

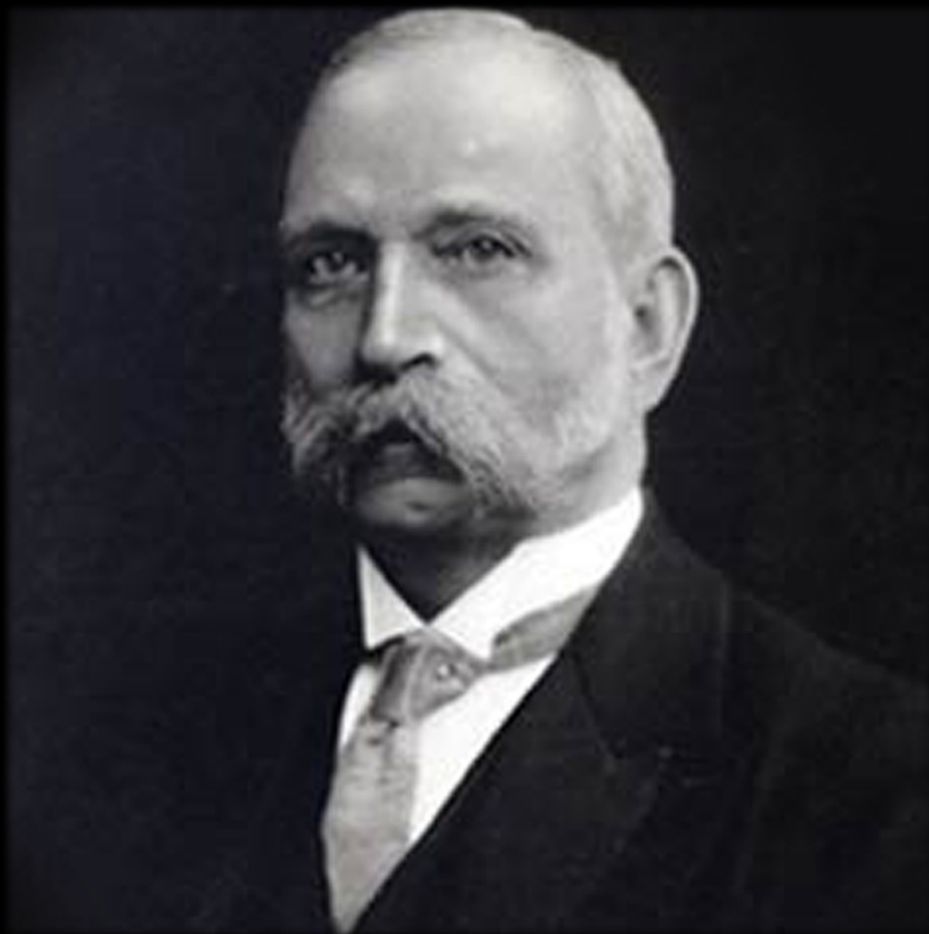
The Chandler Medal Lecture

Columbia University
Thursday, November 6, 2008

K.C. Nicolaou

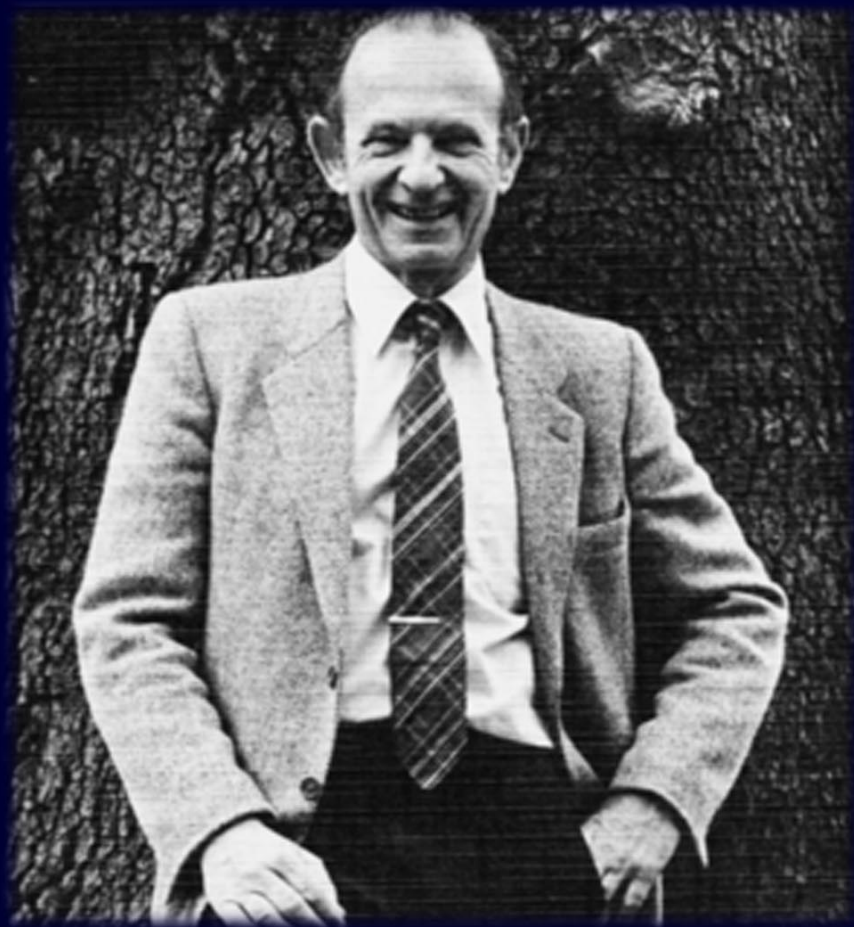
***“The Continuing Saga of the Polyether
Marine Biotoxins”***

Charles Frederick Chandler

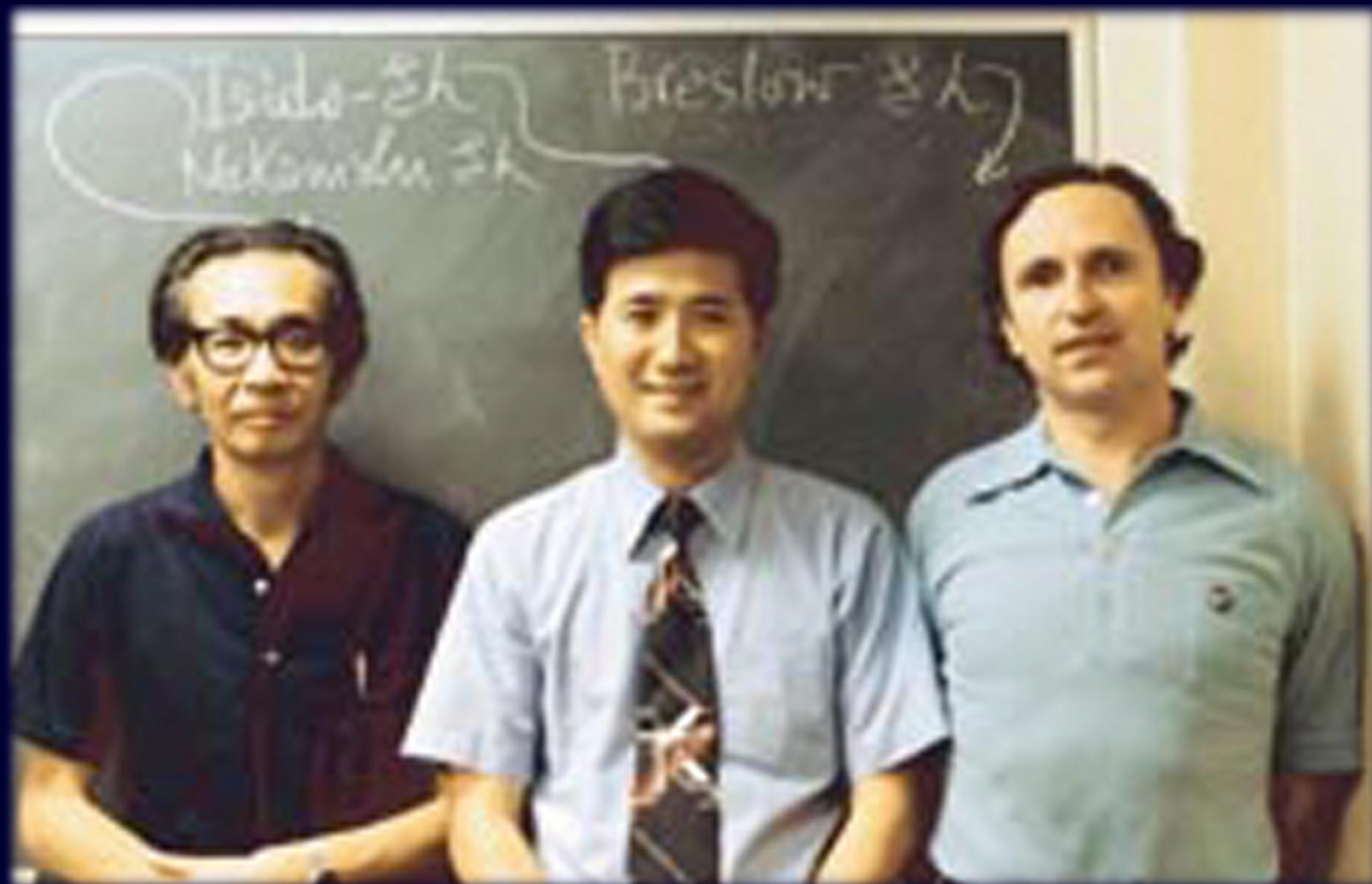


“He has placed the entire world in his debt, and brought added dignity and prestige to the profession of which he is such a conspicuous ornament.”

— Perkin Medal citation, 1920

















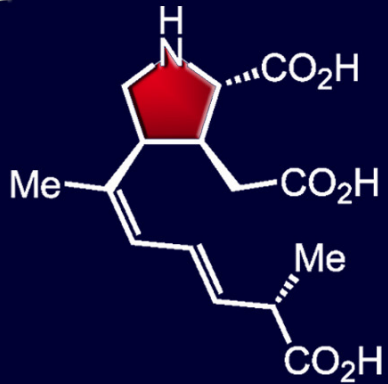


WHO'S WHO? - COURTESY OF PROF. EMANUEL VOGEL



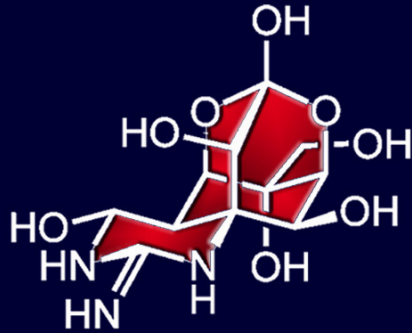


INFAMOUS MARINE BIOTOXINS



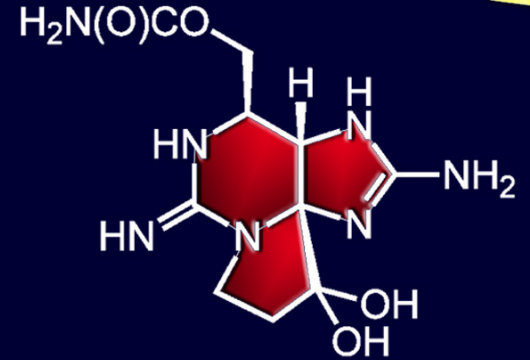
domoic acid (1958)

[Amnesic Shellfish Poisoning, ASP]



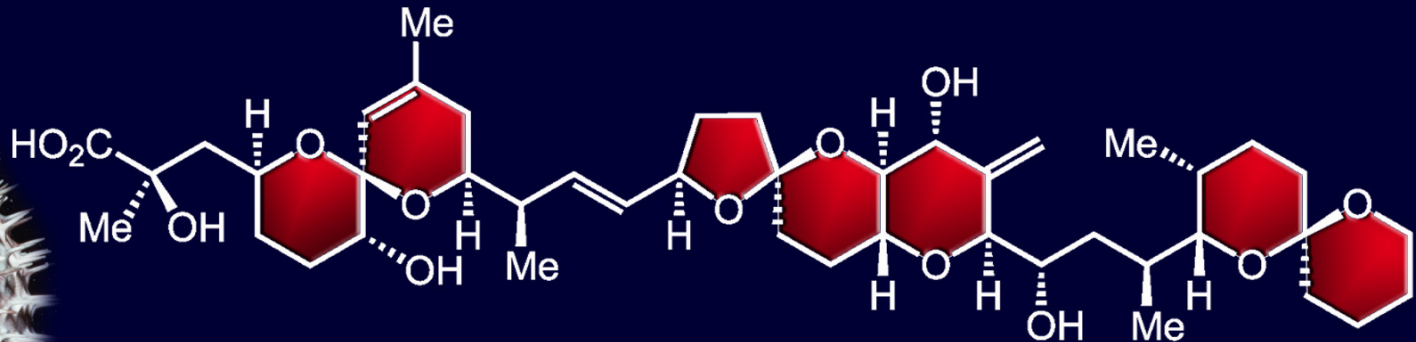
tetrodotoxin (1964)

[Tetrodotoxin Poisoning, TP]



saxitoxin (1975)

[Paralytic Shellfish Poisoning, PSP]



okadaic acid (1981)

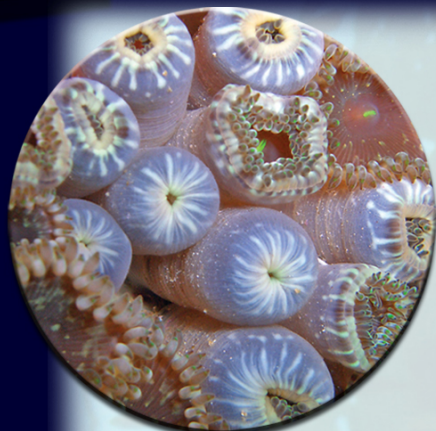
[Diarrhetic Shellfish Poisoning, DSP]



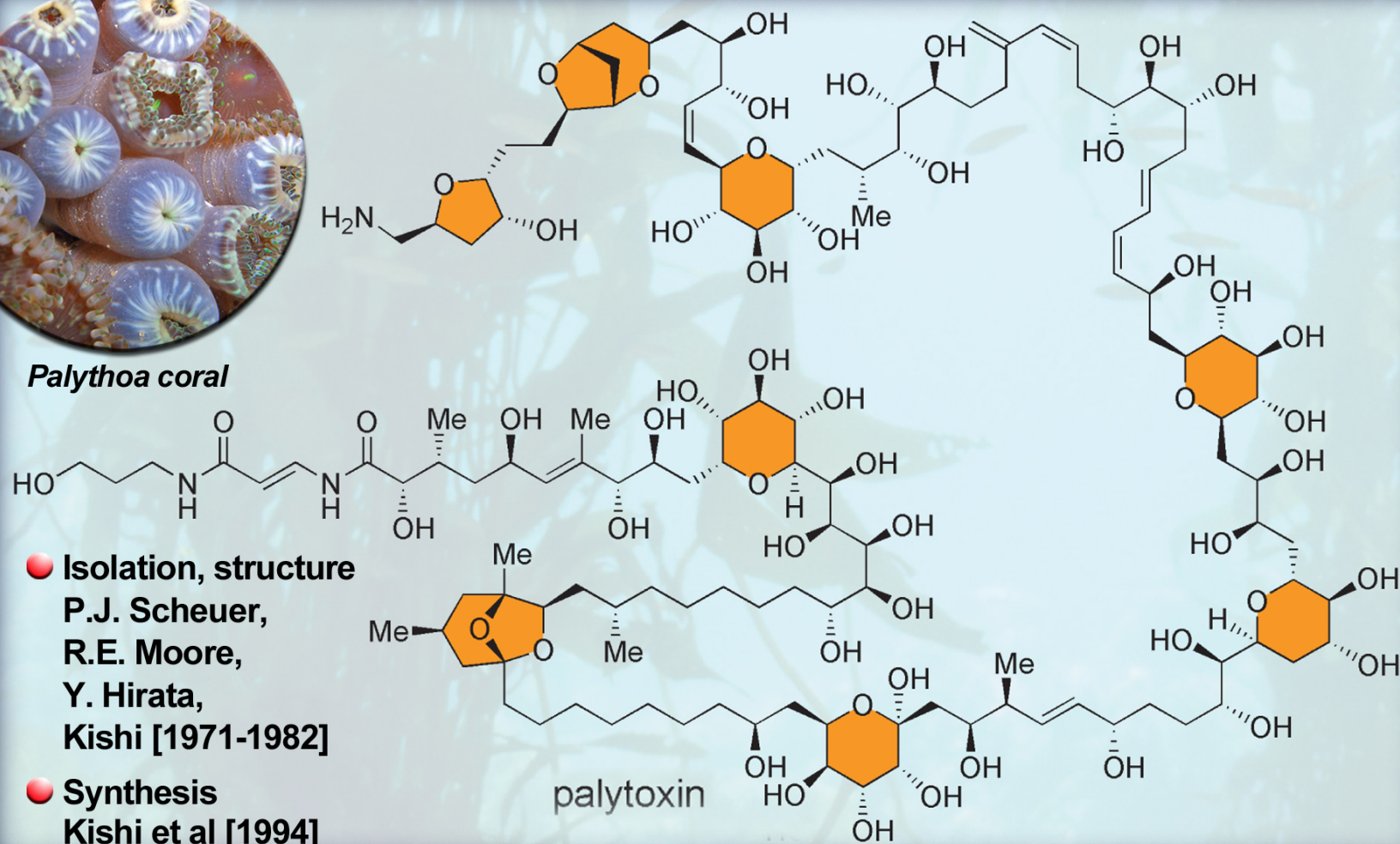
Fugu (Puffer fish)



PALYTOXIN



Palythoa coral



● **Isolation, structure**

P.J. Scheuer,
R.E. Moore,
Y. Hirata,
Kishi [1971-1982]

● **Synthesis**

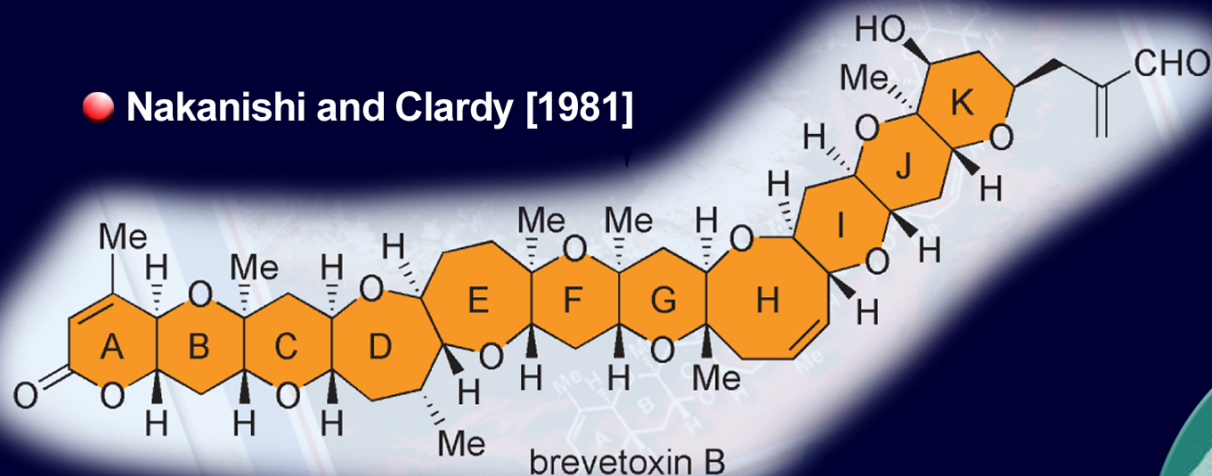
Kishi et al [1994]



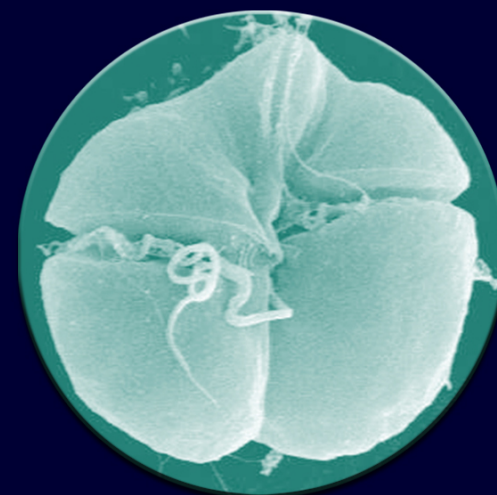
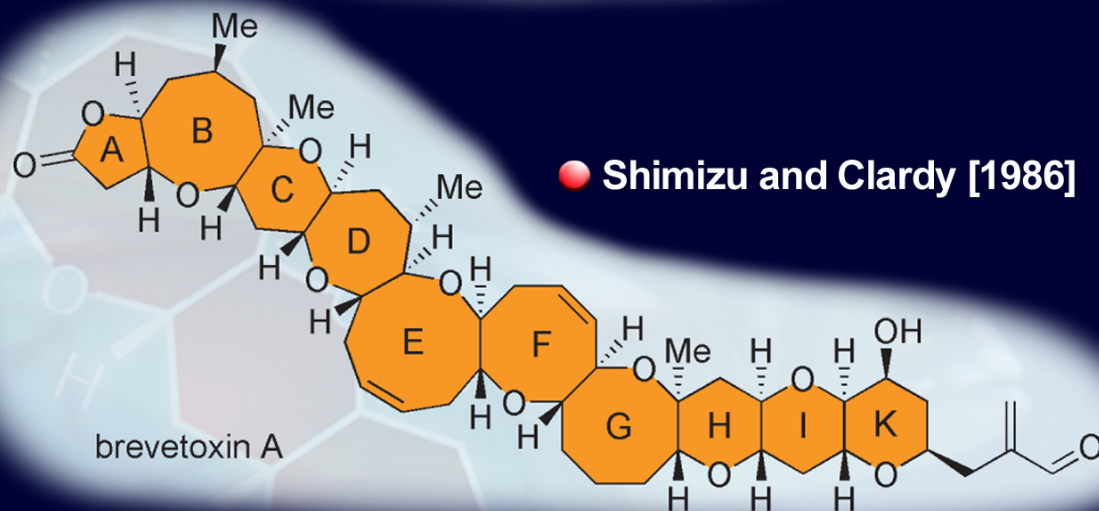
BREVETOXIN B AND BREVETOXIN A



● Nakanishi and Clardy [1981]



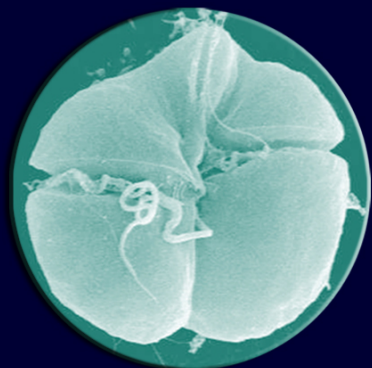
● Shimizu and Clardy [1986]



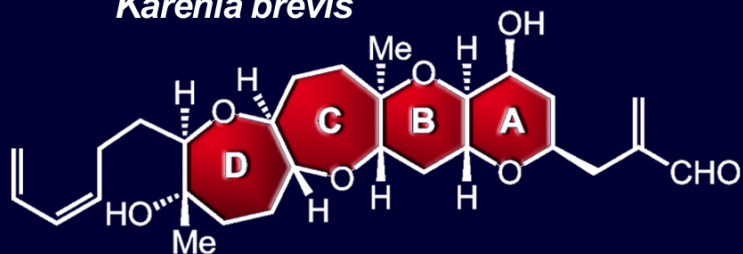
Karenia brevis



POLYETHER MARINE BIOTOXINS SYNTHESIZED TO DATE, 2008, I



Karenia brevis



hemibrevetoxin

[Nicolaou et al., 1992]

[Yamamoto et al., 1995, 2007]

[Nakata et al., 1996]

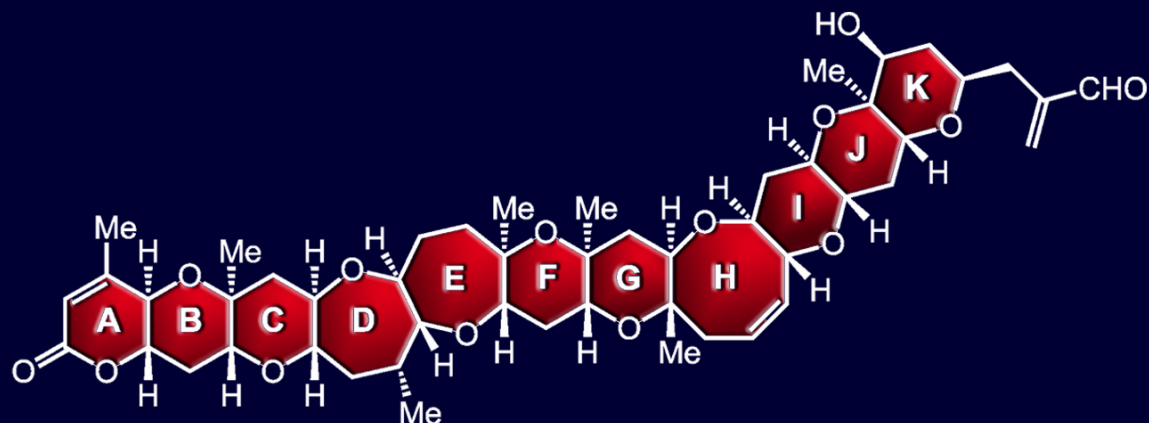
[Mori et al. (formal), 1997]

[Rainier et al. (formal), 2001]

[Nelson et al. (formal), 2001]

[Holton et al., 2003]

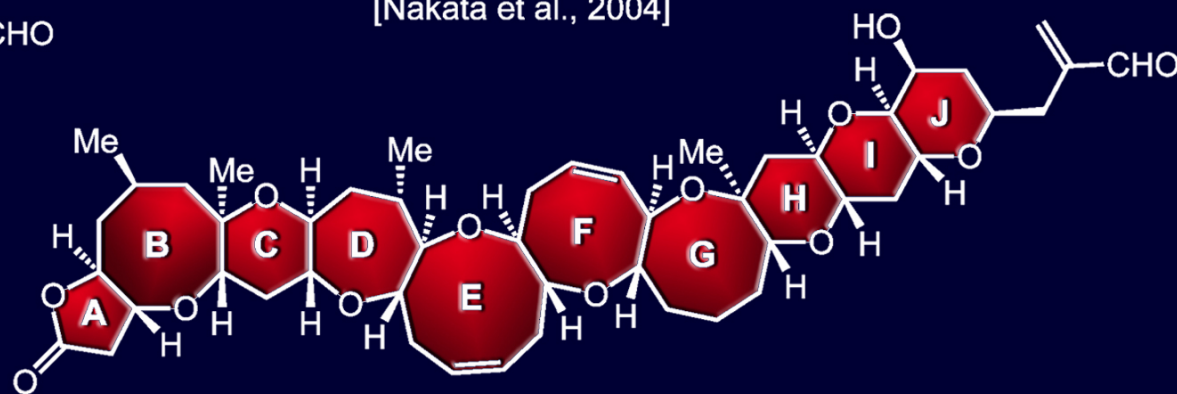
[Fujiwara et al. (formal), 2004]



brevetoxin B

[Nicolaou et al., 1995]

[Nakata et al., 2004]



brevetoxin A

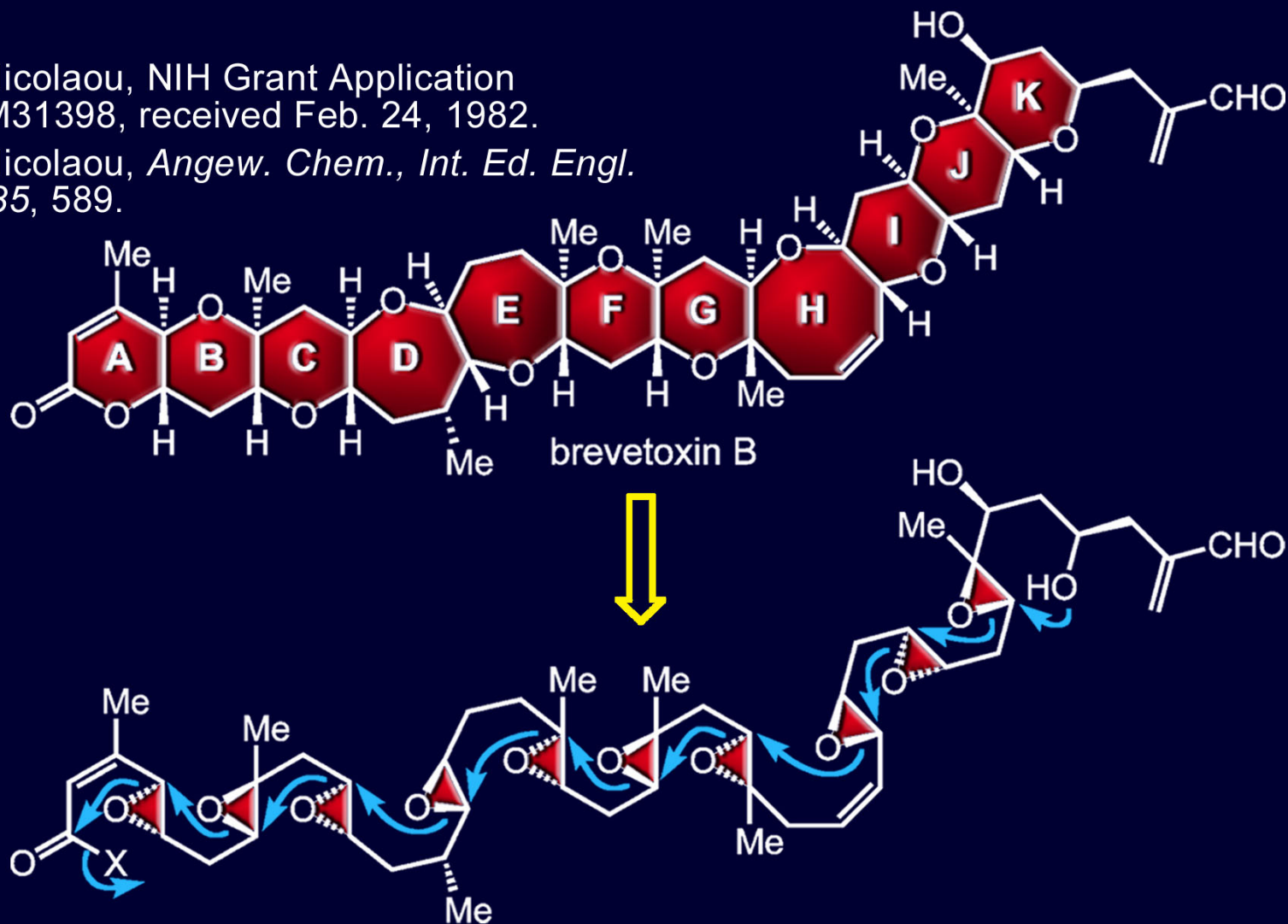
[Nicolaou et al., 1998]



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.

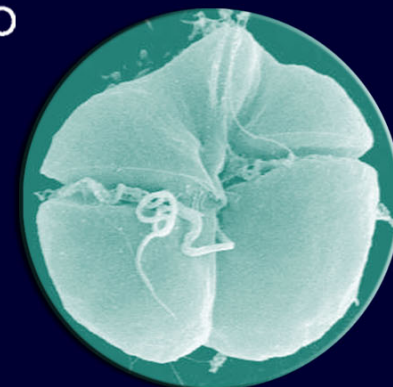
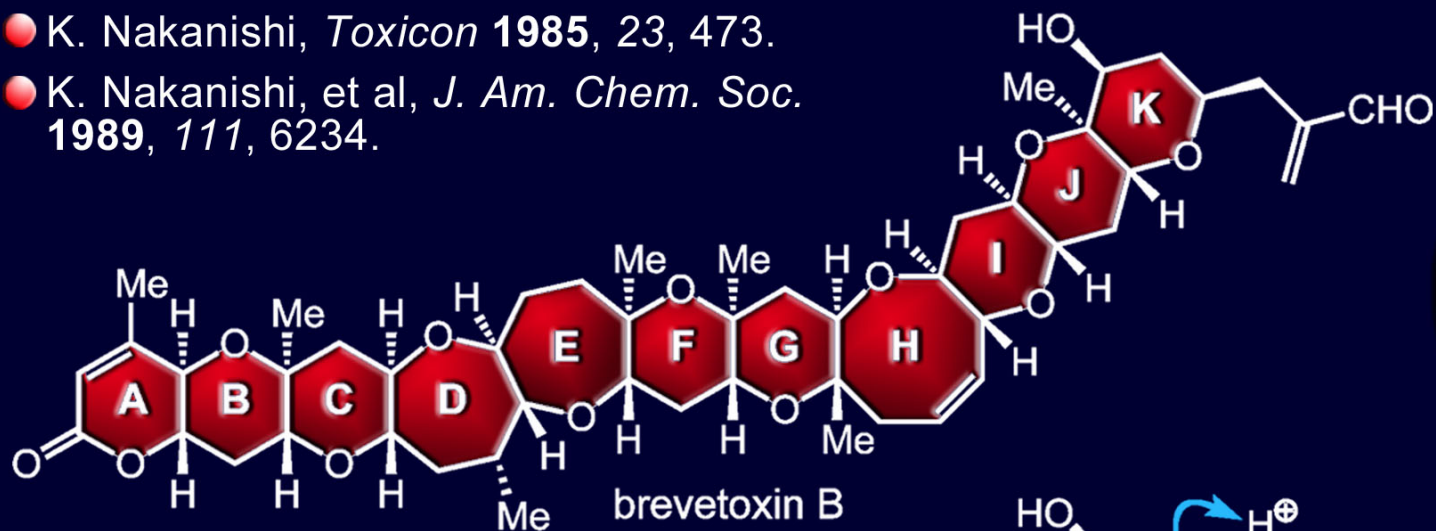




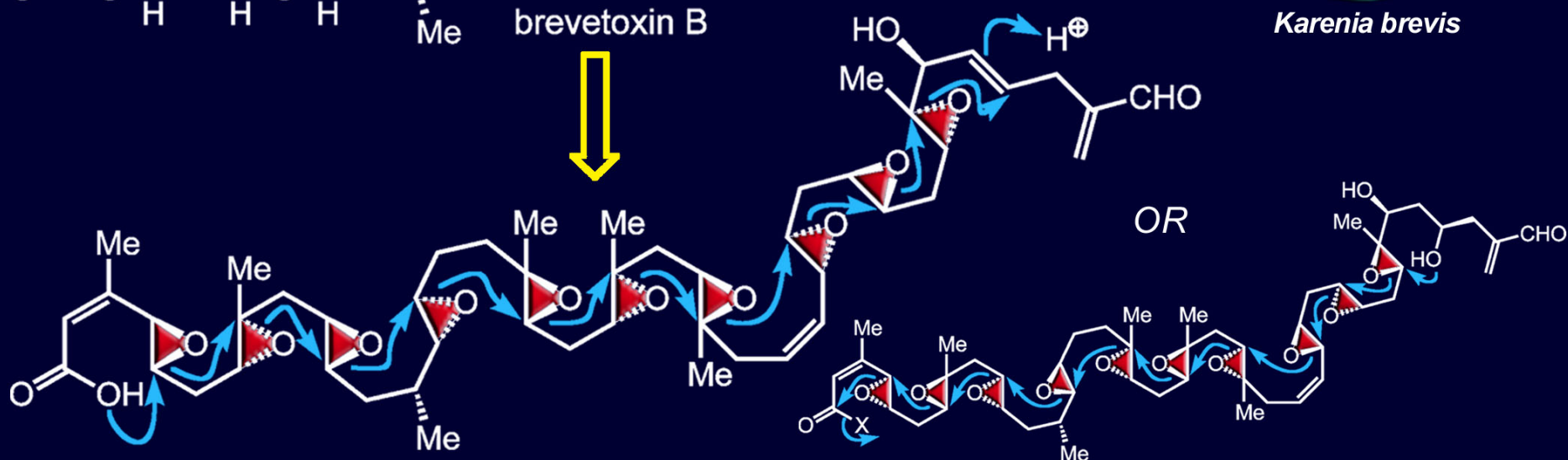
THE NAKANISHI HYPOTHESIS FOR THE BIOSYNTHESIS OF BREVETOXIN B [1985]



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

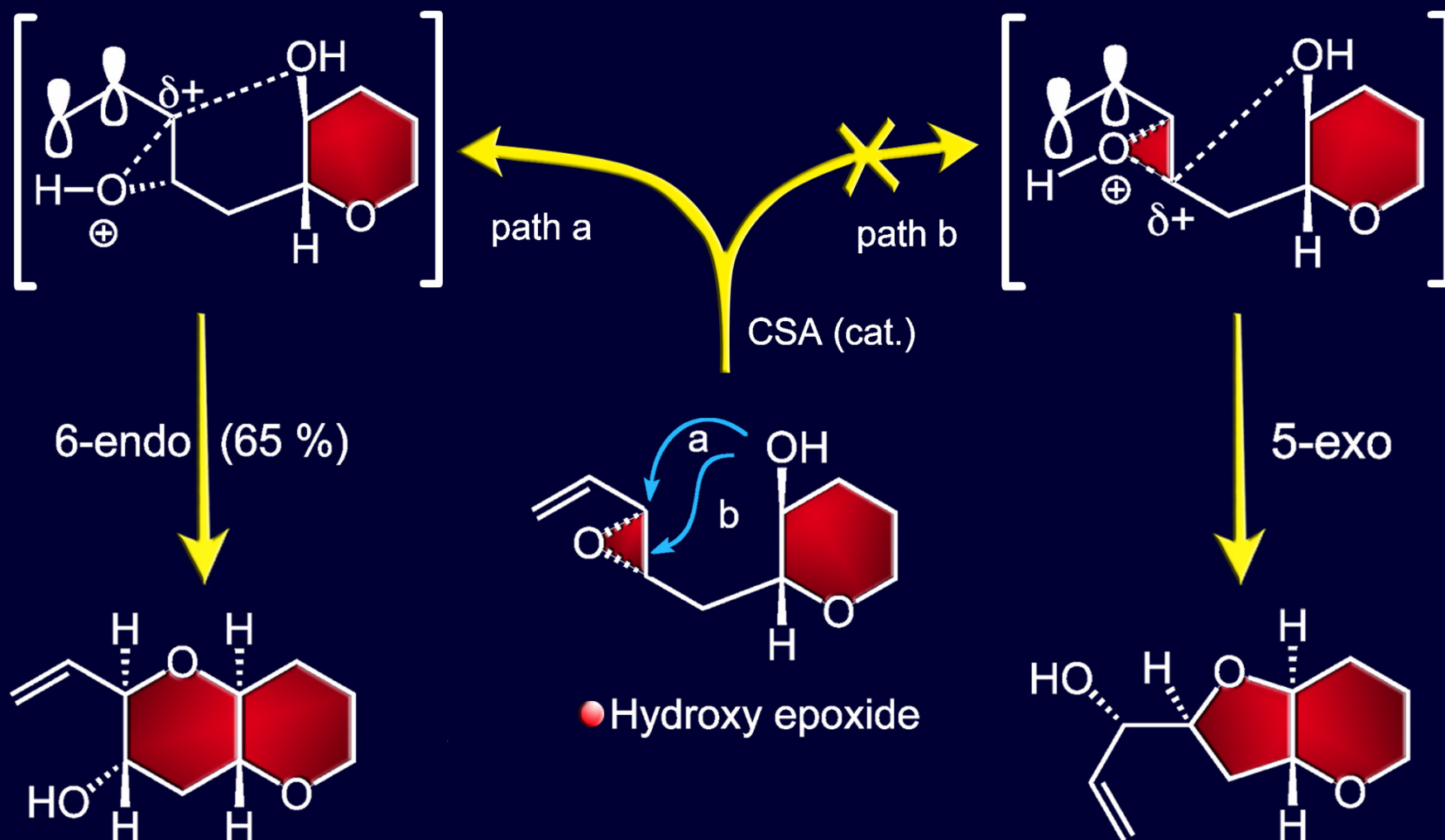


Karenia brevis



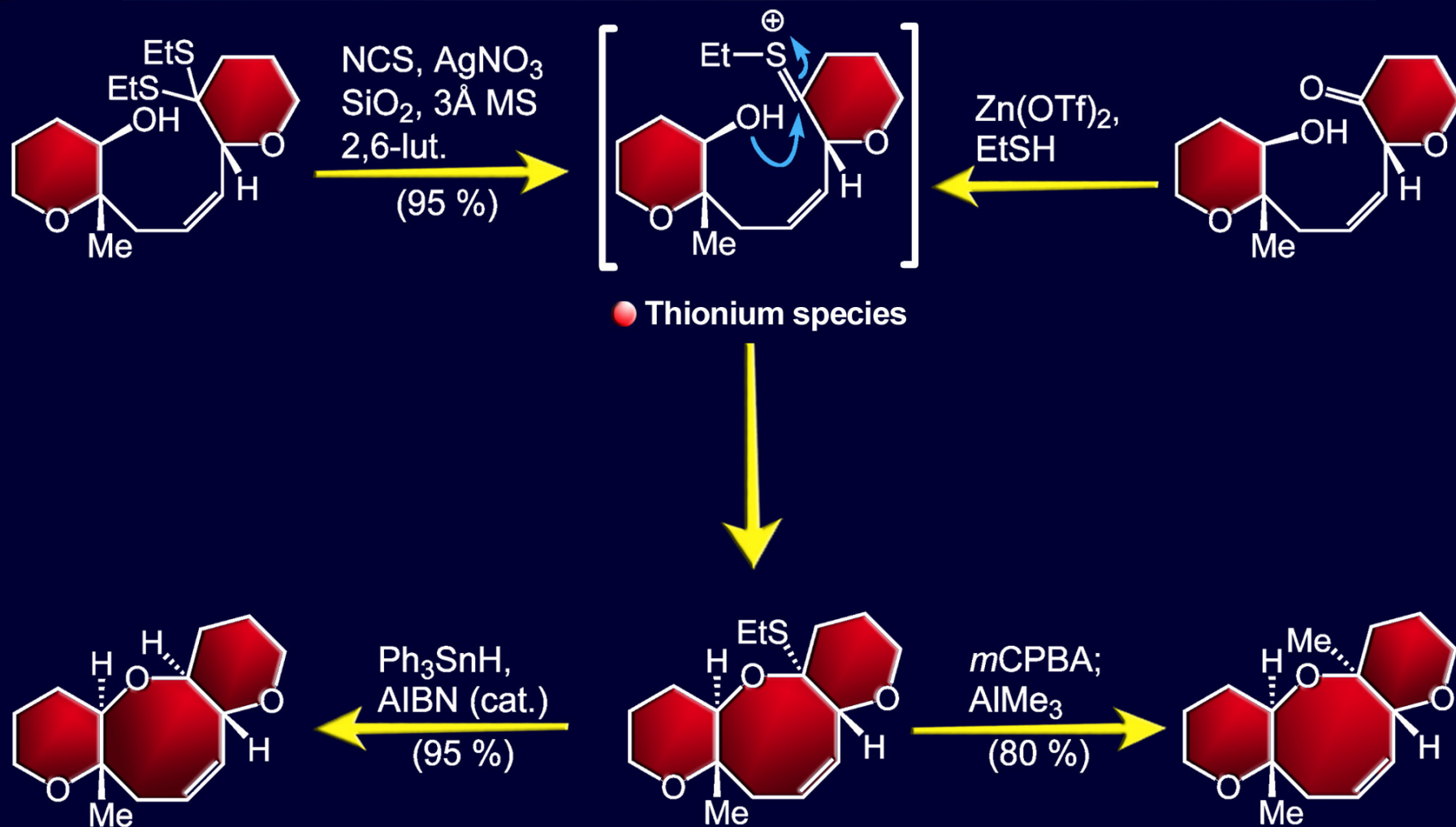


THE 6-ENDO EPOXIDE OPENING METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU *et al.*, 1985)



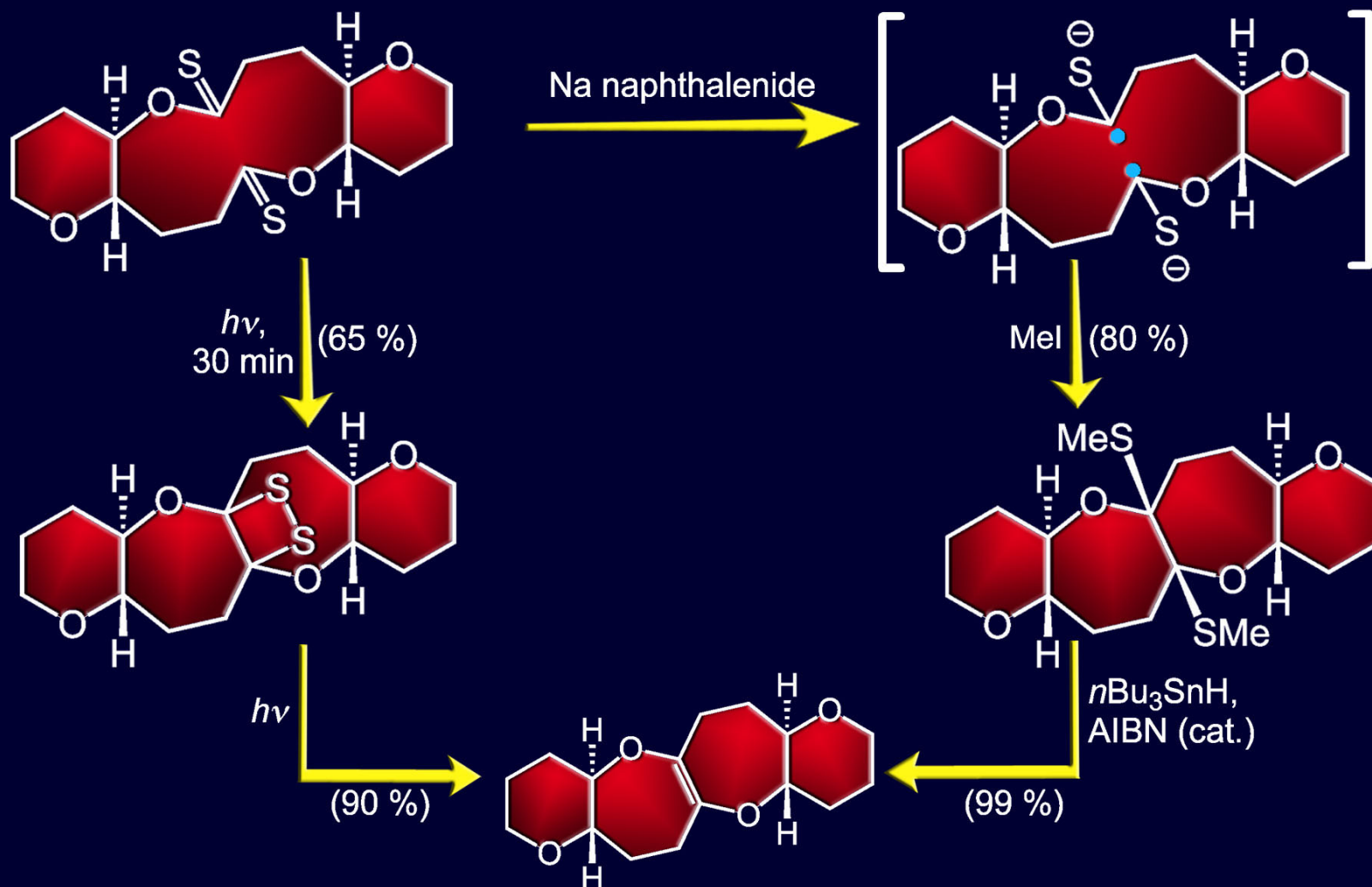


THE HYDROXY DITHIOKETAL CYCLIZATION METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU *et al.*, 1986)



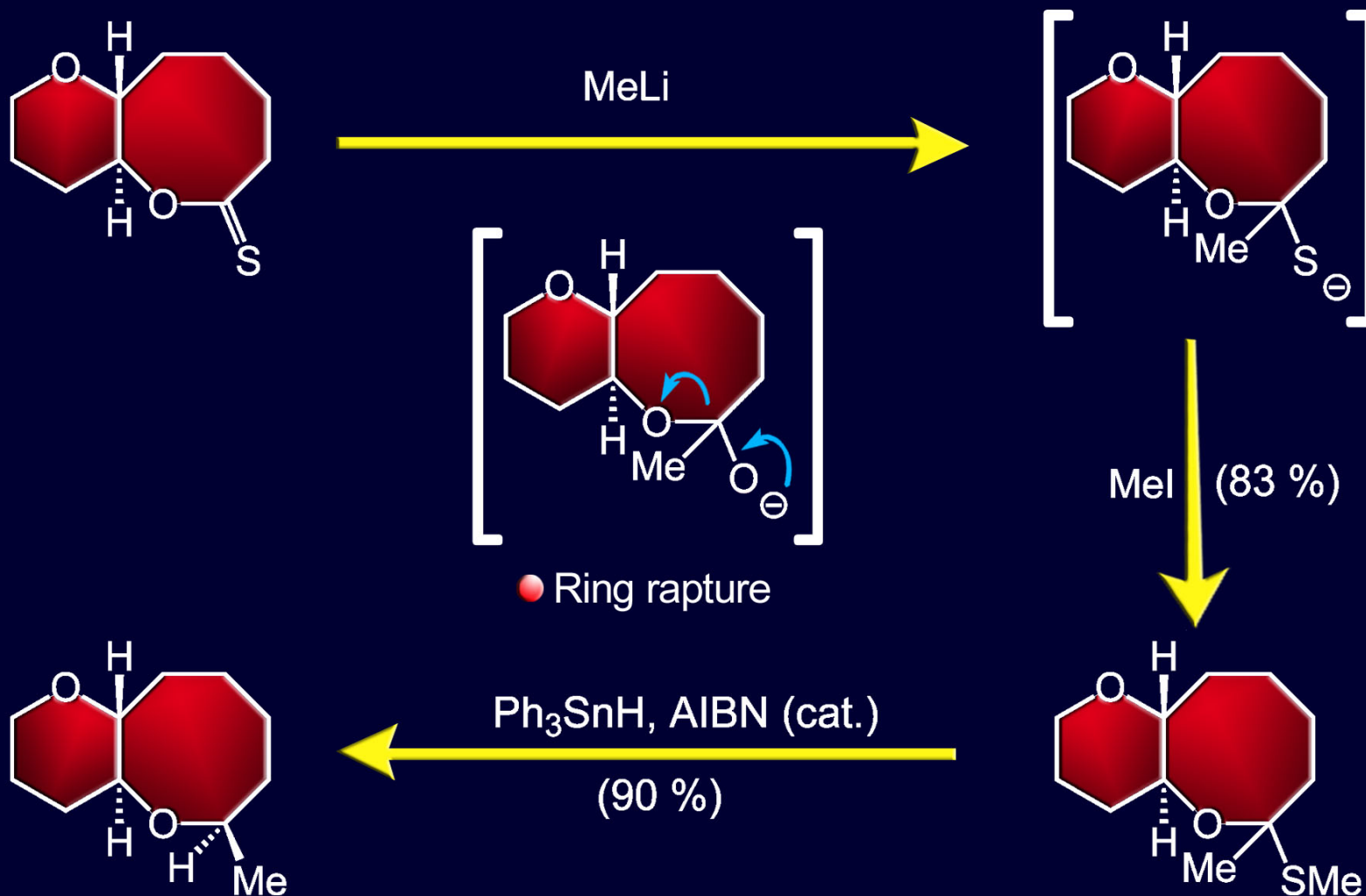


THE DITHIONOLACTONE BRIDGING METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU *et al.*, 1986)





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



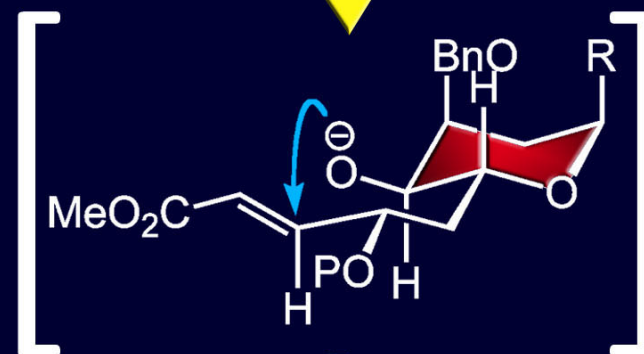


THE HYDROXY MICHAEL ADDITION METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU *et al.*, 1989)



NaH

● chair-like transition state ensures trans junction

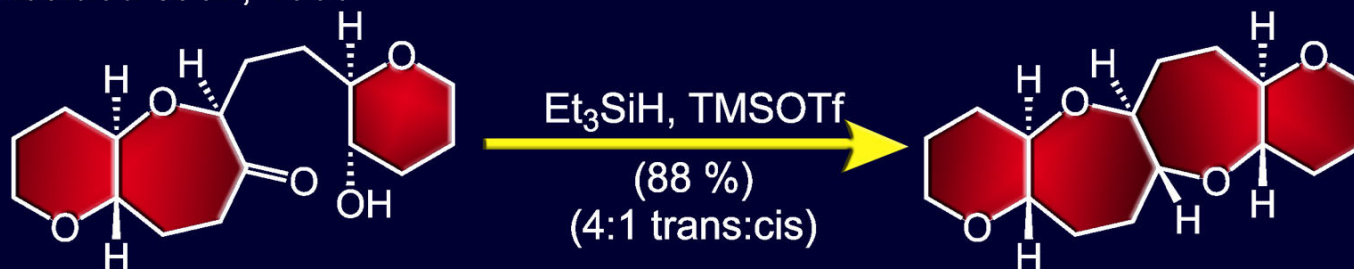


(92 %)



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

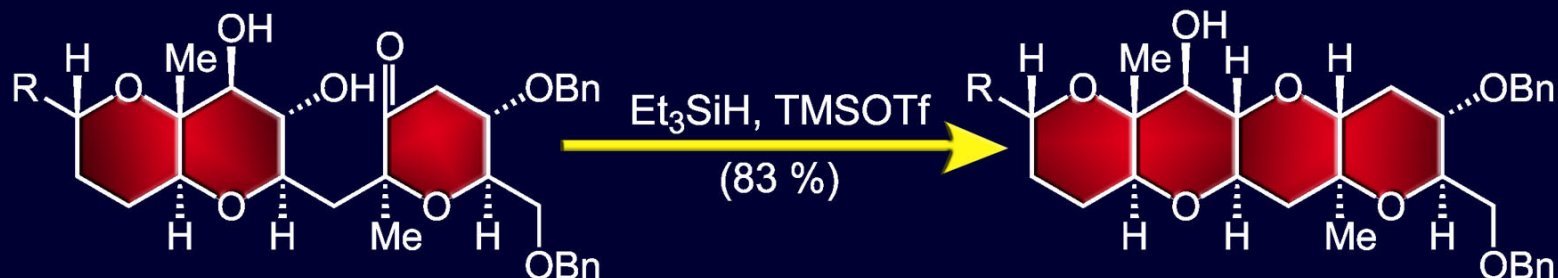
a: Nicolaou *et al.*, 1989



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

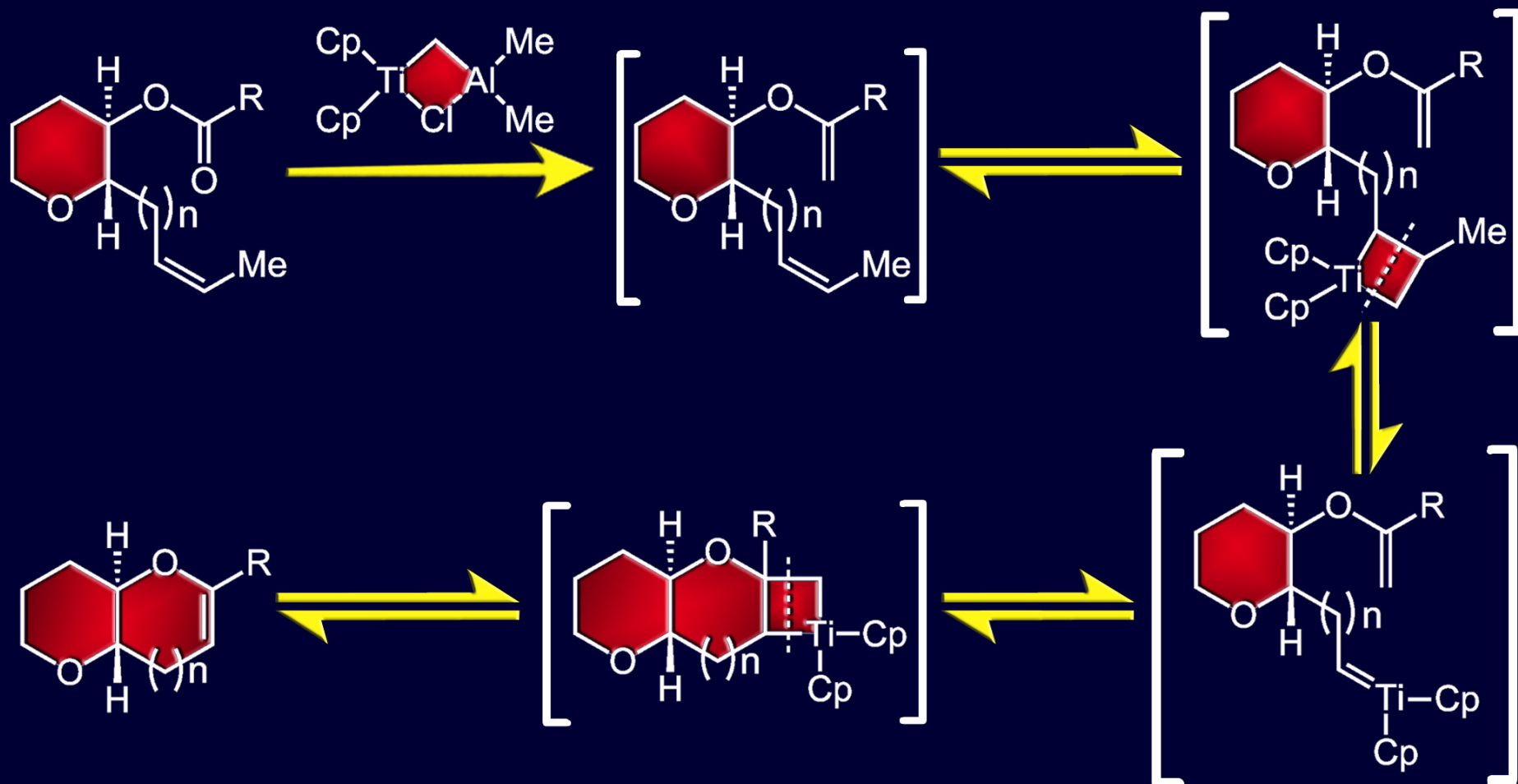


c: Sasaki *et al.*, 2007





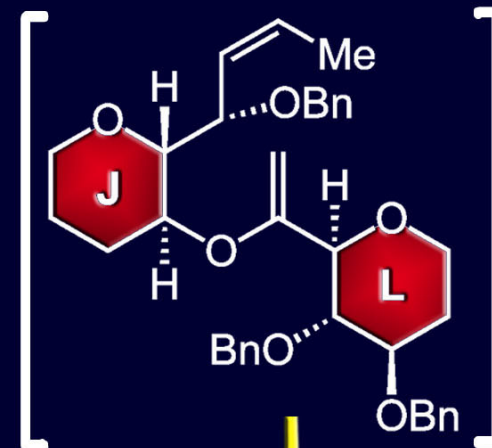
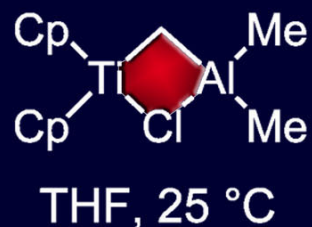
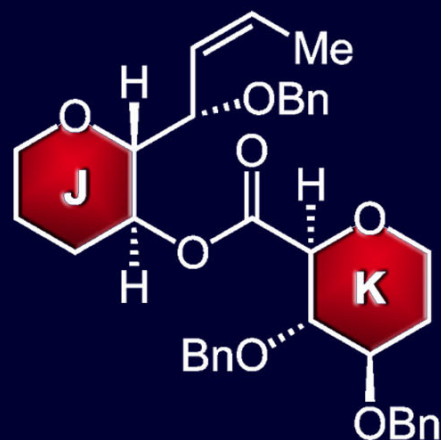
THE ESTER METHYLENATION/METATHESIS METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU et al., 1996)



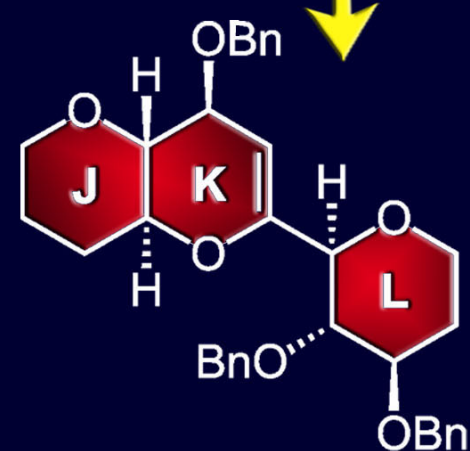
see also: G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 5426; G. C. Fu, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 9856.



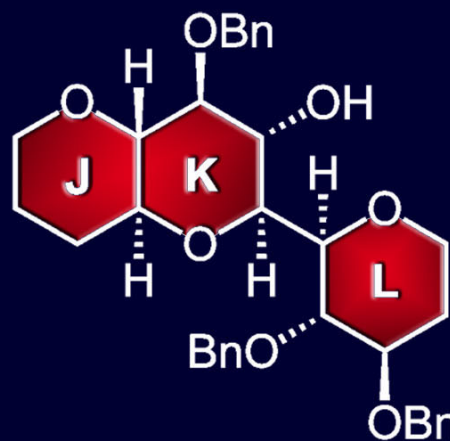
SYNTHESIS OF MAITOTOXIN JKL MODEL SYSTEM (NICOLAOU et al., 1996)



(20 %) 40 °C

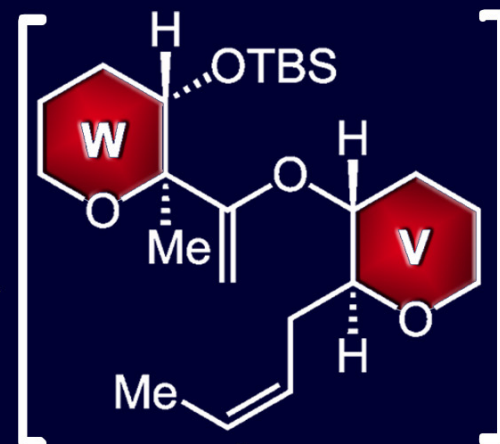
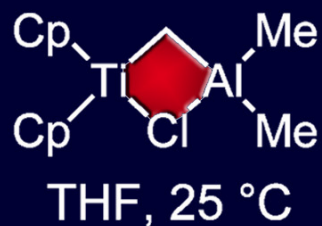
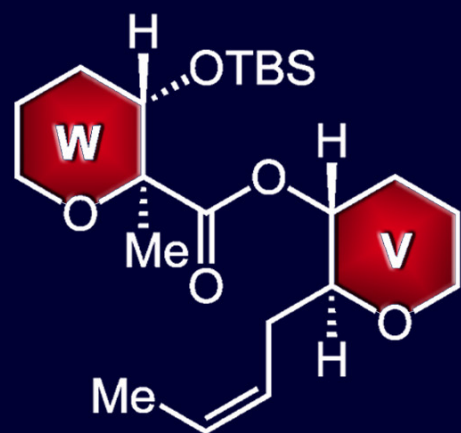


BH_3 ; then
 NaOH , H_2O_2
(89 %)

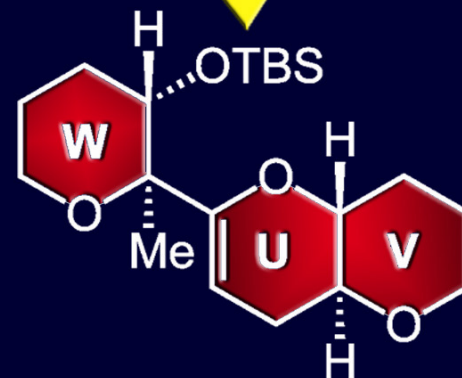


maitotoxin model system

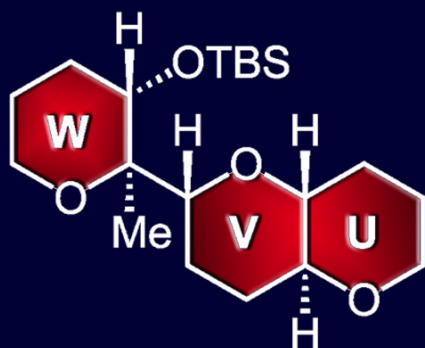
SYNTHESIS OF MAITOTOXIN UVW MODEL SYSTEM (NICOLAOU et al., 1996)



(36 %) 40 °C



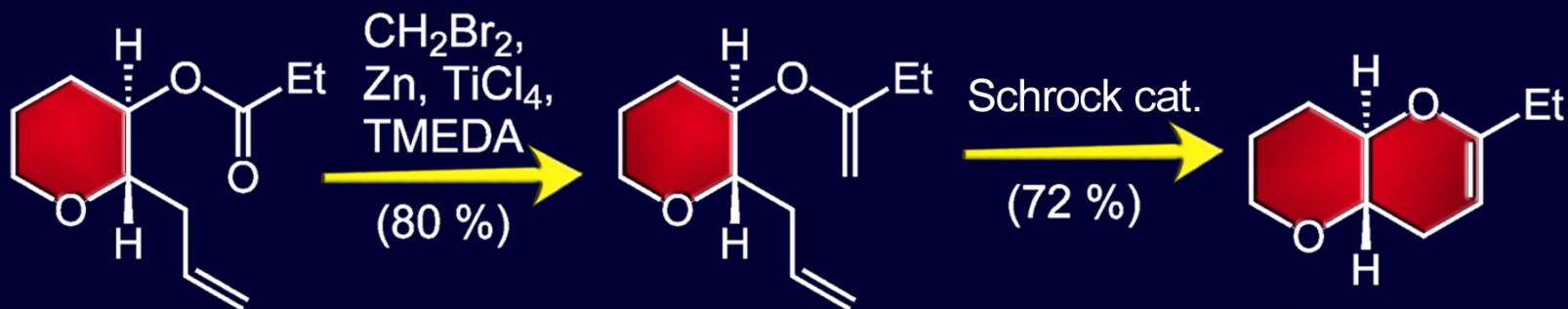
Et_3SiH , TFA
(80 %)



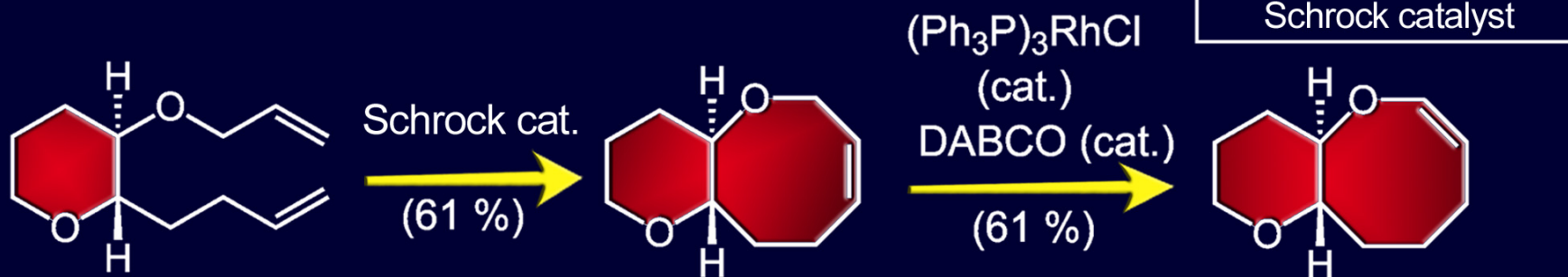
maitotoxin model system



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



Takai olefination



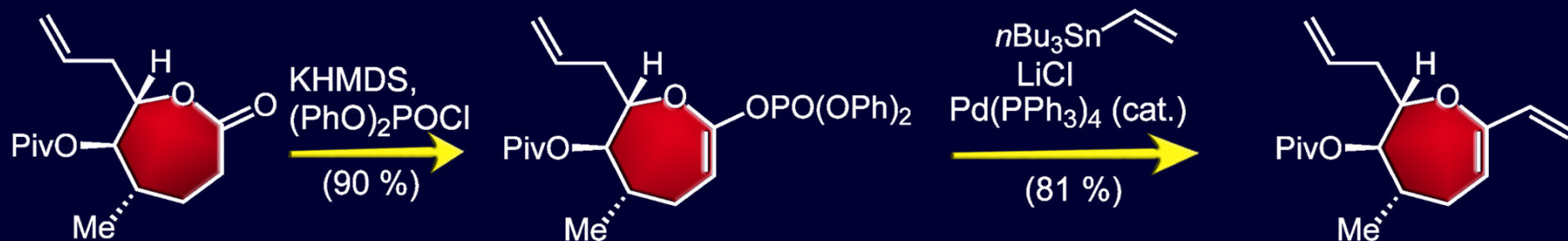
see also: G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 5426; G. C. Fu, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 9856.



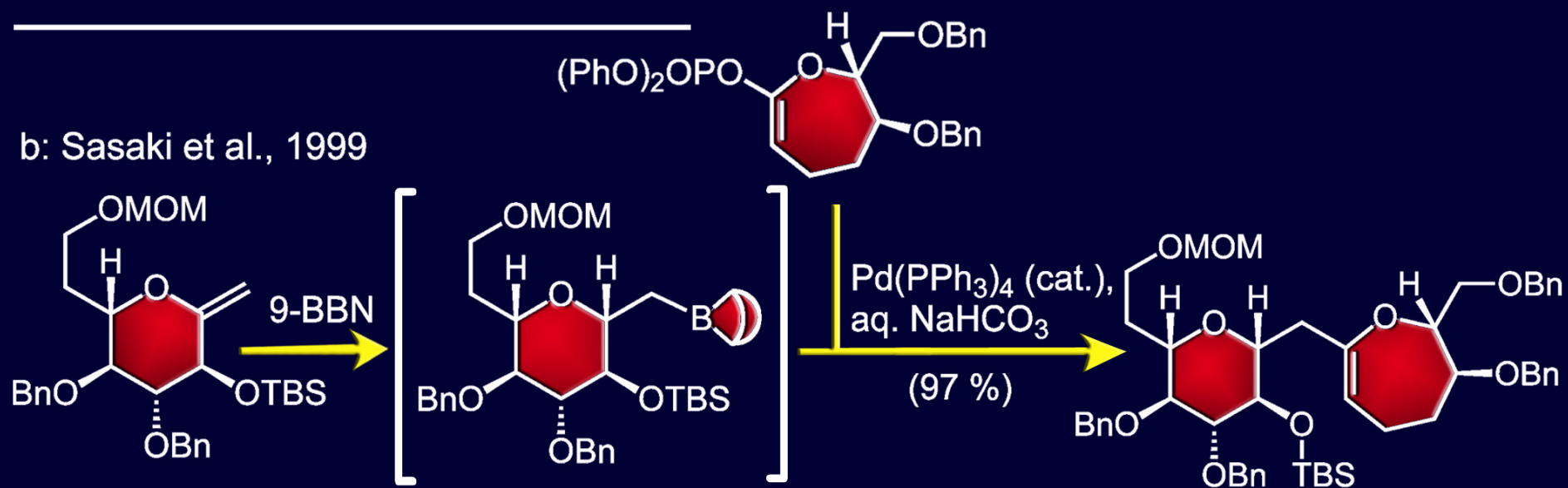
THE VINYL PHOSPHATE/CROSS-COUPLING METHODS FOR CYCLIC ETHER FORMATION (NICOLAOU *et al.*, 1997, SASAKI *et al.*, 1999)



a: Nicolaou *et al.*, 1997

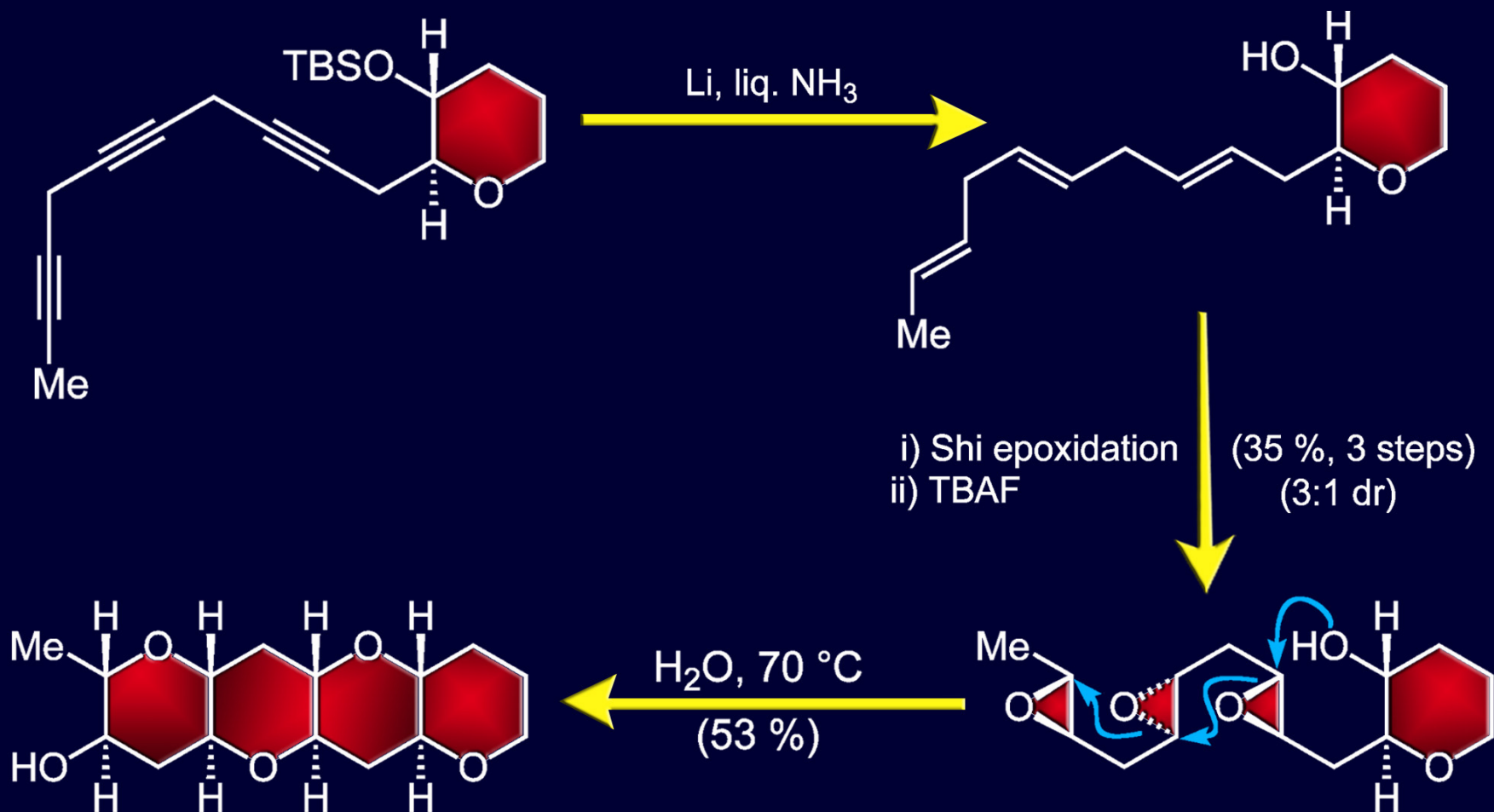


b: Sasaki *et al.*, 1999



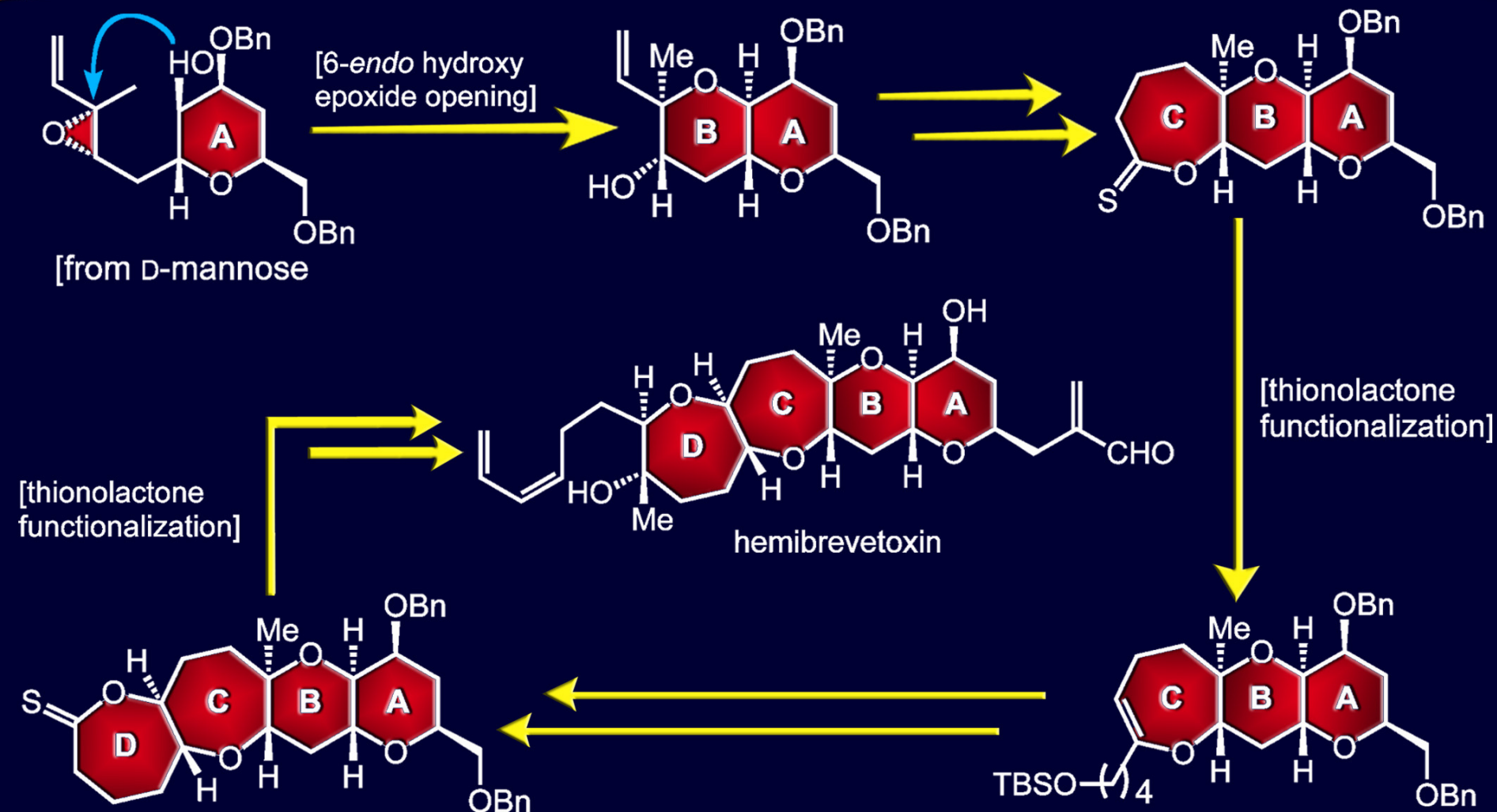


THE THERMALLY-INDUCED HYDROXY POLYEPOXIDE OPENING IN WATER FOR CYCLIC ETHER FORMATION (JAMISON and VILOTIJEVIC, 2007)



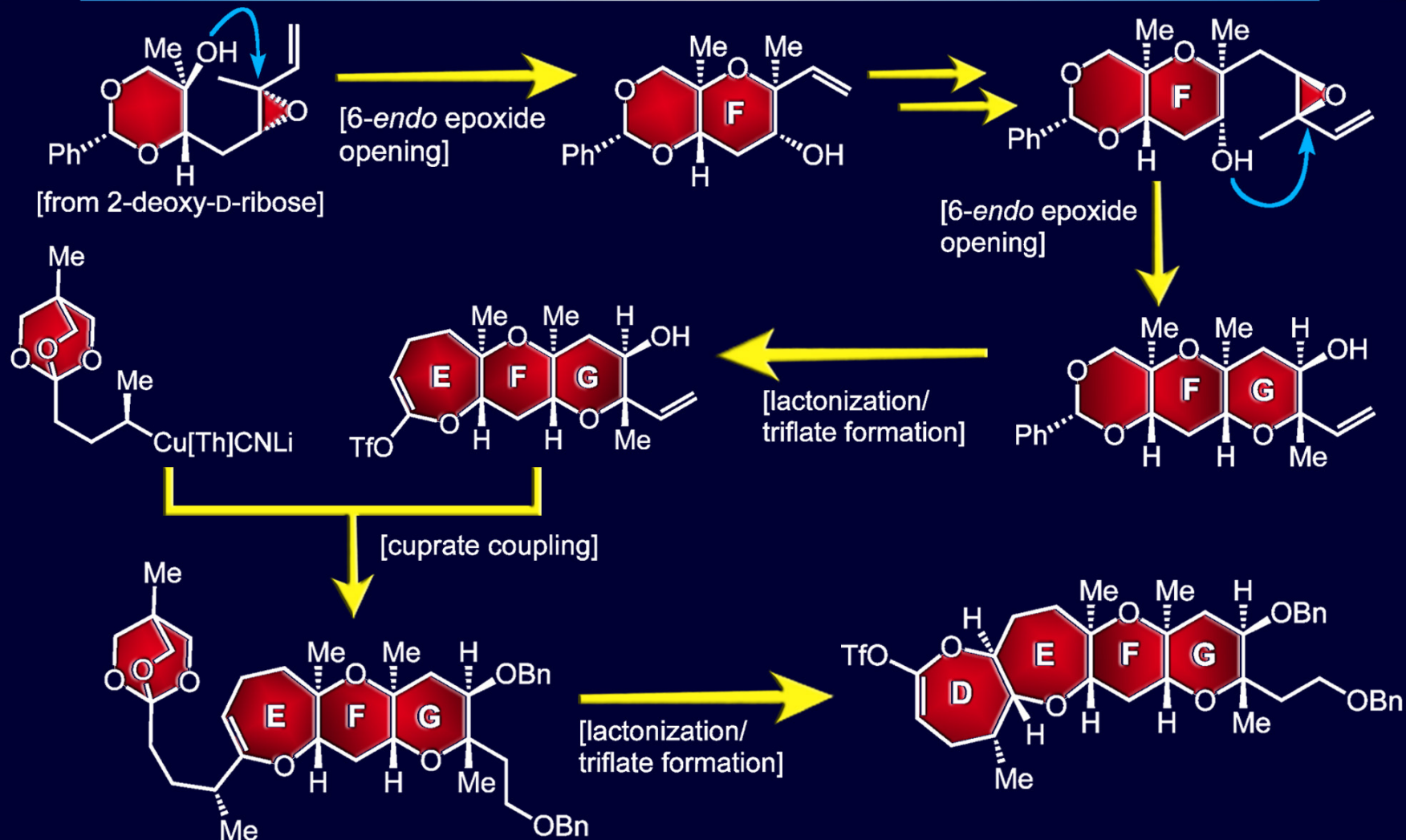


SYNTHESIS OF HEMIBREVETOXIN (NICOLAOU *et al.*, 1992)



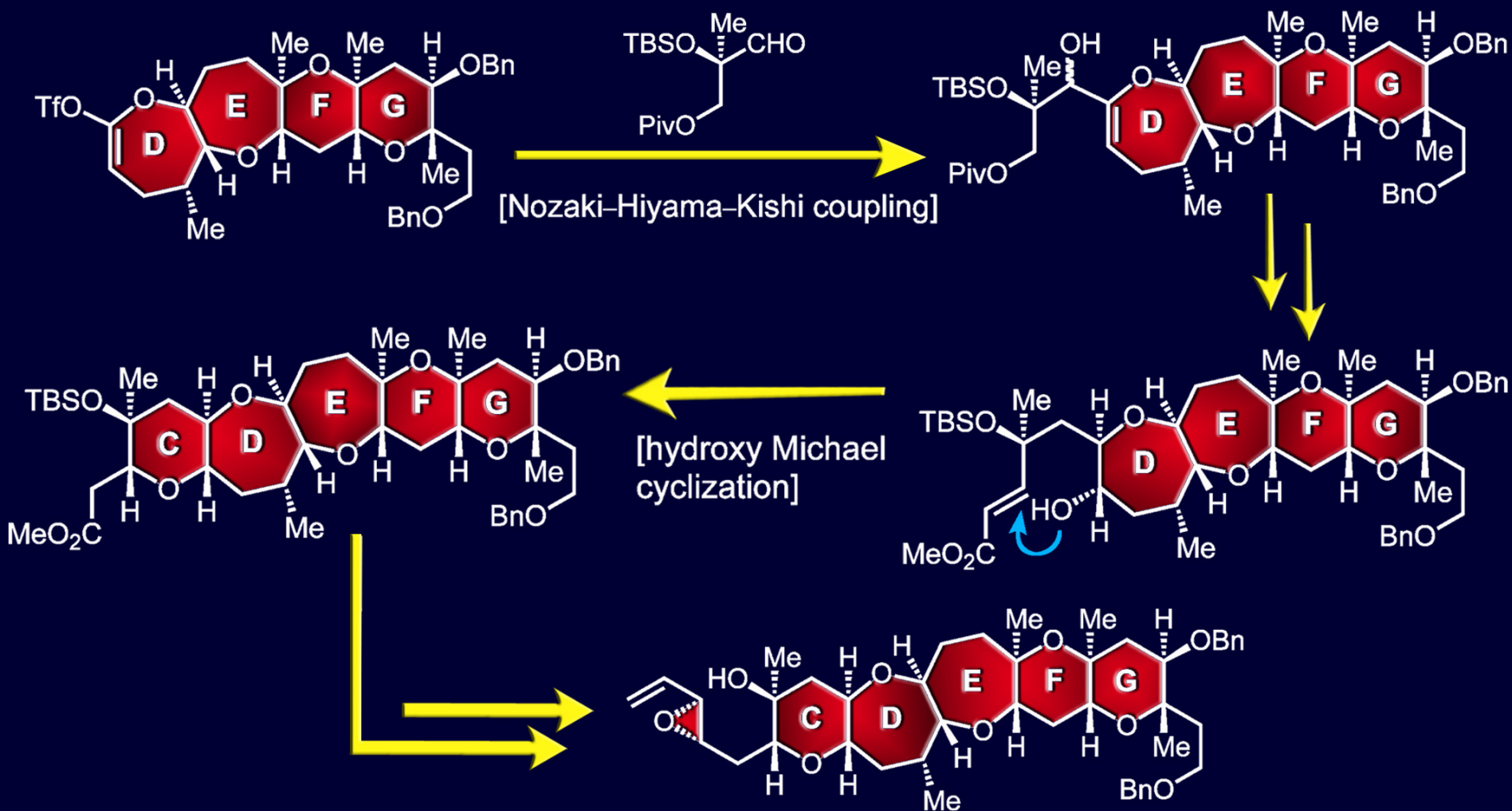


SYNTHESIS OF THE DEFG DOMAIN OF BREVETOXIN B (NICOLAOU et al., 1995) I



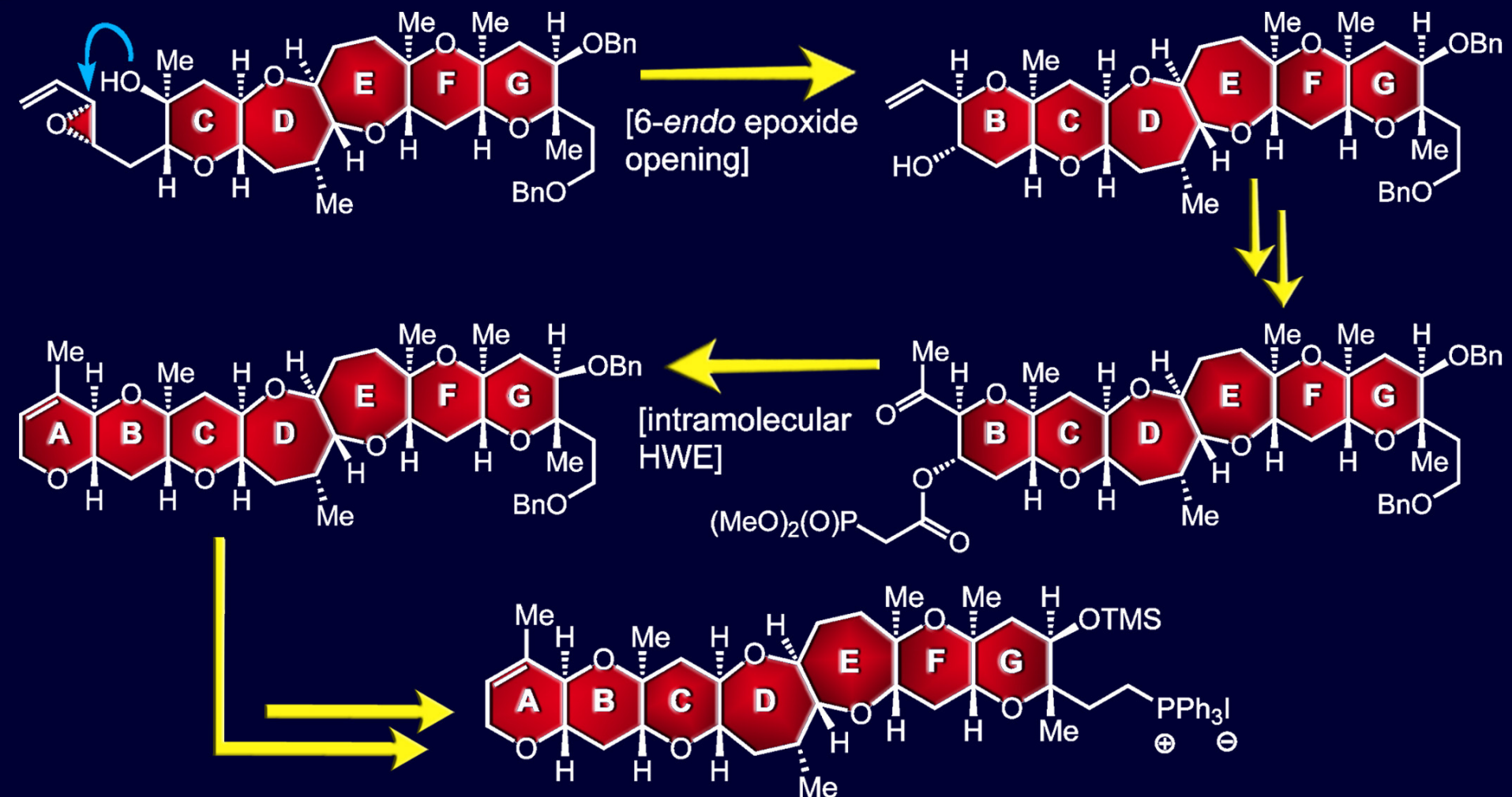


SYNTHESIS OF THE CDEFG DOMAIN OF BREVETOXIN B (NICOLAOU et al., 1995) II



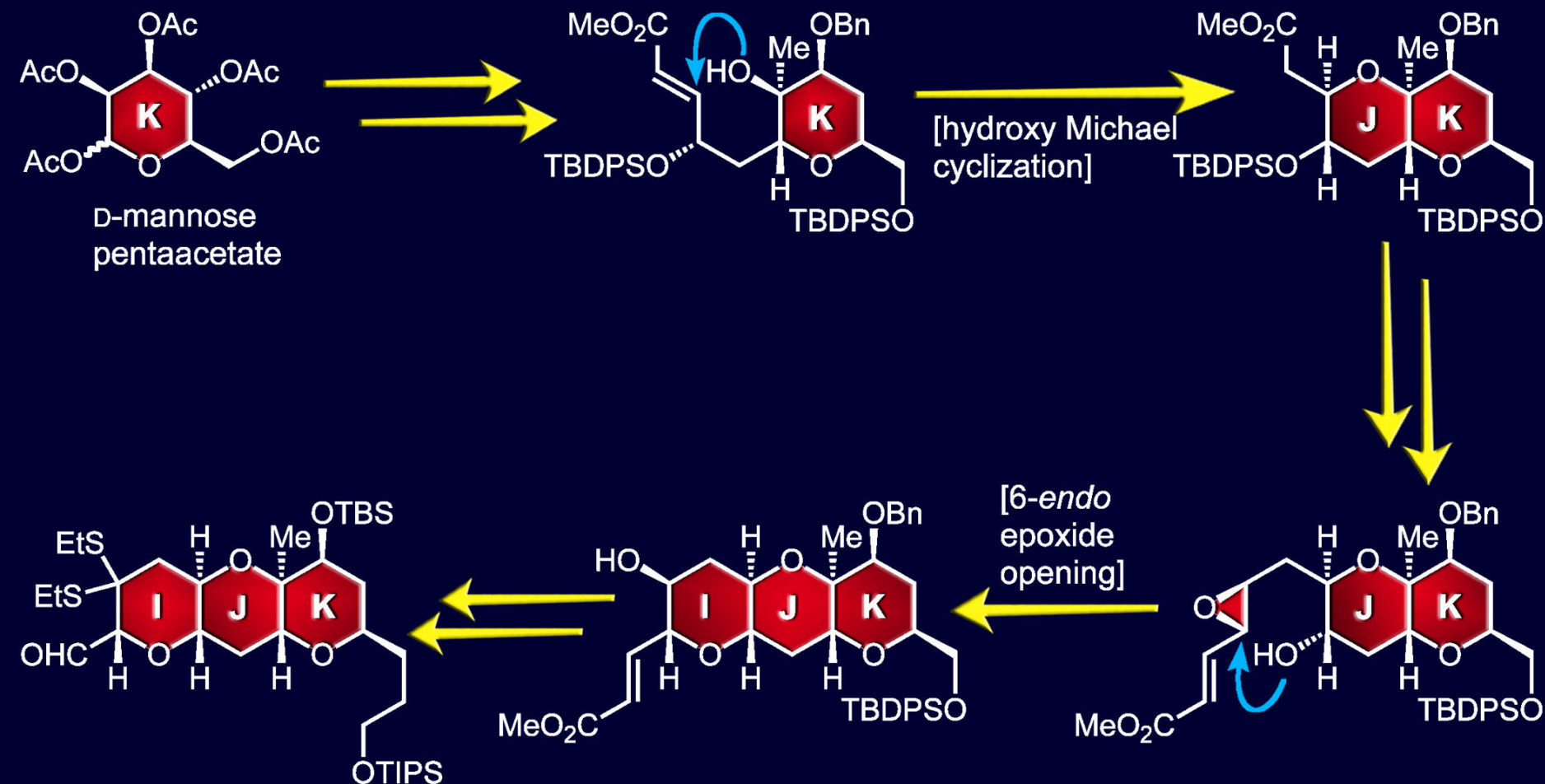


SYNTHESIS OF THE ABCDEFG DOMAIN OF BREVETOXIN B (NICOLAOU et al., 1995) III



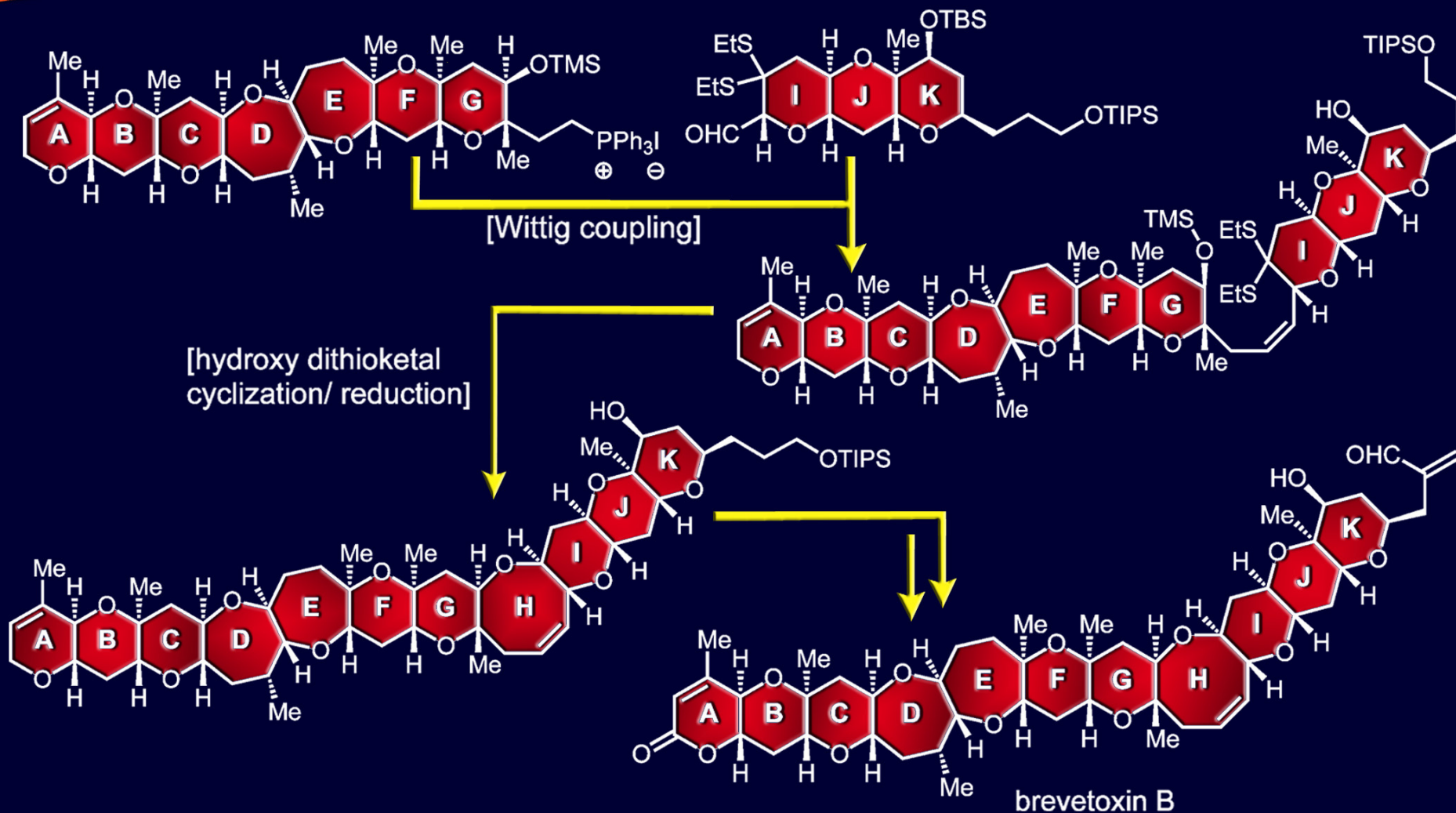


SYNTHESIS OF THE IJK DOMAIN OF BREVETOXIN B (NICOLAOU et al., 1995) IV



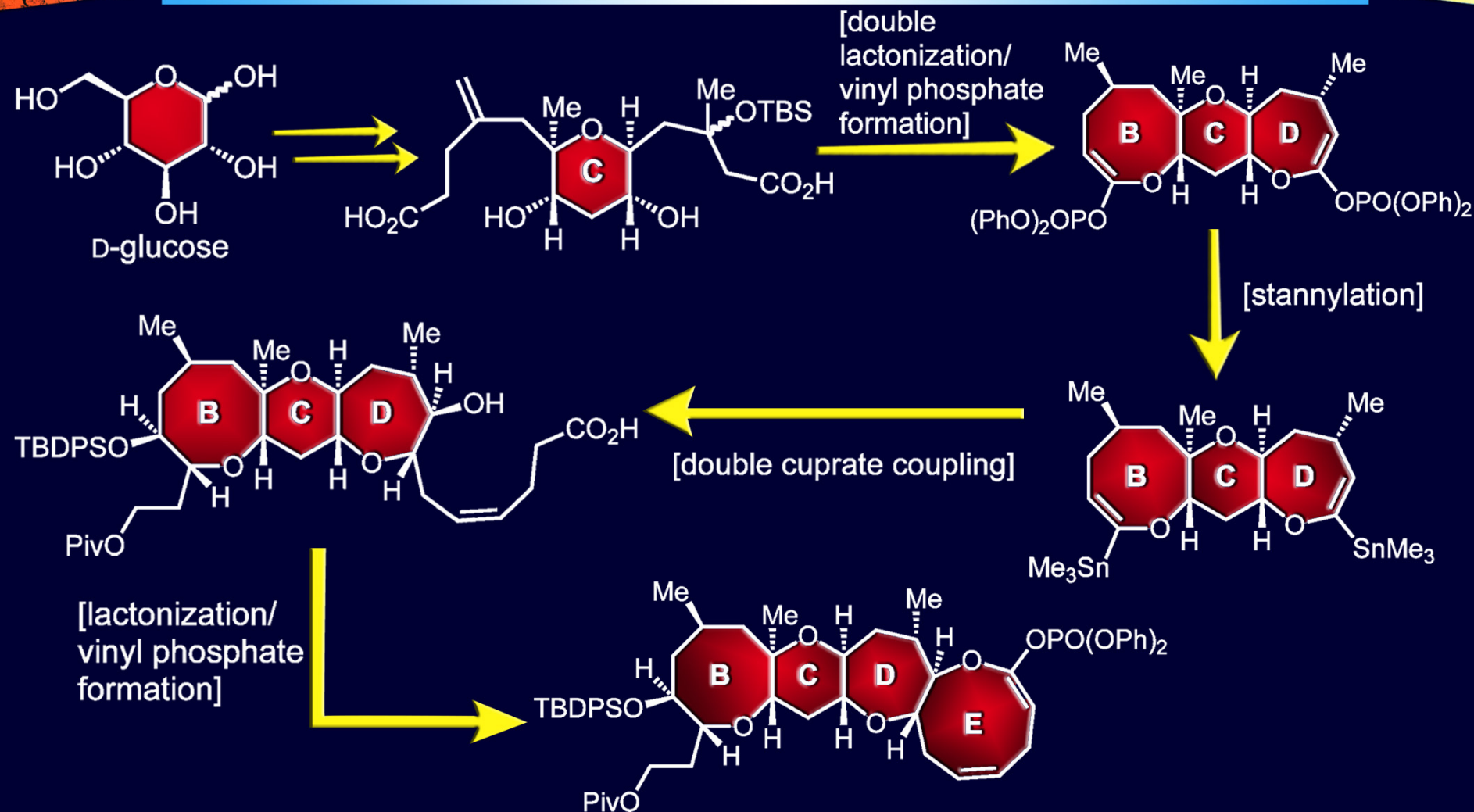


COMPLETION OF THE TOTAL SYNTHESIS OF BREVETOXIN B (NICOLAOU et al., 1995) V



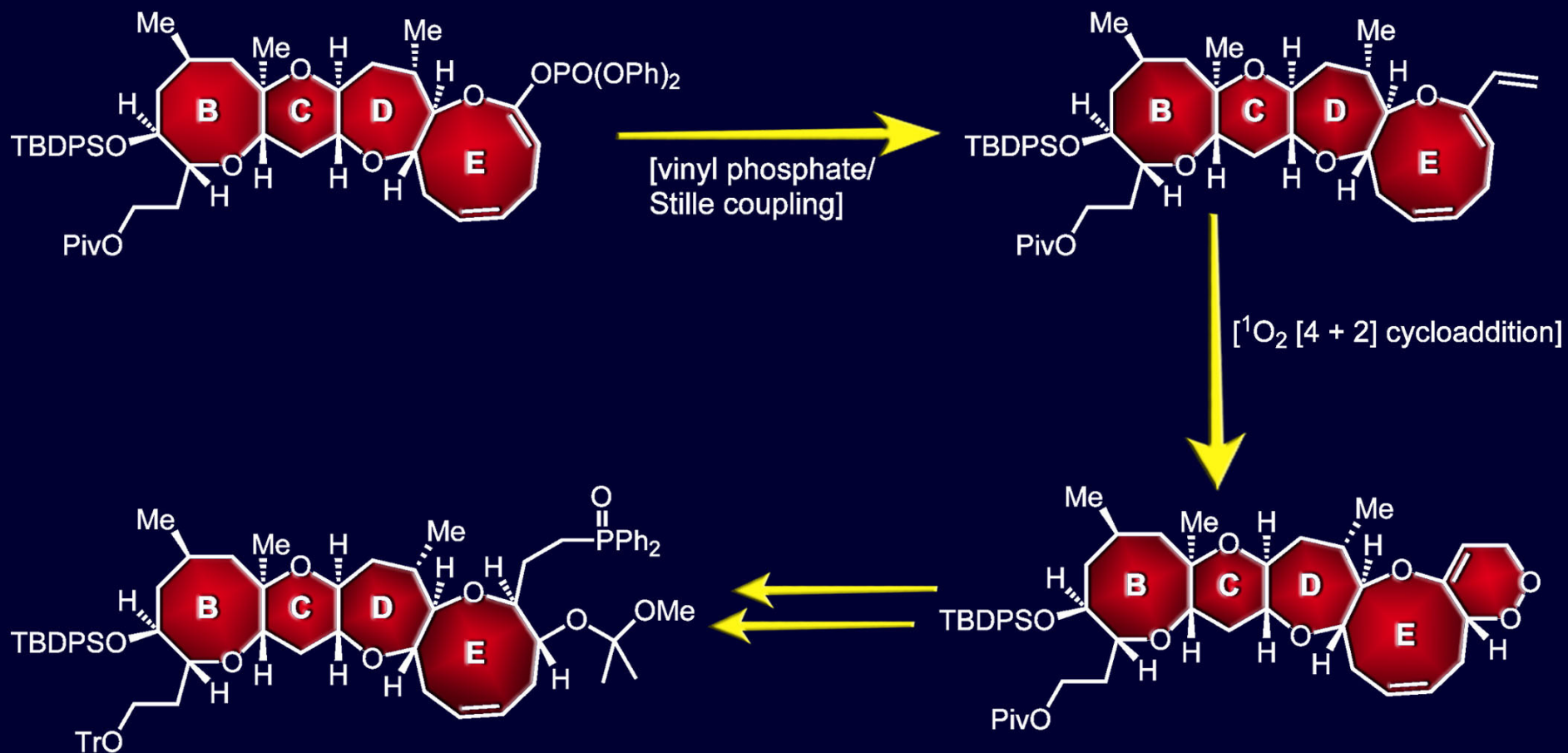


SYNTHESIS OF THE BCDE DOMAIN OF BREVETOXIN A (NICOLAOU et al., 1998) I



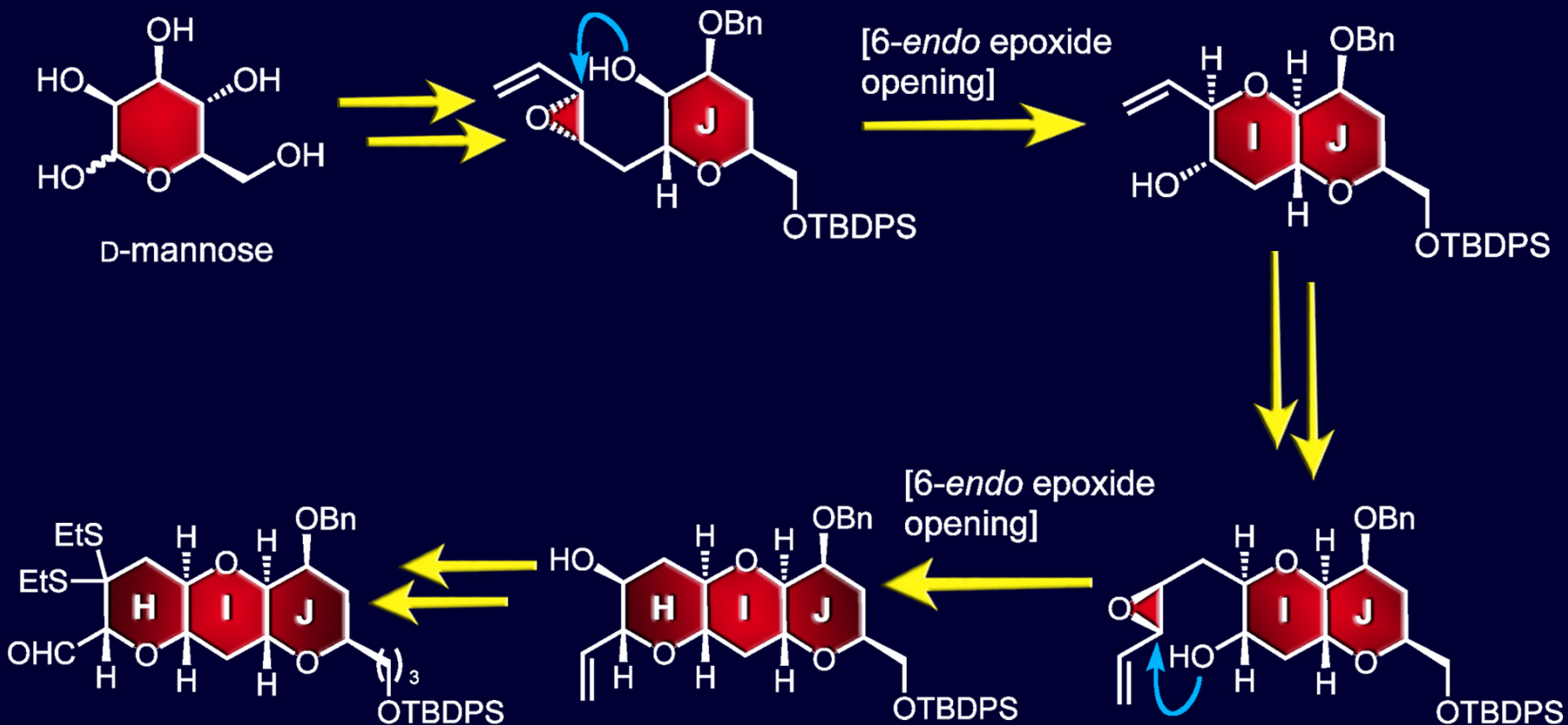


SYNTHESIS OF THE BCDE DOMAIN OF BREVETOXIN A (NICOLAOU et al., 1998) II



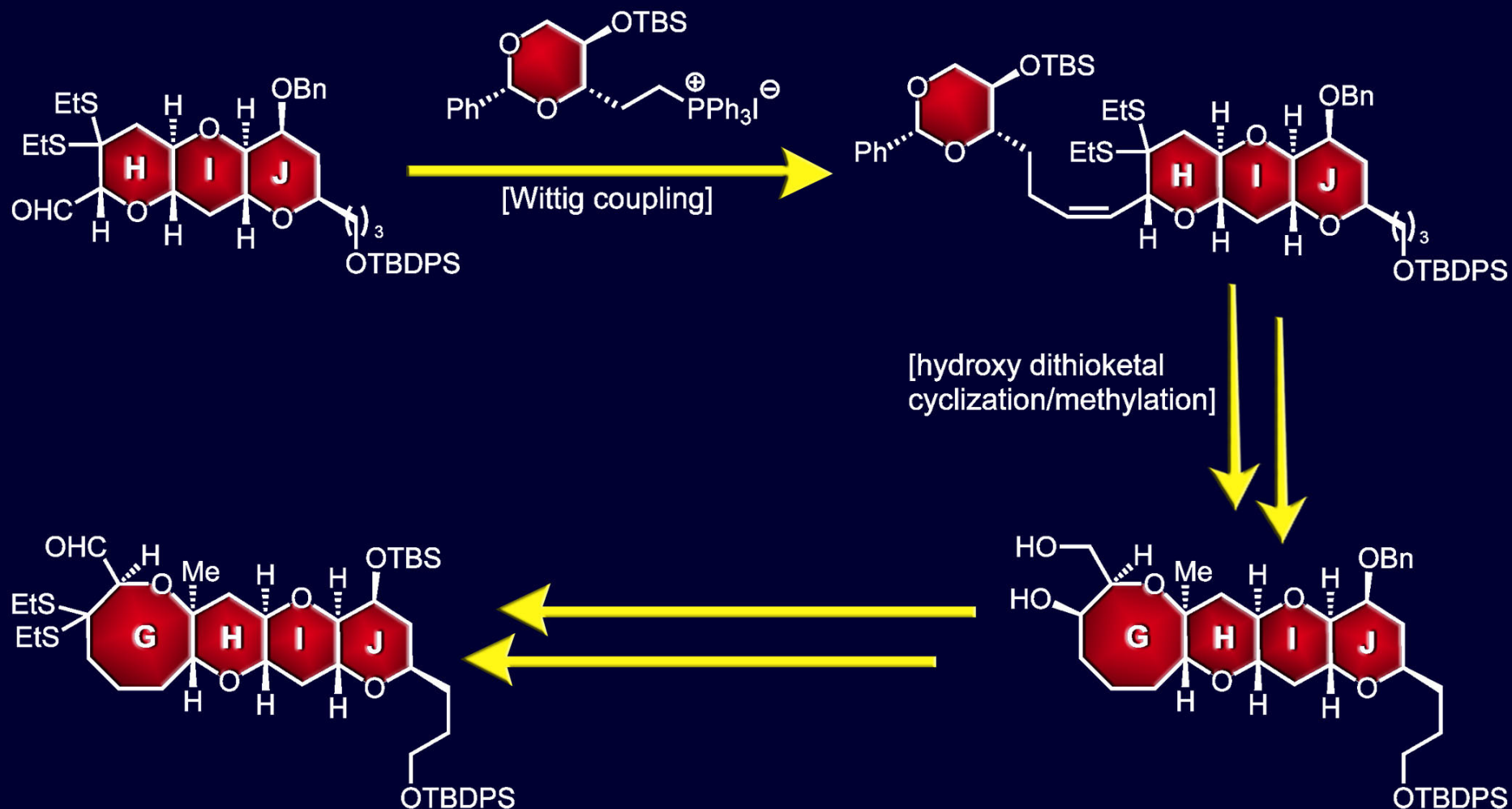


SYNTHESIS OF THE HIJ DOMAIN OF BREVETOXIN A (NICOLAOU et al., 1998) III



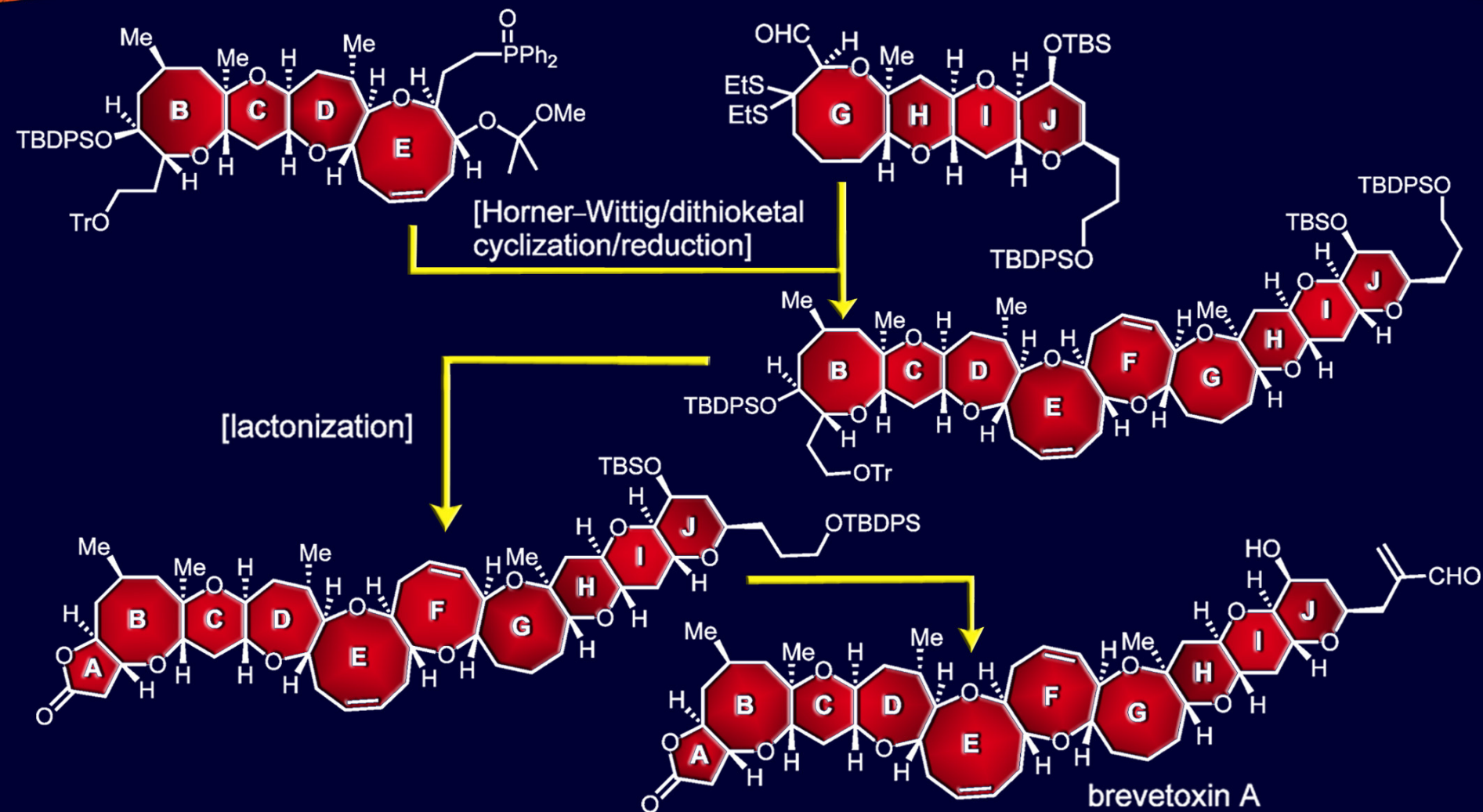


SYNTHESIS OF THE GHIJ DOMAIN OF BREVETOXIN A (NICOLAOU et al., 1998) IV



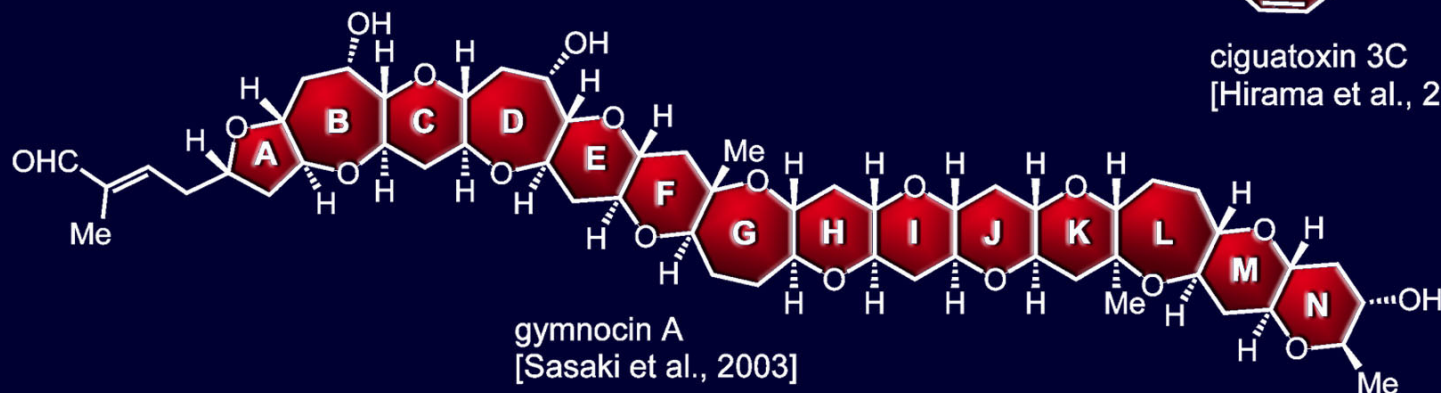
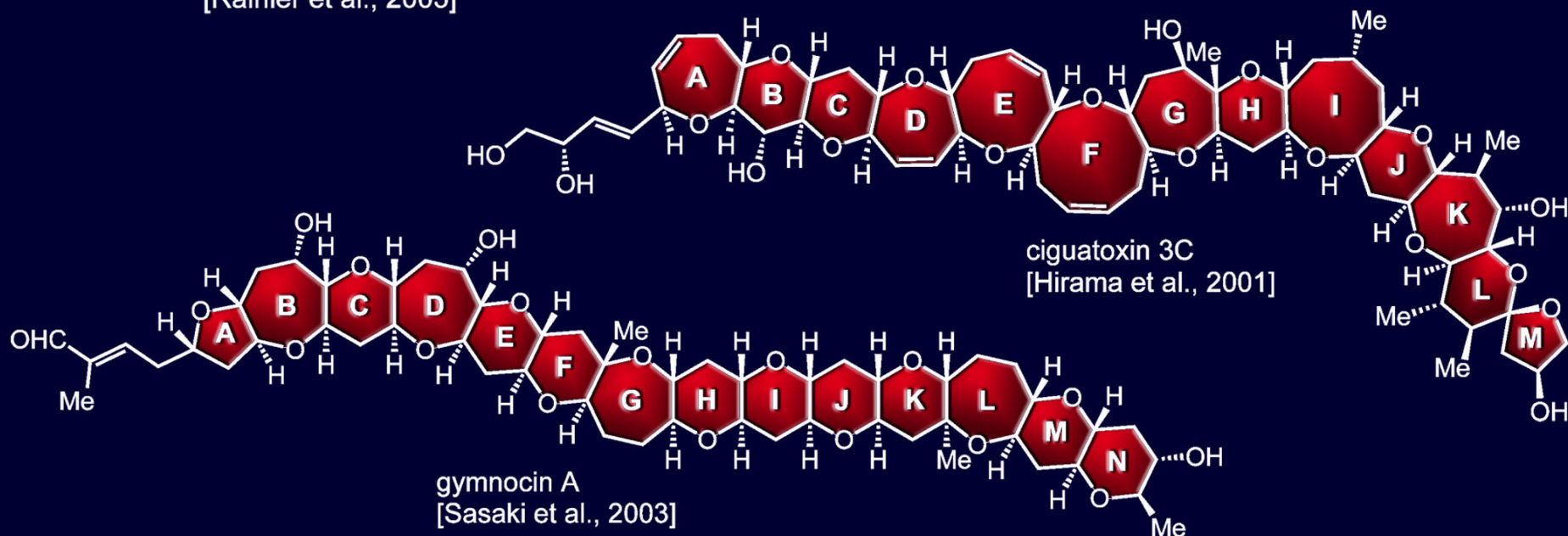
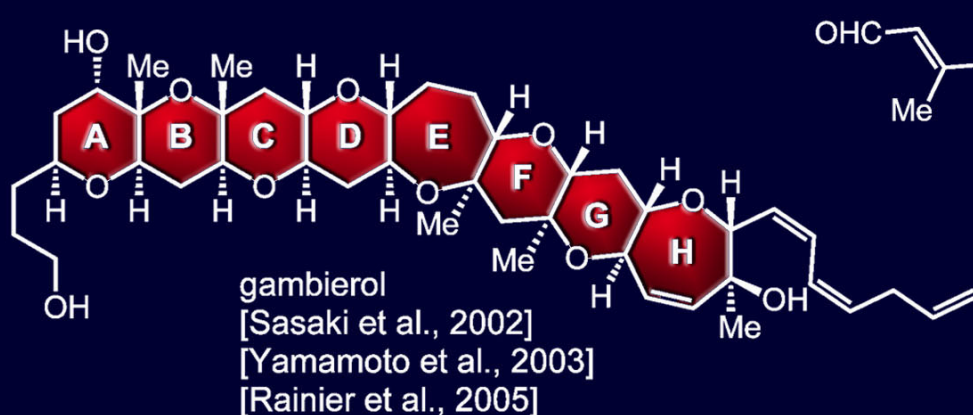


COMPLETION OF THE TOTAL SYNTHESIS OF BREVETOXIN A (NICOLAOU et al., 1998) V





POLYETHER MARINE BIOTOXINS SYNTHESIZED TO DATE, 2008, II



Ciguatera Fish Poisoning

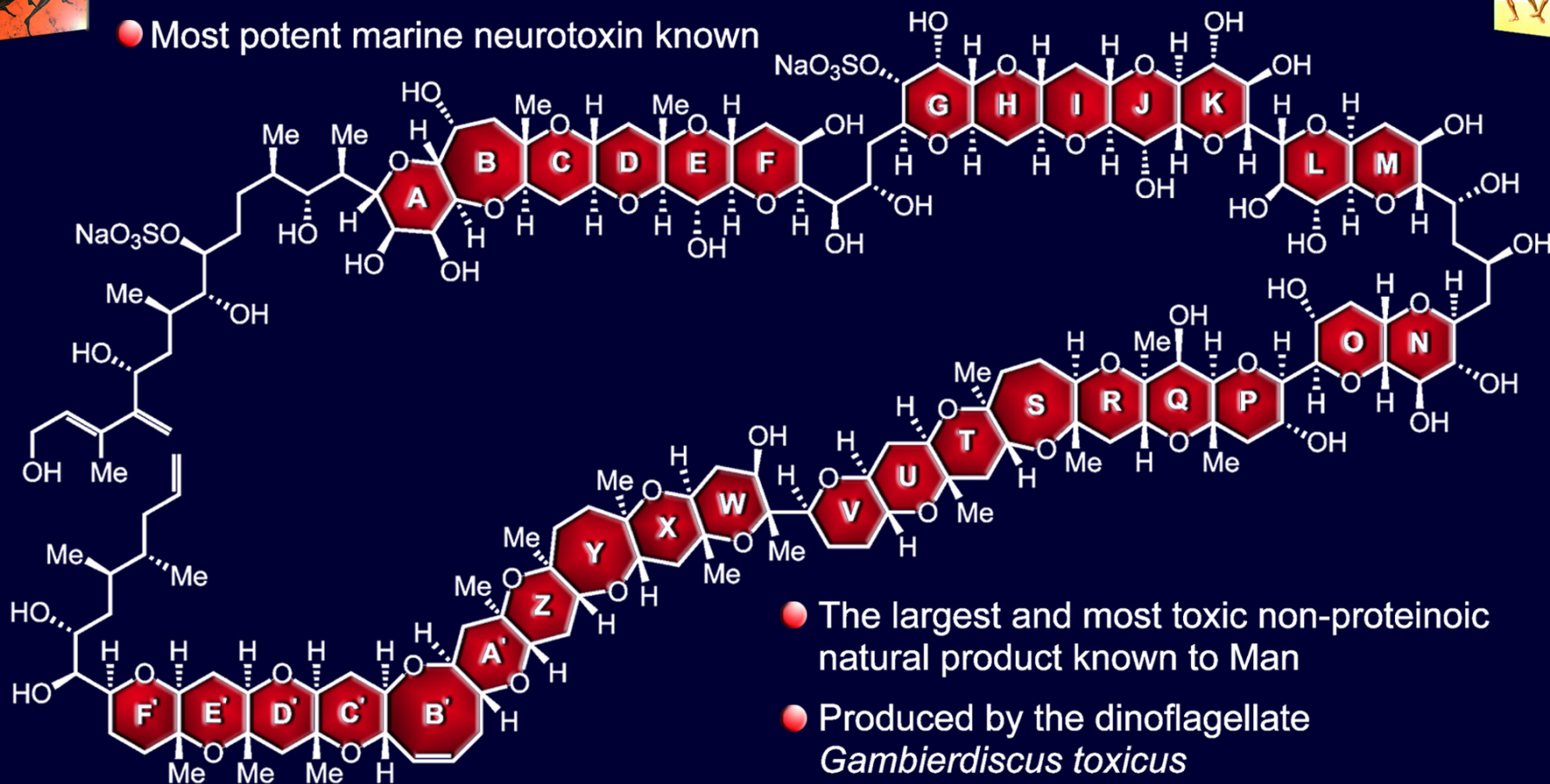




PROPOSED STRUCTURE OF MAITOTOXIN



- Most potent marine neurotoxin known



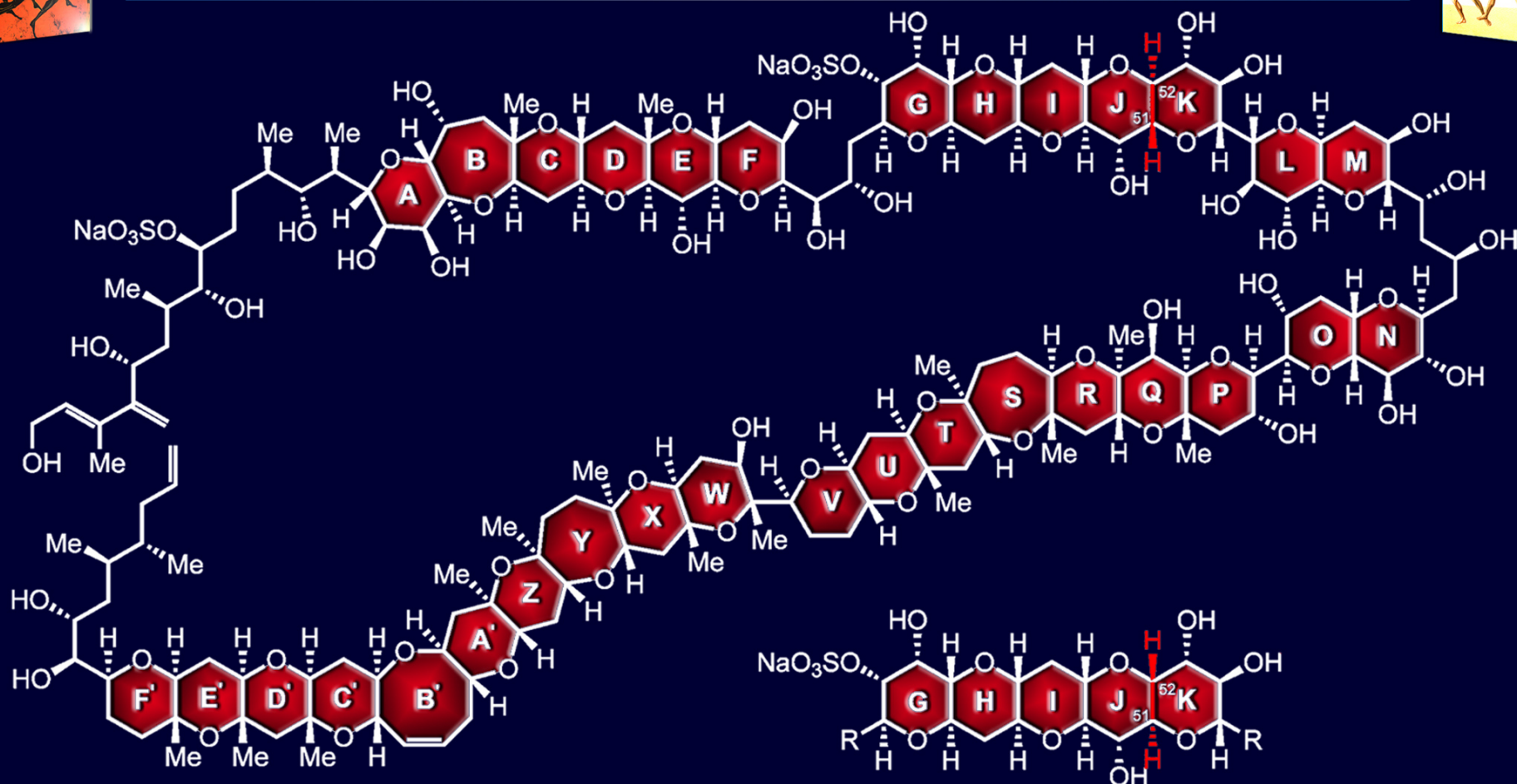
● $C_{164}H_{256}O_{68}S_2Na_2$ [MW 3422 Da]

● 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

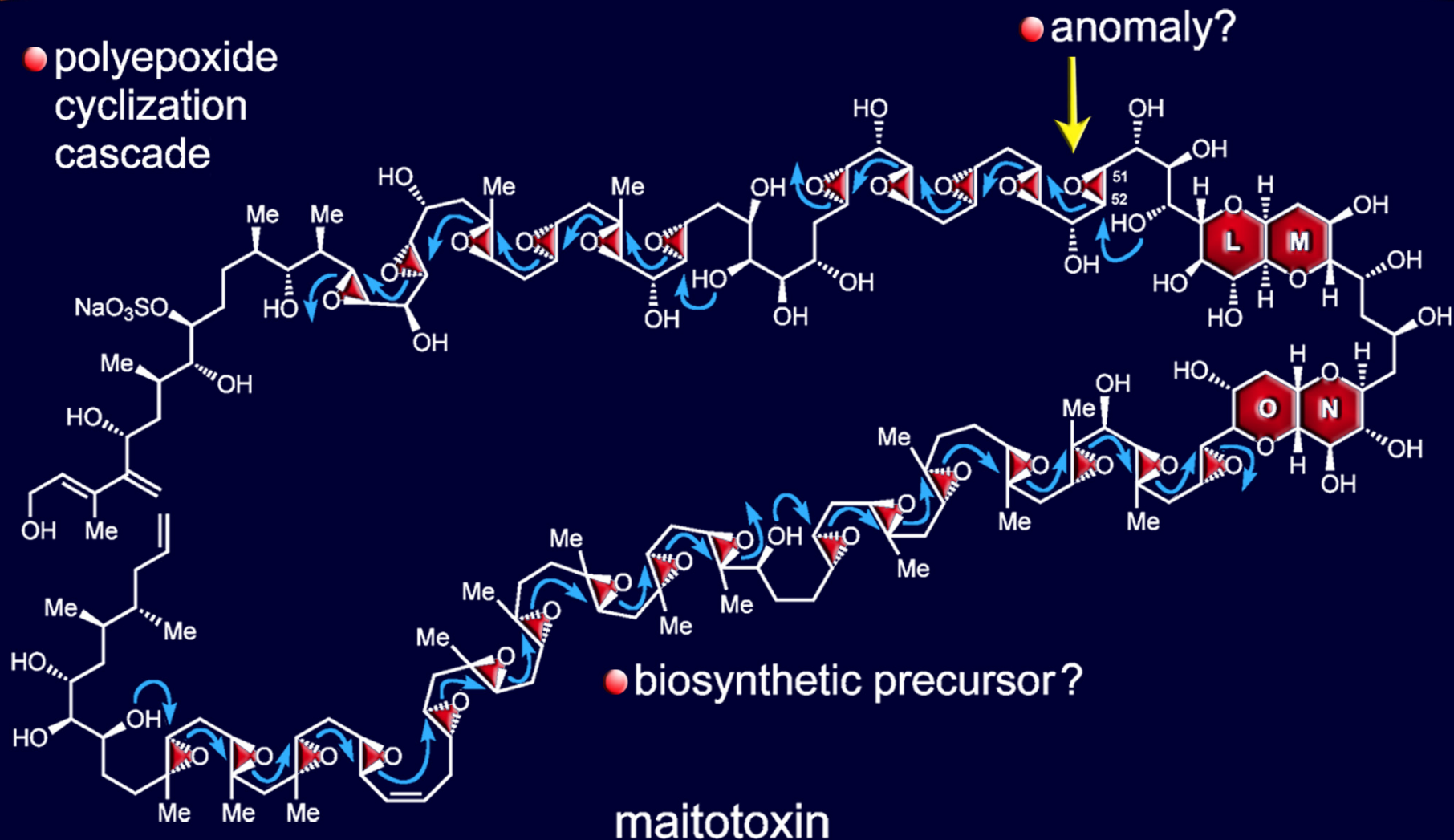


originally proposed maitotoxin structure
[Yasumoto, Tachibana, Kishi, 1996]

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

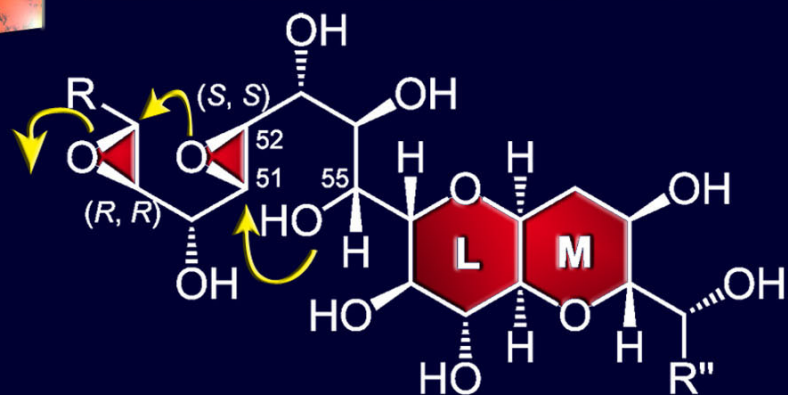


PROPOSED BIOSYNTHESIS OF MAITOTOXIN [NAKANISHI/GALLIMORE-SPENCER]

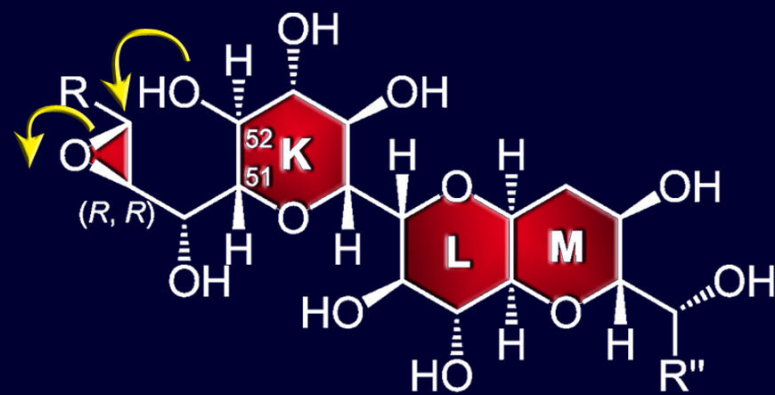




MAITOTOXIN STRUCTURE-3



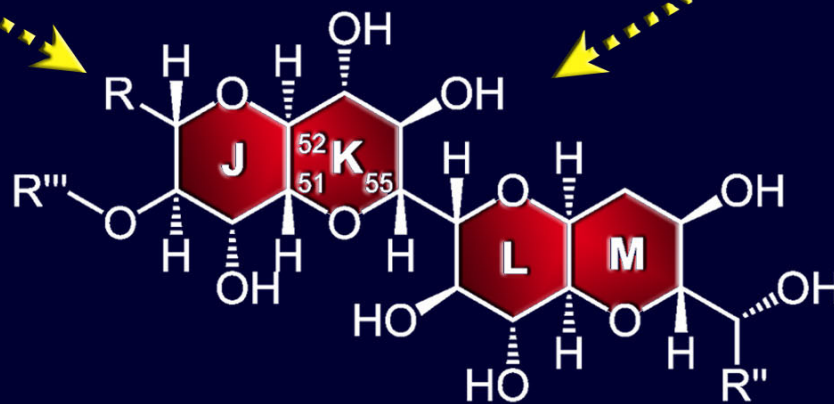
[Gallimore and Spencer]



[alternative biosynthesis, KCN and MOF]

proposed
biosynthesis

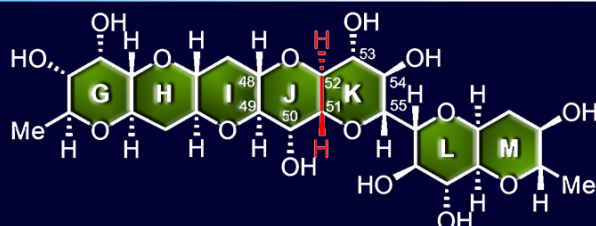
prefabrication
of ring K



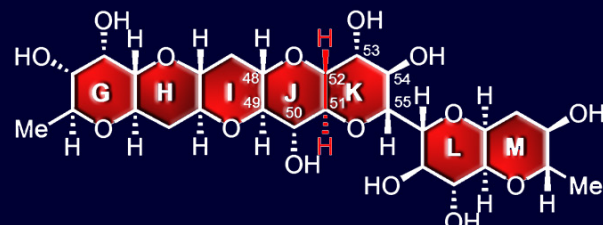
originally proposed JKLMNO domain of maitotoxin



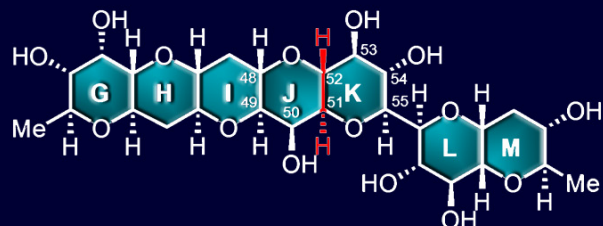
MAITOTOXIN STRUCTURE-2 (2007)



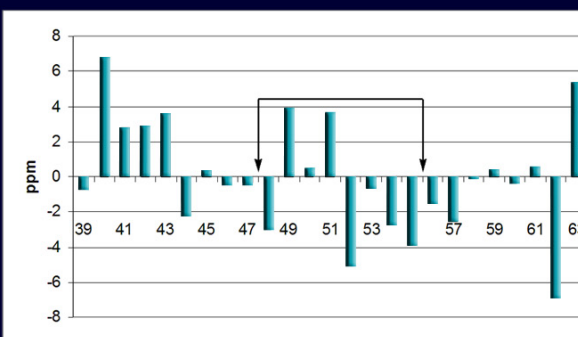
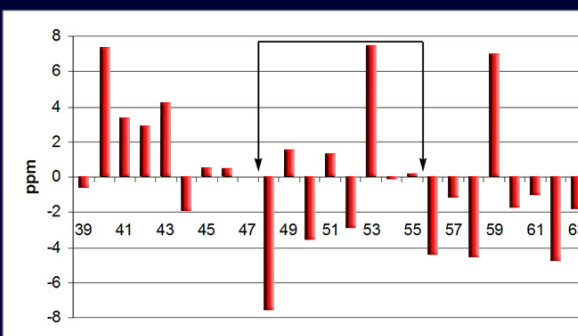
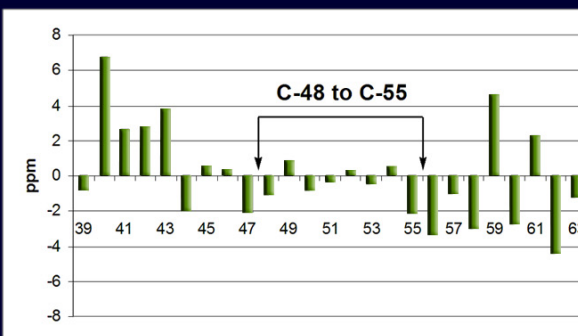
Originally proposed G-K domain
Average difference (C-48 to C-55) = 0.78 ppm
Maximum difference = 2.1 ppm



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



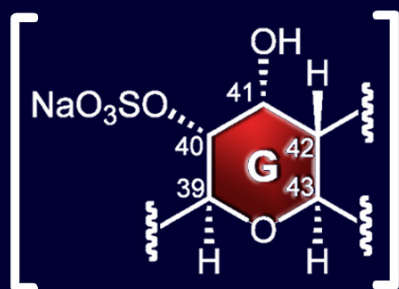
- SPARTAN 06 computer program
- Difference of calculated ^{13}C chemical shifts from experimental values



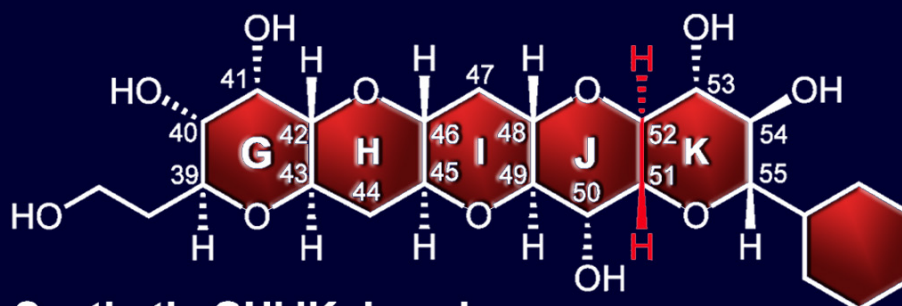
MAITOTOXIN STRUCTURE-3



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



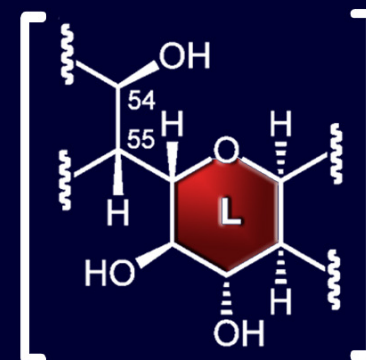
maitotoxin
structure



Synthetic GHIJK domain

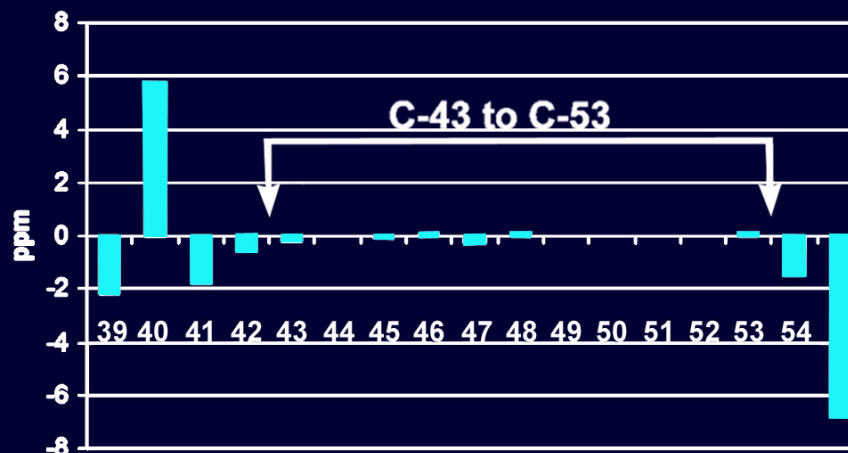
Average difference (C-43 to C-53) = 0.08 ppm

Maximum difference = 0.3 ppm



maitotoxin
structure

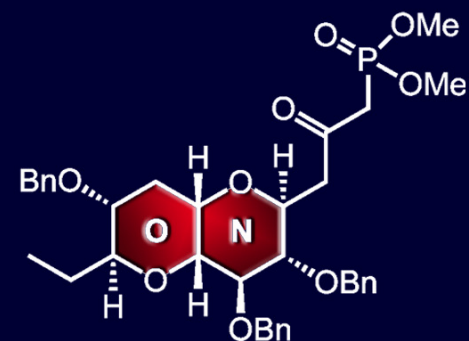
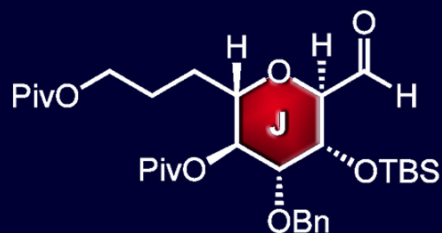
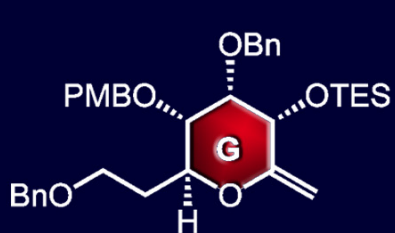
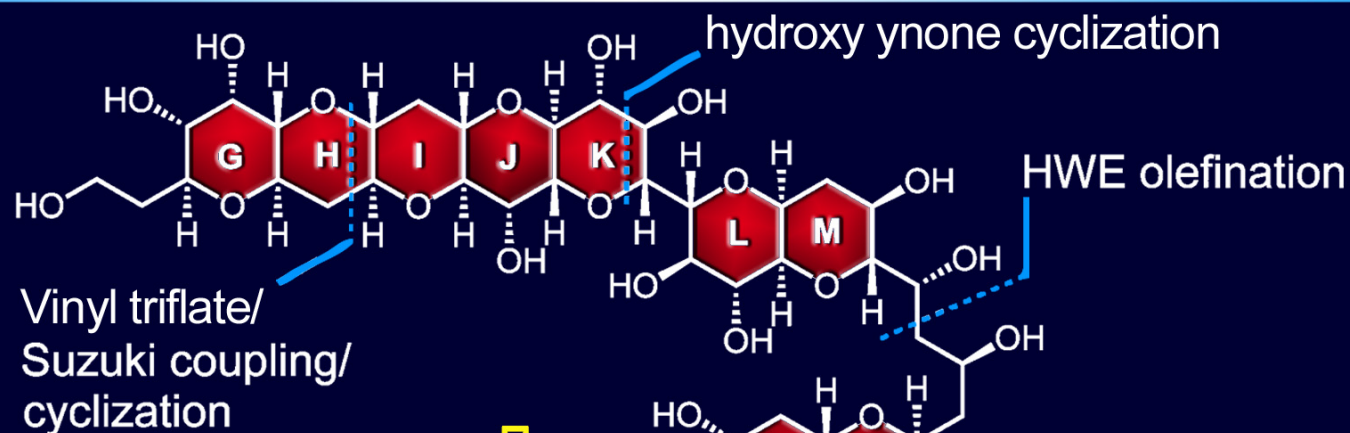
● relatively large $\Delta\delta$ values are due to the absence of a sulfate and presence of cyclohexyl substituent



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

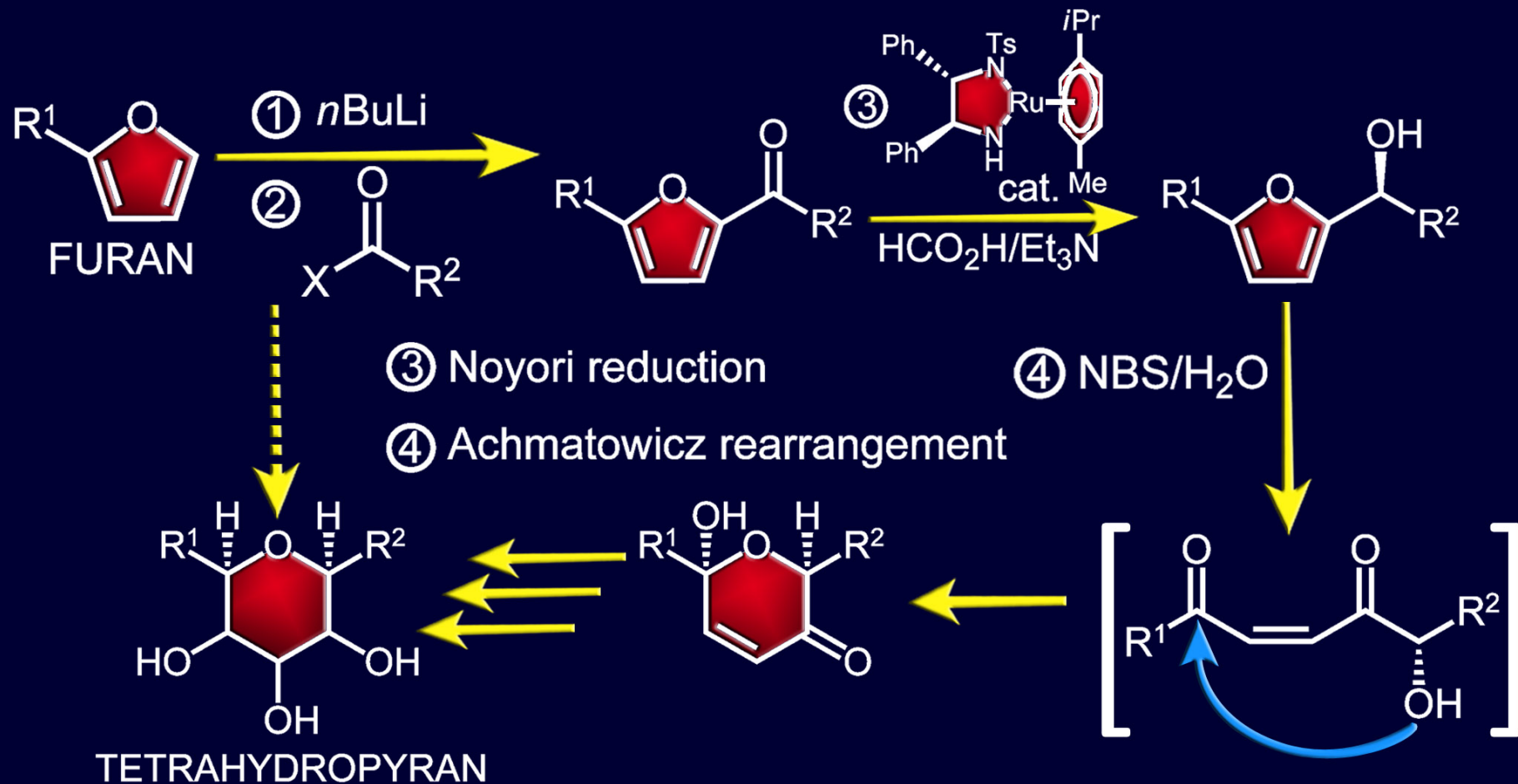


MAITOTOXIN-4: THE FURAN WAY





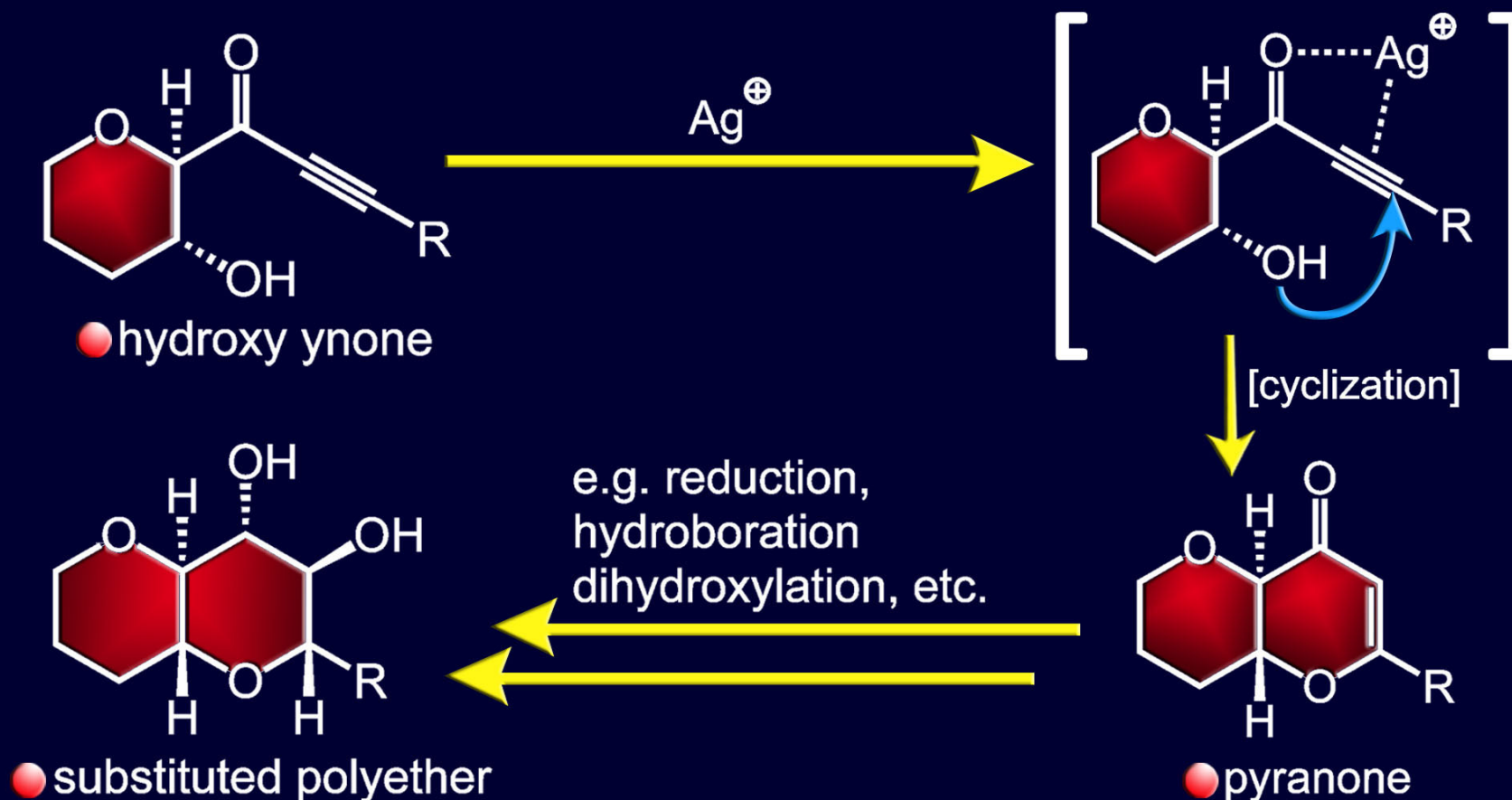
GENERAL METHOD FOR TETRAHYDROPYRAN SYNTHESIS FROM FURANS-THE NOYORI REDUCTION/ACHMATOWICZ REARRANGEMENT METHOD (NICOLAOU ET AL., 2007)



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



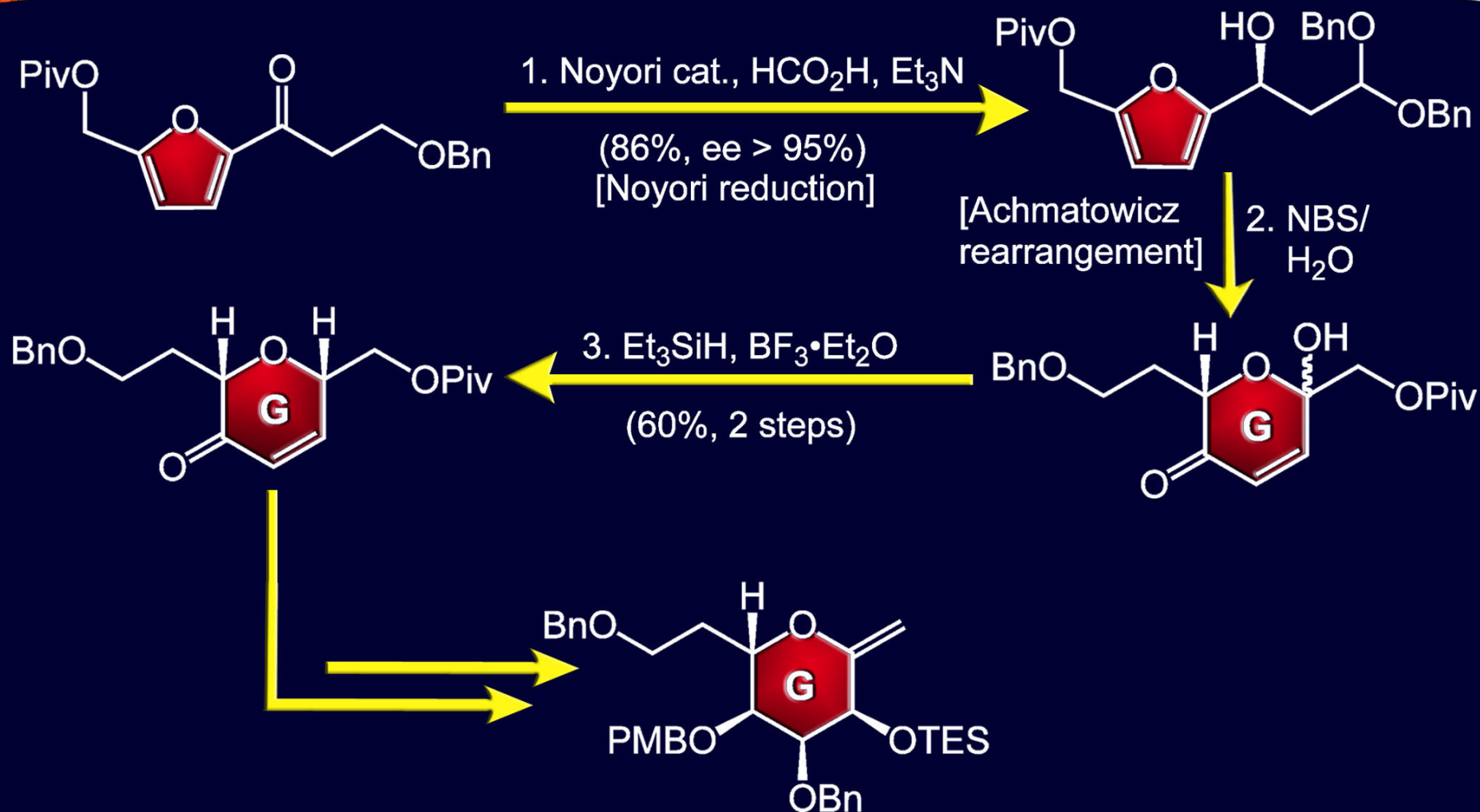
SILVER-PROMOTED, HYDROXY YNONE CYCLIZATION METHOD FOR CYCLIC ETHER FORMATION (NICOLAOU et al., 2007)



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.

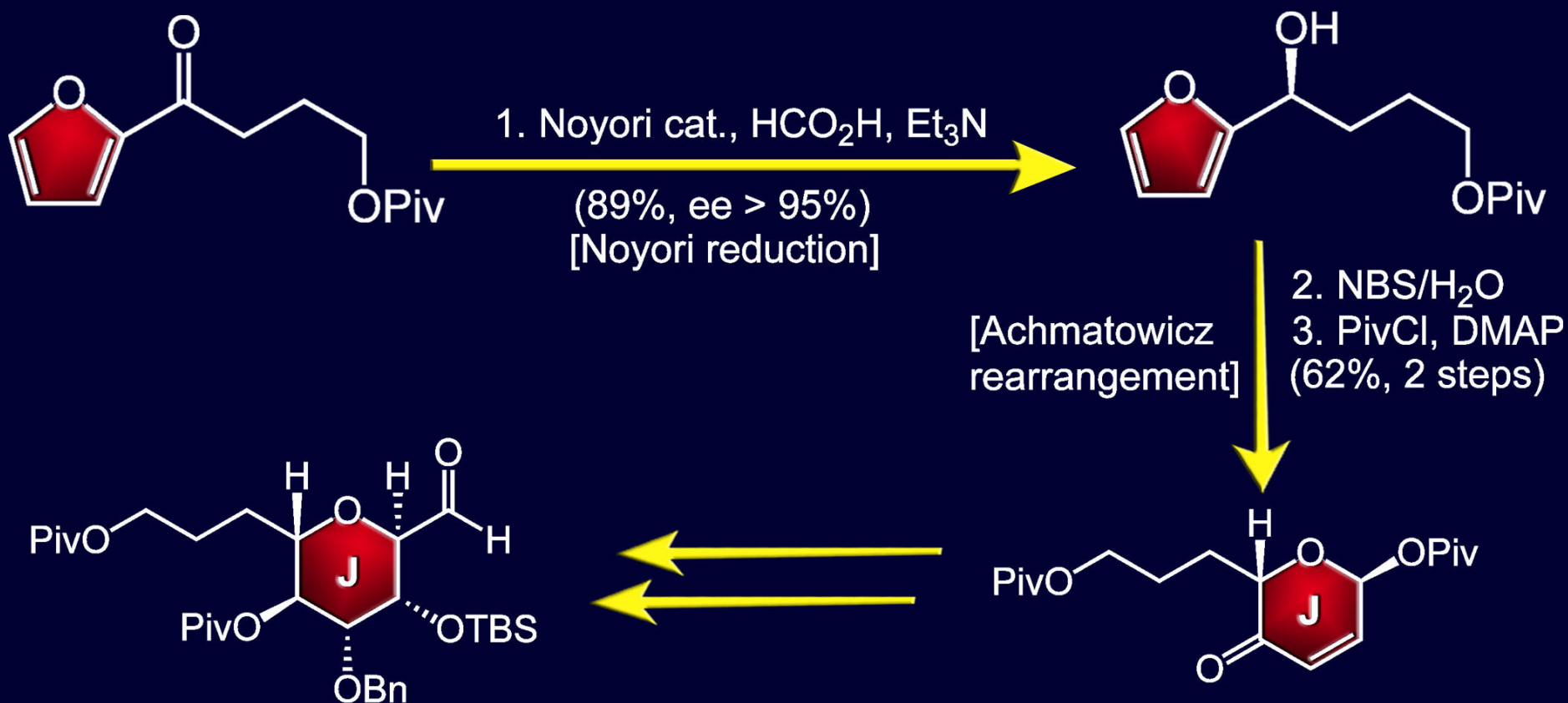


MAITOTOXIN. CONSTRUCTION OF THE G RING SYSTEM



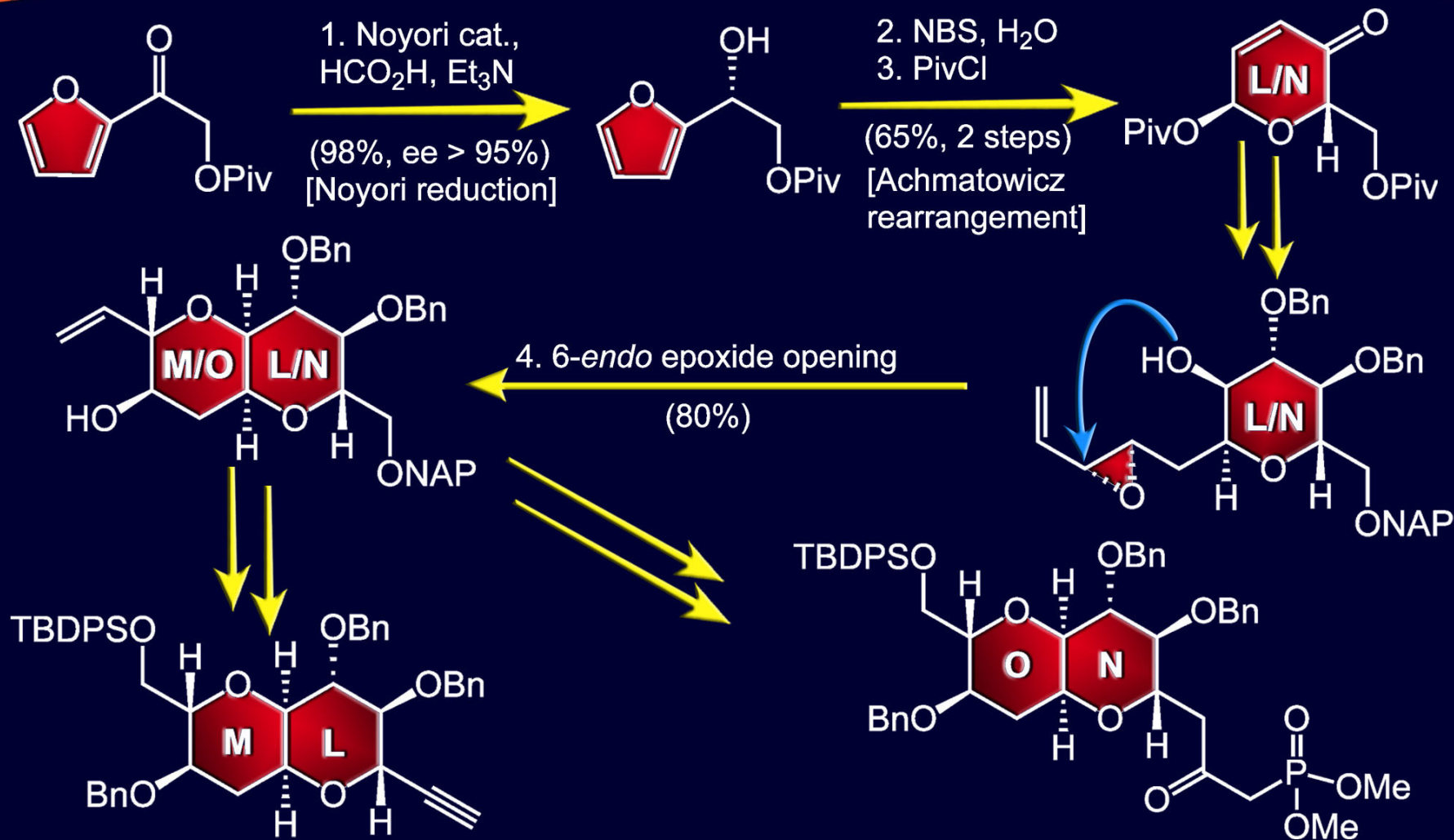


MAITOTOXIN. CONSTRUCTION OF THE J RING SYSTEM



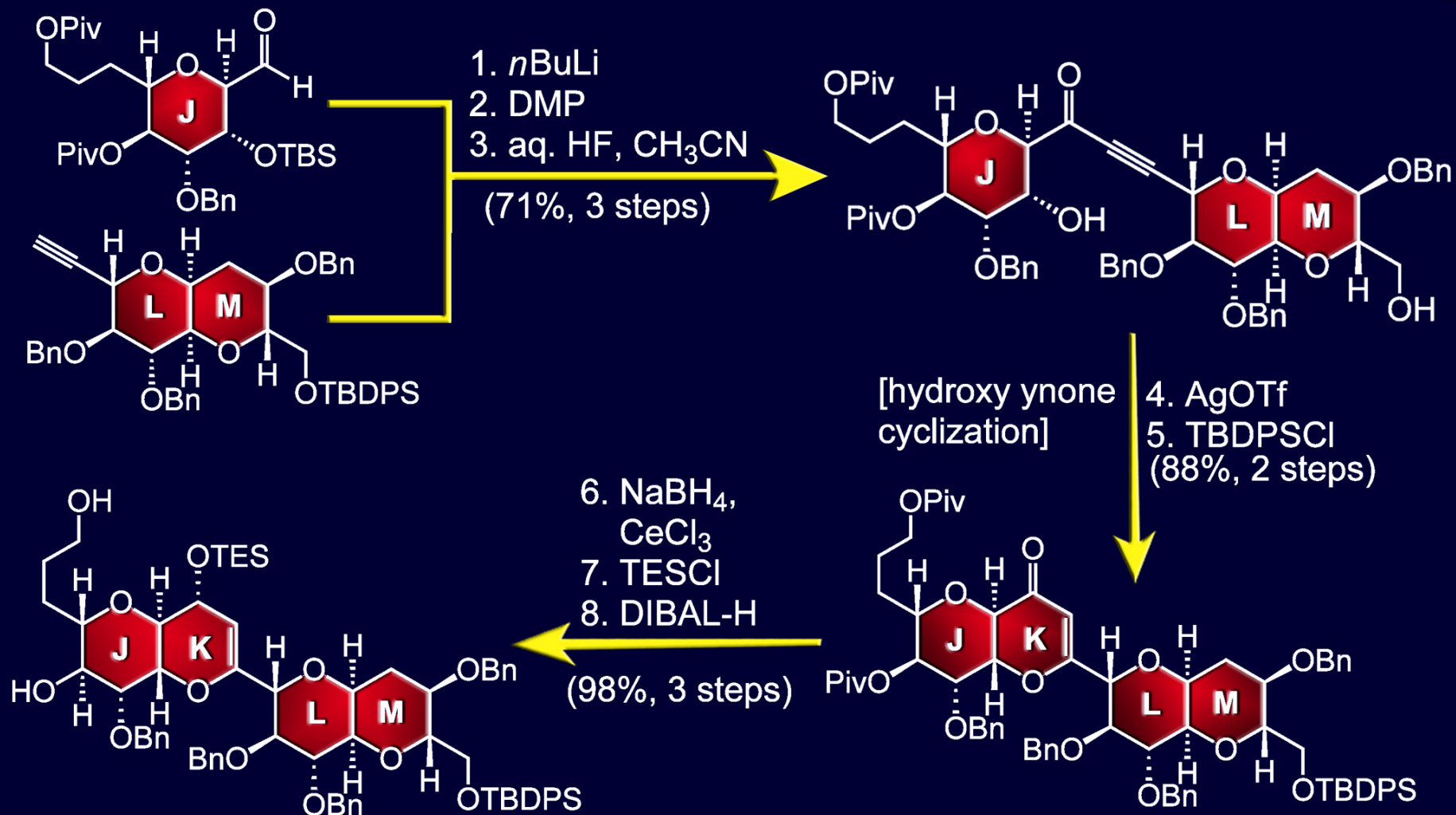


MAITOTOXIN. CONSTRUCTION OF THE LM AND NO RING SYSTEMS



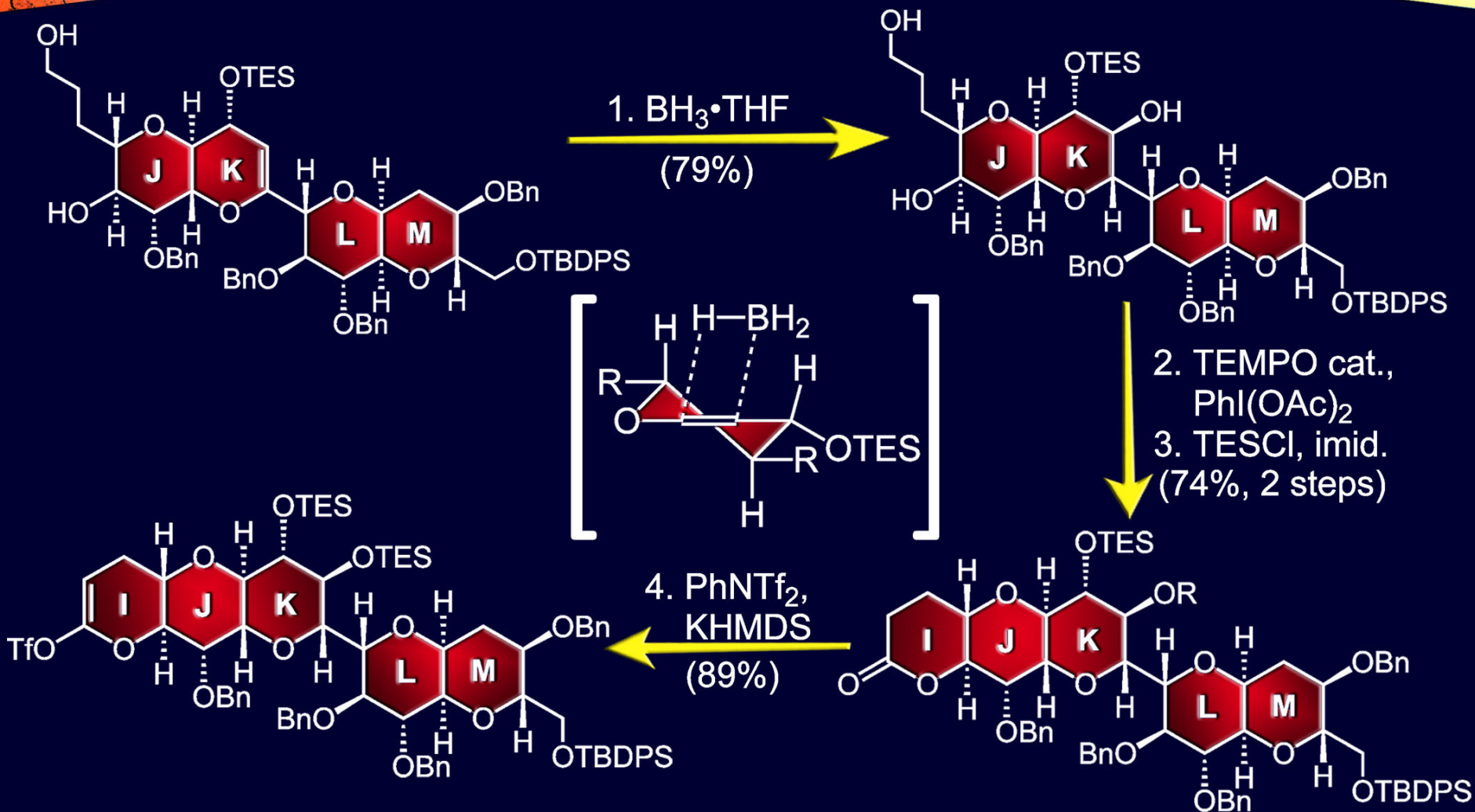


MAITOTOXIN. CONSTRUCTION OF THE JKLM RING SYSTEM



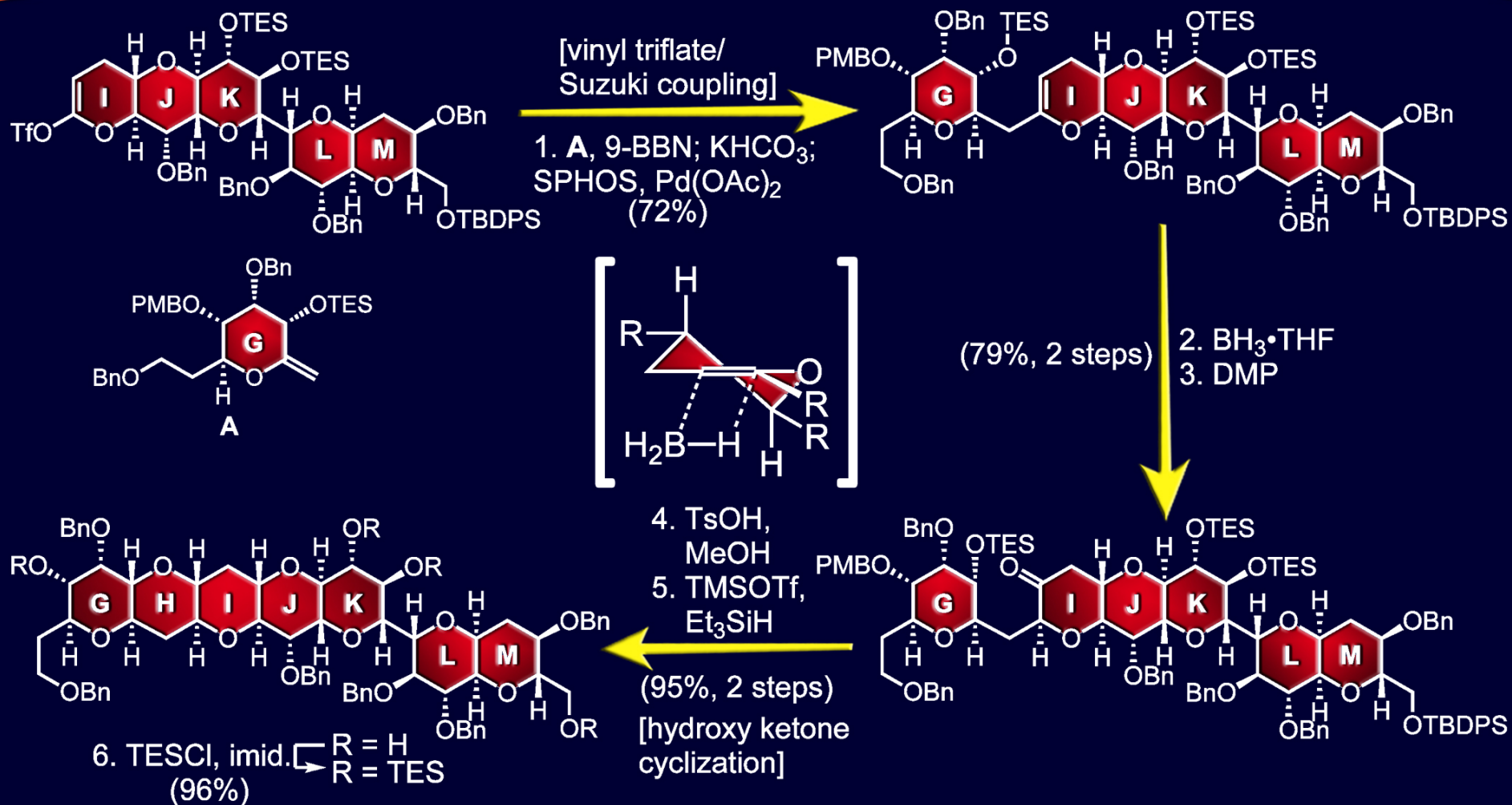


MAITOTOXIN. CONSTRUCTION OF THE IJKLM RING SYSTEM



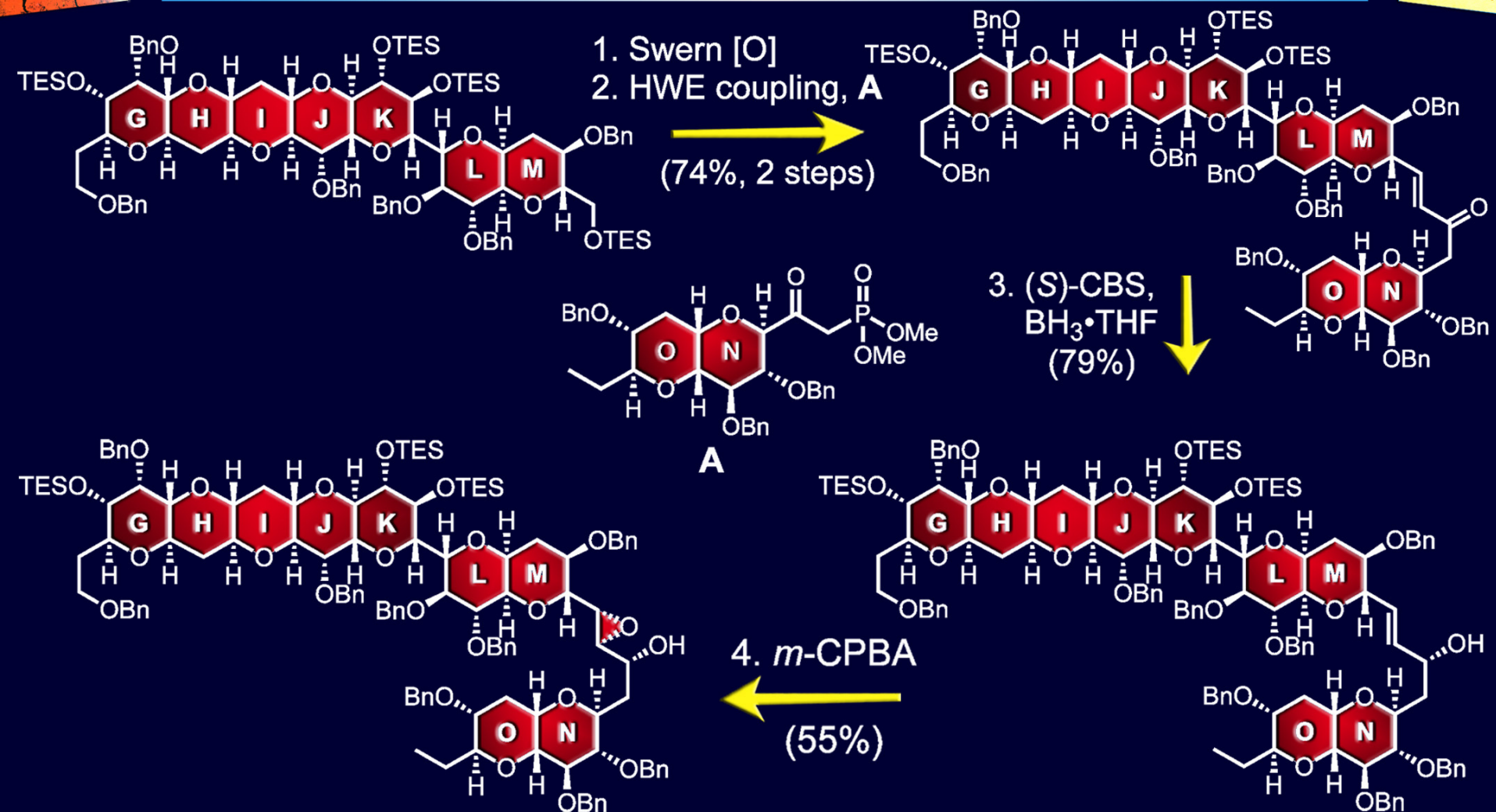


MAITOTOXIN. CONSTRUCTION OF THE GHIJKLM RING SYSTEM



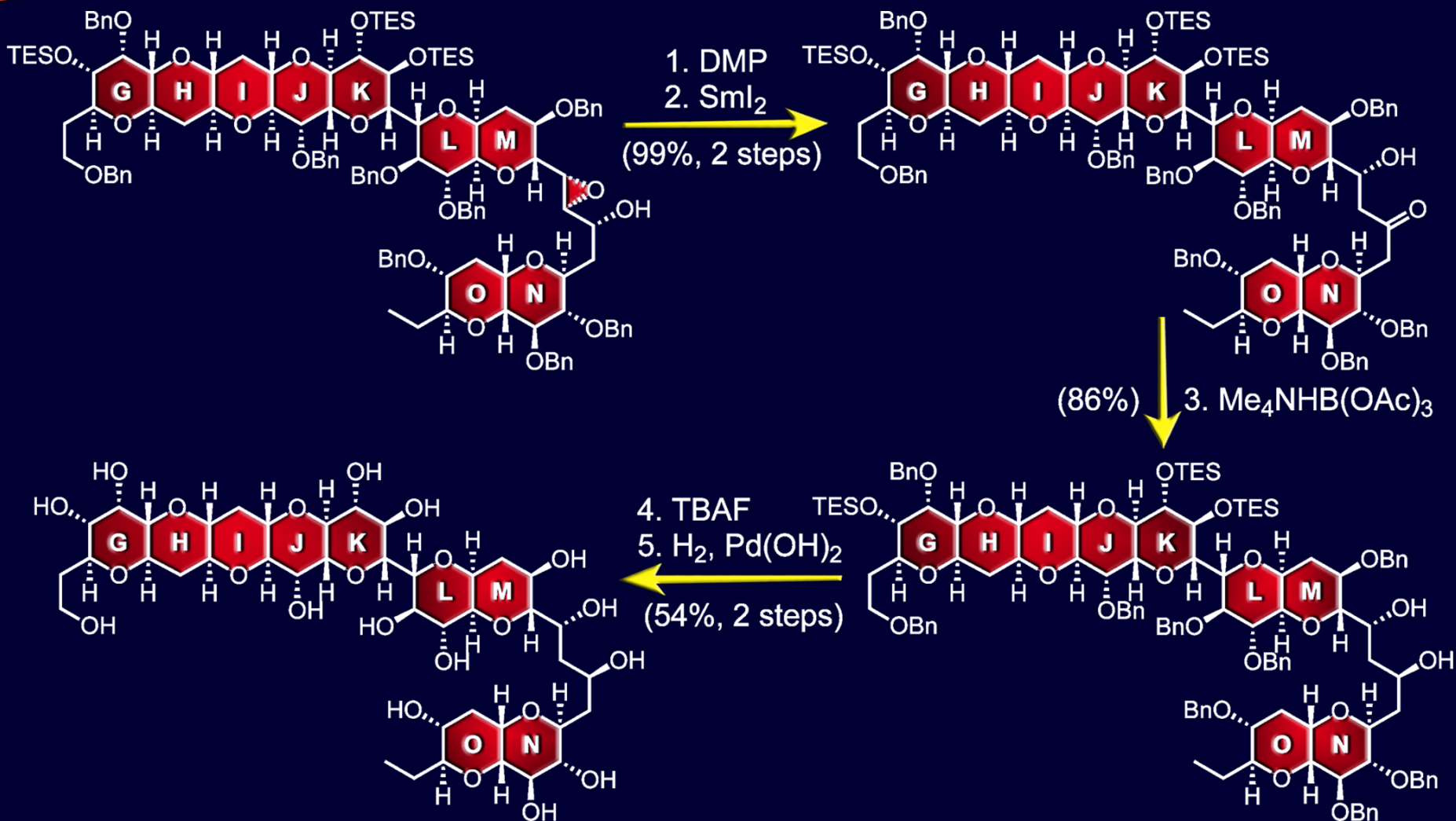


MAITOTOXIN. CONSTRUCTION OF THE GHIJKLMNO RING SYSTEM



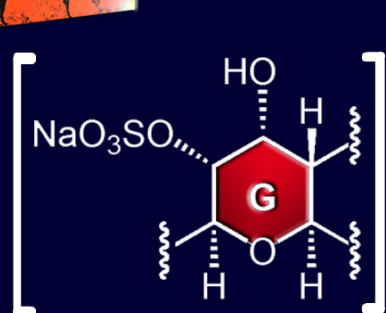


MAITOTOXIN. SYNTHESIS OF THE GHIJKLMNO DOMAIN

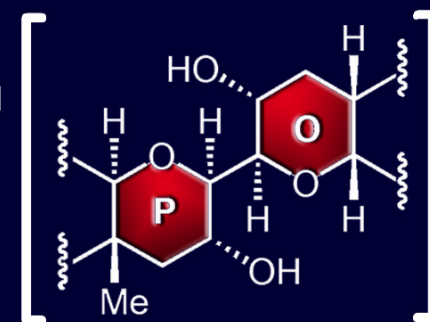
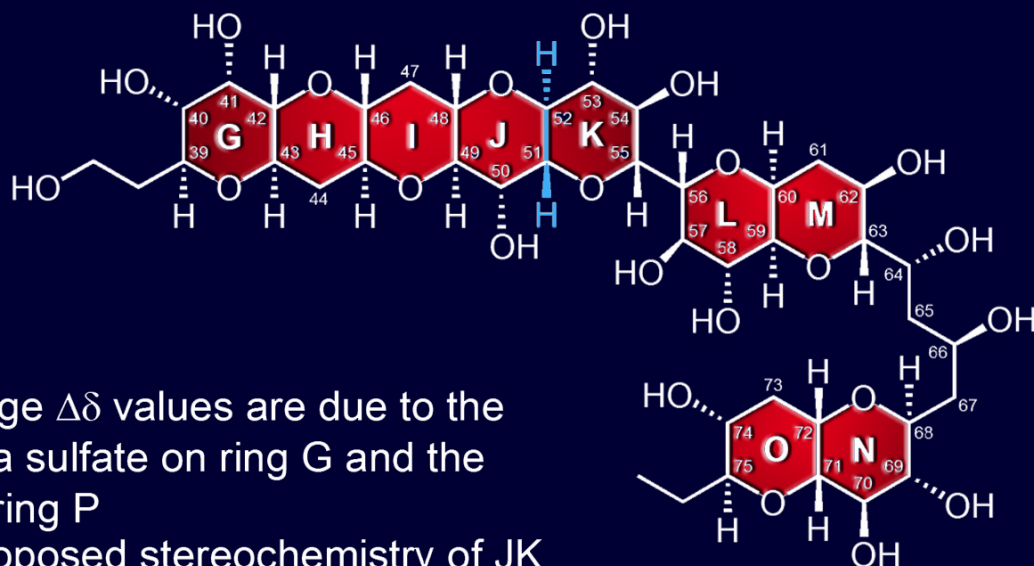




MAITOTOXIN-15

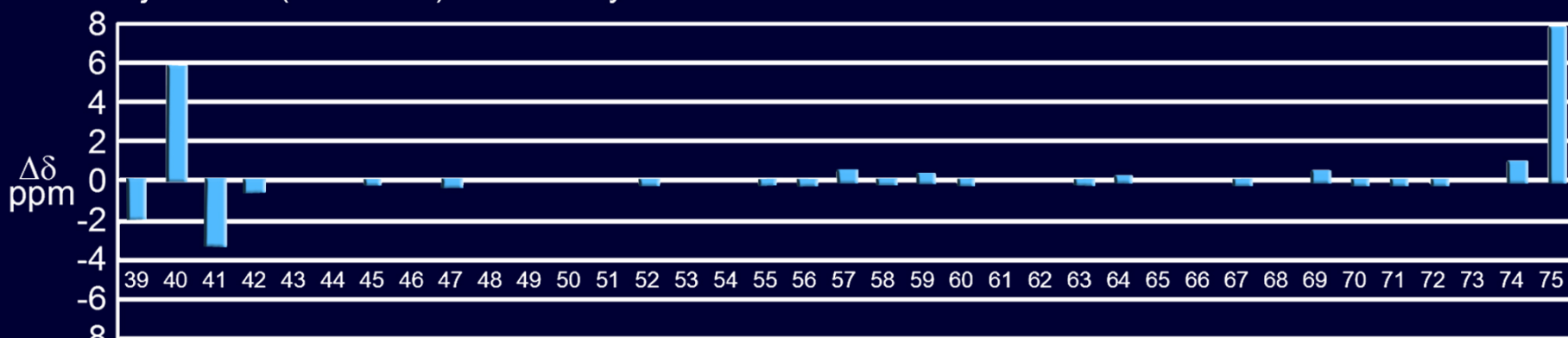


maitotoxin structure



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



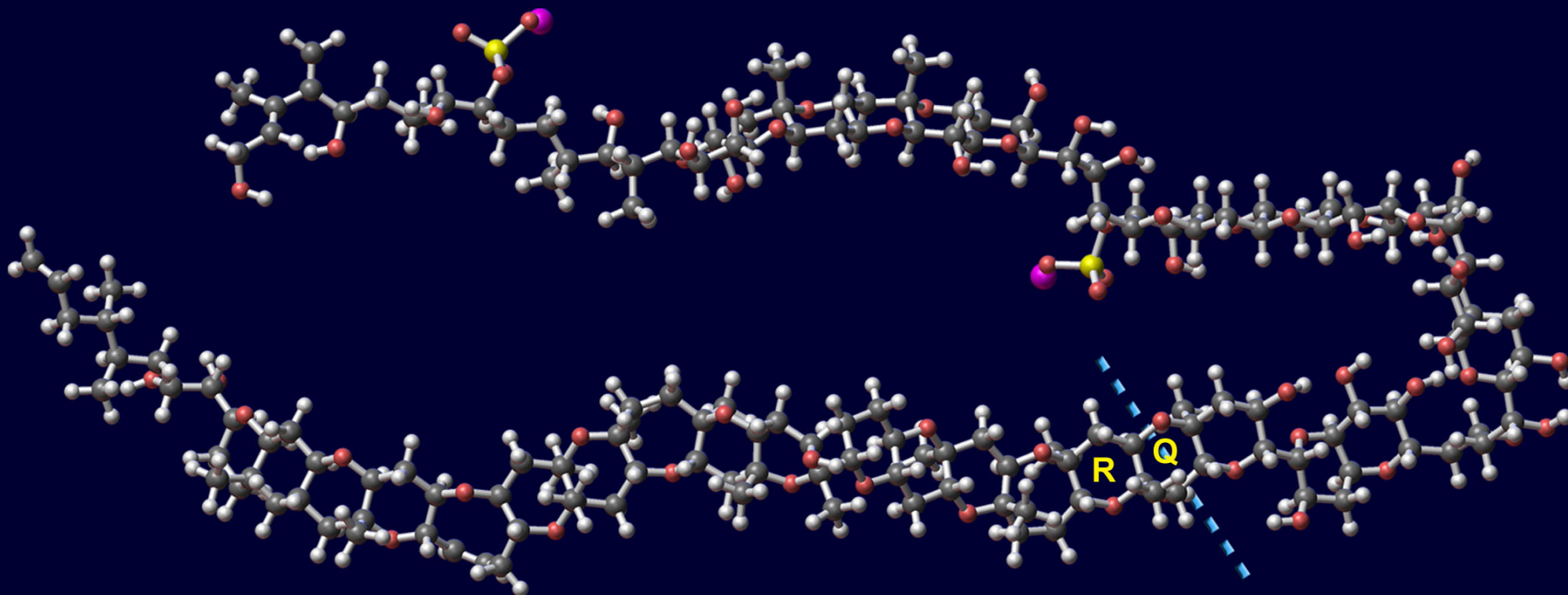
- average $\Delta\delta$ for C42-C73 = 0.09 ppm
- largest $\Delta\delta$ for C42-C73 = 0.4 ppm



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'

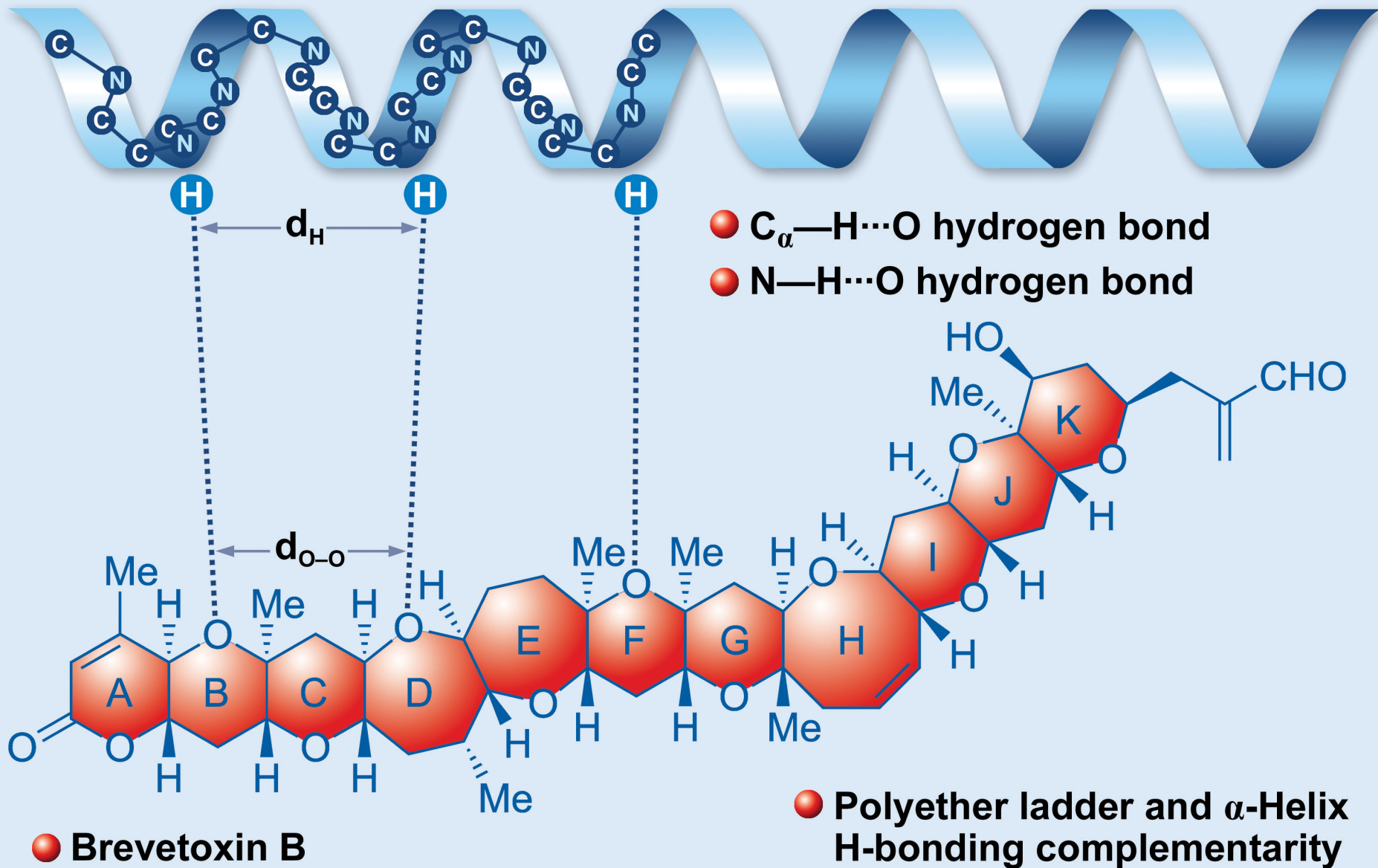
C₁₄₂

● 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 ●

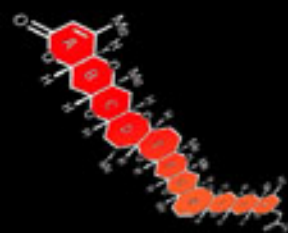
STEREOGENIC CENTERS ●

UNUSUAL, SENSITIVE FUNCTIONALITIES ●

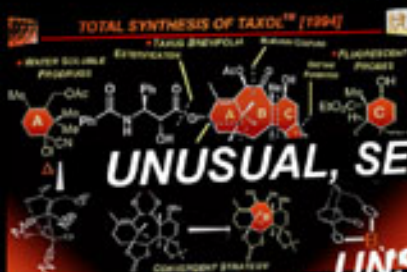
UNSYNTHESIZED MOLECULES ●

IMPORTANT BIOLOGICAL ACTIVITY ●

INTERESTING MECHANISM OF ACTION ●



TOTAL SYNTHESIS OF ELEUTHEROBIN AND SARCOICIC ACID [1987]



DISCOVERIES AND INVENTIONS

● BIOMIMETIC SYNTHETIC STRATEGIES ●

● CASCADE REACTIONS ●

● SOLID PHASE SYNTHESIS ●

● COMBINATORIAL CHEMISTRY ●

● ASYMMETRIC SYNTHESIS ●

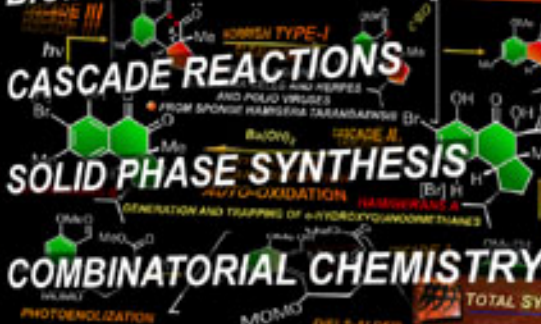
● REAGENTS AND CATALYSTS ●

● EFFICIENT CHEMICAL PROCESSES ●

● GREEN CHEMISTRY ●

● DESIGNED BIOACTIVE MOLECULES ●

TOTAL SYNTHESIS OF HAMIGERANS [2001]





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INSTITUTE

THANKS AND ACKNOWLEDGEMENTS

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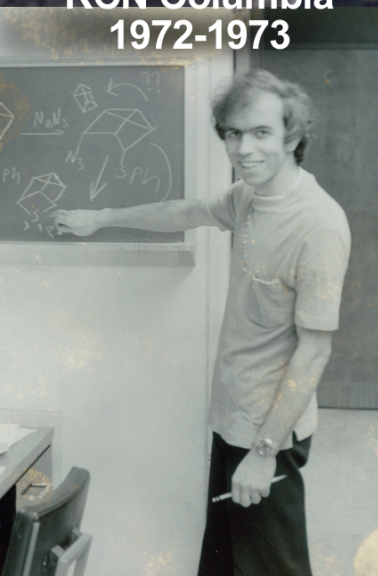
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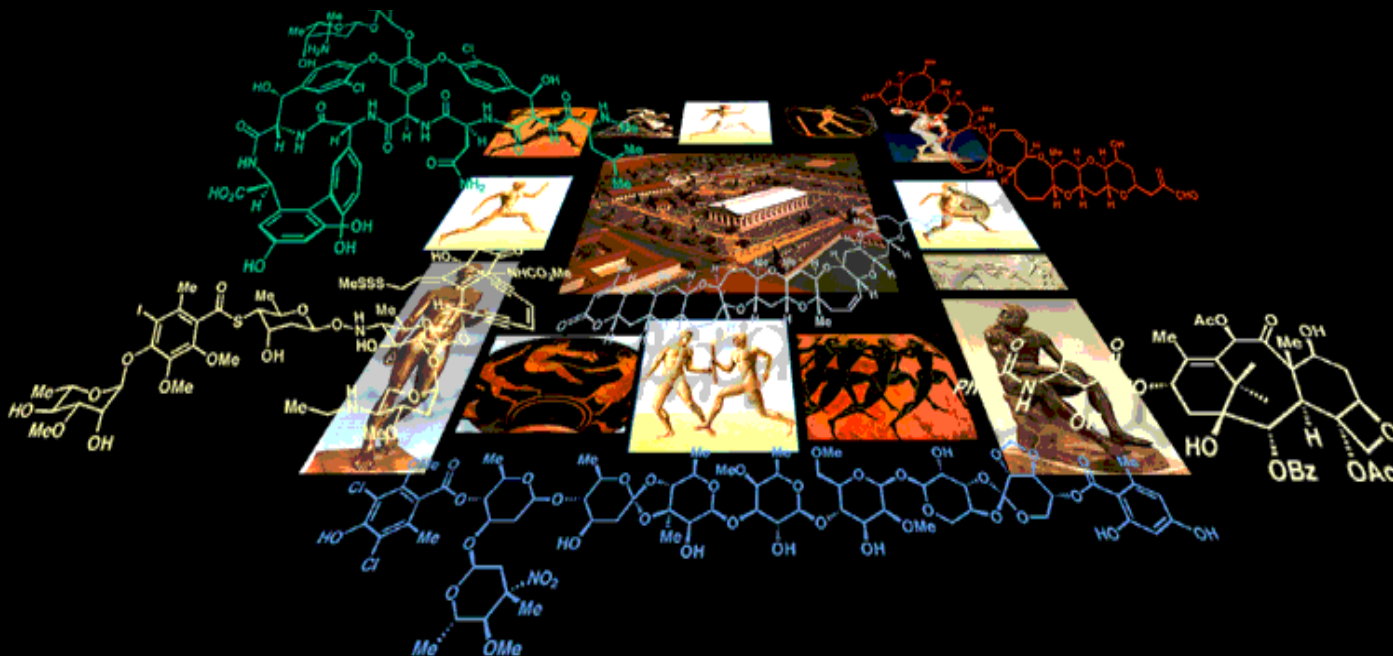
Nicholas J. Turro

Thank You Columbia!

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).

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