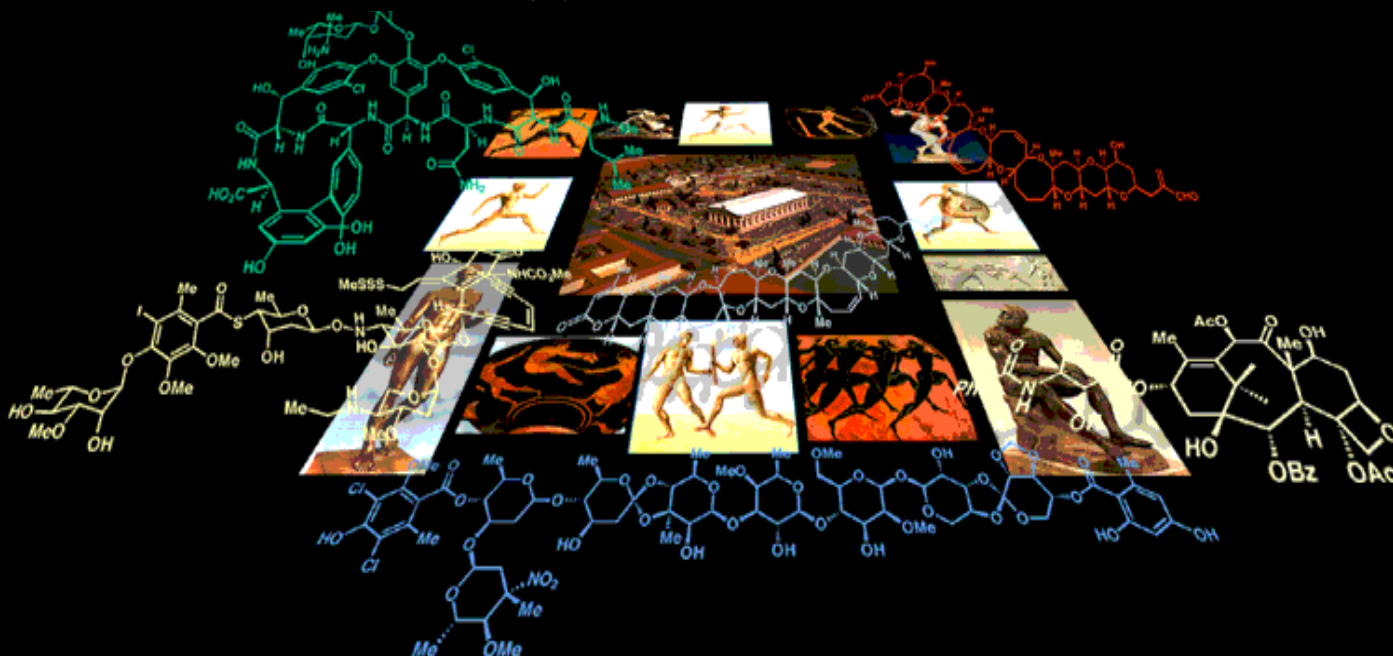


Visit us at scripps.edu/nicolaou

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), and *Molecules That Changed The World* (K. C. Nicolaou and T. Montagnon, Wiley-VCH, 2008).

Enjoy the tour of our world.



**The Fourth Mitsui Chemicals
International Symposium
on Catalysis Science
(MICS2009)**

**March 11 (Wed) - 12 (Thur) 2009
Kazusa Akademia Hall (Kisarazu, Chiba Prefecture, Japan)**

**“Catalysis and Cascade Reactions
in Total Synthesis”**

K. C. Nicolaou, Ph.D.



LECTURE OUTLINE



● ELEGANCE AND EFFICIENCY

● CATALYSIS IN TOTAL SYNTHESIS

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

● CASCADE REACTIONS IN TOTAL SYNTHESIS

● LIGHT AND HEAT IN TOTAL SYNTHESIS

● ECONOMY AND GREEN CHEMISTRY



THE ESSENCE OF TOTAL SYNTHESIS



- 1. Rendering Scarce Natural Products and their Analogs Readily Available for Biological Investigations**
 - 2. Providing Opportunities for Discovery and Invention of New Synthetic Methods and Strategies**
 - 3. Opening Access to Otherwise Inaccessible Natural Product Analogs for Biological Evaluation**
 - 4. Structural Elucidation of Natural Products – Assigning Absolute Configurations and Revising Wrongly Assigned Structures**
 - 5. For Advancing the Art of Total Synthesis for its Own Sake and for the Excitement it Provides**
-



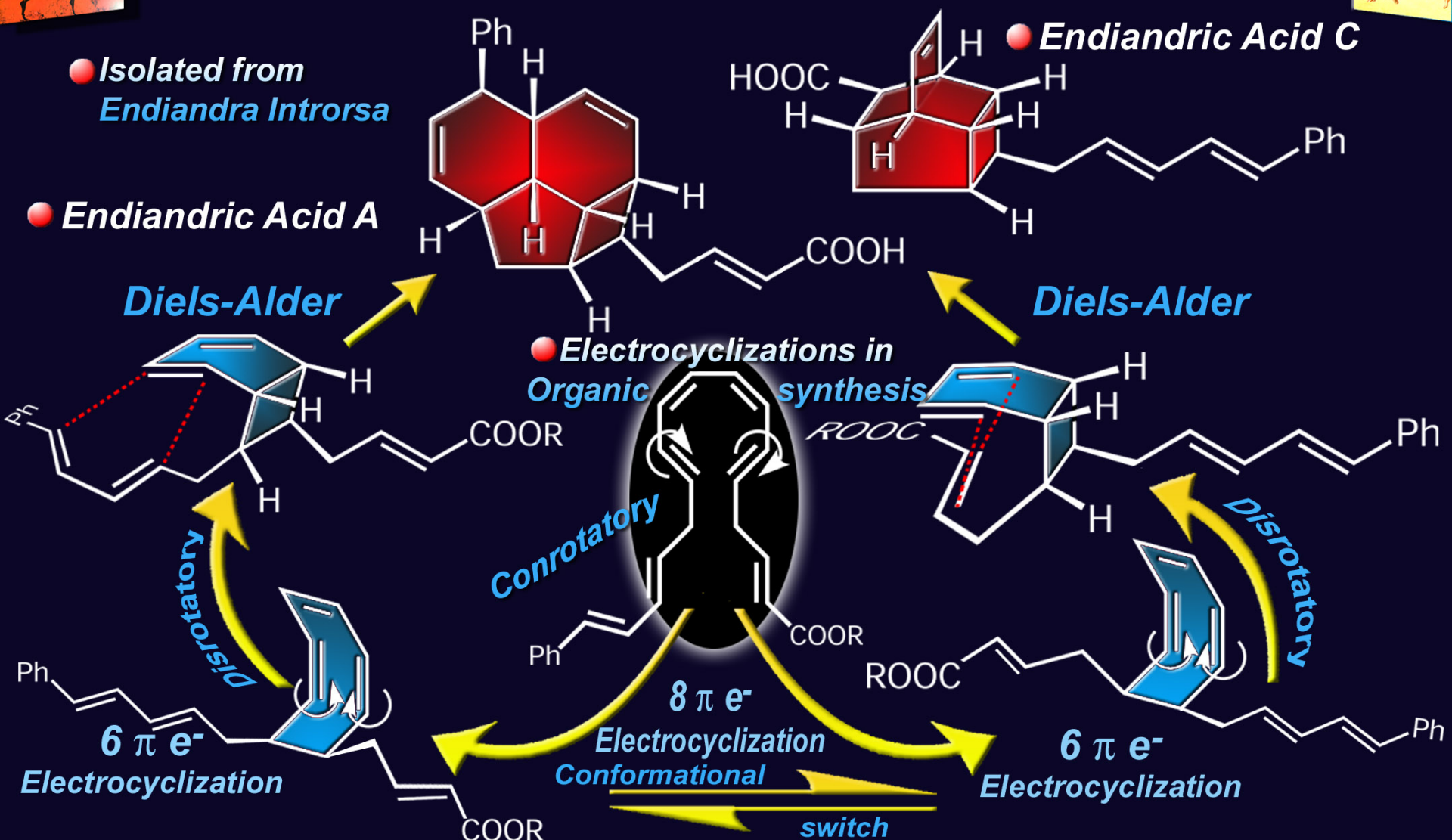
CASCADE REACTIONS IN TOTAL SYNTHESIS



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



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



● The Diels-Alder Reaction

● The Woodward-Hoffmann Rules

● Cascade Reactions



TOTAL SYNTHESIS OF COLEOPHOMONES B AND C [2002]



● From fungi *Stachybothys cylindrospora* RF-5900

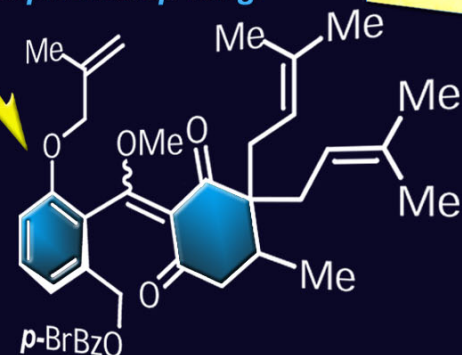
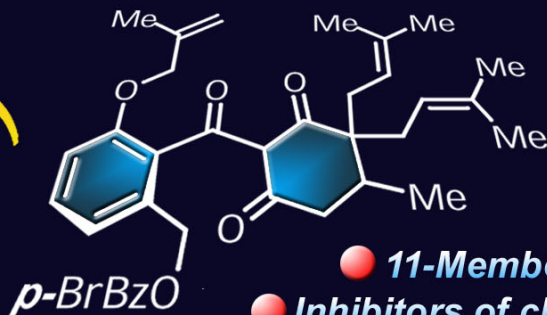
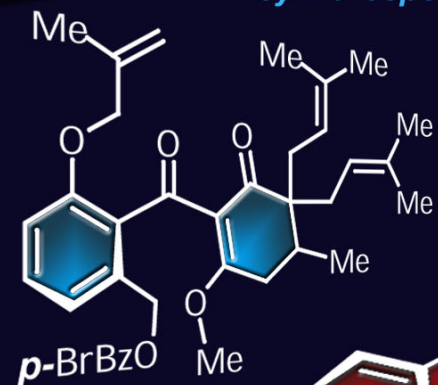
● From *Coleophoma* sp fungi

CH_2N_2

CH_2N_2

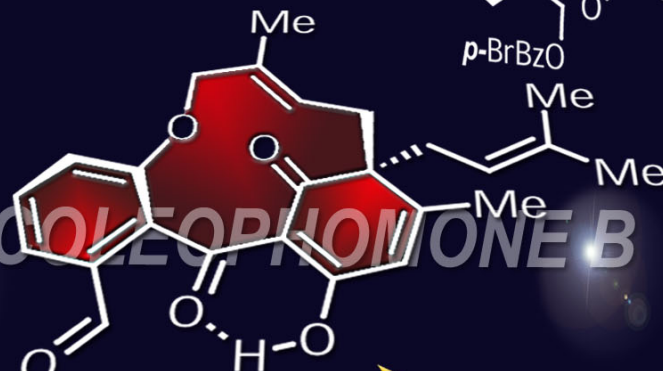
● 11-Membered rings

● Inhibitors of chymase



CATALYST
Stereoselective
ring closing
metathesis

Stereoselective
ring closing
metathesis
CATALYST

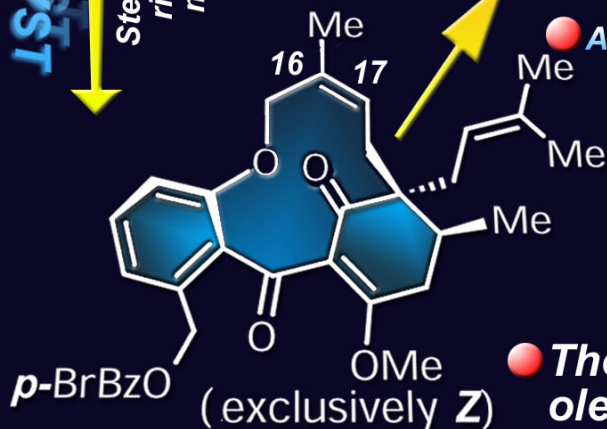


● Antibiotics

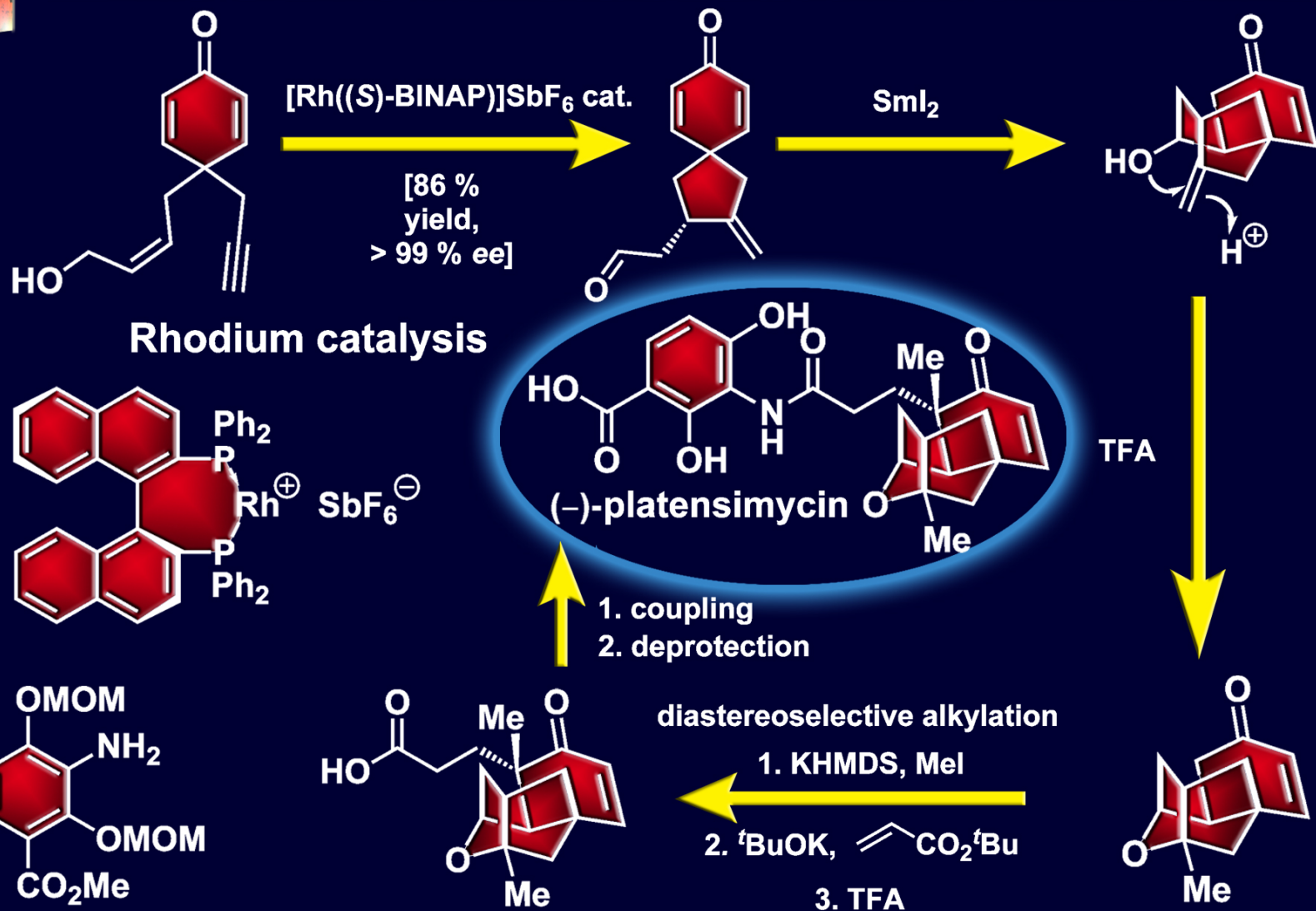
● Antifungal



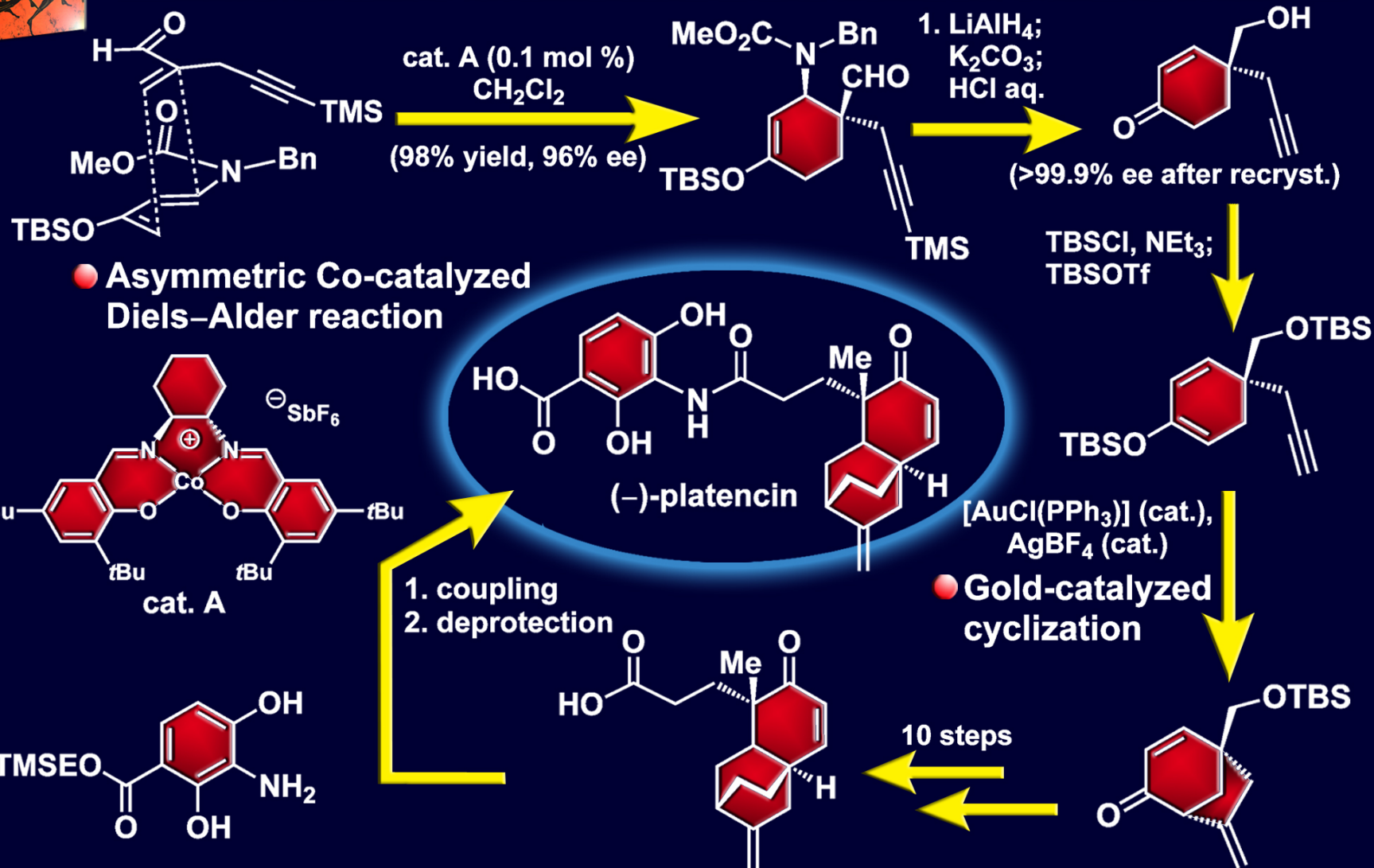
● The magic of the olefin metathesis reaction



ASYMMETRIC SYNTHESIS OF PLATENSIMYCIN [2008]



ASYMMETRIC TOTAL SYNTHESIS OF PLATENCIN I [2008]



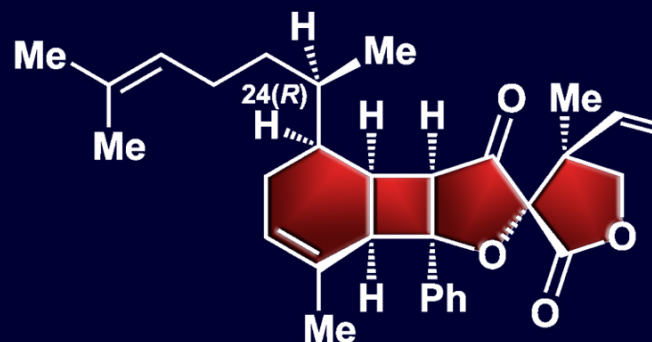
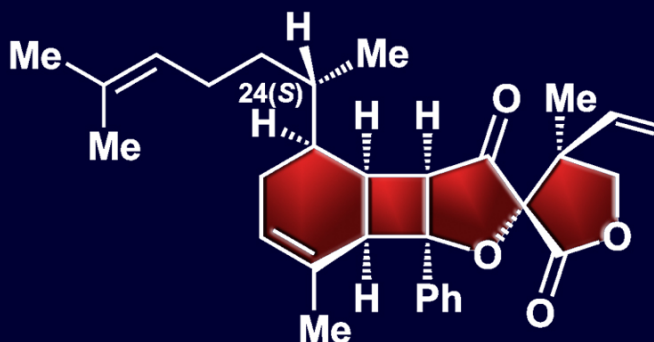




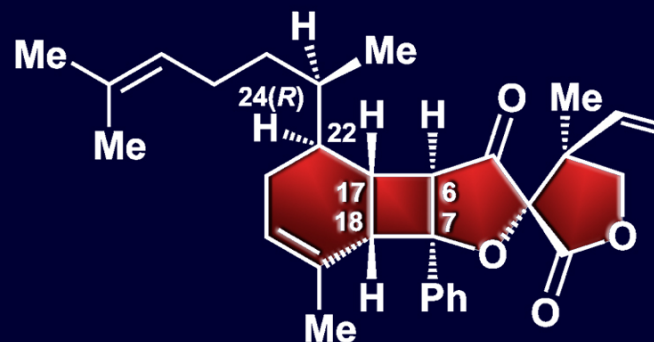
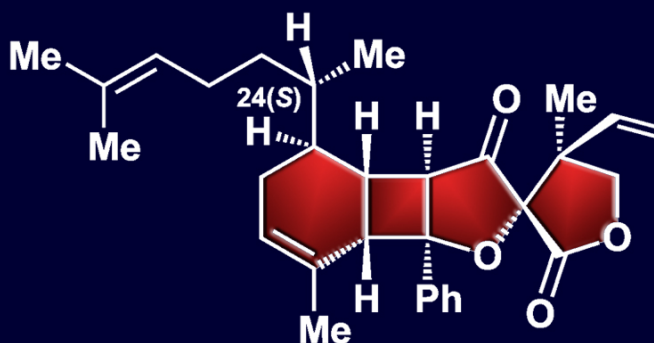
POTENTIAL STRUCTURES OF BIYOUYANAGIN A



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



cis, cis, cis, cis structures: assigned structures



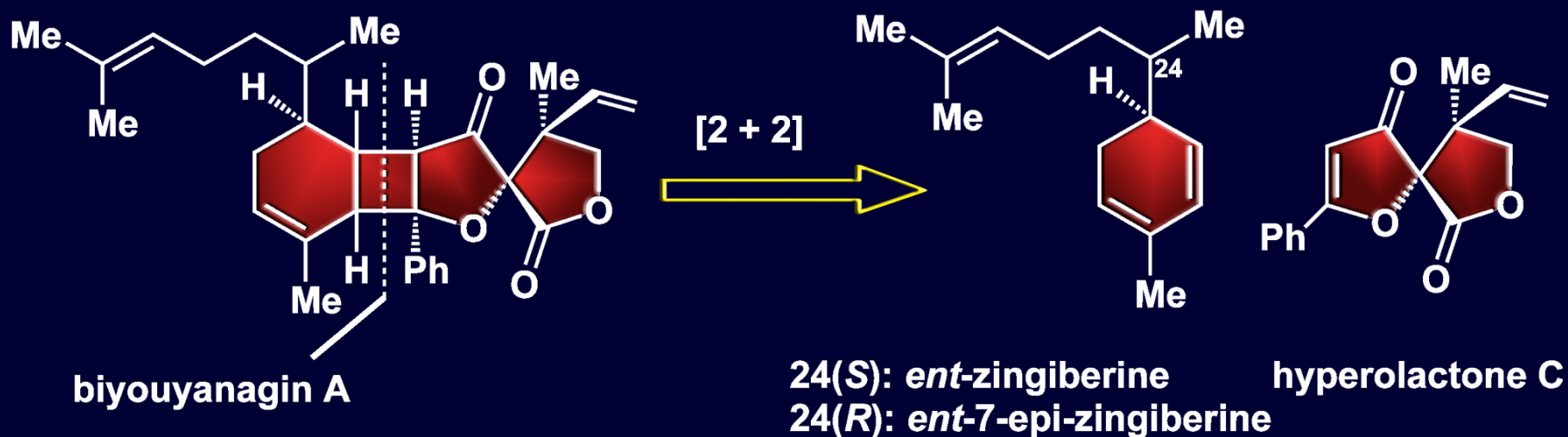
trans, cis, trans, cis structures: potential structures



BIOGENETICALLY INSPIRED RETROSYNTHESIS (2007)

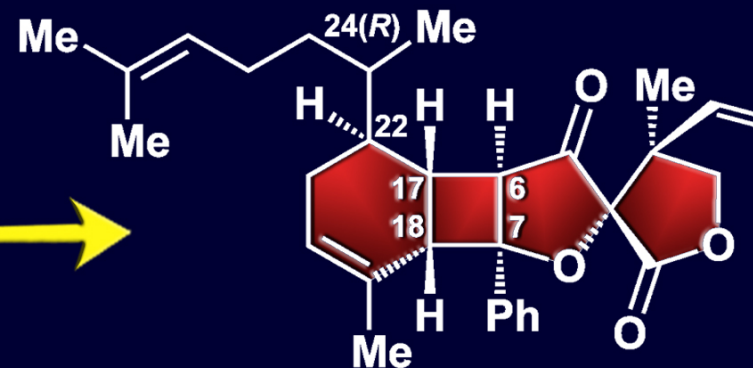
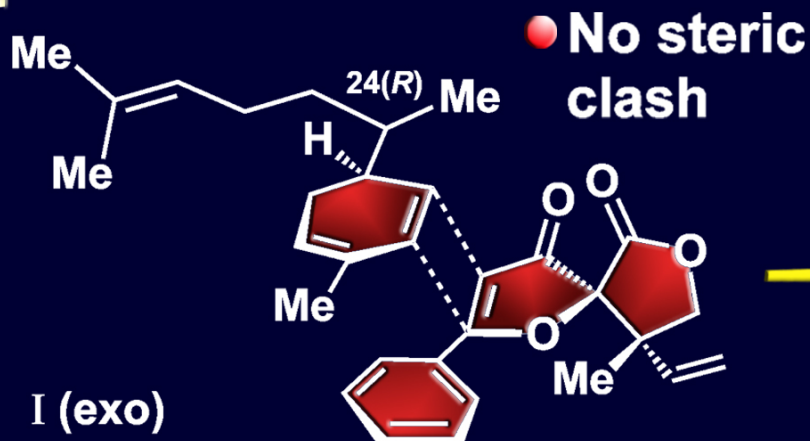


● Photo-induced [2 + 2] cycloaddition

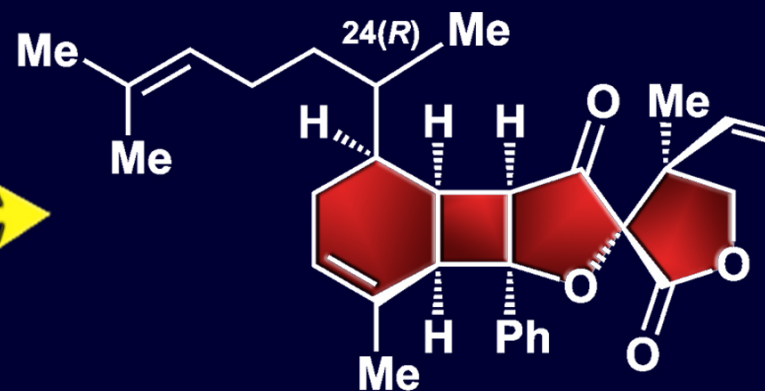
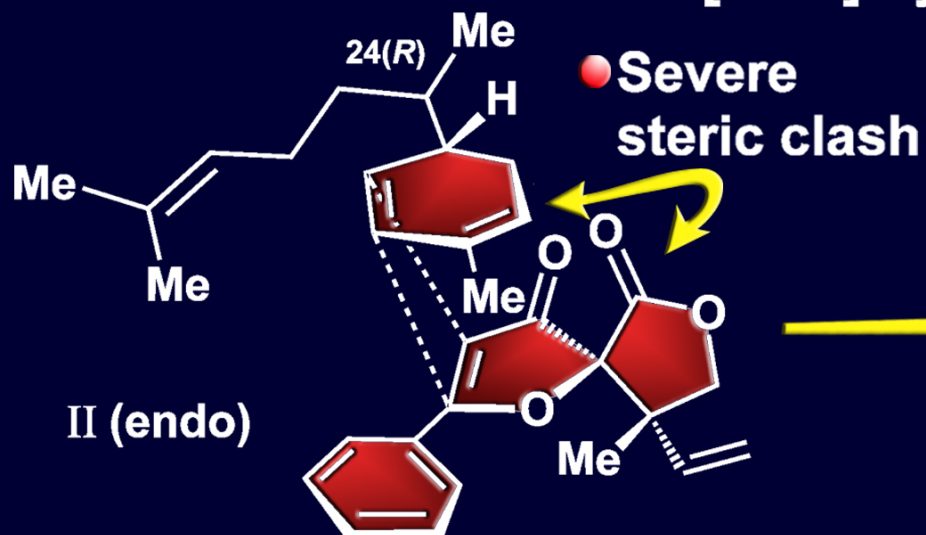




EXO- AND ENDO- TRANSITION MODES

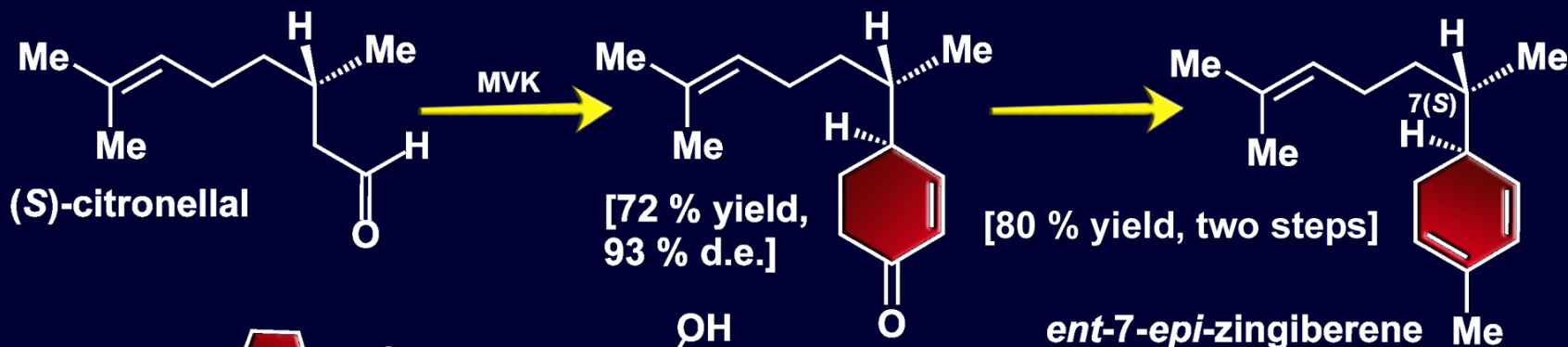


[2 +2] cycloaddition

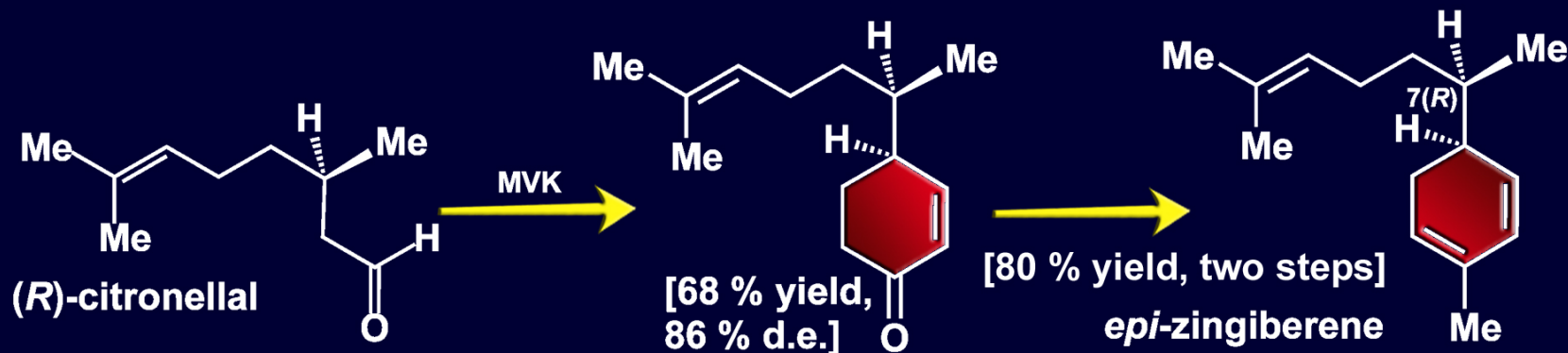
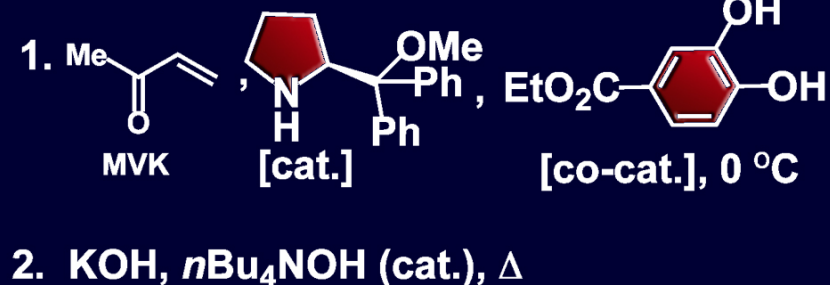




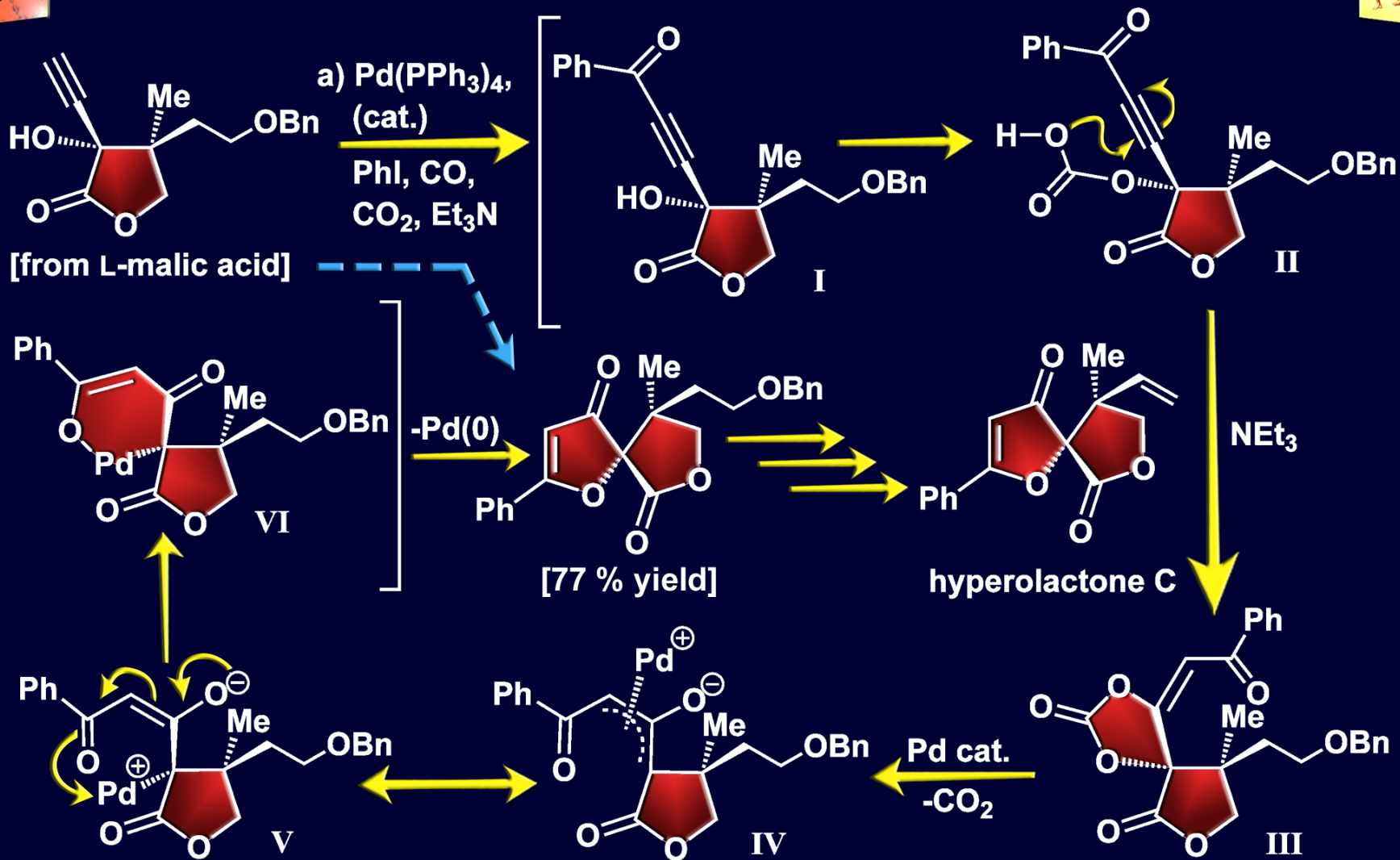
SYNTHESIS OF *ent*-7-*epi*-ZINGIBERENE AND *ent*-ZINGIBERENE



1. KHMDS, Comins' reagent
2. MeMgI, CuI (cat.)

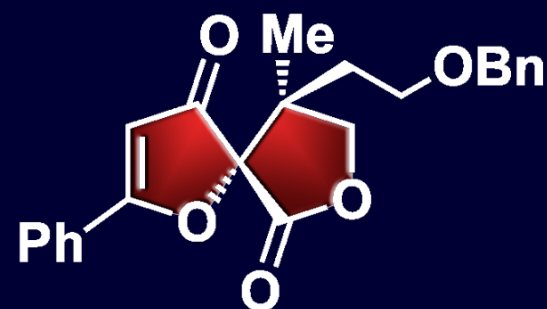
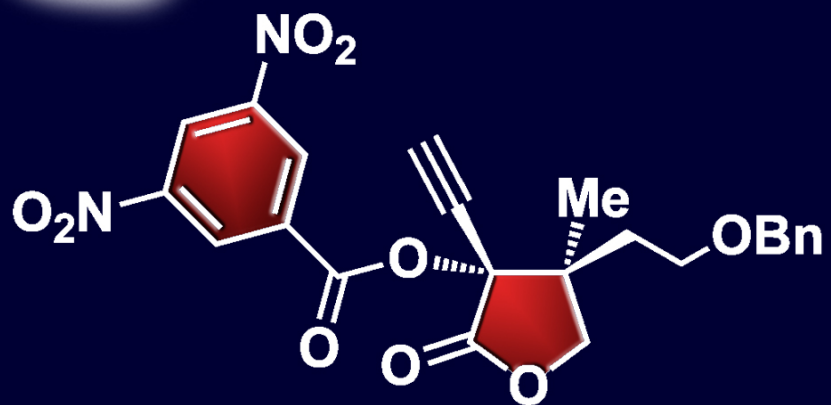
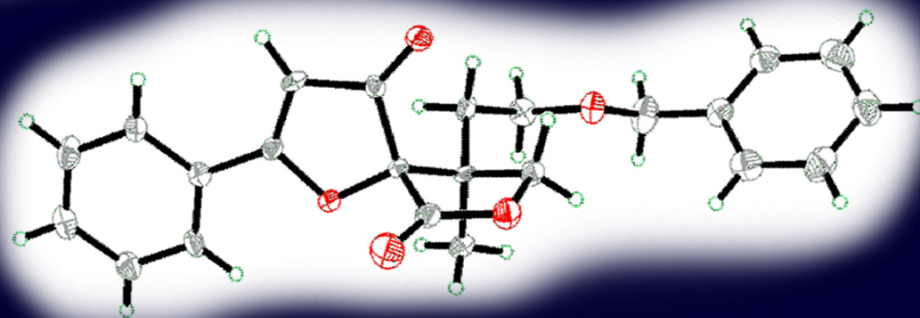
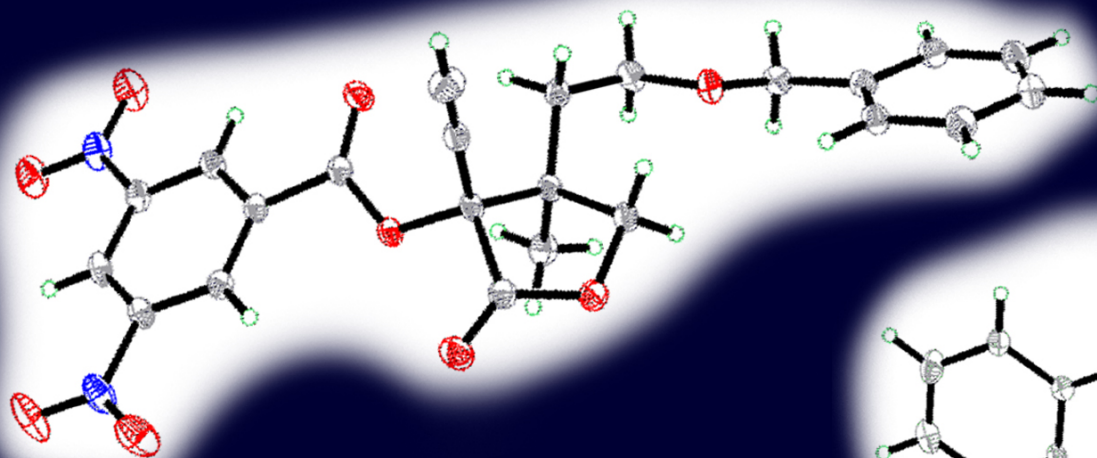


SYNTHESIS OF HYPEROLACTONE C



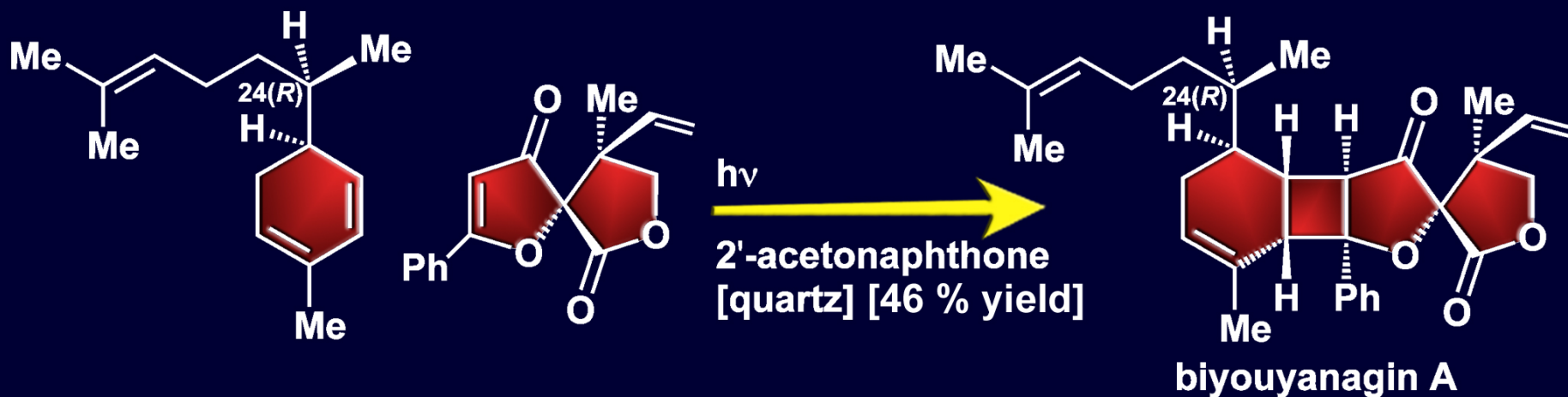
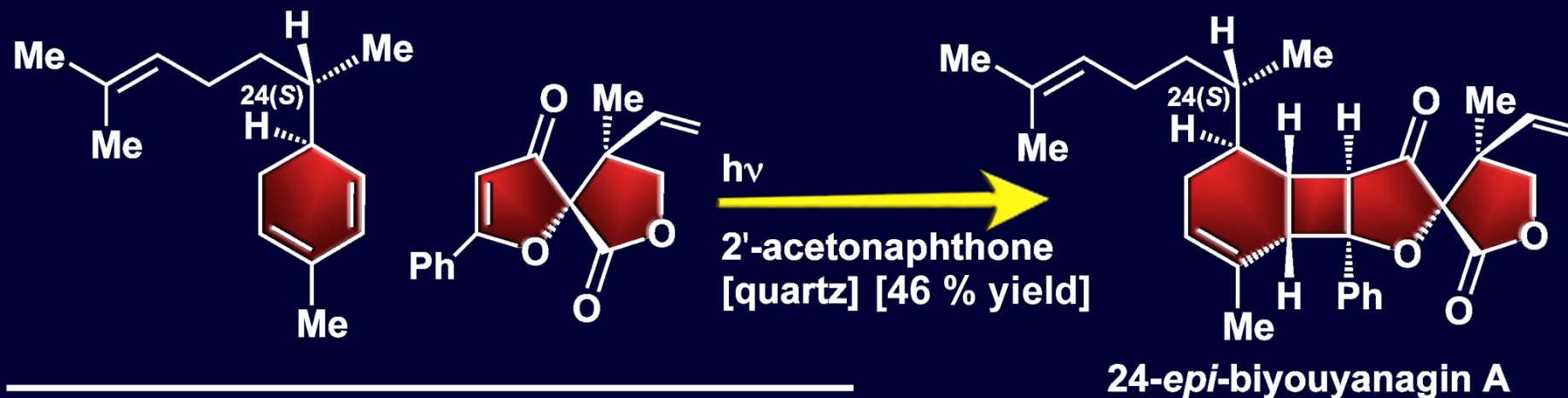


PROOF OF STEREOCHEMICAL RETENTION



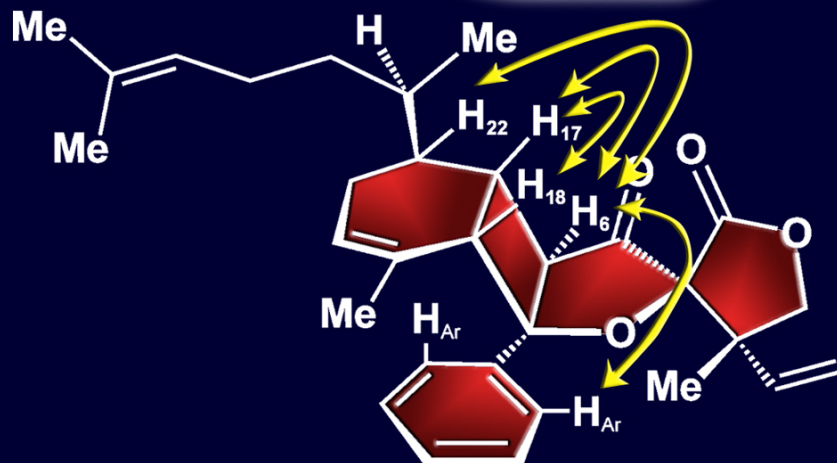
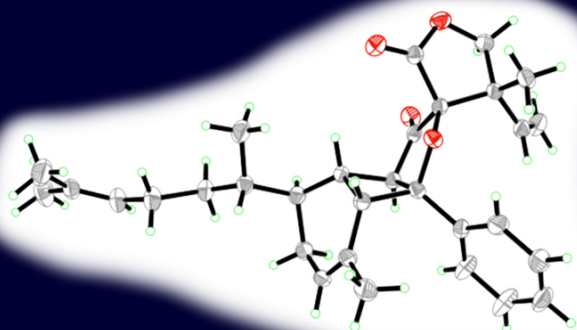


TOTAL SYNTHESIS OF BIYOUYANGIN A AND 24-*epi*-BIYOUYANAGIN A



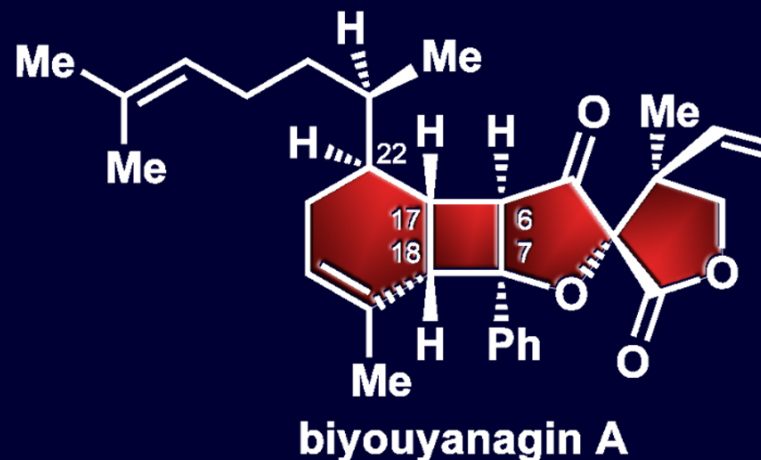


DIAGNOSTIC NUCLEAR OVERHAUSER EFFECTS FOR THE STEREOCHEMISTRY OF BIYOUYANAGIN A



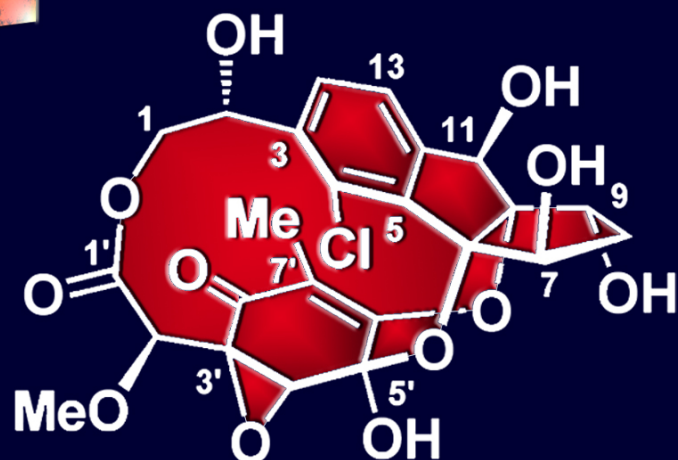
● *trans, cis, trans, cis (anti)* structure of biyouyanagin A

- nOe's between H_6-H_{17} , H_6-H_{22} , $H_{17}-H_{18}$
- nOe between H_6-H_{Ar} 128-fold larger than nOe between $H_{18}-H_{Ar}$
- nOe between H_6-H_{22} larger than nOe between H_6-H_{17}
- no nOe between H_6-H_{18}

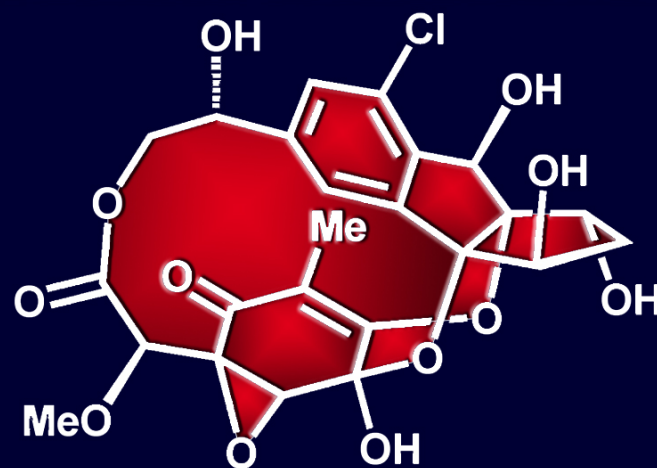




MOLECULAR STRUCTURES OF SPOROLIDES A AND B [2005]

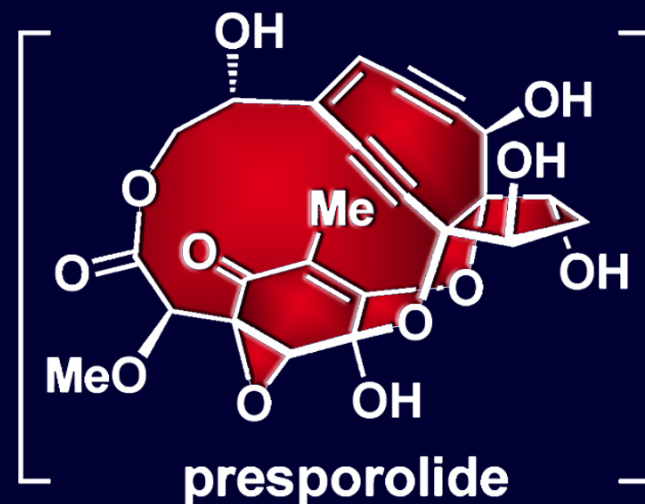


sporolide A



sporolide B

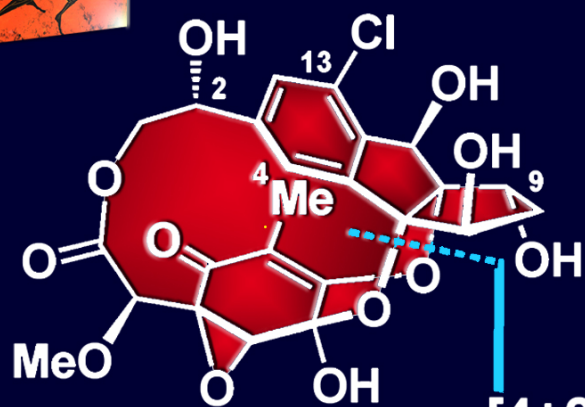
- Isolated from the marine actinomycete *Salinospora tropica* [Fenical and coworkers, *Org. Lett.* 2005, 7, 2731.]
- Proposed metabolite of an, as yet unidentified, enediyne natural product [presporolide, *Proc. Natl. Acad. Sci.* 2007, 104, 10376.]
- Novel molecular architecture
- Unknown biological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



presporolide

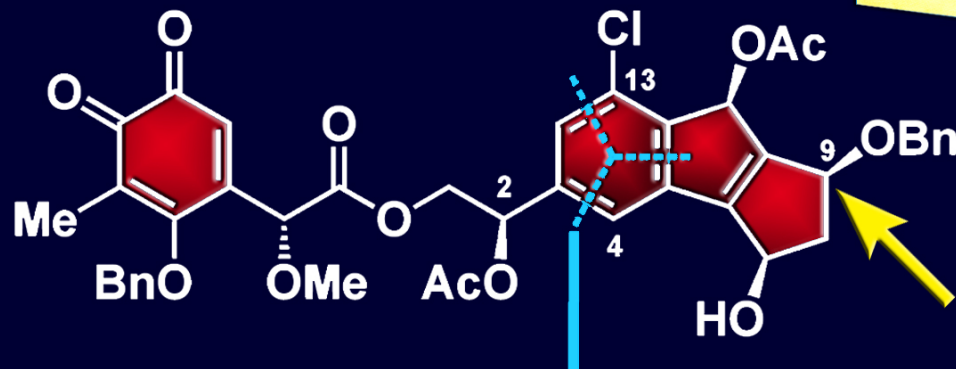


SPOROLIDE B 1. RETROSYNTHETIC ANALYSIS [2009]

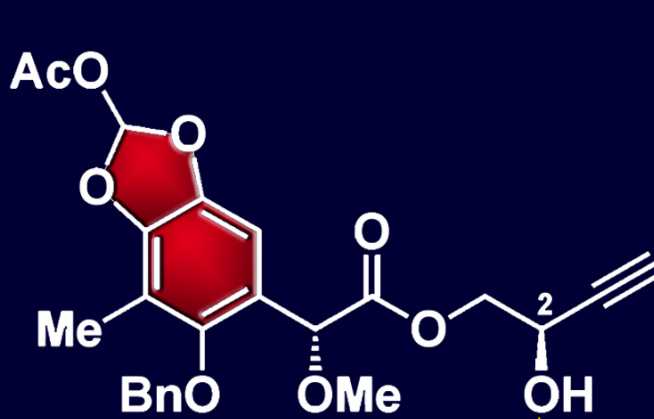


sporolide B

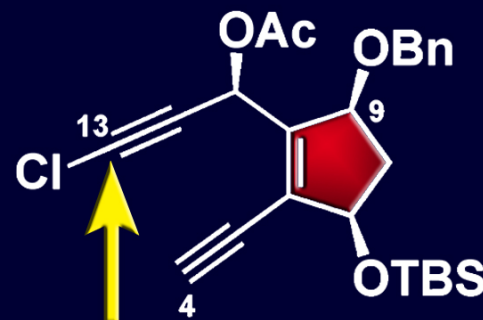
[4+2] cycloaddition
[thermal]



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



B

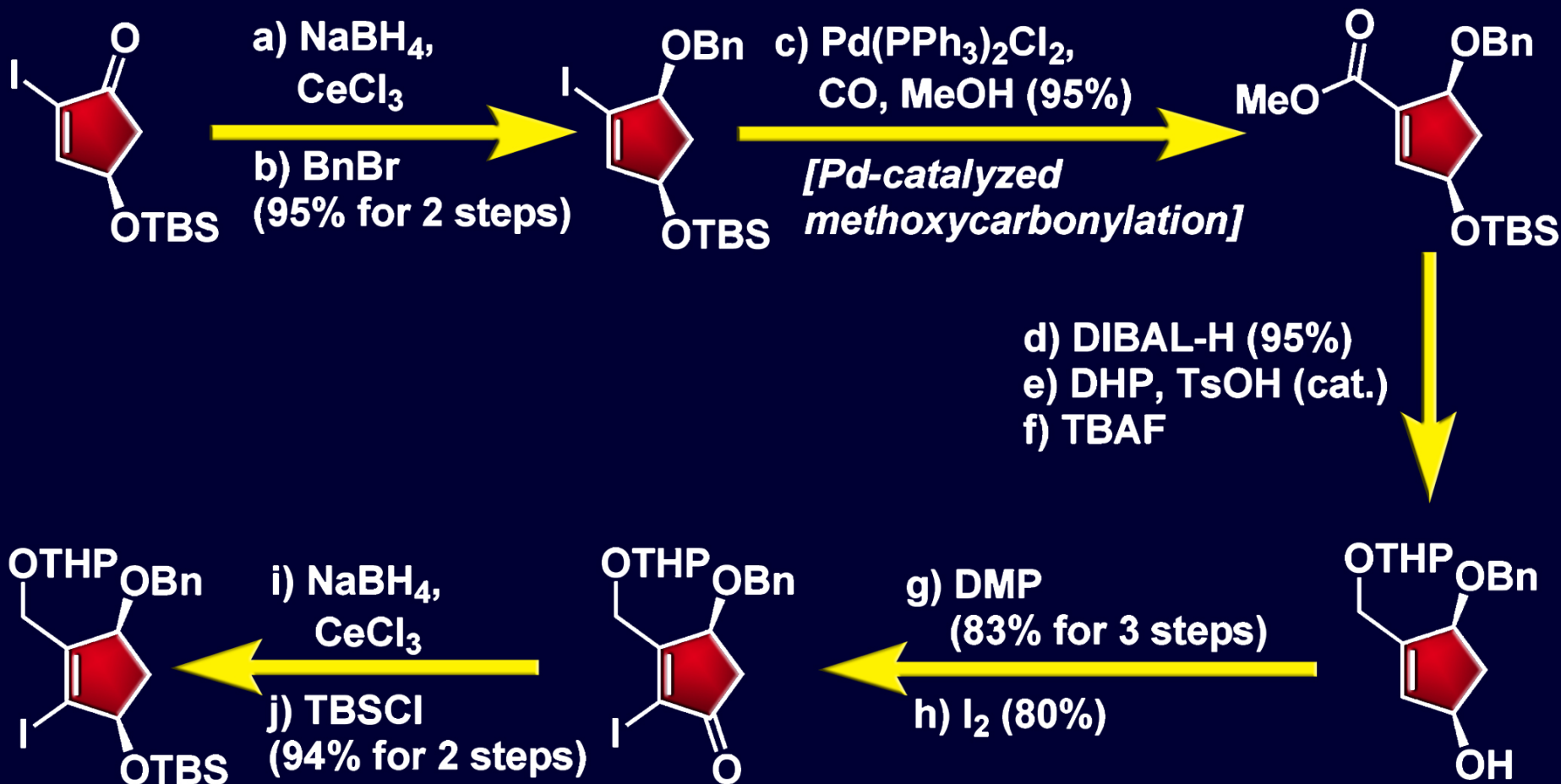


A

NOTE

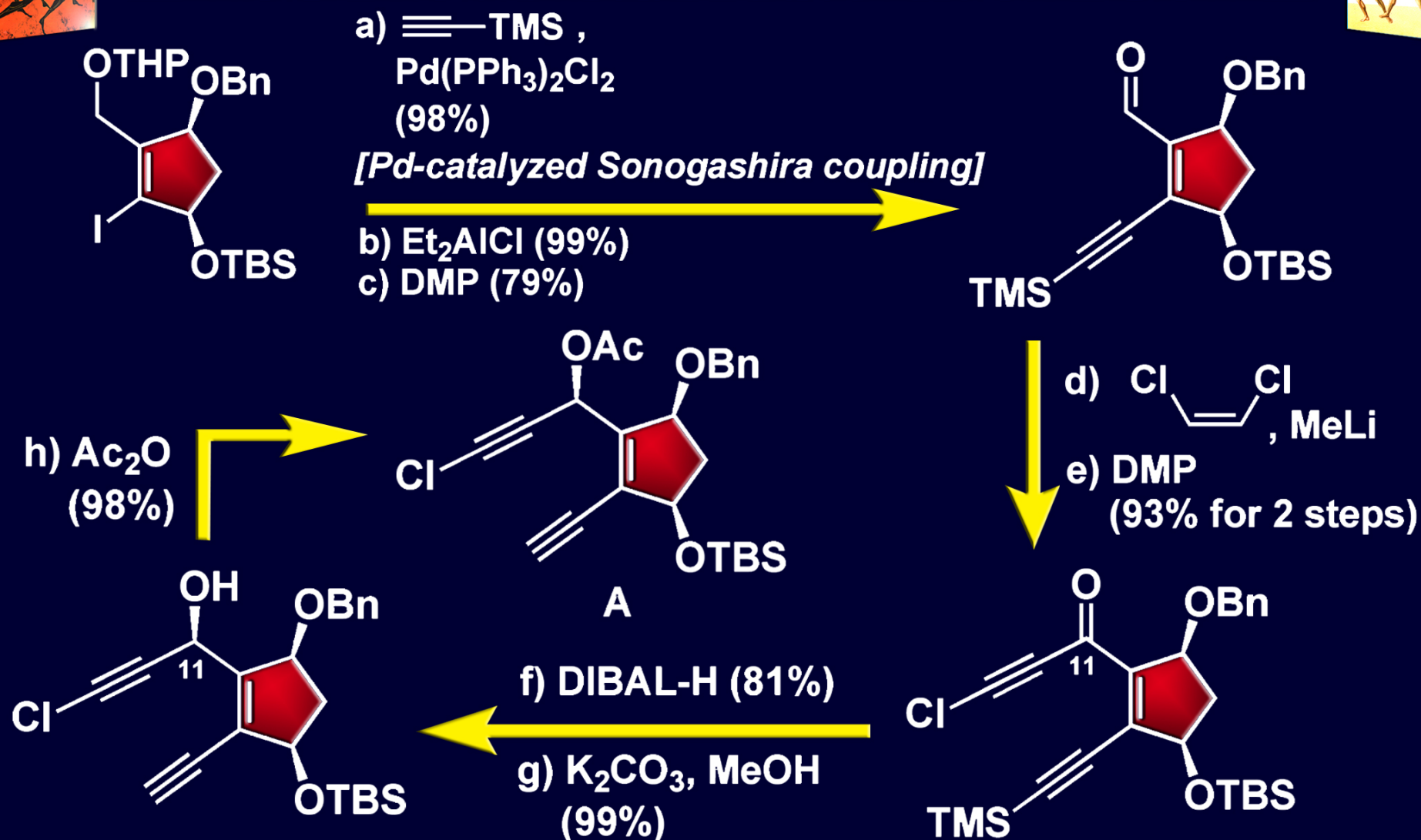
- C-9 inversion to avoid steric congestion
- C-13 regiochemistry
- Free C-2 OH to facilitate [2+2+2] cycloaddition

SPOROLIDE B 2. BUILDING BLOCK A [2009]



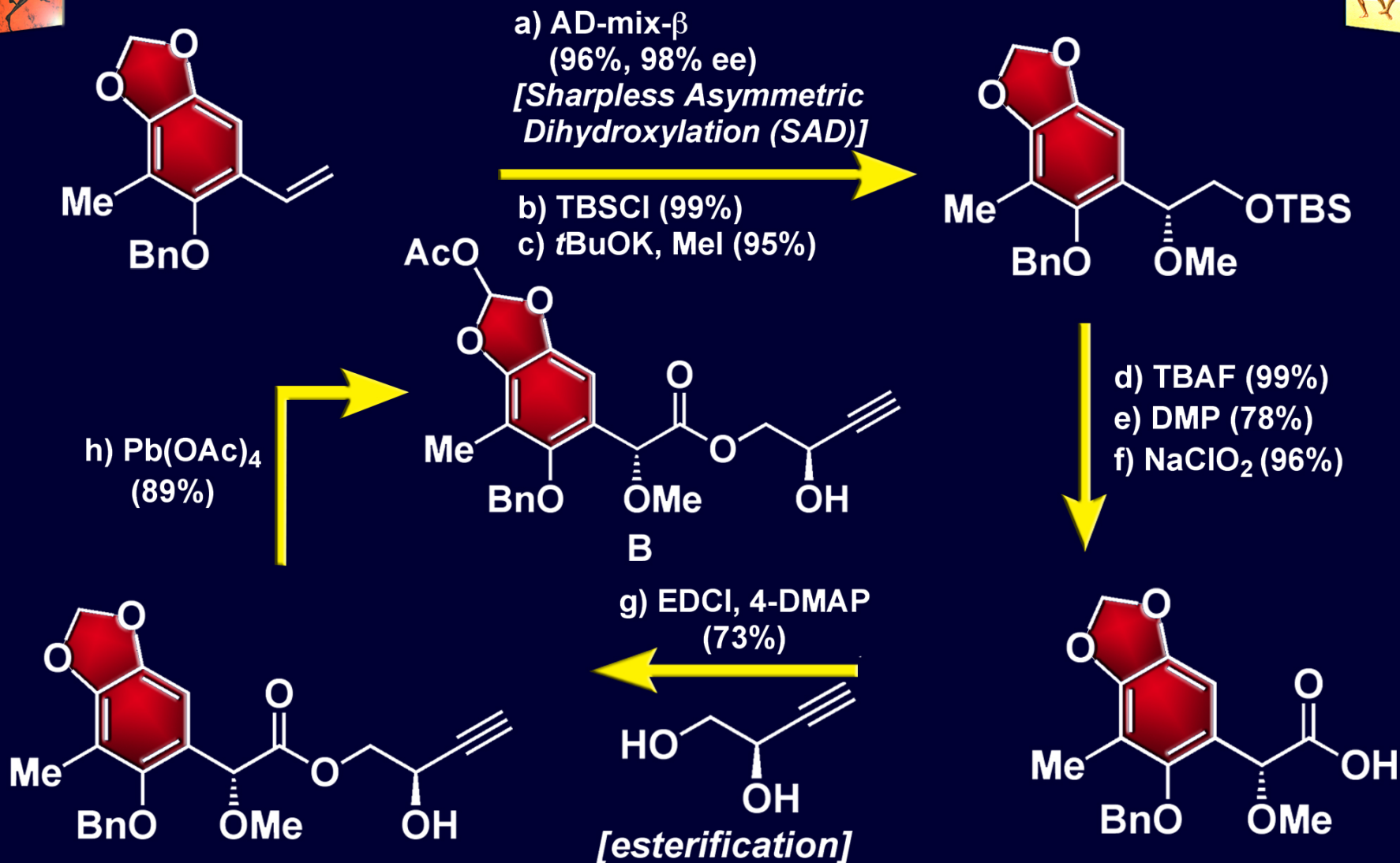


SPOROLIDE B 3. BUILDING BLOCK A [2009]



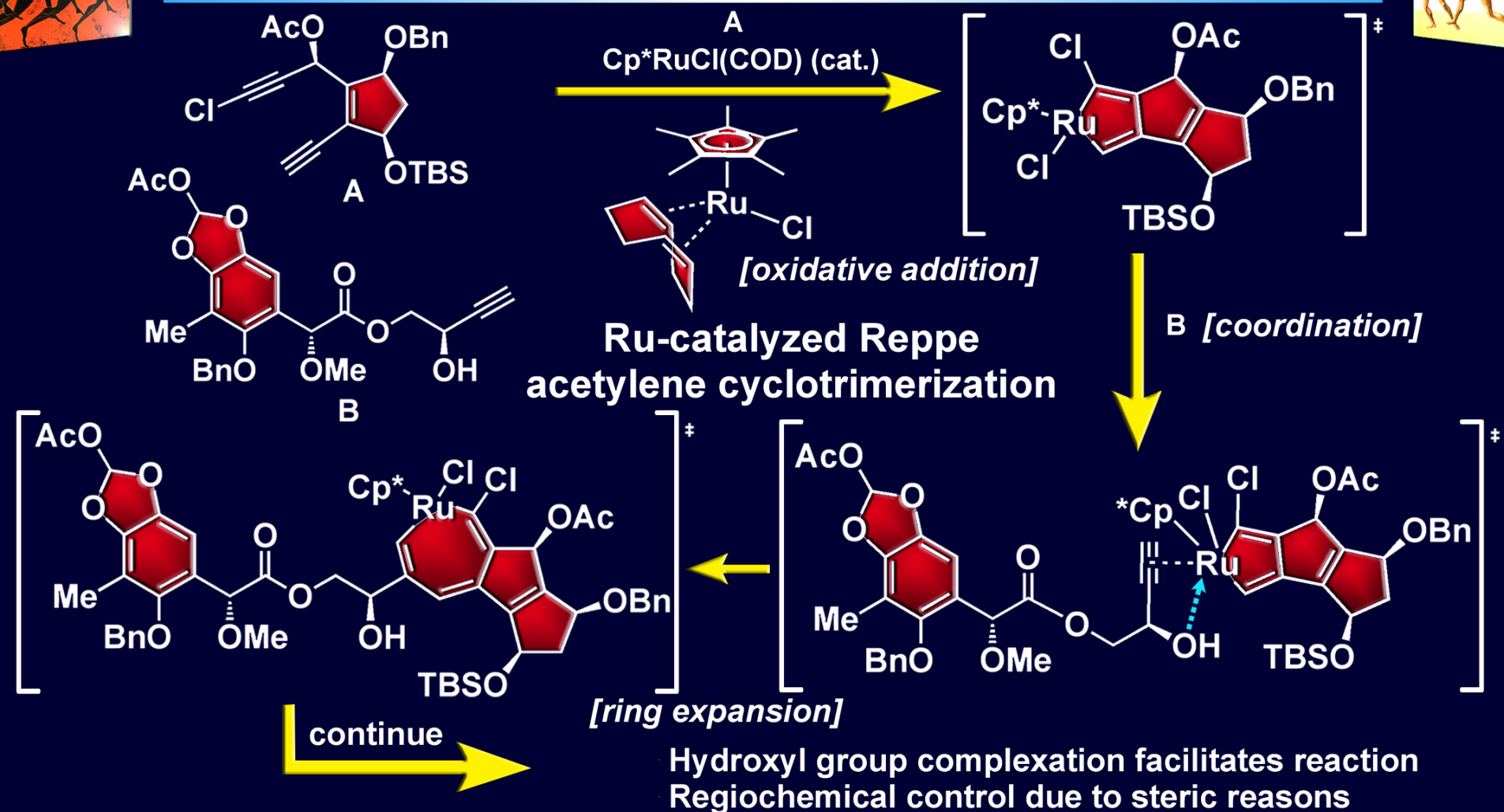


SPOROLIDE B 4. BUILDING BLOCK B [2009]





SPOROLIDE B 5. [2+2+2] CYCLOADDITION [2009]

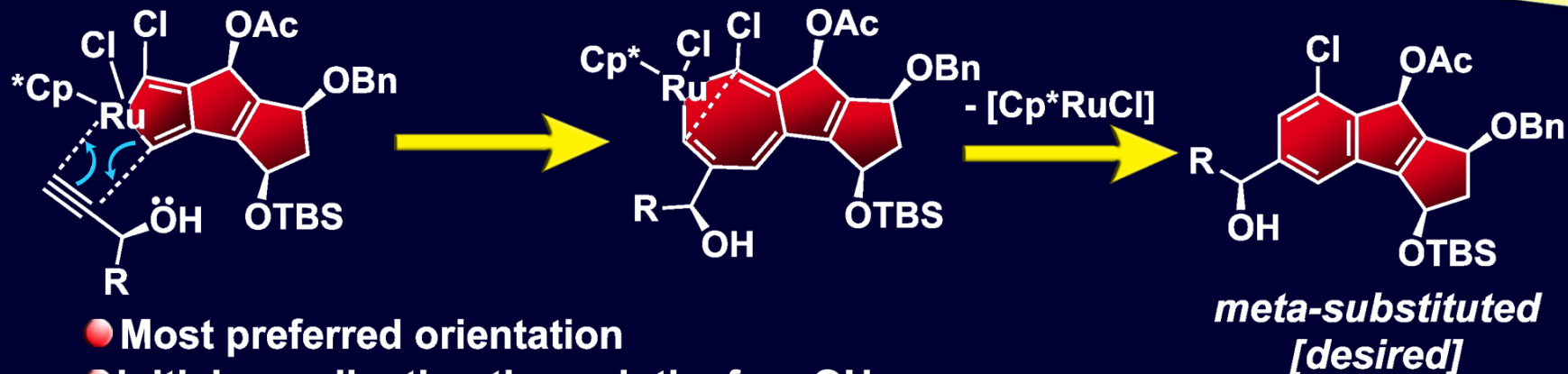


a) Y. Yamamoto, R. Ogawa, K. Itoh, *Chem. Commun.* 2000, 549;

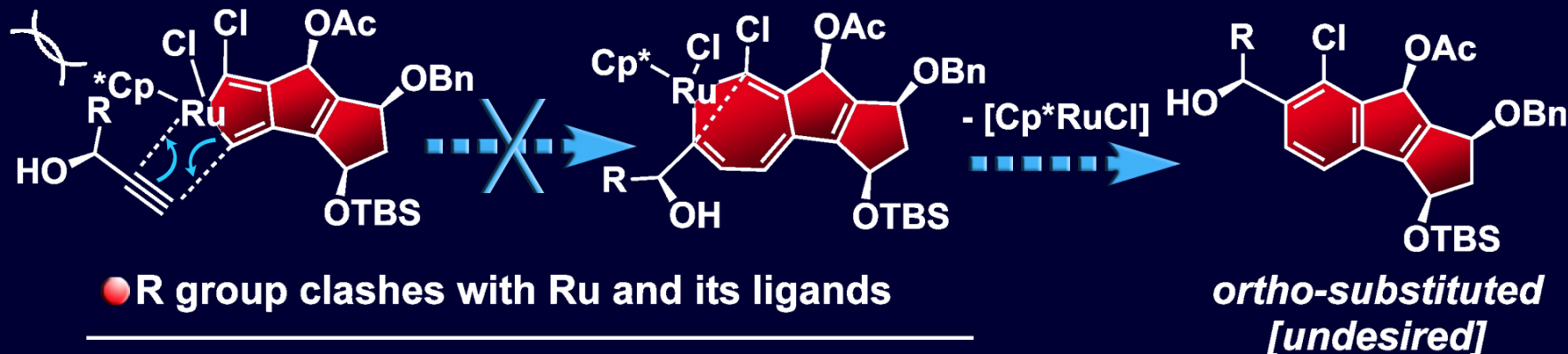
b) Y. Yamamoto, T. Arakawa, R. Ogawa, K. Itoh, *J. Am. Chem. Soc.* 2003, 125, 12143.



ORIGIN OF REGIOSELECTIVITY OF THE Ru-CATALYZED [2+2+2]-CYCLOADDITION



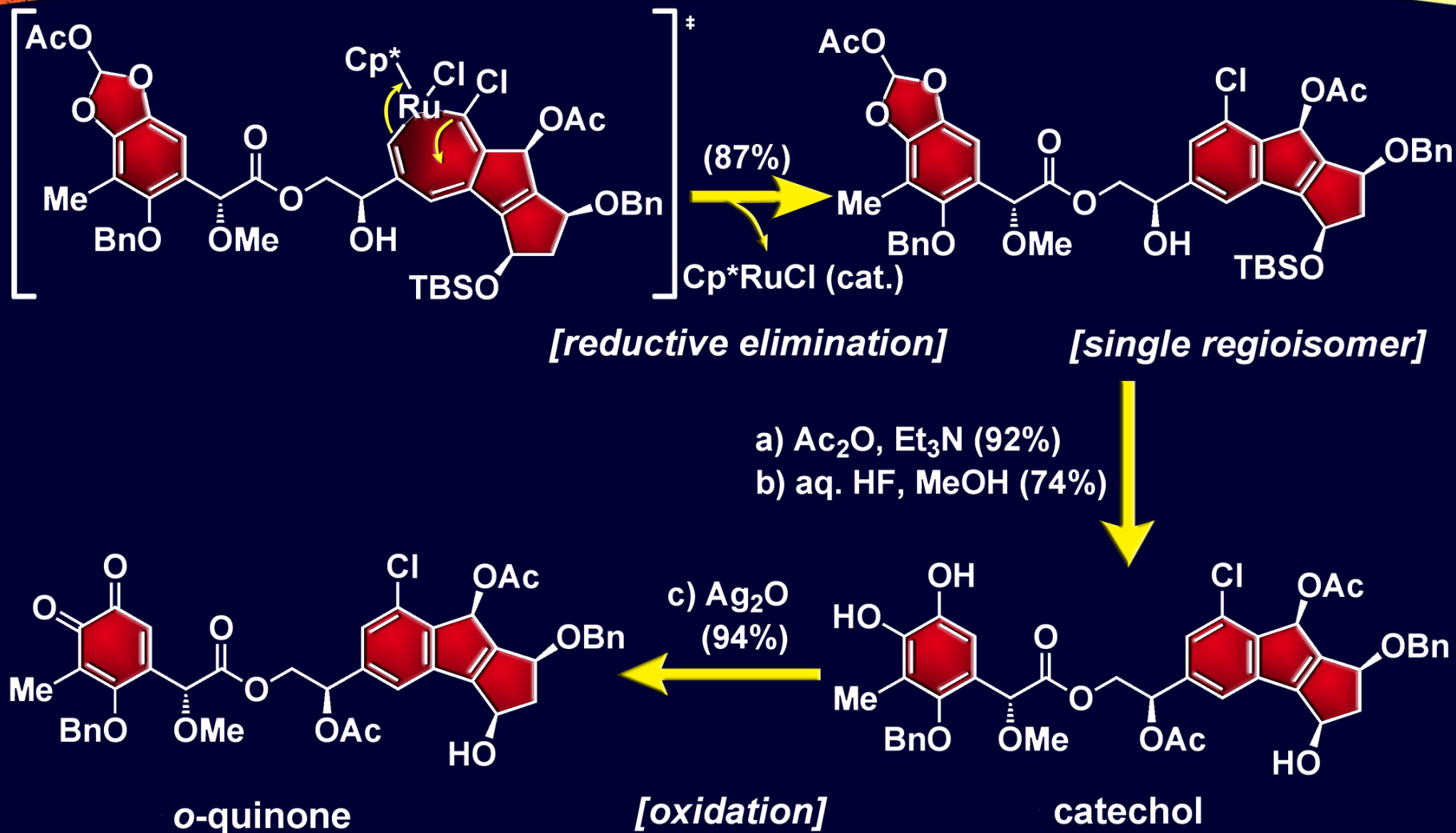
- Most preferred orientation
- Initial coordination through the free OH group may explain fast reaction time (0.5 h)



- R group clashes with Ru and its ligands
- The other two orientations on the side of the Cl suffer from steric congestion with either Ru moiety or Cl residue

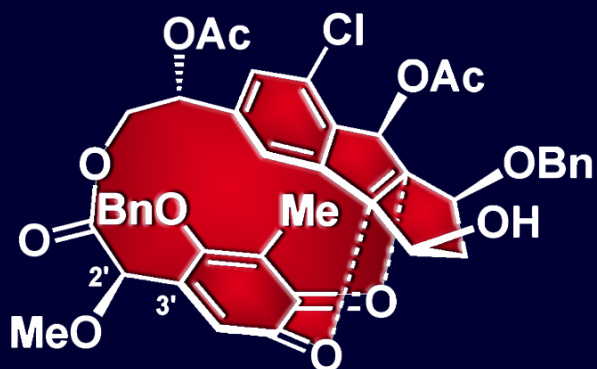


SPOROLIDE B 6. [2+2+2] CYCLOADDITION [2009]



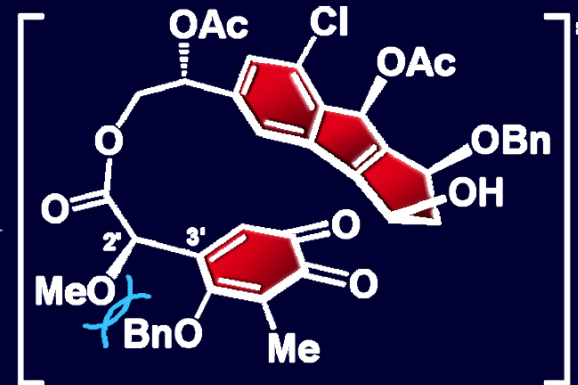
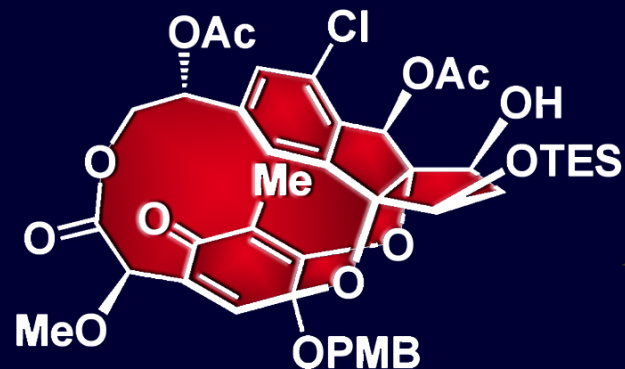


SPOROLIDE B 7. [4+2] CYCLOADDITION [2009]

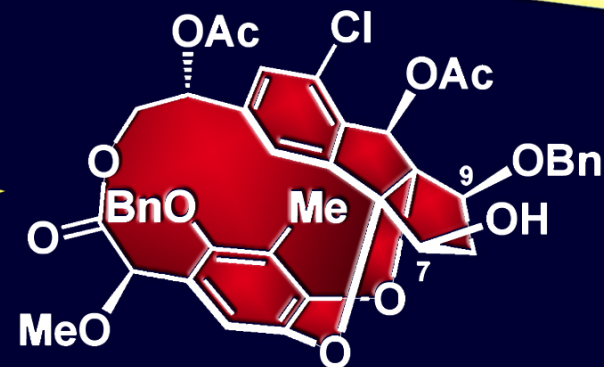


pre-organized o-quinone

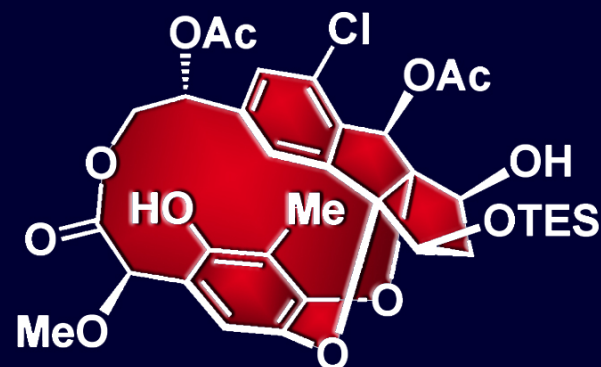
1,3-allylic strain →



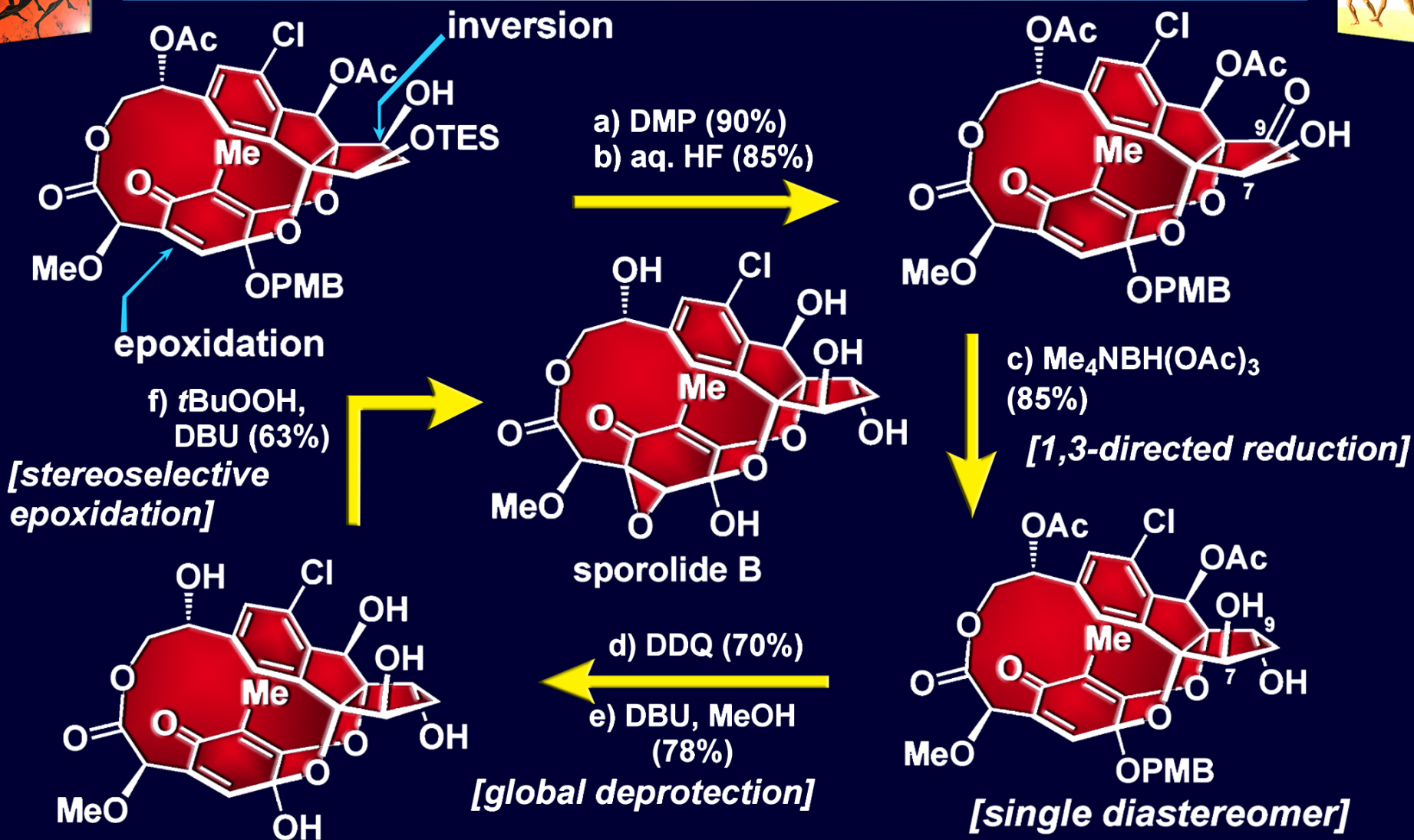
PhI(OCOCF₃)₂,
PMBOH (75%)

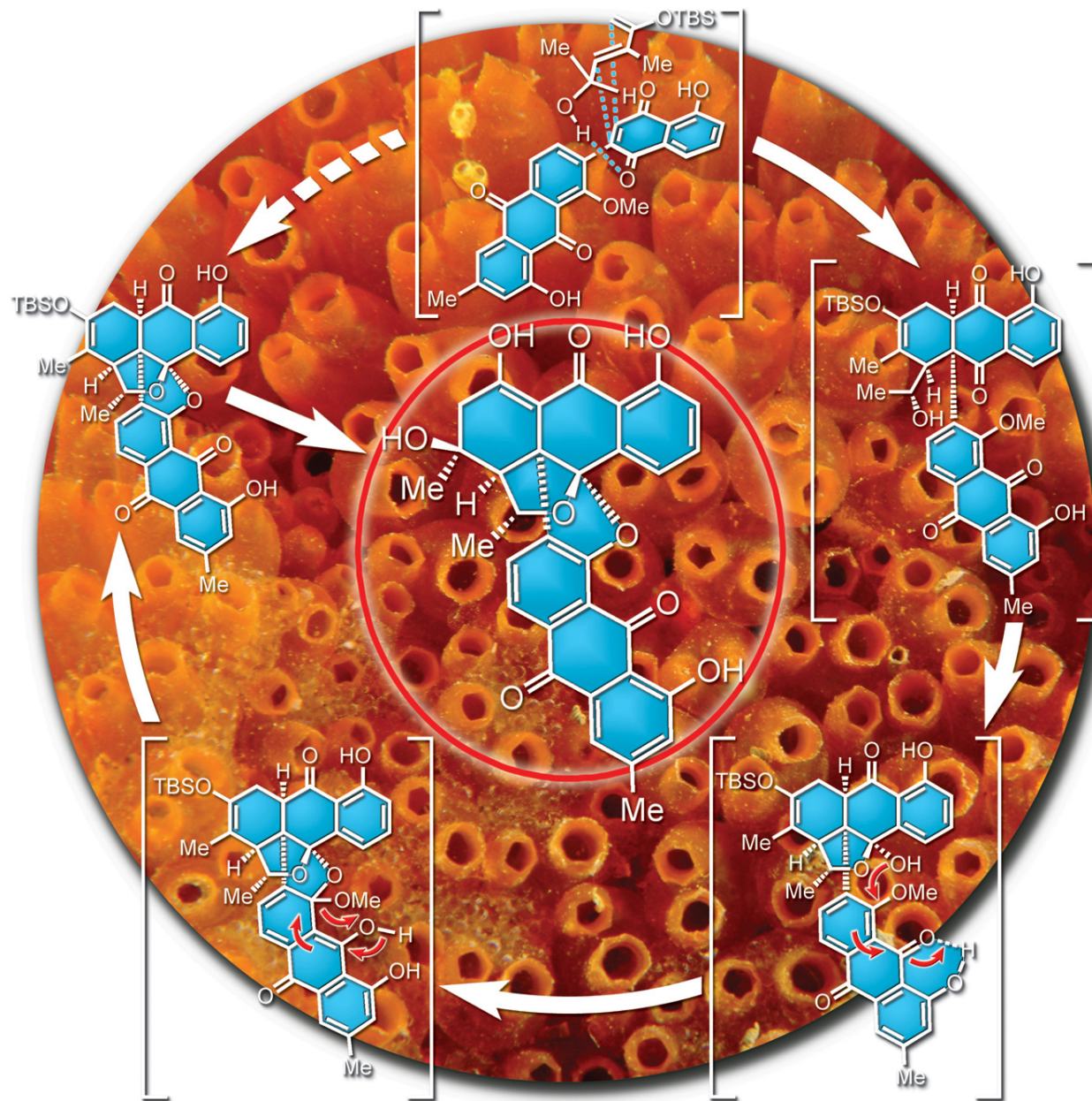


1. TESOTf (95%)
2. H₂, Pd(OH)₂ (92%)
[debenzylolation]



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



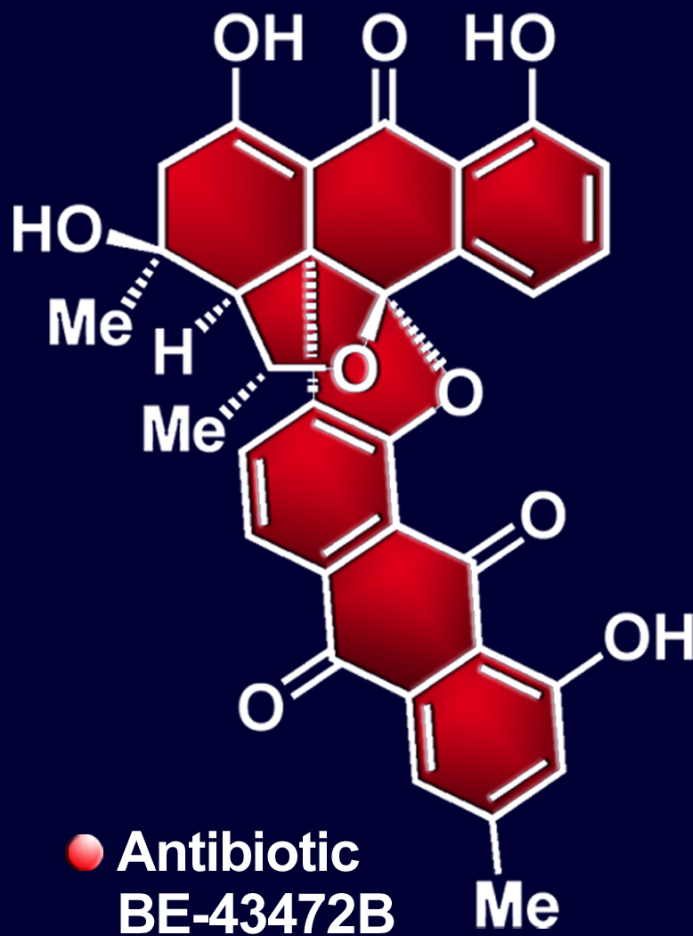




BISANTHRAQUINONE ANTIBIOTIC BE-43472B 1. [2009]

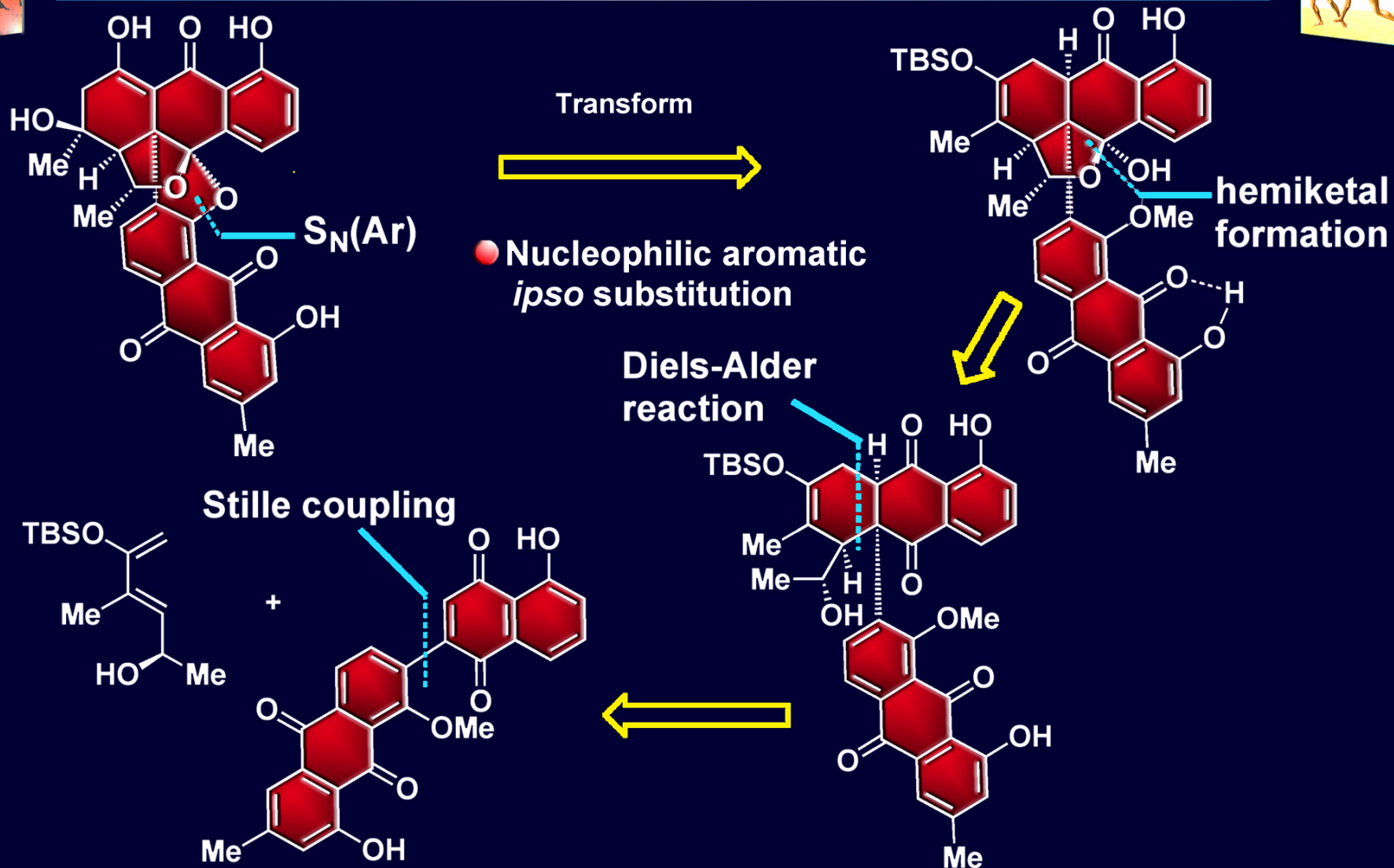


- First isolated from a *Streptomyces* sp. and reported in a Japanese patent as an antitumor agent [gross structure only: H. Kushida et al, JP 08143569, 1996]
- Potent antibiotic activity against MSSA, MRSA, TRSA and VRE and antibactericidal activity (99.9 % kill) against MSSA, MRSA and VRE



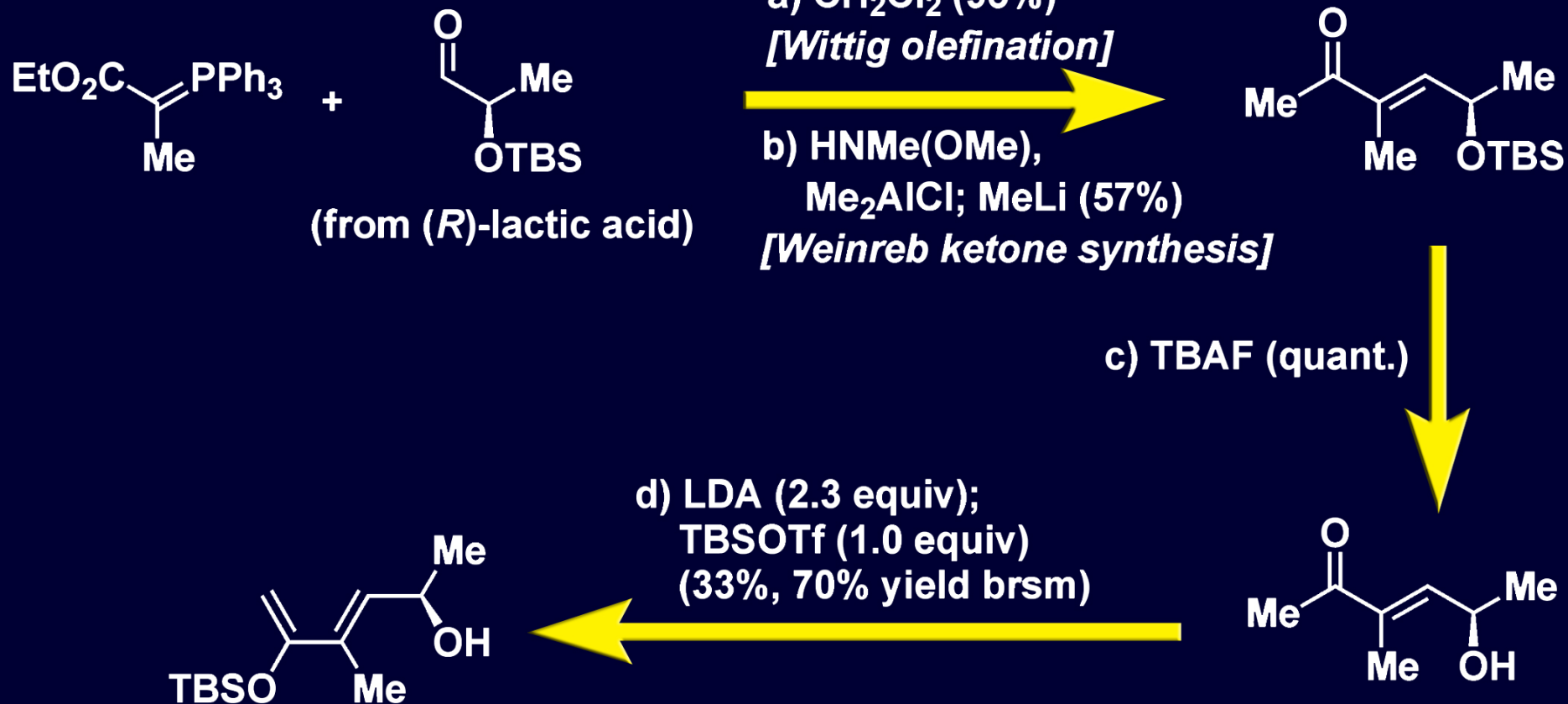
- Re-isolated by D. C. Rowley and co-workers from a *Streptomyces* sp. found in a green algae isolated from the ascidian *Ecteinascidia turbinata*, collected from La Parguera, Puerto Rico [relative, but no absolute configuration: *J. Nat. Prod.* 2006, 69, 1070; *Bioorg. Med. Chem.* 2006, 14, 8664.]

BE-43472B 2. RETROSYNTHETIC ANALYSIS [2009]

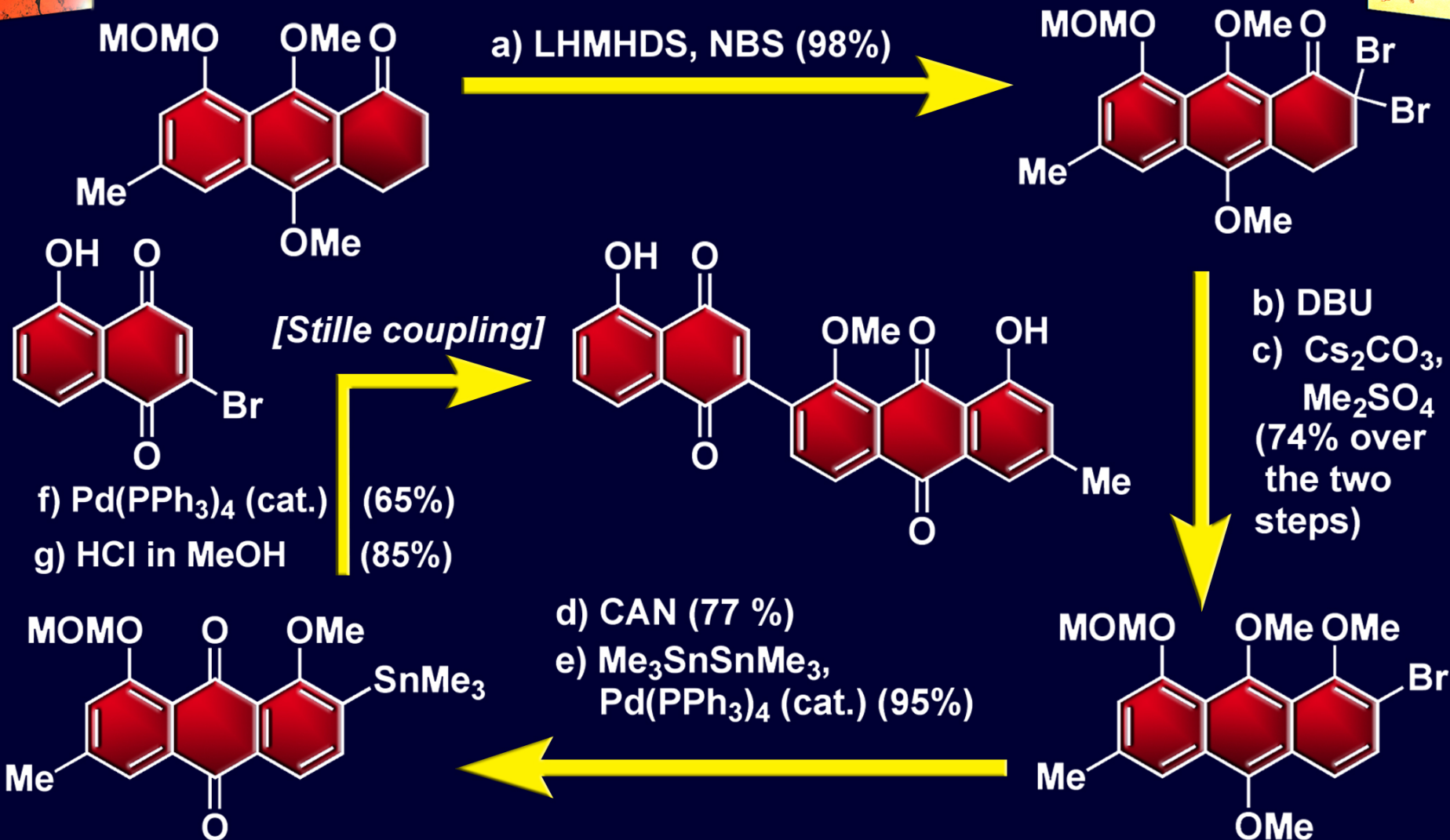




ANTIBIOTIC BE-43472B 3. DIENE [2009]



ANTIBIOTIC BE-43472B 4. DIENOPHILE [2009]

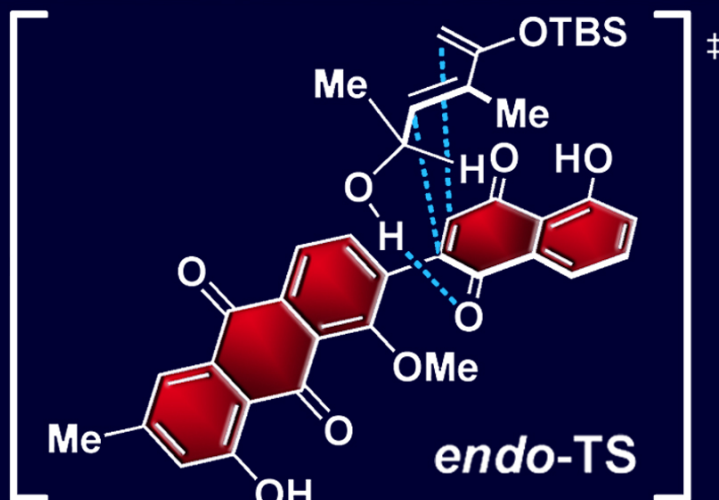




ANTIBIOTIC BE-43472B 5. CASCADE I [2009]



- preorganization of diene and dienophile

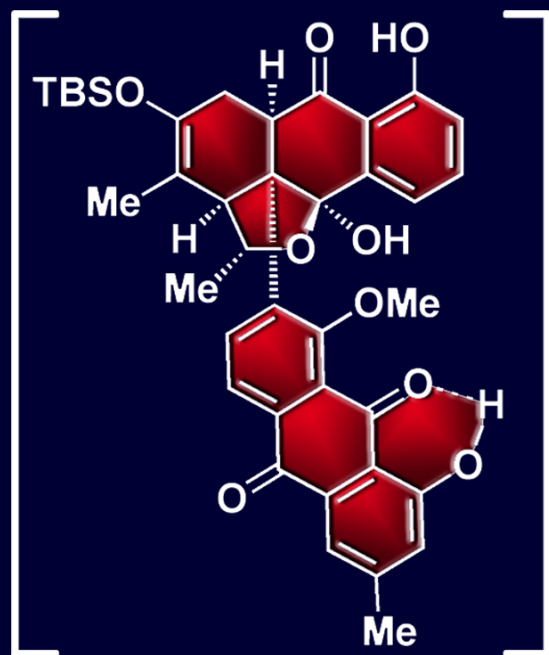
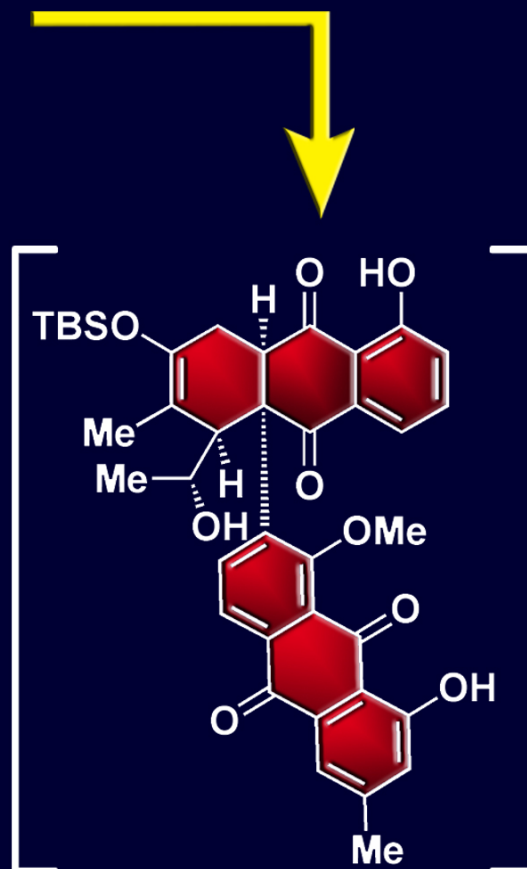


[Diels-Alder reaction]

[hemiketal formation]



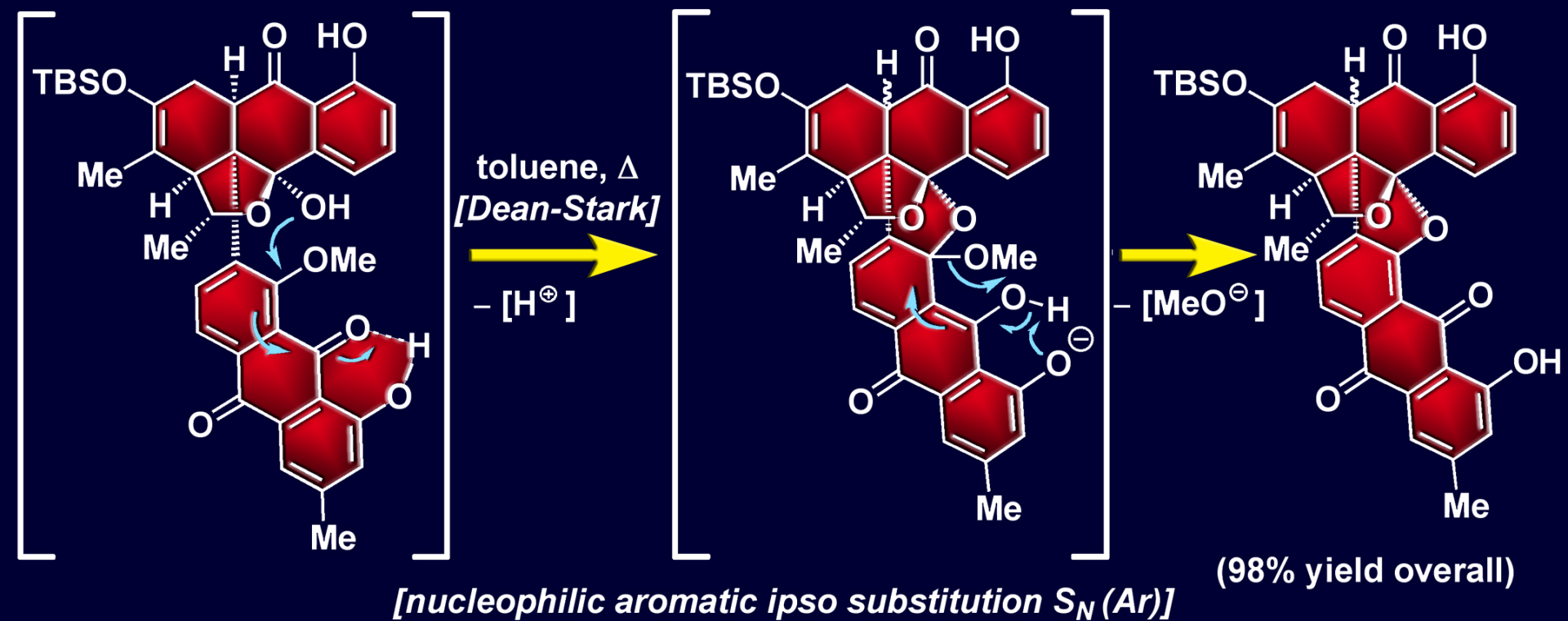
CH_2Cl_2 , Δ ;
[sealed tube]



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

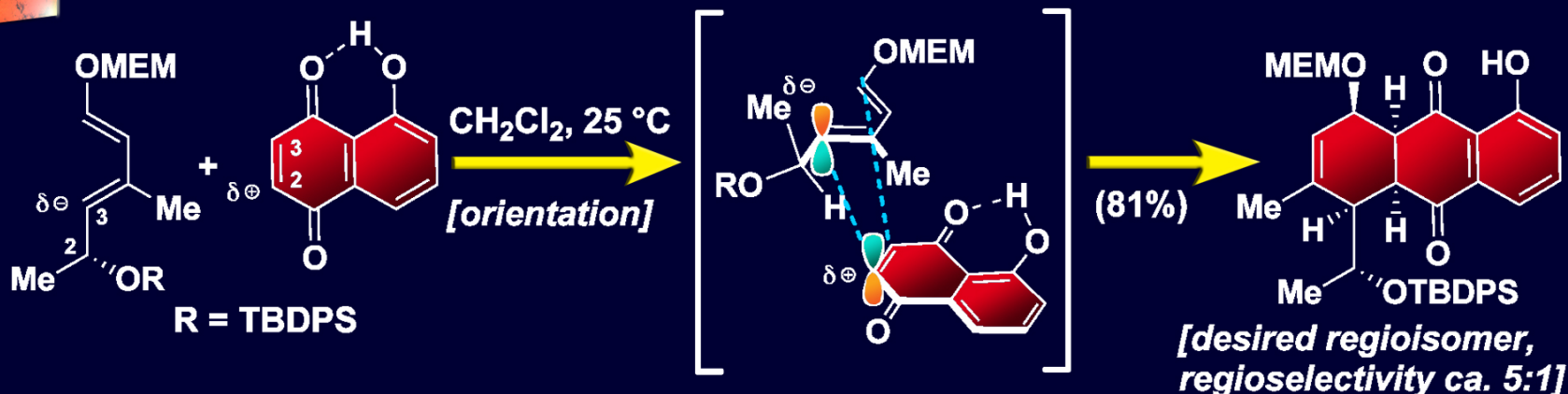


continue

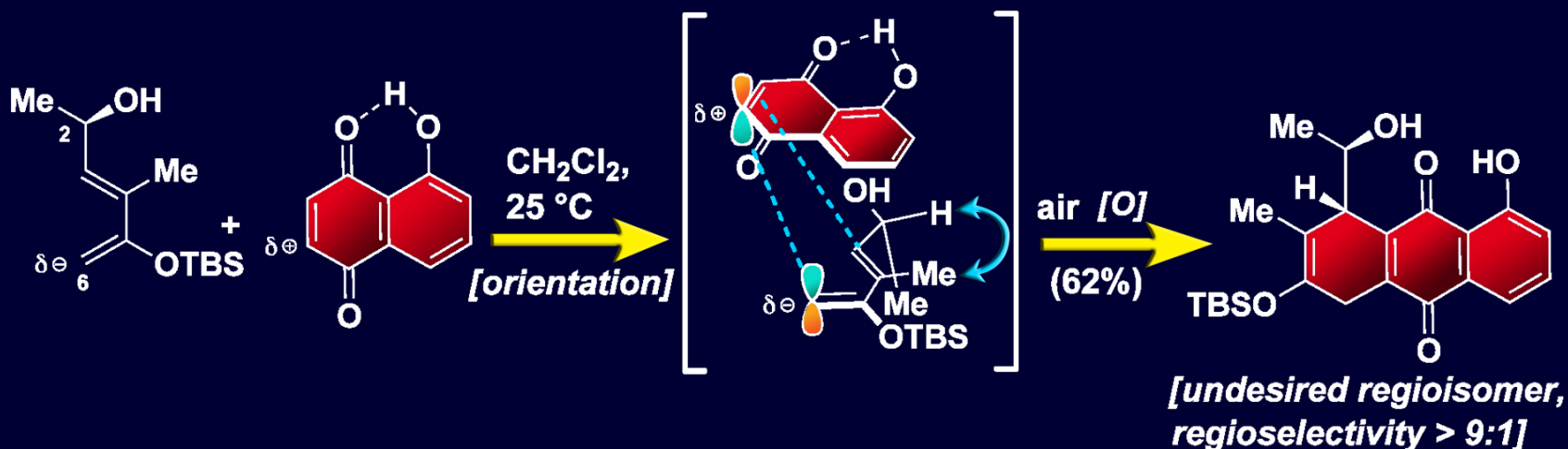




ANTIBIOTIC BE-43472B 11. THE JUGLONE CASE [2009]

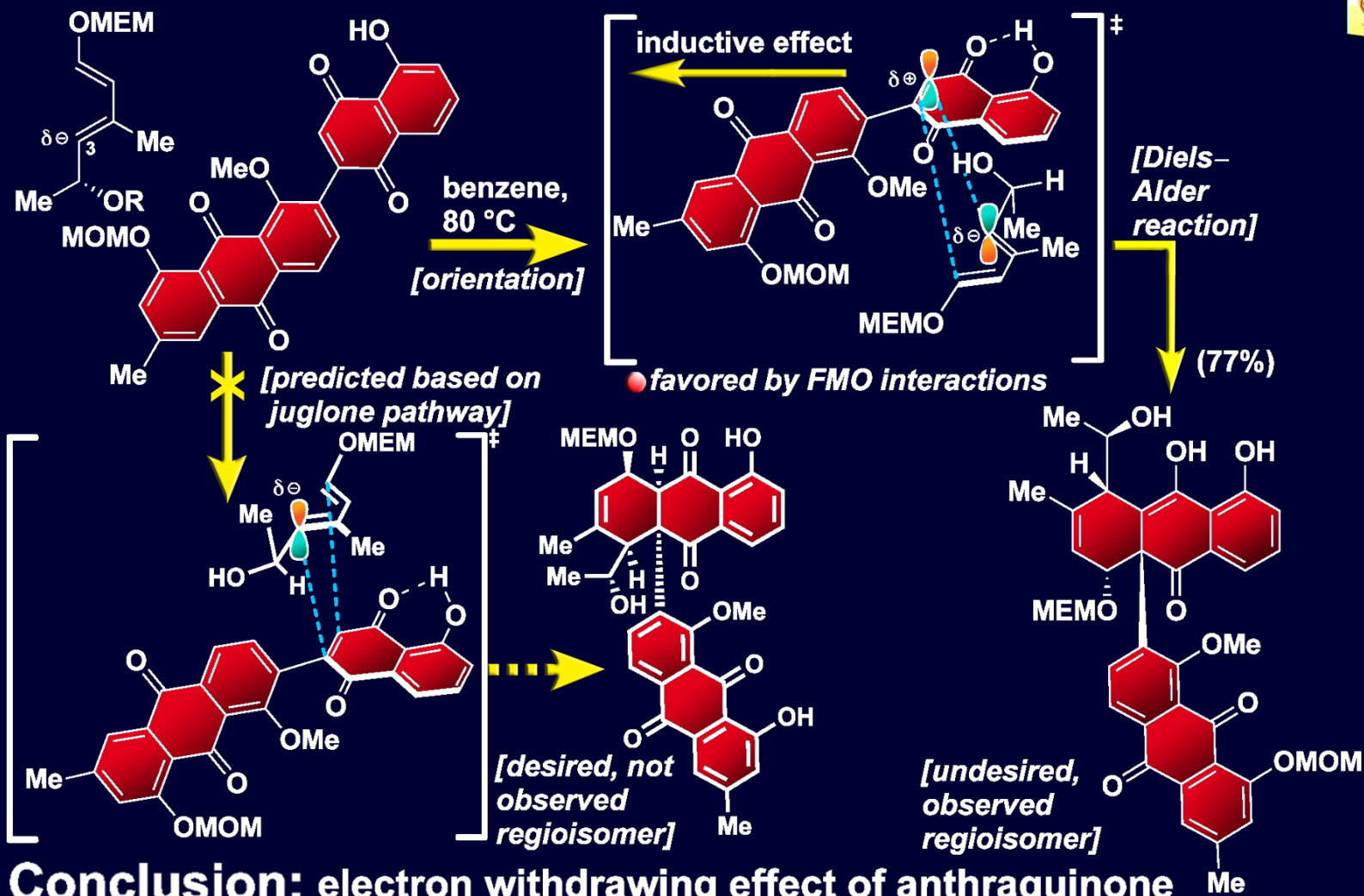


- Regioselectivity controlled by frontier molecular orbitals (FMOs)
- Facial selectivity controlled by C-2 stereocenter (1,3-allylic strain)



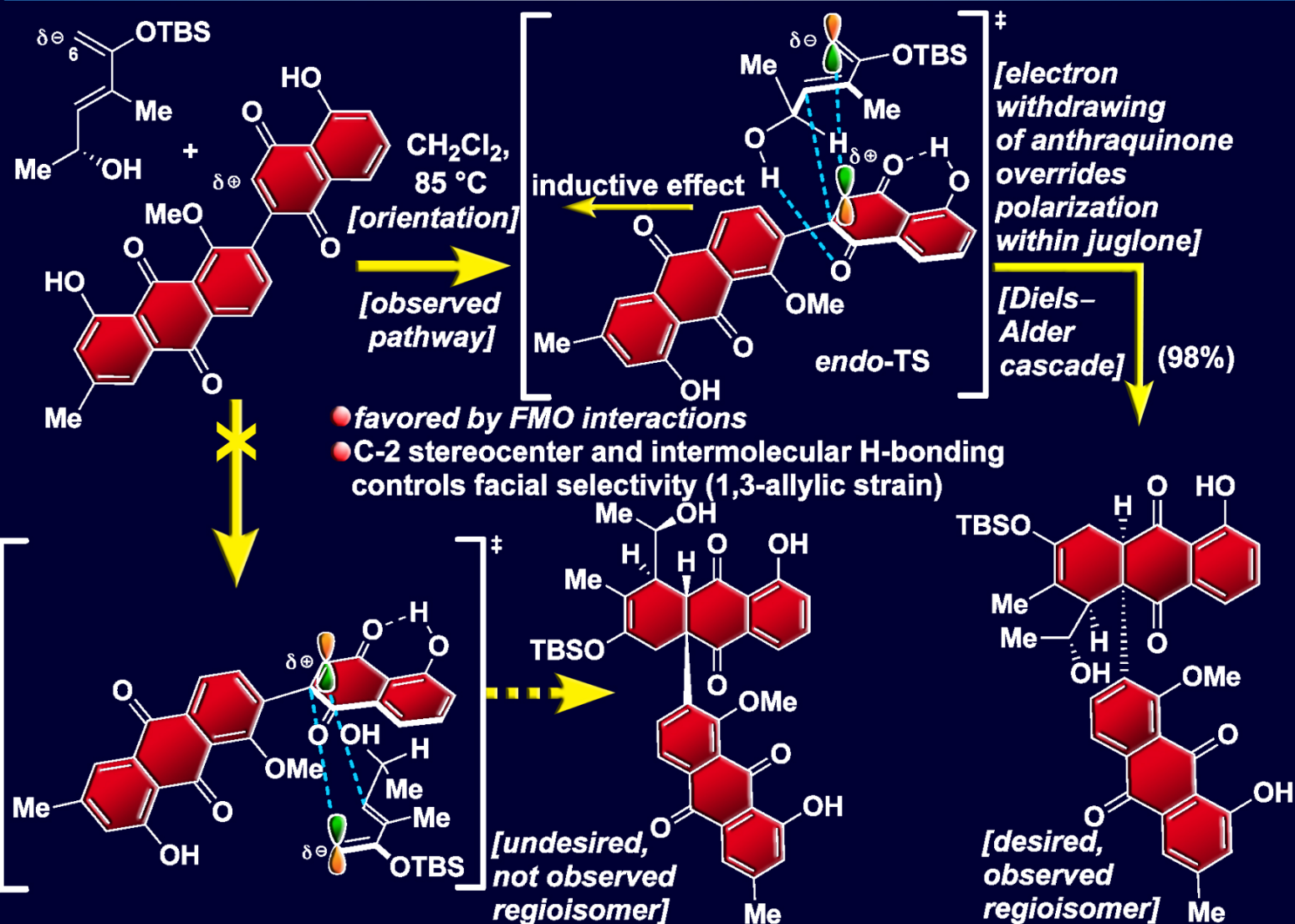


ANTIBIOTIC BE-43472B 12. DIELS-ALDER REACTION [2009]



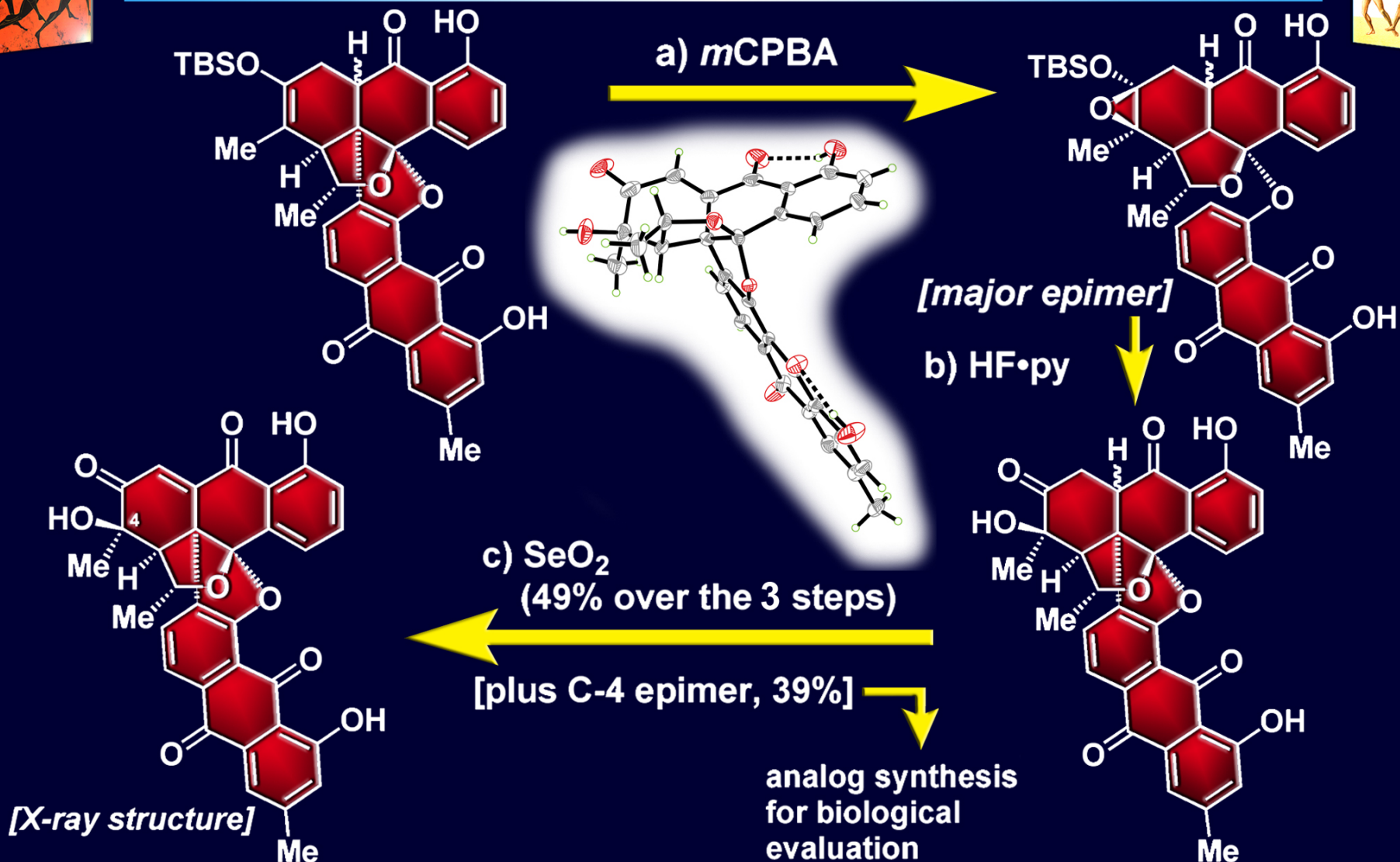
Conclusion: electron withdrawing effect of anthraquinone overrides polarization within juglone

ANTIBIOTIC BE-43472B 13. DIELS-ALDER REACTION [2009]



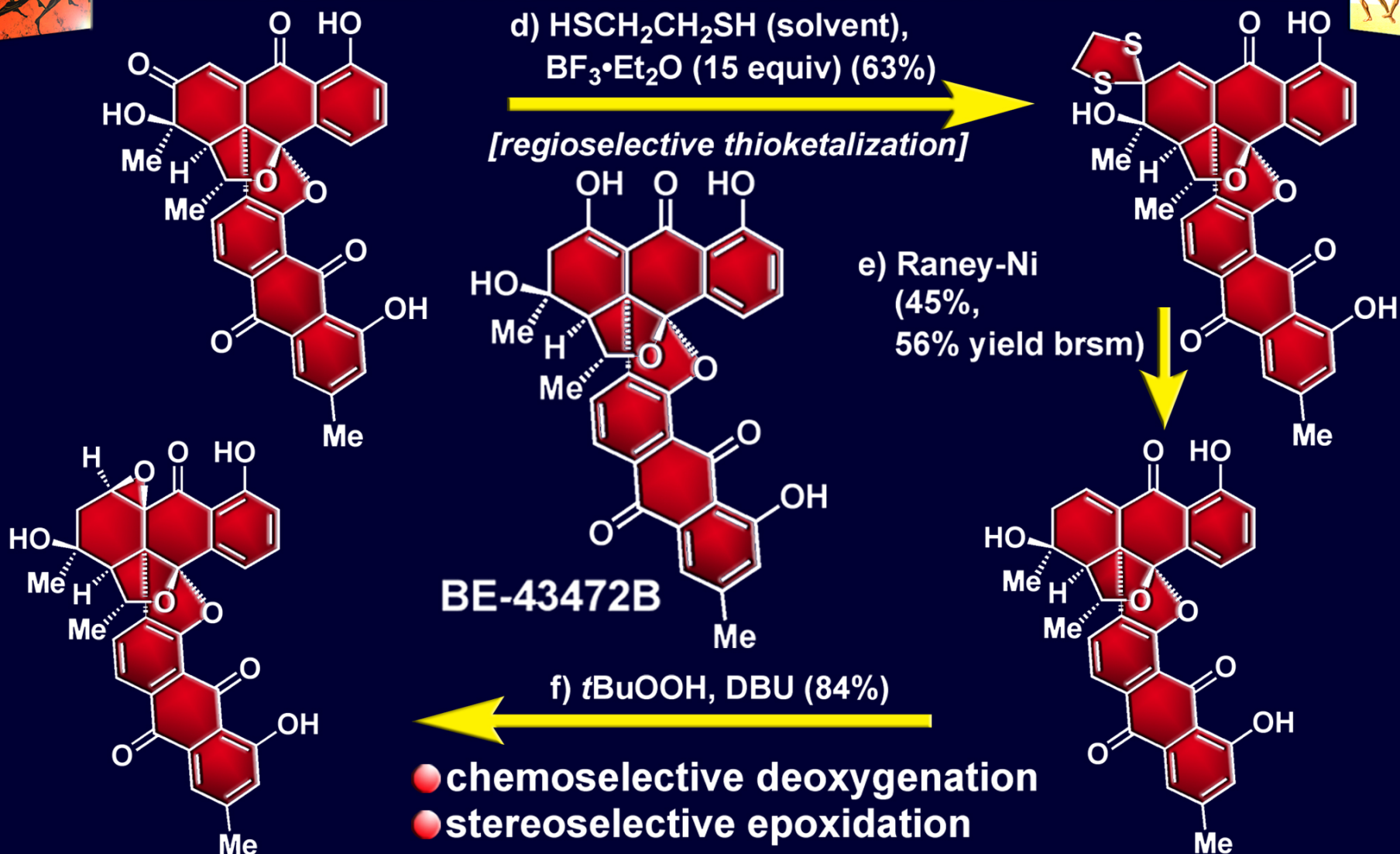


ANTIBIOTIC BE-43472B 7. INTRODUCTION OF C4-OH [2009]

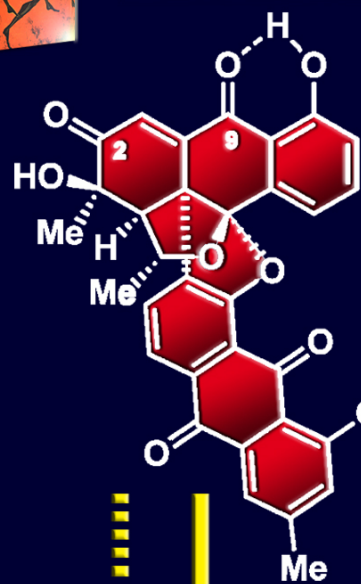




ANTIBIOTIC BE-43472B 8. EPOXY KETONE FORMATION [2009]



ANTIBIOTIC BE-43472B 14. THIOKETALIZATION [2009]

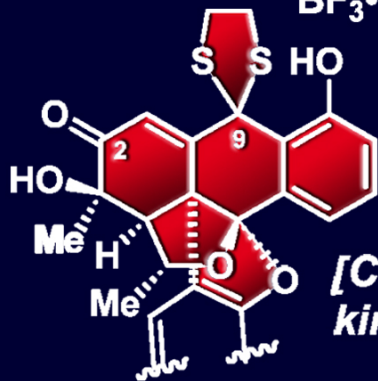


HSCH₂CH₂SH (solvent),
BF₃•Et₂O (15 equiv), 25 °C (63%)

[regioselective thioketalization]

● C-9 carbonyl more reactive than
C-2 carbonyl due to H-bonding

HSCH₂CH₂SH (4.0 equiv), CH₂Cl₂,
BF₃•Et₂O (6.0 equiv), 25 °C (55%);



more forcing conditions

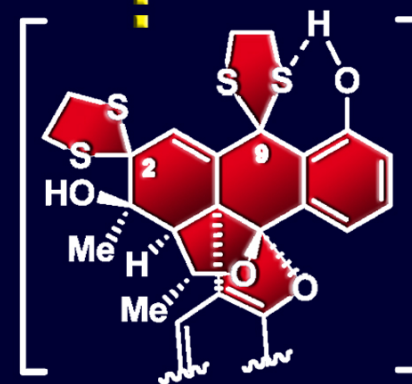
[C-9 dithiolane,
kinetic, isolable product]

● C-2 carbonyl stabilizes C-9 dithiolane



[C-2 dithiolane,
thermodynamic
product]

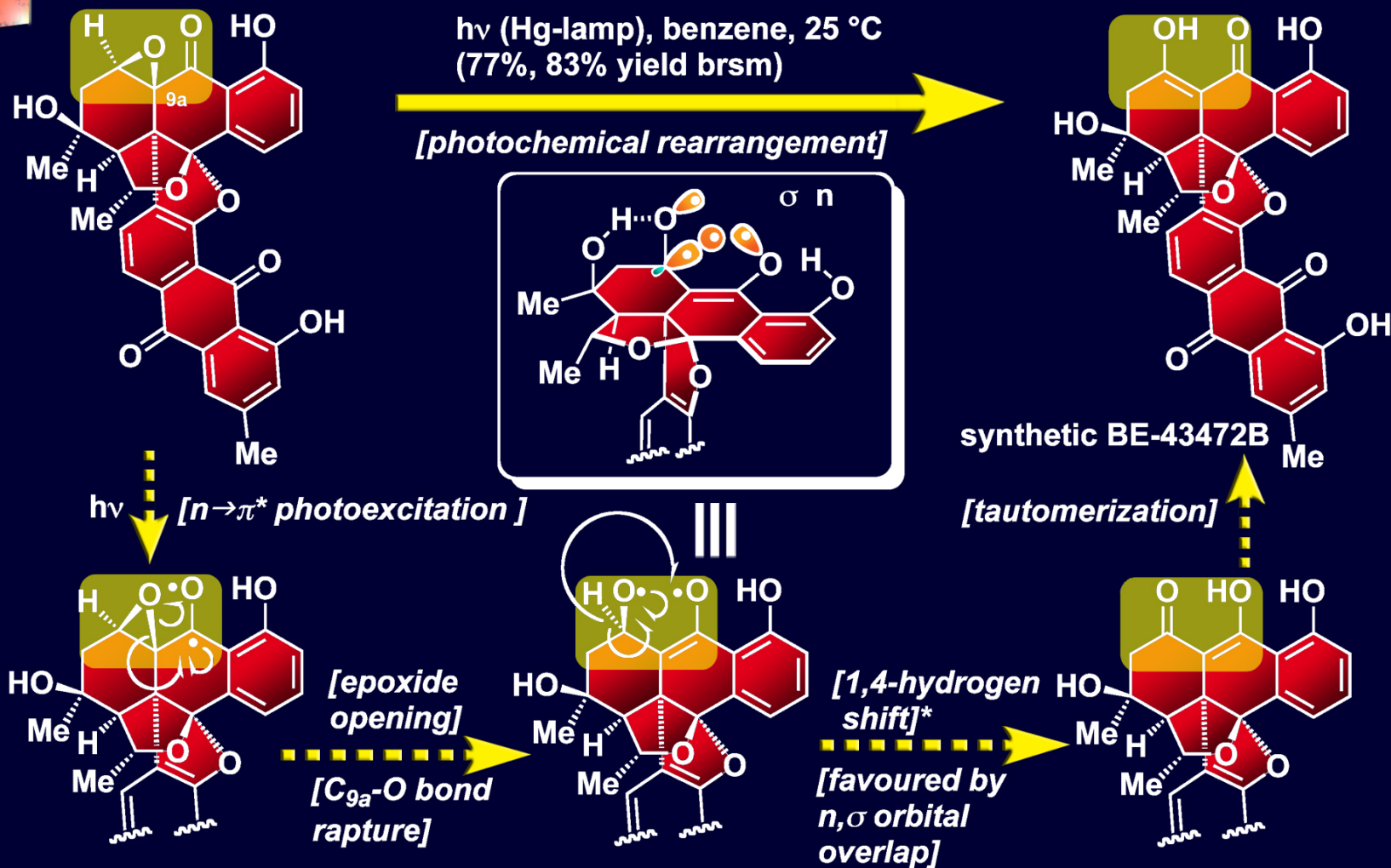
H₂O



[labile
intermediate]

● H-bonding destabilizes C-9 dithiolane

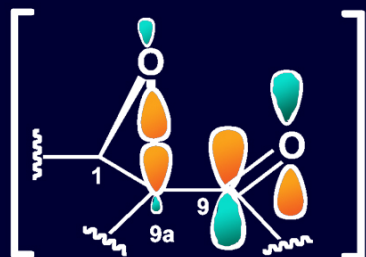
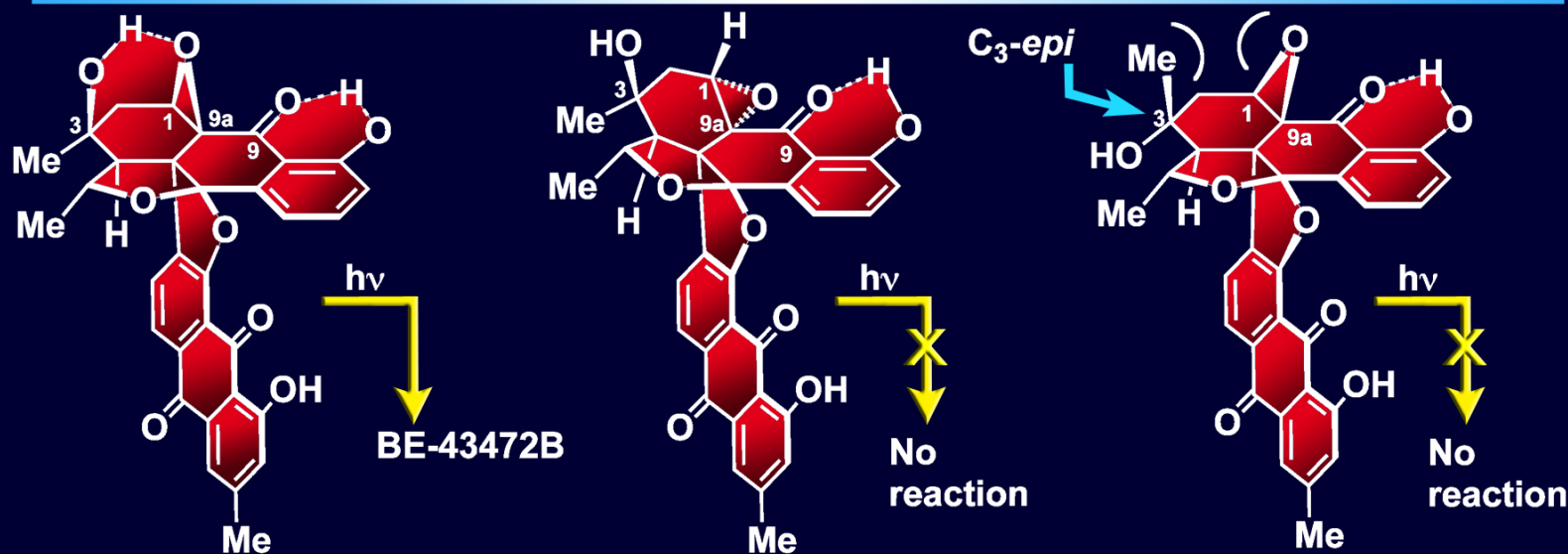
ANTIBIOTIC BE-43472B 9. FINAL STEP [2009]



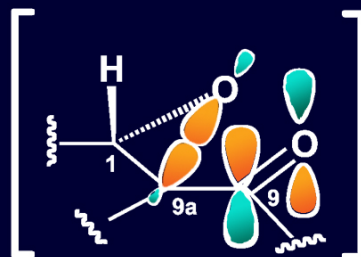
* 1,4-hydrogen shift observed by laser flash photolysis methods: a) H. Kim, T. G. Kim, J. Hahn, D.-J. Jang, D. J. Chang, B. S. Park, *J. Phys. Chem. A*. 2001, 105, 3555.



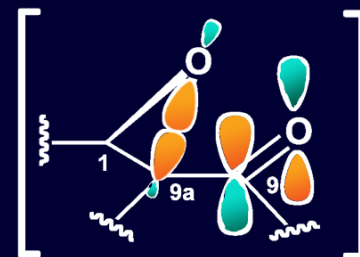
ANTIBIOTIC BE-43472B 10. STEREOELECTRONIC EFFECTS IN THE PHOTOCHEMICAL α,β -EPOXYKETONE REARRANGEMENT*



- *H-bonding aligns σ (C_{9a}-O) and π^* (C=O) orbitals of axial oxirane optimally for interaction*



- *inadequate overlap of σ (C_{9a}-O) and π^* (C=O) orbitals due to equatorial position of oxirane*



- *steric repulsion between Me and pseudoaxial oxirane results in insufficient overlap of σ (C_{9a}-O) and π^* (C=O) orbitals*

* We thank Professor Albert Eschenmoser for insightful discussions, La Jolla, February 2009.

Ciguatera Fish Poisoning

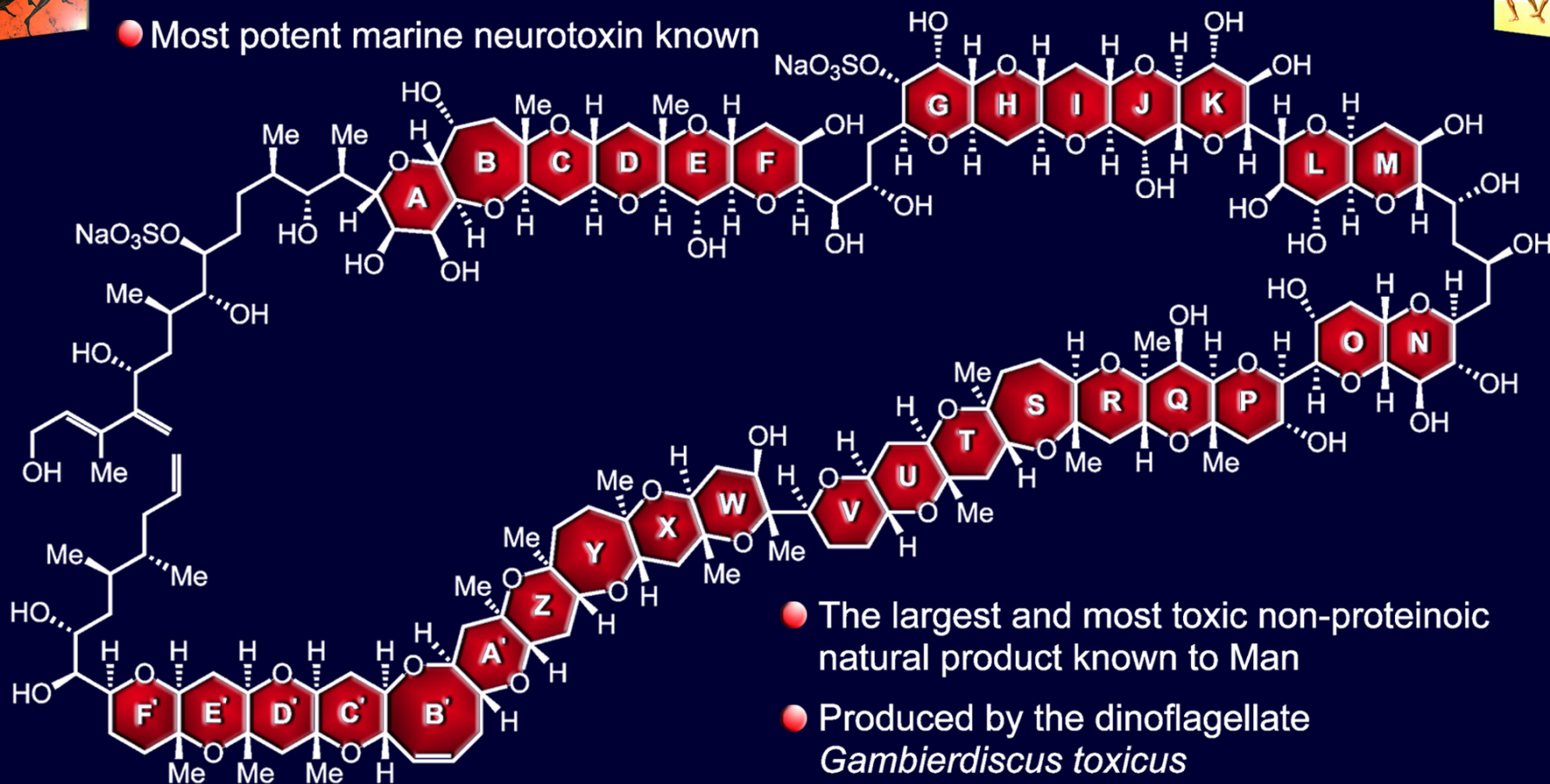




PROPOSED STRUCTURE OF MAITOTOXIN



- Most potent marine neurotoxin known



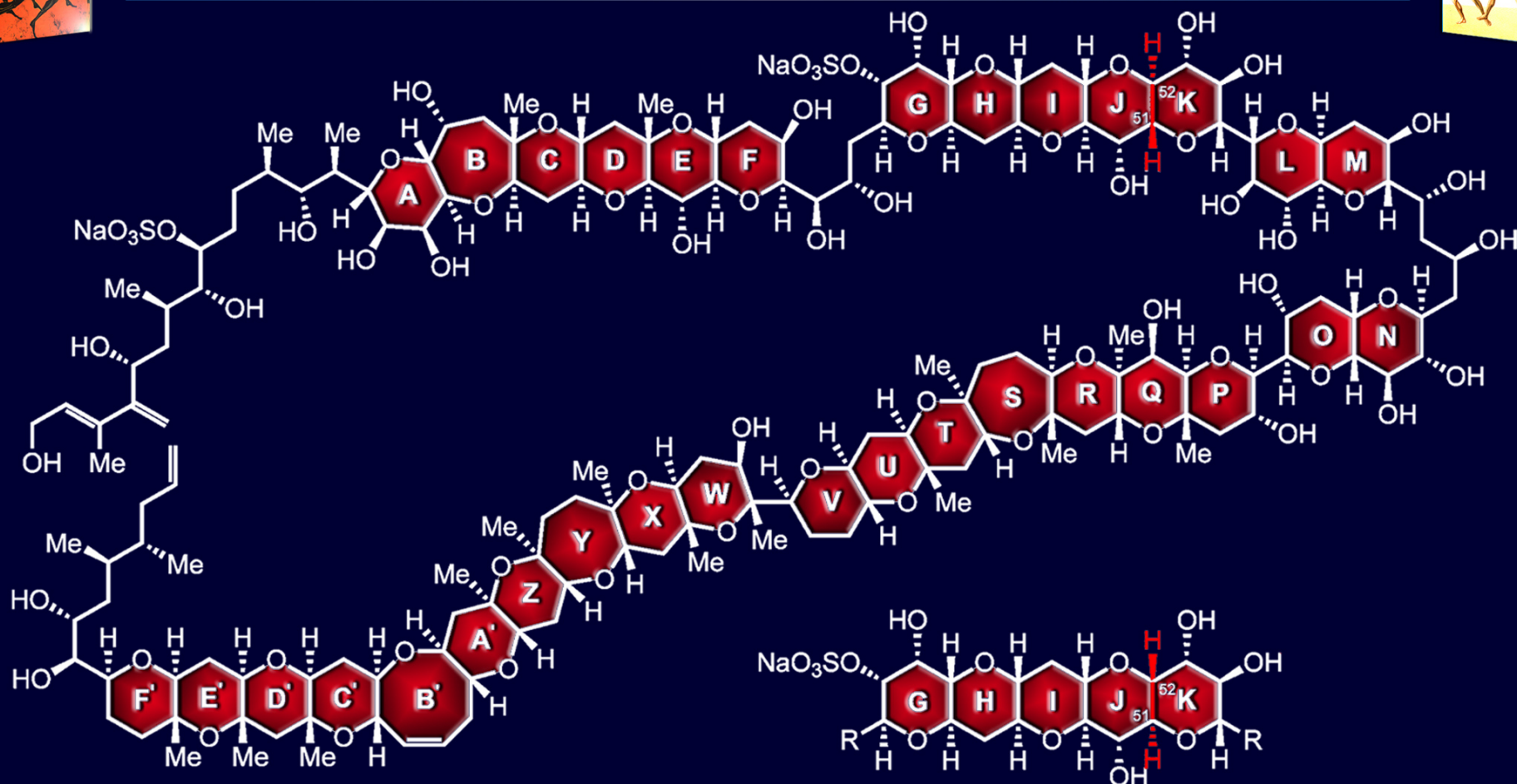
● $C_{164}H_{256}O_{68}S_2Na_2$ [MW 3422 Da]

● 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



MAITOTOXIN STRUCTURE-1



originally proposed maitotoxin structure
[Yasumoto, Tachibana, Kishi, 1996]

revised structure with C-51 and C-52
stereocenters inverted
[Gallimore and Spencer, 2006]

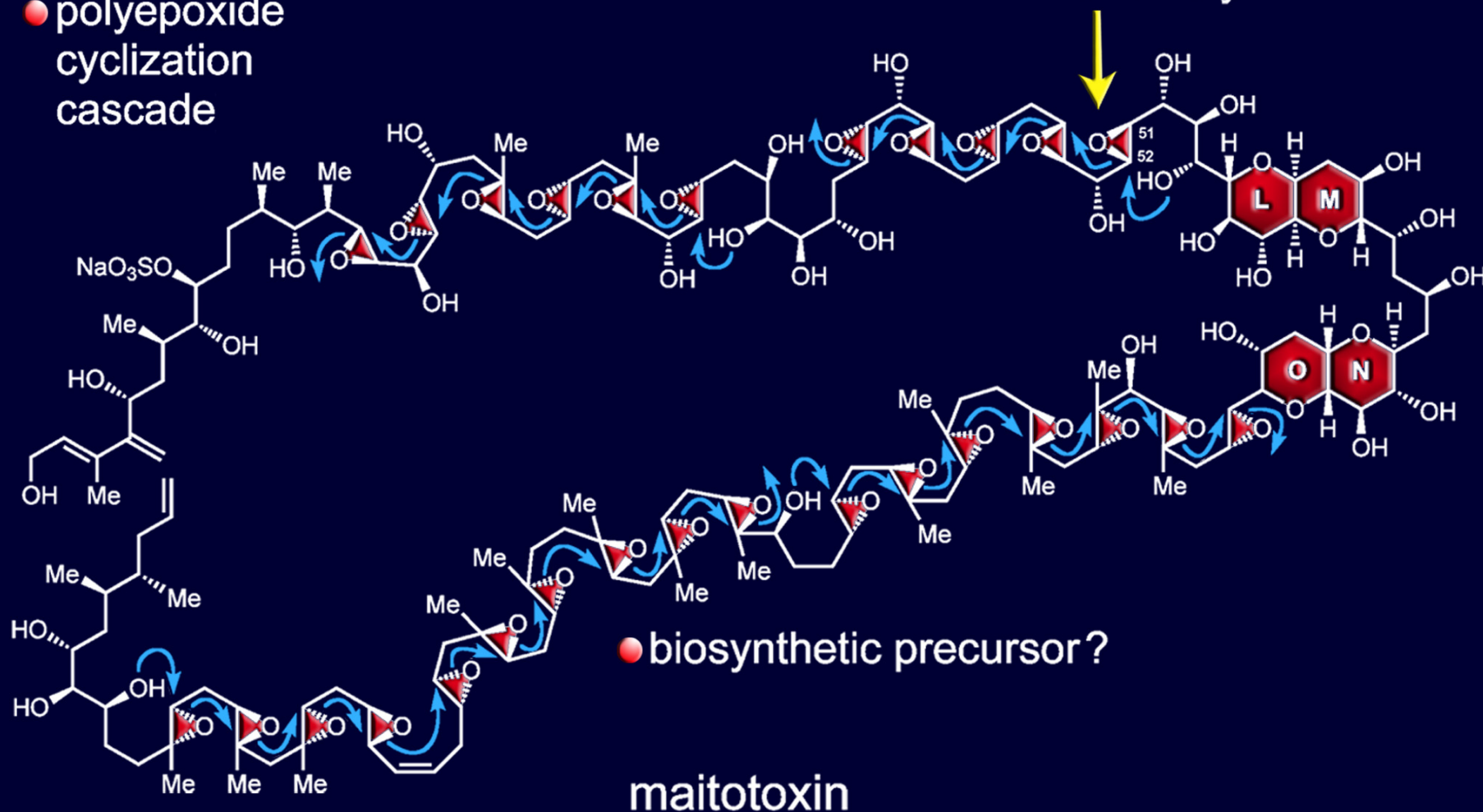


PROPOSED BIOSYNTHESIS OF MAITOTOXIN [NAKANISHI/GALLIMORE-SPENCER]



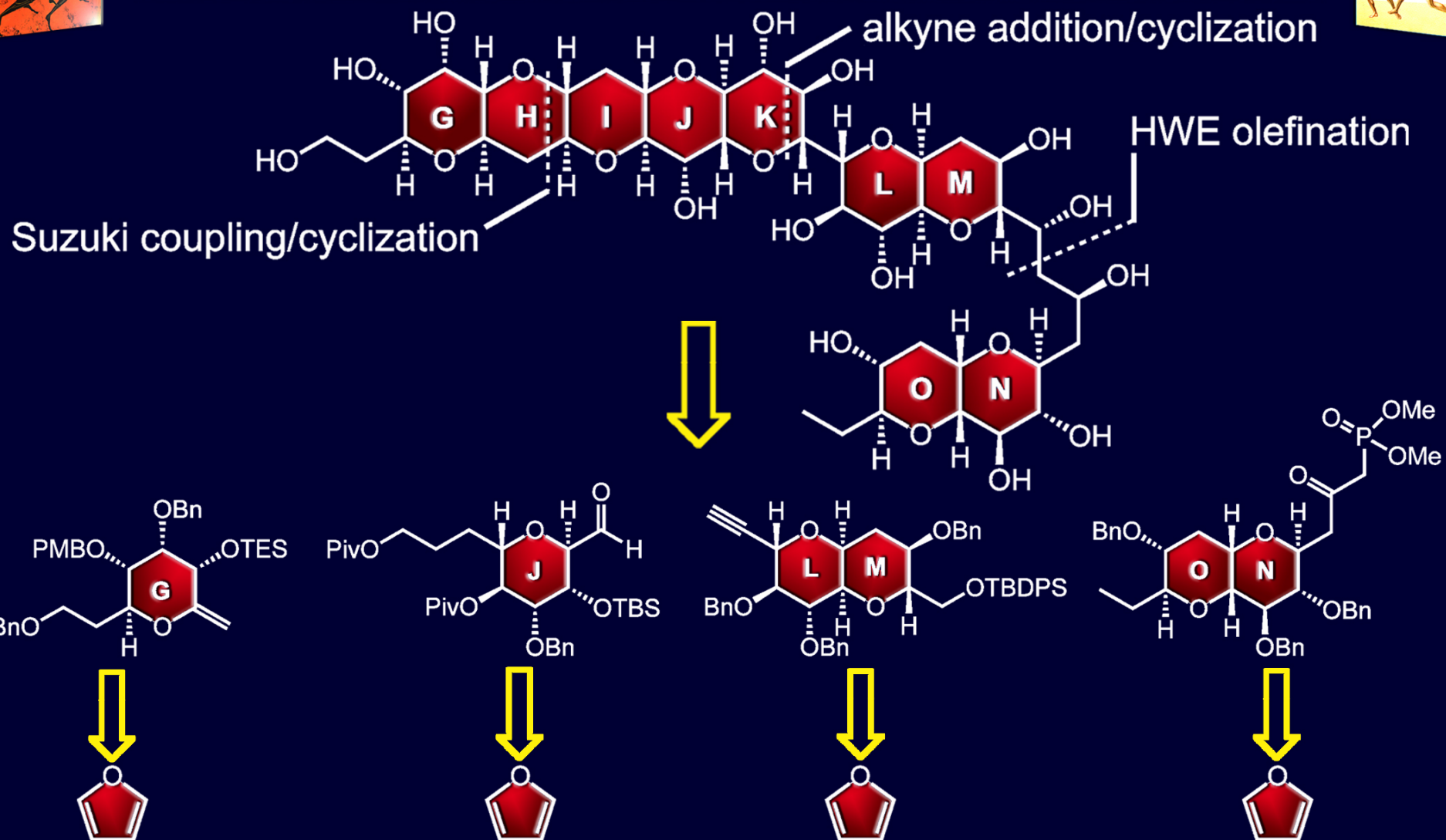
● polyepoxide
cyclization
cascade

● anomaly?

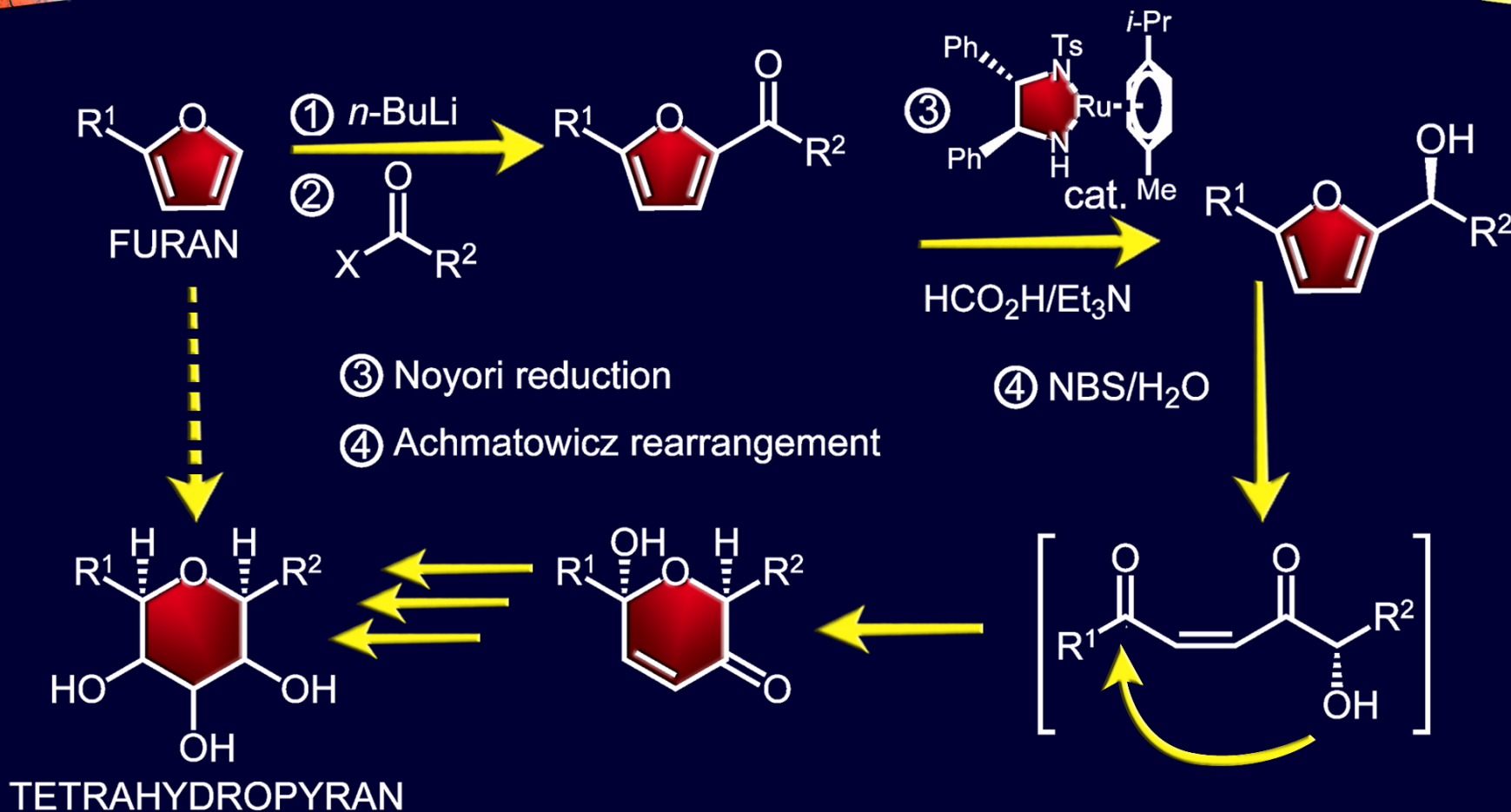




MAITOTOXIN-4: THE FURAN WAY



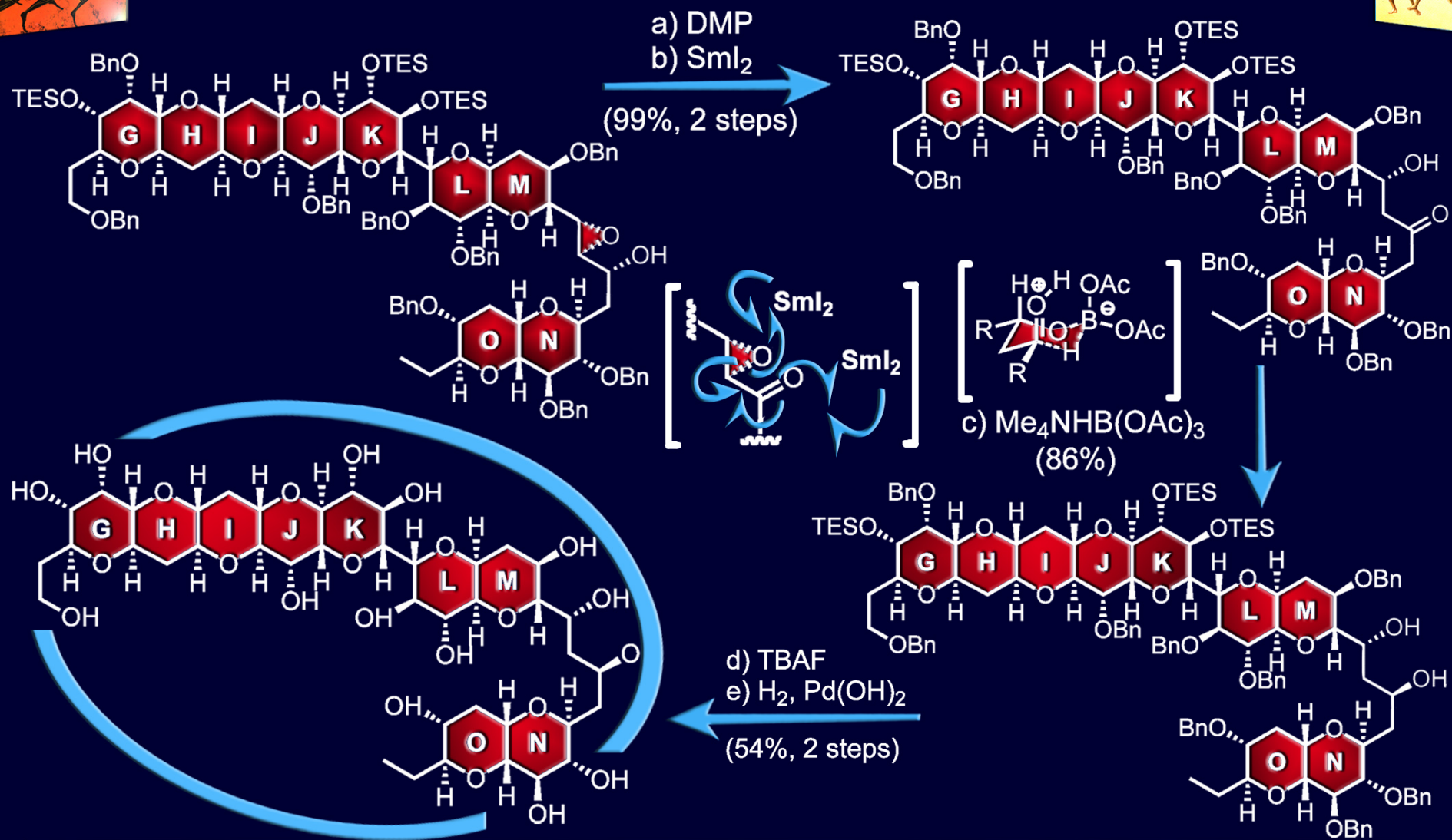
GENERAL METHOD FOR TETRAHYDROPYRAN SYNTHESIS FROM FURANS



Noyori, R., et al. *J. Am. Chem. Soc.* **1996**, *118*, 2521.
 Achmatowicz, O. et al. *Carbohydr. Res.* **1977**, *55*, 165.
 Nicolaou, K. C. et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 8875.

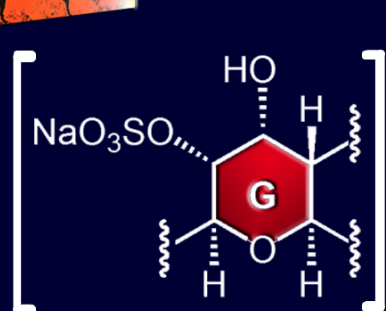


MAITOTOXIN-14

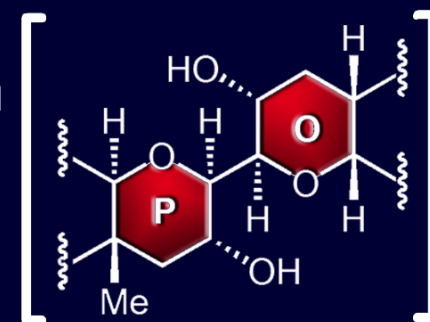
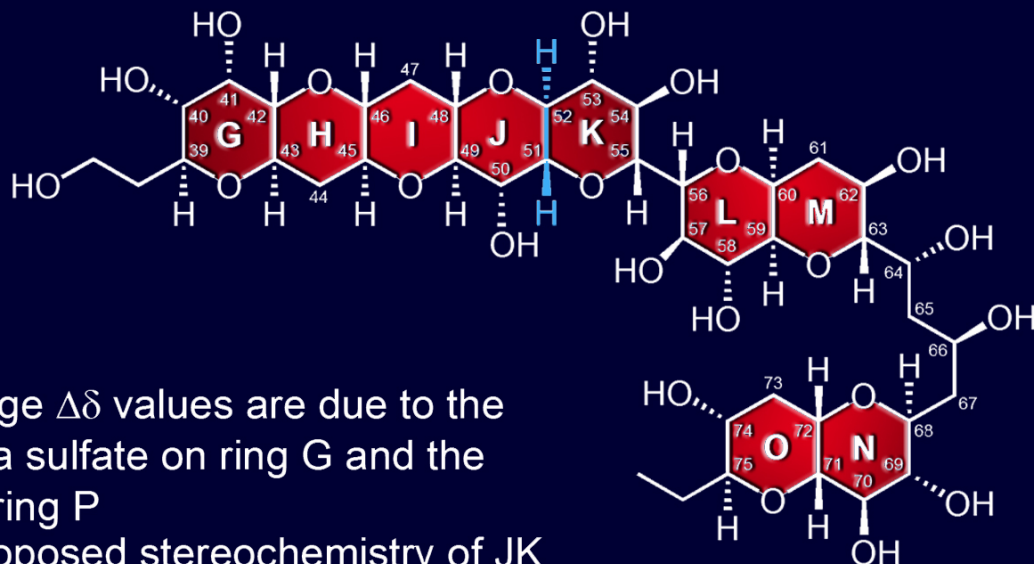




MAITOTOXIN-15

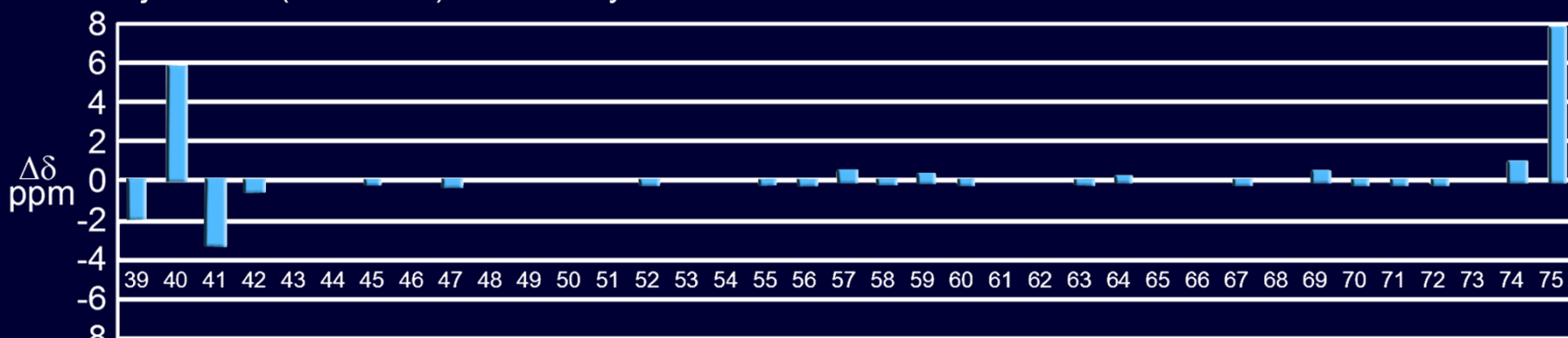


maitotoxin structure



maitotoxin structure

- relatively large $\Delta\delta$ values are due to the absence of a sulfate on ring G and the absence of ring P
- originally proposed stereochemistry of JK junction (C51-C52) most likely correct



- average $\Delta\delta$ for C42-C73 = 0.09 ppm
- largest $\Delta\delta$ for C42-C73 = 0.4 ppm

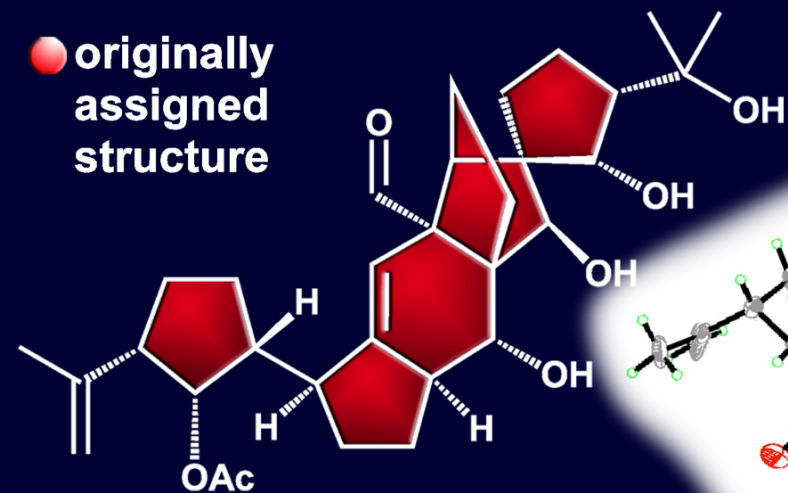


ORIGINALLY ASSIGNED AND REVISED STRUCTURES OF VANNUSAL B [2009]

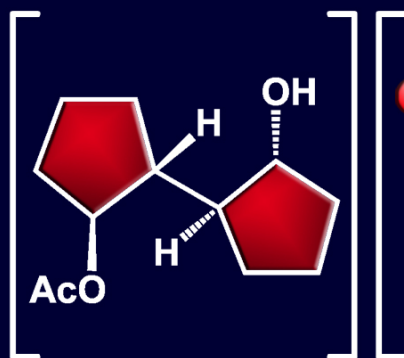
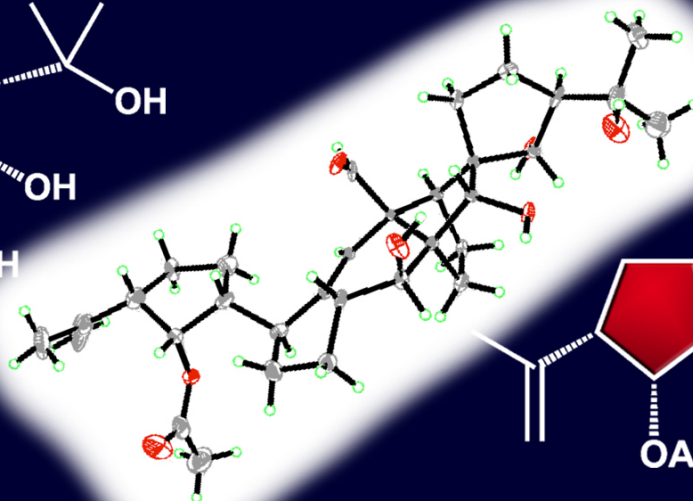
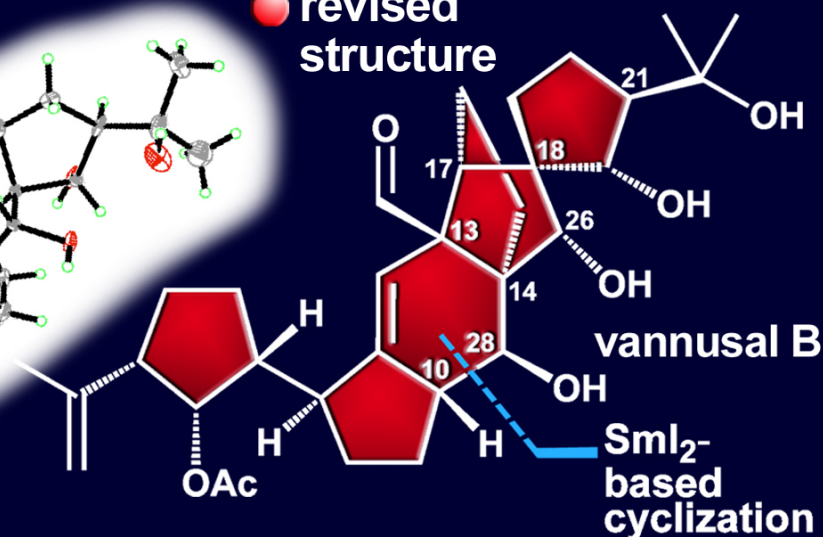


● Isolated from the tropical interstitial ciliate *Euplotes vannus* strains Si121 and BUN3 by Guella, Dini, and Pietra [1999].

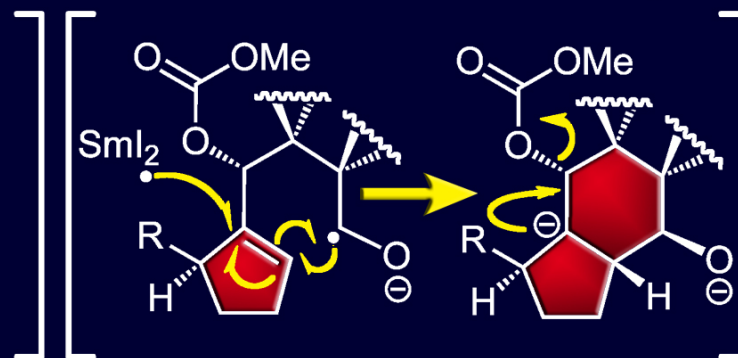
● originally assigned structure



● revised structure



● Enzymatic catalysis
[Amano Lipase PS]
from *meso bis*-acetate.
[100 % yield, 99 % ee]



● Kagan reagent [Sml₂]



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

DISCOVERIES AND INVENTIONS

BIOMIMETIC SYNTHETIC STRATEGIES

CASCADE REACTIONS

SOLID PHASE SYNTHESIS

COMBINATORIAL CHEMISTRY

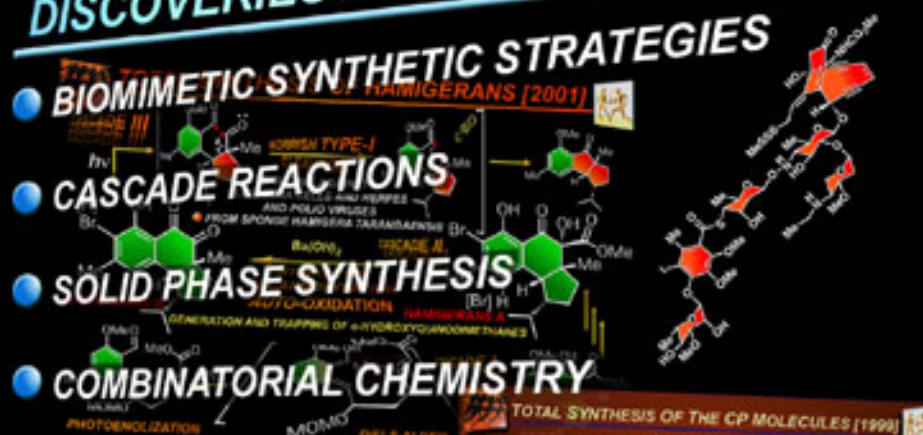
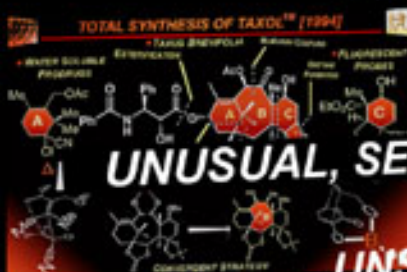
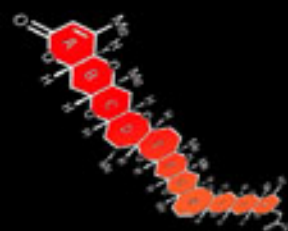
ASYMMETRIC SYNTHESIS

REAGENTS AND CATALYSTS

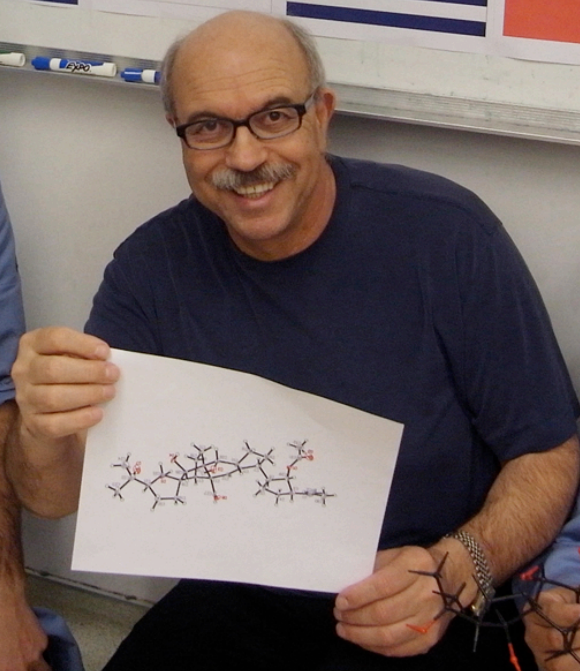
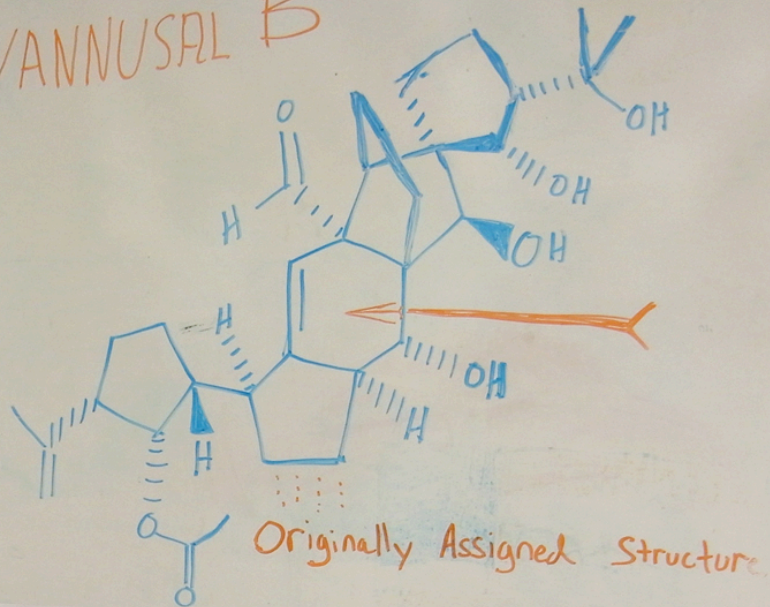
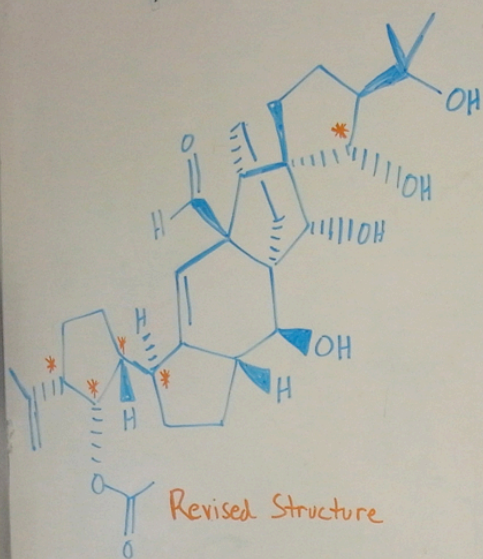
EFFICIENT CHEMICAL PROCESSES

GREEN CHEMISTRY

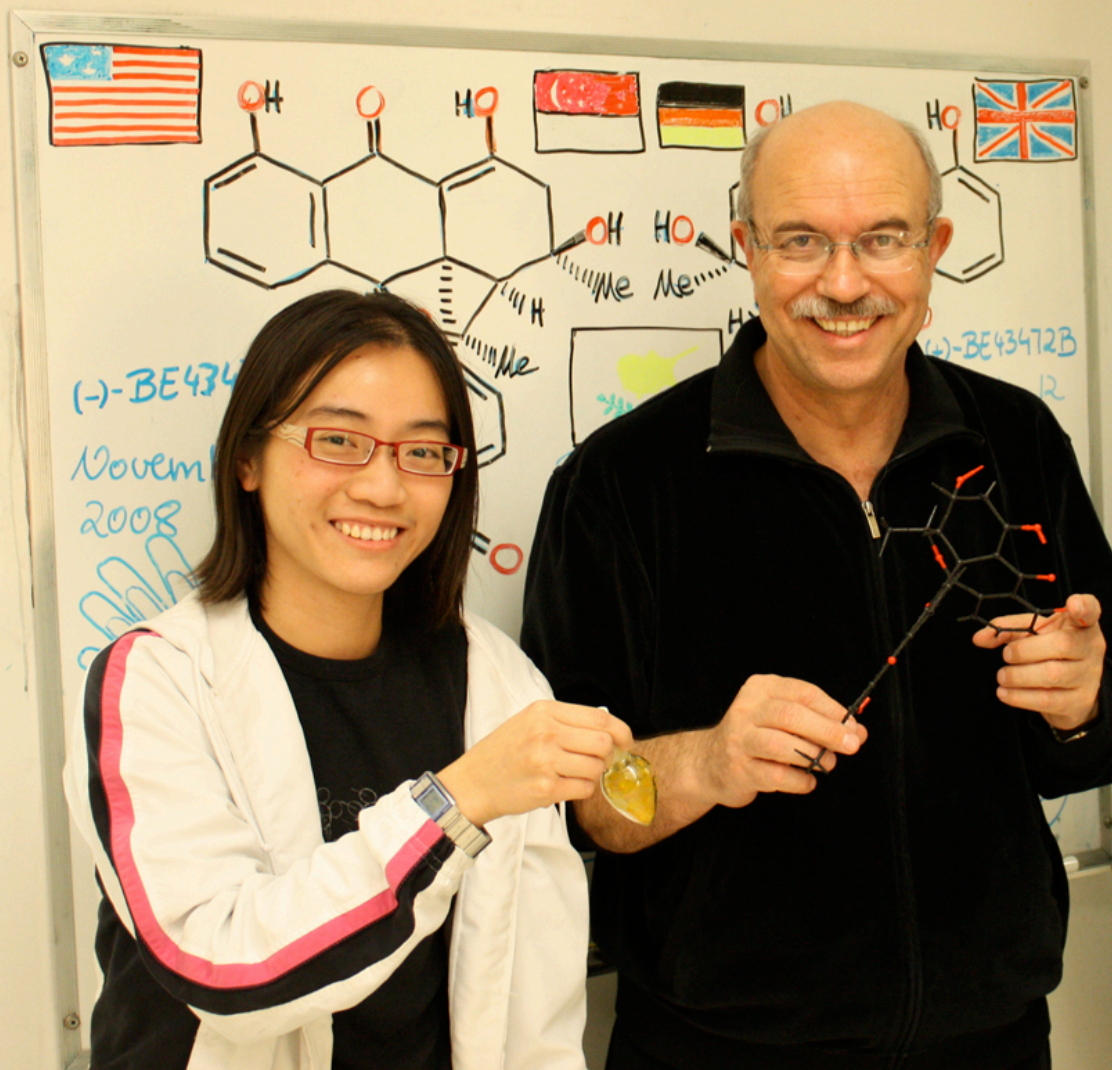
DESIGNED BIOACTIVE MOLECULES



VANNUSAL B









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- The National Institutes of Health – USA
- The Skaggs Institute for Research – USA
- The National Science Foundation – USA



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THANKS AND ACKNOWLEDGEMENTS

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(1976-PRESENT)



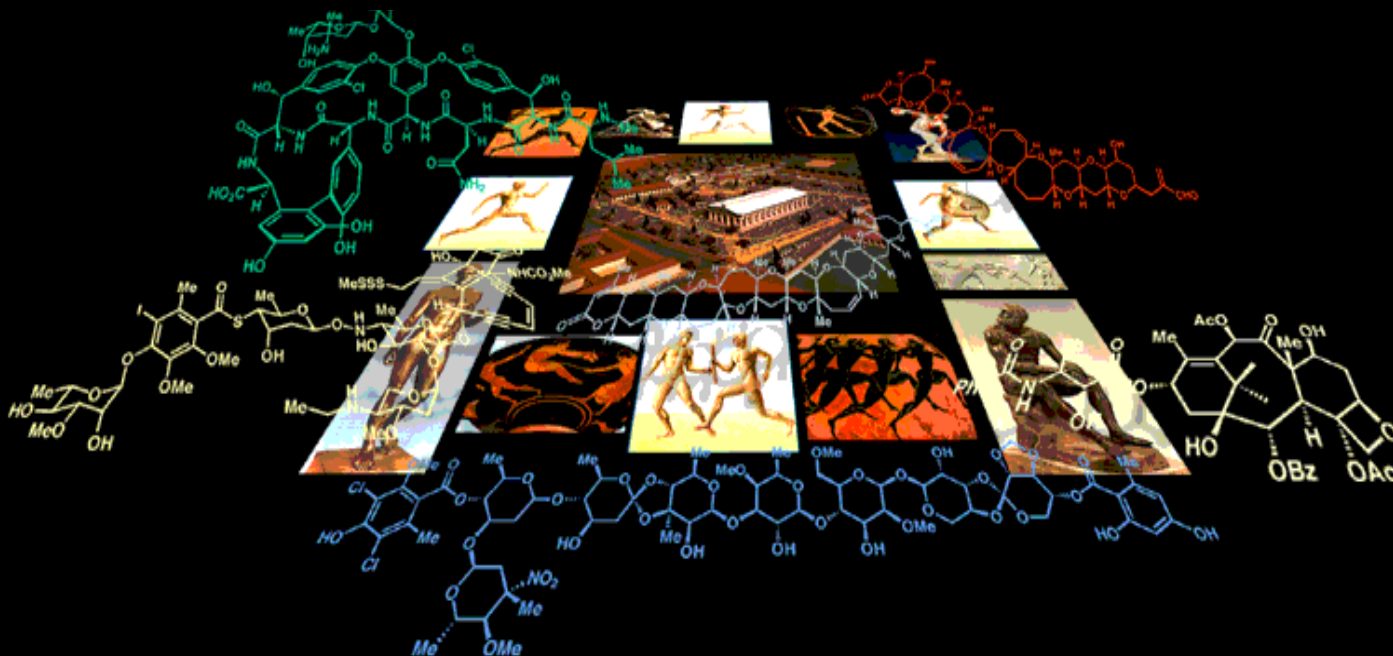
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Mary, Robbyn, Natasha, Vicky, Janise

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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), and *Molecules That Changed The World* (K.C. Nicolaou and T. Montagnon, Wiley-VCH, 2008).

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