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Wednesday, September 26, 2012



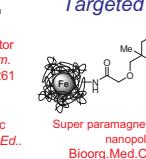
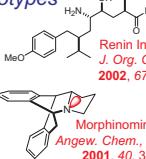
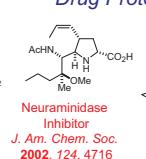
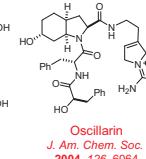
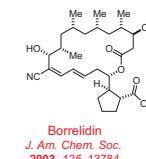
Lecture outline

- Definitions
- The *Why*, *What*, and *How* of synthesis
- The visual dialogue with molecules
- The psychobiology of heuristic synthesis planning
- Living through a total synthesis
- Synthesis: from whence we came, to where we are going
- Ciao

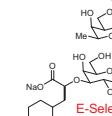
Relevant Chemistry in the Hanessian Group

Website: <http://osiris.org.umontreal.ca>

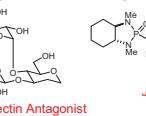
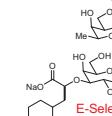
Natural Product Synthesis



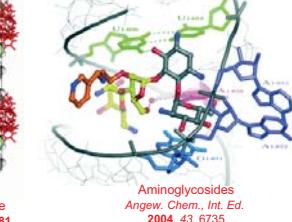
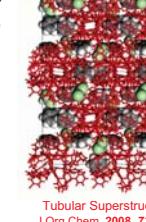
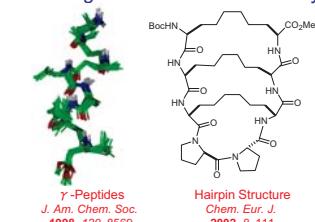
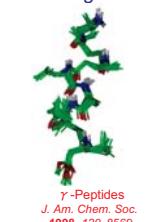
Carbohydrates



Asymmetric Synthesis

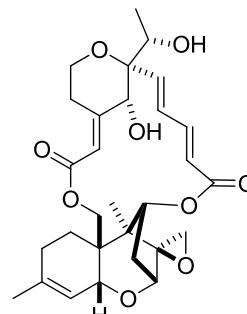


Molecular Recognition and Self-Assembly



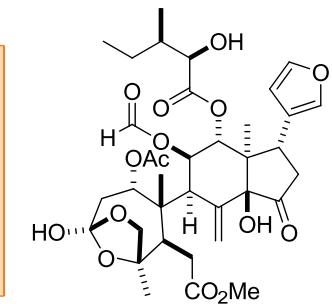
The 'academic' Synthetic Chemist's Dilemma

1. Incentives, reasons, and rationales for synthesis (The *Why* of synthesis)
2. Which molecule should I synthesize ? (The *What* of synthesis)
3. How can I make sure I have an efficient and viable route ? (The *How* of synthesis)
4. Where and with what do I begin?



Satratoxin H
(Household mold)

Molecule of your choice

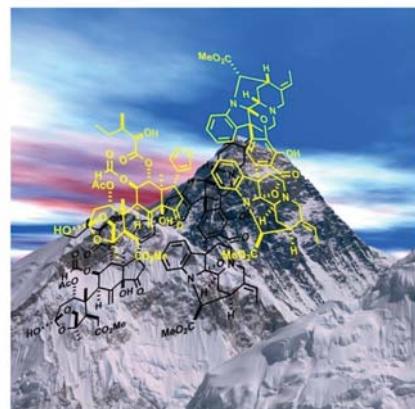


Nymania 1
(Anti-proliferative activity)

18 Chapters
Over 900 pages

Design and Strategy in Organic Synthesis

From the Chiron Approach to Catalysis



Expected before
end of 2012

The Why of Synthesis

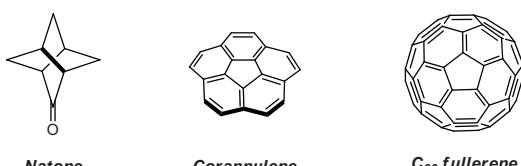
- Nature: the provider, the healer and the enticer (new antibiotics)
- The supply problem (practical syntheses of sparse compounds)
- Synthesis as a seeker of truth (correction of misassigned structures)
- Beyond the molecule (buckeyballs and friends)
- Exploring new dimensions in methodology (efficiency and practicality)
- Creating new entities and materials (nanomolecules and beyond)

The What of Synthesis

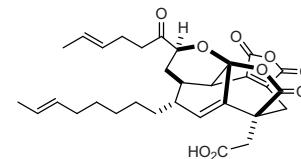
Fascinating Molecular Shapes



Cubane Adamantane Homopentaprismane Dodecahedrane Bullvalene Twistane

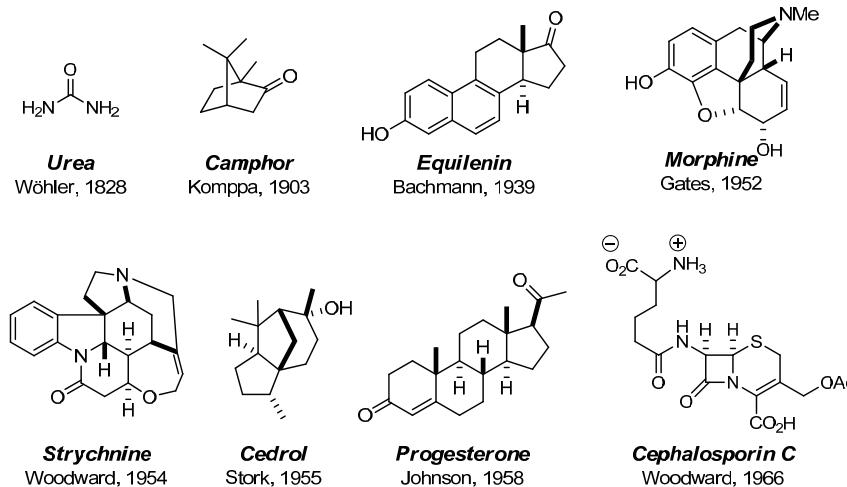


Natone Corannulene C₆₀ fullerene



CP-263,114 (Phomoidride B)

Selected Highlights in Total Synthesis



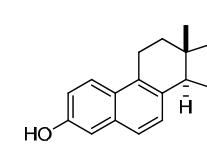
Urea

Wöhler, 1828



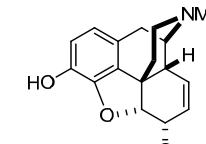
Camphor

Komppa, 1903



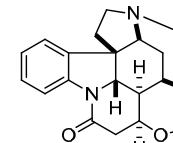
Equilenin

Bachmann, 1939



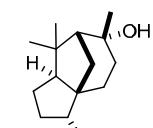
Morphine

Gates, 1952



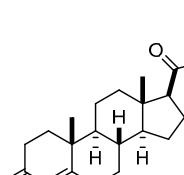
Strychnine

Woodward, 1954



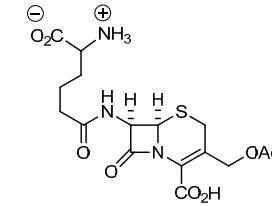
Cedrol

Stork, 1955



Progesterone

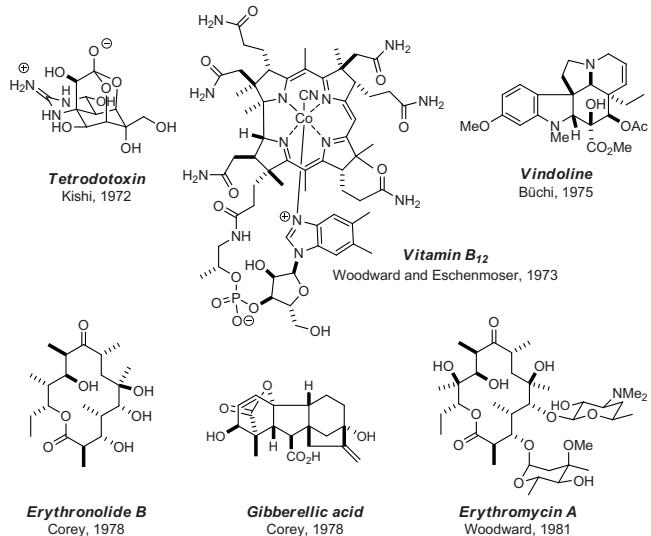
Johnson, 1958



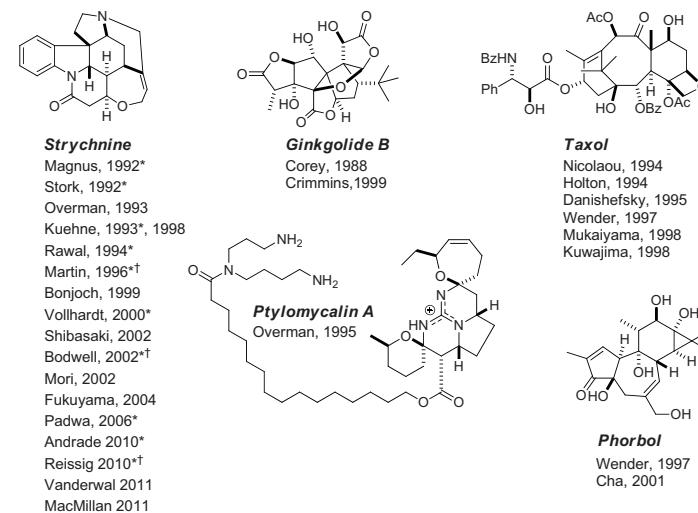
Cephalosporin C

Woodward, 1966

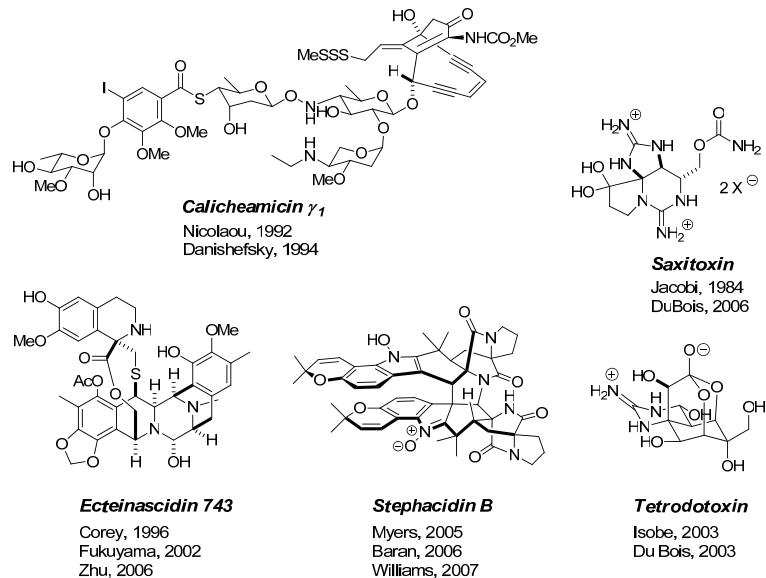
Selected Highlights in Total Synthesis of Complex Natural Products



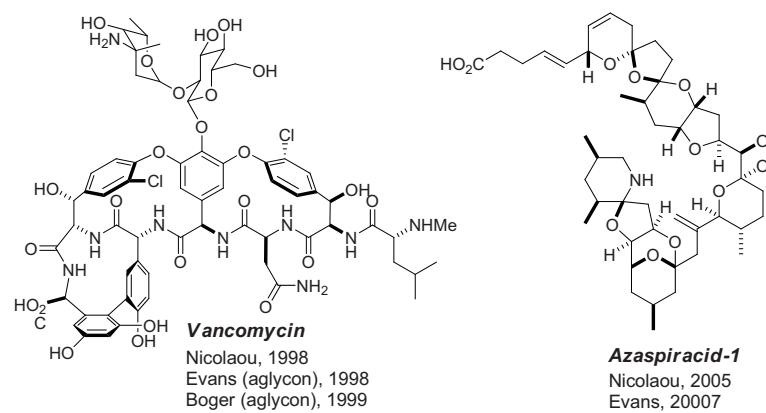
Selected Highlights in Total Synthesis of Complex Natural Products



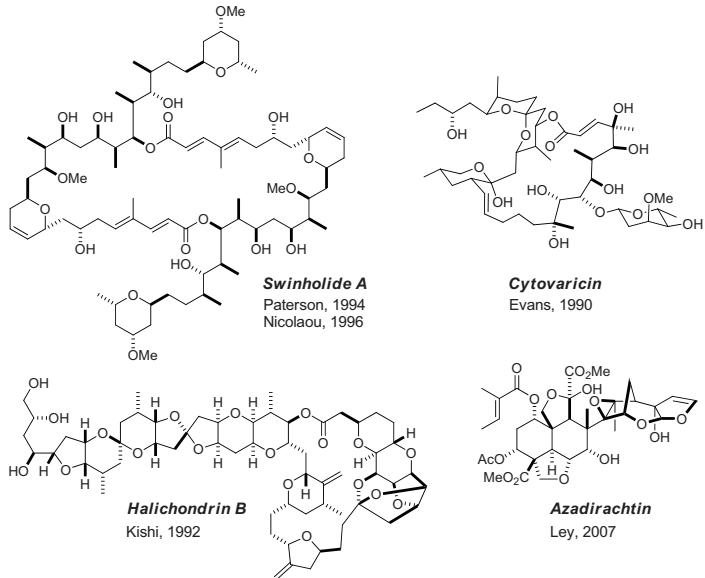
Selected Highlights in Total Synthesis of Complex Natural Products



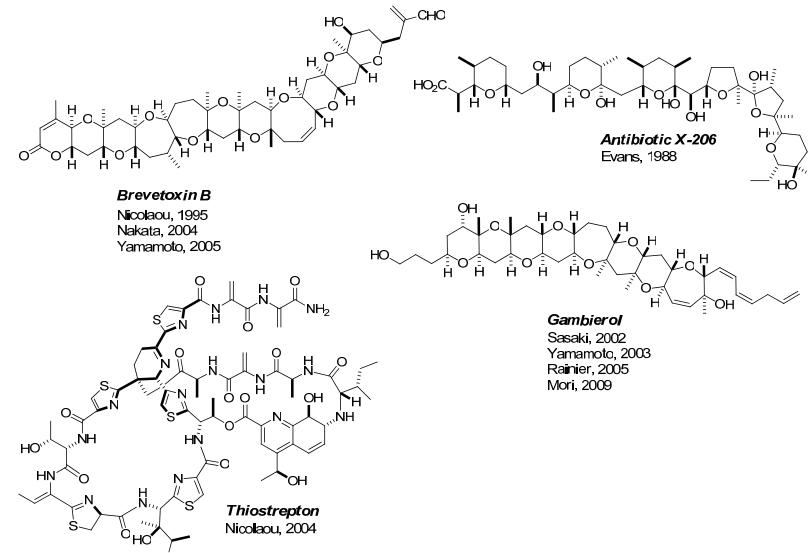
Selected Highlights in Total Synthesis of Highly Oxygenated Complex Natural Products



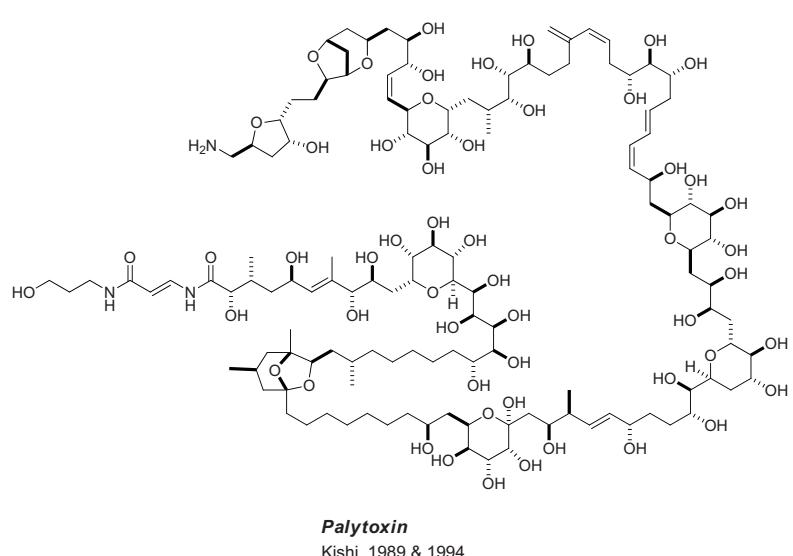
Selected Highlights in Total Synthesis of Highly Oxygenated Complex Natural Products



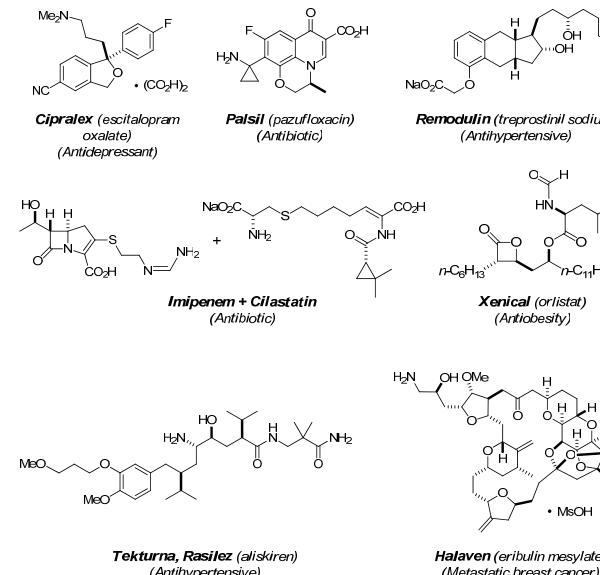
Selected Highlights in Total Synthesis of Highly Oxygenated Complex Natural Products



Highlights in Total Synthesis of Highly Oxygenated Complex Natural Products



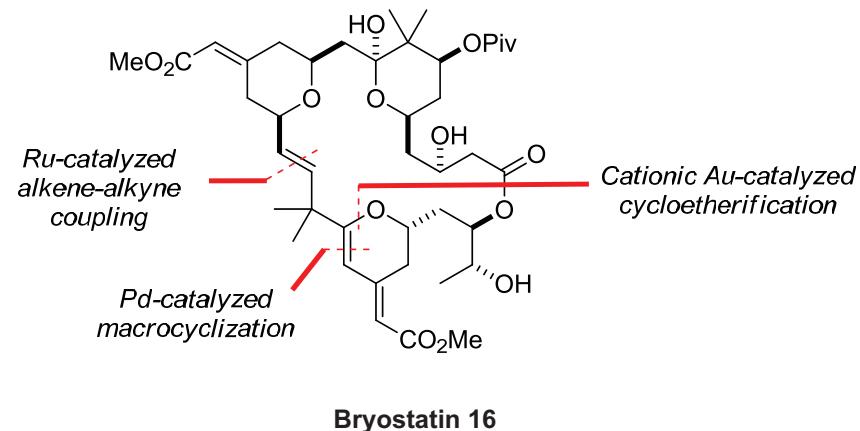
Selected examples of recently marketed drugs produced by total synthesis



The How of Synthesis

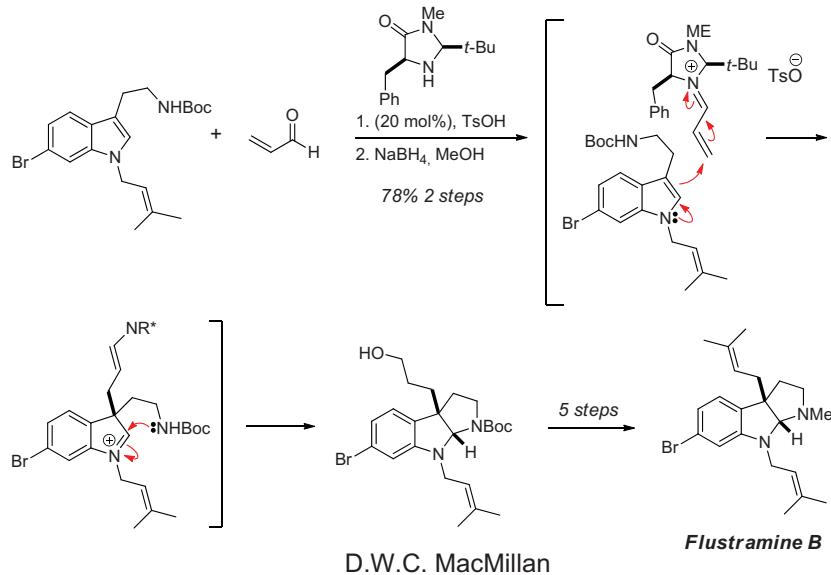
- Asymmetric Synthesis:
 - Resident-chirality control (substrate control)
 - Reagent or catalyst control (external control).
 - a. Metal and ligand-based;
 - b. Metal-free based (organocatalysis)
- The '**Chiron Approach**' : (Structural and stereochemical elements dictate strategy)
- Maximizing chirality and structural convergence using nature's chiral non-racemic molecules (amino acids, carbohydrates, hydroxy acids, terpenes)
- The '**Synthon Approach**' (Reaction feasibility dictates strategy)
- Biomimetic Synthesis

Metal-catalyzed Chemistry

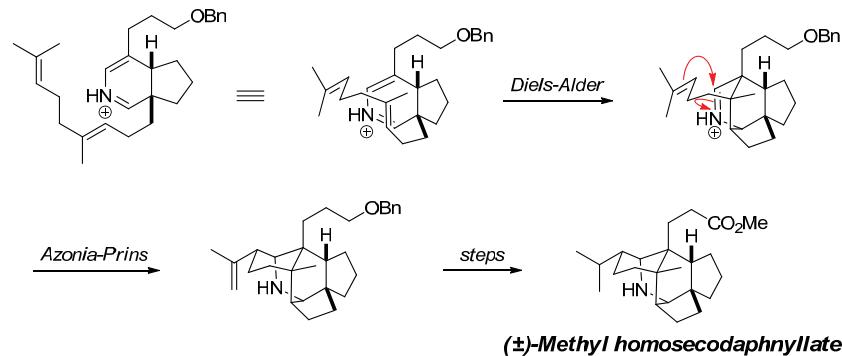


B.M. Trost

Organocatalysis in Natural Product Synthesis



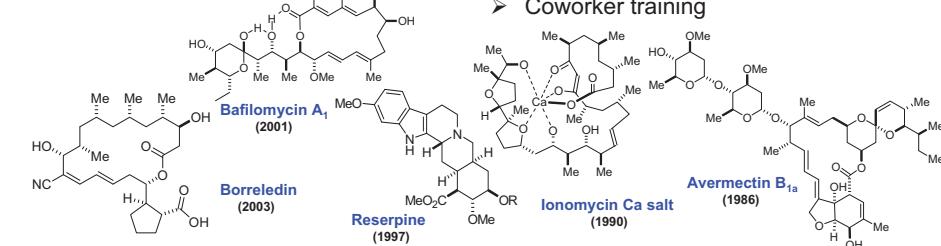
Biomimetic Cascade Reactions in Total Synthesis



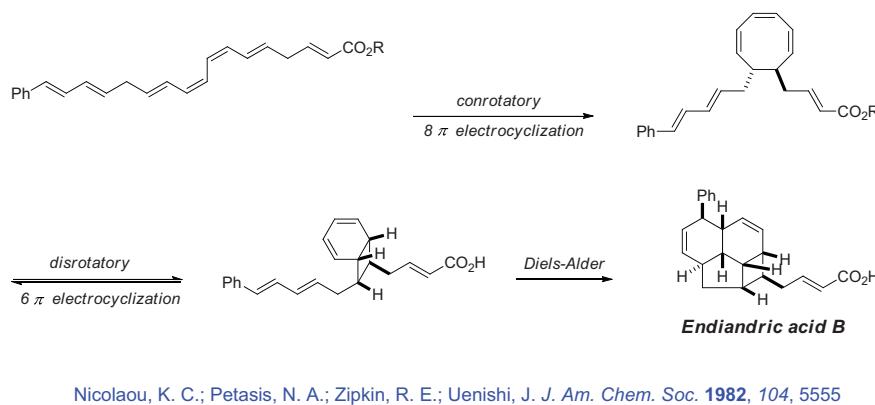
Ruggeri, R. B.; Hansen, M. M.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734

Living Through a Total Synthesis

- A. Choice of target molecule
- B. Perceptive powers and seeing through the mind's eye
- C. Emergence of a strategy
- D. Generation of a synthesis plan
- E. Execution
- F. Endurance
- G. Contribution to science
- H. Recognition
- I. Lasting value
- Relevance
- Heuristics, open-eyed serendipity, and personal bias
- Individual prowess, creativity
- Attention to detail, possible fixation (beware!)
- Efficiency, practicality
- What price synthesis?
- New concepts, reactions, reagents, etc.
- Fame, fortune, legacy
- Coworker training

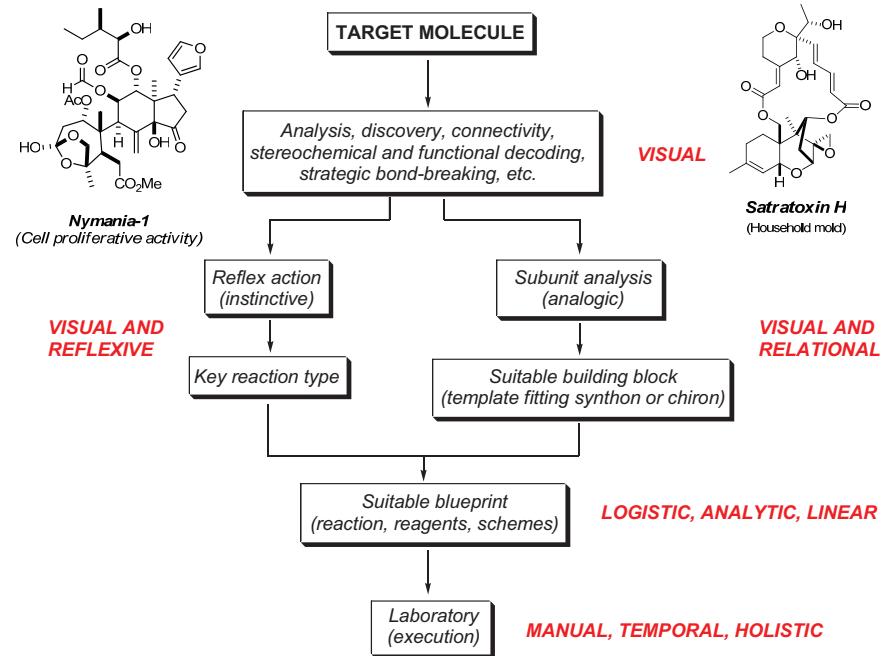
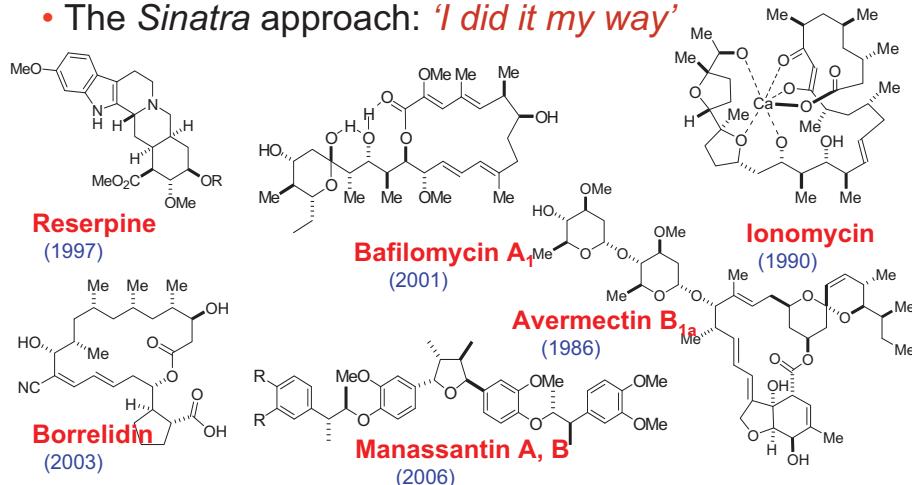


Biomimetic Cascade Reactions in Total Synthesis

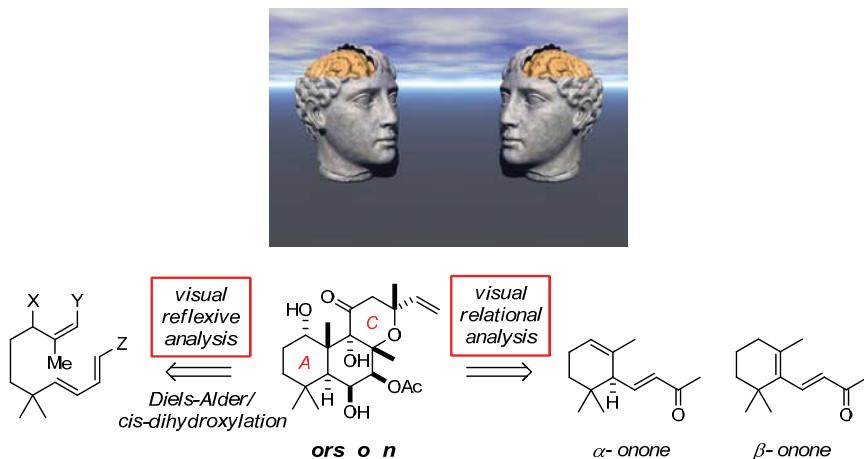


Total Synthesis Scenarios (*synthephilia*)

- The *Nike* approach: '*Just do it*'
- The *Kekulé* approach: '*I dreamed of it*'
- The *Archimedes* approach: '*Eureka, eureka*'
- The *Sinatra* approach: '*I did it my way*'



The psychobiology of heuristic synthesis planning:
Visual and mental thought processing



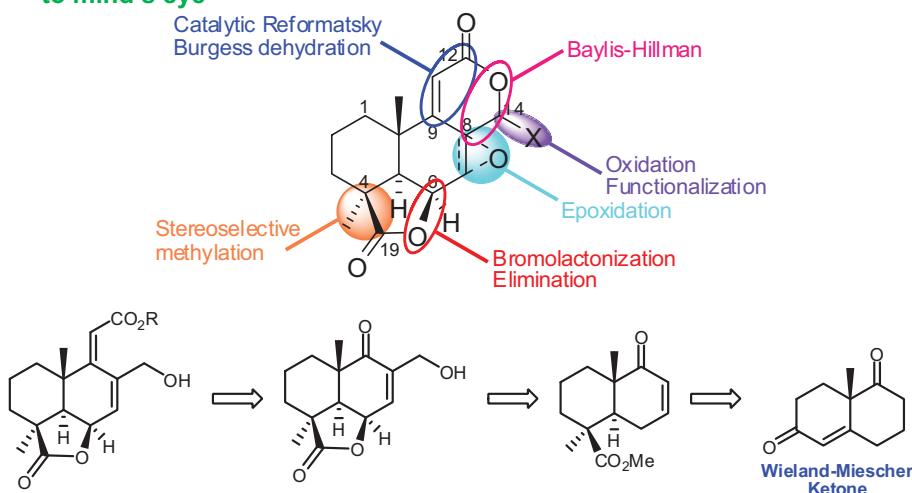
Whereas the left hemisphere of the brain analyses over time,
the right hemisphere synthesizes over space



August 17 issue,
2012

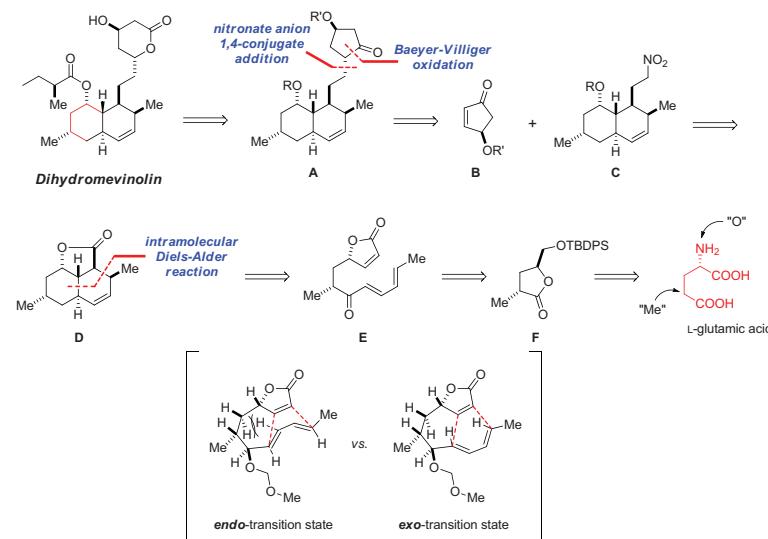
Oidiolactones: The synthesis in a capsule

Visual relational and visual reflexive thought processing from eye to mind's eye



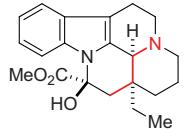
with Boyer, N.; Reddy, G. J.; Deschenes-Simard, B. *Org Lett.* **2009**, *11*, 4640

As an entity, the target molecule is different from the sum its parts, but the visual chasm that separates the two gradually disappears, as the synthesis plan takes shape, like a progressive epiphany of thoughts and images



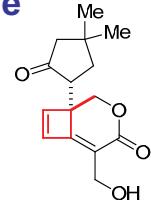
with Roy, P.; Petrini, M.; Hodges, P. J.; Di Fabio, R.; Caganico, G. *J. Org. Chem.* **1990**, *55*, 5766

Synthesis and the mind's eye



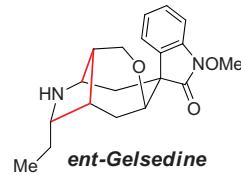
Vincamine
[L-Aspartic acid]

H. Rappoport



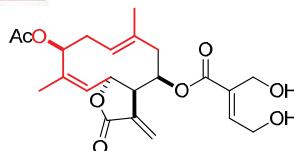
Fomannosin

L. A. Paquette



H. Hiemstra

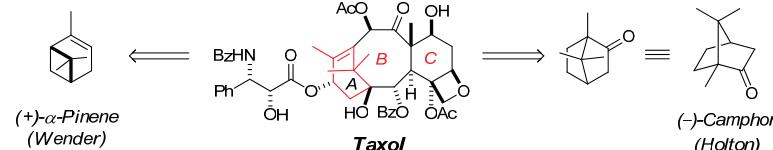
The False Mirror
R. Magritte
(1928)



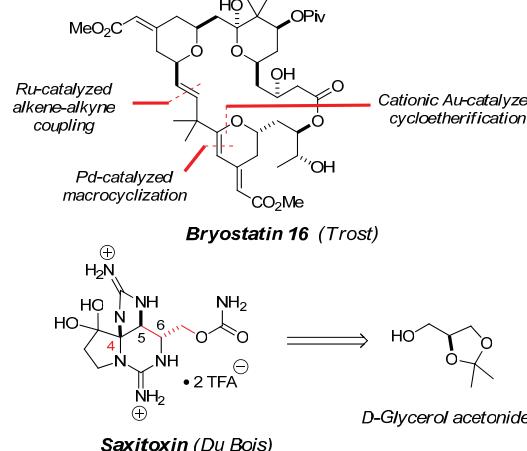
Eucannabinolide
[(S)-Carvone]

W. C. Still

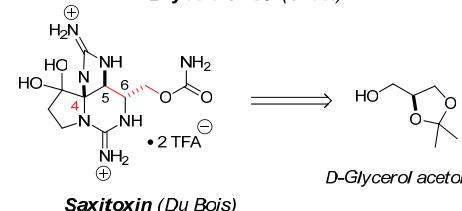
Synthesis and the mind's eye



Mechanism and knowledge-based visual relational thinking



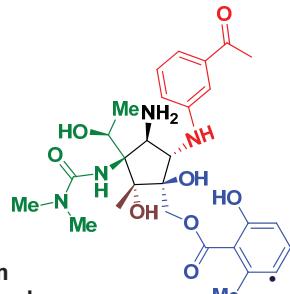
Bryostatin 16 (Trost)



D-Glycerol acetonide

Functional group and chiral template-based visual relational thinking

Pactamycin



Isolation

- Isolated in 1961 from *Streptomyces pactum* by scientists at the former Upjohn Company.
- Proposed structure of pactamycin was reported in 1970 and corrected in 1972 with help of X-ray crystallographic studies.

Structure:

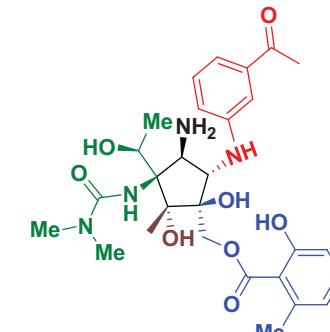
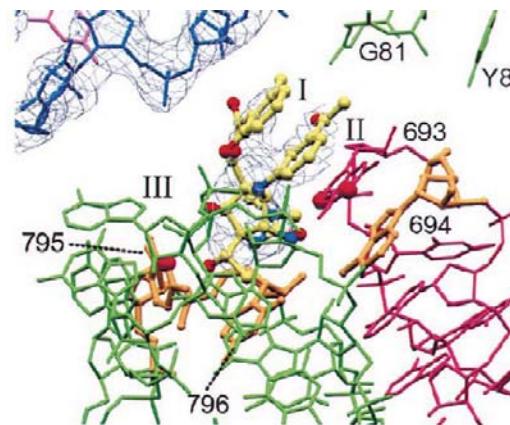
Wiley, P. F., et al. J. Org. Chem. 1970, 35, 1420.

Duchamp, D. J., et al. American Crystallographic Association Meeting. 1972, April, p. 23.

Biology

- Exhibits activity against Gram positive and Gram negative bacteria.
- Potent in vivo and in vitro cytotoxic effects as well as antimicrobial activity.
- Potent protein synthesis inhibitory activity in prokaryotes as well as in eukaryotes.

Unique interactions



- Aromatic stacking in pactamycin mimics two consecutive mRNA bases.

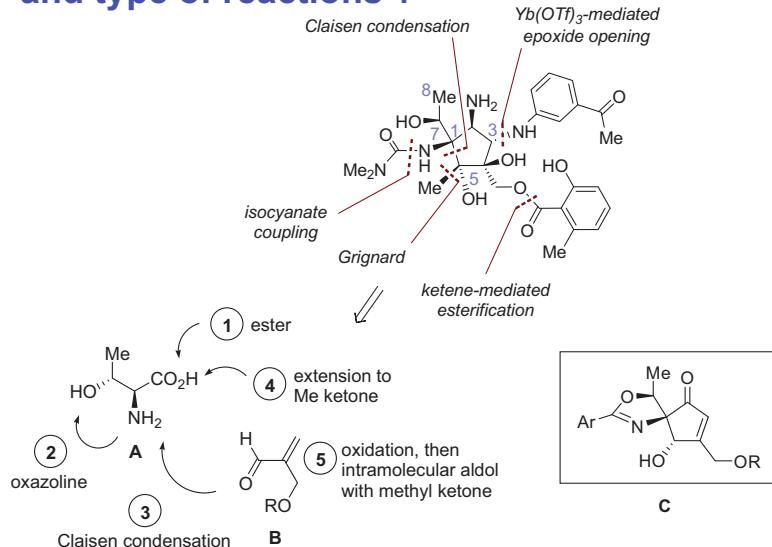
Pactamycin displaces mRNA in the E-site, preventing movement through the 30S subunit.

Isolation and biological activity:

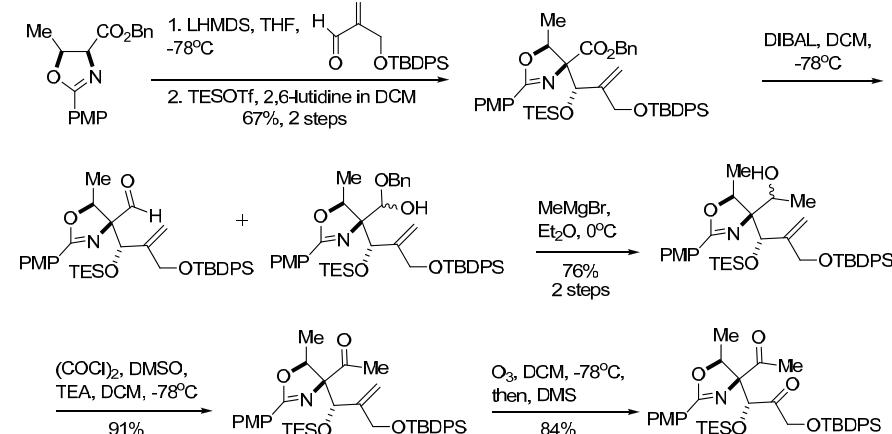
Bhuyan, B. K., et al. Antimicrob. Agents Chemother., 1961, 184.
Argoudelis, A. D., et al. Antimicrob. Agents Chemother., 1961, 191

Ramakrishnan, V. et al. Cell 2000, 103, 1143

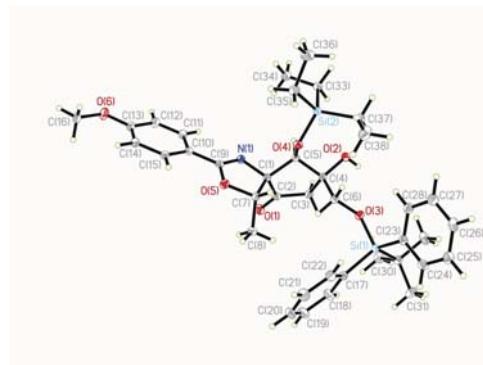
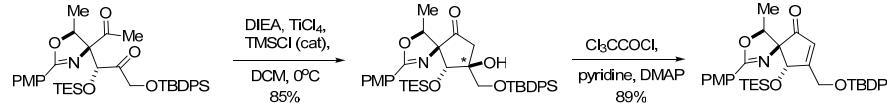
Major challenge: How to orchestrate the sequence and type of reactions ?



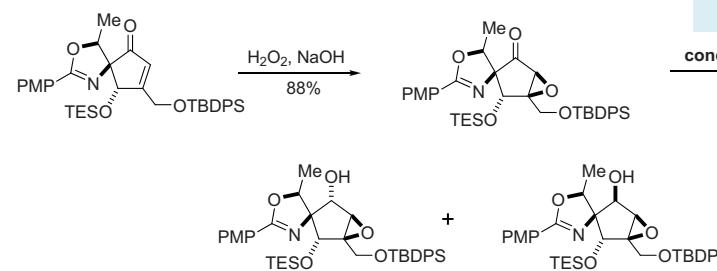
Cyclopentenone core



Absolute configuration

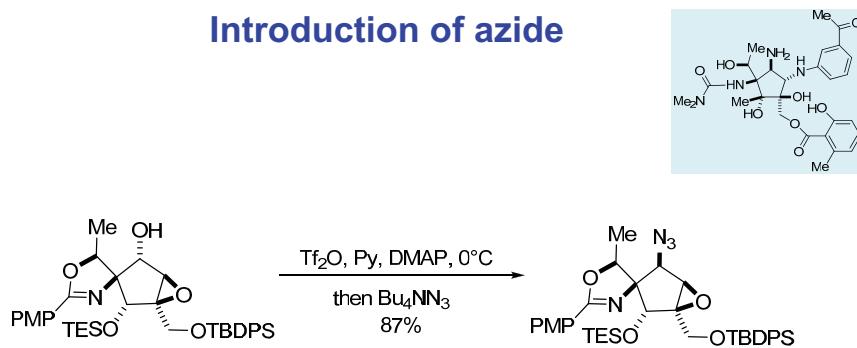


Epoxidation and Reduction

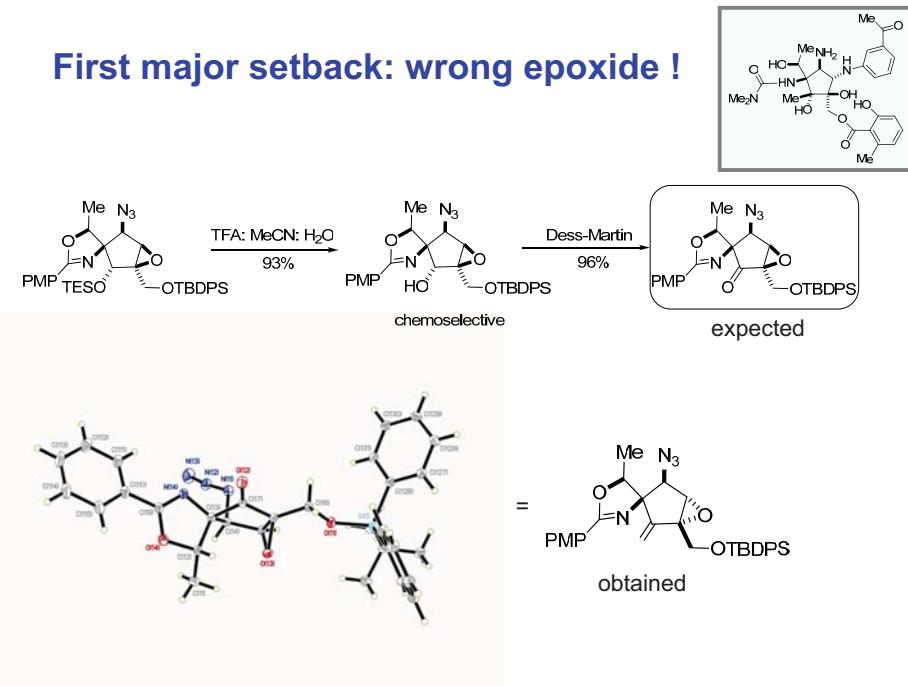


NaBH_4 , CeCl_3	> 20 : 1
NaBH_4	5.25 : 1
LiBH_4	10 : 1
KBH_4	5 : 1
$\text{Zn}(\text{BH})_4$	> 20 : 1
$\text{BH}_3\text{-THF}$	decomposition

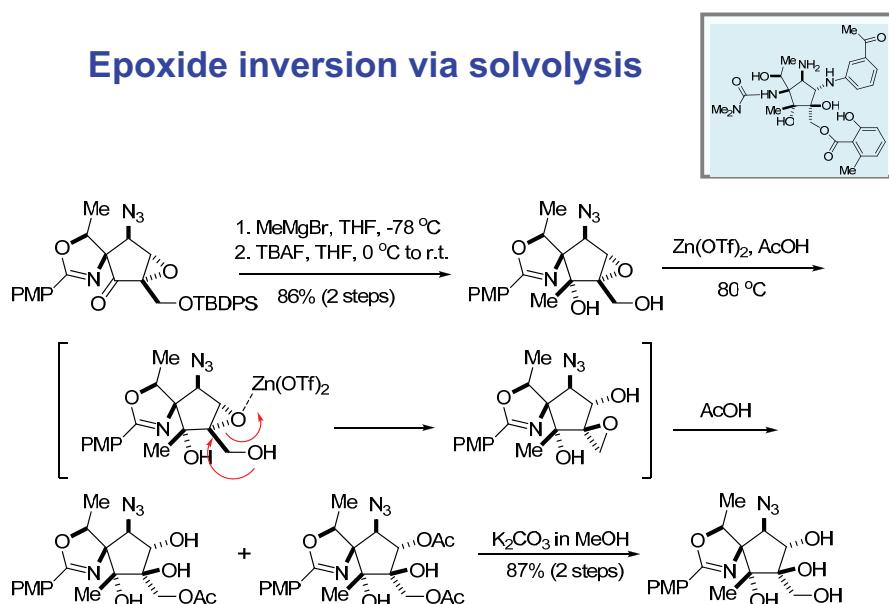
Introduction of azide



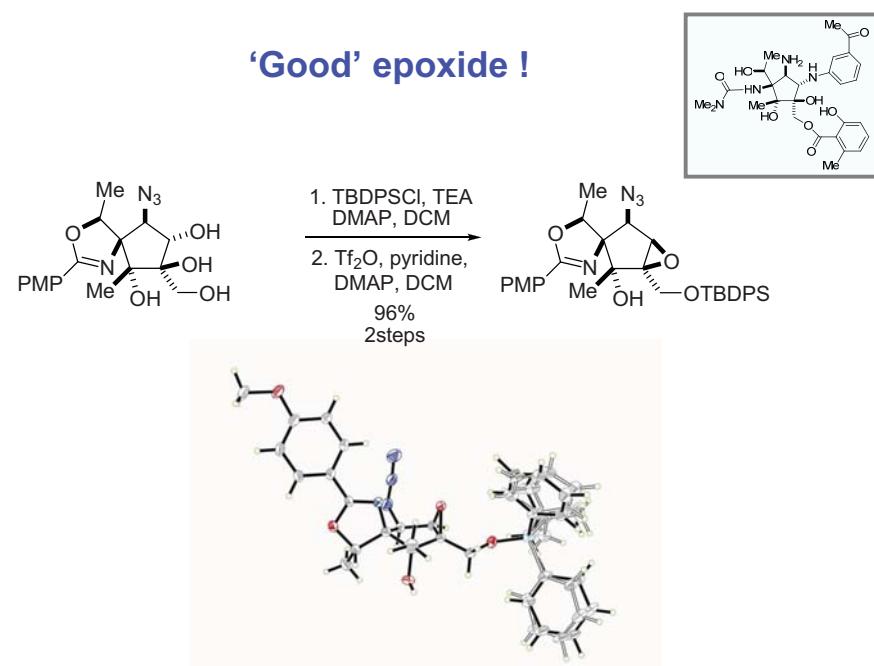
First major setback: wrong epoxide !



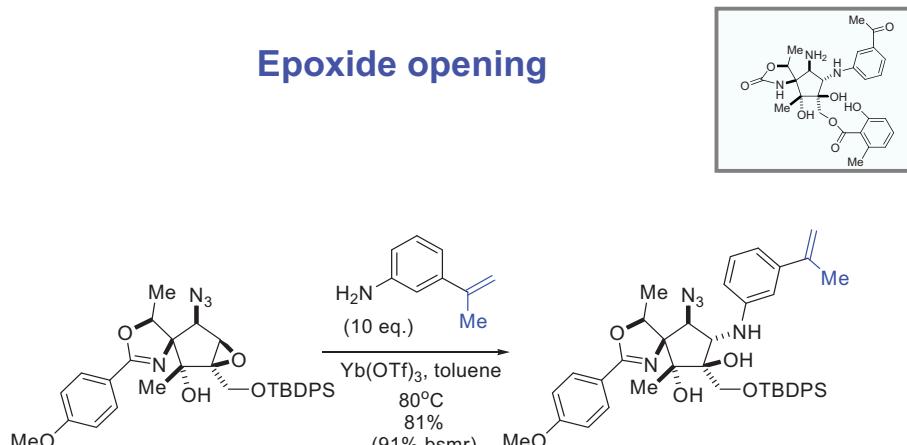
Epoxide inversion via solvolysis



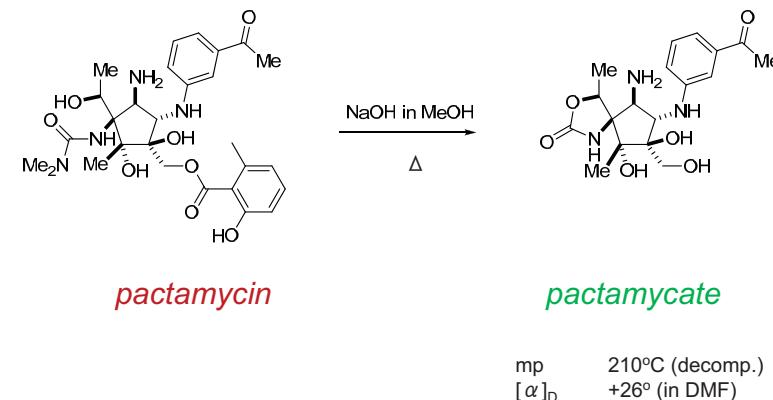
'Good' epoxide !



Epoxide opening

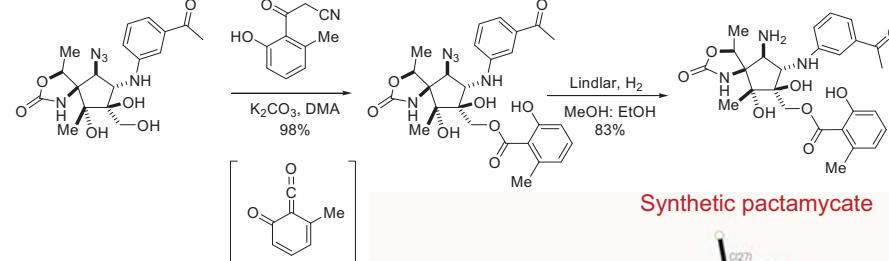


Pactamycin and Pactamycate



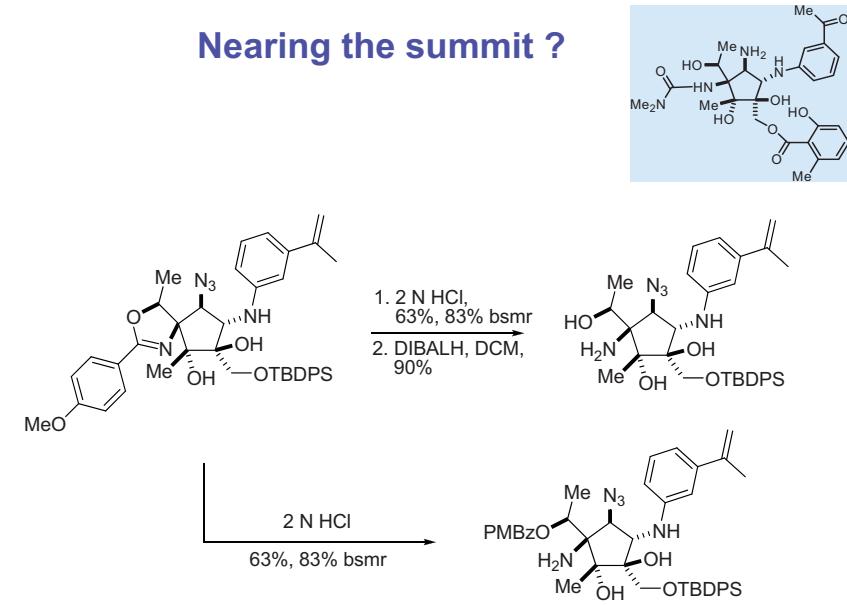
Wiley, P.F.; Jahnke, H.K.; MacKellar, F.; Kelly, R.B.; Argoudelis, A.D.
J. Org. Chem. 1969, 35, 1420.

Crystalline pactamycate !



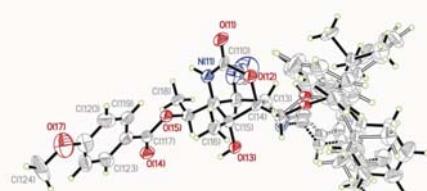
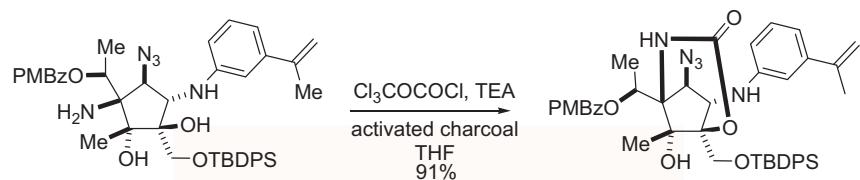
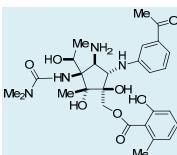
Synthetic pactamycate

Nearing the summit ?

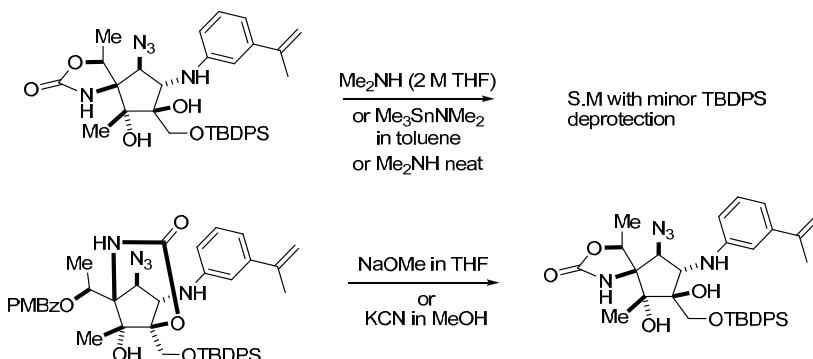
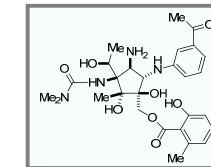


Esterification method, Porco, J. A et al
Org.Lett. 2002, 4, 3103

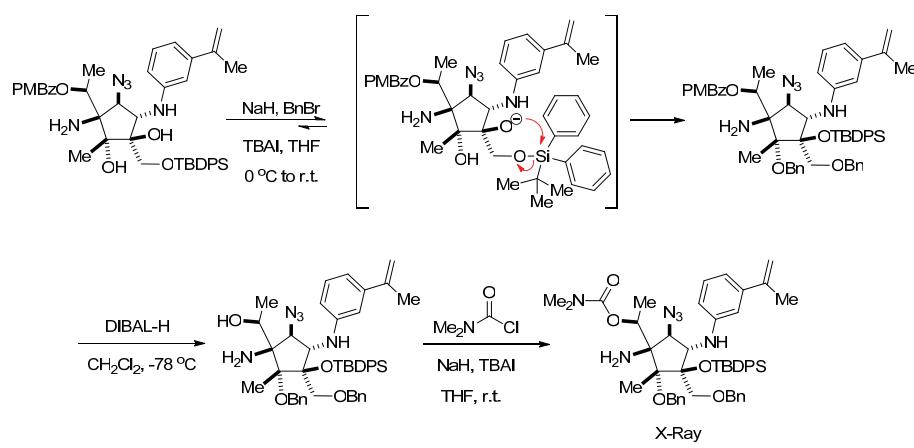
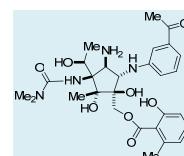
D### Carbamate !



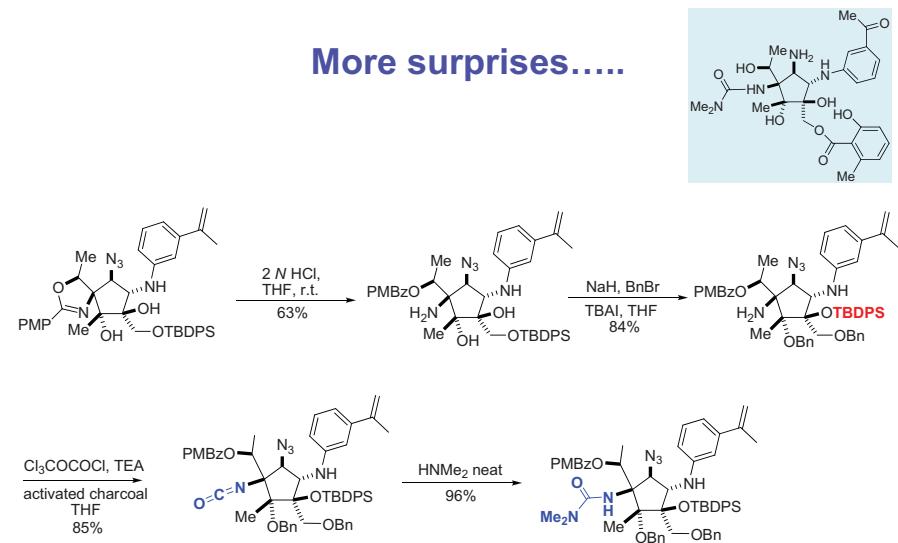
Extreme proximity effects



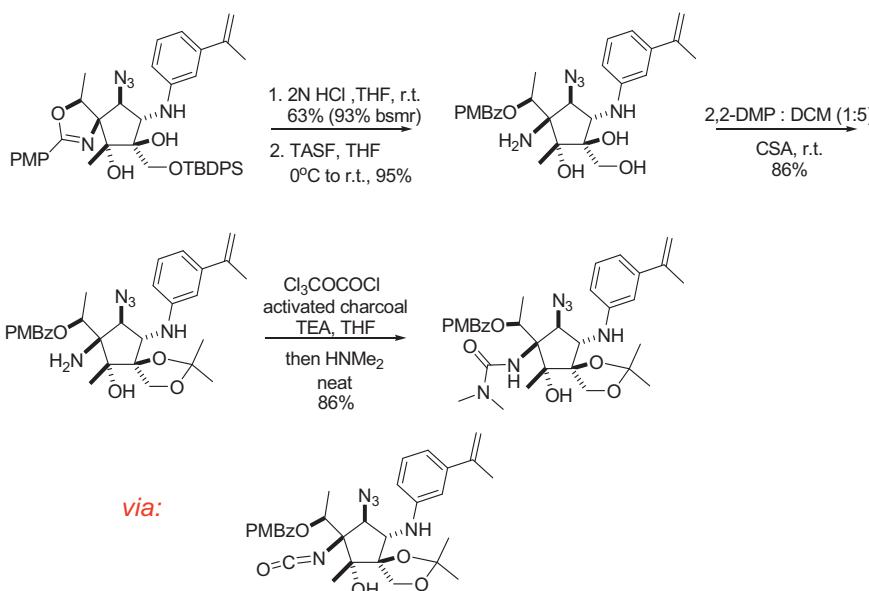
A very uncooperative amine !



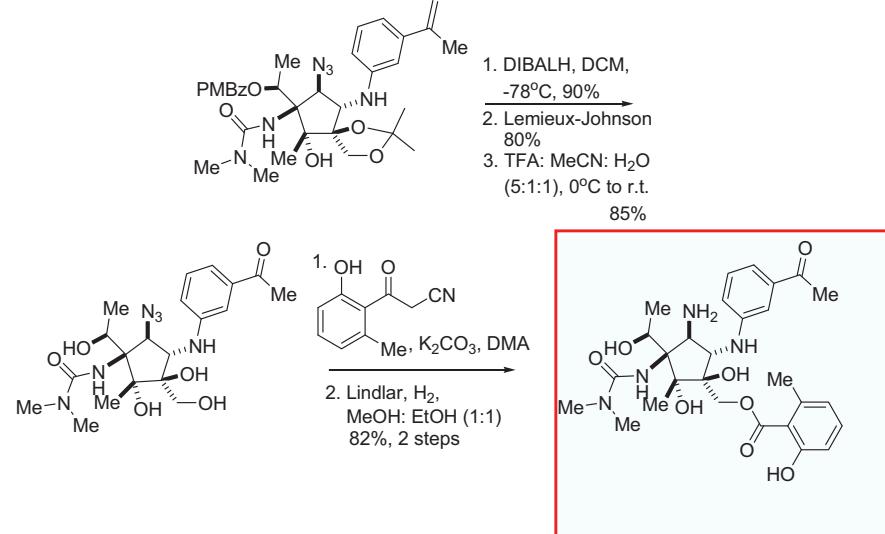
More surprises.....



Neutralizing the ‘enemy’



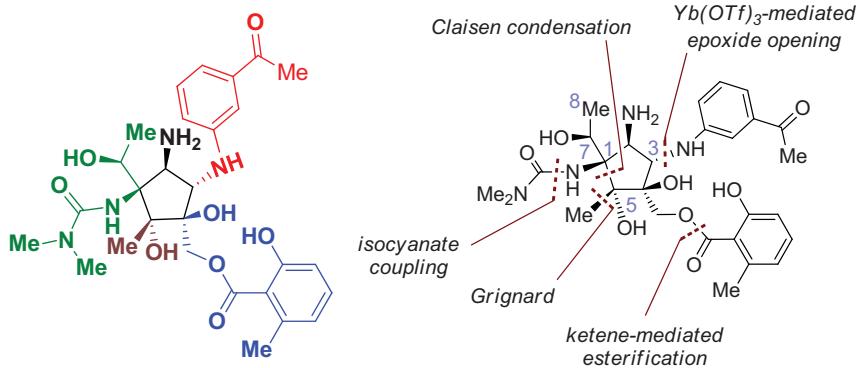
Pactamycin: reaching the summit !



29 linear steps, 3% overall yield

700 MHz nmr, HPLC,
HRMS; optical rotation

The long and arduous climb to the summit...



with Vakiti, R.R.; Dorich, S.; Banerjee, S.; Lecomte, F.; Del Valle, J. R.; Zhang, J.; Deschesnes-Simard, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 3497

