

# **Convergent Synthesis of Macrolide Antibiotics, Solithromycin**

**Literature Seminar**

**2016.07.09**

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# Today's contents

## 1. Introduction

## 2. Andrade's synthesis of 4-desmethyl telithromycin

2-1 Andrade's purpose of this synthesis

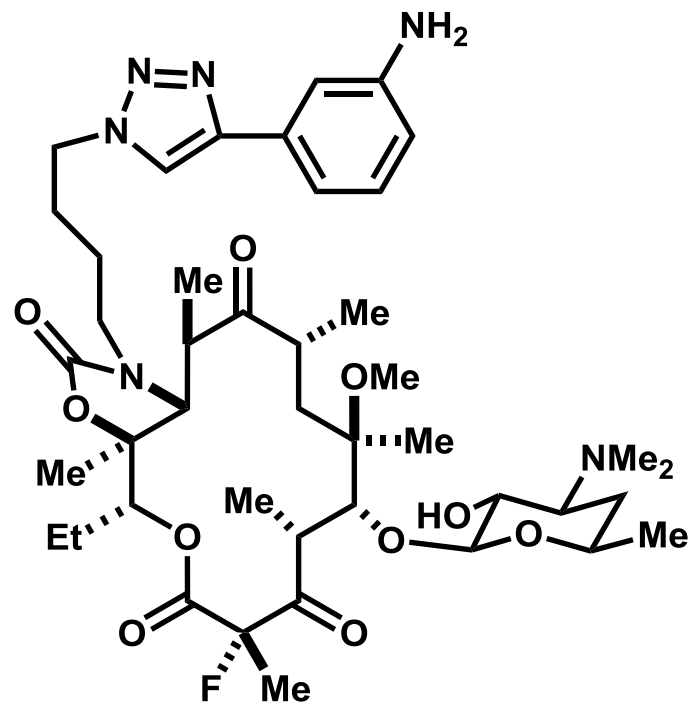
2-2 Retrosynthetic analysis

2-3 Total synthesis of 4-desmethyl telithromycin

## 3. Myers' synthesis of solithromycin (main paper)

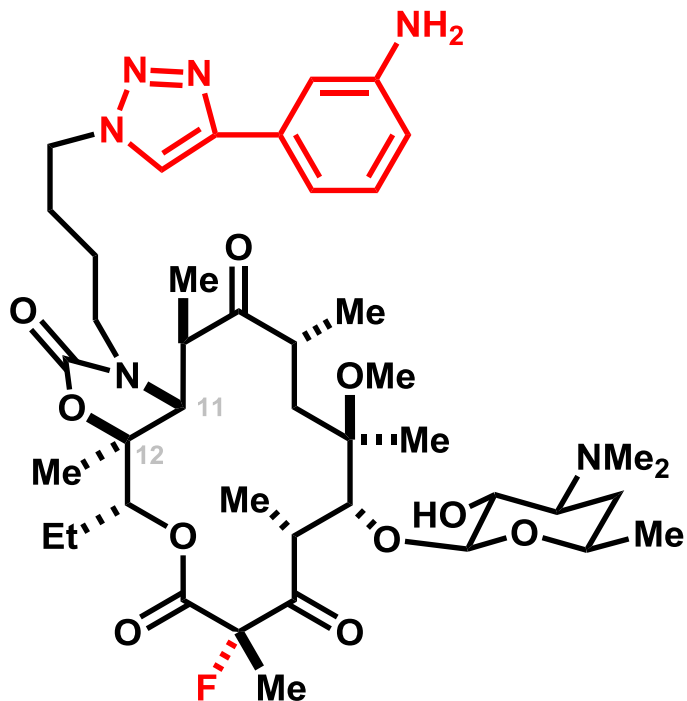
3-1 Synthetic strategy

3-2 Total synthesis of solithromycin



Solithromycin

## -solithromycin and telithromycin-



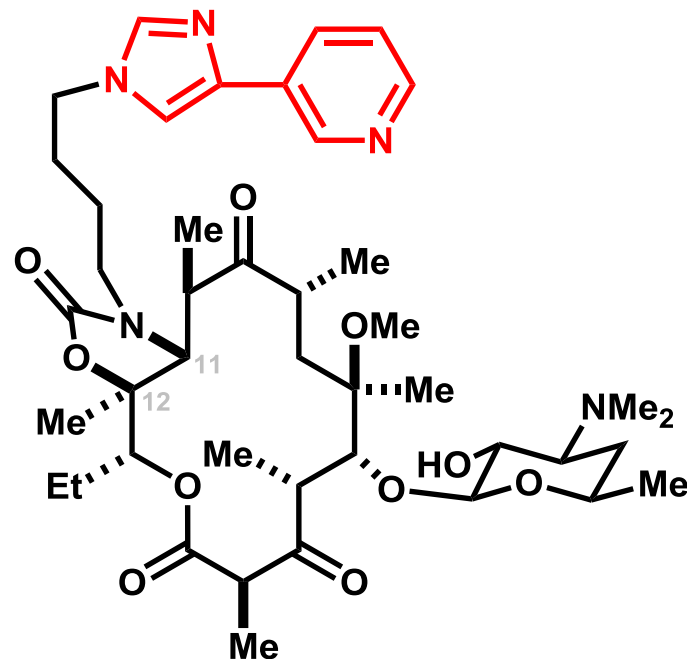
# Solithromycin

## Semisynthesis

U.S. Patent(WO2010048599), April 29, 2010.  
(16 steps from erythromycin)

## Structural feature

- 14-membered lactone ring
- 9 asymmetric centers
- 1 unusual sugar (D-desosamine)
- C-11–C-12 oxazolidinone



## telithromycin

## Semisynthesis

U.S. Patent(WO2009053259 A1), April 30, 2009.  
(12 steps from erythromycin)

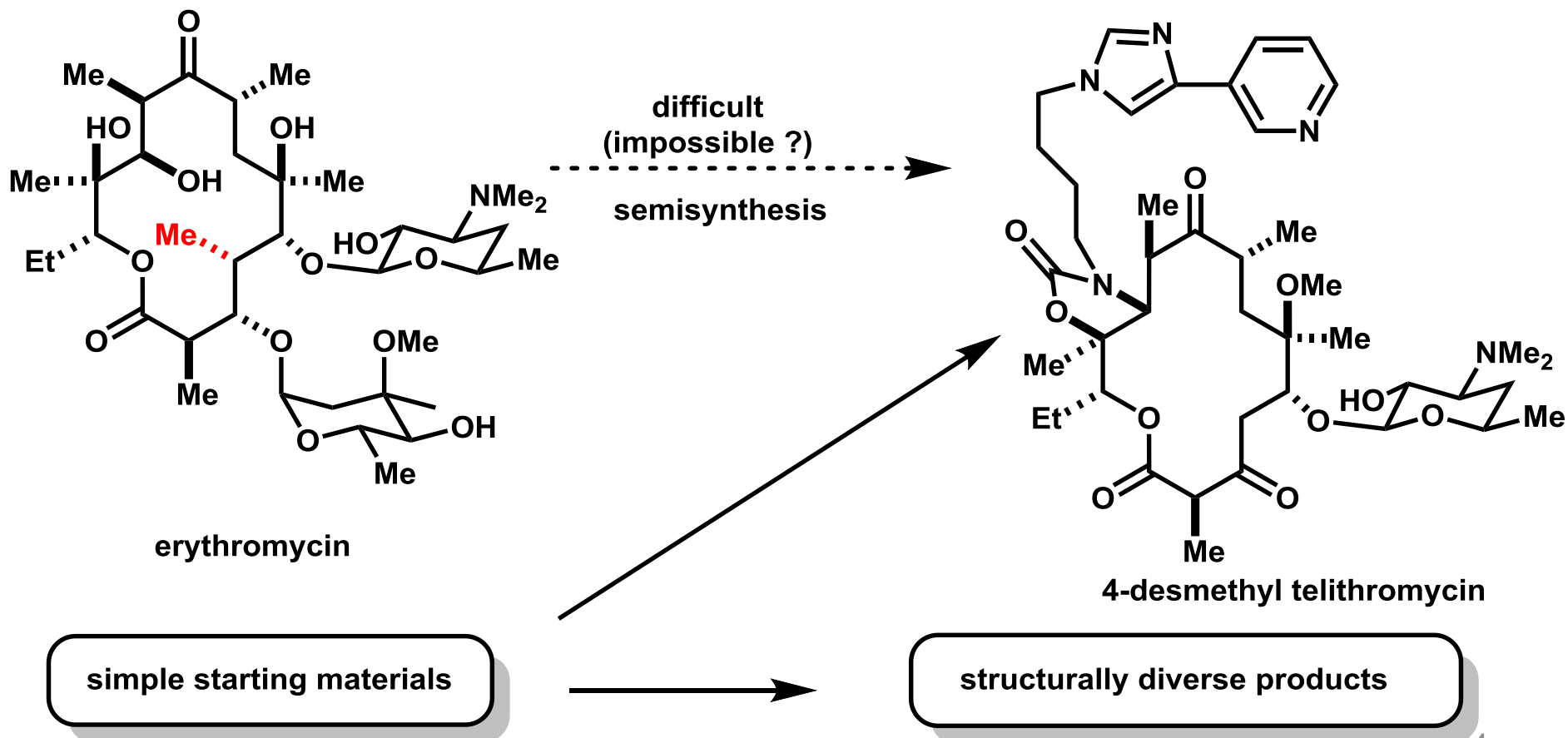
## Structural feature

- 14-membered lactone ring
- 9 asymmetric centers
- 1 unusual sugar (D-desosamine)
- C-11–C-12 oxazolidinone

# Introduction

## -semisynthesis of macrolides from erythromycin-

- To date, all macrolide antibiotics are produced by chemical modification of erythromycin.
- Semisynthesis is limited because it is challenging to modify structurally complex materials (below).
- Synthesis from simple building blocks enable to prepare the diverse structures (main paper).



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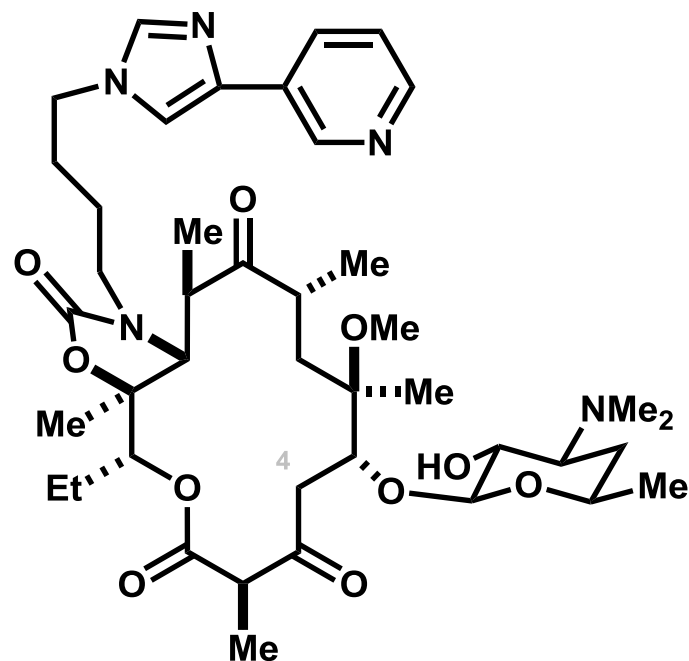
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### 3-1 Synthetic strategy

### 3-2 Total synthesis of solithromycin

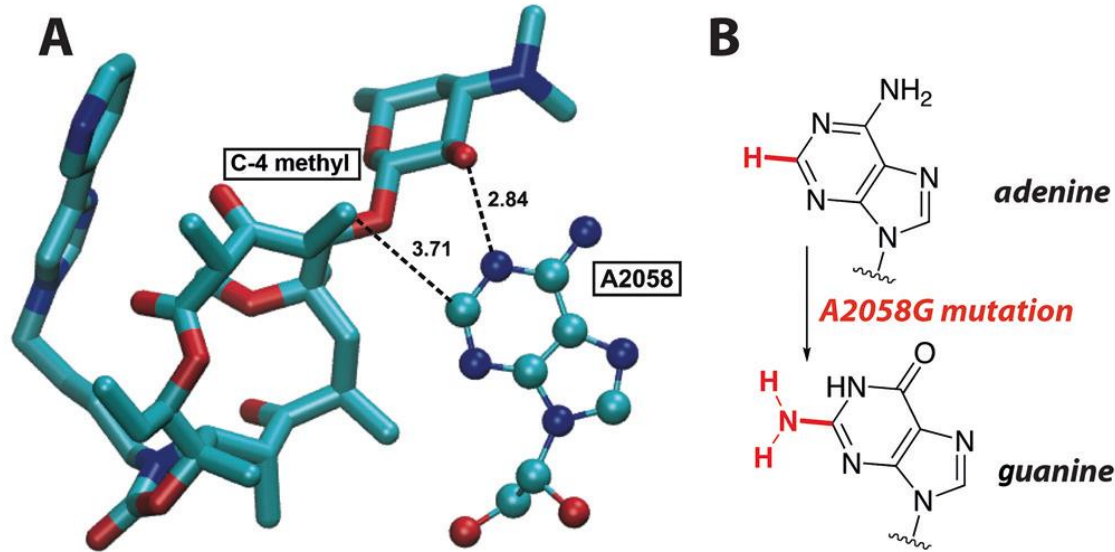


## 4-desmethyl telithromycin

The term '**desmethyl**' refers to the replacement of a methyl group with hydrogen (Me → H).

# Andrade's purpose of this synthesis

## -why 4-desmethyl telithromycin?-

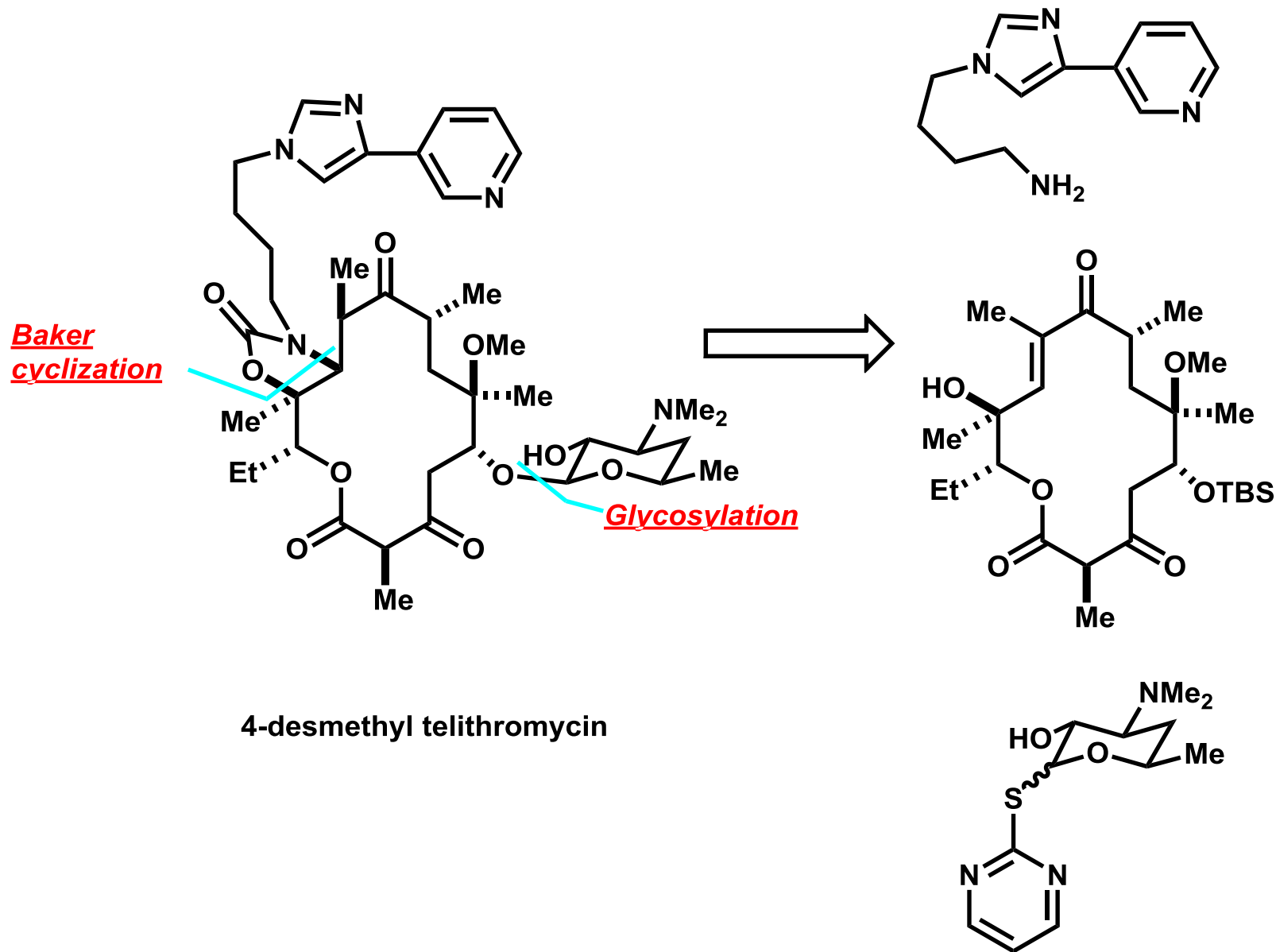


**Figure 1**

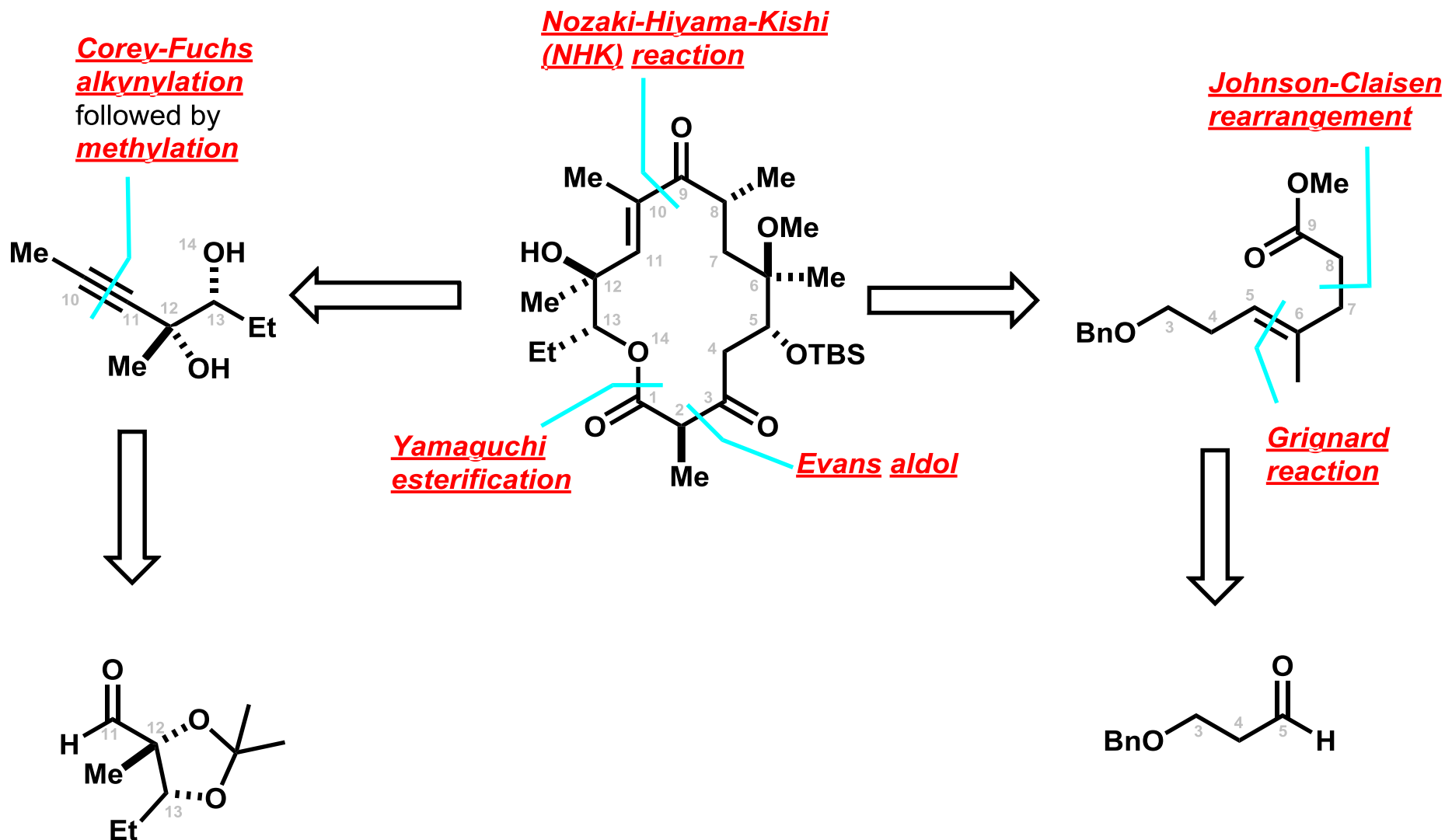
- (A) telithromycin and A2058 interactions  
(B) consequences of A2058G mutation

- ribosomal mutation of adenine to guanine at position 2058 resulted in a steric clash between the C-4 methyl group of the macrolide/ketolide and the exocyclic amino group of guanine (**Figure 1**).
- the author hypothesized that 'mutating' the C-4 methyl group into hydrogen (producing desmethyl analogues) would recapitulate binding and restore bioactivity against such resistant strains.

# Retrosynthetic analysis of 4-desmethyl telithromycin (1)

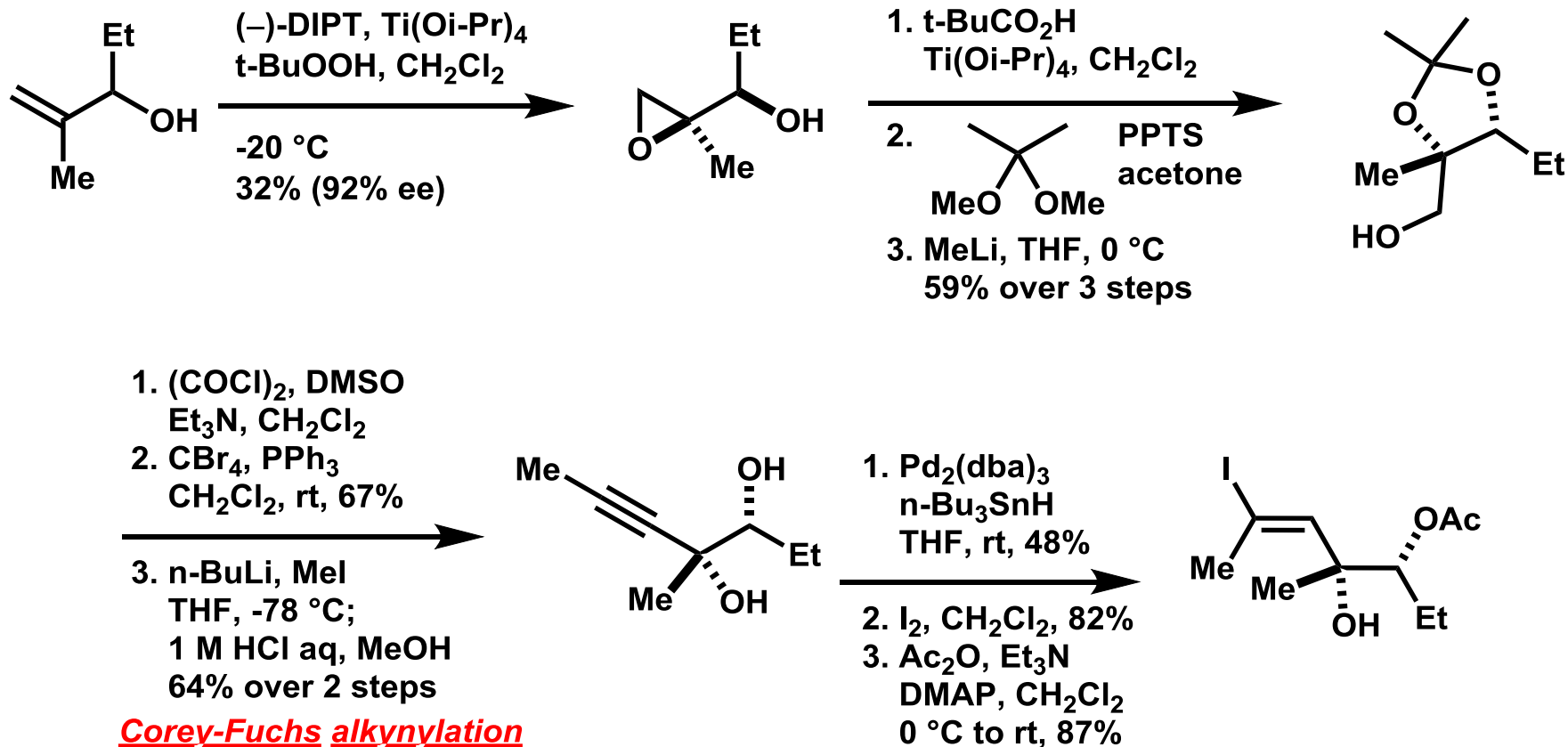
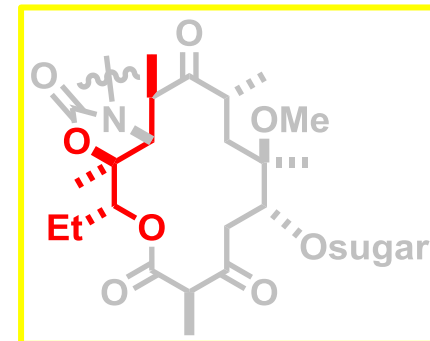


# Restosynthetic analysis of 4-desmethyl telithromycin (2)

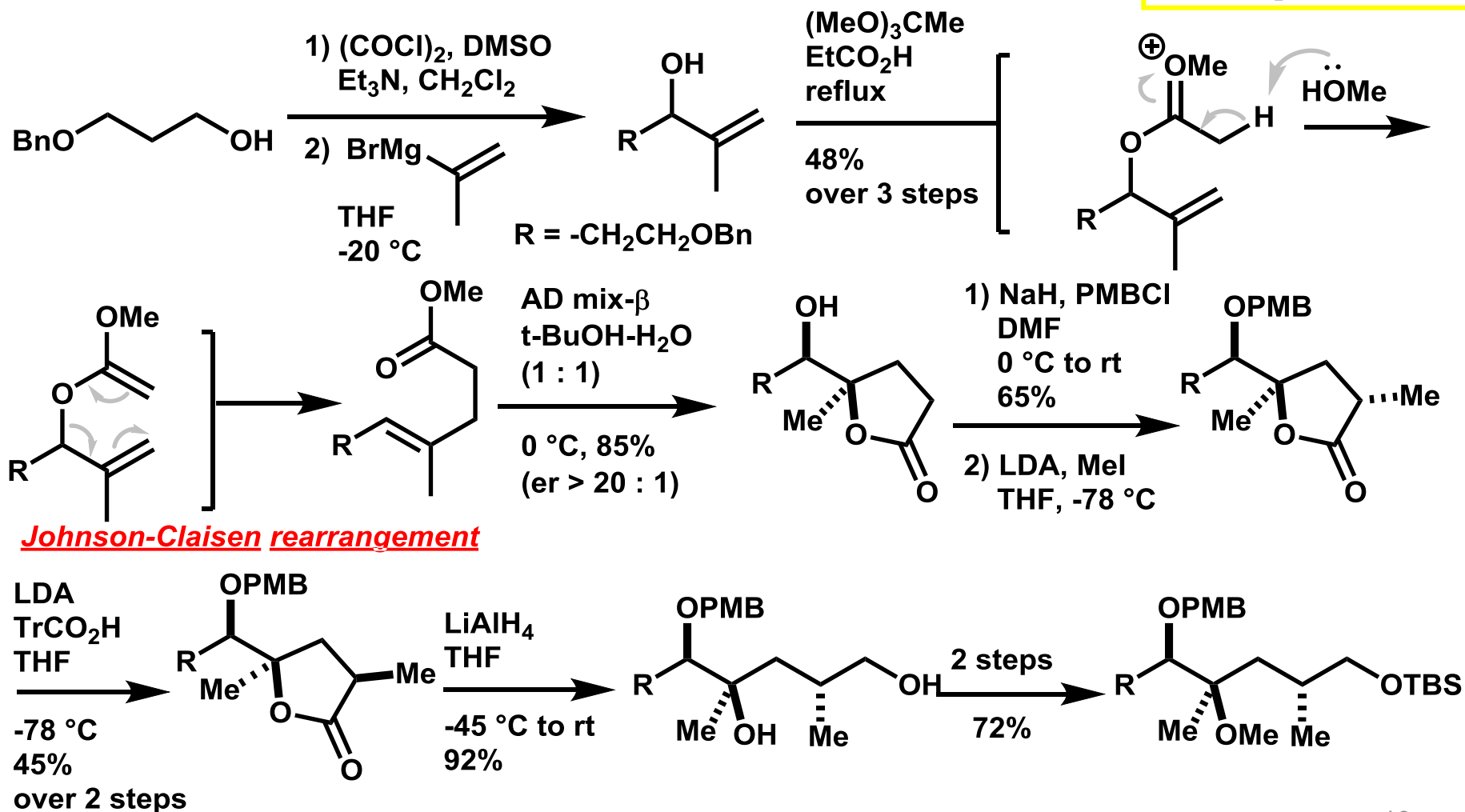
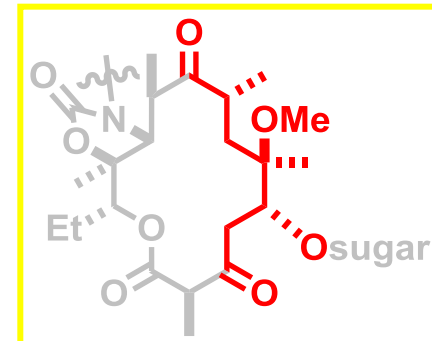




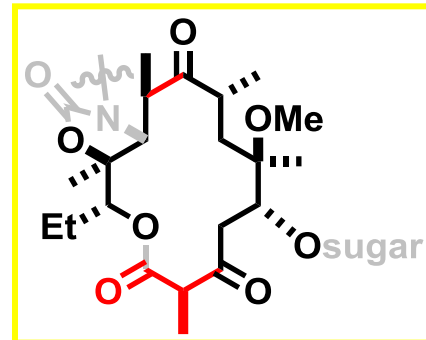
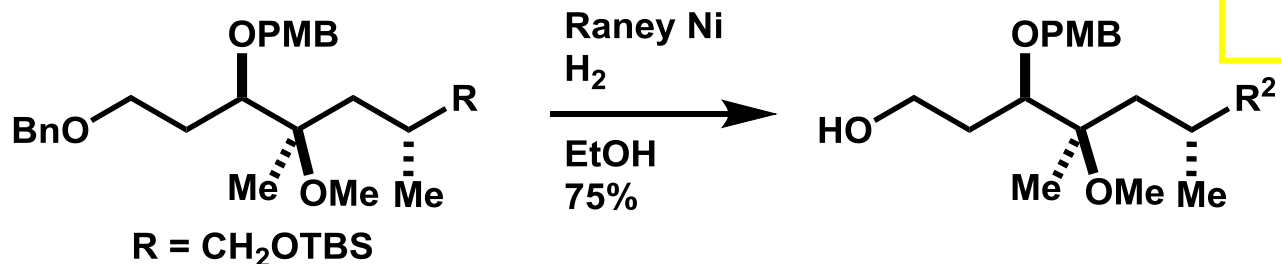
# Total synthesis of 4-desmethyl telithromycin (1)



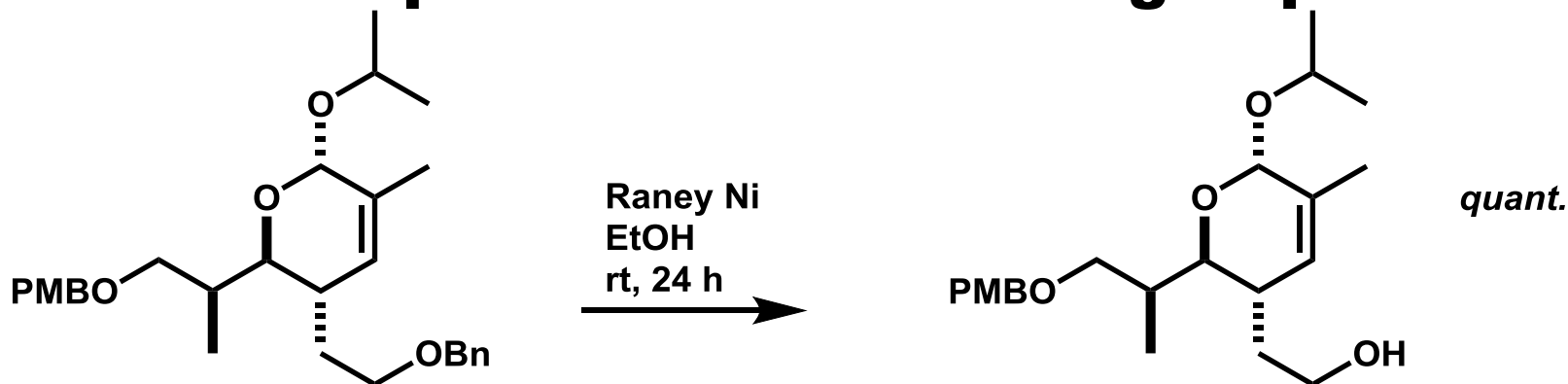
# Total synthesis of 4-desmethyl telithromycin (2)



# Total synthesis of 4-desmethyl telithromycin (3)

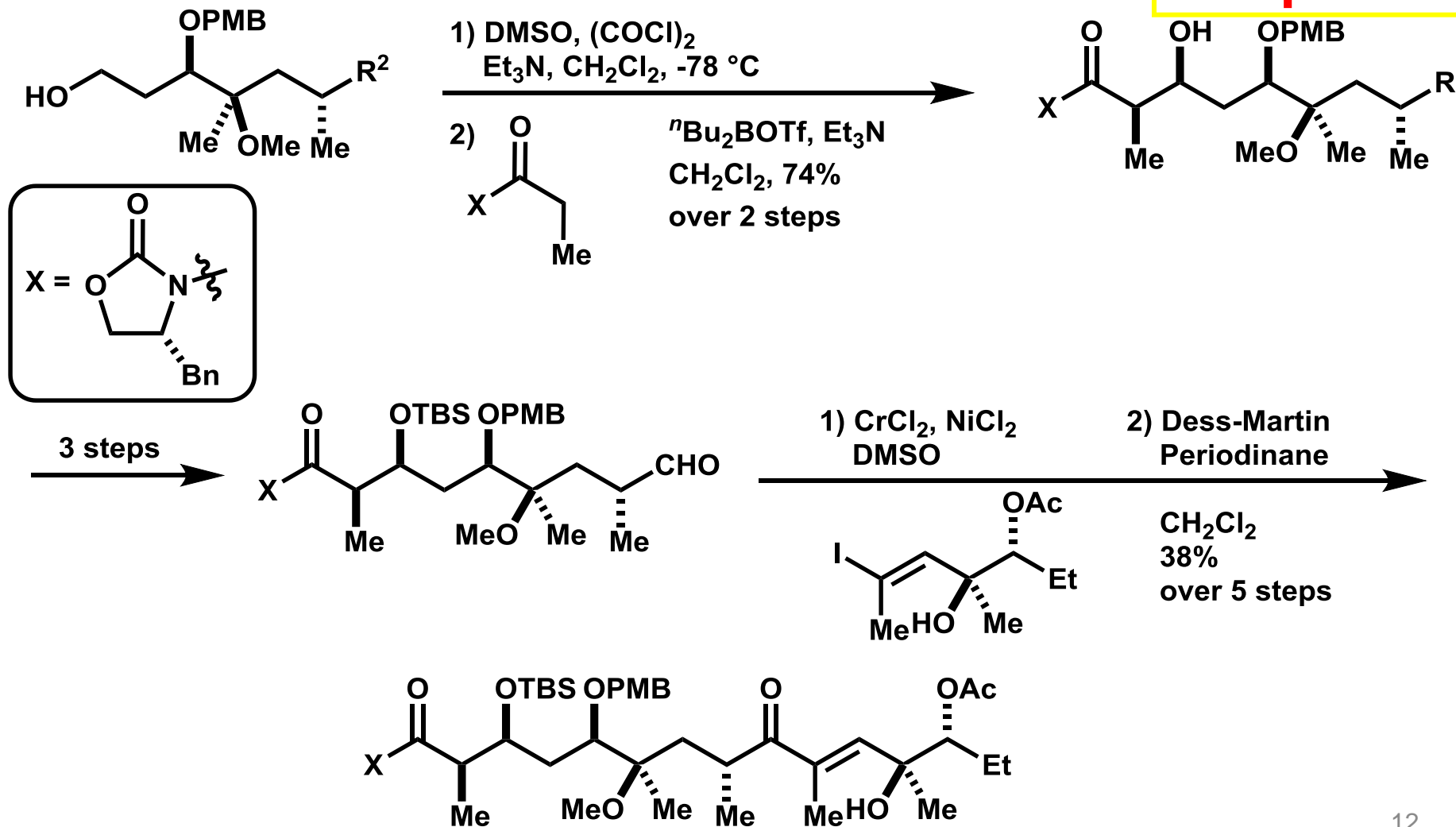
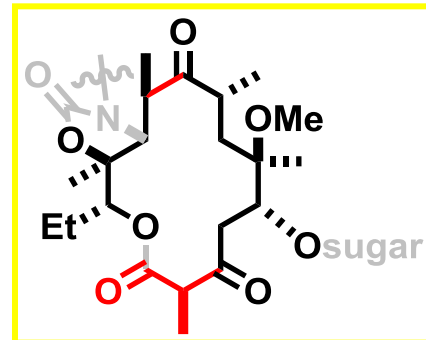


## Chemoselective removal of the Bn group in the presence of the PMB group

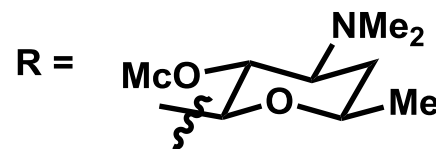
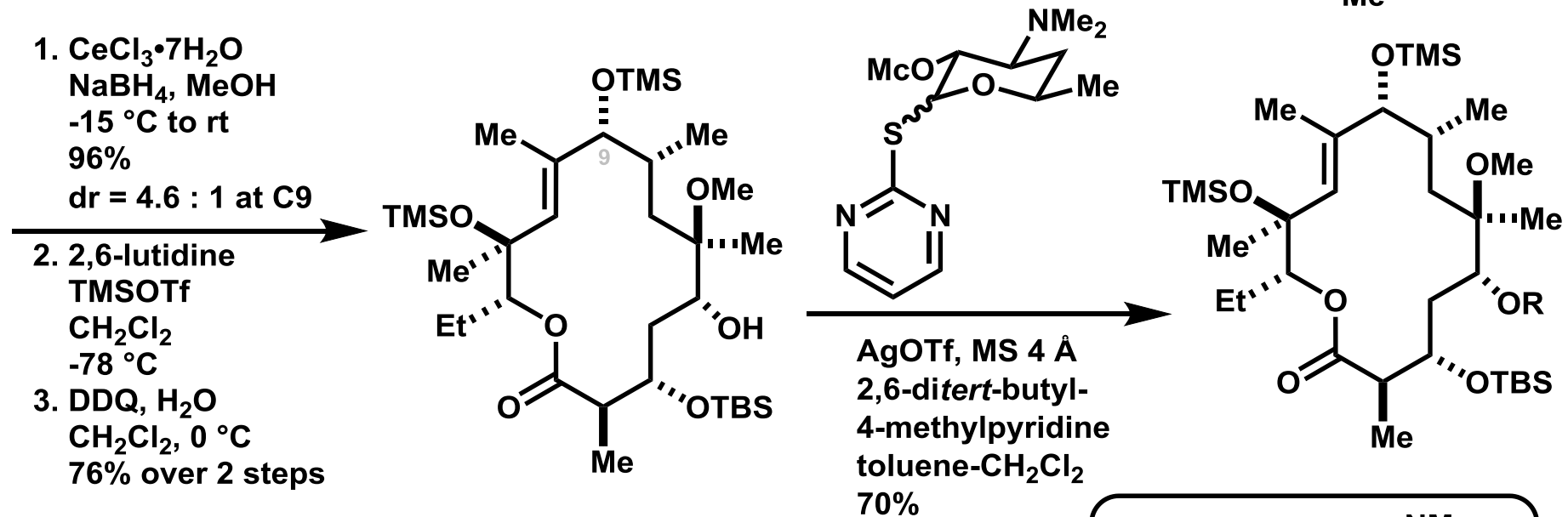
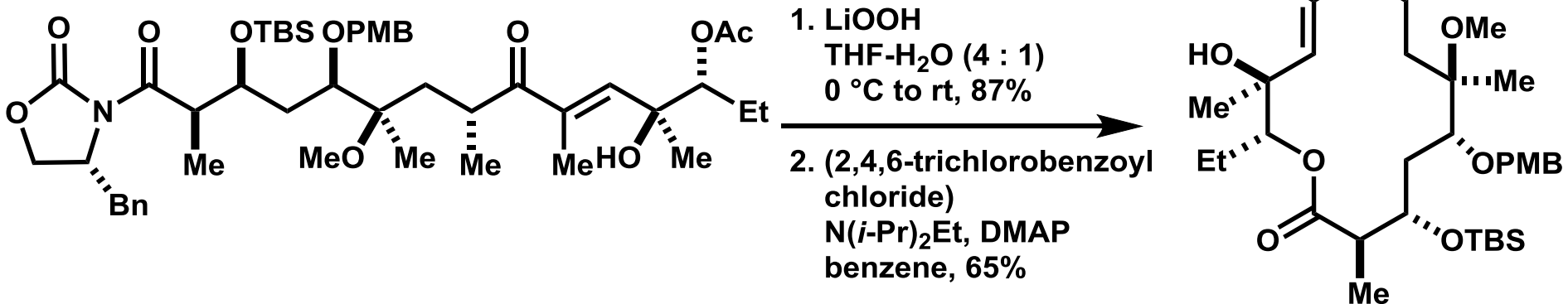


Oikawa, Y.; Tanaka, T.; Horita, K.; Yonemitsu, O. *tetrahedron lett.* **1984**, 25, 5397-5400.

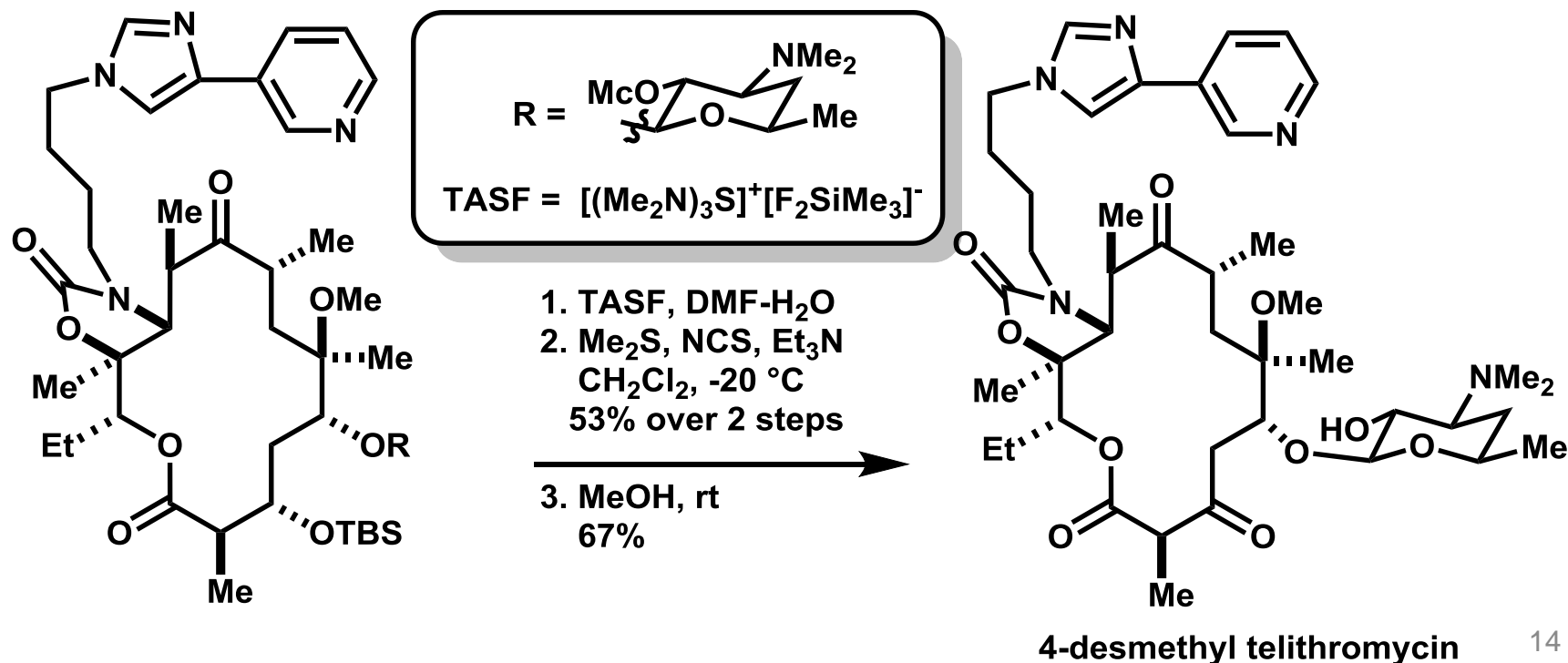
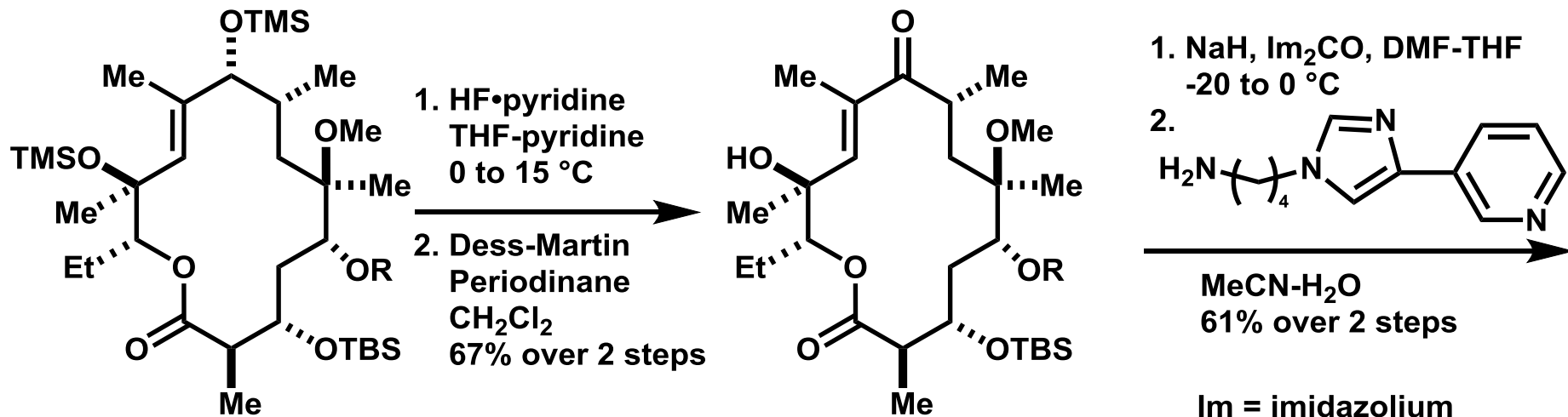
# Total Synthesis of 4-desmethyl telithromycin (4)



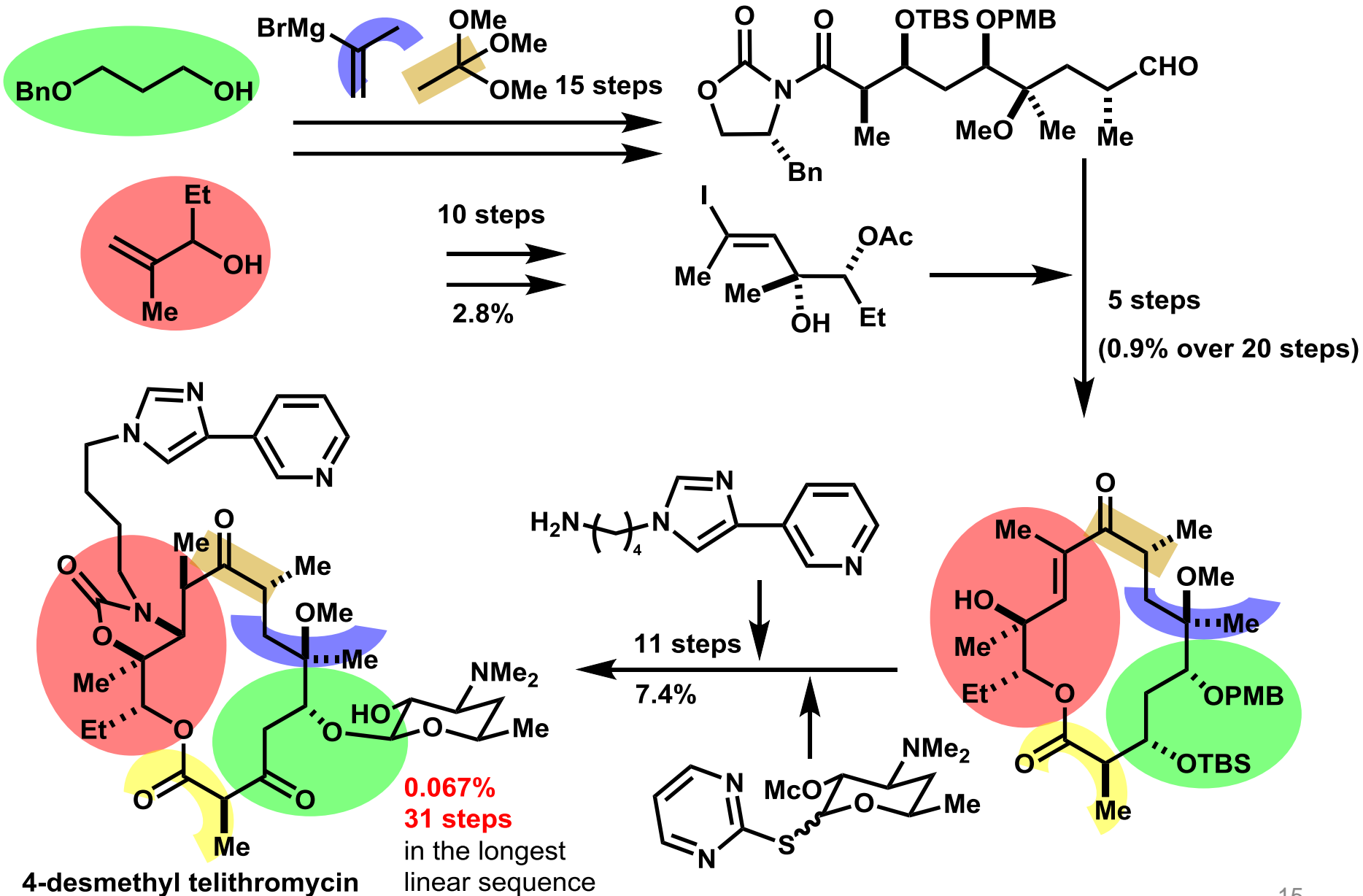
# Total synthesis of 4-desmethyl telithromycin (5)



# Complete synthesis of 4-desmethyl telithromycin



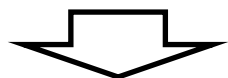
# Short summary



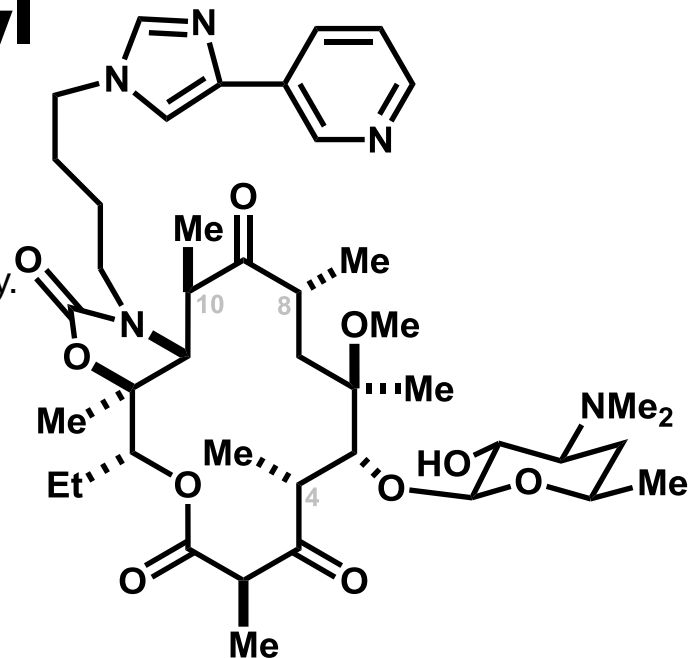
# Biological evaluation of desmethyl telithromycin analogues

The total syntheses of **3-6** allowed to test the.....

- (1) the roles of the C-4, C-8 and C-10 methyl groups on biological activity.
- (2) the desmethylation hypothesis (replacing the 4-methyl group with hydrogen would avoid the attendant steric clash with ribosomes bearing the A2058G mutation).



- (1) as methyl groups are progressively added to the macrolide, the antibacterial activity increase.
- (2) **6** was fourfold less potent than **2** against the A2058G mutant.



**Telithromycin**

**Table 1** Biological evaluation of analogues of telithromycin showing Minimum Inhibitory Concentration Values for 4,8,10-telithromycin (**3**), 4,10-telithromycin (**4**), 4,8-telithromycin (**5**), 4-telithromycin (**6**), and comparator telithromycin (**2**)

Entry	Strain	Bacteria	wt/mutant	Minimum inhibitory values (µg/mL)				
				<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>2</b>
1	SQ171/2058G	<i>E. coli</i>	A2058G	>512	>256	>256	>256	
2	DK/pKK3535	<i>E. coli</i>	wt	32	8	4	0.5	0.5
3	DK/2058G	<i>E. coli</i>	A2058G	64	16	32	4	1
4	UCN14	<i>S. aureus</i>	A2058T	32	>256	>256	>256	>128
5	ATCC33591	<i>S. aureus</i>	ermA	>128	>128	>64	>128	>128



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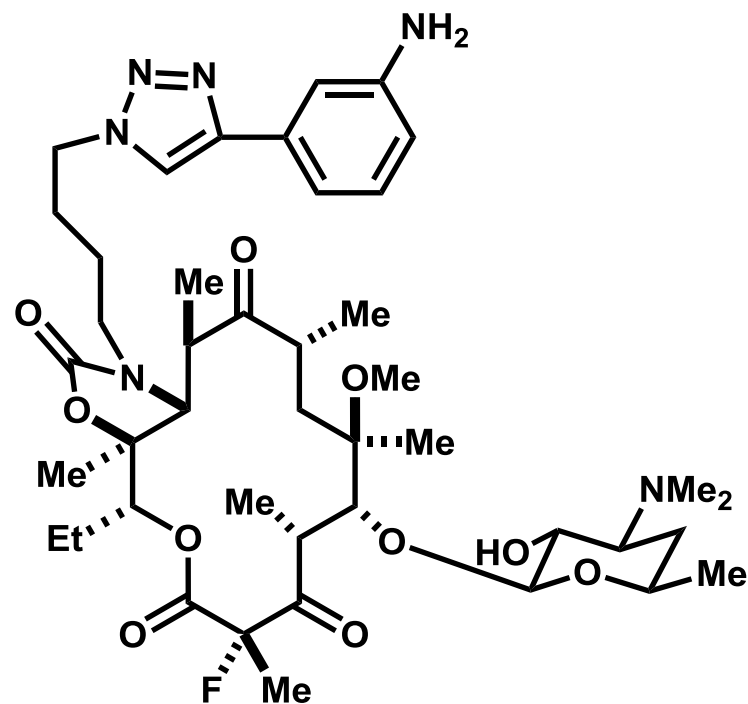
2-2 Retrosynthetic analysis

2-3 Total synthesis of 4-desmethyl telithromycin

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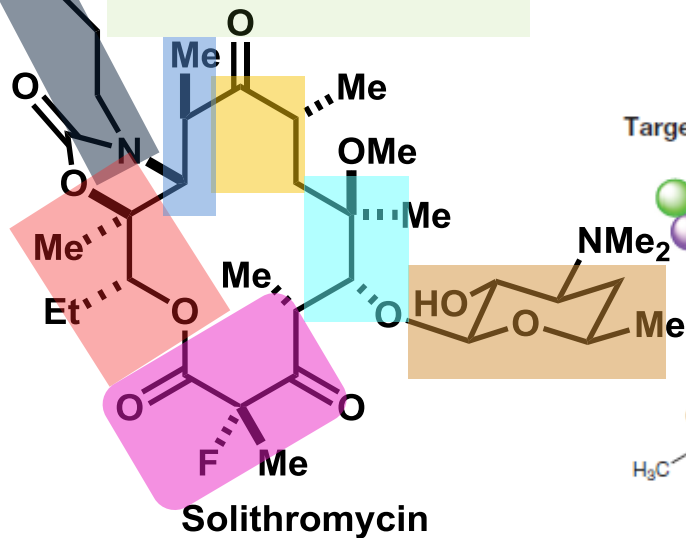
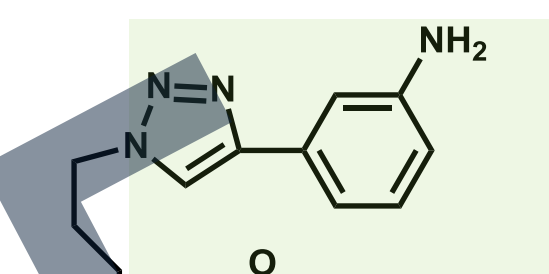
3-1 Synthetic strategy

3-2 Total synthesis of solithromycin

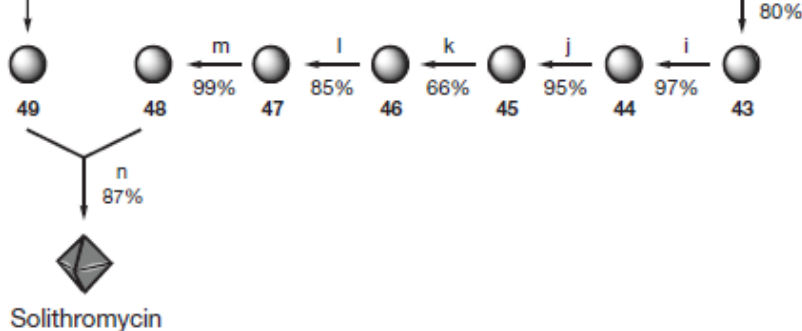
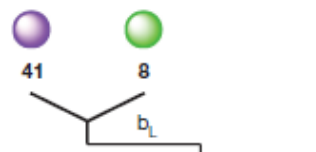
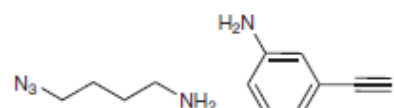
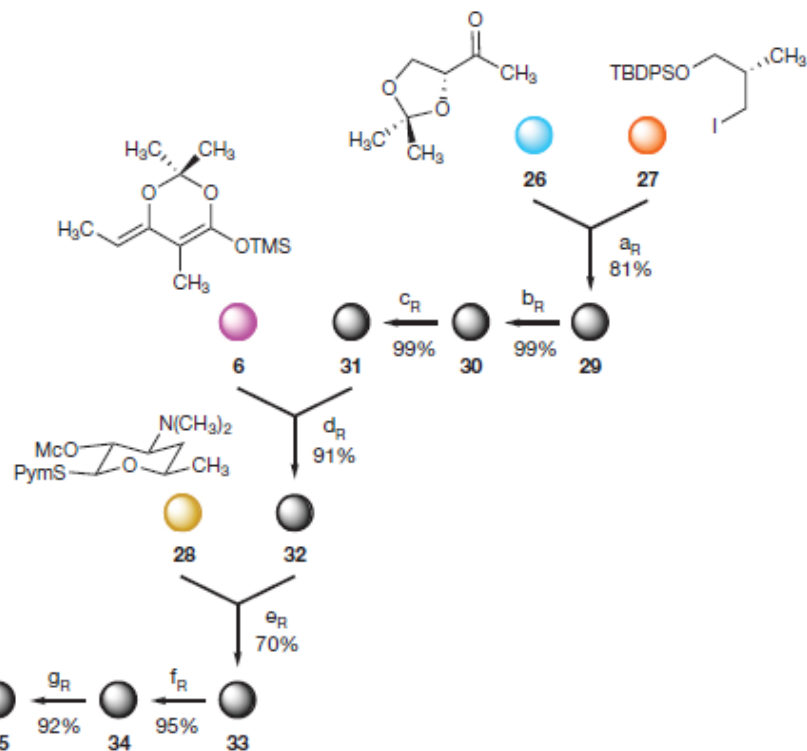
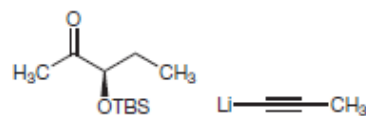


Solithromycin

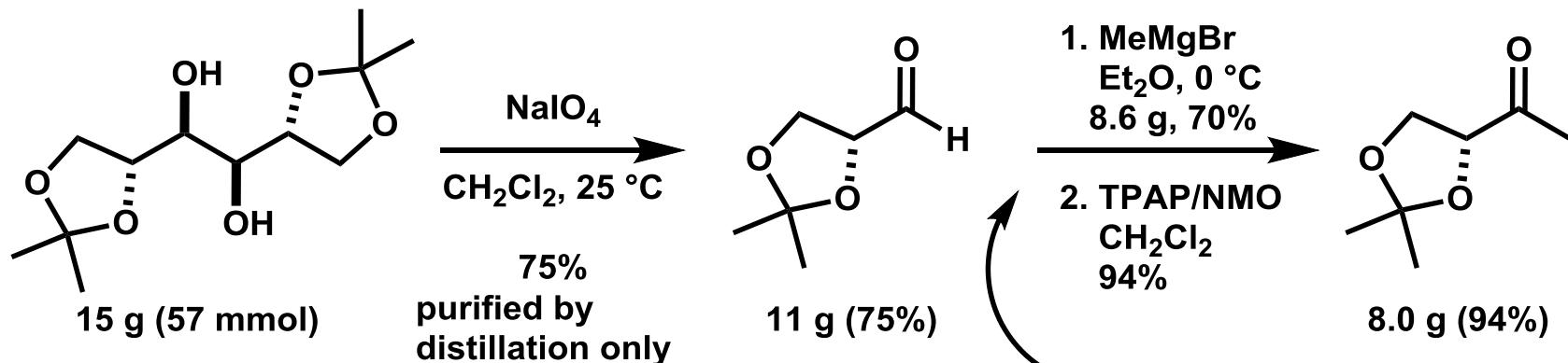
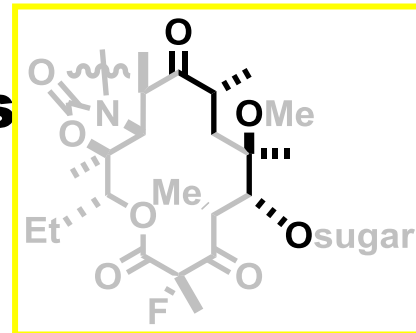
# Synthetic strategy



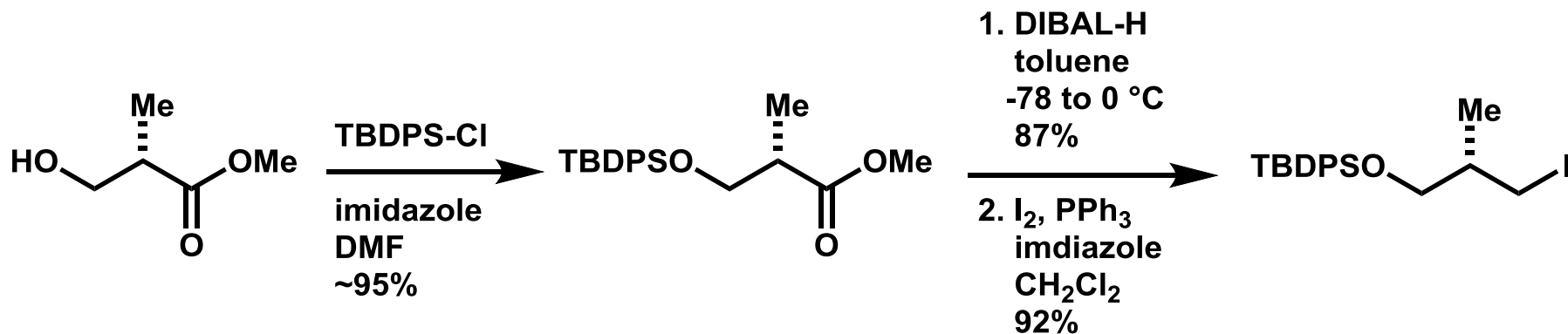
Target topology



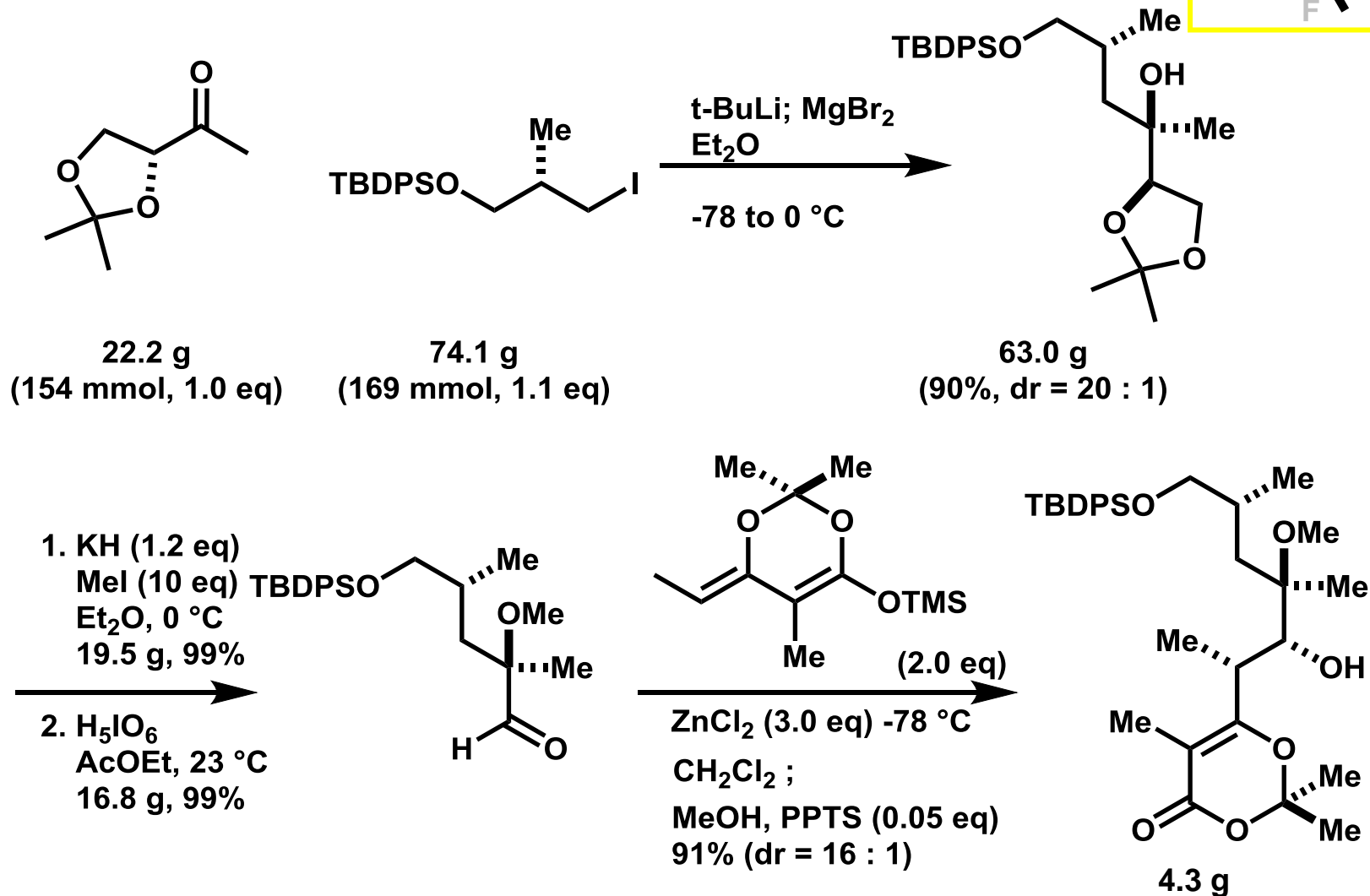
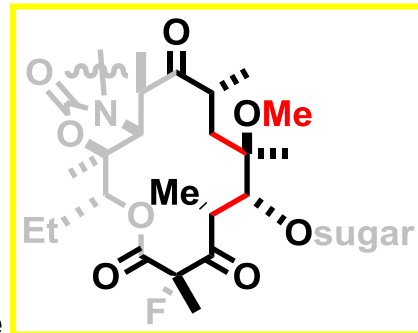
# Preparation of building blocks



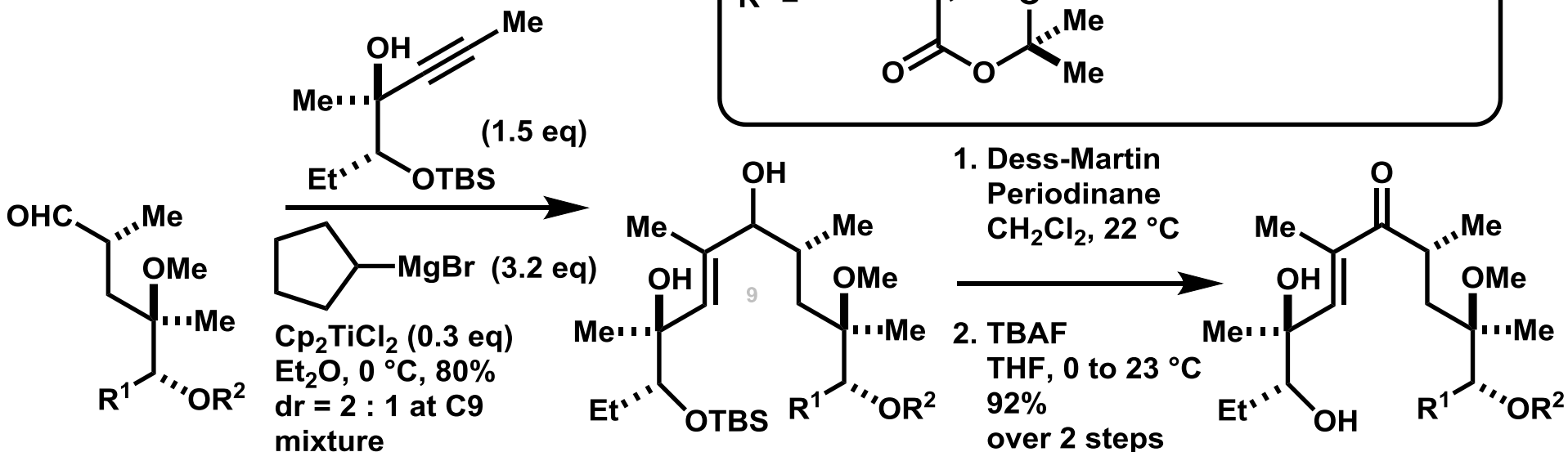
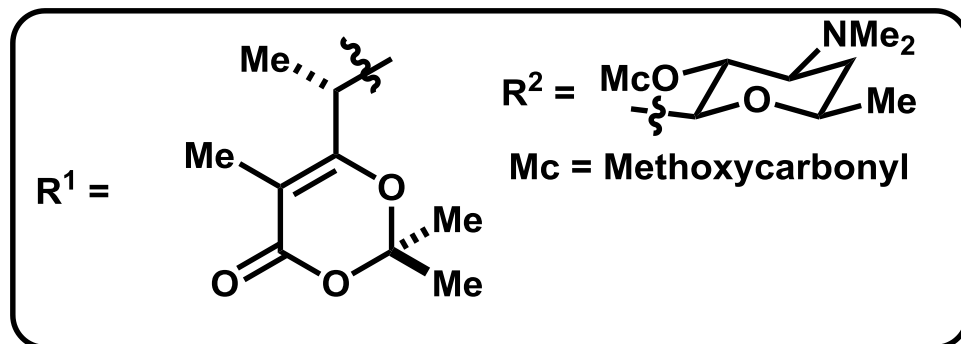
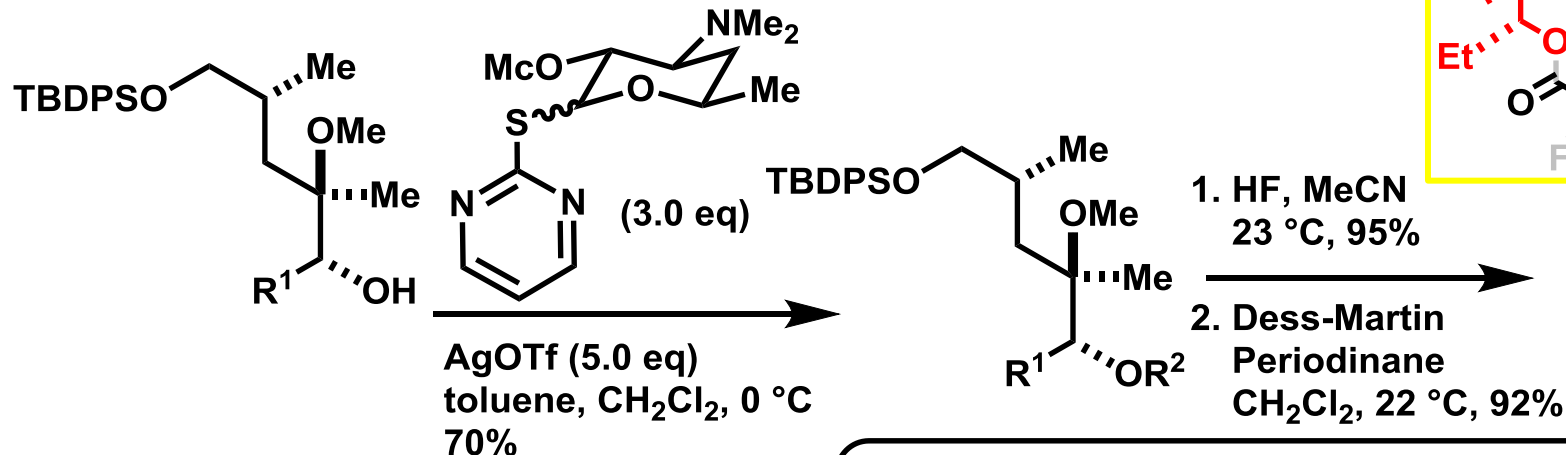
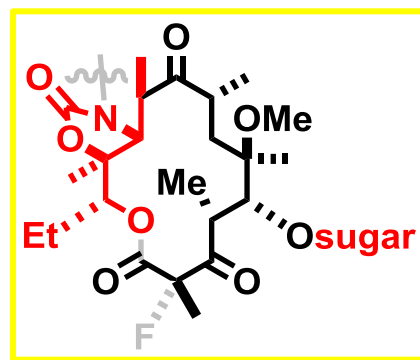
- 1) used in the next step without further purification  
 2) short pad column and washed with  $\text{CuSO}_4$  aq, brine and water



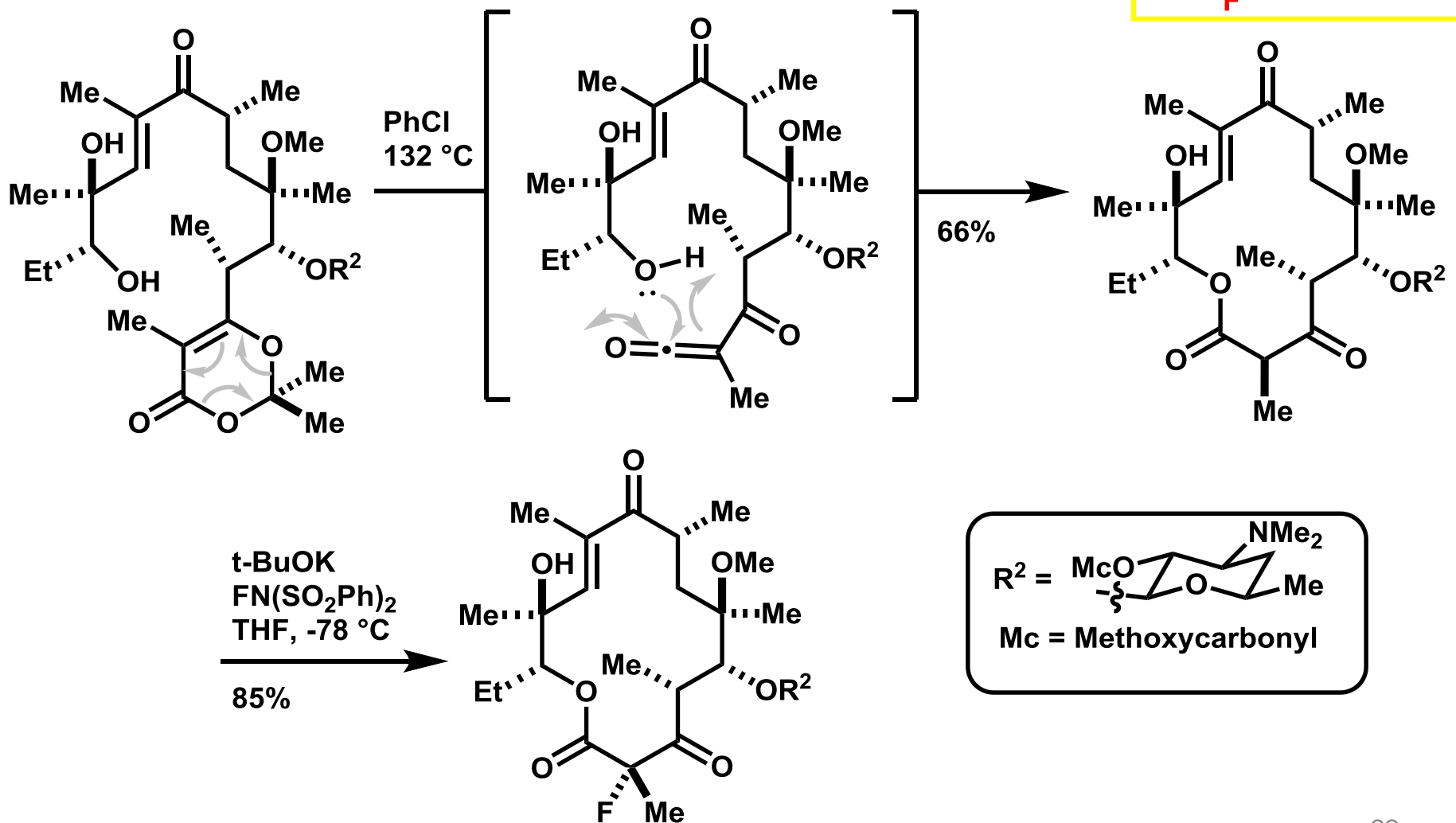
# Total synthesis of solithromycin (1)



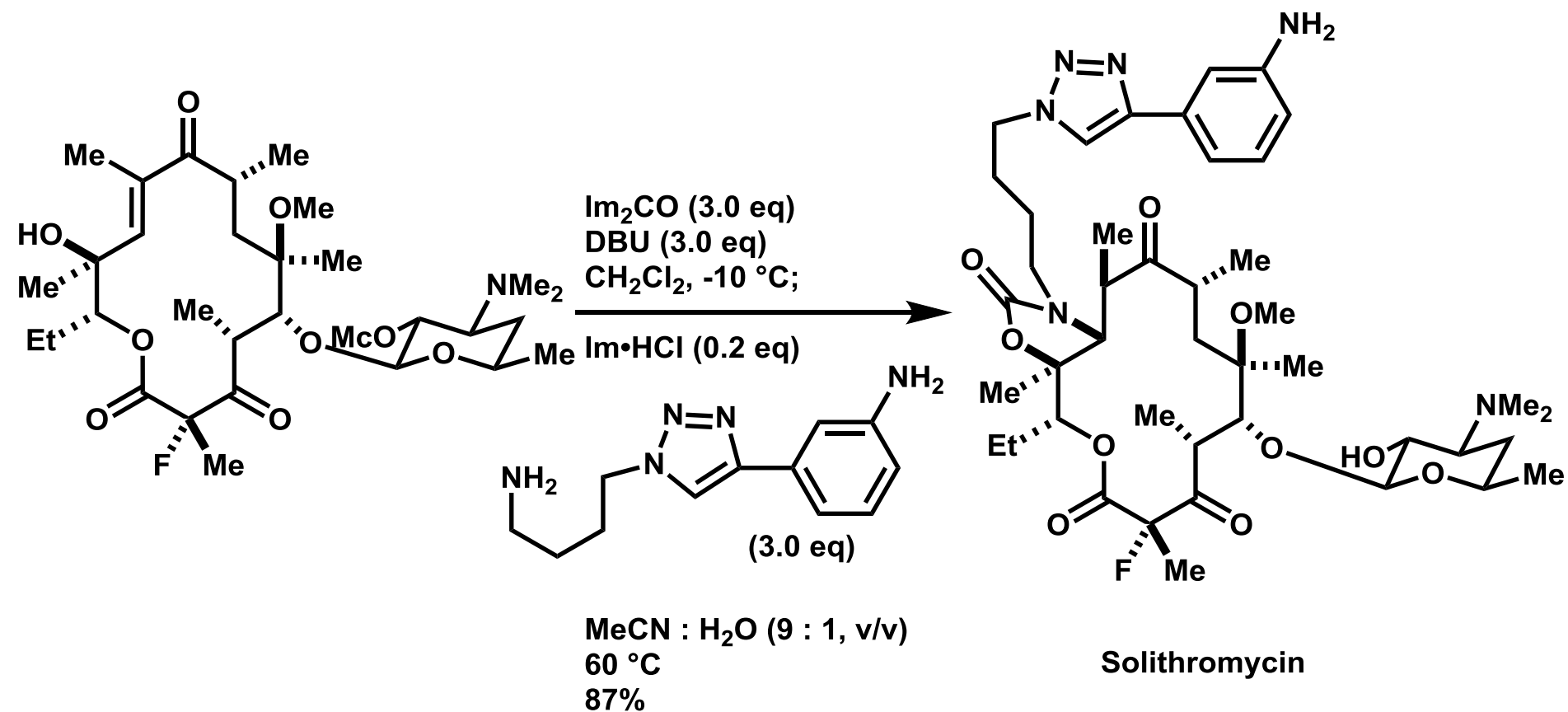
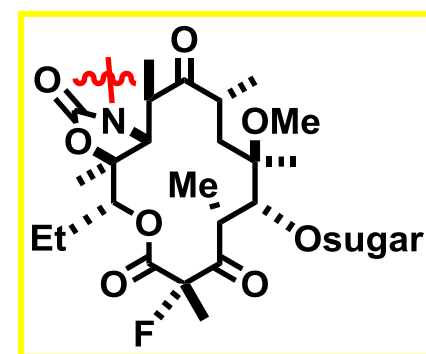
# Total synthesis of solithromycin (2)



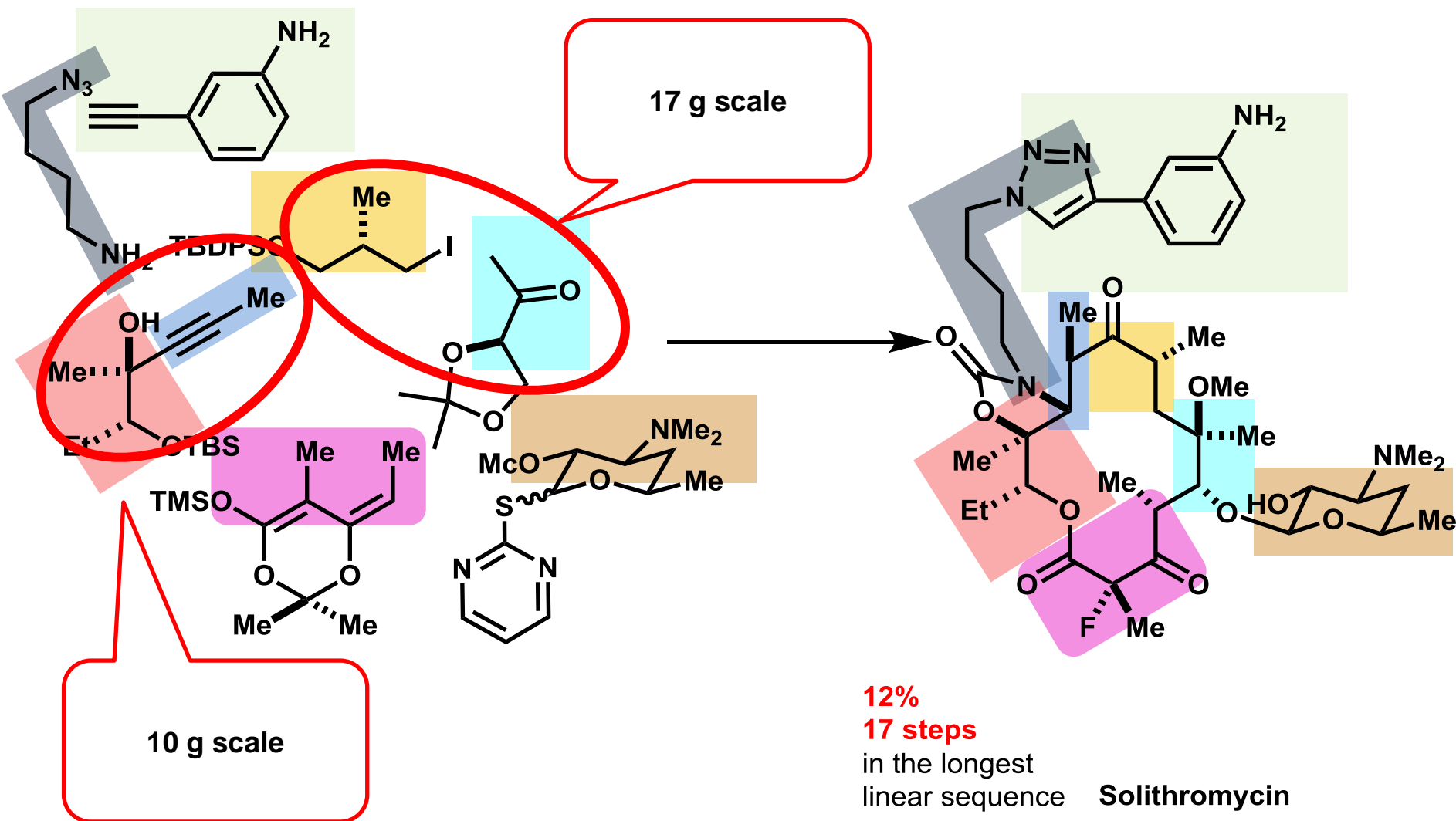
# Completion total synthesis of solithromycin (1)



# Completion total synthesis of solithromycin (2)

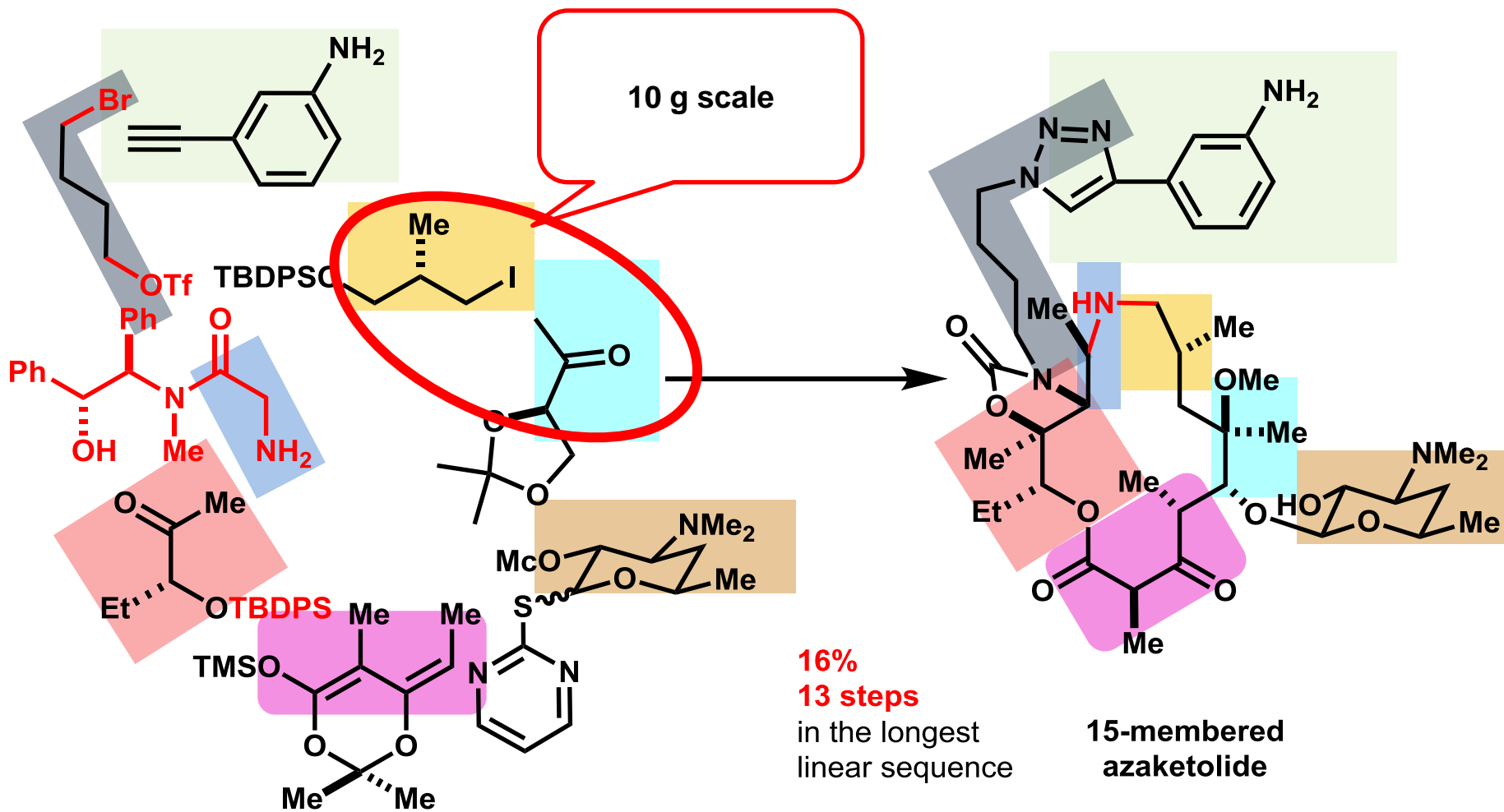


## Short summary (2)

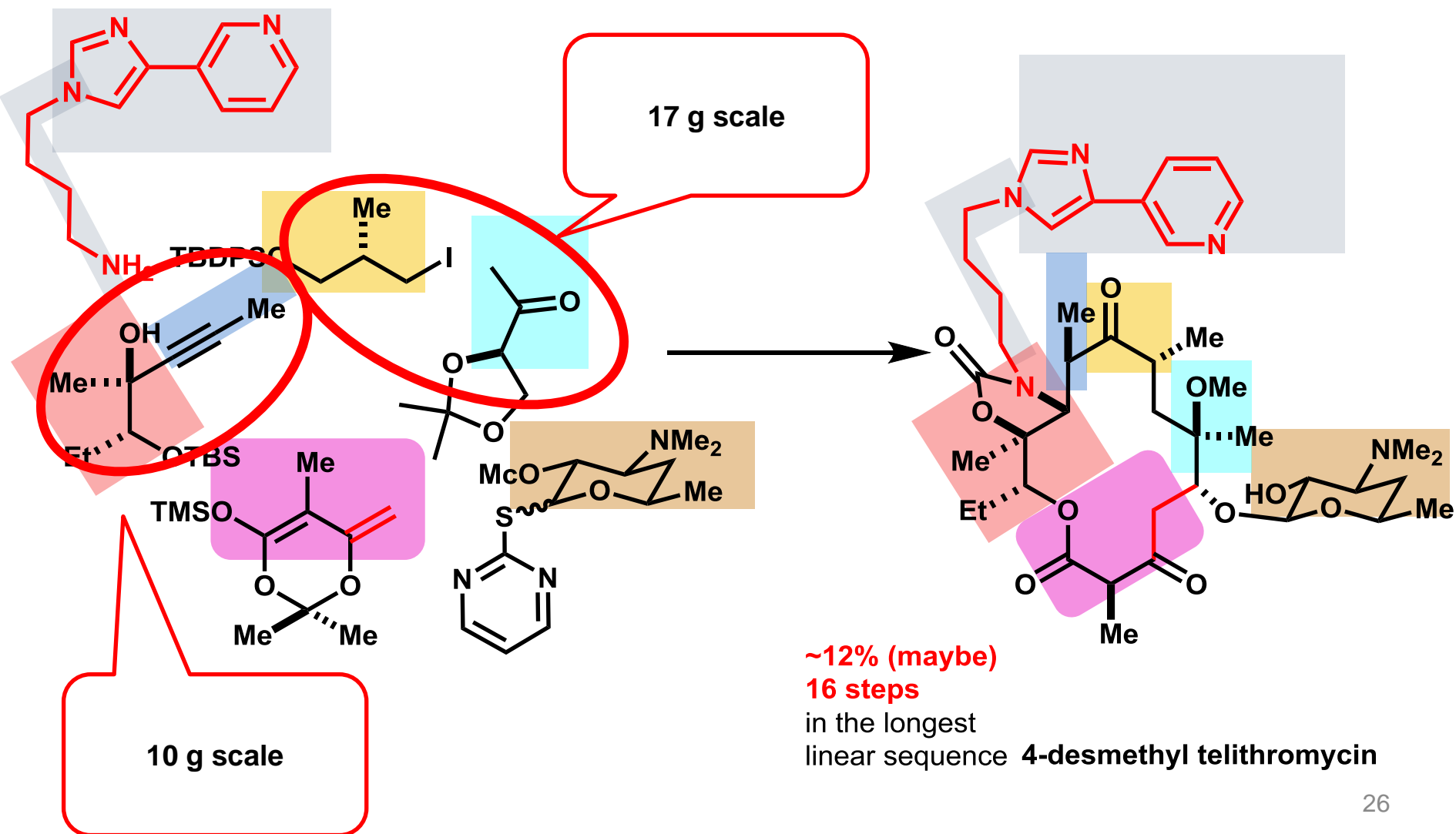




## Synthesis of 15-membered azaketolide using the strategy



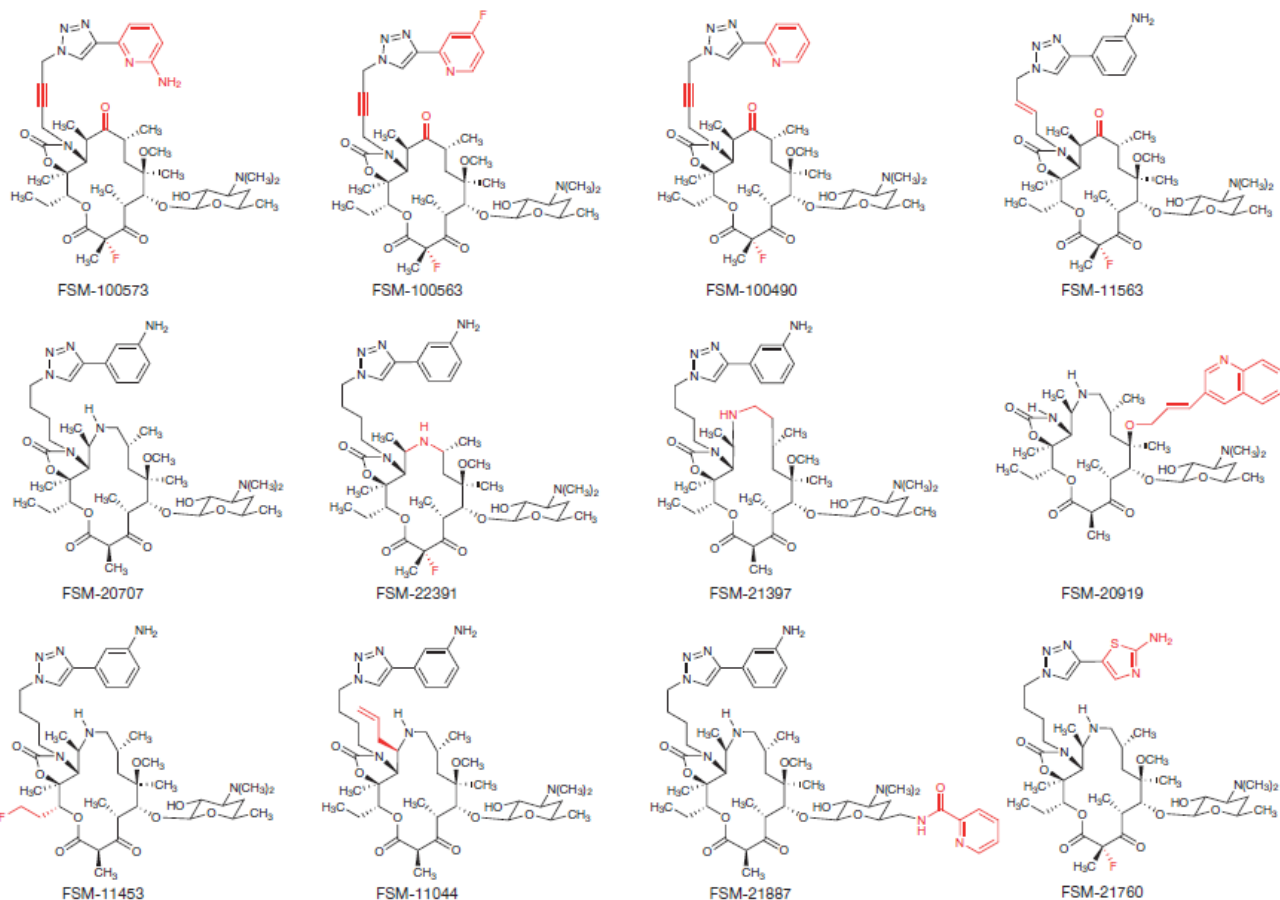
# Synthesis of 4-desmethyl telithromycin using the strategy..... (in my opinion)



# Evaluation for antibiotic activity

>300 fully synthetic macrolide antibiotic candidates were prepared to modify readily diversifiable elements.

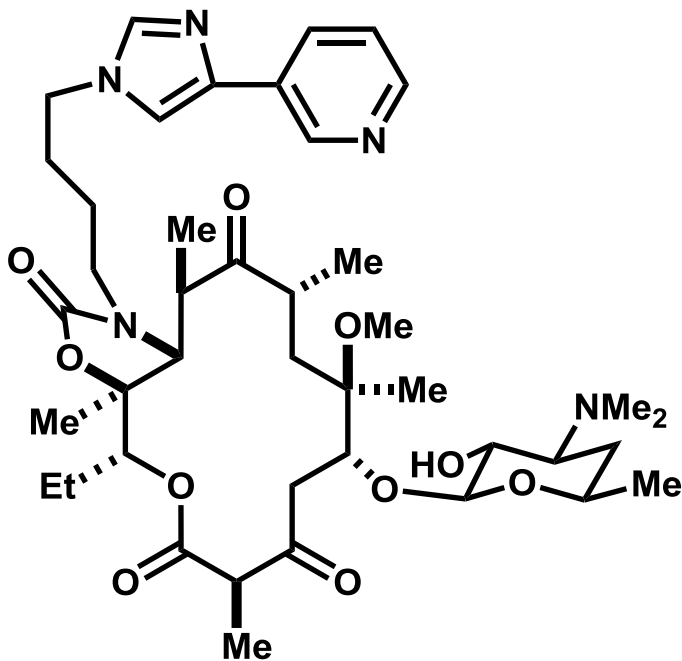
a majority of compounds in the candidates exhibit demonstrable antibiotic activity.



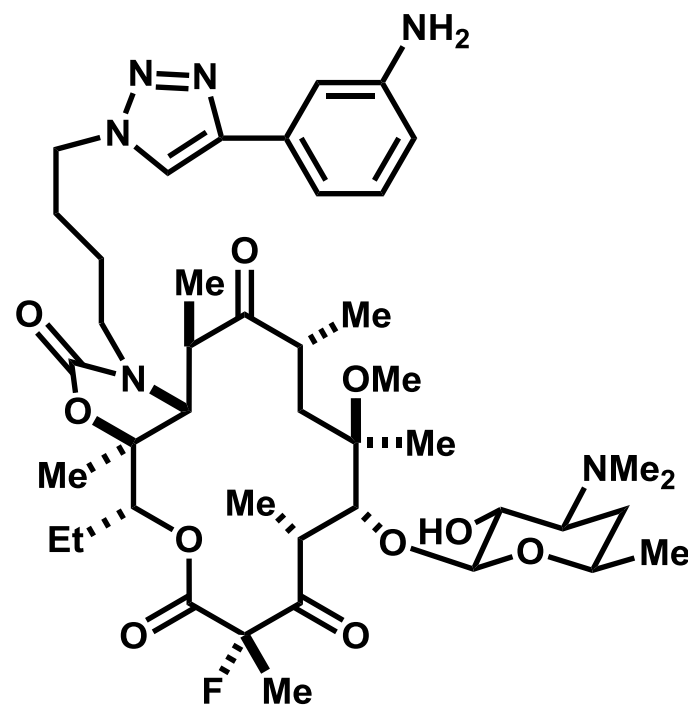
		Species	Strain description	Erythro	Azithro	Telithro	Solithro	100573	100563	100490	11563	20707	22391	21397	20919	11453	11044	21887	21760
Gram-positive		<i>S. aureus</i>	ATCC 29213	0.5	1	0.125	0.125	0.06	≤0.03	≤0.03	0.06	0.5	0.25	4	0.25	1	1	8	0.5
		<i>S. aureus</i>	BAA-977; iErmA	>256	>256	0.06	≤0.03	0.06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

# Summary

	Andrade's approach	Myers' approach
modular building blocks	6	8
convergent coupling reactions	5	7
protection reactions	5	2
deprotection reactions	6	2
<b>results</b>	<b>0.067%</b> <b>31 steps</b> in the longest linear sequence	<b>12%</b> <b>17 steps</b> in the longest linear sequence



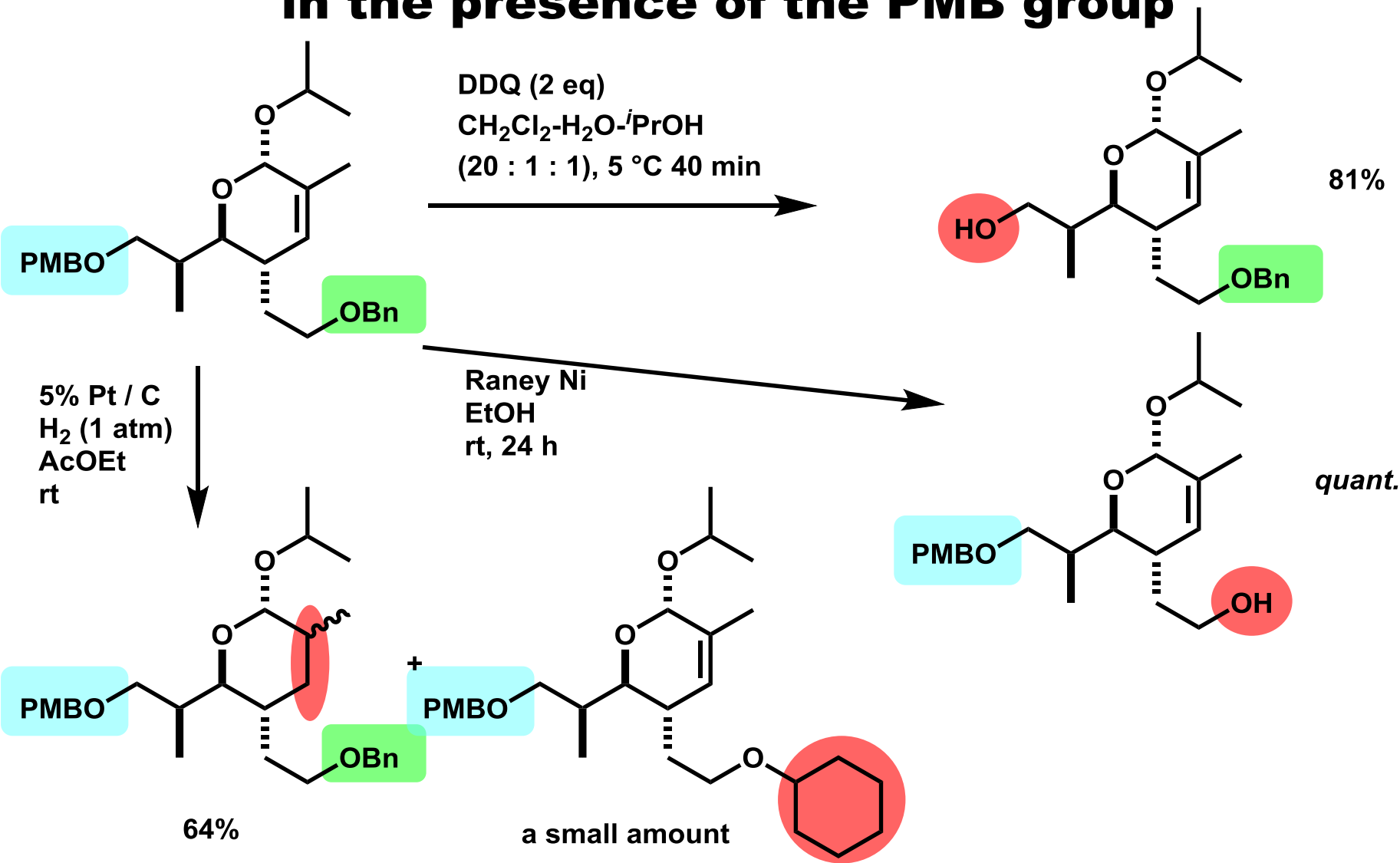
4-desmethyl telithromycin



Solithromycin

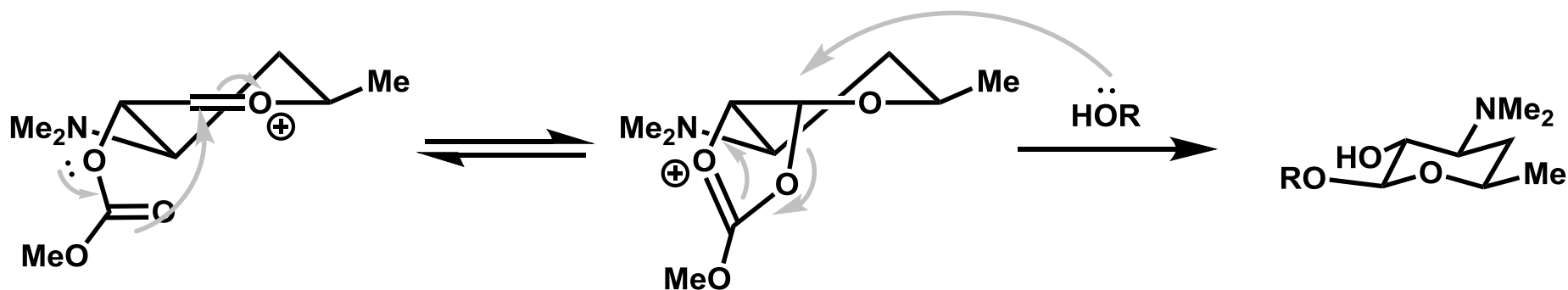
# Appendix

## Chemoselective removal of the Bn group in the presence of the PMB group



# Appendix

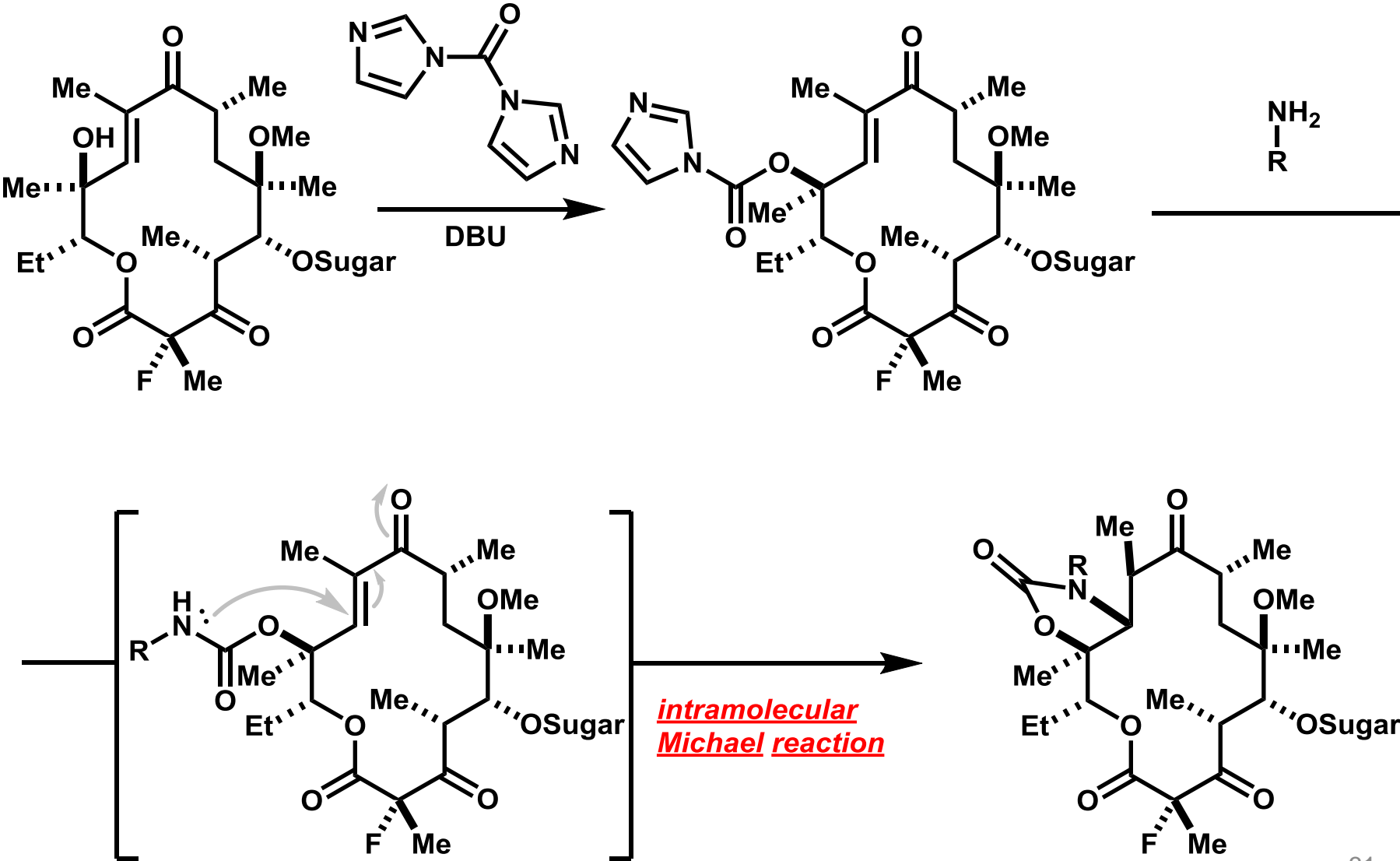
## 1,2-*trans* type glycosylation



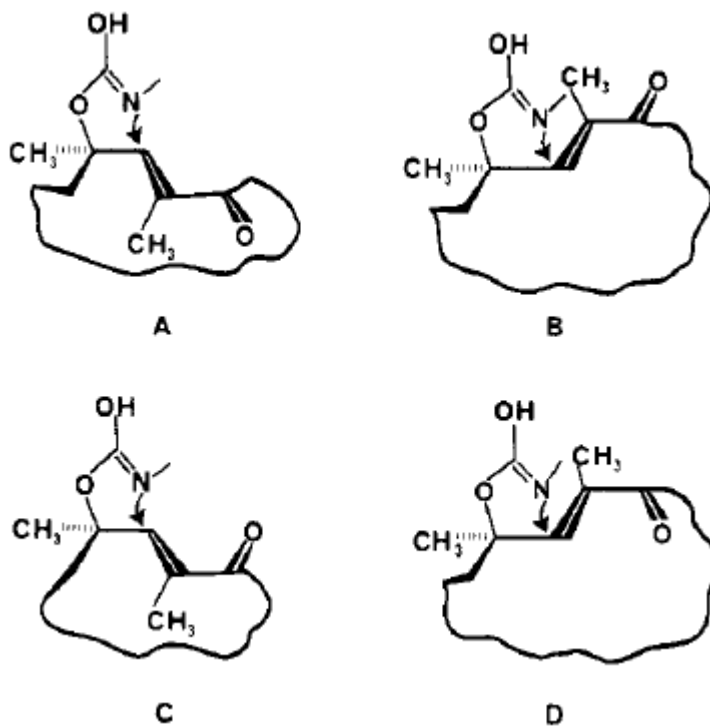
Neighboring group participation

# Appendix

## Baker cyclization



## Stereochemical of carbamate



**Figure A-1** Four low energy conformations of the unsaturated ketone (derived from erythromycin) with calculated (MM2) energies of **(A)** 58.8, **(B)** 52.3, **(C)** 56.6, and **(D)** 53.7 kcal/mol.