

Paphos, Cyprus
**International Symposium on Chemistry,
Biology & Medicine**



“The Art and Science of Total Synthesis”

May 28 - June 1, 2006



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**

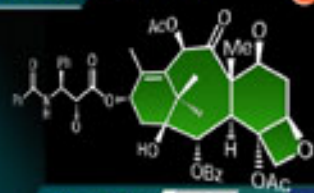
● **COMBINATORIAL CHEMISTRY**

● **PROCESS CHEMISTRY**

● **COST: \$500 MILLION AND RISING**

● **MEDICINAL CHEMISTRY**

● **REVIEW PROCESS**



\$

\$\$

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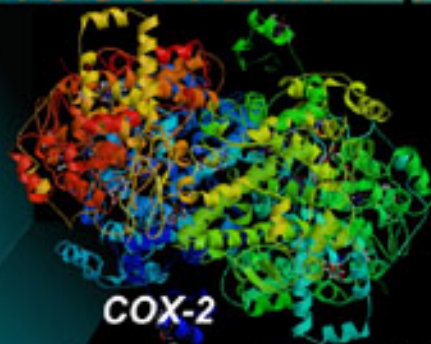


DISCOVERY

PRECLINICAL

CLINICAL

APPROVAL



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

● **HUMAN TRIALS**

● **TIME: 5-10 YEARS AND FALLING**



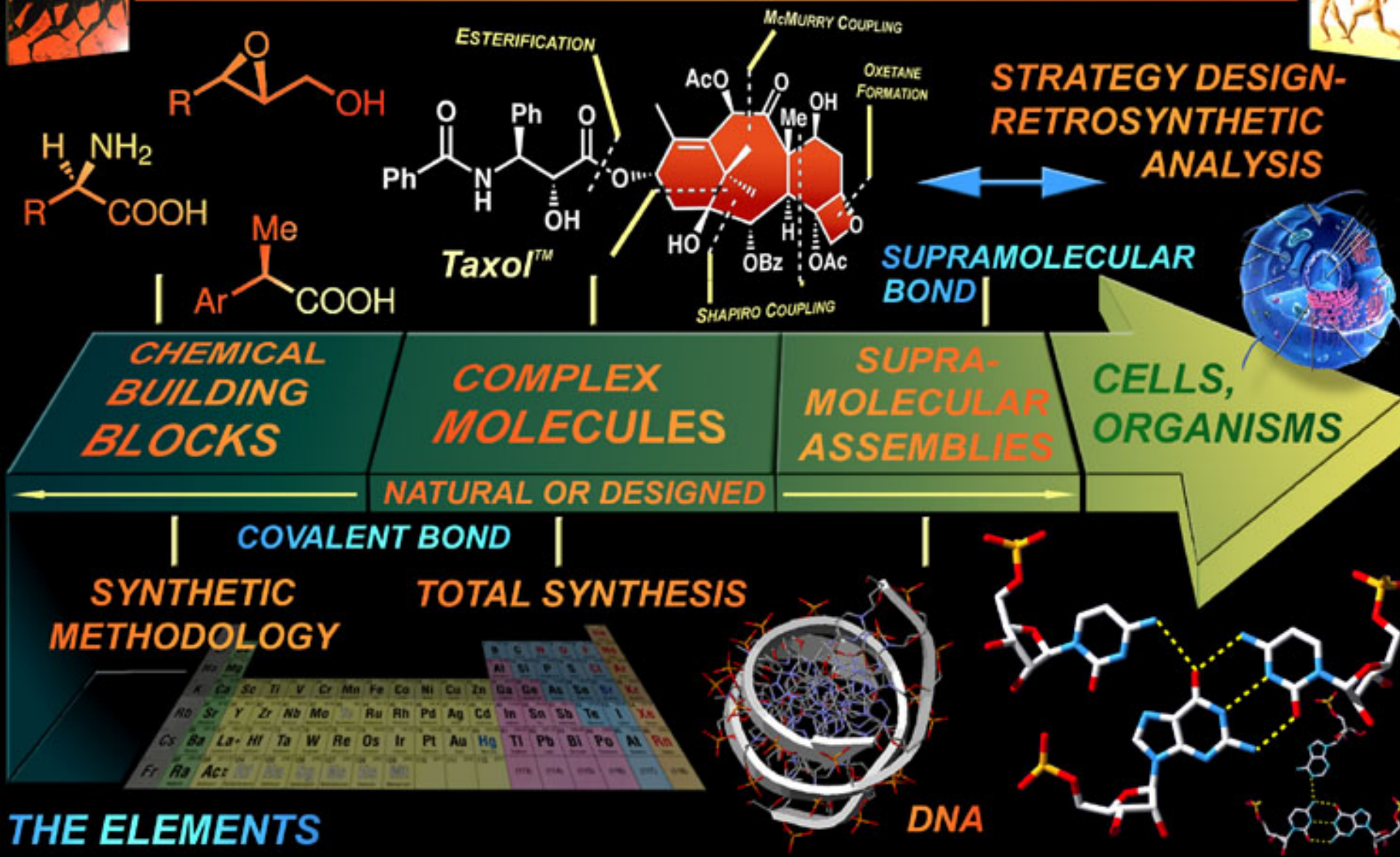
● **BIOLOGICAL TARGETS**

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

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



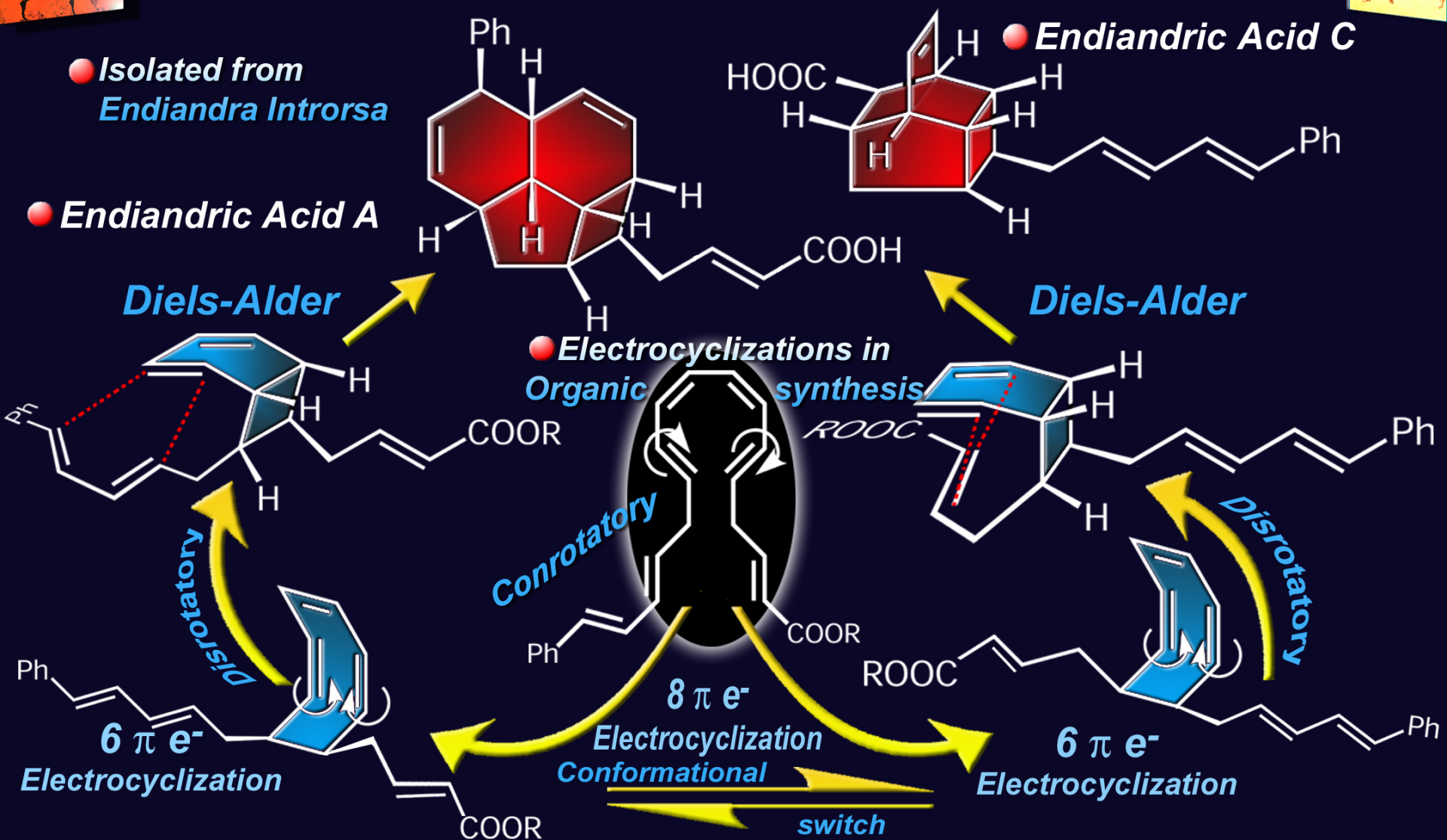
MOLECULAR COMPLEXITY and CHEMICAL SYNTHESIS





● **Endiandric Acid A**

● *Endiandric Acid C*



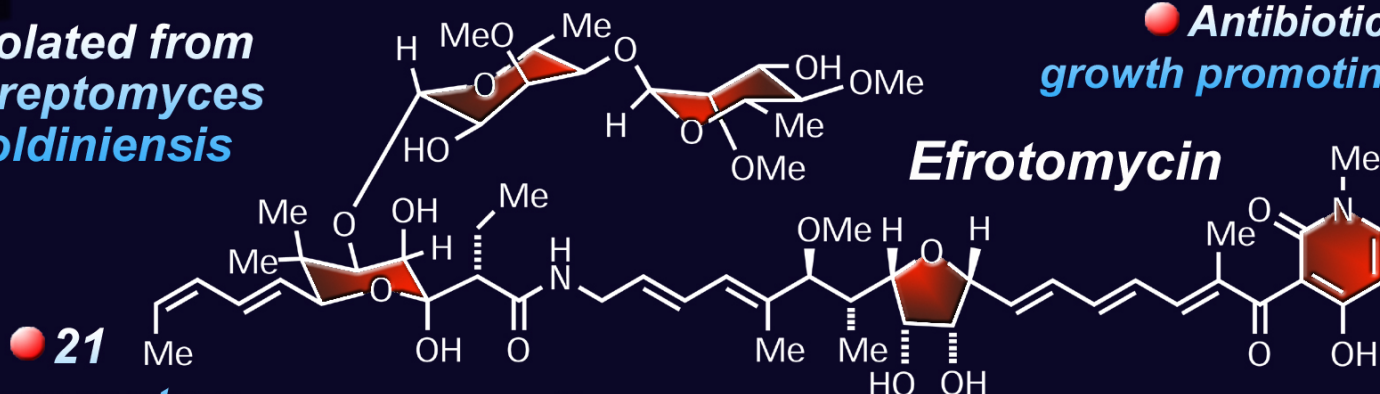


TOTAL SYNTHESIS OF EFROTOMYCIN [1984]

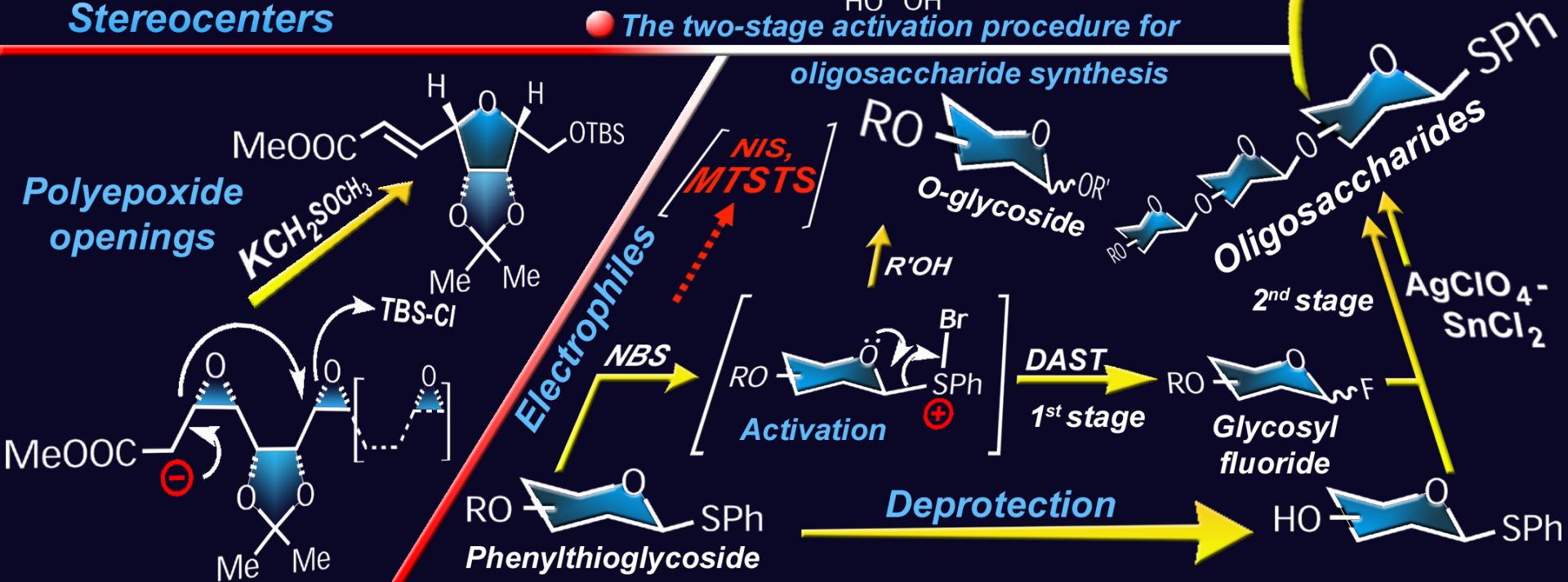


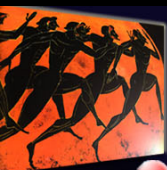
● Isolated from *streptomyces goldiniensis*

● Antibiotic with growth promoting properties



Stereocenters

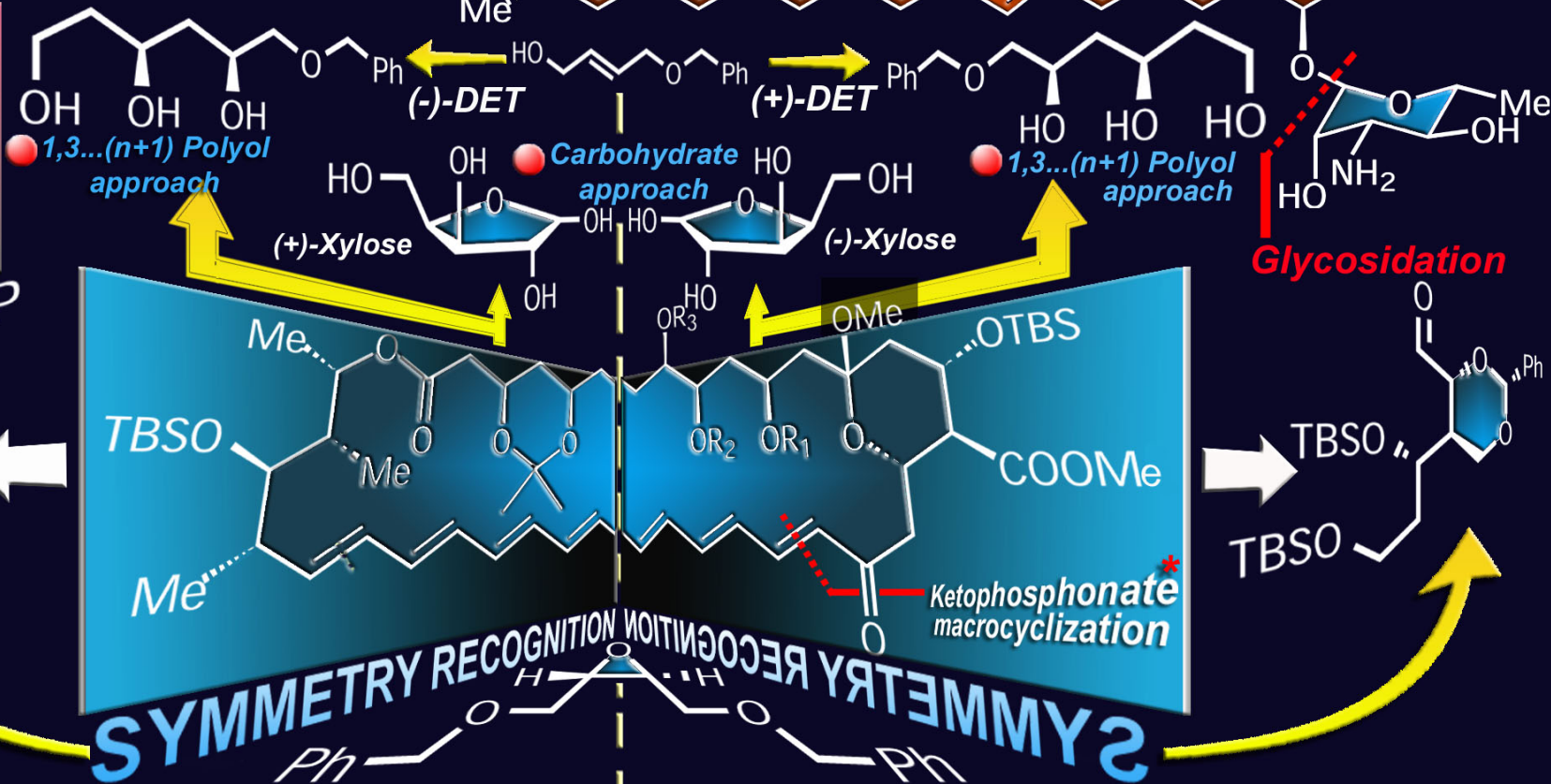
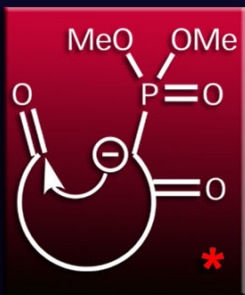
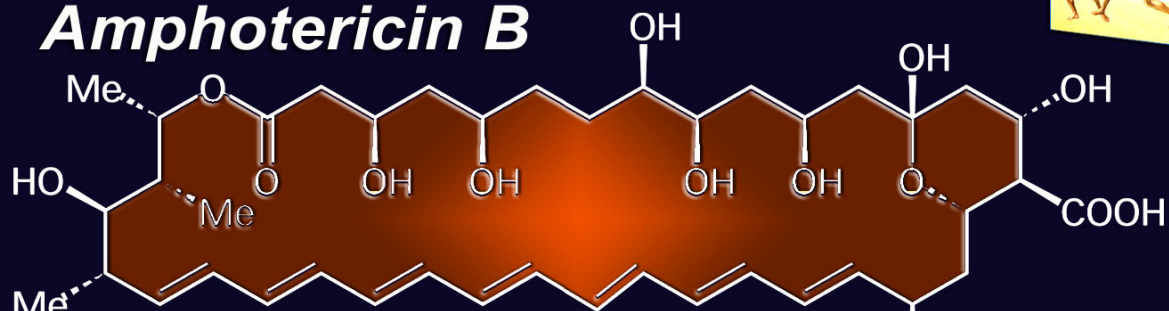




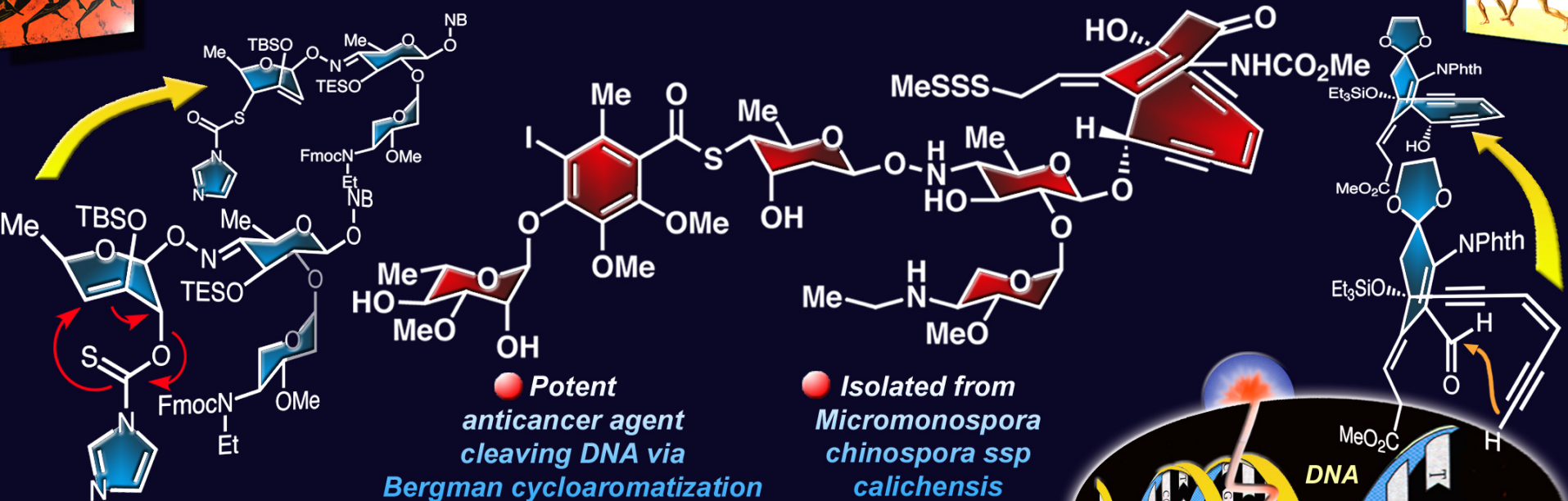
TOTAL SYNTHESIS OF AMPHOTERICIN B [1987]

- Isolated from *Streptomyces nodosus*
- Antifungal agent
- 38-Membered ring
- 19 Stereocenters

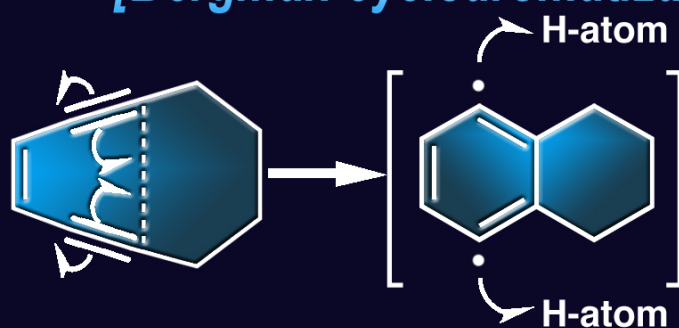
Amphotericin B



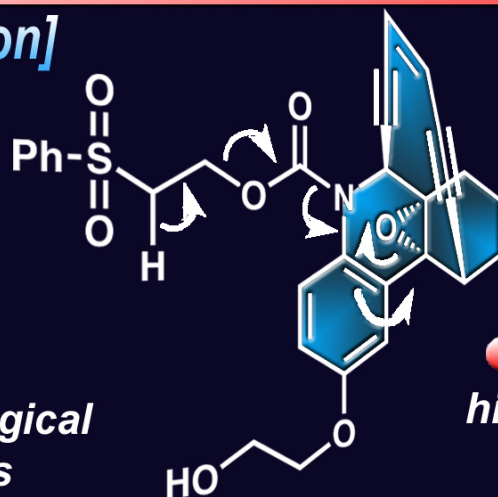
TOTAL SYNTHESIS OF CALICHEAMICIN γ_1' [1992]



[Bergman cycloaromatization]



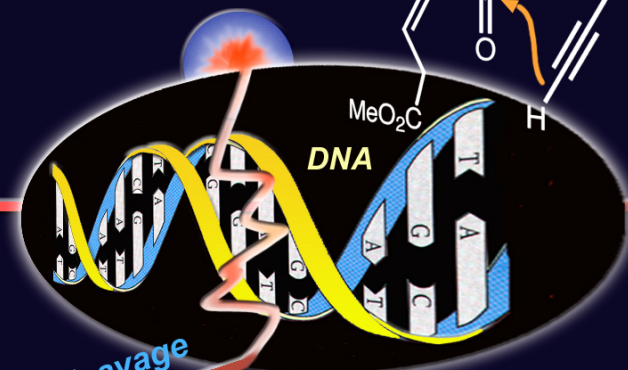
● **Elucidation of chemical and biological properties of cyclic enediynes**



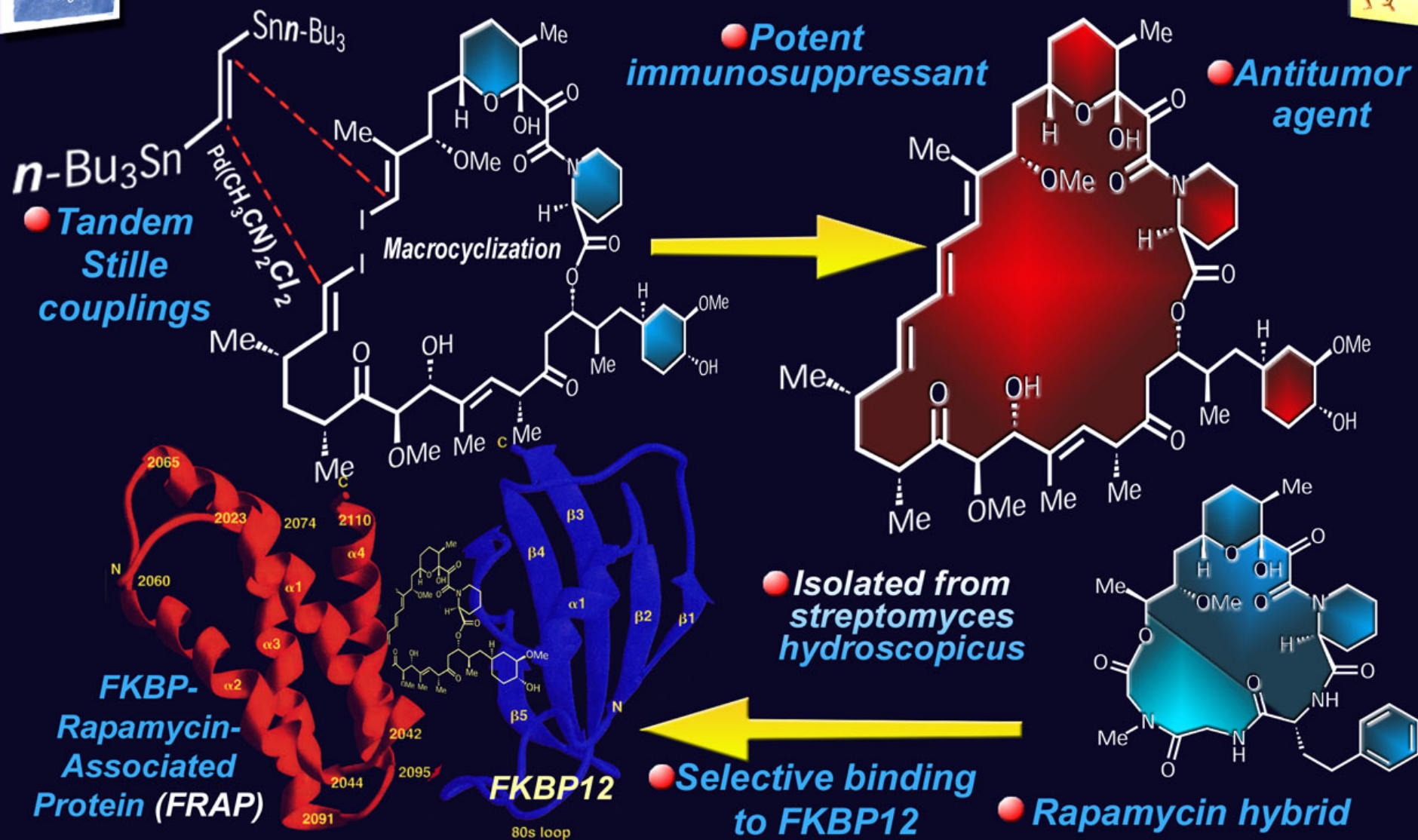
DNA cleavage
Cell death

Double strand cuts

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



TOTAL SYNTHESIS OF RAPAMYCIN [1993]

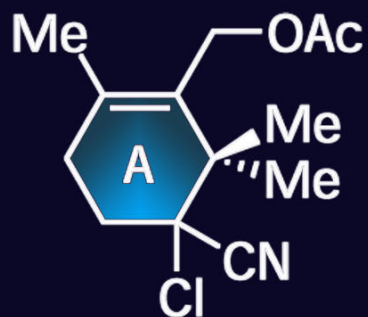




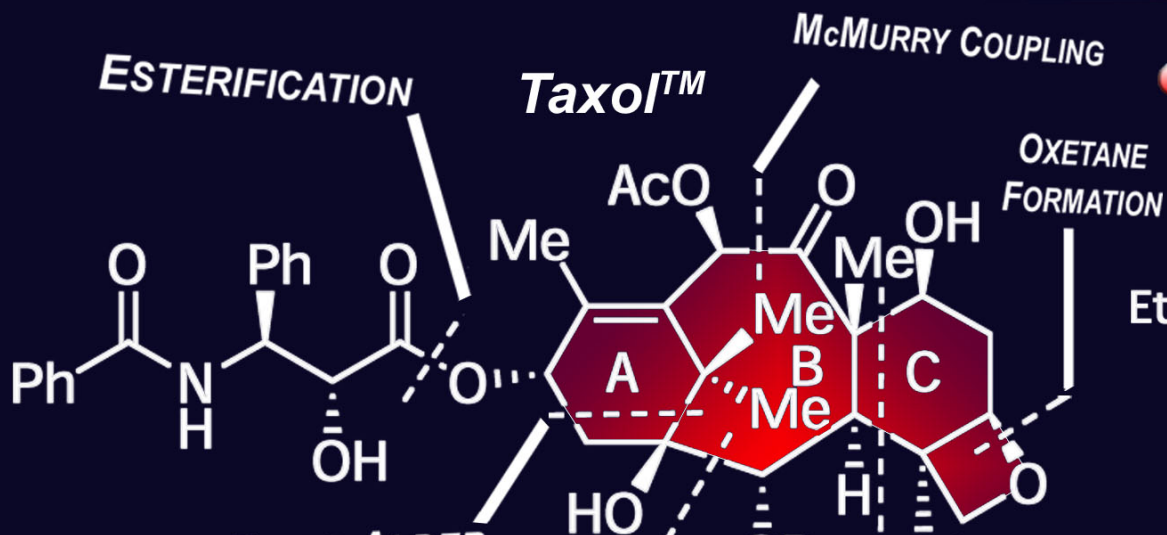
TOTAL SYNTHESIS OF TAXOL™ [1994]



● Water soluble pro-drugs



ESTERIFICATION



Taxol™

McMURRY COUPLING

● Fluorescent probes

OXETANE FORMATION



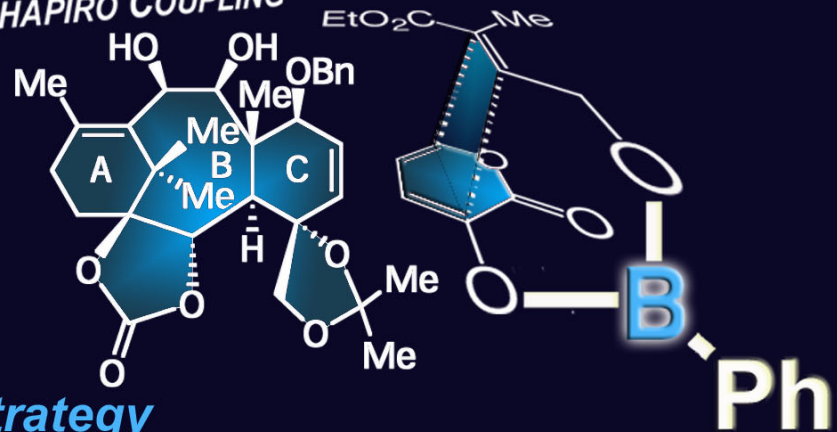
DIELS-ALDER

● Isolated from *Taxus brevifolia*

Convergent strategy

SHAPIRO COUPLING

DIELS-ALDER





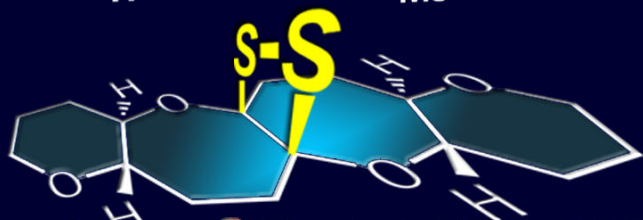
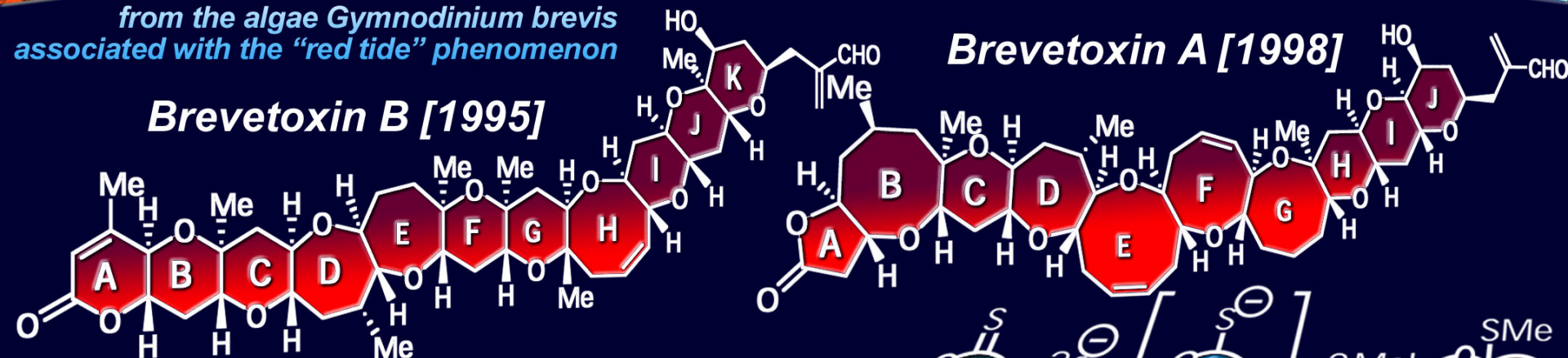
TOTAL SYNTHESIS OF BREVETOXINS B AND A [1982-1998]



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

Brevetoxin B [1995]

Brevetoxin A [1998]

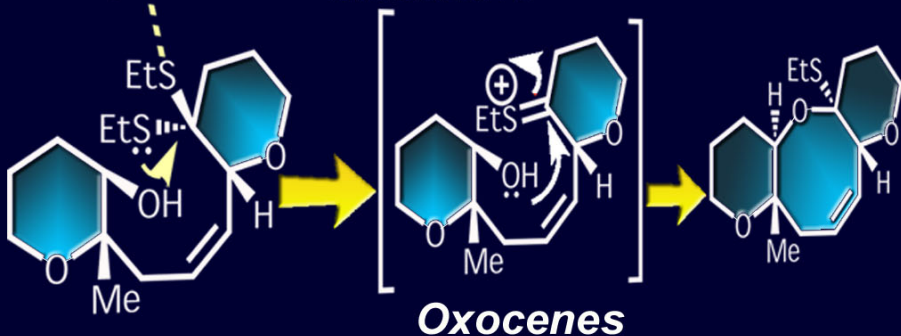


● First stable dithietane

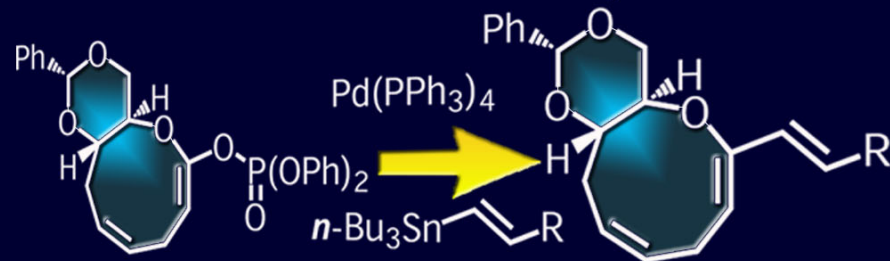
● New synthetic technologies



● 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

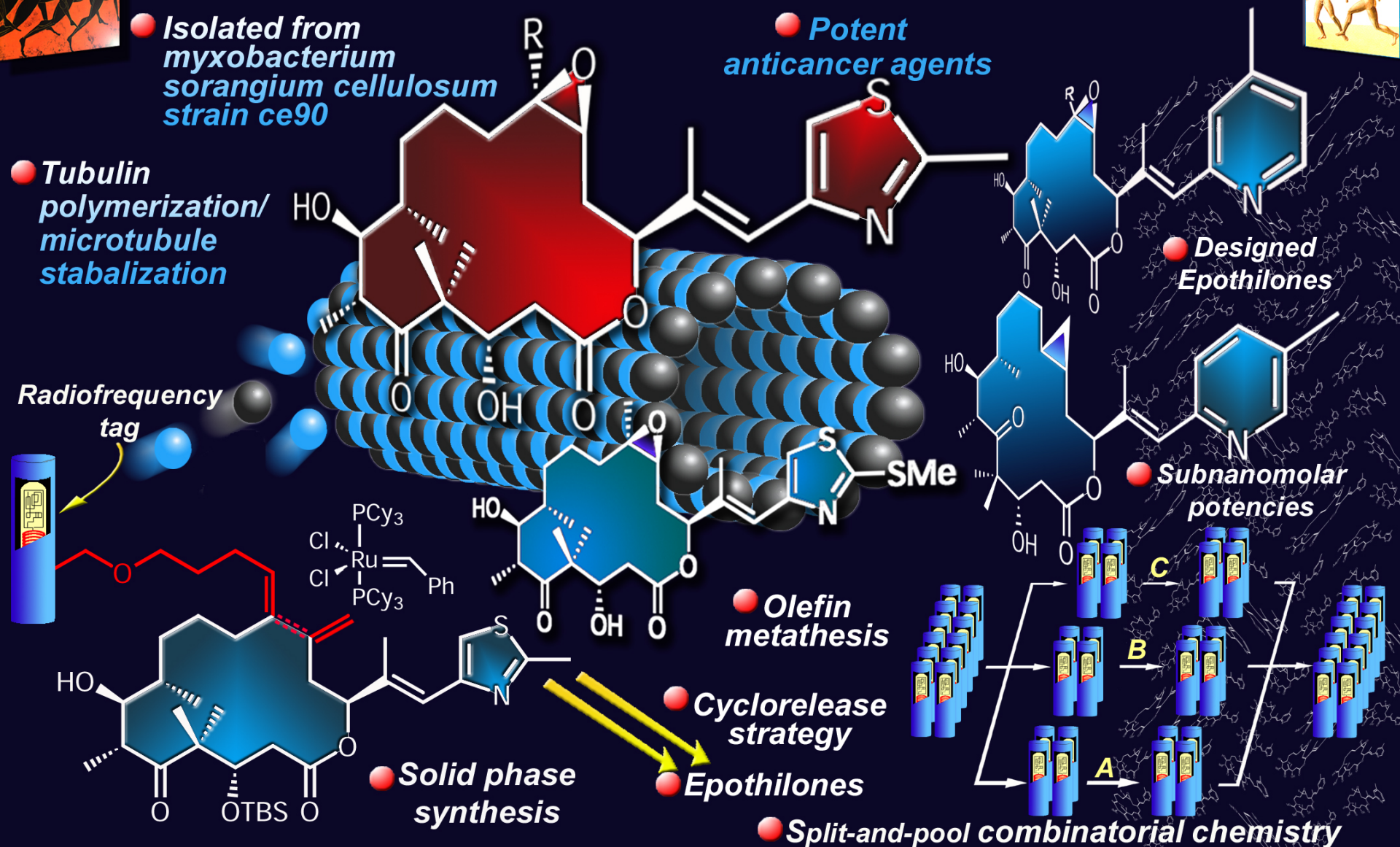
● Olefin metathesis

● Cyclorelease strategy

● Solid phase synthesis

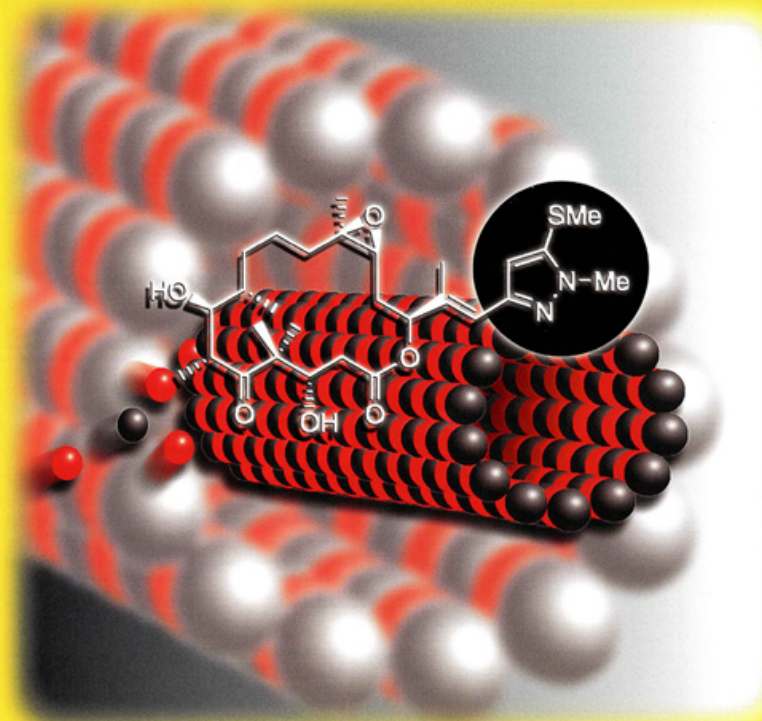
● Epothilones

● Split-and-pool combinatorial chemistry



CHEM**MED**CHEM

CHEMISTRY ENABLING DRUG DISCOVERY



1/2006



Review: Current Developments in HIV Chemotherapy

Concept: The Hit-to-lead Process

Editorial: The Pipeline is Filled

 **WILEY-VCH**

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



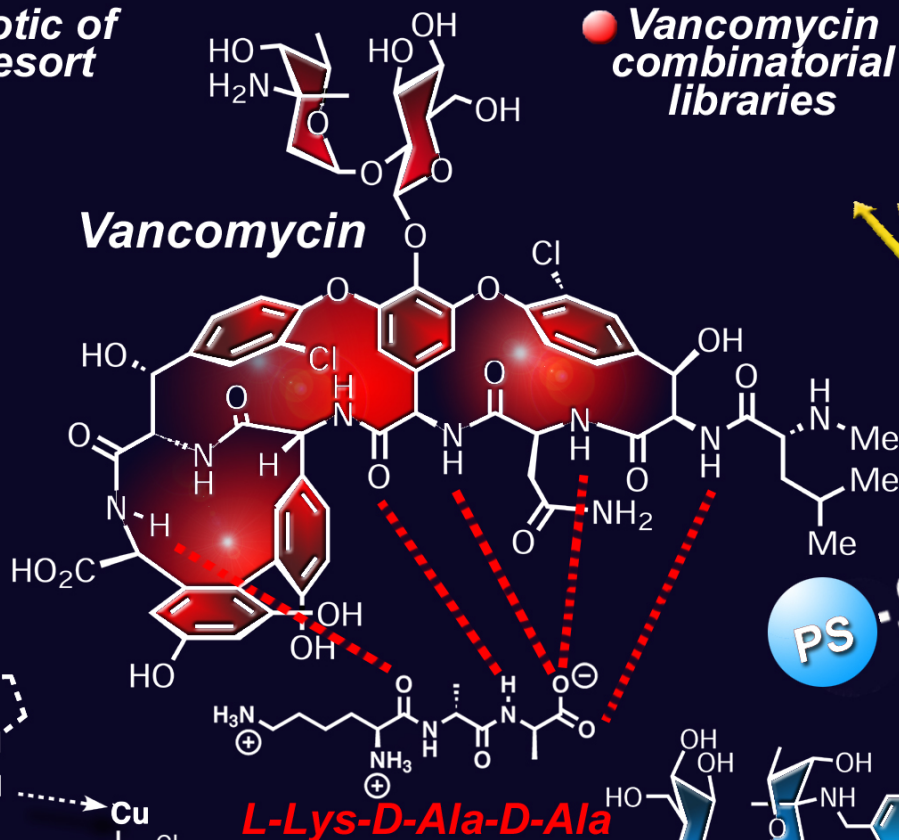
● **Antibiotic of last resort**

● **Vancomycin combinatorial libraries**

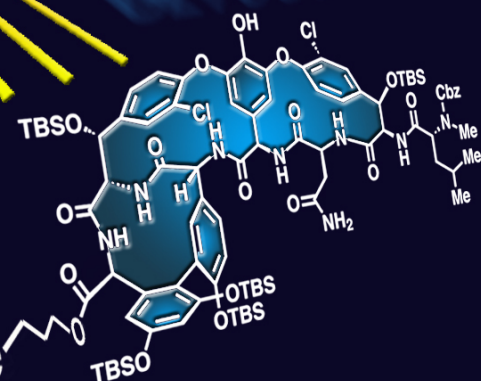
● **Isolated from the Actinomycete *amycolatopsis orientalis***

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

Vancomycin



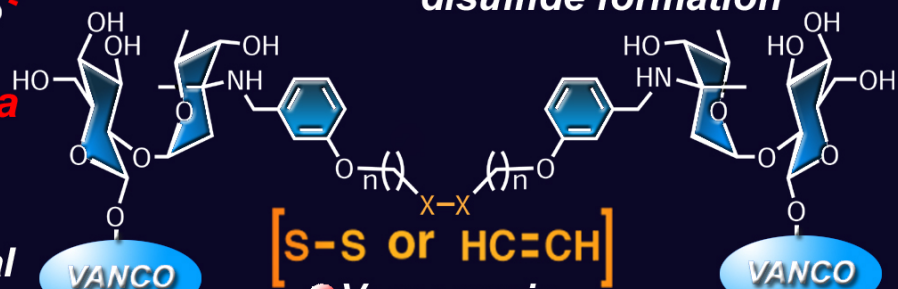
DEPROTECTIONS
CLEAVAGE
GLYCOSIDATIONS



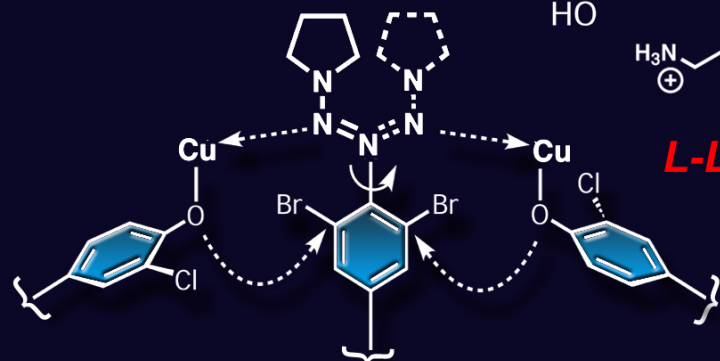
● **Olefin metathesis or disulfide formation**

L-Lys-D-Ala-D-Ala

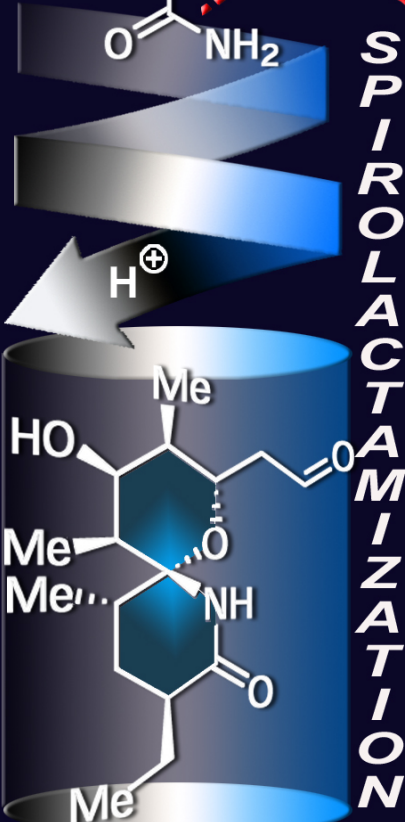
● **Target-accelerated combinatorial synthesis**



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



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

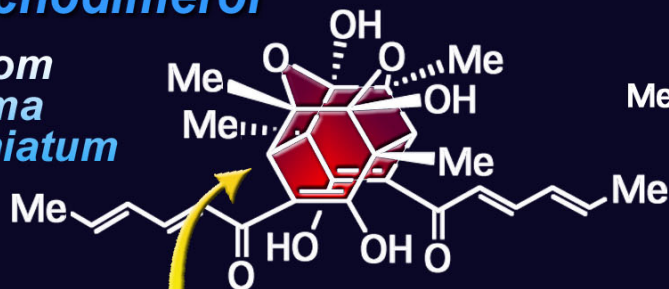


BIOMIMETIC TOTAL SYNTHESIS OF BISORBICILLINOIDS [1999]



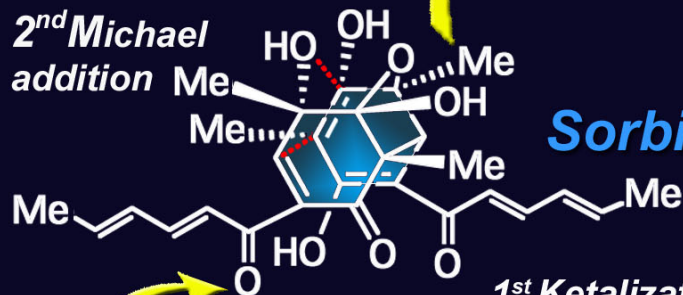
Trichodimerol

● Isolated from *Trichoderma longibrachiatum*



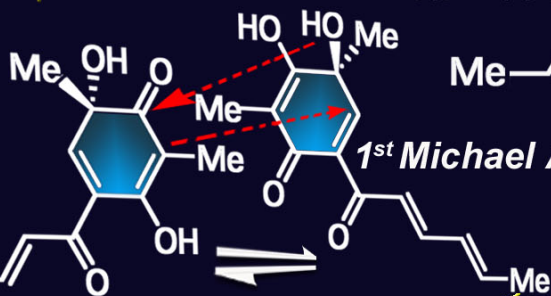
2nd Ketalization

2nd Michael addition



1st Ketalization

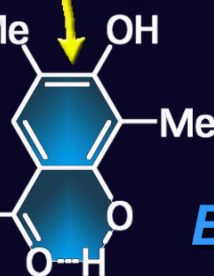
1st Michael Addition



Sorbicillin

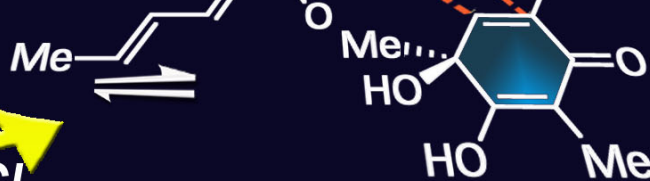
Bisorbibutenolide

Pb(OAc)₄



Bisorbicillinol

Diels-Alder



● Inhibition of tumor necrosis factor α (TNF- α) production (septic shock)

KHMDS; HCl

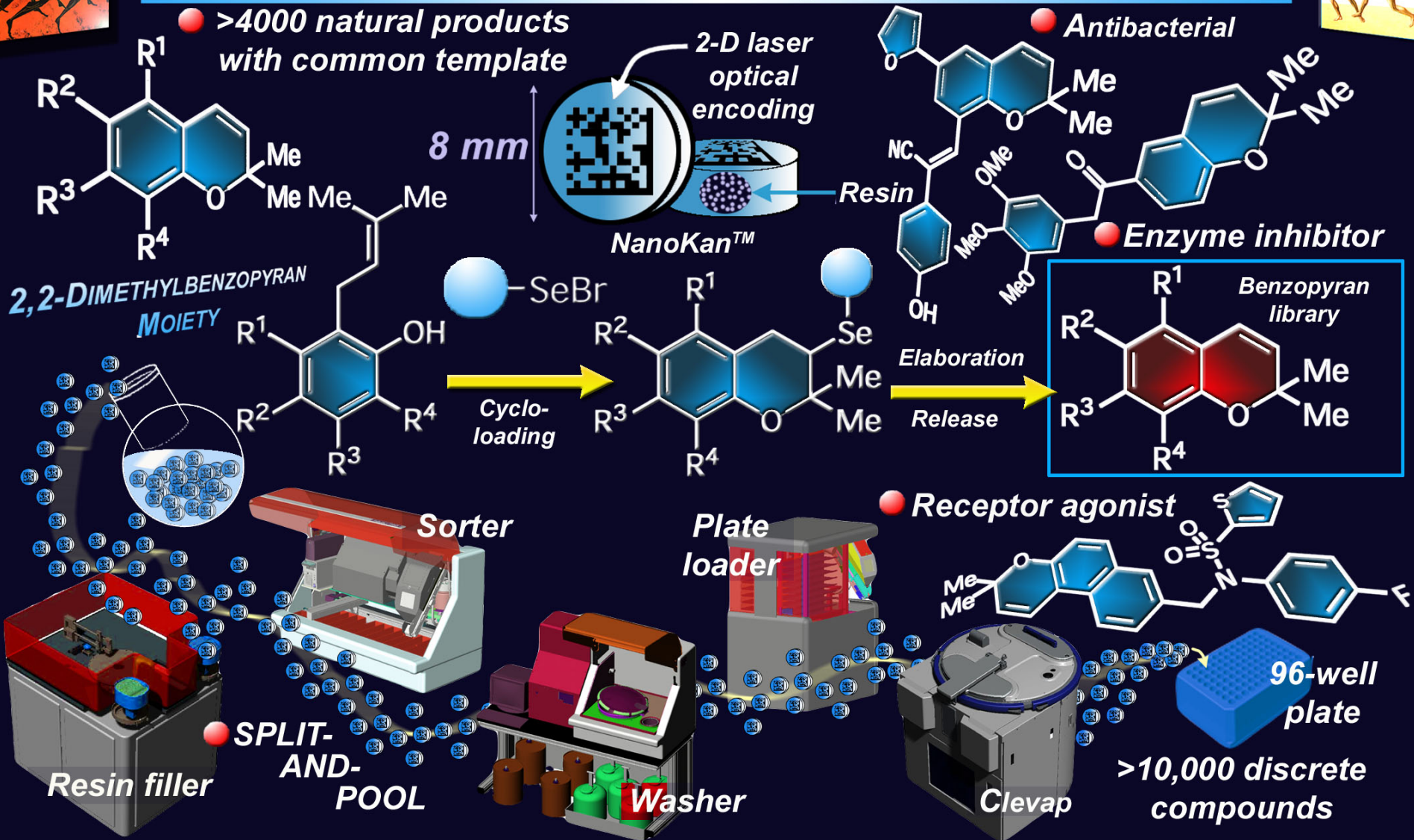
[O]

● DIMERIZATION OF QUINOLS

CsOH; NaHPO₄ KOH; HCl

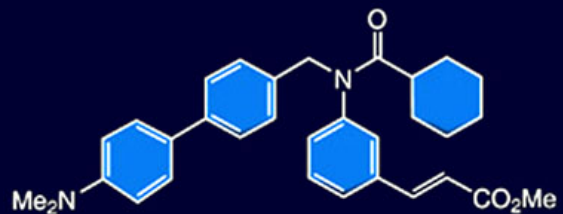
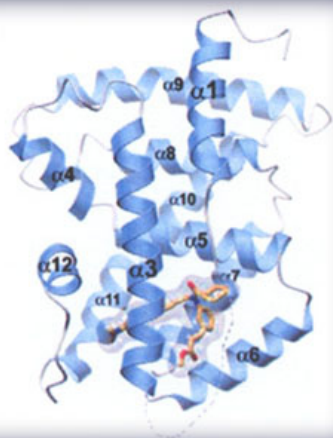
OPTICALLY ENCODED COMBINATORIAL CHEMISTRY: BENZOPYRANS[2000]

- >4000 natural products with common template





The Farnesoid X recetor (FXR) bound to fexaramine and CDCA

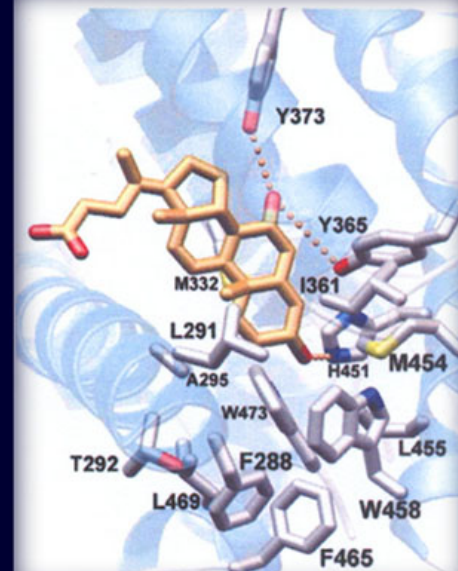
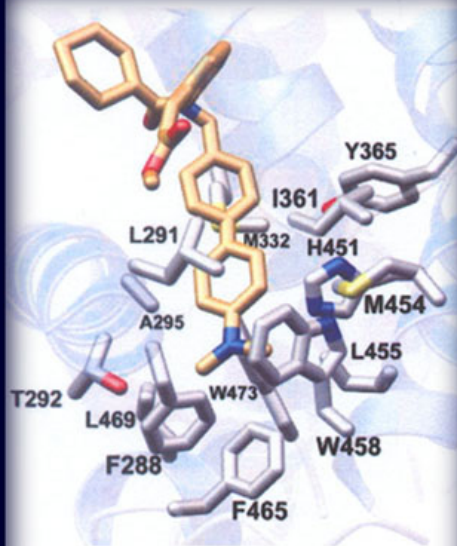
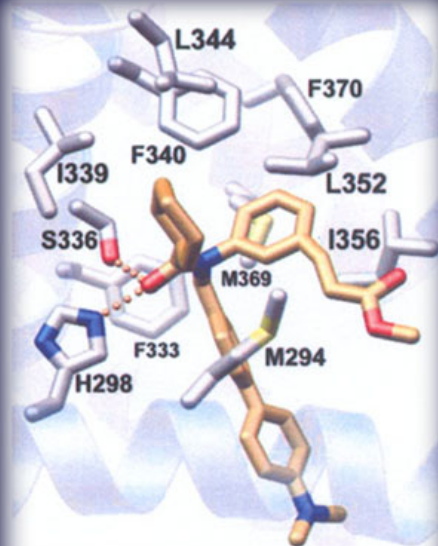


Fexaramine



CDCA

(low affinity endogenous agonist)





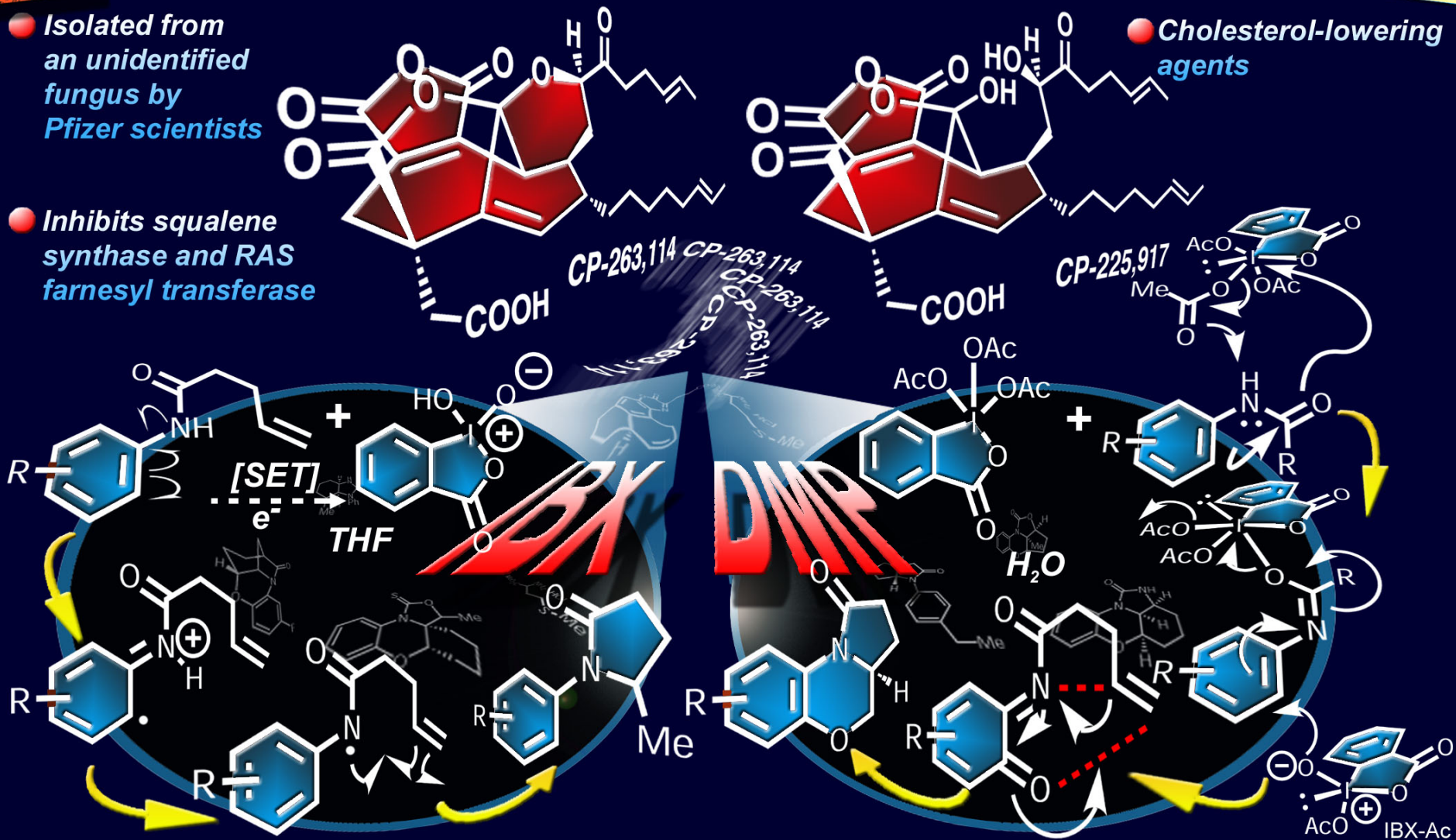
TOTAL SYNTHESIS OF THE CP MOLECULES [1999]



● Isolated from an unidentified fungus by Pfizer scientists

● Inhibits squalene synthase and RAS farnesyl transferase

● Cholesterol-lowering agents



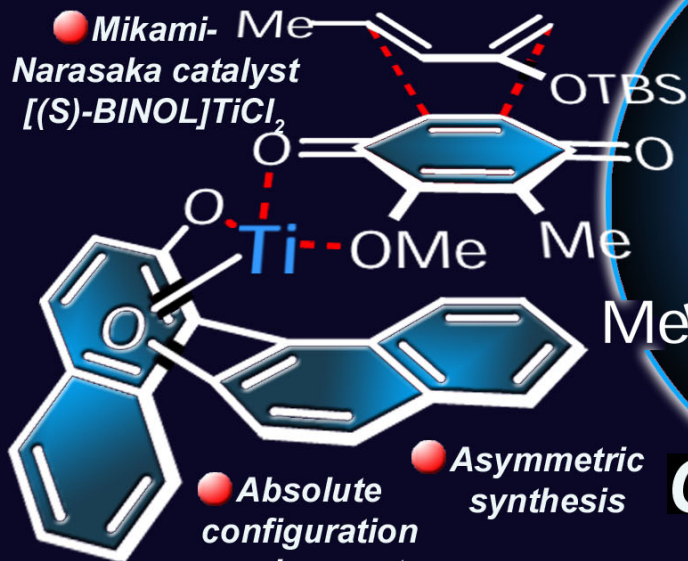


TOTAL SYNTHESIS OF COLOMBIASIN A [2001]

Possibly active against
Mycobacterium tuberculosis H37Rv

Isolated from coral
pseudopterogorgia elisabethae

Mikami-
Narasaka catalyst
[(S)-BINOL]TiCl₂

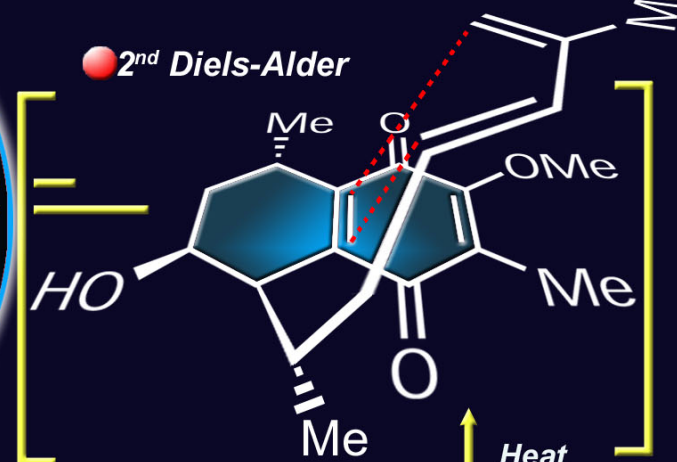


Absolute
configuration
assignment

Asymmetric
synthesis

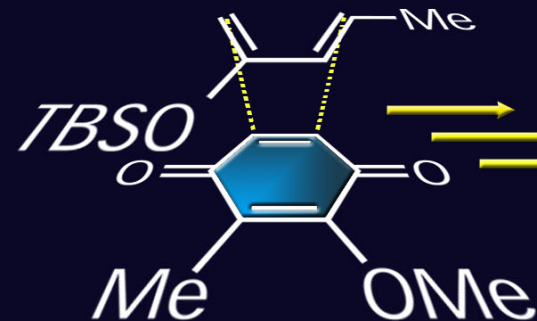
Colombiasin A

2nd Diels-Alder

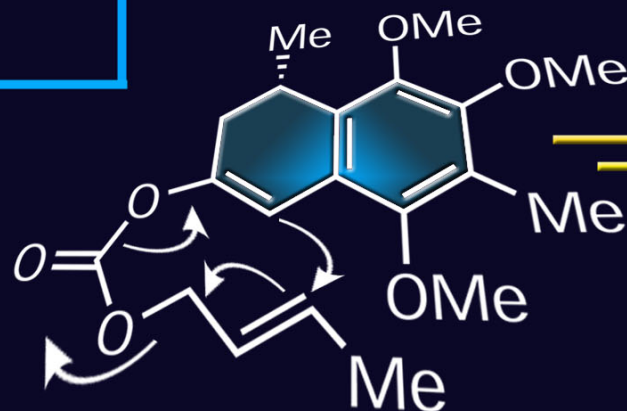


Heat
[dark]

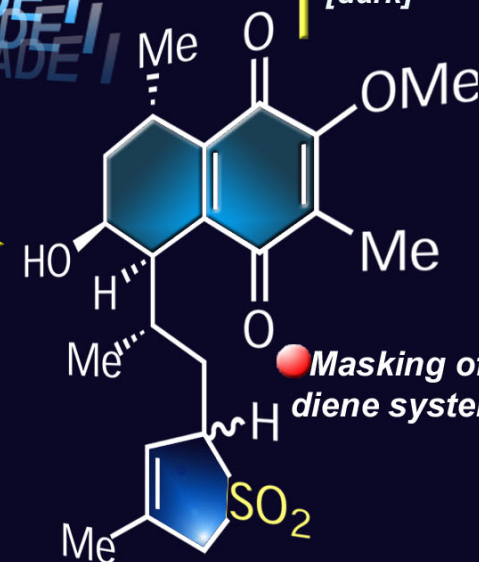
CASCADE I
CASCADE I
CASCADE I



1st Diels-Alder

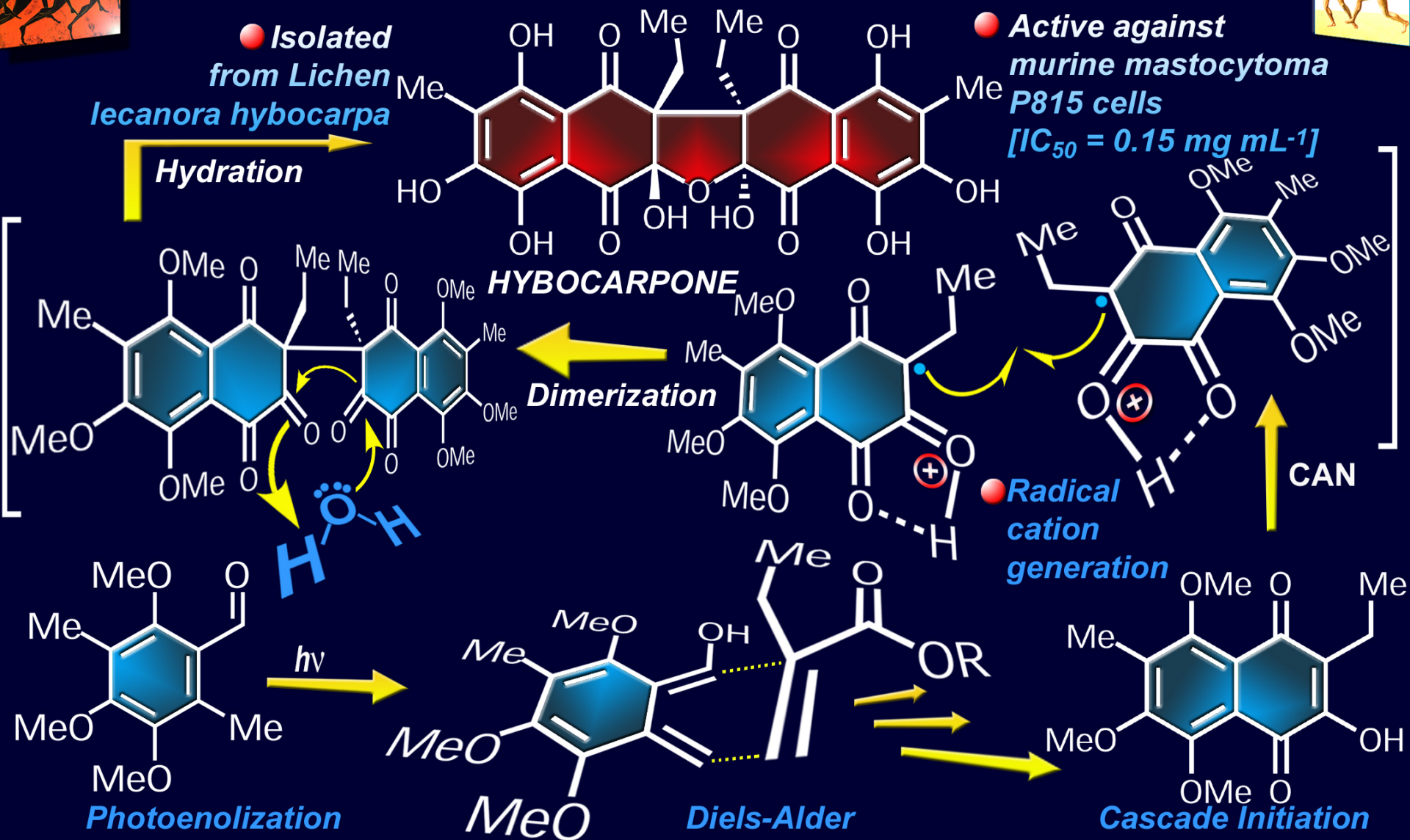


Palladium-catalyzed
rearrangement



Masking of
diene system

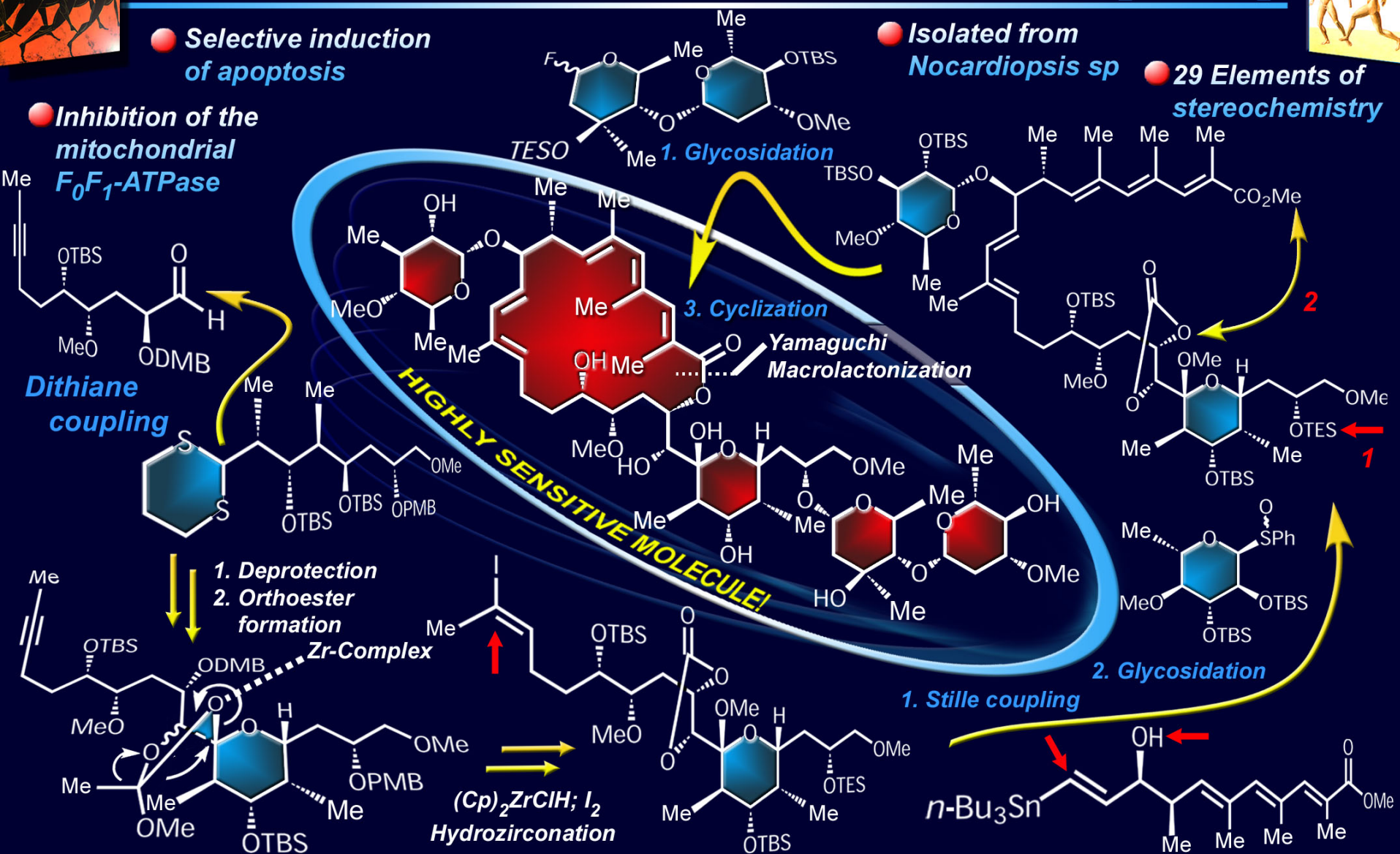
● **Active against murine mastocytoma P815 cells**
[IC₅₀ = 0.15 mg mL⁻¹]





**● Inhibition of the
mitochondrial
 F_0F_1 -ATPase**

● 29 Elements of stereochemistry





TOTAL SYNTHESIS OF COLEOPHOMONES B AND C [2002]



● From fungi *Stachybothys cylindrospora* RF-5900

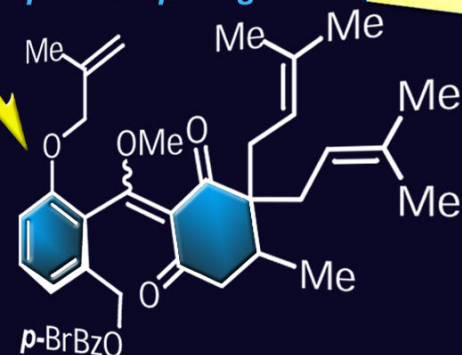
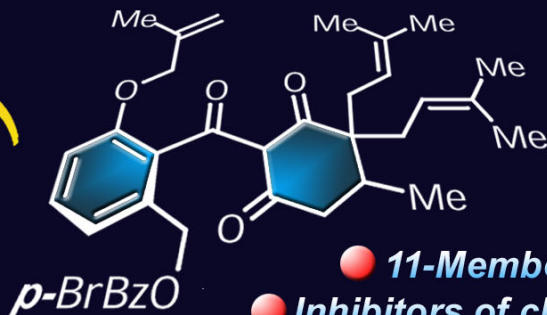
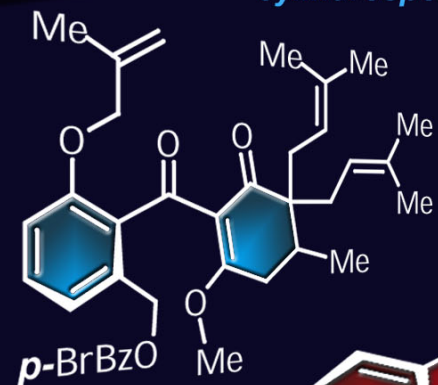
● From *Coleophoma* sp fungi

CH_2N_2

CH_2N_2

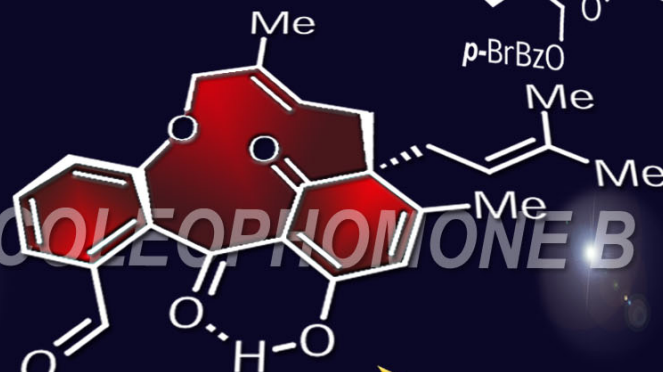
● 11-Membered rings

● Inhibitors of chymase



CATALYST
Stereoselective
ring closing
metathesis

Stereoselective
ring closing
metathesis
CATALYST



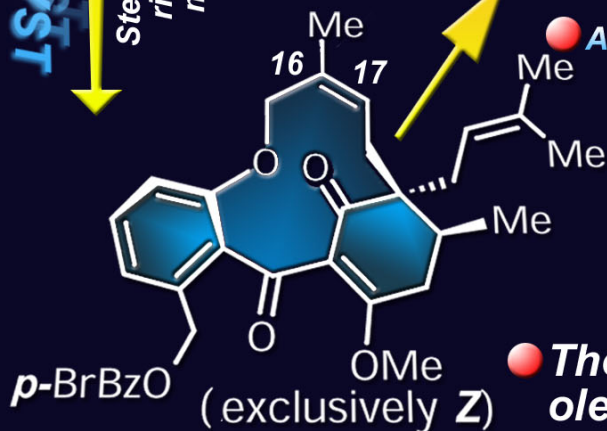
● Antibiotics

● Antifungal



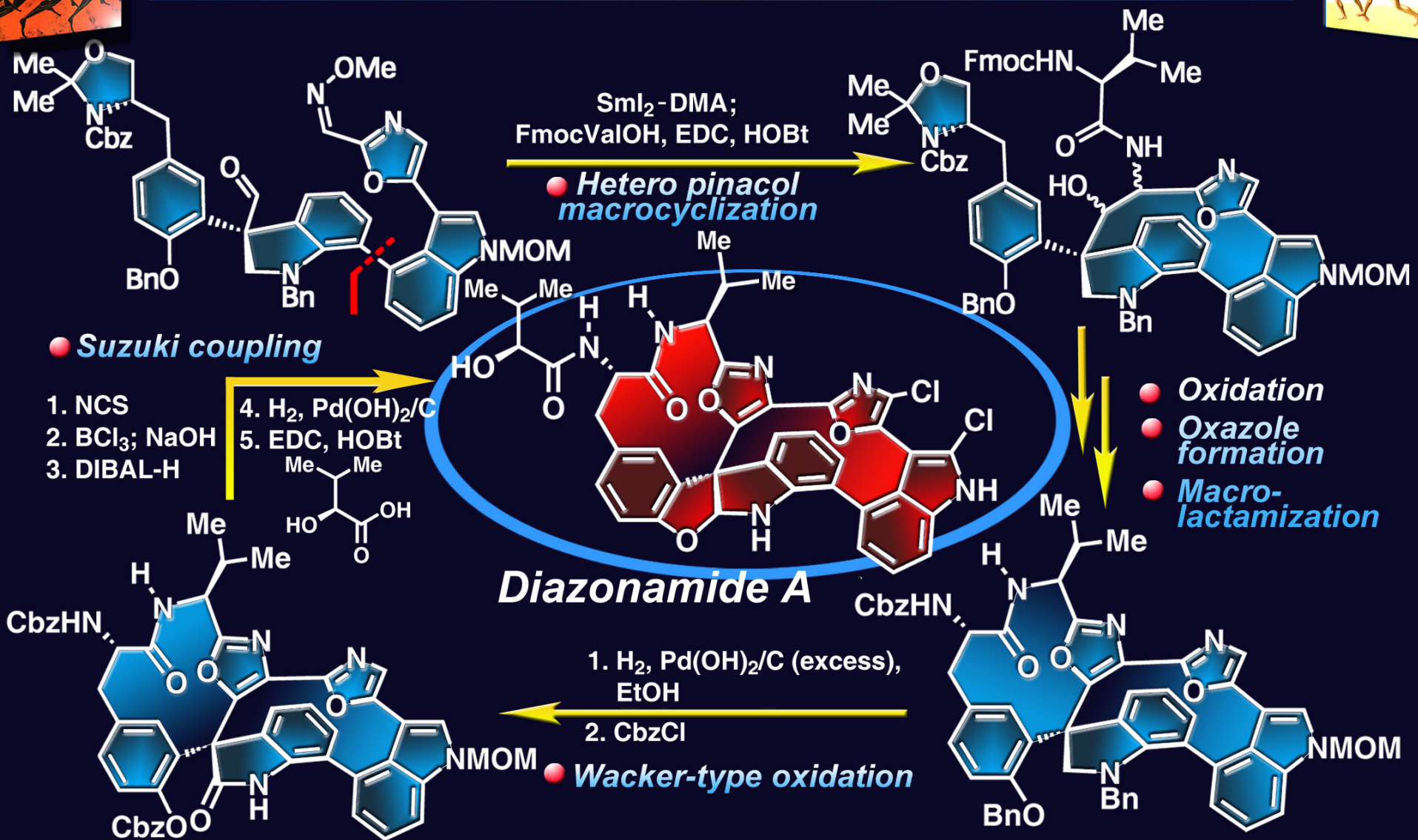
● The magic of the
olefin metathesis reaction

CATALYST
CATALYST





THE SmI_2 ROUTE TO DIAZONAMIDE A [2003]



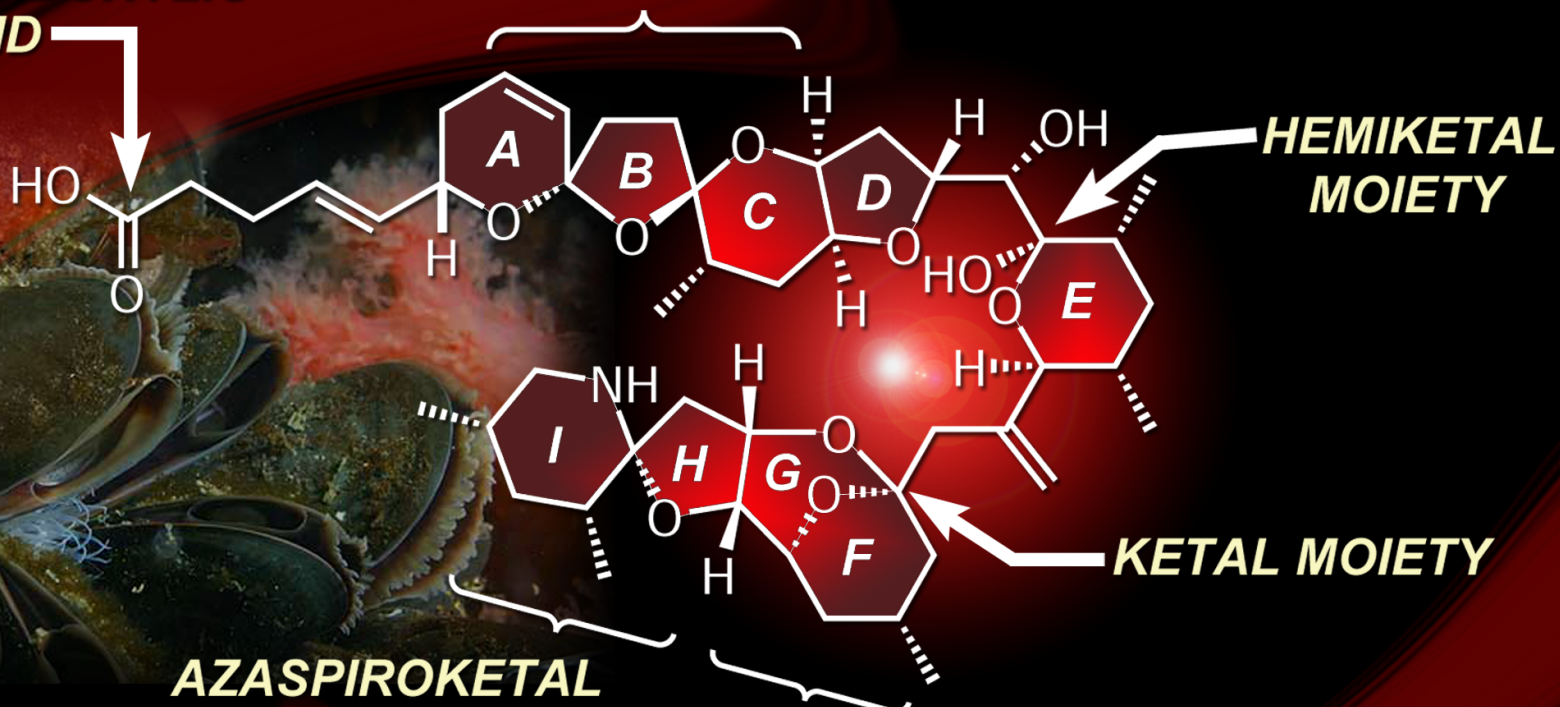


AZASPIRACID-1: PROPOSED STRUCTURE (1998)



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.

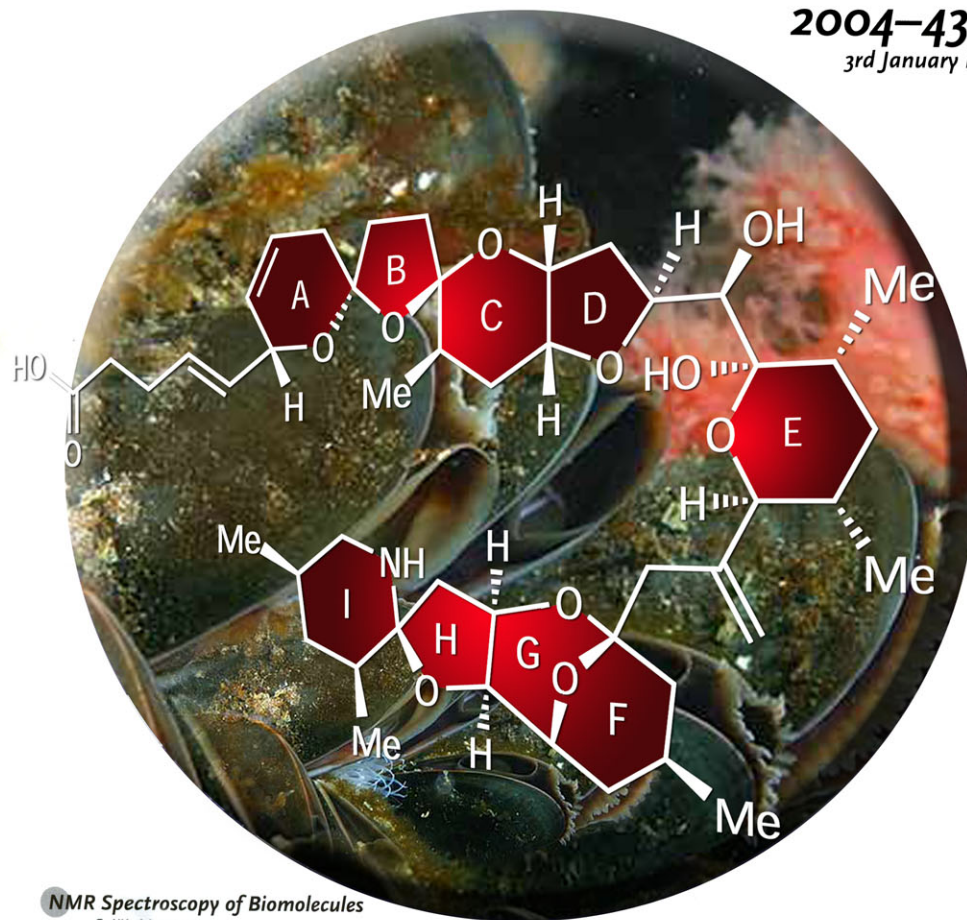
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Angewandte Chemie

International Edition

D 3461

2004-43/3
3rd January Issue



NMR Spectroscopy of Biomolecules
S. W. Homans

Drug-Delivery Systems
R. Haag

Enantioselective Addition
D. J. Ramón, M. Yus

www.angewandte.org

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 **WILEY-V**

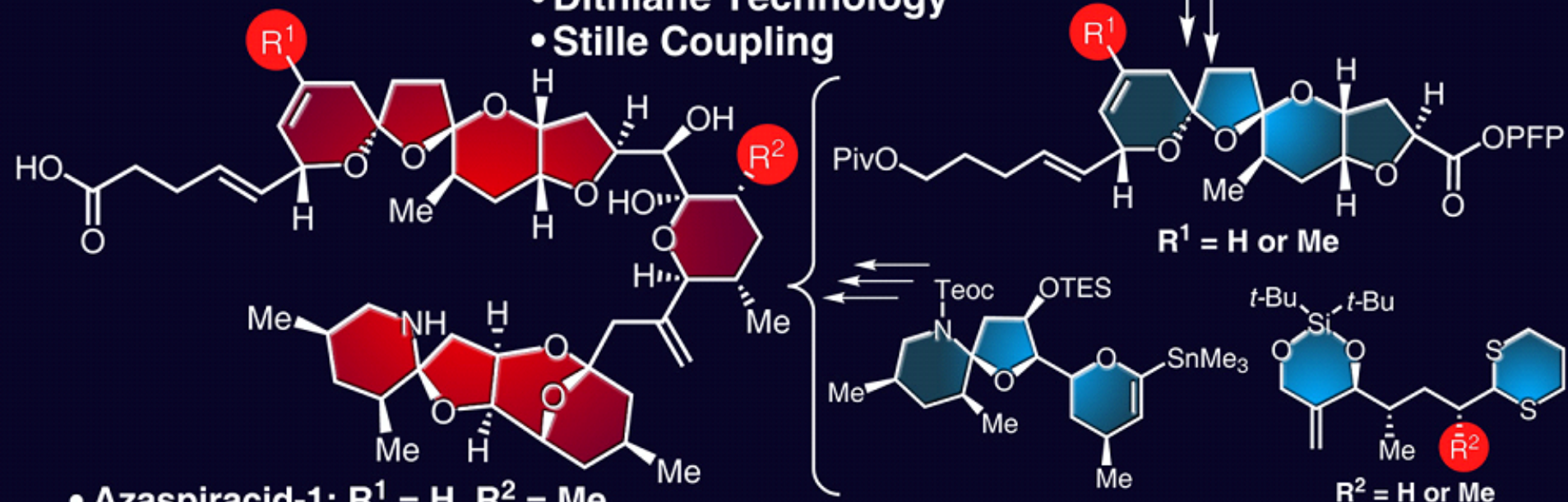
TOTAL SYNTHESIS OF AZASPIRACIDS -1, -2, AND -3 [2006]



$R^1 = \text{H or Me}$

- Cascade Polycyclization
- Olefin Metathesis
- Dithiane Technology
- Stille Coupling

$R^1 = \text{H or Me}$



- Azaspiracid-1: $R^1 = \text{H}, R^2 = \text{Me}$
- Azaspiracid-2: $R^1 = R^2 = \text{Me}$
- Azaspiracid-3: $R^1 = R^2 = \text{H}$

- Isolated from the mussels *Mytilus edulis*
- Potent neurotoxins

THIOSTREPTON: X-RAY STRUCTURE

FROM
STREPTOMYCES
AZUREUS

DEHYDROPIPERIDINE

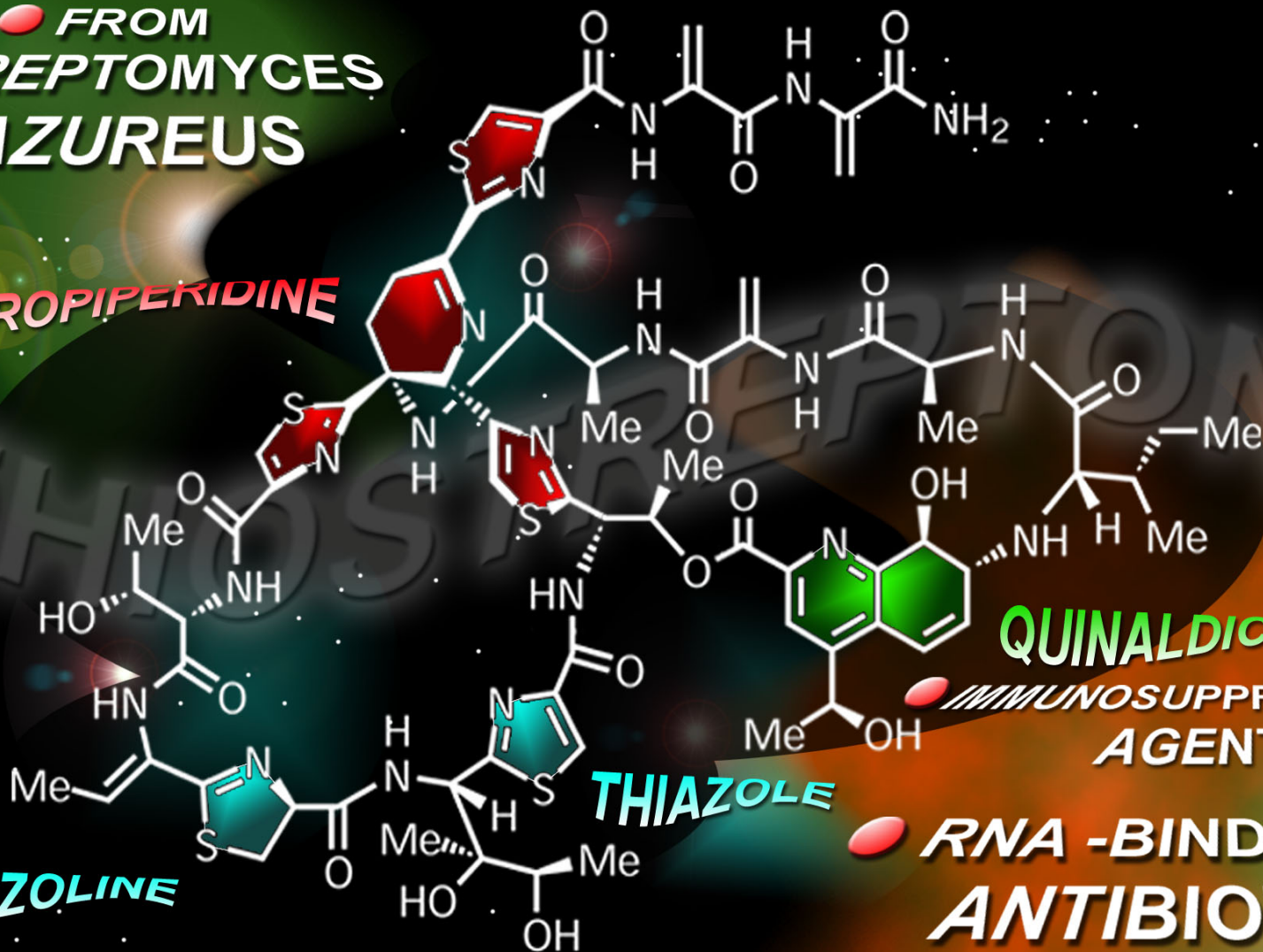
THIAZOLINE

THIAZOLE

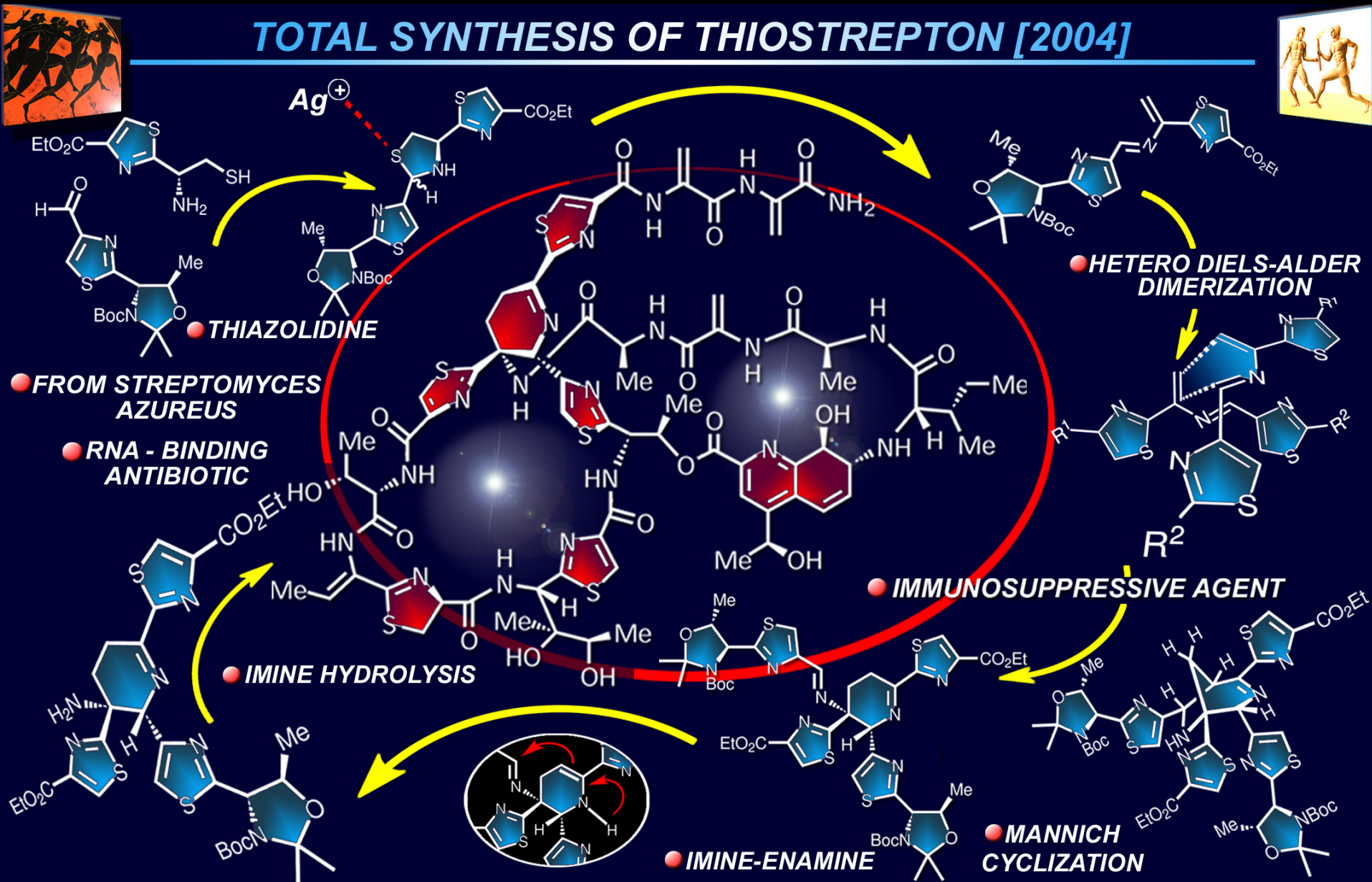
QUINALDIC ACID

IMMUNOSUPPRESSIVE
AGENT

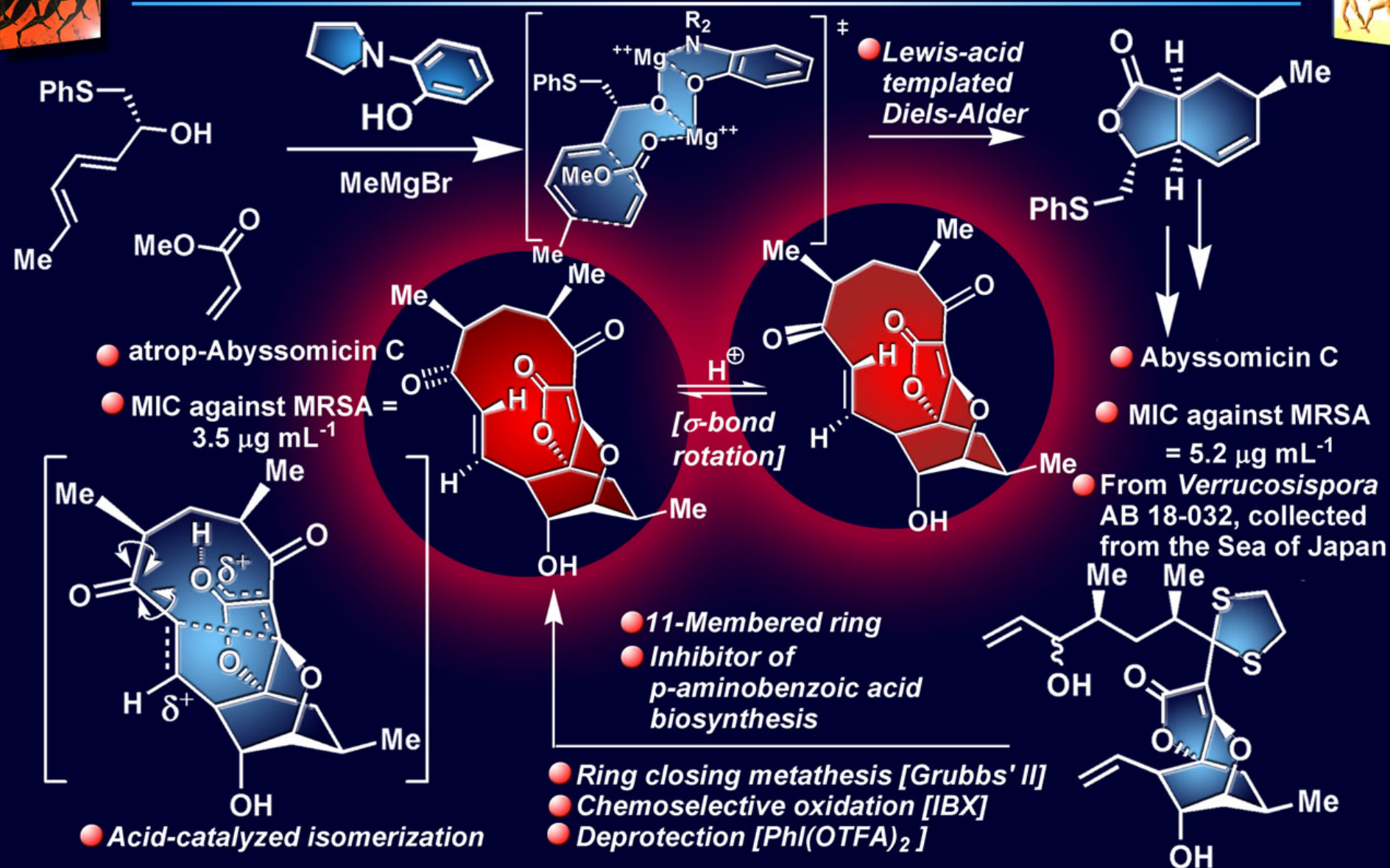
RNA-BINDING
ANTIBIOTIC



TOTAL SYNTHESIS OF THIOSTREPTON [2004]

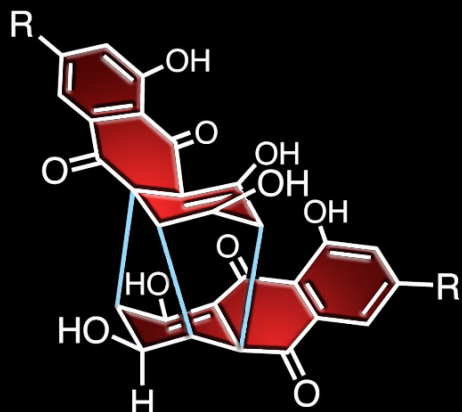


TOTAL SYNTHESIS OF ABYSSOMICIN C AND ATROP-ABYSSOMICIN C



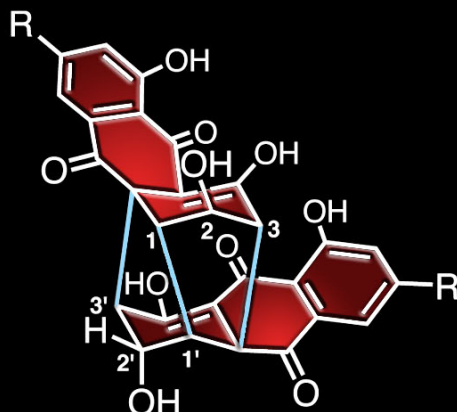


SELECTED NATURALLY OCCURRING BISANTHRAQUINONES -DNA INTERACTING CYTOTOXIC AGENTS



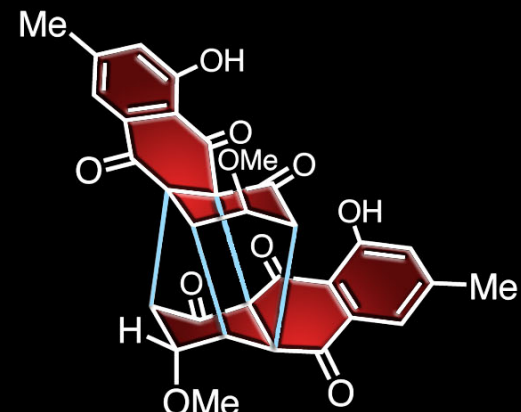
Ia: R = OMe: (+)-cytoskyrin A

Ib: R = Me: (+)-graciliformin

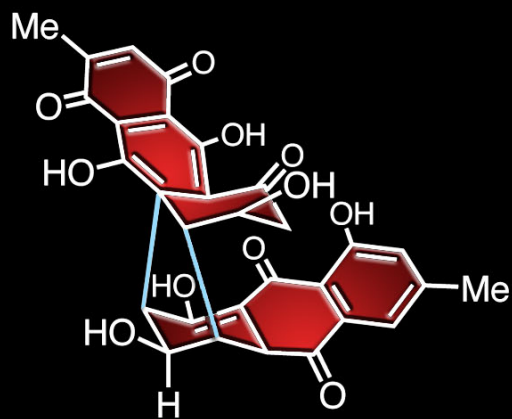


IIa: R = OMe: (+)-2,2'-*epi*-cytoskyrin A

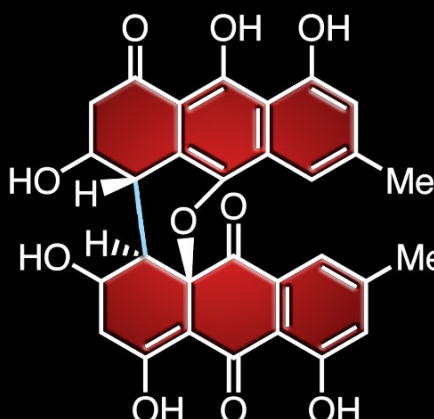
IIb: R = Me: (+)-rugulosin (also anti-HIV)



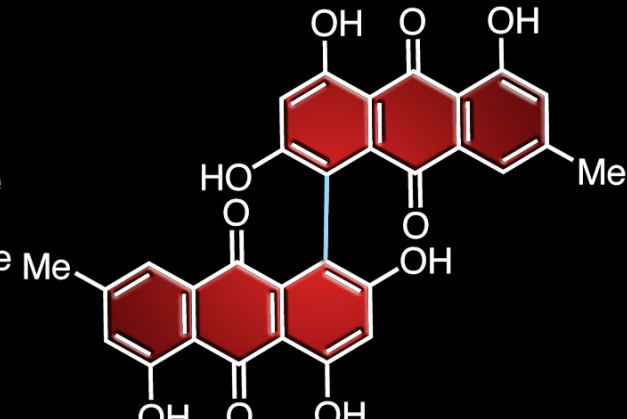
III: rugulin (also antibiotic)



IV: deoxyrubroskyrin



IV: flavoskyrin



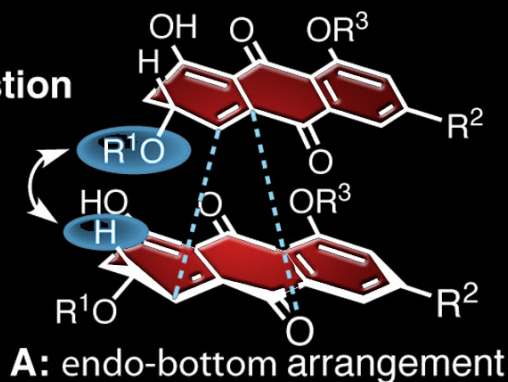
V: skyrin



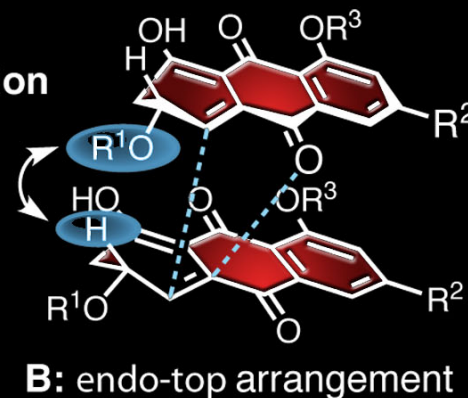
POSSIBLE ORIENTATIONS OF ANTHRAQUINONE UNITS IN THE DIMERIZATION STEP [FOR CYTOSKYRIN AND RUGULOSIN]



● Steric congestion



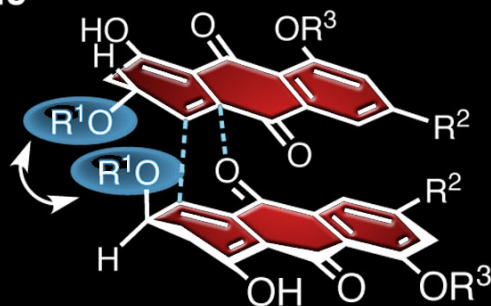
● Steric congestion



A: endo-bottom arrangement

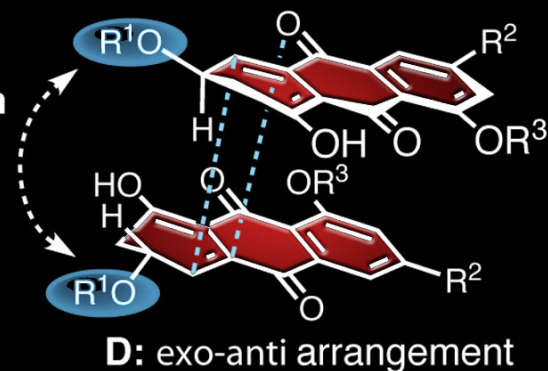
B: endo-top arrangement

● Severe steric congestion



C: exo-syn arrangement

● Favored orientation



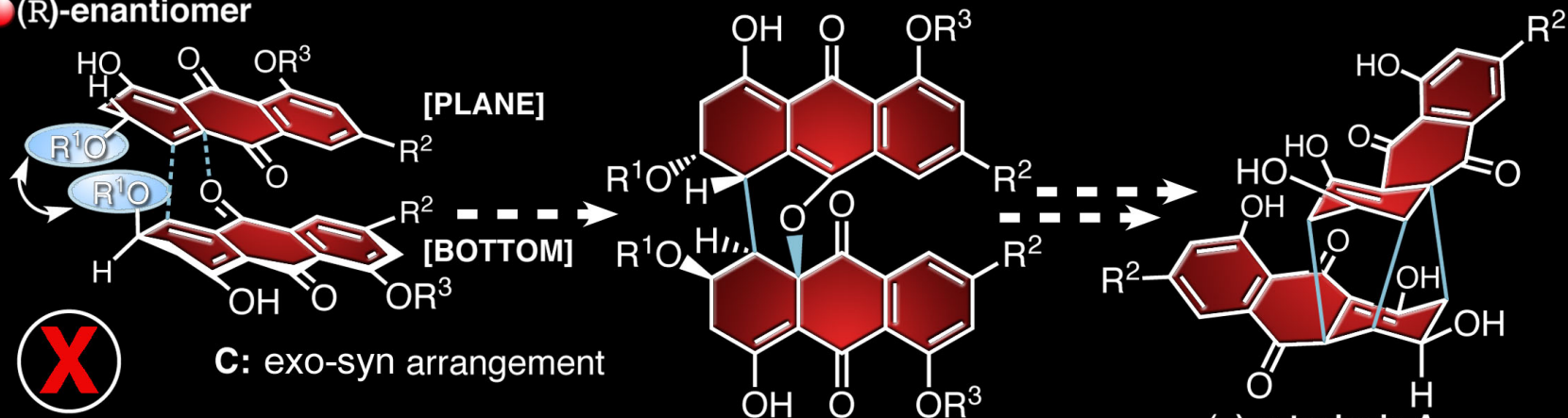
D: exo-anti arrangement



THE INTRIGUING STEREOCHEMICAL ASPECTS OF THE DIMERIZATION STEP

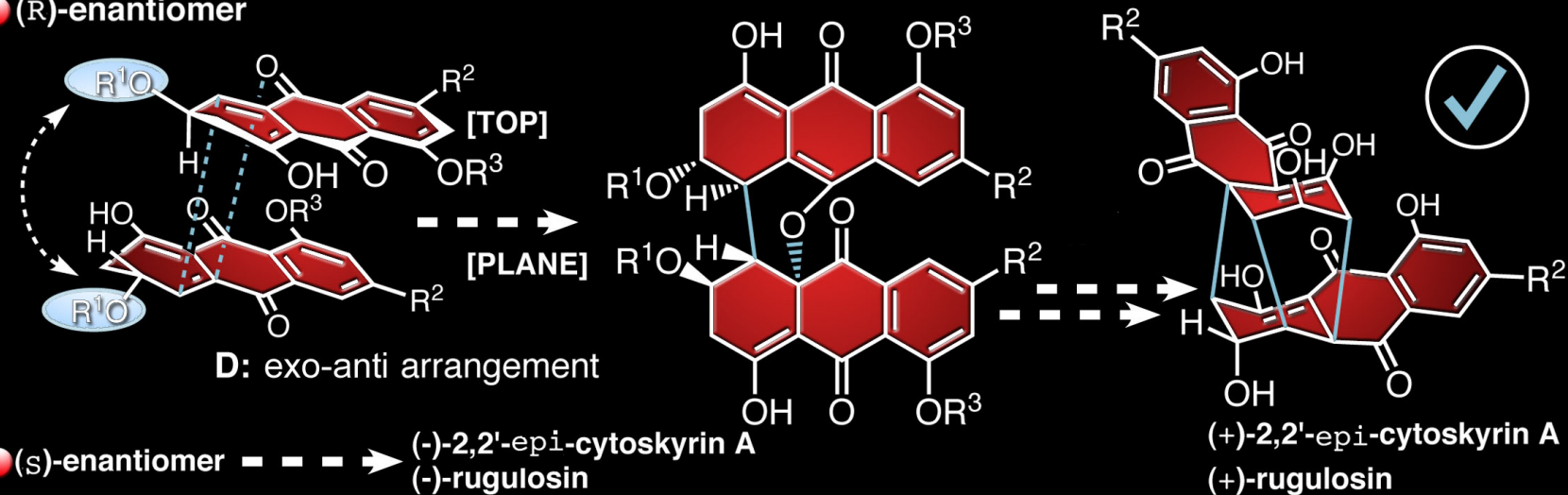


● (R)-enantiomer



● (S)-enantiomer → (+)-cytoskyrin A
(+)-graciliformin

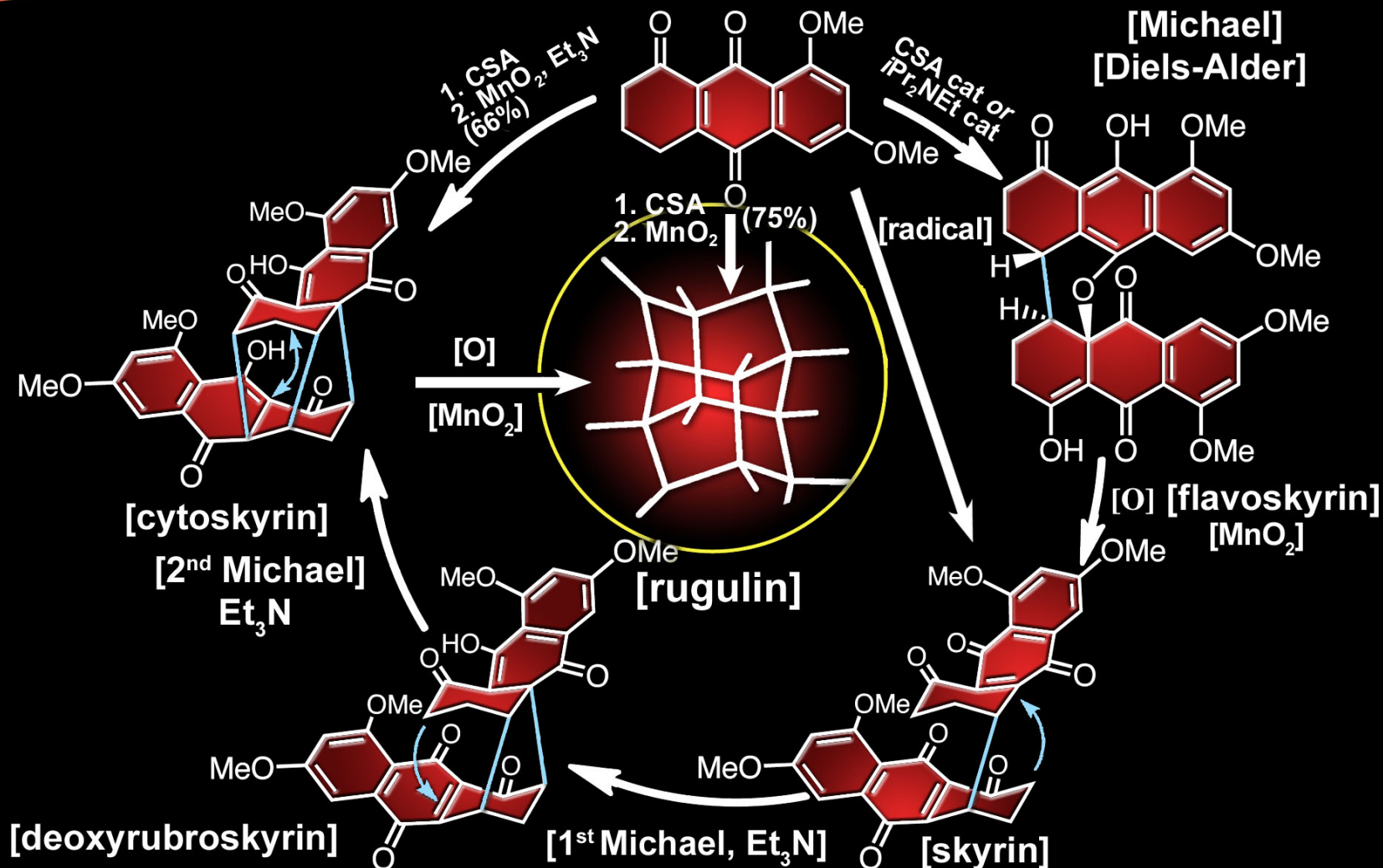
● (R)-enantiomer



● (S)-enantiomer → (-)-2,2'-*epi*-cytoskyrin A
(-)-rugulosin

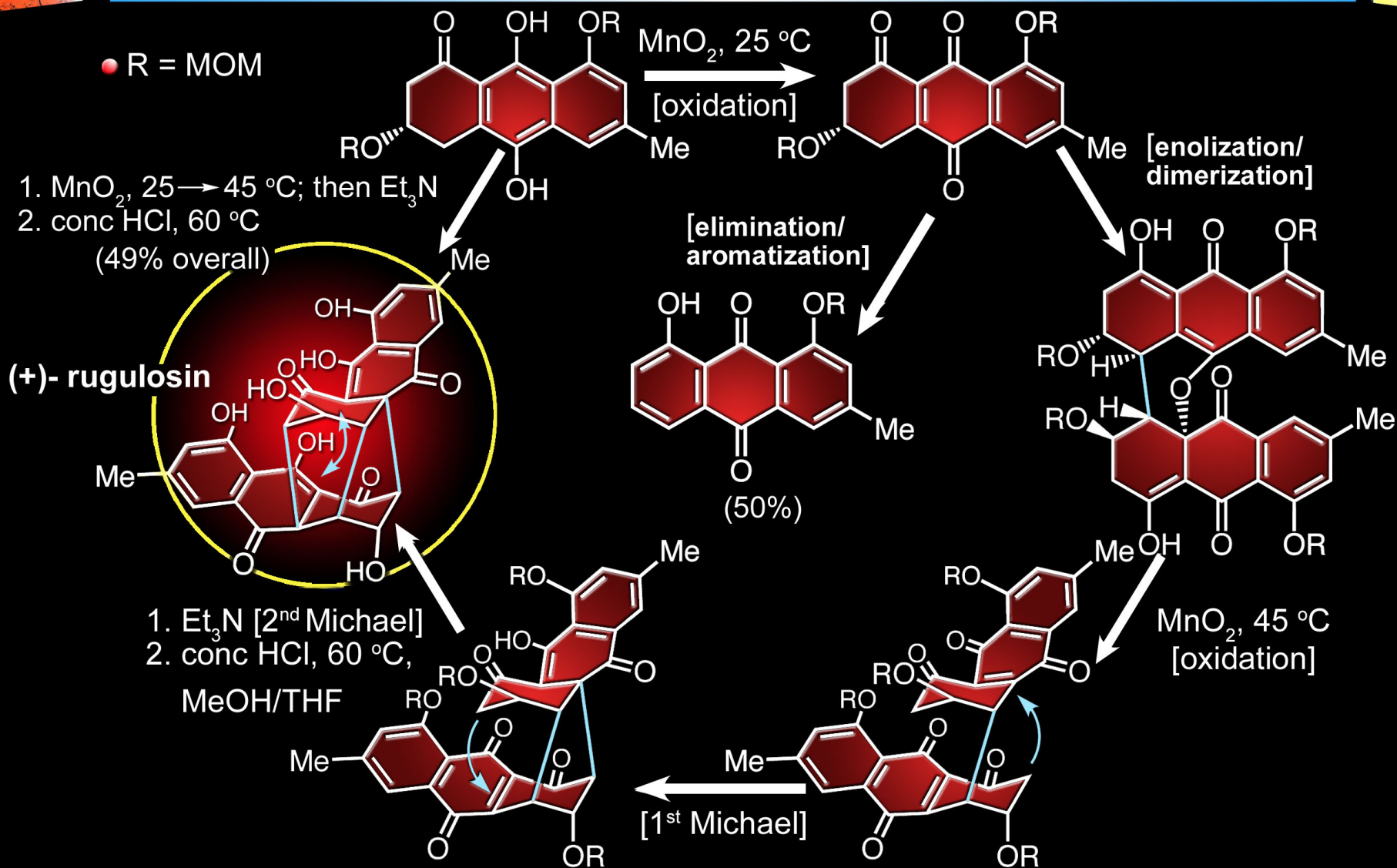


THE CYTOSKYRIN CASCADE: MODEL SYSTEMS



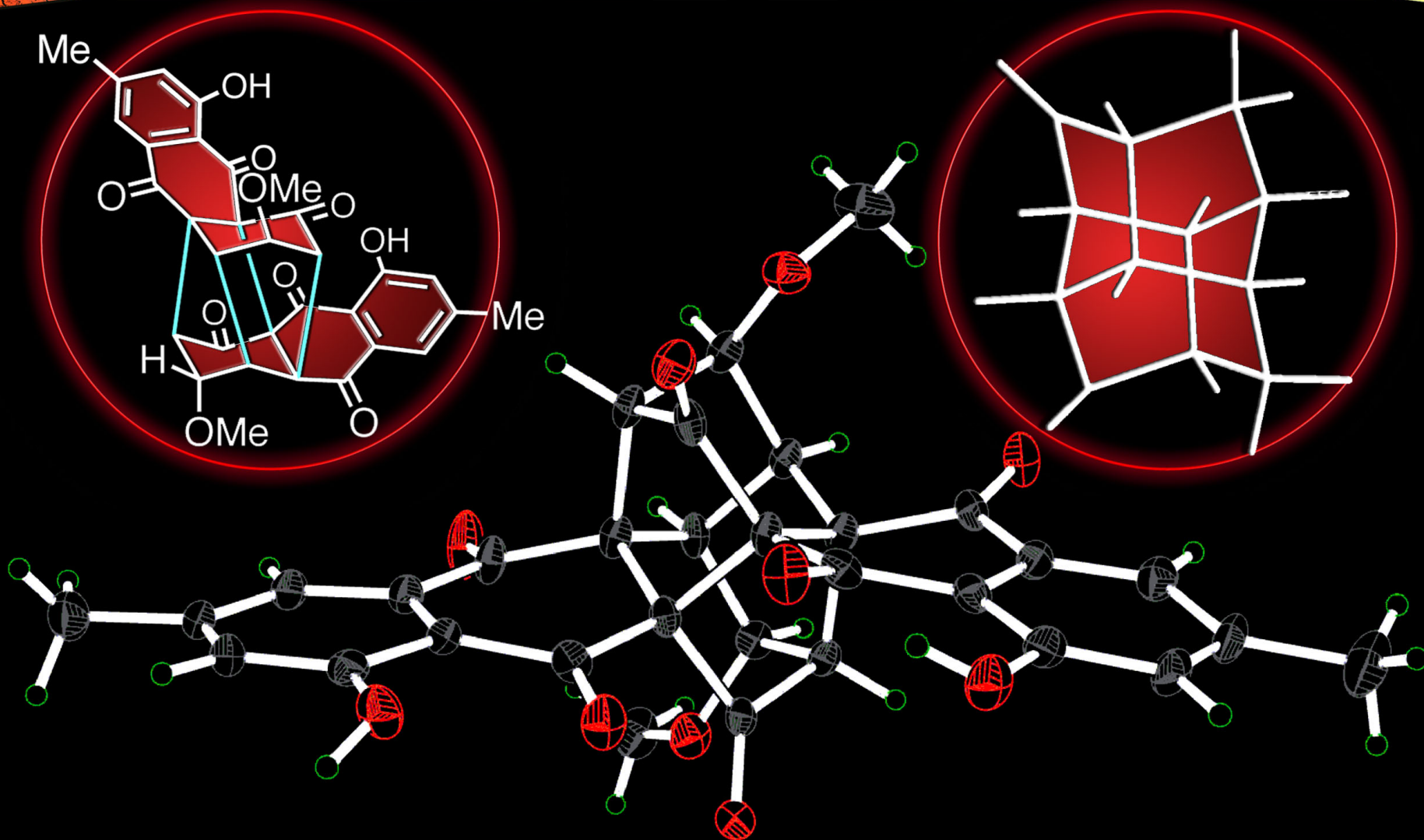
TOTAL SYNTHESIS OF (+)- RUGULOSIN

• R = MOM



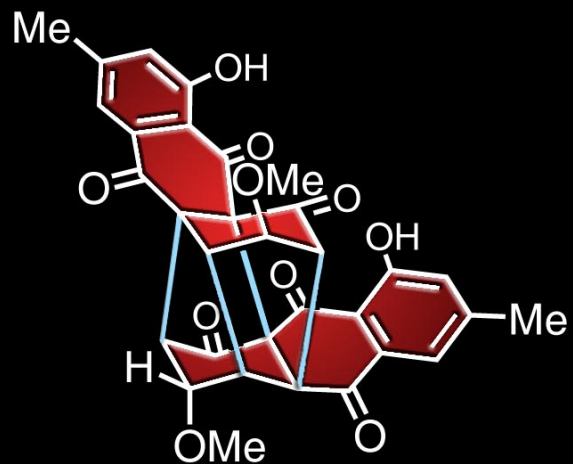


X-RAY STRUCTURE OF THE ALLEGED STRUCTURE OF RUGULIN

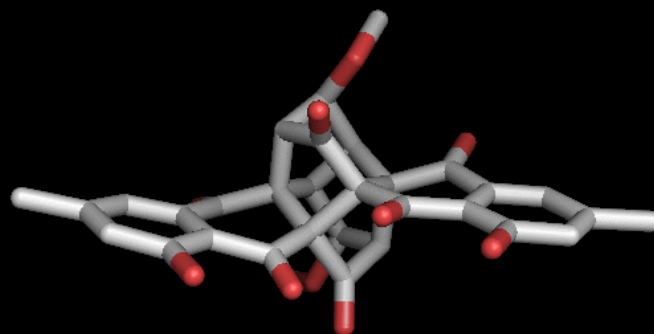




X-RAY STRUCTURE OF THE ALLEGED STRUCTURE OF RUGULIN



● ORTEP drawing of X-Ray structure

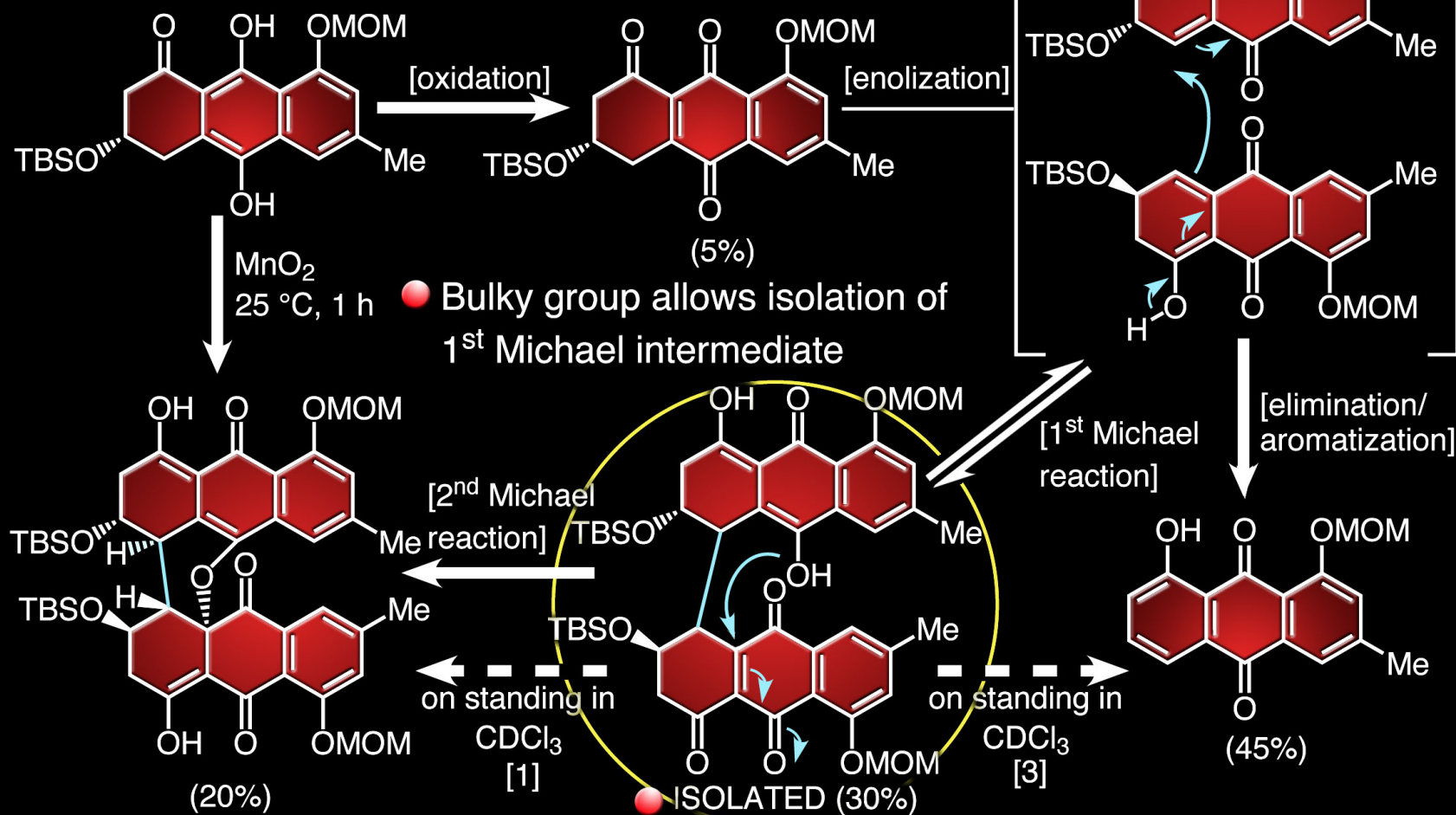




MECHANISTIC ASPECTS OF THE DIMERIZATION STEP-ISOLATION OF 1ST MICHAEL INTERMEDIATE



- Isolation of key intermediates
- Reaction proceeds via two consecutive Michael reactions rather than a Diels-Alder reaction



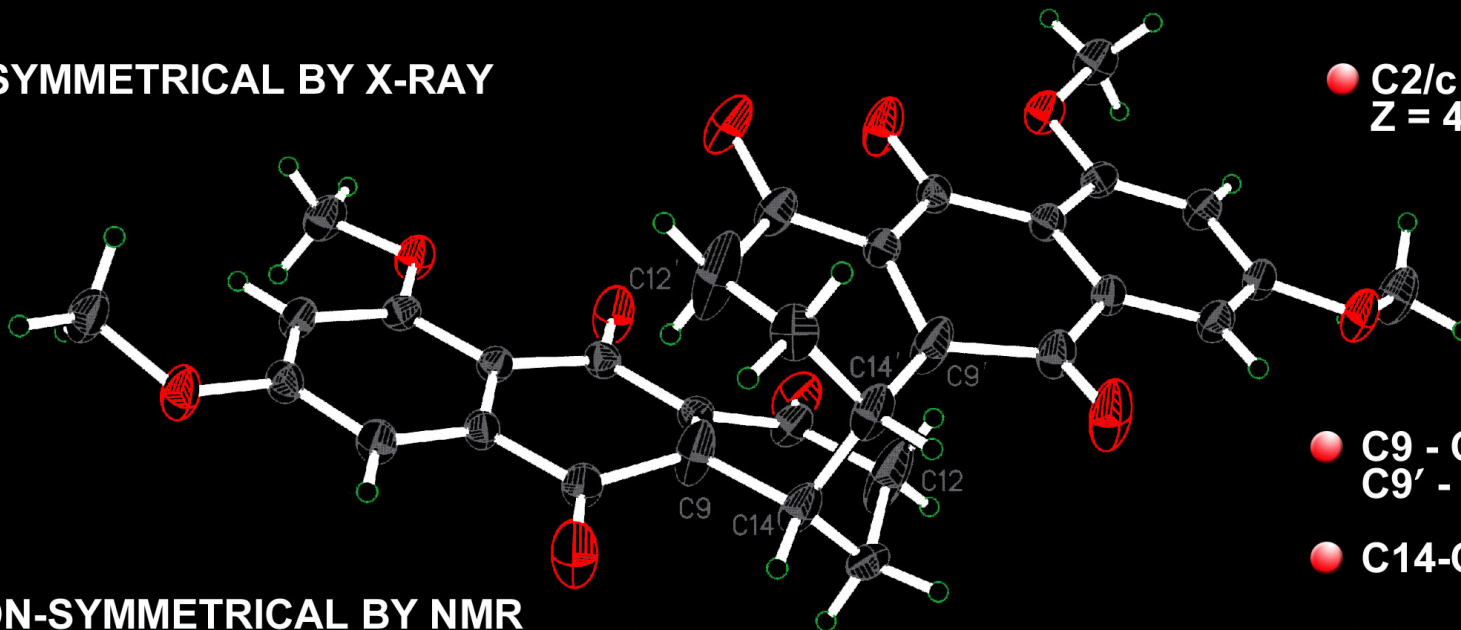


DEOXYRUBROSKYRIN MODEL: A CASE OF BOND MIGRATION? [MISLEADING X-RAY STRUCTURE]



● SYMMETRICAL BY X-RAY

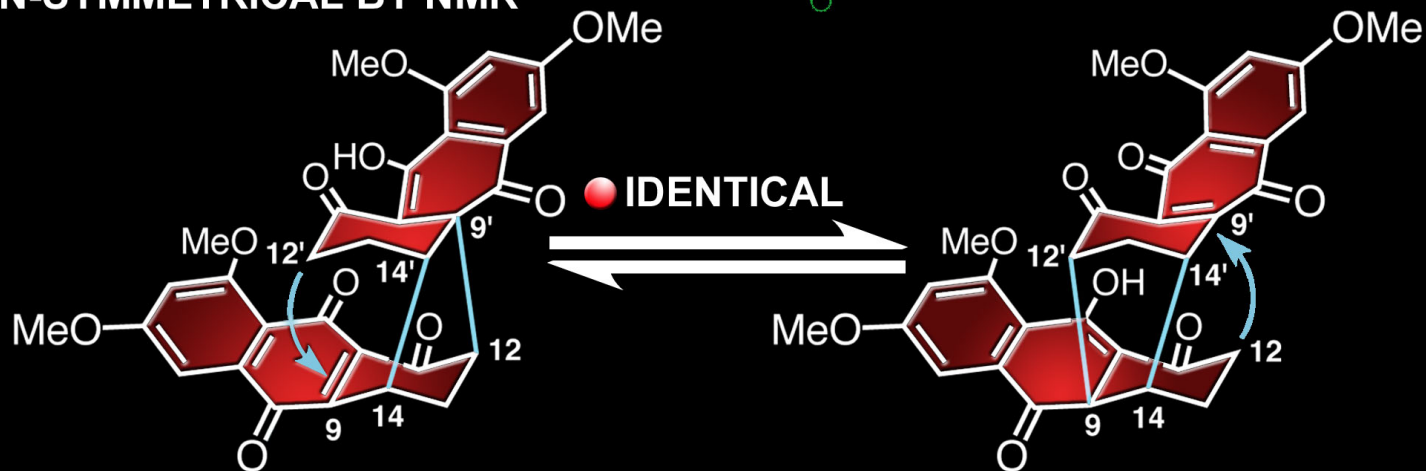
● C2/c space group
Z = 4



● C9 - C12' =
C9' - C12 = 2.372 Å

● C14-C14' = 1.56 Å

● NON-SYMMETRICAL BY NMR



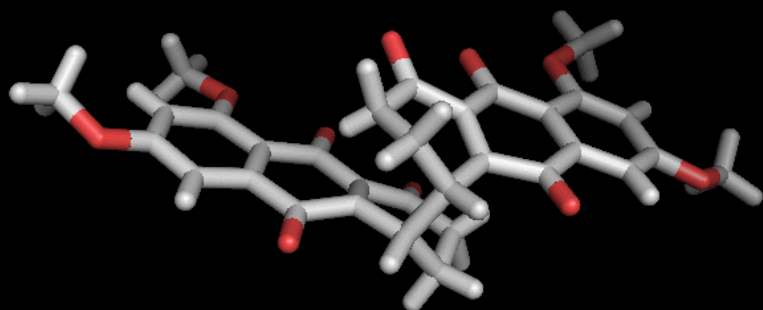
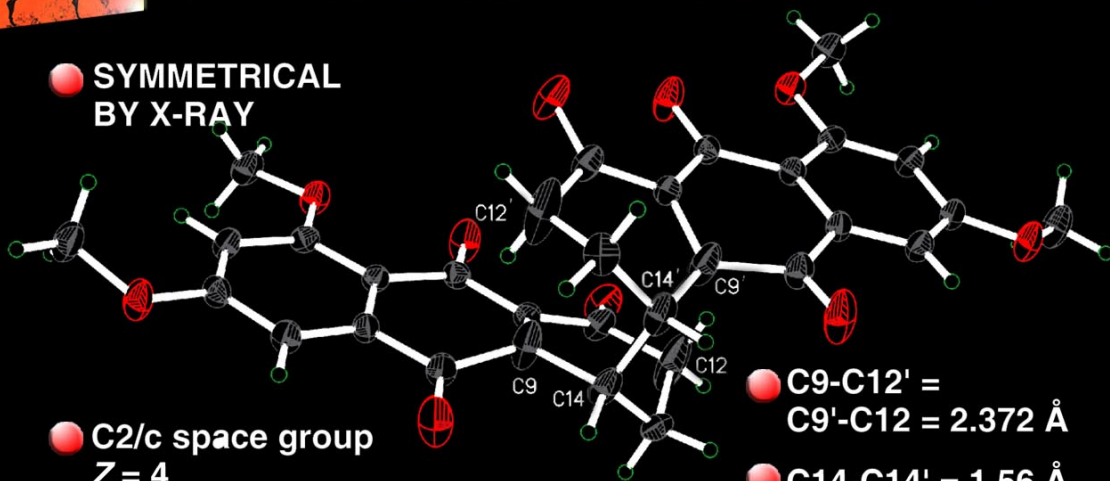


DEOXYRUBROSKYRIN MODEL: A CASE OF BOND MIGRATION [MISLEADING X-RAY STRUCTURE]

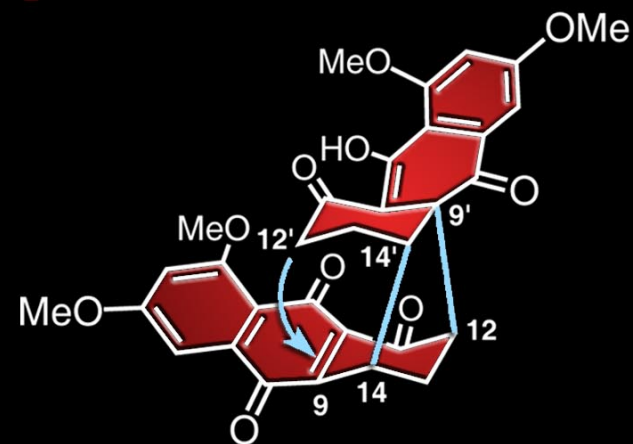


● SYMMETRICAL
BY X-RAY

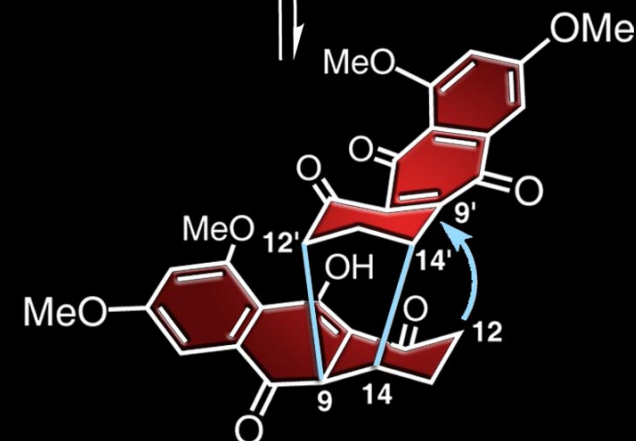
● C2/c space group
Z = 4



● NON-SYMMETRICAL BY NMR



● IDENTICAL

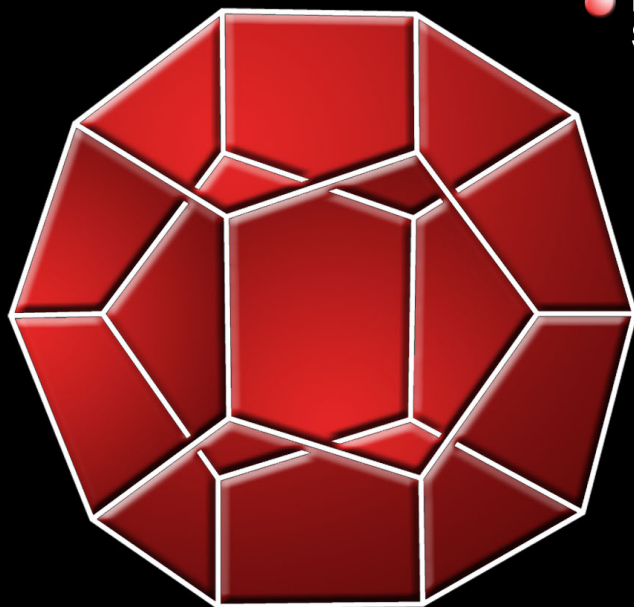




THE DODECAHEDRANE CONUNDRUM: NMR SPECTROSCOPY VS X-RAY CRYSTALLOGRAPHY [MISLEADING X-RAY STRUCTURE]

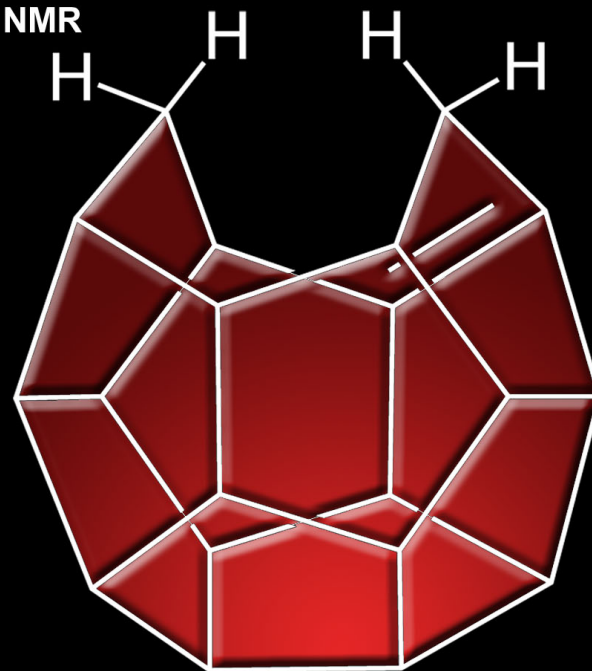


- SYMMETRICAL BY X-RAY CRYSTALLOGRAPHY
- CRYSTALLOGRAPHIC DISORDER
- NON-SYMMETRICAL BY NMR SPECTROSCOPY



- LAUE SYMMETRY $m\bar{3} (T_h)$
- CUBIC CRYSTAL SYSTEM

O.ERMER *Angew.Chem.Int.Ed.*1983, 251



- STRUCTURE AVERAGED OVER 30 PREFERRED ORIENTATIONS DIFFERS ONLY SLIGHTLY FROM THAT OF SYMMETRICAL DODECAHEDRANE

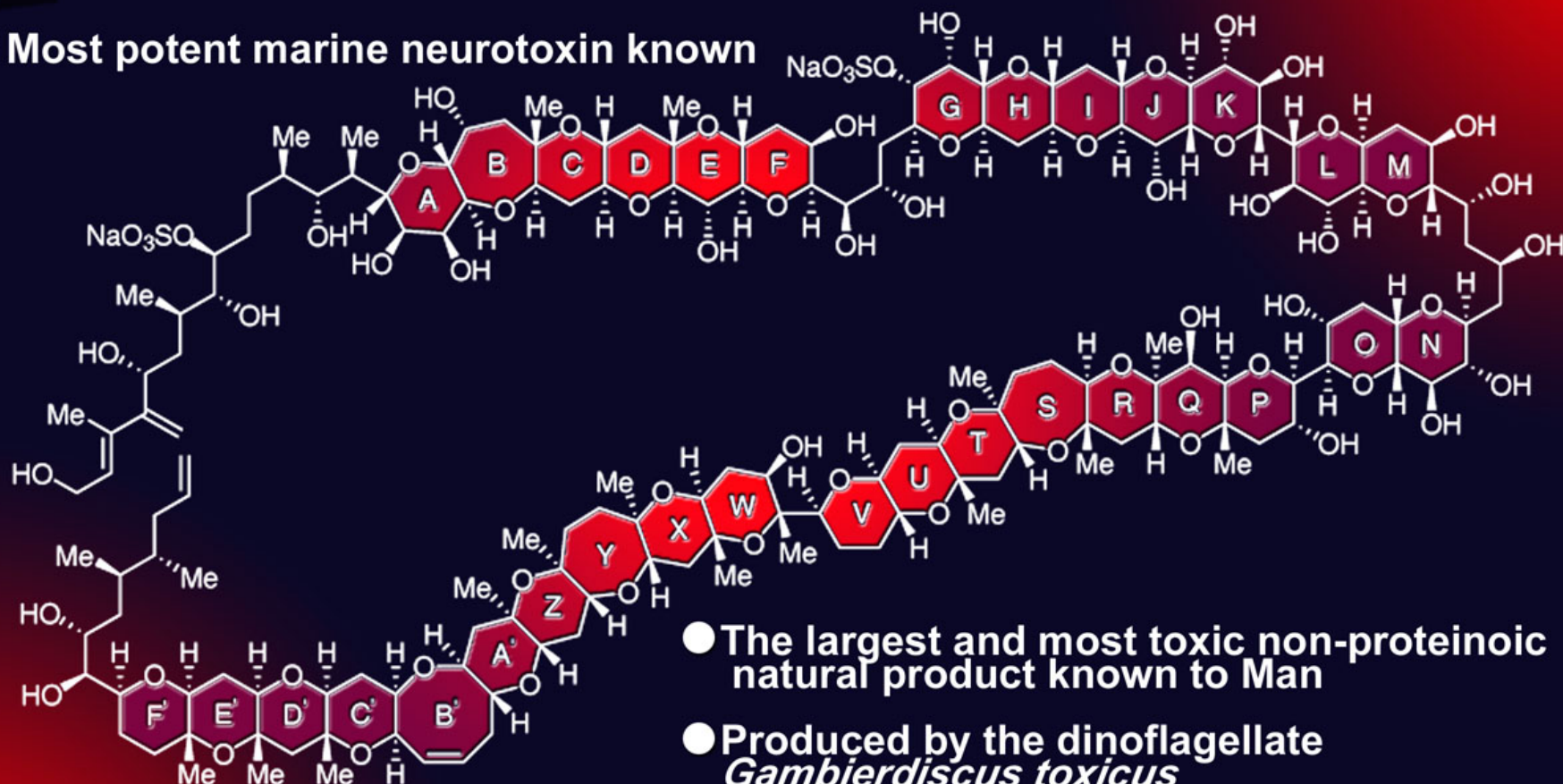
L.A. PAQUETTE et al. *J. Am. Chem. Soc.* 1982,4503



PROPOSED STRUCTURE OF MAITOTOXIN



- Most potent marine neurotoxin known



- The largest and most toxic non-proteinoic natural product known to Man
- Produced by the dinoflagellate *Gambierdiscus toxicus*
- $C_{164}H_{256}O_{68}S_2Na_2$ [MW 3422 Da]
- $LD_{50}=50\text{ng/Kg}$, 1 mg can kill a million mice
- Activates voltage-dependent Ca ion channels



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 ●

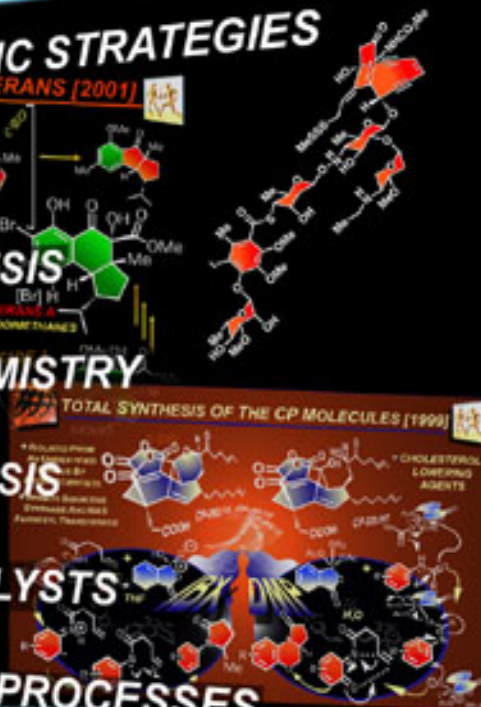
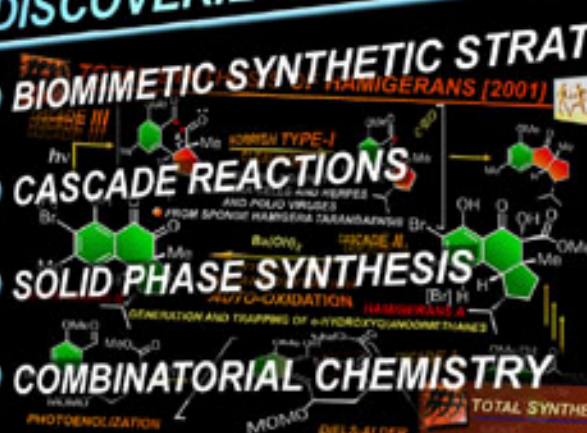
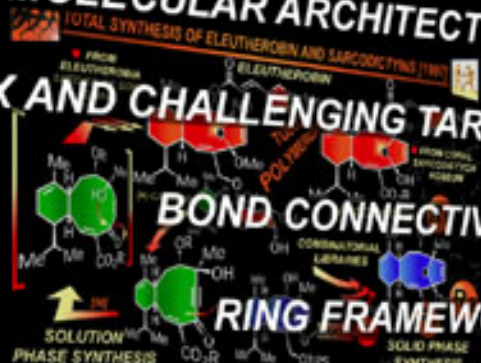
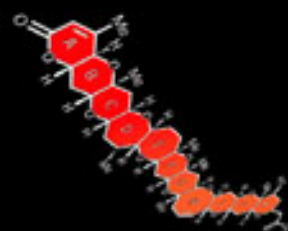
● ASYMMETRIC SYNTHESIS ●

● REAGENTS AND CATALYSTS ●

● EFFICIENT CHEMICAL PROCESSES ●

● GREEN CHEMISTRY ●

● DESIGNED BIOACTIVE MOLECULES ●



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● X-RAY CRYSTALLOGRAPHY:
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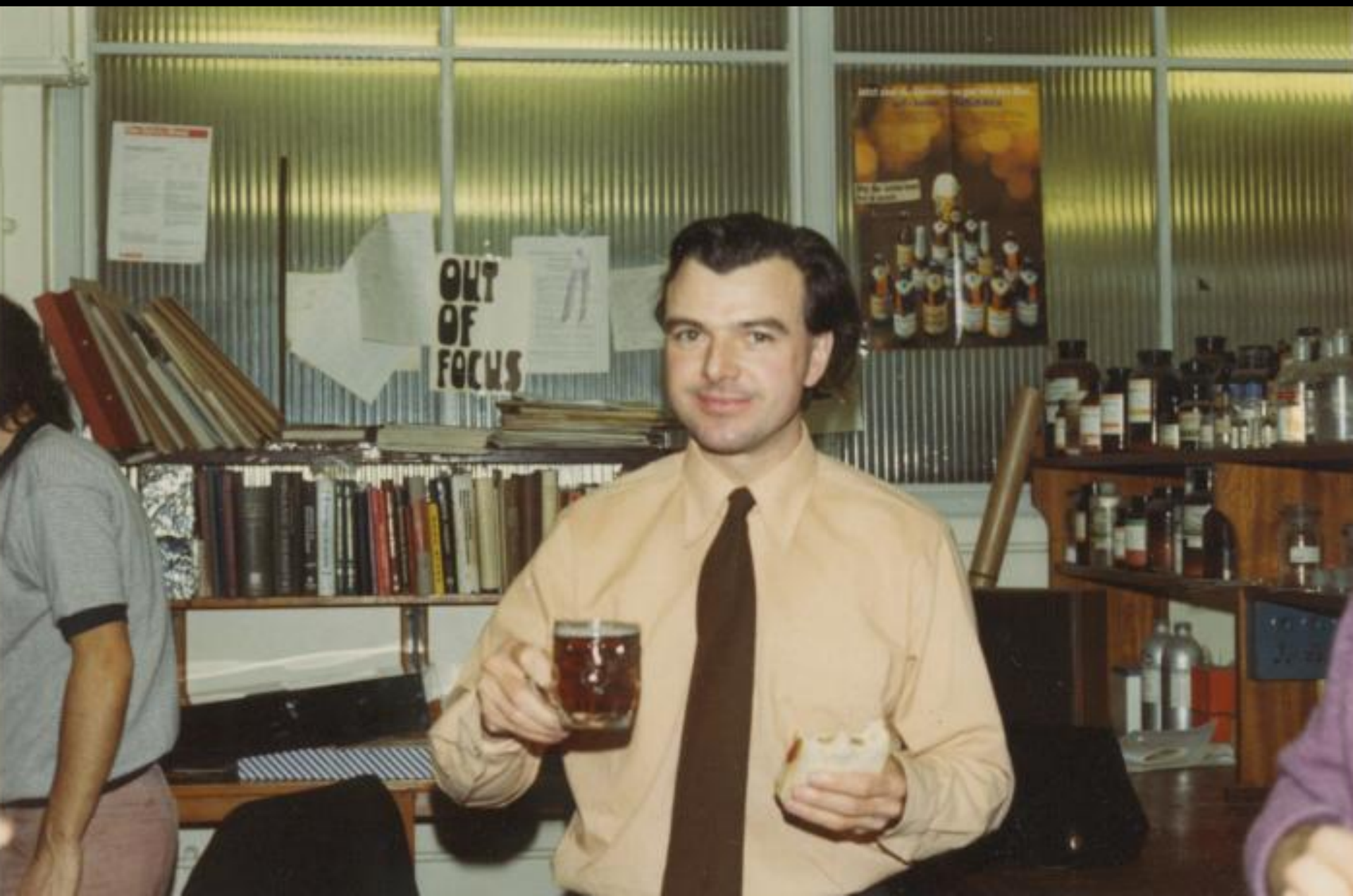
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(1976-PRESENT)



The Office Staff:

Natasha, Robbyn, Vicky, Janise







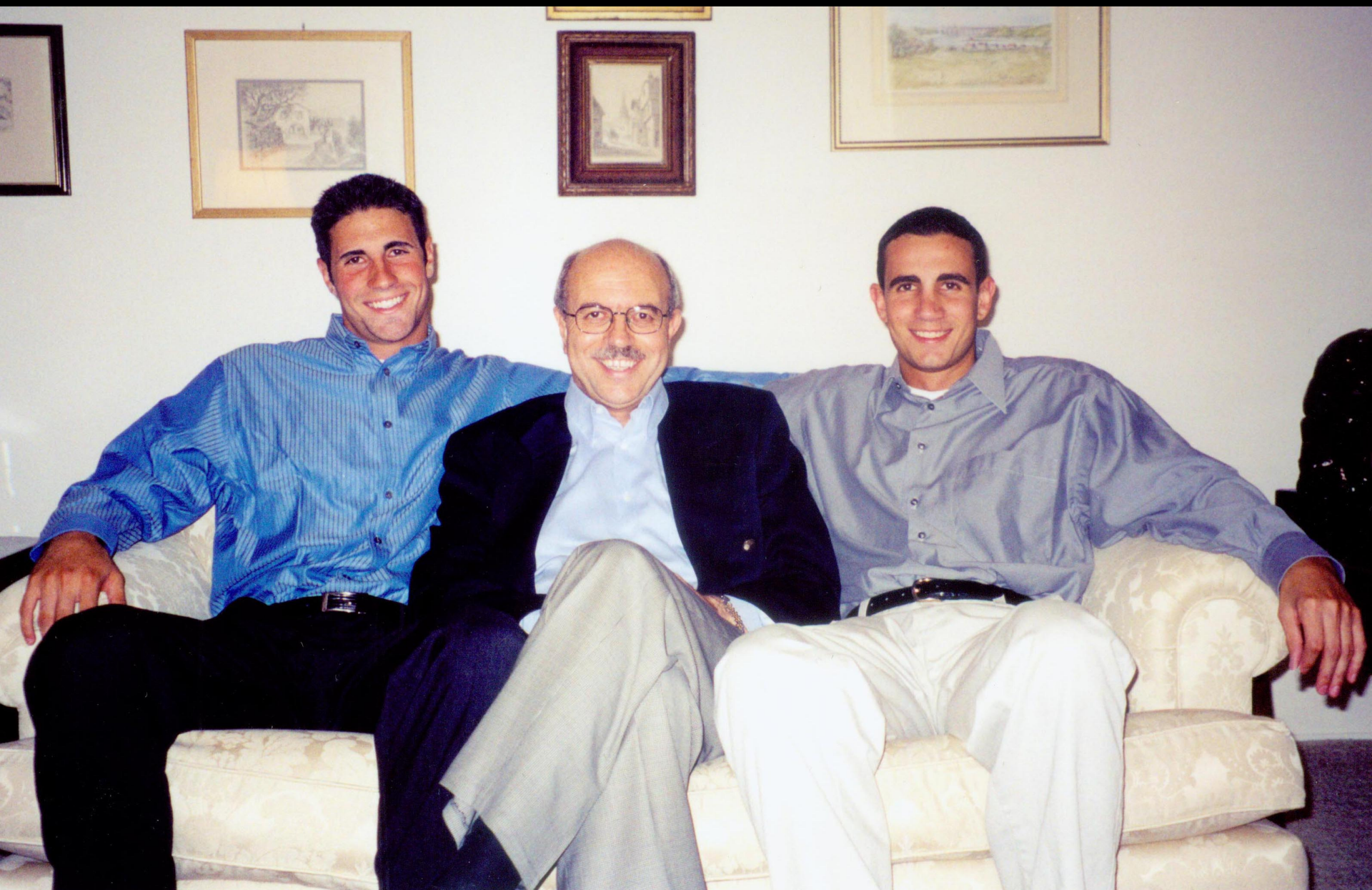














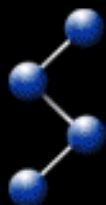


Rita, Mom (Eleni), Despo, Vaso, Nicolis, Kyriacos,
Maro (cousin), Grandma (Despina), Yianna, Runner (most likely George Kariolis)
KARAVAS, outside our patriko spiti, *circa* 1965



KARAVAS





THE
SCRIPPS
RESEARCH
INSTITUTE

THE K.C. NICOLAOU GROUP DEPARTMENT OF CHEMISTRY

SCRIPPS ● SKAGGS ● UCSD



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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) and *Classics in Total Synthesis II* (K.C. Nicolaou and Scott A. Snyder, Wiley-VCH, 2003). Enjoy the tour of our world.*

