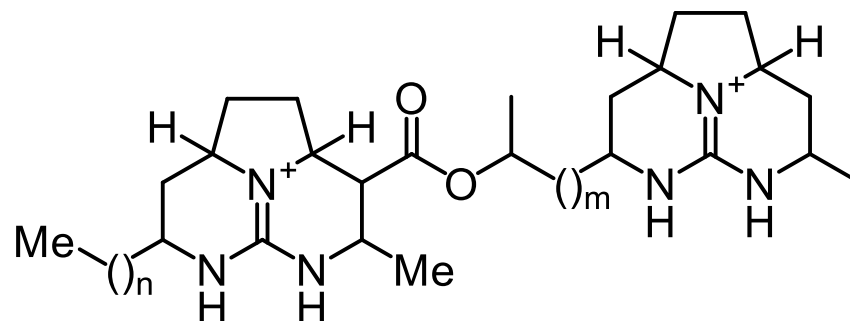


Misassigned Natural Products: The Curious Case of Batzelladine F



Toni T. Metsänen

Synthesis Club

May 30th 2017

Misassigned Natural Products: Reviews

“Chasing Molecules That Were Never There: Misassigned Natural Products and the Role of Chemical Synthesis in Modern Structure Elucidation”

K. C. Nicolaou & S. A. Snyder

ACIE **2005**, 44, 1012

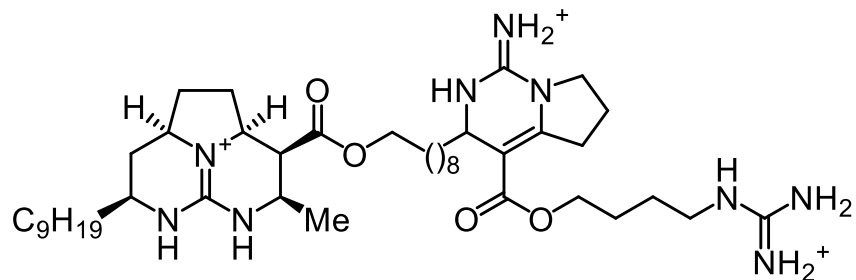
“Oops, I Did It Again: Structural Misassignment of Natural Product”

J. Lipshultz

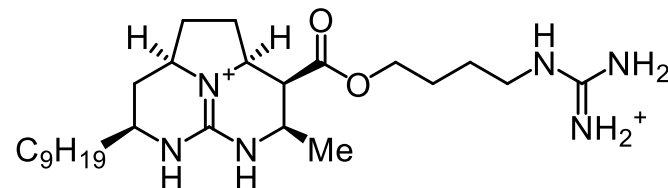
MacMillan group seminar, April 26, **2016**

<http://chemlabs.princeton.edu/macmillan/wp-content/uploads/sites/6/structure-misassignment-gp-meeting-JML.pdf>

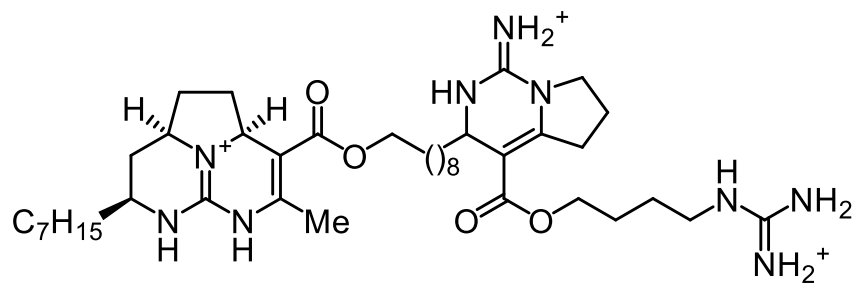
Batzelladines: Proposed structures



Batzelladine A



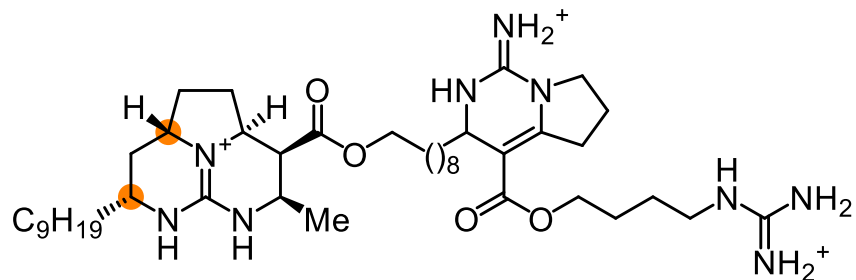
Batzelladine D



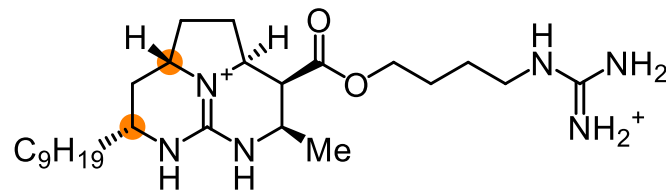
Batzelladine B

“...inhibit the binding of HIVgp-120 to CD4 and are therefore potential inhibitors of HIV.”

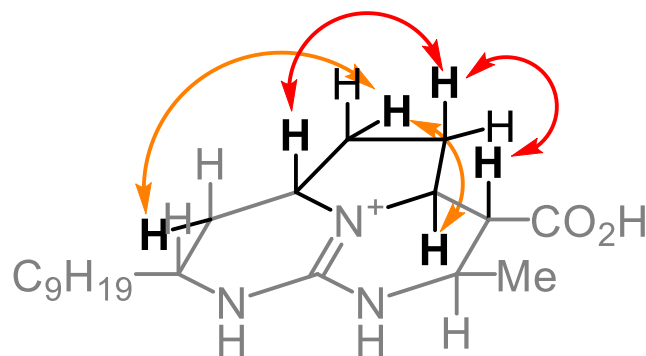
Semisynthesis and $^1\text{H}/^1\text{H}$ NOE: *anti*, not *syn*



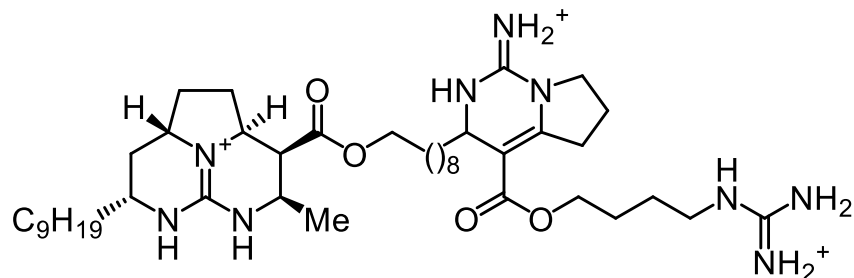
Batzelladine A



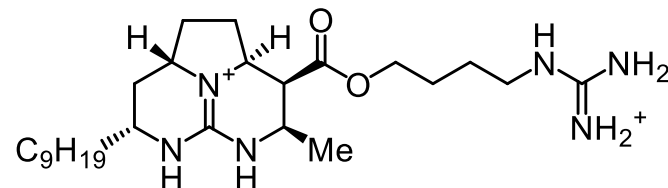
Batzelladine D



Proposed structure of Batzelladine F



Batzelladine A

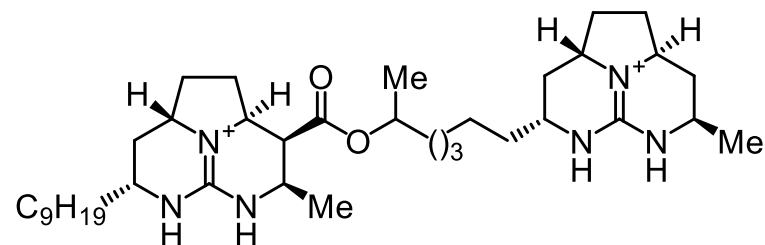


Batzelladine D

“There was a subset of the ¹H and ¹³C NMR signals which occurred at the same chemical shifts as those of the tricyclic guanidinium moiety in batzelladine A, and a second subset of signals which were similar but not identical to the first subset.

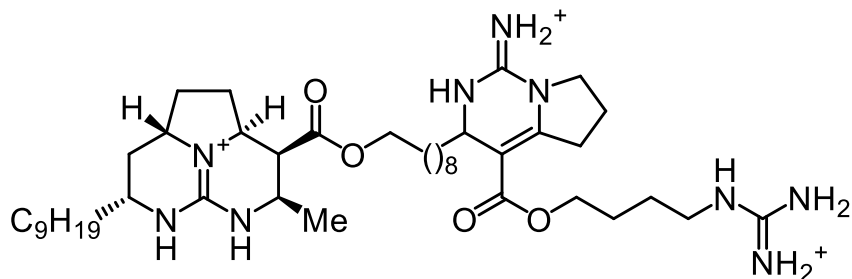
...

Thus batzelladine F consisted of two nearly identical tricyclic guanidinium ring systems connected through an ester linkage. The mass spectral fragmentation patterns required five methylene groups in the connecting chain.”



Batzelladine F

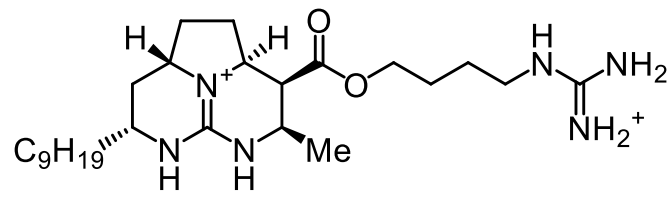
Selected syntheses of Batzelladines before 2006



Batzelladine A **CONFIRMED**

2004 Nagasawa

2006 Gin



Batzelladine D **CONFIRMED**

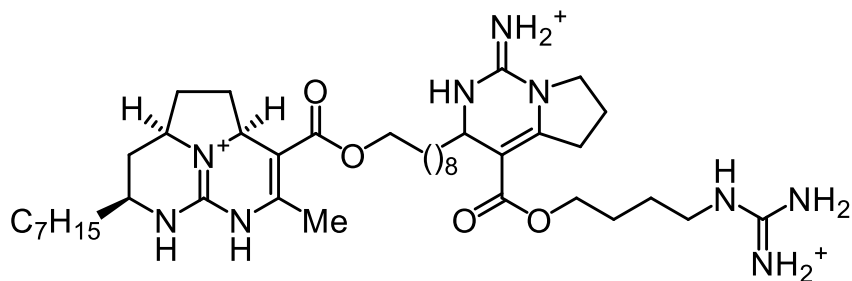
1999 Overman

2004 Nagasawa

2005 Nagasawa

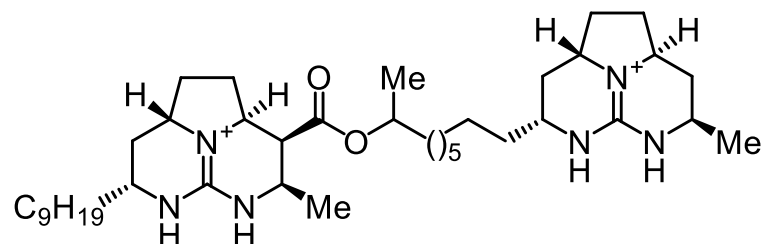
2006 Gin

2007 Evans



Batzelladine B **CONFIRMED**

1999 Overman

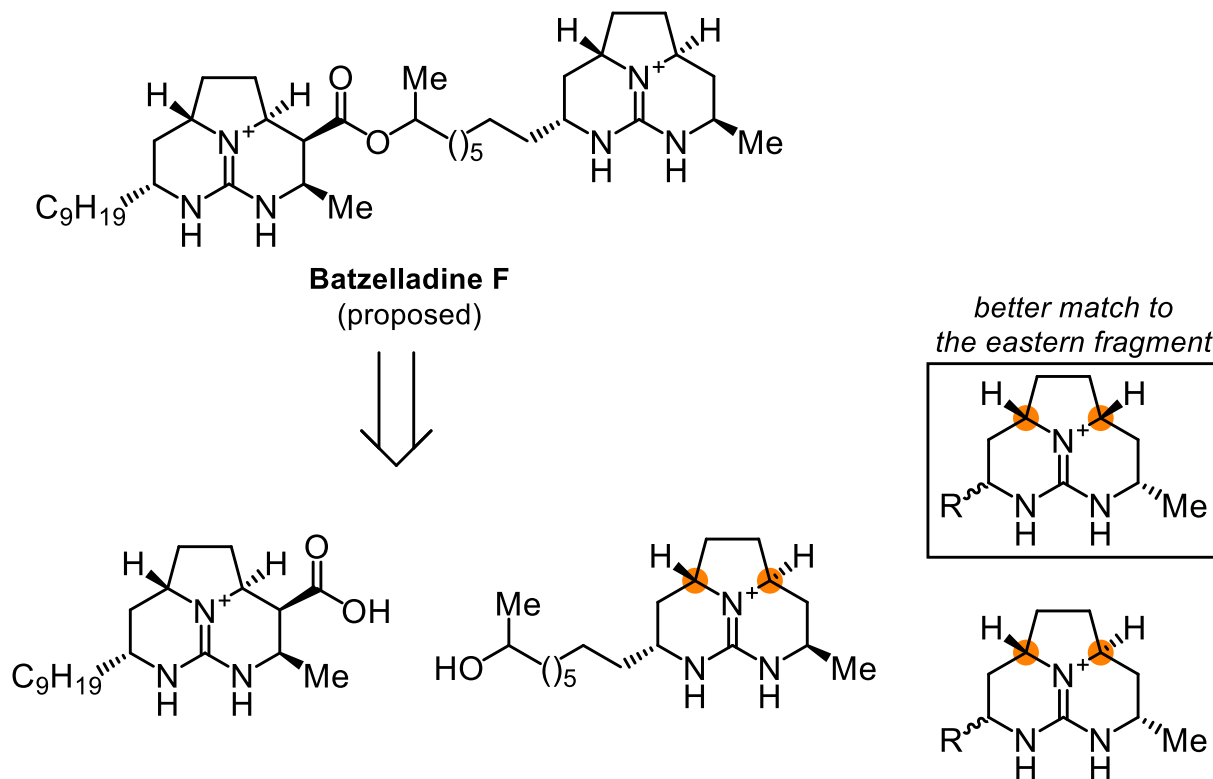


Batzelladine F ?

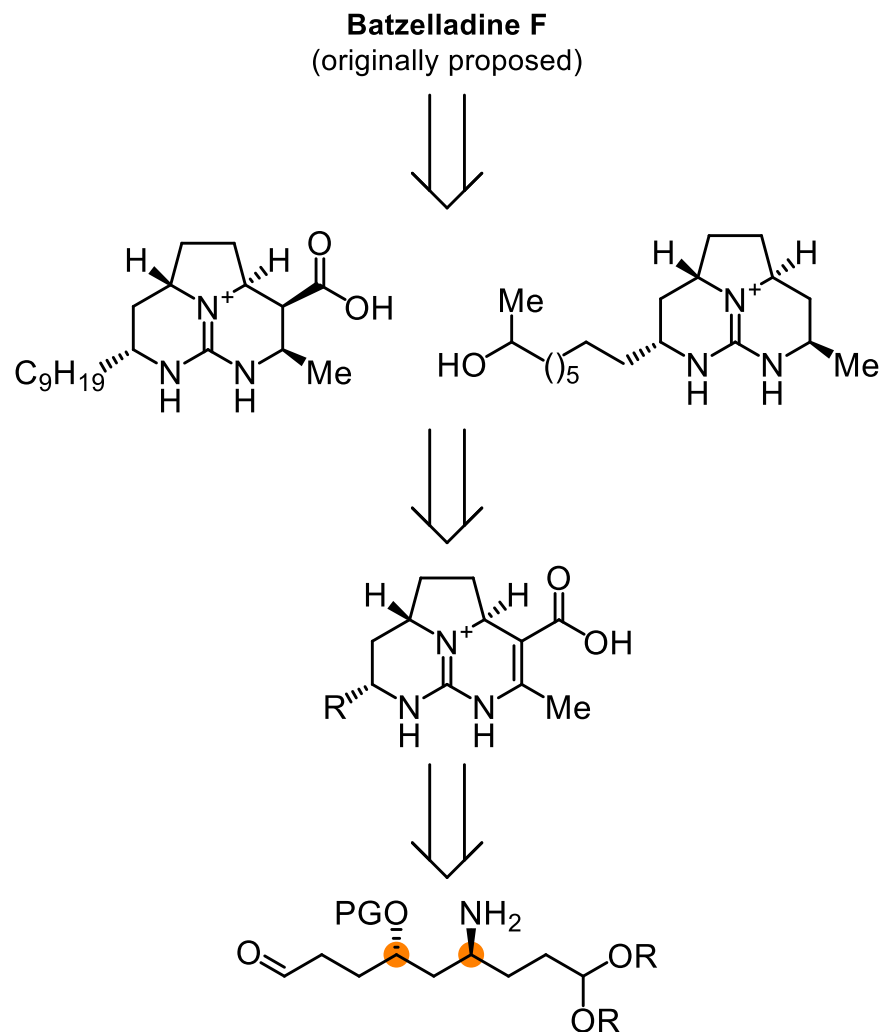
Batzelladine A–E: A. D. Patil *et al. J. Org. Chem.* **1995**, 60, 1182

Batzelladine F–I: A. D. Patil *et al. J. Org. Chem.* **1997**, 62, 1814

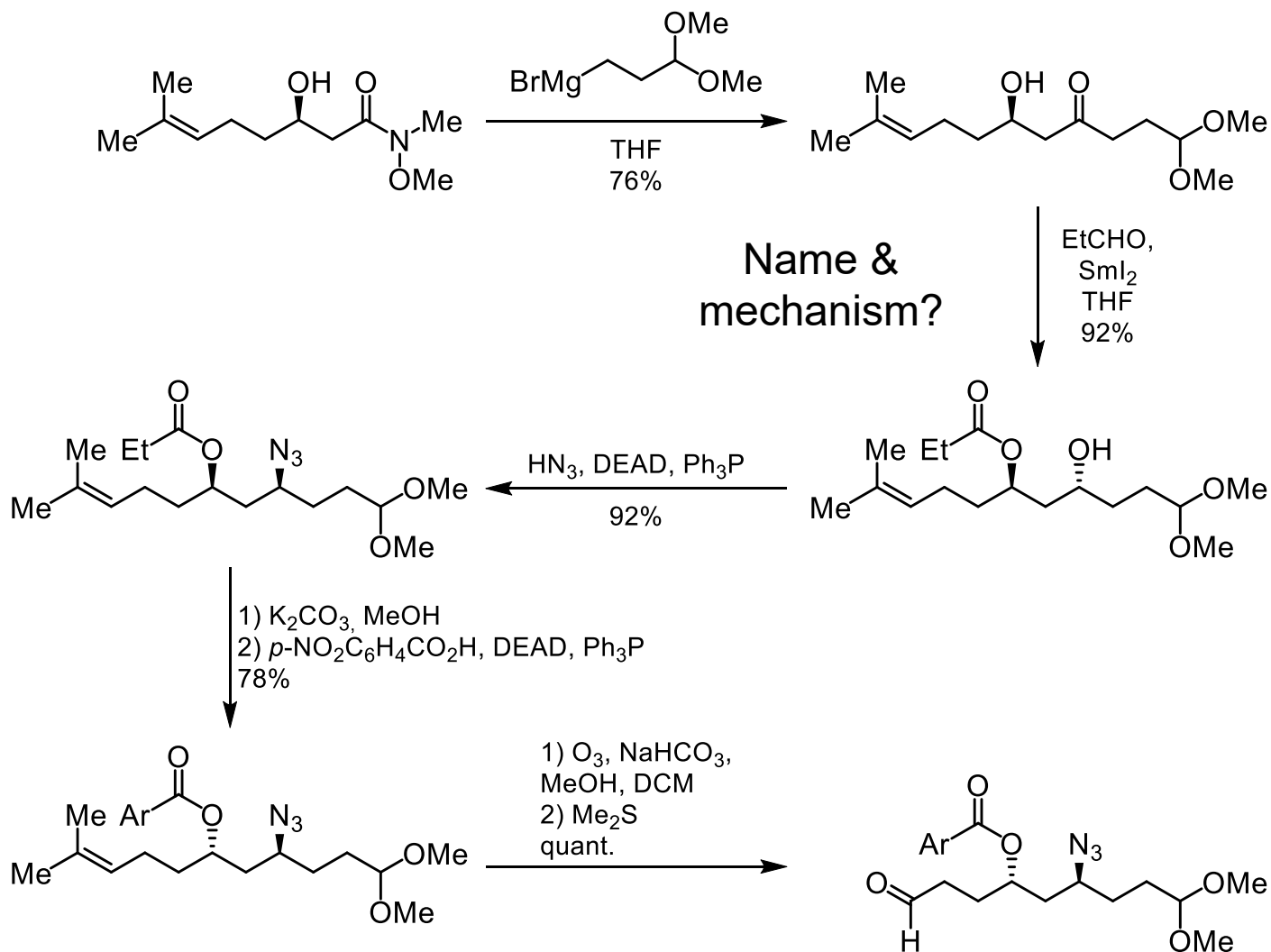
Revision of Batzelladine F Eastern Fragment: *syn*, not *anti*?



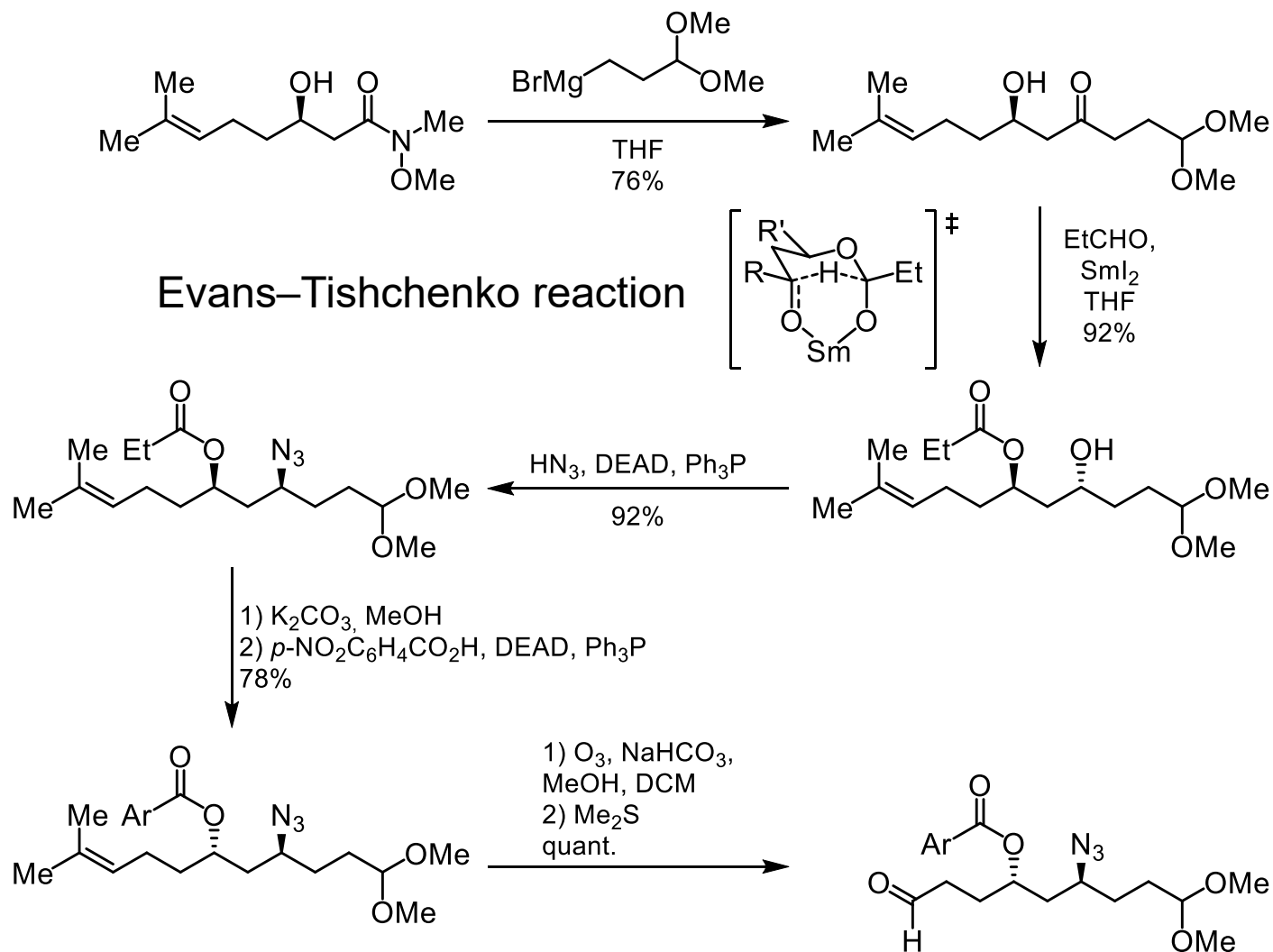
Overman's Retrosynthesis of Batzelladine F



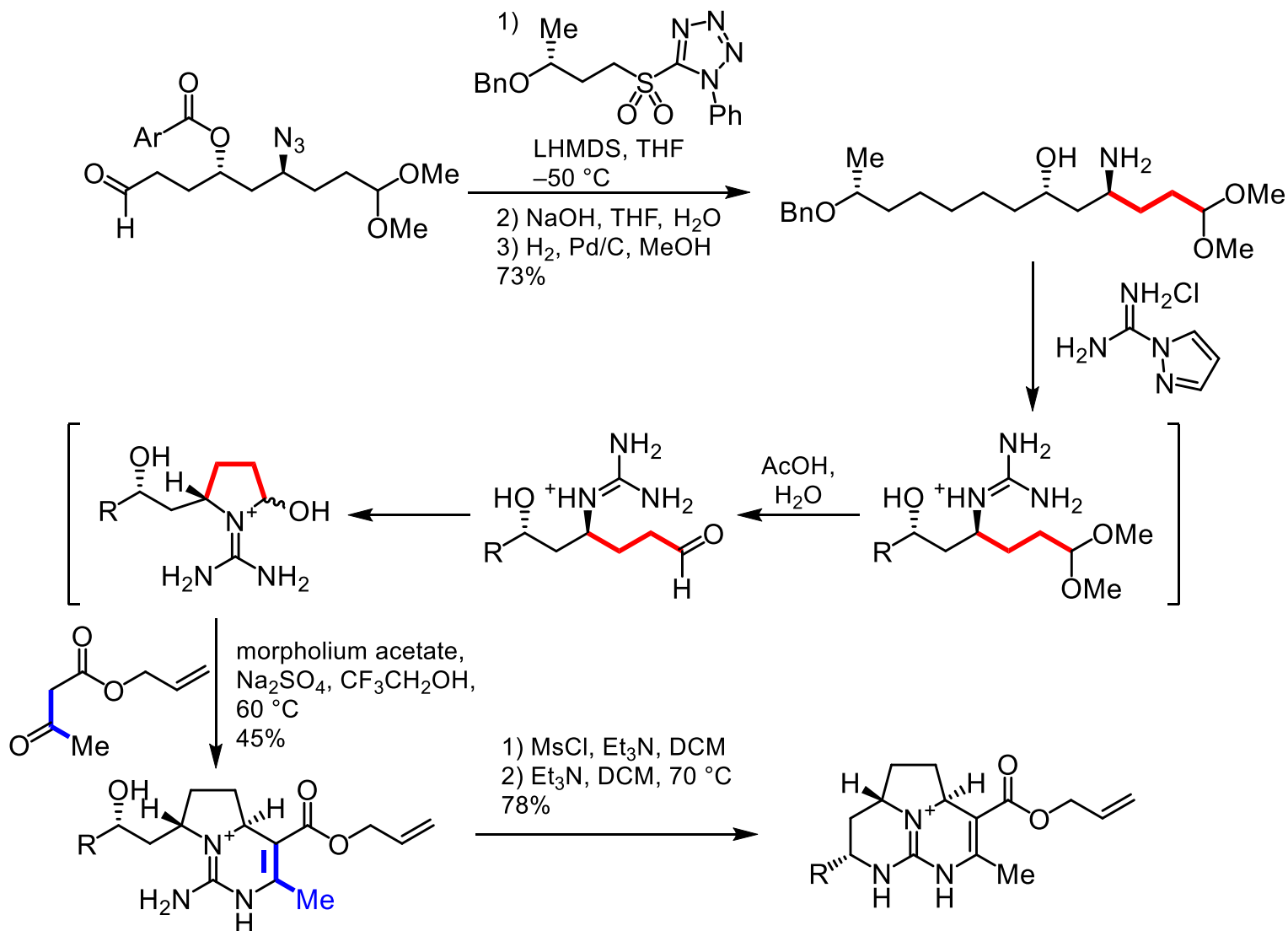
Overman's synthesis of Batzelladine F: Eastern Fragment



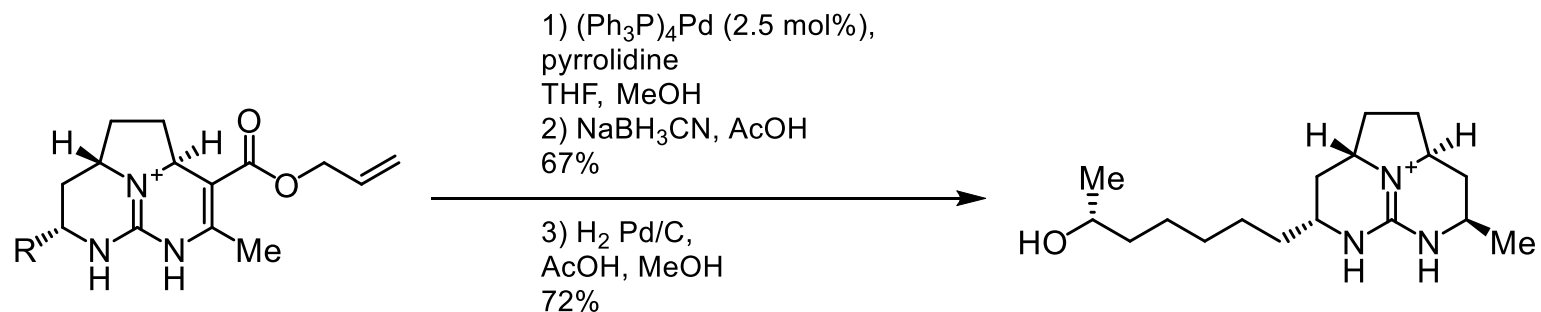
Overman's synthesis of Batzelladine F: Eastern Fragment



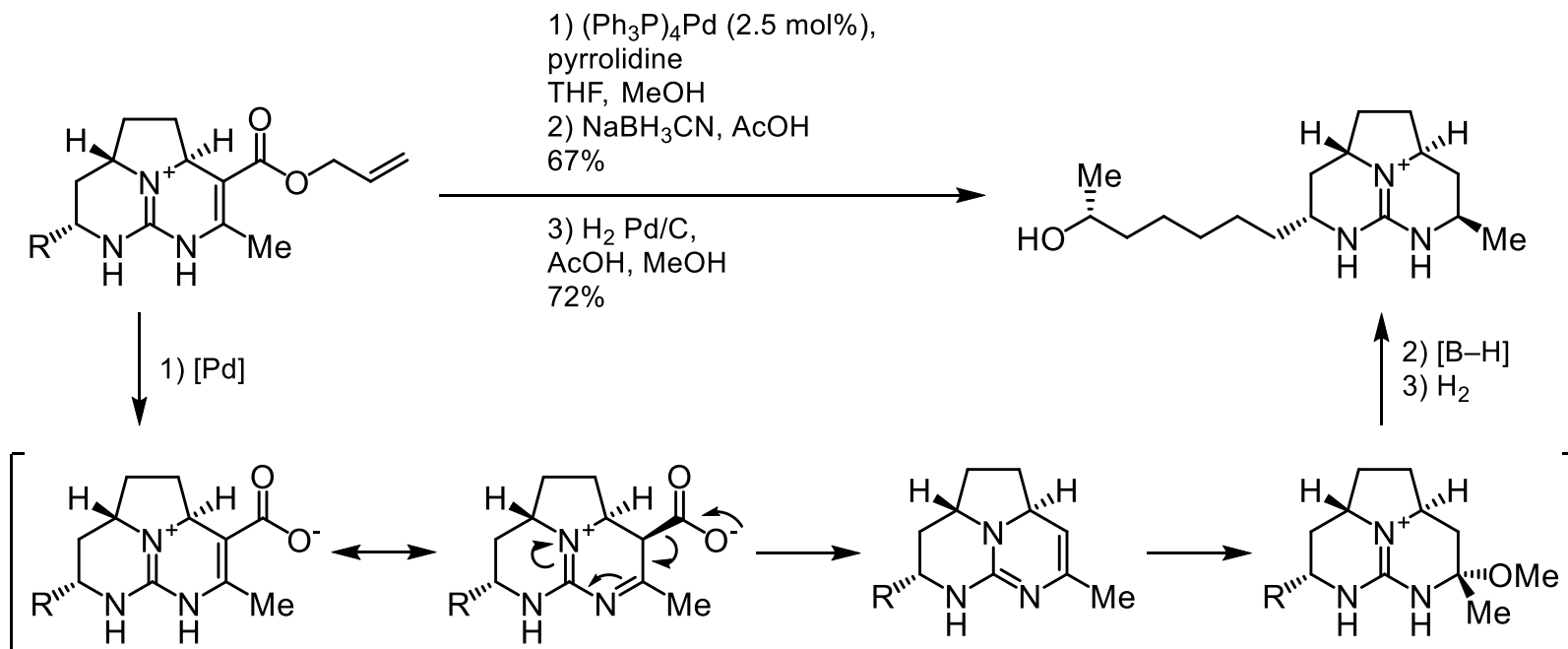
Overman's synthesis of Batzelladine F: Eastern Fragment



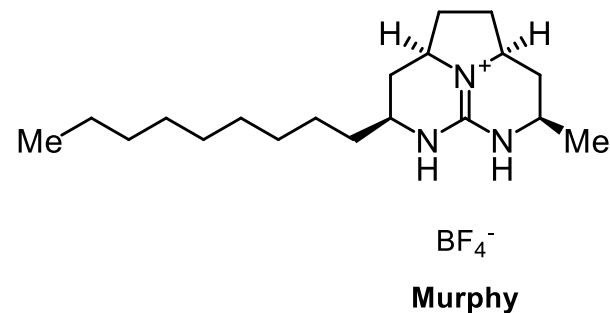
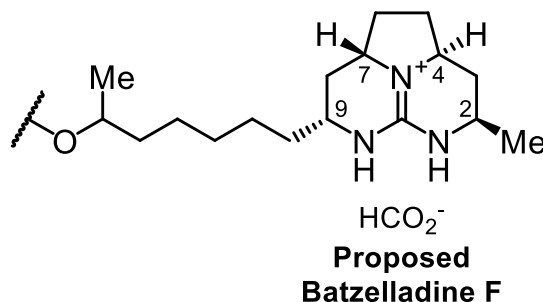
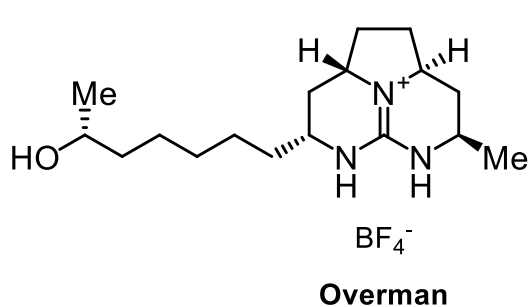
Overman's synthesis of Batzelladine F: Eastern Fragment



Overman's synthesis of Batzelladine F: Eastern Fragment

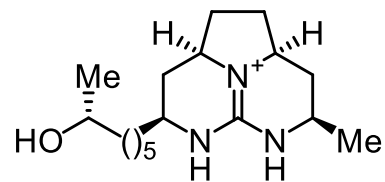
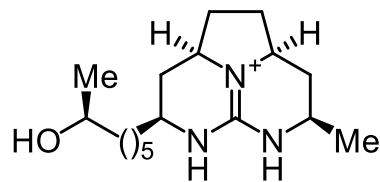
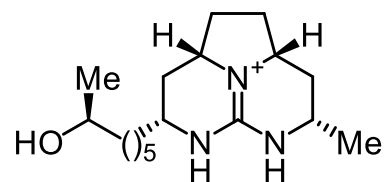
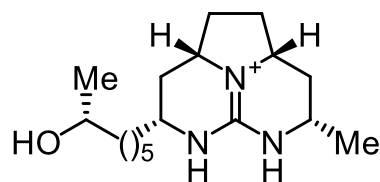


^{13}C NMR shift comparison of Eastern Fragment: *syn* it is

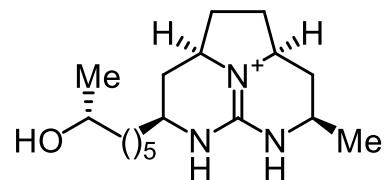
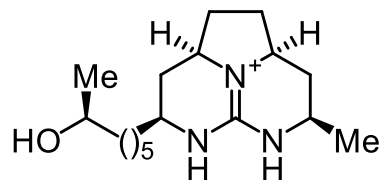
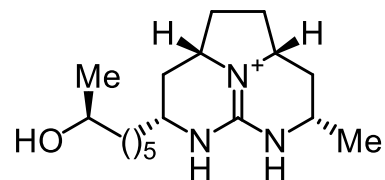
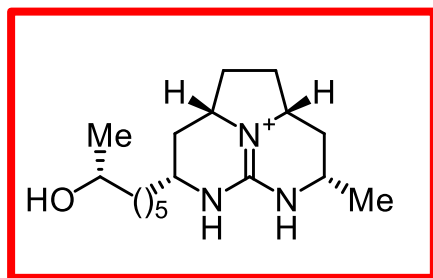


Carbon number	Overman	Batzelladine F	Murphy
1	21.7	20.7	20.7
2	48.9	47.2	47.3
4	56.5	57.5	57.5
7	56.4	57.4	57.5
9	53.1	51.6	51.6

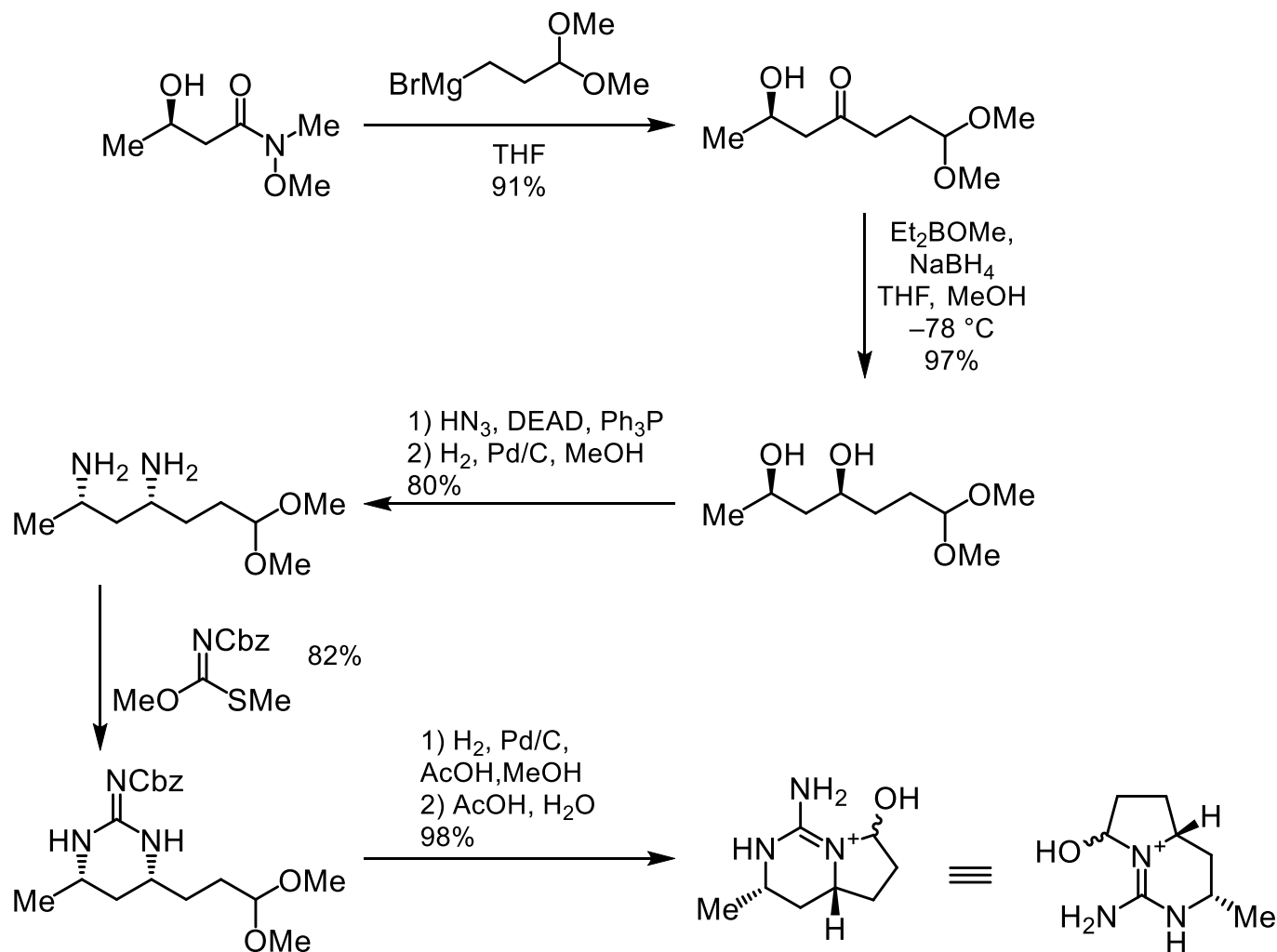
Plausible Structures of Eastern Fragment



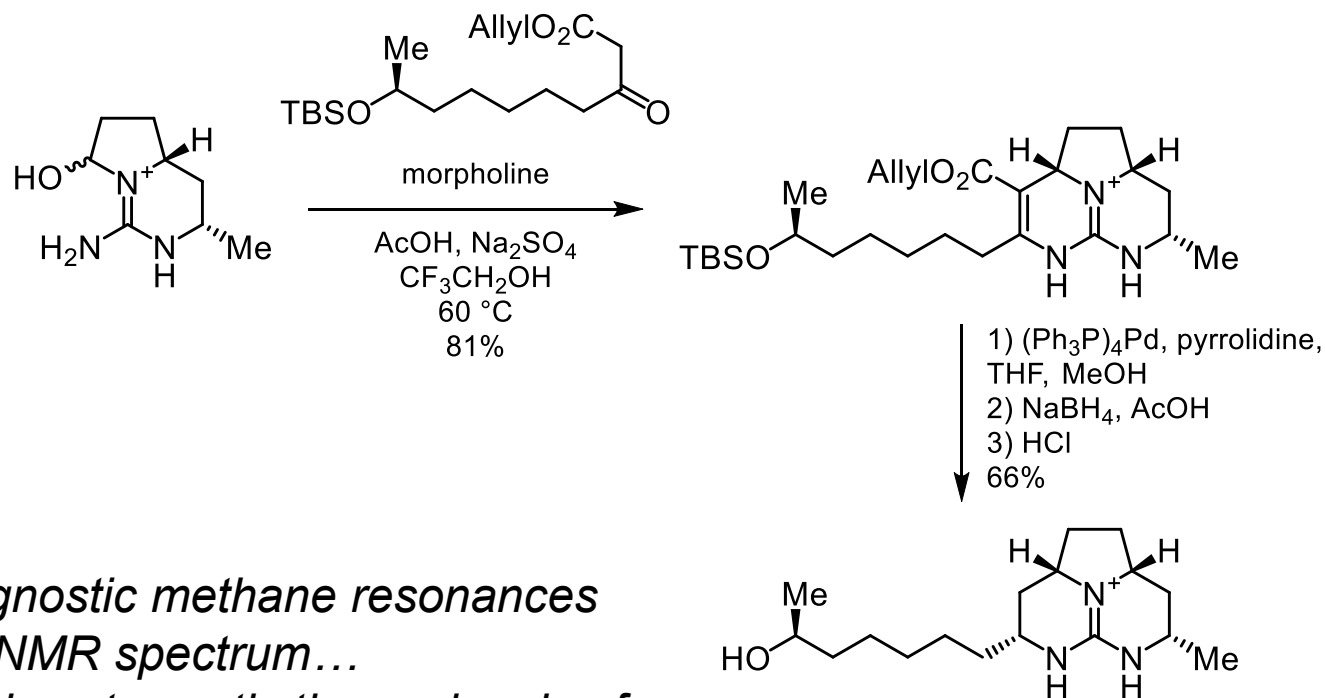
Plausible Structures of Eastern Fragment



Overman's synthesis of Batzelladine F: Eastern Fragment(s)

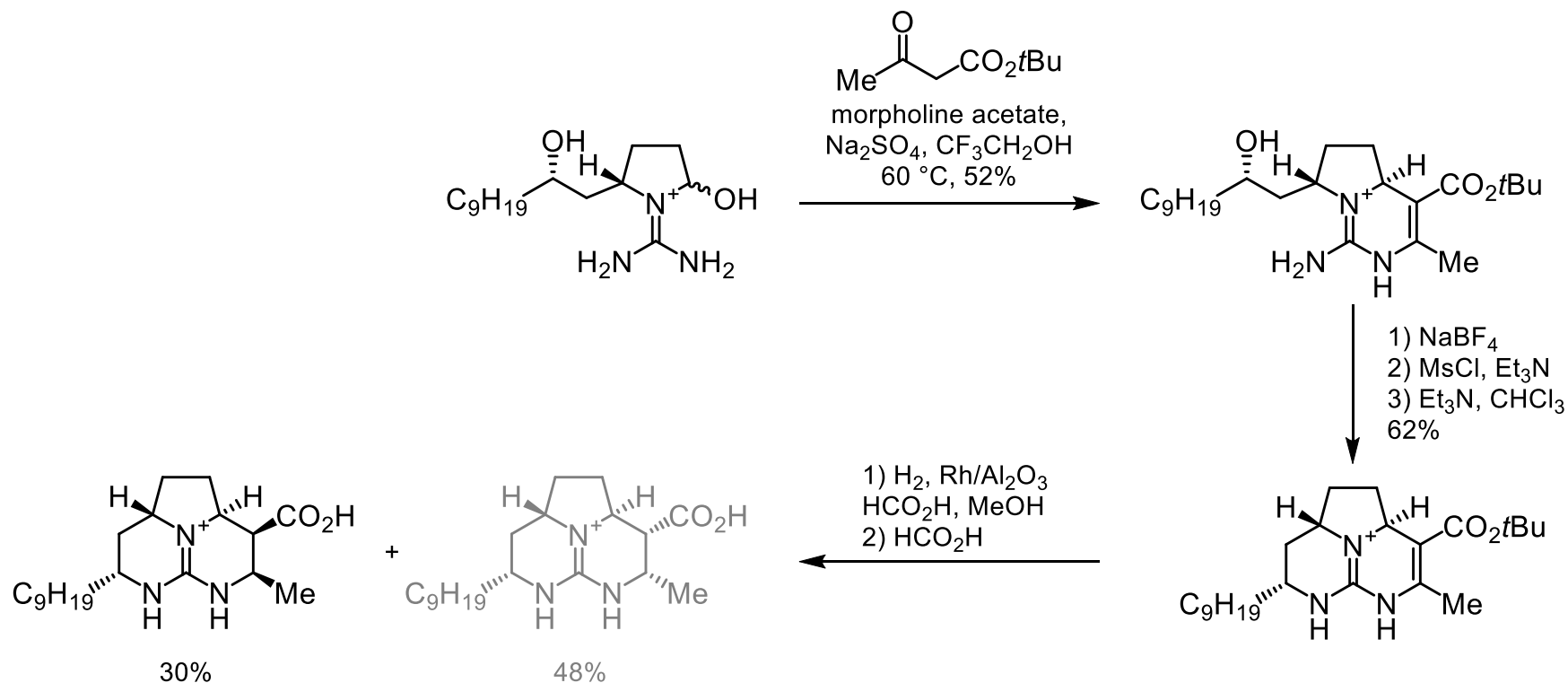


Overman's synthesis of Batzelladine F: Eastern Fragment(s)

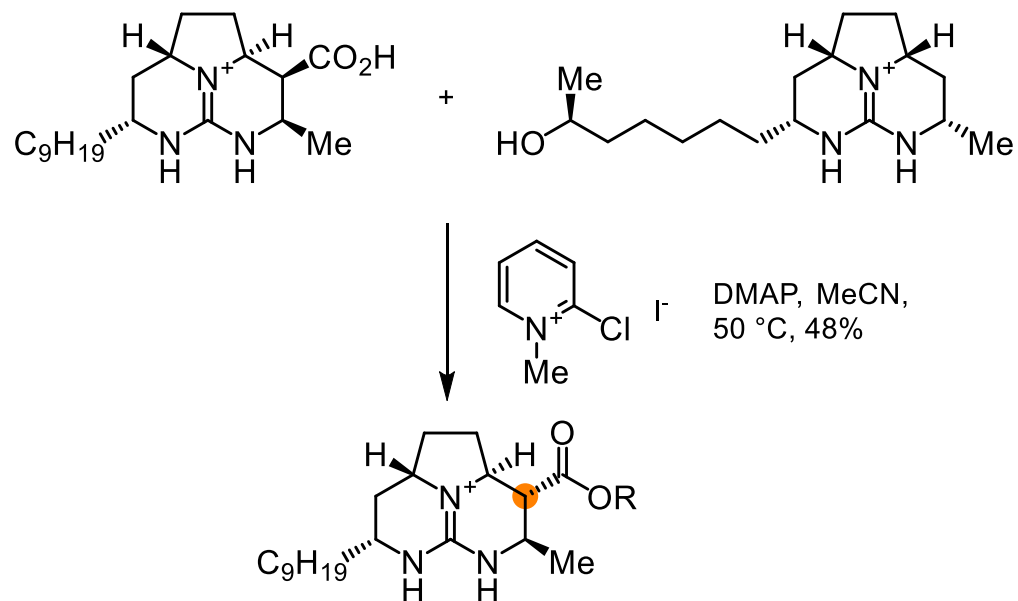


“...the diagnostic methane resonances in the ¹³C NMR spectrum... matched almost exactly those signals of batzelladine F...”

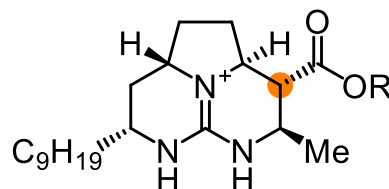
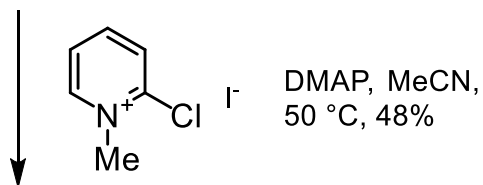
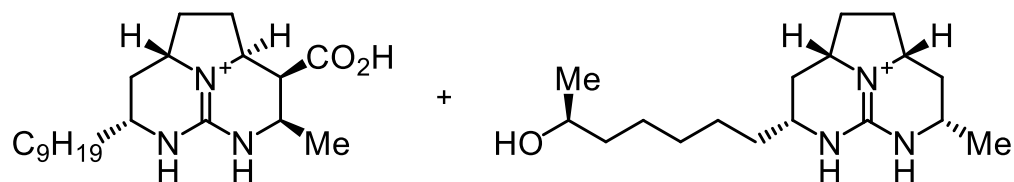
Overman's synthesis of Batzelladine F: Western Fragment



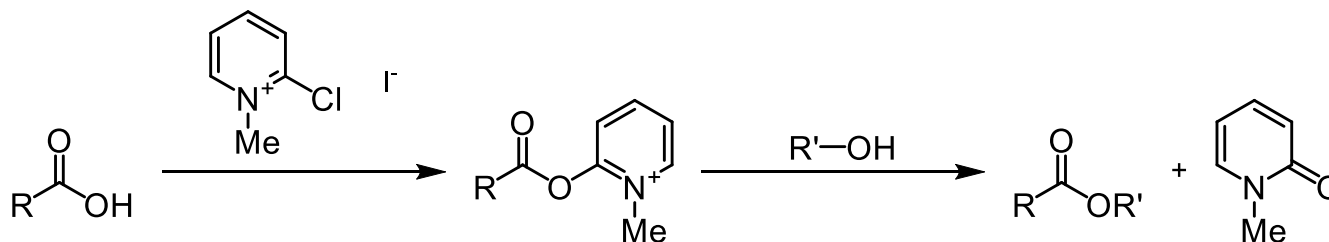
Overman's synthesis of Batzelladine F: Coupling



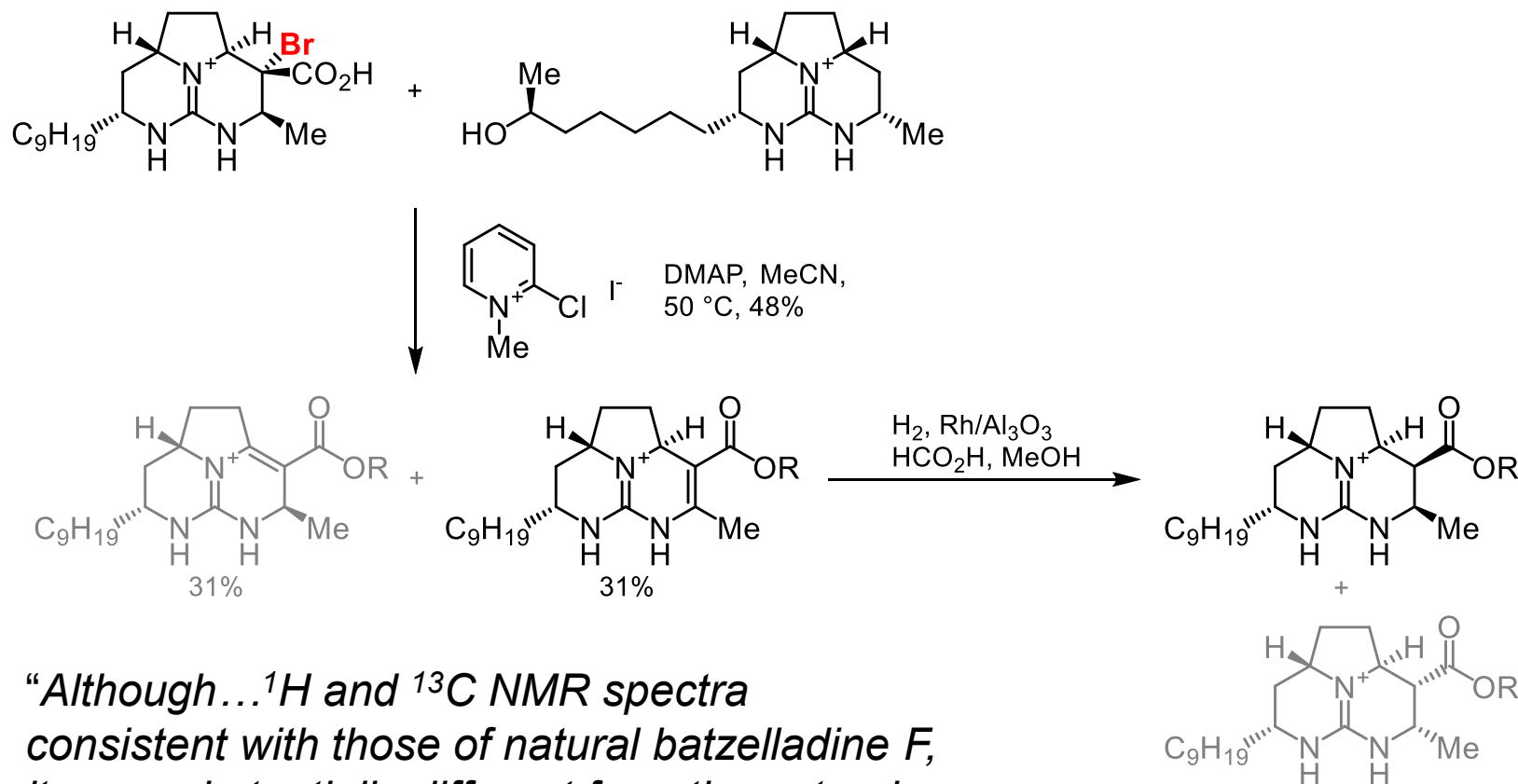
Overman's synthesis of Batzelladine F: Coupling



Mukaiyama's salt

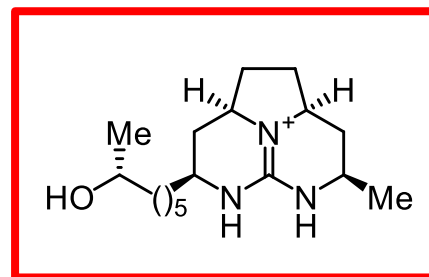
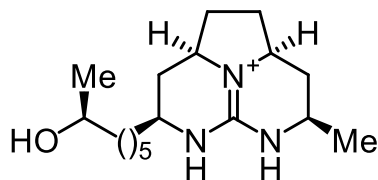
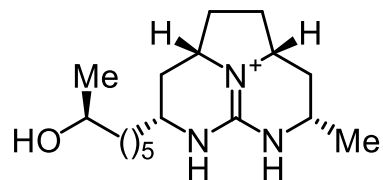
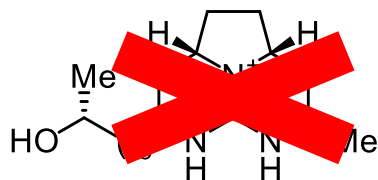


Overman's synthesis of not-Batzelladine F

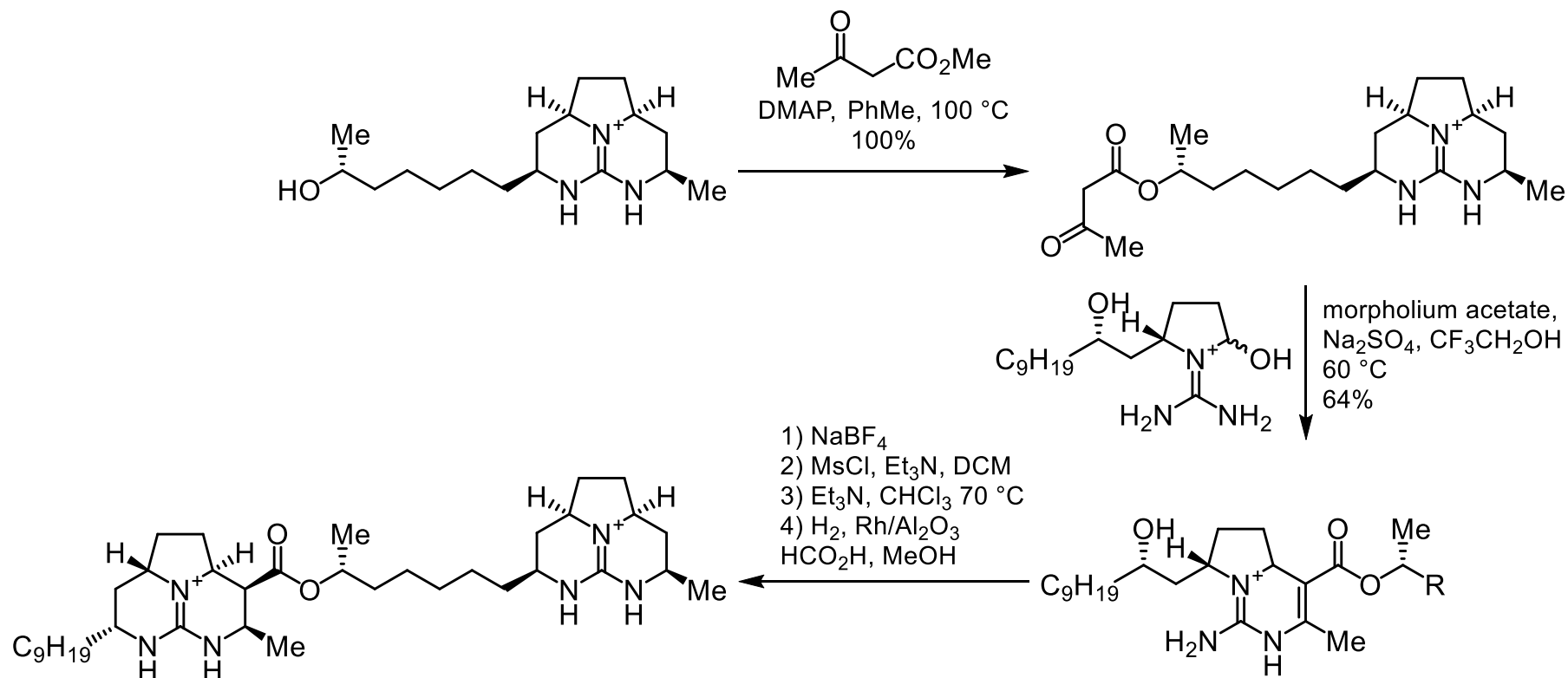


“Although...¹H and ¹³C NMR spectra consistent with those of natural batzelladine F, it was substantially different from the natural product by HPLC analysis.”

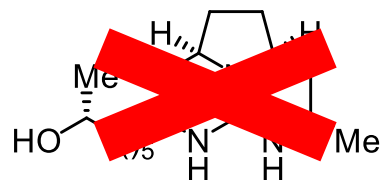
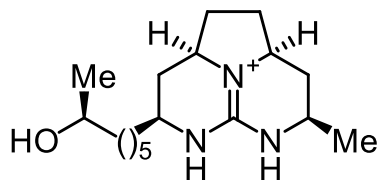
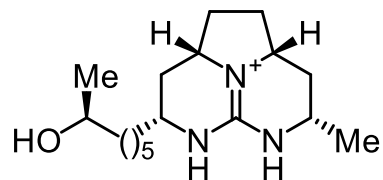
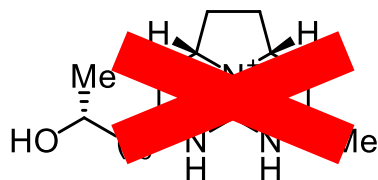
Plausible Structures of Eastern Fragment



Overman's synthesis of another not-Batzelladine F

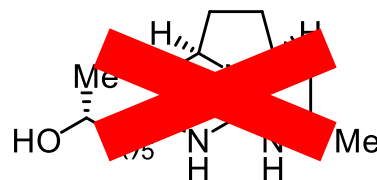
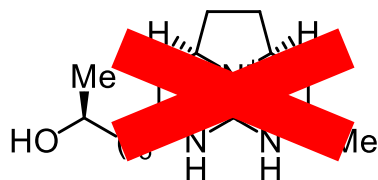
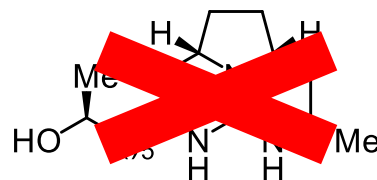
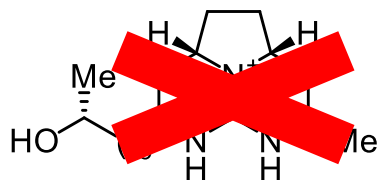


Plausible Structures of Eastern Fragment



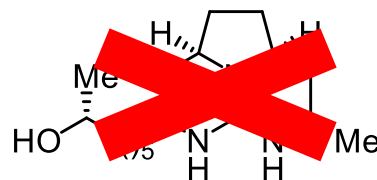
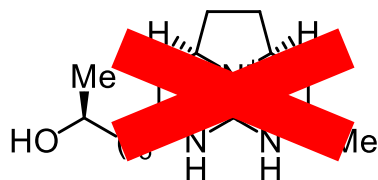
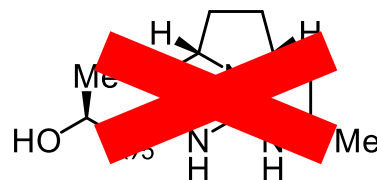
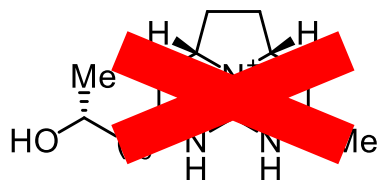
Plausible Structures of Eastern Fragment

“To our chagrin, these isomers were also distinct from an authentic sample of batzelladine F by HPLC comparisons.”

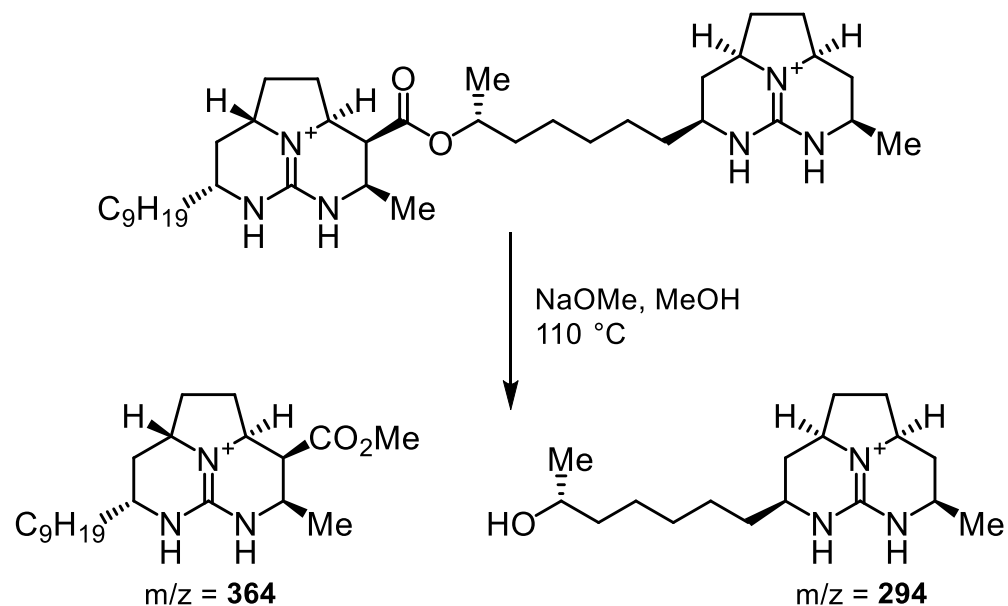


So what is Batzelladine F?

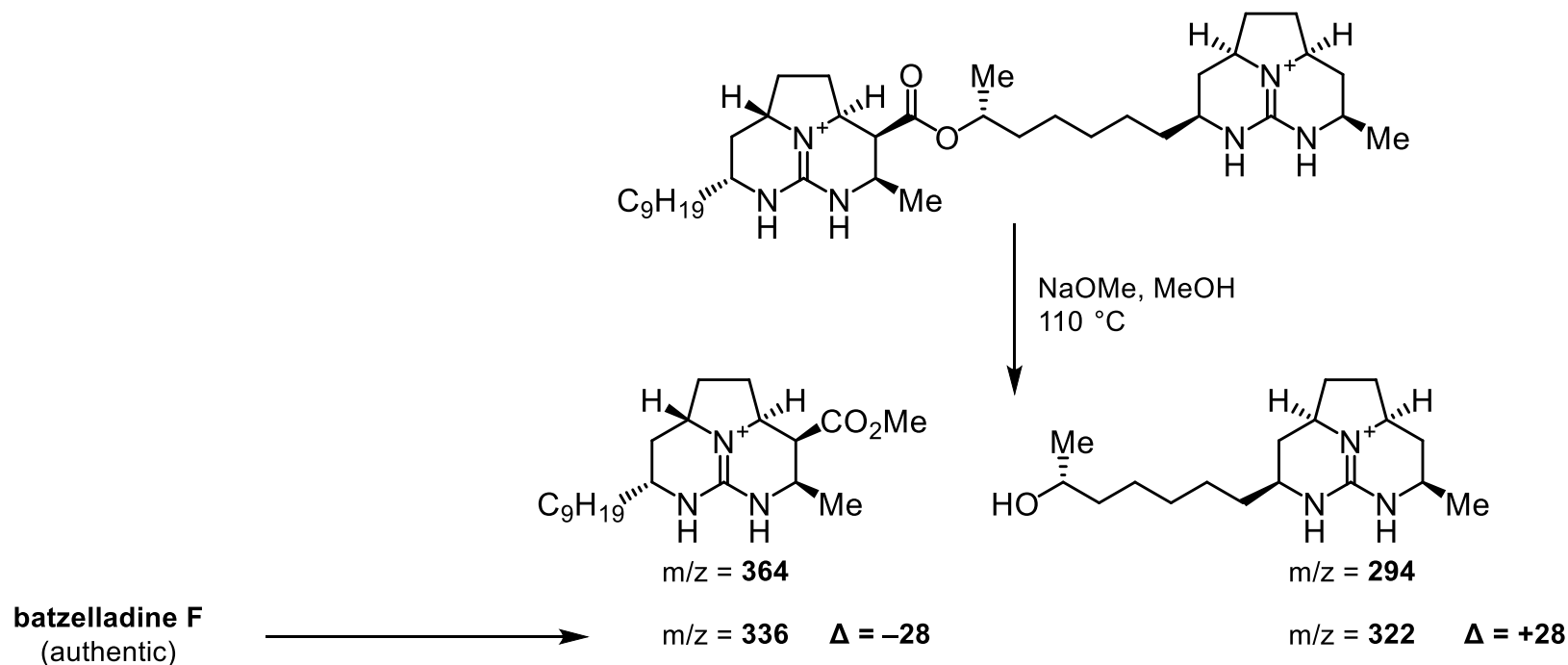
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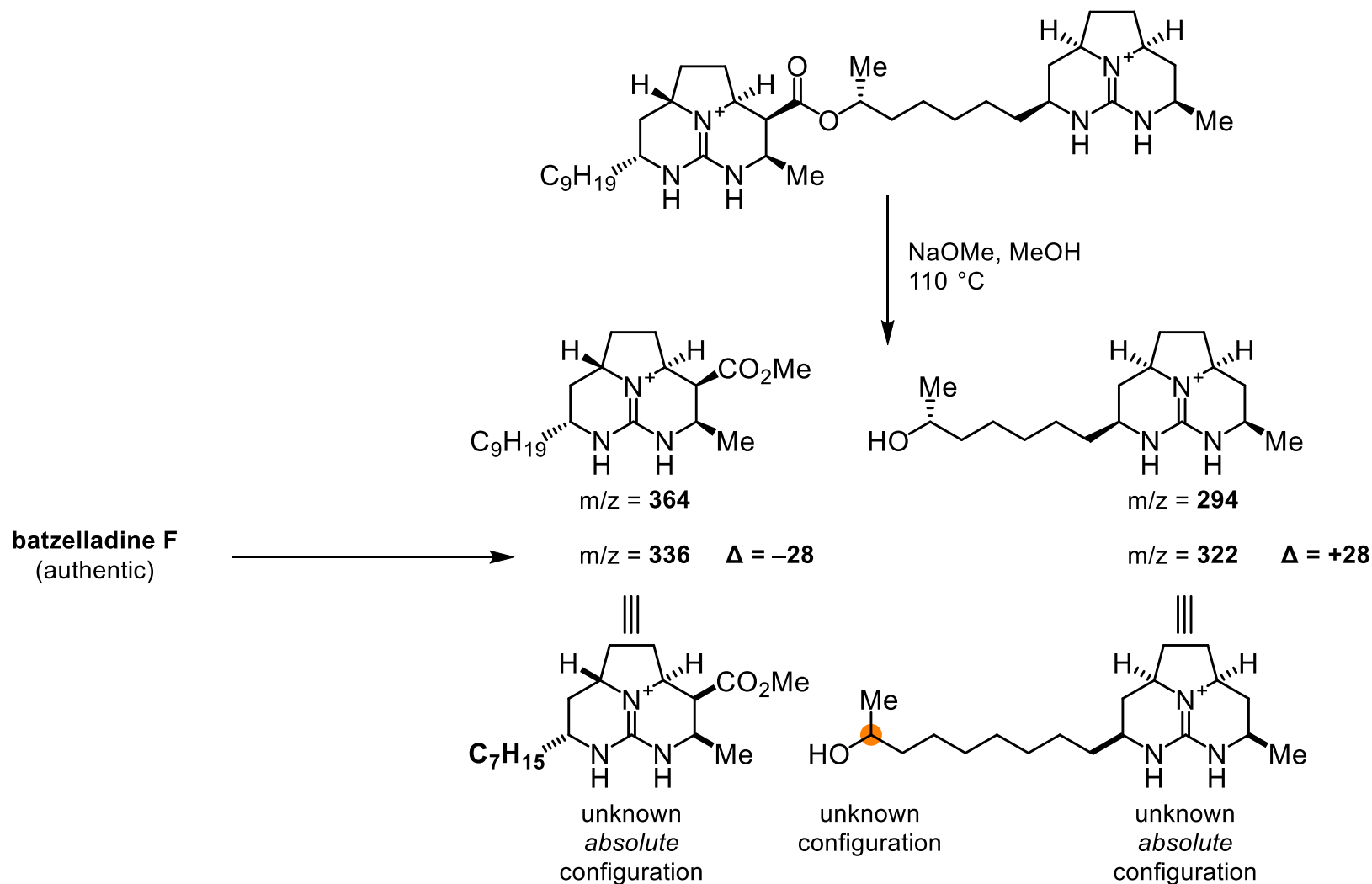
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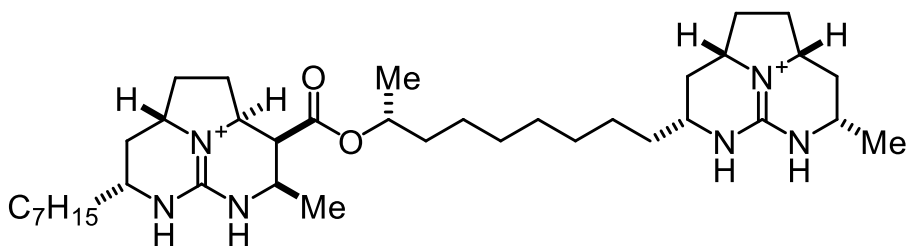
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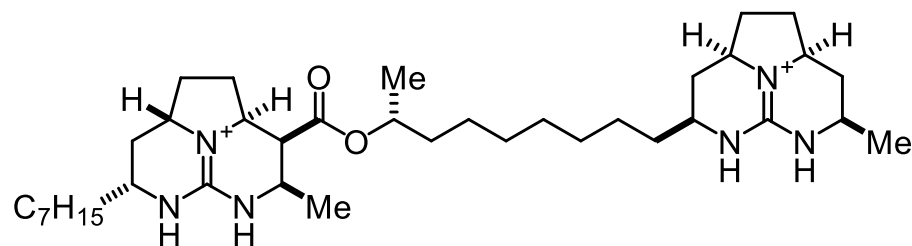
So what is Batzelladine F?



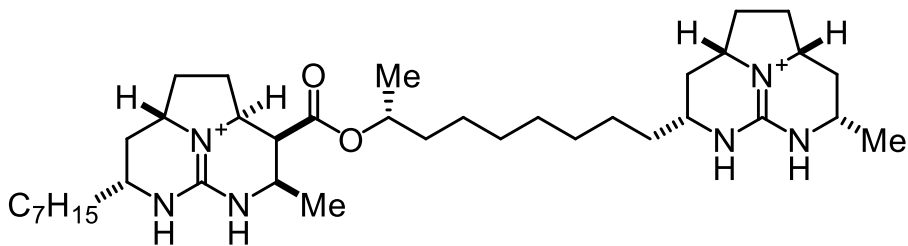
So what is Batzelladine F: 8 possible structures



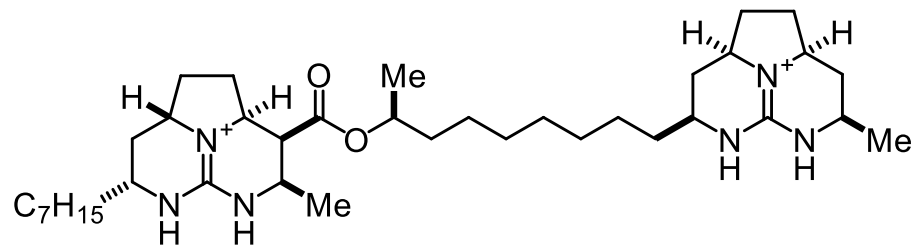
A



B

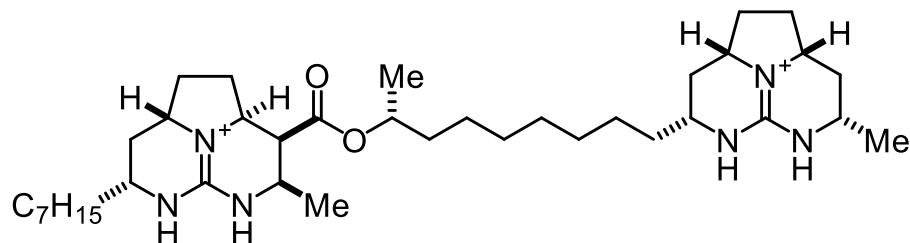


C



D

So what is Batzelladine F



13 steps total

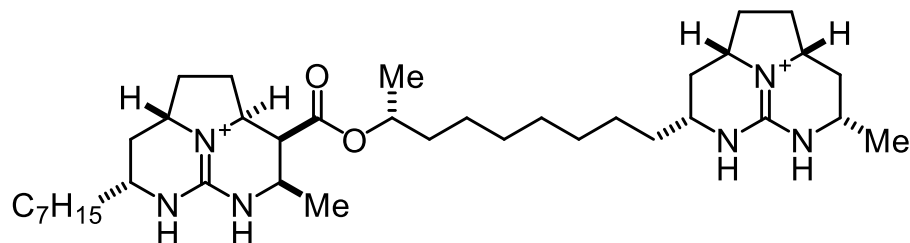
A

*“NMR spectra of synthetic **A** agreed well with the corresponding data reported for natural batzelladine **F**.*

...

*to establish rigorously the stereostructure of batzelladine **F**, we synthesized stereoisomers **B–D**”*

So what is Batzelladine F



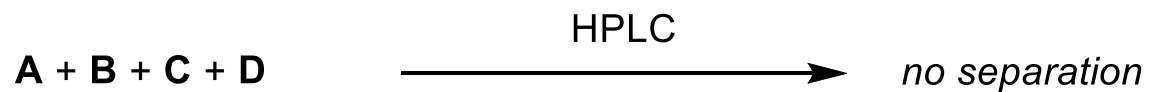
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...

*to establish rigorously the stereostructure of batzelladine **F**, we synthesized stereoisomers **B–D**”*

But how to distinguish them from each other?

So what is Batzelladine F: HPLC studies



So what is Batzelladine F: HPLC studies

A + B + C + D $\xrightarrow{\text{HPLC}}$ *no separation*

A + C $\xrightarrow{\text{HPLC}}$ *separation*

B + D $\xrightarrow{\text{HPLC}}$ *separation*

So what is Batzelladine F: HPLC studies

A + B + C + D	HPLC →	<i>no separation</i>
A + C	HPLC →	<i>separation</i>
B + D	HPLC →	<i>separation</i>
batzelladine F + D	HPLC →	<i>separation</i>
C + D	HPLC →	<i>no separation</i>

So what is Batzelladine F: HPLC studies

A + B + C + D $\xrightarrow{\text{HPLC}}$ *no separation*

A + C $\xrightarrow{\text{HPLC}}$ *separation*

B + D $\xrightarrow{\text{HPLC}}$ *separation*

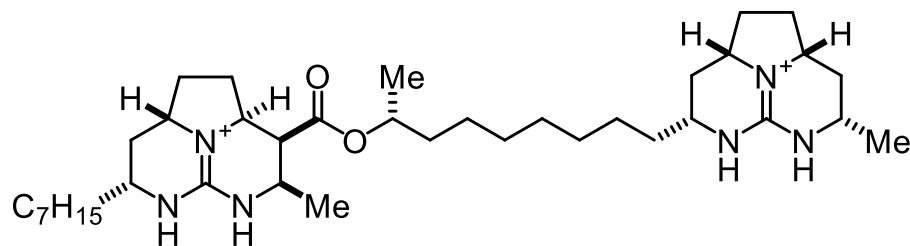
batzelladine F + **D** $\xrightarrow{\text{HPLC}}$ *separation*

C + D $\xrightarrow{\text{HPLC}}$ *no separation*

$\Rightarrow$ **A or B** = Batzelladine F

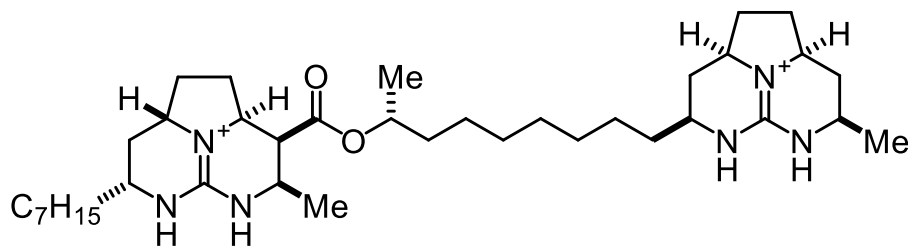
So what is Batzelladine F: Optical rotation

*“Unfortunately isomers **A** and **B** coeluted under all conditions. Moreover, these samples showed ^1H and ^{13}C spectra indistinguishable from one another and batzelladine F.”*



A

$$[\alpha]_{\text{D}}^{24} = -7.7^{\circ} \text{ (c 0.25 MeOH)}$$

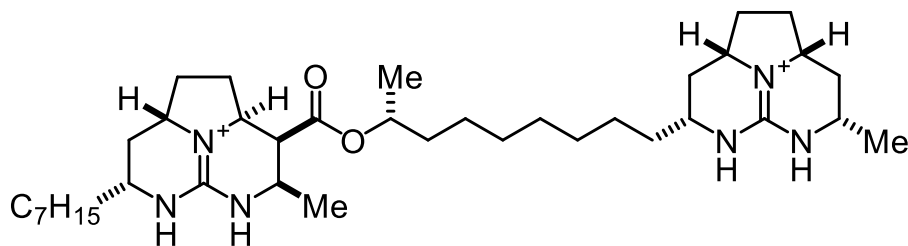


B

$$[\alpha]_{\text{D}}^{24} = -14.1^{\circ} \text{ (c 0.36 MeOH)}$$

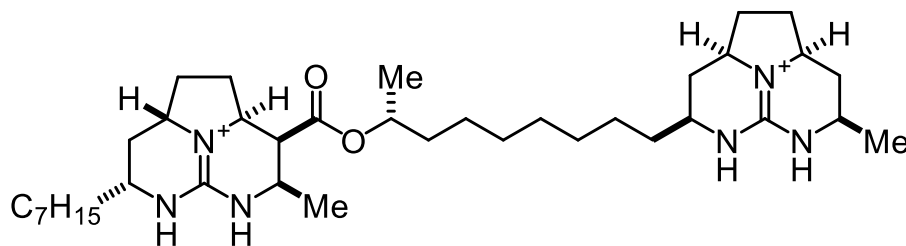
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*“Unfortunately isomers **A** and **B** coeluted under all conditions. Moreover, these samples showed ^1H and ^{13}C spectra indistinguishable from one another and batzelladine F.”*



A

$$[\alpha]_{\text{D}}^{24} = -7.7^{\circ} \text{ (c 0.25 MeOH)}$$



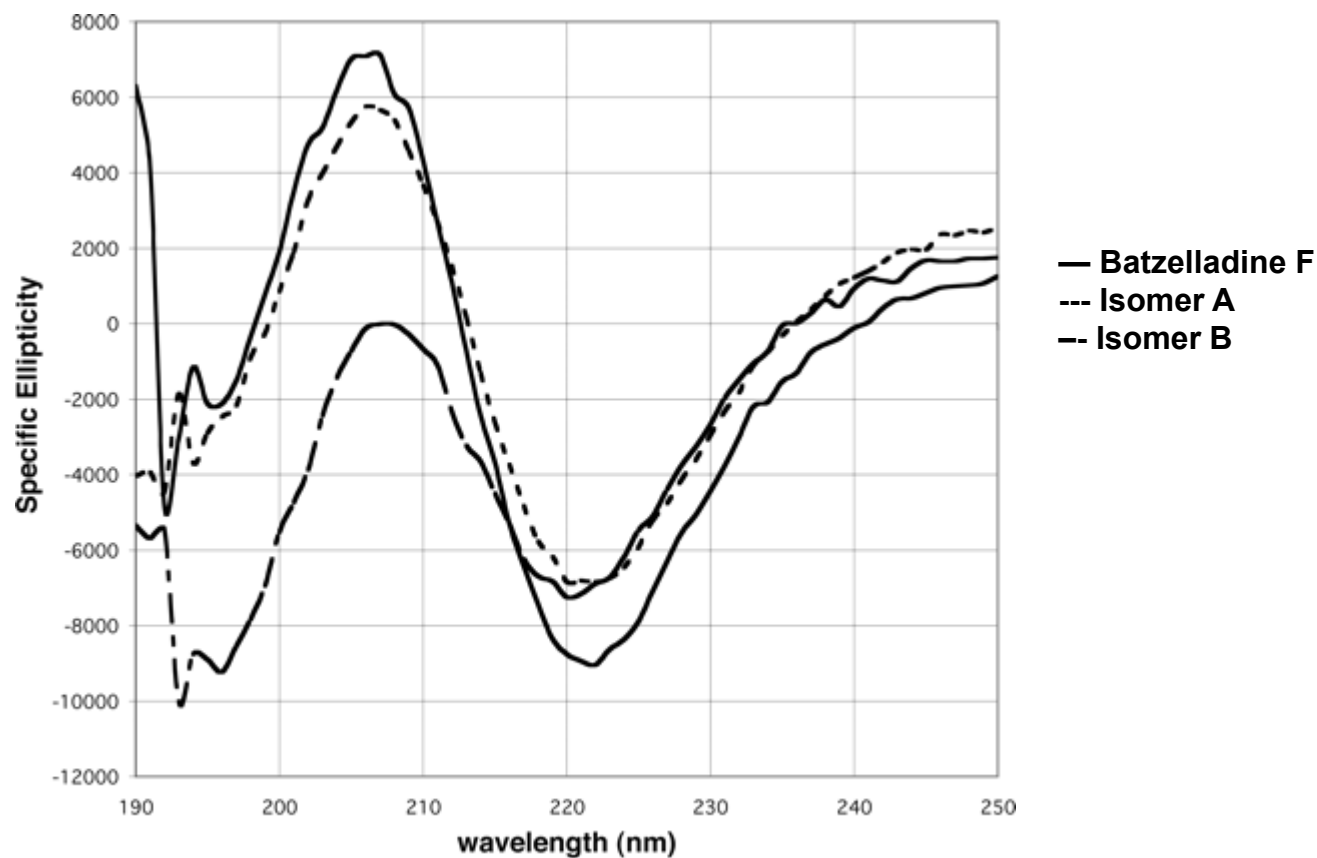
B

$$[\alpha]_{\text{D}}^{24} = -14.1^{\circ} \text{ (c 0.36 MeOH)}$$

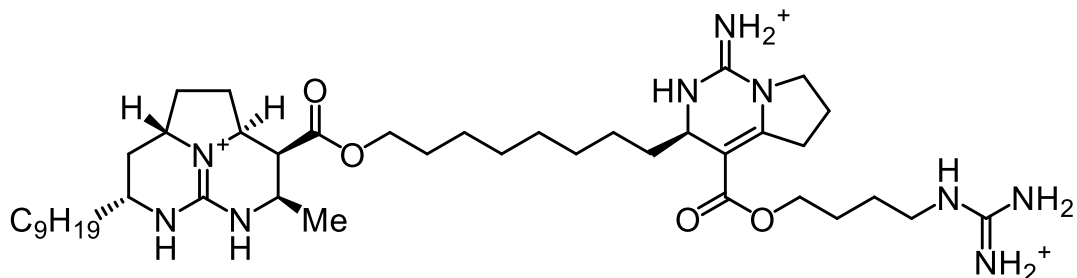
batzelladine F

$$[\alpha]_{\text{D}}^{24} = 19.4^{\circ} \text{ (c 0.87 MeOH)}$$

So what is Batzelladine F: CD spectra

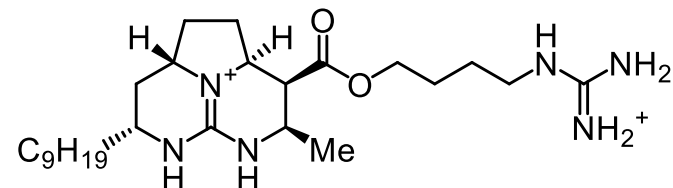


Total syntheses of Batzelladines



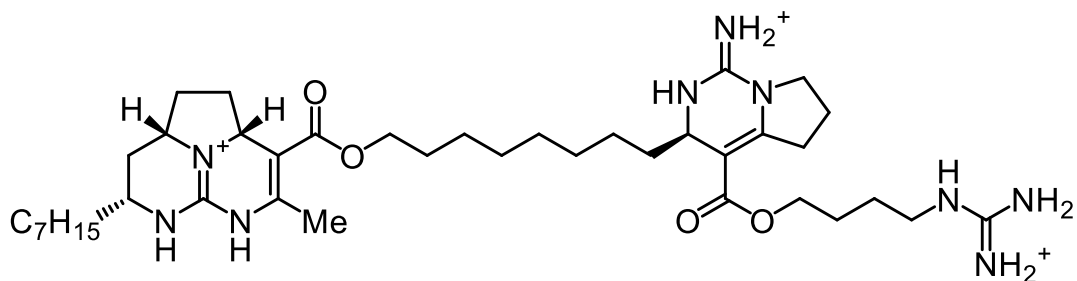
Batzelladine A

2004 Nagasawa *Angew. Chem.* 20 steps
 2006 Gin *JACS* 23 steps



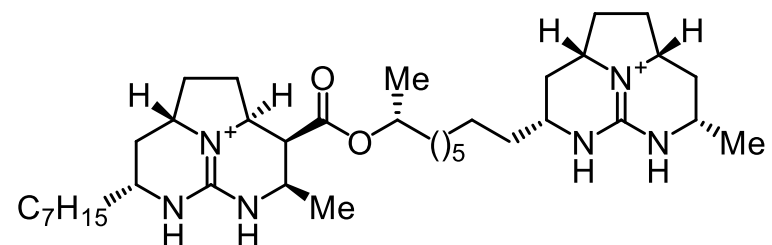
Batzelladine D

1999 Overman *Org. Lett.* 16 steps
 2004 Nagasawa *Org. Lett.* 15 steps, *rac*
 2005 Nagasawa *Chem. Eur. J.* 18 steps
 2006 Gin *JACS* 13 steps
 2007 Evans *Angew. Chem.* 14 steps



Batzelladine B

1999 Overman



Batzelladine F

2006 Overman *JACS* 18 steps

Misassignments and Total synthesis

“Although the past half century has witnessed a remarkable improvement in our ability to isolate and characterize complex natural products, mistakes are still a relatively common occurrence.

However, this state of affairs is far from catastrophic. Indeed, structural misassignments clearly provide opportunities for synthetic chemists to make discoveries through total synthesis, and certainly show that there is still adventure to be had in the process of structure assignment.”

K. C. Nicolaou & S. A. Snyder
ACIE 2005, 44, 1012