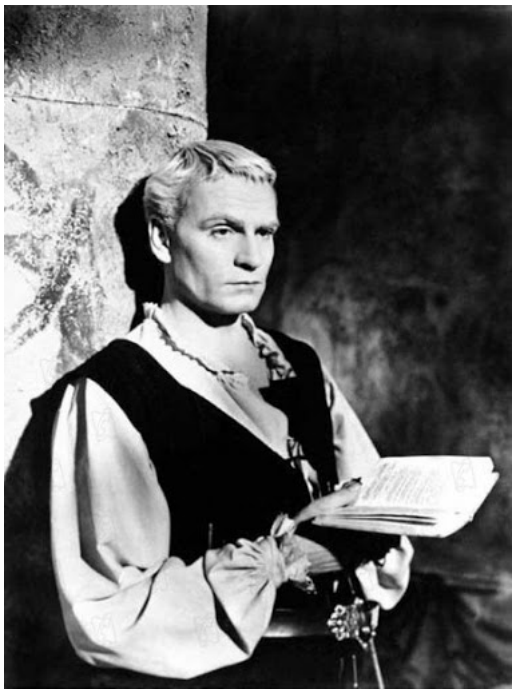
Small Ring Natural Products – Heterocycles Edition



“There are more things in Heaven and Earth, Horatio, than are dreamt of in your philosophy”

- Hamlet, teaching Horatio about natural products

Small (3- and 4-membered) Rings in NPs*:

Carbocycles
- Cyclopropanes: 7039
- Cyclobutanes: 2154
- Cyclobutenes: 50

O-Heterocycles
- Epoxides: 13962
- Oxetanes: 450
    - Roughly half are taxanes
- Beta Lactones: 140

N-Heterocycles
- Aziridines: 50
- Azetidines: 61
- Beta Lactams: 243

Thiiranes: 11
Thietanes: 10

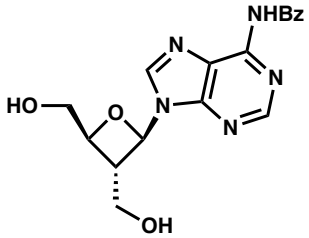
Dictionary of Natural Products

***questionably responsible counting**

O-Heterocycles - Oxetanes

Oxetane Acetals - Does Nature make 4-membered sugars?

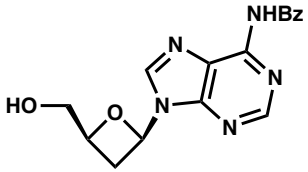
Four-Membered Nucleoside Analogs



Oxetanocin

Isolated 1986
from *B. megaterium*

Antibiotic and Antiviral (HIV) activity

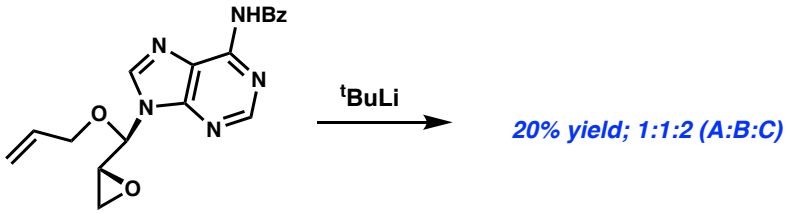


Albucidin

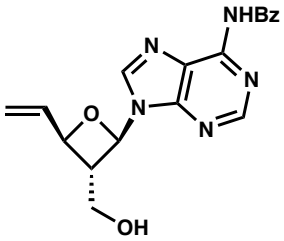
Prepared 1991 by semi-synthesis
Isolated 2009 from *S. albus*

Phytotoxic

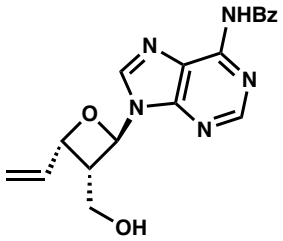
Niitsuma Synthesis (Nippon Kayaku) - 19 steps, key epoxide opening



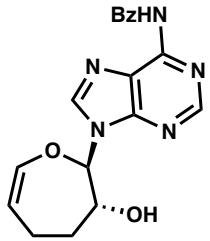
11 steps from ribose



A



B

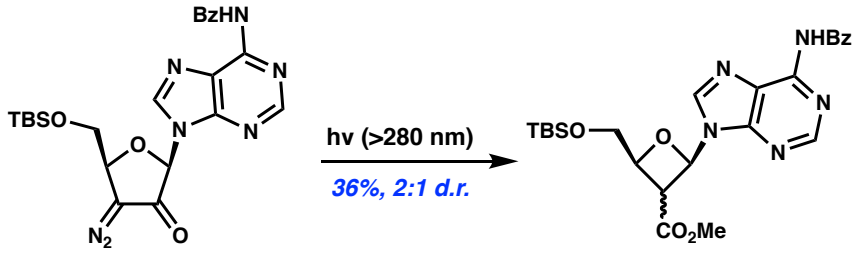


C

Three syntheses form oxetane via 4-exo-tet sulfonate displacement

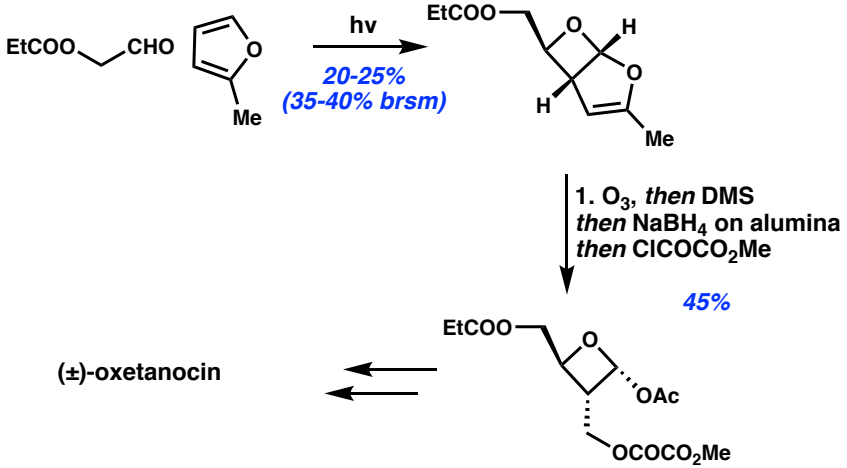
- Yamamura (collab. with Nippon Kayaku, 1988), racemic
- Fleet (collab. with Glaxo, 1990), chiral pool (glucose)
- Chu (2002), *ent*-oxetanocin, chiral pool (L-xylose)

Norbeck Synthesis (Abbott) - 12 steps, key Wolff ring contraction



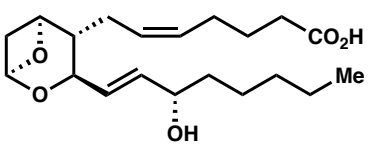
9 steps from adenosine (*28%*)
OR 6 steps from cordycepin

Just Synthesis - racemic, 4 steps, key [2+2]

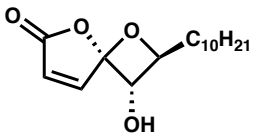


O-Heterocycles - Oxetanes

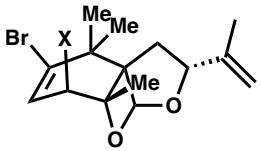
Naturally-Occurring Oxetane Acetals



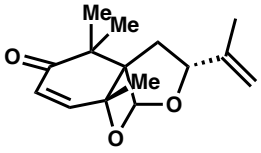
Thromboxane A_2
Platelet Activation Factor



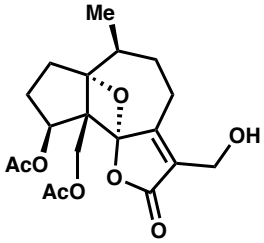
Ramariolide B
Isolated 2012
from *R. cystidiophora*
Confirmed by synthesis



Laureacetal B (X = OH),
D (X = Br), E (X = Cl)

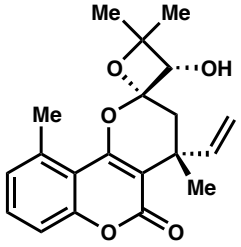


Laureacetal C

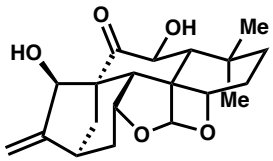


Laureacetal D confirmed by X-ray
Isolated 1979-1983
from *L. nipponica*

Parthoxetine
confirmed by X-ray
Isolated 1986
from *P. fruticosum*



Isoethuliacoumarin B
Isolated 1980
from *E. conyzoides*

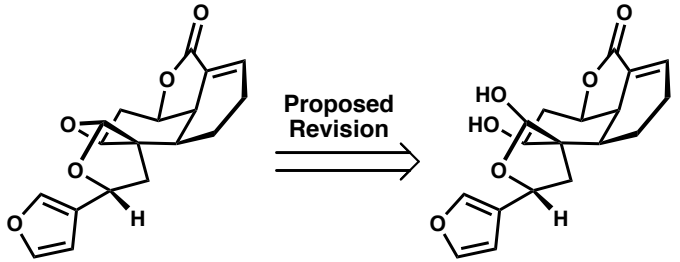


Maoyecrystal I
Isolated 2004
from *I. japonicus*
Cytotoxic against K562 cells
at 7.3 μg/mL (~20 μM)

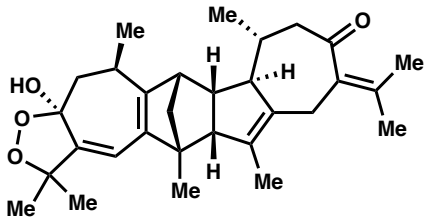
A Cautionary Message:

Some oxetane natural products are likely FAKE NEWS

Proposed reassignments based on
DFT prediction of NMR spectra



Cephaloziellin B (Reported)
Isolated 2013
from *C. kiaeri*

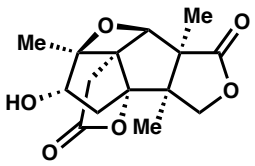


Unnamed dimer (Proposed Revision)
Isolated 1998
from *X. aromatica*
Originally assigned as oxetane acetal

Kutateladze, J. Org. Chem., 2019

O-Heterocycles - Oxetanes

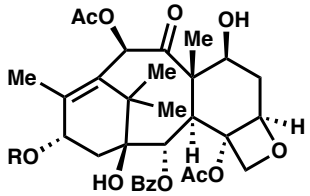
"Strict" Oxetane Natural Products



(—)-merrilactone A

~10 Total and formal syntheses

Oxetane universally formed via epoxide-opening

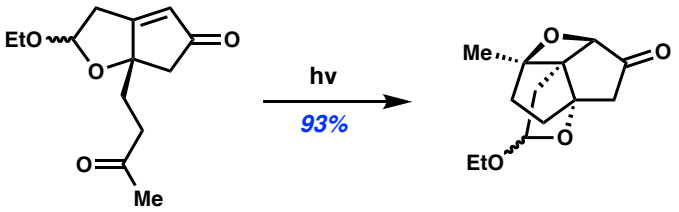


Paclitaxel (Taxol)

11 syntheses

Oxetane universally formed via halide/sulfonate displacement

Greaney's Paterno-Büchi Approach:



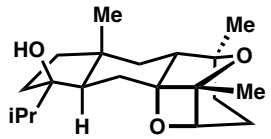
(5 steps)

Tetracyclic Core

Greaney, Org. Lett., 2005

O-Heterocycles - Oxetanes

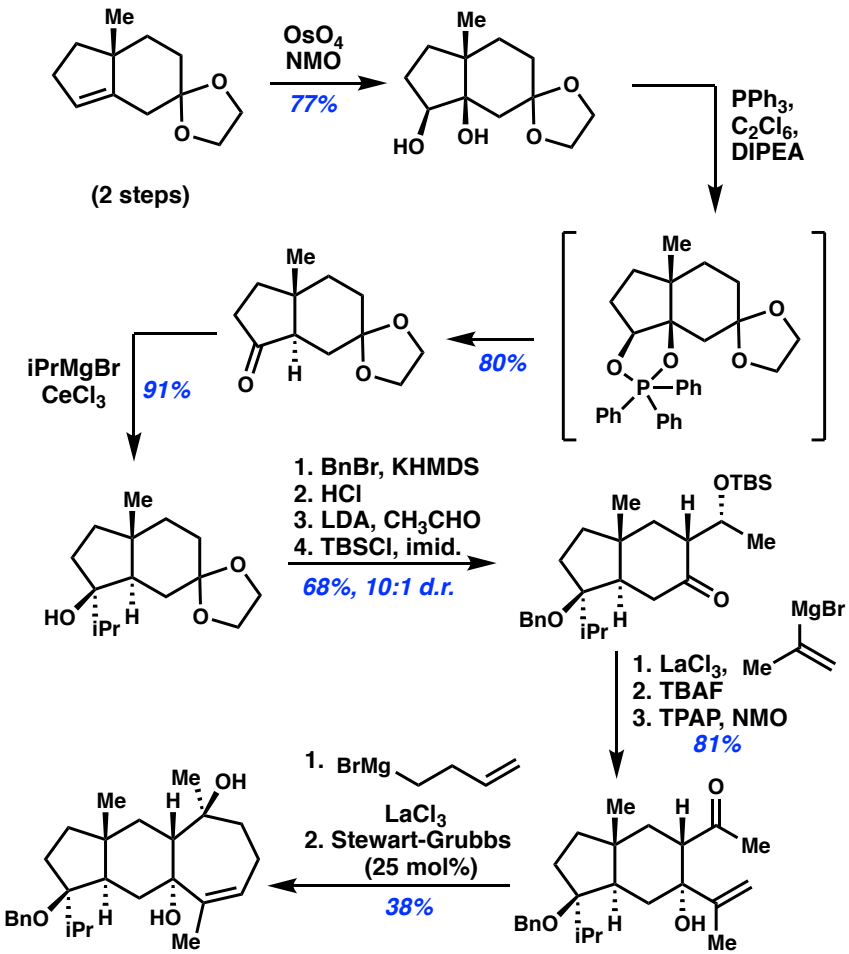
Dictyoxetane



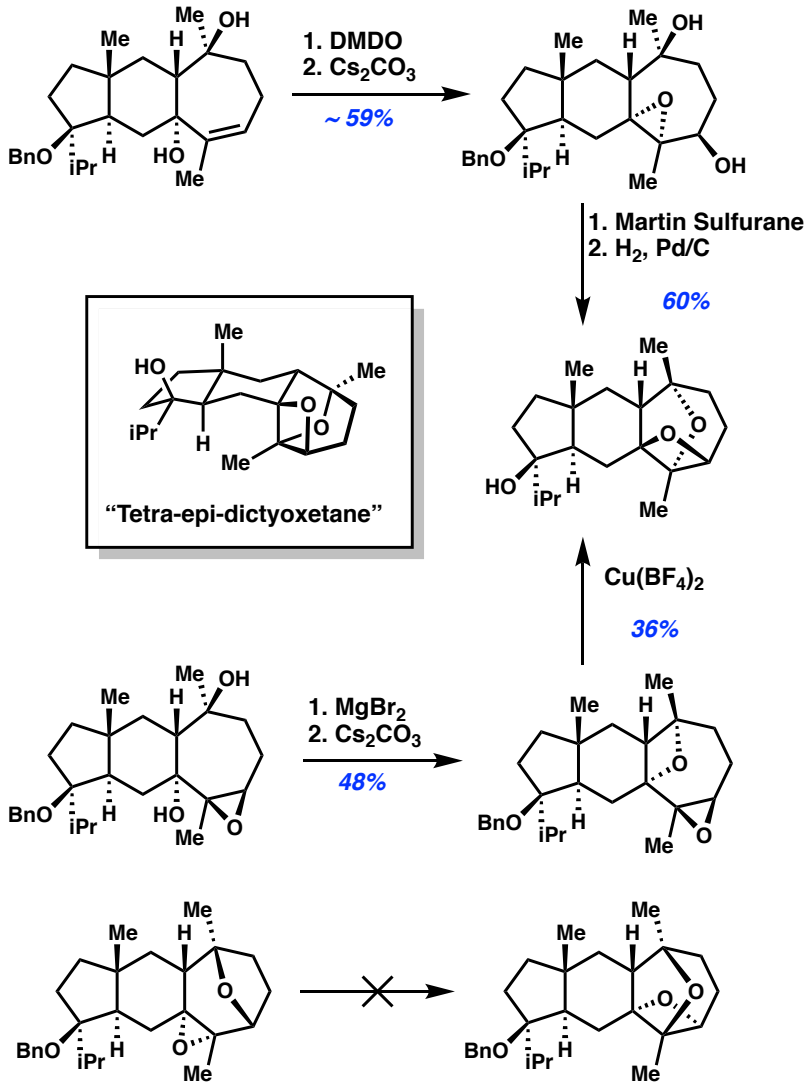
Dictyoxetane
Unknown biological activity

Isolated 1985
from brown alga *D. dichotoma*

Magauer Synthesis (2016)



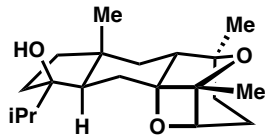
Endgame Strategy 1



Grainger, Org. Biomol. Chem, 2012
Magauer, JACS, 2016

O-Heterocycles - Oxetanes

Dictyoxetane



Dictyoxetane
Unknown biological activity

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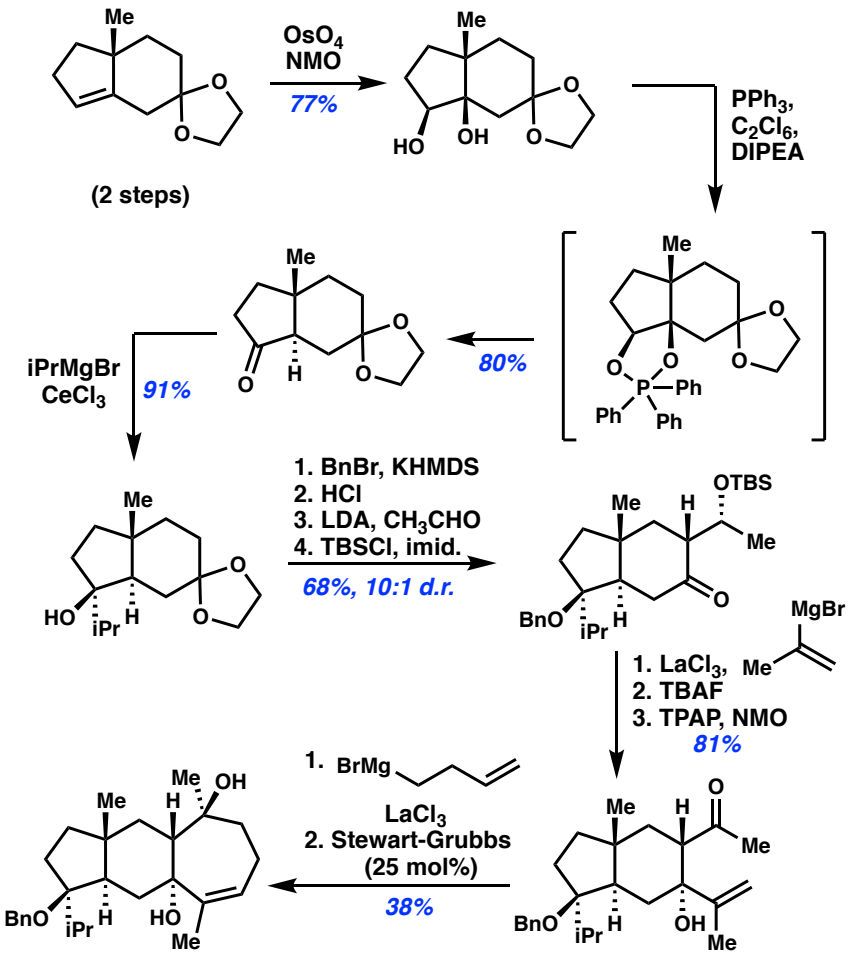
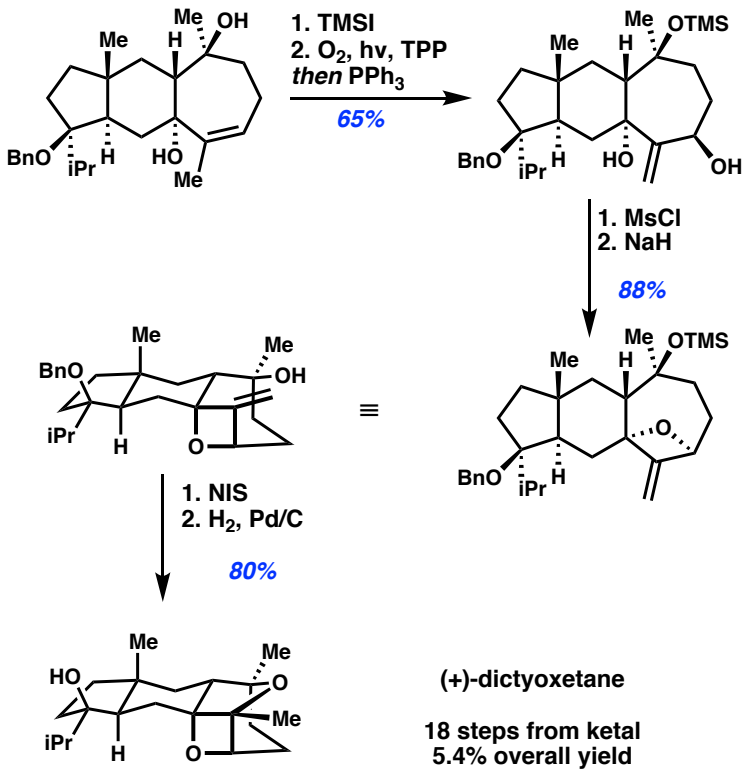
Magauer Synthesis (2016)



Endgame Strategy 2



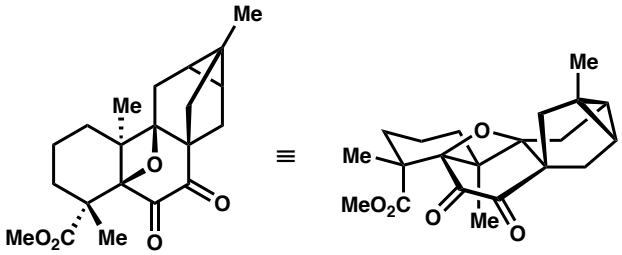
(+)-dictyoxetane

18 steps from ketal
5.4% overall yield

Grainger, Org. Biomol. Chem, 2012
Magauer, JACS, 2016

O-Heterocycles - Oxetanes

Mitrephorone A

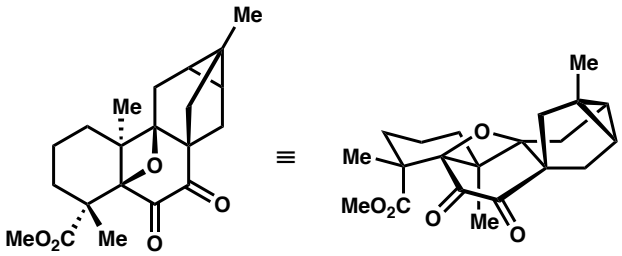


(—)-Mitrephorone A
Cytotoxic
Toxicity linked to oxetane moiety

Isolated 2005 from the
Bornean shrub *M. glabra*

O-Heterocycles - Oxetanes

Mitrephorone A

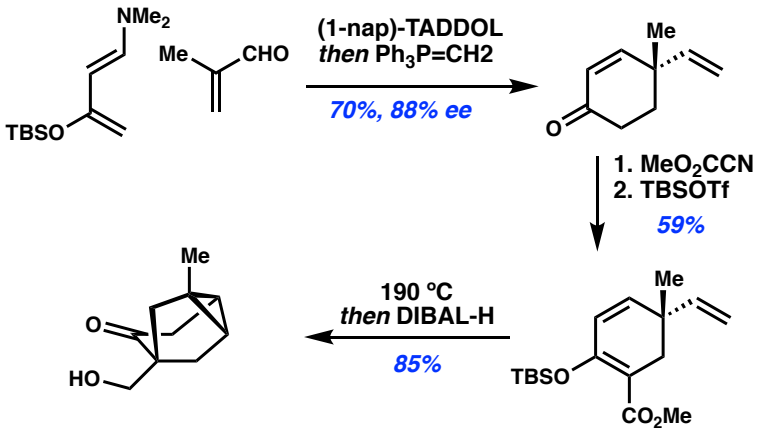


(—)-Mitrephorone A
Cytotoxic
Toxicity linked to oxetane moiety

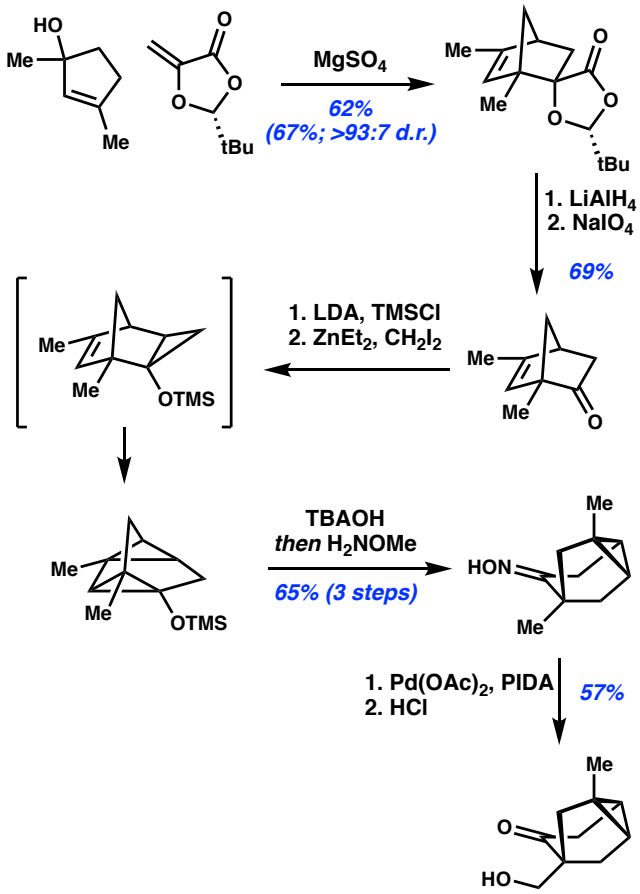
Isolated 2005 from the
Bornean shrub *M. glabra*

Carreira Synthesis

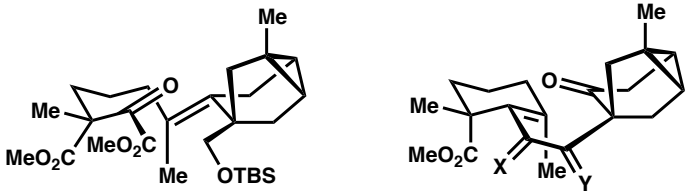
Construction of Tricyclooctane Core



Alternate Approach to Tricyclooctane - More Scalable, Improved ee



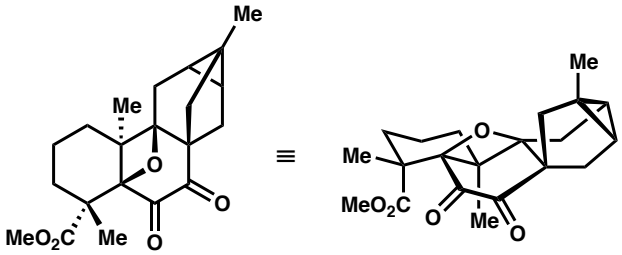
Unsuccessful Paterno-Büchi Substrates



X, Y = O *or* CH_2

O-Heterocycles - Oxetanes

Mitrephorone A

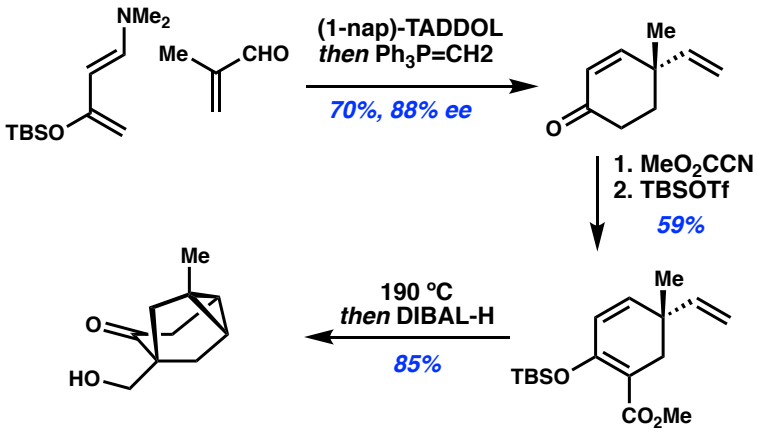


(—)-Mitrephorone A
Cytotoxic
Toxicity linked to oxetane moiety

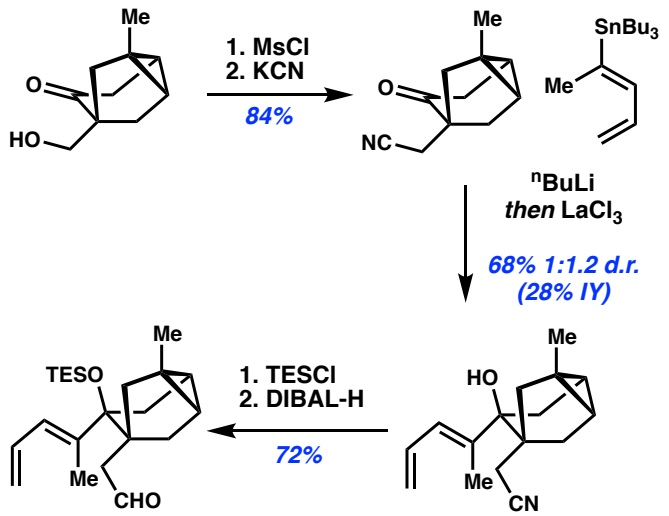
Isolated 2005 from the
Bornean shrub *M. glabra*

Carreira Synthesis

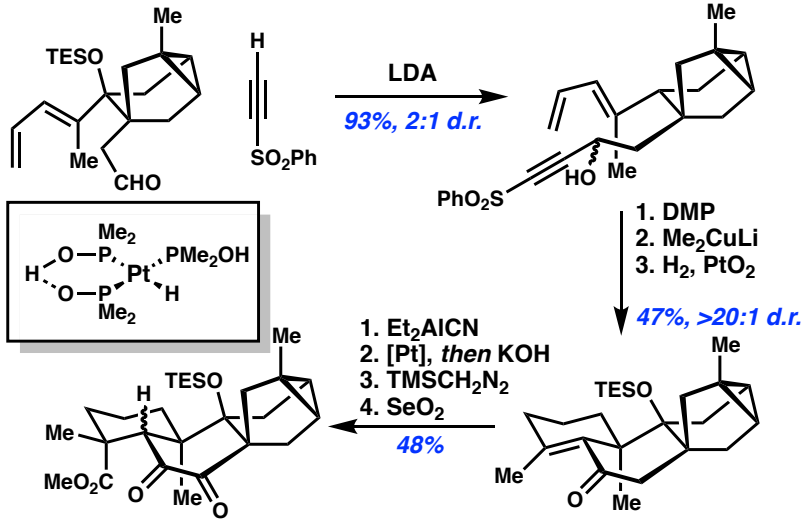
Construction of Tricyclooctane Core



Setup for 3rd Diels-Alder

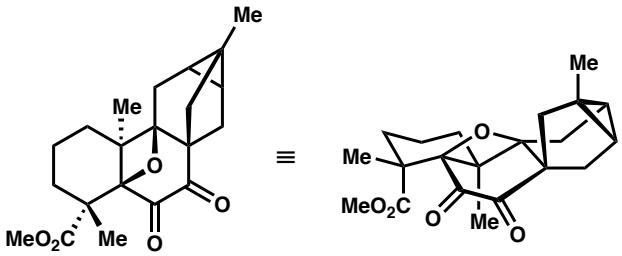


Completing the Carbon Skeleton



O-Heterocycles - Oxetanes

Mitrephorone A

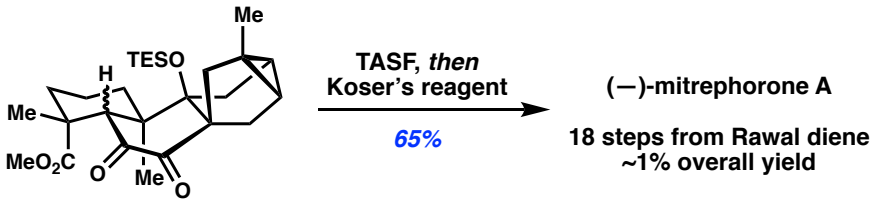


(—)-Mitrephorone A
Cytotoxic
Toxicity linked to oxetane moiety

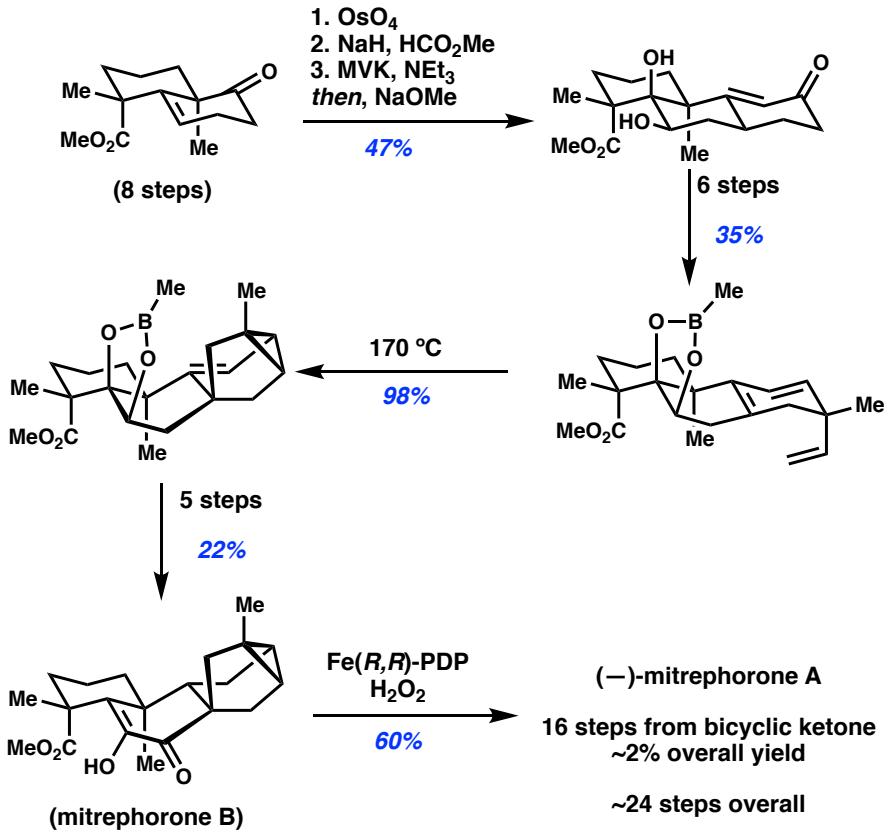
Isolated 2005 from the
Bornean shrub *M. glabra*

Carreira Synthesis

Endgame

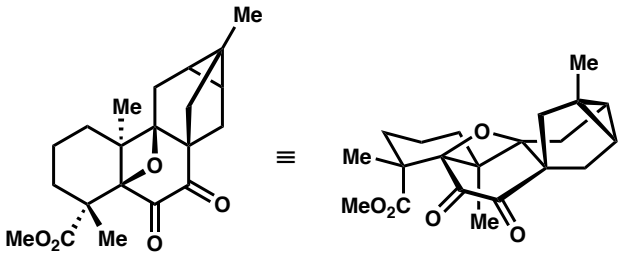


Magauer Synthesis



O-Heterocycles - Oxetanes

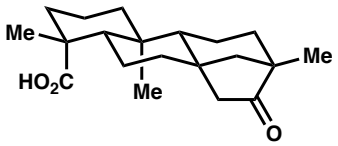
Mitrephorone A



(—)-Mitrephorone A
Cytotoxic
Toxicity linked to oxetane moiety

Isolated 2005 from the
Bornean shrub *M. glabra*

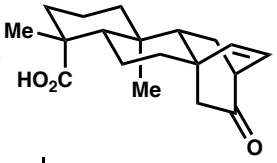
Renata Synthesis (Chemoenzymatic)



isosteviol
(1 step from stevioside

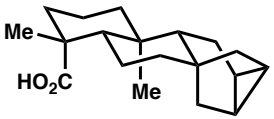
1. [O]
2. TfOH

81%



1. L-Selectride
2. BF_3OEt_2, Et_3SiH

"55%" (3 cycles of step 2)



1. [O]
2. PDC
3. [O]
4. CH_2N_2
***then* DMP**

46%

(—)-mitrephorone B

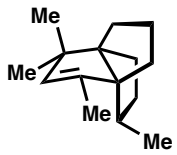
air
7 or 14 days

45 or 65%

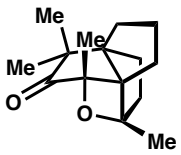
(—)-mitrephorone A

O-Heterocycles - Oxetanes

Dichrocephone B



Modhephene



Dichrocephone B
(Revised absolute stereochem.)

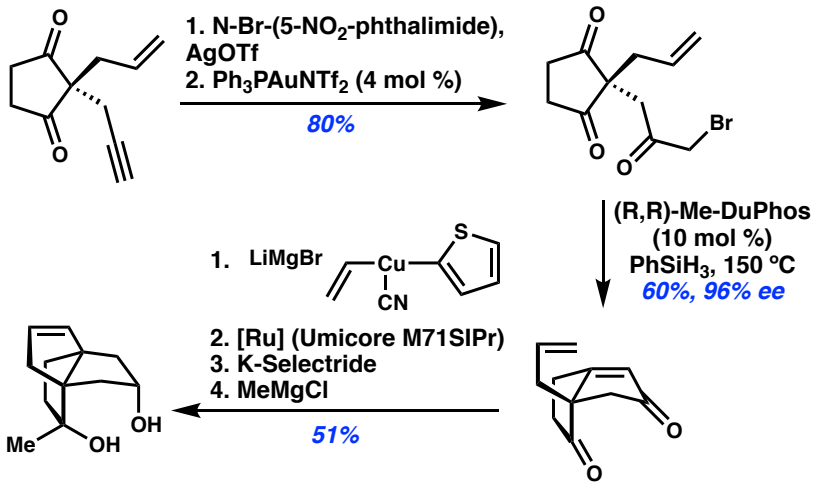
Isolated 2013
from D. benthamii

Rare carbocyclic propellanes

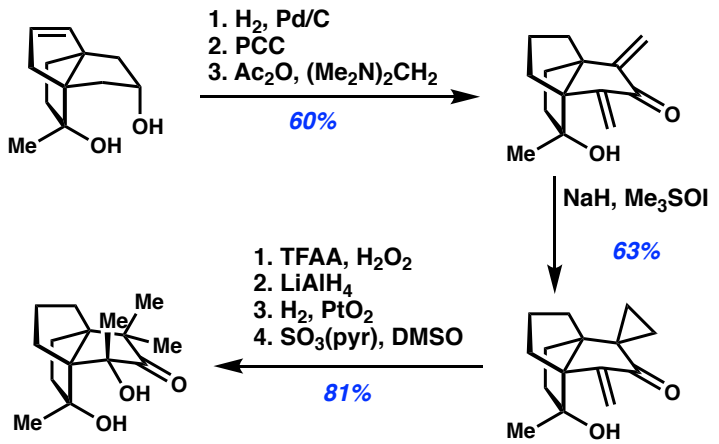
Dichrocephones are
most oxidized family members

Tantillo and Christmann Synthesis (*ent*-Dichrocephone B, 2018)

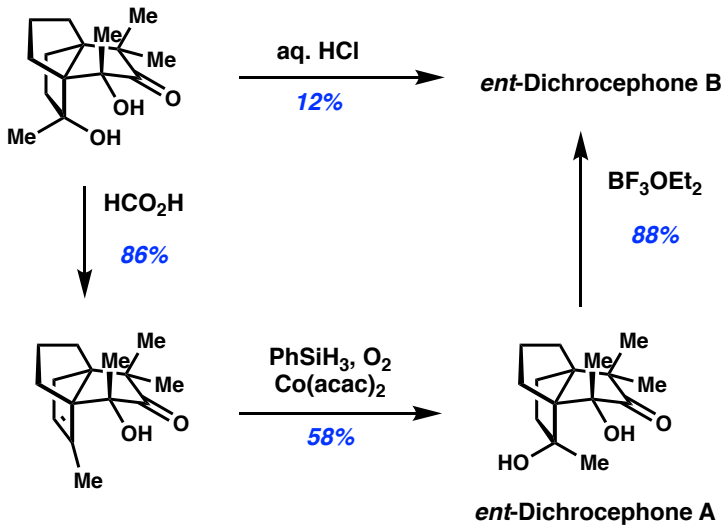
Propellane Core:



Functionalization to (nominal) Dichrocephone A:

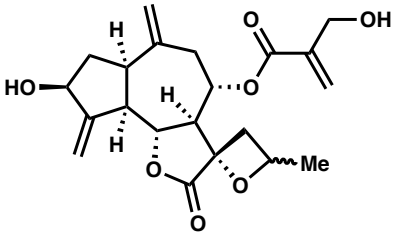


Endgame (and Structural Revision):



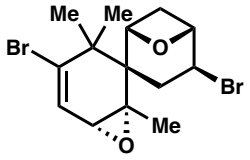
Food for Thought

Some Un-Synthesized Oxetane Natural Products:



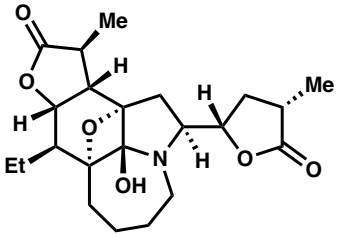
Clementein A/B

Isolated 1983
Confirmed by semi-synthesis



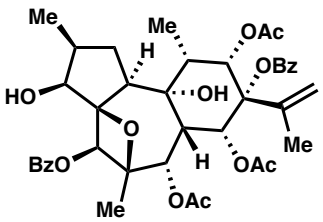
Compositacin D

Isolated 2017



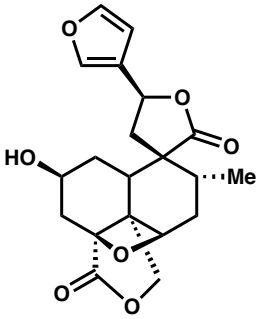
Stemona-amine B

Isolated 2013
(X-ray)



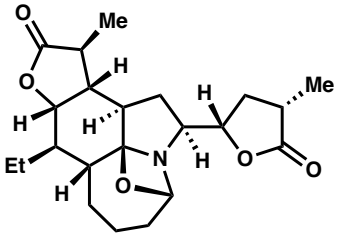
Trigochinin A

Isolated 2010
(X-ray)



Chamaedroxide

Isolated 1982
(X-ray)

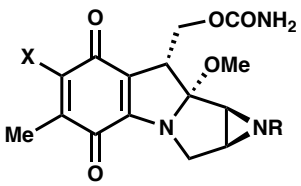


Sessifoline A

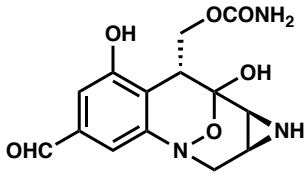
Reported 2007

N-Heterocycles - Aziridines

Mitomycins



Mitomycin A-D (X = OMe, NH_2; R = H, Me)



(+)-FR-900482

Antitumor Antibiotics from *Streptomyces*

"The complexity of the problem arises from the need to accomodate highly interactive functionality in a rather compact matrix and to orchestrate the chemical progression such as to expose and maintain vulnerable structural elements as the synthesis unfolds. *The synthesis of a mitomycin is the chemical equivalent of walking on egg shells.*" — Danishefsky

"… the compact tetracyclic framerwork of these fascinating alkaloids bears a deceptive guise of simplicity. Scores of competent and innocent synthetic organic chemists have been taken advantage of by the allure of the prospect of building these molecules…" — Robert Williams

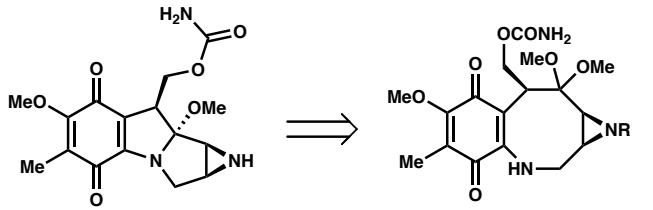
Williams, Chem. Rev., 2013

Key Challenges

— Facile elimination of -OMe

— Spring-Loaded Aziridine

— Quinone limits workable transforms

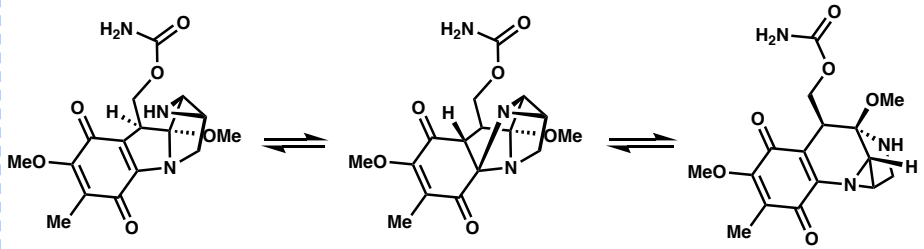


Mitomycin A

44 steps overall

4 members synthesized

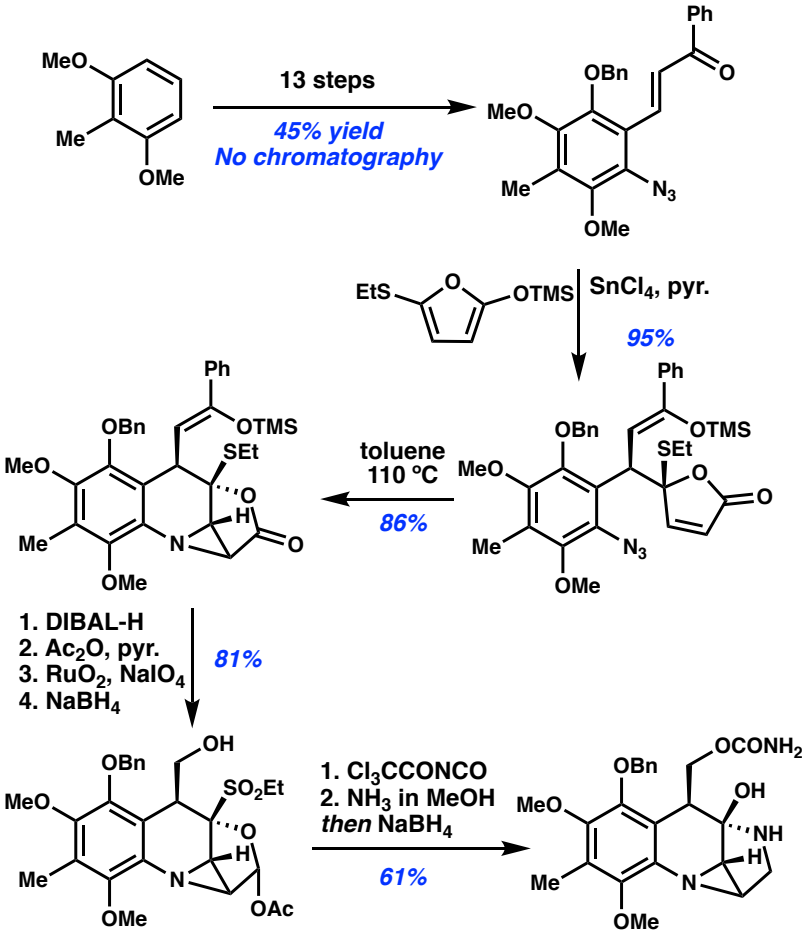
Kishi, JACS, 1977
Kishi, JACS, 1977
Kishi, Tet. Lett., 1977

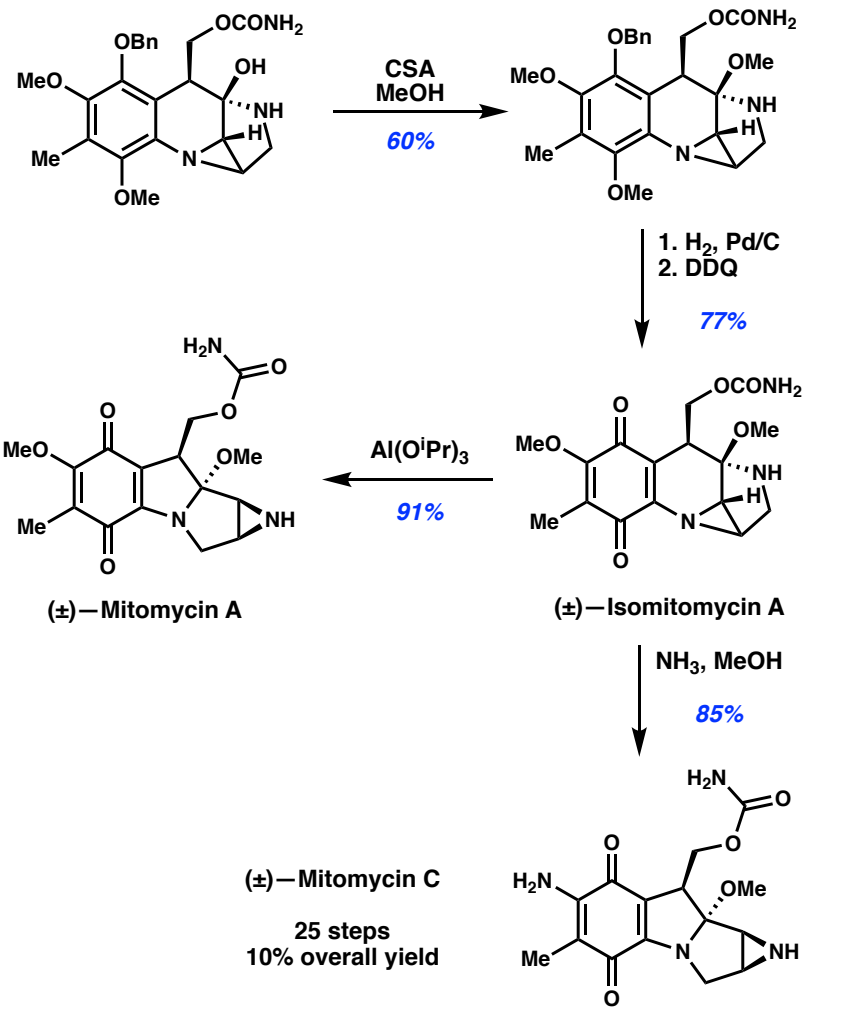


Mitomycin A — Albomitomycin — Isomitomycin

Kono, JACS, 1987

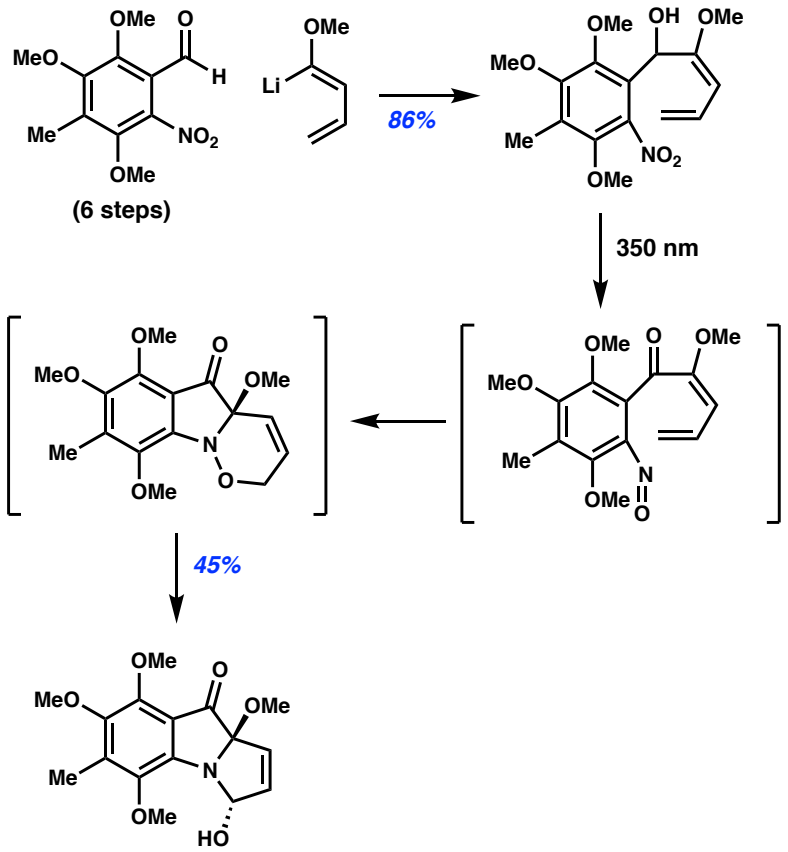
Fukuyama Synthesis of Mitomycin C

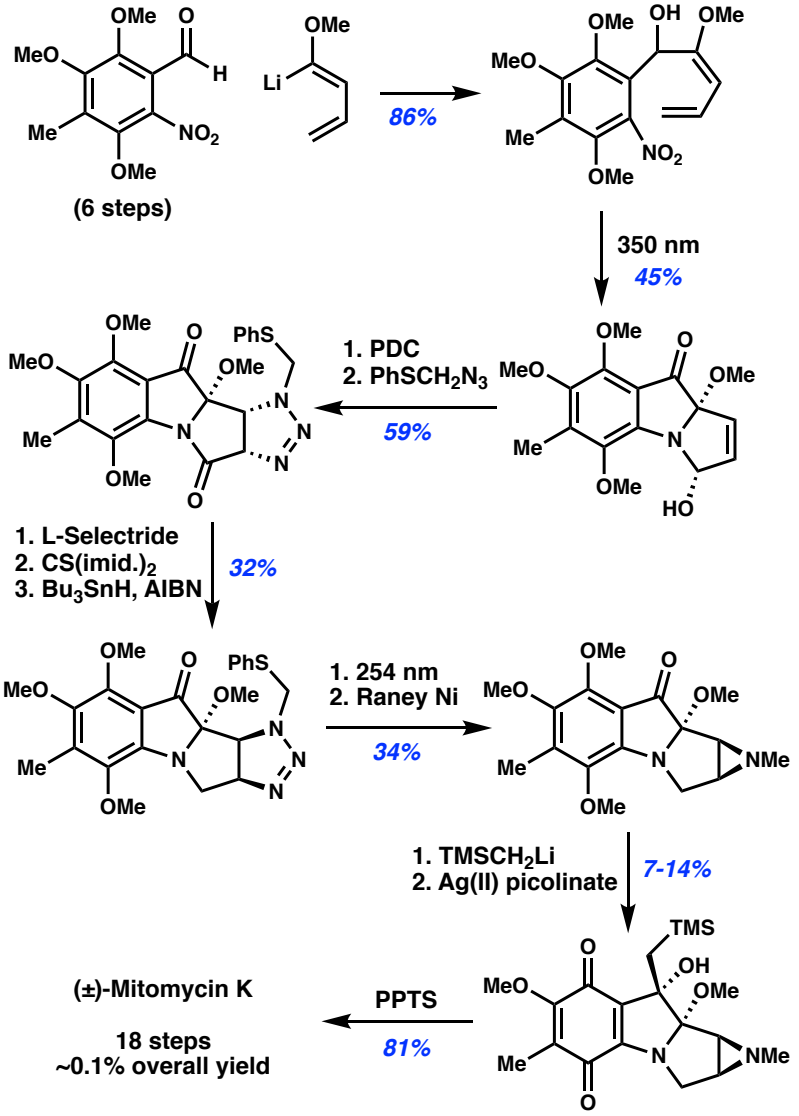




Fukuyama, Tet. Lett., 1986
Fukuyama, JACS, 1987
Fukuyama, JACS, 1989

Danishefsky Synthesis of Mitomycin K

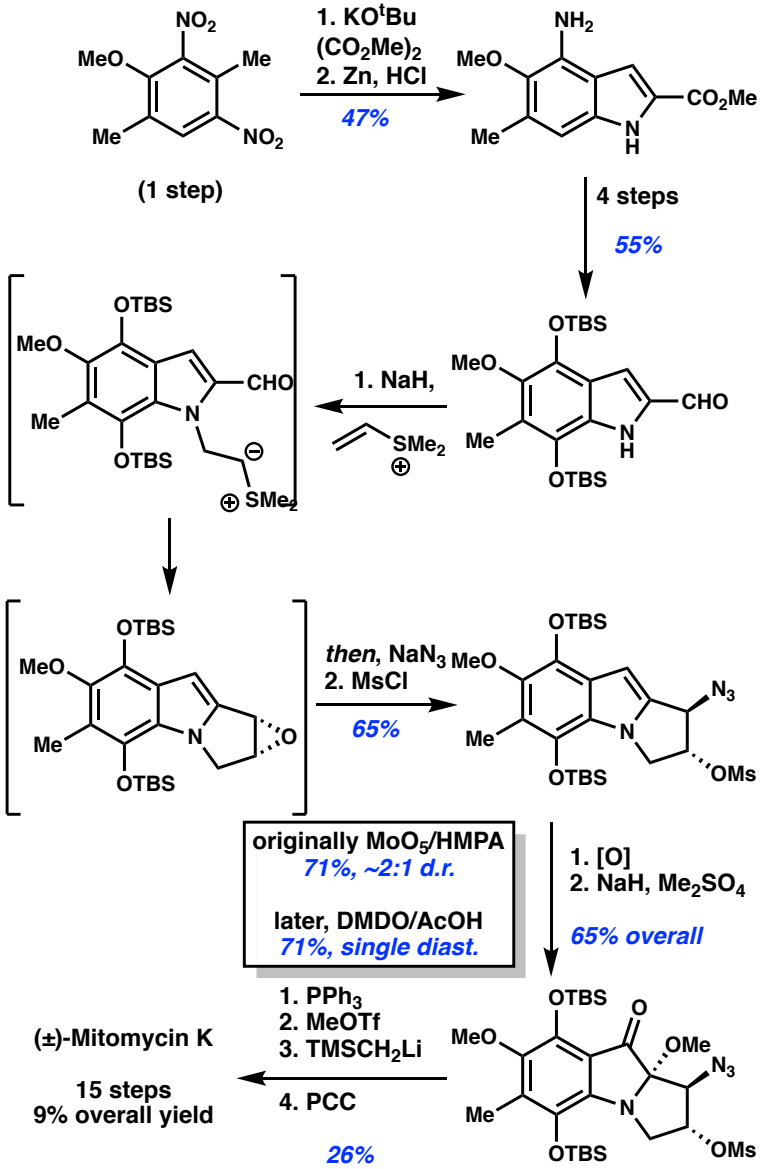




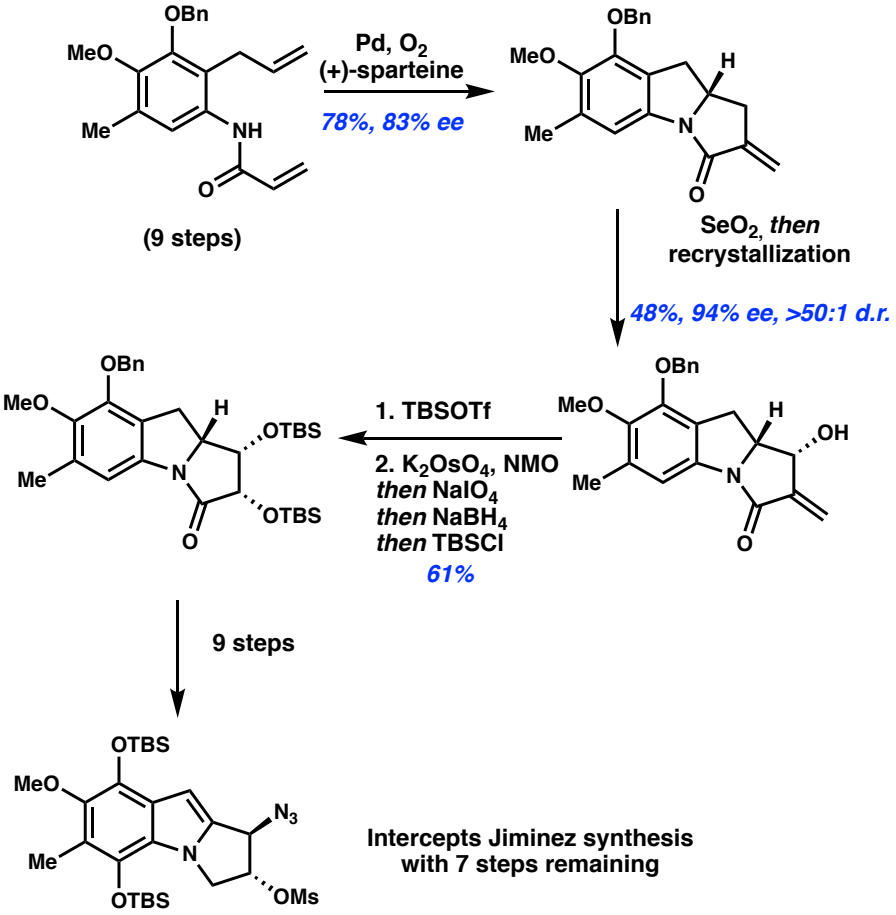
Danishefsky, JACS, 1991
Danishefsky, ACIE, 1992

N-Heterocycles - Aziridines

Jimenez Synthesis of Mitomycin K



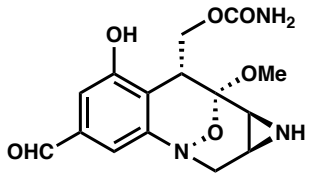
Yang Synthesis of Mitomycin K (enantioselective)



Jimenez, J. Org. Chem., 1996
Jimenez, Tet. Lett., 1996
Jimenez, Org. Lett., 2003
Yang, ACIE, 2017

N-Heterocycles - Aziridines

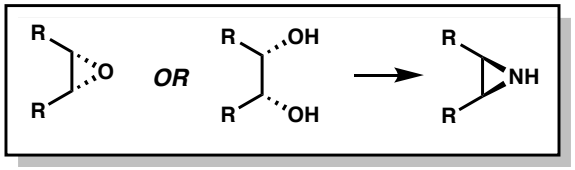
(+)-FR-900482



Dynamic Hemiacetal Stereochemistry

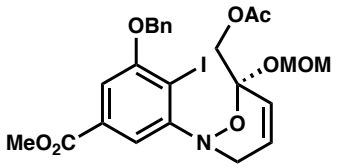
Much less elimination-prone

9 completed syntheses



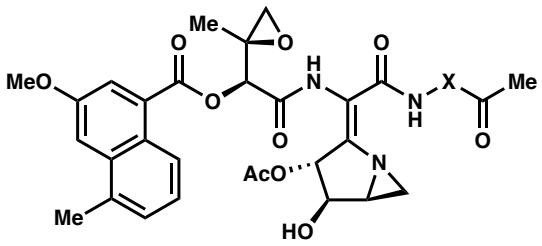
Primary differences are in access to 8-membered ring intermediate for ketalization

Danishefsky's Route (1995) stands out through sequential 6-membered ring constructions



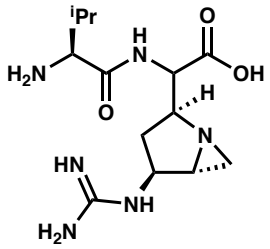
N-Heterocycles - Aziridines

Carzinophilin and Related Bicycles



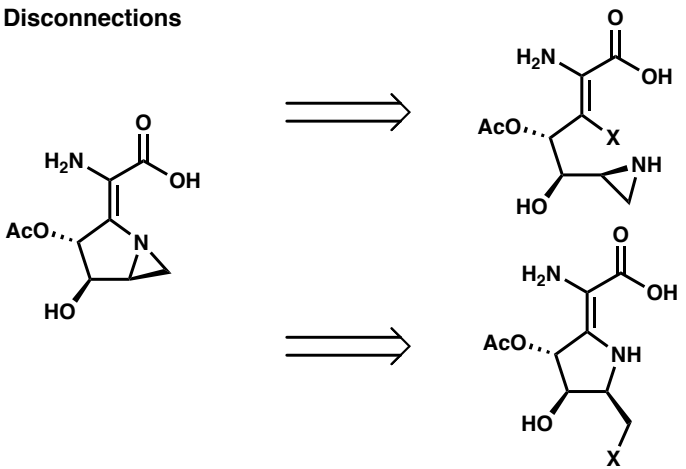
Carzinophilin (X = C=CHOH)
aka Azinomycin B
Isolated 1984
from Streptomyces
Antitumor Antibiotic
(Major Groove Crosslinker)

Azinomycin A (X = CH_2)
Isolated 1986

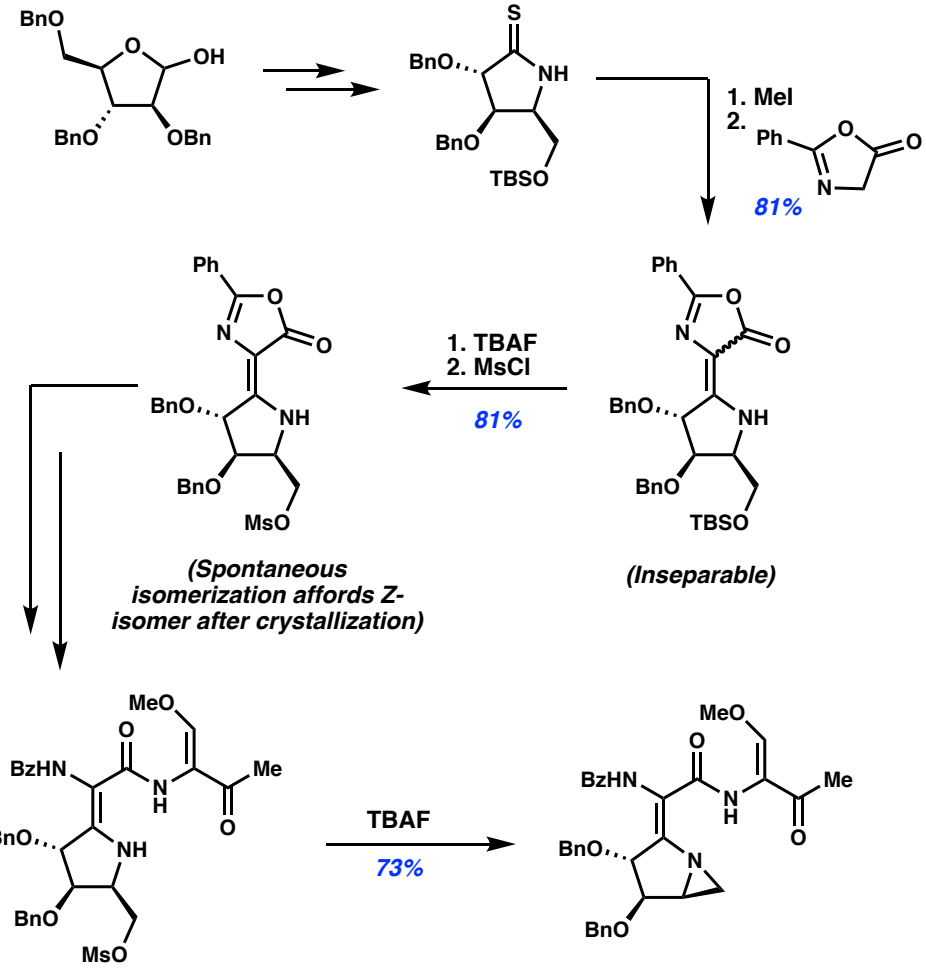


Ficellomycin
Isolated 1976
from Streptomyces ficellus

Primary Disconnections



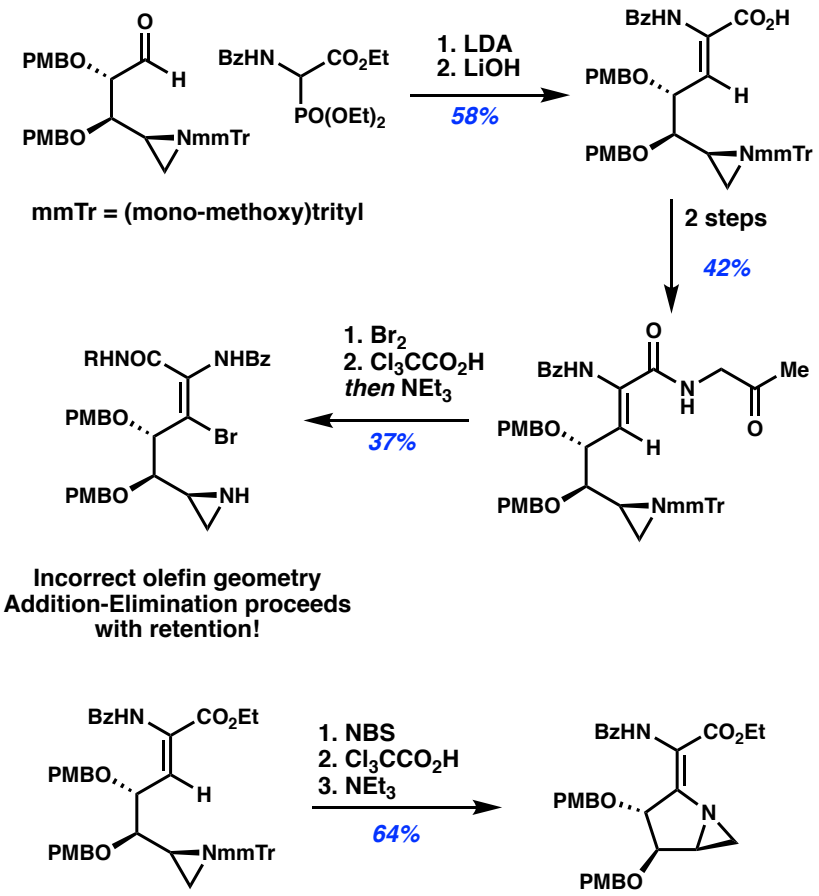
3-Exo Tet Approach:



Terashima, Tet. Lett. 1994
Terashima, Tetrahedron 2003

N-Heterocycles - Aziridines

Addition-Elimination Approach:

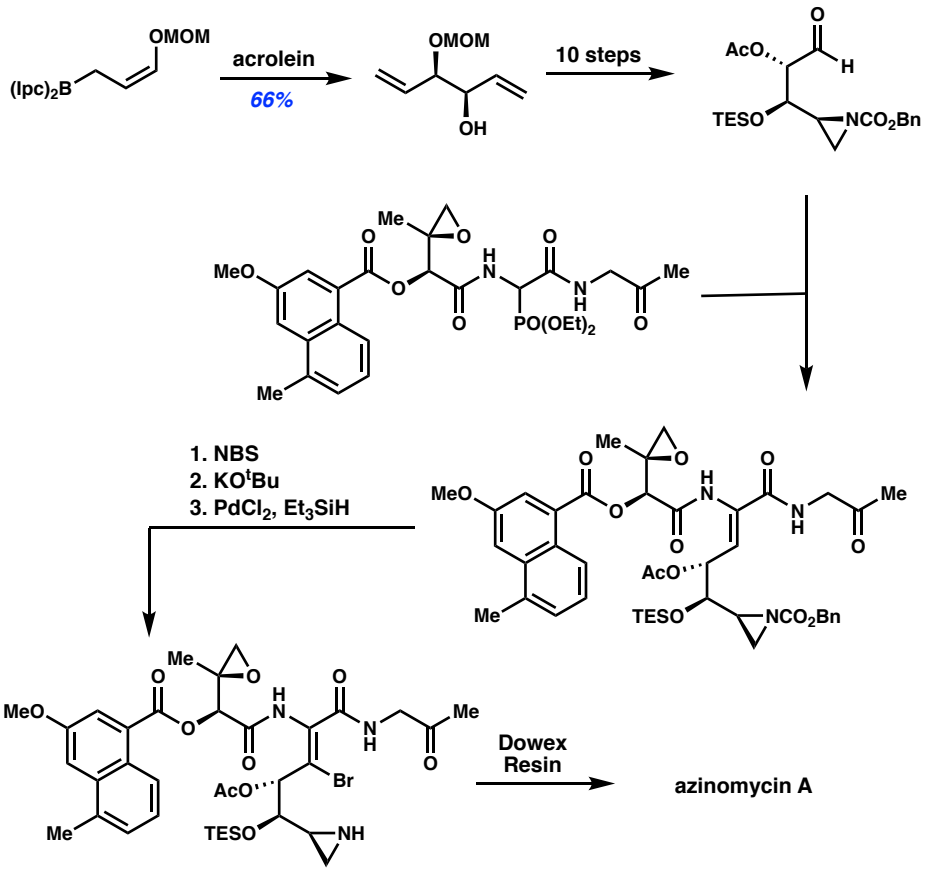


mmTr = (mono-methoxy)trityl

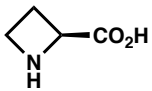
Incorrect olefin geometry
Addition-Elimination proceeds with retention!

3 similar approaches from Coleman, et al.

Coleman's Completed Synthesis:



N-Heterocycles – Amino Acids

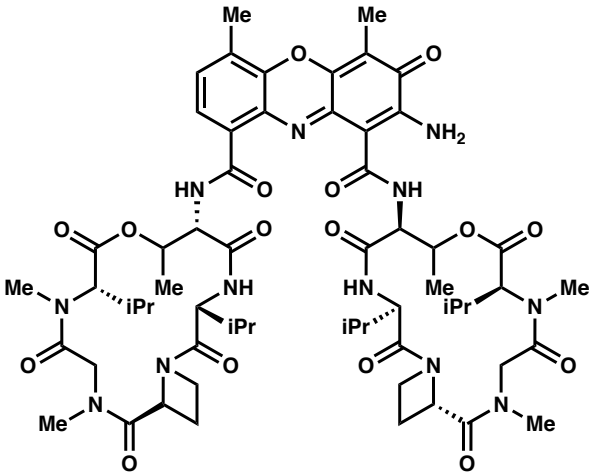


Azetidine-2-Carboxylic Acid

Isolated 1955 from *C. majalis*
(Lily-of-the-valley)

Biosynthesis from SAM cofactor

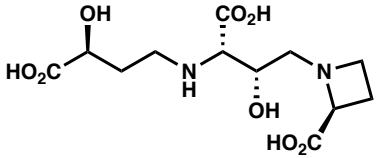
Fowden, Nature 1955
Leete, JACS 1964



Azetomycin

Quasi-natural analog of Actinomycin D
Produced by *S. antibioticus* when
cultured with AzC

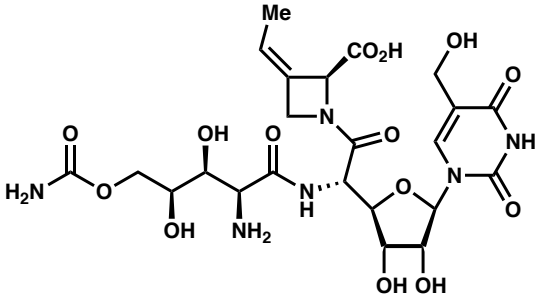
Formica, Antimicrob. Agents Chemother. 1976



Mugineic Acid
Phytosiderophore

Isolated 1976
7 members in family

Takemoto, et al. Proc. Jpn. Acad. Ser. B 1978



Polyoxin A
Antifungal/Antibiotic

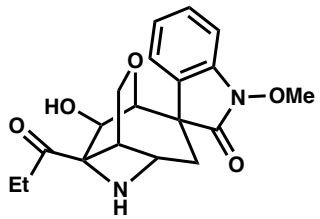
12 members in family
Isolated 1968 from Streptomyces

Olefin Stereochem. revised 1993

Isono, et al. Agric. Biol. Chem. 1966
Isono, et al. JACS 1969

N-Heterocycles - Azetidines

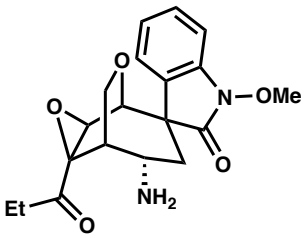
Gelsemoxonine



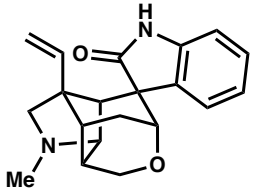
Gelsemoxonine

Isolated 1991
Revised 2003 (X-Ray)

Syntheses 2011, 2013, 2018



Proposed Structure



Gelsemine

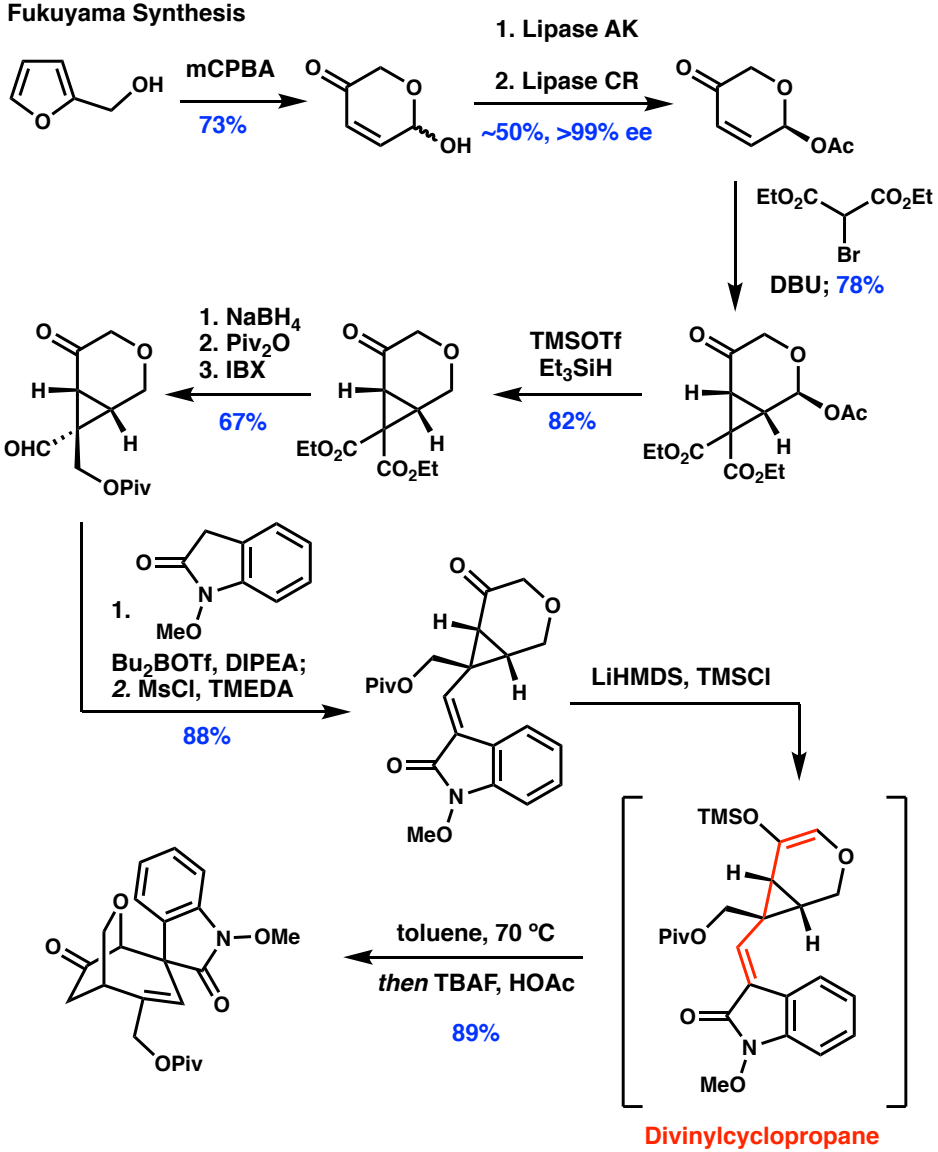
Fukuyama (2011) - 23 steps, epoxide opening

Carreira (2013) - 21 steps, isoxazolidine ring contraction

Ma (2018) - 9 steps, epoxide opening

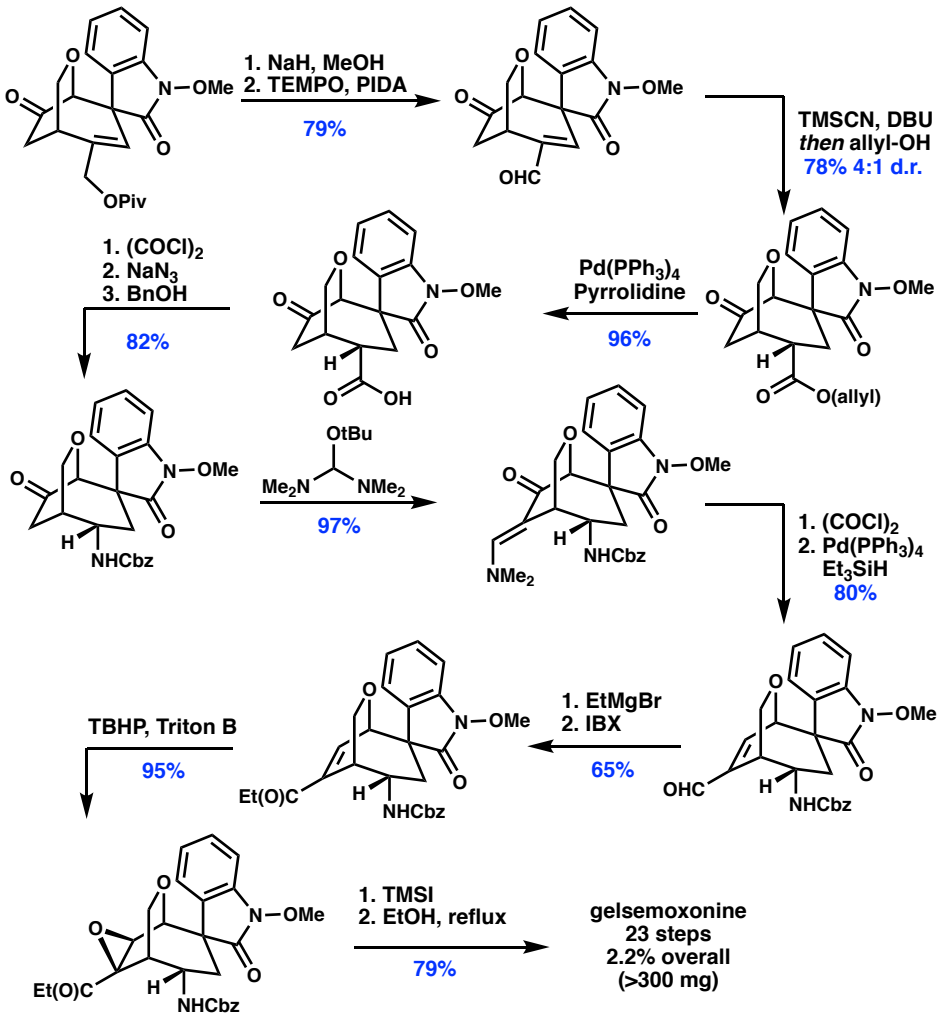
Cordell, Phytochemistry, 1991
Kitajima, et al. Org. Lett. 2003

Fukuyama Synthesis

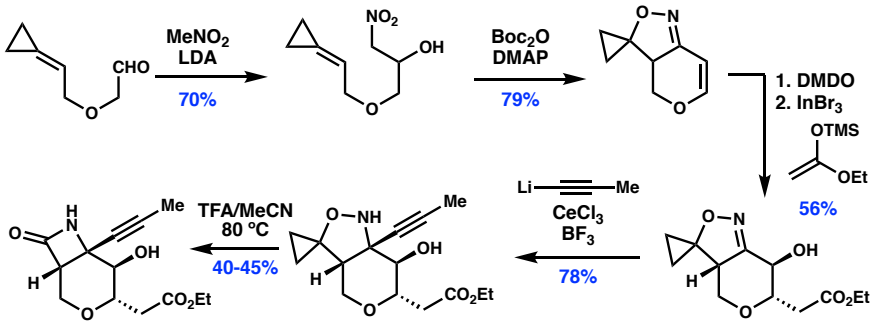


Fukuyama, JACS, 2011

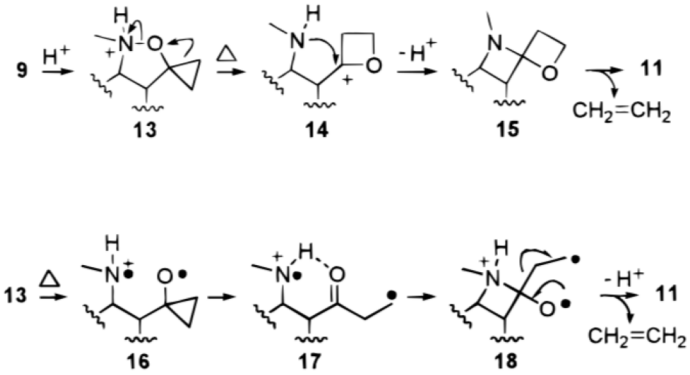
N-Heterocycles - Azetidines



Fukuyama, JACS, 2011

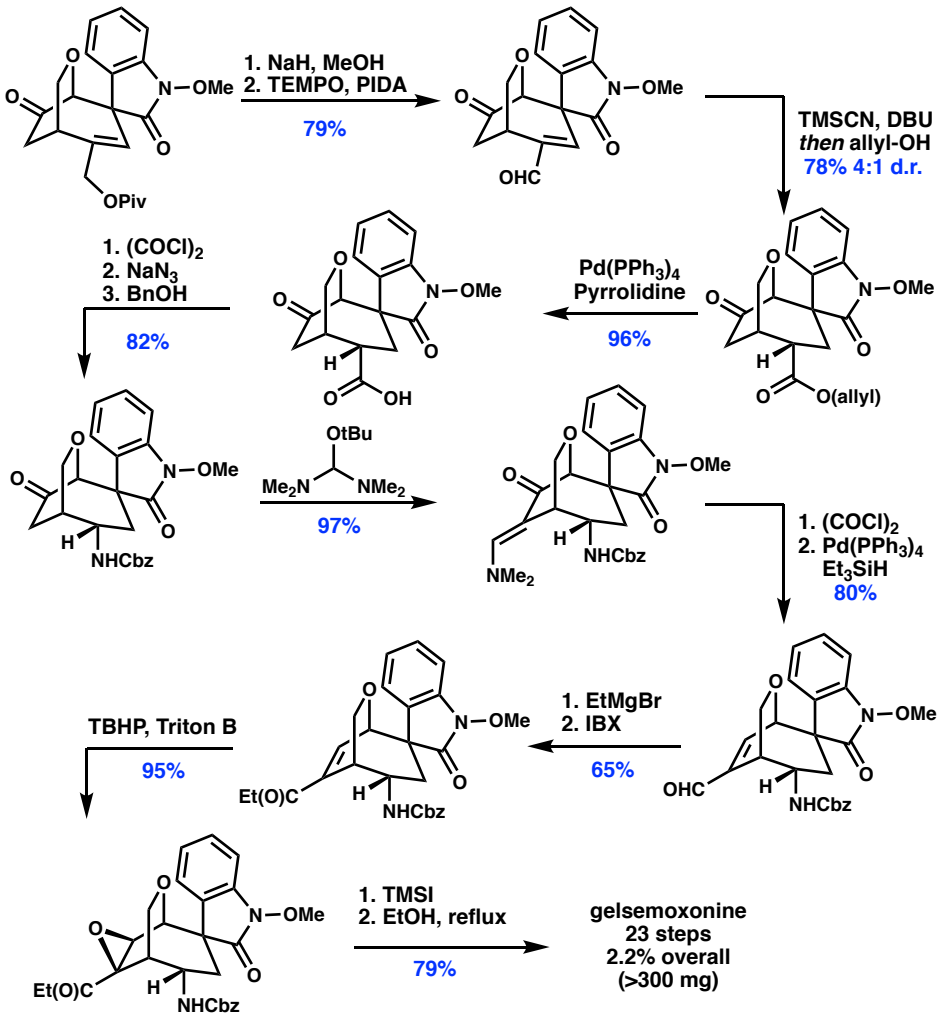


Carreira, JACS, 2013

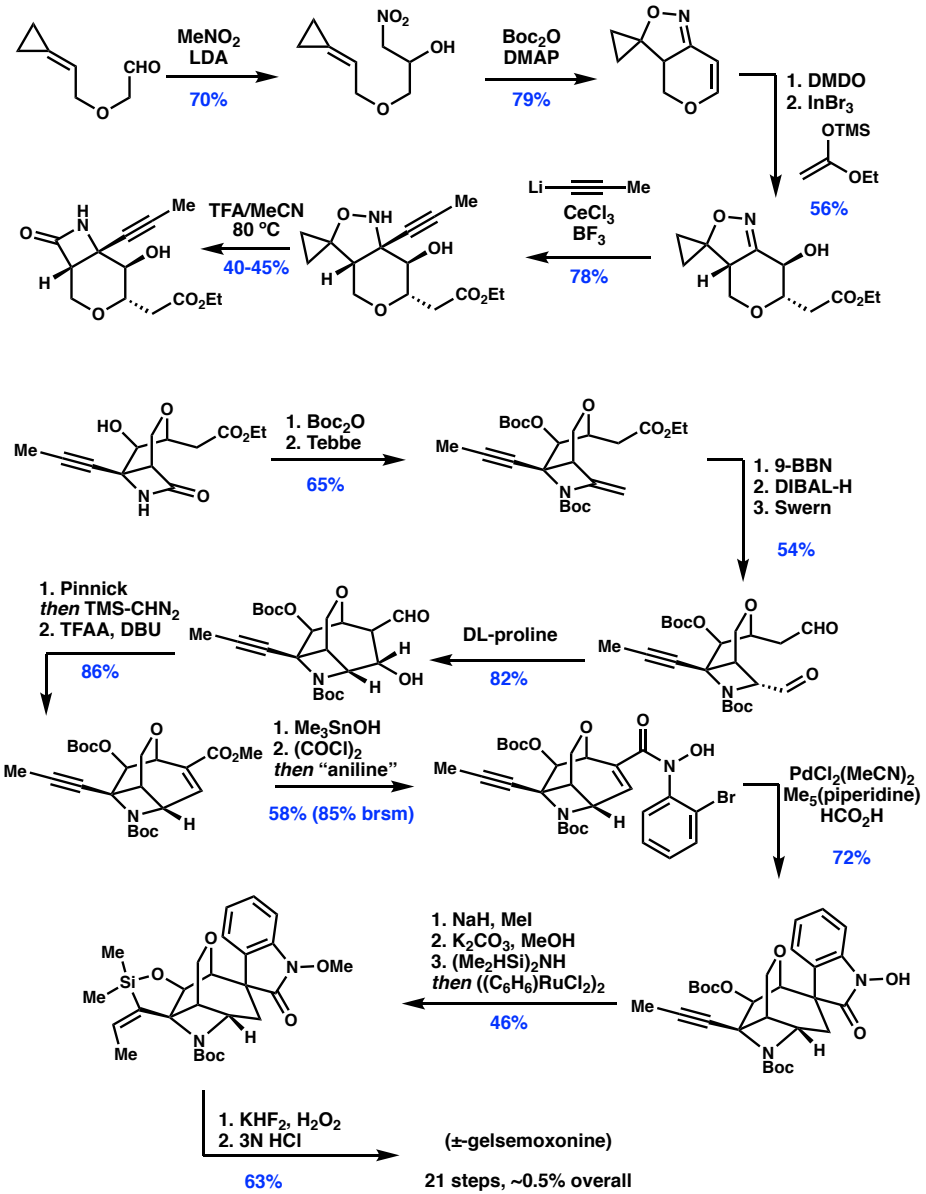


Brandi, JACS, 2000

N-Heterocycles - Azetidines

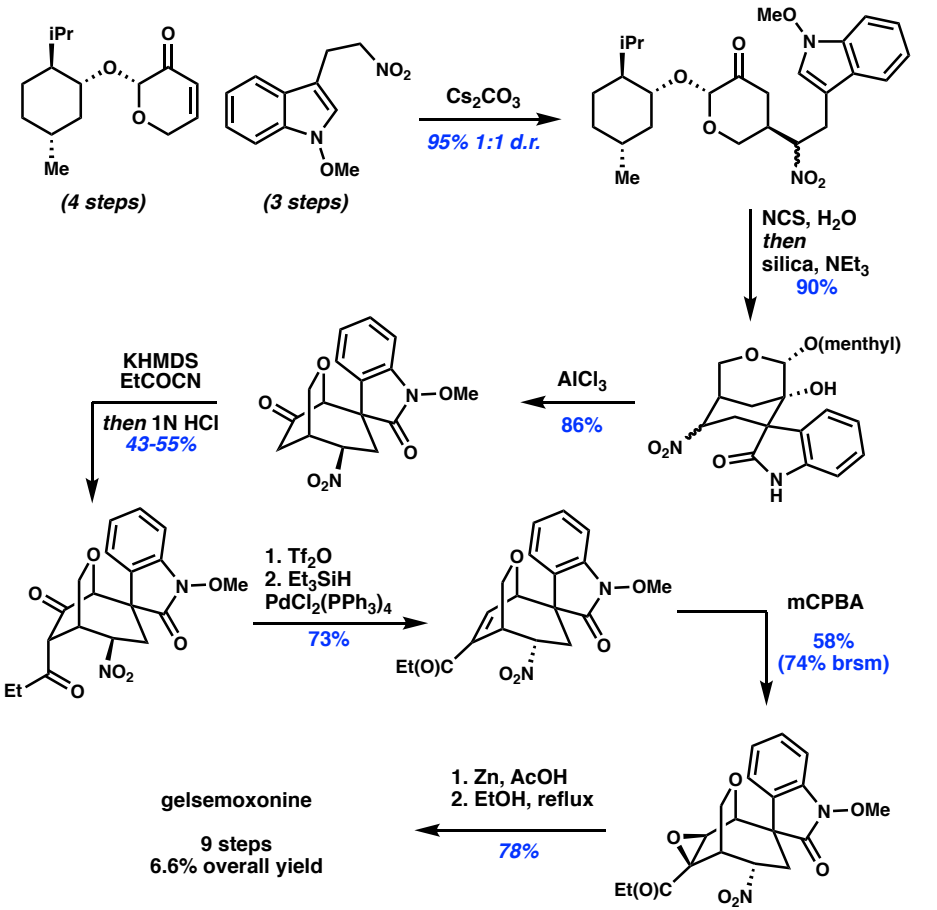


Fukuyama, JACS, 2011



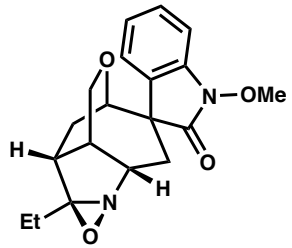
Carreira, JACS, 2013
Carreira, JACS, 2015

N-Heterocycles - Azetidines



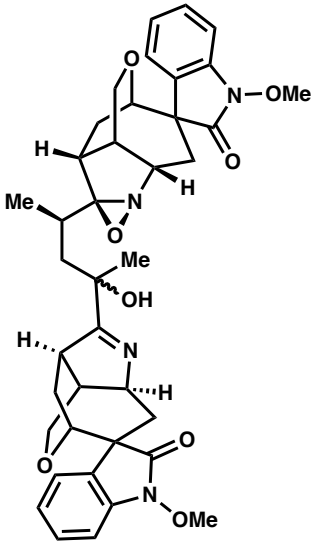
Ma, JACS, 2018

Other unusual *Gelsemium* alkaloids - Oxaziridines (!)



Gelseziridine

Isolated 2011

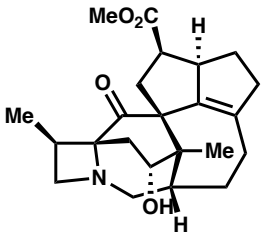


Geleganamide A & B

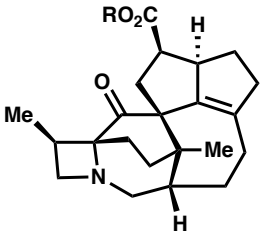
Isolated 2013

Moderate (~10 uM) Anti-inflammatory Activity

Daphniphyllum Alkaloids



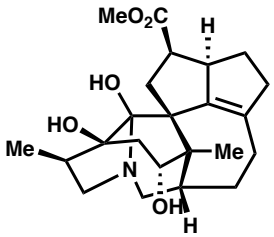
Calydaphinone
Zhu and Hao, Org. Lett. 2007
(no antitumor activity)



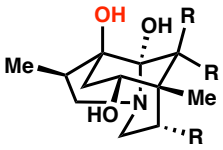
Calyciphylline C (R = Me)
Calyciphylline J (R = H)

Kobayashi, Tet. Lett. 2007
Tetrahedron 2008

Formal 1,2 Shift



≡

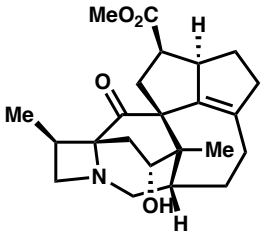


[O] analogue of
yunnandaphnine B

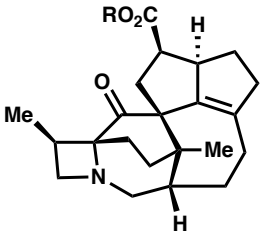
Synthesis of yunnandaphnine B
or other yuruzimines has not been achieved!

N-Heterocycles - Azetidines

Daphniphyllum Alkaloids



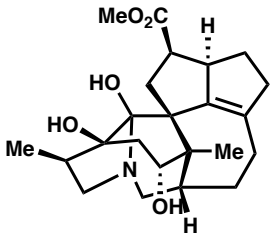
Calydaphinone
Zhu and Hao, Org. Lett. 2007
(no antitumor activity)



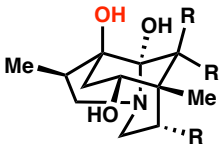
Calyciphylline C (R = Me)
Calyciphylline J (R = H)

Kobayashi, Tet. Lett. 2007
Tetrahedron 2008

Formal 1,2 Shift



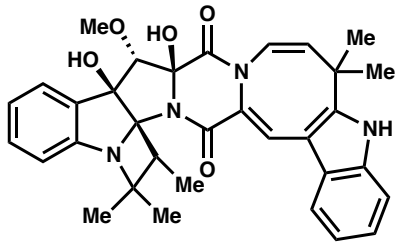
≡



[O] analogue of
yunnandaphnine B

Synthesis of yunnandaphnine B or other yuruzimines has not been achieved!

Okaramines



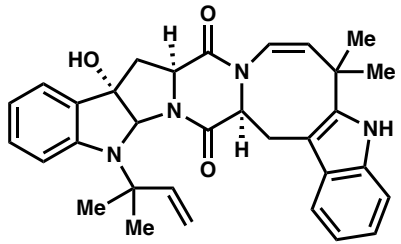
Okaramine B
Isolated 1988, from Penicillium simplicissium
Insecticide - activates glutamate-dependent anion channels

Four other related members feature 4-membered ring motif

No syntheses of azetidine-containing members

No syntheses of azetidine-containing members

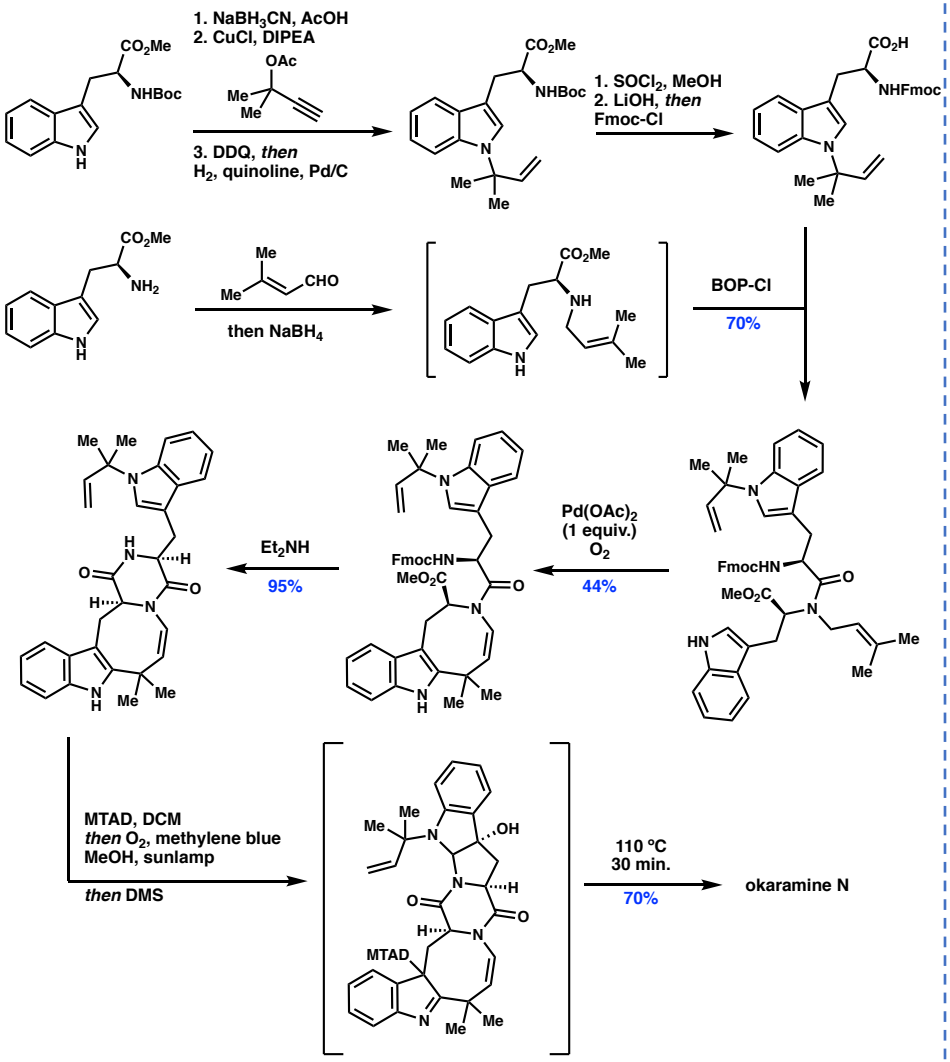
First "in-family" synthesis of Okaramine N (Corey, JACS, 2003)



"In many respects, the development of the synthesis of [okaramine N] was similar to finding a way up a vertical cliff that offers just a limited number of small cracks and handholds"

N-Heterocycles – Azetidines

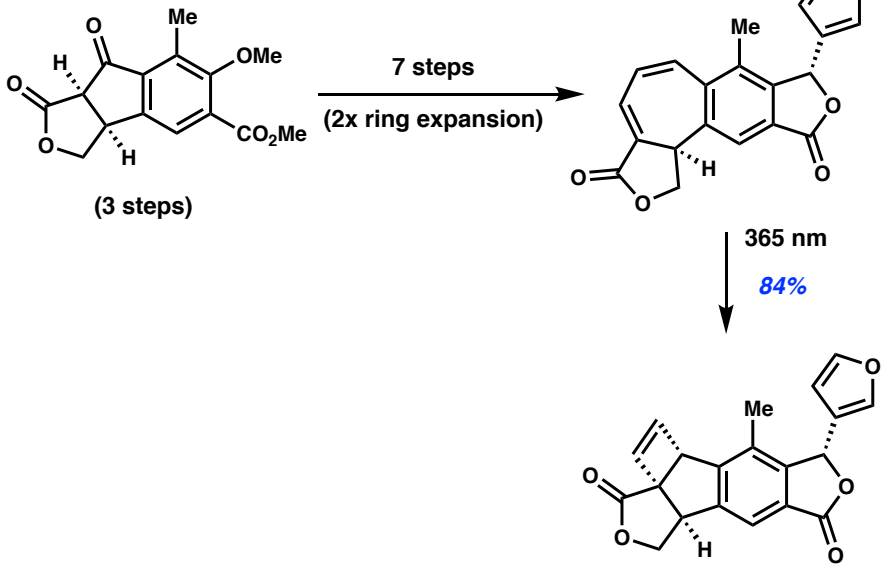
Corey Synthesis of Okaramine N



Corey, JACS, 2003

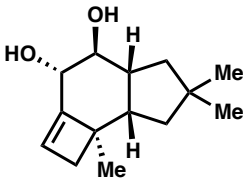
Carbocycles – Some Cyclobutene Snippets

Synthesis of Salvileucalin C



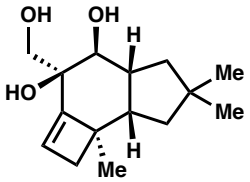
Food for Thought - "Unusual" Cyclobutenes

Double bond in "exo" position



Sulcatine A

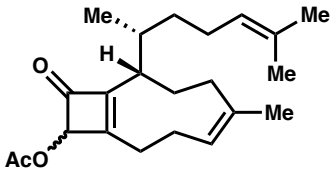
Isolated 1987



Sulcatine B

Isolated 1992

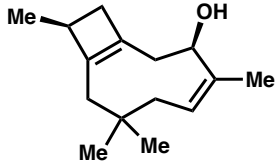
Double bond at ring fusion



(iso-) acetylcoriacenone

Isolated from brown algae
P. coriaceum (1983)
and D. ligulatus (1993)

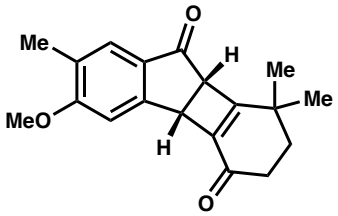
"Cytotoxic" (~12 μM EC_{50})



capillosanol

Isolated from soft coral
S. capillosa (2009)

No cytotoxicity



Neofavelanone

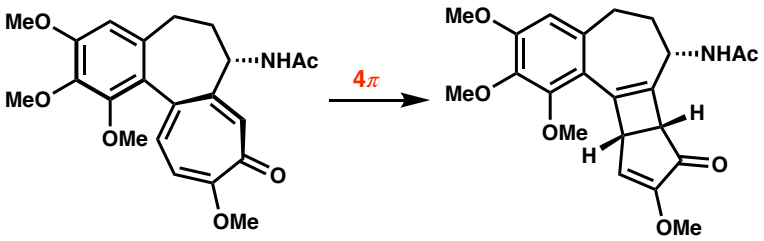
Isolated from Brazilian plant
C. phyllacanthus (1992)

No known biological activity

Carbocycles - Some Cyclobutene Snippets

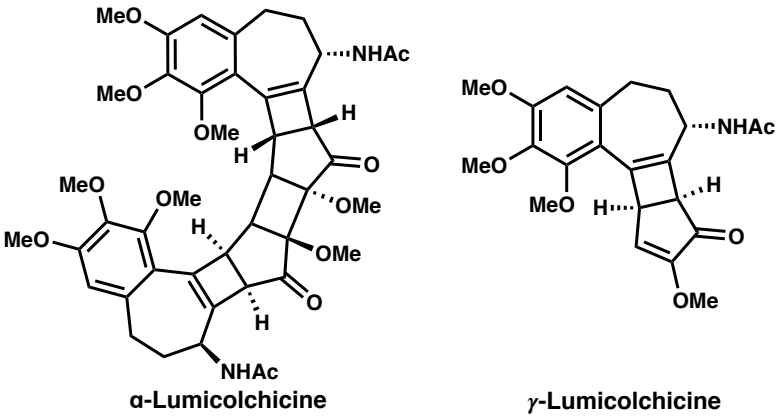
Double bond at ring fusion

Lumicolchicine & Derivatives

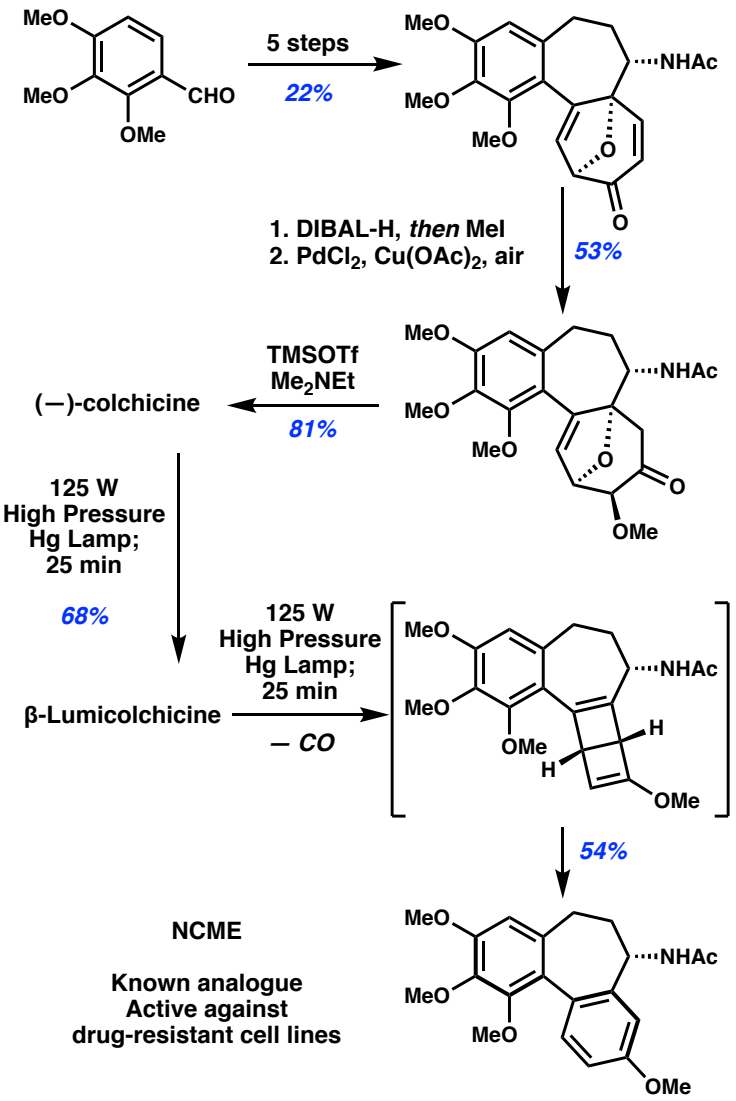


Colchicine β-Lumicolchicine

Photochemical 4Pi was known, but required two months and additionally produces a mixture of products:



α-Lumicolchicine γ-Lumicolchicine

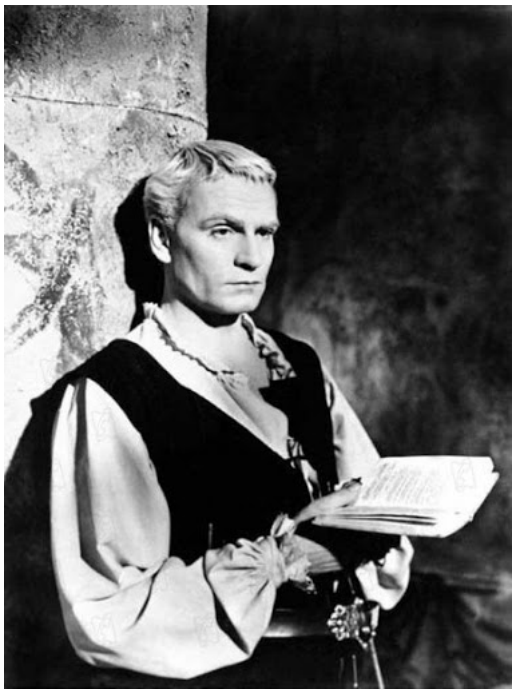


NCME

Known analogue
Active against
drug-resistant cell lines

Li, Org. Lett., 2017

Small Ring Natural Products – Heterocycles Edition



“There are more things in Heaven and Earth, Horatio, than are dreamt of in your philosophy”

- Hamlet, teaching Horatio about natural products

Small (3- and 4-membered) Rings in NPs*:

Carbocycles
- Cyclopropanes: 7039
- Cyclobutanes: 2154
- Cyclobutenes: 50

O-Heterocycles
- Epoxides: 13962
- Oxetanes: 450
    - Roughly half are taxanes
- Beta Lactones: 140

N-Heterocycles
- Aziridines: 50
- Azetidines: 61
- Beta Lactams: 243

Thiiranes: 11
Thietanes: 10

Dictionary of Natural Products

***questionably responsible counting**