A Platform for the Discovery of New Macrolide Antibiotics

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Presented by Alexander Chatterley

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The Myers Group

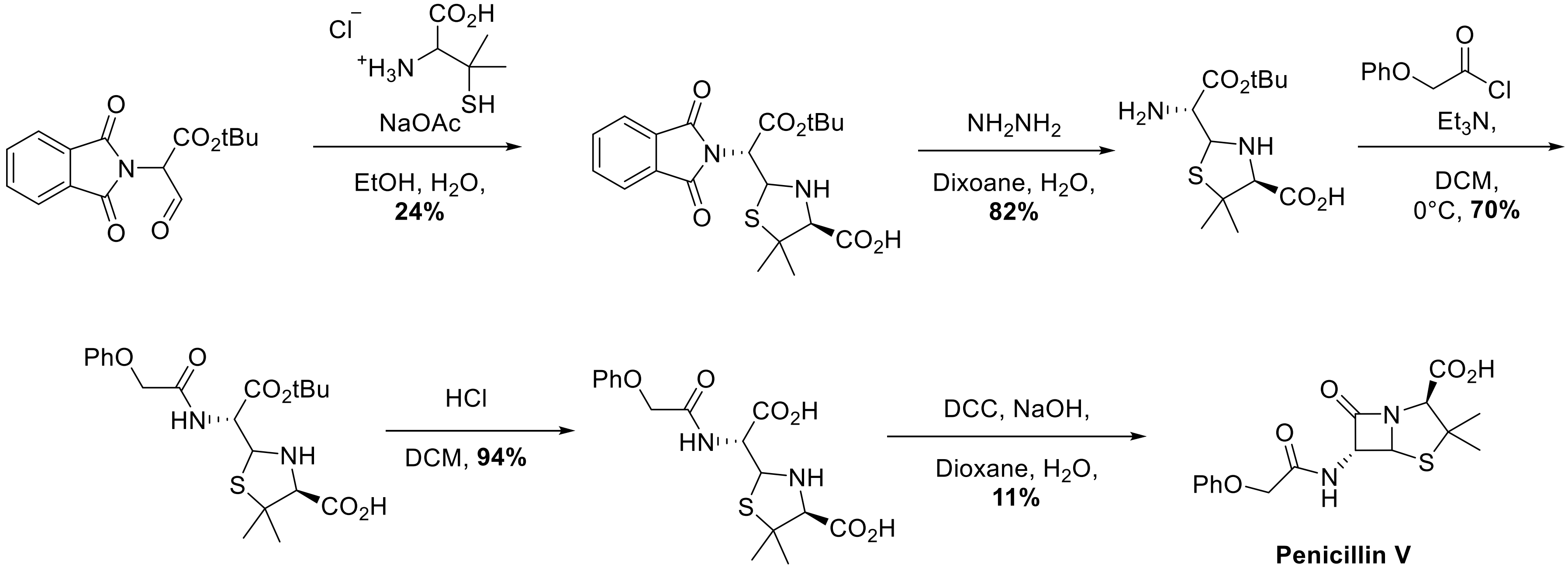
- Andrew Myers graduated from MIT 1981 with Bachelors of science. Graduate student and a brief post doc with E. J. Corey. Began independent career at Caltech (1986) then moved to Harvard in 1998.
- Comprised of 17 members (6 grad students/8 post docs/3 staff).
- Research focuses include synthesis of complex natural antibiotics and the development of methodology to aid in this.

Antibiotics

Antibiotics are one of the major corner stones of modern medicine.

- Early reports of using mould as a poultice in pre-BC times to treat open wounds by applying moulds.
- Use became more refined throughout history, particularly in the late renaissance through to early industrial. For example the use of mould by apothecaries in England to treat injuries.
- First anti-biotic isolated by British biologist Sir Andrew Fleming in 1928, arguably began the modern anti-bacterial era.
- First chemical synthesis of penicillin in 1957 by Dr Edward Sheehan (supervisor to E. J. Corey).

First synthesis of Pencillin



Antibacterial Apocalypse

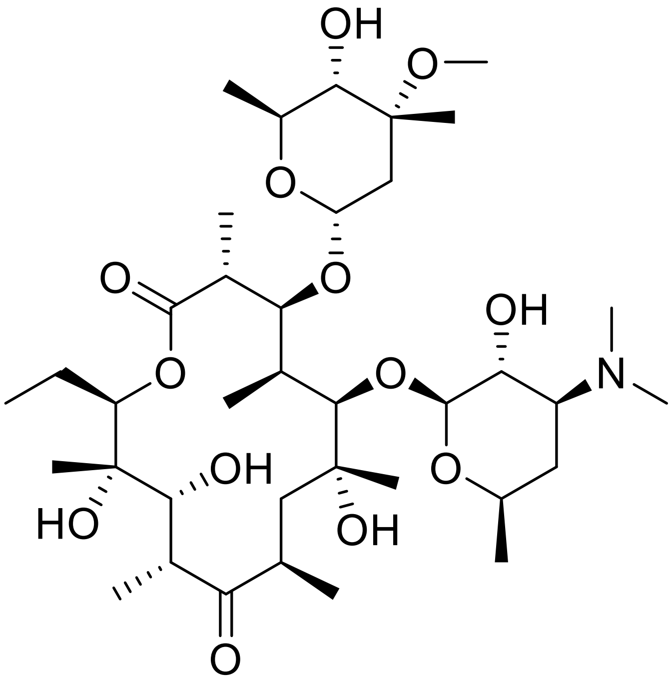
Antibiotic resistance is rapidly becoming a global health concern.

- Over use of antibiotics in people and animals has caused multiple strains of drug resistance bacteria to evolve.
- No new class of antibiotics have been discovered in the 1980's.
- Antibiotic research while crucial, is not attractive to the private sector due to the business model.

Classes of antibiotics

There are several classes of antibiotics:

- ❖ Penicillin's
- ❖ Aminoglycosides
- ❖ Carbapenems
- ❖ Cephalosporin's
- ❖ Fluoroquinolones
- ❖ Sulphonamides
- ❖ **Marcolides**



Erythromycin A

Macrolide Antibiotics

Erythromycin, one of the earliest macrolides was isolated from Philippine soil samples in 1949.

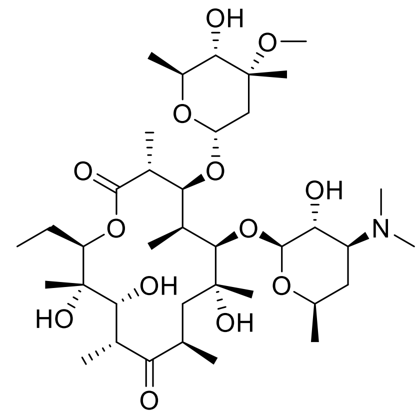
- Characterised by their large macrocyclic ring structure, Usually 14, 15 or 16 membered.
- Active against Gram-positive and to limited Gram-negative bacteria.
- Binds reversibly to the P site on the 50S subunit of the bacterial ribosome. This inhibits protein synthesis resulting in bacterial cell death.

Antibiot. Chemother. **1952**, 2, 281.; Antimicrob. Agents Chemother. **1991**, 35,2016.

Macrolide synthesis

First total synthesis of Erythromycin A was completed by Woodward in 1981.

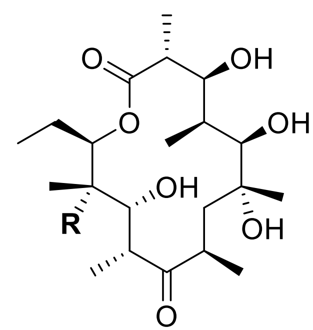
- 0.089% total yield,
- 52 steps total.
- 48 students worked on it.



Erythromycin A

Total synthesis of Erythronolide A and B carried out by Corey in 1978/9.

Again, these were very complex synthesis, involving multiple students (including K.C. Nicolaou).



R = OH A
H B

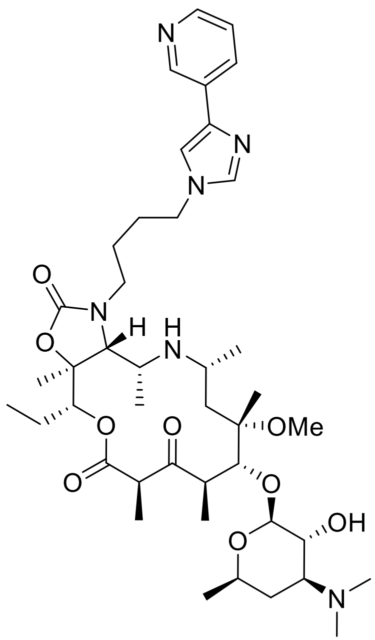
Erythronolide

J. Am. Chem. Soc. **1981**, 103, 3210, 3213 and 3215; J. Am. Chem. Soc. **1978**, 100, 4618 and 4620; J. Am. Chem. Soc **1979**, 101, 7131.

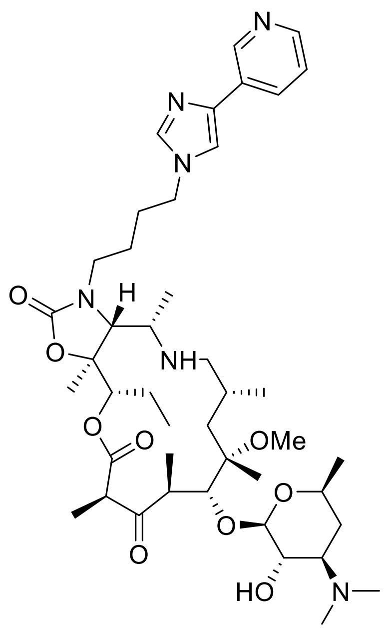
This Paper

Meyers group embarked on a quest to synthesise a library of macrolides as a platform for the discovery of new antibiotics.

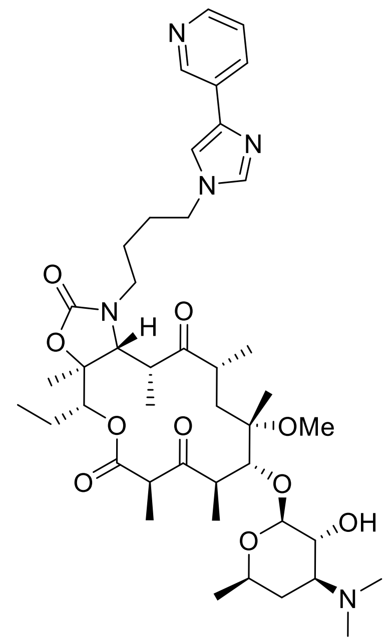
They divided this approach into three classes:



14-Membered azaketolides

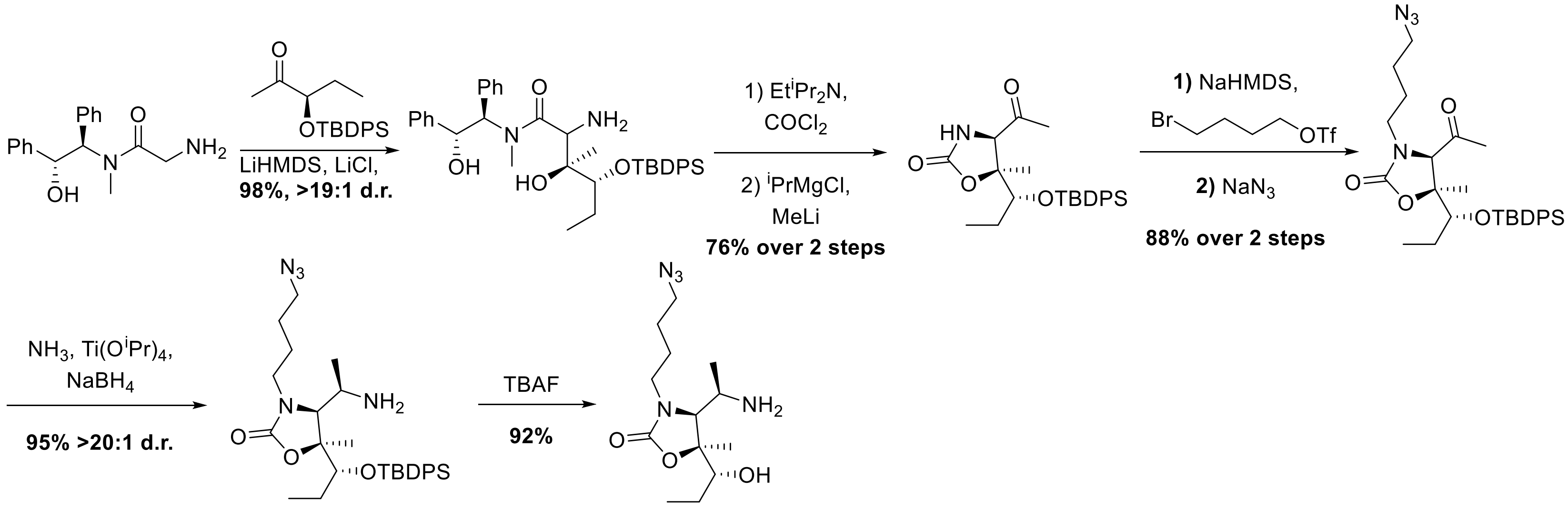


15-Membered azaketolides

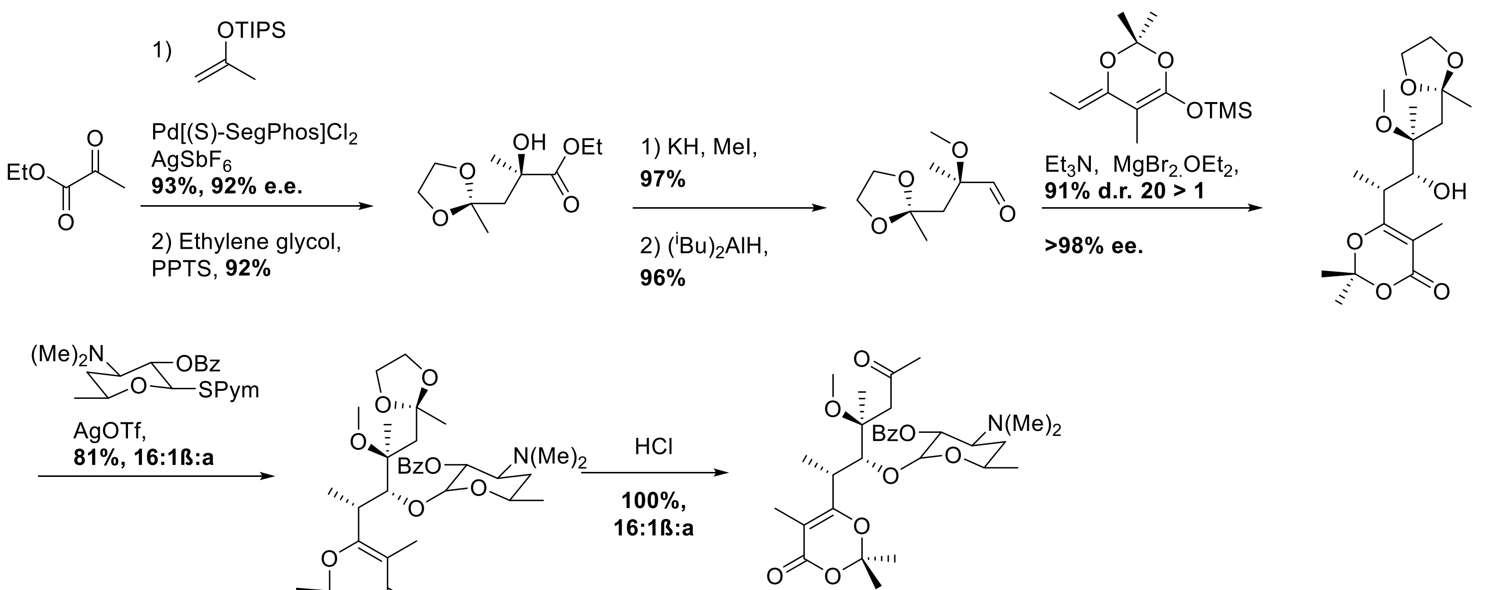


15-Membered ketolides

14-Membered Azaketolides 1

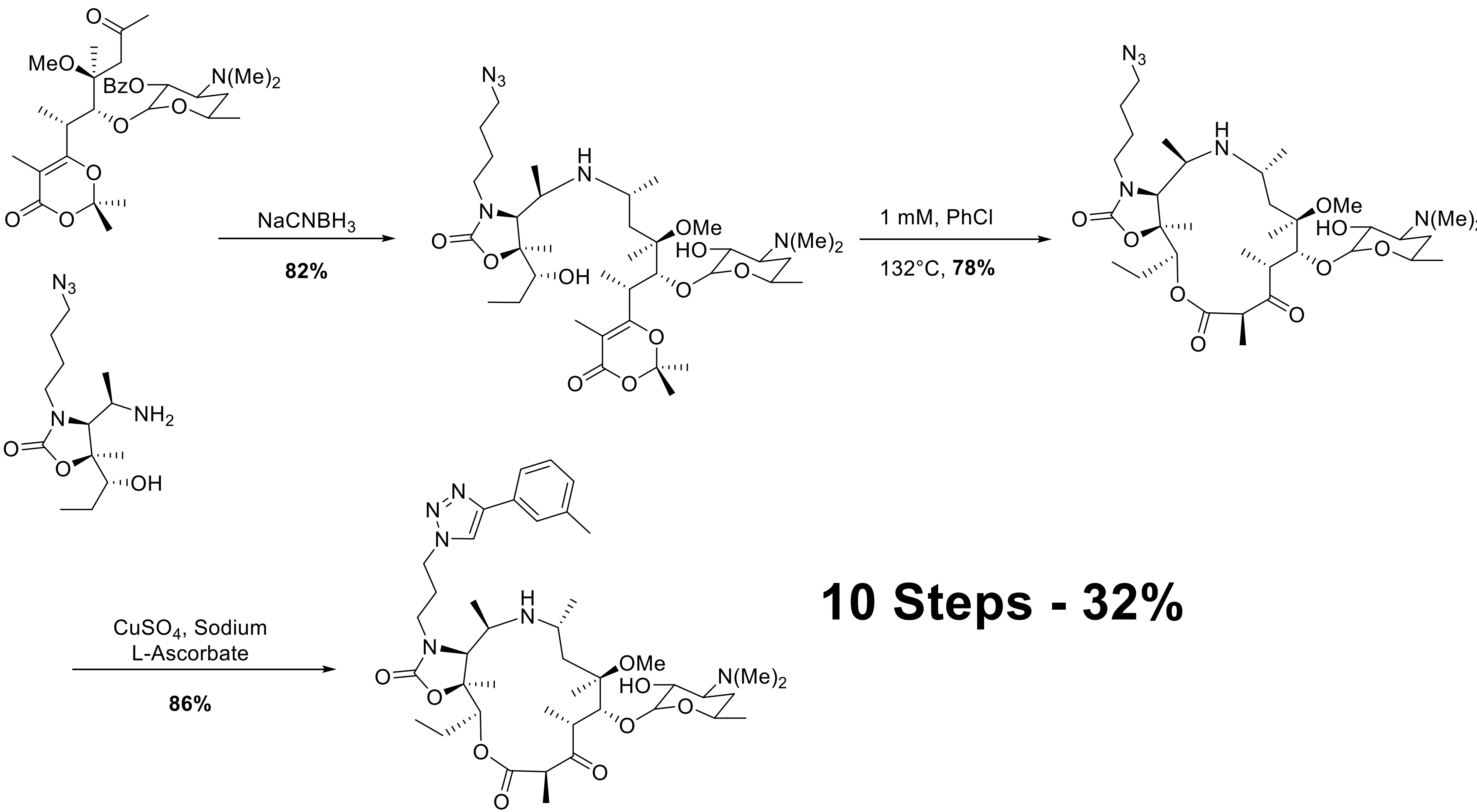


1



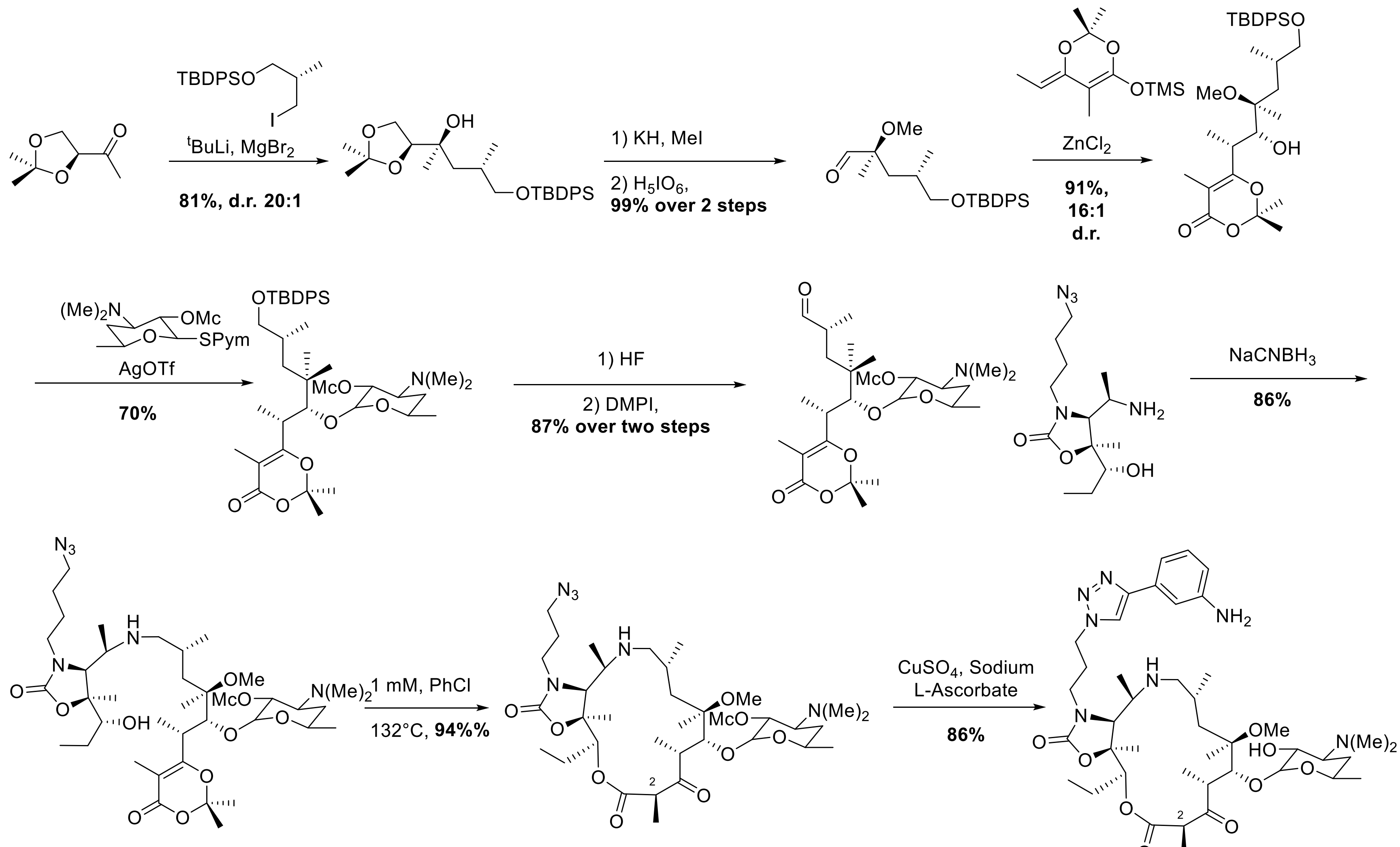
2

14-Membered Azaketolides 2



10 Steps - 32%

15-Membered Azaketolides

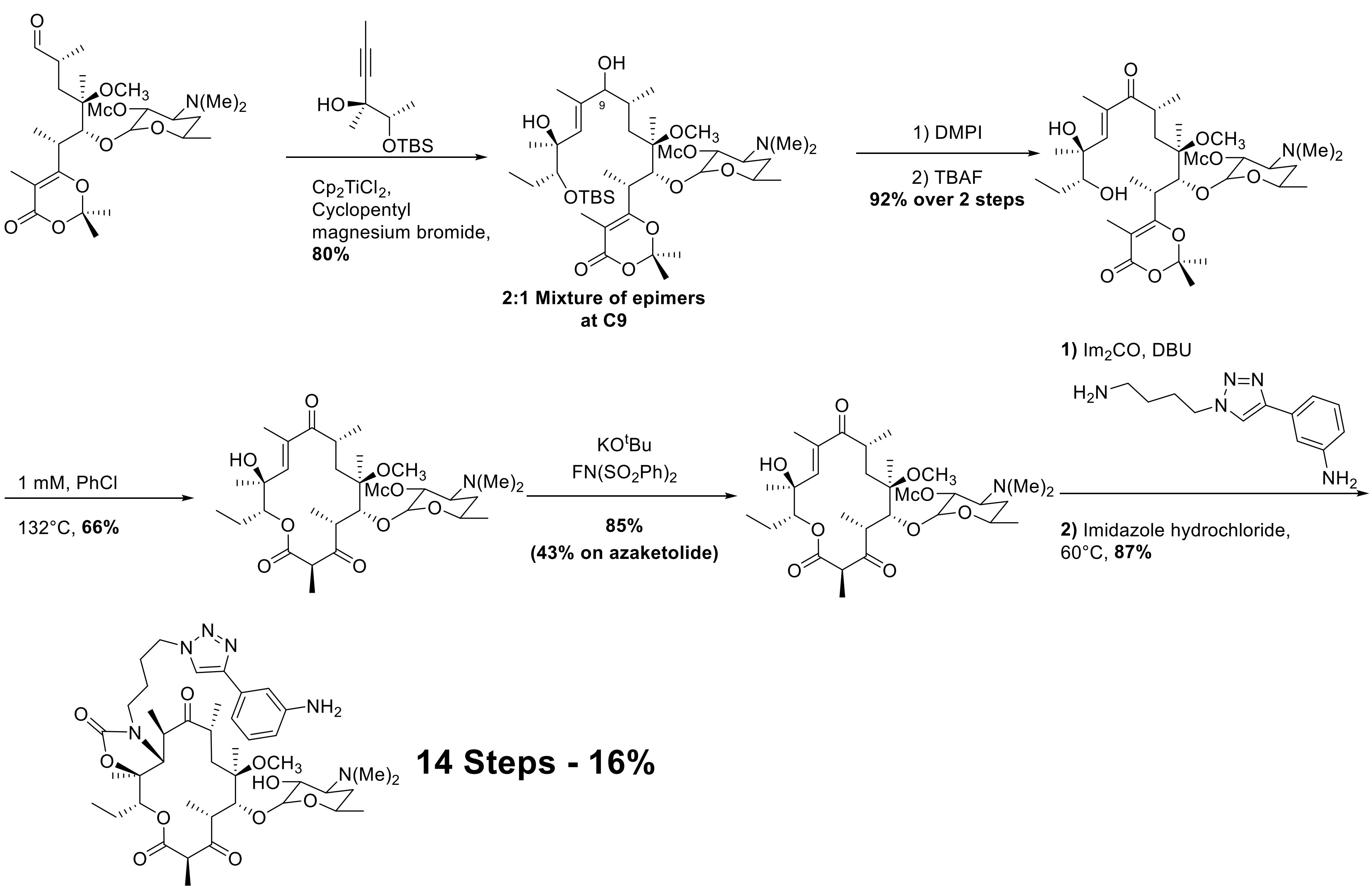


7:1 Mixture of epimers at C2

10 Steps - 43% or 33%

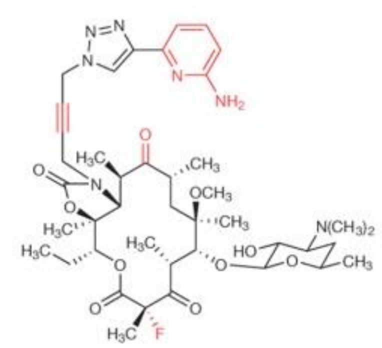
7:1 Mixture of epimers at C2

14 Membered Ketolides



14 Steps - 16%

Library construction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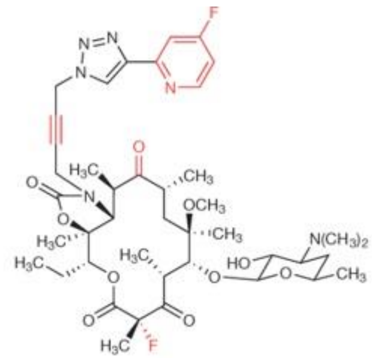
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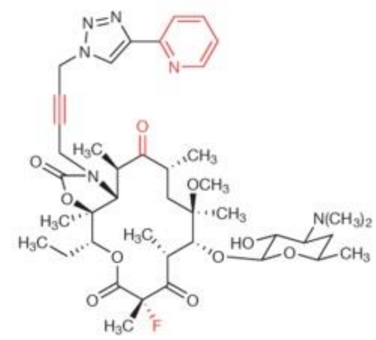
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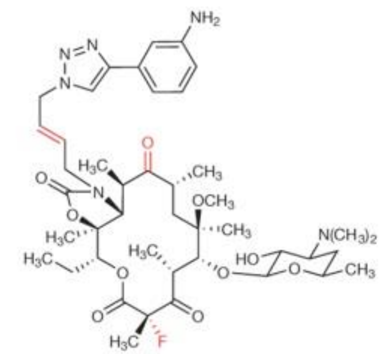
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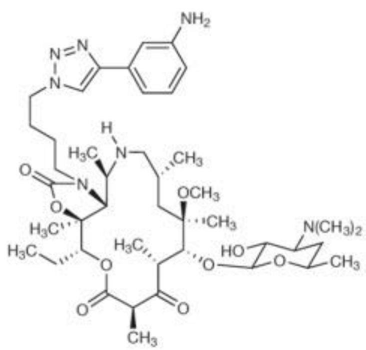
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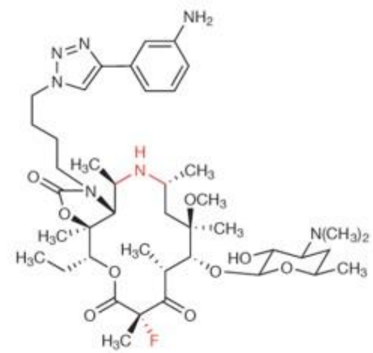
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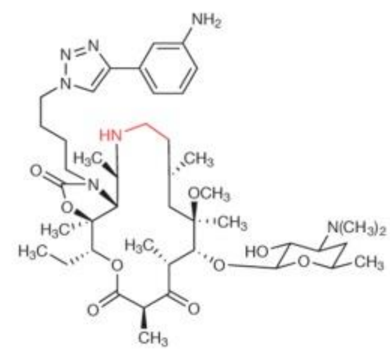
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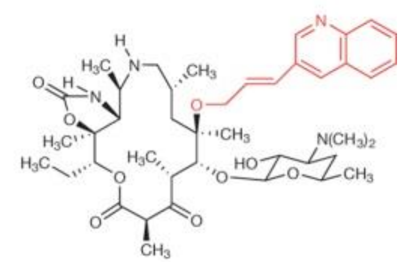
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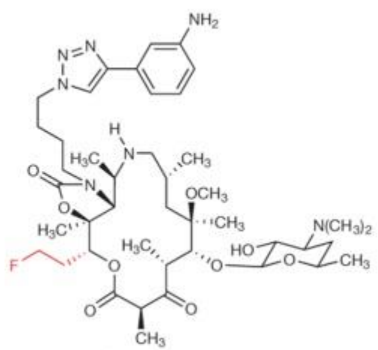
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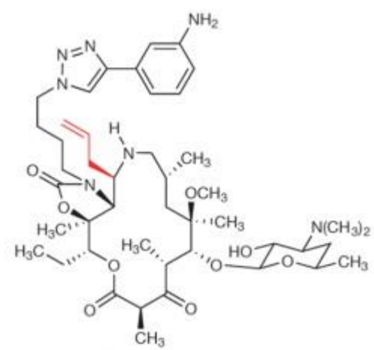
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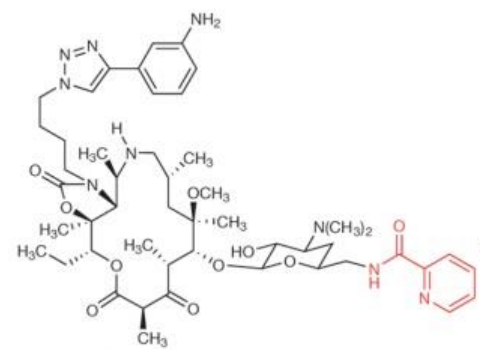
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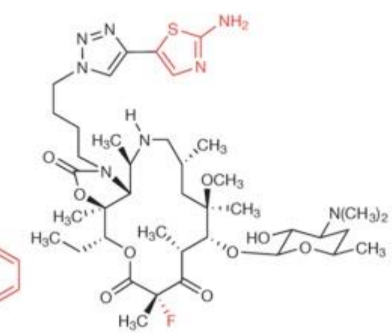
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Microbiological testing

	Species	Strain description	Erythro	Azithro	Telithro	Solithro	100573	100563	100490	11563	20707	22391	21397	20919	11453	11044	21887	21760
Gram-positive	*S. aureus*	ATCC 29213	0.5	1	0.125	0.125	0.06	≤0.03	≤0.03	0.06	0.5	0.25	4	0.25	1	1	8	0.5
	S. aureus	BAA-977; iErmA	>256	>256	0.06	≤0.03	0.06	0.06	0.03	0.06	0.5	0.5	4	0.5	1	1	8	1
	S. aureus	MP513; MRSA; cErmA	>256	>256	256	>64	16	16	64	64	>64	64	64	64	>64	>64	>64	64
	S. aureus	NRS384; MRSA; MsrA	64	128	0.125	0.25	0.06	0.125	0.06	0.125	1	1	8	0.5	2	2	16	4
	S. pneumoniae	ATCC 49619	0.03	0.06	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	0.06	≤0.03	≤0.03	≤0.03	0.06	≤0.03
	S. pneumoniae	UNT-042; ErmB/MefA	>256	>256	0.125	0.25	≤0.03	≤0.03	≤0.03	≤0.03	2	0.125	8	0.5	2	8	1	1
	S. pyogenes	ATCC 19615	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	0.06	≤0.03	≤0.03	≤0.03	0.06	≤0.03
	E. faecalis	ATCC 29212	1	4	≤0.03	≤0.03	0.03	0.03	0.03	≤0.03	0.125	0.06	0.5	0.25	0.125	0.125	0.5	0.06
	E. faecalis	UNT-047; VRE; ErmB	>256	>256	16	32	1	2	2	4	>64	32	64	>64	>64	64	>64	>64
Gram-negative	*H. influenzae*	ATCC 49247	4	2	2	4	2	2	2	2	2	4	8	4	4	8	16	4
	A. baumannii	ATCC 19606	16	32	4	16	2	8	8	4	4	4	16	16	4	32	32	32
	K. pneumoniae	ATCC 10031	4	2	4	4	2	8	4	4	2	4	8	16	2	8	8	4
	E. coli	ATCC 25922	64	4	16	32	8	16	16	16	4	8	32	4	8	64	16	8
	P. aeruginosa	ATCC 27853	64	64	64	64	16	32	64	32	64	64	64	64	>64	>64	>64	64

MIC colour scale (μg ml^{-1})	<0.03	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	>256

- Screened 305 compounds against a panel of pathogens comprising of Gram + and Gram – stains.
  - 83% of the candidates showed a MIC of less than 4μg ml^{-1} against WT *S. pneumoniae*.
- Most promising candidates were screened against an expanded panel that had developed various antibacterial resistance strategies.
  - FSM-100573 and 100563 showed were more active than any current clinical macrolide against mutated *S. pneumoniae*. and *Pseudomonas aeruginosa.*

Conclusions

In conclusion the Meyers group have made several contributions with this publication:

- Designed and executed several efficient and highly convergent routes to three macrolide skeletons.
- Further functionalised and furnished these skeletons to generate a synthetic library of 300+ macrolides.
- Demonstrated that these candidates represent possible avenues to new antimicrobial agents in the war against drug resistant bacteria.