

THE
SCRIPPS
RESEARCH
INSTITUTE

THE K.C. NICOLAOU GROUP DEPARTMENT OF CHEMISTRY

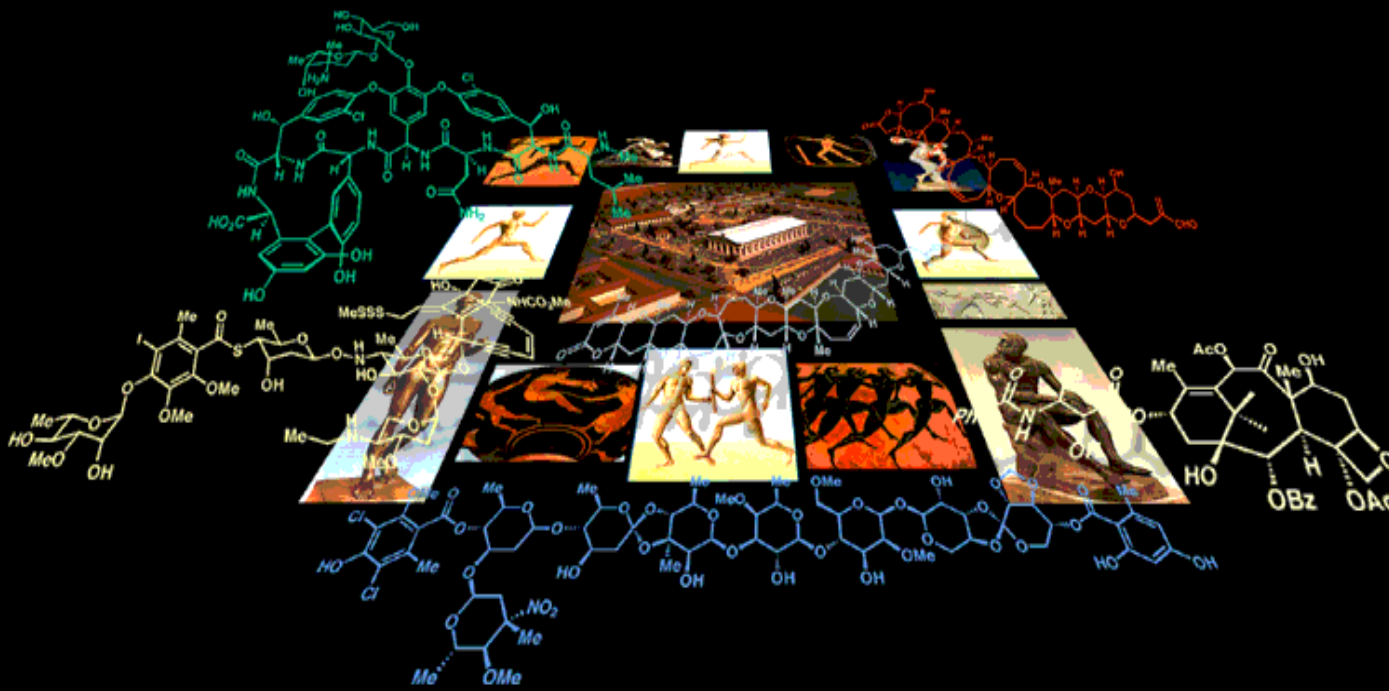
SCRIPPS ● SKAGGS ● UCSD

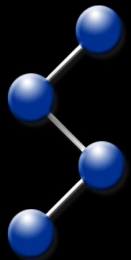


UNIVERSITY OF
CALIFORNIA, SAN DIEGO

Visit us at <http://www.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) and *Classics in Total Synthesis II* (K.C. Nicolaou and Scott A. Snyder, Wiley-VCH, 2003). Enjoy the tour of our world.*





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UNIVERSITY OF
CALIFORNIA, SAN DIEGO

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Chairman, Department of Chemistry

Aline W. and L.S. Skaggs

Professor of Chemical Biology, and

Darlene Shiley Chair in Chemistry

***The Scripps Research Institute, La Jolla, California
and***

The University of California, San Diego, California

PERSPECTIVES IN TOTAL SYNTHESIS

***Singapore
December 16, 2004***



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**

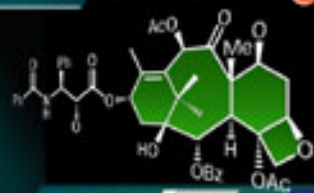
● **COMBINATORIAL CHEMISTRY**

● **PROCESS CHEMISTRY**

● **COST: \$500 MILLION AND RISING**

● **MEDICINAL CHEMISTRY**

● **REVIEW PROCESS**



\$

\$\$

\$\$\$

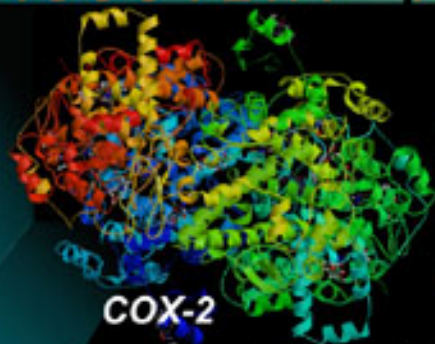


DISCOVERY

PRECLINICAL

CLINICAL

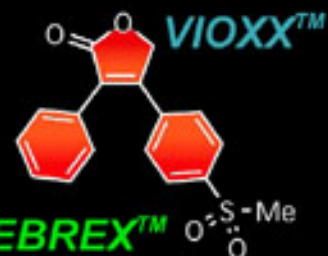
APPROVAL



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

● **HUMAN TRIALS**

● **TIME: 5-10 YEARS AND FALLING**



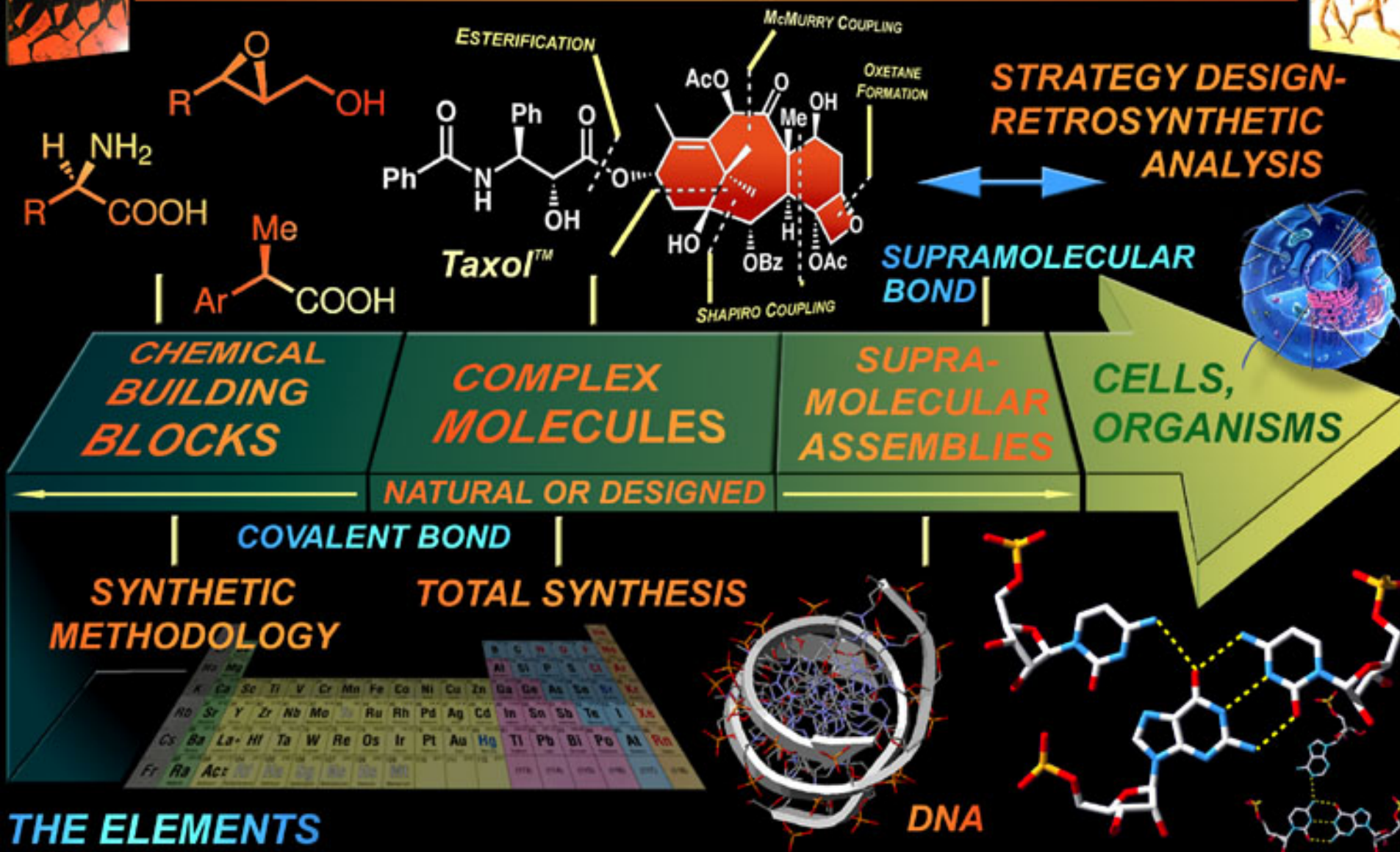
● **BIOLOGICAL TARGETS**

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

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

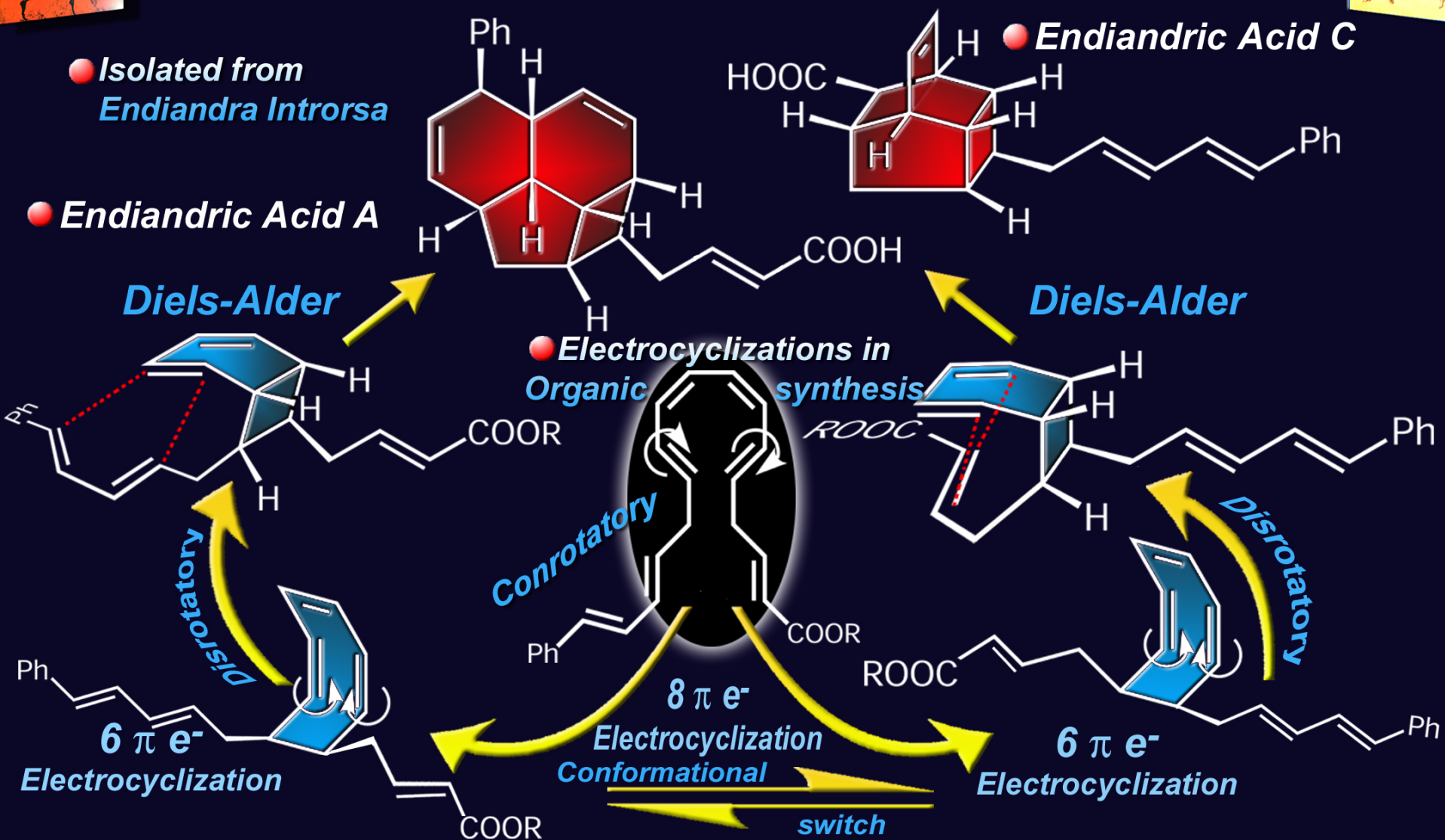


MOLECULAR COMPLEXITY and CHEMICAL SYNTHESIS



● **Endiandric Acid A**

● *Endiandric Acid C*



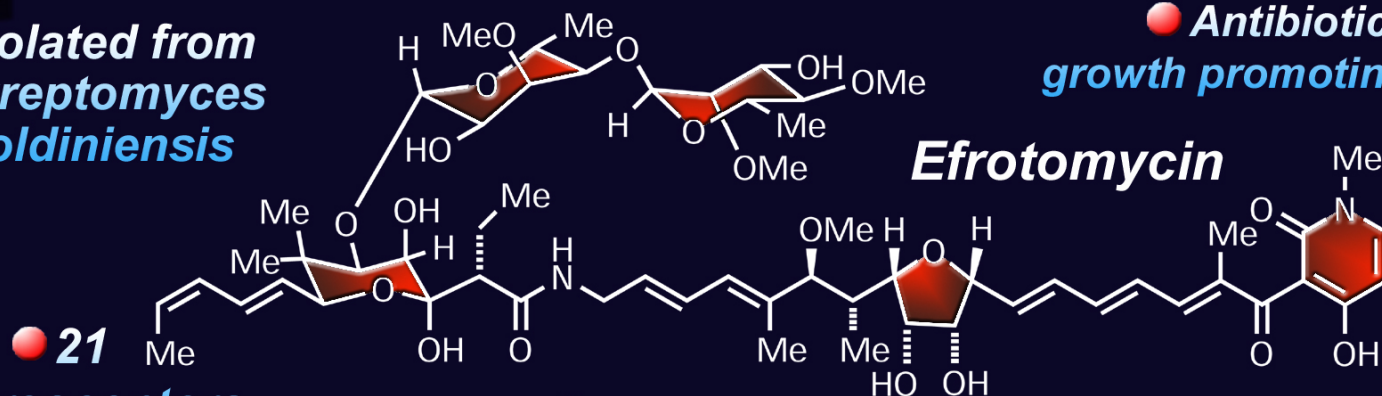


TOTAL SYNTHESIS OF EFROTOMYCIN [1984]

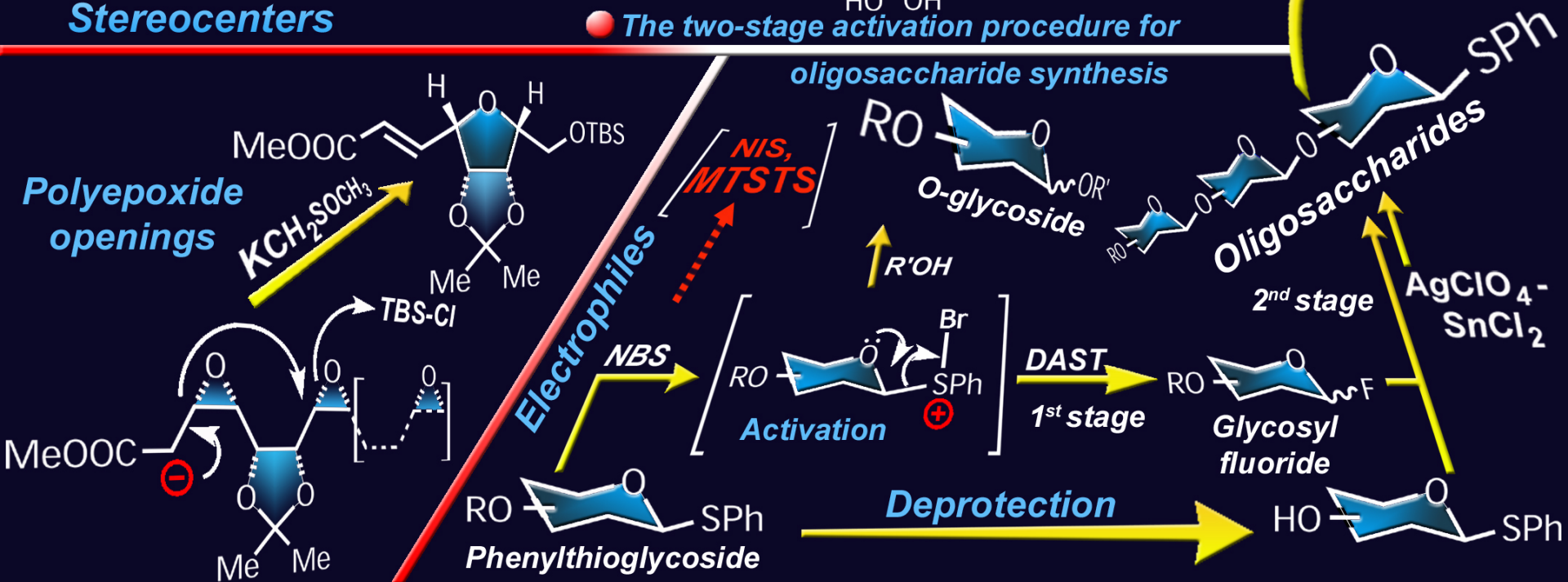


● Isolated from *Streptomyces goldiniensis*

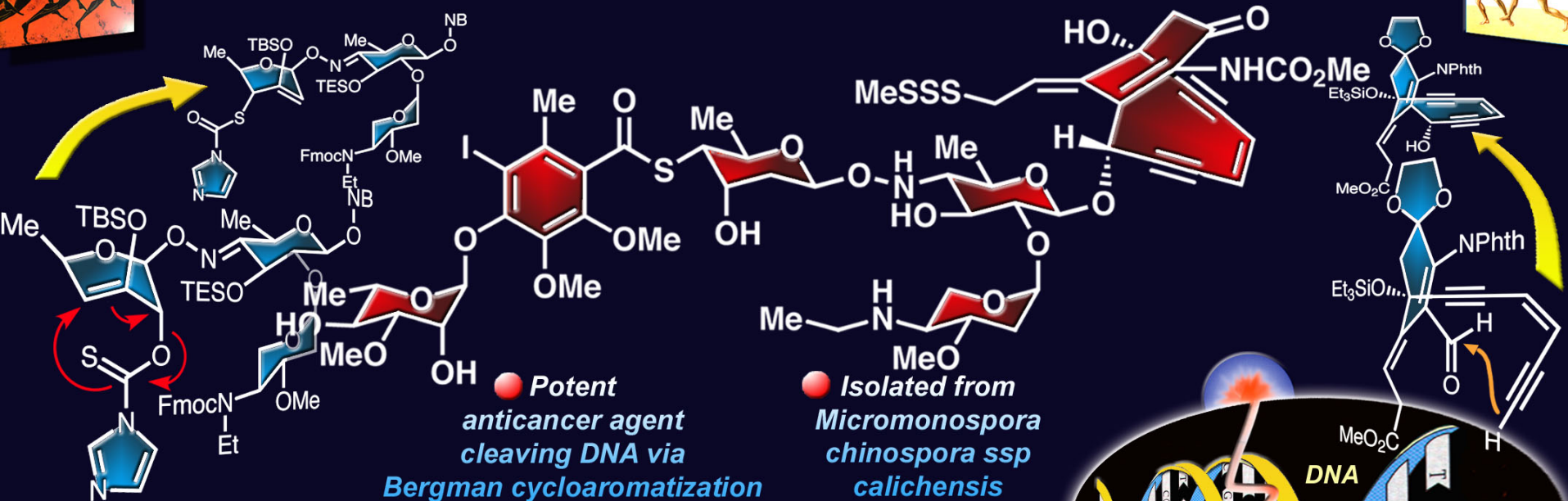
● Antibiotic with growth promoting properties



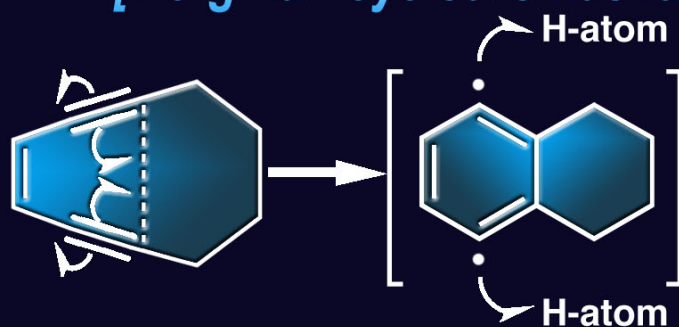
Stereocenters



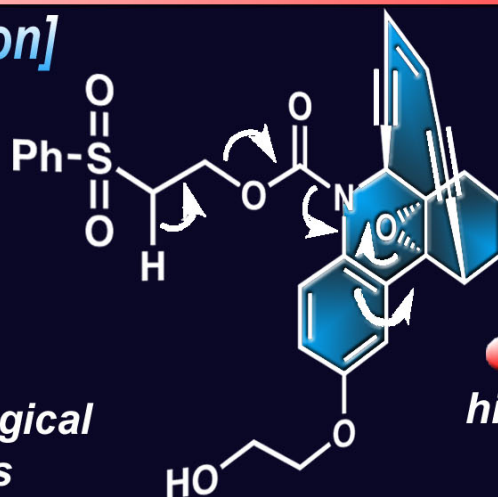
TOTAL SYNTHESIS OF CALICHEAMICIN γ_1' [1992]



[Bergman cycloaromatization]



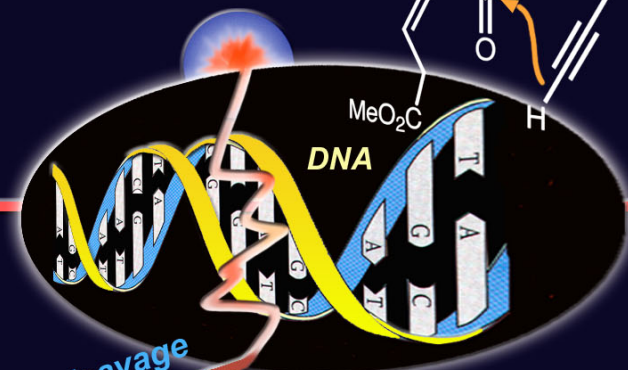
● **Elucidation of chemical and biological properties of cyclic enediynes**

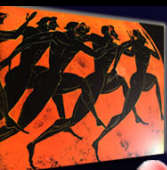


DNA cleavage
Cell death

Double strand cuts

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

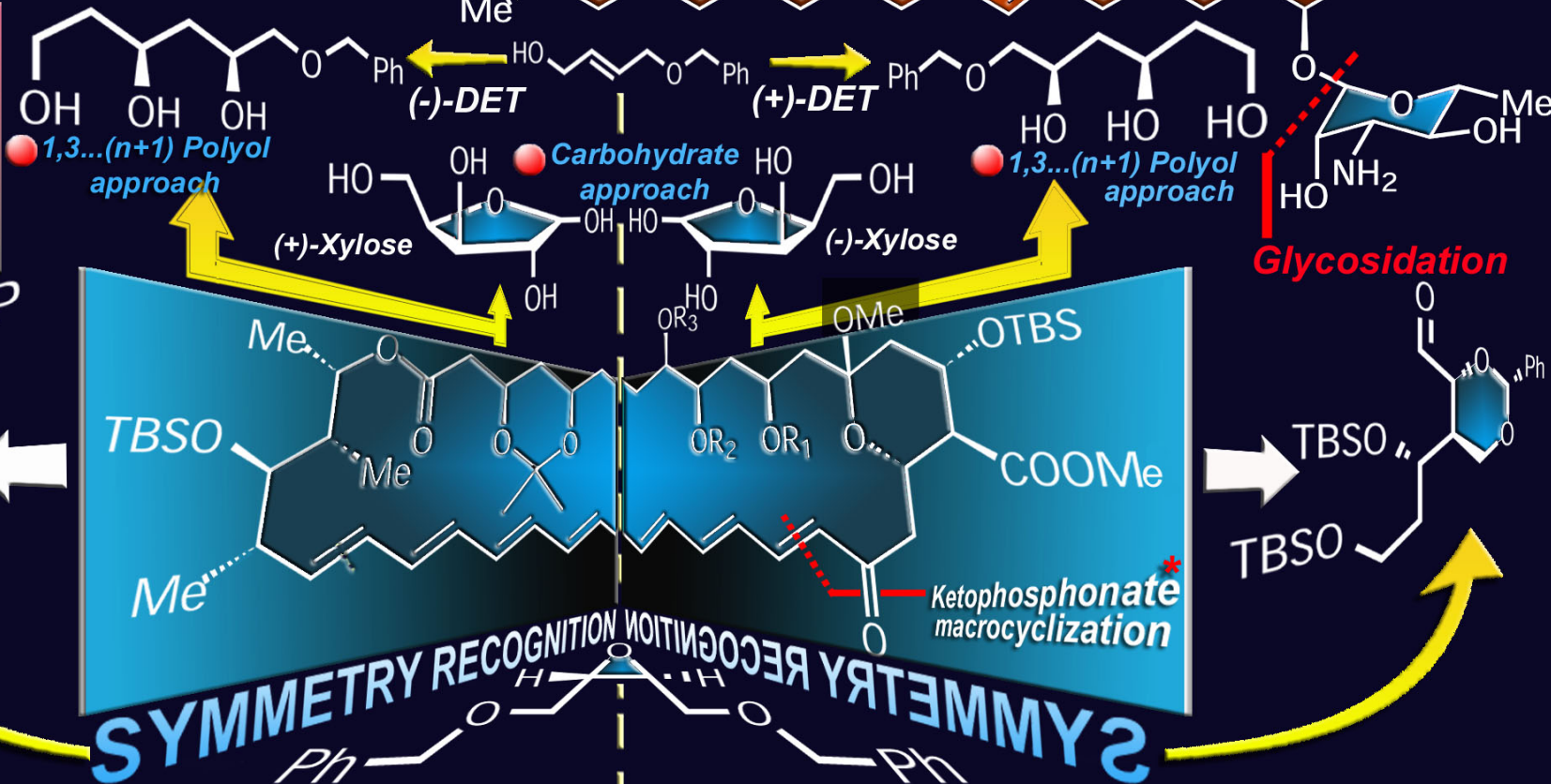
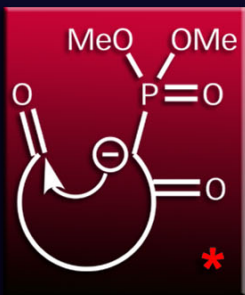
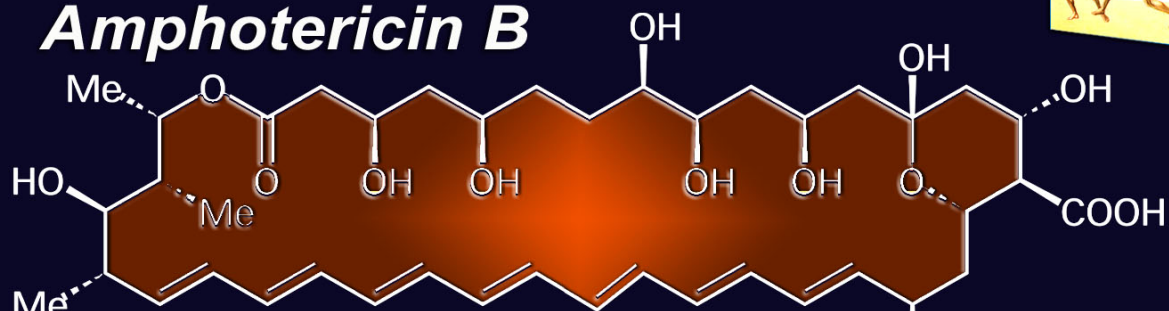




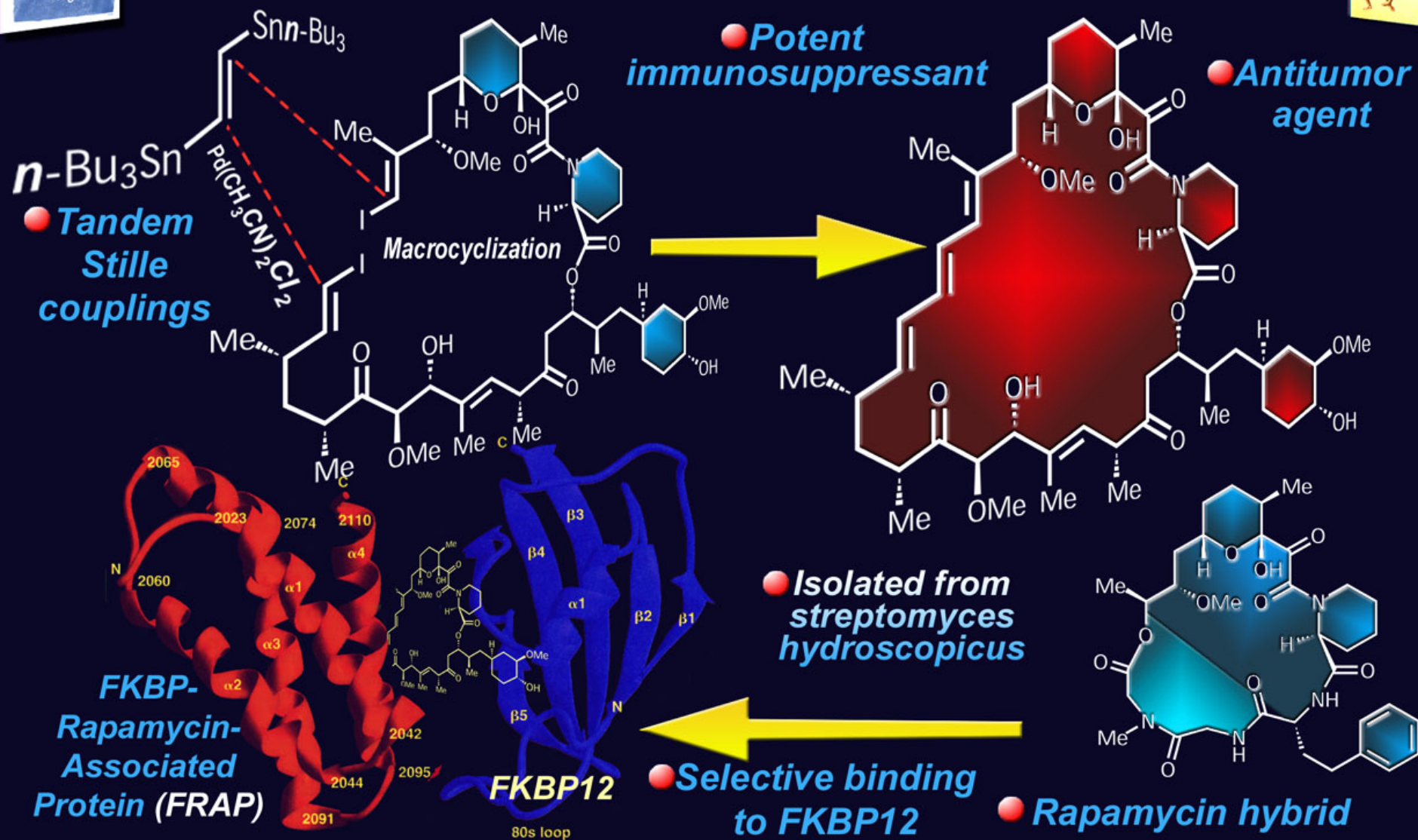
TOTAL SYNTHESIS OF AMPHOTERICIN B [1987]

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

Amphotericin B



TOTAL SYNTHESIS OF RAPAMYCIN [1993]

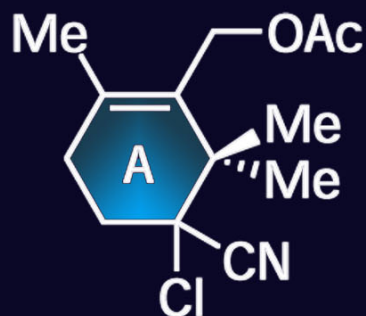




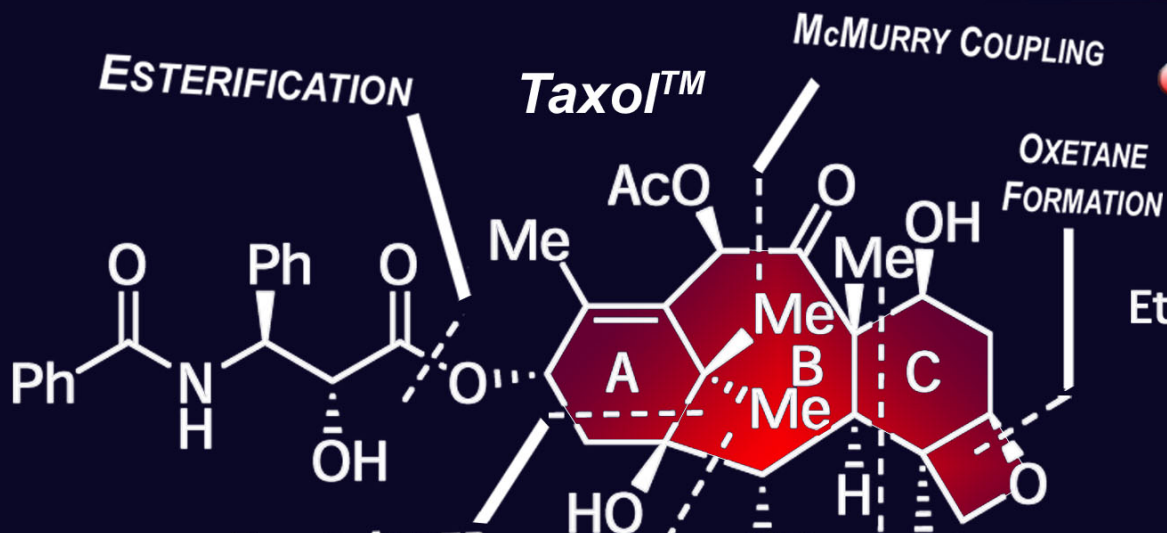
TOTAL SYNTHESIS OF TAXOL™ [1994]



● Water soluble pro-drugs



ESTERIFICATION



Taxol™

McMURRY COUPLING

● Fluorescent probes

OXETANE FORMATION



DIELS-ALDER

● Isolated from *Taxus brevifolia*

Taxus brevifolia

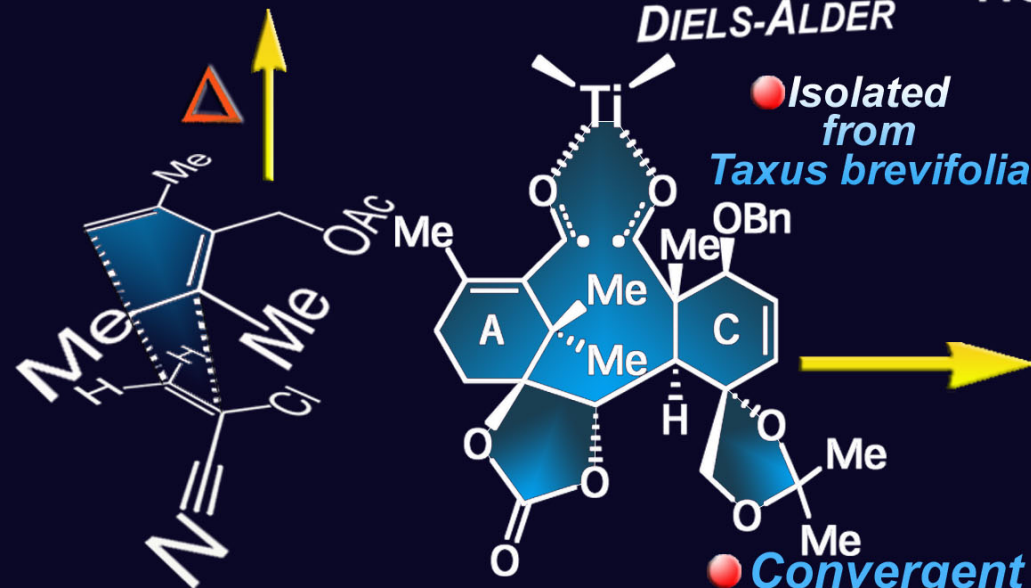
SHAPIRO COUPLING

DIELS-ALDER



Ph

● Convergent strategy





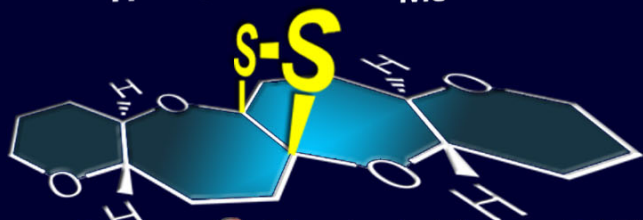
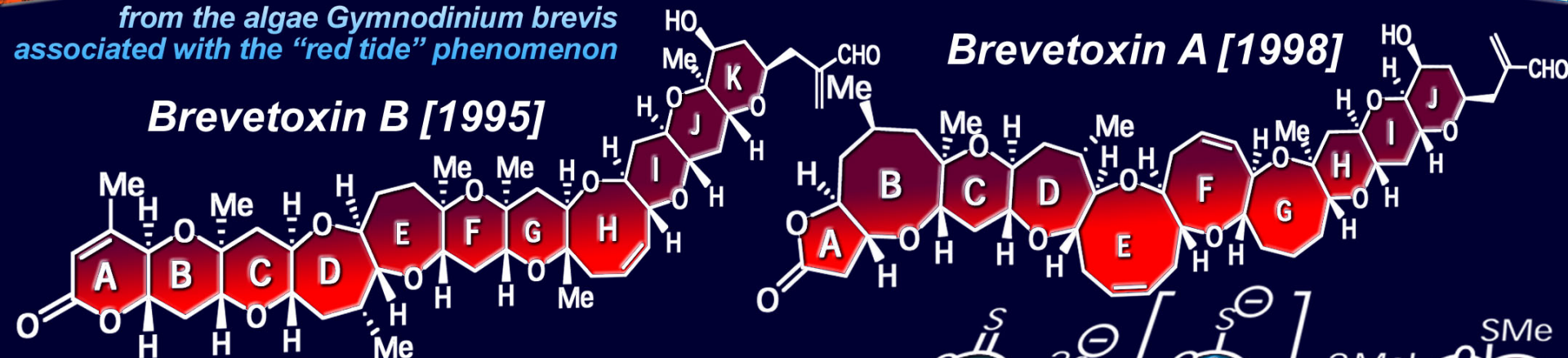
TOTAL SYNTHESIS OF BREVETOXINS B AND A [1982-1998]



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

Brevetoxin B [1995]

Brevetoxin A [1998]

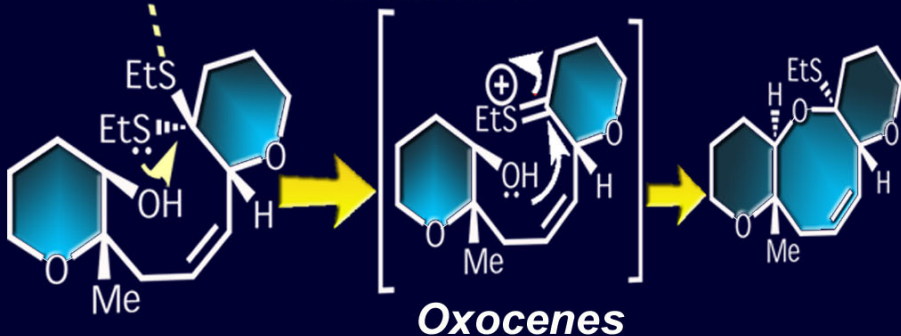


● First stable dithietane

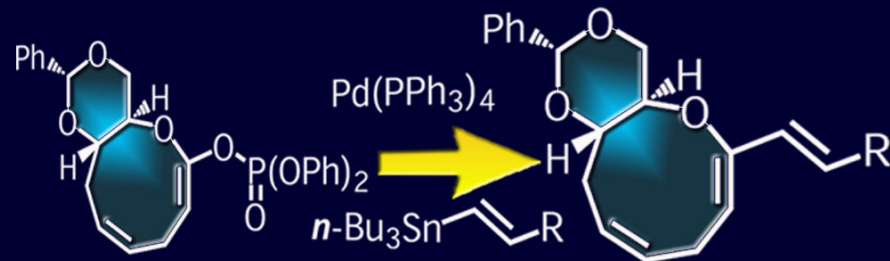
● New synthetic technologies



● Macrocycles to bicycles



Oxocenes



Palladium-catalyzed couplings



CHEMICAL SYNTHESIS AND BIOLOGY OF EPOTHILONES [1996-2003]



● Isolated from myxobacterium *sorangium cellulosum* strain ce90

● Potent anticancer agents

● Tubulin polymerization/ microtubule stabilization

● Designed Epothilones

● Subnanomolar potencies

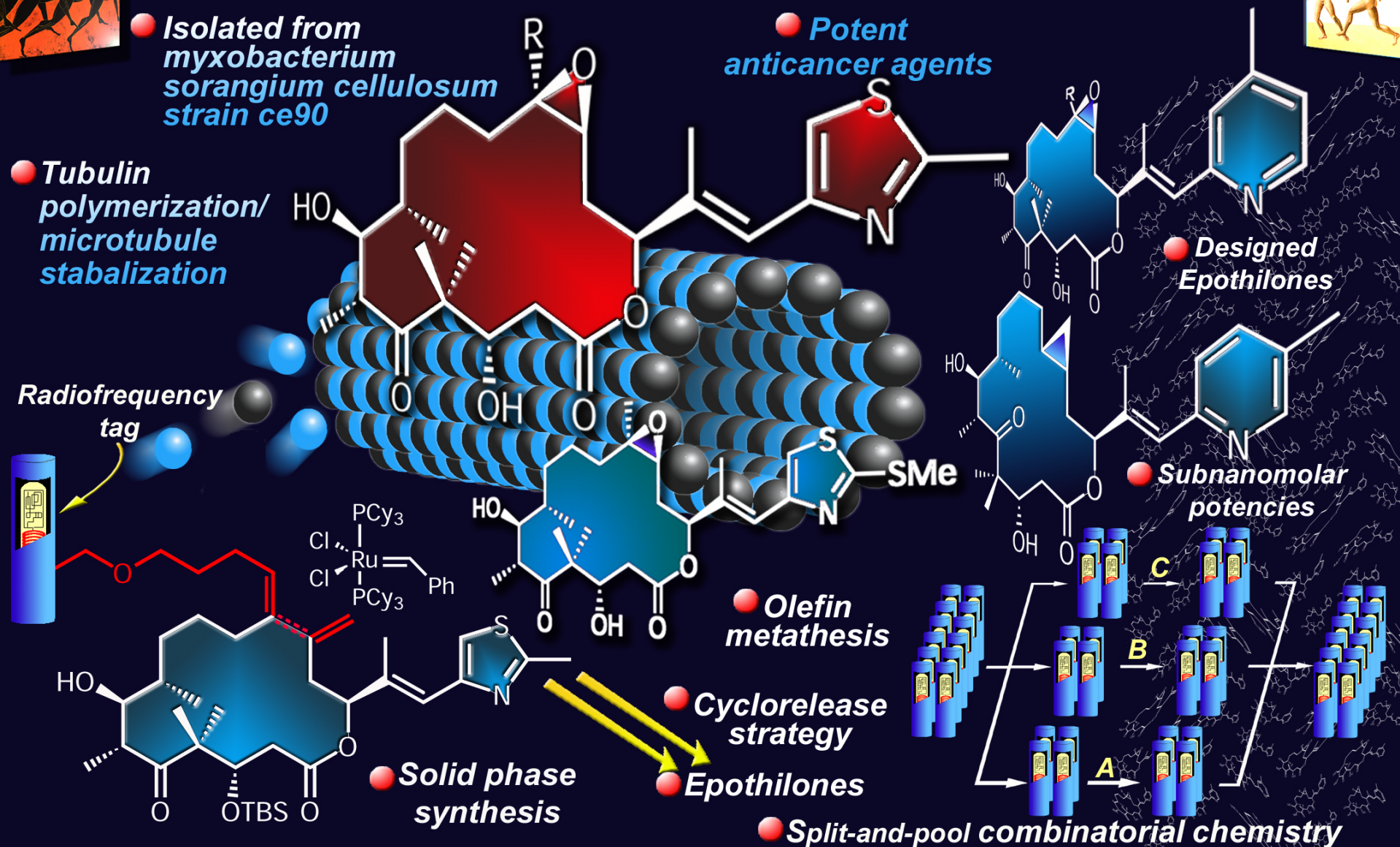
● Olefin metathesis

● Cyclorelease strategy

● Solid phase synthesis

● Epothilones

● Split-and-pool combinatorial chemistry



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



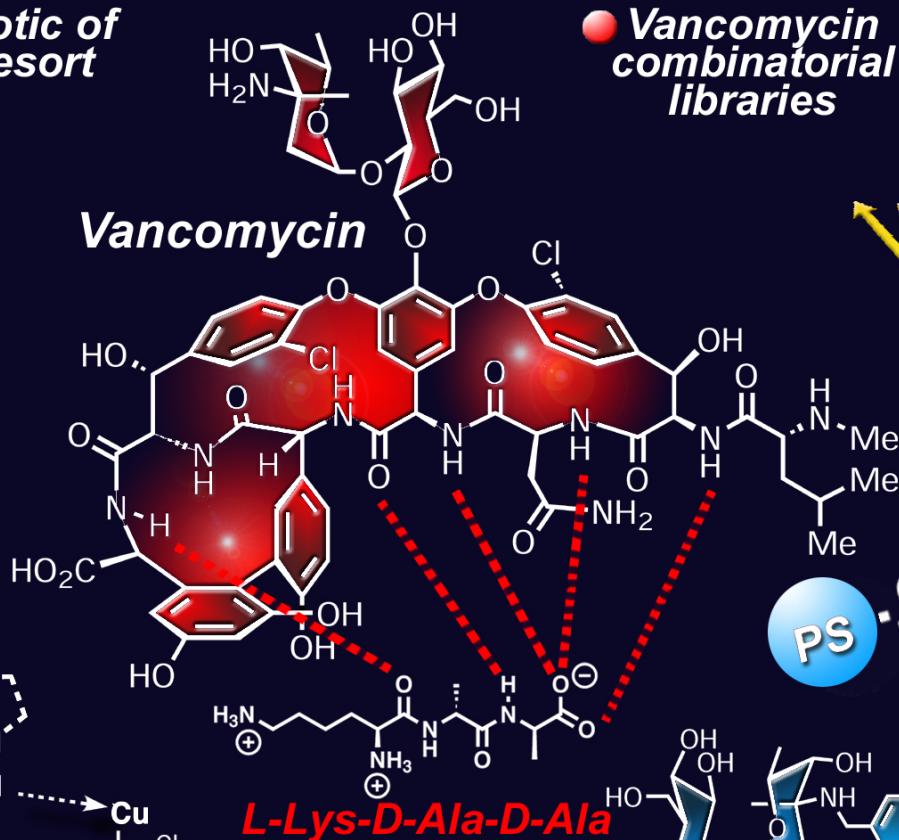
● **Antibiotic of last resort**

● **Vancomycin combinatorial libraries**

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

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

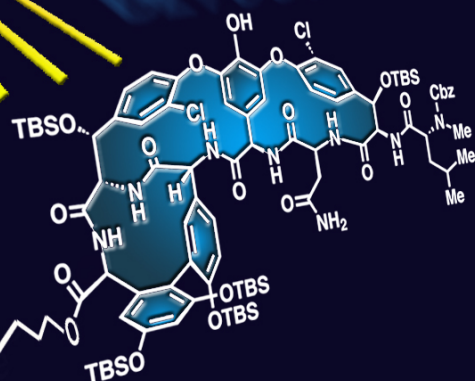
Vancomycin



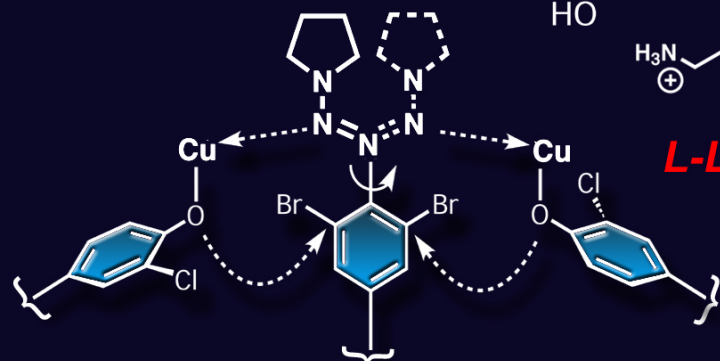
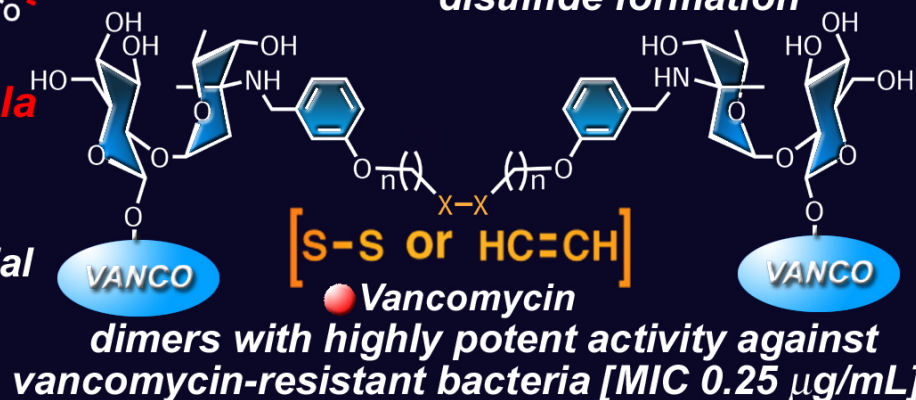
L-Lys-D-Ala-D-Ala

● **Target-accelerated combinatorial synthesis**

DEPROTECTIONS
CLEAVAGE
GLYCOSIDATIONS



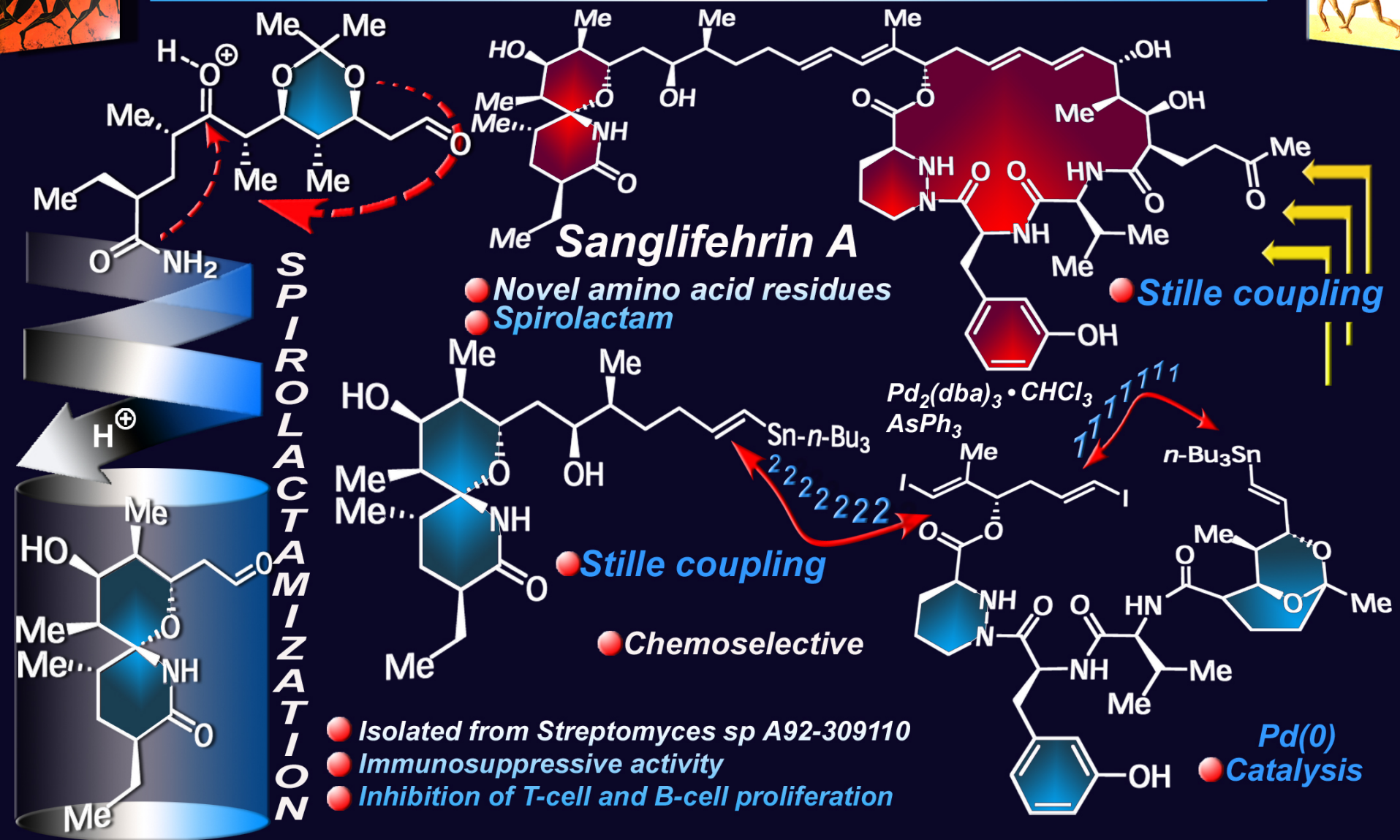
● **Olefin metathesis or disulfide formation**



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



TOTAL SYNTHESIS OF SANGLIFEHRIN A [1999]

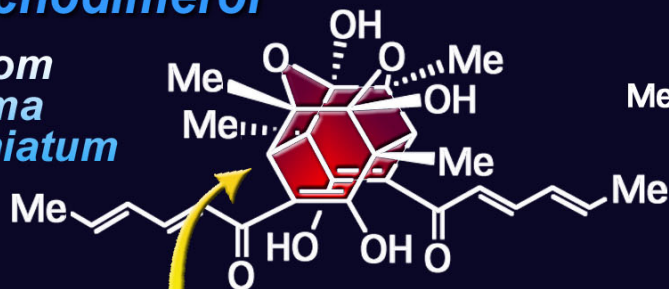


BIOMIMETIC TOTAL SYNTHESIS OF BISORBICILLINOIDS [1999]



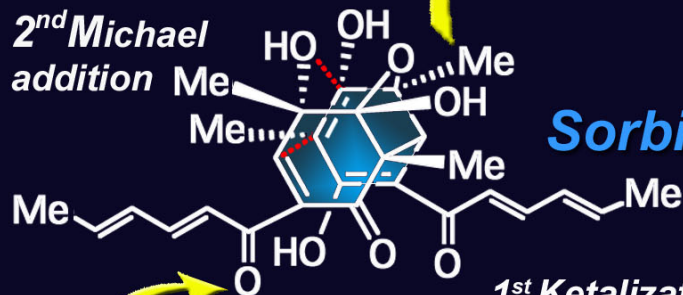
Trichodimerol

● Isolated from *Trichoderma iongibrachiatum*



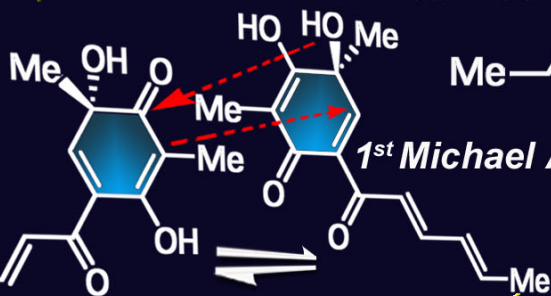
2nd Ketalization

2nd Michael addition



1st Ketalization

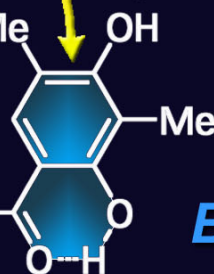
1st Michael Addition



Sorbicillin

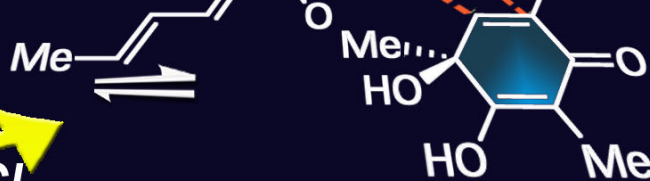
Bisorbibutenolide

Pb(OAc)₄



Bisorbicillinol

Diels-Alder



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

KHMDS; HCl

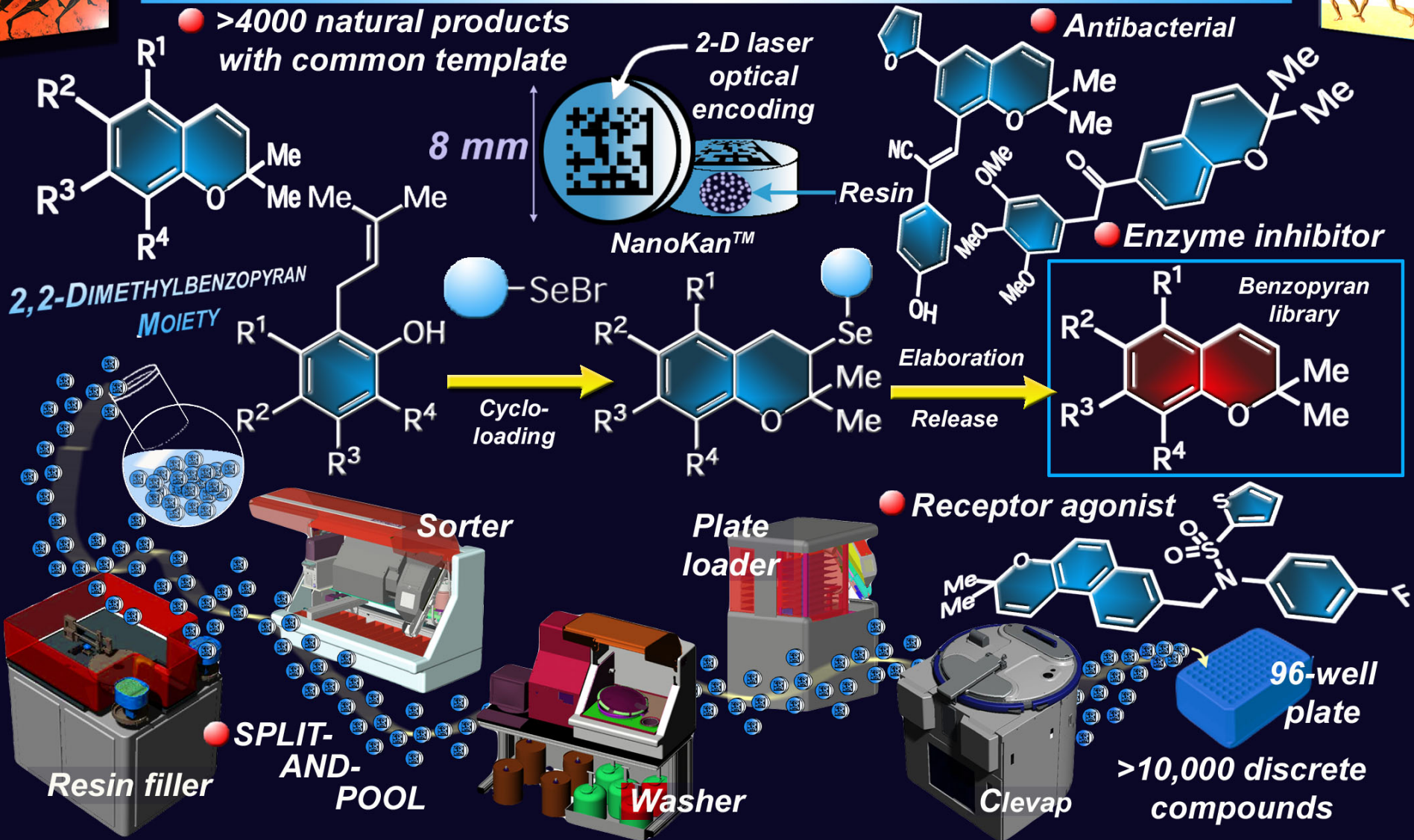
[O]

● DIMERIZATION OF QUINOLS

CsOH; NaHPO₄ KOH; HCl

OPTICALLY ENCODED COMBINATORIAL CHEMISTRY: BENZOPYRANS[2000]

- >4000 natural products with common template





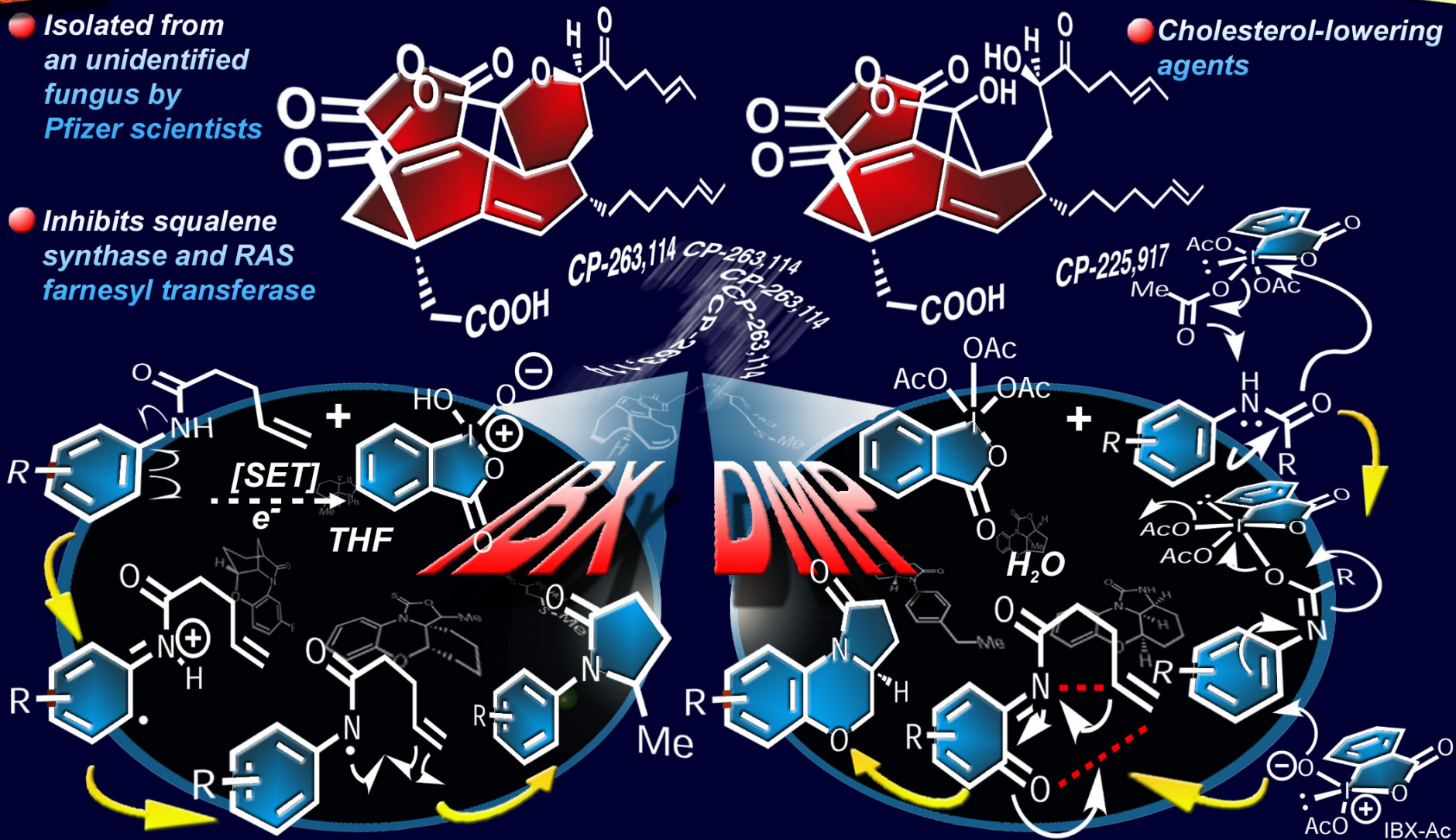
TOTAL SYNTHESIS OF THE CP MOLECULES [1999]



● Isolated from an unidentified fungus by Pfizer scientists

● Inhibits squalene synthase and RAS farnesyl transferase

● Cholesterol-lowering agents



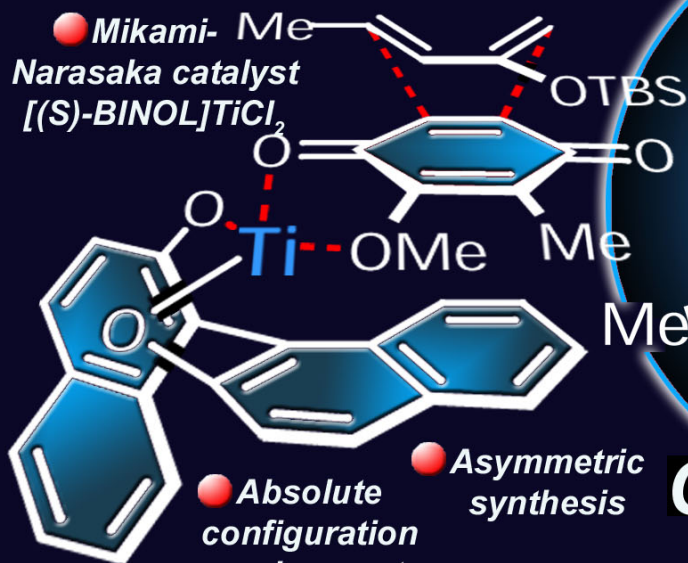


TOTAL SYNTHESIS OF COLOMBIASIN A [2001]

● Possibly active against *Mycobacterium tuberculosis* H37Rv

● Isolated from coral *pseudopterogorgia elisabethae*

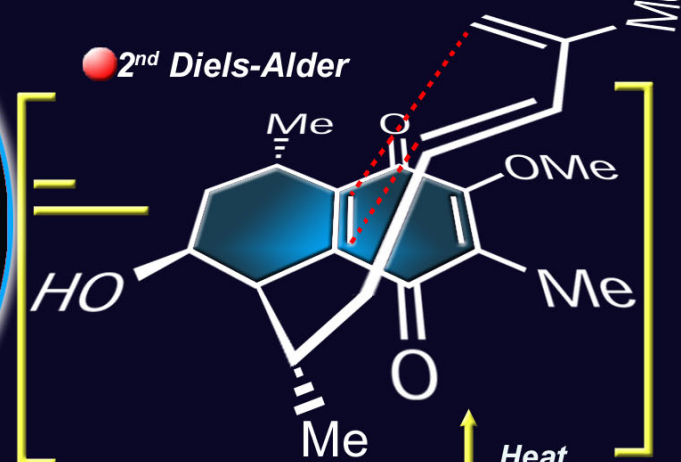
● Mikami-Narasaka catalyst
[(S)-BINOL]TiCl₂



● Absolute configuration assignment
● Asymmetric synthesis

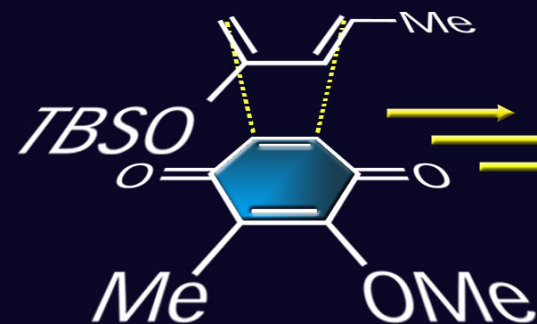
Colombiasin A

● 2nd Diels-Alder

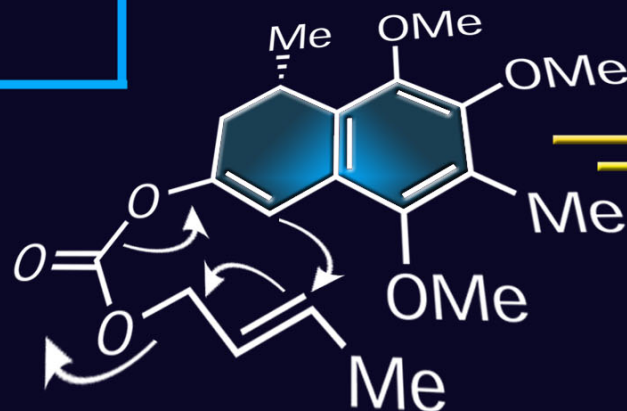


Heat [dark]

CASCADE I
CASCADE I
CASCADE I



● 1st Diels-Alder

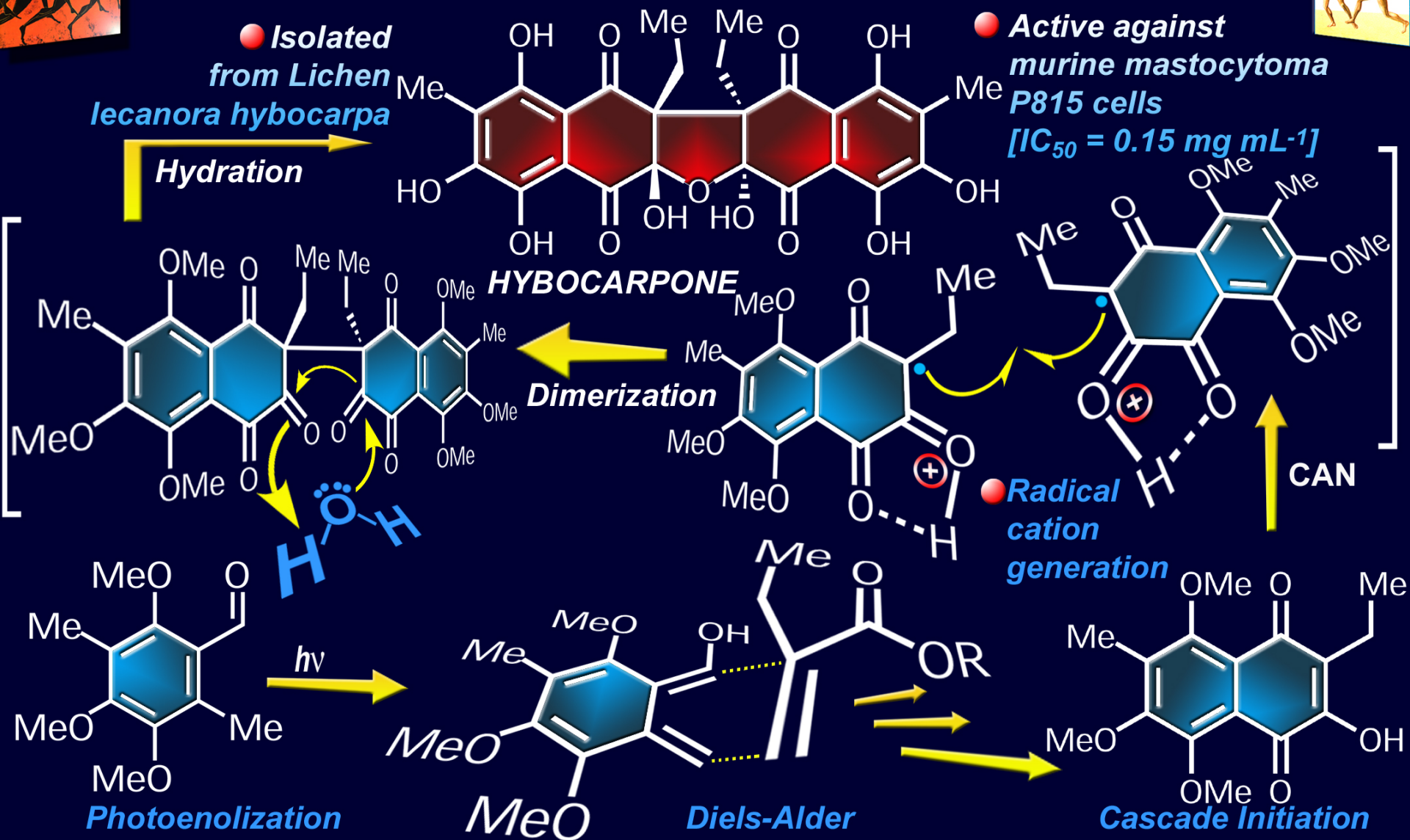


● Palladium-catalyzed rearrangement



● Masking of diene system

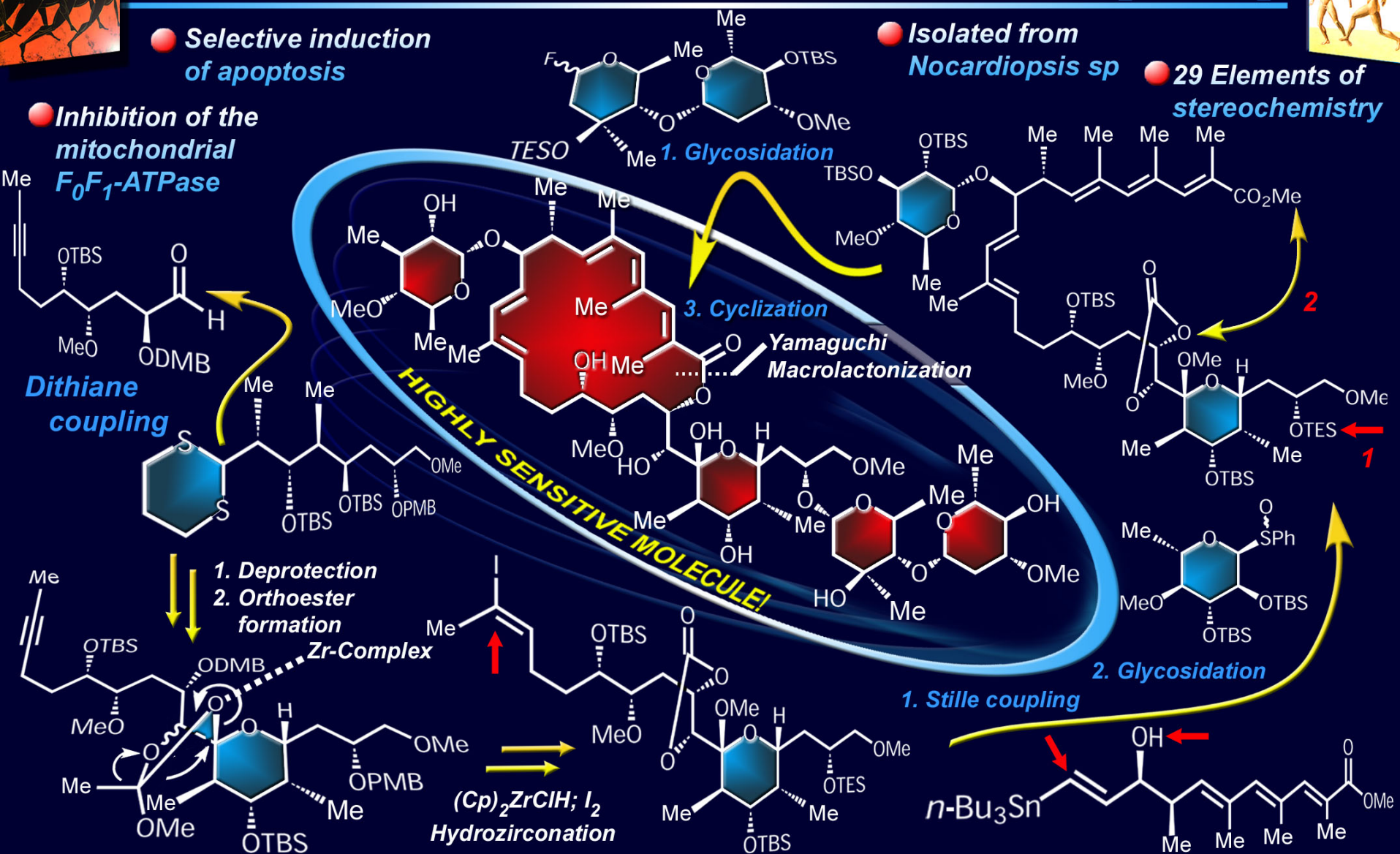
● **Active against murine mastocytoma P815 cells**
[IC₅₀ = 0.15 mg mL⁻¹]





● 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

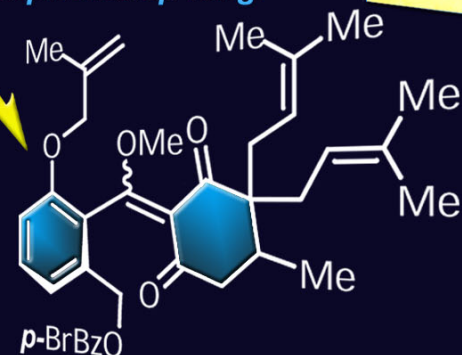
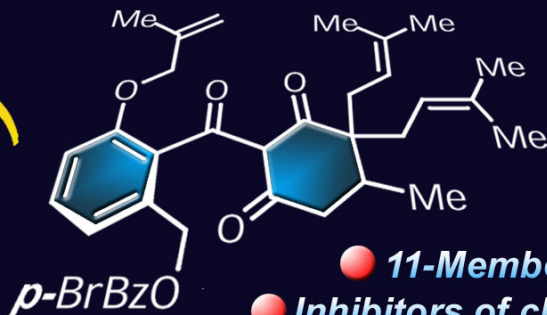
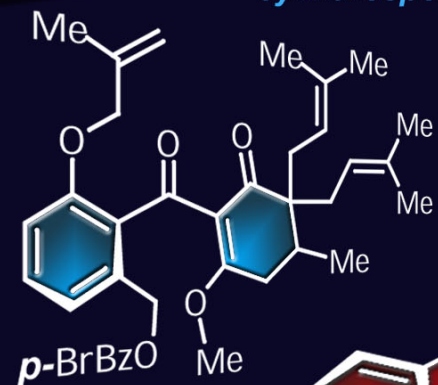
● From *Coleophoma* sp fungi

CH_2N_2

CH_2N_2

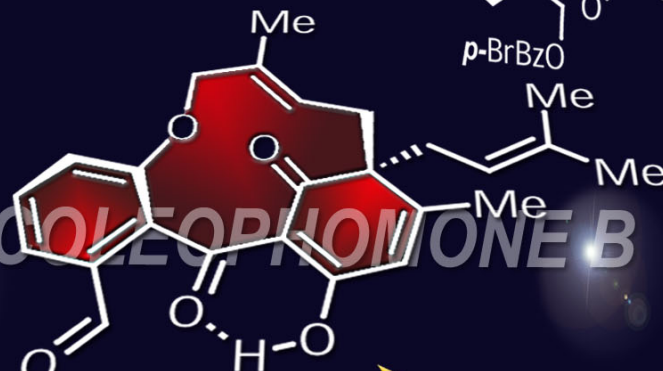
● 11-Membered rings

● Inhibitors of chymase



CATALYST
Stereoselective
ring closing
metathesis

Stereoselective
ring closing
metathesis
CATALYST



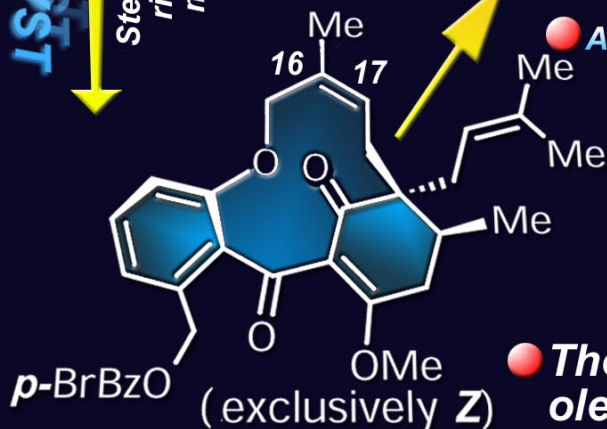
● Antibiotics

● Antifungal



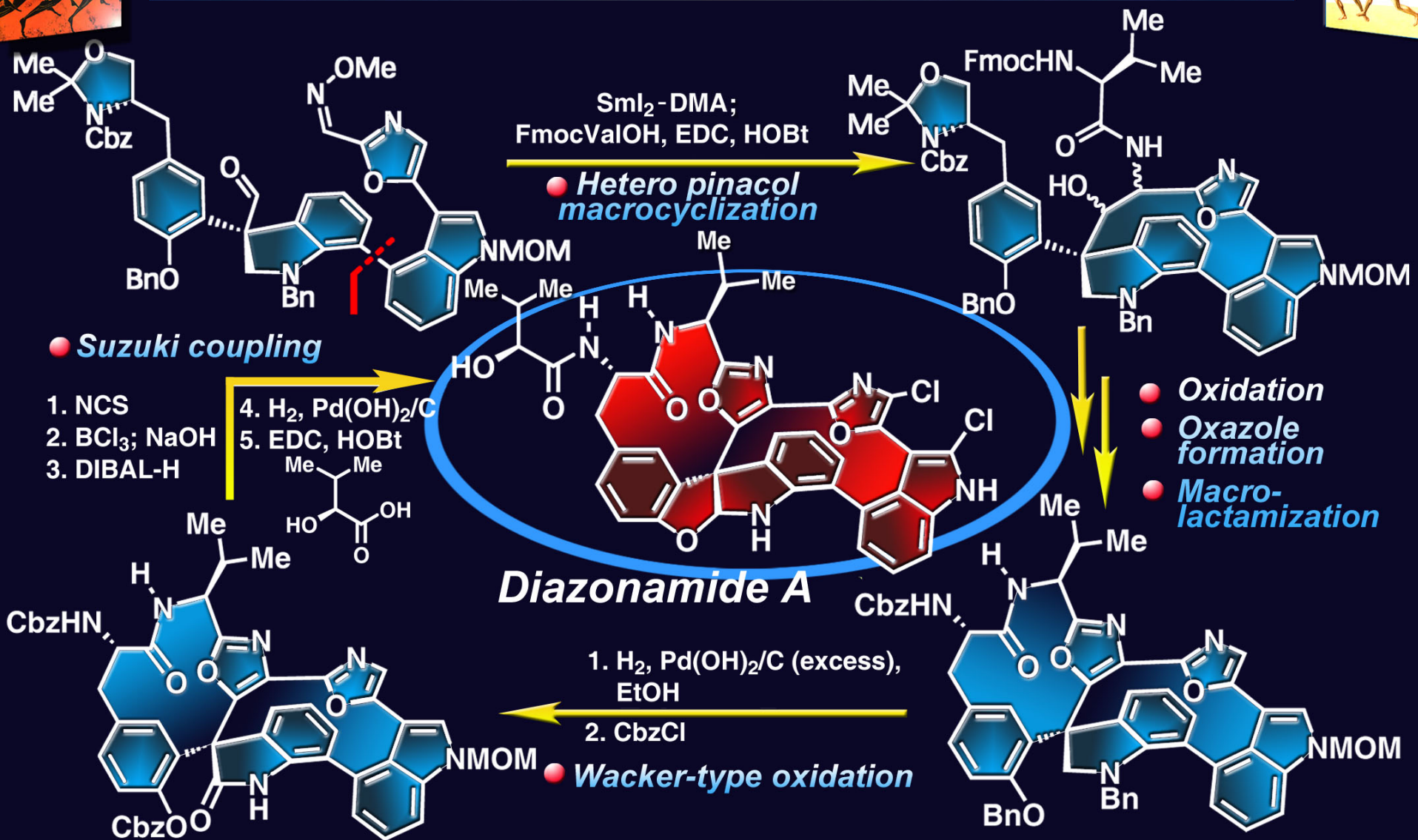
● The magic of the
olefin metathesis reaction

CATALYST
CATALYST



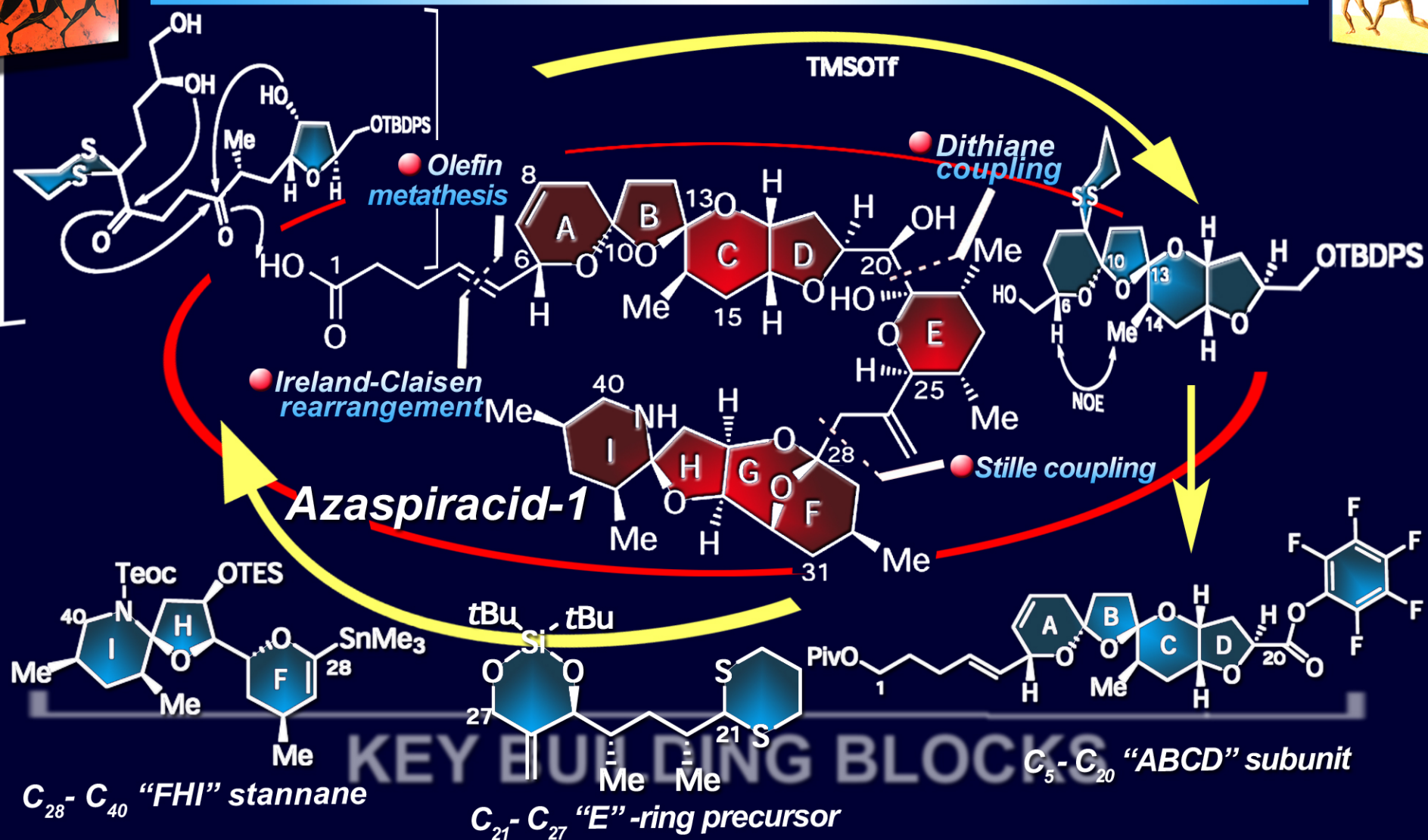


THE Sml_2 ROUTE TO DIAZONAMIDE A [2003]

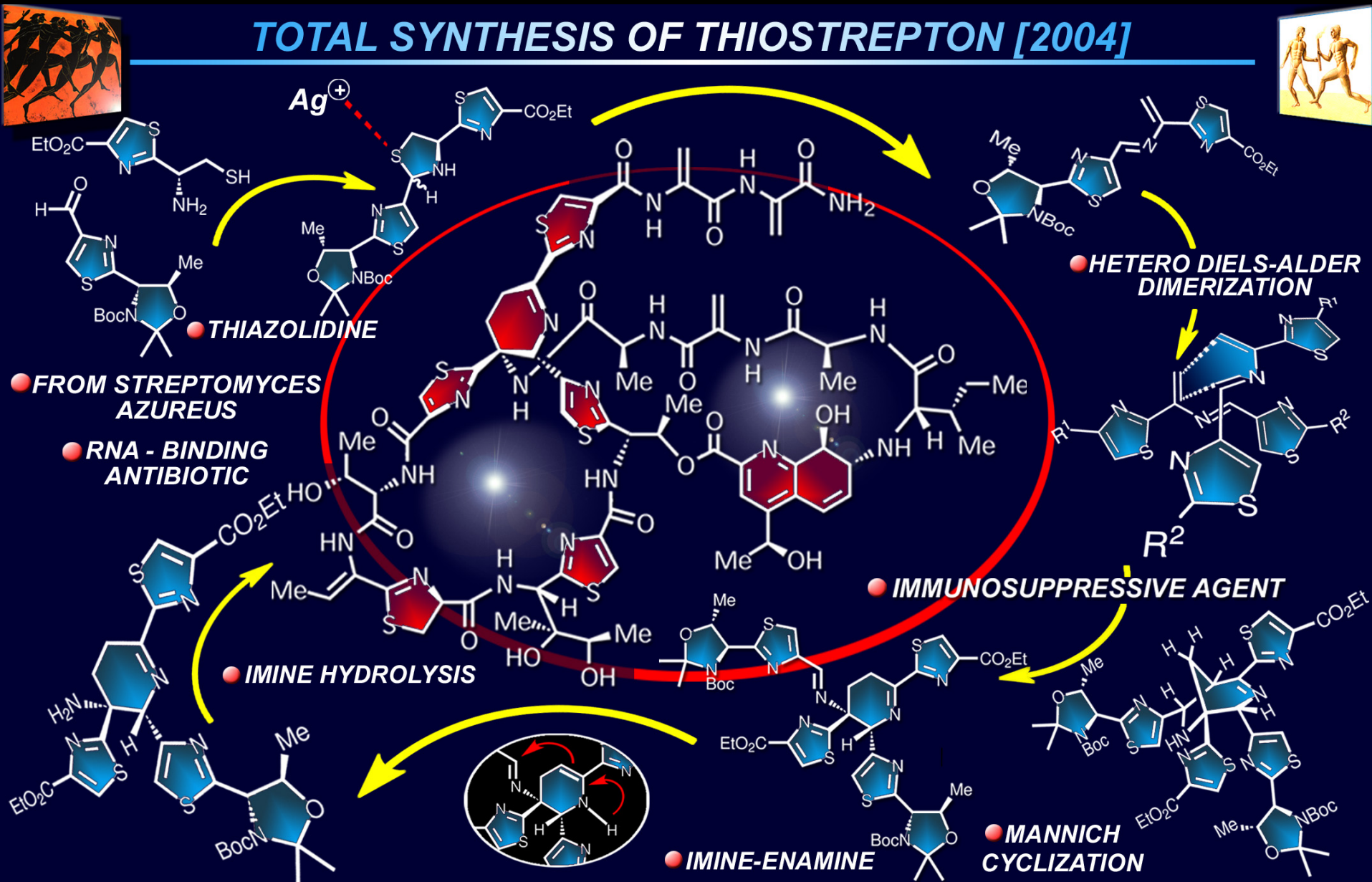




TOTAL SYNTHESIS OF AZASPIRACID-1 [2004]



TOTAL SYNTHESIS OF THIOSTREPTON [2004]





BREAKING NEW GROUND IN TOTAL SYNTHESIS

INSPIRATIONS FROM NATURE

NOVEL MOLECULAR ARCHITECTURES

COMPLEX AND CHALLENGING TARGETS

BOND CONNECTIVITIES

RING FRAMEWORKS

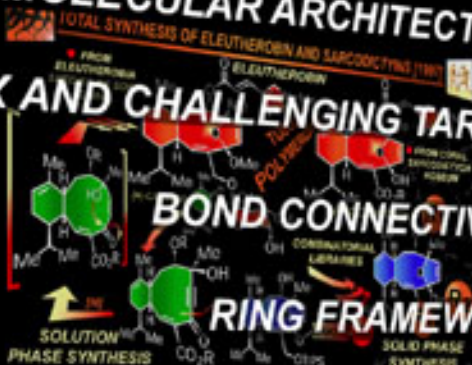
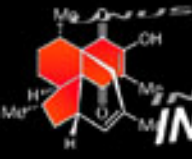
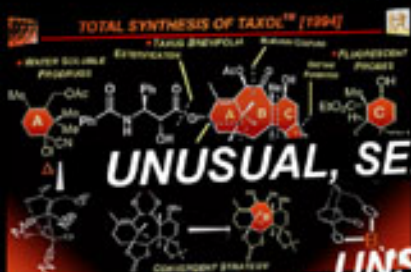
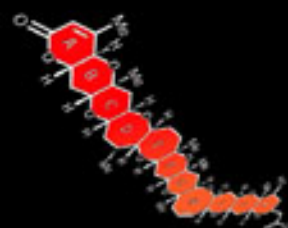
STEREOGENIC CENTERS

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

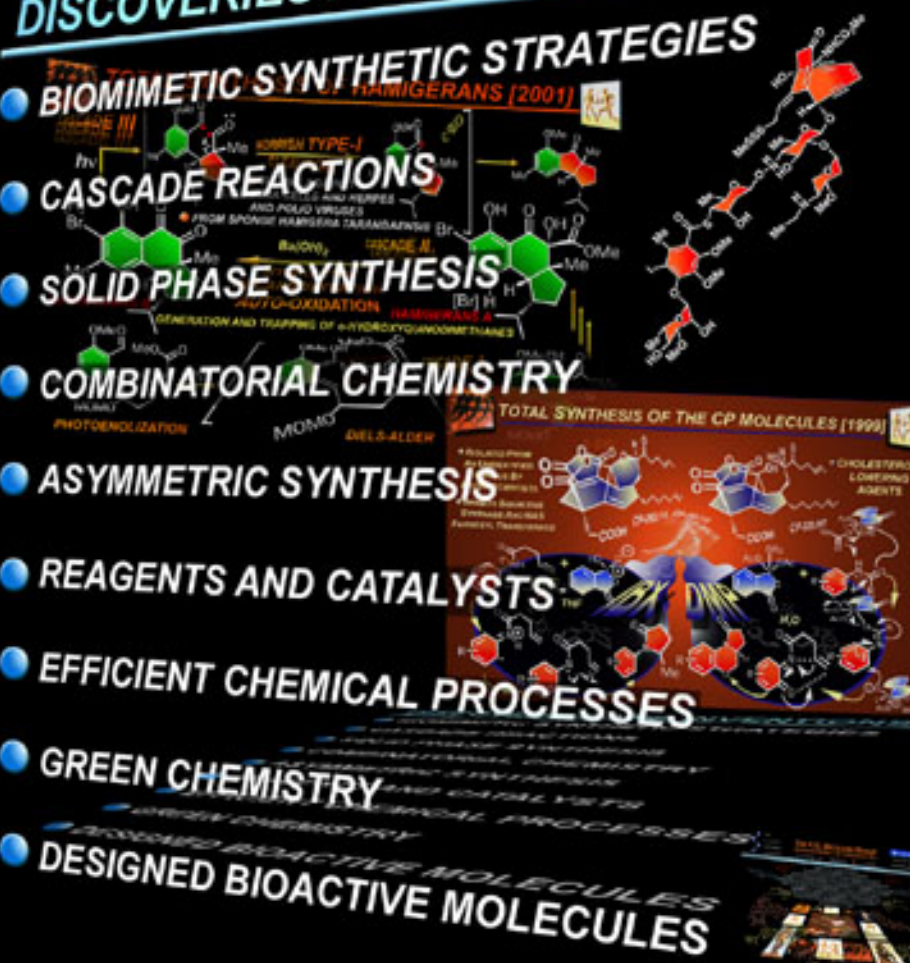
ASYMMETRIC SYNTHESIS

REAGENTS AND CATALYSTS

EFFICIENT CHEMICAL PROCESSES

GREEN CHEMISTRY

DESIGNED BIOACTIVE MOLECULES



THANKS AND ACKNOWLEDGEMENTS

GRADUATE STUDENTS AND POSTDOCTORAL FELLOWS

- THE SKAGGS INSTITUTE FOR CHEMICAL BIOLOGY
- THE NATIONAL INSTITUTES OF HEALTH
- THE GEORGE E. HEWITT FOUNDATION
- THE CAPCURE FOUNDATION

● NMR SPECTROSCOPY:
DEE-HUA HUANG, Ph.D.,
L. B. PASTERNAK, Ph.D.

● MASS SPECTROMETRY:
GARY SIUZDAK, Ph.D.

● X-RAY CRYSTALLOGRAPHY:
RAJ K. CHADHA, Ph.D.

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Curtis Adams
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Kyo Han Ahn
Keiichi Ajito
Elirini Alexopoulou
Andreas Anagnostopoulos
Mariana Anagnostopoulos
Katherine Arbanasin
Corrine E. Augelli-Szafran
Radl Awartani
Rachid Baati
Kai-Uwe Baldenius
Toshikazu Bando
Phil Baran
Sofia Barluenga
William Barnett
Thomas Barth
Olivier Baudoin
Marco Bella
Mikael Berghdahl
Federico Bernal
Peter Bertinato
Guiseppe Bifulco
Antony Bigot
Ted Bleckman
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Mark Duggan
Takashi Ebata
Michael Elliseseou
Virginia Estevez-Jacobsen
Anthony Estrada
Luc Even
M. Ray Finlay
Holger Flörke
Markus Follmann
Kin Chiu Fong
Tasha Francis
Michael Frederick
John Frederick Fox
Christian Funke
Shuichi Furuya
Tina Fylaktakidou
Jose Garcia-Navio
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Luigi Gomez-Paloma
Otto Gräther
David Gray
Robert Gronenberg
Jonathan Gross
Josh Gruber
Mugesh Govindasamy
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Janet Gunzner
Rodney (Kip) Guy
Nizar Haddad
Christos Hadjilistephanou
Michael Härter
Richard Hark
Bruce Harris
Scott Harrison
Junliang Hao
Hiroyuki Hayakawa
Yoshio Hayashi
Hu-Ming He

Yun He
David Hepworth
Pedro Hernández-Abad
Jürgen Hinrichs
Yong-Pyo Hong
Seiji Hosokawa
Xianhai Huang
Robert Huber
Robert Hughes
Conrad Hummel
Kevin Hunt
John Hutchinson
Jack C.K. Hwang
Ioannis Ioannou
Kiyoshi Ikeda
Kunio Isshiki
Yoshiharu Iwabuchi
Mark Izraelwicz
Naresh Kumar Jain
Bernad Jandeleit
Rolf Jautelat
Michael Jennings
Zhendong Jin
Jae kyu Jung
Florian Kaiser
Balreddy Kamireddy
Hideaki Kataoka
Harry Katerinopoulos
Michael Kerr
Jilali Kessabi
Haripada Khatuya
Byeang Hyeon Kim
David Kim
Sanghee Kim
N. Paul King
Theocharis Koftis
Kazunori Koide
Hironori Komatsu
Alexandros Koumbis
Remo Kranich
Michael Krel
Shuhei Kubota
Toshiaki Kumazawa
Tamara Ladduwahetty
Susan La Greca
Sanghyup Lee
Robert Lemus
James Leresche
Bernard Leroux
Hui Li
Jim Li
Tianhu Li
Wen-Sen Li

David Nugiel
Yuji Ogawa
William Ogilvie
Kouichi Ohe
Takashi Ohshima
Michel Ouellette
Demetris Papahadjis
Bheema Rao Paraselli
Joaquin Pastor
Andrew Patron
K. Paulvannan
Michael Pavia
Jeff Pelletier
Manuela Pereira
Nicos Petasis
Jeffrey Pfefferkorn
Ainollisa Pihko
Petri Pihko
Sherrie Pietranico-Cole
Anthony Piscopio
Emmanuel Pitsinos
Ean Plotkin
Maarten Postema
C.V.C. Prasad
Benjamin Pratt
Wenyuan Qian
Joshi Ramanjulu
John Ramphal
Jared Randall
Geracimos Rassias
Dandu Reddy
K. Raja Reddy
Mali Venkat Reddy
Johanne Renaud
Paul Richter
Claus Riemer
Andreas Ritzten
Rosa Maria Rodriguez
A.J. Roecker
Frank Roschhangar
M.T. Nunez Ruano
Brent Rubo
Frank Rübsam
Floris Rutjes
Brian Safina
Hiroyuki Saimoto
Joe Salvino
Francisco Sarabia
Pradip Kumar Sasmal
Fuminori Sato
Mitsunobu Sato
Gerard Scarlato

Rita Scarpelli
Thomas Schäfer
Erwin Schreiner
Thomas Schulze
Edwin Schweiger
Dana Seigel
Steven Seitz
Mike Sertic
Guo-Qiang Shi
Shuhao Shi
Katsuhiko Shibayama
Jongheon Shin
Mitsuru Shoji
Klaus Simonsen
Nigel Simpkins
William Sipio
Golfo Skokotas
Chris Smethurst
Adrian Smith
Brian Smith
Scott Snyder
Michael Solomon
Patty Somers
Erik Sorensen
Rolando Spanevello
Paul Spurr
Wilhelm Stahl
Alex Strongillos
Nicolas Stylianides
Hiroshi Suemune
Kazuyuki Sugita
Xiaowen Sun
Hideo Suzuki
Toshio Suzuki
Jinsung Tae
Masaru Takayanagi
David Tanner
Emmanuel Theodorakis
Jörg Tiebes
Mirek Tomaszewski
Yasuhiro Torisawa
Takeshi Toru
Kazunobu Toshima
Vinh Tran
John Trujillo
Susan Shwu-Chen Tsay
Tatsuo Tsuru
Jun'ichi Uenishi
Hiroaki Ueno
Noriaki Uesaka
Trond Ulven
Eduard Untersteller

Hans Vallberg
Floris van Delft
Ruben Vansummeren
Giorgios Vassilikogiannakis
Christopher Veale
Juan Antonio Vega
Dionisios Vourloumis
Stepan Vysokil
Paul Wallace
Nobuhide Watanabe
Yoshihiko Watanabe
Stephen Webber
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)

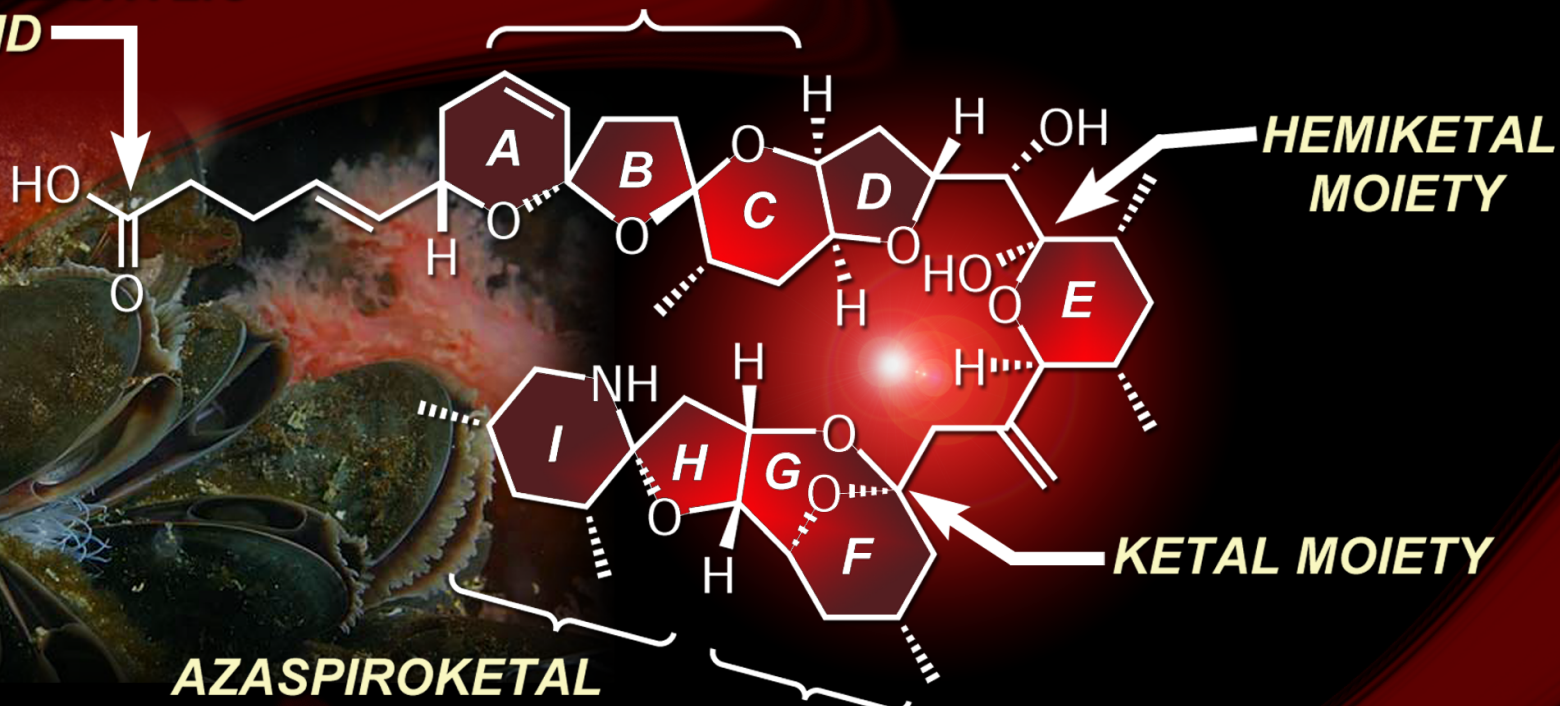
The Azaspiracid-1 Saga

AZASPIRACID-1: PROPOSED STRUCTURE (1998)



CARBOXYLIC
ACID

TRIOXADISPIROKETAL

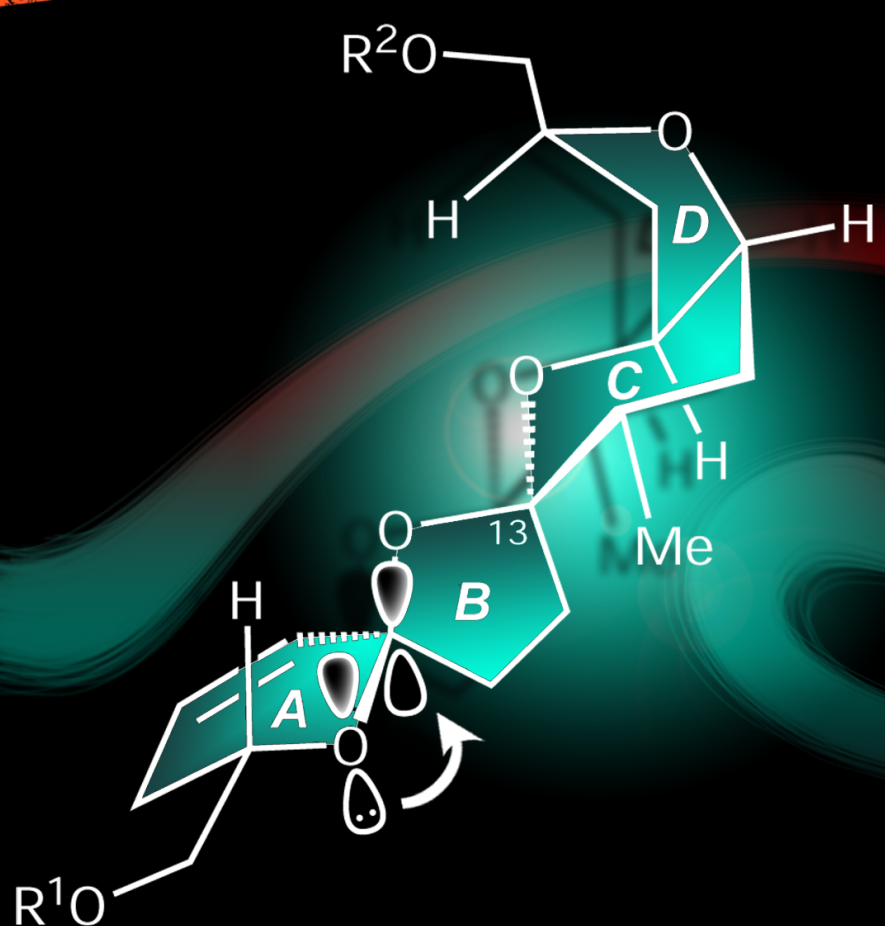


AZASPIROKETAL

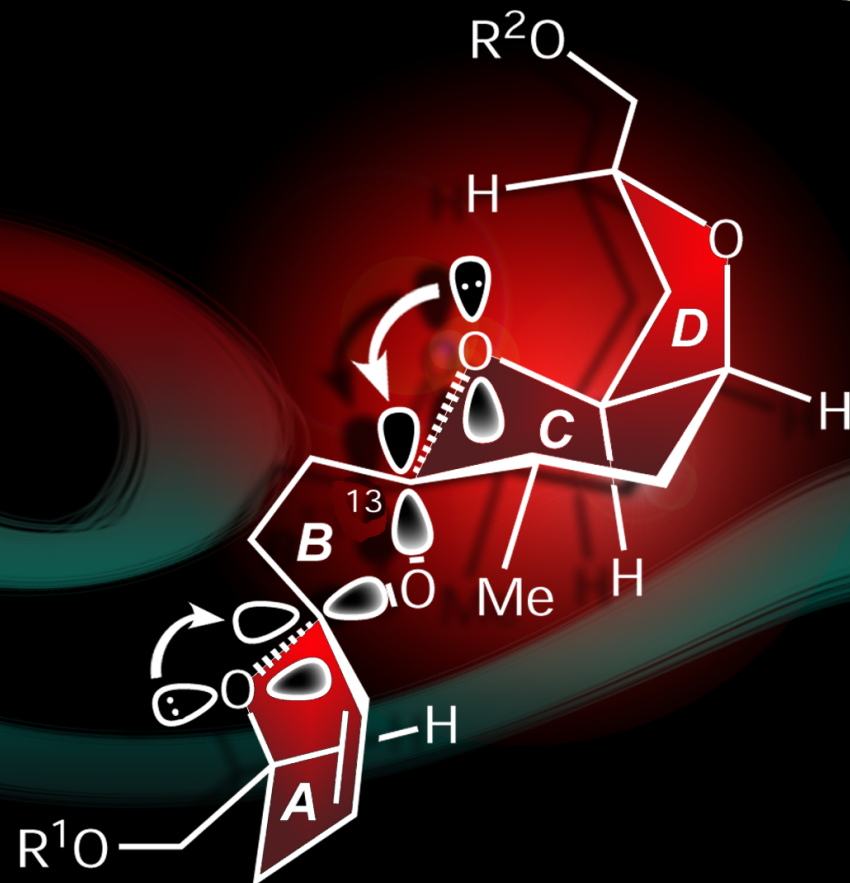
2,9-DIOXACYCLO[3.3.1]NONANE

- 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.



13(R) [DESIRED]
FAVORED BY SINGLE ANOMERIC EFFECT



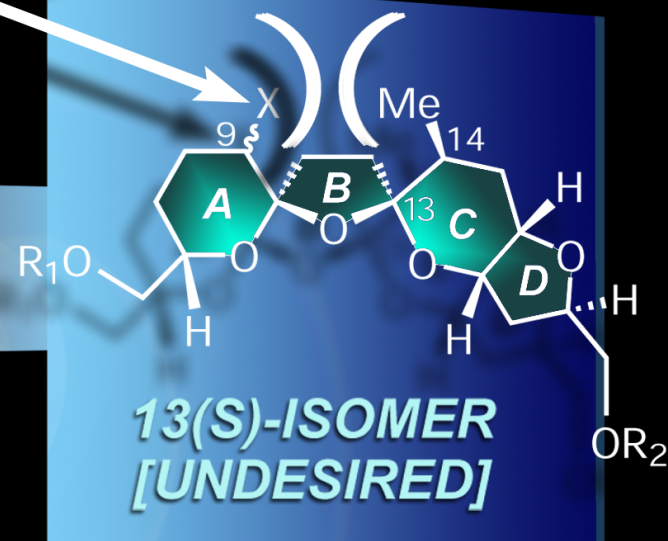
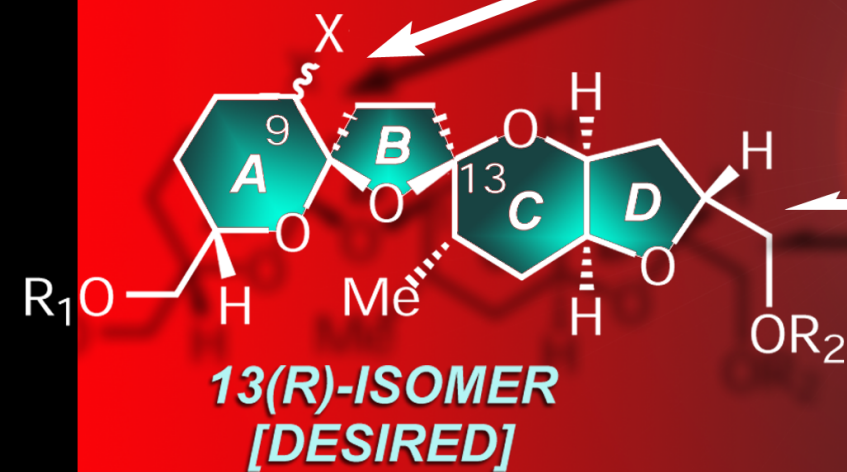
**13(S) [UNDESIRE]
FAVORED BY DOUBLE ANOMERIC EFFECT**

INSTALLATION OF THE C-13 STEREOCENTER: FIRST GENERATION APPROACH - STERIC CONTROL



● **BULKY
SUBSTITUENT**

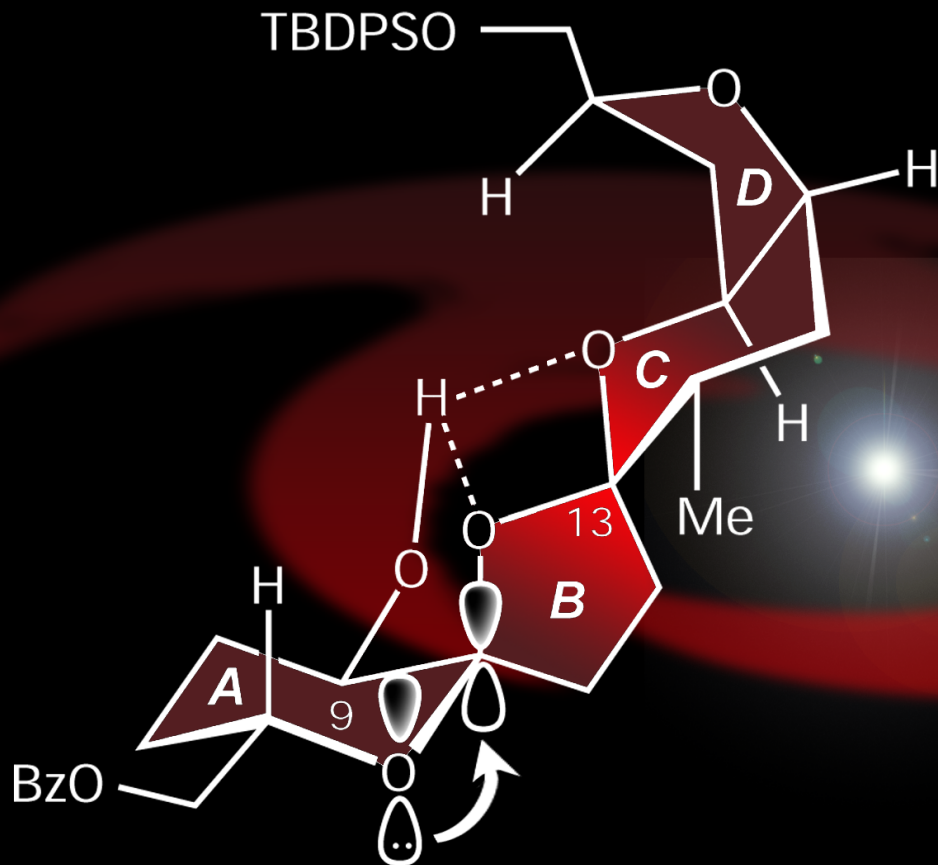
● **STERIC CONGESTION**



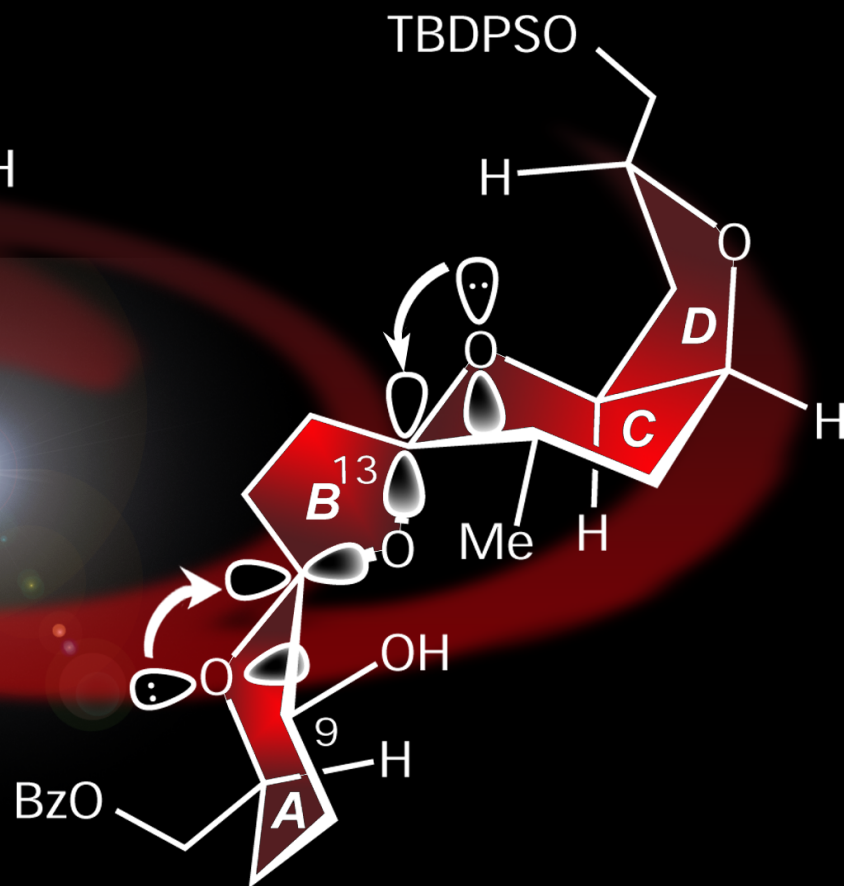
● **COULD STERIC CONGESTION OVERRIDE THE DOUBLE ANOMERIC EFFECT AND DRIVE EQUILIBRIUM TO THE 13(R)-ISOMER ?**



AZASPIRACID-1: INSTALLATION OF THE C-13 STEREOCENTER: SECOND GENERATION APPROACH - H-BONDING CONTROL



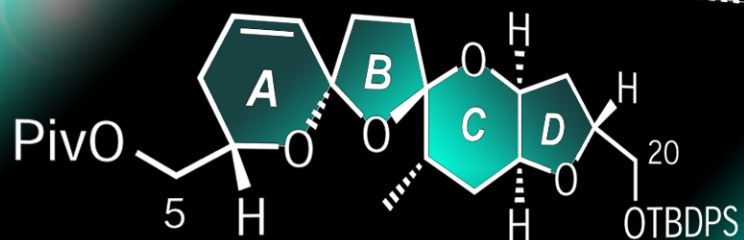
● **13(R)-ISOMER [DESIRED]**
FAVORED BY SINGLE ANOMERIC EFFECT AND
H-BONDING



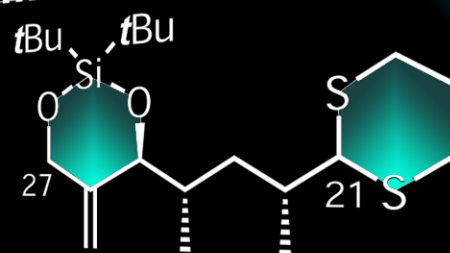
● **13(S)-ISOMER [UNDESIRE]**
FAVORED BY DOUBLE ANOMERIC EFFECT

AZASPIRACID-1: RETROSYNTHETIC ANALYSIS

KEY BUILDING BLOCKS



**C₅-C₂₀ "ABCD" SUBUNIT
AND ENANTIOMER**



**C₂₁-C₂₇ "E"-RING PRECURSOR
AND ENANTIOMER**

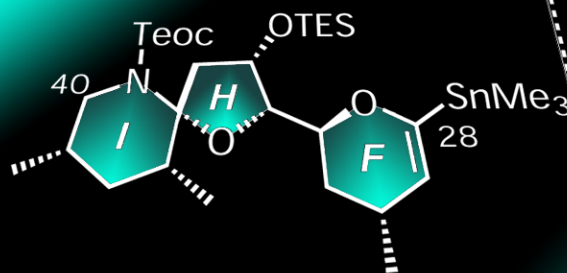
DITHIANE COUPLING TECHNOLOGY

IRELAND-CLAISEN
REARRANGEMENT

AZASPIRACID-1

●: IODOETHERIFICATION

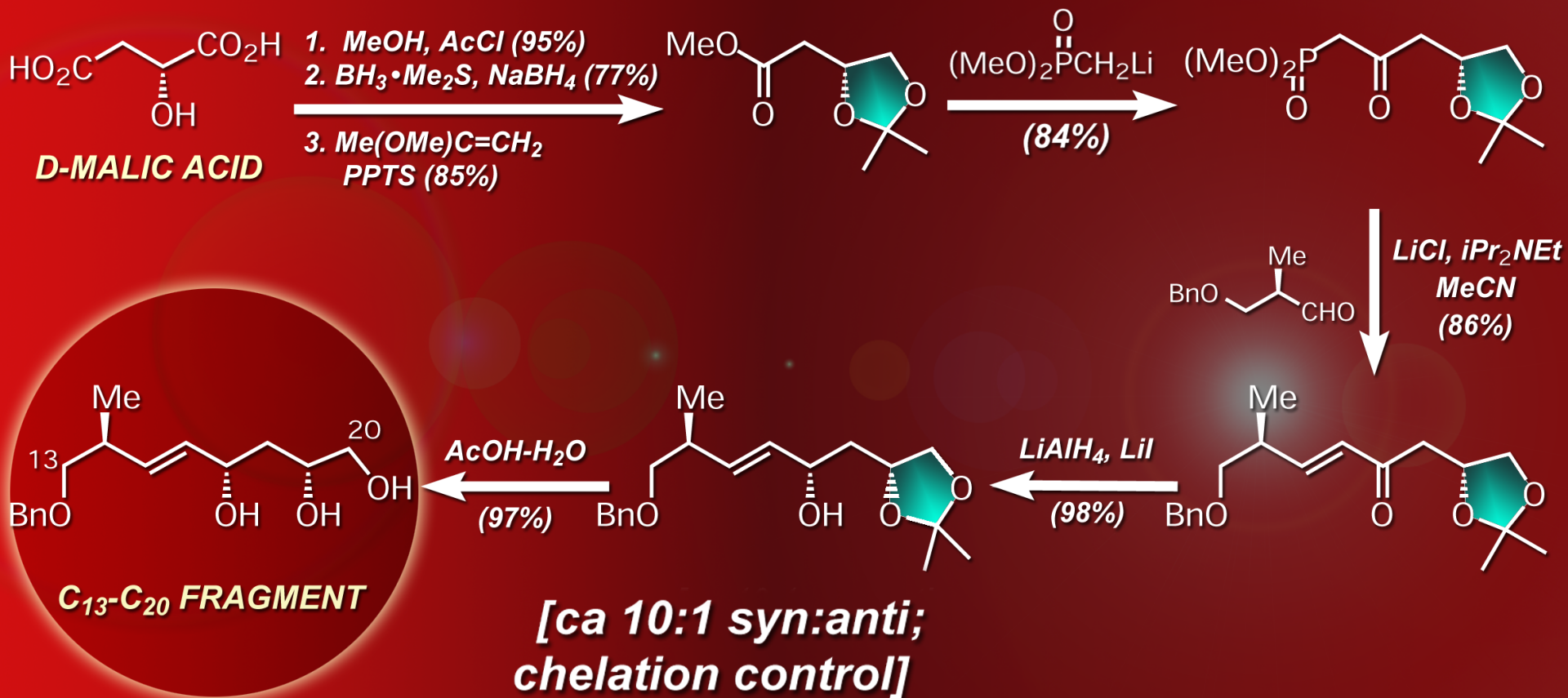
STILLE
COUPLING



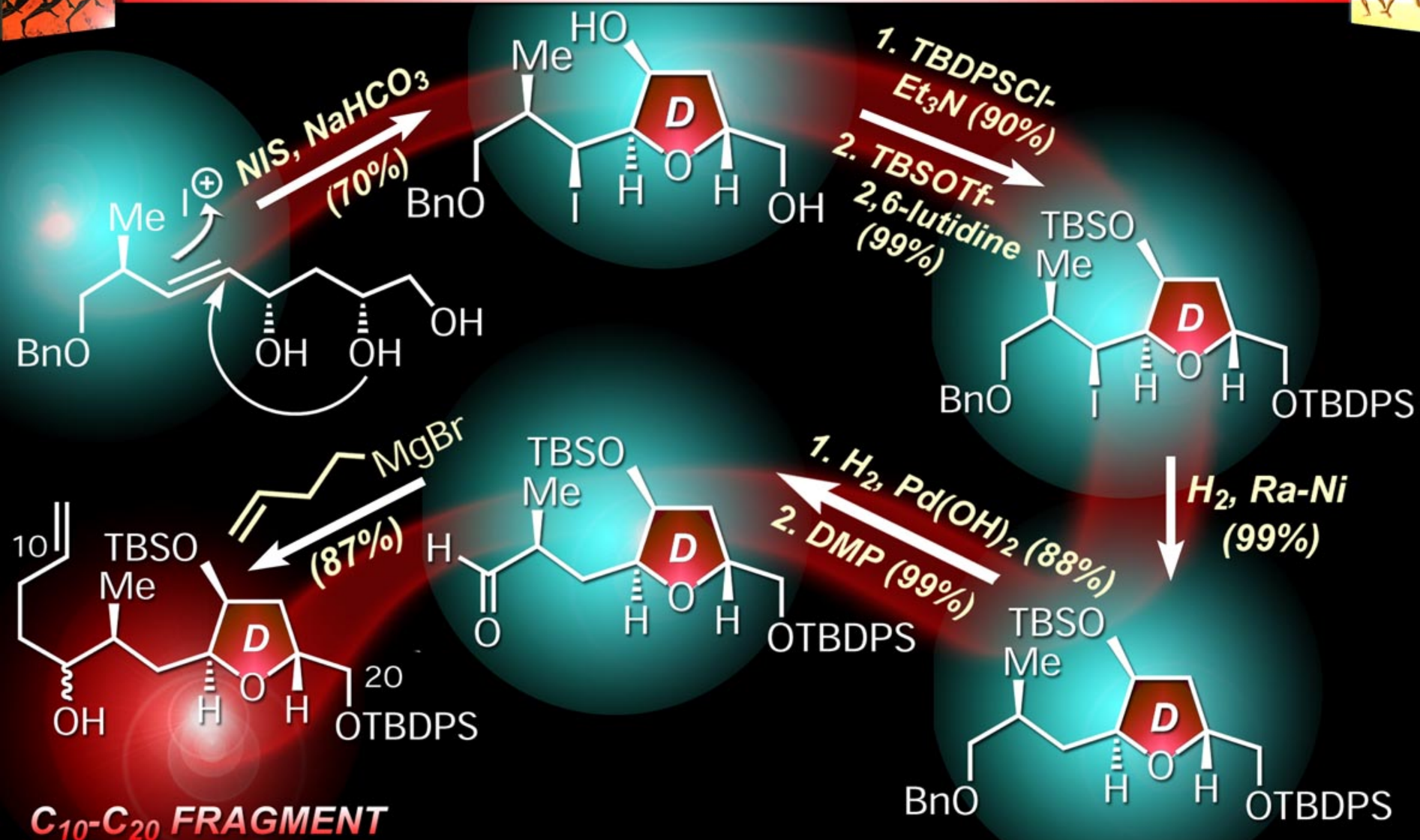
**C₂₈-C₄₀ "FHI" STANNANE
AND ENANTIOMER**



AZASPIRACID-1: SYNTHESIS OF "ABCD" RING SYSTEM: PREPARATION OF LINEAR CYCLIZATION PRECURSOR

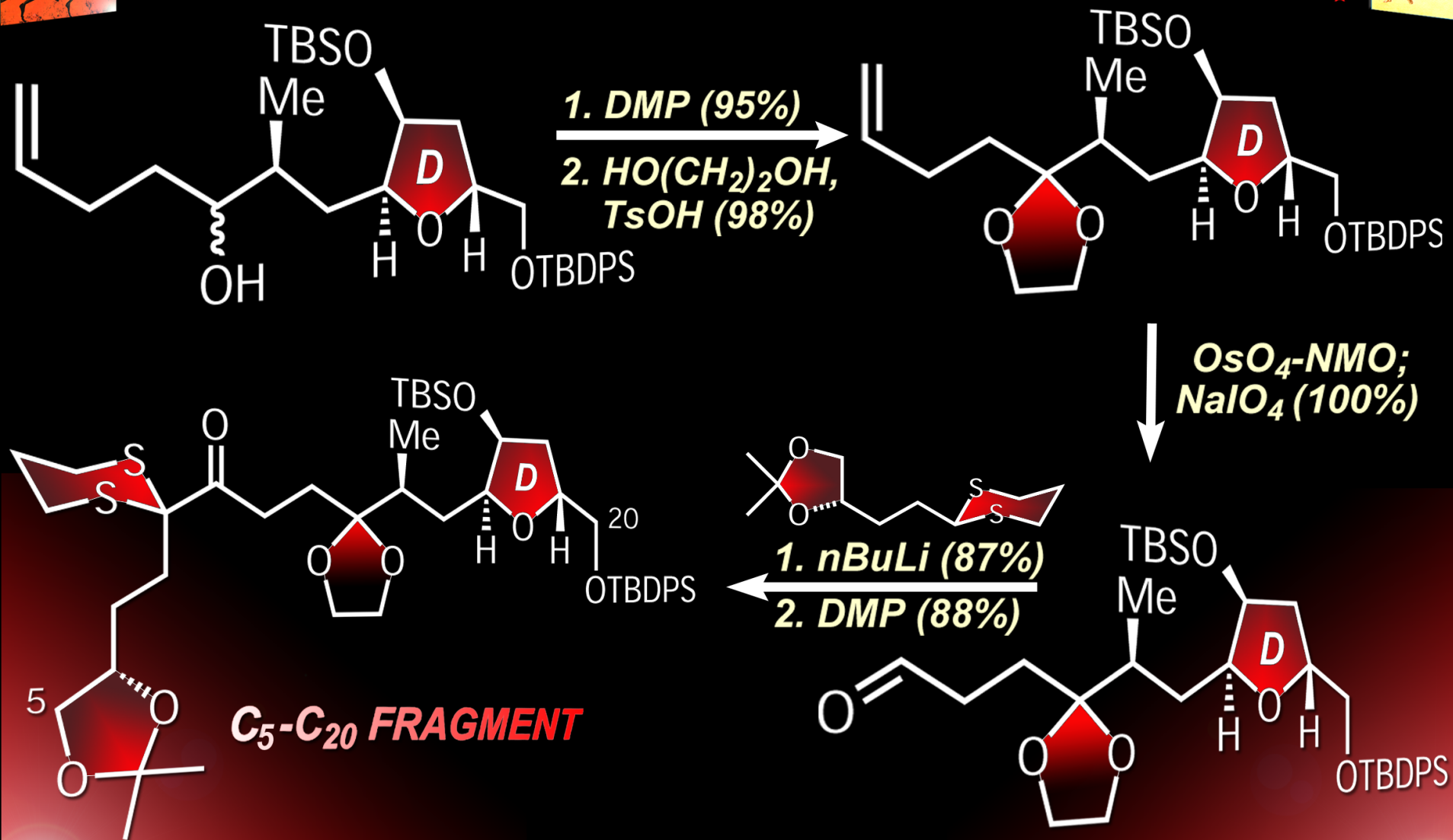


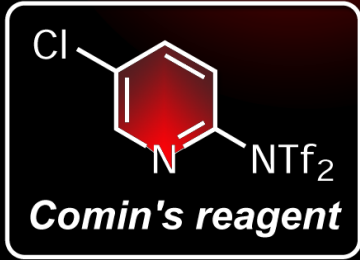
AZASPIRACID-1: CONSTRUCTION OF THE "ABCD" RING SYSTEM - 1





AZASPIRACID-1: CONSTRUCTION OF THE "ABCD" RING SYSTEM - 2

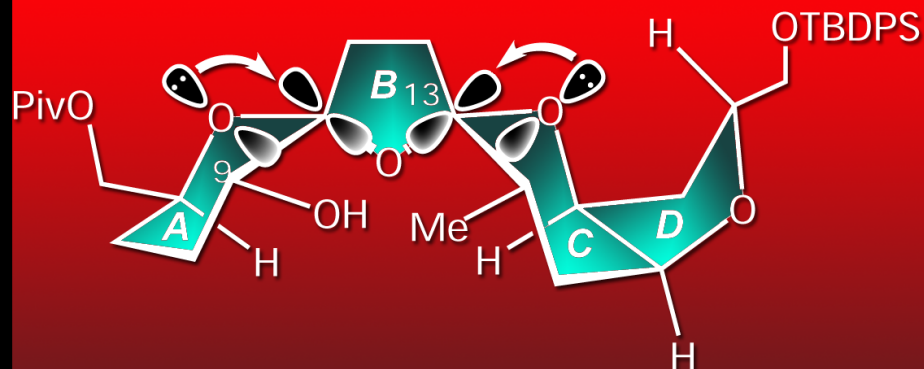




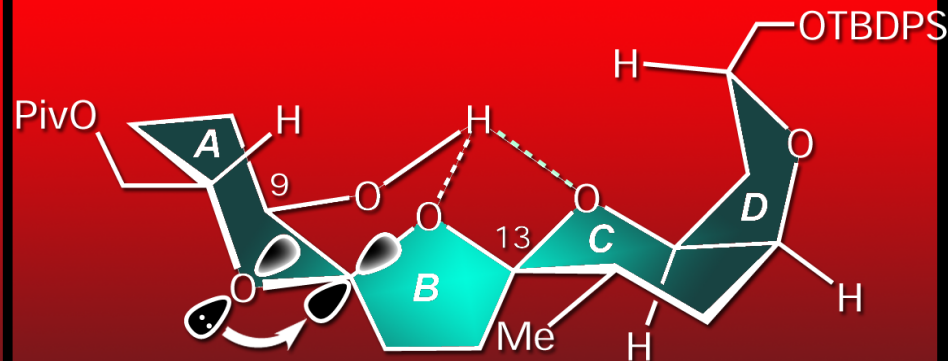


AZASPIRACID-1:

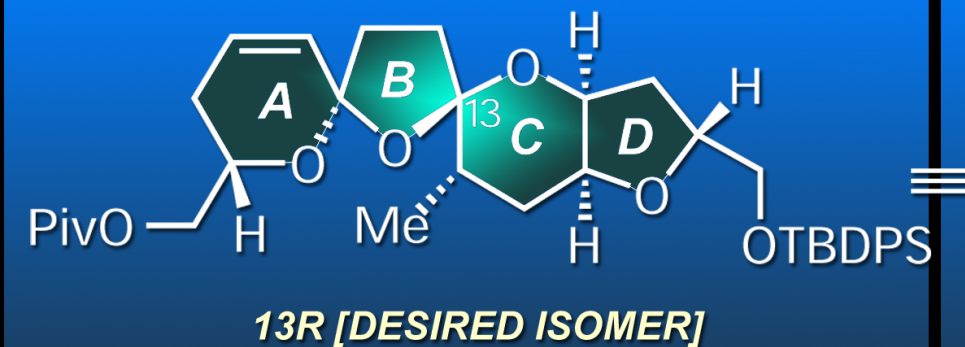
RATIONAL FOR THE REVERSAL OF C-13 STEREOCHEMISTRY



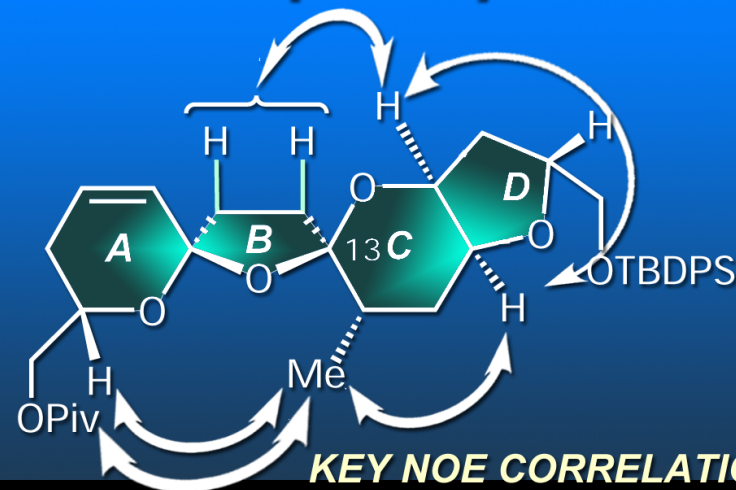
(13S) FAVORED BY DOUBLE ANOMERIC EFFECT [UNDESIRE]



(13R) FAVORED BY H - BONDING AND SINGLE ANOMERIC EFFECT [DESIRED]

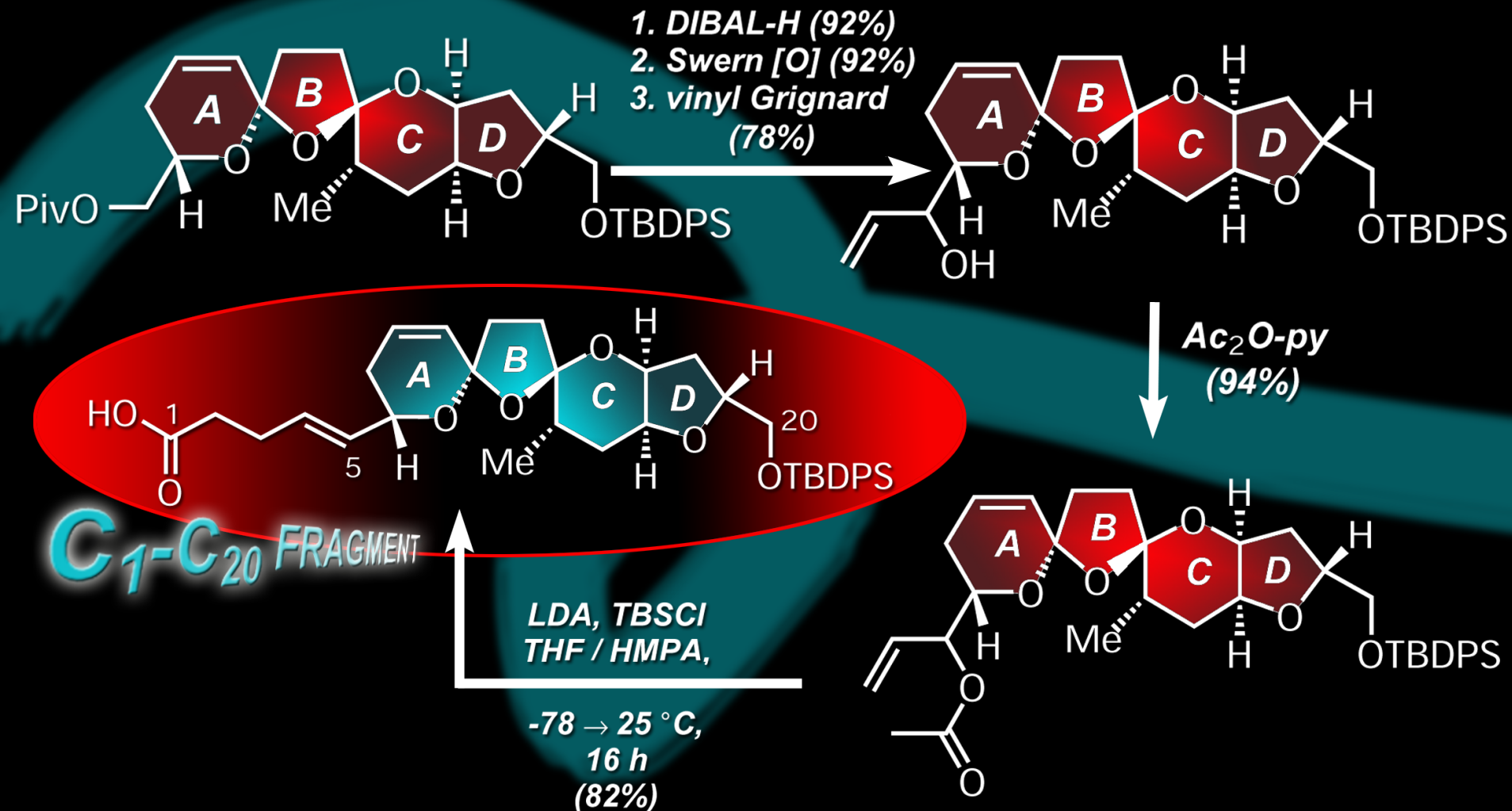


13R [DESIRED ISOMER]



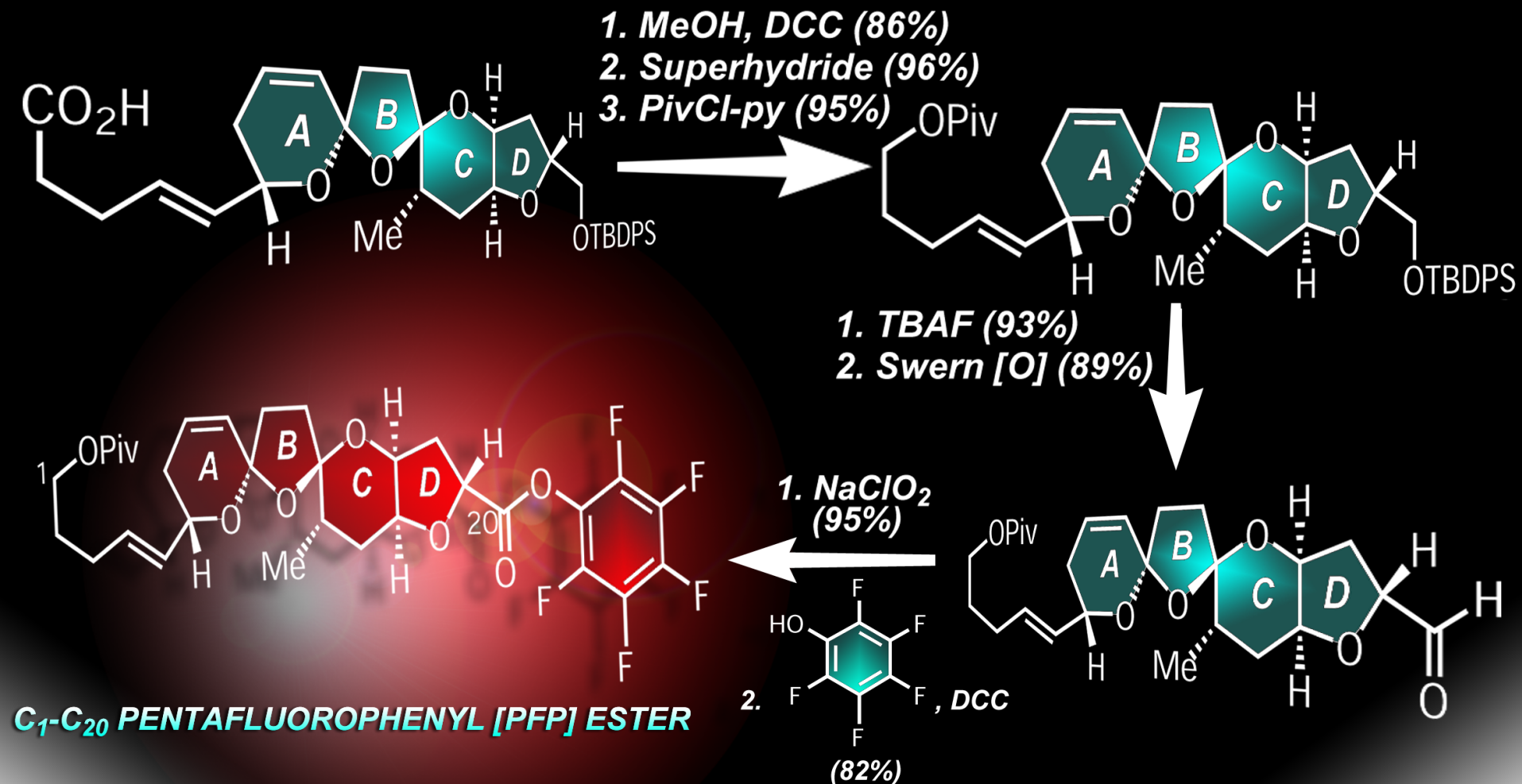
KEY NOE CORRELATIONS

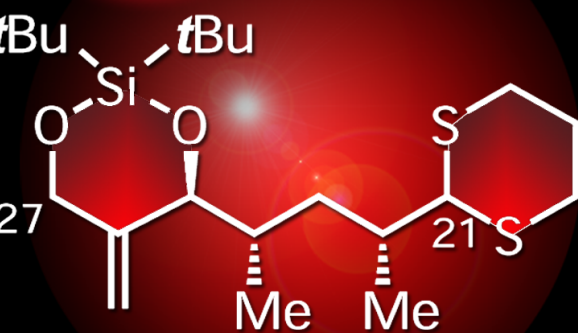
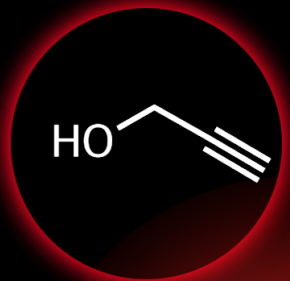
AZASPIRACID-1: ELONGATION OF THE "ABCD" SIDE CHAIN VIA IRELAND-CLAISEN REARRANGEMENT





AZASPIRACID-1: ACTIVATION OF C-20 CARBOXYLIC ACID AS PENTAFLUOROPHENYL ESTER

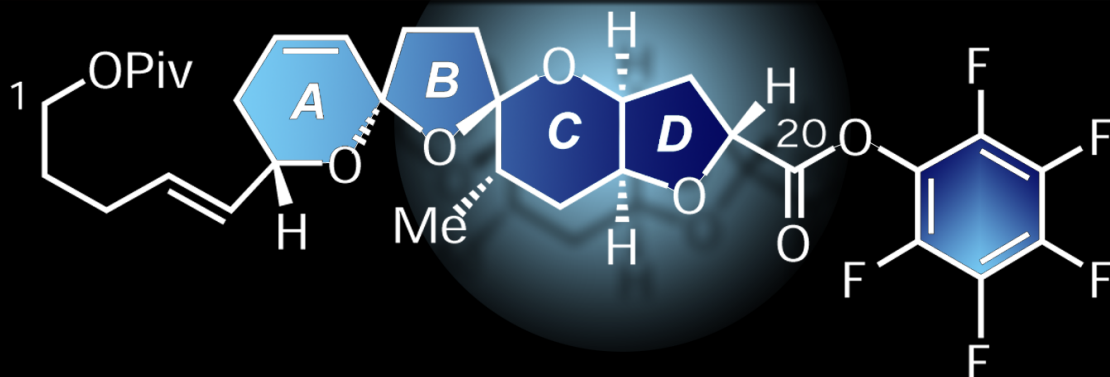




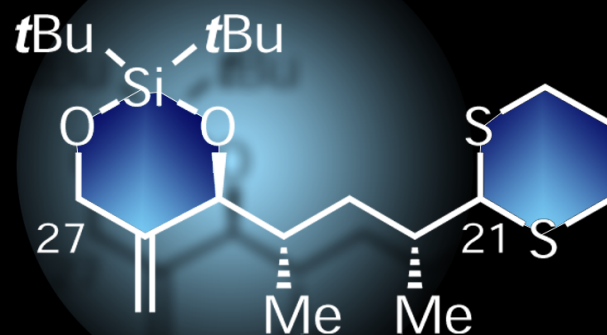
C₂₁-C₂₇ DITHIANE FRAGMENT



AZASPIRACID-1: UNION OF C₁-C₂₀ AND C₂₁-C₂₇ FRAGMENT VIA DITHIANE COUPLING TECHNOLOGY



C₁-C₂₀ PENTAFLUOROPHENYL [PFP] ESTER FRAGMENT

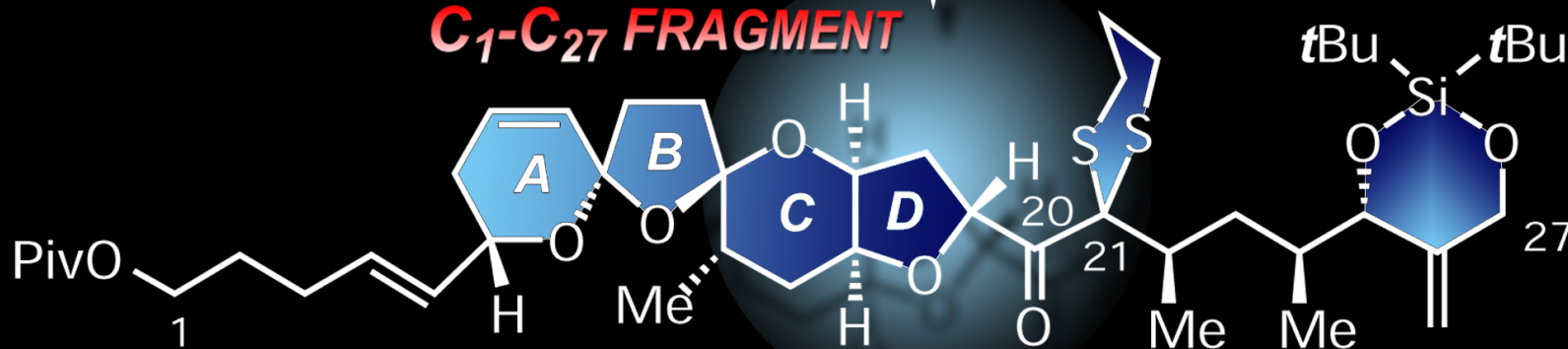


C₂₁-C₂₇ DITHIANE FRAGMENT

2. PFP ESTER
-100 °C, 15 min
(63%)

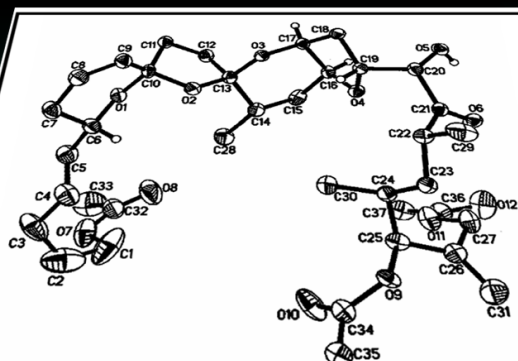
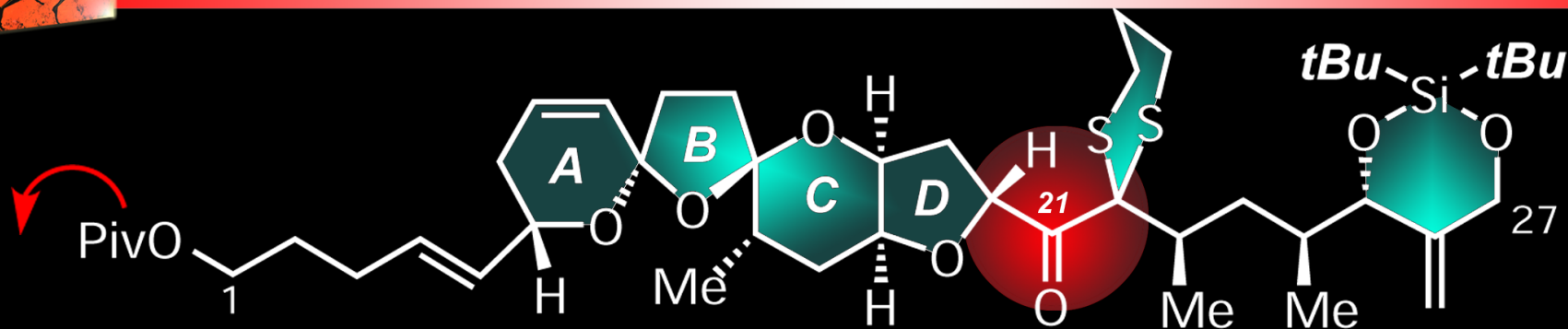
1. *n*BuLi-*n*Bu₂Mg,
THF, 0 → 25 °C,
1.5 h; then 2.

C₁-C₂₇ FRAGMENT



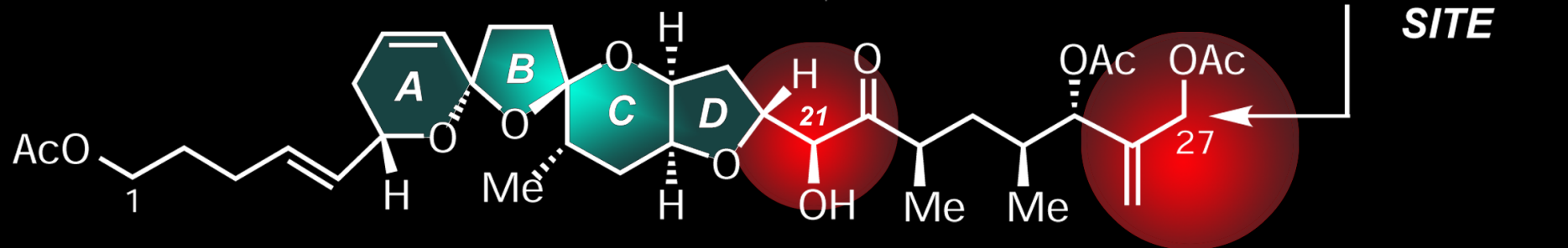


AZASPIRACID-1: GROOMING C₁-C₂₇ DOMAIN FOR STILLE COUPLING



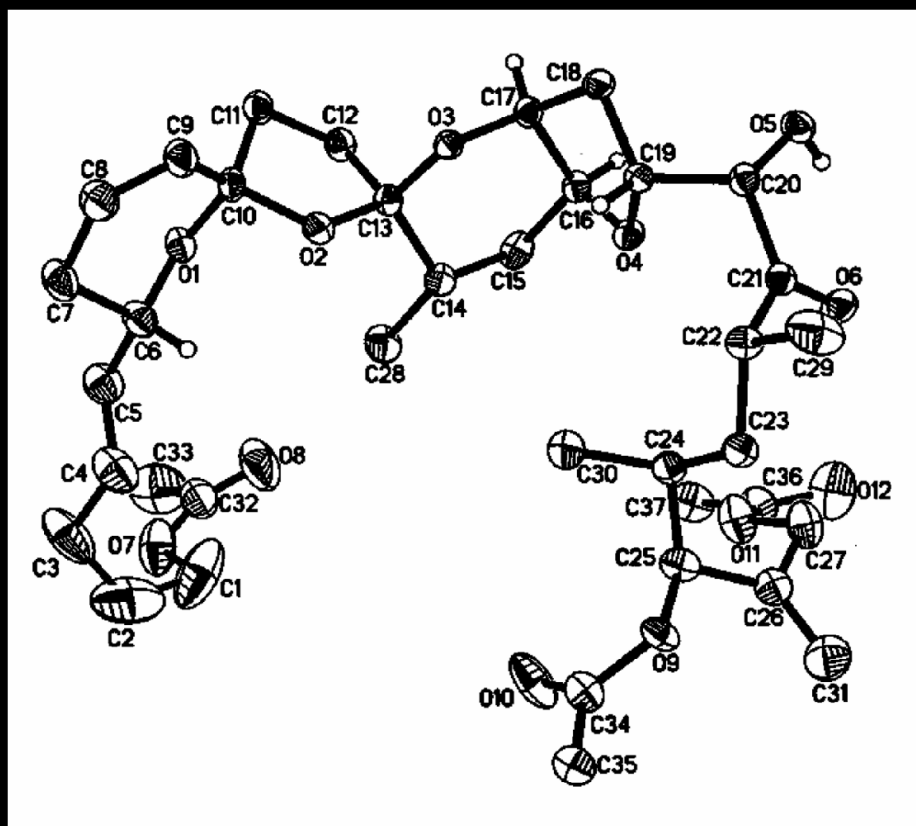
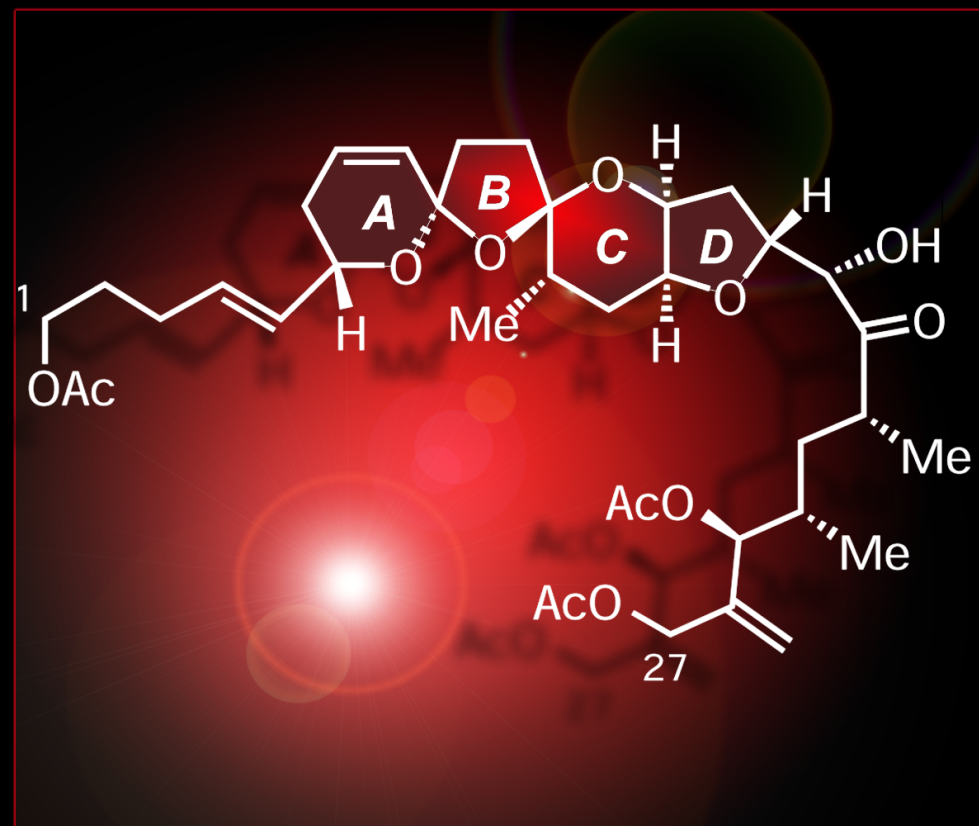
X-RAY STRUCTURE OF C₁-C₂₇ DOMAIN

1. DIBAL-H (single diastereomer, 55%)
2. TBAF (78%)
3. Ac₂O-py (84%)
4. PhI(OCOCF₃)₂ (78%)

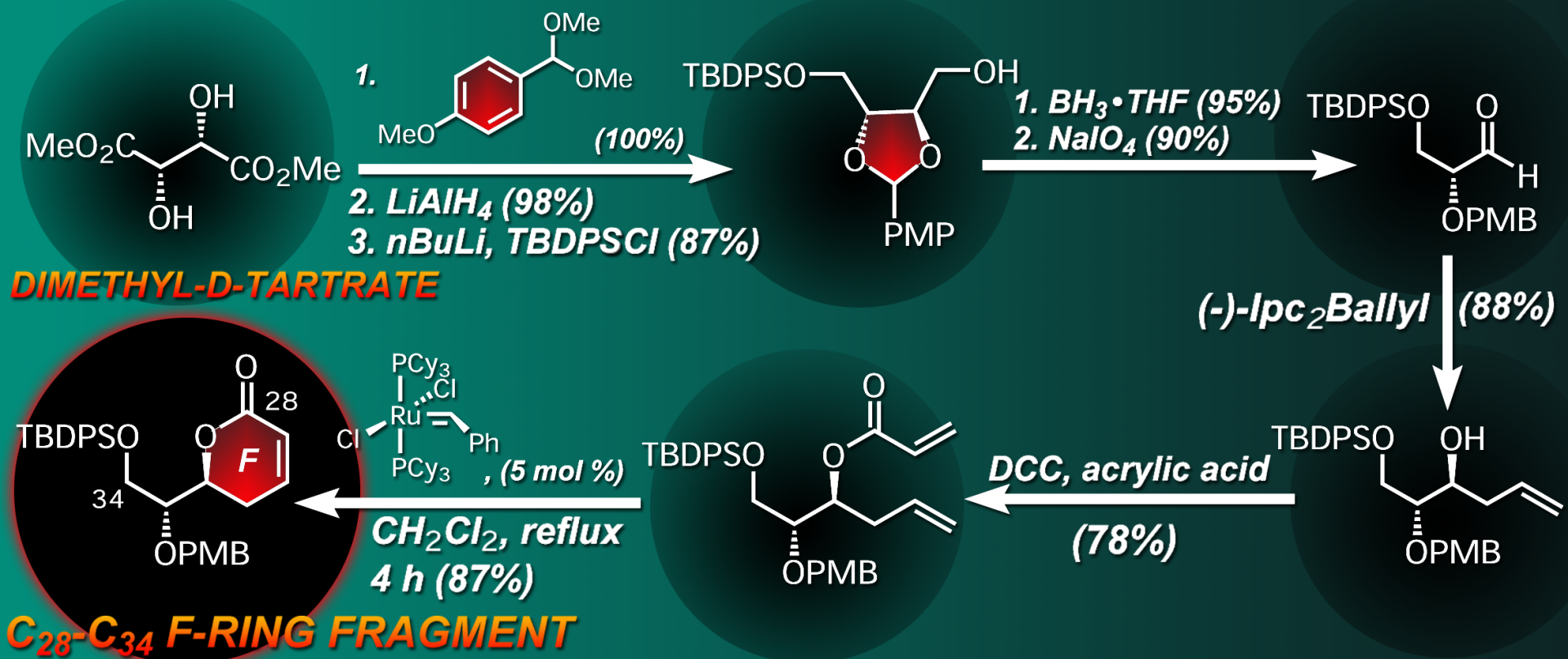




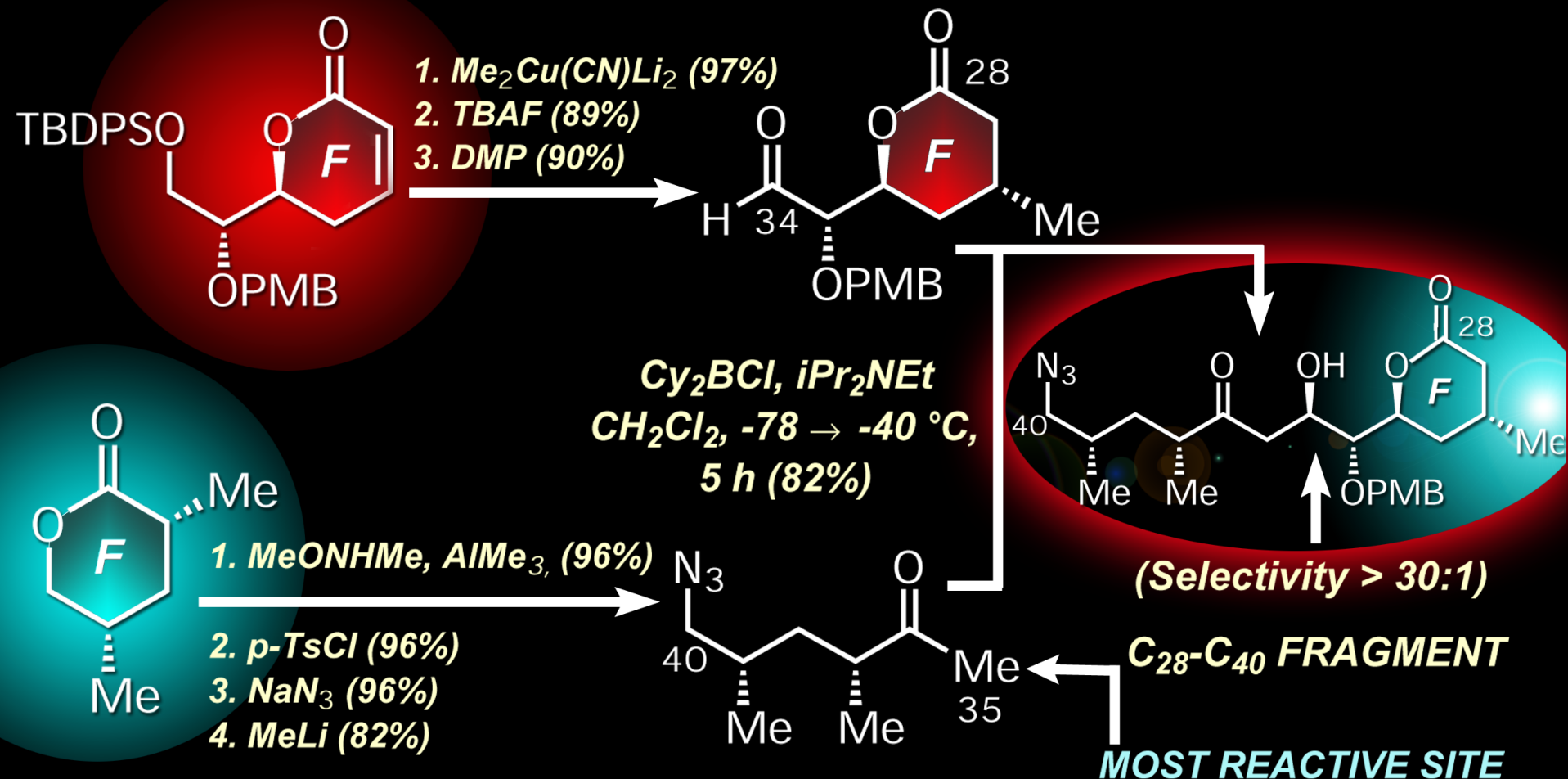
X-RAY STRUCTURE OF C₁-C₂₇ DOMAIN



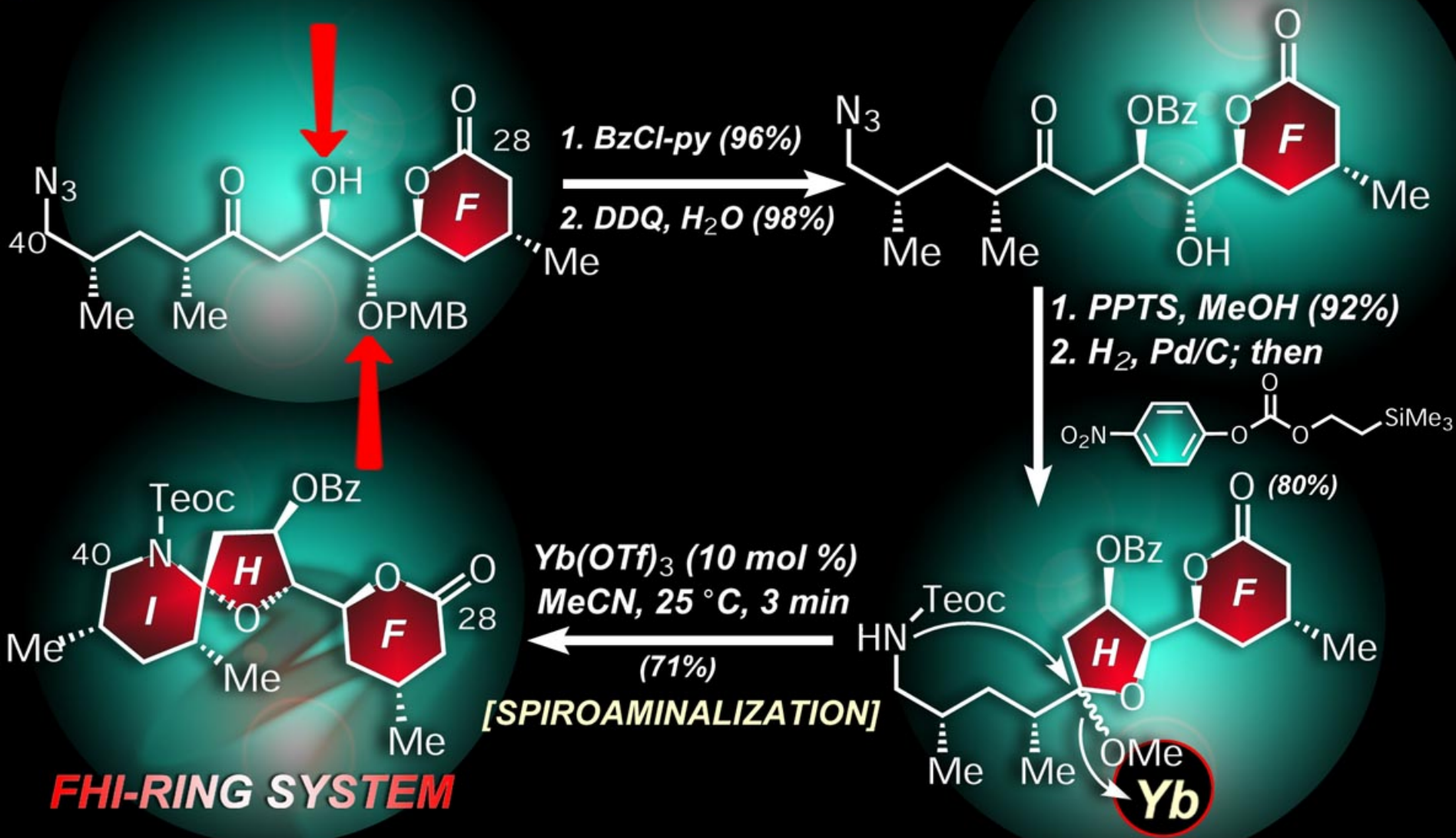
AZASPIRACID-1: CONSTRUCTION OF F-RING VIA OLEFIN METATHESIS



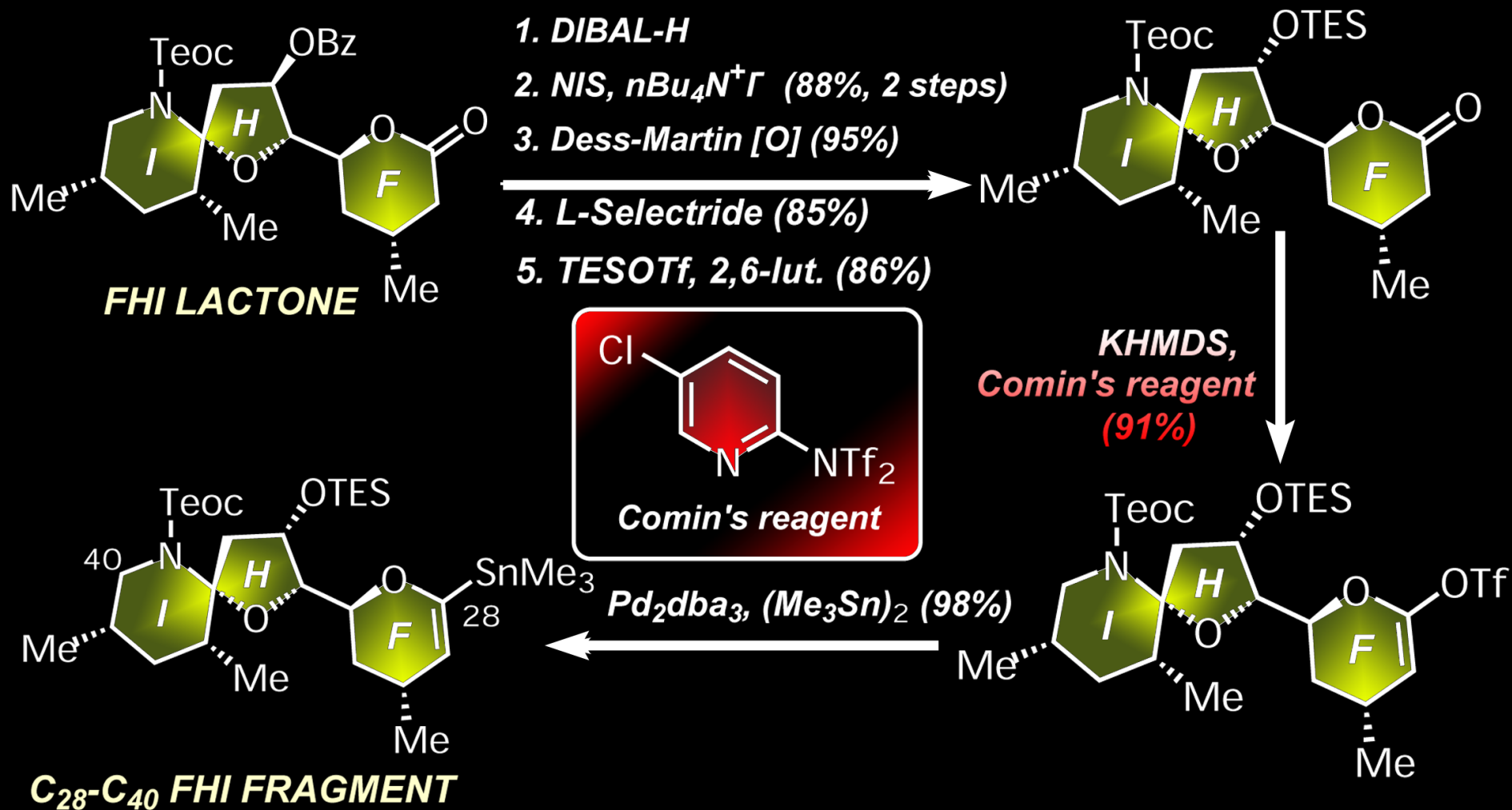
AZASPIRACID-1: CONSTRUCTION OF C₂₈-C₄₀ FRAGMENT VIA A HIGHLY SELECTIVE METHYL KETONE ALDOL REACTION



AZASPIRACID-1 : SELECTIVE CONSTRUCTION OF THE HI SPIROAMINAL [FHI-RING SYSTEM]

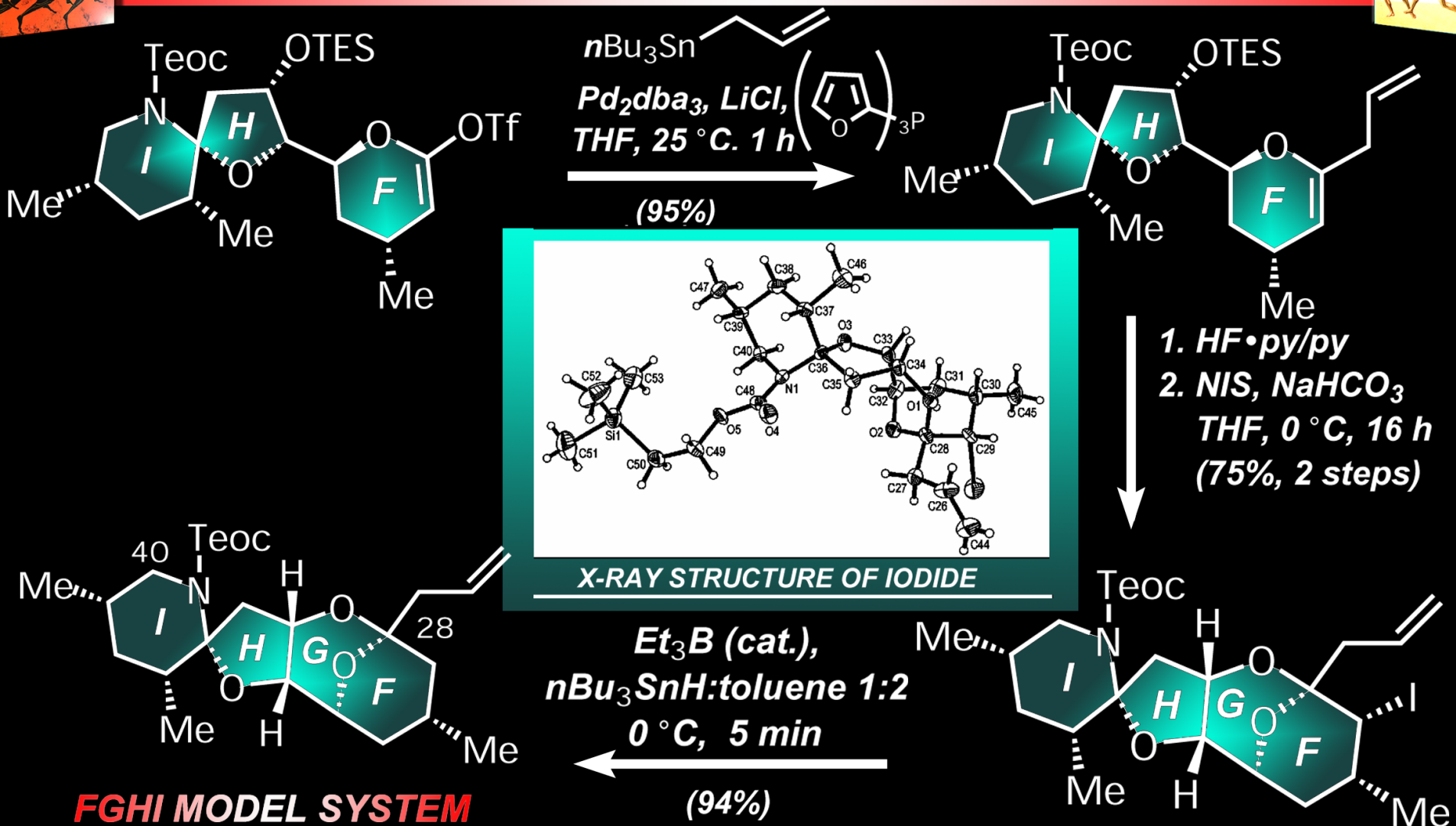


AZASPIRACID-1: CONSTRUCTION OF C₂₈-C₄₀ FHI FRAGMENT





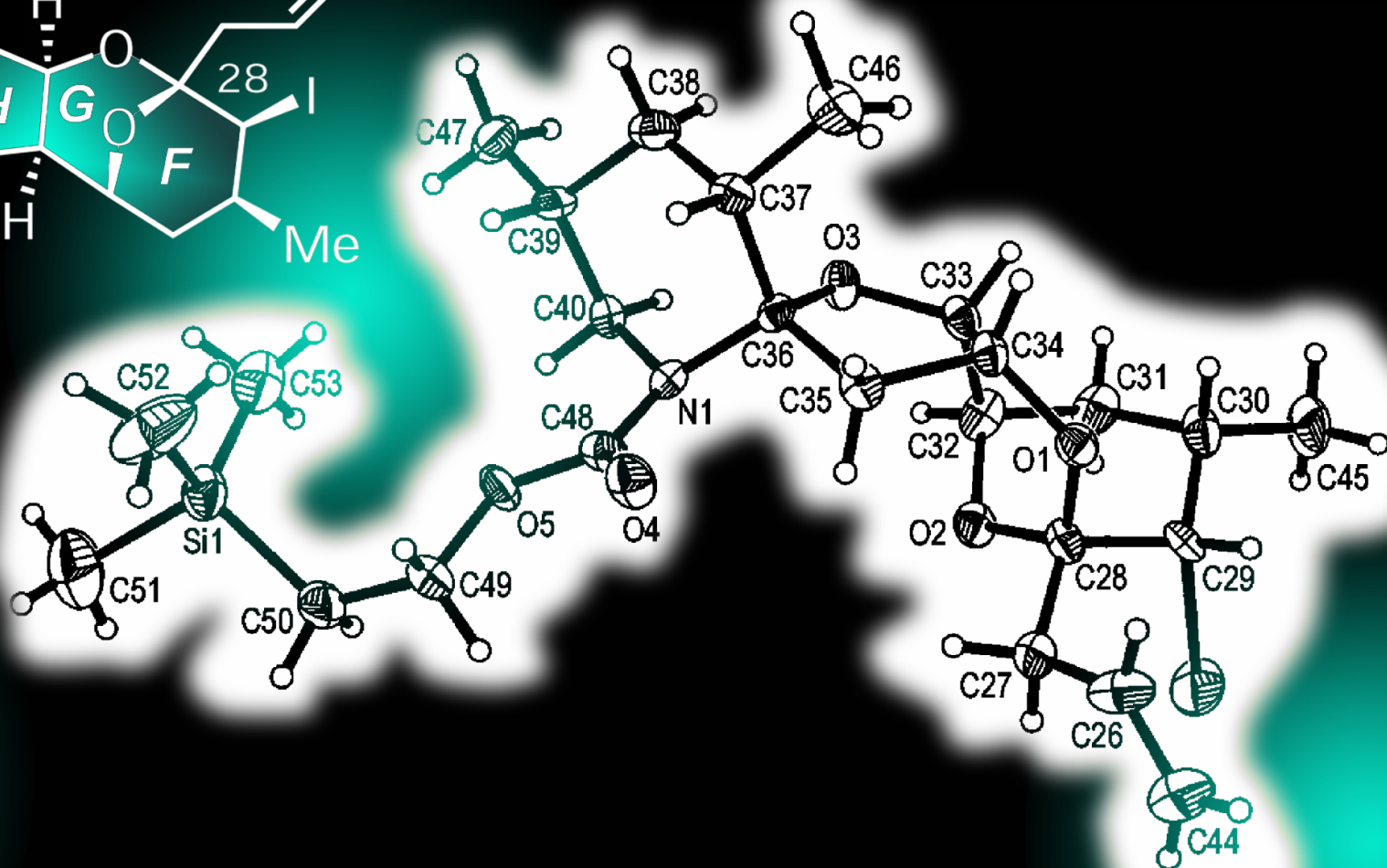
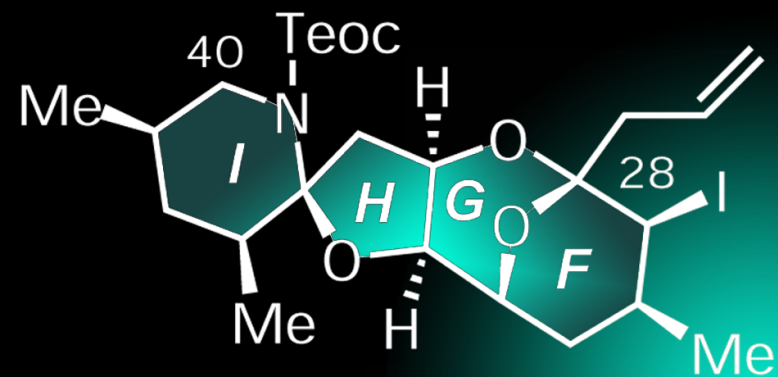
AZASPIRACID-1: CONSTRUCTION OF FGHI MODEL SYSTEM



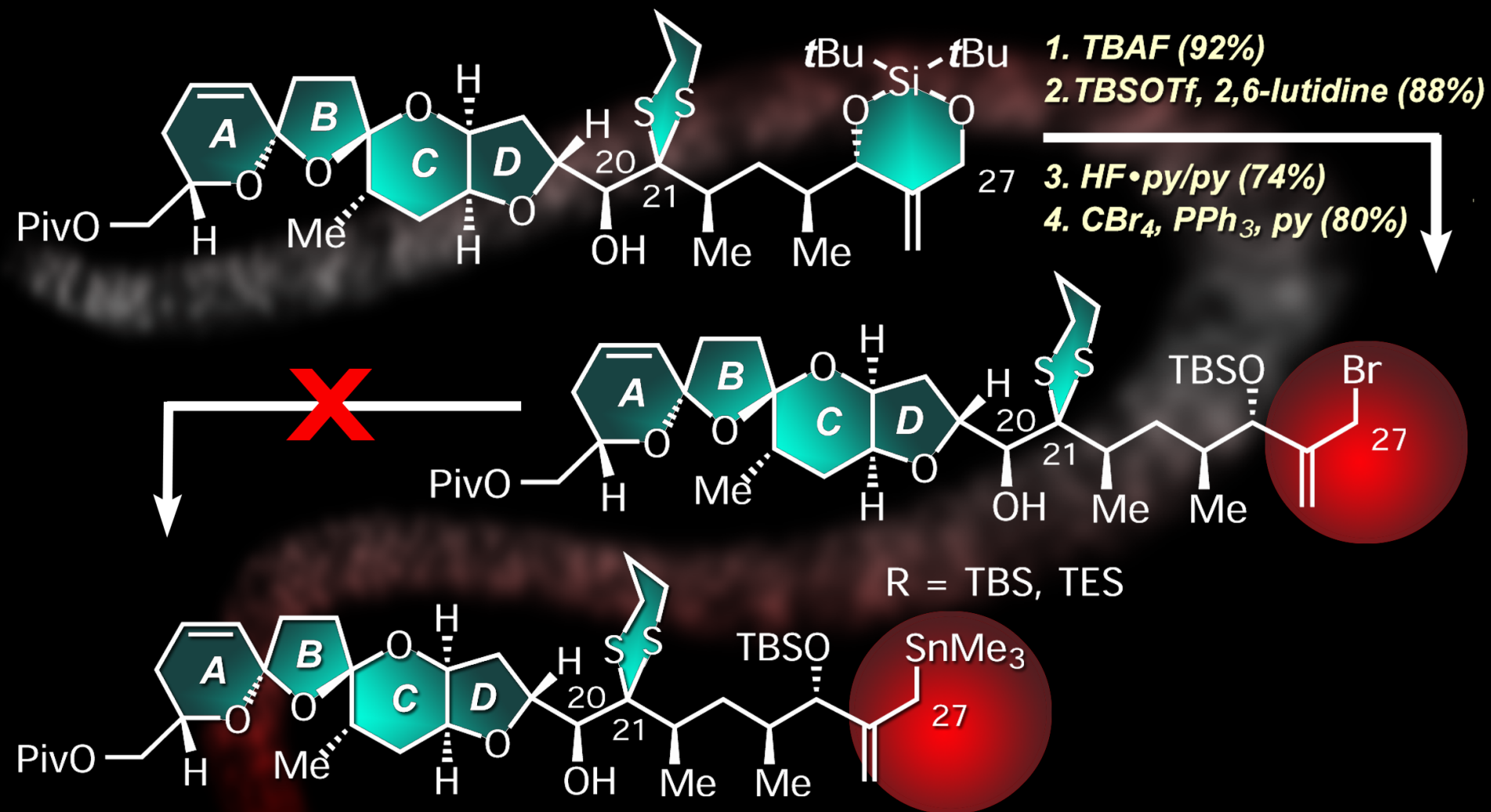
FGHI MODEL SYSTEM



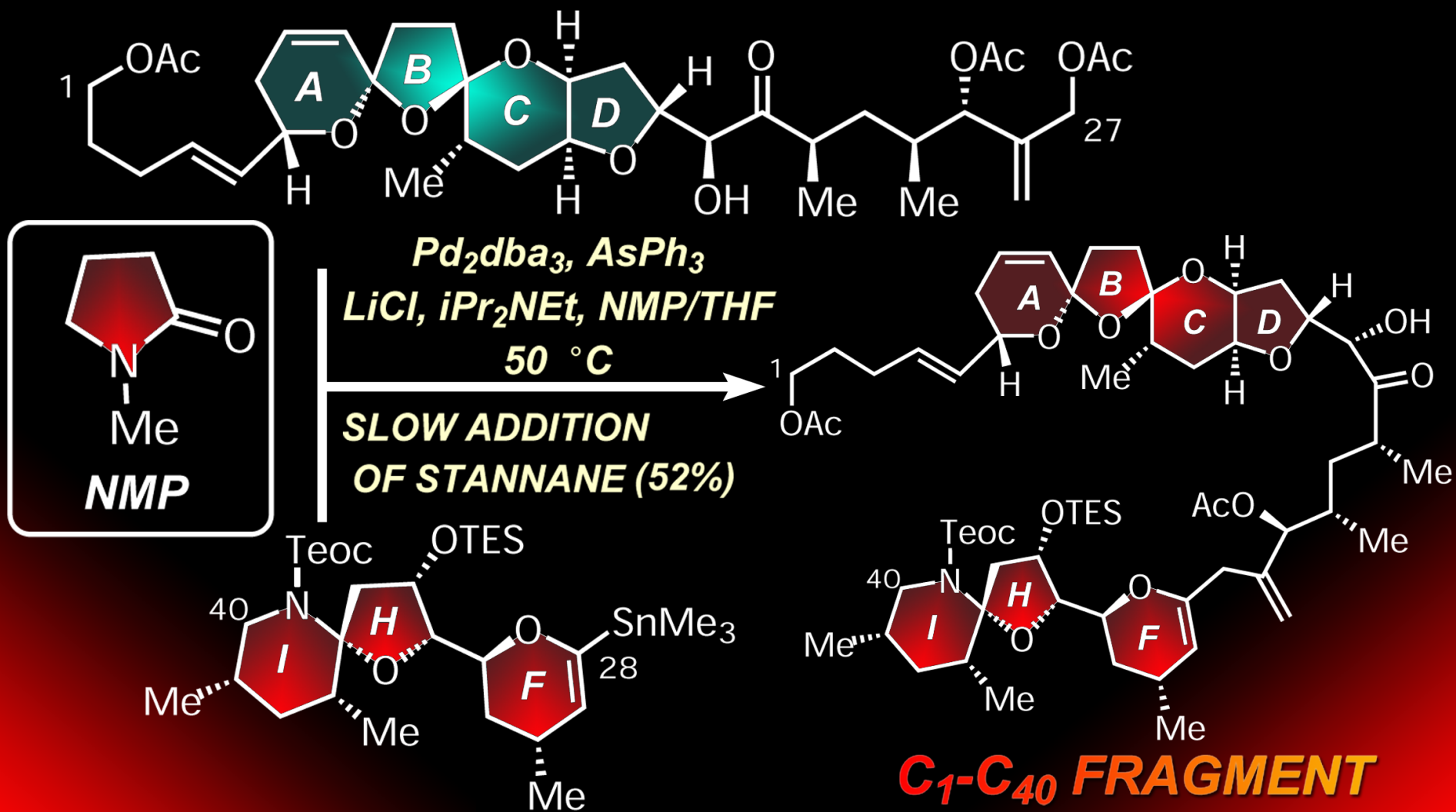
X-RAY STRUCTURE OF FGHI MODEL SYSTEM



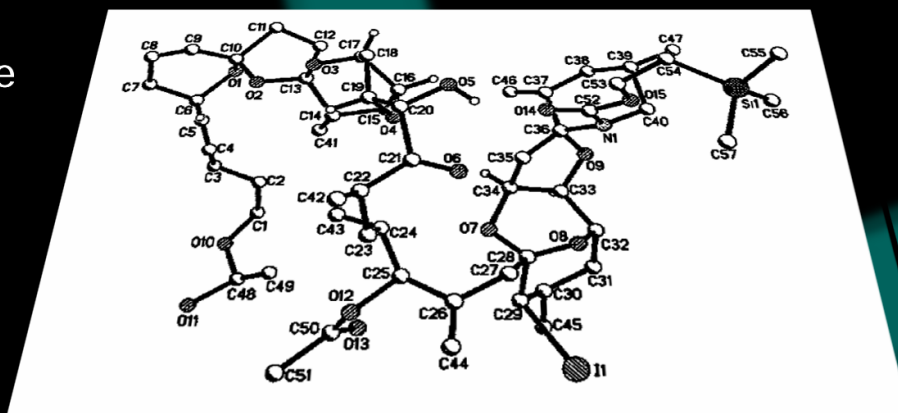
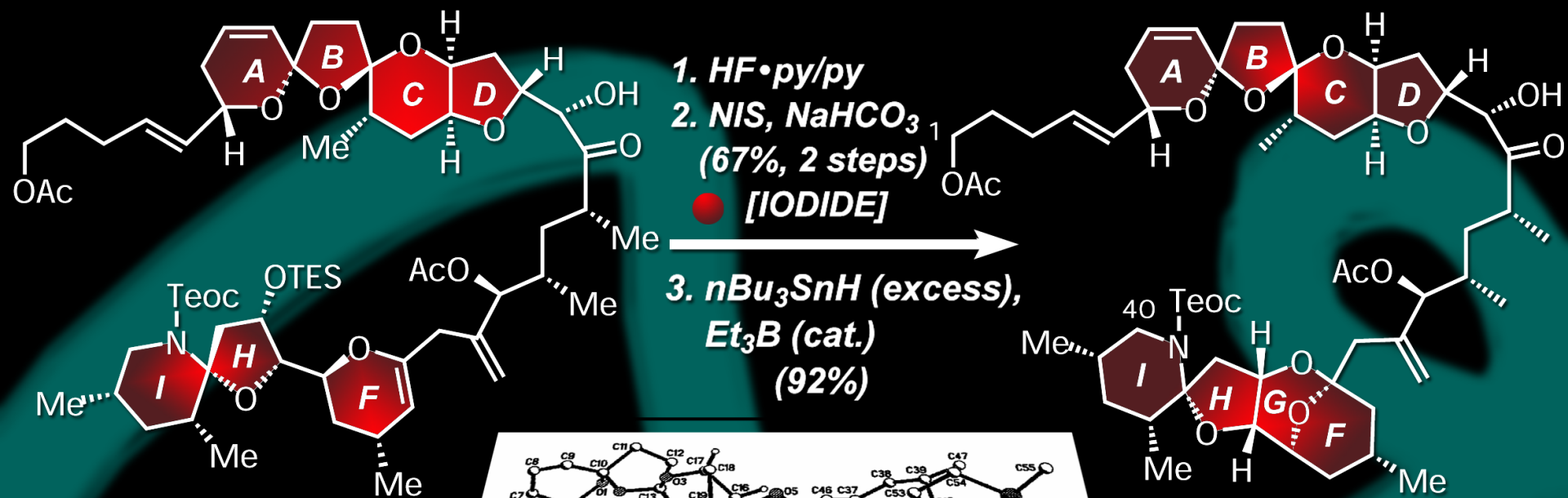
AZASPIRACID-1: REVERSAL OF STILLE COUPLING PARTNER



AZASPIRACID-1: UNION OF C₁-C₂₇ AND C₂₈-C₄₀ FRAGMENTS VIA STILLE COUPLING



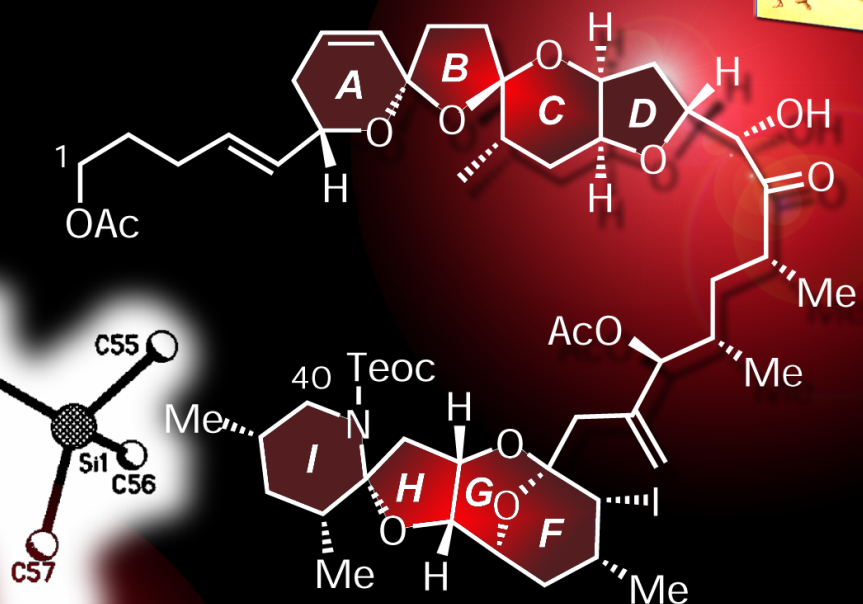
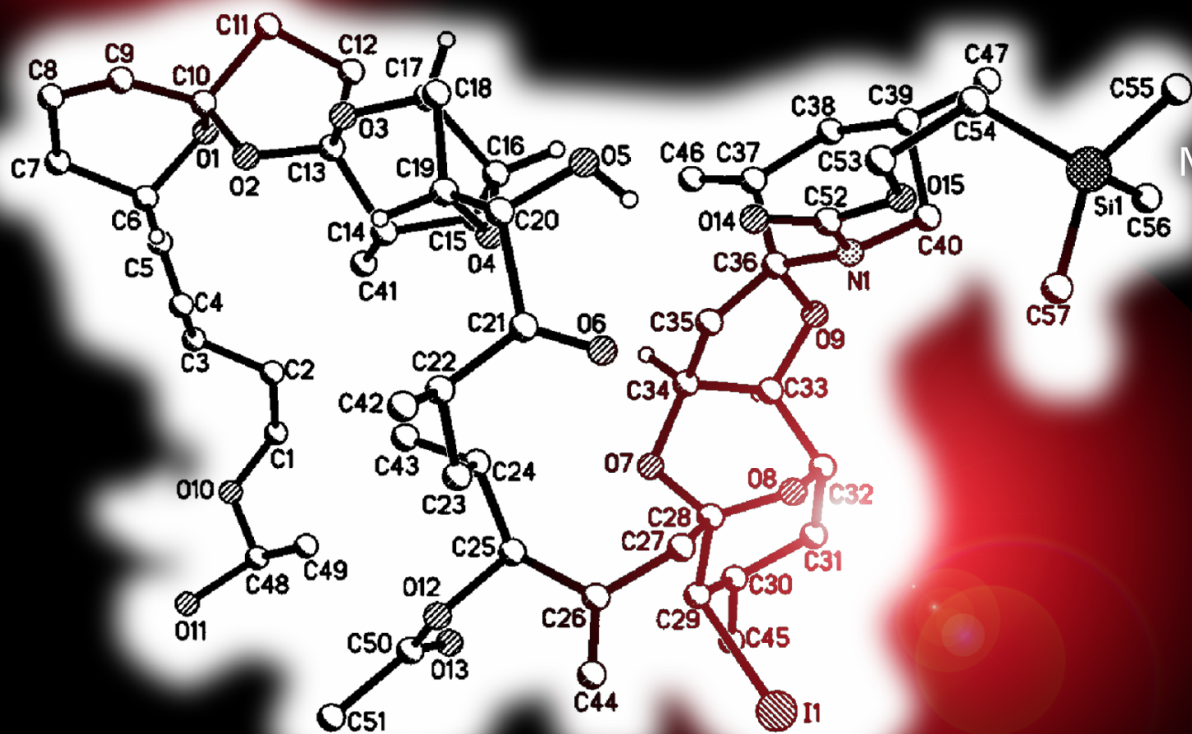
AZASPIRACID-1: CLOSURE OF G-RING AND CONFIRMATION OF STRUCTURE



● X-RAY STRUCTURE OF IODIDE

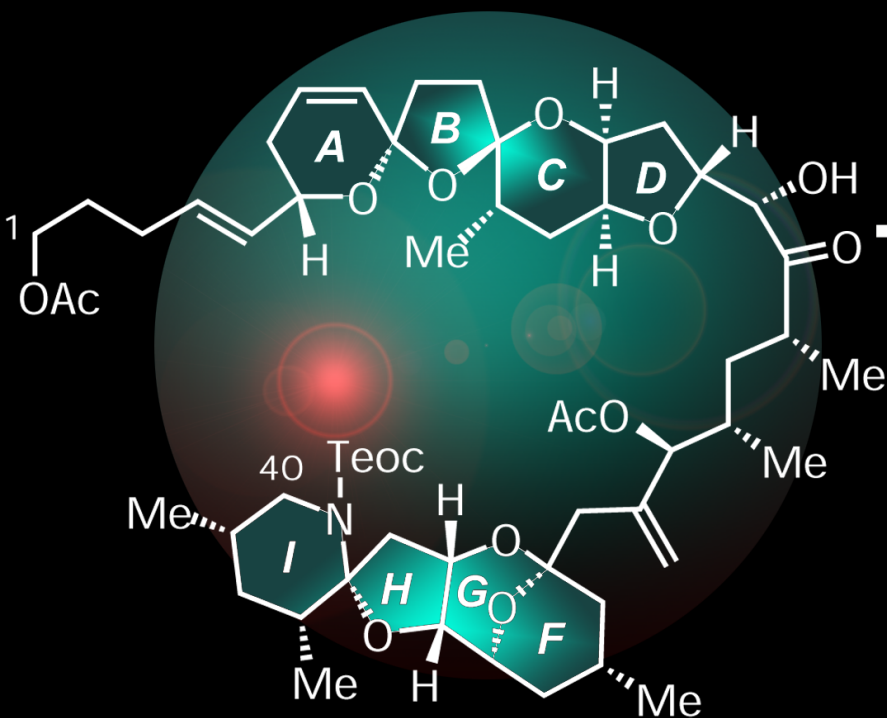


AZASPIRACID-1: X-RAY STRUCTURE OF IODIDE

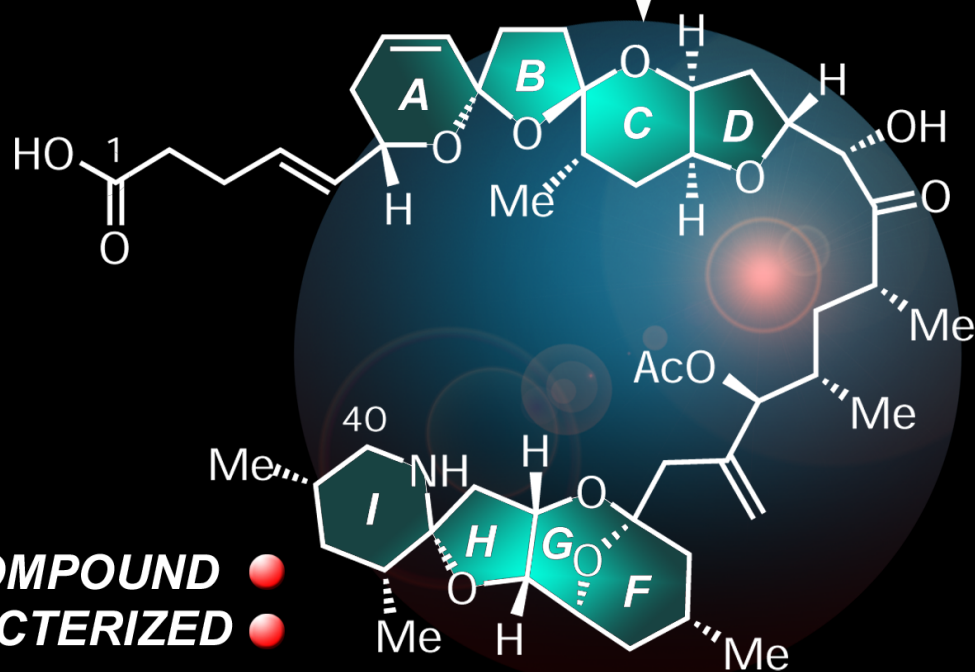




AZASPIRACID-1: COMPLETION OF TOTAL SYNTHESIS OF PROPOSED STRUCTURE [DIASTEREOMER 1]



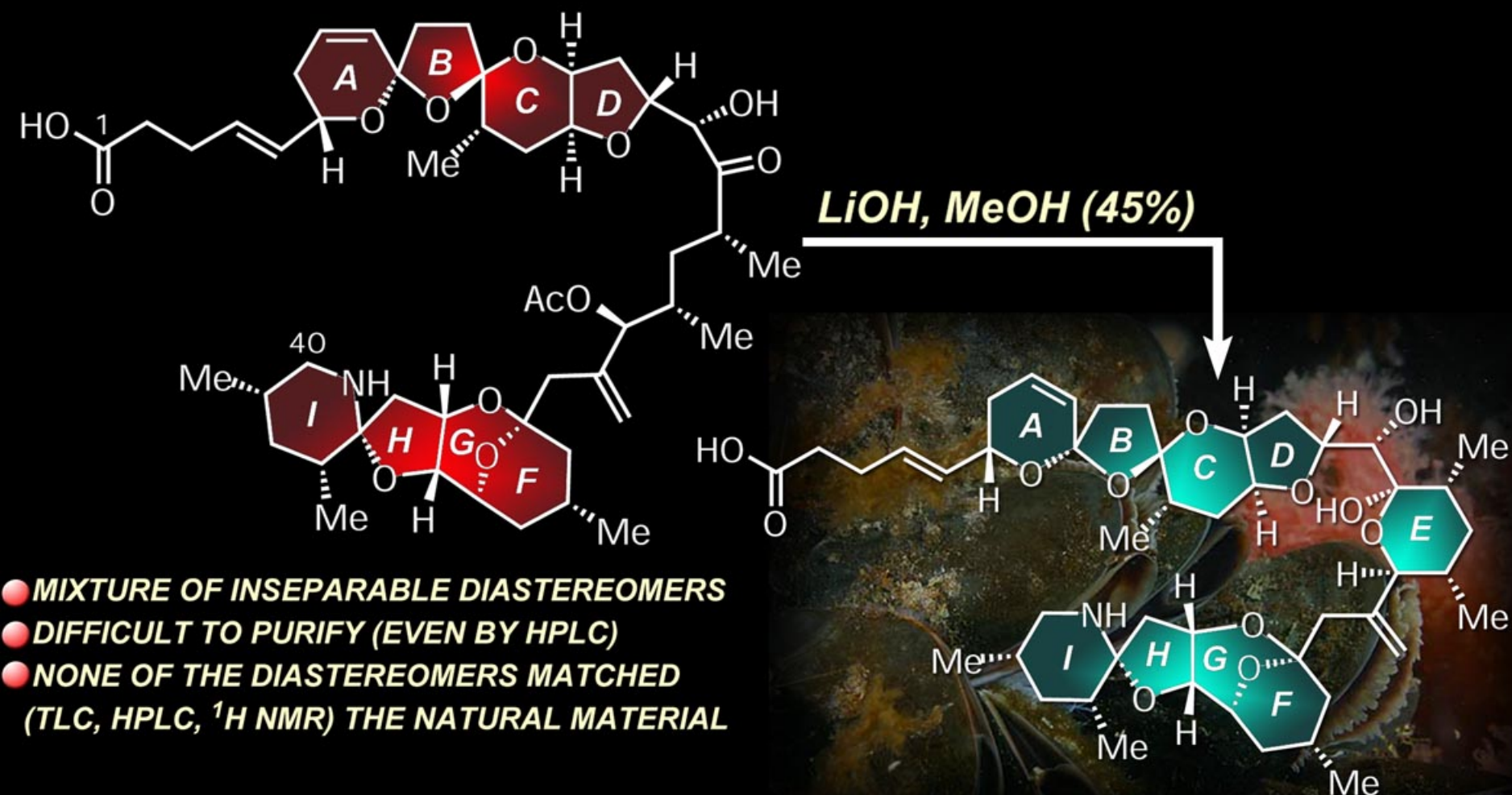
1. TESOTf, 2,6-lutidine
2. K_2CO_3 , MeOH
3. Swern [O]
4. $NaClO_2$ (48%, 4 steps)
5. TBAF (87%)



SINGLE COMPOUND ●
FULLY CHARACTERIZED ●



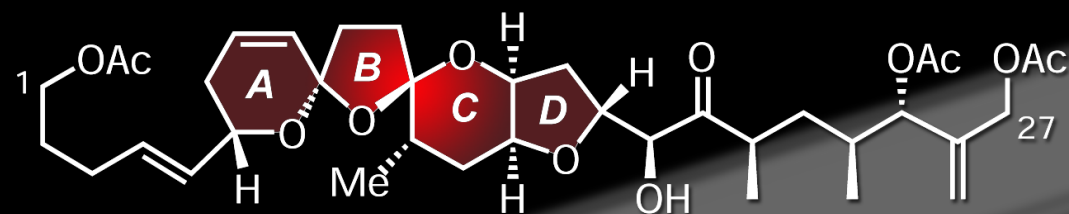
AZASPIRACID-1: COMPLETION OF TOTAL SYNTHESIS OF PROPOSED STRUCTURE [DIASTEREOMER 1]



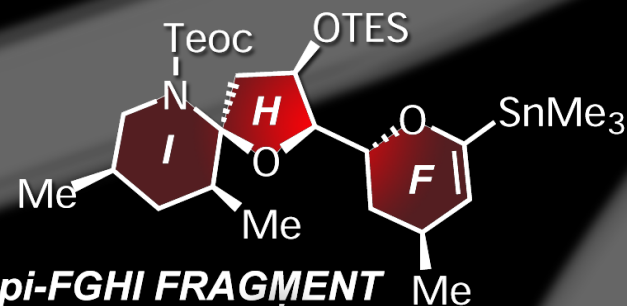
- MIXTURE OF INSEPARABLE DIASTEREOMERS
- DIFFICULT TO PURIFY (EVEN BY HPLC)
- NONE OF THE DIASTEREOMERS MATCHED (TLC, HPLC, ^1H NMR) THE NATURAL MATERIAL



AZASPIRACID-1: TOTAL SYNTHESIS OF FGHI-*epi*-AZASPIRACID-1 [DIASTEREOMER 2]



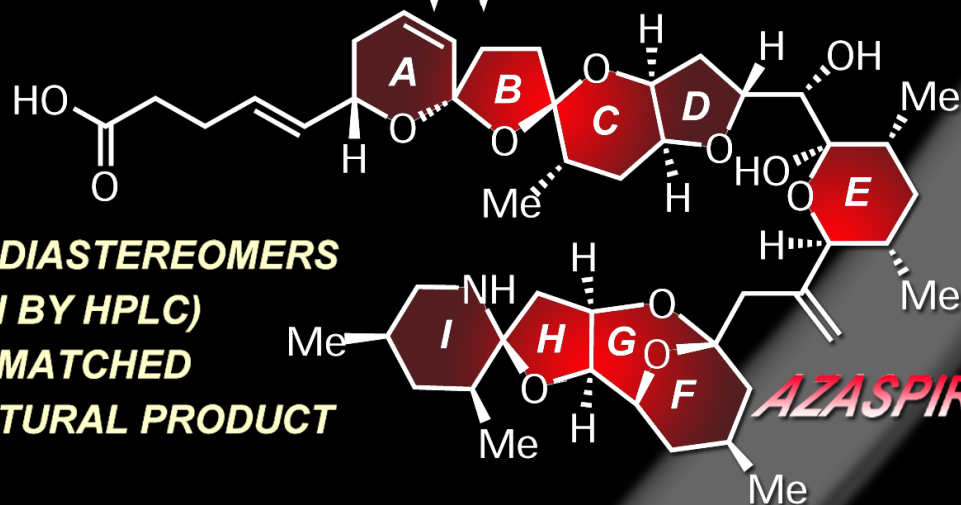
*C*₁-*C*₂₇ FRAGMENT



epi-FGHI FRAGMENT



10 steps ↓ (7.5% overall)



AZASPIRACID-1? NO!

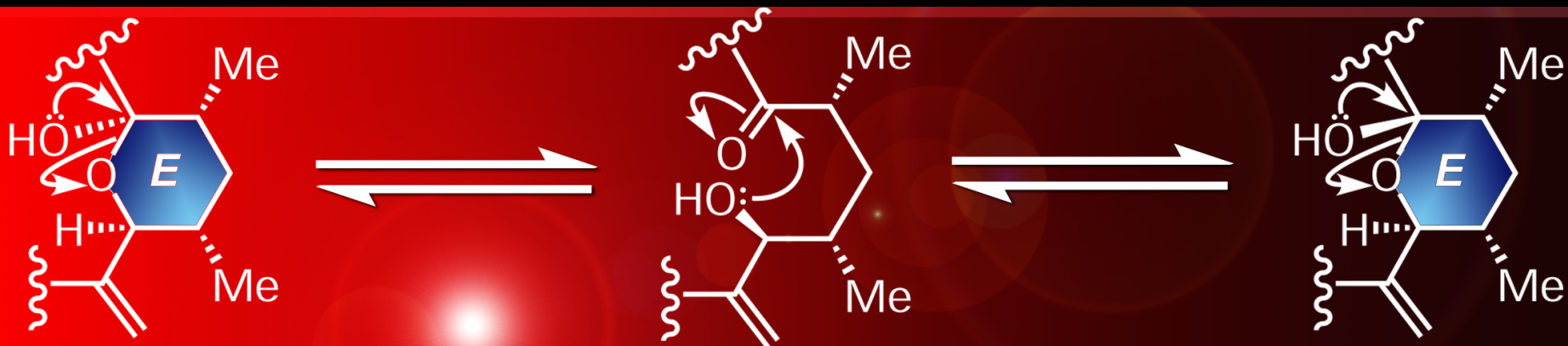
- MIXTURE OF INSEPARABLE DIASTEREOMERS
- DIFFICULT TO PURIFY (EVEN BY HPLC)
- NONE OF DIASTEREOMERS MATCHED (TLC, HPLC, ¹H NMR) THE NATURAL PRODUCT



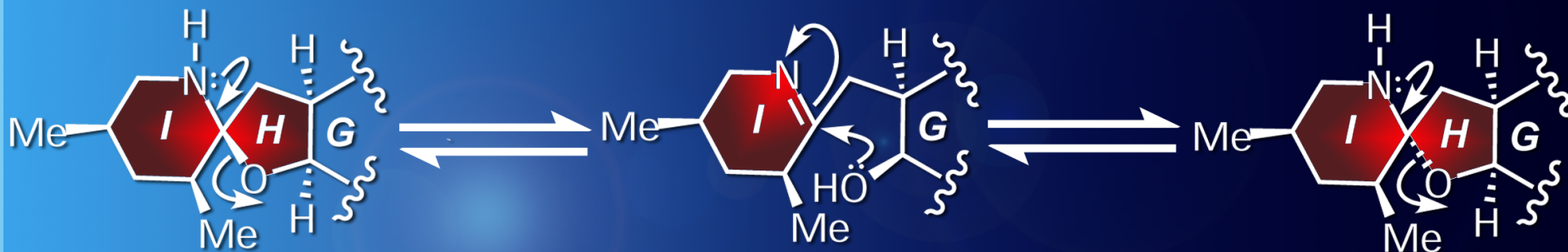
TWO FACILE EPIMERIZATION PATHWAYS OPEN TO AZASPIRACID-1



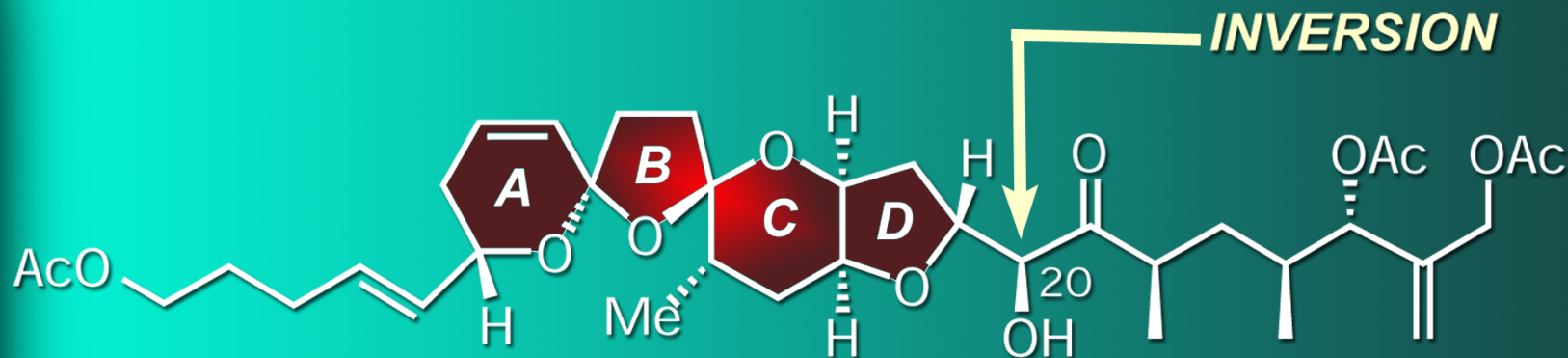
● *E*-RING ISOMERIZATION



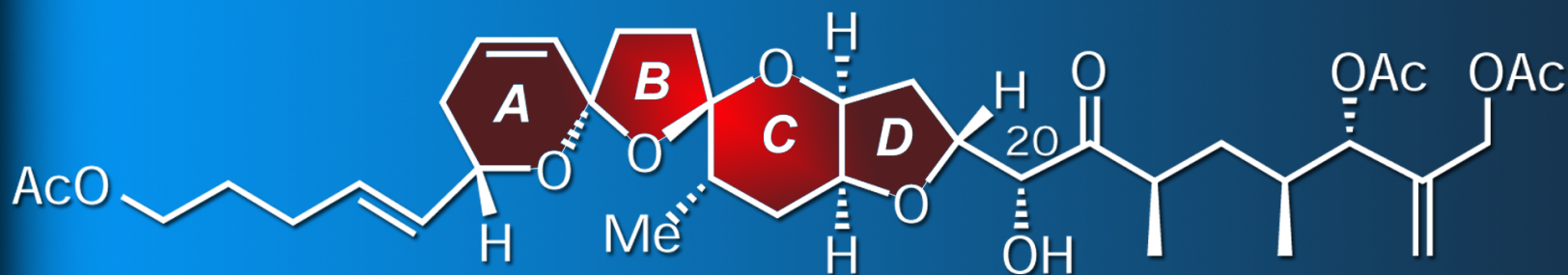
● *HI*-RING SYSTEM ISOMERIZATION



AZASPIRACID-1: INVERSION AT C-20 SYNTHESIS OF C-20-*epi*-AZASPIRACID-1 AND C-20-*epi*-FGHI AZASPIRACID-1

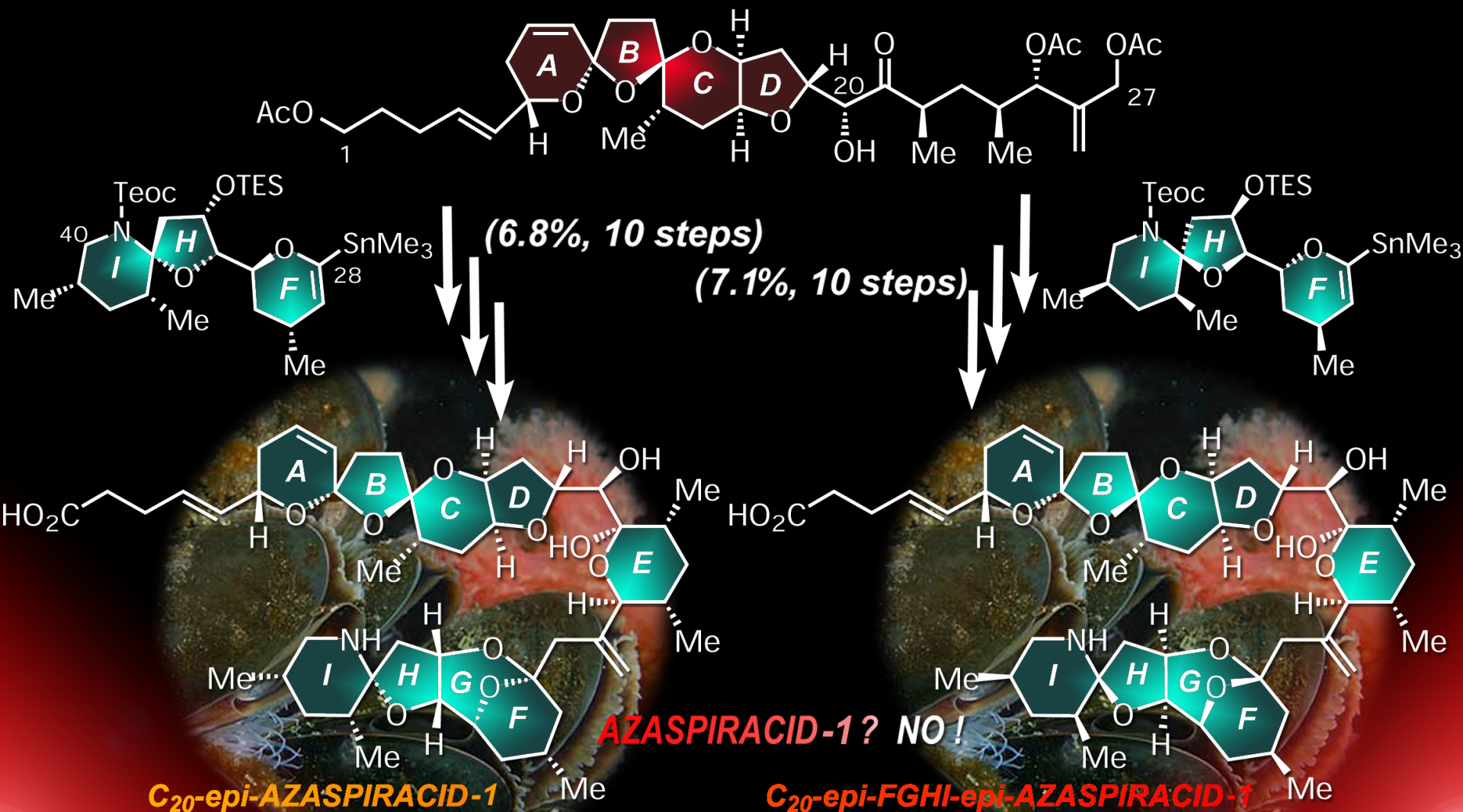


1. Tf_2O -py, 4-DMAP (60%)
2. KNO_2 , 18-Crown-6 (71%)



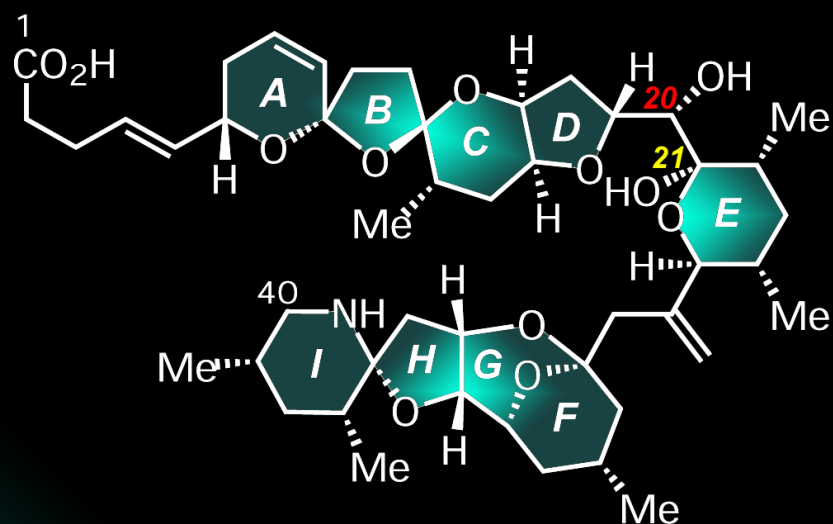


AZASPIRACID-1: STRUCTURAL REVISION. SYNTHESIS OF C-20-*epi*-AZASPIRACID-1 AND C-20-*epi*-FGHI-AZASPIRACID-1



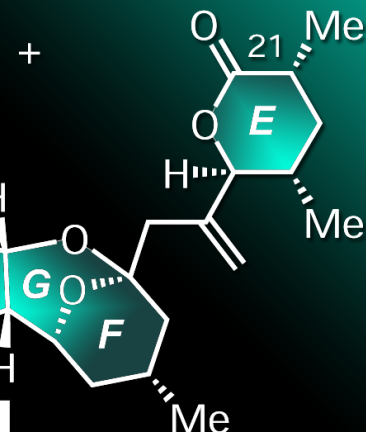
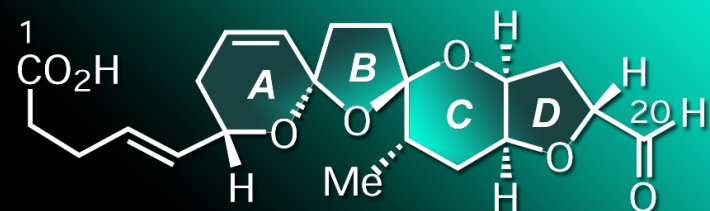
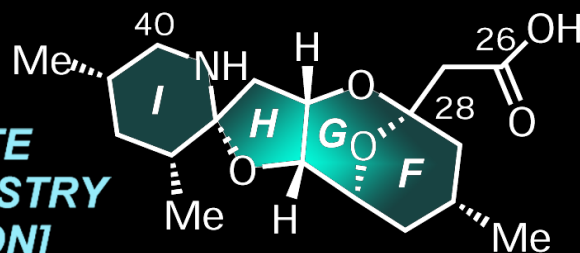


AZASPIRACID-1: STRUCTURAL REVISION. DEGRADATION STUDIES (PROFESSOR MASAYUKI SATAKE)



**PROPOSED STRUCTURE FOR
AZASPIRACID-1 [1998]**

**[FOR ABSOLUTE
STEREOCHEMISTRY
DETERMINATION]**



**[FOR RELATIVE
STEREOCHEMISTRY
DETERMINATION]**

**[CHEMICAL
DEGRADATION]**

● NATURALLY DERIVED MATERIALS FOR COMPARISON WITH SYNTHETIC SAMPLES

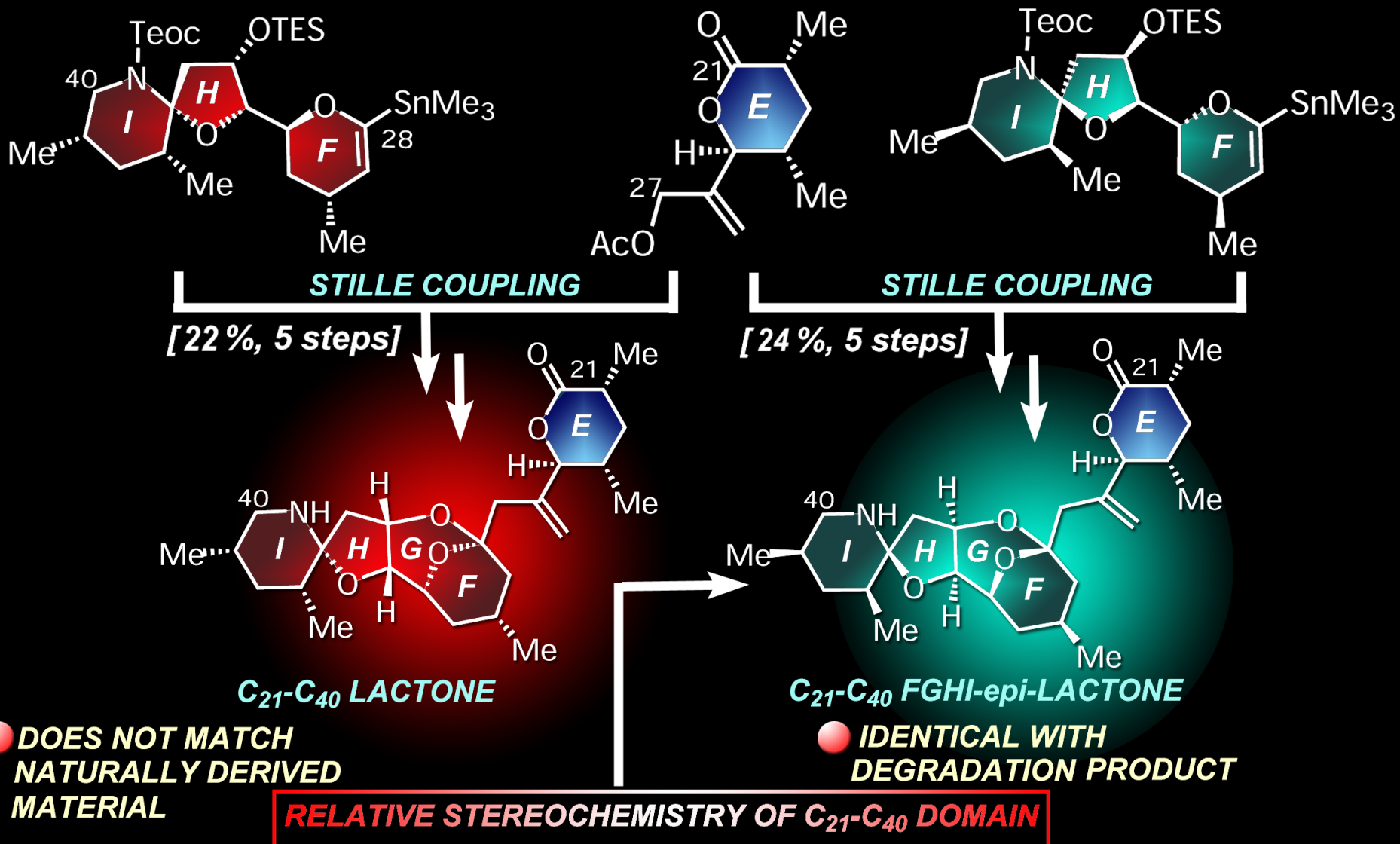
PROFESSOR MASAYUKI SATAKE, TOHOKU UNIVERSITY, JAPAN [2003]



AZASPIRACID-1: STRUCTURAL REVISION.

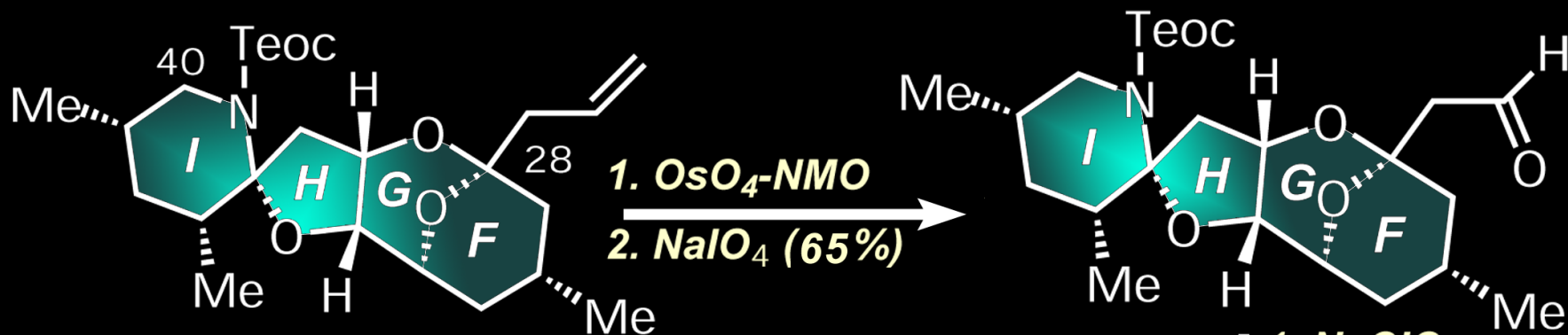
SYNTHESIS OF C₂₁-C₄₀ LACTONE:

ESTABLISHING RELATIVE STEREOCHEMISTRY

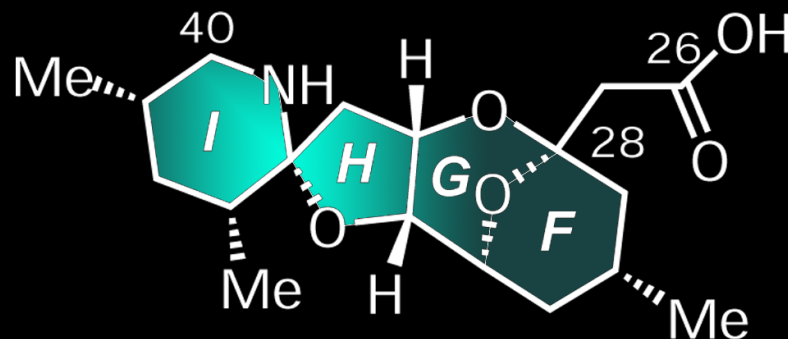




AZASPIRACID-1: STRUCTURAL REVISION SYNTHESIS OF C₂₆-C₄₀ AMINO ACID: ESTABLISHING ABSOLUTE STEREOCHEMISTRY



1. NaClO_2
2. TBAF
(53%, 2 steps)



**ABSOLUTE
STEREOCHEMISTRY OF C₂₈-C₄₀ DOMAIN**

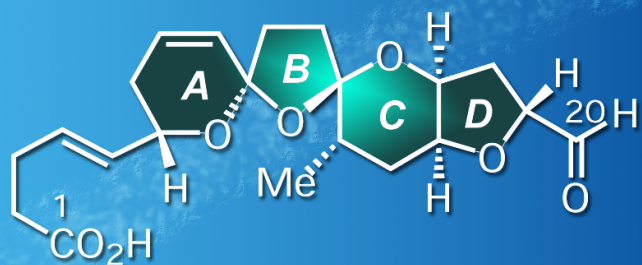
SYNTHETIC: $[\alpha]_D^{25} = +52$ ($c = 0.1$, CH_2Cl_2)
NATURAL: $[\alpha]_D^{25} = -59$ ($c = 0.016$, CH_2Cl_2)



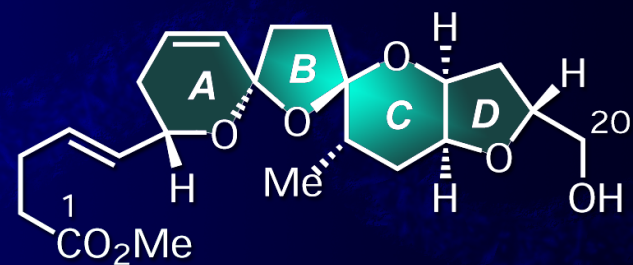
AZASPIRACID-1: STRUCTURAL REVISION OF C₁-C₂₀ DOMAIN [ABCD RING SYSTEM]



NATURALLY DERIVED MATERIAL [SATAKE GROUP]

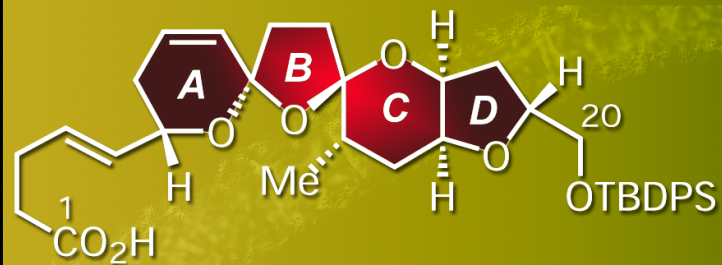


1. CH₂N₂
2. NaBH₄



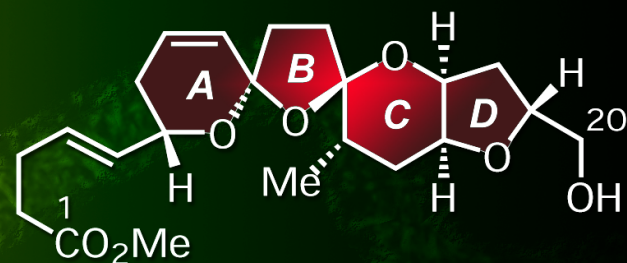
● **FOR COMPARISON PURPOSES**

SYNTHETIC INTERMEDIATE [NICOLAOU GROUP]



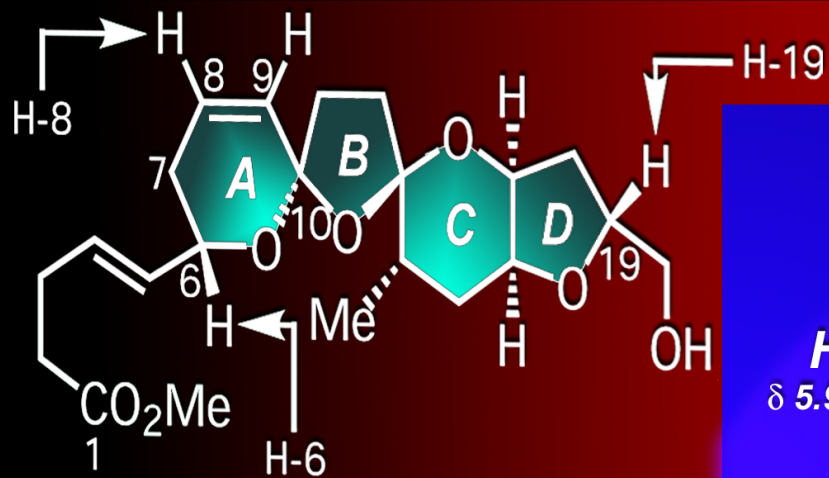
C₁-C₂₀ FRAGMENT

1. MeOH, DCC (86%)
2. TBAF (95%)

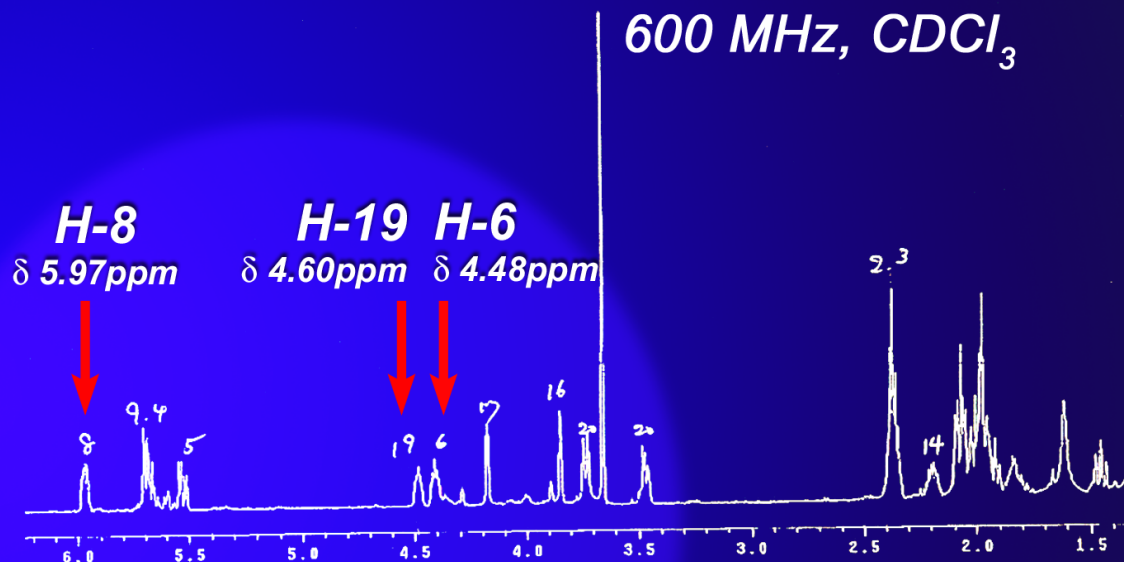




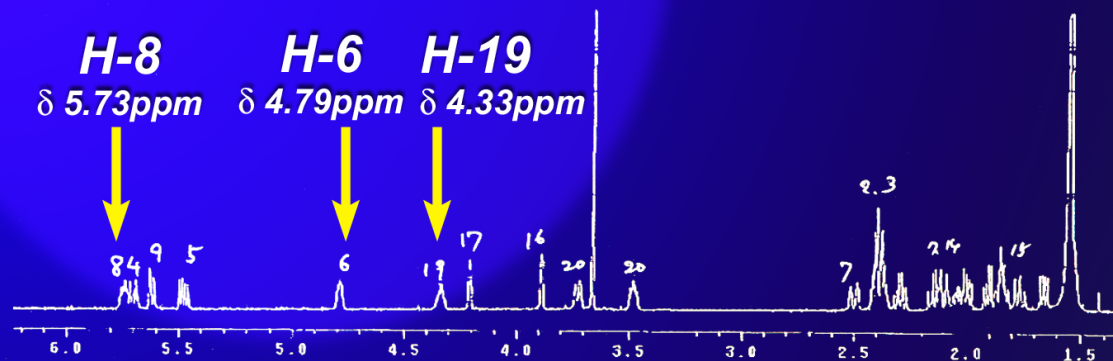
AZASPIRACID-1: STRUCTURAL REVISION OF C₁-C₂₀ DOMAIN [ABCD RING SYSTEM] - ¹H NMR COMPARISON



YY1038 (Synthetic)



Natural (M. Satake)





AZASPIRACID-1: STRUCTURAL REVISION OF C₁-C₂₀ DOMAIN

A PLAUSIBLE STRUCTURE FOR THE RING-A SUBUNIT

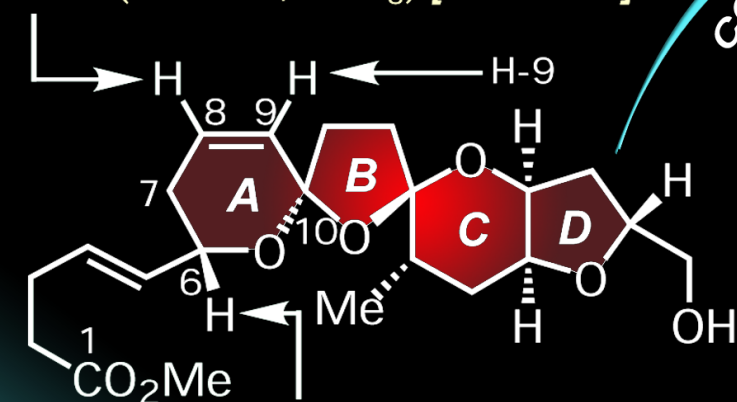


- CHEMICAL SHIFTS FOR H-8 IN NATURAL AND SYNTHETIC MATERIALS ARE SIGNIFICANTLY DIFFERENT.
- IN NATURAL MATERIAL:

- 1. WEAK COSY CORRELATION BETWEEN H-6 AND H-7. ❌
- 2. WEAK HMBC CORRELATION BETWEEN H-9 AND C-10. ❌

● H-8 ($\delta = 5.97$, CDCl₃) [SYNTHETIC]

● H-8 ($\delta = 5.73$, CDCl₃) [NATURAL]

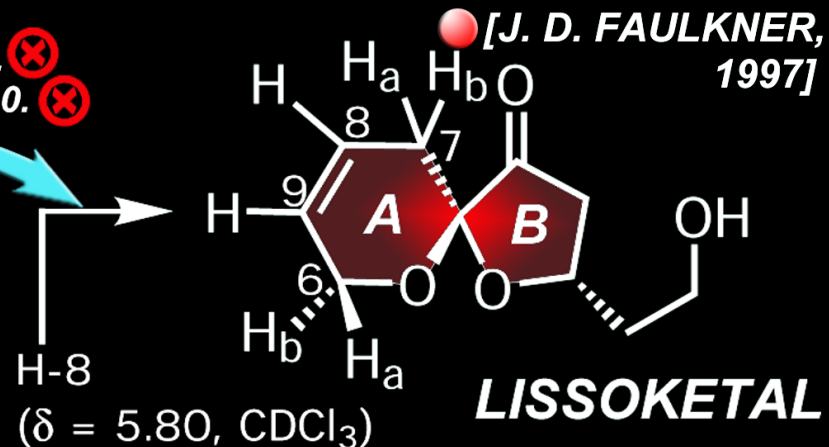


● H-6 ($\delta = 4.40$, CDCl₃) [SYNTHETIC MATERIAL]

● H-6 ($\delta = 4.79$, CDCl₃) [NATURAL MATERIAL]

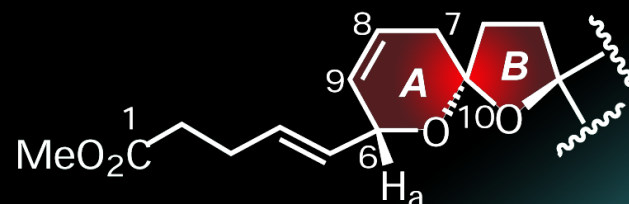
● ELECTRONIC DESHIELDING EFFECT

● DOUBLE ALLYLIC SYSTEM



● NO COSY CORRELATION BETWEEN H-6a AND H-9. ✔

REVISED STRUCTURE FOR RING-A



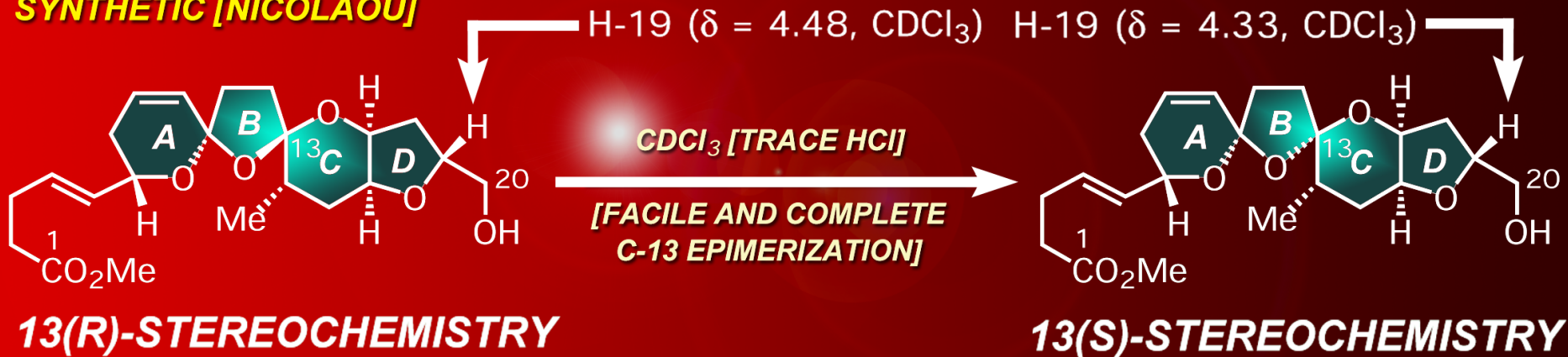
● NO COSY CORRELATION BETWEEN H-6a AND H-9. ✔



AZASPIRACID-1: STRUCTURAL REVISION OF C₁-C₂₀ DOMAIN EVIDENCE FOR DOUBLE ANOMERIC STABILIZED ABC RING SYSTEM



SYNTHETIC [NICOLAOU]

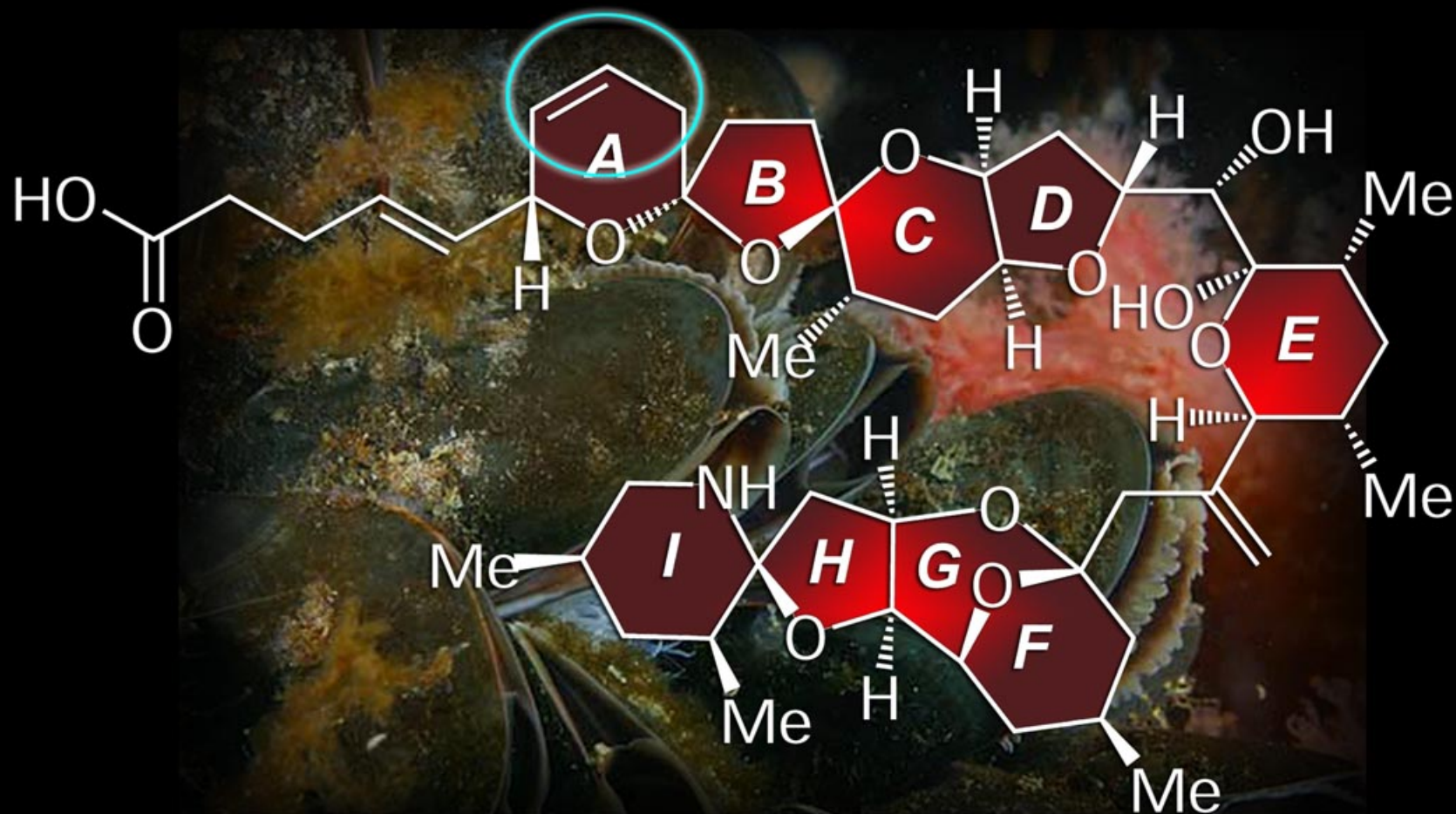


NATURAL [SATAKE]





AZASPIRACID-1: REVISED STRUCTURE, INCLUDING RELATIVE AND ABSOLUTE STEREOCHEMISTRY



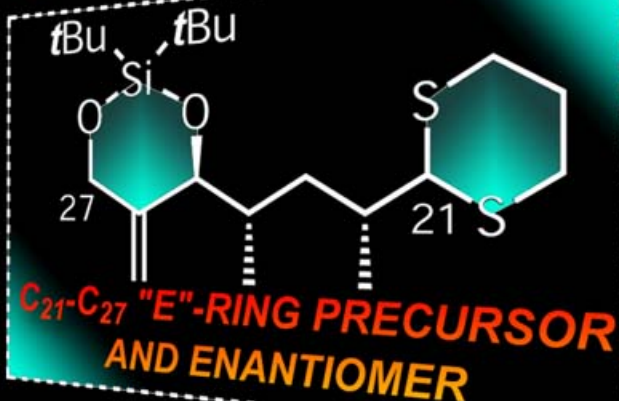
[NICOLAOU AND SATAKE GROUPS, 2003]

AZASPIRACID-1: RETROSYNTHETIC ANALYSIS

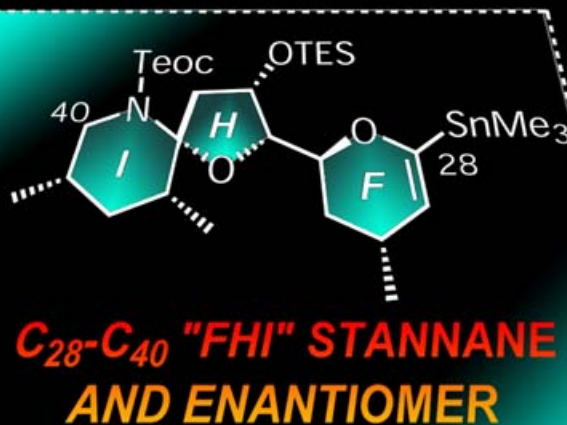
KEY BUILDING BLOCKS



"STICKY FRAGMENT"



DITHIANE COUPLING TECHNOLOGY



STILLE COUPLING

IRELAND-CLAISEN REARRANGEMENT

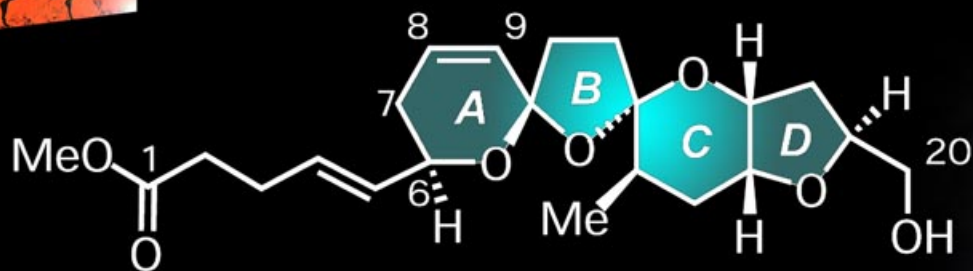
AZASPIRACID-1

• IODOETHERIFICATION

OLEFIN METATHESIS

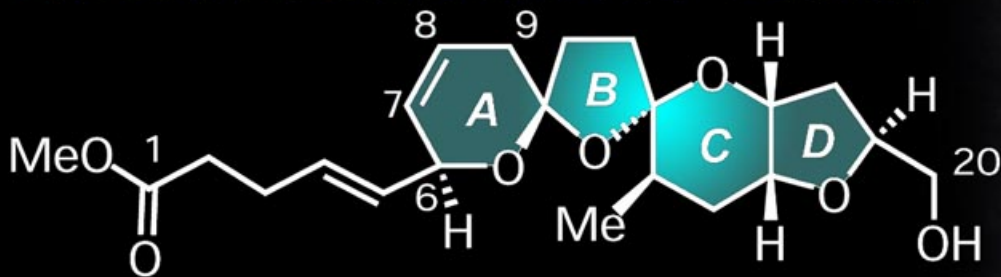


SECOND PROPOSED STRUCTURE FOR AZA-1 ABCD DOMAIN

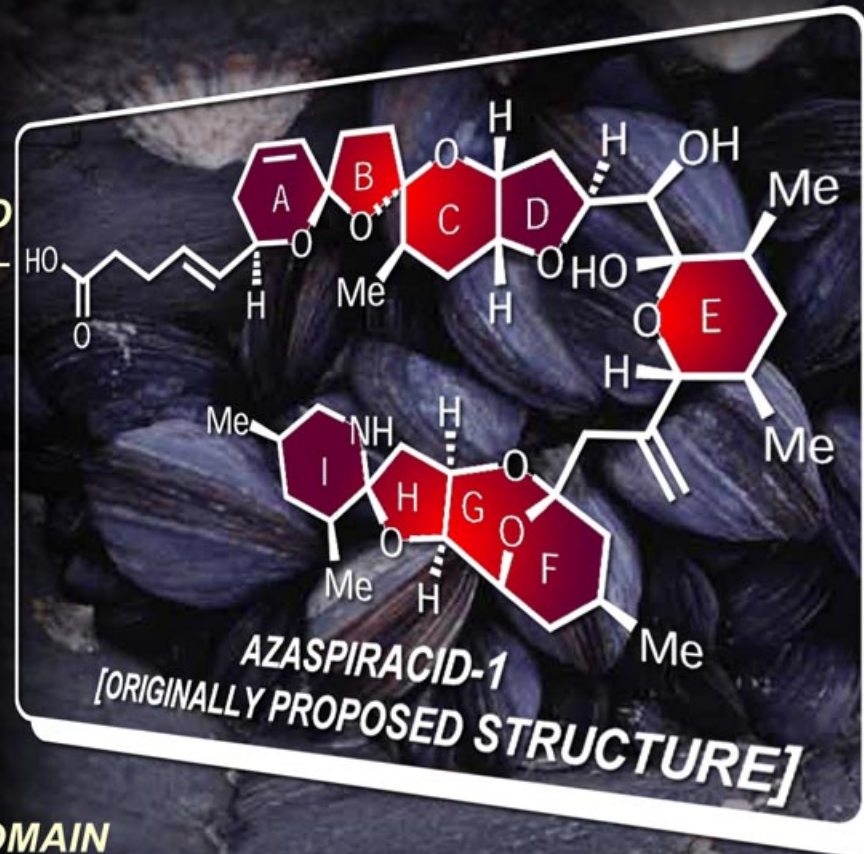


- **ORIGINALLY PROPOSED STRUCTURE FOR ABCD DOMAIN** [SYNTHETIC: NOT IDENTICAL TO DEGRADATION PRODUCT] [YASUMOTO - SATAKE, 1998]

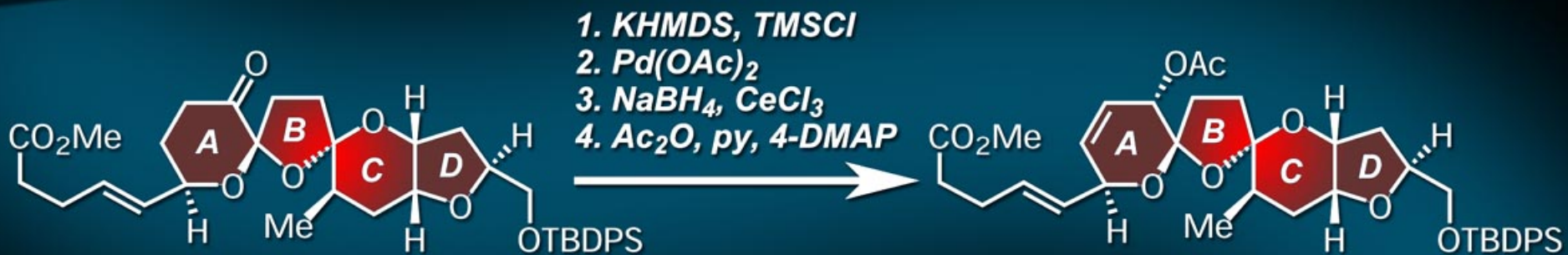
- **RELOCATE DOUBLE BOND TO $\Delta^{7,8}$ POSITION**



- **SECOND PROPOSED STRUCTURE FOR ABCD DOMAIN**
[NICOLAOU et.al, 2003]



SYNTHESIS OF SECOND PROPOSED STRUCTURE

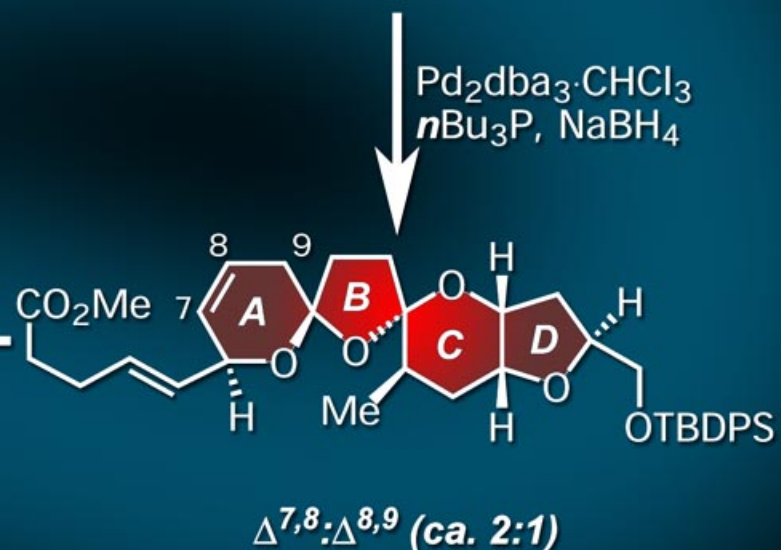


● [FROM ORIGINAL SYNTHESIS]



[NOT IDENTICAL TO DEGRADATION PRODUCT!]

● WHAT NEXT?



TBAF



NON-IDENTITY OF ABCD FRAGMENTS OF AZA-1



- **MORE THAN JUST THE LOCATION OF RING A DOUBLE BOND:**



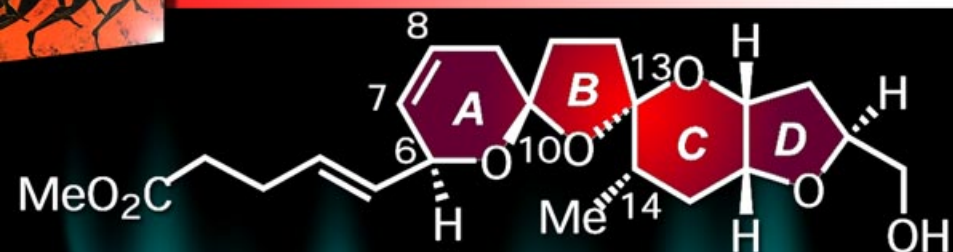
- **SKELETAL PROBLEM!**

- **STEREOCENTER(S)?**

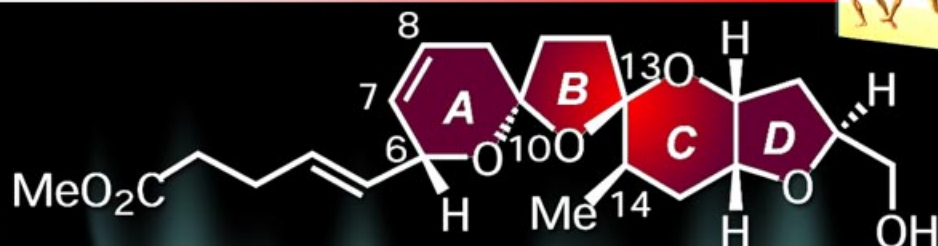
- **WHAT NEXT?**



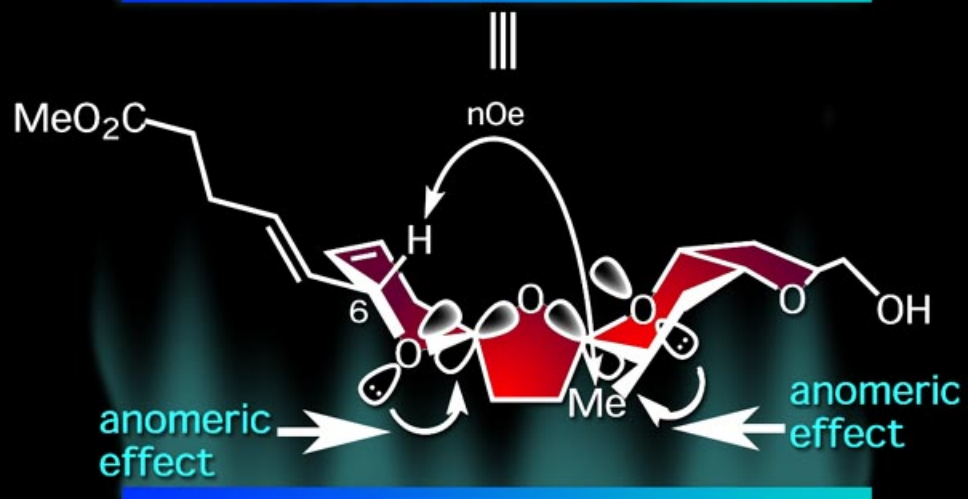
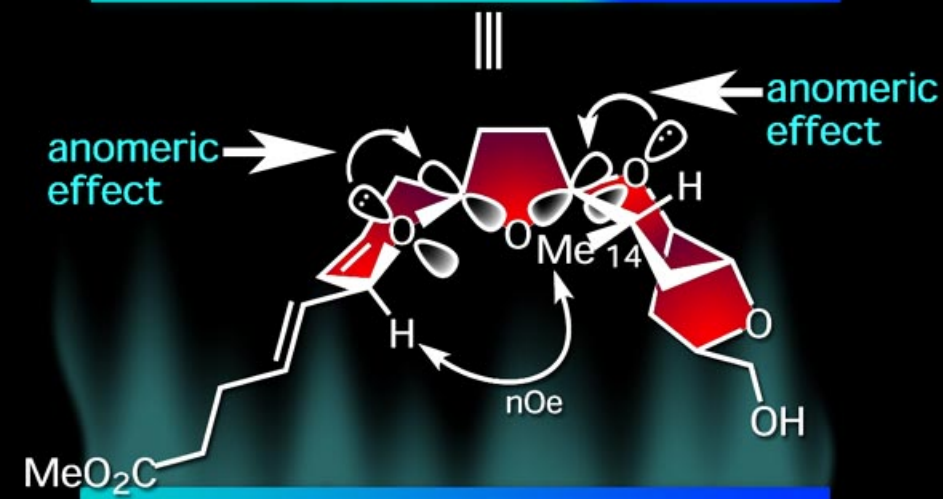
THIRD AND FOURTH ABCD PROPOSED STRUCTURES



THIRD PROPOSED STRUCTURE
[$\Delta^{7,8}$ AND INVERT C-14]



FOURTH PROPOSED STRUCTURE
[$\Delta^{7,8}$ AND INVERT C-6, C-10 AND C-13]



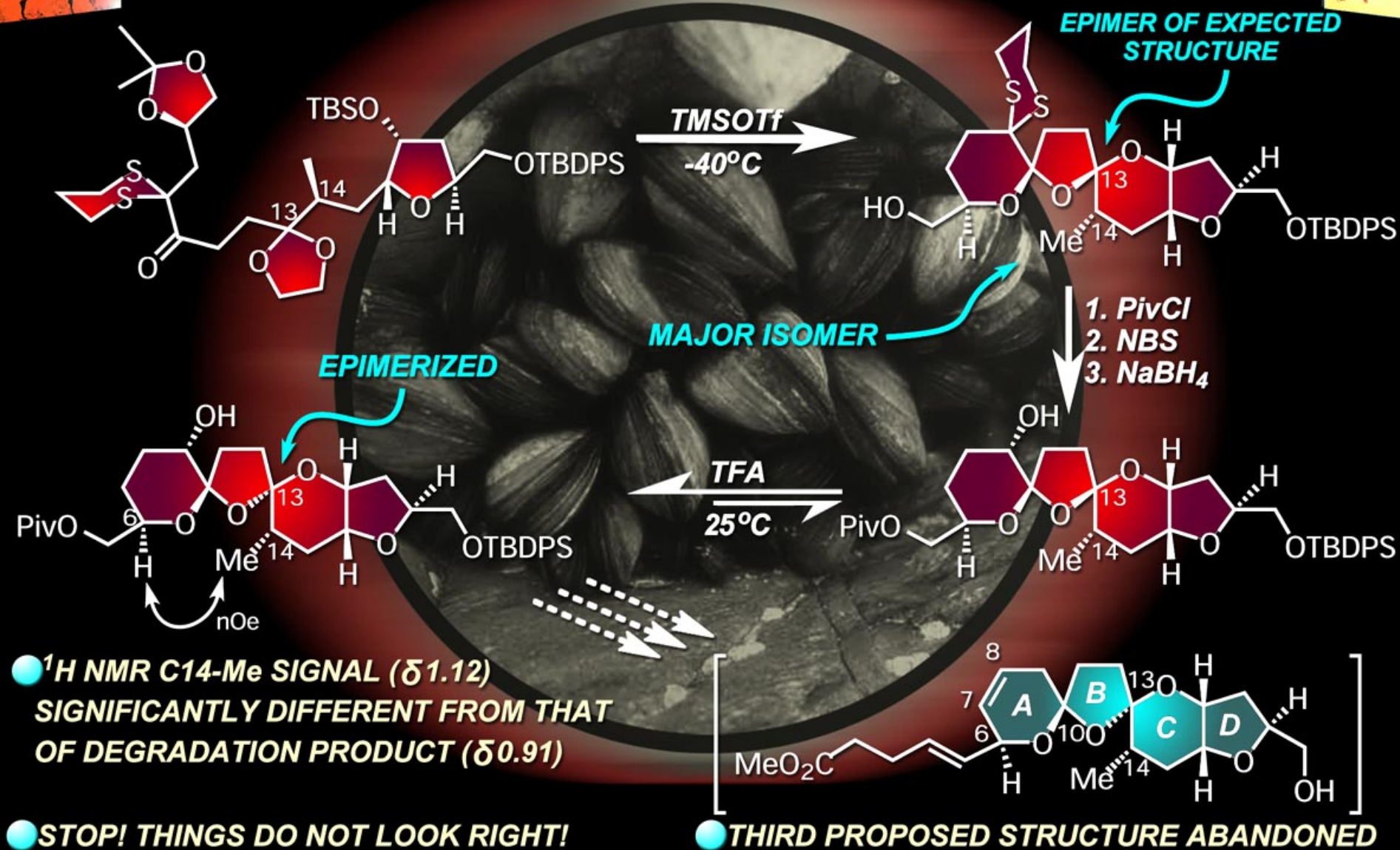
● FROM MOLECULAR MODELING

● EXPECTED THERMODYNAMIC STABILITY AND $nOes$

● NEXT TARGET



ATTEMPTED CONSTRUCTION OF THIRD PROPOSED STRUCTURE

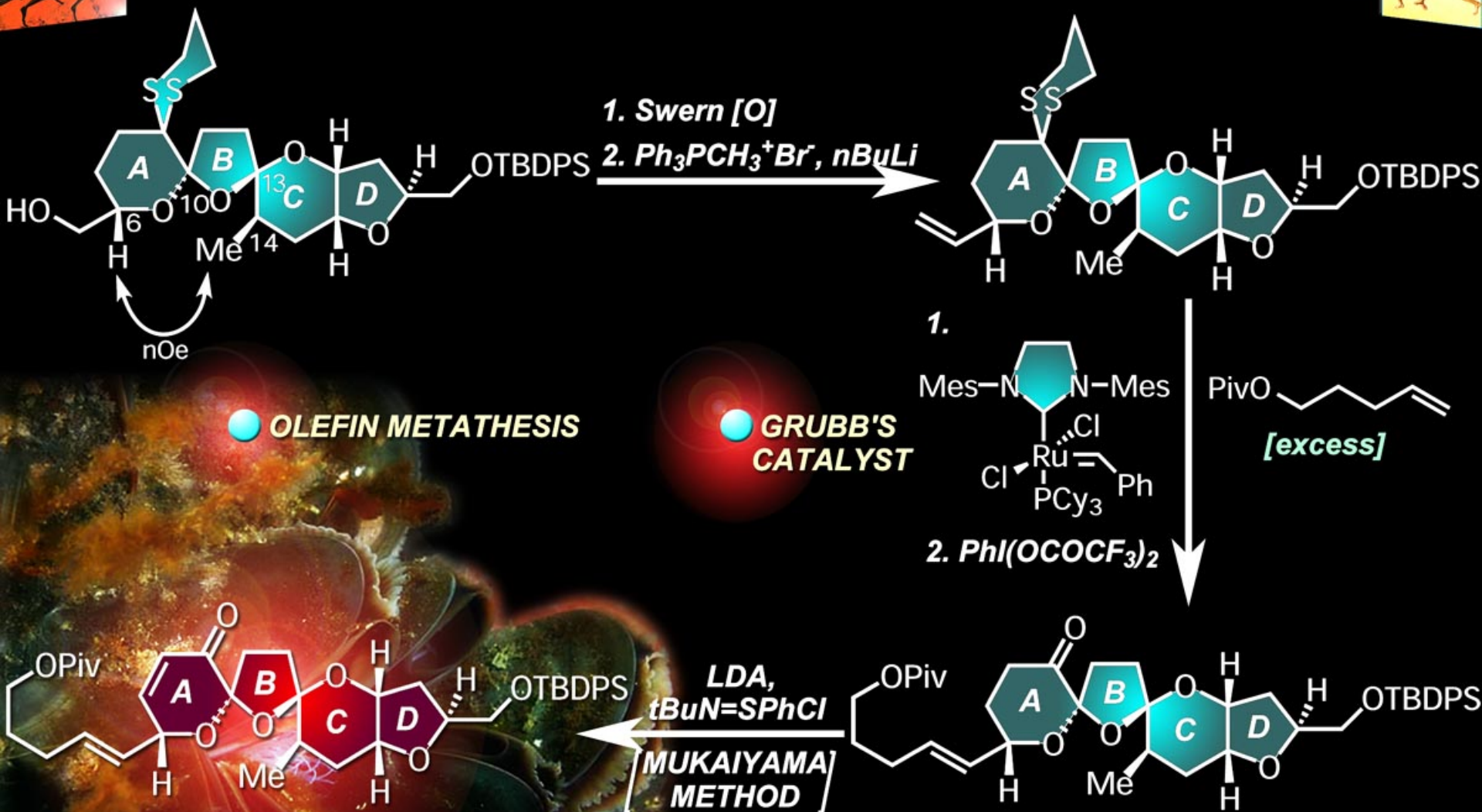




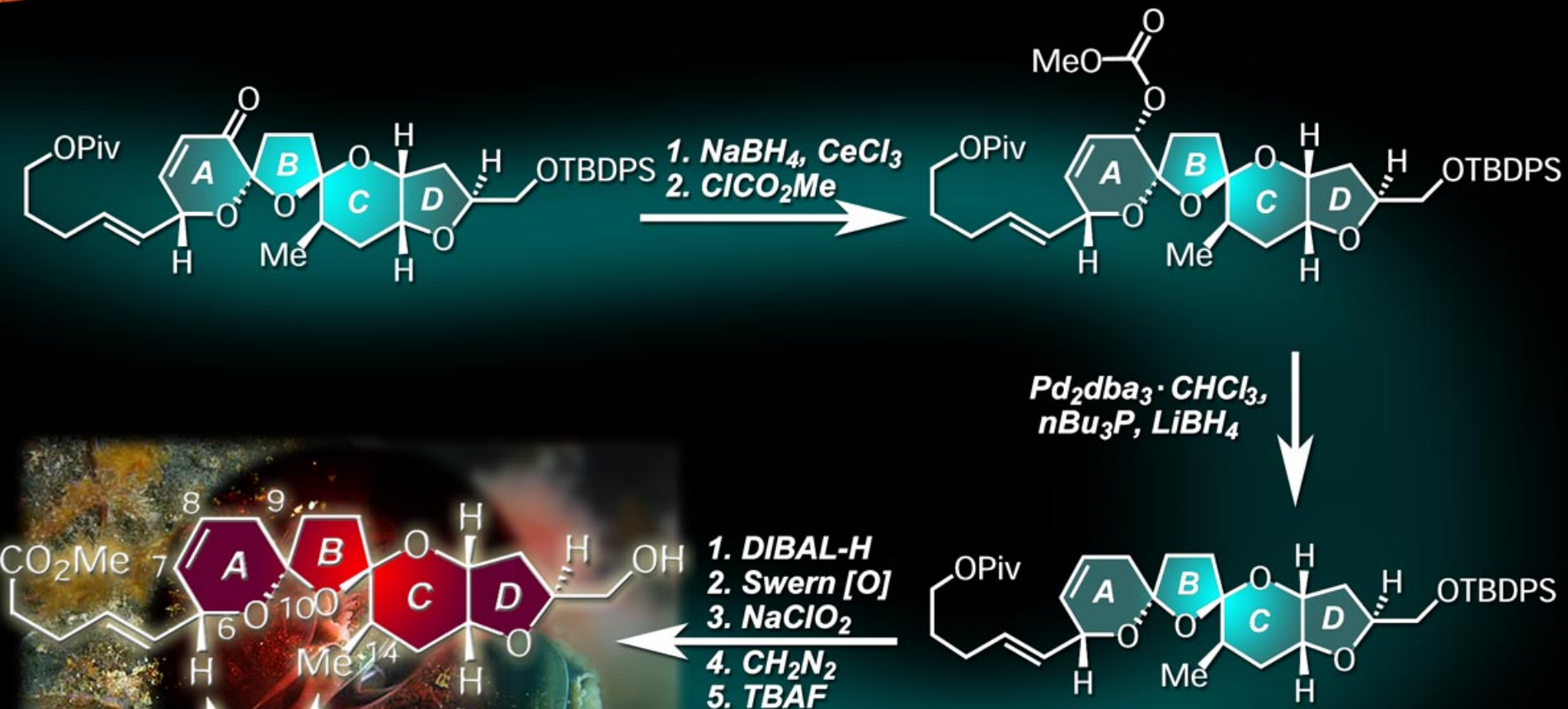
A photograph of two muscular men in a physical struggle. One man is holding a torch, and they appear to be in a competitive or confrontational pose.



CONSTRUCTION OF FOURTH PROPOSED STRUCTURE. II



CONSTRUCTION OF FOURTH PROPOSED STRUCTURE. III



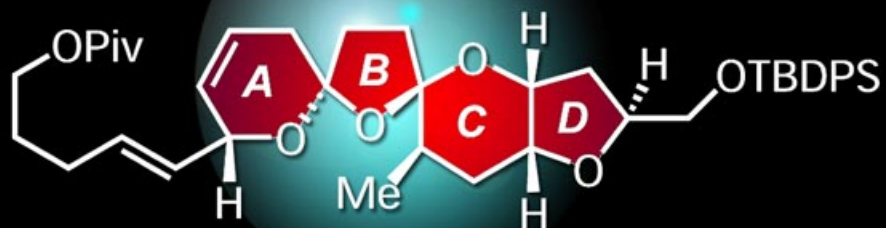
● SYNTHETIC IDENTICAL WITH DEGRADATION PRODUCT! ● GREAT NEWS!



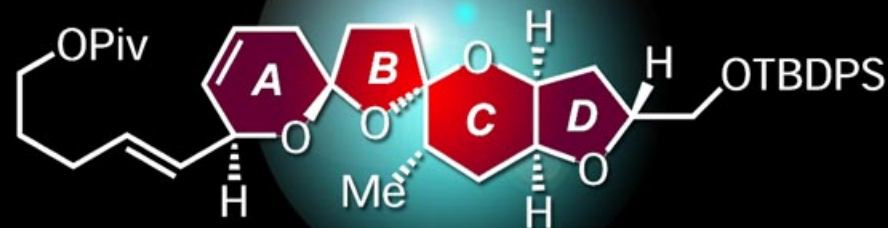
THE FINAL [?] DRIVE TOWARD AZASPIRACID-1. I



- AN ABSOLUTE STEREOCHEMISTRY DILEMMA... BECAUSE
- OPTICAL ROTATION OF DEGRADATION PRODUCT NOT MEASURED DUE TO MINUTE AMOUNTS
- ABSOLUTE CONFIGURATION OF ABCD DOMAIN UNKNOWN



[FROM L-MALIC ACID]



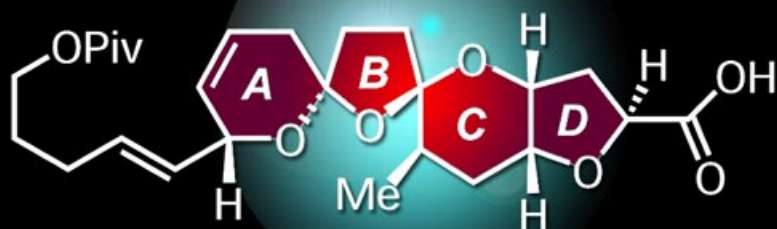
[FROM D-MALIC ACID]

● WHICH ENANTIOMER?

[REACHED THE END FIRST...BUT TO NO AVAIL!]

1. TBAF
2. Swern [O]
3. NaClO₂

● PENTAFLUOROPHENYLESTER

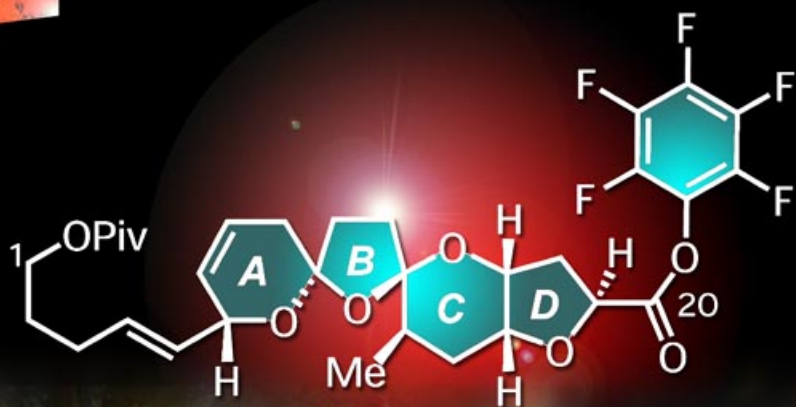


PFPOH, DCC

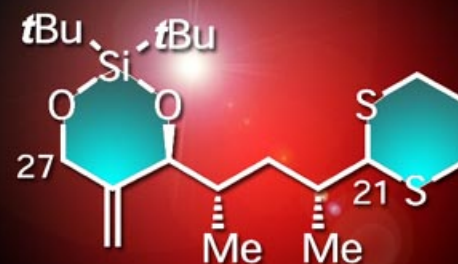


C1-C20 FRAGMENT

THE FINAL [?] DRIVE TOWARD AZASPIRACID-1. II

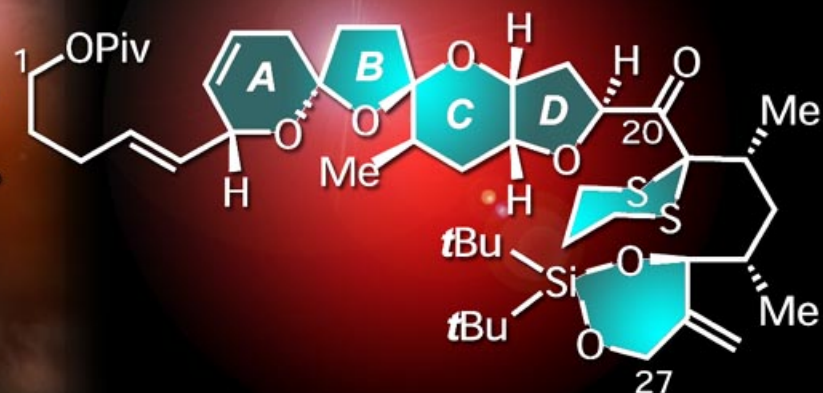


C1-C20 FRAGMENT



C21-C27 FRAGMENT

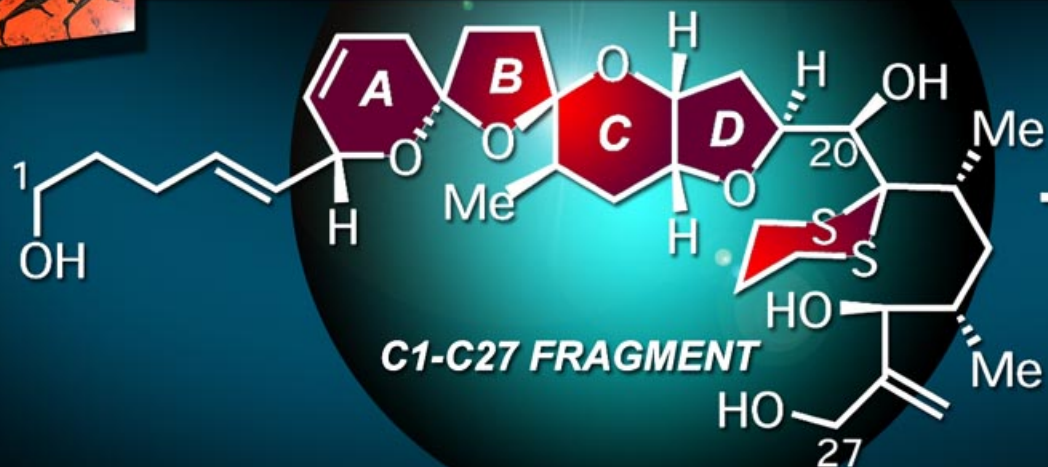
$n\text{BuLi} - n\text{Bu}_2\text{Mg}$
 -90°C



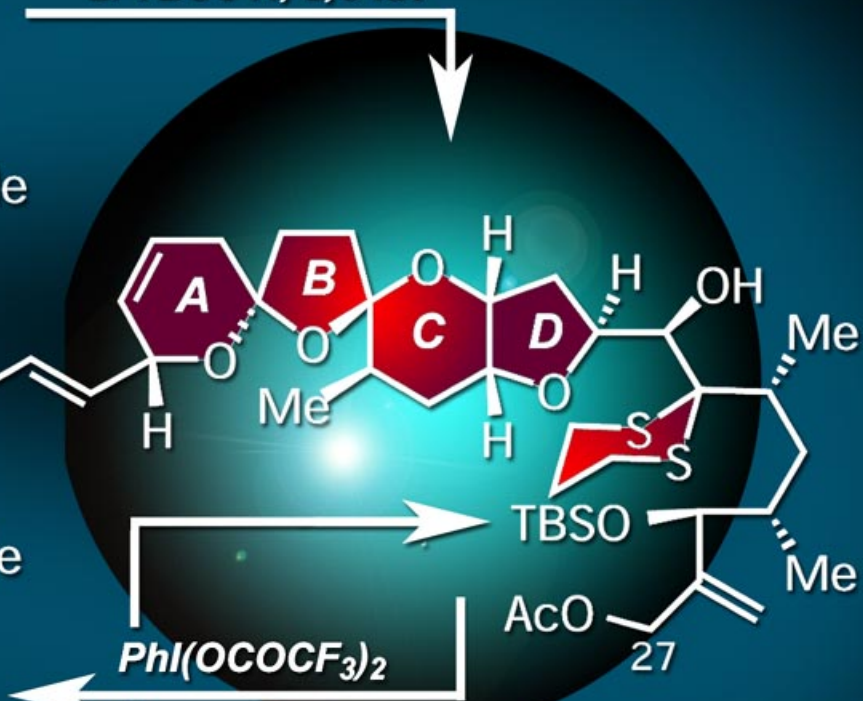
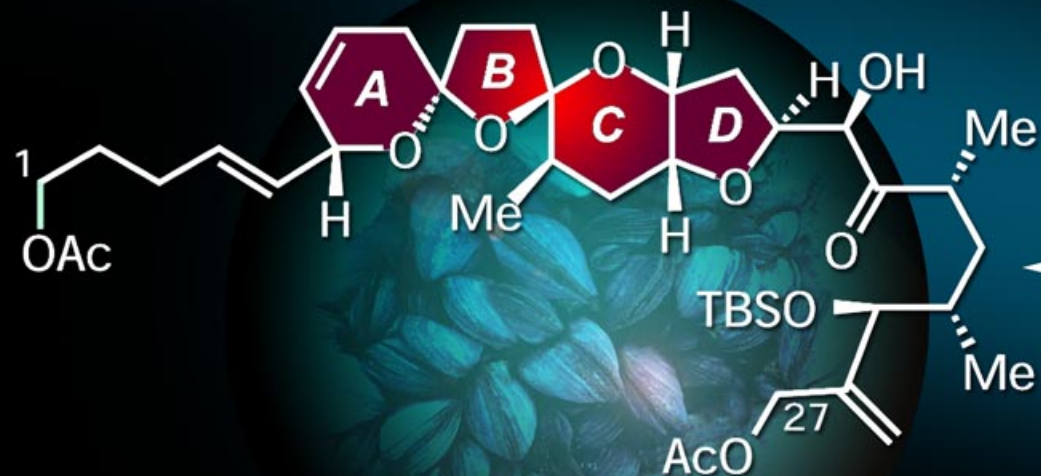
1. DIBAL-H
2. TBAF

C1-C27 FRAGMENT

THE FINAL [?] DRIVE TOWARD AZASPIRACID-1. III



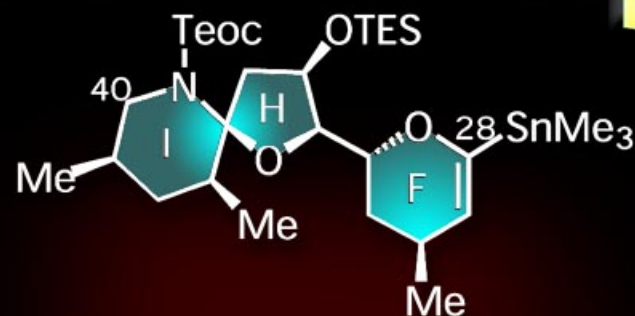
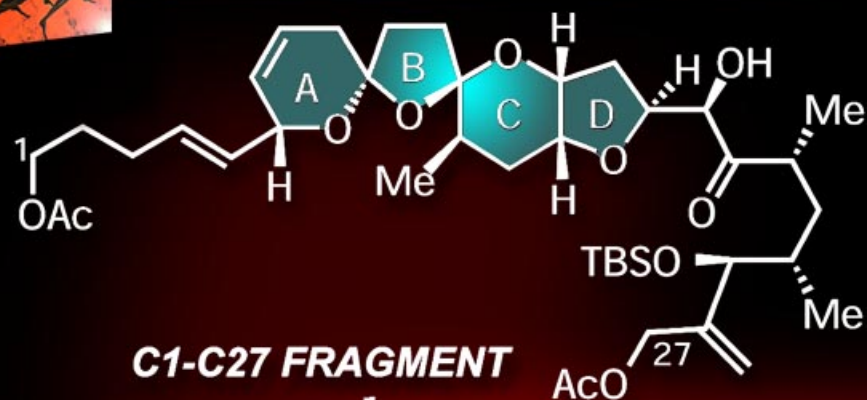
1. AcCl, 2,4,6-col
2. TBSOTf, 2,6-lut



● **TBS INSTEAD OF Ac TO IMPROVE LAST STEP!**

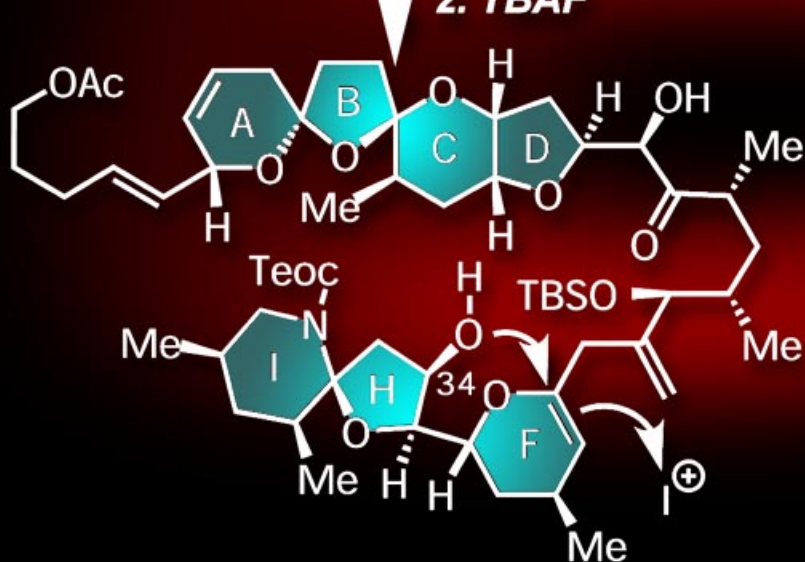


THE FINAL [?] DRIVE TOWARD AZASPIRACID-1. IV

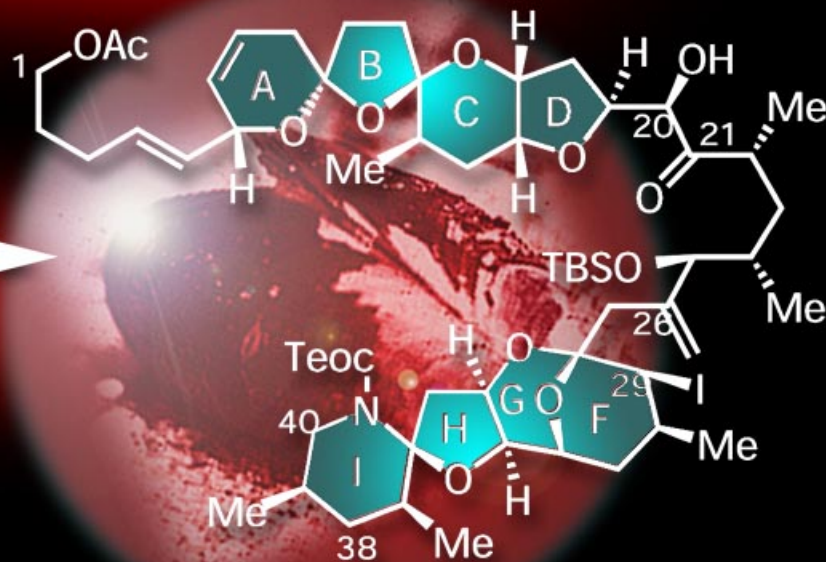


● **STILLE COUPLING**

1. Pd_2dba_3 , LiCl , AsPh_3 , EtNiPr_2
2. TBAF



NIS

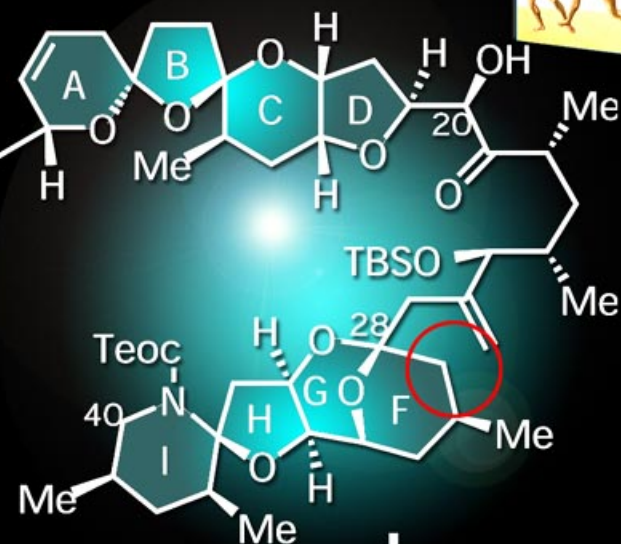
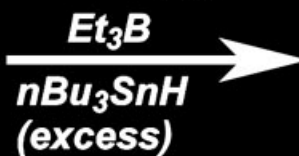
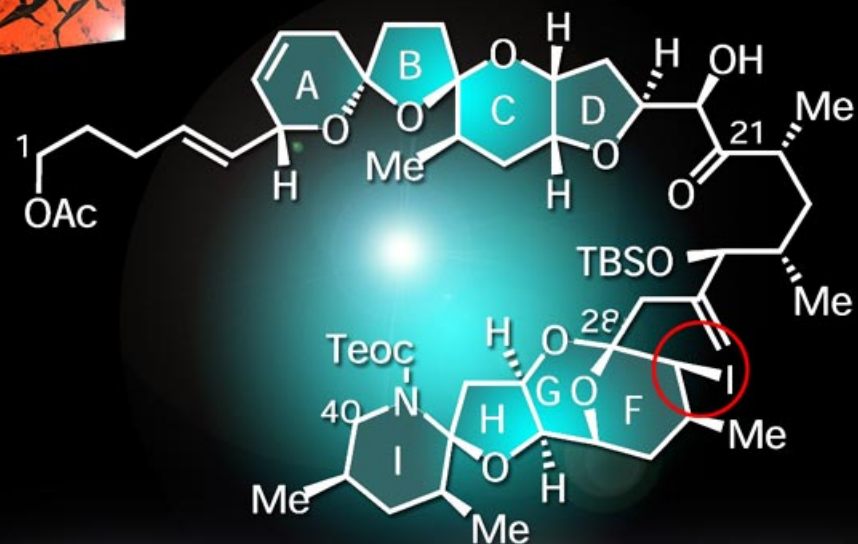


● **IDOETHERIFICATION**

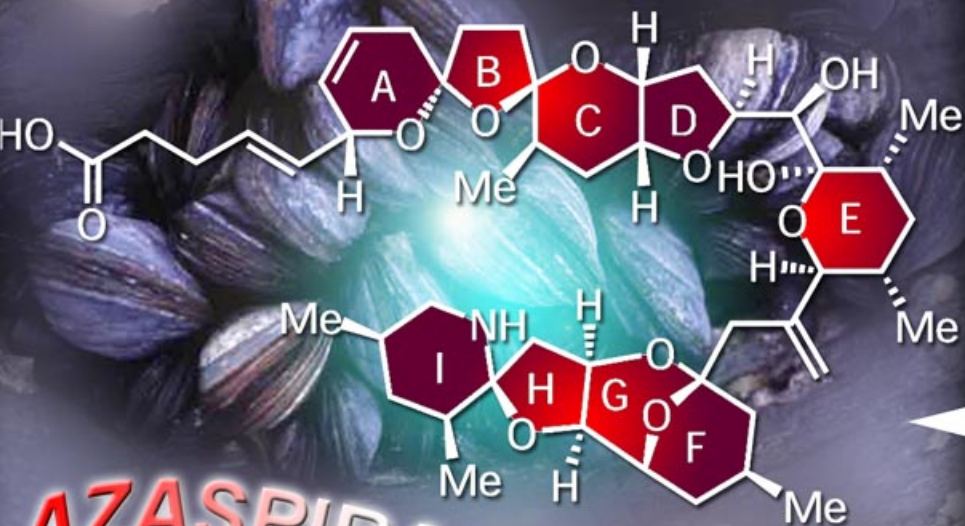
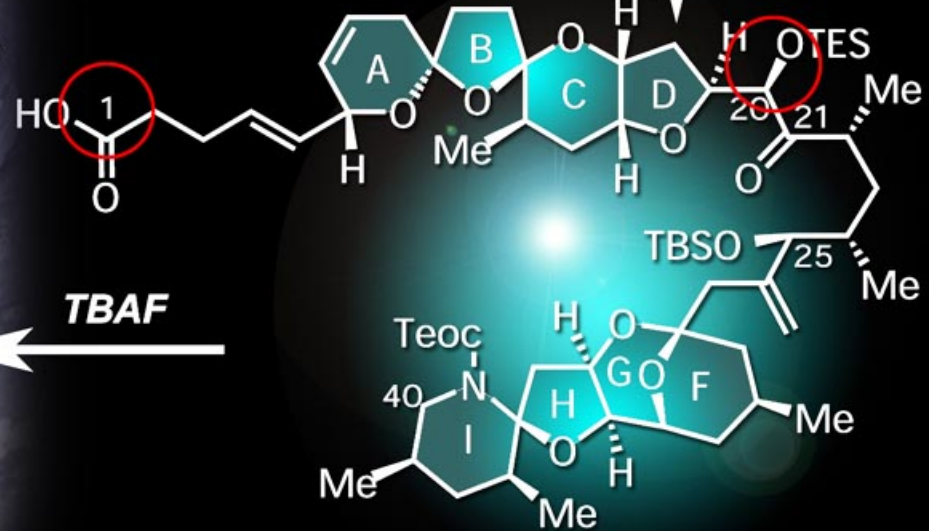
● **ALL CARBON ATOMS IN PLACE**
● **C1-C40 SKELETON**



THE FINAL [?] DRIVE TOWARD AZASPIRACID-1. V



1. TESOTf, 2,6-lut
2. K_2CO_3 , MeOH
3. Swern [O]
4. NaClO_2



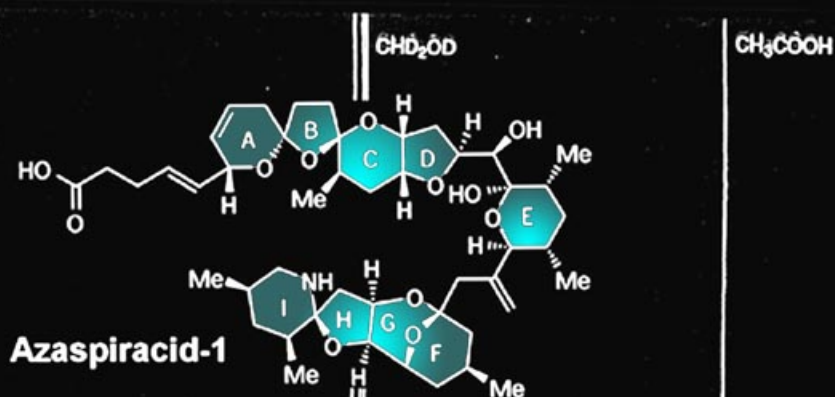
AZASPIRACID-1 [?]



THE END OF AN ODYSSEY: THE FIRST ^1H NMR SPECTRUM

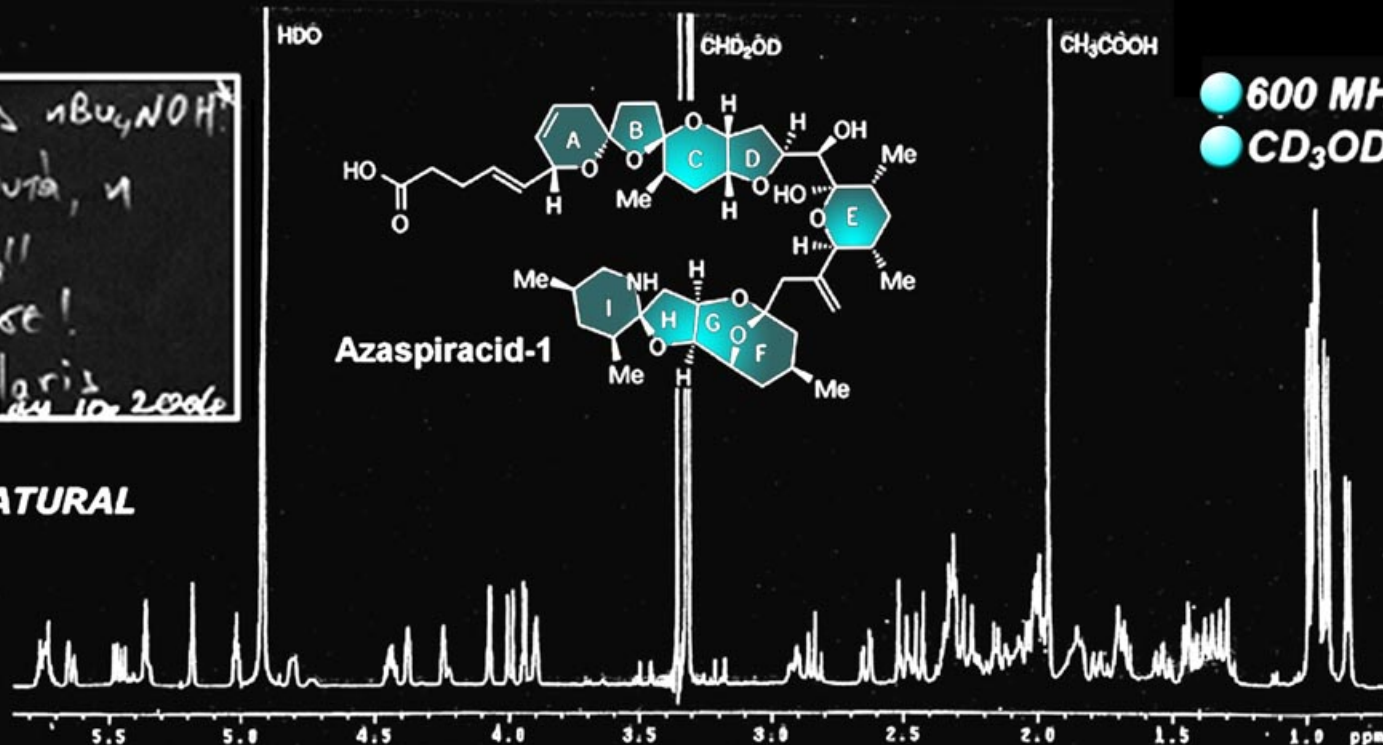


It contains $\text{H}_2\text{N}_2\text{NOH}$
Παρόλα αυτά, η
"Οδύσσεια"
τελείωσε!
Monday, May 10, 2004

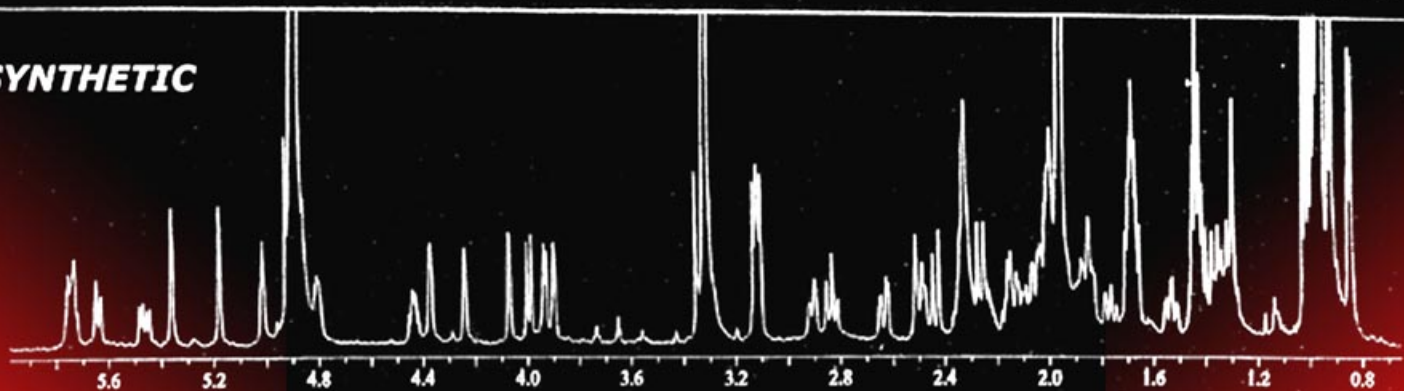


● 600 MHz
● $\text{CD}_3\text{OD}/\text{CD}_3\text{COOD}$

● **NATURAL**

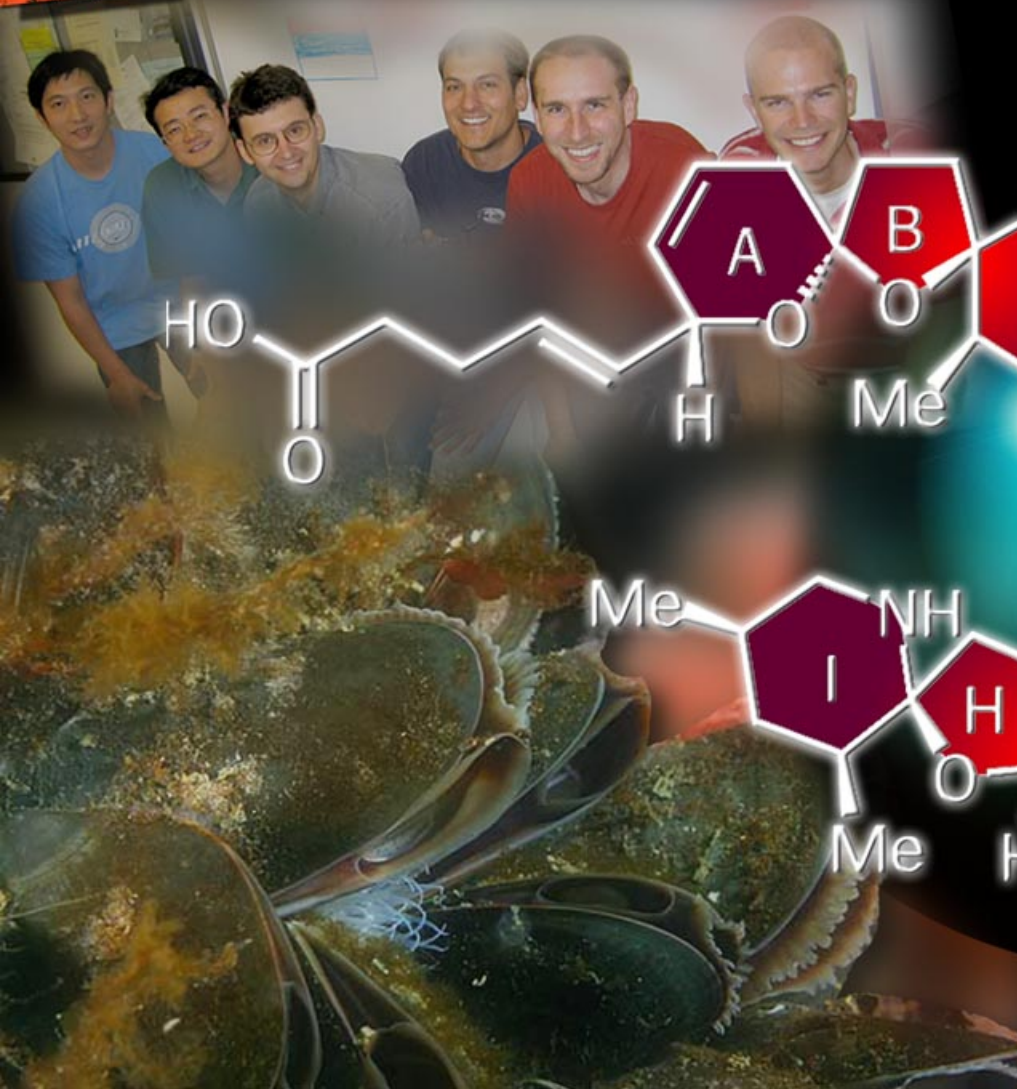


● **SYNTHETIC**





A WILD MOLECULE TAMED



AZASPIRACID-7





THE
SCRIPPS
RESEARCH
INSTITUTE

ACKNOWLEDGEMENTS



UNIVERSITY OF
CALIFORNIA, SAN DIEGO



CHEMISTRY

- FEDERICO BERNAL
- DAVID Y.-K. CHEN
- NICOLE DIEDRICH
- MICHAEL FREERICK
- MUGESH GOVINDASAMY
- JURGEN HINRICH
- THEOCHARIS KOFTIS
- YIWEI LI
- TAOTAO LING
- GORAN PETROVIC
- PETRI M. PIHKO
- WENYUAN QIAN
- WENJUN TANG
- NORIAKI UESAKA
- STEPAN VYSKOCIL
- YOICHI M.A. YAMADA
- NING ZOU

- THE SKAGGS INSTITUTE FOR
CHEMICAL BIOLOGY
- THE NATIONAL INSTITUTES OF HEALTH
- SHERING AG [S.V.]
- NSF [M.F.]

- NMR SPECTROSCOPY:
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- MASS SPECTROMETRY:
GARY SIUZDAK, Ph.D.
- X-RAY CRYSTALLOGRAPHY:
RAJ K. CHADHA, Ph.D.

- OFFICE STAFF:
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XISTA, ROBBYN

- PROFESSOR MASAYUKI SATAKE, TOHOKU UNIVERSITY
(STRUCTURAL ELUCIDATION)



THE END