

The Role of Thioureas in Total Synthesis

Group Seminar

Friedhelm Dreßler

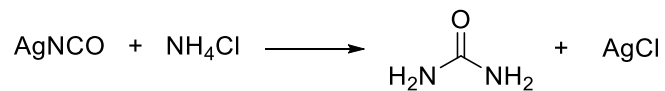
24.04.2020

Institute of Organic Chemistry, Justus Liebig University Giessen





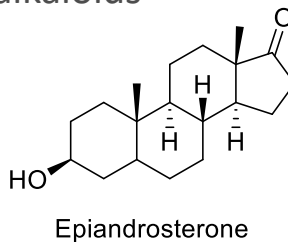
- F. Wöhler: 1828 synthesis of urea with inorganic starting material



→ start of Organic Chemistry

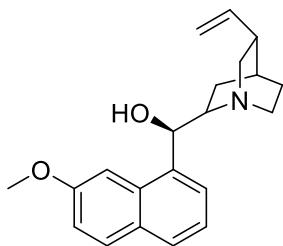


- R. Robinson: 1948 Nobel Prize “for his investigations on plant products of biological importance, especially the alkaloids”

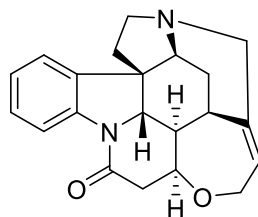




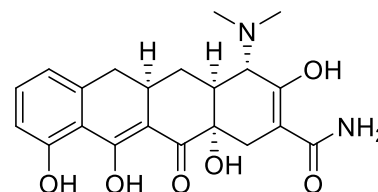
- R. B. Woodward: 1965 Nobel Prize “for his outstanding achievements in the art of organic synthesis”



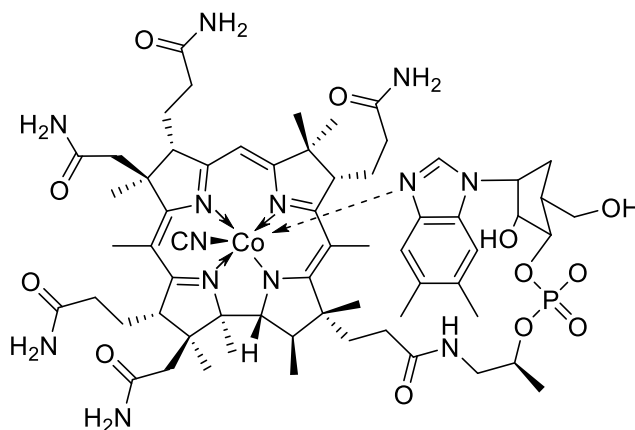
Quinine



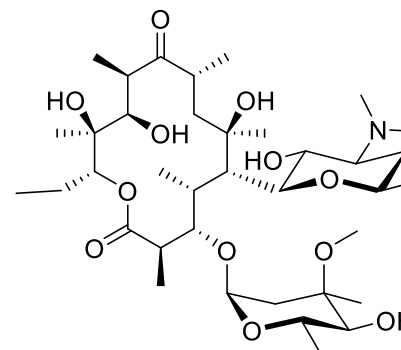
Strychnine



Tetracycline



Vitamine B₁₂

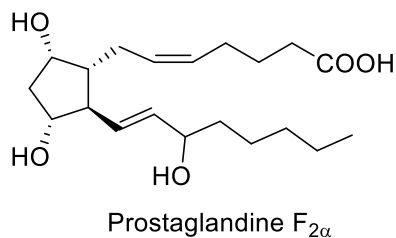
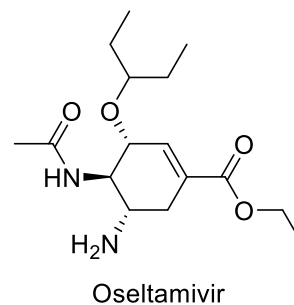
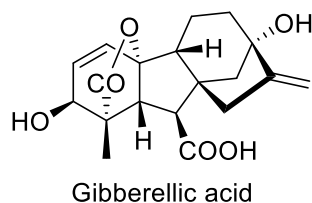


Erythromycin

R. B. Woodward, W. E. Doering, *J. Am. Chem. Soc.* **1944**, *66*, 849-849; R. B. Woodward, M. C. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *J. Am. Chem. Soc.* **1954**, *76*, 4749-4751; R. B. Woodward, M. C. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *Tetrahedron* **1963**, *19*, 247-288; Erythromycin: R. B. Woodward, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B. W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3210-3213; R. B. Woodward, B. W. Au-Yeung, P. Balaram, L. J. Browne, D. E. Ward, B. W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3213-3215; R. B. Woodward, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B. W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3215-3217; L. H. Conover, K. Butler, J. D. Johnston, J. J. Korst, R. B. Woodward, *J. Am. Chem. Soc.* **1962**, *84*, 3222-3224.



- E. J. Corey: 1990 Nobel Prize “for his development of the theory and methodology of organic synthesis”





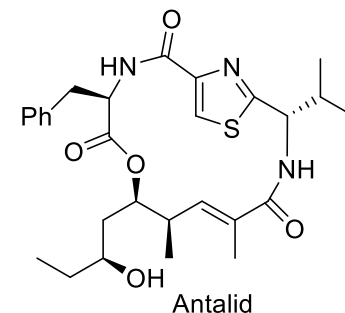
- Until the second half of the 20th century: Total synthesis the evidence of structure and configuration
- Structure analysis
 - Elemental analysis: Liebig
 - Degradation reactions: (Hofmann, Curtius, Schmidt, Lossen)
 - Erythromycin (3 years)
 - NMR (1946)
 - X-ray crystallography
 - 1964: Vitamin B₁₂ (Nobel Price D. C. Hodgkin)
 - Mass spectrometrie
 - Peptides and proteins
 - IR spectroscopy



J. Liebig, *Ann. Phys.* **1831**, 21, 1-43; P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal Jr., O. Weaver, U. C. Quarck, R. R. Chauvette, R. Monahan, *J. Am. Chem. Soc.* **1957**, 79, 6062-6070; E. M. Purcell, H. C. Torrey, R. V. Pound, *Phys. Rev.* **1946**, 69, 37-38; F. Bloch, *Phys. Rev.* **1946**, 70, 461-474; C. Brink, D. C. Hodgkin, J. Lindsey, J. Pickworth, J. H. Robertson, J. G. Whit, *Nature* **1954**, 174, 1169-1171; P. Marfey, *Carlsberg Res. Commun.* **1984**, 49, 591-596; J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, 34, 2543-2549.



- Analysis 2D-structure finished
- What's absolute configuration of stereogenic centers?
 - Mosher ester for alcohols
 - Marfey reagent for amino acids
 - $\text{Mo}(\text{OAc})_2$ and CD spectroscopy for 1,2 Diols
 - Computations
 - For PKS: Analysis of biosynthetic gene cluster (statistic model)
- Most natural products contain functional groups
 - → full structure elucidation possible!?



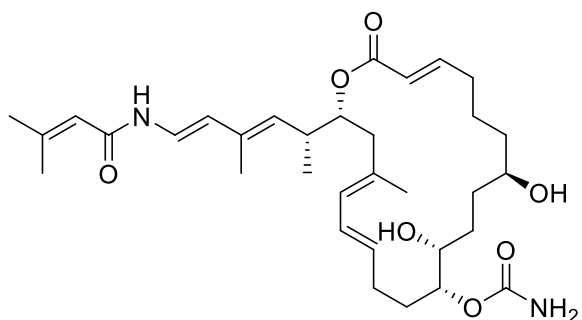
- Do we still need total synthesis for structure elucidation?

J. Liebig, *Ann. Phys.* **1831**, 21, 1-43; P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal Jr., O. Weaver, U. C. Quarck, R. R. Chauvette, R. Monahan, *J. Am. Chem. Soc.* **1957**, 79, 6062-6070; E. M. Purcell, H. C. Torrey, R. V. Pound, *Phys. Rev.* **1946**, 69, 37-38; F. Bloch, *Phys. Rev.* **1946**, 70, 461-474; C. Brink, D. C. Hodgkin, J. Lindsey, J. Pickworth, J. H. Robertson, J. G. Whit, *Nature* **1954**, 174, 1169-1171; P. Marfey, *Carlsberg Res. Commun.* **1984**, 49, 591-596; J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, 34, 2543-2549.

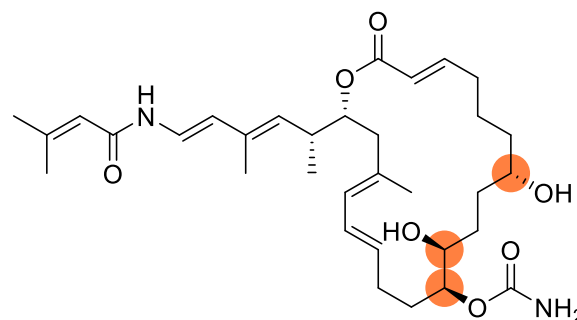
Palmerolide A



- Isolated from tunicate *Synoicum adareanum*
- Activity against melanoma cell
- Structure elucidation
 - NOE contacts → relative configuration
 - Mosher ester of C7 and bis-ester → absolute configuration
- Problem: low optical rotation
 - Compare CV spectrum with computed spectrum not possible



original proposed structure



revised structure after total synthesis

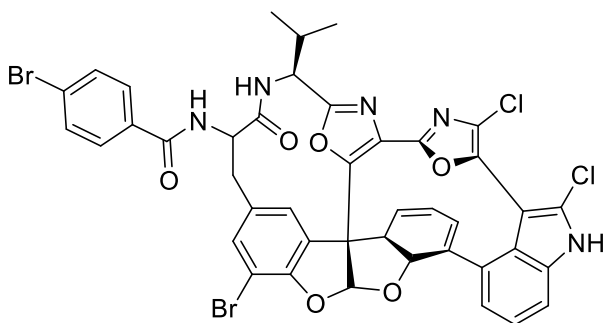
T. Diyabalanage, C. D. Amsler, J. B. McClintock, B. J. Baker, *J. Am. Chem. Soc.* **2006**, *128*, 5630–5631; K. C. Nicolaou, R. Guduru, Y.-P. Sun, B. Banerji, D. Y.-K. Chen, *Angew. Chem. Int. Ed.* **2007**, *46*, 5896–5900.

https://www.meerwasser-lexikon.de/tiere/9164_Synoicum_adareanum.htm (22.04.2020; 16:16)

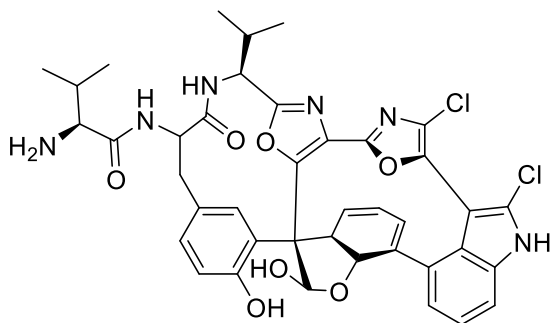
Diazonamide A



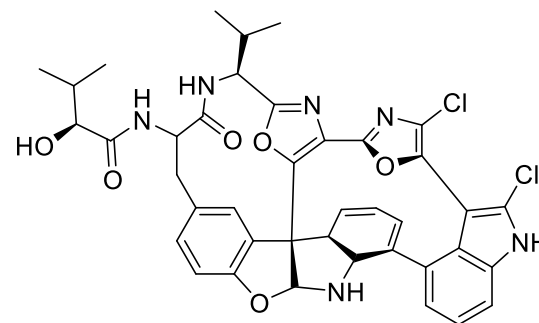
- Isolated from ascidia *Diazona chinensis*
- Anti cancer activity
- Structure elucidation *via* MS and NMR



- X-ray structure of benzoic ester derivative of Diazonamide B for X-ray analysis



postulated structure



revised structure

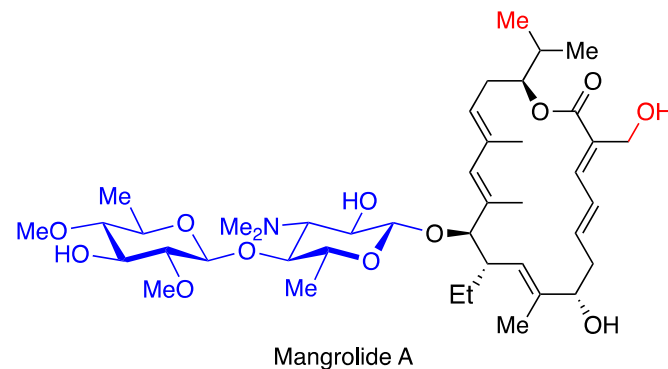
N. Lindquist, W. Fenical, G. D. Van Duyne, J. Clardy, *J. Am. Chem. Soc.* **1991**, *113*, 2303-2304; J. Li, A. W. G. Burgett, L. Esser, C. Amezcua, P. G. Harran, *Angew. Chem. Int. Ed.* **2001**, *40*, 4770-4773.

https://www.meerwasser-lexikon.de/tiere/5926_Diazona_violacea.htm (22.04.2020; 18:40)

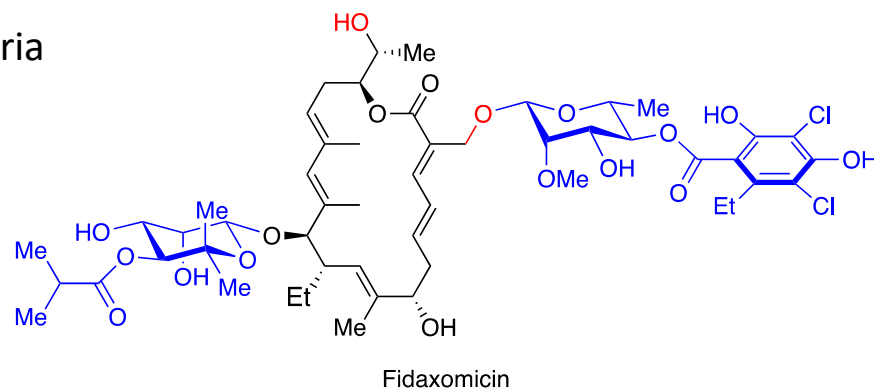


- Isolated from the SNA18 strain of *Actinoalloteichus species*

- Similar structure to FDX
 - FDX: Approved in 2011 for *C. diff.* infections
 - Bactericidal

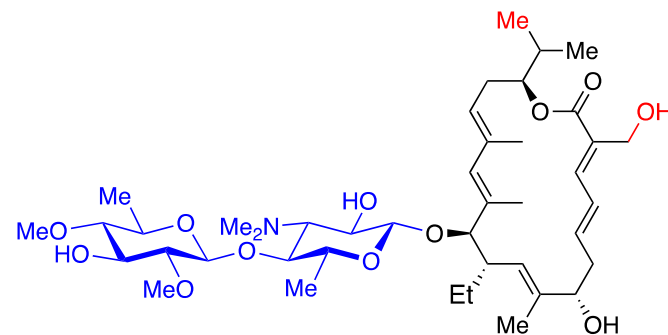


- Originale sample
 - High activity against Gram-negative bacteria
 - Acinetobacter baumannii*
 - Pseudomonas aeruginosa*
 - Fidaxomicin: only Gram-positive

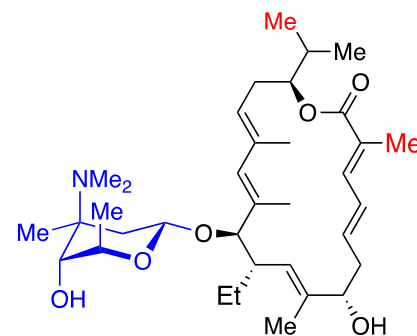




- In 2018 total synthesis by Gademann
- NMR spectrum fits to original sample
 - Synthetic compound without any activity
- New extraction of crude extract
 - Mangrolide D
- Mystery: Where is the active compound



Mangrolide A



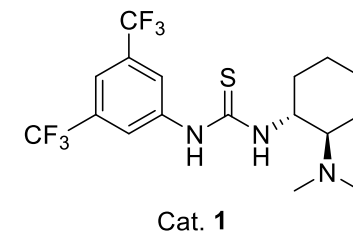
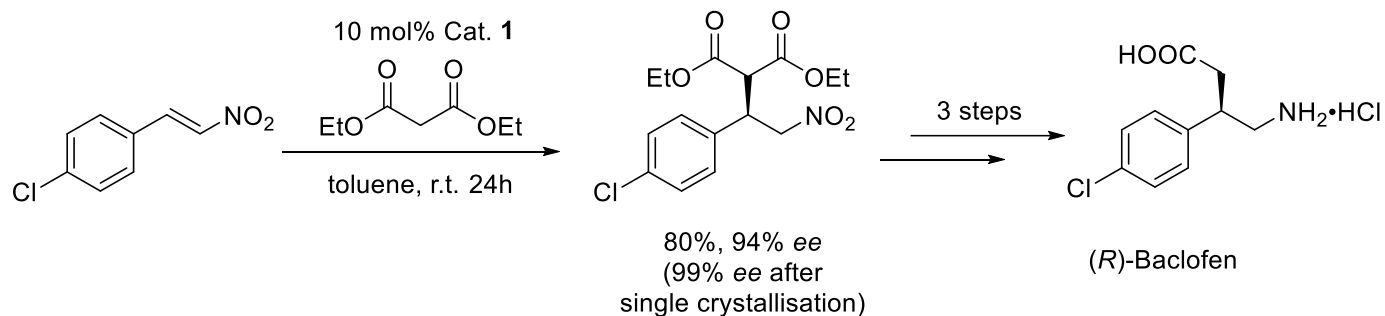
Mangrolide D

	<i>Acinetobacter baumannii</i>	<i>Pseudomonas aeruginosa</i>
Mangrolide A (isolated)	0.25	1.0
Mangrolide A (synthesized)	>16*	>16*
Fidaxomicin	>32*	>32*
Mangrolide D (synthesized)	-	>256*

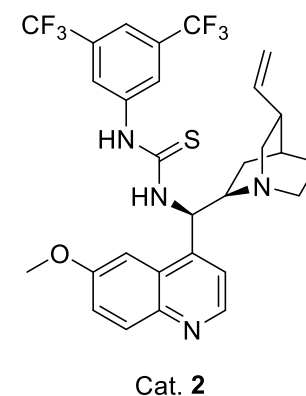
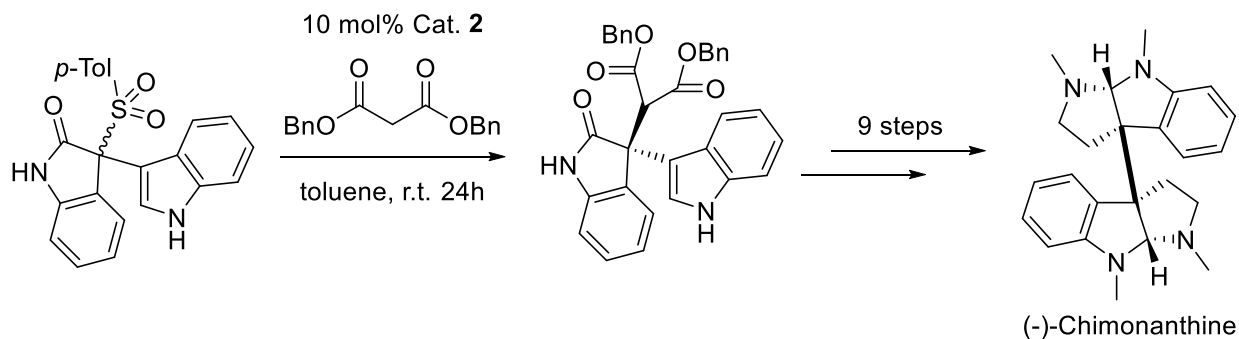
MIC in µg/mL *only tested to this concentrations



- Takemoto 2003

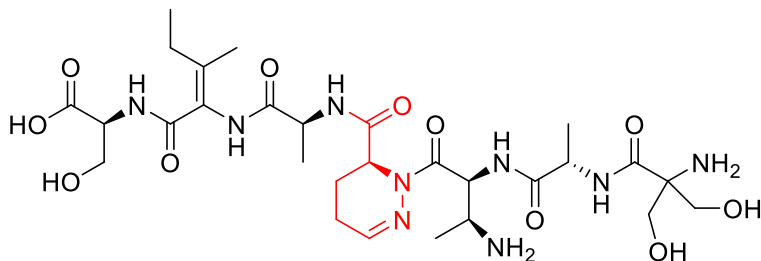


- Bisai 2018

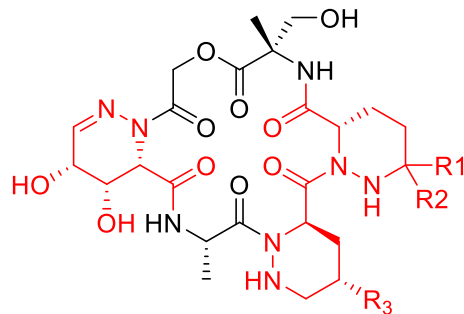




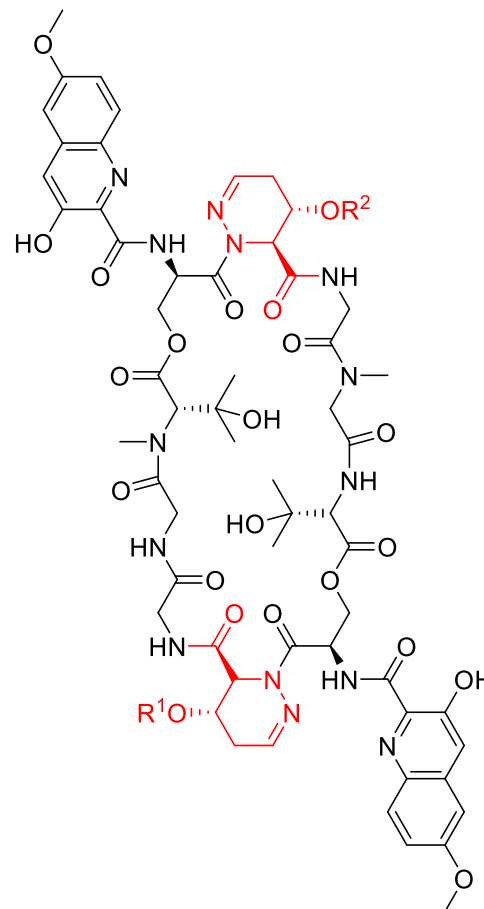
- Many compounds with bioactivity against bacteria



Antrimycin A



Svetamycin A	R1 = R2 = H	R3 = Cl
Svetamycin C	R1 = R2 = Me	R3 = Cl
Svetamycin I	R1 = R2 = Me	R3 = Br



Luzopeptin A: R¹ = R² = Ac

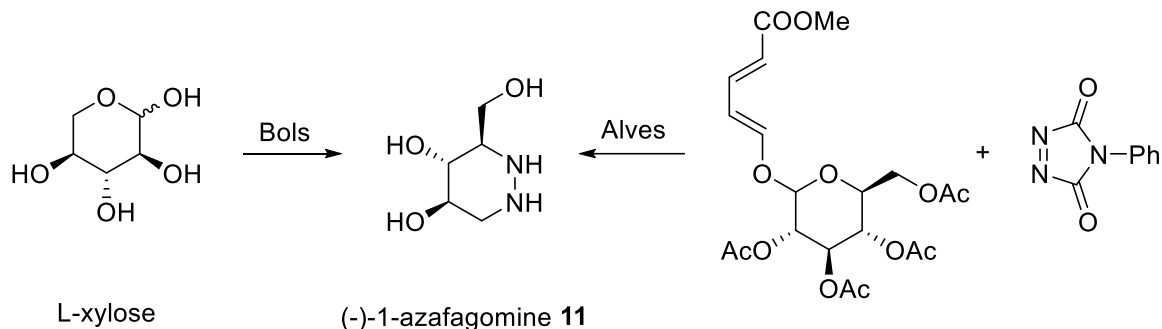
Luzopeptin B: R¹ = Ac, R² = H

Luzopeptin C: R¹ = R² = H

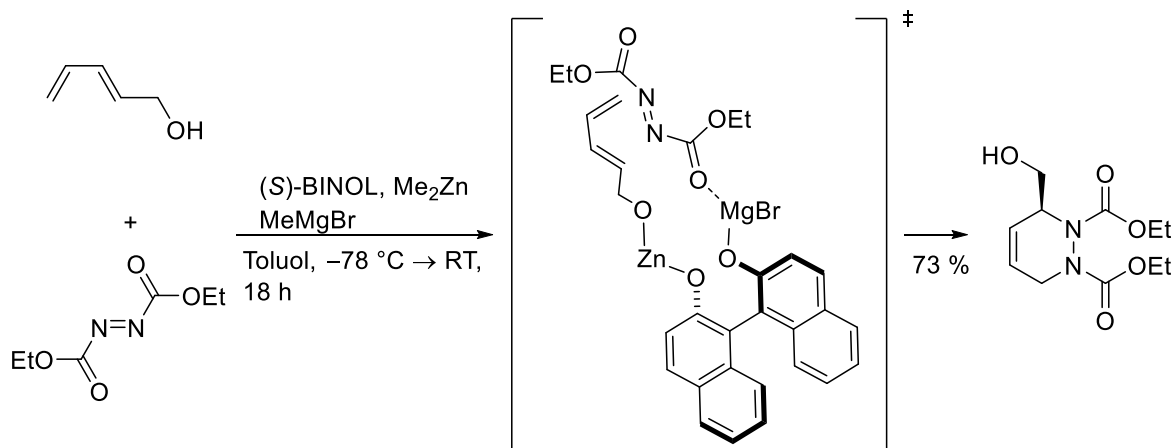
N. Shimada, K. Morimoto, H. Naganawa, T. Takita, M. Hamada, M. Maeda, T. Takeuchi, H. Umezawa, *J. Antibiot.* **1981**, *34*, 1613-1614; W. C. Rose, J. E. Schuring, J. B. Huftalen, W. T. Bradner, *Cancer Res.* **1983**, *43*, 1504-1510; D. L. Boger, M. W. Ledebor, M. Kume, M. Searcey, Q. Jin, *J. Am. Chem. Soc.* **1999**, *121*, 11375-11383; D. Dardic, G. Lauro, G. Bifulco, P. Laboudie, P. Sakhaii, A. Bauer, A. Vilcinskas, P. E. Hammann, A. Plaza, *J. Org. Chem.* **2017**, *82*, 6032-6043.



- 1-Azafagomine
 - Glycosidase inhibitor

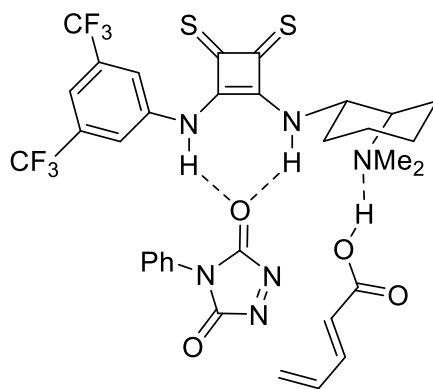


- Enantioselective synthesis by Alves





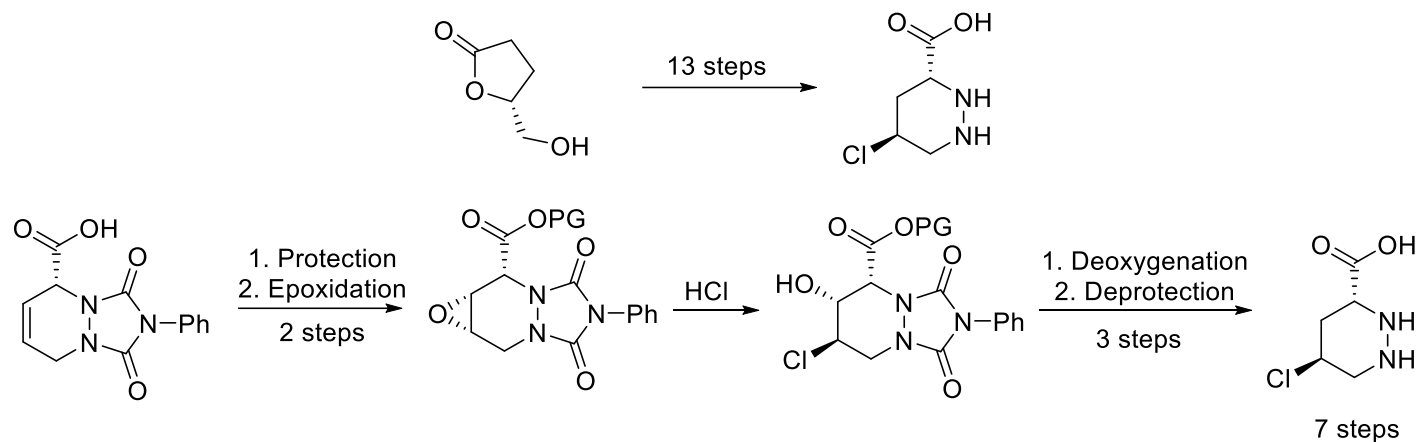
- No enantioselective synthesis of piperacic acids known
- With enantioselective synthesis → total synthesis of many peptides possible
- Working hypothesis



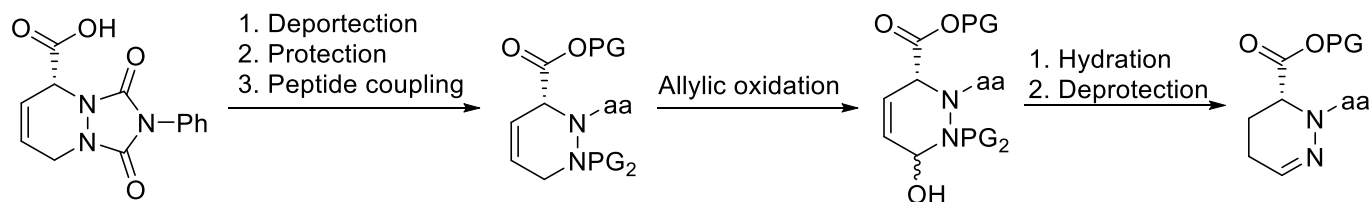
- Activation of the dienophile *via* double hydrogen bonding
- Activation of dien *via* amine moiety



- Short pathway
- Derivatization possible
- Easier synthesis of many derivatives

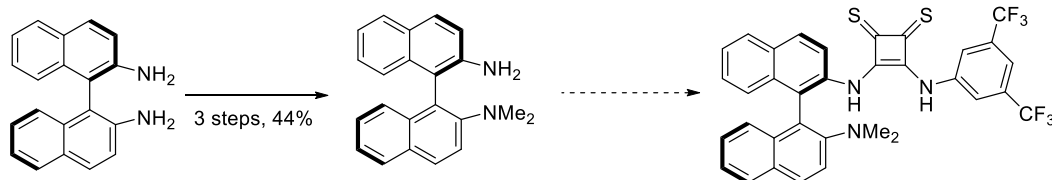
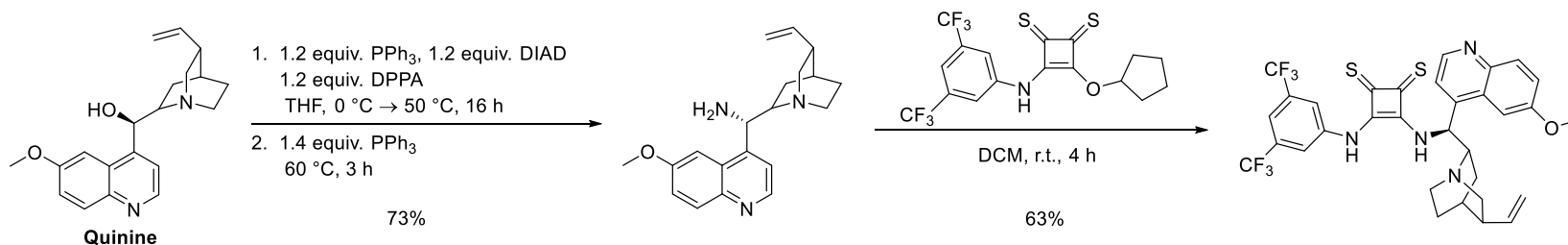
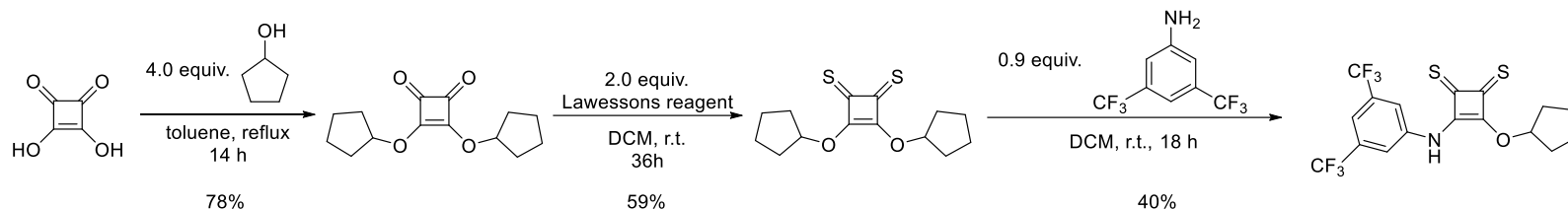


- Unsaturated derivative possible



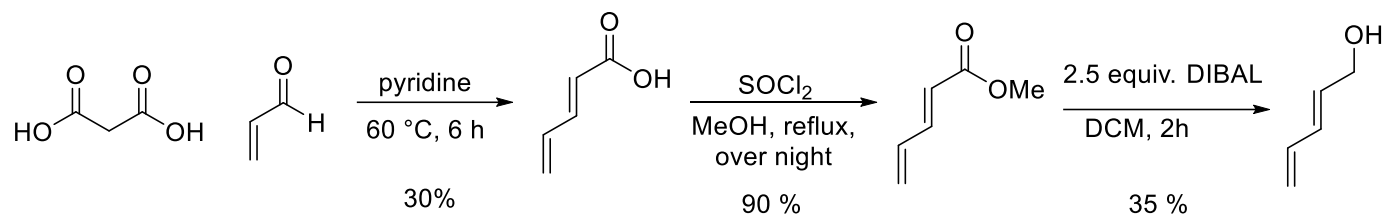


- Thiosquaramides more acidic
 - Brønsted acid

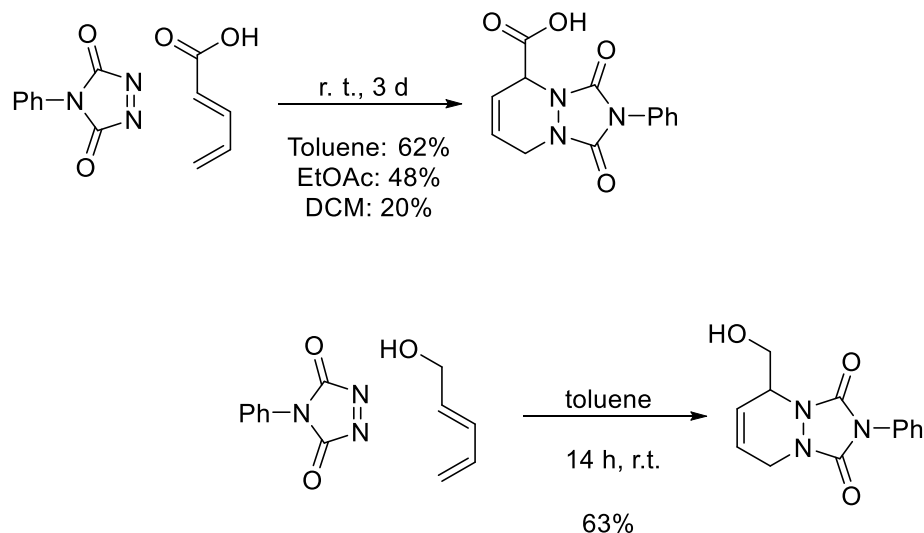




- Synthesis of dien



- Testing solvents





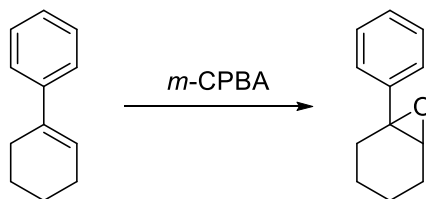
- Total synthesis:
 - Developing of many methods for organic chemistry
 - Still the evidence of structure
 - Many Nobel Prices
- Piperazic acids: many bioactive secondary metabolites
- No known enantioselective synthesis of piperacic acids
- Thiosquaramides as enantioselective catalyst in cycloaddition
- Synthesis of standards
 - Separation of enantiomers *via* HPLC successful



- Testing available thiosquaramides
- Variation of azo-dienophile: PTAD, DBAD, DIAD, DEAD
- Synthesis of more thiosquaramides
- Derivatization of amino acids
 - Epoxidation / dihydroxylation
 - Mono deprotection of amides
- Writing book chapter about “anion binding catalysis”

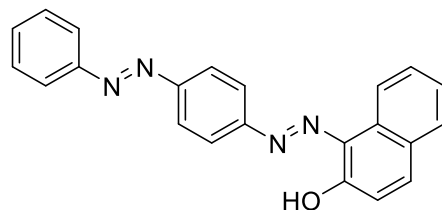


- Some guys reported problems with the Macherey silica
- Merck silica is now available (technical grade and high purify)
- Testing:

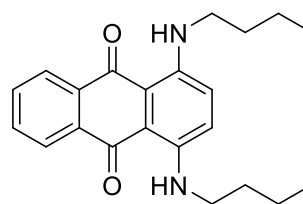


with Macherey silica: epoxide decompose on column

- Separation performance



Solvent Red 23



Oil Blue 35



- Prof. Peter R. Schreiner
- Toppi
- B205/B205
- Toppi, Lukas, Freddy, Finn
- Bastian, Gina
- Analytics and Chemical storage department
- PRS Group

