

THE EIGHTH TETRAHEDRON SYMPOSIUM
[Tetrahedron 50th Anniversary Meeting (1957-2007)]

“Challenges in Organic Chemistry”

Berlin, Germany
June 26-29, 2007

K.C. Nicolaou

***“Total Synthesis at the Limits
of Molecular Complexity”***



RECIPIENTS OF THE TETRAHEDRON PRIZE FOR CREATIVITY IN ORGANIC CHEMISTRY



1981 Albert Eschenmoser
1983 Elias J. Corey
1985 Gilbert Stork
1987 Arthur J. Birch
1989 Michael J. S. Dewar
1991 William S. Johnson
1993 Ryoji Noyori; K. Barry Sharpless
1995 Alan R. Battersby; A. Ian Scott
1996 Samuel Danishefsky
1997 Stuart L. Schreiber
1998 David A. Evans; Teruaki Mukaiyama
1999 Henri B. Kagan
2000 Peter B. Dervan
2001 Yoshito Kishi
2002 Kyriacos C. Nicolaou
2003 Robert H. Grubbs; Dieter Seebach
2004 Koji Nakanishi
2005 Bernd Giese
2006 Hisashi Yamamoto





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**

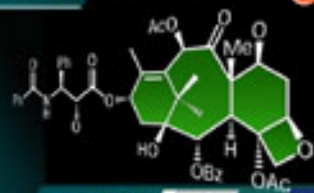
● **COMBINATORIAL CHEMISTRY**

● **PROCESS CHEMISTRY**

● **COST: \$500 MILLION AND RISING**

● **MEDICINAL CHEMISTRY**

● **REVIEW PROCESS**



\$

\$\$

\$\$\$

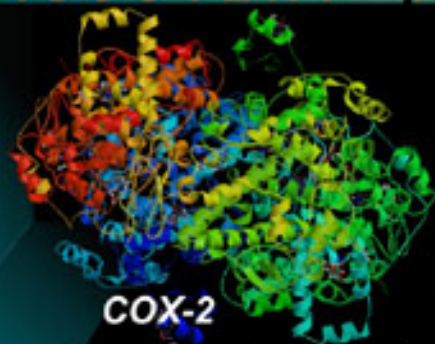


DISCOVERY

PRECLINICAL

CLINICAL

APPROVAL



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

● **HUMAN TRIALS**

● **TIME: 5-10 YEARS AND FALLING**



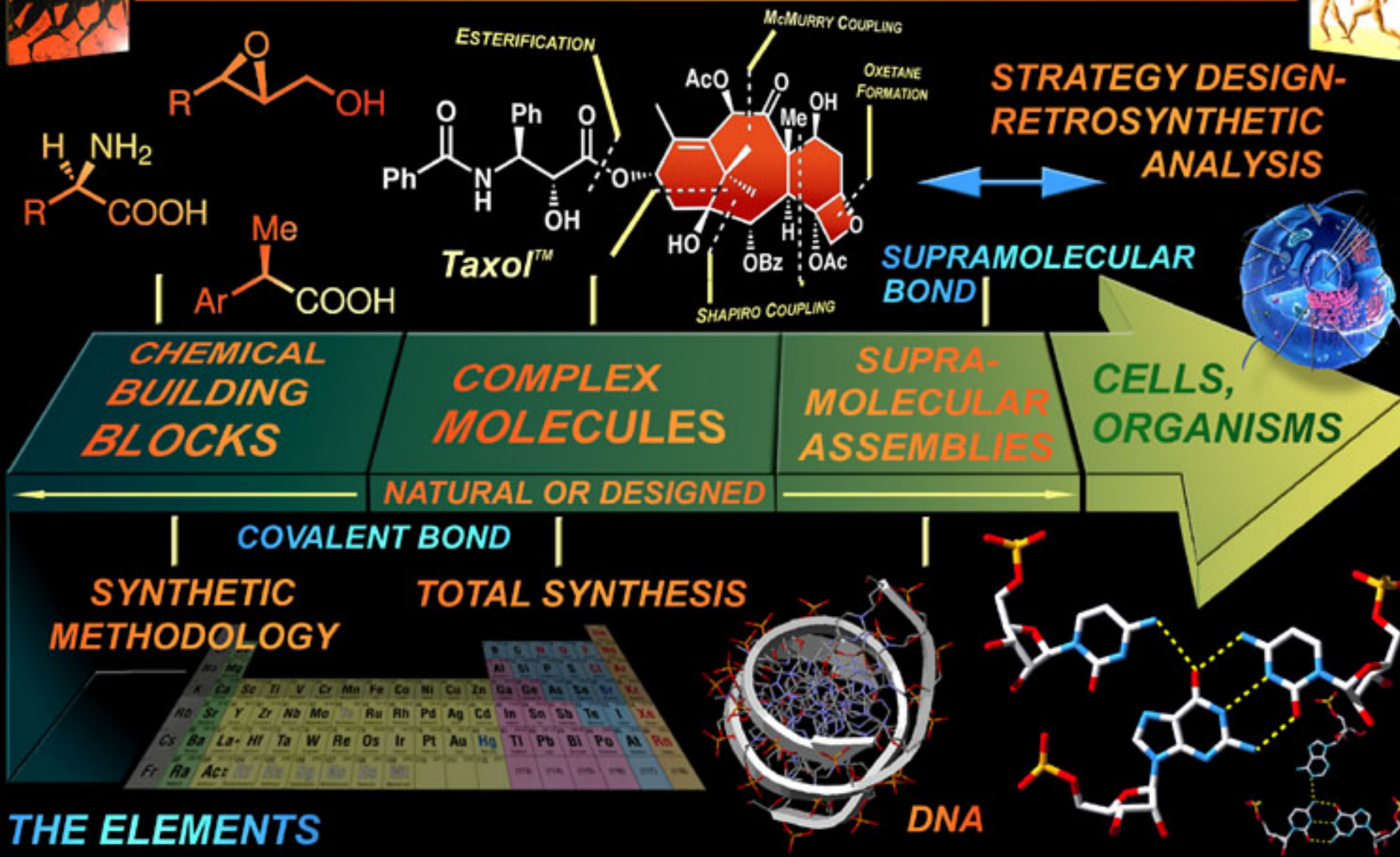
● **BIOLOGICAL TARGETS**

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

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



MOLECULAR COMPLEXITY and CHEMICAL SYNTHESIS





CASCADE REACTIONS IN TOTAL SYNTHESIS

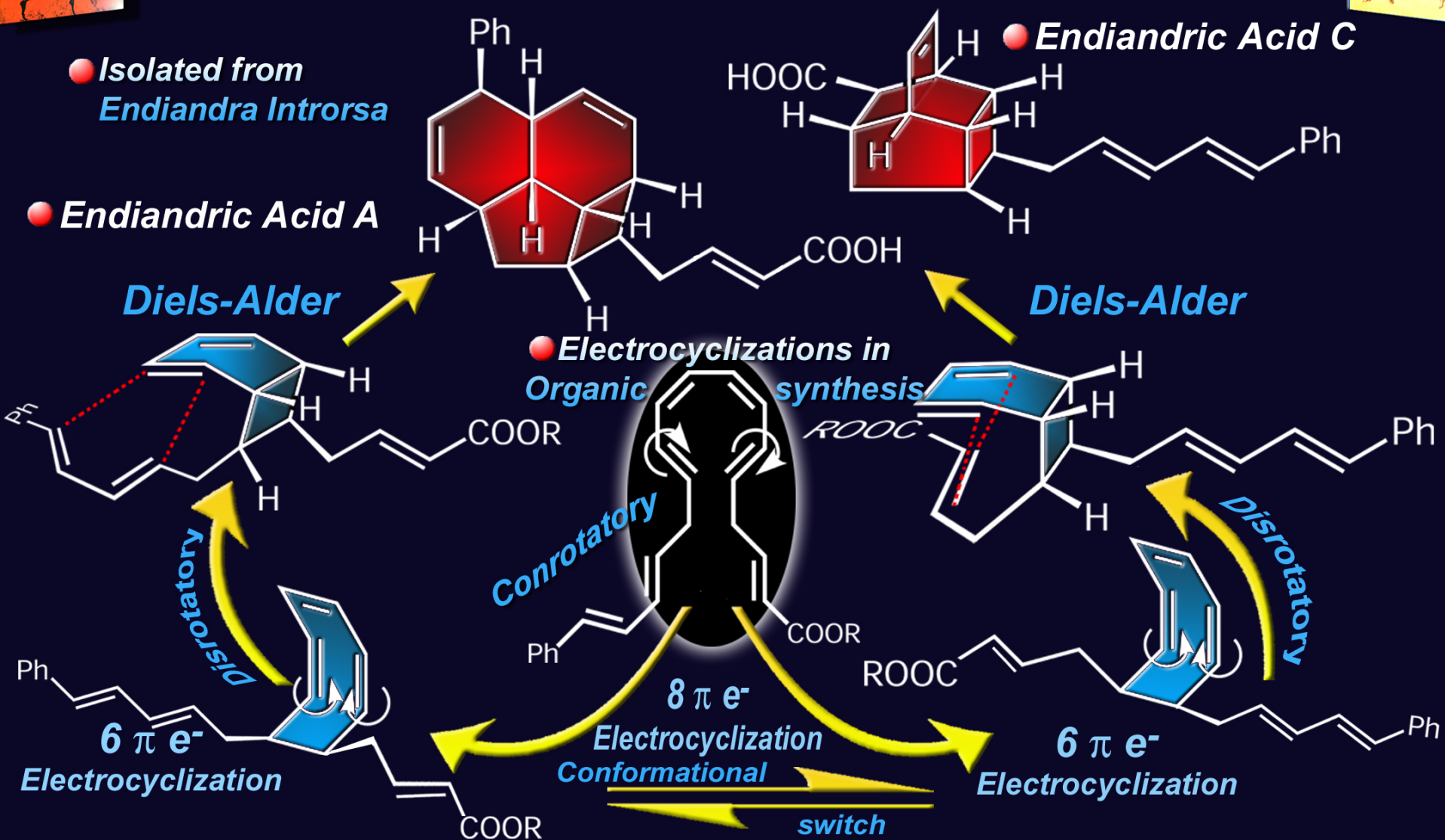


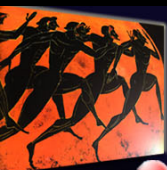
¹Cascade Reactions in Total Synthesis, K.C. Nicolaou, D.J. Edmonds, P.G. Bulger, *Angew. Chem. Int. Ed.*, in press.

²Cascade Reactions in Total Synthesis, K.C. Nicolaou and Scott A. Snyder, *l'actualité chimique*, avril-mai 2003, 83.

● **Endiandric Acid A**

Endiandric Acid C

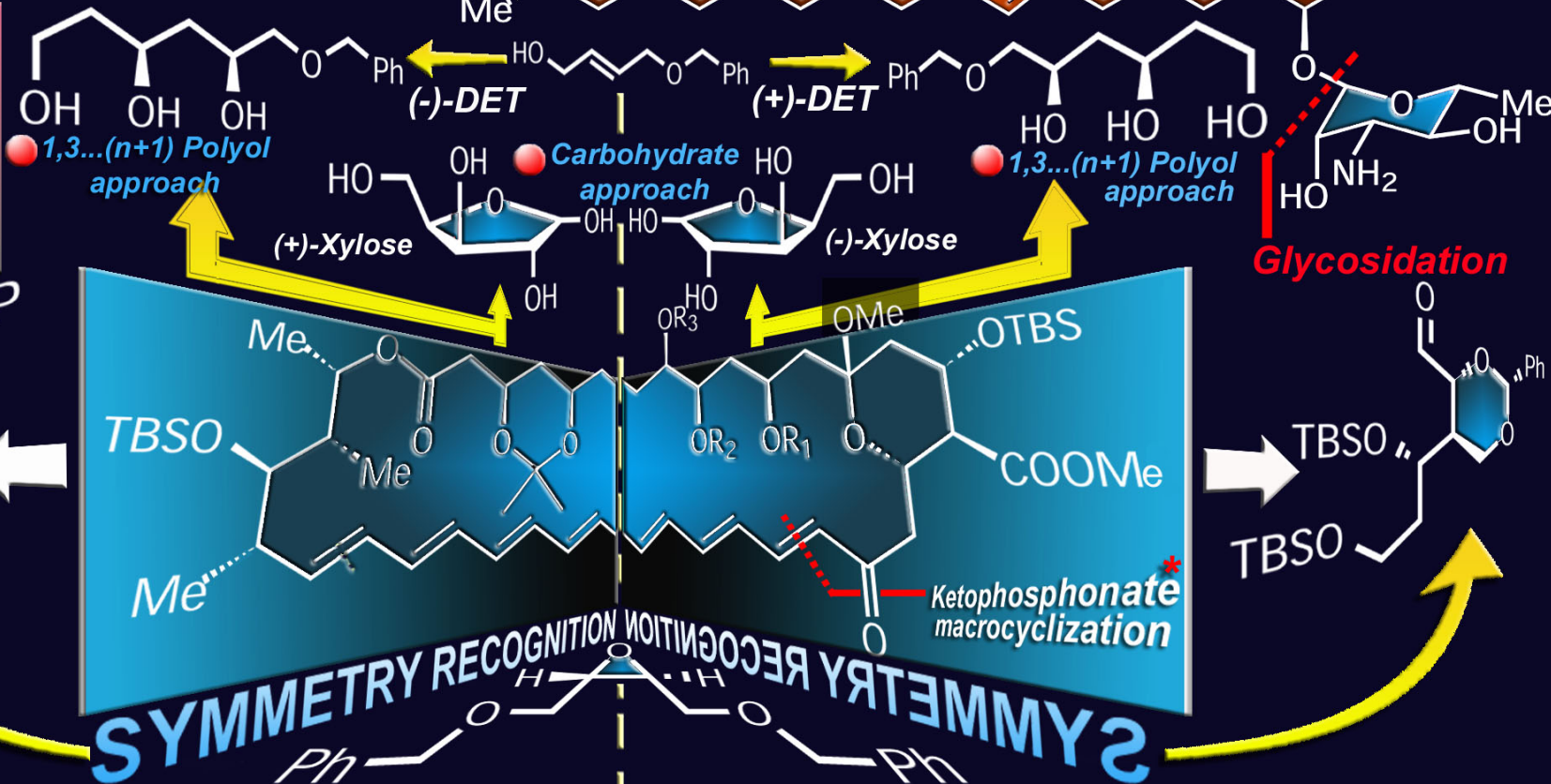
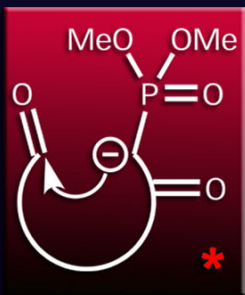
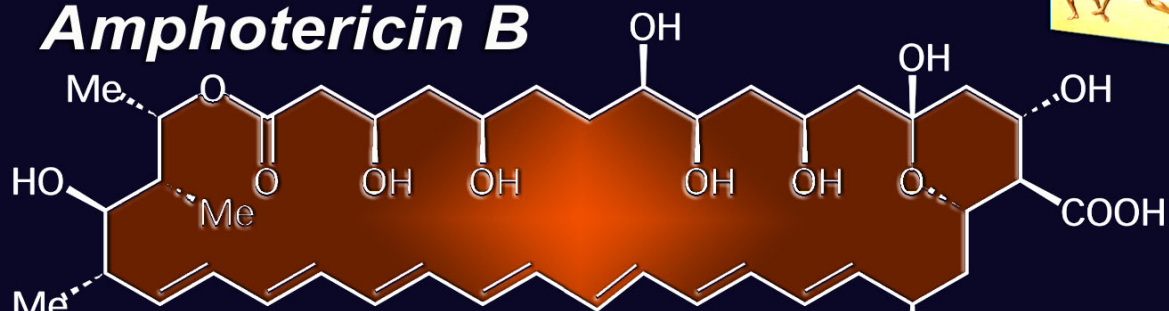




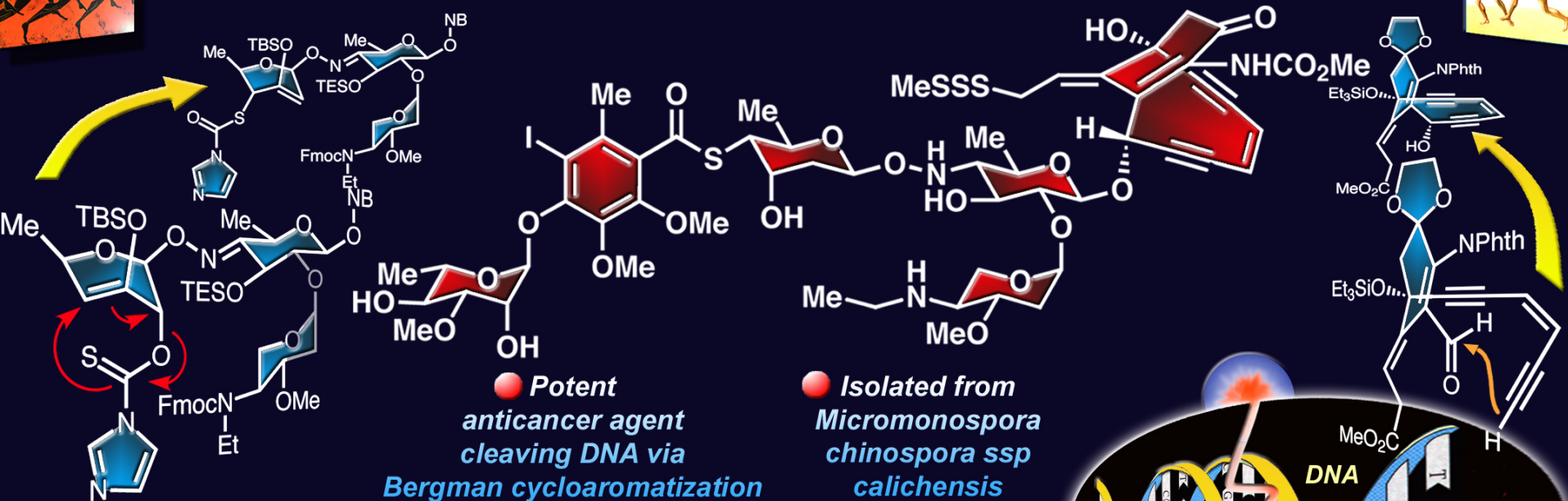
TOTAL SYNTHESIS OF AMPHOTERICIN B [1987]

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

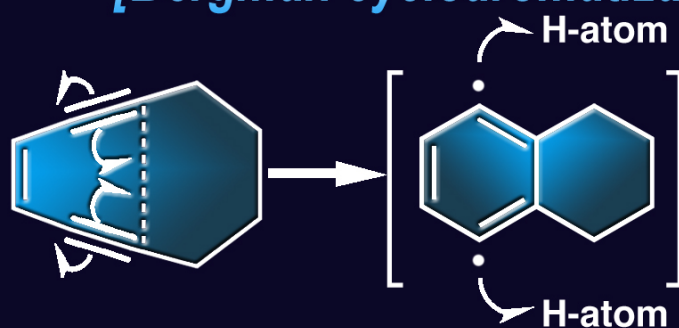
Amphotericin B



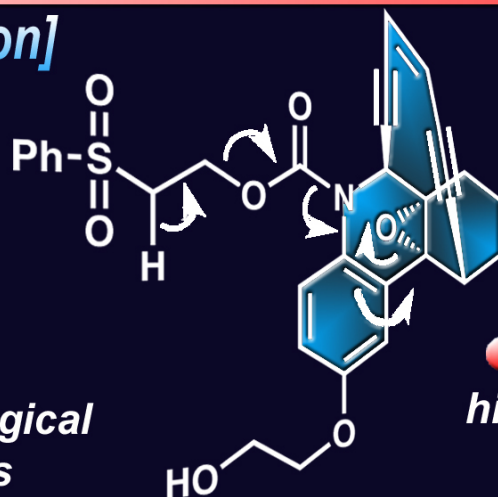
TOTAL SYNTHESIS OF CALICHEAMICIN γ_1' [1992]



[Bergman cycloaromatization]



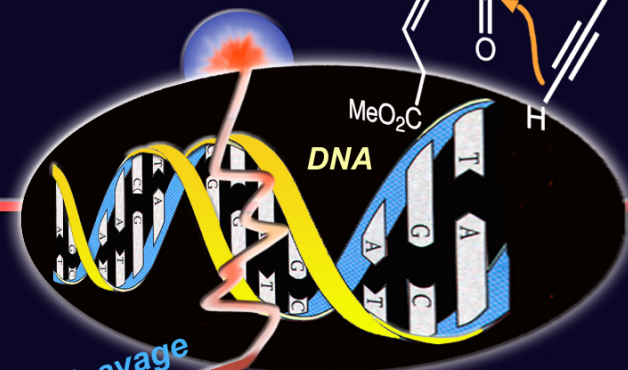
● **Elucidation of chemical and biological properties of cyclic enediynes**



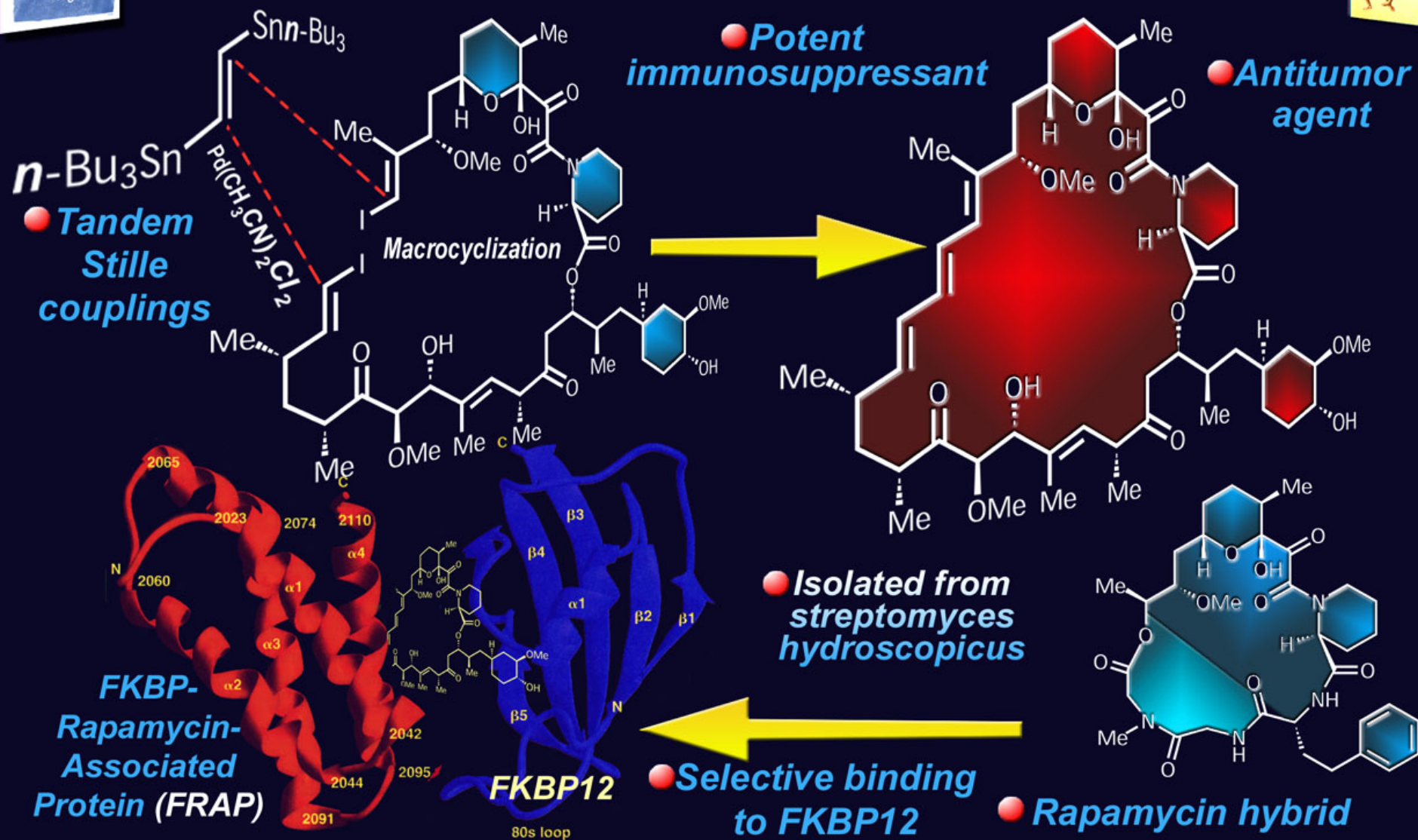
DNA cleavage
Cell death

Double strand cuts

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



TOTAL SYNTHESIS OF RAPAMYCIN [1993]

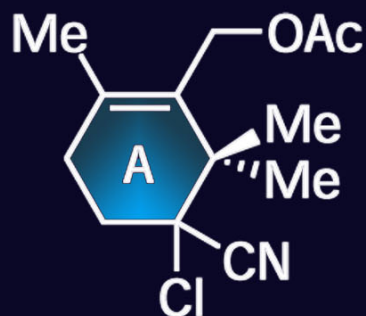




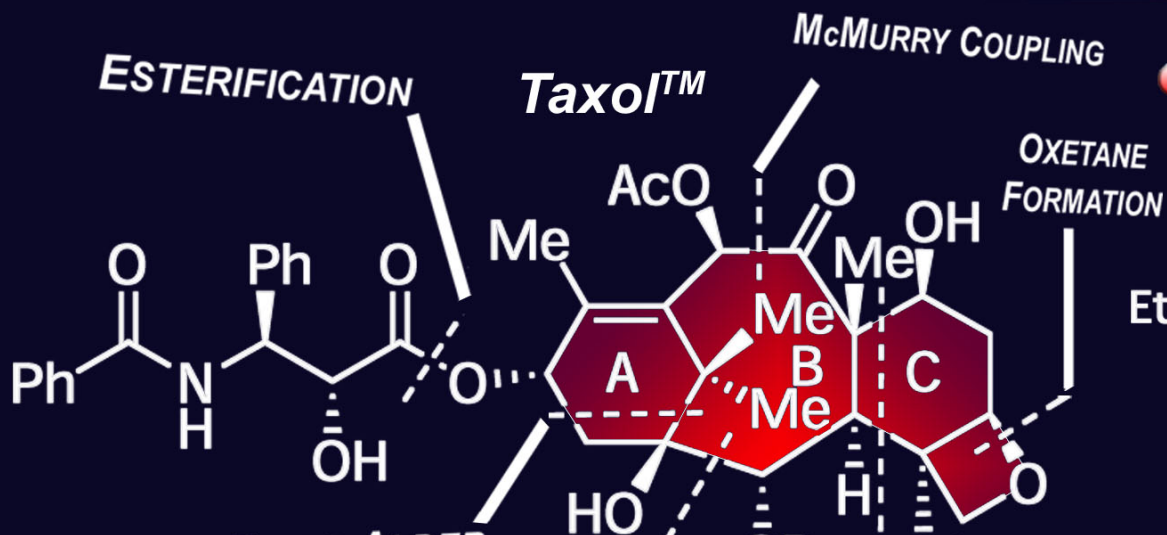
TOTAL SYNTHESIS OF TAXOL™ [1994]



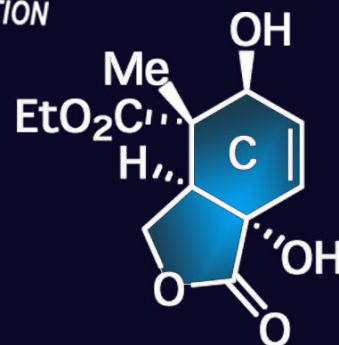
● Water soluble pro-drugs



ESTERIFICATION



● Fluorescent probes



OXETANE FORMATION

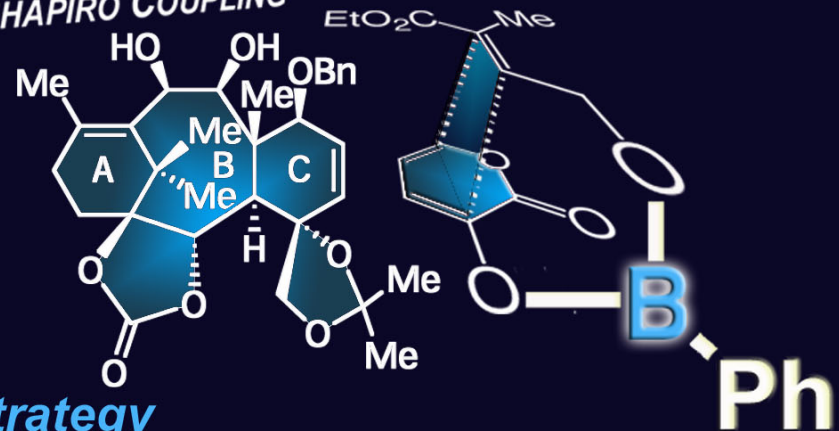
DIELS-ALDER

● Isolated from *Taxus brevifolia*

Convergent strategy

SHAPIRO COUPLING

DIELS-ALDER





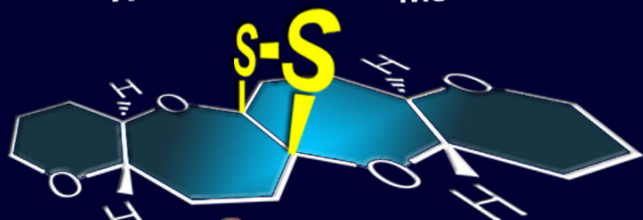
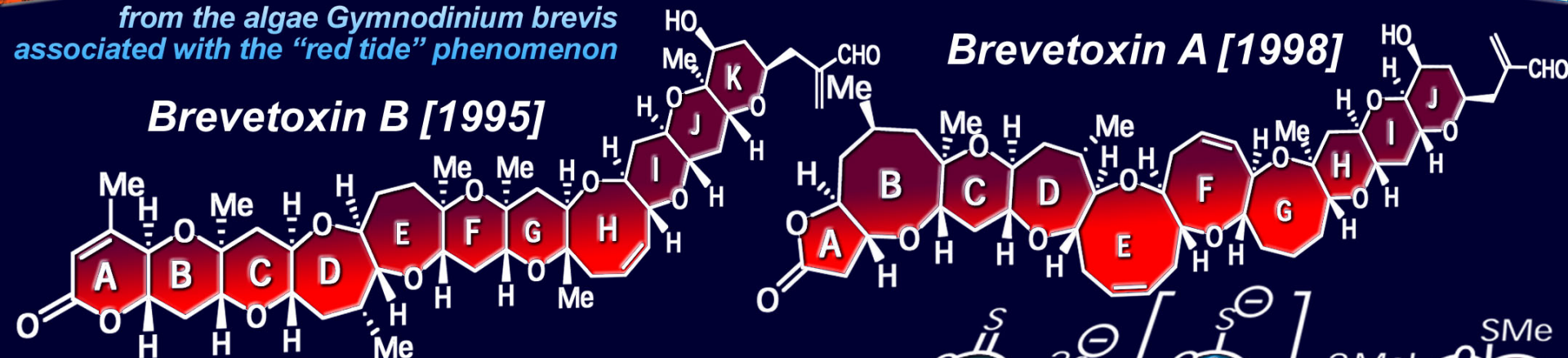
TOTAL SYNTHESIS OF BREVETOXINS B AND A [1982-1998]



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

Brevetoxin B [1995]

Brevetoxin A [1998]

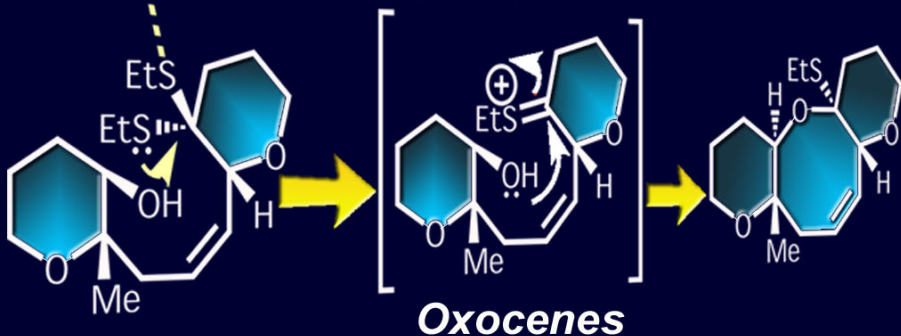


● First stable dithietane

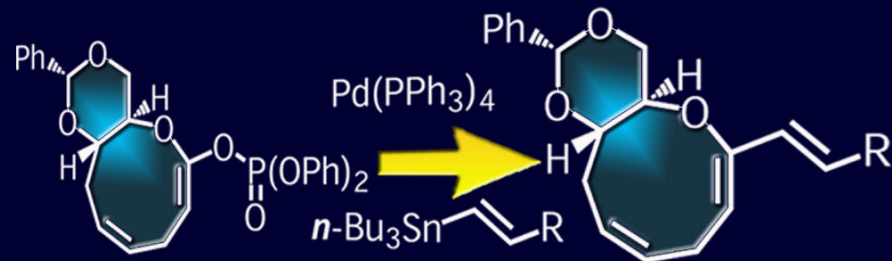
● New synthetic technologies



● 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

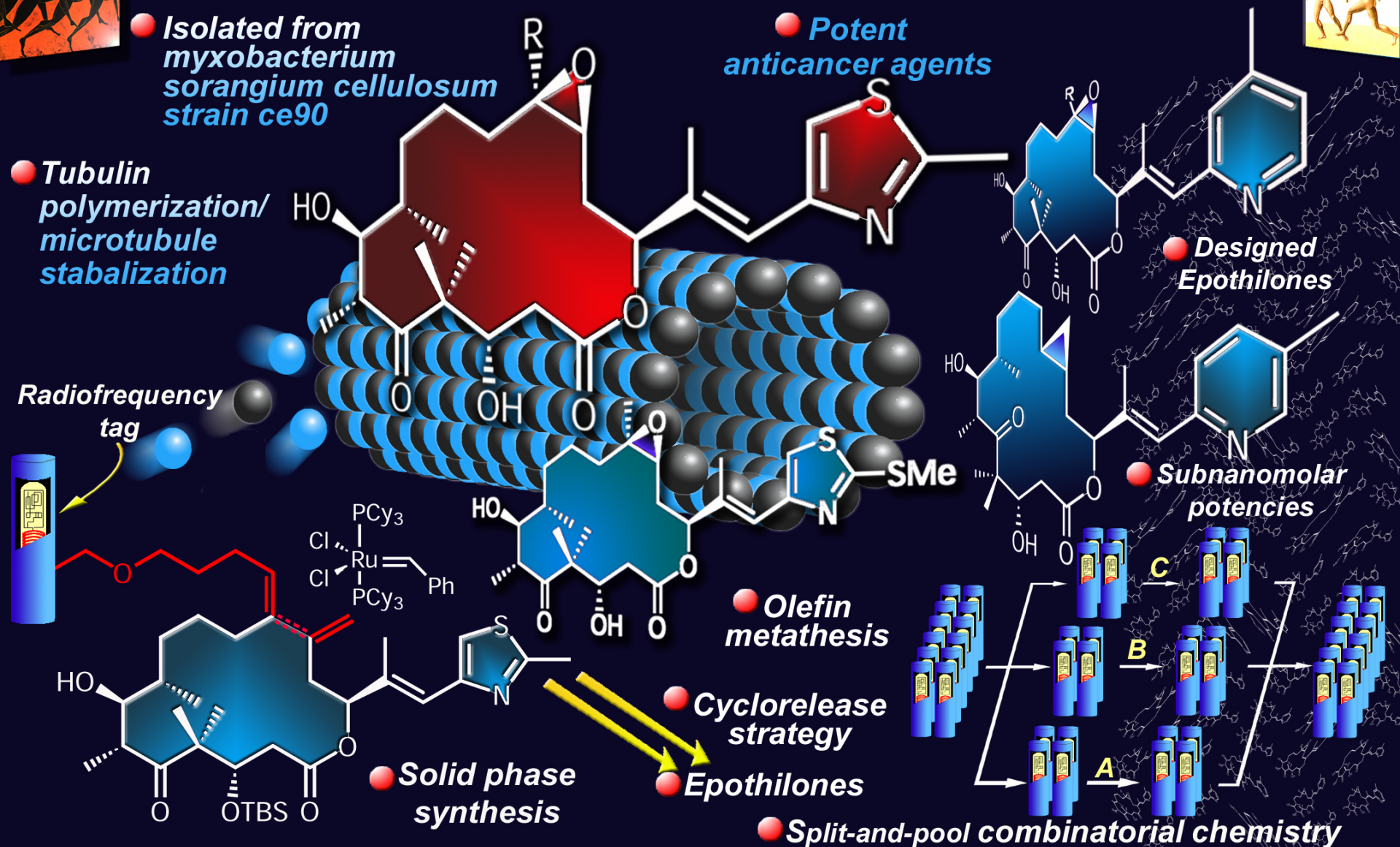
● Olefin metathesis

● Cyclorelease strategy

● Solid phase synthesis

● Epothilones

● Split-and-pool combinatorial chemistry





Cell Line	IC ₅₀	EpoB	RA _{EpoB}
1A9	0.06	0.99	16.5
1A9/PTX10	0.1	7.8	78.0
1A9/A8	0.6	10.0	16.7
KB-31	0.99	0.42	4.7
KB-3811	0.14	0.39	2.8

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



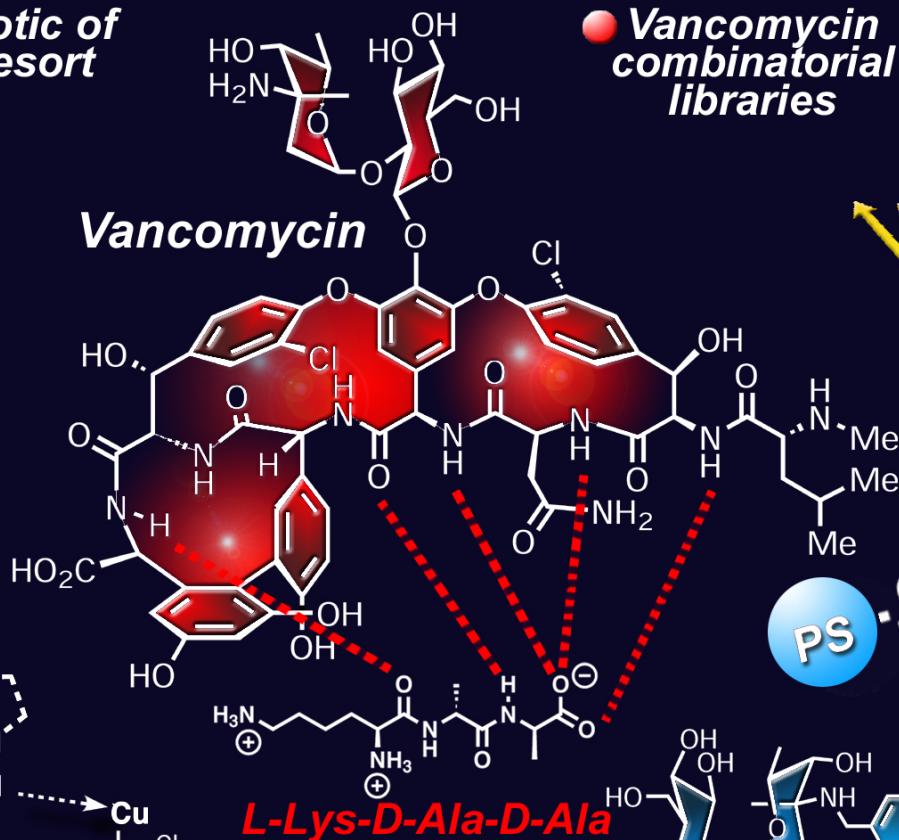
● **Antibiotic of last resort**

● **Vancomycin combinatorial libraries**

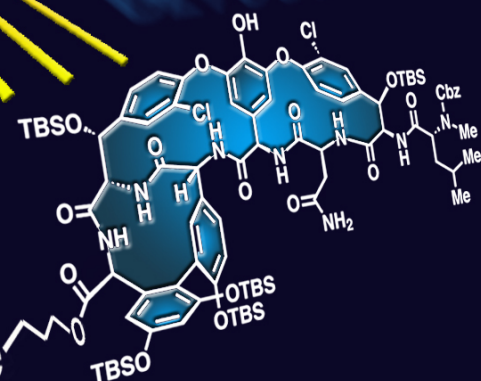
● **Isolated from the Actinomycete *amycolatopsis orientalis***

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

Vancomycin



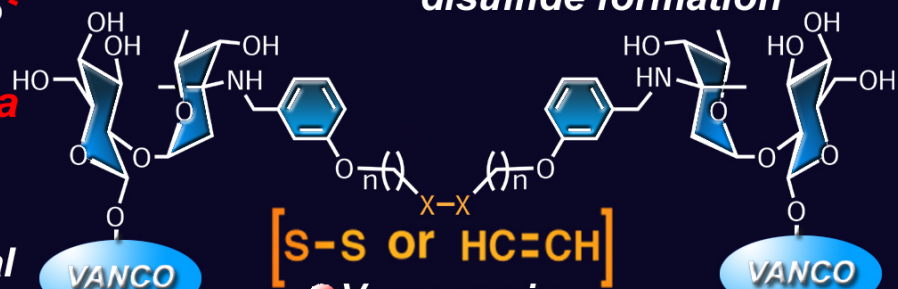
DEPROTECTIONS
CLEAVAGE
GLYCOSIDATIONS



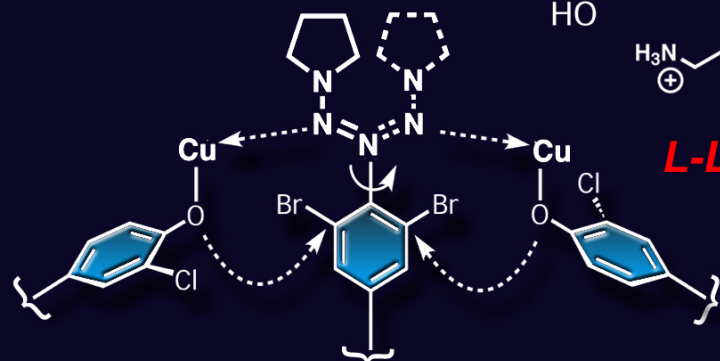
● **Olefin metathesis or disulfide formation**

L-Lys-D-Ala-D-Ala

● **Target-accelerated combinatorial synthesis**



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



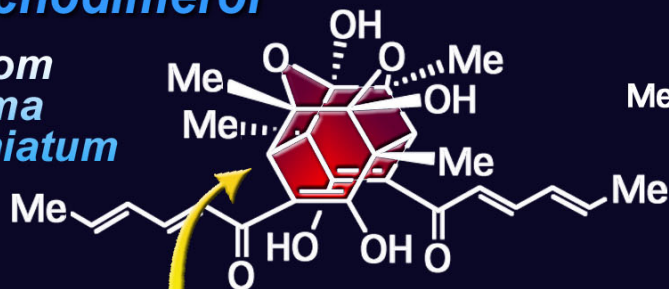
● **Development of triazene-driven bisaryl ether formation**

BIOMIMETIC TOTAL SYNTHESIS OF BISORBICILLINOIDS [1999]



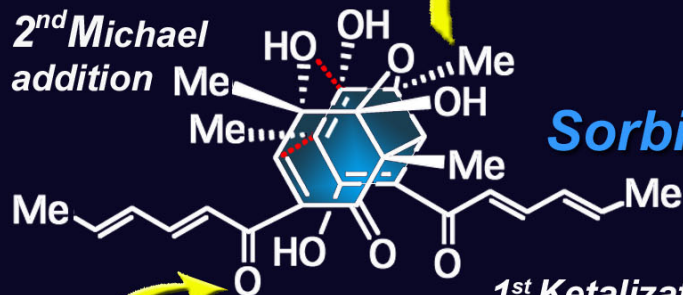
Trichodimerol

● Isolated from *Trichoderma longibrachiatum*



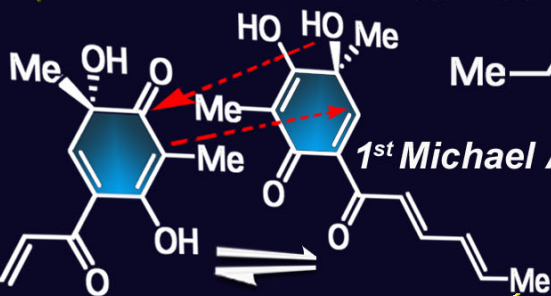
2nd Ketalization

2nd Michael addition



1st Ketalization

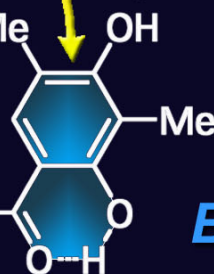
1st Michael Addition



Sorbicillin

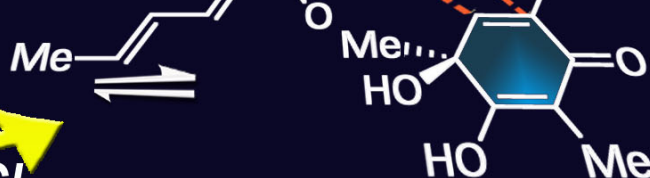
Bisorbibutenolide

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



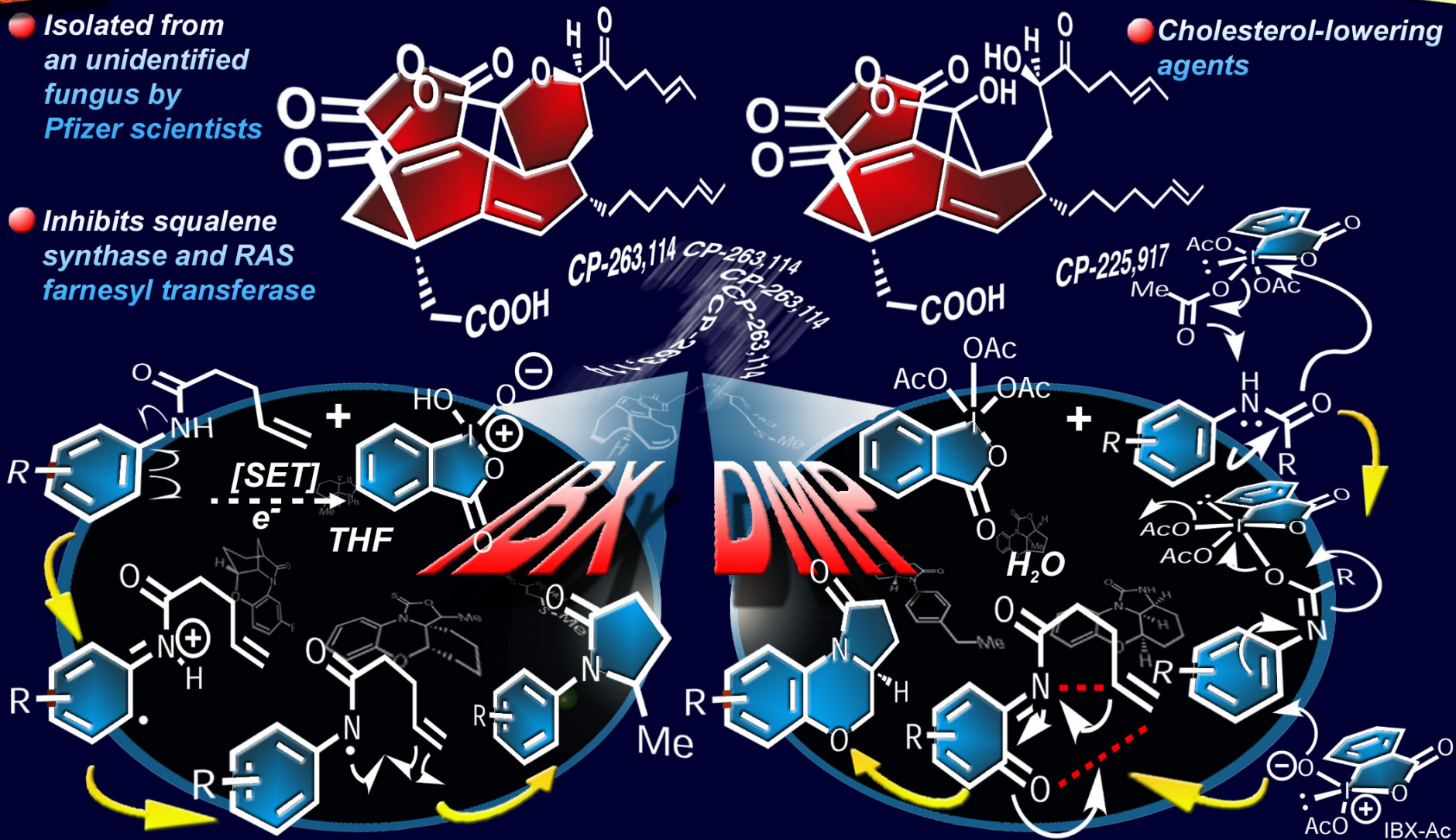
TOTAL SYNTHESIS OF THE CP MOLECULES [1999]



● Isolated from an unidentified fungus by Pfizer scientists

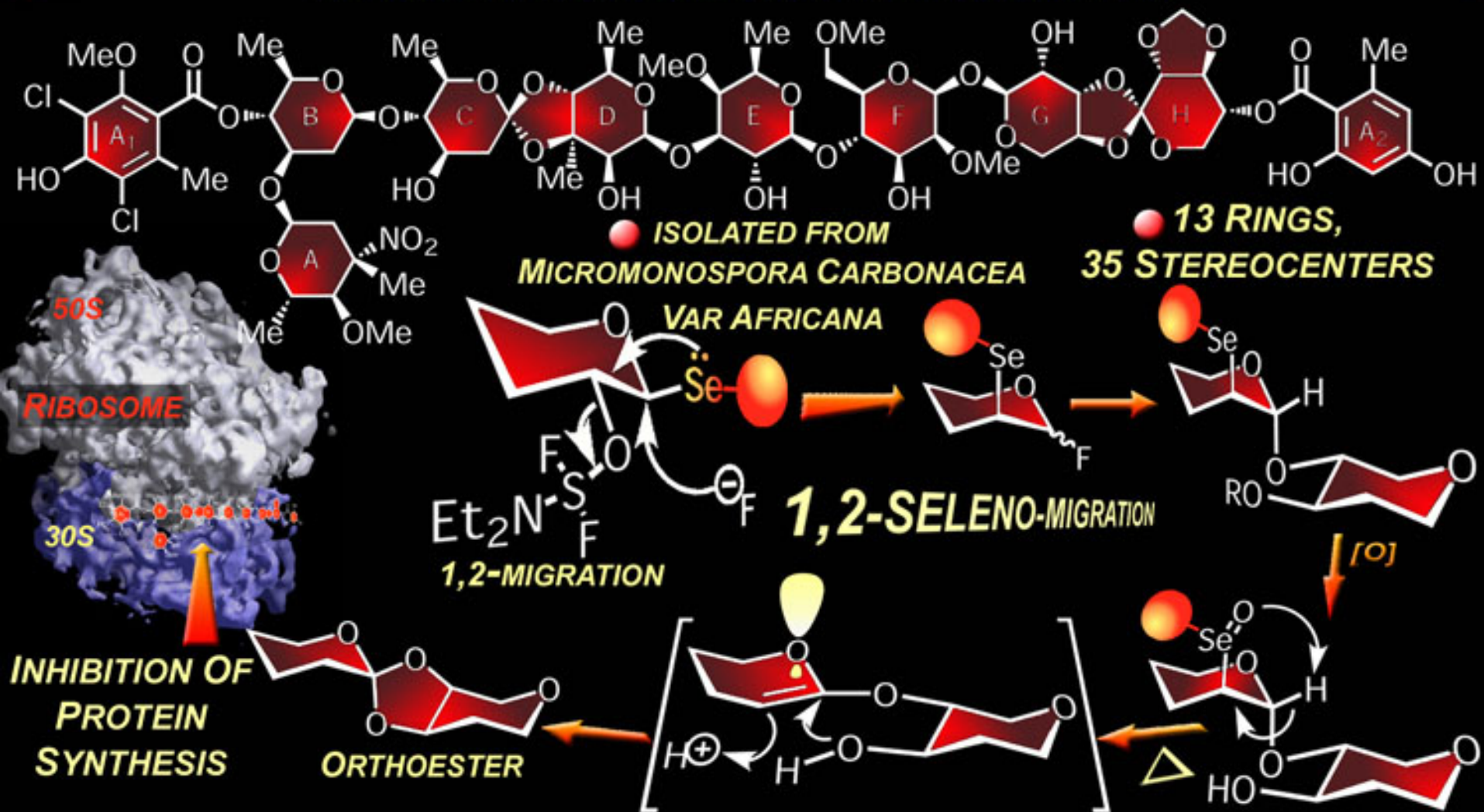
● Inhibits squalene synthase and RAS farnesyl transferase

● Cholesterol-lowering agents





ANTIBIOTIC ACTIVE AGAINST DRUG RESISTANT BACTERIA



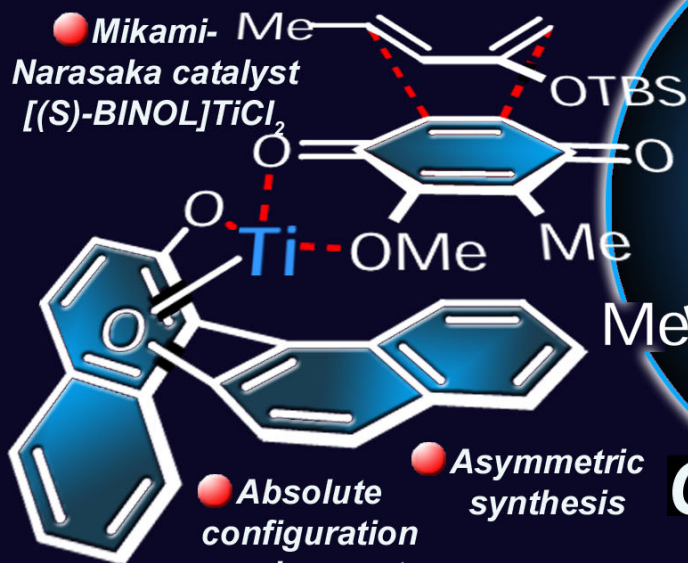


TOTAL SYNTHESIS OF COLOMBIASIN A [2001]

Possibly active against
Mycobacterium tuberculosis H37Rv

Isolated from coral
pseudopterogorgia elisabethae

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

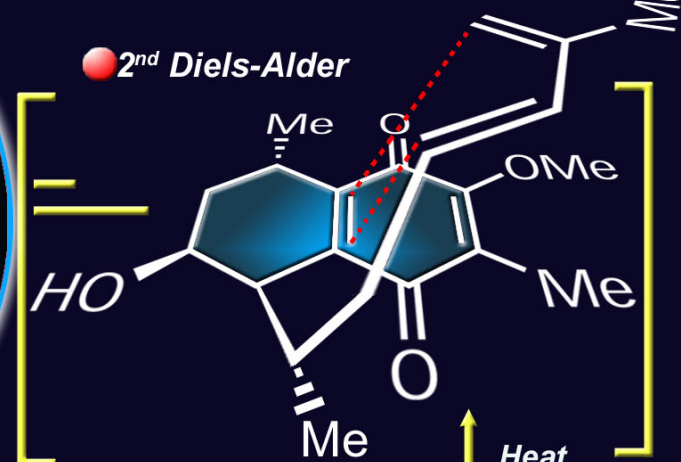


Absolute
configuration
assignment

Asymmetric
synthesis

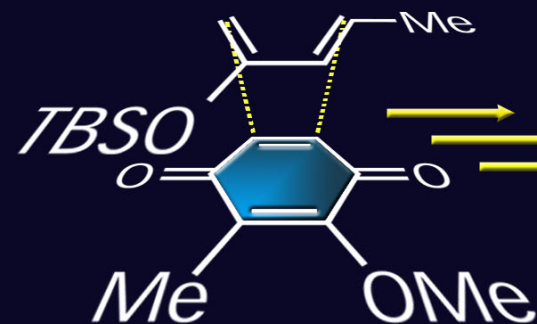
Colombiasin A

2nd Diels-Alder

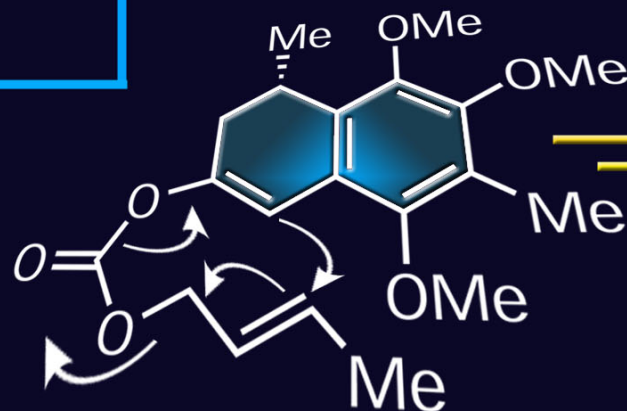


Heat
[dark]

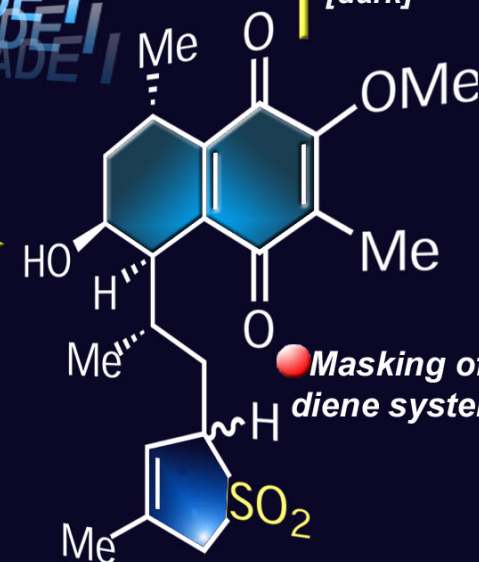
CASCADE I
CASCADE I
CASCADE I



1st Diels-Alder

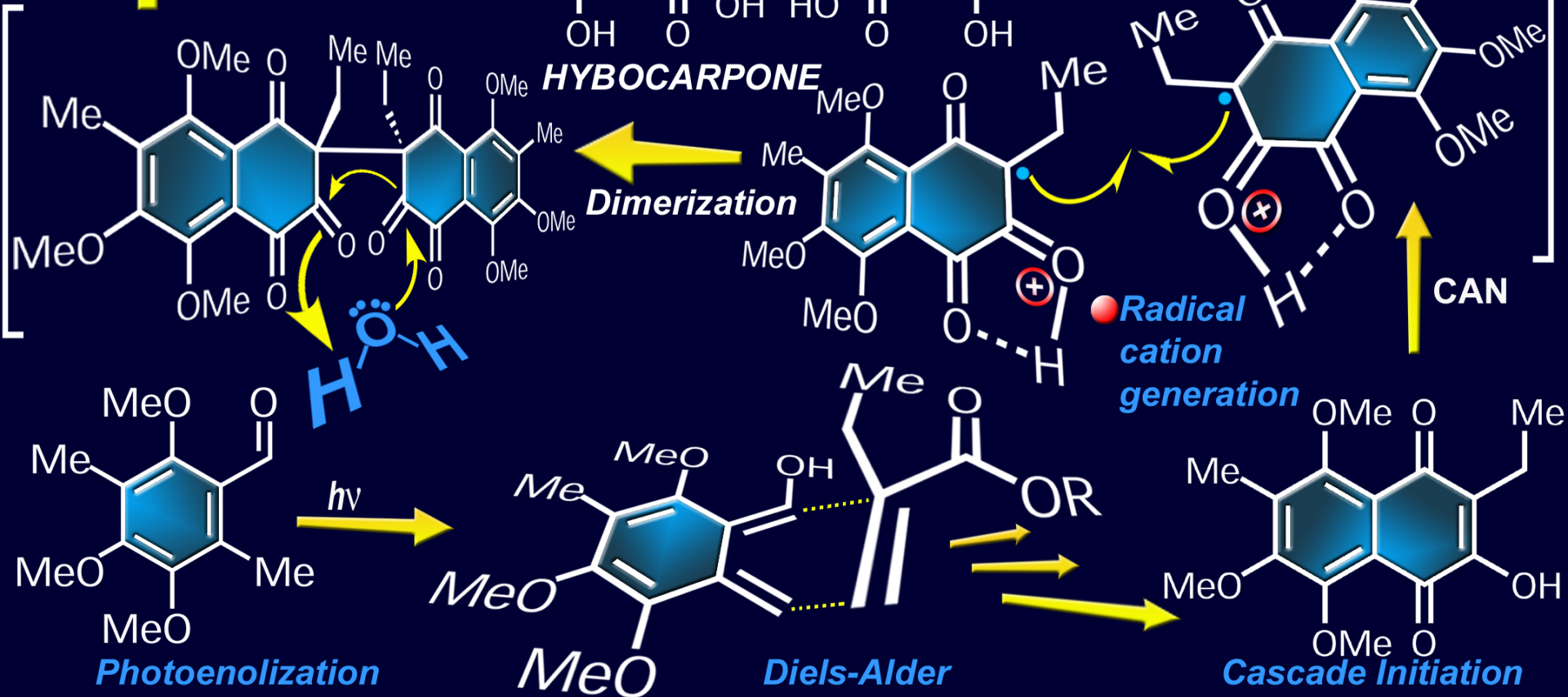


Palladium-catalyzed
rearrangement



Masking of
diene system

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





TOTAL SYNTHESIS OF COLEOPHOMONES B AND C [2002]



● From fungi *Stachybothys cylindrospora* RF-5900

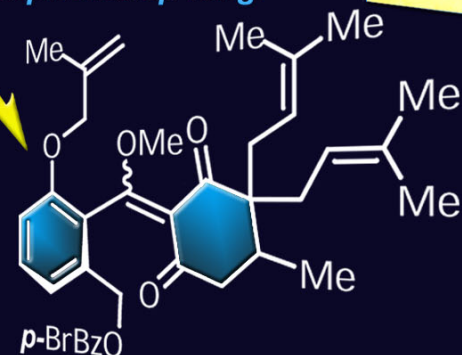
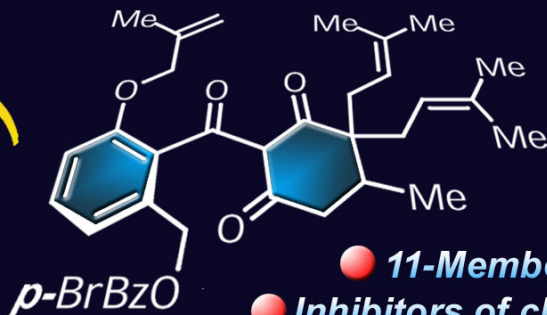
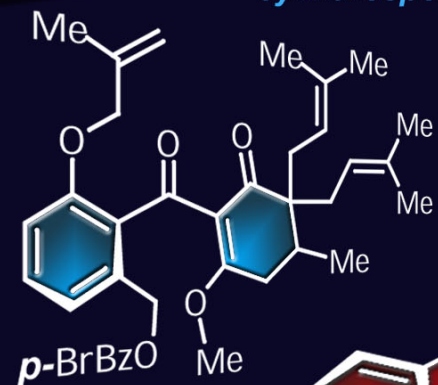
● From *Coleophoma* sp fungi

CH_2N_2

CH_2N_2

● 11-Membered rings

● Inhibitors of chymase



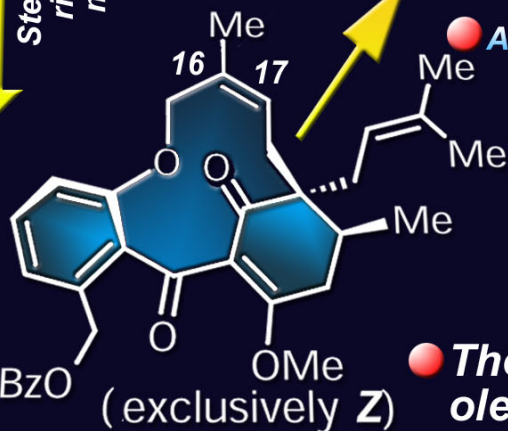
CATALYST
Stereoselective
ring closing
metathesis

Stereoselective
ring closing
metathesis
CATALYST

COLEOPHOMONE C COLEOPHOMONE B

● Antibiotics

● Antifungal

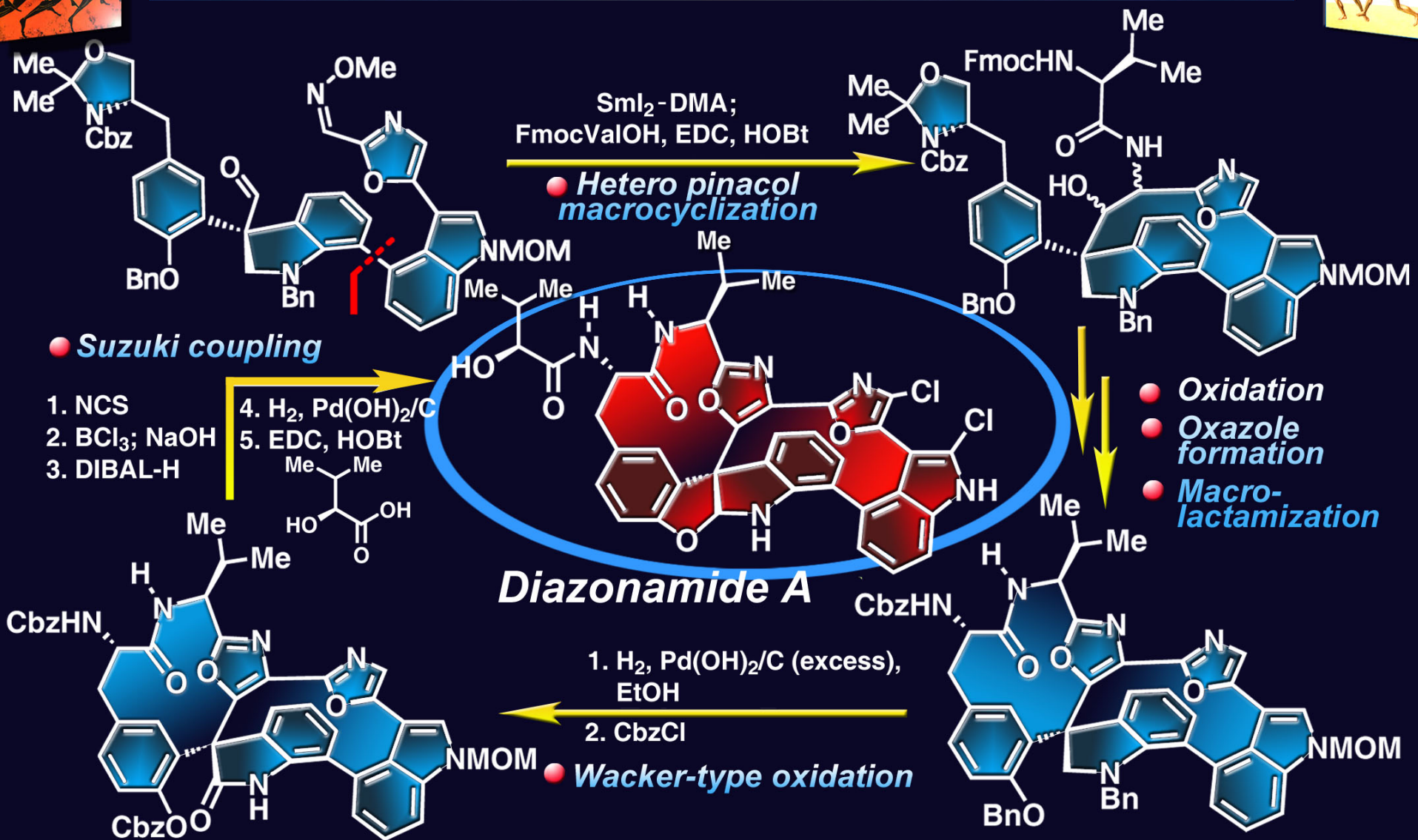


● The magic of the
olefin metathesis reaction





THE Sml_2 ROUTE TO DIAZONAMIDE A [2003]



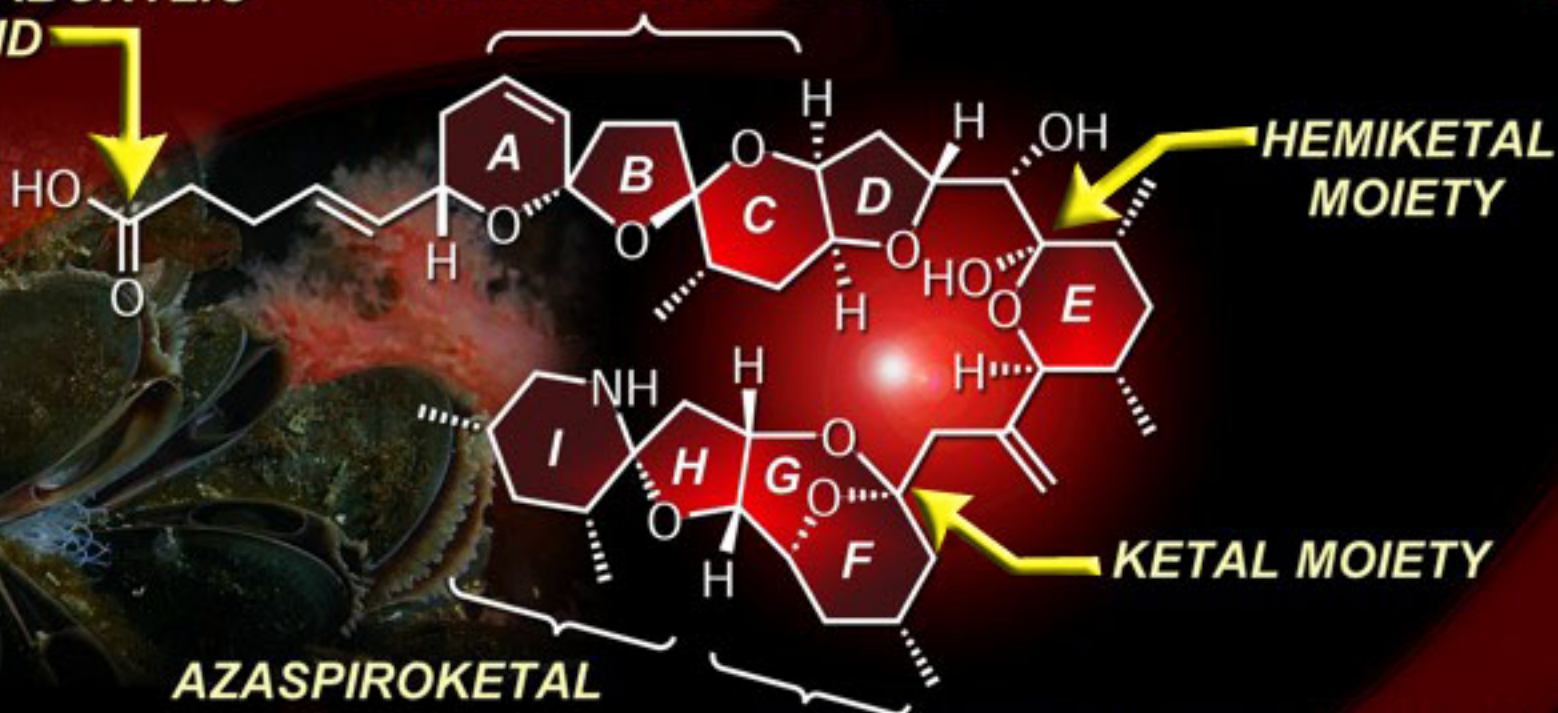


AZASPIRACID-1: PROPOSED STRUCTURE (1998)



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.

AZASPIRACID-1: PROPOSED STRUCTURE (1998)



CARBOXYLIC
ACID

TRIOXADISPIROKETAL

HEMIKETAL
MOIETY

KETAL MOIETY

2,9-DIOXACYCLO[3.3.1]NONANE

Killary Harbour, Ireland.

symptoms included vomiting, severe diarrhea.
ings and twenty stereocenters.
eochemistry between the ABCDE and FGHI

Satake, M.,
Soc. 1998. 120. 5

., Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. J. Am. Chem.

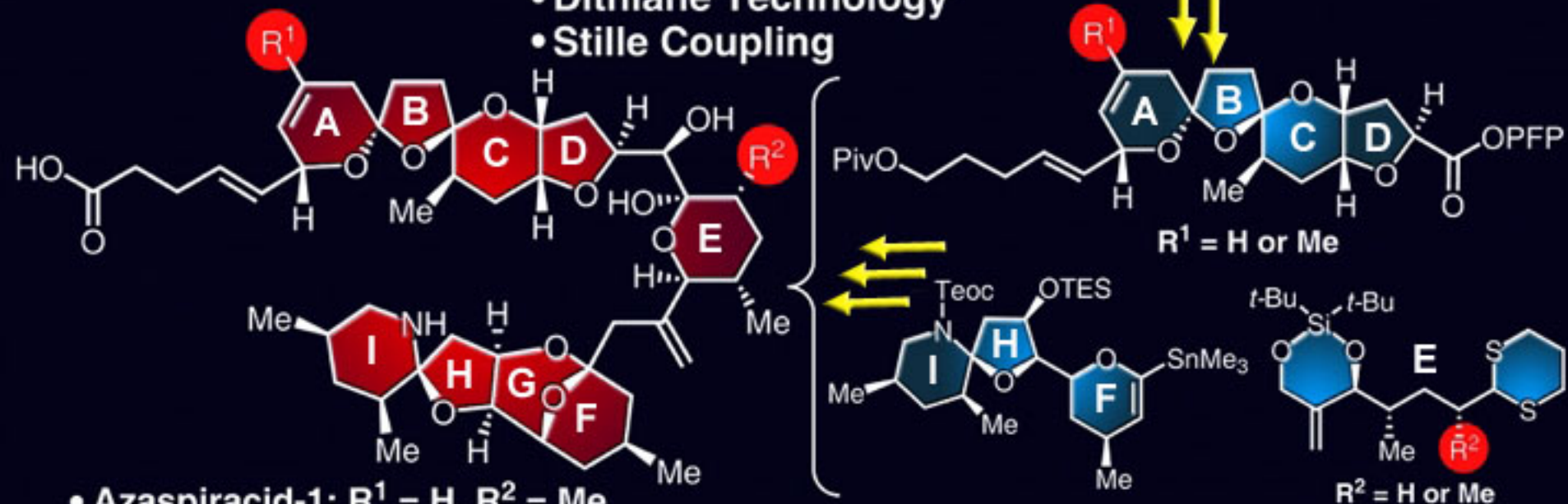
TOTAL SYNTHESIS OF AZASPIRACIDS -1, -2, AND -3 [2006]



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

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

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



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

$R^2 = \text{H or Me}$

- 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

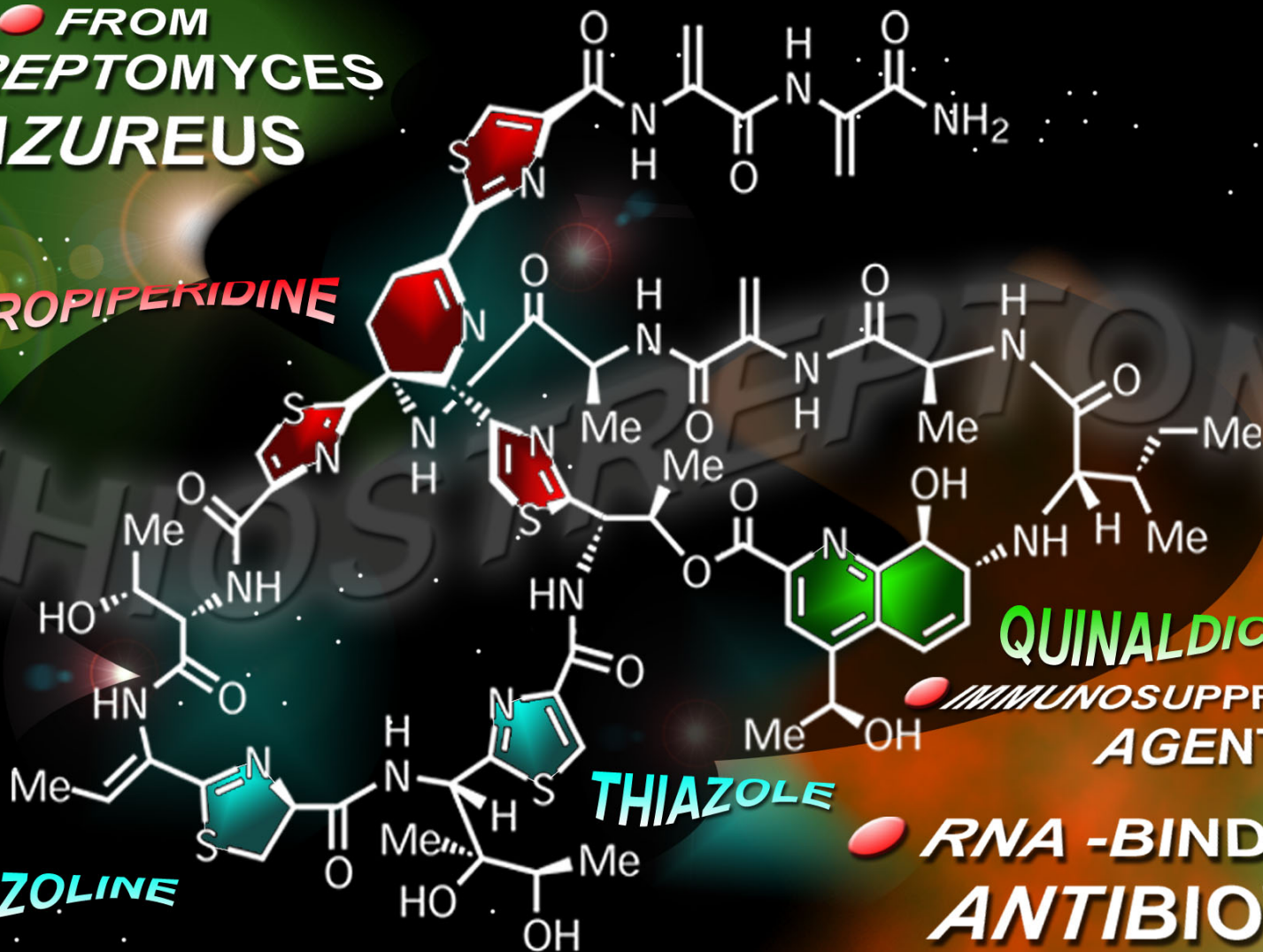
THIAZOLINE

THIAZOLE

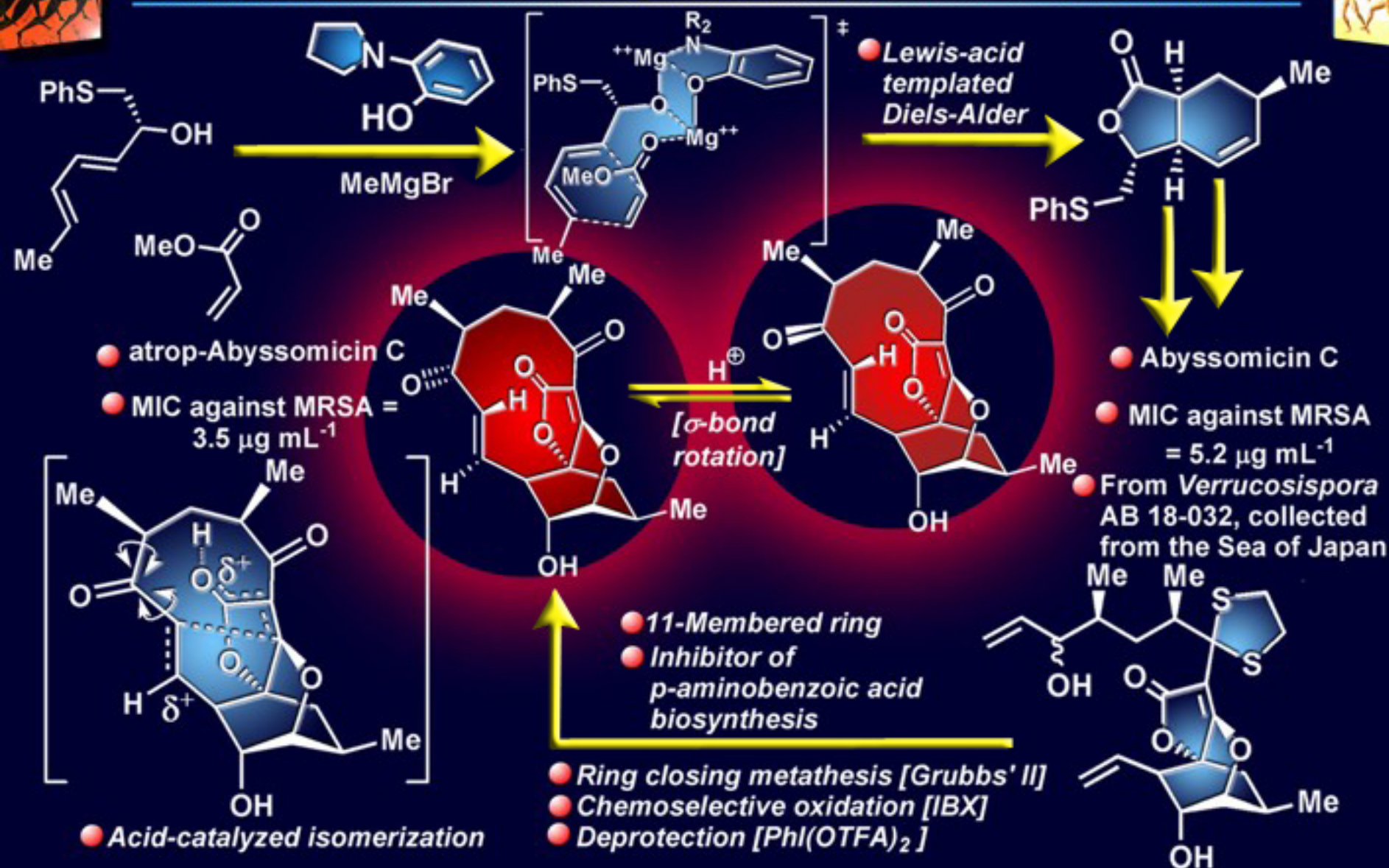
QUINALDIC ACID

IMMUNOSUPPRESSIVE
AGENT

RNA-BINDING
ANTIBIOTIC

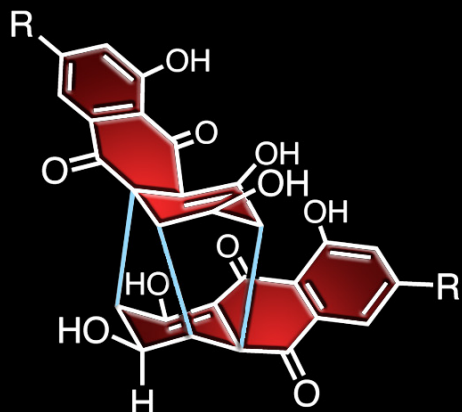


TOTAL SYNTHESIS OF ABYSSOMICIN C AND ATROP-ABYSSOMICIN C



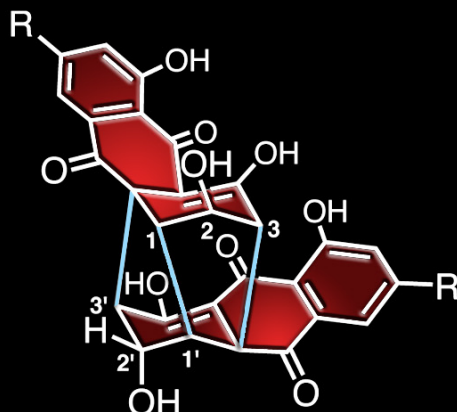


SELECTED NATURALLY OCCURRING BISANTHRAQUINONES -DNA INTERACTING CYTOTOXIC AGENTS (2006-2007)



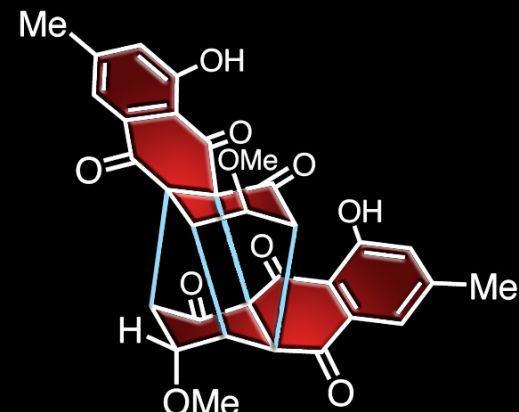
Ia: R = OMe: (+)-cytoskyrin A

Ib: R = Me: (+)-graciliformin

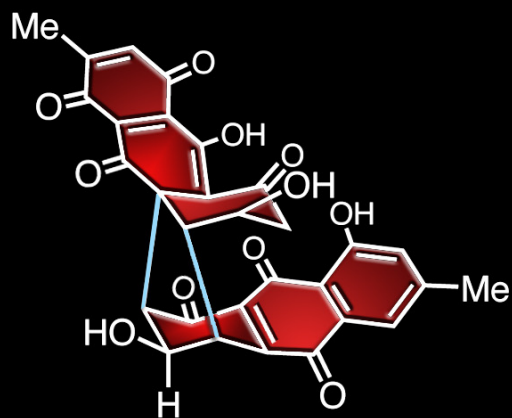


IIa: R = OMe: (+)-2,2'-*epi*-cytoskyrin A

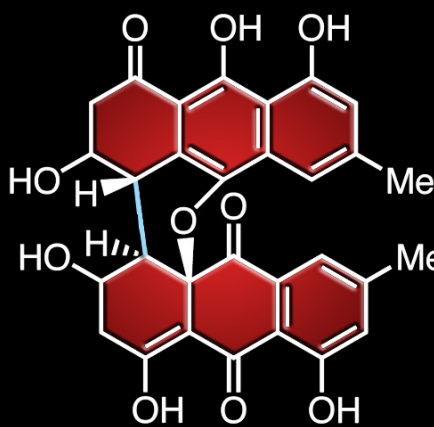
IIb: R = Me: (+)-rugulosin (also anti-HIV)



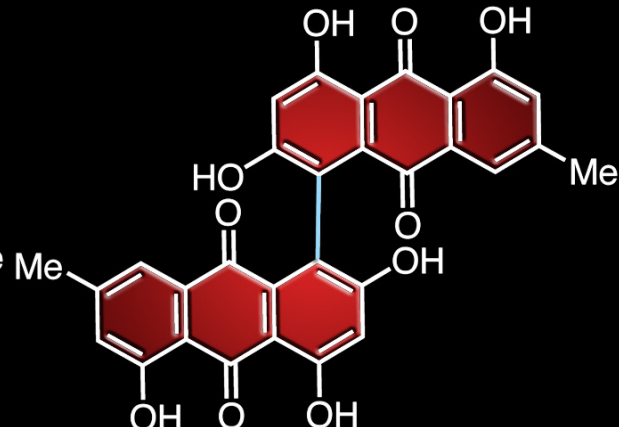
III: rugulin (also antibiotic)



IV: deoxyrubroskyrin



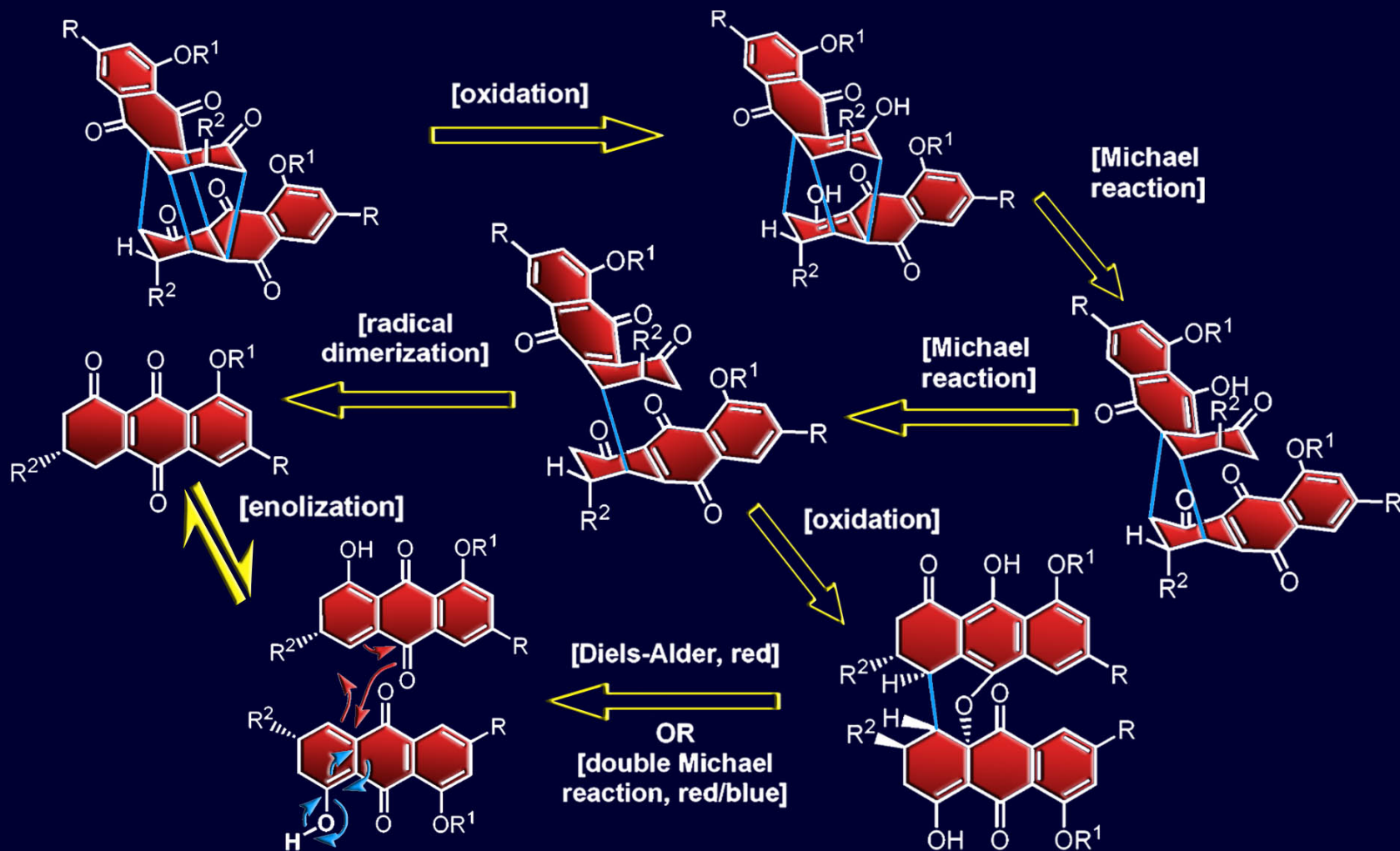
IV: flavoskyrin



V: skyrin



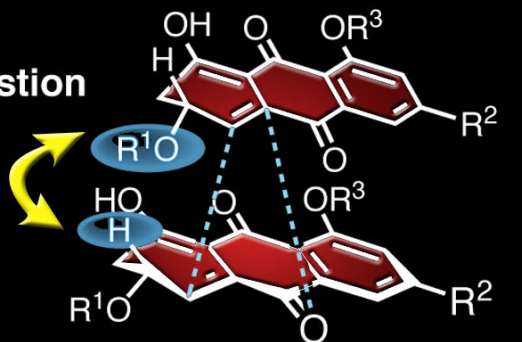
GENERAL RETROSYNTHETIC ANALYSIS OF MODIFIED BISANTHRAQUINONES



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

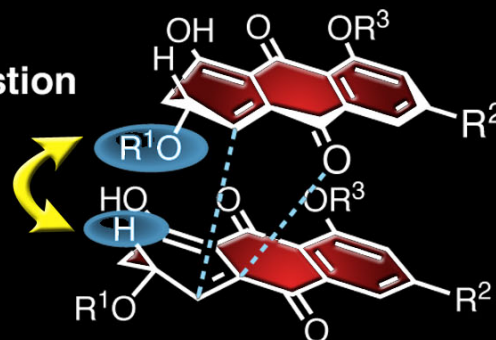


● Steric congestion



A: endo-bottom arrangement

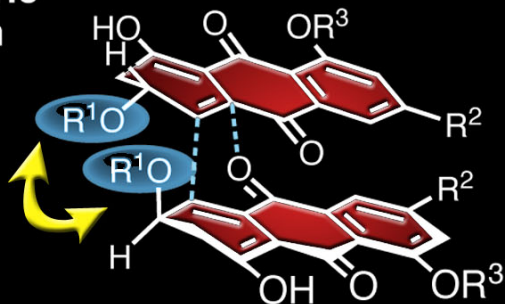
● Steric congestion



B: endo-top arrangement

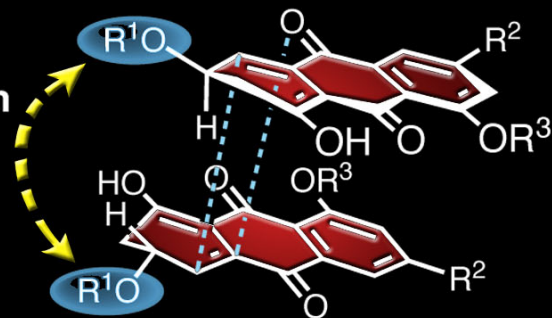


● Severe steric congestion



C: exo-syn arrangement

● Favored orientation

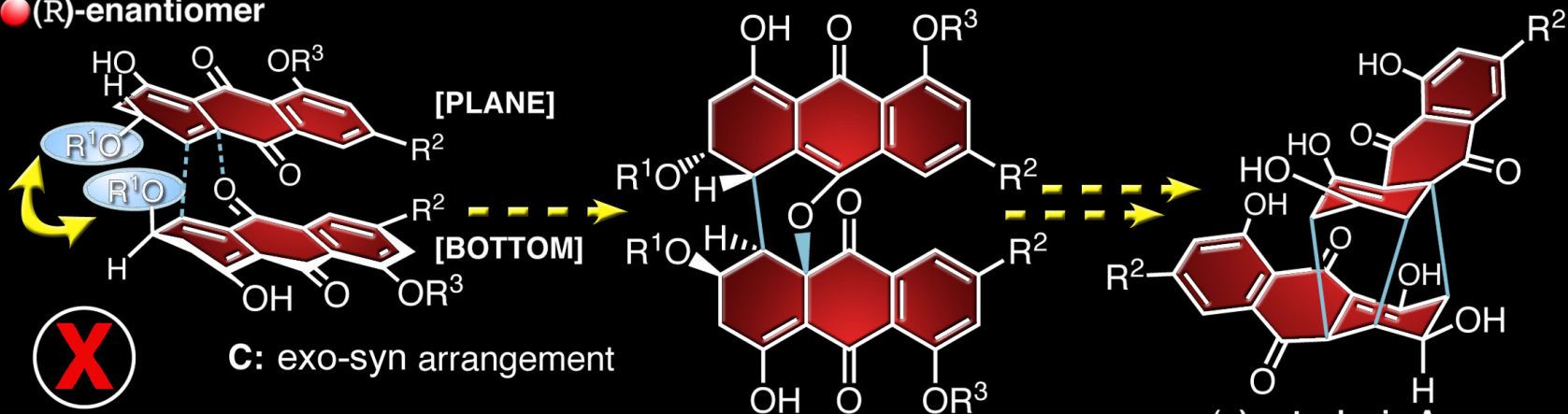


D: exo-anti arrangement



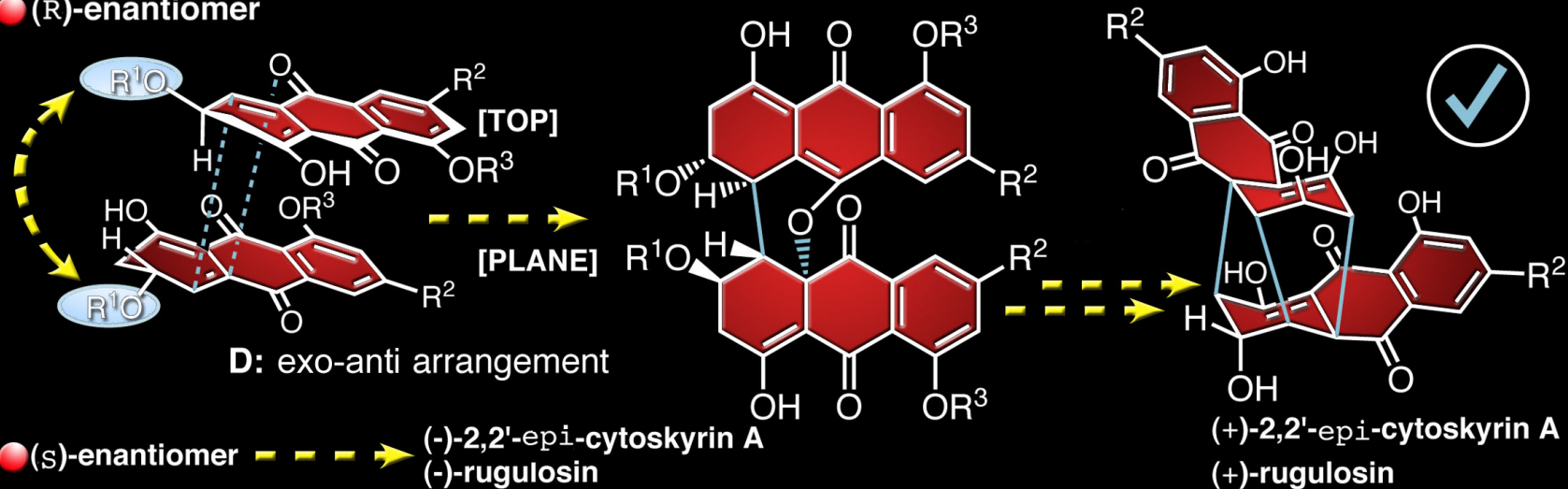
THE INTRIGUING STEREOCHEMICAL ASPECTS OF THE DIMERIZATION STEP

● (R)-enantiomer



● (S)-enantiomer $\dashrightarrow$ (+)-cytoskyrin A
(+)-graciliformin

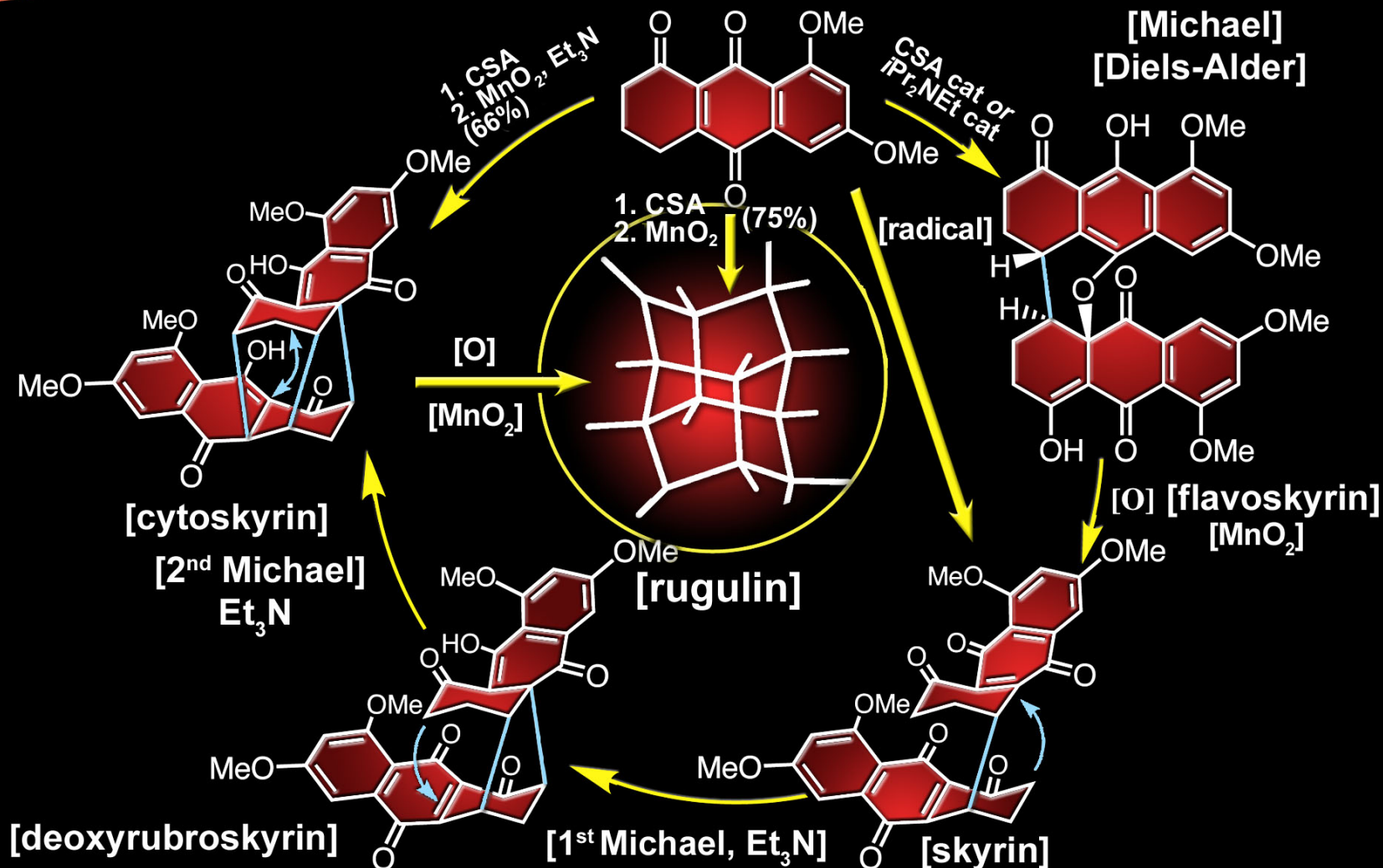
● (R)-enantiomer



● (S)-enantiomer $\dashrightarrow$ (-)-2,2'-epi-cytoskyrin A
(-)-rugulosin

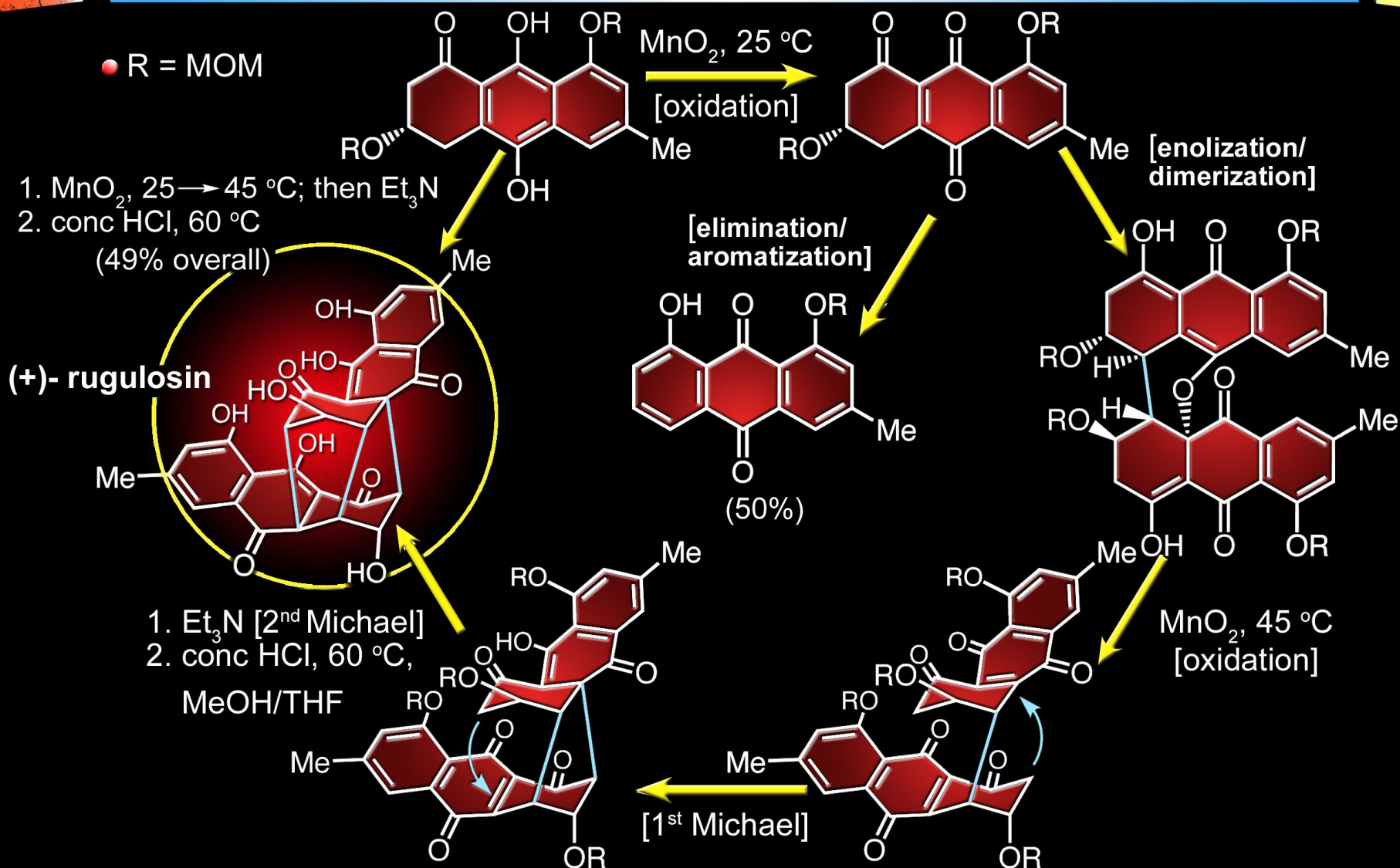


THE CYTOSKYRIN CASCADE: MODEL SYSTEMS



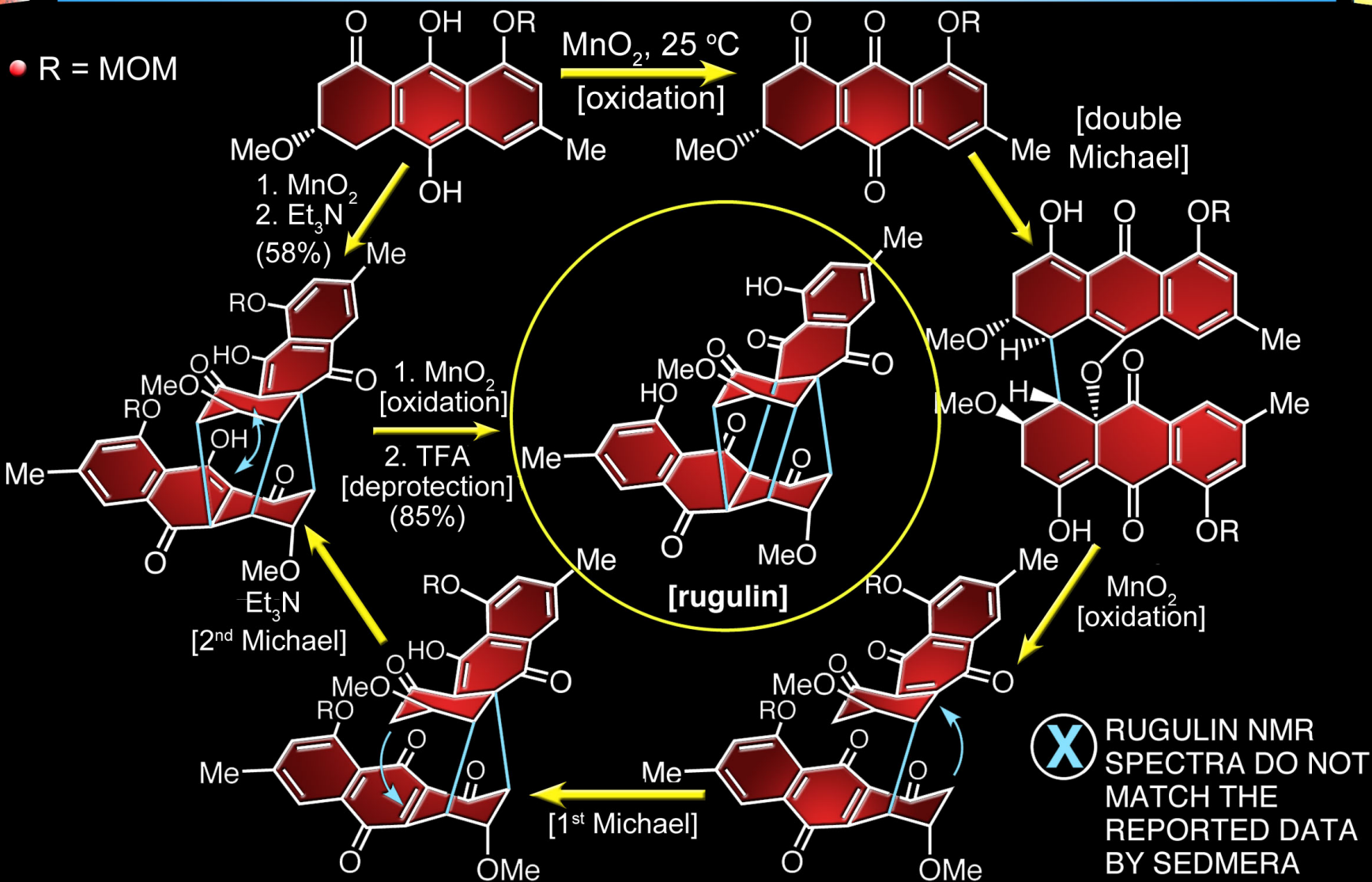
TOTAL SYNTHESIS OF (+)- RUGULOSIN

● R = MOM



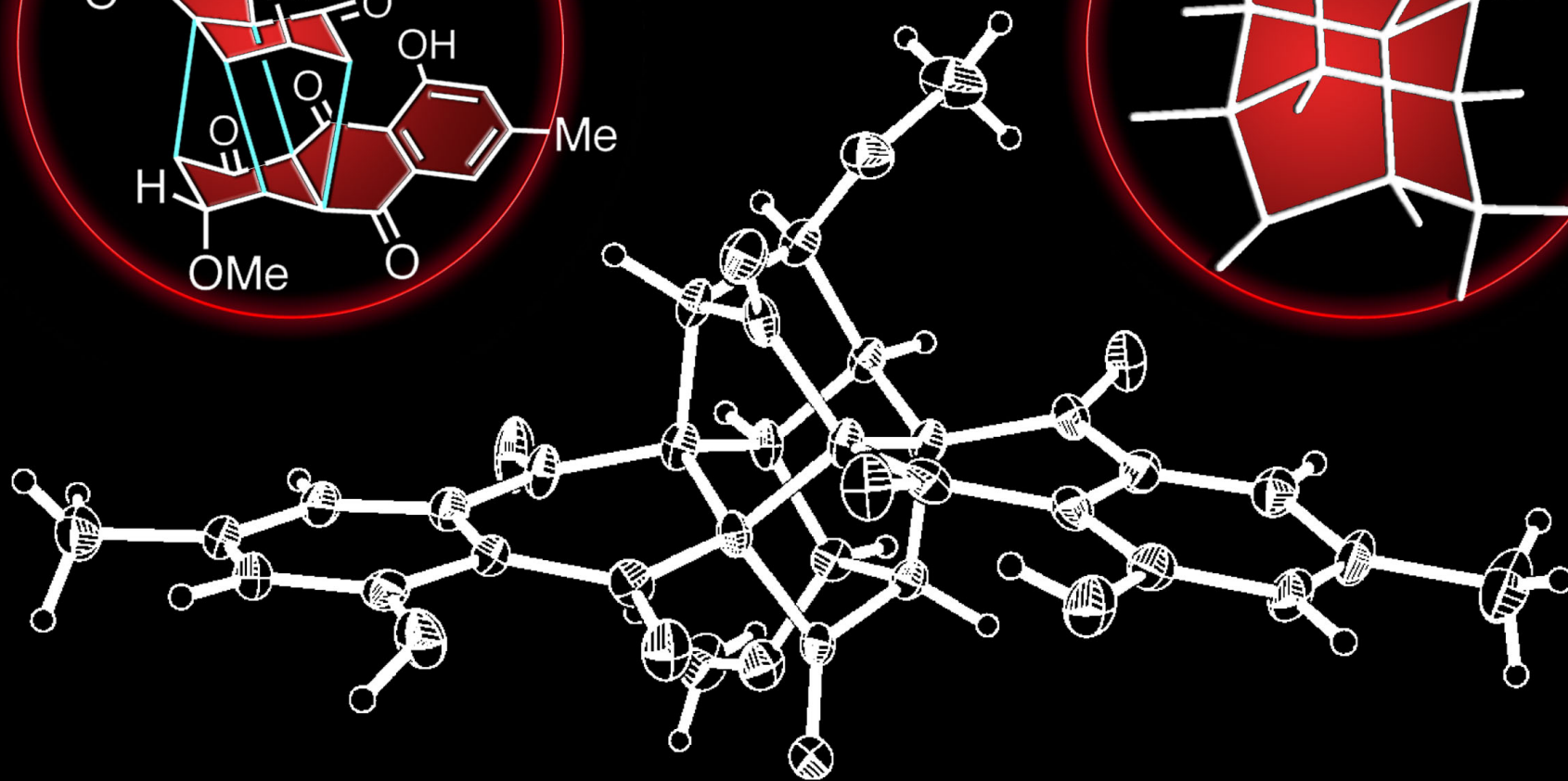
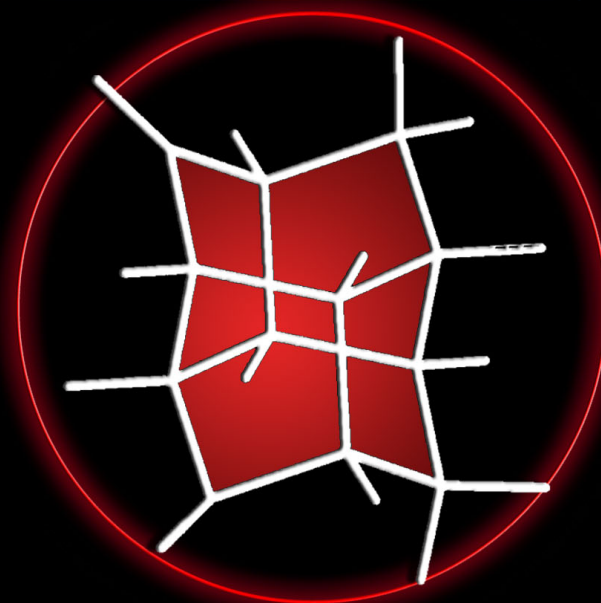
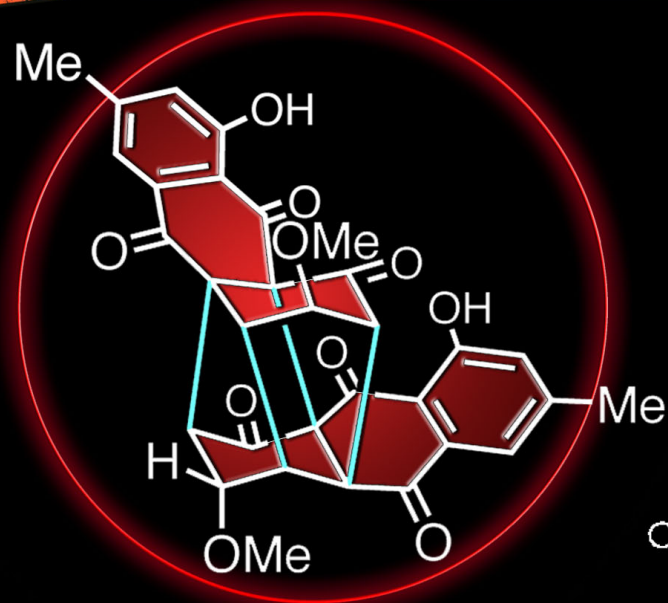


THE RUGULIN CASCADE: STRUCTURE PROVEN WRONG [2006]





X-RAY STRUCTURE OF THE ALLEGED STRUCTURE OF RUGULIN

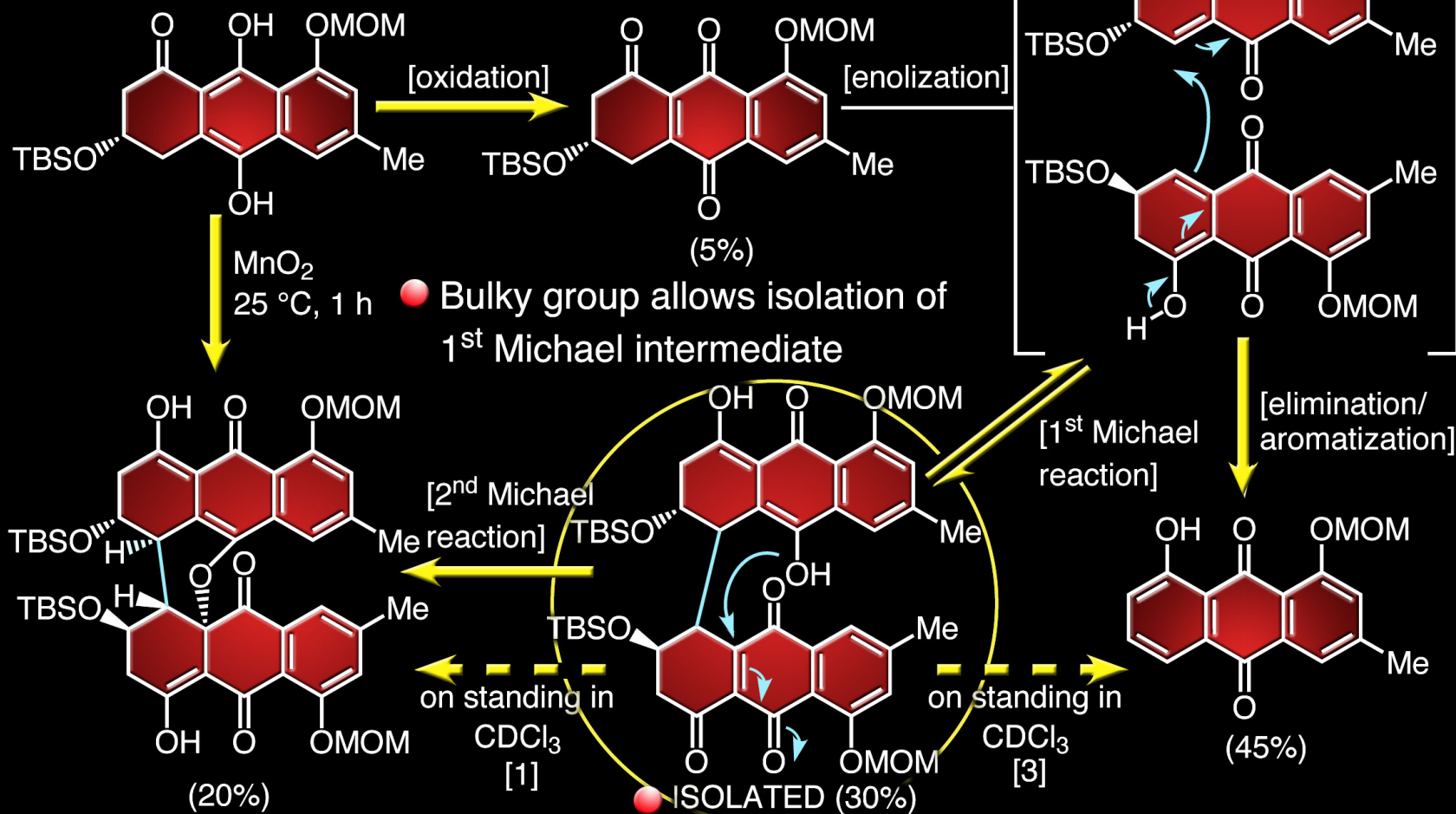




MECHANISTIC ASPECTS OF THE DIMERIZATION STEP-ISOLATION OF 1ST MICHAEL INTERMEDIATE



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



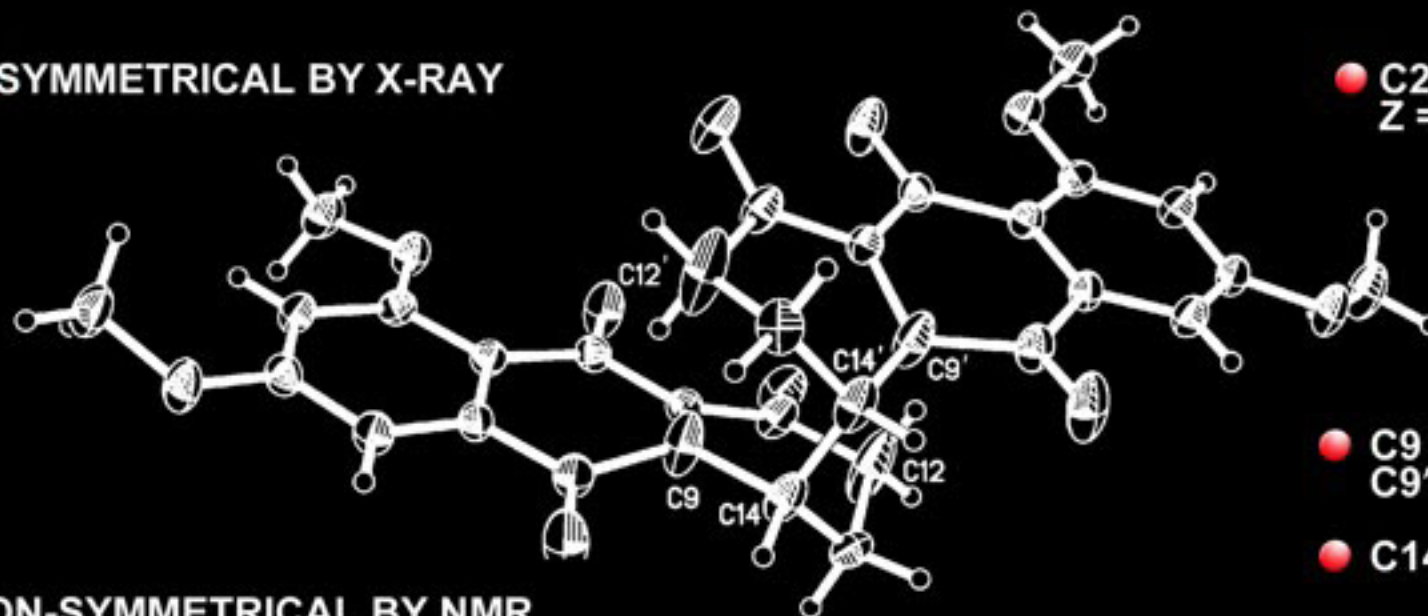


DEOXYRUBROSKYRIN MODEL: A CASE OF BOND MIGRATION? [MISLEADING X-RAY STRUCTURE]



● SYMMETRICAL BY X-RAY

● C2/c space group
 $Z = 4$



● $C9 - C12' =$
 $C9' - C12 = 2.372 \text{ \AA}$

● $C14 - C14' = 1.56 \text{ \AA}$

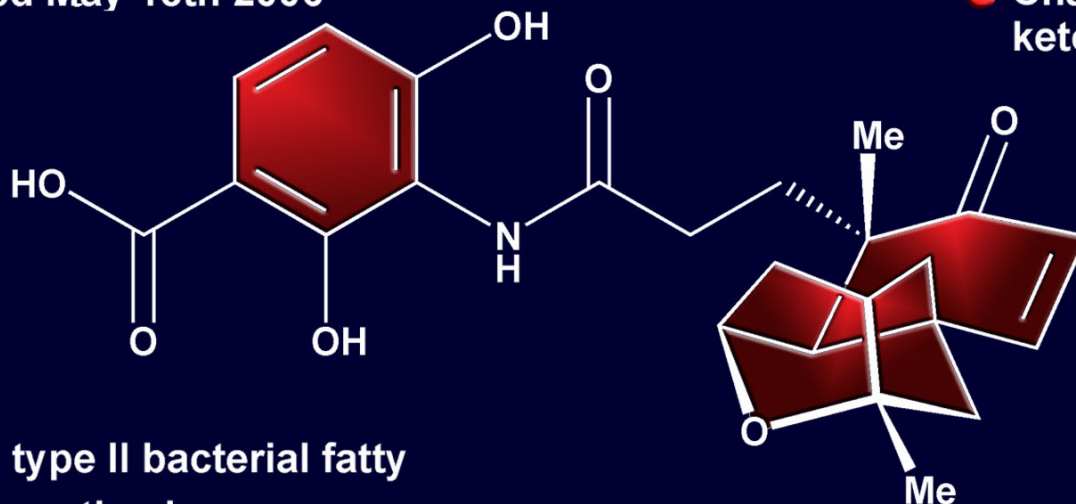
● NON-SYMMETRICAL BY NMR





PLATENSIMYCIN: DISCOVERY AND BIOLOGICAL PROPERTIES

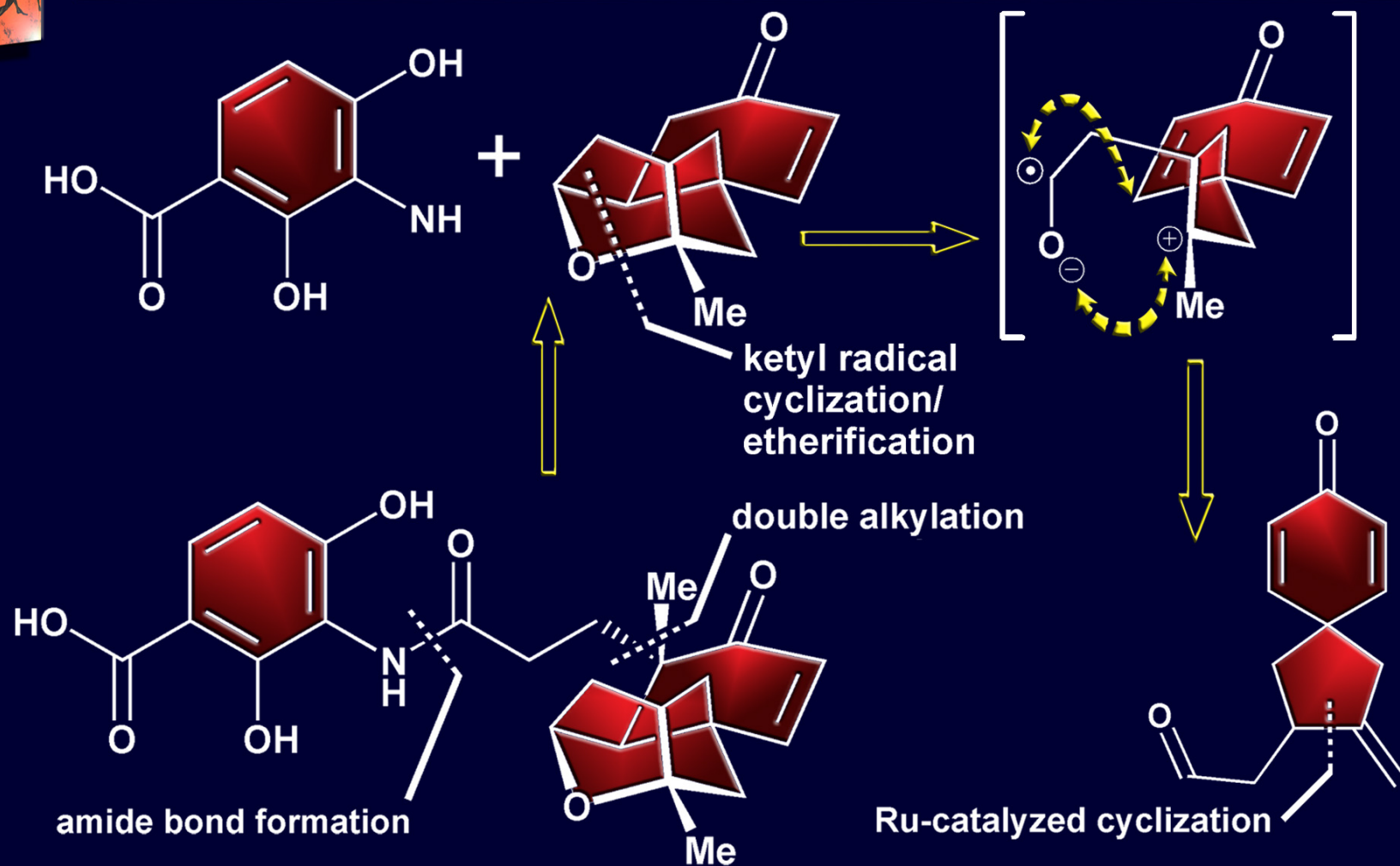
- Isolated by Merck from a *Streptomyces platensis* strain collected in South Africa
- Reported May 18th 2006
- Two structural domains:
 - Polar aromatic amino acid
 - Challenging pentacyclic ketolide



- Inhibits type II bacterial fatty acid biosynthesis
- Binds the acyl protein intermediate of the FabF enzyme
- Active *in vitro* against a broad spectrum of Gram-positive pathogens including methicillin and vancomycin resistant strains
- Effective *in vivo* - clears MRSA infection from mice
- No mammalian toxicity observed



TOTAL SYNTHESIS OF PLATENSIMYCIN: RETROSYNTHESIS (2006)

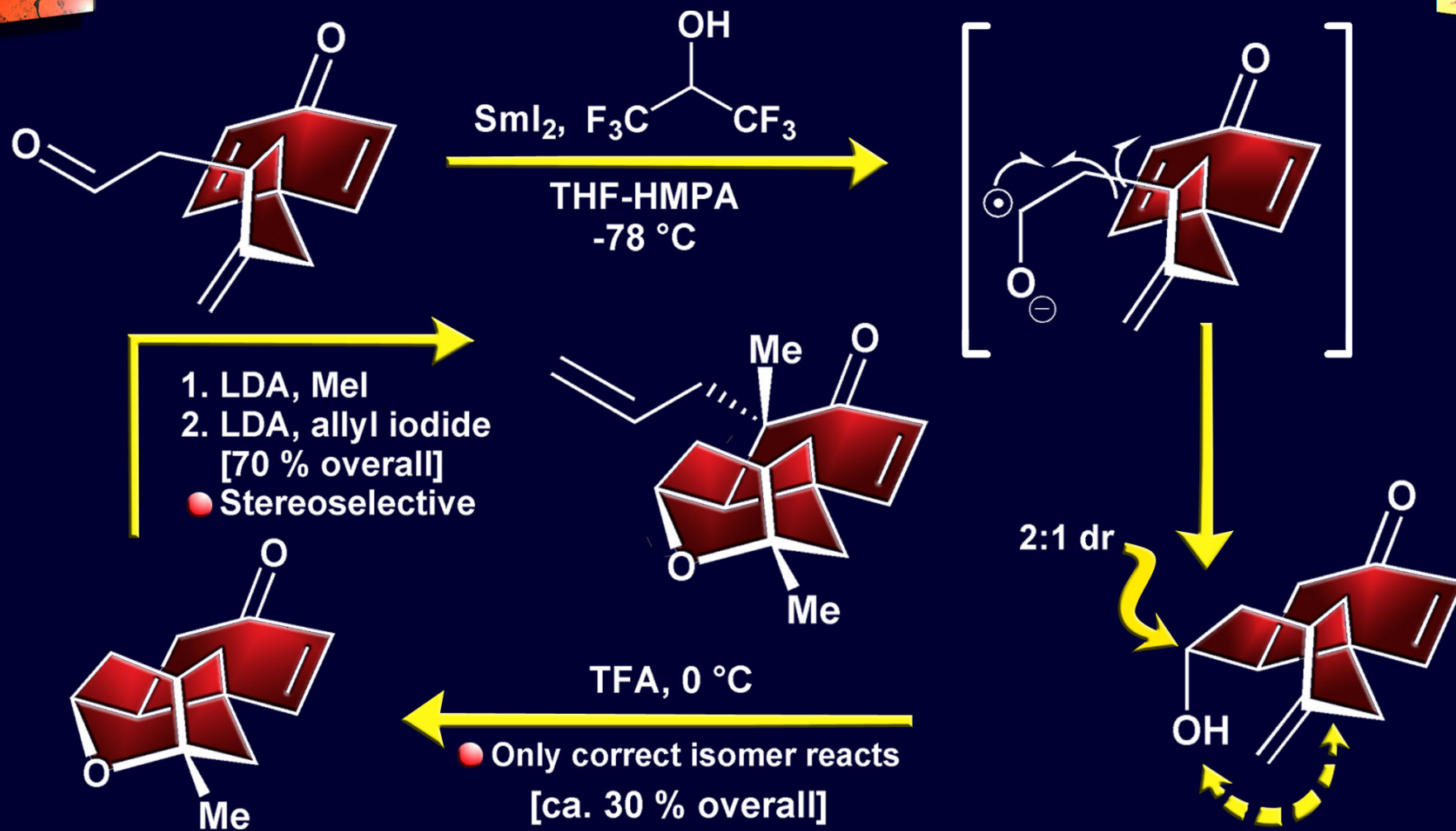


K. C. Nicolaou, A. Li, D. J. Edmonds, *Angew. Chem. Int. Ed.* **2006**, 45, 7086–7090.

K. C. Nicolaou, David J. Edmonds, Ang Li, and G. Scott Tria, *Angew. Chem Int. Ed.* **2007**, 46, 3942–3945



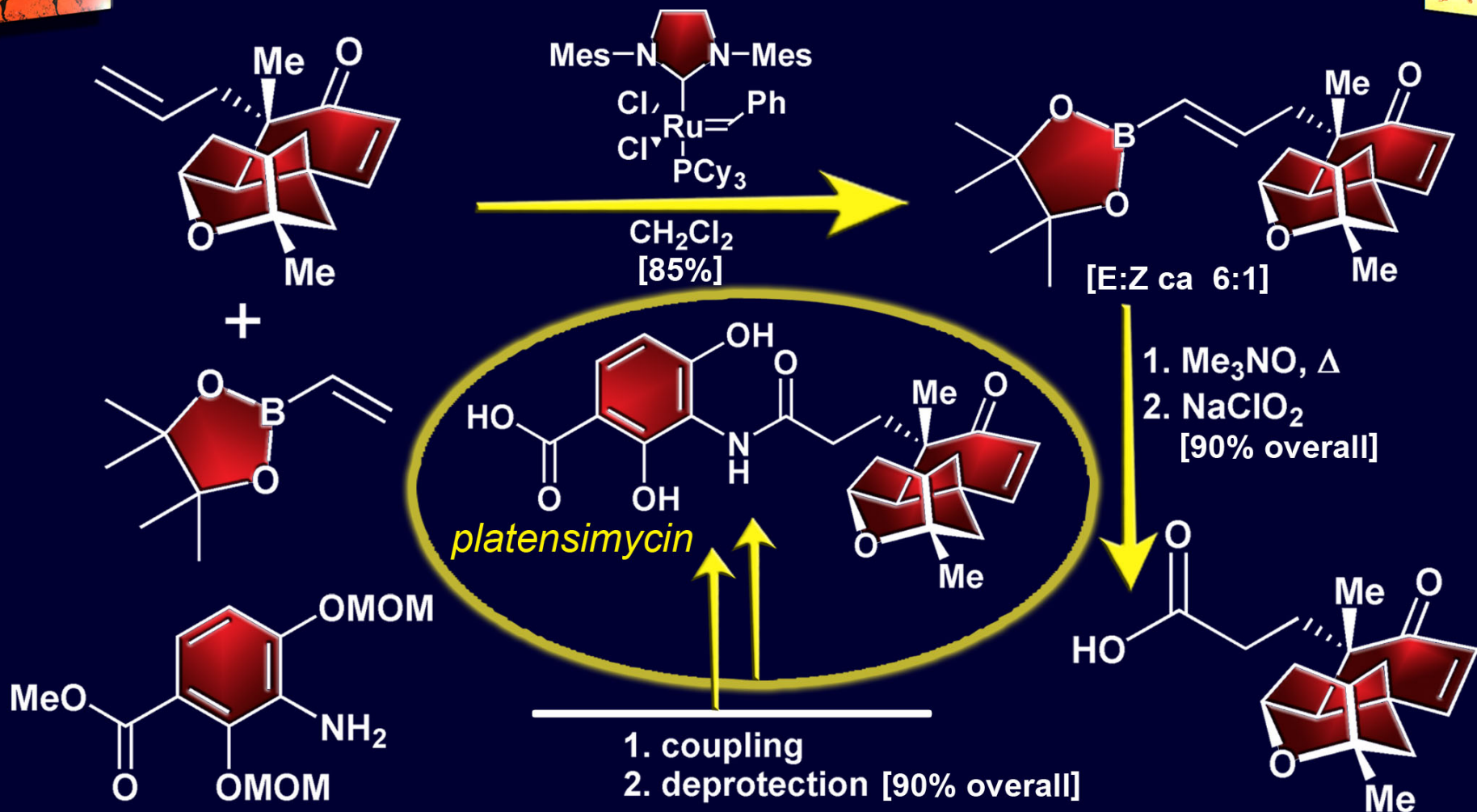
TOTAL SYNTHESIS OF PLATENSIMYCIN: CAGE-LIKE CORE



J.-L. Namy, P. Girard, H. B. Kagan, *New J. Chem.* **1977**, 1, 5 7.

H. B. Kagan, *Tetrahedron* **2003**, 59, 10351 10327.

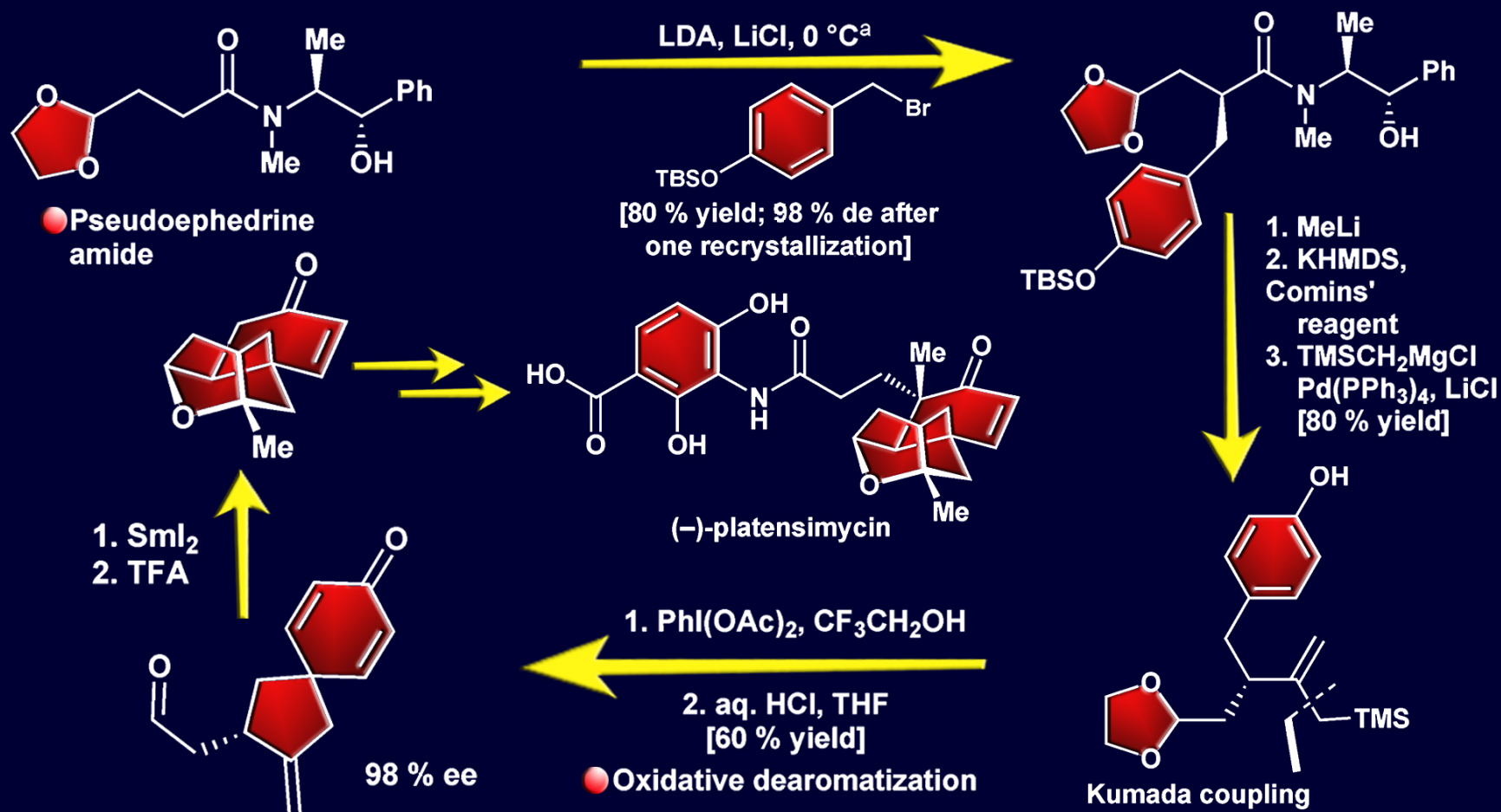
TOTAL SYNTHESIS OF PLATENSIMYCIN





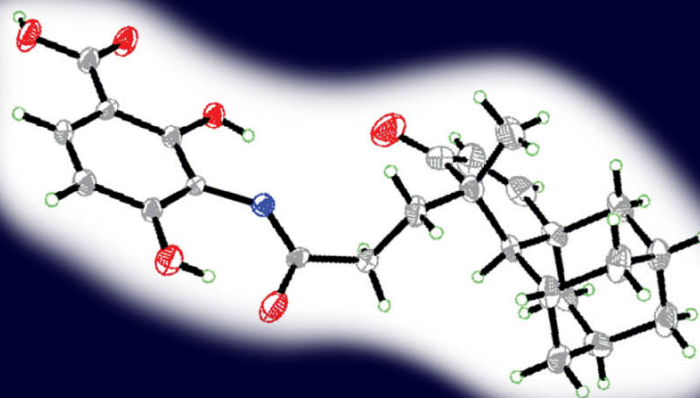
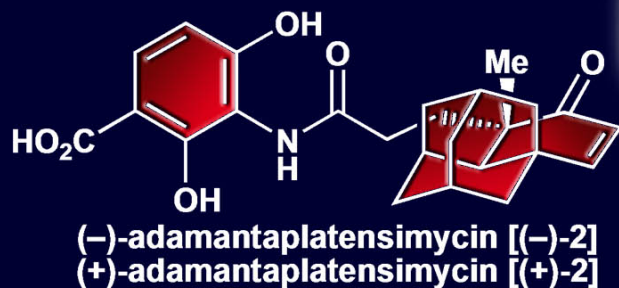
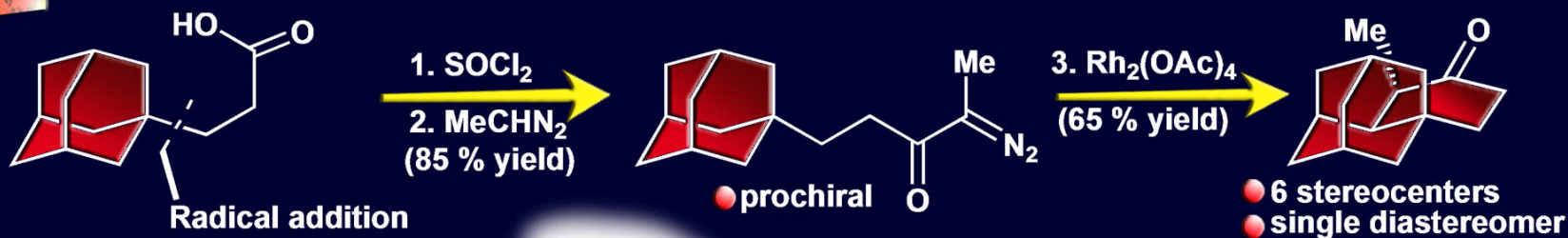


ASYMMETRIC TOTAL SYNTHESIS OF PLATENSIMYCIN – CHIRAL AUXILLARY



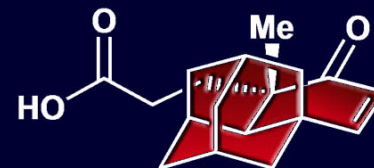
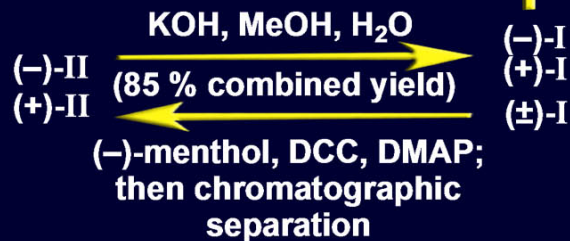
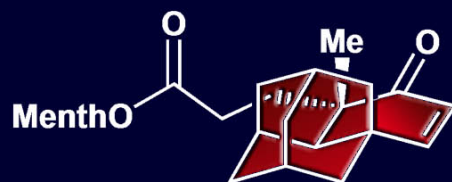
a. A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky,
J. L. Gleason, *J. Am. Chem. Soc.* **1997**, 119, 6496-6511

ADAMANTAPLATENSIMYCIN



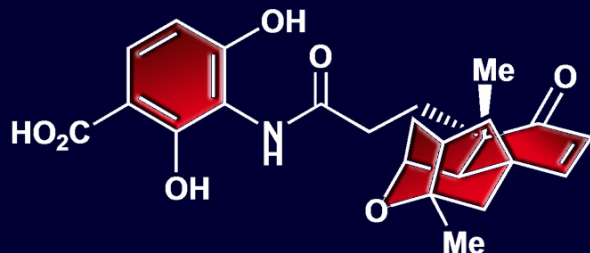
9. Coupling
10. Deprotection
(65 % yield)

4. LDA, PhSeBr;
 H_2O_2
5. KHMDS, allyl
iodide
6. Cross-metathesis
7. Me_3NO
8. NaClO_2
(57 % yield)

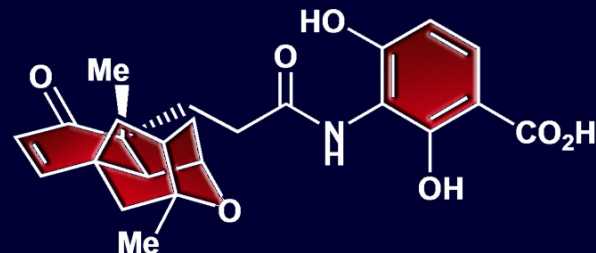




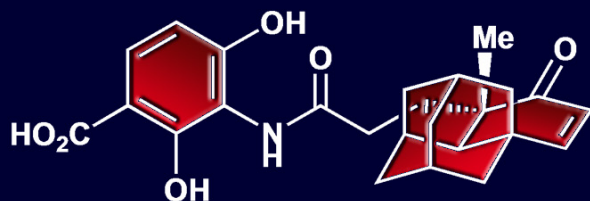
ANTIBACTERIAL ACTIVITY OF ADAMANTAPLATENSIMYCIN (2007)



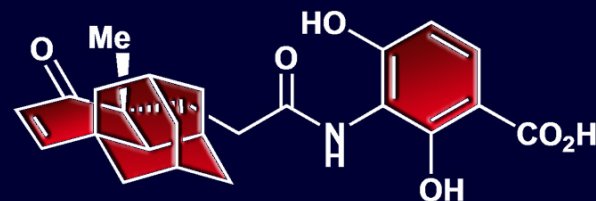
(-)-1: platensimycin



(+)-1: *ent*-platensimycin



(-)-2: adamantaplatensimycin



(+)-2: *ent*-adamantaplatensimycin

Table 1. Minimum inhibitory concentration (MIC) values ($\mu\text{g/mL}$) of (+)-, (?)-, and ($\pm$)-adamantaplatensimycins [(+)-2, (+)-2, and ($\pm$)-2] against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VREF), and *E. coli*, respectively.

	(+)-2	(-)-2	($\pm$)-2	(-)-1	($\pm$)-1
MRSA	> 88	1.3–1.8	2.6–3.6	0.2–0.4	0.4–0.8
VREF	> 88	1.3–1.8	2.6–3.6	0.4–0.8	0.8–1.6
<i>E. coli</i>	> 88	> 88	> 88	> 88	> 88



UNCIALAMYCIN: STRUCTURE



1a: 26(S)-uncialamycin

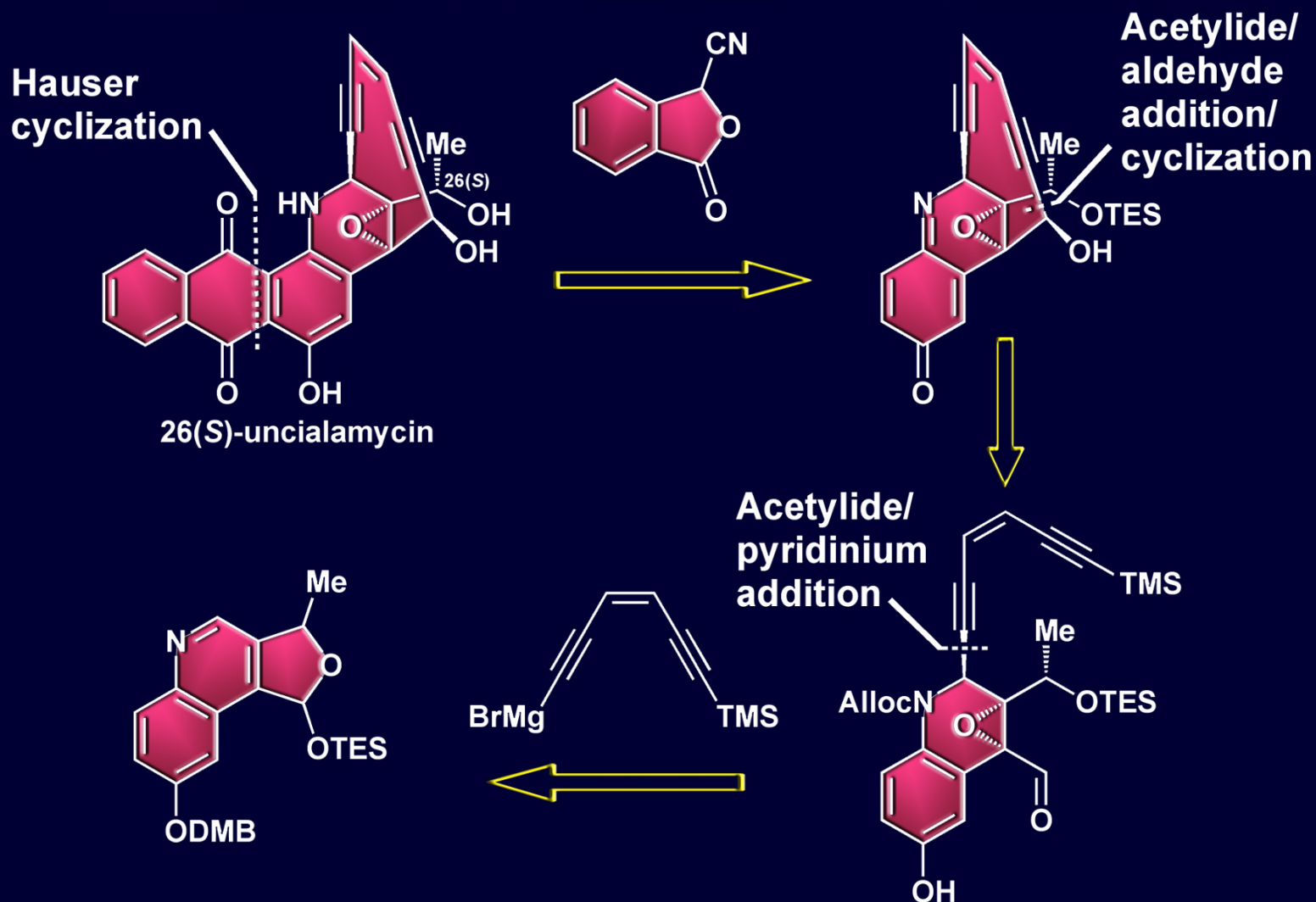


1b: 26(R)-uncialamycin

- Isolated from Streptomycete strain related to *Streptomyces cyanogenus*
- MIC = 0.0000064 $\mu\text{g/mL}$ against *Staphylococcus aureus*
MIC = 0.002 $\mu\text{g/mL}$ against *Escherichia coli*
MIC = 0.001 $\mu\text{g/mL}$ against *Burkholderia cepacia* complex
(Bcc; infects cystic fibrosis patients)
- Only 300 μg isolated.
- C-26 stereochemistry unassigned.

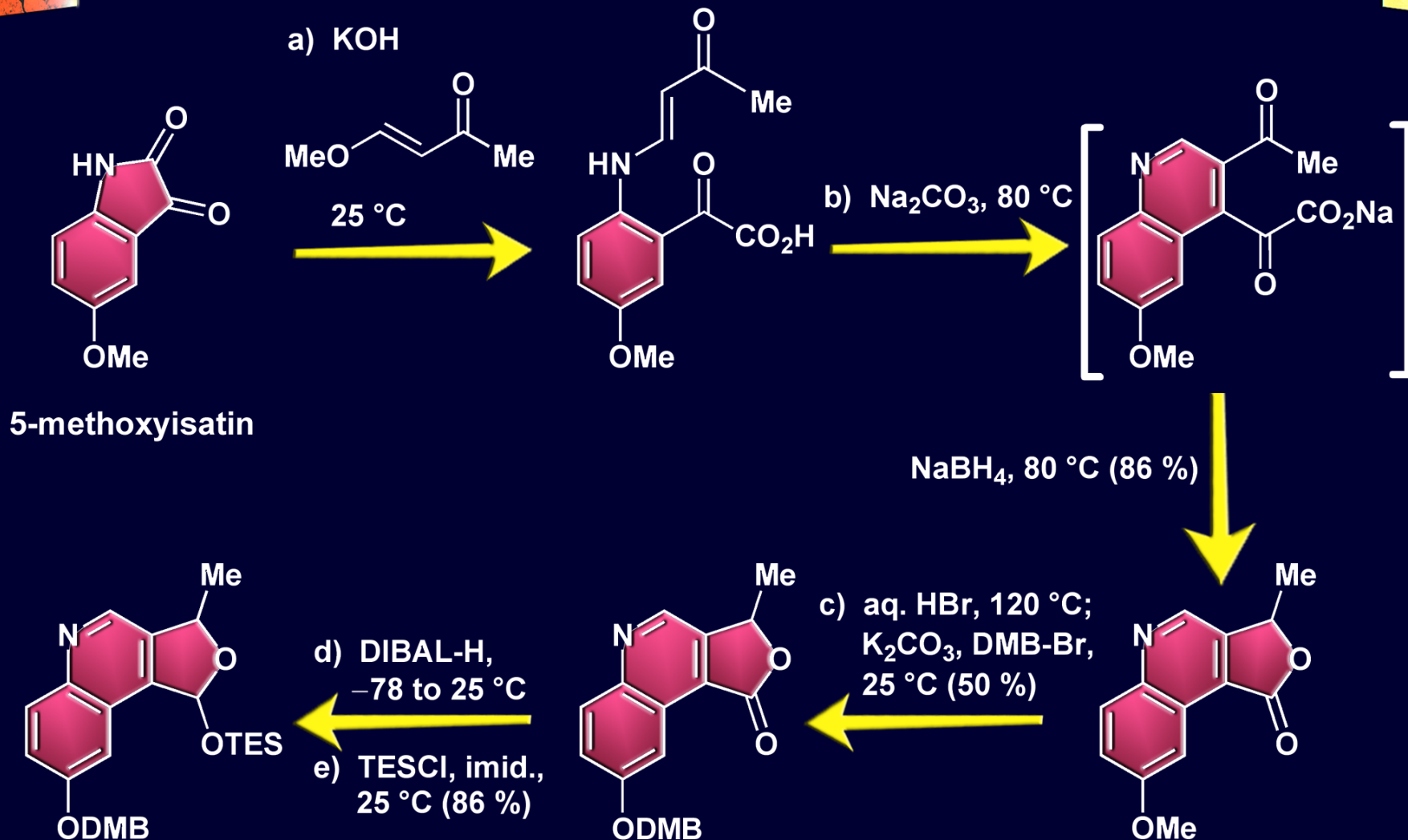


UNCIALAMYCIN: RETROSYNTHETIC ANALYSIS (2007)



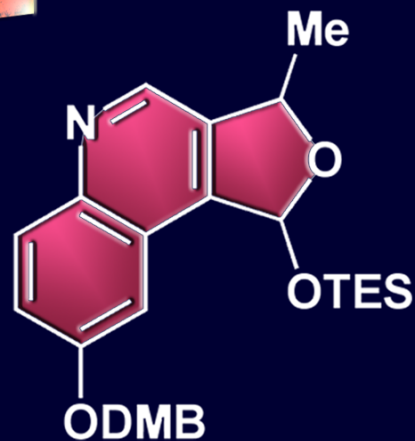


UNCIALAMYCIN TOTAL SYNTHESIS – 1





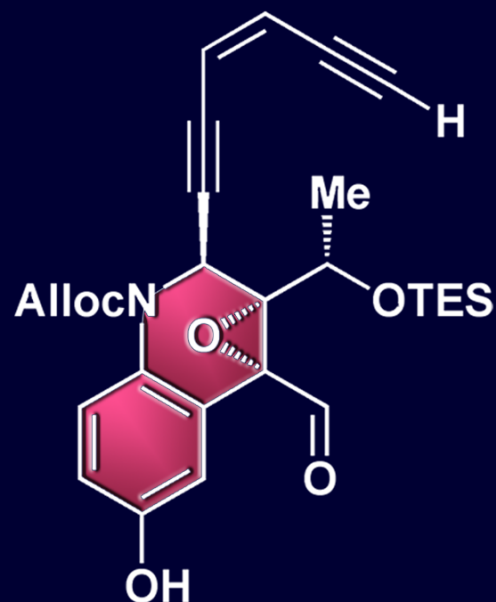
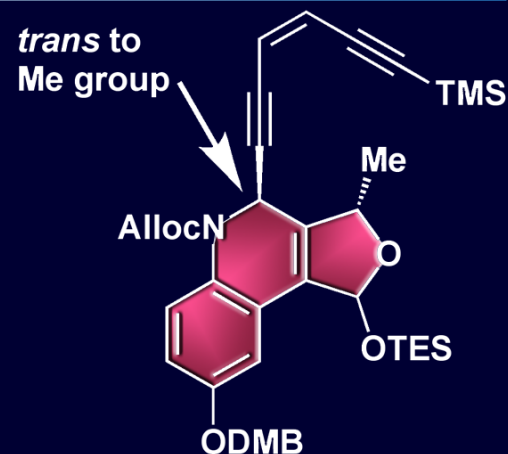
UNCIALAMYCIN TOTAL SYNTHESIS – 2



THF, 25 °C

ii. AllocCl, 25 °C

(92 %, 80 % conv.)



b) AcOH, 25 °C (91 %)

c) NaBH₄, 25 °C

f) TESCl, imid., 0 °C

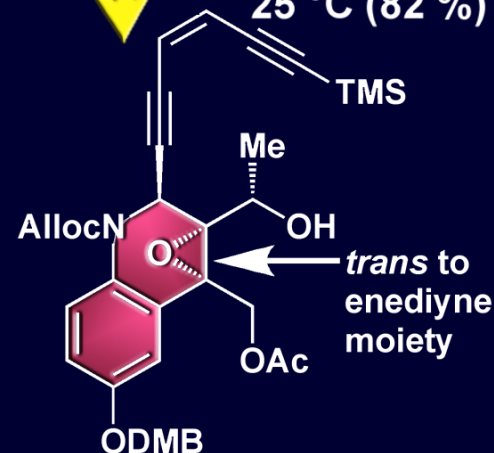
g) K₂CO₃, MeOH,
0 °C (78 %)

h) DMP, 25 °C (87 %)

i) DDQ, 25 °C (87 %)

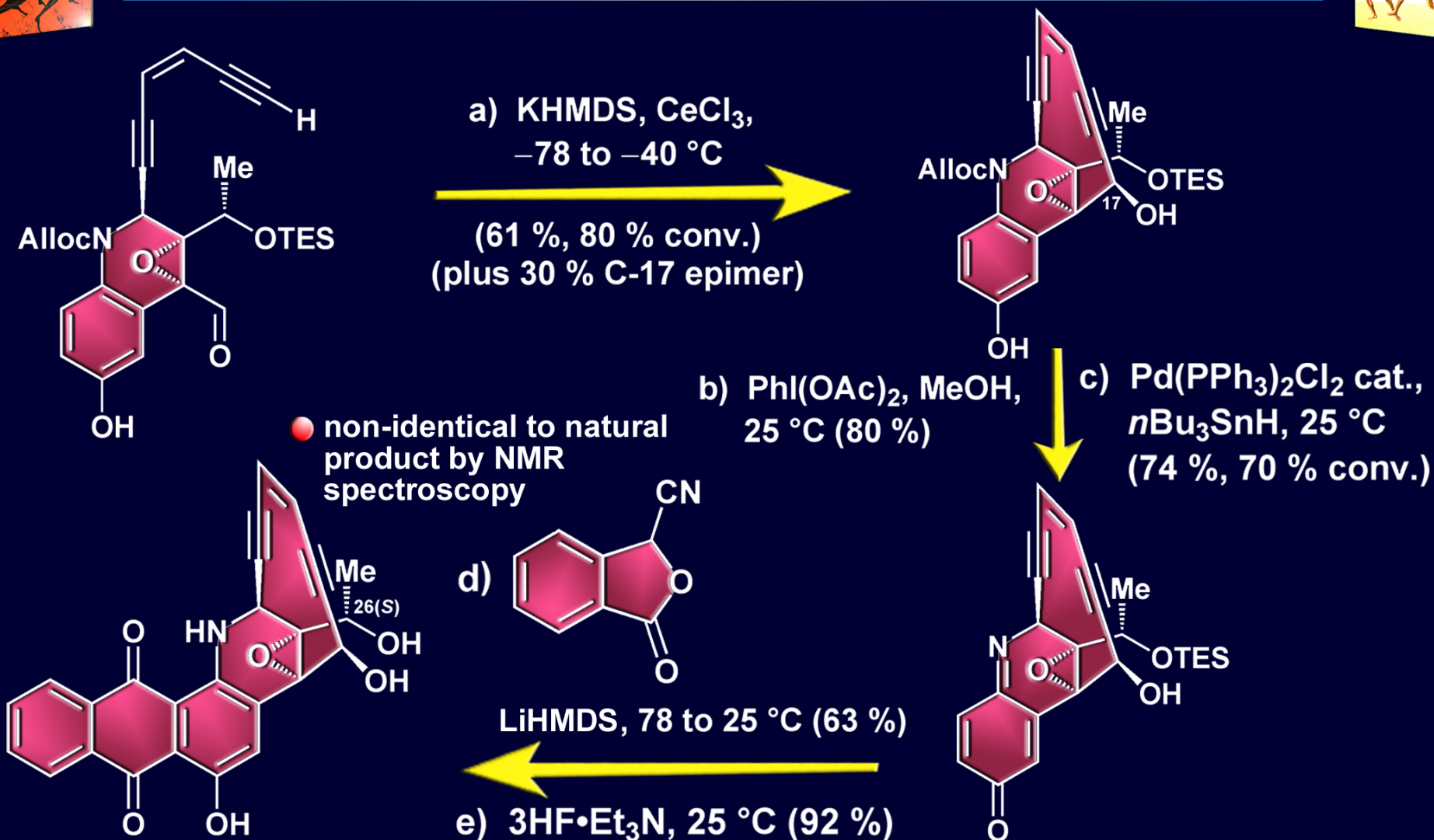
d) *m*-CPBA, 0 °C
(80 %)

e) AcCl, coll., 0 to
25 °C (82 %)





UNCIALAMYCIN TOTAL SYNTHESIS – 3

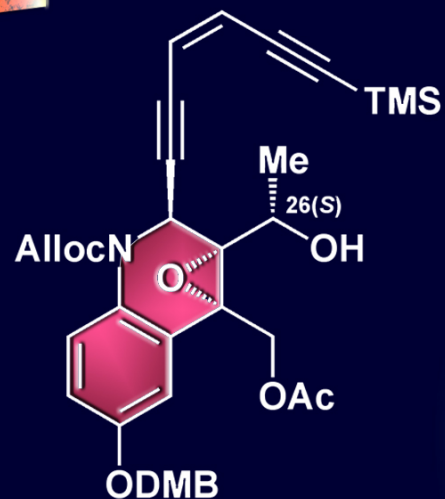




UNCIALAMYCIN TOTAL SYNTHESIS – 4



a) DMP, 25 °C (92 %)
b) NaBH₄, 25 °C (98 %)
(> 96 % d.r.)

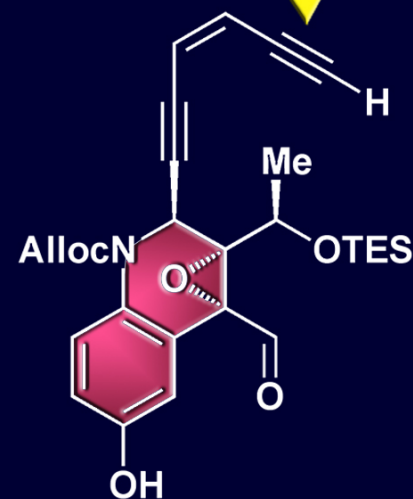
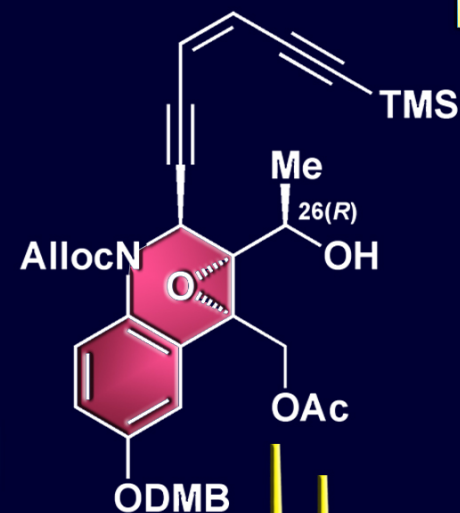
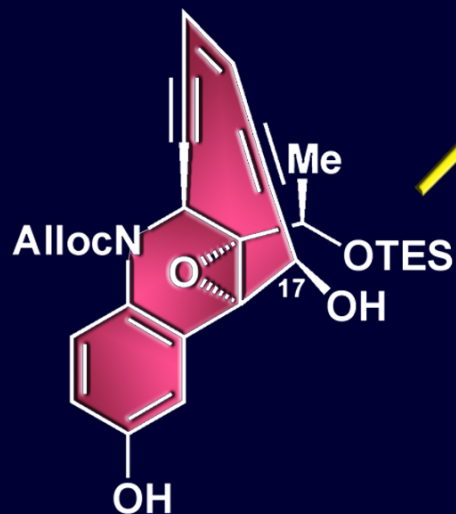


uncialamycin
● identical with
natural product

c) KHMDS, CeCl₃,
-78 to -40 °C (67 %)

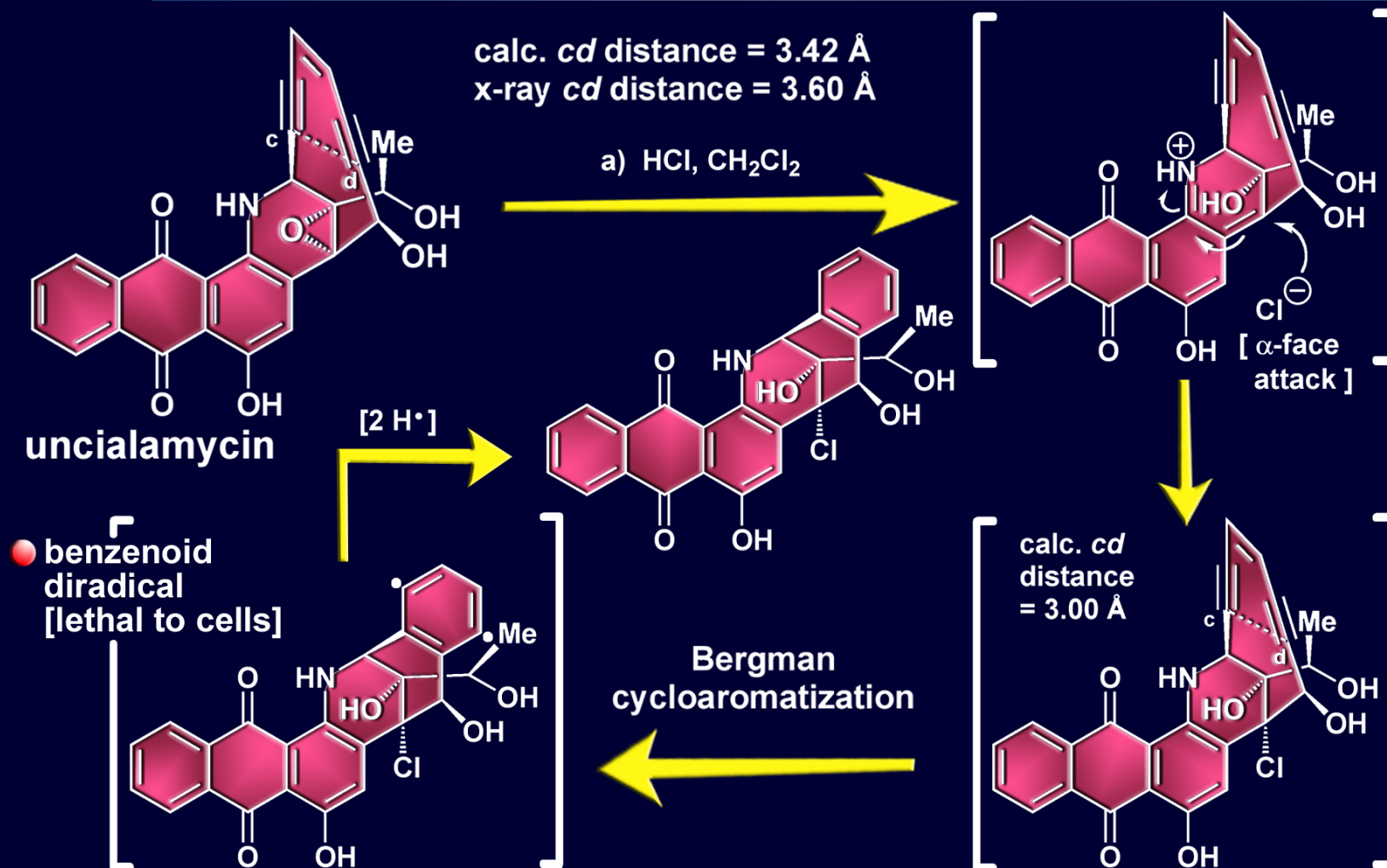


(plus 13 % C-17 epimer)



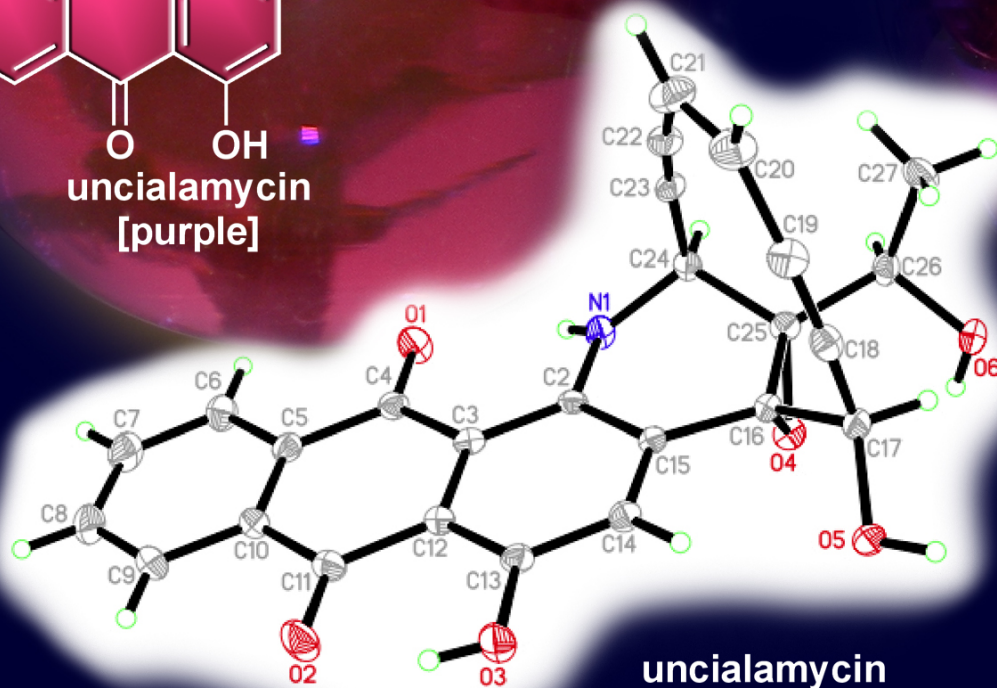
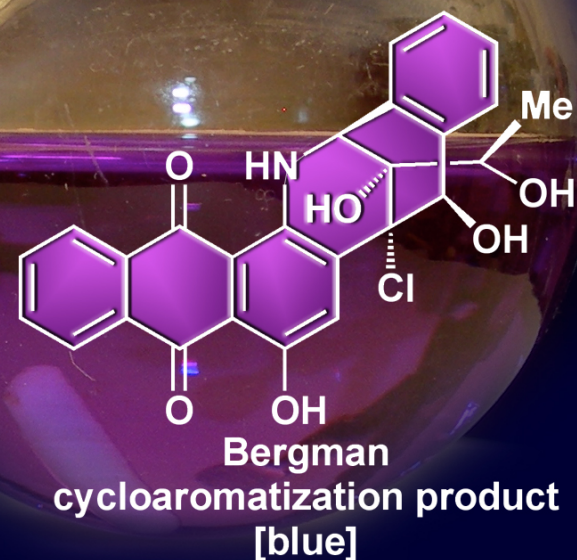


THE UNCIALAMYCIN CASCADE: BERGMAN CYCLOAROMATIZATION



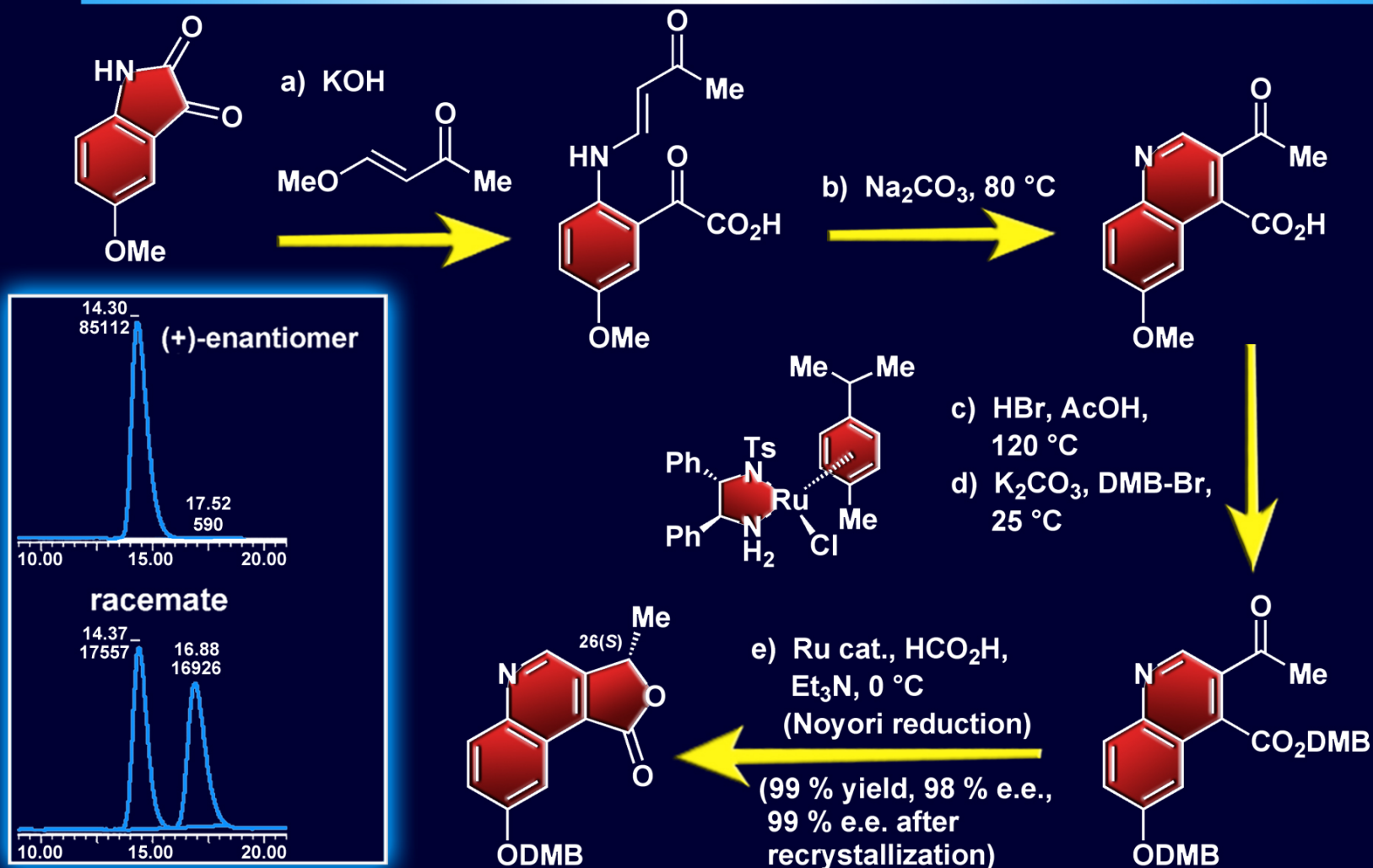


UNCIALAMYCIN: X-RAY STRUCTURE





CATALYTIC ENANTIOSELECTIVE SYNTHESIS OF UNCIALAMYCIN

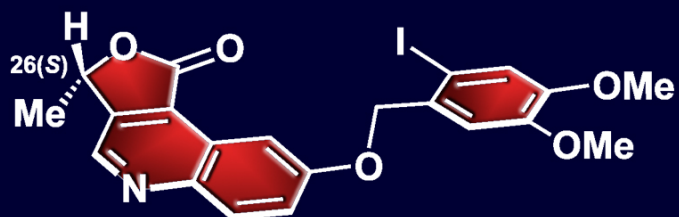




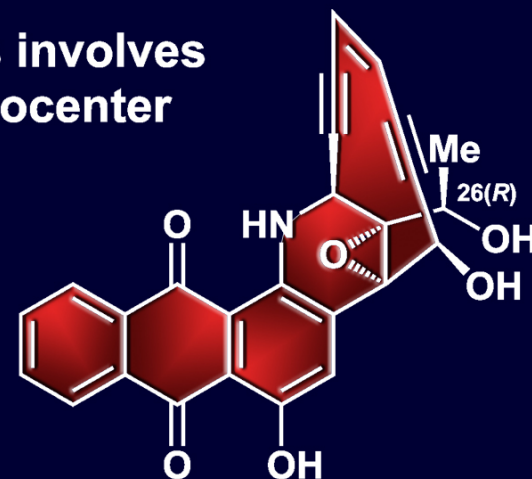
DETERMINATION OF ABSOLUTE STEREOCHEMISTRY OF UNCIALAMYCIN



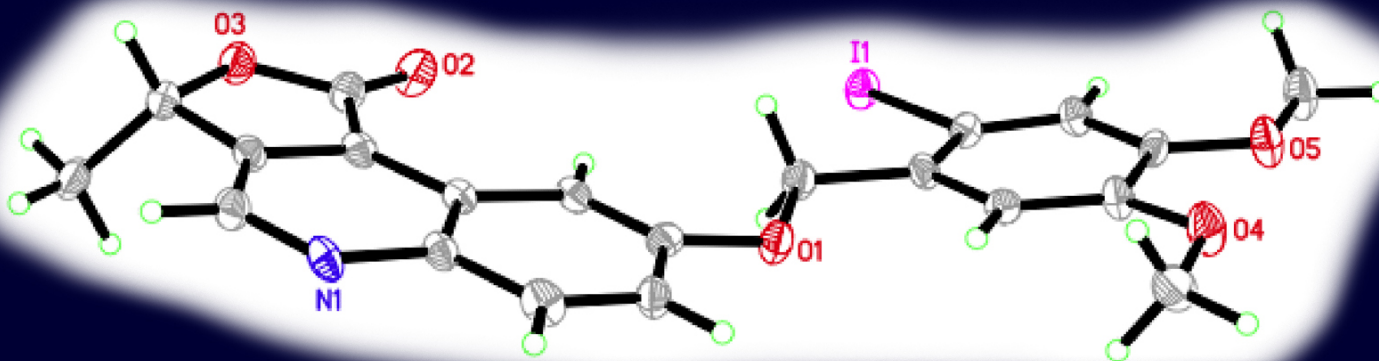
- asymmetric synthesis involves inversion of C26 stereocenter



- absolute stereochemistry determined by x-ray crystallography

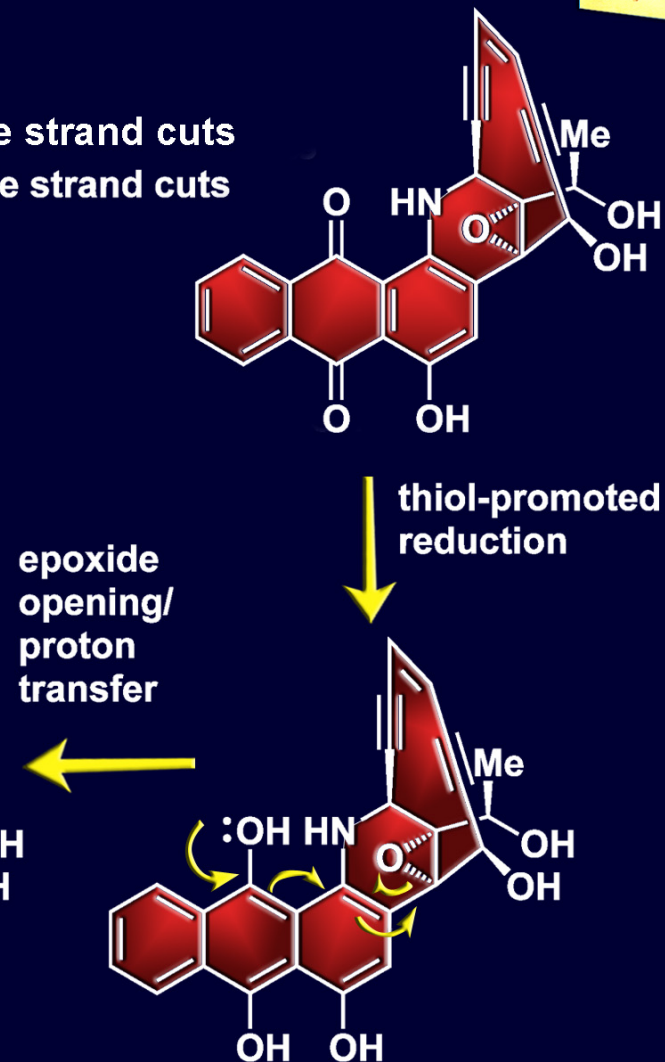
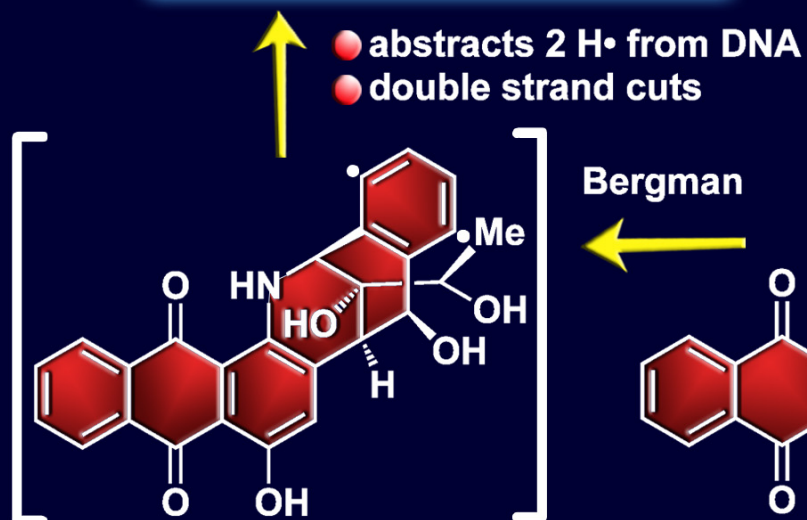
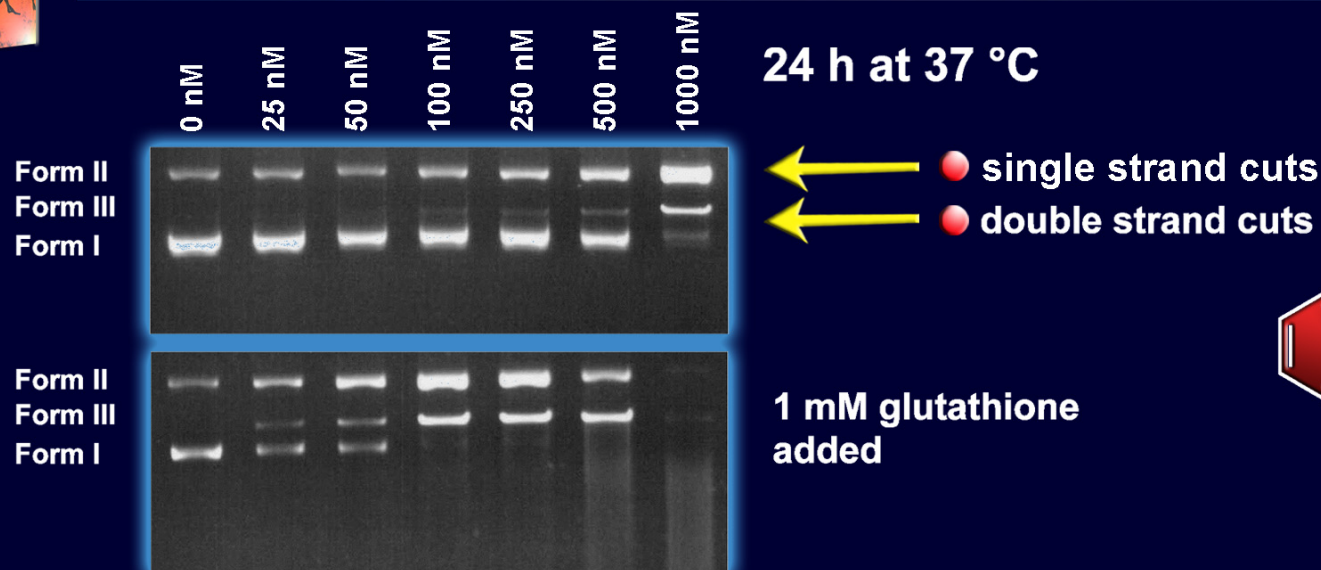


(+)-uncialamycin





DNA CLEAVAGE BY UNCIALAMYCIN





BIOLOGICAL PROPERTIES OF UNCIALAMYCIN

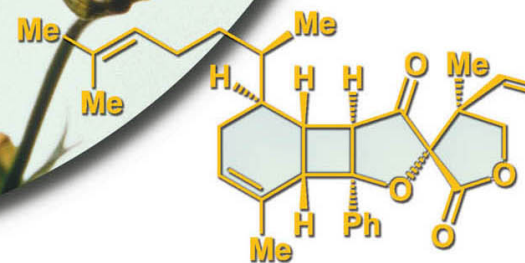


Table 1. Antibiotic activity (MIC) of uncialamycin and its 26(S) diastereomer

Bacterial strain	26(R)-uncialamycin	26(S)-uncialamycin
Methicillin resistant <i>Staphylococcus aureus</i> (MRSA)	0.0002 µg/mL	0.001 µg/mL
<i>Staphylococcus aureus</i>	0.0002 µg/mL	0.0009 µg/mL
<i>Staphylococcus epidermidis</i>	0.00009 µg/mL	0.0003 µg/mL
<i>Bacillus cereus</i>	0.0003 µg/mL	0.002 µg/mL
<i>Lysteria monocytogenes</i>	0.001 µg/mL	0.006 µg/mL
Vancomycin resistant <i>Enterococcus faecium</i> (VRE)	0.002 µg/mL	0.007 µg/mL
<i>Escherichia coli</i>	0.006 µg/mL	0.02 µg/mL
<i>Burkholderia cepacia</i> (Cystic Fibrosis patients)	0.0004 µg/mL	0.006 µg/mL
<i>Salmonella typhimurium</i>	0.009 µg/mL	0.02 µg/mL
<i>Pseudomonas aeruginosa</i>	0.02 µg/mL	0.04 µg/mL

Table 2. Cytotoxicity (IC₅₀) of uncialamycin and its 26(S) diastereomer

Cancer cell line	26(R)-uncialamycin	26(S)-uncialamycin	Taxol®	epothilone B
1A9 (ovarian)	1 x 10 ⁻¹¹ M	6 x 10 ⁻¹¹ M	2 x 10 ⁻⁹ M	4 x 10 ⁻¹⁰ M
PTX10 (Taxol® resistant)	6 x 10 ⁻¹¹ M	6 x 10 ⁻¹⁰ M	4 x 10 ⁻⁸ M	8 x 10 ⁻¹⁰ M
PTX22 (Taxol® resistant)	3 x 10 ⁻¹¹ M	2 x 10 ⁻¹⁰ M	5 x 10 ⁻⁸ M	5 x 10 ⁻¹⁰ M
A8 (epothilone resistant)	9 x 10 ⁻¹² M	1 x 10 ⁻¹⁰ M	1 x 10 ⁻⁸ M	4 x 10 ⁻⁹ M

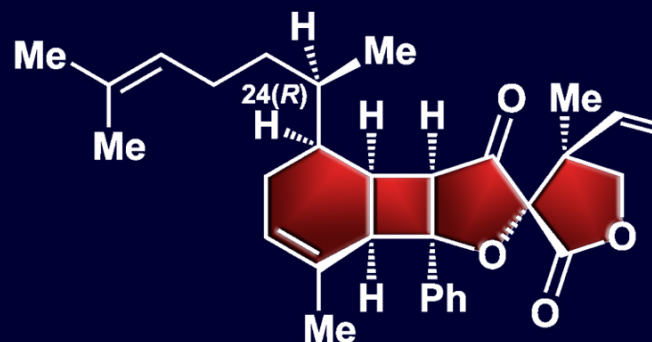
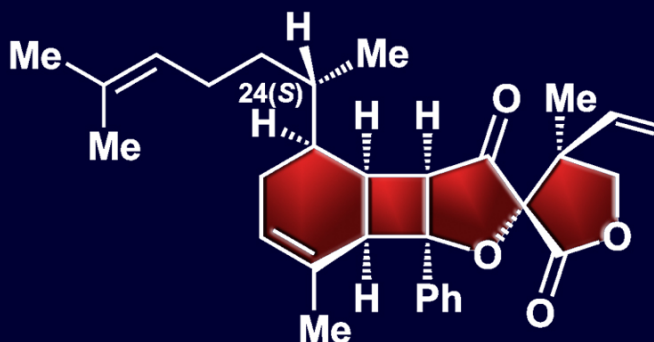




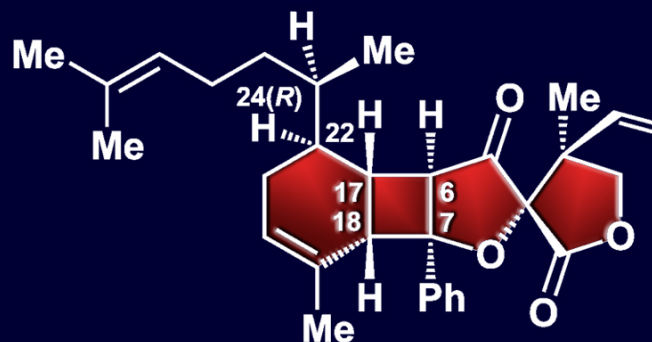
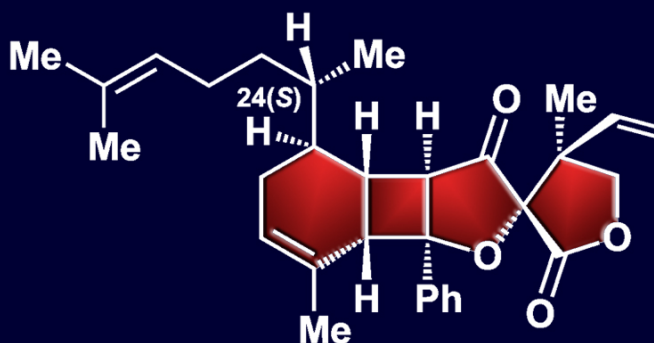
POTENTIAL STRUCTURES OF BIYOUYANAGIN A



- 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



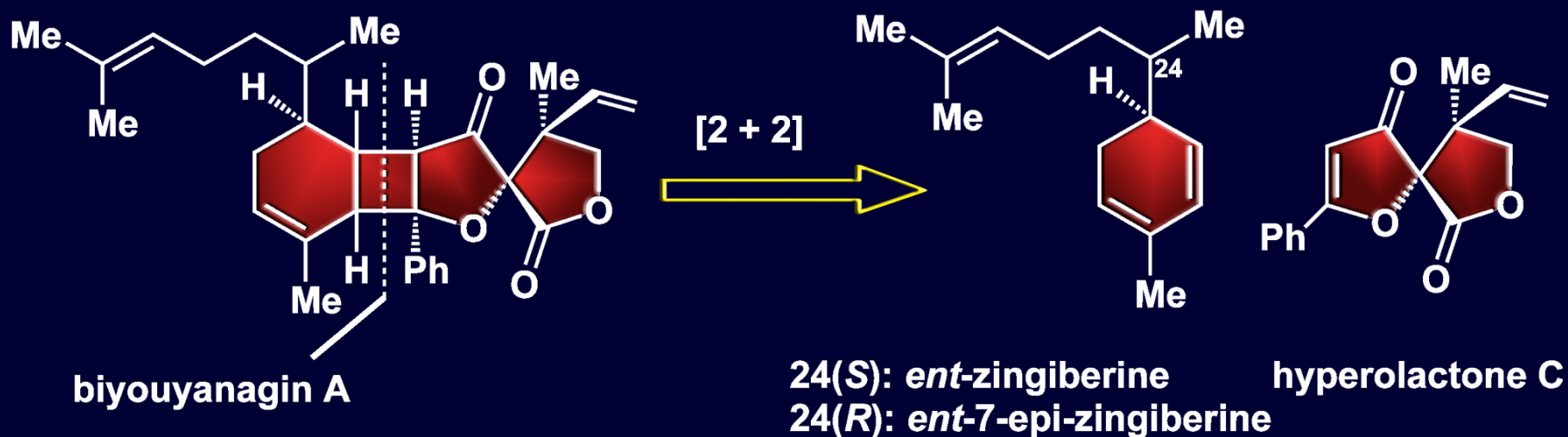
trans, cis, trans, cis structures: potential structures



BIOGENETICALLY INSPIRED RETROSYNTHESIS (2007)

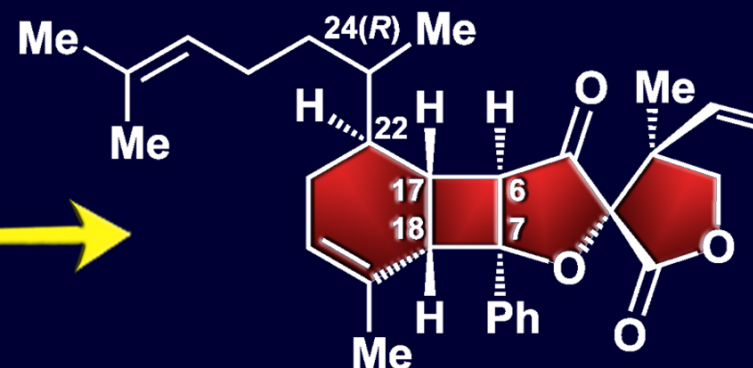
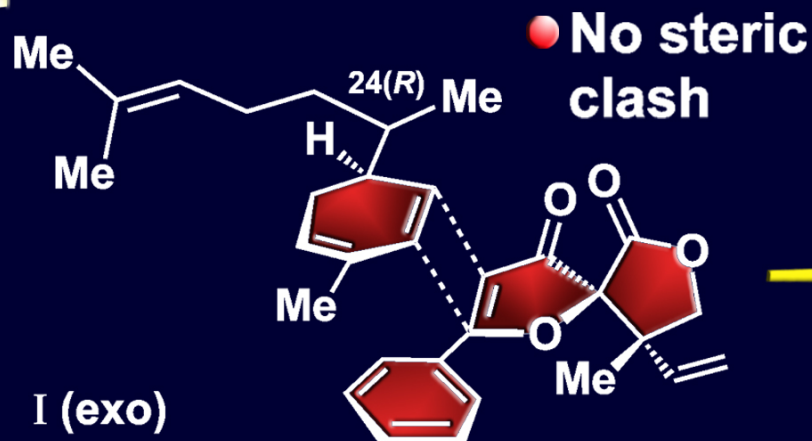


● Photo-induced [2 + 2] cycloaddition

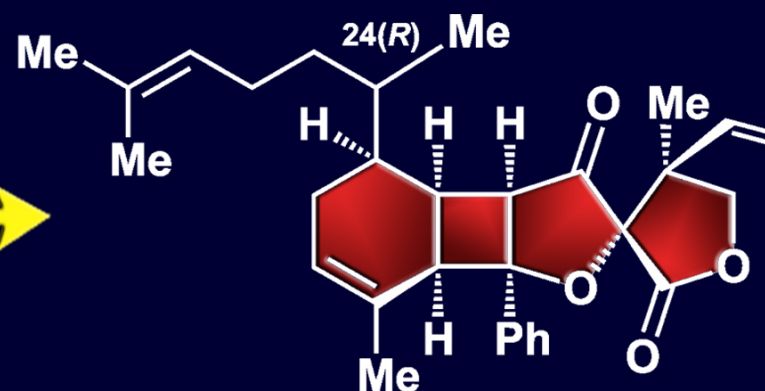
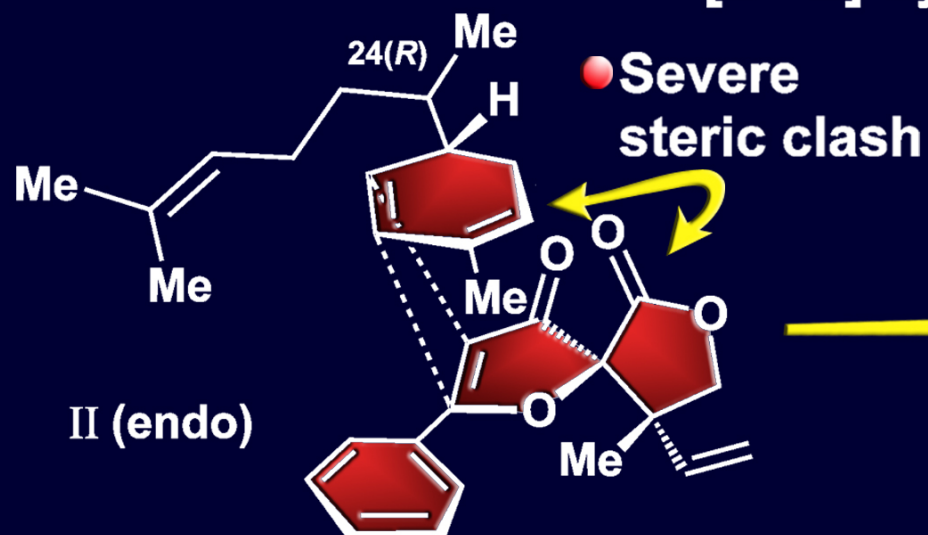




EXO- AND ENDO- TRANSITION MODES

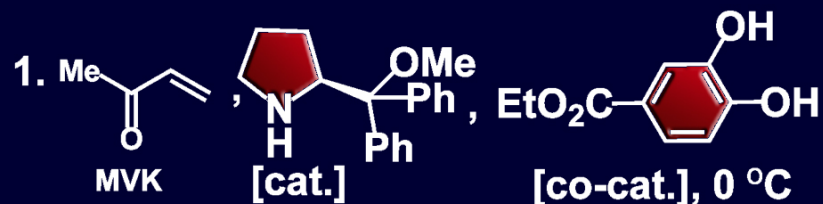
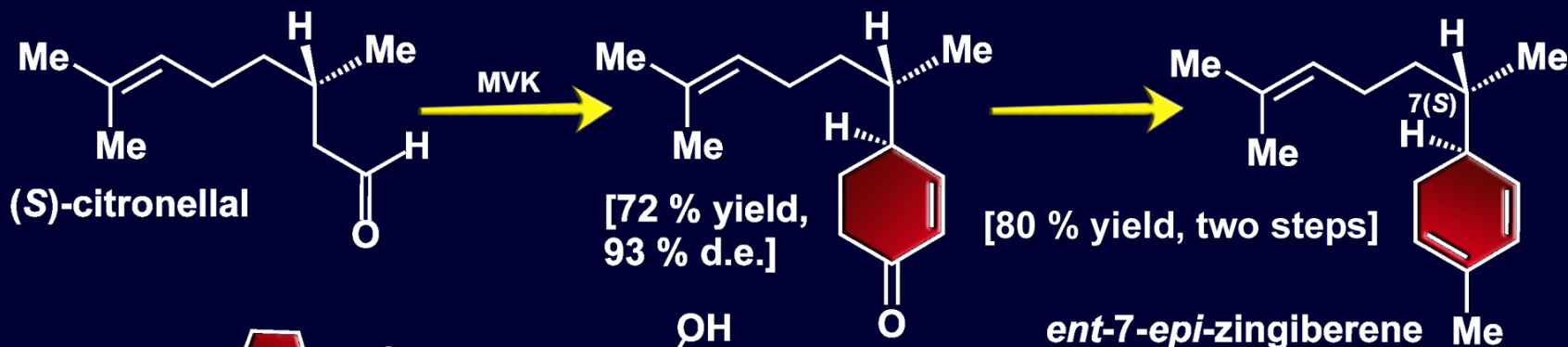


[2 + 2] cycloaddition



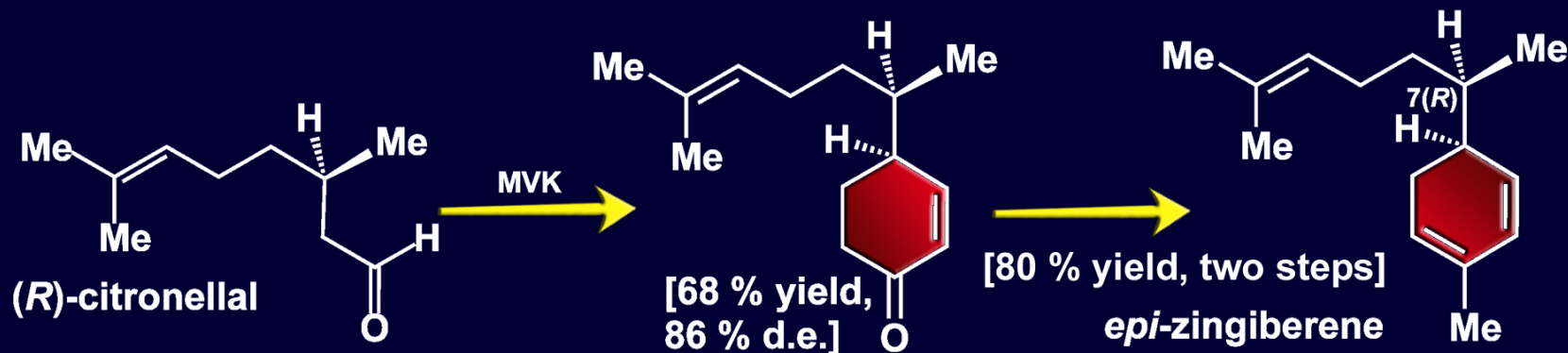


SYNTHESIS OF *ent*-7-*epi*-ZINGIBERENE AND *ent*-ZINGIBERENE

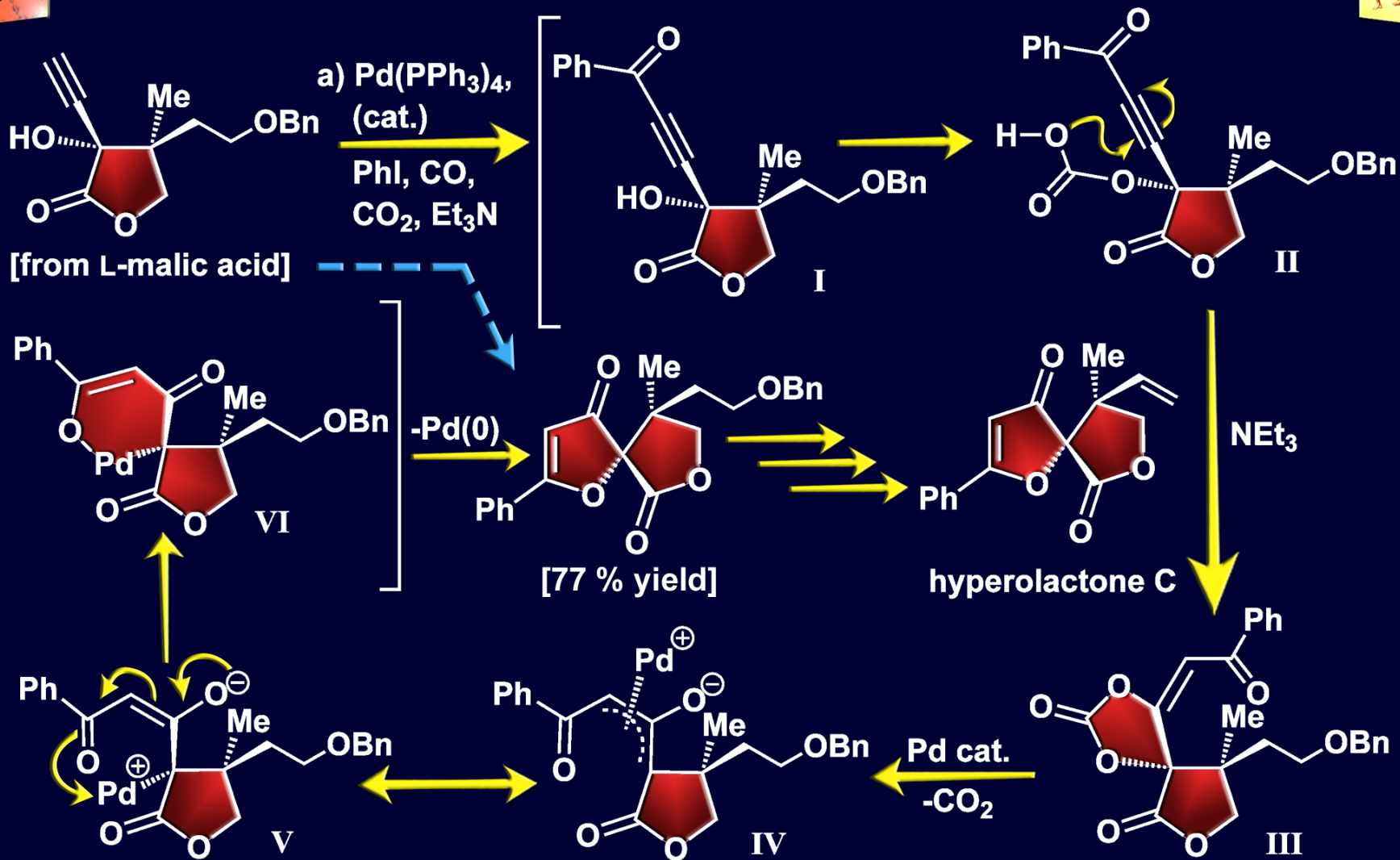


1. KHMDS, Comins' reagent
2. MeMgI, CuI (cat.)

2. KOH, *n*Bu₄NOH (cat.), Δ

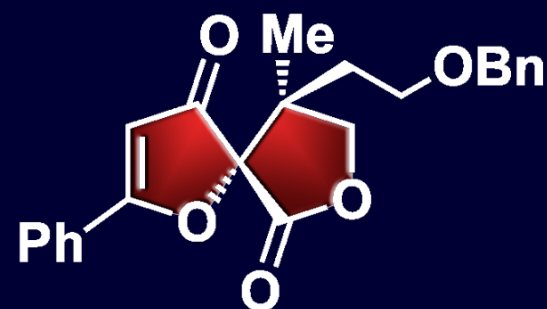
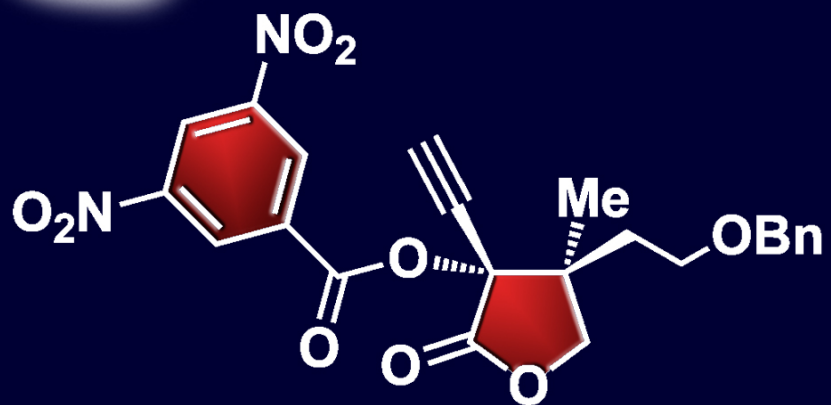
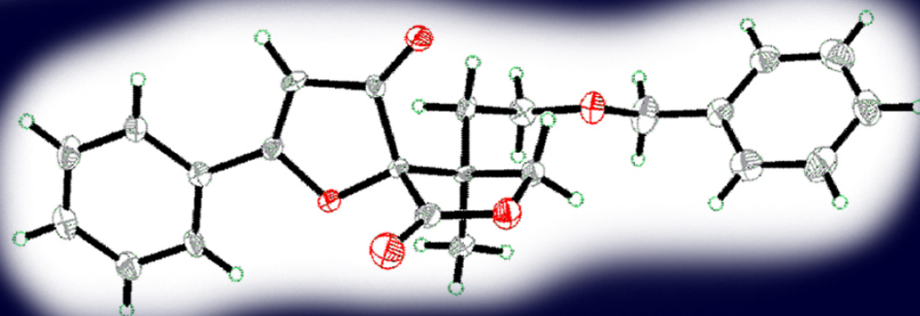
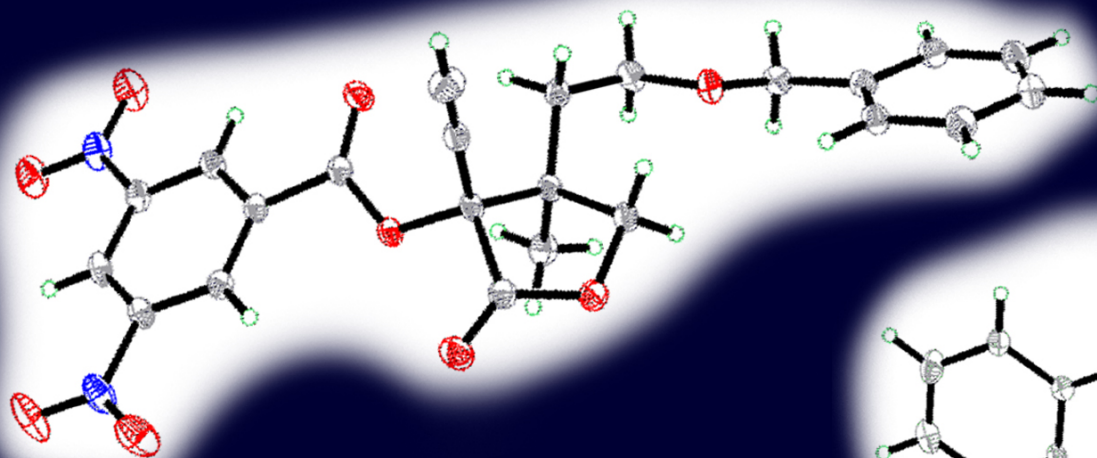


SYNTHESIS OF HYPEROLACTONE C



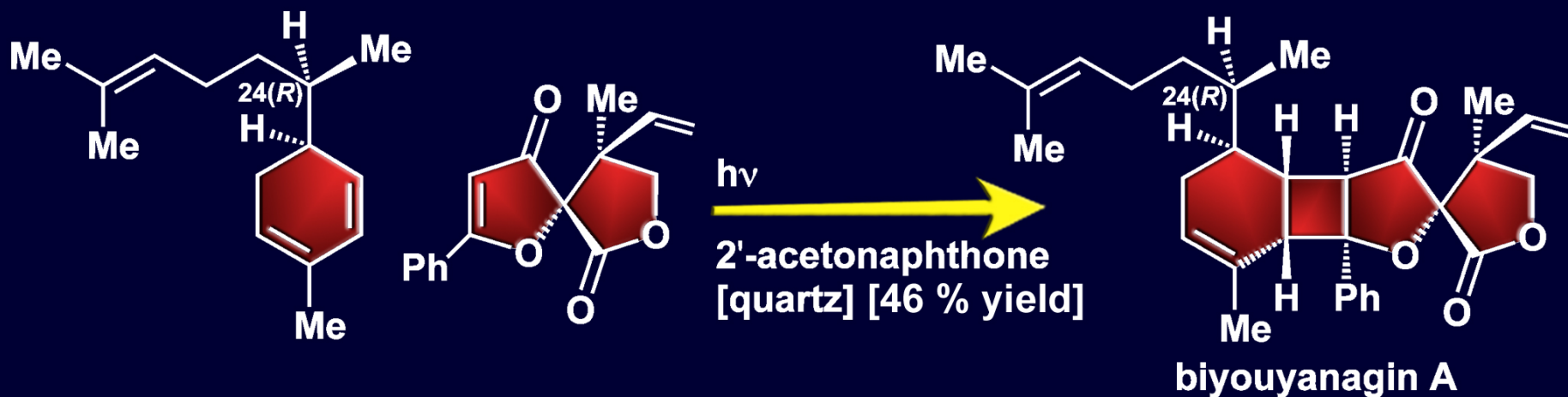
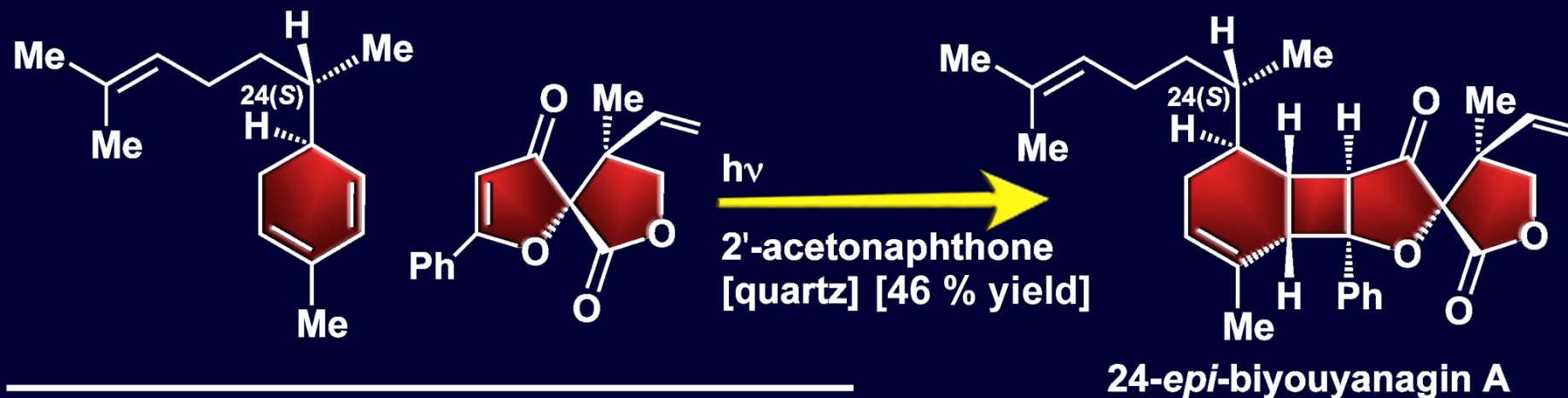


PROOF OF STEREOCHEMICAL RETENTION



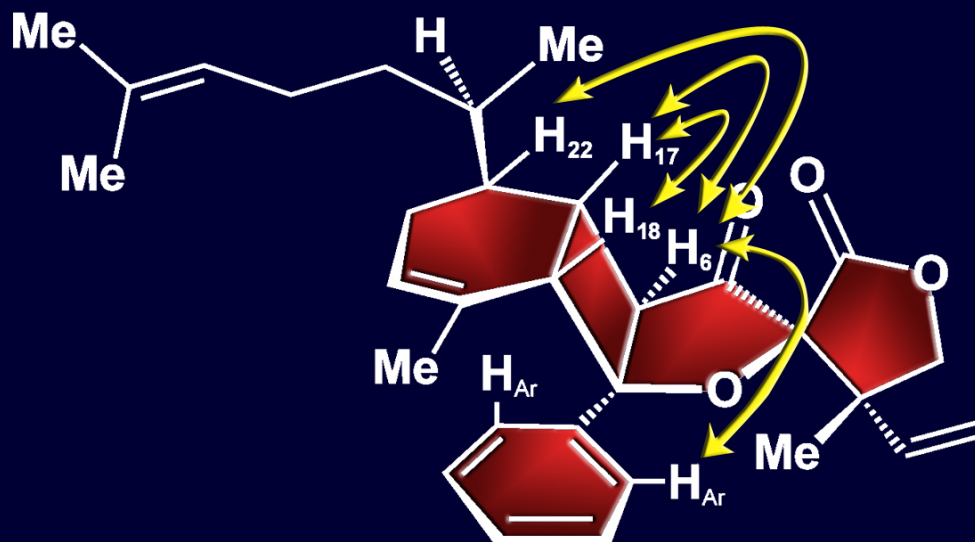


TOTAL SYNTHESIS OF BIYOUYANGIN A AND 24-*epi*-BIYOUYANAGIN A



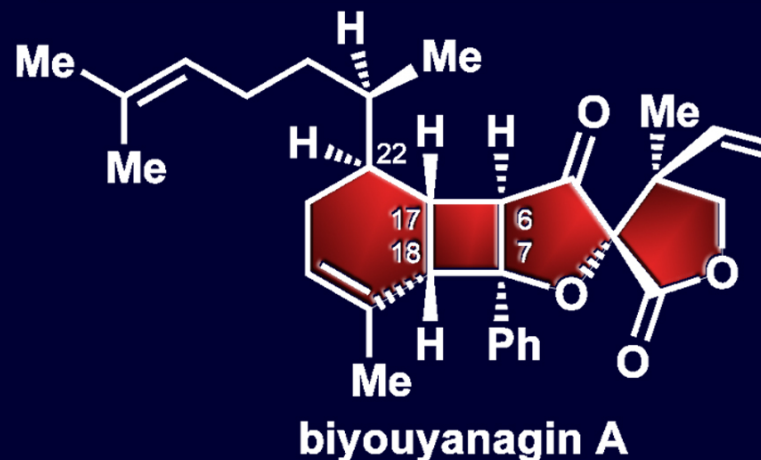


DIAGNOSTIC NUCLEAR OVERHAUSER EFFECTS FOR THE STEREOCHEMISTRY OF BIYOUYANAGIN A



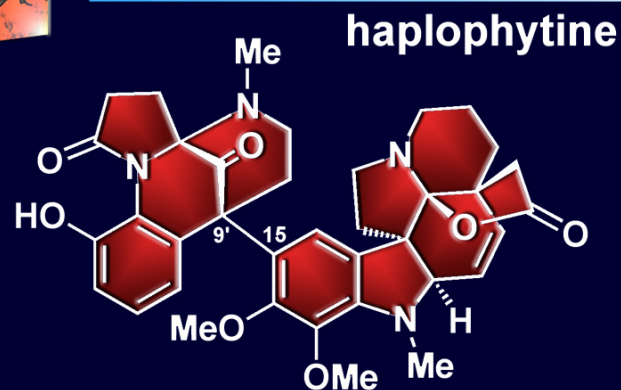
● *trans, cis, trans, cis (anti)* structure of biyouyanagin A

- nOe's between H₆-H₁₇, H₆-H₂₂, H₁₇-H₁₈
- nOe between H₆-H_{Ar} 128-fold larger than nOe between H₁₈-H_{Ar}
- nOe between H₆-H₂₂ larger than nOe between H₆-H₁₇
- no nOe between H₆-H₁₈

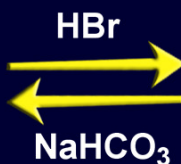
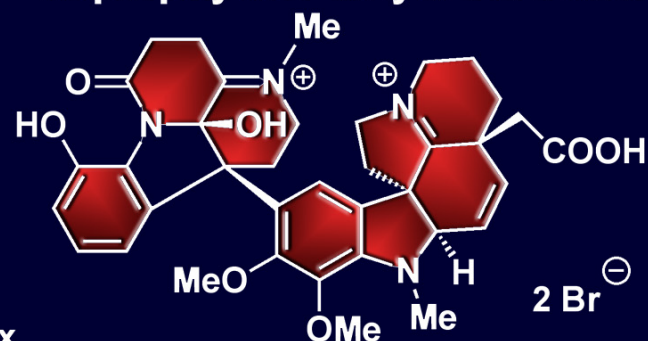




HAPLOPHYTINE

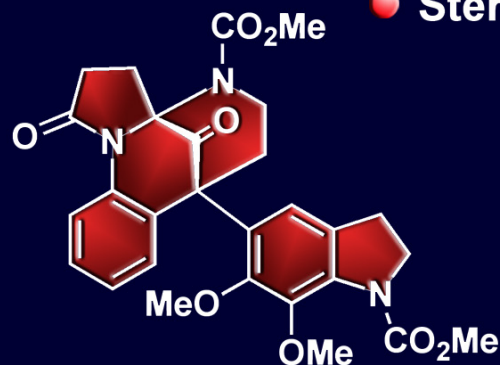


haplophytine dihydrobromide



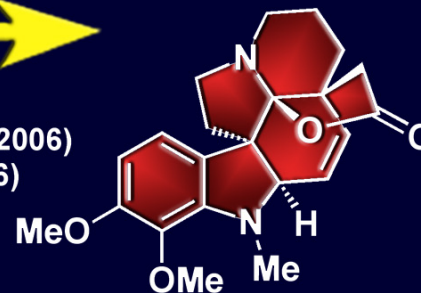
aq. HCl, reflux

- From Mexican plant *Haplophyton cimicidum*
- Interesting insecticidal properties
- 10 rings, 6 stereocenters (5 tetrasubstituted)
- Sterically congested C-C bond (C9'–C15)



“left domain” of haplophytine

E. J. Corey *et. al.* (1999)
T. Fukuyama *et. al.* (2003)
A. Padwa, J. M. Mejia-Oneto (2006)
J. P. Marino, C. Ganfeng (2006)

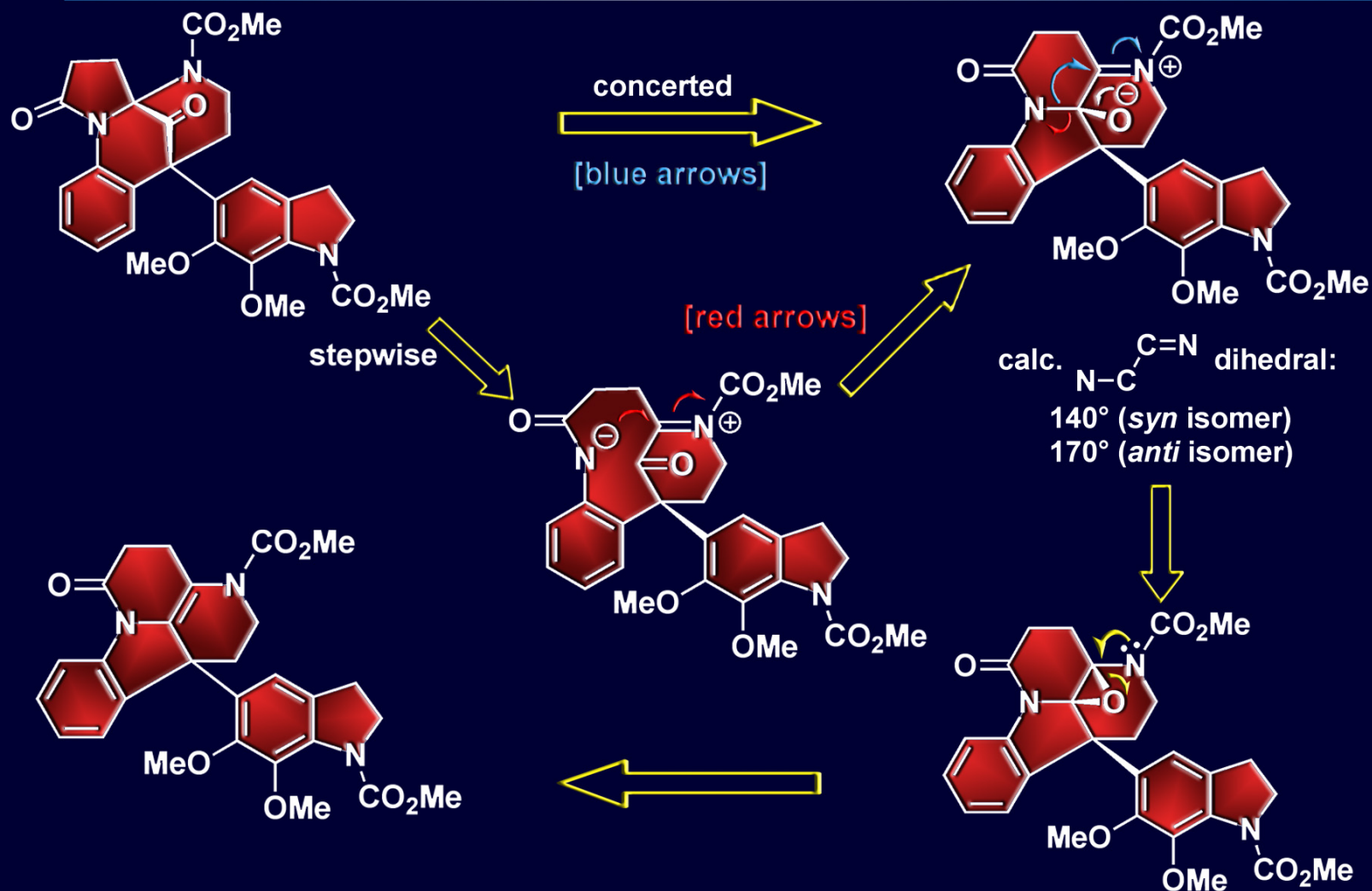


aspidophytine

Isolation and structural elucidation: Snyder, Yates, Cava, Zacharias, *et. al.* (1952–1973)

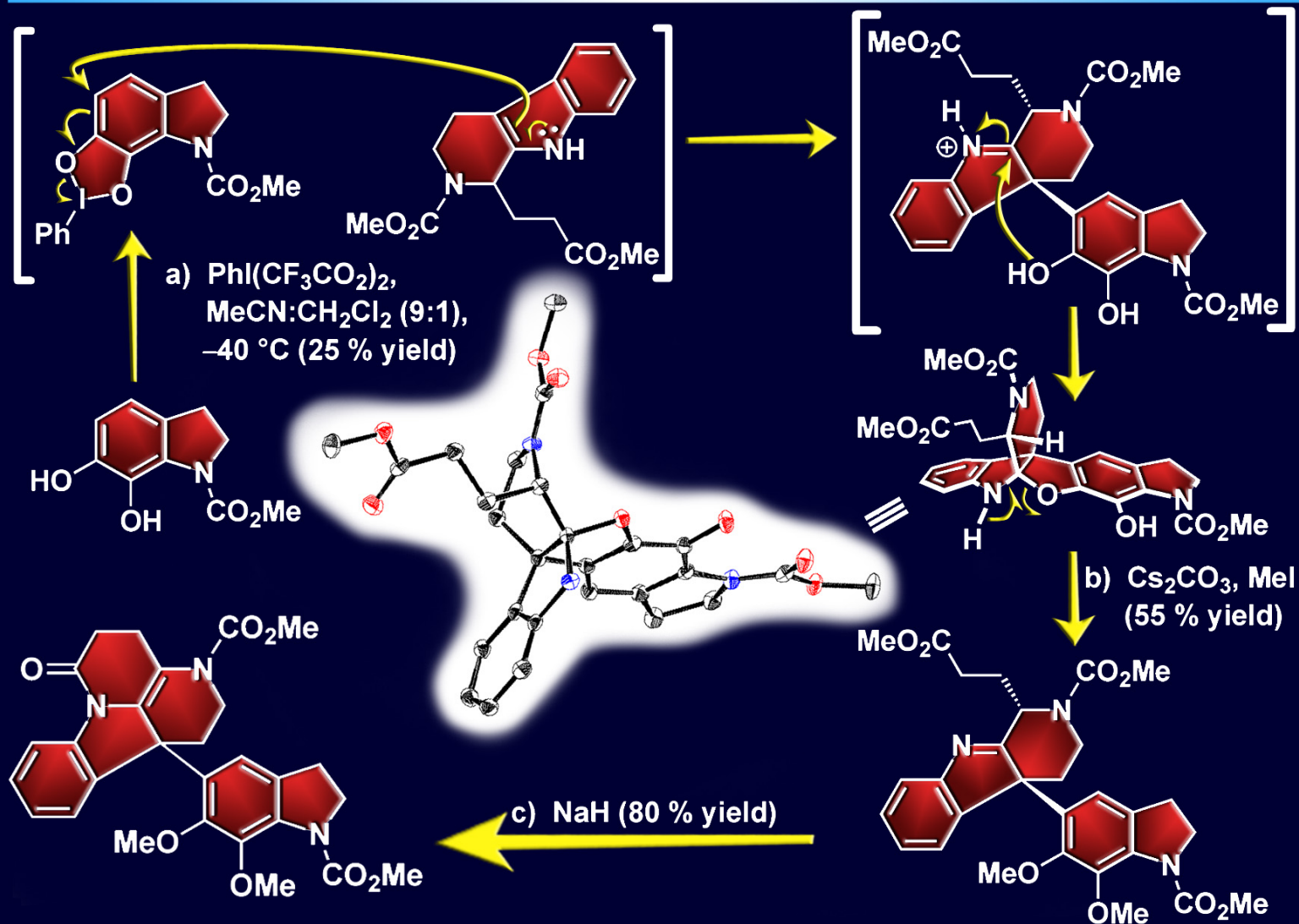


RETROSYNTHETIC ANALYSIS OF THE LEFT DOMAIN OF HAPLOPHYTINE



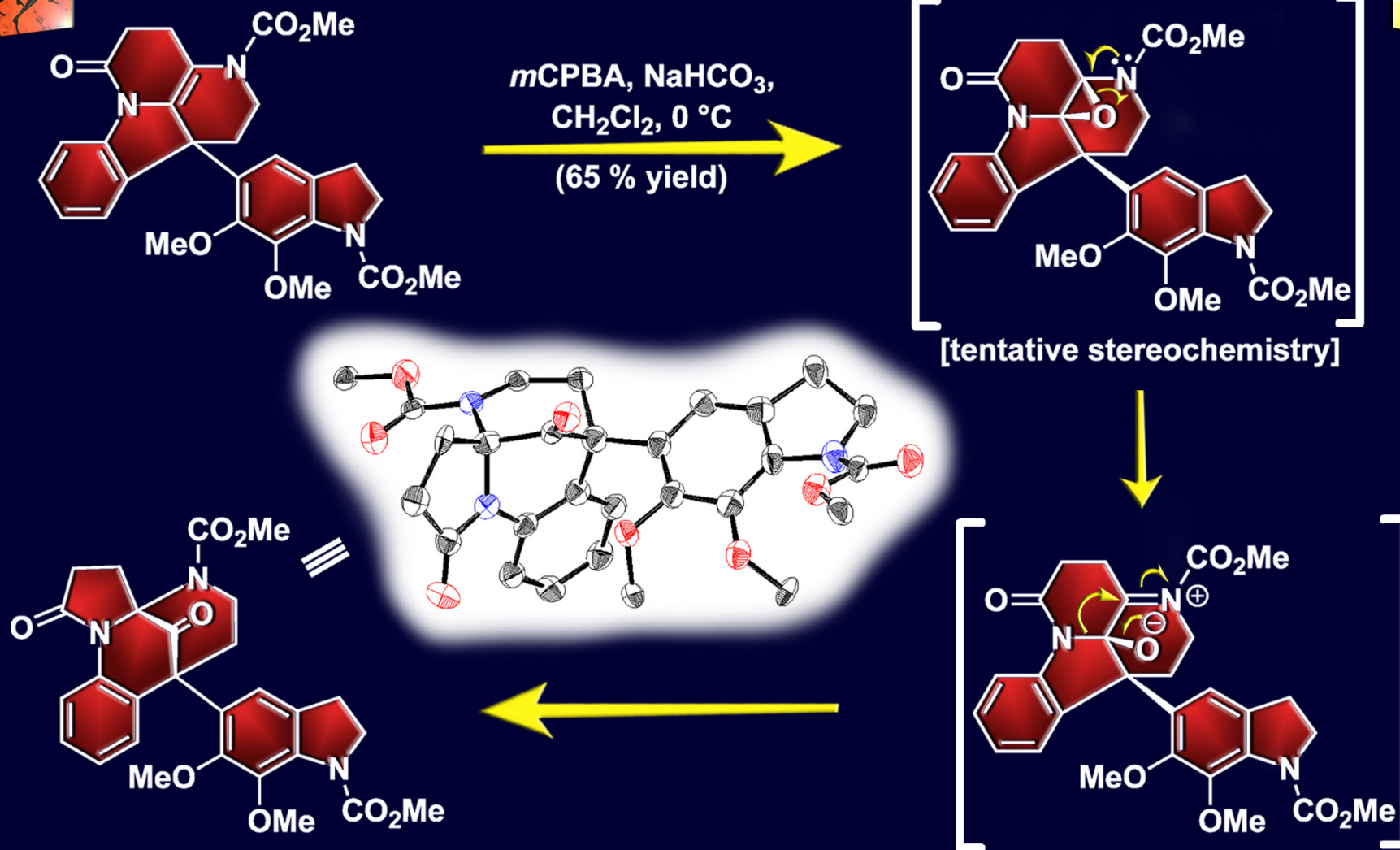


HAPLOPHYTINE: CONSTRUCTION OF ARYL LINKAGE



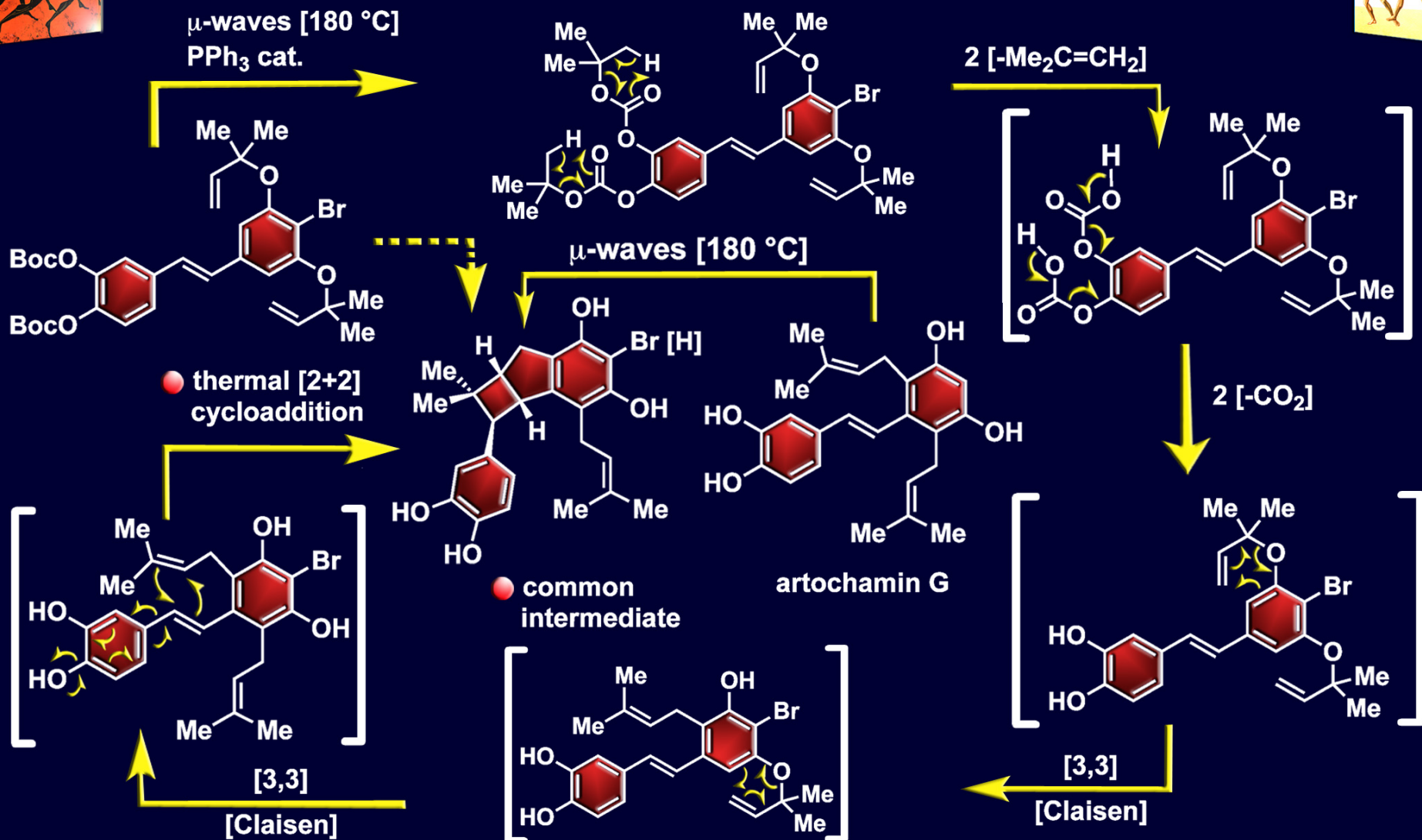


CONSTRUCTION OF THE LEFT DOMAIN OF HAPLOPHYTINE (2007)





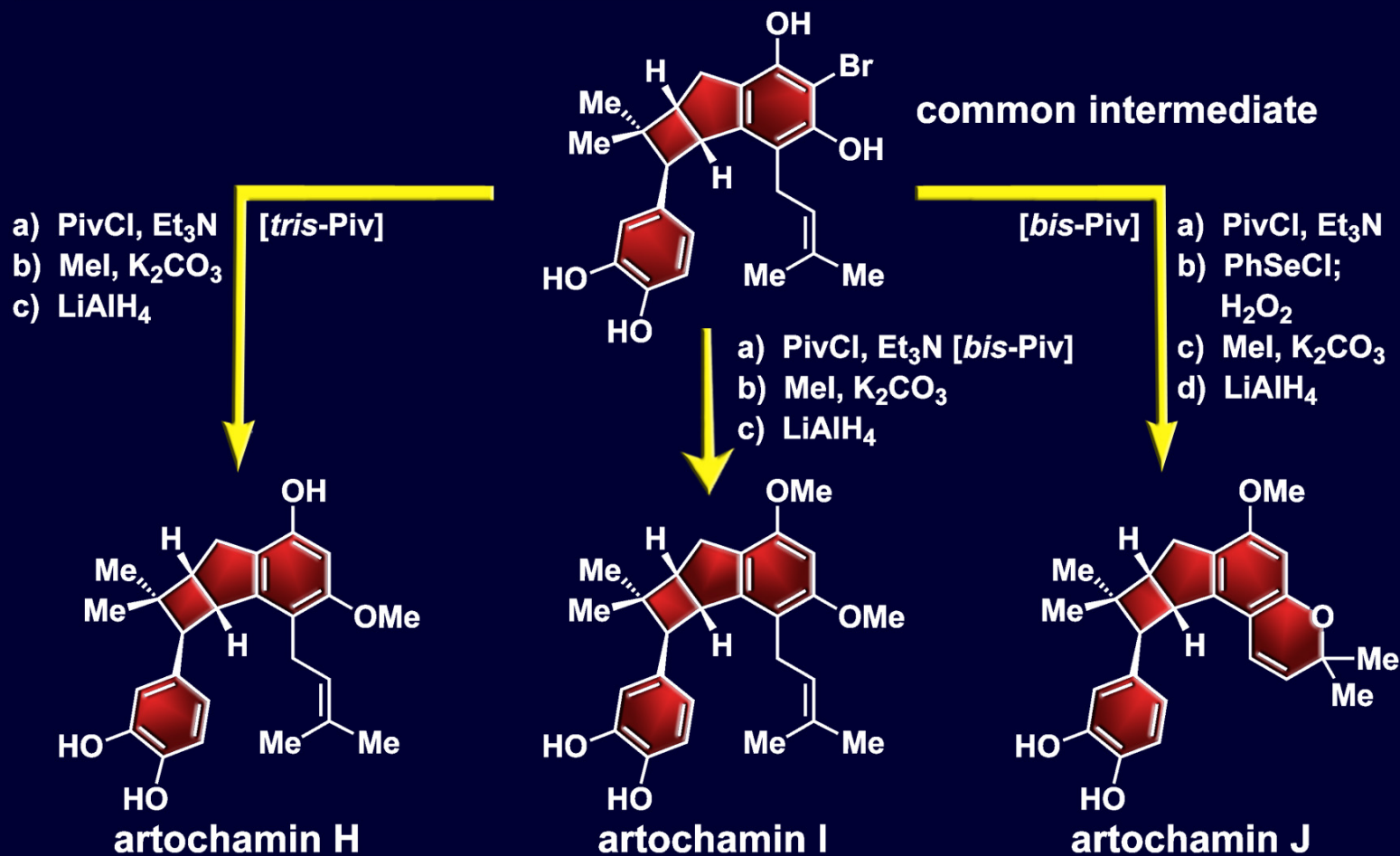
THE ARTOCHAMIN CASCADE (2007)





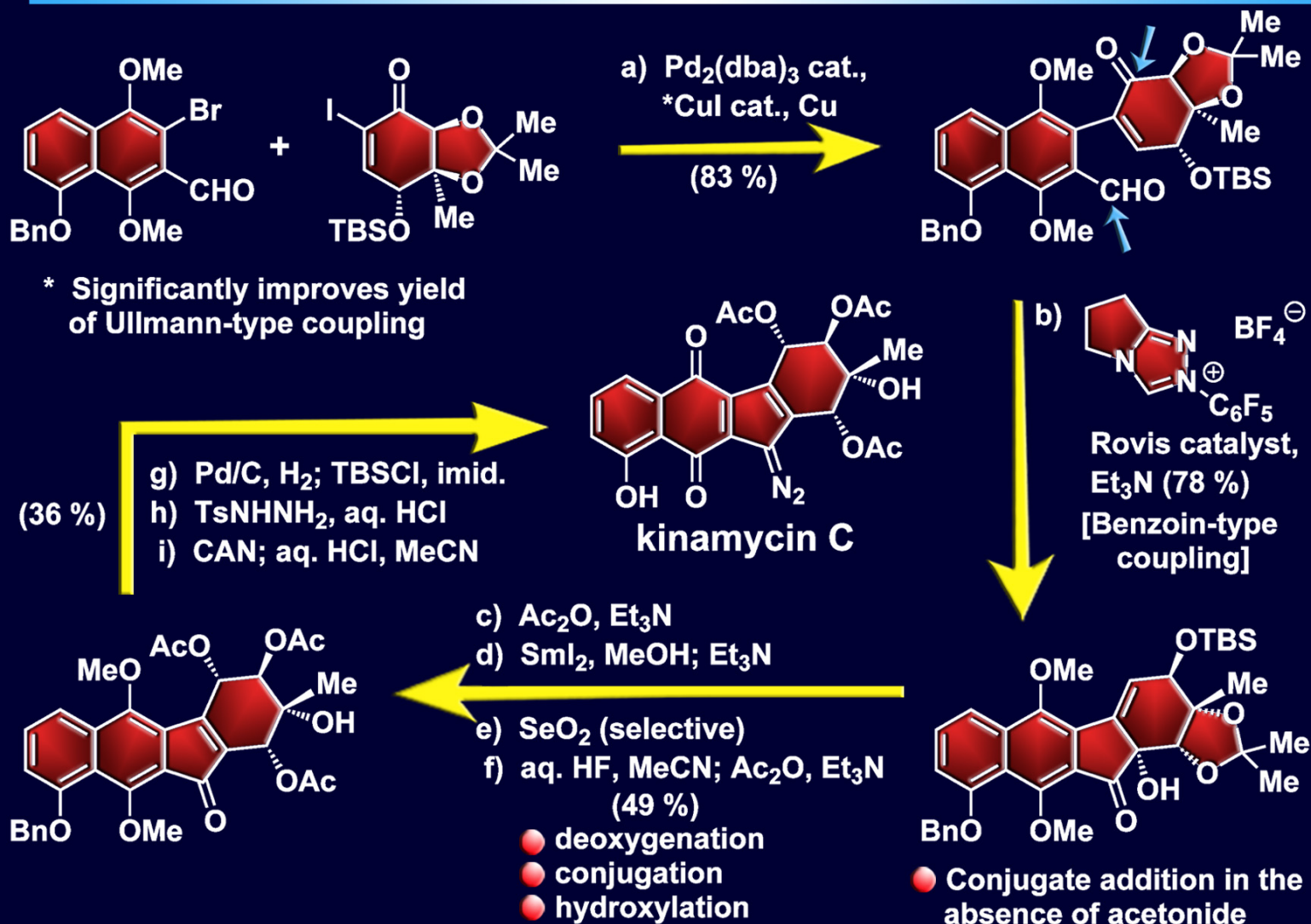
TOTAL SYNTHESIS OF ARTOCHAMINS H, I, AND J (2007)

- Isolated in 2006 from *Artocarpus chama*
- Exhibit weak cytotoxicity





TOTAL SYNTHESIS OF KINAMYCIN C (2007)

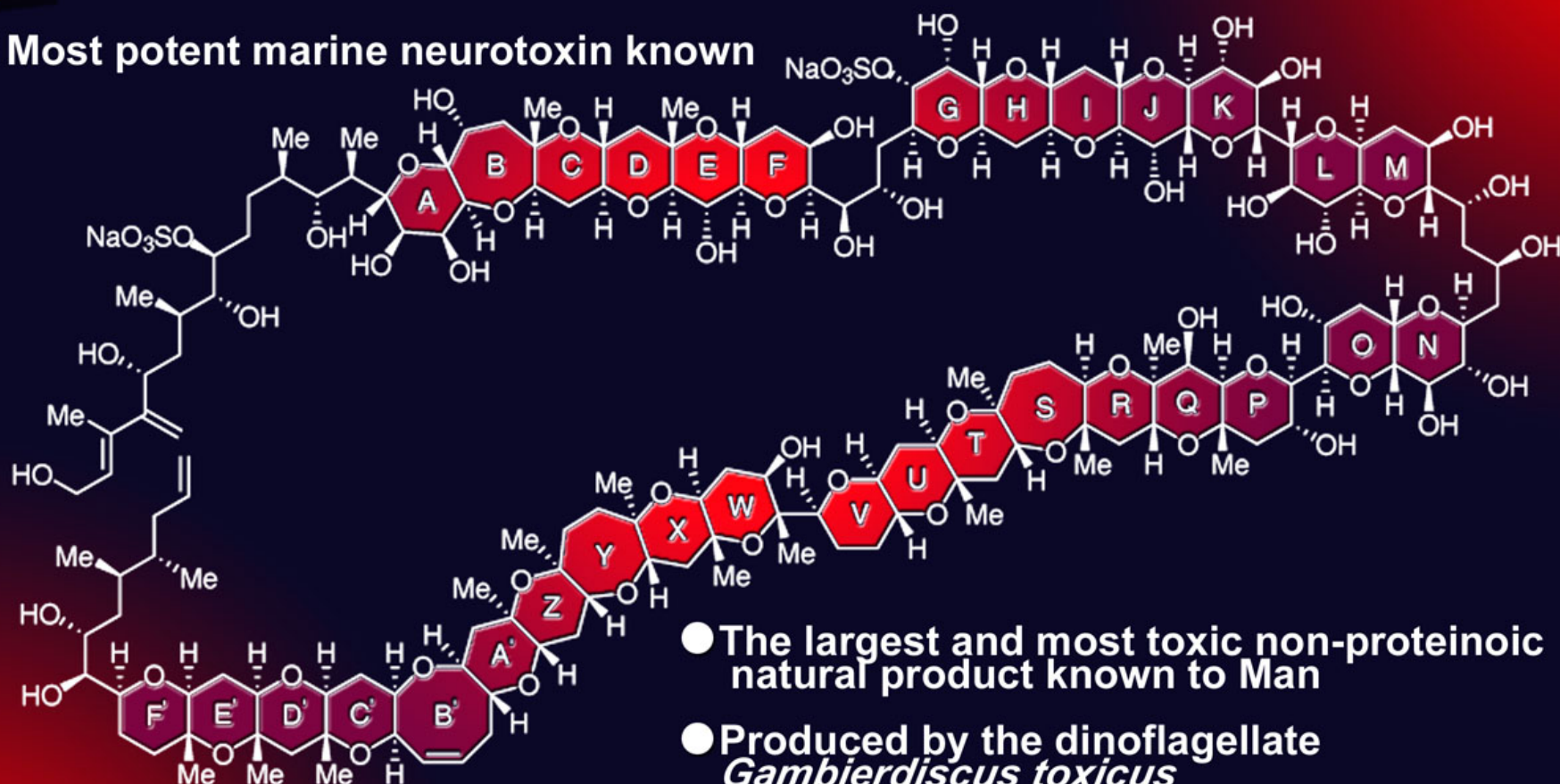




PROPOSED STRUCTURE OF MAITOTOXIN



- 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-proteinoic natural product known to Man

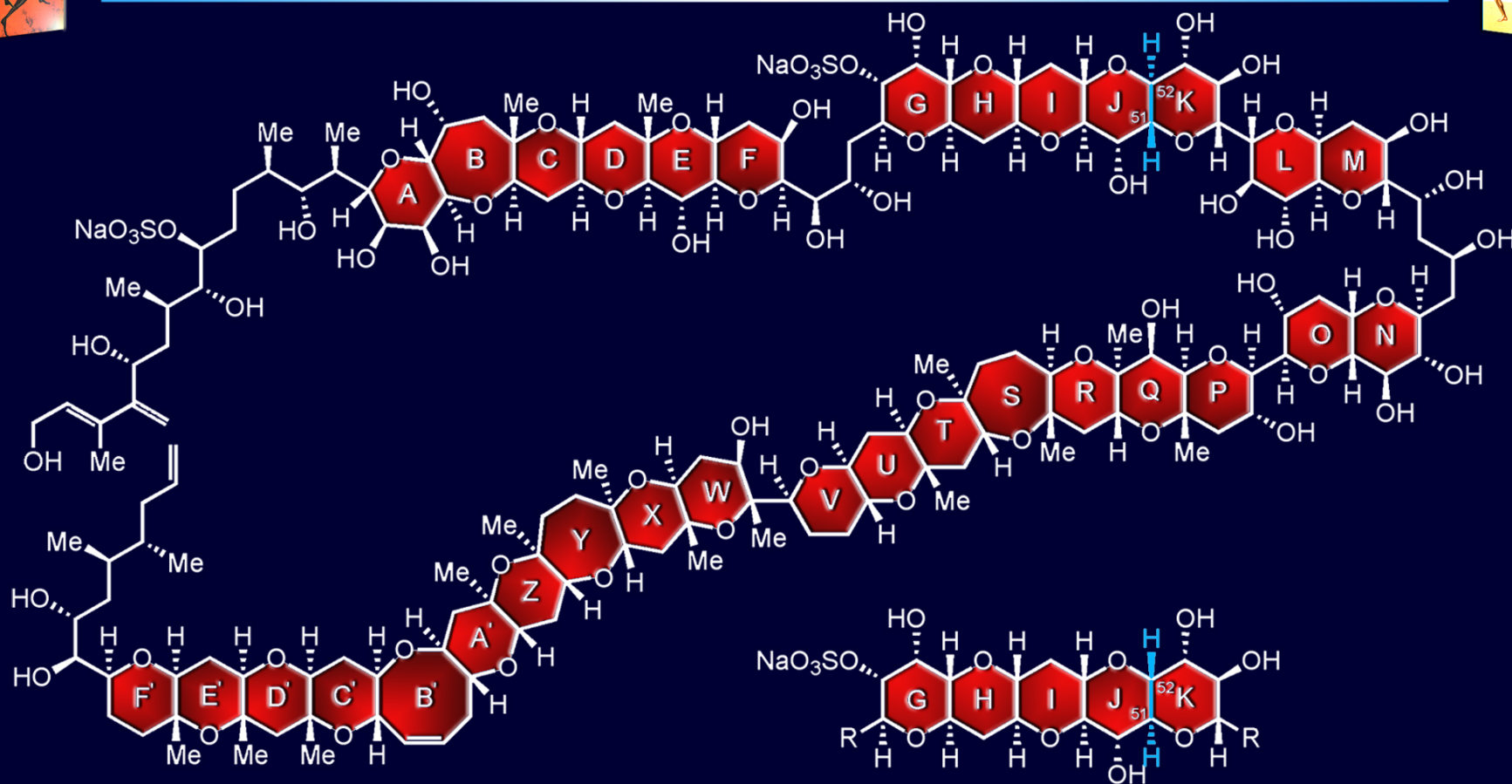
- Produced by the dinoflagellate *Gambierdiscus toxicus*

- LD_{50} = 50 ng/Kg, 1 mg can kill a million mice

- Activates voltage-dependent Ca ion channels



MAITOTOXIN STRUCTURE-1

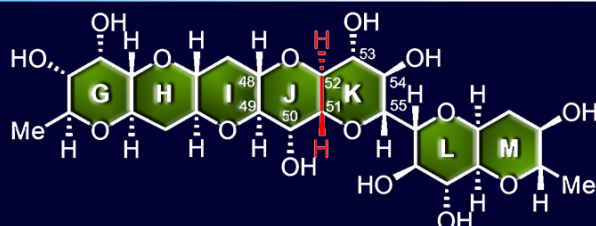


originally proposed maitotoxin structure
[Yasumoto, Tachibana, Kishi]

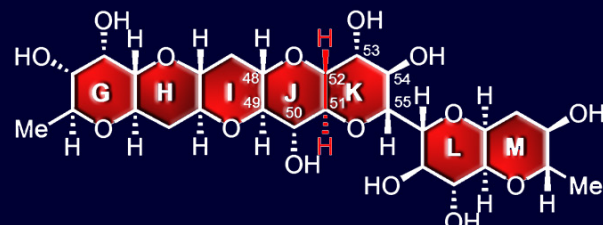
revised structure with C-51 and C-52
stereocenters inverted
[Gallimore and Spencer]



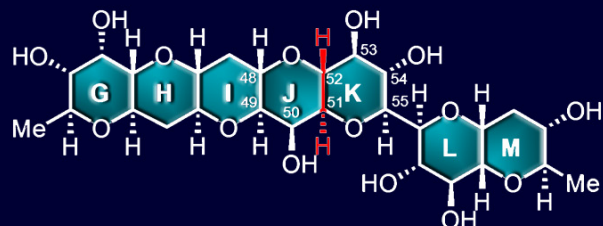
MAITOTOXIN STRUCTURE-2 (2007)



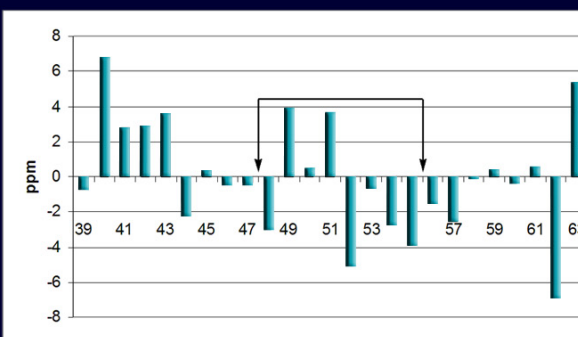
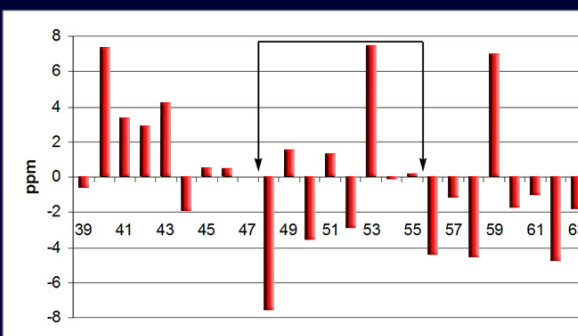
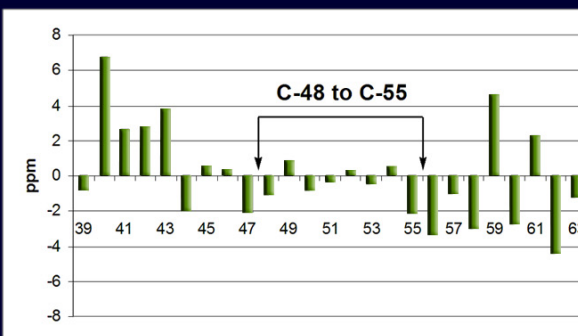
Originally proposed G-K domain
Average difference (C-48 to C-55) = 0.78 ppm
Maximum difference = 2.1 ppm



Revised structure with C-51 and C-52 (J/K ring junction) reversed
Average difference (C-48 to C-55) = 3.03 ppm
Maximum difference = 7.5 ppm



Revised structure with stereocenters C-50 to C-55 reversed
Average difference (C-48 to C-55) = 2.89 ppm
Maximum difference = 5.0 ppm



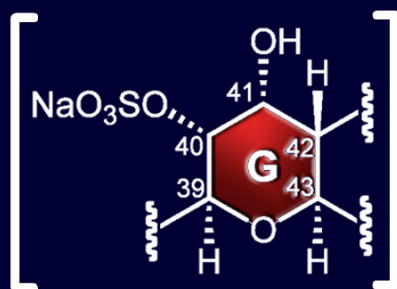
- SPARTAN 06 computer program
- Difference of calculated ^{13}C chemical shifts from experimental values



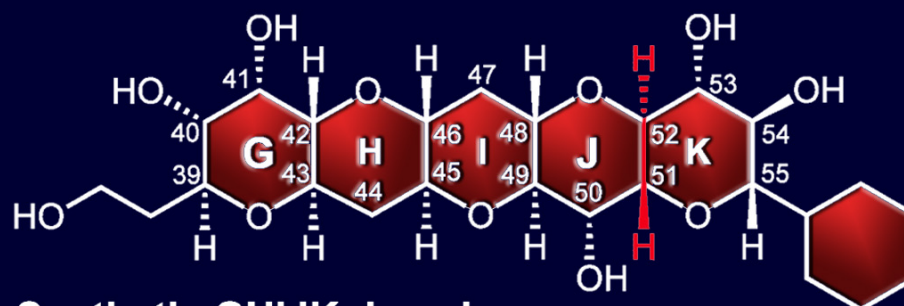
MAITOTOXIN STRUCTURE-3



¹³C chemical shift differences between synthetic GHIJK domain and natural maitotoxin



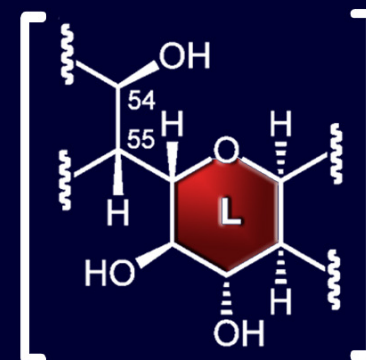
maitotoxin
structure



Synthetic GHIJK domain

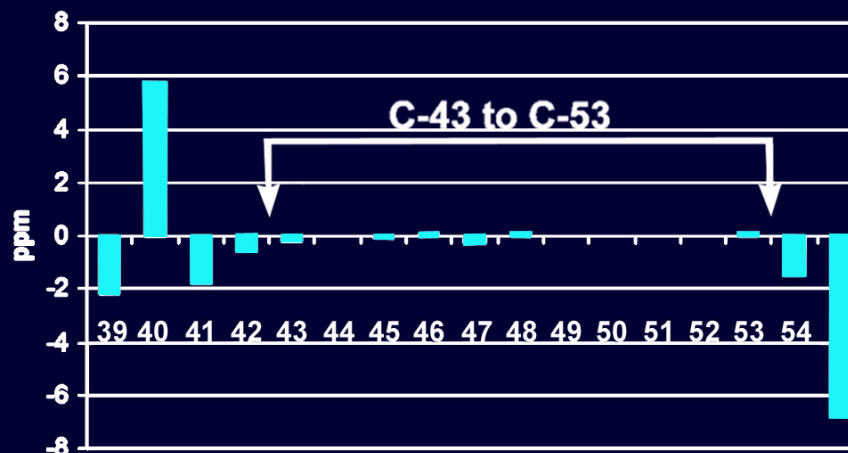
Average difference (C-43 to C-53) = 0.08 ppm

Maximum difference = 0.3 ppm



maitotoxin
structure

● relatively large $\Delta\delta$ values are due to the absence of a sulfate and presence of cyclohexyl substituent



● originally proposed stereochemistry of JK junction (C51-C52) most likely correct



TALES IN TOTAL SYNTHESIS



Brevetoxin B: A molecule whose total synthesis led to the discovery of several new synthetic technologies and strategies.

atrop-Abyssomycin C: A molecule whose discovery in nature was inspired by its total synthesis.

Platensimycin: A molecule whose novel analogs could only be made available by total synthesis.

Biyouyannagin: A molecule whose true structure could only be known by total synthesis.

Uncialamycin: A molecule whose biology could only be explored by total synthesis.

Haplophytine: A molecule whose total synthesis could only be justified by the sheer excitement of the endeavor!



BREAKING NEW GROUND IN TOTAL SYNTHESIS

INSPIRATIONS FROM NATURE

DISCOVERIES AND INVENTIONS

NOVEL MOLECULAR ARCHITECTURES

BIOMIMETIC SYNTHETIC STRATEGIES

COMPLEX AND CHALLENGING TARGETS

CASCADE REACTIONS

BOND CONNECTIVITIES

SOLID PHASE SYNTHESIS

RING FRAMEWORKS

COMBINATORIAL CHEMISTRY

STEREOGENIC CENTERS

ASYMMETRIC SYNTHESIS

UNUSUAL, SENSITIVE FUNCTIONALITIES

REAGENTS AND CATALYSTS

UNSYNTHESIZED MOLECULES

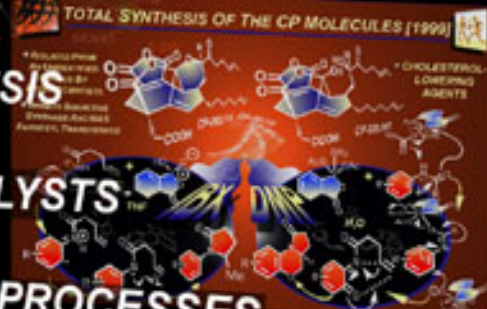
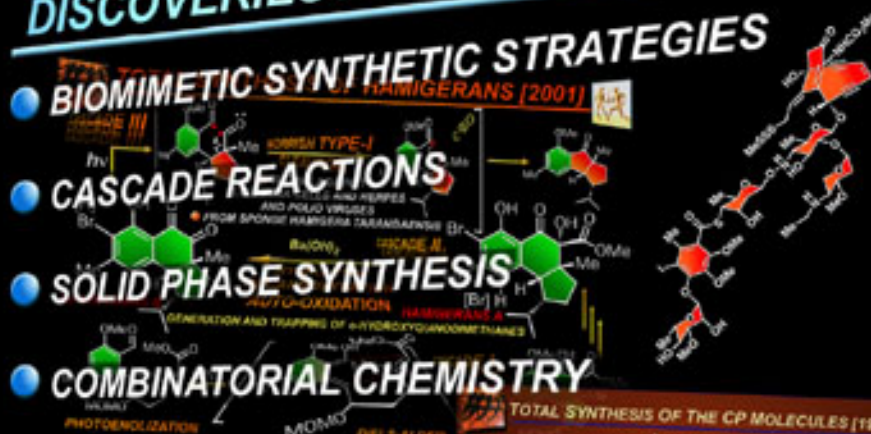
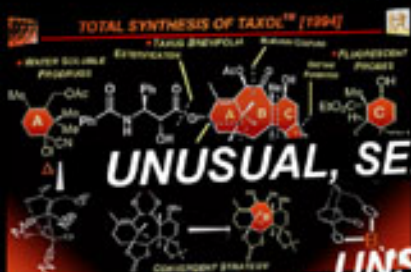
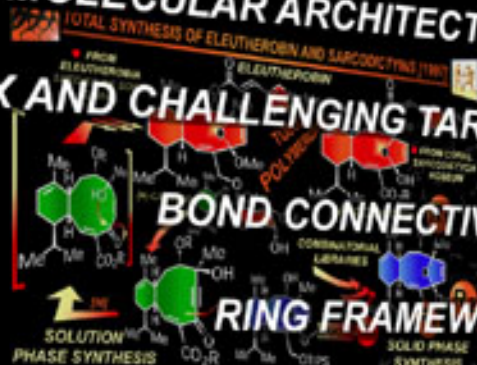
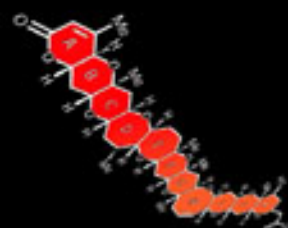
EFFICIENT CHEMICAL PROCESSES

IMPORTANT BIOLOGICAL ACTIVITY

GREEN CHEMISTRY

INTERESTING MECHANISM OF ACTION

DESIGNED BIOACTIVE MOLECULES



THANKS AND ACKNOWLEDGEMENTS

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Yoshihiko Watanabe
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Heng-Xu Wei
David Weinstein
Sebastian Wendeborn
Barbara Werschkun
Bernad Weyershausen
Keith Wilcoxon
Nicolas Winsinger
Michael Woodrow
Xiao-Yi (Charlie) Xiao
Zhao-Feng Xie
Hao Xu
Jinyou Xu
Yoichi Yamada
Guang Yang
Zhen Yang
George Yiannikourous
Won Hyung Yoon
Eddy Yue
Tai-Yuen Yue
Mark Zak
Frédéric Zécri
Zijian Zeng
Yong-li Zhong
Robert Zipkin
Ning Zou
Guido Zuccarello

TOTAL: 342
(1976-PRESENT)

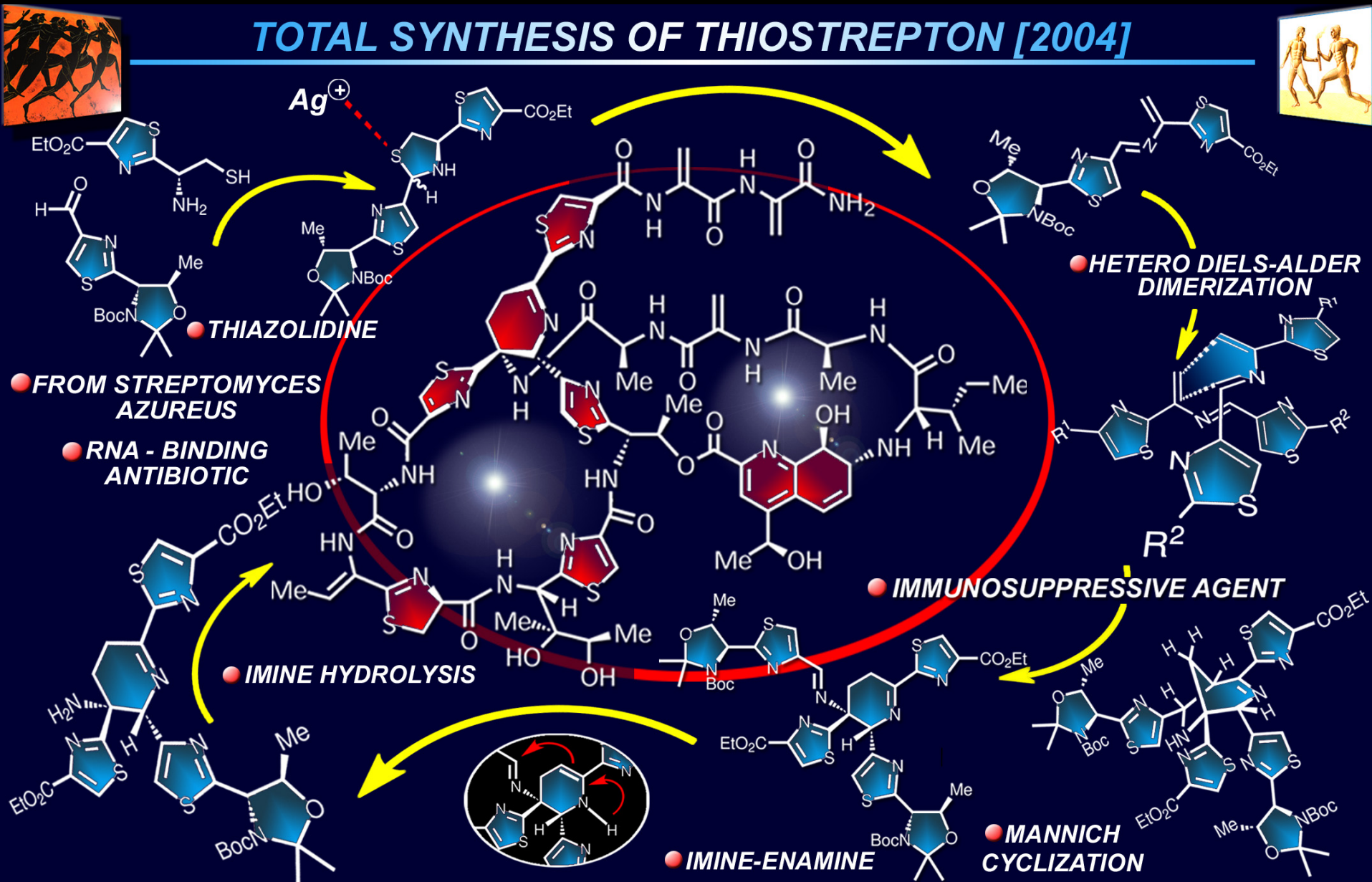


The Office Staff:

Robbyn, Natasha, Vicky, Janise

The End

TOTAL SYNTHESIS OF THIOSTREPTON [2004]



TOTAL SYNTHESIS OF FLORESOLIDE B AND 6,7-Z-FLORESOLIDE B [2006]

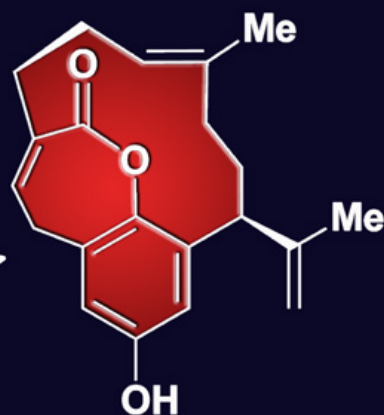
● From ascidian of *Aplidium*

E-geometry

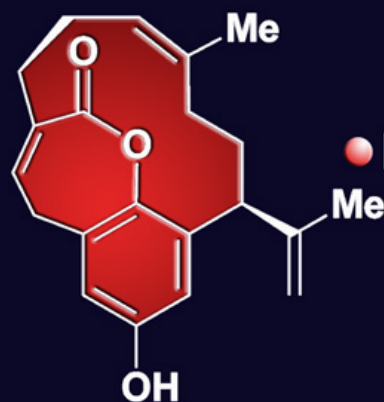
Z-geometry

● 7-membered lactone bridge

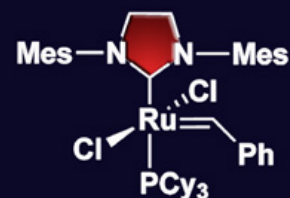
● Cytotoxic against KB tumor cells



Floresolide B [1 : 2.9] $\Delta^{6,7}$ -Z-Floresolide B



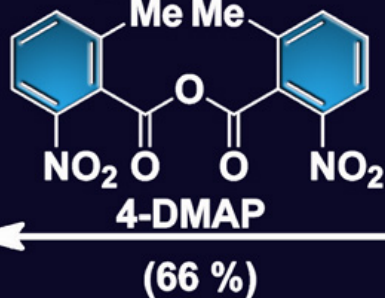
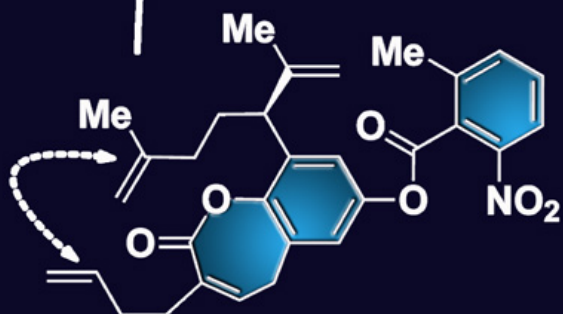
● [10] metacyclophane



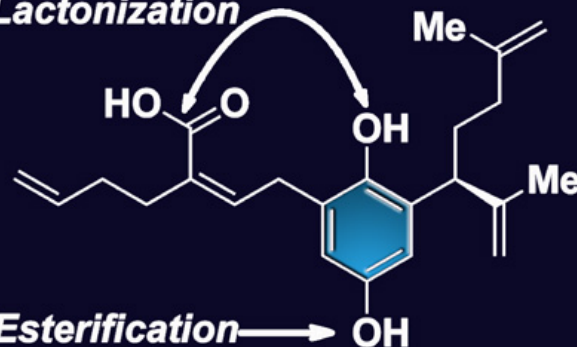
Grubbs II cat.

1. Ring closing metathesis [Grubbs II, 89 %]

2. Deprotection [K_2CO_3 , 90 %]



● Lactonization

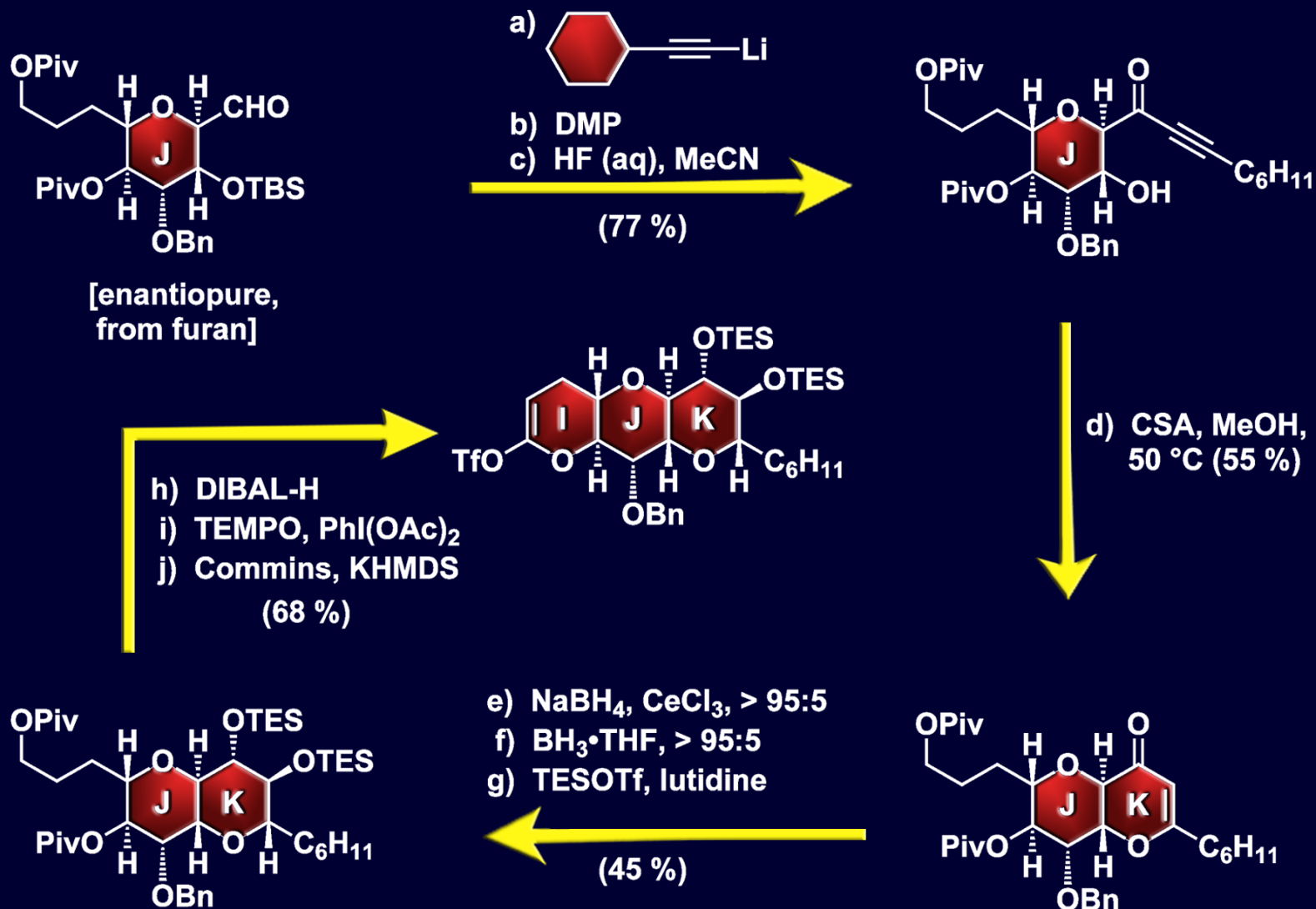


● Esterification



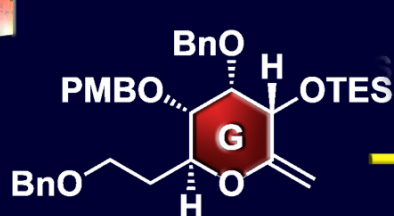


SYNTHESIS OF GHIJK DOMAIN OF MAITOTOXIN (2007) – 1





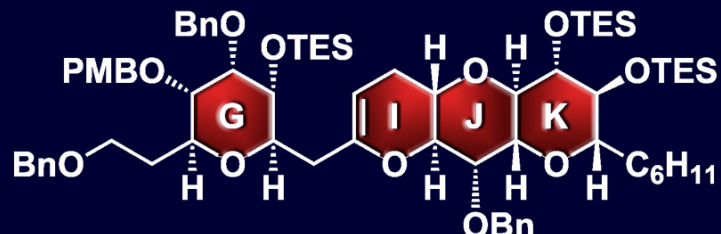
SYNTHESIS OF GHIJK DOMAIN OF MAITOTOXIN (2007) – 2



[enantiopure,
from furan]

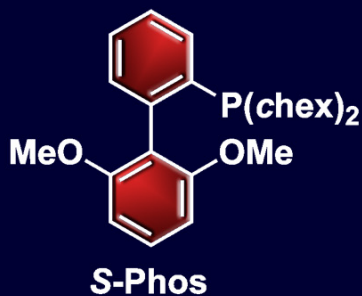
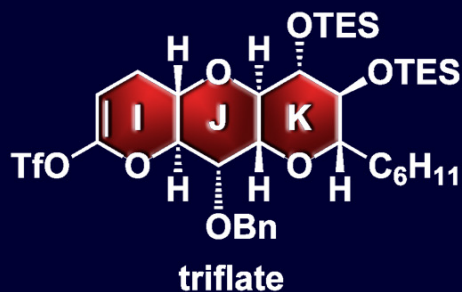
a) 9-BBN, THF, 60 °C;
NaHCO₃, Pd(OAc)₂,
S-Phos, 0.5 eq triflate

(71 %)

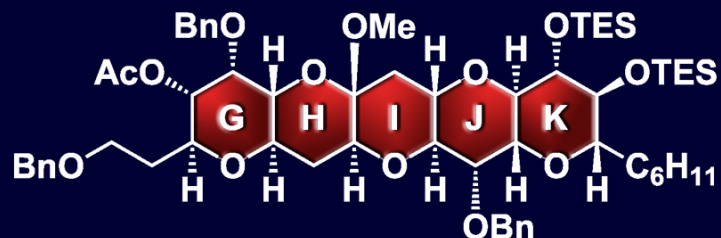


b) BH₃•THF
c) DMP

d) MeOH, pTsOH
e) Ac₂O (51 %)

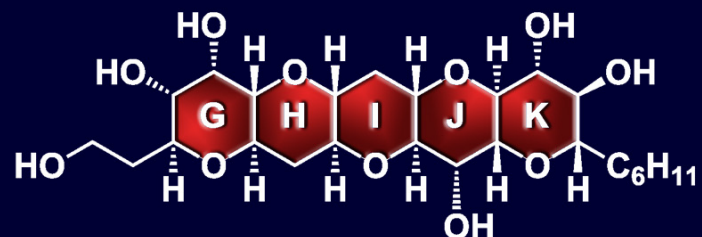


S-Phos



f) BF₃•OEt₂, TES-H
g) K₂CO₃, MeOH

h) H₂, Pd(OH)₂/C
(81 %)



CONSTRUCTION OF THE JKL RING SYSTEM OF MAITOTOXIN [1996]

