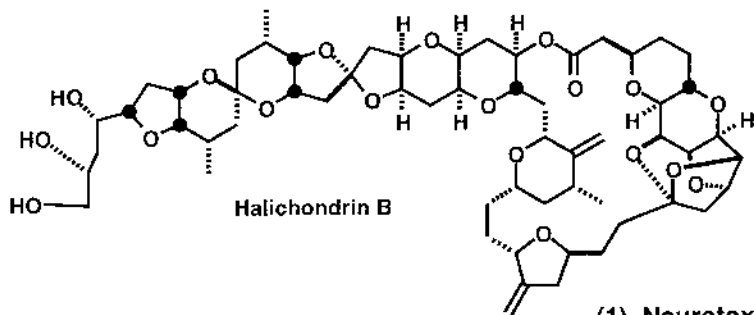
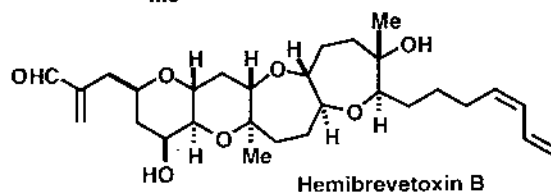
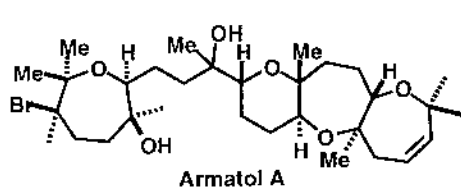
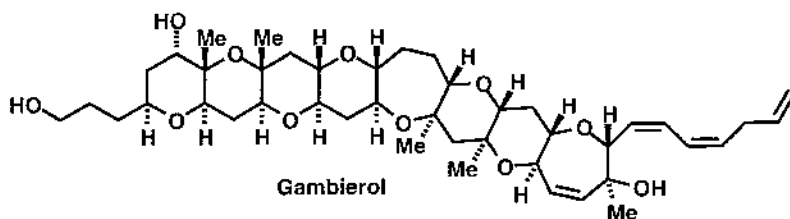


C-GLYCOSIDES IN ORGANIC SYNTHESIS: PROGRESS TOWARDS THE MARINE LADDER TOXIN GAMBIEROL

IASOC
SEPTEMBER 24, 2002

JON D. RAINIER
UNIVERSITY OF UTAH



FUSED POLYCYCLIC ETHER
TARGETS

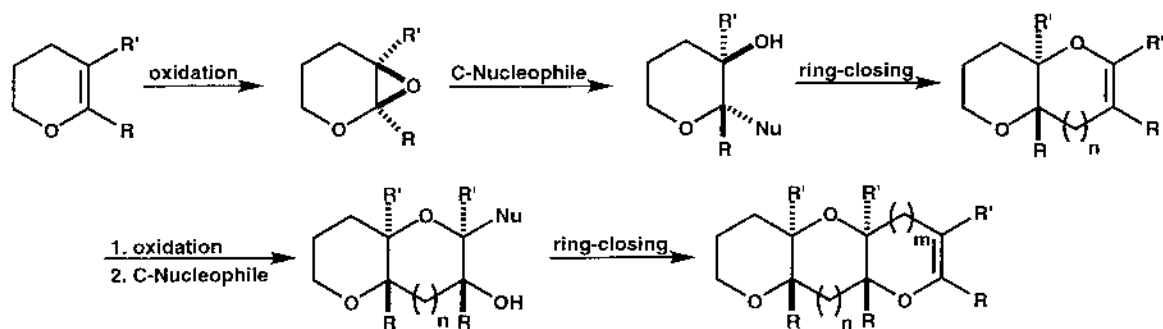
BIOACTIVITY

(1) Neurotoxicity (hemibrevetoxin B, gambierol)

(2) Cytotoxicity (armatol A)

(3) Anticancer activity (halichondrin B)

C-GLYCOSIDES TO FUSED POLYCYCLIC ETHERS



FEATURES

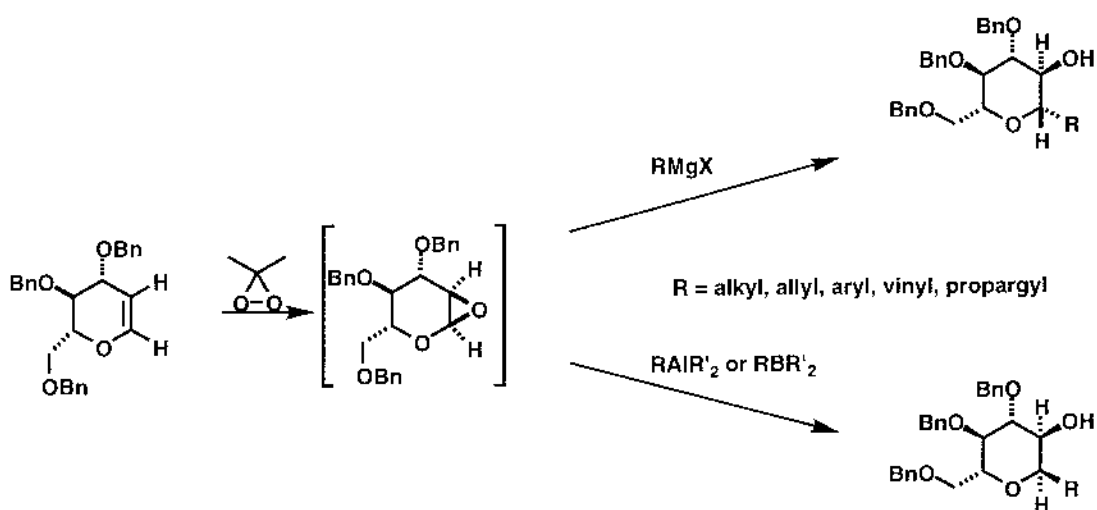
C-Glycosides Lead to:

- O- and Some of the C-Atoms for the Subsequent Ring
- The Ring Junction Stereochemistry

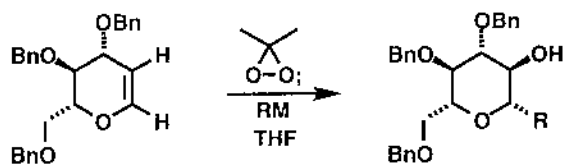
CHALLENGES

- Stereoselective Epoxidation
- Stereoselective C-C Bond Formation
- Flexibility

OXIDATION C-C BOND FORMATION TO α -CARBON GLYCOSIDES



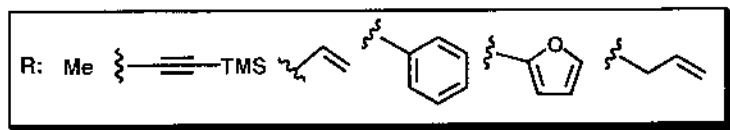
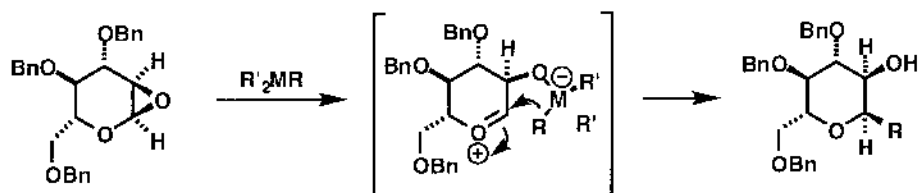
THE GENERATION OF β -C-GLUCOSIDES



| ENTRY | REAGENT | YIELD |
|-------|-------------------------------|-------|
| 1 | Me_2CuLi | 82% |
| 2 | BrMg | 57% |
| 3 | BrMg | 78% |
| 4 | Ph_2CuLi | 84% |
| 5 | ZnCl_2 , Li | 78% |
| 6 | ClMg | 80% |
| 7 | BrMgCu | 65% |
| 8 | BrMgCu | 63% |

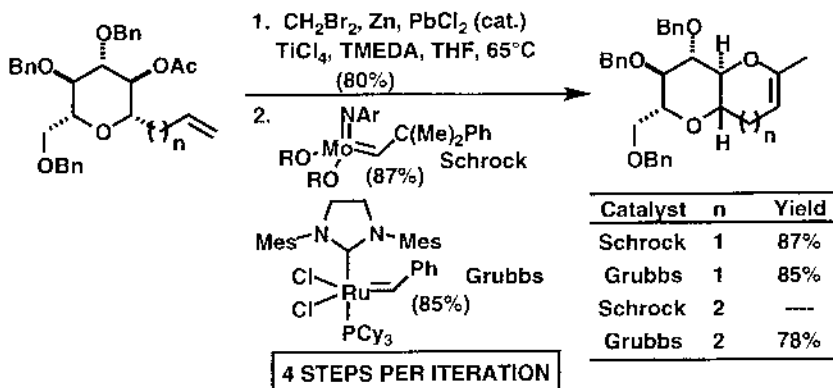
Jason M. Cox
&
Shawn P. Allwein

THE GENERATION OF α -C-GLUCOSIDES



| Entry | $\text{R}'_2\text{MR}$ | Yield |
|-------|--|-------|
| 1 | AlMe_3 | 82% |
| 2 | $\text{Me}_2\text{Al}(\text{alkynyl})$ | 80% |
| 3 | $\text{Al}(\text{vinyl})_3$ | 76% |
| 4 | $\text{Al}(\text{phenyl})_3$ | 79% |
| 5 | $\text{Al}(\text{2-furyl})_3$ | 85% |
| 6 | $\text{B}(\text{allyl})_3$ | 70% |

Jason M. Cox



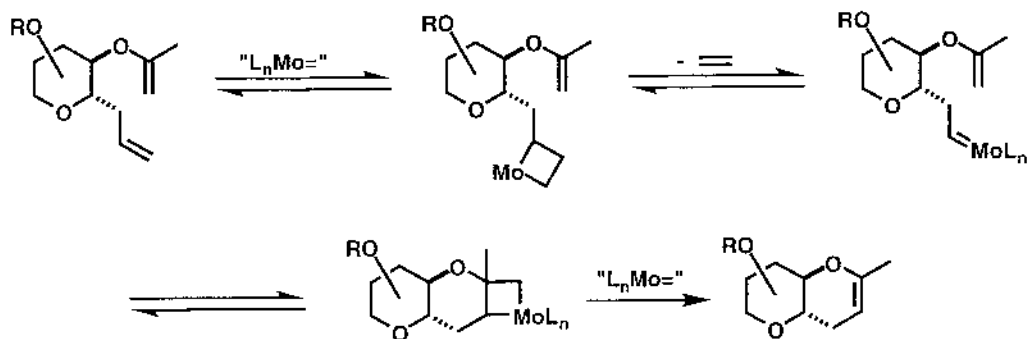
Rainier, J. D.; Allwein S. P. *J. Org. Chem.* (1998), 63, 5310.

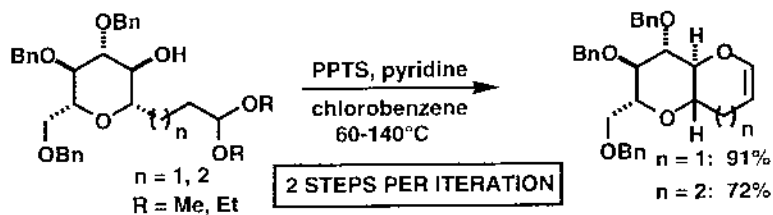
Rainier, J. D.; Allwein S. P. *Tetrahedron Lett.* (1998), 39, 9610.

Rainier, J. D.; Cox, J. M. Allwein, S. P. *Tetrahedron Lett.* (2001), 42, 179.

Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* (2002), 58, 1997.

METATHESIS CYCLIZATIONS TO FUSED ENOL ETHERS





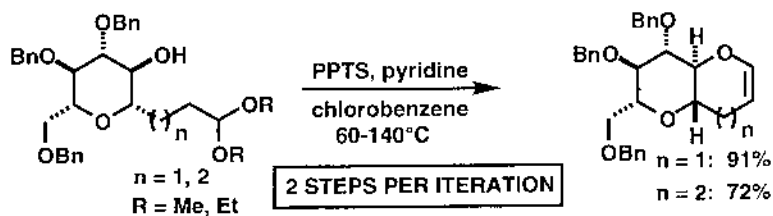
Rainier, J. D.; Allwein S. P. *J. Org. Chem.* (1998), 63, 5310.

Rainier, J. D.; Allwein S. P. *Tetrahedron Lett.* (1998), 39, 9610.

Rainier, J. D.; Cox, J. M. Allwein, S. P. *Tetrahedron Lett.* (2001), 42, 179.

Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* (2002), 58, 1997.

ACID MEDIATED CYCLIZATIONS TO FUSED ENOL ETHERS



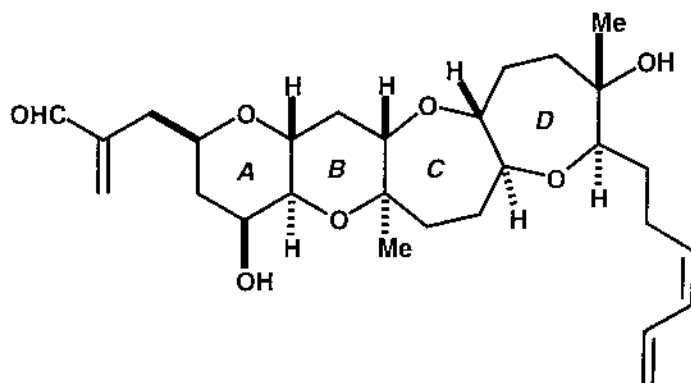
Rainier, J. D.; Allwein S. P. *J. Org. Chem.* (1998), 63, 5310.

Rainier, J. D.; Allwein S. P. *Tetrahedron Lett.* (1998), 39, 9610.

Rainier, J. D.; Cox, J. M. Allwein, S. P. *Tetrahedron Lett.* (2001), 42, 179.

Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* (2002), 58, 1997.

**HEMIBREVETOXIN B
PROOF OF CONCEPT**

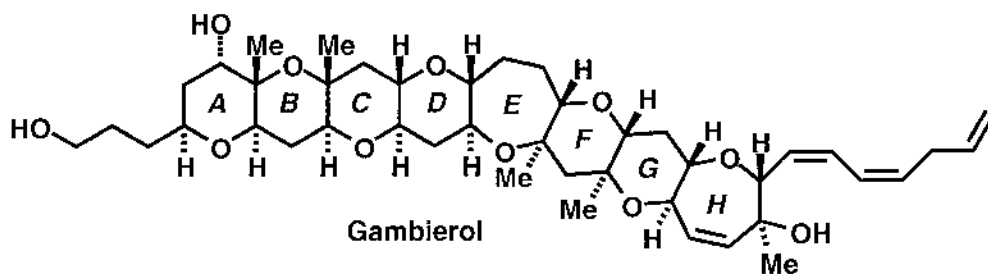


Rainier Group Formal Total Synthesis: 14 Steps to the Tetracyclic Core, 7.5% Overall Yield

Rainier, J. D.; Allwein, S. P.; Cox, J. M. *Org. Lett.* (2000), 2, 231.

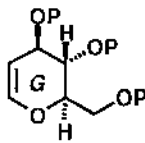
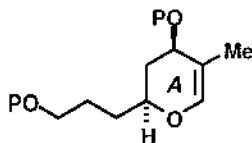
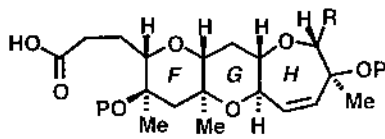
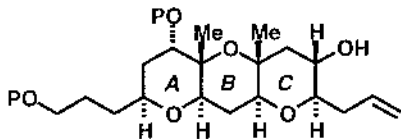
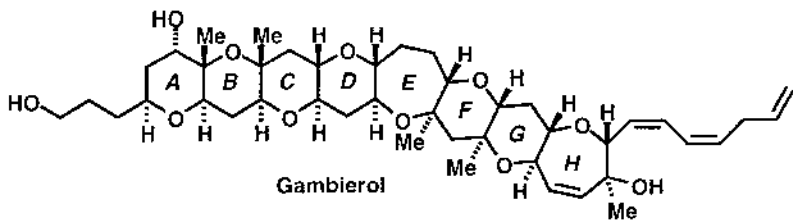
Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* (2001), 66, 1380.

GAMBIEROL

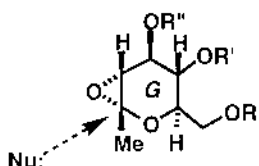
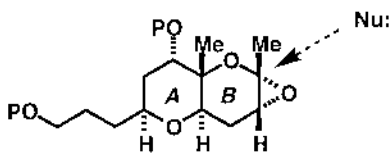
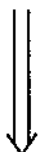
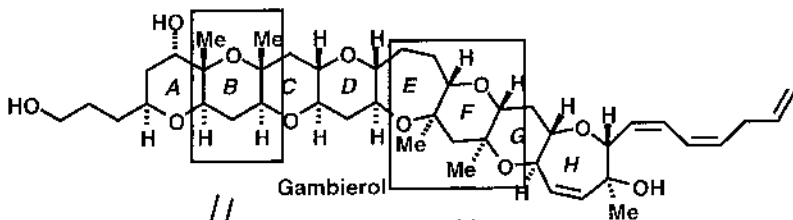


Isolated in 1993 by Yasumoto from the marine dinoflagellate *Gambierdiscus Toxicus* at Rangiroa Atoll, Tuamotu Archipelago, French Polynesia

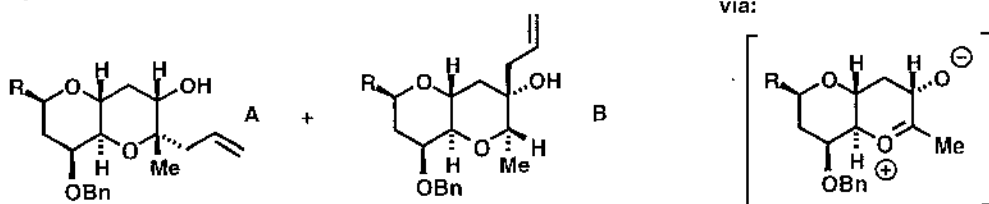
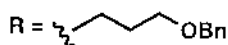
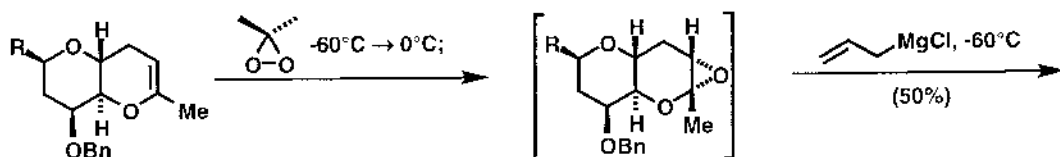
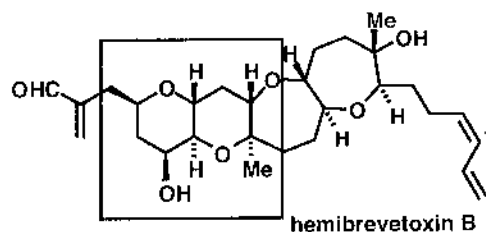
Neurotoxin associated with ciguatera poisoning.



ALL THE SYNTHESIS OF THE GAMBIEROL B- AND F- RINGS GIVE US PROBLE

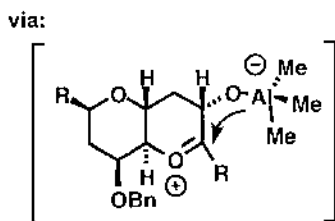
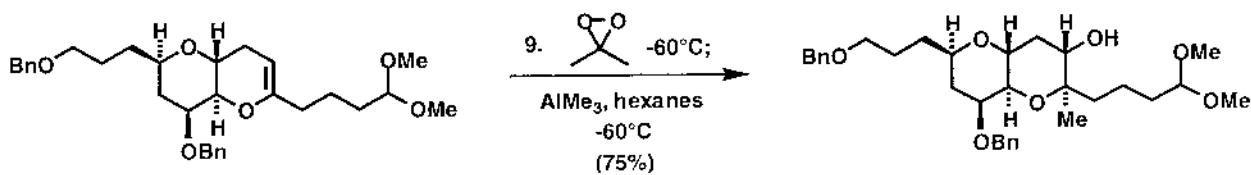
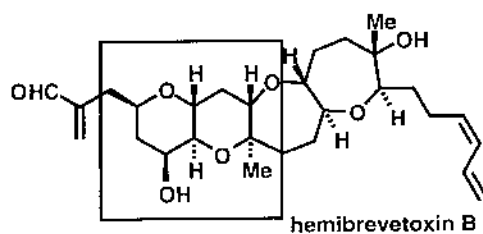


HEMIBREVETOXIN B-1ST GENERATION APPROACH

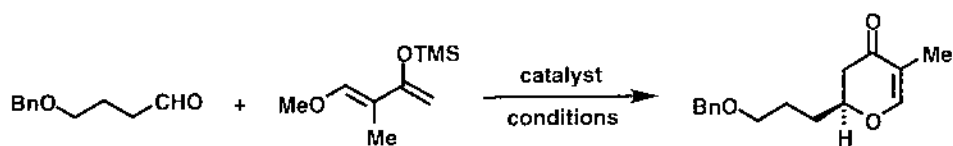


A:B = 10:3

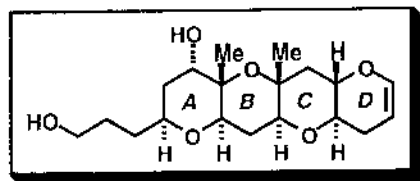
HEMIBREVETOXIN B-2nd GENERATION APPROACH



HETERO-DIELS ALDER CYCLOADDITIONS TO THE GAMBIEROL A-RING

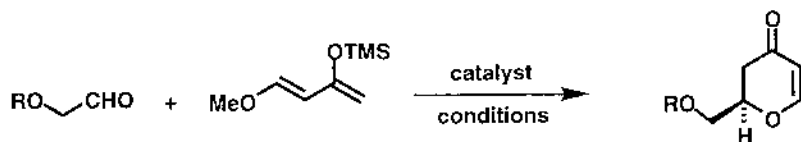


| Catalyst | Conditions | Yield | ee% |
|----------|---|-------|-----|
| | Ti(<i>i</i> -OPr) ₄ , CF ₃ COOH | 0% | --- |
| | Me ₃ Al; CF ₃ COOH | 69% | 0% |
| | B(OPh) ₃ ; CF ₃ COOH | 10% | 8% |
| | 4Å MS, 70 h; TFA, CH ₂ Cl ₂ , 0°C, 1 h | 90% | 94% |



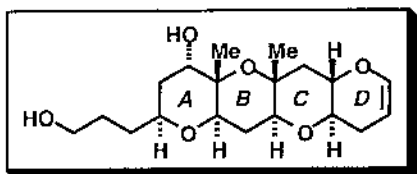
Jason M. Cox

HETERO-DIELS ALDER CYCLOADDITIONS

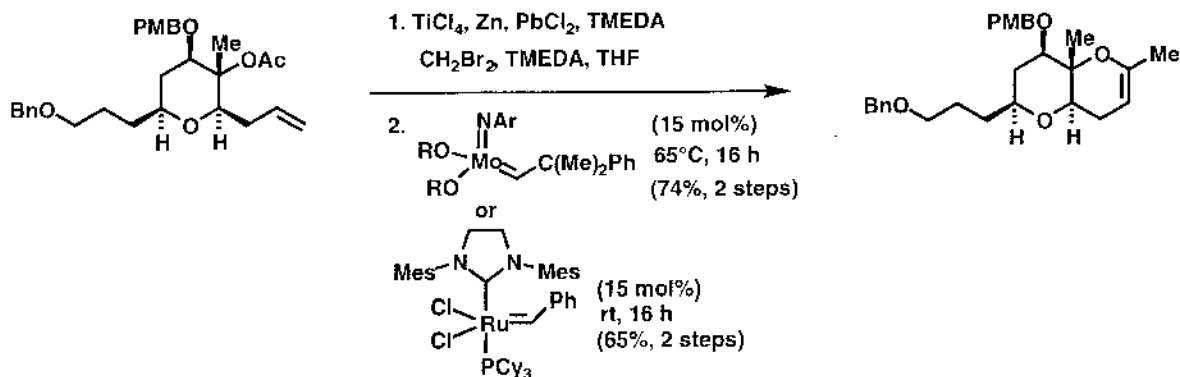
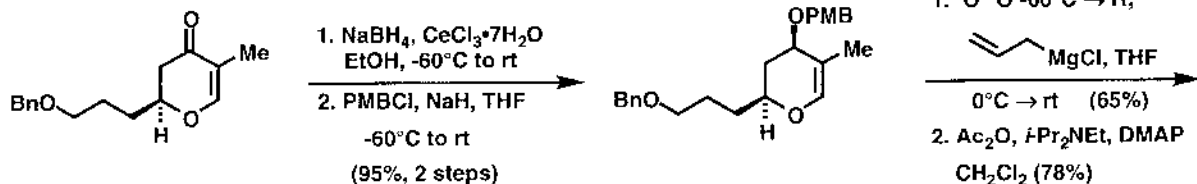


| Catalyst | Conditions | R | Yield | ee% |
|----------|---|-------|-------|-----|
| | Ti(<i>i</i> -OPr) ₄ , CF ₃ COOH | TBS | 4-32% | 0% |
| | Ti(<i>i</i> -OPr) ₄ , CF ₃ COOH | TBDPS | 9% | 5% |
| | 4Å MS; TFA | TBS | 10% | 7% |
| | 4Å MS; TFA | TBDPS | 9% | 5% |

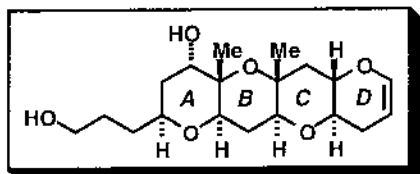
Henry Johnson



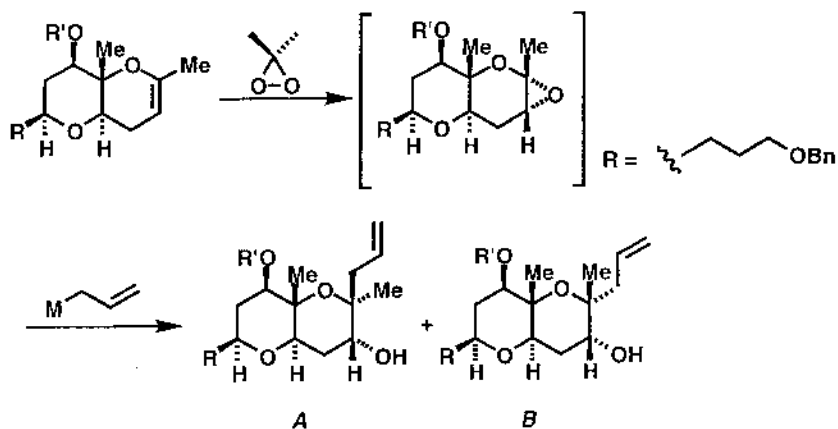
GAMBIEROL A,B-RING SYSTEM



Jason M. Cox

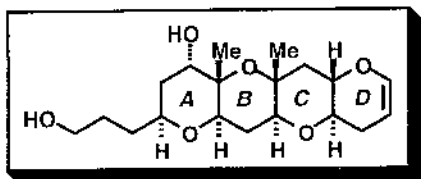
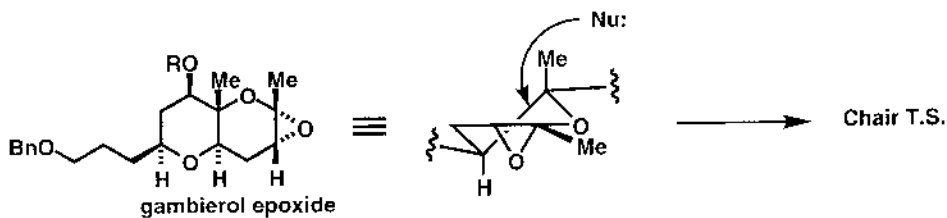
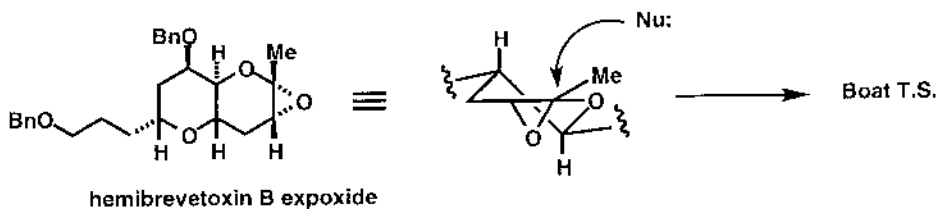


GAMBIEROL A,B-RING SYSTEM

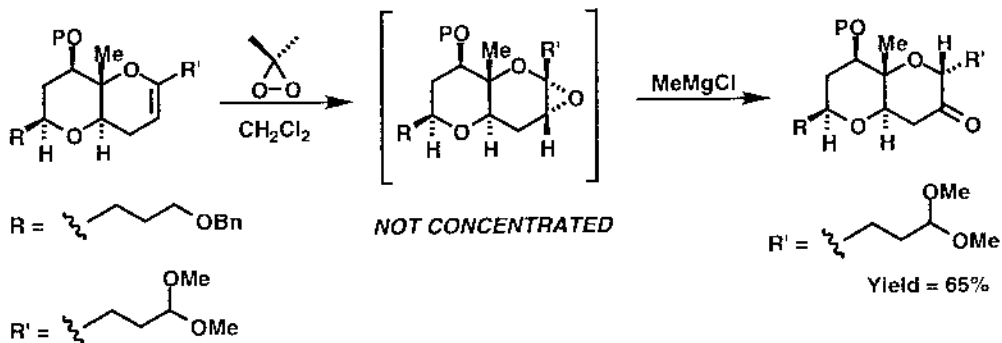


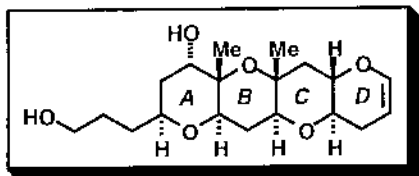
| ENTRY | NU: | A | B | YIELD |
|-------|-----|-----|-----|-------|
| 1 | | 1 | 0 | 45% |
| 2 | | 1.5 | 1 | 40% |
| 3 | | 1 | 1.5 | 40% |

Jason M. Cox

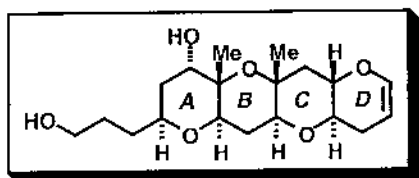
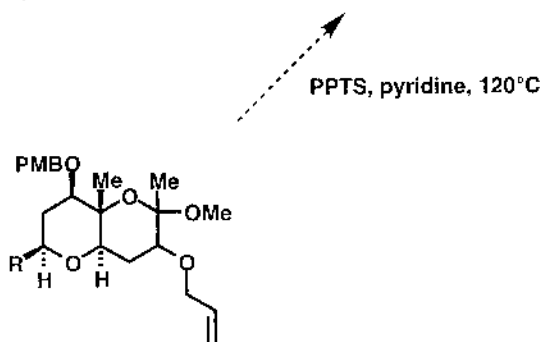
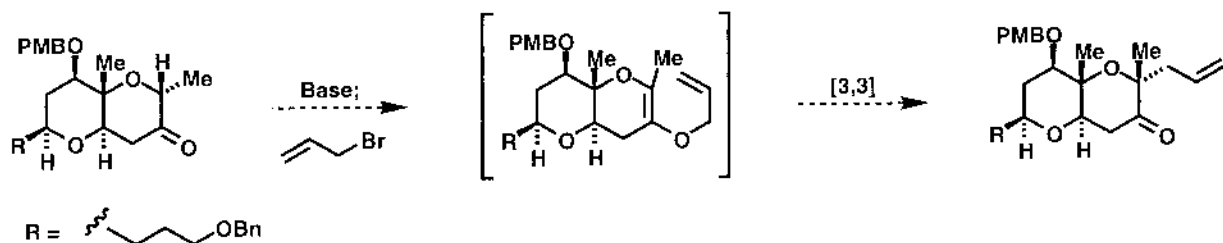


**GAMBIEROL A,B-RING SYSTEM
PINACOL REARRANGEMENT**

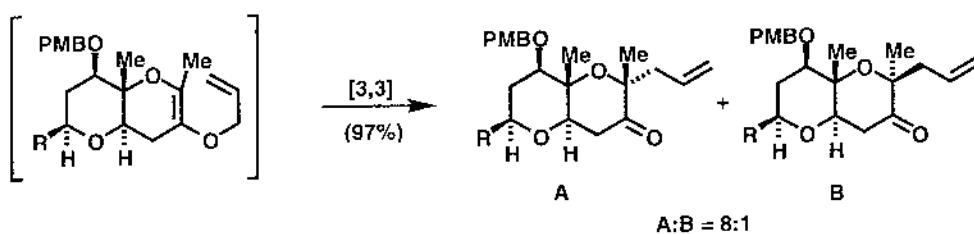
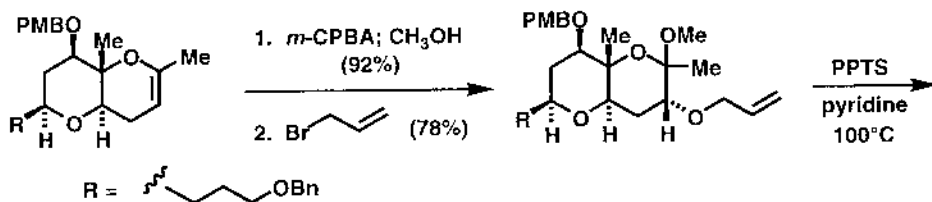


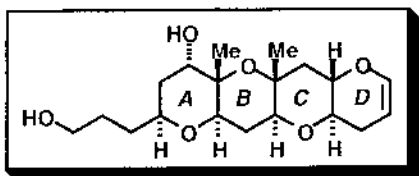


*CAN A CLAISEN REARRANGEMENT SOLVE
THE STEREOCHEMICAL PROBLEM?*

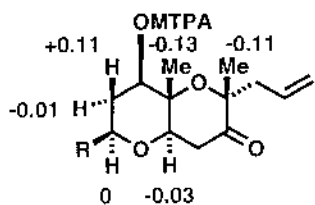


*CLAISEN REARRANGEMENTS
TO C-GLYCOSIDES*



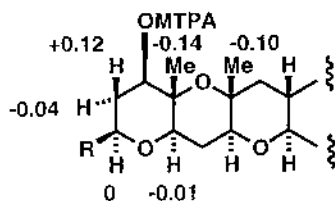


ABSOLUTE STEREOCHEMISTRY ASSIGNMENT



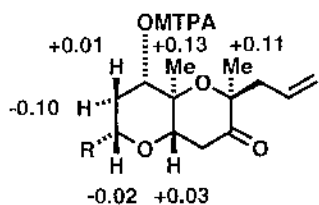
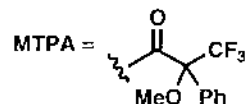
Cox, Rainier compd.

500 MHz, ^1H NMR (CD_2Cl_2)



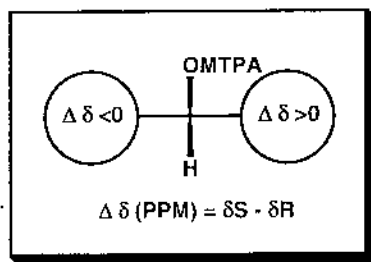
Yasumoto Gambierol C-3 Epimer

600 MHz, ^1H NMR ($\text{CD}_2\text{Cl}_2:\text{CD}_3\text{OD}$)



Cox, Rainier compd.

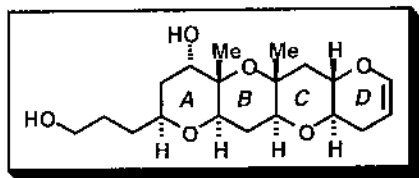
500 MHz, ^1H NMR (CD_2Cl_2)



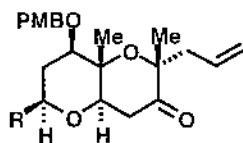
Jason M. Cox

Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* (1991), 113, 4092.

Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* (1999), 40, 97.

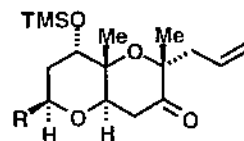


2° ALCOHOL INVERSION

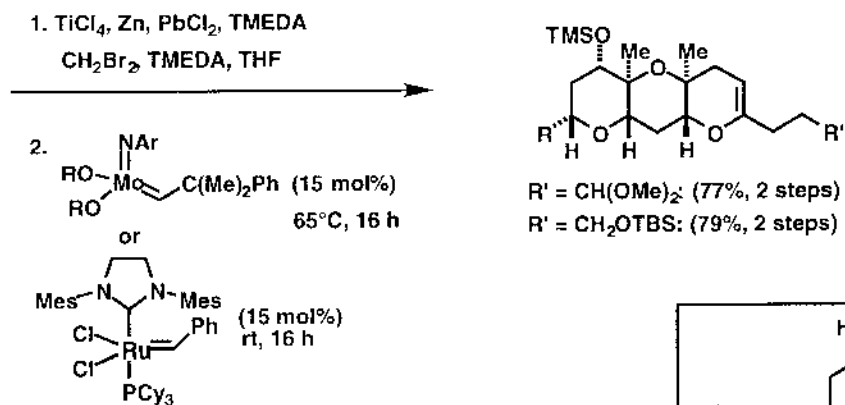
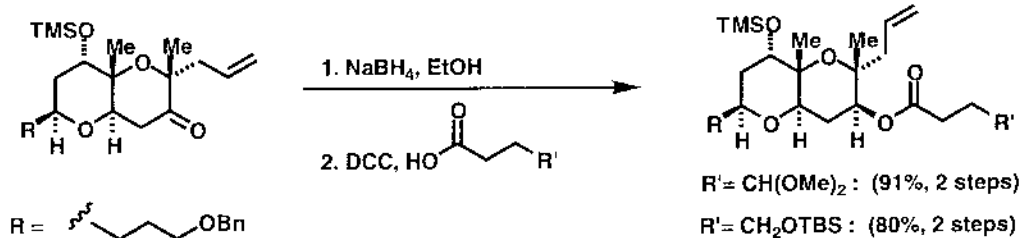


R =

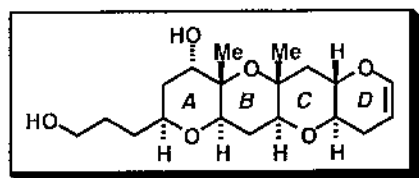
1. DDQ, CH_2Cl_2 , H_2O (93%)
2. DEAD, PPh_3 , $p\text{-NO}_2\text{C}_6\text{H}_4\text{CO}_2\text{H}$, PhCH_3
3. NaOH , H_2O , THF, MeOH (70%, 2 steps)
4. TMSOTf, $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 (87%)



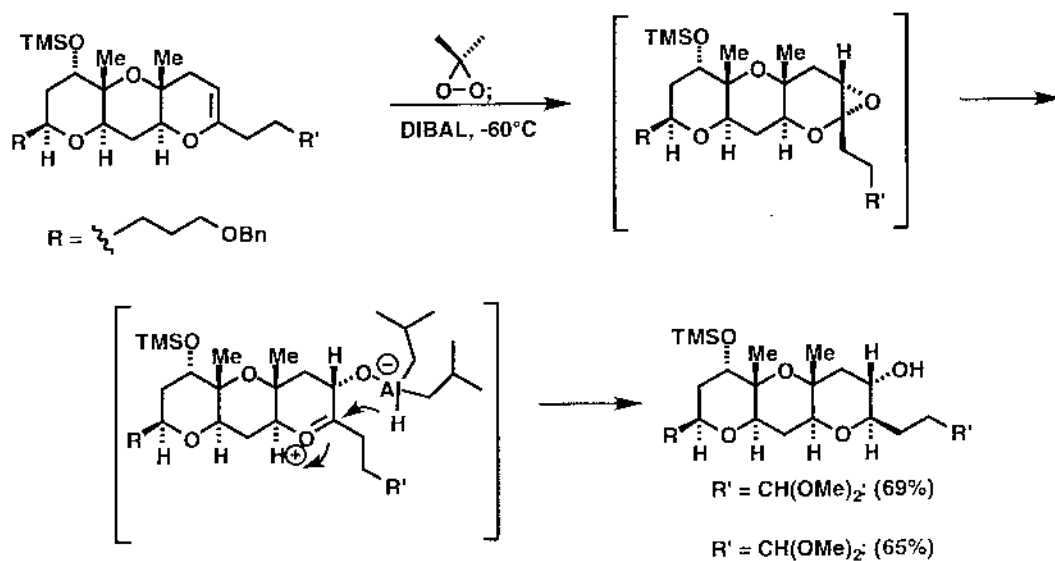
GAMBIEROL C-RING SYNTHESIS



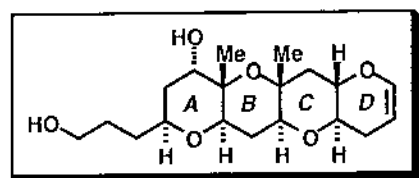
Jason M. Cox



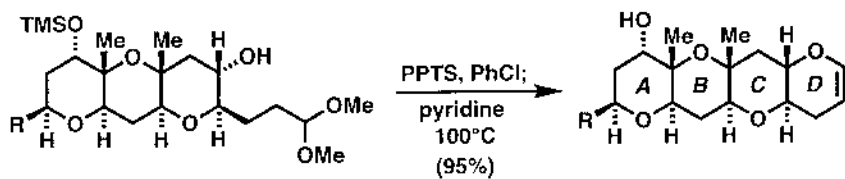
GAMBIEROL C-RING DIRECTED REDUCTION



Jason M. Cox



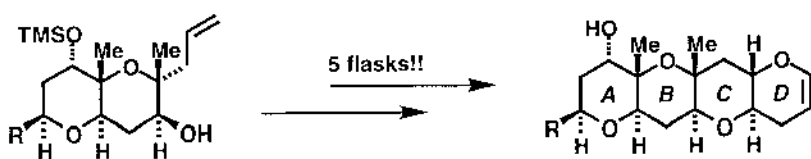
GAMBIEROL D-RING



20 STEPS TO THE GAMBIEROL A-D RING SYSTEM!!

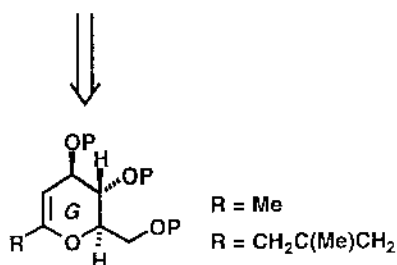
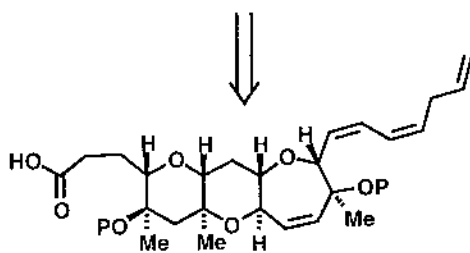
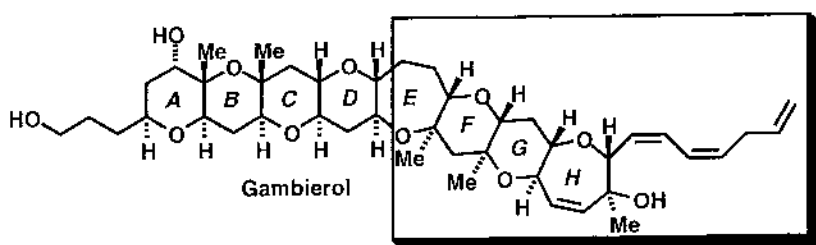
HIGHLIGHTS

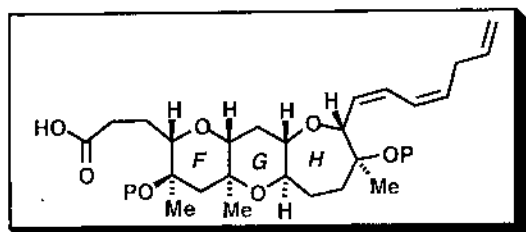
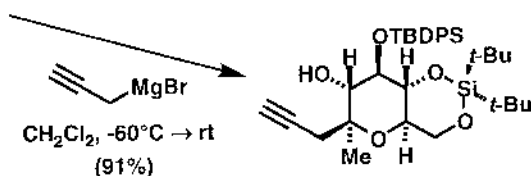
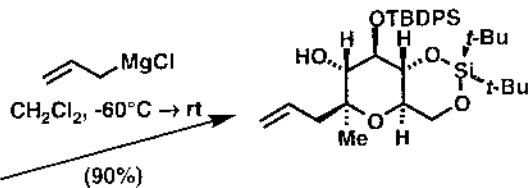
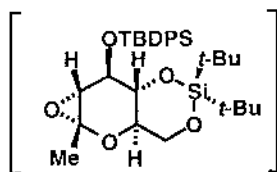
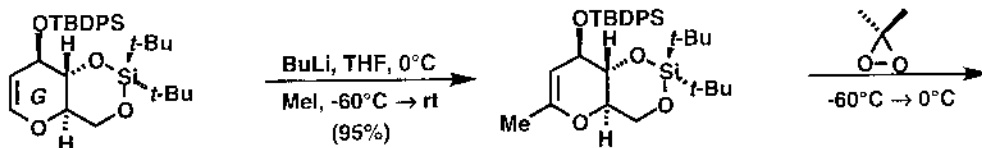
1. A single stereocenter was used to establish all of the stereocenters in the A-C ring system
2. New C-Glycoside synthesis using a Claisen Rearrangement to generate the C-11 angular methyl group.



Cox, J. M.; Rainier, J. D. *Org. Lett.* (2001), 3, 2919.

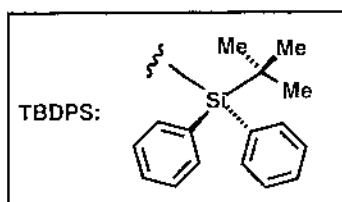
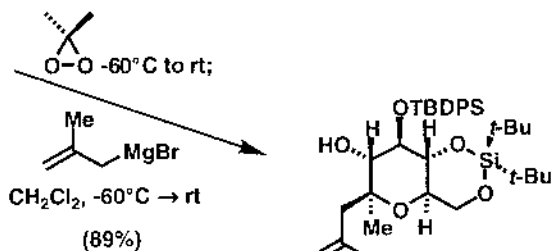
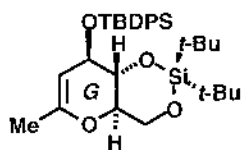
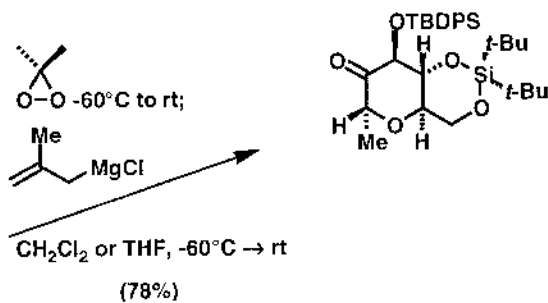
GAMBIEROL F-H SUBUNIT ANALYSIS





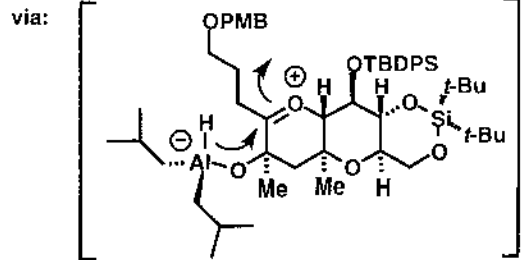
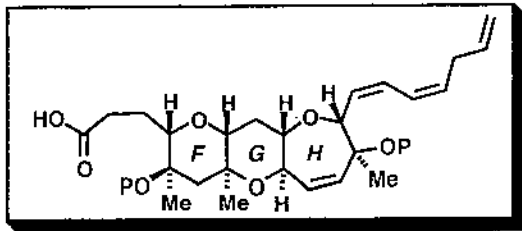
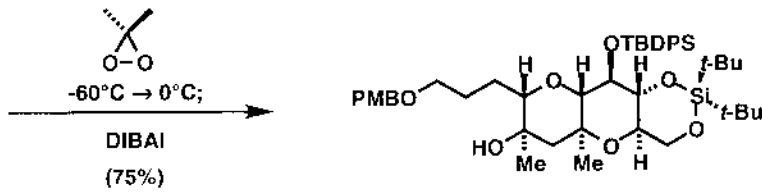
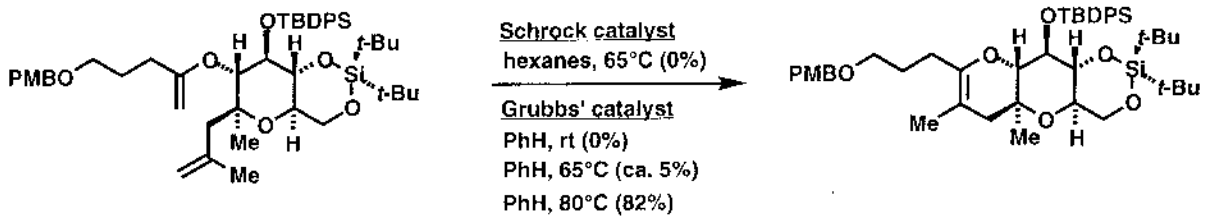
Jason M. Cox

GAMBIEROL G-RING



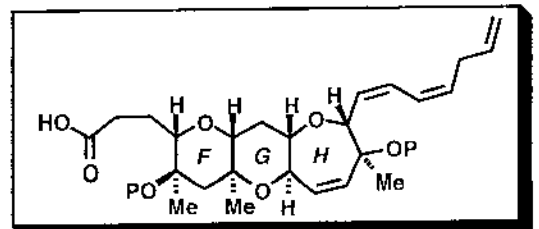
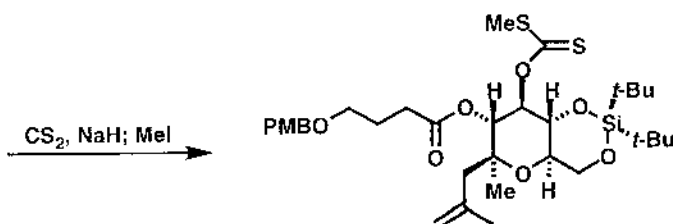
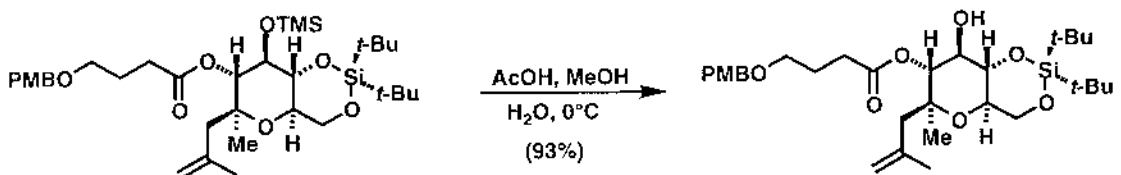
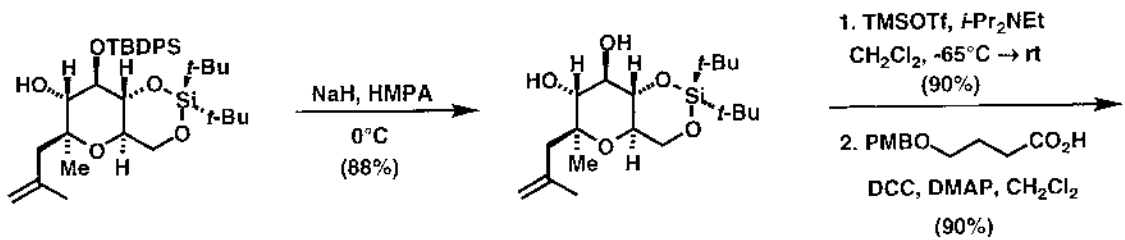
Jason M. Cox
&
Utpal Majumder

GAMBIEROL F-RING



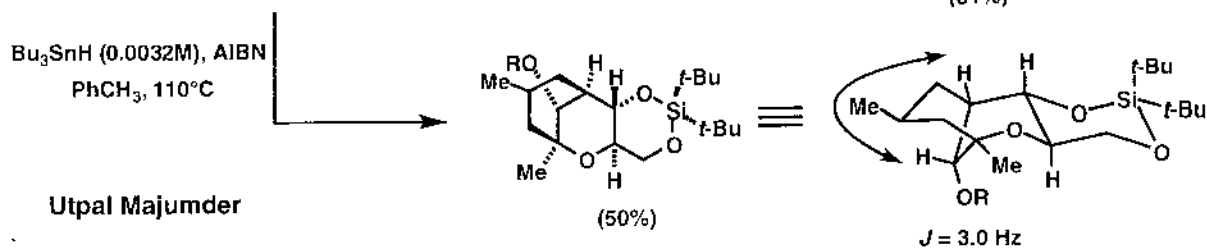
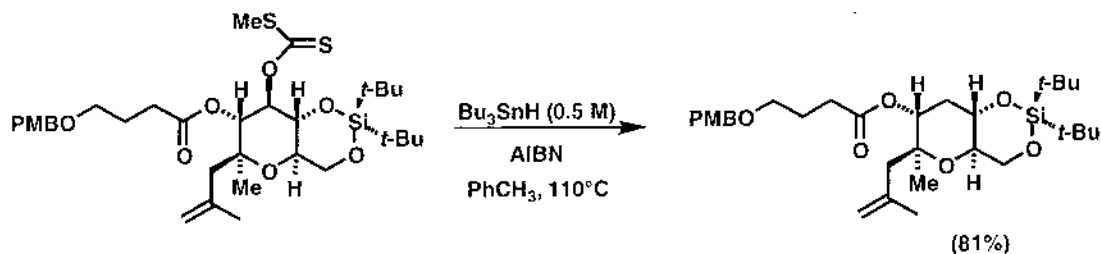
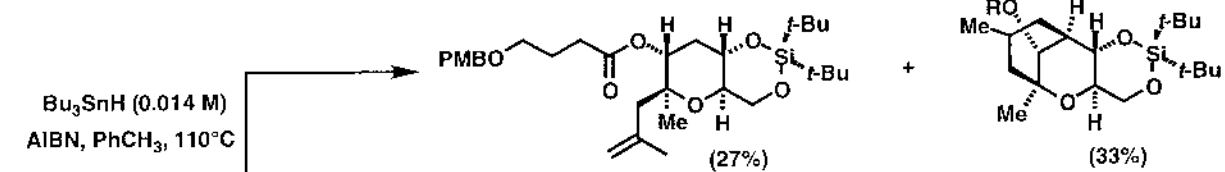
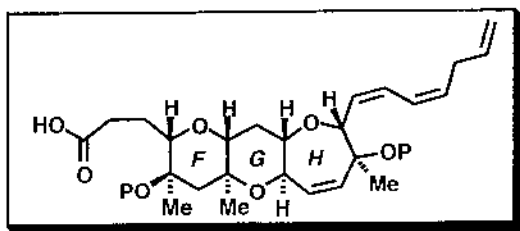
Utpal Majumder

GAMBIEROL G-RING MANIPULATION

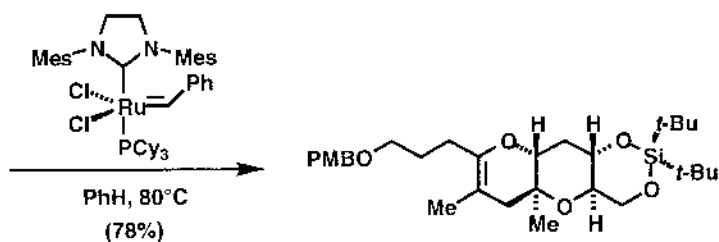
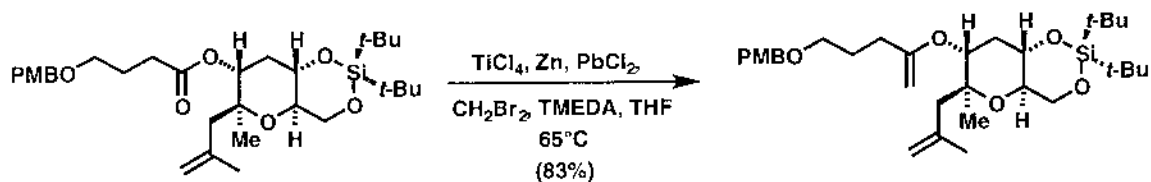
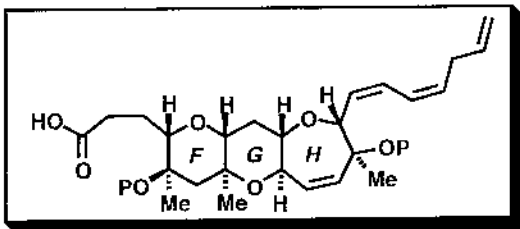


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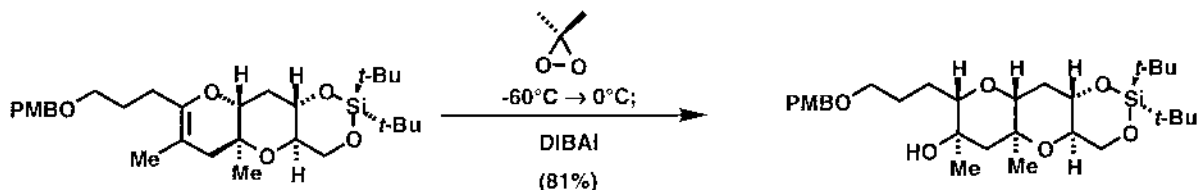
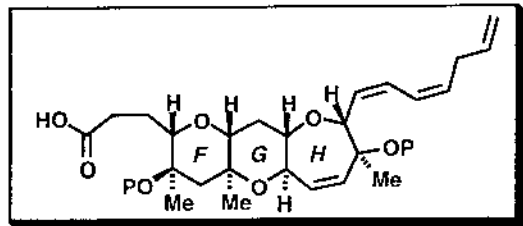
GAMBIEROL G-RING MANIPULATION



GAMBIEROL G-RING MANIPULATION



GAMBIEROL F-RING-COMPETITION



F-H SUMMARY

1. An interesting C-3 protecting group influence on C-glycoside formation has been observed.
2. Takai protocol to enol ethers is influenced by the steric environment about the ester starting material.
3. The coupling of C-glycoside formation with metathesis results in a highly concise entry into polycyclic ethers having angular methyl groups in a 1,3-disposition.

Utpal Majumder