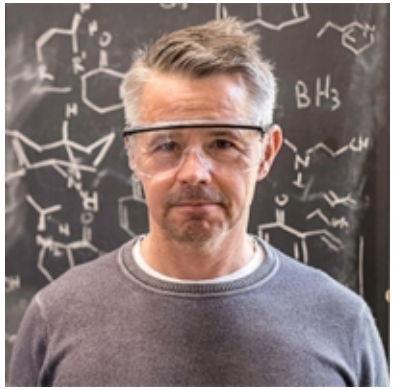
Andrew G. Myers

Meghan Baker

Biography



1981: B.S. Chemistry
Advisor: Prof. William R. Roush (Synthesis)
"Antibiotic X-14547A: Total Synthesis of the Right-Hand Half"

1981-1986: Ph.D., Chemistry, Harvard University
Advisor: Prof. E. J. Corey
6 publications, limonoid system and antheridium-inducing factor

Independent Career:

1986-1994: Assistant and Associate Professor, Caltech

1994-1998: Full Professor, Caltech

1998-2002: Full Professor, Harvard

2007-2010: Department Chair, Harvard
Department of Chemisty and Chemical Biology

Now: Amory Houghton Professor of Chemistry

2006: Opening of Tetraphase Pharmaceuticals

Awards (not listed online)**:**
- Arthur C. Cope Scholar Award (1993)
- ACS Award for Creative Work in Synthetic Organic Chemistry (2002)

154 Total Publications, 9 Patents

Research Program:

"Chemical synthesis directed towards amelioration of problems in human health"

Five classes of molecules currently being pursued:
1. Avrainvillamides and Stephacidin B - antiproliferative
2. Cortistatins - anti-angiogenic
3. Daphniglaucins - anti-cancer
4. Tetracyclines - antibiotic
5. Trioxacarcins - antiproliferative

Students in academia:
David Gin (Sloan Kettering), Mo Movassaghi (MIT), Seth Herzon (Yale), Scott Schaus (Boston U.) Ian Seiple (UCSF), Dionicio Siegel (UCSD)

Current Group (according to group website):
6 postdocs; 5 graduate students, 1 masters

Top five cited papers:
1. "Pseudophedrine as a practical chiral auxiliary for the synthesis of highly enantiomerically enriched carboxylic acids, alcohols, aldehydes, and ketones"
J. Am. Chem. Soc. **1997**, 118, 28, 6496-6511

2. "Development of a decarboxylative palladation reaction and its use in a Heck-type olefination of arene carboxylates"
J. Am. Chem. Soc. **2002**, 124, 38, 11250-11251

3. On the mechanism of the palladium(II)-catalyzed decarboxylative olefination of arene carboxylic acids
J. Am. Chem. Soc. **2005**, 127, 29, 10323-10333

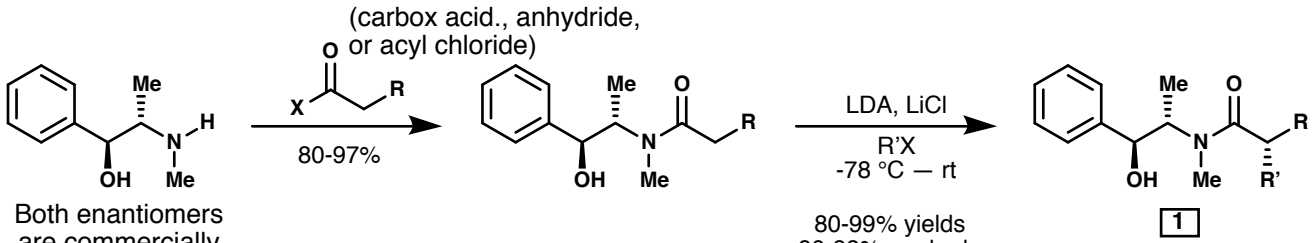
4. A Mechanism for the Nucleophilic Activation of Neocarzinostatin
Tett. Lett. **1987**, 28, 39, 4493-4496

5. New and Stereospecific Synthesis of Allenes from Propargylic Alcohols
J. Am. Chem. Soc. **1996**, 118, 18, 4492-4493

Shenvi Lab Group Meeting
July 24th, 2017

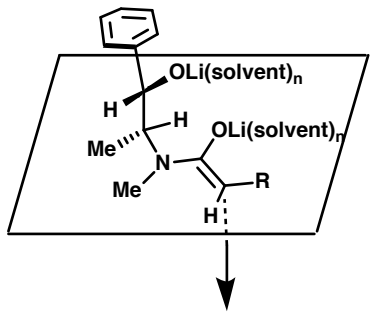
Pseudoephedrine-A Practical Chiral Auxiliary for Asymmetric Synthesis

Meghan Baker

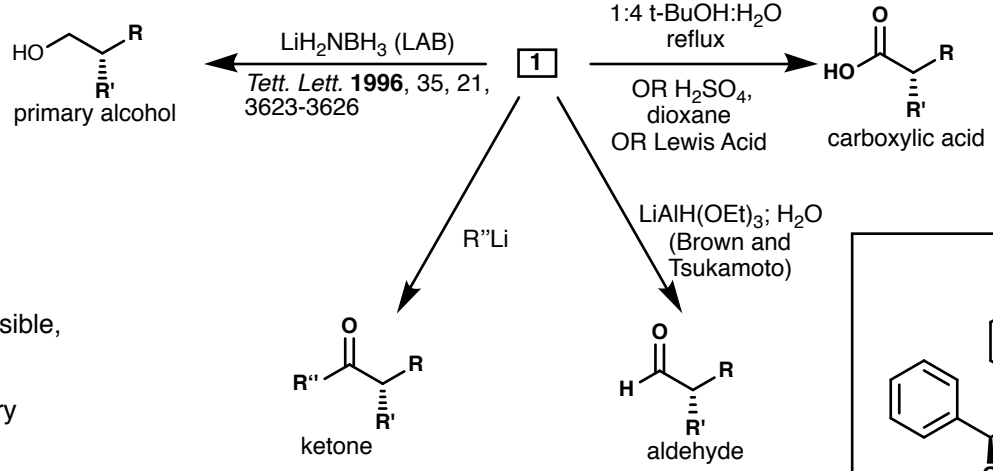


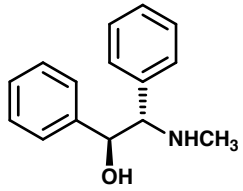
Both enantiomers are commercially available

Proposed Reactive Conformation



- Pseudoephedrine amides are easily prepared and frequently crystalline.
- LiCl is essential to accelerate the reaction and to prevent *O*-alkylation.
- Alkylation with *beta*-branched primary alkyl iodides and secondary alkyl iodides for the formation of quat. centers is possible, although they are quite slow.
- After cleavage, the chiral auxiliary can be reused.





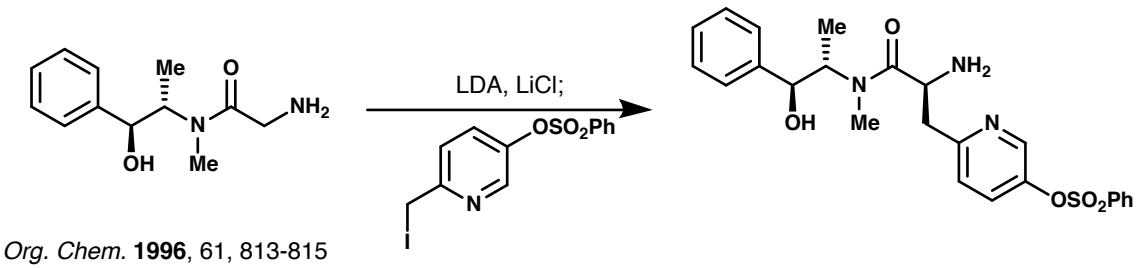
Due to its use in the synthesis of methamphetamine, pseudophedrine is heavily restricted.

Myers recently reported the utility of pseudophenamine as an alternative chiral auxiliary in alkylation reactions.

ACIE, **2012**, 51, 4568-4571

J. Am. Chem. Soc. **1997**, 119, 6496-6511
(**#1 Most Cited Paper** - Web of Science)

Application to a Practical Synthesis of L-Azatyrosine



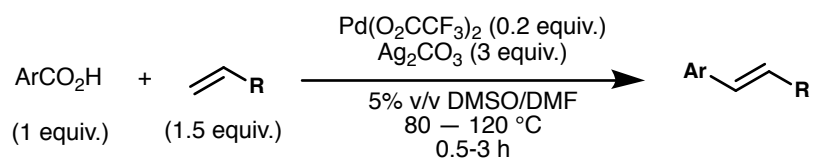
J. Org. Chem. **1996**, 61, 813-815

· antibiotic, shown to restore normal phenotypic behavior to cells bearing oncogenic Ras genes

Decarboxylative Palladation Reaction

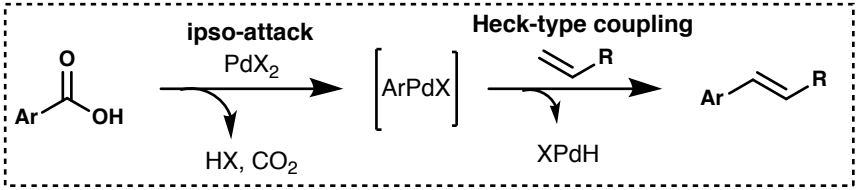
Meghan Baker

DECARBOXYLATIVE OLEFINATION METHOD:

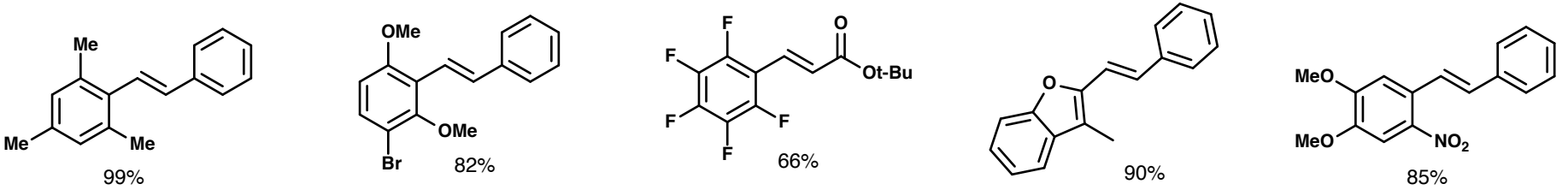


- At least one ortho substituent is necessary
- Common side reaction are occur through *ortho*-palladtion and C-H insertion.
- Use of small quantity of DMSO in DMF accelerates reaction and prevents *ortho*-palladation.
- Reaction can be conducted in air and small amounts of water.

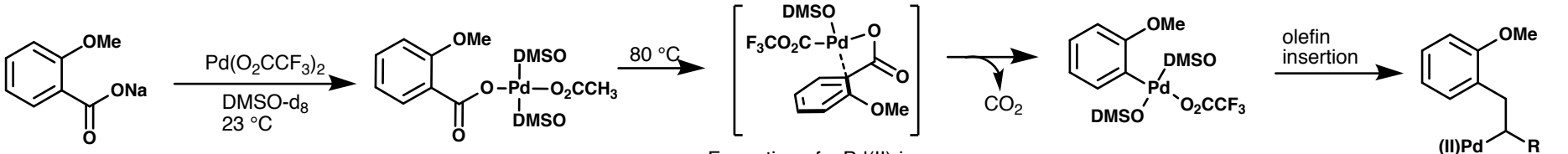
INITIAL MECHANISTIC INSIGHT



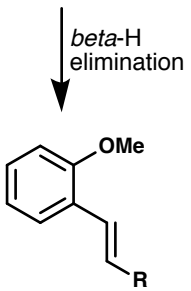
- Evidence in support of proposed mechanism:
  - Heating of a solution of $ArCO_2H$ with $Pd(O_2CCH_3)_2$ in DMSO leads to evolution of CO_2 and dissapearance (by NMR) of $ArCO_2H$ starting material. Subsequent addition of styrene led to coupling product.
  - Heating the supposed arylPd species with excess TFA leads to protonolysis.



Mechanistic Studies:



- Formation of a Pd(II)-ipso carbon bond.



- The decarboxylation step is the rate-determining step of the reaction, and involves intramolecular coordination of an electron-deficient Pd-center to the ipso-carbon of the arene.

- Reactivities differ from Heck coupling:
  - Electron-rich olefins and electron-poor Pd-centers are preferred.

- TFA ligands play a key role in decarboxylation step and in stabilizaing intermediates formed upon olefin insertion.

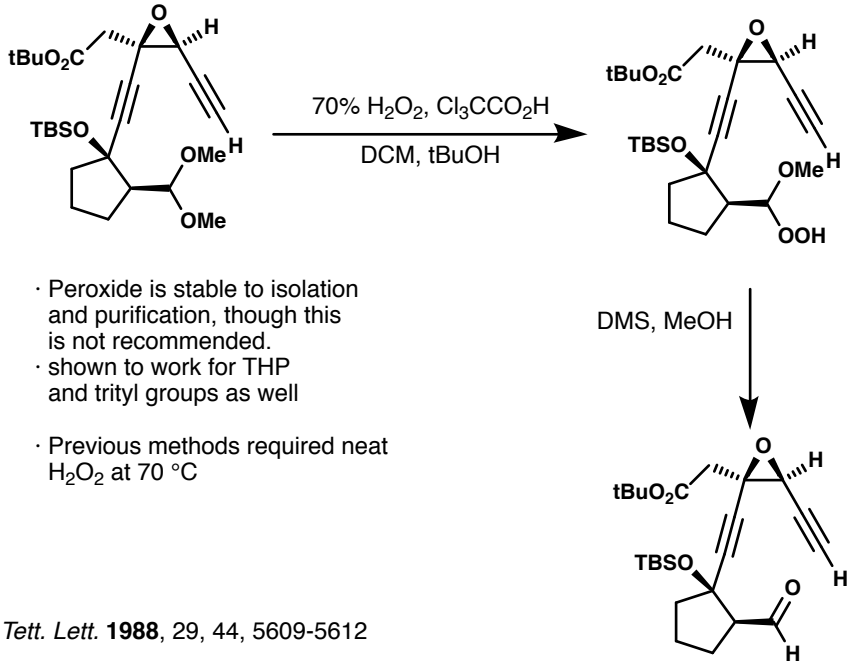
JACS, **2002**, 124, 11250-11251; *JACS,* **2005**, 127, 10323-10333

Shenvi Lab Group Meeting
July 24th, 2017

Other Methods

Meghan Baker

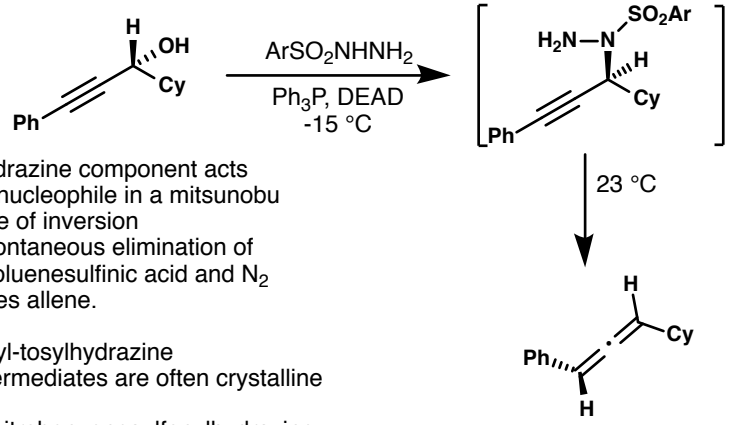
1. Mild Conditions for the Removal of Acid-Labile Protective Groups



- Peroxide is stable to isolation and purification, though this is not recommended.
- shown to work for THP and trityl groups as well
- Previous methods required neat H_2O_2 at 70 °C

Tett. Lett. **1988**, 29, 44, 5609-5612

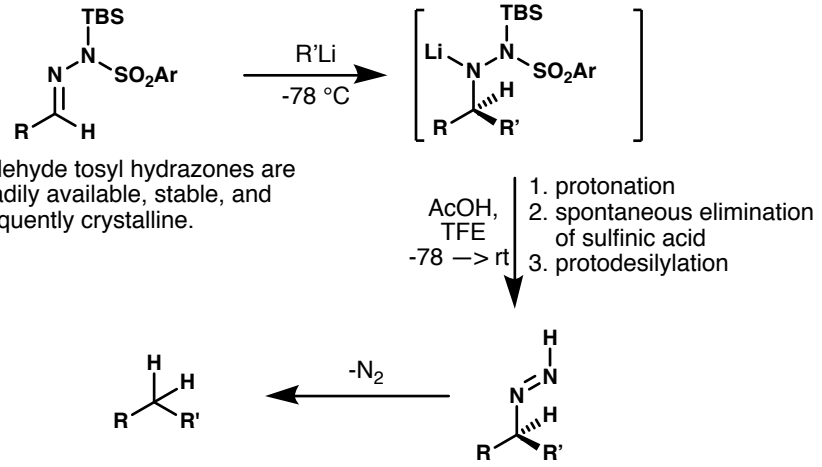
2. One-step Stereospecific Synthesis of Allenes from Propargylic Alcohols



- Hydrazine component acts as nucleophile in a mitsunobu type of inversion
- Spontaneous elimination of *p*-toluenesulfinic acid and N_2 gives allene.
- alkyl-tosylhydrazine intermediates are often crystalline
- *O*-nitrobenzenesulfonylhydrazine is best.

J. Am. Chem. Soc. **1996**, 118, 4492-4493

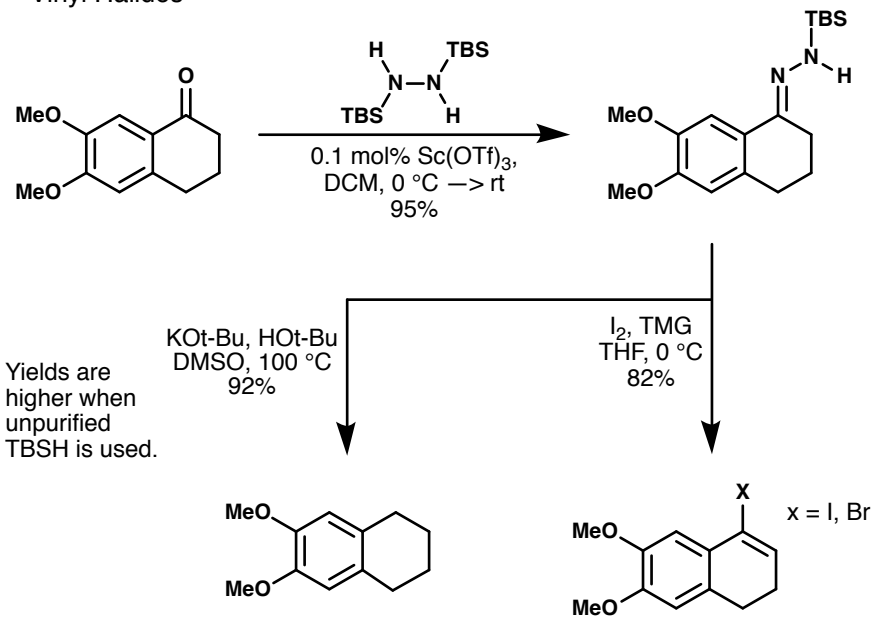
3. Reductive Coupling of Aldehyde Tosylhydrazones and Alkyllithium Reagents



- Aldehyde tosyl hydrazones are readily available, stable, and frequently crystalline.

J. Am. Chem. Soc. **1998**, 120, 34

4. Use of TBSH in Modified Wolff-Kishner Reductions and in Synthesis of Vinyl Halides

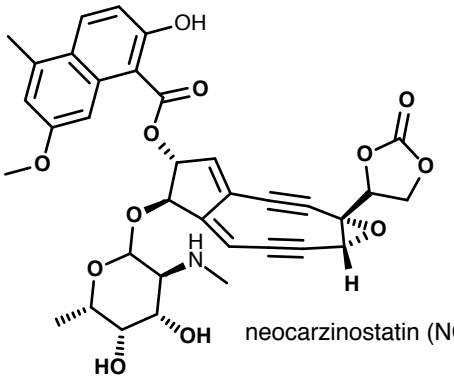


- Yields are higher when unpurified TBSH is used.

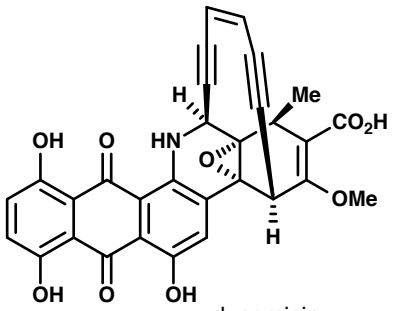
J. Am. Chem. Soc. **2004**, 126, 17, 5436-5445

The Enediyne Antibiotics

Meghan Baker



neocarzinostatin (NCS)



dynemicin

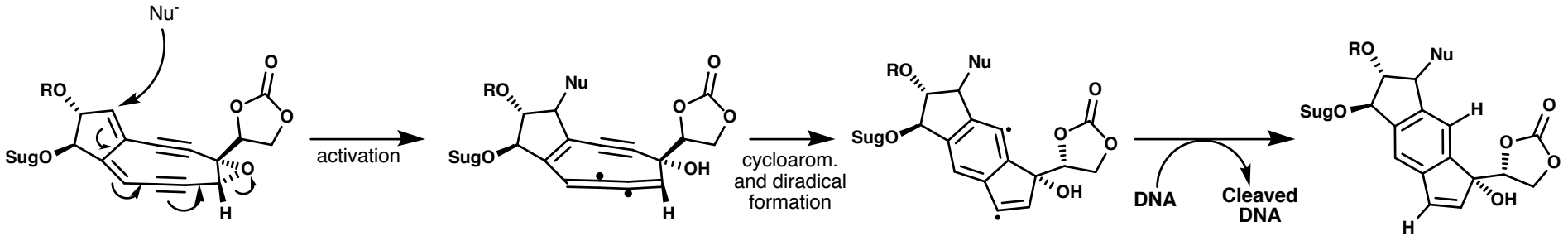
Others:
kedarcidin
calicheamicins
esperamicins

designer
enediynes

· The enediyne antibiotics share many common properties:
  · they are noncovalently associated complexes between unstable chromophores and stable proteins.
  · they exhibit potent antitumor properties
  · and they posses DNA-cleaving properties

· The enediyne antibiotics are characterized by the high reactivity of their "enediyne" chromophore components.
· This high reactivity makes the enediynes a sythetic challenge, but it is also a driving force in their DNA-cleaving abilities.

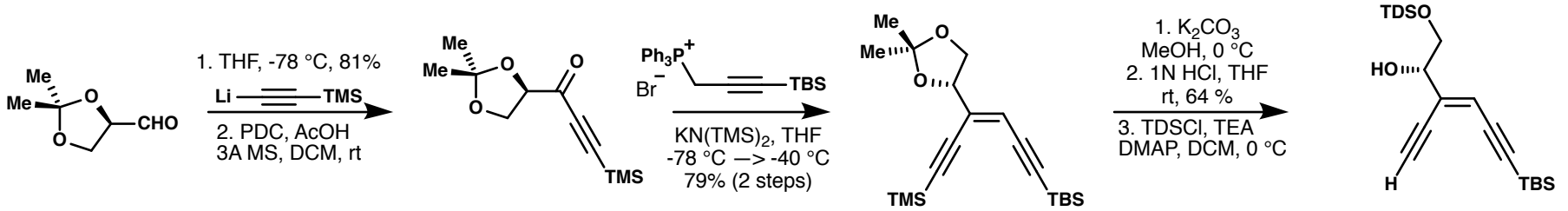
· *in situ*, they are hypothesized to undergo an activation event leading to cycloaromatization and formation of a diradical that would be positioned to cleave DNA.



A proposed route for activation of NCS and subsequent DNA cleavage.

Neocarzinostatin

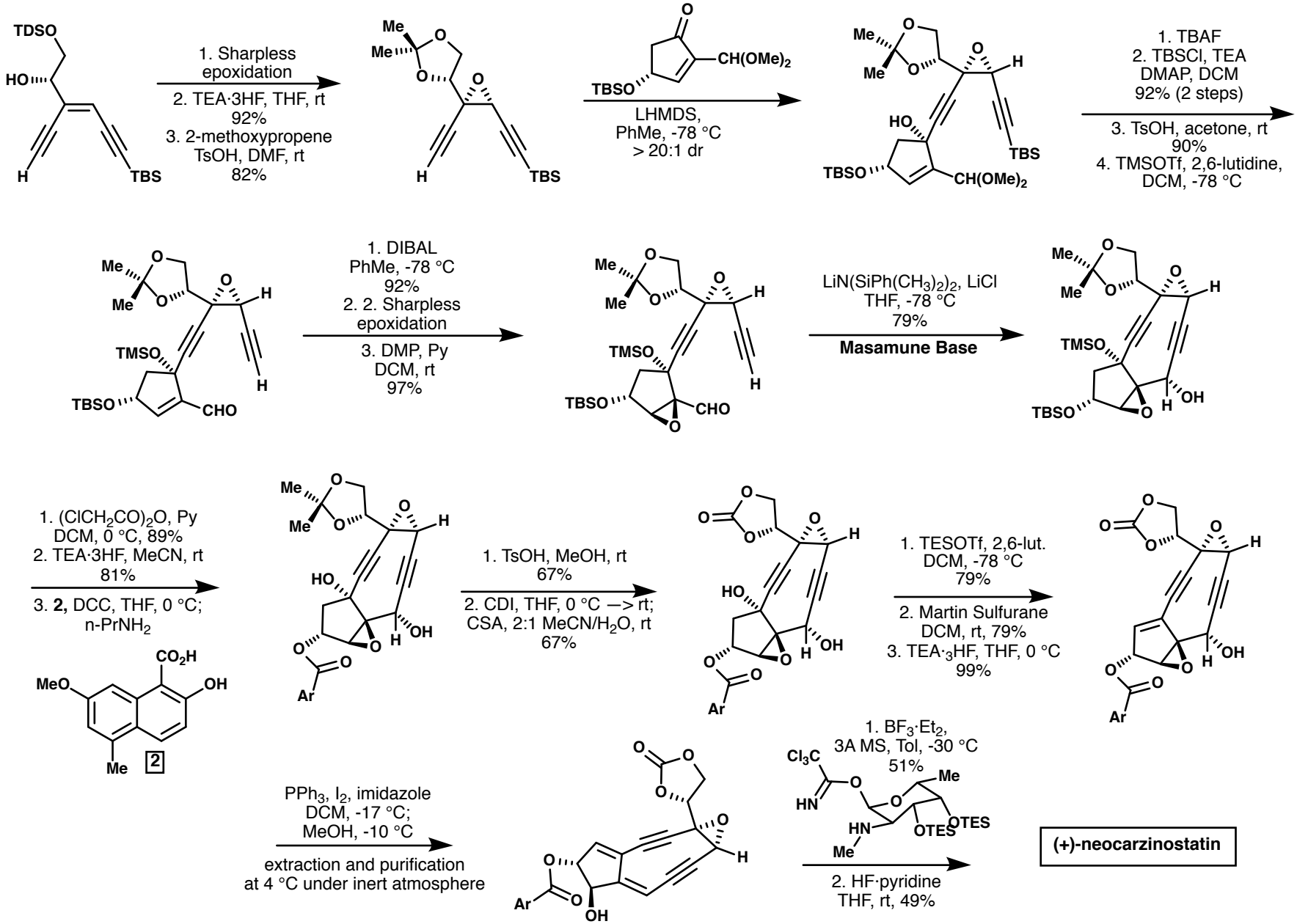
· NCS was isolated as a non-covalently associated mixture of the chromophore shown above and a 113 amino acid apoprotein. NCS itself is rather unstable.
· The Myers group has published 22 papers detailing their biological and synthetic studies of neocarzinostatin.



J. Am. Chem. Soc. **1991**, 113, 695-696
Nicolaou, K. C. *J. Med. Chem.* **1996**, 39, 11

Neocarzinostatin

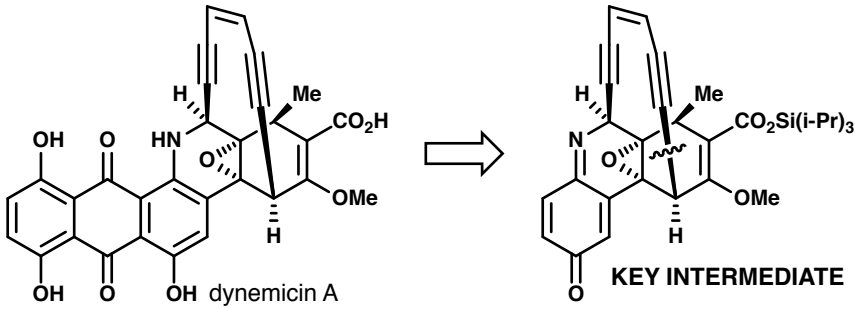
Meghan Baker



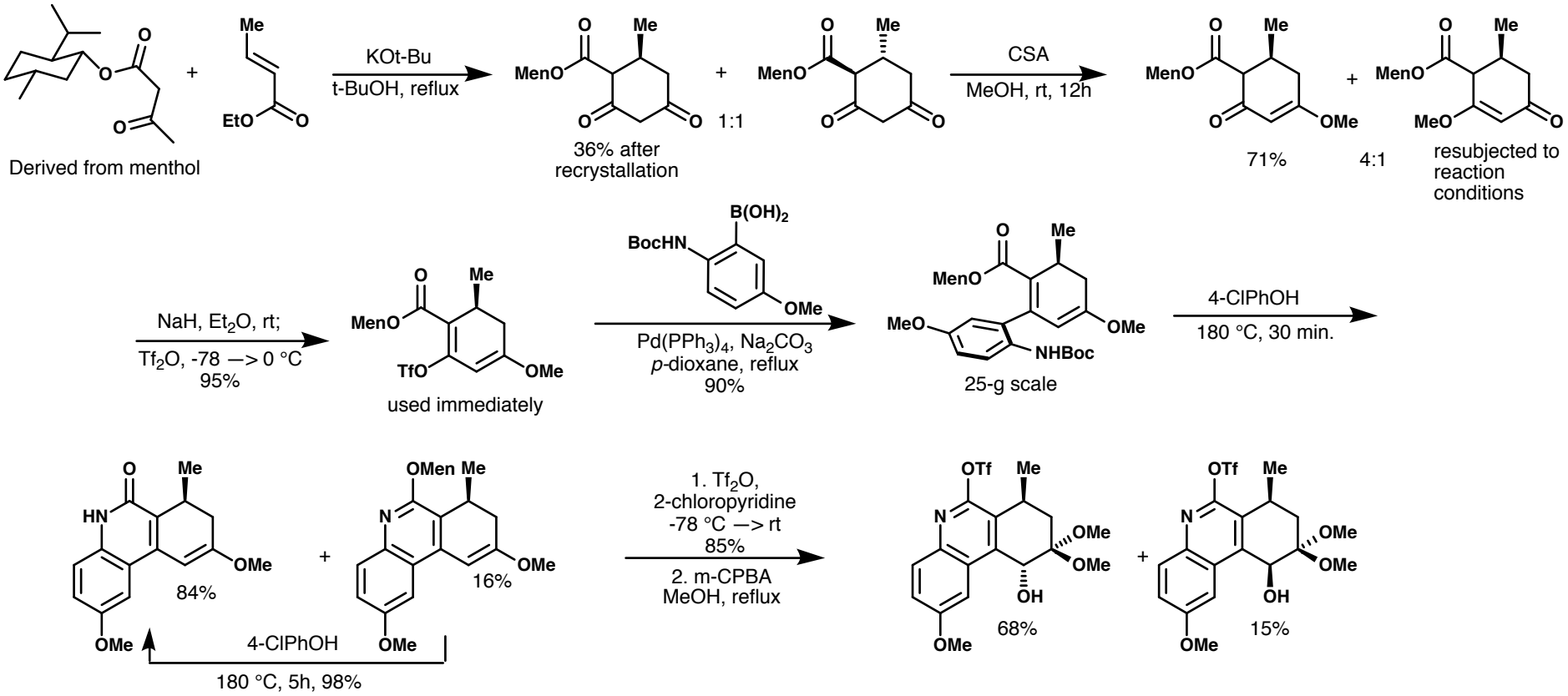
J. Am. Chem. Soc. **1991**, 113, 695-696

Synthesis of Dynemicin and Analogues

Meghan Baker



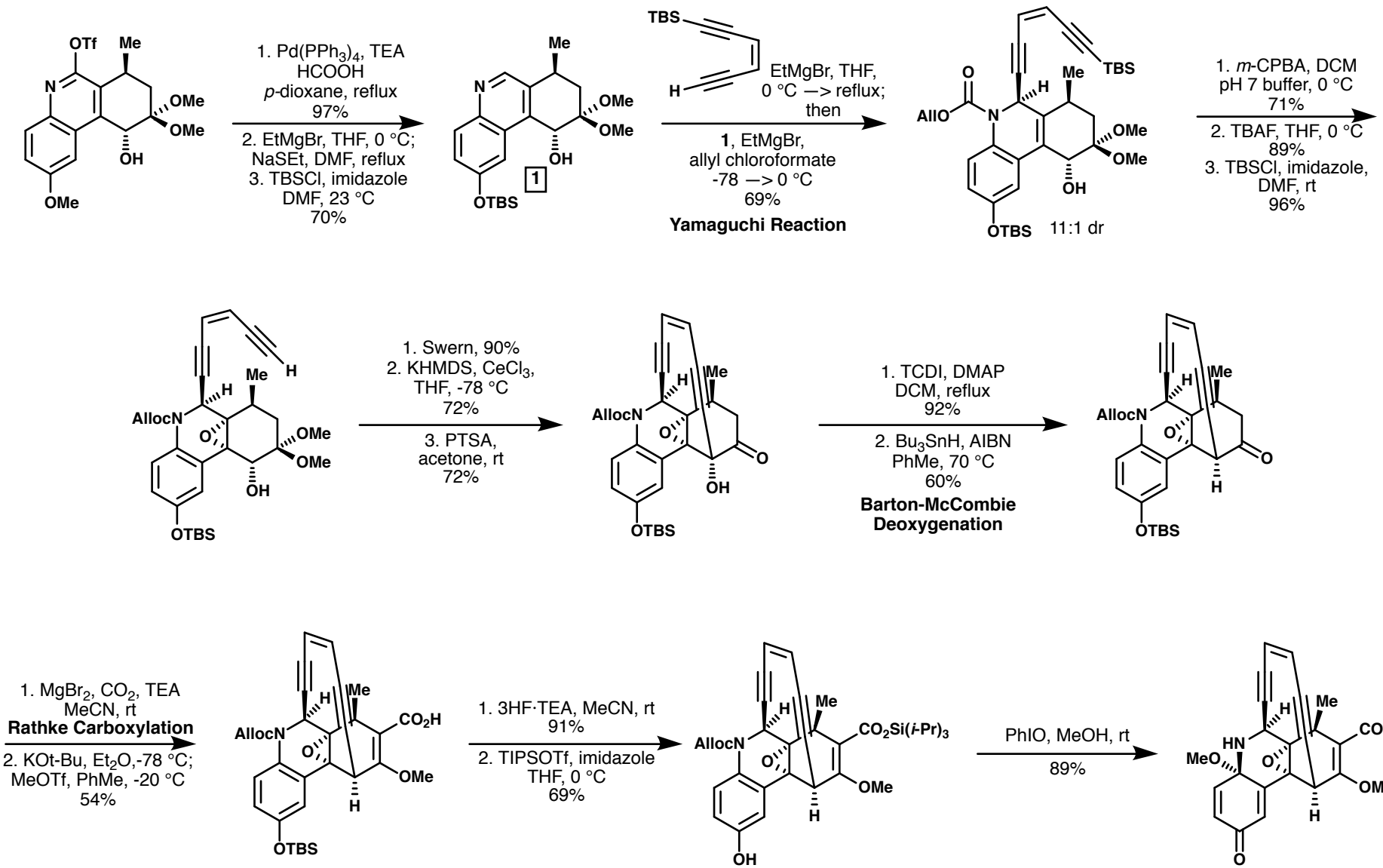
- Dynemicin A displays potent *in vitro* and *in vivo* cytotoxicity against many murine and human tumor cell lines, and it exhibits potent antibacterial activity *in vivo* with low levels of toxicity.
- Dynemicin A is distinctive amongst the ene-diyne natural products due to its anthraquinone functionality that is believed to aid in the molecules' anticancer properties by intercalating the DNA that it is bound to.
- The anthraquinone moiety is also believed to be the initial site of reduction in the activation of dynemicin for DNA-cleavage.



J. Am. Chem. Soc. **1997**, 119, 6072-6094

Synthesis of Dynemicin and Analogues

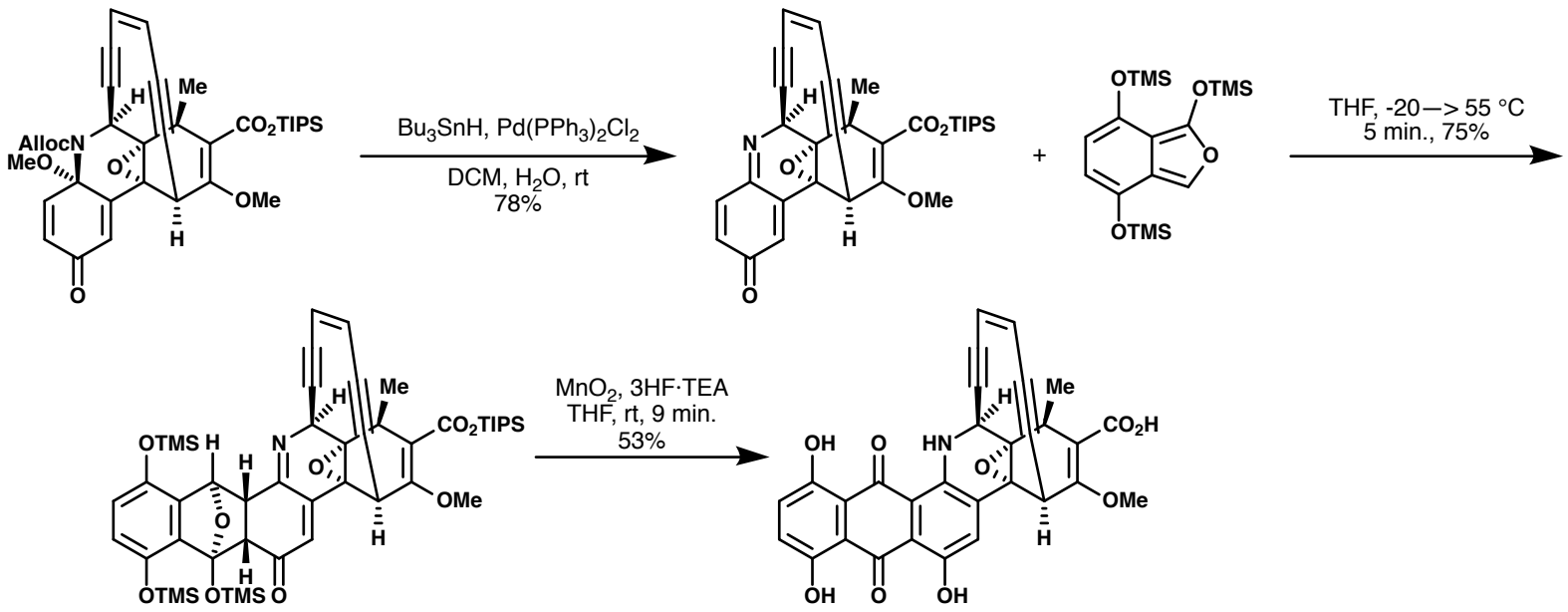
Meghan Baker



1. *J. Am. Chem. Soc.* **1997**, 119, 6072-6094
2. *J. Org. Chem.* **1985**, 50, 4877-4879

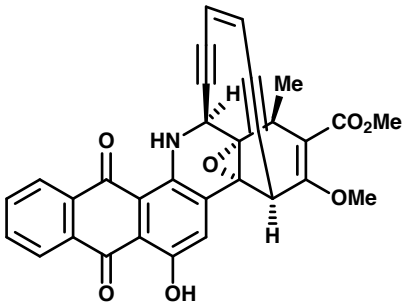
Synthesis of Dynemicin and Analogues

Meghan Baker

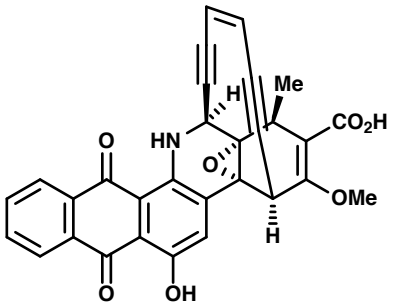


Dynemicin A
24 linear steps

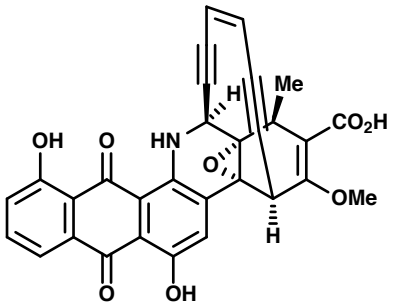
ANALOGUES



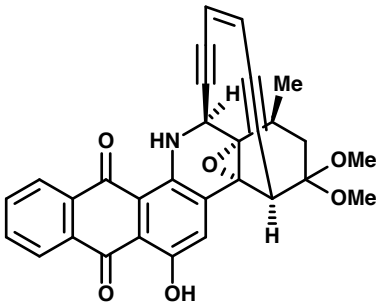
dideoxydynemicin methyl ester



dideoxydynemicin



monodeoxydynemicin



1. J. Am. Chem. Soc. **1997**, 119, 6072-6094
2. *J. Org. Chem.* **1985**, 50, 4877-4879

Tunicamycin Natural Products

Meghan Baker

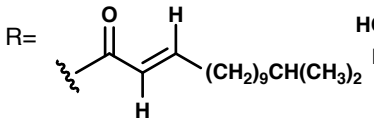
· The tunicamycins inhibit various enzymatic processes involving the formation of phopholipid-linked intermediates.
· As a result, the tunicamycins elicit a range of biological responses including antimicrobial, antifungal, antiviral, and antitumor activities.

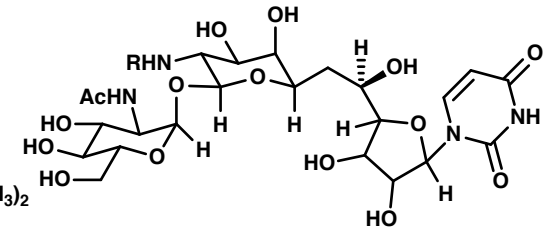
· Studies of the tunicamycins have led to the proposal that they function as bisubstrate analoges for the enzymes they inhibit.

· Due to their ability to inhibit oligosaccharide synthesis in eukartyotic cells, they have been used as biochemical probes to study the roles of glycosylation on protein structure and function.

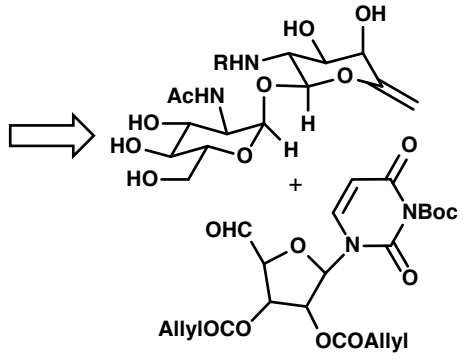
R=long-chain branched, linear, saturated, or unsaturated actyl substituents.

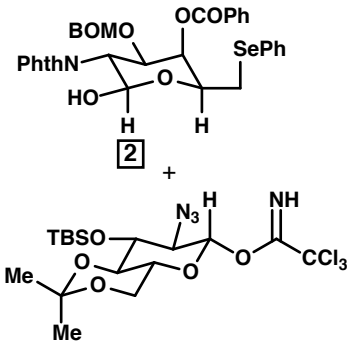
(+)-tunicamycin V:





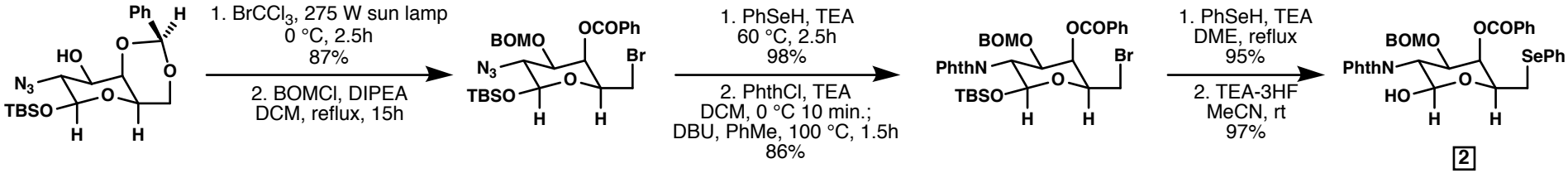
1: R=H

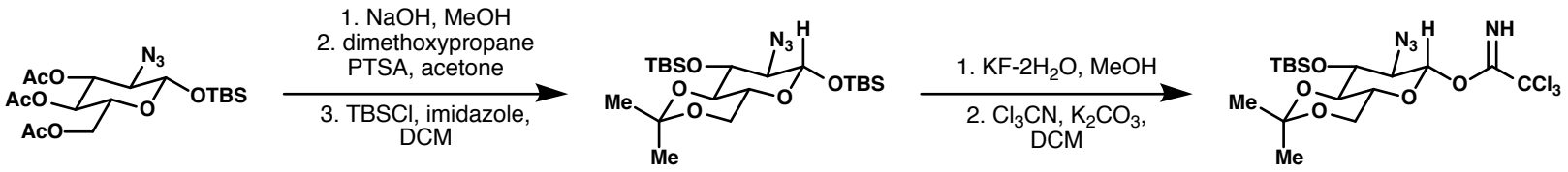




A concise synthesis of (+)-tunicamycin V

Synthesis of the undecose core (tunicaminyluracil) were described in a previous publication.[1]



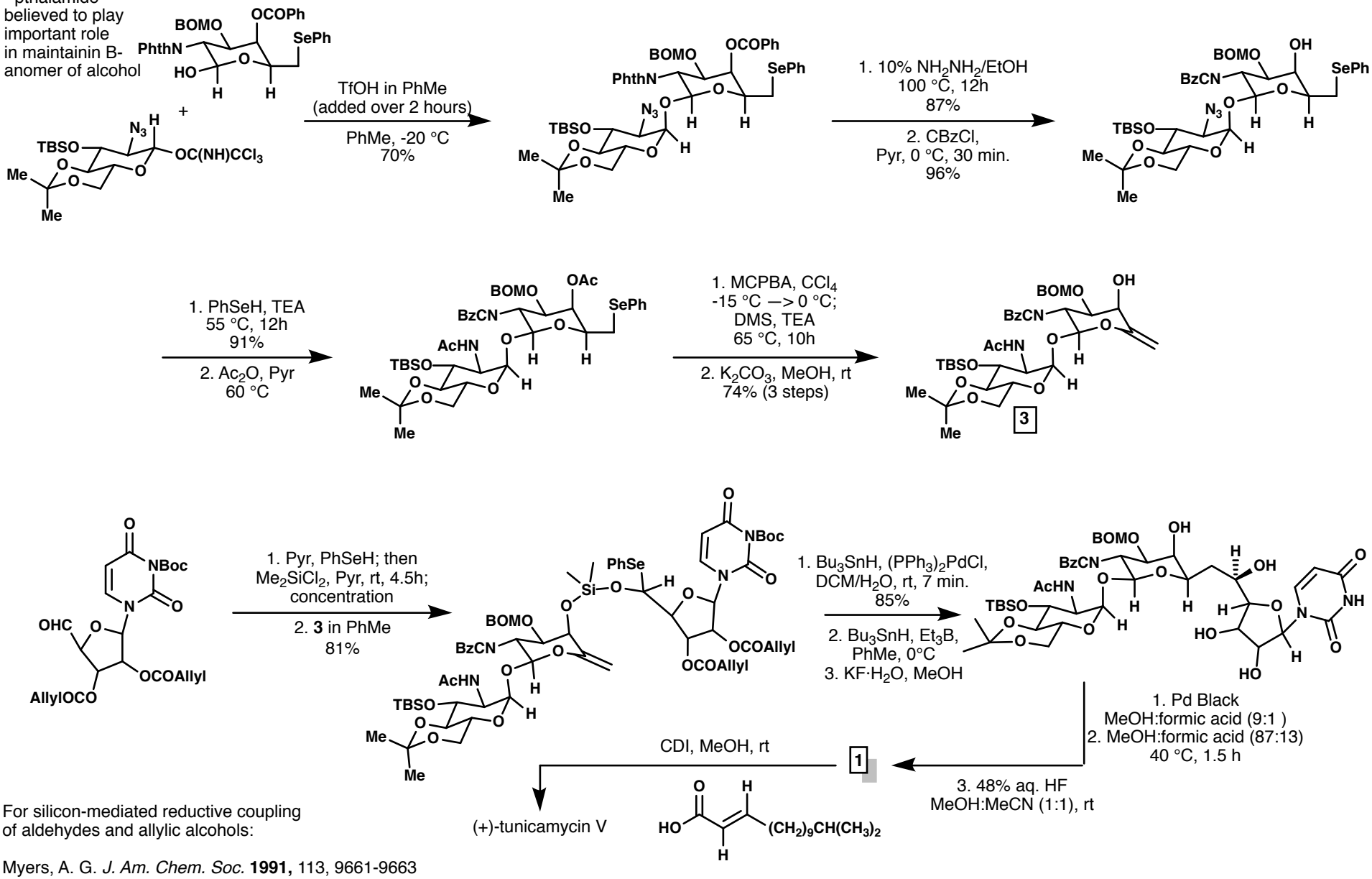


1. *J. Am. Chem. Soc.* **1991**, 113, 9661
2. *J. Am. Chem. Soc.* **1993,** 115, 2036-2038
3. *J. Am. Chem. Soc.* **1994**, 116, 4697-4718

Tunicamycin Natural Products

Meghan Baker

- pthalamide believed to play important role in maintainin B-anomer of alcohol



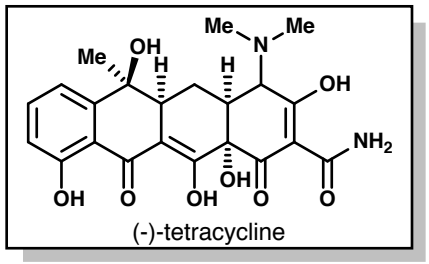
For silicon-mediated reductive coupling of aldehydes and allylic alcohols:

Myers, A. G. *J. Am. Chem. Soc.* **1991,** 113, 9661-9663

1. *J. Am. Chem. Soc.* **1991**, 113, 9661
2. *J. Am. Chem. Soc.* **1993,** 115, 2036-2038

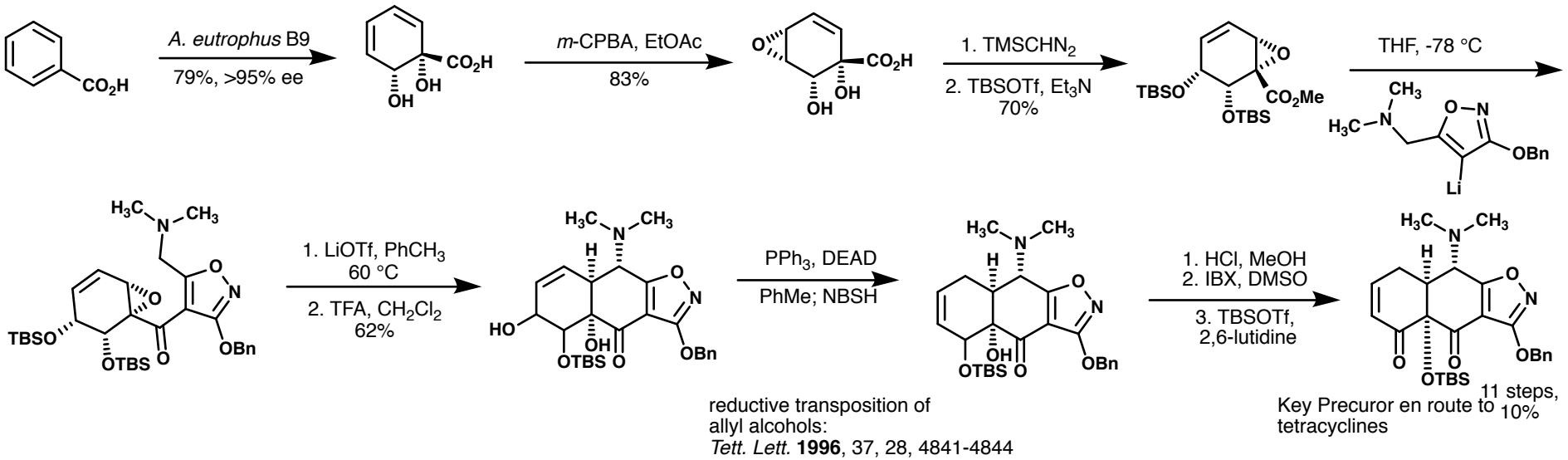
Tetracycline Antibiotics

Meghan Baker



(-)-tetracycline

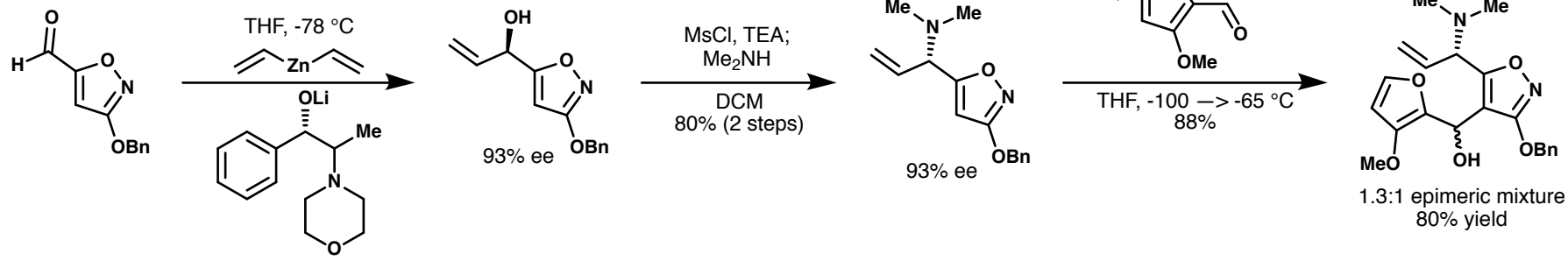
- The tetracycline antibiotics inhibit protein synthesis, specifically translation, by preventing attachment of aminoacyl-tRNA to the ribosome. They have been widely used in the treatment of bacterial infections, contributing to the emergence of widespread antibiotic resistance.
- To combat this, Myers first synthesized 6-deoxytetracycline and other analogues of tetracycline, introducing structural variability at the D ring as prior work had indicated that analogues with no C6 hydroxyl group are more resistant to degradation while showing equal or greater potencies.
- Since the initiial synthesis, a 2nd generation route has been developed, and over 2000 analogues have been made, many with potent antibacterial activity.



reductive transposition of allyl alcohols:
Tett. Lett. **1996**, 37, 28, 4841-4844

11 steps,
Key Precuror en route to 10%
tetracyclines

2nd Generation Route (developed at Tetraphase Pharmacueticals)

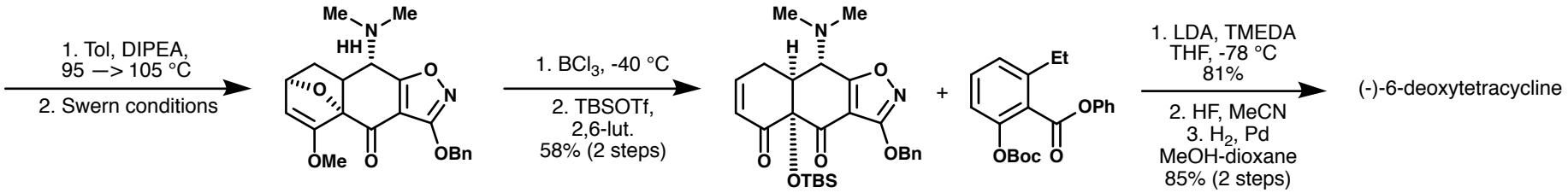


1.3:1 epimeric mixture
80% yield

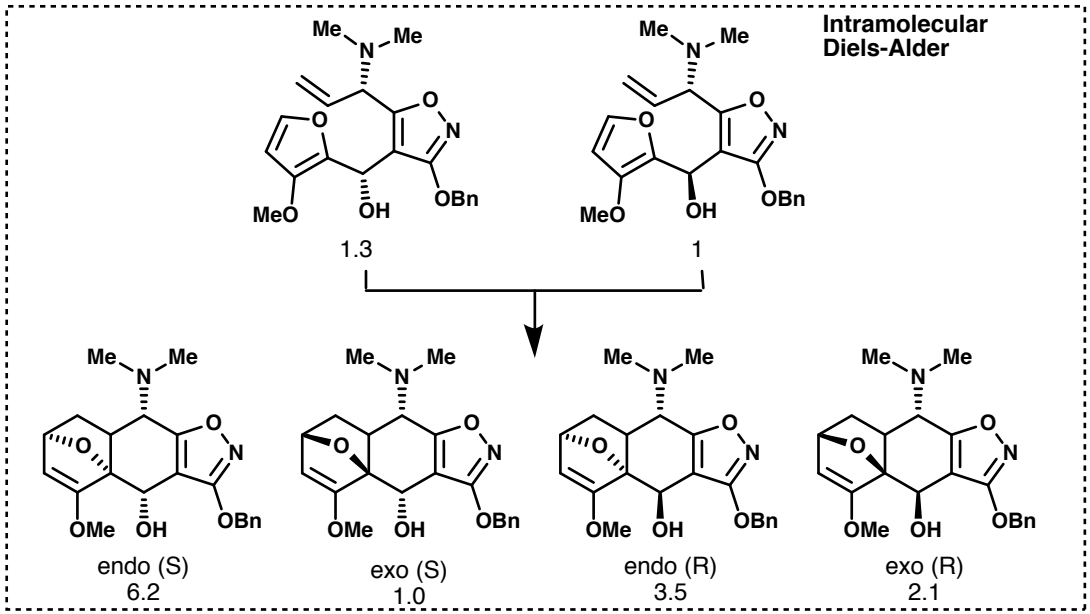
1. Charest, M. G., Lerner, C. D., Brubaker, J. D., Siegel, D. R., Myers, A. G. *Science*, **2005**, 308
2. Charest, M. G., Siegel, D. R., Myers, A. G. *J. Am. Chem. Soc.* **2006,** 127, 8292-8293
Org. Lett. **2007,** 9, 18, 3523-3525

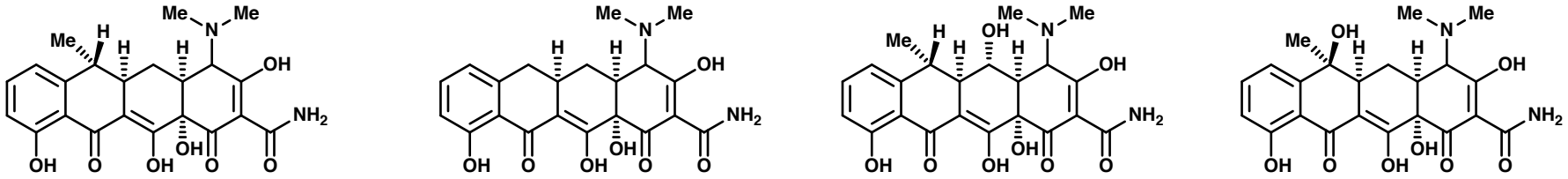
Tetracyclines

Meghan Baker



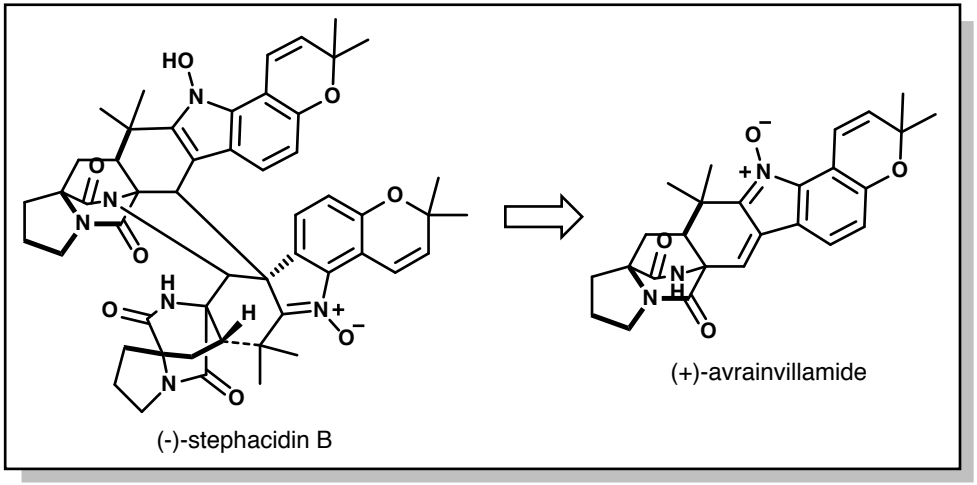
9 steps, 21% yield





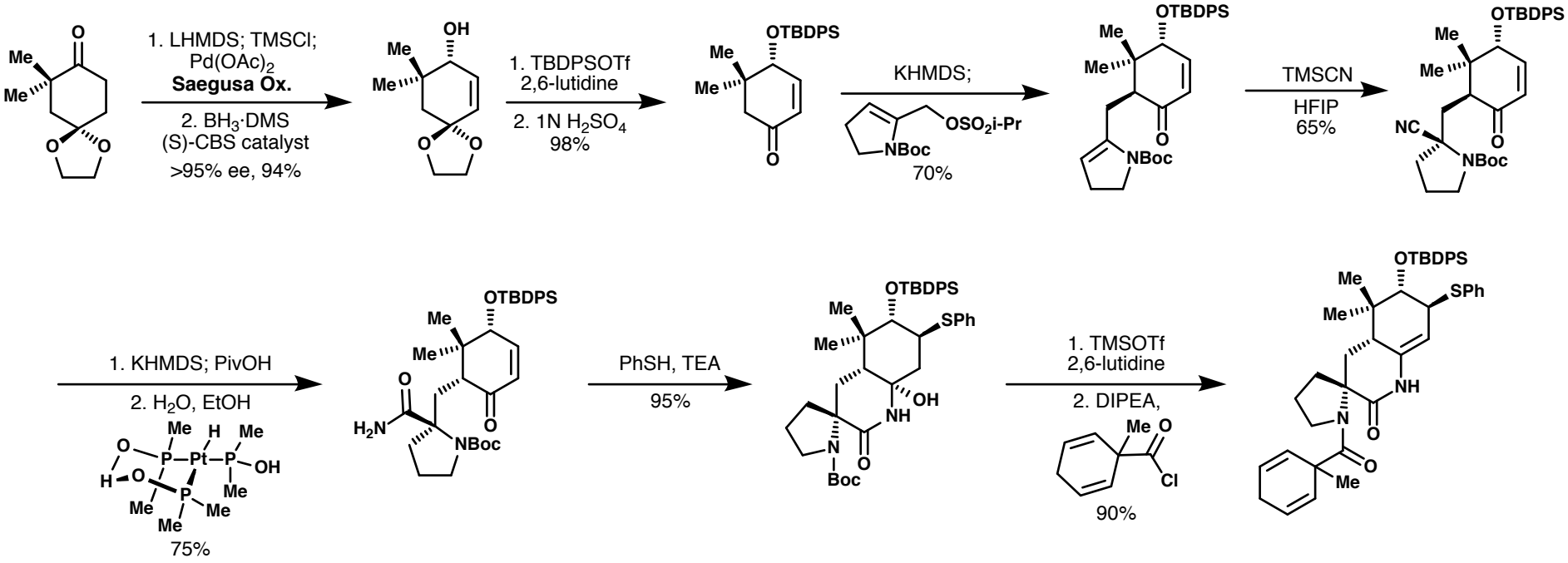
Synthesis of Stephacidin B

Meghan Baker



· Isolated from a fungal culture of *Aspergillus ochraceus*
· Both inhibit growth of cultured human cancer cells (IC_{50} ~ 50-100 nM)
· Recent studies show that they readily interconvert in solution.

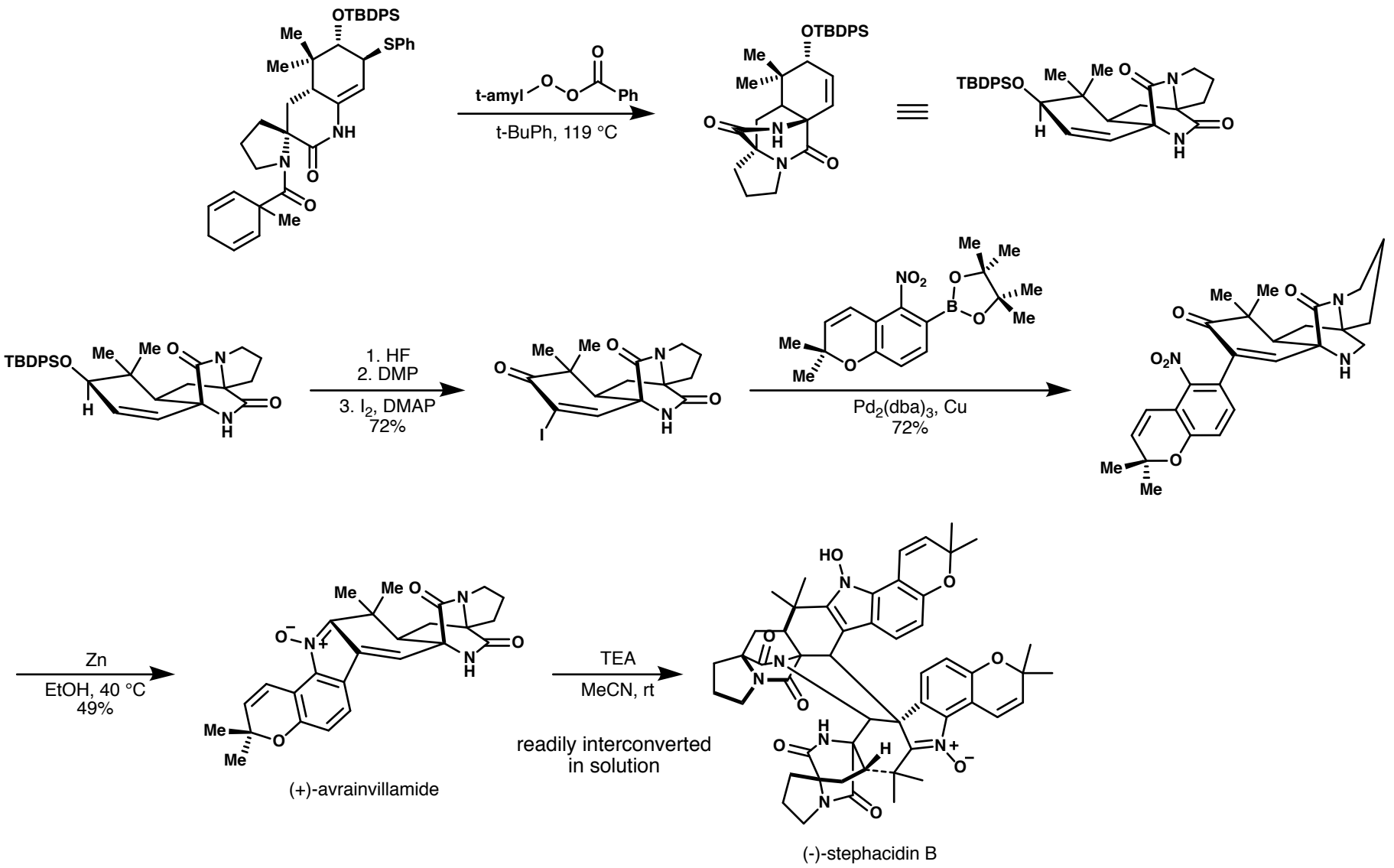
· The previously reported antiproliferative activity of stephacidin B may arise from its disociation to form avrainvillamide, which may then bind to one or more proteins



1. Herzon, S. B., Myers, A. G. *J. Am. Chem. Soc.* **2005**, 127, 15, 5342-5344

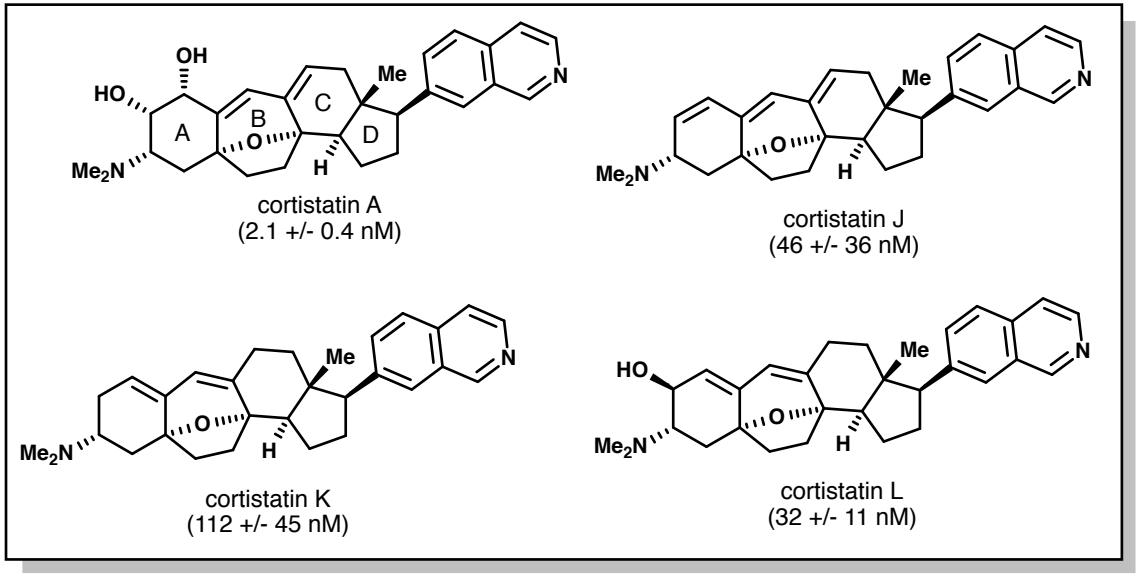
Synthesis of Stephacidin B

Meghan Baker

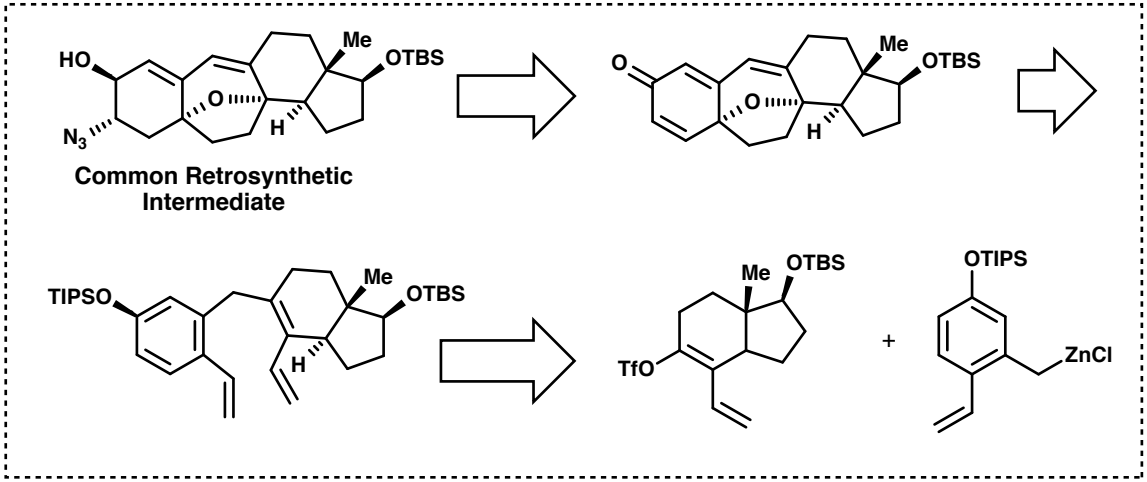


1. Herzon, S. B., Myers, A. G. *J. Am. Chem. Soc.* **2005**, 127, 15, 5342-5344
2. *J. Am. Chem. Soc.* **2007,** 129, 4898-4899

Cortistatins

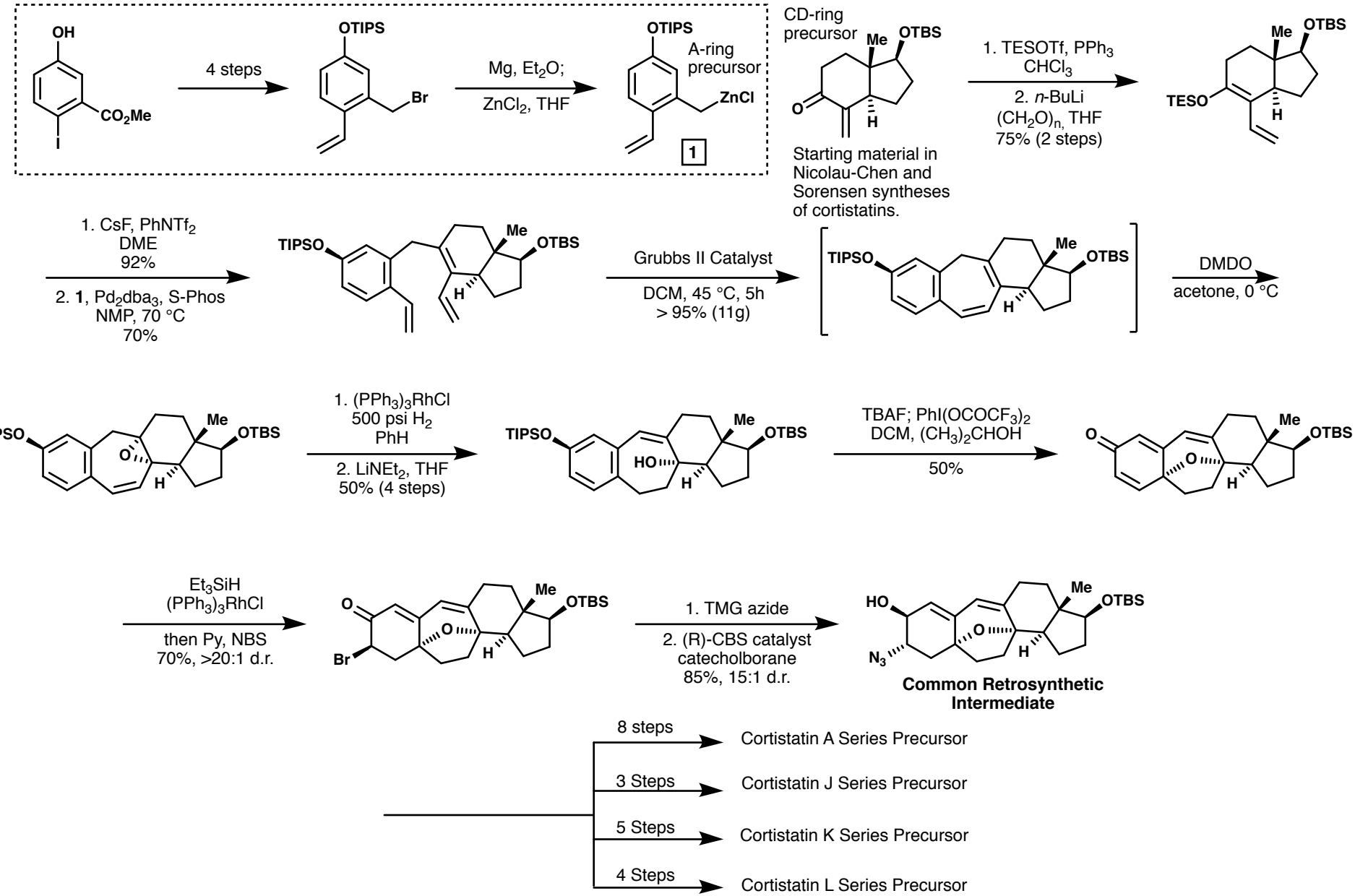


- More than 10 natural cortistatins have been described since the elucidation of cortistatin A structure in 2006.
- Some cortistatins exhibit potent and selective cytostatic activity against human umbilical vein endothelial cells.
- SAR studies have shown that the 7-substituted isoquinoline is a key determinant of these phenotypic effects.
- A 2015 Nature paper demonstrates that cortistatin A also inhibits mediator kinases, thereby upregulating super-enhancer genes and having anti-leukaemia activity.



1. *Nature Chemistry*, **2010**, 2, 886-892
2. *Nature, **2015**, 526, 273*

Cortistatins

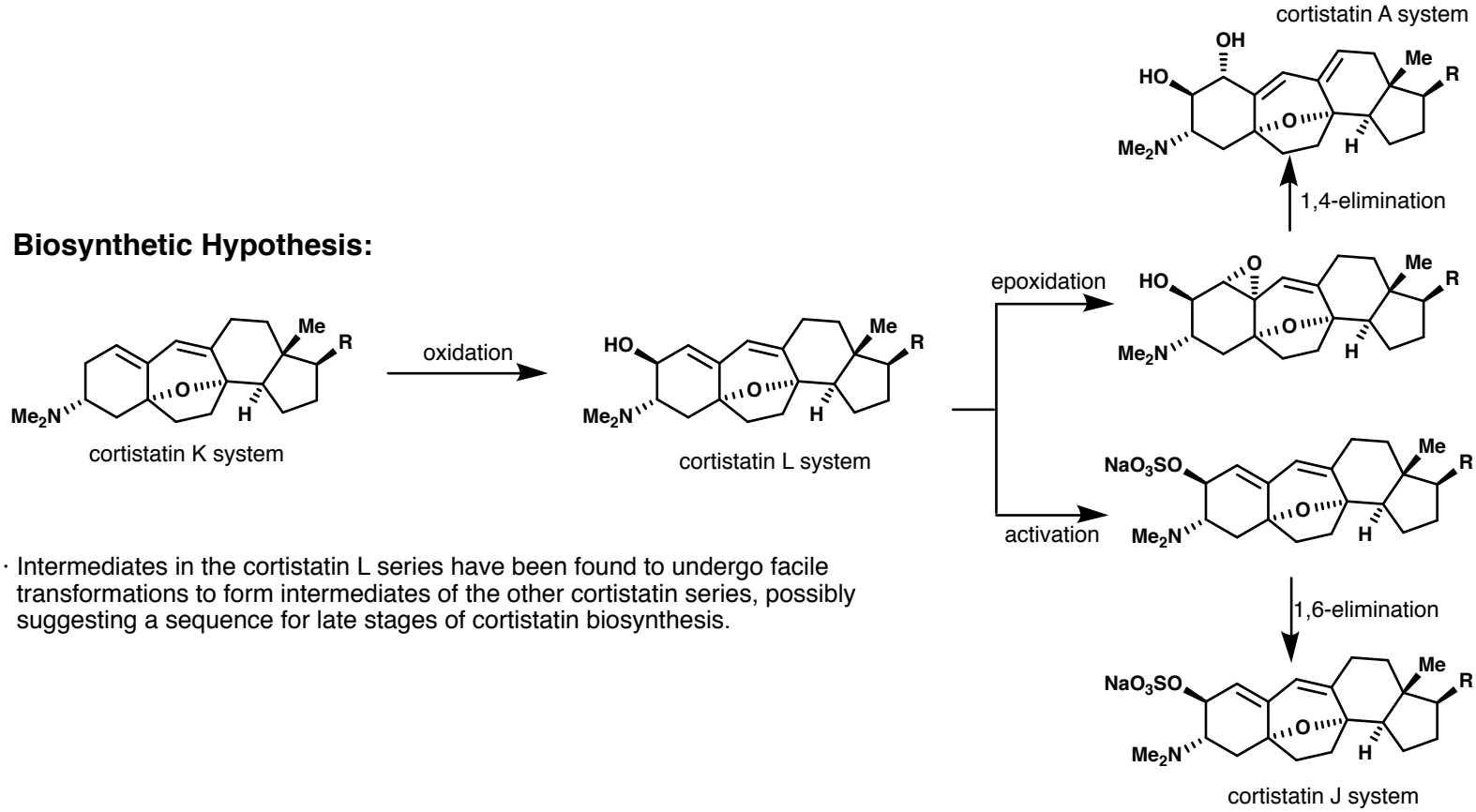


1. *Nature Chemistry*, **2010**, 2, 886-892

Cortistatins

Meghan Baker

Biosynthetic Hypothesis:

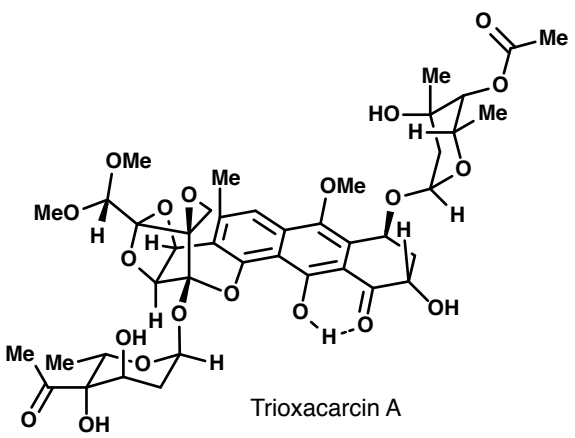


· Intermediates in the cortistatin L series have been found to undergo facile transformations to form intermediates of the other cortistatin series, possibly suggesting a sequence for late stages of cortistatin biosynthesis.

1. *Nature Chemistry*, **2010**, 2, 886-892
2. *Nature, **2015**, 526, 273*

Trioxacarcin A

Meghan Baker

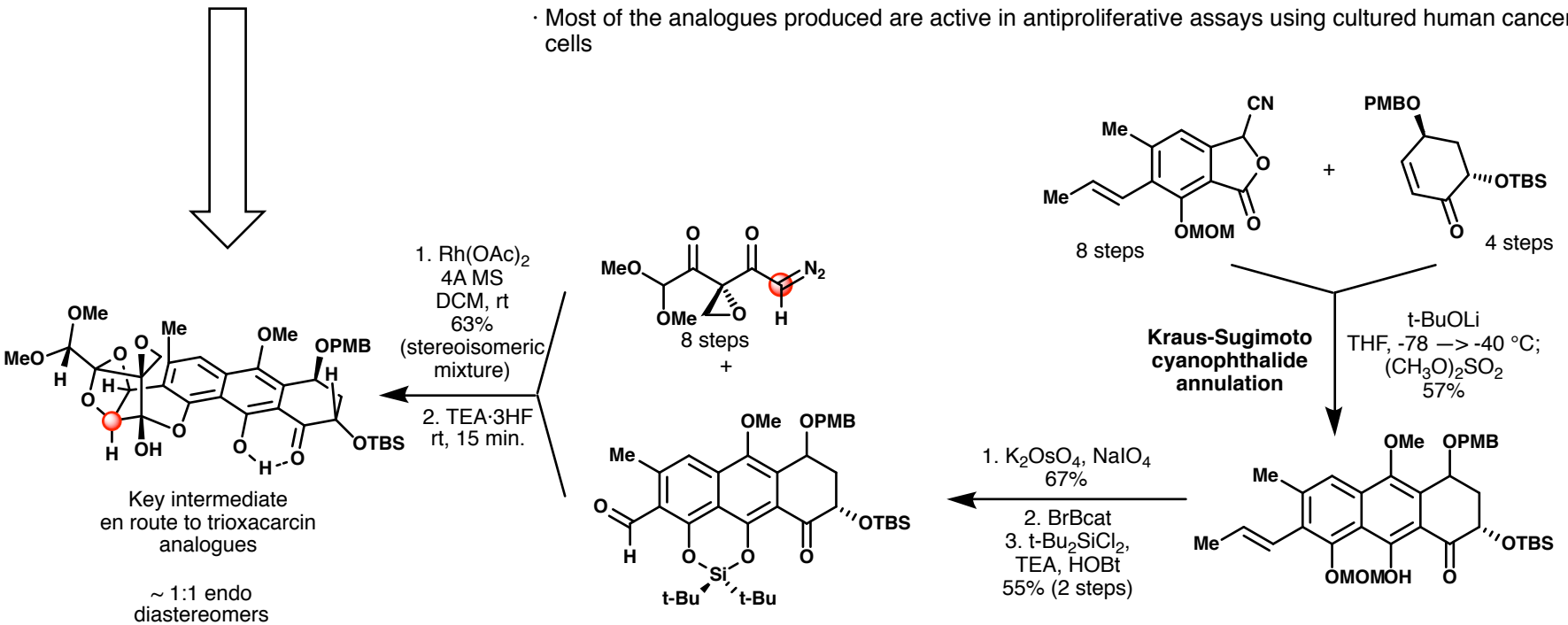

Trioxacarcin A

· The trioxacarcins are bacterial metabolites that potently inhibit the growth of cultured human cancer cells and bacterial cells. The most potent family member, trioxacarcin A, displays subnanomolar 70% growth inhibition against many human cancer cell lines.
· This is believed to be a result of efficient and irreversible alkylation of guanine residues in DNA

· Unusual Chemical Features:
· Rigid, highly oxygenated skeleton
· Fused spiro epoxide
· five ketal or hemiketal groups
· At least one unusual glycosidic residue

· Key features of the synthesis:
· late-stage glycosylation reactions of differentially protected aglycon substrates allow for facile construction of analogues
· Identification of appropriate ways to activate and protect the two 2-deoxysugar components, trioxacarcinose A and B, and viable sequencing of glycosidic coupling.
· Modularity allows for rapid construction of structurally diverse synthetic analogues

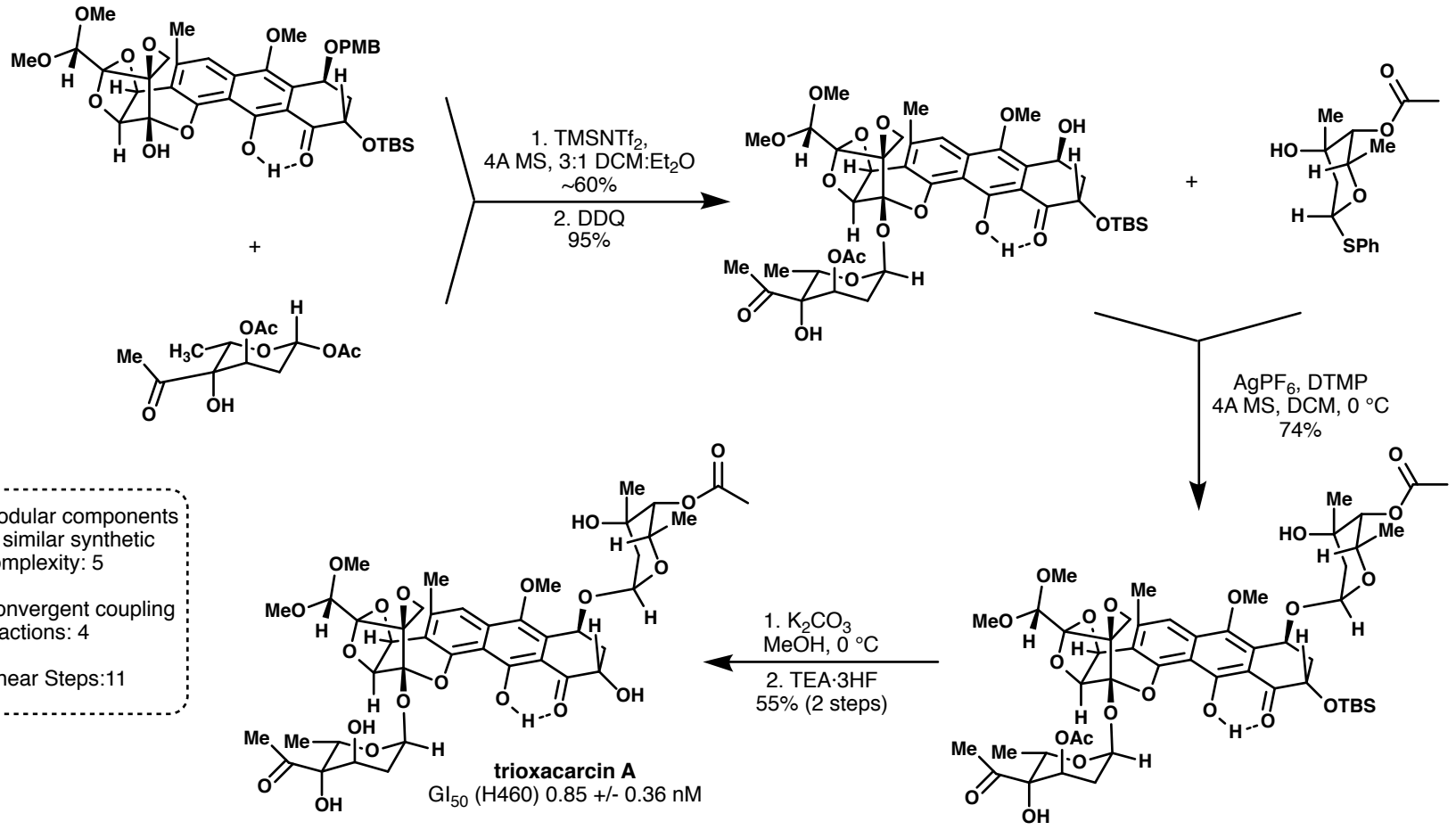
· Most of the analogues produced are active in antiproliferative assays using cultured human cancer cells



Nature Chemistry, **2013**, 5, 886-892
Nucleic Acid Res. **2008**, 36, 10, 3508-3514 (for crystal structure of trioxacarcin A bound to DNA)
PNAS, **2011**, 108, 17, 6709-6714

Trioxacarcin A

Meghan Baker

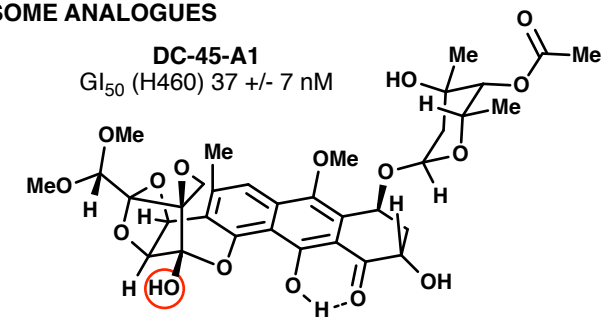


Modular components of similar synthetic complexity: 5

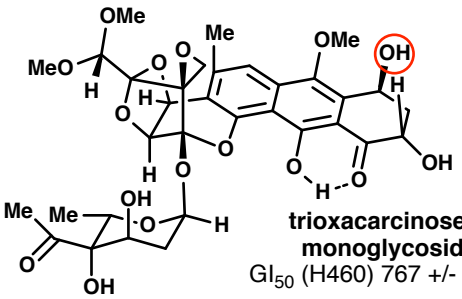
Convergent coupling reactions: 4

Linear Steps:11

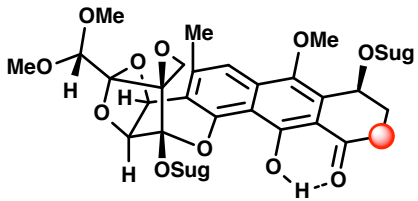
SOME ANALOGUES



DC-45-A1
GI_{50} (H460) 37 +/- 7 nM



trioxacarcinose B monoglycoside
GI_{50} (H460) 767 +/- 74 nM



GI_{50} (H460) 4.5 +/- 2.0 nM nM

Nature Chemistry, **2013**, 5, 886-892