

The tethered Biginelli condensation in natural product synthesis

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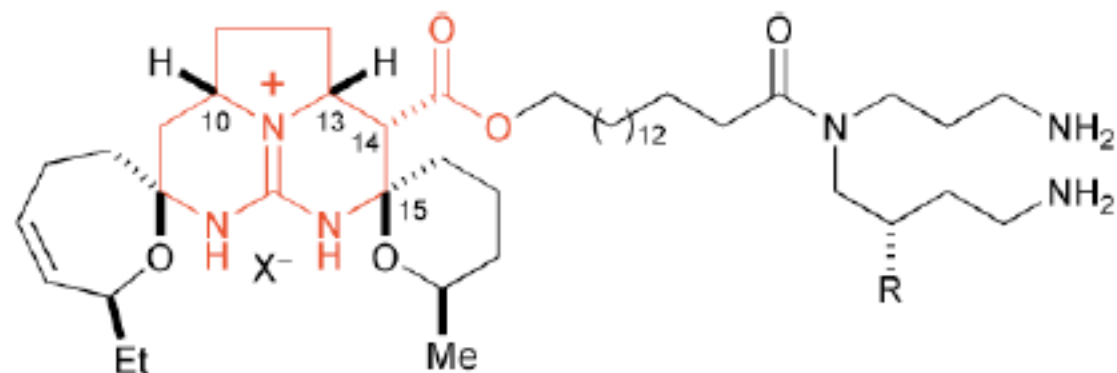
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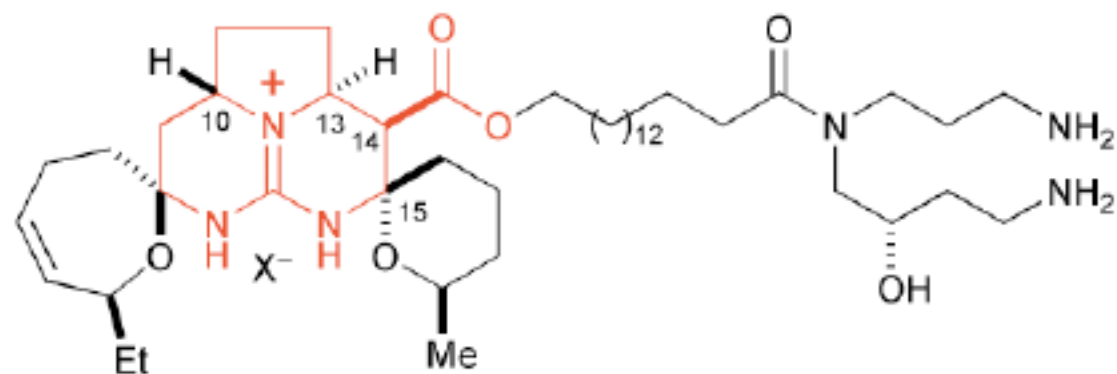
Received (in Cambridge, UK) 19th August 2003, Accepted 1st October 2003

First published as an Advance Article on the web 27th October 2003

Guanidine Alkaloids from Marine Sponges



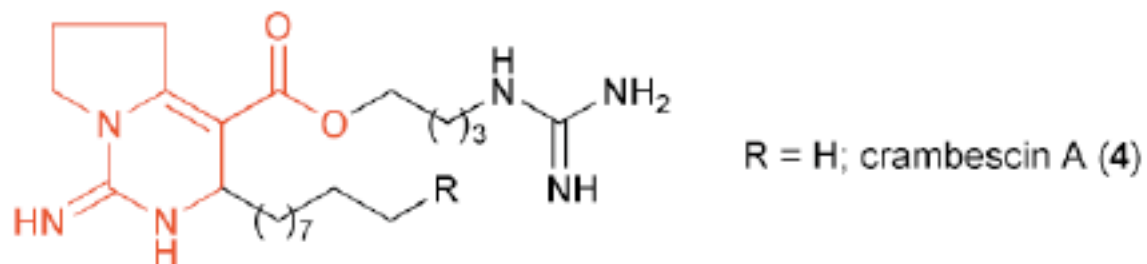
R = H, ptilomycalin A (1)
R = OH, crambescidin 800 (2)



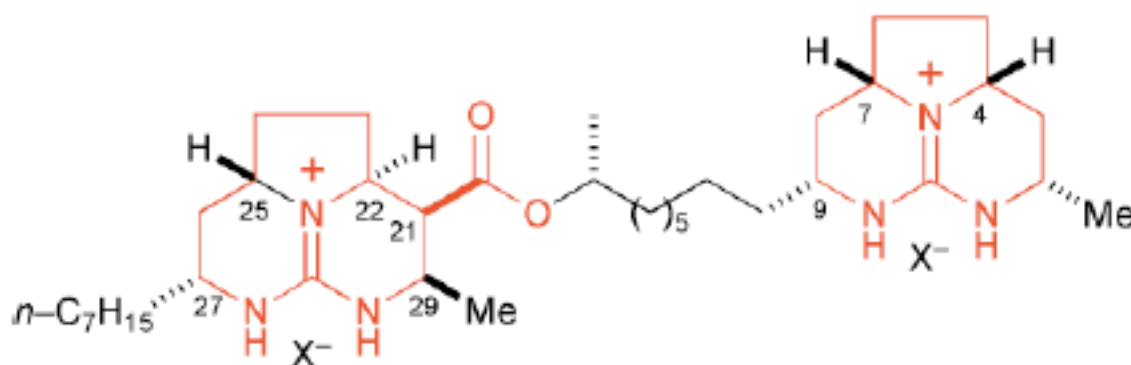
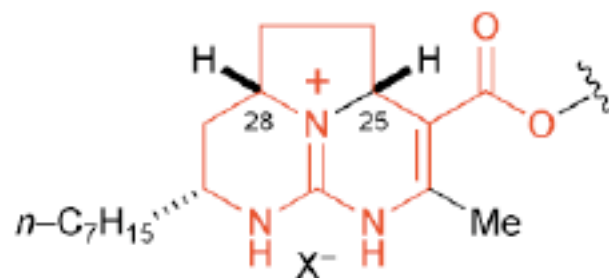
13, 14, 15-isocrambescidin 800 (3)

Guanidine Alkaloids from Marine Sponges

Continued

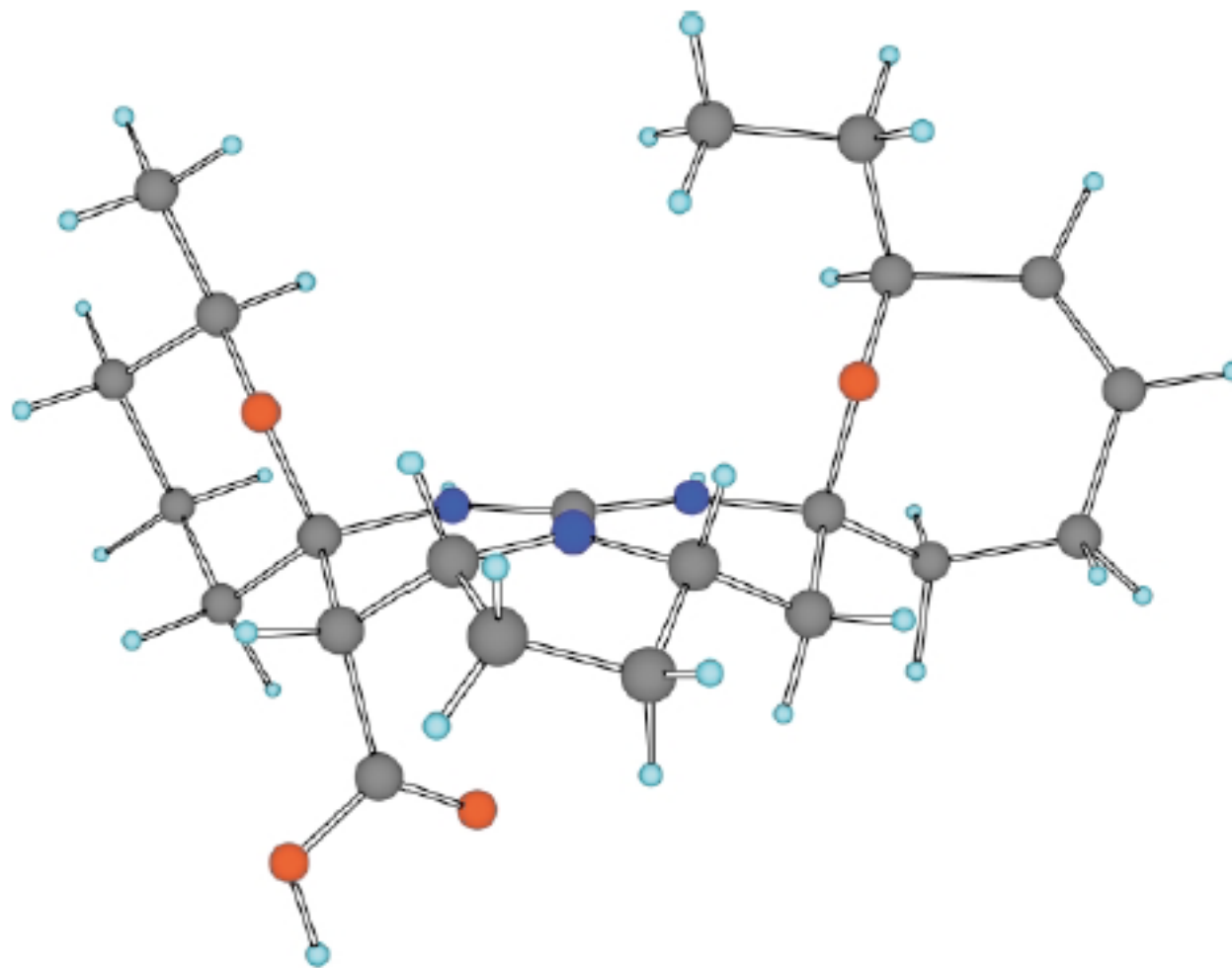


batzelladine B (5); R =

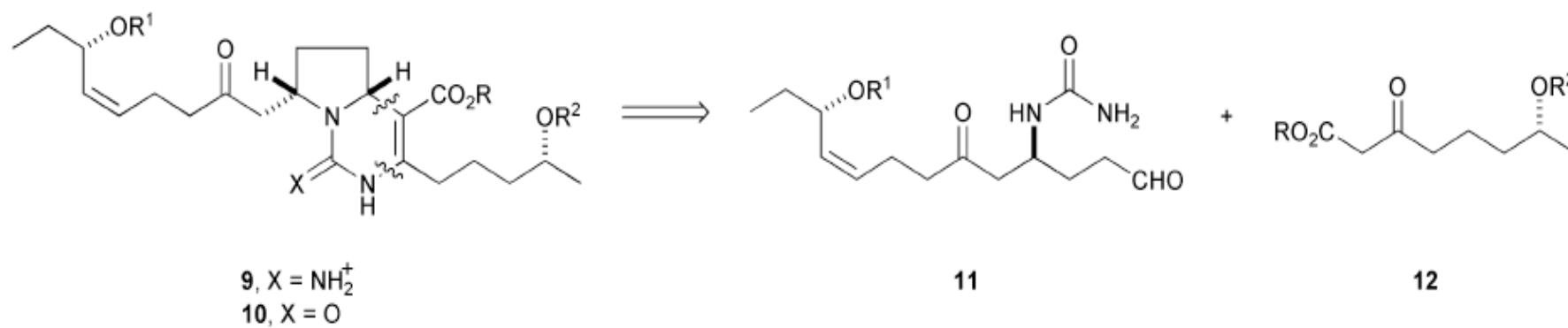
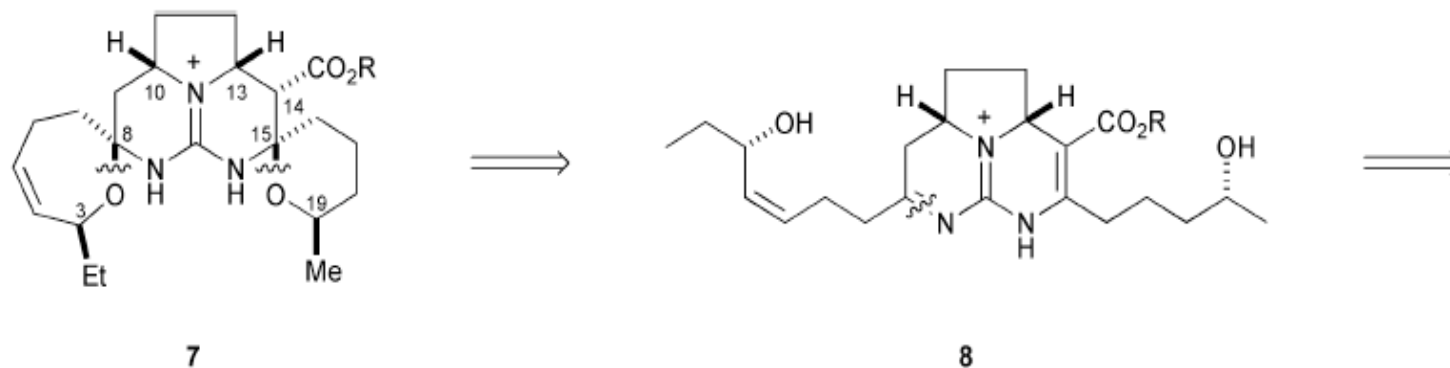


batzelladine F (6)

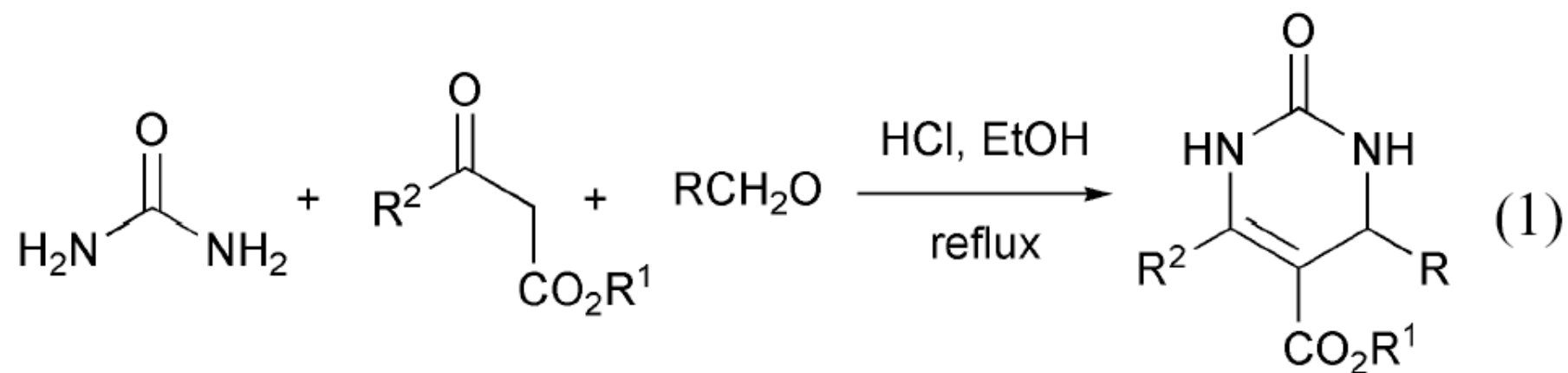
Model of the Pentacyclic Crambescidin Core



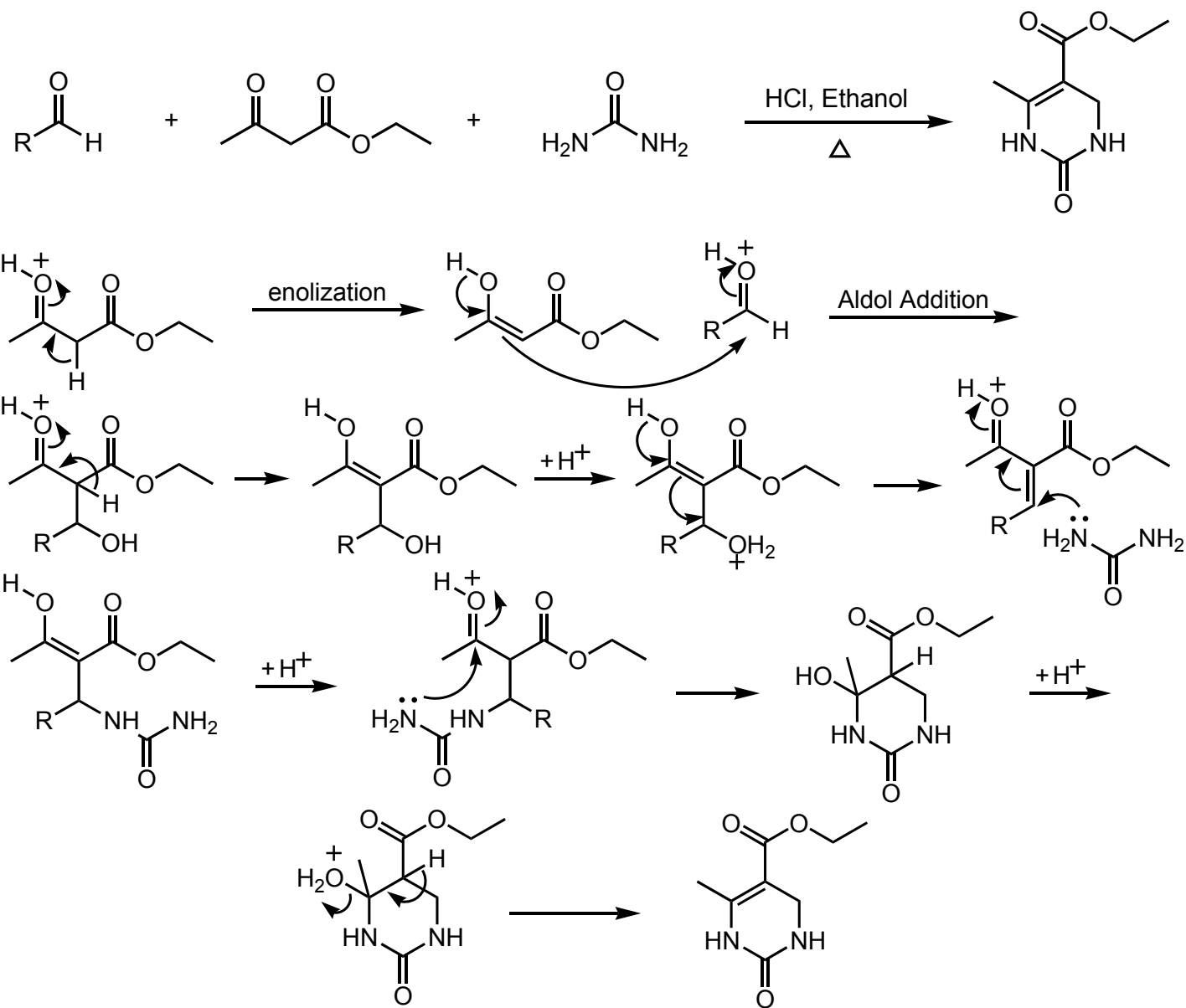
Retrosynthetic Analysis of Crambescidin 800/ Ptilomycalin A



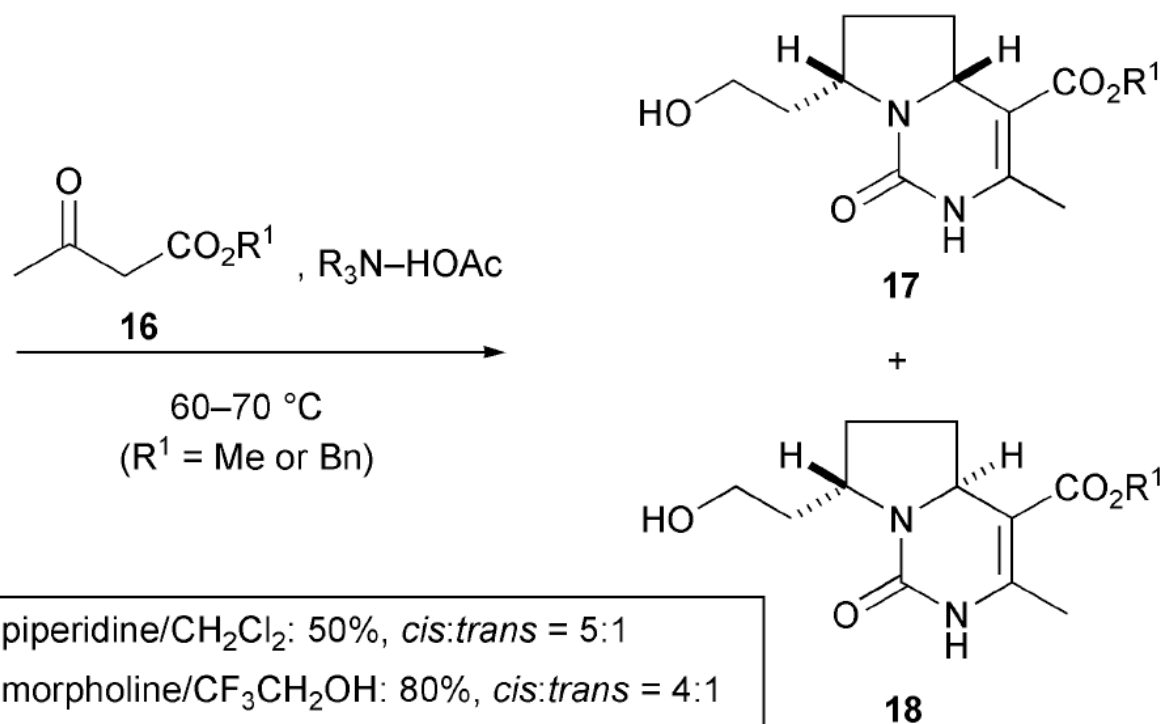
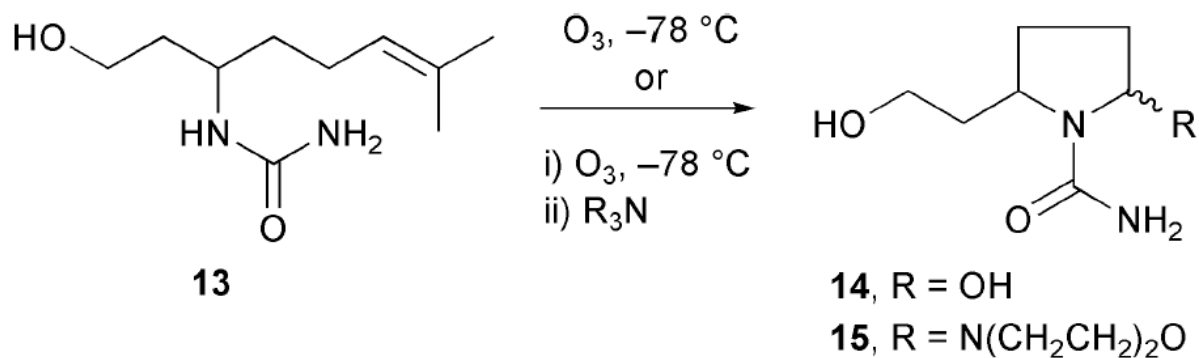
The Three Component Construction of Dihydropyrimidinones



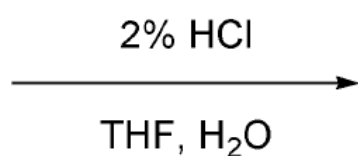
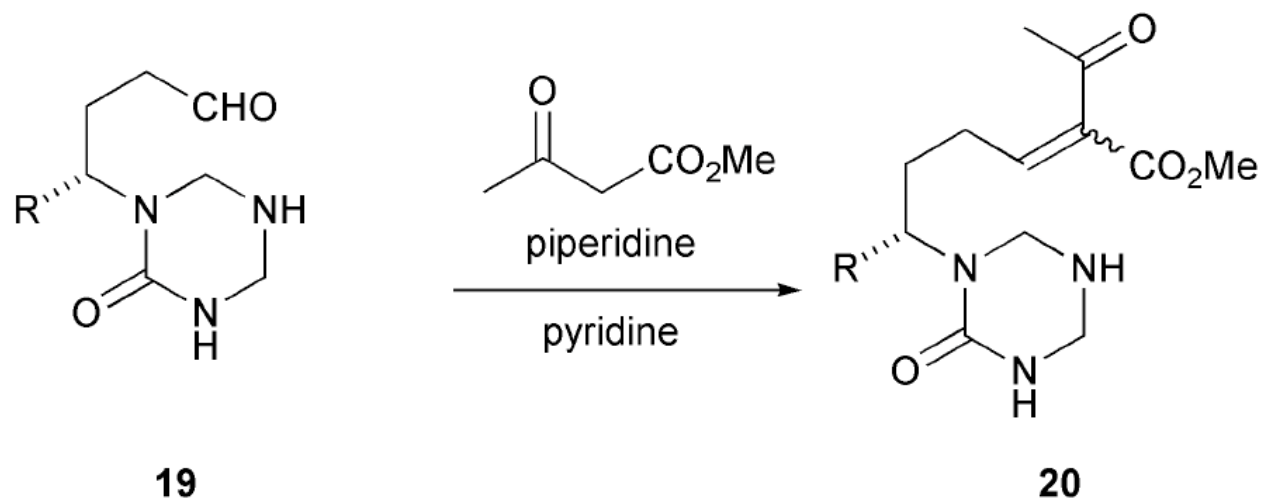
Mechanism of the Biginelli Condensation



The Tethered Biginelli Condensation



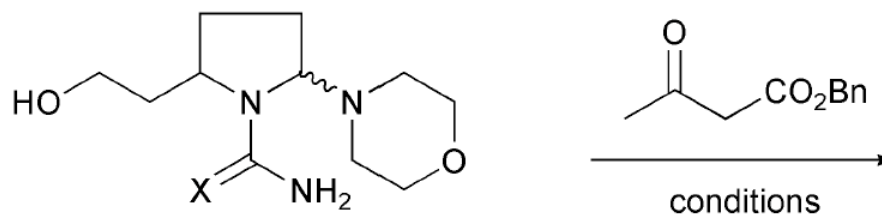
A Stepwise Tethered Biginelli Condensation



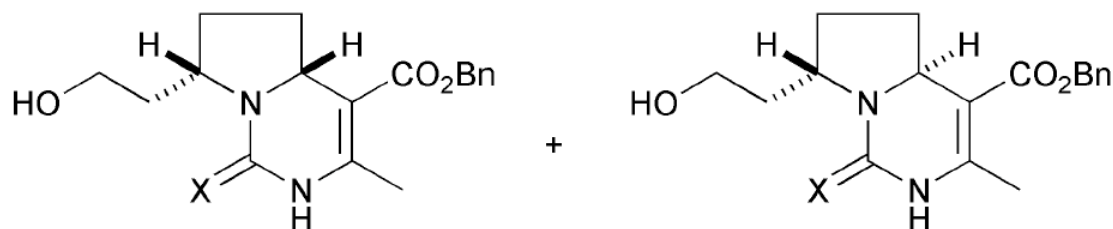
R = CH₂CH₂OTIPS

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Tunning Selectivity



15, X = O
22, X = NH₂⁺
23, X = NSO₂Ar



17, X = O
24, X = NH₂⁺
25, X = NSO₂Ar

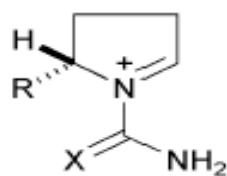
18, X = O
26, X = NH₂⁺
27, X = NSO₂Ar

(Ar = 2,3,6-trimethyl-4-methoxybenzene)

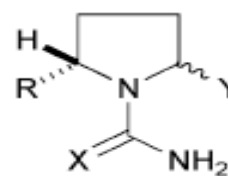
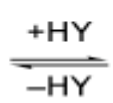
Conditions	X = O	X = NH ₂ ⁺	X = NSO ₂ Ar
CF ₃ CH ₂ OH, 60 °C morpholine-HOAc	80%, 4:1 (17:18)	42%, (26)	61%, 6:1 (25:27)
PPE, CH ₂ Cl ₂ , 23 °C	60%, 1:4 (17:18)	N/A	61%, 1:20 (25:27)

Stereorationale of Tethered Biginelli

Imminium Ion Pathway



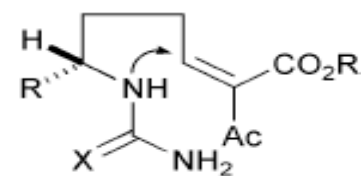
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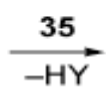
28,

X = O, NSO₂Ar, NH·HCl

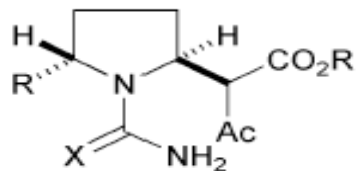
Knoevenagel Pathway



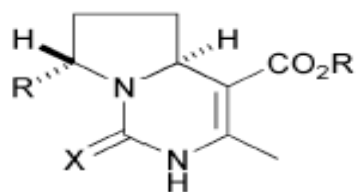
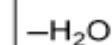
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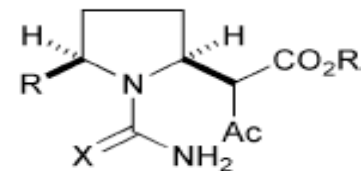
35 or 36



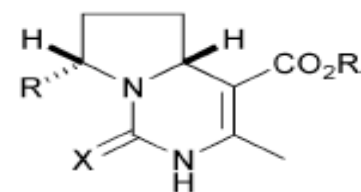
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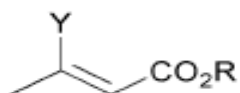
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33



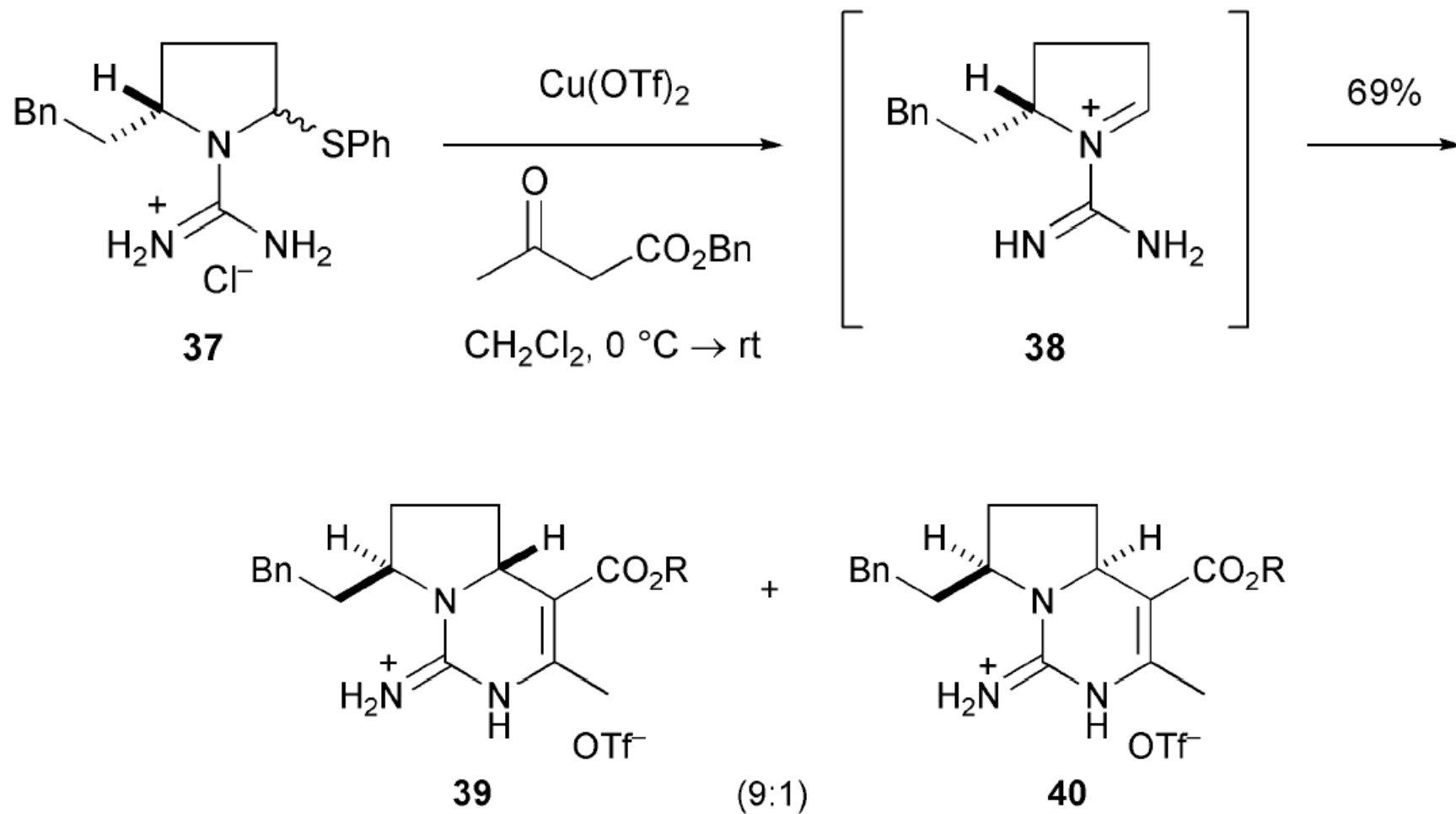
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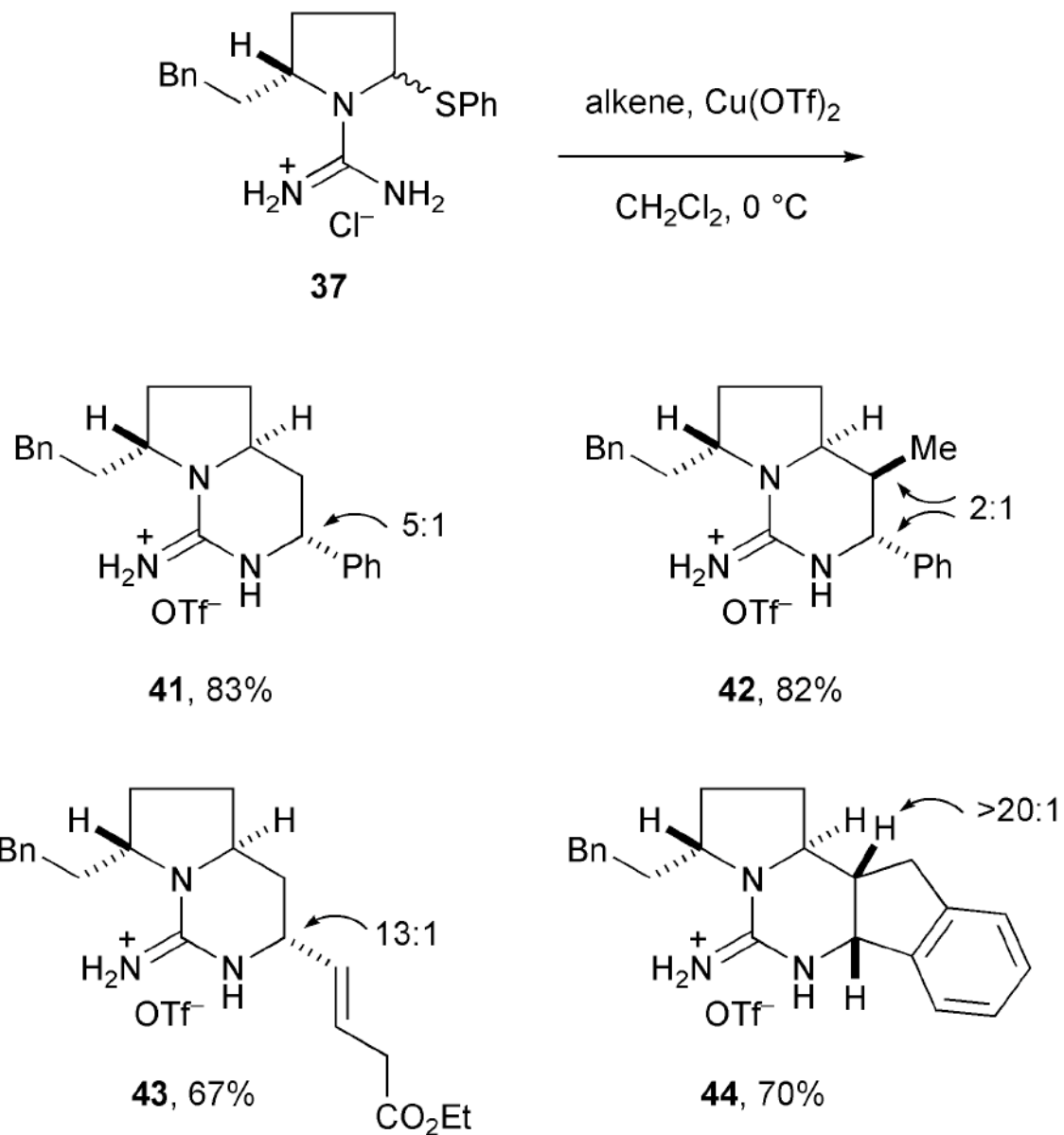
35, Y = N(CH₂CH₂)₂O

36, Y = OH

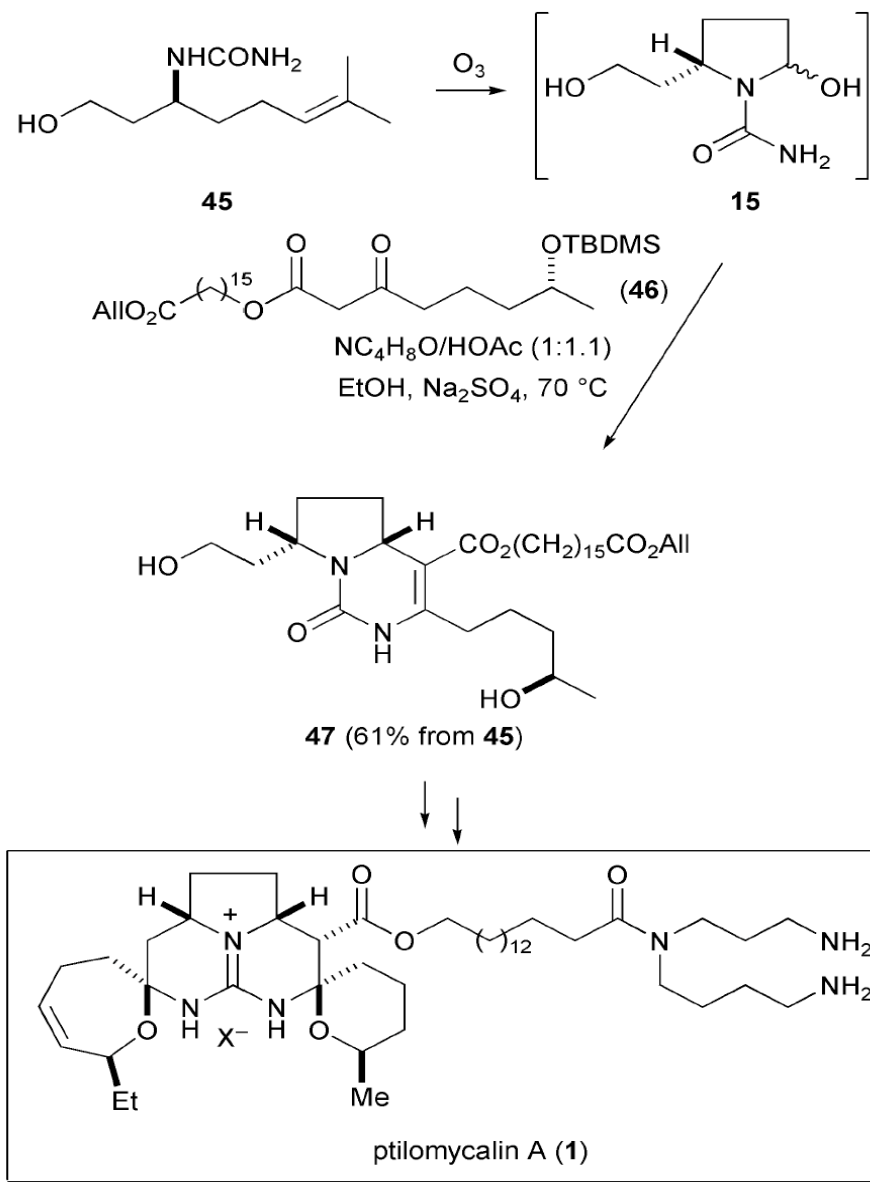
Copper-Initiated Tethered Biginelli Condensation



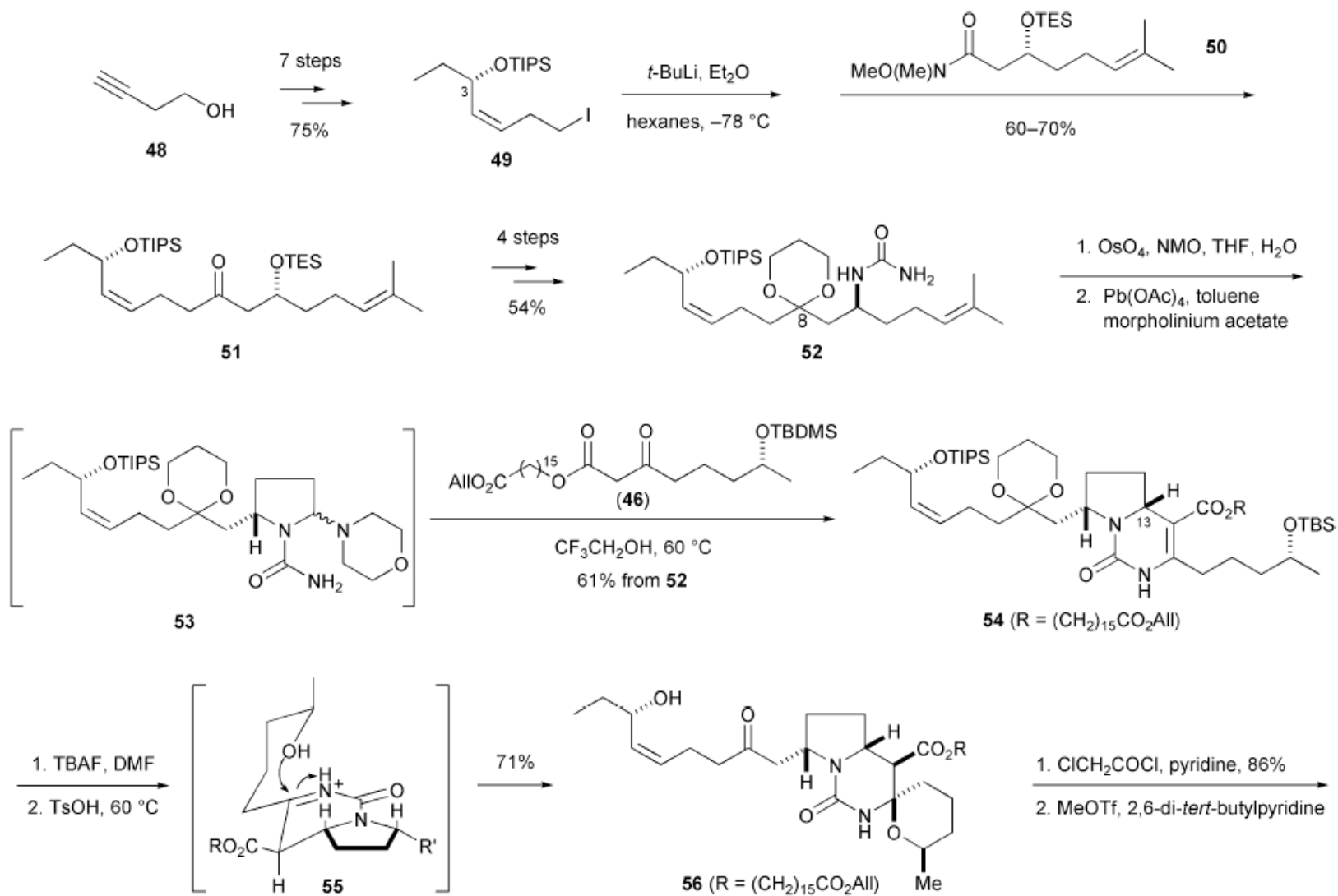
Cyclocondensations of N-Amidinyliminium Ions



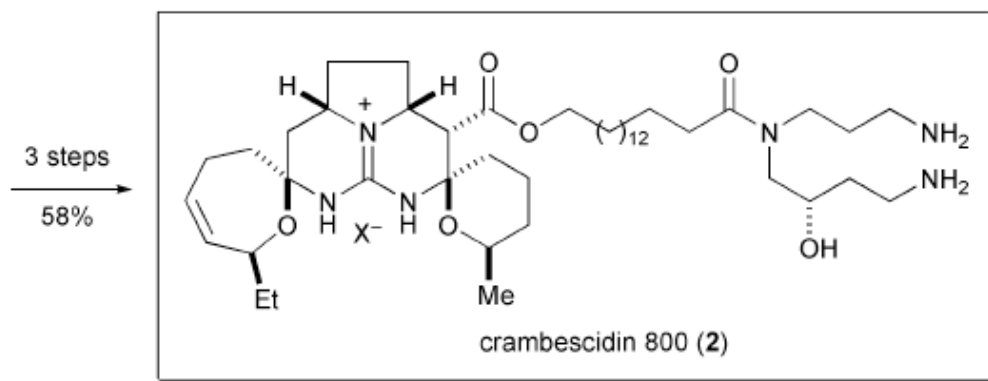
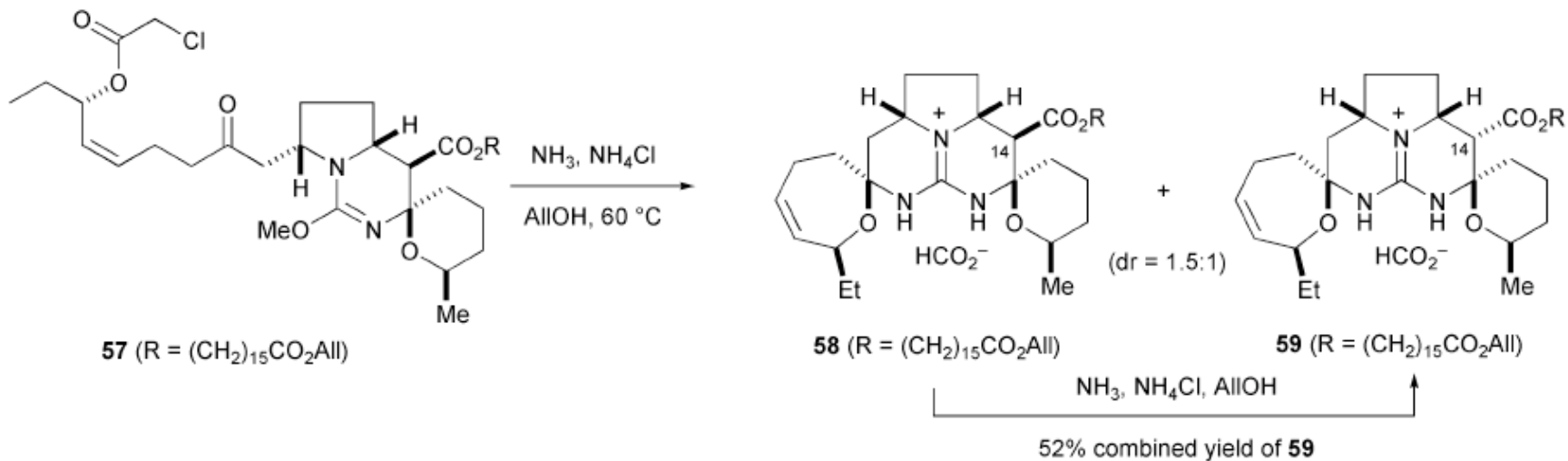
Application in the Total Synthesis of Ptilomycalin A



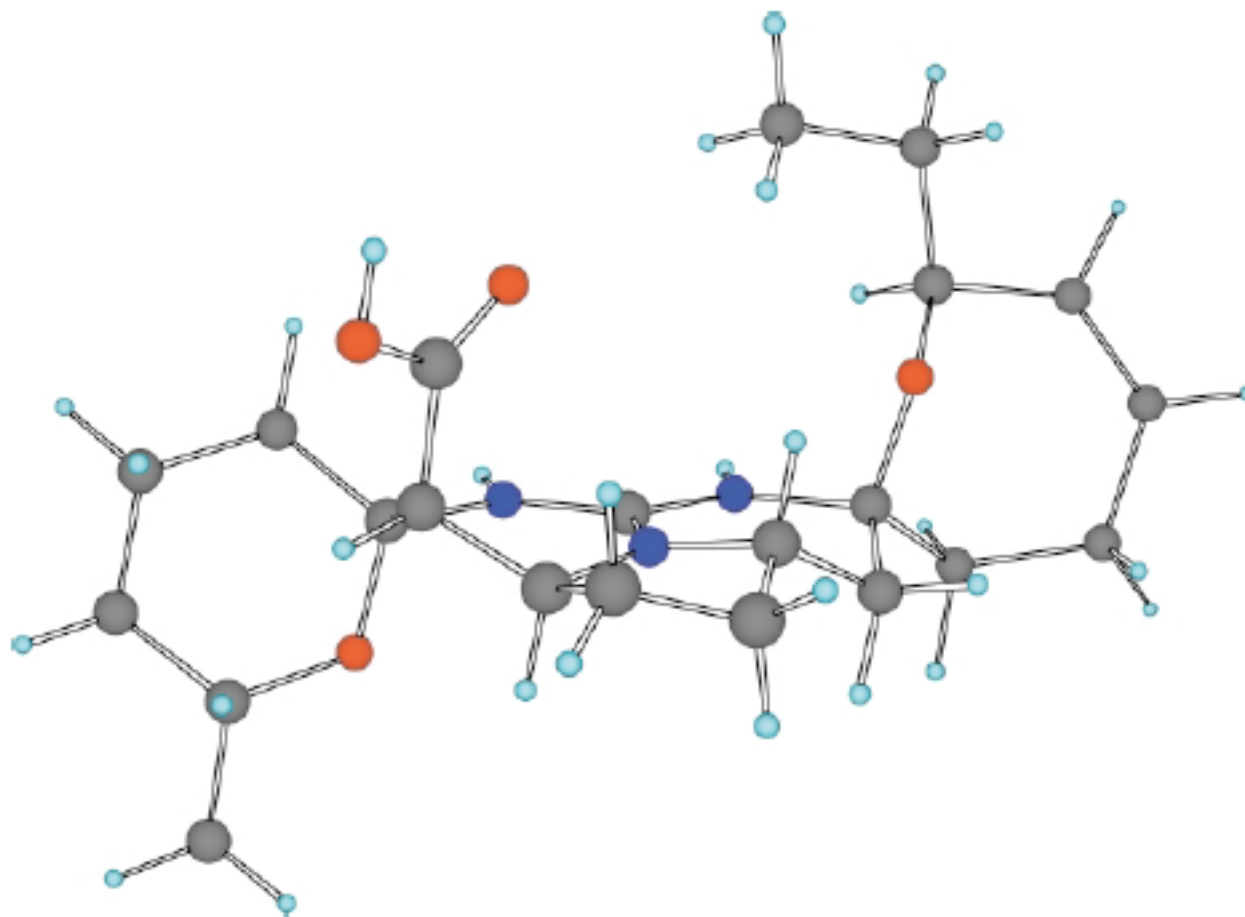
Application in the Total Synthesis of Crambescidin 800



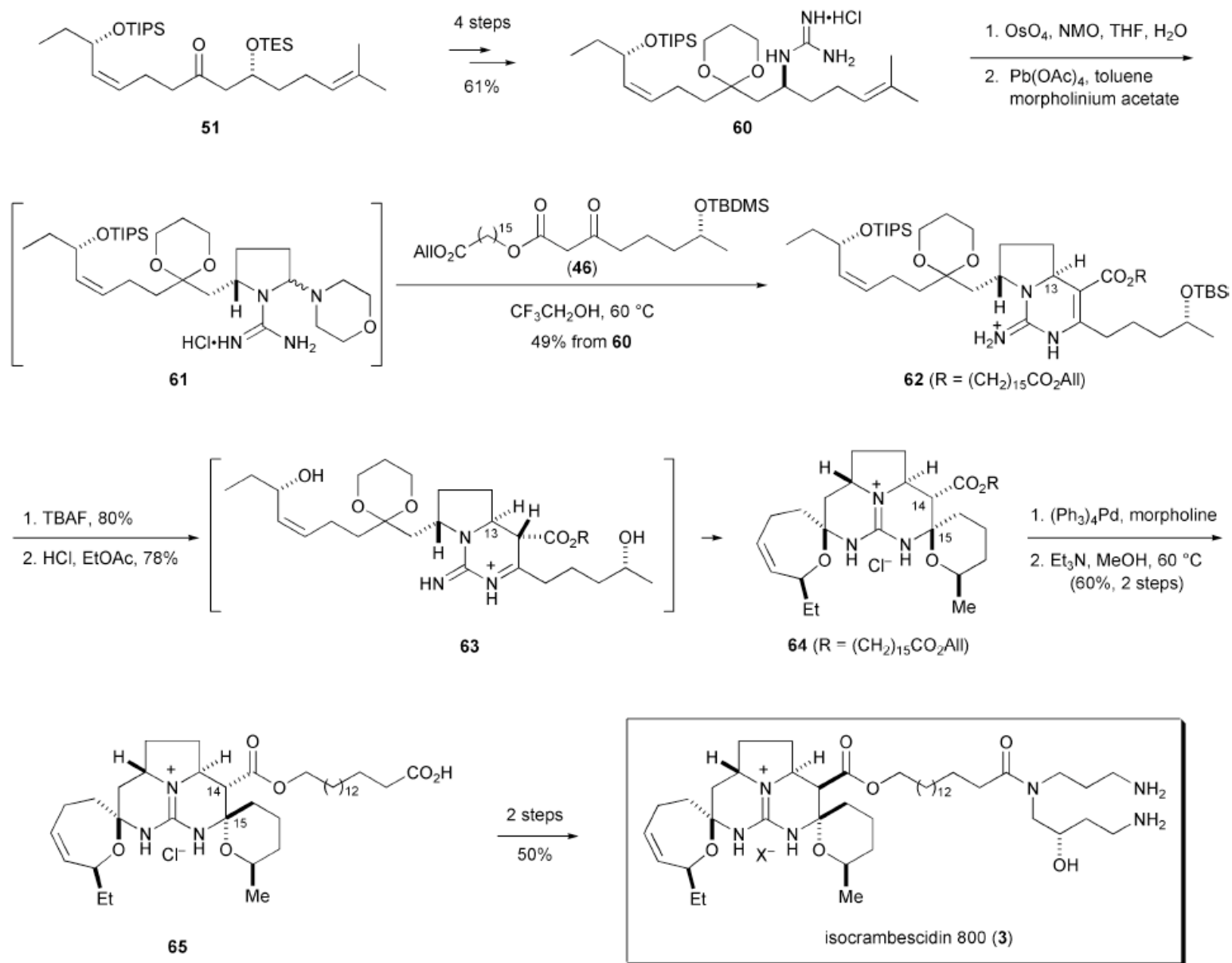
Application in the Total Synthesis of Crambescidin 800 Continued



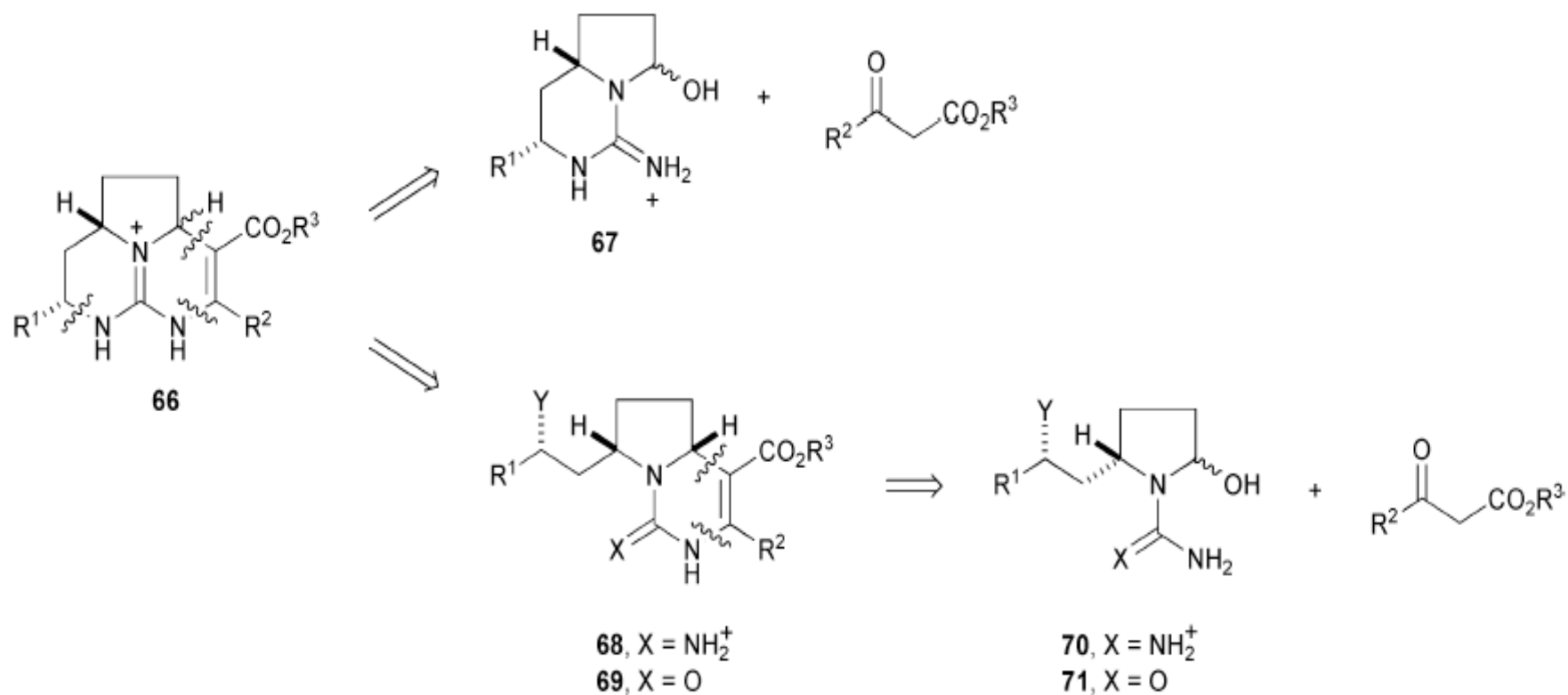
Model of the Isocrambescidin Core



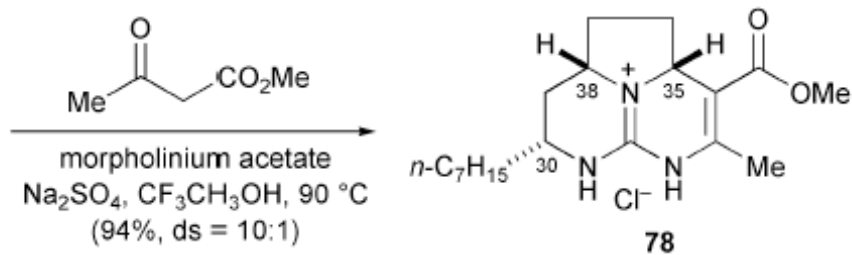
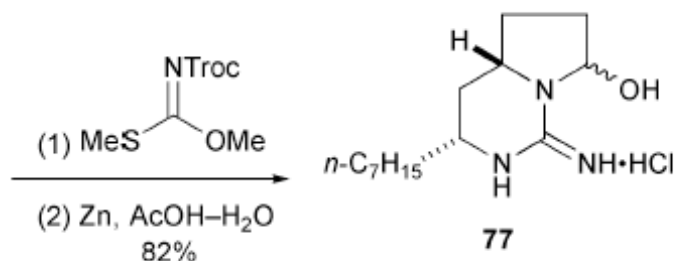
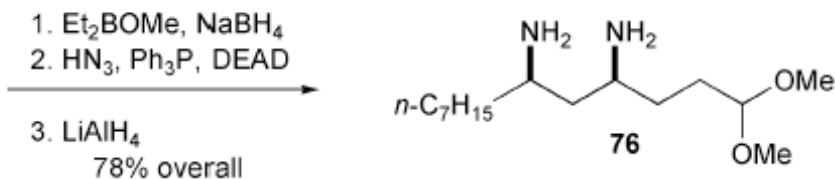
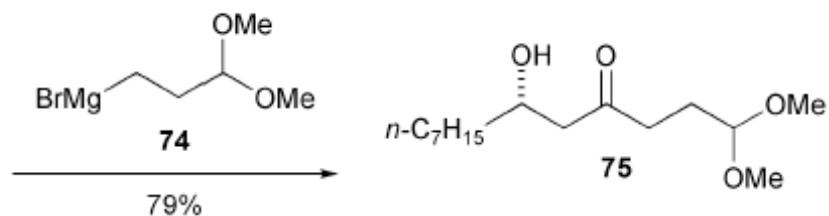
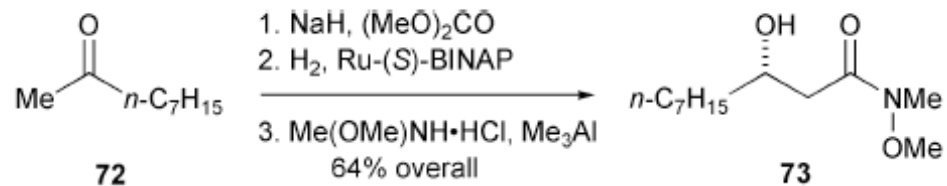
Application to the total Synthesis of 13,14,15- Isocrambescidin 800



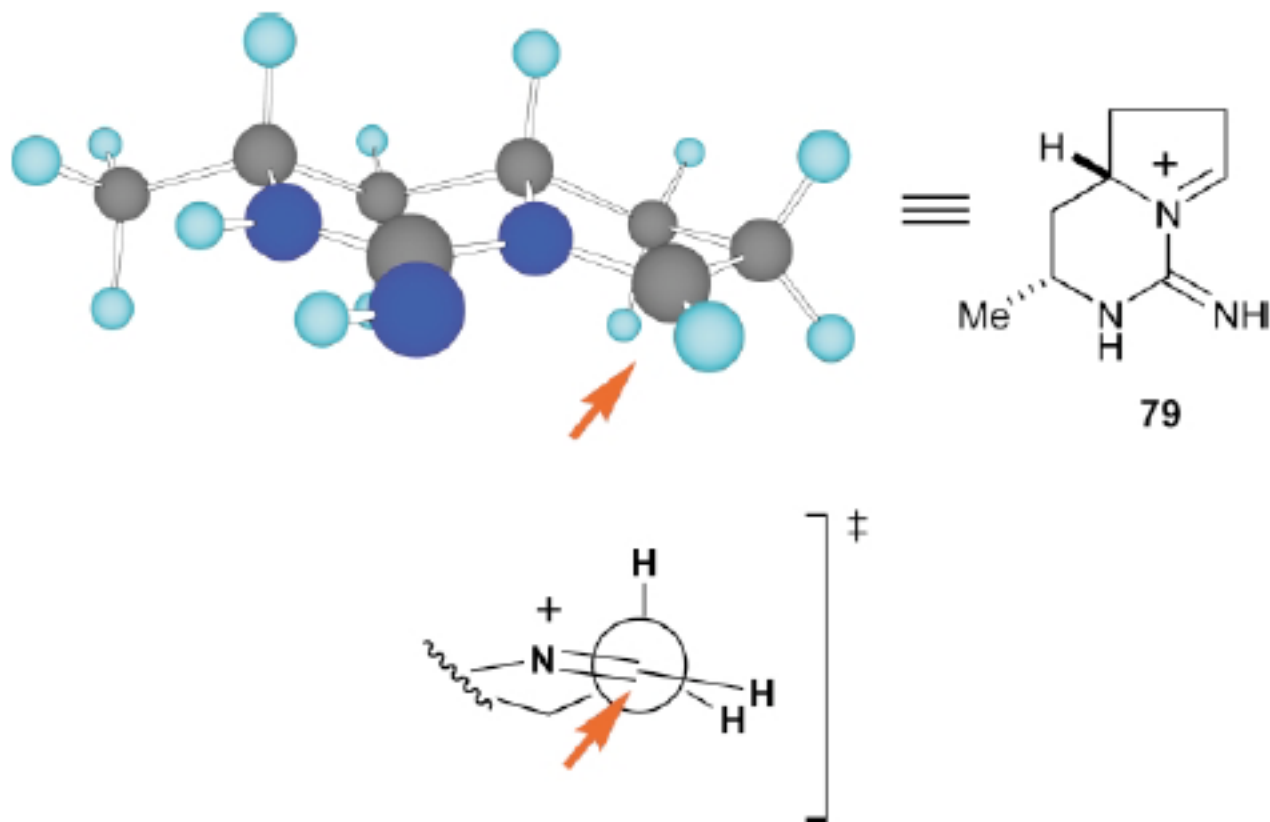
Strategies for Triazaacenaphthalene Synthesis



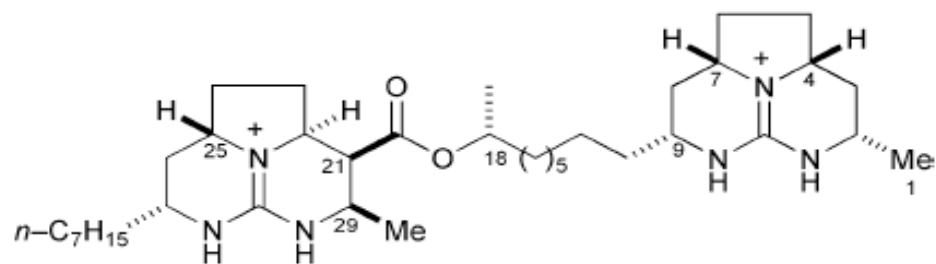
Synthesis of Batzelladine B Methyl Ester



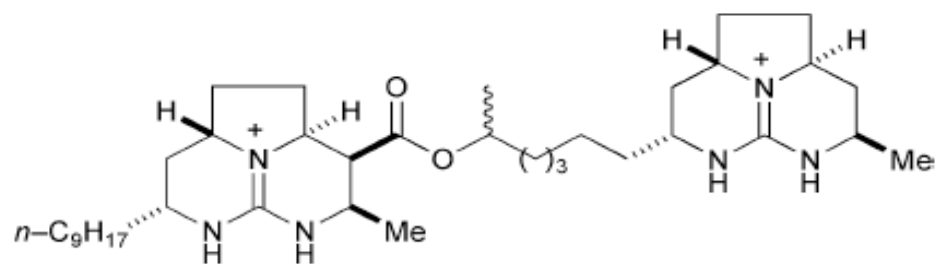
Rationale for Stereochemistry



Batzelladine F and Incorrect Earlier Proposed Structures

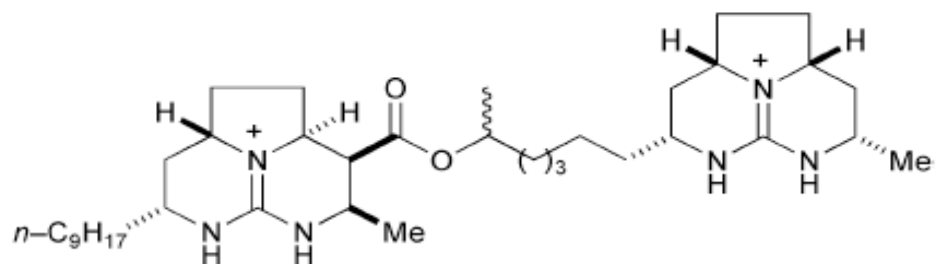


Batzelladine F (6)



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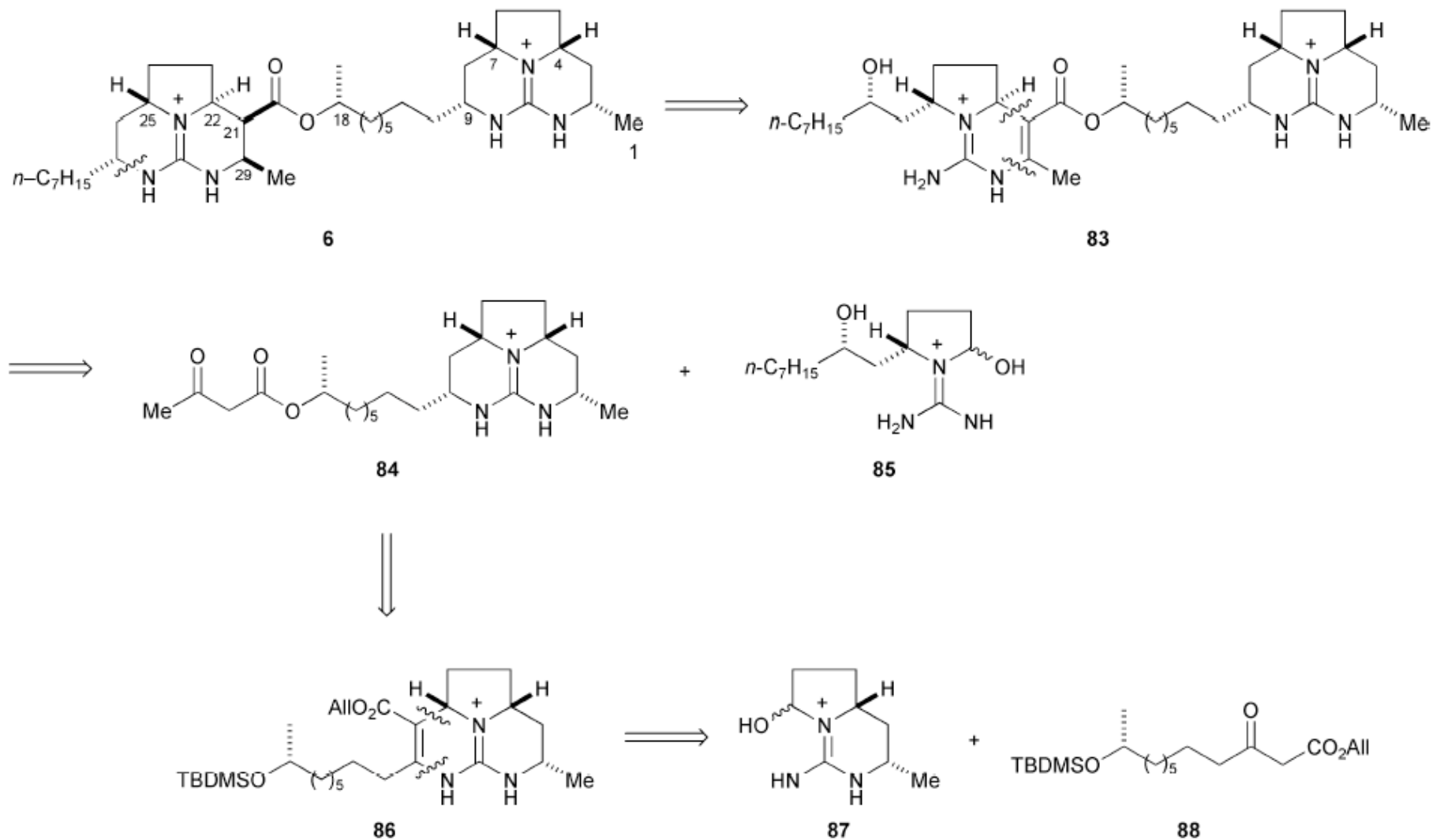
structure originally proposed in 1997



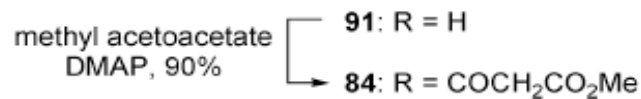
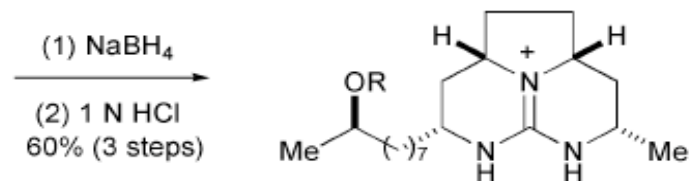
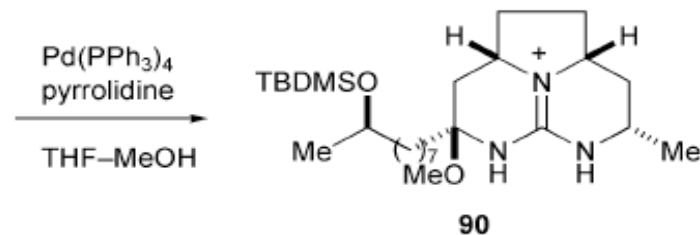
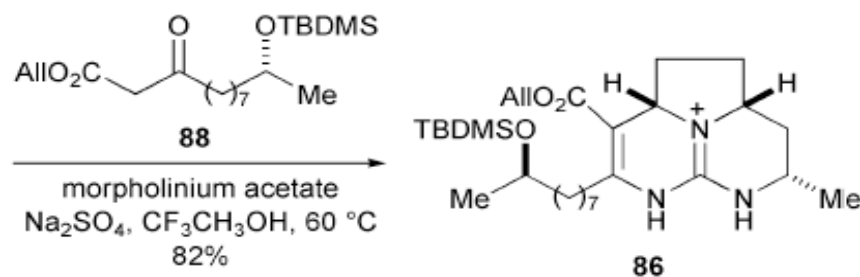
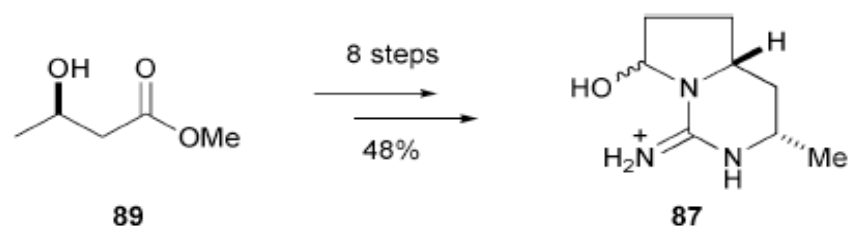
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one of several possible structures circa 1999

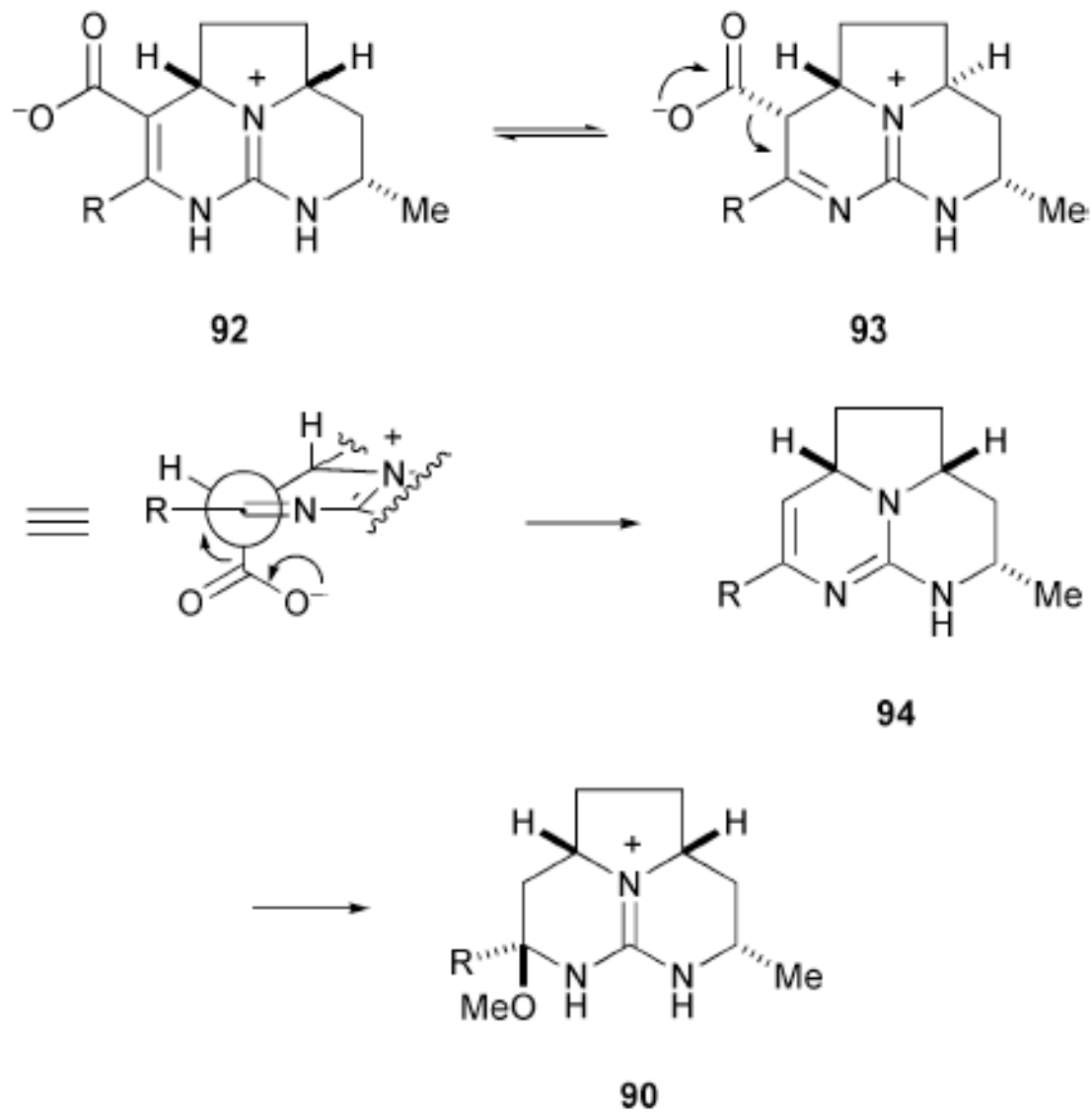
Fragment Coupling Tethered Biginelli Strategy for Preparing Batzelladine F



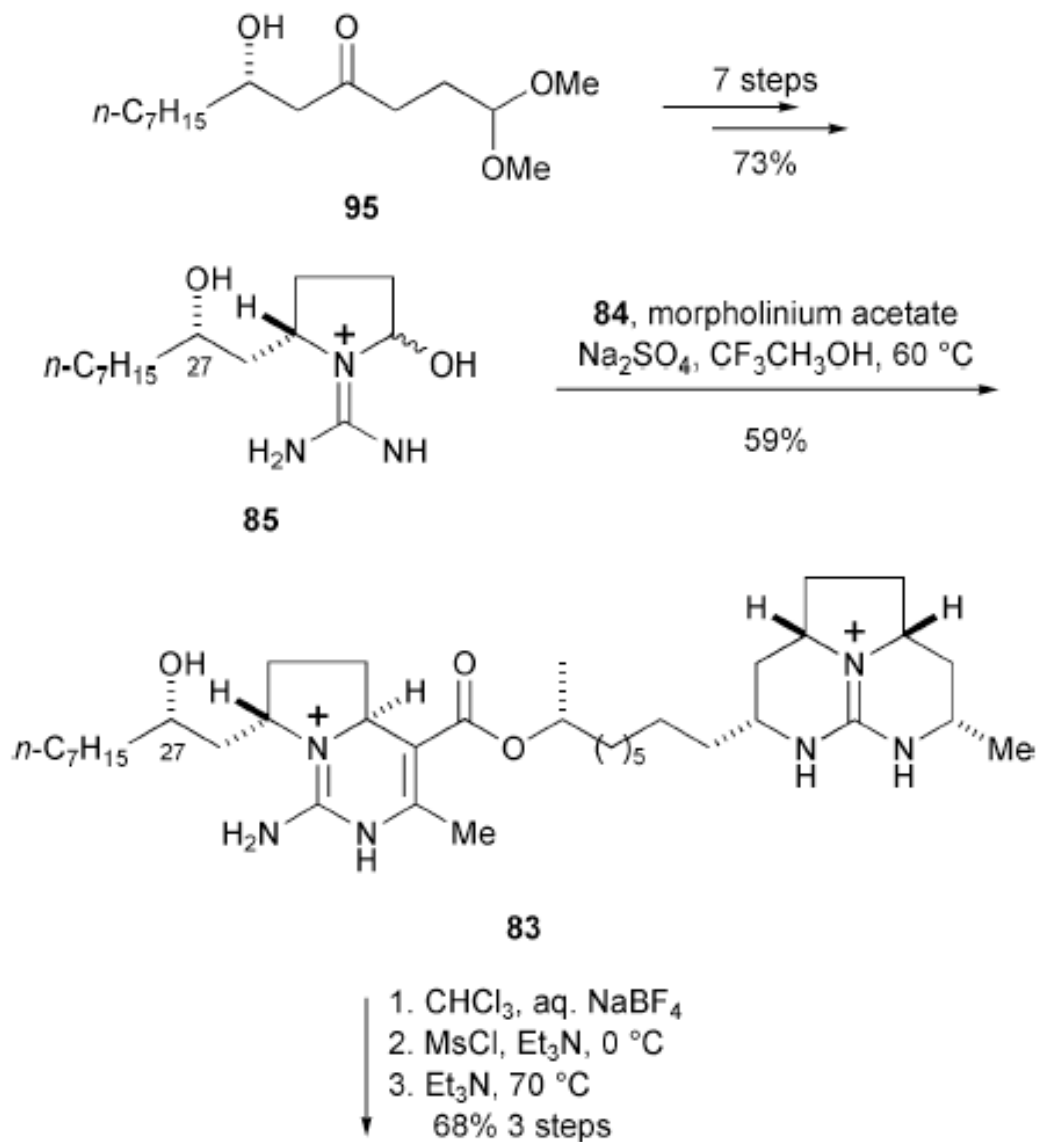
Synthesis of the Right Hand Portion of Batzelladine F



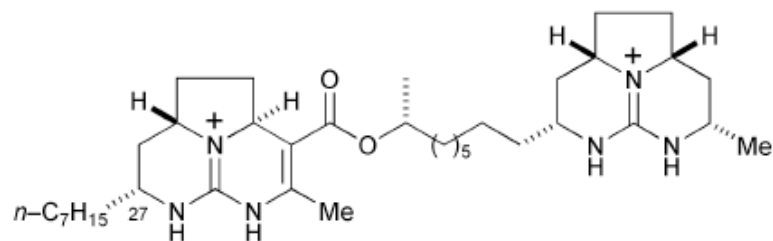
Proposed Decarboxylation Mechanism



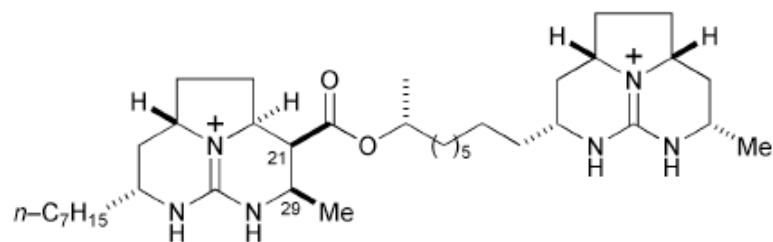
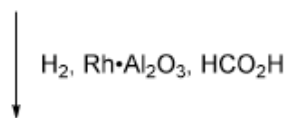
Completion of the Total Synthesis of Batzelladine F



Completion of the Total Synthesis of Batzelladine F Continued

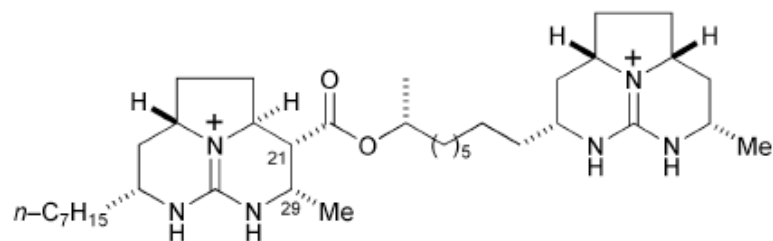


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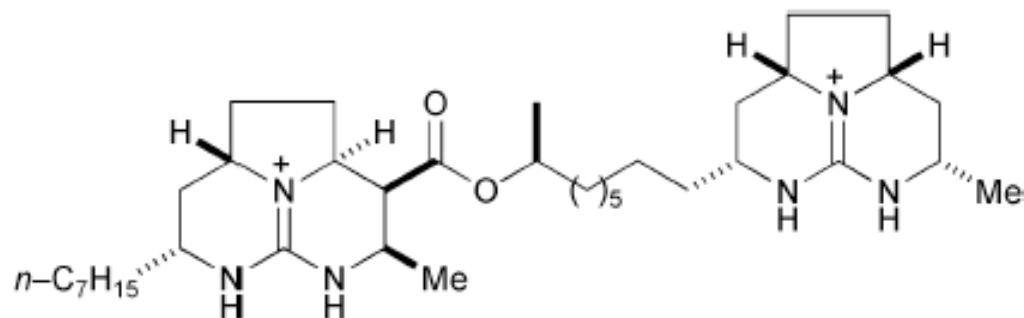
21%, batzelladine F (6)

+

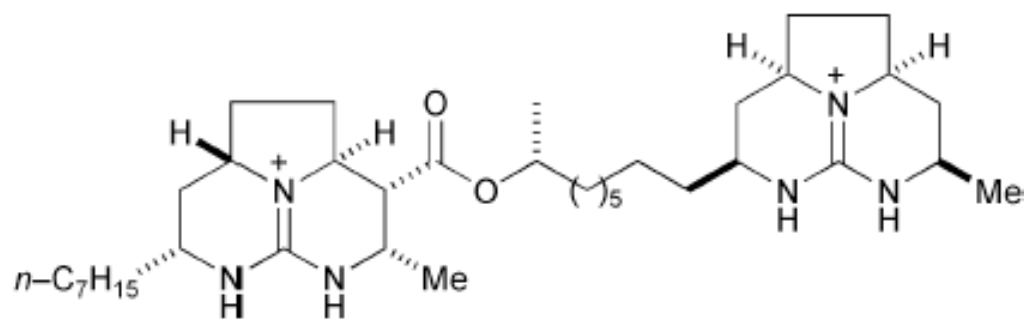


33%, 97

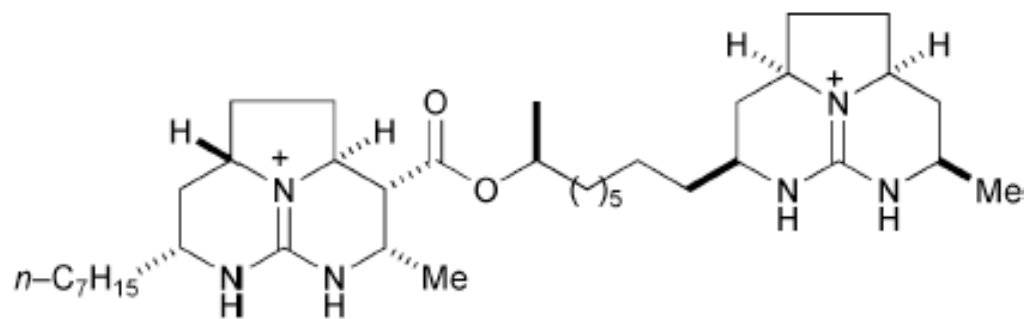
Synthetic Analogs of Batzelladine F



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