



### Some other accomplishments:

- co-authored 3 textbooks
- authored 18 review articles
- published > 300 papers
- mentored > 150 graduate students
- >50 years of tenure at UPenn

### Areas of research:

- heterocyclic chemistry
- medicinal chemistry
- natural product total synthesis
- physical chemistry
- chemical education

### Historical Timeline:

1927:



Construction of Mt. Rushmore begins

### Other events:

- US President: Calvin Coolidge
- first trans-Atlantic phone call
- Stalin takes control
- Formation of Pan-Am airways

### Cost of Living:

- new car: \$475
- loaf of bread: \$0.09
- a man's suit: \$15.85

1949:



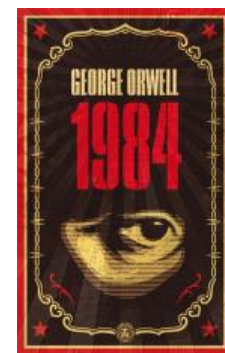
1st non-stop circumnav. of globe



first polaroid camera

### Other events:

- US President: Truman
- NATO established
- Geneva Convention
- Stalin lifts Berlin Blockade
- founding of NBA
- People's Republic of China est.



1984 is published

### Madeleine Joullié (MJ) Timeline:

- 1927: MJ was born, Paris, France
  - She grew up in Rio de Janeiro, Brazil
- 1949: B.S. Chemistry, Simmons College
- 1950: M.S. Chemistry, UPenn
- 1953: Ph.D., Chemistry, UPenn (Allen Day)
- 1953-1957: Instructor, UPenn
- 1957-1959: Research Associate
- 1959-1968: Assistant Prof. of Chemistry
- 1965 Fullbright lecturer, Rio de Janeiro
- 1968-1974: Associate Prof. of Chemistry
- 1975-present: Full Professor
- Visiting professorships:
  - Columbia (1968)
  - Grenoble, France (1987)
  - UC Santa Barbara (1989)
  - Cambridge (1997)
  - TSRI, Nicolaou (1998)

1953:



Coronation of Queen Elizabeth II

First color television,  
\$1,175

### Other events:

- cigarettes are reported as carcinogenic
- first polio vaccine
- end of Korean war
- Soviet H-bomb



- Franklin, Wilkins, Watson and Crick reveal double helix.

### Select Awards:

- 1978: ACS Garvan Award
- 1985: Scroll Award
- 1994: ACS Henry Hill Award
- 1998: ACS Award for Encouraging Women into Careers in the Chemical Sciences
- 2001: 76 Smartest People in Philadelphia
- 2002: Arthur C. Cope Award

1975:



Microsoft is founded.

### Other events:

- Vietnam war ends
- US Pres. Ford

### Cost of living:

- new car: \$4250
- sport coat: \$32
- new house: \$11,800



first 'mobile' phone

"I wanted to do chemistry because I thought I could save the world" - MJ

## MJ's Early Career as a Woman in Chemistry

Grad. students at UPenn were not reticent about reminding her of her place. "Girls don't do well" in science, they told her. "At first they tried to discouraged me and made fun of me," she remembers, "but when they realized that I was doing well, they wanted to copy my class notes."

- After graduating with her Ph.D. MJ was denied a job at Dupont because they didn't hire women at the time.
- Instead she joined the faculty at UPenn (1953) as the first female in the chemistry department. She went on to become the first female tenure track chemistry professor at an American university.
- When she started, there were no women's restrooms in the chemistry building and no men would join her lab.



"My experience as a woman in chemistry, even by those days' standards, was horrible. Nobody paid attention to me, it was like I didn't exist. I didn't mind it so much because I wasn't paying attention to other people. I could do my work and that's all I cared about. But it was tough. It was all about men, and women were clearly at the bottom of the list"

"When you feel discriminated against," she says, "you should of course speak up and fight, but the thing you shouldn't do is let yourself feel hurt, because then you're playing the game of the people who are trying to put you down. Why should you help other people make you feel bad? I think what saved me is that I didn't care what other people thought. I always managed to ignore it and I think that's probably the reason that I survived. It doesn't matter what other people think, unless it is constructive criticism."

*On why reaching gender parity in organic chemistry is so slow:*

"I think the reason for that is that organic chemistry is an old science, so it's still attached to the old boys' club. Other fields have a different culture."

## A True Advocate and Mentor



MJ with UPenn's director of the Office of Equal Opportunity (1979)

- MJ served as the first affirmative action officer at UPenn and played a seminal role in recruiting women and minority faculty.
- In 1970, she served on the Committee on the Status of Women which documented the second-class standing of women on Penn's faculty, finding that < 7% of university faculty were women. Those present were underpaid and underpromoted.

"I used to say the best thing affirmative action did for women was to put a ladies' room on every floor, which is true by the way. But it's really done more than that. I think now, if they really want to, women can essentially do anything. Progress is slow, but it works."



"First, one should never be discouraged by a rocky beginning. Tomorrow is another day."

"Do not try to imitate men. Women have a different intuition and should take advantage of it."

"Enjoy each day and appreciate change and evolution. We live in an exciting time for science."

*Others on the topic of MJ:*

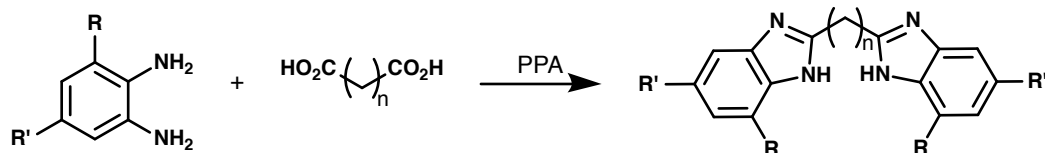
"She really cares about individual development and wants to know about her students as people.... She has the ability to create that kind of friendly atmosphere that brings out the best in most people. She's very special in that way."

"MJ is one of my personal heroes. An excellent synthetic chemist with a sense of humor that allowed her to thrive during a time when there was a scarcity of women in the field."

"In addition to being an outstanding scientist and mentor, Prof. Joullié has many unique personal qualities that make her unforgettable, the distinct voice, the lively conversation, the ever-inquisitive mind and the amazing dedication to her chemistry and teaching."

"She's a brave human being and just plain honest."

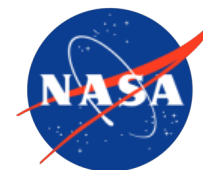
- MJ conducted pioneering work on fluorinated heterocycles. This began with work on synthesis of various bisbenzimidazoles that inhibit the growth of some yeast and bacteria. Fluorinated benzimidazoles were synthesized in 1958, followed by numerous other fluorinated heterocycles. These compounds were known to kill *E. coli*.



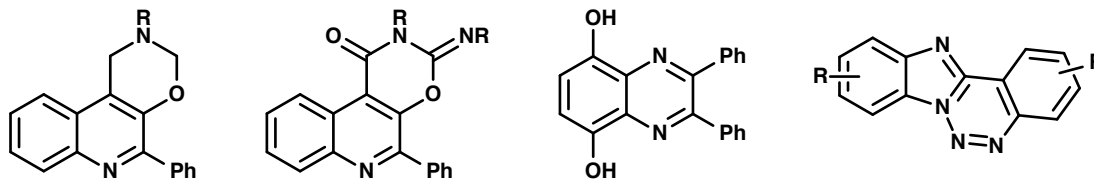
bisbenzimidazoles

J. Am. Chem. Soc., 1957, 79(21), 5706-5708 (first paper of independent career)

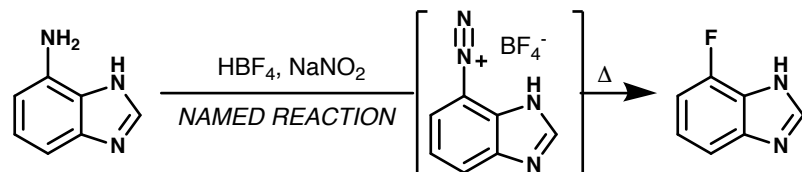
During a lot of this time, no graduate students would work with her. She worked in collab. with undergraduates until women joined the grad. program and would work with her.



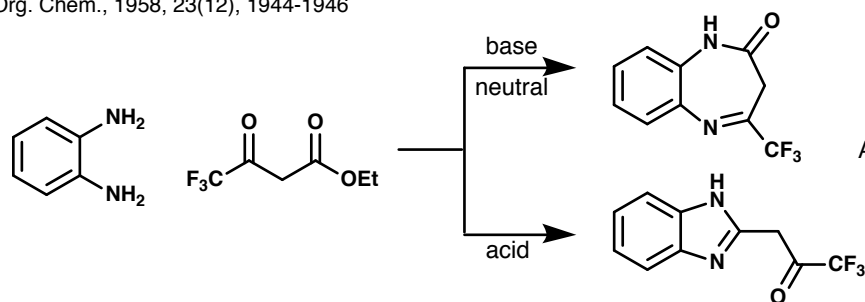
1958 - founding of NASA



## Fluorinated Heterocycles:



J. Org. Chem., 1958, 23(12), 1944-1946



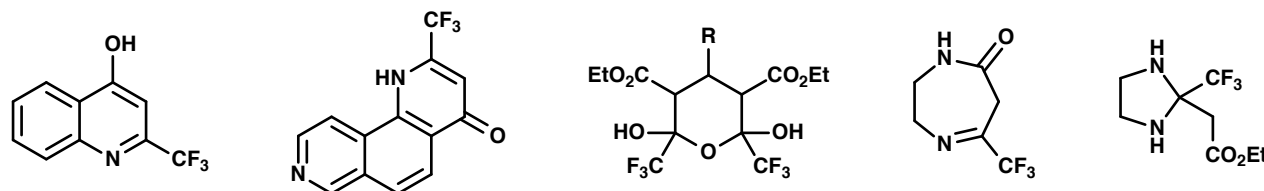
Alexei Leonov, first person to walk in space.



1965 civil rights marches from Selma, AL to Montgomery, AL.



1965 - LBJ signs Voting Rights Act



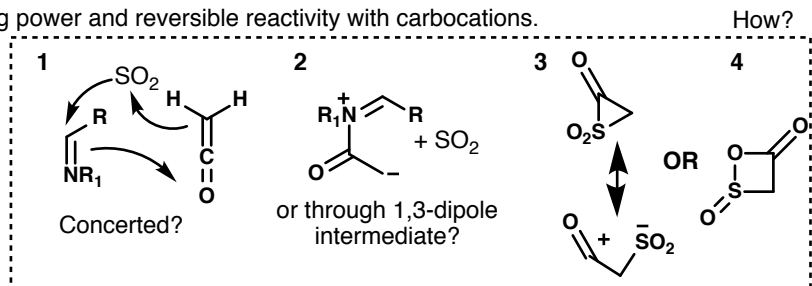
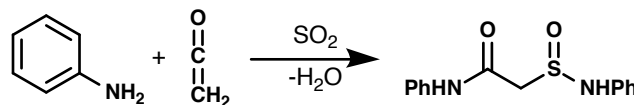
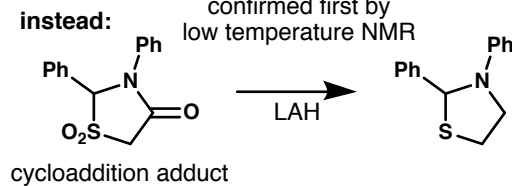
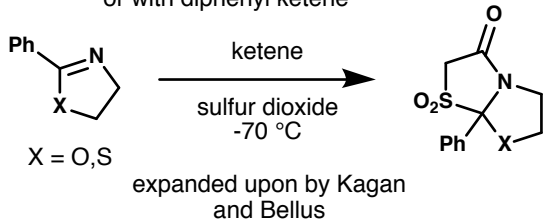
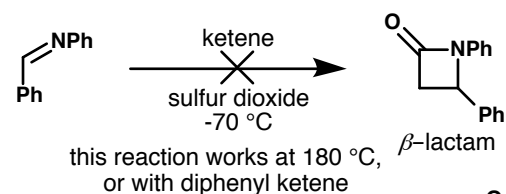
J. Am. Chem. Soc., 1959, 81(19), 5212-5215; J. Heterocyclic Chem., 1965, 2(2), 113; J. Org. Chem., 1965, 30(9), 3237

Usually tested against *Plasmodium berghei* (malaria)

# Madeleine Joullié, 60s: Ketenes and Cycloadditions

## The chemistry of a ketene-sulfur dioxide adduct:

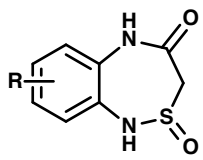
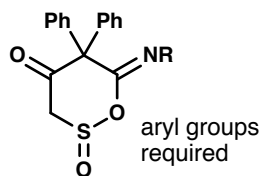
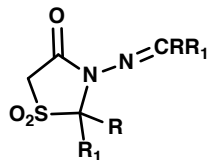
- at the time, sulfur dioxide was a widely used solvent for reactions of carbocations due to high ionizing power and reversible reactivity with carbocations.



Decomposes to SM,  
not to lactam.

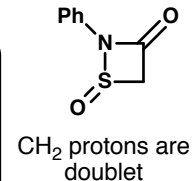
NMR of ketene in liquid  
SO<sub>2</sub> shows new singlet  
for adduct (CH<sub>2</sub>).

## Other products formed with adduct:



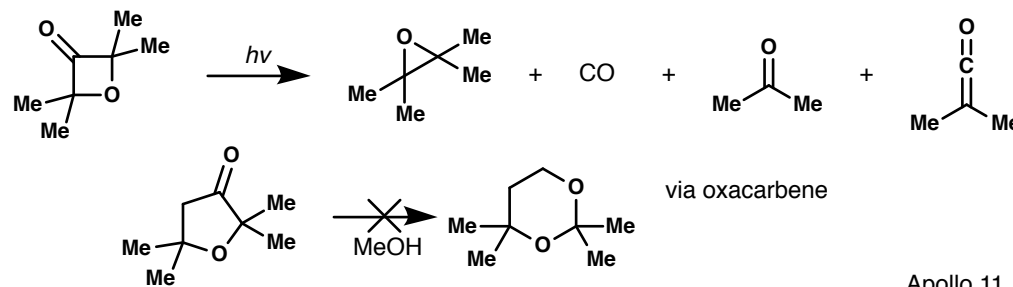
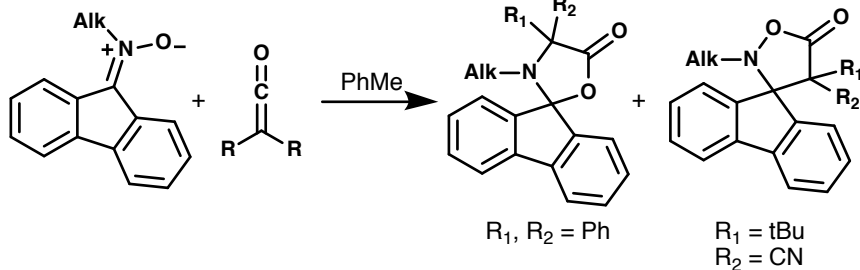
"I was trying to avoid choosing problems where there are a lot of people so I wouldn't have much competition. So I tried to work on things that nobody wanted to do. And I succeeded pretty well in that."

Gilbert Stork to MJ: "Well Madeleine, if you choose the two worst chemicals in the world to work with, you can be sure you're not going to have a lot of competition."

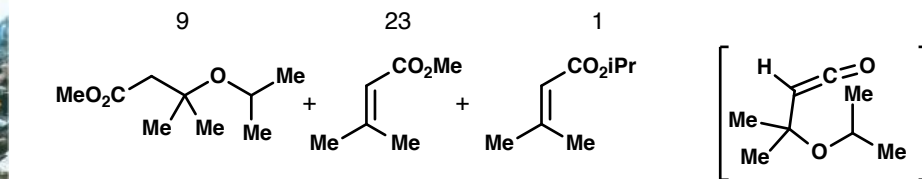


1964: first Japanese bullet train, or Shinkansen

## 1972 ACS Philadelphia Section Award, with Peter Yates: Photolysis of oxacycloalkanones



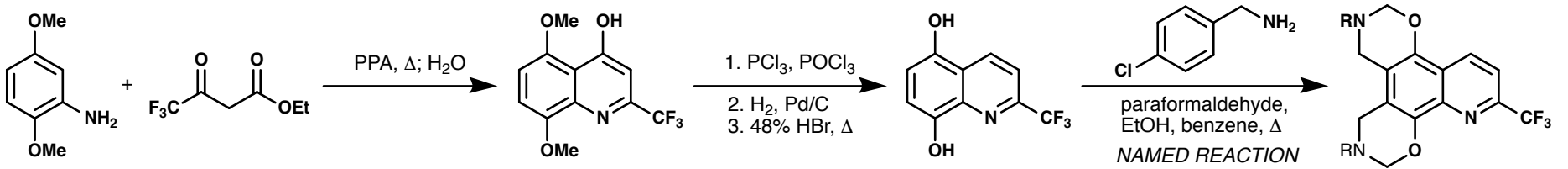
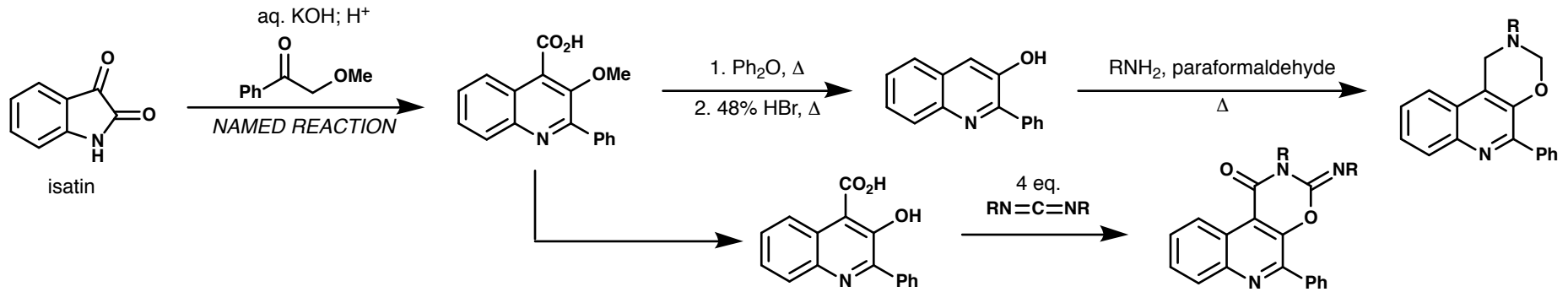
Woodstock



Chem. Commun., 1967, 936; J. Heterocyclic Chem., 1969, 6 (5), 729

Apollo 11

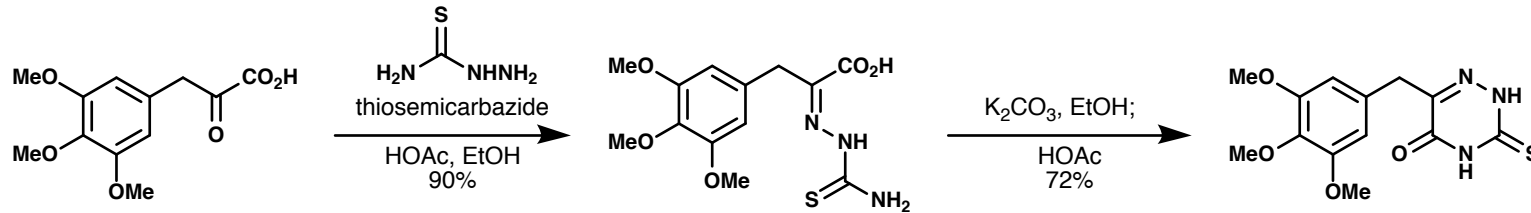




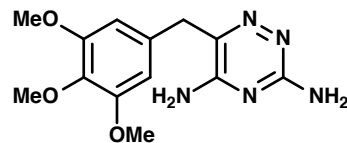
**6-aza-trimethoprim analogue and 3,5-diamino triazines:**

- Trimethoprim has been effective in cases of blood induced Vivax malaria.

significantly prolonged life of malaria infected animals

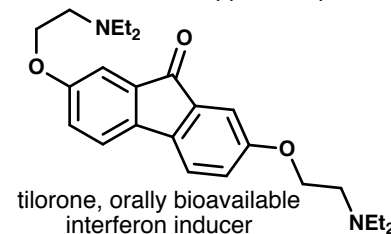


1.  $\text{P}_2\text{S}_5$ , pyridine  
115 °C, 42%  
2.  $\text{NH}_3$ , 160 °C  
MeOH, autoclave  
10%



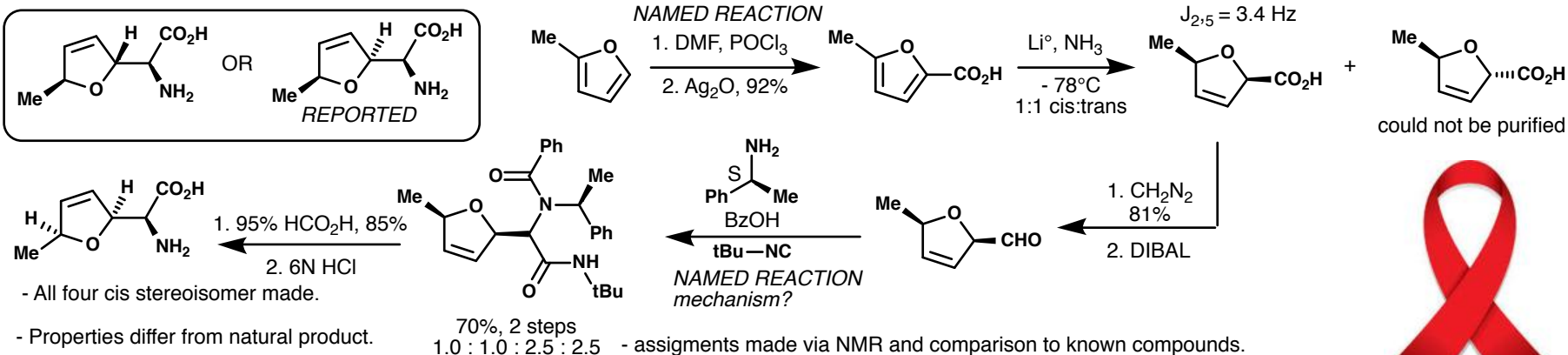
trimethoprim analogue  
unsuccessful attempts have  
been made

1976: Apple Computer Co. is formed; first NASA space shuttle (the Enterprise)  
1973, Roe v. Wade (also, Watergate hearings begin)

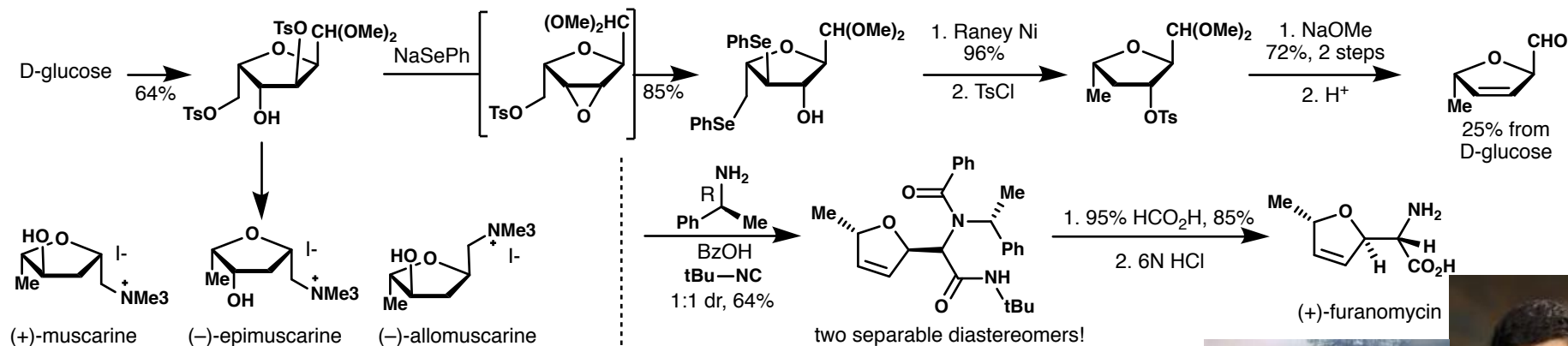


- MJ began her foray into natural products total synthesis with (+)-furanomycin and its stereoisomers. In her first report, six stereoisomers were made, leading to the structural reassignment of (+)-furanomycin and the first synthesis of the naturally occurring isomer. Previous structural assignment was made based on a single J value (6.4 Hz).
- This also marked the first use of the Ugi 4-component coupling reaction in the synthesis of a non-proteinogenic amino acid.

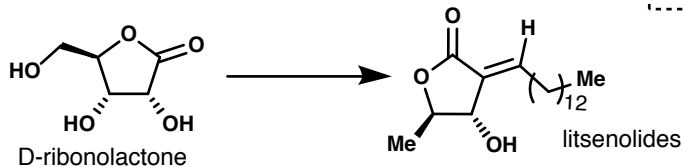
- Furanomycin is an antibiotic  $\alpha$ -amino acid with a 2,5-dihydrofuran.



## Synthesis of *trans*-furanomycins by borrowing chirality from glucose:



1980: cause of AIDS discovered to be HIV retrovirus



MJ coins 'chirality transfer' based on this work.

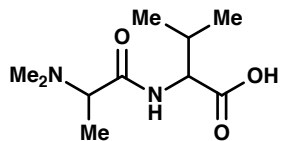
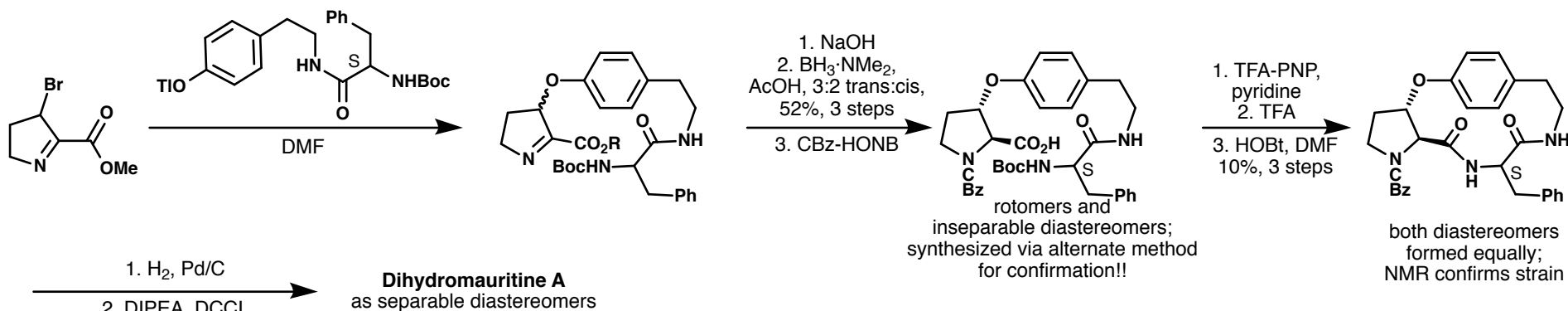
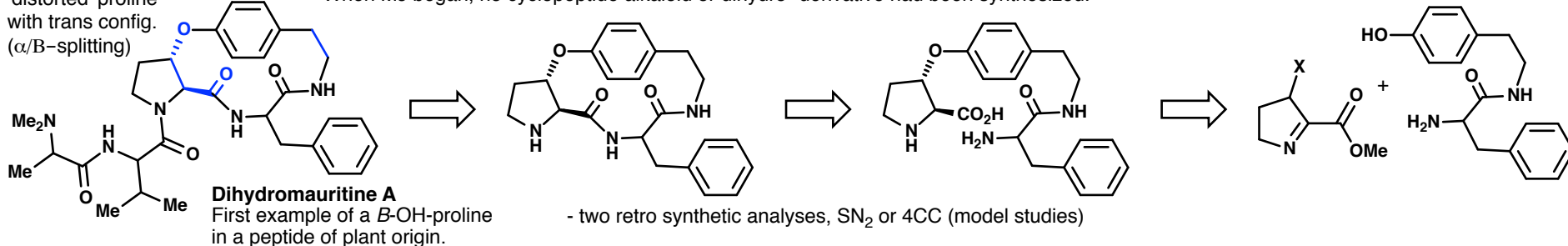
JOC, 1980, 45, 5359; JACS, 1980, 102 (25), 7505; Heterocycles, 1981, 16 (11), 1975; JOC, 1984, 49 (10), 1769



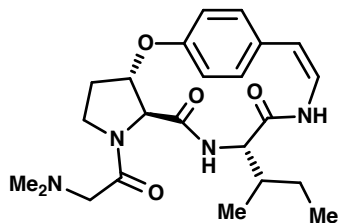
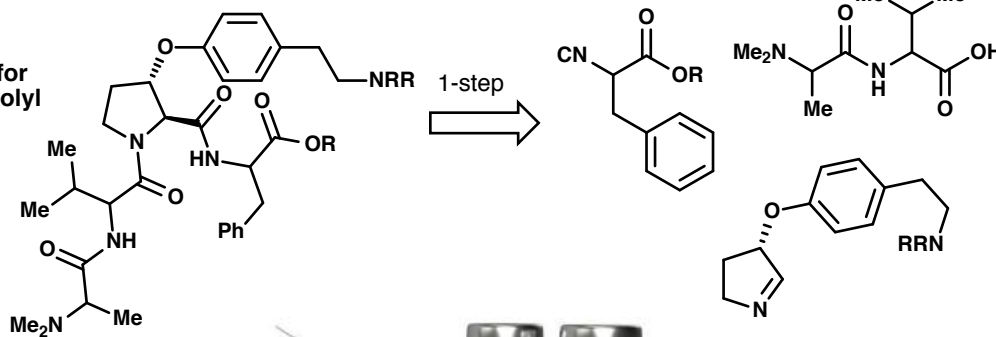
1981

'distorted' proline with trans config. ( $\alpha/B$ -splitting)

- When MJ began, no cyclopeptide alkaloid or dihydro- derivative had been synthesized.



Four component coupling for synthesis of substituted prolyl peptides:

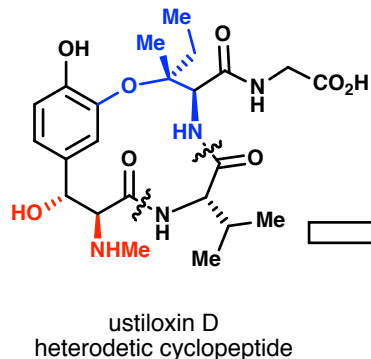


sanjoinine  $G_1$ , detoxinine, astin  $G$ ., nummularine  $F$



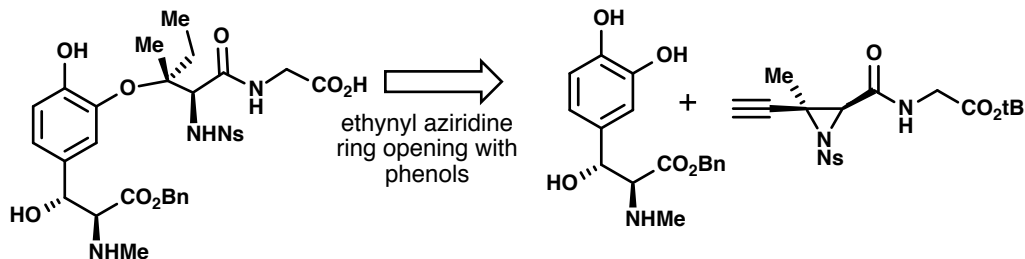
1982: first commercial genetically engineered product (Genentech)





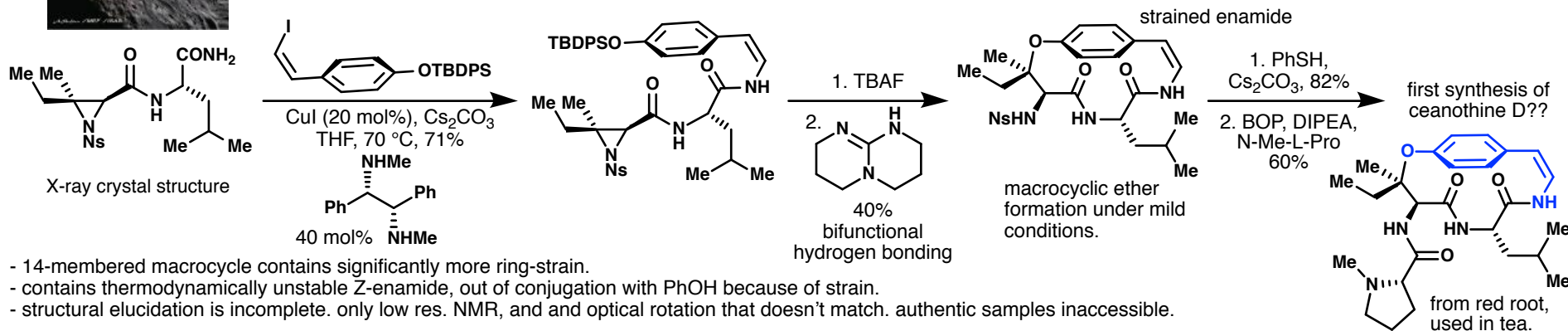
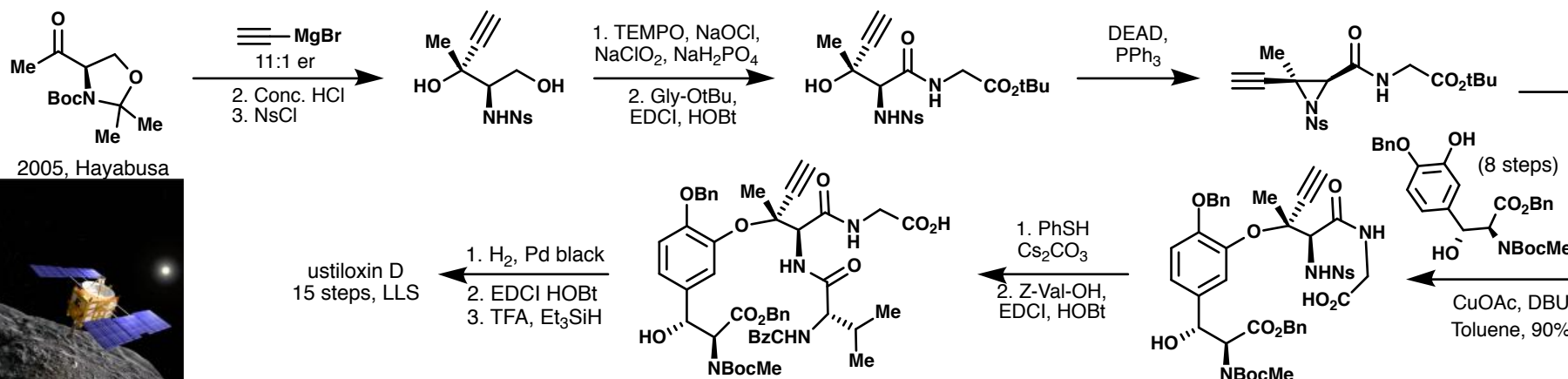
**Isolation:** false smut balls on the panicles of the rice plant caused by a fungus gave rise to ustiloxins B, C, D, and F.  
**Structural features:** 13-membered cyclic depsipeptides with unique chiral tertiary alkyl-aryl ether linkage vicinal to another stereocenter.  
**Biology:** potent antimitotic agents that strongly interferes with tubulin polymerization. In this way, they inhibit cancer cell growth.  
**Prior Syntheses:**

- First synthesis in 2001 by Joullié and coworkers in 31 steps starting from D-Serine. Tertiary alkyl-aryl ether installed via  $S_NAR$ .
- Wandless reported a 20-step synthesis in 2003 using Trost asymmetric allylic O-alkylation with Pd.



**Challenge:** convergency through late-stage stereoselective tertiary alkyl-aryl ether formation ( $S_NAR$  and Mitsunobu not suitable at late-stage, AAA gives mixture of diastereomers).

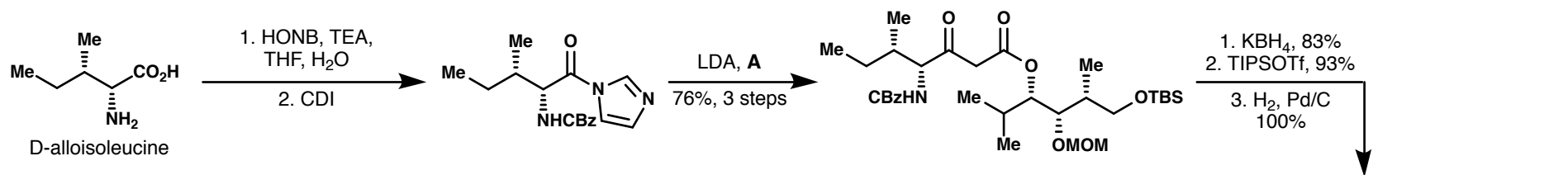
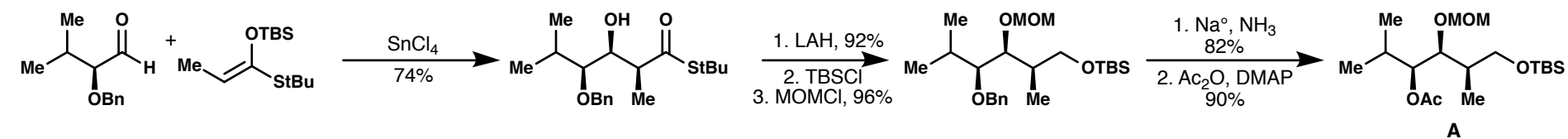
aziridine opening expanded to other functional groups.



- 14-membered macrocycle contains significantly more ring-strain.
- contains thermodynamically unstable Z-enamide, out of conjugation with PhOH because of strain.
- structural elucidation is incomplete. only low res. NMR, and optical rotation that doesn't match. authentic samples inaccessible.

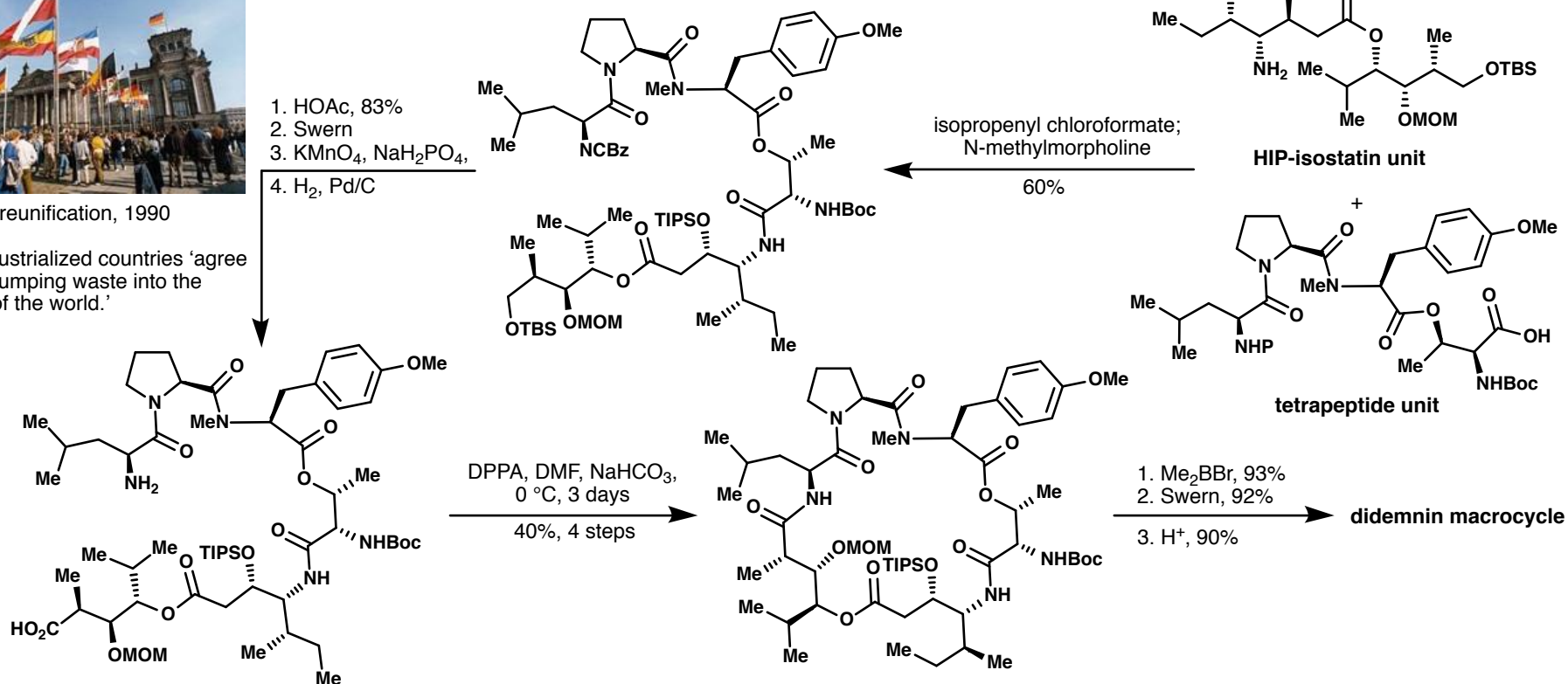


Synthesis of HIP-isostatin unit:

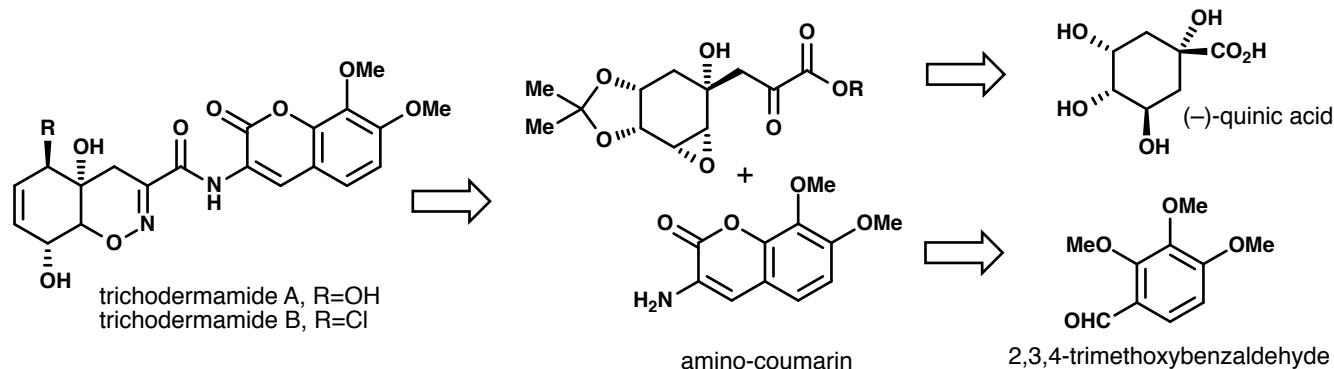


German reunification, 1990

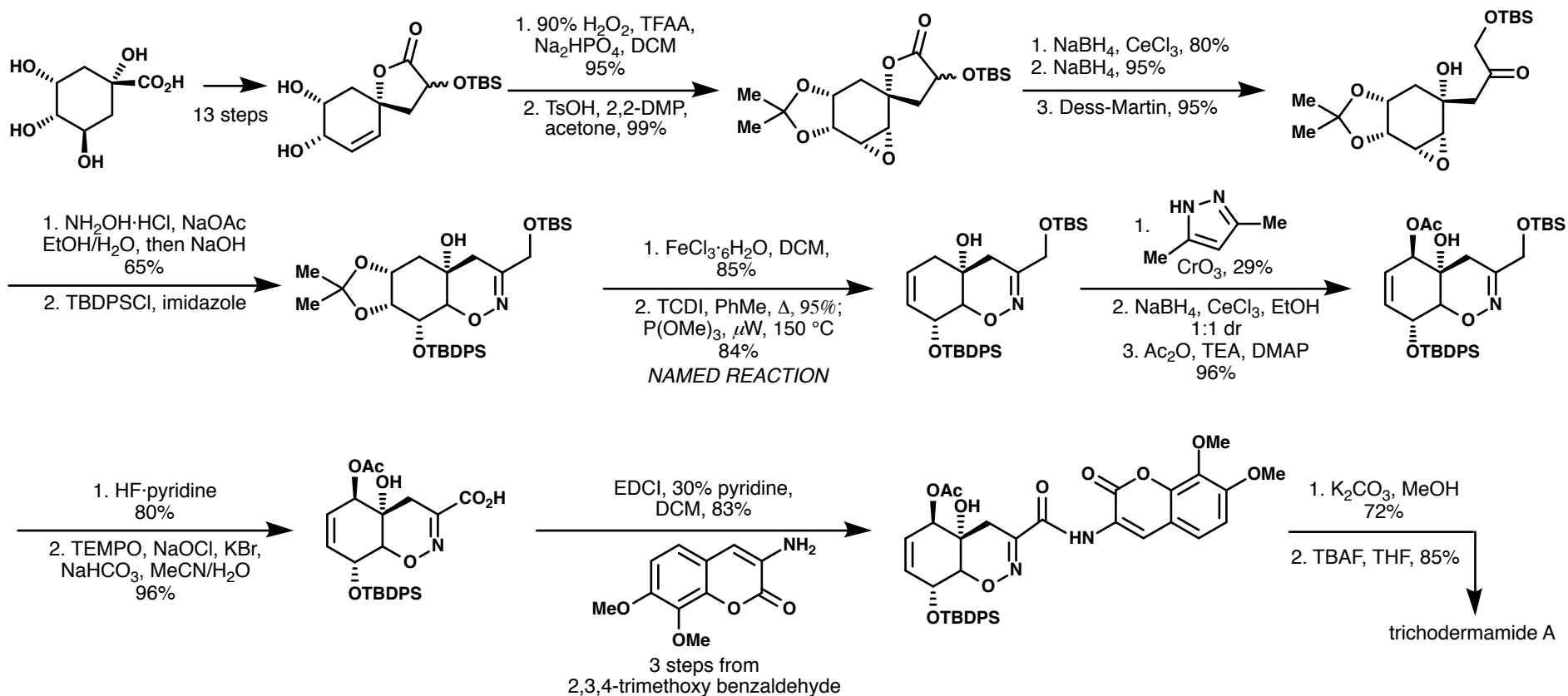
Also, industrialized countries 'agree to stop dumping waste into the oceans of the world.'



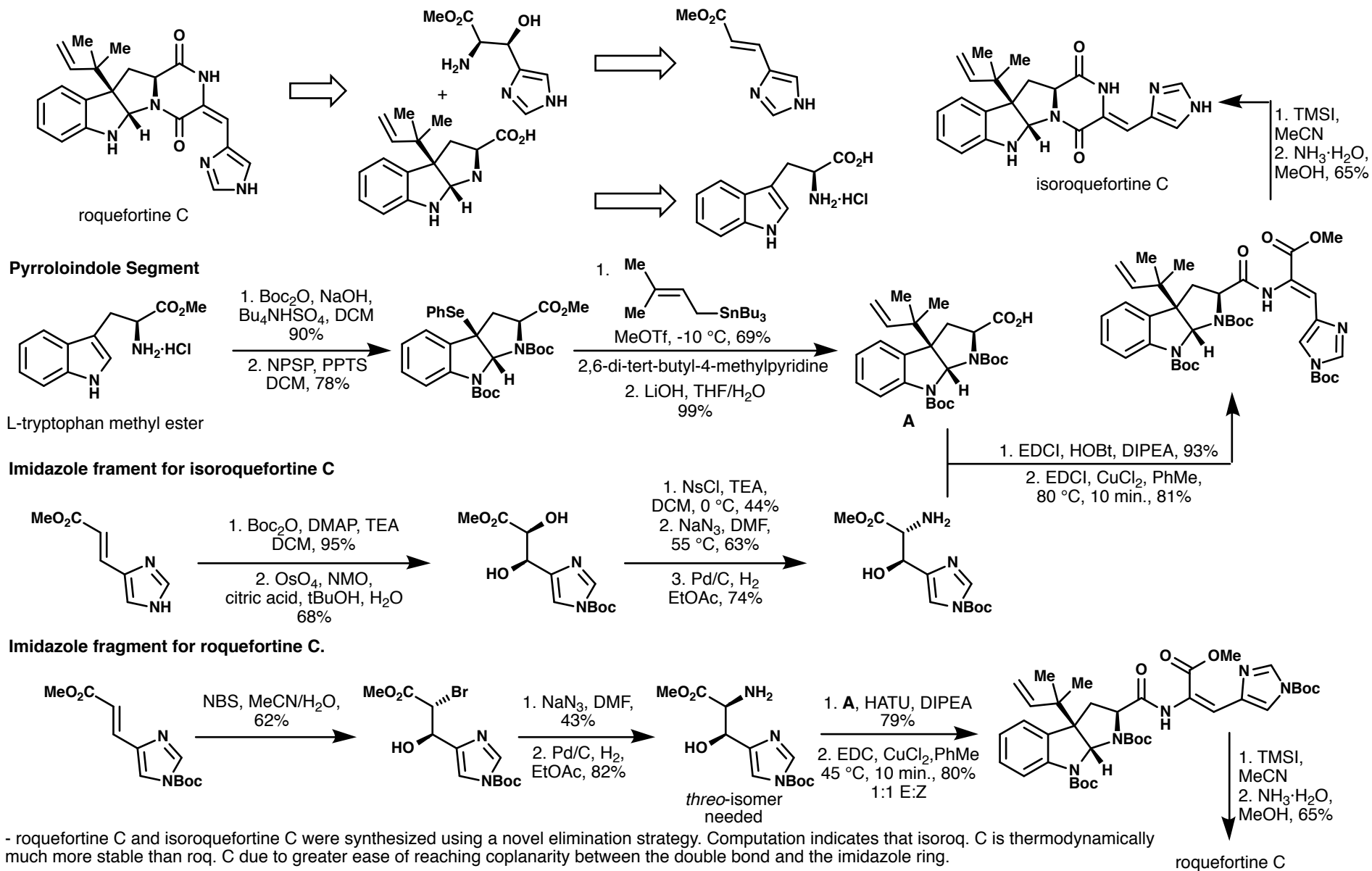
- Trichodermamides are isolated from marine fungal strains and with antitumor activity. They all possess a rare oxazine moiety.
- 1 prior racemic synthesis from Zakarian in 2008. MJ - first enantioselective syntheses.



2008 Bailout

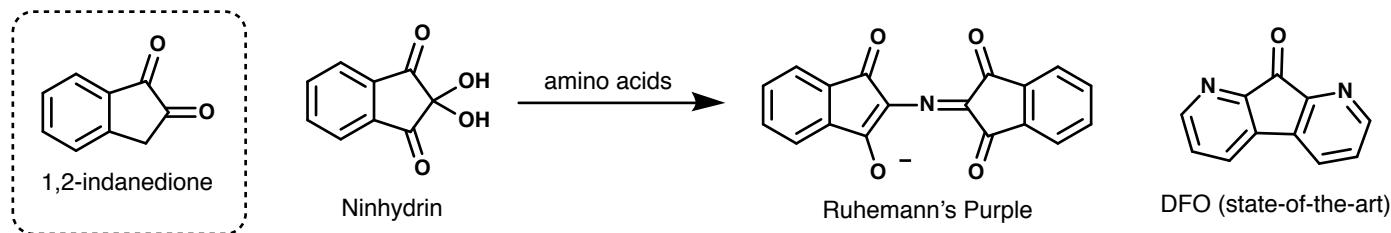


- Roquefortine and isoroquefortine are photo-isomers. The E-dehydrohistidine found in roquefortine C is unstable and undergoes facile isomerization, and for this reason roquefortine C has eluded synthesis in the past. Interestingly, isoroquefortine C is not a natural product and does not bind iron like roquefortine.
- MJ and coworkers became interested in roquefortine C because it is present in all blue cheeses, as well as some other food products, but in some studies it was shown to cause convulsive seizure in mice. However, all mouse studies were done with roquefortine C isolated from different sources and testing of pure synthetic samples is needed.



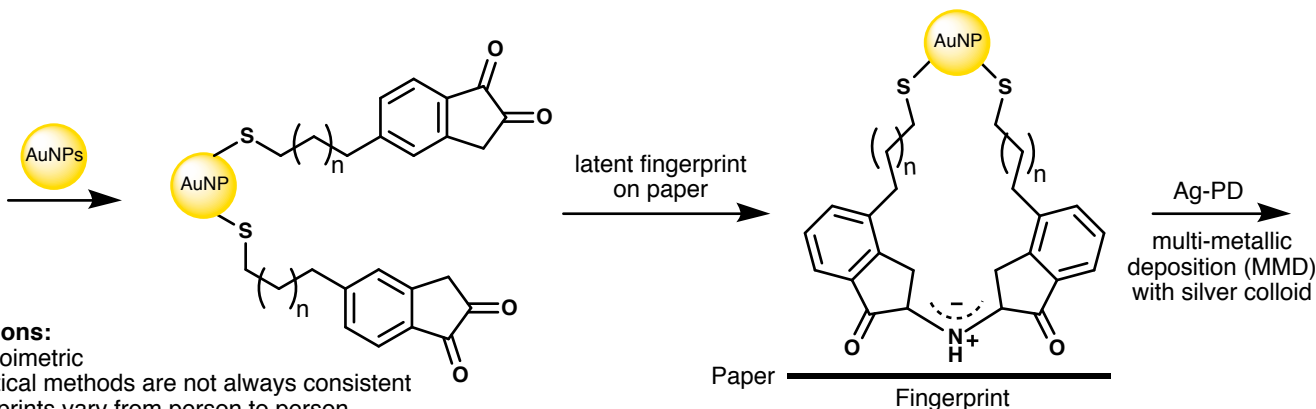
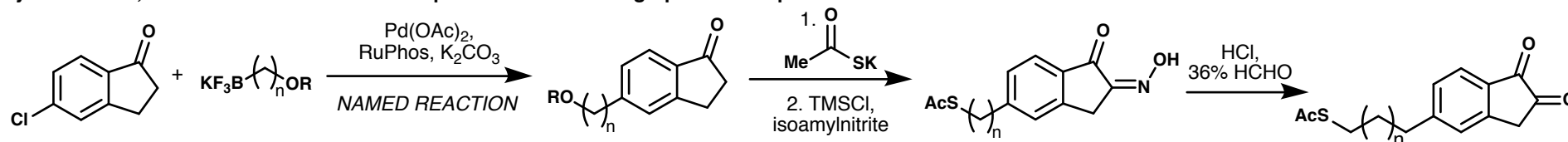
- roquefortine C and isoroquefortine C were synthesized using a novel elimination strategy. Computation indicates that isoroq. C is thermodynamically much more stable than roq. C due to greater ease of reaching coplanarity between the double bond and the imidazole ring.

- For decades, MJ and her lab worked on the synthesis of ninhydrin and its analogues with enhanced chromogenic and fluorogenic properties. Since these molecules are known to react with amino acids to produce colored products, their potential application in forensic science prompted a visit by the secret service. This led to the discovery of 1,2-indanedione as a novel and highly sensitive compound for latent fingerprint analysis. It is now actively used in criminal investigations.



1997, Titanic is released as the most expensive movie ever made (\$295 million)

### Synthesis of 1,2-indanedione derivatives and protocol for latent fingerprint development:



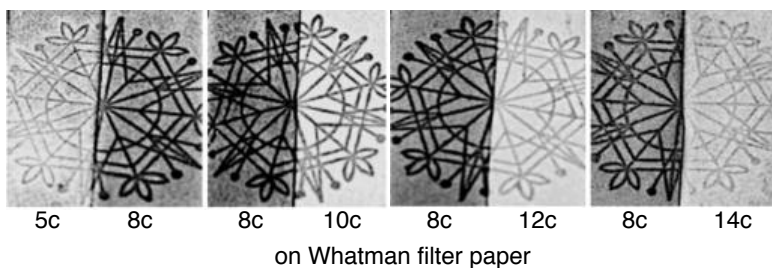
### Limitations:

- stoichiometric
- analytical methods are not always consistent
- fingerprints vary from person to person

This works best on cellulose materials such as paper and cardboard because amino acids adhere to cellulose.

### Variables:

- paper thickness and type
- aggregation state of bifunctional reagents (shorter chain  $\rightarrow$  increased aggregation)
- amount of amino acid
- age of fingerprint



“Today, students are more ‘goal-oriented’ - they just want to finish the molecule. But by doing that, you don’t look at what’s in-between... which sometimes may be more important. And I think the attitude today, with I think the whole generation - you have to have an answer, you have to finish things quickly. They don’t give themselves enough time to really look at what’s going on and enjoy what they’re doing, ok? ... it’s not as common to have them take charge of something, you know? While in the old days, they loved to take over things. They loved to be in charge. I think things have changed. It’s all because the whole society has changed...”

“The creativity of women has already changed organic chemistry....”

“I think what saved me was that I didn’t care what other people thought...”

“I worry these days about the future of chemistry. And I mean, not chemistry to solve a problem. Just chemistry because people like what they’re doing and they want to learn new things. I think that we are destroying the part of chemistry, where, people think they have an idea, it doesn’t matter if its applied to a specific thing.. but it sounds like a good idea. Later that thing might be very important. I think it’s important to give the individual chemist enough freedom and support to pursue what is interesting to them.

“We look at science today like it’s a coke machine. You put in the nickel, out comes the bottle. But science doesn’t work that way.”