The Future of Total Synthesis

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The Future of Total Synthesis

a brief forward

- The idea for tonights topic was from discussions with all of you over the past 1.5 years

- The intent of presentation is to:

  - Discuss a brief history of total synthesis for the purpose of context

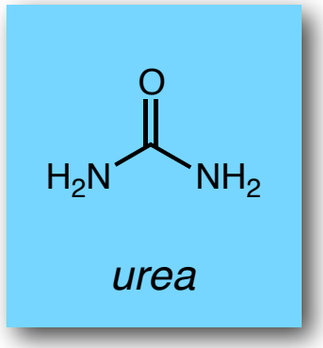
  - Briefly review the the best current work in the field of total synthesis

  - Present examples that underscore the transitions occurring in total synthesis for the purpose of discussion

Total Synthesis of Natural Products

a brief history

- It all began with urea...
  - Wöhlers synthesis of urea demonstrated that organic matter could be produced synthetically
  - Discredited vitalism, the theory that organic matter possessed a vital force inherent to living things



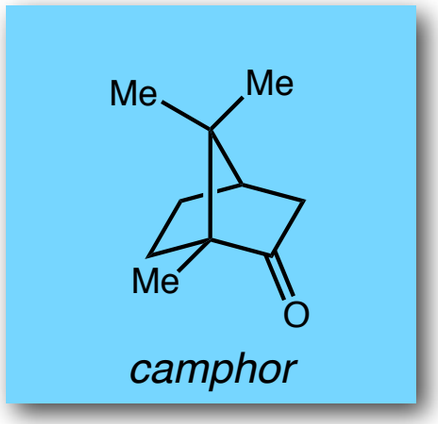
urea

Friedrich Wöhler (1828). "Ueber künstliche Bildung des Harnstoffs". *Annalen der Physik und Chemie* **88** (2): 253–256.

Total Synthesis of Natural Products

a brief history

- Gustaf Komppa's industrial synthesis of camphor in 1903 *via* semi-synthesis from pinene
  - Camphor was a scarce natural product with a worldwide demand
  - Important milestone in synthetic organic chemistry

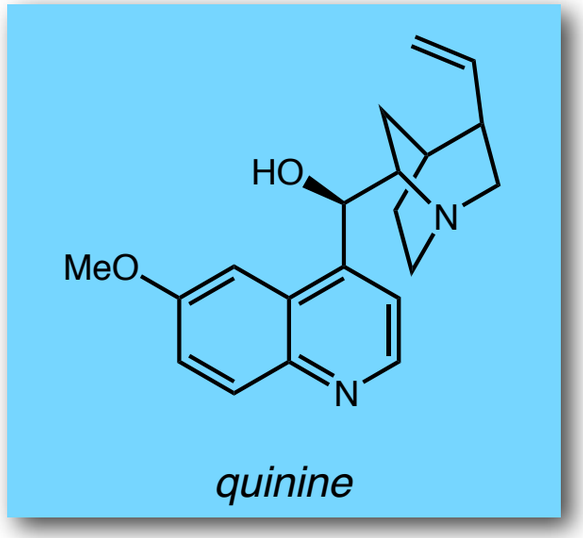


camphor

Total Synthesis of Natural Products

a brief history

- The modern era of total synthesis began with Woodward's synthesis of quinine
  - The ability to utilize a predictive set of known reactions to execute a synthetic plan
  - Ushered in the modern era of total synthesis



quinine

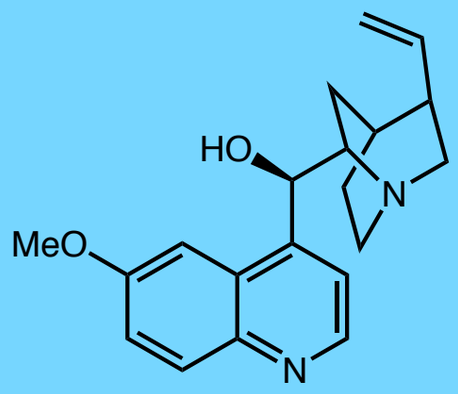
Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1944**, 66: 849-849.

Total Synthesis of Natural Products

why we've made molecules since 1828

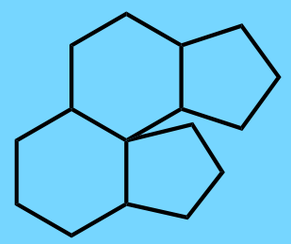
- Three driving forces for undertaking the total synthesis of natural products

Potential Societal Impact



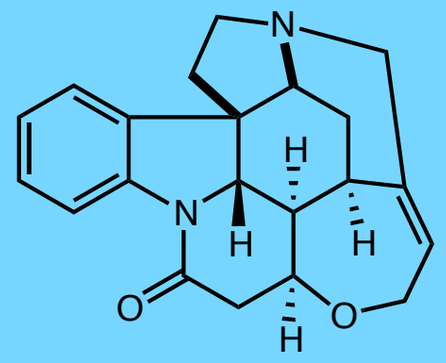
quinine

Assist Structural Identification



originally proposed skeleton of cholesterol

Inspire New Methods



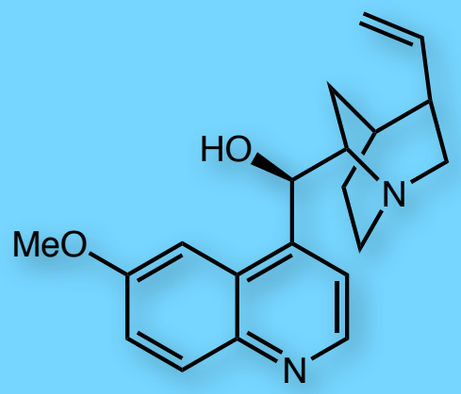
strychnine

Total Synthesis of Natural Products

why we make molecules in 2012

- Modern analytical methods have largely eliminated the need to verify structure through synthesis
- We're now entering an era where chemists can make molecules with unprecedented efficiency
- Focus is largely shifting toward the synthesis of molecules that have the potential for societal impact

Potential Societal Impact



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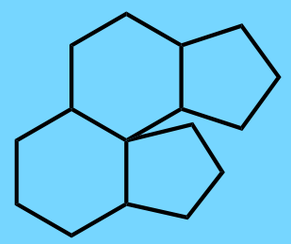

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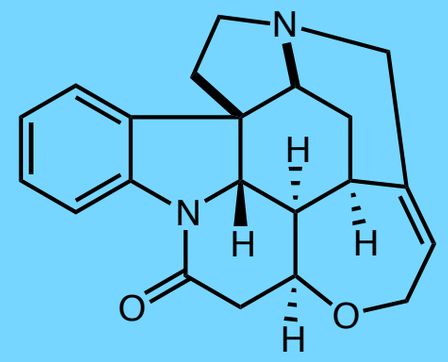


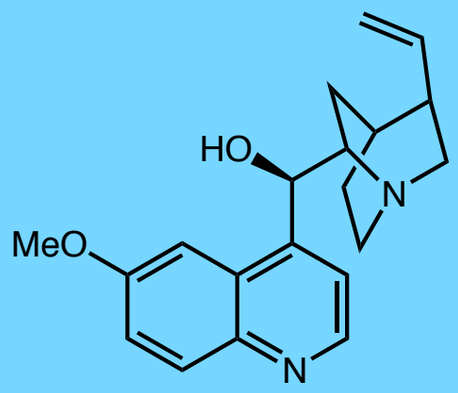
strychnine

What is the Future of Total Synthesis?

topics for discussion

- Brief discussion of how the field of total synthesis has changed over the past 50 years
  - Discussion will be limited to *active* research groups located at U.S. institutions since 1960
- Highlight recent literature that contrast the past and present of total synthesis
  - Use insights from these examples to look toward the future

Potential Societal Impact



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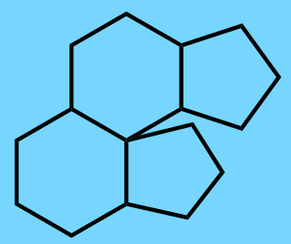

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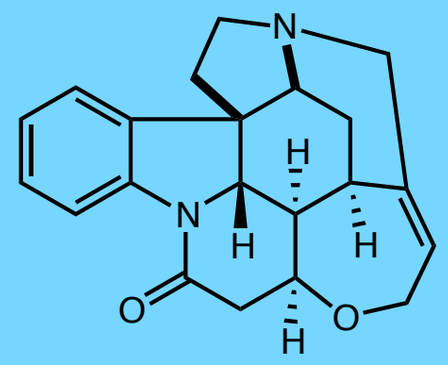

strychnine

Key Research Programs in Total Synthesis

programs initiated from 1961-1972

Barry Trost (1965)

David Evans (1967)

Larry Overman (1970)

Amos Smith (1972)

Also: Phil Magnus, James Marshall, Albert Padwa, James White

- Equipped with the knowledge that complex molecules can be made
- The goals of synthetic efforts from this group largely focused on accessing the desired target

Syntheses completed by 1972

Strychnine - Woodward

Reserpine - Woodward

Prostaglandin - Corey

Progesterone - W. S. Johnson

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- Equipped with the knowledge that complex molecules can be made
- Only a limited selection of reliable “synthons”

Reactions and Reagents that Didn’t Exist in 1972	**Active areas of research at that time**
Chiral Auxiliaries	Hydroboration
Heck, Kumada-Corriu, Stille, and Suzuki Couplings	Controlling enolate geometry
Sharpless epoxidation	Organic photochemistry
TBSCl	Cross-coupling reactions

Key Research Programs in Total Synthesis

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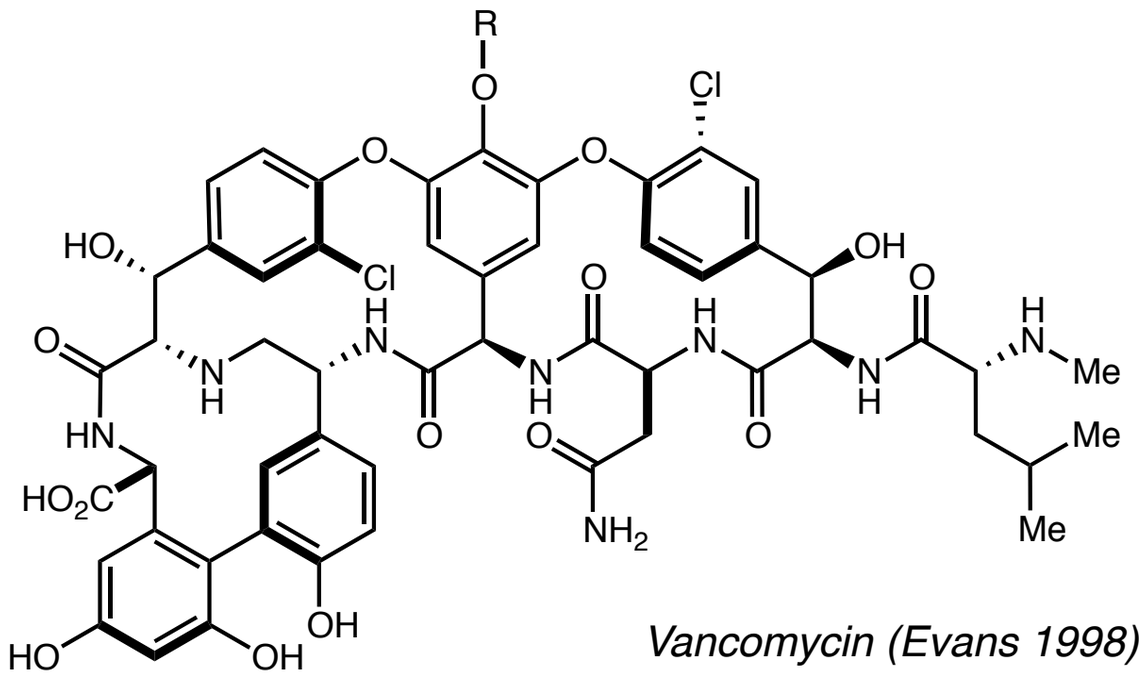
- Throughout their careers they produced many total syntheses which, at the time their programs began, were seeming impossible



Vancomycin (Evans 1998)

Evans, D. A.; Wood, M. R.; Trotter, W. B.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem. Int. Ed.* **1998**, *37*, 2700-2704.

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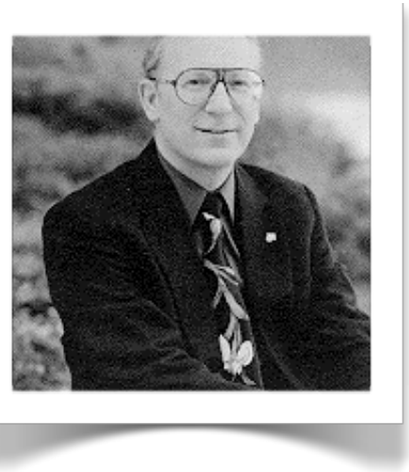

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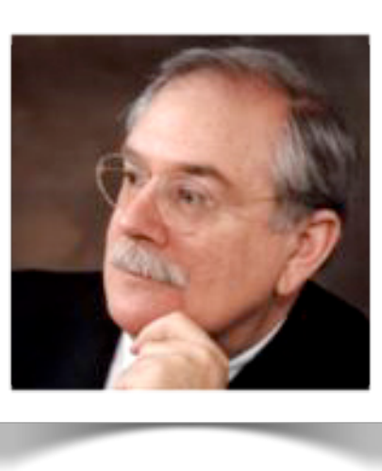
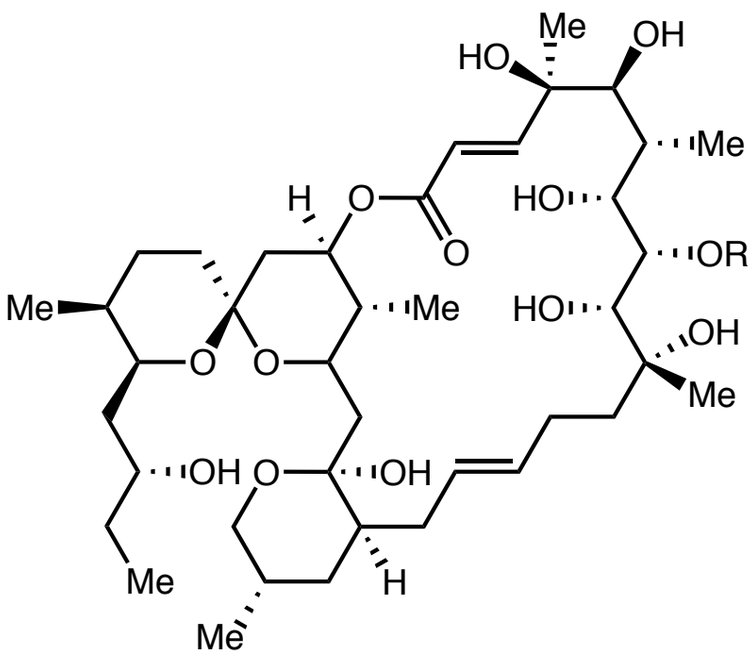


David Evans (1967)

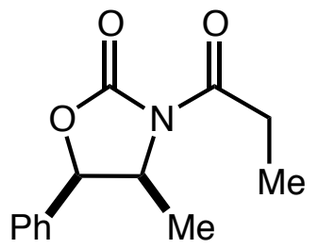
Larry Overman (1970)

Amos Smith (1972)

- Devoted much of their careers to developing new methods to enable the synthesis of natural products



cytovaricin (Evans 1990)



All stereocenters set by asymmetric aldol, alkylation or epoxidation

Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031.

Key Research Programs in Total Synthesis

programs initiated from 1961-1972

Barry Trost (1965)

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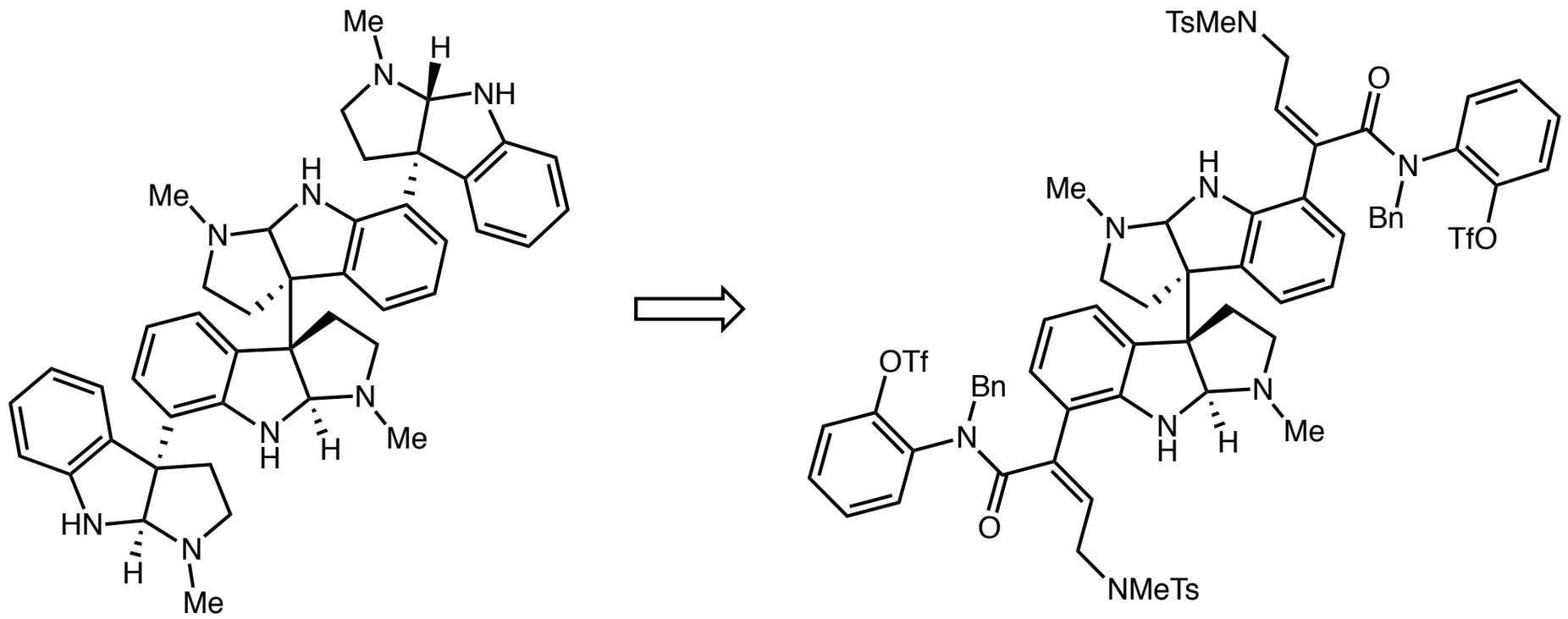
Amos Smith (1972)

- Pioneered many fundamental advances and applications for transition metal chemistry

quadrigemine C
(Overman 2002)



Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008-9009.

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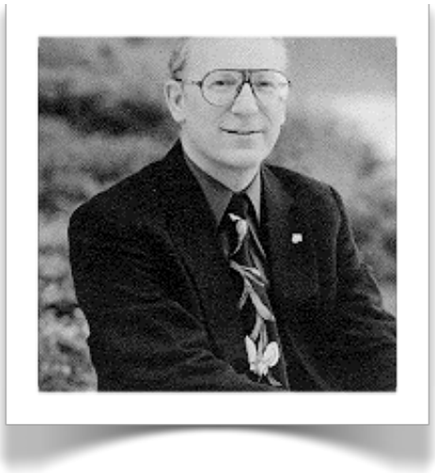

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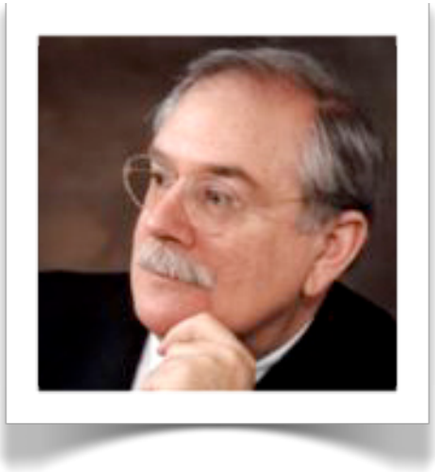


David Evans (1967)

Larry Overman (1970)

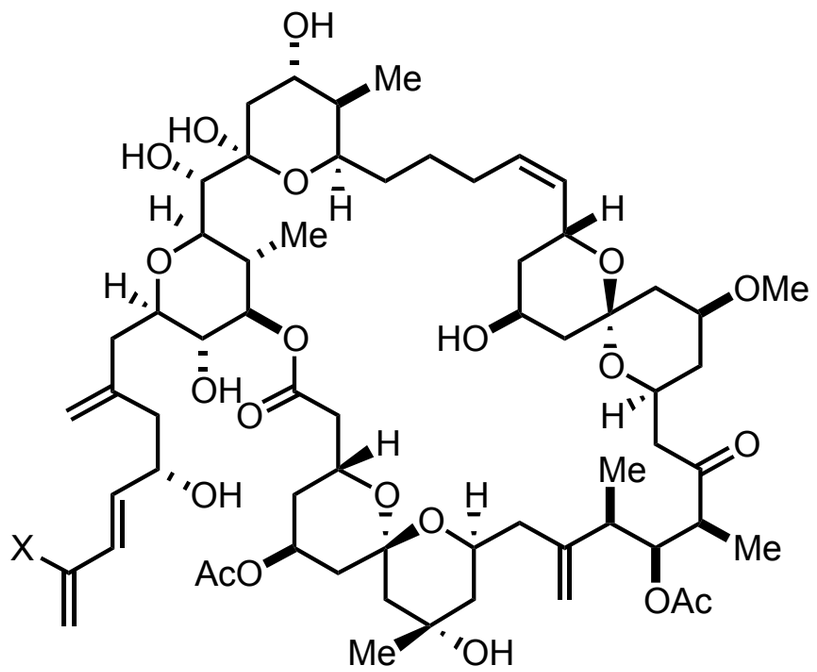
Amos Smith (1972)

- Executed syntheses of natural products with the aim of exploring its therapeutic potential

spongistatin 1 X = Cl

spongistatin 2 X = H

(Evans 1998, Smith 2001)



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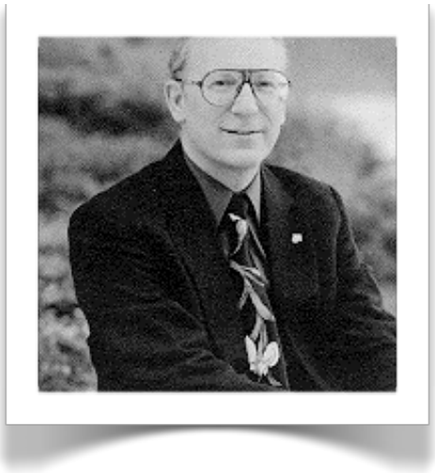

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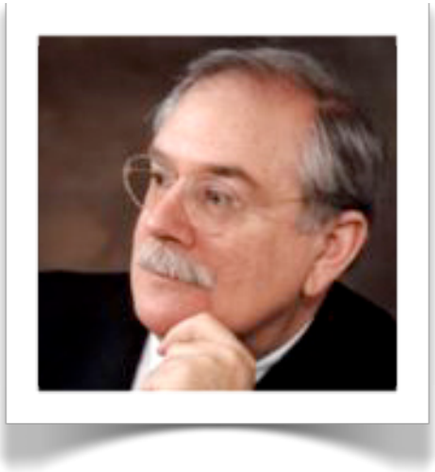
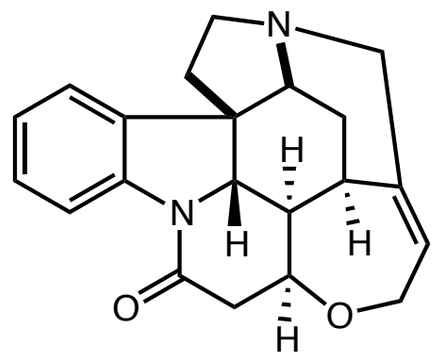


David Evans (1967)

Larry Overman (1970)

Amos Smith (1972)

- Famous molecules as a benchmark for total synthesis and a continued source of inspiration



strychnine

Magnus, Overman, Padwa (Woodward)

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K.C. Nicolaou (1976)

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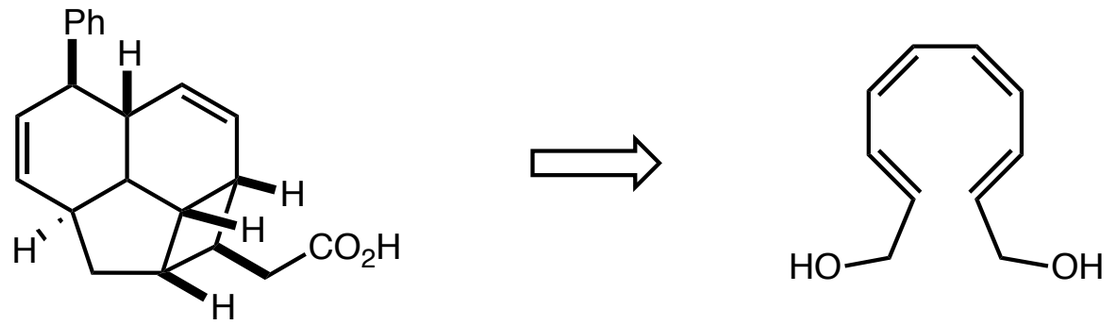
Dale Boger (1979)

Stuart Schreiber (1981)

Also: James Cook, Mike Crimmins, Gary Keck, Tom Hoye, Stephen Martin, Viresh Rawal, Bill Roush, Bob Williams Dave Williams and Jeffrey Winkler

- Applied some of the most vigorously studied research in organic chemistry toward natural products
- Completed brilliant total syntheses of some of the most complicated molecules ever isolated

endiandric acids A-D
(Nicolaou 1982)



Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104*, 5555-5557.

Key Research Programs in Total Synthesis

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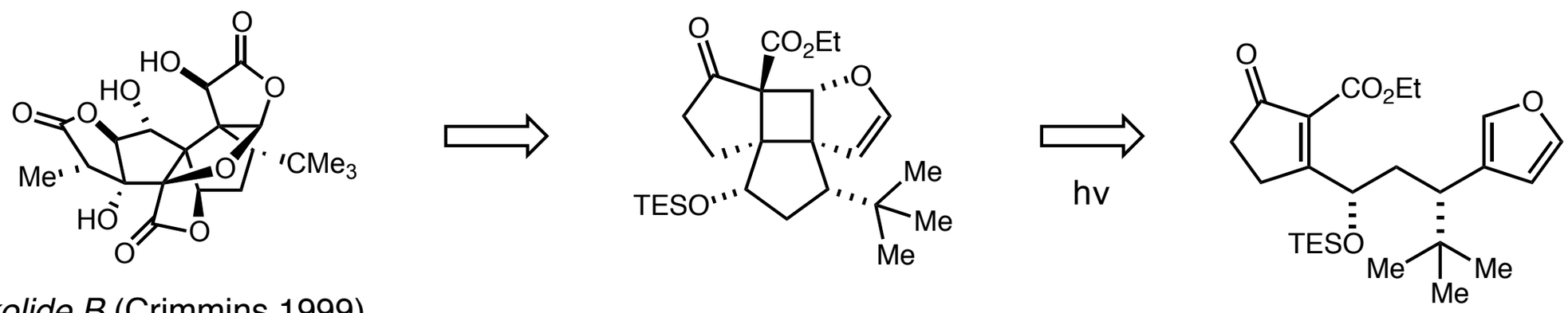

ginkolide B (Crimmins 1999)

Crimmins, M. T. *et al. J. Am. Chem. Soc.* **1999**, *121*, 10249-10250.

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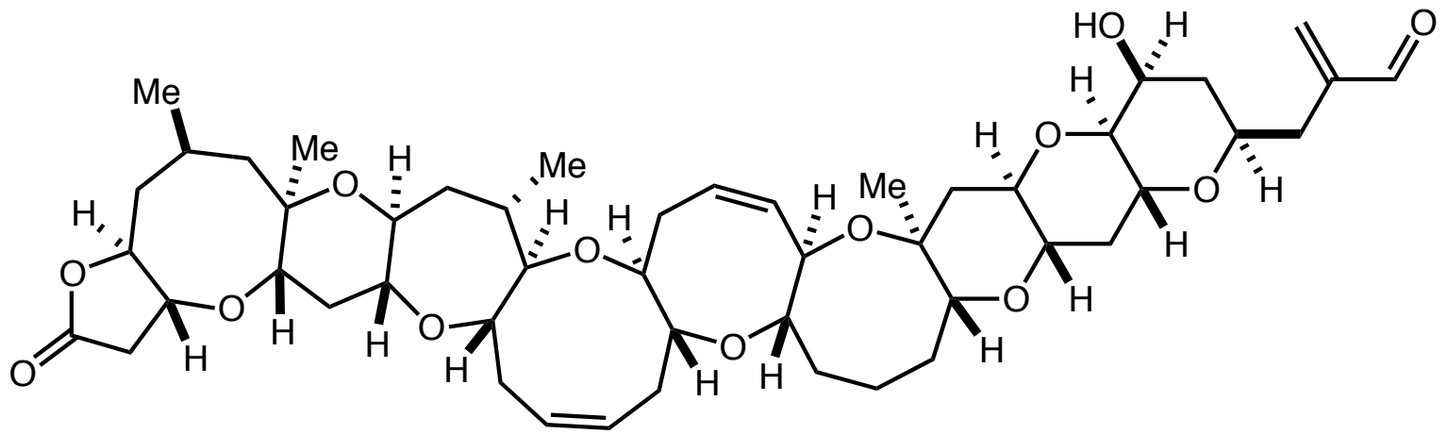
- During their careers the “synthetic toolkit” had expanded drastically
- New transformations provided increased access to exceptionally complicated structures



brevetoxin A (Nicolaou 1998, Crimmins 2008)

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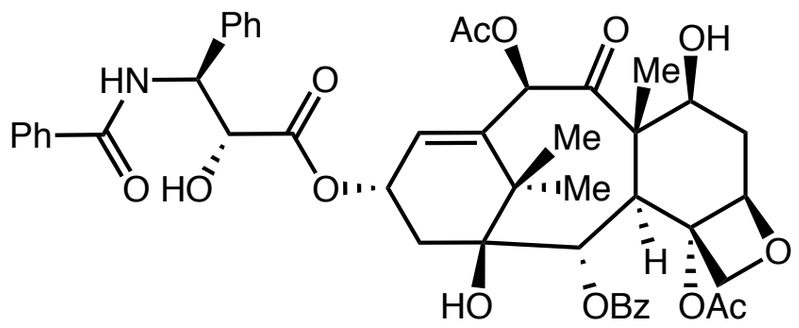
- During their careers the “synthetic toolkit” had expanded drastically
- The synthesis of Nature’s most complicated therapeutic leads became a worthy endeavor



taxol (Nicolaou 1994, Wender 1997)

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most synthetic efforts largely focused on accessing the desired target

Key Research Programs in Total Synthesis

programs initiated between 1985-1996

Andrew Myers (1986)

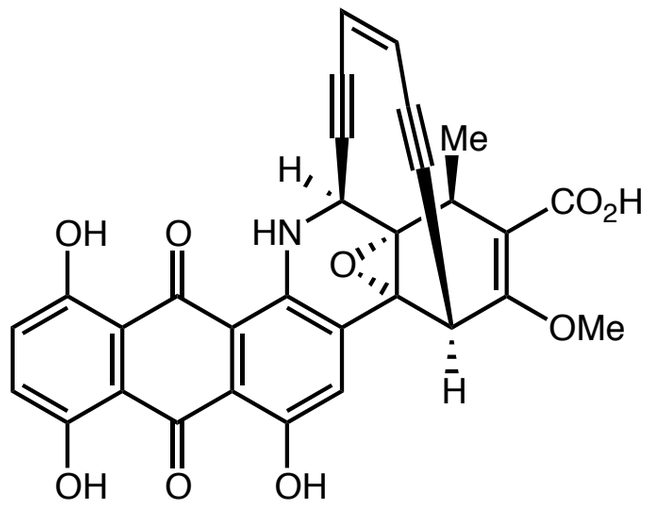
Scott Rychnovsky (1988)

Peter Wipf (1990)

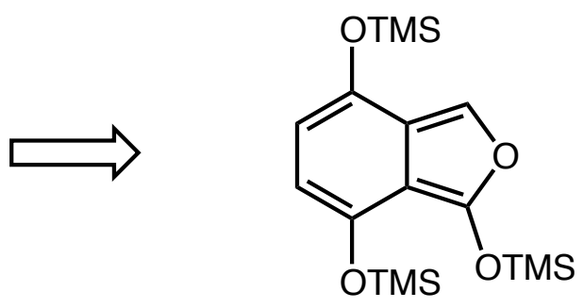
John Wood (1993)

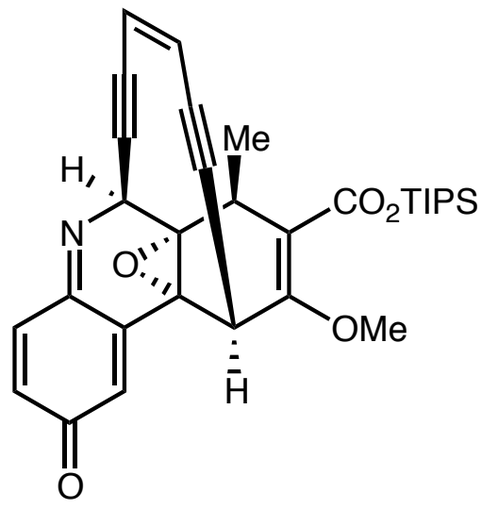
Also: Arun Ghosh, John Montgomery, James Panek, Tom Pettus and John Rainier

- The goals of synthetic efforts from this group largely focused on accessing the desired target
- Constructed molecules of incredible complexity with innovative methods



dynemicin (Myers 1995)





Myers, A. G.; Fraley, M. E.; Tom, N. J. *J. Am. Chem. Soc.* **1994**, *116*, 11556-11557.

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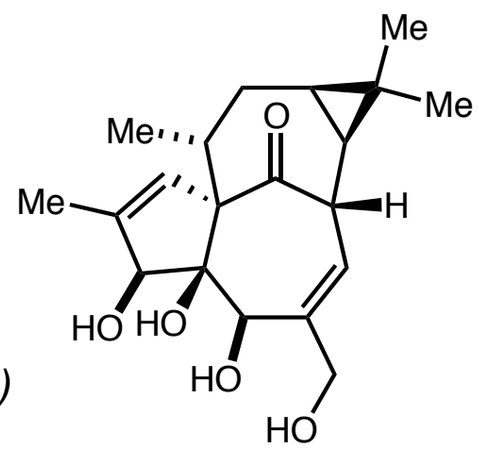
- The goals of synthetic efforts from this group largely focused on accessing the desired target
- Continued the traditions of building molecules of incredible complexity

ingenol (Wood 2004)



Nickel, A,; Maruyama, T.; Tang, H.; Murphy, P. D.; Green, B. Yusuff, N. Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300-16301.

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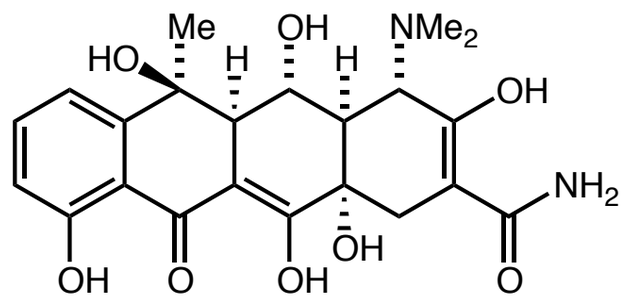


tetracycline (Myers 2005)

Charest, M. G.; Siegel, D. R.; Myers, A. G.; *J. Am. Chem. Soc.* **2005**, *127*, 8292-8293.

A Paradigm Shift in Total Synthesis

"can we make everything" becomes "how well can we make everything"

- A significant aim of the synthetic community from 1940 to ~1995 entailed accessing the desired structure
  - Once the synthetic natural product was obtained the project was over
- Recent years have placed additional focus on how well we access desired targets
  - The shift is evident (not ubiquitous) with total synthesis programs initiated after this period
  - This shift is being increasingly adopted by the research groups initiated before this period

A Paradigm Shift in Total Synthesis

why the mid-1990's

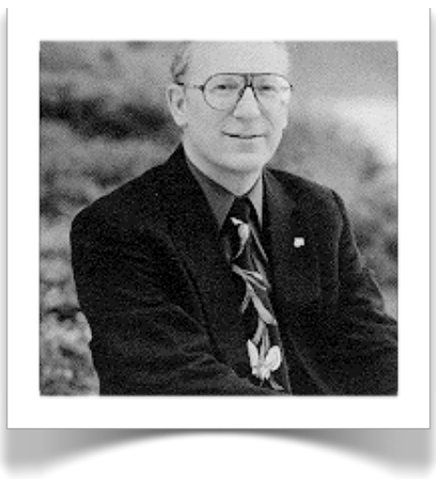
- In 1990 Corey wins the Nobel Prize in Chemistry for the...

"...development of the theory and methodology of organic synthesis".

A Paradigm Shift in Total Synthesis

why the mid-1990's

- A high profile introspective analysis concerning synthetic efficiency was published in 1991.



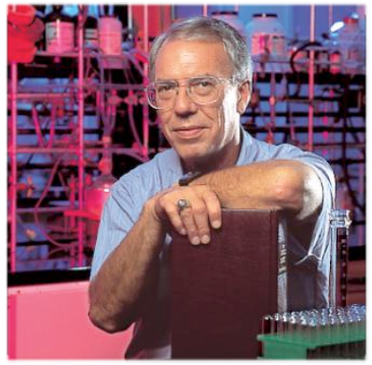
Atom Economy

Trost B. M. *Science* **1991** *254*, 1471-1477.

A Paradigm Shift in Total Synthesis

why the mid-1990's

- The taxol problem exemplified the limitations total synthesis for assembling structures that carry the potential to have societal impact (35 groups worked on taxol)



Robert Holton (1994)

46 longest linear steps

K.C. Nicolaou (1994)

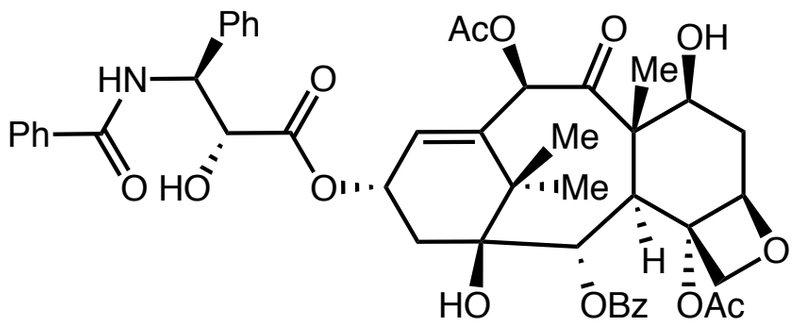
42 longest linear steps

Sam Danishefsky (1996)

49 longest linear steps

Paul Wender (1997)

37 longest linear steps



taxol

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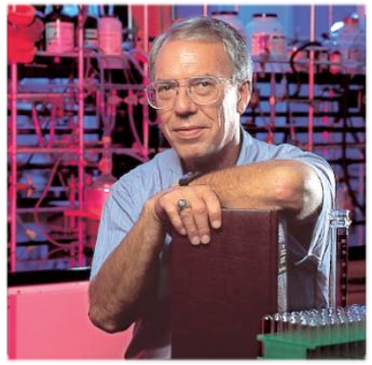
why the mid-1990's

- The taxol problem exemplified the limitations total synthesis for assembling structures that carry the potential to have societal impact (35 groups worked on taxol)



Robert Holton (1994)

46 steps

K.C. Nicolaou (1994)

55 steps

Sam Danishefsky (1996)

49 steps

Paul Wender (1997)

37 steps

Consideration of the chemical complexity of baccatin III, which in suitably protected form would be the likely synthetic intermediate *en route* to taxol, **should have engendered considerable skepticism and even disbelief that total synthesis would supplant natural sources as a route to the drug**. More plausible, though as yet unrealized in practice, is the prospect that mastery of the synthesis of baccatin III will bring with it new nuclei which, upon suitable conjugation with biologically critical side chains, might provide medically promising variants of taxol.

-Samuel Danishefsky

Key Research Programs in Total Synthesis

programs initiated from 1997-2008

David MacMillan (1998)

Erik Sorensen (2001)

Phil Baran (2003)

Mo Movassaghi (2003)

Also: Martin Burke, Steve Castle, Jef De Brabander, Justin Du Bois, Greg Dudley, Paul Floreancig, Neil Garg, Timothy Jamison, Jeff Johnson, Jeff Johnston, Glen Micalizio, Jon Njardarson, Sarah Reisman, Richmond Sarpong, Karl Scheidt, Matthew Shair, Scott Snyder, Brian Stoltz, Regan Thomson, Chris Vanderwal, Lawrence Williams, Armen Zakarian.

- Breakthroughs in catalysis have opened new doors for powerful synthetic methods
- Previous efforts in total synthesis have provided a framework for new researchers to build on
- The result is that highly complex targets are being synthesized with incredible efficiency

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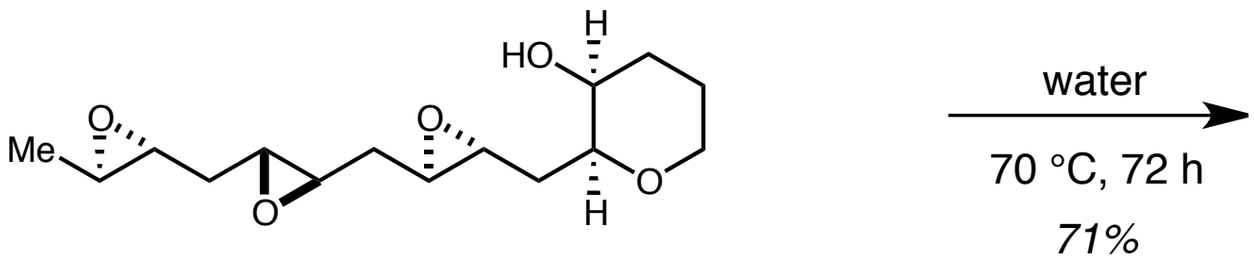
■ Examples of powerful synthetic methods for total synthesis developed in the last 10 years



common ladder toxin subunit

Vilotijevic, I.; Jamison, T. J. *Science* **2007** *317*, 1189-1192

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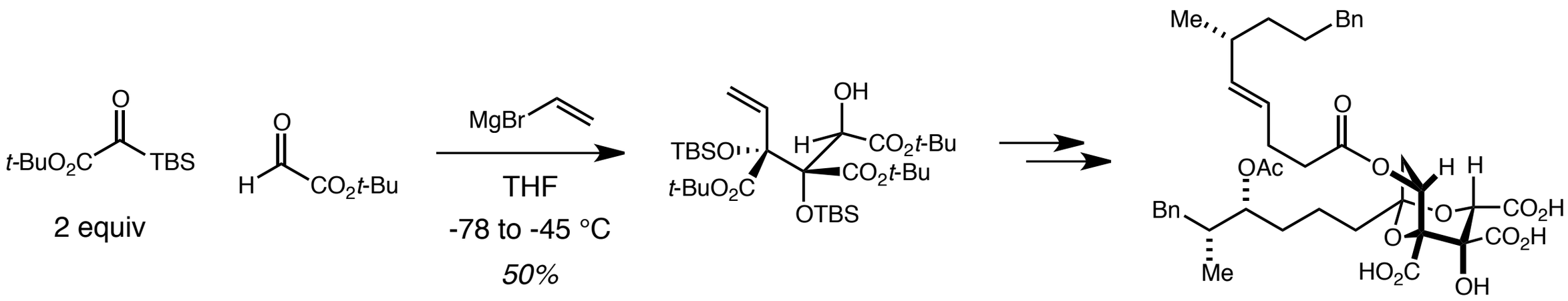

zaragozic acid C

Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C. Johnson, J. S. *J. Am. Chem. Soc.* **2008** *130*, 17281-17283.

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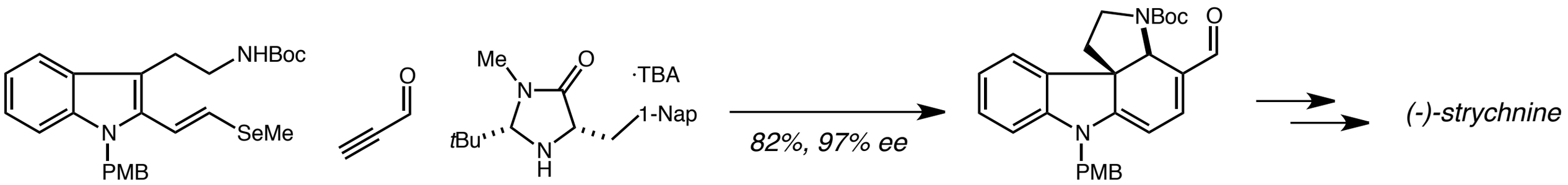

Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011** *850*, 183-188.

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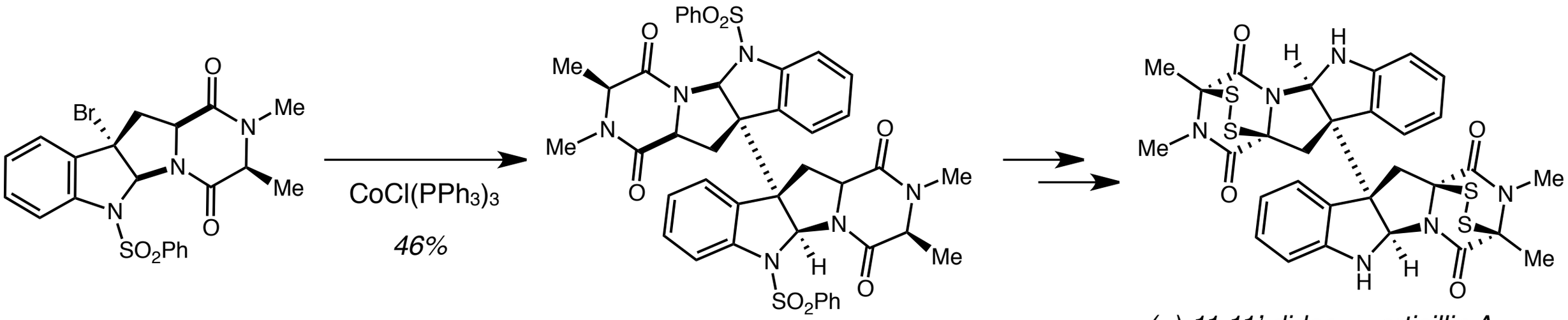

(+)-11,11'-dideoxyverticillin A

Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2011** *324*, 238-241.

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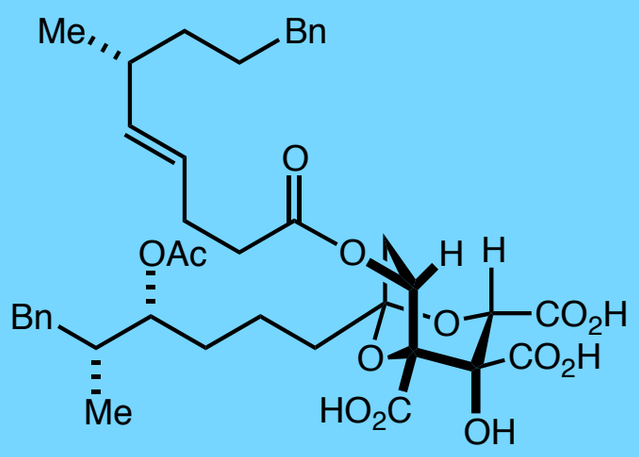
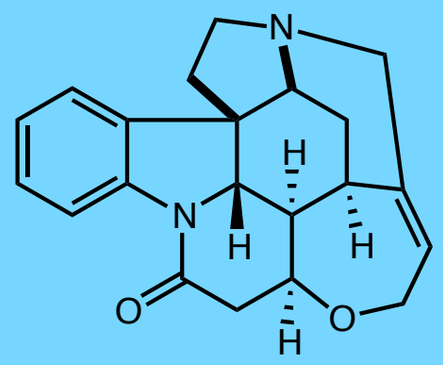
- Advances in new methodologies and synthetic strategies have changed how we view total syntheses
  - Greater emphasis on striving for an “ideal synthesis”
  - To a growing extent, attaining the natural product is no longer the final goal
  - Total synthesis is starting to become an auxiliary function of new research in chemistry

The Future of Total Synthesis

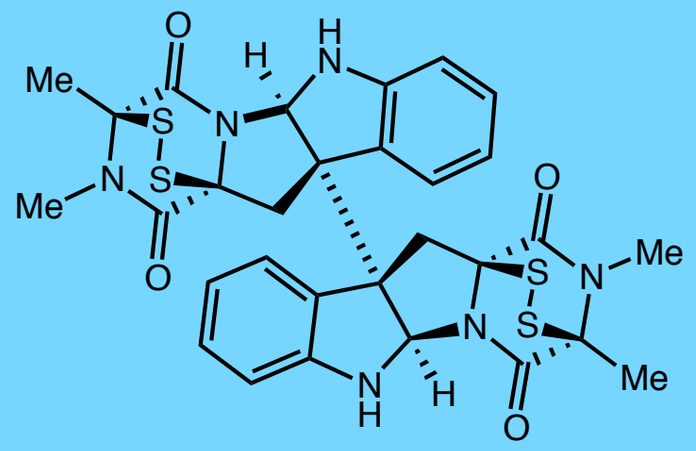
representation of what we strive to accomplish in total synthesis



zaragozic acid C



strychnine

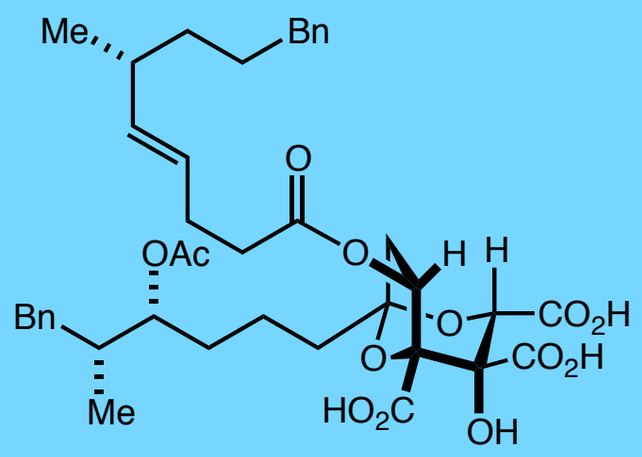


(+)-11,11'-dideoxyverticillin A

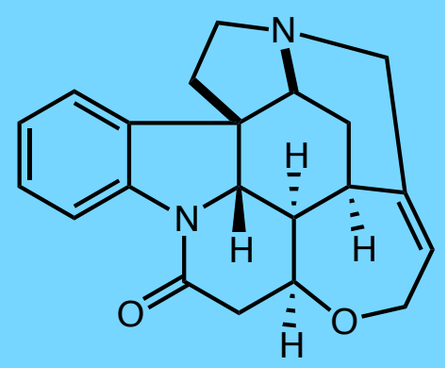
- Two syntheses outlined broadly applicable concepts (cascade catalysis, controlled oligimerization)
- All outlined powerful methods to deliver the natural product in short order(10-15 steps)
- Two syntheses are of molecules with promising bioactivity

The Future of Total Synthesis

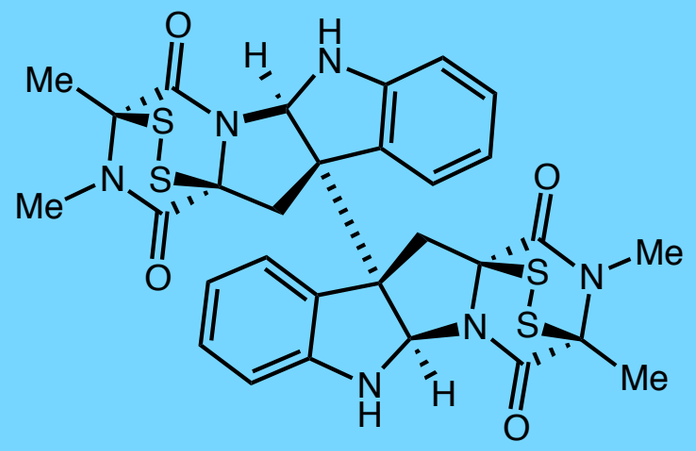
representation of what we strive to accomplish in total synthesis



zaragozic acid C



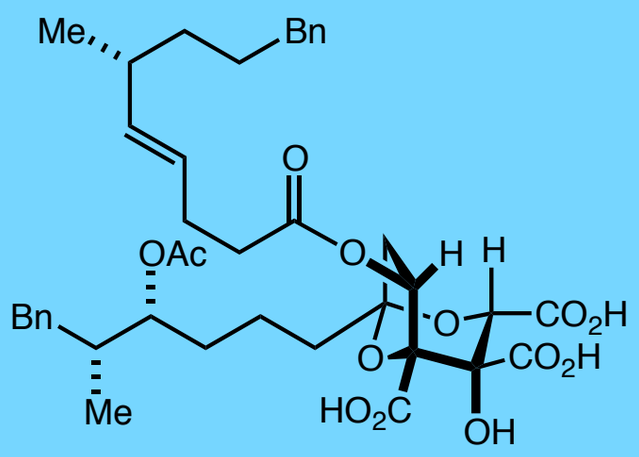
strychnine



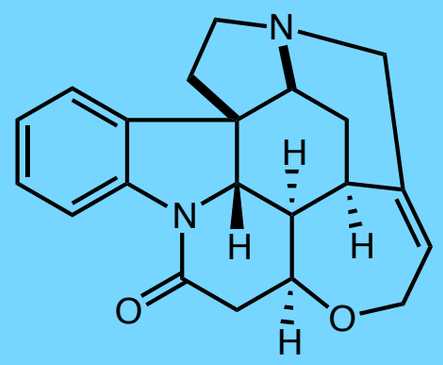
(+)-11,11'-dideoxyverticillin A

The Future of Total Synthesis

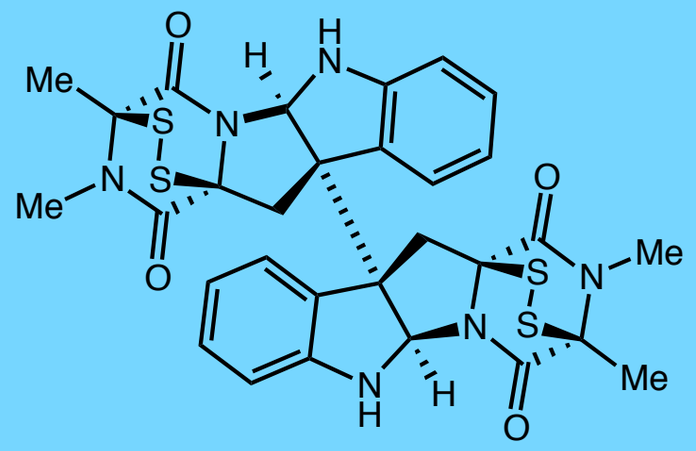
representation of what we strive to accomplish in total synthesis



zaragozic acid C



strychnine



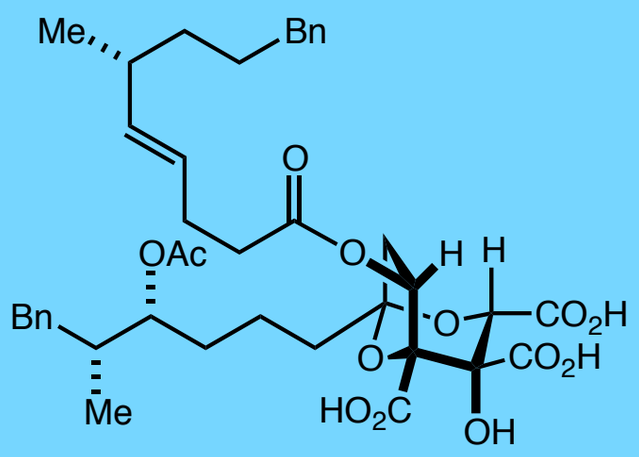
(+)-11,11'-dideoxyverticillin A

Many - some would argue most - natural products can now be synthesized if suitable resources are provided. The challenge in synthesis is therefore increasingly not whether a molecule can be made, but whether it can be made in a practical fashion, in sufficient quantities for the needs of research and/ or society, and in a way that is environmentally friendly if not 'ideal'.

-Paul Wender

The Future of Total Synthesis

representation of what we strive to accomplish in total synthesis



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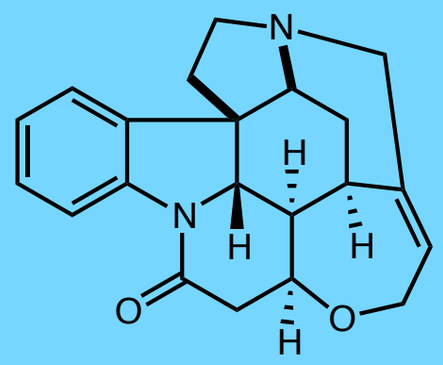

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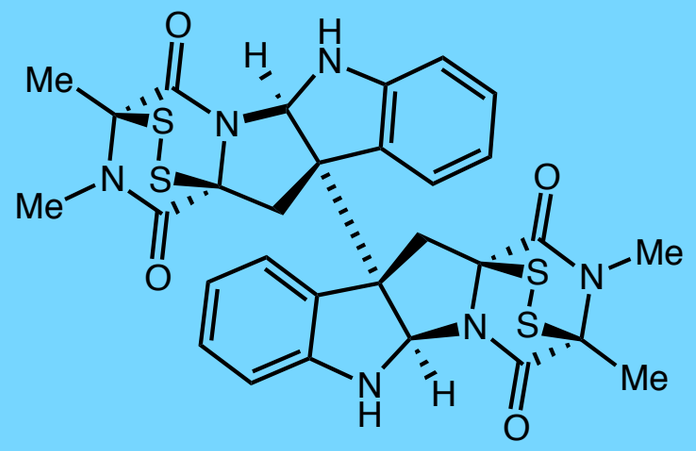


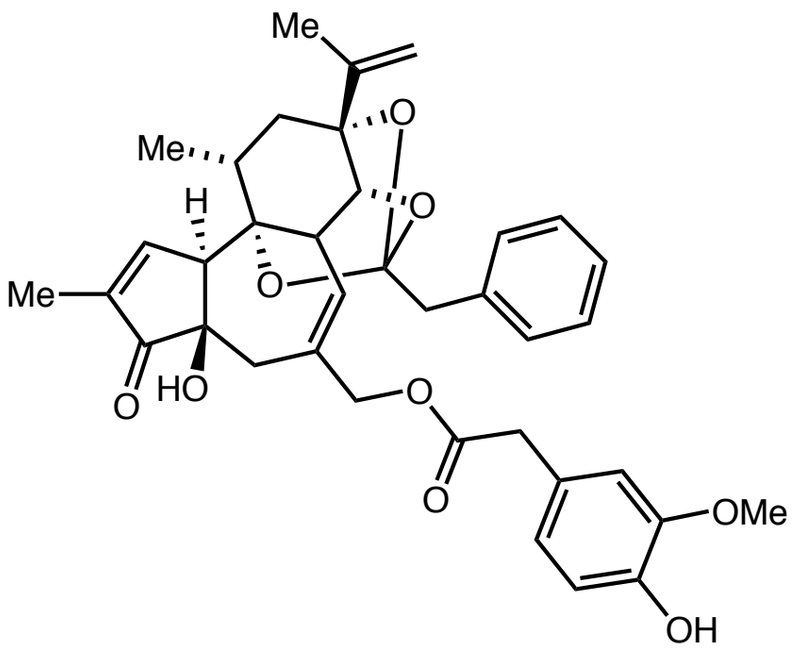
(+)-11,11'-dideoxyverticillin A

- These represent premier total syntheses for our time
- In general, these syntheses are atypical from most syntheses that are published in top journals
- While they embody what we strive to accomplish as synthetic chemists, they are only a small but rapidly growing representation of current work in the field of total synthesis

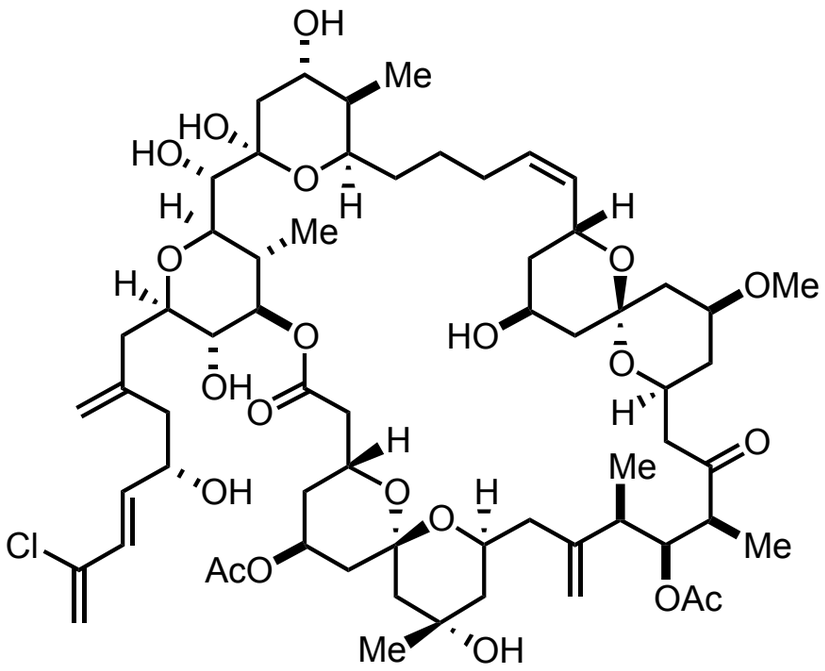
The Future of Total Synthesis

insights from three recent total syntheses of groups from three different era's

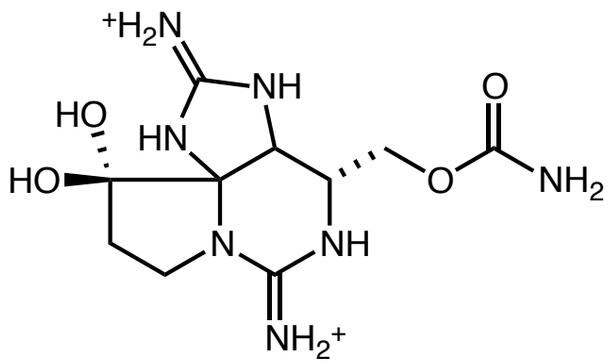
- Three molecules that highlight the perceived divisions for the modern role of total synthesis
  - Which natural products do we make?
    - All, some, any? Structurally interesting, biologically active?
  - What holds more value?
    - The structure, method employed, lessons learned, or future prospects?



resiniferatoxin

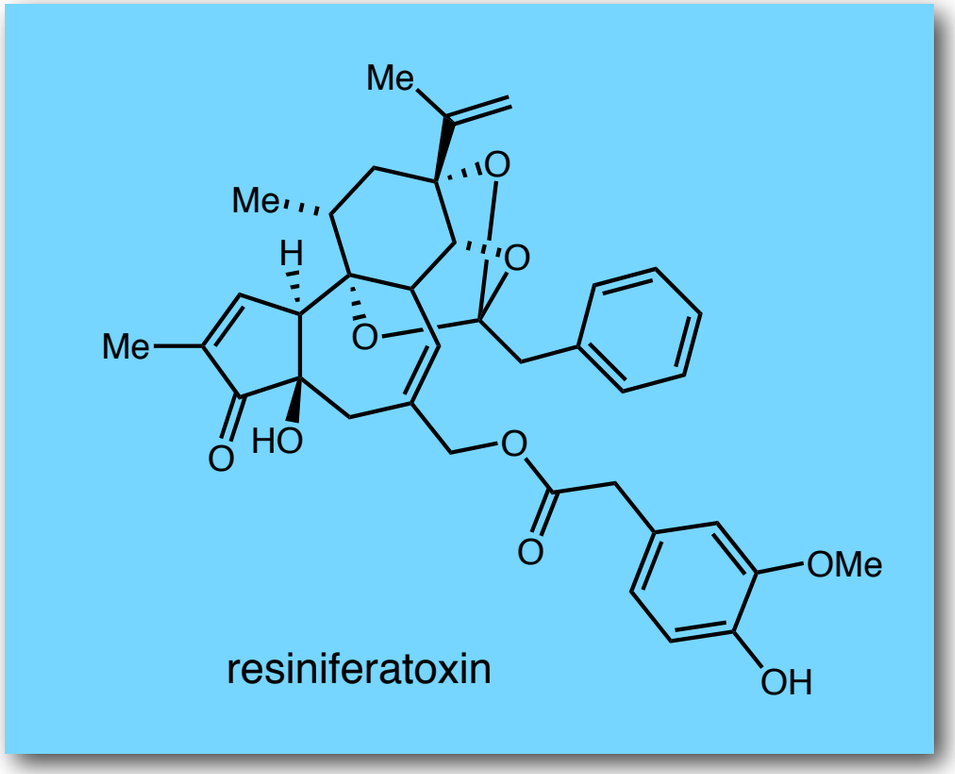


spongistatin 1



(+)-saxitoxin

Wender's Synthesis of Daphnane Diterpene Orthoesters



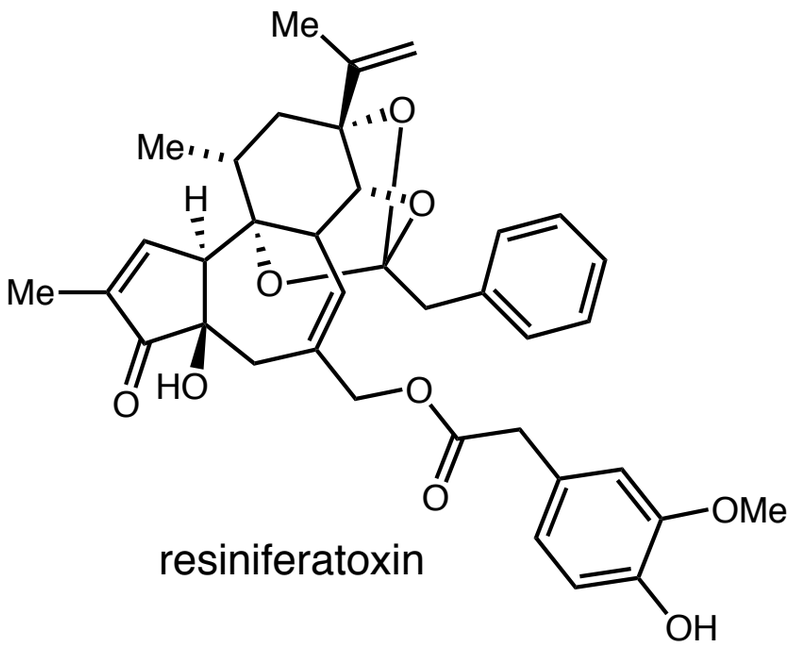
resiniferatoxin

- Plants containing DDOs have been used medicinally for over 2000 years
- Many DDOs are leads for treatment of cancer, diabetes, neurodegenerative disease and pain.
- Resiniferatoxin has advanced into Phase II clinical trials
- Study and use of DDOs are hampered by supply and cost issues

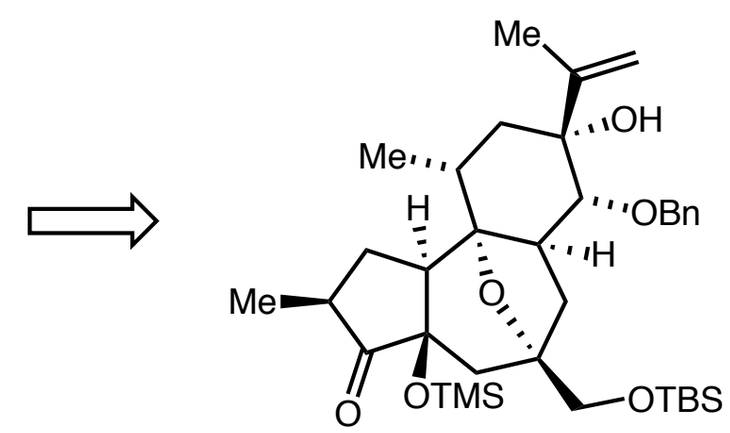
Wender, P. A.; Buschmann, N.; Cardin, N. B.; Jones, L. R.; Kan, C.; Kee, J.-M.; Kowalski, J. A.; Longcore, K. E.; *Nature Chem.* **2011**, *3*, 615-619.

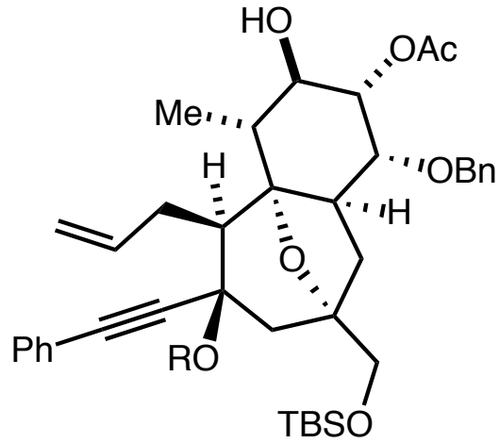
Wender's Synthesis of Daphnane Diterpene Orthoesters

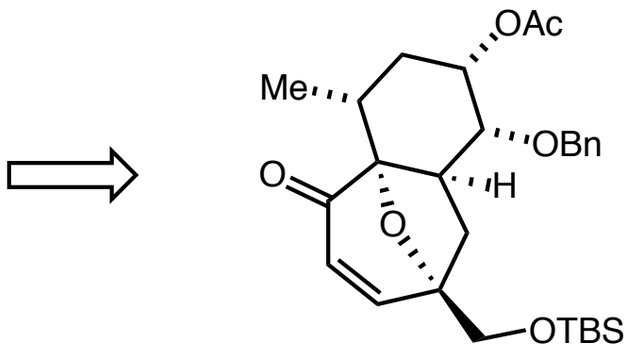
the first synthesis of a daphnane diterpene by Wender in 1997

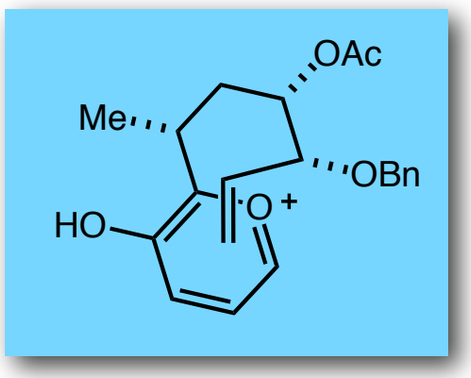


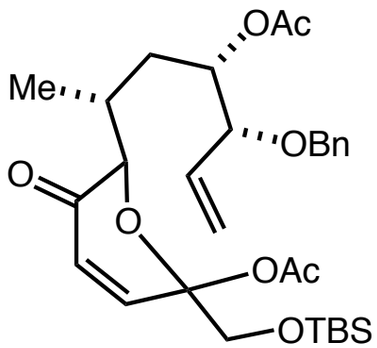
resiniferatoxin











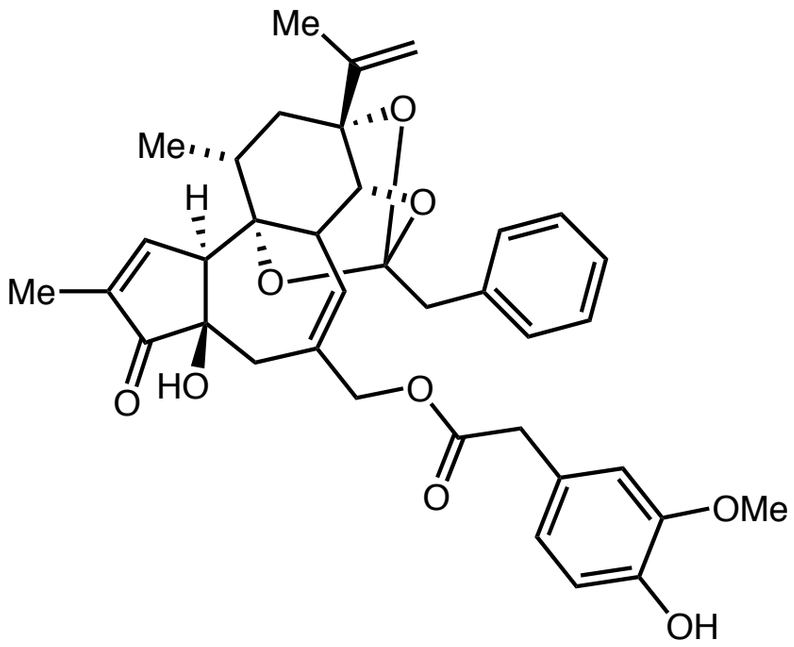
- Total synthesis featured 46 stop and go steps, *tour de force*
- Key disconnections: oxidopyrilium cycloaddition. Enyne ring closure. Applied in highly complex system
- Wender's total synthesis is widely regarded as a "classic"

Wender, P. A.; Jesudason, C. D.; Nikahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976-12977.

Wender's Synthesis of Daphnane Diterpene Orthoesters

function oriented synthesis

- Original total synthesis not ideal from an efficiency or a structural diversification perspective



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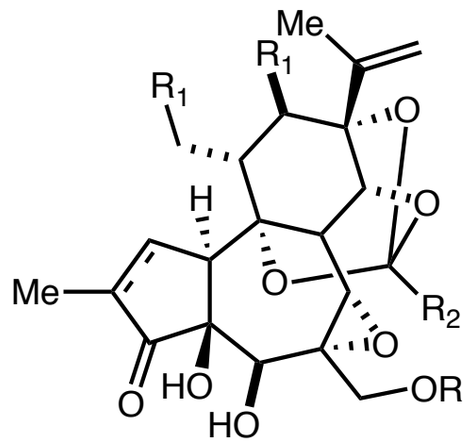
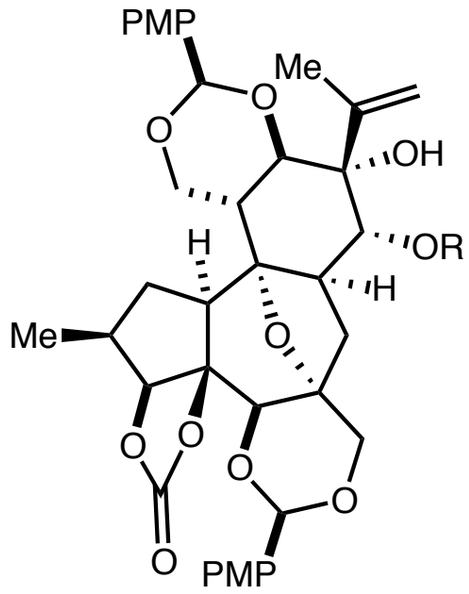


major subset of DDOs
(X = H, 73 congeners)



- Key question:
  - Is a more structurally diverse DDO collection accessible to probe function?
  - Can analog synthesis reveal a more synthetically accessible structure that retains function

Wender, P. A.; Buschmann, N.; Cardin, N. B.; Jones, L. R.; Kan, C.; Kee, J.-M.; Kowalski, J. A.; Longcore, K. E.; *Nature Chem.* **2011**, *3*, 615-619.

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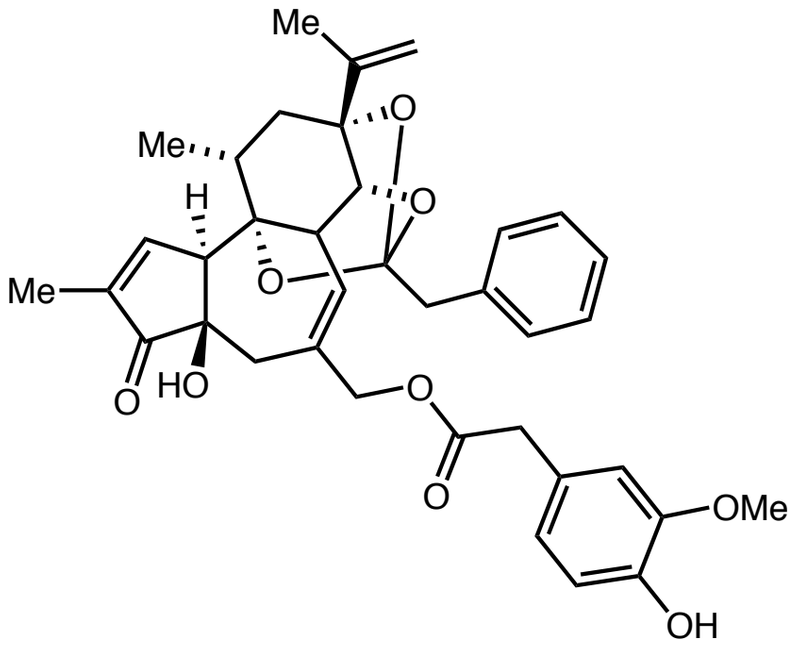

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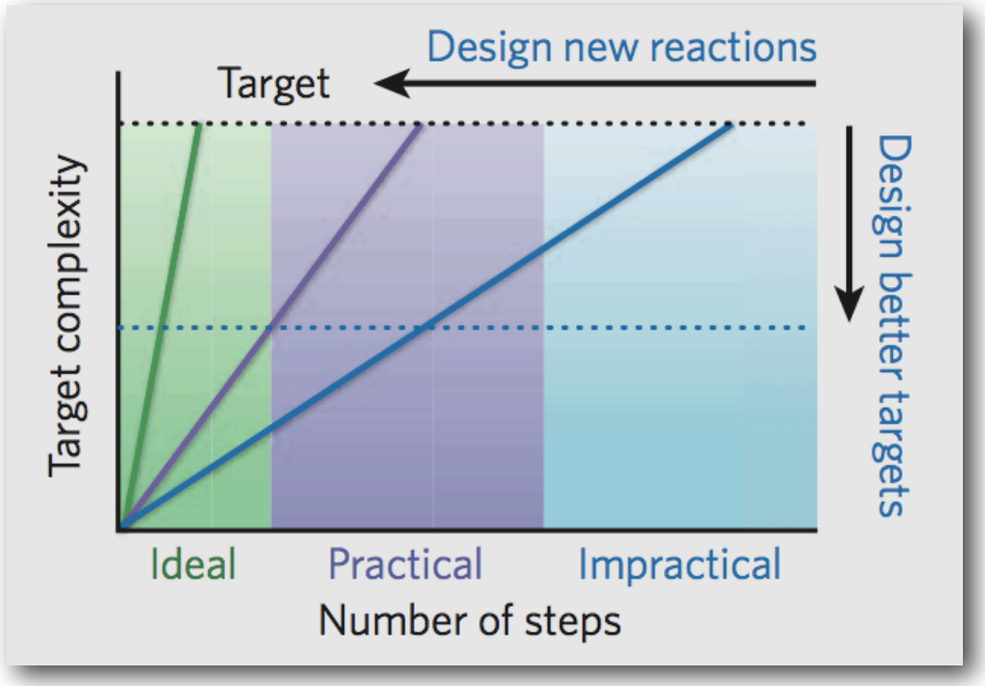

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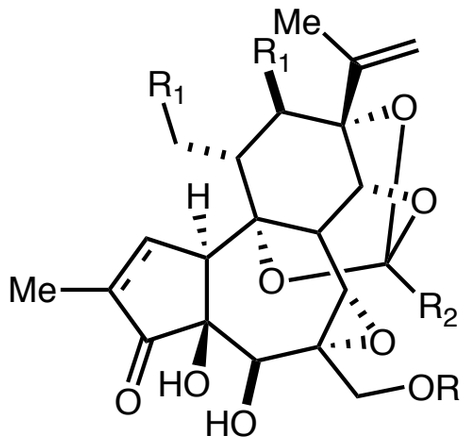

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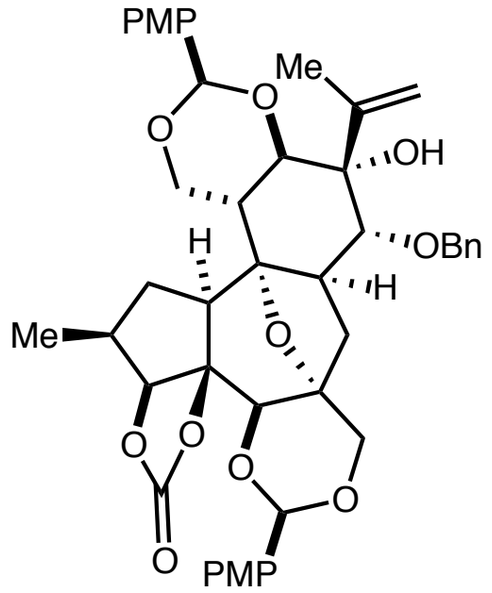
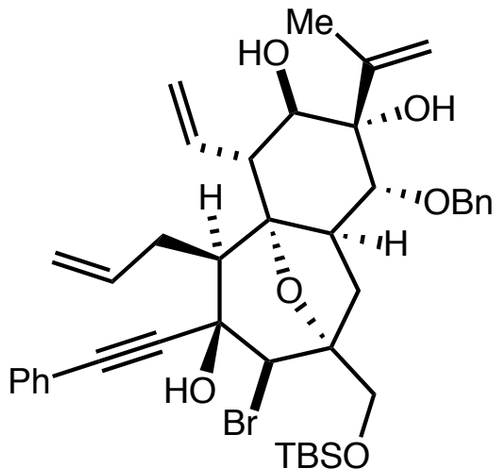
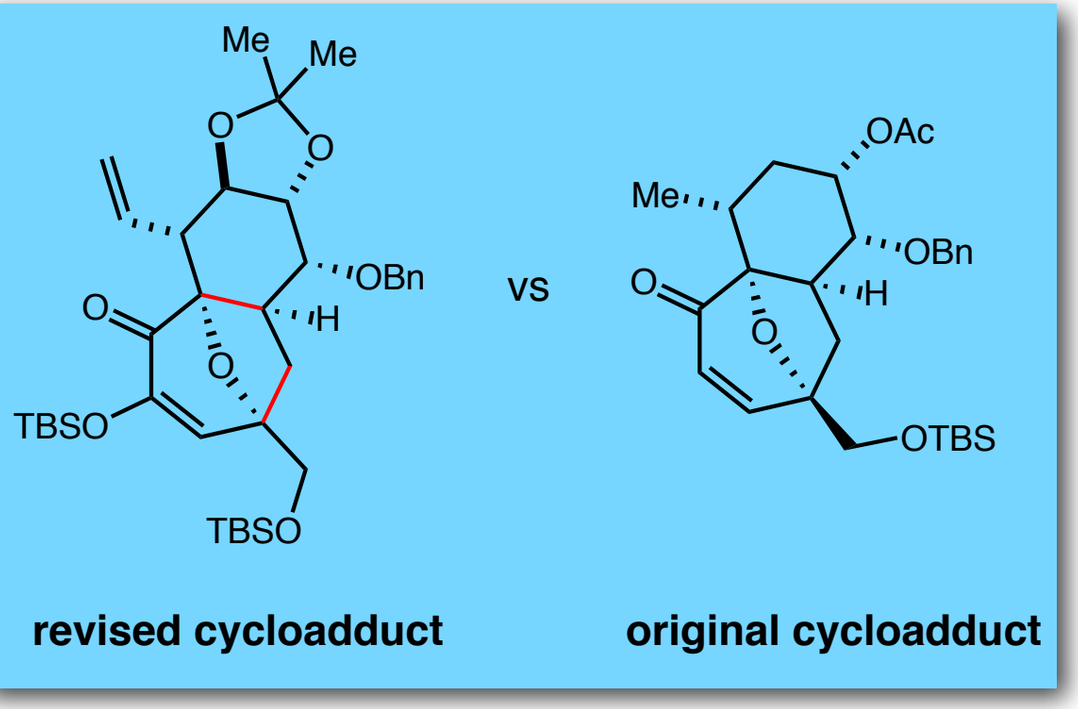


general precursor
(22 steps from commercial)



10 steps from tartrate

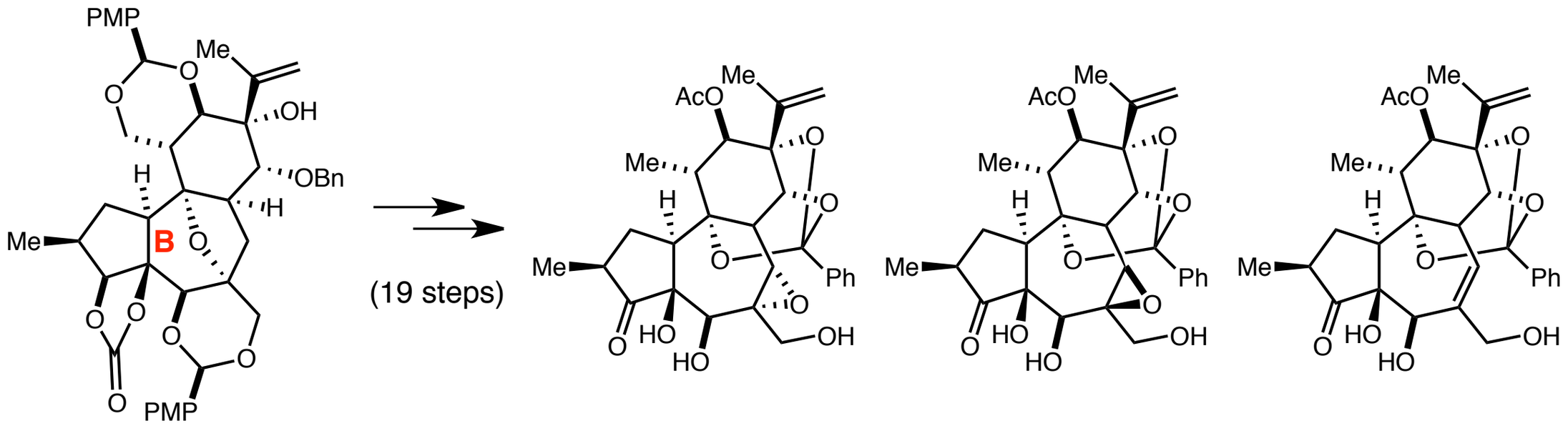


revised cycloadduct **original cycloadduct**

Wender, P. A.; Buschmann, N.; Cardin, N. B.; Jones, L. R.; Kan, C.; Kee, J.-M.; Kowalski, J. A.; Longcore, K. E.; *Nature Chem.* **2011**, *3*, 615-619.

Wender's Synthesis of Daphnane Diterpene Orthoesters

probing the function of the "B" ring



general precursor (22 steps) **1** **2** **3**

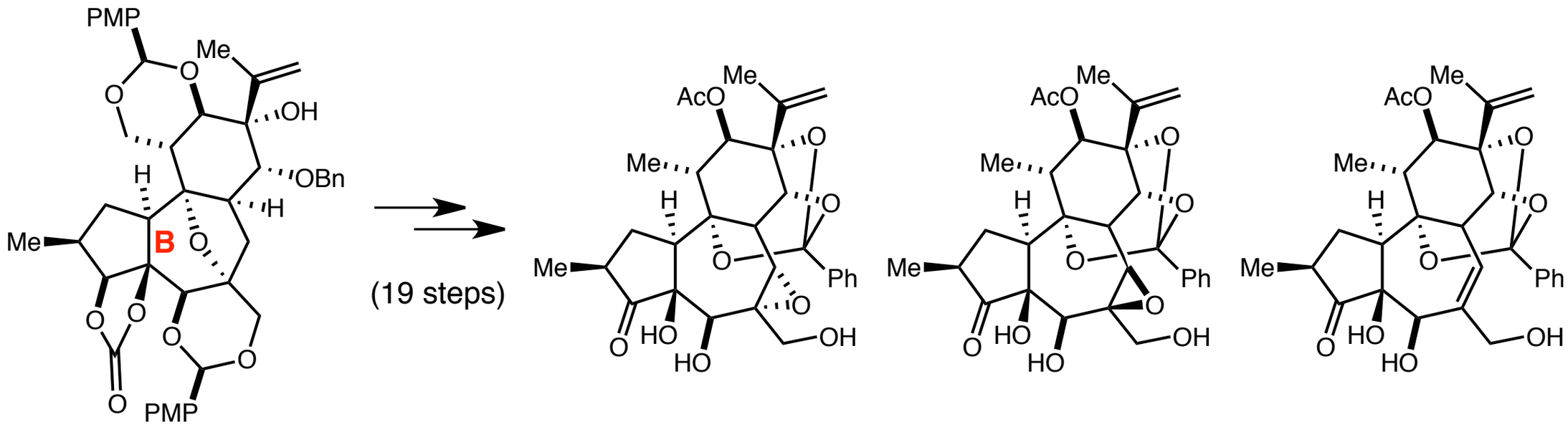
PKC affinity, K_i (nM)[a]		Cellular growth inhibition	
		A549 EC_{50} (nm)[b]	**K562 EC_{50} (nm)[c]**
1	0.48 +/- 0.07	150 +/- 30	7 +/- 1
2	343 +/- 6	> 10,000	> 10,000
3	1.6 +/- 0.1	1500 +/- 60	87 +/- 5

[a]PKC = protein kinase C, a family of serine/threonine kinases [b]A549 = human lung carcinoma [c]K562 = human chronic myleogenous leukaemia.

- Screen of analogs revealed the high potency of DDO's as a ligand for PKC
- Carries the potential for treatment of cancer, alzheimers, and AIDS.

Wender's Synthesis of Daphnane Diterpene Orthoesters

probing the function of the "B" ring



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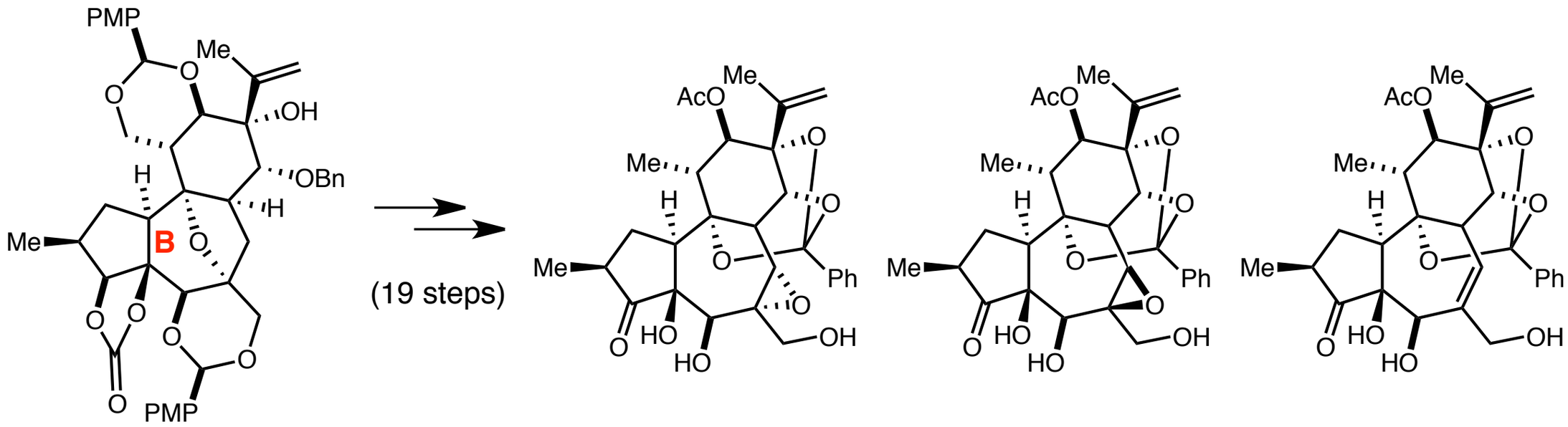
		A549 EC_{50} (nm)[b]	**K562 EC_{50} (nm)[c]**
1	0.48 +/- 0.07	150 +/- 30	7 +/- 1
2	343 +/- 6	> 10,000	> 10,000
3	1.6 +/- 0.1	1500 +/- 60	87 +/- 5

[a]PKC = protein kinase C, a family of serine/threonine kinases [b]A549 = human lung carcinoma [c]K562 = human chronic myleogenous leukaemia.

- An assay against both cancer cell lines reveals the importance of the epoxide stereochemistry
- Interestingly, the simplified *des*-epoxy analog is active

Wender's Synthesis of Daphnane Diterpene Orthoesters

probing the function of the "B" ring

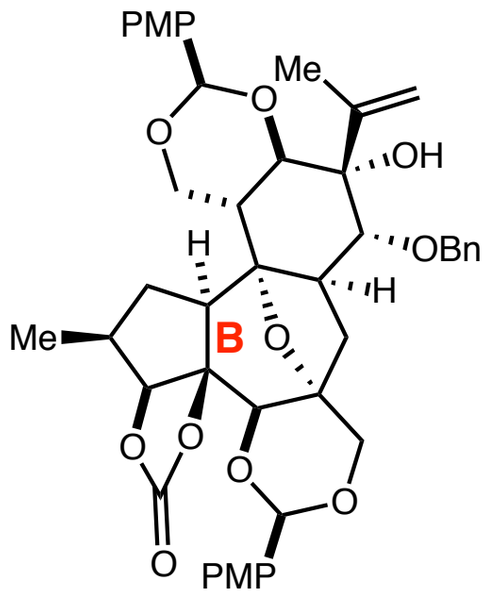


general precursor (22 steps) **1** **2** **3**

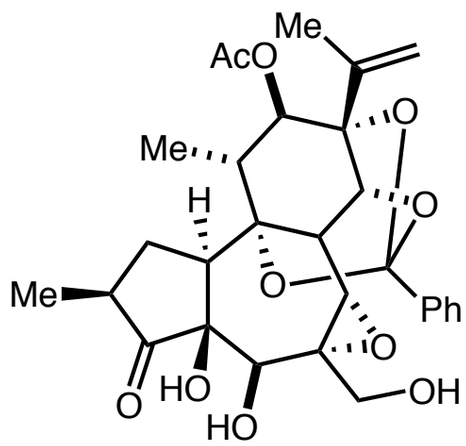
- Calculations showed a preservation of the oxygen spatial arrangement between **1** and **3**
- The β-epoxide of 2, significantly perturbs the orientation of the hydoxymethyl relative to **1**

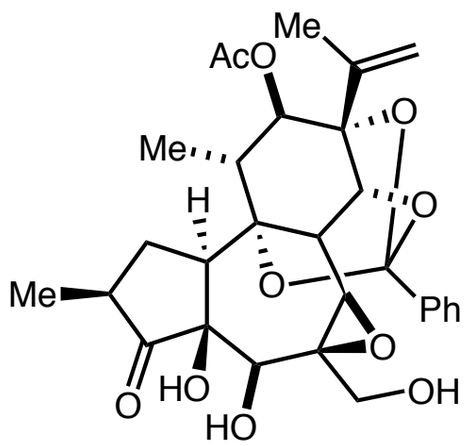
Wender's Synthesis of Daphnane Diterpene Orthoesters

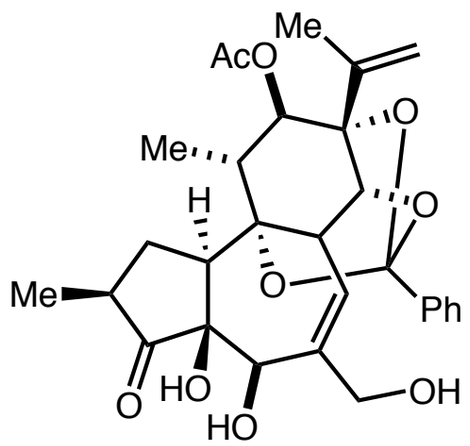
a model for the future?



(19 steps)



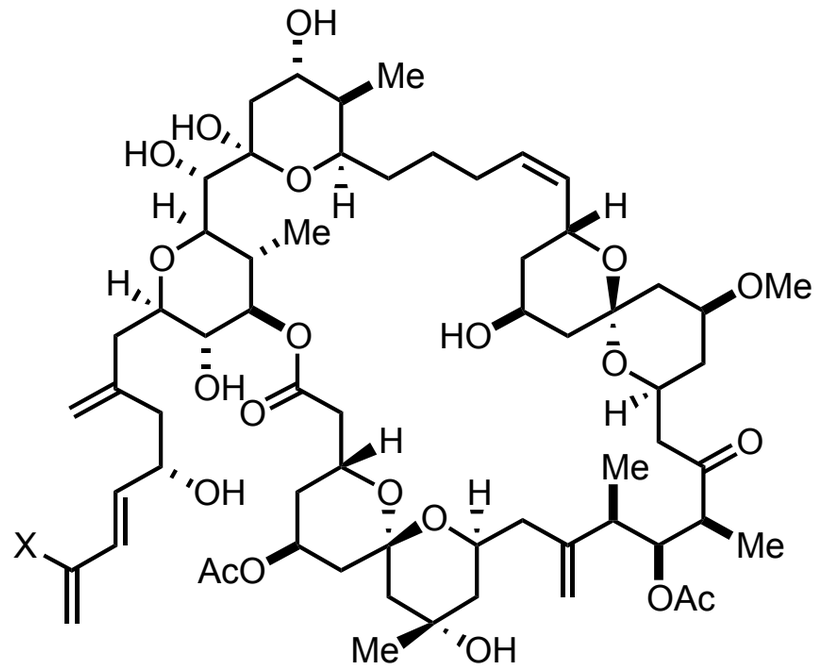




general precursor (22 steps) **1** **2** **3**

- Original synthesis was a *tour de force*, 46 steps, of an incredibly complicated molecule
- They delivered an improved synthesis of a more complicated and functionally versatile molecule
  - Is the *tour de force* synthesis relevant if it delivers additional compound for testing?
  - Is the second generation route more valuable than the synthesis of another natural product?
  - Does a molecules potential for societal impact alter how we perceive its total synthesis?

Smiths' Synthesis of the Spongistatins



spongistatin 1 X = Cl

spongistatin 2 X = H

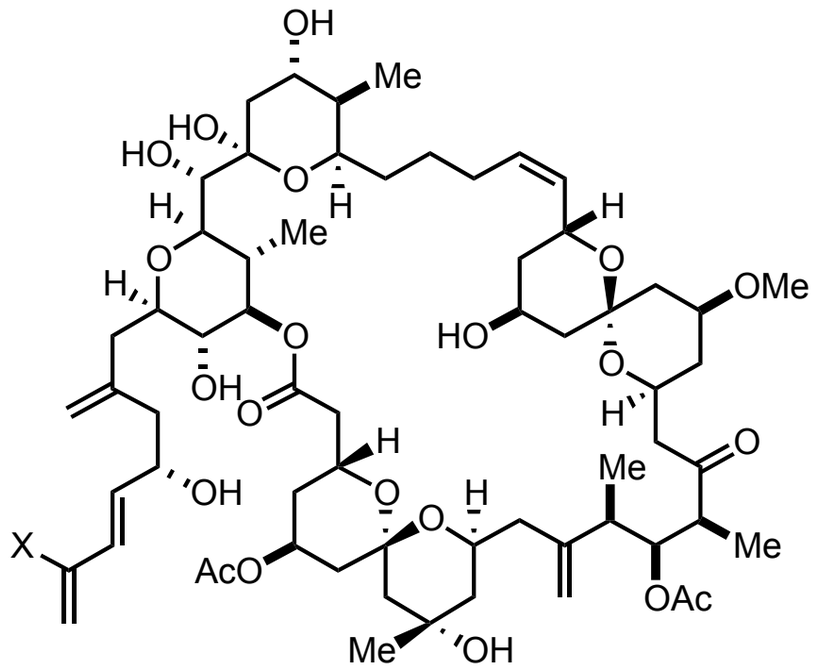
Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 196-199.

Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 197-201.

Smith, A. B., III; Zhu, W.; Shirakami, S.; Sfouggatakis, C.; Doughty, V. A.; Bennett, C. S.; Sakamoto, Y. *Org. Lett.* **2003**, *5*, 761-764.

Smiths' Synthesis of the Spongistatins

history of the spongistatins



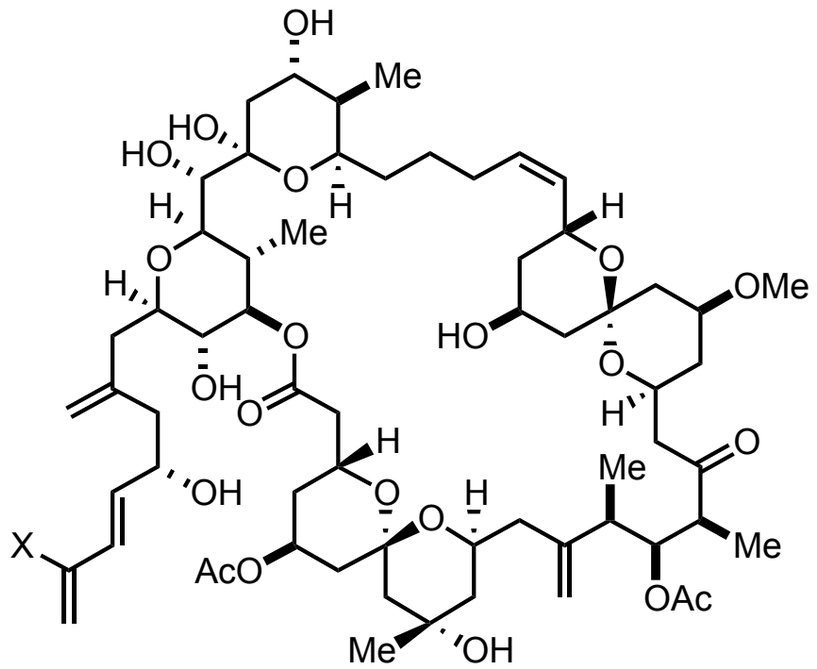
spongistatin 1 X = Cl

spongistatin 2 X = H

- Isolated in the early 1990's by the Pettit, Fusetani, and Kitagawa laboratories
- Pettit's attempted re-isolation delivered 35 mg of spongistatin 1 from **13 TONS** of sponge!
- Two spiroketals, two tetrahydropyrans, hemiketal, 42 membered macrolide

Smiths' Synthesis of the Spongistatins

history of the spongistatins



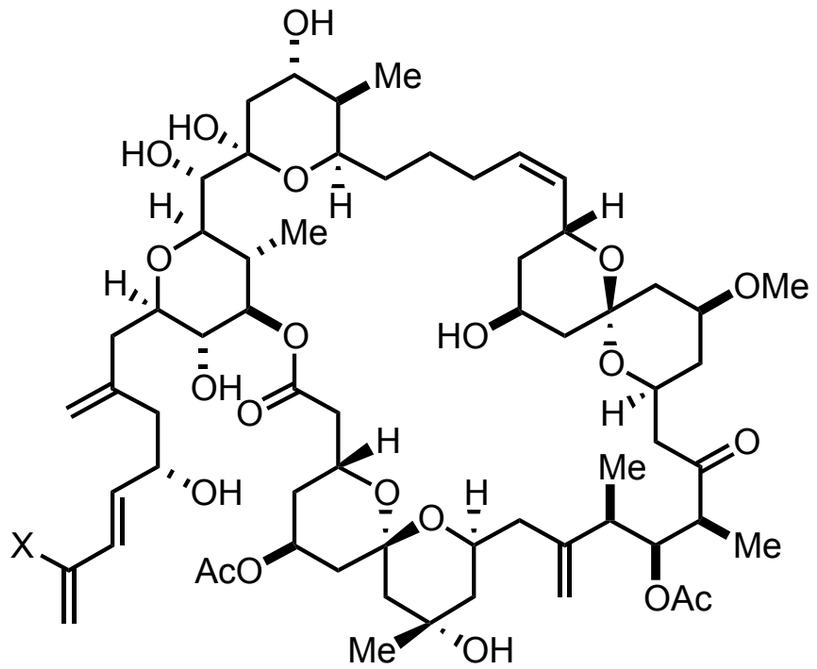
spongistatin 1 X = Cl

spongistatin 2 X = H

- Spongistatin 1 has been recognized as one of the most selective cytotoxic agents known
- Average IC_{50} value of 0.12 nM against the NCI panel of 60 human cancer cell lines
- Proposed to bind β-tubulin near, but distinct from, the *vinca* domain where vinca alkaloids bind

Smiths' Synthesis of the Spongistatins

history of the spongistatins



spongistatin 1 X = Cl

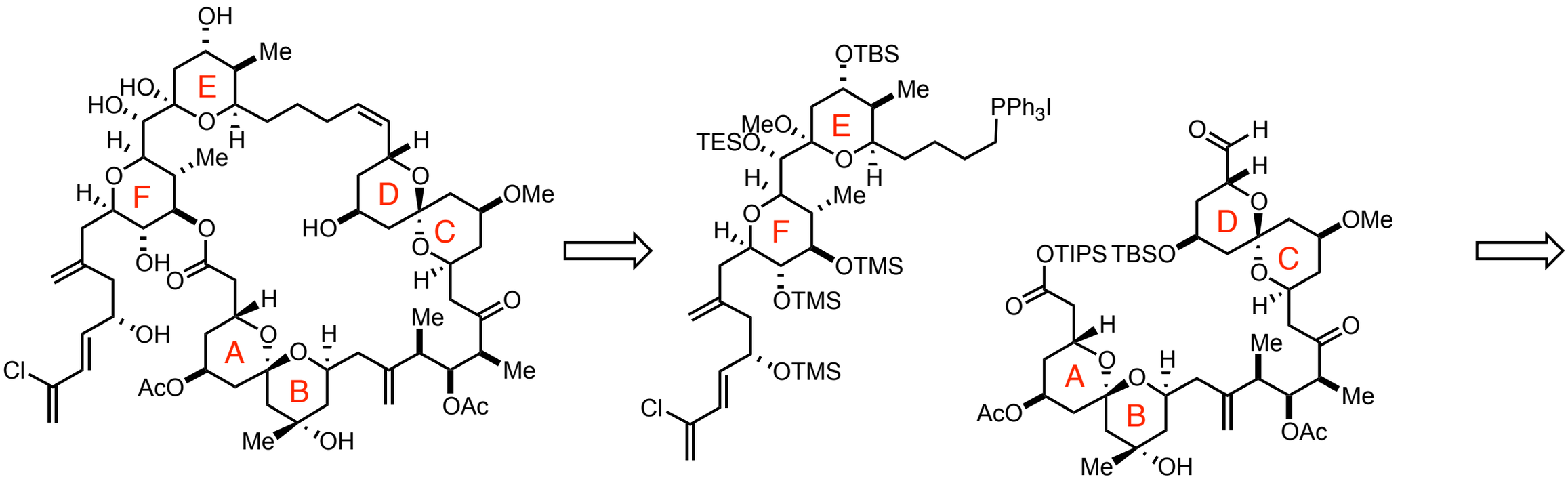
spongistatin 2 X = H

- Promising therapeutic potential and daunting structure drew much interest as a synthetic target
- Total syntheses of 1 and 2: Kishi & Evans (1998), Smith, Paterson, Crimmins, Ley, Heathcock and others
- Smith completed the total synthesis of spongistatin 2 in 2001 and 1 in 2003 (48 longest linear steps)

Smiths' Synthesis of the Spongistatins

Smiths' first generation synthesis

Retrosynthetic analysis

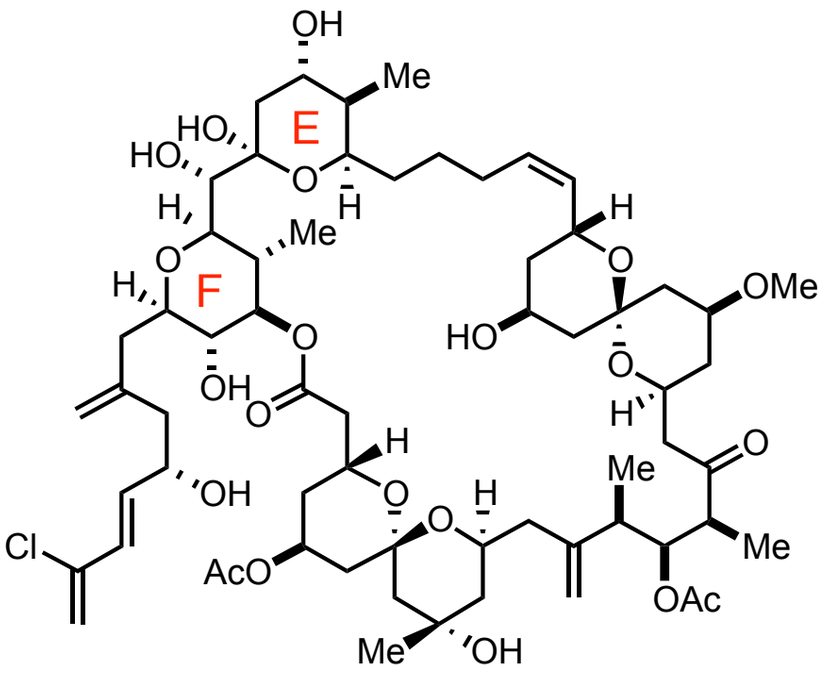


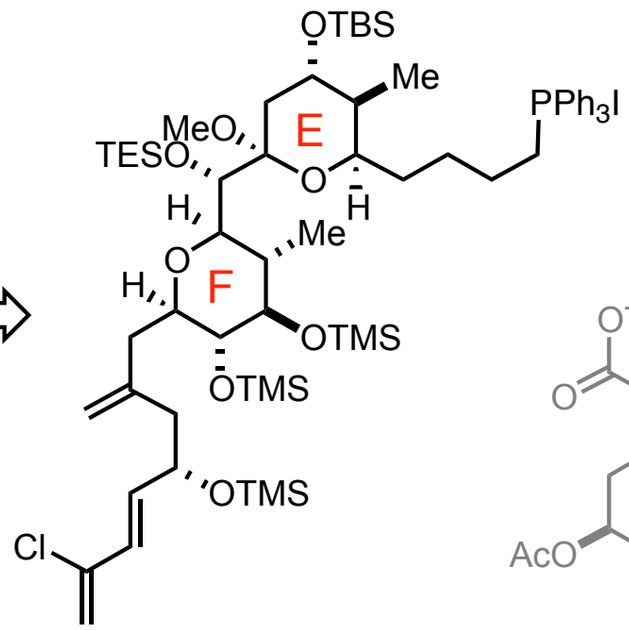
- Late stage Yamaguchi macrolactonization to form the macrocycle
- A Wittig olefination unites the eastern and western halves of the molecule

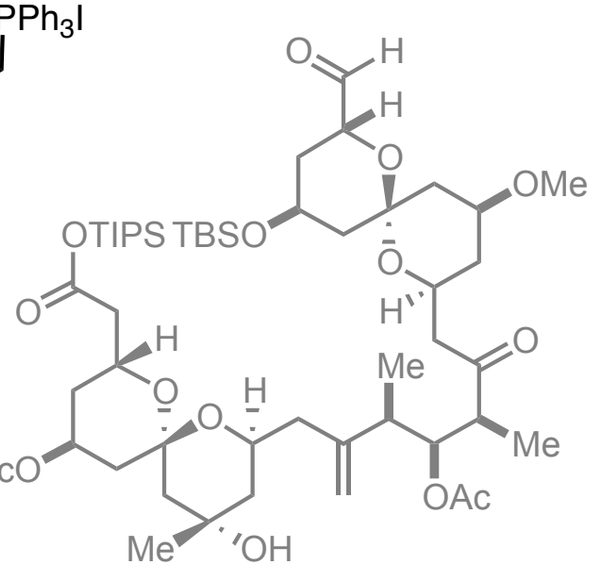
Smiths' Synthesis of the Spongistatins

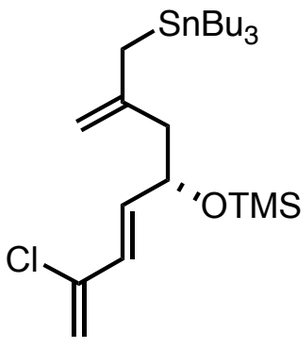
Smiths' first generation synthesis

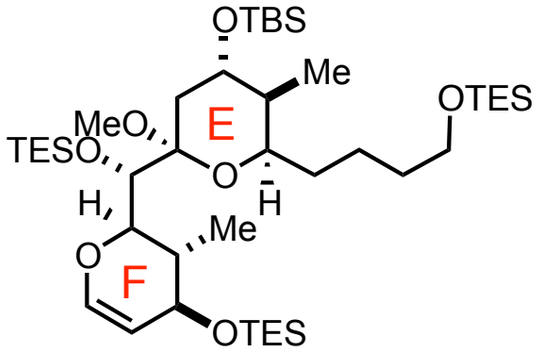
Retrosynthetic analysis

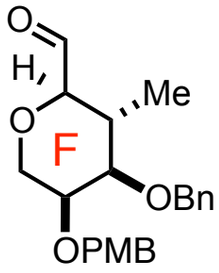


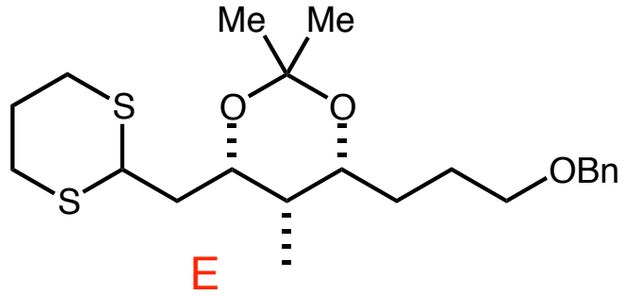








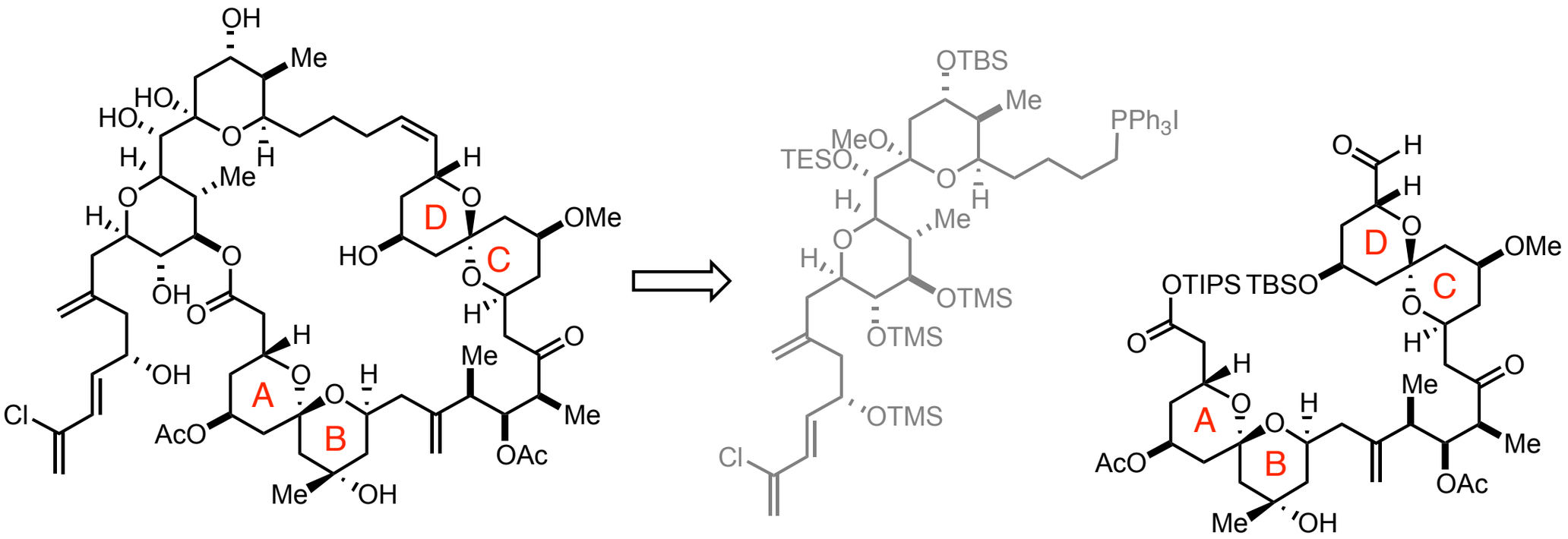




Smiths' Synthesis of the Spongistatins

Smiths' first generation synthesis

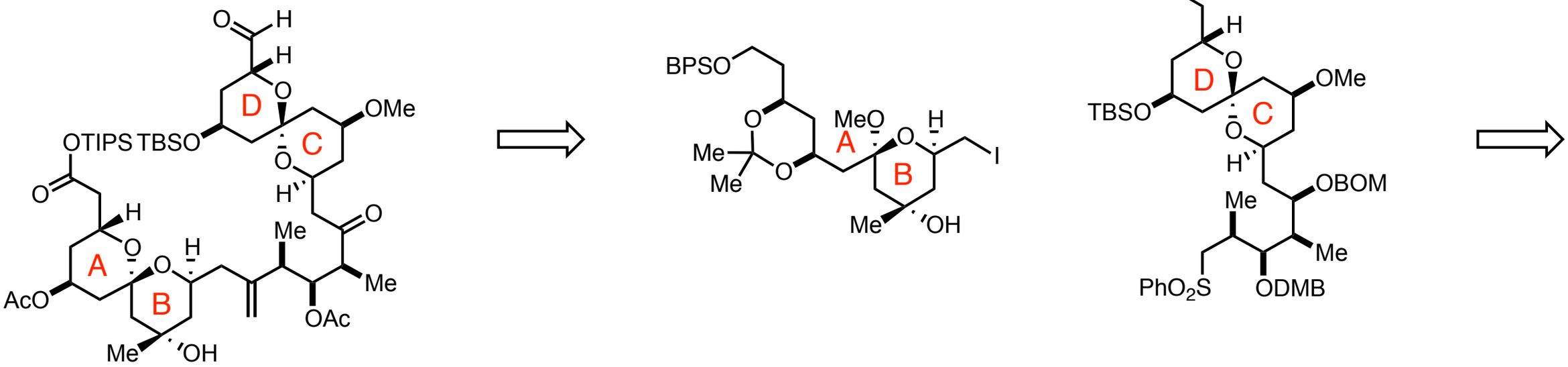
Retrosynthetic analysis



Smiths' Synthesis of the Spongistatins

Smiths' first generation synthesis

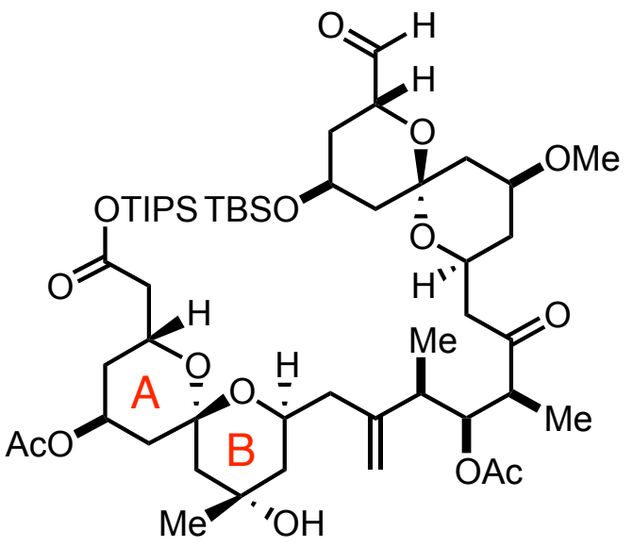
Retrosynthetic analysis

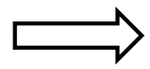


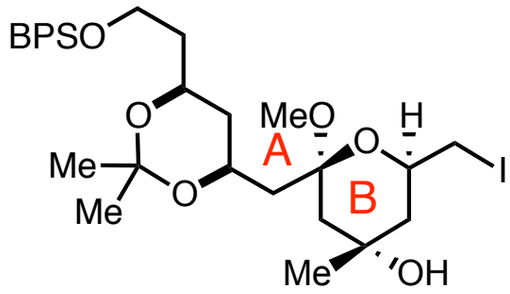
Smiths' Synthesis of the Spongistatins

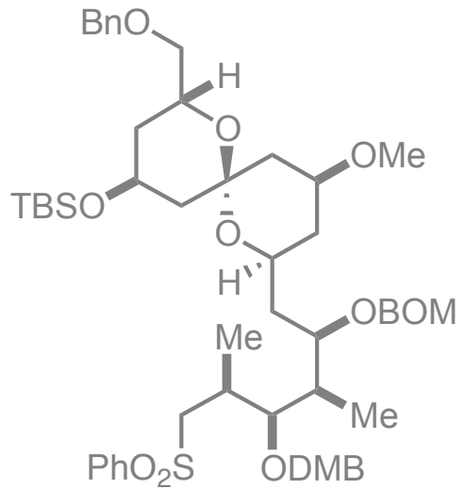
Smiths' first generation synthesis

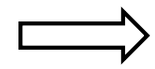
Retrosynthetic analysis

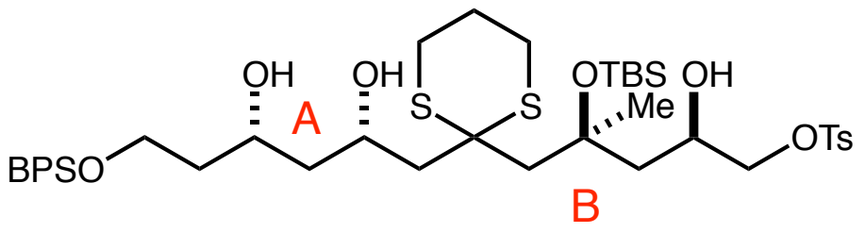


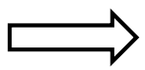


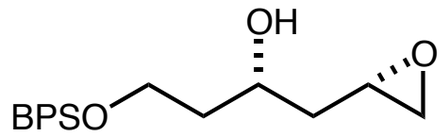


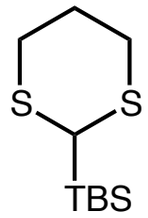


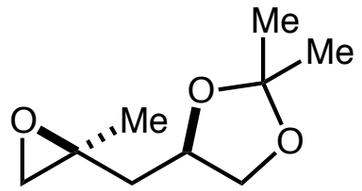








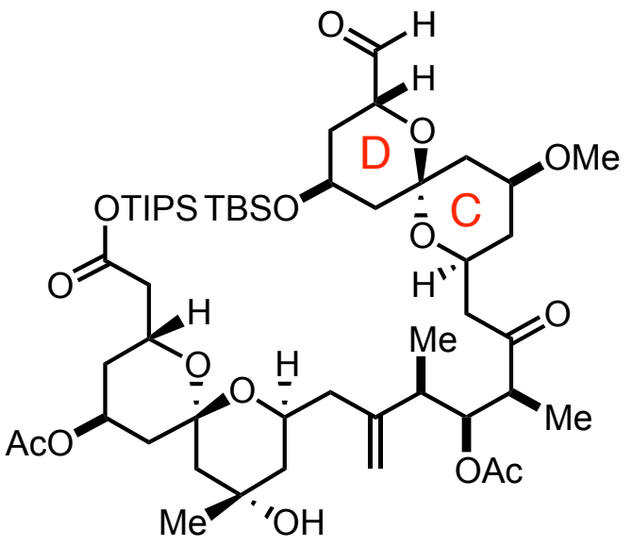


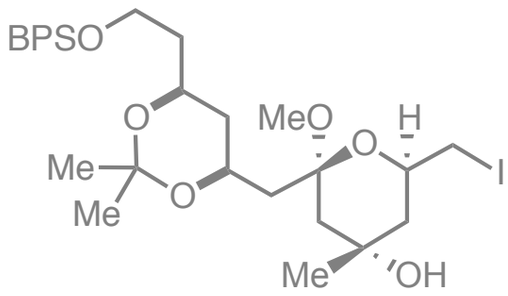


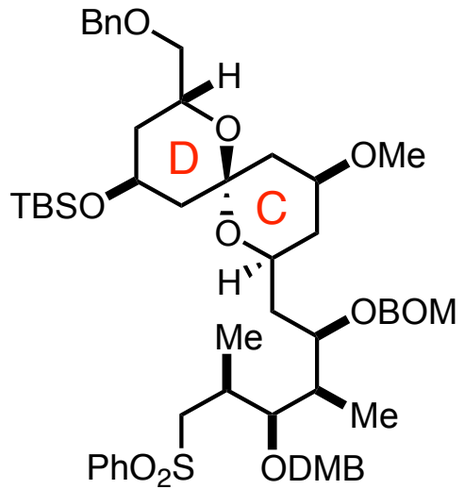
Smiths' Synthesis of the Spongistatins

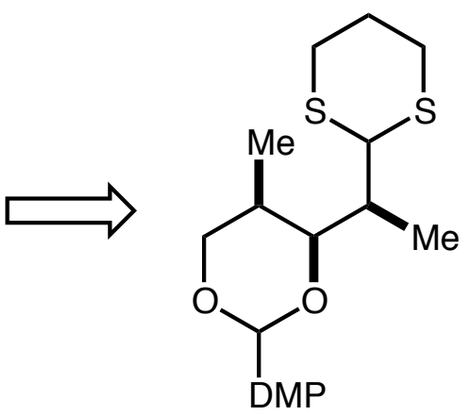
Smiths' first generation synthesis

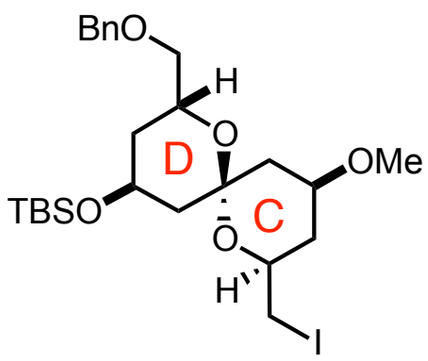
Retrosynthetic analysis

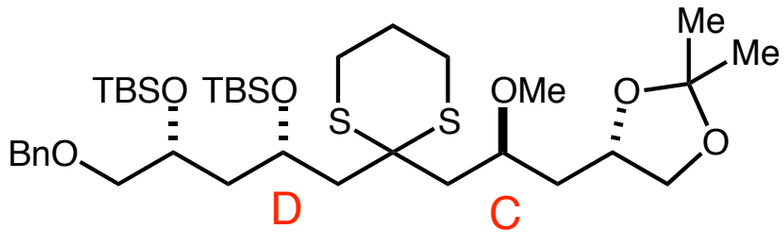


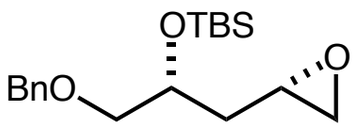


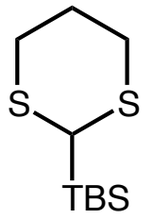


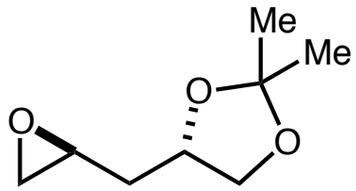








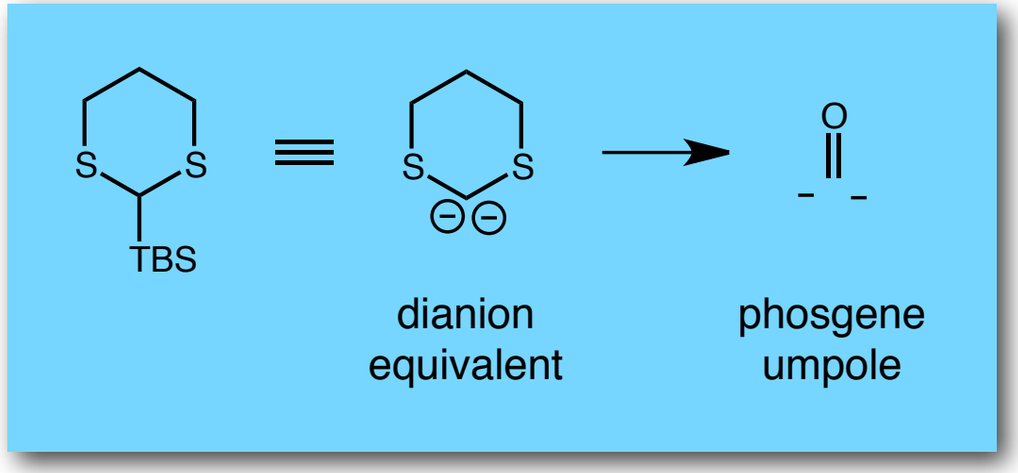


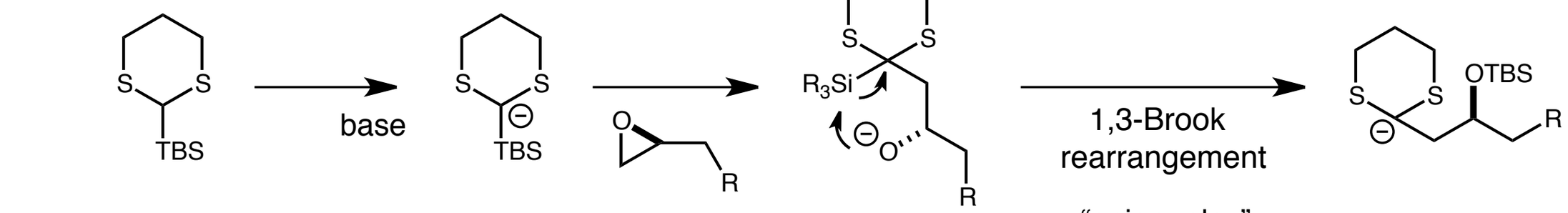


Smiths' Synthesis of the Spongistatins

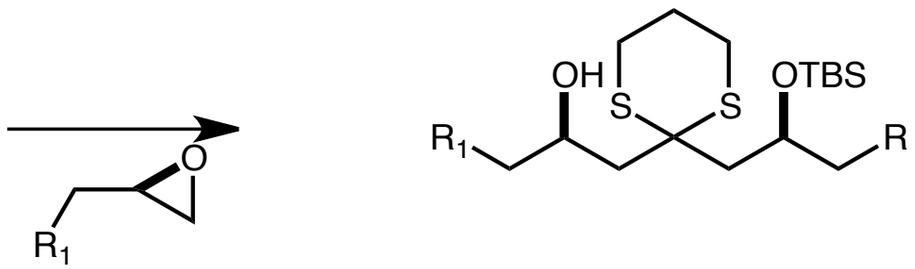
anion relay chemistry

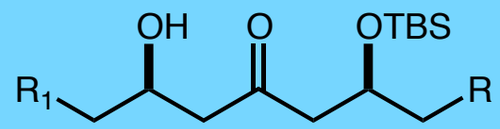
- A versatile method for polyketide synthesis - used to form AB and CD fragments





bifunctional nucleophile
linchpin



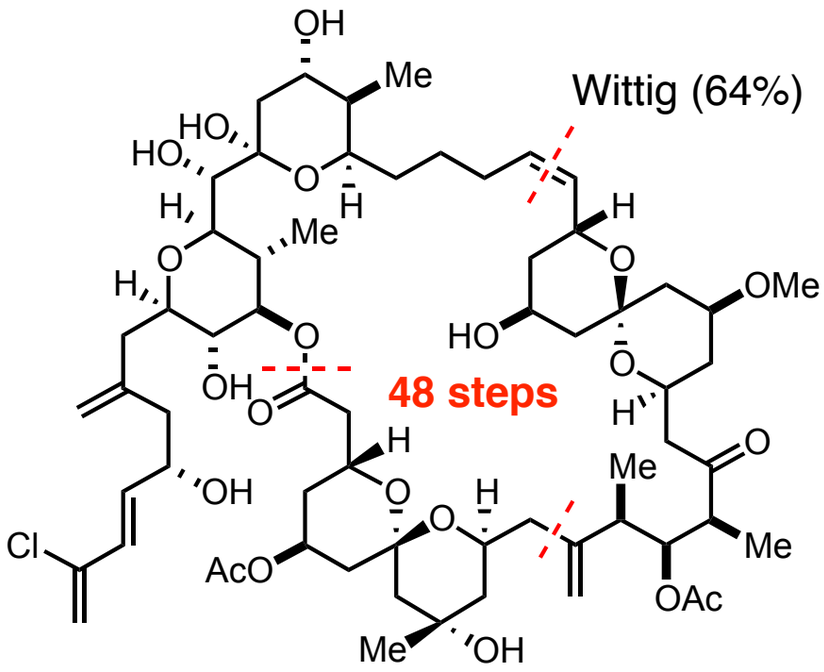


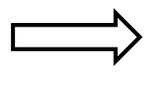
readily accessible

Smiths' Synthesis of the Spongistatins

review of their initial synthetic efforts

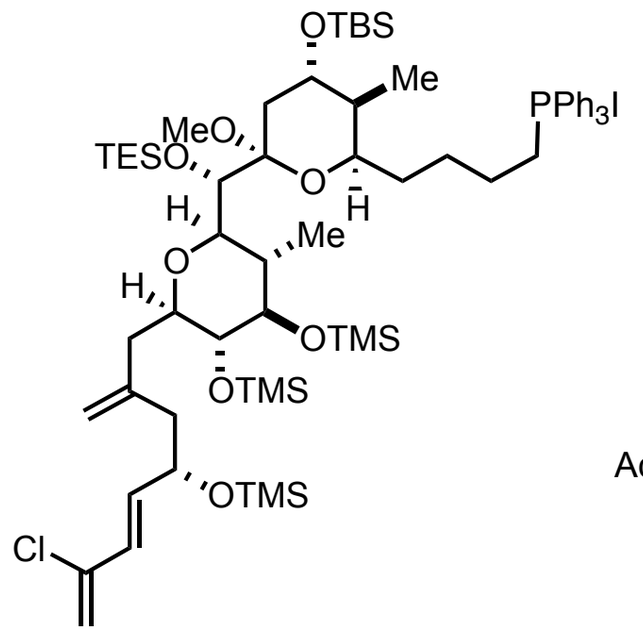
Overview of their entire synthesis and strategy



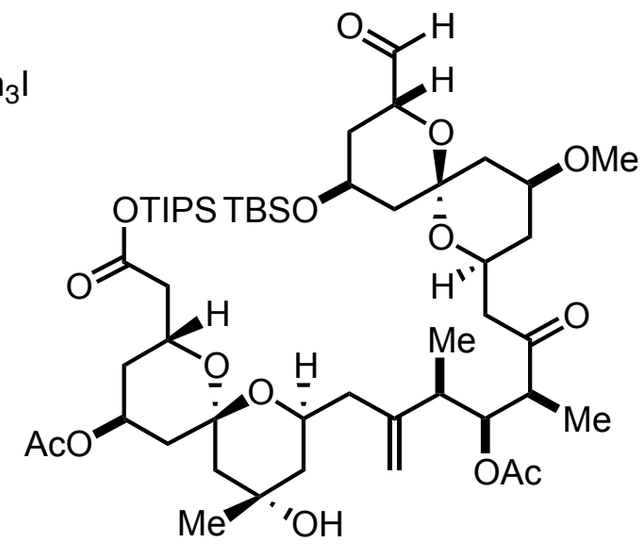


5 steps

Alkylation (92%)

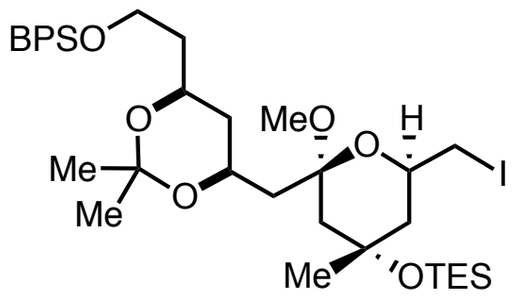


24 steps, 0.3%

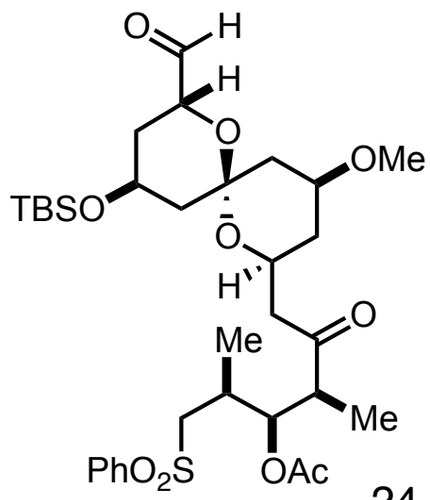


43 steps

19 steps



11 steps

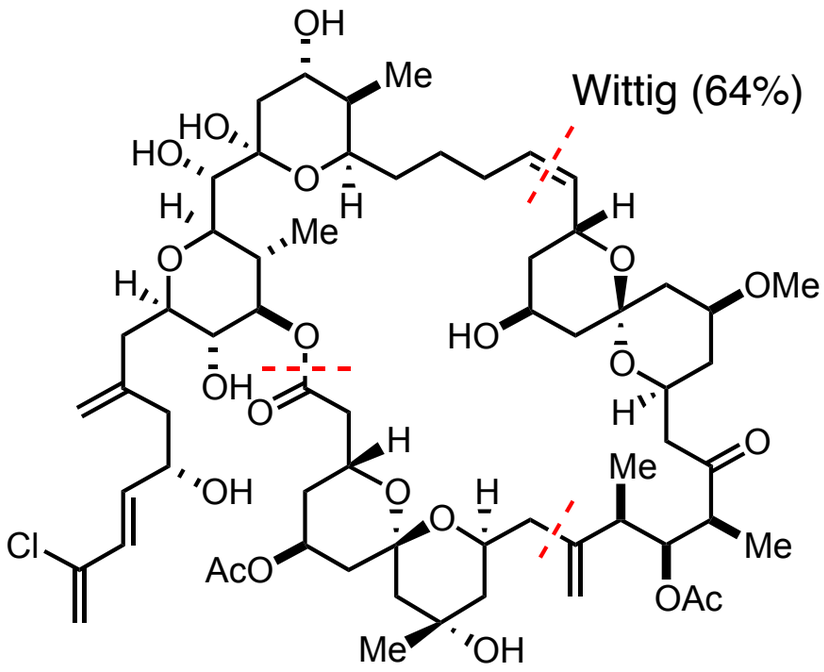


24 steps

Smiths' Synthesis of the Spongistatins

review of their initial synthetic efforts

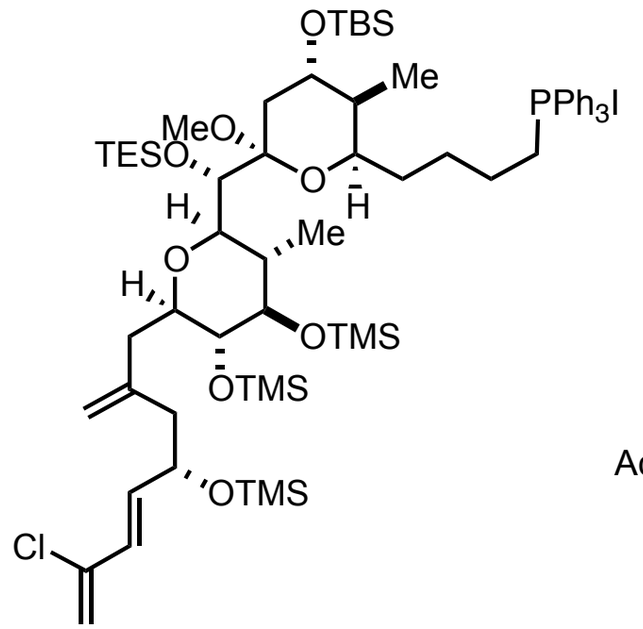
Overview of their synthesis and strategy



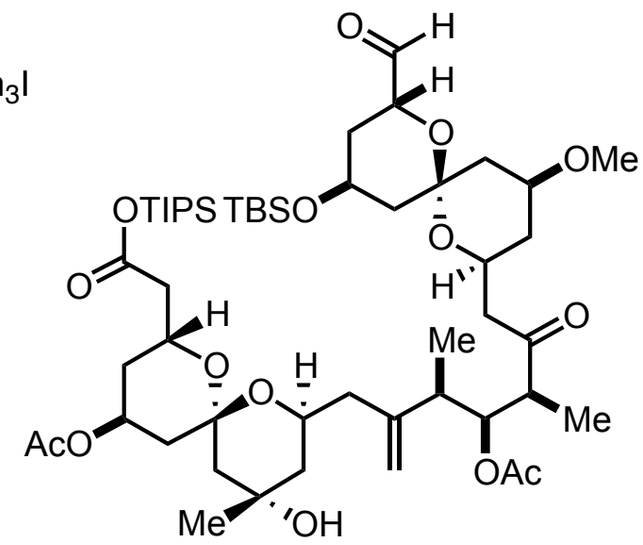
Yamaguchi (81%)

Alkylation (92%)

5 steps



24 steps, 0.3%



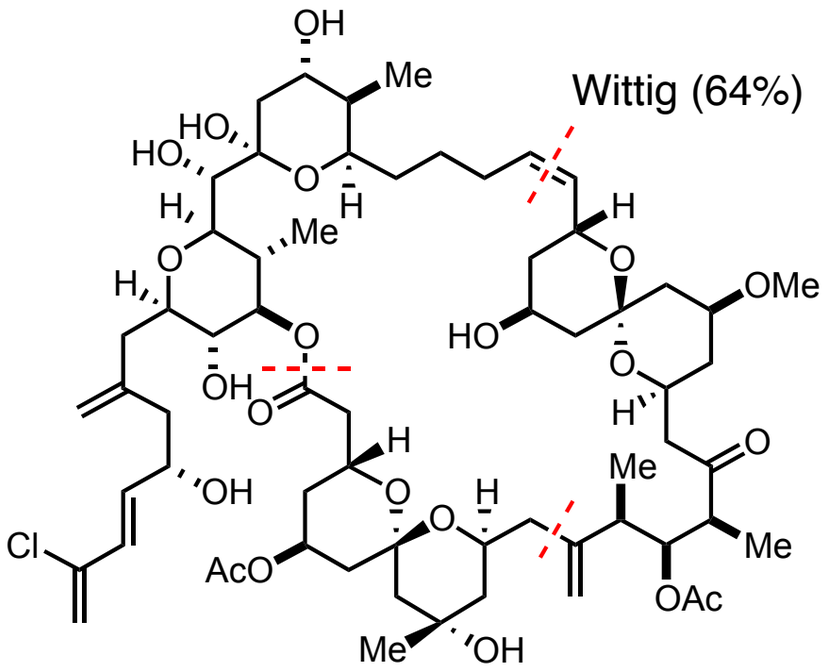
43 steps

- Versatile synthetic route that accommodated necessary changes in routes and strategies
- Methods employed in the synthesis were designed to access many structurally diverse natural products
- Methods employed were not ideally suited for this specific molecule
- Allowed them to complete the total synthesis, not ideal for scale up or analog synthesis

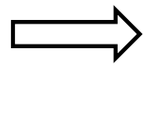
Smiths' Synthesis of the Spongistatins

review of their initial synthetic efforts

Overview of their synthesis and strategy

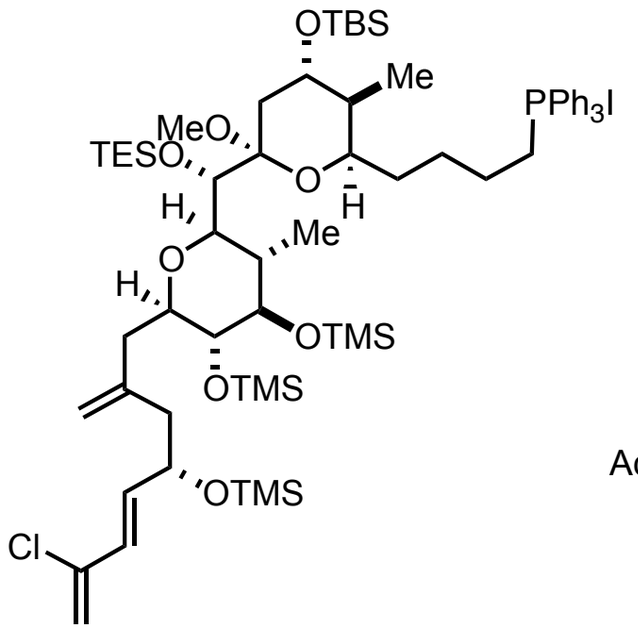


Yamaguchi (81%)

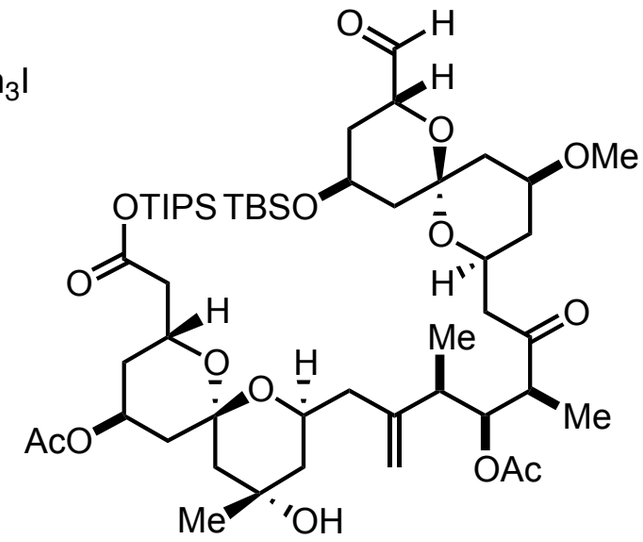


5 steps

Alkylation (92%)



24 steps, 0.3%



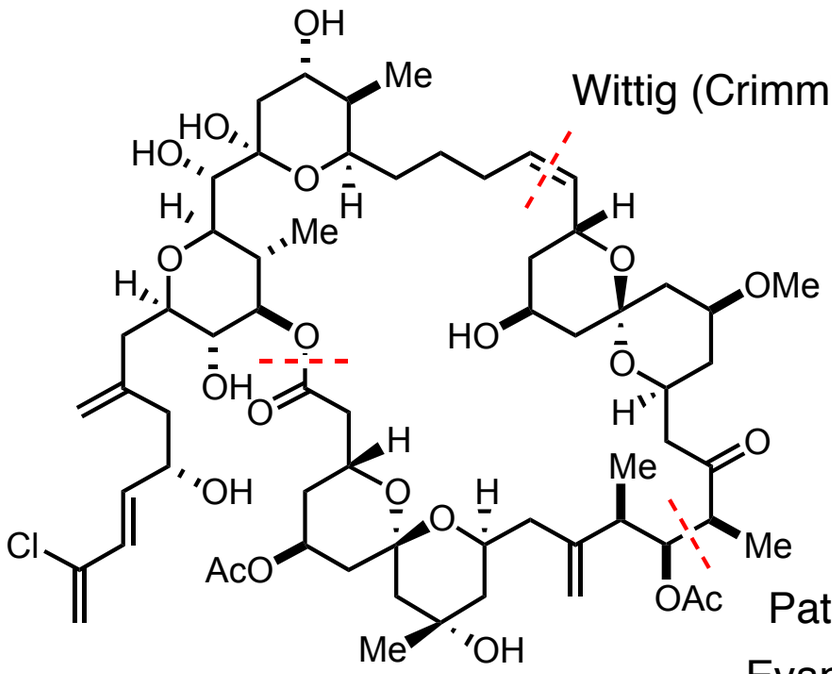
53 steps

- Should we attempt the total synthesis of molecules this large and complex?
- Are these types of *tour de force* syntheses worth undertaking in 2012?
- Should versatile methods (diverse array of accessible structures) continue to be employed?
- Should methods be more ideally suited (and scalable) for a specific molecule?

Smiths' Synthesis of the Spongistatins

review of their second generation synthesis

Vastly Improved Second Generation Synthesis



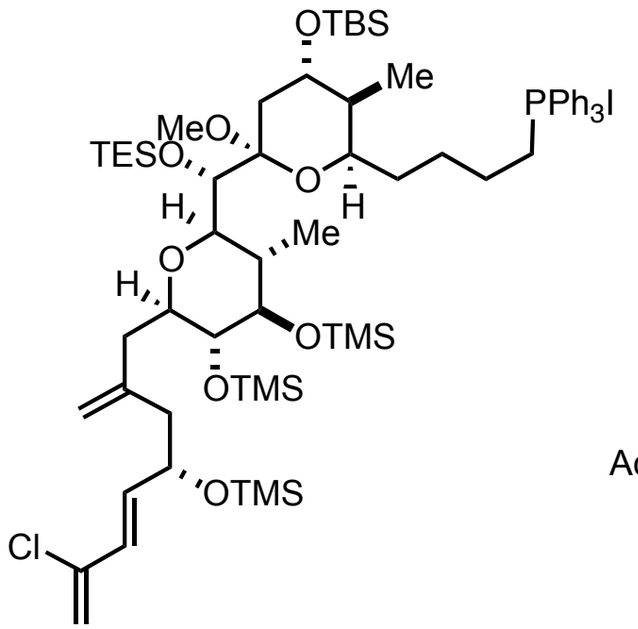
Wittig (Crimmins, 64%)

1.009 g prepared

4 steps

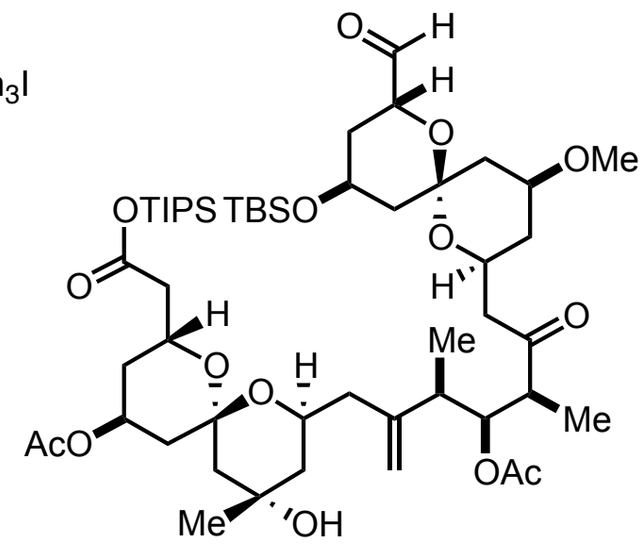
Paterson Aldol

Evans, Crimmins
Paterson, Heathcock



24 steps, 9.5% yield

5.8 g prepared



22 steps, 6.5% yield

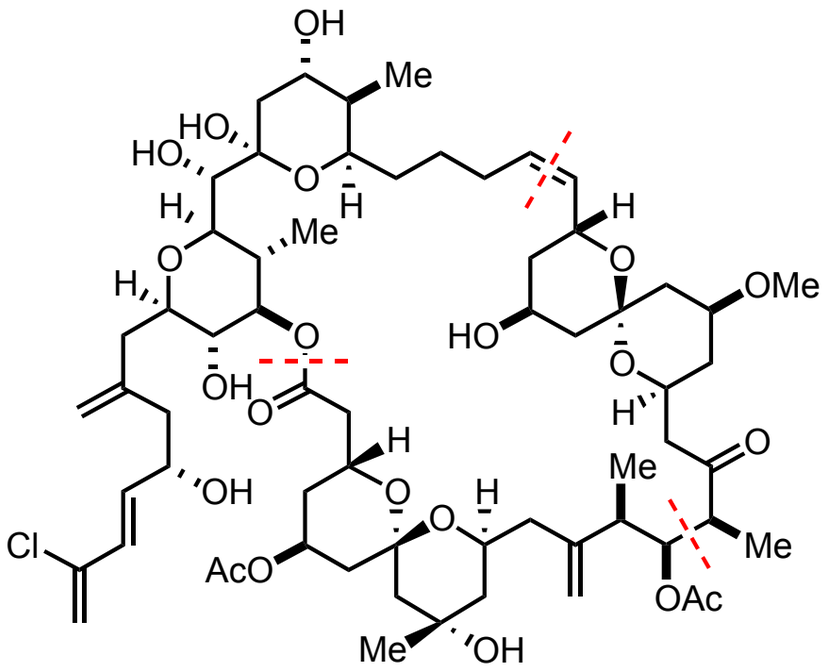
- Took cues from previous syntheses to revise their overall retrosynthetic strategy
- Adopted changes to fragment syntheses that were more specifically tuned toward this molecule
- Vastly improved efficiency and scalability

Smith, A. B., III; Tomioka, T.; Risatti, C. A.; Sperry, J. B.; Sfouggatakis, C. *Org. Lett.* **2008**, *10*, 4359-4362.

Smiths' Synthesis of the Spongistatins

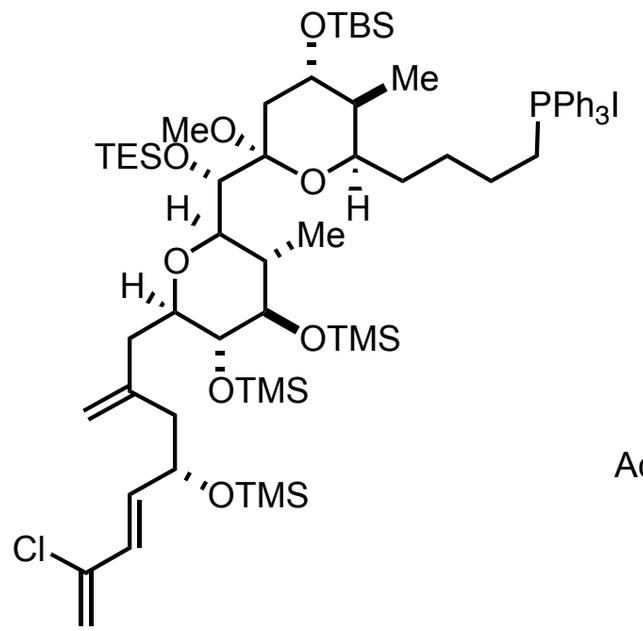
review of their second generation synthesis

■ Vastly Improved Second Generation Synthesis

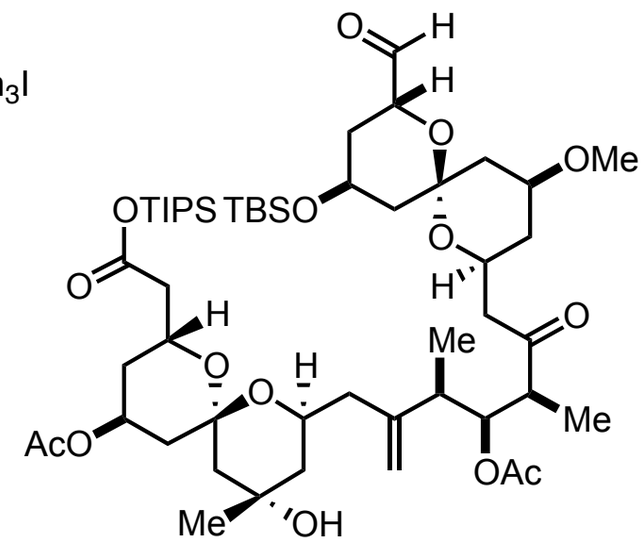


1.009 g prepared

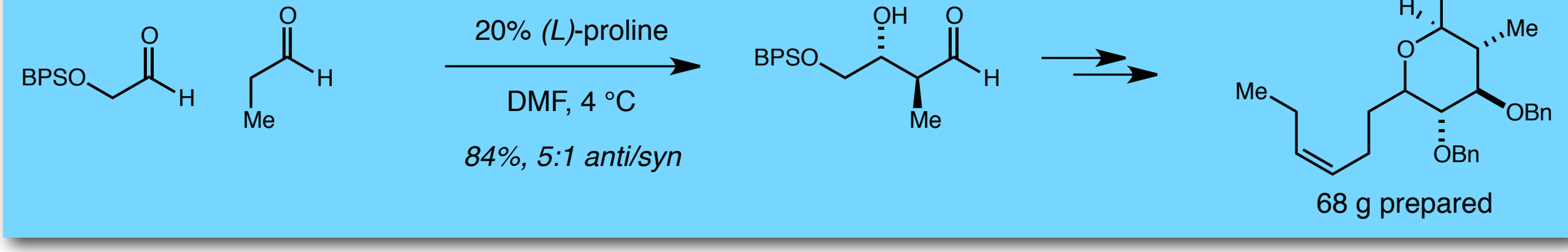
4 steps



24 steps, 9.5% yield



22 steps, 6.5% yield

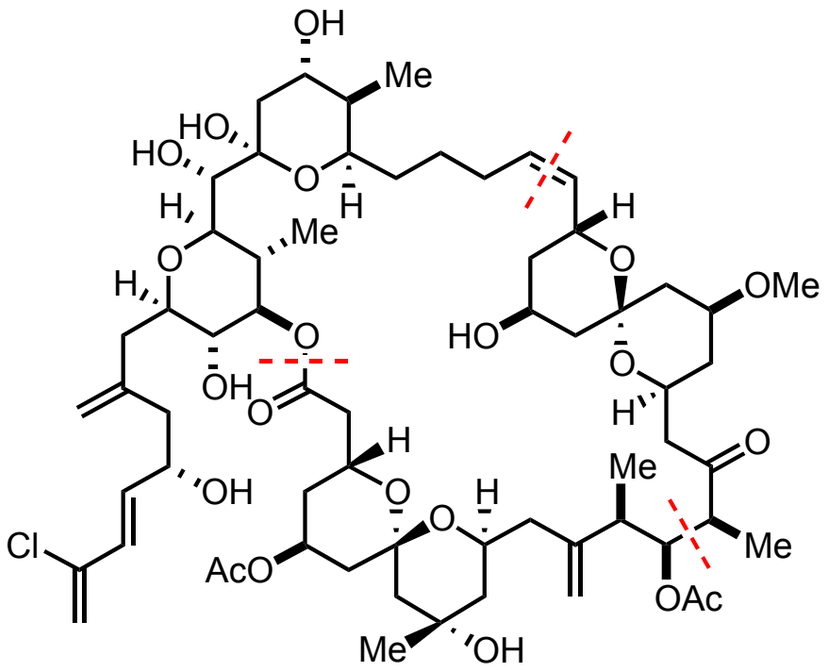


68 g prepared

Smiths' Synthesis of the Spongistatins

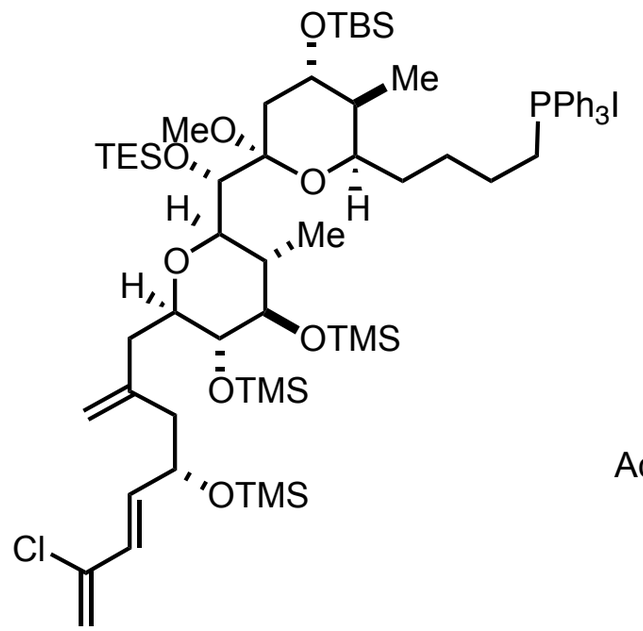
review of their second generation synthesis

Vastly Improved Second Generation Synthesis

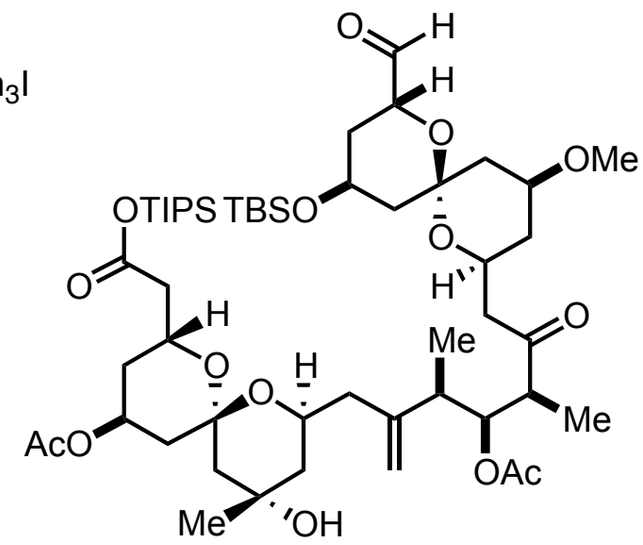


1.009 g prepared

4 steps



24 steps, 9.5% yield



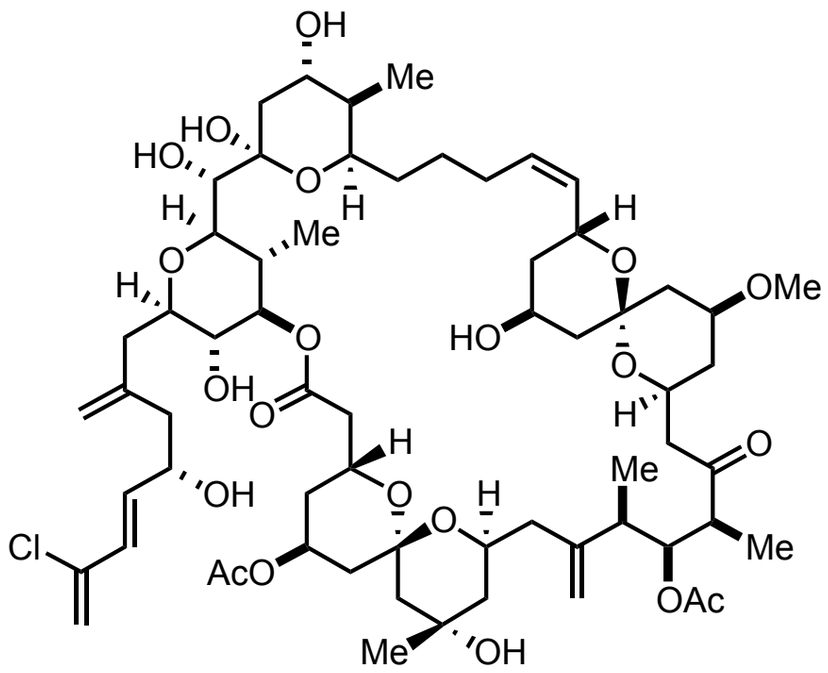
22 steps, 6.5% yield

- How important is efficiency in a gram scale total synthesis of a bioactive natural product of low availability?
- Do 2nd Gen syntheses have value for identifying more robust methods (proline aldol vs dithiane)?
- Since earlier *tour de force* efforts enabled a highly efficient synthesis, do they hold more value?

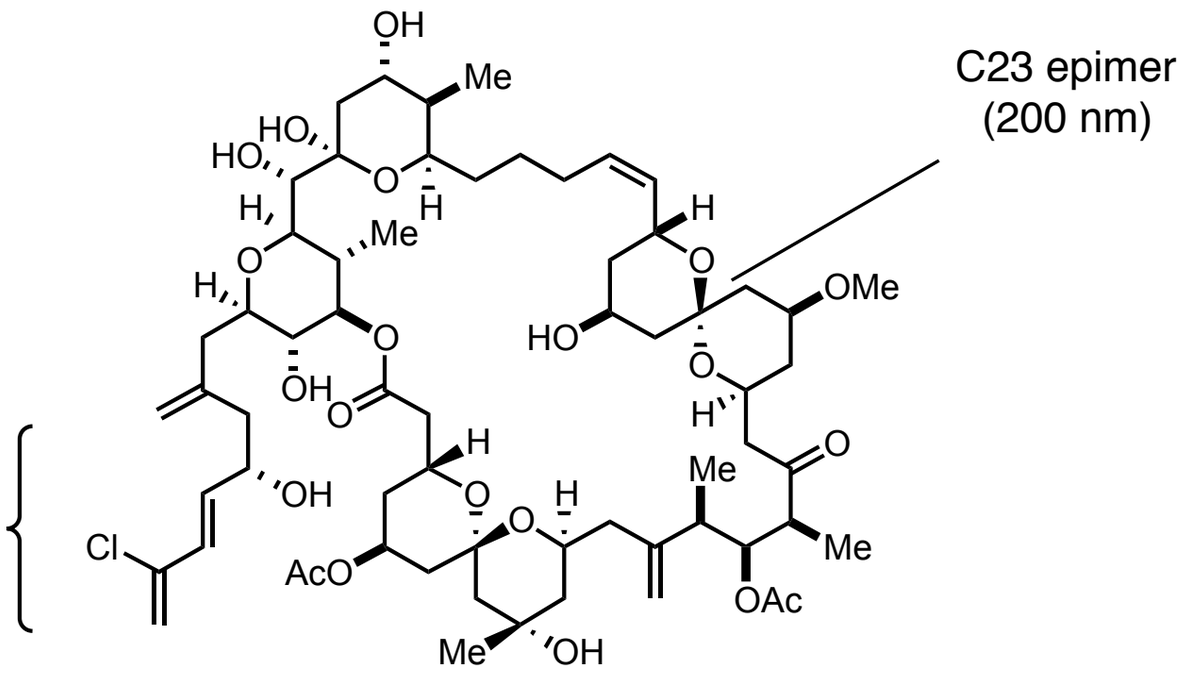
Smiths' Synthesis of the Spongistatins

analog syntheses from multiple groups provide insight regarding bioactivity

- What was known about structural features required for activity



spongistatin 1



Diene section
required for activity

Smiths' Synthesis of the Spongistatins

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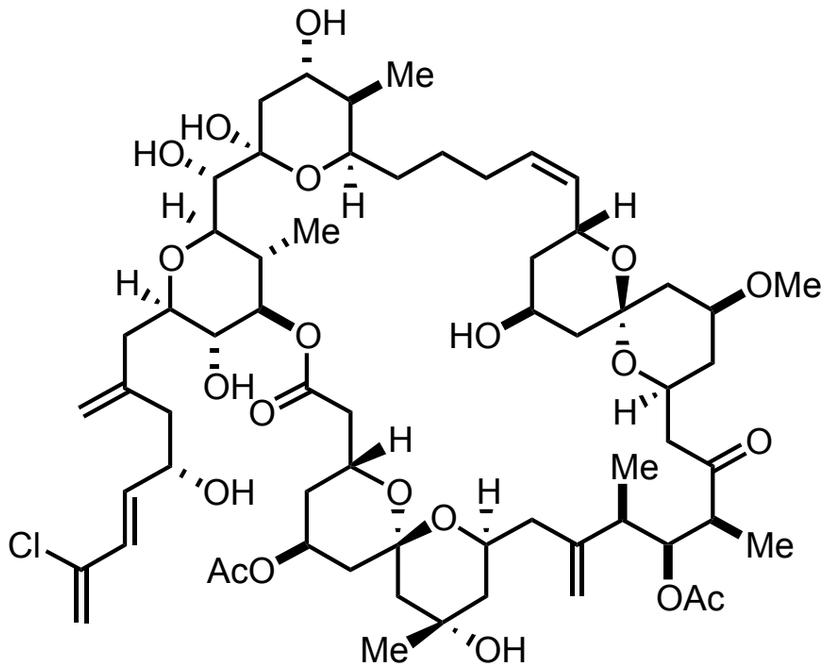
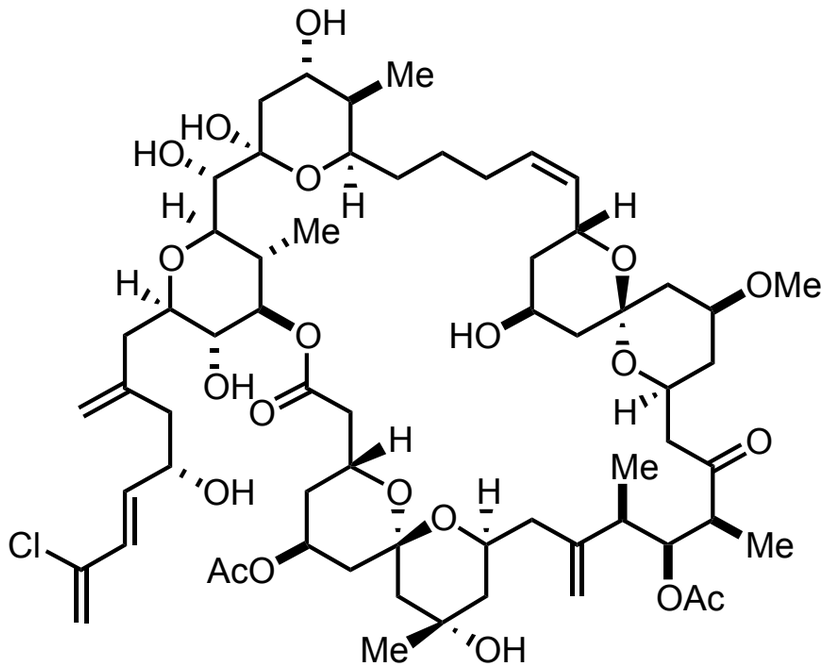


spongistatin 1

Smiths' Synthesis of the Spongistatins

analog syntheses from multiple groups provide insight regarding bioactivity

- Appeared that the CD spiroketal wasn't critical but does play some role



spongistatin 1

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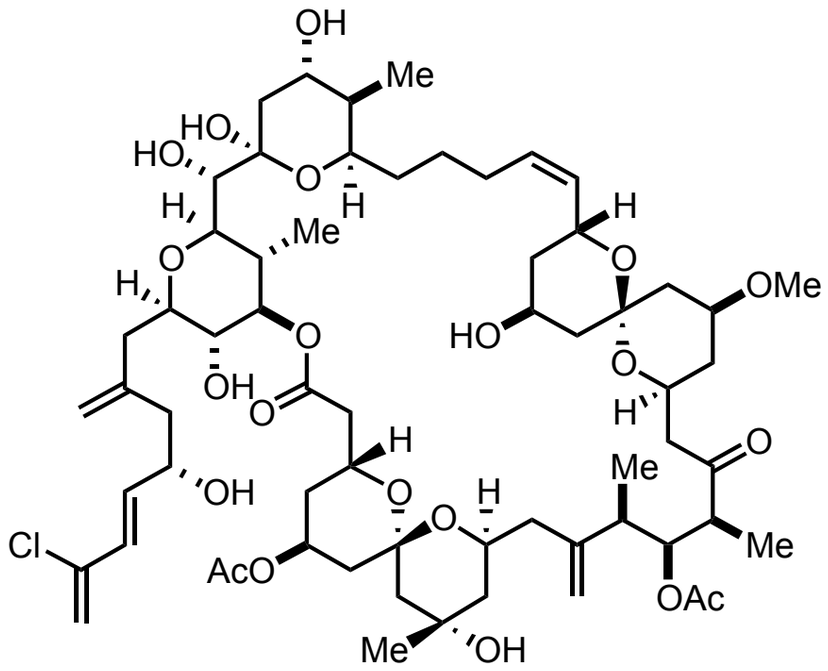
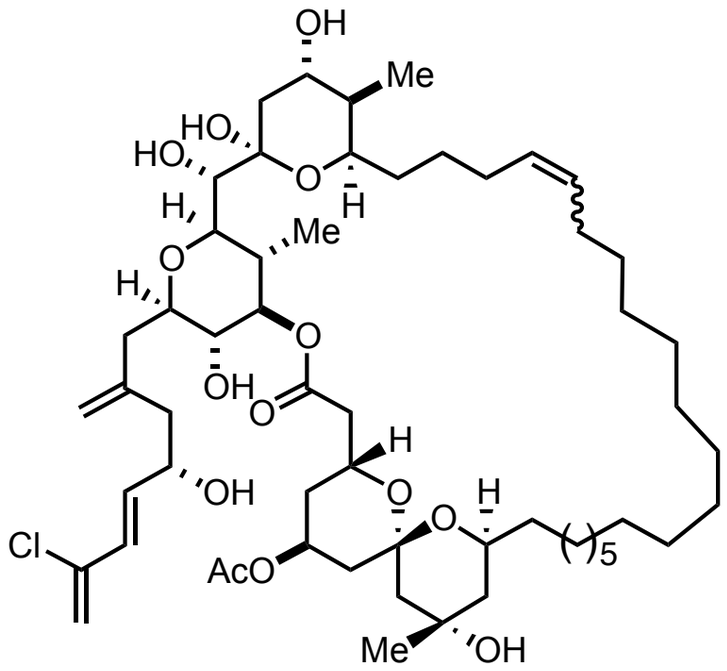


spongistatin 1



480 nm (Heathcock)

Smiths' Synthesis of the Spongistatins

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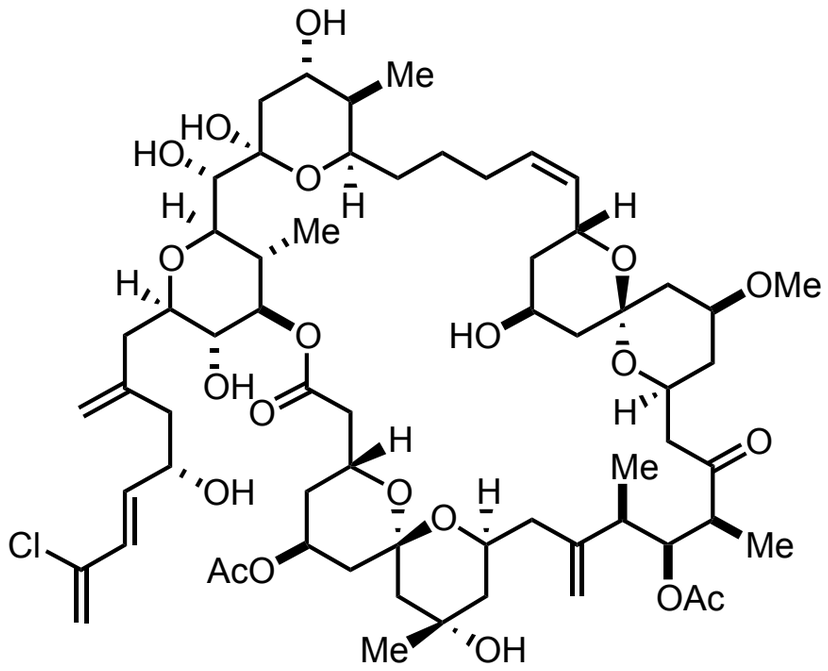
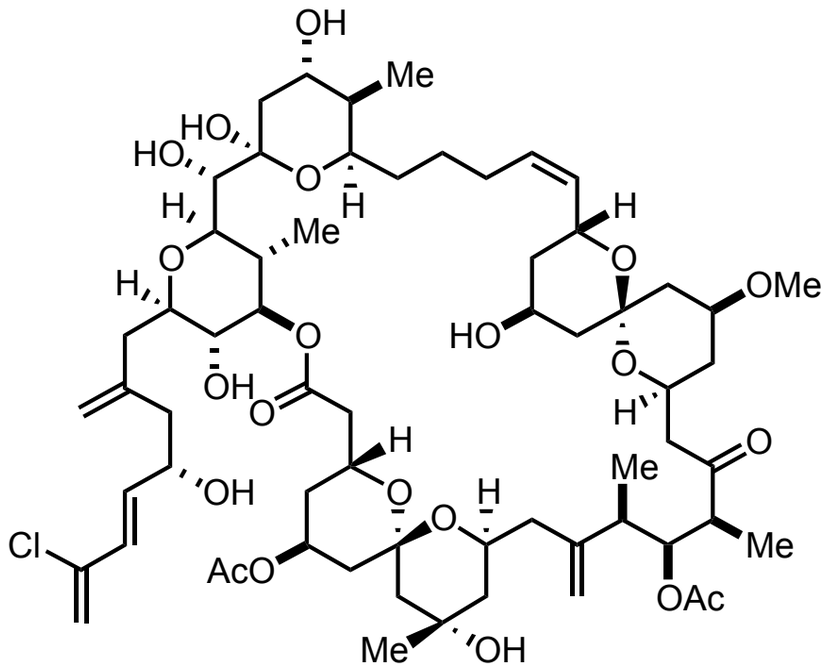


spongistatin 1

Smiths' Synthesis of the Spongistatins

analog syntheses from multiple groups provide insight regarding bioactivity

- Also appears that the AB spiroketal wasn't critical but does play some role



spongistatin 1

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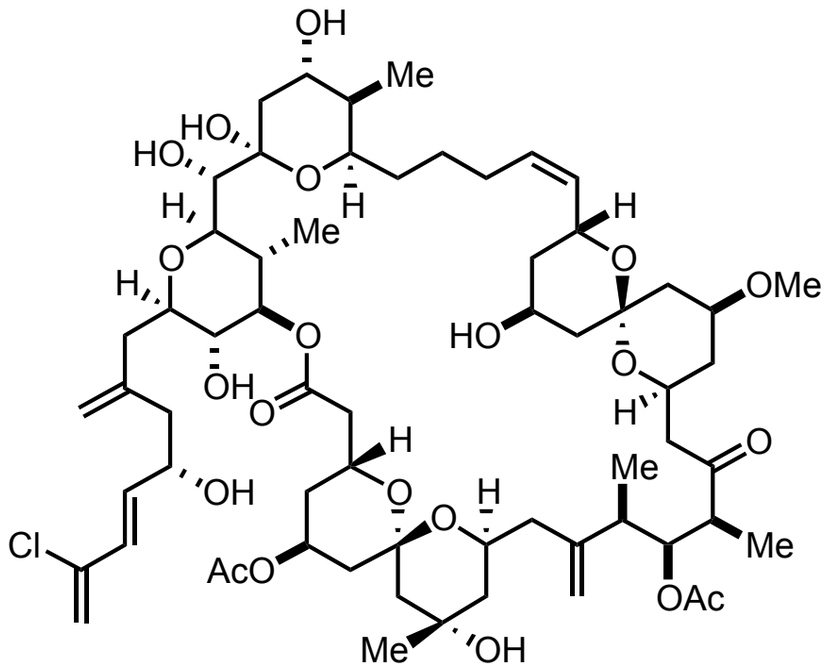
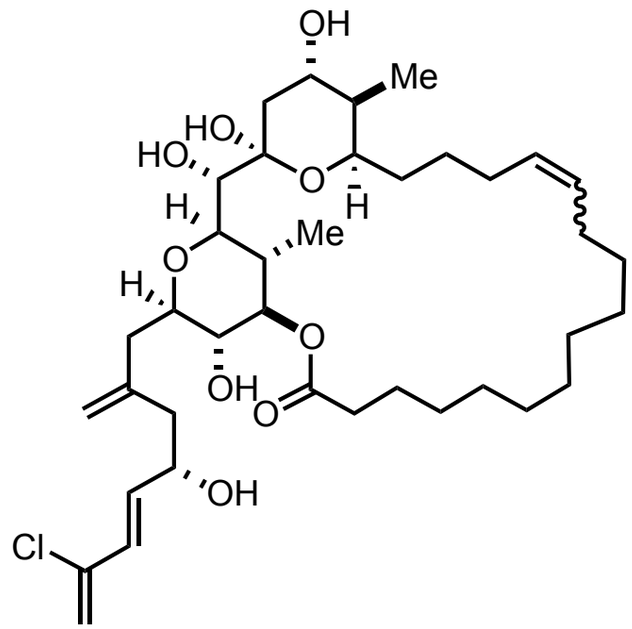


spongistatin 1



460 nm (Heathcock)

Smiths' Synthesis of the Spongistatins

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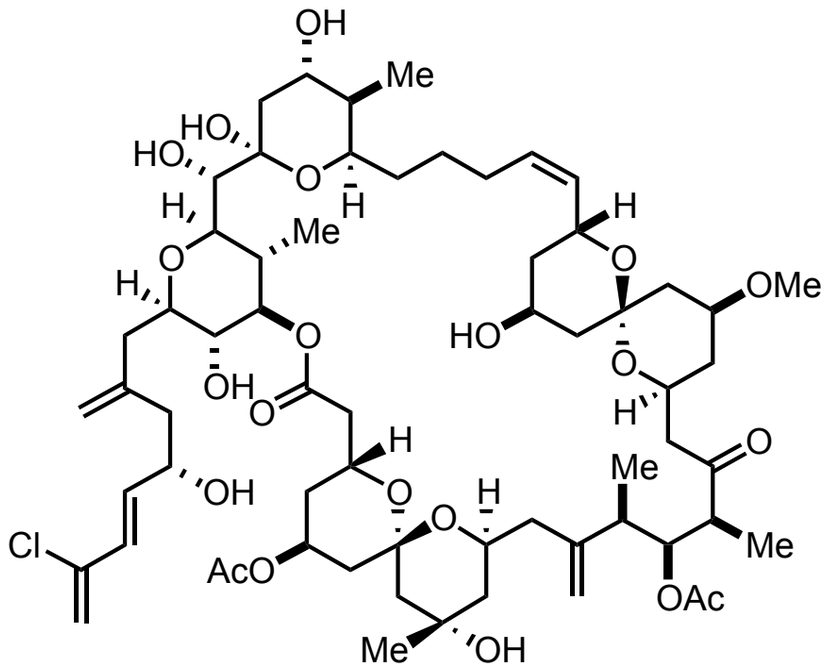
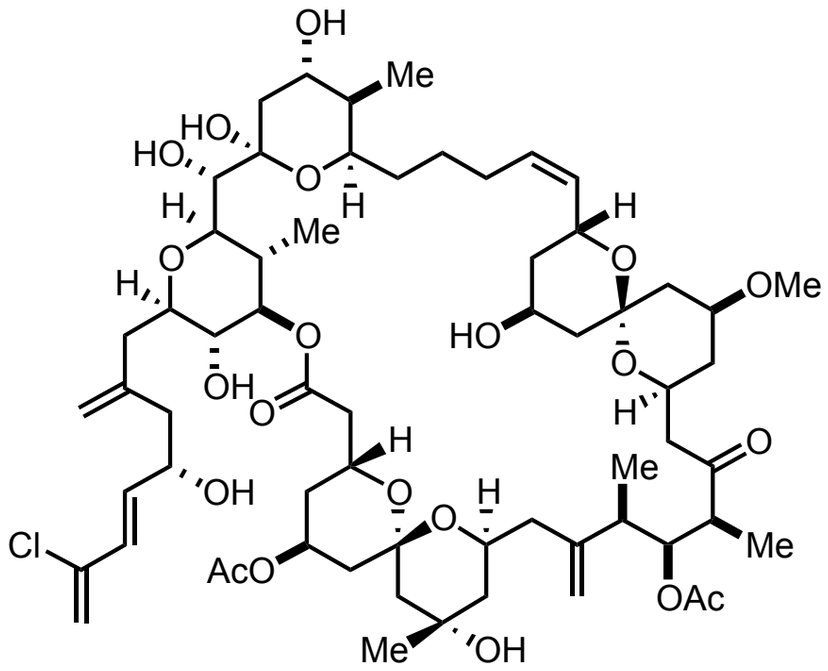


spongistatin 1

Smiths' Synthesis of the Spongistatins

analog syntheses from multiple groups provide insight regarding bioactivity

- The “western” portion of spongistatin (diene & E, F rings) constitute the recognition domain
- The “eastern” portion of spongistatin (A,B and C,D-spiroketals) imparts conformational restraints on the western portion

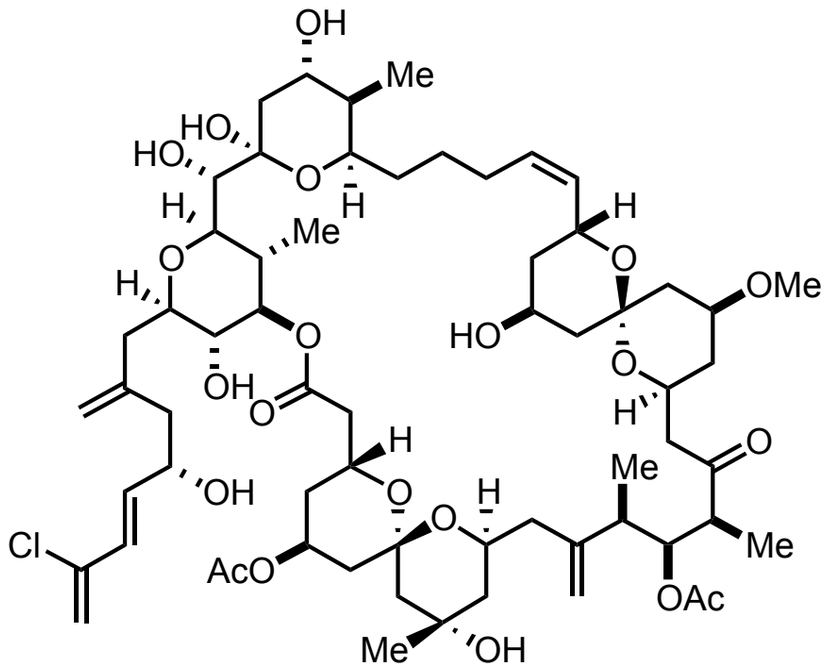


spongistatin 1

Smiths' Synthesis of the Spongistatins

examining the conformational restraint hypothesis

- How can the hypothesis of conformational restraint imparted by the eastern half be tested?
- Random analog synthesis seemed cumbersome and unattractive
- Molecular modeling may provide some insights



spongistatin 1

Smith, A. B., III; Risatti, C. A.; Atasoylu, O.; Bennett, C. S.; Liu, J.; Cheng, H.; TenDyke, K. Xu, Q. *J. Am. Chem. Soc.* **2011**, *133*, 14042-14053.

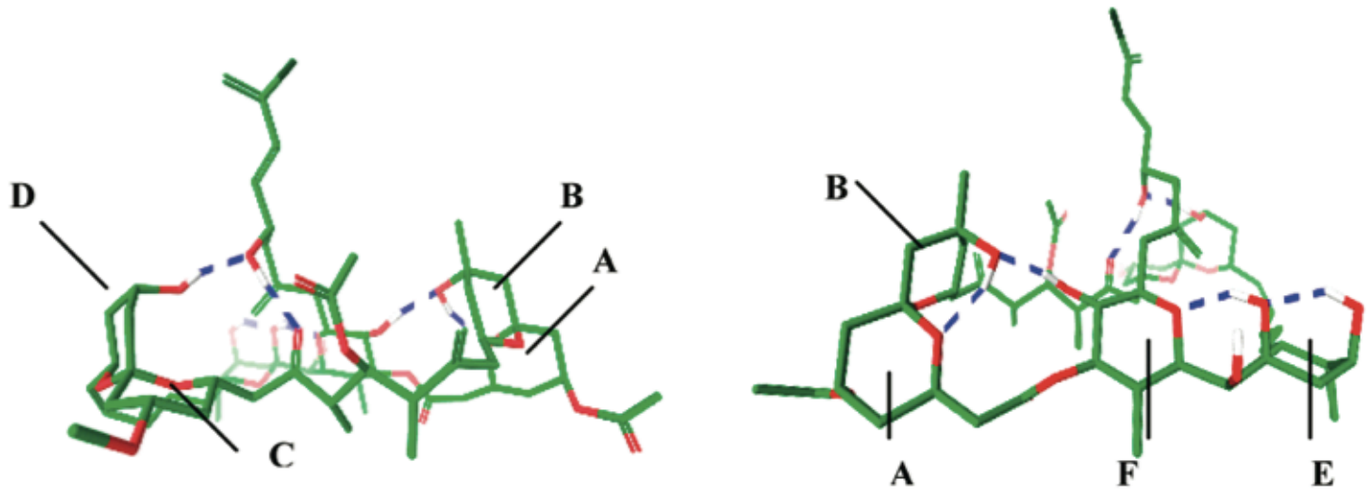
Smiths' Synthesis of the Spongistatins

insights from molecular modeling

- Molecular modeling revealed two major an two minor conformations
- Chloroform - “Flat” maximized intramolecular hydrogen bonds
- Water - “Twisted” oxygens oriented toward solvent

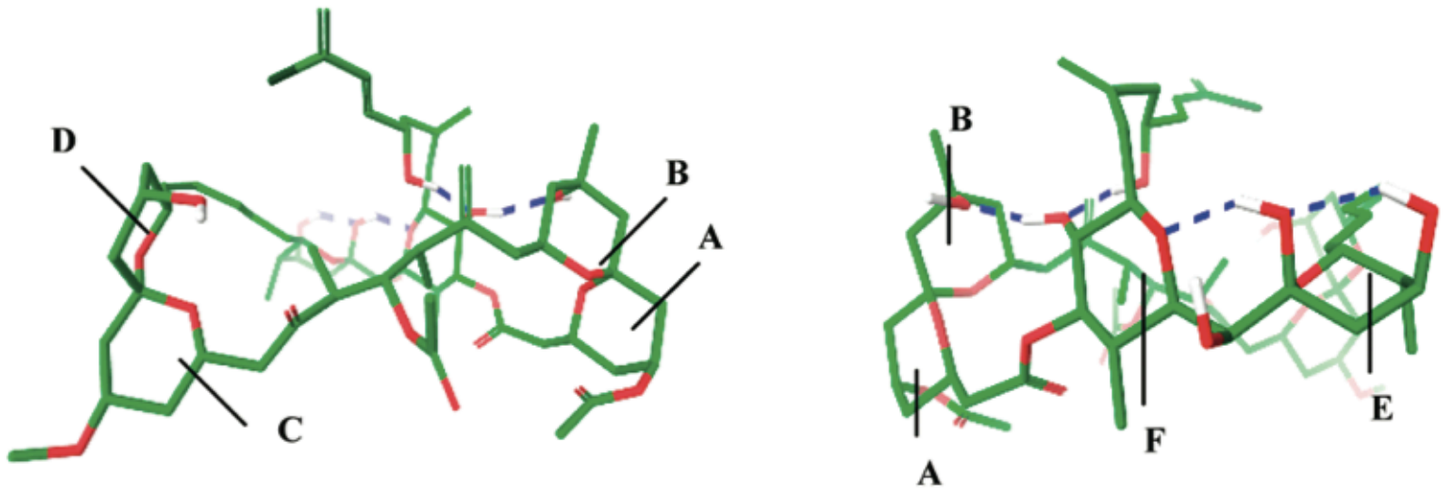
I

“FLAT”



II

“TWISTED”



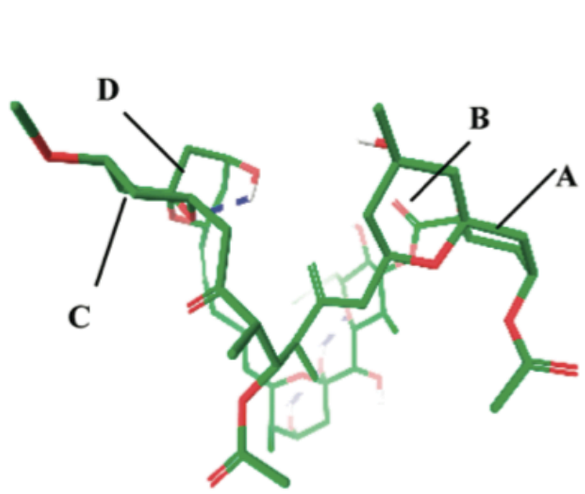
Smiths' Synthesis of the Spongistatins

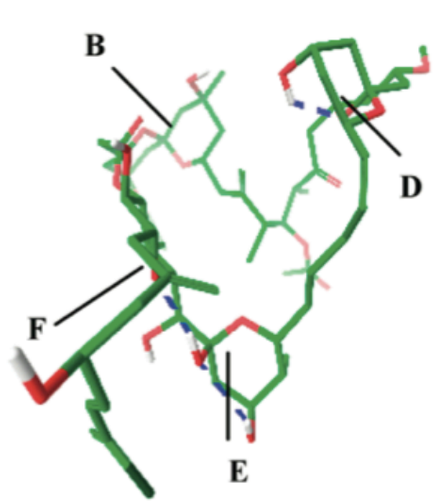
insights from molecular modeling

- Molecular modeling revealed two major an two minor conformations
- DMSO & Acetonitrile - “Saddle”
- Kitagawa original solution state structure from isolation report

III

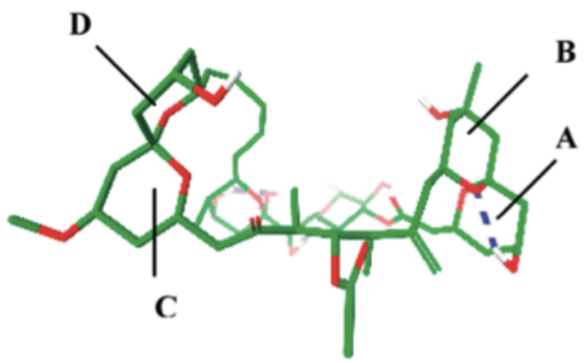
“SADDLE”

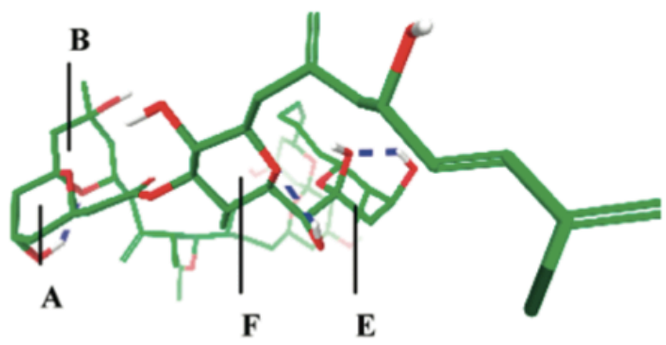




IV

Kitagawa





Smiths' Synthesis of the Spongistatins

molecular dynamics simulations

- Focused on water as the solvent
- Used molecular dynamics simulations to identify rigid and flexible regions
- Lead to the development of “DISCON” (DIstrubution of Solution CONformations) MD software

Smiths' Synthesis of the Spongistatins

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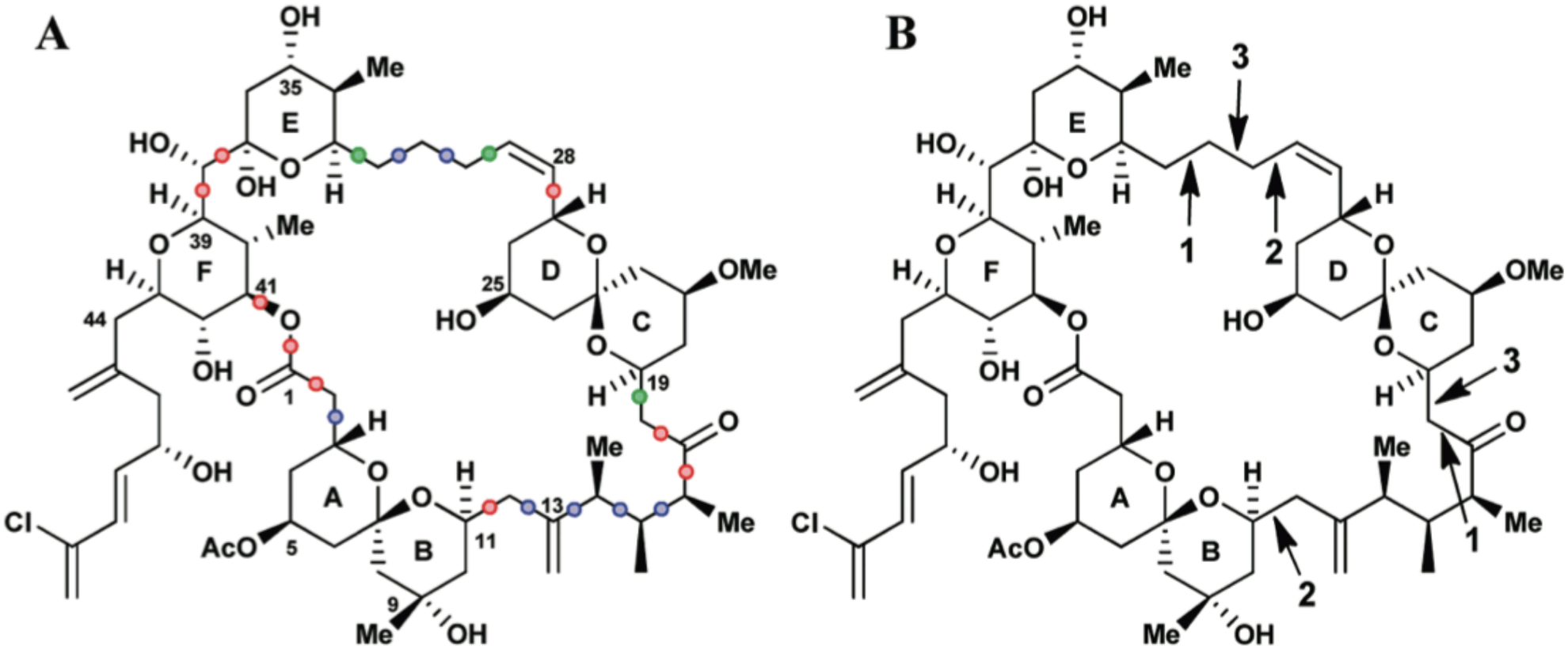
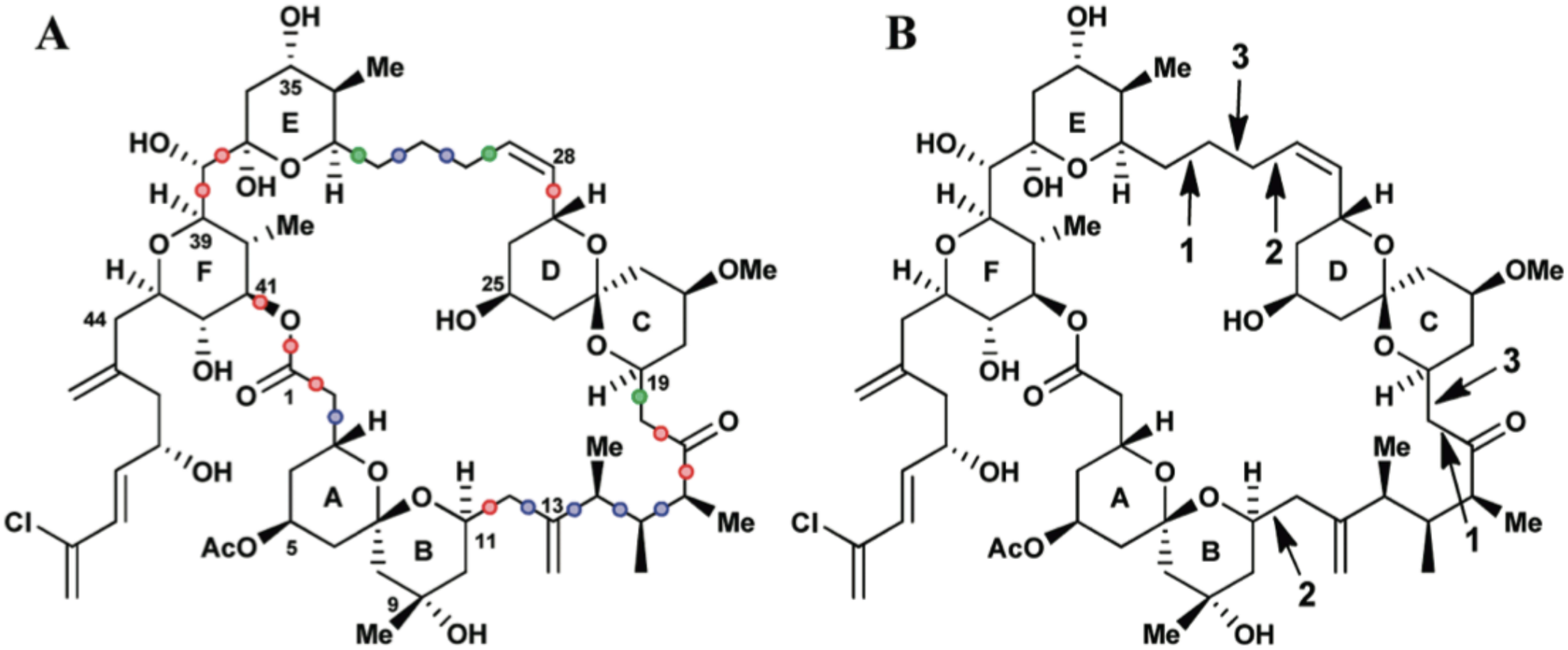


- Red = Rigid, Blue = Intermediate, Green = Flexible; Number indicates bond pair where torsions change together

Smiths' Synthesis of the Spongistatins

molecular dynamics simulations

- The EFAB region is extremely rigid whereas the CD region is very flexible
- The only rigidity in the “eastern” half comes from the CD spiroketal
- The ends of the EFAB region tend to move as a single unit



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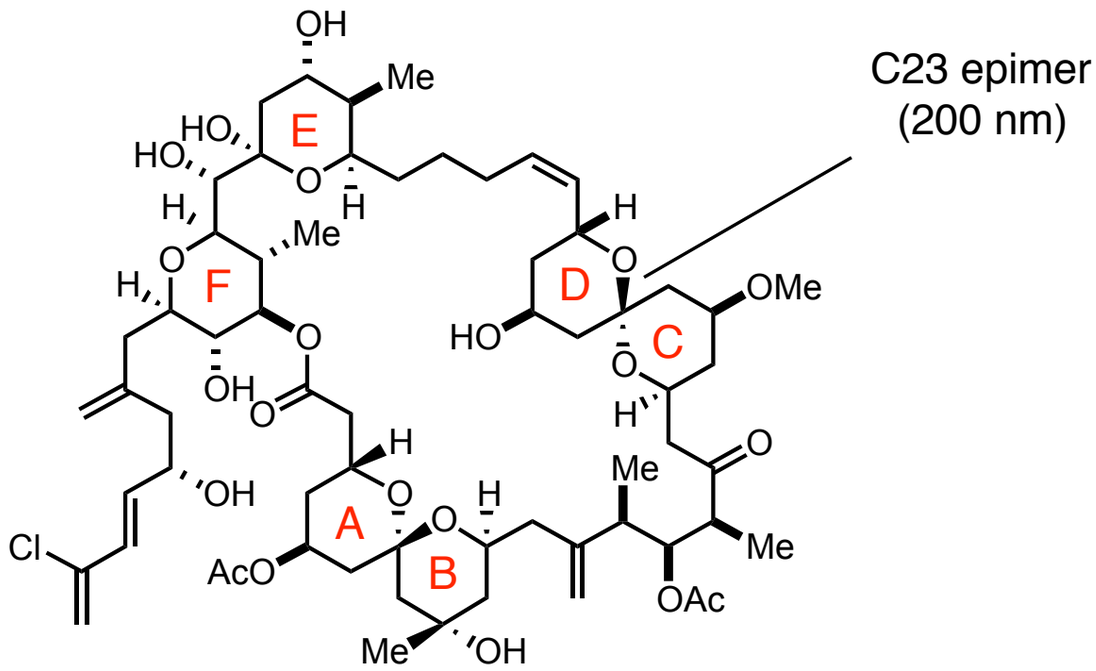
Smiths' Synthesis of the Spongistatins

molecular dynamics simulations

- The EFAB region is extremely rigid whereas the CD region is very flexible
- The only rigidity in the “eastern” half comes from the CD spiroketal
- The ends of the EFAB region tend to move as a single unit
- Explains why the C23 epimer results in loss of activity even as its not involved in recognition

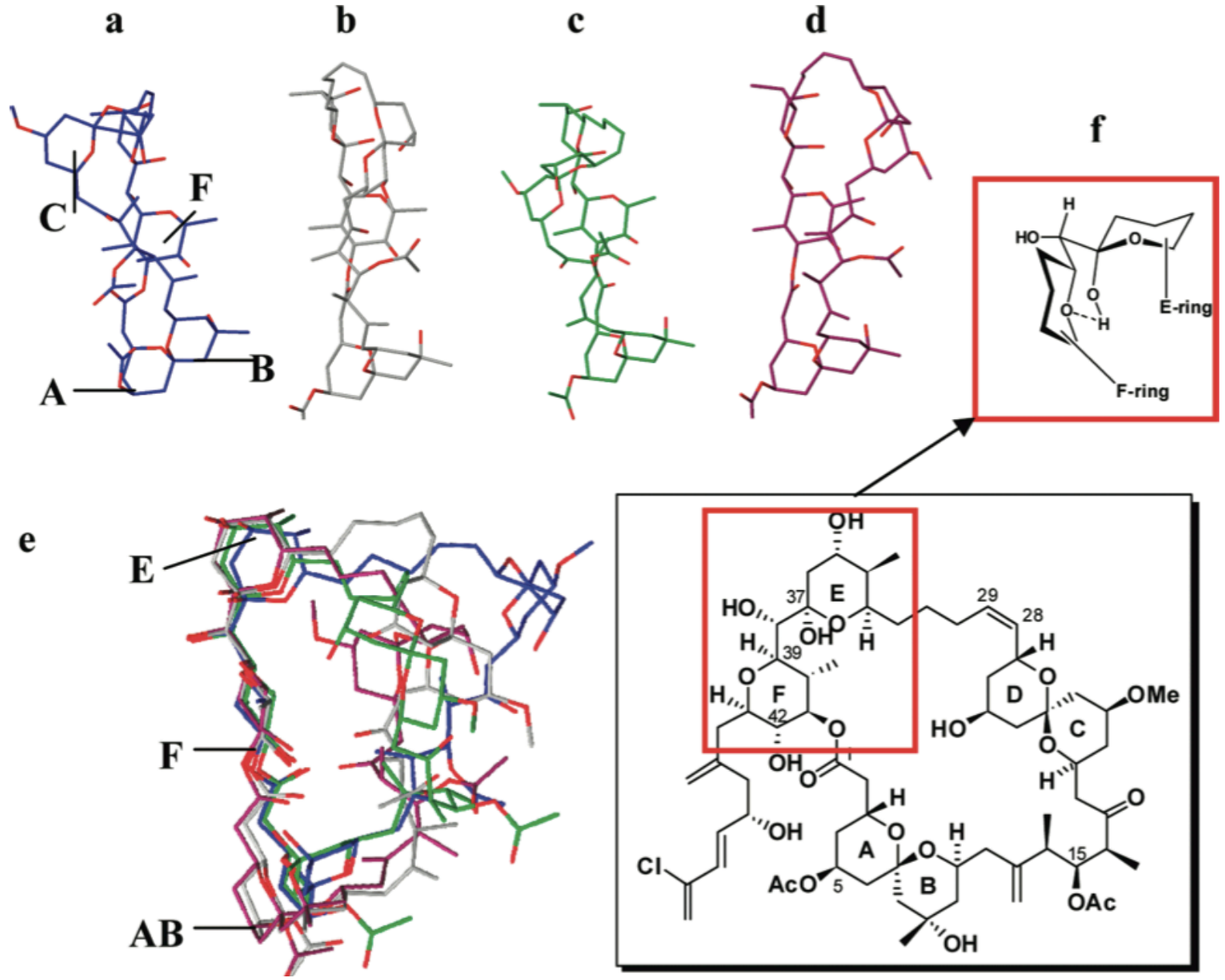


C23 epimer
(200 nm)

Smiths' Synthesis of the Spongistatins

molecular dynamics simulations

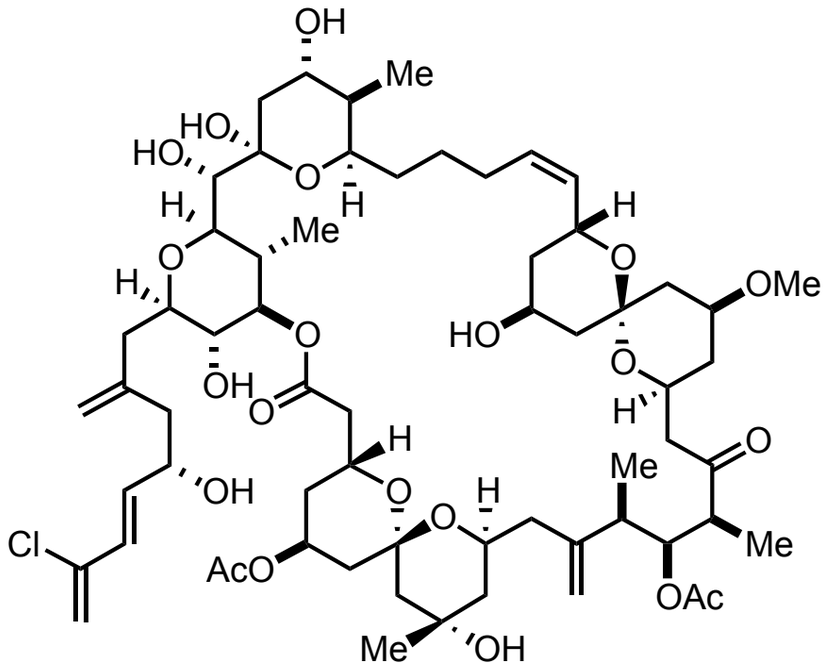
- An overlay of all the most populated solution state conformations is revealing
- The rigid EFAB region is highly conserved



Smiths' Synthesis of the Spongistatins

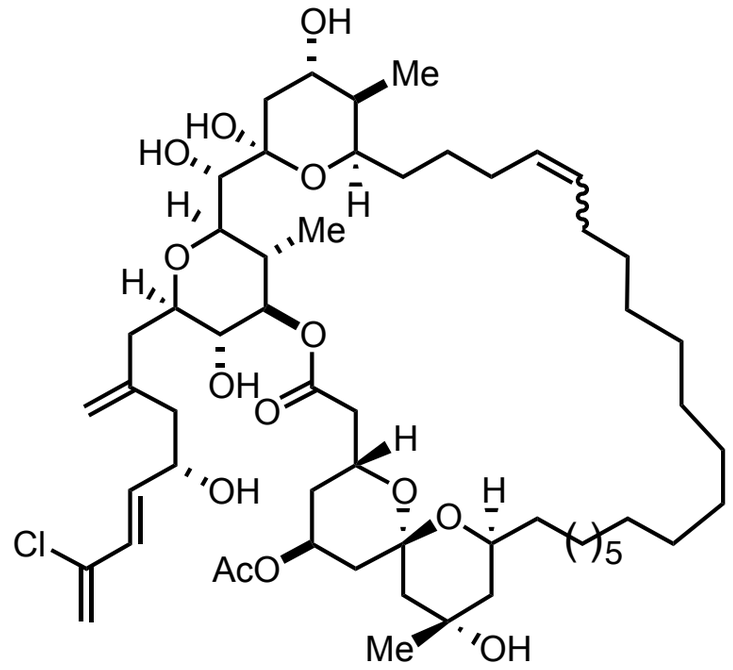
molecular dynamics simulations

- The tether employed by Heathcock didn't impart enough conformational restraint on the EFAB region
- Can an appropriate tether be designed to simplify the structure while maintaining activity?



spongistatin 1

< 1 nm



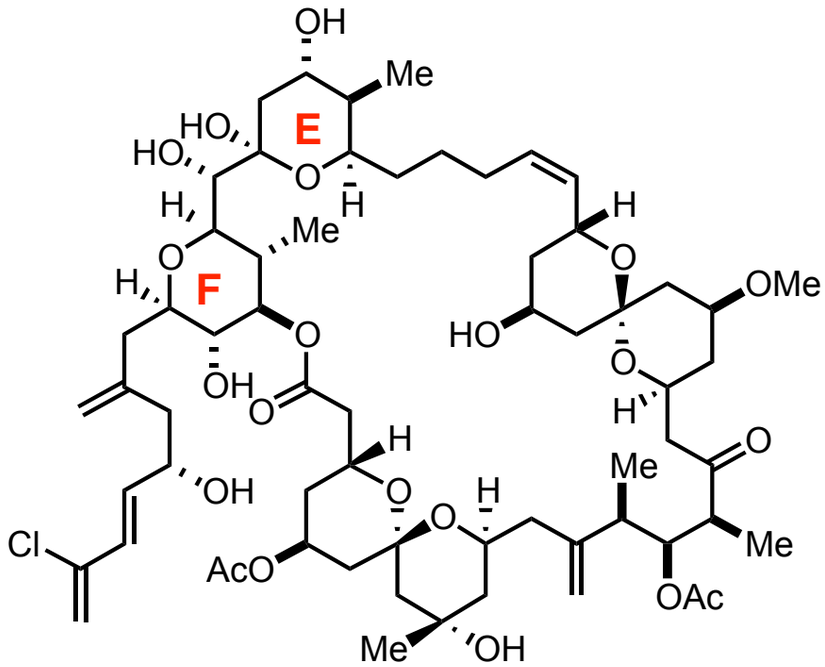
ABEF analog (Heathcock)

480 nm (Heathcock)

Smiths' Synthesis of the Spongistatins

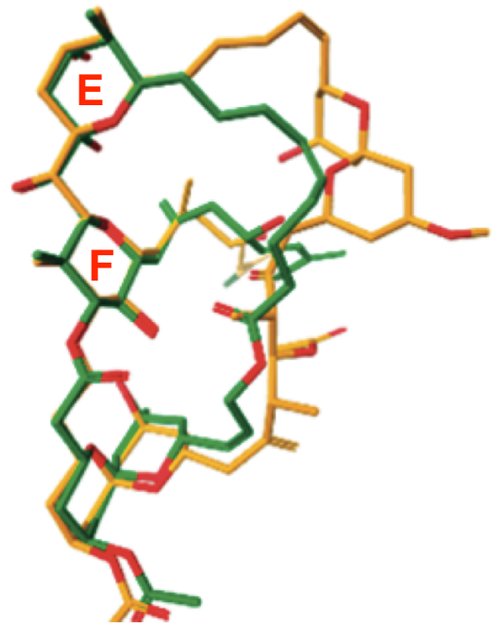
computationally aided analog design

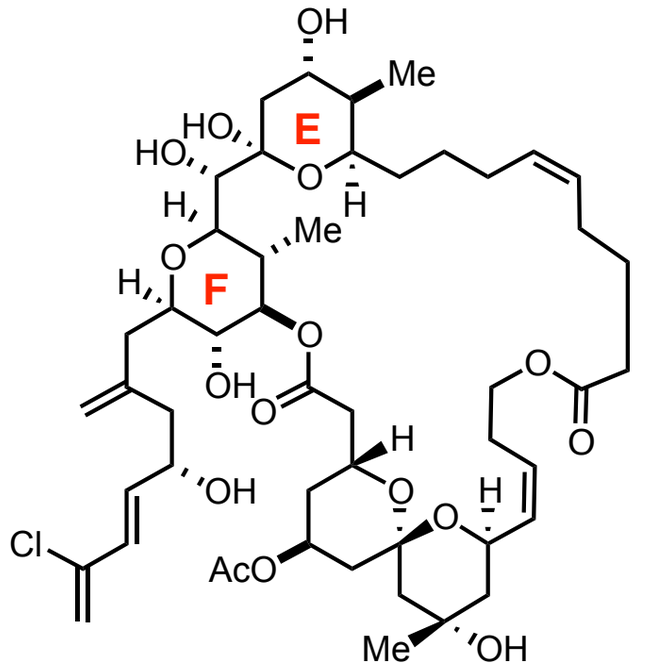
■ Computationally aided analog design found ABEF analog with high structural homology to spongistatin



spongistatin 1

macrolide strain energy = 8.3 kJ/mol





ABEF analog (Smith)

macrolide strain energy = 9.1 kJ/mol

Smiths' Synthesis of the Spongistatins

computationally aided analog design

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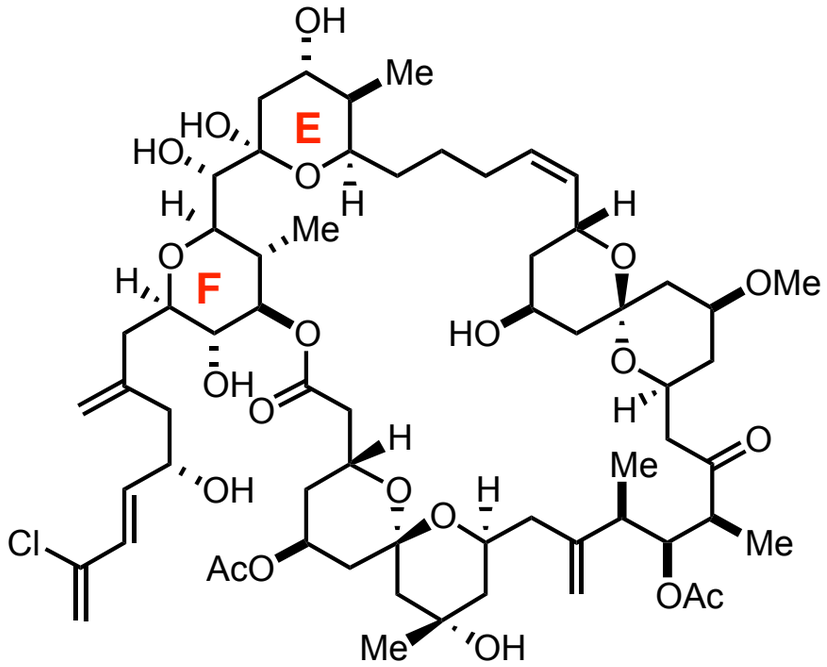

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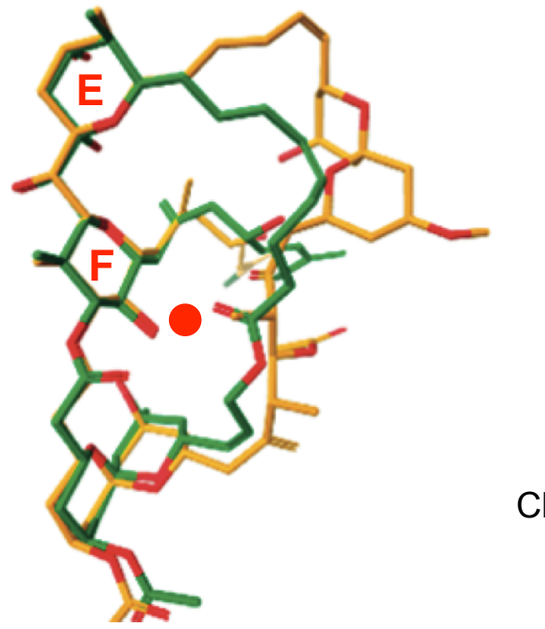
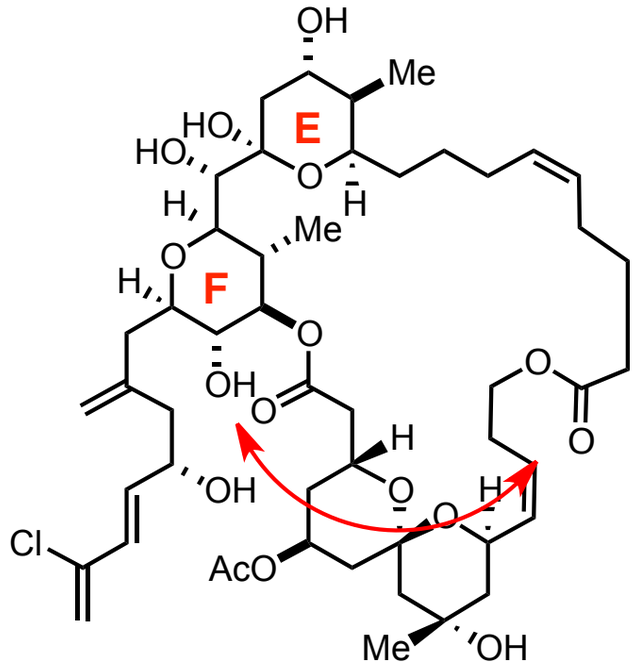




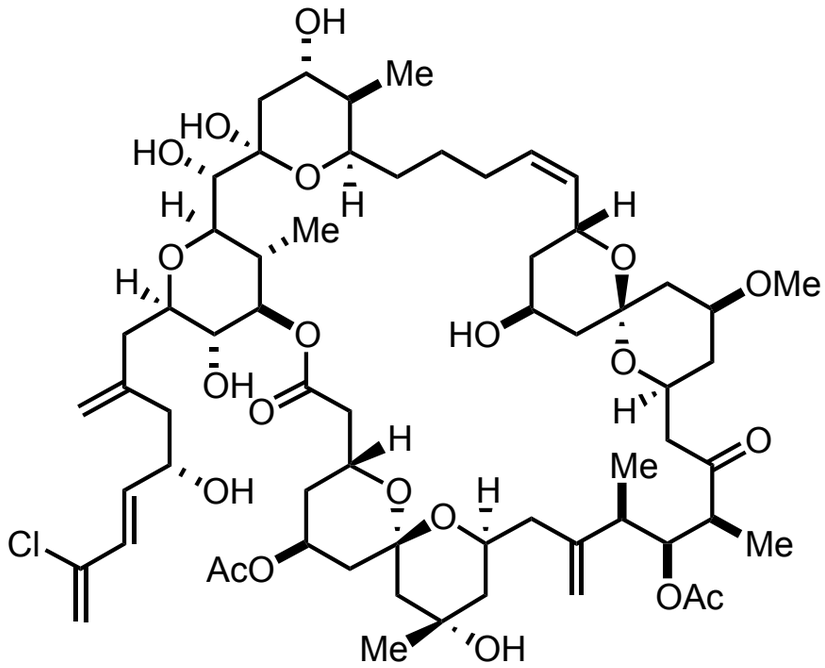
ABEF analog (Smith)

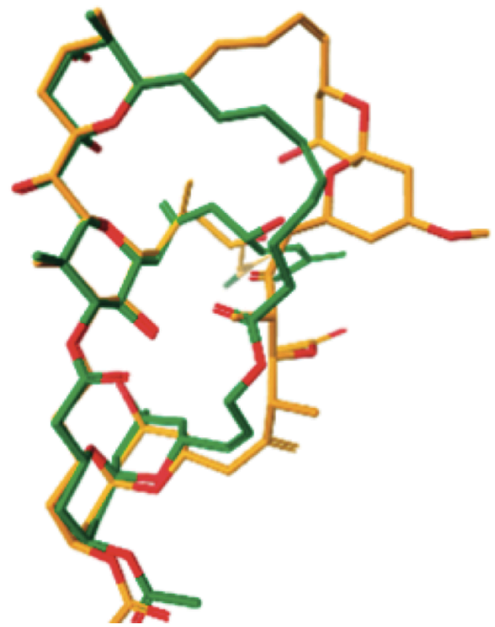
macrolide strain energy = 9.1 kJ/mol

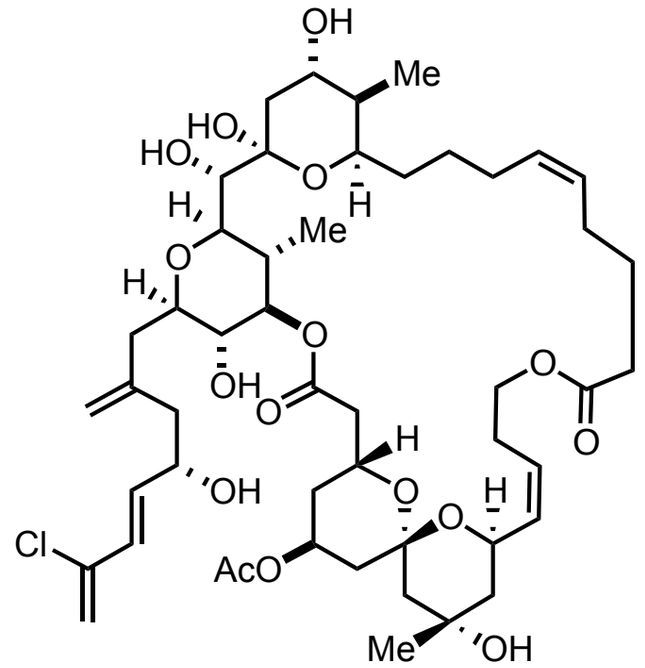
Smiths' Synthesis of the Spongistatins

a highly potent spongistatin analog

- Similar activity present after having deleted nearly 1/3 of the original structure
- ABEF analog determined to have the same mode of action







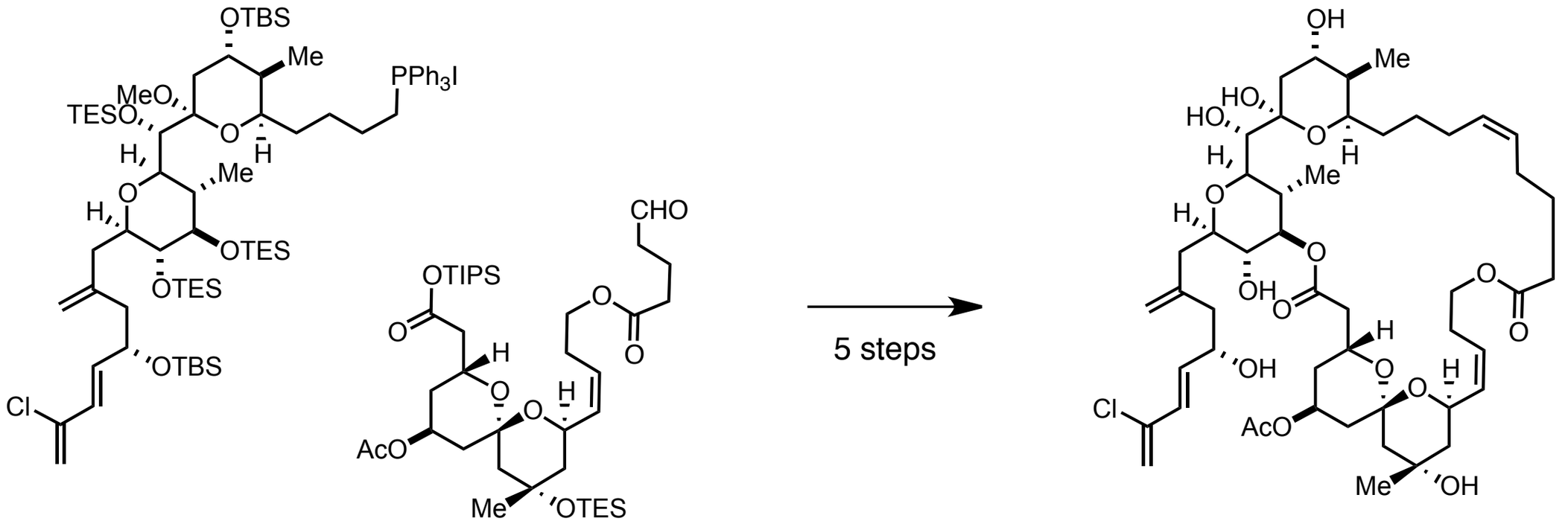
spongistatin 1

ABEF analog (Smith)

	MDA-MB-435	**HT-29**	**H522-T1**	**U937**
spongistatin	0.0225	0.058	0.16	0.059
ABEF analog	82.8	161.2	297.2	60.5

Smiths' Synthesis of the Spongistatins

a review of their analog work

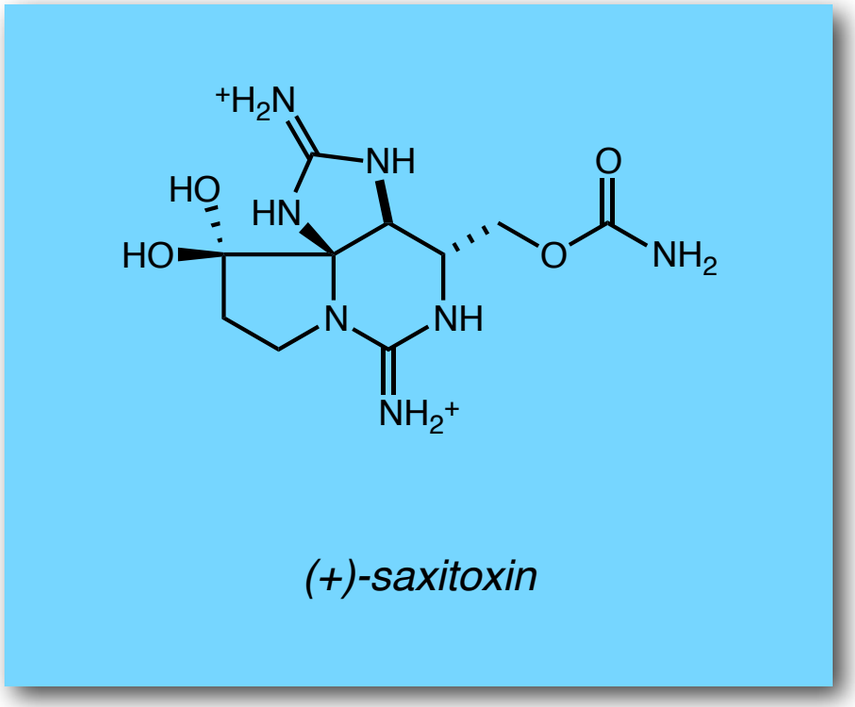


29 steps

(20 steps shorter!!!)

- Are the post total synthesis opportunities in computational chemistry and analog design worth the effort?
- Do 2nd Gen syntheses have value for identifying more robust methods (proline aldol vs dithiane)?
- Since earlier *tour de force* efforts enabled a highly efficient synthesis, do they hold more value?
- Are these types of projects worth undertaking in 2012?

DuBois' Total Synthesis of Saxitoxin



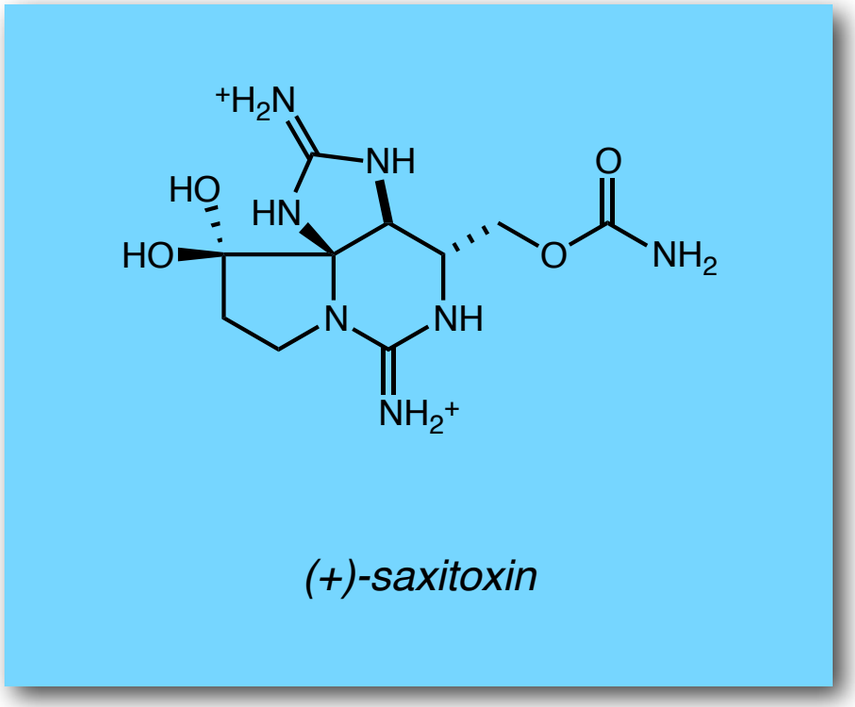
(+)-saxitoxin

- A highly oxidized and polar neurotoxic agent
- Toxicity arises from disabling ionic conductance through voltage-gated sodium channel.
- Exhibits nanomolar affinity for binding the extracellular mouth of the ion channel.

Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964-9975.

DuBois' Total Synthesis of Saxitoxin

- Why synthesize a neurotoxic agent?



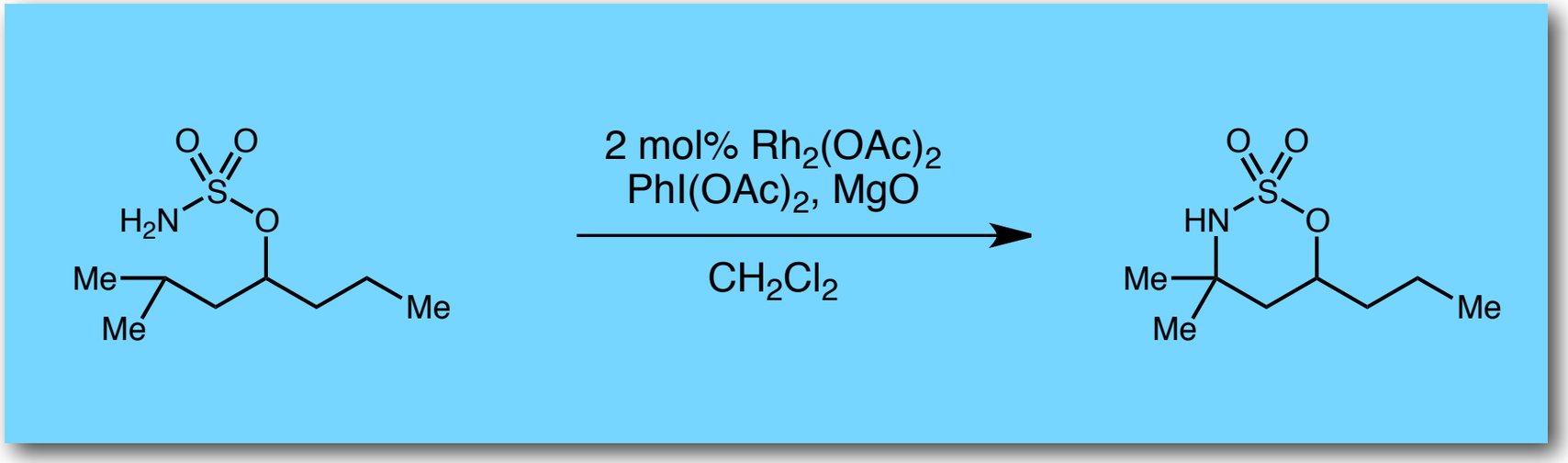
(+)-saxitoxin

- Ion flux is crucial for many important biochemical processes
- Small molecules that modulate ion flux may provide the discovery of new drugs
- Chemically modified guanidinium toxin could be used to probe structure and function of ion channels

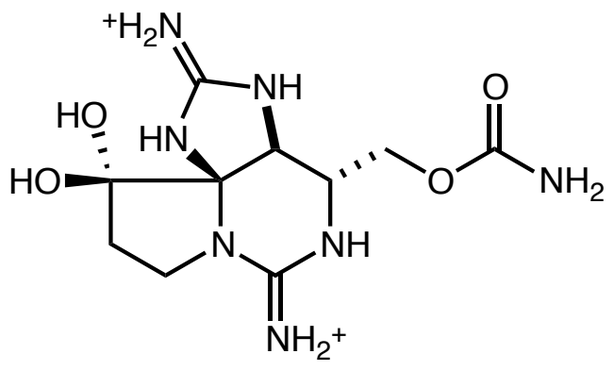
Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964-9975.

DuBois' Total Synthesis of Saxitoxin

Rhodium catalyzed C-H amination

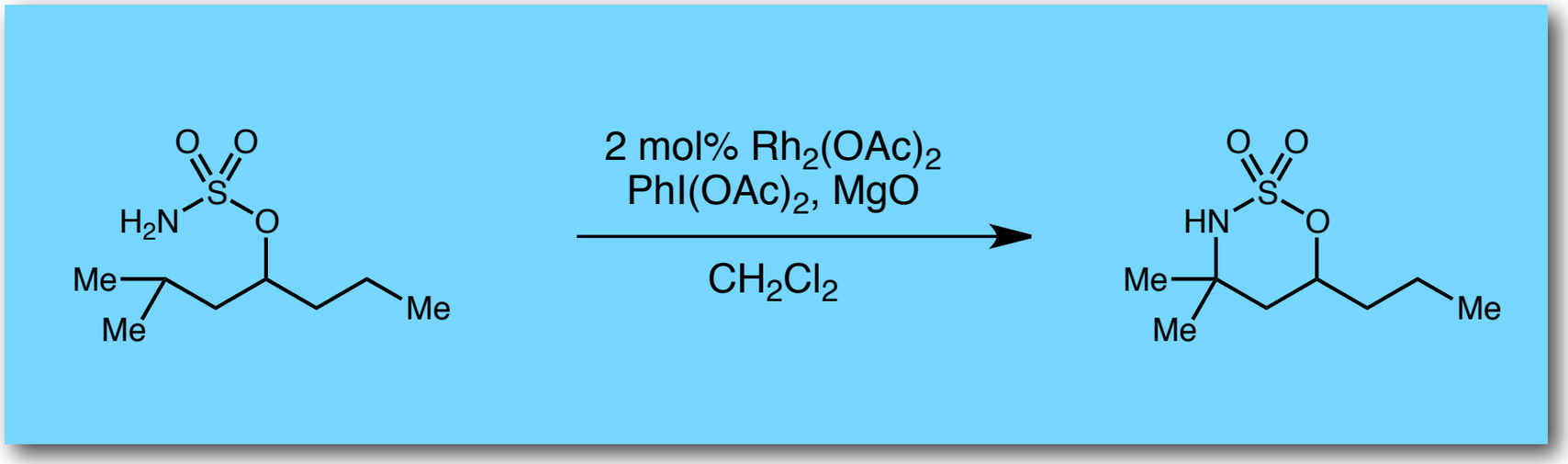


Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935-6936.

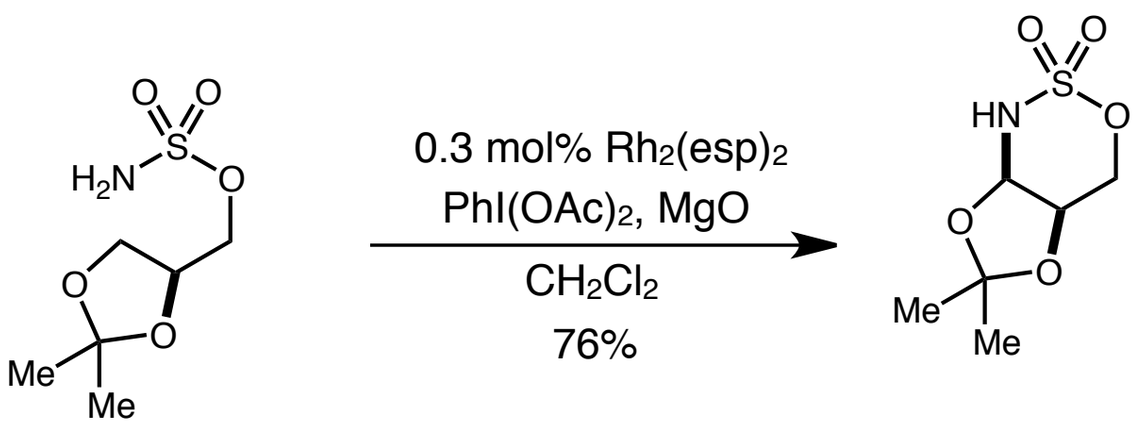


DuBois' Total Synthesis of Saxitoxin

Rhodium catalyzed C-H amination



Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935-6936.



Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964-9975.

DuBois' Total Synthesis of Saxitoxin

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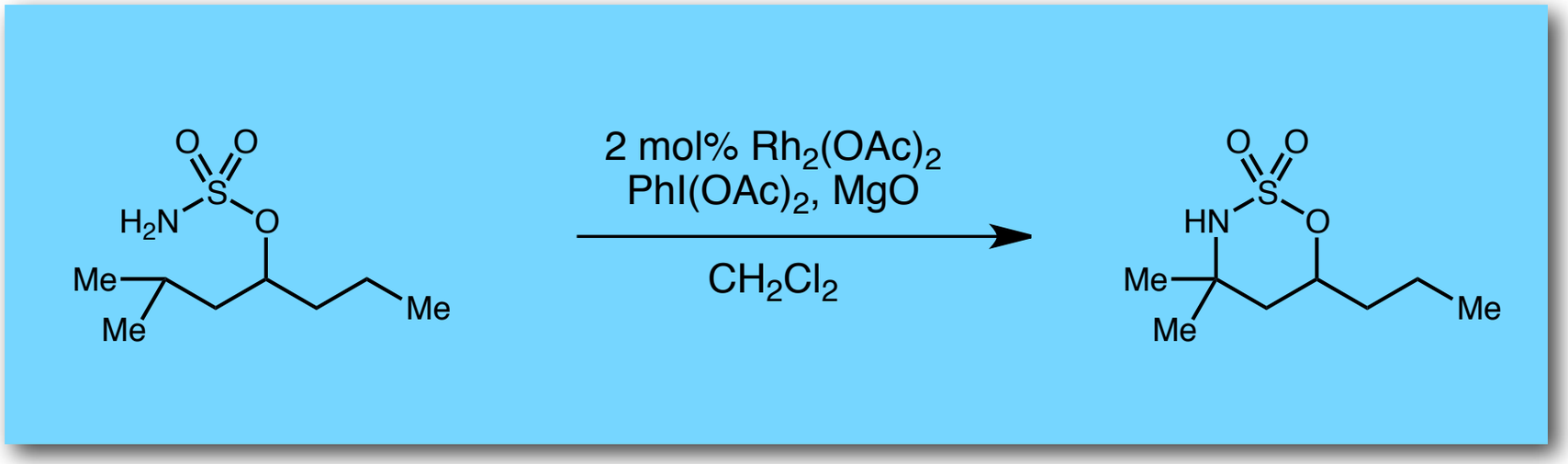
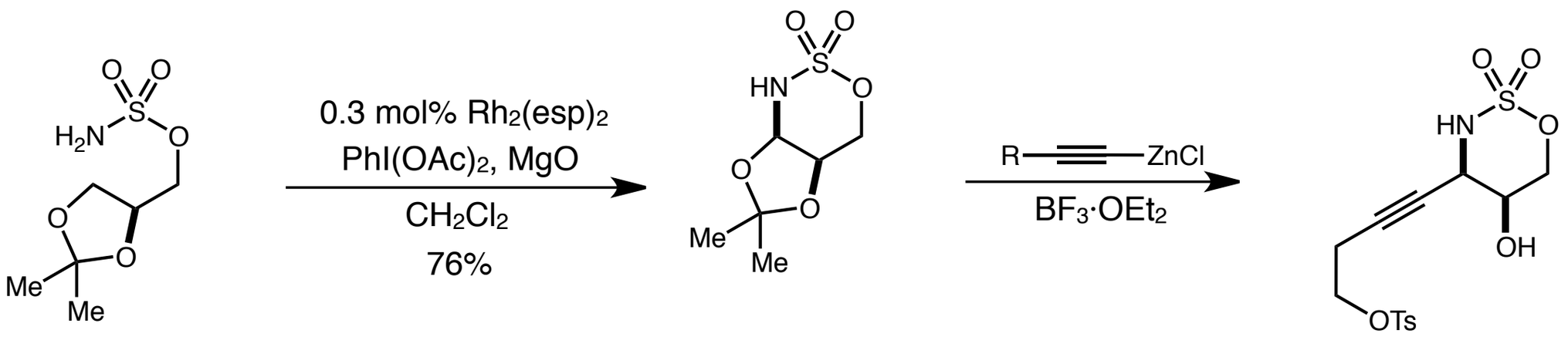


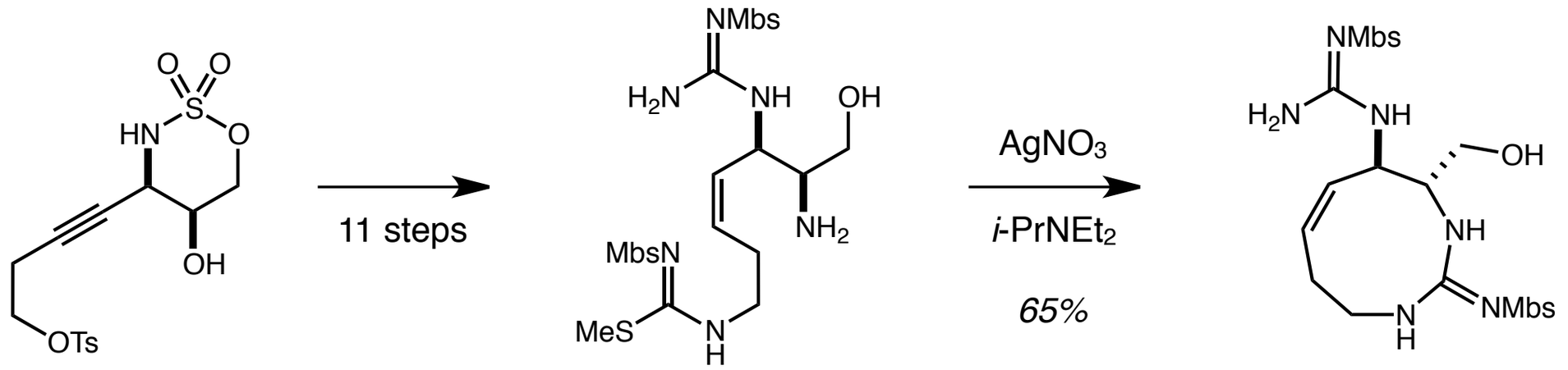
Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935-6936.



Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964-9975.

DuBois' Total Synthesis of Saxitoxin

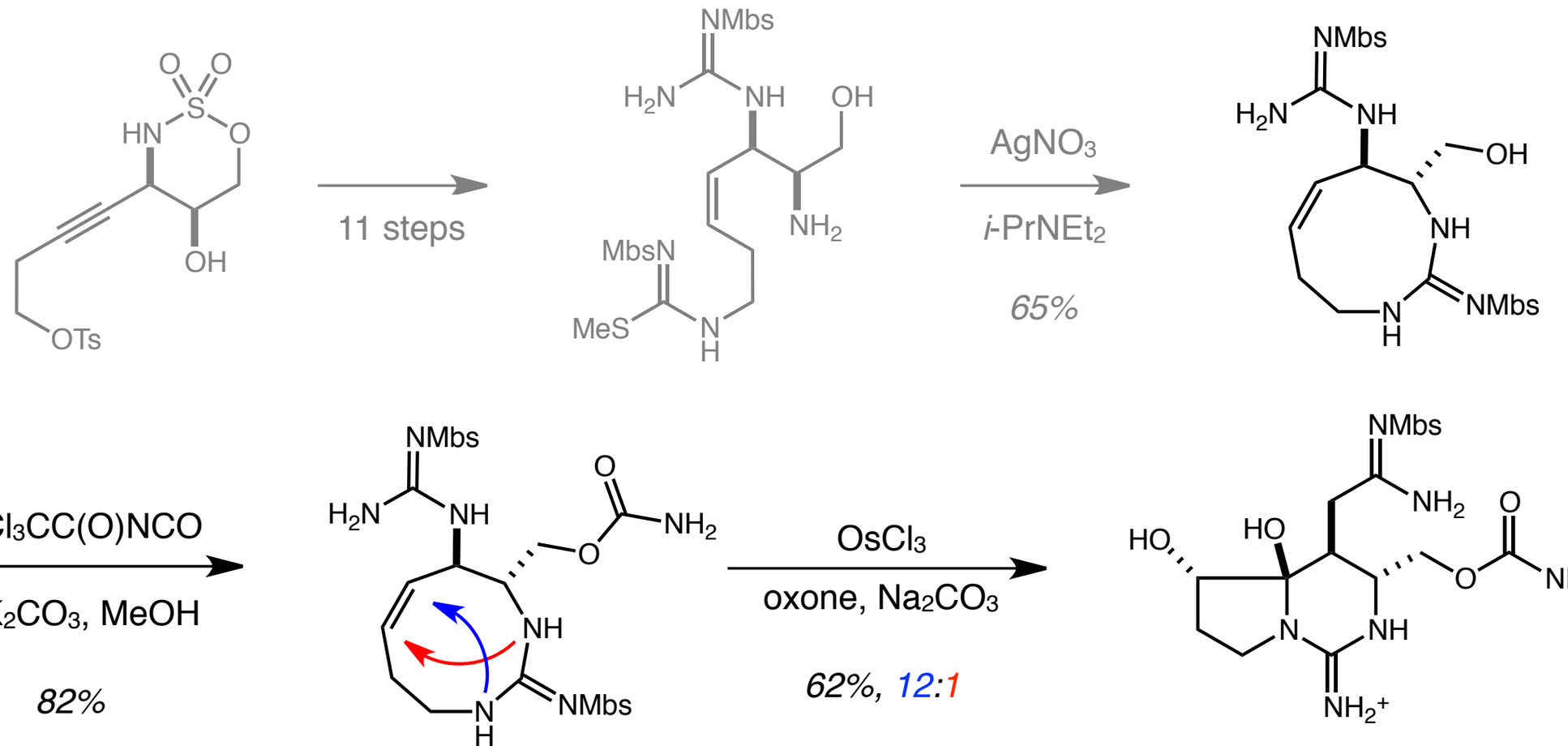
first generation total synthesis



Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964-9975.

DuBois' Total Synthesis of Saxitoxin

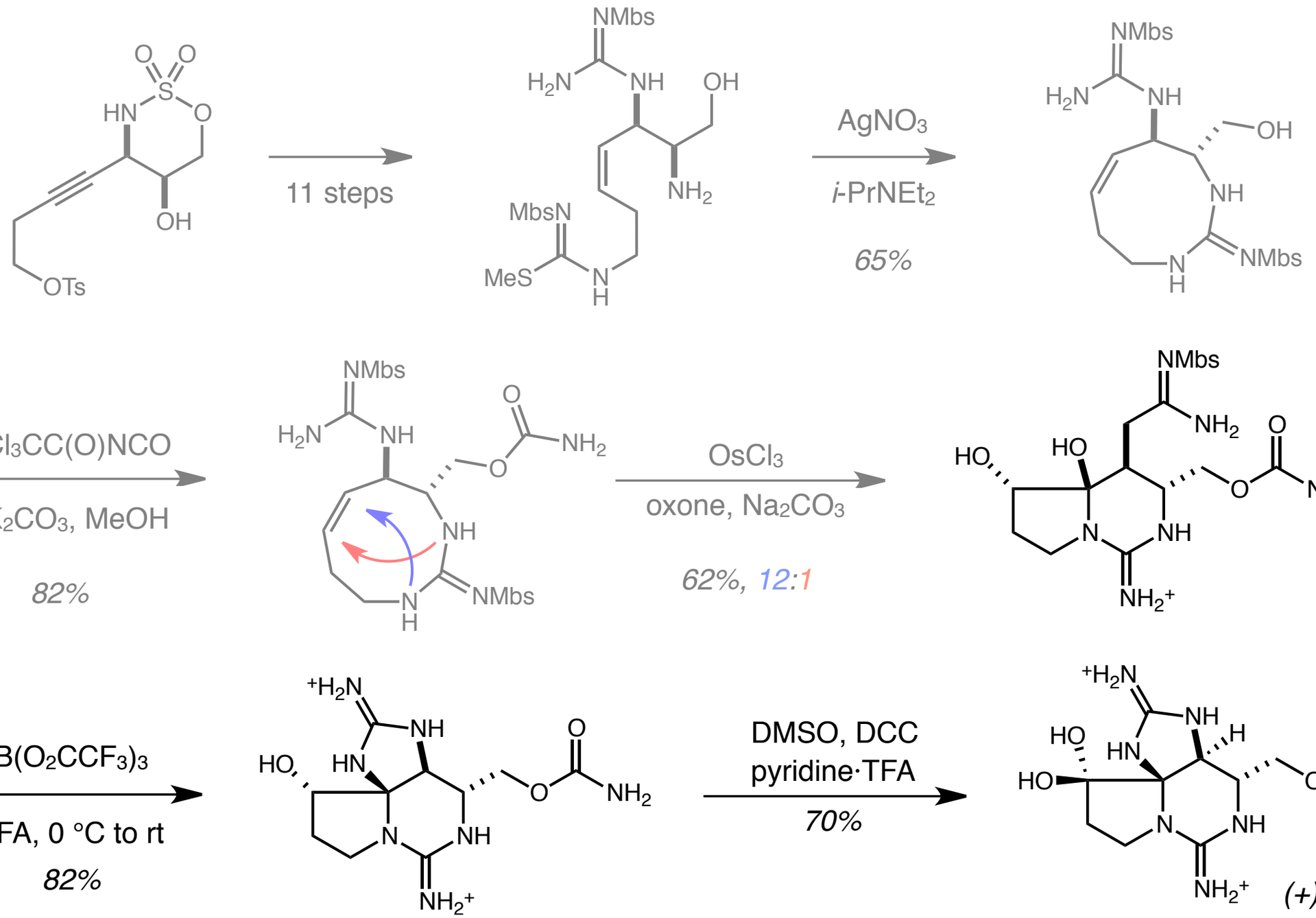
first generation total synthesis



Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964-9975.

DuBois' Total Synthesis of Saxitoxin

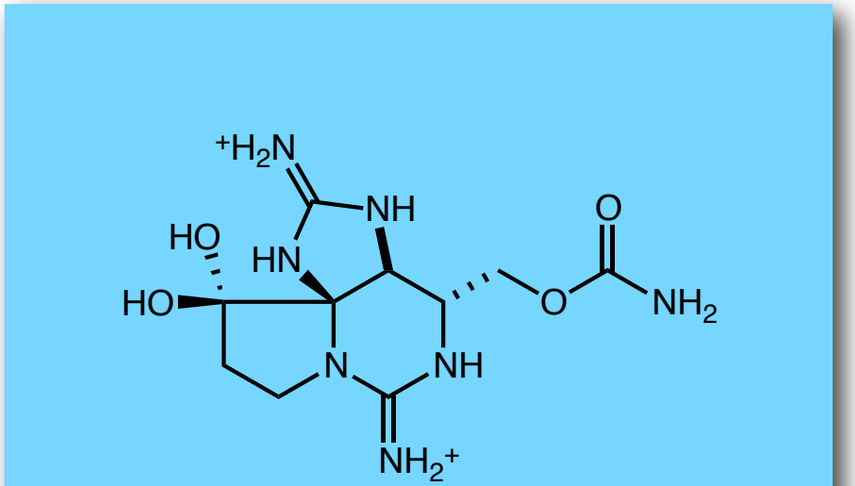
first generation total synthesis



Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964-9975.

DuBois' Total Synthesis of Saxitoxin

first generation recap

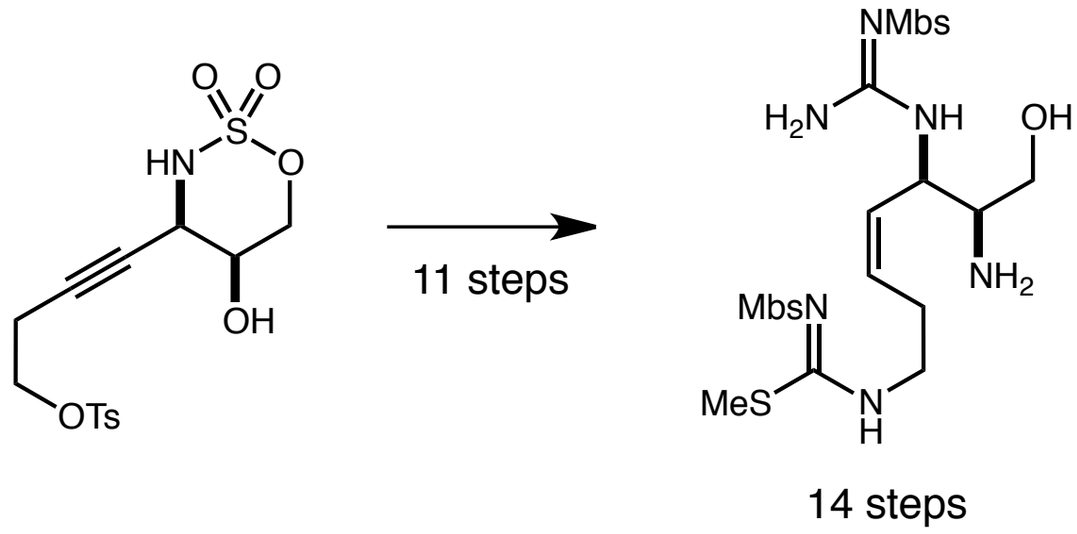


(+)-saxitoxin

- Utilizing their C-H amination method in a total synthesis fostered the development of a better catalyst
- The first enantioselective synthesis
- Du Bois synthesis was longer than both the Kishi and Jacobi racemic syntheses (17 and 15 steps)

DuBois' Total Synthesis of Saxitoxin

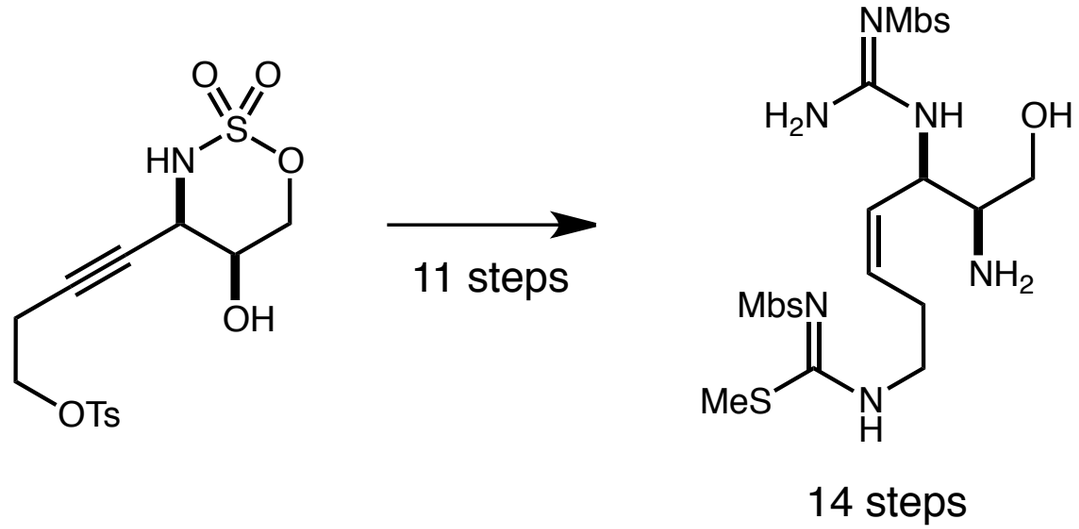
rethinking their original route

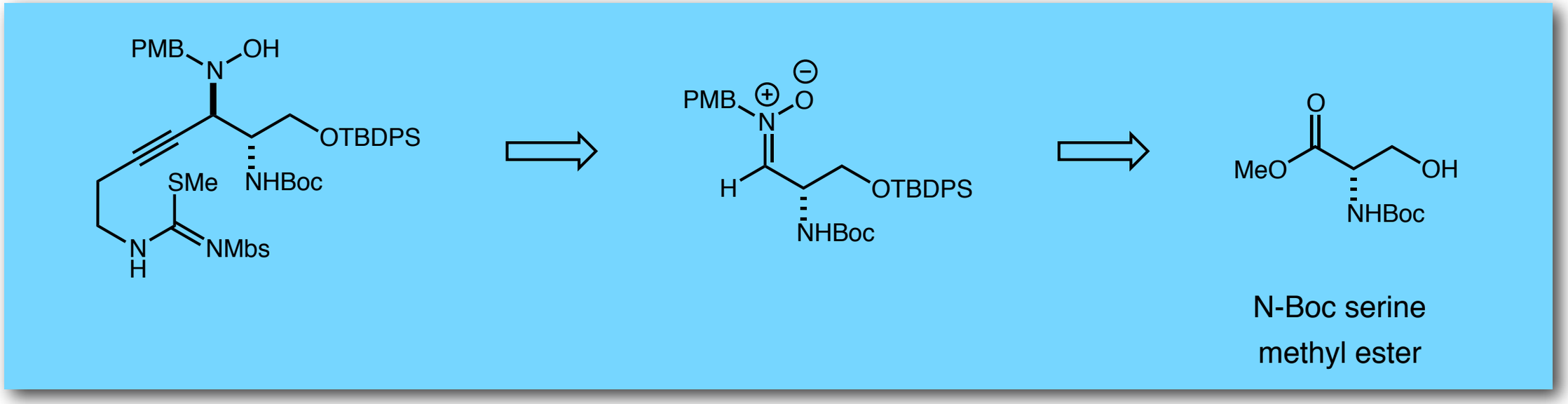


Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964-9975.

DuBois' Total Synthesis of Saxitoxin

rethinking their original route

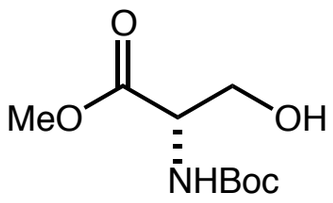




Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964-9975.

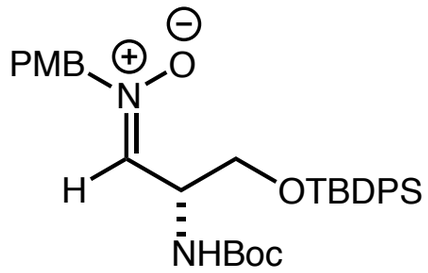
DuBois' Total Synthesis of Saxitoxin

14 step second generation total synthesis

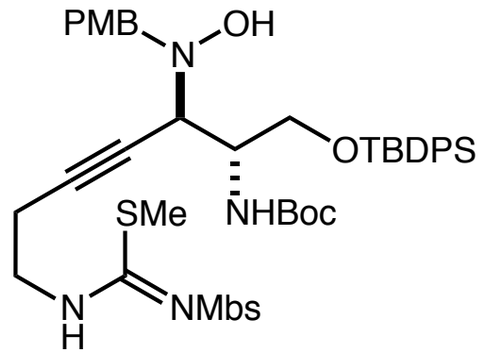


N-Boc serine
methyl ester

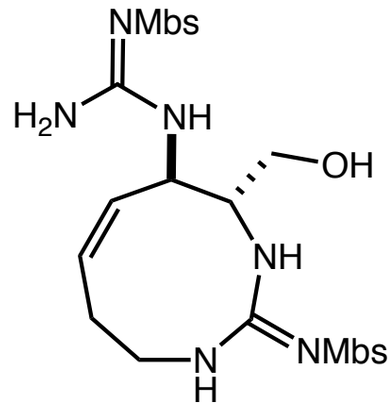
3 steps



alkyne
i-PrMgCl
THF, -78 °C
78%, 5:1 anti/syn

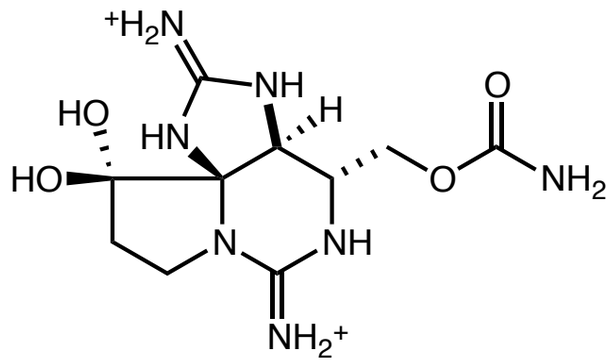


6 steps



10 steps vs 16 steps

4 steps

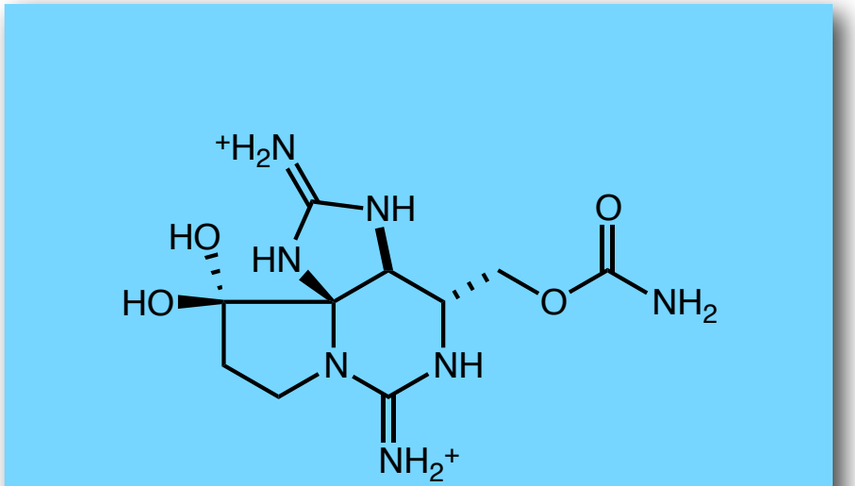


(+)-saxitoxin

Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964-9975.

DuBois' Total Synthesis of Saxitoxin

second generation recap



(+)-saxitoxin

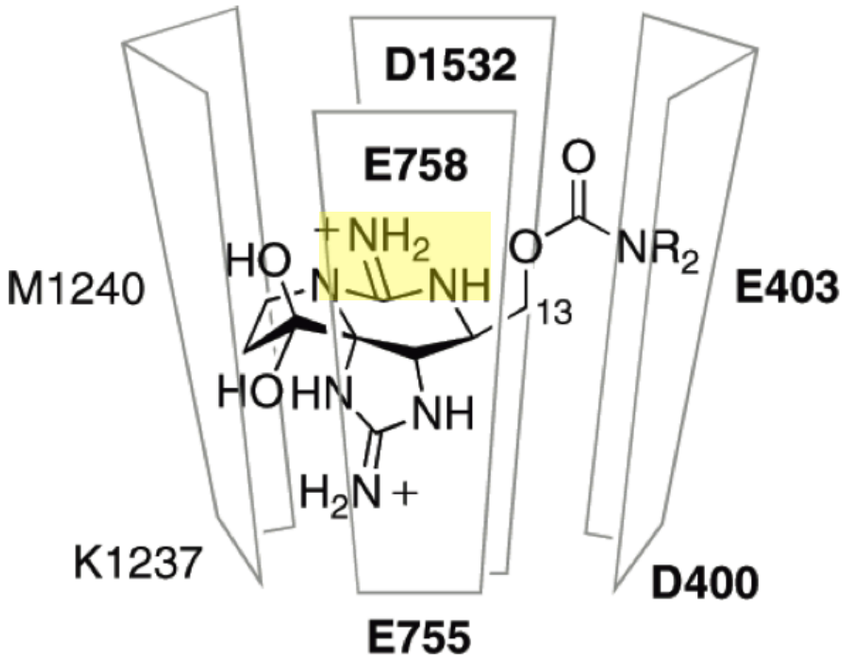
- Their second generation approach provided the most efficient synthesis of the (+)-saxitoxin
- The second generation synthesis was scalable, preparing 5 g of the 9 membered ring
- Provided enough material to initiate ion channel studies.

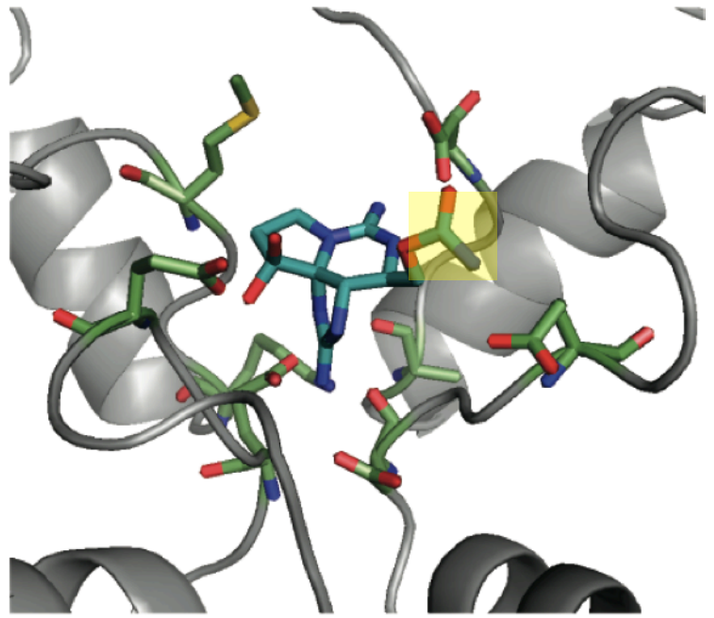
Saxitoxin as a Small Molecule Probe for Ion Channel Studies

- Difficulty in chemically modifing natural saxitoxin limits its use as a small molecular probe
- Through *de novo* total synthesis an array of diverse molecular probes can be synthesized readily

7,8,9-guanidine residue
proposed to bind the selectivity filter

carbomyl group proposed to be H bond donor



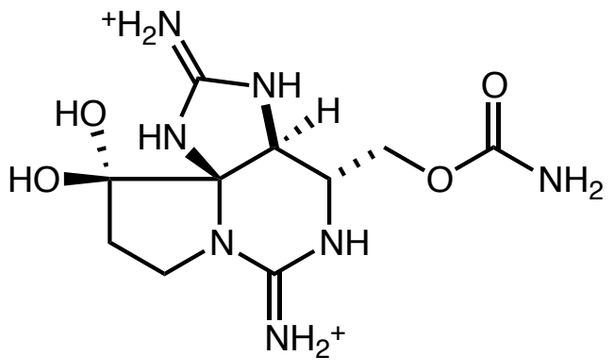


Andersen, B. M.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 12524-12525.

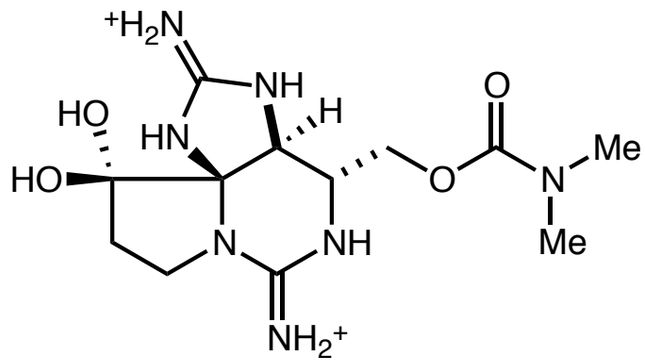
Saxitoxin as a Small Molecule Probe for Ion Channel Studies

initial question

- Is the carbamate, specifically as an H-bond donor, important for saxitoxin binding the ion channel?



(+)-saxitoxin



N,N-dimethyl-(+)-saxitoxin

Saxitoxin as a Small Molecule Probe for Ion Channel Studies

initial question

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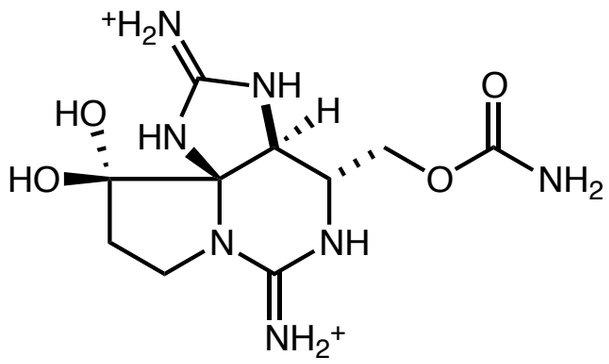
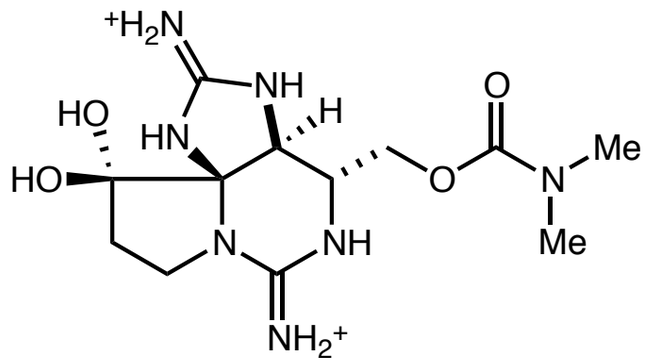


(+)-saxitoxin



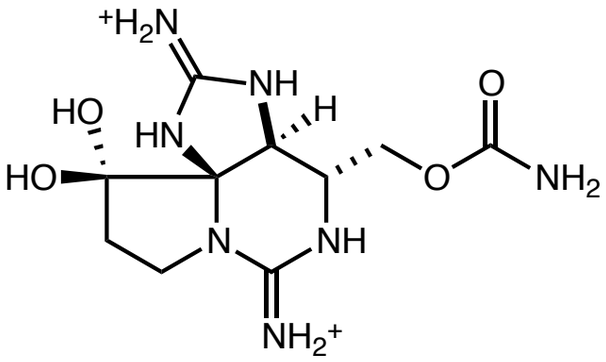
N,N-dimethyl-(+)-saxitoxin

- Strategy: Remove the hydrogen bonds and measure the voltage across the ion channel

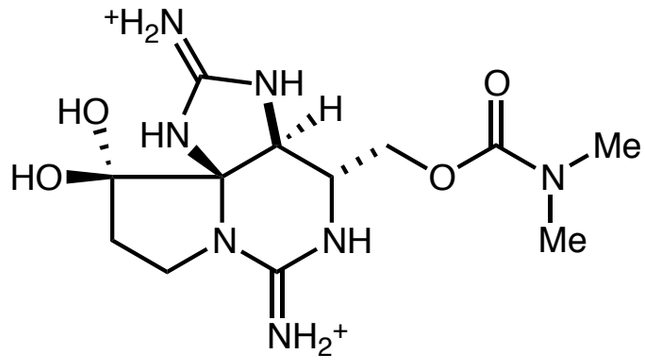
Saxitoxin as a Small Molecule Probe for Ion Channel Studies

initial question

- Is the carbamate, specifically as an H-bond donor, important for saxitoxin binding the ion channel?

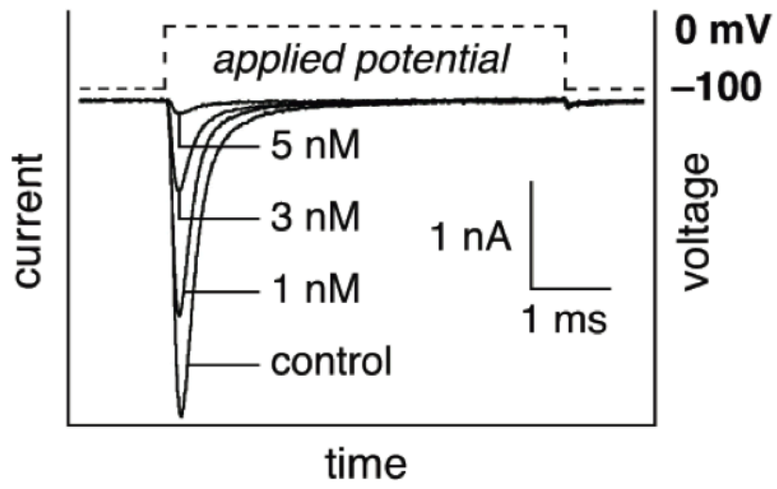


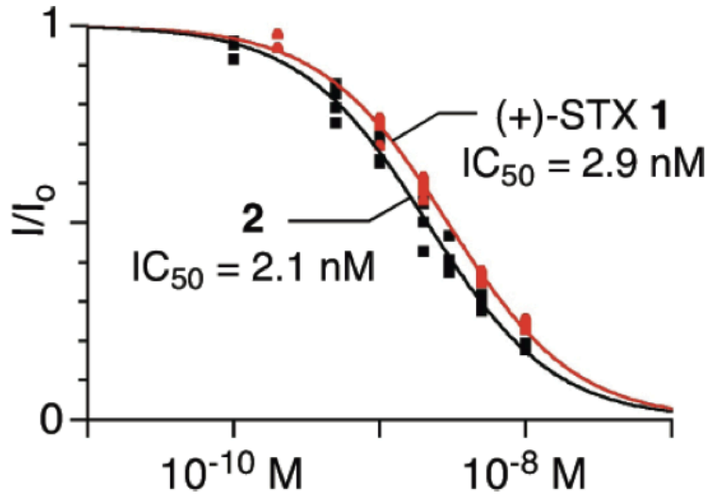
(+)-saxitoxin



N,N-dimethyl-(+)-saxitoxin

- Increasing conc. of both saxitoxin and *N,N*-dimethylsaxitoxin result in decreased peak current



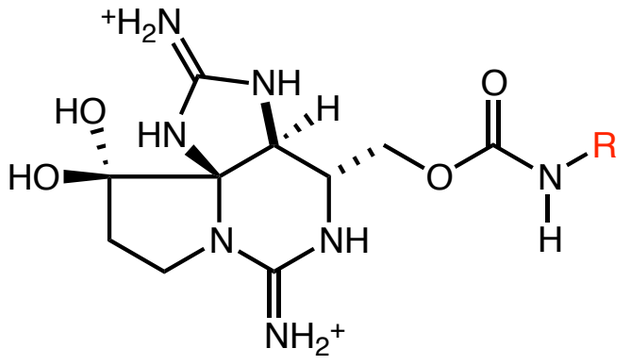


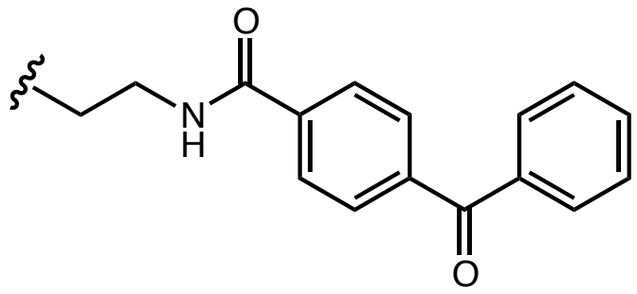
carbomyl unit not likely a hydrogen bond donor

Saxitoxin as a Small Molecule Probe for Ion Channel Studies

initial question

- Do further modifications to the carbomyl unit effect binding?



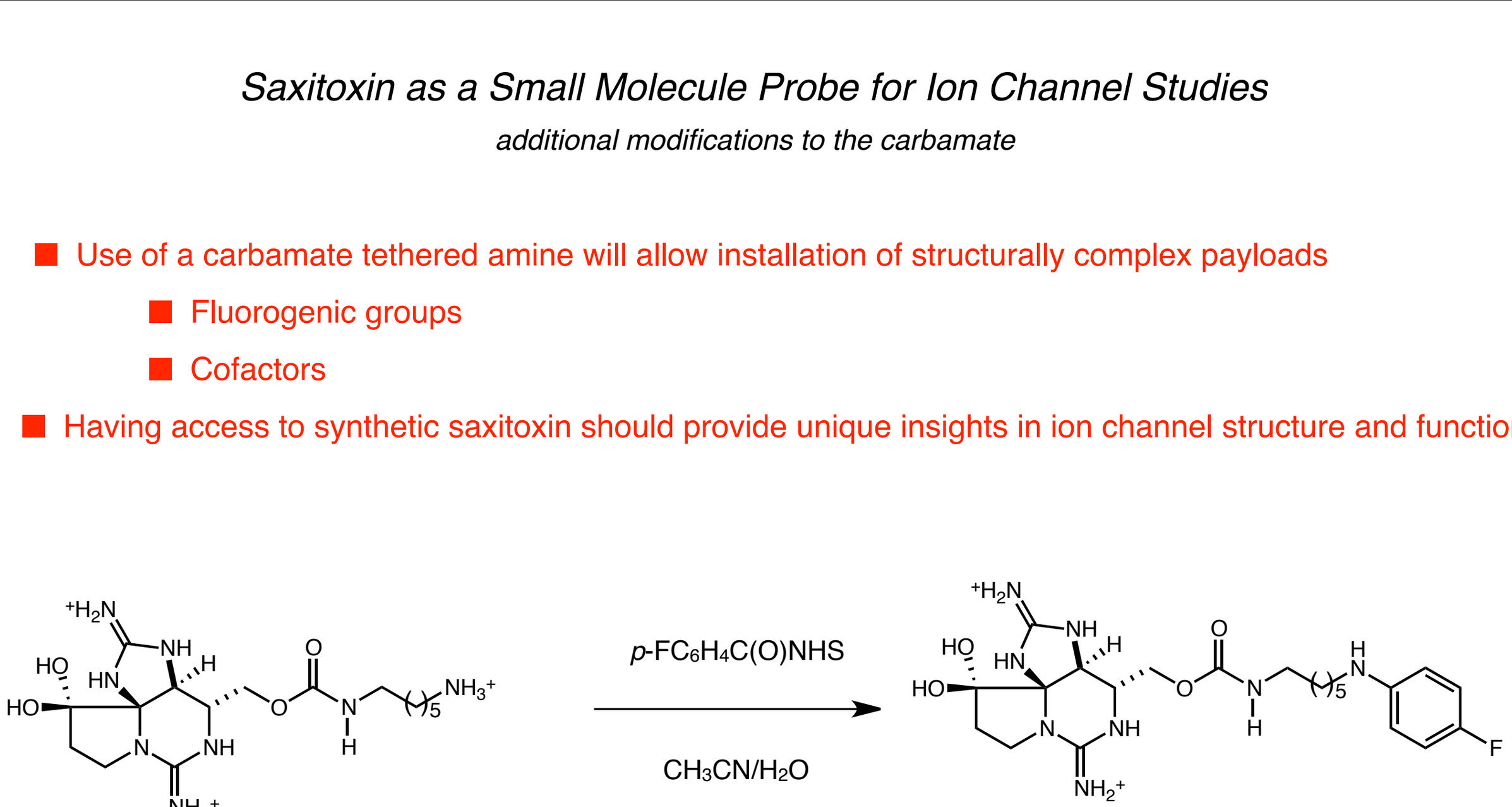
R	IC_{50} (nM)
C_7H_{15}	26 +/- 3
i-Pr	83 +/- 13
$C_6H_{12}NH_3^+$	19 +/- 0.8
$C_5H_{10}CO_2^-$	135 +/- 7
	87 +/- 9

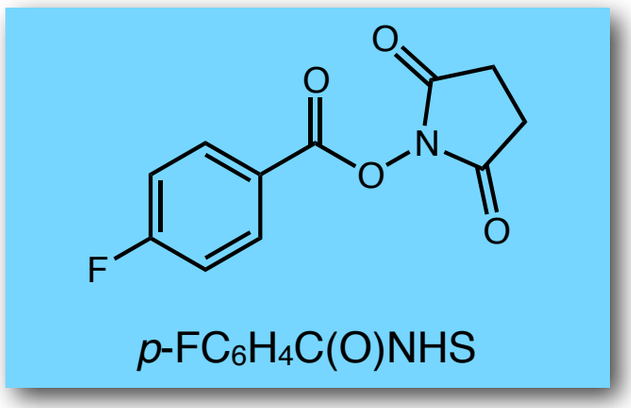
- Despite steric, electronic, and polar modifications, all retained activity within 1-1.5 orders of magnitude
- Allowed for the installation of the first saxitoxin photoaffinity probe

Saxitoxin as a Small Molecule Probe for Ion Channel Studies

additional modifications to the carbamate

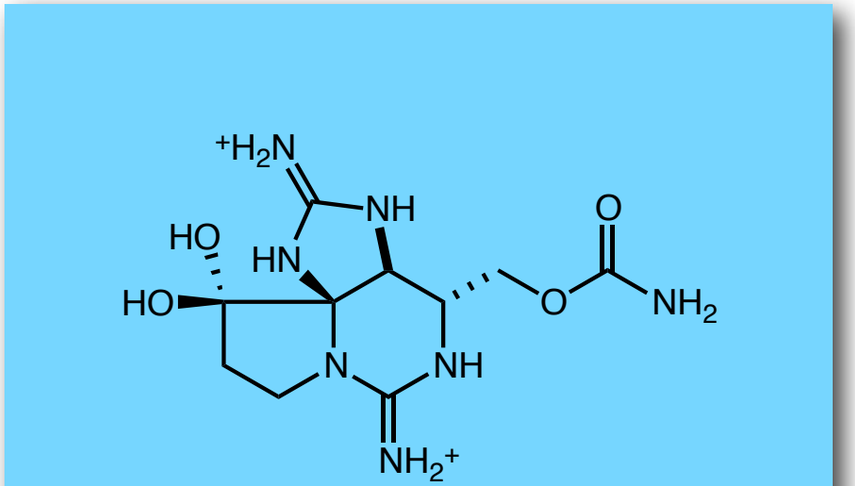
- Use of a carbamate tethered amine will allow installation of structurally complex payloads
  - Fluorogenic groups
  - Cofactors
- Having access to synthetic saxitoxin should provide unique insights in ion channel structure and function





DuBois' Total Synthesis of Saxitoxin

overview of saxitoxin synthesis

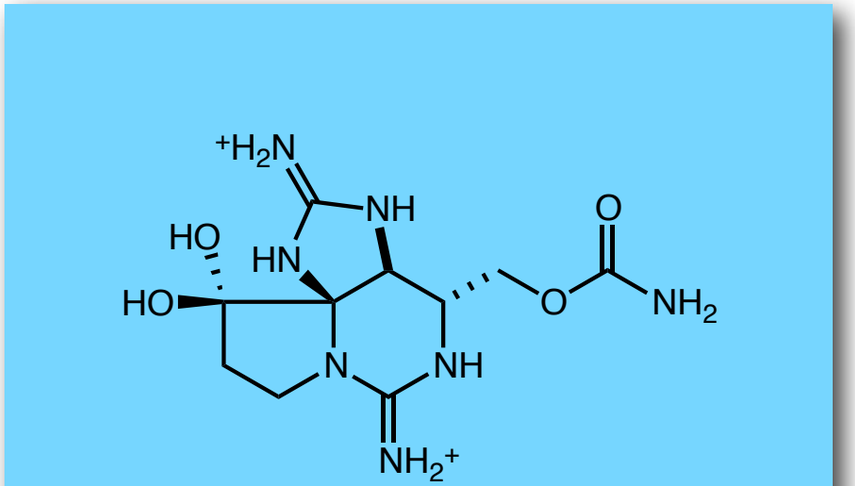


(+)-saxitoxin

- Their initial synthesis enabled a very elegant and scalable synthesis of an important molecule
- Application of their chemistry toward a total synthesis identified a better C-H amination catalyst
- The result of their work enabled a new area of academic research on ion channels.

DuBois' Total Synthesis of Saxitoxin

overview of saxitoxin synthesis



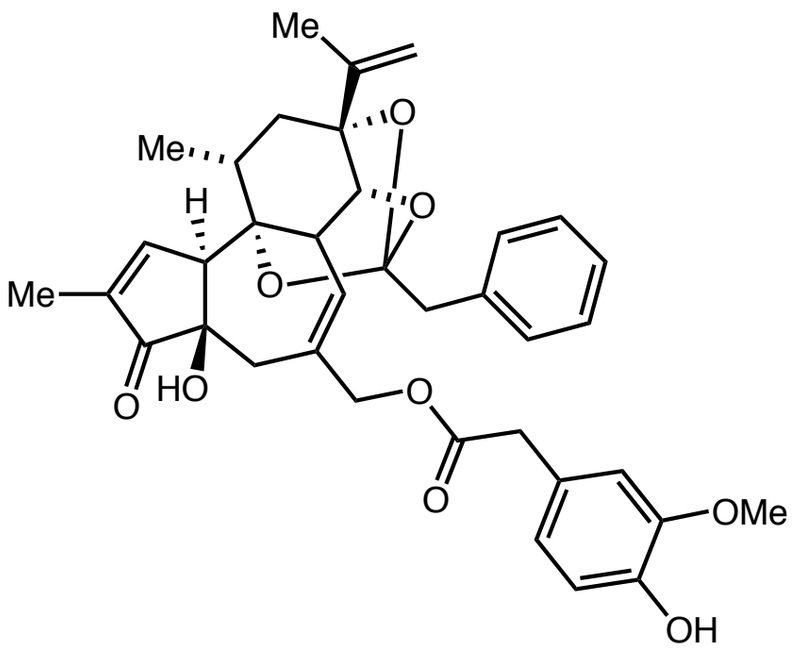
(+)-saxitoxin

- Should total syntheses be used to apply methodology if the resulting initial synthesis isn't the "best"?
- Is post synthetic research becoming mainstream?

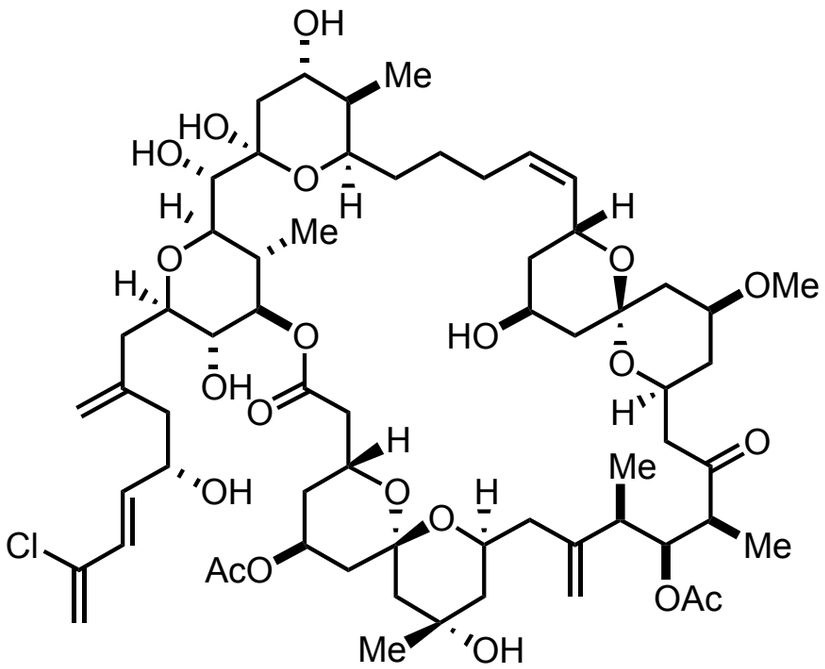
The Future of Total Synthesis

summary of themes from selected examples

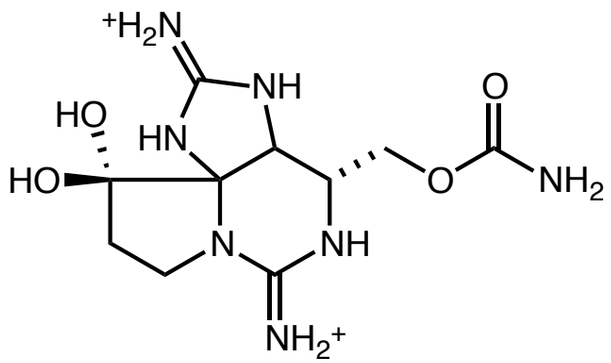
- Three molecules that highlight the perceived divisions for the modern role of total synthesis
  - Which natural products do we make?
    - All, some, any? Structurally interesting, biologically active?
  - What holds more value?
    - The structure, method employed, lessons learned, or future prospects?



resiniferatoxin



spongistatin 1

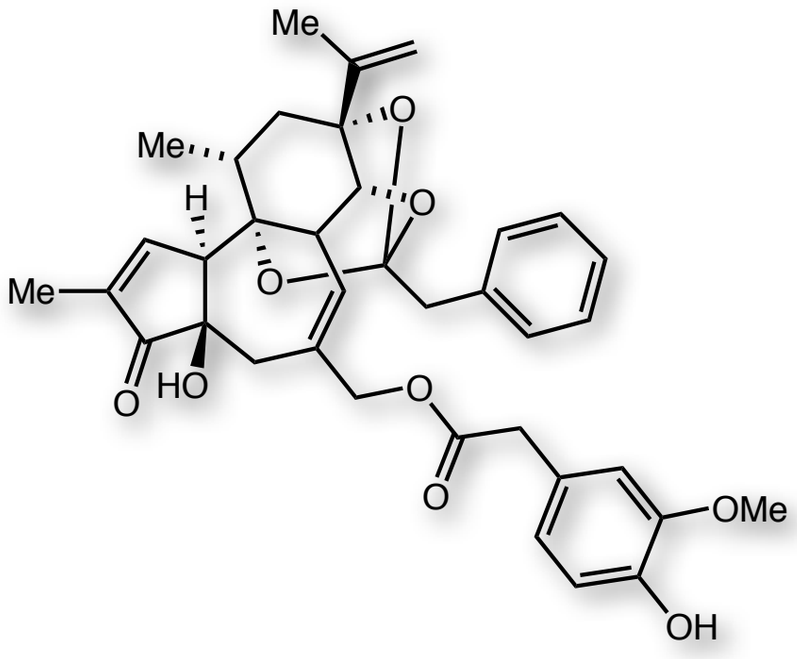


(+)-saxitoxin

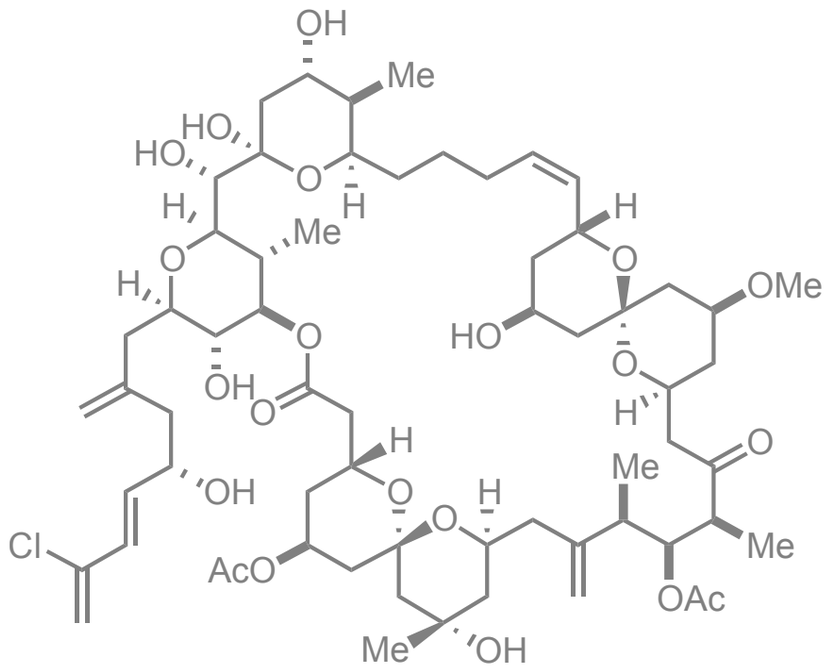
The Future of Total Synthesis

final thoughts

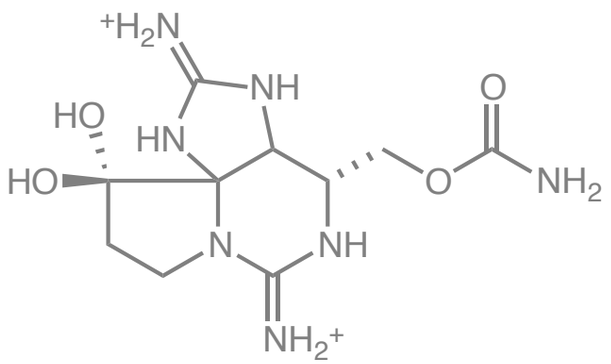
- Wender's synthesis of resiniferatoxin
  - Which natural products to we make?
    - A *tour de force synthesis* is worth undertaking if the target is important and the goal of the research is to understand the SAR of the molecule to provide new therapeutic leads
  - What holds more value?
    - The structure and future prospects are what drives the value in these types of syntheses



resiniferatoxin



spongistatin 1

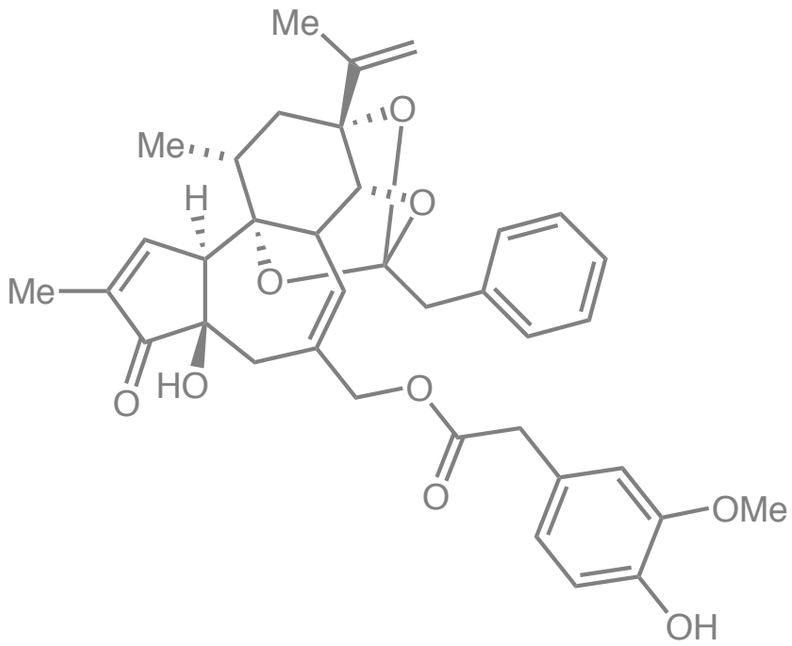


(+)-saxitoxin

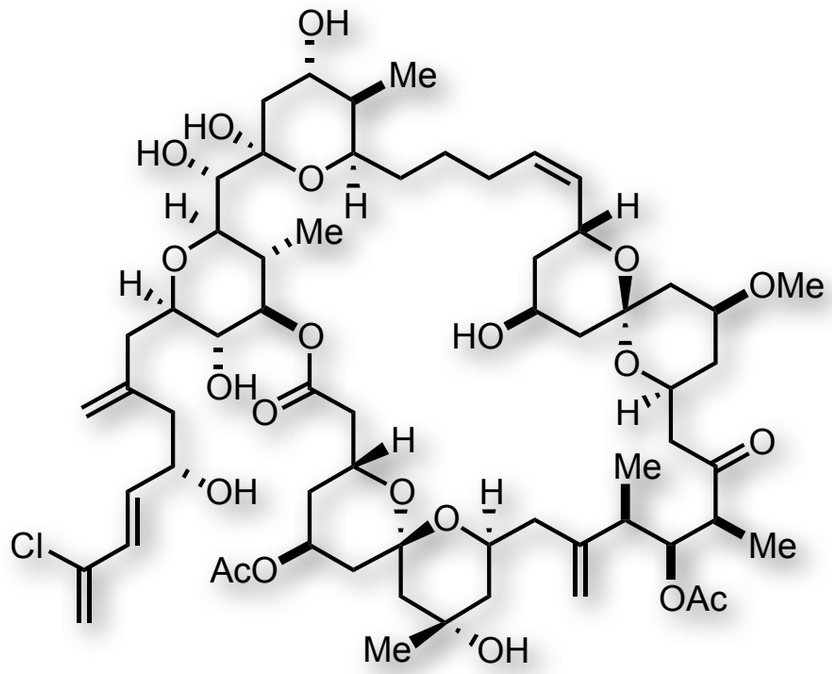
The Future of Total Synthesis

final thoughts

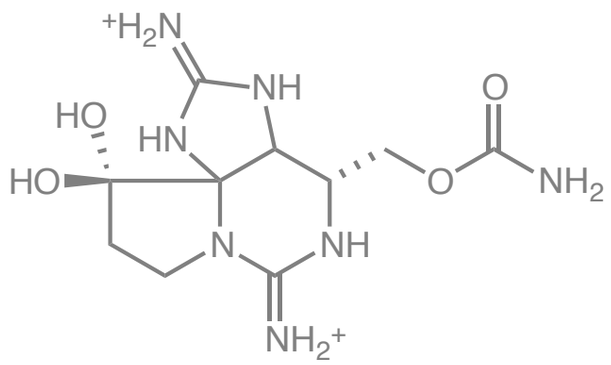
- Smiths synthesis of spongistatin 1
  - Which natural products to we make?
    - Focused efforts toward very complex and important molecules offer a testing ground for synthetic methods and provided multiple opportunities for post total synthesis research
  - What holds more value?
    - The structure, method employed, lessons learned, and future prospects all provided value



resiniferatoxin



spongistatin 1

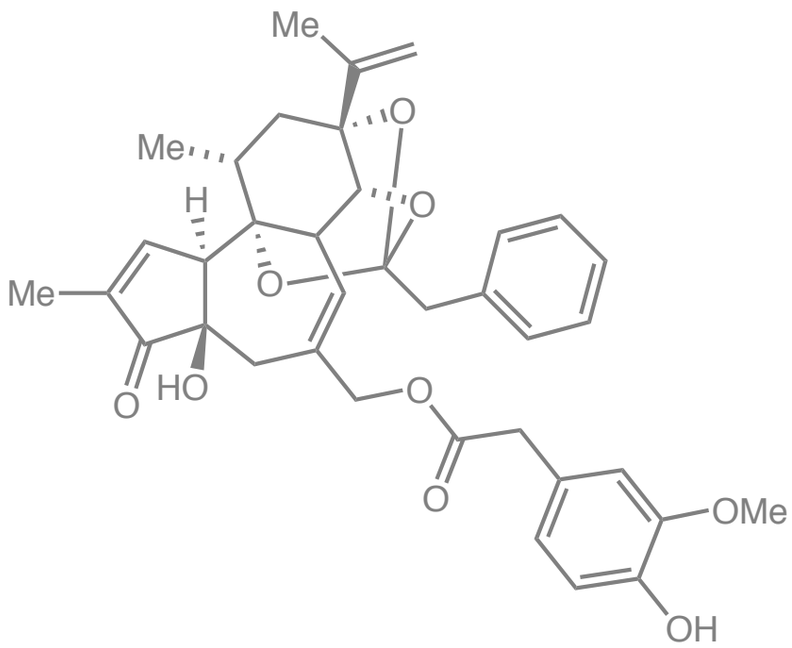


(+)-saxitoxin

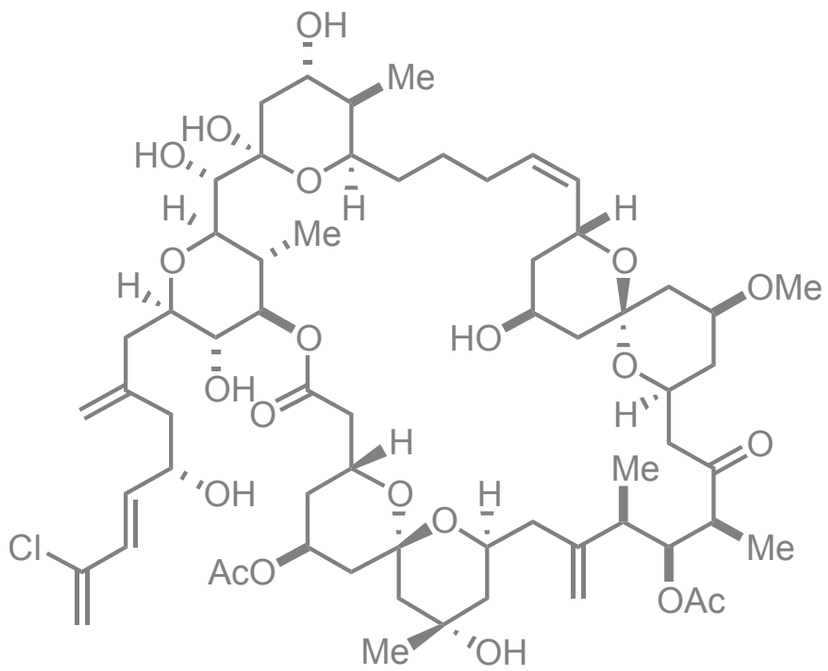
The Future of Total Synthesis

final thoughts

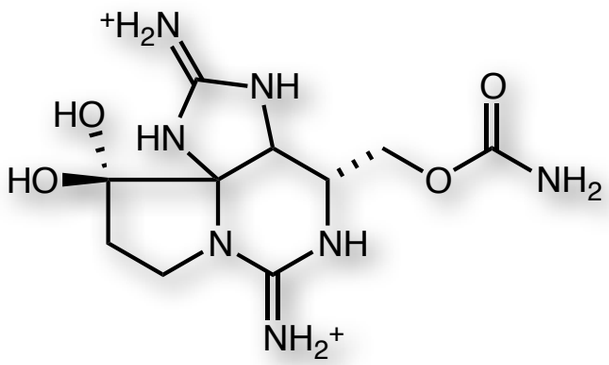
- Du Bois synthesis of saxitoxin
  - Which natural products to we make?
    - Focused efforts toward very complex and important molecules often leads to improvements in synthetic methods and provide opportunities for post total synthesis research
  - What holds more value?
    - Methods employed, lessons learned, and future prospects drove the value of this program



resiniferatoxin



spongistatin 1

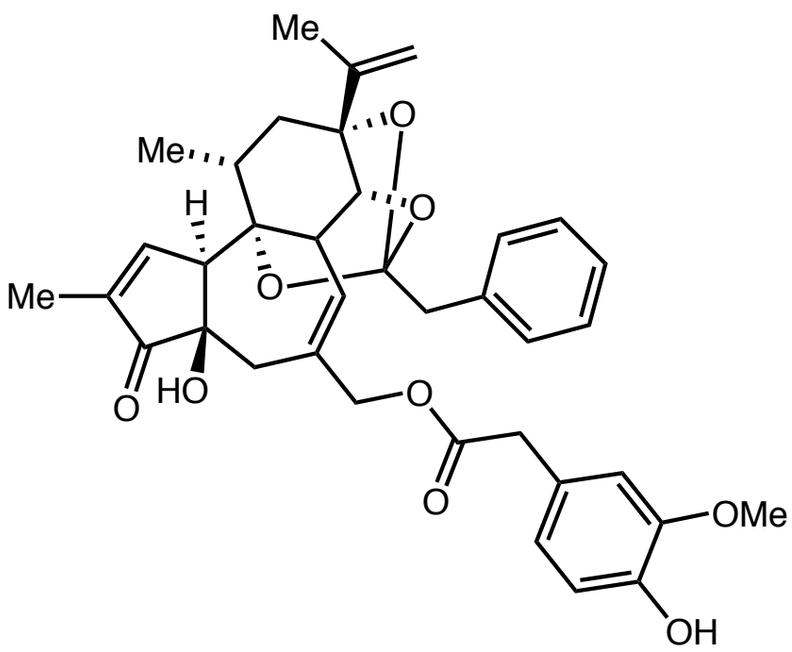


(+)-saxitoxin

The Future of Total Synthesis

final thoughts

- All three examples entailed focused research programs directed toward a single natural product
  - They all provided additional supplies of valuable targets that initiated further research
  - They all encountered pitfalls in synthetic strategies that facilitated future focused efforts
  - They all generated an improved synthetic transformation or method for fragment synthesis



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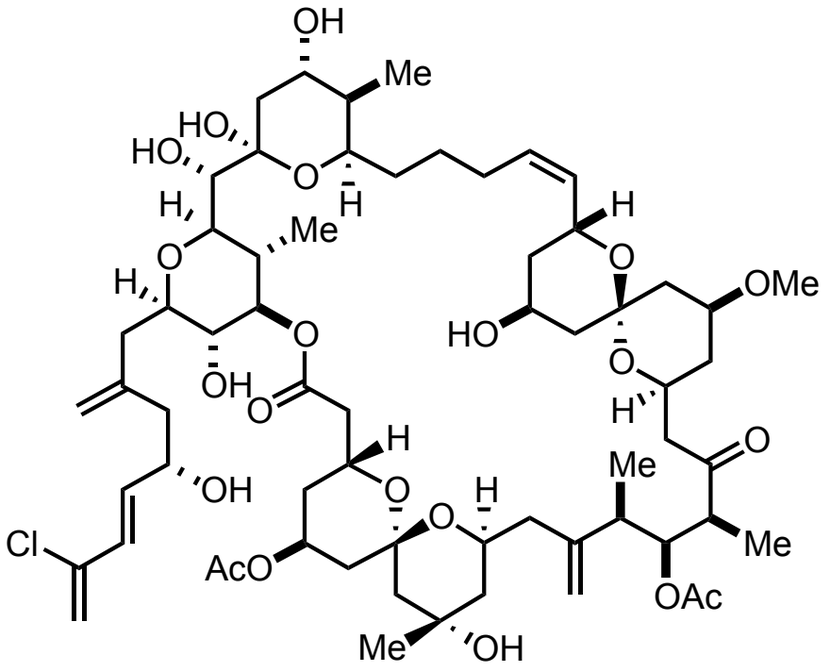

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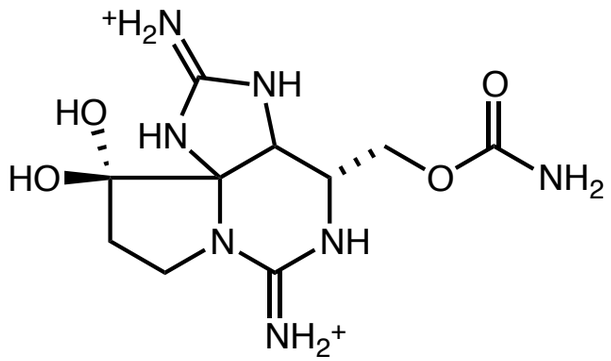
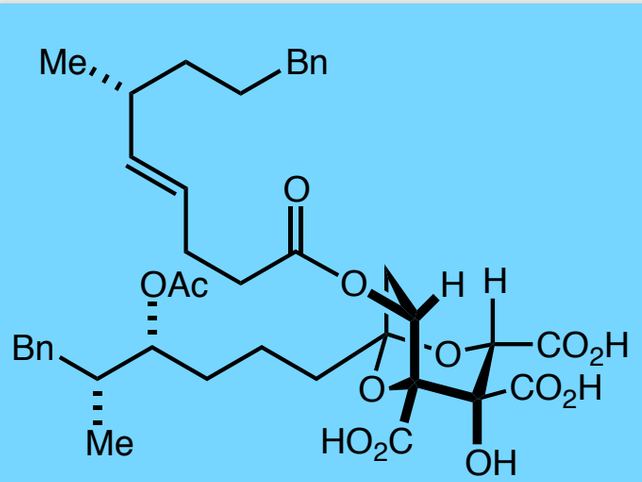


(+)-saxitoxin

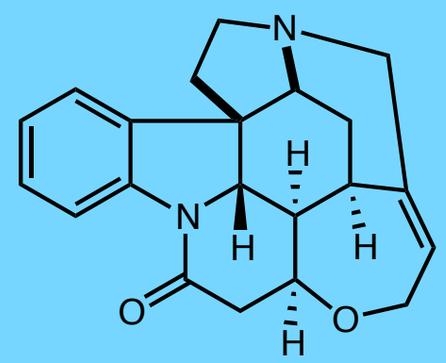
The Future of Total Synthesis

final thoughts

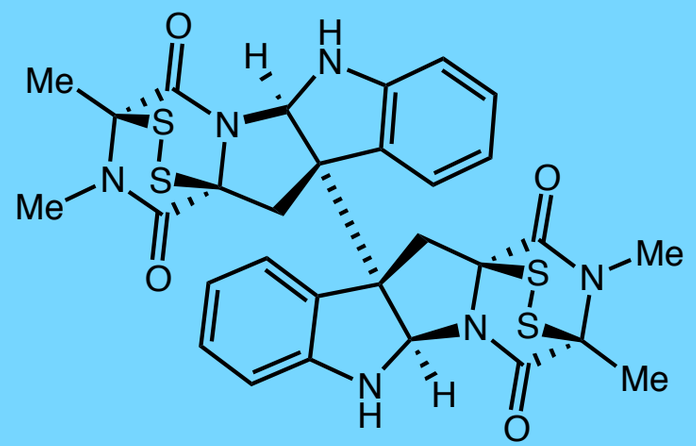
- Powerful new methods will continue to push toward the ideal total synthesis



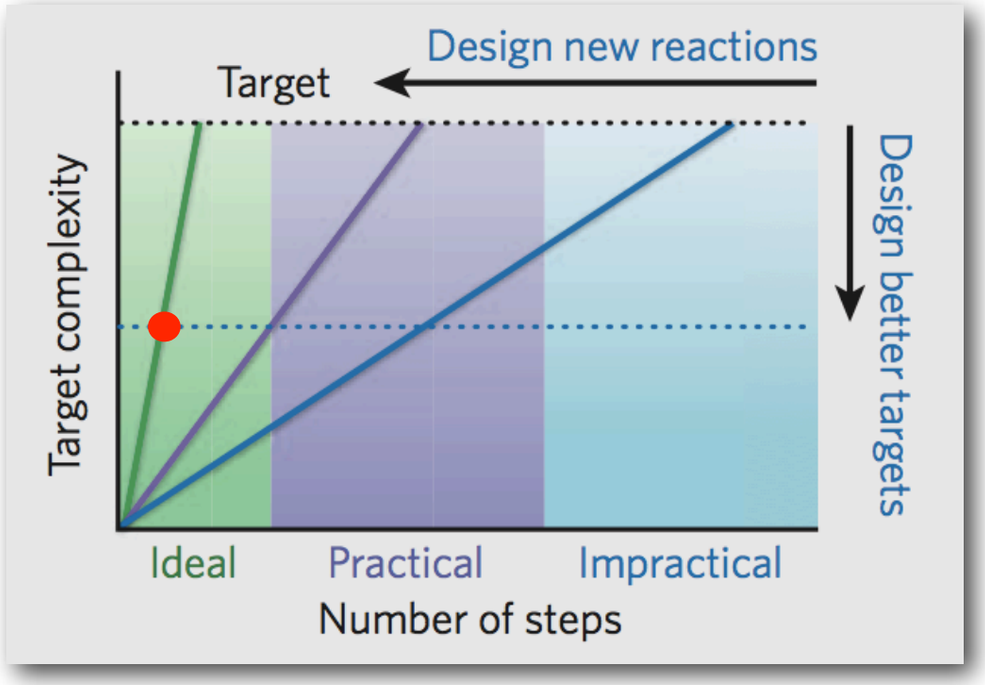
zaragozic acid C



strychnine



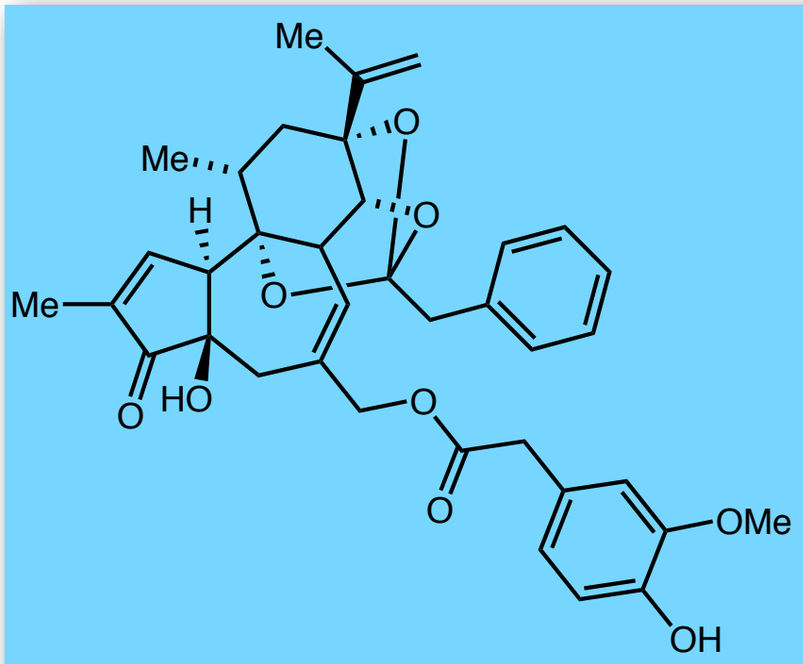
(+)-11,11'-dideoxyverticillin A



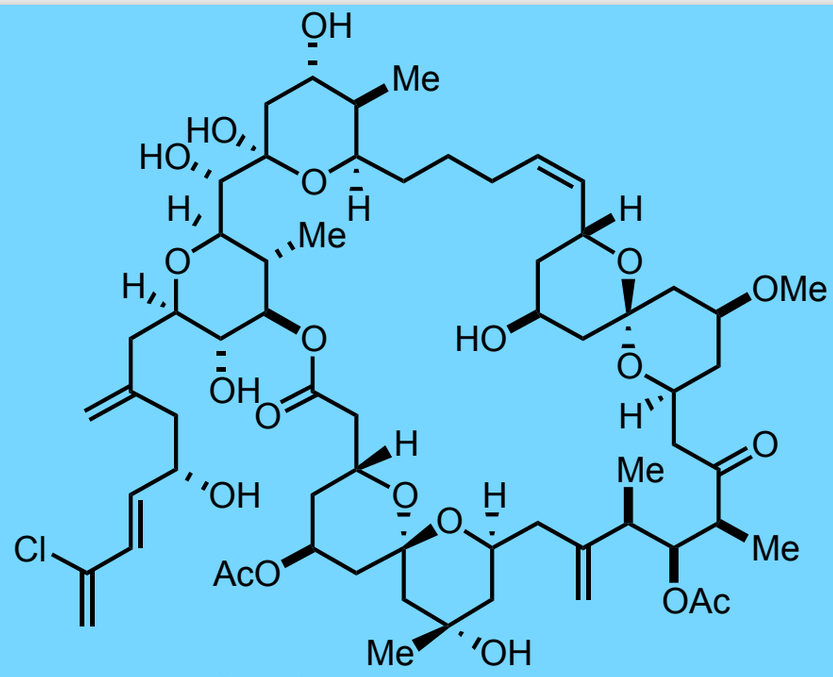
The Future of Total Synthesis

final thoughts

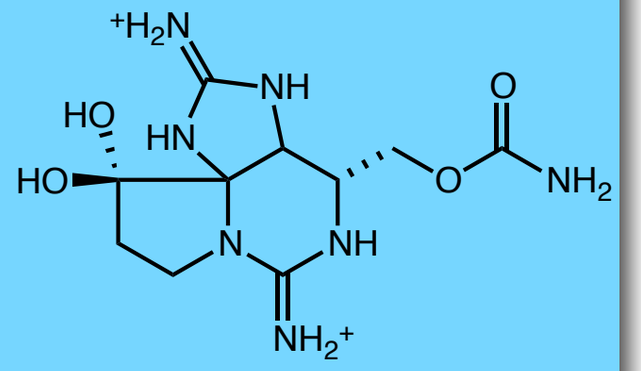
- Focused efforts toward a single natural product will continue to be a productive area of research



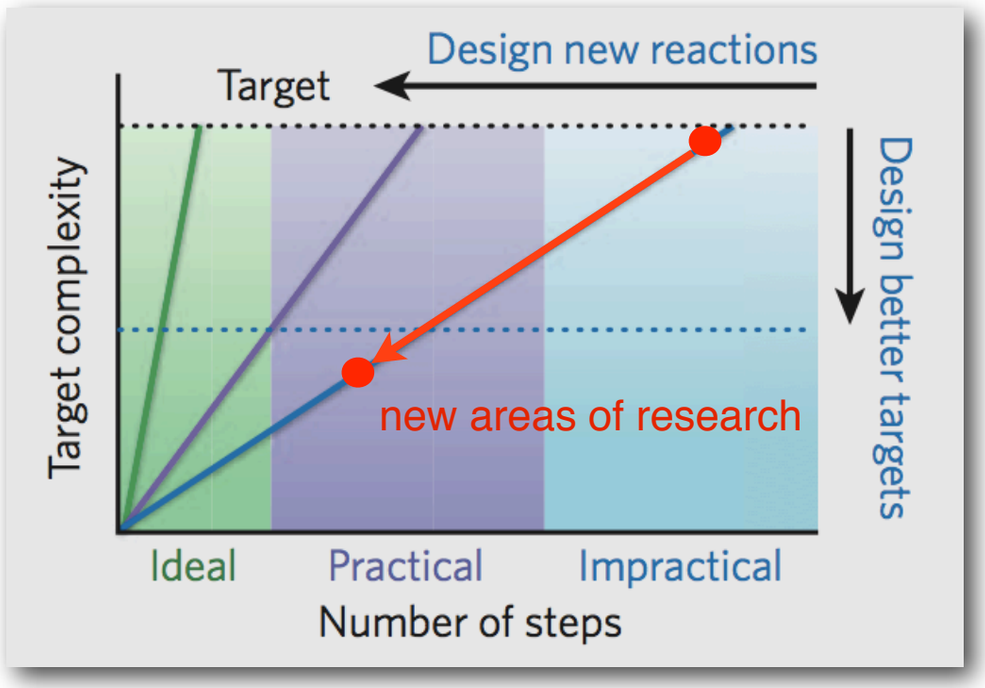
resiniferatoxin



spongistatin 1



(+)-saxitoxin

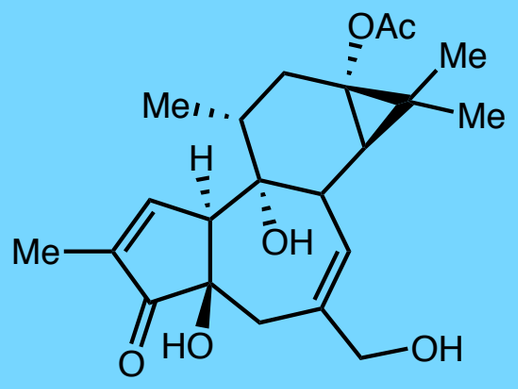


The Future of Total Synthesis

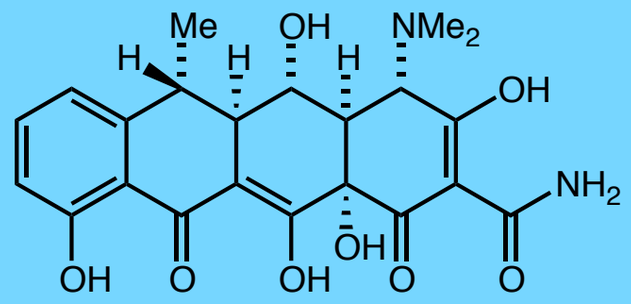
final thoughts

- Focused efforts toward a single natural product will continue to be a productive area of research

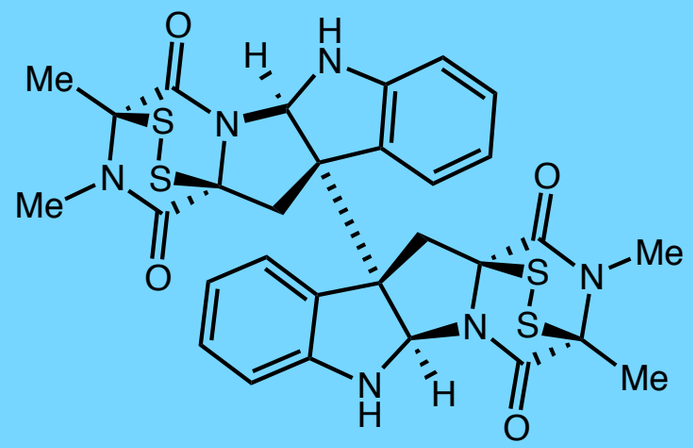
Last total syntheses to be published in Science



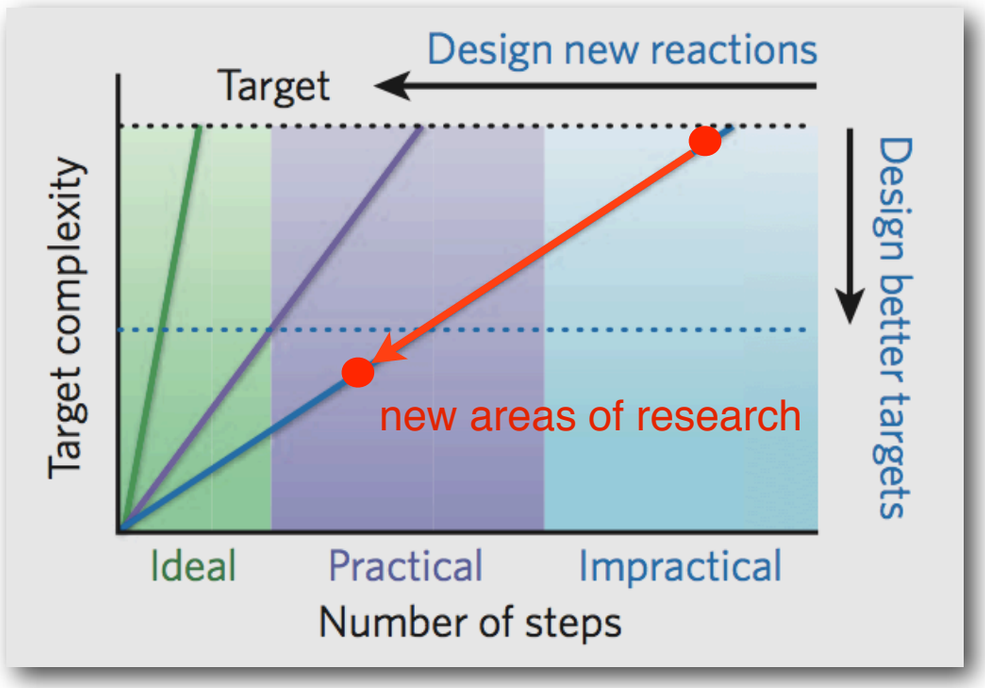
prostratin (Wender)



(-)-doxycycline (Myers)



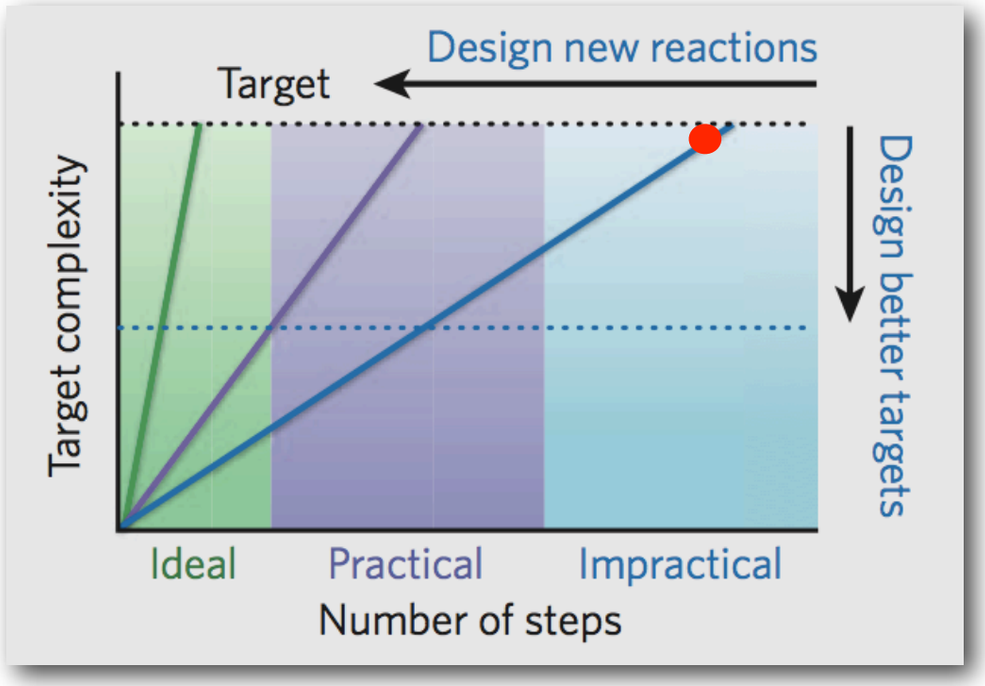
dideoxyverticillin A (Movassaghi)



The Future of Total Synthesis

final thoughts

- Groups that undertake impractical syntheses of many different targets will become irrelevant



The Future of Total Synthesis

final thoughts

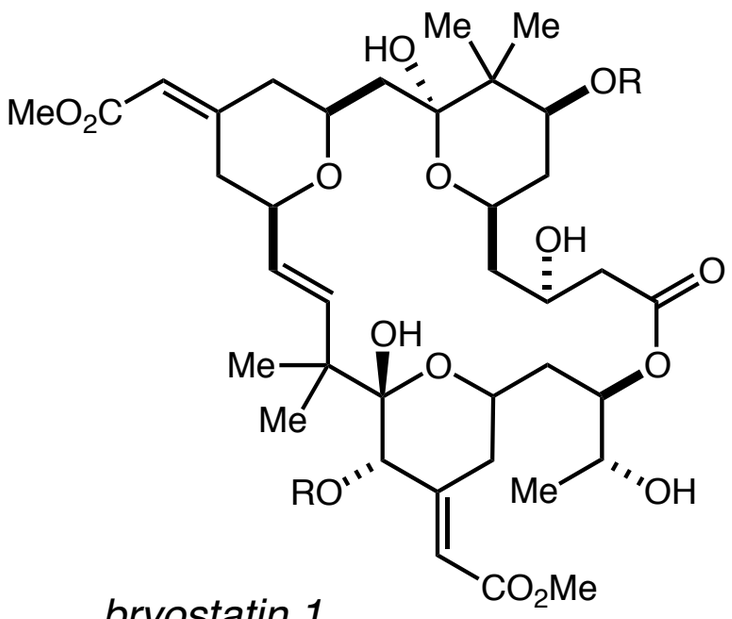
- These sentiments are being increasingly observed across the spectrum of total synthesis
- More focused efforts toward fewer targets is likely the future of total synthesis

Barry Trost (1965)

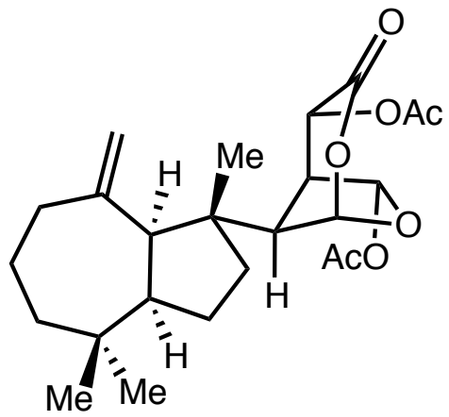
David Evans (1967)

Larry Overman (1970)

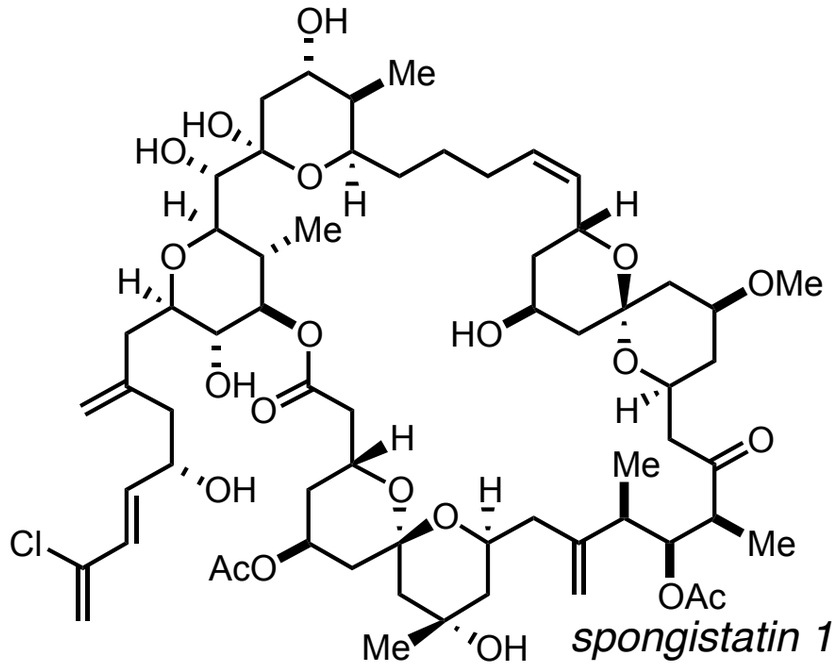
Amos Smith (1972)



bryostatin 1



macfarlandin



spongistatin 1

The Future of Total Synthesis

final thoughts

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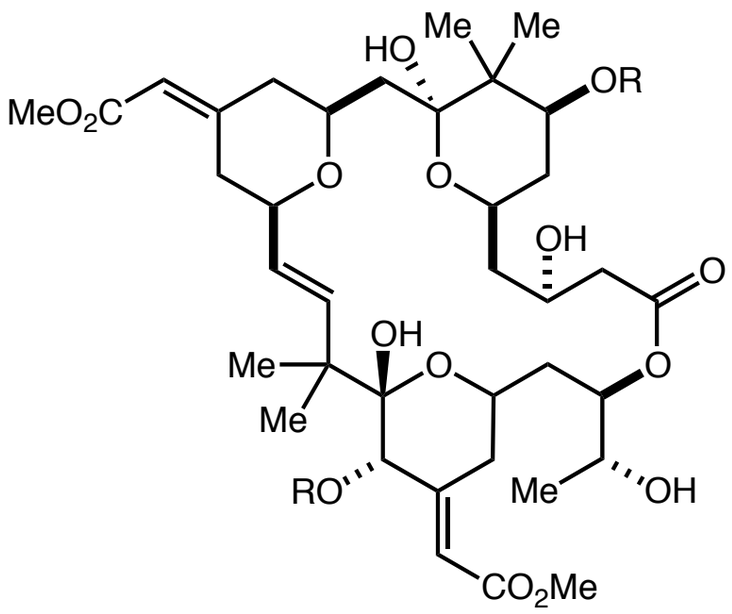
K. C. Nicolaou (1976)

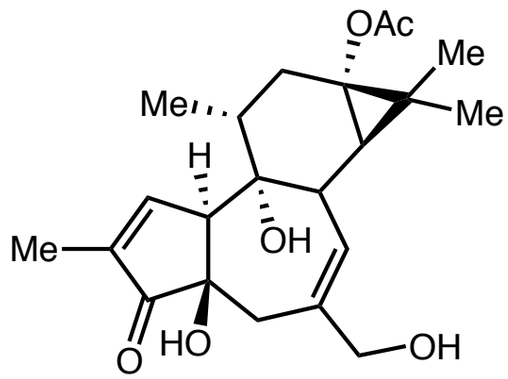
Paul Wender (1976)

Dale Boger

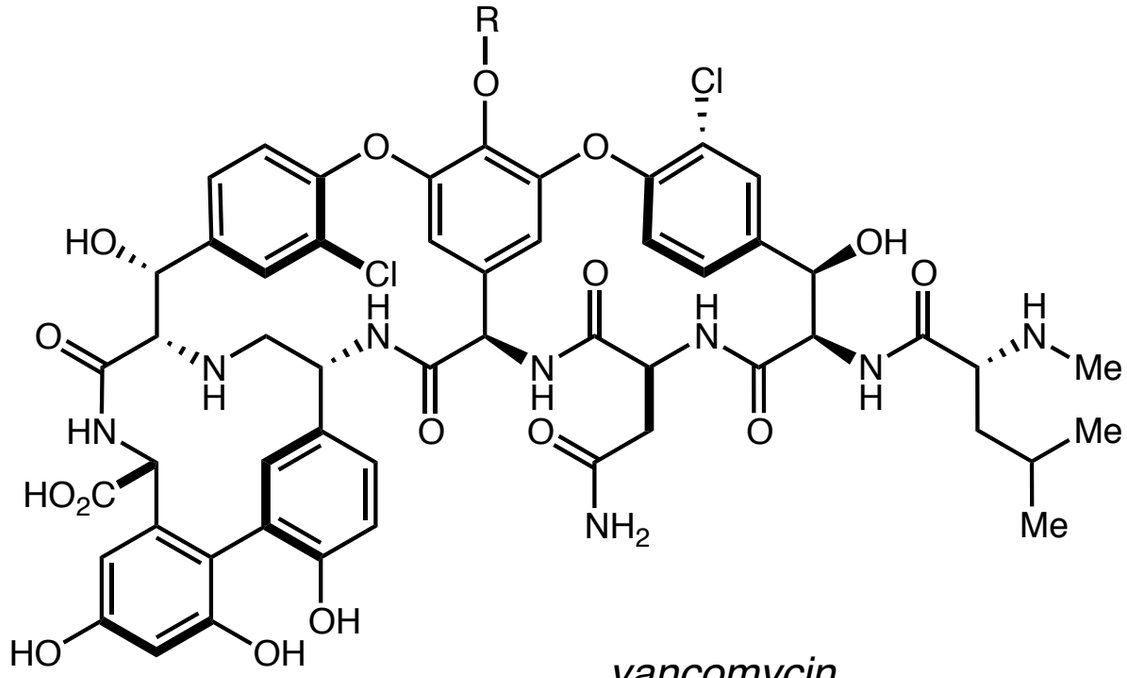
Stuart Schreiber



bryostatin 1



prostratin



vancomycin

The Future of Total Synthesis

final thoughts

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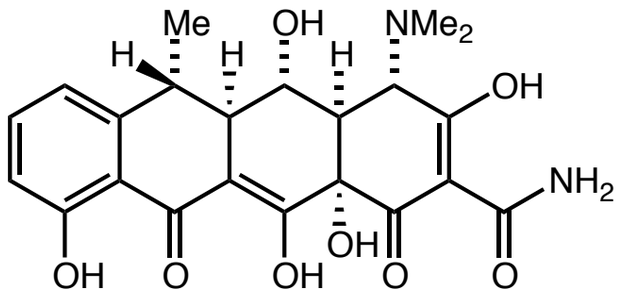
Andrew Myers (1986)

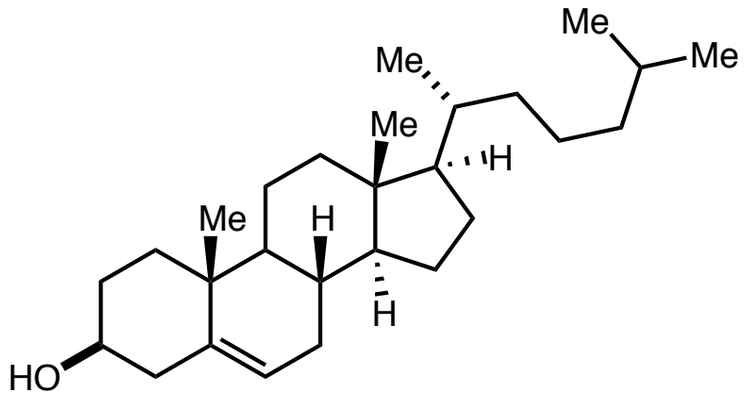
Scott Rychnovsky (1988)

Peter Wipf (1990)

John Wood (1993)



doxycyclin



cholesterol

The Future of Total Synthesis

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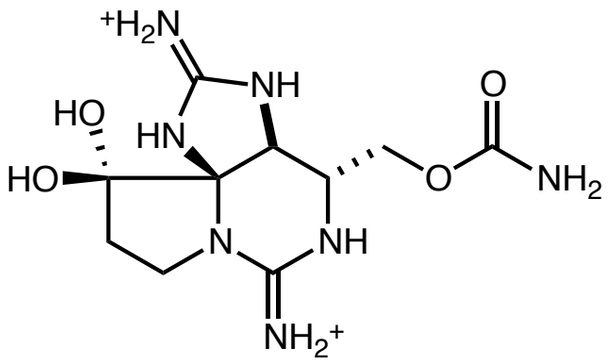
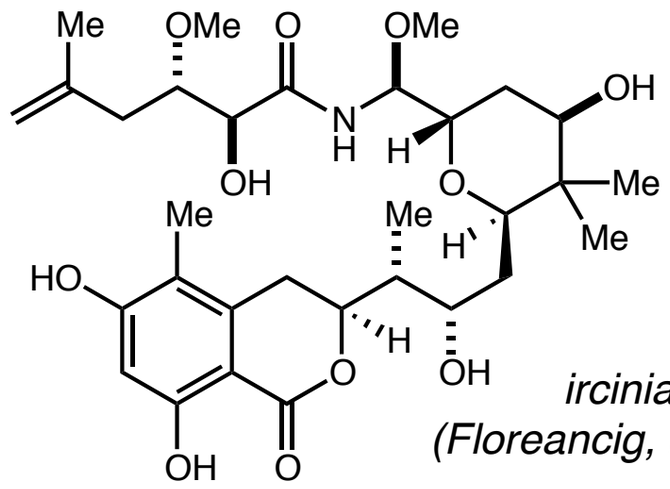
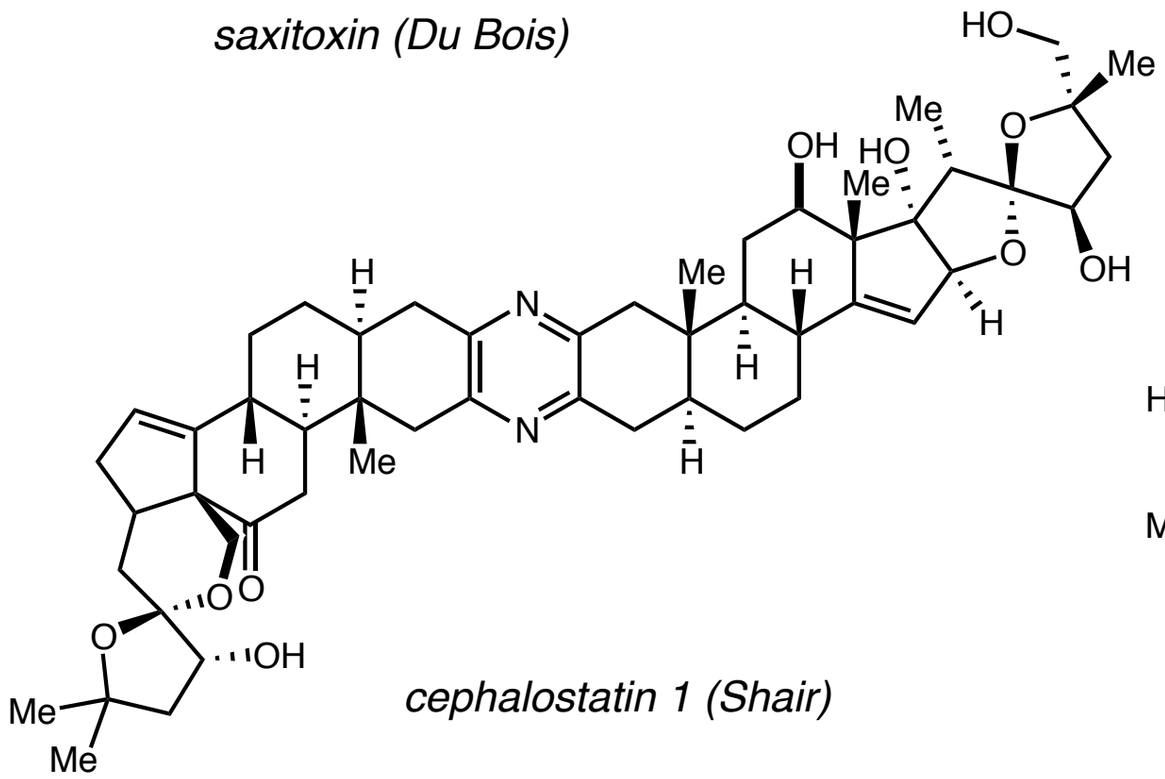


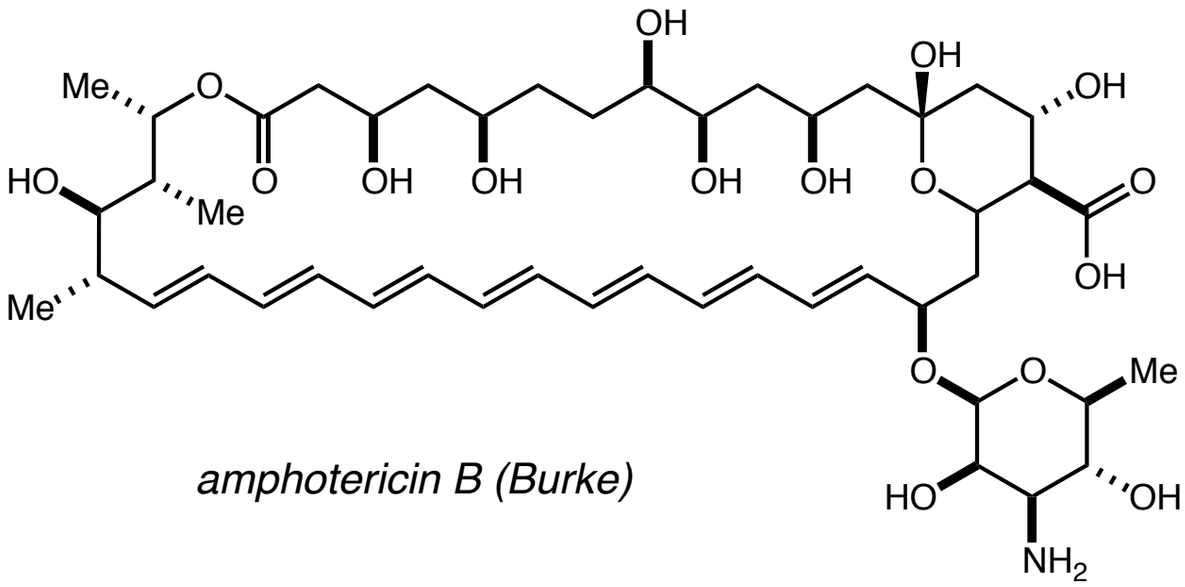
saxitoxin (Du Bois)



irciniastatin A (Floreancig, De Brabander)



cephalostatin 1 (Shair)



amphotericin B (Burke)

The Future of Total Synthesis

final thoughts

- If the overall goal is for chemistry to benefit society and if natural products are to play a role...
  - Continuing to strive for new reactions will deliver increasingly complex targets in short order
  - Applying methods in complex settings will lead to better and more useful methods
  - Focused efforts toward fewer targets will lead to better targets and more active areas of research
- Whether or not total synthesis directly benefits society, and thus it's future, depends on the targets we choose and what we choose to do with those targets...

The Future of Total Synthesis

final thoughts

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which is entirely up to us