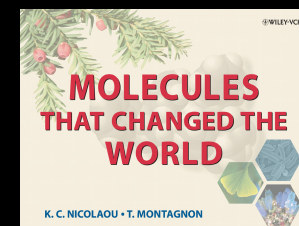
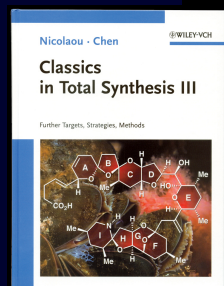
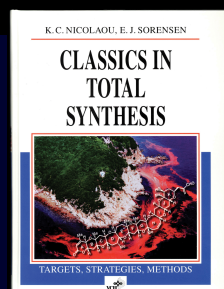


Visit us at scripps.edu/nicolaou

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



Second Symposium Francophone de Synthèse Totale

**Paris, France
June 7-8, 2012**

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

**“Total Synthesis of Natural Products of Biological
and Medicinal Importance”**

Ludwig-Maximilians University

Munich

Monday, June 11, 2012

K.C. Nicolaou, Ph.D.

*The Scripps Research Institute
and*

University of California, San Diego

**“Total Synthesis of Natural Products of Biological
and Medicinal Importance”**

Technical University of Munich

Tuesday, June 12, 2012

K.C. Nicolaou, Ph.D.

*The Scripps Research Institute
and*

University of California, San Diego

**“Total Synthesis of Natural Products of Biological
and Medicinal Importance”**

University of Leipzig

Wednesday, June 13, 2012

K.C. Nicolaou, Ph.D.

*The Scripps Research Institute
and*

University of California, San Diego

**“Total Synthesis of Natural Products of Biological
and Medicinal Importance”**

Bayer Pharma AG, Wuppertal

Thursday, June 14, 2012

K.C. Nicolaou, Ph.D.

*The Scripps Research Institute
and*

University of California, San Diego

**“Total Synthesis of Natural Products of Biological
and Medicinal Importance”**

**Institute for Organic Chemistry,
RWTH Aachen**

Friday, June 15, 2012

K.C. Nicolaou, Ph.D.

*The Scripps Research Institute
and*

University of California, San Diego

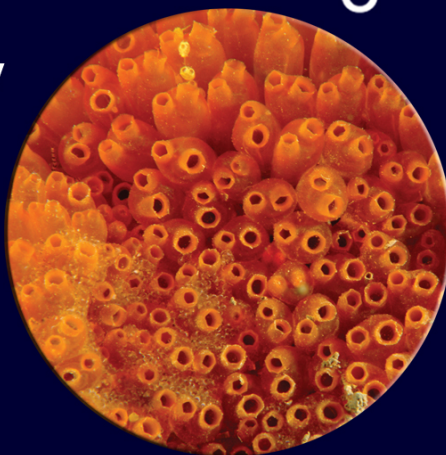
**“Total Synthesis of Natural Products of Biological
and Medicinal Importance”**

Lecture Outline

- **Antibiotic BE-43472B**
 - **Sporolide B**
 - **Bielschowskysin Studies**
 - **Epidithiodiketopiperazines Studies**
 - **Maitotoxin Studies**
-



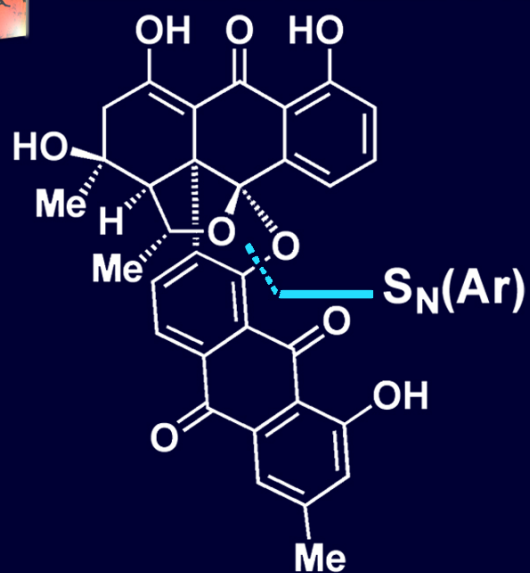
- **First isolated from a *Streptomyces* sp. and reported in a Japanese patent as an antitumor agent [gross structure only: H. Kushida et al, JP 08143569, 1996]**
- **Potent antibiotic activity against MSSA, MRSA, TRSA and VRE and antibactericidal activity (99.9 % kill) against MSSA, MRSA and VRE**



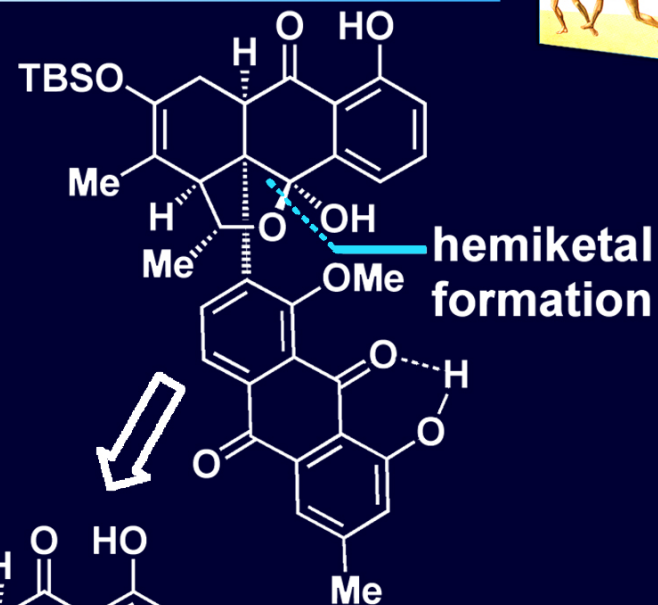
- Re-isolated by D. C. Rowley and co-workers from a *Streptomyces* sp. found in a green algae isolated from the ascidian *Ecteinascidia turbinata*, collected from La Parguera, Puerto Rico [relative, but no absolute configuration: *J. Nat. Prod.* 2006, 69, 1070; *Bioorg. Med. Chem.* 2006, 14, 8664.]



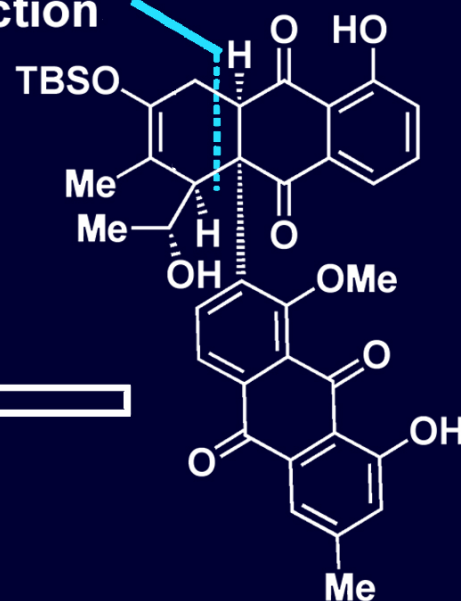
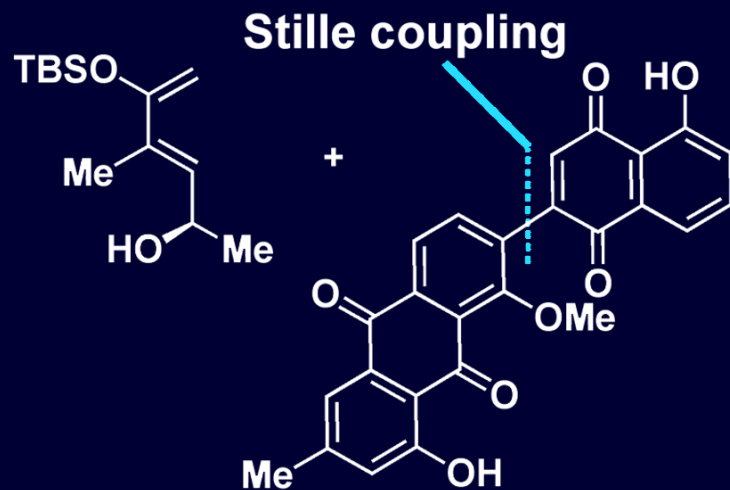
BE-43472B 2. RETROSYNTHETIC ANALYSIS [2009]

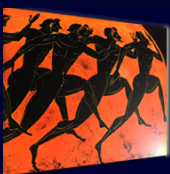


Transform
→
● Nucleophilic aromatic
ipso substitution



Diels-Alder
reaction

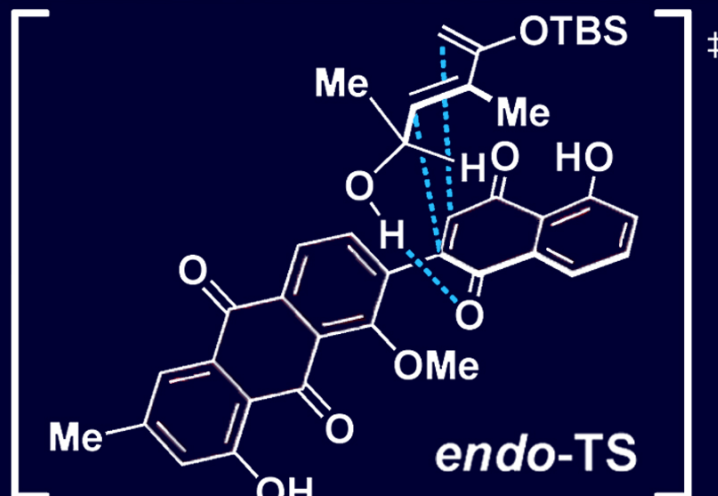




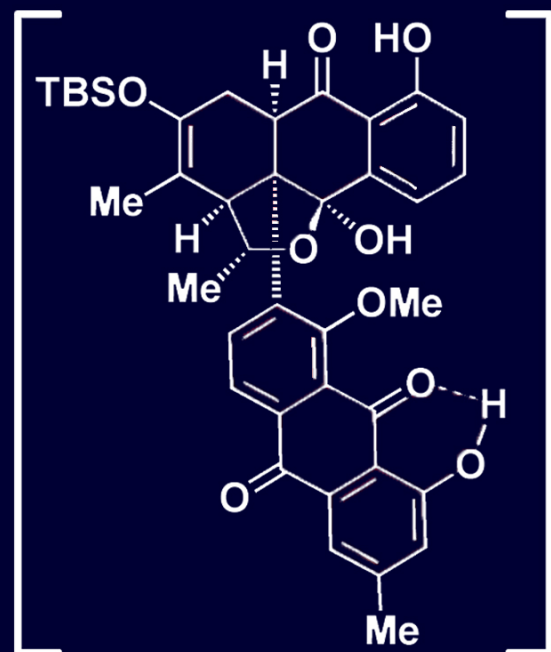
ANTIBIOTIC BE-43472B 5. CASCADE I [2009]



- preorganization of diene and dienophile



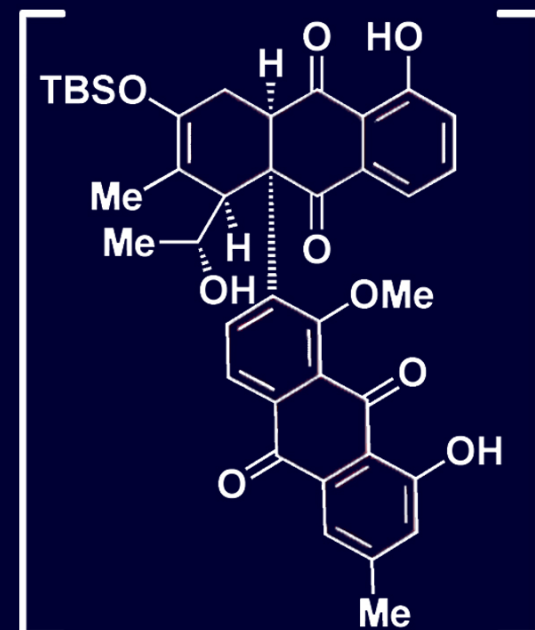
$\text{CH}_2\text{Cl}_2, \Delta$;
[sealed tube]



[Diels-Alder reaction]

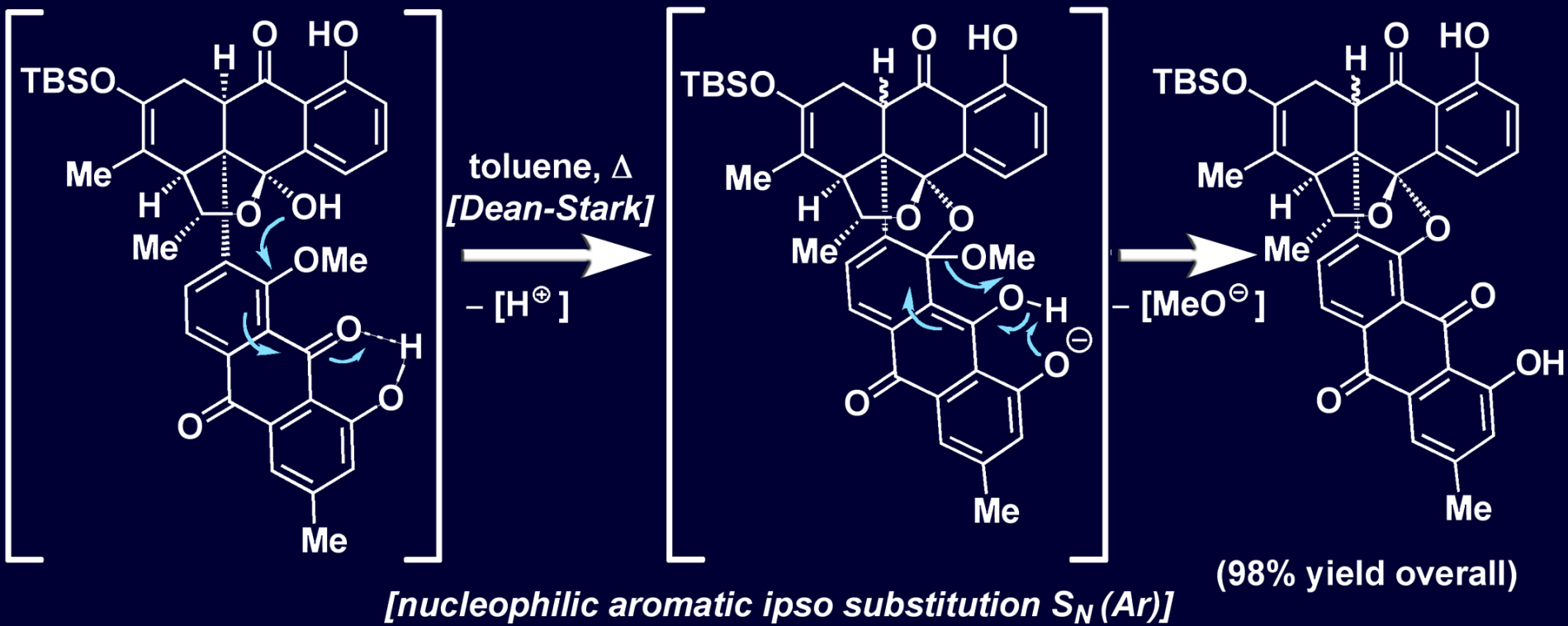
[hemiketal formation]

continue

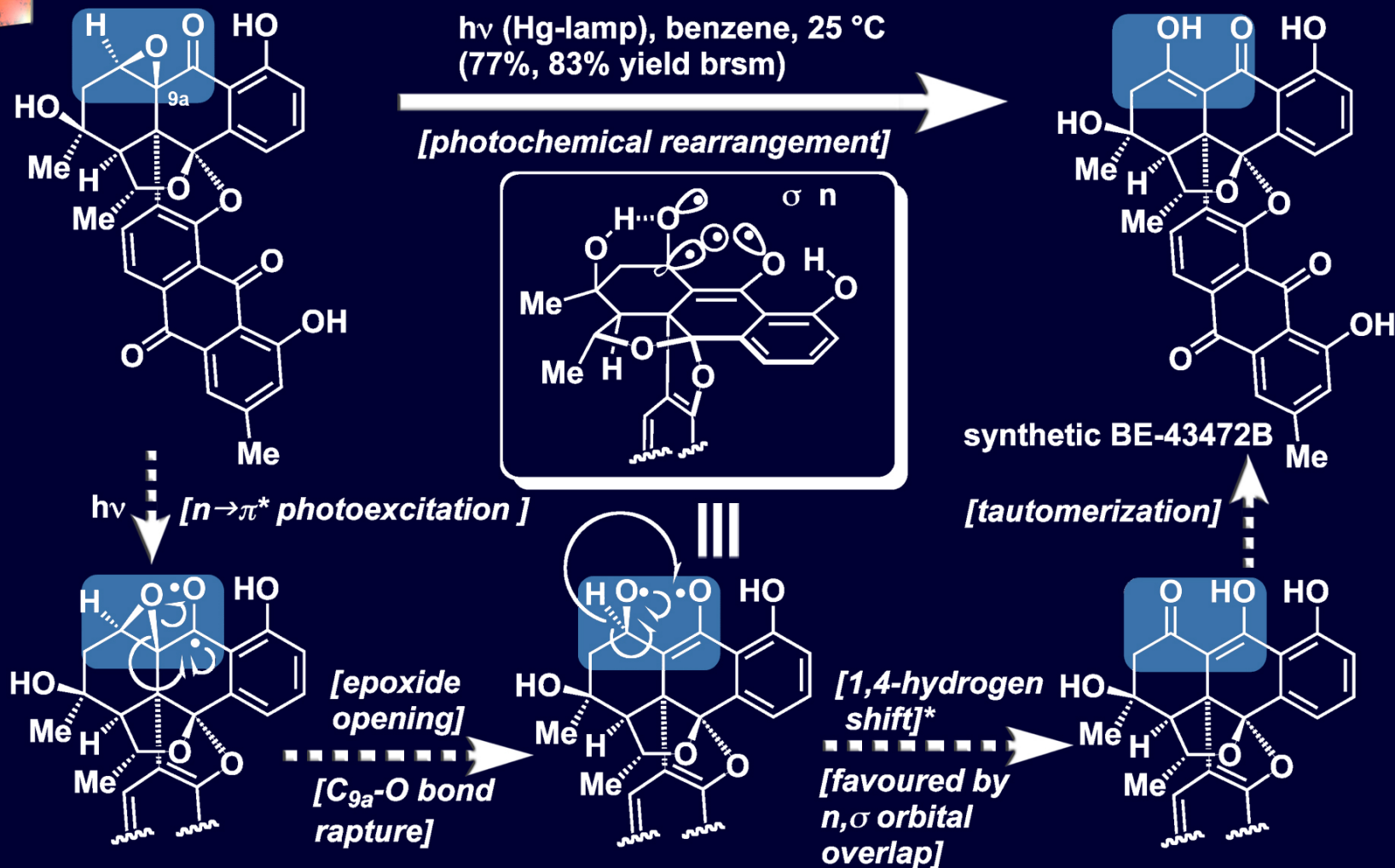


ANTIBIOTIC BE-43472B 6. CASCADE II [2009]

continue



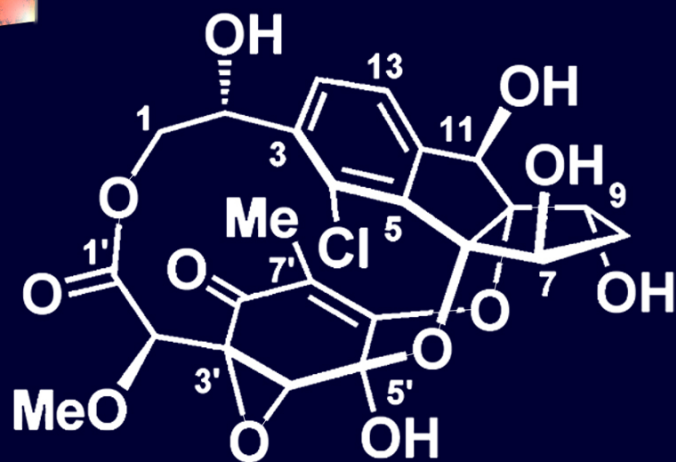
ANTIBIOTIC BE-43472B 9. FINAL STEP [2009]



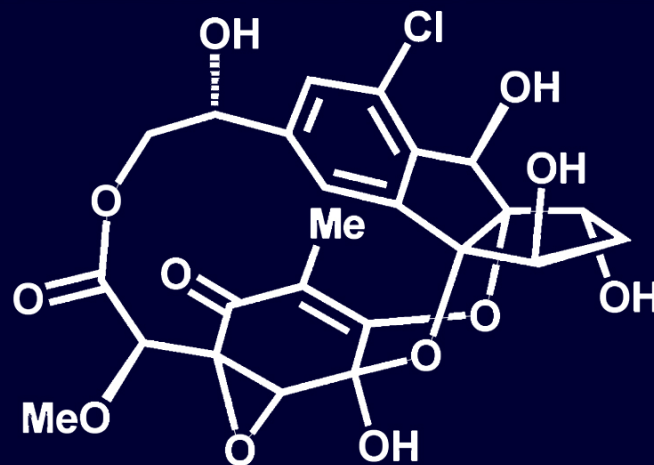
* 1,4-hydrogen shift observed by laser flash photolysis methods: a) H. Kim, T. G. Kim, J. Hahn, D.-J. Jang, D. J. Chang, B. S. Park, *J. Phys. Chem. A* 2001, 105, 3555.



MOLECULAR STRUCTURES OF SPOROLIDES A AND B [2005]

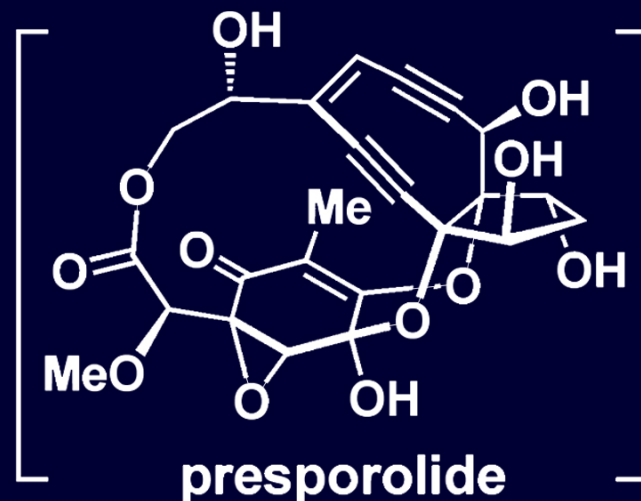


sporolide A



sporolide B

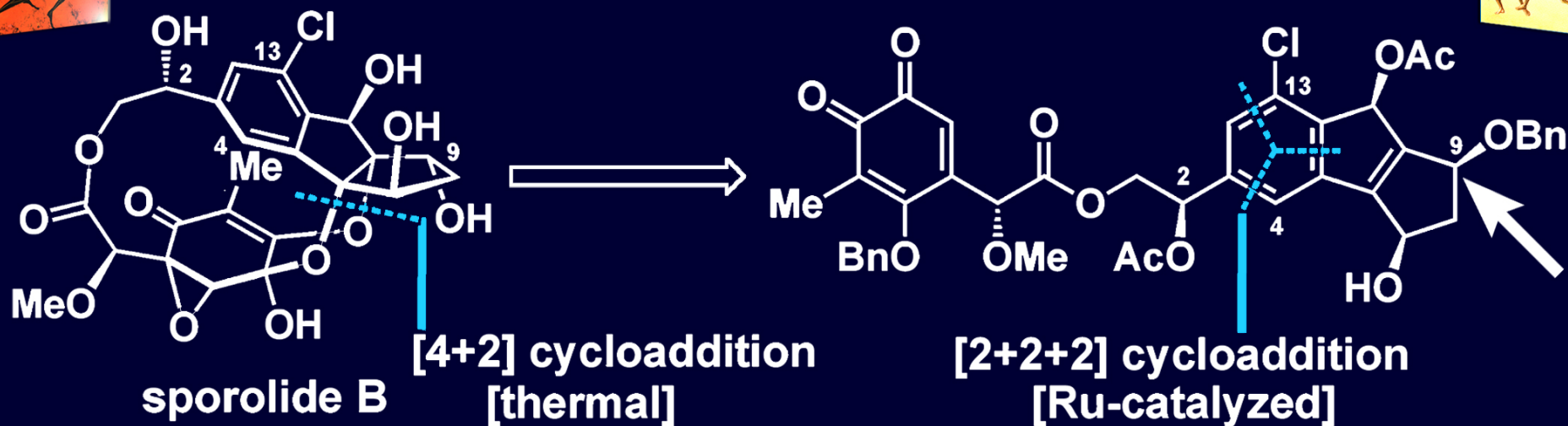
- Isolated from the marine actinomycete *Salinospora tropica* [Fenical and coworkers, *Org. Lett.* 2005, 7, 2731.]
- Proposed metabolite of an, as yet unidentified, enediyne natural product [presporolide, *Proc. Natl. Acad. Sci.* 2007, 104, 10376.]
- Novel molecular architecture
- Unknown biological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



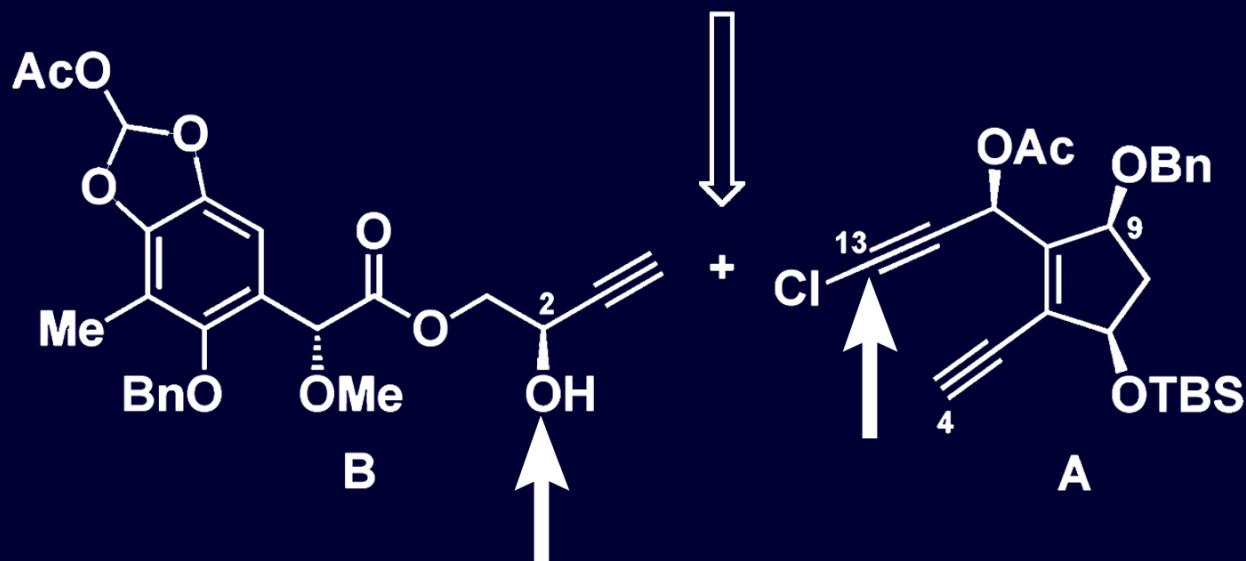
presporolide



SPOROLIDE B 1. RETROSYNTHETIC ANALYSIS [2009]

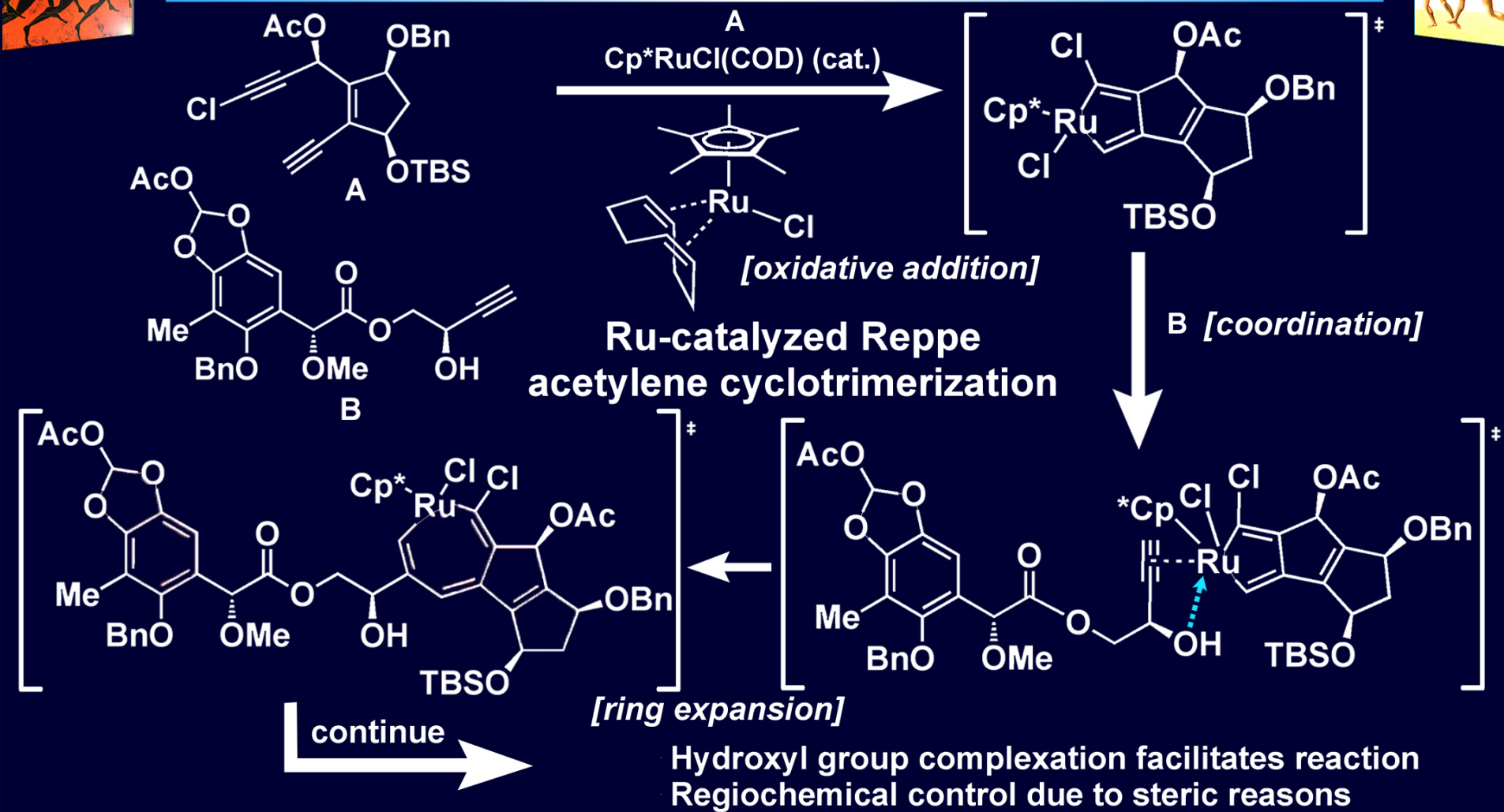


- NOTE
- C-9 inversion to avoid steric congestion
- C-13 regiochemistry
- Free C-2 OH to facilitate [2+2+2] cycloaddition





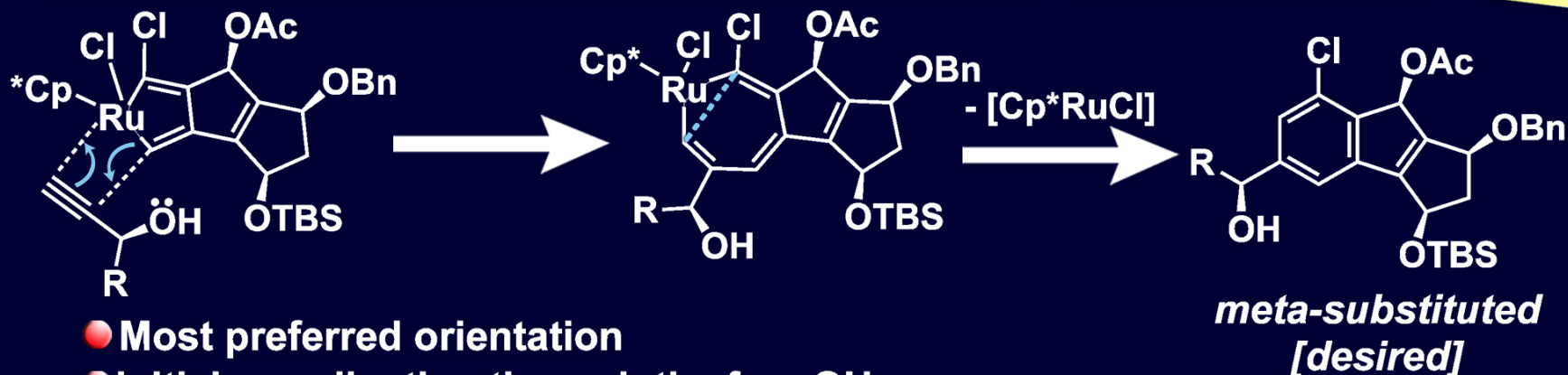
SPOROLIDE B 5. [2+2+2] CYCLOADDITION [2009]



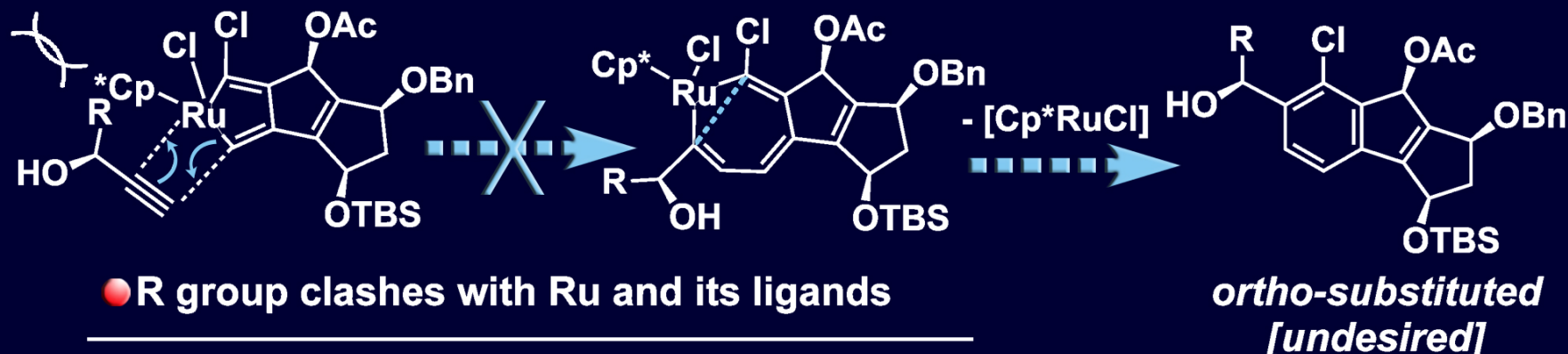
- a) Y. Yamamoto, R. Ogawa, K. Itoh, *Chem. Commun.* 2000, 549;
b) Y. Yamamoto, T. Arakawa, R. Ogawa, K. Itoh, *J. Am. Chem. Soc.* 2003, 125, 12143.



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



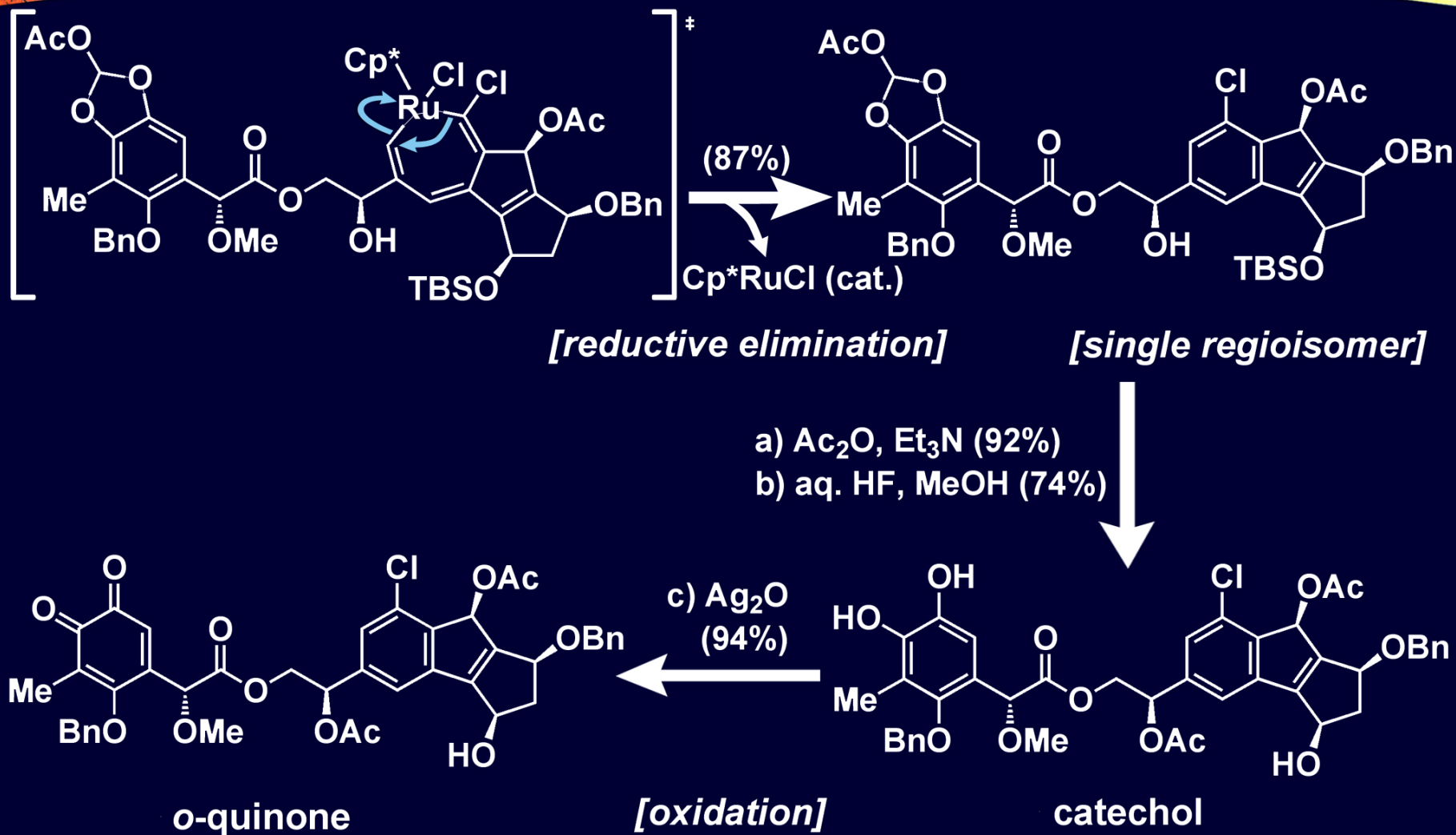
- Most preferred orientation
- Initial coordination through the free OH group may explain fast reaction time (0.5 h)

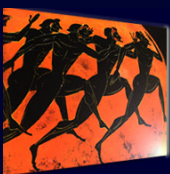


- R group clashes with Ru and its ligands
- The other two orientations on the side of the Cl suffer from steric congestion with either Ru moiety or Cl residue

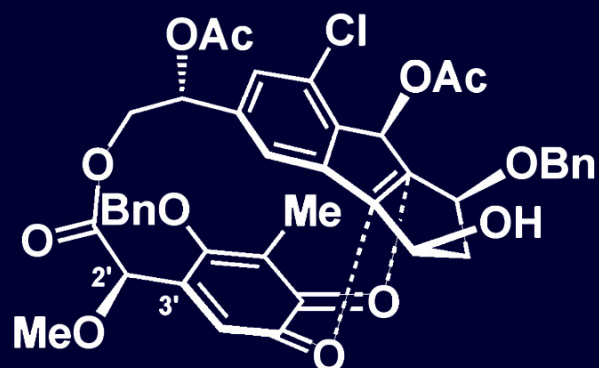


SPOROLIDE B 6. [2+2+2] CYCLOADDITION [2009]



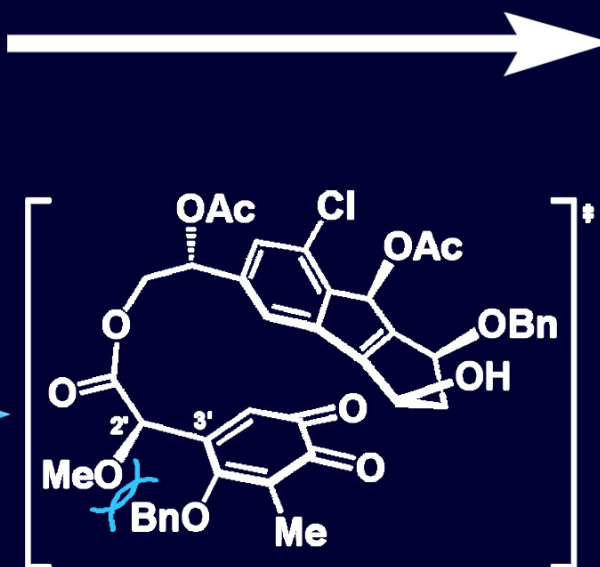
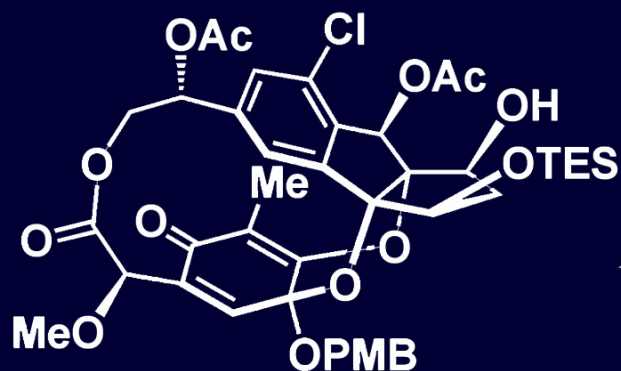


SPOROLIDE B 7. [4+2] CYCLOADDITION [2009]

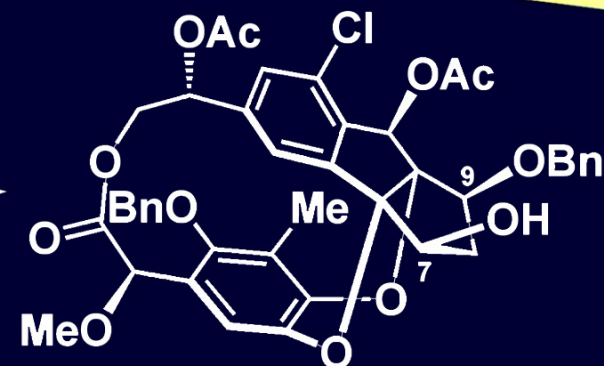


pre-organized o-quinone

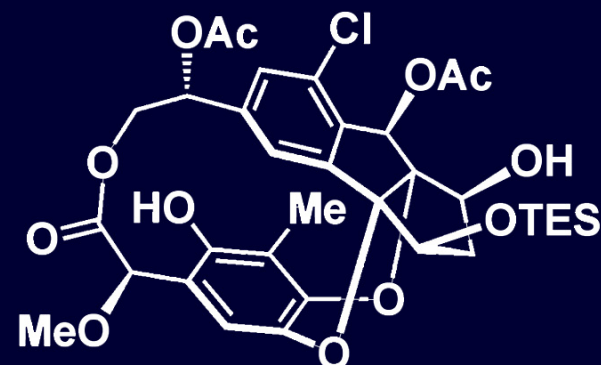
1,3-allylic strain →



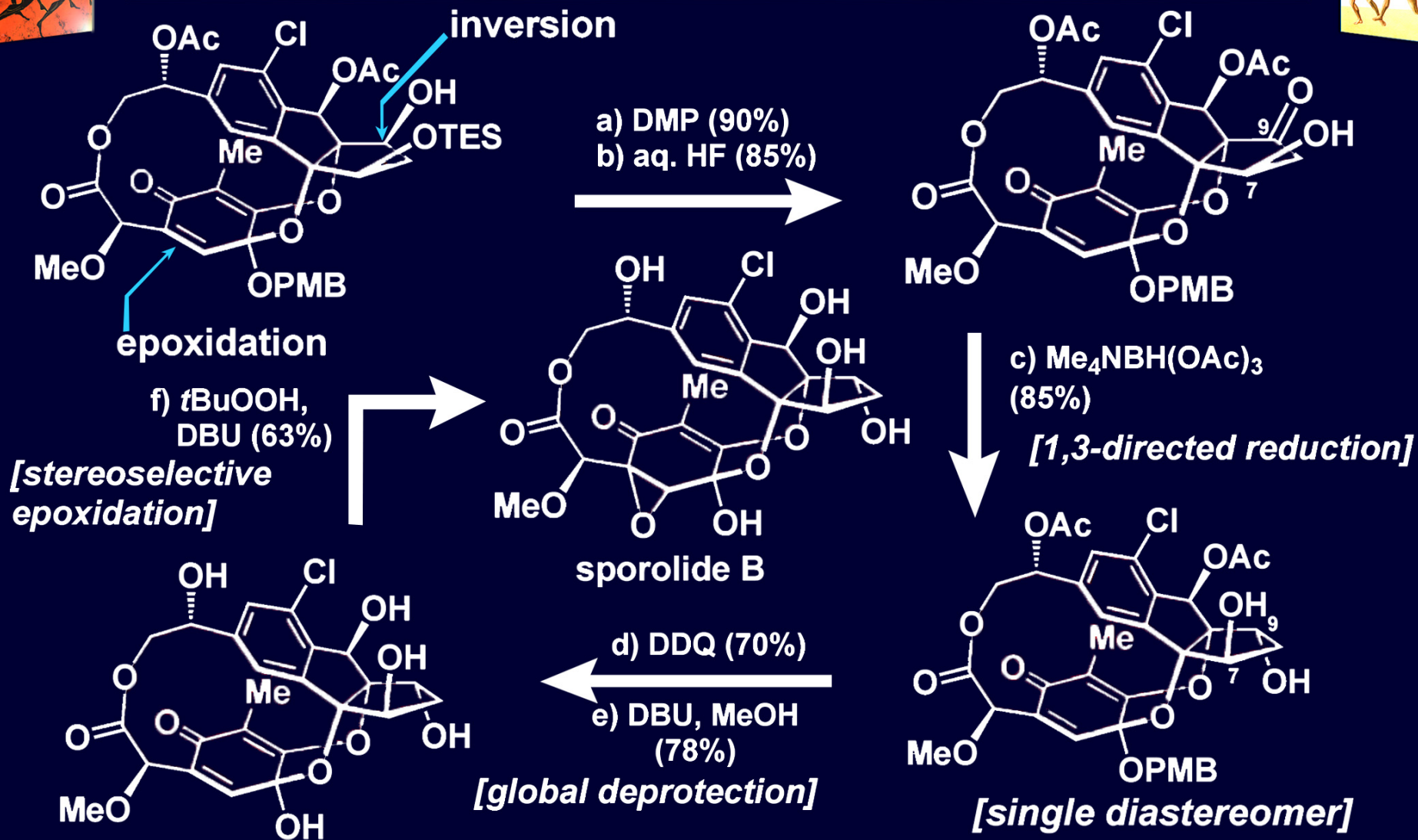
PhI(OCOCF₃)₂,
PMBOH (75%)

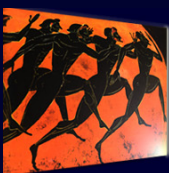


1. TESOTf (95%)
2. H₂, Pd(OH)₂ (92%)
[debenzylation]



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

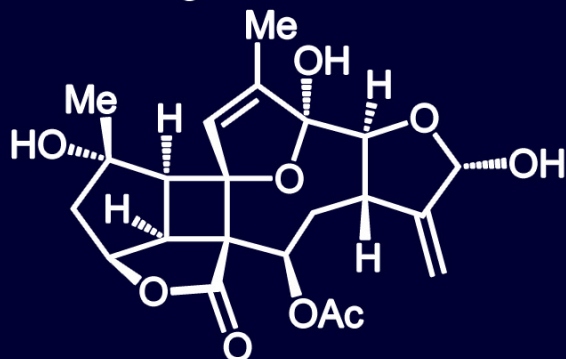




Bielschowskysin. Structure and Possible Construction (2011)



- bielschowskysin: a marine antimalarial and antitumor agent

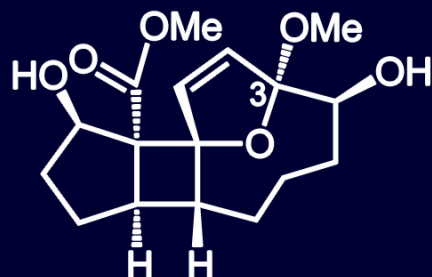


- Isolated from *Pseudopterogorgia kallos*
- $IC_{50} = 10 \mu\text{g/mL}$ against *Plasmodium falciparum*
- $GI_{50} < 10 \text{ nM}$ against EKVX nonsmall lung cancer cell
- $GI_{50} = 510 \text{ nM}$ against CAKI-1 renal cancer cell

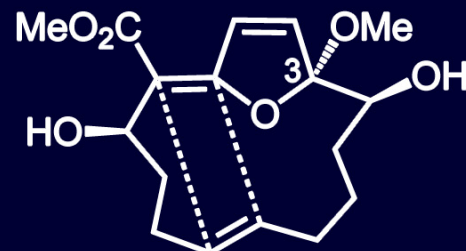
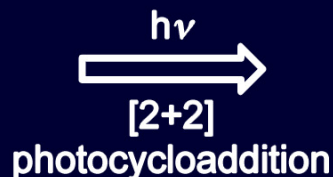
- carbocyclic core structure



- tricyclo[9.3.0.0]tetradecane ring system



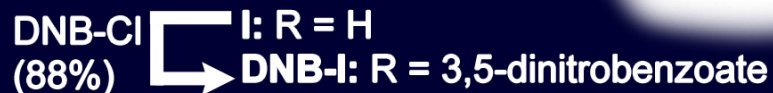
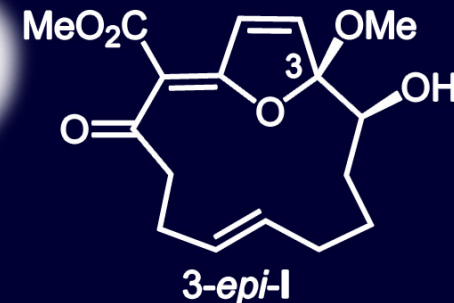
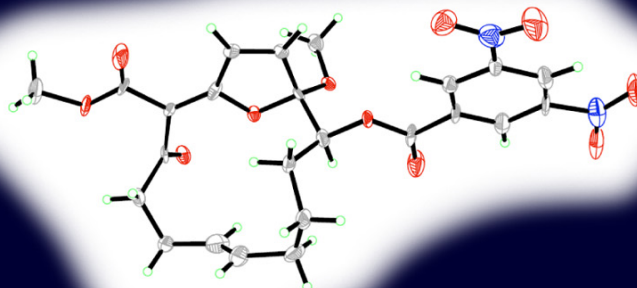
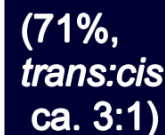
- functionalized tricyclo[9.3.0.0]tetradecane ring system



- postulated macrocyclic precursor

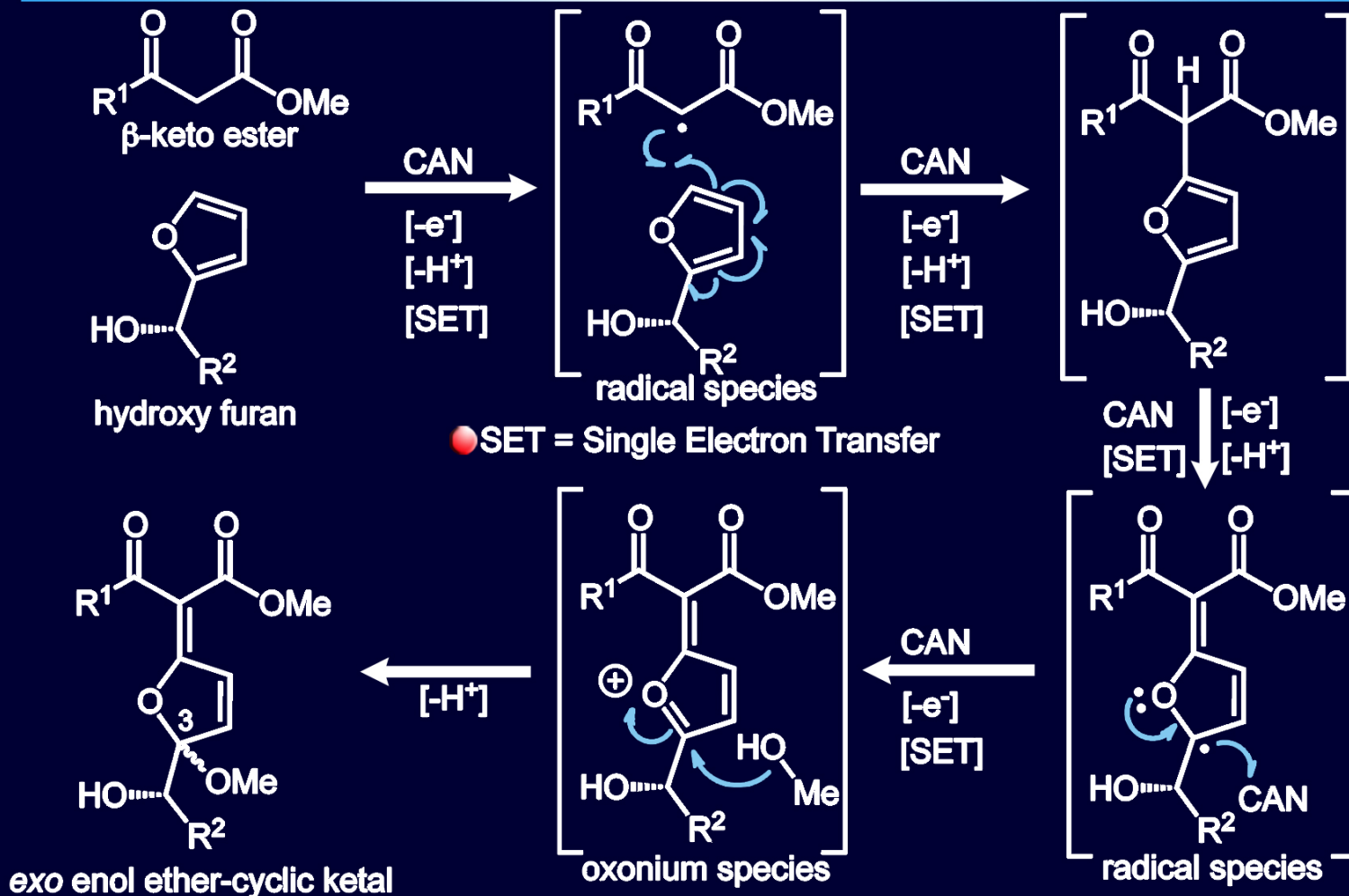


(90%, *trans:cis* ca. 15:1)





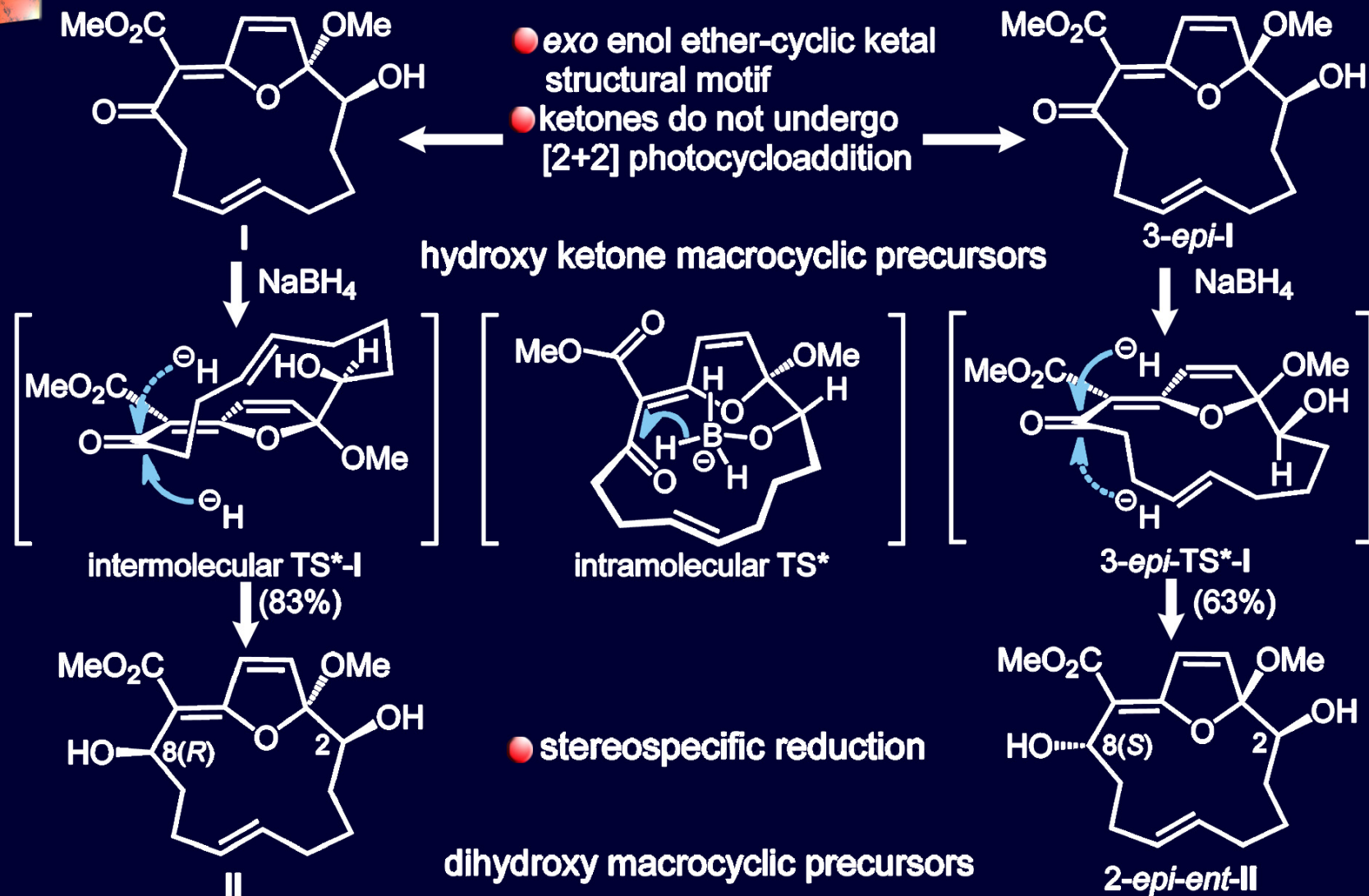
Mechanism of Oxidative Coupling of Furans with β -Keto Esters



Inspiration: a) L. M. Weinstock, E. Corley, N. L. Abramson, A. O. King, S. Karady, *Heterocycles* **1988**, 27, 2627.
 b) J-M. Simone, F. Loiseau, D. Carcache, P. Bobal, J. Jeanneret-Gris, R. Neier, *Monatshefte für Chemie* **2007**, 138, 131.
 For related work, see: c) M. Jessing, P. S. Baran, *Heterocycles* **2011**, 82, 1739–1745; d) P. S. Baran, N. B. Ambhaikar, C. A. Guerrero, B. D. Hafensteiner, D. W. Lin, J. M. Richter, *ARKIVOC* **2006**, 310–325 [Oxidative C–C Bond Formation in Heterocyclic Chemistry (review)].

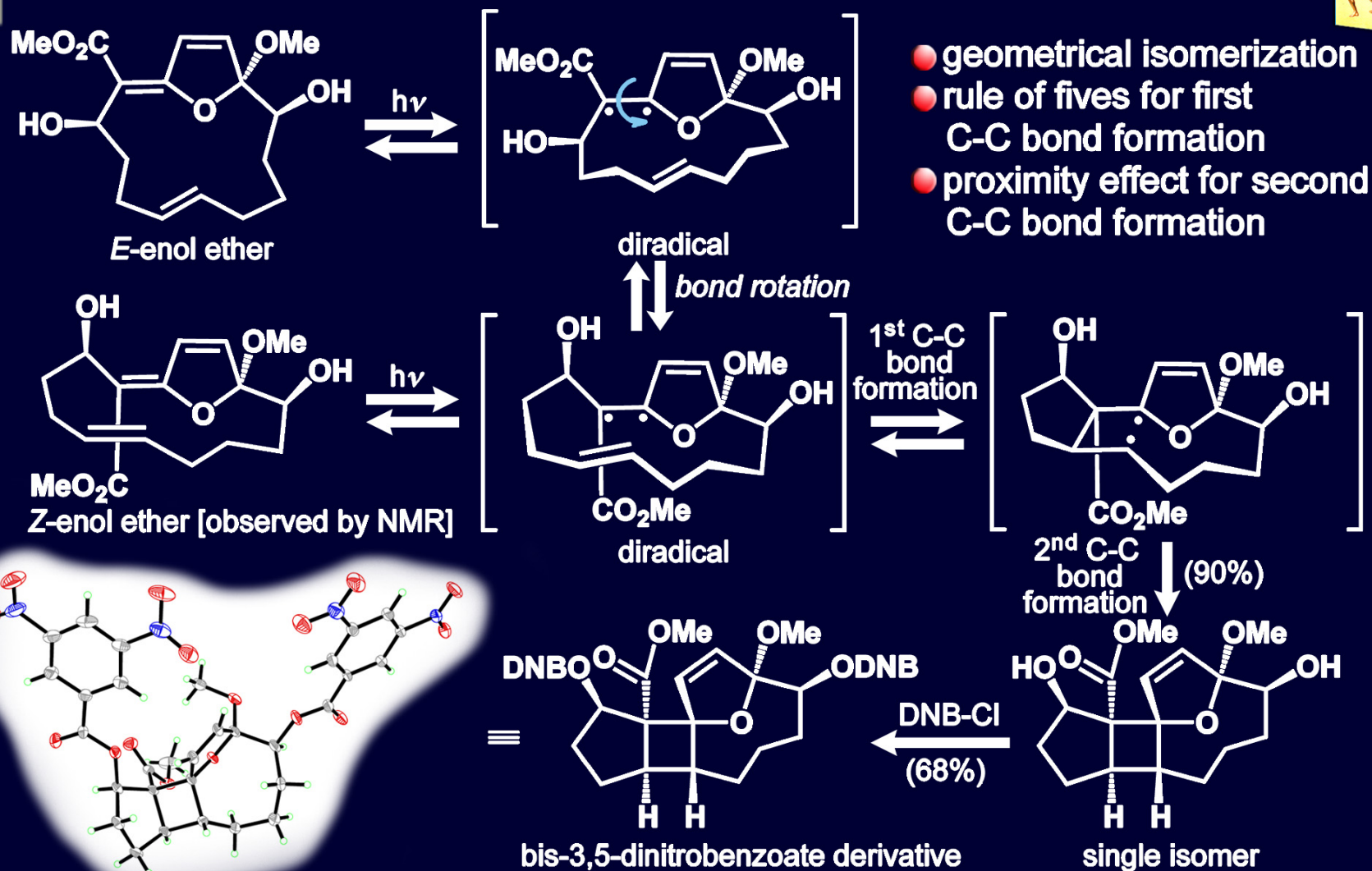


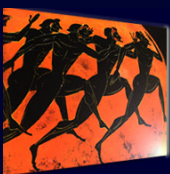
Construction of [2+2] Photocycloaddition Precursors 2.



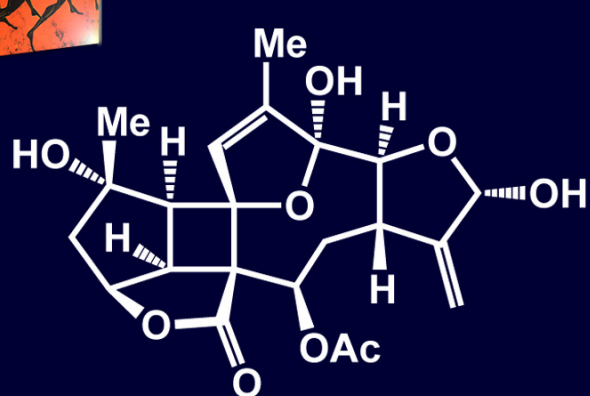


Transannular Cascade [2+2] Photocycloaddition



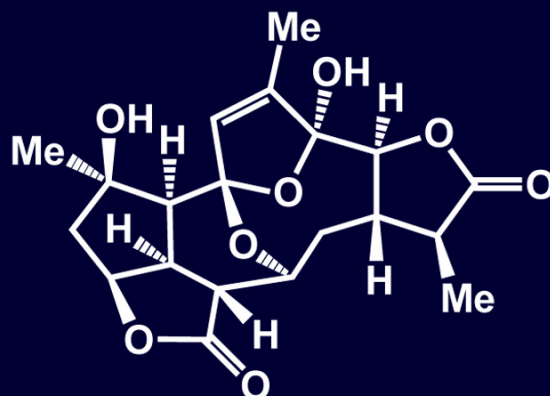
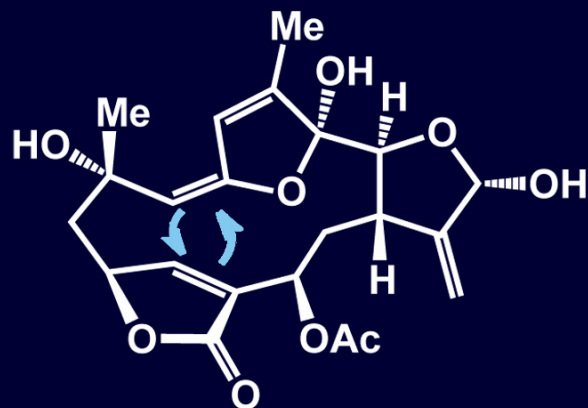


Biosynthetic Hypotheses of Marine Natural Products



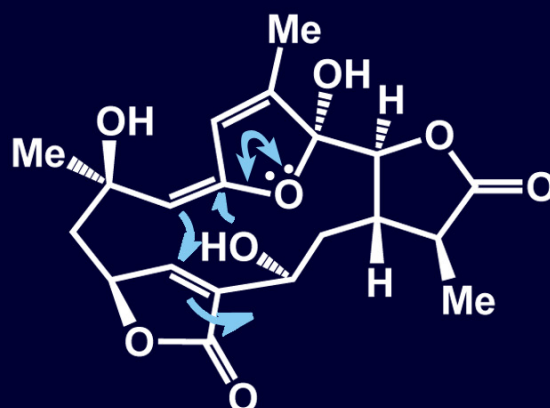
● bielschowskysin
[cytotoxic, antimalarial]

↓ [2+2] cycloaddition



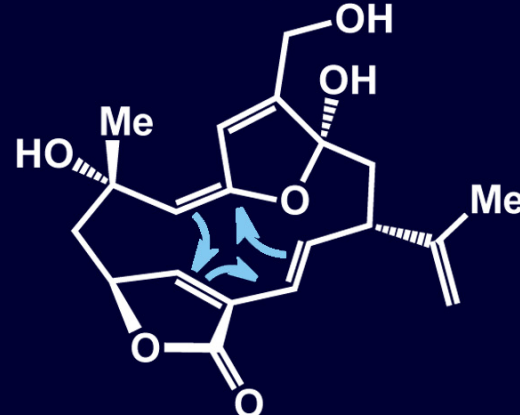
● verrillin
[not enough material
for biological screening]

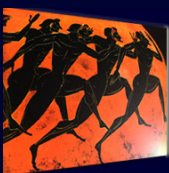
↓ conjugate addition/
ketalization



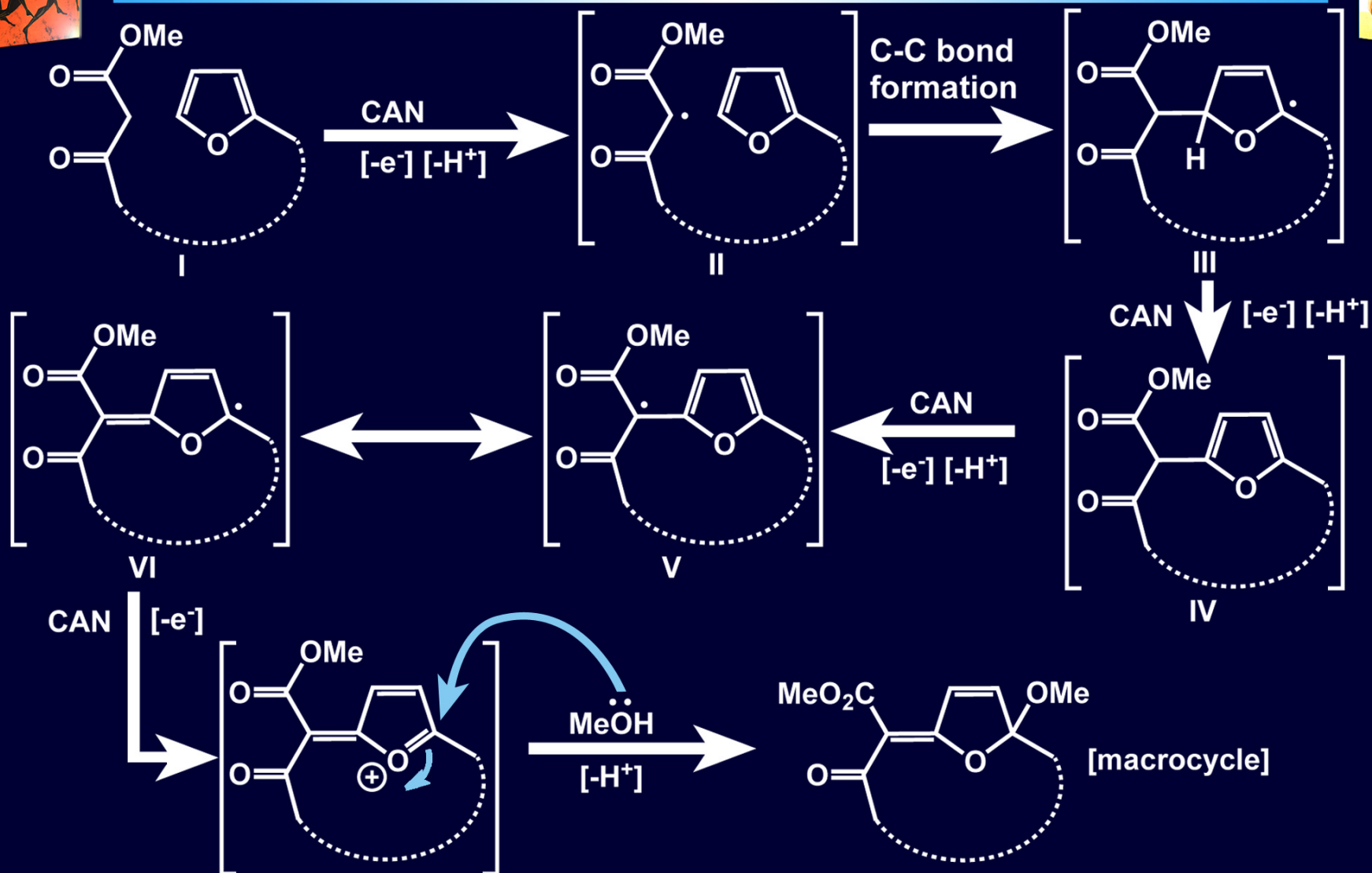
● plumarellide

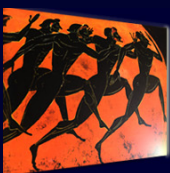
↓ Diels-Alder



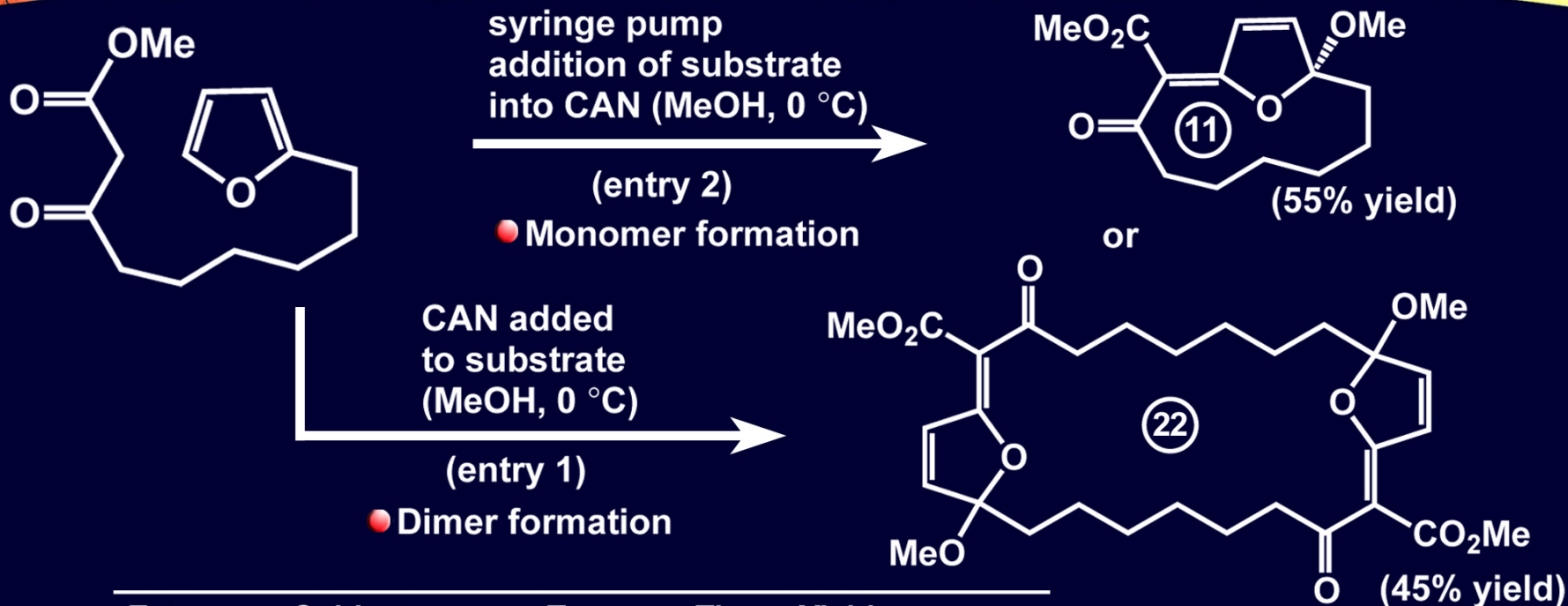


Mechanistic Rationale for the Oxidative Macrocyclization





Oxidative Macrocyclization of β -Ketoesters to Monomers and Dimers

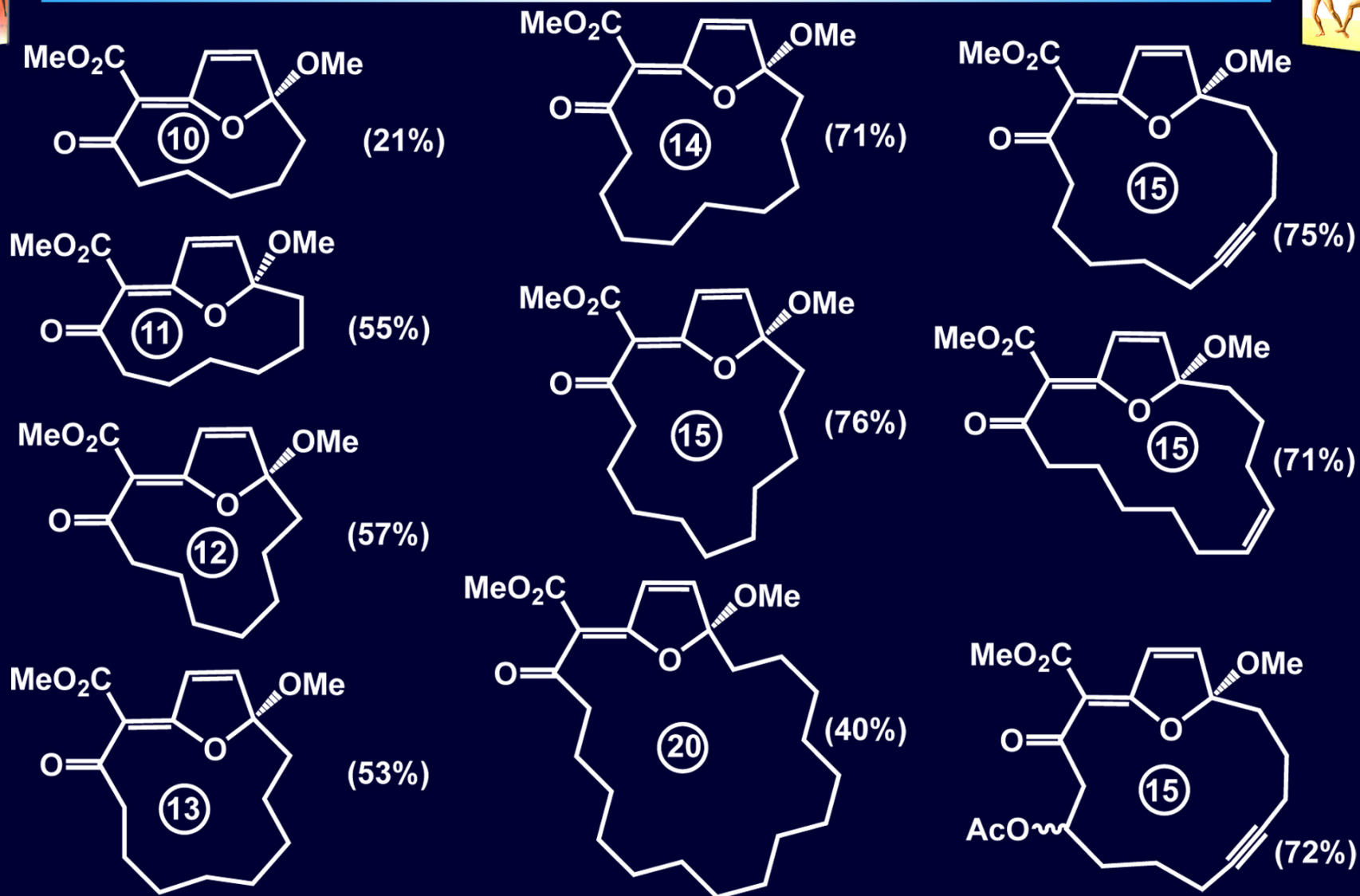


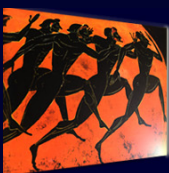
Entry	Oxidant	Temp	Time	Yield
1	CAN	0 °C	15 m	45% (dimer)
2	CAN	0 °C	90 m	55% (monomer)
3	Ce(OTf) ₄	0-25 °C	18 h	--
4	Mn(OAc) ₃	0-60 °C	18 h	--
5	Mn(OAc) ₃ /Cu(OTf) ₂	0-60 °C	18 h	--
6	(Cp ₂ Fe)PF ₆	0-25 °C	18 h	--
7	Co(OAc) ₂	0-60 °C	18 h	--



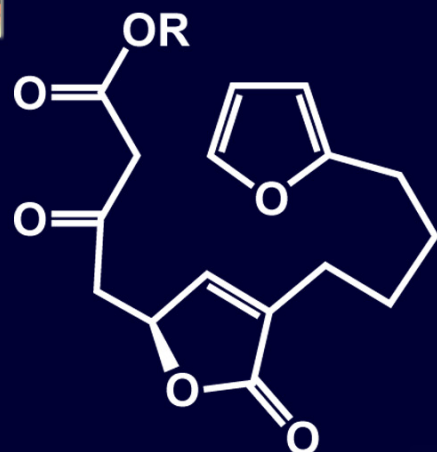


Monomeric *exo-Enol Ether/Cyclic Acetals*



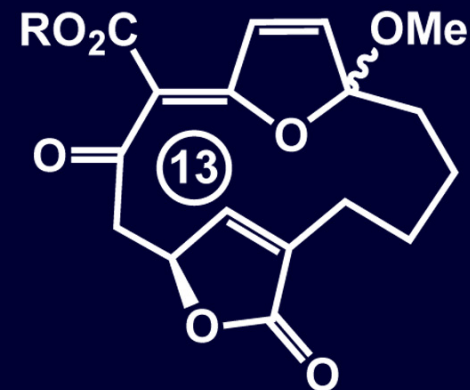


Butenolide 13-Membered Monomeric Macrocycle

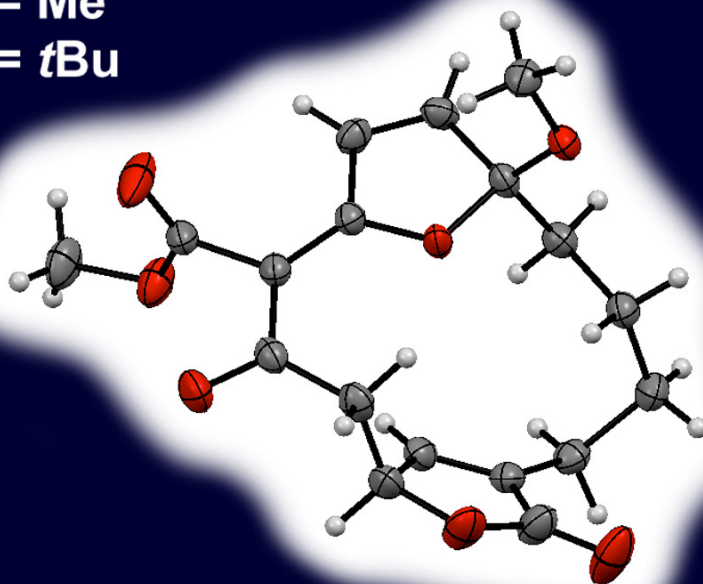


R = Me
R = *t*Bu

[monomer conditions]



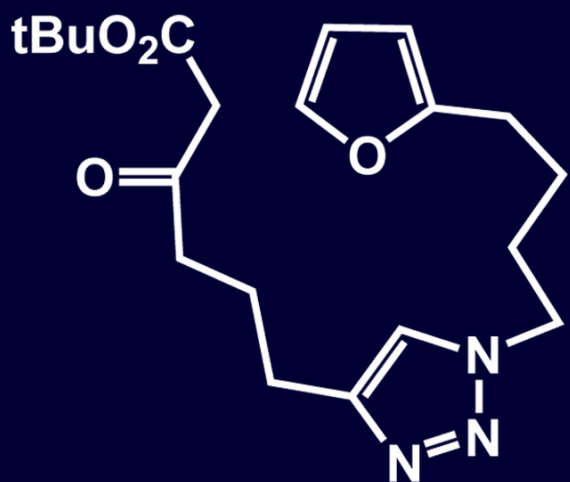
R = Me ($\alpha:\beta = 2:3$, 15% β isolated)
R = *t*Bu ($\alpha:\beta = 1:2$, 40% combined)



R = Me, β -isomer



Triazole 15-Membered Monomeric Macrocycle



syringe pump addition
of substrate into CAN

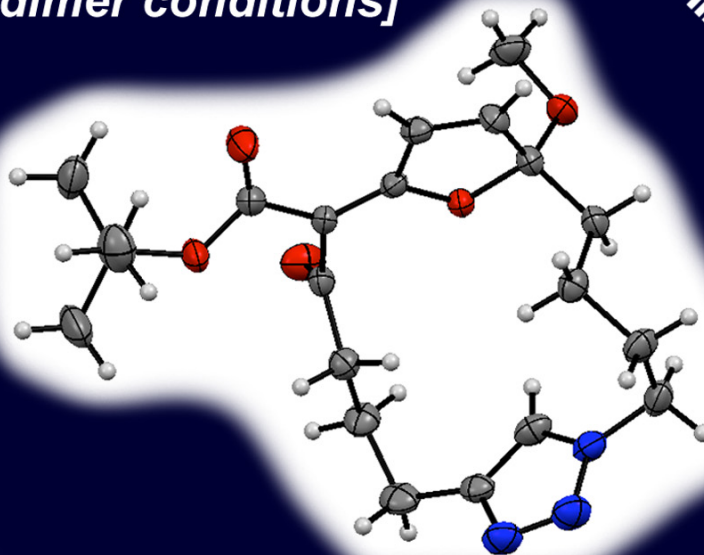
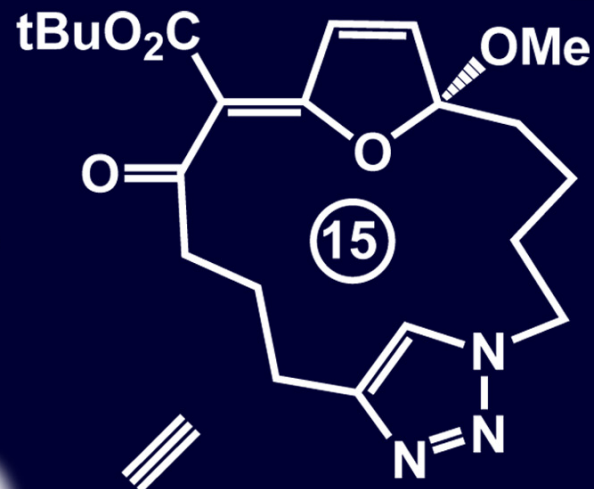
(91%)

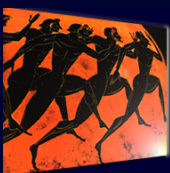
[monomer conditions]
OR

addition of CAN into
substrate in one portion

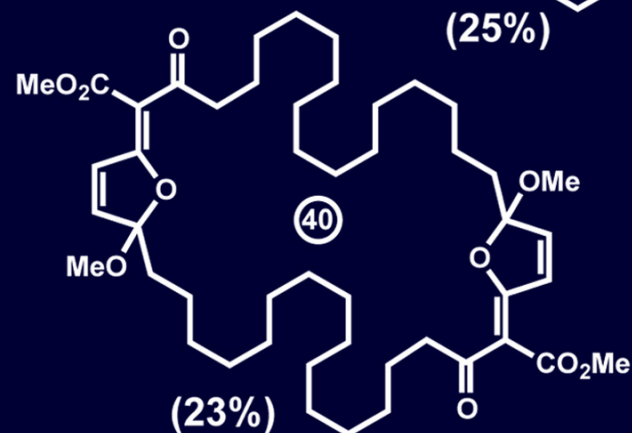
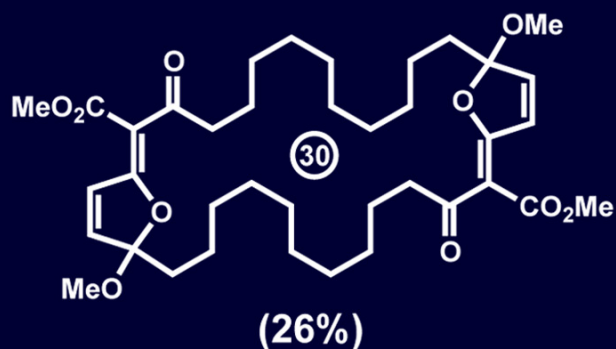
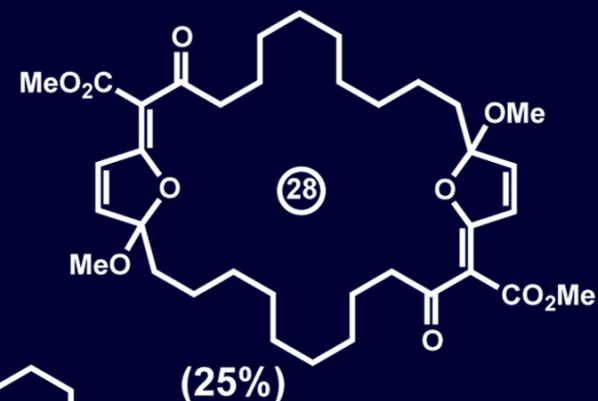
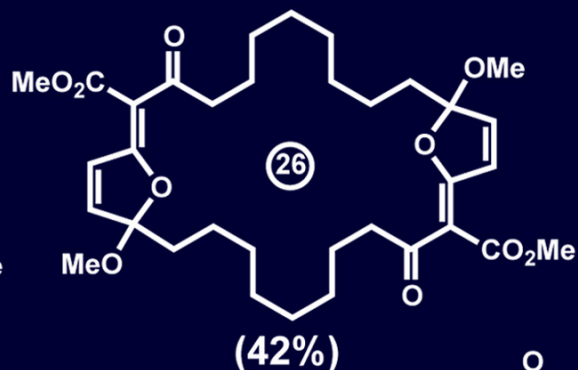
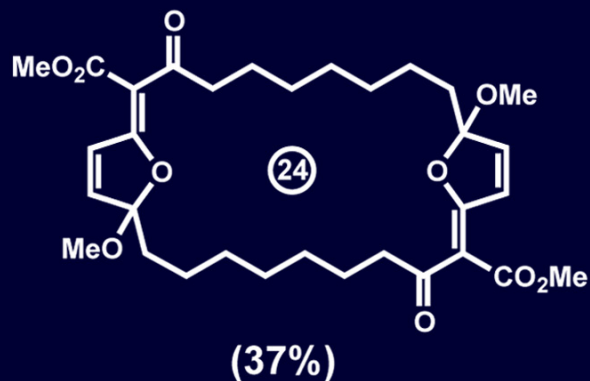
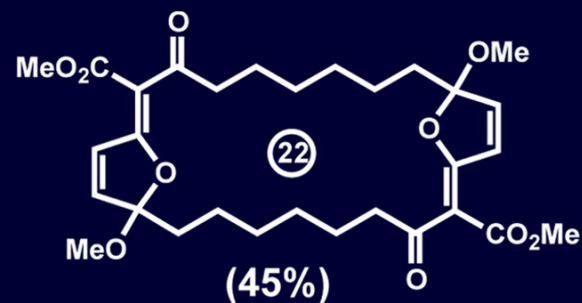
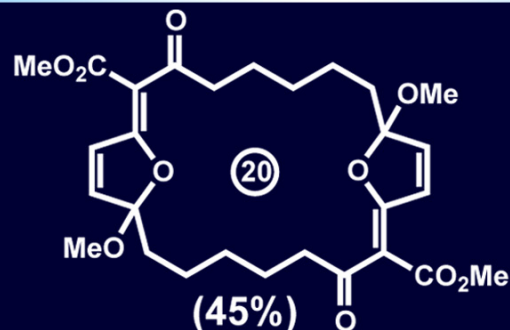
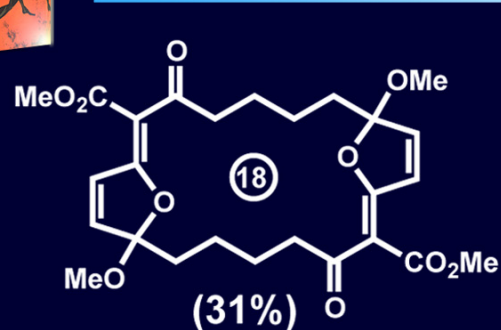
(75%)

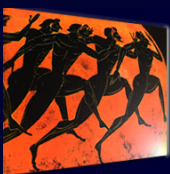
[dimer conditions]



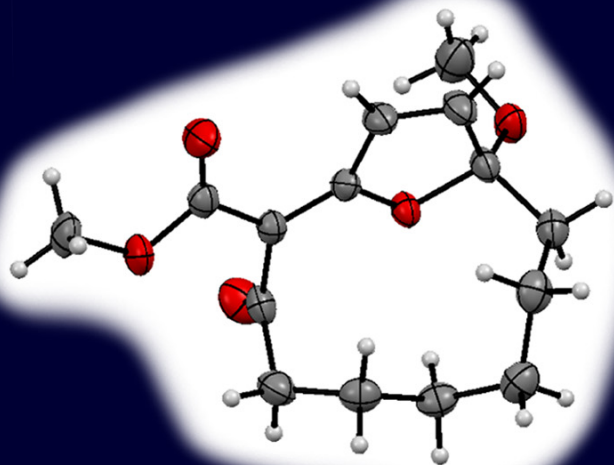
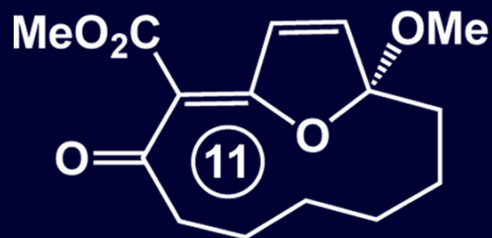


Dimeric Macrocyclic *exo*-Enol Ether/Cyclic Acetals

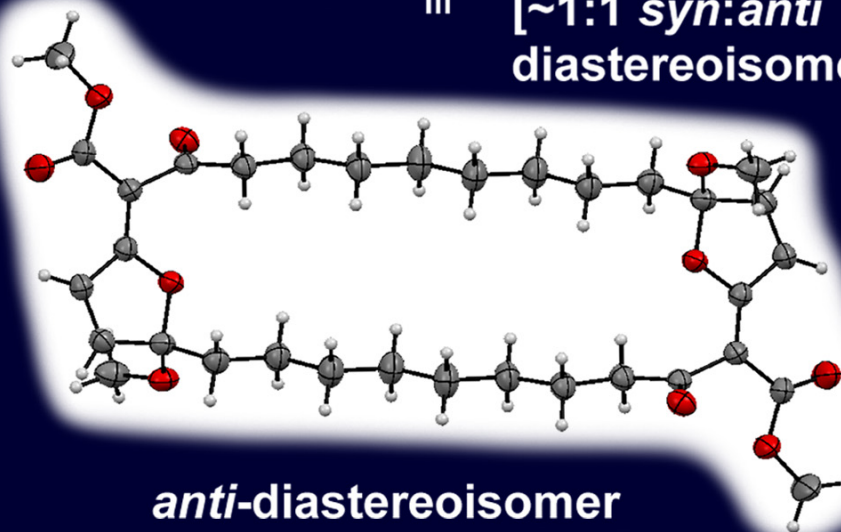




X-Ray Derived ORTEP of 11-Membered Monomer and anti-26-Membered Dimer



[~1:1 *syn:anti*
diastereoisomers]



***anti*-diastereoisomer**



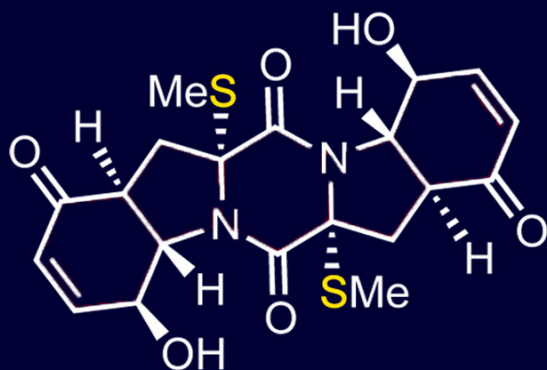
Epicoccin G and Related Natural Products



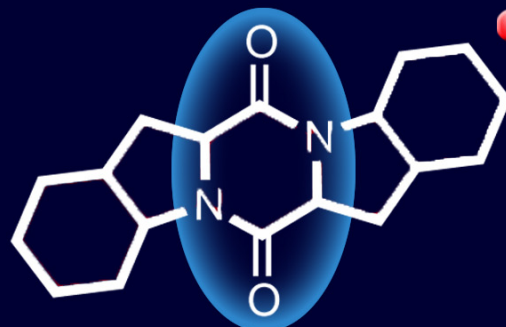
● **Dithiodiketopiperazines**



epicoccin G [anti-HIV]



**exserohilone
[antibacterial, antifungal]**

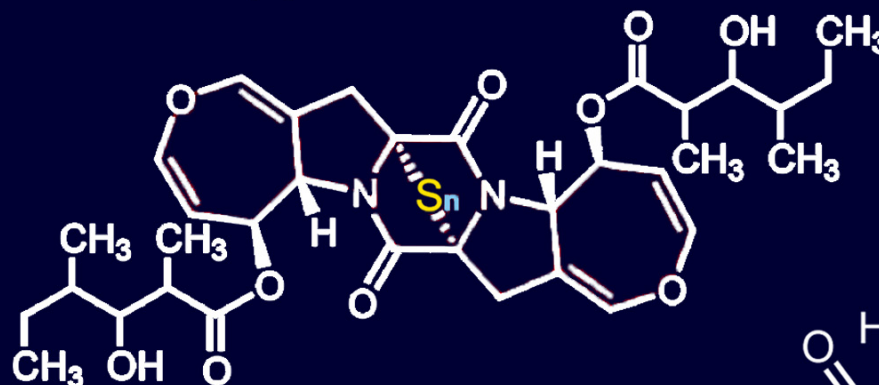


diketopiperazine framework

● **Epidithiodiketopiperazines**



rostratin B [cytotoxic]



SCH 64874: $n = 2$: disulfide: [1.0 $\mu\text{g/mL}$]
SCH 64875: $n = 3$: trisulfide: [1.0 $\mu\text{g/mL}$]
SCH 64877: $n = 4$: tetrasulfide: [1.25 $\mu\text{g/mL}$]

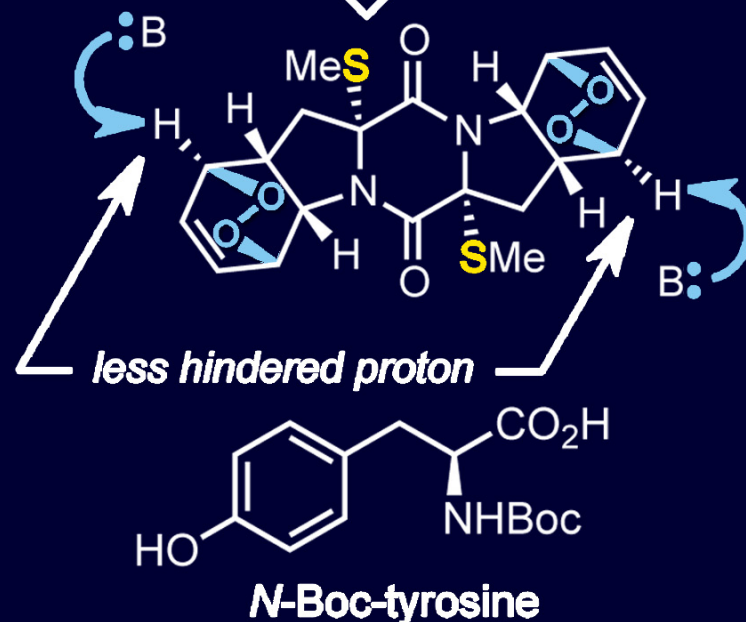
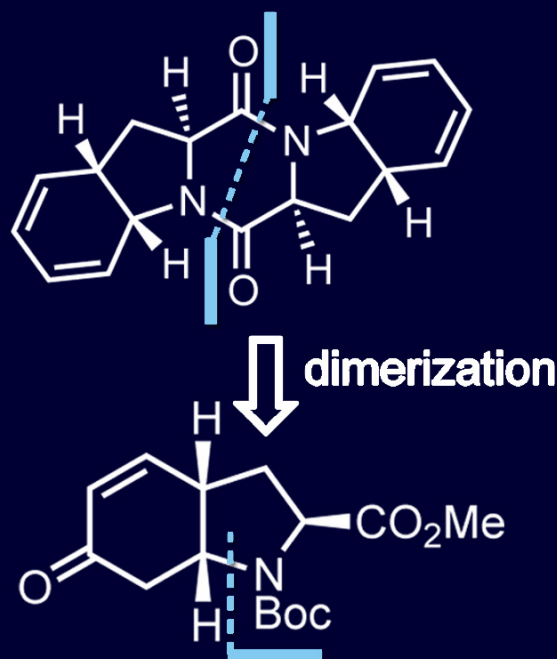
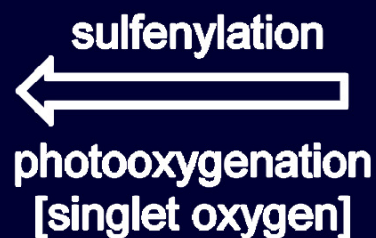
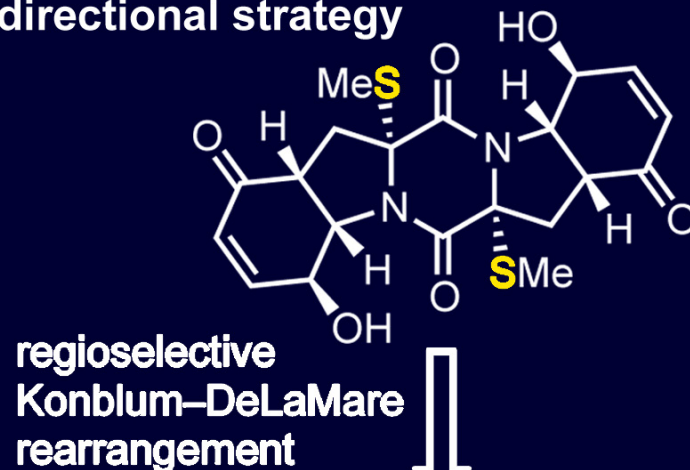
**EGF (epidermal growth factor)
receptor antagonists**



**8,8'-*epi-ent*-rostratin B
[biological activity unknown]**

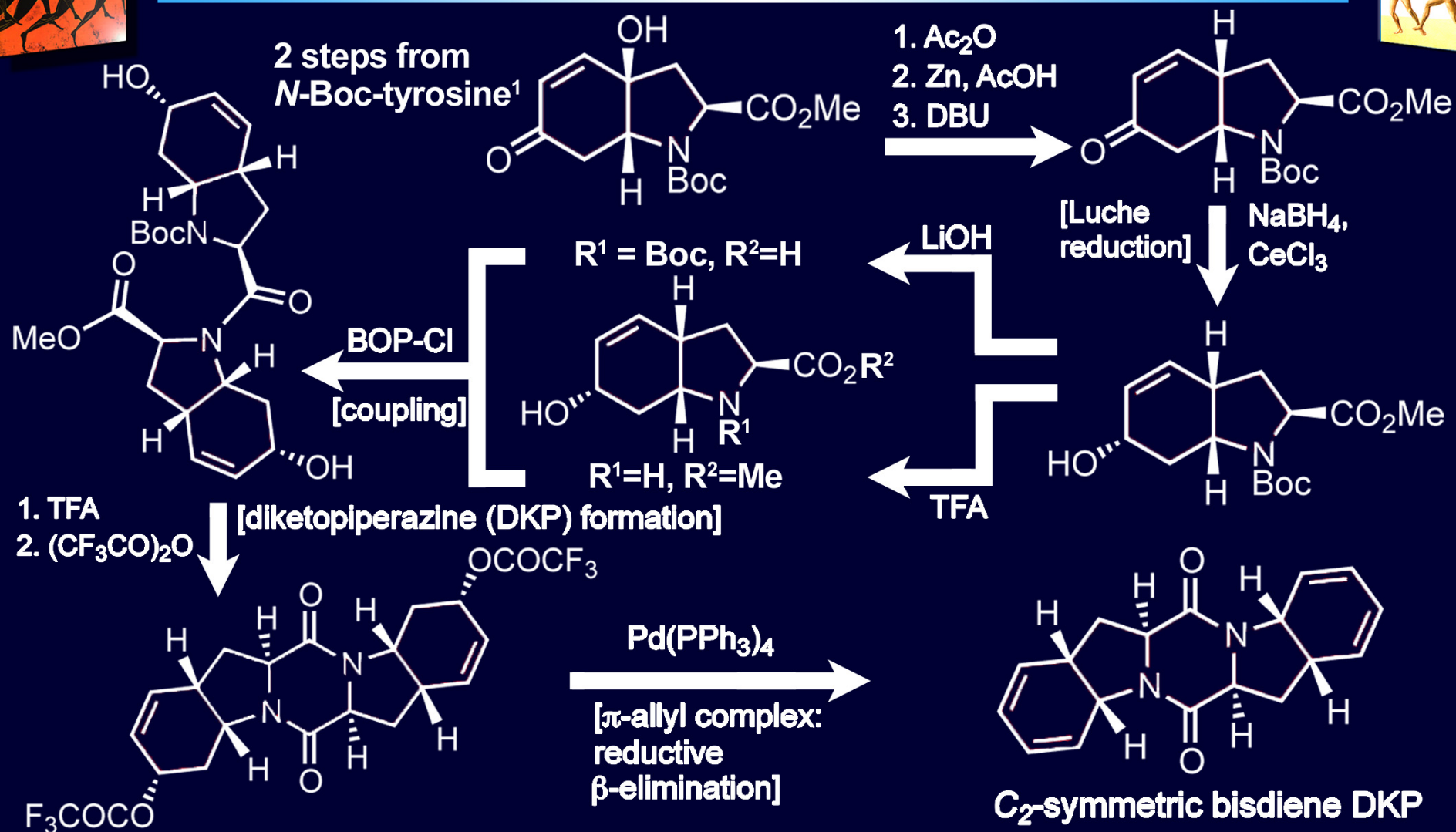
Retrosynthetic Analysis of Epicoccin G

● C₂-symmetry allows two-directional strategy



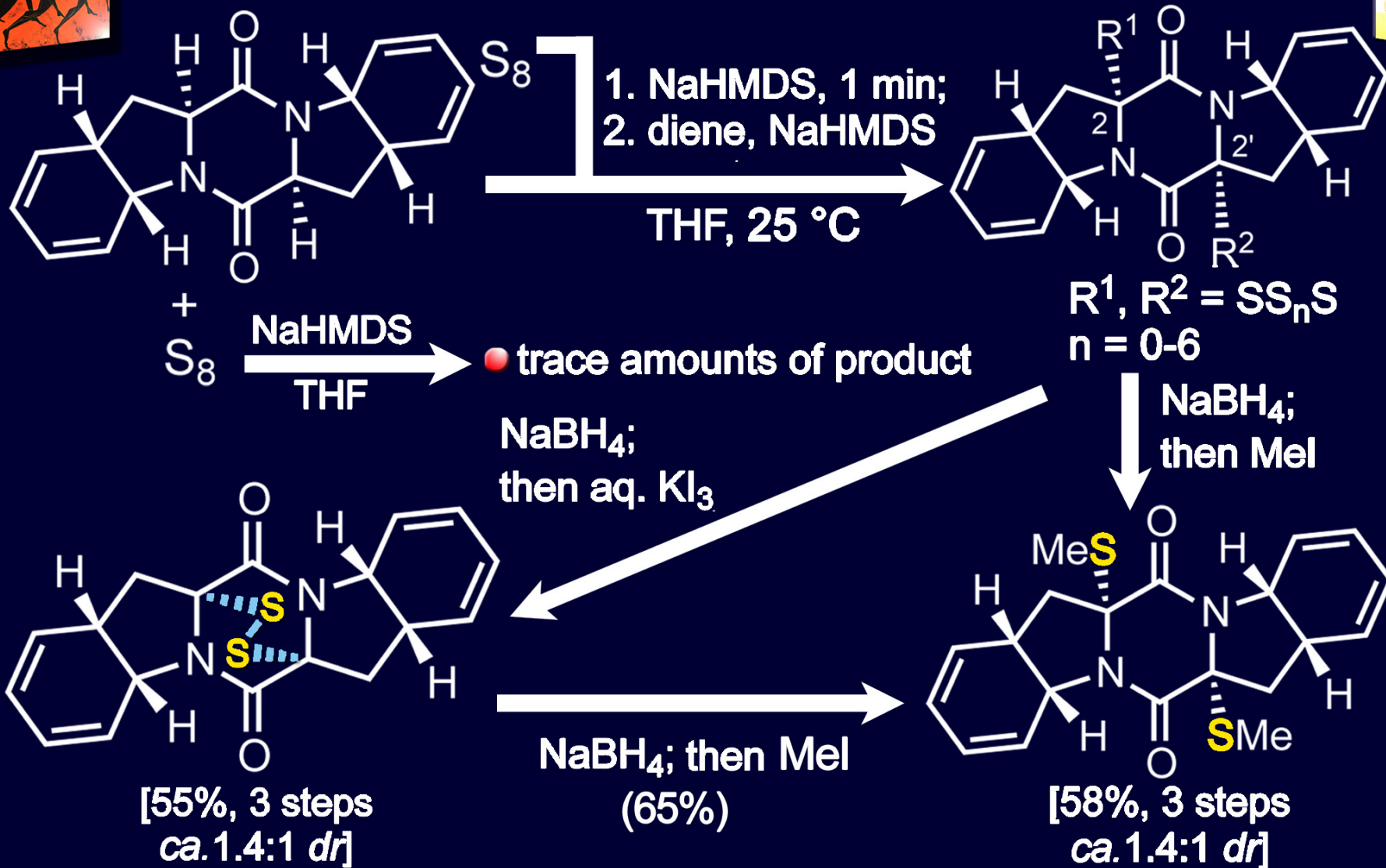


Construction of C_2 -Symmetric Diene Precursor



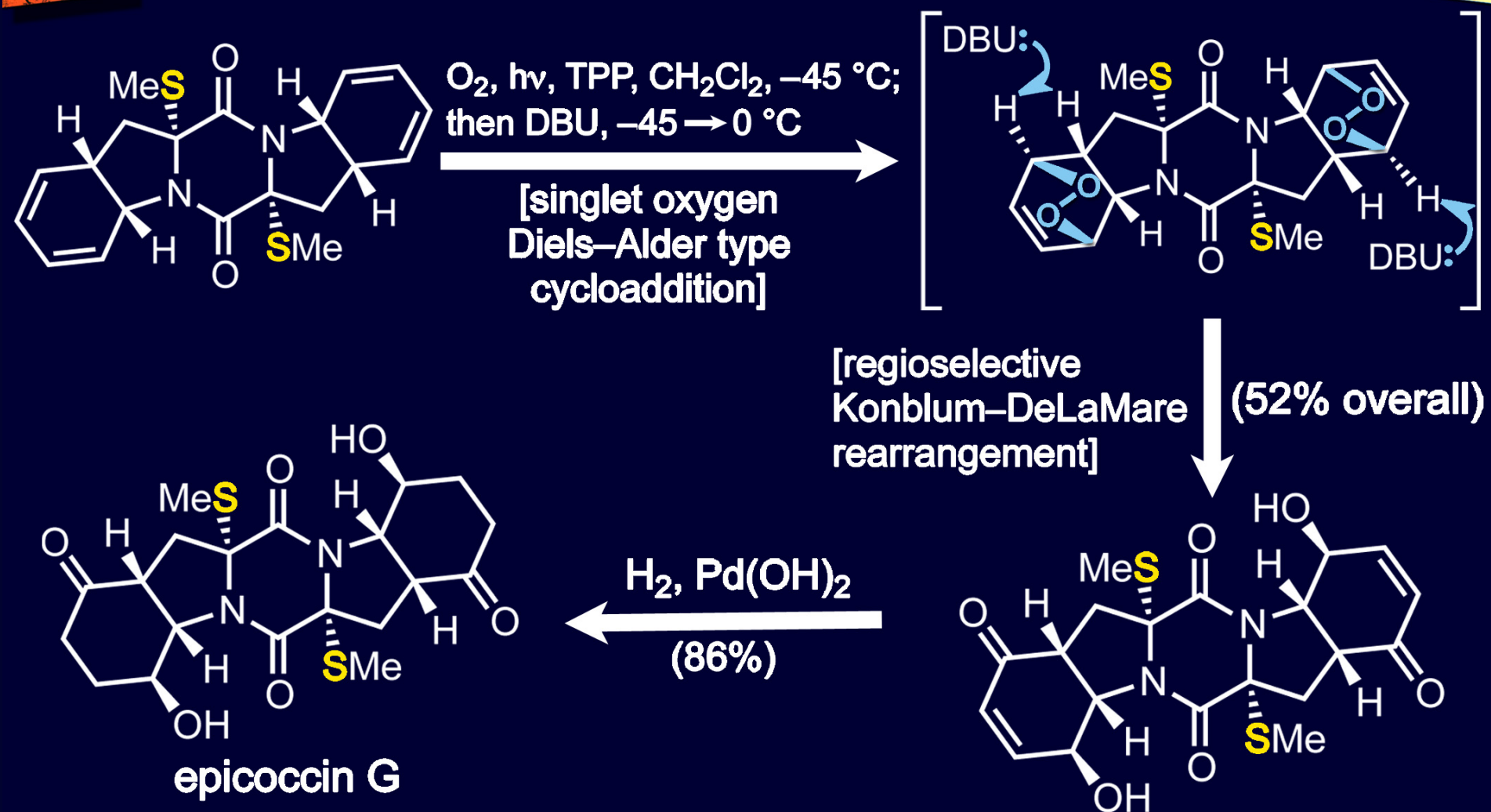
¹Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, 33, 5477

Synthesis of Dithiodiketopiperazines



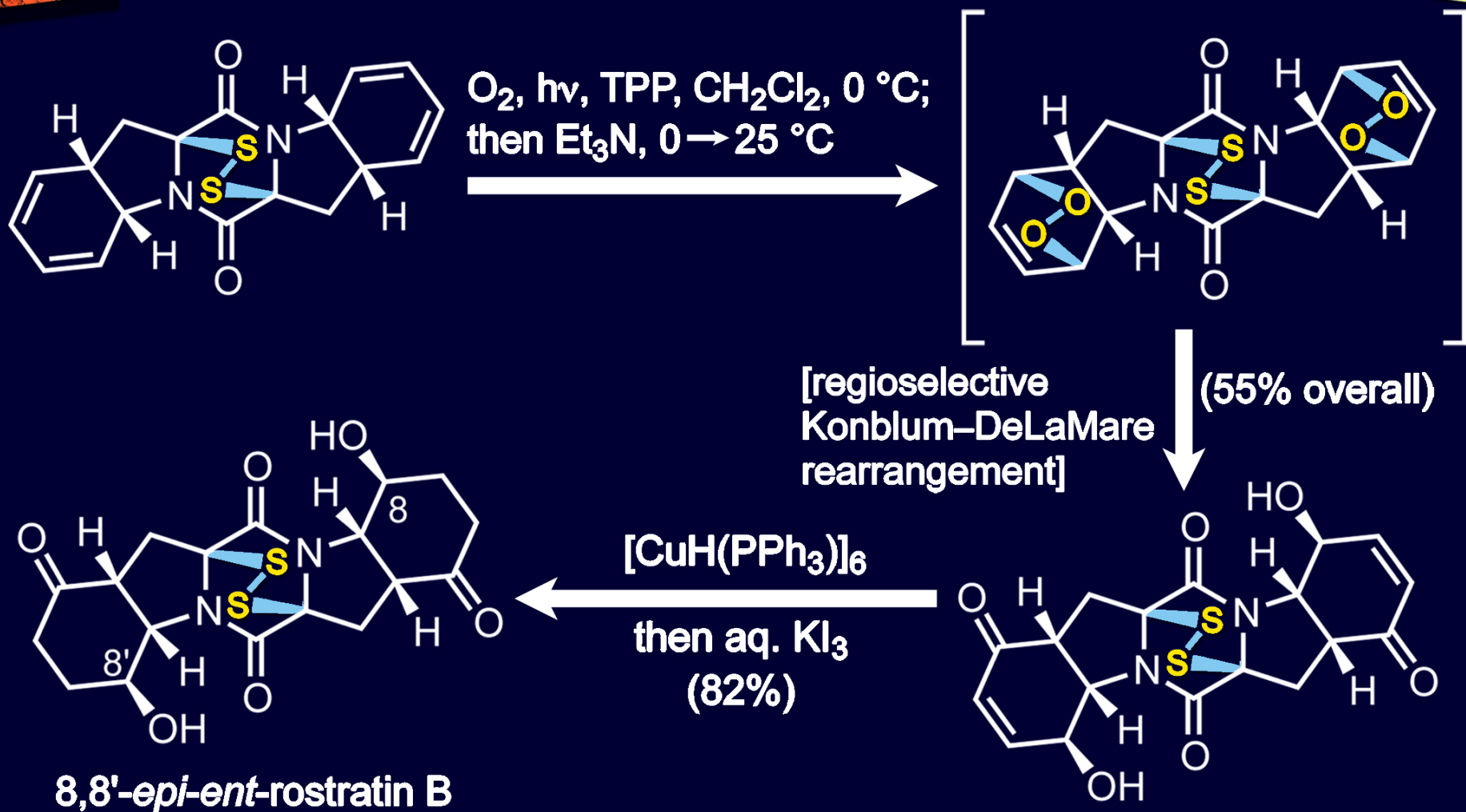


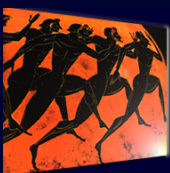
Total Synthesis of Epicoccin G



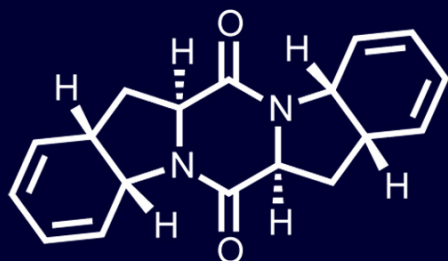


Total Synthesis of 8,8'-*epi-ent-rostratin B*

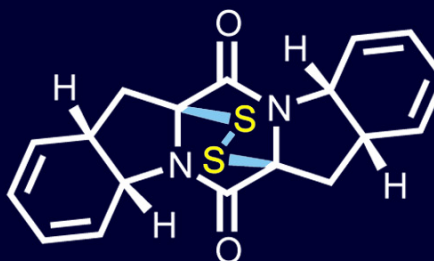




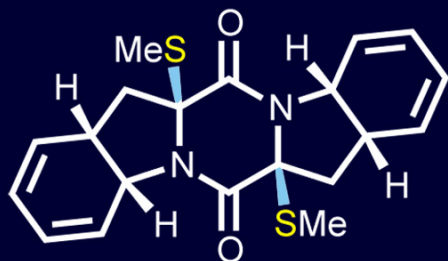
Biological Evaluation of Dithiodiketopiperazines Against Polio Virus and Plasmodium Falciparum



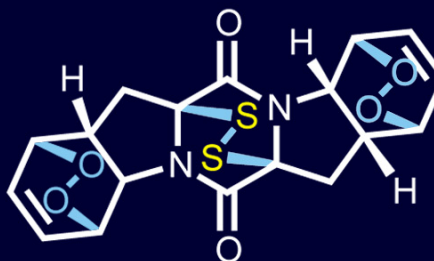
KCN-7 [inactive]



KCN-2,2'-epi-19 [*Polio virus*: $EC_{50} < 28$ nM]
[*P. falciparum*: $IC_{50} = 2.7$ μ M]

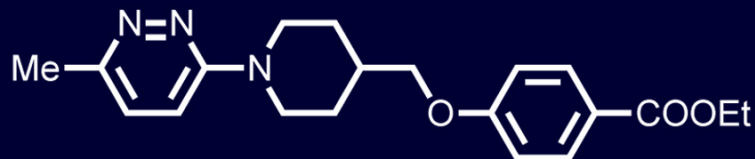


KCN-2,2'-epi-18 [inactive]



KCN-21 [*Polio virus*: $EC_{50} < 23$ nM]
[*P. falciparum*: $IC_{50} = 2.5$ μ M]

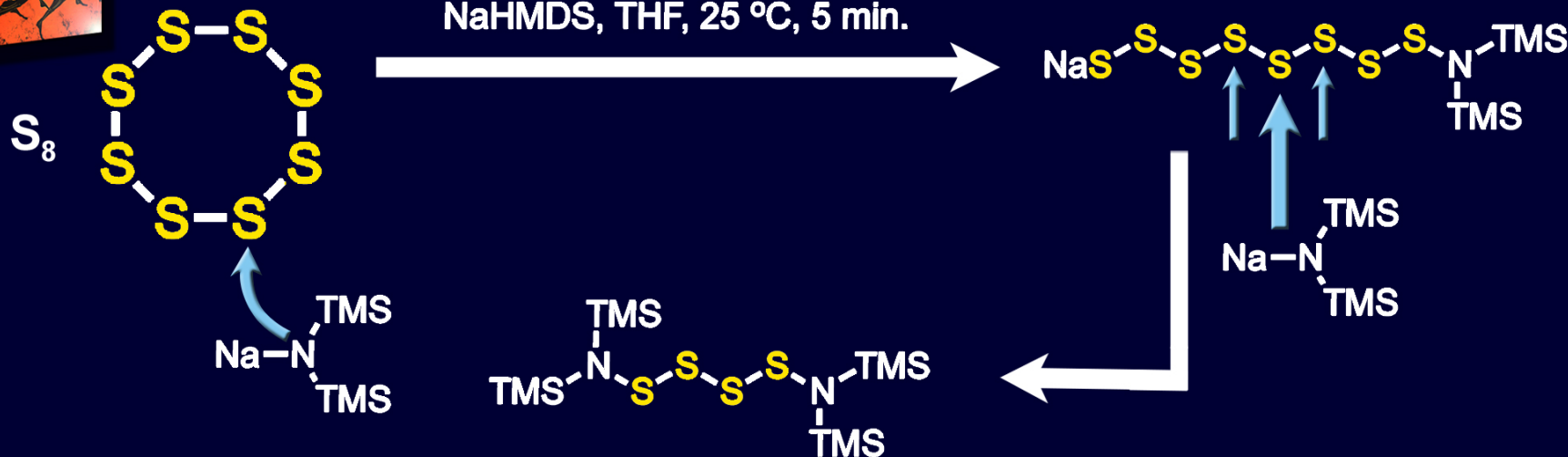
Polio Virus: NIH
Plasmodium Falciparum:
TSRI (Dr. Winzeler)



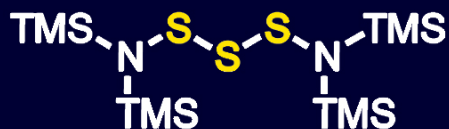
control: Pirodavir [*Polio virus*: $EC_{50} = 850$ nM]

The NaHMDS Reaction with S_8

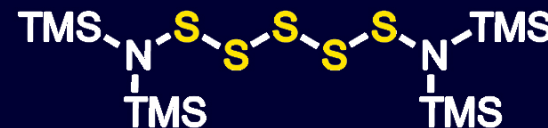
NaHMDS, THF, 25 °C, 5 min.



HRMS [$M+H^+$]: calcd for $C_{12}H_{36}N_2O_2S_4+H$
449.0911; found: 449.0908
 1H NMR ($CDCl_3$, 600 MHz): δ = 0.26 ppm
 ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 2.4 ppm

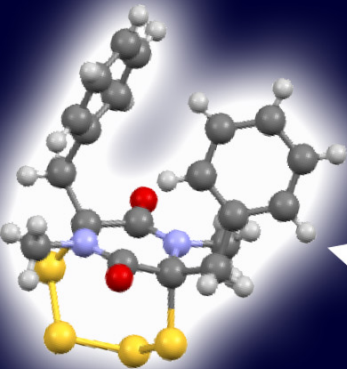


HRMS [$M+H^+$]: calcd for $C_{12}H_{36}N_2O_2S_3+H$
417.1190; found: 417.1186



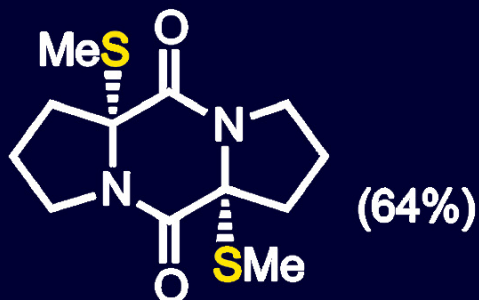
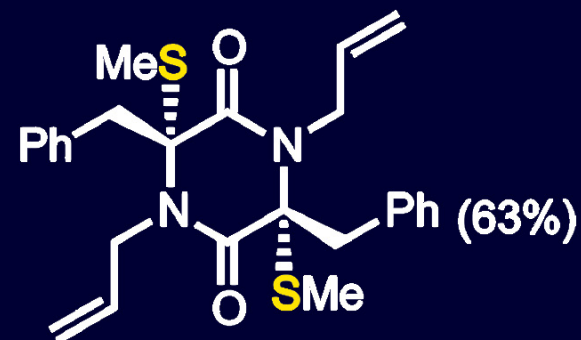
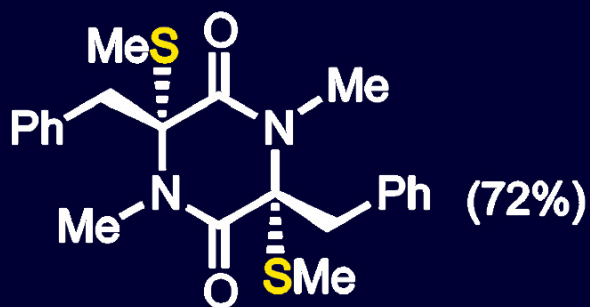
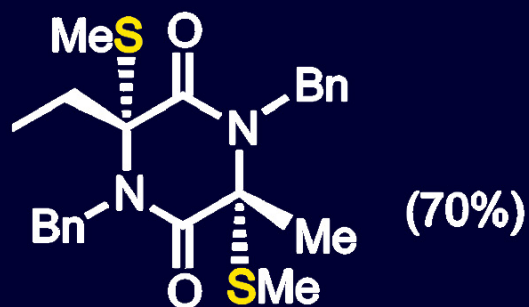
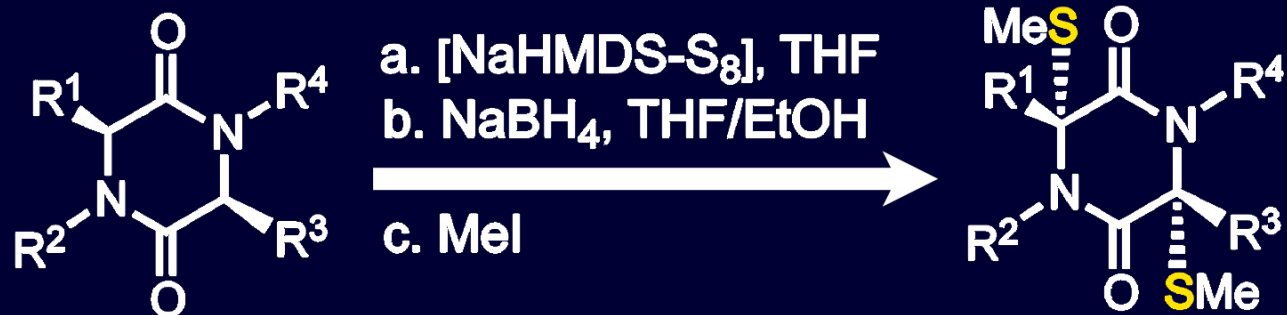
HRMS [$M+H^+$]: calcd for $C_{12}H_{36}N_2O_2S_5+H$
512.0280; found: 512.0241

O. Scherer, M. Schmidt, *Naturwissenschaften*, **1963**, 50, 302; J. Siivari, A. Maaninen, E. Haapaniemi, R. S. Laitinen, T. Chivers, *Z. Naturforsch. B*, **1995**, 50, 1575.



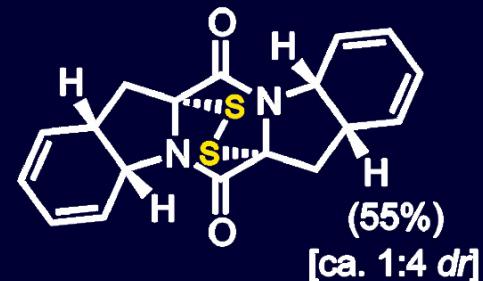
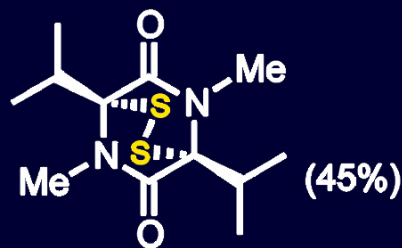
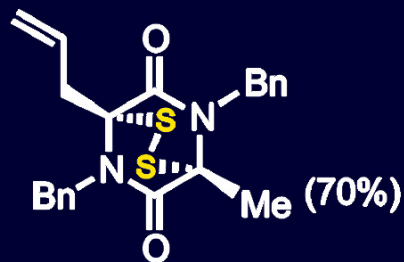
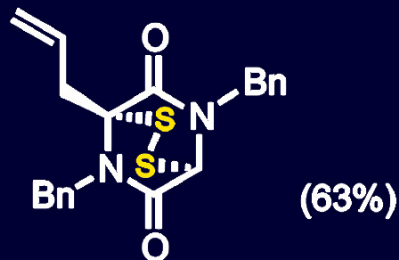
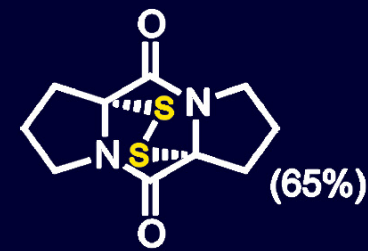
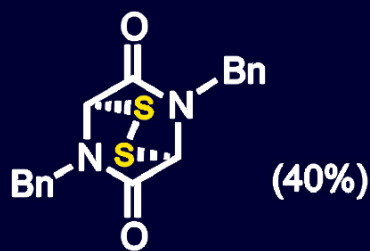
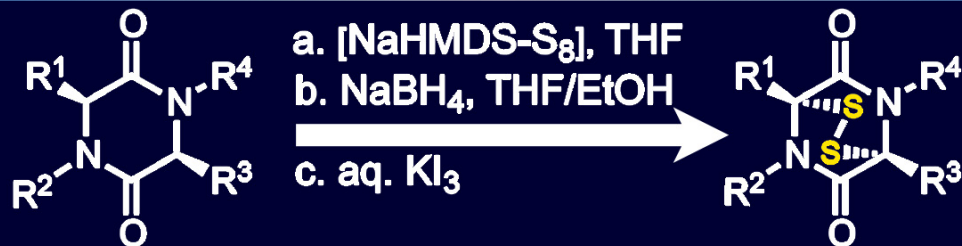


Preparation of bis-Methylthiodiketopiperazines

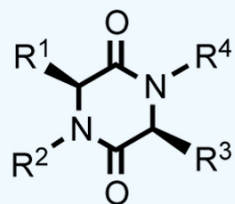




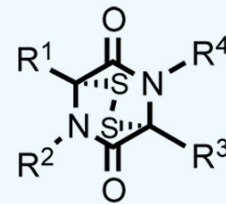
Preparation of Epidithiodiketopiperazines



Influence of the HMDS-base on Epidithiodiketopiperazine Formation^[a]



a) [base-S₈], THF
b) NaBH₄, THF/EtOH
c) KI₃ aq.



Entry	Substrate	Product ^[b]	LiHMDS	NaHMDS Yield [%] ^[c]	KHMDS
1			45	68	50
2			50	65	53
3			53	69	43

[a] Reactions were performed on 50 mg scale at 25 °C. [b] Racemic mixtures. [c] Yield of isolated products after chromatography.

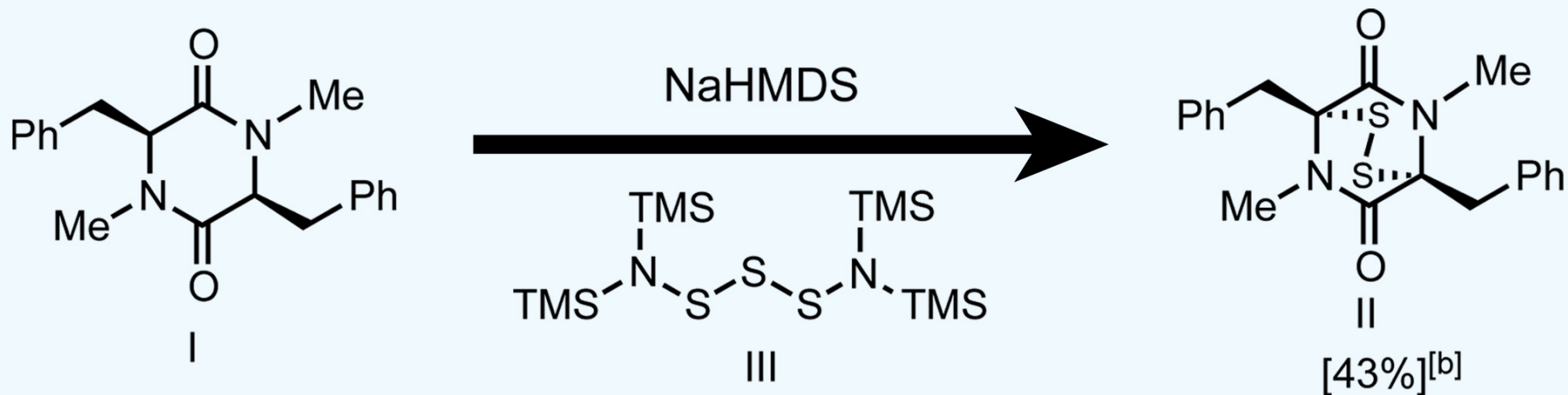
Optimization Study of the Sulfenylation of Diketopiperazine I^[a]



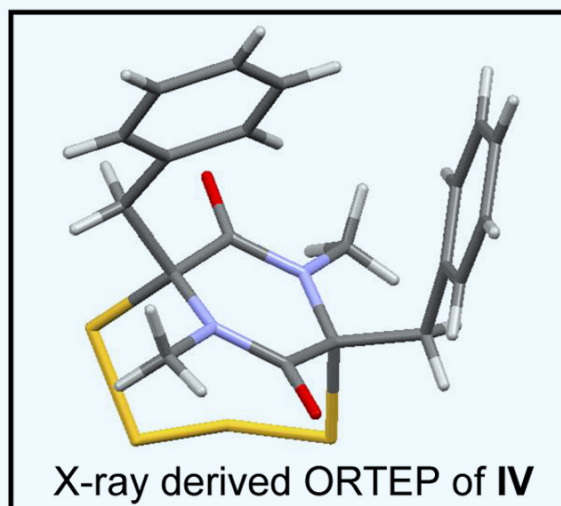
Entry	Solvent	LiHMDS	NaHMDS	KHMDS
Yield of II (%) [rsm, %] ^[b]				
1	THF	20 [70]	10 [40]	<5 [35]
2	CH ₂ Cl ₂	<5 [<5]	<5 [<5]	<5 [<5]
3	PhMe	15 [70]	<5 [45]	<5 [30]
4	Et ₂ O	25 [60]	15 [35]	<5 [35]
5	THF ^[c]	45 [42]	28 [30]	<5 [40]

a] Reactions were performed on 5 mg scale at 25 °C. [b] Yield was determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. [c] Reverse addition of preformed sulfenylation reagent to substrate and base.

Reaction of Diketopiperazine I with pure bis(bis[trimethylsilyl]amino)trisulfide III^[a]



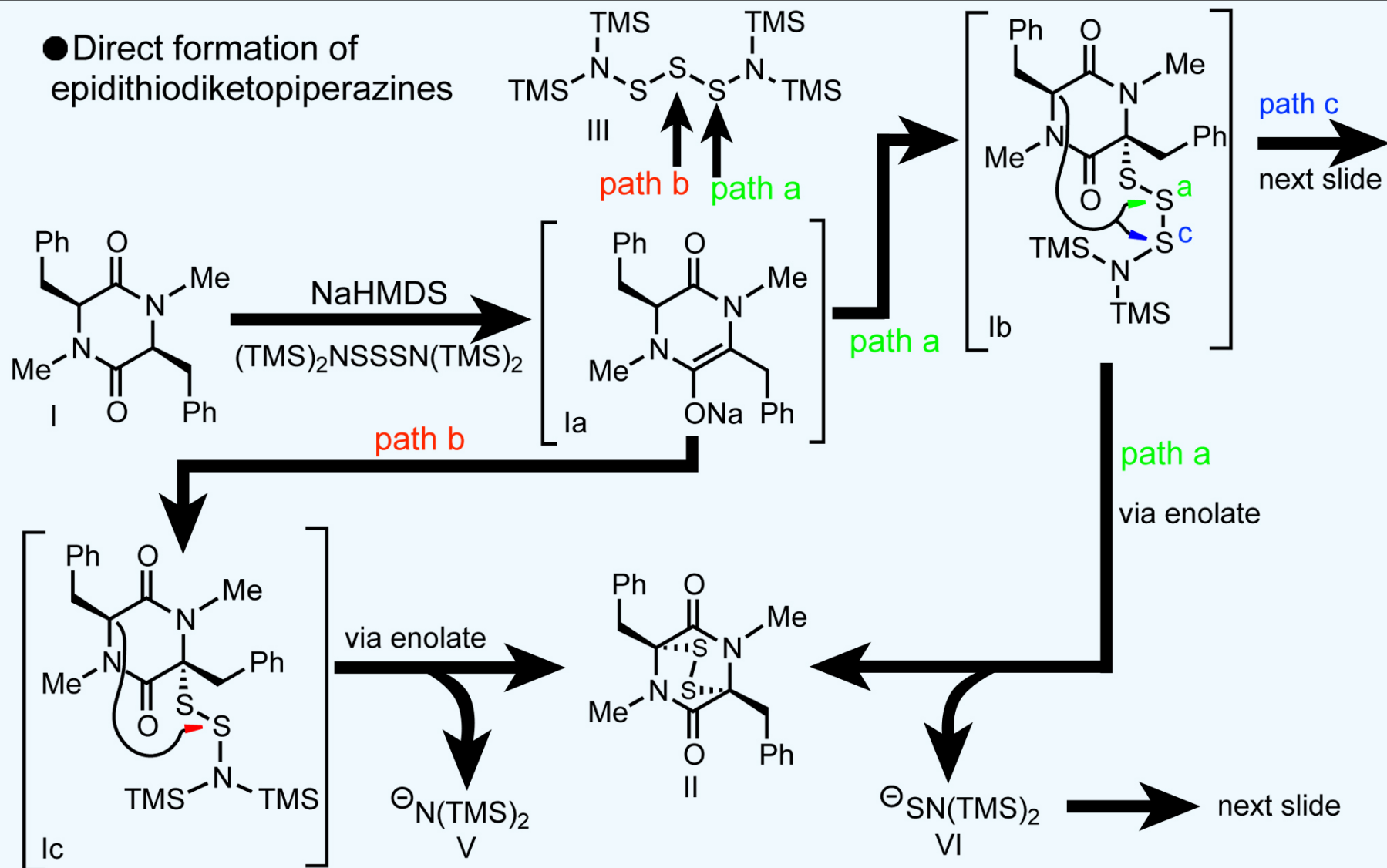
● Direct formation of epidithiodiketopiperazines and epitetrathiodiketopiperazines from diketopiperazines



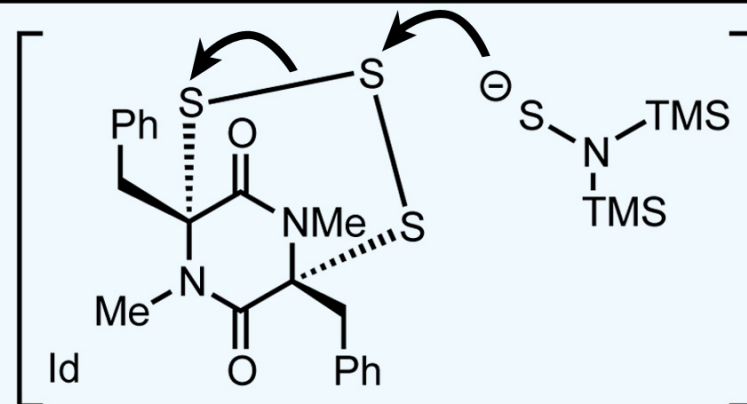
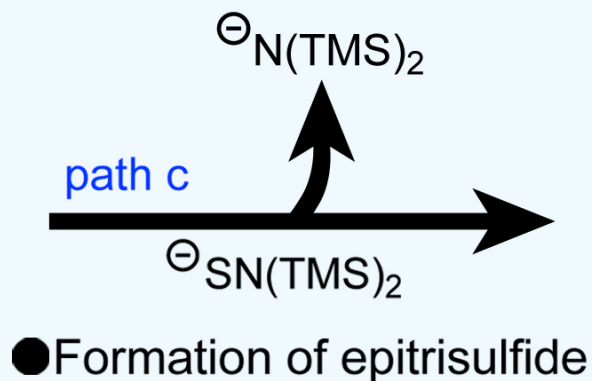
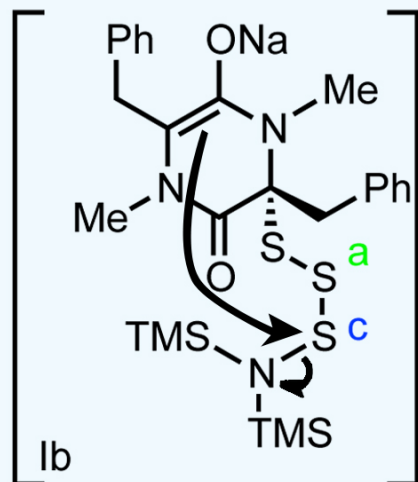
[a] For preparation, see: Scherer, O.; Schmidt, M. *Naturwissenschaften* **1963**, 50, 304; . [b] Racemic mixture. Yield of isolated product after chromatography.

Speculative Mechanism for the Formation of Epidithiodiketopiperazine II

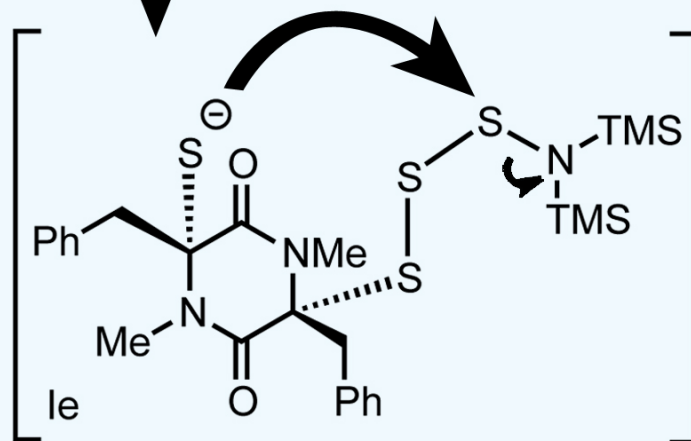
● Direct formation of epidithiodiketopiperazines



Proposed Mechanism for the Formation of Epitetrathiodiketopiperazine IV

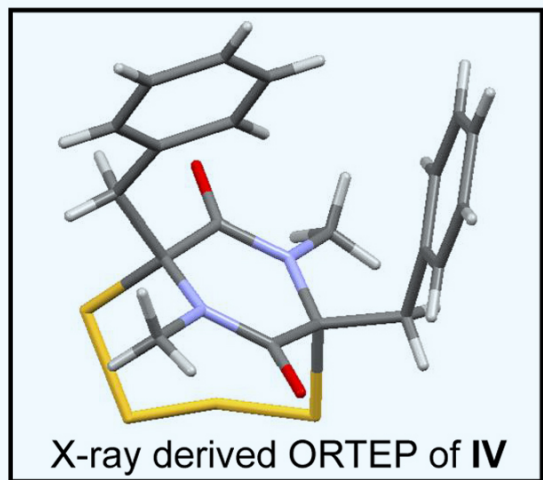
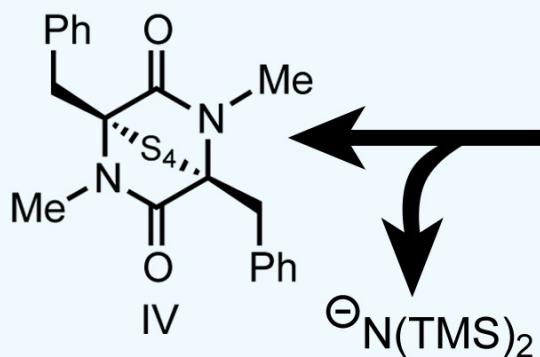


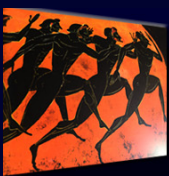
● Attack at the less hindered sulfur atom



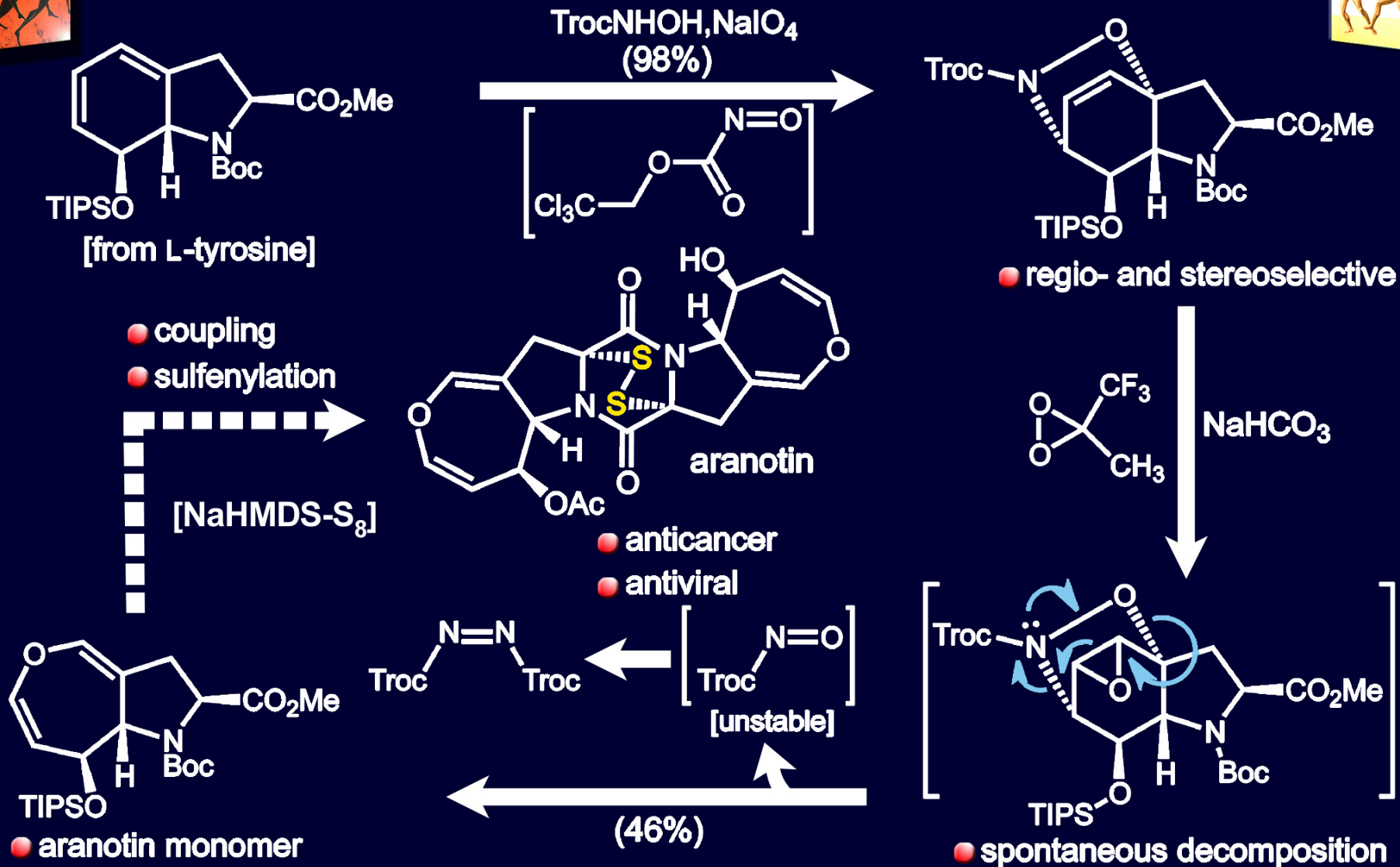
● Hindrance overcome by intramolecularity

● Epitetrasulfide formation

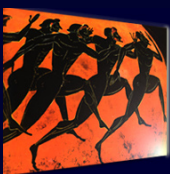




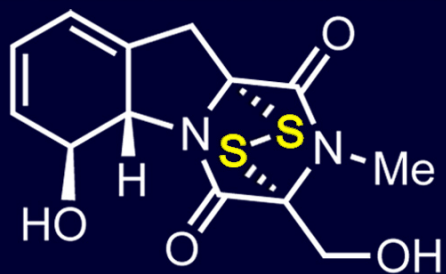
Preparation of oxepine epidithiodiketopiperazines





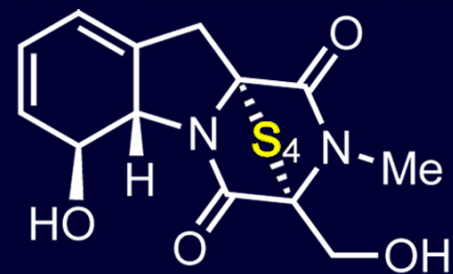


Additional Dithiodiketopiperazines Synthesized

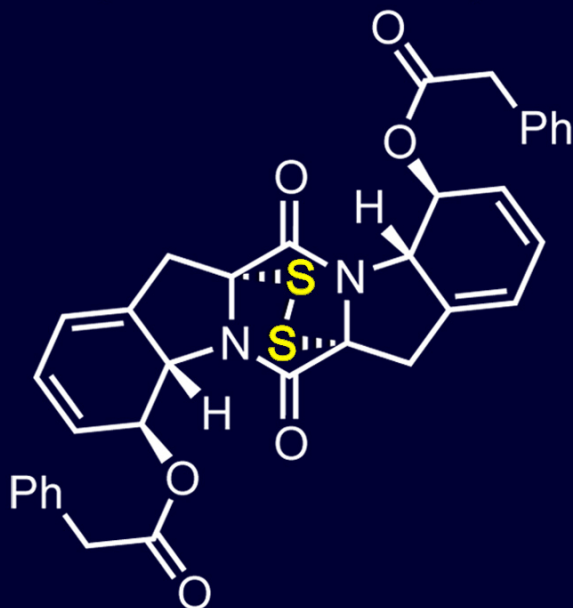


gliotoxin

[antiviral, antibiotic]



gliotoxin G



emethallicin E

[immunosuppressant]



haematocin

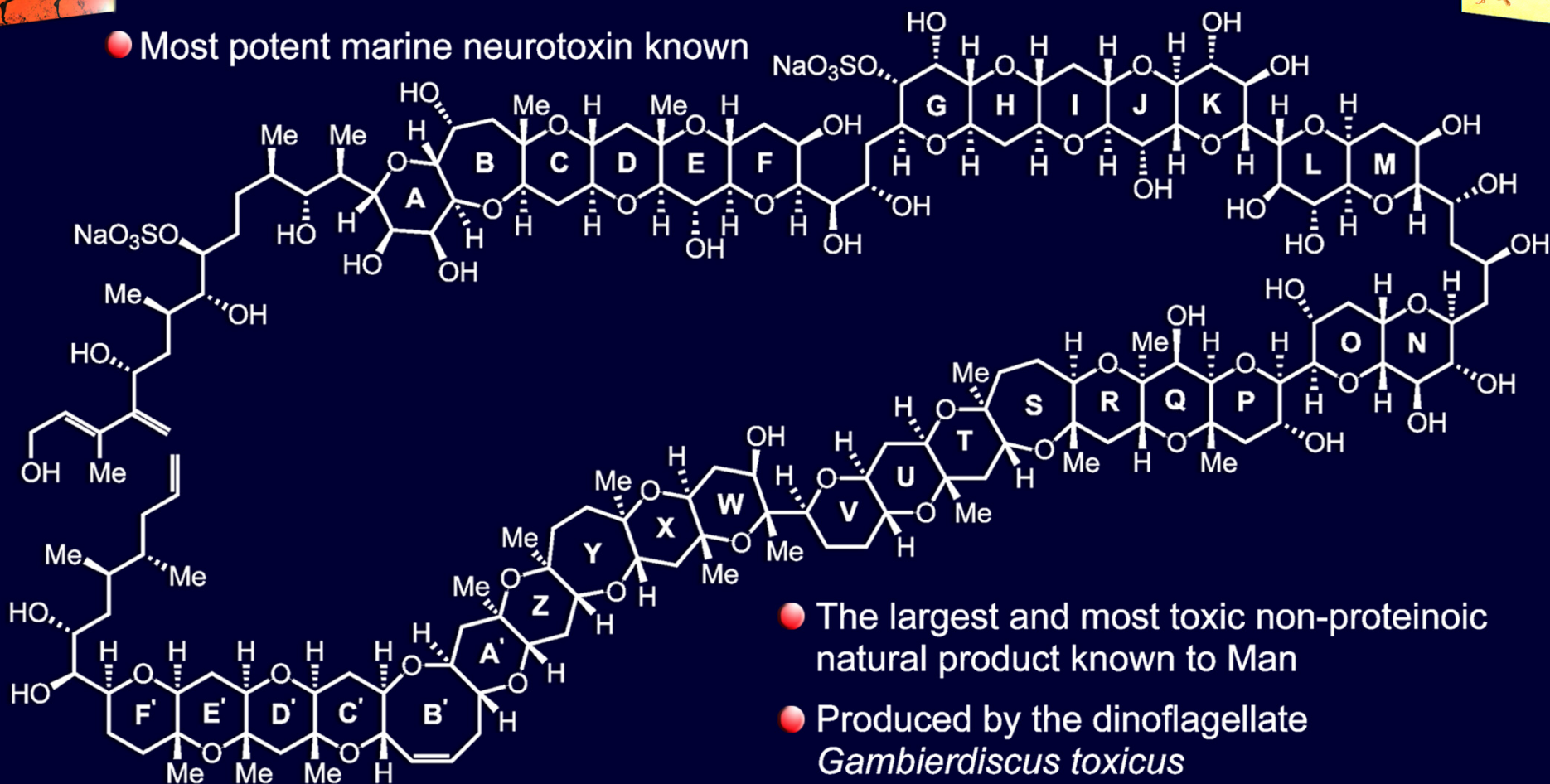
[antifungal]



Proposed Structure of Maitotoxin



- Most potent marine neurotoxin known



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

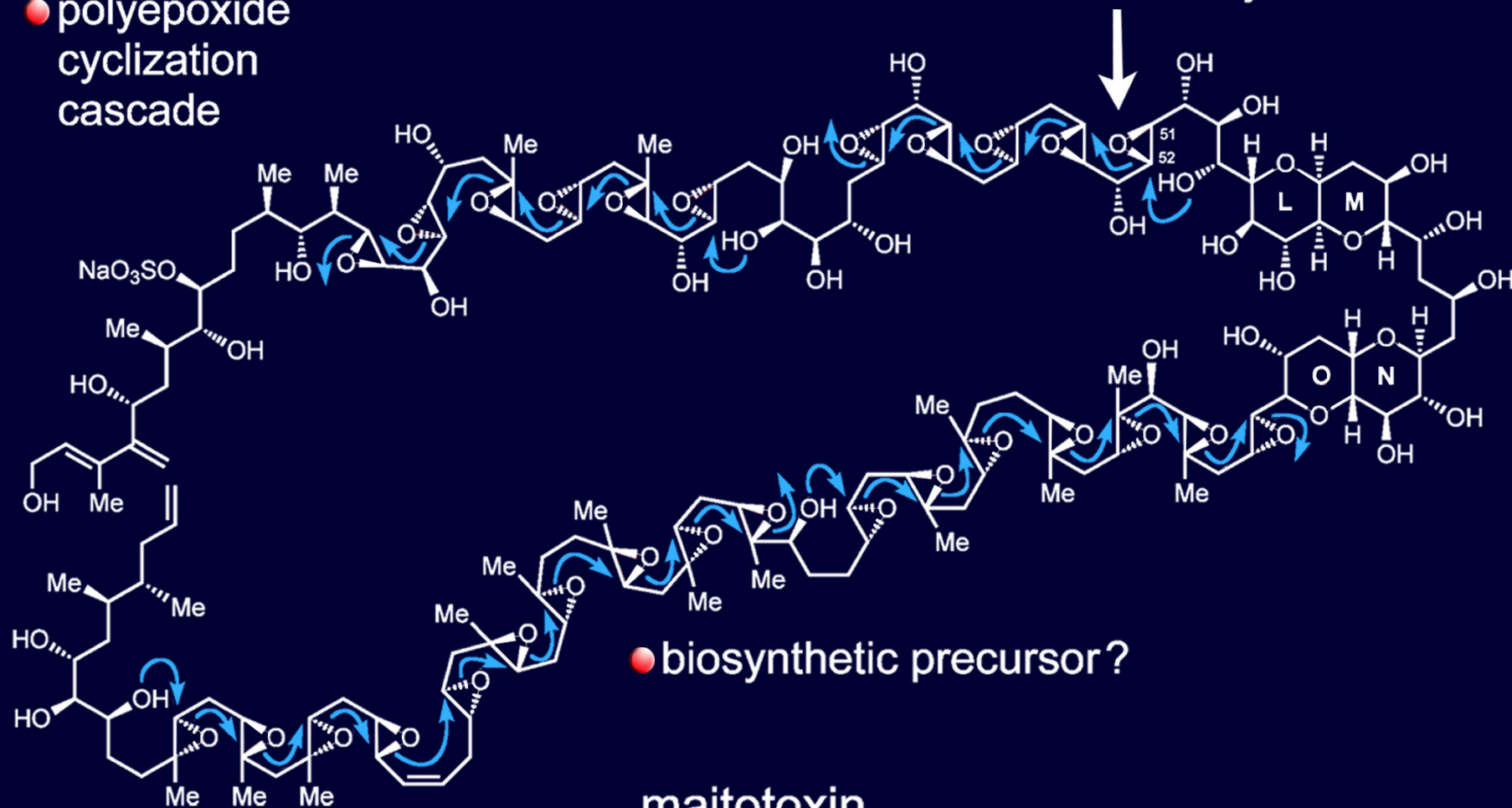
- 32 rings, 98 stereogenic centers

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



● polyepoxide
cyclization
cascade

● anomaly?

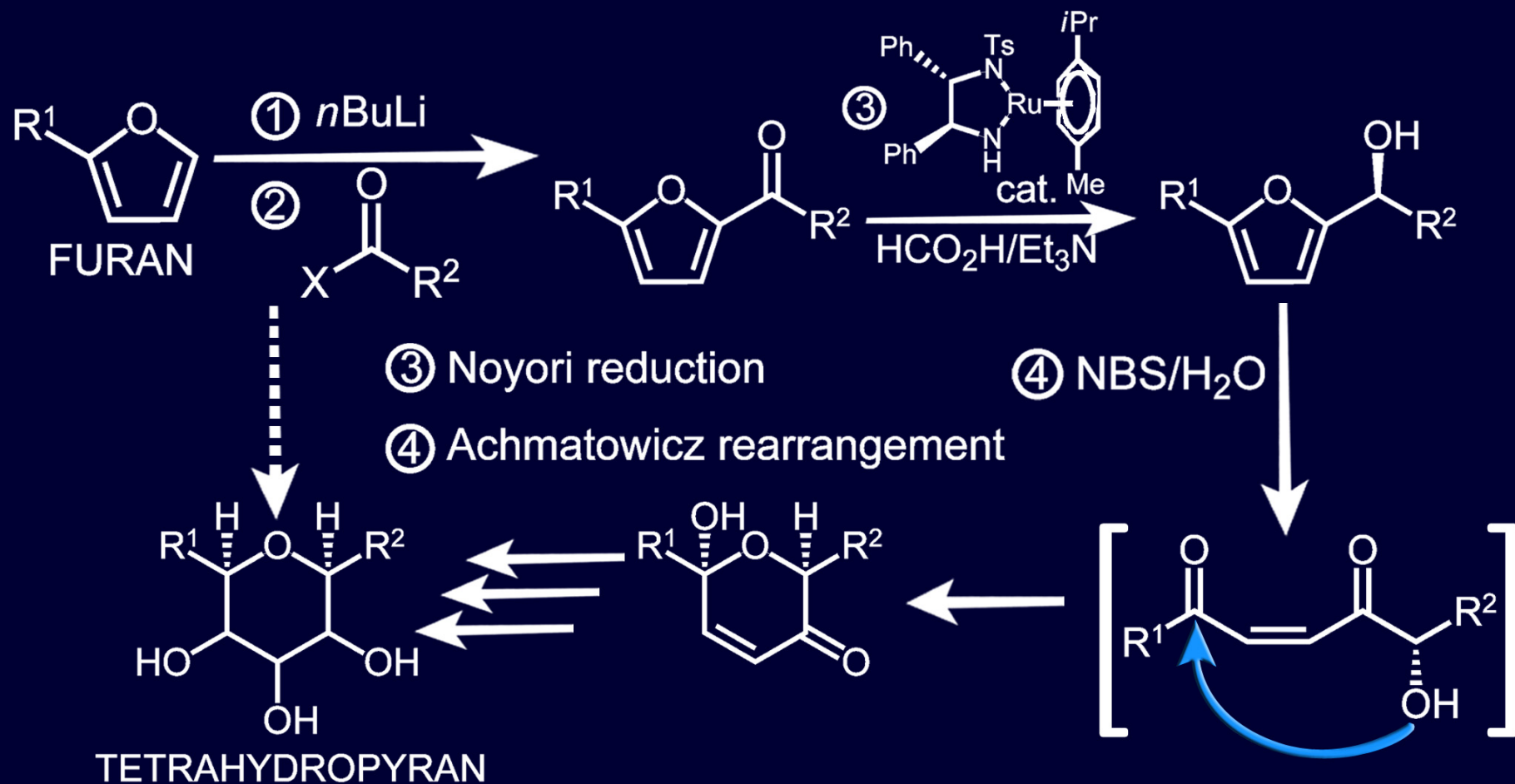


● biosynthetic precursor?

maitotoxin

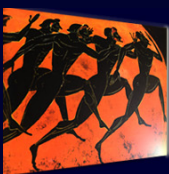


GENERAL METHOD FOR TETRAHYDROPYRAN SYNTHESIS FROM FURANS-THE NOYORI REDUCTION/ACHMATOWICZ REARRANGEMENT METHOD (NICOLAOU et al., 2007)

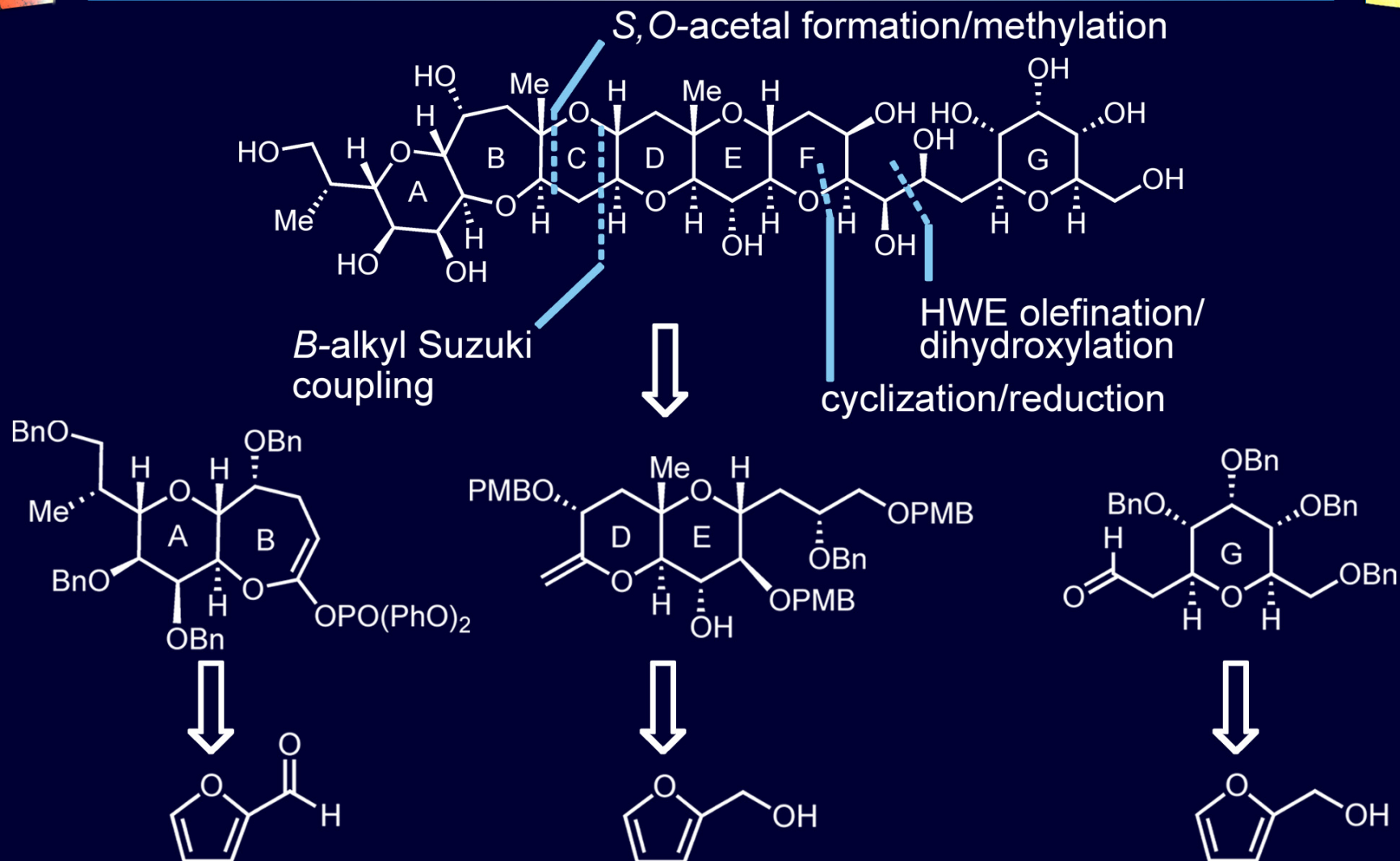


Noyori, R., et al. *J. Am. Chem. Soc.* **1996**, 118, 2521.

Achmatowicz, O. et al. *Carbohydr. Res.* **1977**, 55, 165.

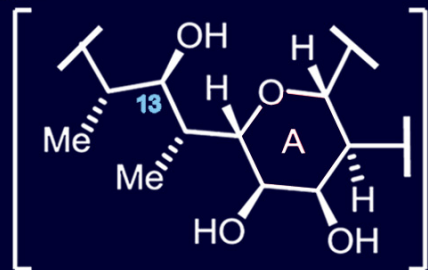


RETROSYNTHETIC ANALYSIS OF MAITOTOXIN ABCDEFGH RING SYSTEM

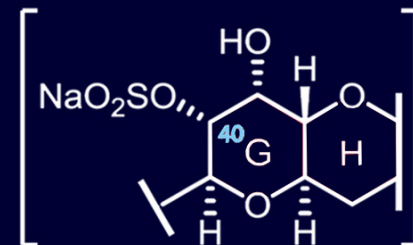




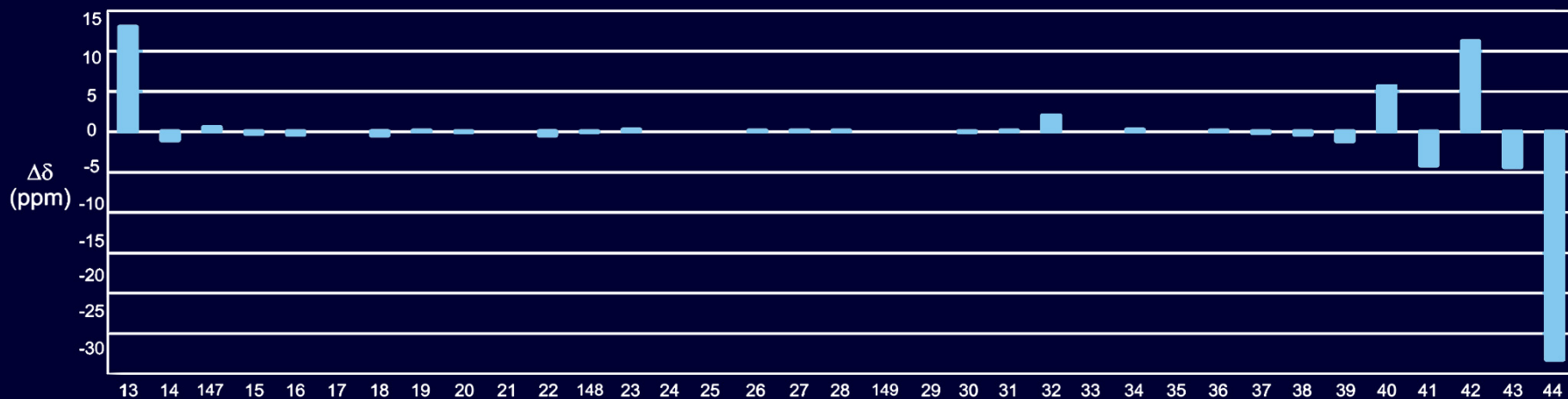
MAITOTOXIN. ^{13}C NMR DATA FOR THE ABCDEFG DOMAIN



maitotoxin structure

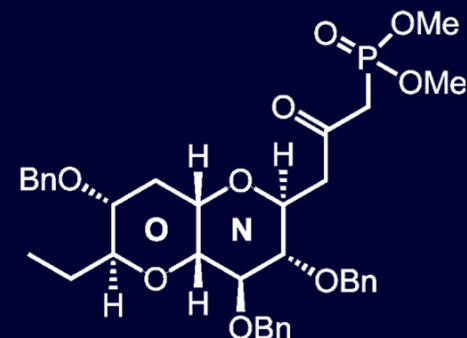
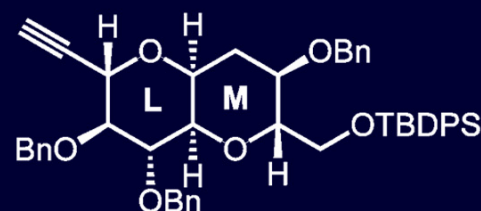
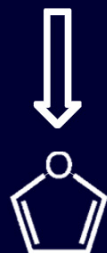
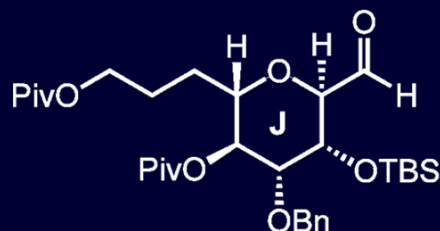
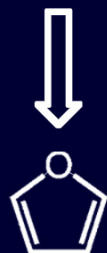
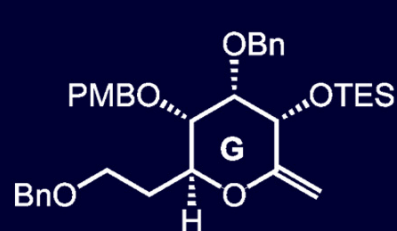
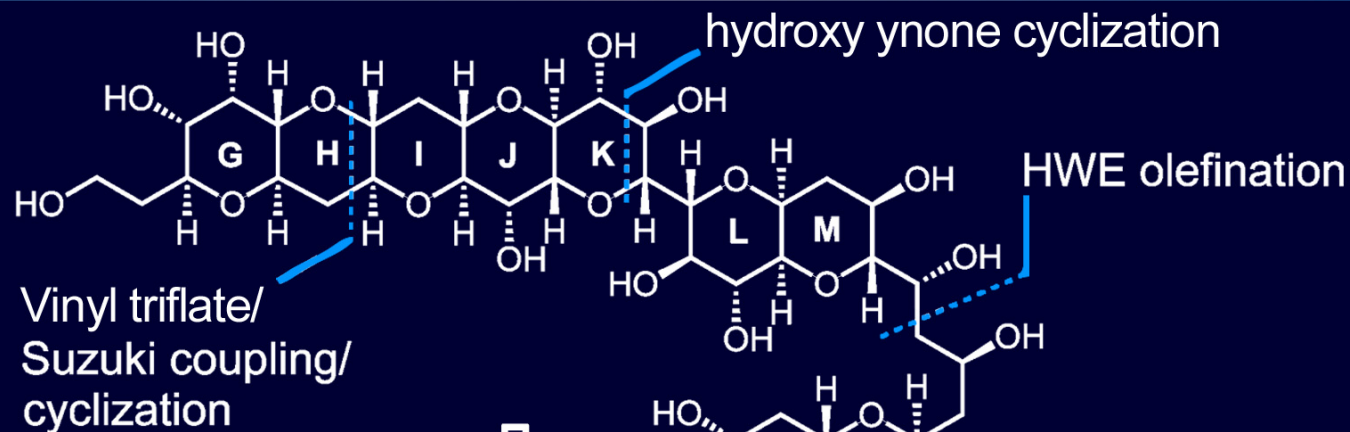


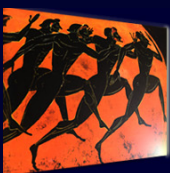
maitotoxin structure



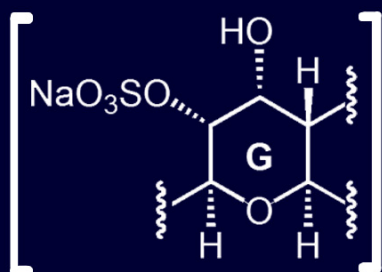


MAITOTOXIN-4: THE FURAN WAY

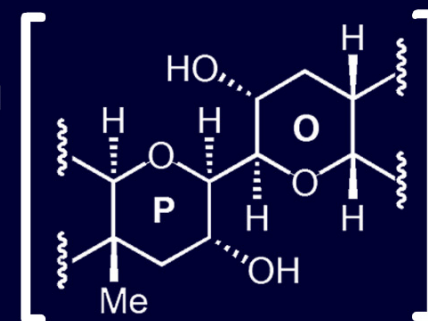
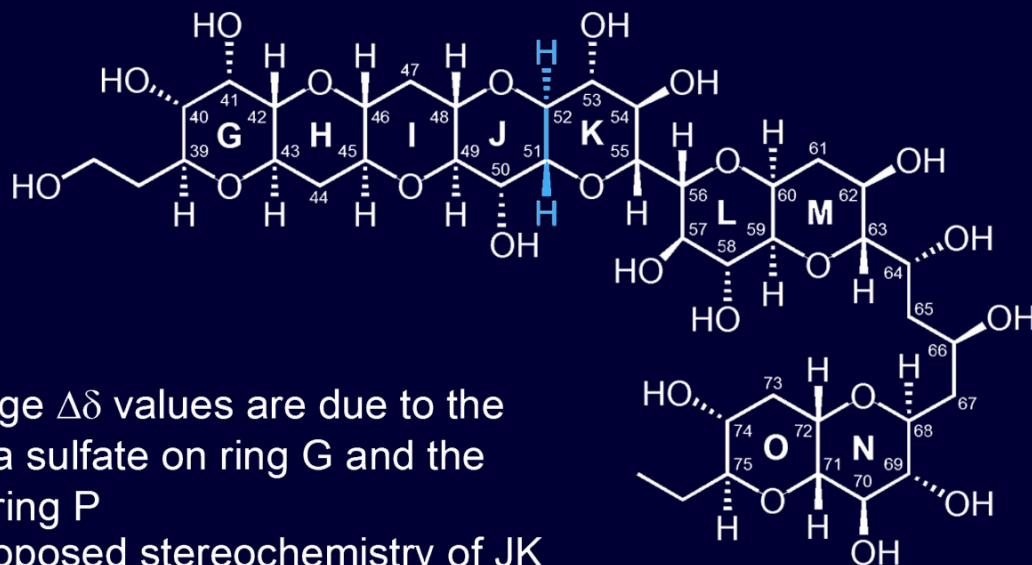




MAITOTOXIN-15

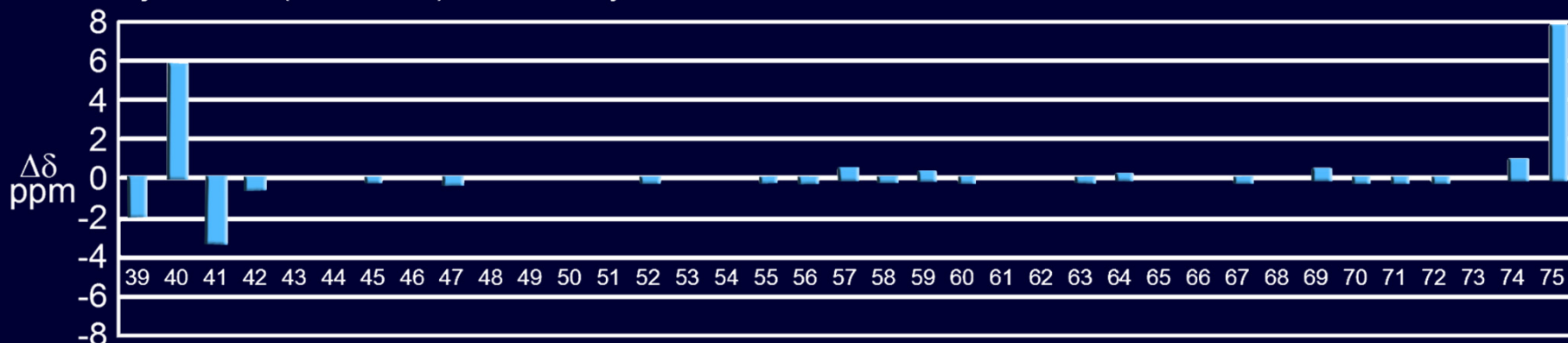


maitotoxin structure



maitotoxin structure

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

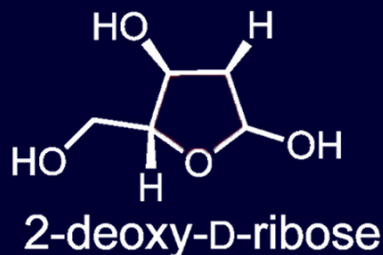
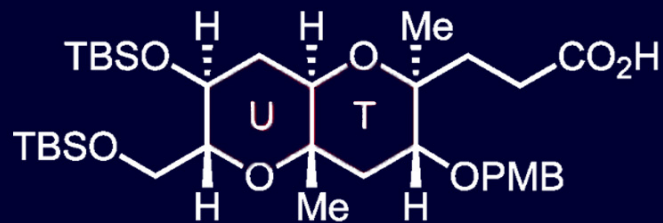
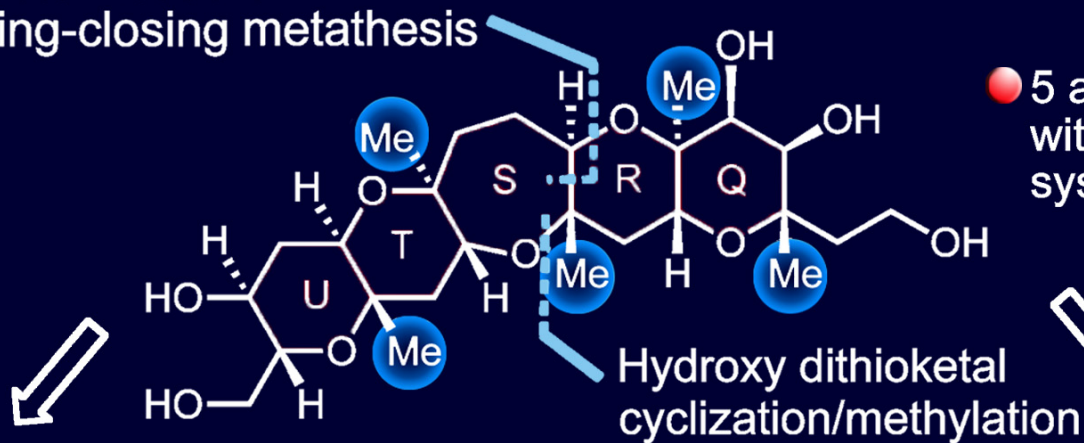


- average $\Delta\delta$ for C42-C73 = 0.09 ppm
- largest $\Delta\delta$ for C42-C73 = 0.4 ppm

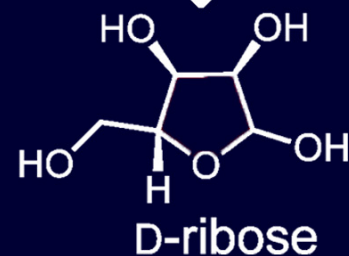
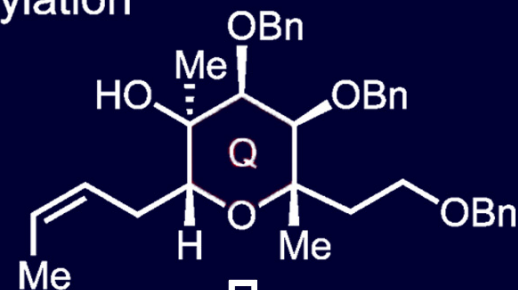
RETROSYNTHETIC ANALYSIS OF MAITOTOXIN QRSTU RING SYSTEM

Esterification/
ring-closing metathesis

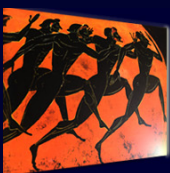
● 5 angular Me groups within a pentacyclic system



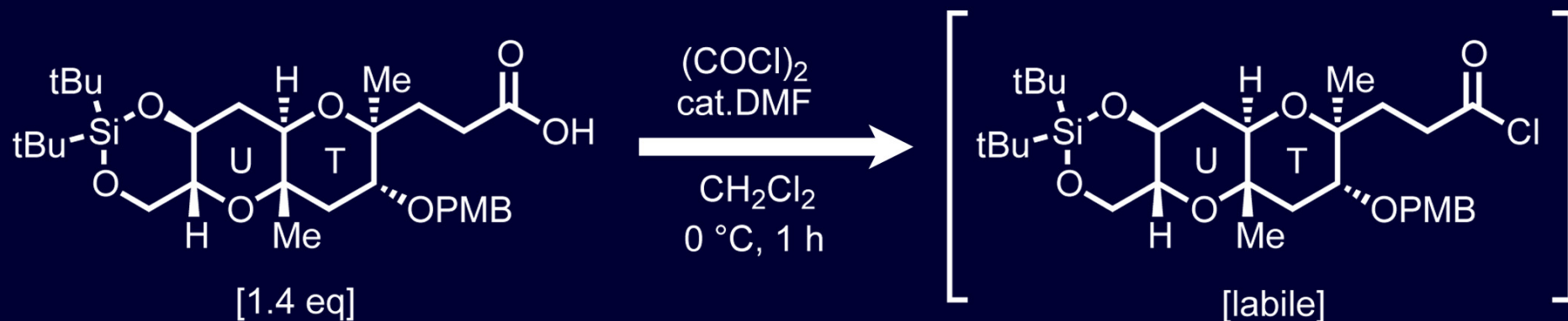
2-deoxy-D-ribose



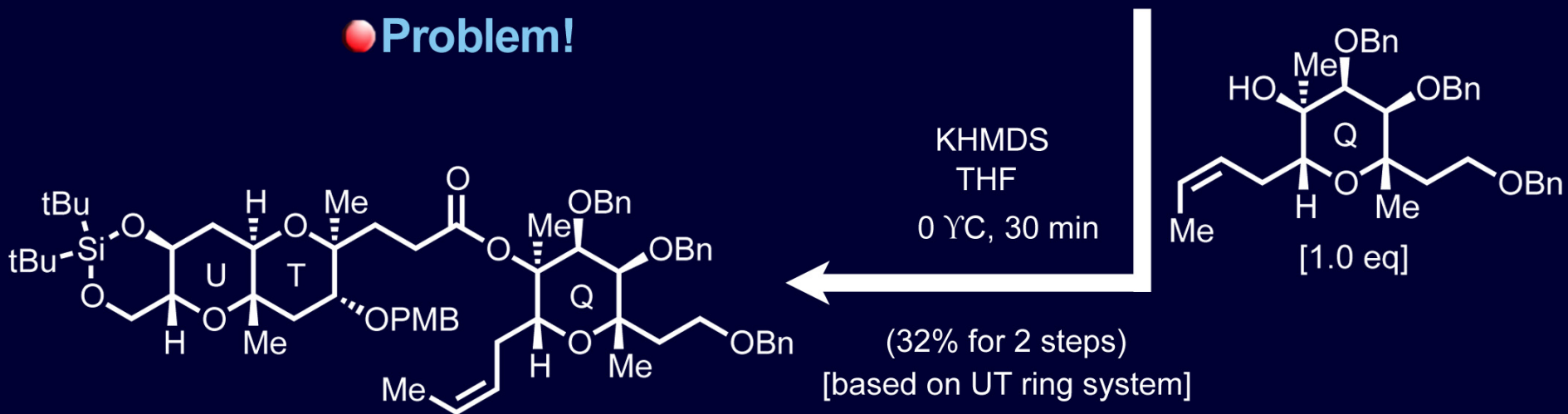
D-ribose

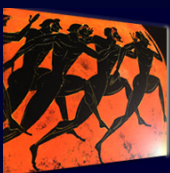


Maitotoxin: *Esterification of UT and Q ring fragment via acid chloride*

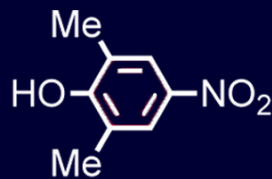
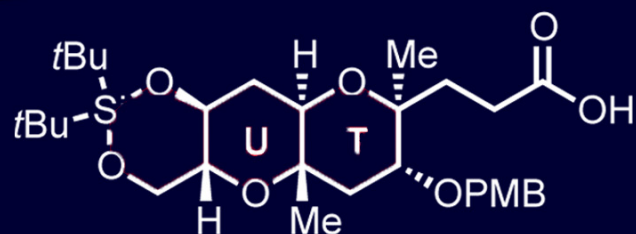


● **Problem!**

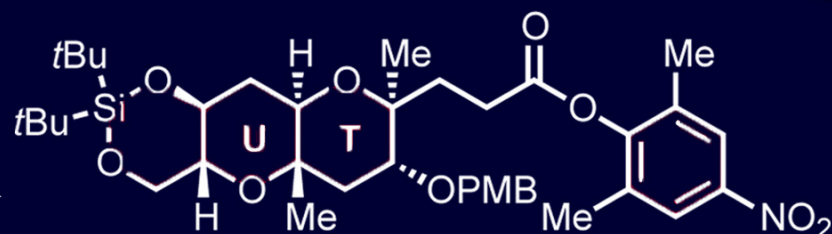




Maitotoxin: Esterification of UT and Q ring fragment via 2,6-dimethyl-4-nitrophenyl ester

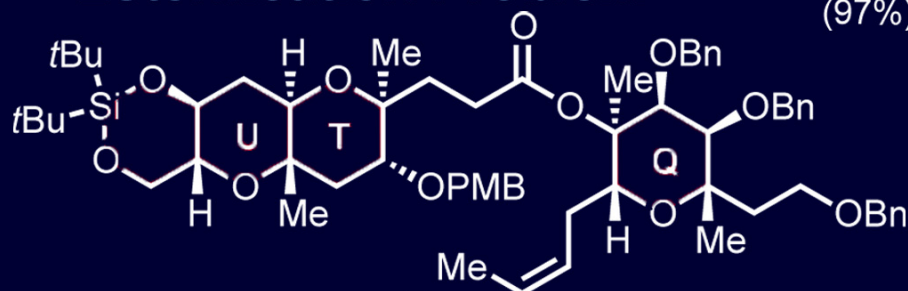


Et₃N, DMAP
BOP, CH₂Cl₂
25 °C, 1 h
(97%)

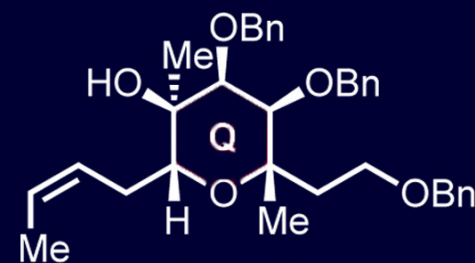


[stable, 1.0 eq]

● Solution of Esterification Problem



KHMDS
toluene
0 °C, 30 min
(84%)

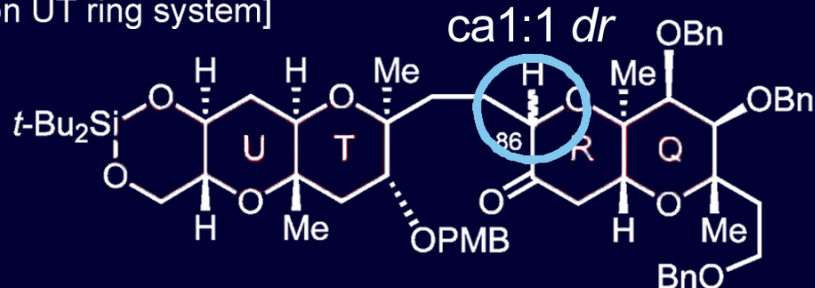
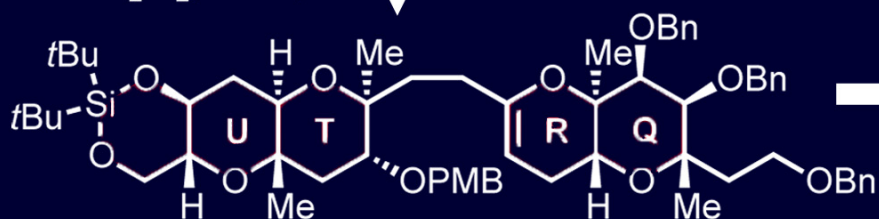


[1.2 eq]

[based on UT ring system]

TiCl₄, TMEDA
Zn, cat. PbCl₂
CH₃CHBr₂
CH₂Cl₂, 60 °C, 1 h

(93%) ● Hydroboration (BH₃·H₂O₂)
● Oxidation (DMP)



ca 1:1 dr

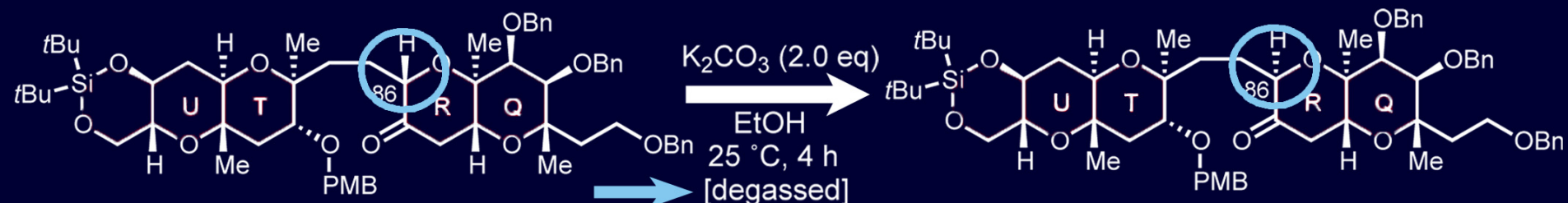
K₂CO₃, EtOH, anaerobic (89%) → β-H₈₆ isomer
● α-H₈₆ isomer



Maitotoxin: C-86 Epimerization - Problem and Solution



● Solution

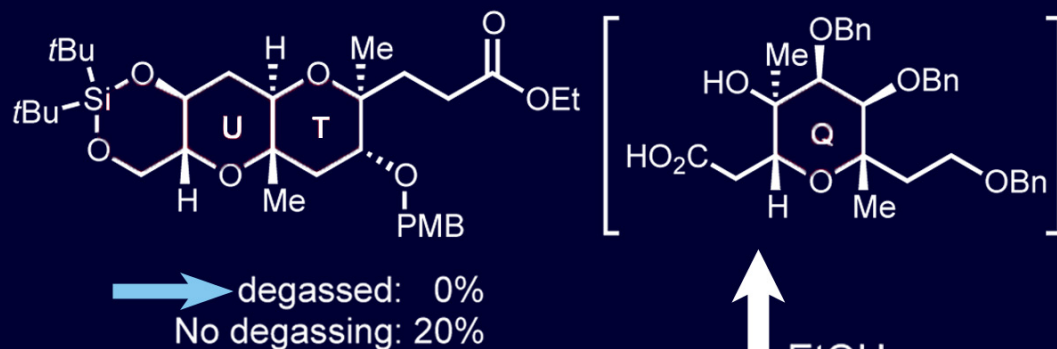


degassed: 89%
No degassing: 30%

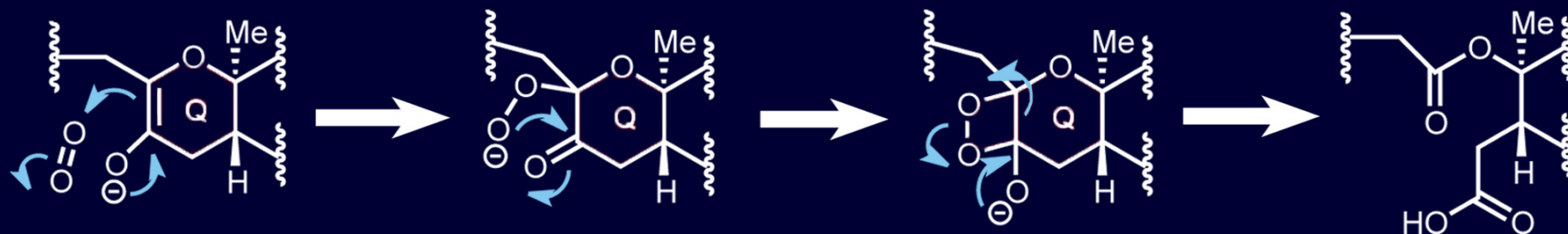
+

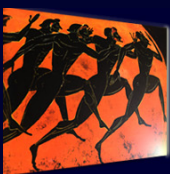
● Problem

K_2CO_3 (2.0 eq)
EtOH
25 °C, 4 h
[No degassing]

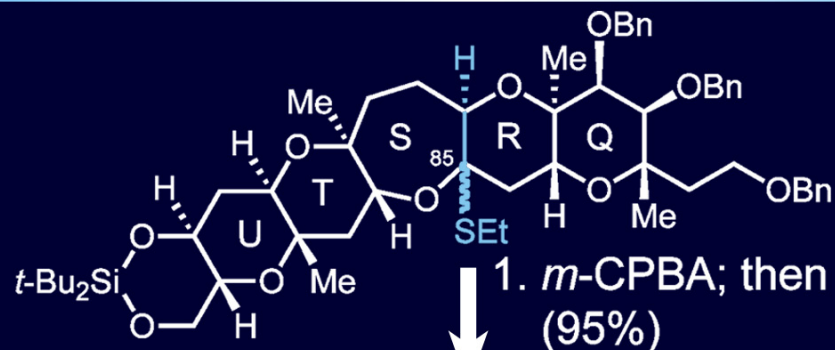


EtOH

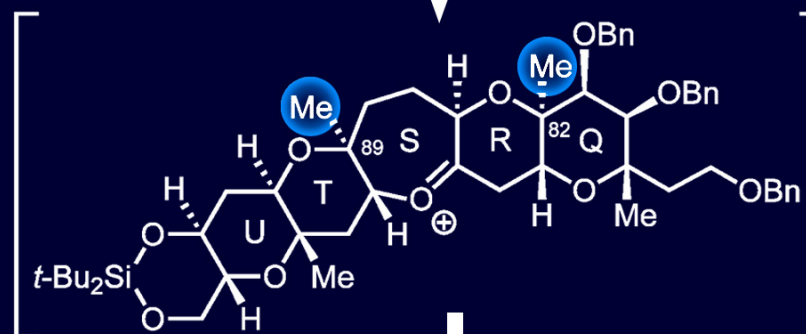




MAITOTOXIN. SYNTHESIS OF THE QRSTU RING SYSTEM

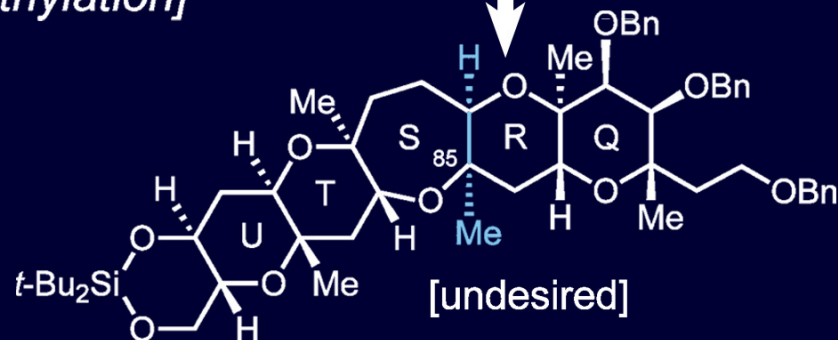
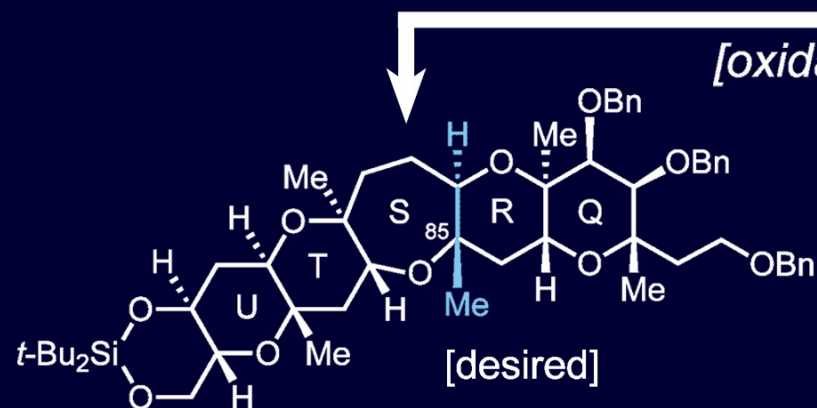


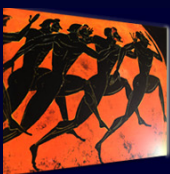
● $\text{C}_{85}\text{-SEt}$ $\beta:\alpha$ ca. 1:3 *dr*



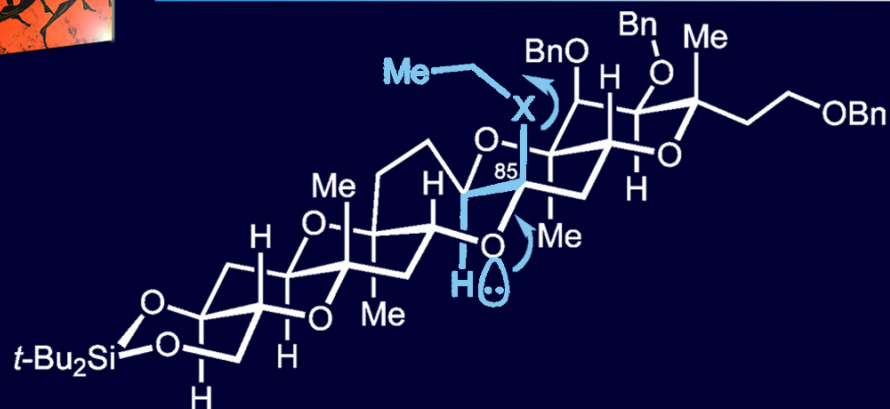
● ratio of substrates does not translate into same ratio of products

● $\text{C}_{85}\text{-Me}$ $\beta:\alpha$ ca. 1:0.8 *dr*





MAITOTOXIN. SYNTHESIS OF THE QRSTU RING SYSTEM

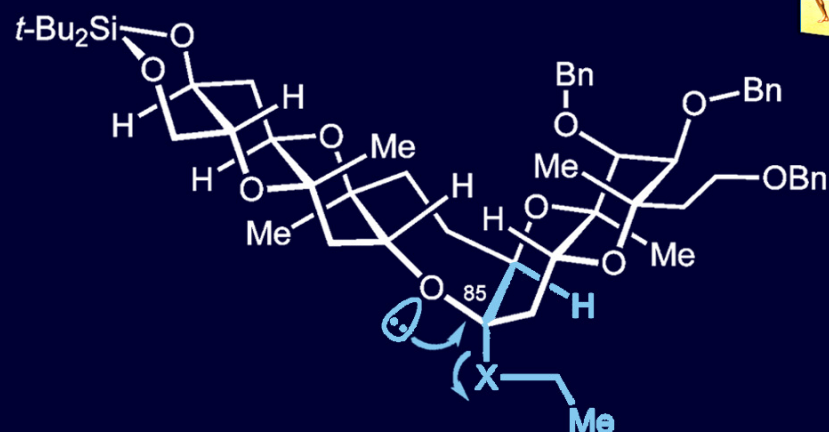
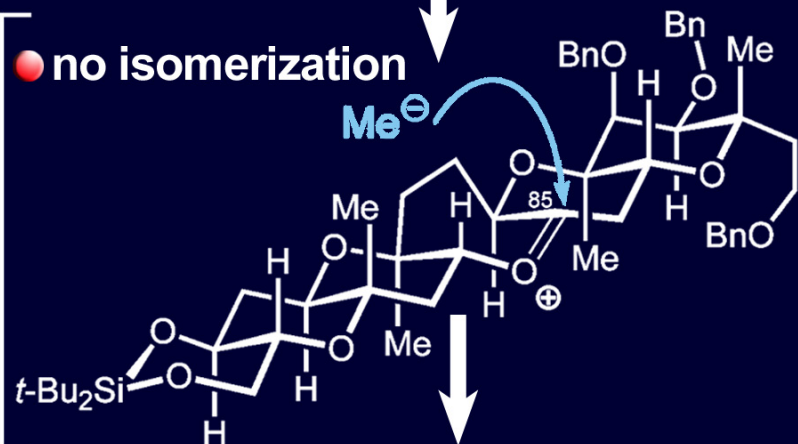


1. *m*-CPBA $\begin{cases} \text{X} = \text{S} \text{ (minor)} \\ \text{X} = \text{SO}_2 \text{ (not isolated)} \end{cases}$

1. then Me_3Al

[oxidation/methylation]

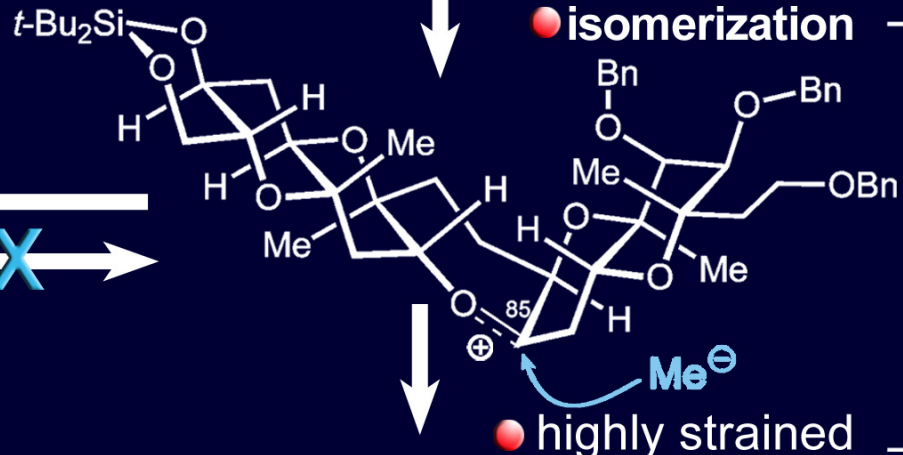
● no isomerization



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

1. then Me_3Al

● isomerization

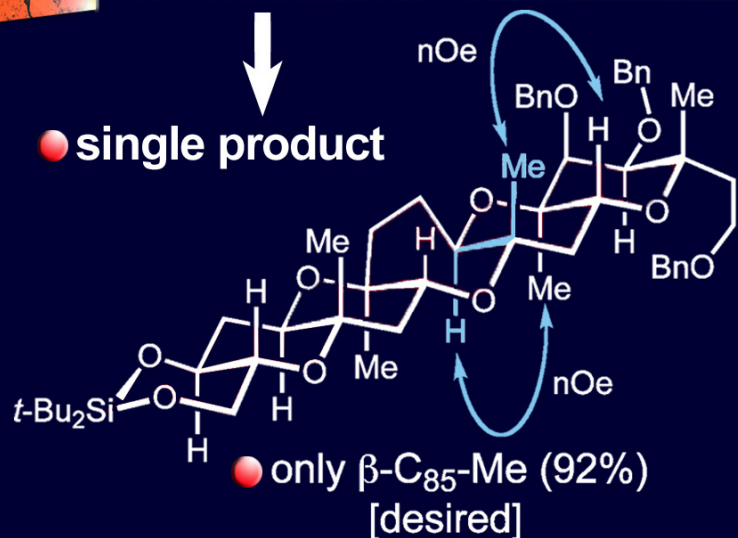




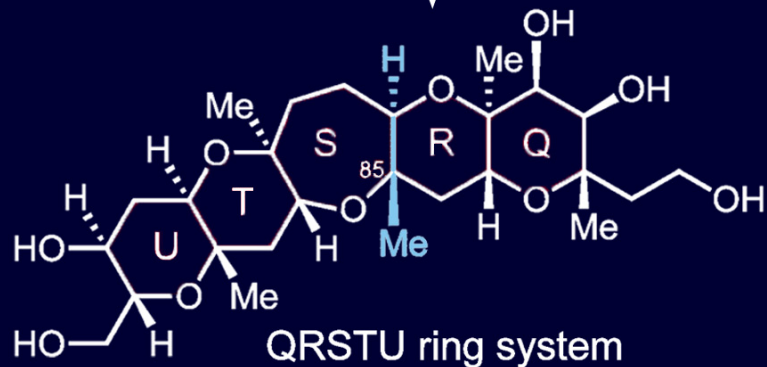
MAITOTOXIN. SYNTHESIS OF THE QRSTU DOMAIN AND THE 85-*epi*-QRSTU RING SYSTEM



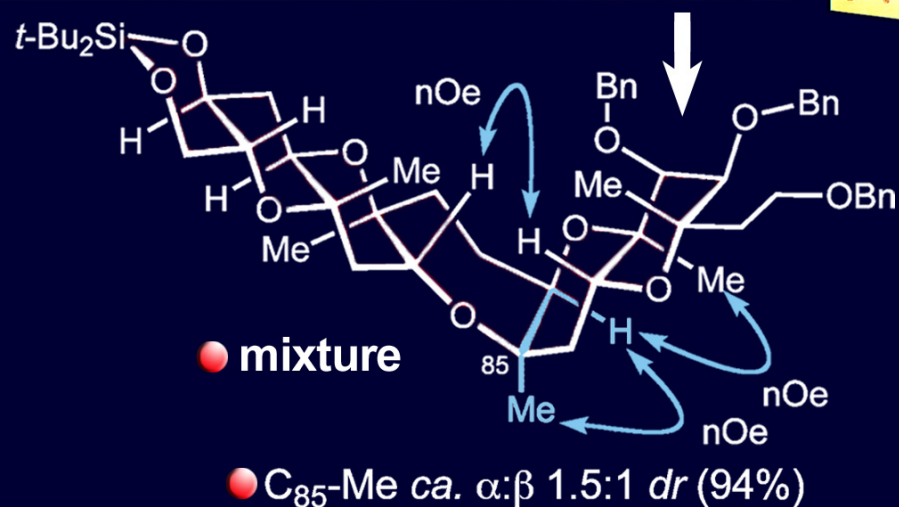
● single product



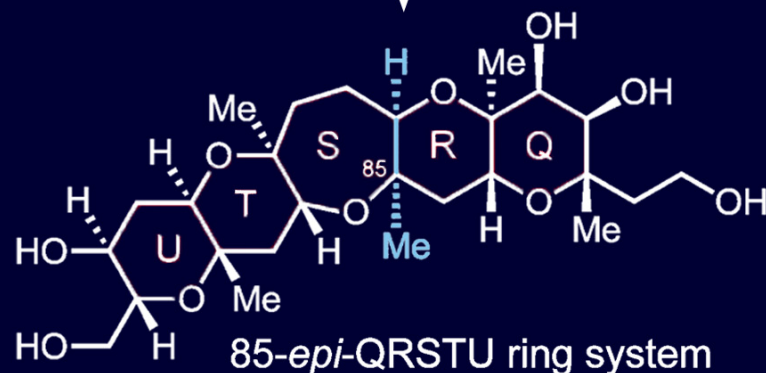
1. TBAF
2. H₂, Pd(OH)₂/C
(87%, 2 steps)



● mixture



1. TBAF
2. H₂, Pd(OH)₂/C
(80%, 2 steps)

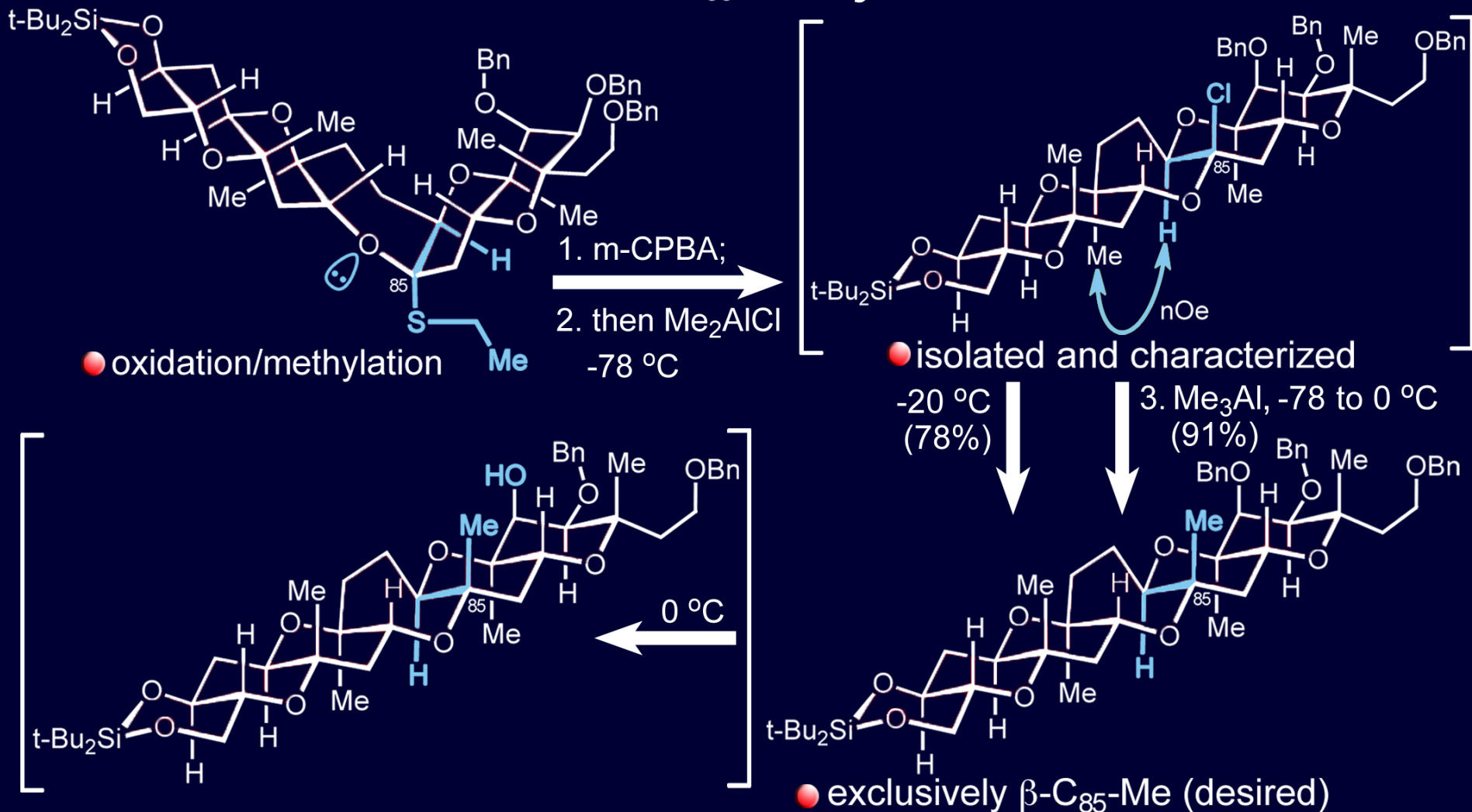


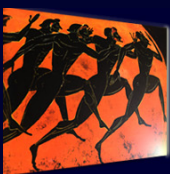


MAITOTOXIN. SYNTHESIS OF THE QRSTU RING SYSTEM



● Solution to the C_{85} -Methylation Problem



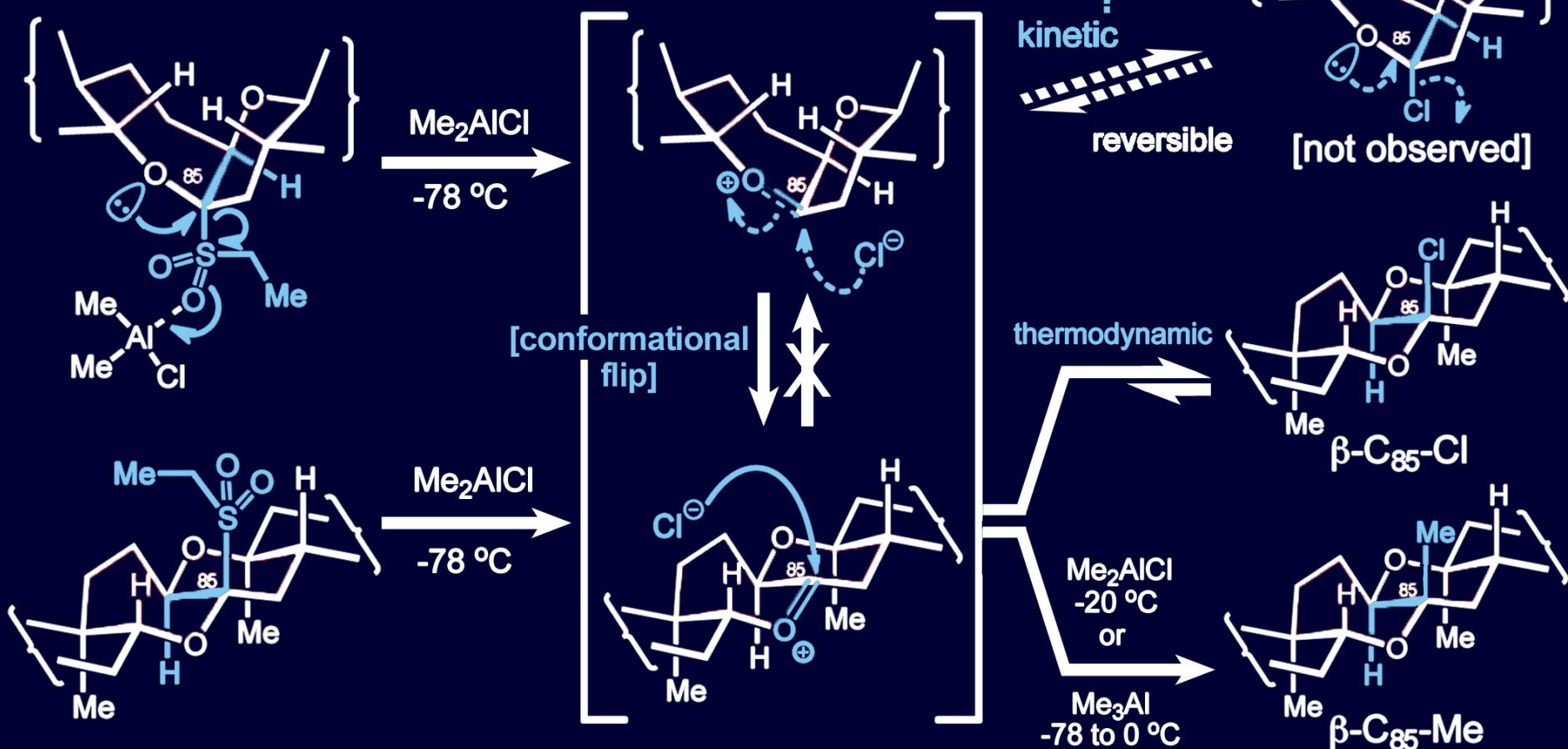


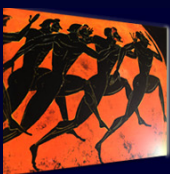
Maitotoxin. Synthesis of the QRSTU Ring System



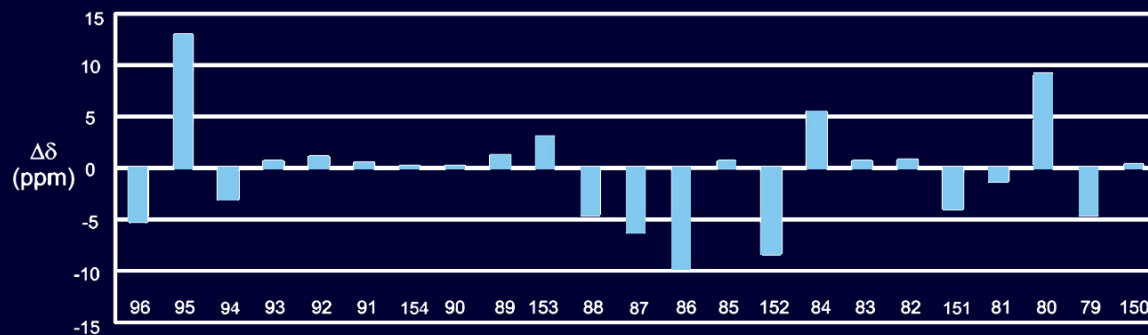
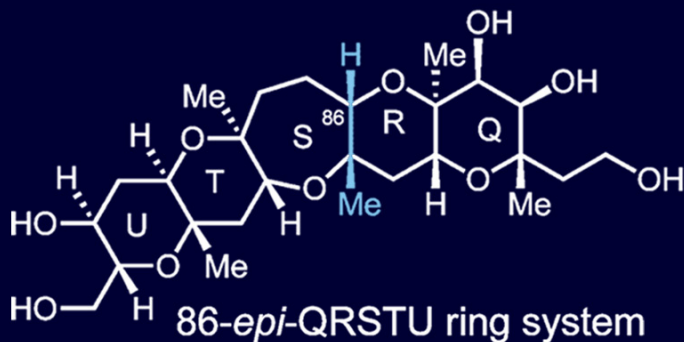
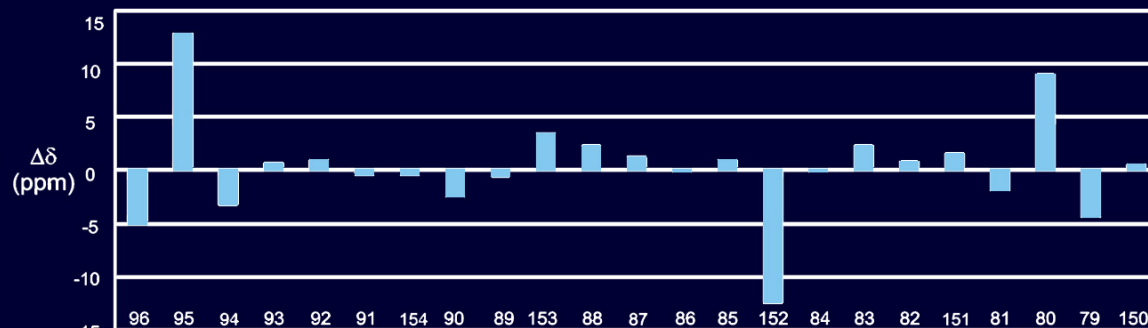
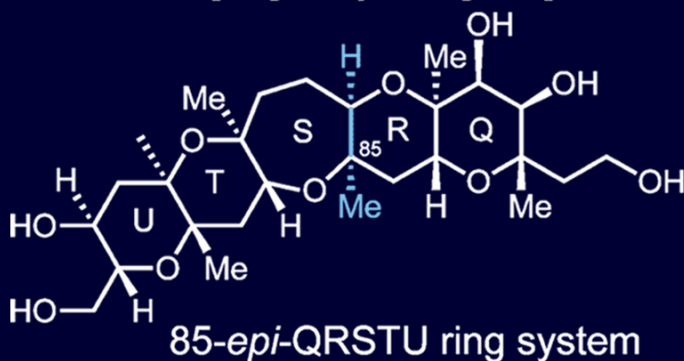
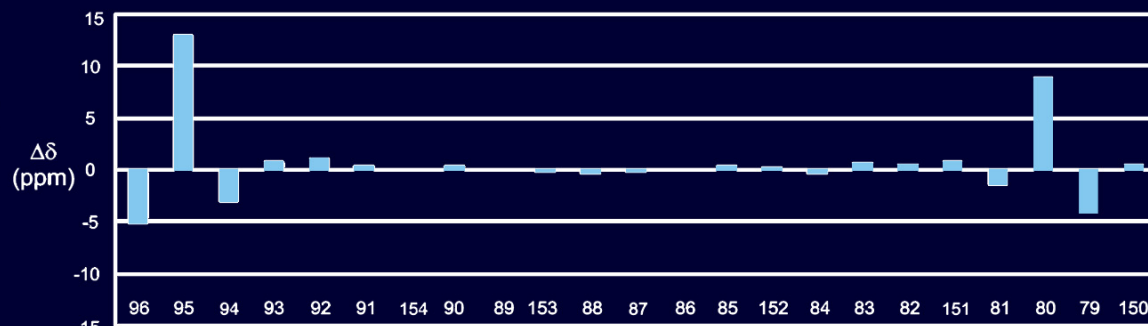
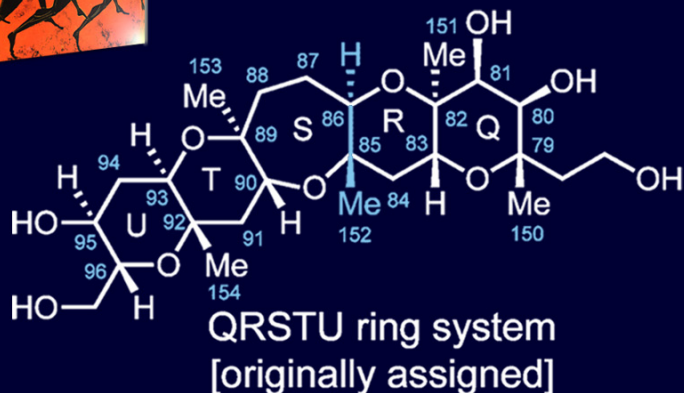
Mechanism of β -C₈₅-Cl Formation

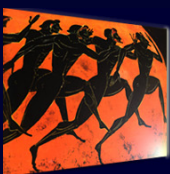
- Most likely ion pair in close proximity to oxonium species





MAITOTOXIN. ^{13}C NMR DATA FOR THE QRSTU DOMAIN





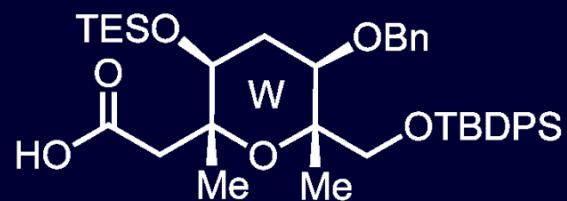
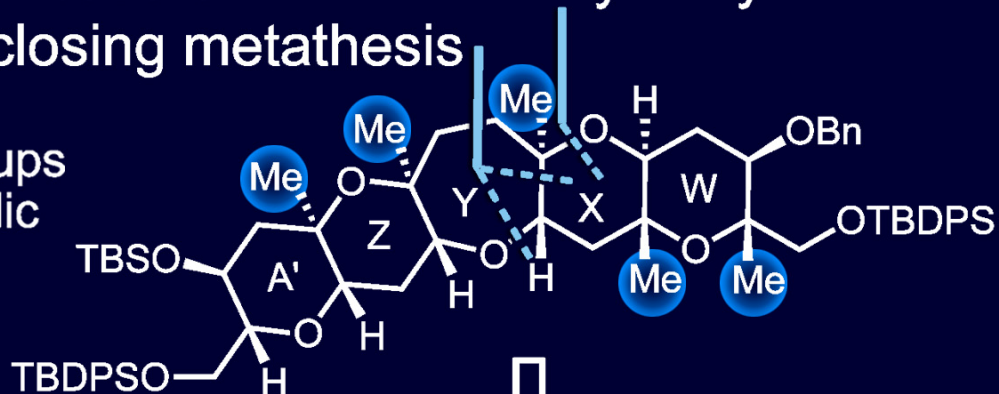
RETROSYNTHETIC ANALYSIS OF MAITOTOXIN WXYZA' RING SYSTEM



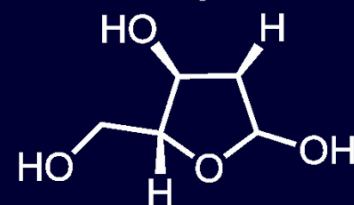
Esterification/
ring-closing metathesis

Hydroxy dithioketal cyclization/
methylation

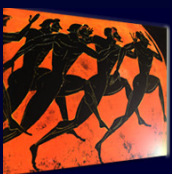
● 5 angular Me groups within a pentacyclic system



2-deoxy-D-ribose



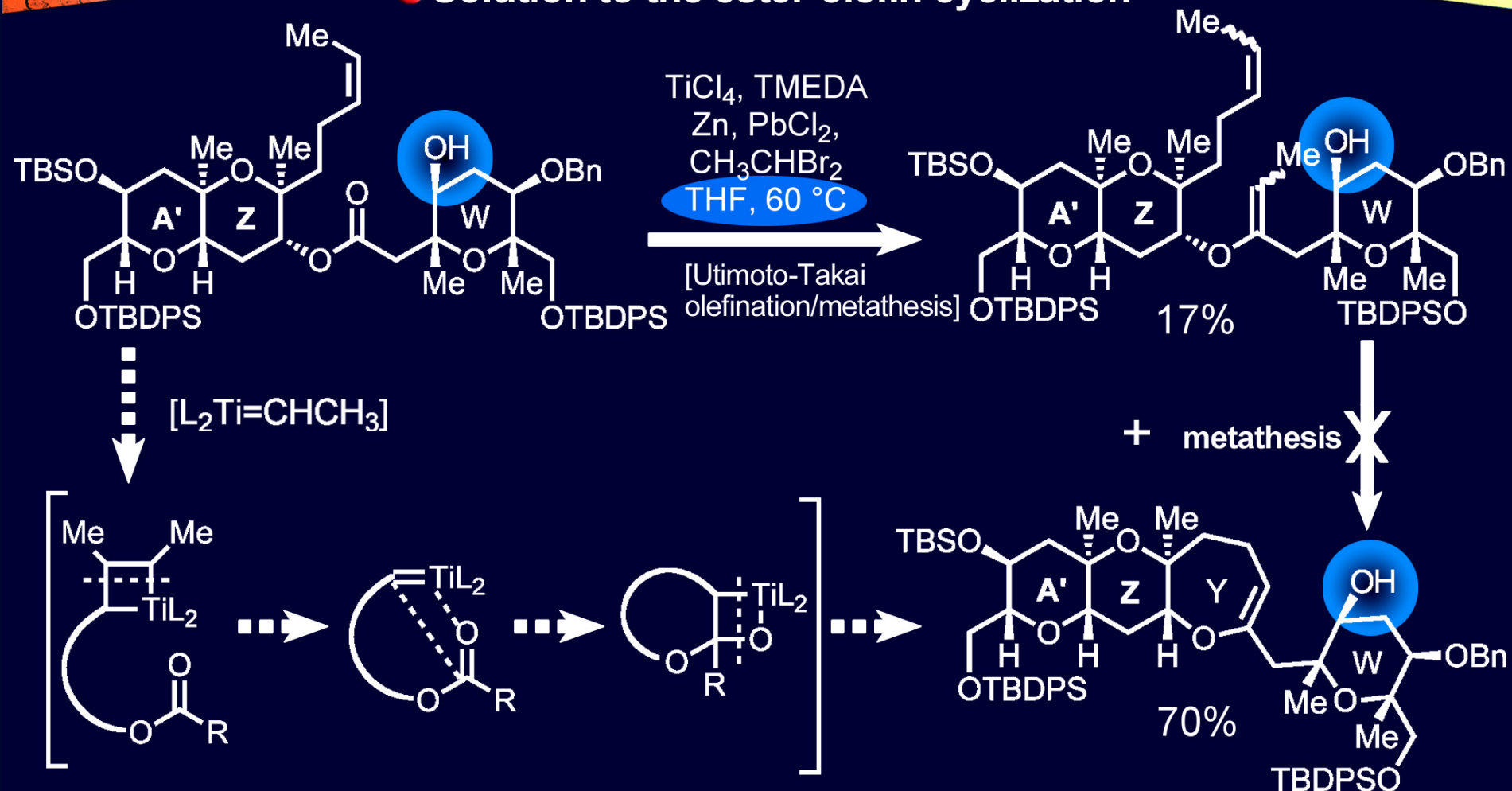




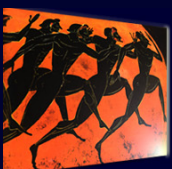
MAITOTOXIN. CONSTRUCTION OF THE A'ZYW RING SYSTEM



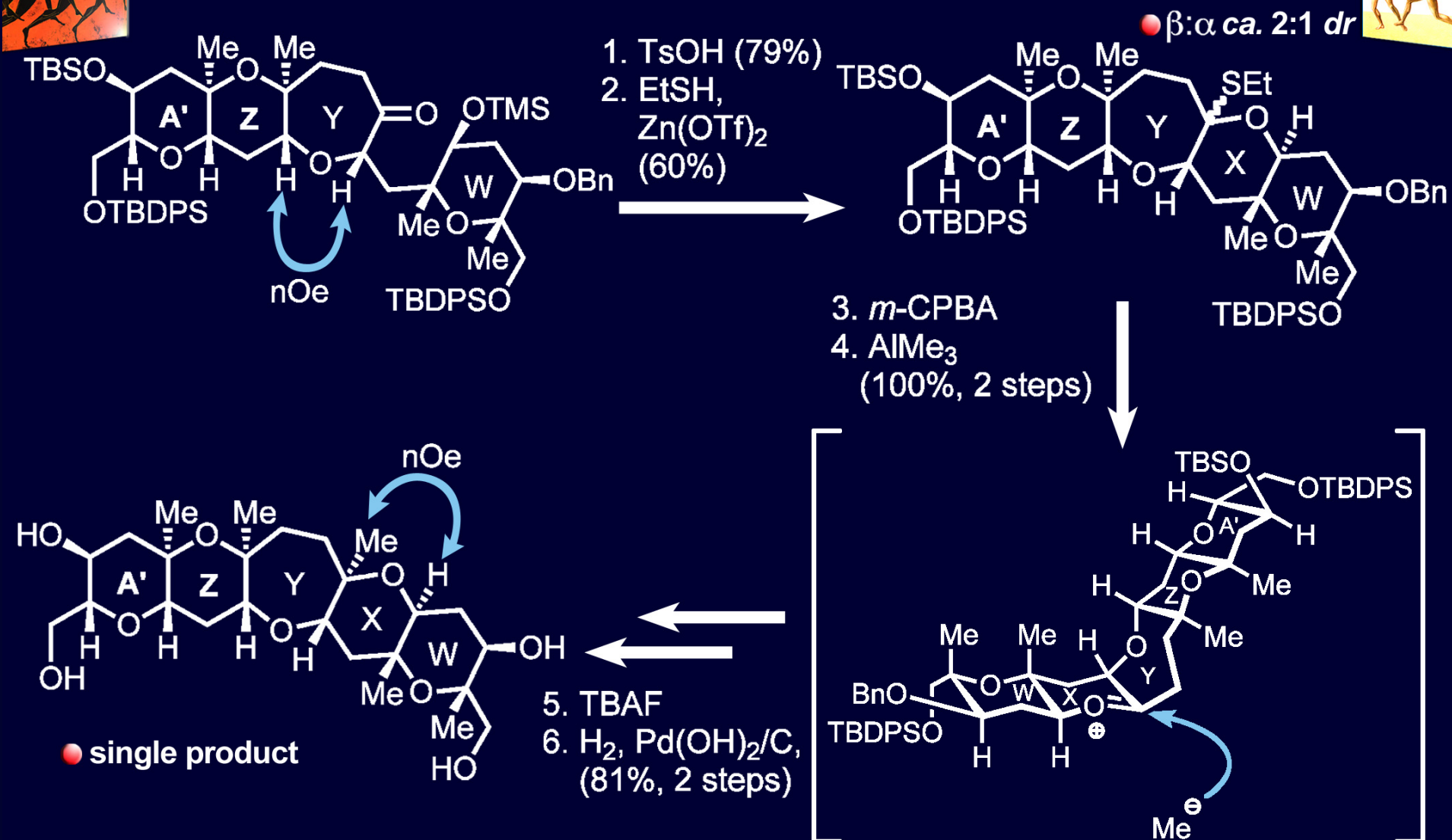
● Solution to the ester-olefin cyclization



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

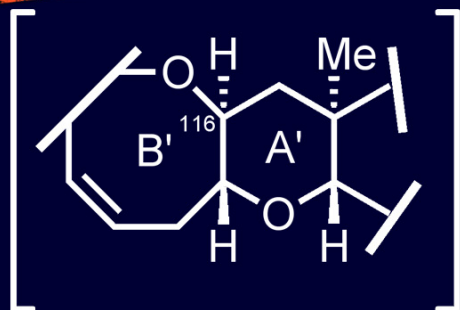


MAITOTOXIN. CONSTRUCTION OF THE A'ZYXW RING SYSTEM

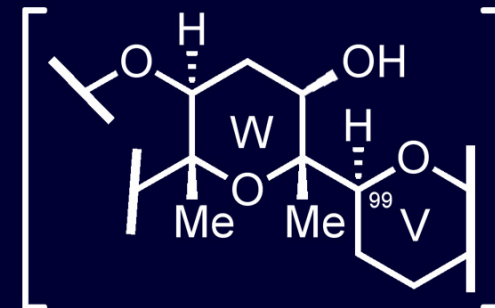
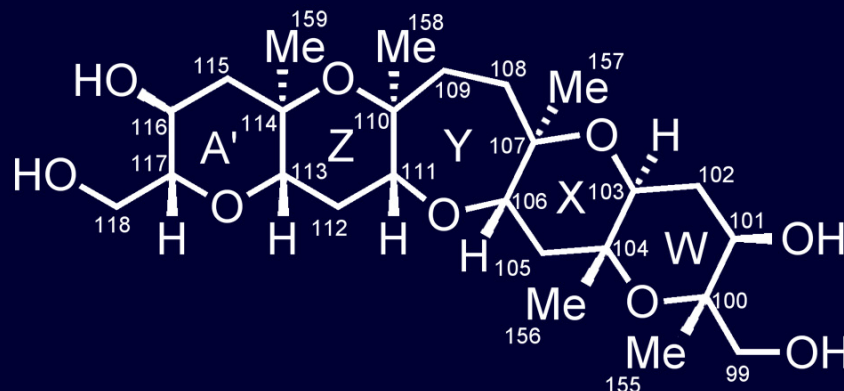




MAITOTOXIN. ^{13}C DATA FOR THE WXYZA' DOMAIN

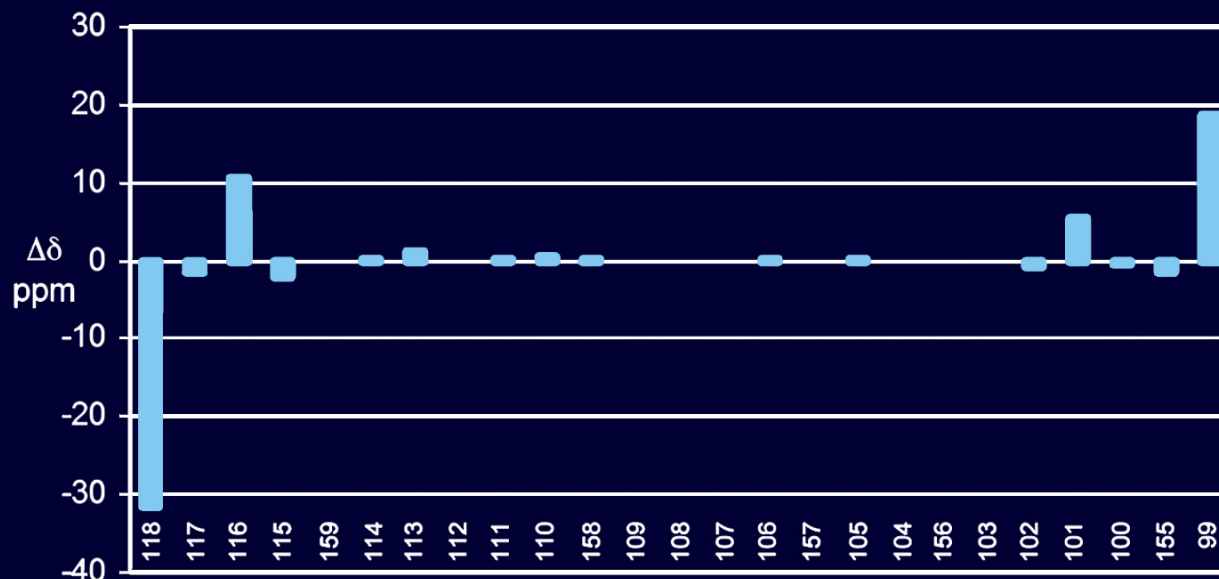


maitotoxin structure



maitotoxin structure

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

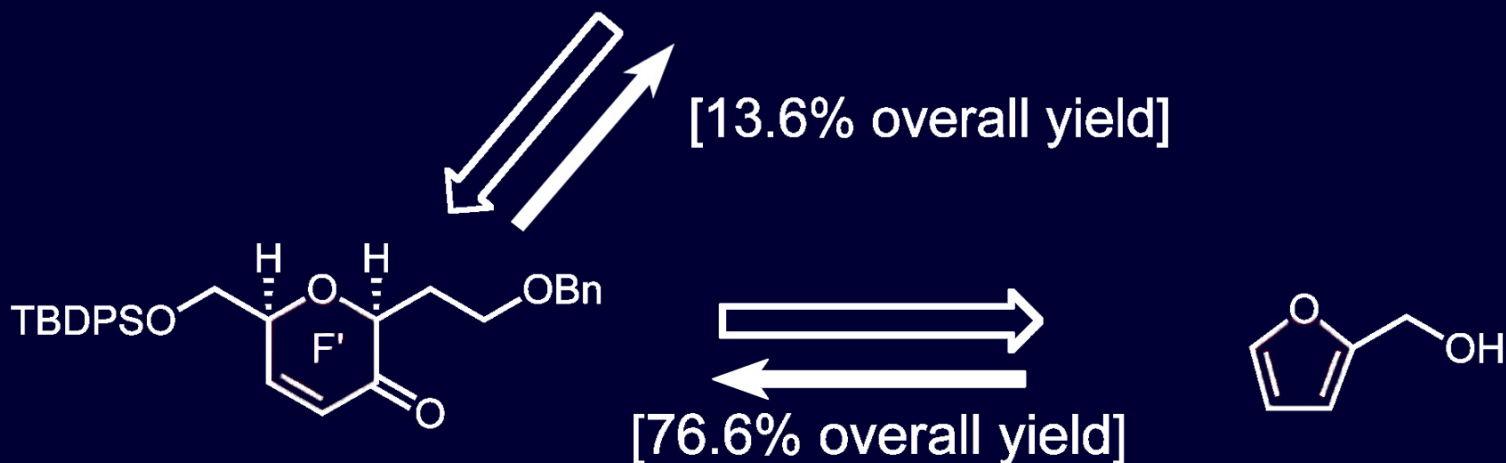
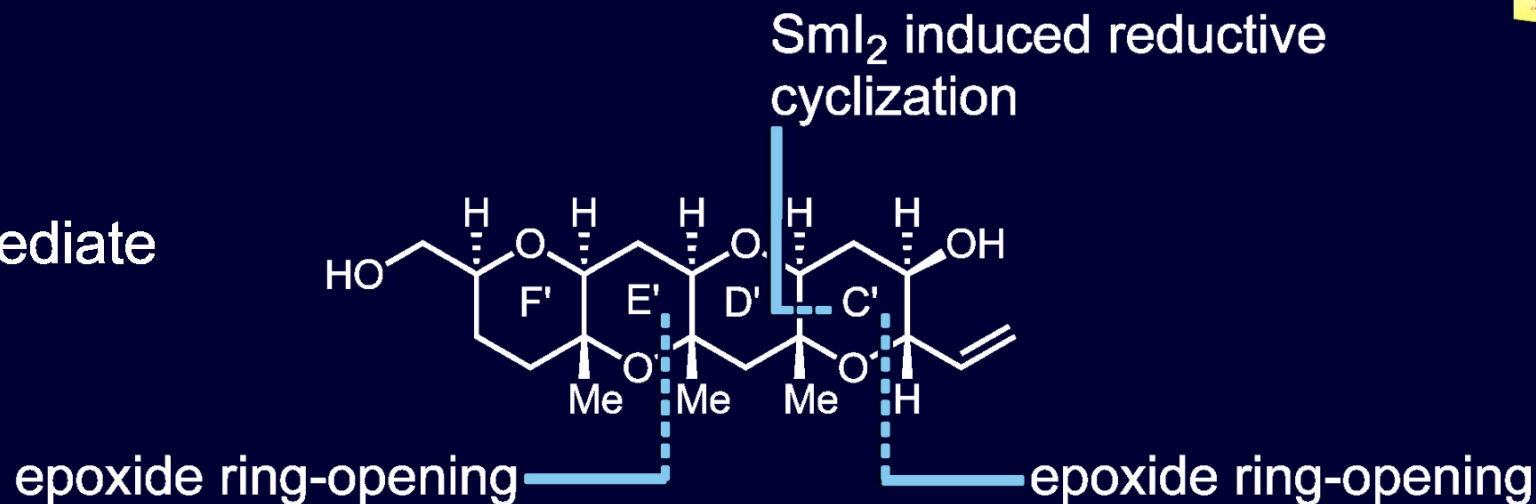


● Larger $\Delta\delta$ at the ends due to a greater degree of structural variation

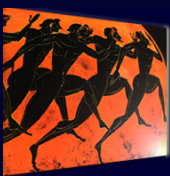
● Average $\Delta\delta$ for C102-C115 = 0.36 ppm. Largest $\Delta\delta$ for C102-C115 = 2.2 ppm

RETROSYNTHETIC ANALYSIS AND CONSTRUCTION OF MAITOTOXIN C'D'E'F' RING SYSTEM

intermediate



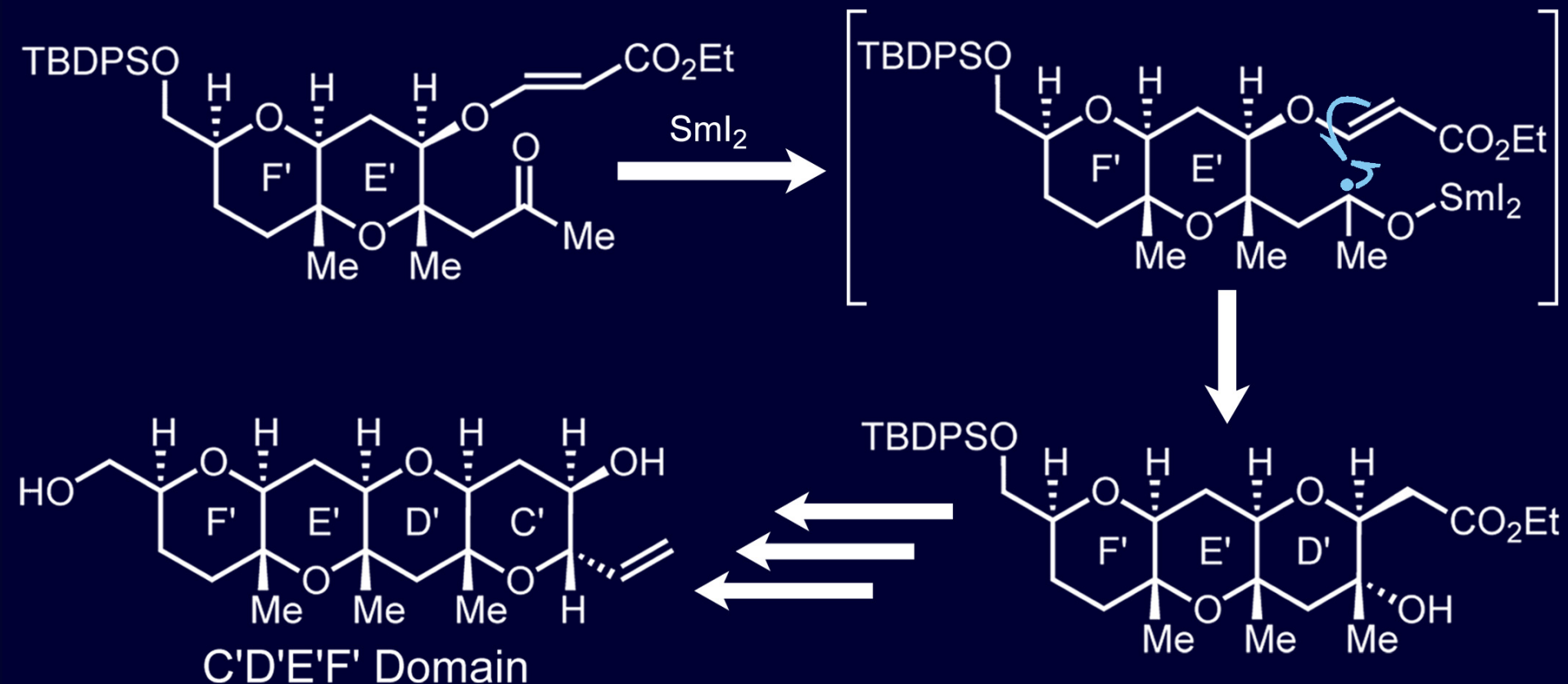
● F' ring intermediate is also used in the construction of ring systems A' and G



MAITOTOXIN. SYNTHESIS OF THE C'D'E'F' RING SYSTEM

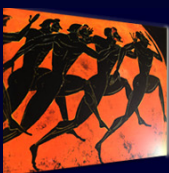


● Polyepoxide cascade failed to produce the desired tetracycle.

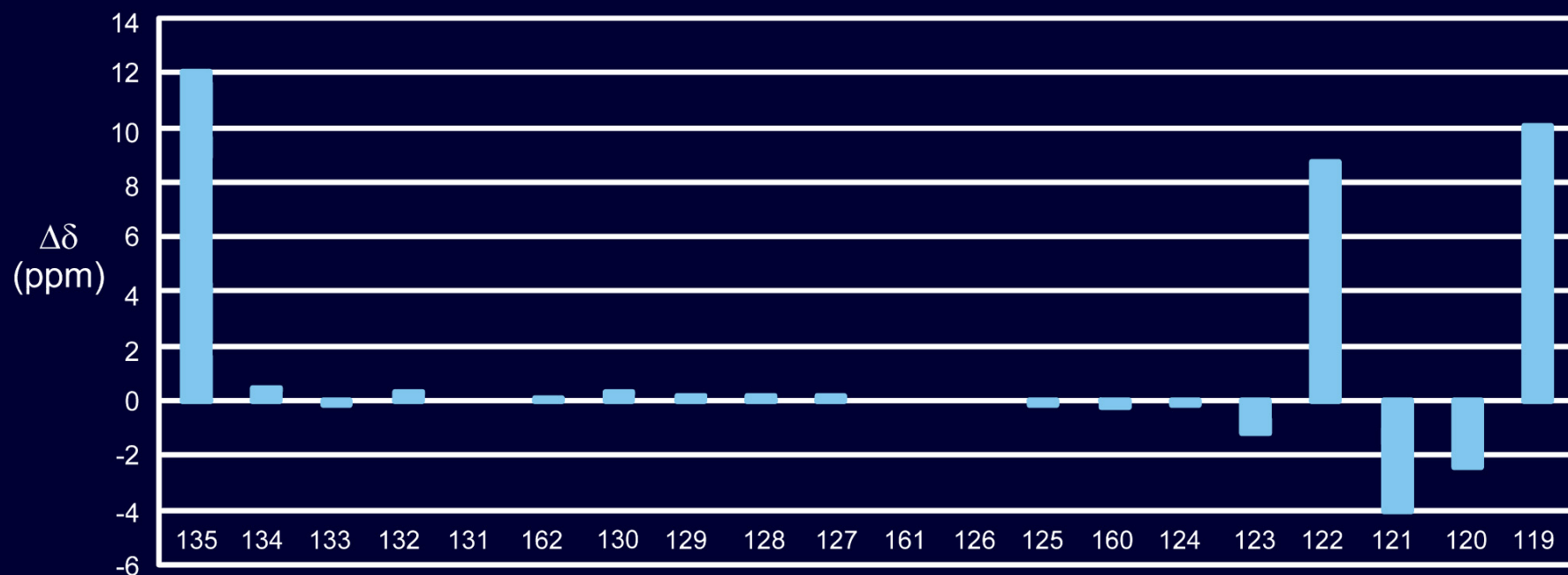
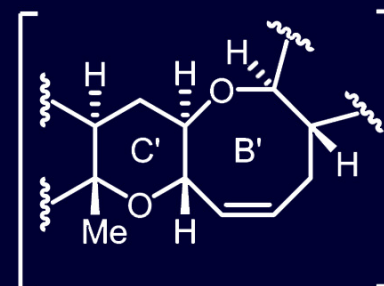
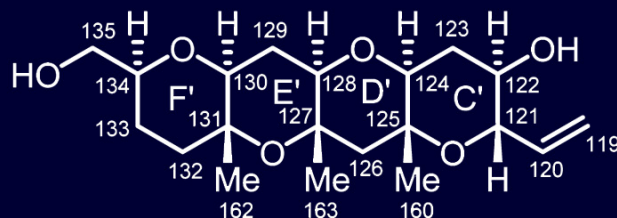
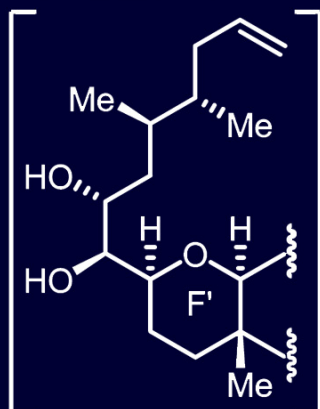


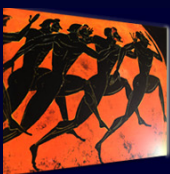
● Nakata's Sml_2 -induced reductive cyclization method

See: Hori, N.; Matsukura, K.; Matsu, G.; Nakata, T. *Tetrahedron Lett.* 1999, 40, 2811;
Nicolaou, K. C.; Seo, J. H.; Nakamura, T.; Aversa, R. *J. Am. Chem. Soc.* 2011, 133, 214.



MAITOTOXIN. ^{13}C NMR COMPARISON FOR THE C'D'E'F' DOMAIN

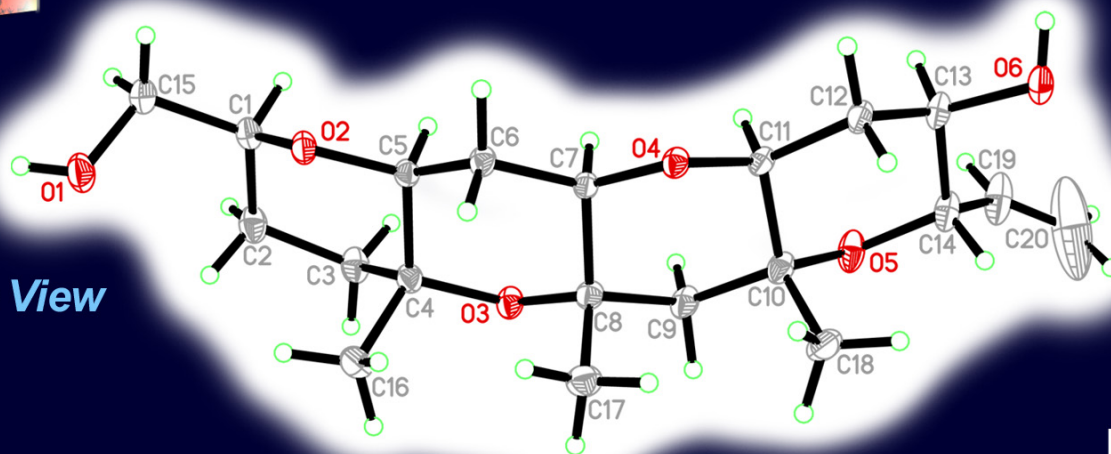




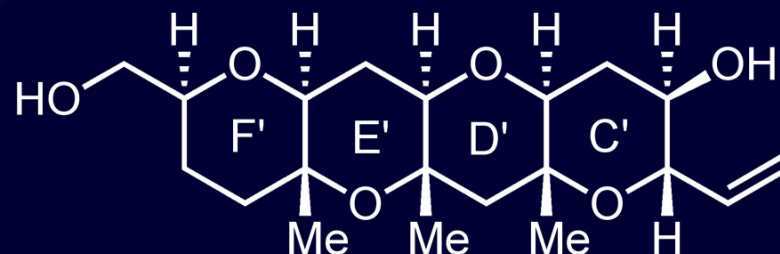
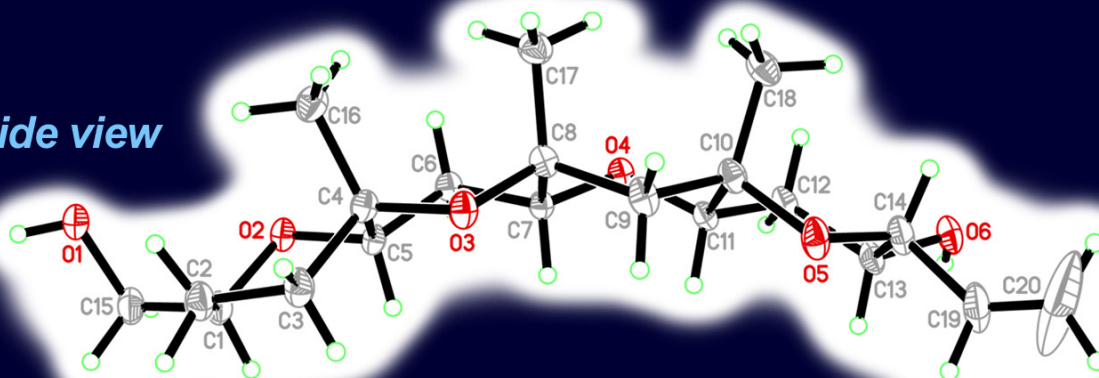
X-RAY STRUCTURE OF C'D'E'F' MAITOTOXIN DOMAIN



Top View



Side view

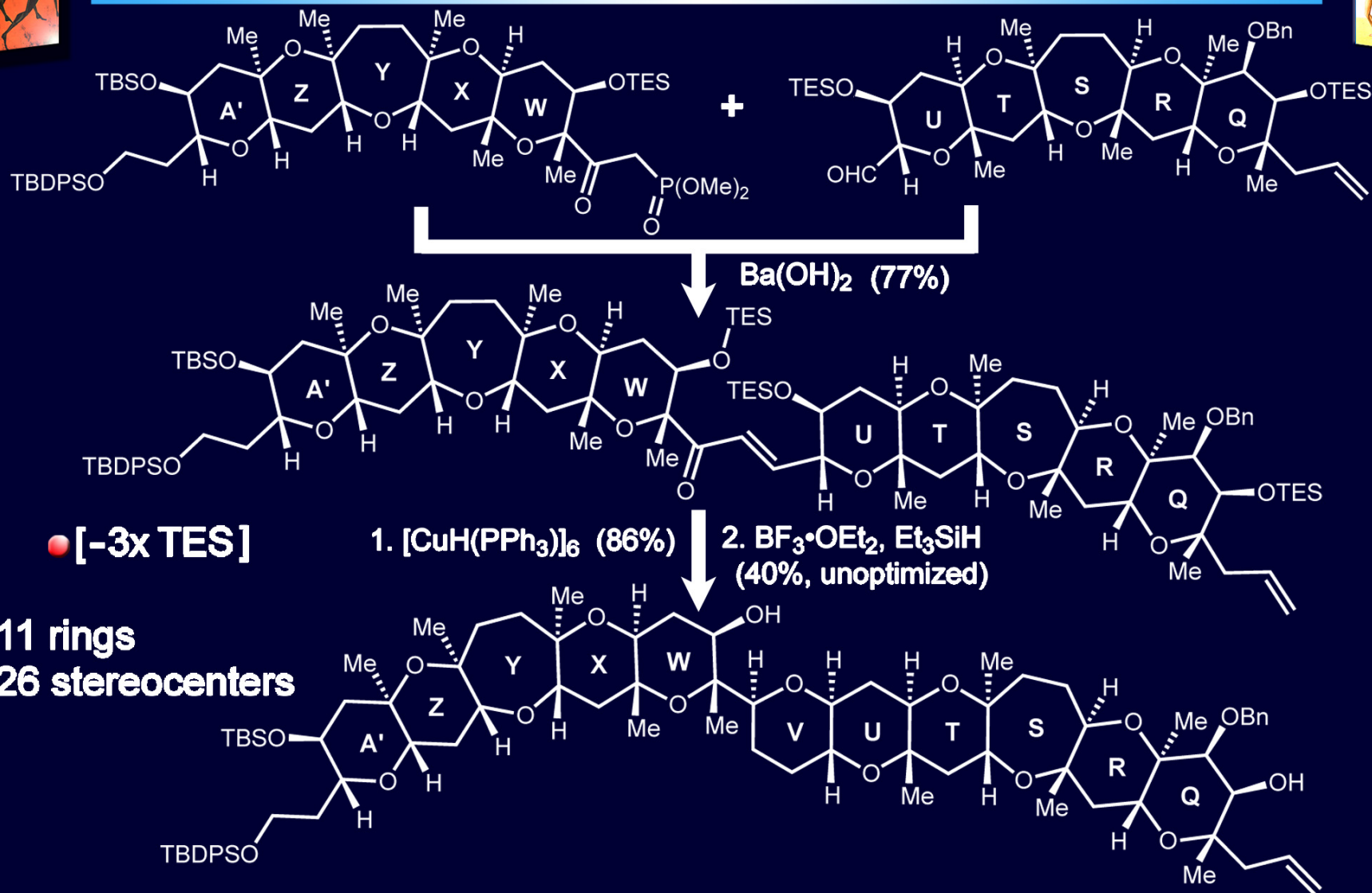


$$d(C_1-C_{13}) = 9.19 \text{ \AA}; d(C_2-C_{13}) = 9.49 \text{ \AA}; d(H_{1A}-H_{13}) = 8.58 \text{ \AA};$$

$$d(H_{2A}-H_{14}) = 10.45 \text{ \AA}; \alpha(C_{14}-C_8-C_2) = 146.42^\circ; \alpha(C_{13}-C_7-C_1) = 153.04^\circ$$

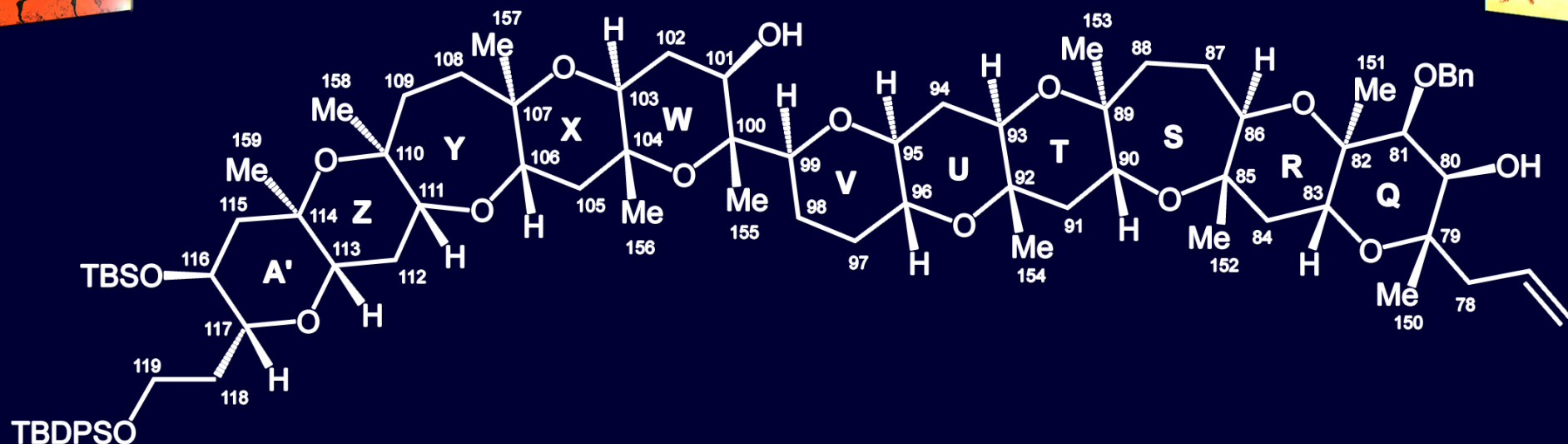


Maitotoxin: Synthesis of QRSTUVWXYZA' Domain

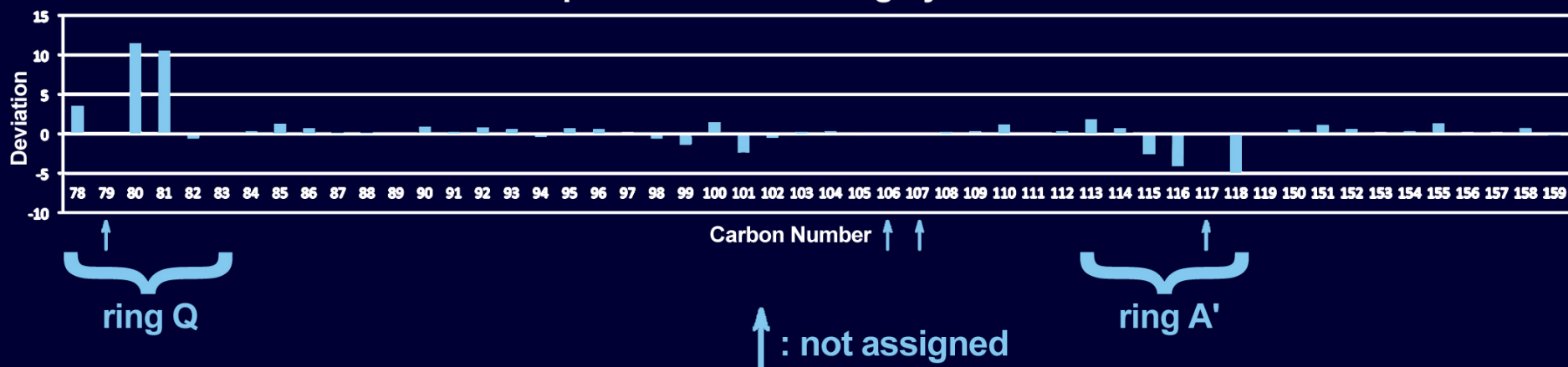


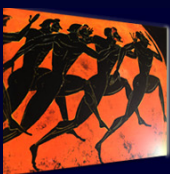


Maitotoxin: Q-A' structure

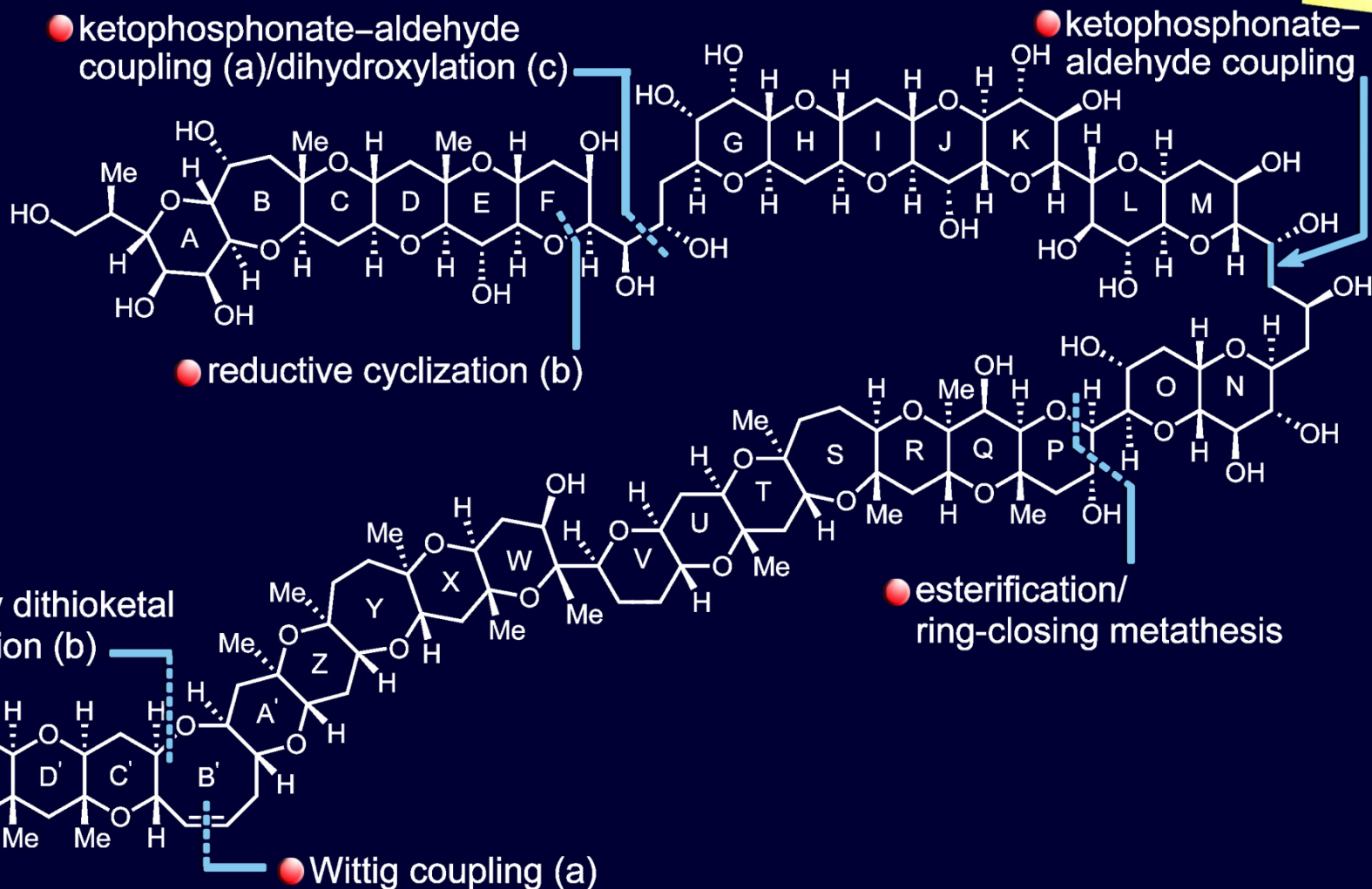


● Carbon Data Comparison of Q - A' Ring System and Natural Maitotoxin





MAITOTOXIN POLYCYCLIC FRAMEWORK: FINAL COUPLINGS AND RING CLOSURES



● Cell exterior

● Hydrophilic environment

● Cell surface

● Cell membrane

● Lipophilic environment

● Cell interior

● C₁–C₈₁ domain
[hydrophilic, 24 hydroxyl
and 2 sulfate groups]

Sulfate

OH

Ring A

Sulfate

C₁

C₈₁

C₈₂

Ring Q

OH

Ring F'

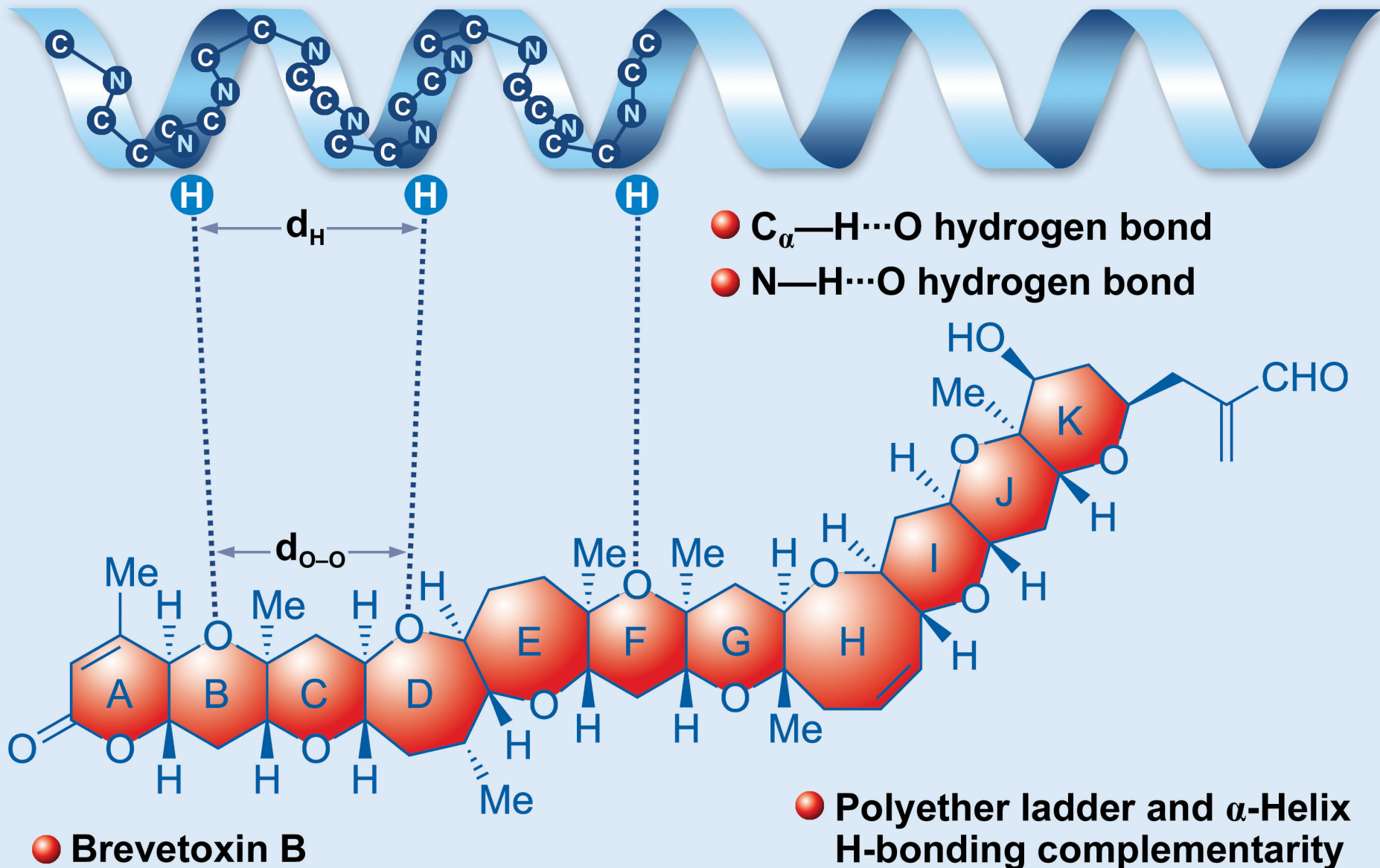
C₁₄₂

● C₈₂–C₁₄₂ domain
[lipophilic, 3 hydroxyl groups]

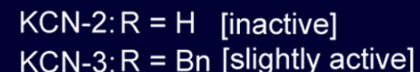
● α -Helix pitch, $d_H = 5.40 \text{ \AA}$

● Average O—O distance between same-side ether oxygen atoms within the brevetoxin B ladder, $d_{O-O} = 5.15 \text{ \AA}$

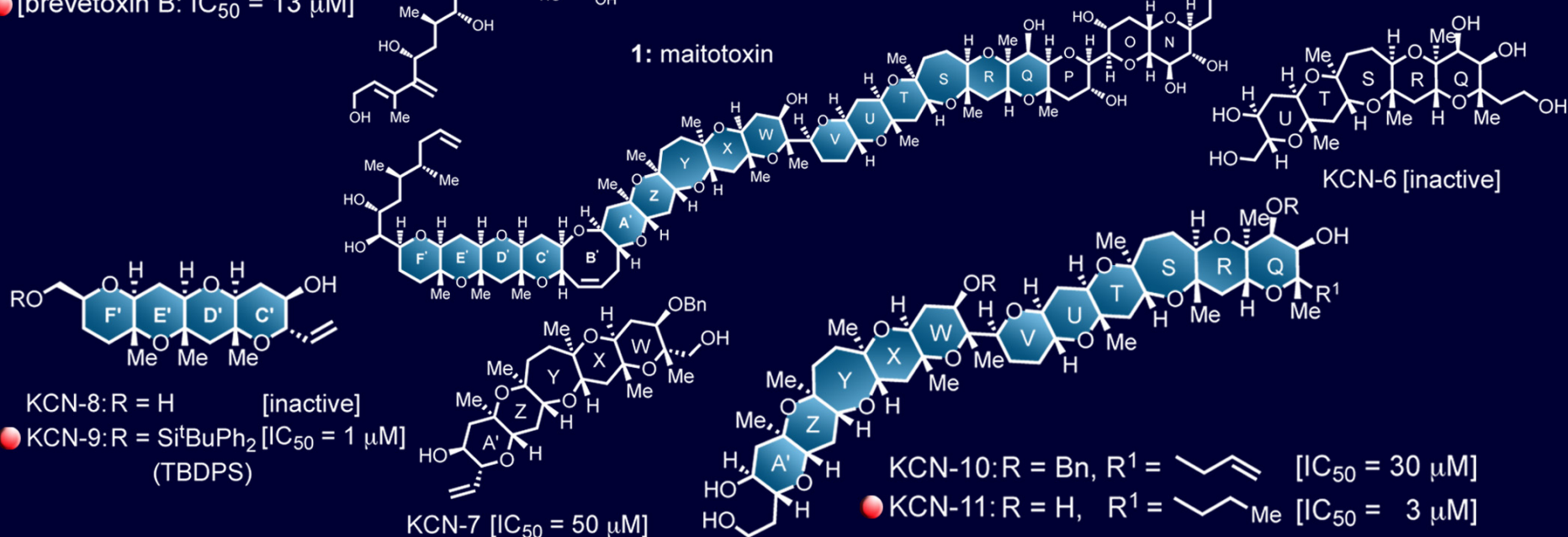
● α -Helix



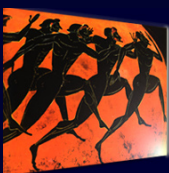
A black and white photograph of a large mural. The mural features several dark, stylized human figures in various dynamic poses, appearing to be running or dancing. They are set against a bright, textured, light-colored background. The figures are rendered in a high-contrast, almost silhouette-like style. The overall composition is energetic and rhythmic.



- d**
-
- Chemical structure of compound 10, a long-chain polyol. The structure is labeled with letters A through M and numbers 1 through 14. The sodium sulfate group is attached to carbon 1. The structure is shown in a perspective view with stereochemistry indicated by wedges and dashes.



- Compounds were tested for their ability to inhibit MTX-elicited $^{45}\text{Ca}^{2+}$ influx in rat C6 glioma cells
- Professor Keiichi Konoki, Tohoku University, Japan



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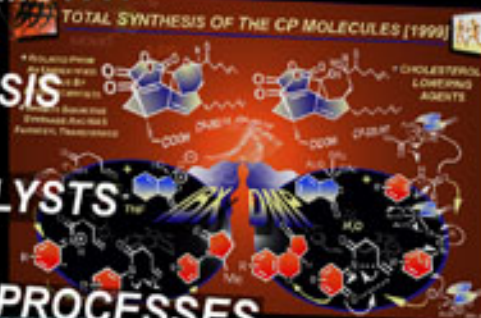
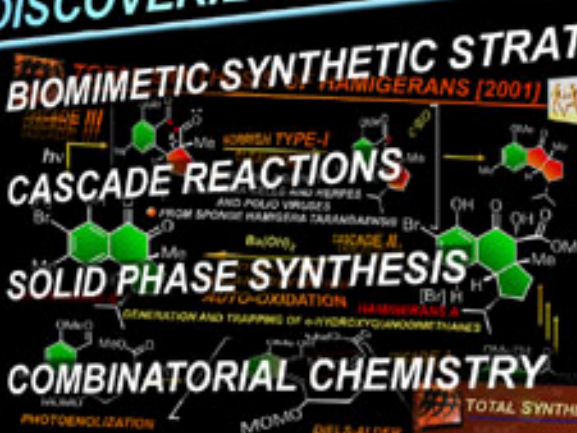
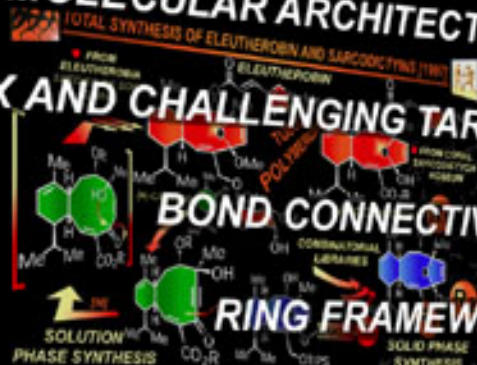
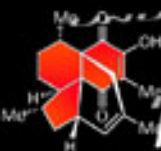
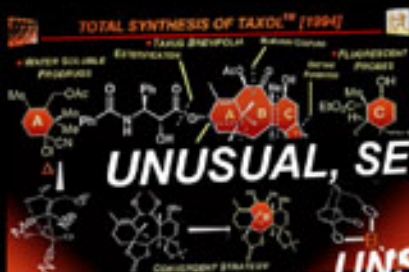
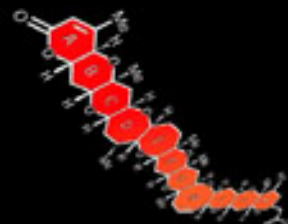
● ASYMMETRIC SYNTHESIS

● REAGENTS AND CATALYSTS

EFFICIENT CHEMICAL PROCESSES

GREEN CHEMISTRY

DESIGNED BIOACTIVE MOLECULES





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