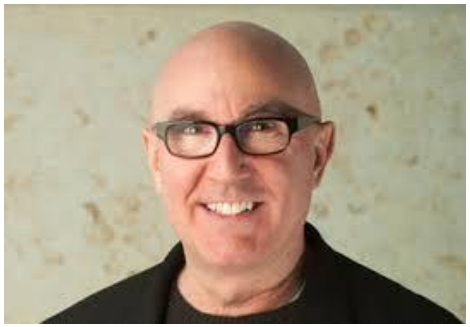
Matthew O'Neill

Stuart Schreiber

Cornella Group Meeting
8.12.2017



Stuart Schreiber

Morris and Loeb Professor of Chemistry and Chemical Biology
Howard Hughes Medical Institute Investigator

Professional Milestones

1956 - born in Virginia
1977 - graduates from University of Virginia
1979 - Woodward passes away - finishes PhD under guidance of Kishi - publishes several single author publications
1981 - earns PhD from Harvard, joins faculty at Yale
1984 - promoted to Associate Professor
1986 - promoted to Full Professor
1988 - moves to Harvard as Morris Loeb Professor
1997 - founding director of Harvard Institute of Chemistry and Cell Biology
2003 - founding core member of the Broad Institute of MIT and Harvard

Research Interests

1. Total Synthesis and Methodology
2. Diversity Oriented Synthesis
3. Chemical Biology
4. Therapeutic Discovery

Companies

Vertex Pharmaceuticals
Ariad Pharmaceuticals
Infinity Pharmaceuticals
Forma Therapeutics

Broad Institute

Selected Awards and Honors

1989 - ACS Award in Pure Chemistry
1993 - Eli Lilly Award in Biological Chemistry
1994 - ACS Award in Synthetic Organic Chemistry
1994 - George Ledlie Prize - Harvard University
1995 - Member of NAS and AAAS
1997 - Tetrahedron Prize for Creativity in Organic Chemistry
2000 - ACS Award for Bioorganic Chemistry
2004 - American Association of Cancer Institutes
2014 - Arthur C. Cope Award
2015 - Nagoza Gold Medal
2016 - Wolf Prize (with K.C. Nicolaou)

Selected Students

Bradley Bernstein, MD PhD - Broad Institute, Harvard Medical School
Jay Bradner, MD - Broad, Dana Farber, currently President of NIBR
Martin Burke, MD PhD - UIUC
Craig Crews, PhD - Yale
Amir Hoveyda, PhD - Boston College
Deborah Hung, MD PhD - Harvard, Broad Broad Institute
Tim Jamison, PhD - MIT
Laura Kiessling, PhD - MIT
Matthew Shair, PhD - Harvard
David Spiegel, MD PhD - Yale

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Small Molecule Targets

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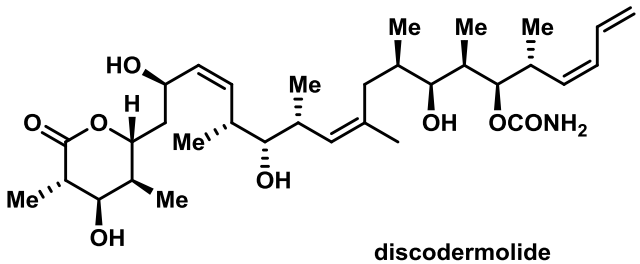
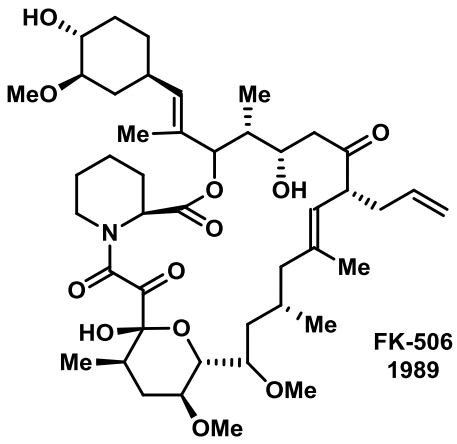
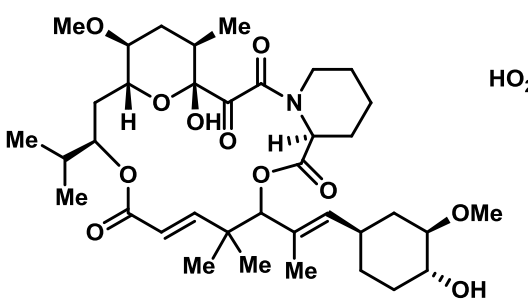
Selected Targets Completed by the Schreiber Lab



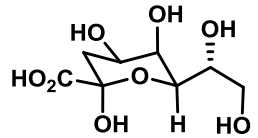
discodermolide
1993



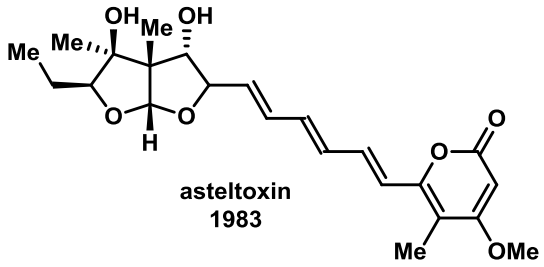
FK-506
1989



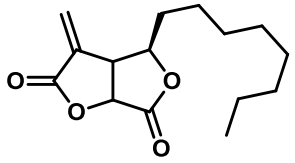
FK-506BD
1989



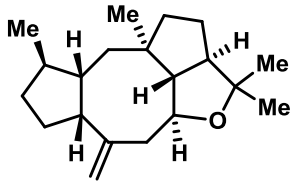
KDO
1990



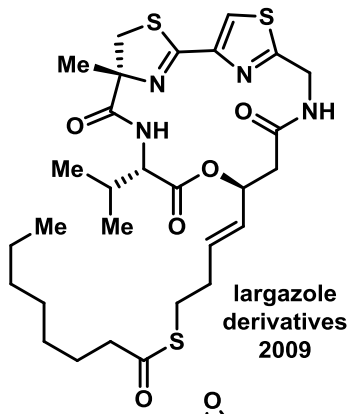
asteltoxin
1983



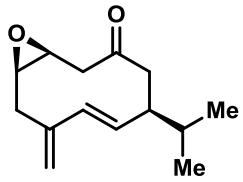
avenaciolide
1984



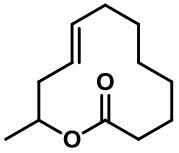
expoxydictymene
1994



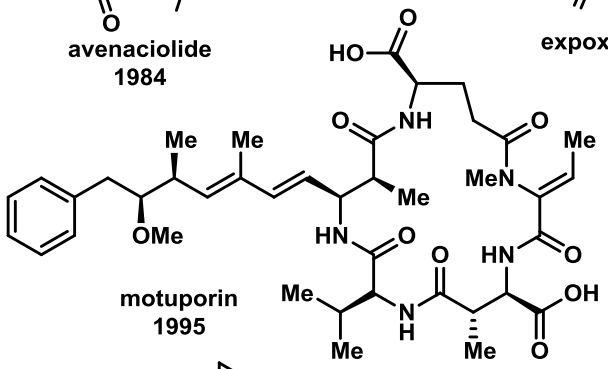
largazole
derivatives
2009



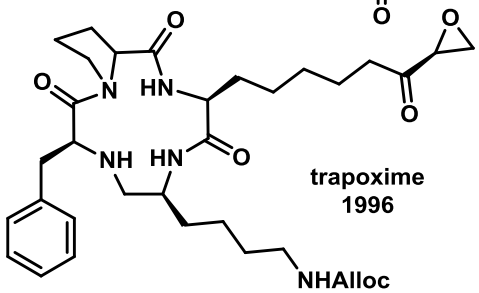
periplanone B
1984



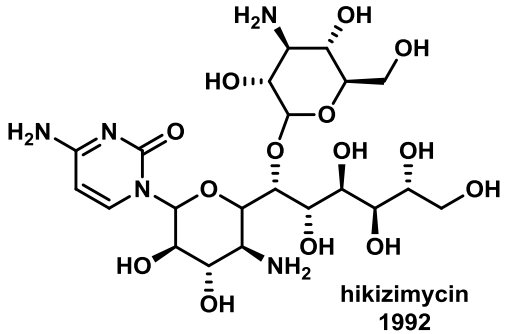
reciferolide
1980



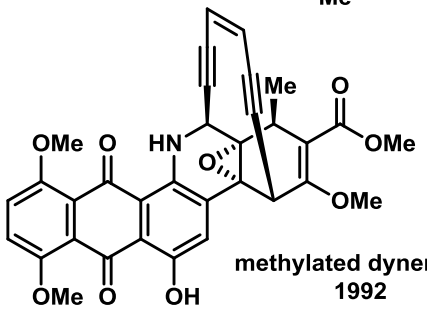
motuporin
1995



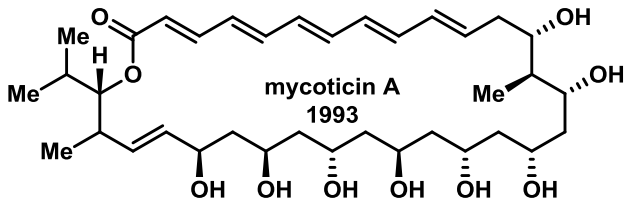
trapoxime
1996



hikizimycin
1992



methylated dynemicin
1992



mycoticin A
1993

"It was simply the aesthetics of these molecules - they are very beautiful art forms. And it was also the intellectual challenge of making them."

Matthew O'Neill

Early Contributions

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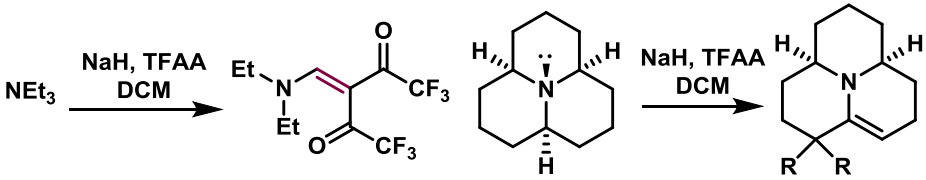
Stuart Schreiber was about to become a college dropout after three weeks at the University of Virginia when he snuck into a chemistry lecture; "Sitting in on one class made me decide what the rest of my life would be like," says Schreiber - HHMI

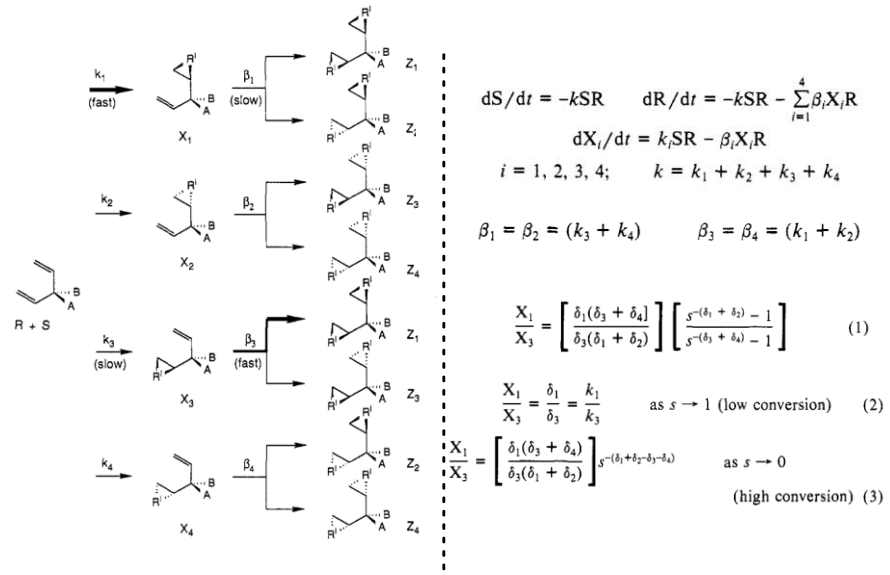
Hydrogen transfer from tertiary amines



First paper at Harvard dedicated to memory of R.B. Woodward R = $COCF_3$

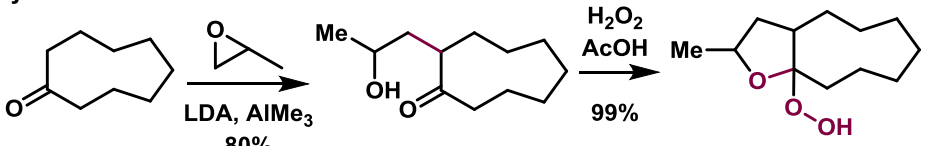
Tet. Lett. 1980, 21, 1027

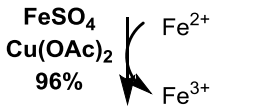
Mathematical model of enantioinduction



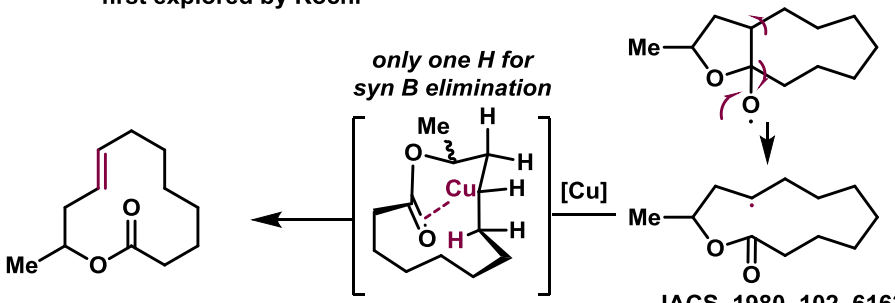
Later invoked in two directional chain synthesis approach JACS, 1987, 109, 1525

Synthesis of recifeiolide





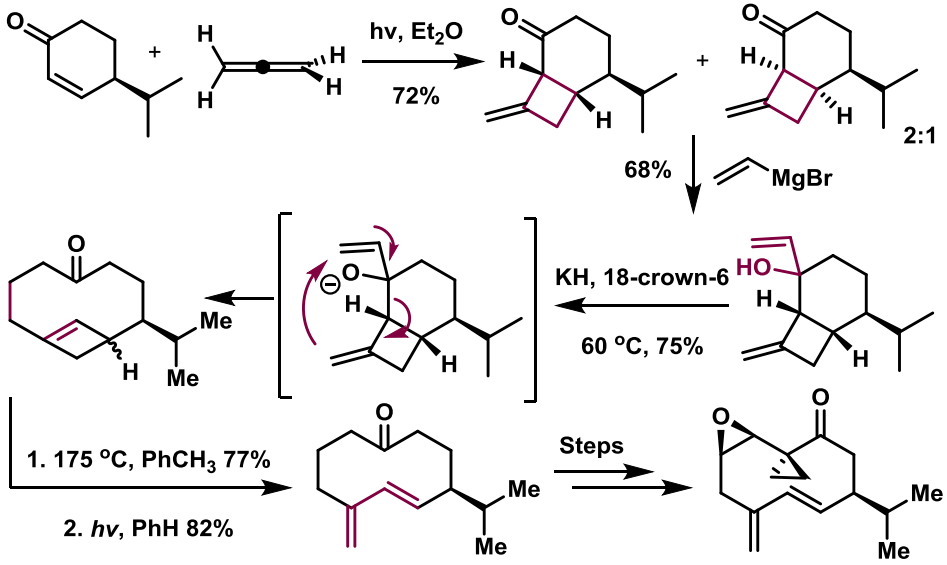
Metal fragmentations of peroxides first explored by Kochi



JACS, 1980, 102, 6163

Molecules covered briefly - periplanone B and asteltoxin

Extensively covered in *Classics in Total Synthesis I*



JACS, 1984, 106, 4038

Furan-Carbonyl Photocycloaddition

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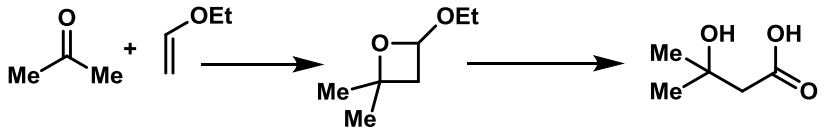
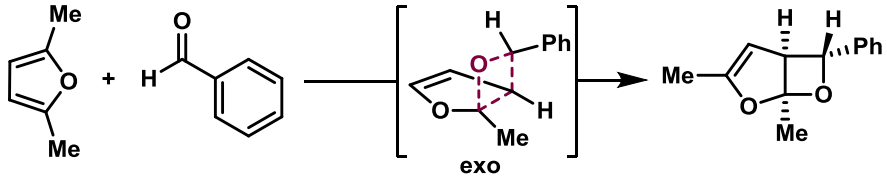


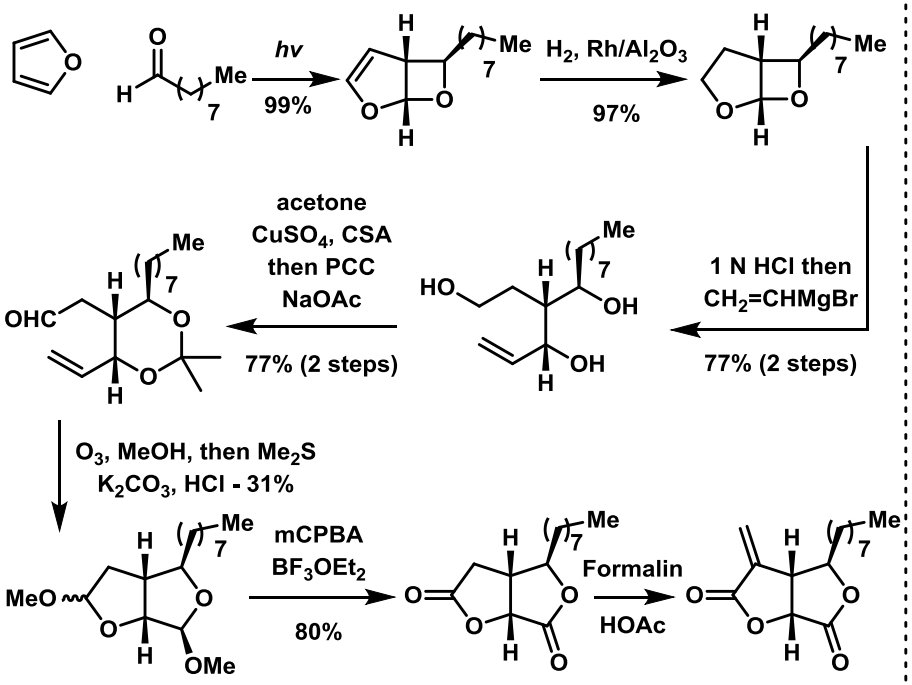
Paterno-Büchi reveals a latent aldol equivalent



Utilize furans as valuable [2+2] partners

Science, 1985, 227, 857.

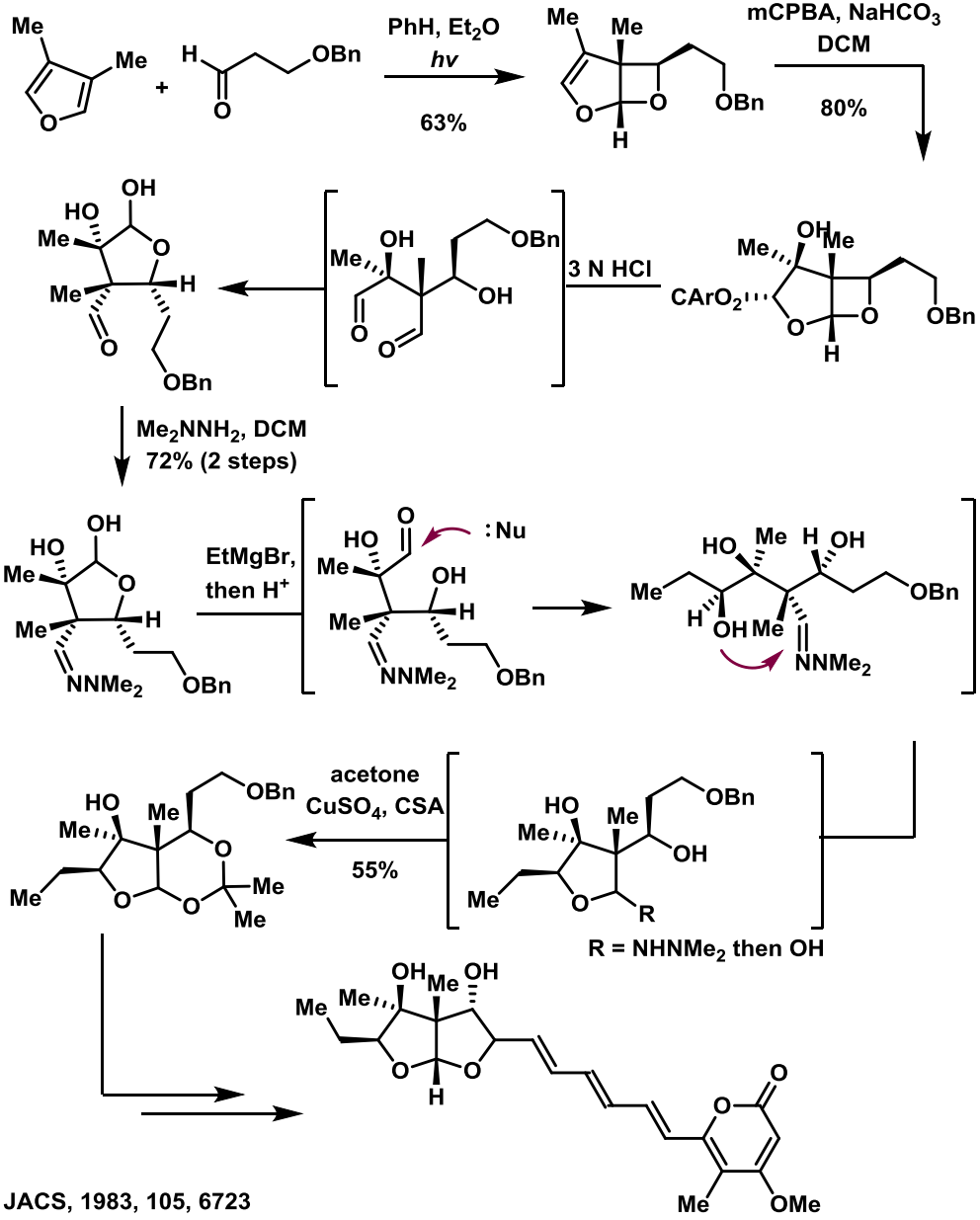
Synthesis of avenaciolide



JACS, 1984, 106, 7200

Synthesis of asteltoxin

Covered extensively in *Classis in Total Synthesis I*



JACS, 1983, 105, 6723

More Synthesis

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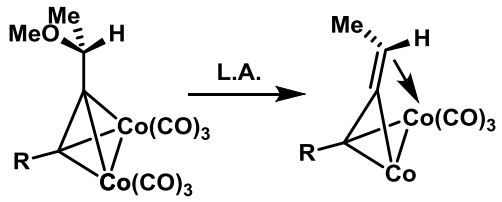
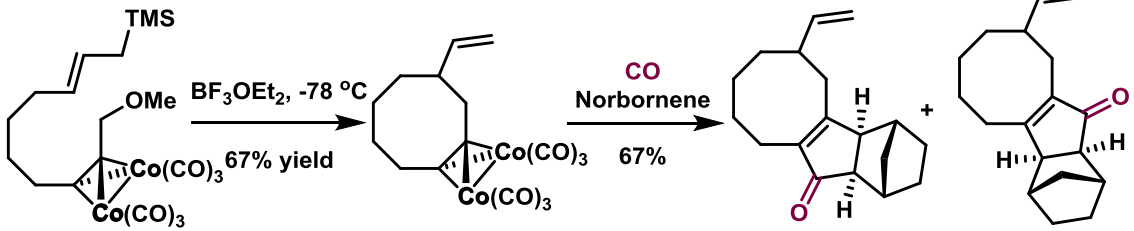
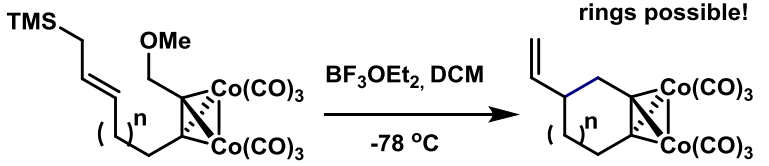
Lewis Acid-Mediated Nicholas Reaction



Telescoping with Phauson-Khand

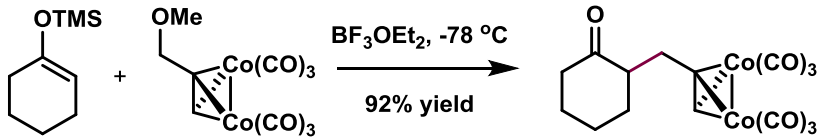


Intramolecular

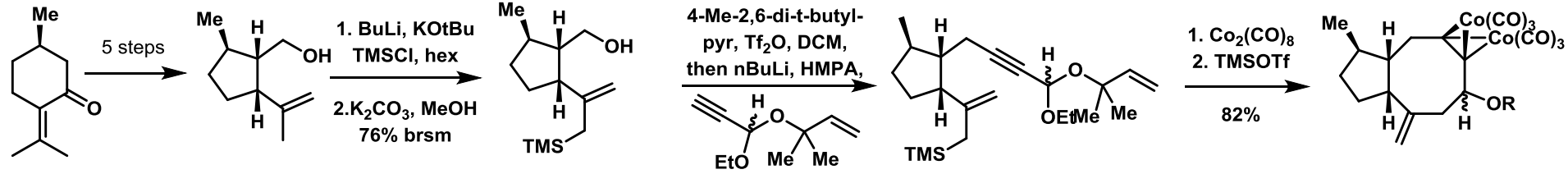


6, 7, or 8 membered rings possible!

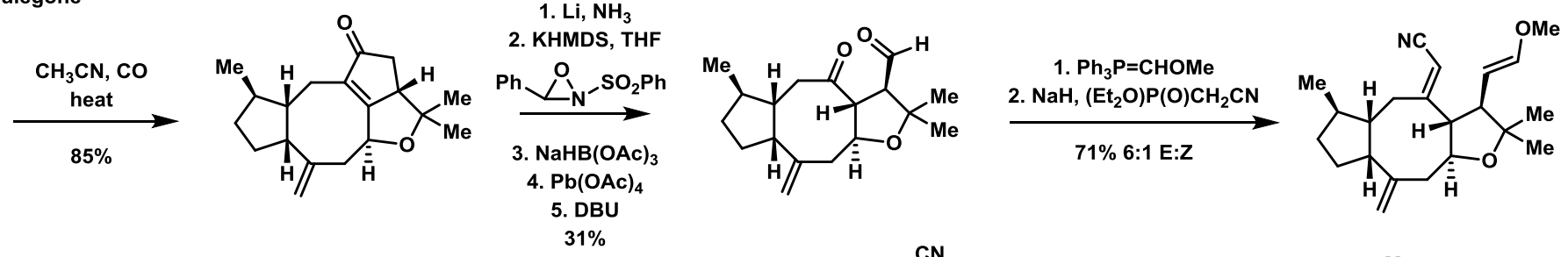
Intermolecular

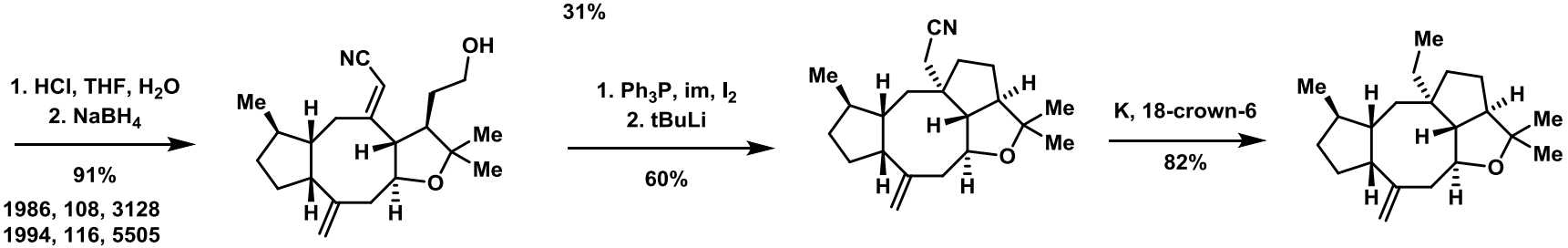


Synthesis of epoxydictimene



(R)-pulegone





JACS, 1986, 108, 3128
JACS, 1994, 116, 5505

Matthew O'Neill

Two Chain Elongation Strategy

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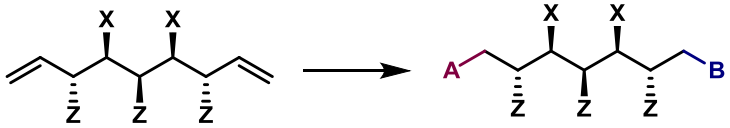
8.12.2017

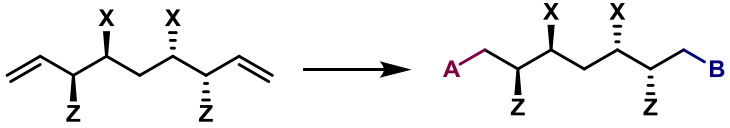
Schreiber helped formalize approach known as 'two directional' chain synthesis strategy 'where simultaneous double processing of chain termini and subsequent differentiation of the resulting homo-, enantio-, or diasterotopic groups at the chain termini are the defining features of the streategy'

Draws on mathematical model described earlier Acc. Chem. Res. 1994, 27, 9

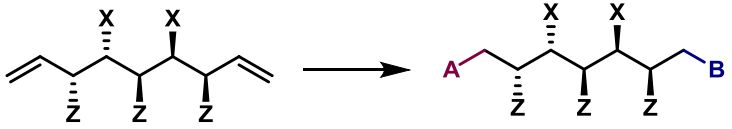
1. Achiral and *meso* Chains



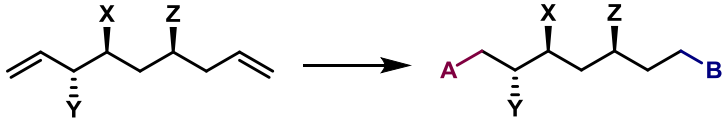
2. C_2 Symmetric Chain



3. Pseudo C_2 Symmetric Chain



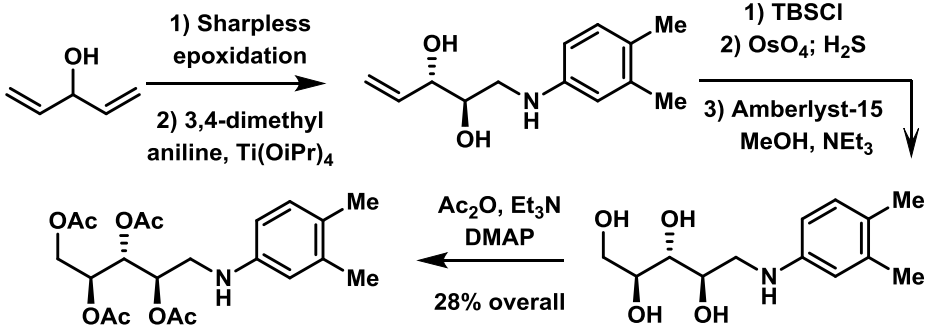
4. Non Symmetric Chain



*Helpful to consider this framework applied to contemporary work of Michael Krische - strikingly elegant approaches to polyketide synthesis

Achiral and Meso Chains

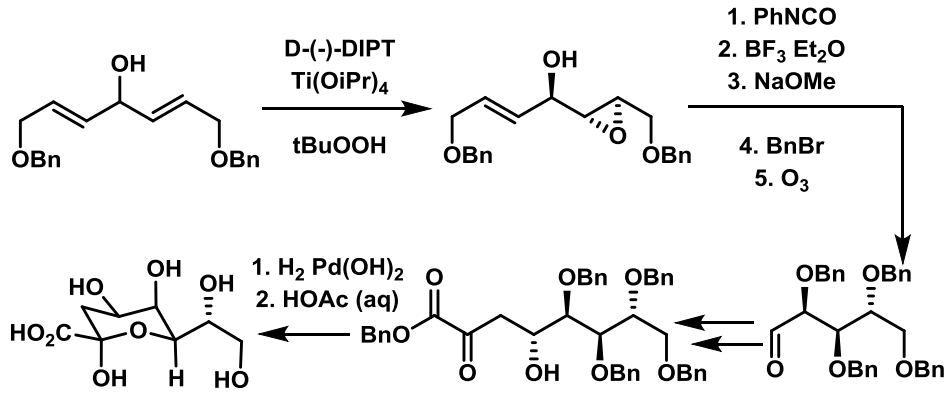
Formal synthesis of riboflavin



Either enantiomer available based on choice of L-(+)-DIPT or D-(-)-DIPT; L-(+)- shown

Tetrahedron, 1990, 46, 4793

Total synthesis of KDO



Tetrahedron, 1990, 46, 4793

"You can't miss the Porsche"
Harvard Crimson - 1996

Matthew O'Neill

Two Chain Elongation Strategy

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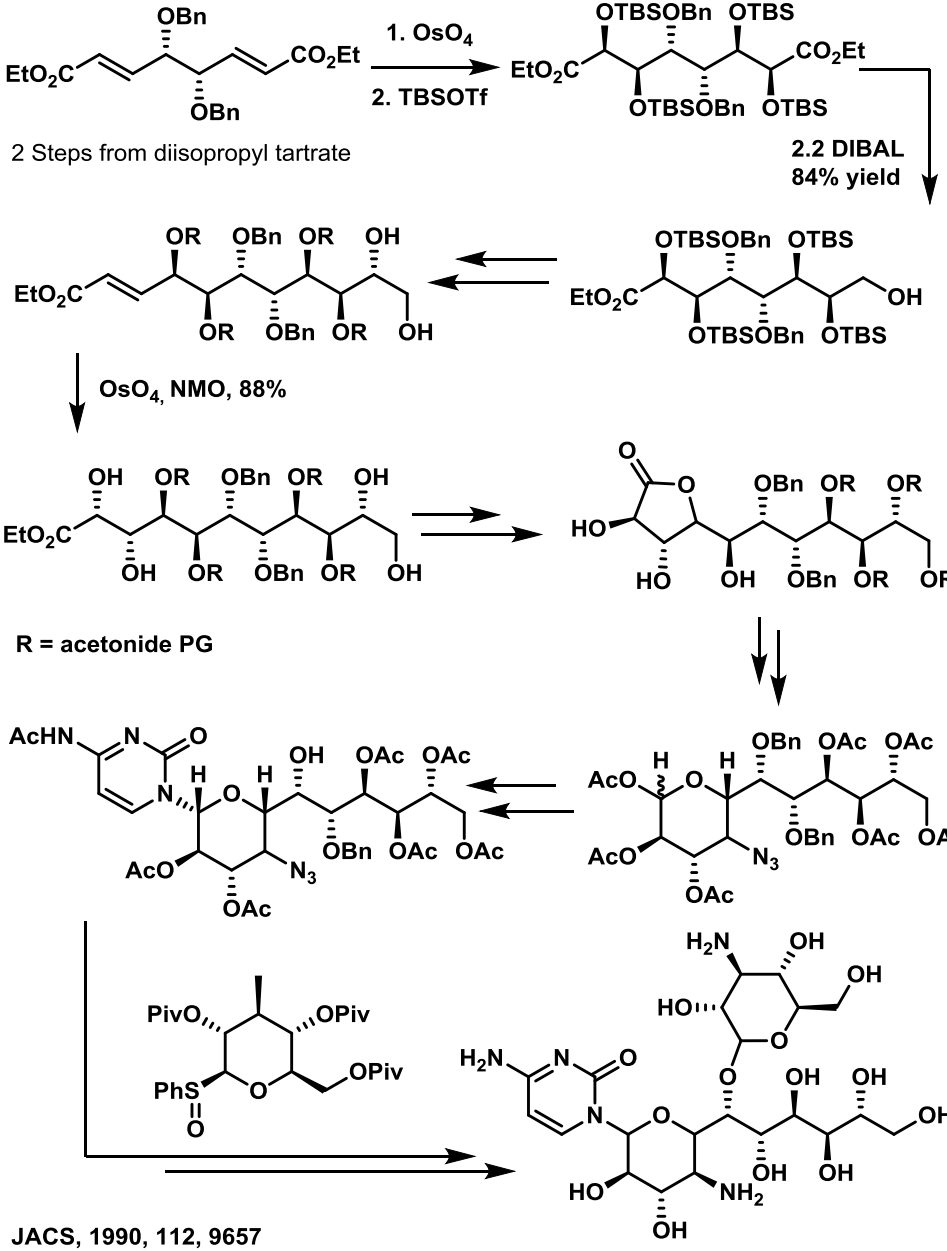
Total synthesis of hizikimycin

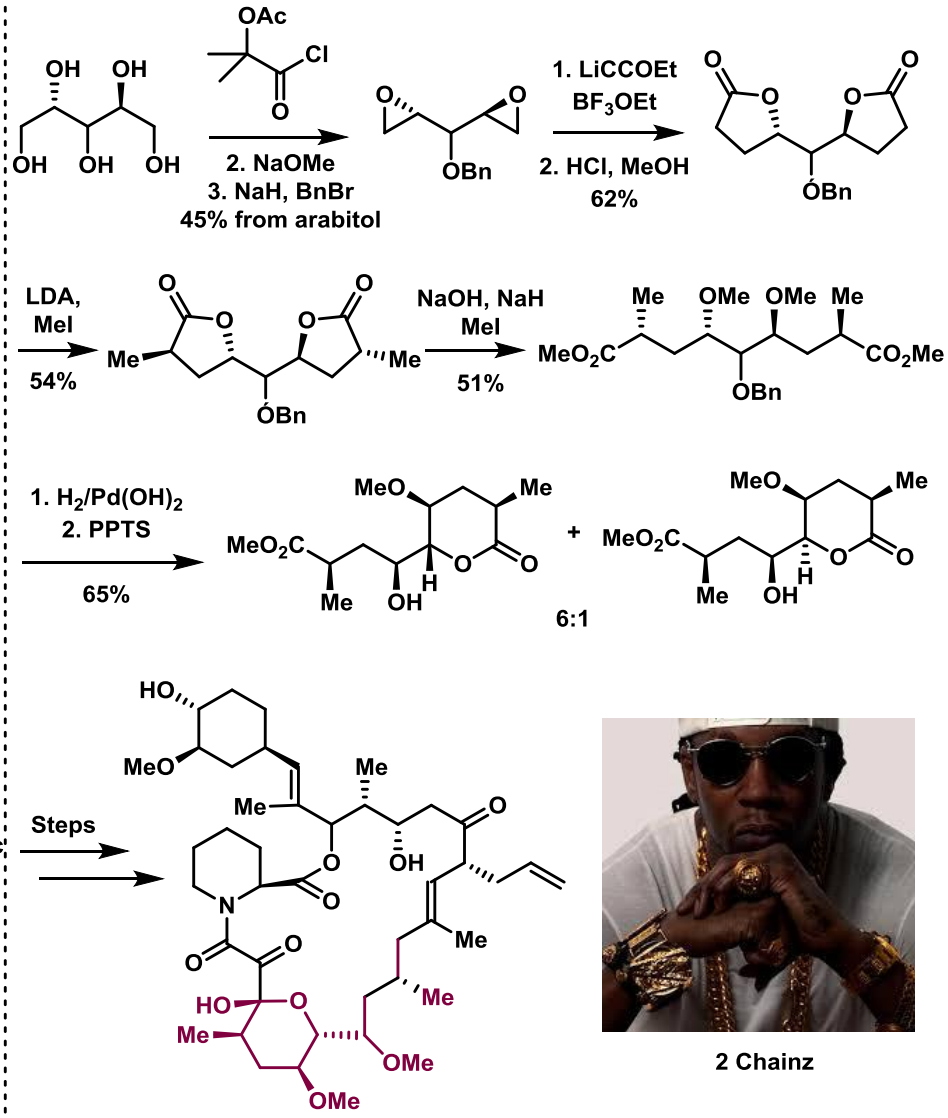
C_2 Symmetric Chain



JACS, 1990, 112, 9657

Total synthesis of FK506

Pseudo C_2 Symmetric Chain



2 Chainz

Non-symmetric Chain

For an example of two chain elongation from non-symmetric precursor chains, please see Nicolaou's synthesis of brevotoxin

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FK506 - Potent Immunosuppresant

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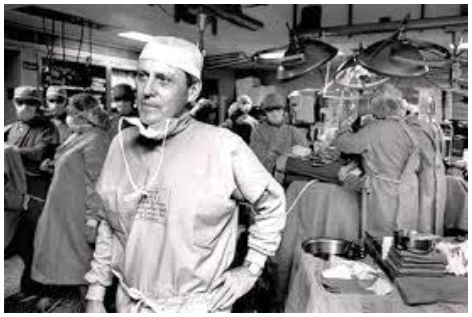


Thomas Starzl

Drug fomulation of FK506

Medical community originally resisted idea of organ transplantation

Transplanted organs expess non-self 'antigens' that trigger immune response causing organ rejection

Thomas Starzl MD PhD was a *pioneering immunologist and surgeon* who made seminal contributions to lung and kideny transplants

FK506 was discovered and quickly identified as a potent immunosuppresant, at which point Starzl began to champion its clinical potential

Schreiber begins synthetic efforts towards synthesizing FK506 and elucidating its mechanism of action - coincides (and clashes) with drug development efforts by Vertex Pharmaceuticals

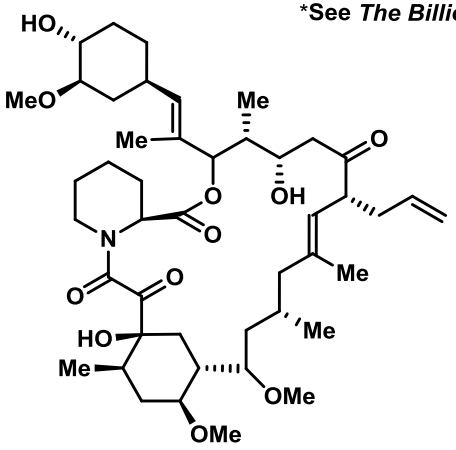
Schreiber's collaboration with Gerald Crabtree at Stanford shows complex MoA

FK506 cellular target is a 'pro drug', and the complex of FK506 and FKBP is itself an inhibitor of calcineurin

This signaling axis leads to nuclear transcription factor assembly and activation of T cell response

Early example of chemistry informing biology and complete understanding of cell signalling

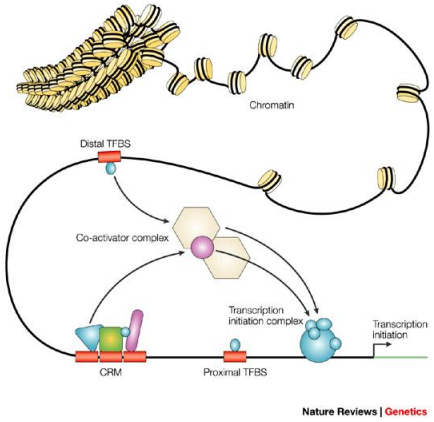
*See *The Billion Dollar Molecule* for a 'popular science' story of this development



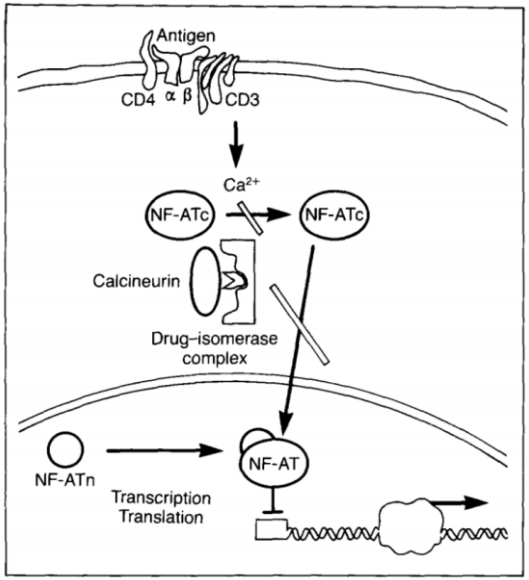
FK506

Led to Calcineuin - NFAT signalling axis identification with collaboration from Gerald Crabtree

First example of complete cell surface signal to nucleus pathway



Overview of gene transcription



Exogenous information from the cell surface is transduced by a signalling cascade to affect gene transcription in the nucleus and form a coordinated cellular response

NF-AT possesses a cytoplasmic and nuclear component - need both to perform function as a transcription factor

Cytoplasmic component must be 'activated' by calcineurin before it crosses into the nucleus to affect gene transcription

Immunology Today, 1992, 13, 136

"My favorite project, that will be in the near future I hope, is the one we point to and say that there are people who would otherwise be suffering, who are able to take medication or medicine of some sort, that really evolved from the structure of the Broad Institute"

Matthew O'Neill

Diversity Oriented Synthesis

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Diversity Oriented Synthesis (DOS) seeks to facilitate drug and probe development

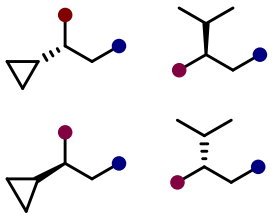
Contemporary small molecule drug development has three phases

1) Discovery - synthesize and screen compounds
2) Optimization - synthesize and analzye variants
3) Manufacturing - large-scale synthesis

How can we better streamline these activities to avoid bottlenecks and increase speed of discovery?

Build, Couple, Pair - General Approach

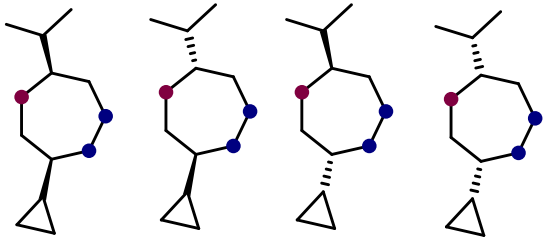
Build collection of small molecules with coupling and pairing functionalities



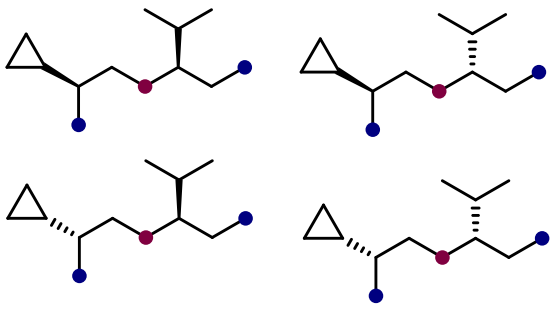
Couple all combinations of stereoisomers

Intermolecular

Aquire the complete complement of stereochemical space



Pair intermolecular adducts *intramolecularly*

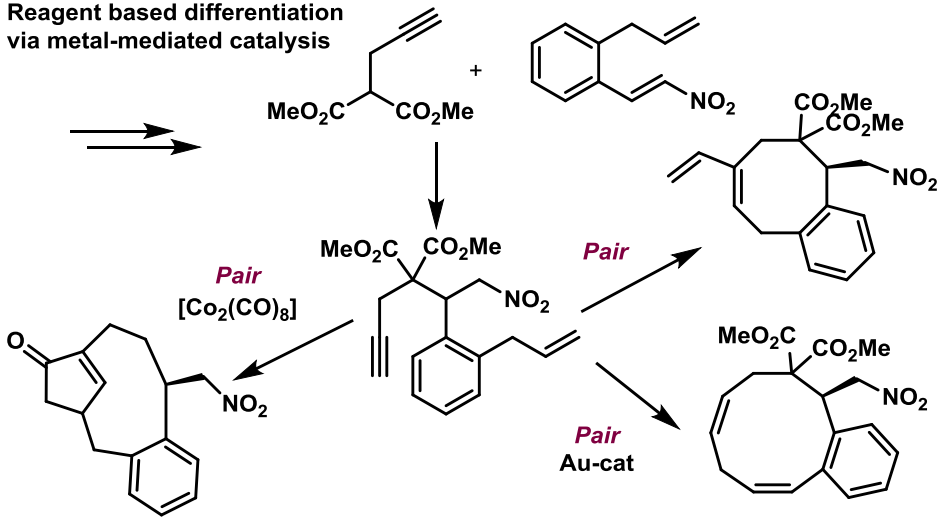


Functional Group Pairings

polar/polar - amine/ester
nonpolar/nonpolar - alkene RCM
polar/nonpolar - alcohol/alkyne

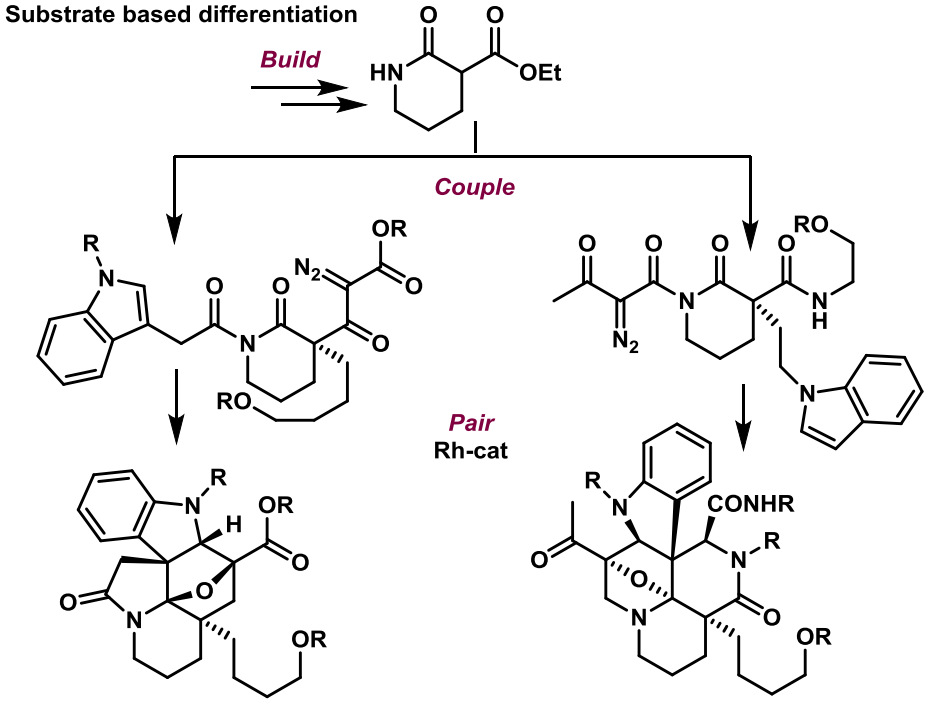
ACIE, 2008, 47, 48-56

Reagent based differentiation via metal-mediated catalysis



Science, 2000, 287, 1964

Substrate based differentiation



Org. Lett. 2005, 7, 47

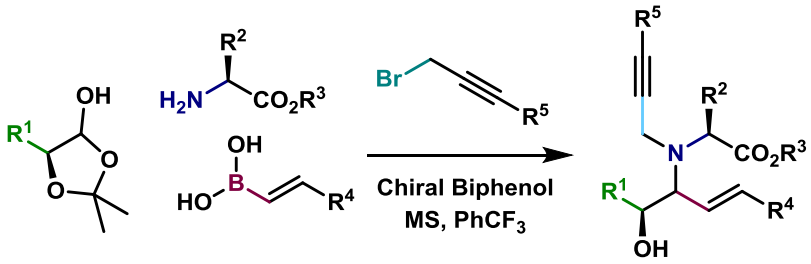
DOS: Evolving Methods

Matthew O'Neill

Cornella Group Meeting
8.12.2017

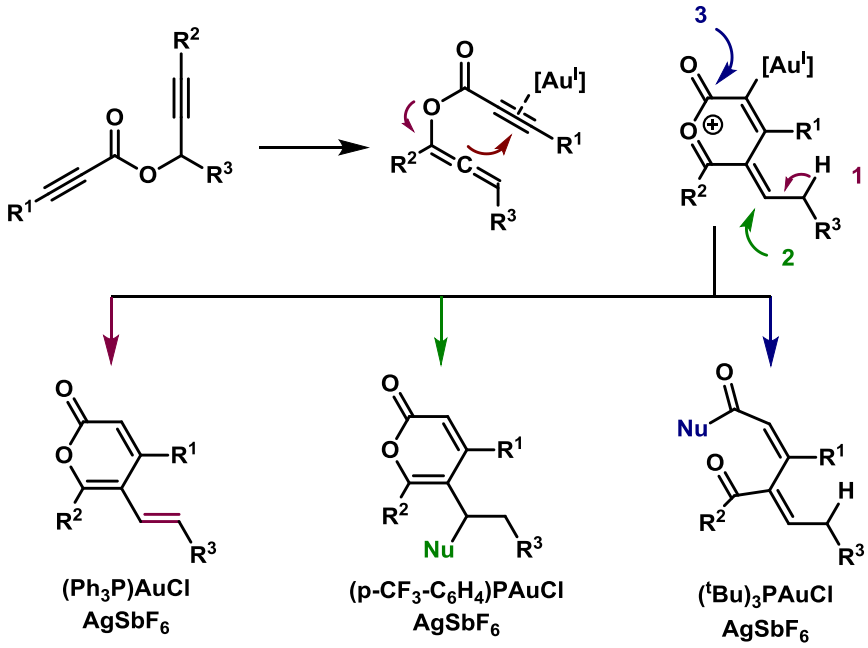
DOS for perturbing PPI - "Admittedly I am biased, but I think one technology that could crack this problem is diversity-oriented synthesis by creating more complex molecular contours that are potentially more relevant to the topographic problem of disrupting protein-protein interactions"

Catalytic diastereoselective Petasis reaction



ACIE, 2011, 50, 8172

Development of complementary gold couplings

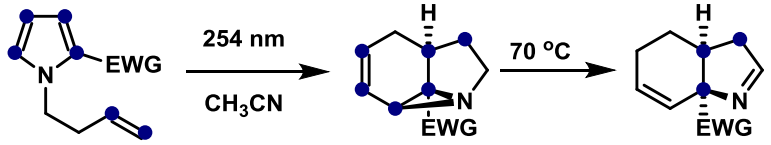


JACS, 2009, *131*, 5667

Control reaction outcome by ligand electronics

Diversity-Oriented-Synthesis Enables Real-Time Biological Annotation of Compounds

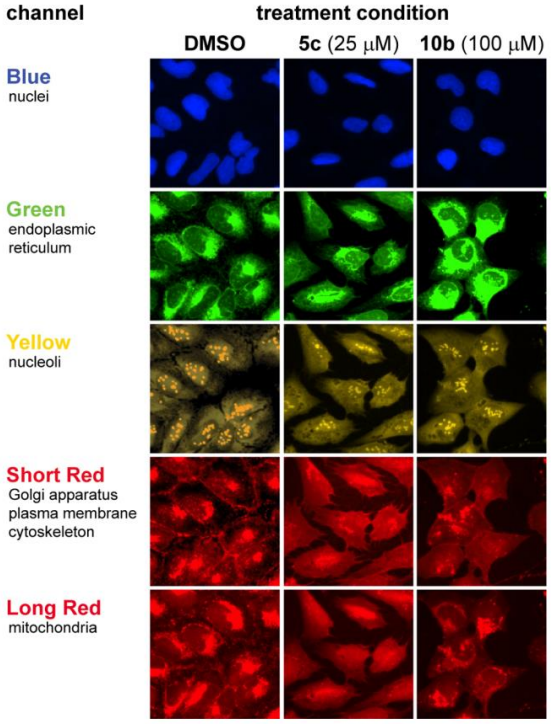
Disconnection between synthesis of compounds and biological testing
Use DOS and 'cell painting' to both structurally and biologically characterize library



ACIE, 2013, 52, 1499

When EWG = Ac, then starting pyrrole has *3 sp^3 C's, no chiral center, and one ring*, but intermediate aziridine contains *7 sp^3 C's, three chiral centers, and three rings*!

'Cell Painting' anaylzes over 1000 morphological changes!



Day 1

Plate cells at 1000-2000 cells/50 uL well
Grow overnight at 37 °C

Day 2

Prepare reagents and stock solutions
Pin compounds
Treat for 24 hours at 37 °C

Day 3

Prepare staining solutions
Remove media from assay and add SS1
Fix cells, wash, permeabilize cells
Wash and add SS2
Wash and seal
Capture images

JACS, 2016, 138, 8920

Matthew O'Neill

Origins of Chemical Biology

Cornella Group Meeting
8.12.2017

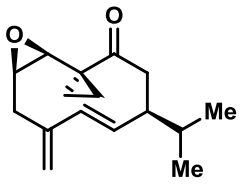
"The marriage of biology and chemistry has never been more important than today"

"In the same way that next-generation sequencing is transforming genetics, next-generation synthesis is transforming molecular biology"

"The chemist simply needs to know what those fields are capable of achieving and how it connects back to their own skill set and discipline"

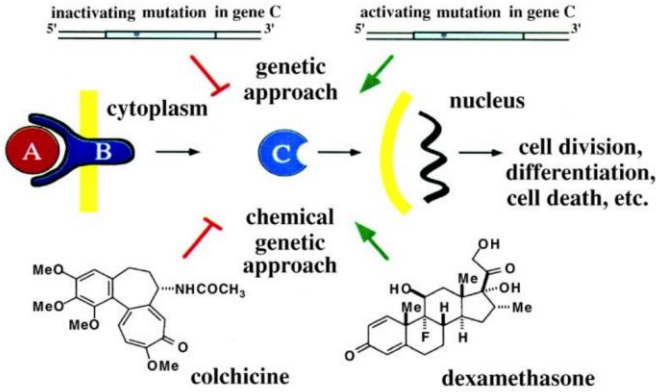
HHMI

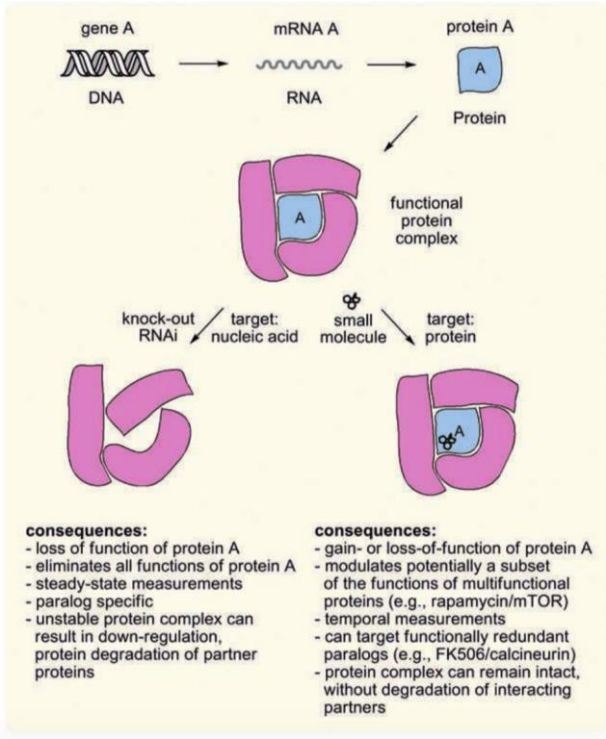
Schreiber first interested by effect of periplanone B due to its potent effects as a cockroach pheremone



Chemical Genetics - biologists perturb with mutations in genes, chemists perturb with small molecules

"If you happened to have a compound that had an interesting effect, then you might be able to study that property. But, if you wanted to study the basis of memoery and cognition, for example, it wasn't so obvious what you would do next."





Traditional genetics vs. chemical genetics

Interesting Thoughts

"The original goal of the human genome project was to 'sequence every gene'. With that goal within sight, I suggest we consider a new goal for this project, one that can only be realized through the creative use of chemistry, 'to identify a small molecule partner for ever gene product"

"Even more ambitiously, will we be able to recapture the many millions of presumed 'transient' natural products that were evolutionarily de-selected along the paths that eventually led to the natural products synthesized on Earth today?"

Bioorg. Med. Chem. 1998, 6, 1127

"It is popular for chemists to say that biologists can't learn chemistry. Let me try to refute that argument. When a chemist makes that statement, they are underestimating how difficult it is to learn biology. I've been studying biology for the past 20 years and I still do not consider myself a card-carrying biologist."

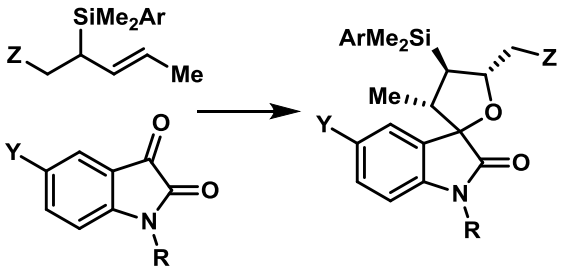
Matthew O'Neill

Chemical Biology: Examples

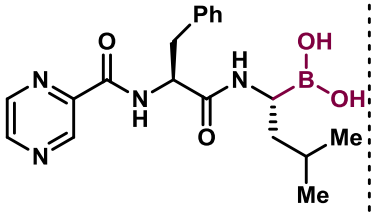
Cornella Group Meeting
8.12.2017

Main Group Incorporation

Annulation of allyl silanes with pi electrophiles

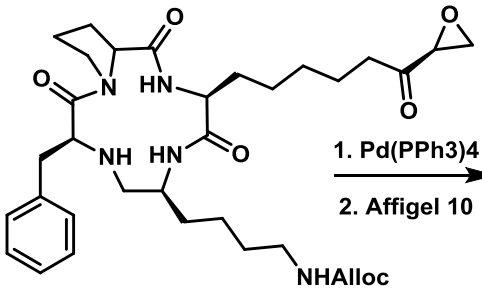


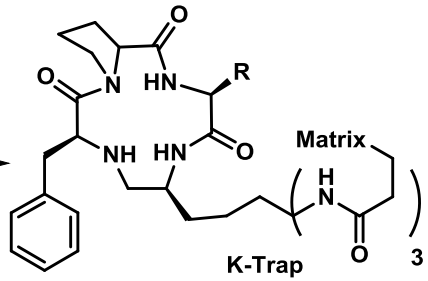
JACS, 2007, 129, 1020



Bortezomib - main group element in a threapeutic context

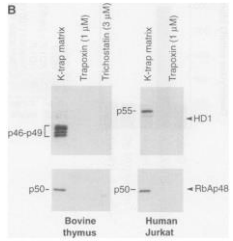
HDACs - Inhibition and Discovery





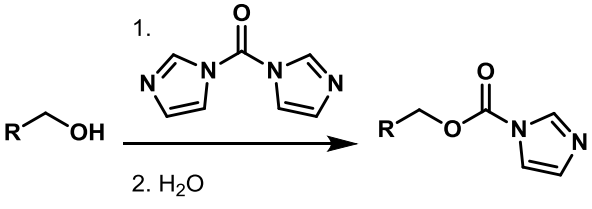
First isolation of a histone deacetylase
HDACs function by regulating the epigome
Huge area of contemporary drug discovery

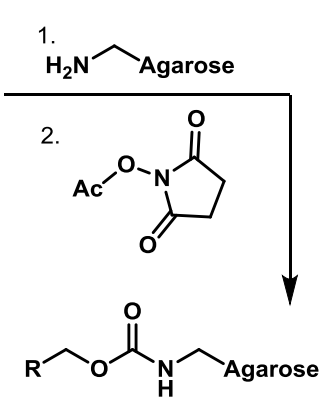
Science, 1996, 272, 408



Affinity Purification - Pull down technique

Problem in biology - how to identify cellular target of molecule?
Different functional groups require different handles
Must be orthogonal to 'active' component of molecule





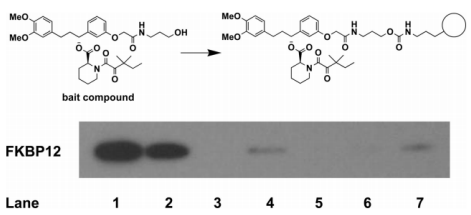
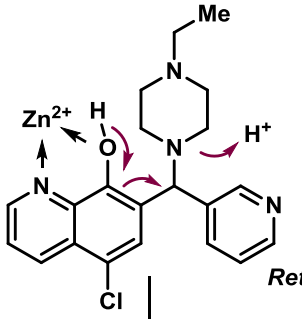


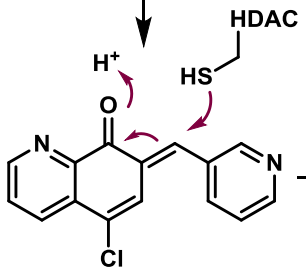
Figure 5. Immobilization of a compound known to bind immunophilin proteins and the affinity purification of FKBP12 from A549 whole cell lysate using the immobilized bait. In the Western blot, lane **1**, affinity-purified protein sample 1 using immobilized bait compound; lane **2**, affinity purified protein sample 2 using immobilized bait compound; lane **3**, affinity purified protein sample 3 using blocked blank beads; lane **4**, A549 whole cell lysate; lane **5**, residue cell lysate 1 after affinity purification using immobilized bait compound; lane **6**, residue cell lysate sample 2 after affinity purification using immobilized bait compound; lane **7**, residue cell lysate sample 3 after affinity purification using blocked blank beads.

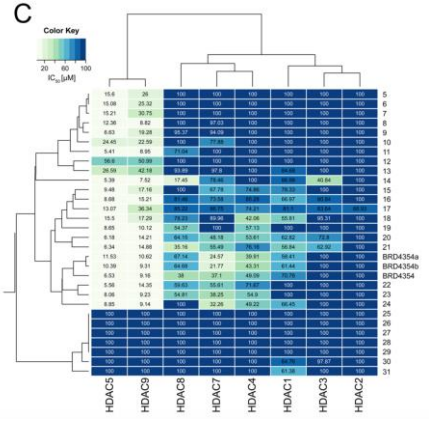
Bioconjugate Chem. 2008, 19, 585

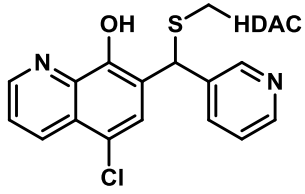
Covalent HDAC Inhibitors



Retro-Mannich







ACS Chem. Biol. 2016, 11, 1844

"But technically speaking, that challenge understates what we really want to do, which is to use small molecules to modulate the individual functions of multifunctional proteins, activating or inactivating individual functions as necessary"

Extra Methods

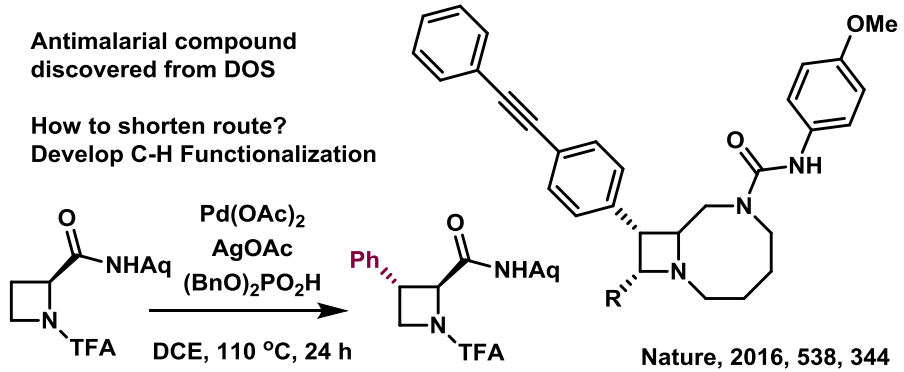
Matthew O'Neill

Cornella Group Meeting
8.12.2017

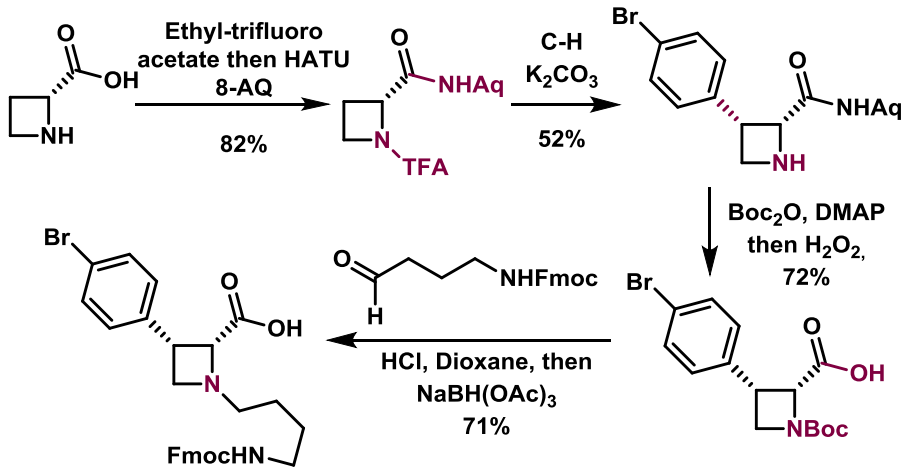
DOS with Methodology to Explore Antimalarial Candidates

Antimalarial compound discovered from DOS

How to shorten route?
Develop C-H Functionalization



Nature, 2016, 538, 344

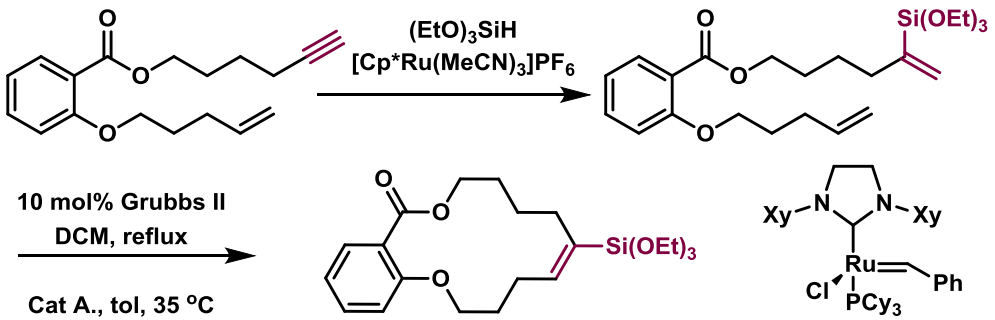


JACS, 2017, 139, 11300

Distinct Apporaches to Macrocycles

RCM Olefin geometry control

JACS, 2011, 133, 9196



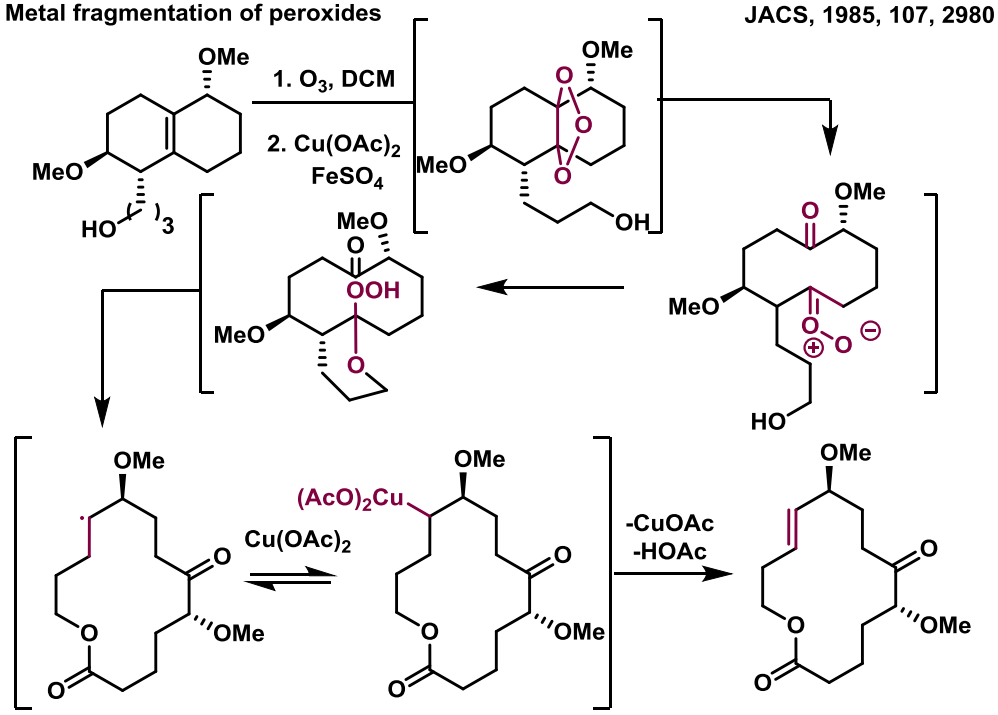
Orginal - n = 1, 27%; n = 2, 3%
Optimal - n = 1, 95%; n = 2, 63%

Cat. A

Protodesilylation with TBAF, AgF, AcOH, THF

Metal fragmentation of peroxides

JACS, 1985, 107, 2980



Matthew O'Neill

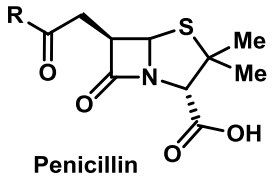
Future Outlook

Cornella Group Meeting
8.12.2017

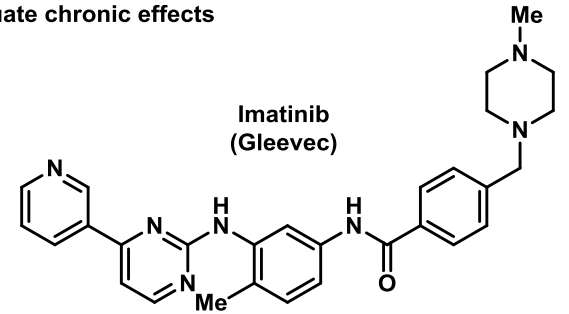
Patient Based Therapeutics

Small molecule drug discovery evolving through 3 stages

Compound-based drug discovery
Discover small molecule - identify potential uses (i.e. penicililn, vancomycin)
Target-based drug discovery
Identify target from molecular/cell biology - develop a ligand and optimize to drug
Patient-based drug discovery
Full characterization of molecular pertubations and specific gene matched drugs to alleviate disorder or attenuate chronic effects



Penicillin

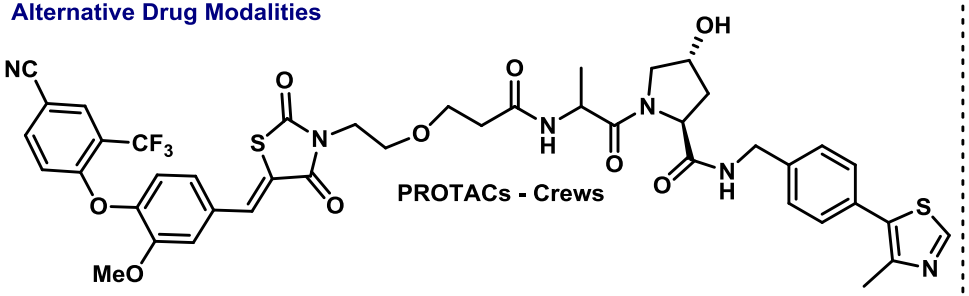


Imatinib
(Gleevec)

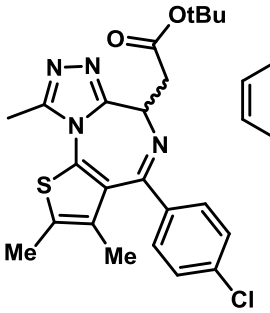
Nature Biotechnology, 2010, 28, 904

Traditional Drug Modalities

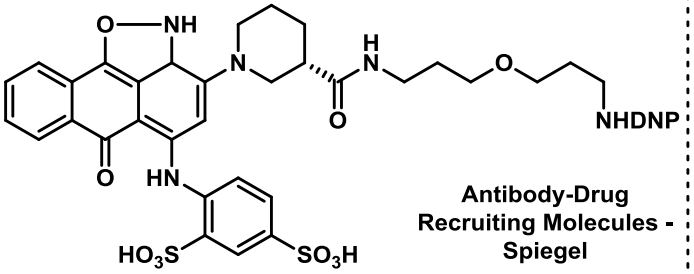
Alternative Drug Modalities



PROTACs - Crews



Bromodomain inhibitors - Bradner



Antibody-Drug Recruiting Molecules - Spiegel

Organic Chemistry as an Enabling Science

Where are we now?

'We shall leave it that the evidence is overwhelming that the creative function of organic chemistry will continue to augment Nature, with great rewards, for mankindand the chemist in equal measure' - Woodward *Perspectives in Organic Chemistry* 1956 p. 180.

For Chemical Biology Context

'Wie werken die Gene?' and 'Was ist das stoffliche Wesen der an bestimmten Orten der Chromosomen lokalisierten Gene?' - Butenandt *Perspectives in Organic Chemistry* 1956 p. 495.

Final message - how can we best harness the intrinisc complentarity of chemistry and biology to realize the greatest advances in contemporary medicine?