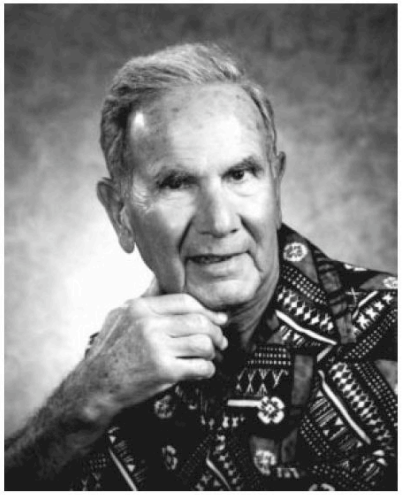
Paul J. Scheuer

Biography

Paul Josef Scheuer was born in Heilbronn, Germany in 1915. Upon his graduation from high school in 1934, he was denied entrance to college by the racial policies of the National Socialist party. He served as a tanner's apprentice in Hungary and elsewhere before immigrating to the United States in 1938. His curiosity about the tanning process led him to study chemistry, and he obtained his BS from Northeastern University in 1943. He began graduate work at Harvard, but was drafted and served in the Chemical Warfare Service and Military intelligence. In 1946, he resumed his graduate work under R. B. Woodward. He defended his thesis on the structure and chemistry of strychnine in 1950.

Career

After receiving his doctorate and marrying, Prof. Scheuer joined the faculty of the University of Hawaii at Manoa. His research initially focused on the natural products chemistry of terrestial Hawaiian plants, but quickly turned to the untapped resources of the surrounding Pacific Ocean. Before the work of Prof. Scheuer, marine natural products were almost unexpolored; indeed, he is credited with coining the term in his 1973 book *Chemistry of Marine Natural Products*. During his prolific career, Prof. Scheuer published some 300 papers. Although he formally retired in 1983, he maintained an active research program unitl his death in January 2003. Notable projects in the Scheuer lab include work on the structure of ciguatoxin and palytoxin, studies on the chemical ecology of marine invertibrates, and the isolation of the peptide kahalalide F, which is presently in clinical trials as a treatment for cancer. Prof. Scheuer was also the first natural products chemist to utilize manned submersibles in sample collection. Interestingly, he had never even been to an aquarium before his arrival at Hawaii.



D. John Faulkner

Biography

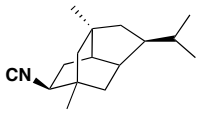
Born in Bournemouth, England in 1942, John Faulkner received his Ph. D. in 1965 under Sir Derek Barton, then undertook postdoctoral research under R.B. Woodward at Harvard and William Johnson at Stanford. In 1968, he was appointed Assistant Professor at the Scripps Institute of Oceanography. He began a program of research directed at the isolation of marine natural products.

Career

During Prof. Faulkner's prolific careeer, he published over 350 papers in the areas of natural products chemistry and chemical ecology. Among his most important discoveries are the realization that halogenation was a prominant biosynthetic pathway in the marine ecosystem. Indeed, he and his co-workers discovered more than 100 halogenated natural products. His studies on shell-less molluscs led to the theory that coevolution with toxic foods had allowed them to lose their shells over evolutionary time. His isolation of manoalide, a terpenoid that inhibits the inflammation enzyme Phospholipase A2 led to the discovery of a new class of antiinflamatory agents and investigations into the functions of PLA2. He was awarded the Paul J. Scheuer Award in Marine Natural Products Chemistry in 2000. He passed away in November 2002.

9-isocyanopupukeanane: The First Marine Defensive Secretion

The Scheuer group was responsible for the isolation of the first natural product identified as a marine feeding deterrent (*JACS*, **1981**, *103*, 2491-4). The nudibranch *Phyllidia varicosa* was identified as having a secretion that was toxic to fish and crustaceans. Subsequent investigation revealed that the active agent, 9-isocyanopupukeanane, was actually a secondary metabolite of the nudibranch's prey, the sponge *Ciocalypta sp.* This was the first observation of an organism concentrating a metabolite of another for its own use.



9-isocyanopupukeanane
First synthesized by Corey (*JACS*, **1979**, *101*, 1608-9) and Yamamoto (*ibid.* 1609-11)

Subsequent investigations on similar isocyano terpenoids reveled that the isocyano group was the biosynthetic precursor to the formamide and isothiacyano analogues. Other experiments revealed that cyanide served as the source of the isocyano group. This is in contrast to terrestial isocyanides, where the isocyano nitrogen is of peptidic origin.

The Ciguatoxin Odyssey (*Terahedron*, **1994**, *50*, 3-18)

In 1957, Scheuer was invited to join an interdisciplinary task force of scientists studying ciguatera by Prof. A. H. Banner, a zoologist at the University of Hawaii. Ciguatera is the name for a diverse collection of symptoms displayed by those whoe have consumed contaminated fish, including vomiting, diarrhea, dizziness, tingling in the extremities, and a sensation of temperature reversal. The team planned four deceptively simple objectives:

1. Elucidate the molecular structure of the toxin
2. Discover the origin of the toxin
3. Devise a diagnotic test to distinguish toxic fish from non-toxic ones
4. Find an effective human therapy

Difficulties:

1. Intermittent occurrence of toxicity in many species of fish/eels
2. Possible presence of >1 related toxin
3. Inability to distinguish toxic from non-toxic fish without bioassay
4. Low purity of extract (LD_{50} of extract 2 x 10^5 μg/kg, LD_{50} of ciguatoxin 0.45 μg/kg)
5. High molecular weight (1111.7 Da)

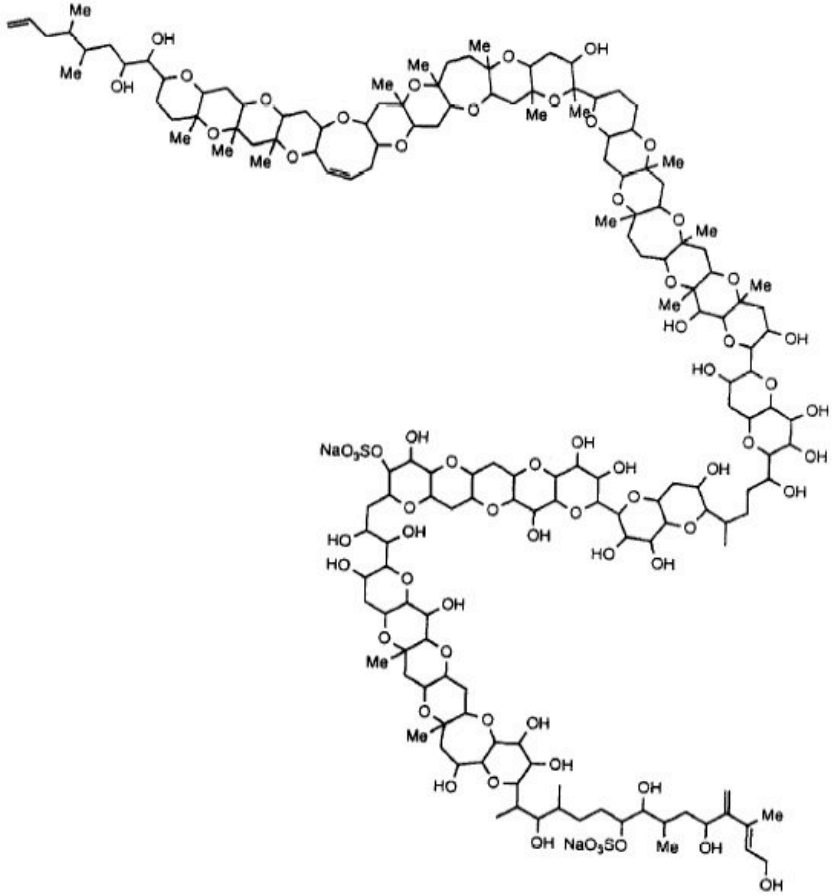
History:

1961: Mouse bioassay replaces mongoose assay
1967 &1971: Identification of ciguatoxin (lipid soluble) and maitotoxin (water soluble)
1980: 1.3 mg ciguatoxin purified from 75 kg eel viscera (1100 kg of eels at ca. 5.5 kg each), mass spectrum, 600 MHz ^{1}H NMR spectrum obtained
1989: pooling of world supply (1.1 mg) gives planar structure (Yasumoto)

Careful study of toxic fish gut contents identified the benthic dinoflagellate *Gambierdiscus toxicus* as source organism. Culture of this organism proved very difficult and yielded only maitotoxin, not ciguatoxin. Eventually, a ciguatoxin analog was obtained (0.7 mg from 1,100 L culture broth).

An antibody based stick test has been developed to detect ciguatoxin, but it is not known if this test is adequate for all related toxins.

A false lead on the path to ciguatoxin led Scheuer to isolate palytoxin, whose planar structure was elucidated by Hirata and Moore, and stereochemistry by Kishi's synthesis of degradation products.



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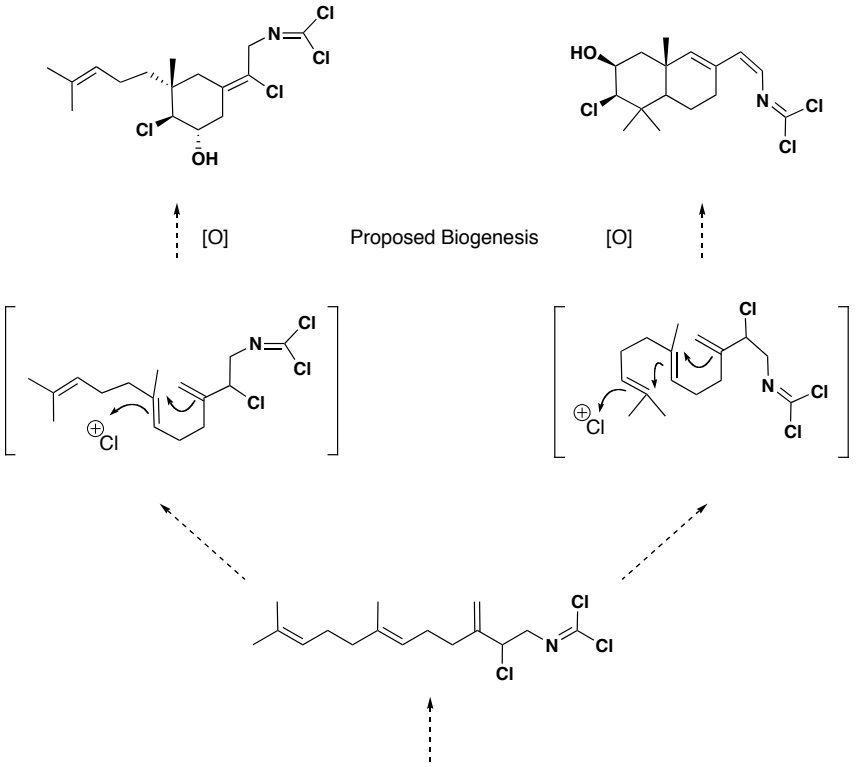
The Carbonimidic Dichlorides

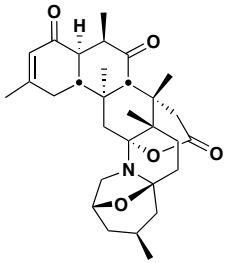
In 1977 and 1978, Faulkner reported the isolation of several natural products containing the carbonimidic dichloride functional group, which at that point was known only in synthetic compounds. (*JACS*, **1977**, *99*, 7367-8, *TL*, **1978**, 1391-4 and 1395-8).



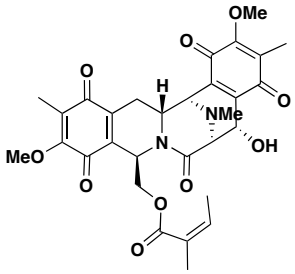
Isonitrile (not isolated) or isothiocyanate (isolated)

None of these natural products have been synthesized

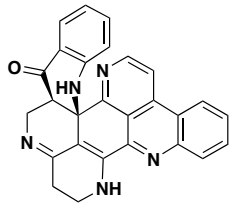
Natural Products Gallery



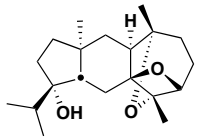
Zoanthamine
Faulkner, *JACS*, **1984**, *106*, 7983-4
Synthesized (Norzoanthamine) by Misyashita *Science*, **2004**, *305*, 495-9



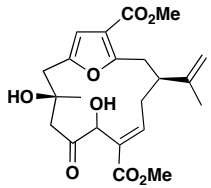
Renieramycin C
Faulkner, *JACS*, **1982**, *104*, 265-9.
JOC, **1989**, *54*, 5822-4 (stereochem reassigned)
Several syntheses, as well as Saframycins and Ecteinascidins.



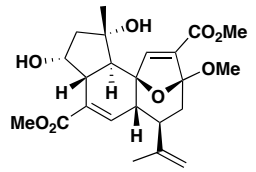
Eudistone A
Faulkner, *JOC*, **1991**, 5369-5371
not synthesized



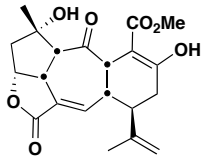
Dictyoxetane
Faulkner *JOC*, **1985**, *50*, 3665-6
not synthesized



Furanocembrane Diester
similar compounds synthesized
e.g. Pukalide (Scheuer isolation)



Mandapamate
not synthesized



Rameswaralide
synthesized by Trost
(reported at ACS Meeting)

Faulkner *Tet. Lett.* **1998**, *39*, 8217-8220

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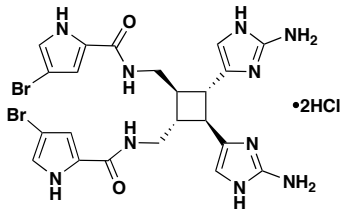
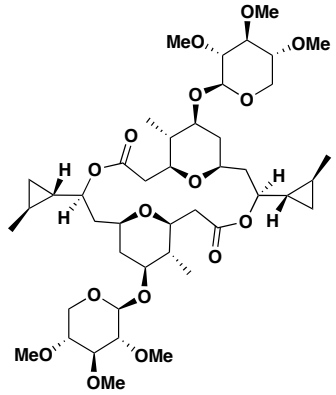
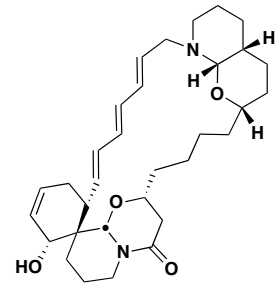


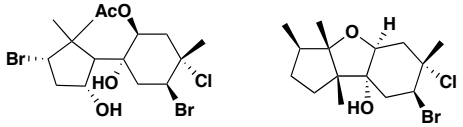
Sceptrin
Faulkner *JACS*, **1981**, *103*, 6772-3
Synthesized



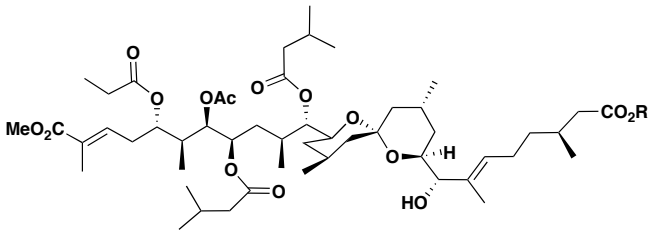
Clavoside A
Faulkner *J. Nat. Prod.* **2002**, *65*, 386-8
Not Synthesized



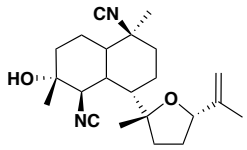
'Upenamide
Scheuer *J. Org. Chem.* **2000**, *65*, 8465-9
Not Synthesized



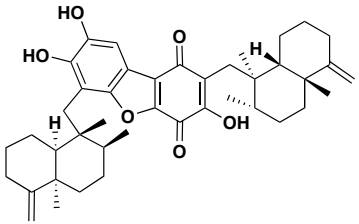
Algolane and Ibhayinol
Faulkner *J. Nat. Prod.* **2002**, *65*, 580-582
Not Synthesized



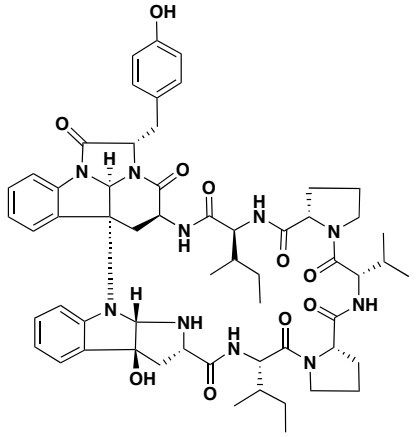
R= Me: Didemnaketal B
R= $CH_2CH_2SO_3Na$: Didemnaketal C
Faulkner *Org. Lett.* **2002**, *4*, 1699-1702
Not Synthesized



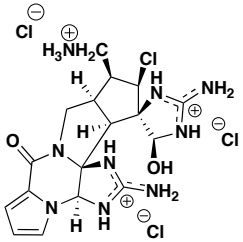
Kalihinol C
Scheuer *JACS*, **1987**, *109*, 6119-6123
Synthezied by Wood
Org. Lett. **2004**, *6*, 1123-6



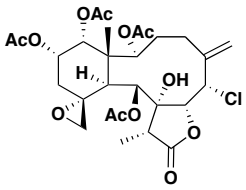
Popolohuanone E
Scheuer *Tet. Lett.* **1993**, *34*, 3727-3730
Not Synthesized



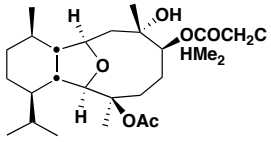
Kapakahine D
Scheuer *JOC*, **1996**, *61*, 7168-7173
Not Synthesized



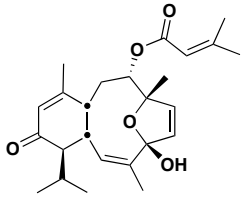
Palau'amine
Scheuer *JOC*, **1998**, *63*, 3281-6
Not Synthesized



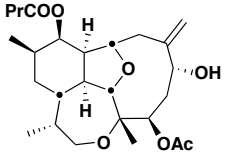
Nuiinoalide A
Scheuer *Heterocycles*, **1996**, *42*, 325-331



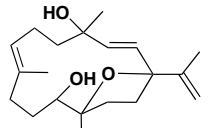
Unnamed cladiellenol
Faulkner *J. Nat. Prod.* **1994**, *57*, 574-580



Valdivone A
Faulkner *Tetrahedron*, **1993**, *49*, 7977-7984

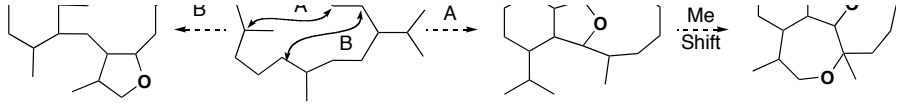


Asbestinin 7
Faulkner *JACS* **1980**, *102*, 5088-5092



Unnamed Oxacembrene
Faulkner *J. Nat. Prod.* **1993**, *56*, 2003-7

Proposed Biosynthetic Relationship



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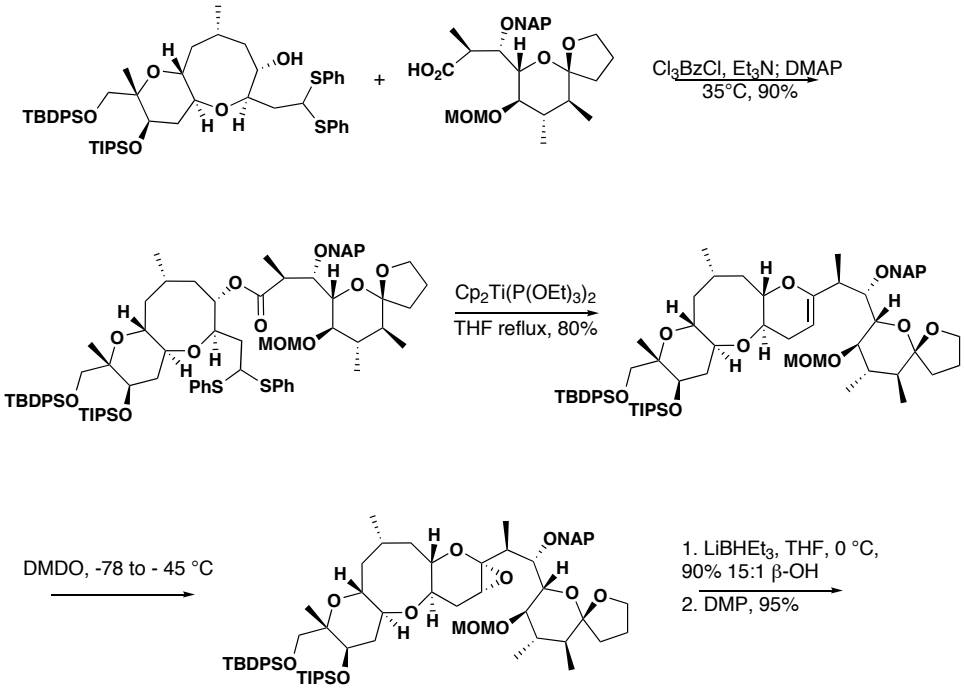
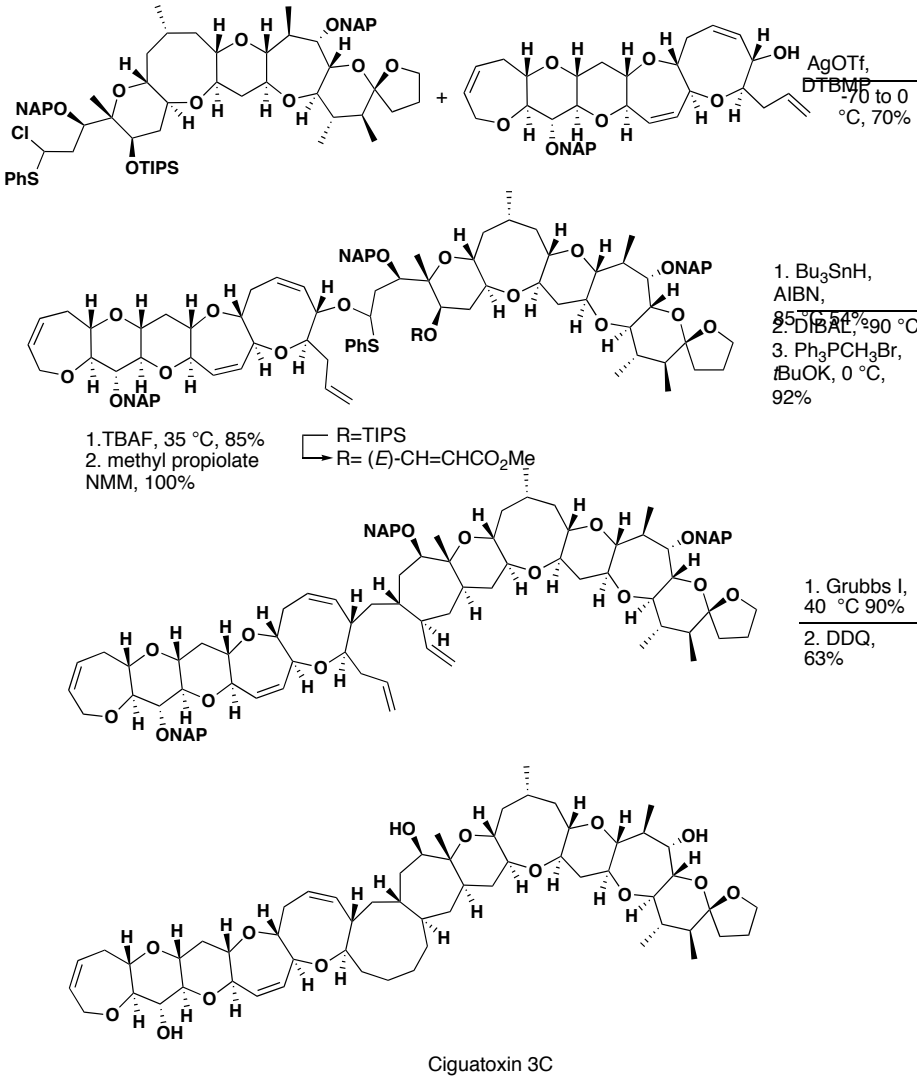
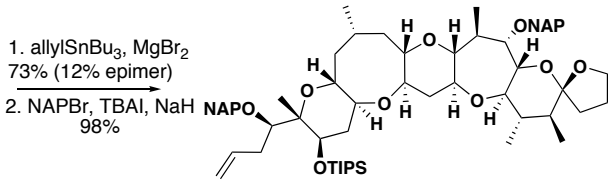
Synthesis of Ciguatoxin CTX3C

Inoue/Hirama *PNAS*, **2004**, *101*, 12013-8 and references therein







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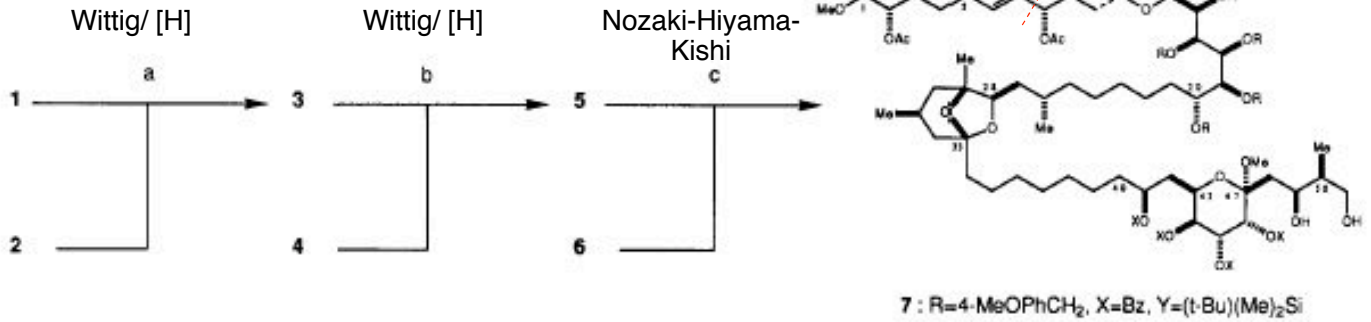
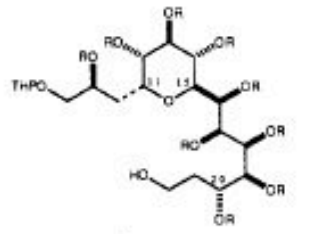
Kishi Palytoxin Synthesis

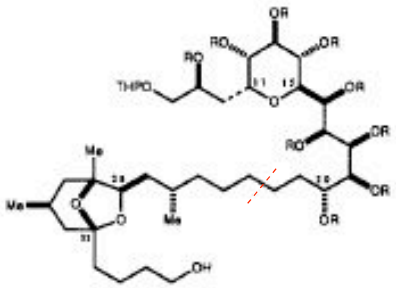
JACS, **1989**, *111*, 7525-7530, 7530-3,
JACS **1994**, *116*, 11205-6



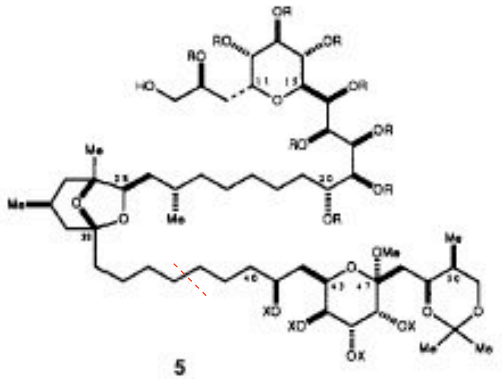
7 : R=4-MeOPhCH$_2$, X=Bz, Y=(t-Bu)(Me)$_2$Si



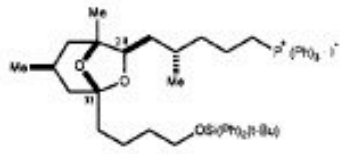
1

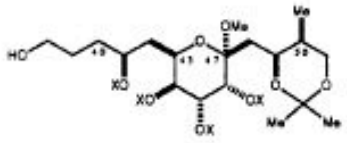


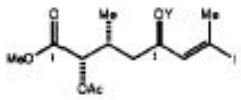
3



5



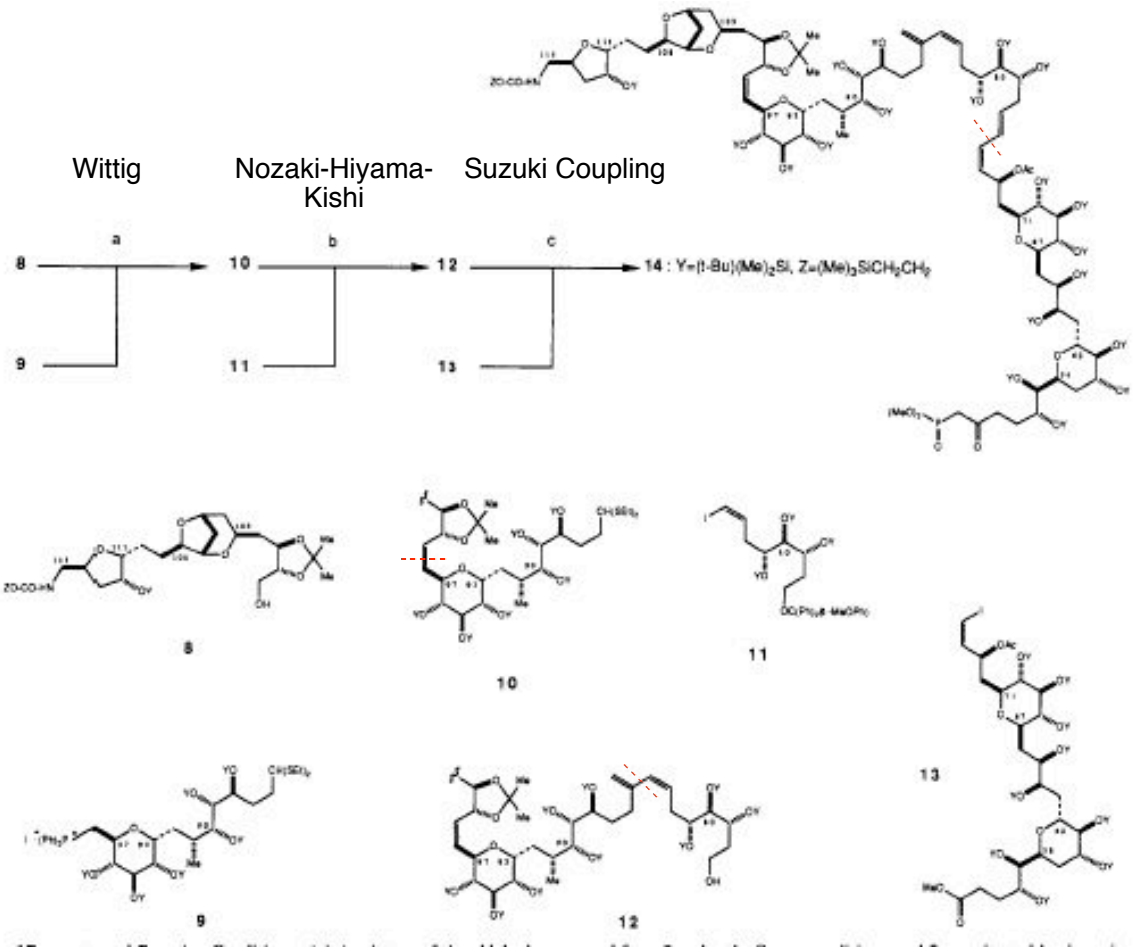




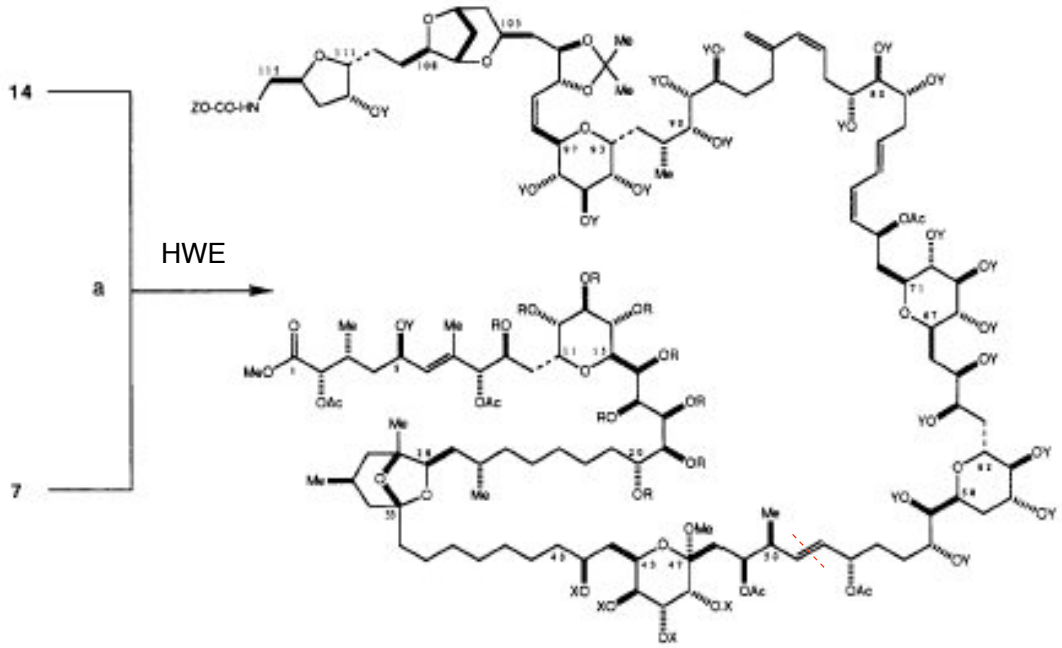
2 4 6

[a] Reagents and Reaction Conditions: (a) (1) The aldehyde, prepared from **1** under the Swern conditions, was treated at −78 to 0 °C with the ylide generated (*n*-BuLi/THF −78 °C) from **2**. (2) H_2 (1 atm)−10% Pd on C/MeOH−Et_2O (1:2), room temperature. (3) $(n\text{-Bu})_4NF$/THF, room temperature. (b) (1) **3**/MsCl−$(Et)_3N/CH_2Cl_2$, 0 °C. (2) NaI/2-butanone, 60 °C. (3) $P(Ph)_3$/DMF, 110 °C. (4) The aldehyde, prepared from **4** under the Swern conditions, was treated at −78 to 0 °C with the ylide generated from the phosphonium salt (*n*-BuLi/THF, −78 °C). (5) H_2 (1 atm)−10% Pd on C/MeOH−Et_2O (2:1), room temperature. (6) PPTS/MeOH−Et_2O (3:1), 42 °C. (7) PPTS/acetone, room temperature. (c) (1) **6** and the aldehyde prepared from **5** under the Swern conditions/$CrCl_2$ containing 0.11% $NiCl_2$/DMSO−THF (1:3), 32 °C. (2) Ac_2O−DMAP/pyridine, room temperature. (3) PPTS/MeOH−Et_2O (3:1), 40 °C. For the conversion of the minor allylic alcohol into the major allylic alcohol: (1) Swern oxidation. (2) $Zn(BH_4)_2/Et_2O$, 0 °C.

6



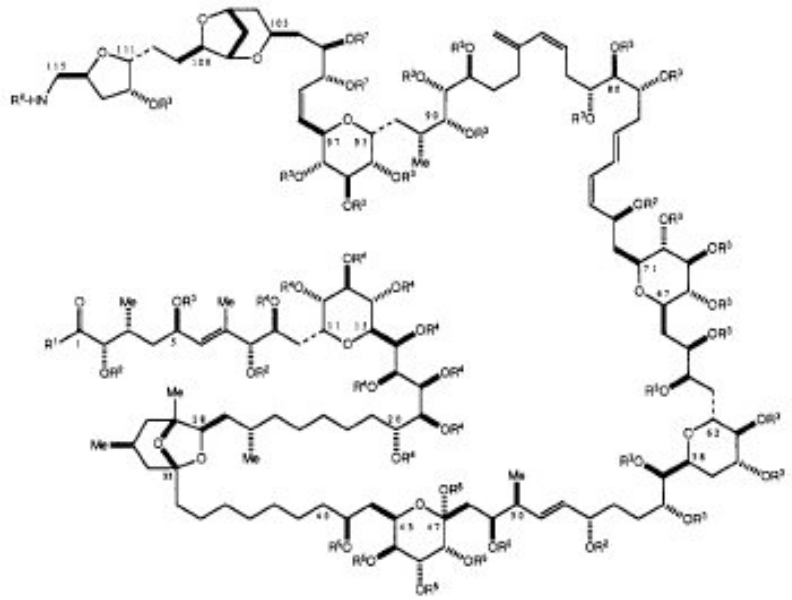
[a] Reagents and Reaction Conditions: (a) A mixture of the aldehyde, prepared from **8** under the Swern conditions, and **9** was titrated by dropwise addition of LDA (0.4 M in THF) in THF–HMPA (5:1) at room temperature. (b) (1) I_2–$NaHCO_3$/acetone–water (19:1), 0 °C. (2) The aldehyde and **11**/$CrCl_2$ containing 0.11% $NiCl_2$/DMSO–THF (3:1), room temperature. (3) PDC–DMF, 0 °C. (4) The α,β-unsaturated ketone and $H_2C{=}P(Ph)_3$/hexanes–THF (2:1), 0 °C. (5) PPTS/MeOH–CH_2Cl_2 (1:5), room temperature. (c) (1) Swern oxidation. (2) The aldehyde and $LiCH[B(OCH_2CH_2CH_2O)]_2$–TMEDA/THF, 0 °C, followed by workup with EtOAc–brine containing 1 N HCl. (3) The vinylboronic acid/TlOH (10% aqueous solution)–hexanes, room temperature, followed by addition of **13** and $Pd[P(Ph)_3]_4$ at room temperature. (4) The methyl ester and $LiCH_2P(O)(OMe)_2$ (30 equiv)/THF, −78 °C.



15 : R=4-MeOPhCH$_2$, X=Bz, Y=(t-Bu)(Me)$_2$Si, Z=(Me)$_3$SiCH$_2$CH$_2$

[a] Reagents and Reaction Conditions: (a) (1) **14**/NaH/THF room temperature, followed by an addition of the aldehyde, prepared from **7**

[$RuCl_2[P(Ph)_3]/C_6H_4$, room temperature], at 0 °C to room temperature. (2) $LiBH_4$–$EuCl_3$/MeOH–Et_2O (1:1), −45 °C. (3) Ac_2O–DMAP/pyridine, 0 °C.



a

1 : R^1=OMe, R^2=Ac, R^3=(t-Bu)$(Me)_2Si$, R^4=4-MeOPhCH$_2$, R^5=Bz, R^6=Me, R^7=acetonide, R^8=$(Me)_3SiCH_2CH_2OCO$

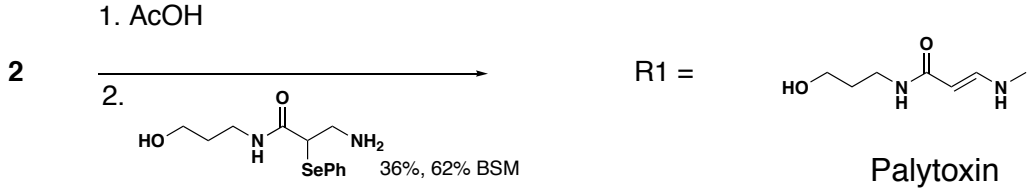
2 : Palytoxin Carboxylic Acid : R^1=OH, R^2=R^3=R^4=R^5=R^6=R^7=R^8=H

b

3 : Palytoxin Amide : R^1=NH_2, R^2=R^3=R^4=R^5=R^6=R^7=R^8=H

[a] Reagents and Reaction Conditions: (a) (1) DDQ/*t*-BuOH–CH_2Cl_2–phosphate buffer (pH 7.0) (1:8:1), sonicator, room temperature, 4.5 h, followed by acetylation (Ac_2O–DMAP/pyridine room temperature).[14] (2) $HClO_4$ [1.18 N, prepared by mixing 9 mL of H_2O–THF (3:7) and 1 mL of concentrated $HClO_4$]–THF (1:12), 25 °C, 8 days. (3) 0.08 N LiOH/H_2O–MeOH–THF (1:2:8), 25 °C, 20 h. (4) (*n*-Bu)$_4$NF in THF, 22 °C, 18

h and then in THF–DMF (1:1), 22 °C, 72 h. (5) AcOH–H_2O (1:350), 22 °C, 36 h. (b) (1) AcOH–H_2O (1:9), room temperature, 12 h. (2) NH_3/pyridine, room temperature, 10 min.



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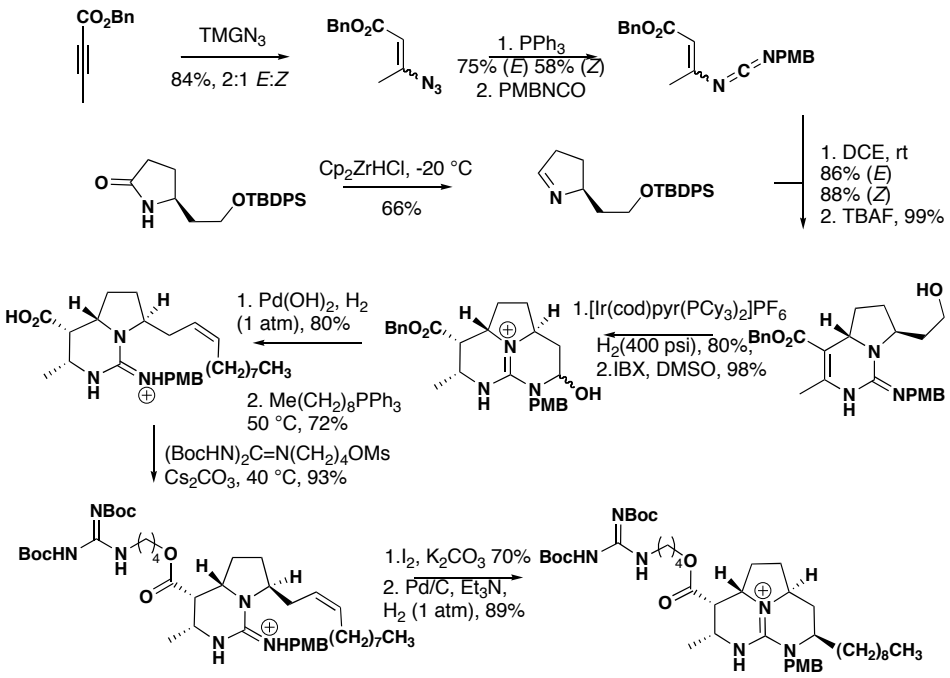
Gin Synthesis of Batzelladine D

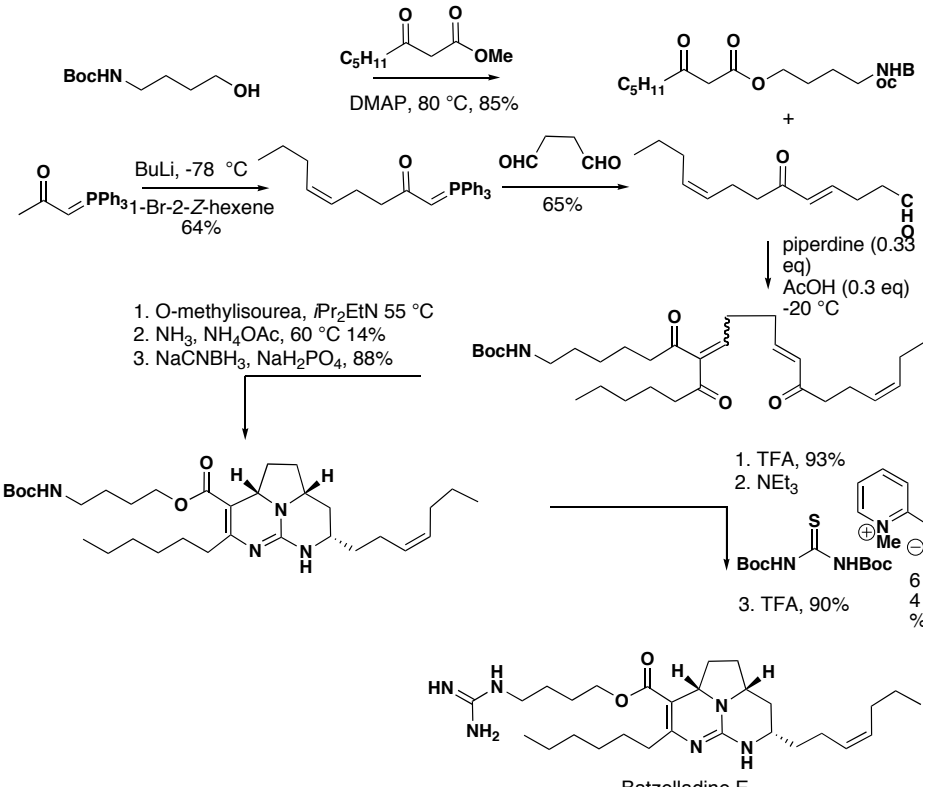
JACS, **2005**, *127*, 6924-5

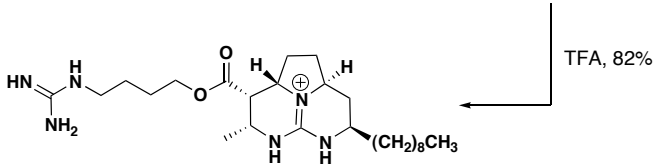
isol: Faulkner, *JOC*, **1997**, *62*, 1814-9



Snider Synthesis of Batzelladine E

Tet. Lett. **1998**, *39*, 5697-5700





Batzelladine D

Batzelladine E

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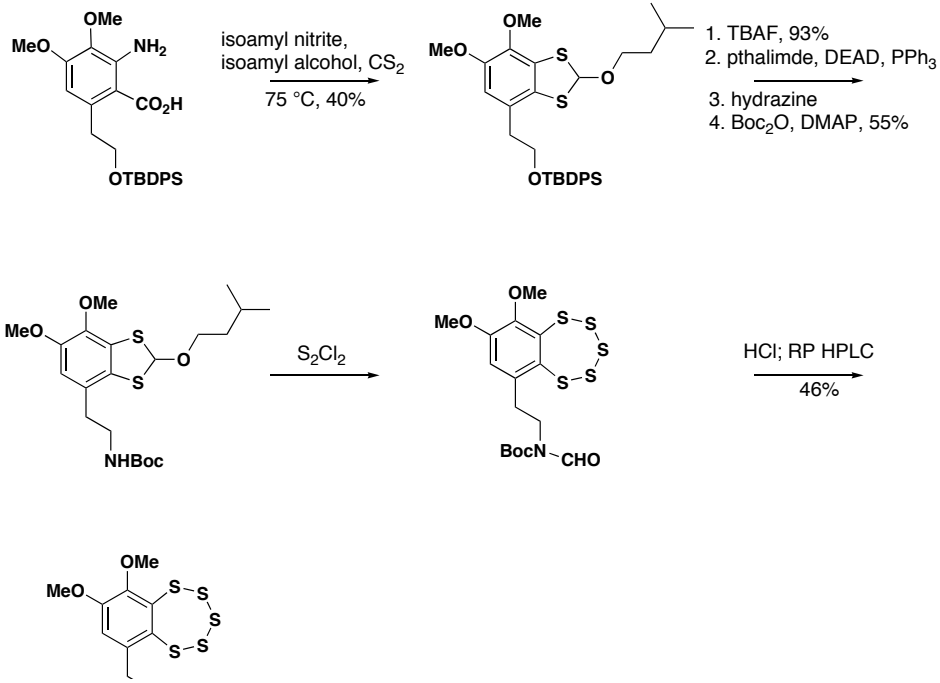
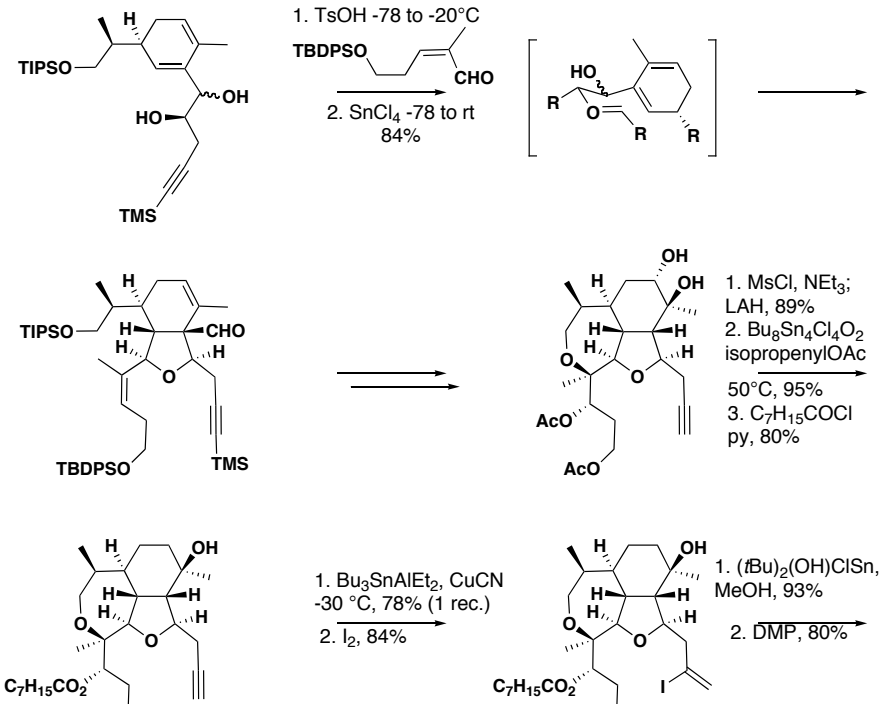
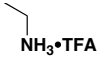
Danishefsky Synthesis of Varacin
JACS, **1993**, *115*, 7017-8.
(Isolated by Ireland, similar to compounds isolated by Faulkner)

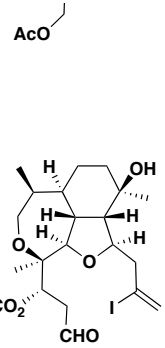


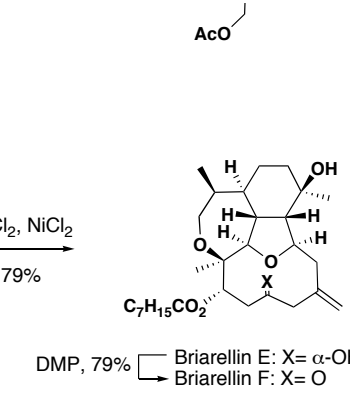
Overman Synthesis of Briarellins E and F
JACS, **2003**, *125*, 6650-2





Varacin





Briarellin E: X= α-OH, β-H
Briarellin F: X= O

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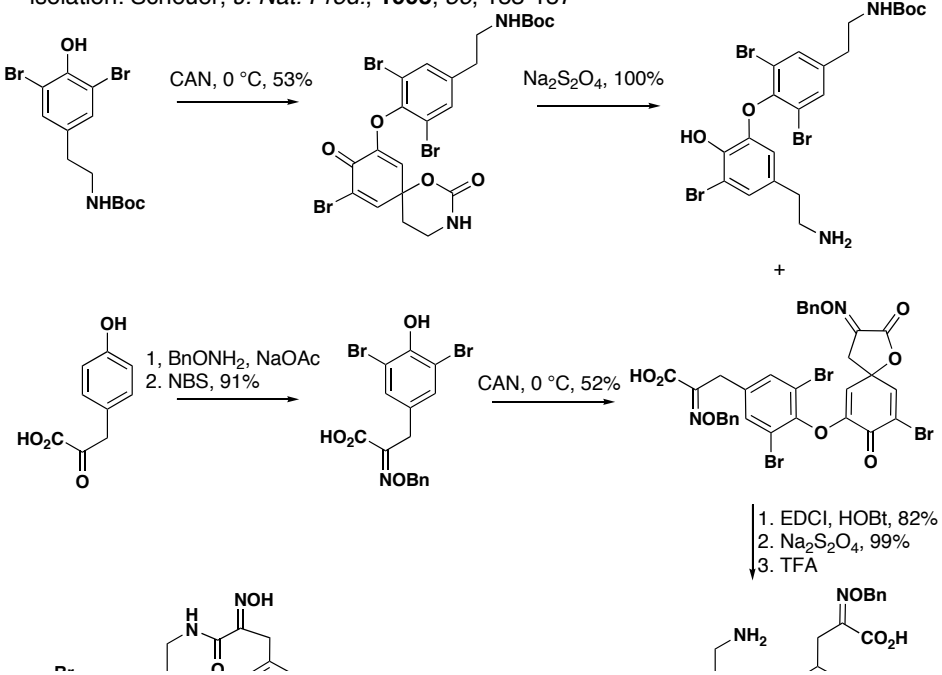
Kobayashi Synthesis of Bastadin 6

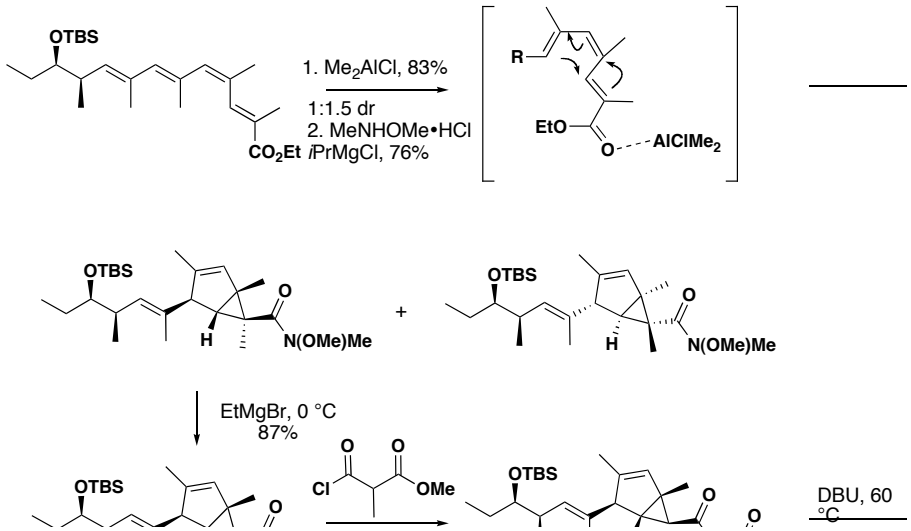
Tetrahedron, **2005**, *61*, 7211-8
isolation: Scheuer, *J. Nat. Prod.*, **1993**, *56*, 153-157

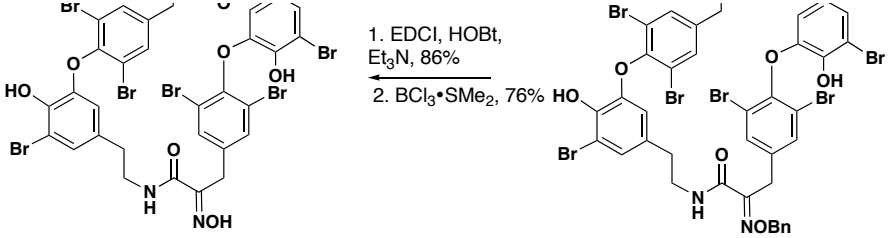


Trauner Synthesis of Crispatene

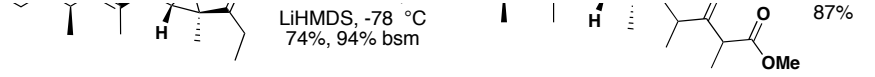
PNAS, **2004**, *101*, 12019-12023
Isolation: Faulkner *Tetrahedron,* **1981**, *37*, 233-240
In Vivo photochemistry: Scheuer *Science*, **1979**, *205*, 922-3.

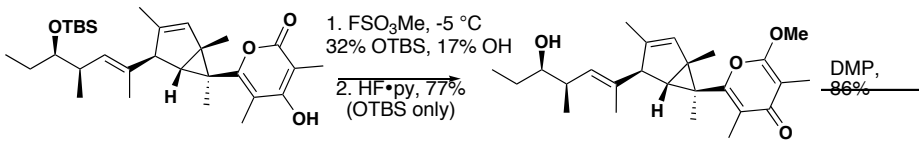
^{14}C Carbonate incorporation: "yellow pigments" 19%, pyrones 21%, "green pigments" 6% "baseline" 42%
"light pulse" experiments show formation of [3.1.0] system from cyclohexadiene system *In Vivo*

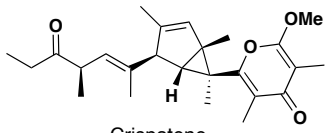




Bastadin 6







Crispatene

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Faulkner and Scheuer

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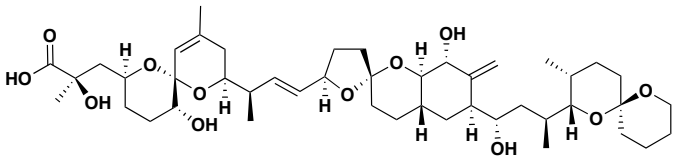
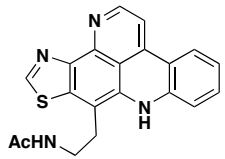
Suggested Reading



Okadaic Acid
Stucture Elucidation: Scheuer *JACS*, **1981**, *103*, 2469-2471
Synthesis: Forsyth *JACS*, **1997**, *119*, 8381-2
Isobe *Tetrahedron*, **1987**, *43*, 4767-4776



Kuoniamines and Dercitins
isolation: Scheuer, *JOC*, **1990**, *55*, 4426
Synthesis: Ciufolini *JACS*, **1992**, *114*, 10081-2
JACS, **1995**, *117*, 12460-9