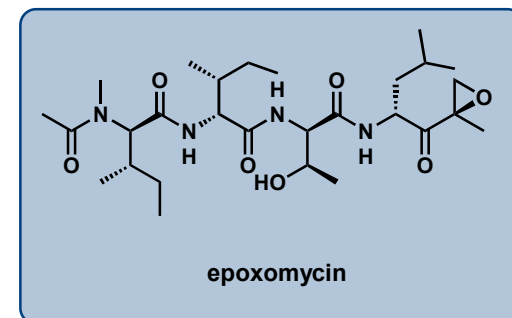
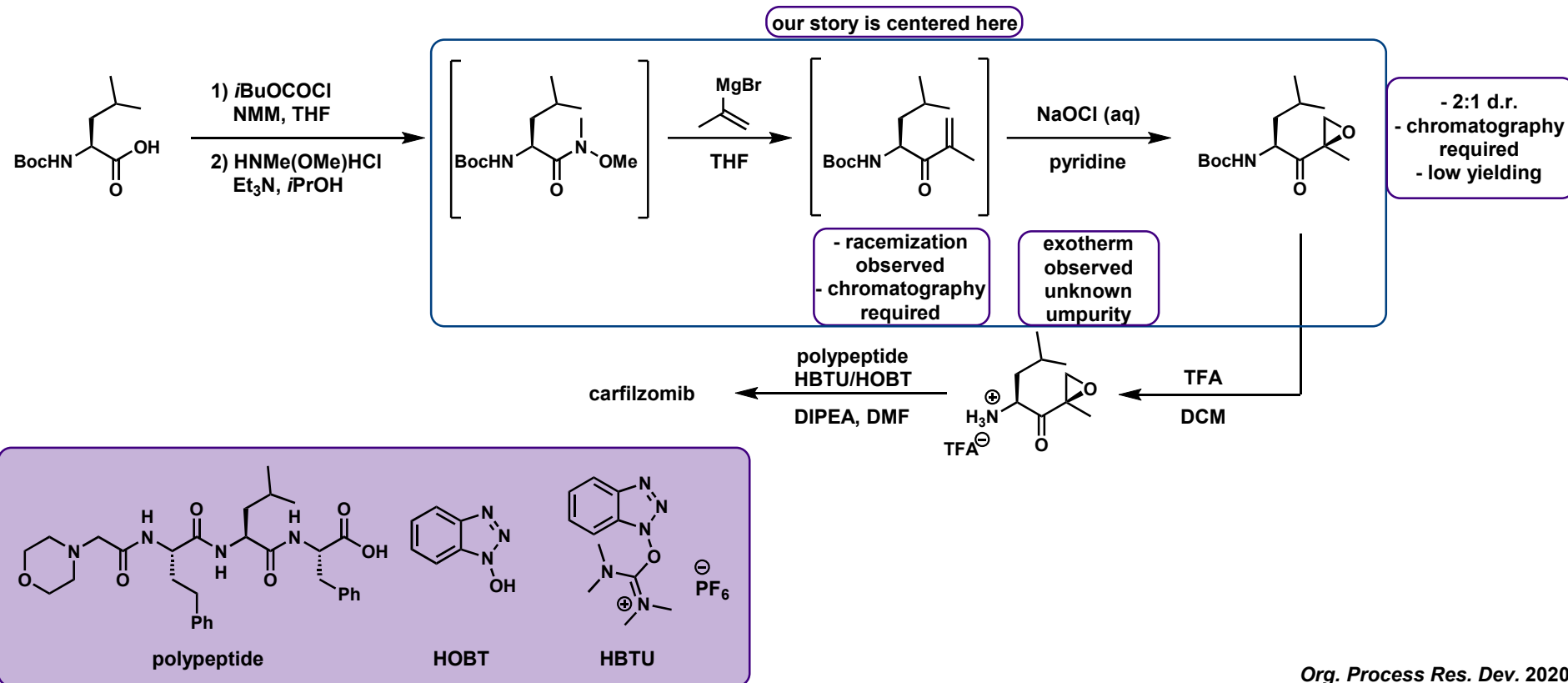


## Brief Overview:

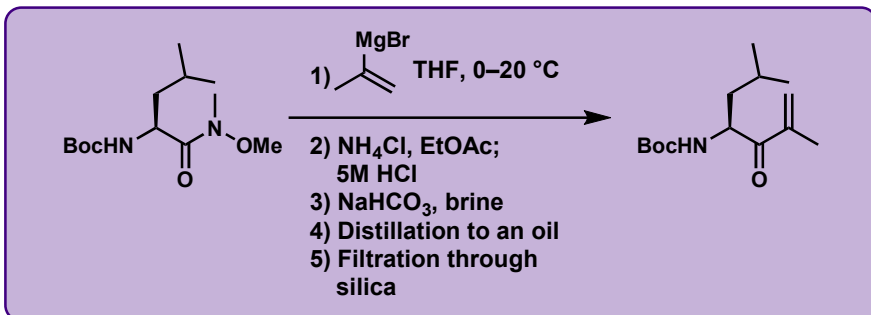
- Approved by the FDA in 2012
- Patients with multiple myeloma
- Disease must have progressed within 60 days of last therapy
- Derived from epoxomicin
- Covalently binds 20S proteasome
  - Build-up of proteins leads to apoptosis
- Initially developed by Onyx (now Amgen)
- 10,000\$ per month of treatment



## Manufacturing Route:

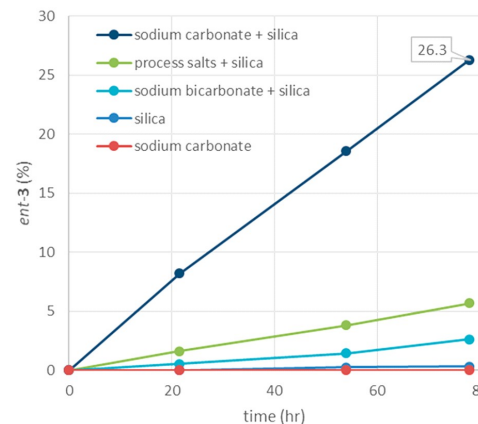
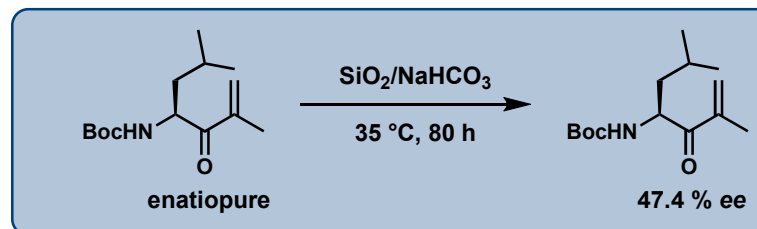


zoom-in of the grignard addition:



- Racemization was noted after the distillation
- Increased racemization was noted if column chromatography preceded distillation
- Subjecting the product to silica did not lead to sufficient racemization

entry	sampling point	% enantiomer			
		A	B	C	D
1	before step 4	<0.05%	<0.05%	<0.05%	<0.05%
2	after step 4	0.19%	0.15%	0.66%	0.05%
3	after step 5	0.41%	0.14%	3.39%	<0.05%



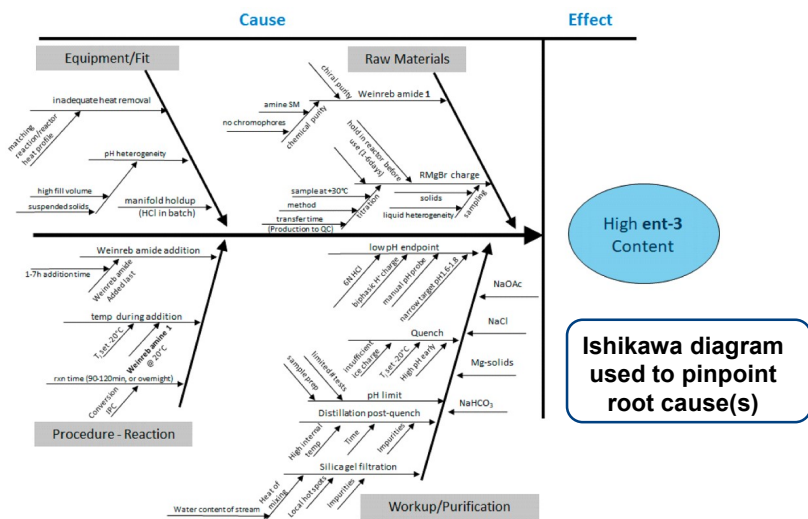
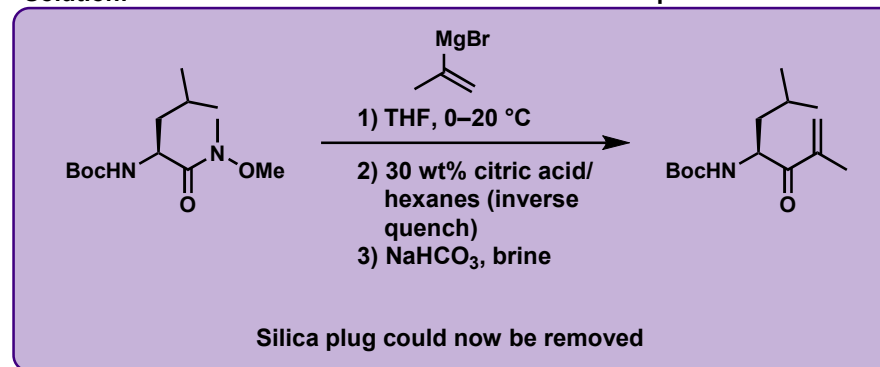
Hypothesis:

- Adsorption onto silica increases the acidity of the alpha proton

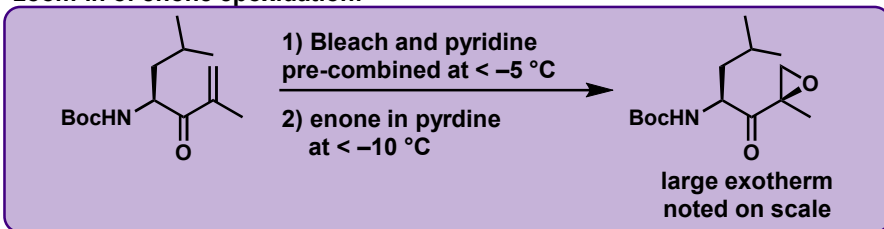
Therefore:

- Upon distillation leftover  $\text{NaHCO}_3$  (observed) would generate  $\text{Na}_2\text{CO}_3$  in large quantities upon removal of  $\text{H}_2\text{O}$  and  $\text{CO}_2$
- This would lead to an increase in the pH that would lead to the racemization of the product

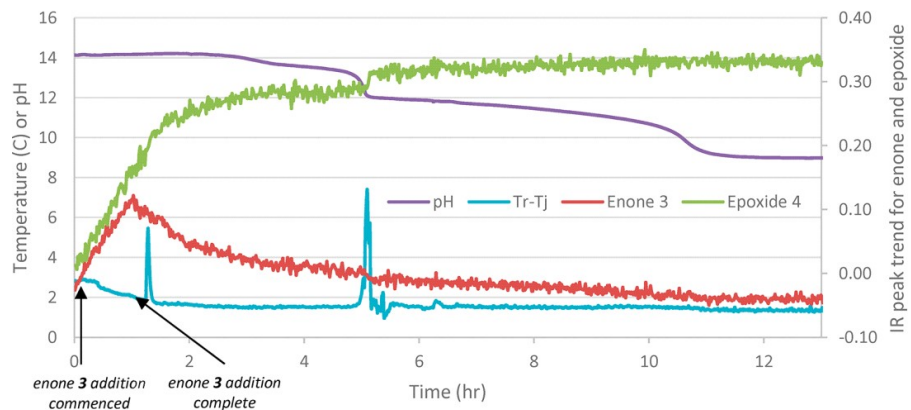
Solution:



zoom-in of enone epoxidation:

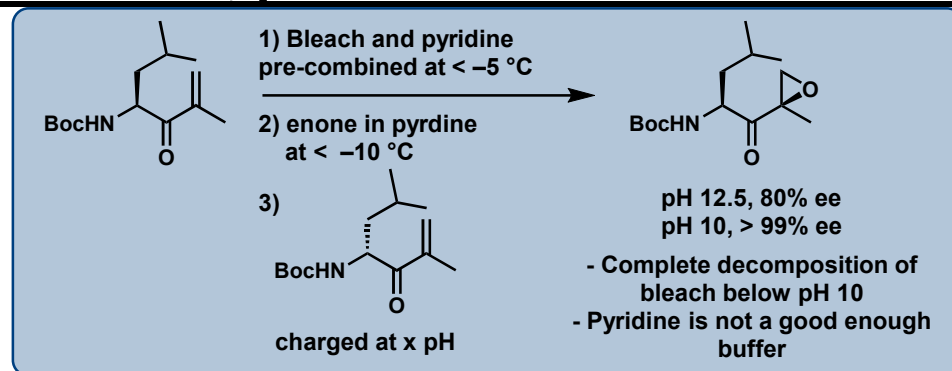
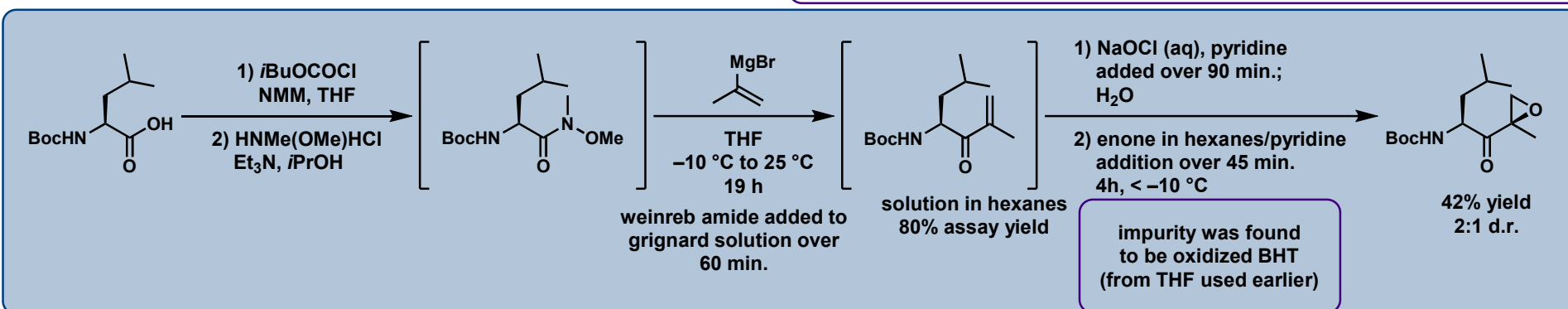


Lab-scale simulation/monitoring



- exotherm upon warming
- pH decreases upon exotherm
- product formation essentially complete

Finalized Procedure:



Pyridine  $\xrightarrow[\text{charged over 100 min. } < -5\text{ }^{\circ}\text{C}]{\text{bleach}}$  bleach/pyridine suspension

entry	pyridine source	modification	bleach/pyridine activity	color
1	vendor 1	none	99%	pale yellow
2	vendor 2, lot 1	none	2.6%	brown
3	vendor 2, lot 2	none	2.3%	brown
4	vendor 2, lot 1	addition over 10 min.	94%	pale yellow
5	vendor 2, lot 1	pretreat with $\text{K}_2\text{CO}_3$ ; filter	96%	pale yellow
6	vendor 1	20 ppm $\text{FeCl}_3$	1.9%	brown

Acidic impurities lead to decomposition of bleach, loss of activity