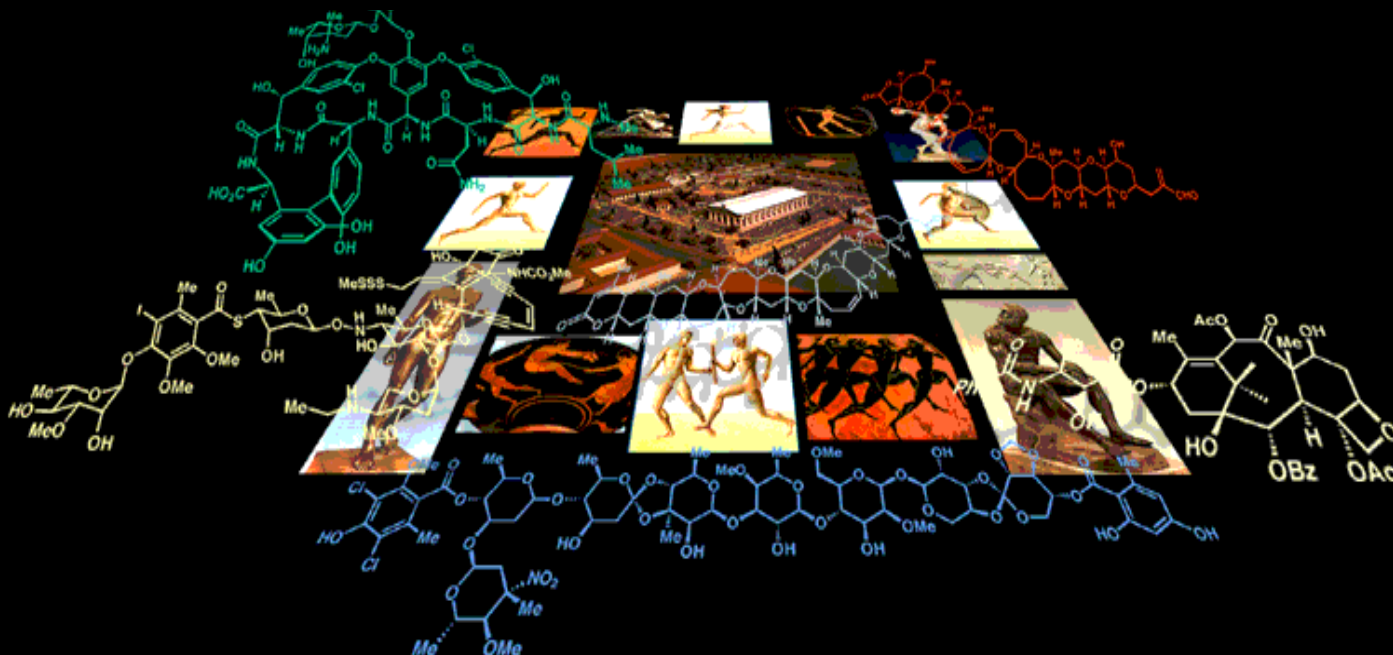


Visit us at scripps.edu/nicolaou

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

Enjoy the tour of our world.



PACIFICHEM 2010

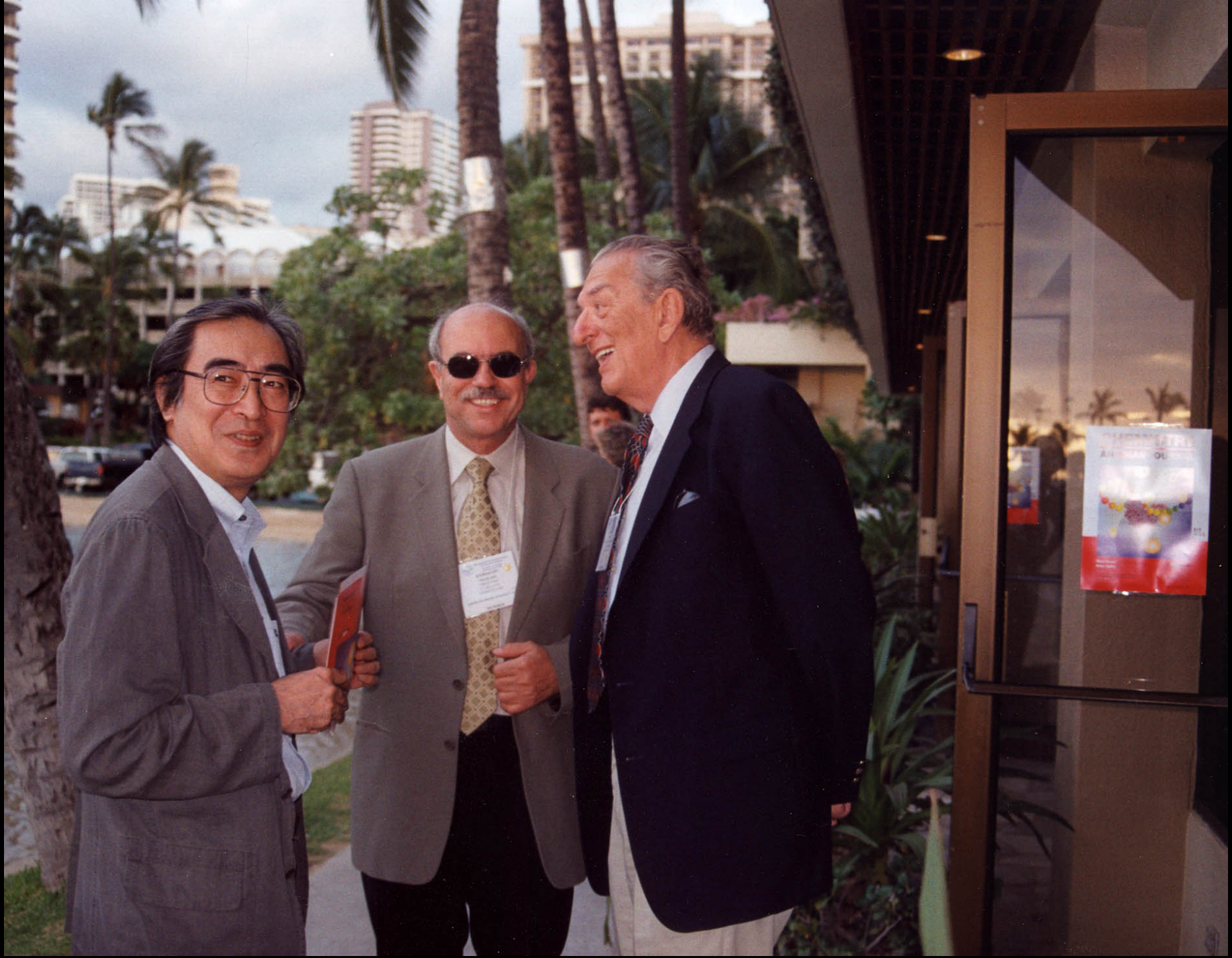
**Honolulu, Hawaii
December 17, 2010**

K.C. Nicolaou, Ph.D.

*The Scripps Research Institute
and*

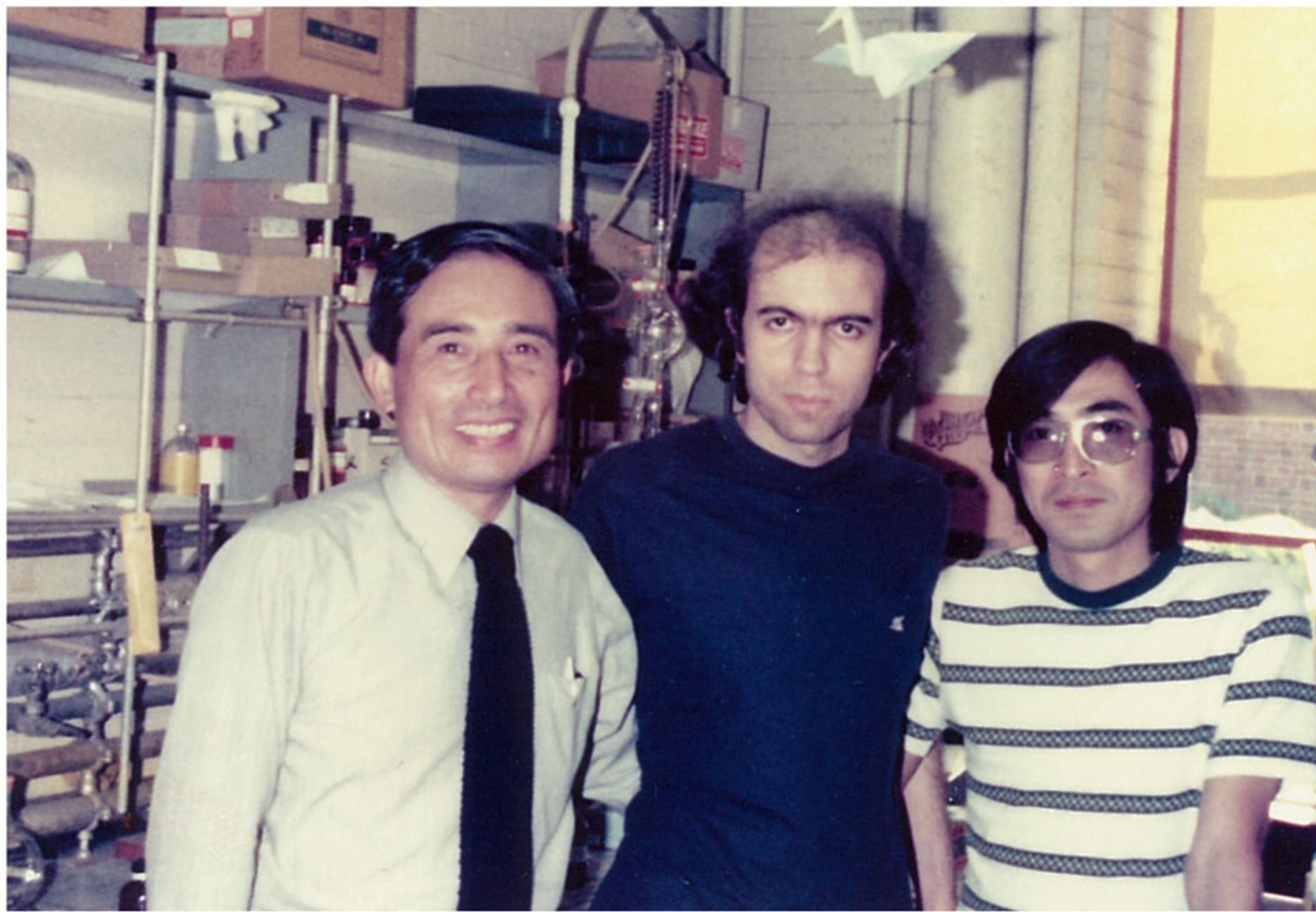
University of California, San Diego

***“Catalysis in Total Synthesis:
The Marine Polyether Biotoxins”***



THE 2004
ANNUAL OIL
REPORT









大助照焼
大助塩焼



Synthesis and the Molecule in Perspective



- The advent of *organic synthesis* coupled with the discovery of the *molecule* in the 19th century is one of the most profound scientific developments of all time.
 - These discoveries set in motion a revolution that shaped the landscape of the molecular sciences and changed the world.
 - The atomic-molecular theory of matter and the art and science of synthesis provided the foundation for understanding and shaping nature at the molecular level.
-



THE ESSENCE OF TOTAL SYNTHESIS



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



THE ART OF TOTAL SYNTHESIS



“But a deeper and more careful inquiry reveals to us that absolutely new ideas are of the very rarest occurrence; almost the whole work of human genius consists in assimilating what others have thought, in combining what others have imagined separate, in recasting the form of their thought, and so producing what seems a perfectly new thing, and yet is only the old under a new aspect. No instance of this is more signal than that of a great composer in music (in total synthesis). The gift of original melody (synthesis), as it is called is rare and precious. The possessor of it is justly considered a genius. But no melody could possibly speak to us except a combination of perfectly well known elements. The only originality is in their assimilation and reproduction.”

J. P. Mahaffy, 1910

J. P. Mahaffy, *What Have the Greeks Done for Modern Civilisation*, G. P. Putnam's Sons, New York, 1910, pp. 214–215, 246–247. *see Alfred, Lord Tennyson, “Locksley Hall” 1835.



THE ART OF TOTAL SYNTHESIS



“...the theory of composing words (molecules) is easy enough, and yet the art a mystery, which only very few can ever attain in perfection,—each, too, after his own fashion, and stamped with his own genius,—so the theory of conversation (total synthesis) may be reduced to a small number of general observations, and yet the perfect practice of it is a mystery, which defies analysis—one of the myriad manifestations of human genius which all can admire but no one can ever explain.”

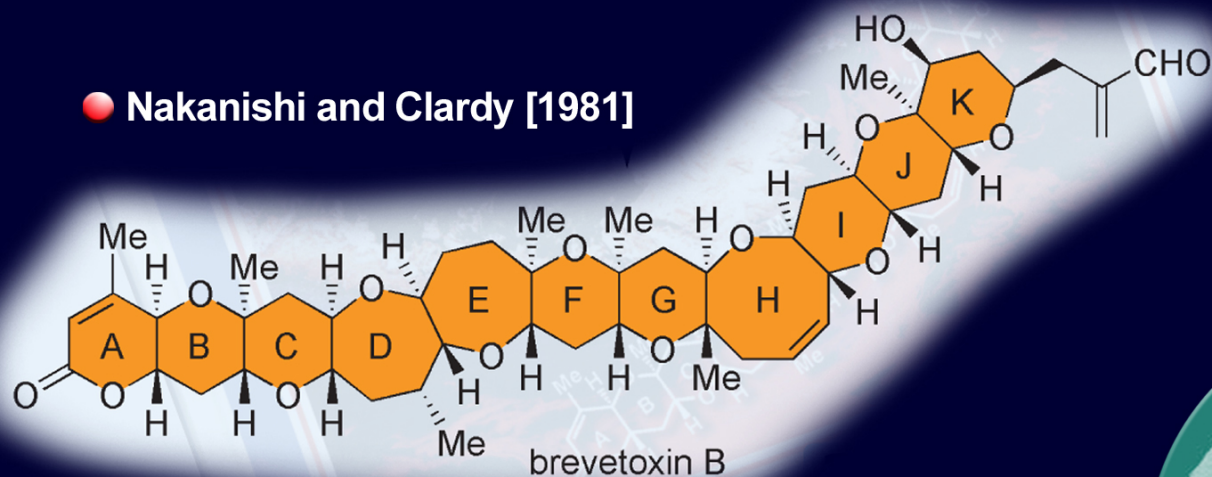
J. P. Mahaffy, 1887



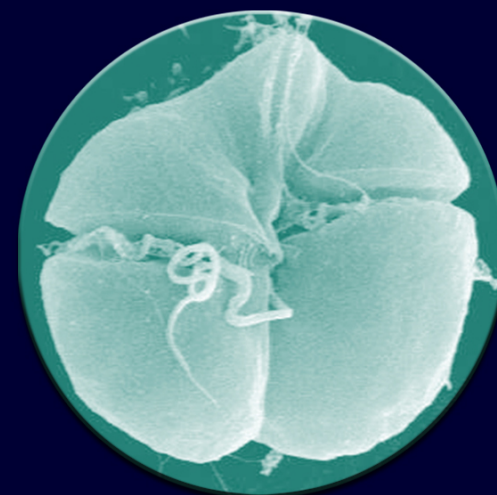
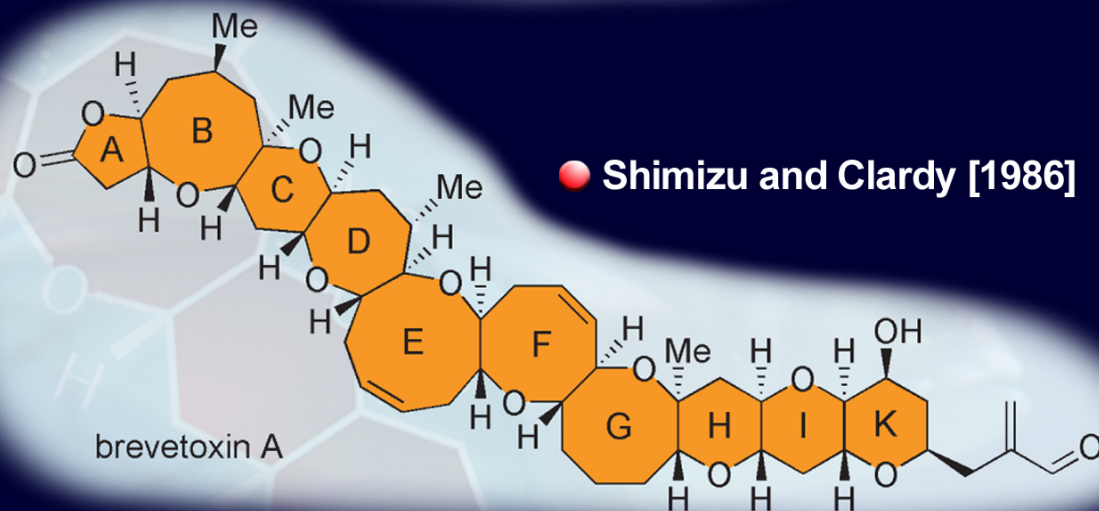
BREVETOXIN B AND BREVETOXIN A



● Nakanishi and Clardy [1981]



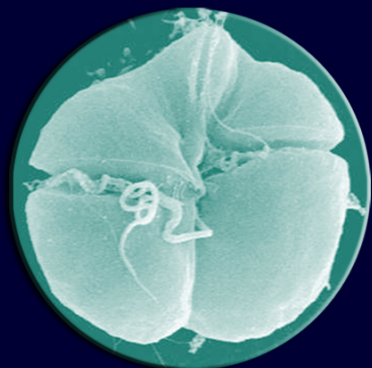
● Shimizu and Clardy [1986]



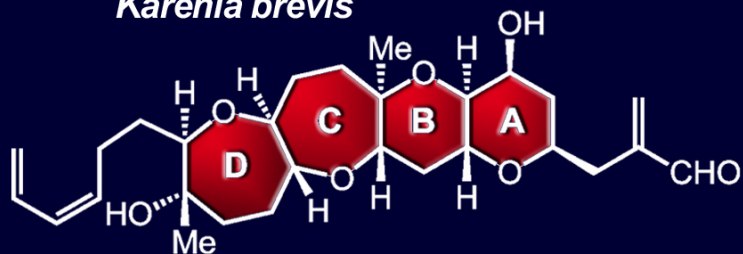
Karenia brevis



POLYETHER MARINE BIOTOXINS SYNTHESIZED TO DATE, 2008, I



Karenia brevis



hemibrevetoxin

[Nicolaou et al., 1992]

[Yamamoto et al., 1995, 2007]

[Nakata et al., 1996]

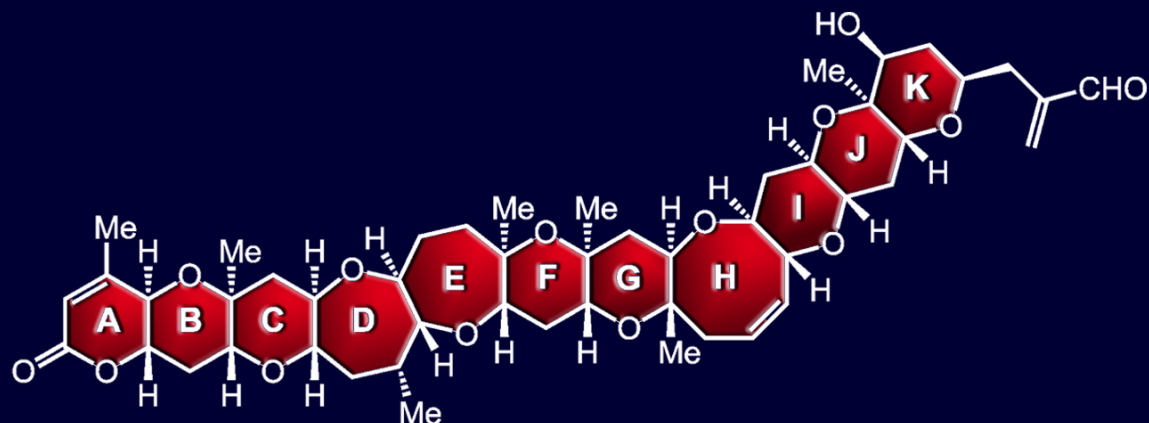
[Mori et al. (formal), 1997]

[Rainier et al. (formal), 2001]

[Nelson et al. (formal), 2001]

[Holton et al., 2003]

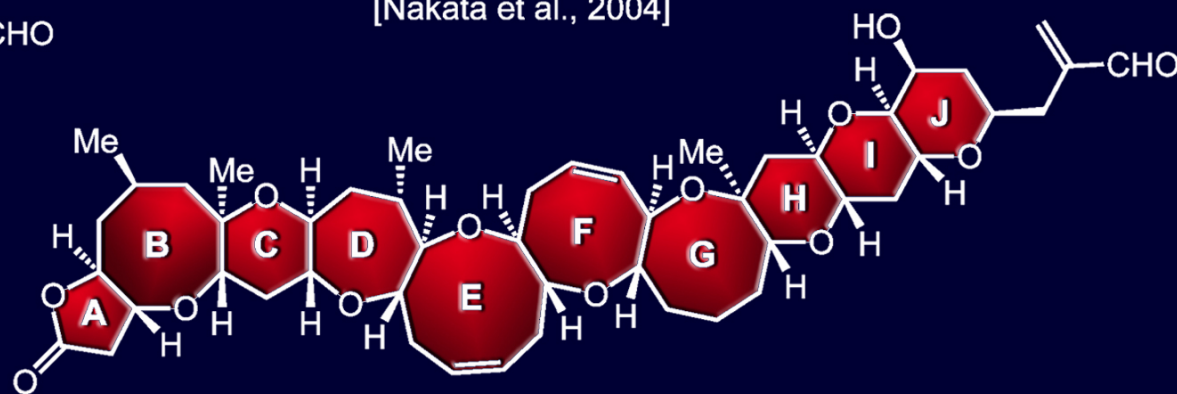
[Fujiwara et al. (formal), 2004]



brevetoxin B

[Nicolaou et al., 1995]

[Nakata et al., 2004]



brevetoxin A

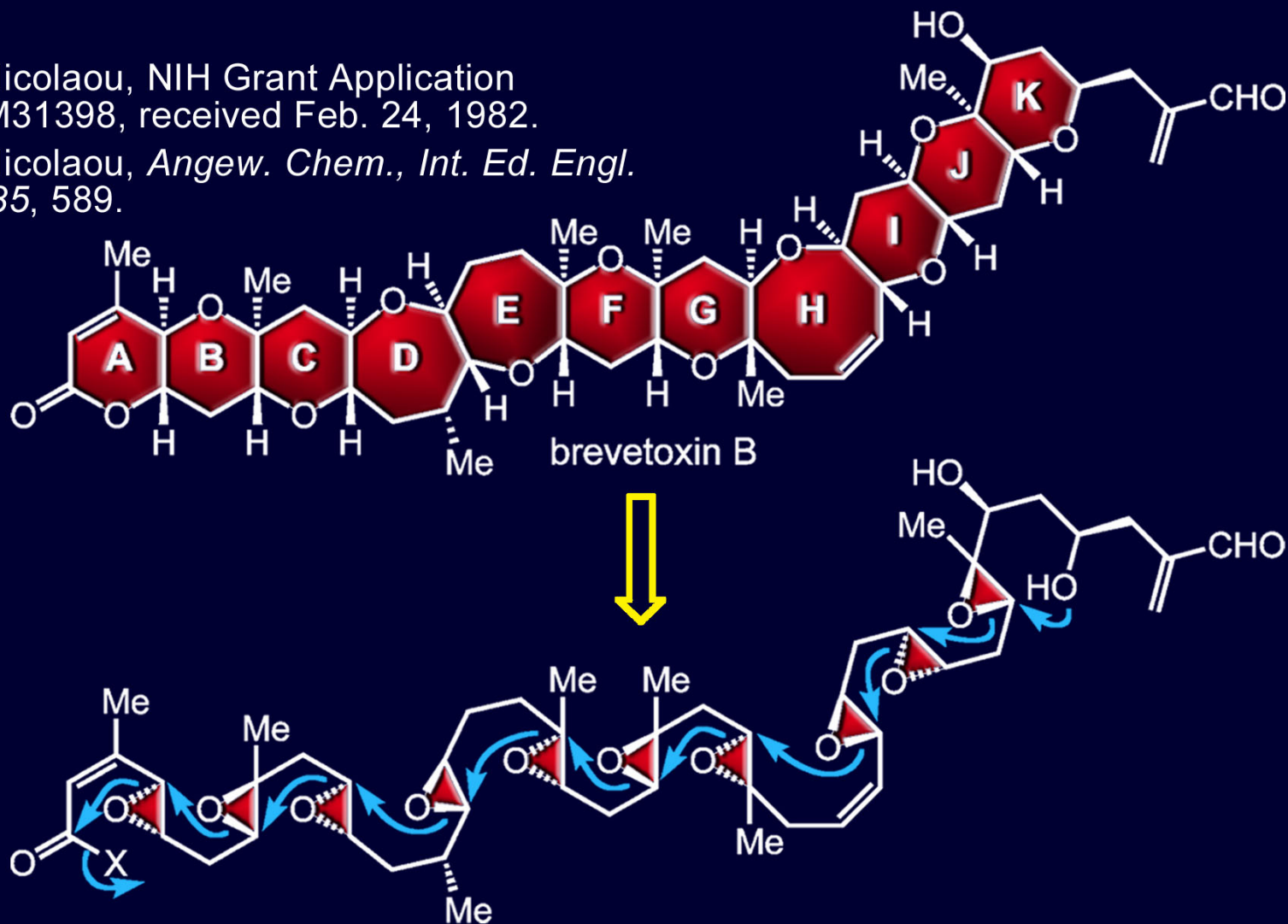
[Nicolaou et al., 1998]



RETROSYNTHETIC ANALYSIS OF BREVETOXIN B [1982]



- K. C. Nicolaou, NIH Grant Application No. GM31398, received Feb. 24, 1982.
- K. C. Nicolaou, *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 589.

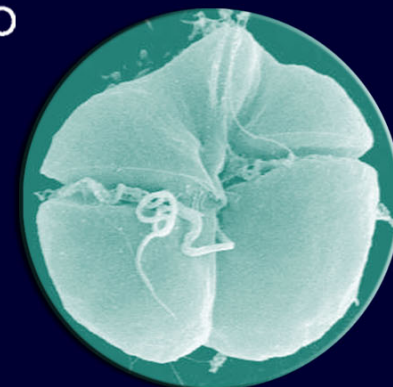
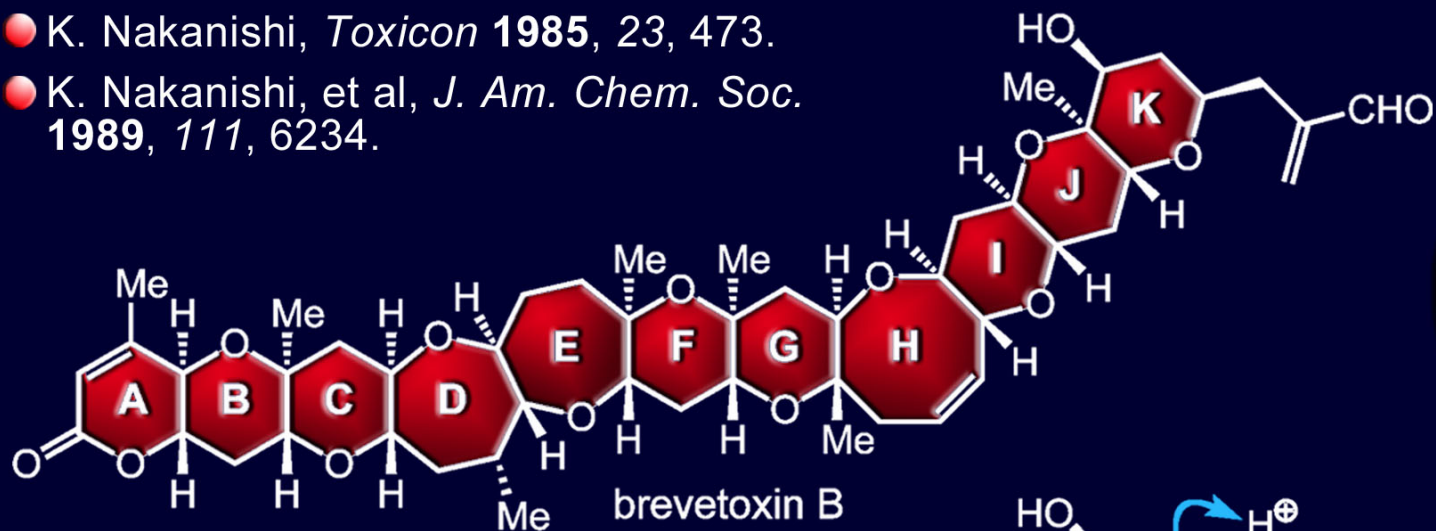




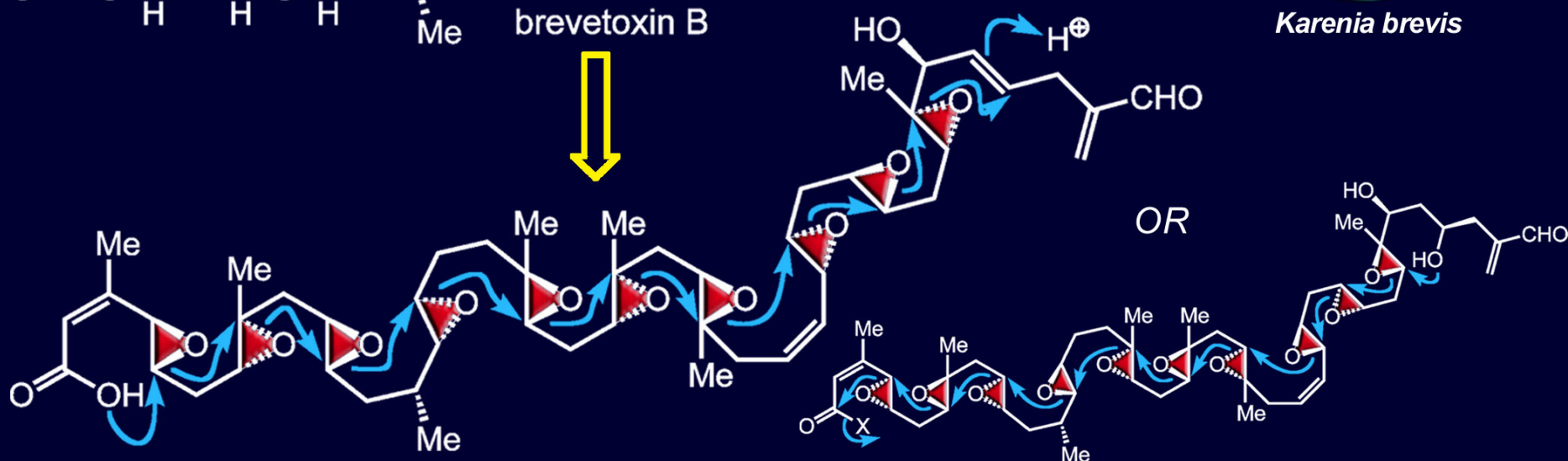
THE NAKANISHI HYPOTHESIS FOR THE BIOSYNTHESIS OF BREVETOXIN B [1985]



- K. Nakanishi, *Toxicon* **1985**, 23, 473.
- K. Nakanishi, et al, *J. Am. Chem. Soc.* **1989**, 111, 6234.

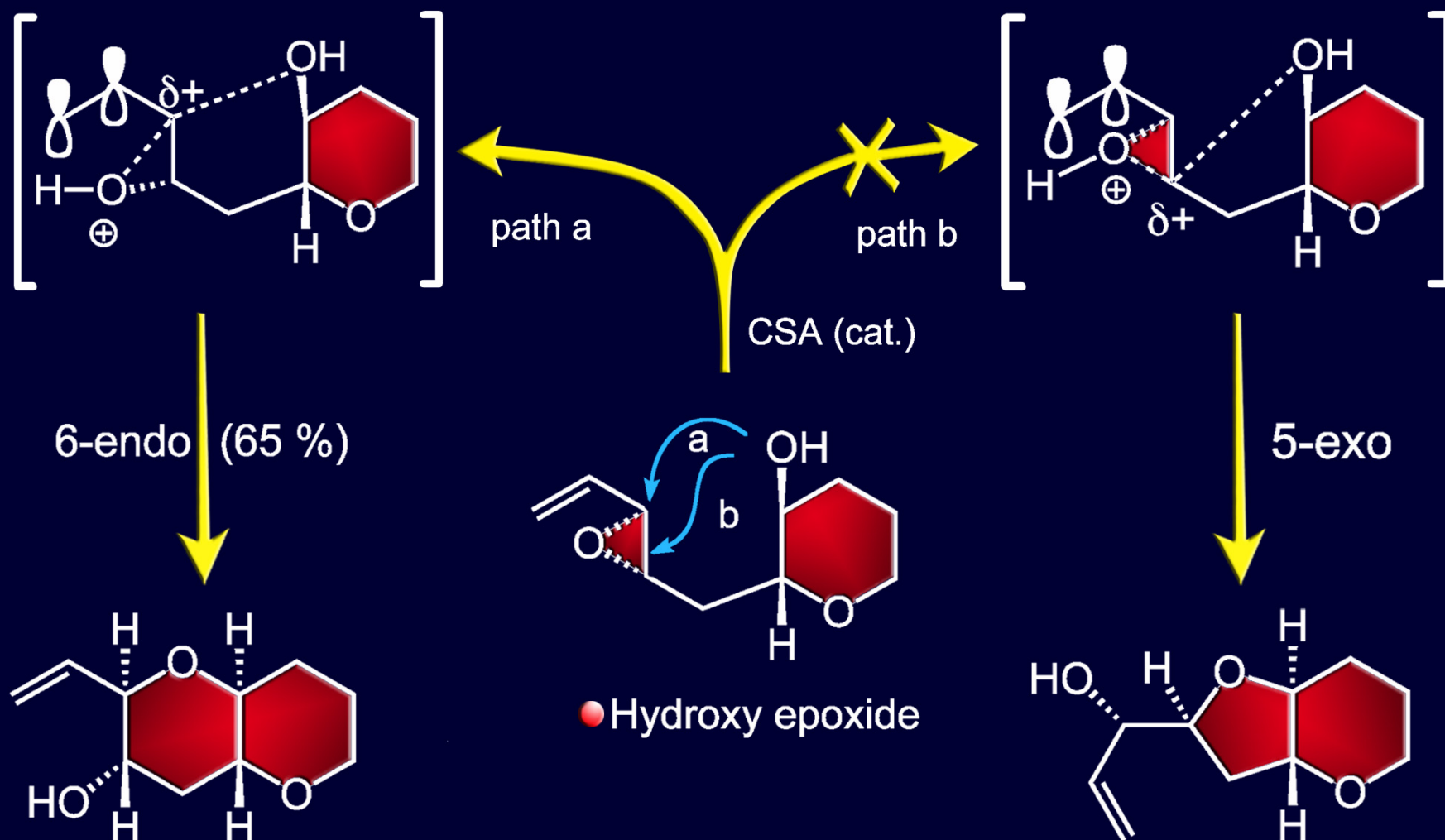


Karenia brevis



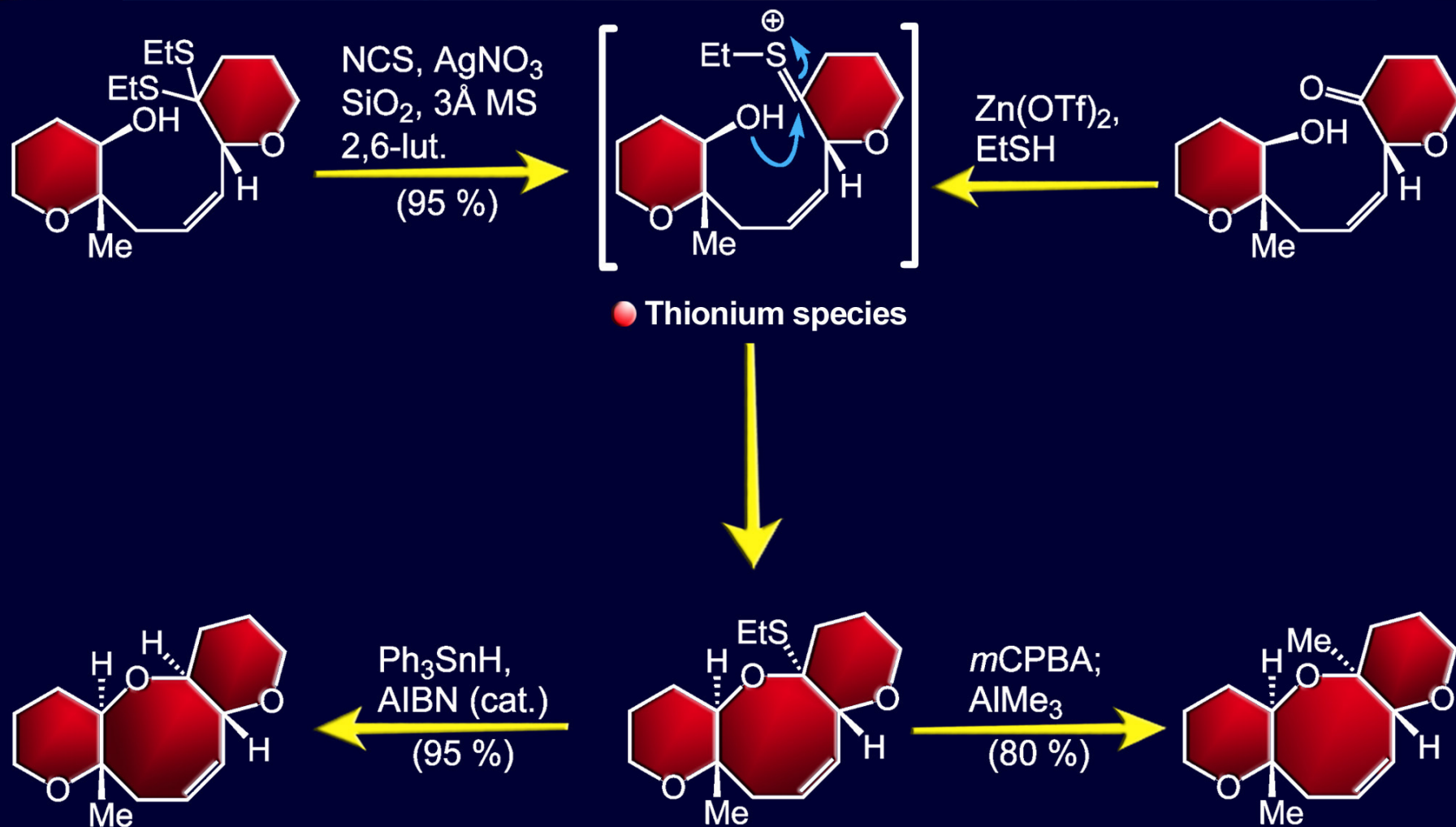


THE 6-ENDO EPOXIDE OPENING METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU *et al.*, 1985)



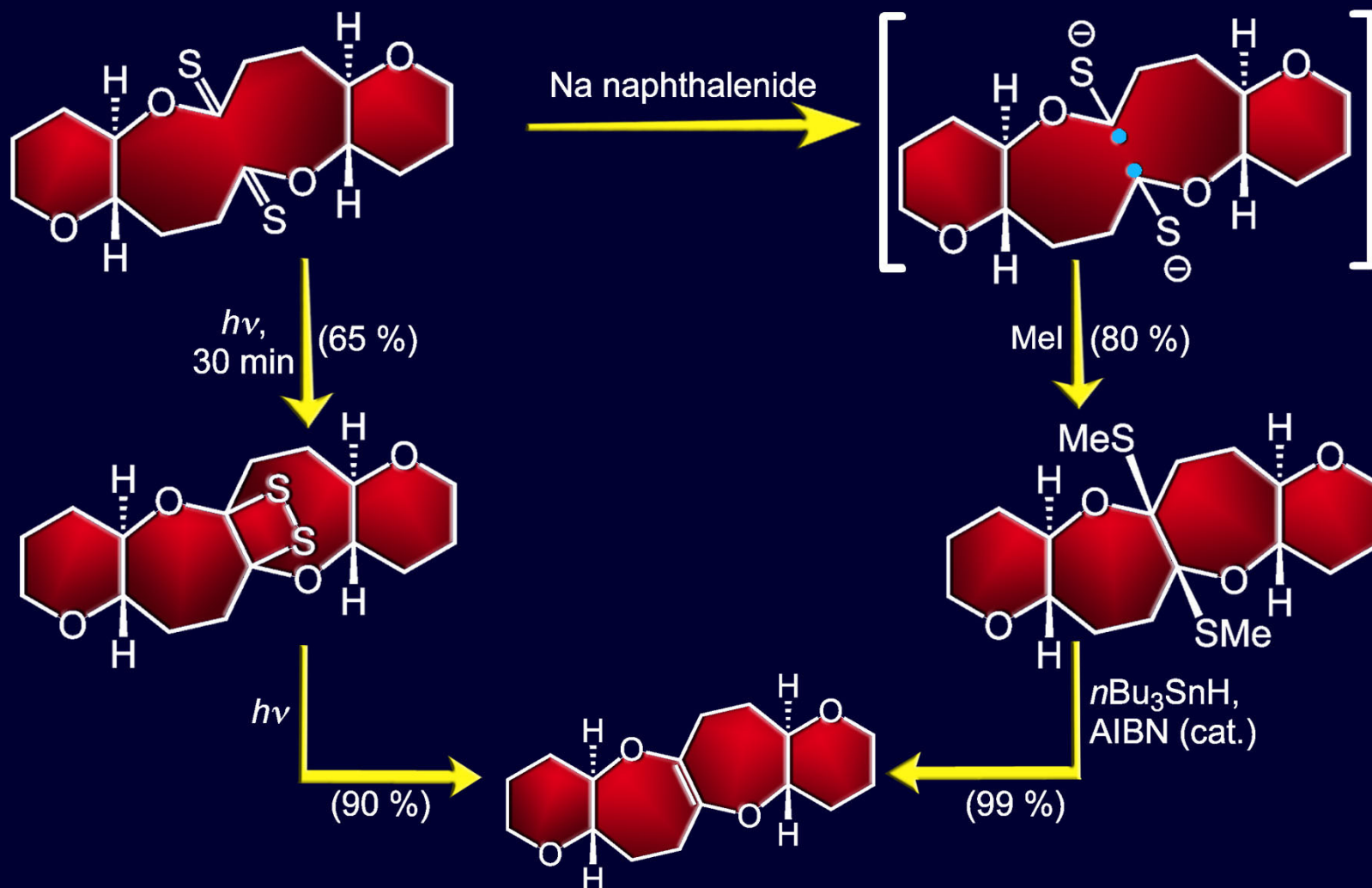


THE HYDROXY DITHIOKETAL CYCLIZATION METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU *et al.*, 1986)



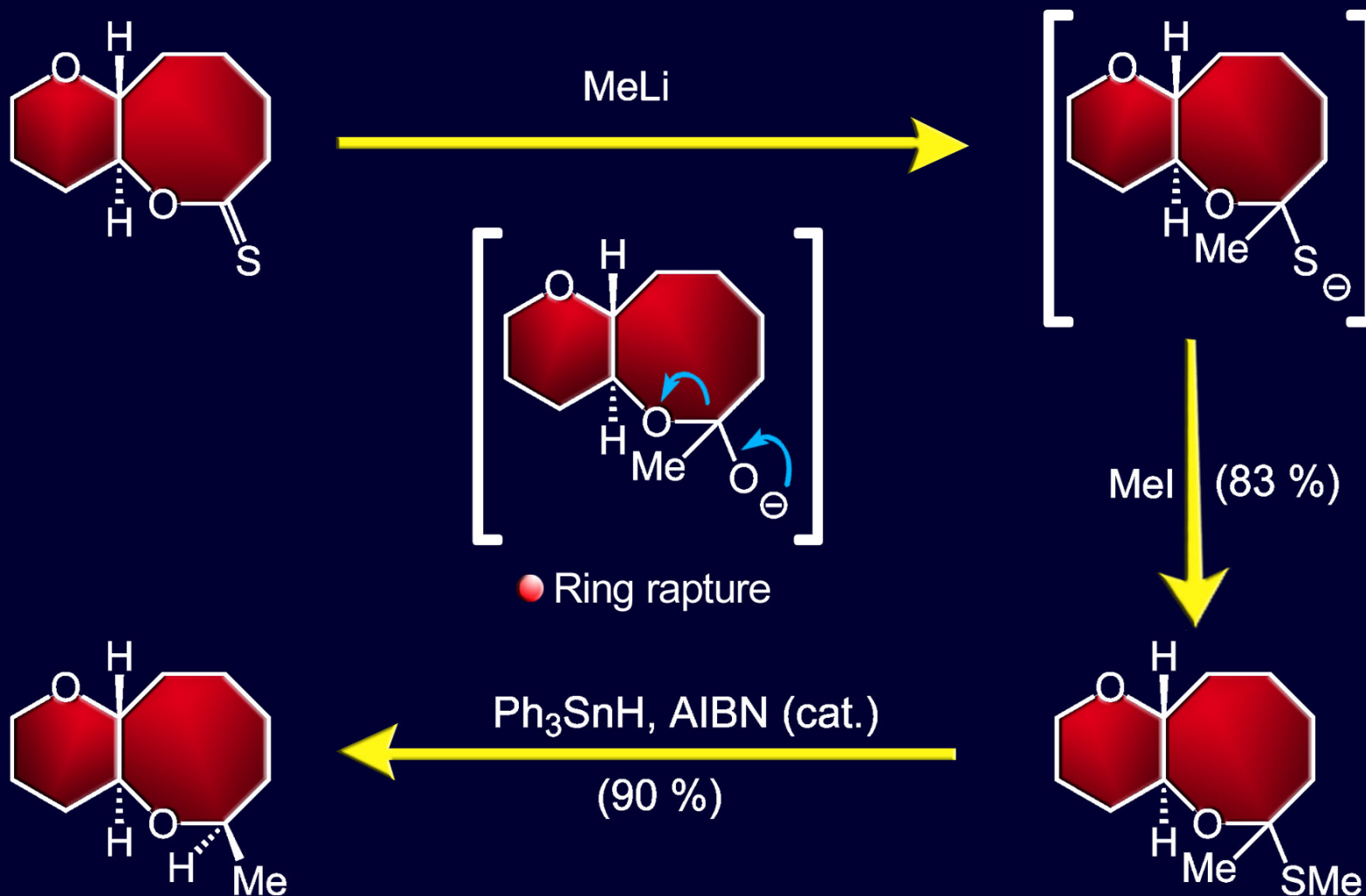


THE DITHIONOLACTONE BRIDGING METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU *et al.*, 1986)





THE THIONOLACTONE ADDITION/REDUCTION METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU *et al.*, 1987)



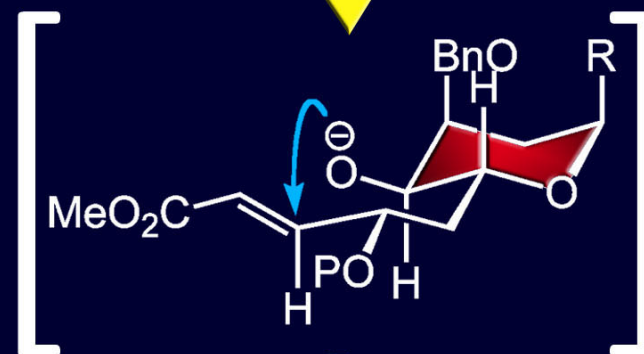


THE HYDROXY MICHAEL ADDITION METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU *et al.*, 1989)



NaH

● chair-like transition state ensures trans junction

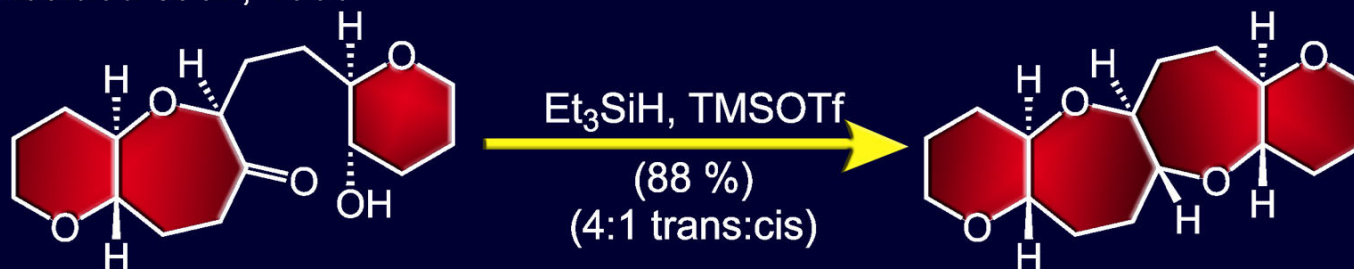


(92 %)



THE HYDROXY KETONE REDUCTIVE CYCLIZATION METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU *et al.*, 1989)

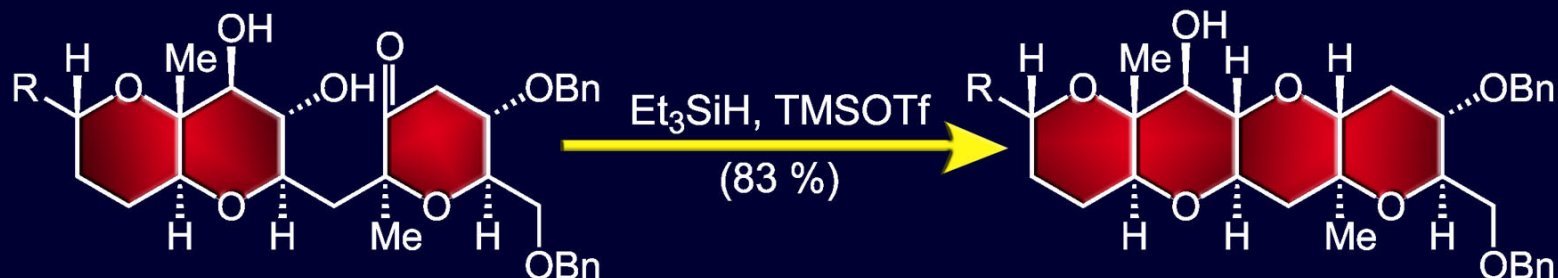
a: Nicolaou *et al.*, 1989



b: P.A. Evans *et al.*, 2003

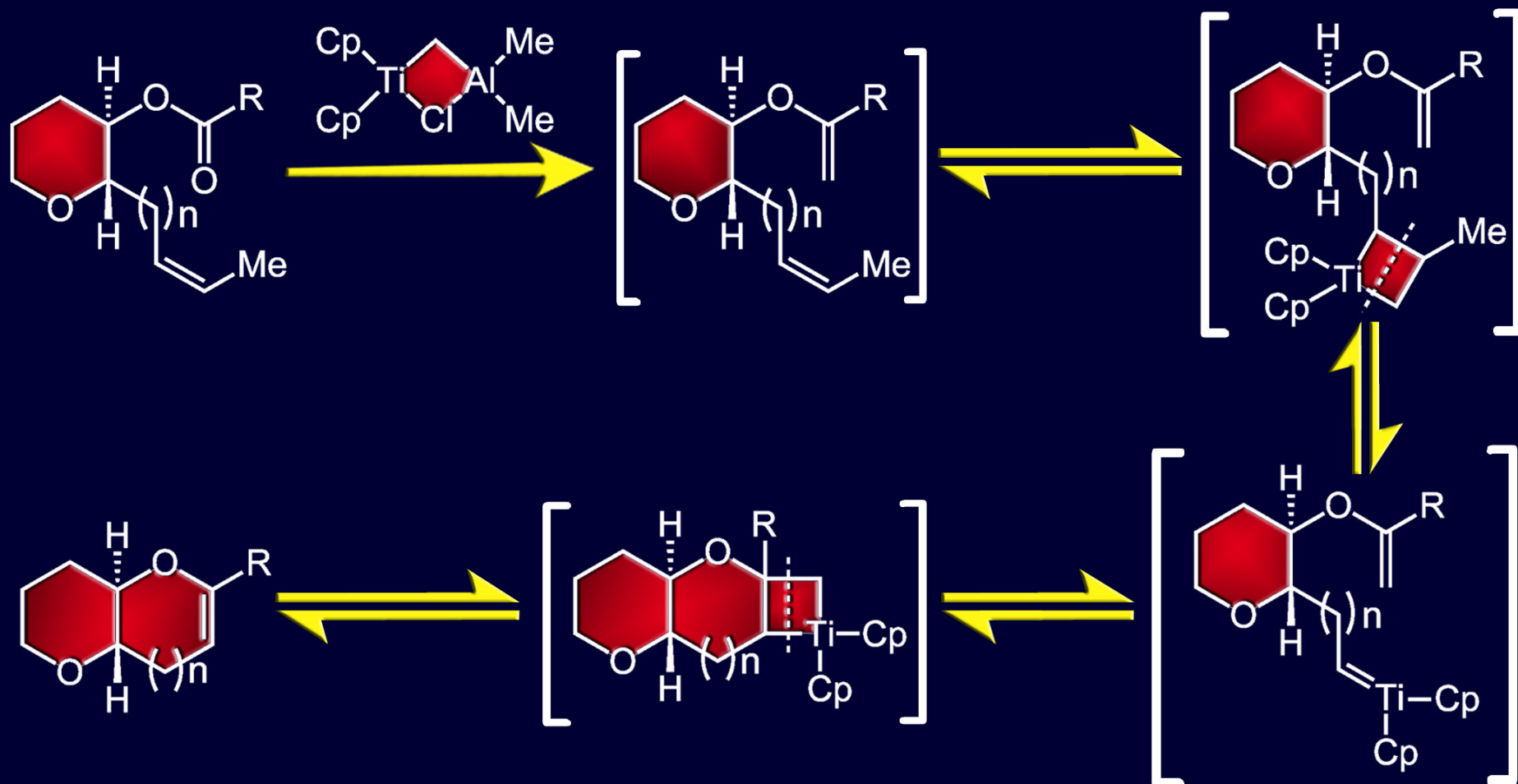


c: Sasaki *et al.*, 2007





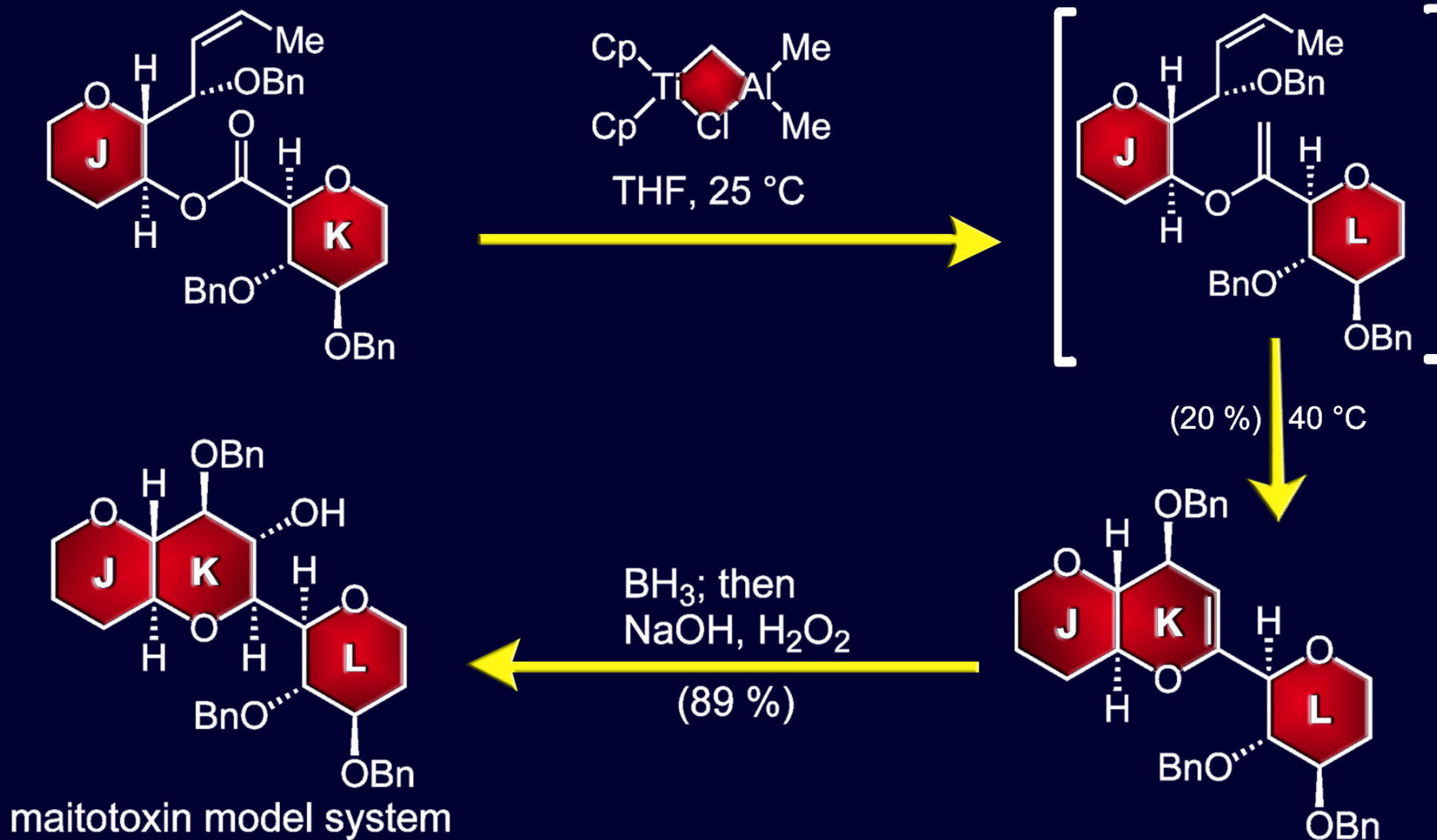
THE ESTER METHYLENATION/METATHESIS METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU et al., 1996)



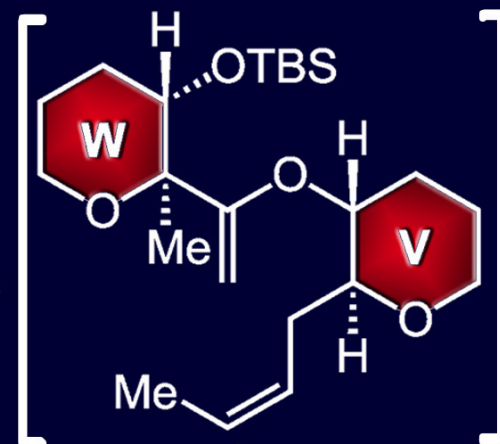
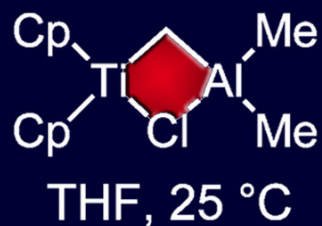
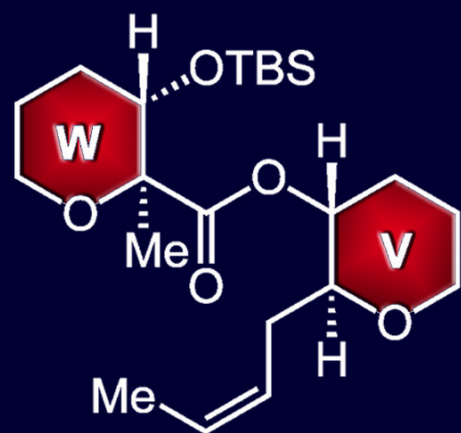
see also: G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 5426; G. C. Fu, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 9856.



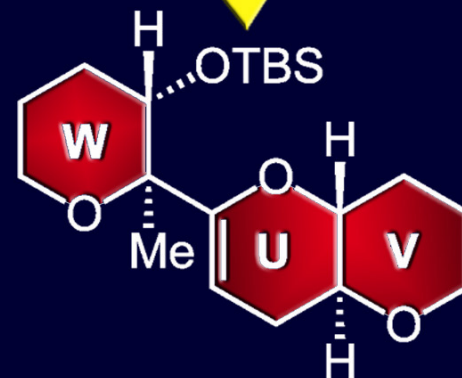
SYNTHESIS OF MAITOTOXIN JKL MODEL SYSTEM (NICOLAOU et al., 1996)



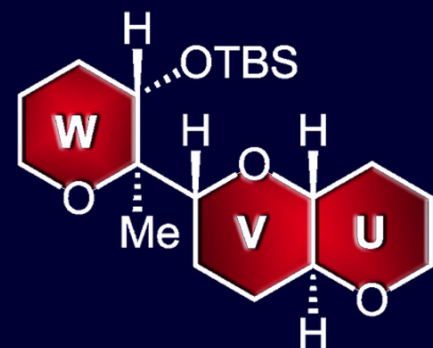
SYNTHESIS OF MAITOTOXIN UVW MODEL SYSTEM (NICOLAOU et al., 1996)



(36 %) 40 °C



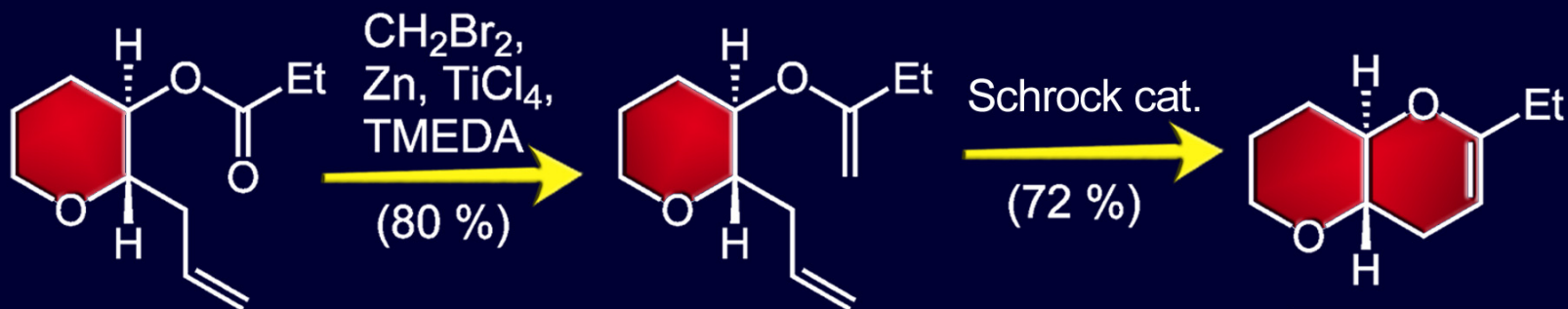
Et_3SiH , TFA
(80 %)



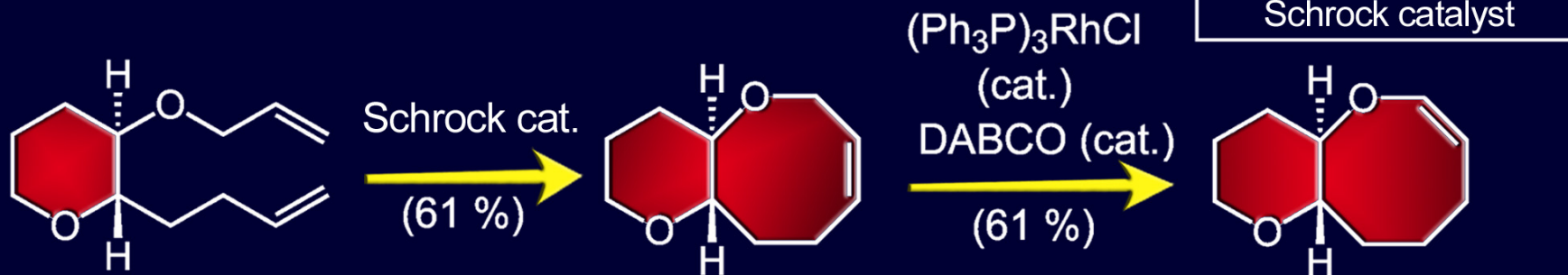
maitotoxin model system



THE TWO-STEP METHYLENATION/METATHESIS METHOD FOR CYCLIC ETHER FORMATION (CLARK et al., 1997)



Takai olefination



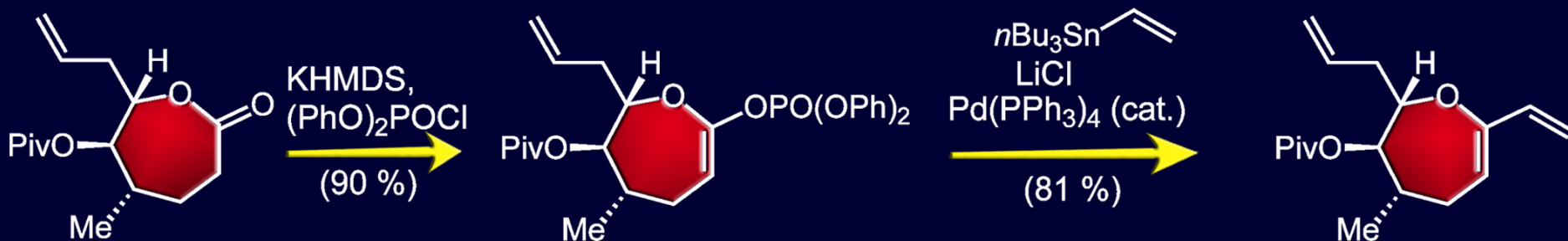
see also: G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 5426; G. C. Fu, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 9856.



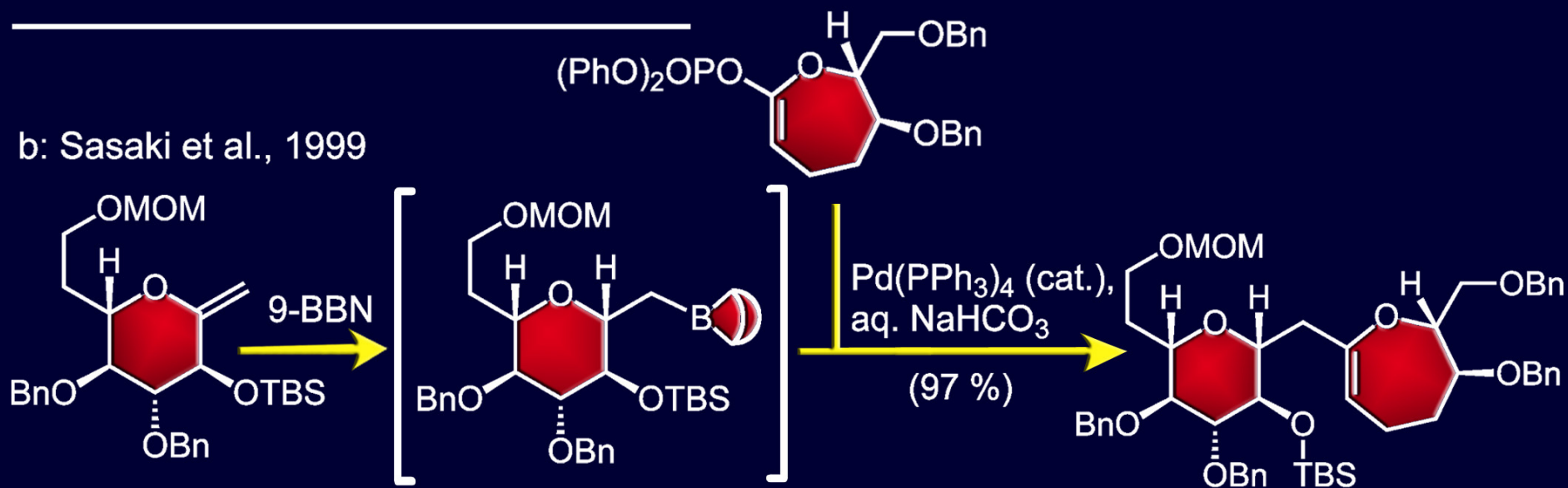
THE VINYL PHOSPHATE/CROSS-COUPLING METHODS FOR CYCLIC ETHER FORMATION (NICOLAOU *et al.*, 1997, SASAKI *et al.*, 1999)



a: Nicolaou *et al.*, 1997

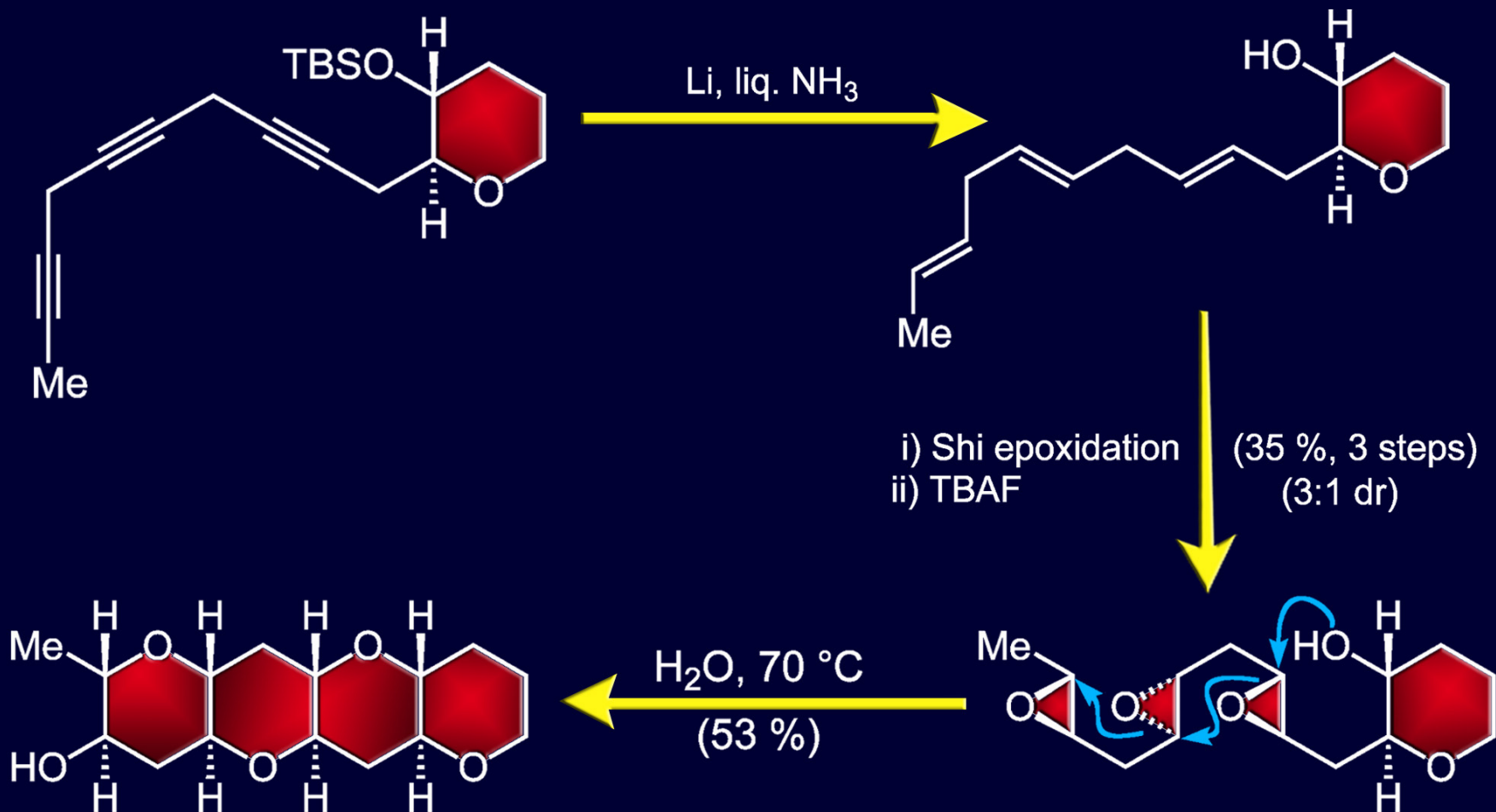


b: Sasaki *et al.*, 1999



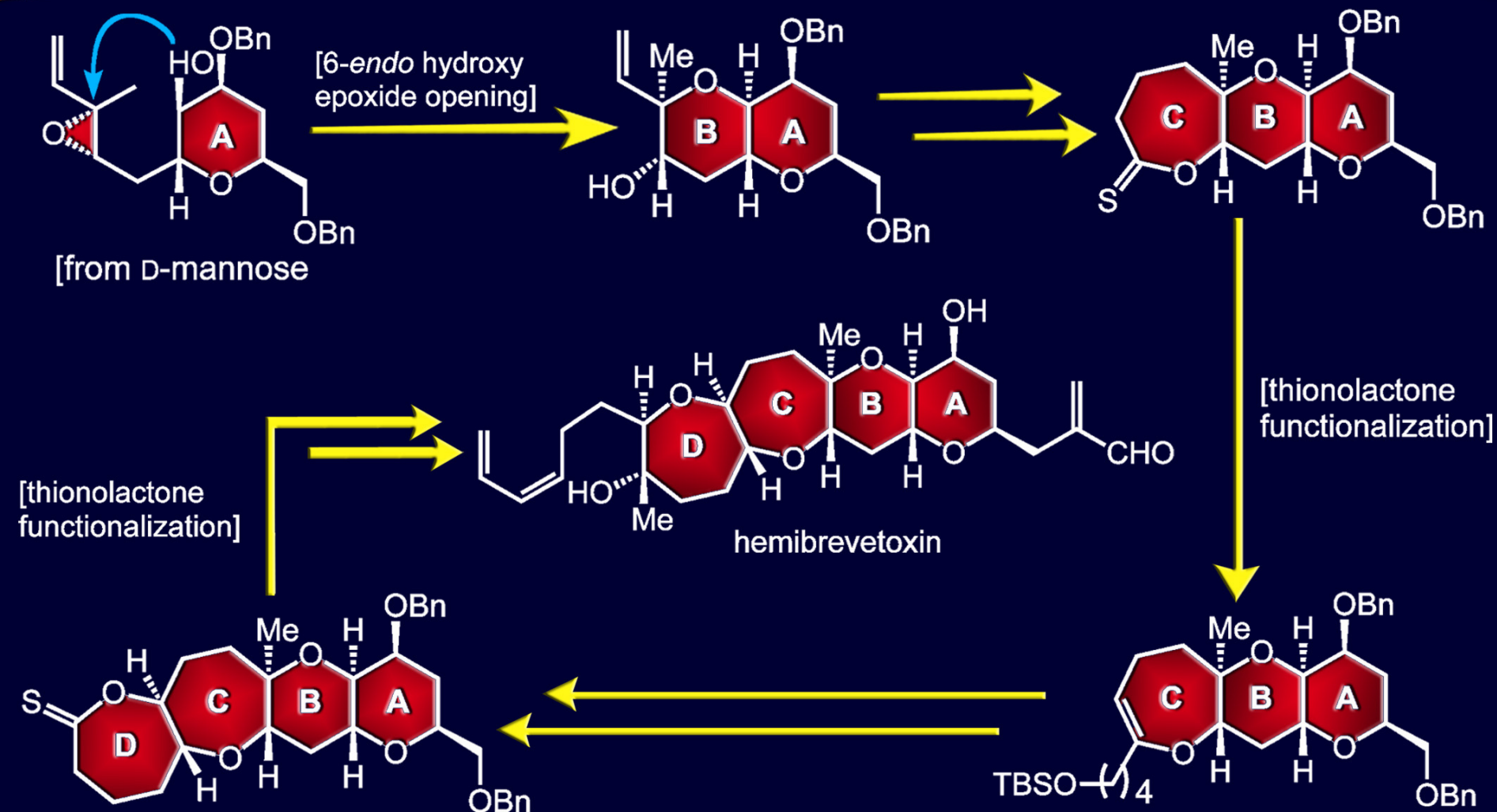


THE THERMALLY-INDUCED HYDROXY POLYEPOXIDE OPENING IN WATER FOR CYCLIC ETHER FORMATION (JAMISON and VILOTIJEVIC, 2007)



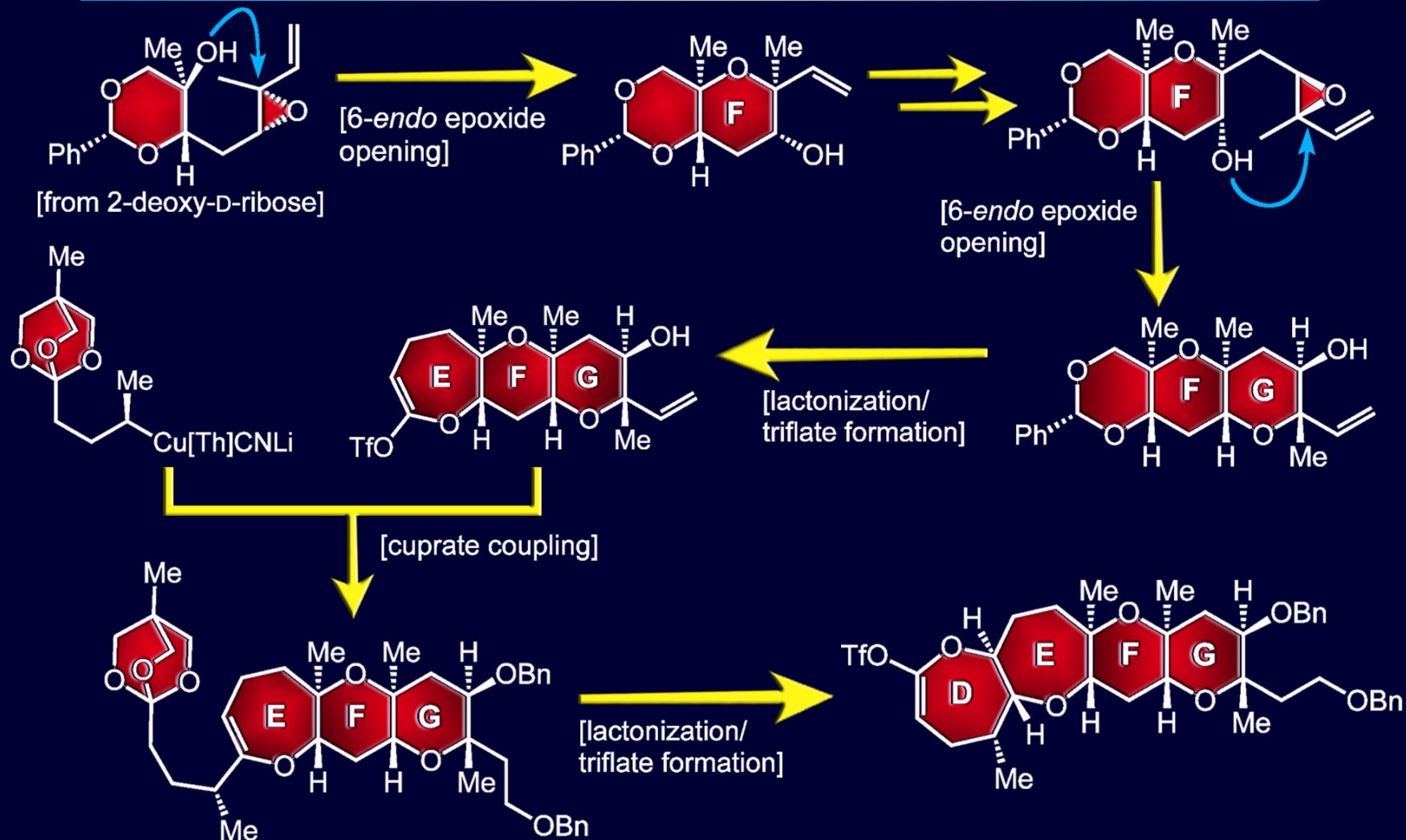


SYNTHESIS OF HEMIBREVETOXIN (NICOLAOU *et al.*, 1992)



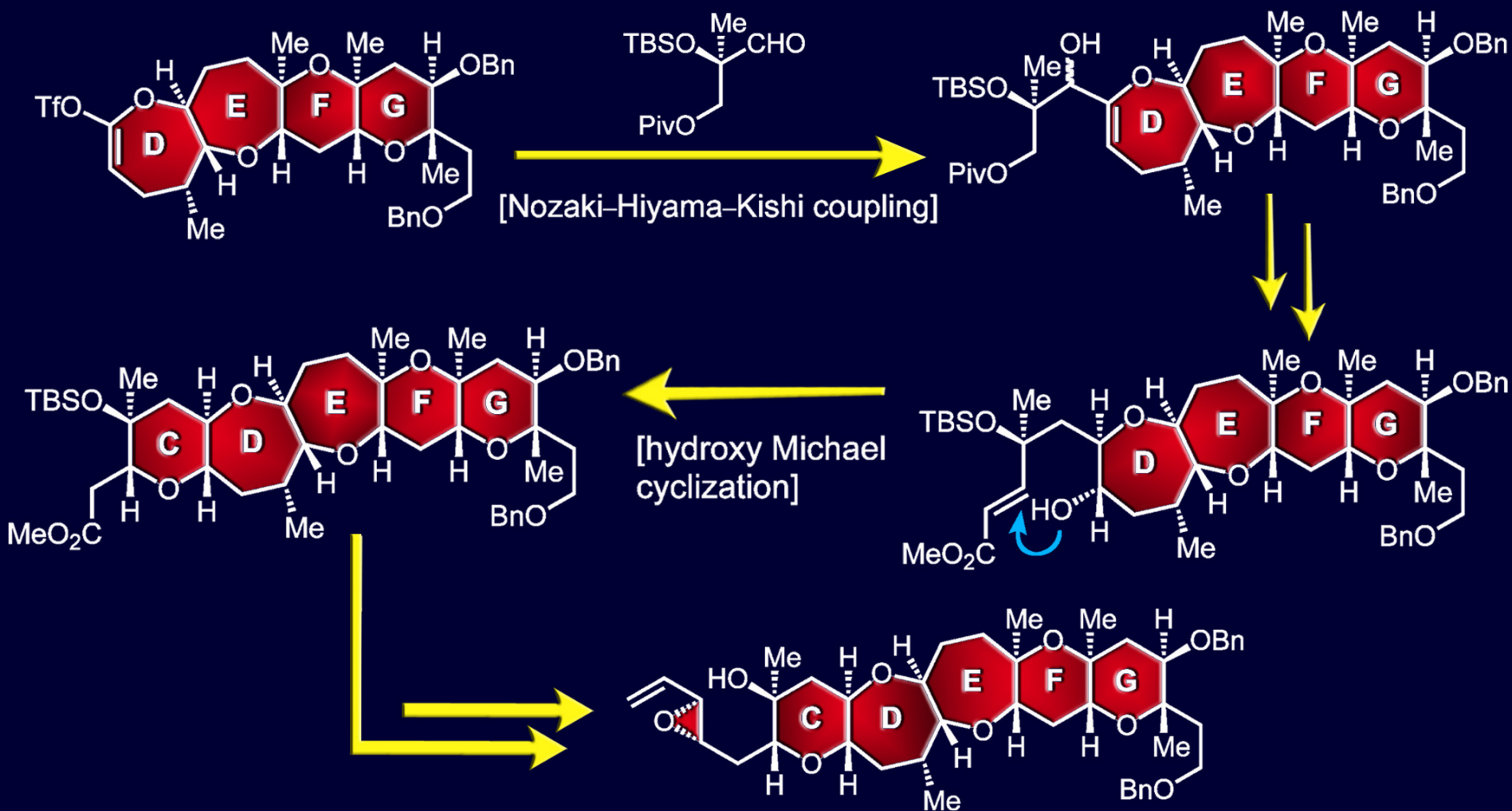


SYNTHESIS OF THE DEFG DOMAIN OF BREVETOXIN B (NICOLAOU et al., 1995) I



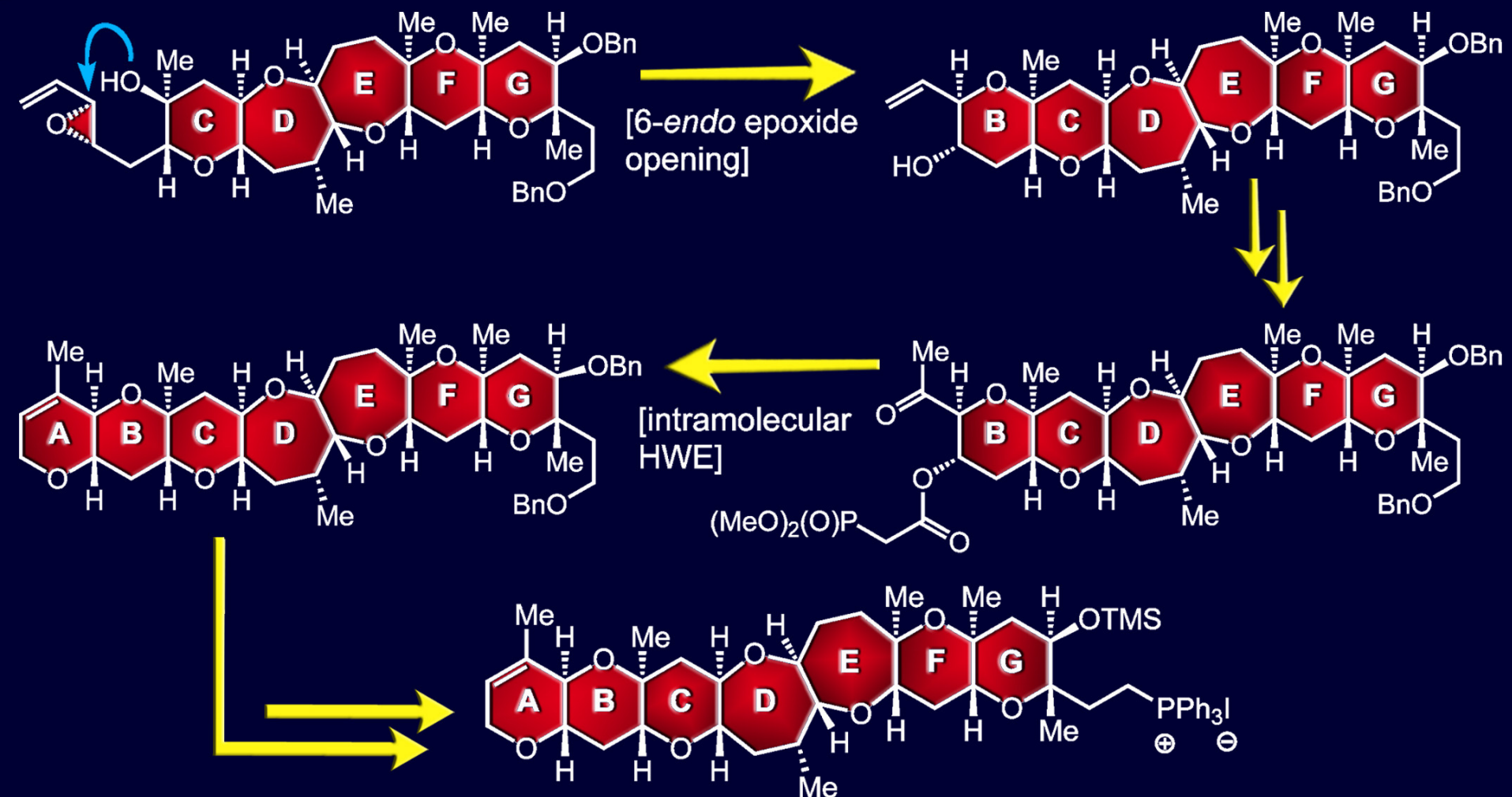


SYNTHESIS OF THE CDEFG DOMAIN OF BREVETOXIN B (NICOLAOU *et al.*, 1995) II



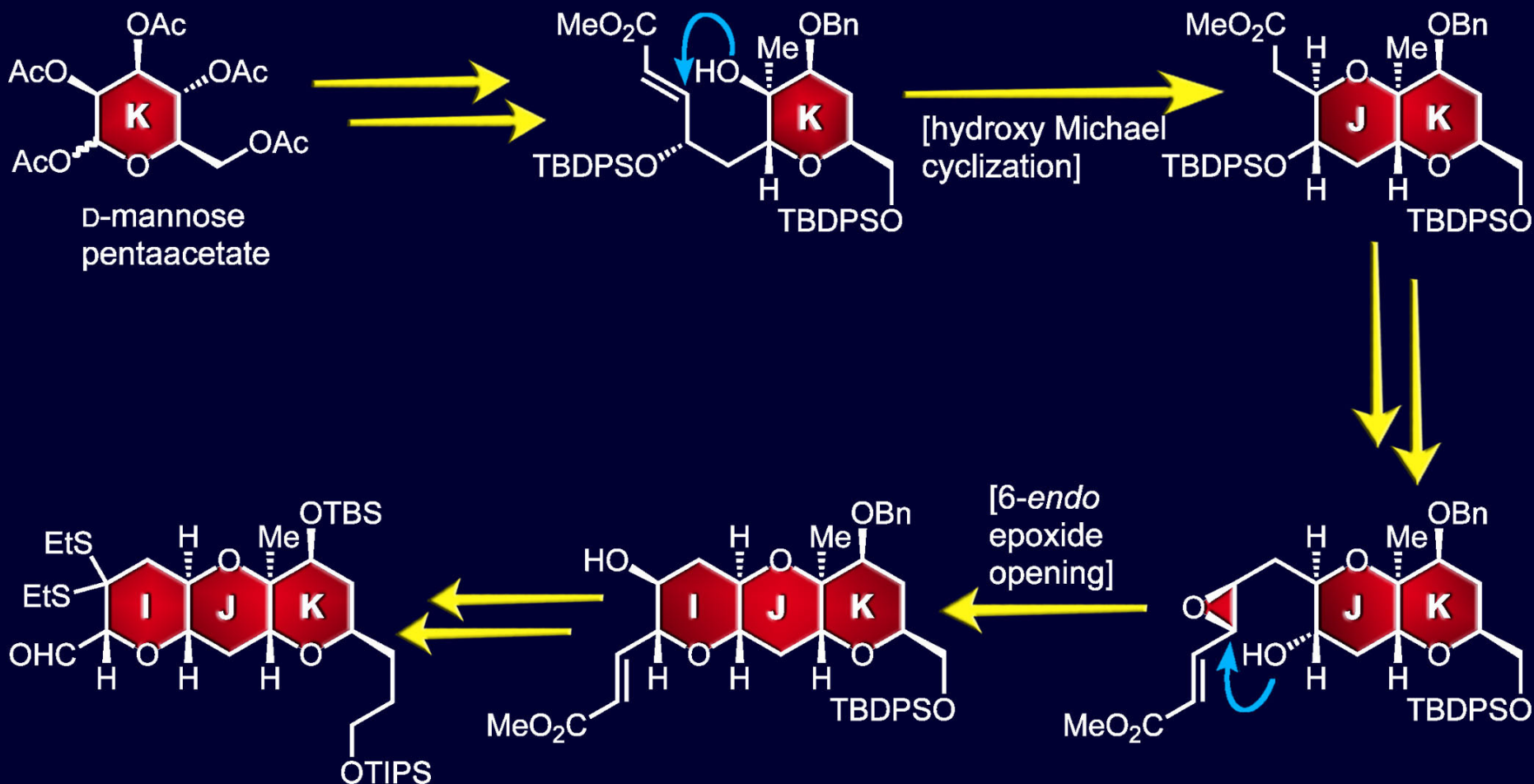


SYNTHESIS OF THE ABCDEFG DOMAIN OF BREVETOXIN B (NICOLAOU et al., 1995) III



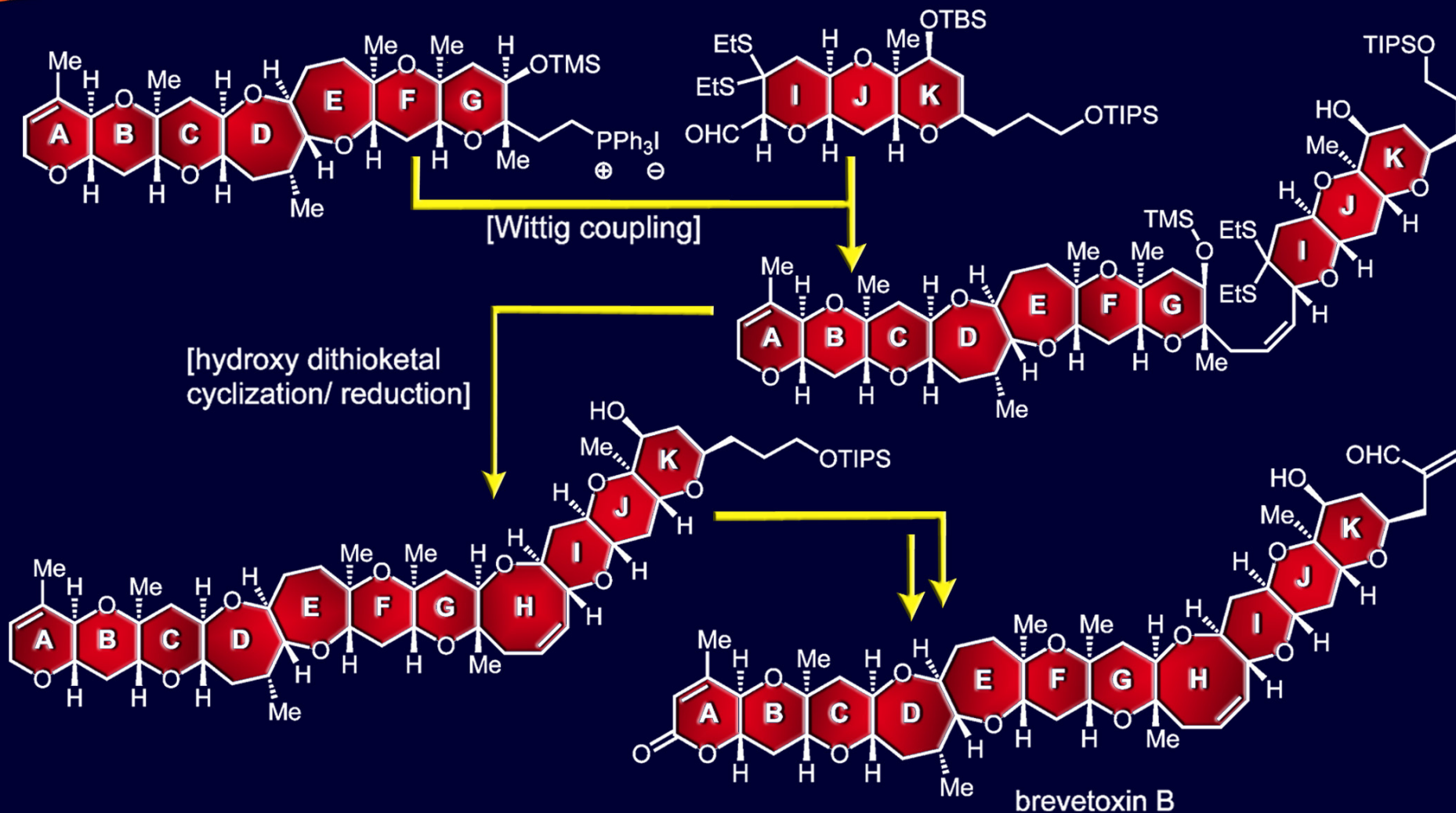


SYNTHESIS OF THE IJK DOMAIN OF BREVETOXIN B (NICOLAOU et al., 1995) IV



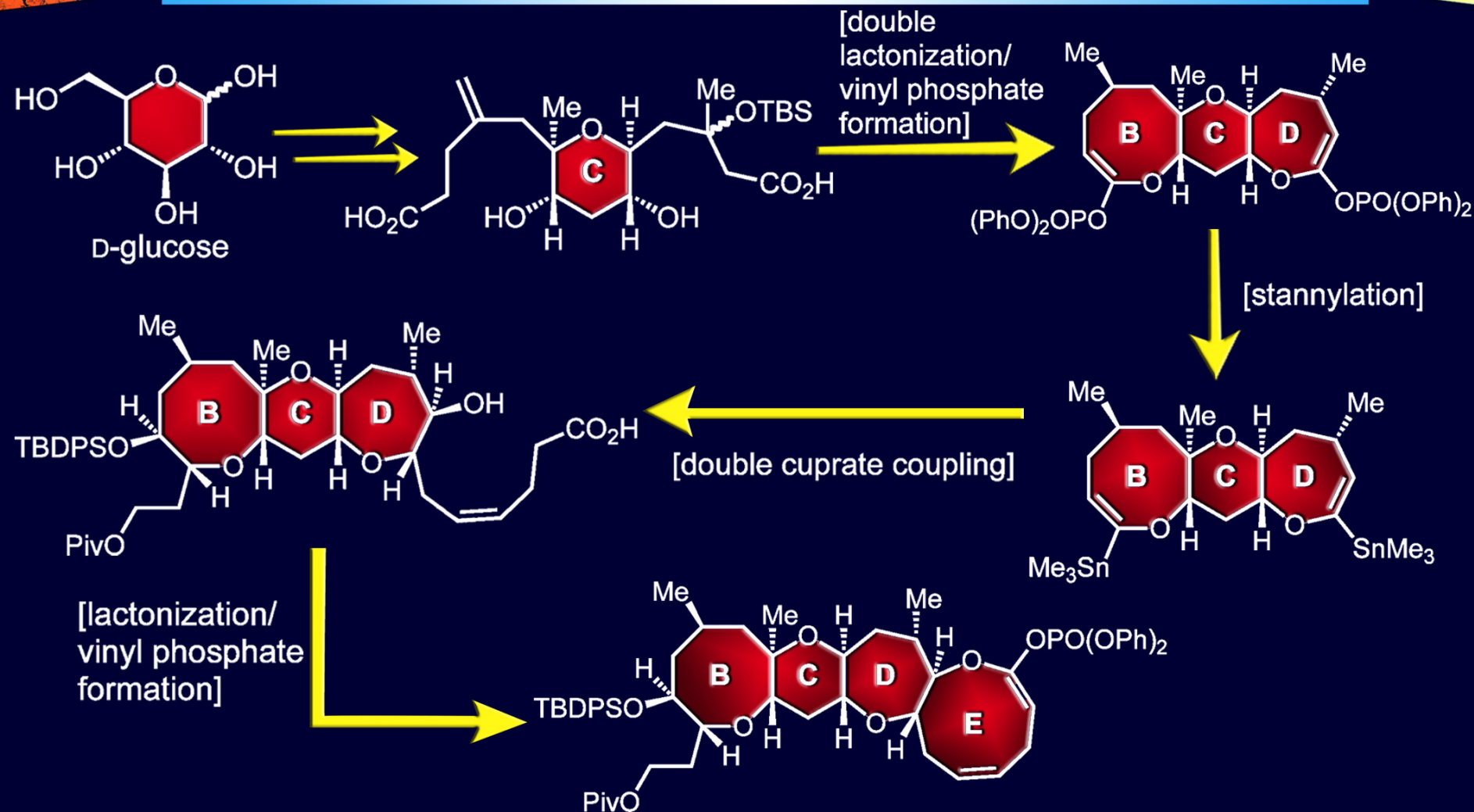


COMPLETION OF THE TOTAL SYNTHESIS OF BREVETOXIN B (NICOLAOU et al., 1995) V



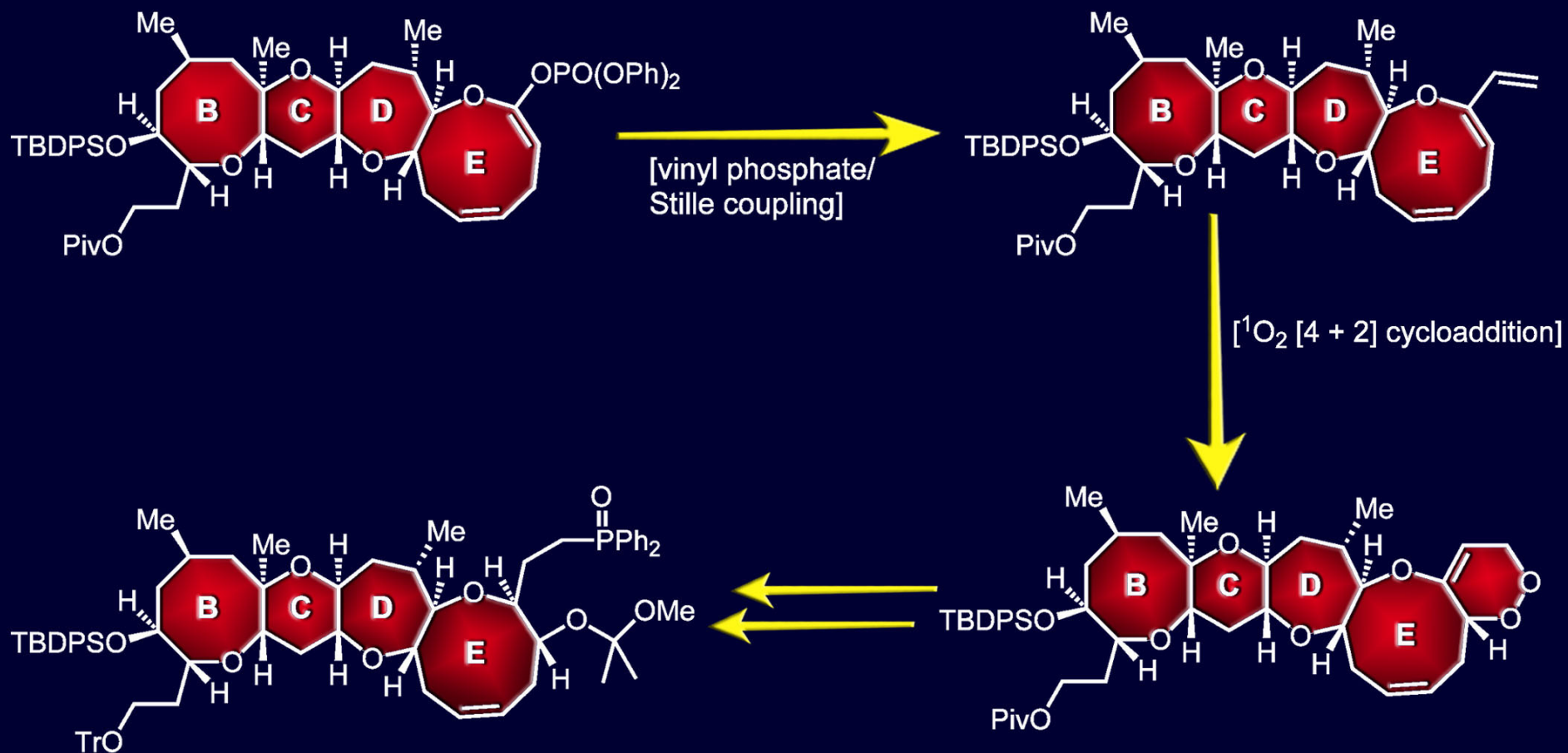


SYNTHESIS OF THE BCDE DOMAIN OF BREVETOXIN A (NICOLAOU et al., 1998) I



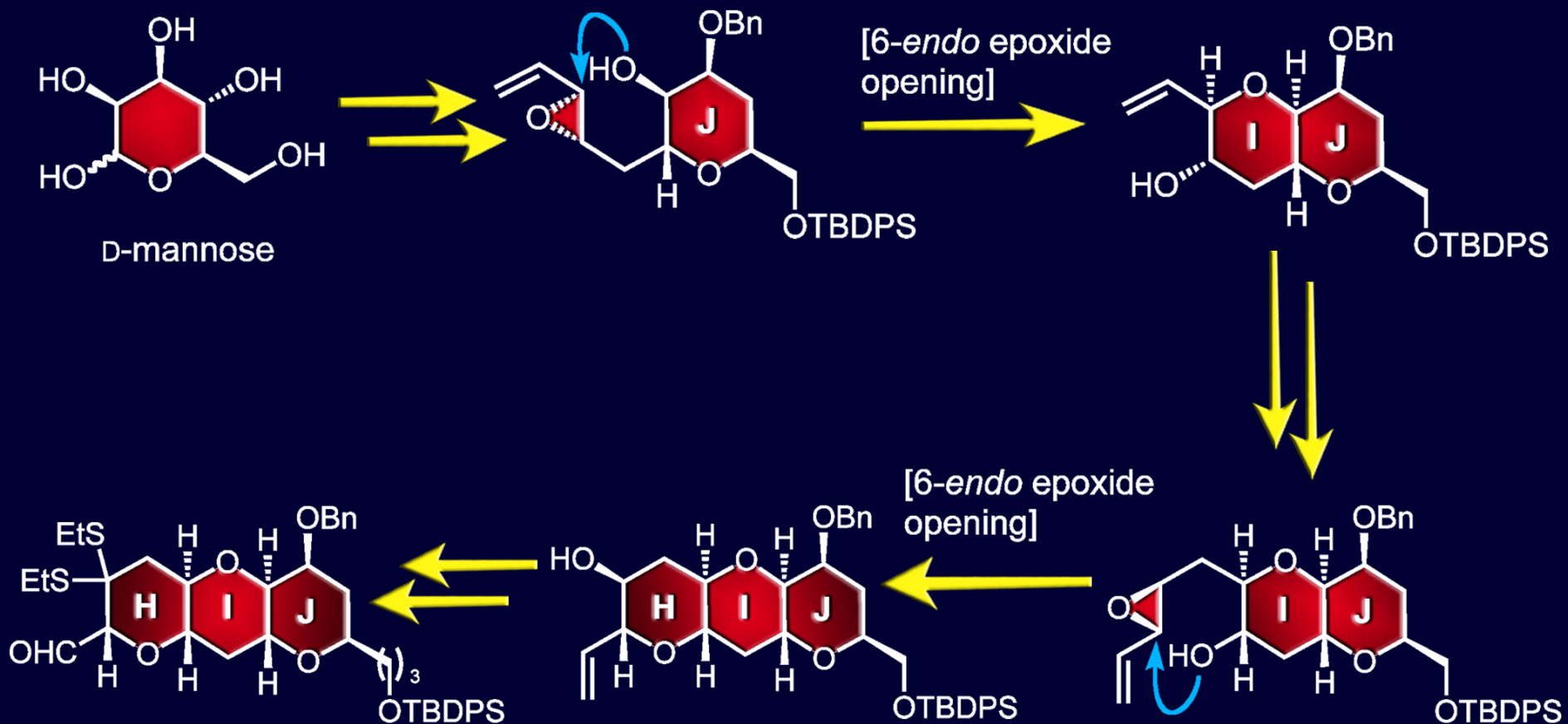


SYNTHESIS OF THE BCDE DOMAIN OF BREVETOXIN A (NICOLAOU et al., 1998) II



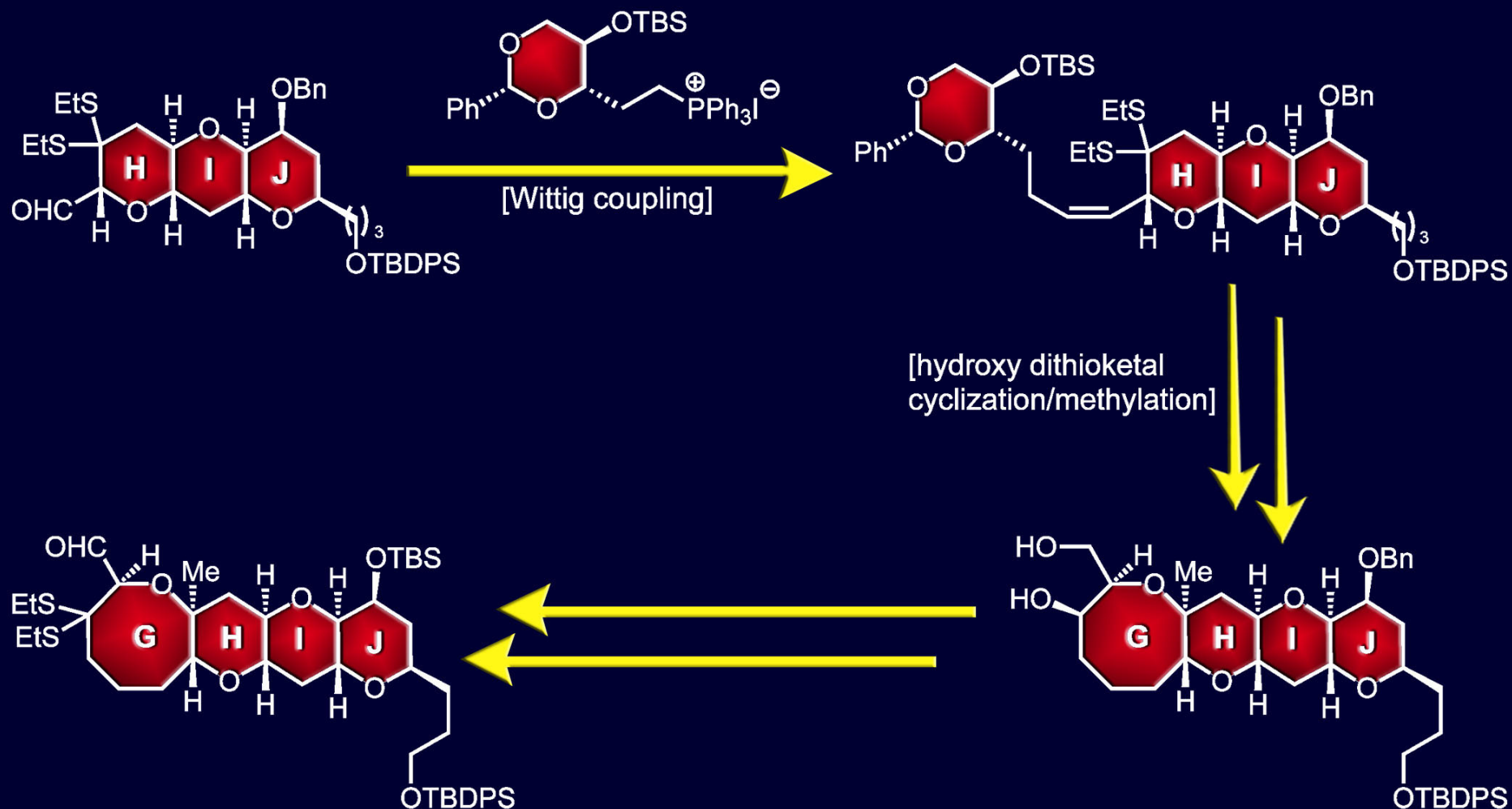


SYNTHESIS OF THE HIJ DOMAIN OF BREVETOXIN A (NICOLAOU et al., 1998) III



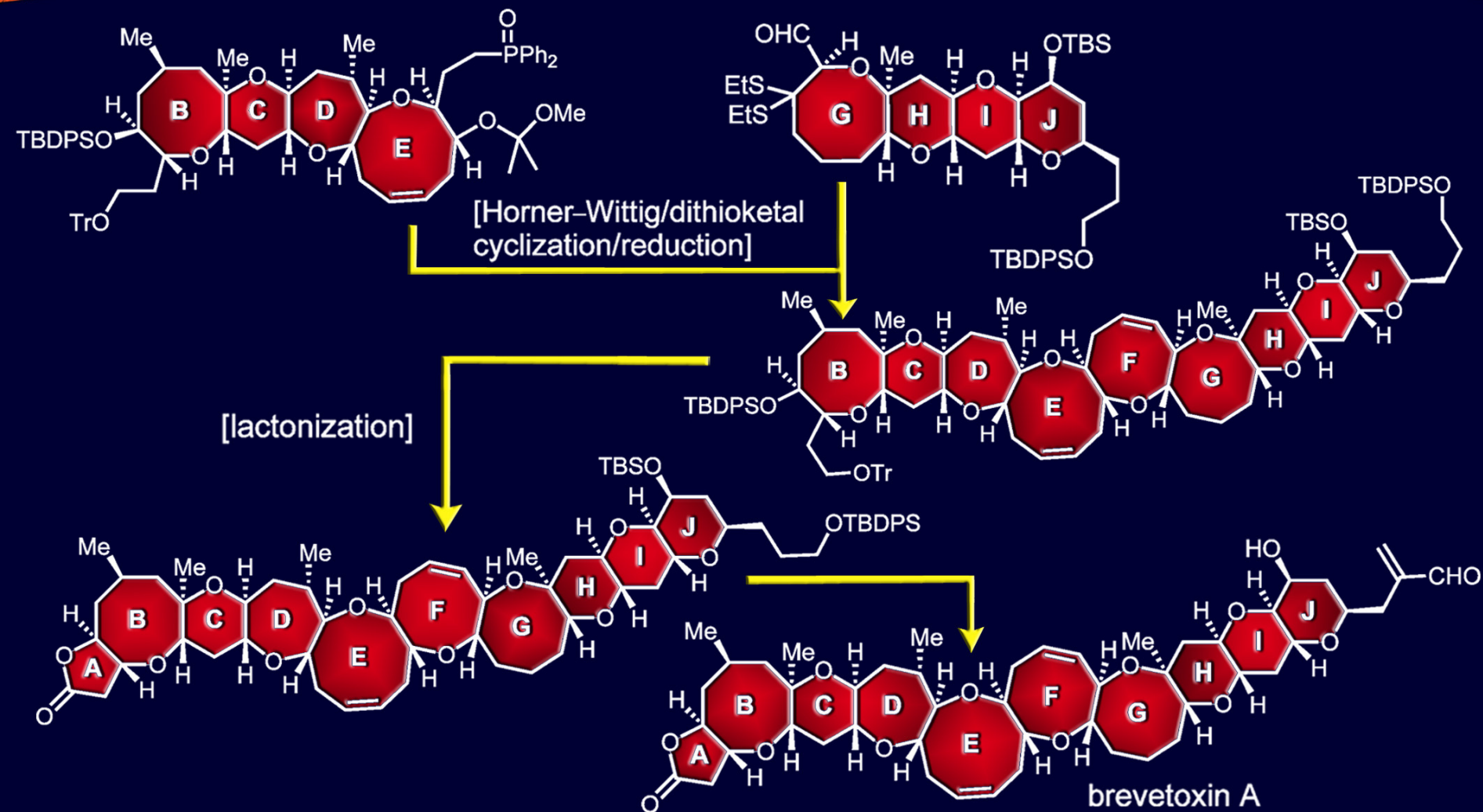


SYNTHESIS OF THE GHIJ DOMAIN OF BREVETOXIN A (NICOLAOU et al., 1998) IV



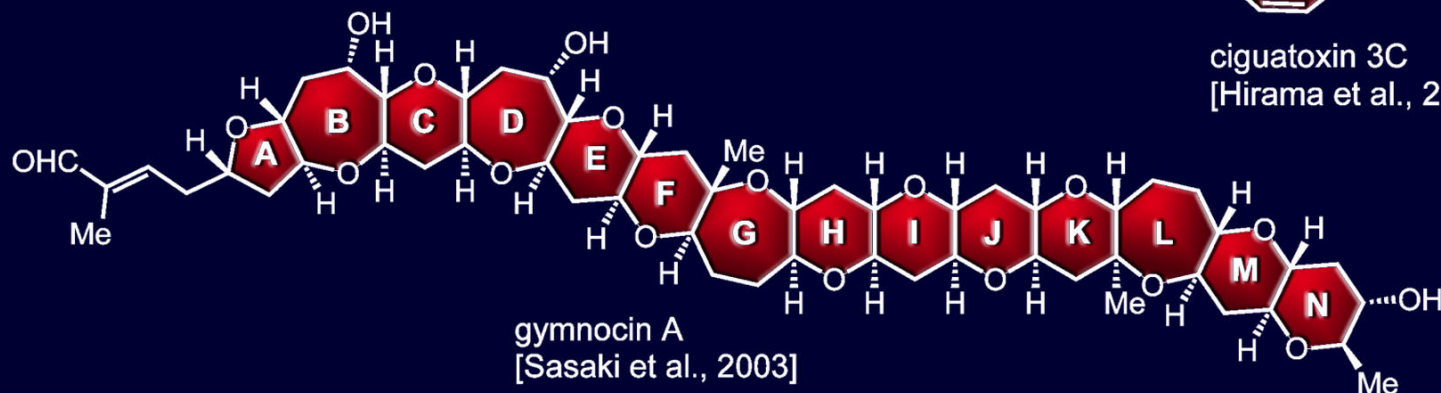
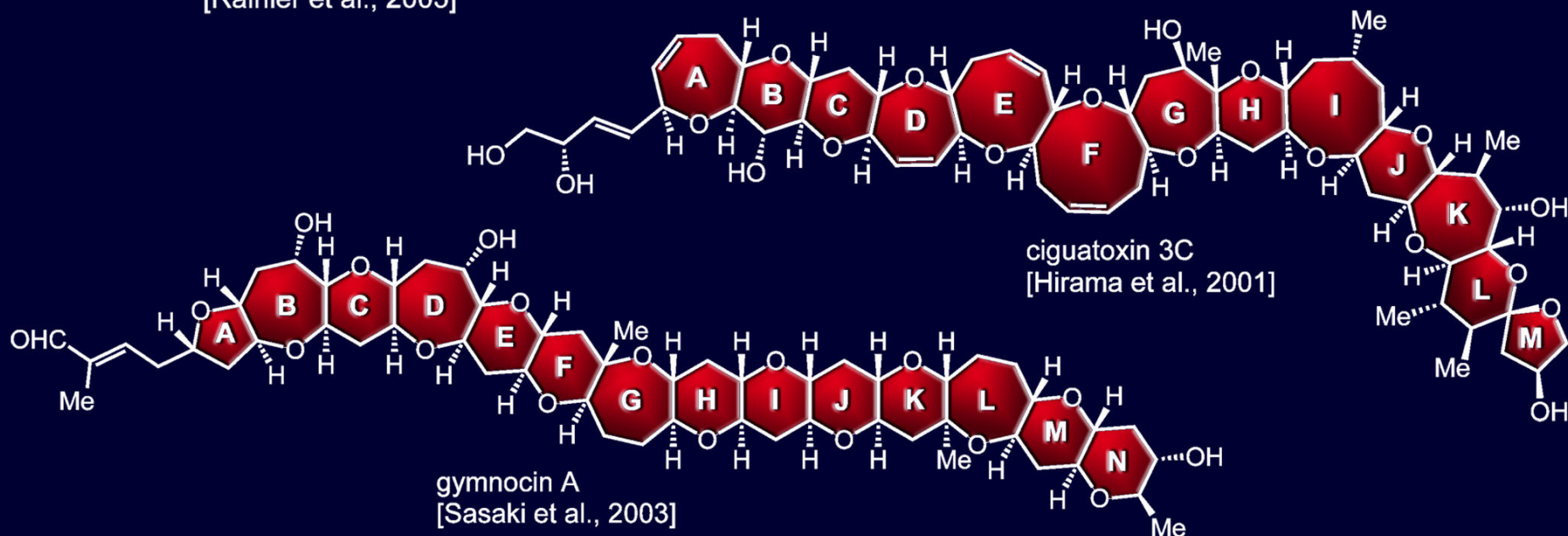
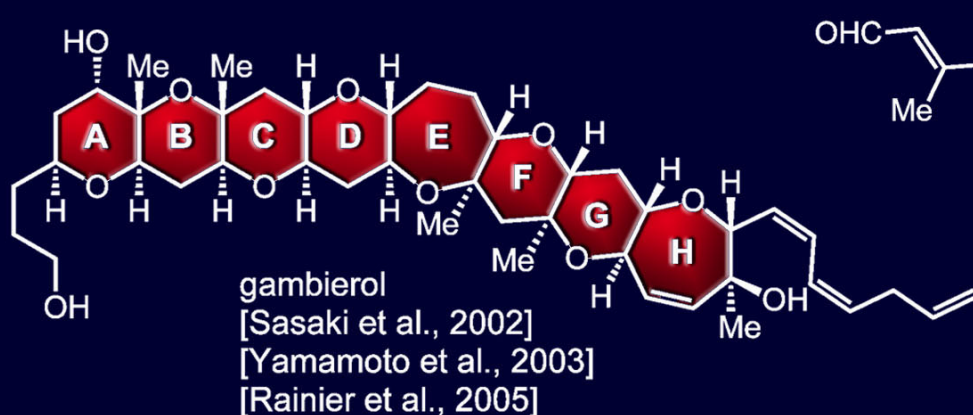


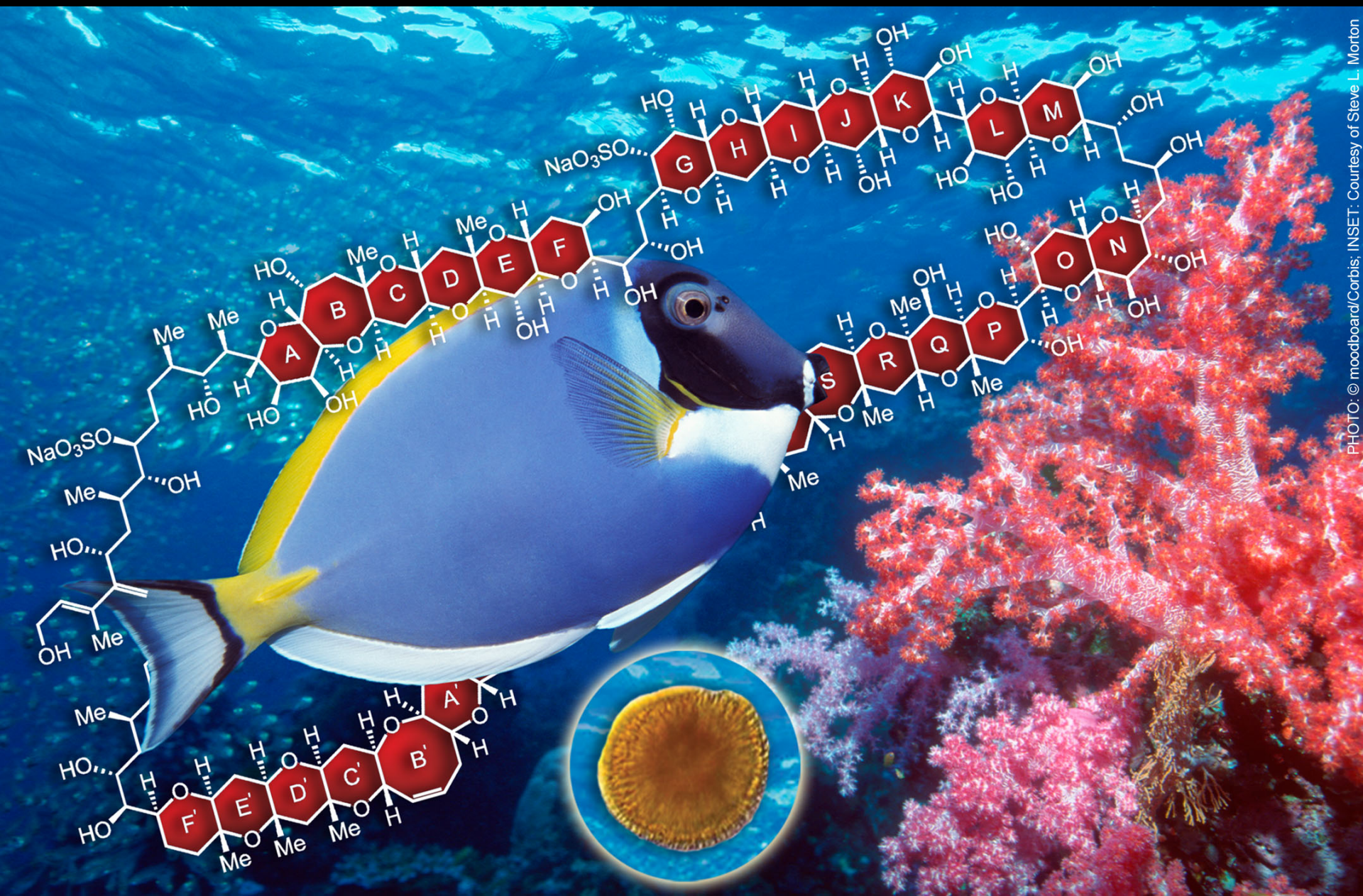
COMPLETION OF THE TOTAL SYNTHESIS OF BREVETOXIN A (NICOLAOU *et al.*, 1998) V





POLYETHER MARINE BIOTOXINS SYNTHESIZED TO DATE, 2008, II



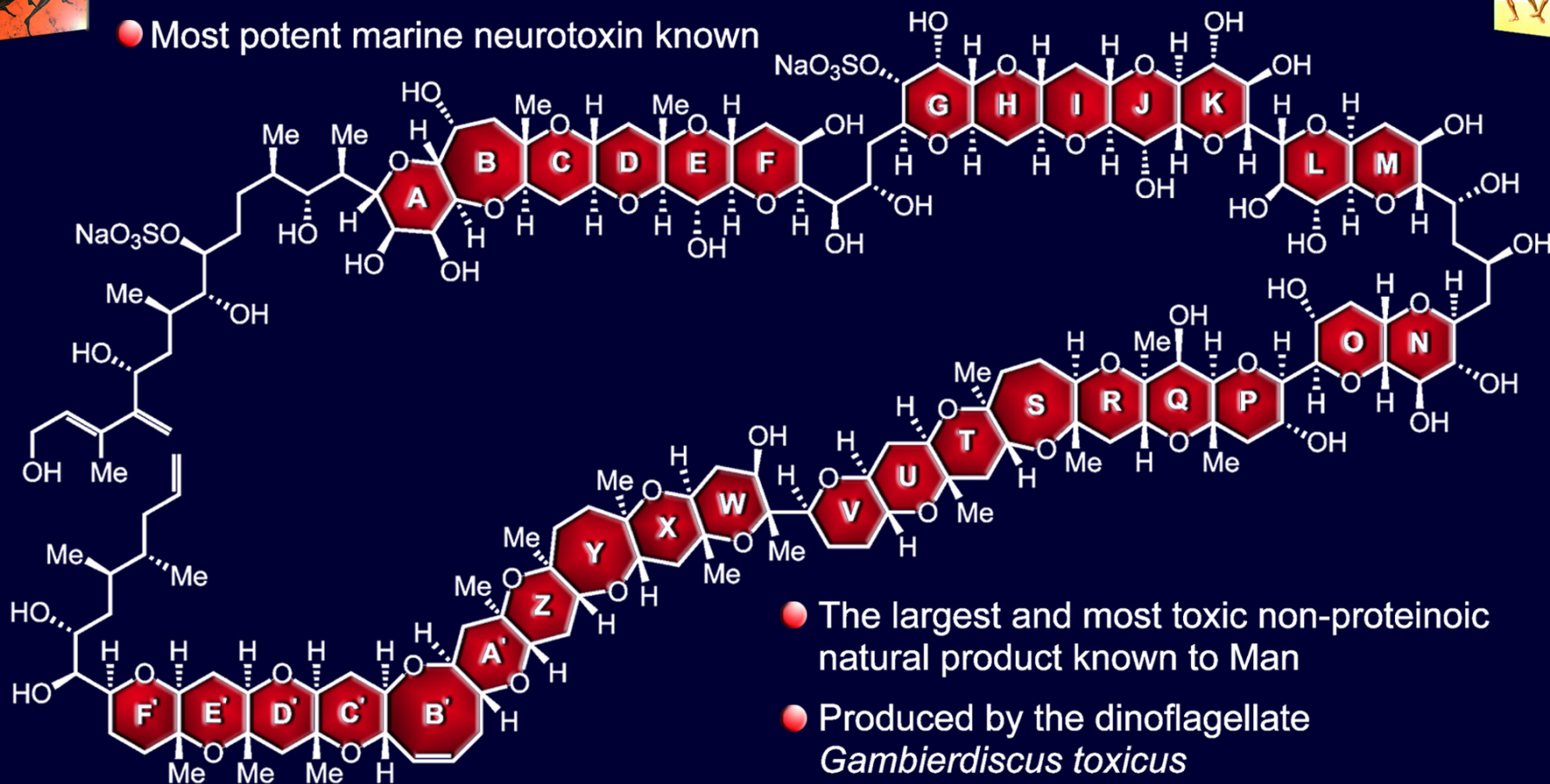




PROPOSED STRUCTURE OF MAITOTOXIN



- Most potent marine neurotoxin known



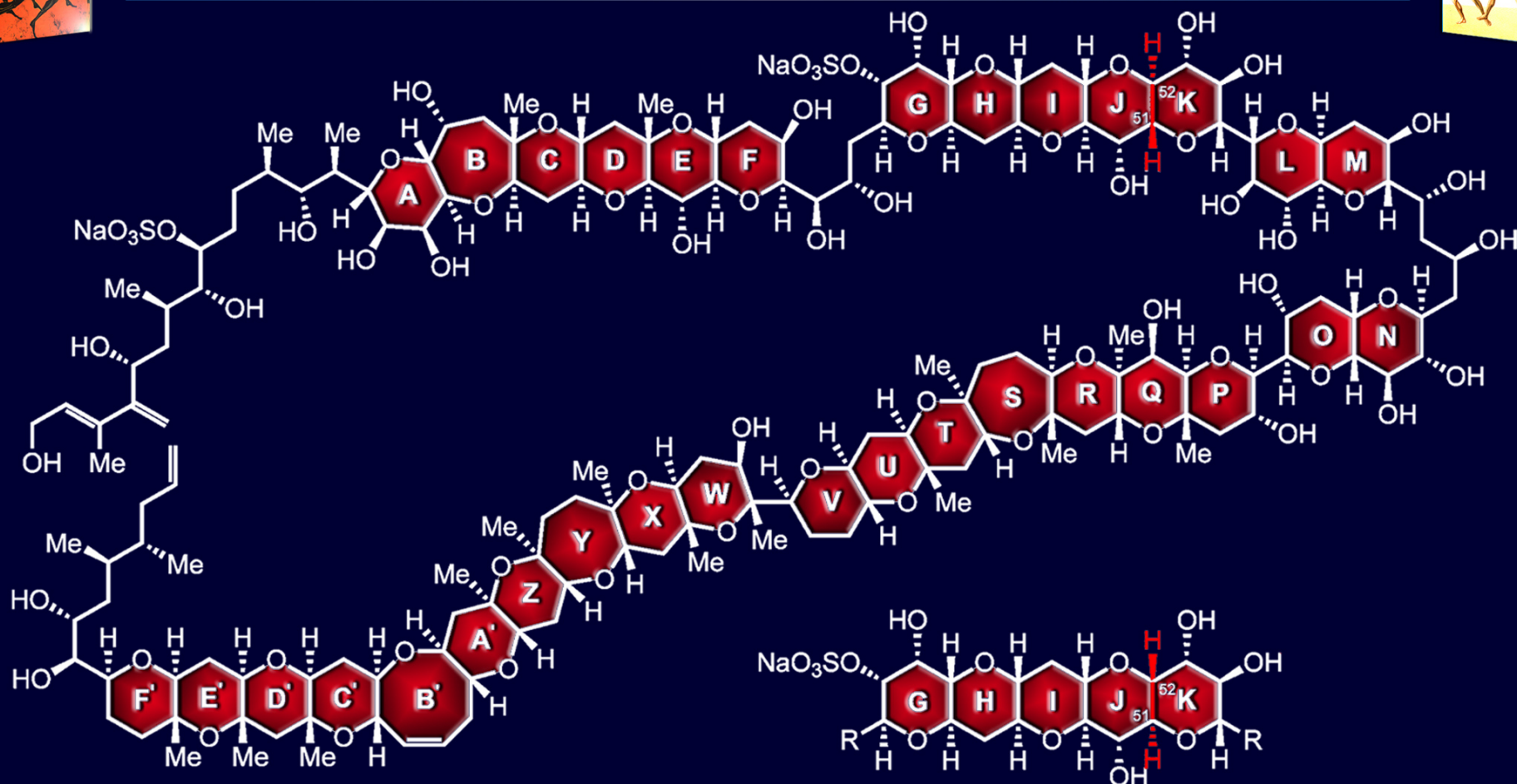
● $C_{164}H_{256}O_{68}S_2Na_2$ [MW 3422 Da]

● 32 rings, 98 stereogenic centers

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



MAITOTOXIN STRUCTURE-1



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

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

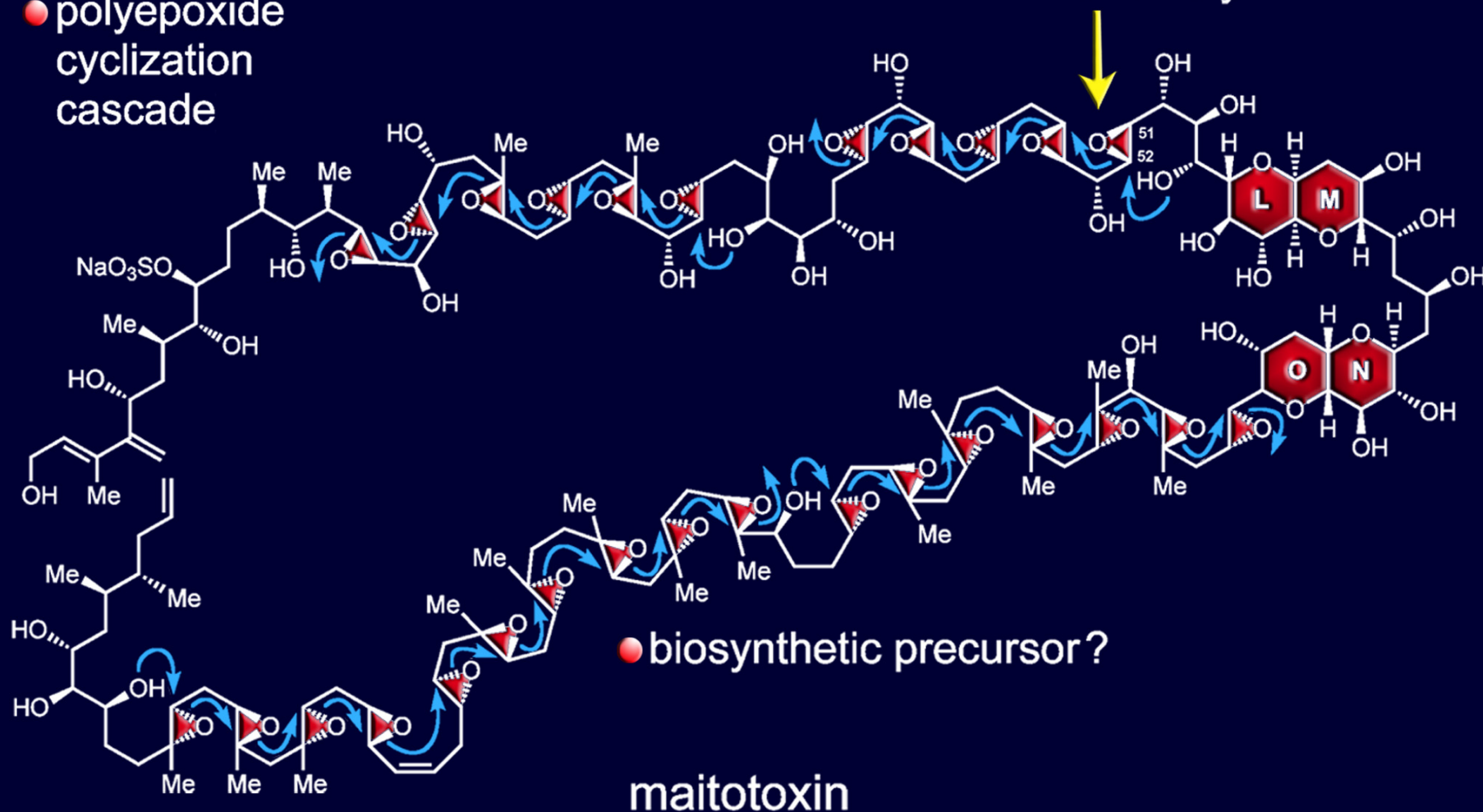


PROPOSED BIOSYNTHESIS OF MAITOTOXIN [NAKANISHI/GALLIMORE-SPENCER]



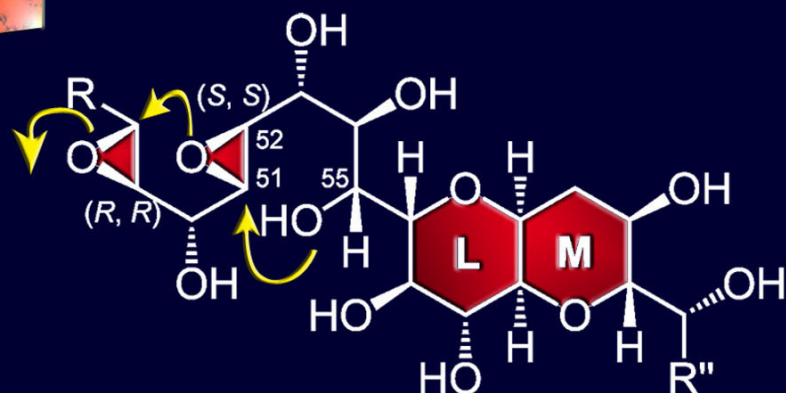
● polyepoxide
cyclization
cascade

● anomaly?

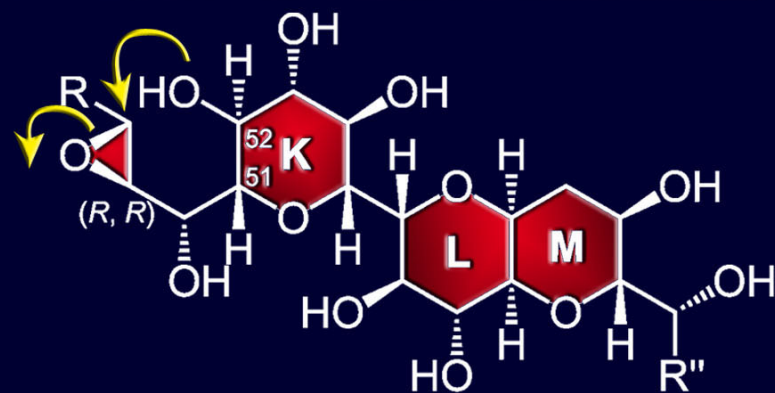




MAITOTOXIN STRUCTURE-3



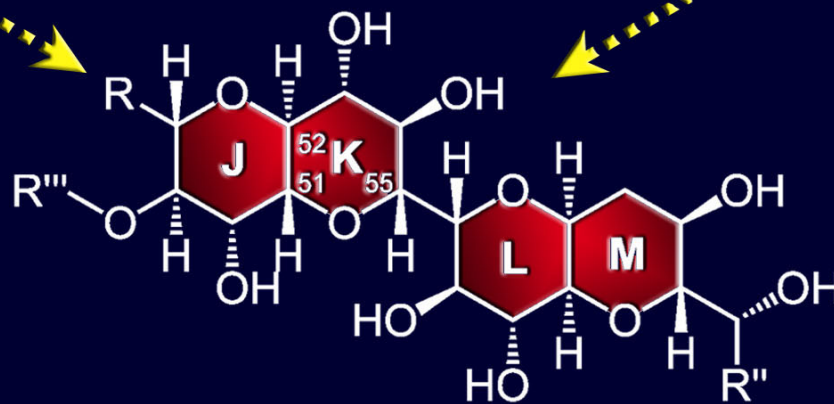
[Gallimore and Spencer]



[alternative biosynthesis, KCN and MOF]

proposed
biosynthesis

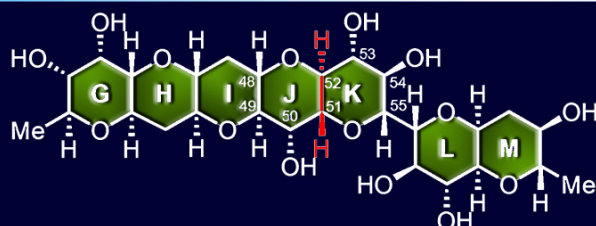
prefabrication
of ring K



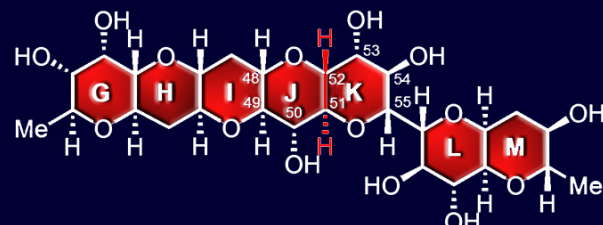
originally proposed JKLMNO domain of maitotoxin



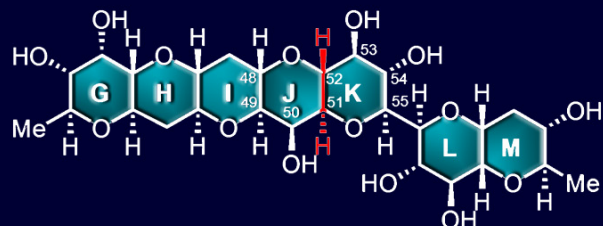
MAITOTOXIN STRUCTURE-2 (2007)



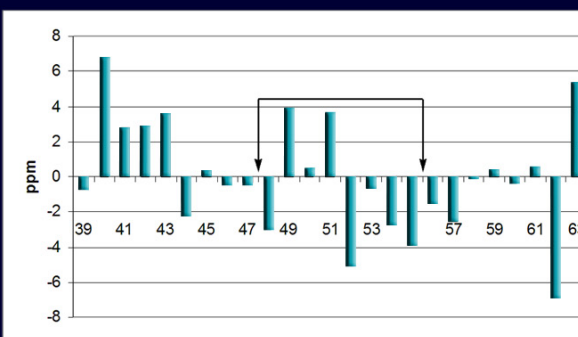
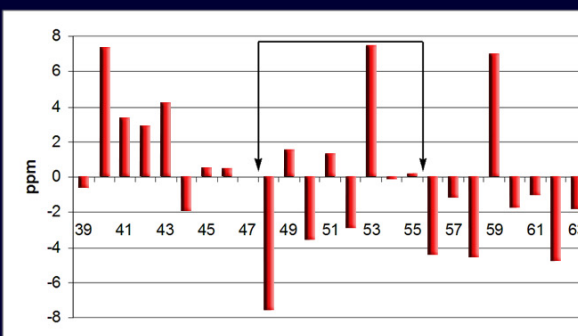
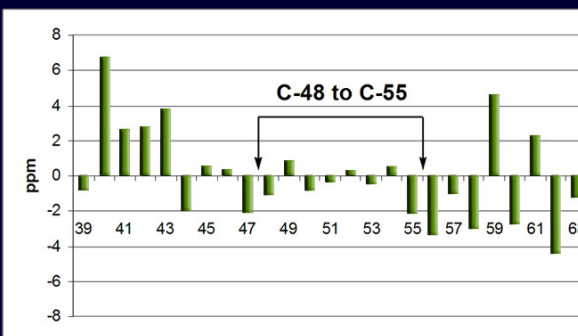
Originally proposed G-K domain
Average difference (C-48 to C-55) = 0.78 ppm
Maximum difference = 2.1 ppm



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



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



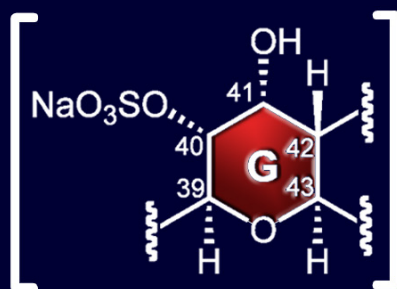
- SPARTAN 06 computer program
- Difference of calculated ^{13}C chemical shifts from experimental values



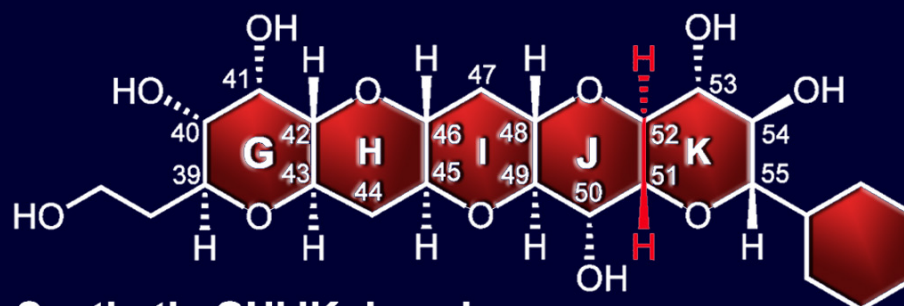
MAITOTOXIN STRUCTURE-3



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



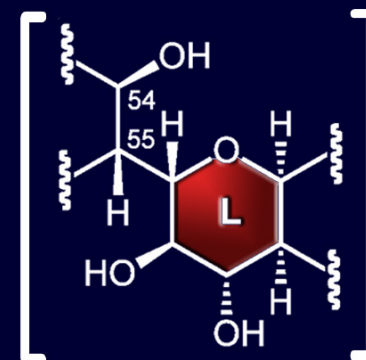
maitotoxin
structure



Synthetic GHIJK domain

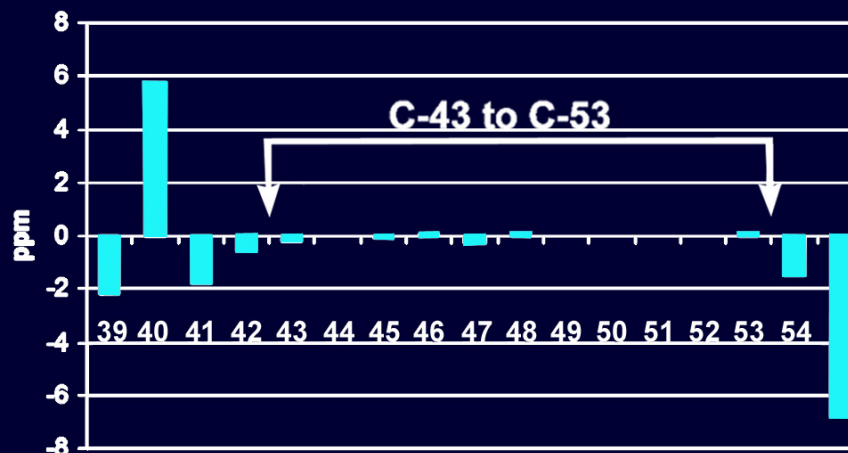
Average difference (C-43 to C-53) = 0.08 ppm

Maximum difference = 0.3 ppm



maitotoxin
structure

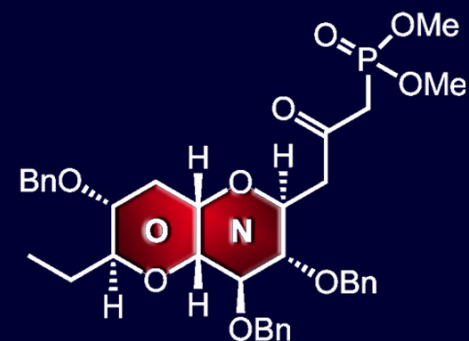
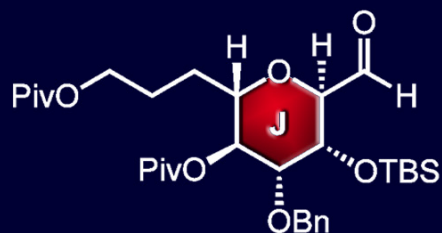
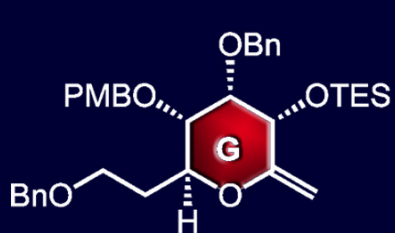
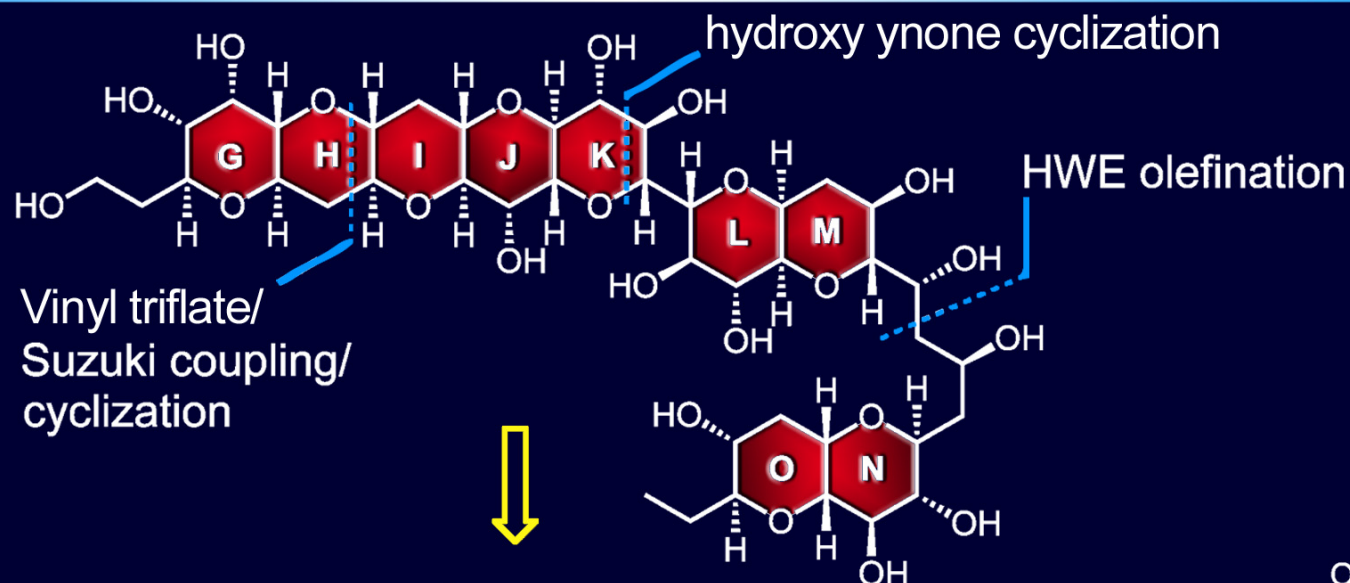
● relatively large $\Delta\delta$ values are due to the absence of a sulfate and presence of cyclohexyl substituent



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

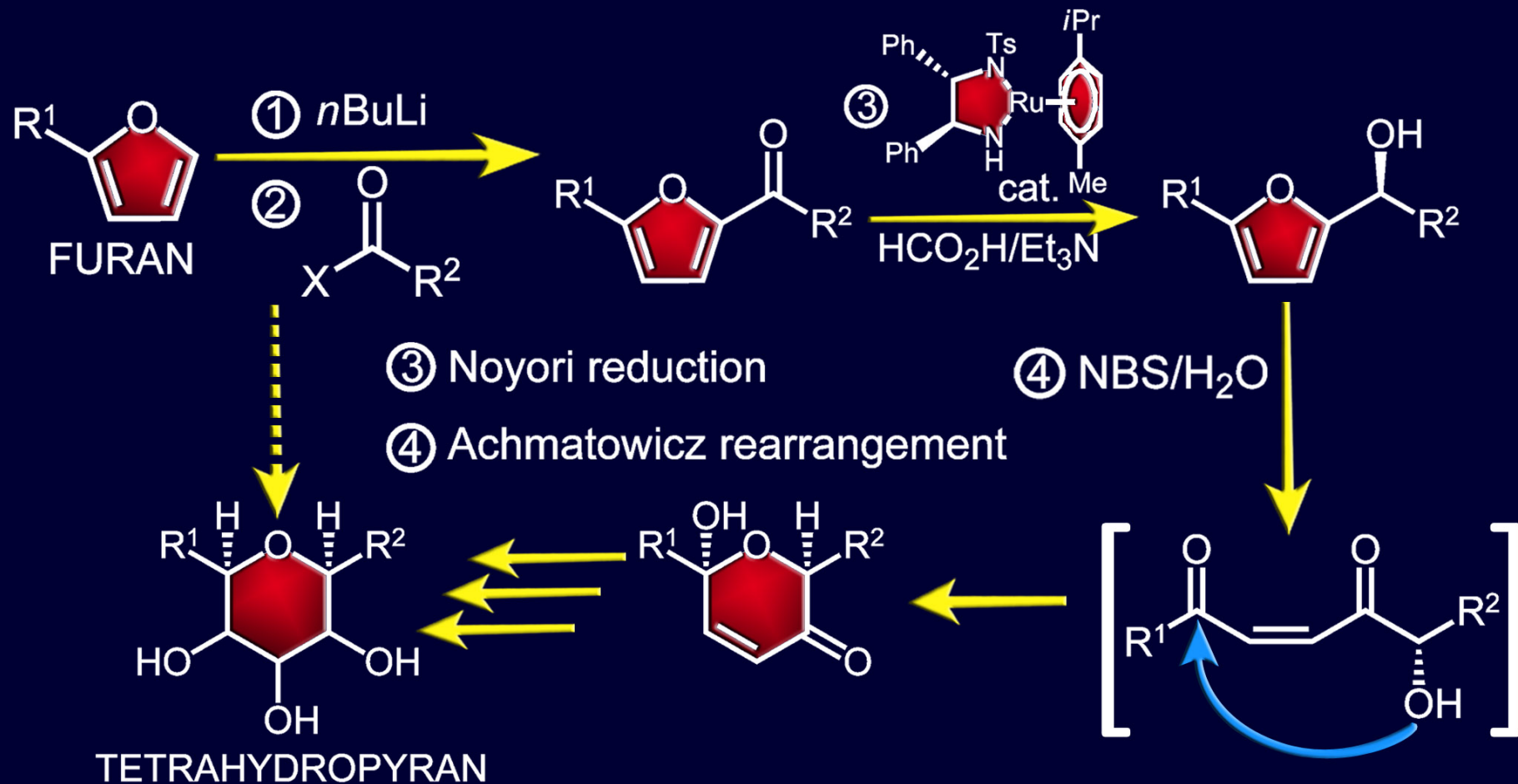


MAITOTOXIN-4: THE FURAN WAY





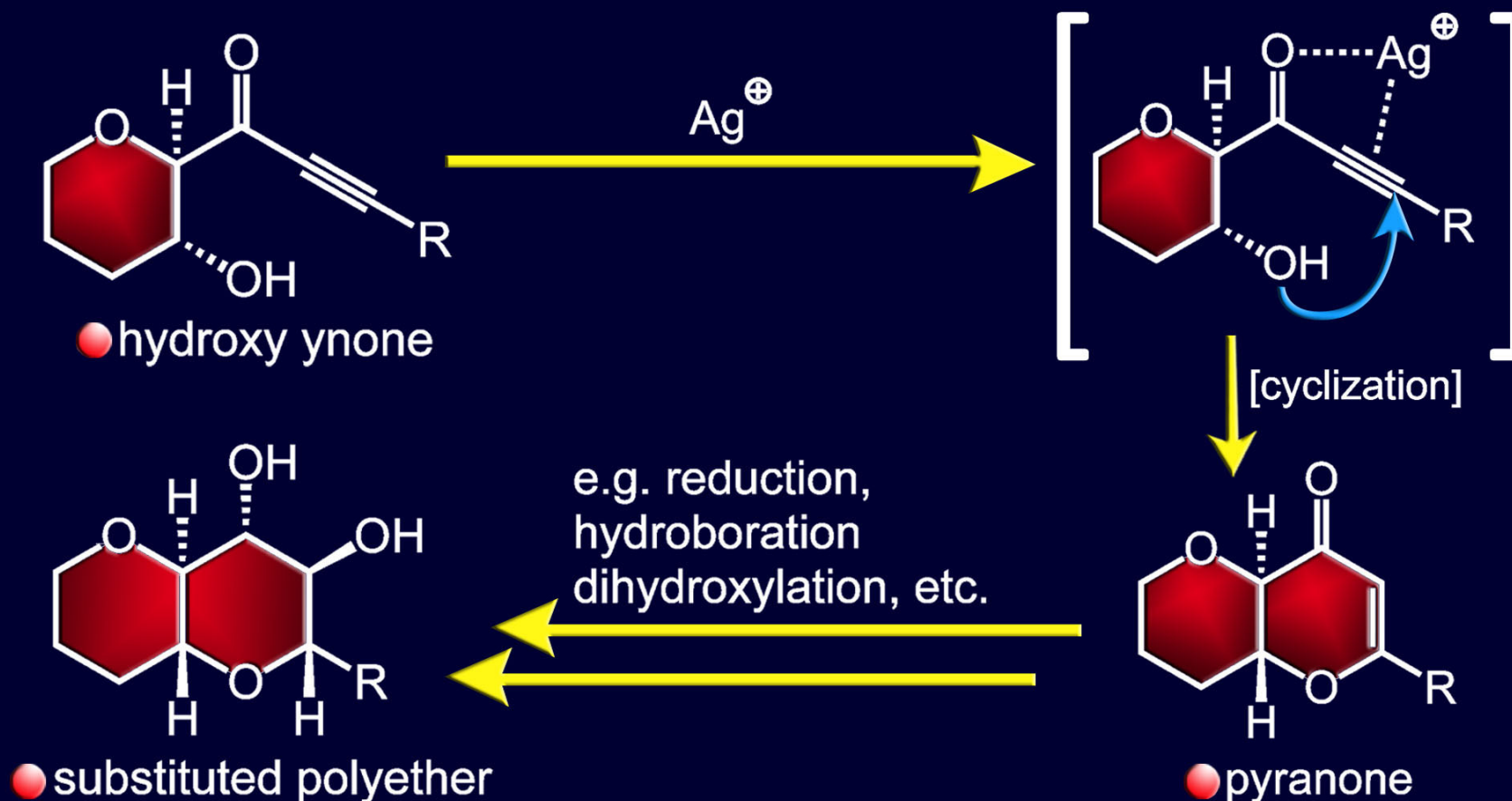
GENERAL METHOD FOR TETRAHYDROPYRAN SYNTHESIS FROM FURANS-THE NOYORI REDUCTION/ACHMATOWICZ REARRANGEMENT METHOD (NICOLAOU ET AL., 2007)



Noyori, R., et al. *J. Am. Chem. Soc.* **1996**, 118, 2521.
Achmatowicz, O. et al. *Carbohydr. Res.* **1977**, 55, 165.



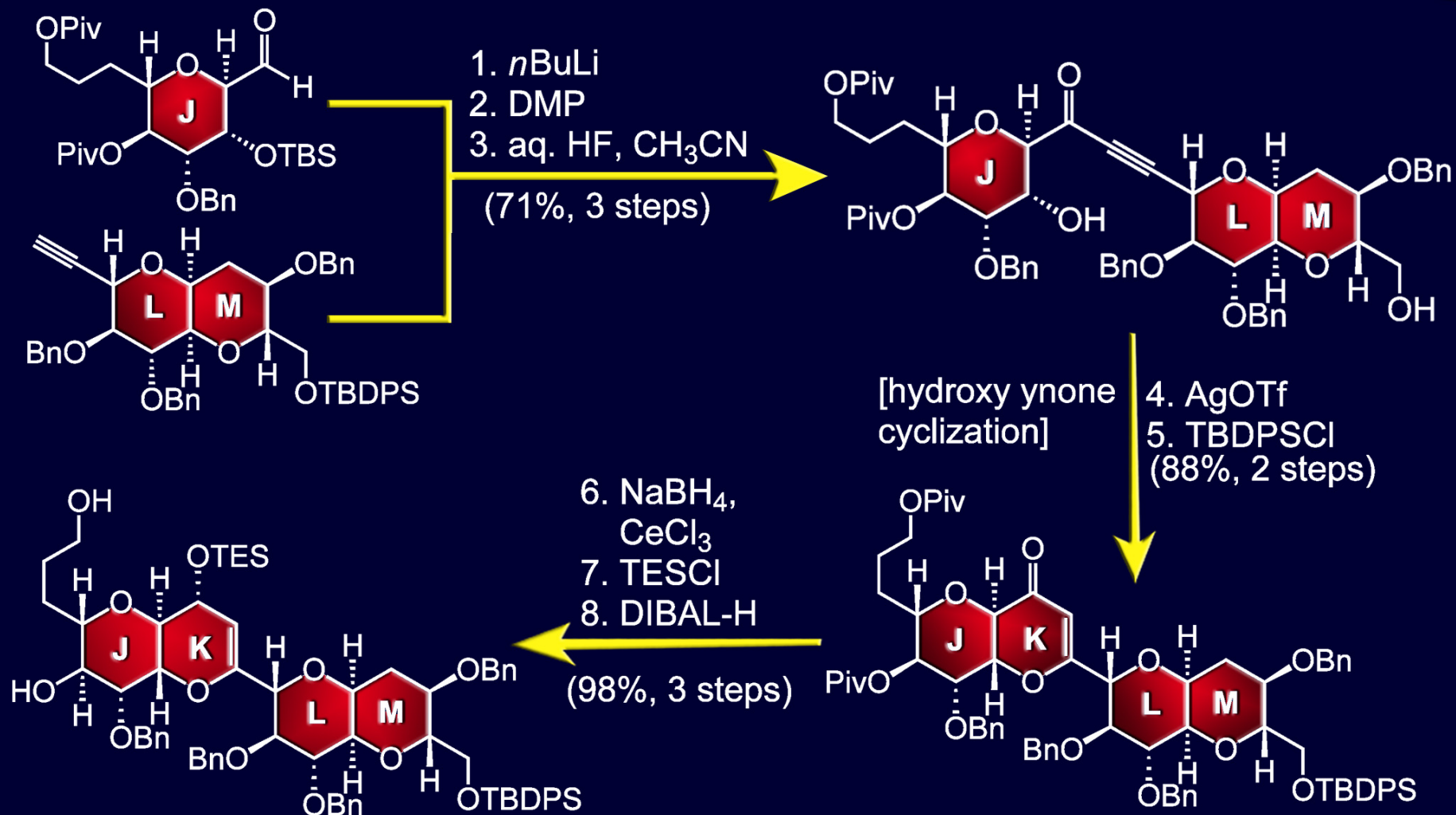
SILVER-PROMOTED, HYDROXY YNONE CYCLIZATION METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU et al., 2007)



see also: C. Wang, C. J. Forsyth, *Org. Lett.* **2006**, 8, 2997; K. C. Nicolaou, K. P. Cole, M. O. Frederick, R. J. Aversa, R. M. Denton, *Angew. Chem. Int. Ed.* **2007**, 46, 8875.

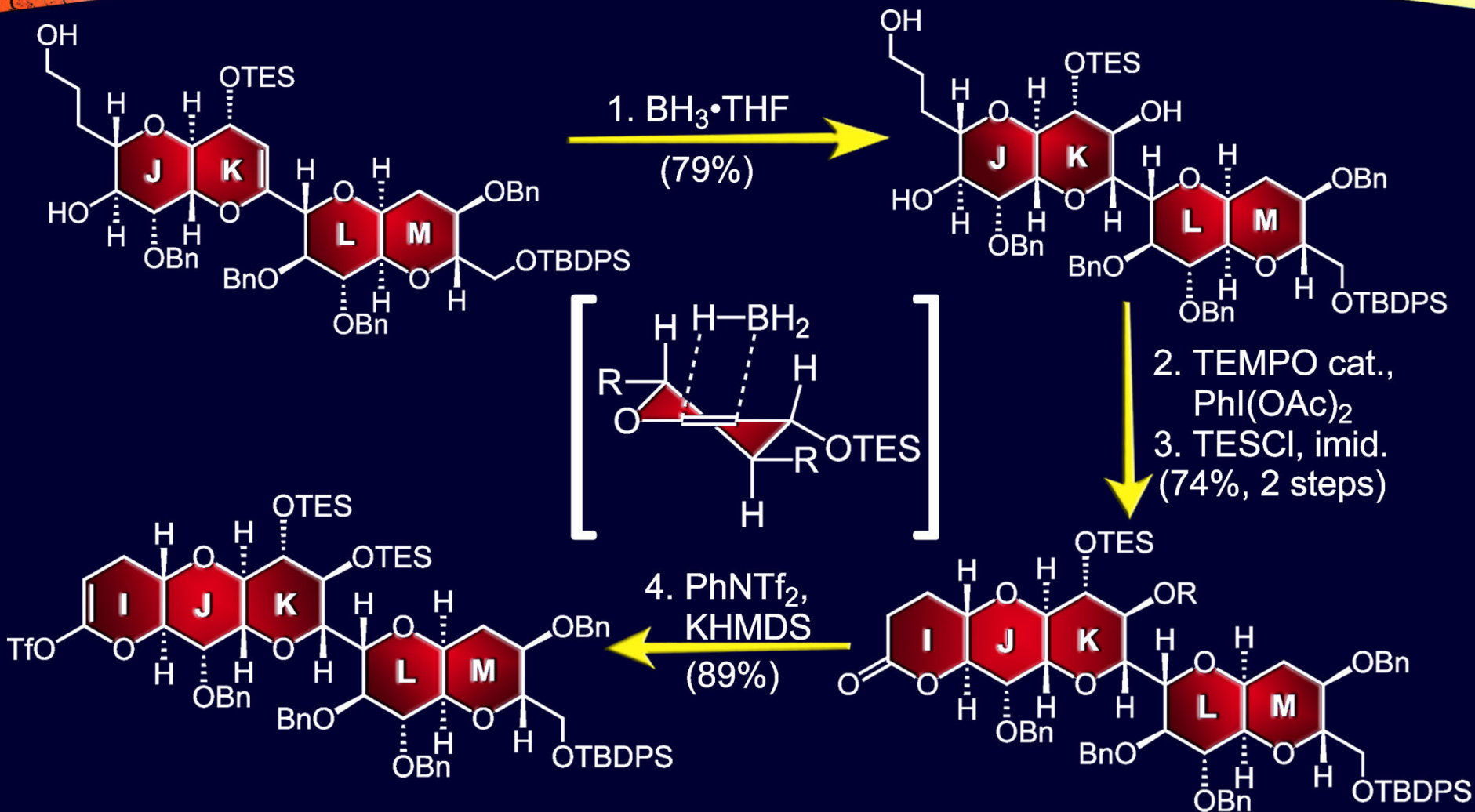


MAITOTOXIN. CONSTRUCTION OF THE JKLM RING SYSTEM



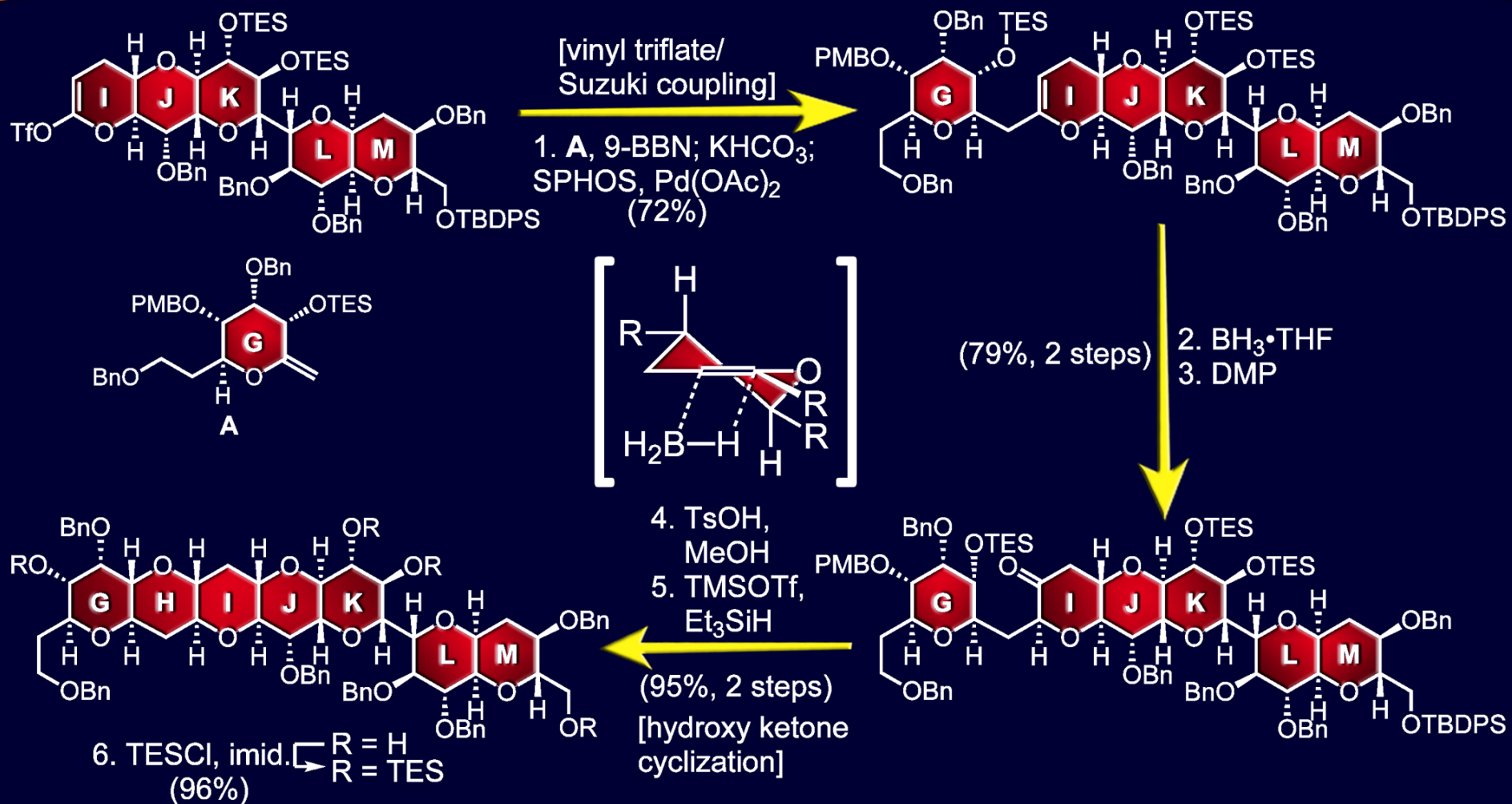


MAITOTOXIN. CONSTRUCTION OF THE IJKLM RING SYSTEM



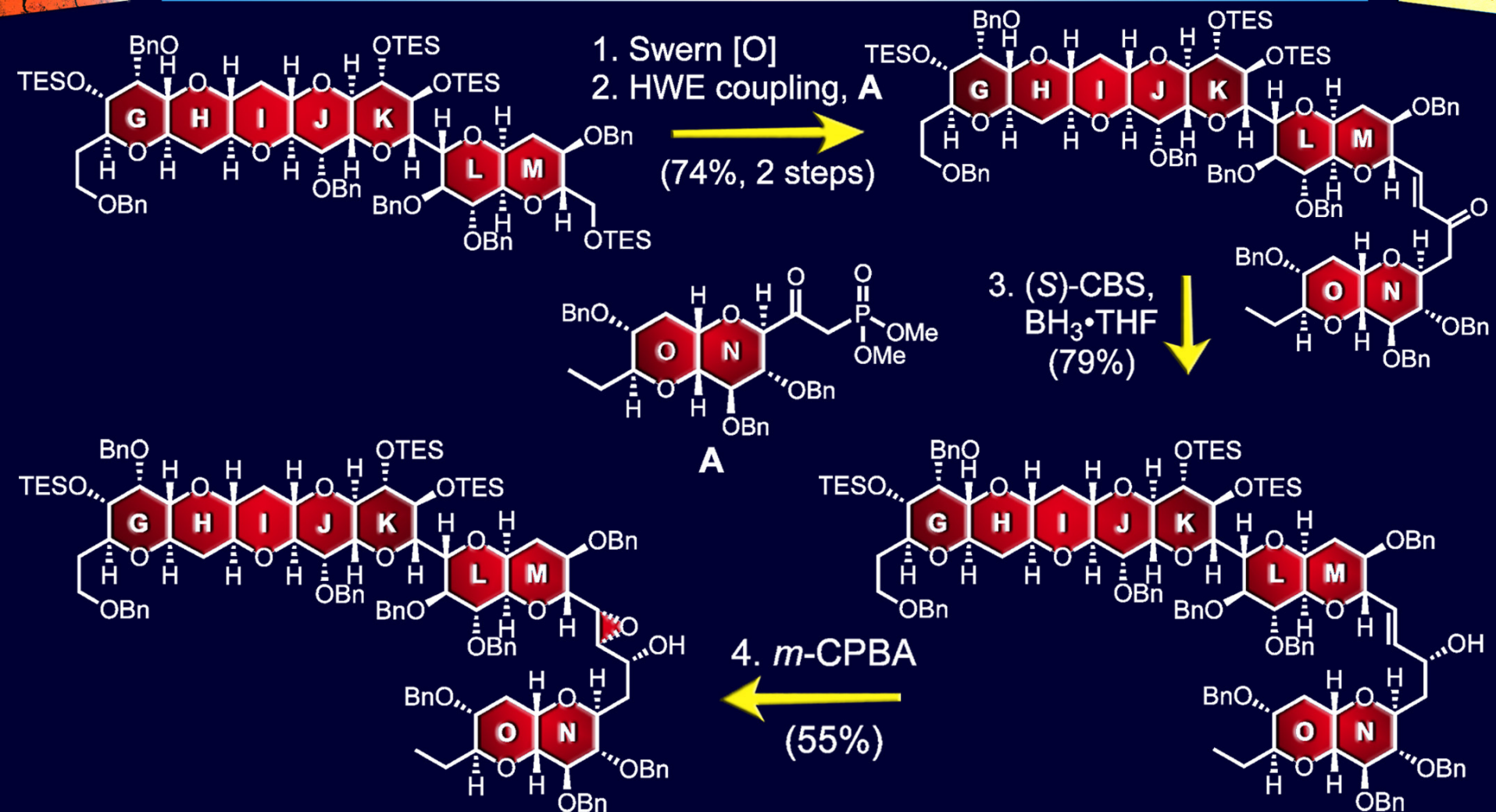


MAITOTOXIN. CONSTRUCTION OF THE GHIJKLM RING SYSTEM



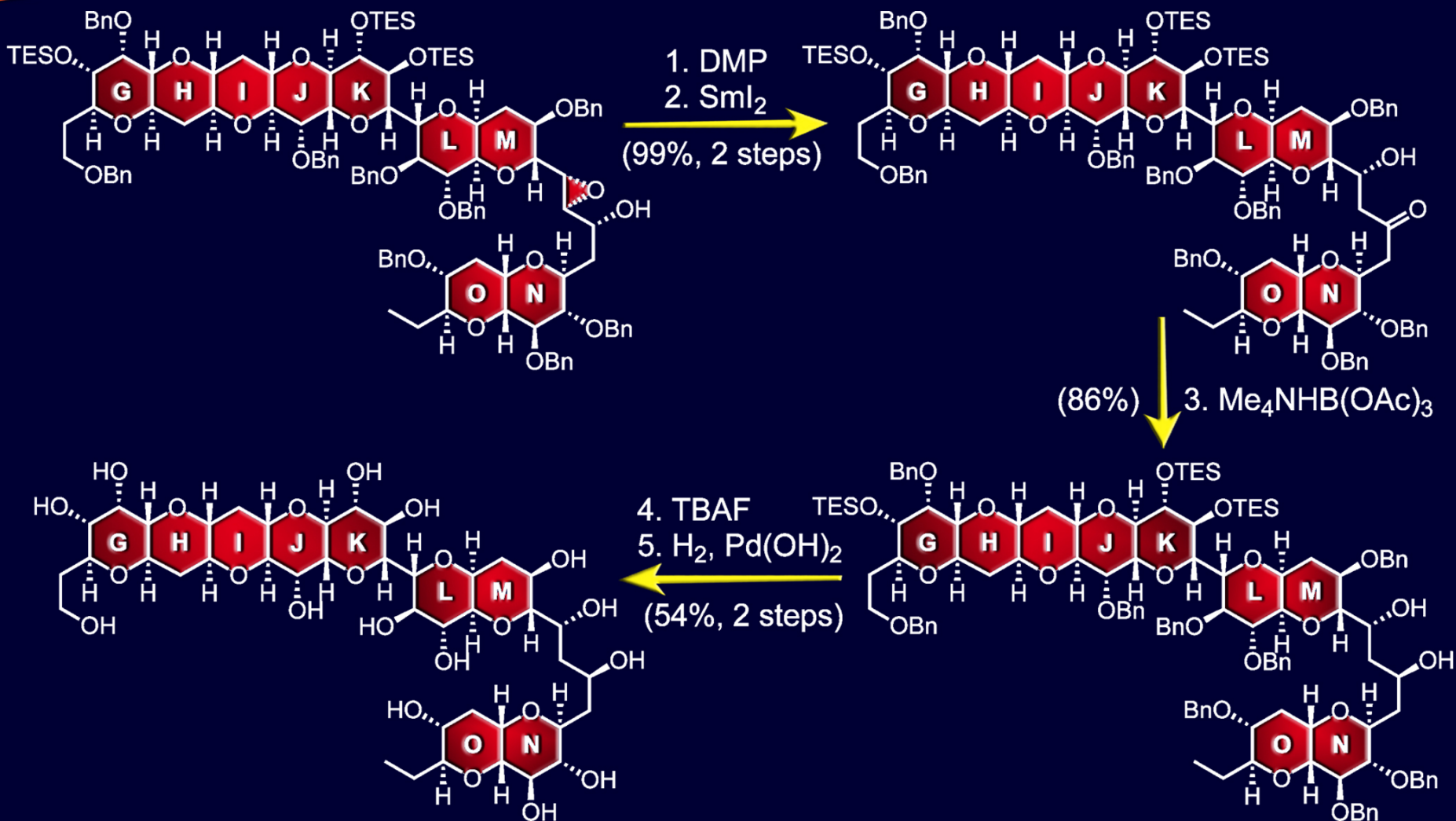


MAITOTOXIN. CONSTRUCTION OF THE GHIJKLMNO RING SYSTEM



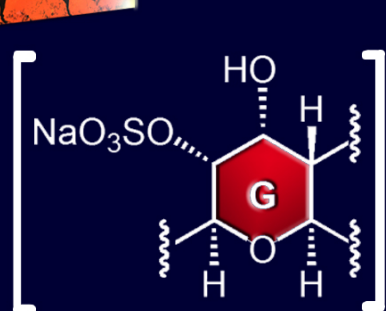


MAITOTOXIN. SYNTHESIS OF THE GHIJKLMNO DOMAIN

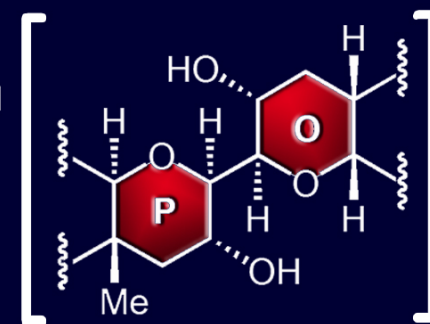
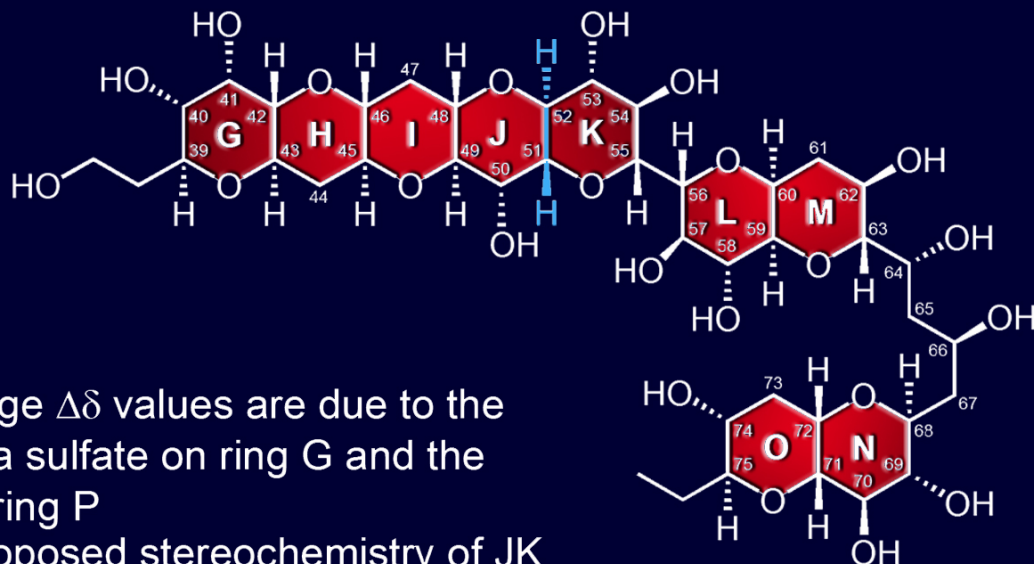




MAITOTOXIN-15

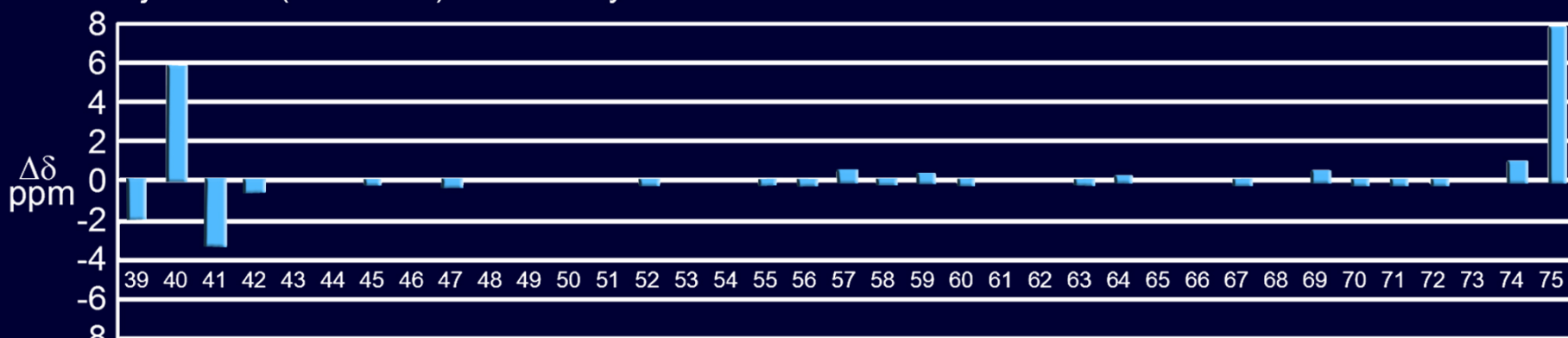


maitotoxin structure



maitotoxin structure

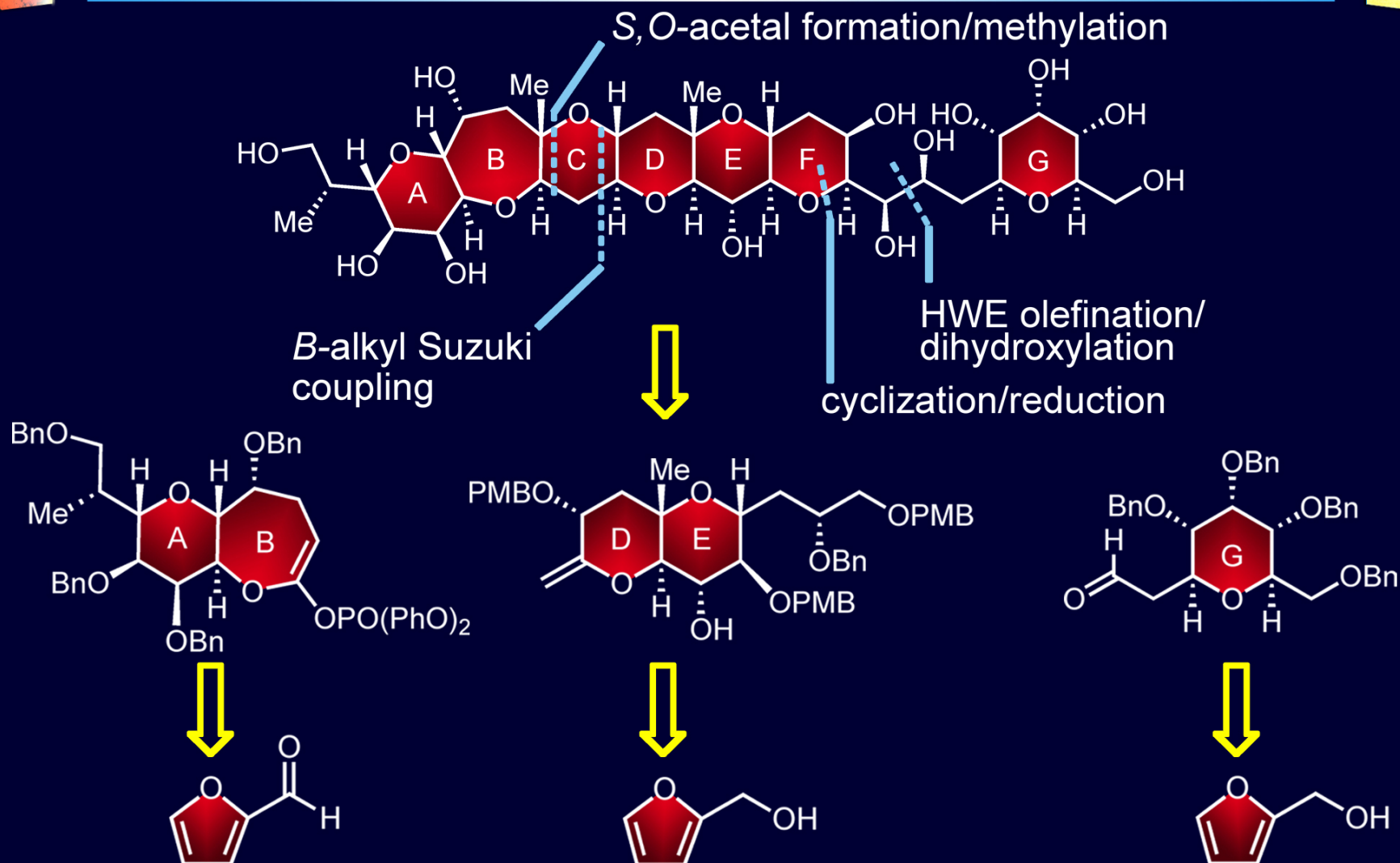
- relatively large $\Delta\delta$ values are due to the absence of a sulfate on ring G and the absence of ring P
- originally proposed stereochemistry of JK junction (C51-C52) most likely correct



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

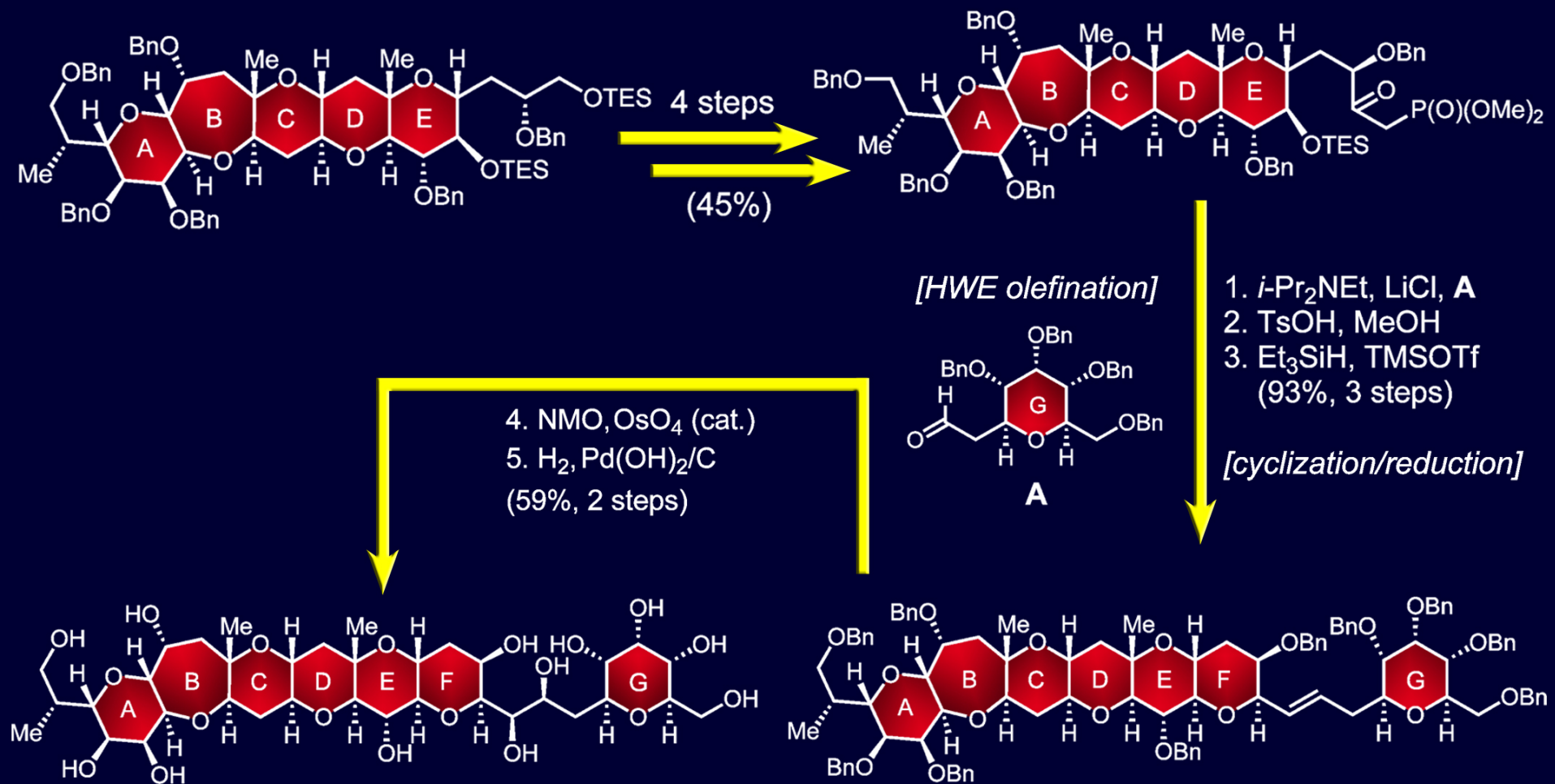


RETROSYNTHETIC ANALYSIS OF MAITOTOXIN ABCDEFGH RING SYSTEM



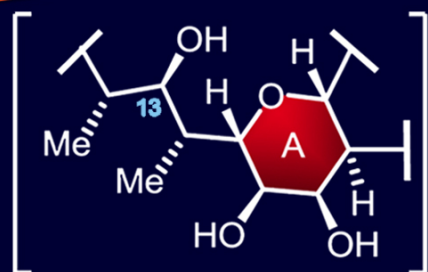


MAITOTOXIN. CONSTRUCTION OF THE ABCDE RING SYSTEM

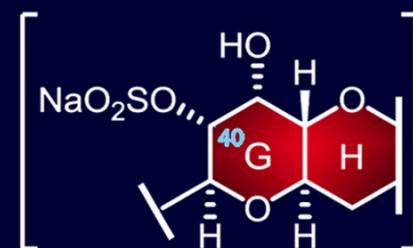




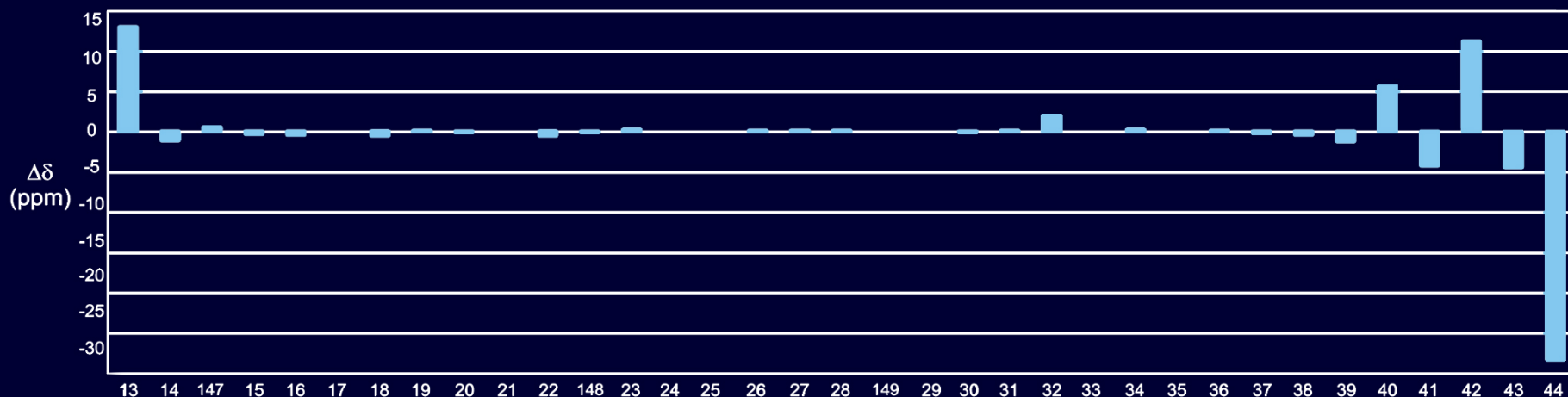
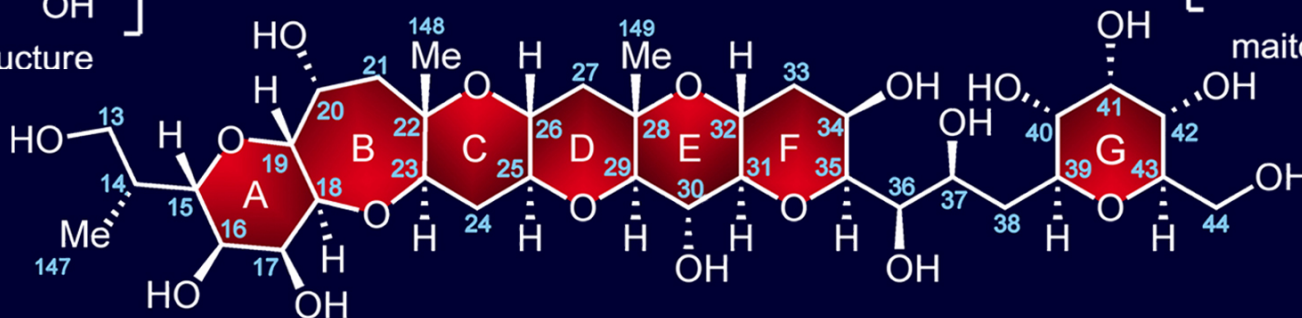
MAITOTOXIN. ^{13}C NMR DATA FOR THE ABCDEFG DOMAIN



maitotoxin structure



maitotoxin structure



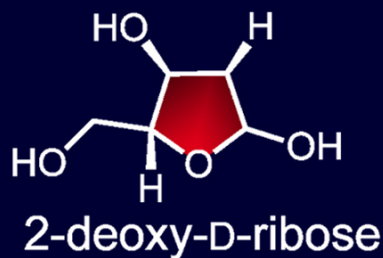
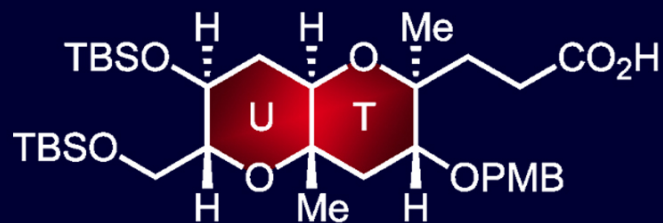
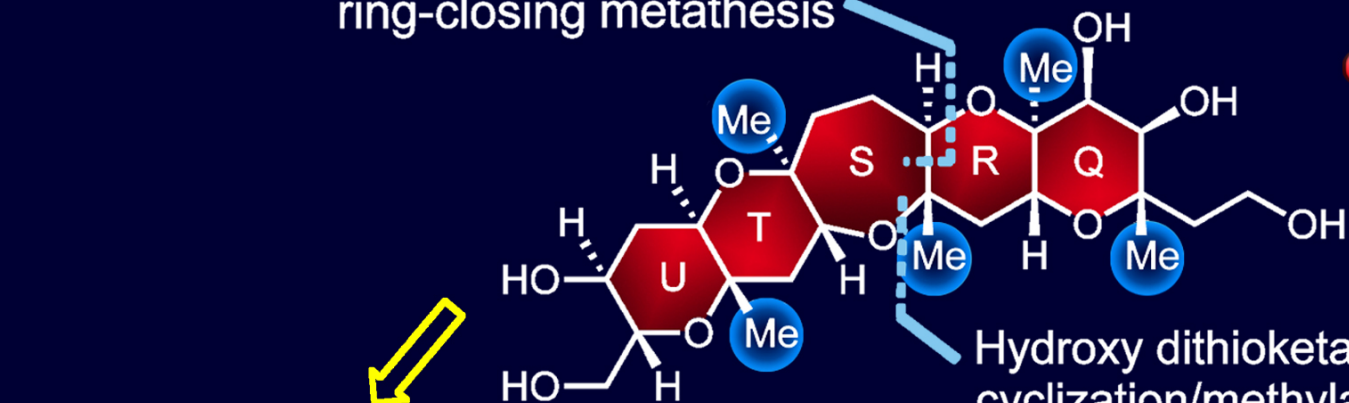


RETROSYNTHETIC ANALYSIS OF MAITOTOXIN QRSTU RING SYSTEM

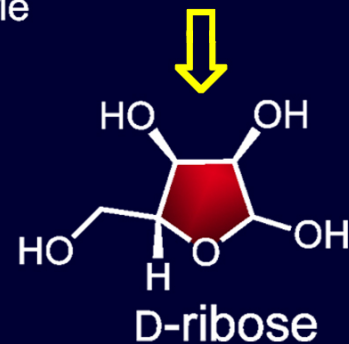


Esterification/
ring-closing metathesis

● 5 angular Me groups
within a pentacyclic
system

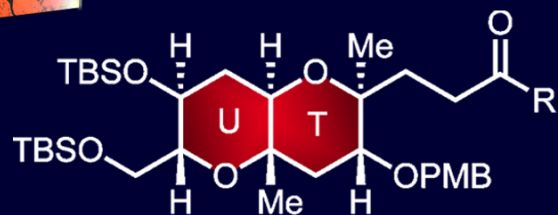


Hydroxy dithioketal
cyclization/methylation

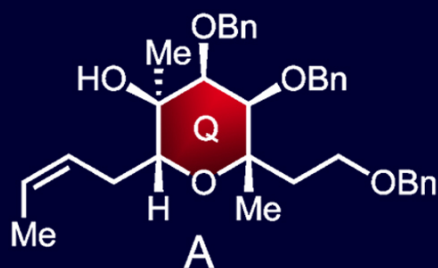




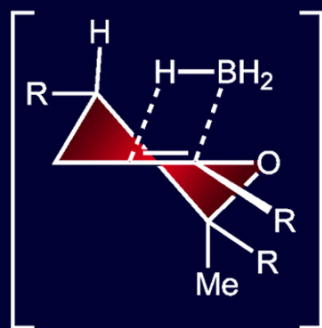
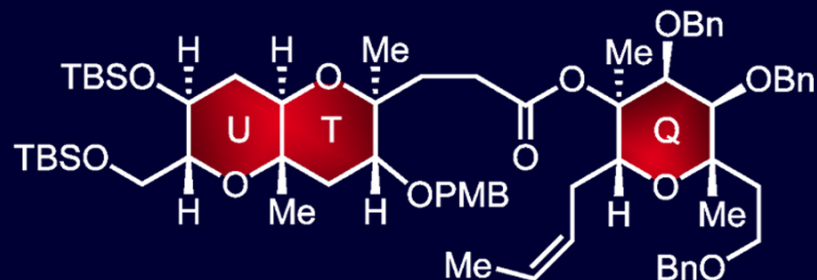
MAITOTOXIN. CONSTRUCTION OF THE QRUT RING SYSTEM



1. $(\text{COCl})_2$ $\rightarrow$ R = OH
B, R = Cl

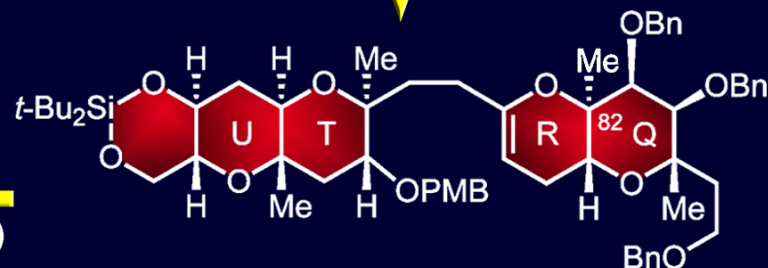


2. A, KHMDS;
then B
(65%,
100% brsm A)



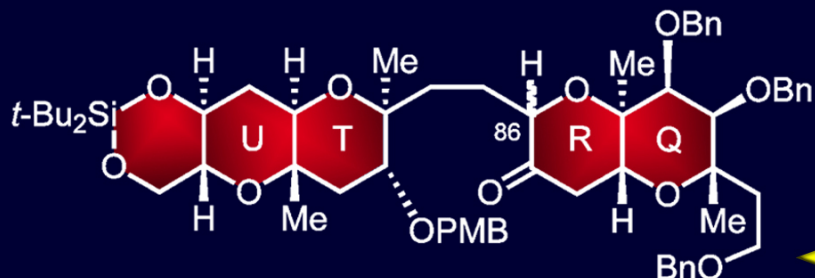
[Takai olefination/
ring-closing
metathesis]

3. TBAF
4. $t\text{-Bu}_2\text{Si}(\text{OTf})_2$
5. TiCl_4 , TMEDA,
Zn, PbCl_2 ,
 CH_3CHBr_2
(87%, 3 steps)



6. $\text{BH}_3 \cdot \text{THF}$;
 H_2O_2
(3:1 dr
 $\text{H}_{86} \beta:\alpha$)

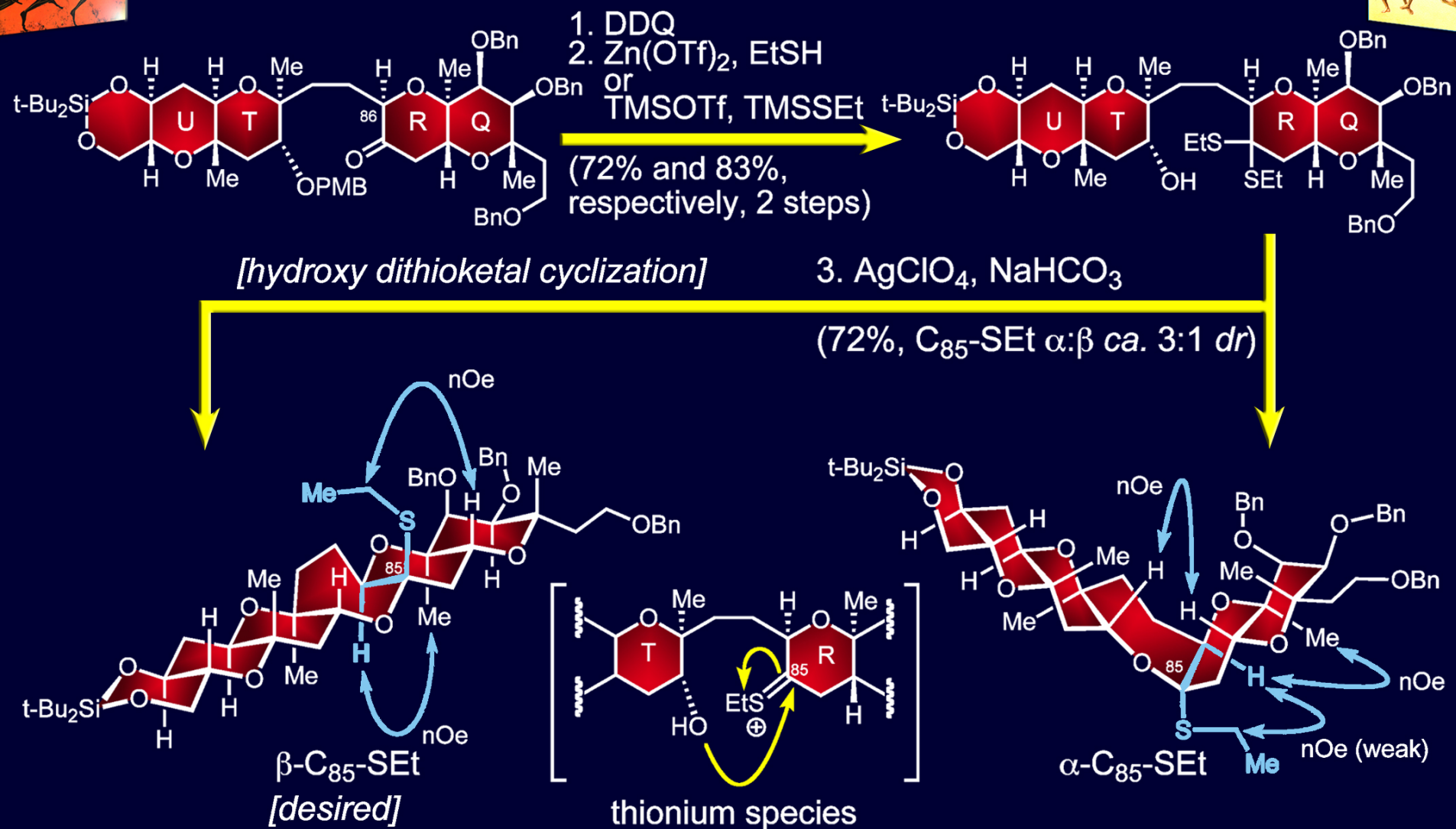
7. DMP
(90%, 2 steps)



8. K_2CO_3 , EtOH,
anaerobic (89%) $\rightarrow$ $\beta\text{-H}_{86}$ isomer
 $\alpha\text{-H}_{86}$ isomer

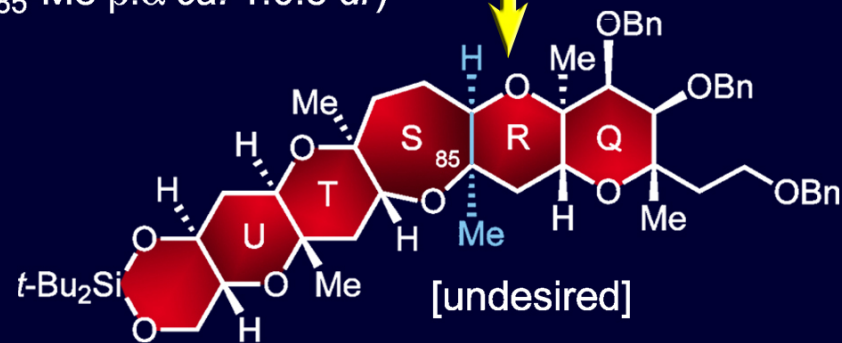
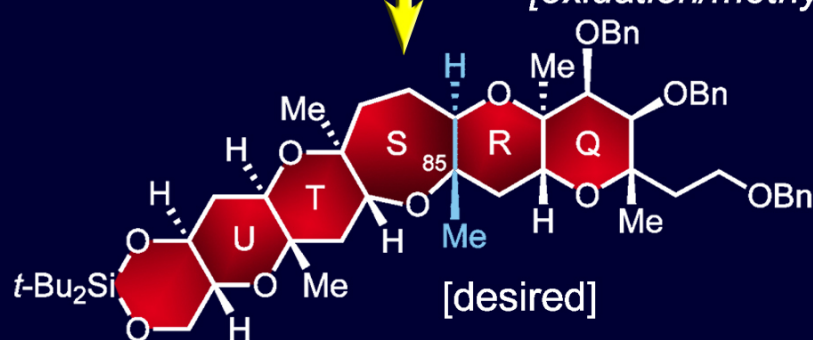
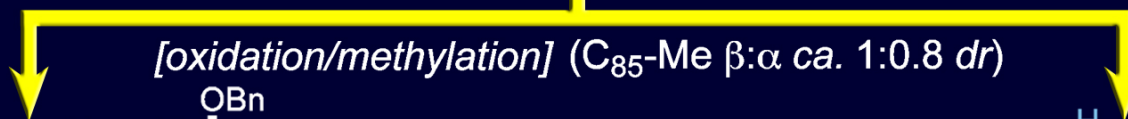
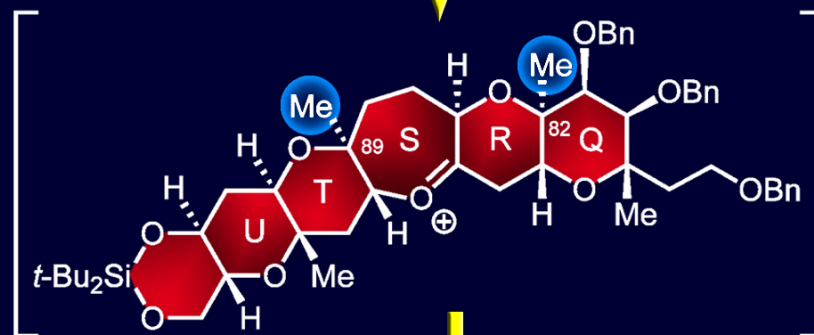
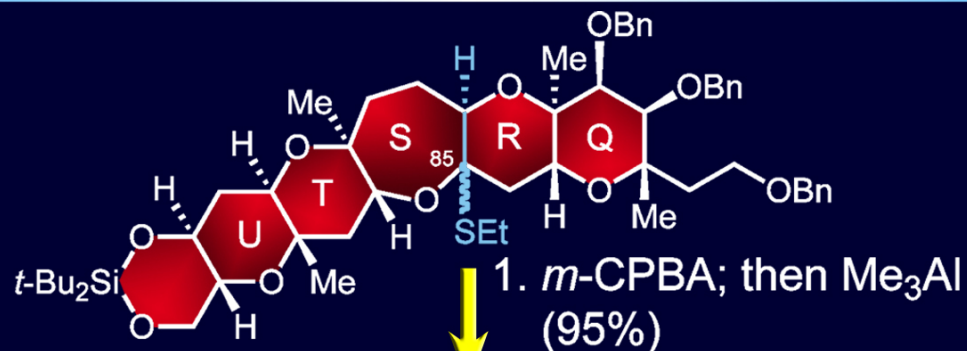


MAITOTOXIN. SYNTHESIS OF THE QRSTU RING SYSTEM



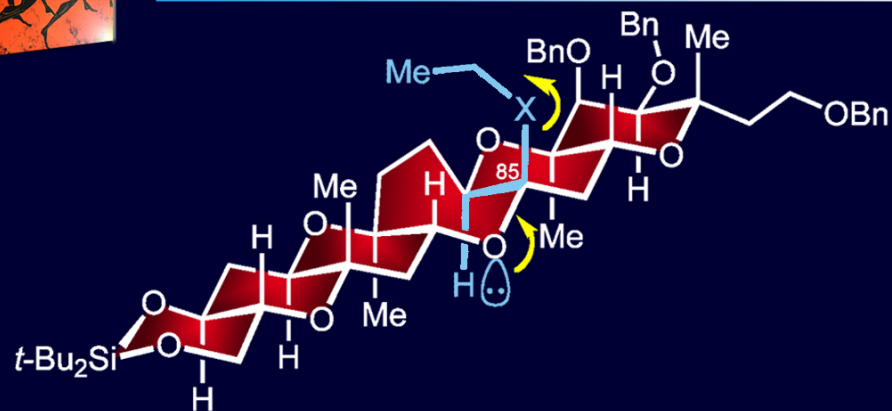


MAITOTOXIN. SYNTHESIS OF THE QRSTU RING SYSTEM





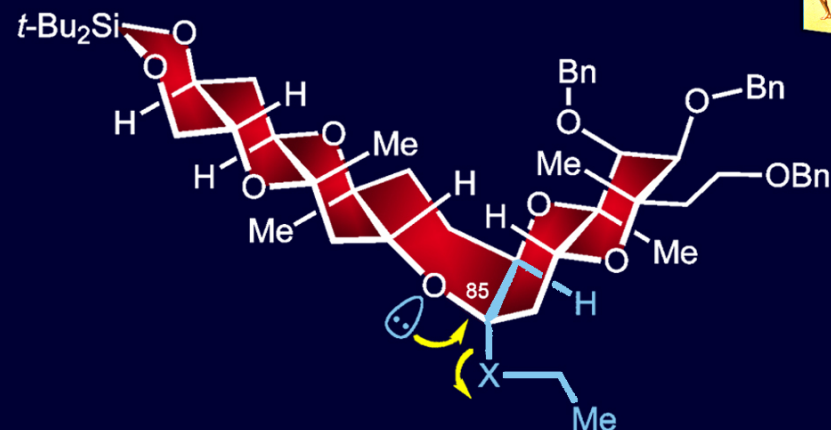
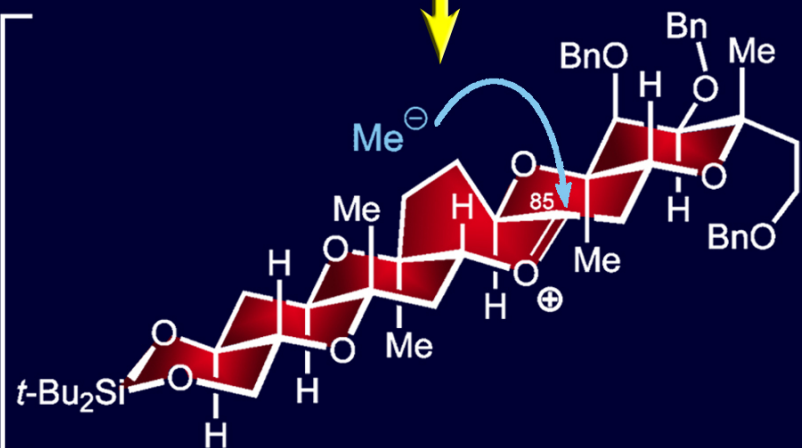
MAITOTOXIN. SYNTHESIS OF THE QRSTU RING SYSTEM



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

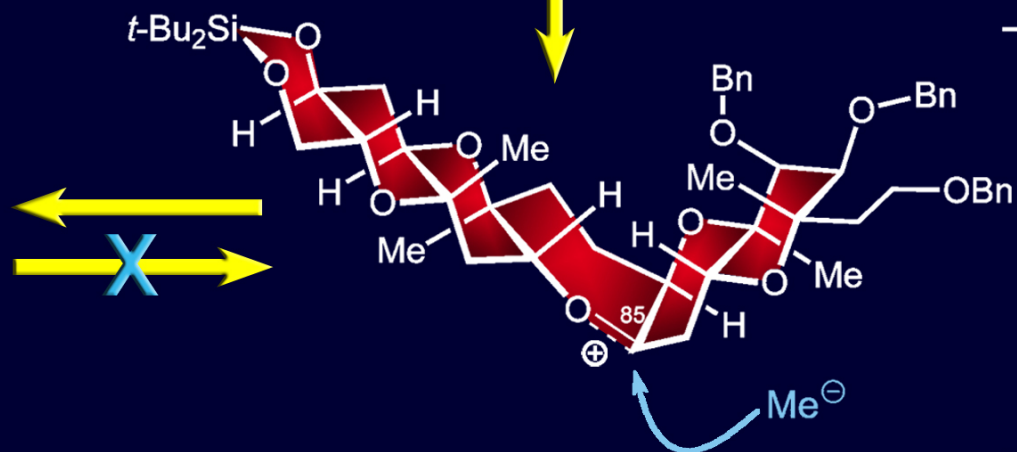
1. then Me_3Al

[oxidation/methylation]



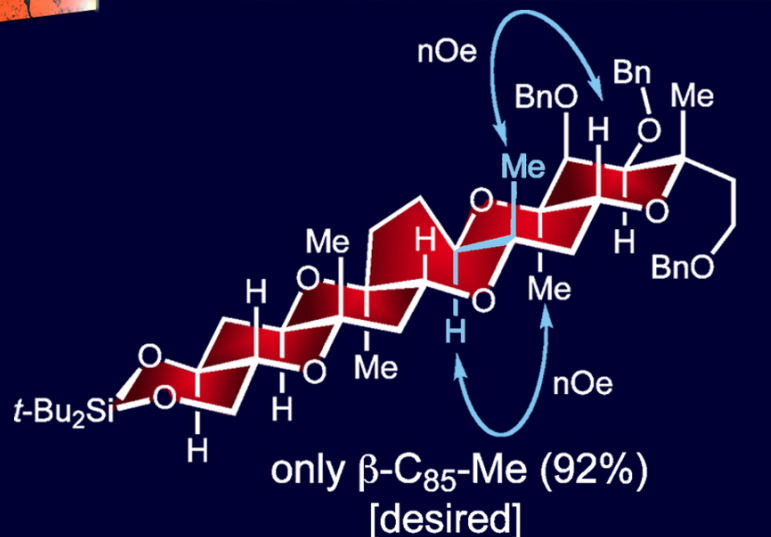
1. *m*-CPBA $\begin{cases} \text{X} = \text{S} \text{ (major)} \\ \text{X} = \text{SO}_2 \text{ (not isolated)} \end{cases}$

1. then Me_3Al

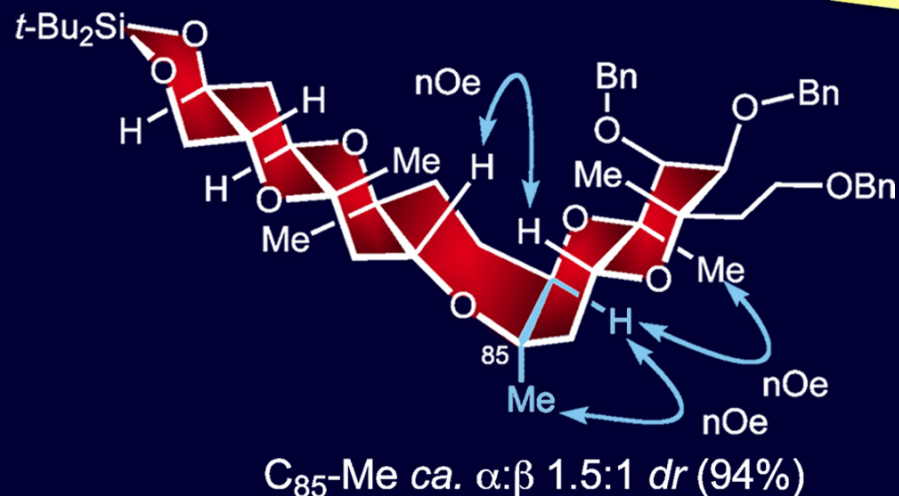
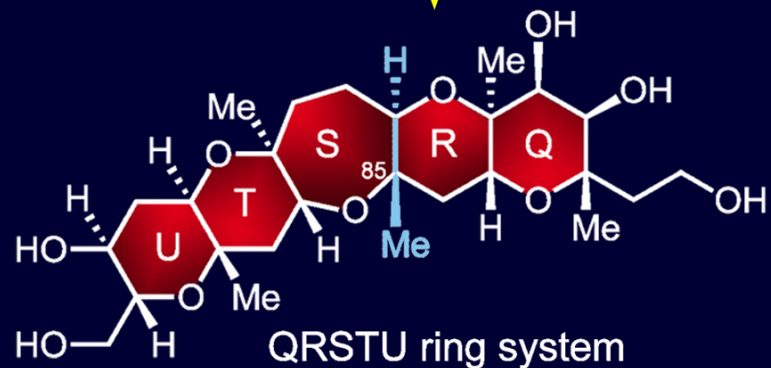




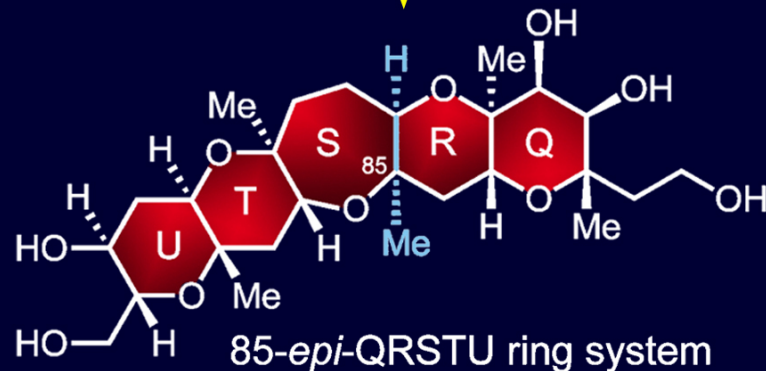
MAITOTOXIN. SYNTHESIS OF THE QRSTU DOMAIN AND THE 85-*epi*-QRSTU RING SYSTEM



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

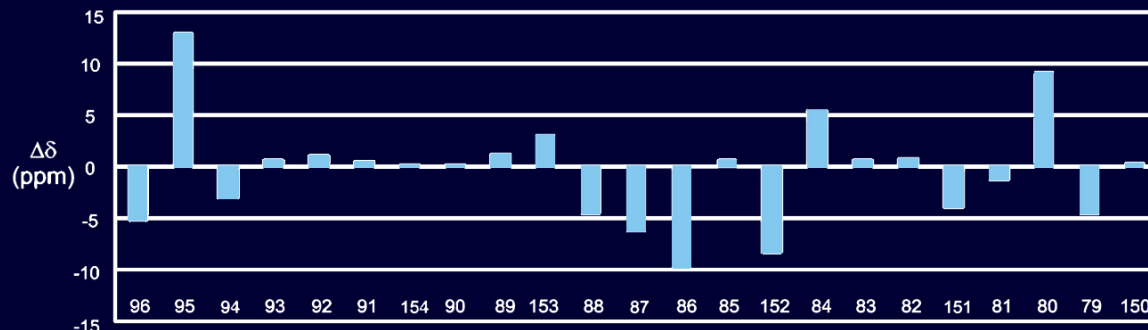
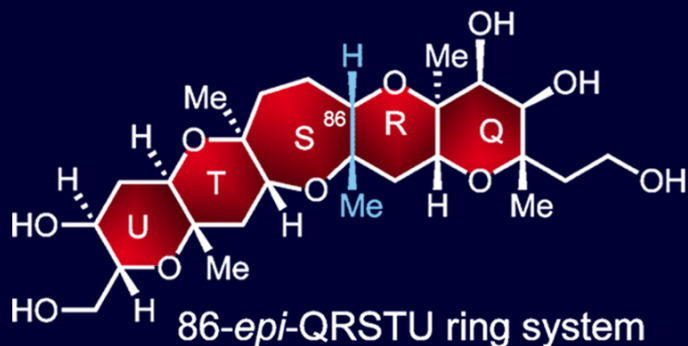
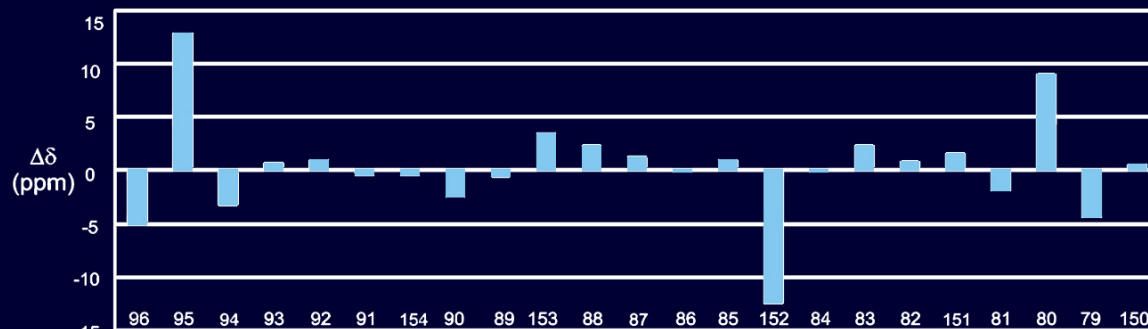
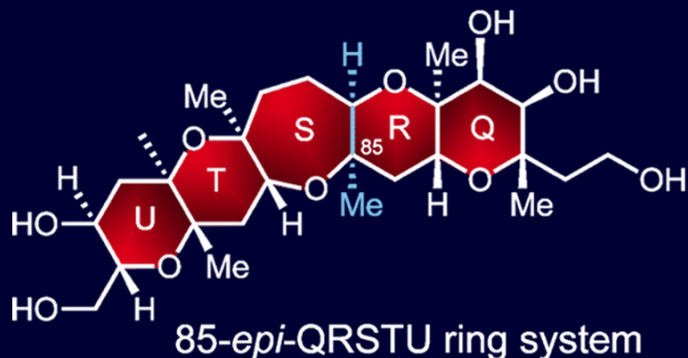
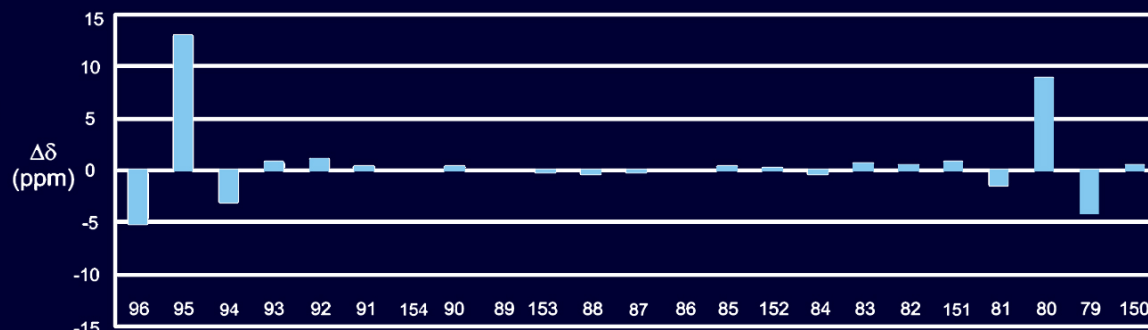
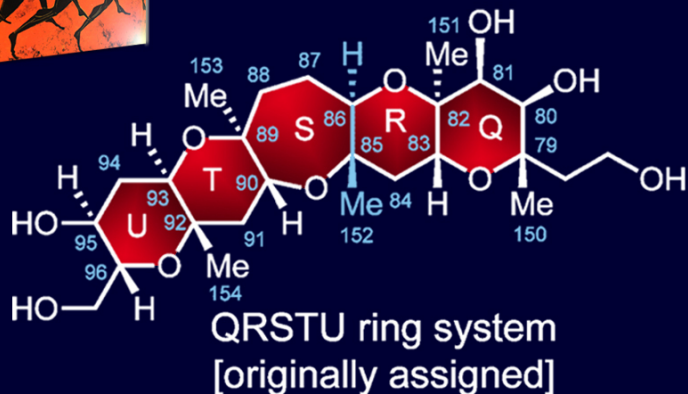


1. TBAF
2. H₂, Pd(OH)₂/C
(80%, 2 steps)



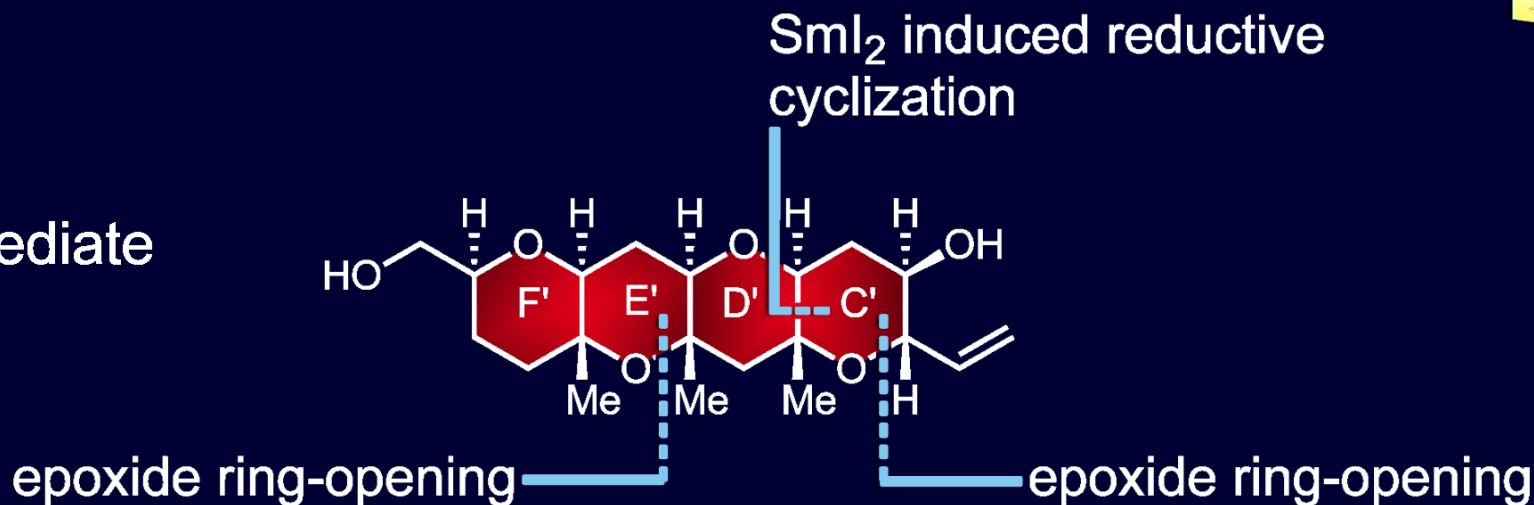


MAITOTOXIN. ^{13}C NMR DATA FOR THE QRSTU DOMAIN

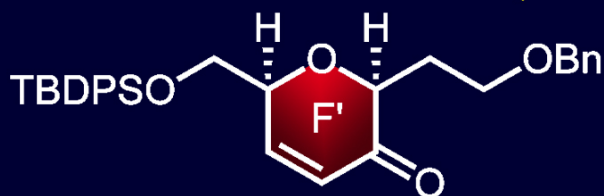


RETROSYNTHETIC ANALYSIS AND CONSTRUCTION OF MAITOTOXIN C'D'E'F' RING SYSTEM

intermediate



[13.6% overall yield]



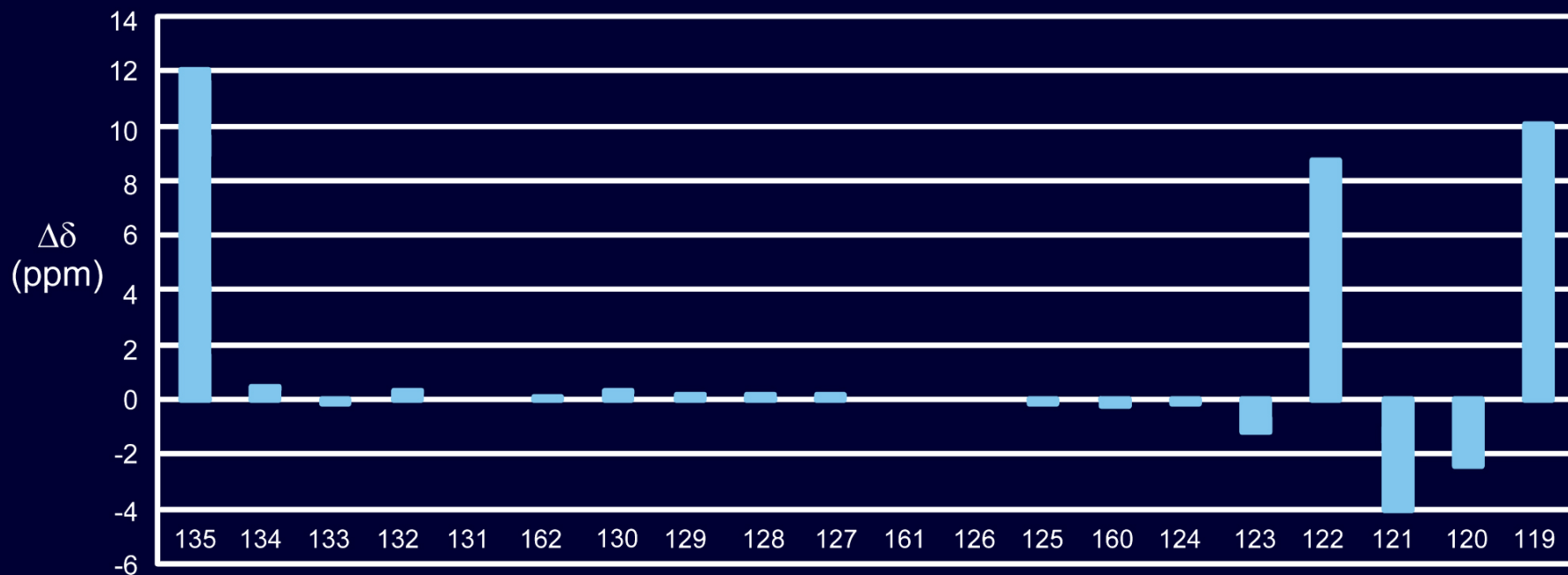
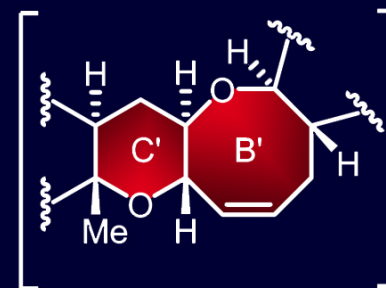
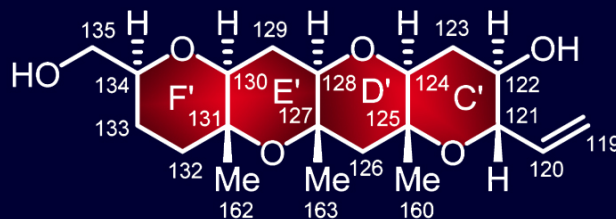
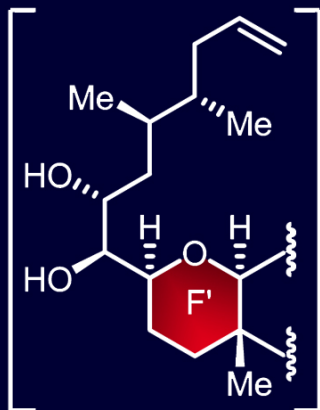
[76.6% overall yield]



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



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

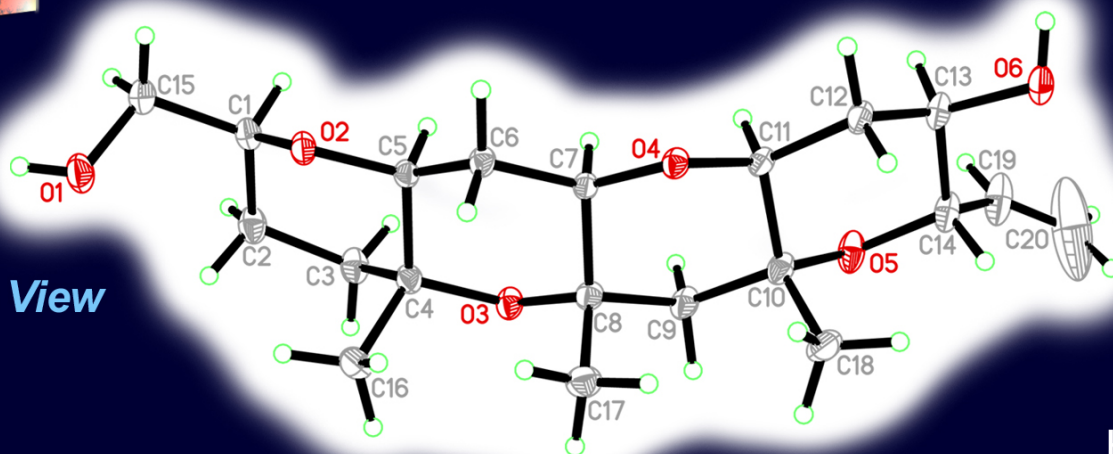




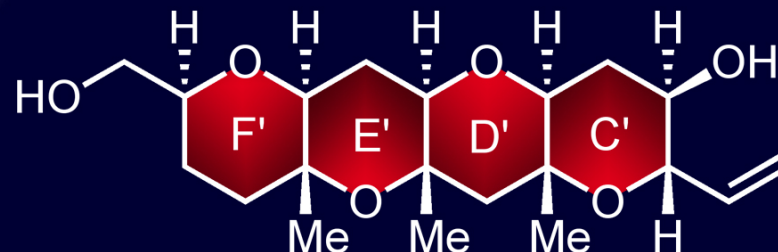
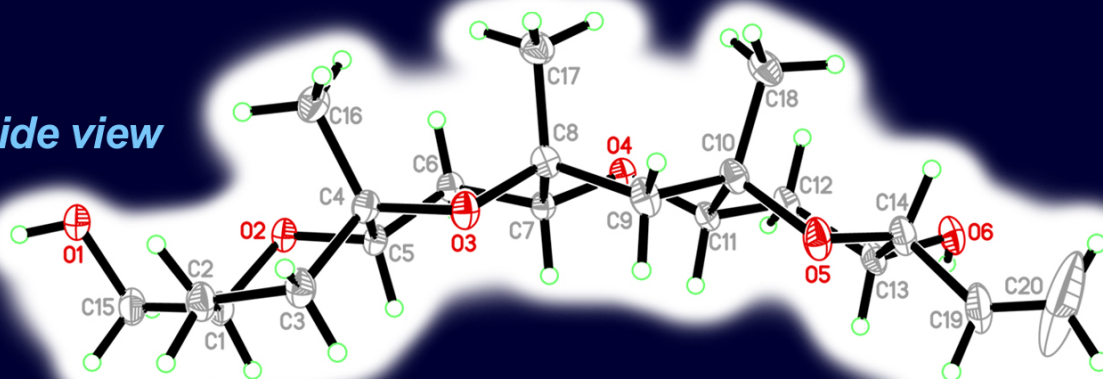
X-RAY STRUCTURE OF C'D'E'F' MAITOTOXIN DOMAIN



Top View



Side view



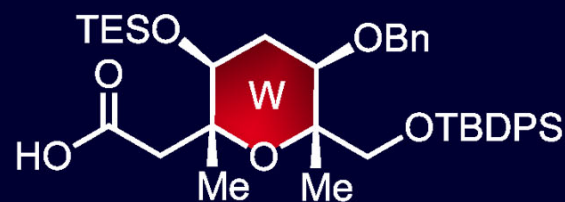
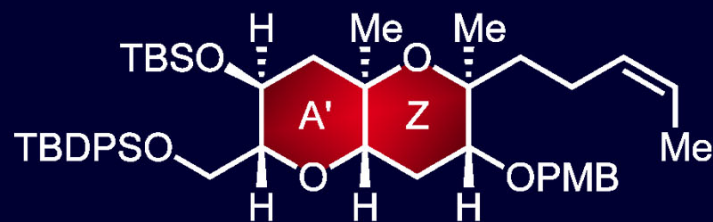
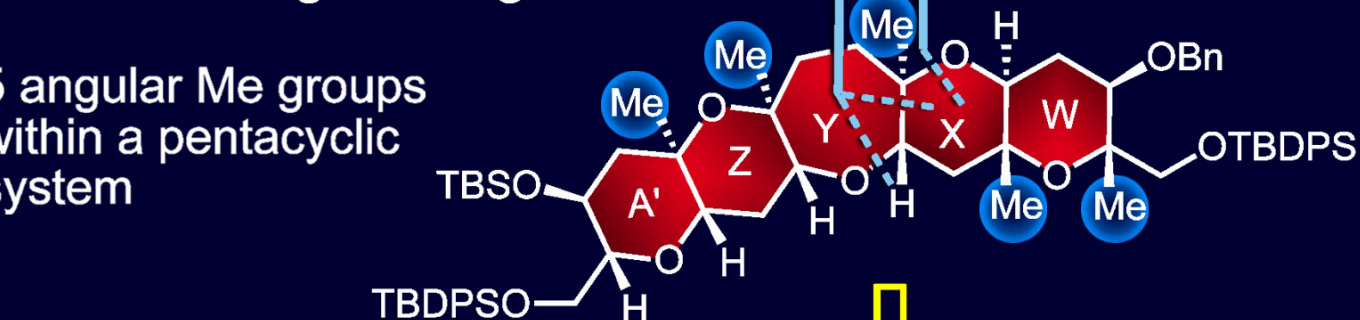
$$\begin{aligned} d(C_1-C_{13}) &= 9.19 \text{ \AA}; d(C_2-C_{13}) = 9.49 \text{ \AA}; d(H_{1A}-H_{13}) = 8.58 \text{ \AA}; \\ d(H_{2A}-H_{14}) &= 10.45 \text{ \AA}; \alpha(C_{14}-C_8-C_2) = 146.42^\circ; \alpha(C_{13}-C_7-C_1) = 153.04^\circ \end{aligned}$$

RETROSYNTHETIC ANALYSIS OF MAITOTOXIN WXYZA' RING SYSTEM

Esterification/
ring-closing metathesis

Hydroxy dithioketal cyclization/
methylation

- 5 angular Me groups within a pentacyclic system

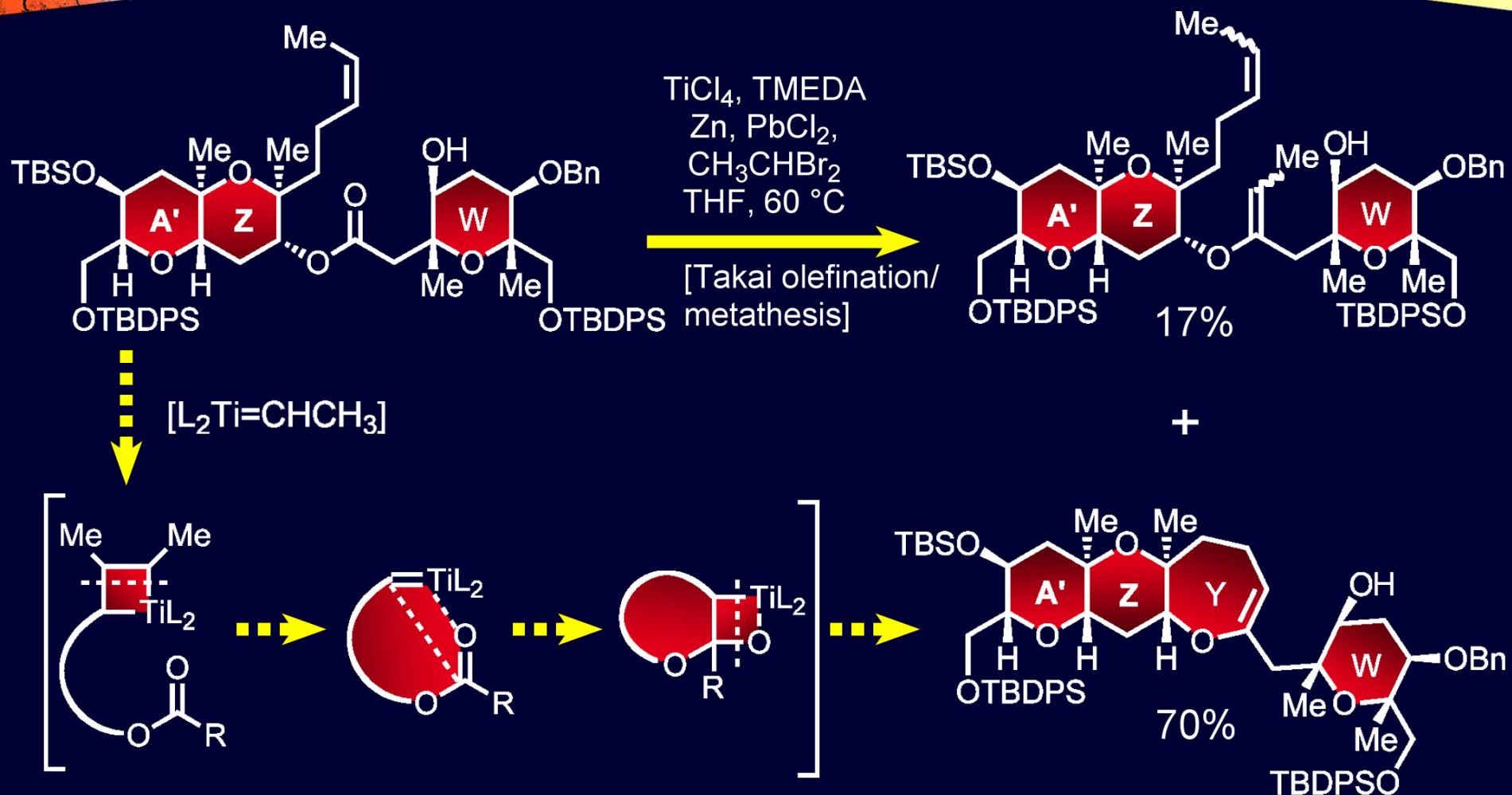


2-deoxy-D-ribose





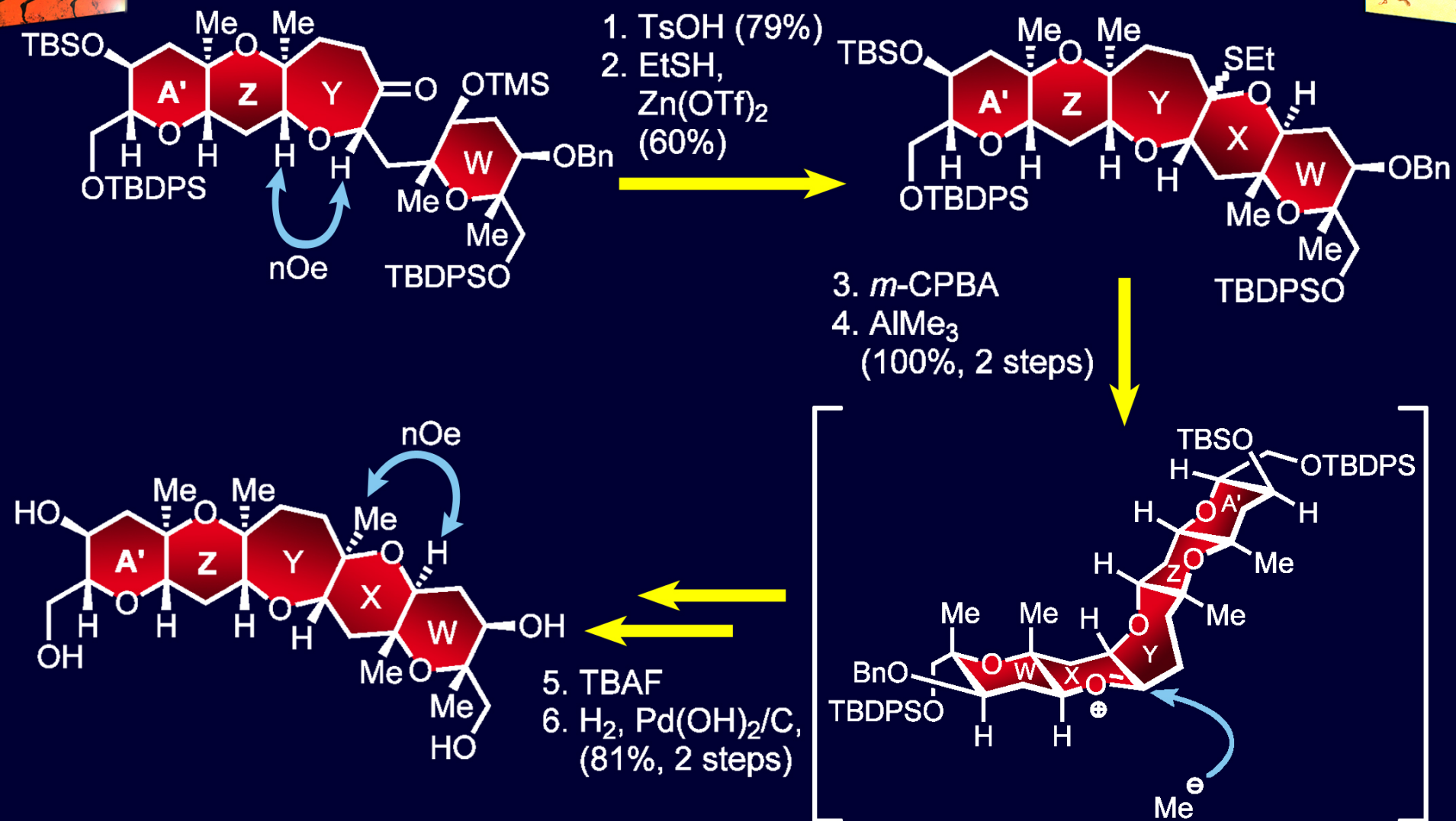
MAITOTOXIN. CONSTRUCTION OF THE A'ZYW RING SYSTEM



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

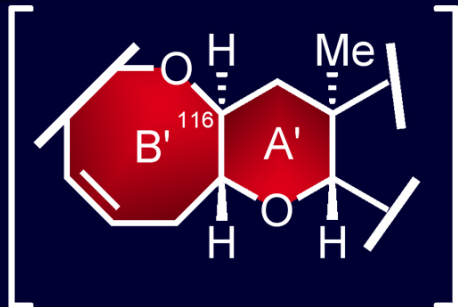


MAITOTOXIN. CONSTRUCTION OF THE A'ZYXW RING SYSTEM

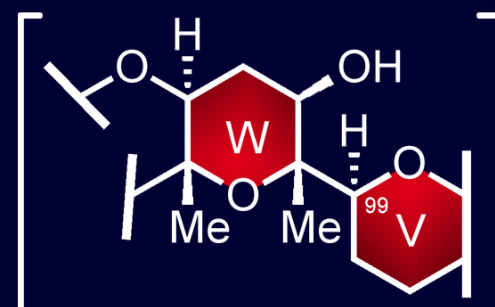
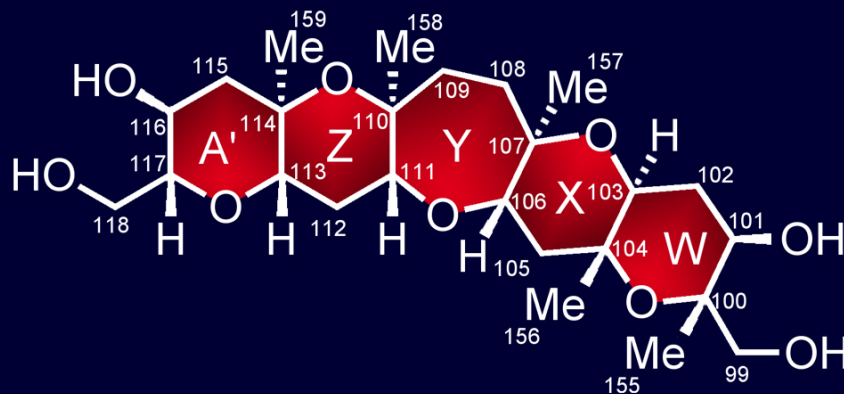




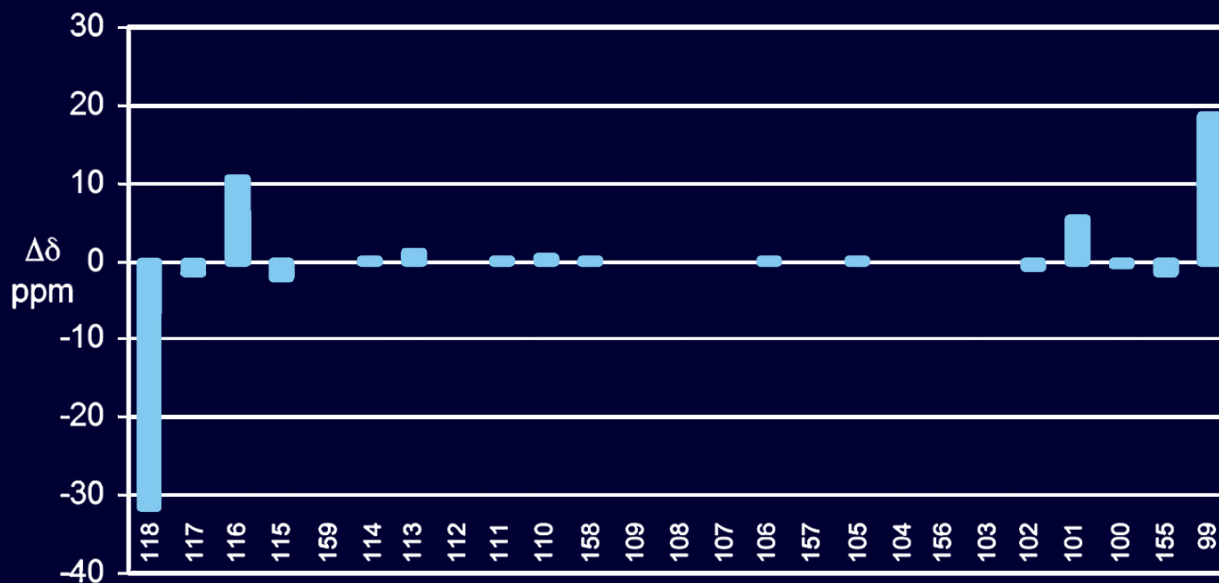
MAITOTOXIN. ^{13}C DATA FOR THE WXYZA' DOMAIN



maitotoxin structure



maitotoxin structure



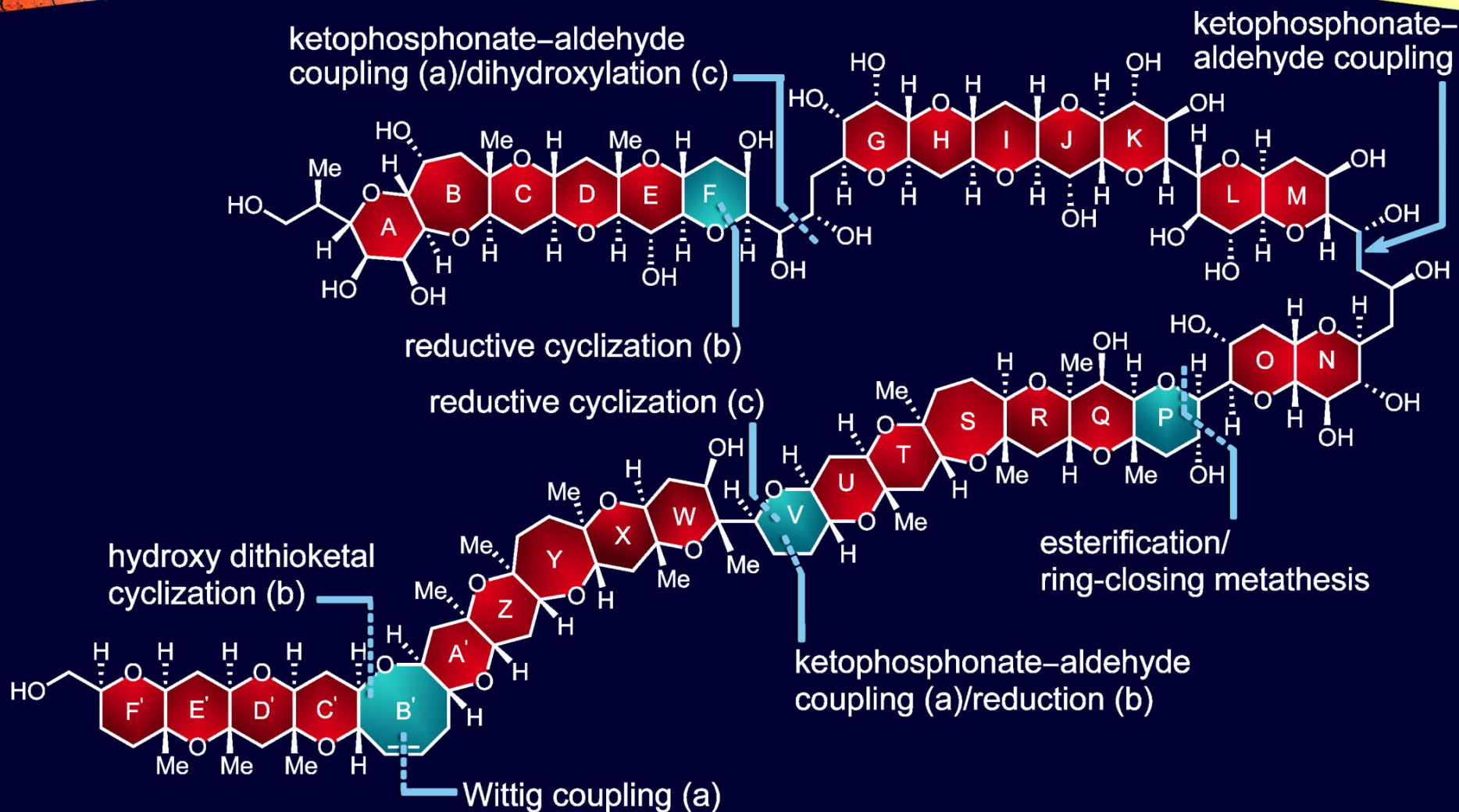
● $\Delta\delta$ values between maitotoxin and synthetic A'ZYXW domain

● 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



MAITOTOXIN POLYCYCLIC FRAMEWORK: FINAL COUPLINGS AND RING CLOSURES

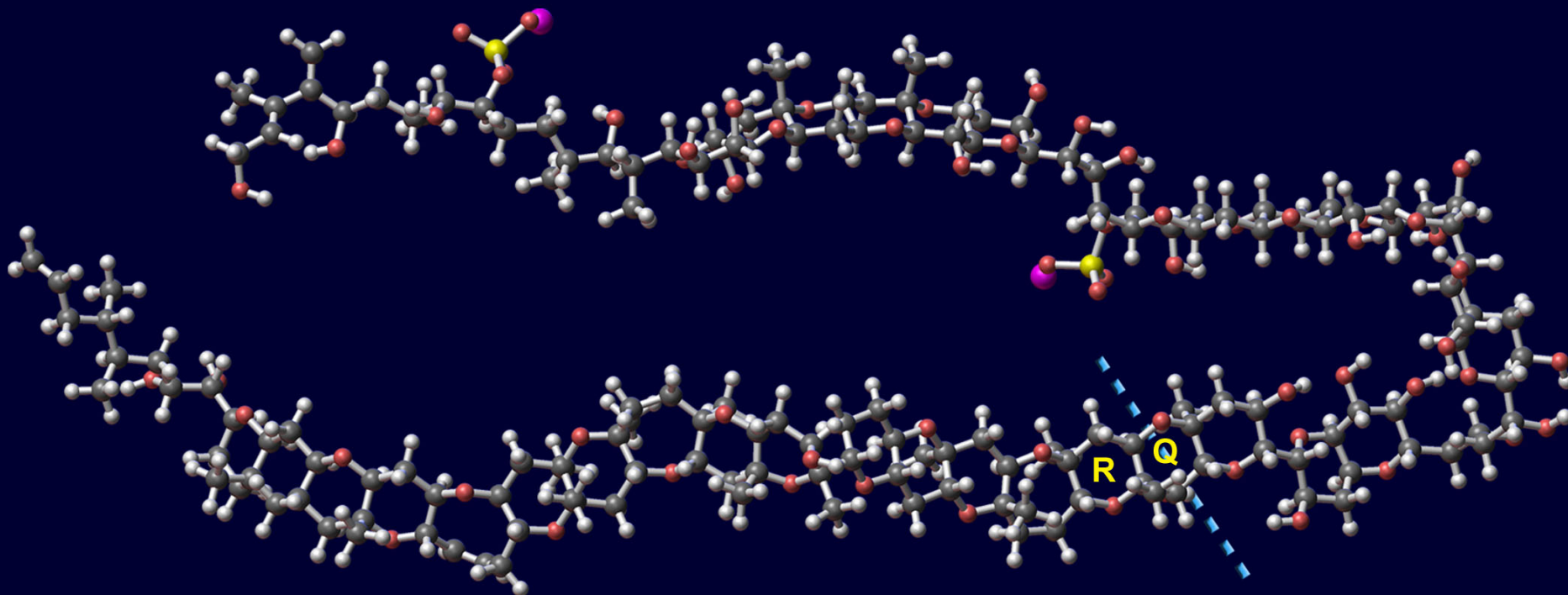




MOLECULAR MODEL OF MAITOTOXIN



● Hydrophilic



● Lipophilic

● 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'

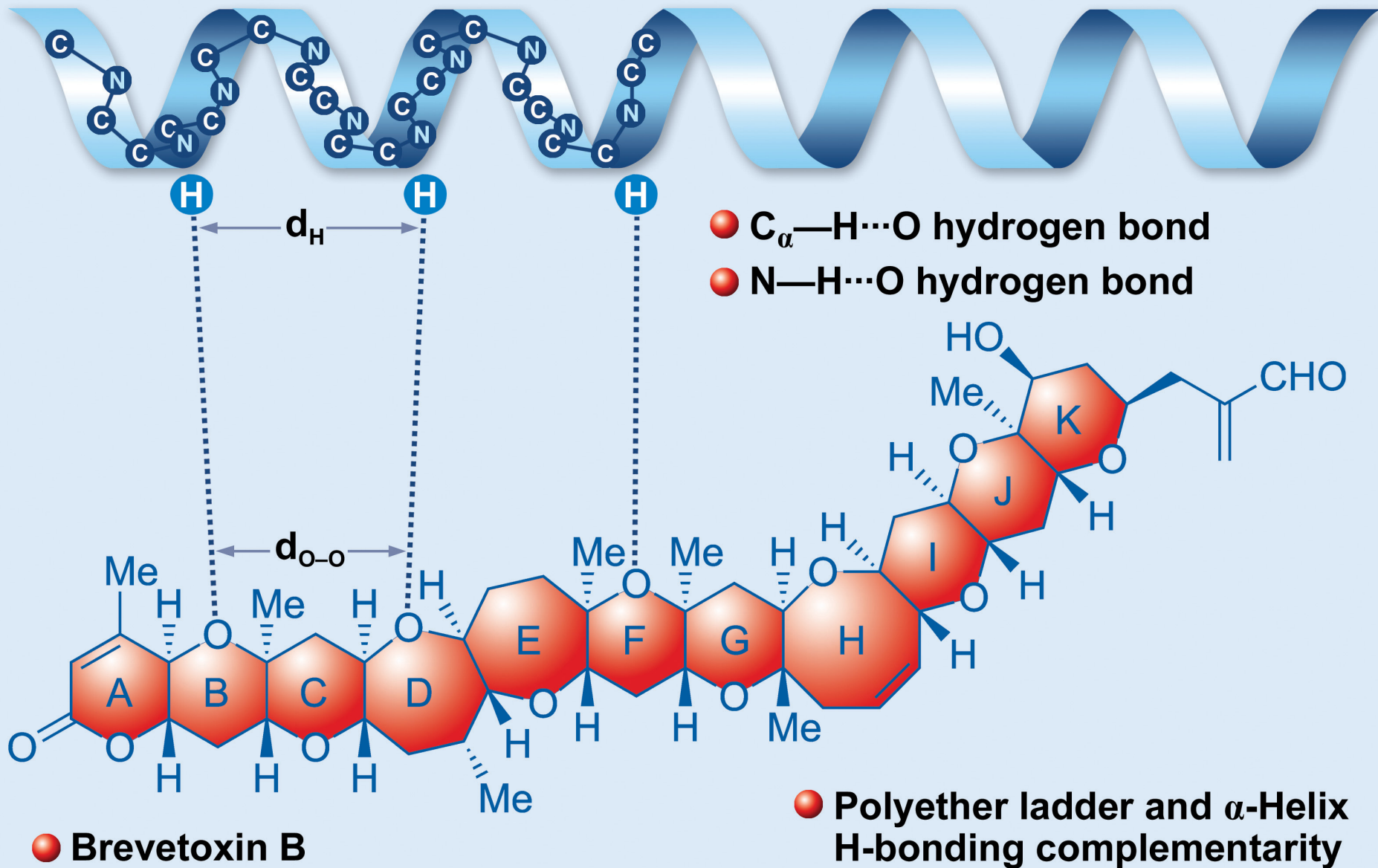
C₁₄₂

● 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





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

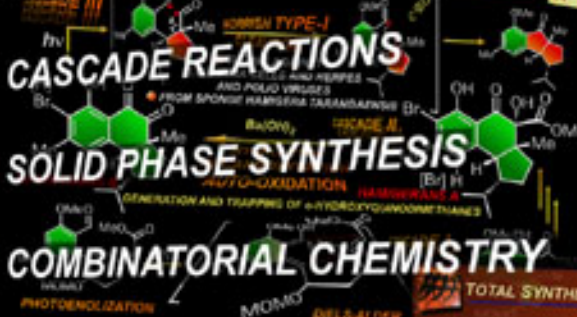
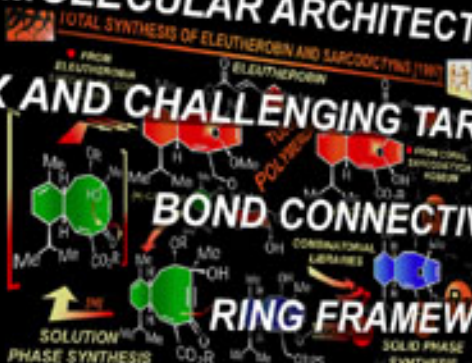
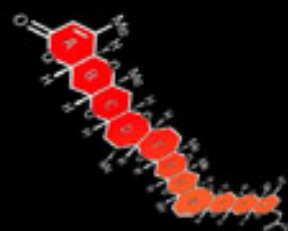
● ASYMMETRIC SYNTHESIS

● REAGENTS AND CATALYSTS

● EFFICIENT CHEMICAL PROCESSES

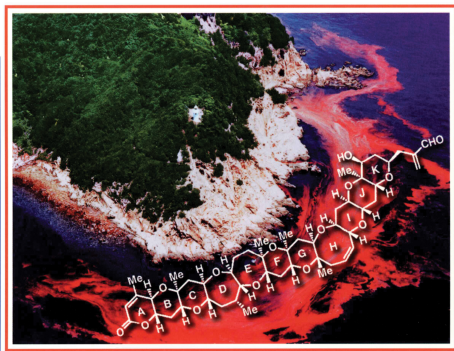
● GREEN CHEMISTRY

● DESIGNED BIOACTIVE MOLECULES



K. C. NICOLAOU, E. J. SORENSEN

CLASSICS IN TOTAL SYNTHESIS



TARGETS, STRATEGIES, METHODS

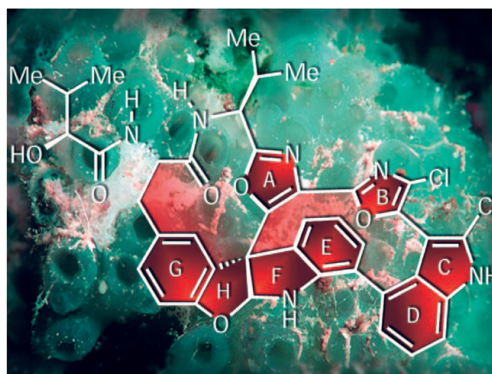


Nicolaou · Snyder

WILEY-VCH

Classics in Total Synthesis II

Targets, Strategies, Methods

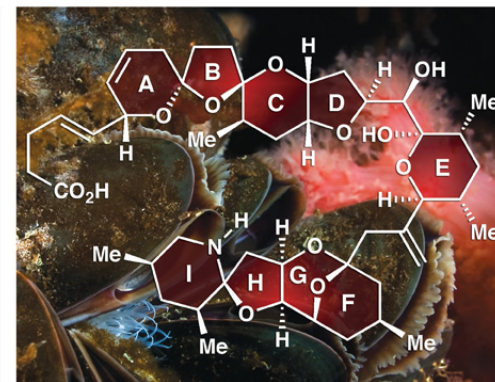


Nicolaou · Chen

WILEY-VCH

Classics in Total Synthesis III

New Targets, Strategies, Methods





EDUCATION



And if academics have done their job right, they should be able to retire with the precious gift of satisfying content as John Pentland Mahaffy proclaimed he did in his time and space:

“So now, when my part in the race is nearly run, there remains to me no higher earthly satisfaction than this, that I have carried the torch of Greek fire alight through a long life — no higher earthly hope than this, that I may pass that torch to others, who in their turn may keep it aflame with greater brilliancy perhaps, but not with more earnest devotion, ‘in the Parliament of men, the Federation of the world.’”*

J. P. Mahaffy, 1910

J. P. Mahaffy, *What Have the Greeks Done for Modern Civilisation*, G. P. Putnam's Sons, New York, 1910, pp. 214–215, 246–247. *see Alfred, Lord Tennyson, “Locksley Hall” 1835.



The Maitotoxin Project: Acknowledgements



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