Synthesis of the QRSTU Domain of Maitotoxin and Its 85-*epi*-and 86-*epi*-Diastereomers

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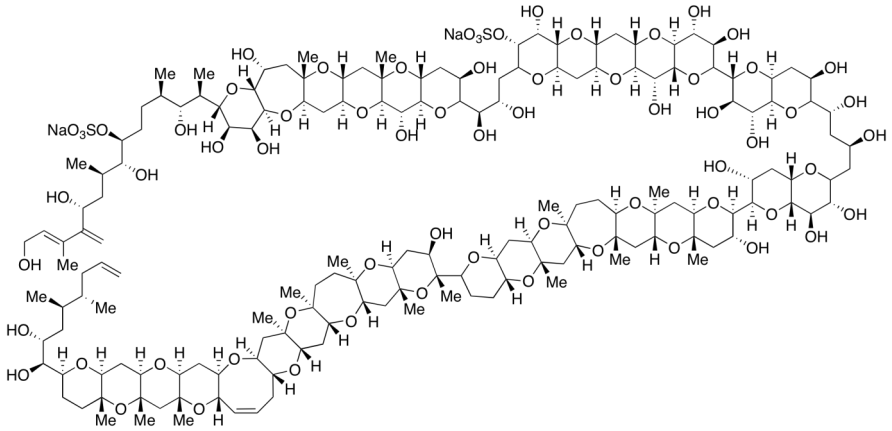
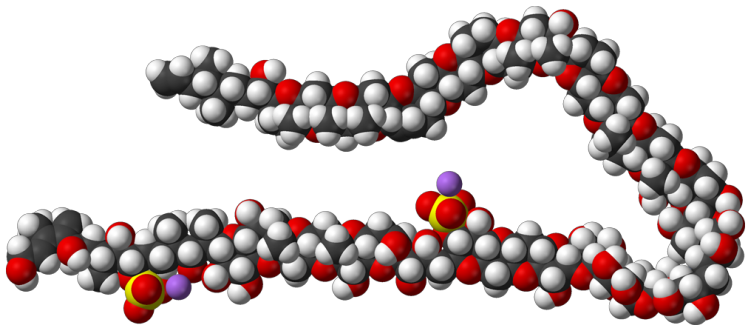
Gary Davis Current Literature 7-10-2010

Isolation

- Isolated in 1988 by Yasumoto and co-workers from broth of the dinoflaggelate *Gambierdiscus toxicus*.
- MW 3422 Da, ($C_{164}H_{256}O_{68}S_2Na_2$), 32 rings 99 elements of stereochemistry.
- 2^{99} = 6.3 x 10^{29} possible stereoisomers.
- Relative configuration for cyclic domains determined in 1993.
- Relative stereochemistry not solved until 1996 by Kishi and Tachibana.

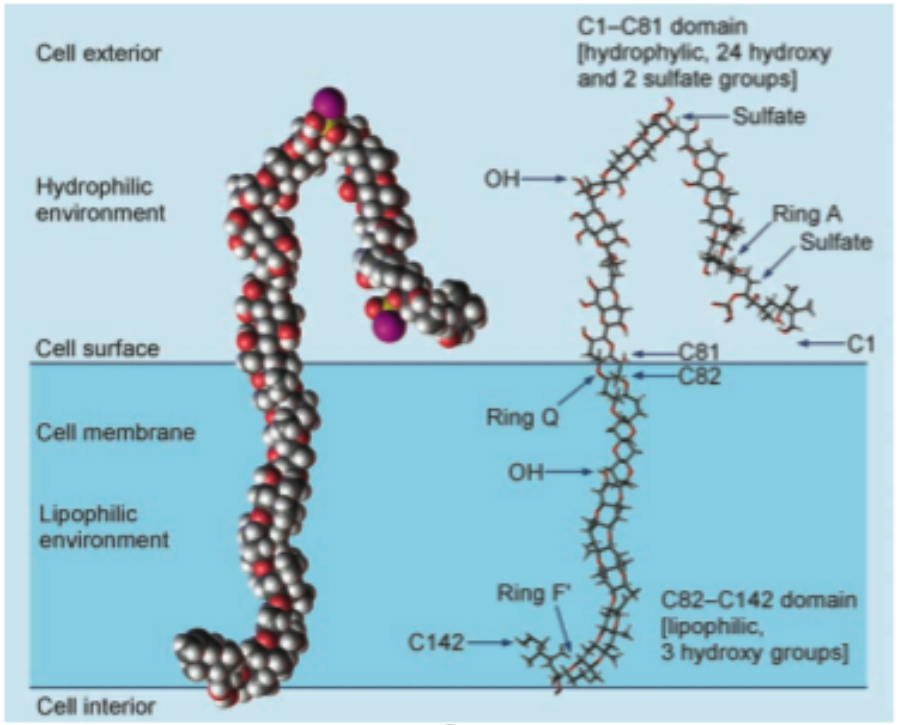




Yokoyama, A.; Murata, M.; Oshima, Y.; Iwashita, T.; Yasumoto, T. *J. Biochem*. **1988**, 104, 184.
Murata, M.; Naoki, H.; Iwashita, T.; Matusunaga, S.; Sasaki, M.; Yokoyama, A.; Yasumoto, T. *JACS* **1993**, 115, 2060.
Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *JACS* **1996**, 118, 7946.
Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tet. Lett.* **1995**, 36, 9007.

Biological Activity

- LD_{50} mice = 0.13 µg/Kg (IP).
- Considered to be the most powerful nonproteinoic biotoxin.
- Neurotoxicity through binding to cell membrane ion channels.
- Specifically, believed to interact with Ca^{2+} channels.
- Influx of Ca^{2+} leading to apoptosis.



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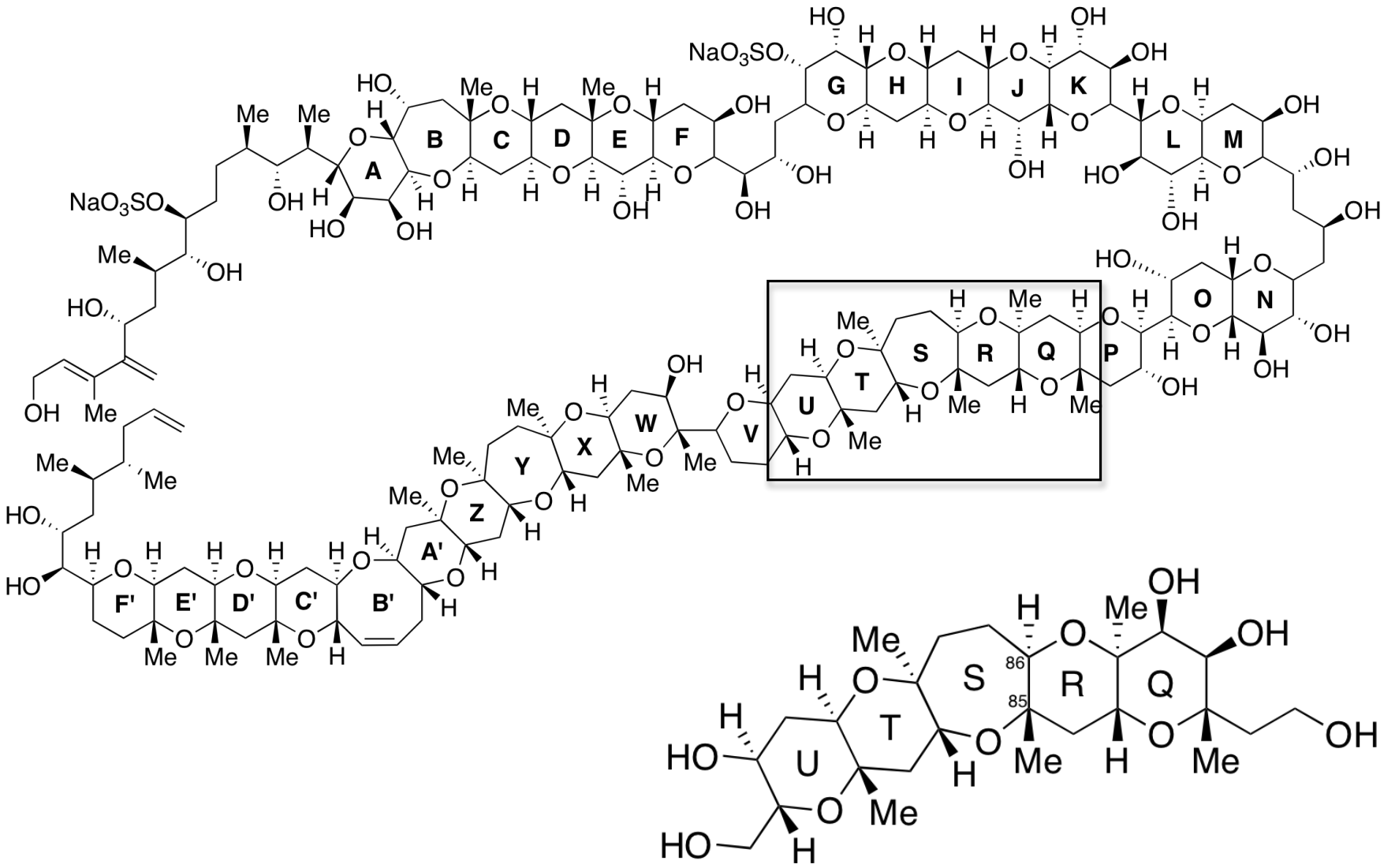
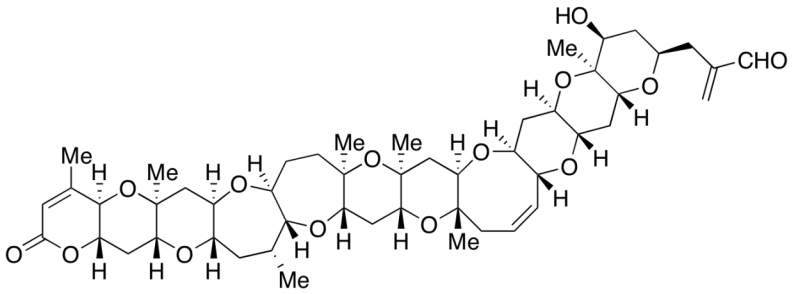
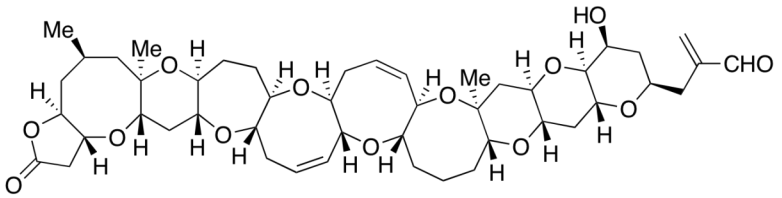
Nomenclature



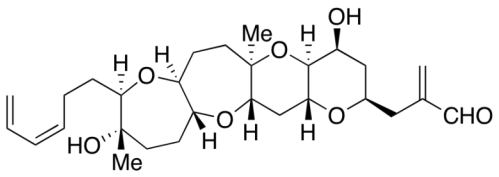
Related Natural Products



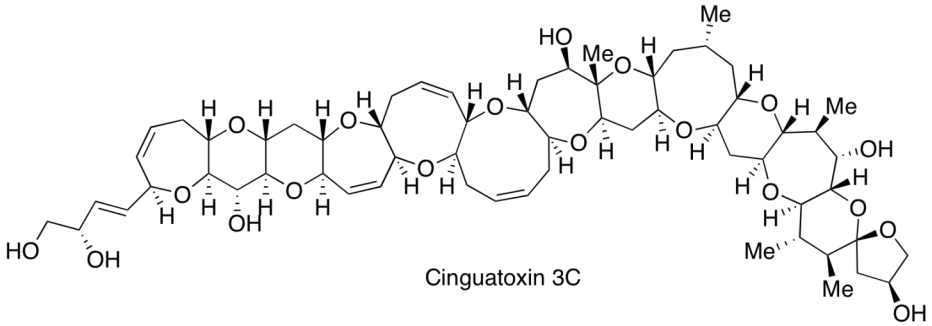
Brevetoxin B



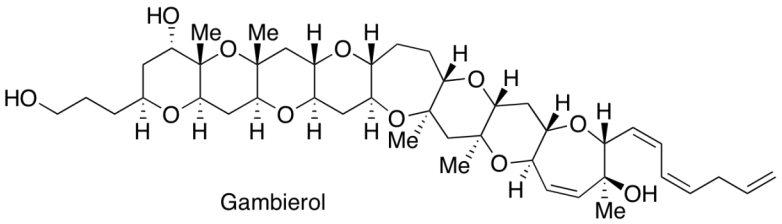
Brevetoxin A



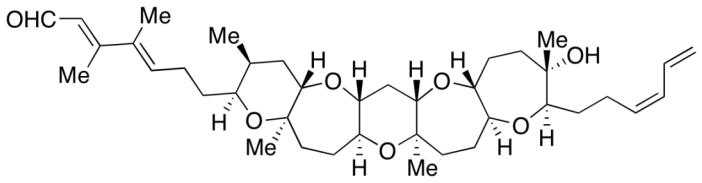
Hemibrevetoxin



Cinguatoxin 3C

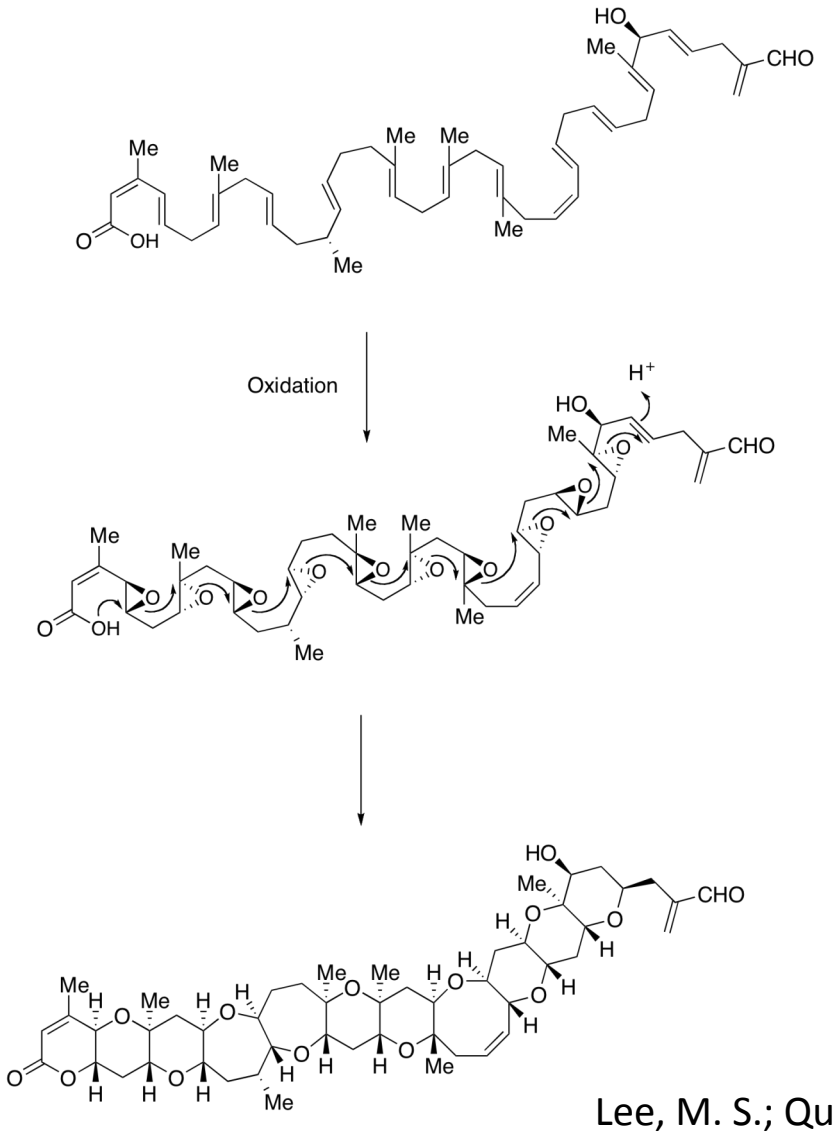


Gambierol



Brevenal

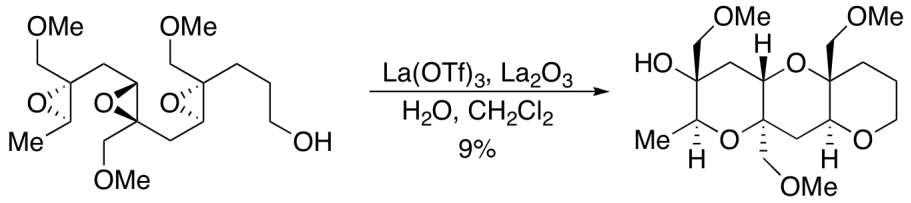
Proposed Biosynthetic Pathway



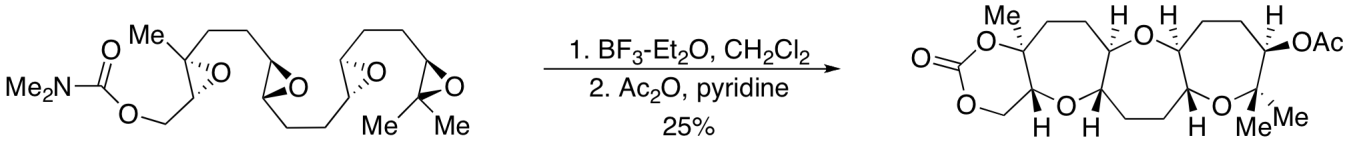
- Oxidation of poly-ene, followed by cascade epoxide opening originally proposed by Nakanishi.
- Several groups have worked to prove this hypothesis.
- Tendency to form the smaller ring (*exo* regioselectivity).
- Jamison group currently working on the hypothesis with some success.
- None of the polyether toxins have been synthesized in this manner.

Lee, M. S.; Quin, G-W.; Nakanishi, K.; Zagorski, M. *JACS* **1989**, 111, 6234.

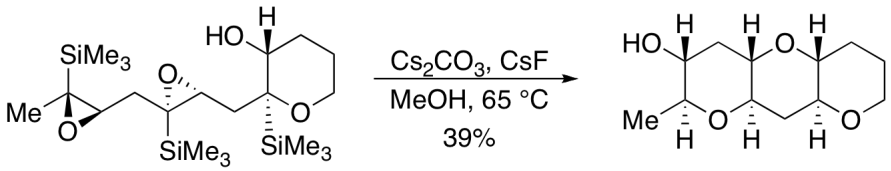
Implementation of Biosynthetic Pathway



Murai, A. et al. *Synlett*. **2000**, 335.



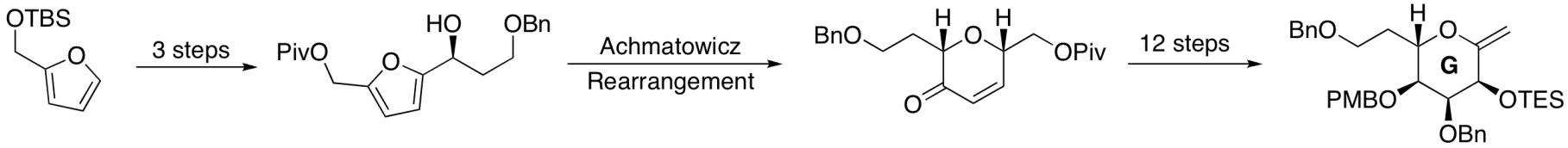
McDonald, F. E. et al. *JACS* **2005**, 127, 4586.



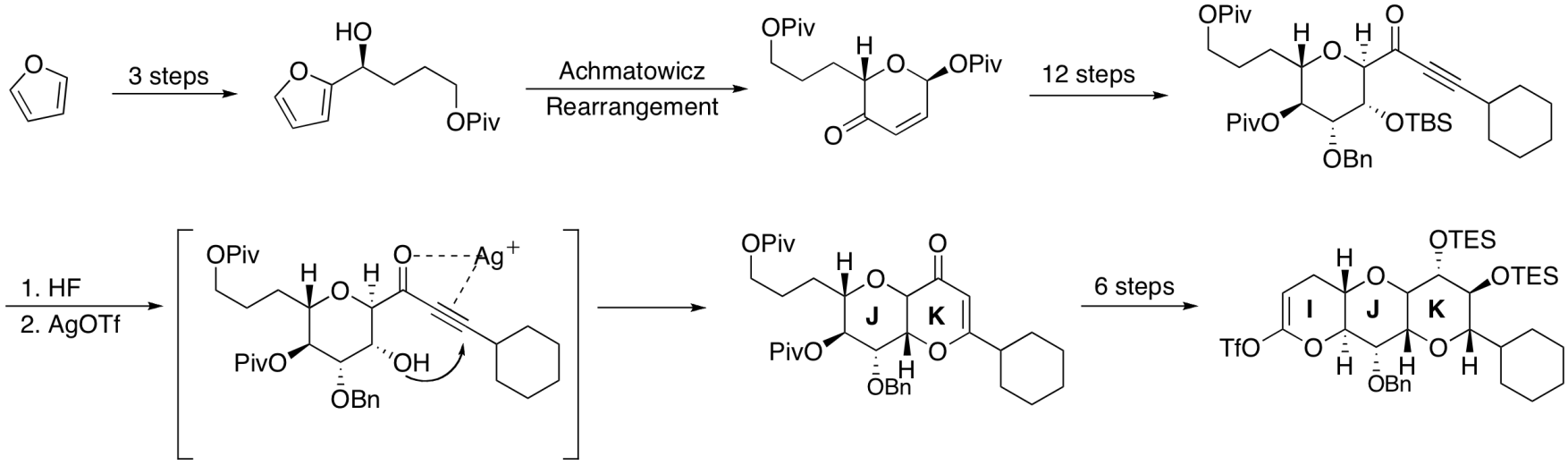
Jamison, T. F. et al. *JOC* **2010**, 2681.

Previously Synthesized Fragments

G Ring Synthesis

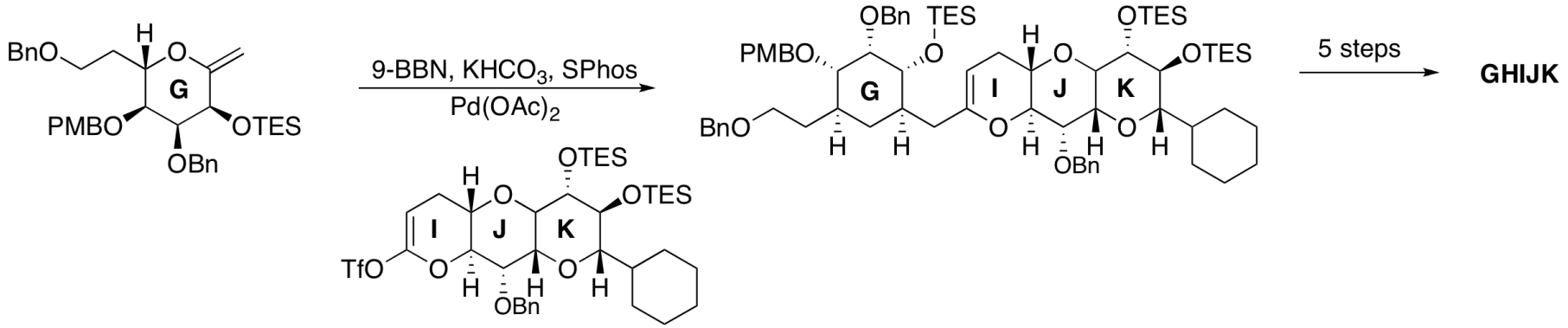


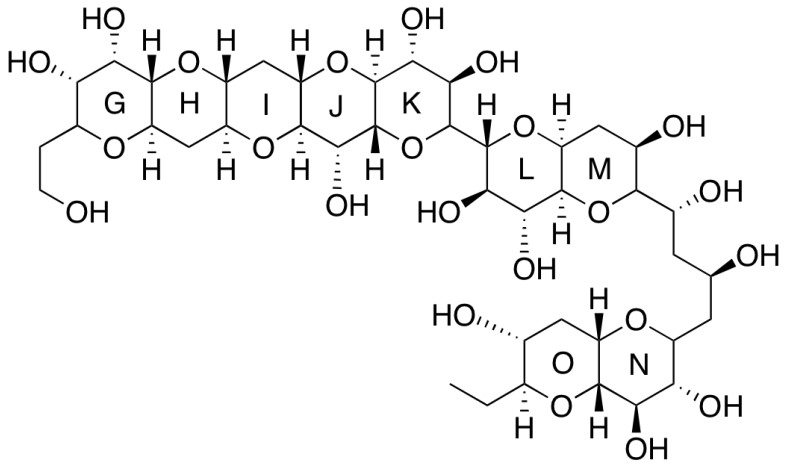
IJK Ring Synthesis

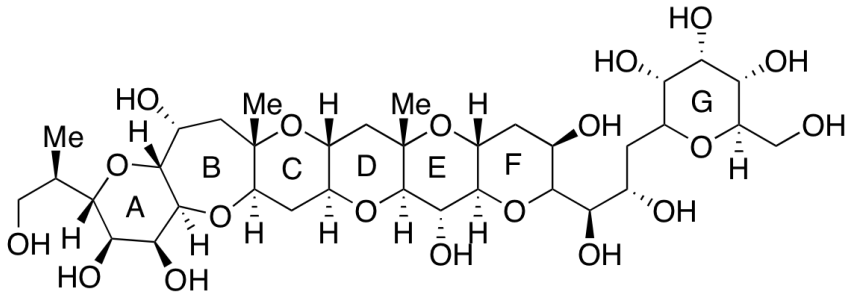


Nicolaou, K. C.; Cole, K., Frederick, M. O.; Aversa, R. J.; Denton, R. M. *ACIE* **2007**, 46, 8875.

Previously Synthesized Fragments



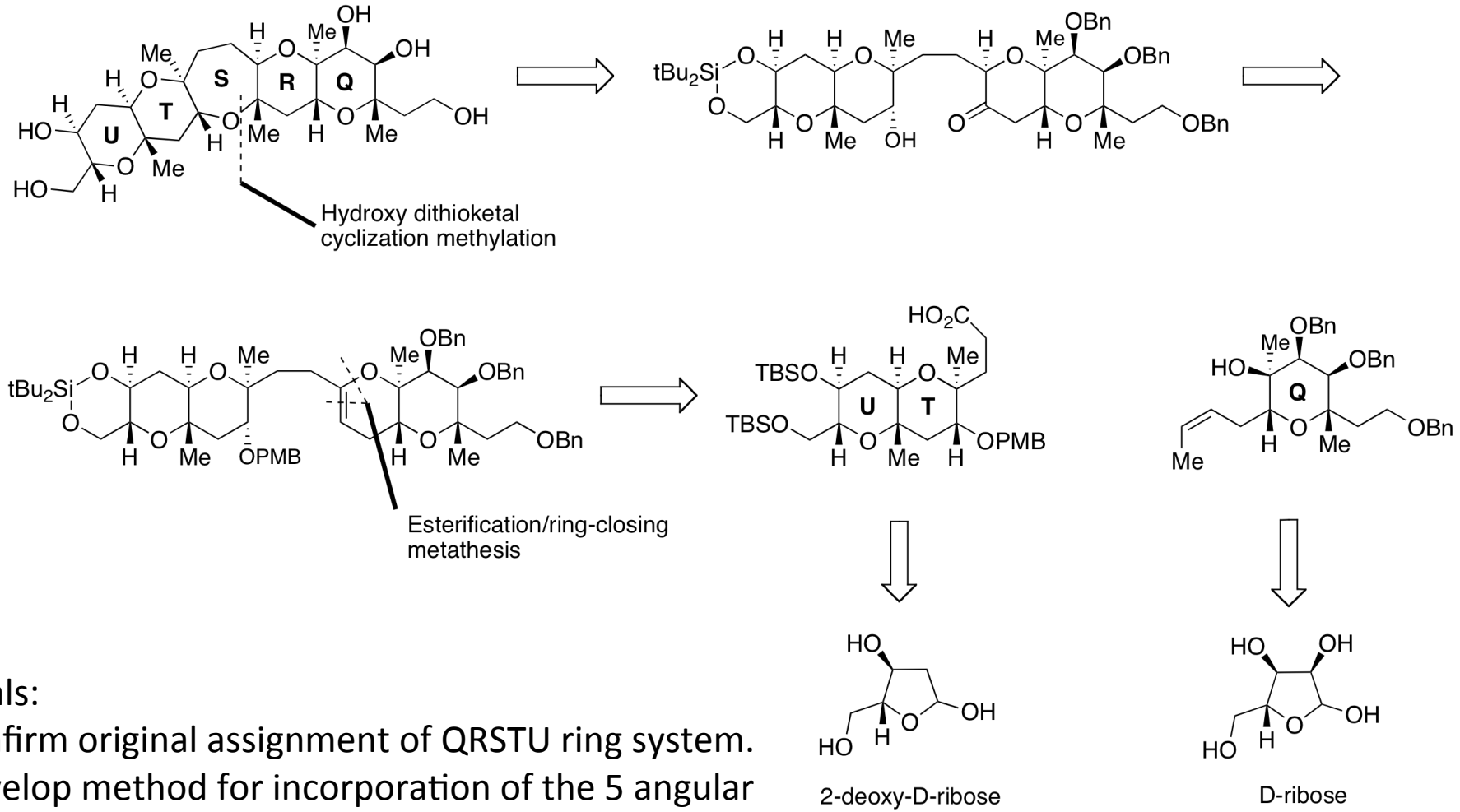




Nicolaou, K. C.; Frederick, M. O.; Burtoloso, A. C. B.; Denton, R. M.; Rivas, F.; Cole, K. P.; Aversa, R. J. Gibe, R.; Umezawa, T.; Suzuki, T. *JACS* **2008**, 130, 7466.

Nicolaou, K. C.; Aversa, R. J.; Jin, J.; Rivas, F. *JACS* **2010**, 132, 6855.

Retrosynthesis

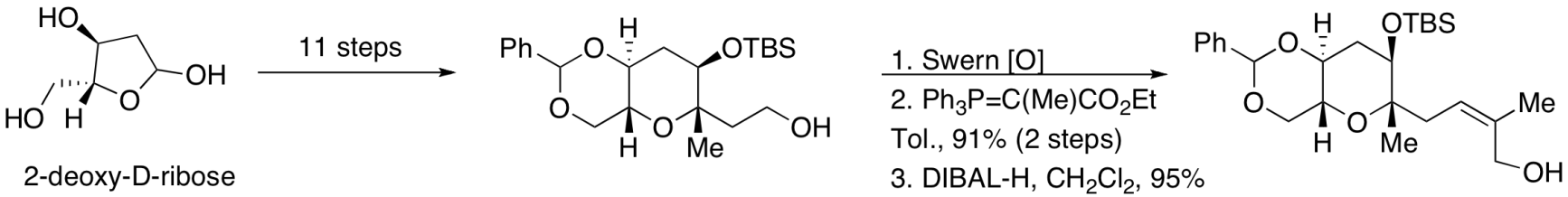


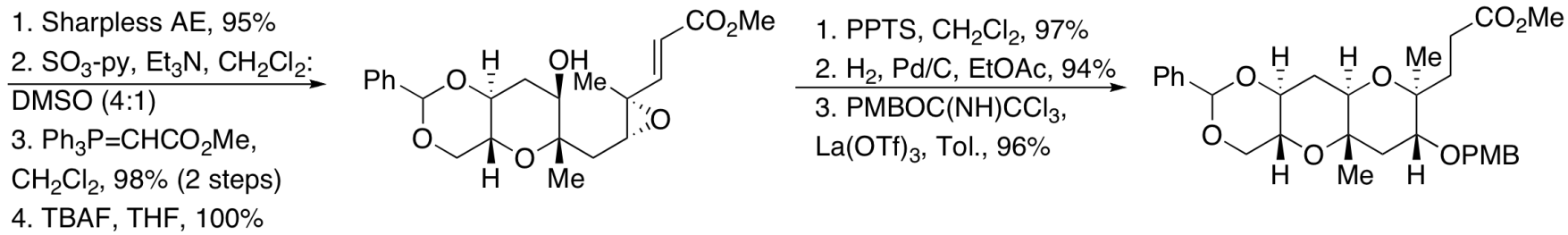
Goals:

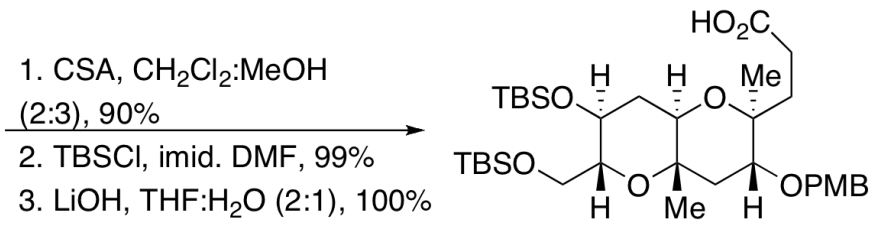
Confirm original assignment of QRSTU ring system.

Develop method for incorporation of the 5 angular Me groups.

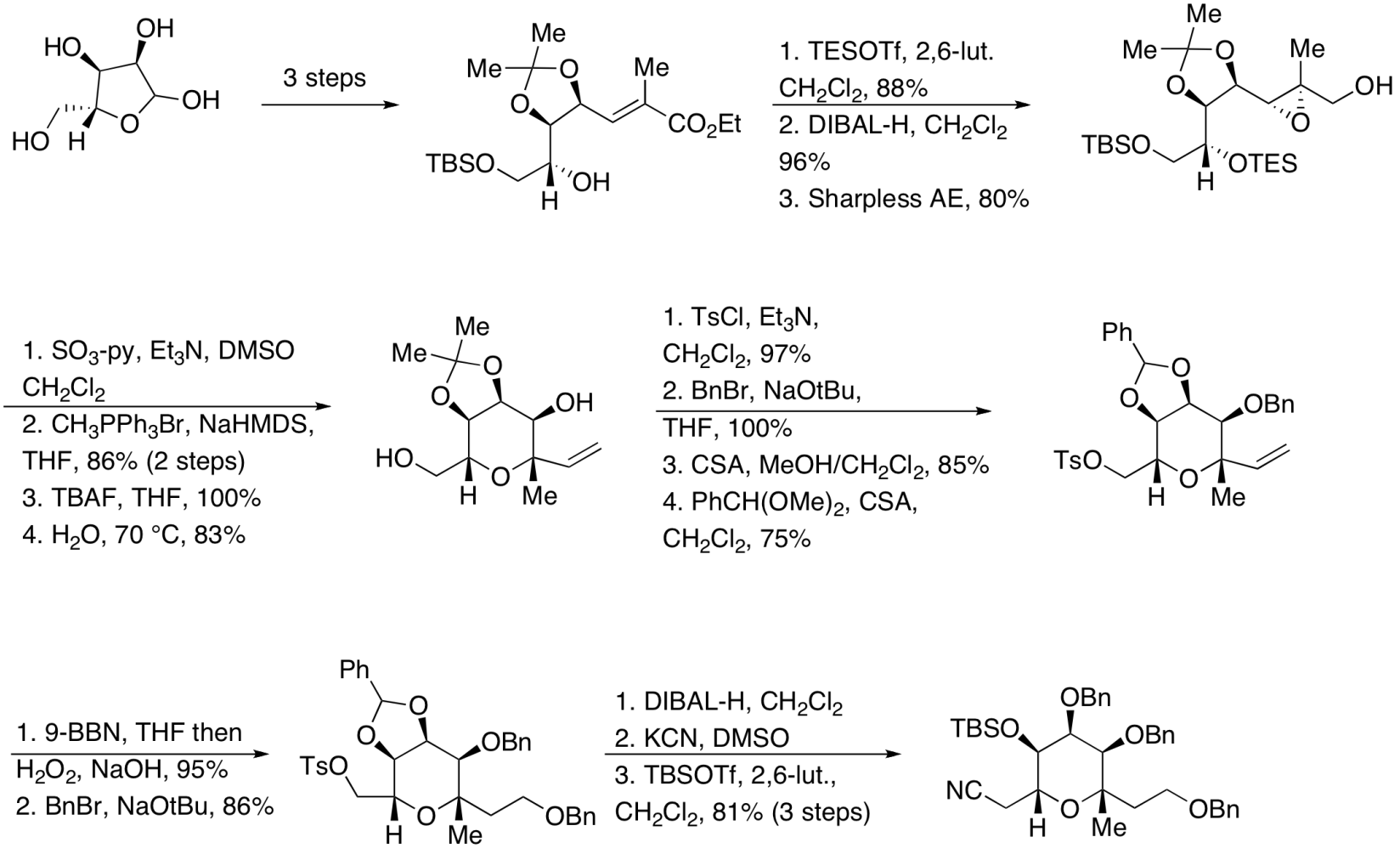
Synthesis of UT Fragment



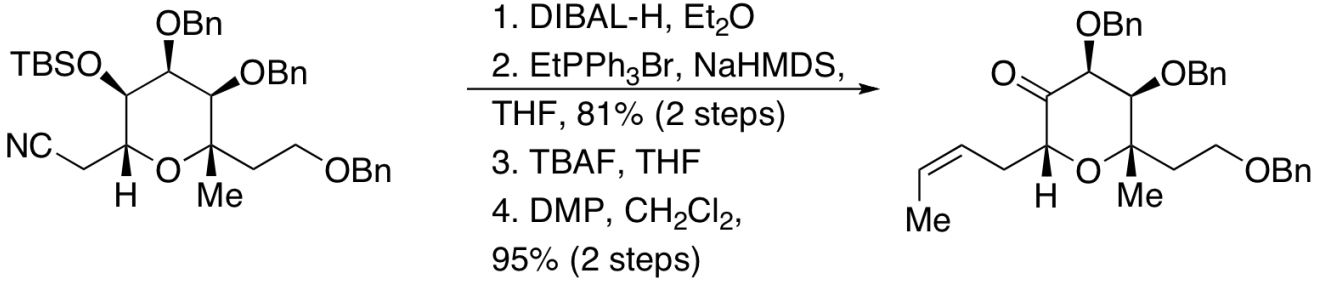


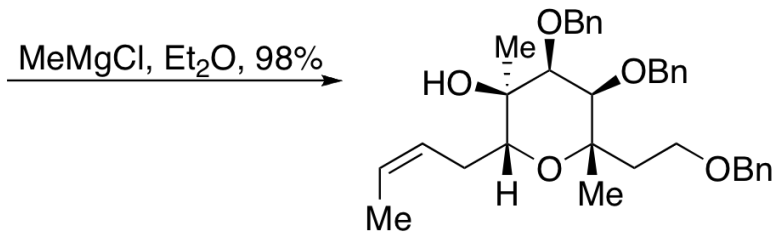


Synthesis of Q Fragment

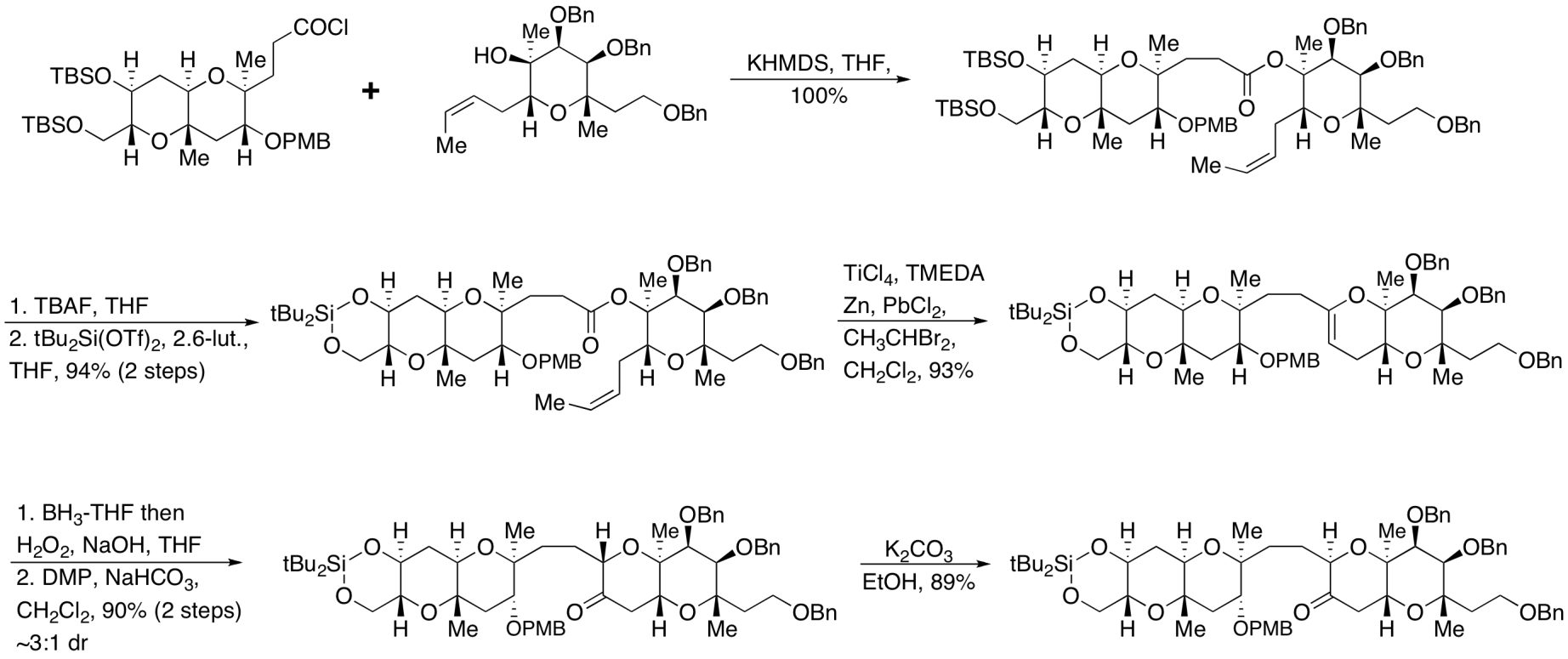


Q Fragment cont.

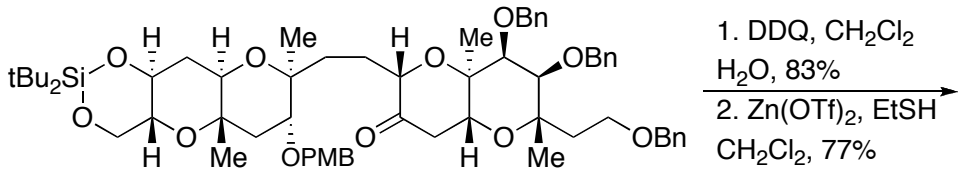


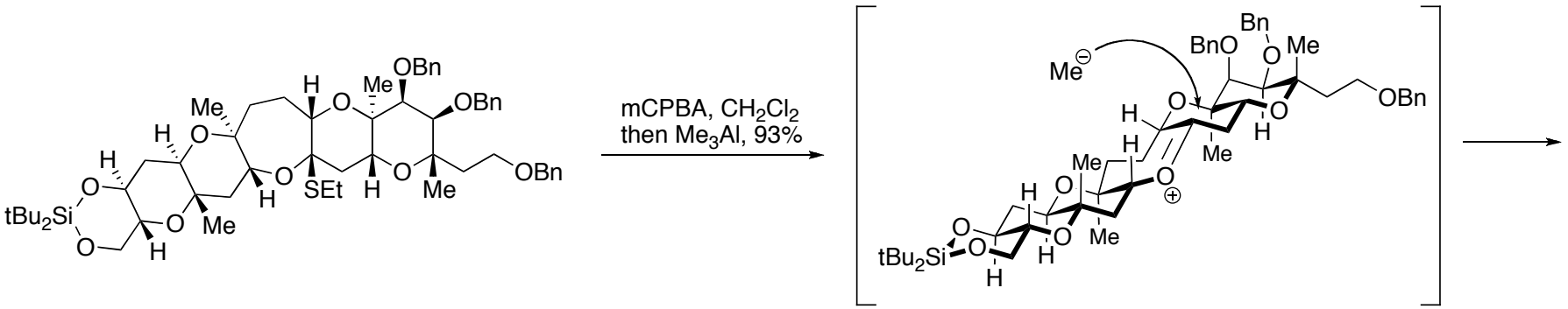


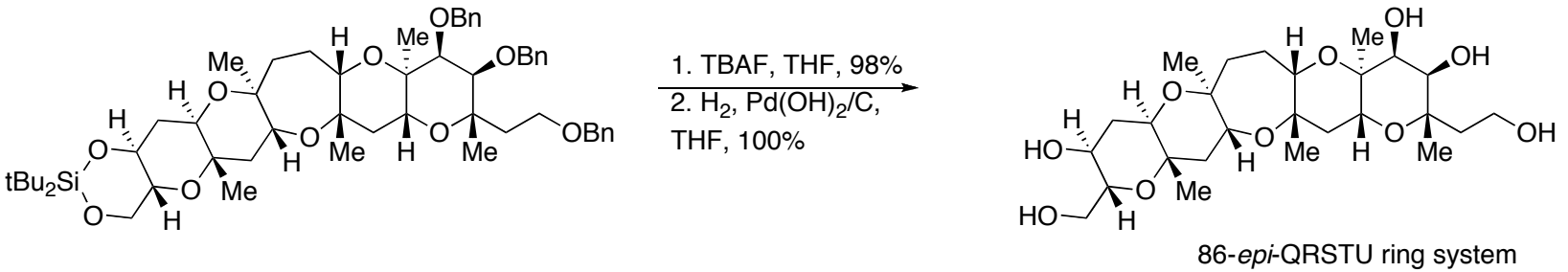
Coupling of Fragments



Synthesis of 86-*epi*-QRSTU System

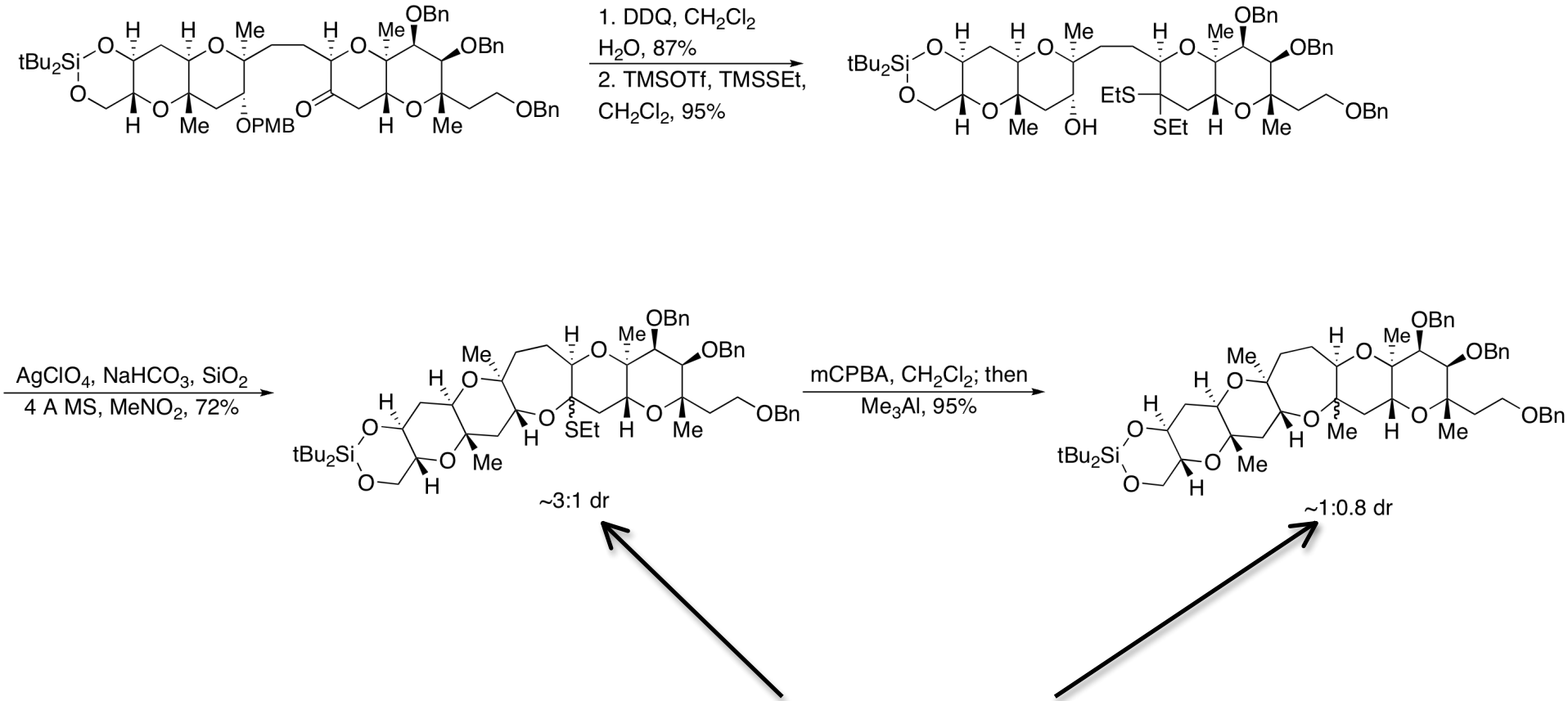


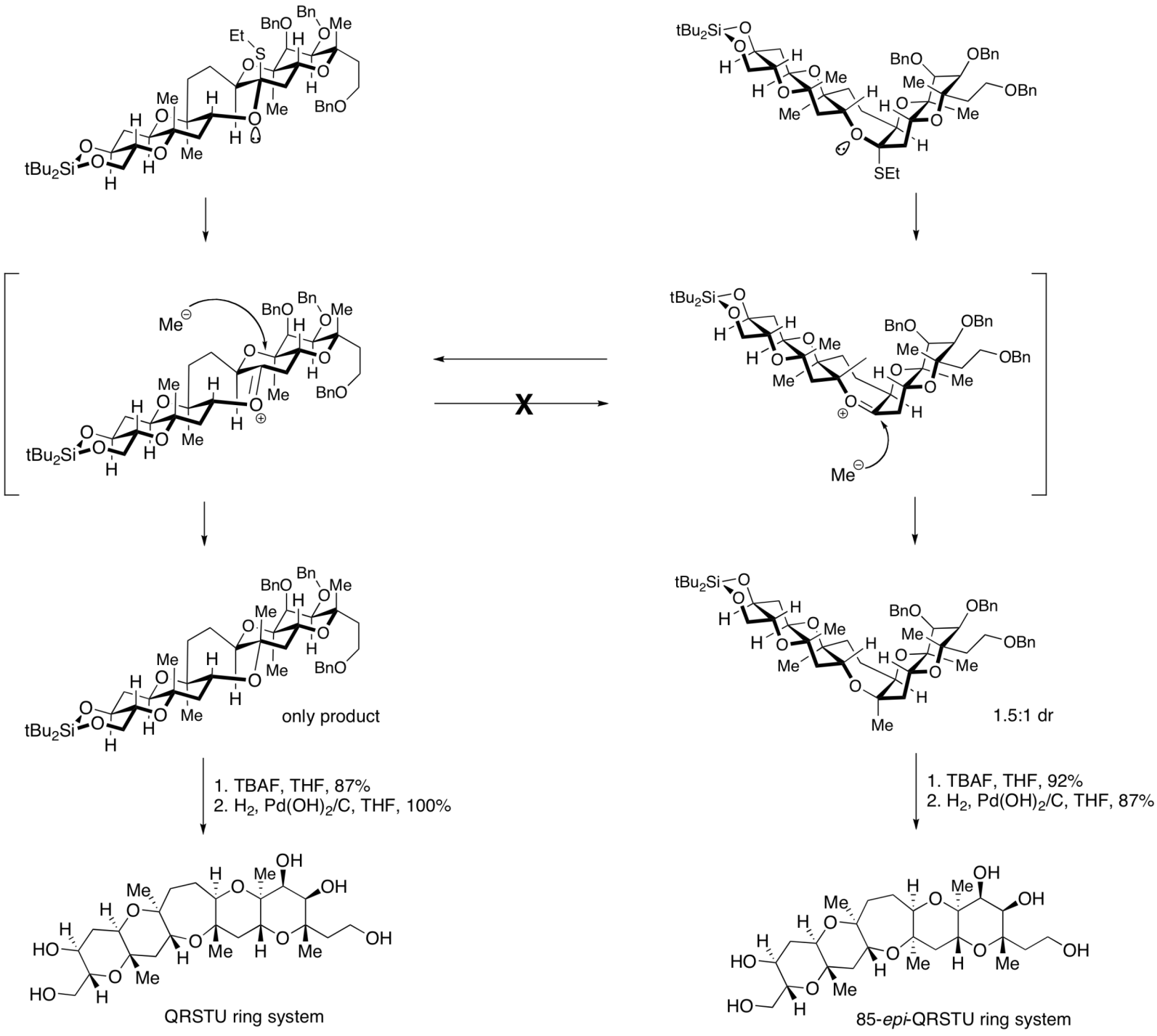




86-*epi*-QRSTU ring system

Synthesis of 85-*epi*- and QRSTU Systems




only product
1. TBAF, THF, 87%
2. H2, Pd(OH)2/C, THF, 100%
QRSTU ring system
1.5:1 dr
1. TBAF, THF, 92%
2. H2, Pd(OH)2/C, THF, 87%
85-epi-QRSTU ring system

Summary and Conclusions

- Convergent synthesis of QRSTU ring system of maitotoxin featuring hydroxy dithioketal cyclization and Takai olefination/ring-closing metathesis cascade.

- Longest linear sequence = 37 steps

- Synthesis incorporates functionality allowing for construction of larger portions of the molecule.