Ottoman turks seized Constantinople (Istanbul) ☛ spice prices ⮭

• **Imbalance in the supply of spice** ☛ 2 consequences:
  • series of war between European spice consumers and the Arabian traders
  • seek of new routes to the spice producing regions
    ☛ European Age of Discovery: many explorations, inventions and discoveries

• Sea exploration and expansionism by European powers
  ☛ Vasco da Gama 1st sea voyage to India by Cape of Good Hope
  ☛ Ferdinand Magellan circumnavigated the world

History

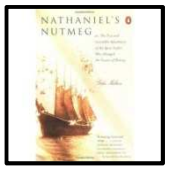
• 1492: discovery of America

• To be funded Columbus brought back many products to the spanish court, including a red chili pepper.

• 1602: Formation of the Dutch East India Company (VOC), a trade association dedicated to the conquest of spice trade.

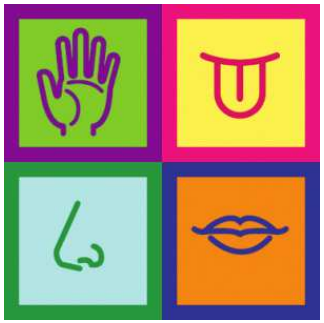
• Trade of New Amsterdam (today Manhattan!) for the deserted spice island of Run.

☛ by 1670 their tactics made VOC the richest company in the world, employing more than 50 000 people.



Nathaniel's Nutmeg, Giles Milton, Penguin Books, 2000.

Biology



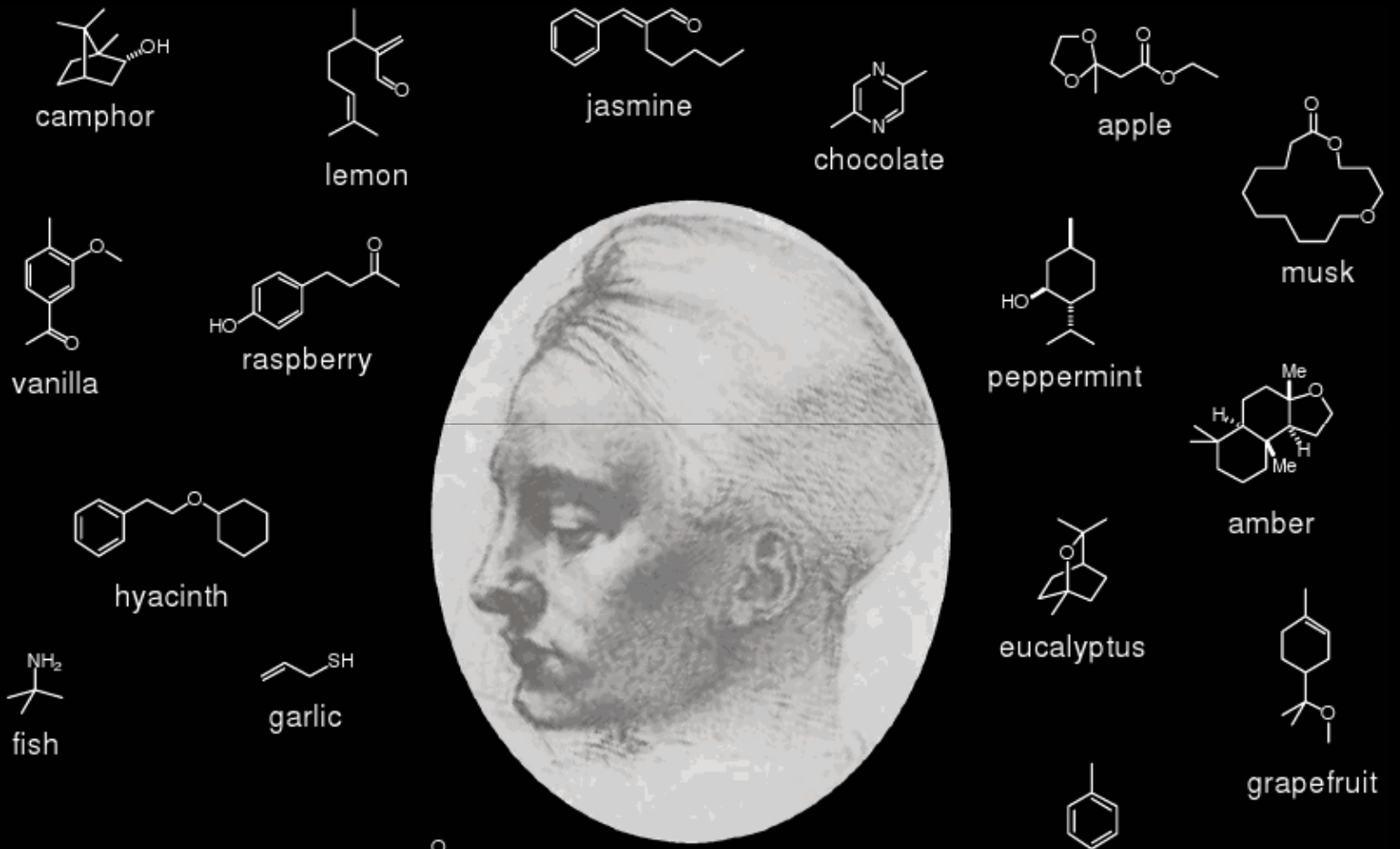
- 3 equally important sensory components of flavor:
  - taste (gustation)
  - smell (olfaction)
  - tactile sensation (termed mouthfeel)

- Taste remains the least understood of our senses.

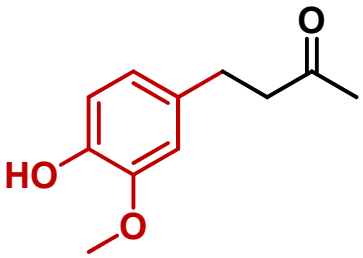
- Richard Axel and Linda Buck were awarded *2004 Nobel Prize in Physiology or Medicine* for their **studies on the olfactory system processes**.

Smell

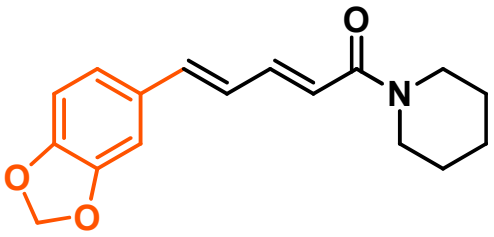
Linda Buck , Nobel Lecture, 2004.



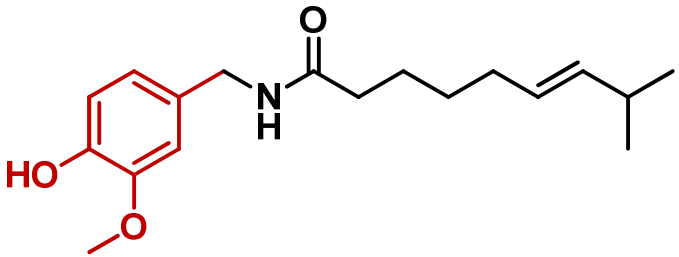
Biology



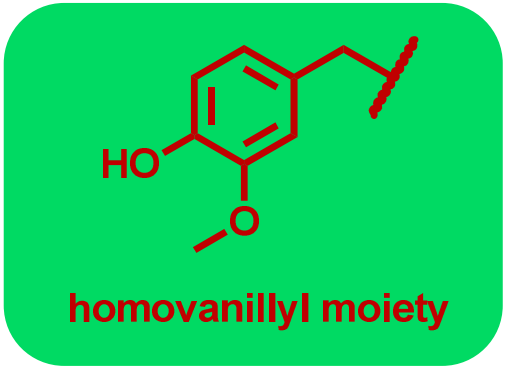
zingerone



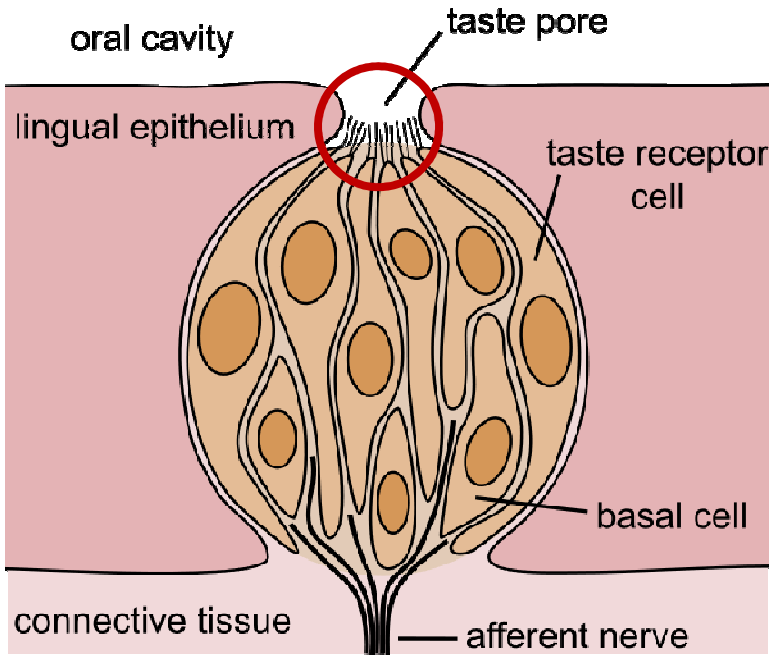
piperine



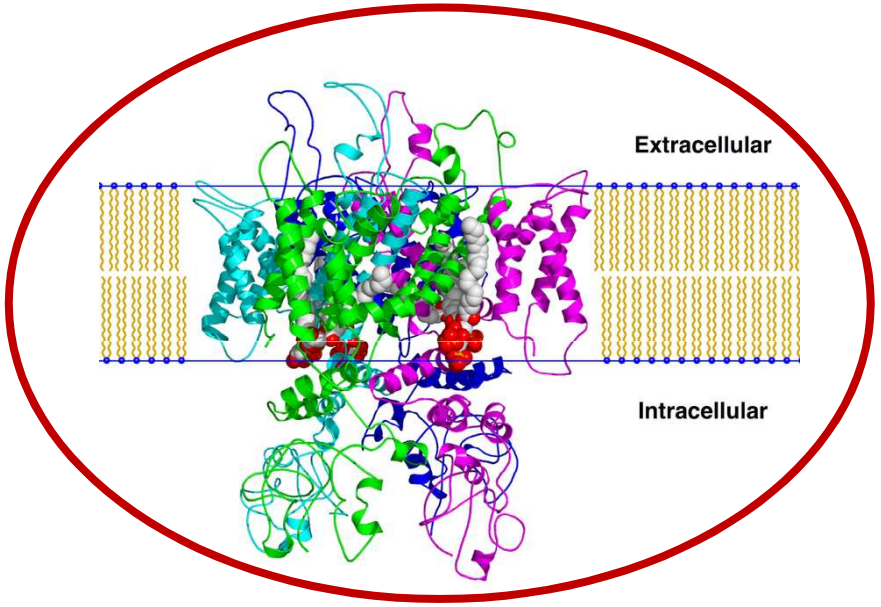
capsaicin



Taste

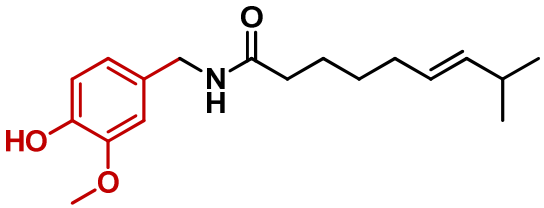


Taste bud

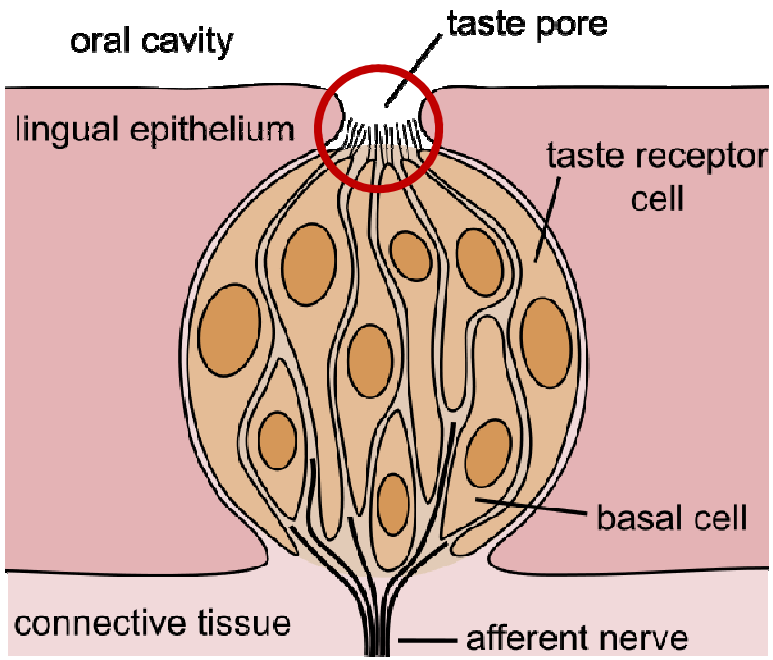


TRPV1
(Transient **R**eceptor
Potential **V**anilloid)

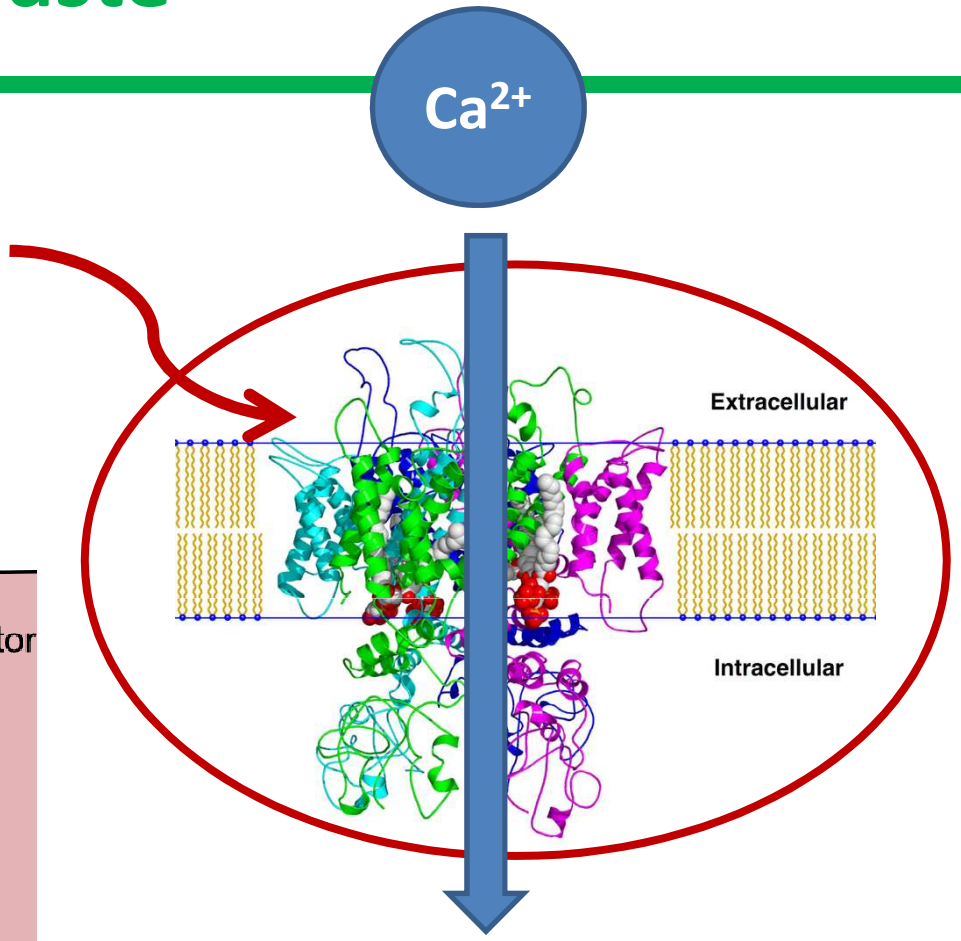
Taste



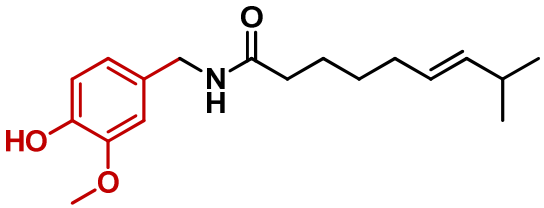
capsaicin



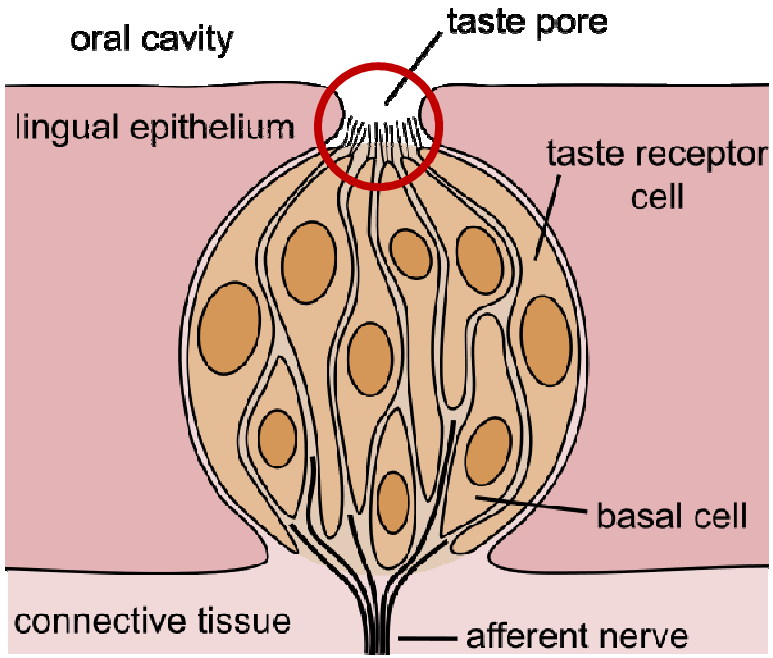
Taste bud



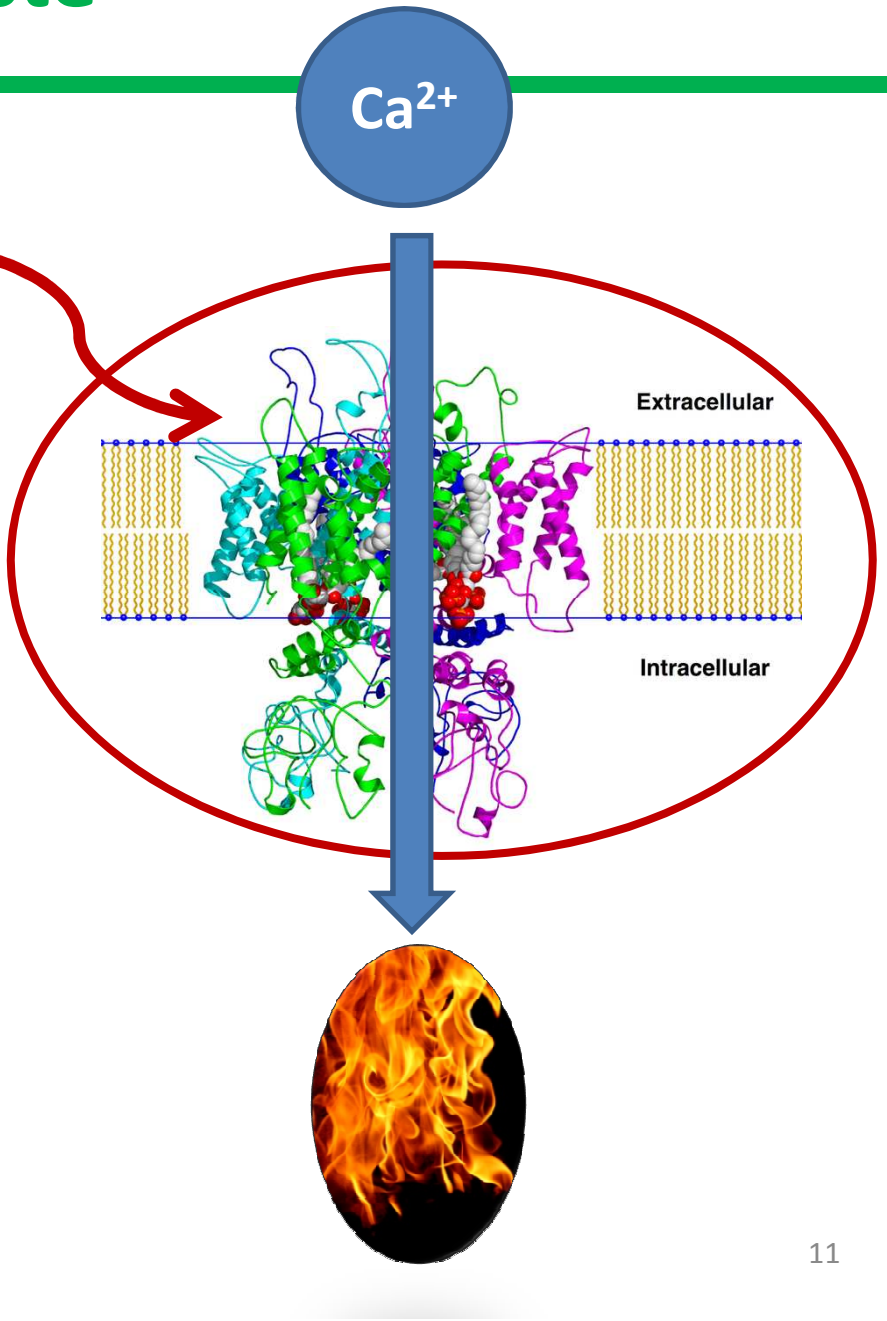
Taste



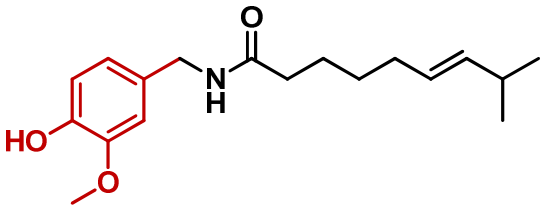
capsaicin



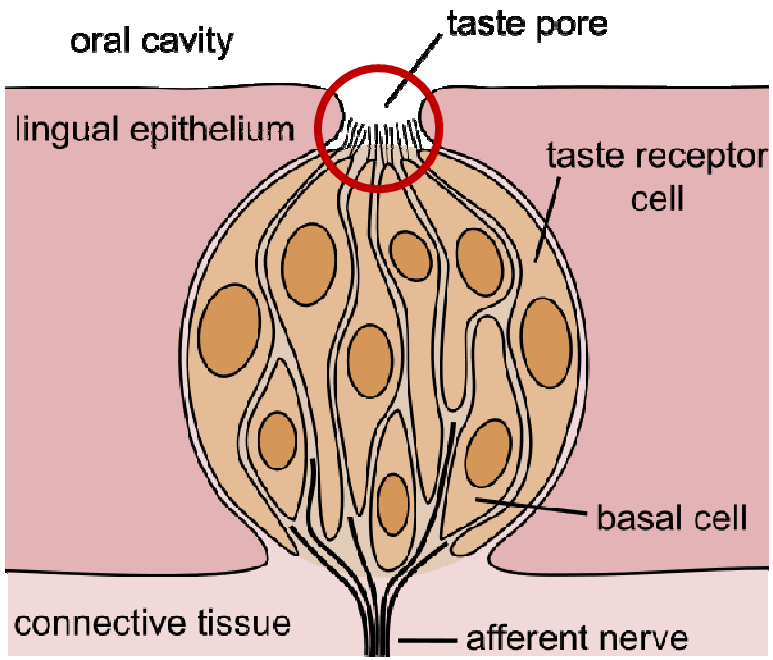
Taste bud



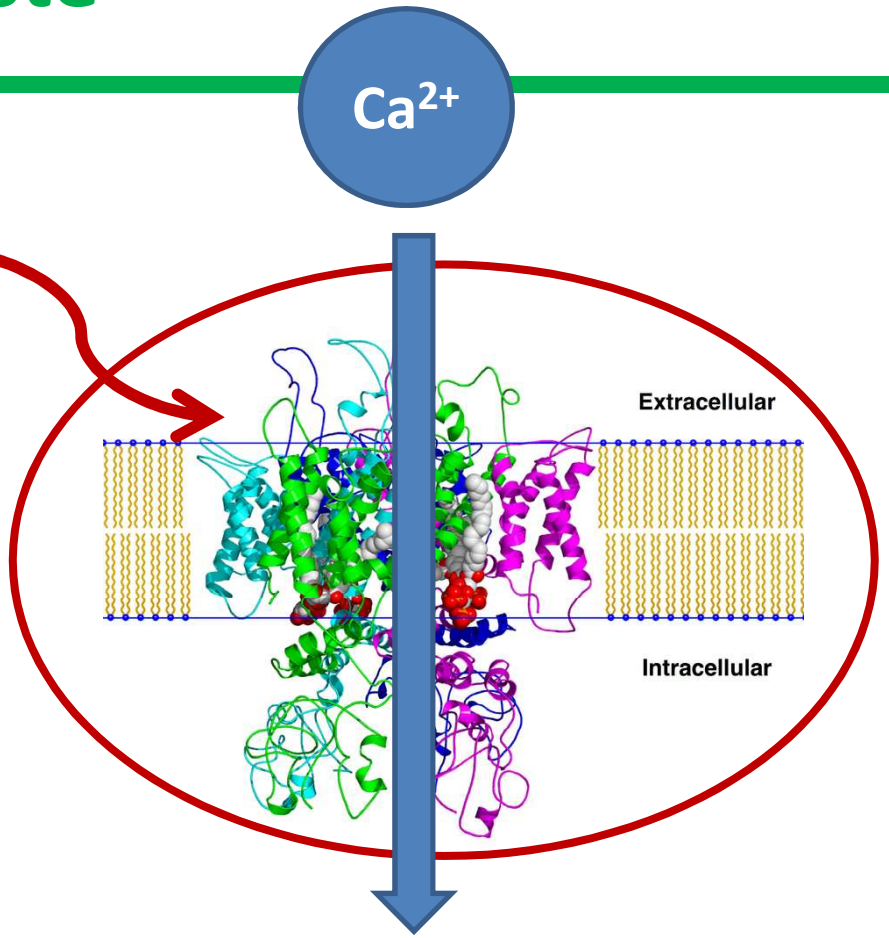
Taste



capsaicin



Taste bud



Scoville scale

Measurement of the spicy heat of a chili pepper

Scoville rating	Type of pepper
15,000,000–16,000,000	Pure capsaicin[4]
9,100,000	Nordihydrocapsaicin
2,000,000–5,300,000	Standard US Grade pepper spray [5]
855,000–1,041,427	Naga Jolokia [6][7][8][9]
350,000–577,000	Red Savina Habanero
100,000–350,000	Habanero Chile [10]
100,000–350,000	Scotch Bonnet [10]
100,000–200,000	Jamaican Hot Pepper [5]
50,000–100,000	Thai Pepper, Malagueta Pepper, Chiltepin Pepper
30,000–50,000	Cayenne Pepper, Ají pepper [10], Tabasco pepper
10,000–23,000	Serrano Pepper
7,000–8,000	Tabasco Sauce (Habanero)[11]
5,000–10,000	Wax Pepper
2,500–8,000	Jalapeño Pepper
2,500–5,000	Tabasco Sauce (Tabasco pepper) [11]
1,500–2,500	Rocotillo Pepper
1,000–1,500	Poblano Pepper
600–800	Tabasco Sauce (Green Pepper) [11]
500–1000	Anaheim pepper
100–500	Pimento [5], Pepperoncini
0	No heat, Bell pepper [5]

Scotch Bonnet

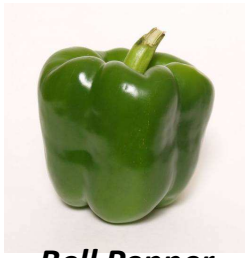
Naga Jolokia

Red Savina

Jalapeño Pepper

Serrano Pepper

Tabasco Sauces



Bell Pepper

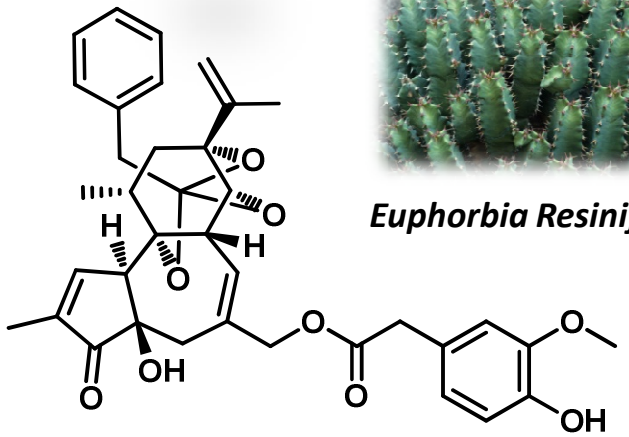
Medicinal use

- Capsaicin showed potential biological activity (arthritis, diabetic neuropathy, …)

painful side effects

☛ Alternative: **resiniferatoxin**

Euphorbia Resinifera

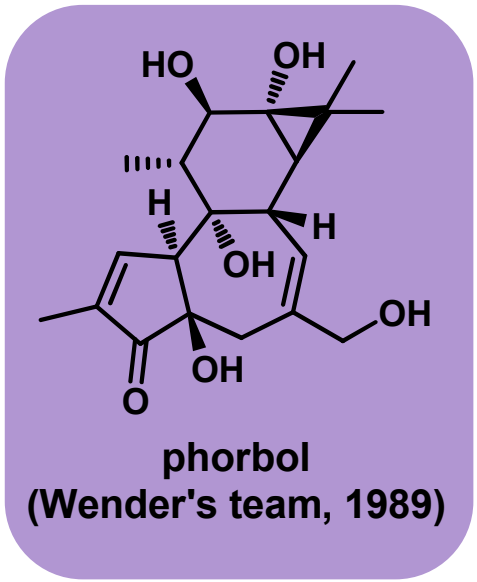


resiniferatoxin (RTX®)

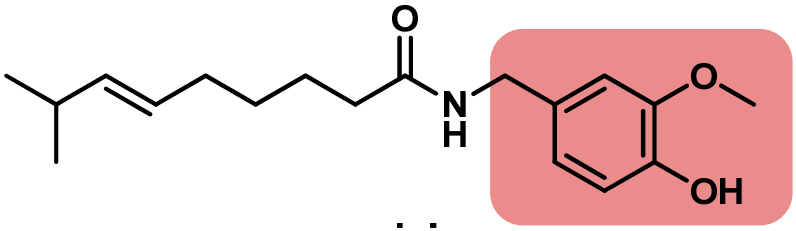
- Desensitizes rather than overstimulates!
- Rare in the nature
  - ☛ Need of a synthetic source

- RTX can kill tumor cells!

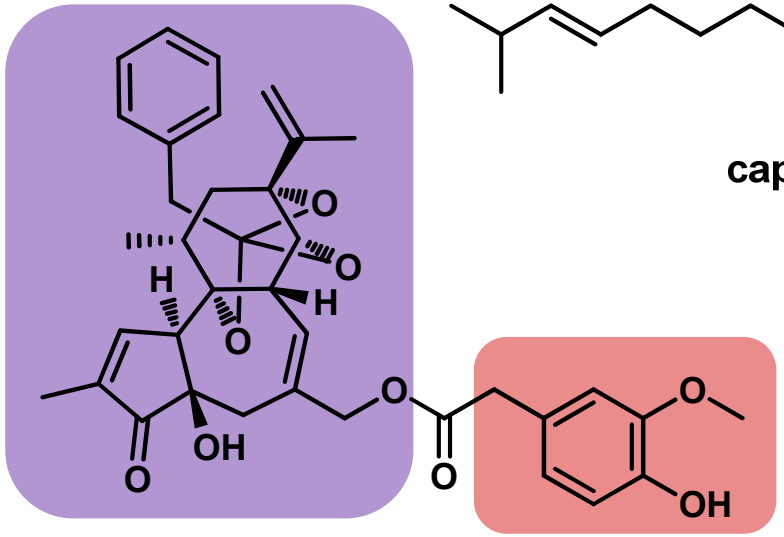
Total Synthesis of Resiniferatoxin



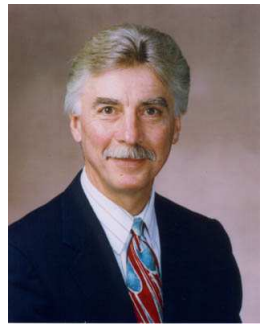
phorbol
(Wender's team, 1989)



capsaicin



resiniferatoxin
(Wender's team, 1997)

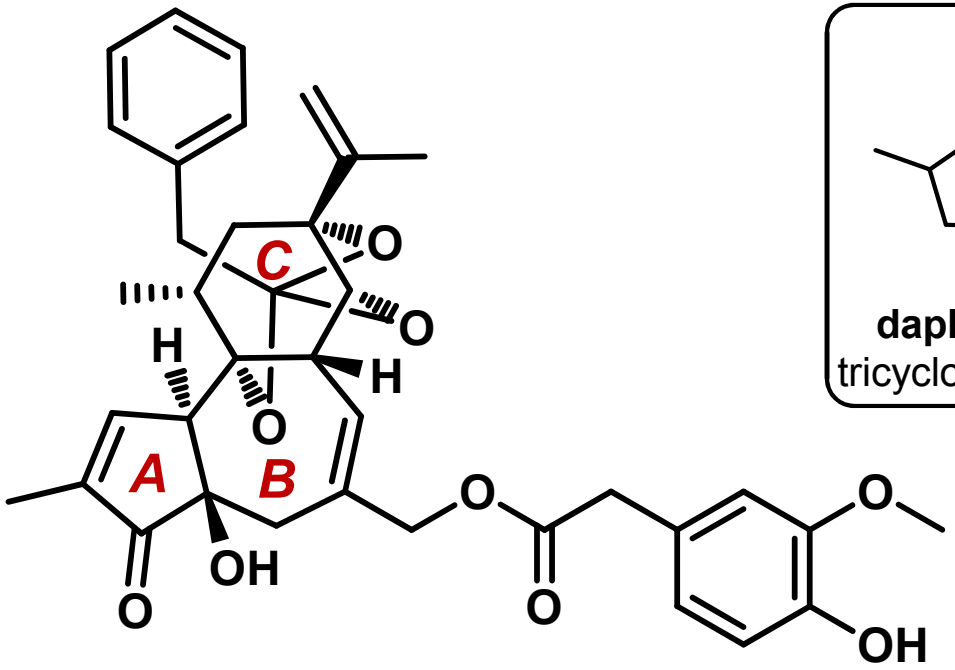


P. A. Wender, K. D. Rice, M. E. Schnute, The First Formal Asymmetric Synthesis of Phorbol, *J. Am. Chem. Soc.* **1997**, *119*, 7897-7898.

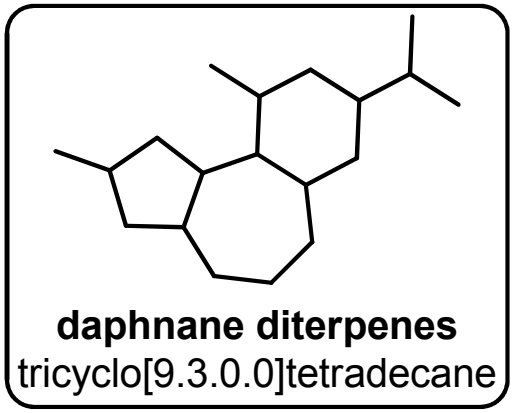
P. A. Wender, C. D. Jesudason, H. Nakahira, N. Tamura, A. L. Tebbe, Y. Ueno, The First Synthesis of a Daphnane Diterpene: The Enantiocontrolled Total Synthesis of (+)-Resiniferatoxin *J. Am. Chem. Soc.* **1997**, *119*, 12976-12977.

Total Synthesis of Resiniferatoxin

[57444-62-9]
$C_{37}H_{40}O_9$
628.71 g/mol
32€/mg



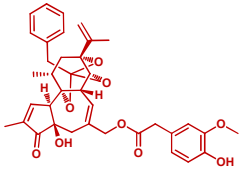
resiniferatoxin

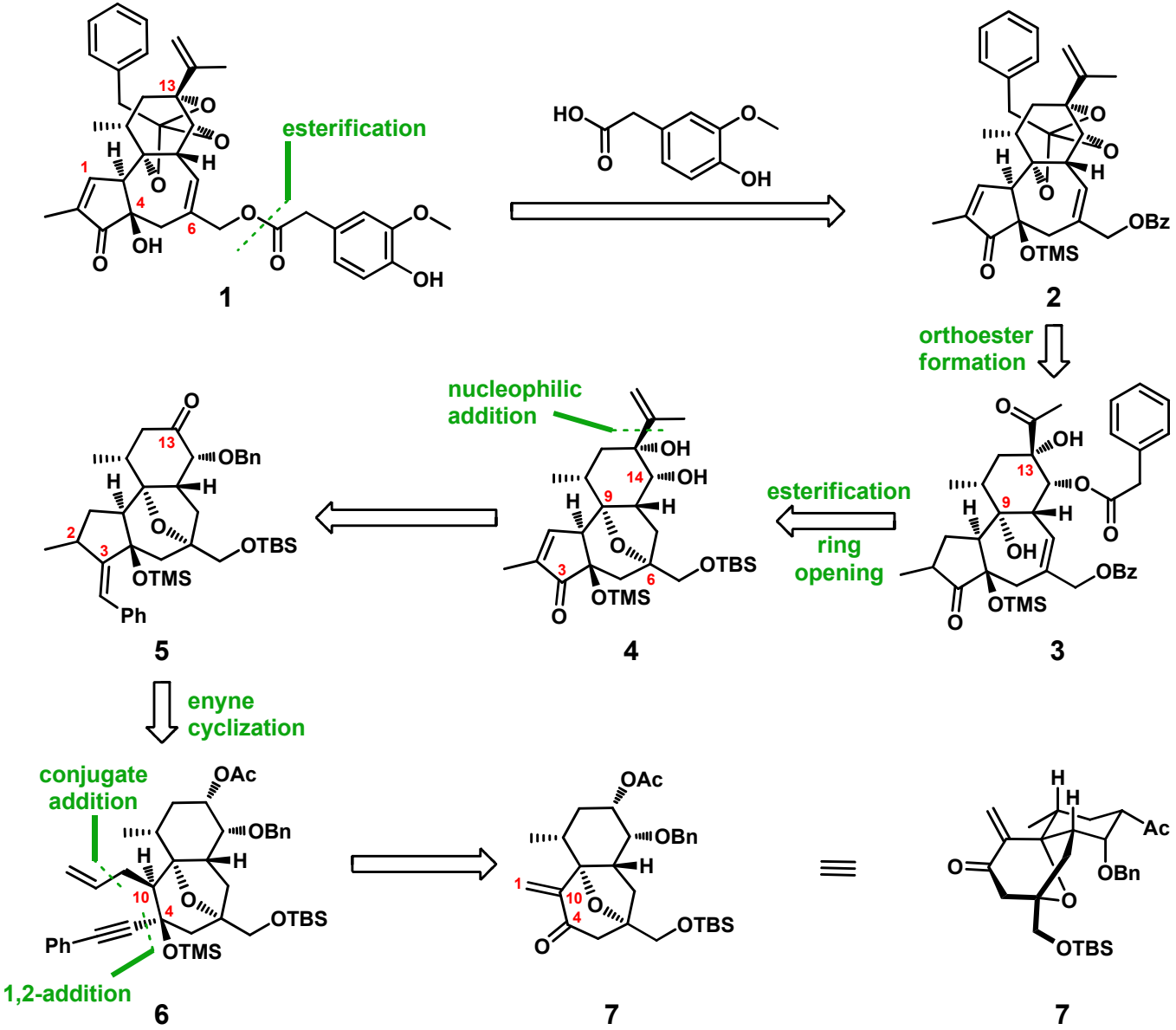


Synthetic challenges:

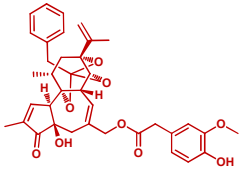
- 7 stereocenters (5 contiguous on ring C)
- *trans*-fused nature of both AB- and BC-ring junctions
- orthoester motif (labile under acid conditions)

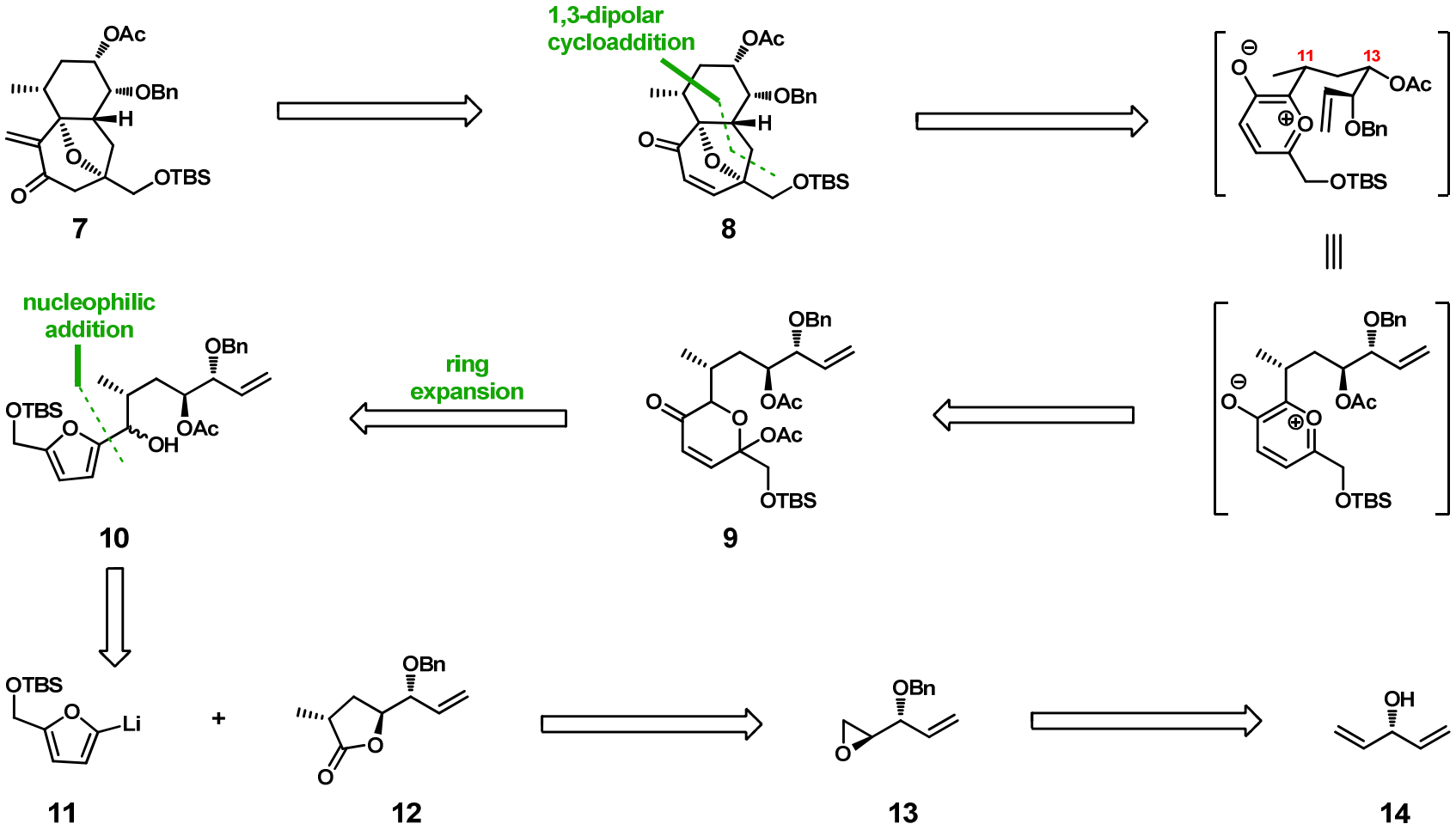
Total Synthesis of Resiniferatoxin



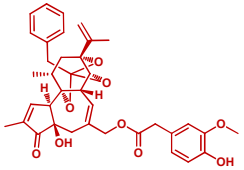


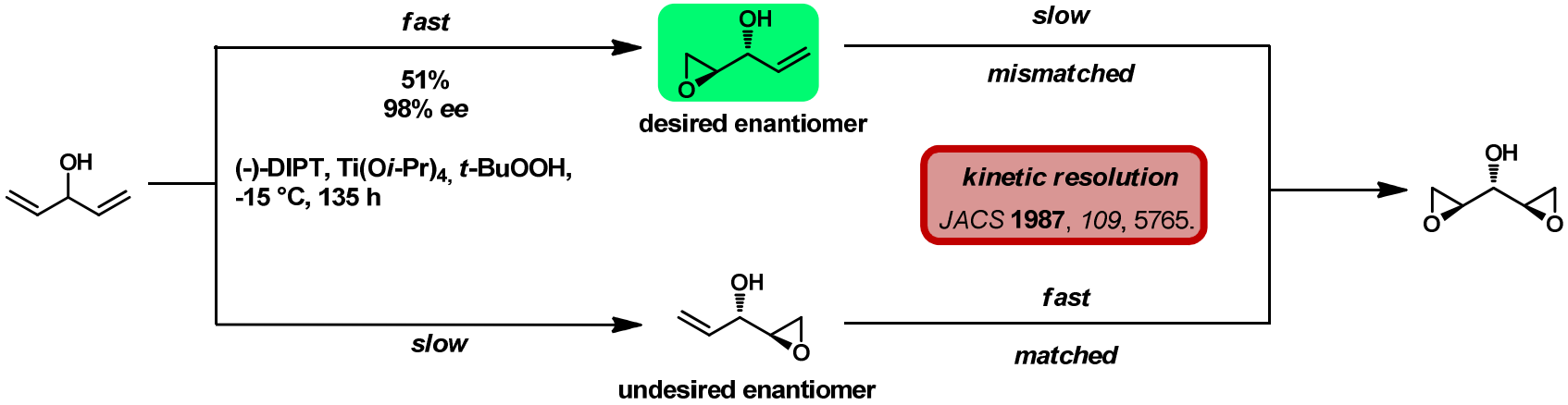
Total Synthesis of Resiniferatoxin



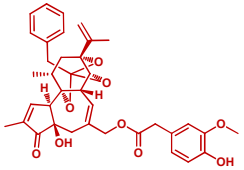


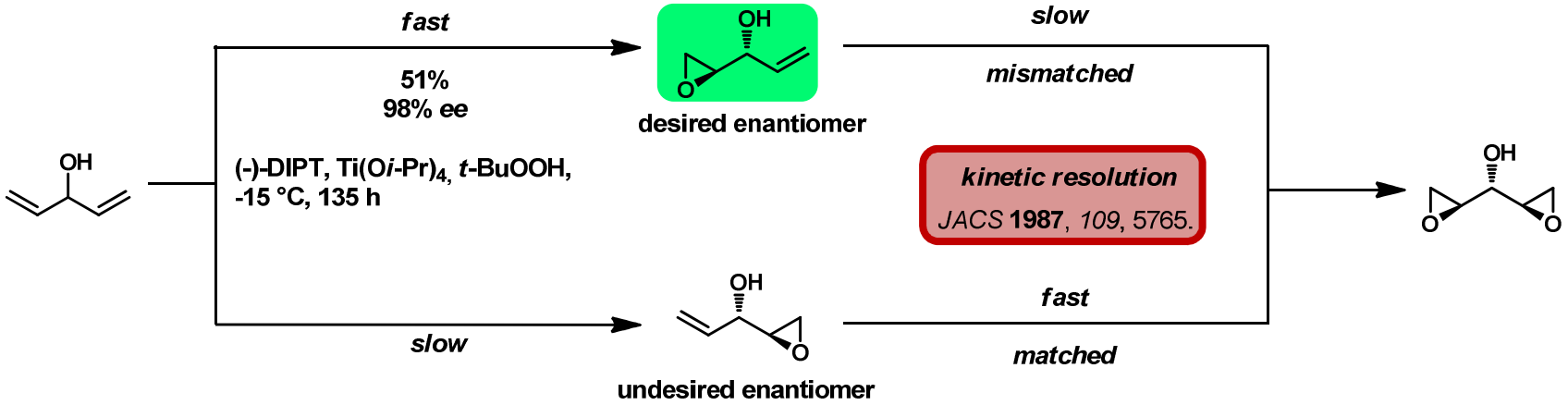
Total Synthesis of Resiniferatoxin

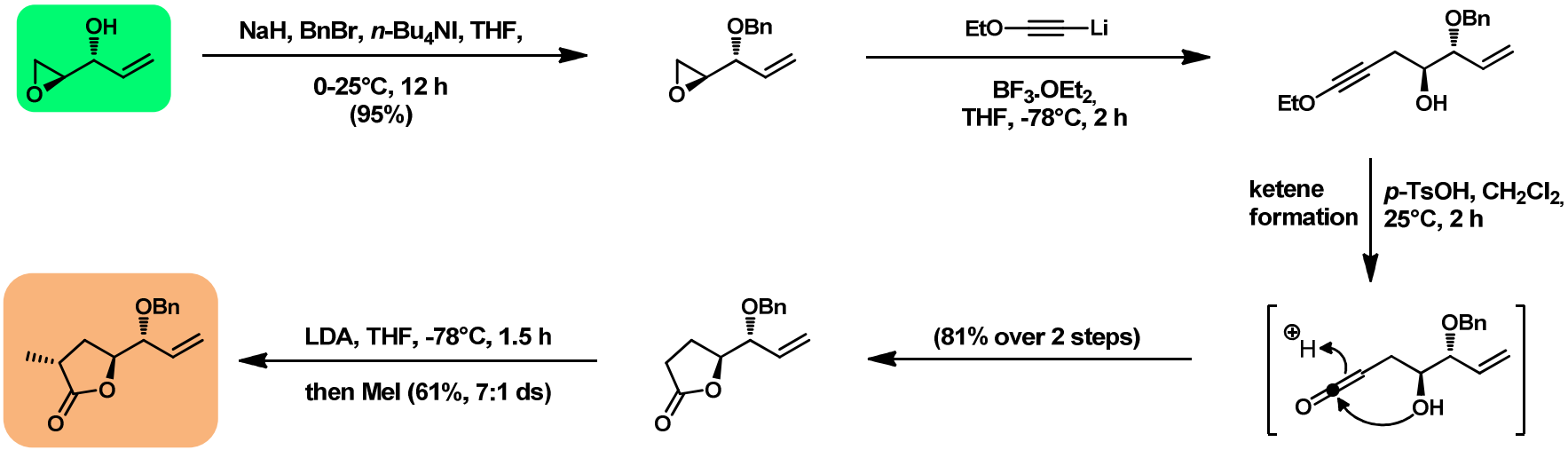




Total Synthesis of Resiniferatoxin

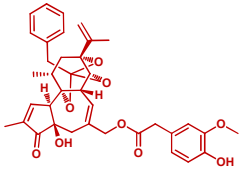


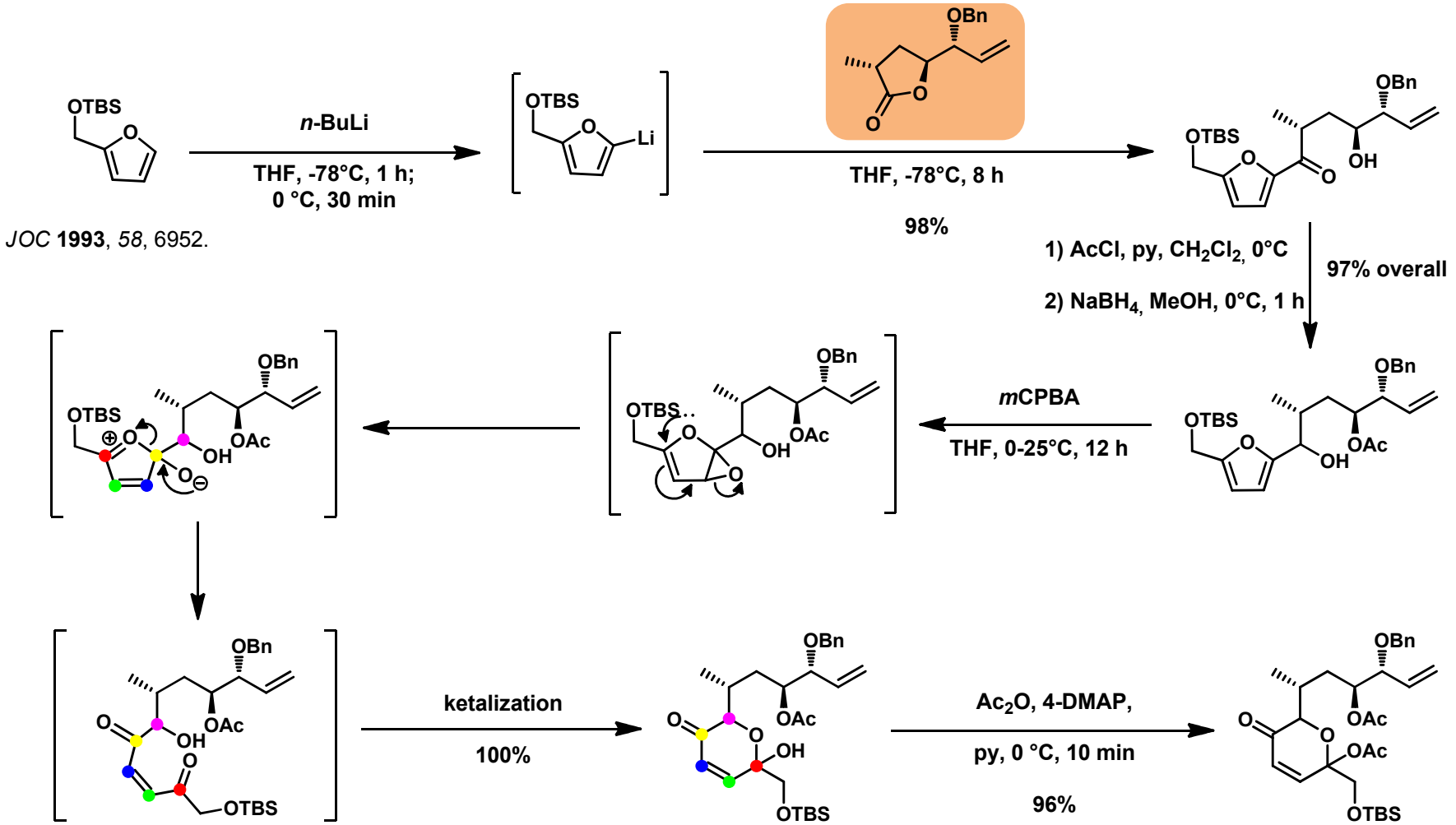




TL **1988**, *29*, 277.
JOC **1989**, *54*, 9.

Total Synthesis of Resiniferatoxin



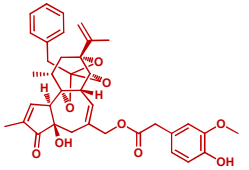


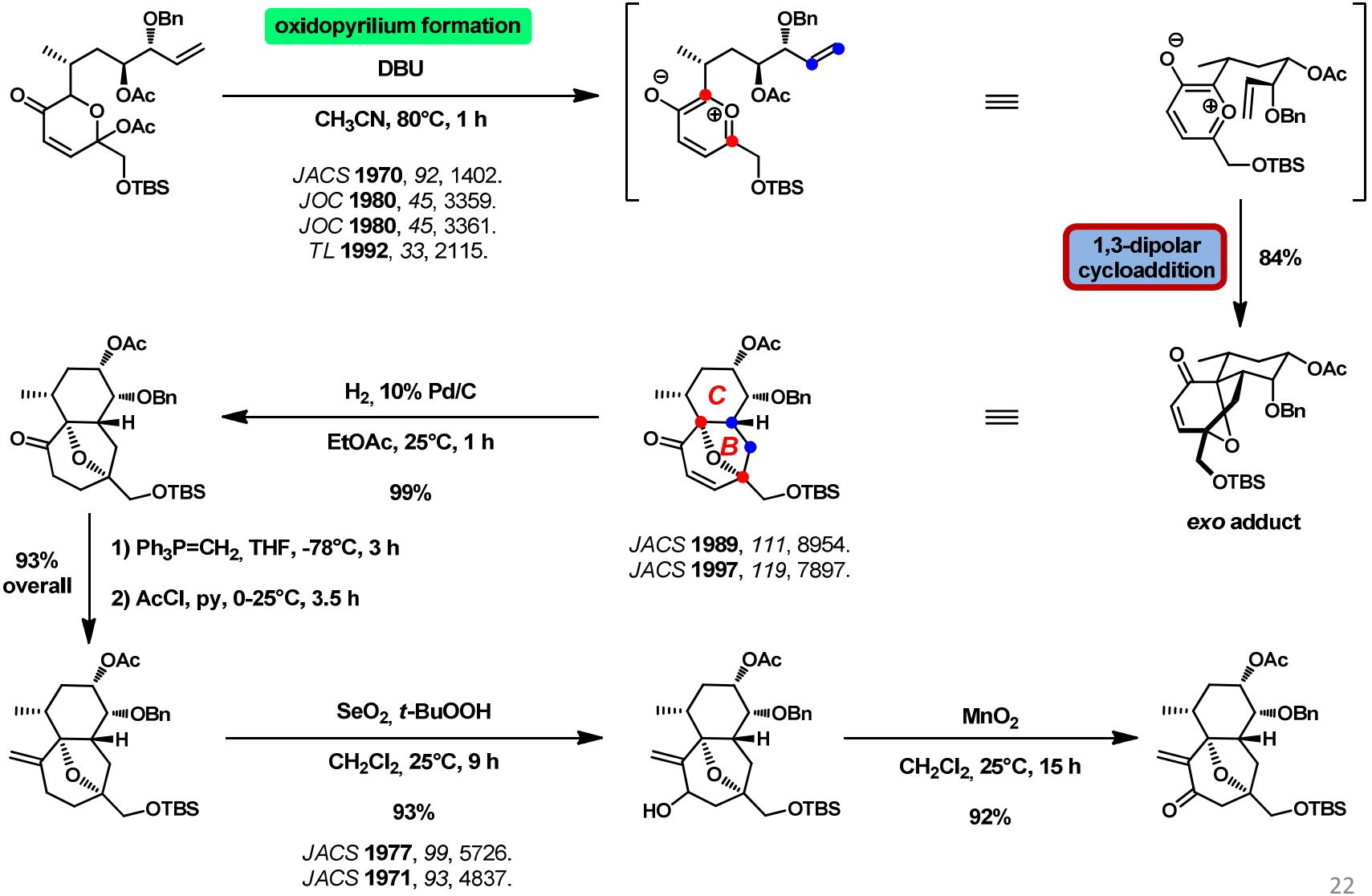
JOC **1993**, *58*, 6952.

4 dia.
(non-problematic)

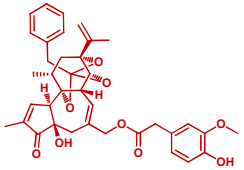
TL **1972**, *13*, 133.

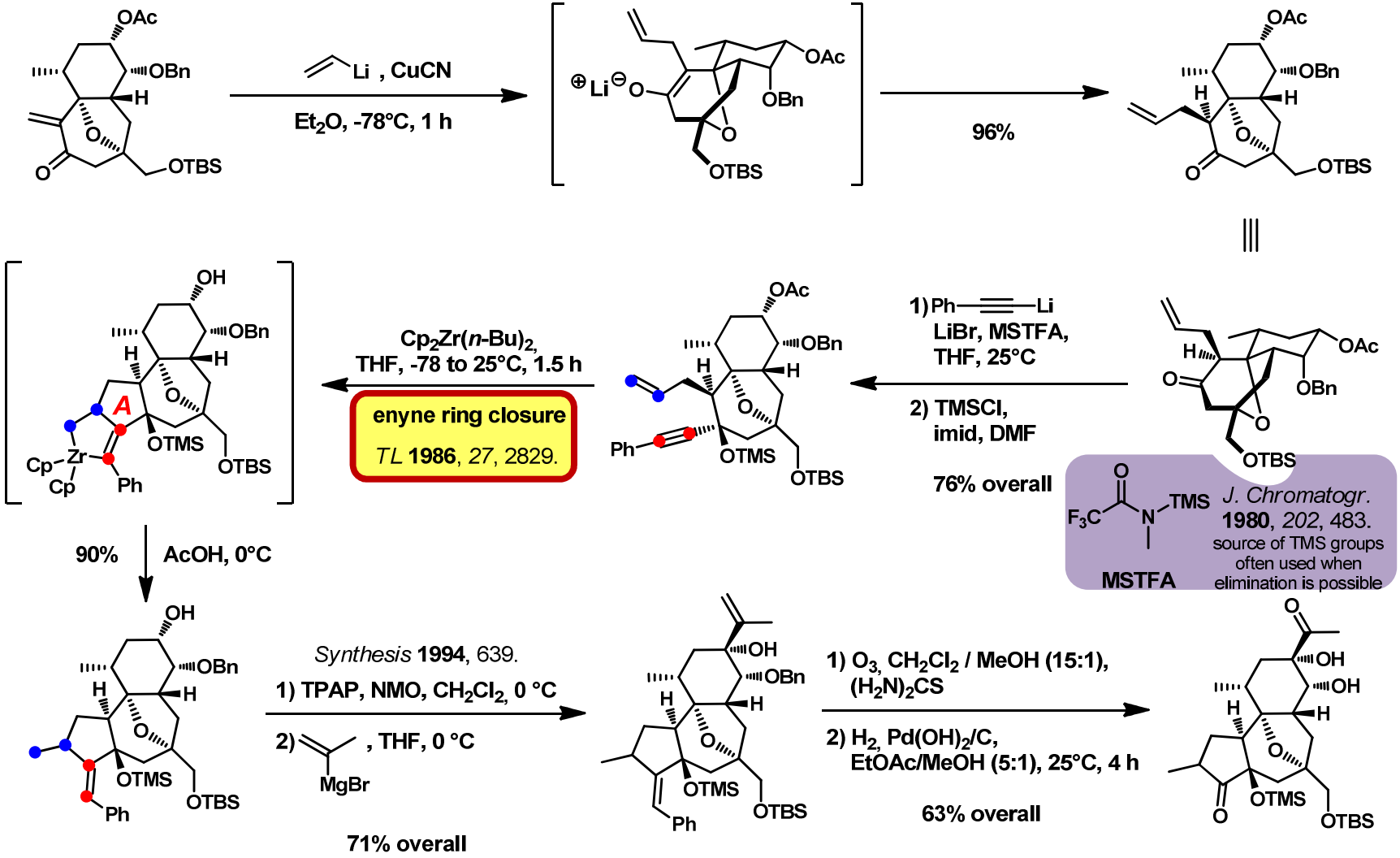
Total Synthesis of Resiniferatoxin



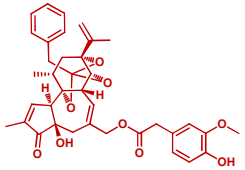


Total Synthesis of Resiniferatoxin





Total Synthesis of Resiniferatoxin



1) Cl_3CO $OCCl_3$, CH_2Cl_2, 0°C
2) 49% aq. HF, CH_3CN, 0 °C
87% overall

1) Tf_2O, py, *n*-Bu_4NI
2) Rieke Zn
Aldrichimica Acta **2000**, *33*, 52.
88% overall

SeO_2, *t*-BuOOH, CH_2Cl_2, 25 °C
then HMPA, 80 °C, 4 h
61%

1) $SOCl_2$, Et_2O, 0 °C
2) AgOBz, KOBz, 18-C-6, CH_3CN, 25 °C
77% overall

1) 0.5 M NaOH, 1,4-dioxane
2)
4-DMAP, Et_3N, THF
Bull. Chem. Soc. Jpn. **1979**, *52*, 1989.
54% overall

orthoester formation
$HClO_4$, MeOH, 25 °C, 1.5 h
46%

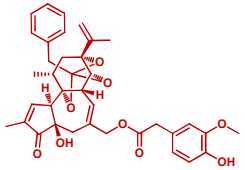
Olefination trials:
Tebbe's reagent [67719-69-1] ✗
Wittig's reagent $Ph_3P{=}$ ✗
Nysted's reagent [41114-59-4] ✗
Peterson olefination *JOC* **1968**, *33*, 780. ✓

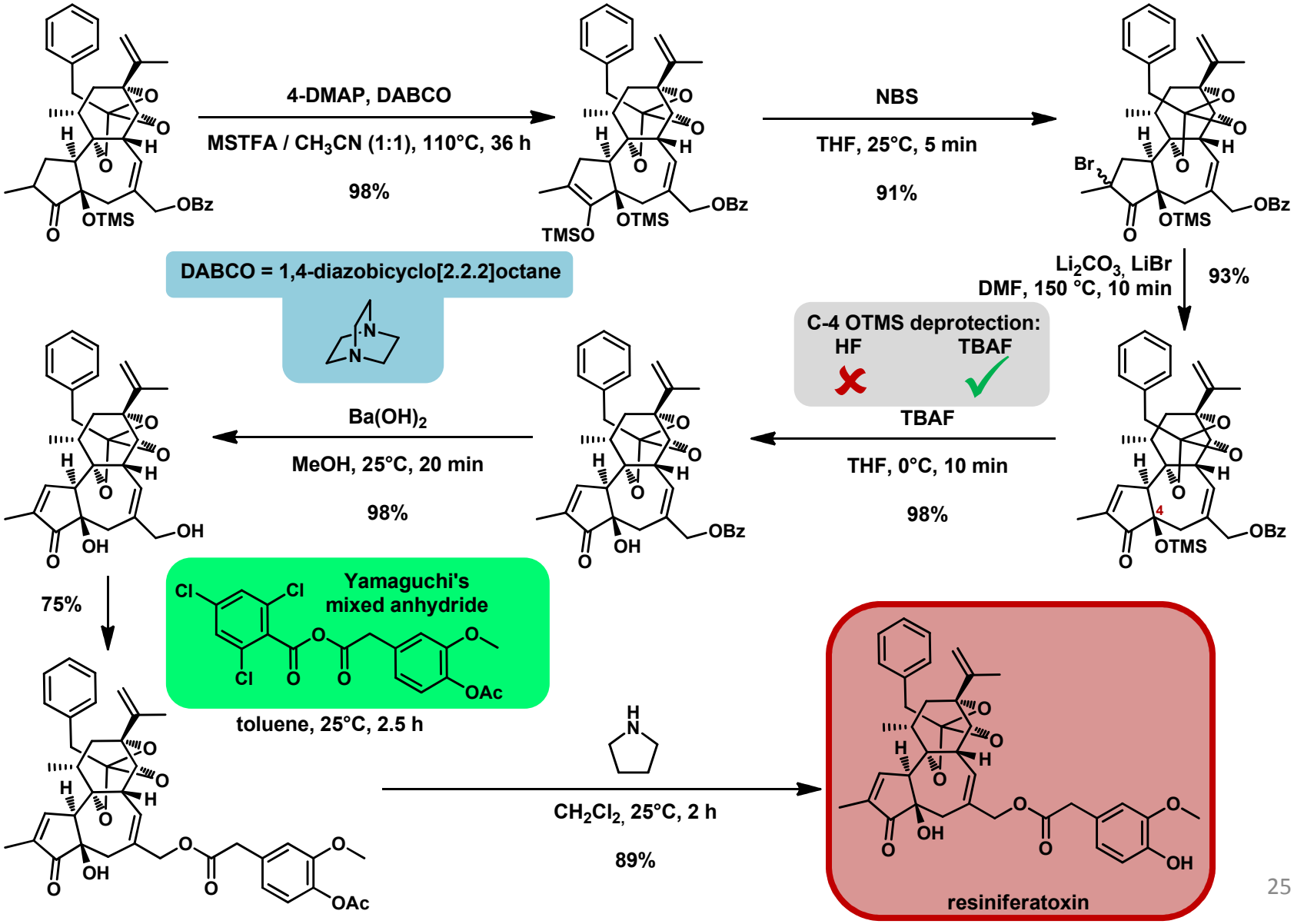
$TMS{-}Li$
THF, -78 °C, 10 min
48%

1) 49% aq. HF, CH_3CN, 25 °C
2) BzCl, py, 4-DMAP, CH_2Cl_2
83% overall

20

Total Synthesis of Resiniferatoxin



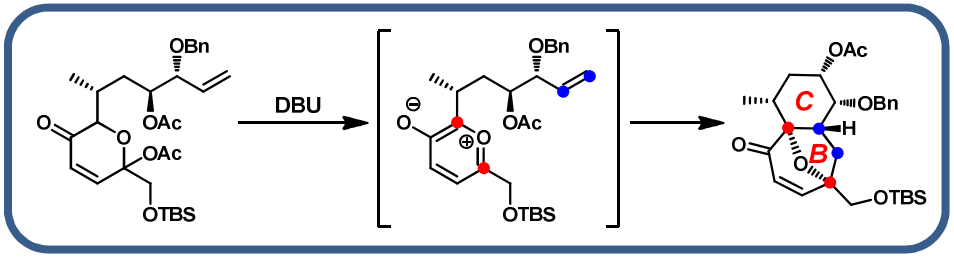


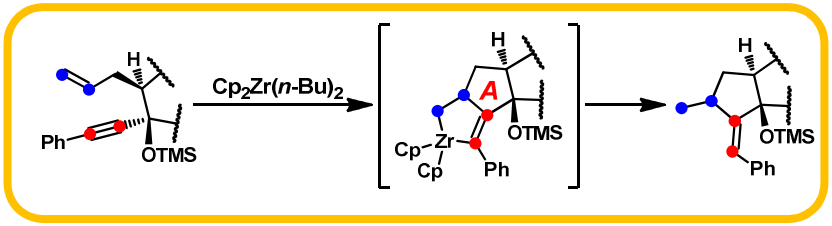
Conclusion

- Synthetic key concepts:

❶ kinetically-controlled enantiomeric enrichment

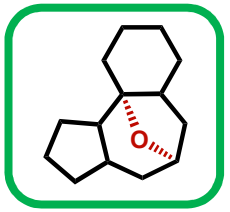
❷1,3-dipolar cycloadditions





❸ Zr-mediated enyne ring closure

❹ elegant **oxido-bridge** stereoinduced strategy



- Resiniferatoxin promising bio studies in progress…

- **From spice trade to resiniferatoxin total synthesis: a long way through globalization!**

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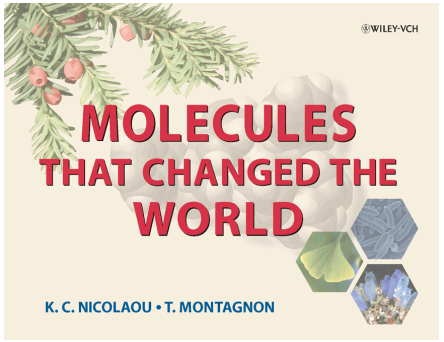

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Thanks to all