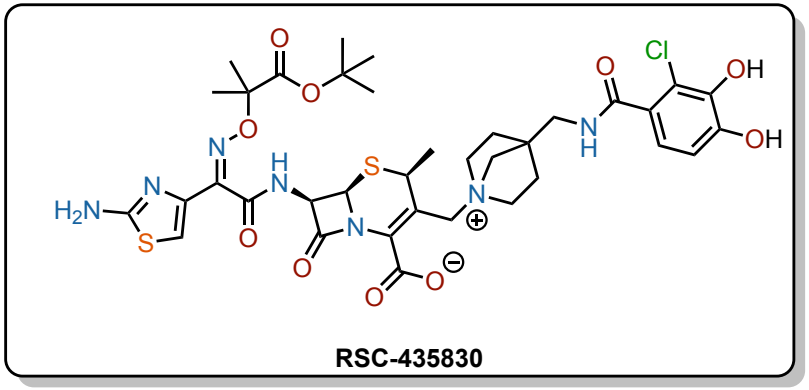
RSC-435830

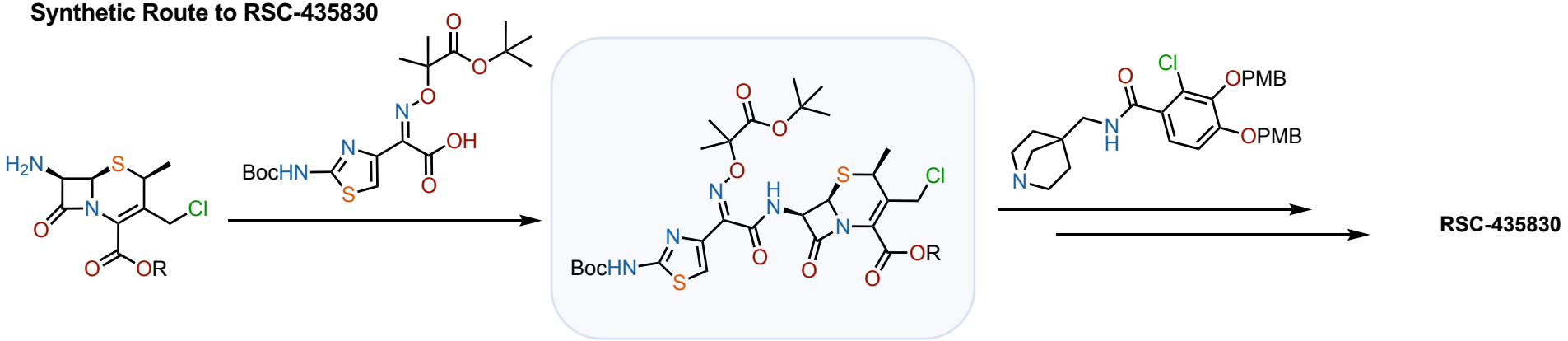
Introduction:

- Novel antibiotic to combat against antimicrobial resistance (AMR)
- Promising candidate against several antibiotic resistant bacteria
- Has advanced to phase I clinical trials
- Potent against β-lactamase-producing Gram negative bacteria
- Identified a key C2 (*S*)-*Methylcephalosporin* intermediate for synthesizing this drug via a stereoselective isomerization of an olefin and optimization of a Mannich-type reaction

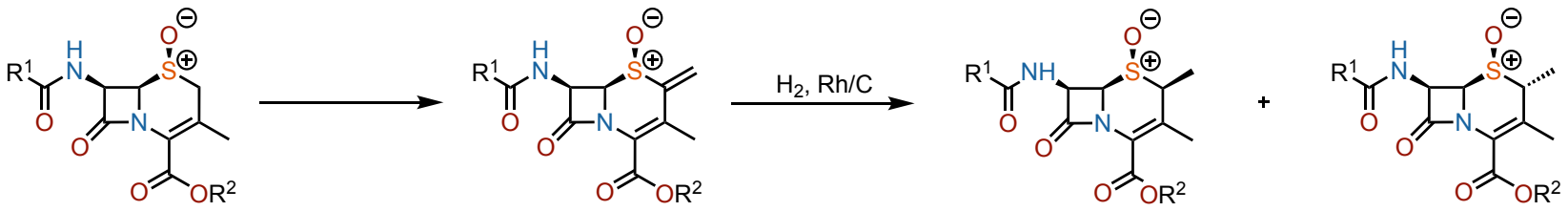
SHIONOGI



Synthetic Route to RSC-435830



Eli Lilly [1971]: Synthesis of 2-Methyl Cephalosporin Analogues



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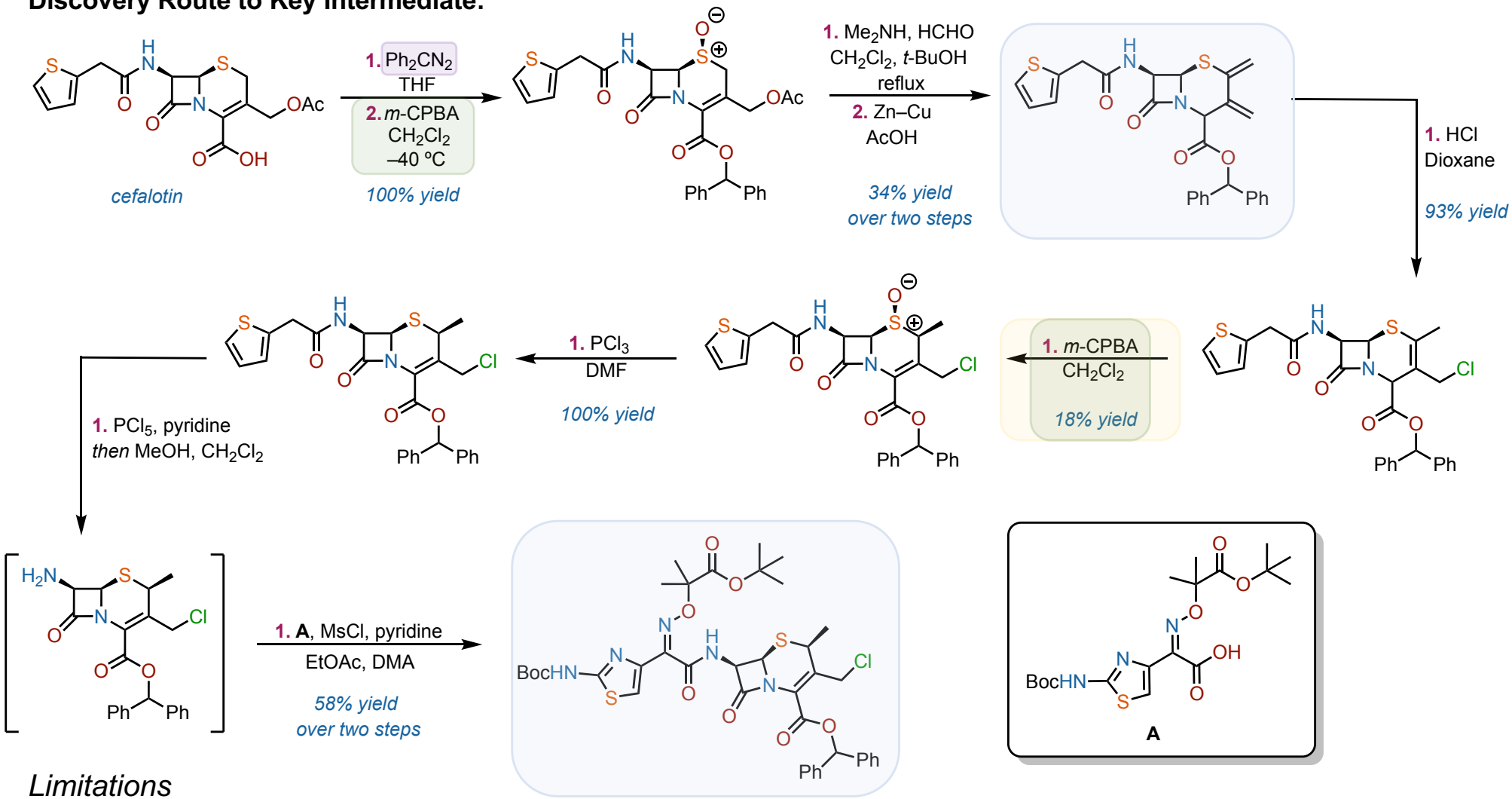
Discovery Route to Key Intermediate:

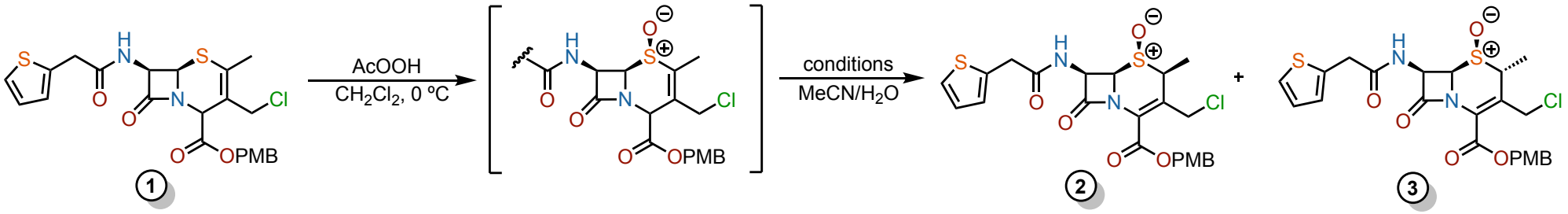


Limitations

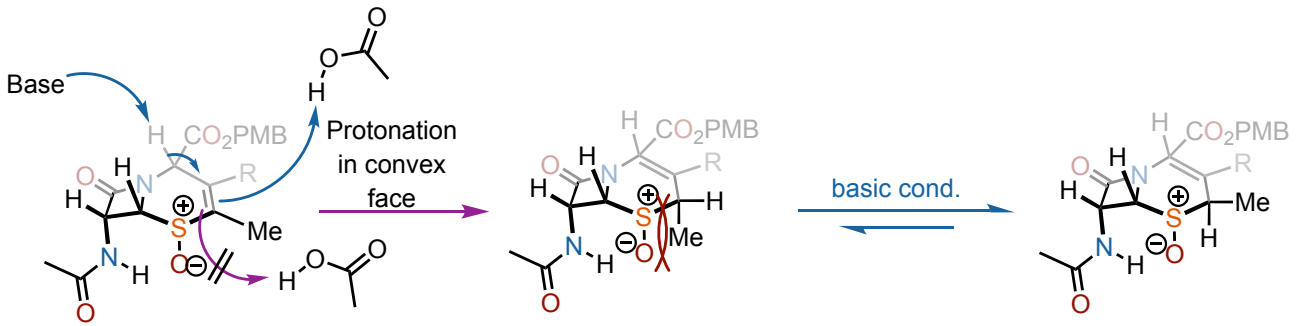
Chromatography	Low throughput
Low Yielding	Hazardous
Total number of steps	

- 9 steps
- Two column chromatography steps
- Overall yield 3%

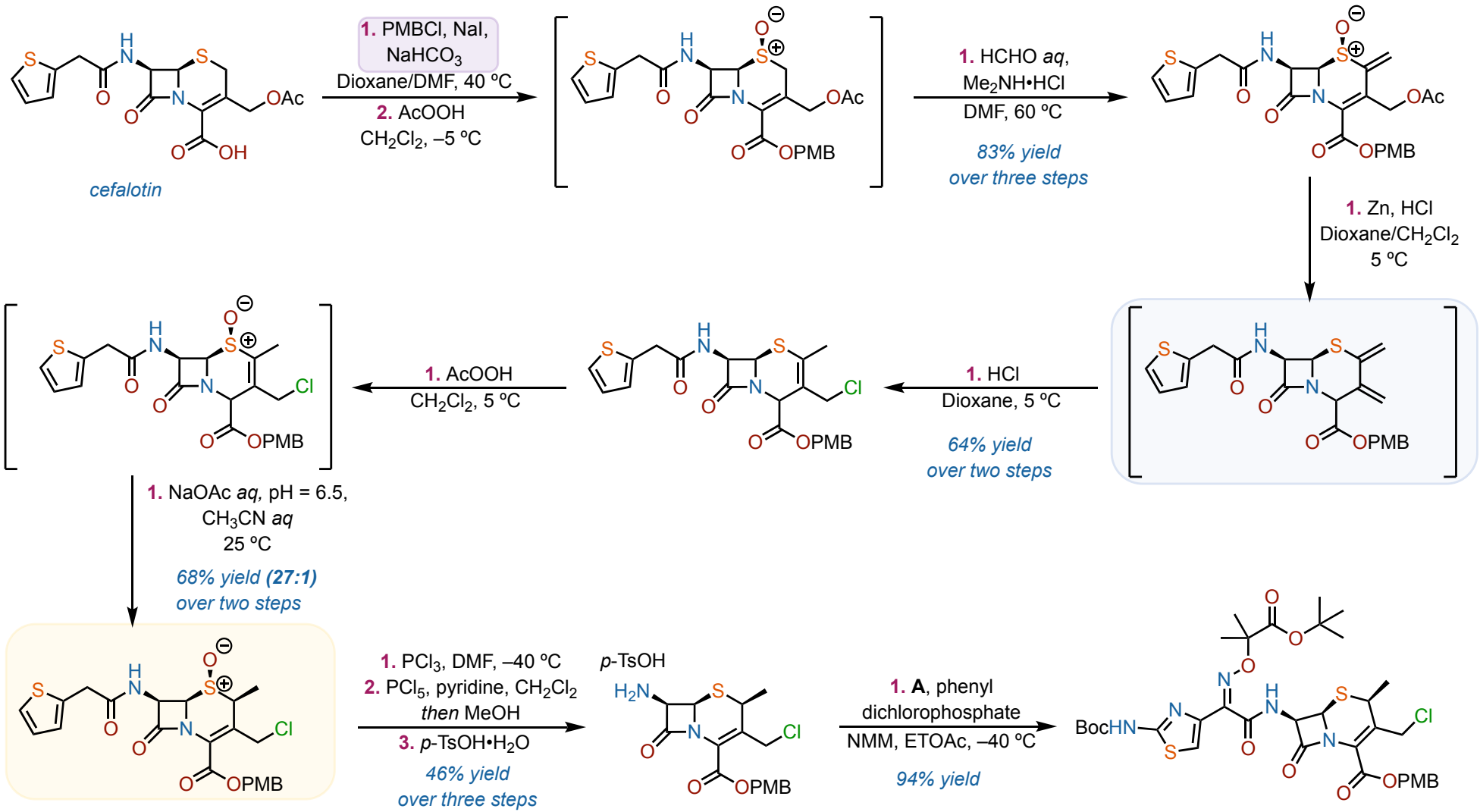
Oxidation and Subsequent Isomerization:



Entry	Base (1 eq)	2:3 (reaction mixture)	pH of reaction mixture	Yield (from 1) (%)	2:3 (after isolation)
1	$NaHCO_3$	5.7:1	not analyzed	66	9.5:1
2	NaOAc	10.8:1	6.7	80	14.1:1
3	NaOAc	7.5:1	7.5	not isolated	
4	$NaHCO_3$	2.4:1	not analyzed	48	5.7:1



First generation Route to Key Intermediate:



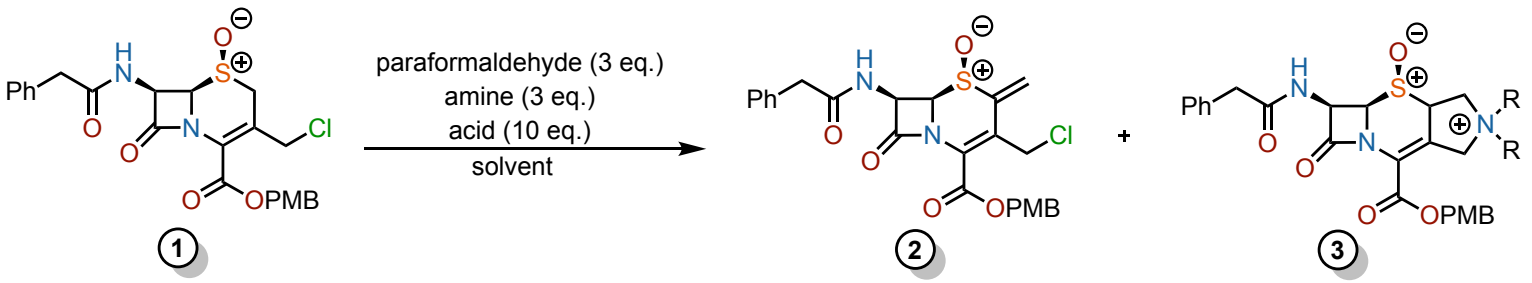
Improvements

- Avoided chromatography
- Elimination of hazardous compound
- Reduced amount of excess solvent
- Improved Yield

Limitations

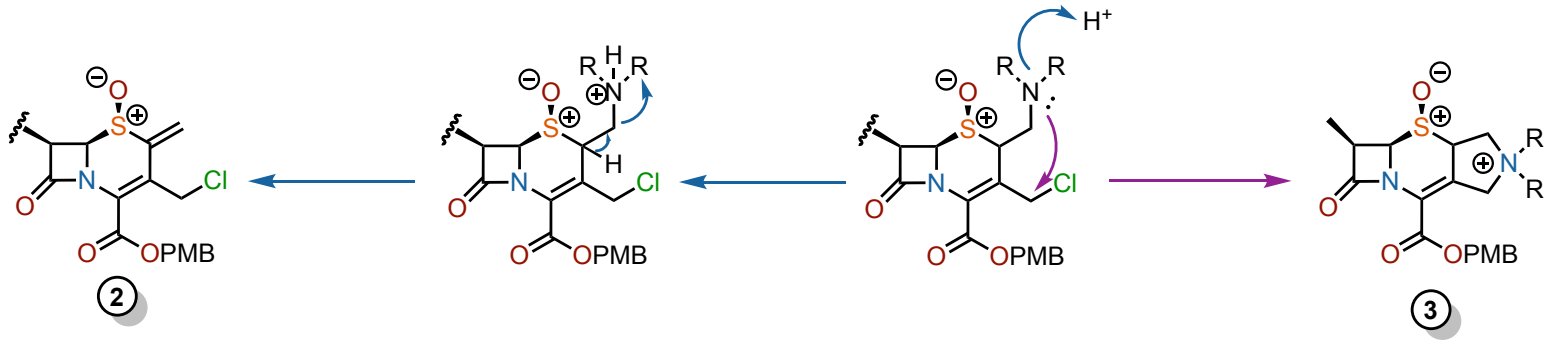
- Total number of steps
- Conversion of C3-acetoxymethyl to chloromethyl

Investigation of Mannich-Type Reaction Using 3-Chloromethyl Cephalosporin



Entry	Base (1 eq)	Acid	Solvent	Temperature	1:2:3
1	Dimethylamine•HCl	AcOH	DMF	75	25:38:23 (26% isolated yield)
2	Dimethylamine•HCl	HCO_2H	DMF	70	25:49:15
3	Dimethylamine•HCl	TFA	DMF	60	29:28:0
4	Dimethylamine•HCl	TFA	DMA	60	31:51:7
5	Dimethylamine•HCl	35% HCl	DMA	60	No reaction
6	Dimethylamine•HCl	64% H_2SO_4	DMA	60	No reaction
7	Piperidine	TFA	DMA	60	7:47:31
8	Morpholine	TFA	DMA	60	7:24:24
9	Dimethylmethyleneiminium chloride	TFA	DMA	60	9:45:20
10*	Diisopropylamine	TFA	DMA	60	2:85:4 (58% isolated yield)

*1.0 eq of amine, 3.0 eq of TFA, & 10 eq of paraformaldehyde



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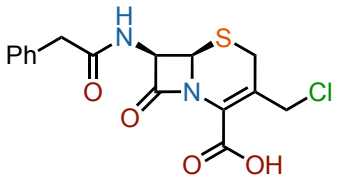
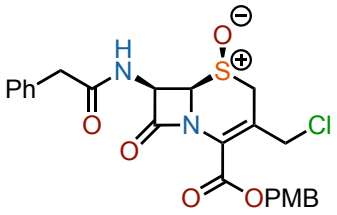
Second generation Route to Key Intermediate:



*GCLE **(24)***

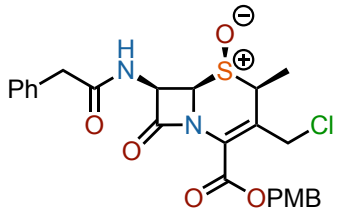
1. AcOOH, DMA
–20 to 0 °C

92% yield



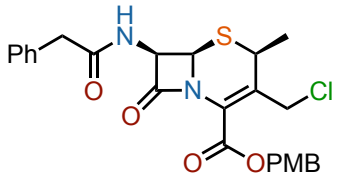
1. $(HCHO)_n$, TFA,
i-Pr_2NH, DMA, 65 °C
2. $NaBH_4$, NMP/MeOH,
–50 °C (**13:1**)

48% yield
over two steps



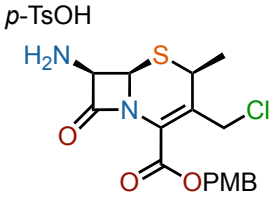
1. PCl_3,
DMF, –50 °C

69% yield



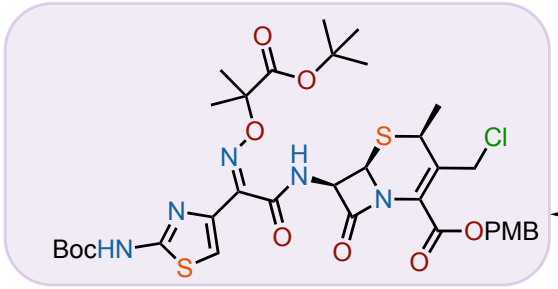
1. PCl_5, pyridine, CH_2Cl_2
then MeOH
2. *p*-TsOH•H_2O

66% yield
over two steps

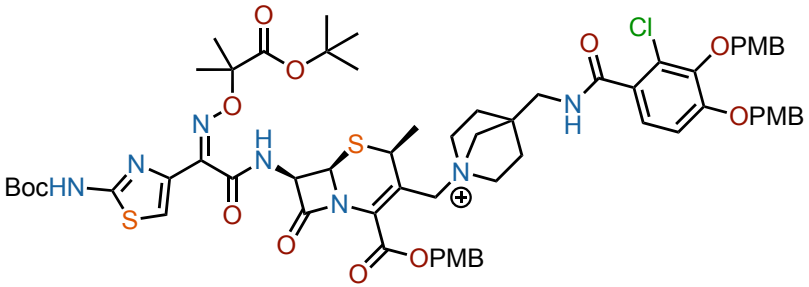


1. **A**, phenyl
dichlorophosphate
NMM, ETOAc, –40 °C

98% yield

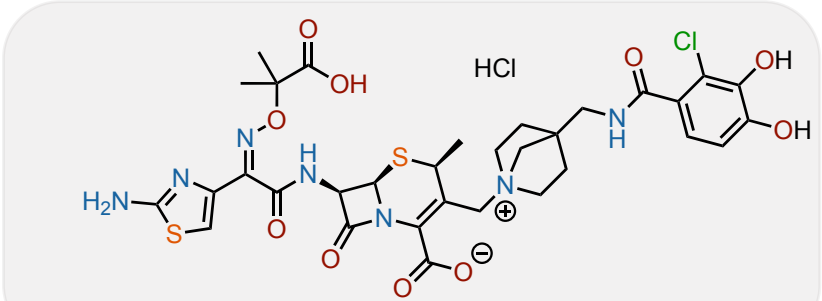


1. NaI, 15 °C,
then, **B** 5 to 15 °C,
DMA



1. H_2SO_4 *aq*,
formic acid, anisole
2. chromatography
(HP-20SS),
recrystallization

60% yield
over three steps



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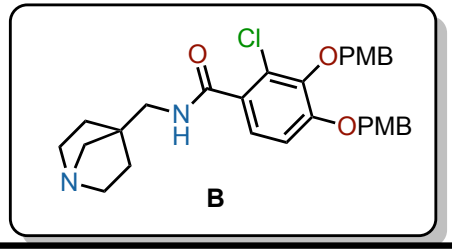

B

Key Improvements

Improved from 10 steps to 6 steps	900 g prepared
Started from chloromethyl analogue	355 g prepared
Improved overall yield from 3% to 17%	