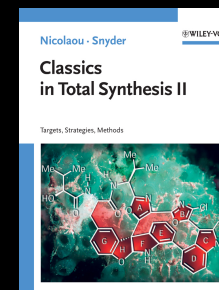
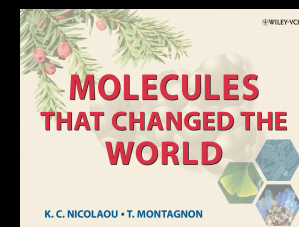
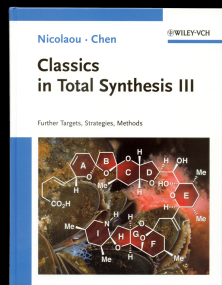
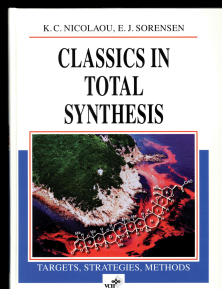


Visit us at [scripps.edu/nicolaou](http://scripps.edu/nicolaou)

Thank you for visiting our website. Our laboratories are situated in the picturesque town of La Jolla, California, and our research is focused on the chemistry, biology, and medicine of natural and designed molecules. The structures below this text represent some of the most intriguing naturally occurring molecules synthesized in our laboratories in recent years. More can be found in the accomplishments section and in the publications listed. In addition to research, we are deeply committed to the education and training of a new generation of men and women in the chemical sciences. The group has published several instructive books, including the advanced and widely used textbooks *Classics in Total Synthesis* (K. C. Nicolaou and Erik J. Sorensen, Wiley-VCH, 1996), *Classics in Total Synthesis II* (K. C. Nicolaou and Scott A. Snyder, Wiley-VCH, 2003), *Classics in Total Synthesis III* (K. C. Nicolaou and Jason S. Chen, Wiley-VCH, 2011), and *Molecules That Changed The World* (K. C. Nicolaou and T. Montagnon, Wiley-VCH, 2008).

Enjoy the tour of our world.



***Chongqing University***  
***Chongqing, China***

***Friday, July 1, 2011***

***K.C. Nicolaou, Ph.D.***  
***The Scripps Research Institute***  
***and***  
***University of California, San Diego***

***“The Art of Total Synthesis and its Applications to  
Chemistry, Biology and Medicine”***





# ***THE ART, SCIENCE, AND TECHNOLOGY OF TOTAL SYNTHESIS***



**CHEMISTRY,  
BIOLOGY,  
PHYSICS**

**MEDICINE**

**MATERIALS  
SCIENCE  
AND NANO-  
TECHNOLOGY**

**SYNTHETIC STRATEGIES**

**NATURAL PRODUCTS**

**SOLID PHASE SYNTHESIS**

**MOLECULAR COMPLEXITY**

**NEW SYNTHETIC  
TECHNOLOGIES**  
**BIOLOGY**  
**CHEMICAL**  
**TOTAL  
SYNTHESIS**

**NATURAL  
PRODUCTS**

**REACTION MECHANISMS**

**MOLECULAR DESIGNS**

**COMBINATIONAL CHEMISTRY**

**MOLECULAR DIVERSITY**

# THE DRUG DISCOVERY AND DEVELOPMENT PROCESS



● **NATURAL PRODUCTS CHEMISTRY**

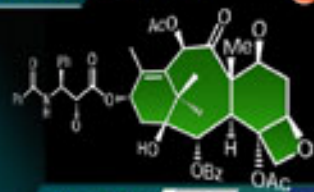
● **COMBINATORIAL CHEMISTRY**

● **PROCESS CHEMISTRY**

● **COST: \$500 MILLION AND RISING**

● **MEDICINAL CHEMISTRY**

● **REVIEW PROCESS**



\$

\$\$

\$\$\$



FDA

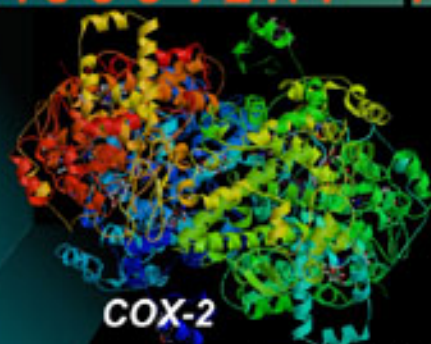


**DISCOVERY**

**PRECLINICAL**

**CLINICAL**

**APPROVAL**



● **ANIMAL MODELS**  
● **TOXICOLOGY**  
● **PHARMACOLOGY**  
● **FORMULATION**

● **HUMAN TRIALS**

● **TIME: 5-10 YEARS AND FALLING**



● **BIOLOGICAL TARGETS**

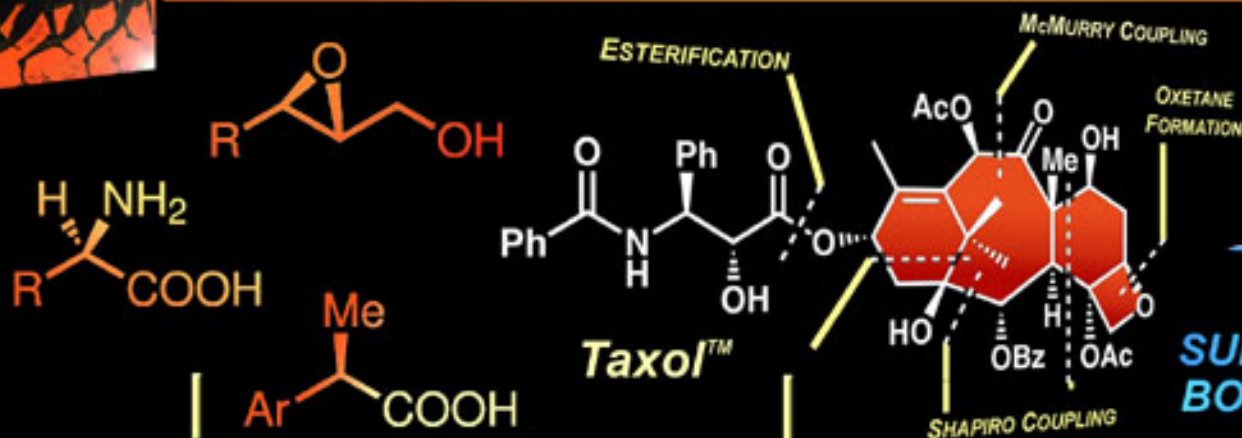
● **GENOMICS**  
● **PROTEOMICS**  
● **BIOLOGICAL SCREENING**

● **FERMENTATION**  
● **GENETIC ENGINEERING**



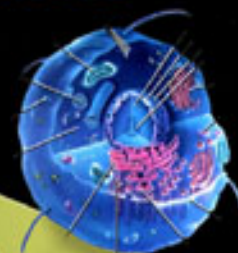


# MOLECULAR COMPLEXITY and CHEMICAL SYNTHESIS



**STRATEGY DESIGN-  
RETROSYNTHETIC  
ANALYSIS**

**SUPRAMOLECULAR  
BOND**



**CHEMICAL  
BUILDING  
BLOCKS**

**COMPLEX  
MOLECULES**

**SUPRA-  
MOLECULAR  
ASSEMBLIES**

**CELLS,  
ORGANISMS**

**NATURAL OR DESIGNED**

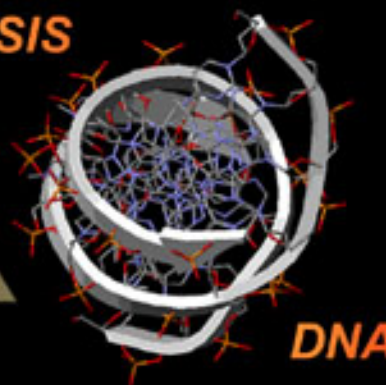
**COVALENT BOND**

**SYNTHETIC  
METHODOLOGY**

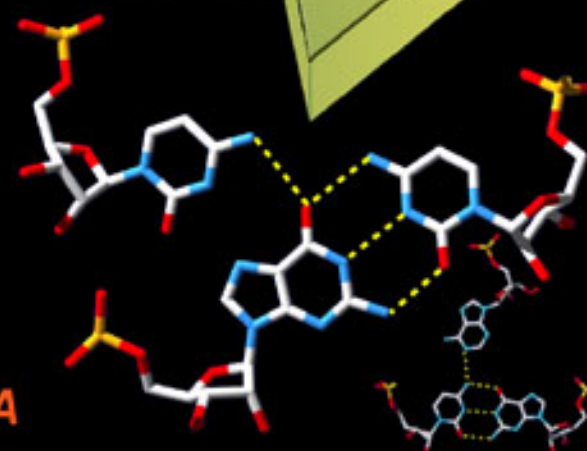
**TOTAL SYNTHESIS**

|                                                     |  |  |  |  |  |  |  |  |  |                                                   |  |  |  |  |  |  |  |  |  |
|-----------------------------------------------------|--|--|--|--|--|--|--|--|--|---------------------------------------------------|--|--|--|--|--|--|--|--|--|
|                                                     |  |  |  |  |  |  |  |  |  | H He                                              |  |  |  |  |  |  |  |  |  |
| K Ca Sc Ti V Cr Mn Fe Co Ni Cu Zn Ga Ge As Se Br Kr |  |  |  |  |  |  |  |  |  | Rb Sr Y Zr Nb Mo Ru Rh Pd Ag Cd In Sn Sb Te I Xe  |  |  |  |  |  |  |  |  |  |
| Cs Ba La Ce Pr Nd Pm Sm Eu Gd Tb Dy Ho Er Tm Yb Lu  |  |  |  |  |  |  |  |  |  | Fr Ra Ac Th Pa U Np Pu Am Cm Bk Cf Es Fm Md No Lr |  |  |  |  |  |  |  |  |  |
| Fr Ra Ac Th Pa U Np Pu Am Cm Bk Cf Es Fm Md No Lr   |  |  |  |  |  |  |  |  |  | Fr Ra Ac Th Pa U Np Pu Am Cm Bk Cf Es Fm Md No Lr |  |  |  |  |  |  |  |  |  |

**THE ELEMENTS**



**DNA**

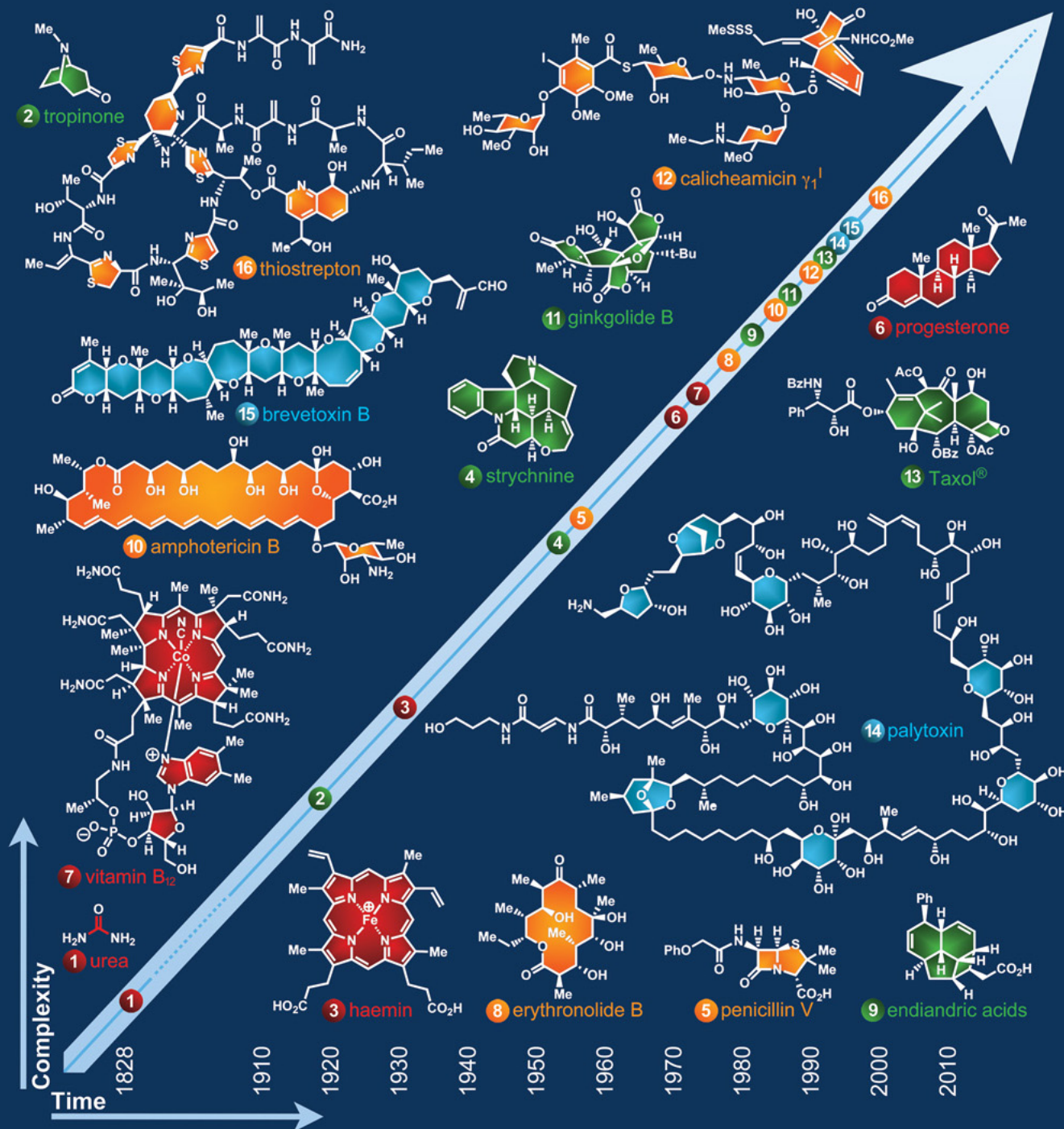


COMYCIN

ALICHEA

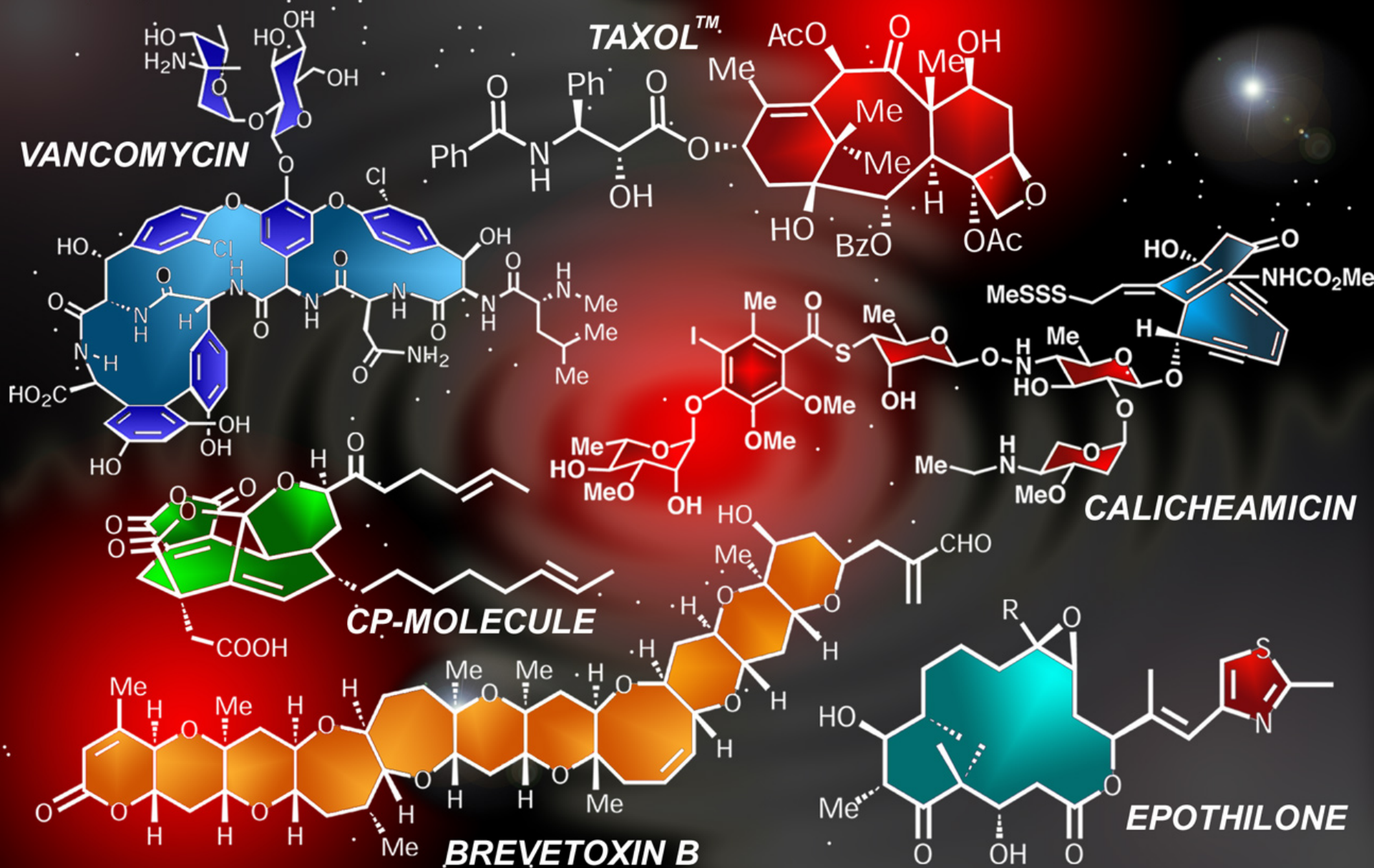
ALICHEA

EPOTHIL





# Molecular Size, Complexity and Diversity





## ***Synthesis and the Molecule in Perspective***

---



- The advent of *organic synthesis* coupled with the discovery of the *molecule* in the 19<sup>th</sup> century is one of the most profound scientific developments of all time.
  - These discoveries set in motion a revolution that shaped the landscape of the molecular sciences and changed the world.
  - The atomic-molecular theory of matter and the art and science of synthesis provided the foundation for understanding and shaping nature at the molecular level.
-





# **THE ESSENCE AND IMPACT OF TOTAL SYNTHESIS**

- **Rendering Scarce Natural Products Readily Available for Biological Investigations**
  - **Providing Opportunities for Discovery and Invention of New Synthetic Methods and Strategies**
  - **Opening Access to Otherwise Inaccessible Natural Product Analogs for Biological Evaluation**
  - **Structural Elucidation of Natural Products – Assigning Absolute Configurations and Revising Wrongly Assigned Structures**
  - **For Advancing the Art of Total Synthesis for its Own Sake and for the Excitement it Provides**
- 
- **Synthesis Provides the Foundation for the Pharmaceutical, Biotechnology, Material, and Nanotechnology Industries**
  - **The Condition of the Art of Total Synthesis Reflects the State of Synthesis in General, and Symbolizes its Power at Any Given Time**
-



## THE ART OF TOTAL SYNTHESIS

---



**“The gift of original melody, as it is called is rare and precious. The possessor of it is justly considered a genius. But no melody could possibly speak to us except a combination of perfectly well known elements. The only originality is in their assimilation and reproduction.”**

**J. P. Mahaffy, 1910**

---

J. P. Mahaffy, *What Have the Greeks Done for Modern Civilisation*, G. P. Putnam's Sons, New York, 1910, pp. 214–215, 246–247. \*see Alfred, Lord Tennyson, “Locksley Hall” 1835.





## CATALYSIS AND LIGANDS: THE NOTES THAT MAKE THE MELODY



### ● CATALYSIS IN TOTAL SYNTHESIS

#### ● ELEGANCE AND EFFICIENCY

---

|                         |   |                          |
|-------------------------|---|--------------------------|
| ● Endiandric Acids      | → | ● No Catalysis           |
| ● Coleophomones B and C | → | ● Ruthenium Catalysis    |
| ● Platensimycin         | → | ● Rhodium Catalysis      |
| ● Platensin             | → | ● Cobalt Catalysis       |
|                         | → | ● Gold Catalysis         |
| ● Biyouyanagin A        | → | ● Organocatalysis, Light |
|                         | → | ● Palladium Catalysis    |
| ● Sporolide B           | → | ● Ruthenium Catalysis    |
| ● Antibiotic BE-43472B  | → | ● Palladium Catalysis    |
| ● Maitotoxin            | → | ● Ruthenium Catalysis    |
| ● Vannusal B            | → | ● Enzymatic Catalysis    |

#### ● Ligands that lead to new reactivity and improve reactions

---

- CASCADE REACTIONS IN TOTAL SYNTHESIS
  - LIGHT AND HEAT IN TOTAL SYNTHESIS
  - ECONOMY AND GREEN CHEMISTRY
-



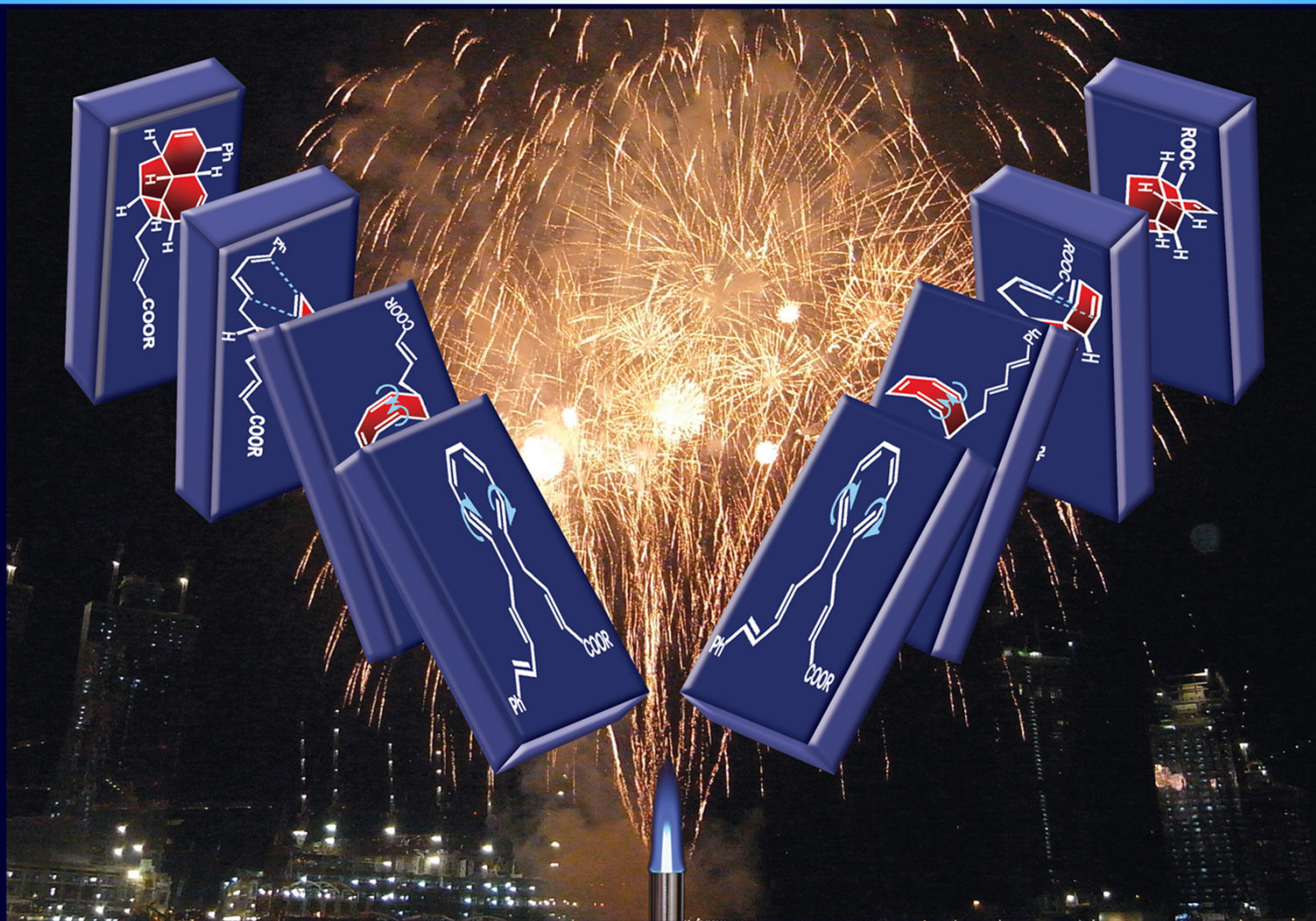
# CASCADE REACTIONS IN TOTAL SYNTHESIS



- <sup>1</sup>Cascade Reactions in Total Synthesis, K.C. Nicolaou, D.J. Edmonds, P.G. Bulger, *Angew. Chem. Int. Ed.*, **2006**, 45, 7134.  
<sup>2</sup>Cascade Reactions in Total Synthesis, K.C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551.



# The Art of Total Synthesis Through Cascade Reactions



K. C. Nicolaou and Jason S. Chen, *Chem. Soc. Rev.*, 2009, 38, 2993–3009.

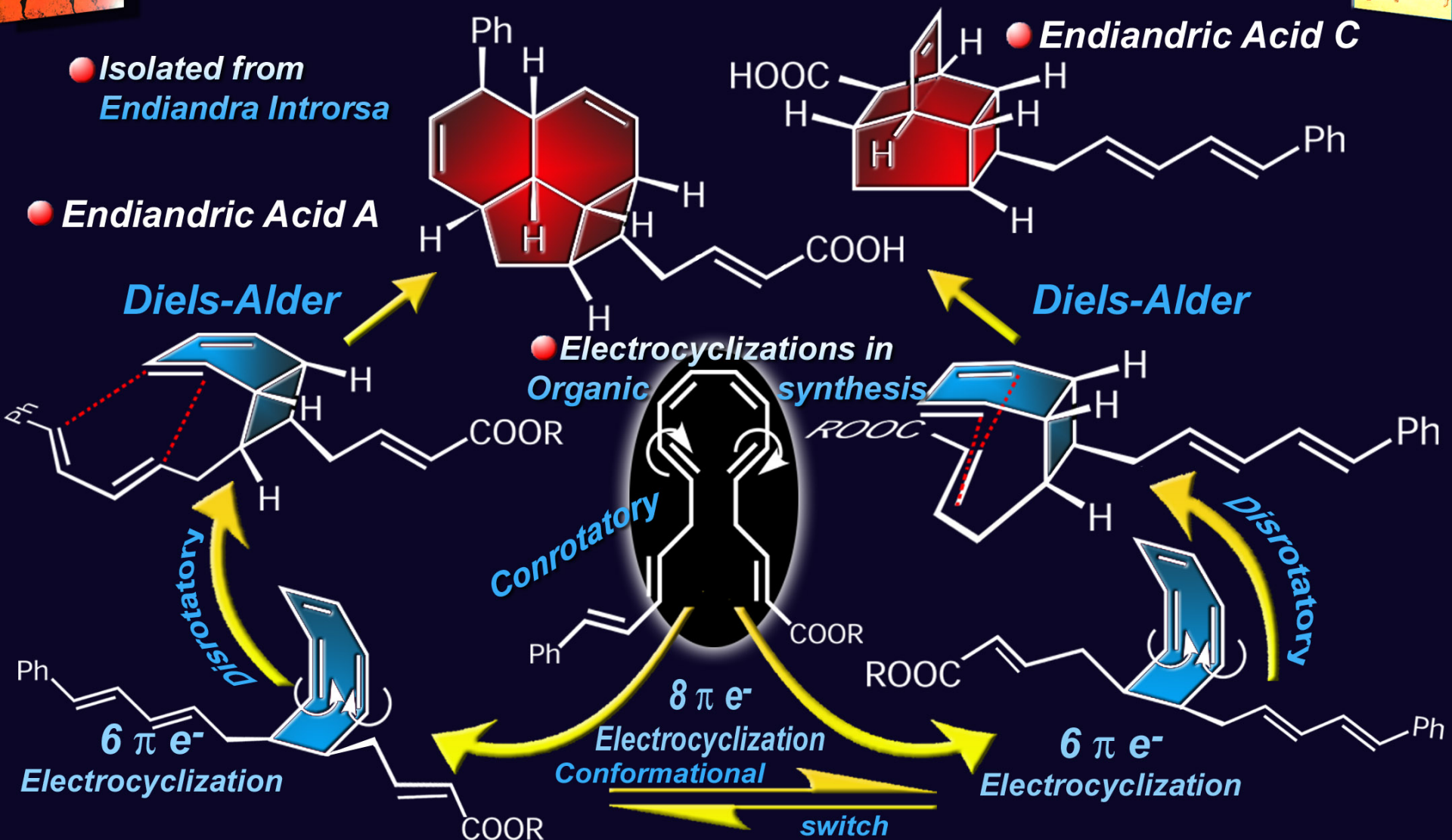


# Biomimetic Total Synthesis of Endiandric Acids A-G [1982]

● Isolated from  
*Endiandra Introrsa*

● Endiandric Acid A

● Endiandric Acid C



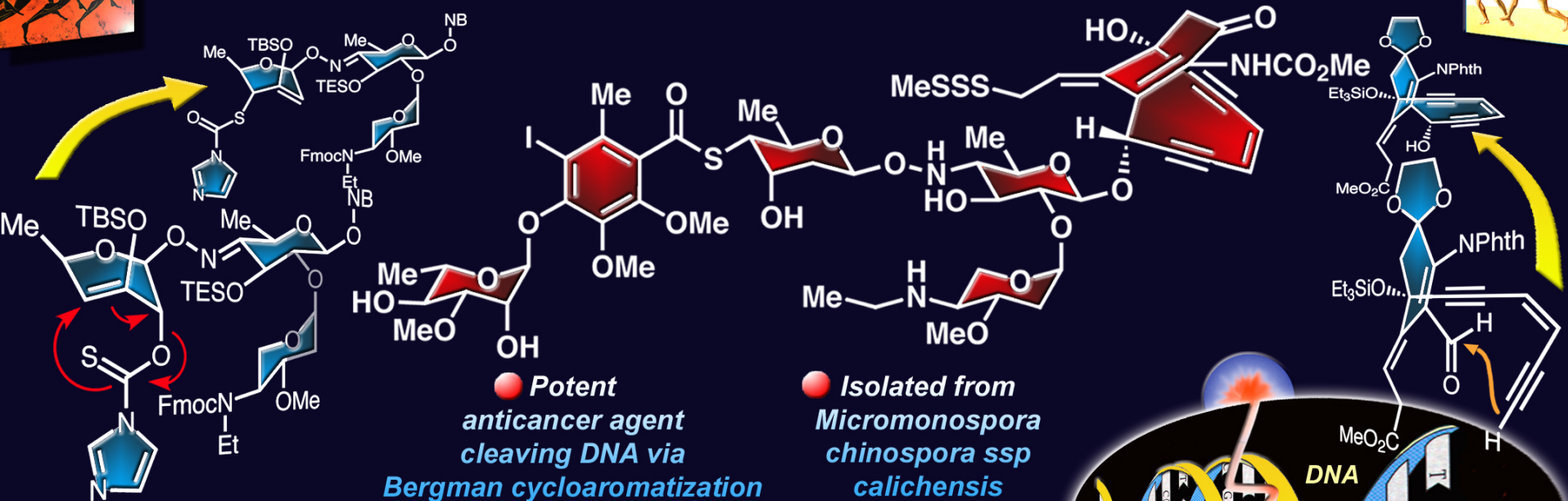
● The Diels-Alder Reaction

● The Woodward-Hoffmann Rules

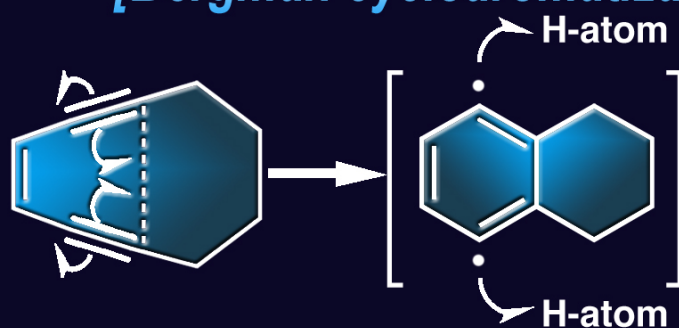
● Cascade Reactions



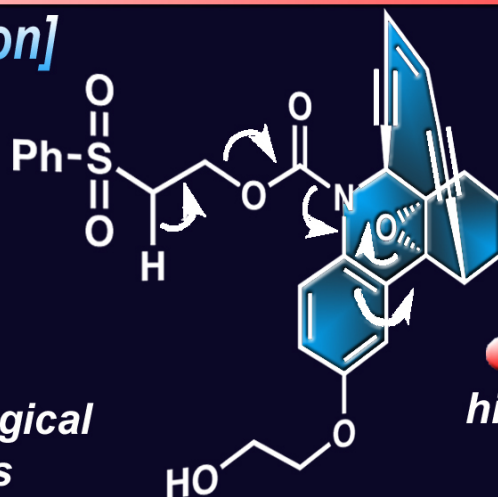
# TOTAL SYNTHESIS OF CALICHEAMICIN $\gamma_1'$ [1992]



## [Bergman cycloaromatization]



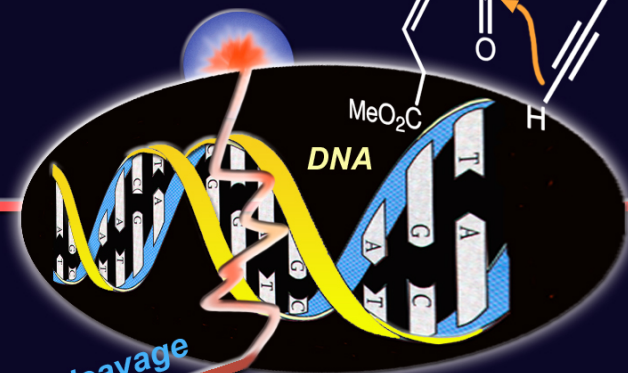
● **Elucidation of chemical and biological properties of cyclic enediynes**



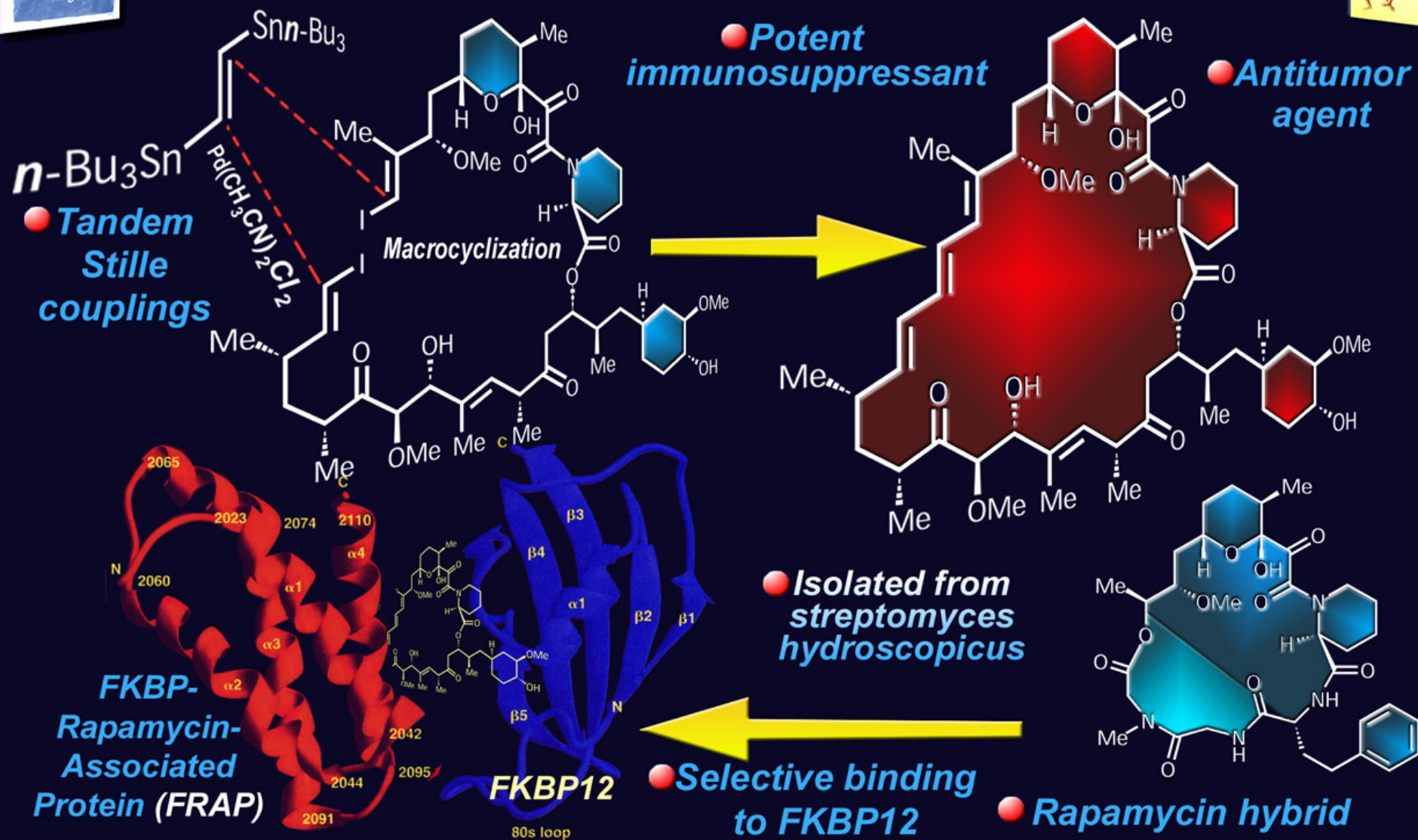
**DNA cleavage**  
**Cell death**

**Double strand cuts**

● **Designed enediynes with highly potent DNA cleaving and antitumor properties**



# TOTAL SYNTHESIS OF RAPAMYCIN [1993]



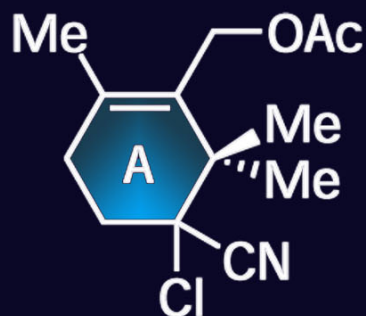




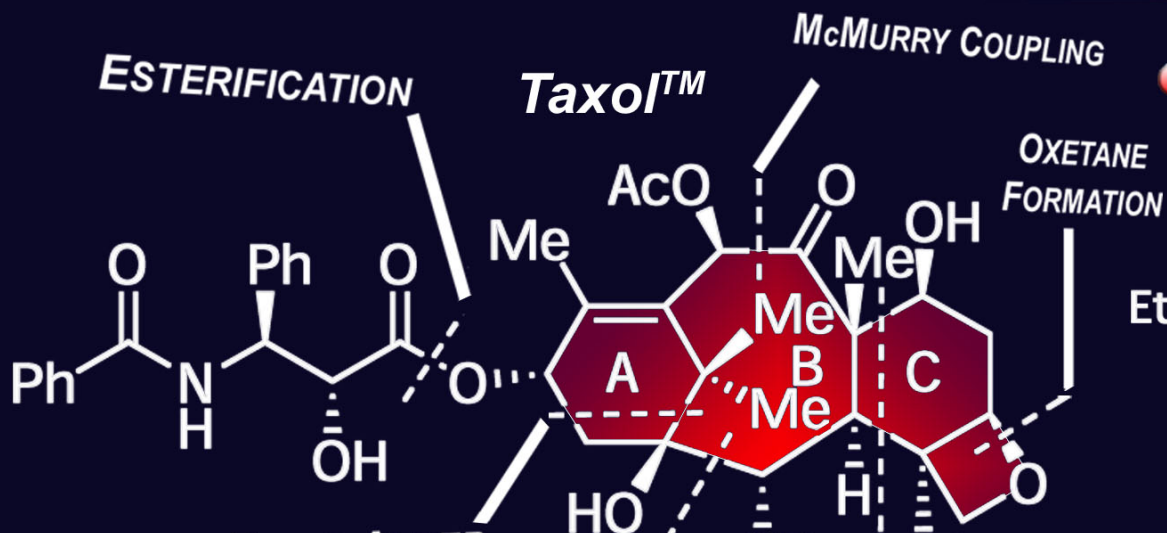
# TOTAL SYNTHESIS OF TAXOL™ [1994]



● Water soluble pro-drugs



ESTERIFICATION

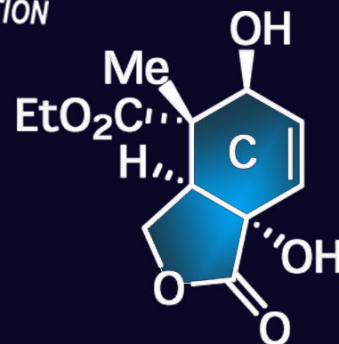


Taxol™

McMURRY COUPLING

● Fluorescent probes

OXETANE FORMATION



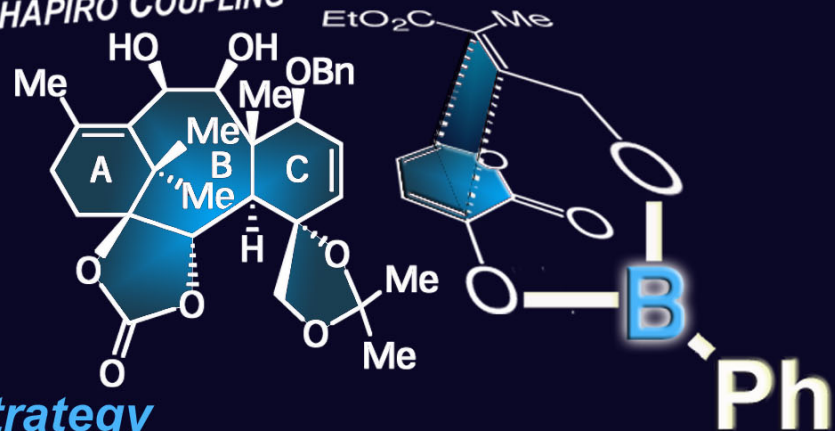
DIELS-ALDER

● Isolated from *Taxus brevifolia*

Convergent strategy

SHAPIRO COUPLING

DIELS-ALDER





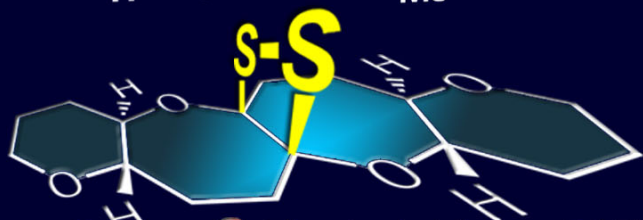
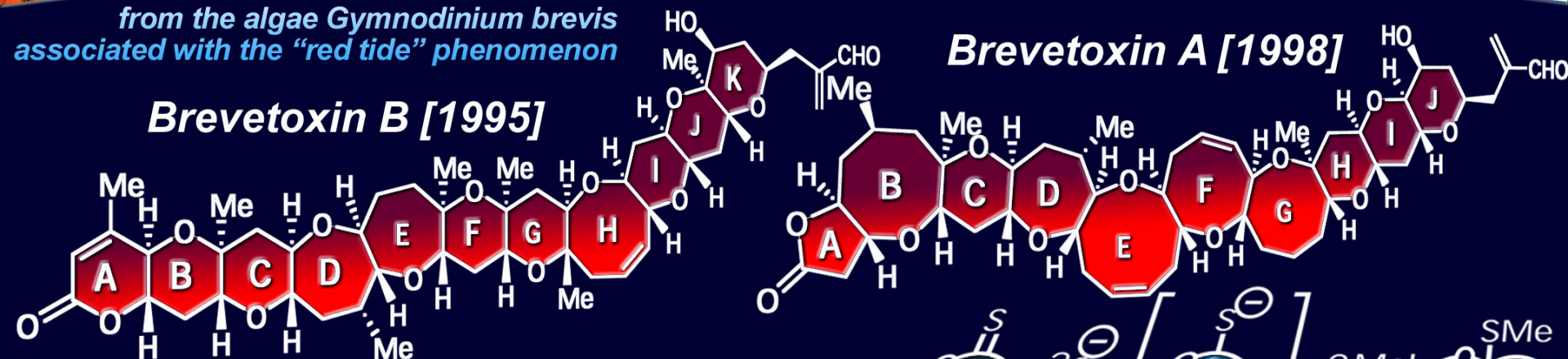
# TOTAL SYNTHESIS OF BREVETOXINS B AND A [1982-1998]



● Marine neurotoxins isolated from the algae *Gymnodinium brevis* associated with the "red tide" phenomenon

## Brevetoxin B [1995]

## Brevetoxin A [1998]

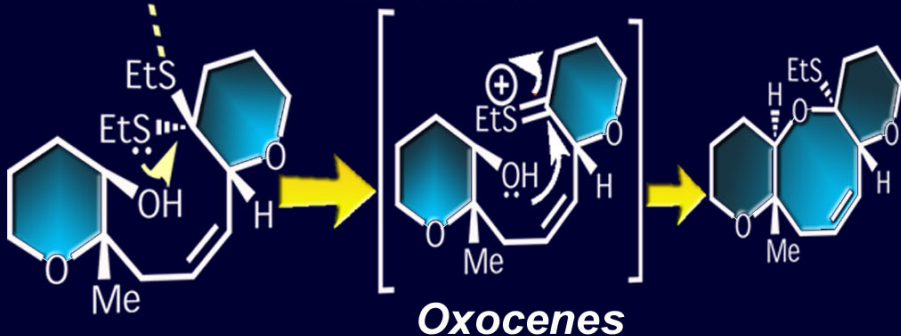


● First stable dithietane

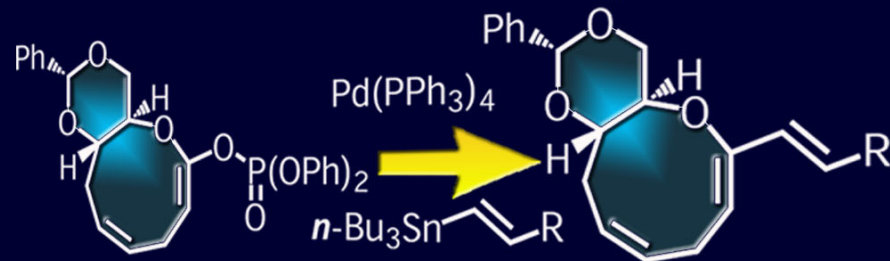
● New synthetic technologies



● Macrocycles to bicycles



Oxocenes



Palladium-catalyzed couplings





# CHEMICAL SYNTHESIS AND BIOLOGY OF EPOTHILONES [1996-2003]



● Isolated from myxobacterium *sorangium cellulosum* strain ce90

● Potent anticancer agents

● Tubulin polymerization/  
microtubule stabilization

● Designed Epothilones

● Subnanomolar potencies

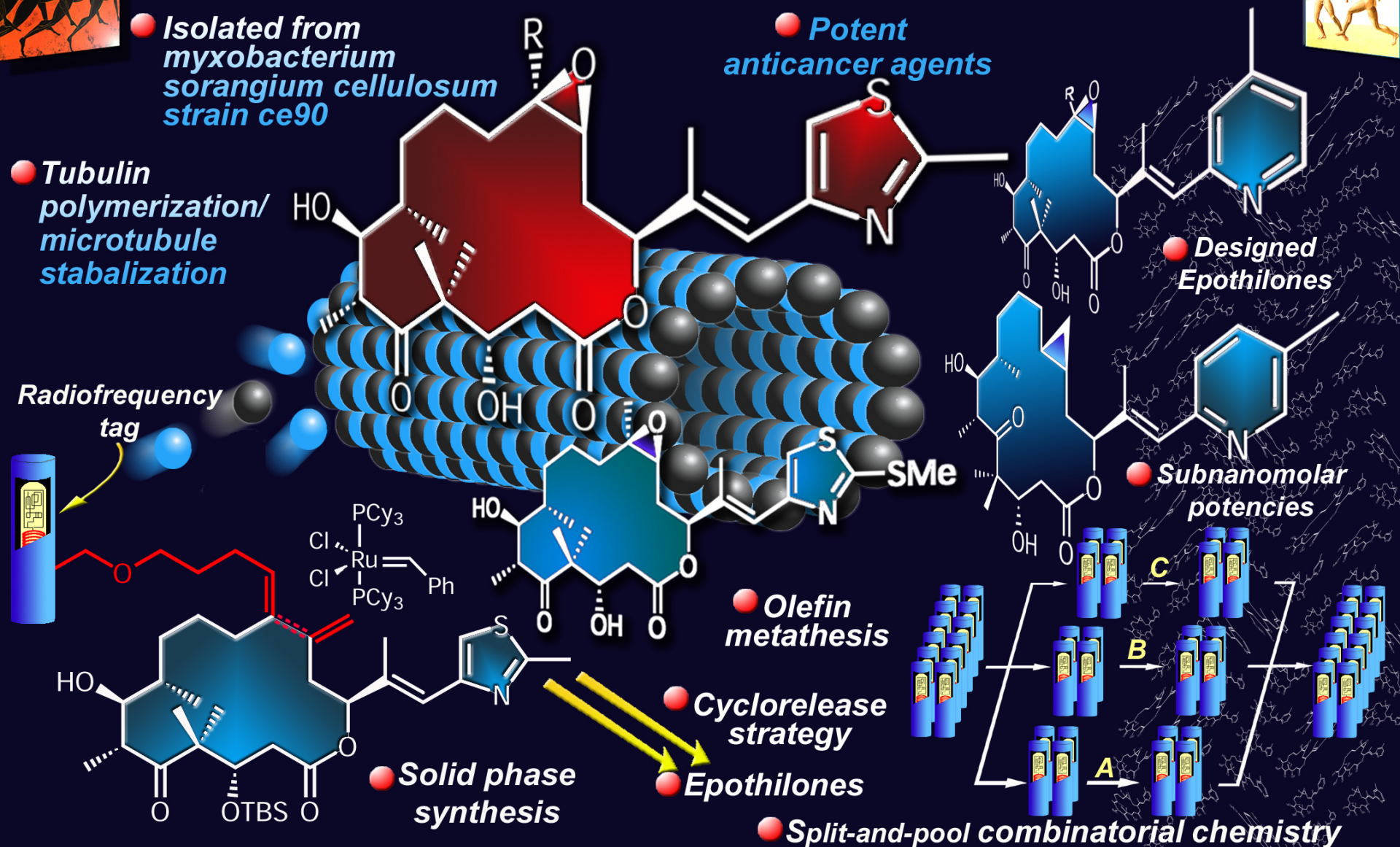
● Olefin metathesis

● Cyclorelease strategy

● Solid phase synthesis

● Epothilones

● Split-and-pool combinatorial chemistry



# TOTAL SYNTHESIS AND CHEMICAL BIOLOGY OF VANCOMYCIN [1998-2002]



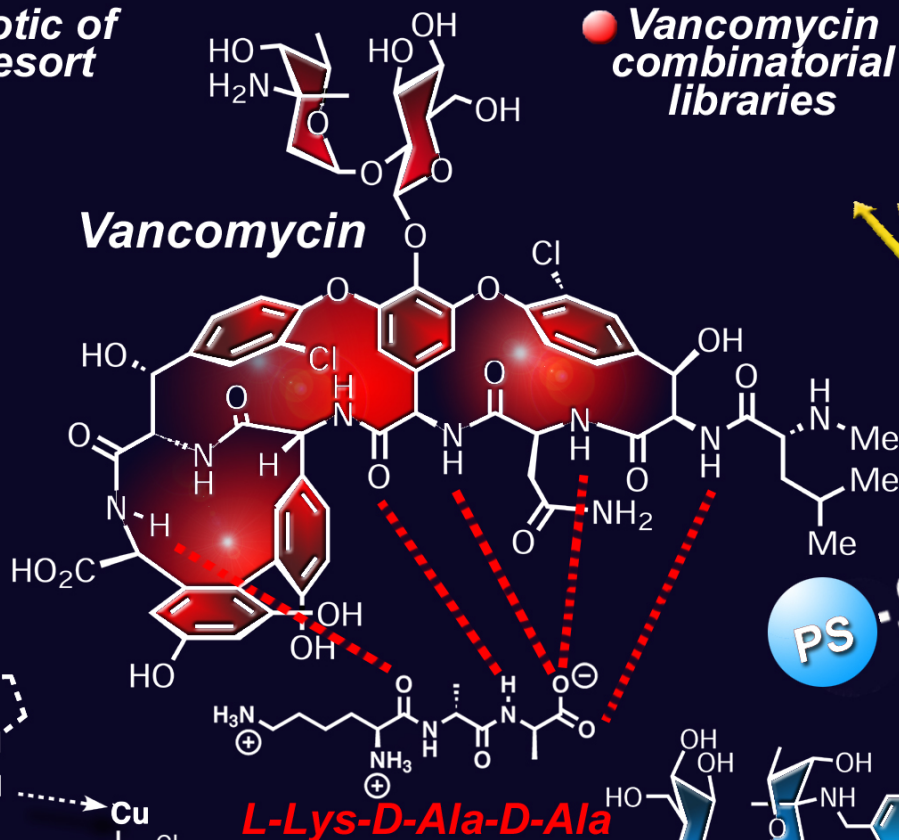
● **Antibiotic of last resort**

● **Vancomycin combinatorial libraries**

● **Isolated from the Actinomycete *amycolatopsis orientalis***

● **Clinically used antibiotic active against drug-resistant bacteria**

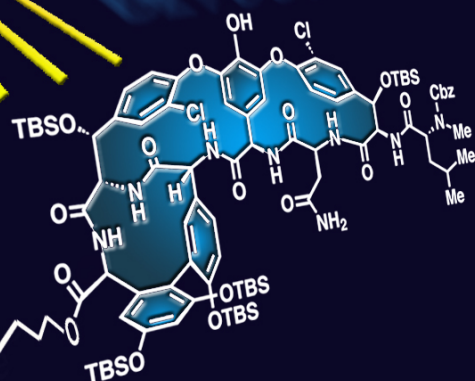
**Vancomycin**



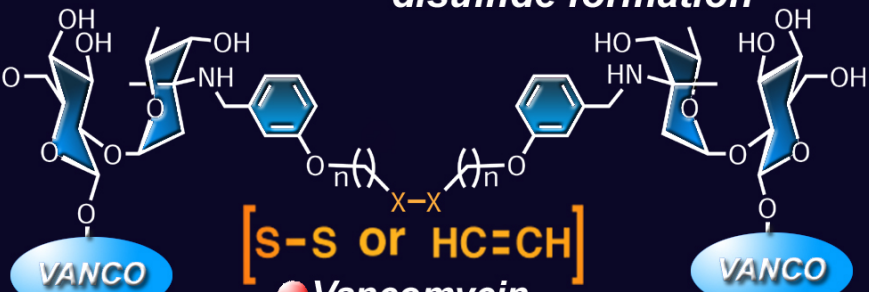
**L-Lys-D-Ala-D-Ala**

● **Target-accelerated combinatorial synthesis**

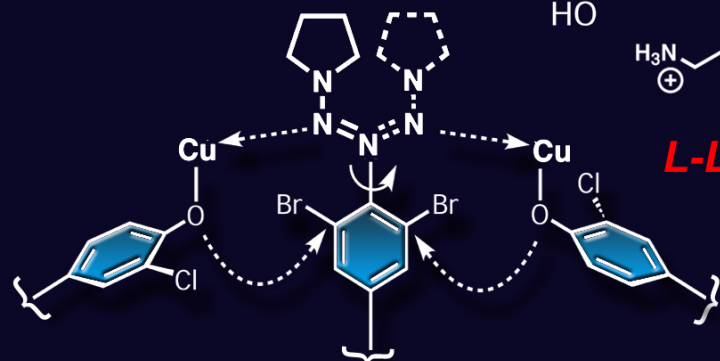
DEPROTECTIONS  
CLEAVAGE  
GLYCOSIDATIONS



● **Olefin metathesis or disulfide formation**



● **Vancomycin dimers with highly potent activity against vancomycin-resistant bacteria [MIC 0.25  $\mu\text{g/mL}$ ]**



● **Development of triazene-driven bisaryl ether formation**





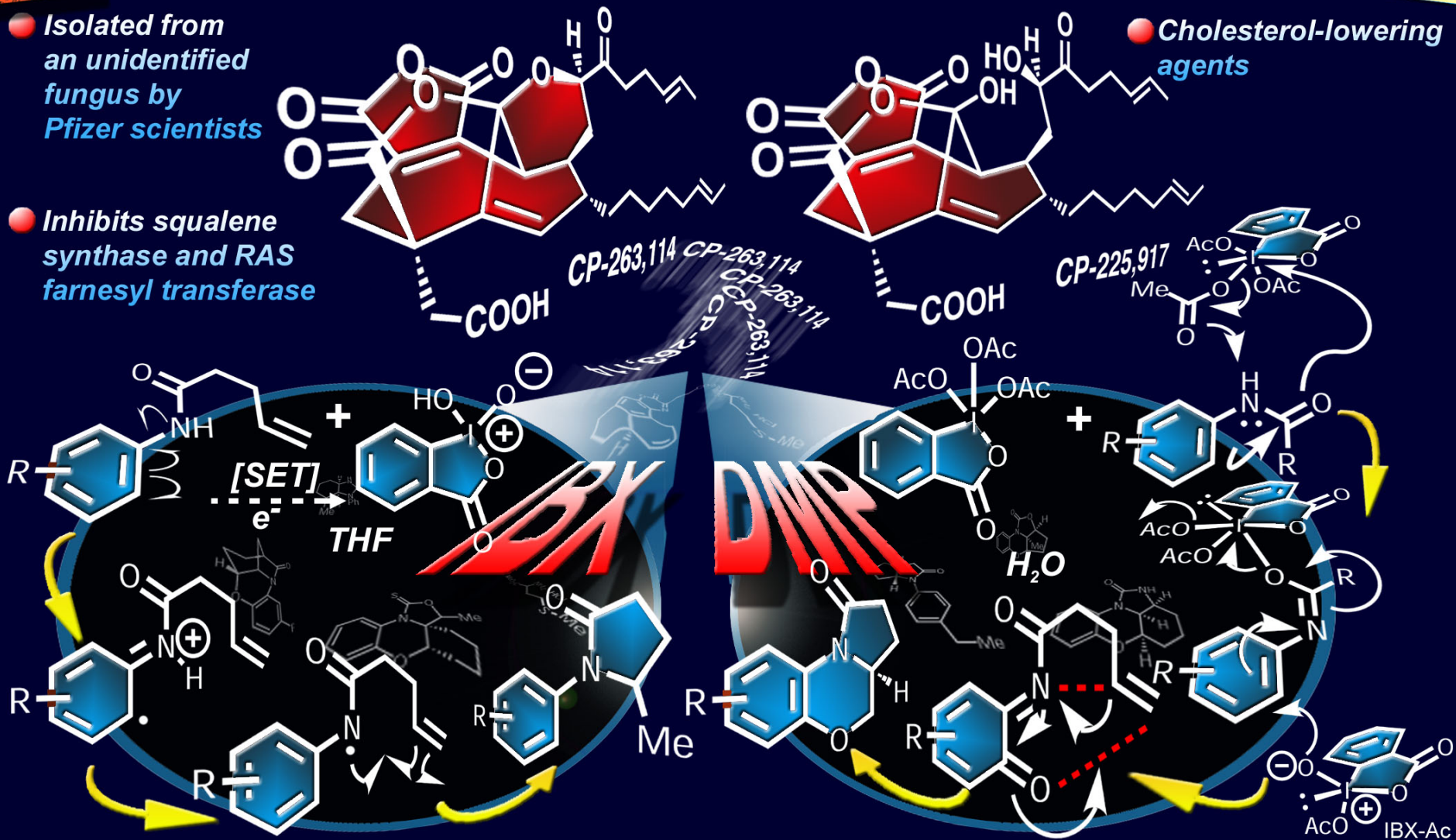
# TOTAL SYNTHESIS OF THE CP MOLECULES [1999]



● Isolated from an unidentified fungus by Pfizer scientists

● Inhibits squalene synthase and RAS farnesyl transferase

● Cholesterol-lowering agents





# TOTAL SYNTHESIS OF COLEOPHOMONES B AND C [2002]



● From fungi *Stachybothys cylindrospora* RF-5900

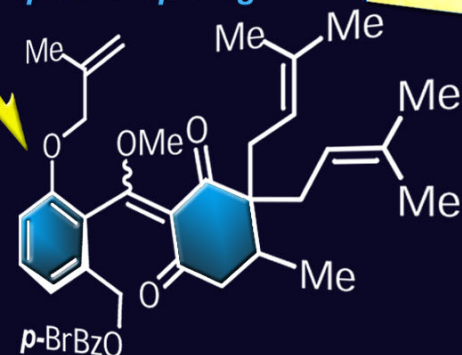
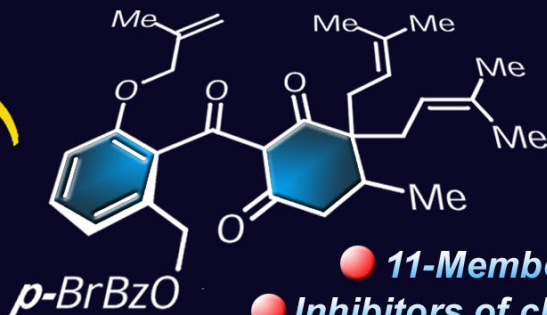
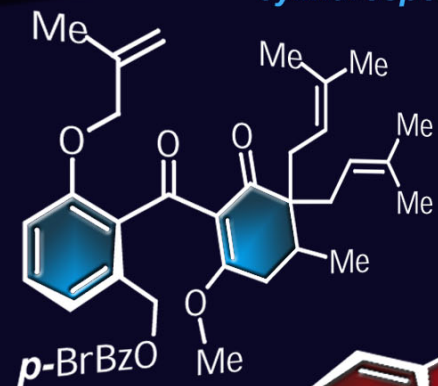
● From *Coleophoma* sp fungi

$\text{CH}_2\text{N}_2$

$\text{CH}_2\text{N}_2$

● 11-Membered rings

● Inhibitors of chymase



CATALYST  
Stereoselective  
ring closing  
metathesis

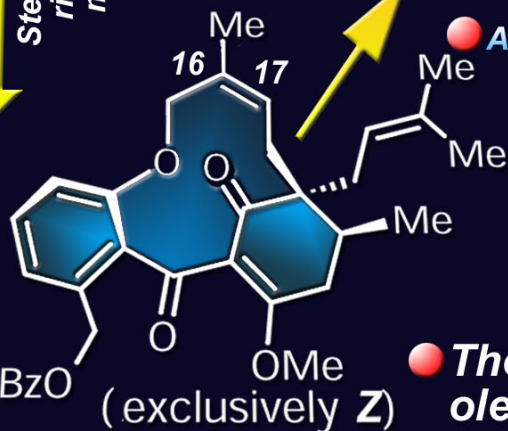
CATALYST  
Stereoselective  
ring closing  
metathesis

COLEOPHOMONE C

COLEOPHOMONE B

● Antibiotics

● Antifungal



CATALYST  
CATALYST

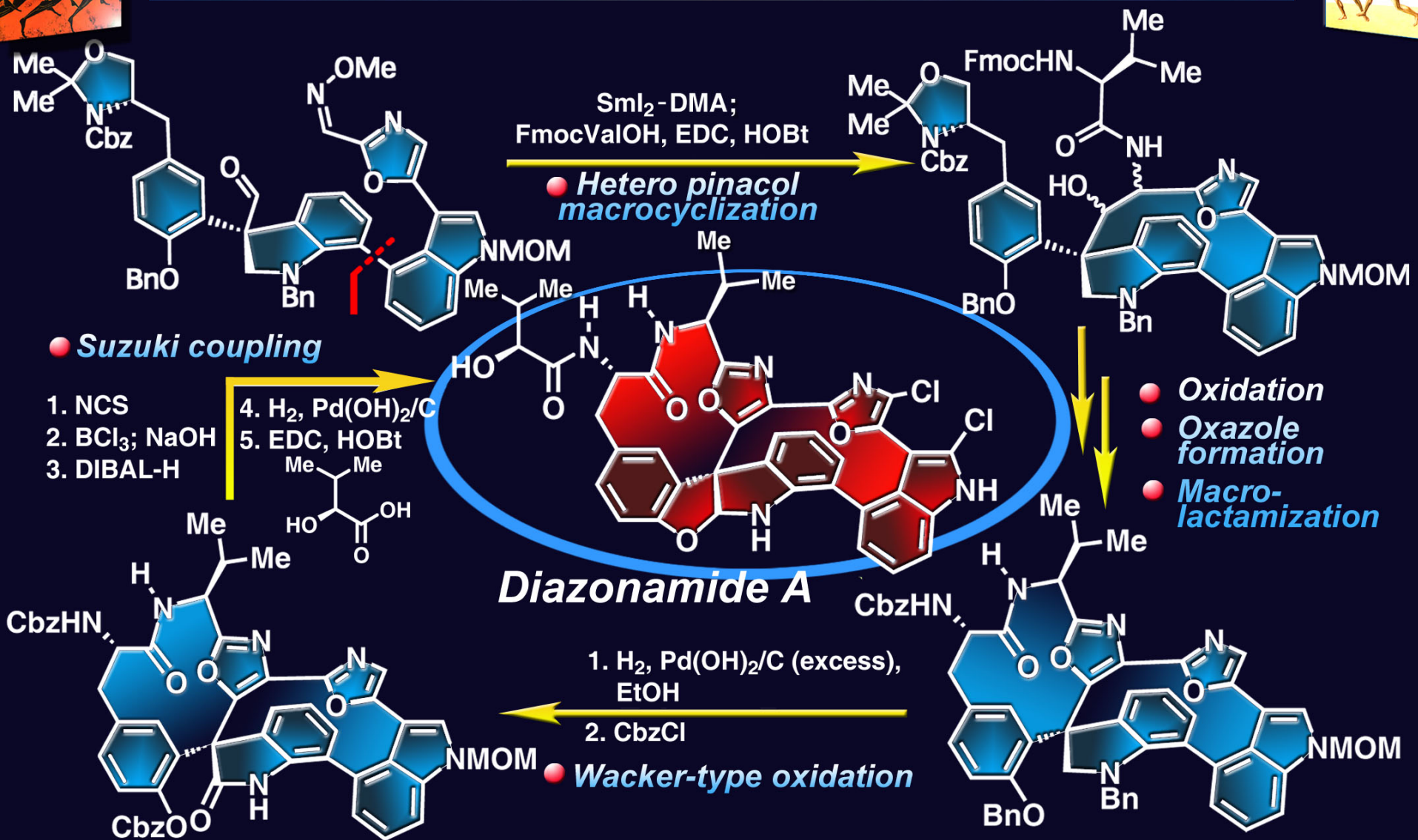
● The magic of the  
olefin metathesis reaction







# THE $\text{SmI}_2$ ROUTE TO DIAZONAMIDE A [2003]





# THIOSTREPTON: X-RAY STRUCTURE [2004]



FROM  
*STREPTOMYCES*  
*AZUREUS*

DEHYDROPIPERIDINE

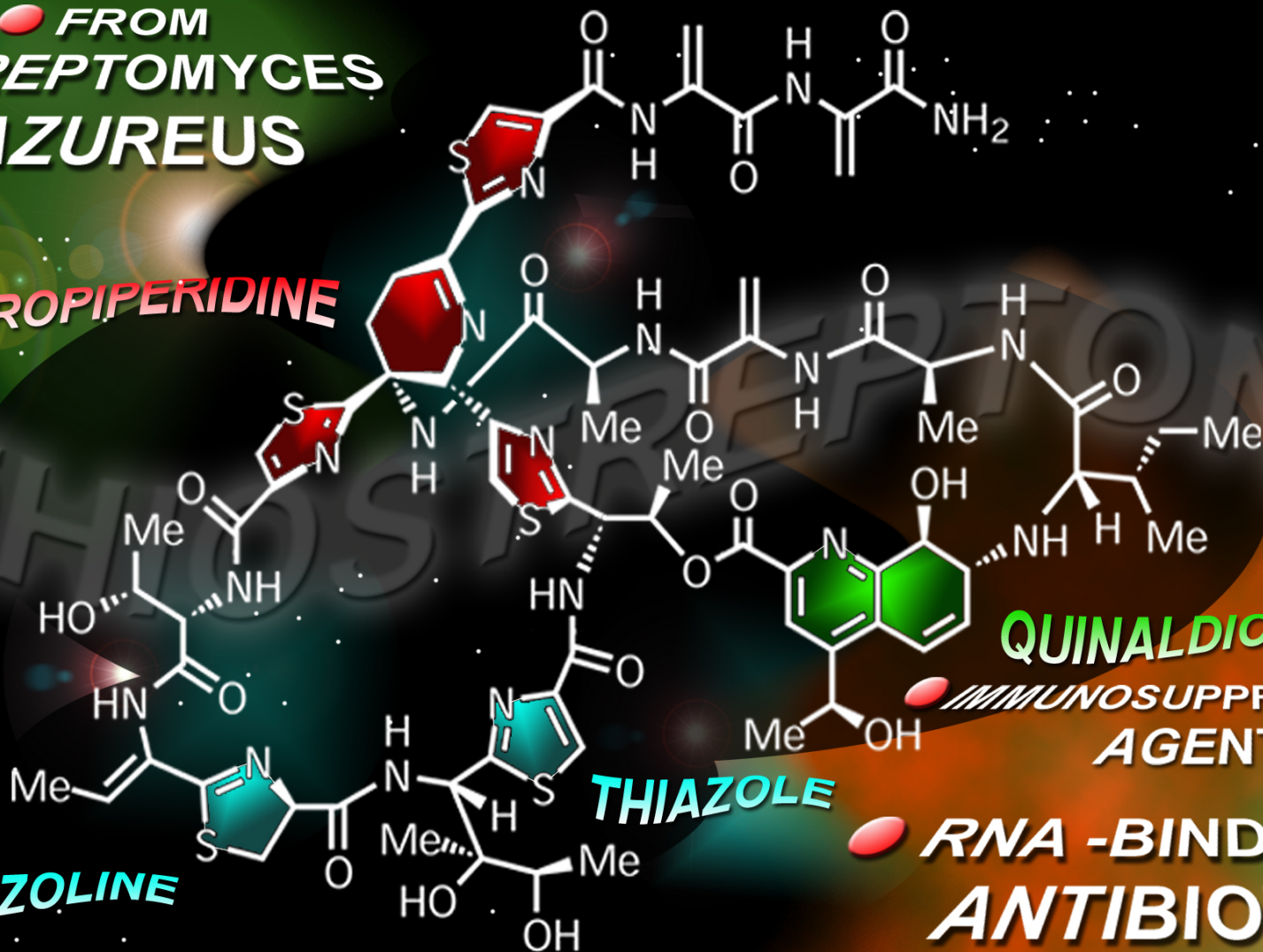
THIAZOLINE

THIAZOLE

QUINALDIC ACID

IMMUNOSUPPRESSIVE  
AGENT

RNA-BINDING  
ANTIBIOTIC







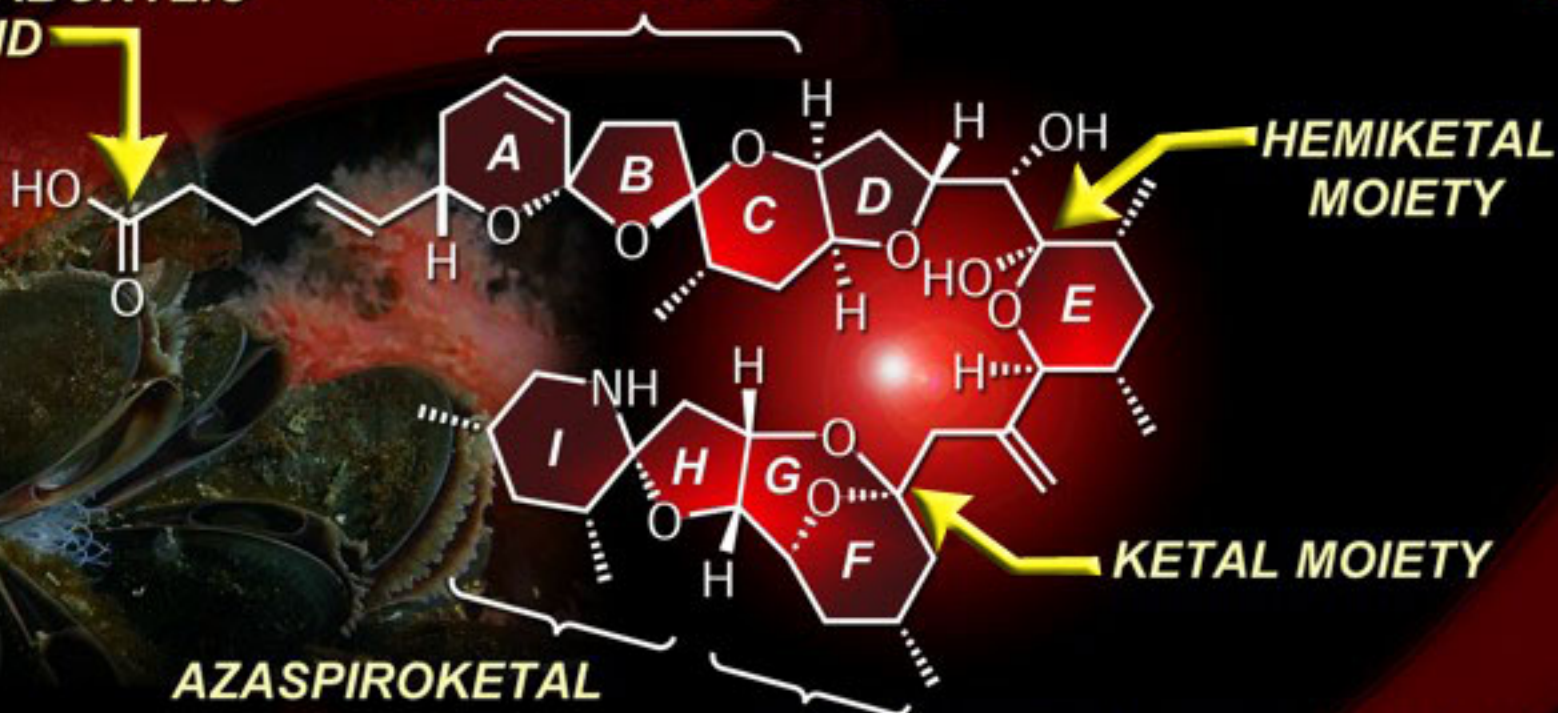


# AZASPIRACID-1: PROPOSED STRUCTURE (1998)



CARBOXYLIC  
ACID

TRIOXADISPIROKETAL



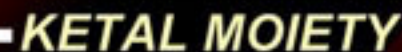
AZASPIROKETAL

2,9-DIOXACYCLO[3.3.1]NONANE

- Architecturally complex marine neurotoxin.
- Azaspiracid syndrome declared in 1998.
- Isolated from mussels *Mytilus edulis* cultivated in Killary Harbour, Ireland.
- People in Netherlands became ill after ingestion, symptoms included vomiting, severe diarrhea.
- Unprecedented molecular framework with nine rings and twenty stereocenters.
- The absolute stereochemistry and relative stereochemistry between the ABCDE and FGHI domains remain unknown.

Satake, M.; Ofuji, K.; Naoki, H.; James, K.J.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. J. Am. Chem. Soc. 1998. 120. 9967.

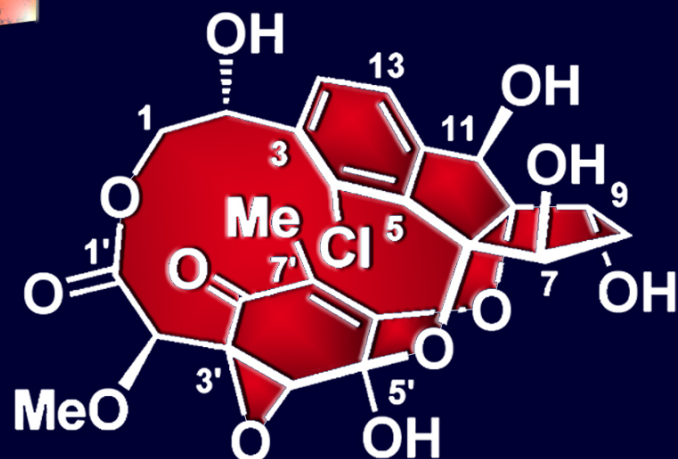


A small, square photograph showing two runners in a race. They are wearing athletic gear and are captured in motion, with one runner slightly ahead of the other. The background is blurred, suggesting speed.

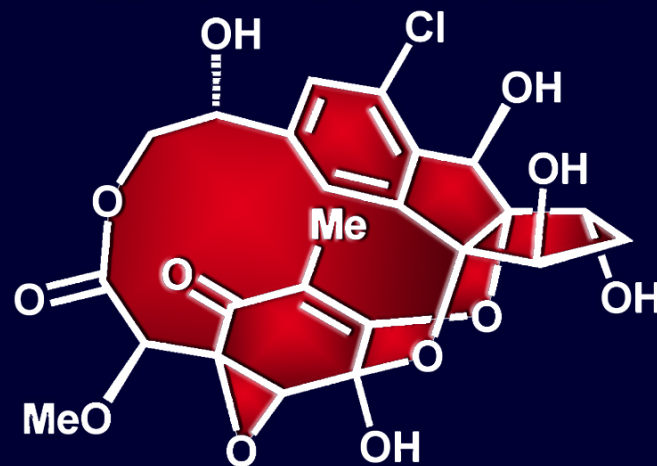
le Killary Harbour, Ireland.  
symptoms included vomiting, severe diarrhea.  
ings and twenty stereocenters.  
biochemistry between the ABCDE and FGHI



## MOLECULAR STRUCTURES OF SPOROLIDES A AND B [2005]

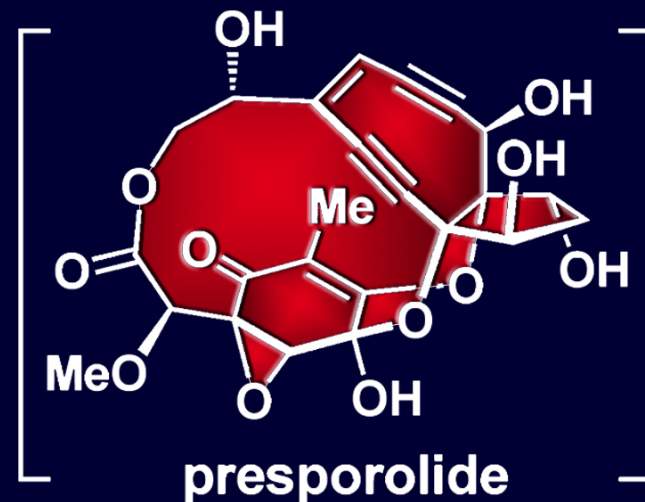


**sporolide A**



**sporolide B**

- Isolated from the marine actinomycete *Salinospora tropica* [Fenical and coworkers, *Org. Lett.* 2005, 7, 2731.]
- Proposed metabolite of an, as yet unidentified, enediyne natural product [presporolide, *Proc. Natl. Acad. Sci.* 2007, 104, 10376.]
- Novel molecular architecture
- Unknown biological activities

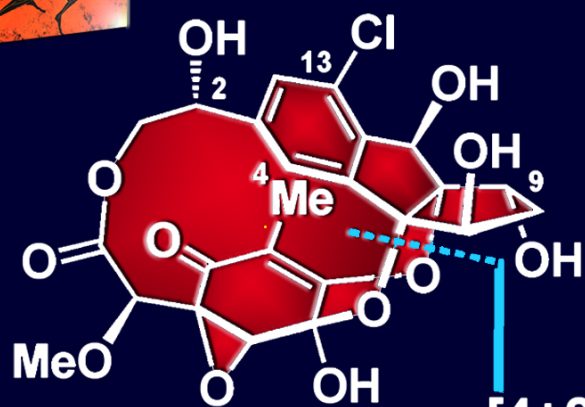


**presporolide**



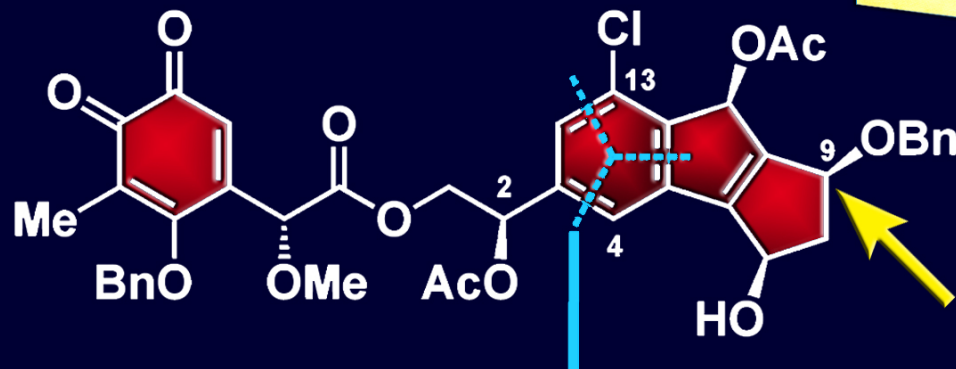


# SPOROLIDE B 1. RETROSYNTHETIC ANALYSIS [2009]

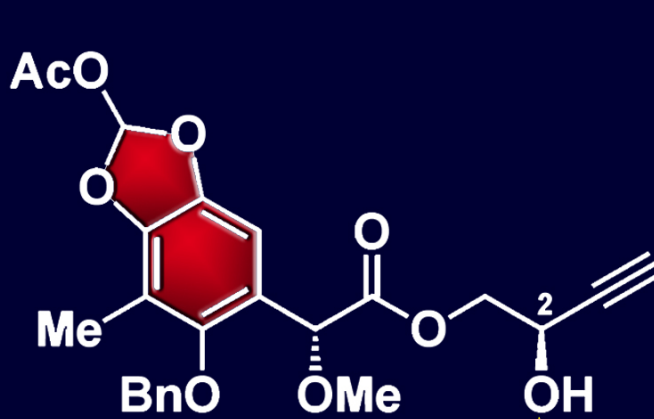


sporolide B

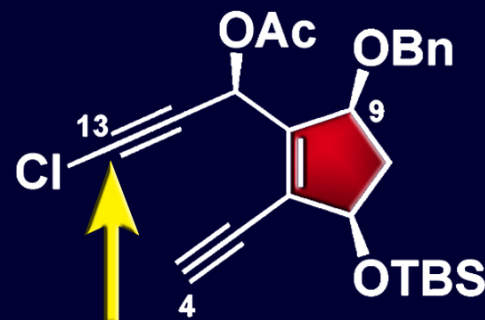
[4+2] cycloaddition  
[thermal]



[2+2+2] cycloaddition  
[Ru-catalyzed]



B



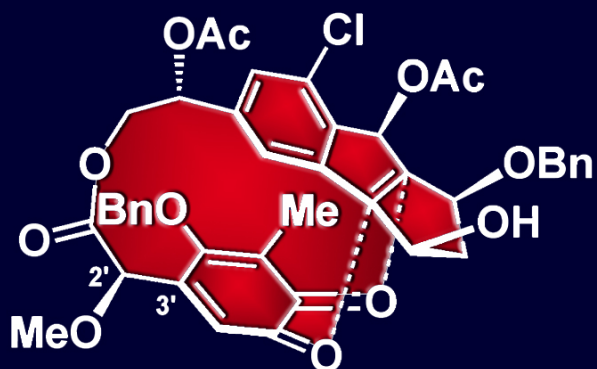
A

## NOTE

- C-9 inversion to avoid steric congestion
- C-13 regiochemistry
- Free C-2 OH to facilitate [2+2+2] cycloaddition

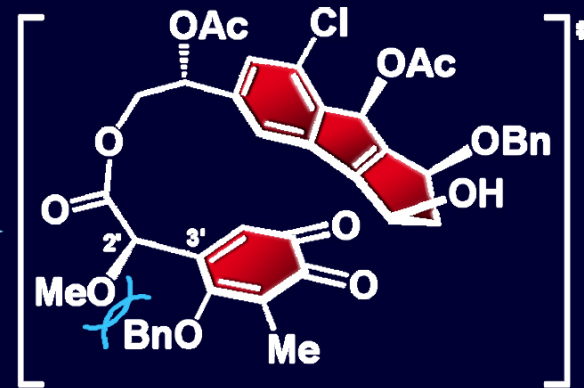
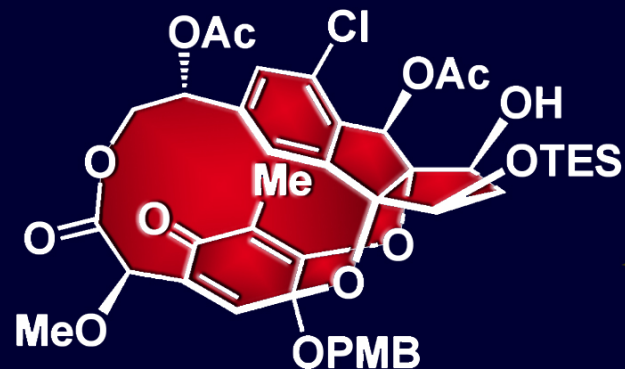


# SPOROLIDE B 7. [4+2] CYCLOADDITION [2009]

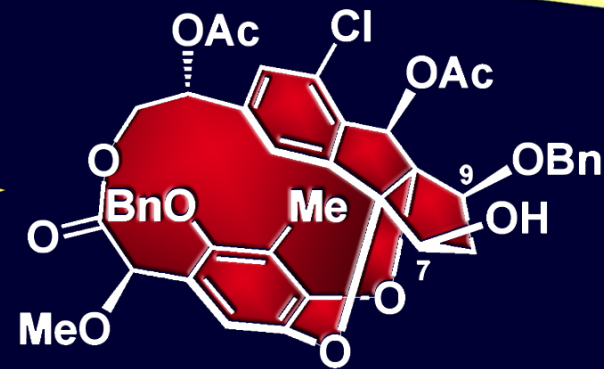


pre-organized o-quinone

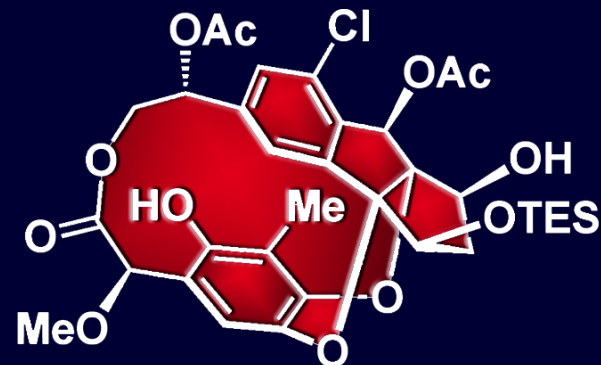
1,3-allylic strain →



$\text{PhI}(\text{OCOCF}_3)_2$ ,  
PMBOH (75%)

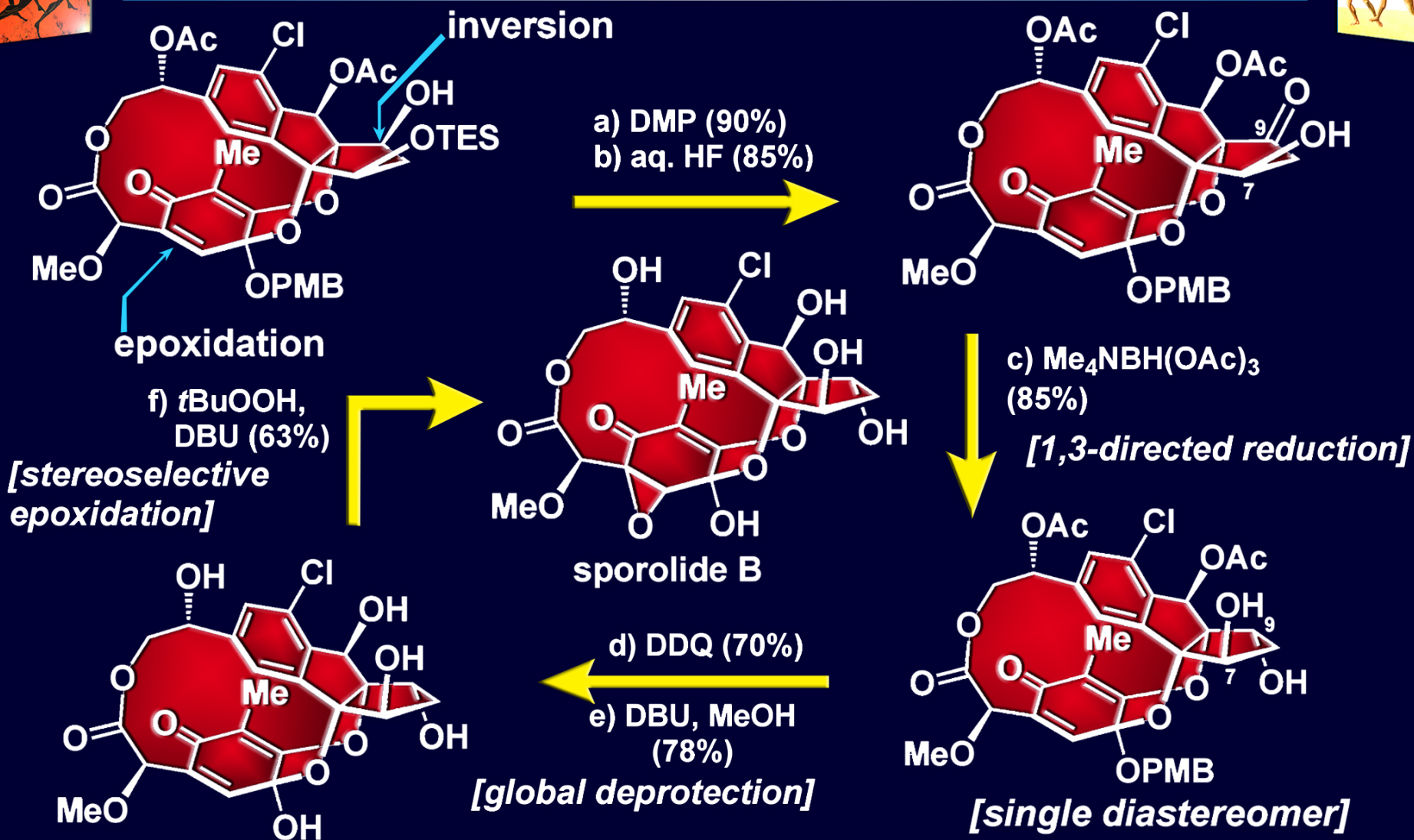


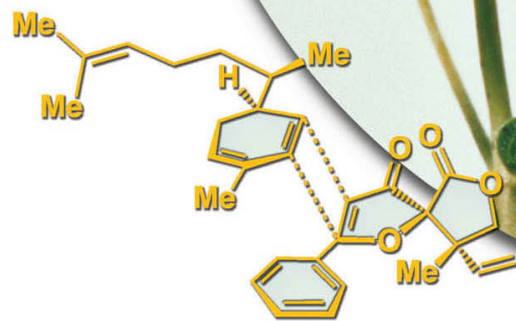
1. TESOTf (95%)  
2.  $\text{H}_2$ ,  $\text{Pd}(\text{OH})_2$  (92%)  
[debenzylation]



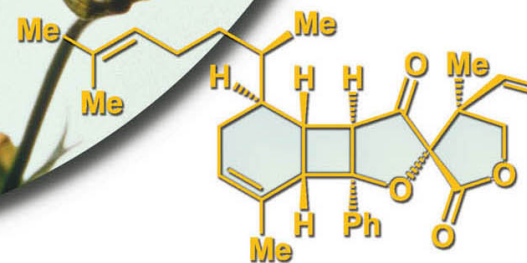


# SPOROLIDE B 8. C-9 INVERSION AND EPOXIDATION [2009]





$h\nu$







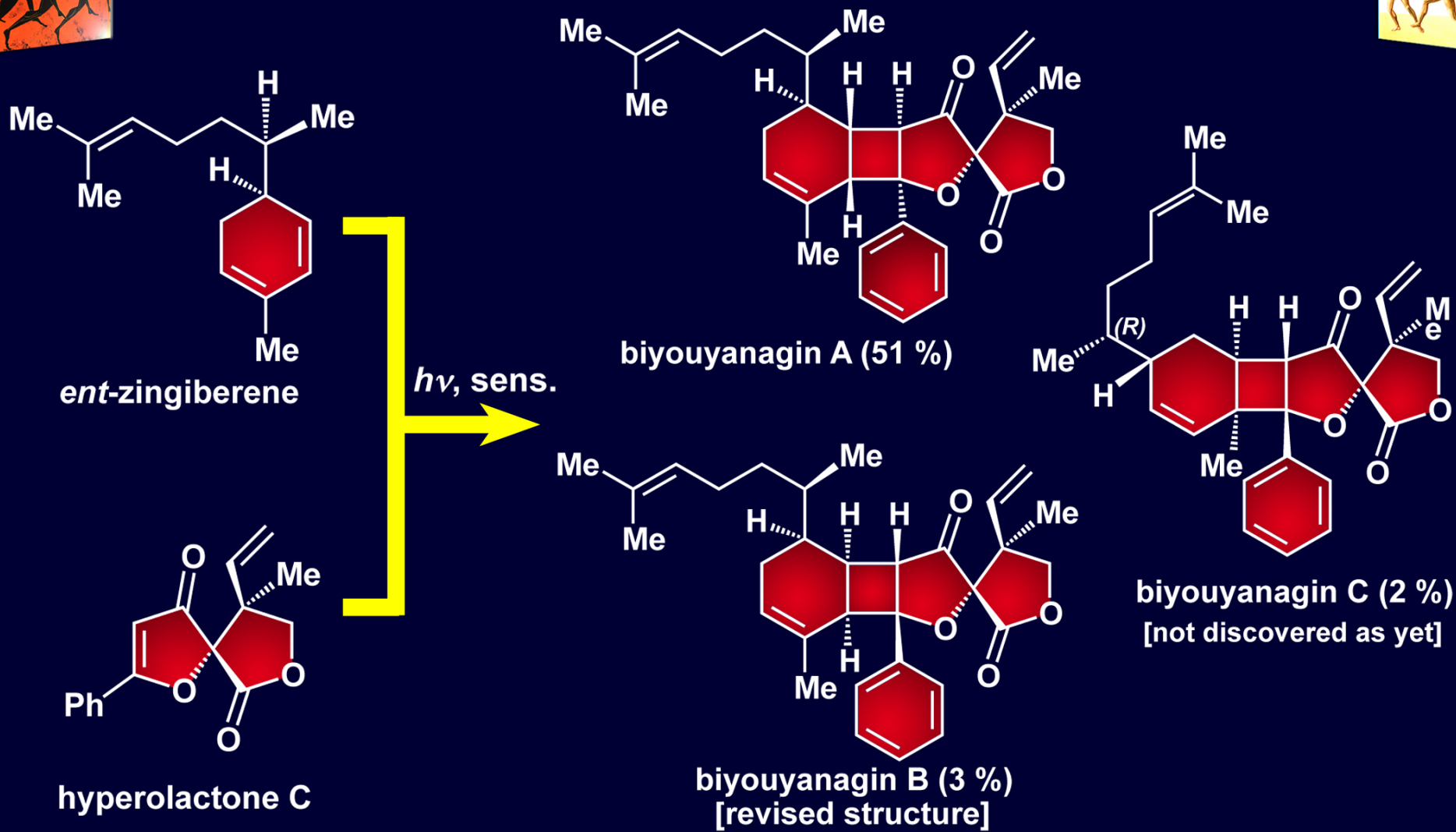
- Isolated from the leaves of *H. chinense* L. var. *salicifolium*, a *Hypericum* species
- Active against HIV ( $EC_{50}$  = 0.798  $\mu$ g/mL, infected H9 lymphocytes)
- Cytokine production inhibitor [10  $\mu$ g/mL]



- Tanaka N, Okasaka M, Ishimaru Y, Yakaishi Y, Sato M, Okamoto M, Oshikawa T, Ahmed SU, Consentino LM, Lee K-H. *Org. Lett.* 2005;7:2997–2999.  
● Nicolaou, K.C., Sarlah, D., Shaw, D.M., *Angew. Chem. Int. Ed.* 46:4708, 2007.  
● Nicolaou, K.C., Wu, T.R., Sarlan, D., Shaw, D.M., Rowcliffe, E., Burton, D.R., *J. Am. Chem. Soc.* 130:11114, 2008.



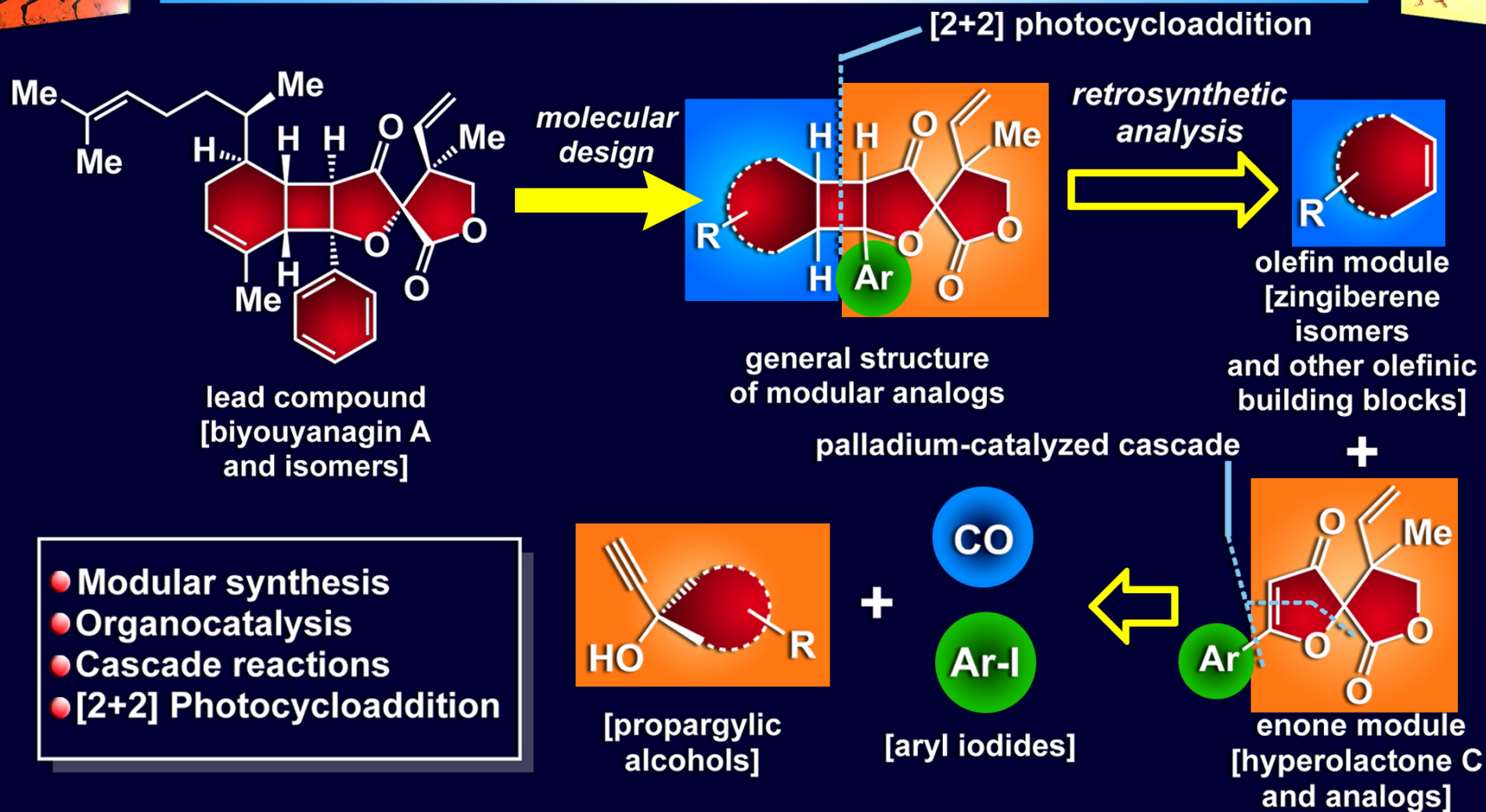
# Synthesis of Biyouyanagins A, B and C





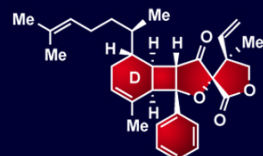


# Modular Biyouyanagin Compound Library Design and its Retrosynthetic Analysis

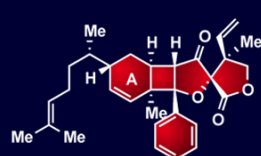




# Biyouyanagin Library from Isomeric Hyperolactones and Zingiberenes



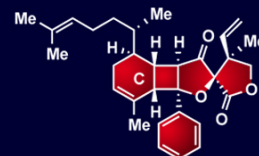
biyouyanagin C



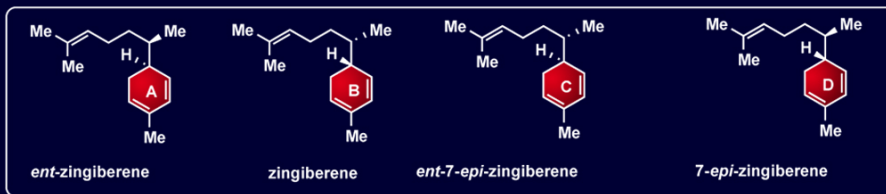
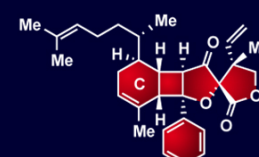
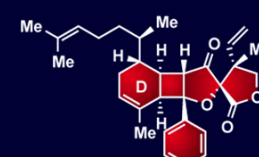
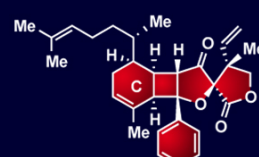
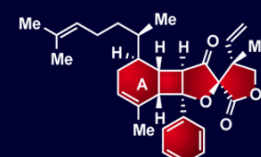
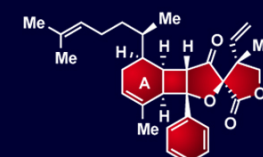
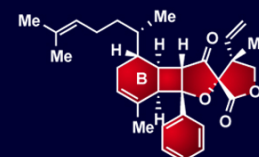
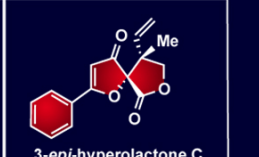
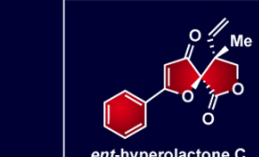
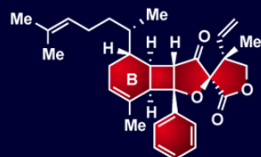
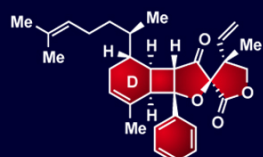
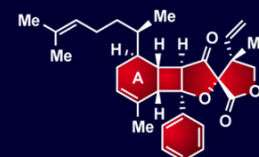
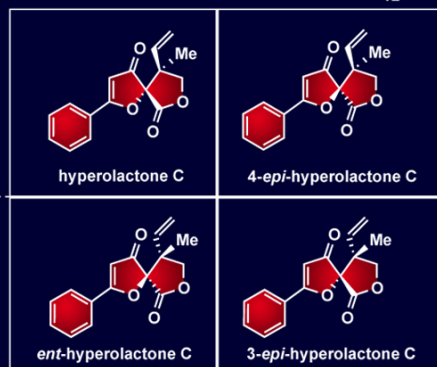
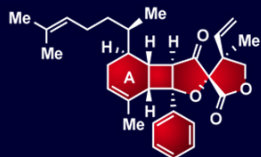
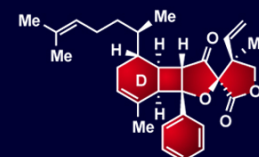
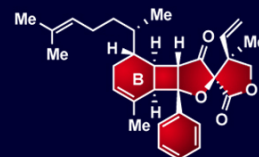
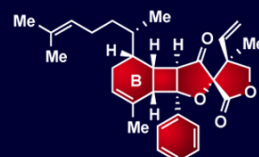
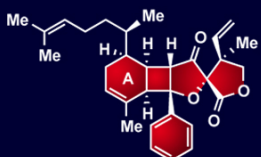
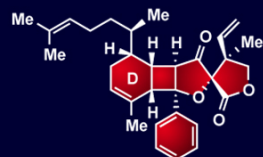
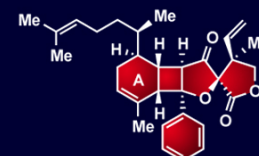
biyouyanagin B



biyouyanagin A



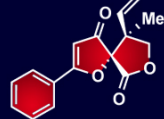
12



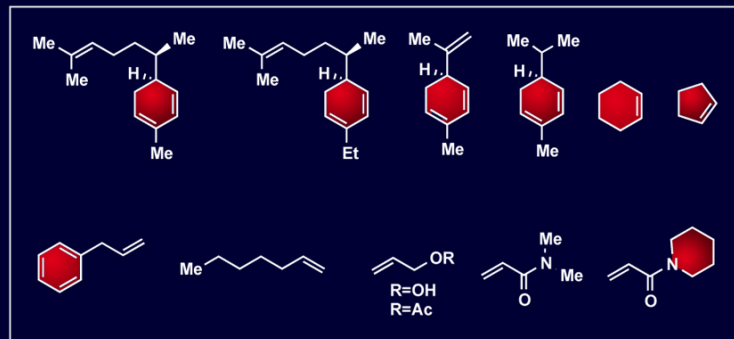
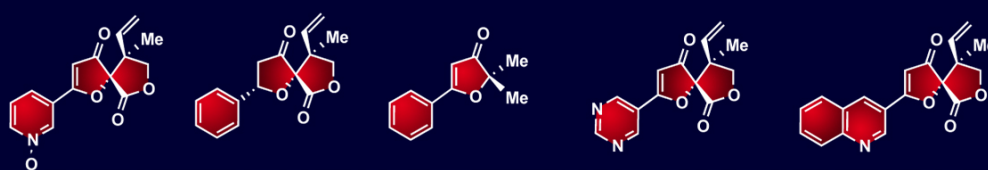
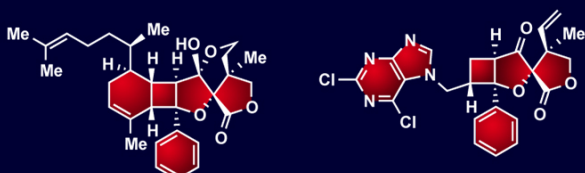
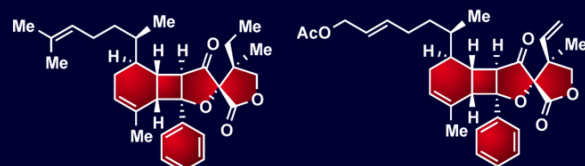
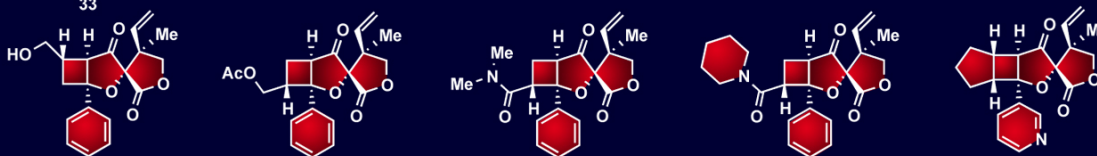
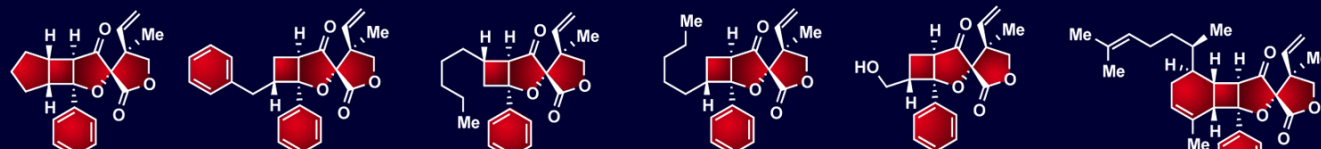
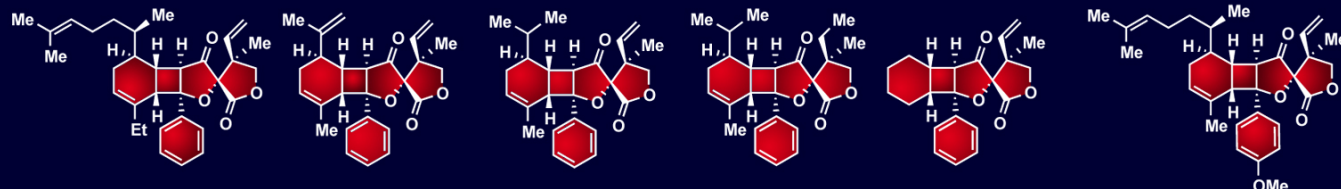
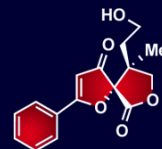
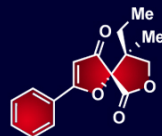
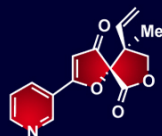
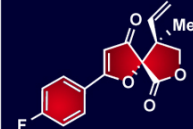
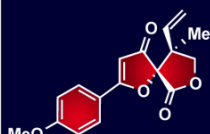




# Biyouyanagin Analogs from Hyperolactones and Olefinic Building Blocks



hyperlactone C

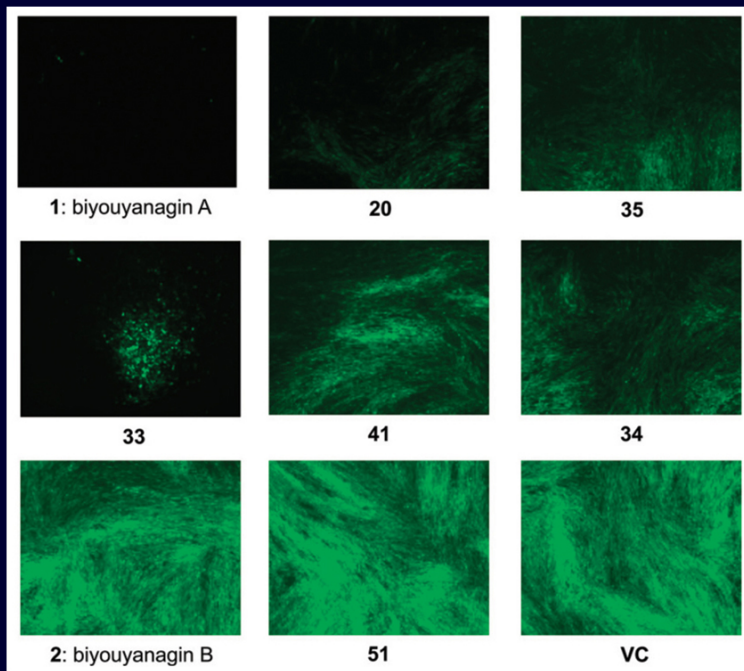
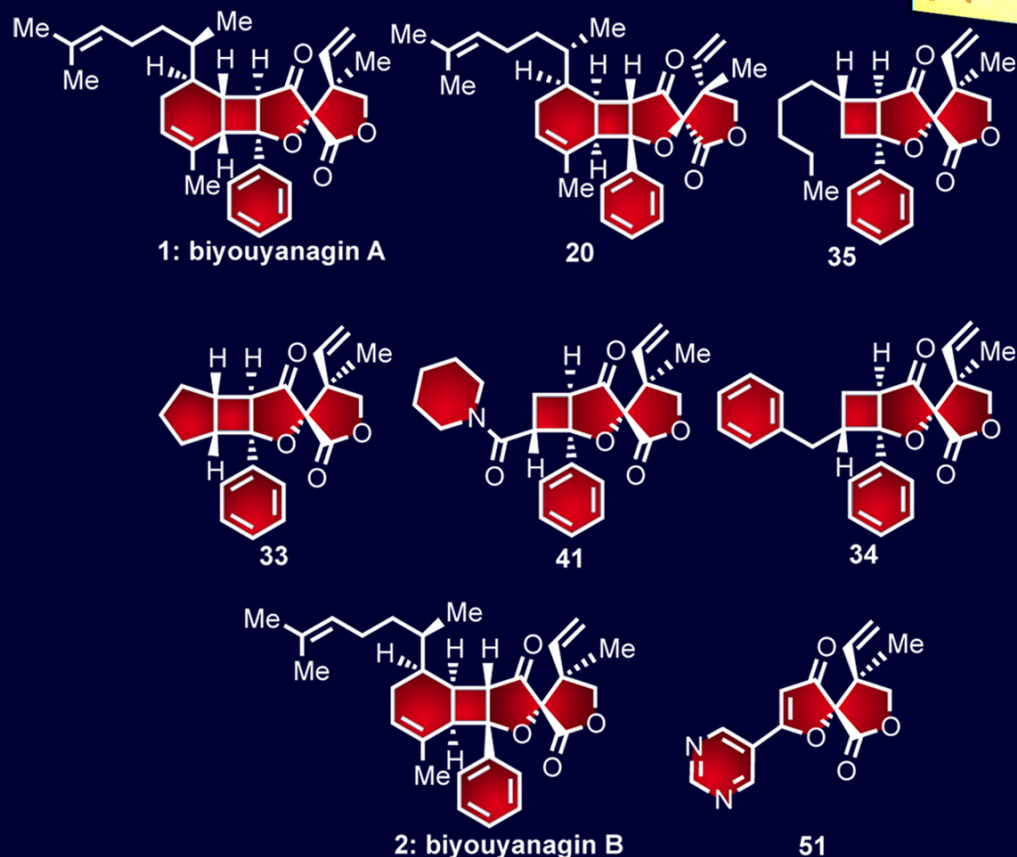




# Biological Screening in an Arenavirus Assay



- Arenaviruses cause hemorrhagic fever. Lassa (LASV, West Africa), Junin (JUNV, Argentina) and LCMV have devastating consequences and are listed on the biodefense list Category A agents.



BHK-21 cells were infected with a recombinant LCM virus expressing GFP, called r3LCMV-GFP at a multiplicity of infection of 0.1 in the presence of the indicated compound (50  $\mu$ M). At 36 h postinfection, cells were fixed in 4 % PFA/PBS, and viral load was assessed based on GFP expression. Compound-associated cell (BHK-21) toxicity was determined by trypan blue. Compounds exhibiting cell toxicity  $\geq 30$  % (at 50  $\mu$ M) were not evaluated for their antiviral activity. VC: treatment with vehicle (DMSO).

- K. C. Nicolaou, Silvano Sanchini, David Sarlah, Gang Lu, T. Robert Wu, Daniel K. Nomura, Benjamin F. Cravatt, Beatrice Cubitt, Juan C. de la Torre, Ann J. Hessel, and Dennis R. Burton, *PNAS*, 2011, doi: 10.1073/pnas.1015258108.

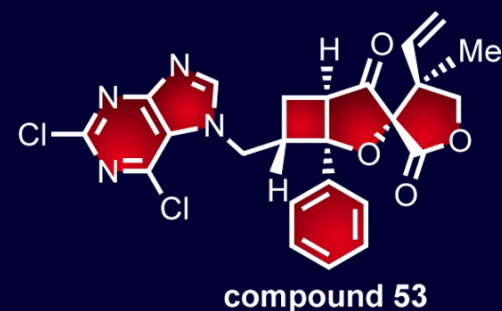
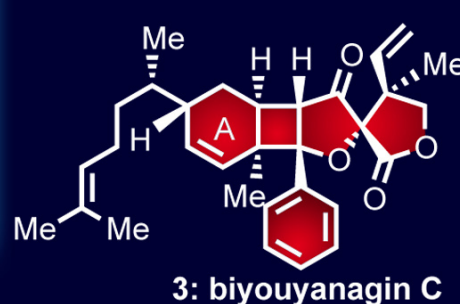
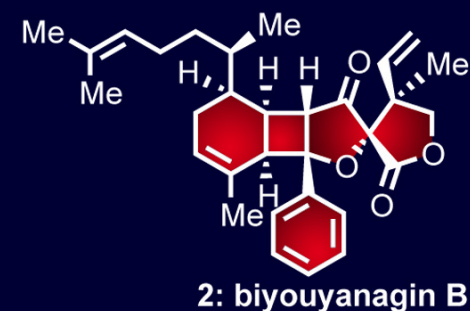
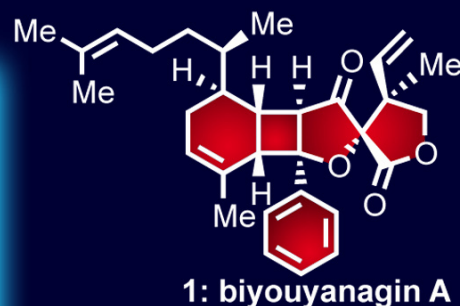
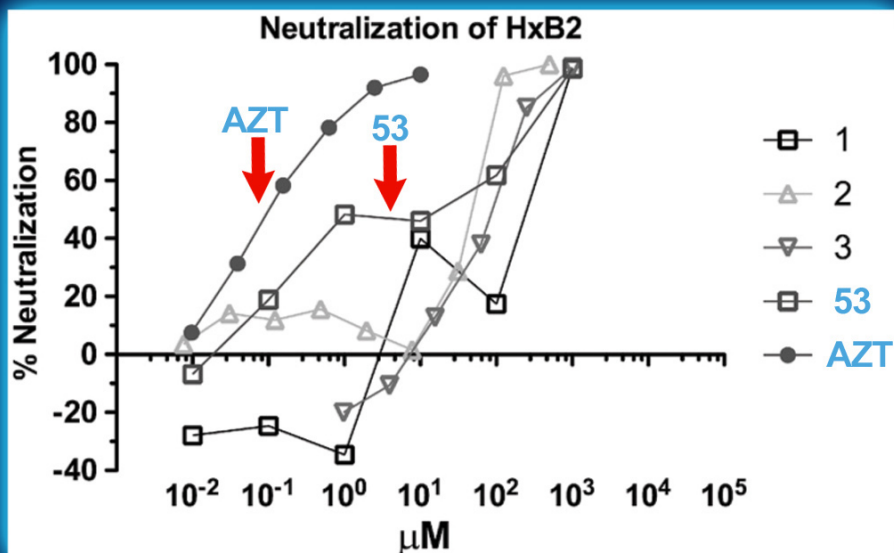




# Biological Evaluation in an HIV Assay



## ● Inhibition of HIV replication in infected H9 lymphocytes (TI=31.3)



Neutralization assay using the molecular clone HIV-1HxB2. Pseudoviruses were generated in 293T cells, and neutralization with single-round infectious pseudovirus was performed using TZM-bl cells as targets for infection. AZT (Azidothymidine) was used as a control.

● K. C. Nicolaou, Silvano Sanchini, David Sarlah, Gang Lu, T. Robert Wu, Daniel K. Nomura, Benjamin F. Cravatt, Beatrice Cubitt, Juan C. de la Torre, Ann J. Hessel, and Dennis R. Burton, *PNAS*, 2011, doi: 10.1073/pnas.1015258108.



# LPS-Induced Cytokine Inhibition Assays



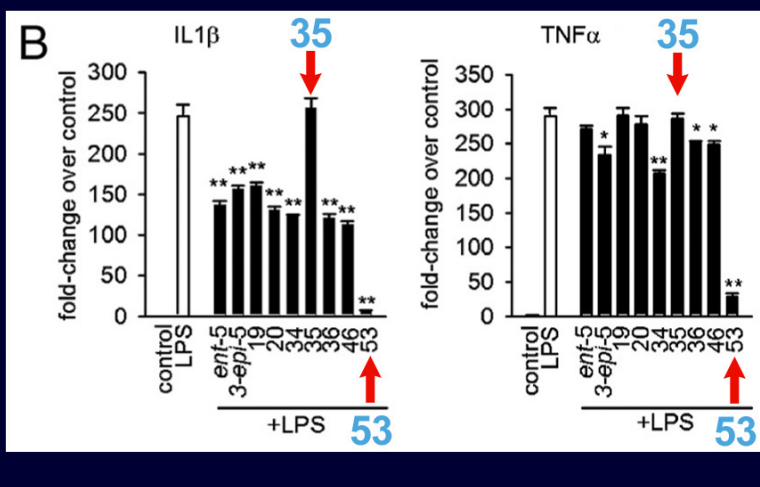
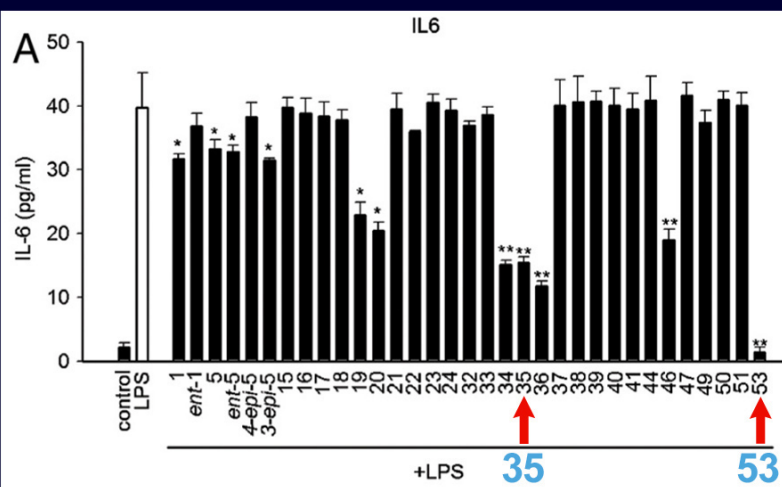
- Lipopolysaccharide-induced cytokine production leads to inflammation.
- Potent inhibition of IL-6, IL1 $\beta$  and TNF $\alpha$  [compound 53].
- Selective inhibition of IL-6 vs. IL1 $\beta$  and TNF $\alpha$  [compound 35].



**compound 53**  
[potent inhibitor]



**compound 35**  
[selective inhibitor]



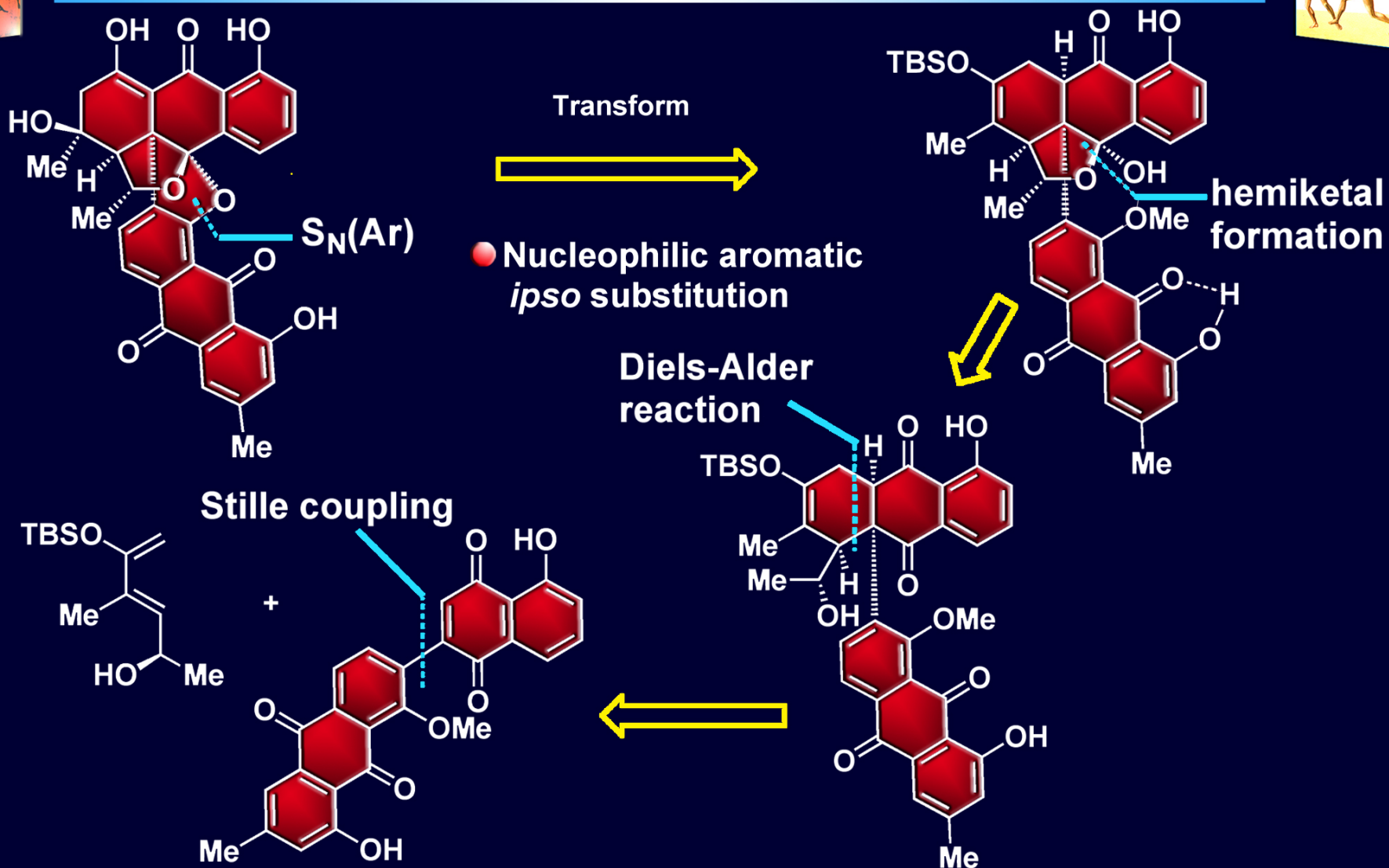
Anti-inflammatory screen of 33 members of the biyouyanagin library. A. Human macrophage THP-1 cells were pretreated with each compound (10  $\mu$ M) for 1 h before stimulating the cells with LPS (2  $\mu$ g/ml) for 6 h. B. Several of the compounds that inhibited IL6 release in this screen were further assessed for inhibition of IL1 $\beta$  and TNF $\alpha$ . Control denotes no compound and LPS denotes LPS-treatment alone without any compound. IL6 release was assessed. Data are with n = 3-5/group. Significance is expressed as \*p<0.05, \*\*p<0.01 compared to LPS alone.

● K. C. Nicolaou, Silvano Sanchini, David Sarlah, Gang Lu, T. Robert Wu, Daniel K. Nomura, Benjamin F. Cravatt, Beatrice Cubitt, Juan C. de la Torre, Ann J. Hessel, and Dennis R. Burton, *PNAS*, 2011, doi: 10.1073/pnas.1015258108.





## BE-43472B 2. RETROSYNTHETIC ANALYSIS [2009]

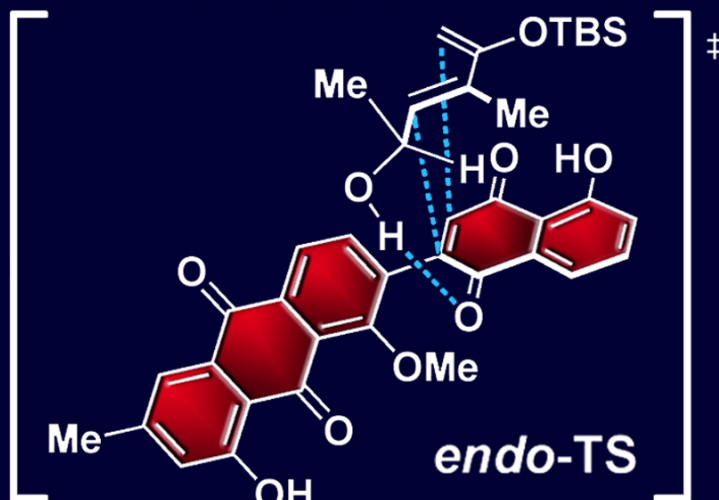




# ANTIBIOTIC BE-43472B 5. CASCADE I [2009]



- preorganization of diene and dienophile

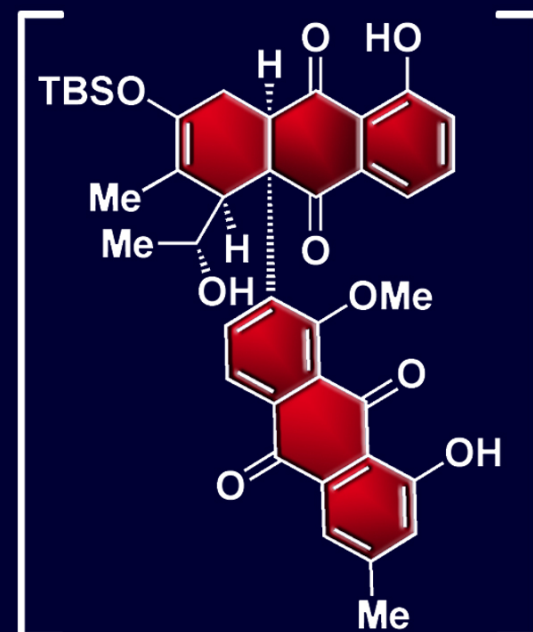
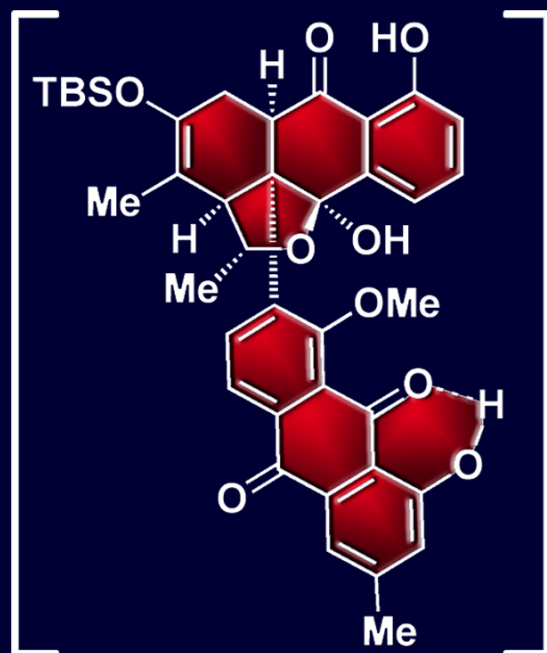


[Diels-Alder reaction]

[hemiketal formation]

continue

$\text{CH}_2\text{Cl}_2, \Delta$ ;  
[sealed tube]

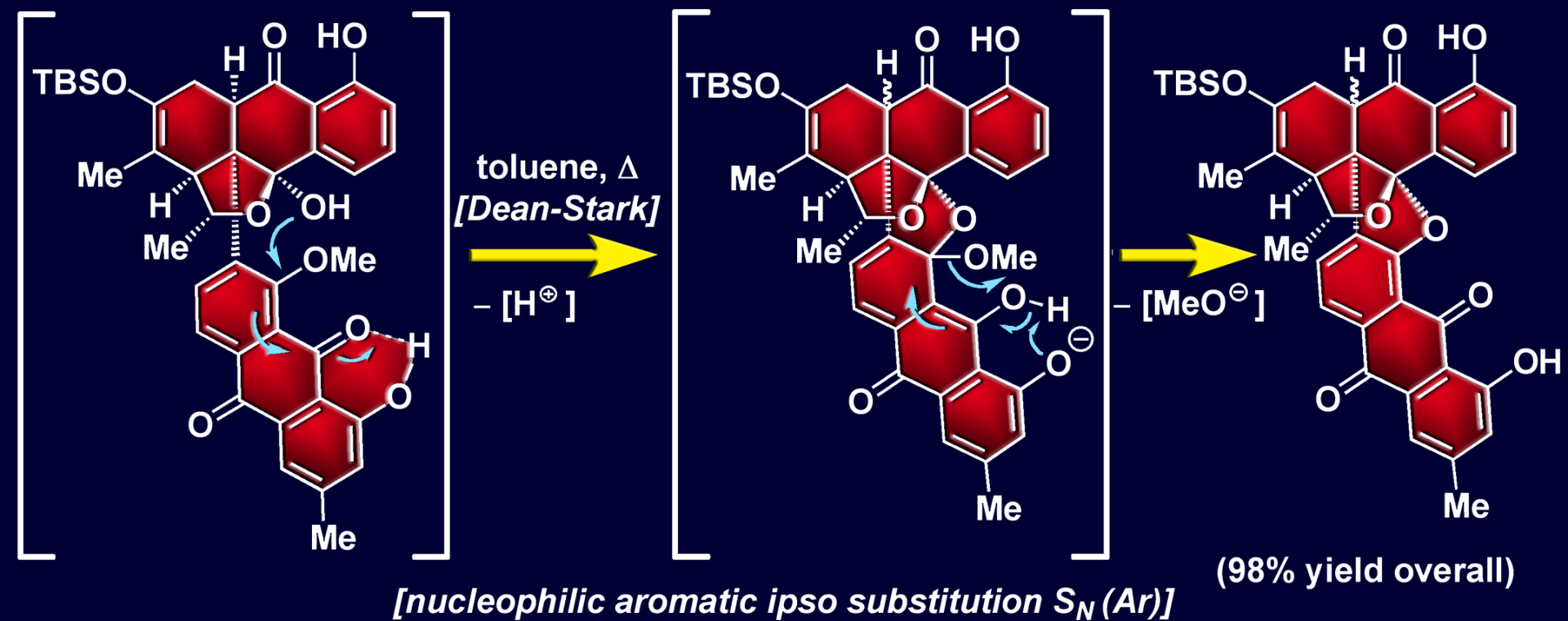




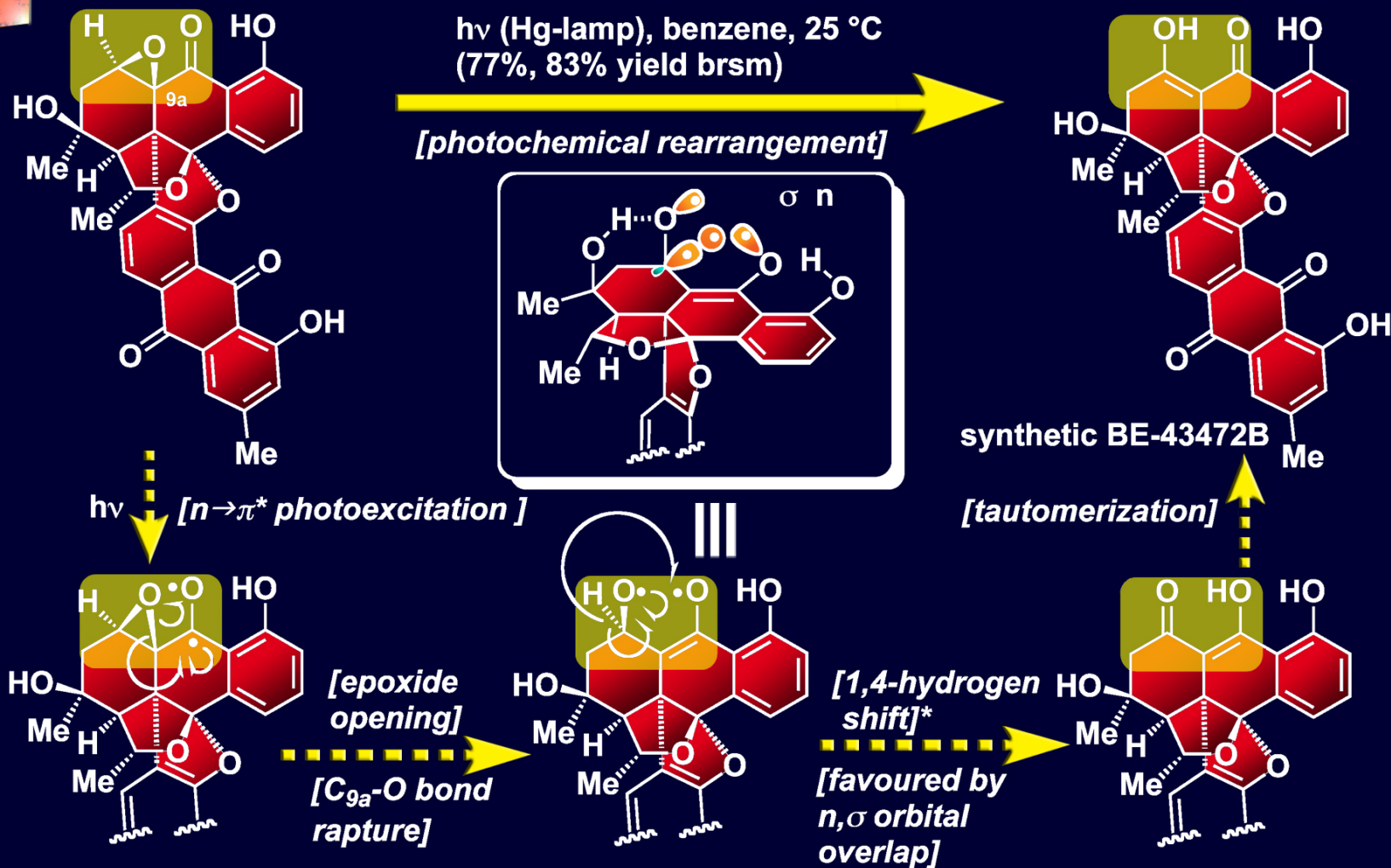
# ANTIBIOTIC BE-43472B 6. CASCADE II [2009]



continue



# ANTIBIOTIC BE-43472B 9. FINAL STEP [2009]



\* 1,4-hydrogen shift observed by laser flash photolysis methods: a) H. Kim, T. G. Kim, J. Hahn, D.-J. Jang, D. J. Chang, B. S. Park, *J. Phys. Chem. A*. 2001, 105, 3555.

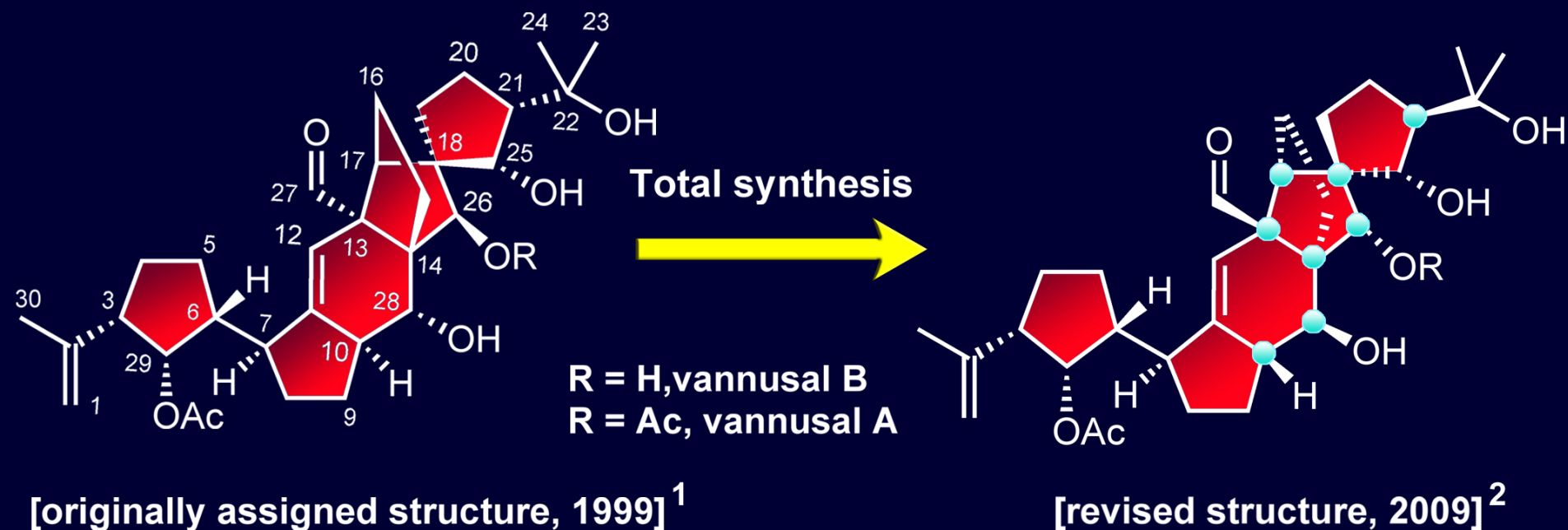




# *The Structures of the Vannusals: Originally Assigned (1999) and Revised (2009)*



## ● The Vannusal Files: A Chemical Detective Story



● Isolated from interstitial ciliate *Euplotes vannus*, strains Si121 and BUN3

<sup>1</sup>G. Guella, F. Dini, F. Pietra, *Angew. Chem. Int. Ed.* **1999**, 38, 1134-1136

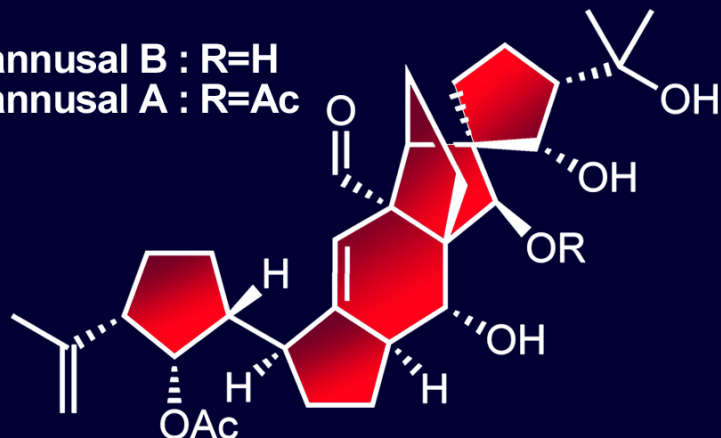
<sup>2</sup>K. C. Nicolaou, A. Ortiz, H. Zhang, *Angew. Chem. Int. Ed.* (2009)



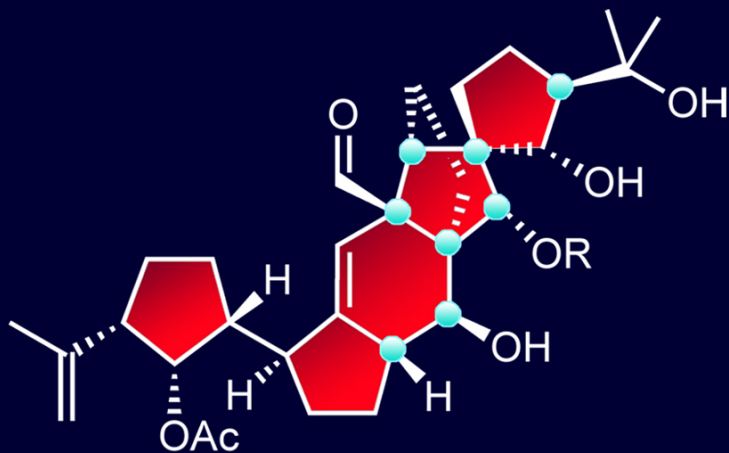
# Interstitial Ciliate *Euplotes vannus*: A Unicellular Marine Organism



Vannusal B : R=H  
Vannusal A : R=Ac



[originally assigned structures, 1999]



[revised structures, 2009]

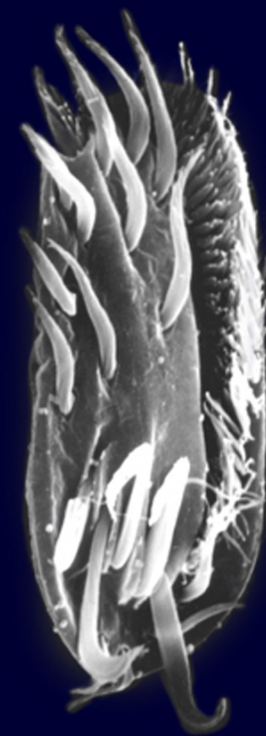
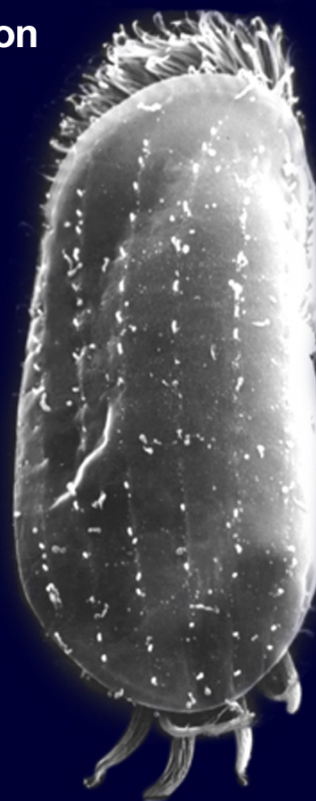
Scanning Electron  
Micrographs  
Philips SEM 515

87  $\mu\text{m}$  long  
43  $\mu\text{m}$  wide

*Euplotes vannus*, strain Sil21

Dorsal view

Ventral view

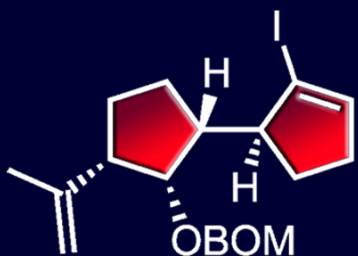


Courtesy of: Prof. Graziano Guella





## Coupling of the Two Fragments of $C_{25}$ -*epi*-Vannusal B (oas)

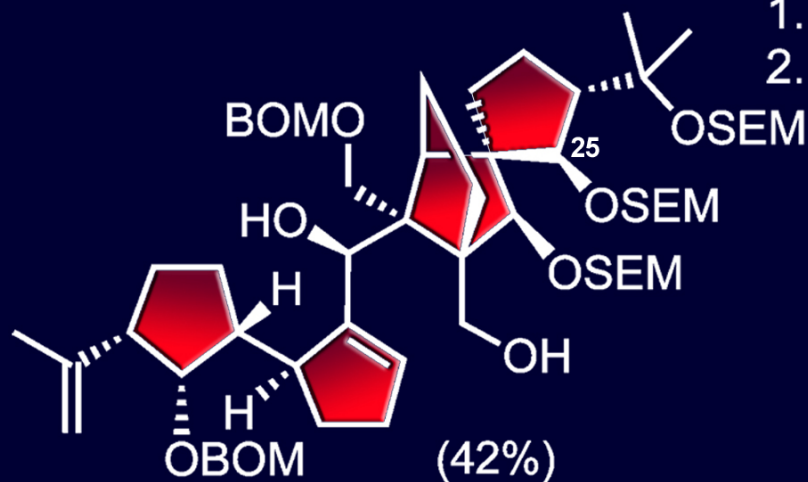


enantiopure

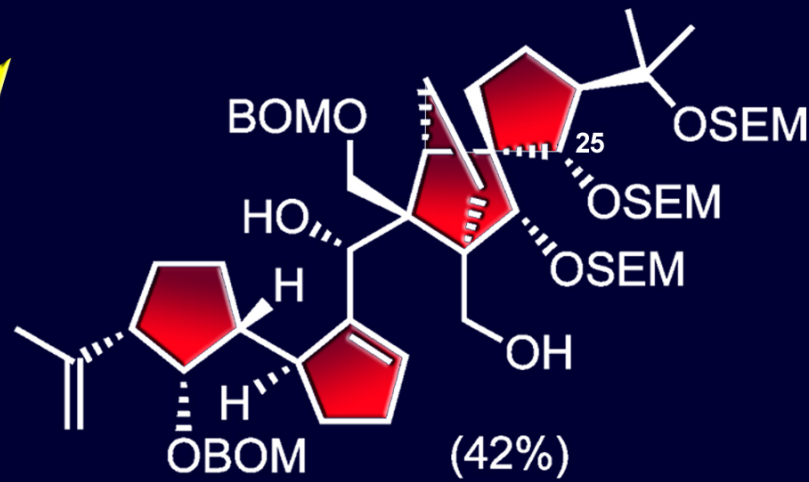


racemic

1. *t*-BuLi  
2. TBAF



(42%)

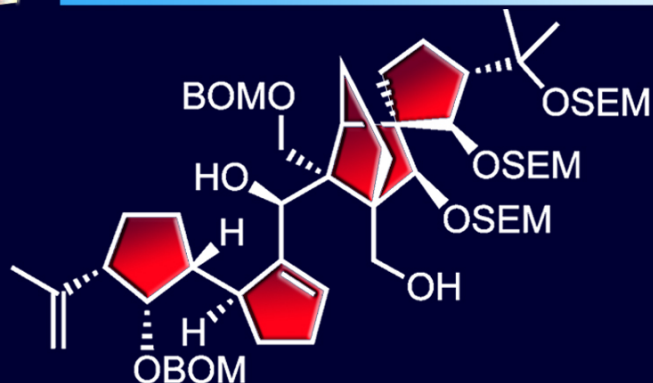


(42%)

● Chromatographically separated

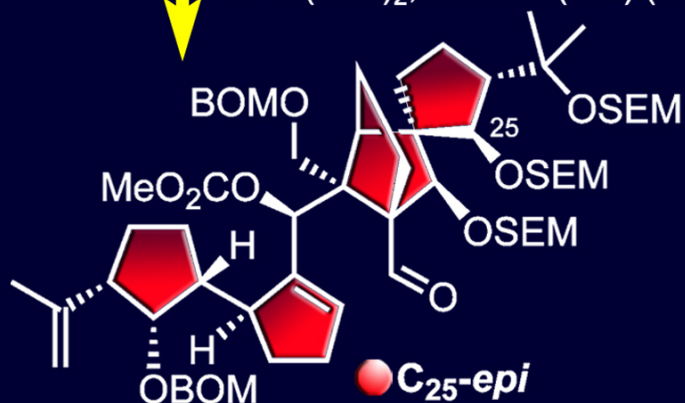


# Synthesis of $S_{\text{ml}}2$ Cyclization $C_{25}$ -*epi* Precursors

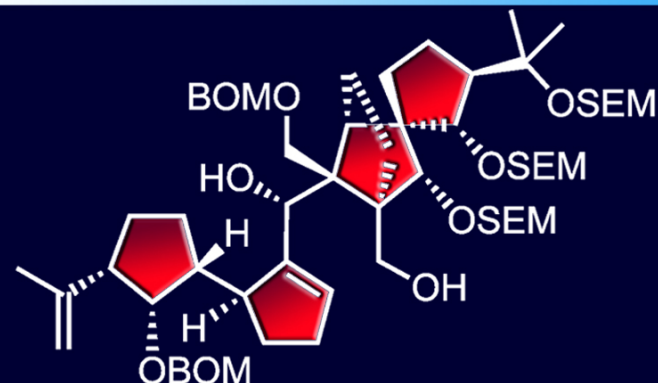


**$C_{25}$ -*epi* vannusal coupling diastereomer**

1. TESCI
2. KHMDS,  $\text{ClCO}_2\text{Me}$
3.  $\text{HF}\cdot\text{py}$  (89%)
4.  $\text{PhI}(\text{OAc})_2$ , AZADO (cat.) (96%)

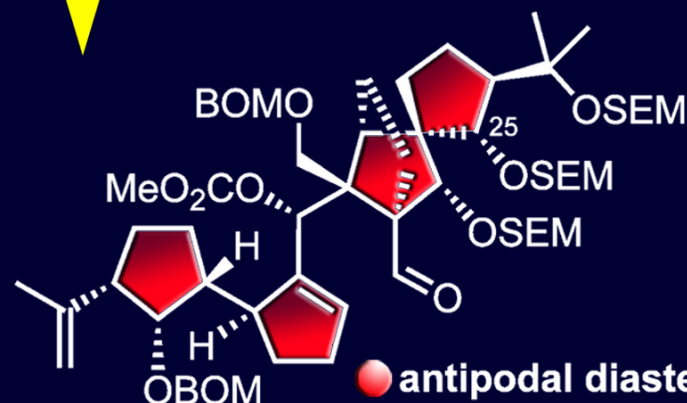


**$C_{25}$ -*epi***



**antipodal "right domain" coupling diastereomer**

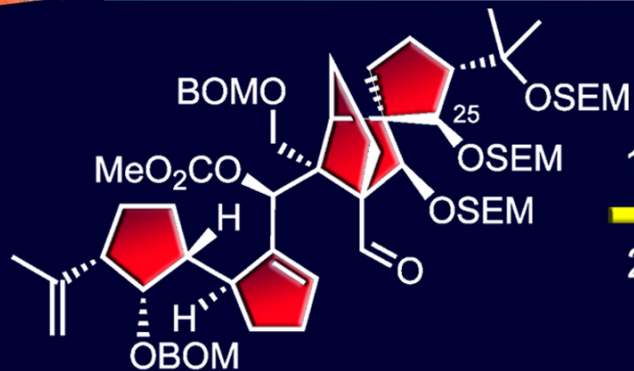
1. TESCI
2. KHMDS,  $\text{ClCO}_2\text{Me}$
3.  $\text{HF}\cdot\text{py}$  (96%)
4.  $\text{PhI}(\text{OAc})_2$ , AZADO (cat.) (97%)



**antipodal diastereomer**

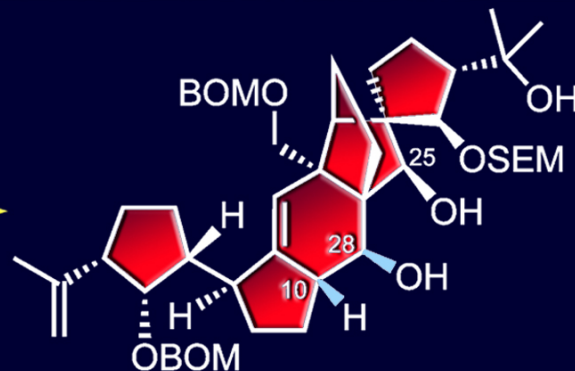


# *Sml<sub>2</sub>-Induced Cyclizations of the Two Diastereomeric Precursors*

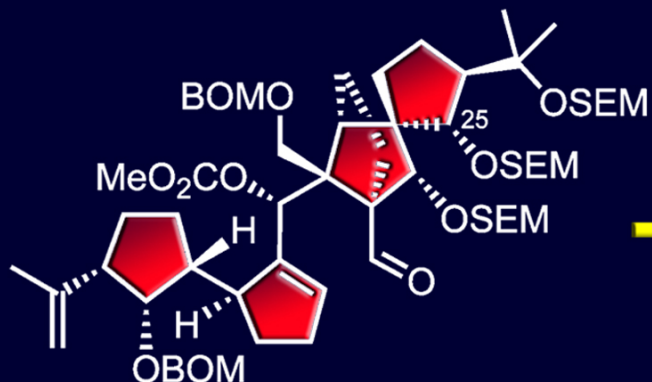


correct “right” precursor [25-*epi*]  
(per originally assigned structure)

1. aq. HF (81%)  
2. Sml<sub>2</sub>, HMPA  
(67%)

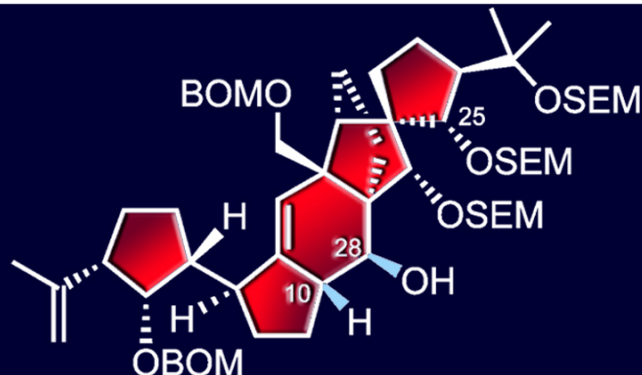


● C<sub>10</sub> and C<sub>28</sub> stereocenters are of the undesired stereochemistry relative to the adjacent centers and need to be inverted



antipodal “right domain” precursor  
(per originally assigned structure)

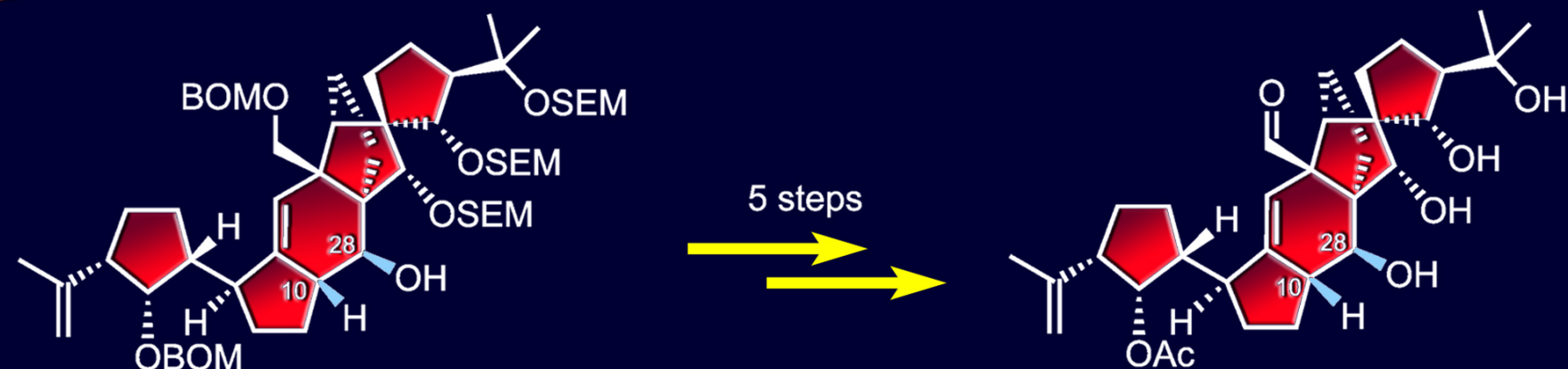
Sml<sub>2</sub>, HMPA  
(81%)



● C<sub>10</sub> and C<sub>28</sub> stereocenters are of the correct stereochemistry relative to the adjacent centers and, therefore, need no configurational adjustment



# Total Synthesis of $C_{25}$ -*epi Vannusal B* (oas) and Real *Vannusal B*



● No need to invert  $C_{10}$ ,  $C_{28}$  stereochemistry

● NMR data ??? those of the natural product!



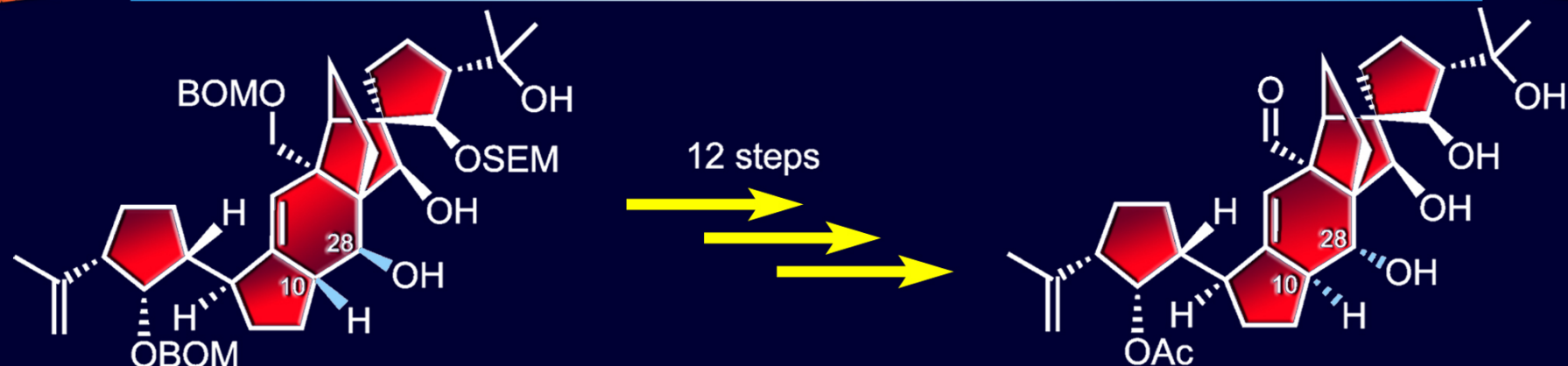
Adrian Ortiz

- 500 MHz  $^1\text{H}$  NMR spectrum close to that of the natural product (600MHz)
- Now we are convinced that the shortly-to-arrive vannusal B isomer derived from the “correct” coupling diastereomer must be the right one!





# Total Synthesis of $C_{25}$ -epi Vannusal B (oas) and Real Vannusal B



● Need to invert  $C_{10}$ ,  $C_{28}$  stereochemistry

● NMR data very close, but do not quite match those of the natural product!

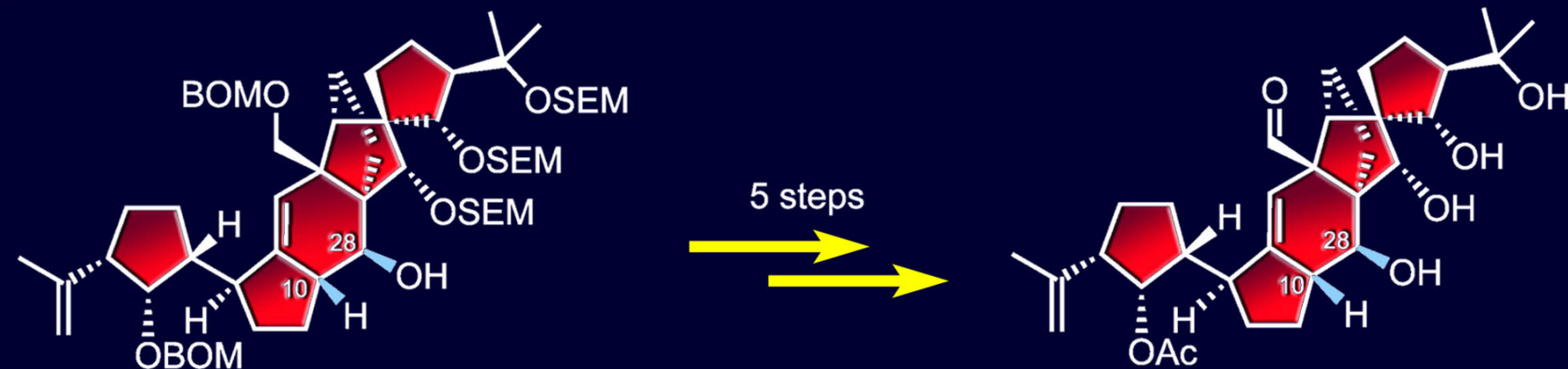


Hongjun Zhang

- 600 MHz  $^1\text{H}$  NMR spectrum does not match that of natural vannusal B!
- Now what?
- Go back to the first-to-arrive diastereomer and run a 600 MHz  $^1\text{H}$  NMR spectrum:



# Total Synthesis of $C_{25}$ -*epi* Vannusal B (oas) and Real Vannusal B



● No need to invert  $C_{10}$ ,  $C_{28}$  stereochemistry

● NMR data **match** those of the natural product!



Adrian Ortiz

● 600 MHz  $^1\text{H}$  NMR spectrum matches perfectly those of the natural product (600MHz) !

● Done!

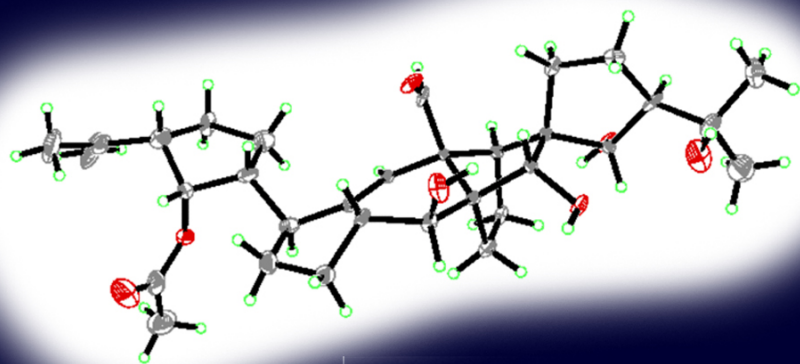


Hongjun Zhang





# X-Ray Crystallographic Analysis of Vannusal B, and Total Synthesis and Revised Structure of Vannusal A



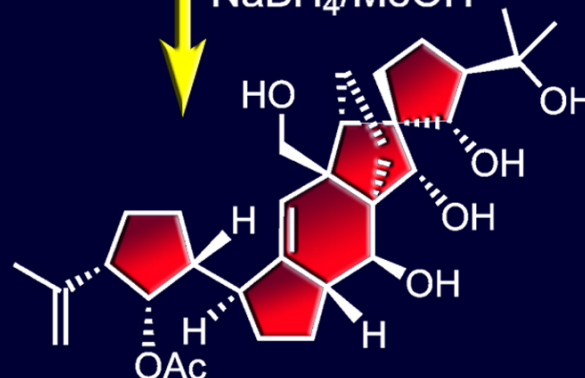
X-ray derived ORTEP



synthetic vannusal B

colorless needles (EtOAc/THF, m.p. >200 °C, dec.)

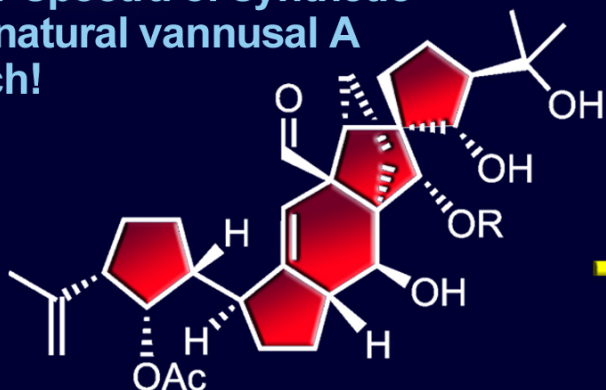
NaBH<sub>4</sub>/MeOH



vannusal pentaol

● NMR spectra of synthetic and naturally derived material match!

● NMR spectra of synthetic and natural vannusal A match!



natural vannusal A (R = Ac)  
or B (R = H)

NaBH<sub>4</sub>/MeOH

[G. Guella et al]





# Journey from the Originally Assigned to the Revised Structure of Vannusal B



●  $2^{13} = 8192$  Possible isomers

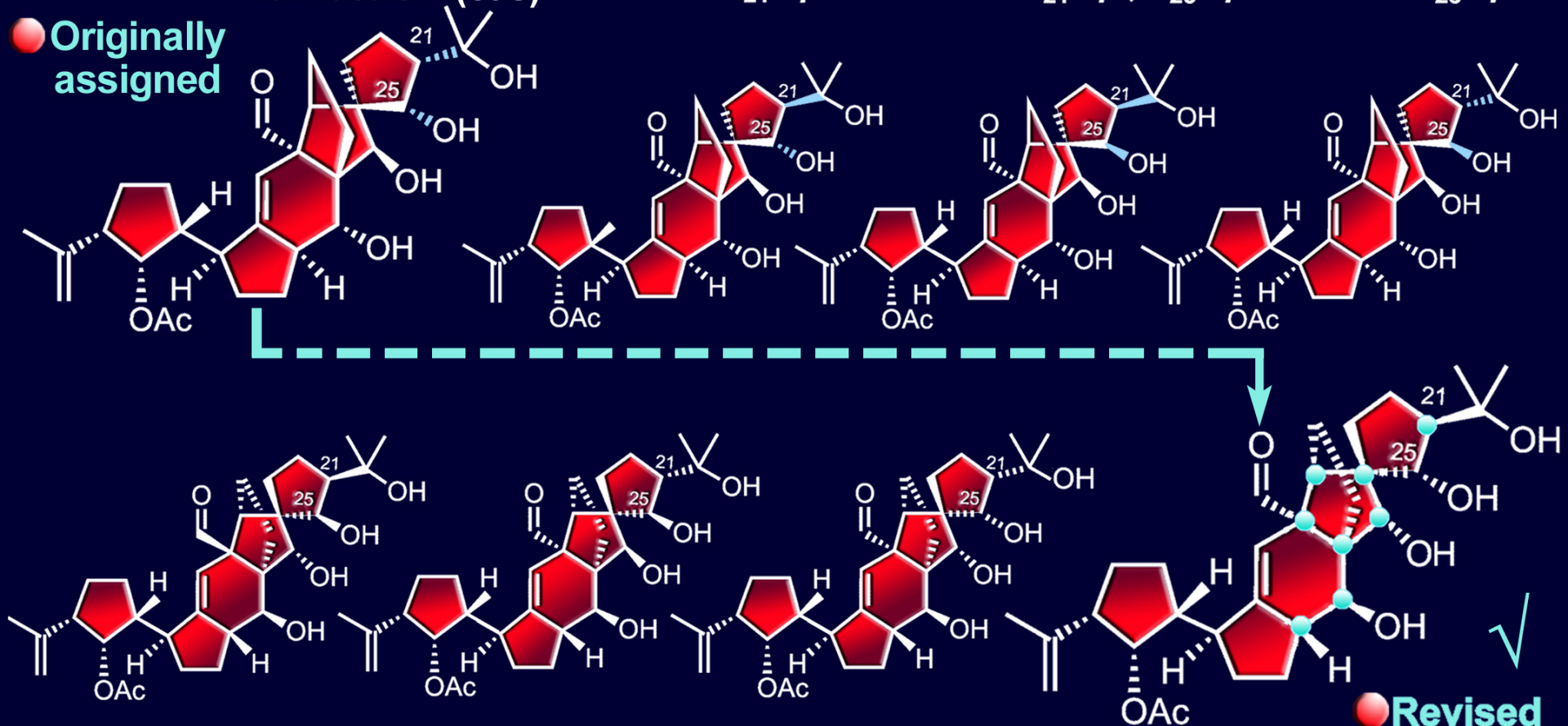
● Originally assigned

I: vannusals B (oas)

II: C<sub>21</sub>-*epi*

III: C<sub>21</sub>-*epi*, C<sub>25</sub>-*epi*

IV: C<sub>25</sub>-*epi*



● Revised

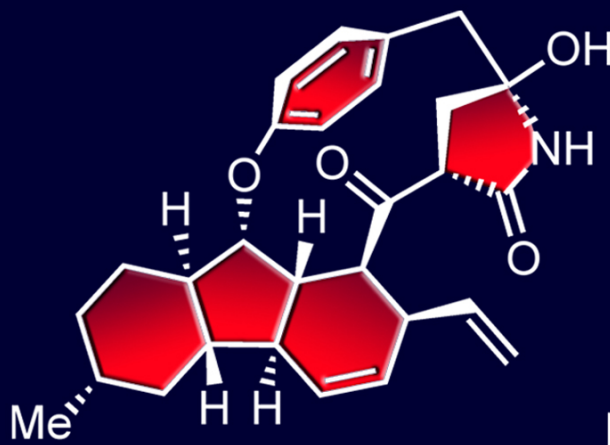




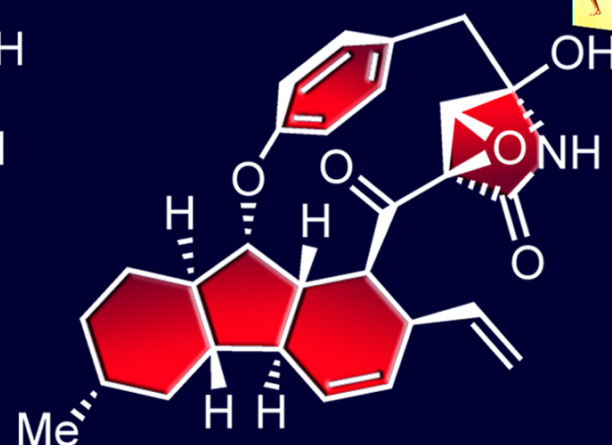
## Hirsutellones A, B and C [2009]



hirsutellone A



hirsutellone B



hirsutellone C

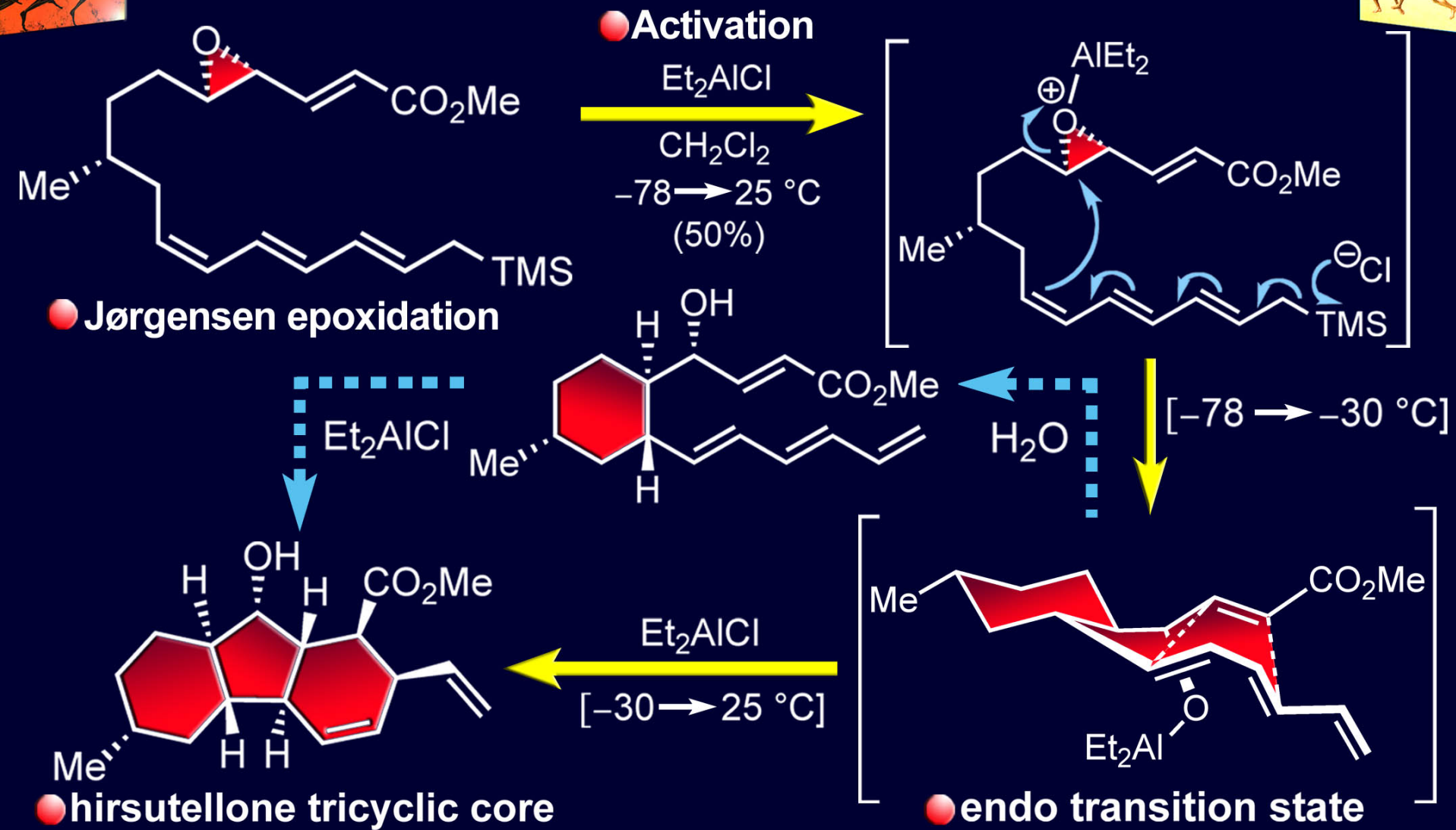
- Isolated from a *Hirsutella nivea* BCC 2594 by Isaka and co-workers: *Tetrahedron*, 2005, 61, 5577.
- Hirsutellones displayed significant growth inhibitory activity against *Mycobacterium tuberculosis* [Hirsutellone B: MIC=0.78  $\mu\text{g/mL}$ ].
- [6.5.6] fused tricyclic core
- highly strained 12- or 13-membered ring
- 5-membered imide or lactam ring



*H. nivea* on a leafhopper



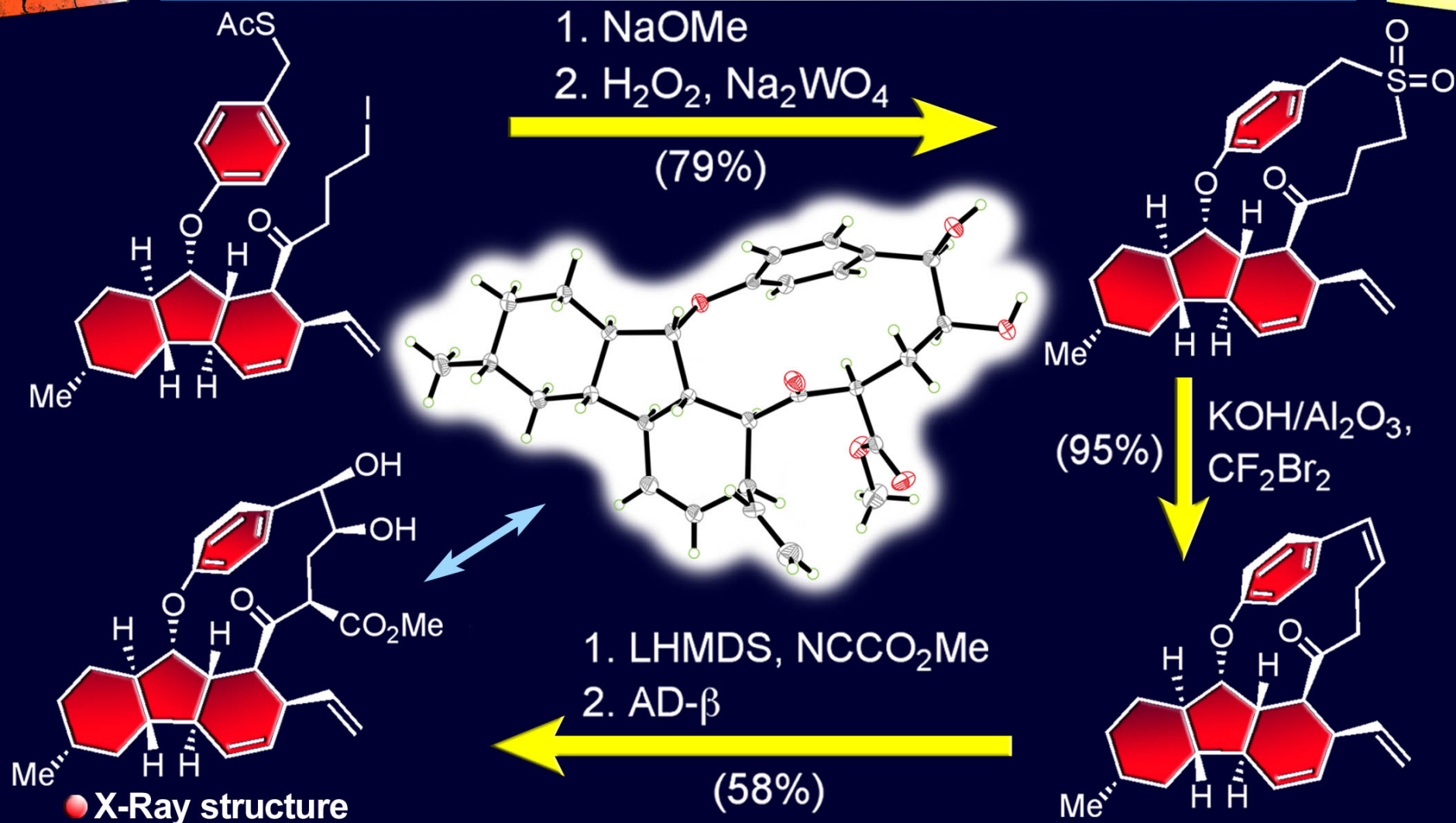
# The Hirsutellone Cascade







# Synthesis and X-Ray Crystallographic Analysis of Hirsutellone B Methyl Ester Diol

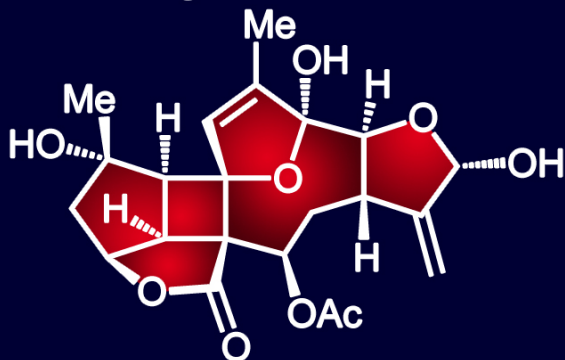




## Bielschowskysin. Structure and Possible Construction (2011)

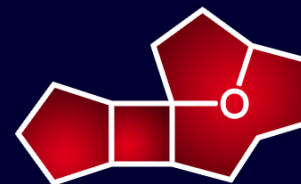


- bielschowskysin: a marine antimalarial and antitumor agent

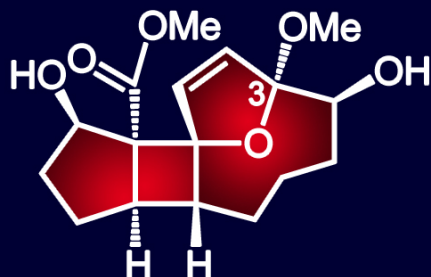


- Isolated from *Pseudopterogorgia kallos*
- $IC_{50} = 10 \mu\text{g/mL}$  against *Plasmodium falciparum*
- $GI_{50} < 10 \text{ nM}$  against EKVX nonsmall lung cancer cell
- $GI_{50} = 510 \text{ nM}$  against CAKI-1 renal cancer cell

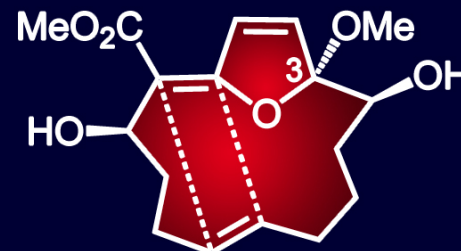
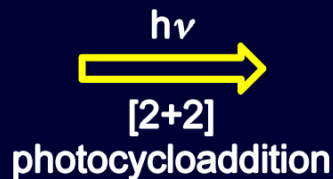
- carbocyclic core structure



- tricyclo[9.3.0.0]tetradecane ring system

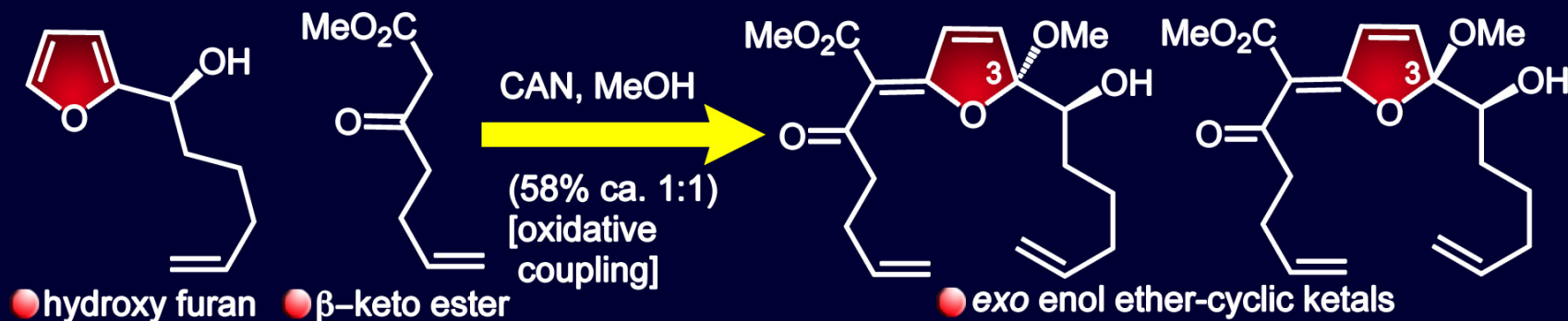


- functionalized tricyclo[9.3.0.0]tetradecane ring system



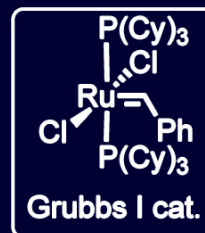
- postulated macrocyclic precursor

# Construction of Macrocyclic Precursors 1. Oxidative Coupling of Furans with $\beta$ -Keto Esters

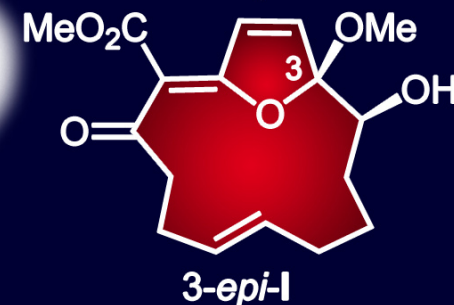
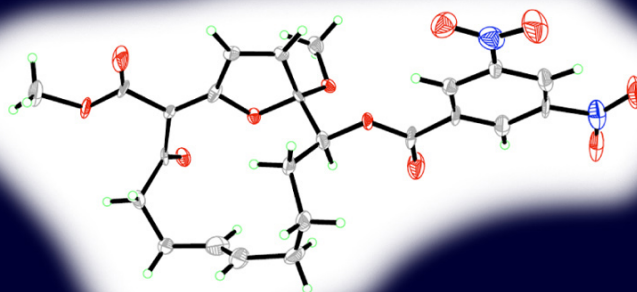
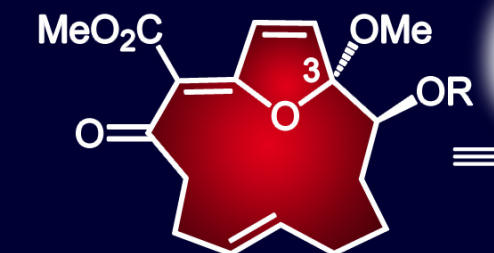


[ring closing metathesis]

(90%, *trans:cis* ca. 15:1)



(71%, *trans:cis* ca. 3:1)

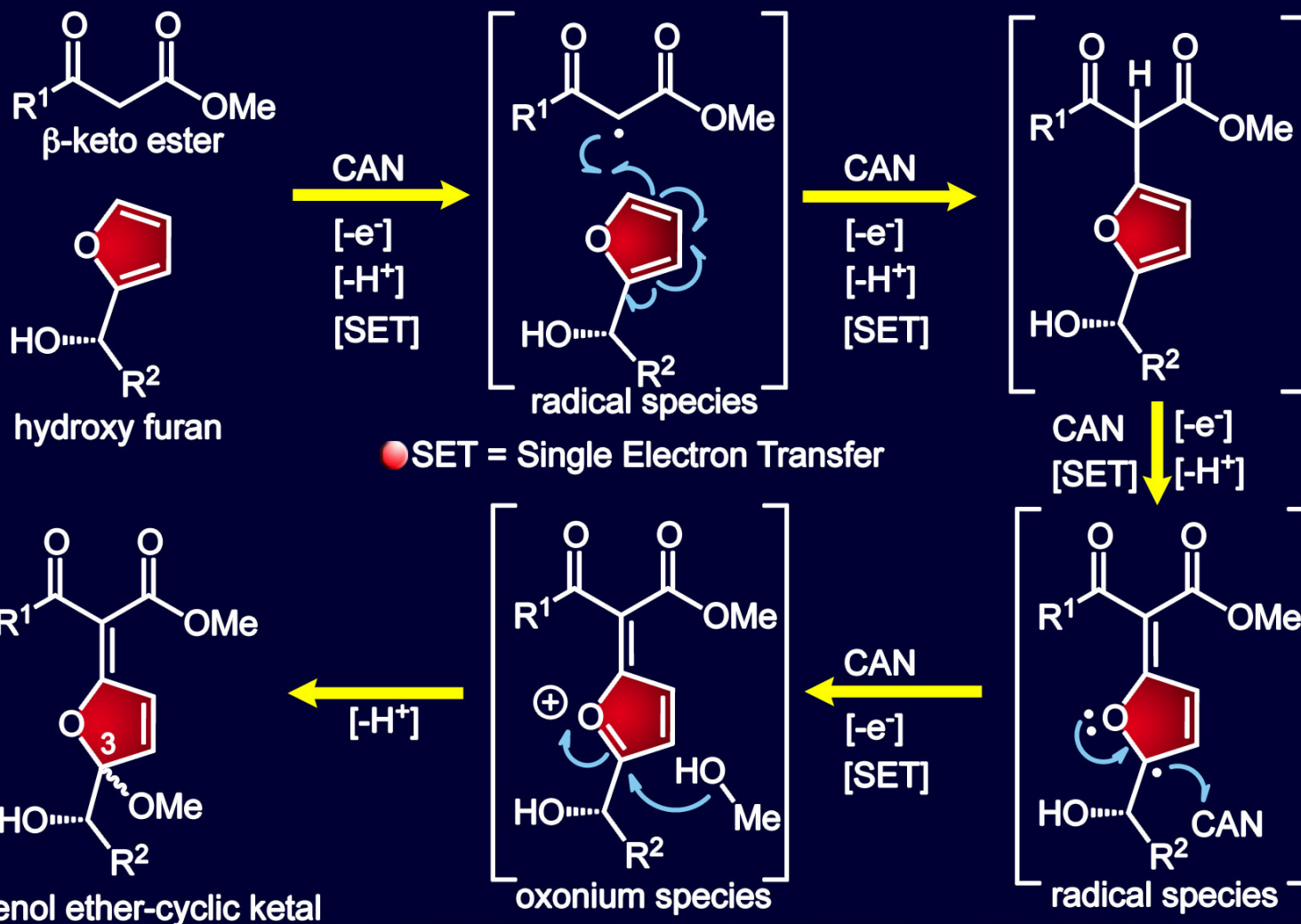


DNB-Cl (88%)  $\xrightarrow{\text{I: R = H}}$  DNB-I: R = 3,5-dinitrobenzoate





## Mechanism of Oxidative Coupling of Furans with $\beta$ -Keto Esters

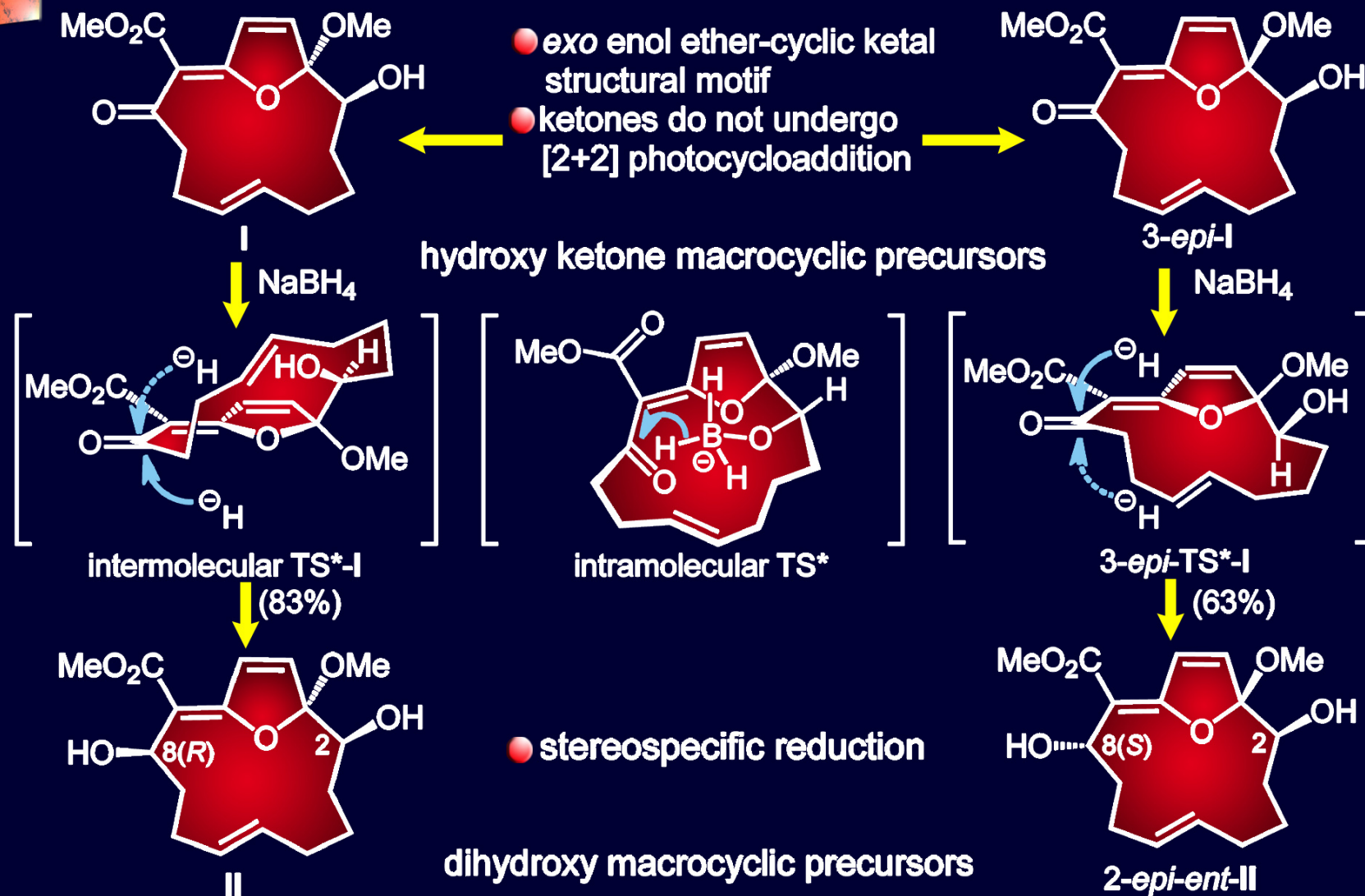


see: a) L. M. Weinstock, E. Corley, N. L. Abramson, A. O. King, S. Karady, *Heterocycles*, **1988**, 27, 2627.

b) J-M. Simone, F. Loiseau, D. Carcache, P. Bobal, J. Jeanneret-Gris, R. Neier, *Monatshefte für Chemie* **2007**, 138, 131.

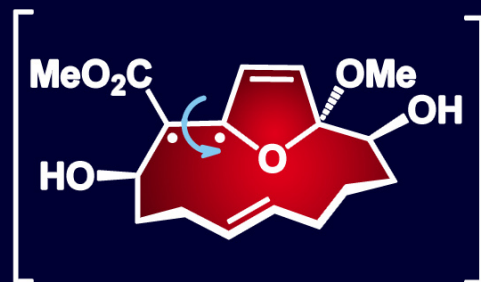
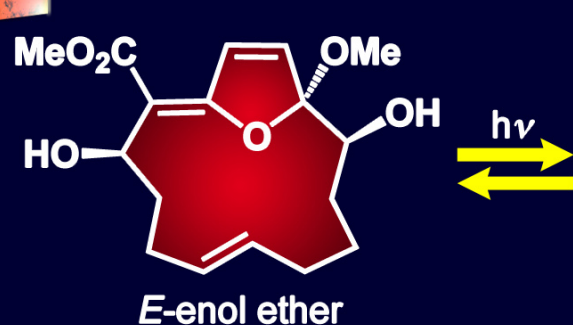


## Construction of [2+2] Photocycloaddition Precursors 2.

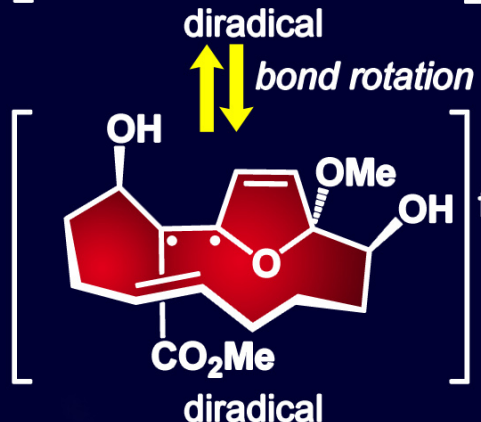
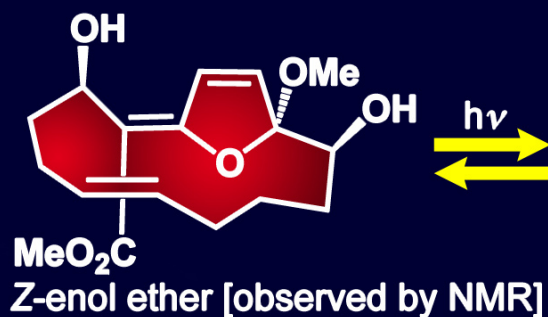




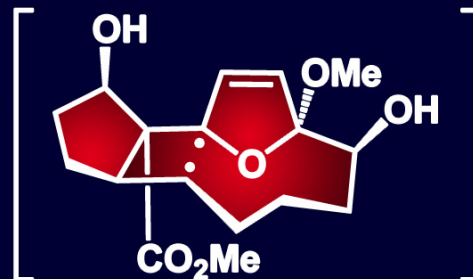
# Transannular Cascade [2+2] Photocycloaddition



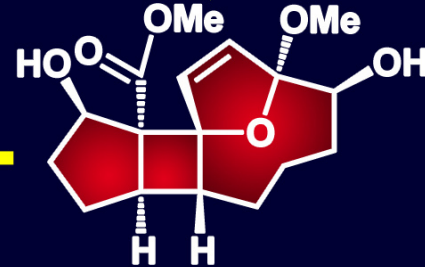
- geometrical isomerization
- rule of fives for first C-C bond formation
- proximity effect for second C-C bond formation



1<sup>st</sup> C-C  
bond  
formation

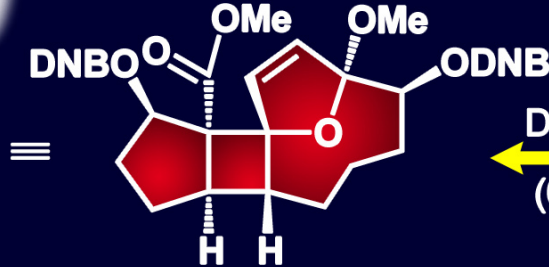


2<sup>nd</sup> C-C  
bond  
formation (90%)

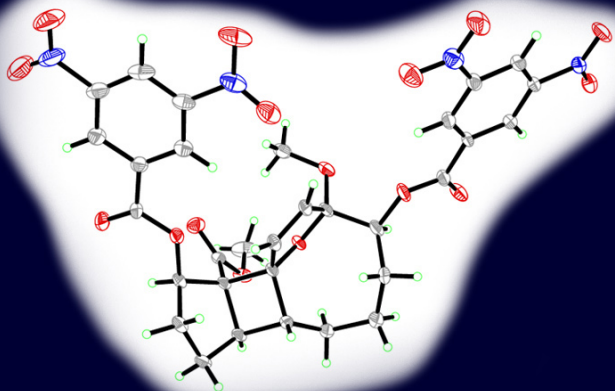


single isomer

DNB-Cl  
(68%)



bis-3,5-dinitrobenzoate derivative







# *Epicoccin G and Related Natural Products*



## ● Dithiodiketopiperazines



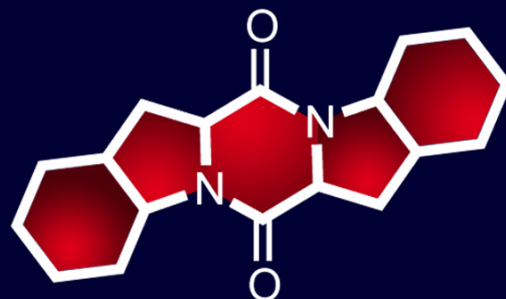
**epicoccin G**

[IC<sub>50</sub>=13.5  $\mu$ M in C8166 cells]



**exserohilone**

[antibacterial, antifungal]



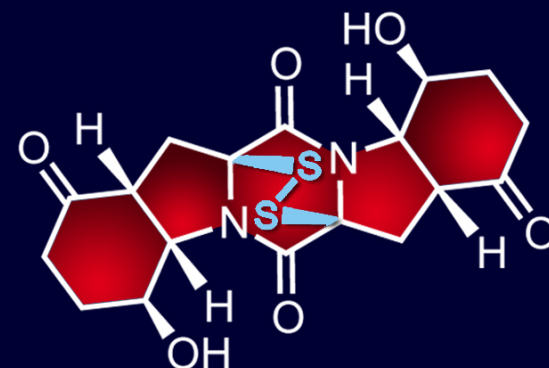
**diketopiperazine framework**

## ● Epidithiodiketopiperazines



**rostratin B**

[IC<sub>50</sub>=1.9  $\mu$ M against HTC-116 cells]

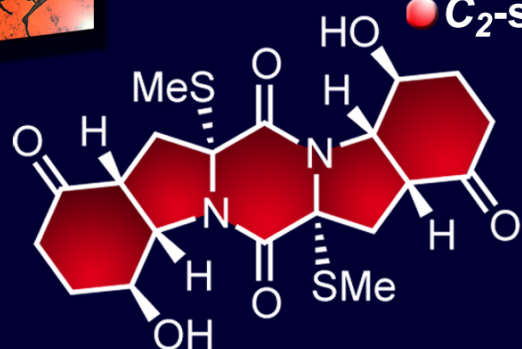


**8,8'-epi-ent-rostratin B**

[biological activity unknown]

# Retrosynthetic Analysis of Epicoccin G

● C<sub>2</sub>-symmetry allows two-directional strategy



epicoccin G

reduction



regioselective  
Konblum–DeLaMare  
rearrangement

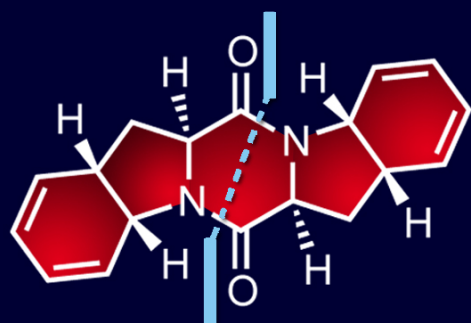


less hindered proton

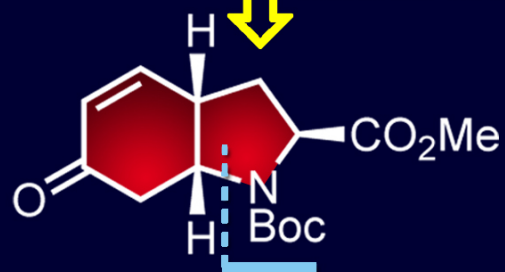
sulfenylation



photooxygenation  
[singlet oxygen]



dimerization



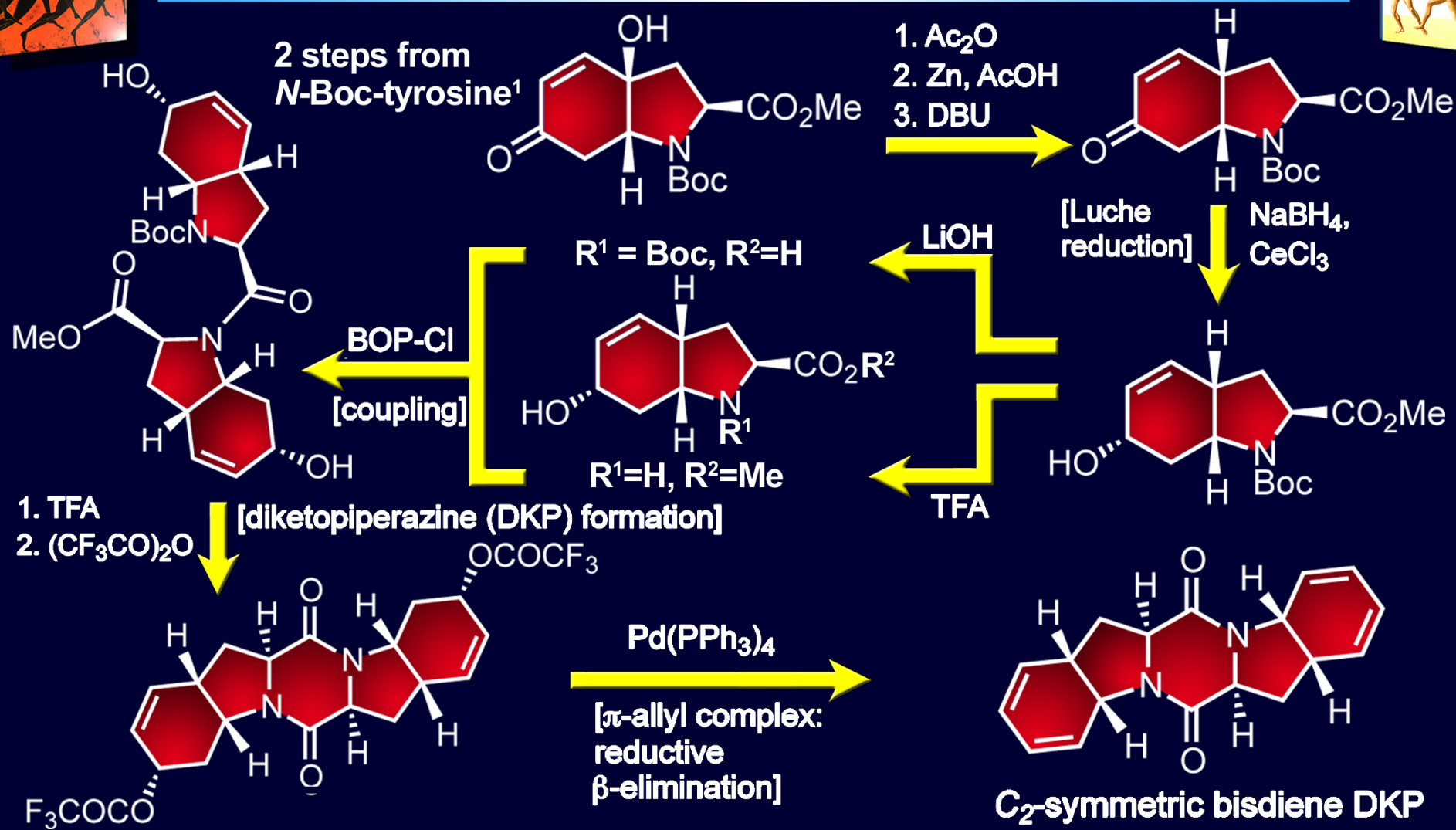
elaboration



N-Boc-tyrosine



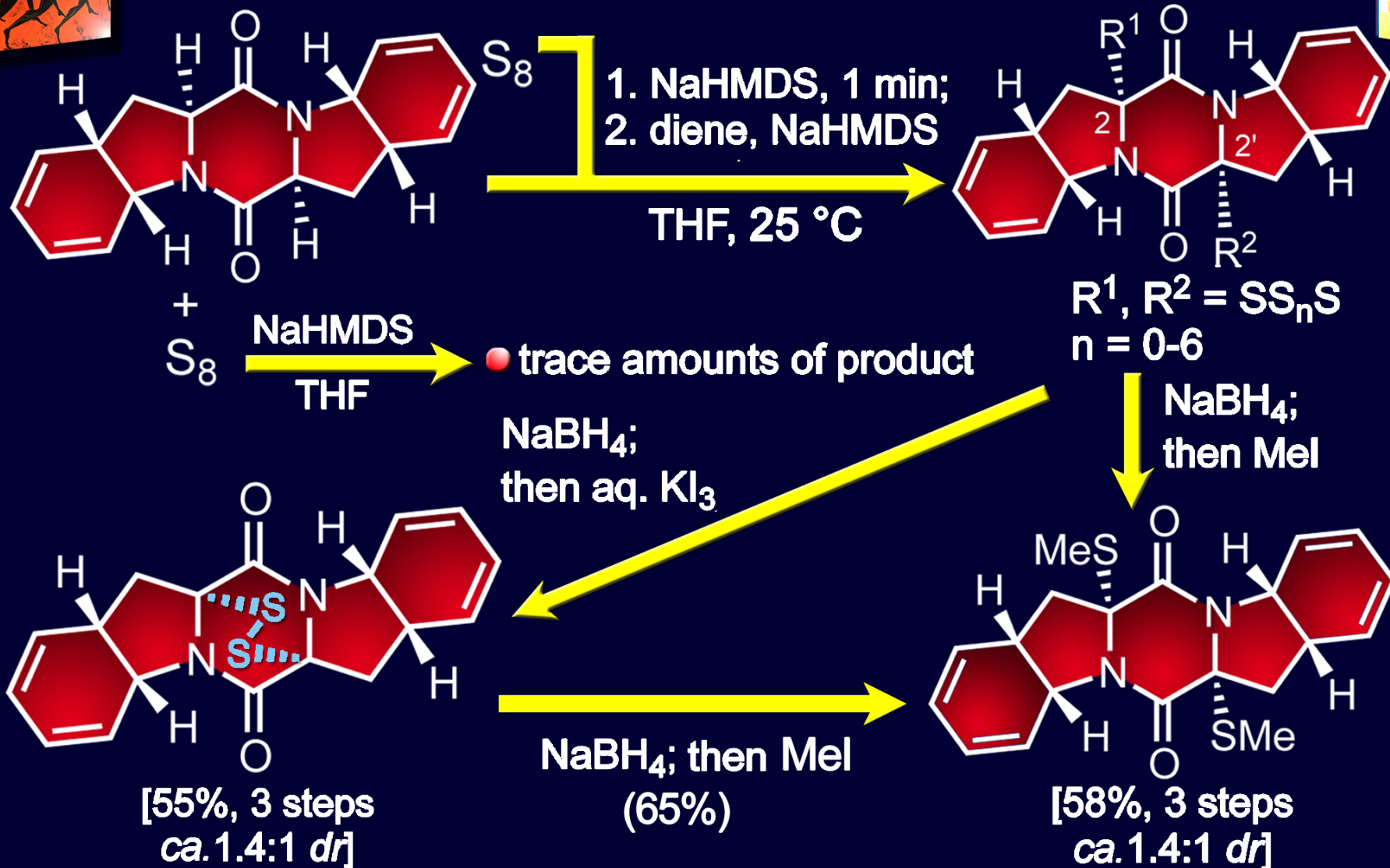
# Construction of $C_2$ -Symmetric Diene Precursor



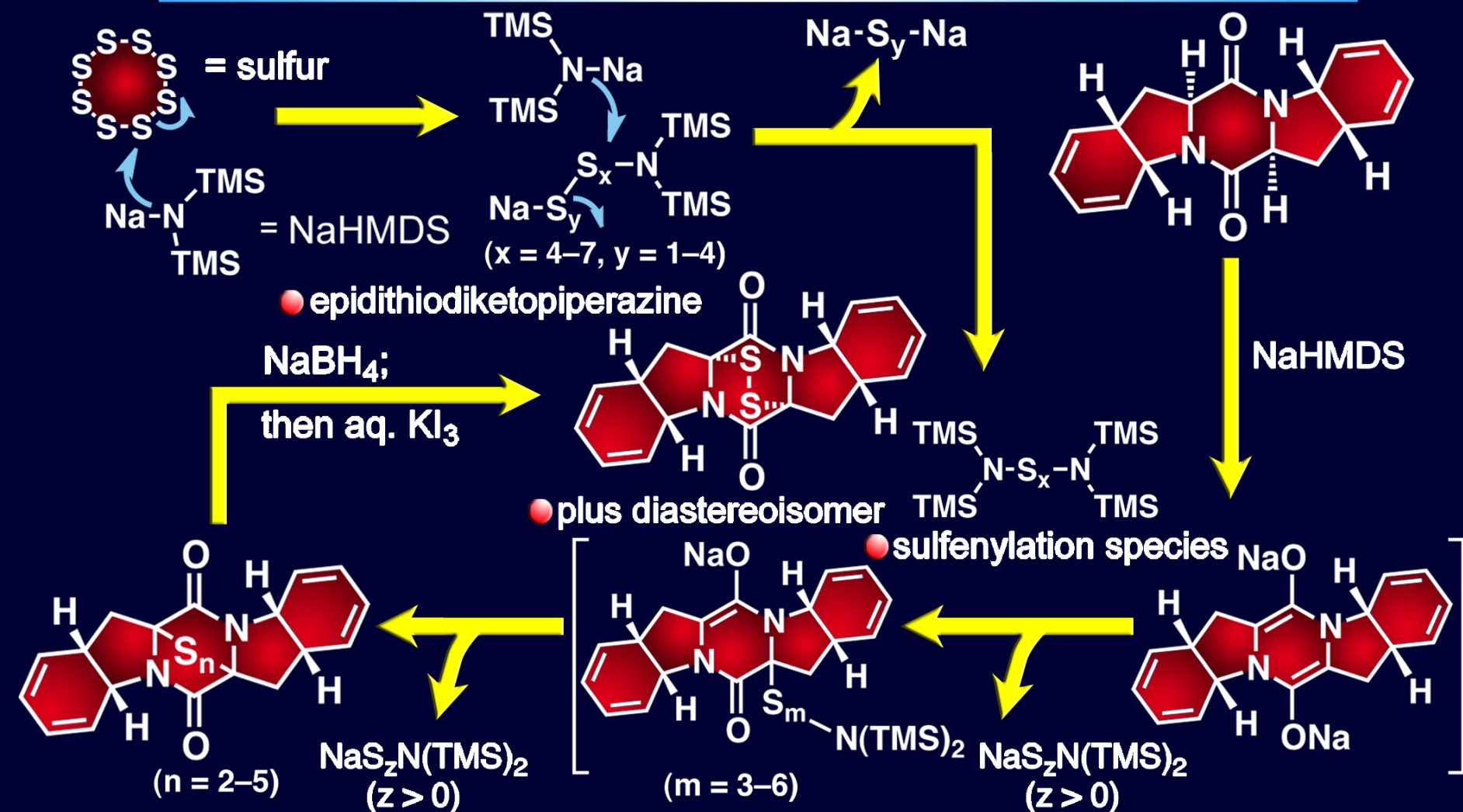
<sup>1</sup>Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, 33, 5477



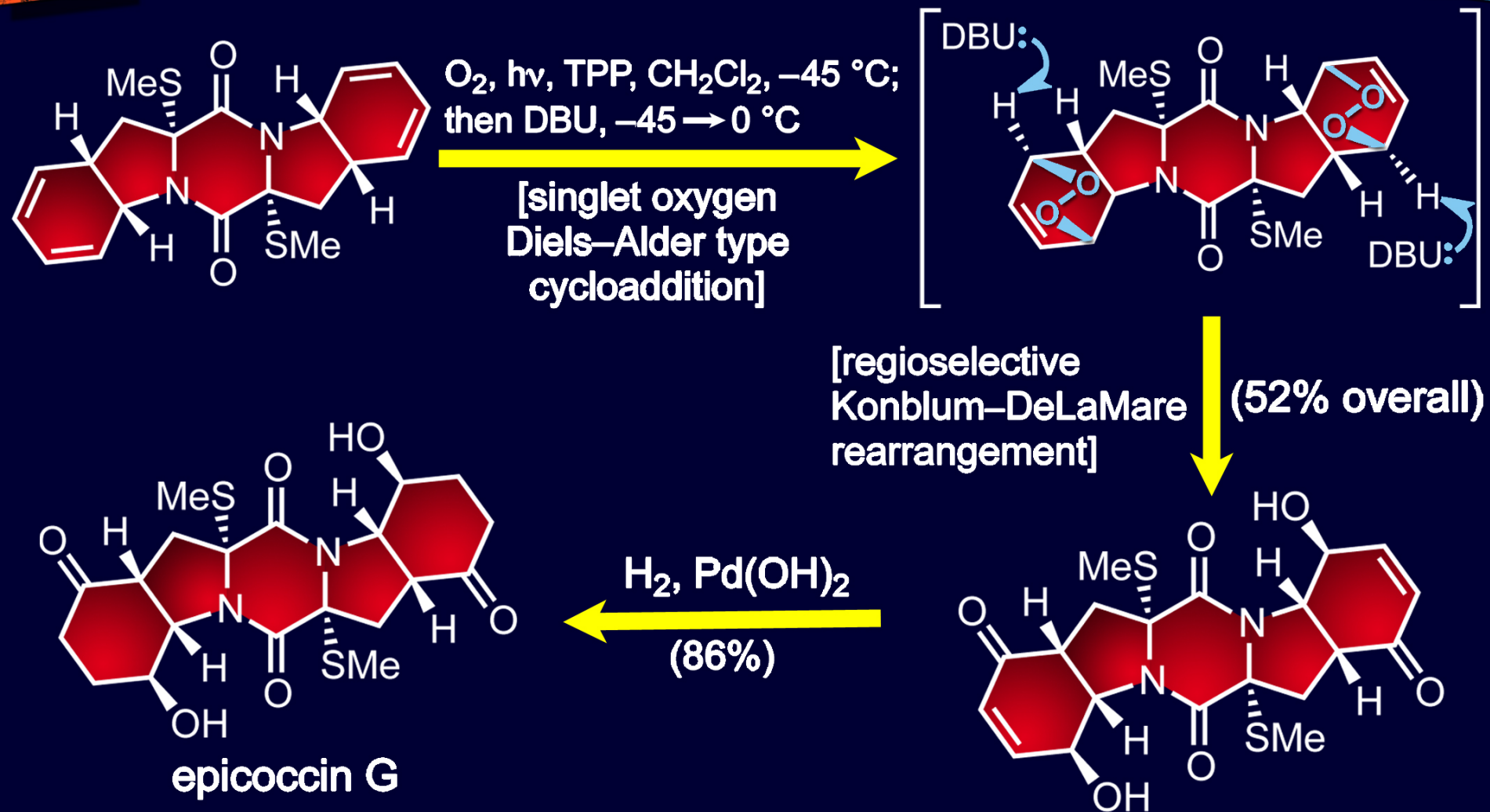
# Synthesis of Dithiodiketopiperazines



# Plausible Mechanism of the Sulfenylation Reaction of Diketopiperazines



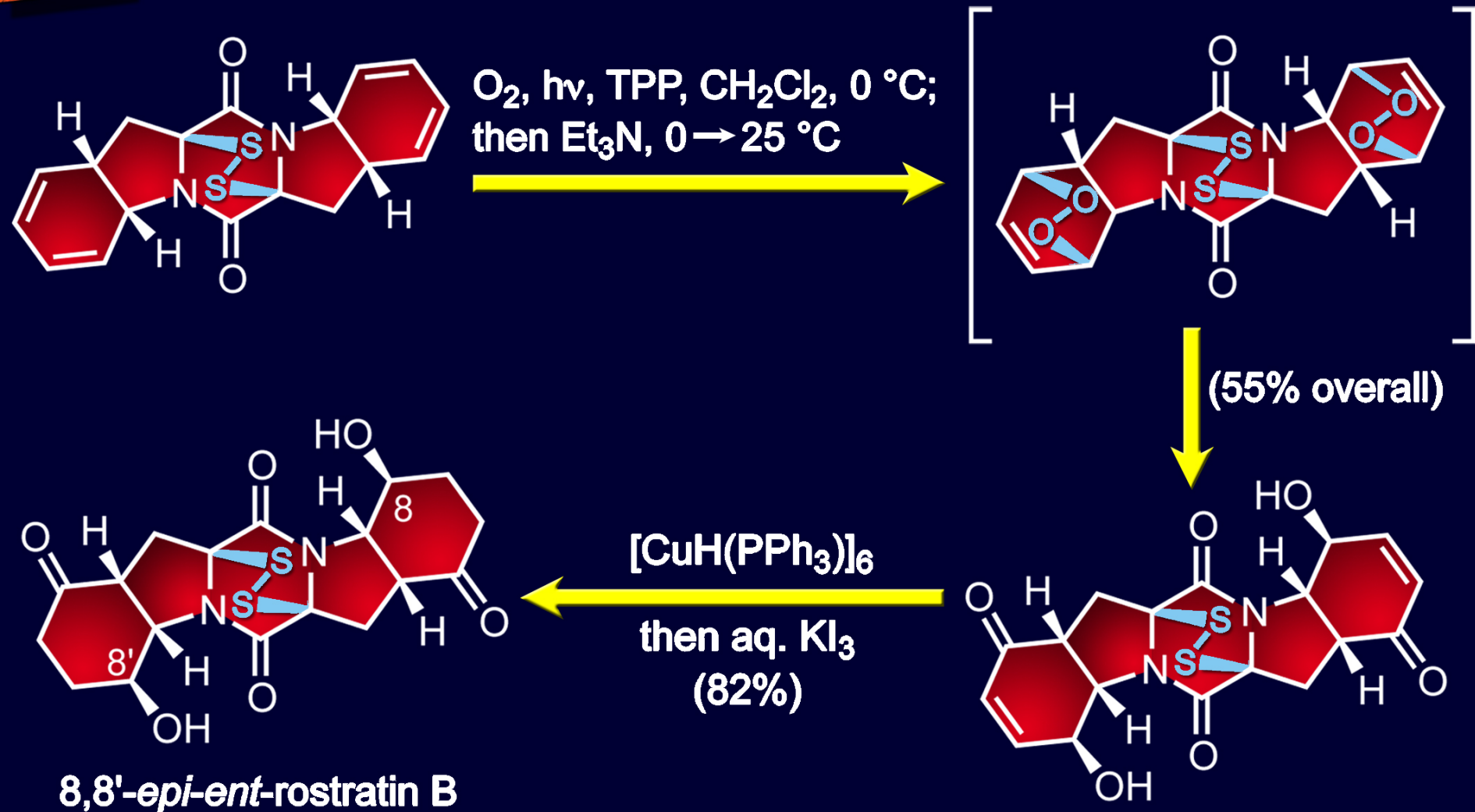
# Total Synthesis of Epicoccin G



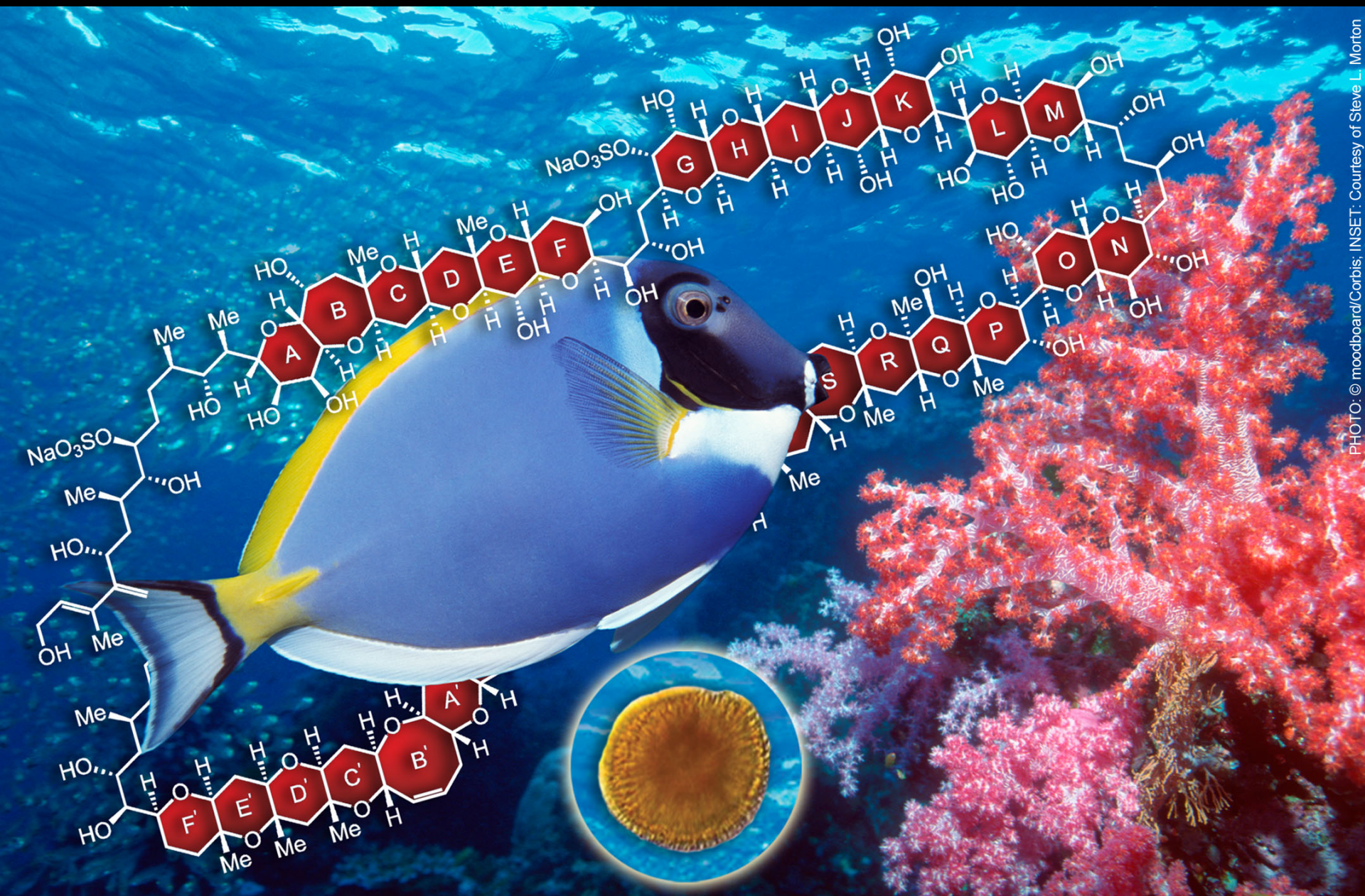




# Total Synthesis of 8,8'-*epi-ent-rostratin B*







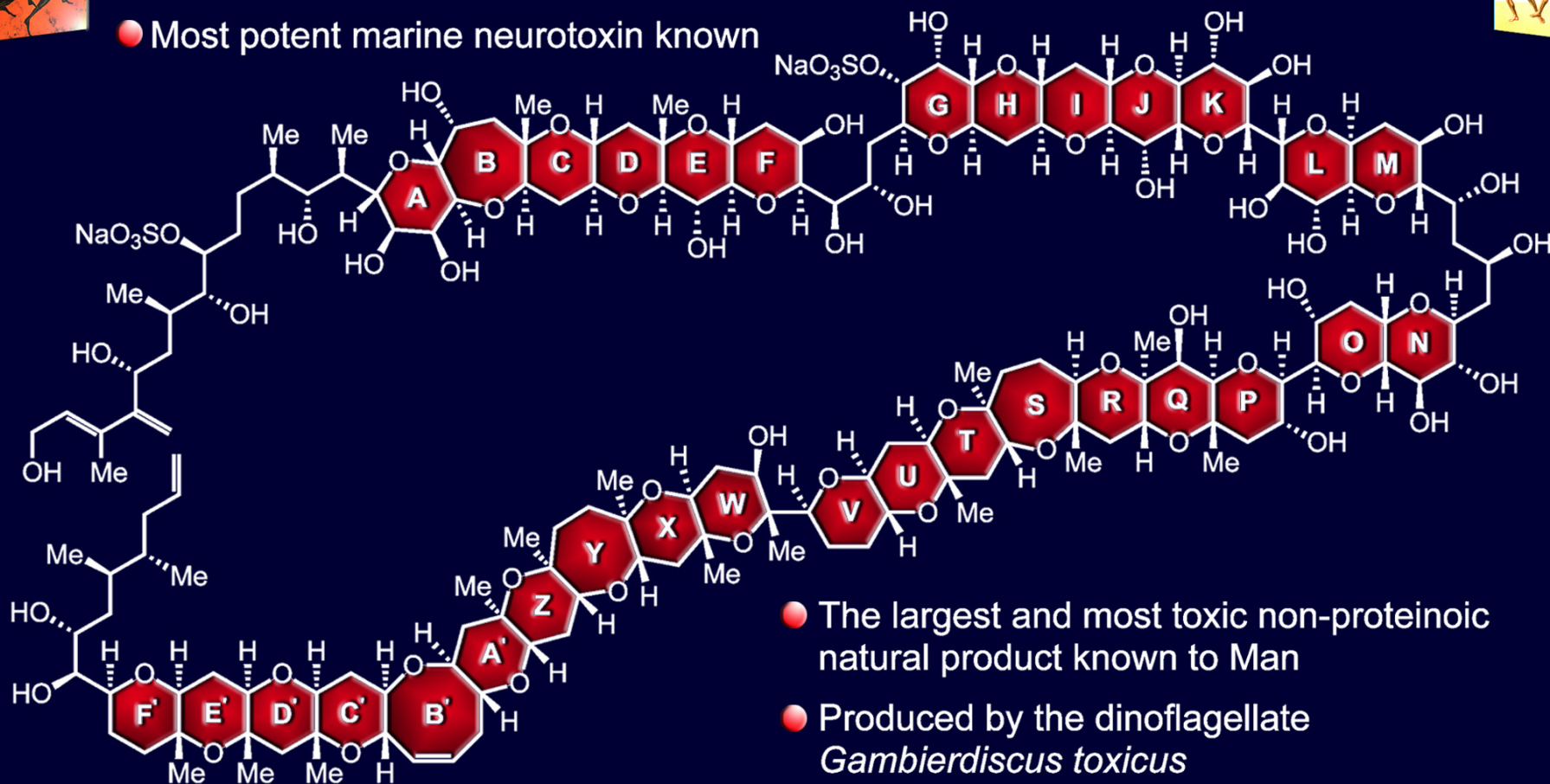




# PROPOSED STRUCTURE OF MAITOTOXIN



- Most potent marine neurotoxin known



- $C_{164}H_{256}O_{68}S_2Na_2$  [MW 3422 Da]

- 32 rings, 98 stereogenic centers

- The largest and most toxic non-proteinogenic natural product known to Man
- Produced by the dinoflagellate *Gambierdiscus toxicus*
- $LD_{50}=50\text{ng/Kg}$ , 1 mg can kill a million mice
- Activates voltage-dependent Ca ion channels



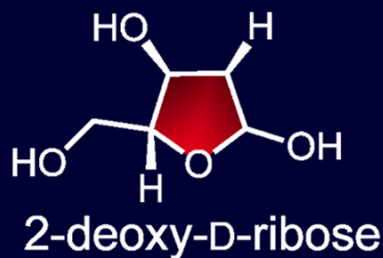
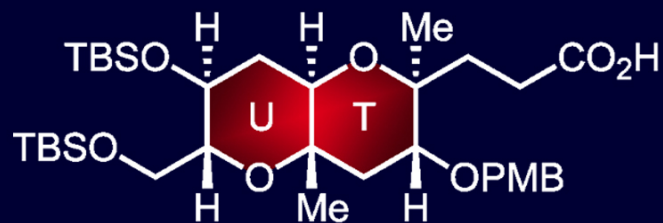
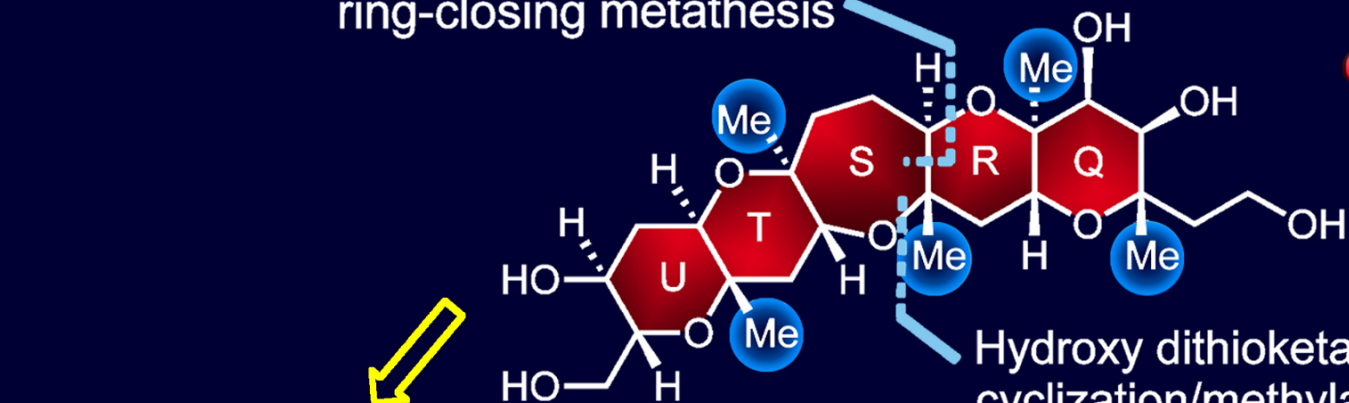


# RETROSYNTHETIC ANALYSIS OF MAITOTOXIN QRSTU RING SYSTEM

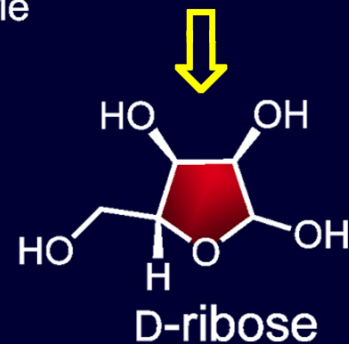


Esterification/  
ring-closing metathesis

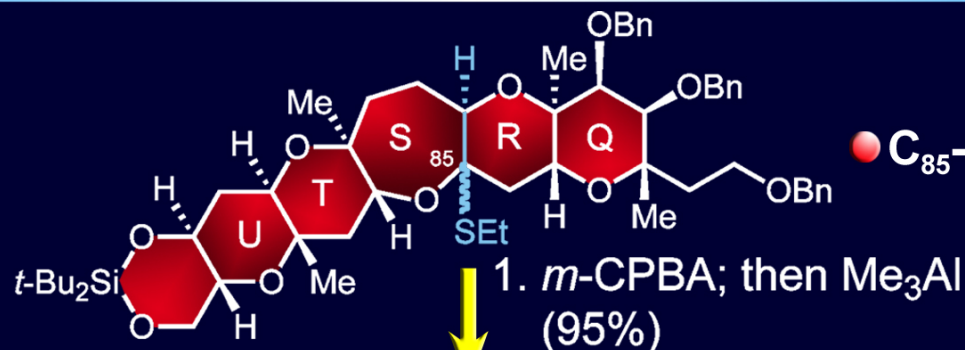
● 5 angular Me groups  
within a pentacyclic  
system



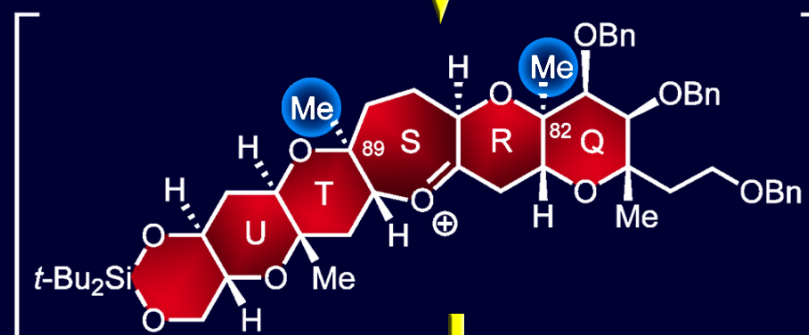
Hydroxy dithioketal  
cyclization/methylation



# MAITOTOXIN. SYNTHESIS OF THE QRSTU RING SYSTEM

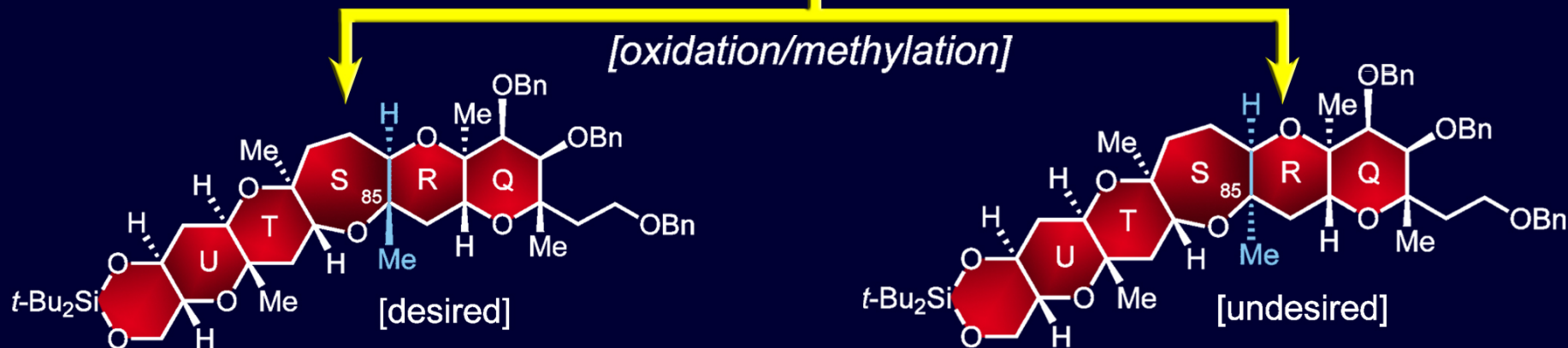


● C<sub>85</sub>-SEt β:α ca. 1:3 *dr*



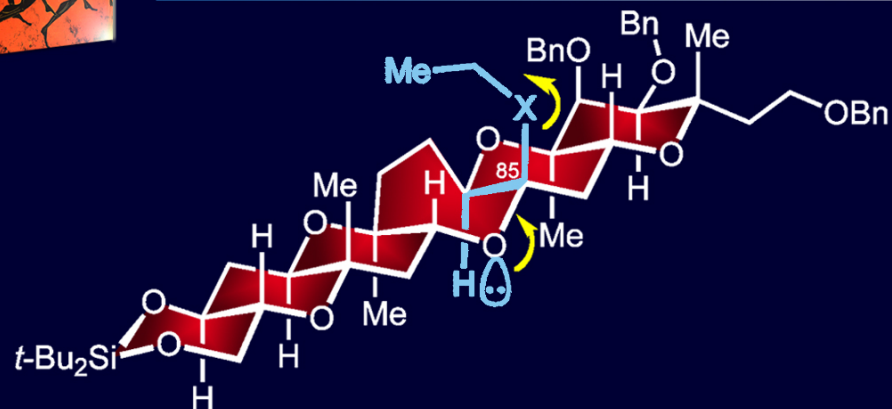
● ratio of substrates  
does not translate  
into same ratio of  
products

● C<sub>85</sub>-Me β:α ca. 1:0.8 *dr*





# MAITOTOXIN. SYNTHESIS OF THE QRSTU RING SYSTEM

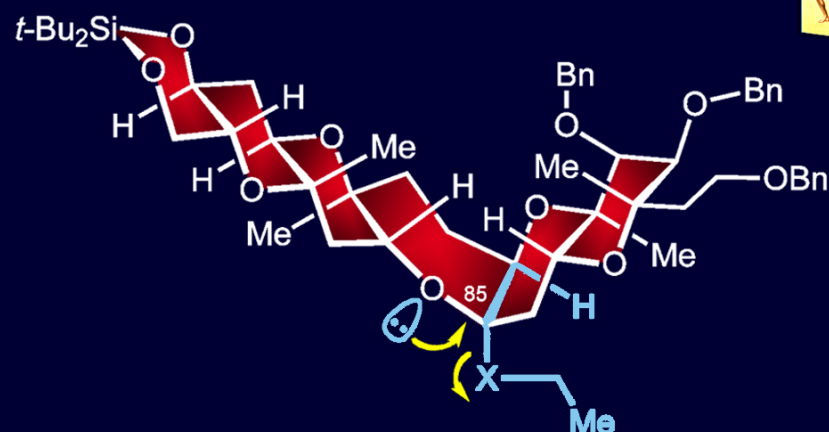
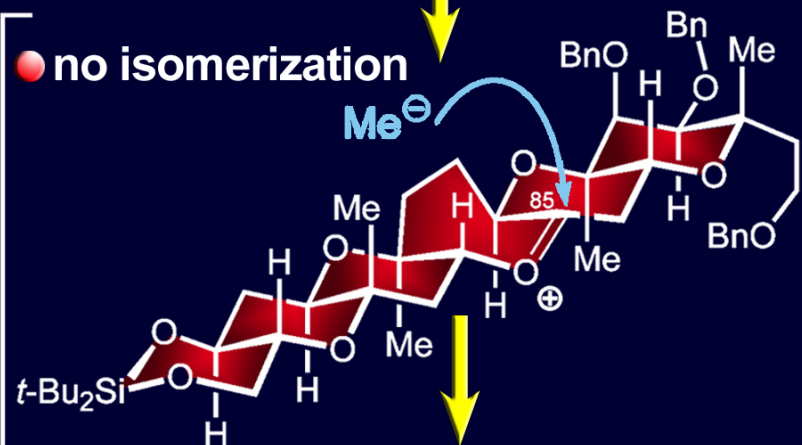


1. *m*-CPBA  $\begin{cases} \text{X} = \text{S} \text{ (minor)} \\ \text{X} = \text{SO}_2 \text{ (not isolated)} \end{cases}$

1. then  $\text{Me}_3\text{Al}$

[oxidation/methylation]

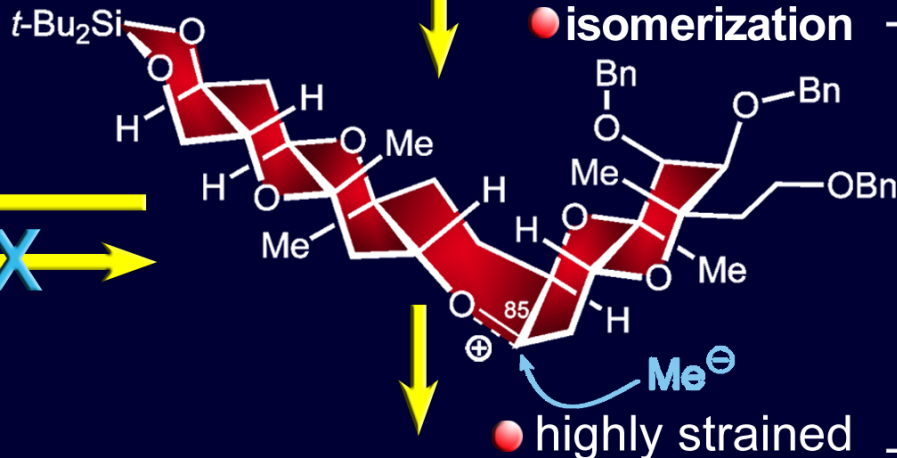
● no isomerization



1. *m*-CPBA  $\begin{cases} \text{X} = \text{S} \text{ (major)} \\ \text{X} = \text{SO}_2 \text{ (not isolated)} \end{cases}$

1. then  $\text{Me}_3\text{Al}$

● isomerization

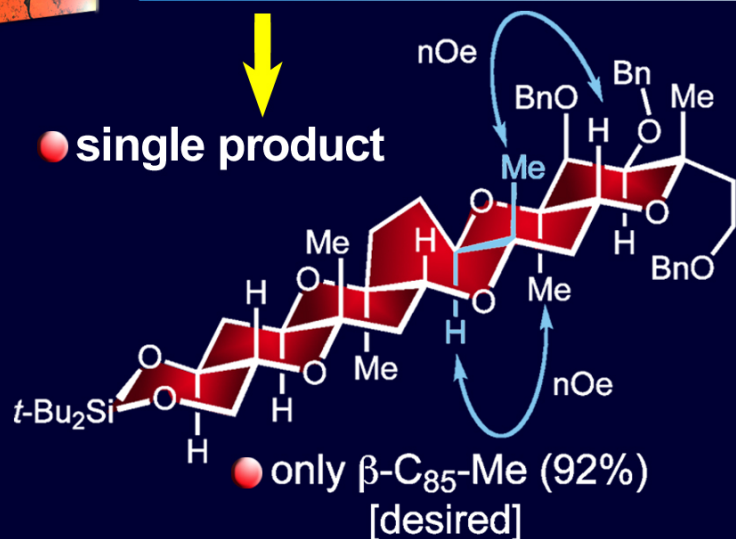


● highly strained

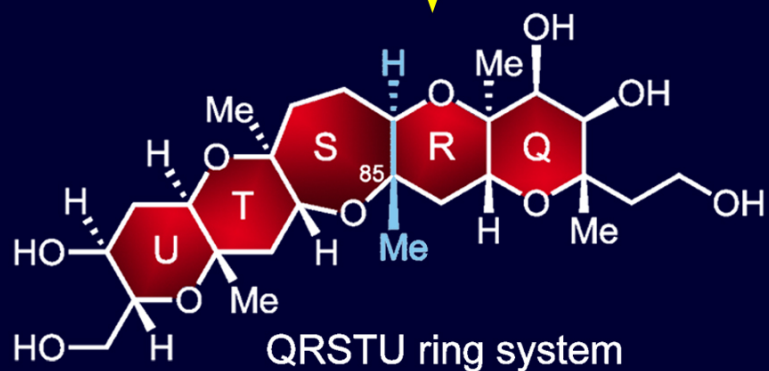


# MAITOTOXIN. SYNTHESIS OF THE QRSTU DOMAIN AND THE 85-*epi*-QRSTU RING SYSTEM

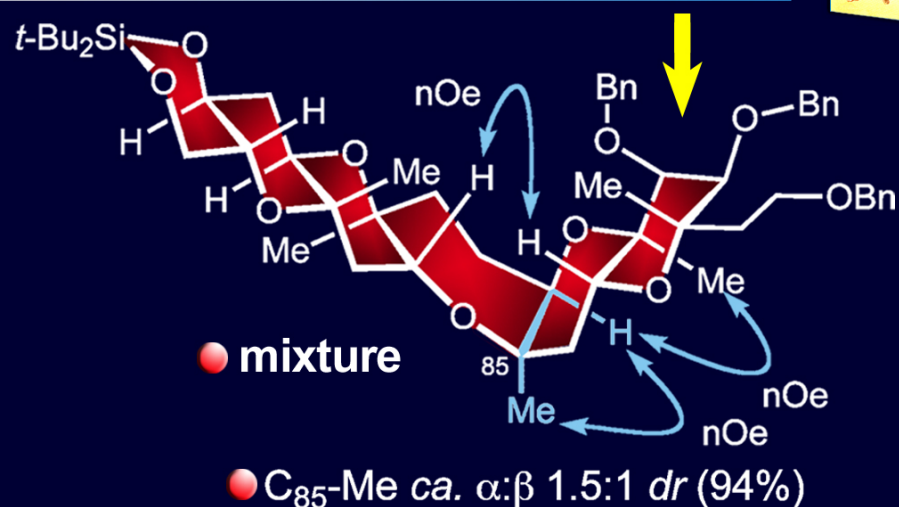
● single product



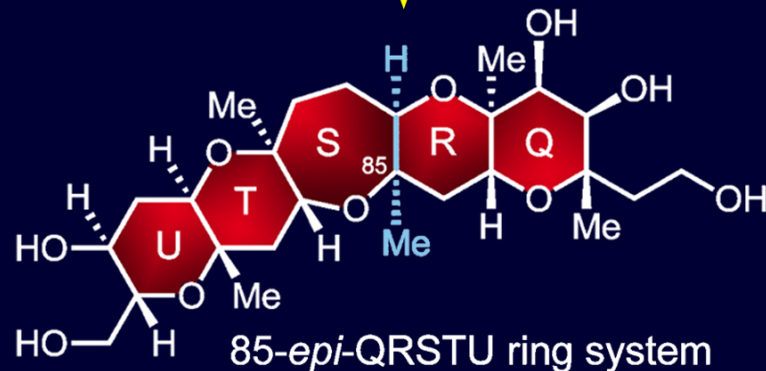
1. TBAF  
2. H<sub>2</sub>, Pd(OH)<sub>2</sub>/C  
(87%, 2 steps)



● mixture



1. TBAF  
2. H<sub>2</sub>, Pd(OH)<sub>2</sub>/C  
(80%, 2 steps)

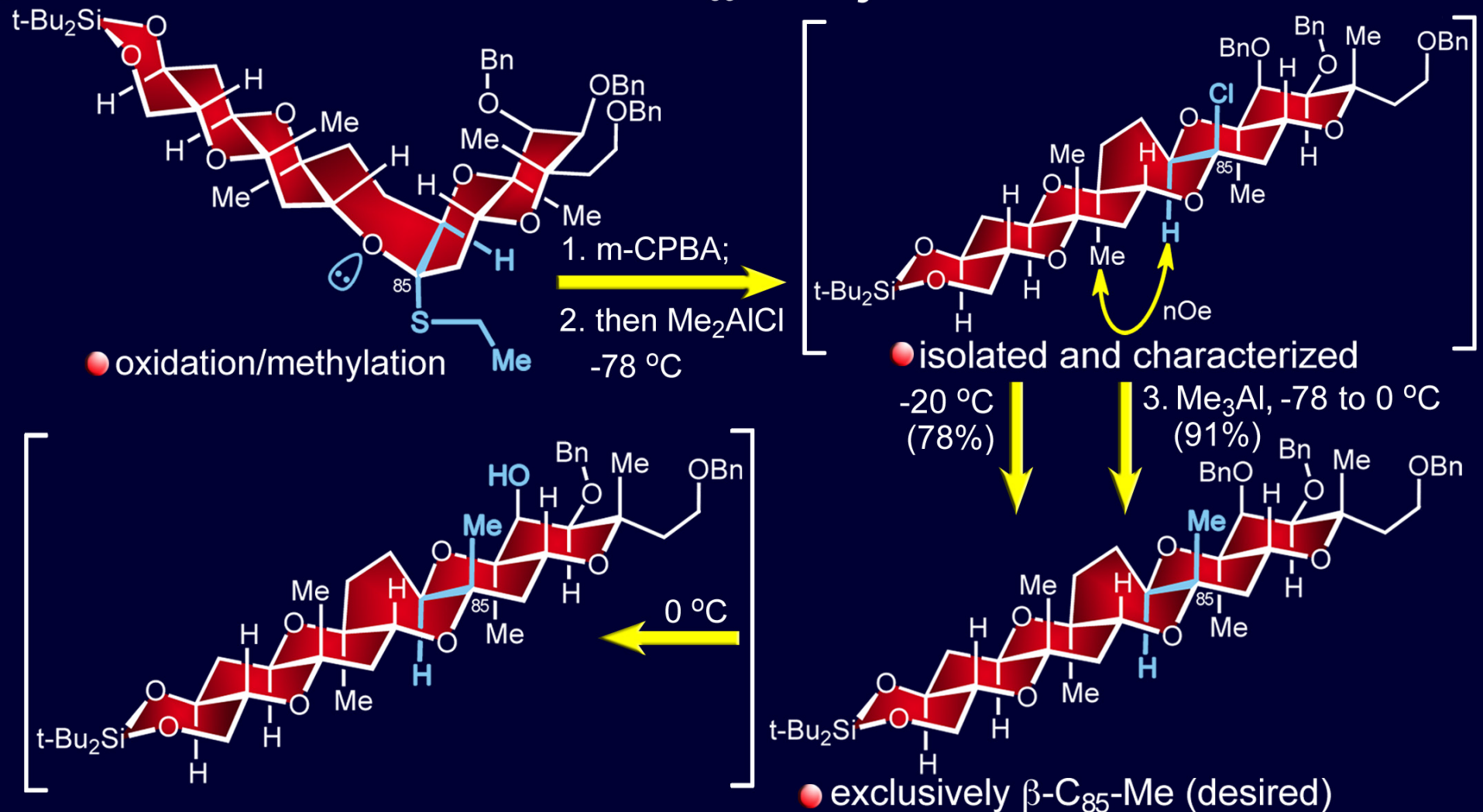




# MAITOTOXIN. SYNTHESIS OF THE QRSTU RING SYSTEM



## ● Solution to the C<sub>85</sub>-Methylation Problem



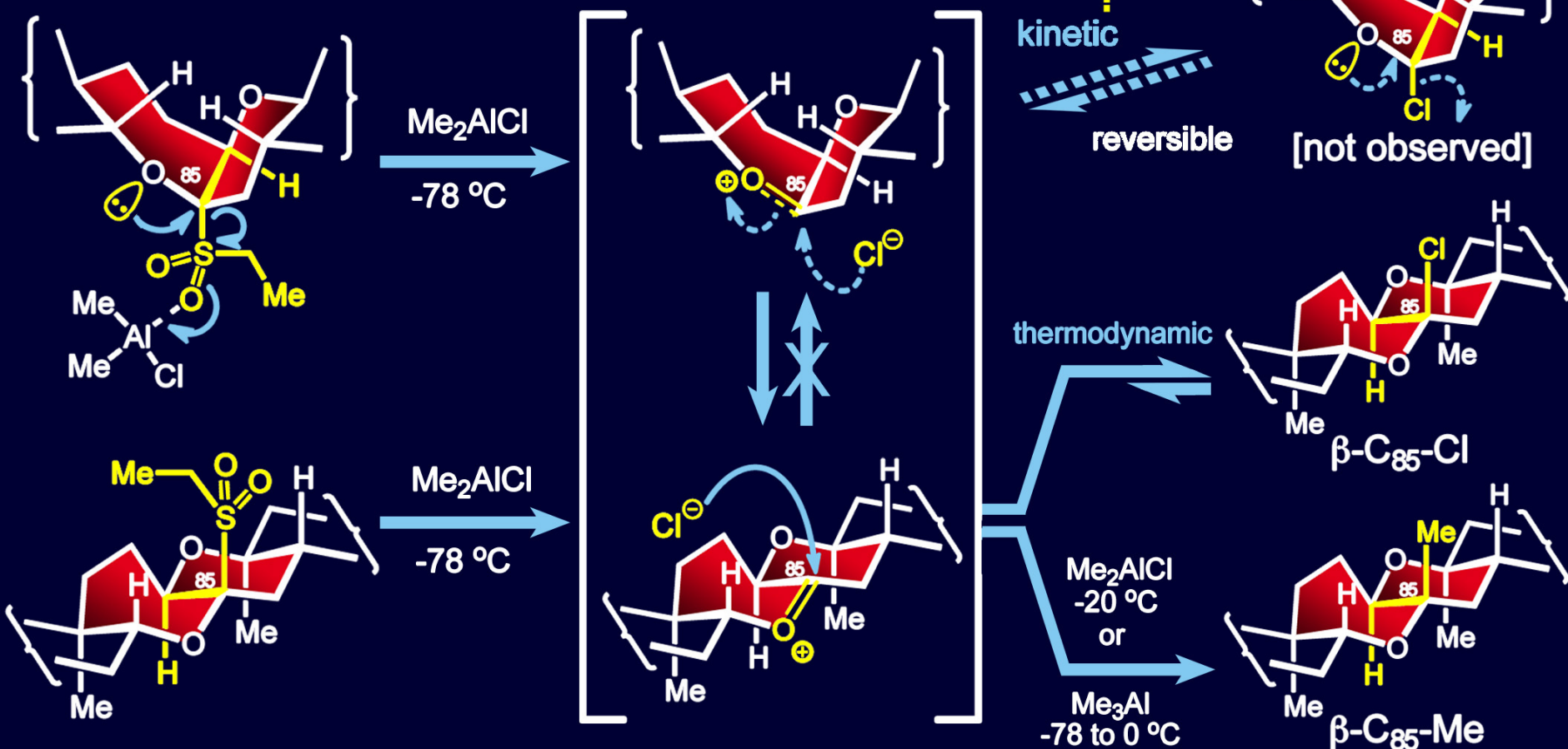


# Maitotoxin. Synthesis of the QRSTU Ring System



## Mechanism of $\beta$ -C<sub>85</sub>-Cl Formation

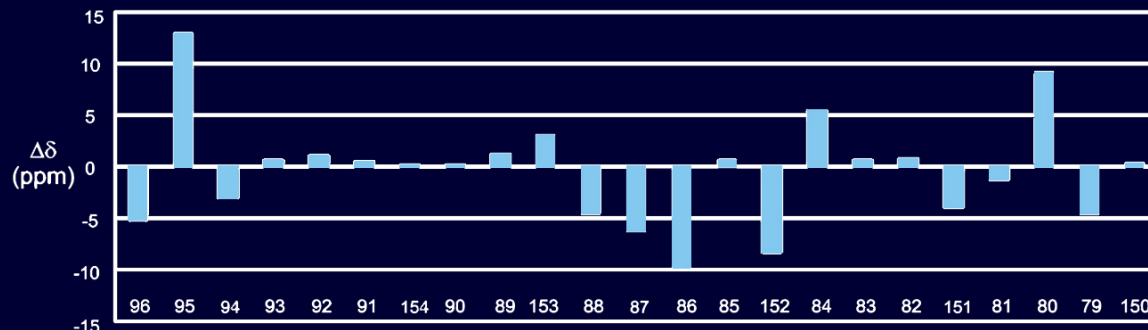
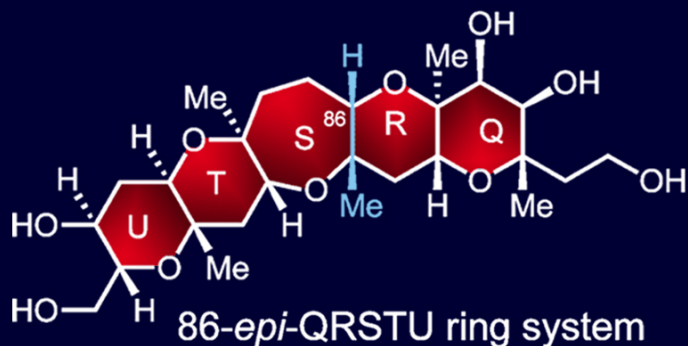
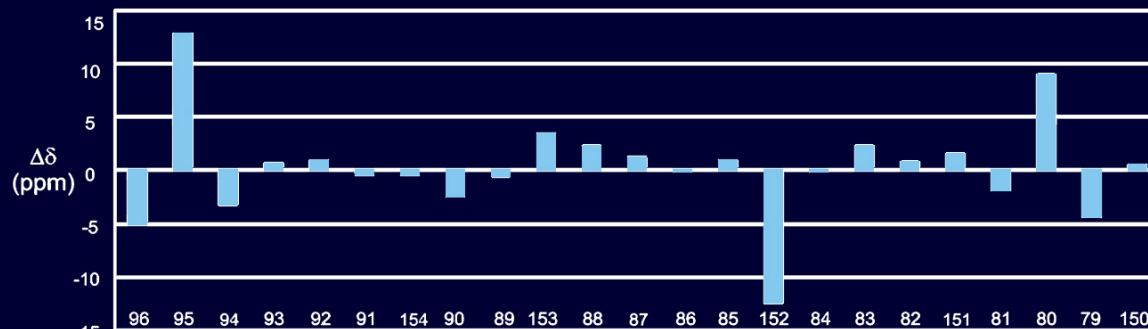
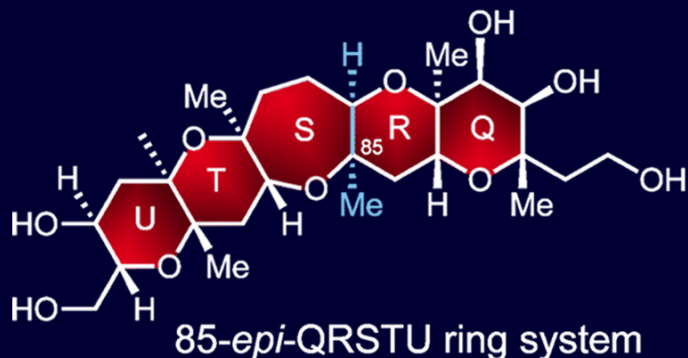
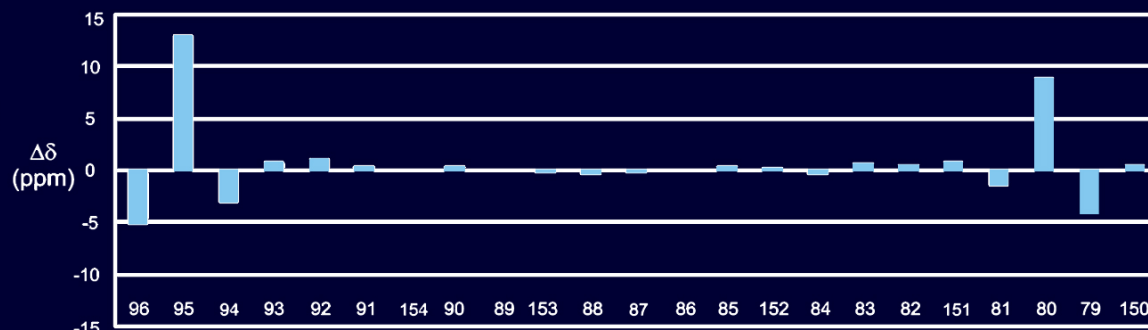
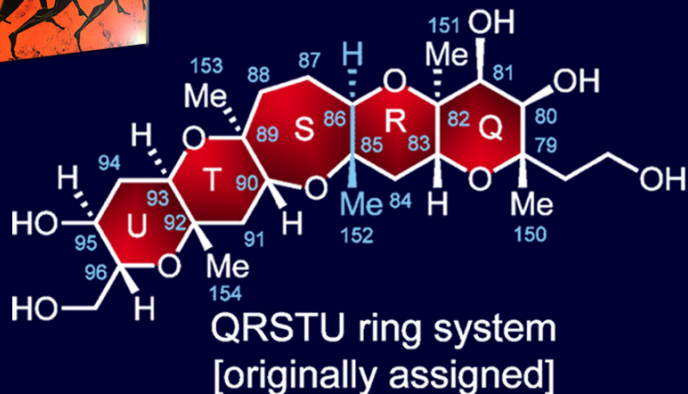
- Most likely ion pair in close proximity to oxonium species







# MAITOTOXIN. $^{13}\text{C}$ NMR DATA FOR THE QRSTU DOMAIN

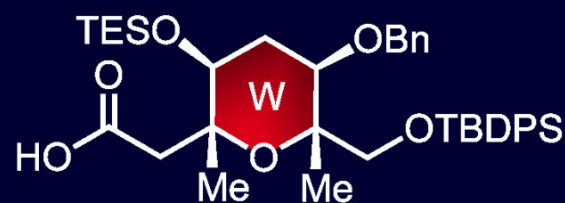
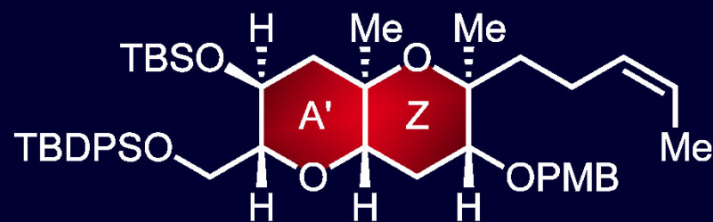
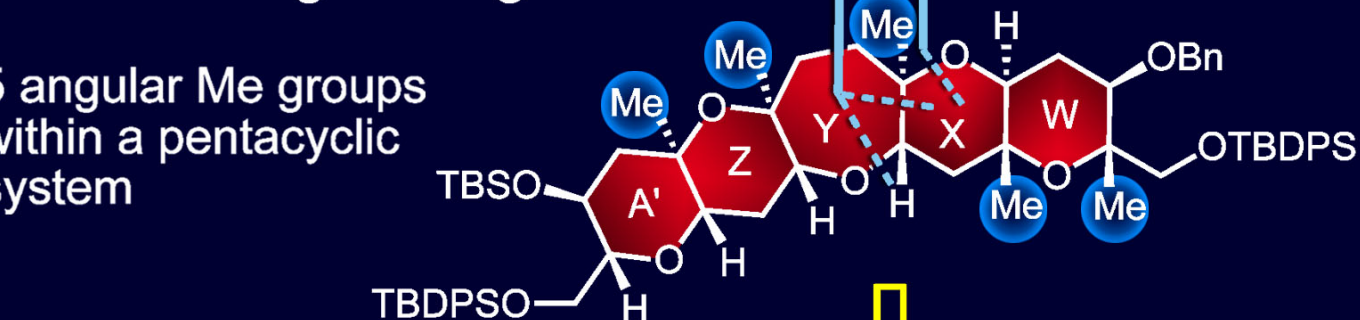


# RETROSYNTHETIC ANALYSIS OF MAITOTOXIN WXYZA' RING SYSTEM

Esterification/  
ring-closing metathesis

Hydroxy dithioketal cyclization/  
methylation

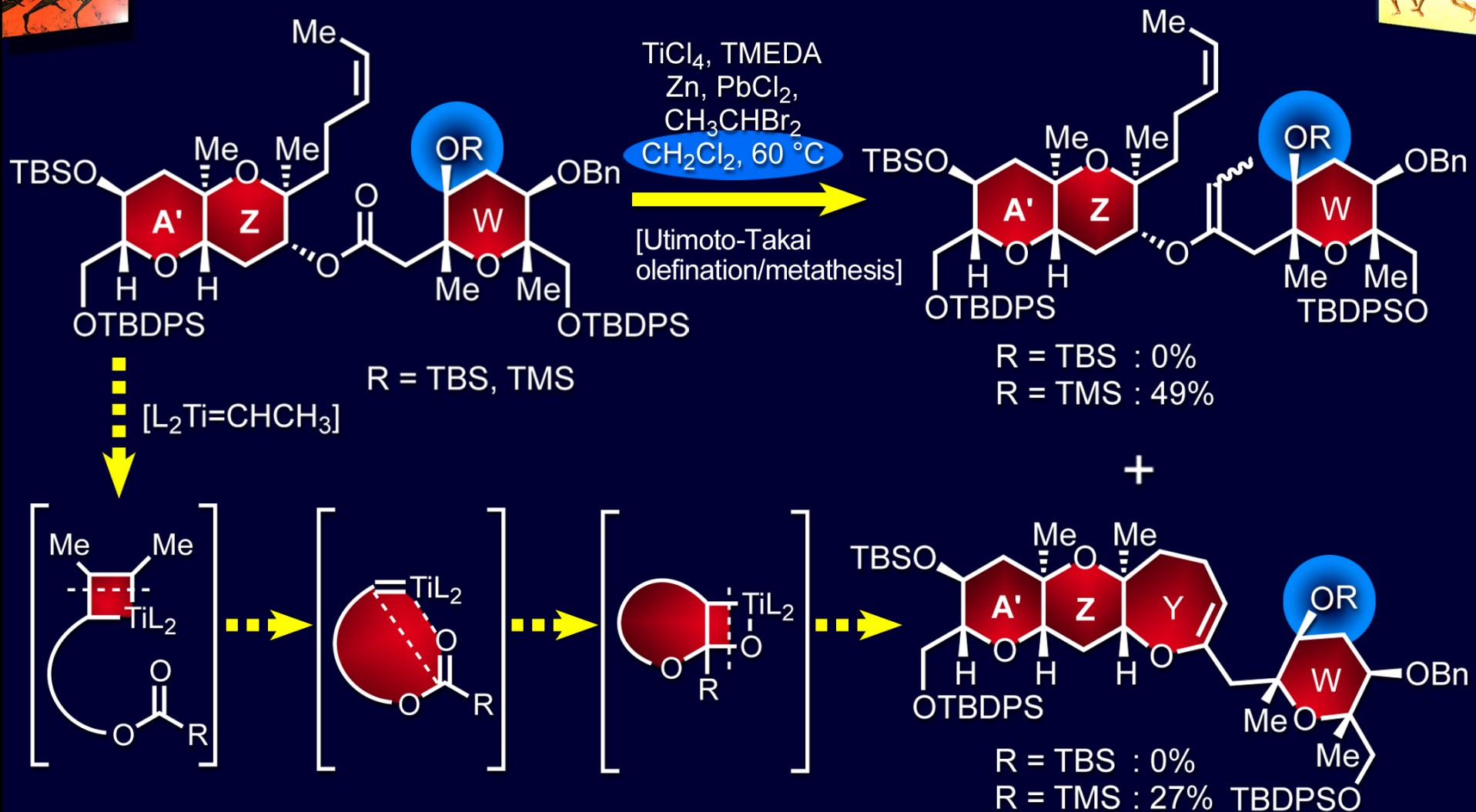
- 5 angular Me groups within a pentacyclic system



2-deoxy-D-ribose



# MAITOTOXIN. CONSTRUCTION OF THE A'ZYW RING SYSTEM



see also: H. W. B. Johnson, U. Majumder, and J. D. Rainier; *Chem. Eur. J.* **2006**, 12, 1747 – 1753

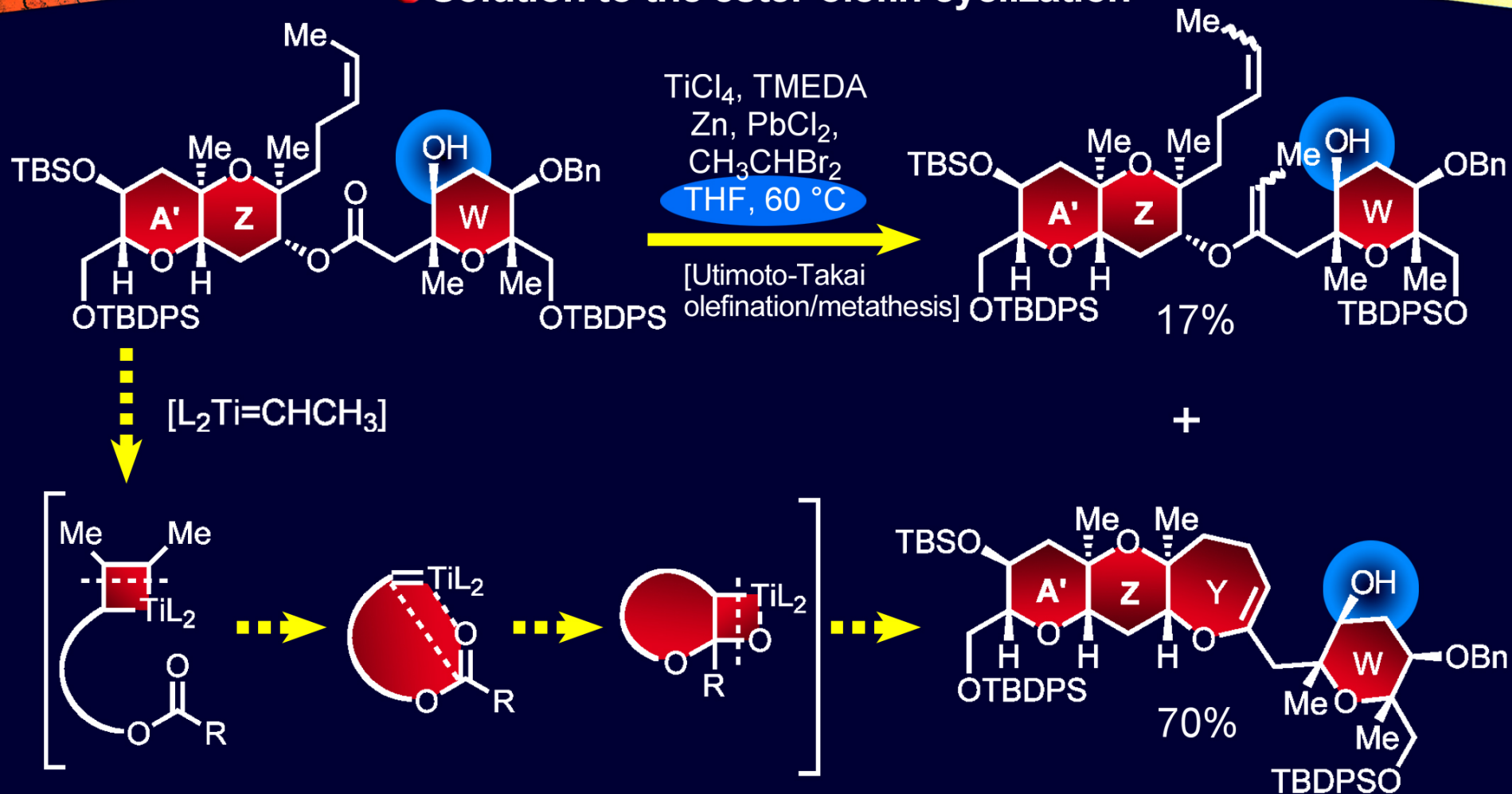




# MAITOTOXIN. CONSTRUCTION OF THE A'ZYW RING SYSTEM



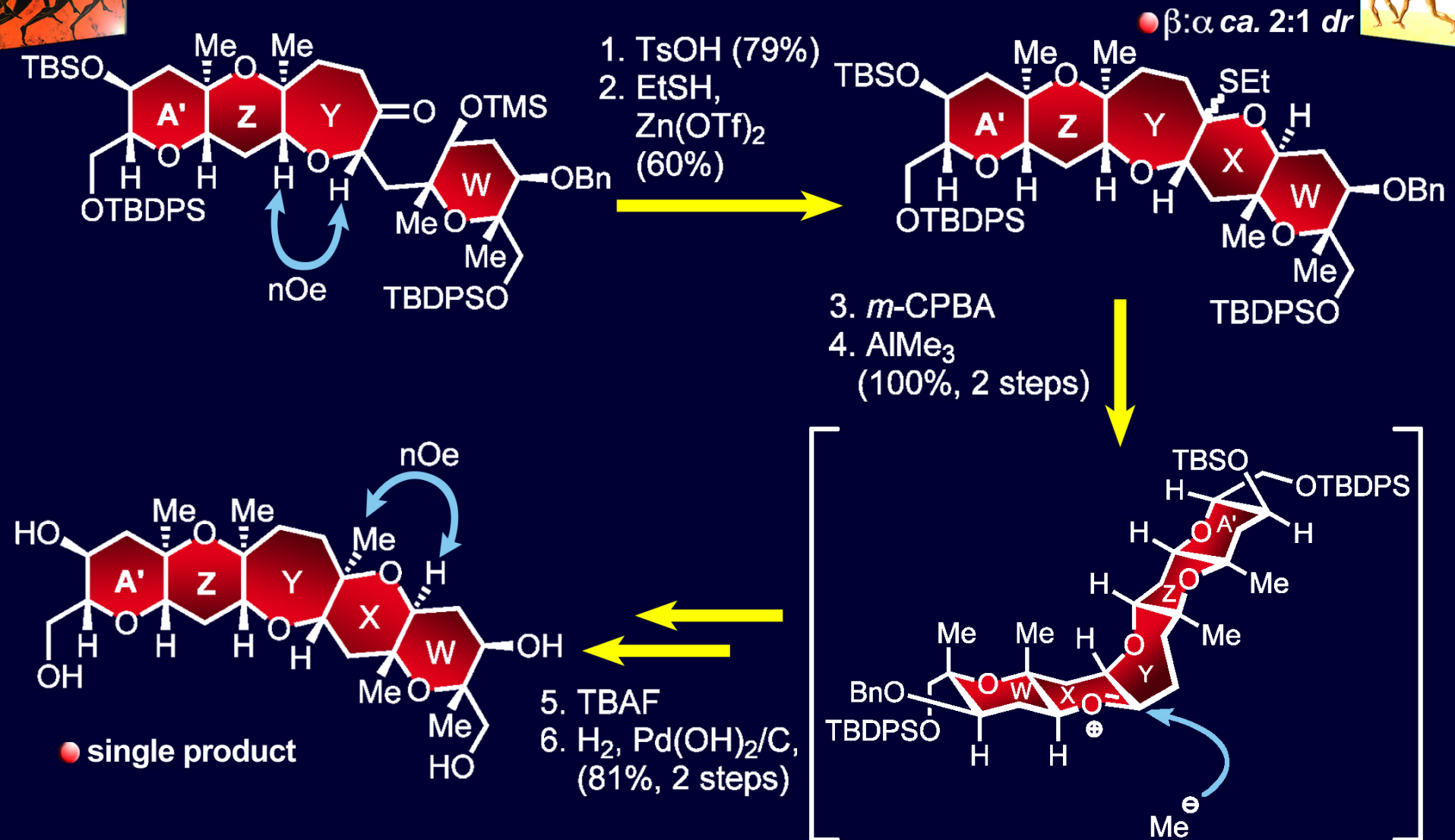
## ● Solution to the ester-olefin cyclization



see also: H. W. B. Johnson, U. Majumder, and J. D. Rainier; *Chem. Eur. J.* **2006**, 12, 1747 – 1753

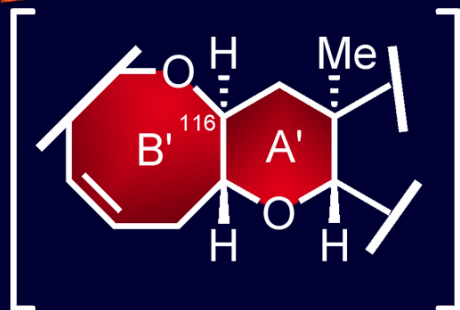


# MAITOTOXIN. CONSTRUCTION OF THE A'ZYXW RING SYSTEM

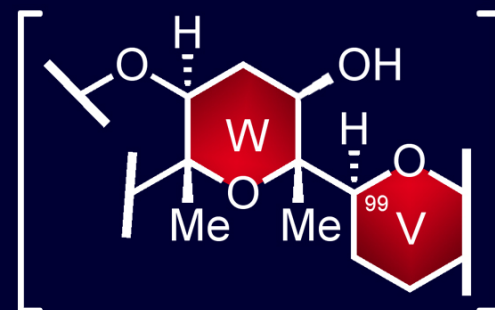
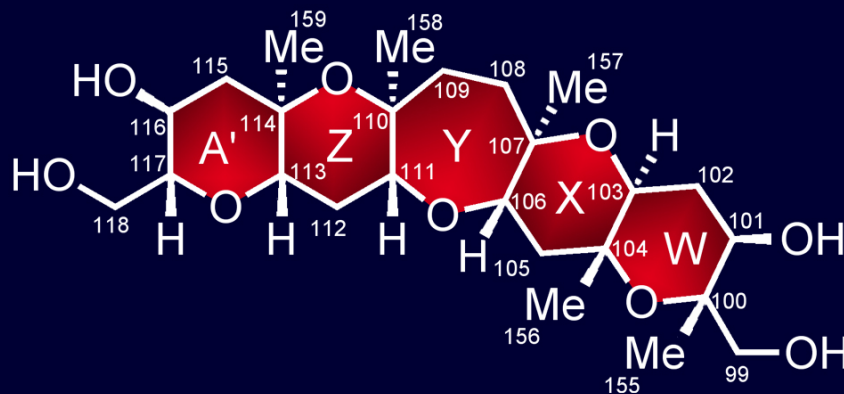




# MAITOTOXIN. $^{13}\text{C}$ DATA FOR THE WXYZA' DOMAIN

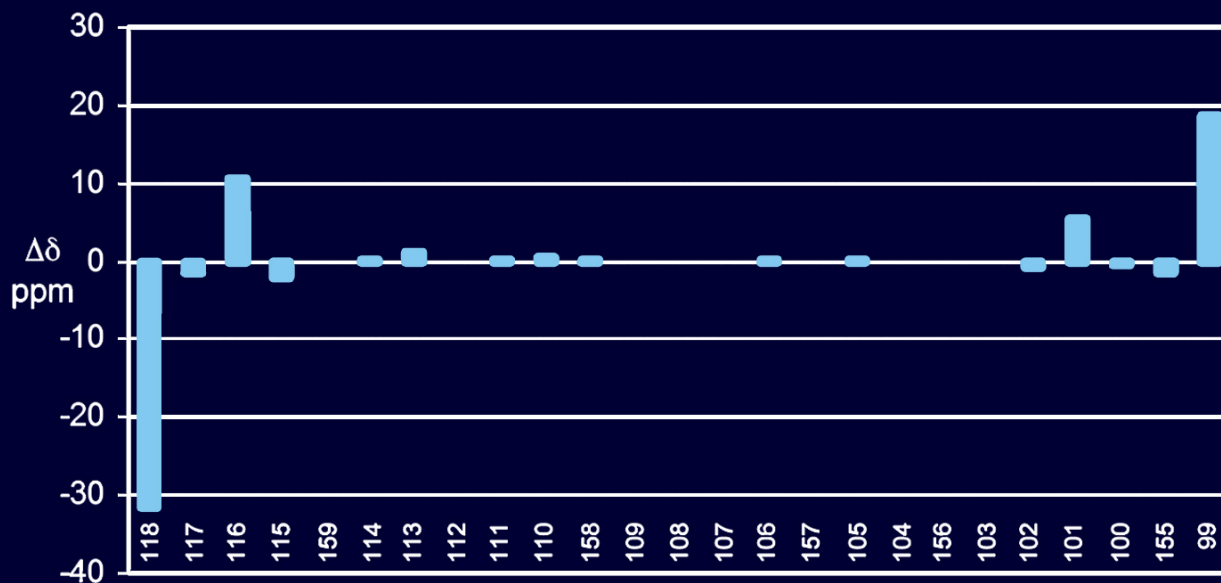


maitotoxin structure



maitotoxin structure

●  $\Delta\delta$  values between maitotoxin and synthetic A'ZYXW domain



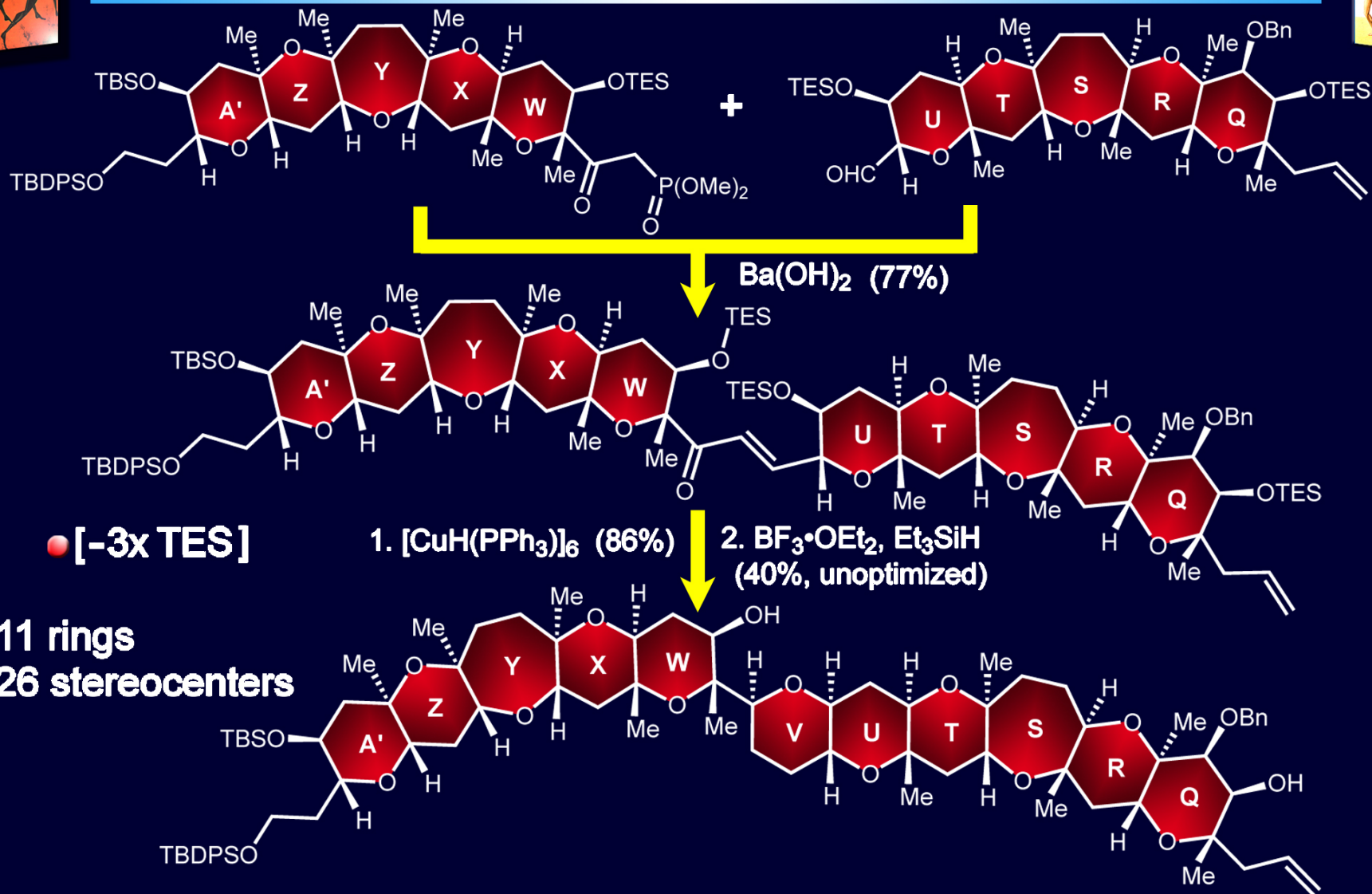
● Larger  $\Delta\delta$  at the ends due to a greater degree of structural variation

● Average  $\Delta\delta$  for C102-C115 = 0.36 ppm. Largest  $\Delta\delta$  for C102-C115 = 2.2 ppm



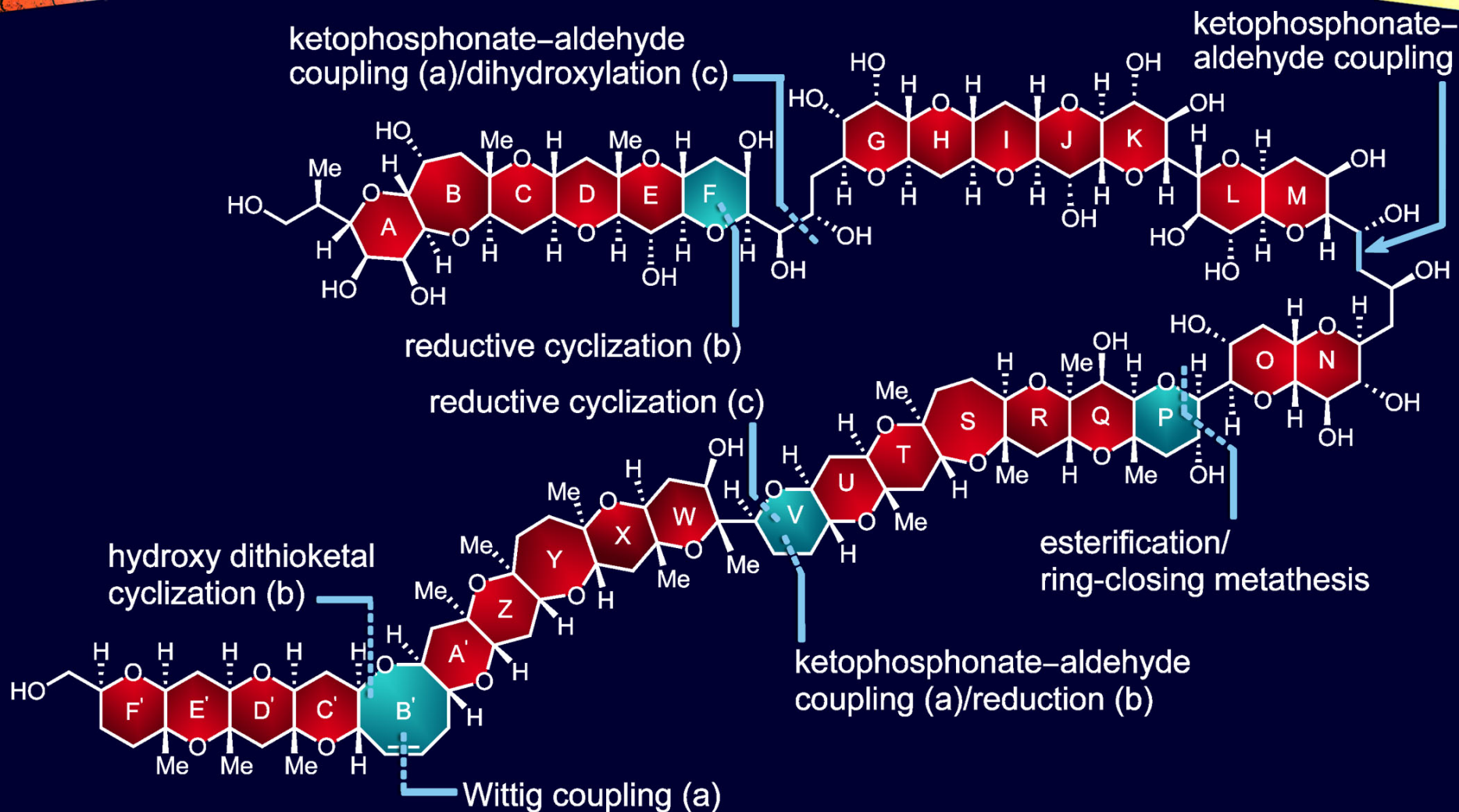


# Maitotoxin: Synthesis of QRSTUVWXYZA' Domain





# MAITOTOXIN POLYCYCLIC FRAMEWORK: FINAL COUPLINGS AND RING CLOSURES







# BREAKING NEW GROUND IN TOTAL SYNTHESIS

## INSPIRATIONS FROM NATURE

NOVEL MOLECULAR ARCHITECTURES ●

COMPLEX AND CHALLENGING TARGETS ●

BOND CONNECTIVITIES ●

RING FRAMEWORKS ●

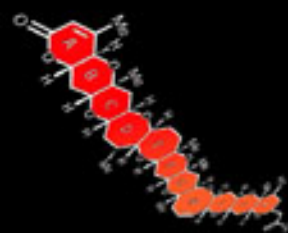
STEREOGENIC CENTERS ●

UNUSUAL, SENSITIVE FUNCTIONALITIES ●

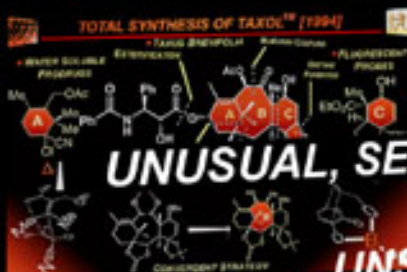
UNSYNTHESIZED MOLECULES ●

IMPORTANT BIOLOGICAL ACTIVITY ●

INTERESTING MECHANISM OF ACTION ●



TOTAL SYNTHESIS OF ELEUTHEROBIN AND SARCOICIC ACID [1987]



## DISCOVERIES AND INVENTIONS

● BIOMIMETIC SYNTHETIC STRATEGIES

● CASCADE REACTIONS

● SOLID PHASE SYNTHESIS

● COMBINATORIAL CHEMISTRY

● ASYMMETRIC SYNTHESIS

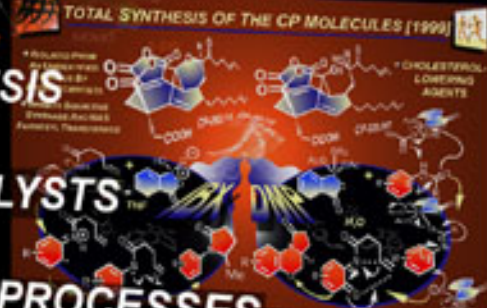
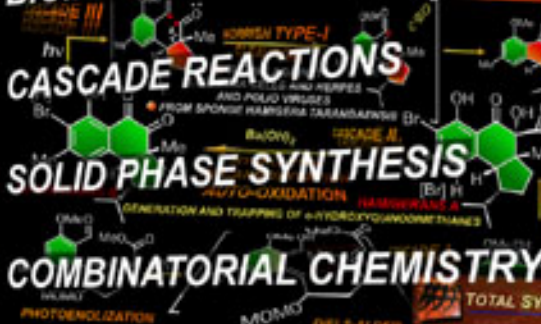
● REAGENTS AND CATALYSTS

● EFFICIENT CHEMICAL PROCESSES

● GREEN CHEMISTRY

● DESIGNED BIOACTIVE MOLECULES

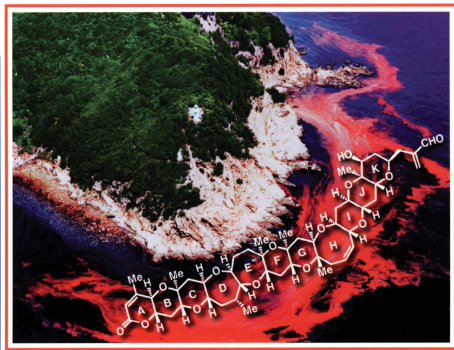
TOTAL SYNTHESIS OF HAMIGERANS [2001]





K. C. NICOLAOU, E. J. SORENSEN

# CLASSICS IN TOTAL SYNTHESIS



TARGETS, STRATEGIES, METHODS

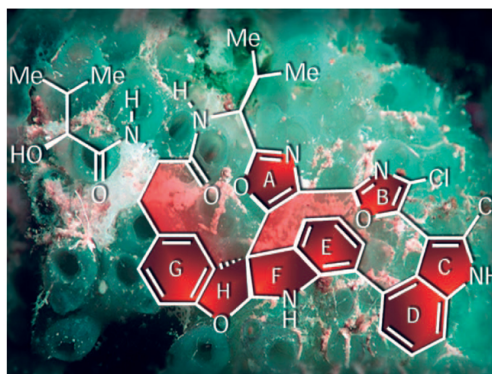


Nicolaou · Snyder

WILEY-VCH

## Classics in Total Synthesis II

Targets, Strategies, Methods

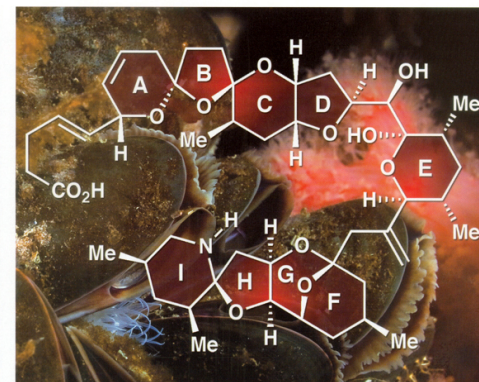


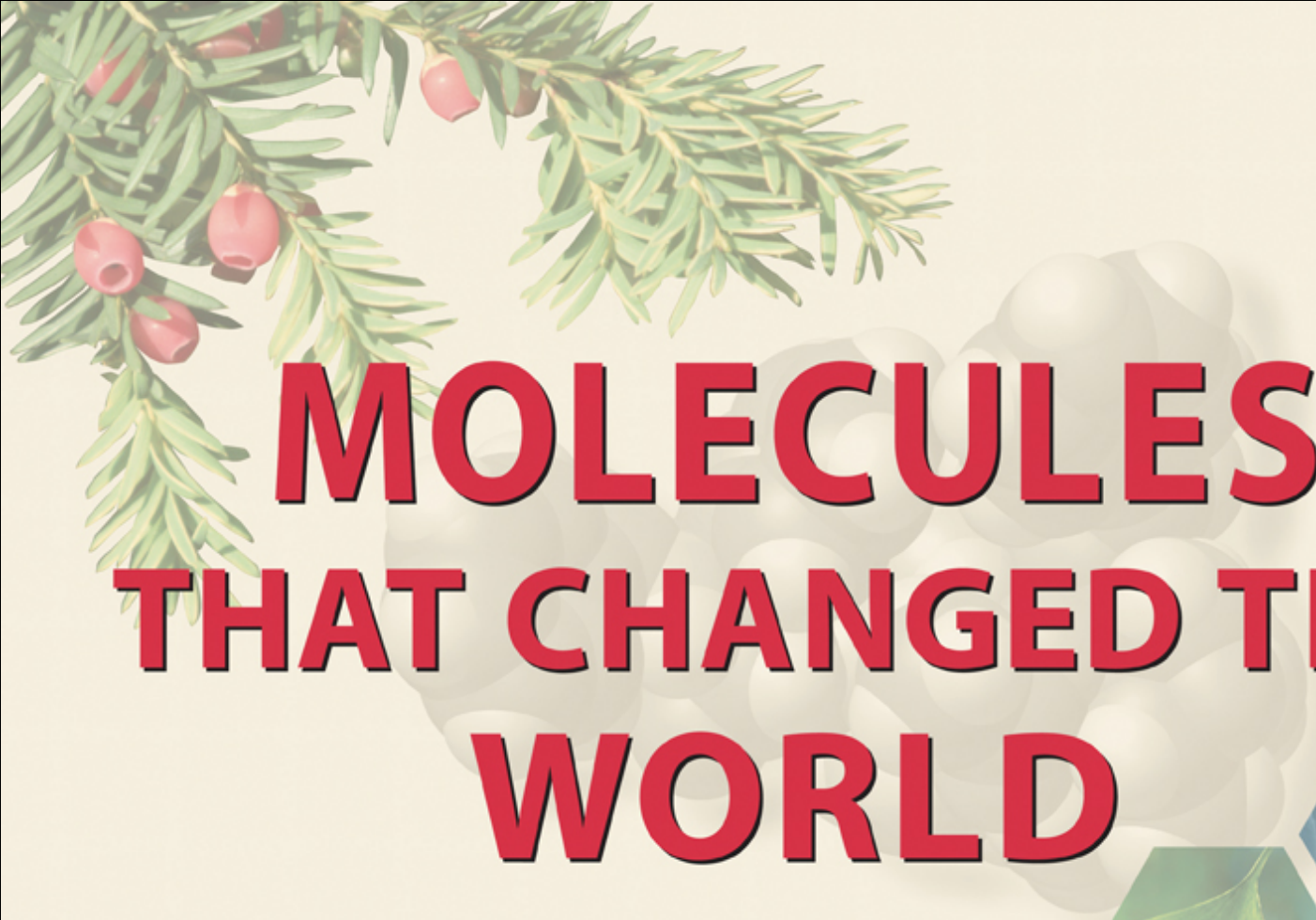
Nicolaou · Chen

WILEY-VCH

## Classics in Total Synthesis III

Further Targets, Strategies, Methods





# MOLECULES THAT CHANGED THE WORLD

K. C. NICOLAOU • T. MONTAGNON







## **Education: Essay. 24**

**K.C. Nicolaou, Angew. Chem. Int. Ed. 2011, 50, 63–74.**



**And if academics have done their job right, they should be able to retire with the precious gift of satisfying content as John Pentland Mahaffy proclaimed he did in his time and space:**

---

***“So now, when my part in the race is nearly run, there remains to me no higher earthly satisfaction than this, that I have carried the torch of Greek fire alight through a long life — no higher earthly hope than this, that I may pass that torch to others, who in their turn may keep it aflame with greater brilliancy perhaps, but not with more earnest devotion, ‘in the Parliament of men, the Federation of the world.’\*”***

**J. P. Mahaffy, 1910**

---

J. P. Mahaffy, *What Have the Greeks Done for Modern Civilisation*, G. P. Putnam's Sons, New York, **1910**, pp. 214–215, 246–247. \*see Alfred, Lord Tennyson, “Locksley Hall” 1835.





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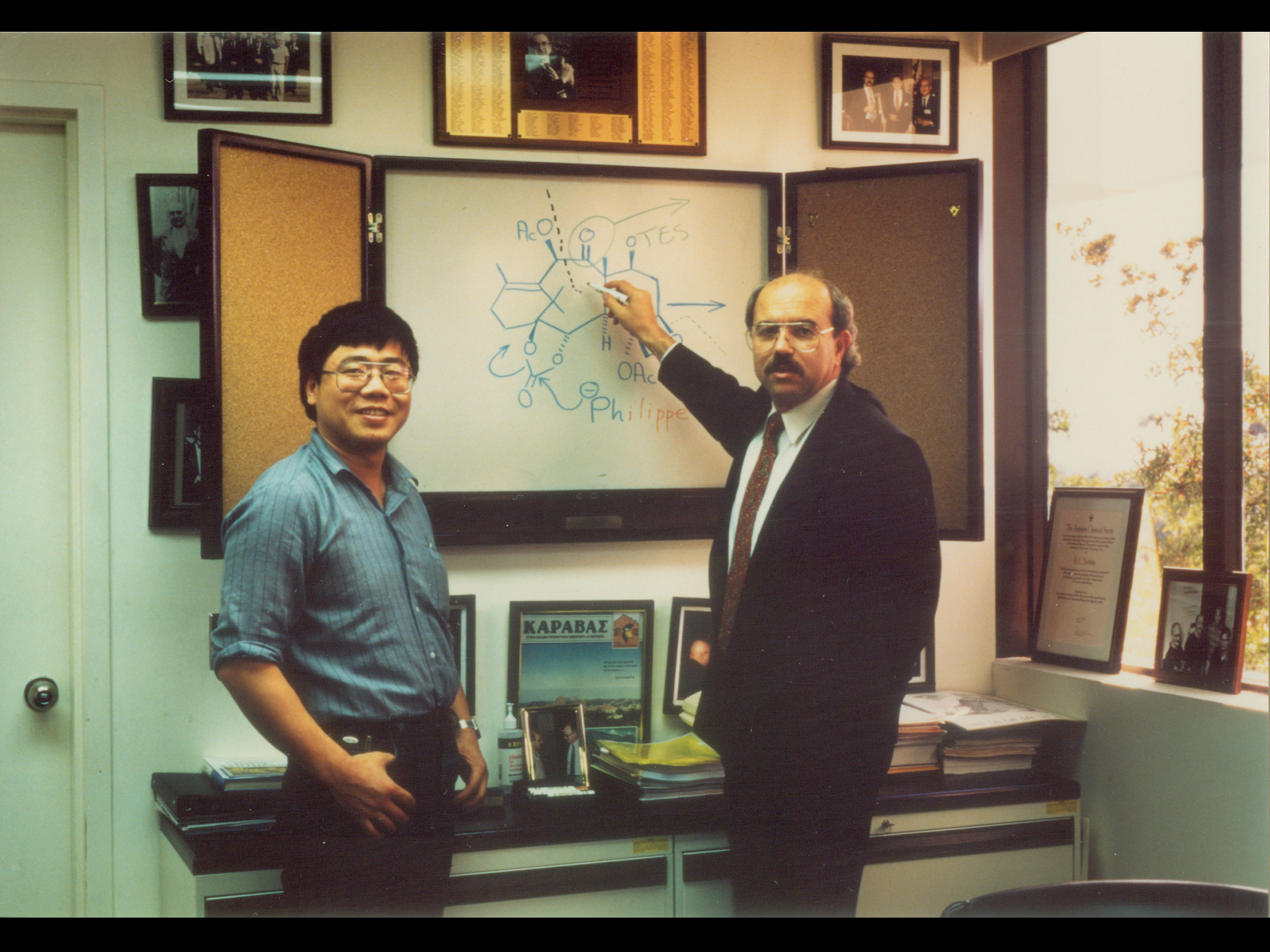
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