

Total Syntheses of (-)-Pyrimidoblamic Acid and P-3A

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J. Am. Chem. Soc., 2014, 136 (5), 2119–2125

DOI: 10.1021/ja412298c

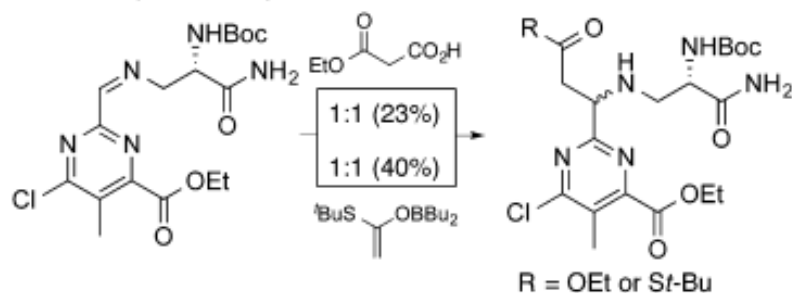


Streptomyces verticillus

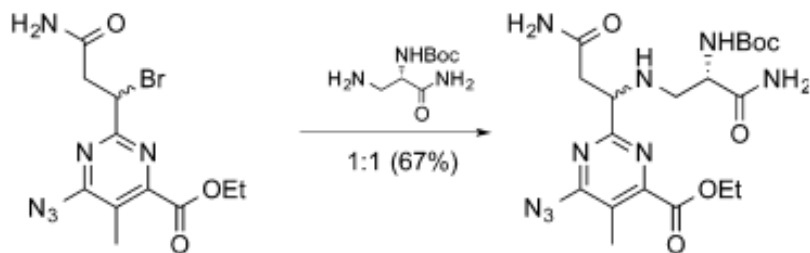
Current literature
Andrey Kuzovlev
06.03.2014

Prior Late Stages Installations of the Benzylic C₂-Stereocenter of (-)-Pyrimidoblamic Acid

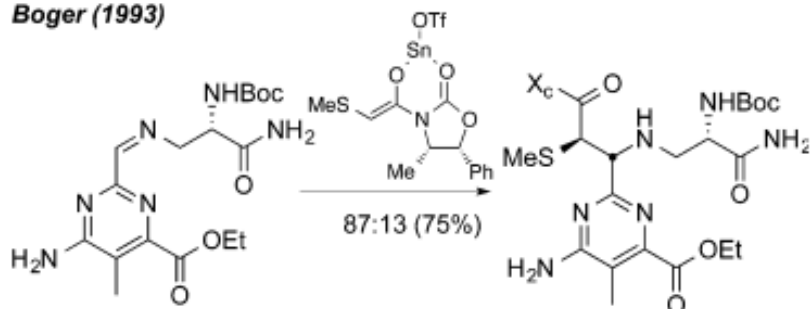
Umezawa (1980, 1985)



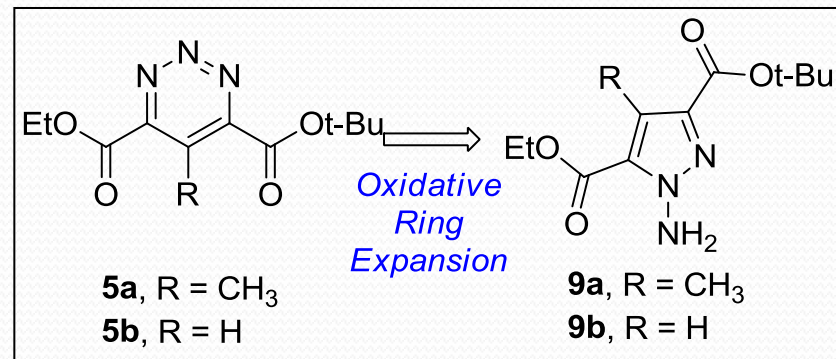
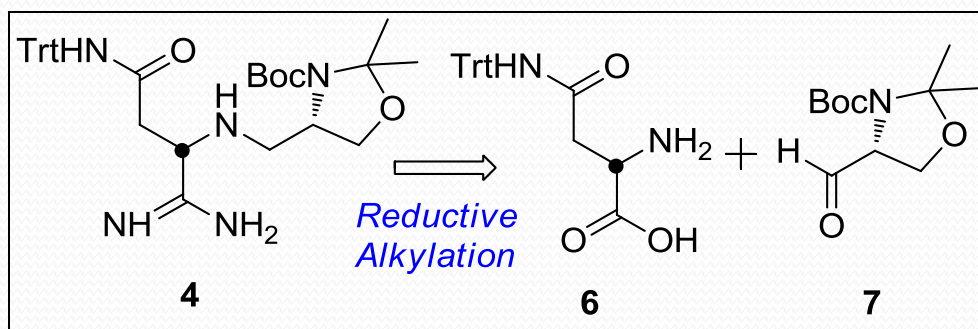
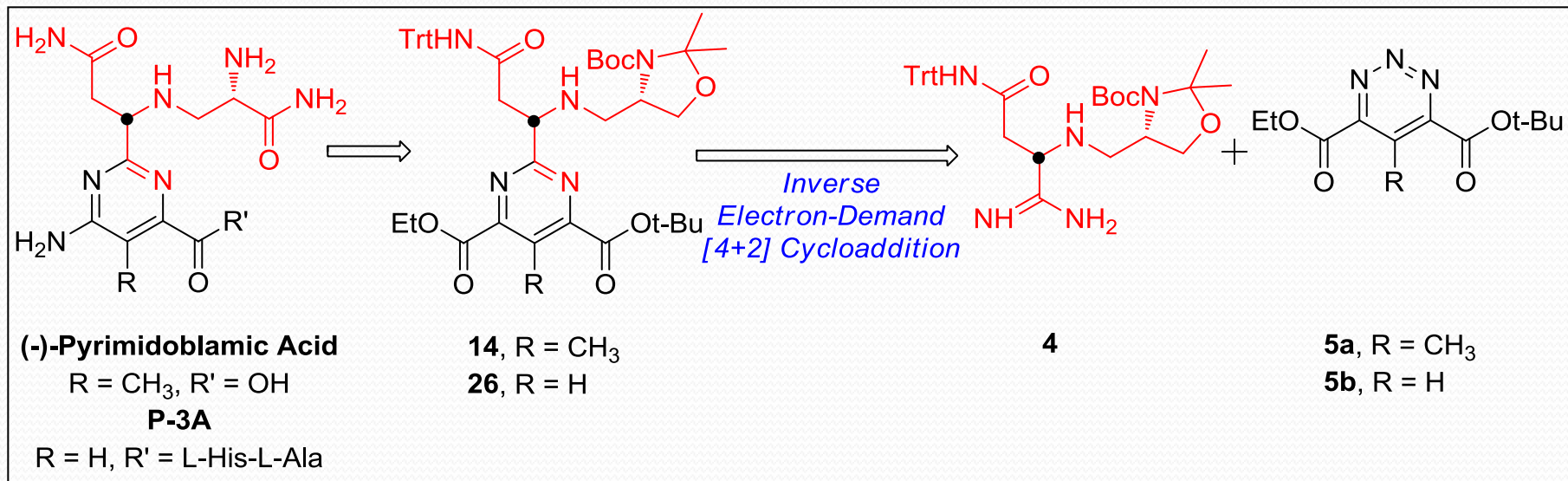
Hecht (1980)



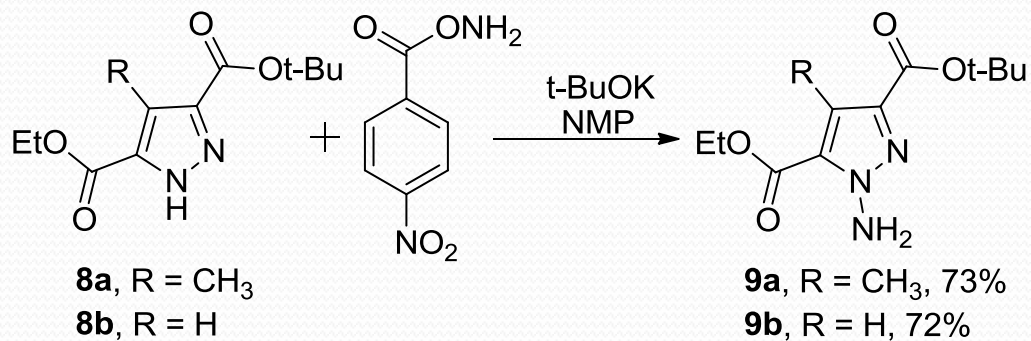
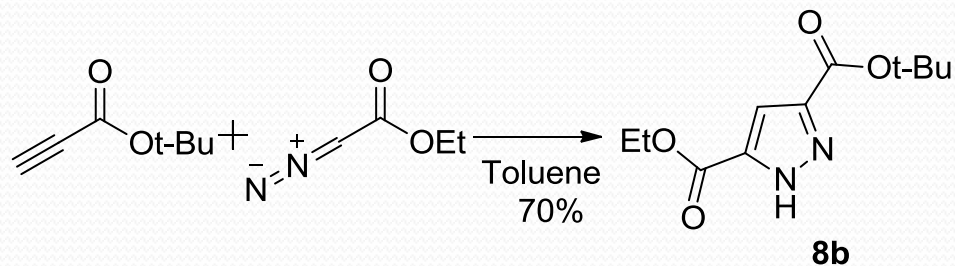
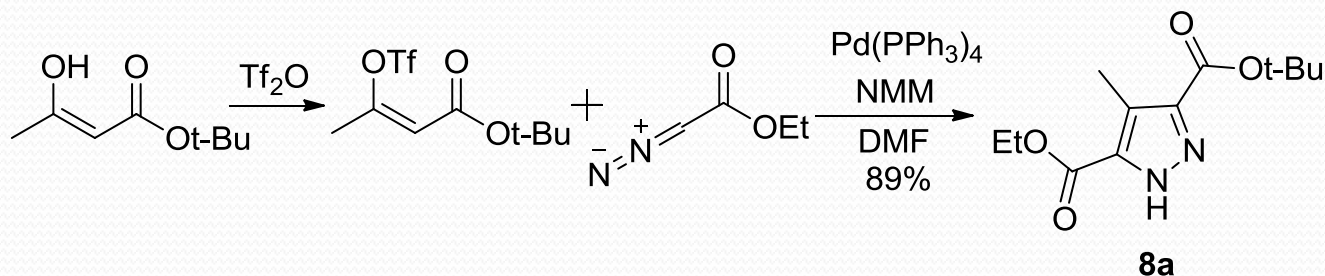
Boger (1993)



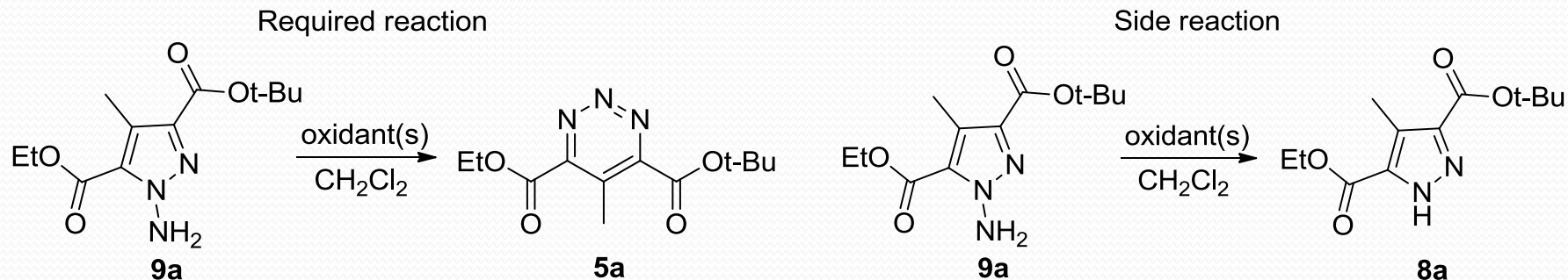
Retrosynthetic Analysis



Synthesis of Requisite N-Aminopyrazoles

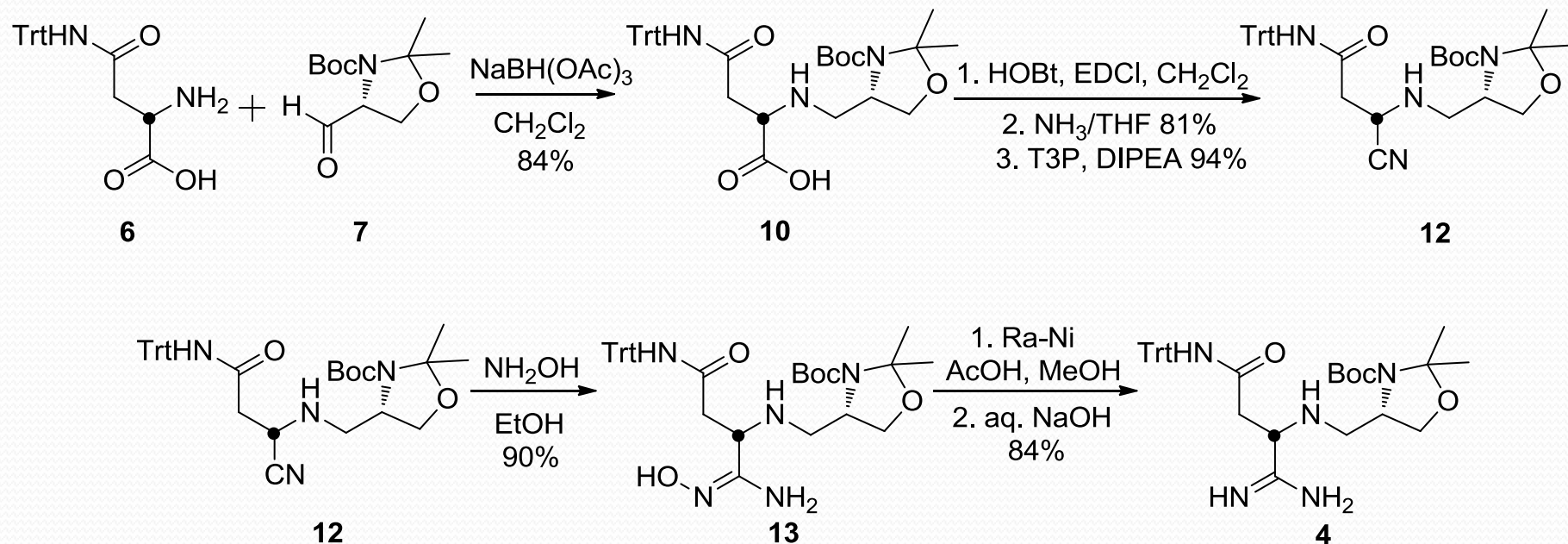


Oxidative ring expansion survey

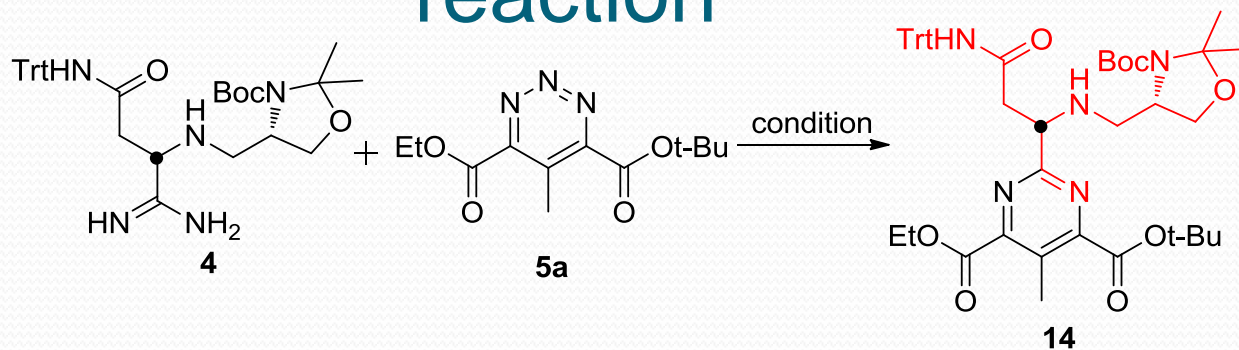


<i>Oxidant(s)</i>	<i>Product(s)</i> (% yield)
Ni ₂ O ₃	8a
MnO ₂	8a
Pb(OAc) ₄	8a
Pb(OAc) ₄ + Ni ₂ O ₃	8a
AgNO ₃	no reaction
AgNO ₃ + PIDA	5a (34%), 8a (49%)
NaIO ₄	5a (28%), 9a (70%)
NaIO ₄ , Bu ₄ NBr	5a (68-70%)
Bu ₄ NIO ₄	no reaction
I ₂ , 20% aq. KHCO ₃	5a (75%)

Synthesis of Chiral Amidine 4

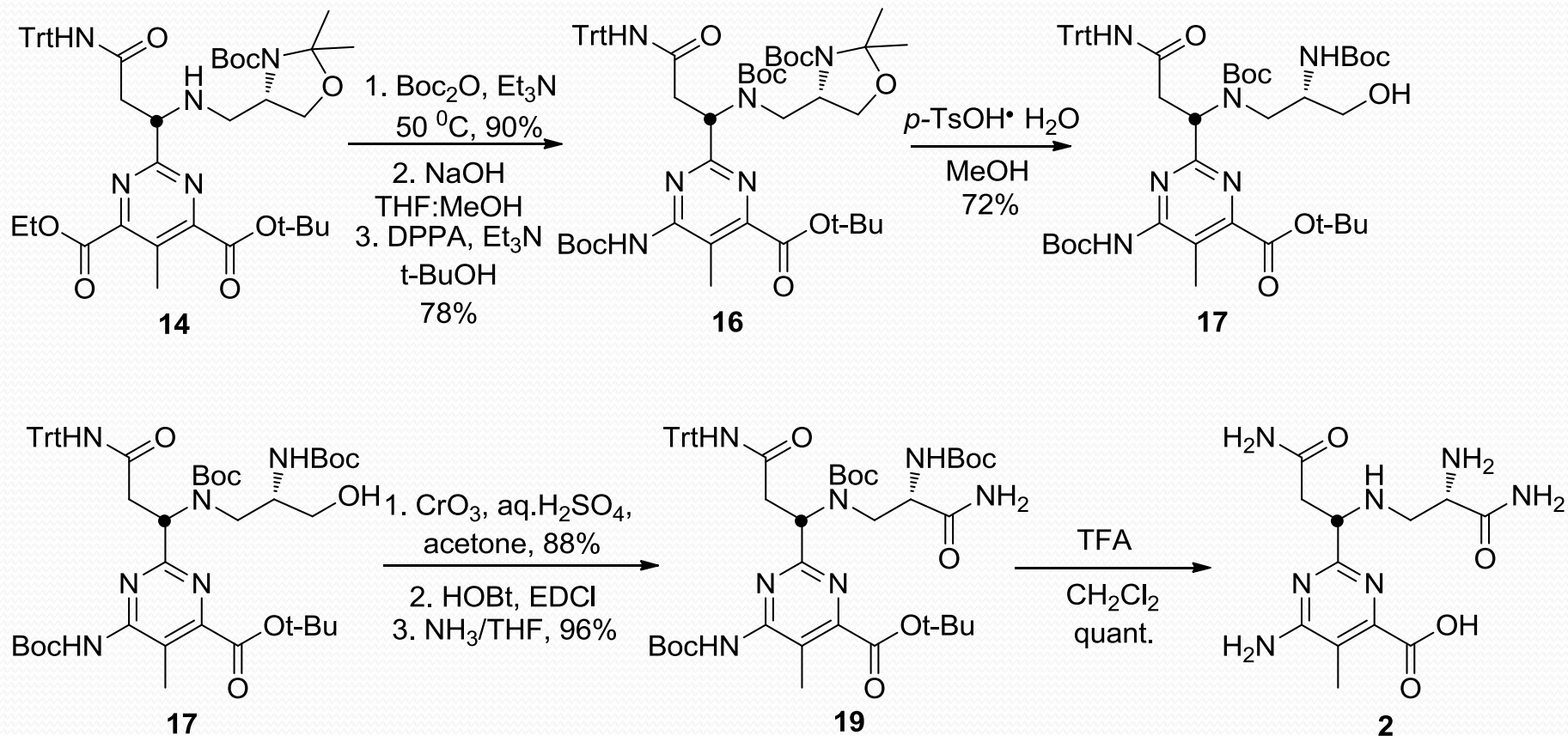


Optimization of the [4+2] cycloaddition reaction

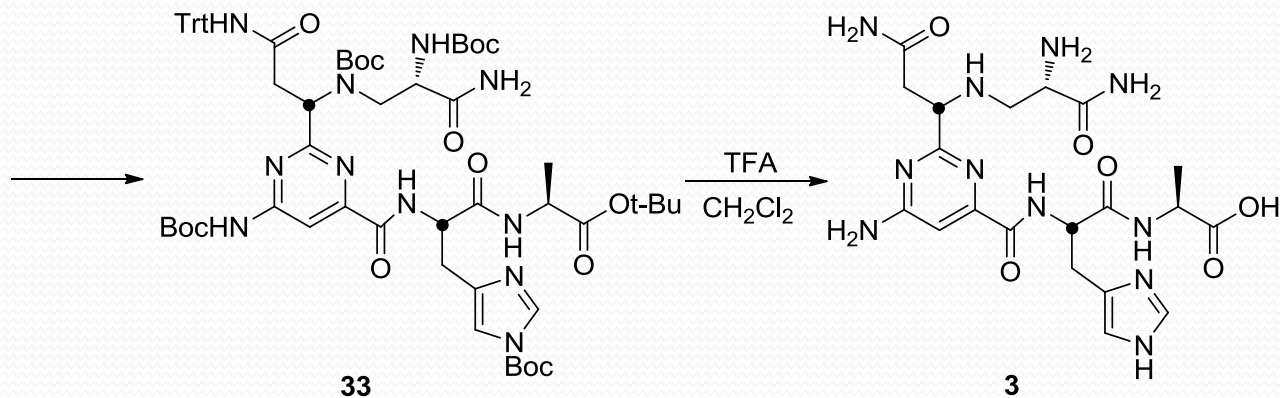
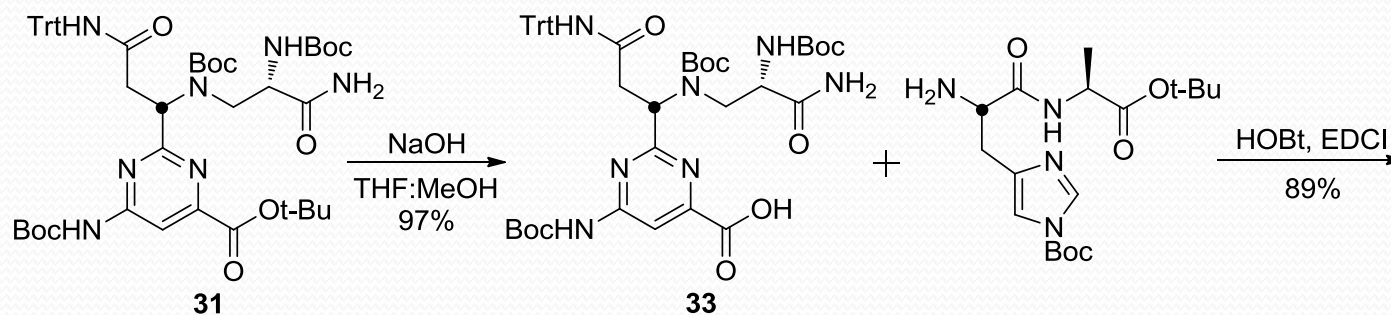
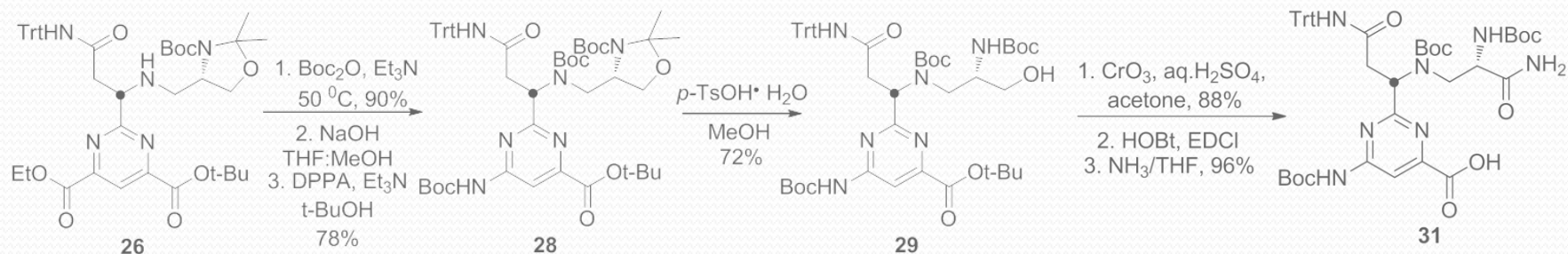


Reactants	Condition	Yield, dr
2.0 equiv. amidine	CH ₃ CN, 15h, 25°C	35%, 7:1
	CH ₃ CN, 15h, 25°C	40%, 4:1
	CH ₃ CN, 15h, 85°C	58%, 3:1
	CH ₃ CN, 39h, 25°C	50%, 7:1
	CH ₃ CN, 39h, 5°C	33%, single diastereomer
	CH ₃ CN, 39h, 5°C	22%, 7:1
	CH ₃ CN, 24h, 5°C then 17h, 25°C	43%, single diastereomer
2.0 equiv. triazine	CH ₃ CN, 20h, 5°C then 1h, 25°C	46%, single diastereomer
	CH ₃ CN, 14h, 5°C then 6h, 25°C	54%, single diastereomer

Completion of the Total Synthesis of (-)-Pyrimidoblamic Acid



Total Synthesis of P-3A



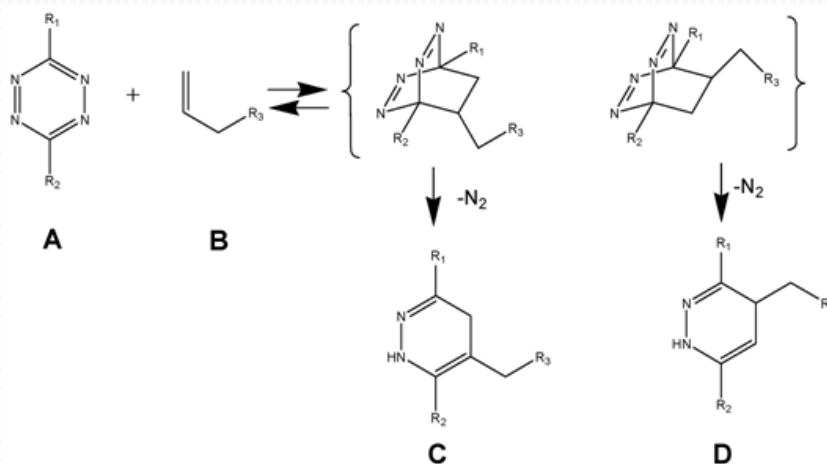
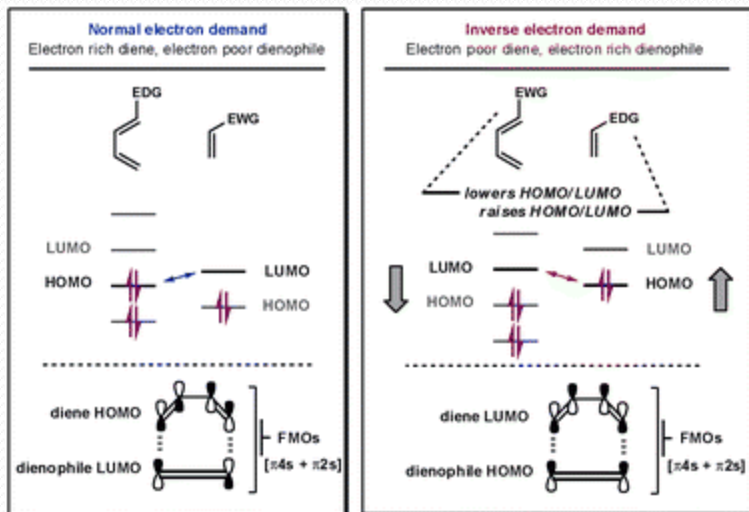
Conclusions

- Convergent total syntheses of (–)-pyrimidoblamic acid and P-3A with full control of the natural product stereochemistry.
- Powerful inverse electron demand [4+2] cycloaddition.
- This Diels-Alder reaction extend ability for synthesis of highly substituted and functionalized heterocycles found in complex natural products.

Thank you for your attention!



Diels-Alder reactions



Mechanism of the cycloaddition reaction

