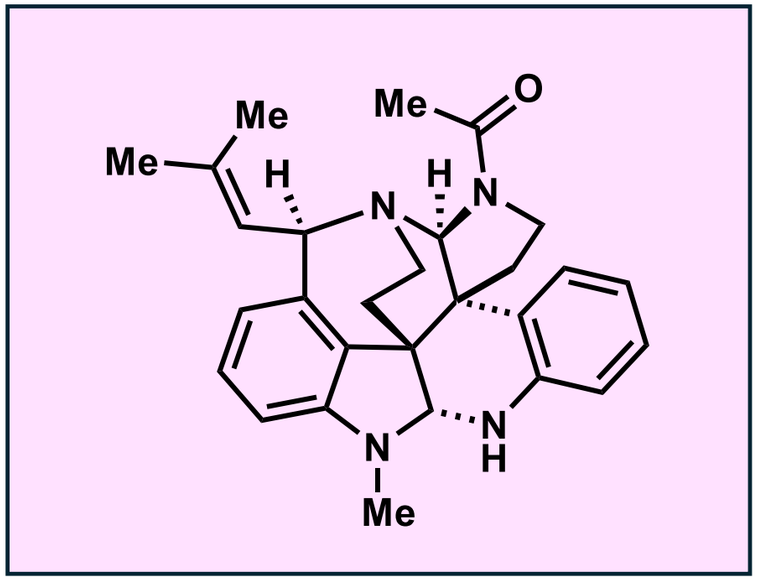
Synthetic Approaches to Alkaloid Communesin F



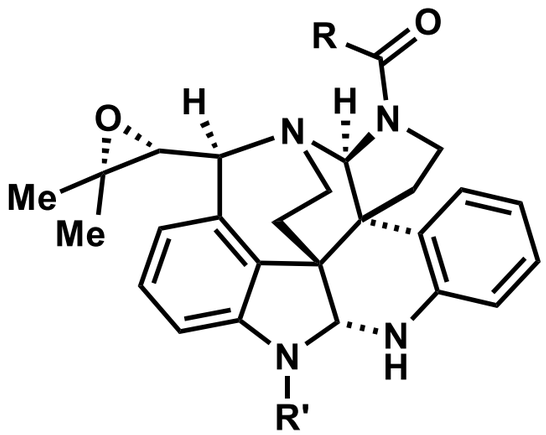
(-) Communesin F

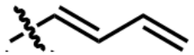
Grace Fleury

Literature Presentation

February 14th, 2025

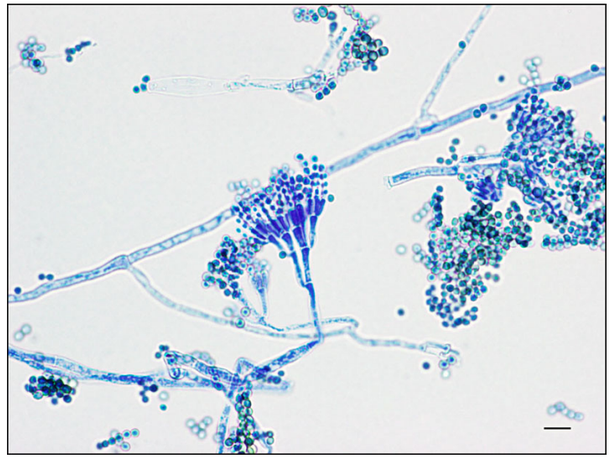
Introduction to the Communesin Family



Communesin A: R = R' = Me
Communesin B: R' = Me, R = 

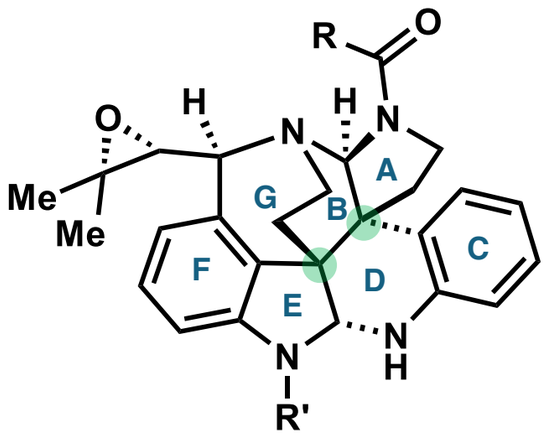
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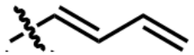




Hasegawa, T. *et al. Tet Lett.* **1993**, *34 (14),* 2355-2358.

Introduction to the Communesin Family

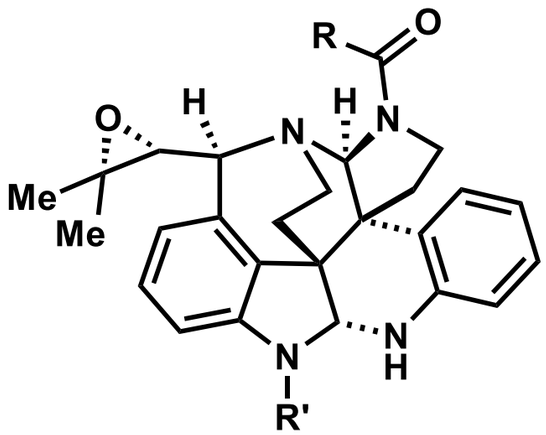


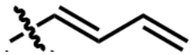
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Introduction to the Communesin Family

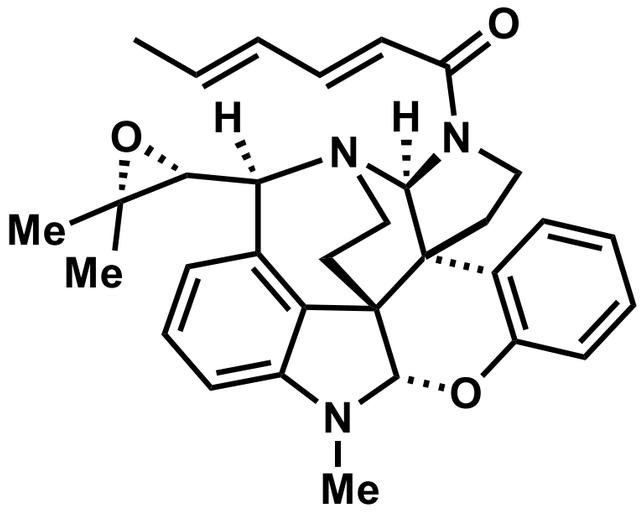


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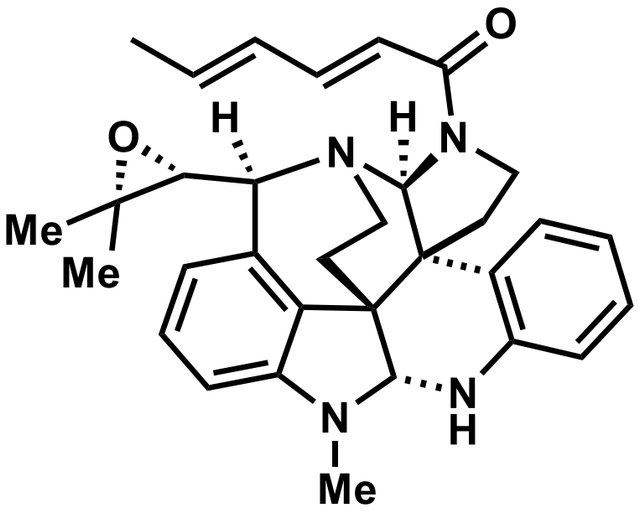
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Structural Debate Interlude



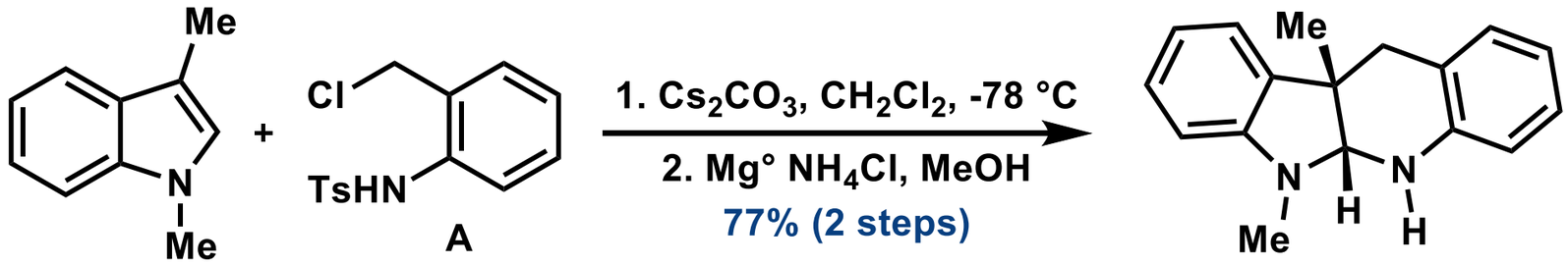
"Nomofungin"

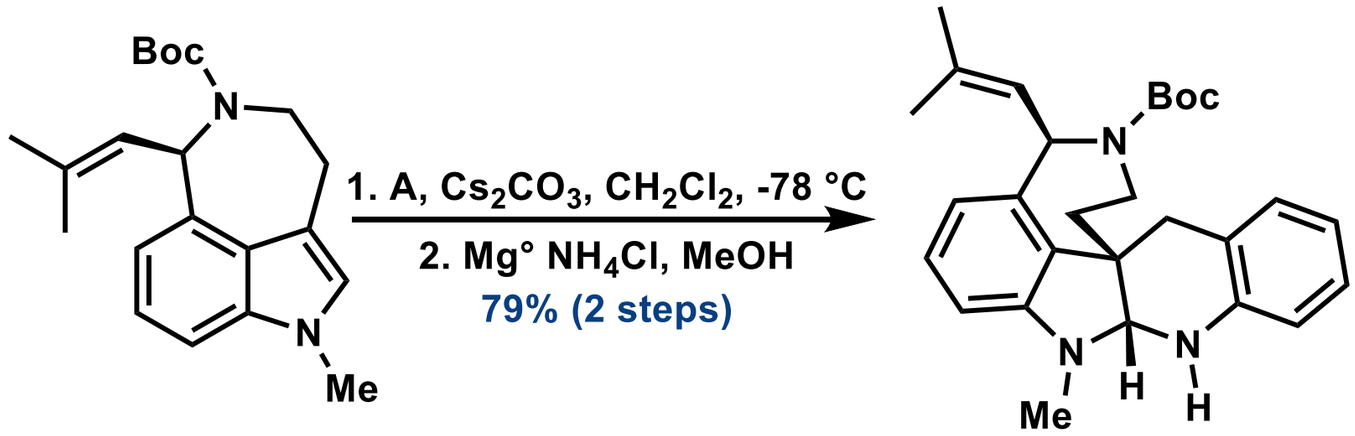


Communesin B

Structural Debate Interlude

Stoltz Biomimetic Approach

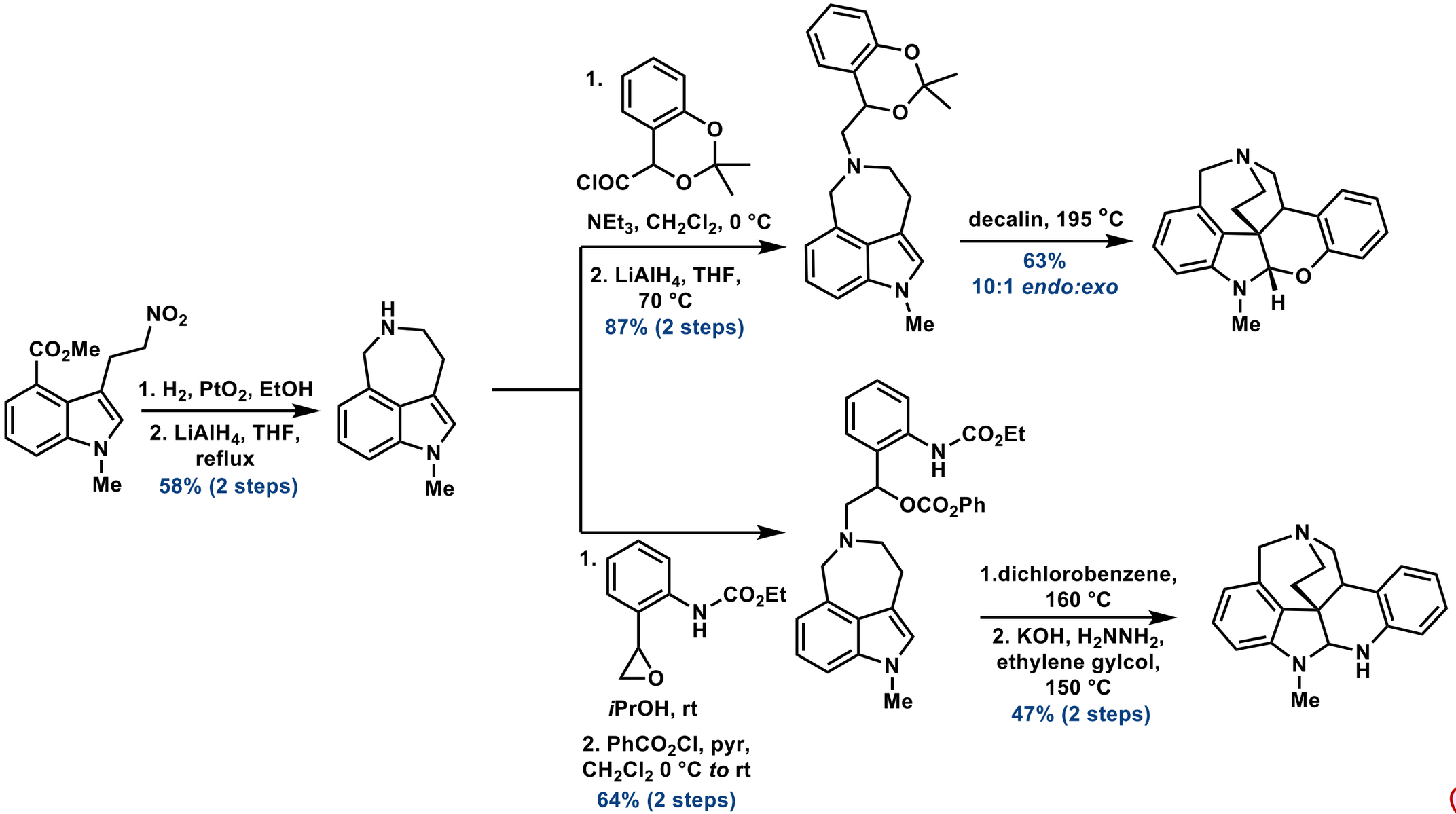




Stoltz, B. *et al. Tet Lett.* **2003**, *44 (6),* 1203-1205

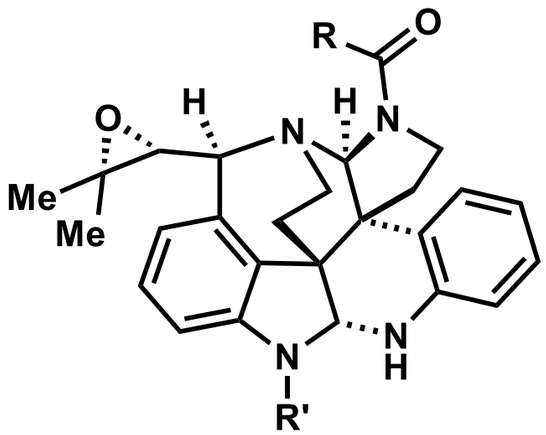
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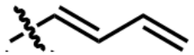
Funk Hetero-Diels-Alder Approach

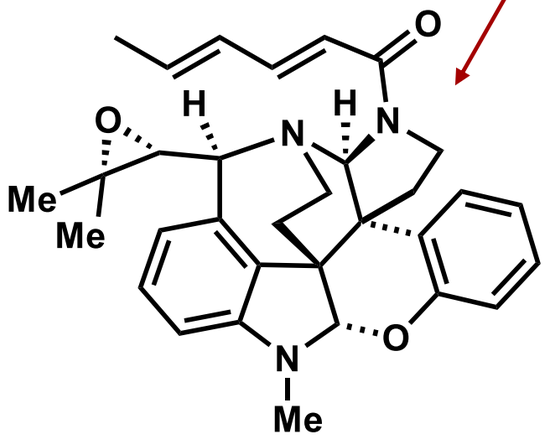


Crawley, S., Funk, R. *Org Lett*. **2003**, *5 (18),* 3169-3171

Introduction to the Communesin Family



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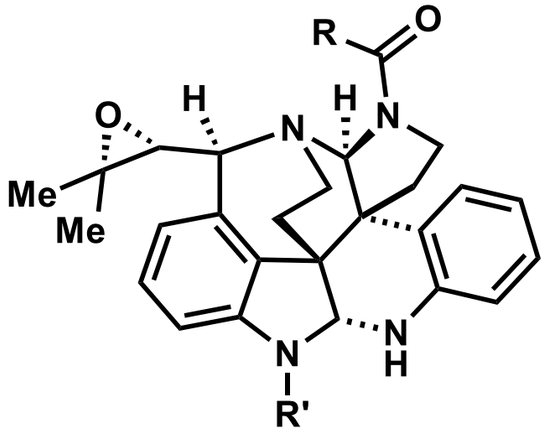
"Nomofungin"

2001 Hemscheidt reported, isolated from fungus on bark of *Ficus microcarpa* in Hawaii

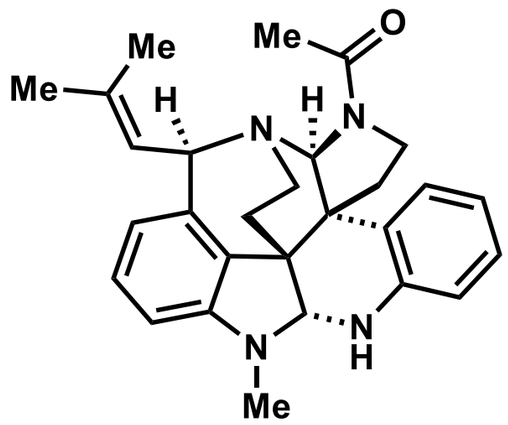
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Introduction to the Communesin Family



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Communesin G: R' = Me, R = Et
Communesin H: R' = Me, R = Pr

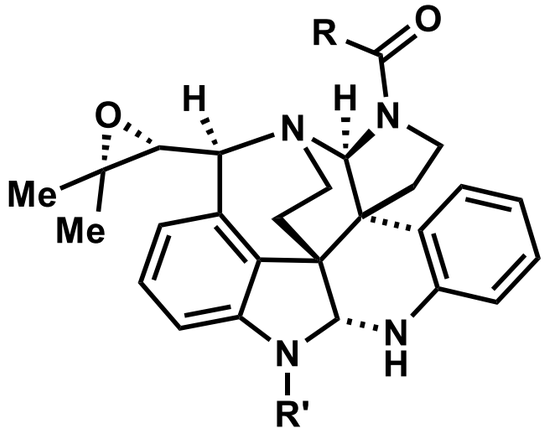


Communesin F

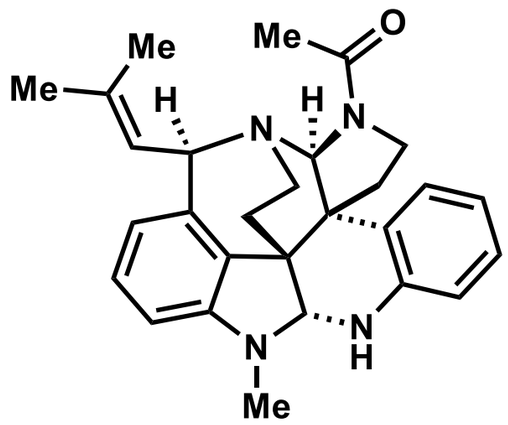
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Proksch, P. *et al. J. Nat. Prod.* ***2003****, 67 (1),* 78-81. Hayashi, H. *et al. Biosci. Biotech. Biochem.* **2004***, 68 (3)*, 753-756. Christophersen. *et al. Biosci. Biotech. Biochem.* **2004***, 68 (3)*, 753-756.

Introduction to the Communesin Family



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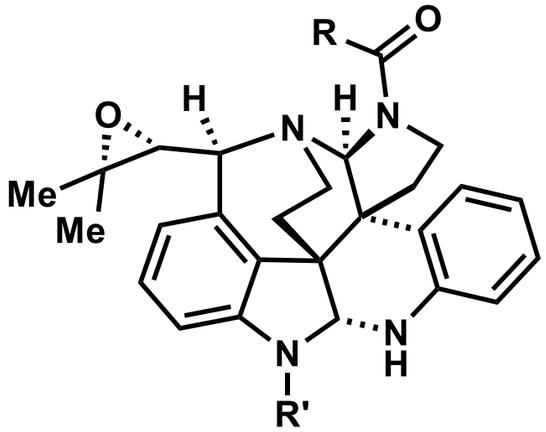
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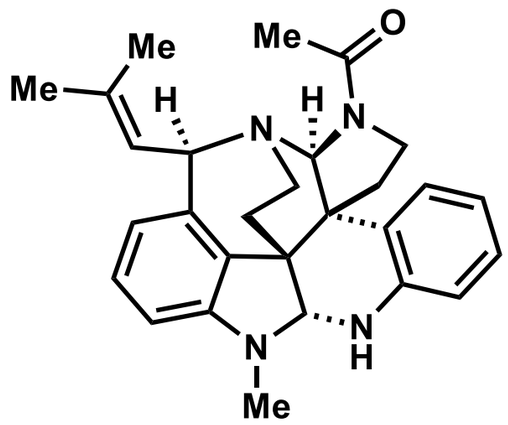
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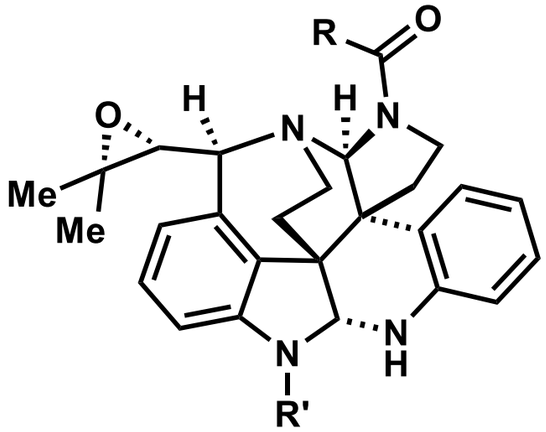


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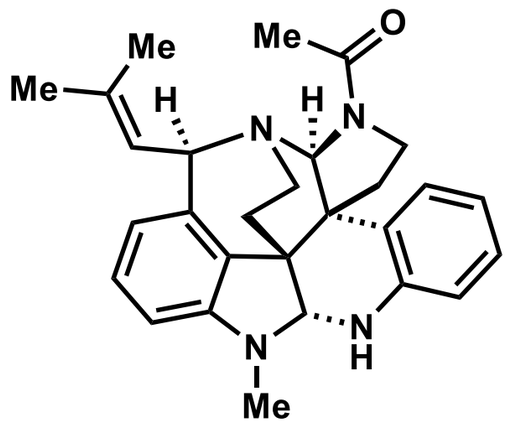
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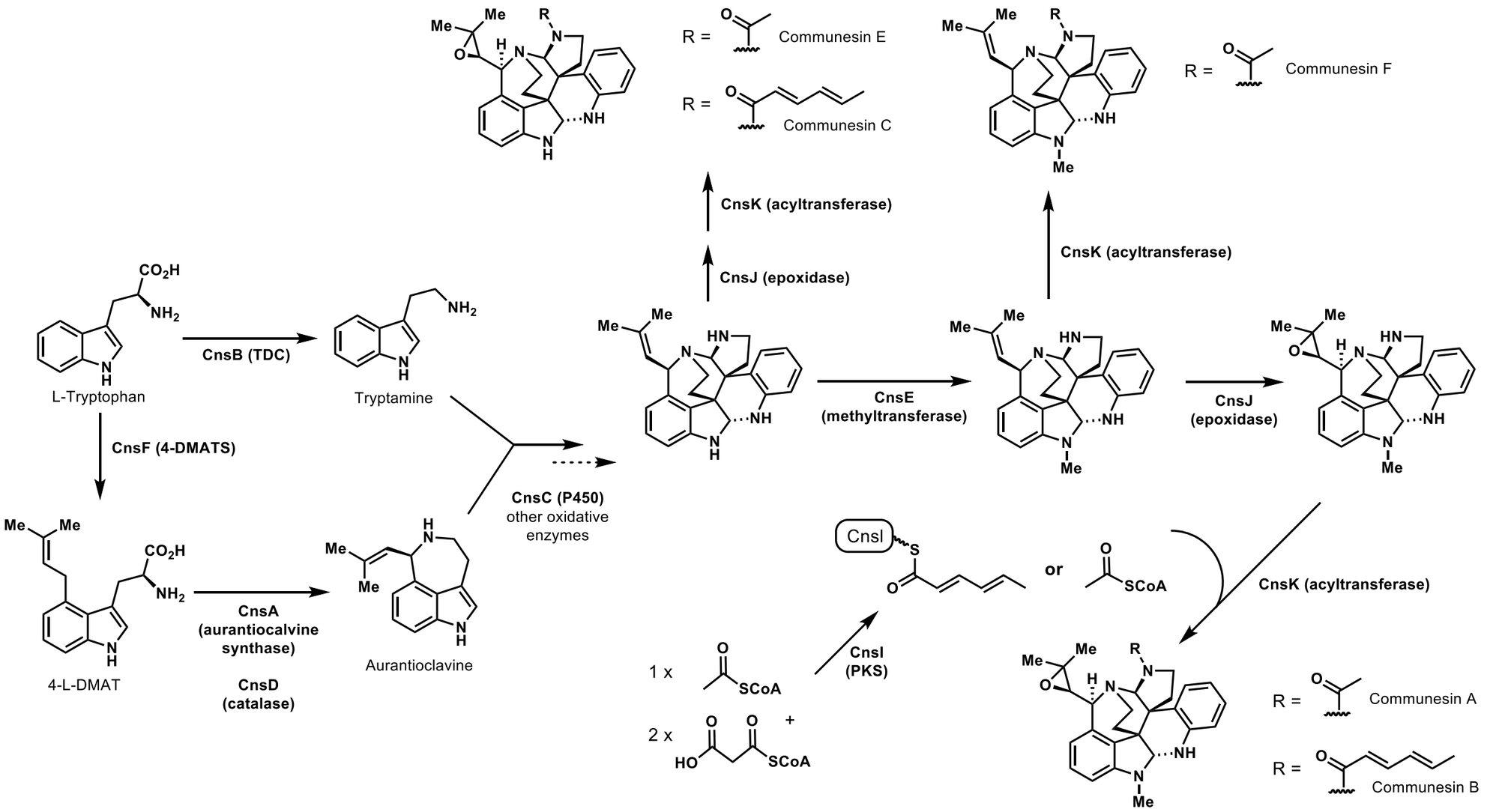
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Introduction to the Communesin Family

Biosynthetic Pathway



Tang, Y. *et al., Angew. Chem. Int. Ed.* **2015**, *54*, 3004 –3007

Syntheses of Communesin F

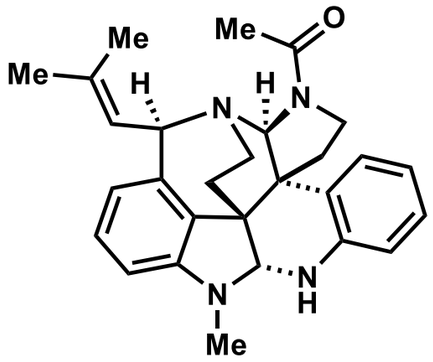
Racemic

Qin – 2007:
2.6% in 23 steps

Weinreb – 2010:
0.93% in 29 steps

Funk – 2012:
6.7% in 15 steps

Stoltz – 2014:
9.0% to intermediate in Qin synth. in 17 steps
(11 more to NP)



Communesin F

Enantioselective

Ma – 2010:
5.6% in 19 steps

Movassaghi – 2016:
1.3% in 21 steps

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3.7% in 15 steps

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Syntheses of Communesin F

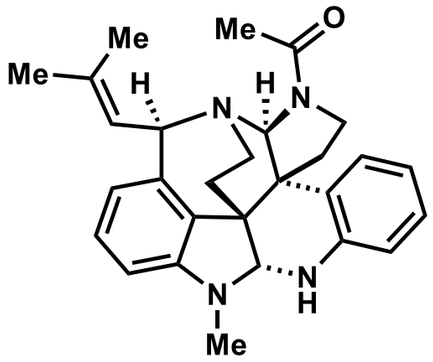
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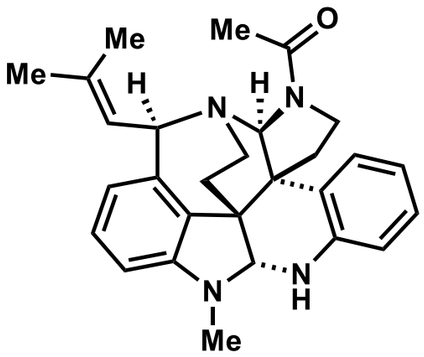
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Racemic Synthesis of Communesin F – Qin (2007)

Retrosynthetic Analysis

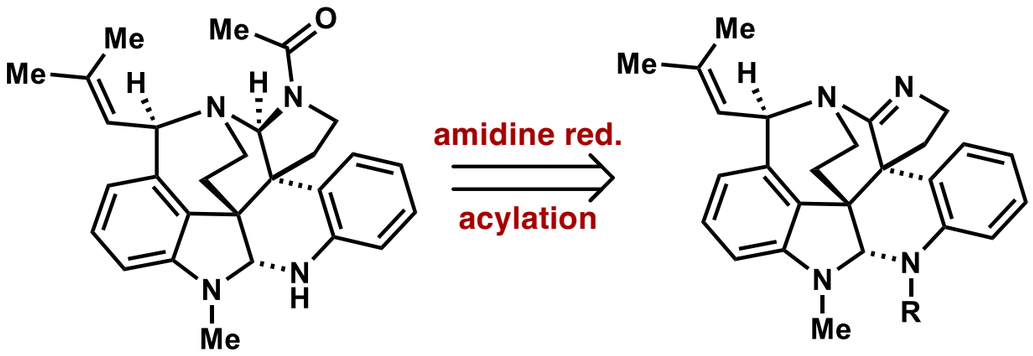


Communesin F

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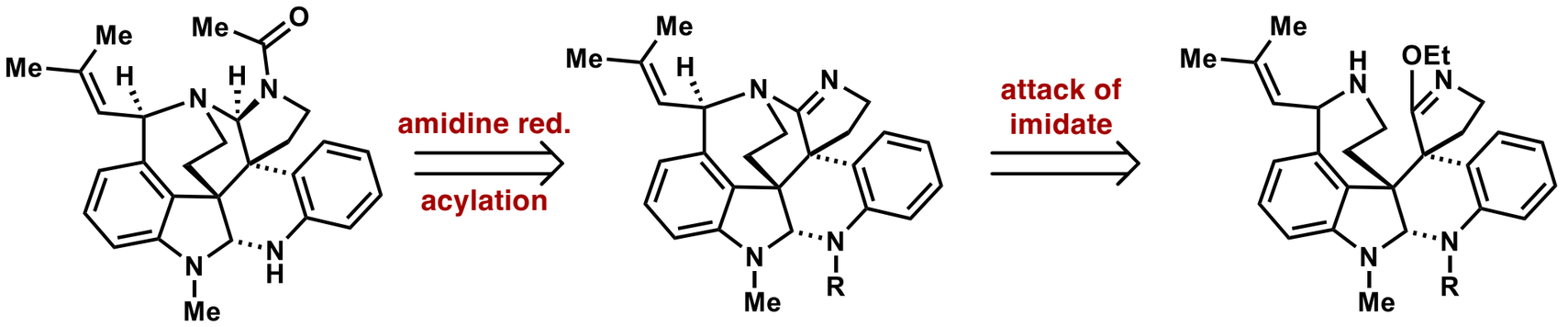


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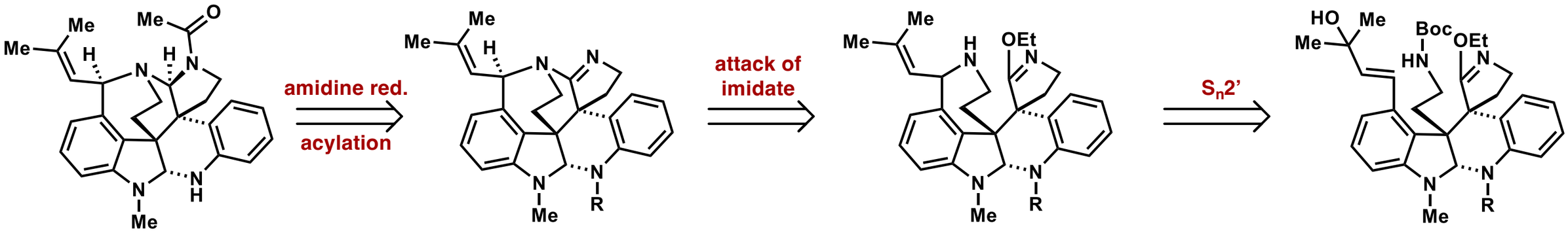


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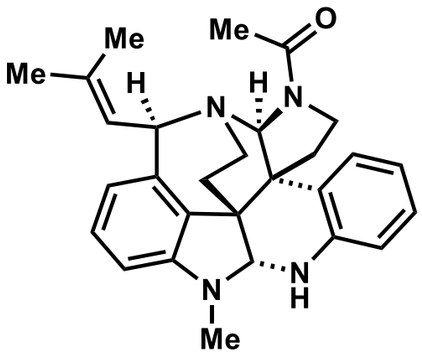


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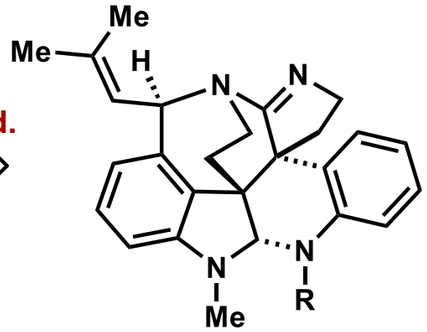
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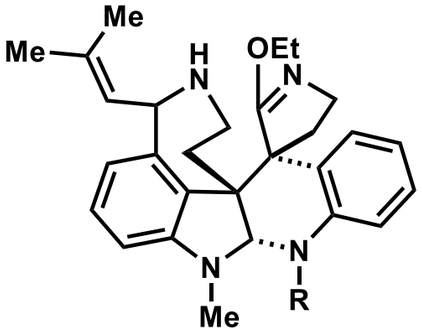
Communesin F

amidine red.

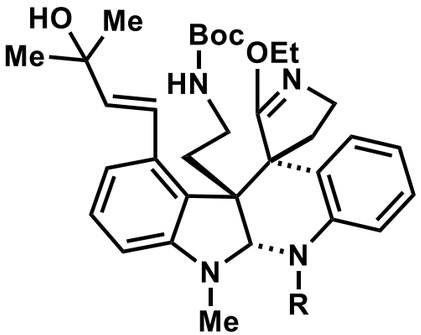
acylation



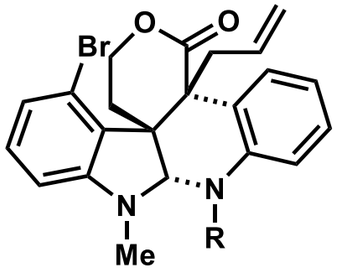
attack of imidate



S_n2'



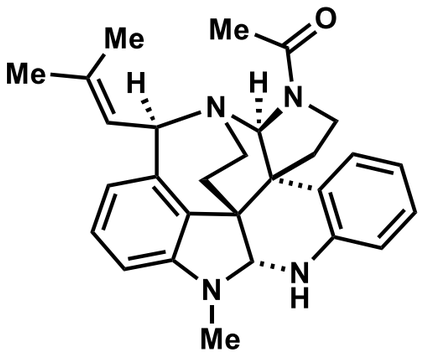
Lemieux-Johnson ox.
imidate formation
Heck



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Racemic Synthesis of Communesin F – Qin (2007)

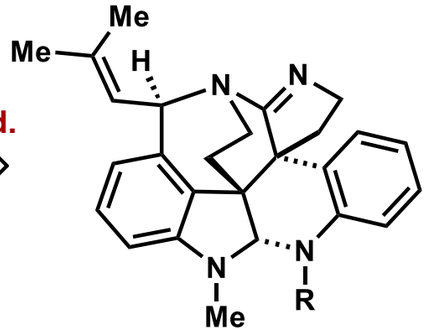
Retrosynthetic Analysis



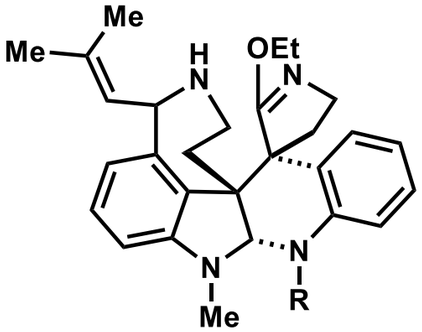
Communesin F

amidine red.

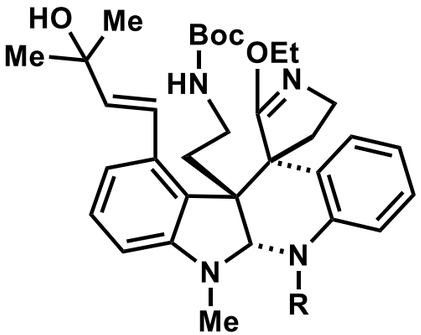
acylation



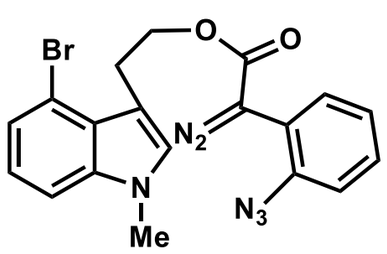
attack of imidate



S_n2'

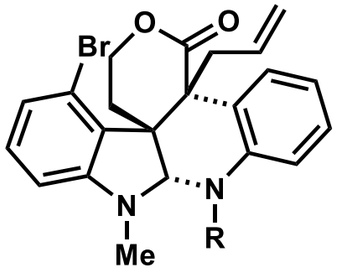


Lemieux-Johnson ox.
imidate formation
Heck



cyclopropane formation and opening

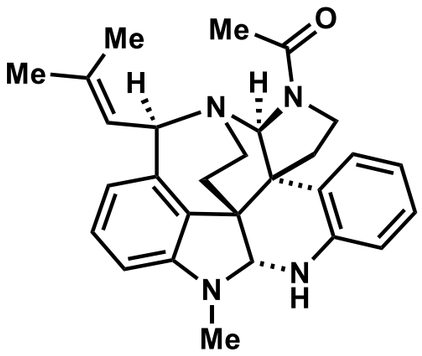
allylation



Qin, Y. *et al. J. Am. Chem. Soc. Comm.* **2007**, *129 (5),* 13794-13795

Racemic Synthesis of Communesin F – Qin (2007)

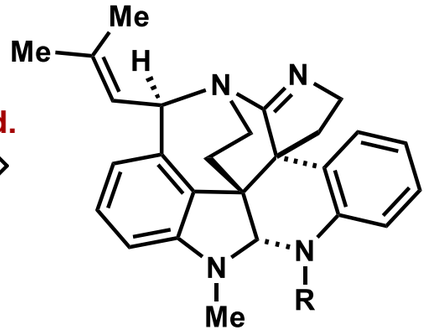
Retrosynthetic Analysis



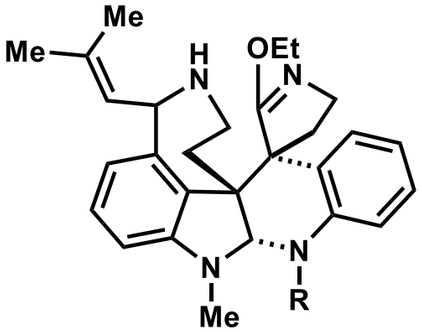
Communesin F

amidine red.

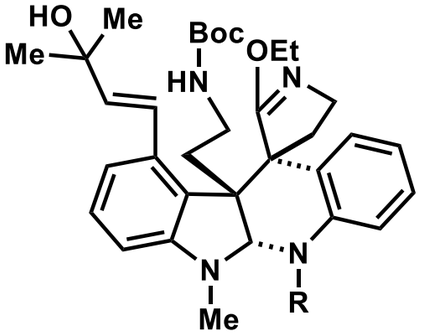
acylation



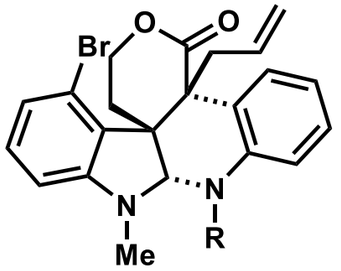
attack of imidate



S_n2'

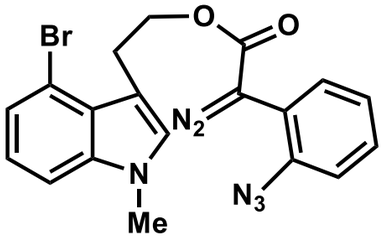


Lemieux-Johnson ox.
imidate formation
Heck



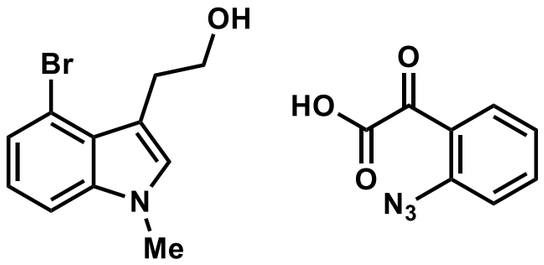
cyclopropane formation and opening

allylation



condensation

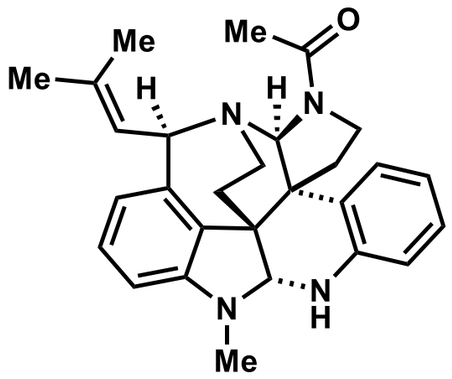
FGI



Qin, Y. *et al. J. Am. Chem. Soc. Comm.* **2007**, *129 (5),* 13794-13795

Racemic Synthesis of Communesin F – Weinreb (2010)

Retrosynthetic Analysis



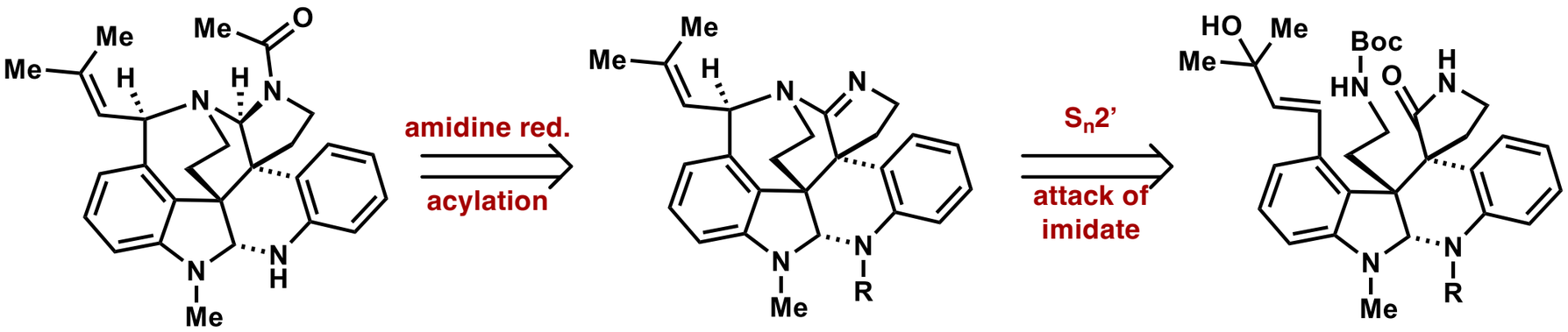
Communesin F

-

Weinreb, S. *et al*. *Angew*. *Chem*. *Int*. *Ed*. **2010**, *49*, 2000 –2003

Racemic Synthesis of Communesin F – Weinreb (2010)

Retrosynthetic Analysis

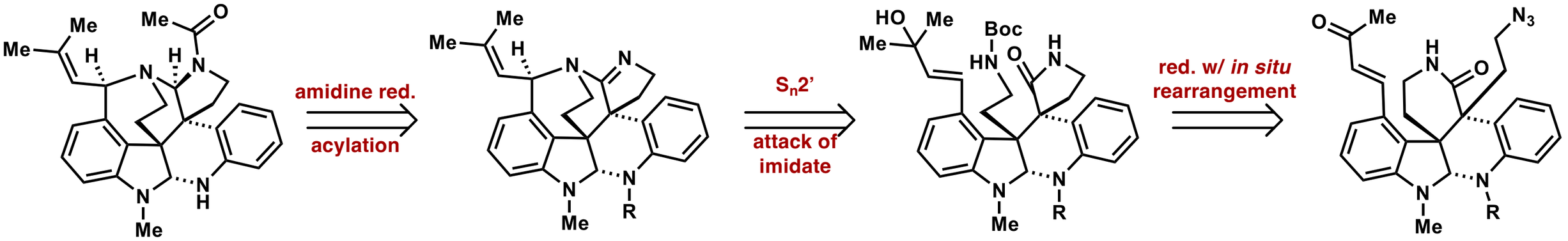


Communesin F

Weinreb, S. *et al*. *Angew*. *Chem*. *Int*. *Ed*. **2010**, *49*, 2000 –2003

Racemic Synthesis of Communesin F – Weinreb (2010)

Retrosynthetic Analysis

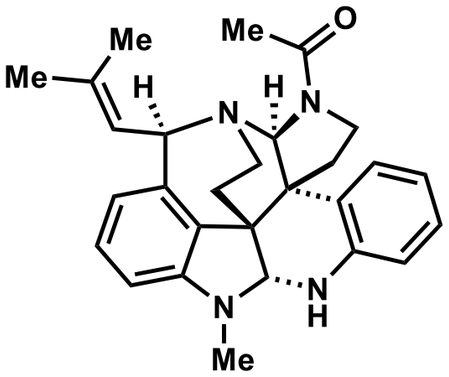


Communesin F

Weinreb, S. *et al*. *Angew*. *Chem*. *Int*. *Ed*. **2010**, *49*, 2000 –2003

Racemic Synthesis of Communesin F – Weinreb (2010)

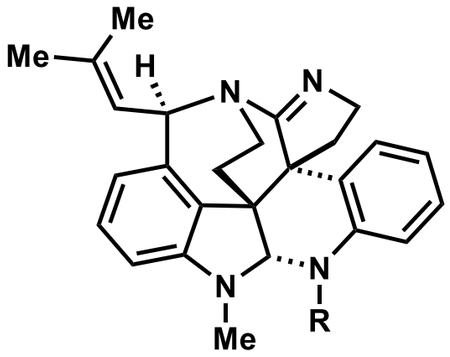
Retrosynthetic Analysis



Communesin F

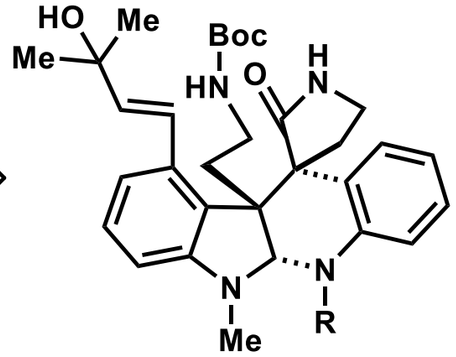
amidine red.

acylation

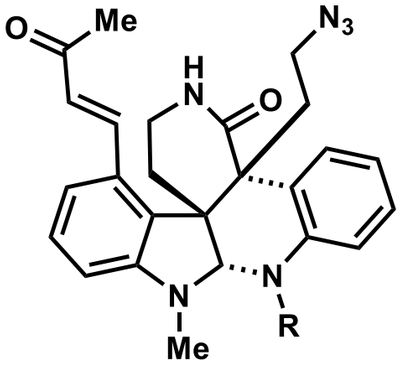


S_n2'

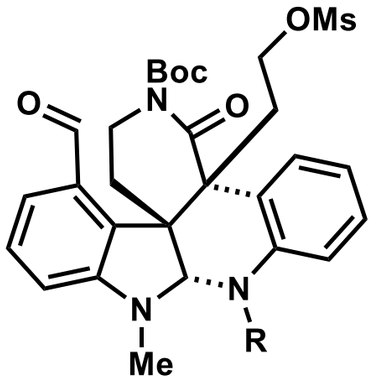
attack of imidate



red. w/ *in situ* rearrangement



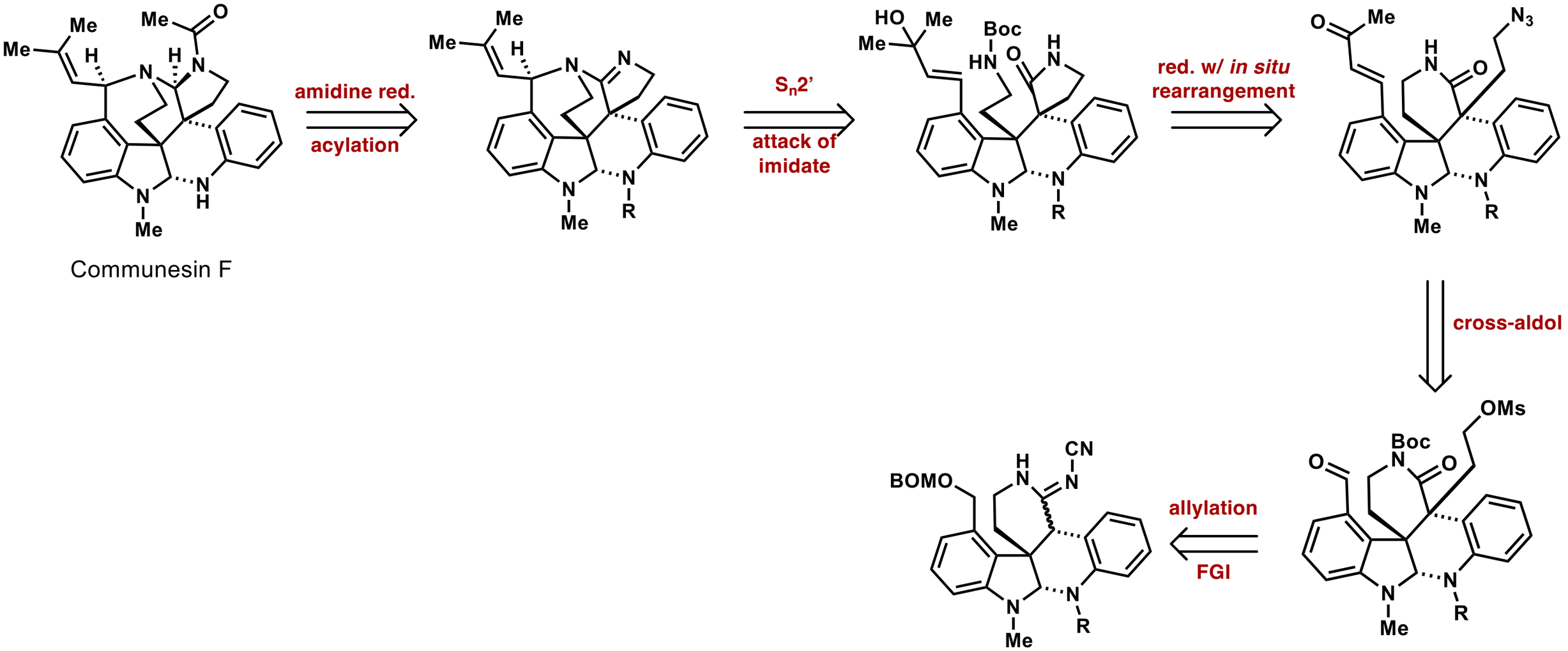
cross-aldol



Weinreb, S. *et al*. *Angew*. *Chem*. *Int*. *Ed*. **2010**, *49*, 2000 –2003

Racemic Synthesis of Communesin F – Weinreb (2010)

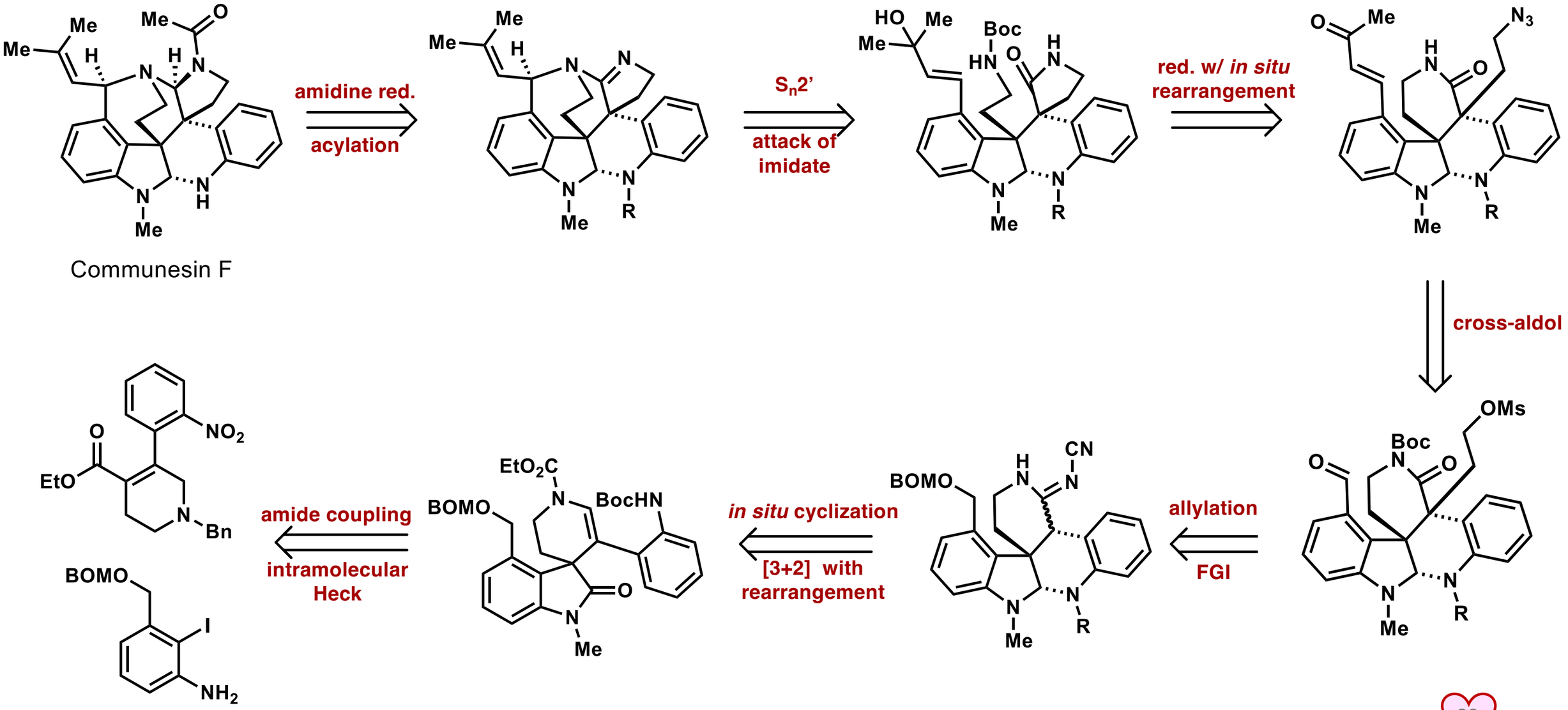
Retrosynthetic Analysis



Weinreb, S. *et al*. *Angew*. *Chem*. *Int*. *Ed*. **2010**, *49*, 2000 –2003

Racemic Synthesis of Communesin F – Weinreb (2010)

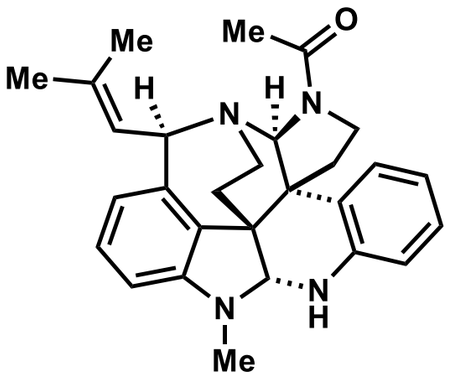
Retrosynthetic Analysis



Weinreb, S. *et al*. *Angew*. *Chem*. *Int*. *Ed*. **2010**, *49*, 2000 –2003

Racemic Synthesis of Communesin F – Funk (2012)

Retrosynthetic Analysis

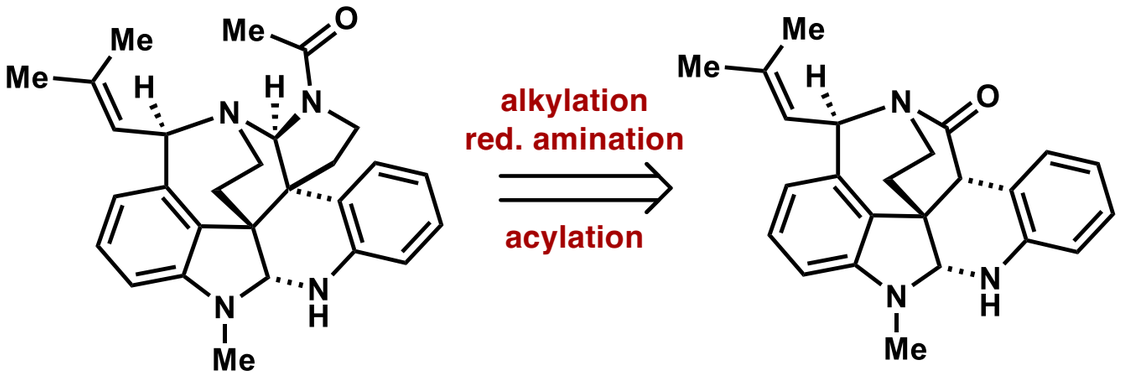


Communesin F

Funk, R., Belmar, J. *J. Am. Chem. Soc.* **2012**, *134 (41)*, 16941-16943

Racemic Synthesis of Communesin F – Funk (2012)

Retrosynthetic Analysis

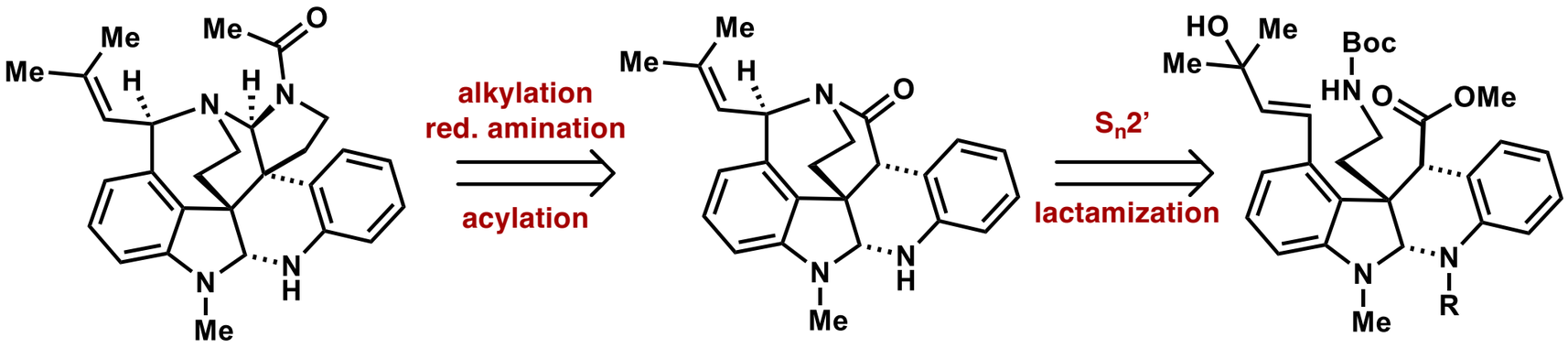


Communesin F

Funk, R., Belmar, J. *J. Am. Chem. Soc.* **2012**, *134 (41)*, 16941-16943

Racemic Synthesis of Communesin F – Funk (2012)

Retrosynthetic Analysis

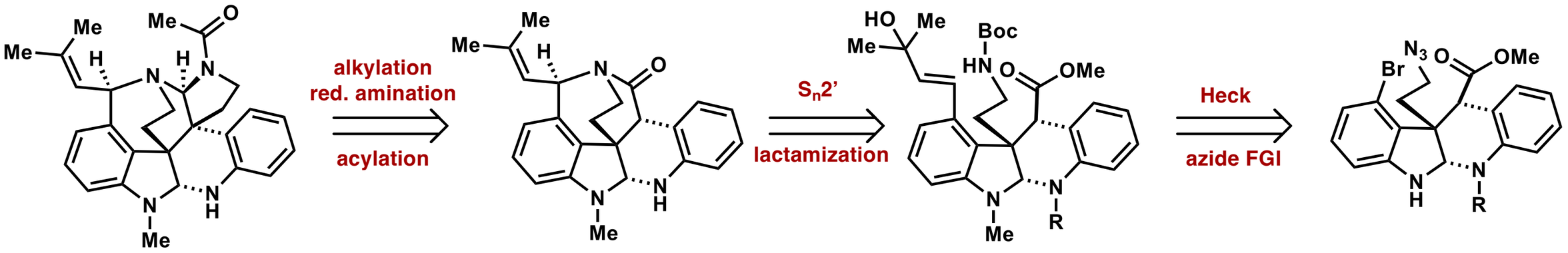


Communesin F

Funk, R., Belmar, J. *J. Am. Chem. Soc.* **2012**, *134 (41)*, 16941-16943

Racemic Synthesis of Communesin F – Funk (2012)

Retrosynthetic Analysis

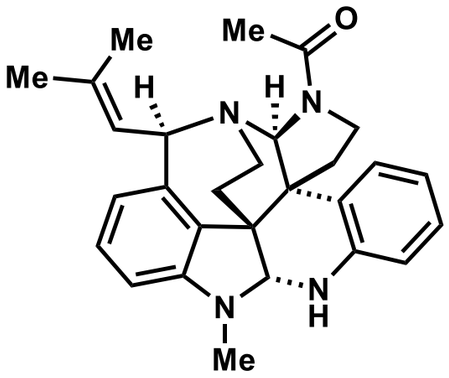


Communesin F

Funk, R., Belmar, J. *J. Am. Chem. Soc.* **2012**, *134 (41)*, 16941-16943

Racemic Synthesis of Communesin F – Funk (2012)

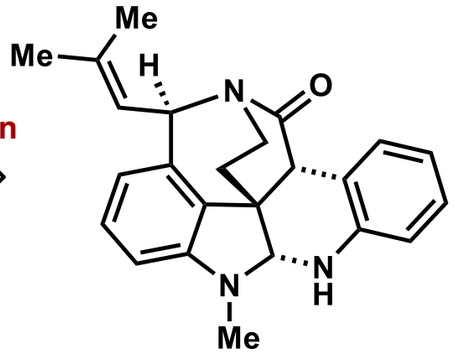
Retrosynthetic Analysis



Communesin F

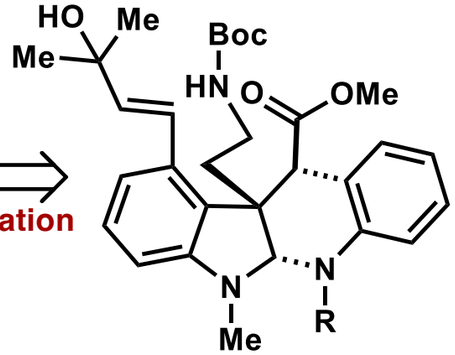
alkylation
red. amination

acylation



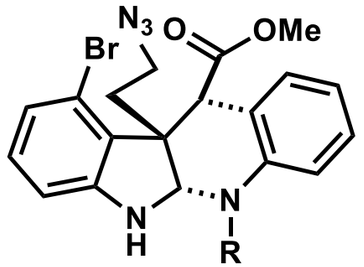
S_n2'

lactamization

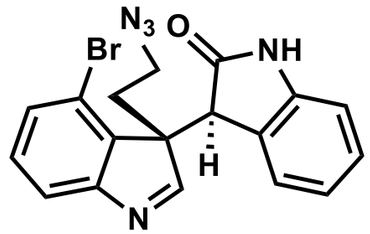


Heck

azide FGI



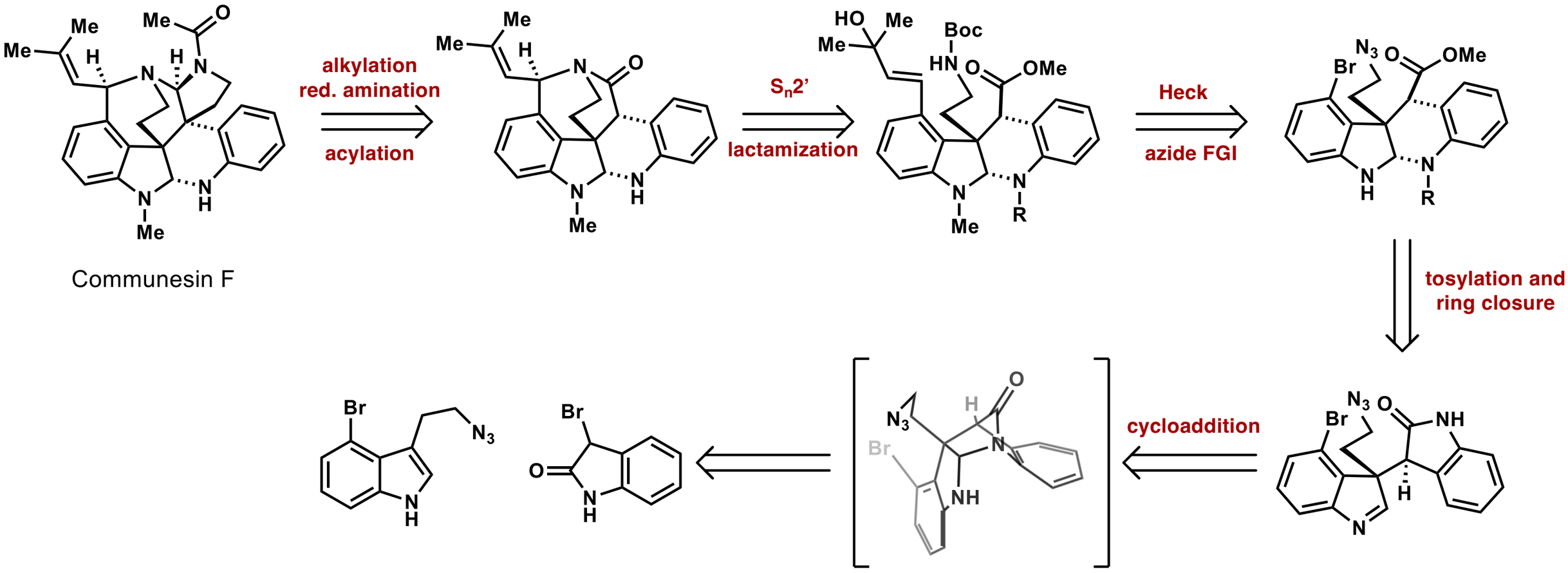
tosylation and
ring closure



Funk, R., Belmar, J. *J. Am. Chem. Soc.* **2012**, *134 (41)*, 16941-16943

Racemic Synthesis of Communesin F – Funk (2012)

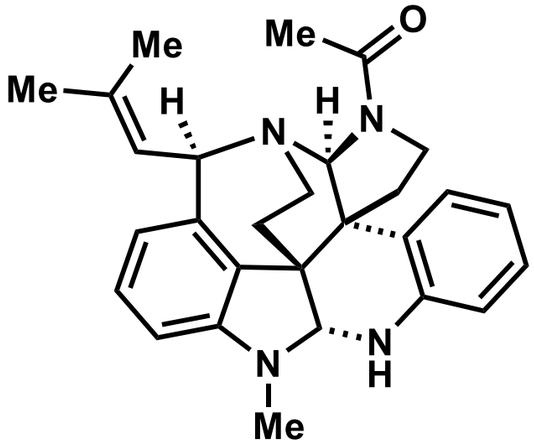
Retrosynthetic Analysis



Funk, R., Belmar, J. *J. Am. Chem. Soc.* **2012**, *134 (41)*, 16941-16943

Formal Racemic Synthesis of Communesin F – Stoltz (2014)

Retrosynthetic Analysis

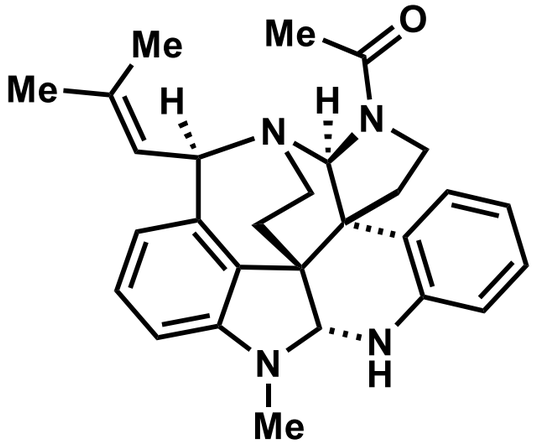


Communesin F

Stoltz, B. *et al*. *Org. Lett*. **2014**, *16 (2)*, 3316-3319

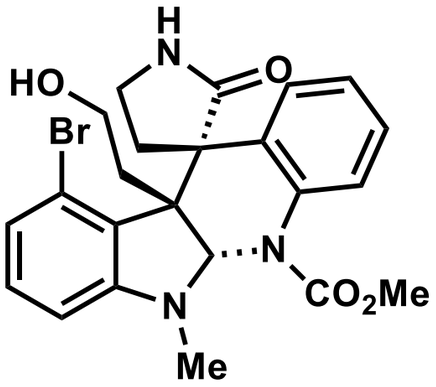
Formal Racemic Synthesis of Communesin F – Stoltz (2014)

Retrosynthetic Analysis



Communesin F

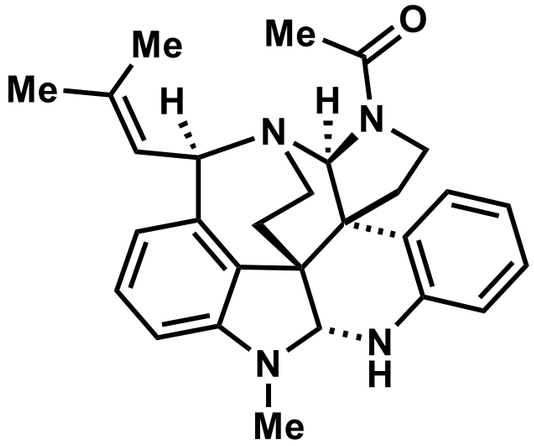
Qin's synthesis



Stoltz, B. *et al. Org. Lett.* **2014**, *16 (2)*, 3316-3319

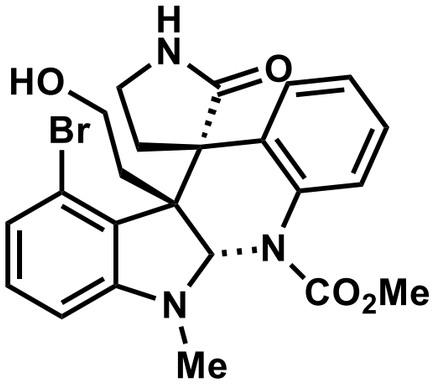
Formal Racemic Synthesis of Communesin F – Stoltz (2014)

Retrosynthetic Analysis



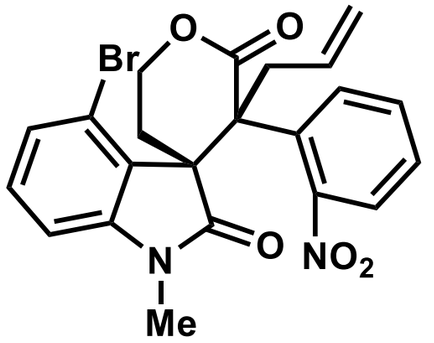
Communesin F

Qin's synthesis



translactamization

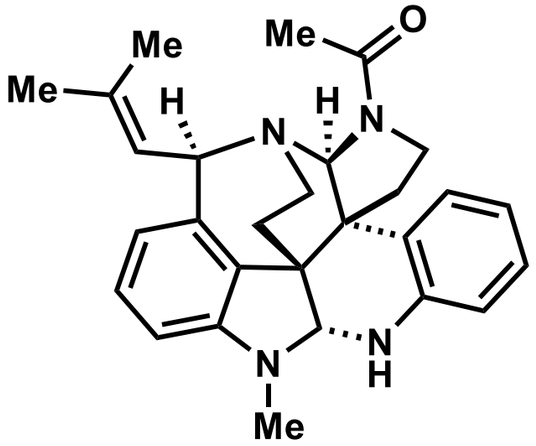
red. amination



Stoltz, B. *et al. Org. Lett.* **2014**, *16 (2)*, 3316-3319

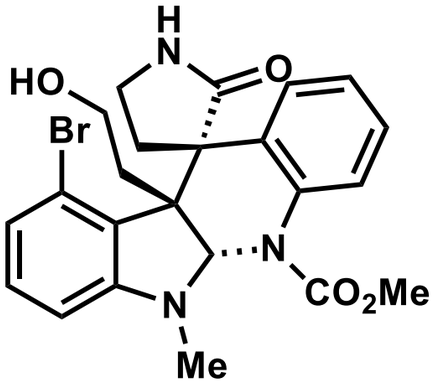
Formal Racemic Synthesis of Communesin F – Stoltz (2014)

Retrosynthetic Analysis



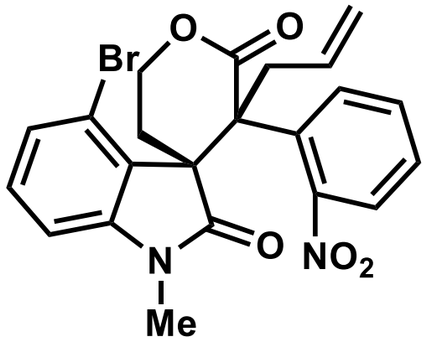
Communesin F

Qin's synthesis

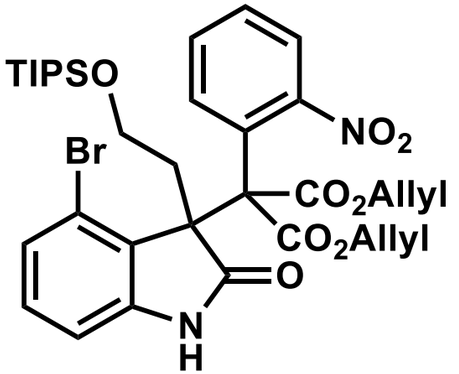


translactamization

red. amination



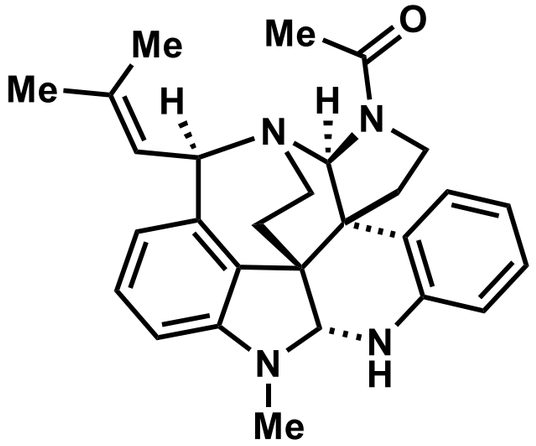
lactonization and allylation



Stoltz, B. *et al. Org. Lett.* **2014**, *16 (2)*, 3316-3319

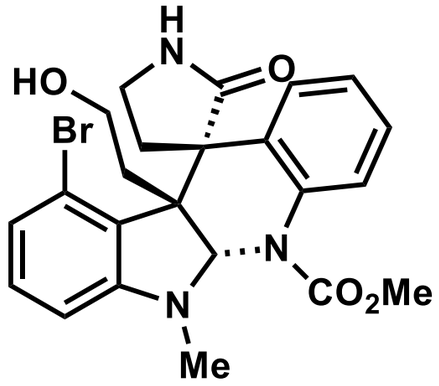
Formal Racemic Synthesis of Communesin F – Stoltz (2014)

Retrosynthetic Analysis



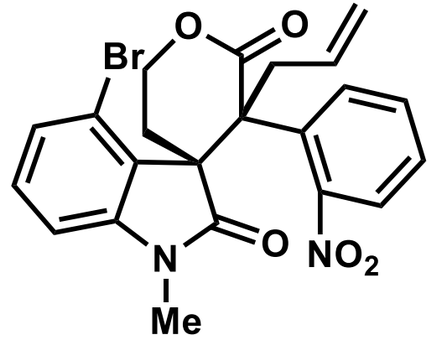
Communesin F

Qin's synthesis

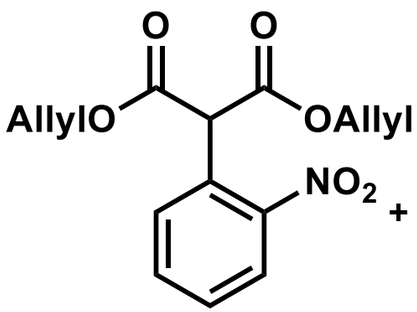


translactamization

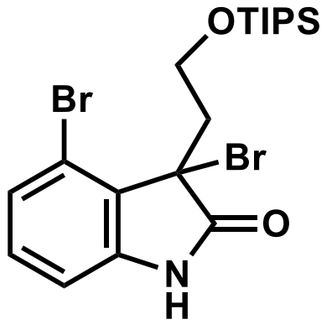
red. amination



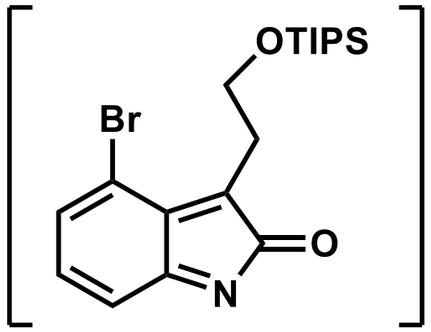
lactonization and allylation



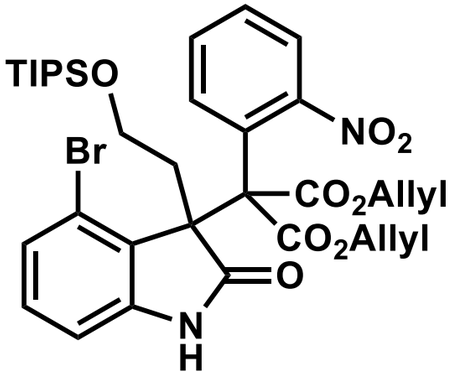
+



in situ o-azaxylylene



base promoted alkylation



Stoltz, B. *et al. Org. Lett.* **2014**, *16 (2)*, 3316-3319

Syntheses of Communesin F

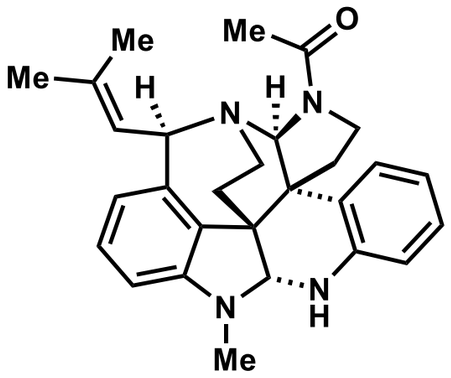
Racemic

Qin – 2007:
2.6% in 23 steps

Weinreb – 2010:
0.93% in 29 steps

Funk – 2012:
6.7% in 15 steps

Stoltz – 2014:
9.0% to intermediate in Qin synth. in 17 steps
(11 more to NP)



(-) Communesin F

Enantioselective

Ma – 2010:
5.6% in 19 steps

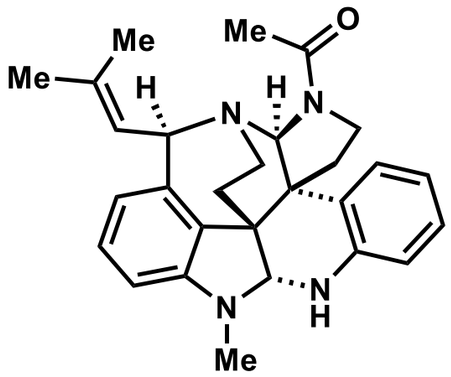
Movassaghi – 2016:
1.3% in 21 steps

Yang – 2017:
3.7% in 15 steps

Qin, Y. *et al. J. Am. Chem. Soc. Comm.* **2007**, *129 (5),* 13794-13795. Weinreb, S. *et al. Angew. Chem. Int. Ed.* **2010**, *49*, 2000 –2003. Funk, R., Belmar, J. *J. Am. Chem. Soc.* **2012**, *134 (41)*, 16941-16943. Stoltz, B. *et al. Org. Lett.* **2014**, *16 (2)*, 3316-3319. Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228. Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769. Yang, R. *et al. J. Am. Chem. Soc. Comm.* **2017**, *139 (9)*, 3364-3367

Synthesis of (-) Communesin F – Ma (2010)

Retrosynthetic Analysis

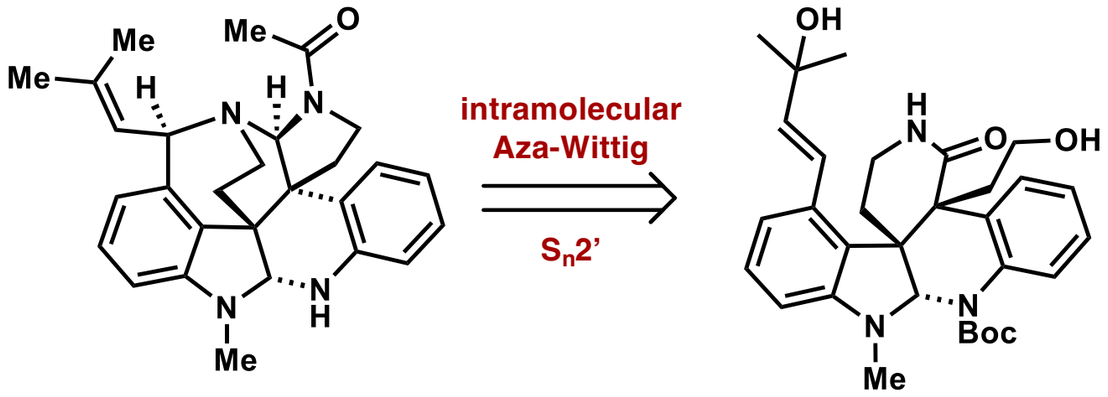


(-) Communesin F

Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

Retrosynthetic Analysis

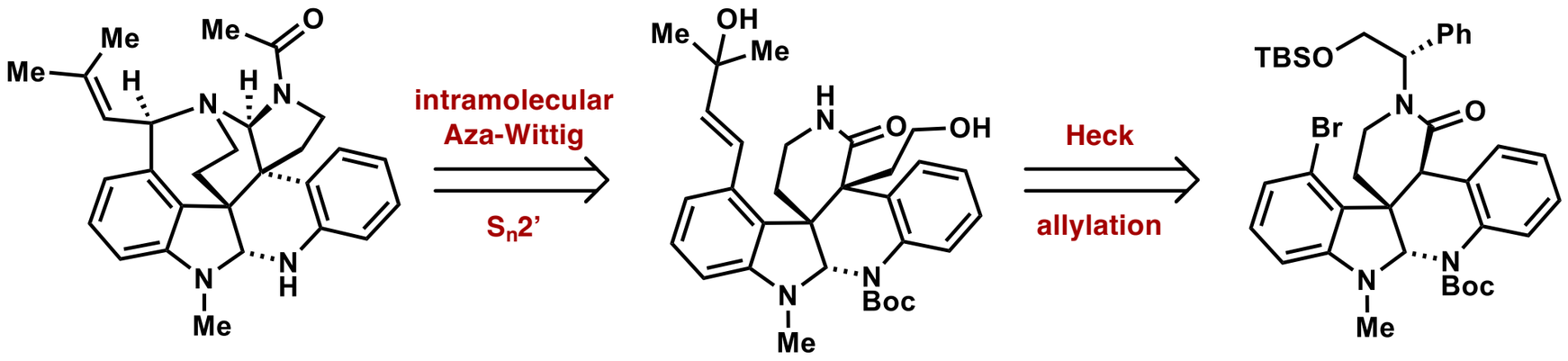


(-) Communesin F

Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

Retrosynthetic Analysis

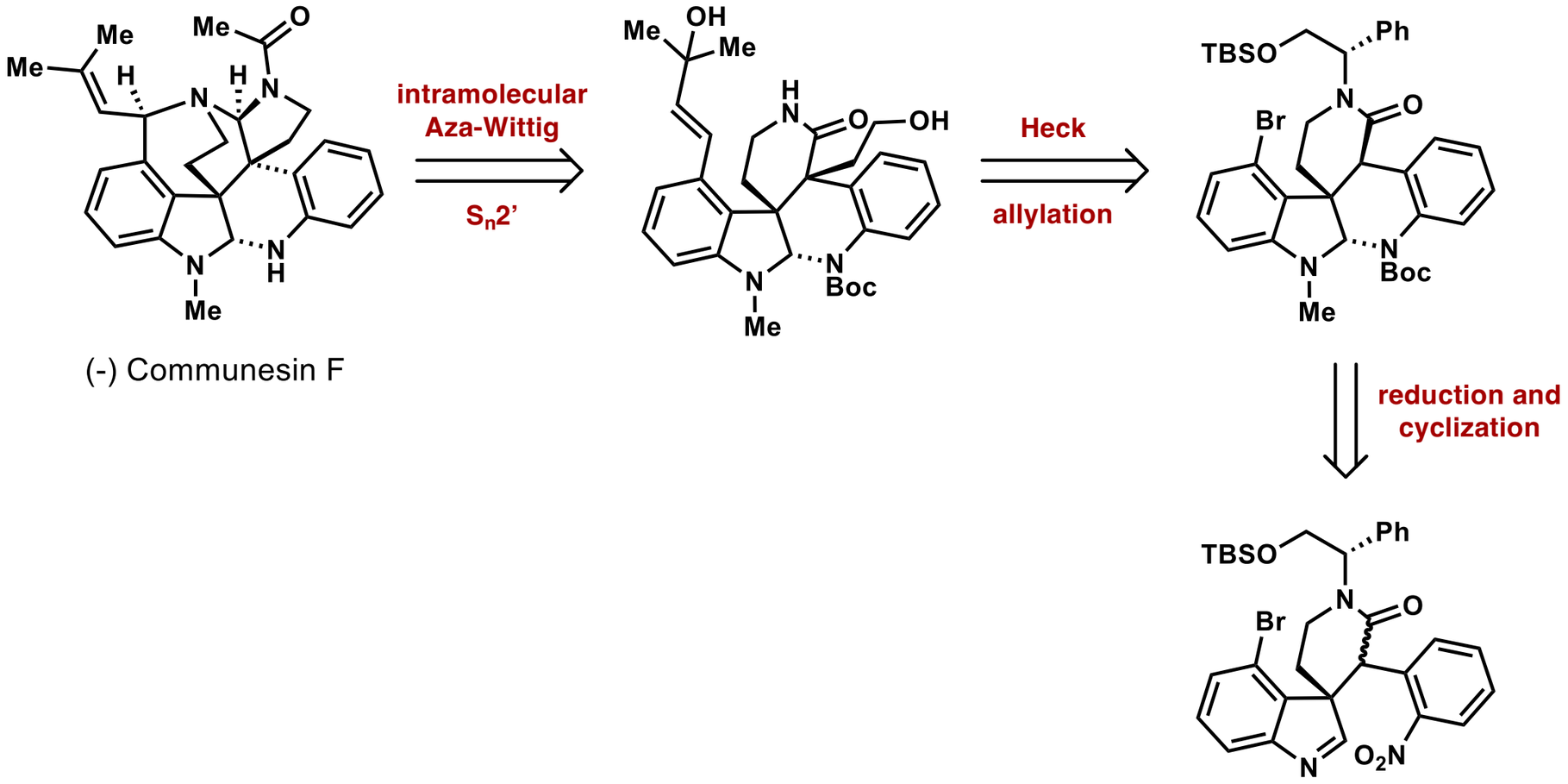


(-) Communesin F

Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

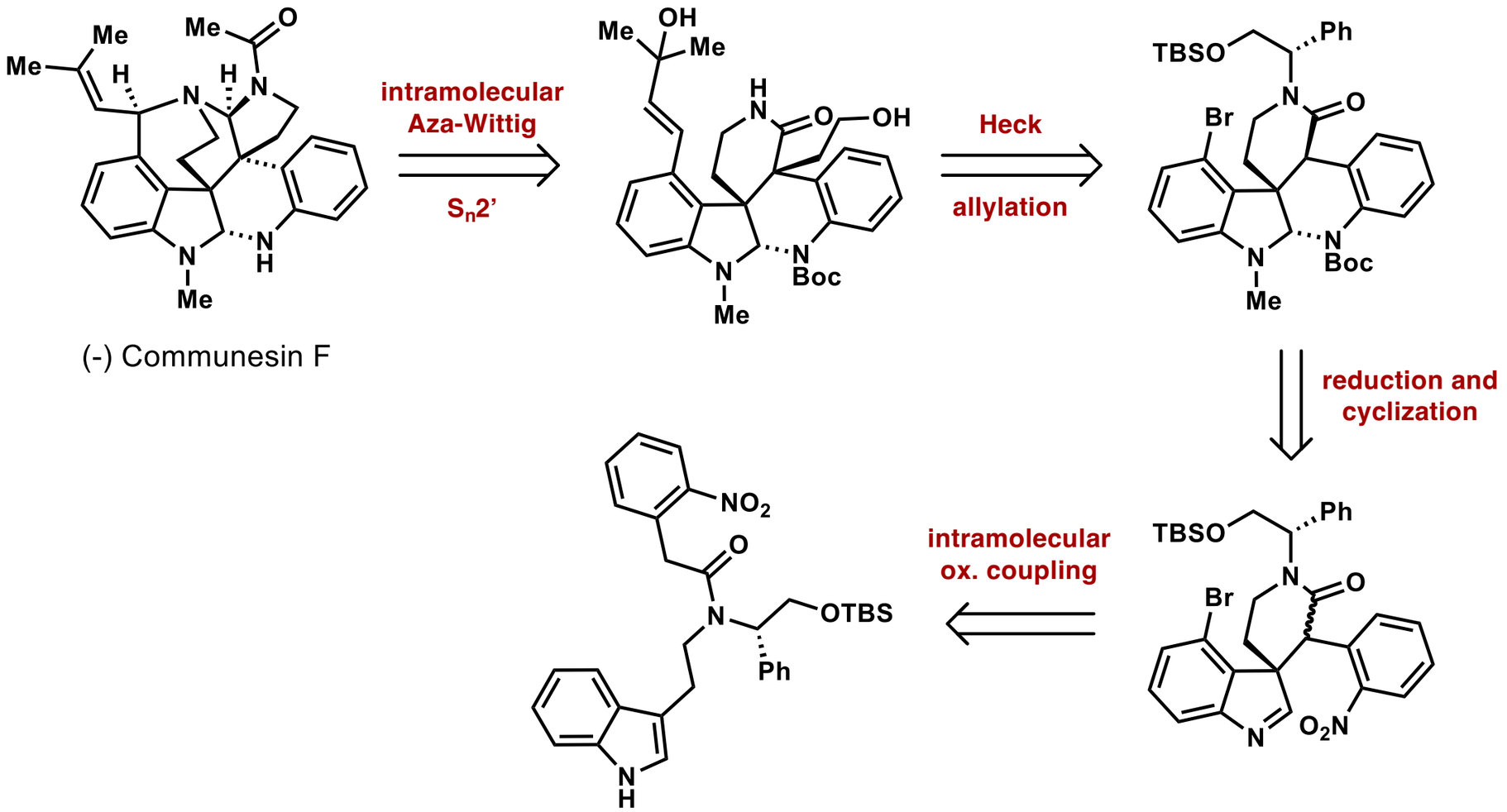
Retrosynthetic Analysis



Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

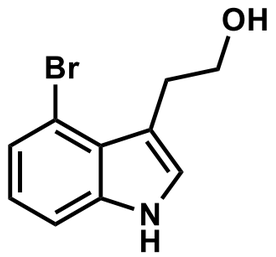
Retrosynthetic Analysis



Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

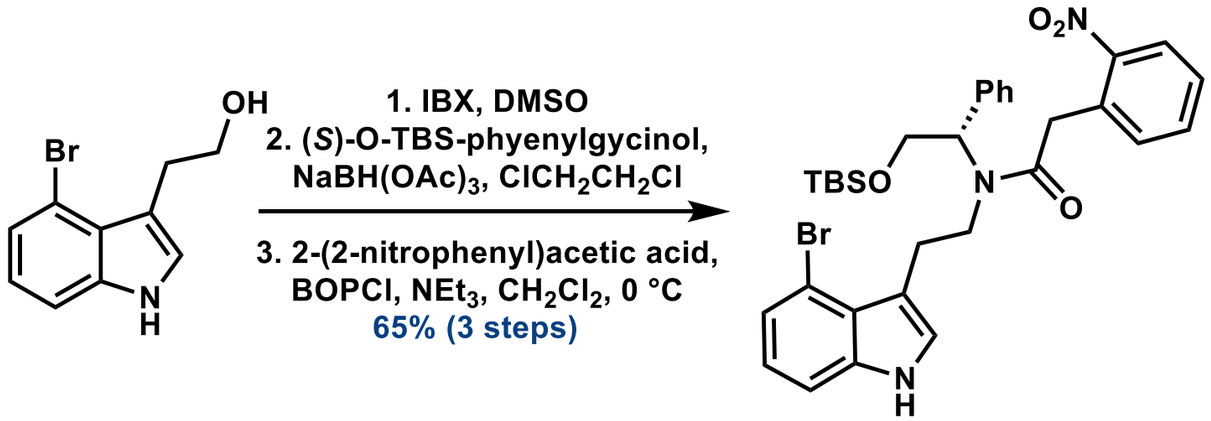
Forward Synthesis



Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

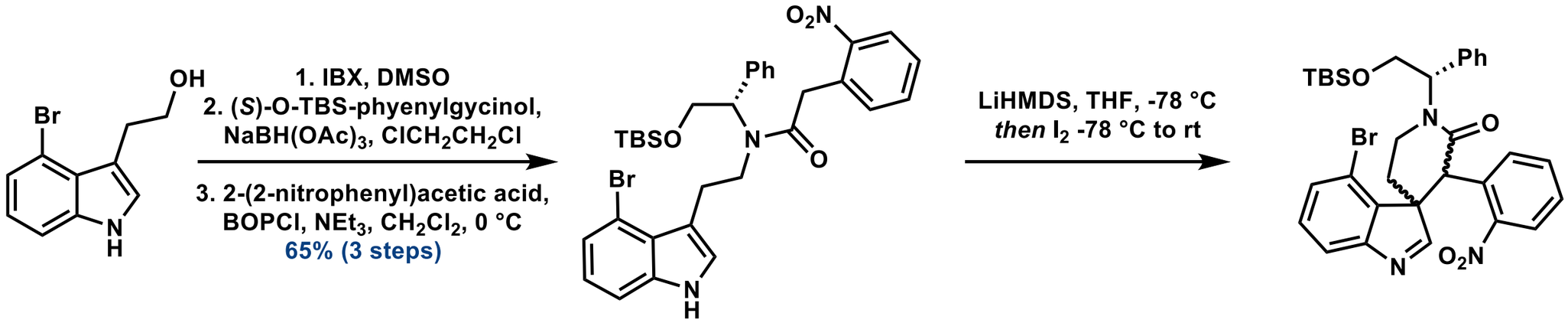
Forward Synthesis



Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

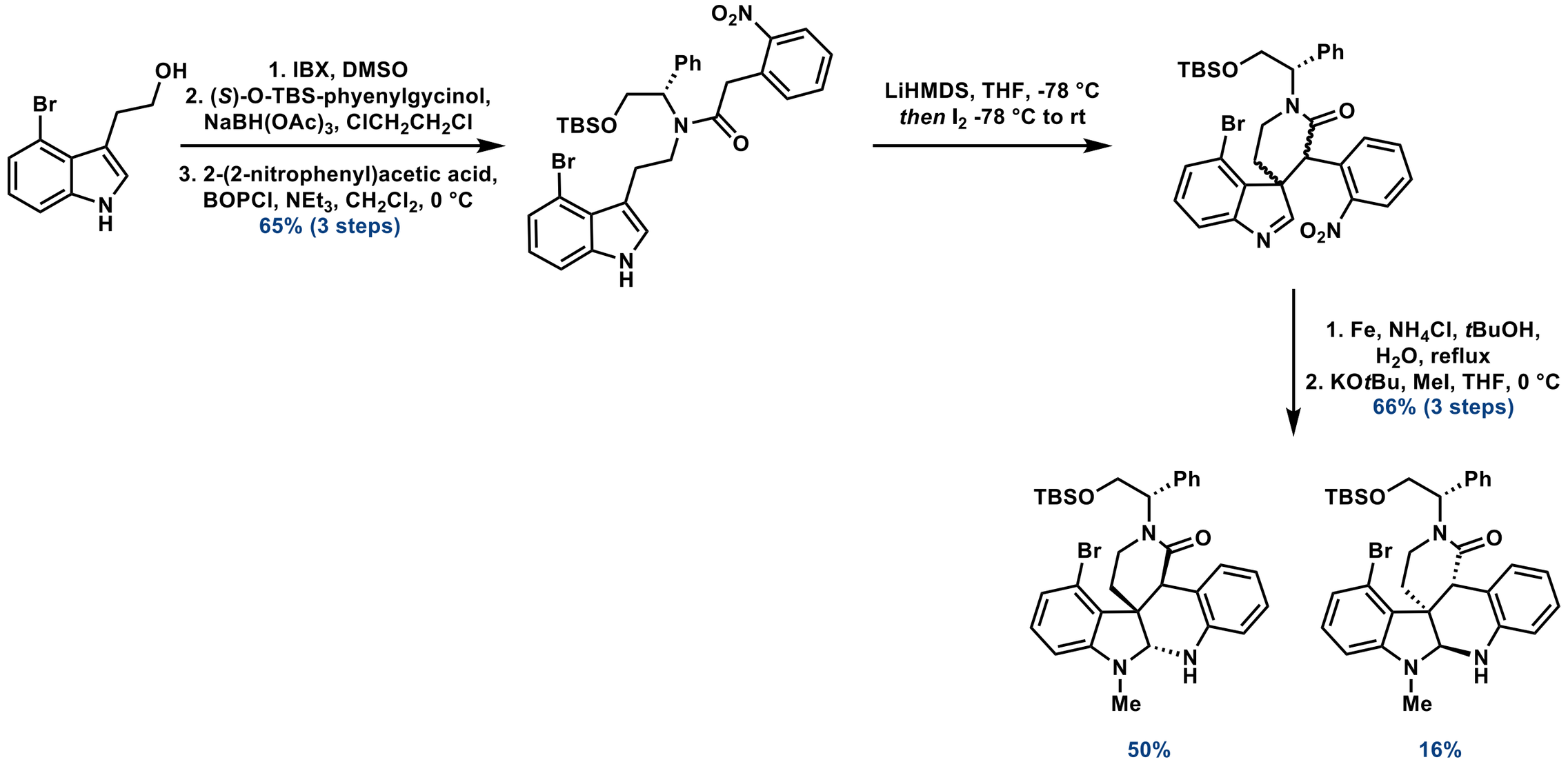
Forward Synthesis



Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

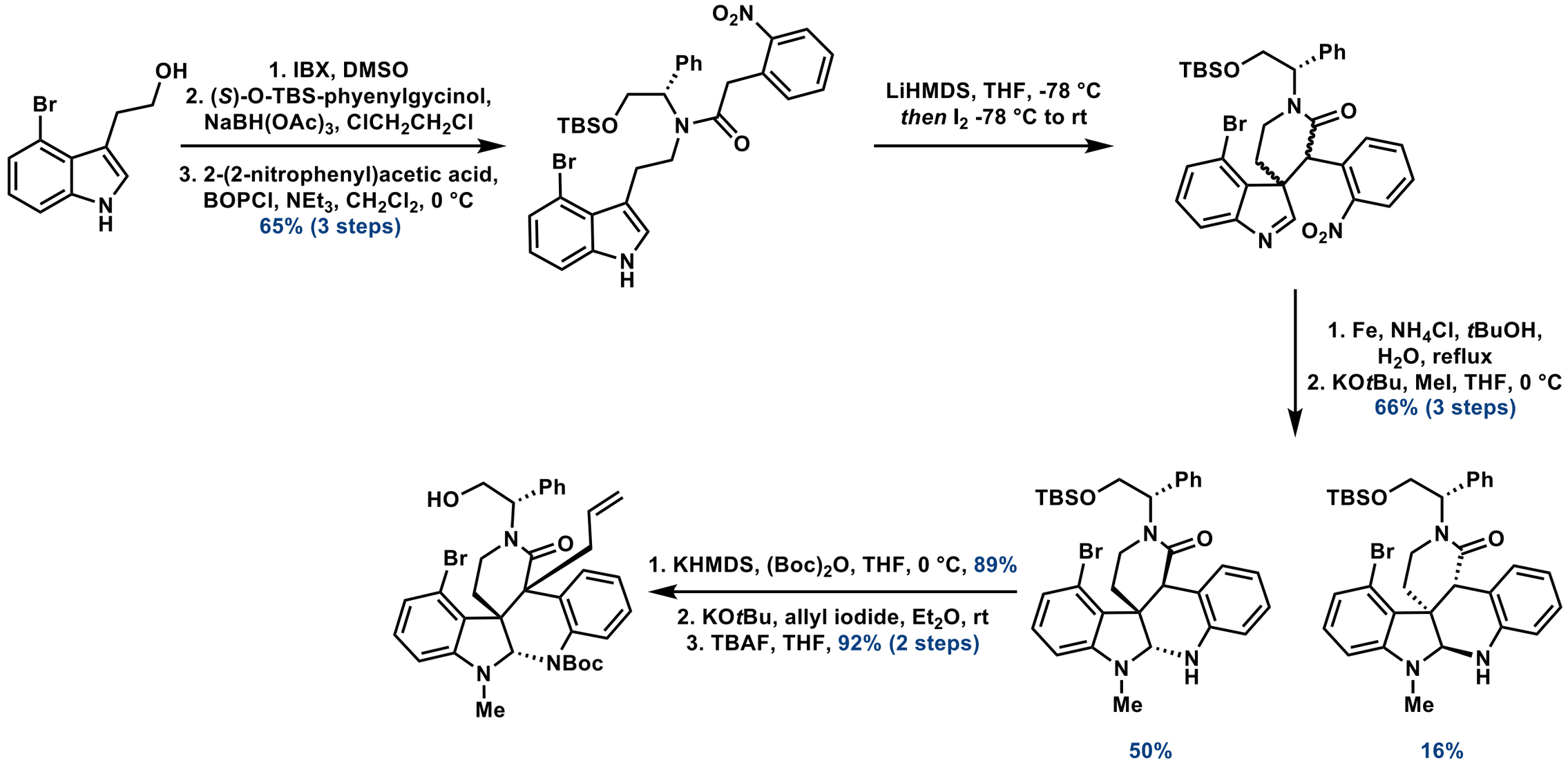
Forward Synthesis



Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

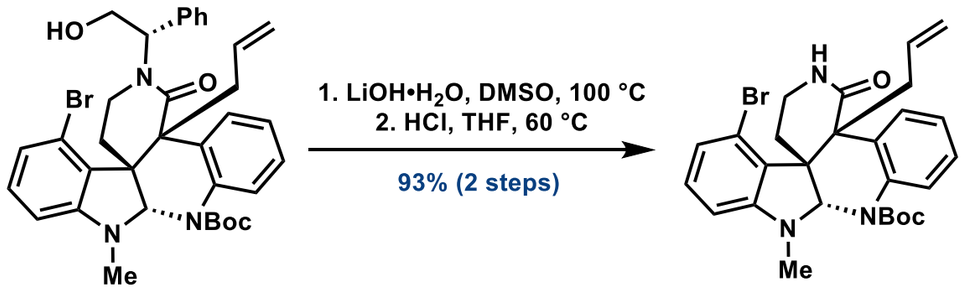
Forward Synthesis



Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

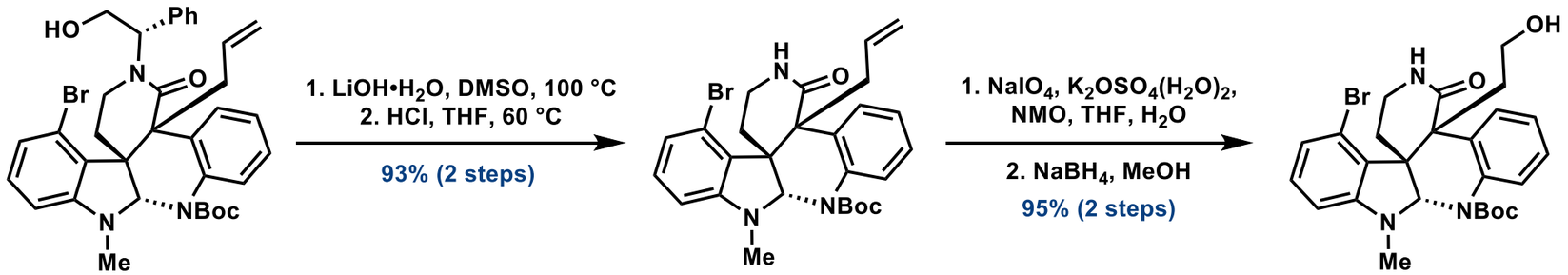
Forward Synthesis



Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

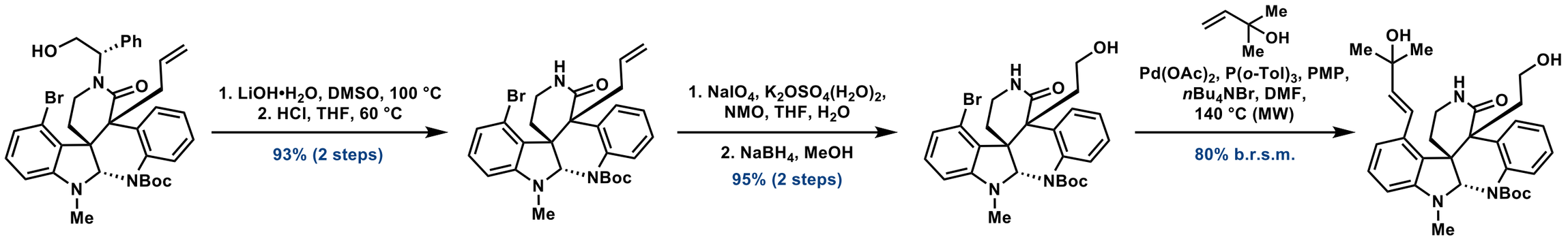
Forward Synthesis



Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

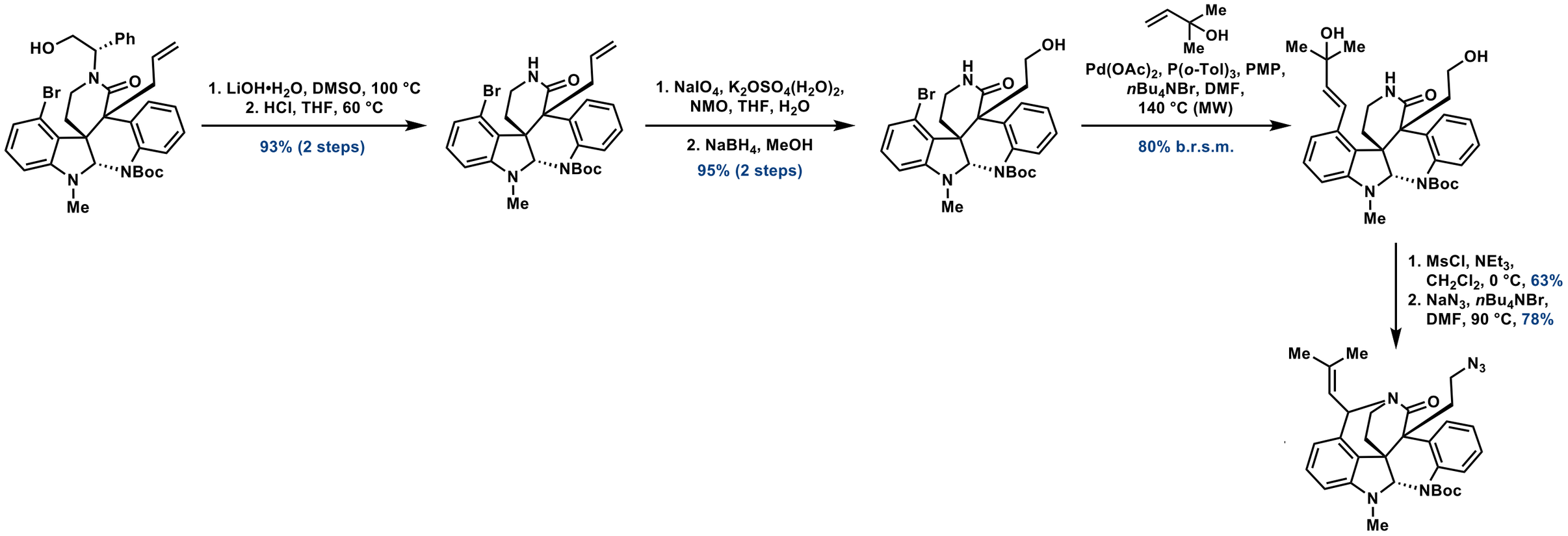
Forward Synthesis



Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

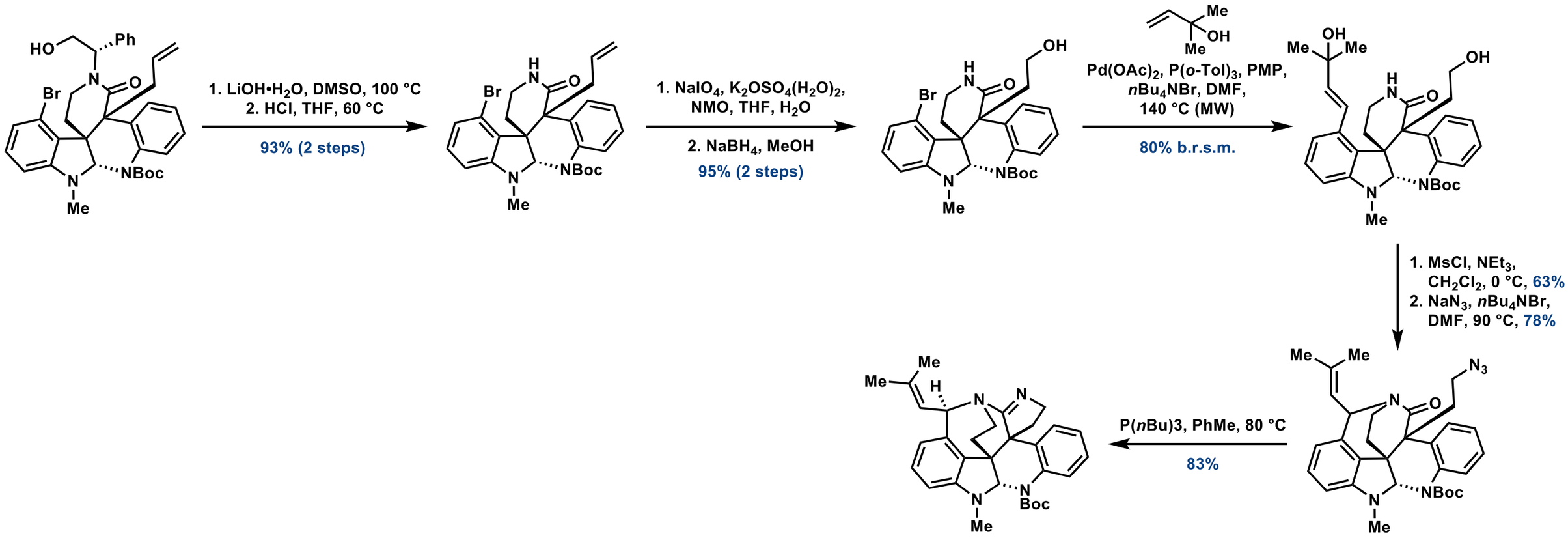
Forward Synthesis



Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

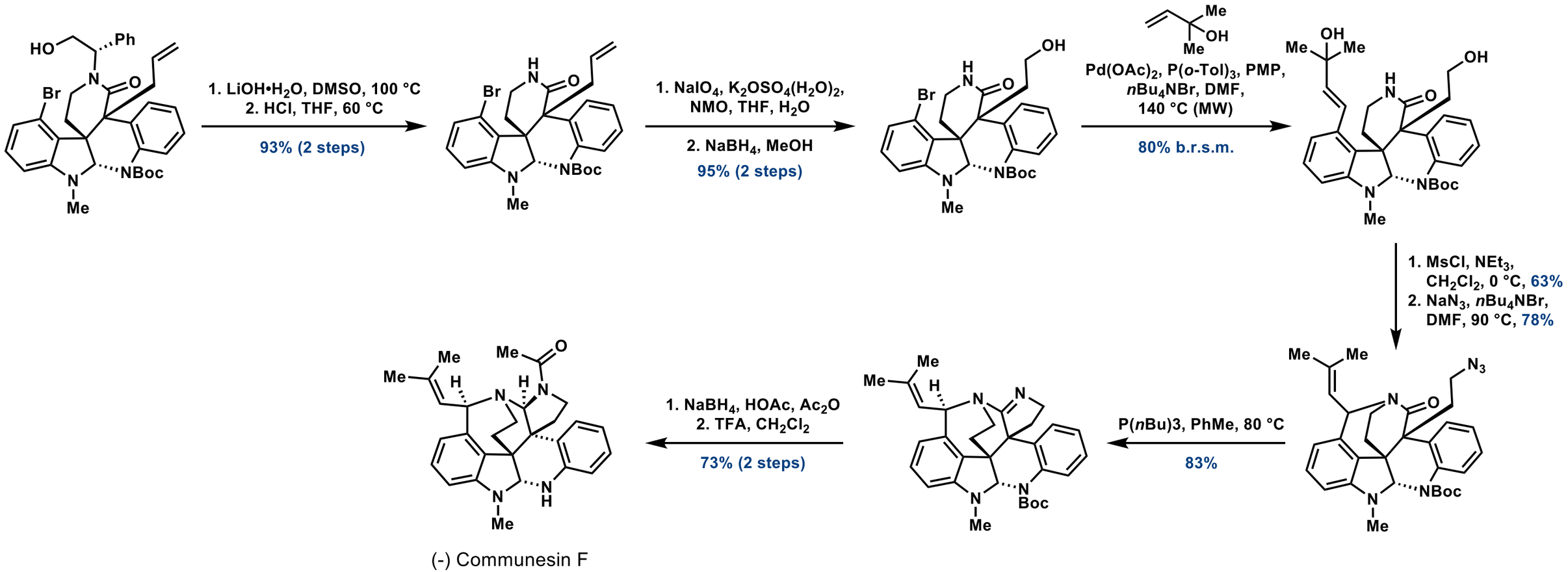
Forward Synthesis



Ma, D. *et al*. *J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Ma (2010)

Forward Synthesis

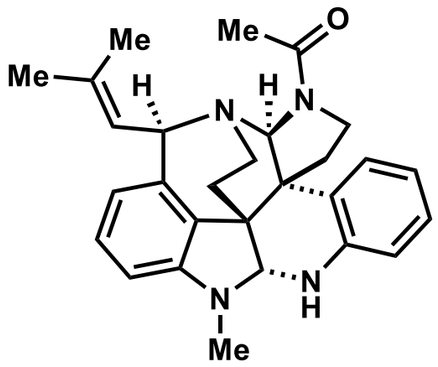


(-) Communesin F

Ma, D. *et al. J. Am. Chem. Soc.* **2010**, *132 (38)*, 13226-13228

Synthesis of (-) Communesin F – Movassaghi (2016)

Retrosynthetic Analysis

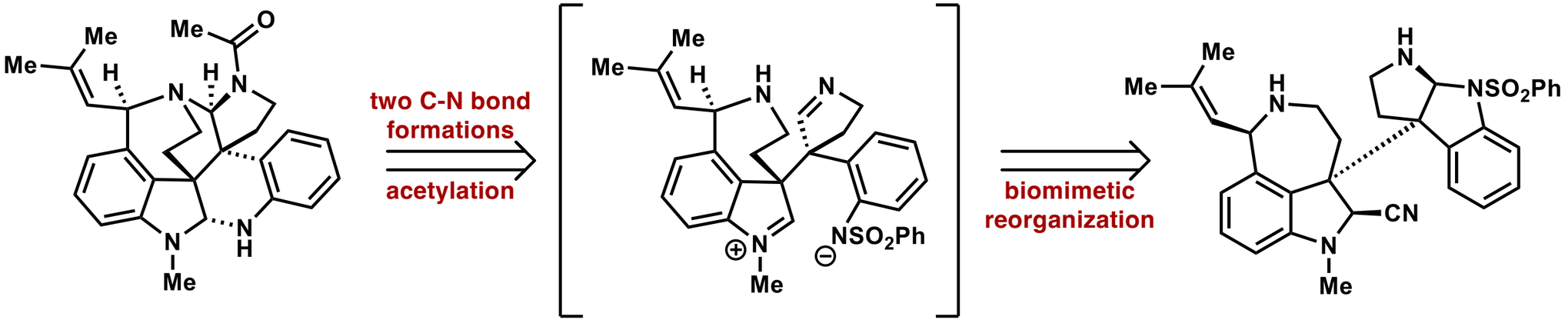


(-) Communesin F

Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

Retrosynthetic Analysis

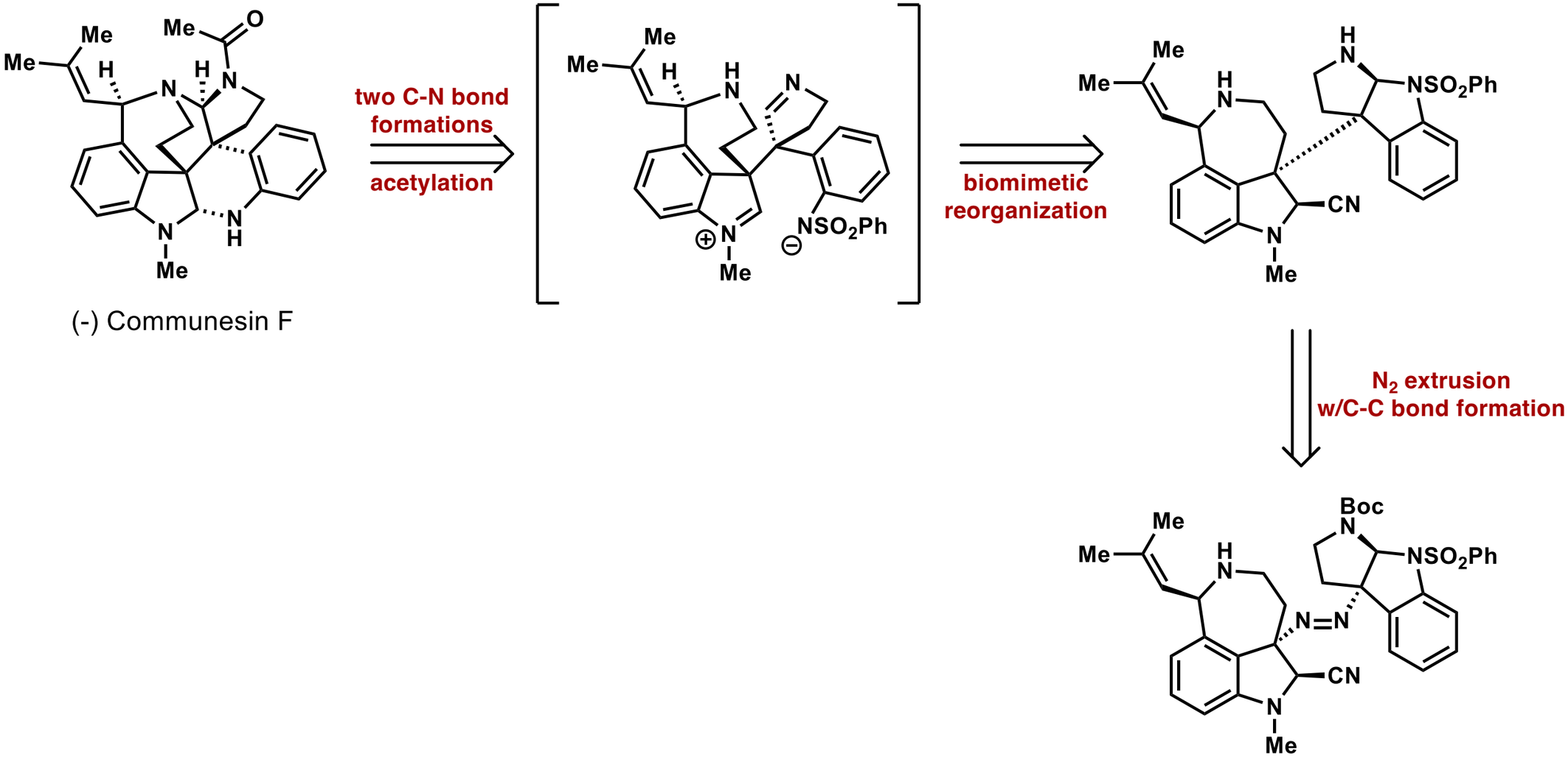


(-) Communesin F

Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

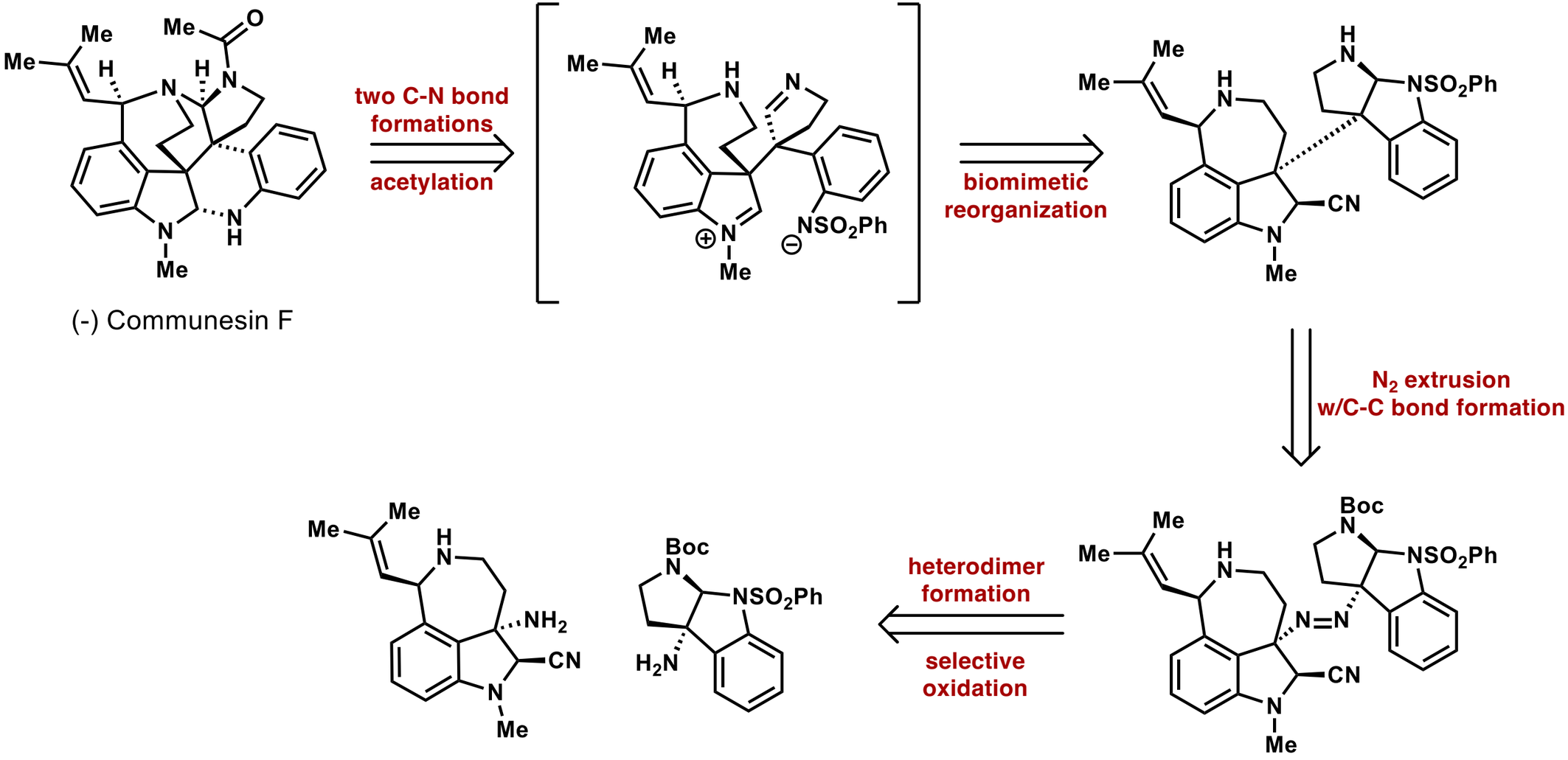
Retrosynthetic Analysis



Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

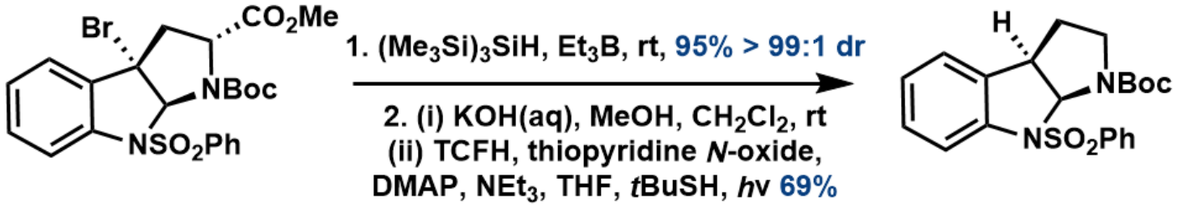
Retrosynthetic Analysis



Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

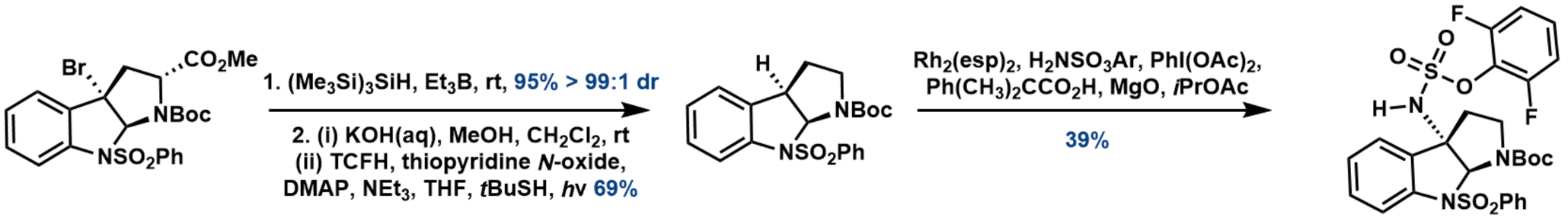
Fragment Preparation



Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

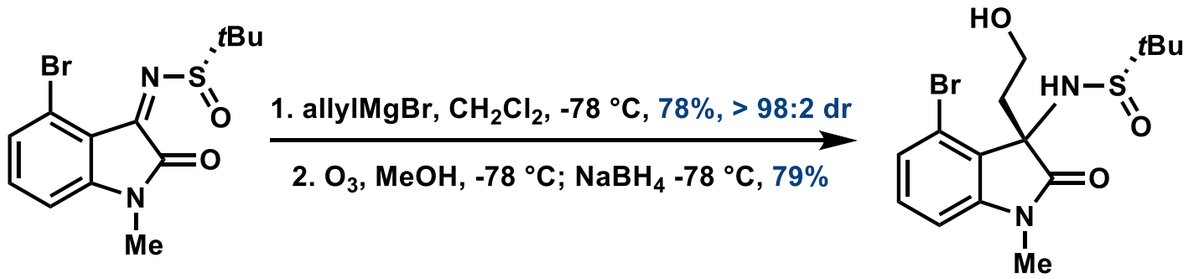
Fragment Preparation



Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

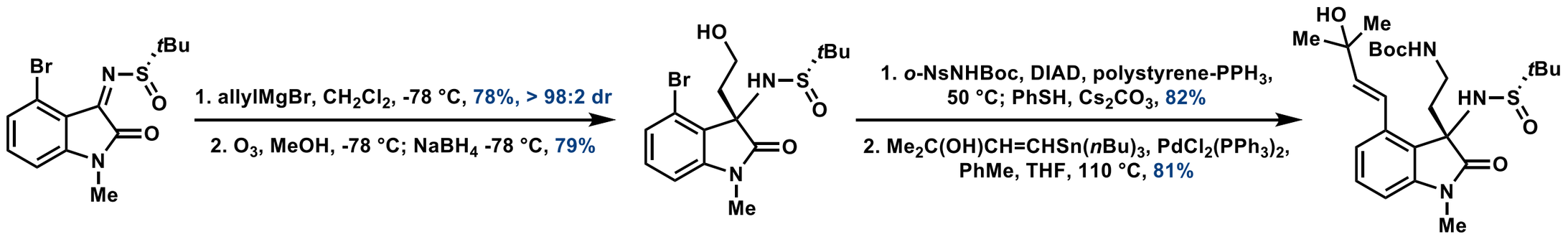
Fragment Preparation



Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

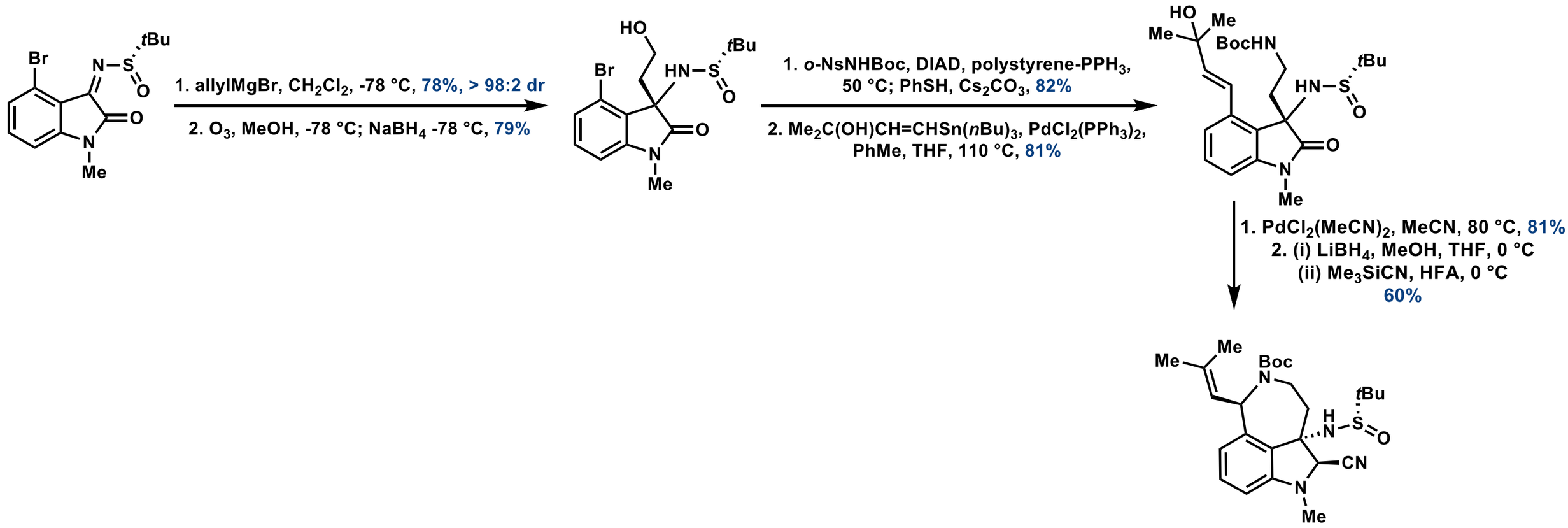
Fragment Preparation



Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

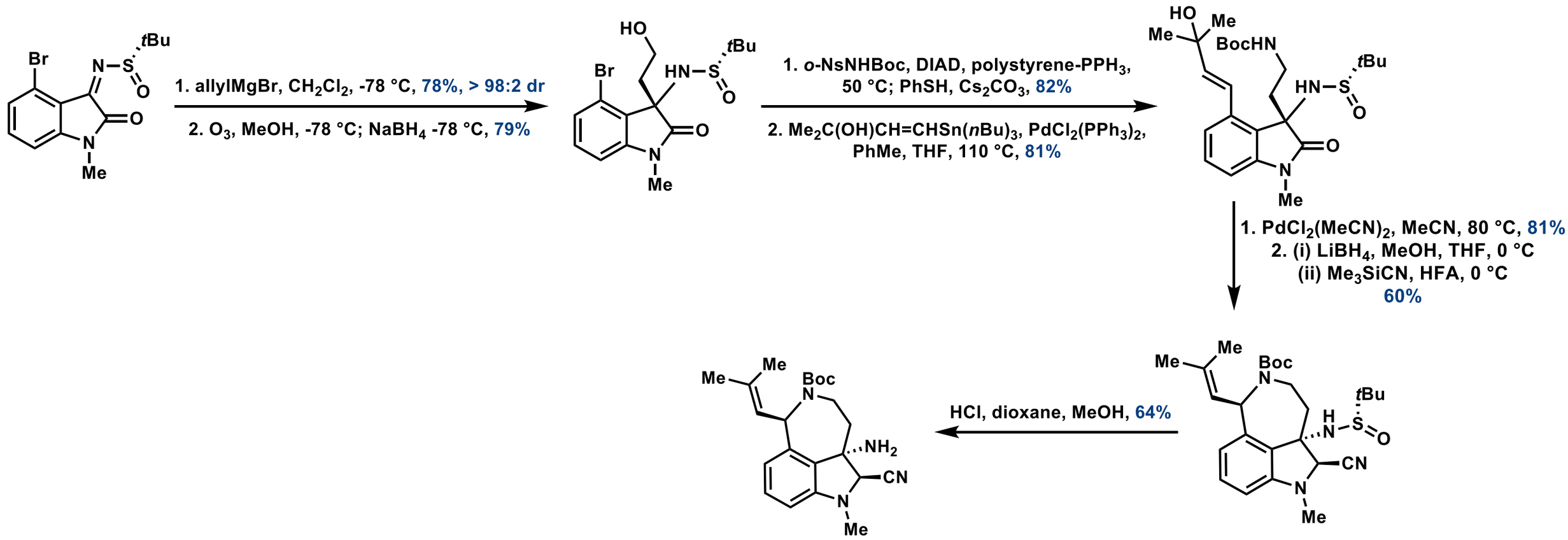
Fragment Preparation



Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

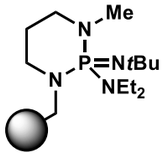
Fragment Preparation



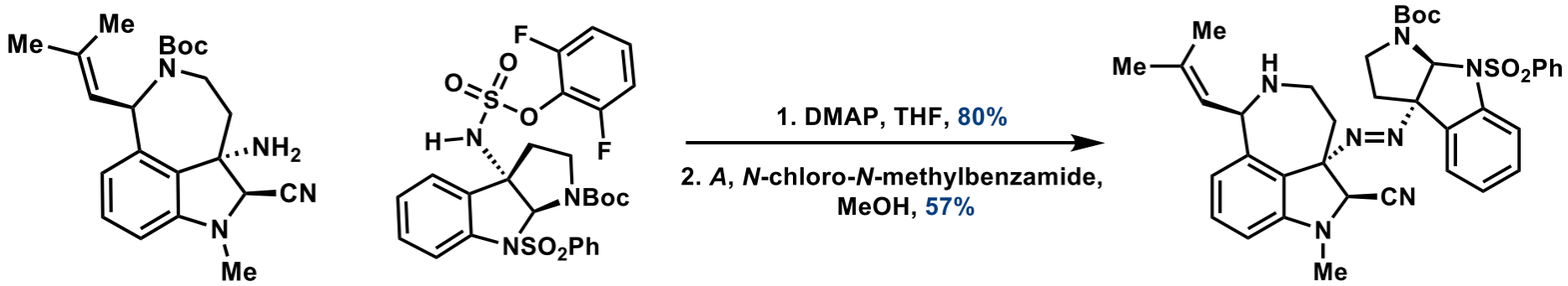
Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

Fragment Coupling / Completing the Synthesis



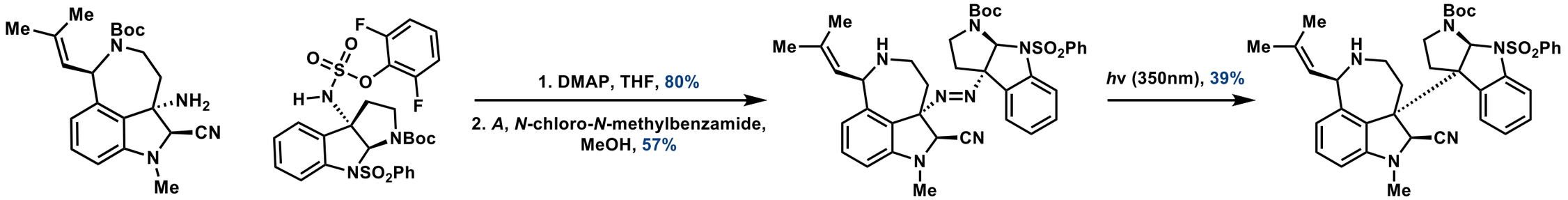
A



Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

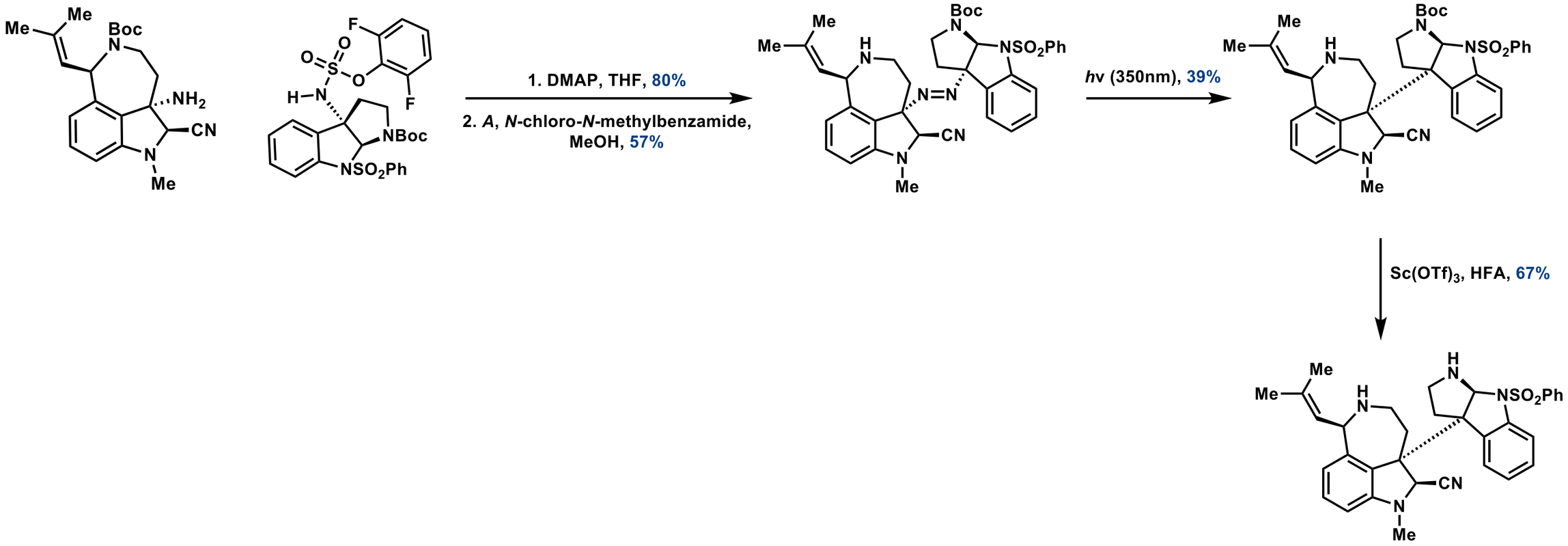
Fragment Coupling / Completing the Synthesis



Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

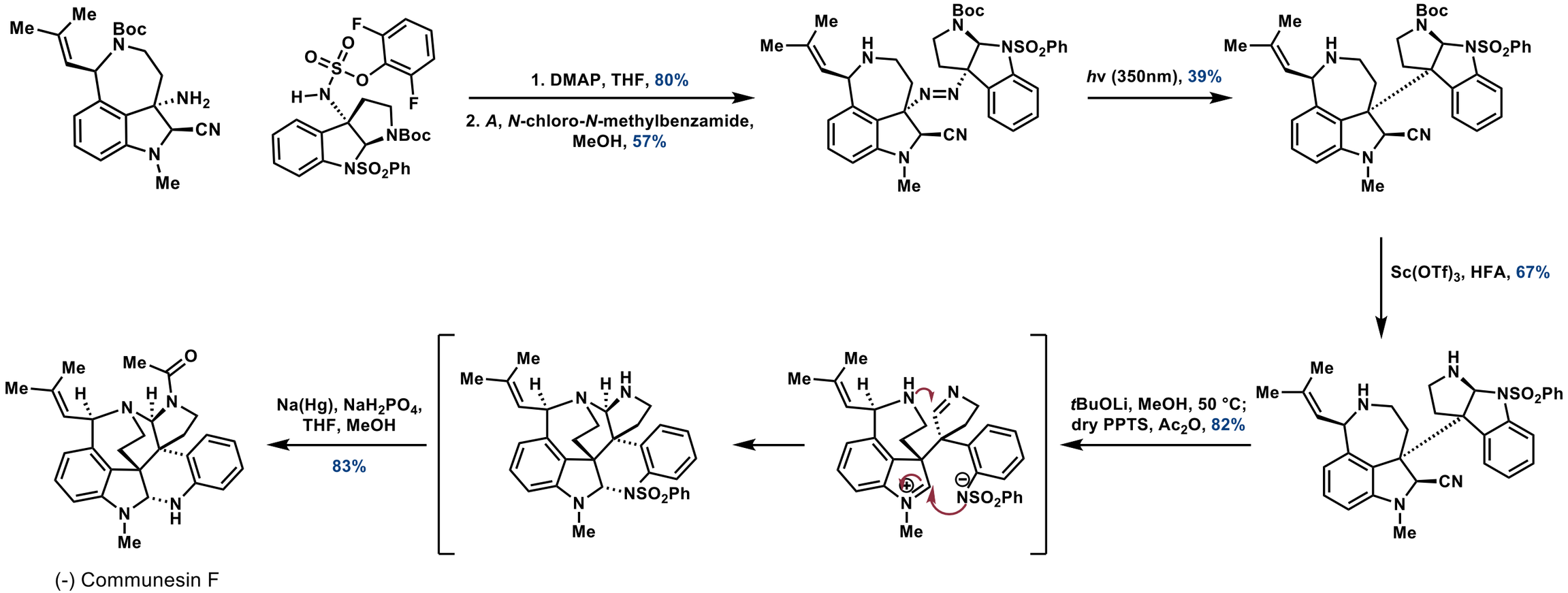
Fragment Coupling / Completing the Synthesis



Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Movassaghi (2016)

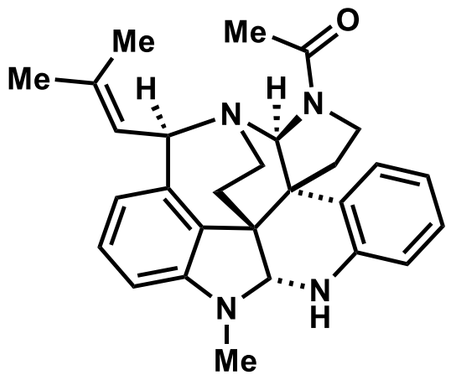
Fragment Coupling / Completing the Synthesis



Movassaghi, M. *et al. J. Am. Chem. Soc.* **2016**, *138 (24)*, 7763-7769

Synthesis of (-) Communesin F – Yang (2017)

Retrosynthetic Analysis

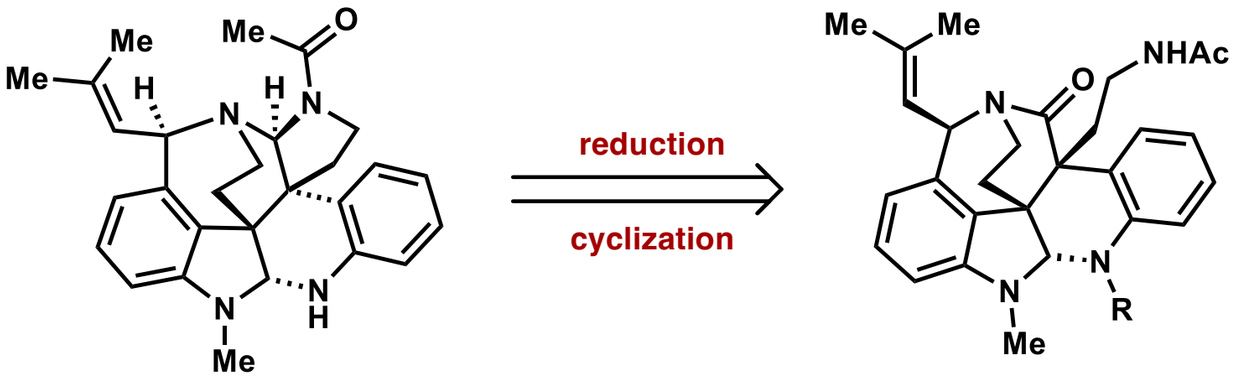


(-) Communesin F

Yang, R. *et al. J. Am. Chem. Soc. Comm.* **2017**, *139 (9)*, 3364-3367

Synthesis of (-) Communesin F – Yang (2017)

Retrosynthetic Analysis

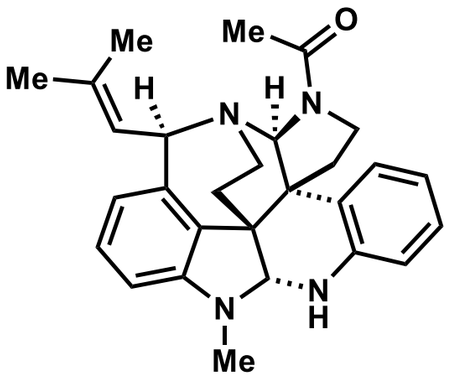


(-) Communesin F

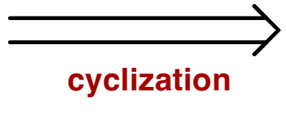
Yang, R. *et al. J. Am. Chem. Soc. Comm.* **2017**, *139 (9)*, 3364-3367

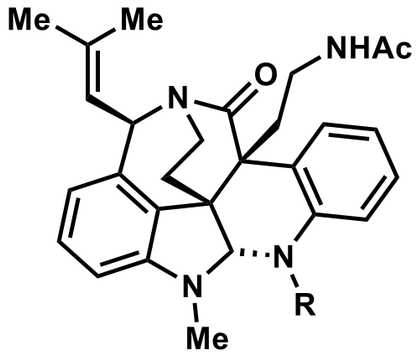
Synthesis of (-) Communesin F – Yang (2017)

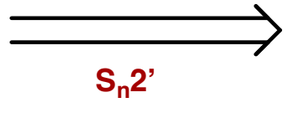
Retrosynthetic Analysis

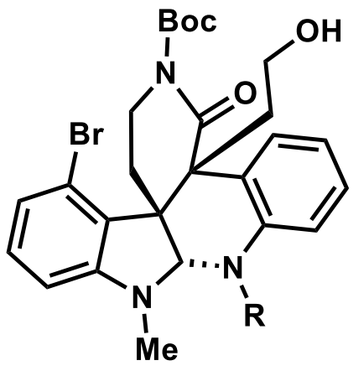


(-) Communesin F





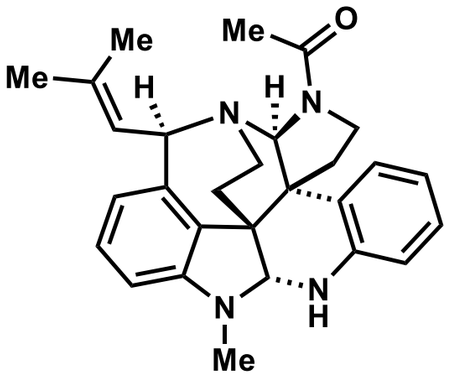




Yang, R. *et al. J. Am. Chem. Soc. Comm.* **2017**, *139 (9)*, 3364-3367

Synthesis of (-) Communesin F – Yang (2017)

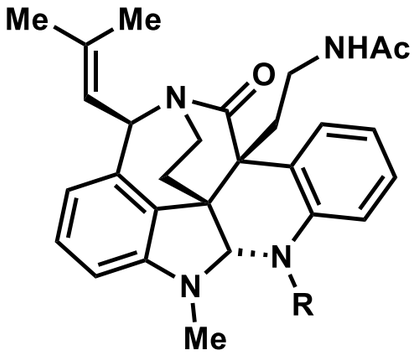
Retrosynthetic Analysis



(-) Communesin F

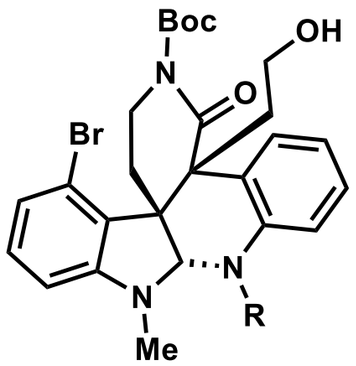
reduction

cyclization

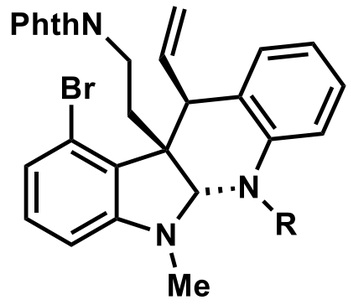


Heck

S_n2'



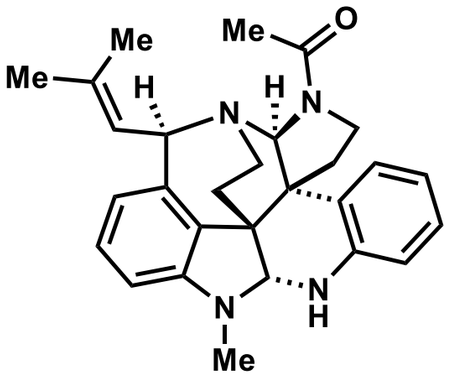
Lemieux-Johnson ox. (x2)
Pinnick ox.
lactamization



Yang, R. *et al. J. Am. Chem. Soc. Comm.* **2017**, *139 (9)*, 3364-3367

Synthesis of (-) Communesin F – Yang (2017)

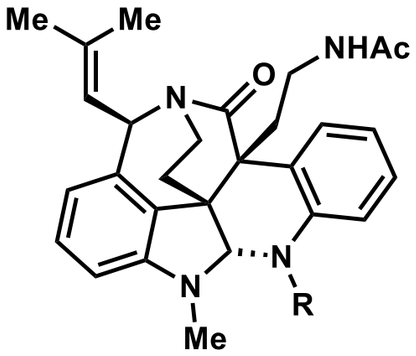
Retrosynthetic Analysis



(-) Communesin F

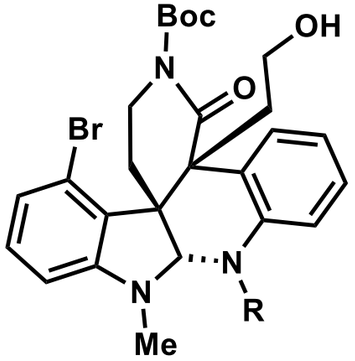
reduction

cyclization

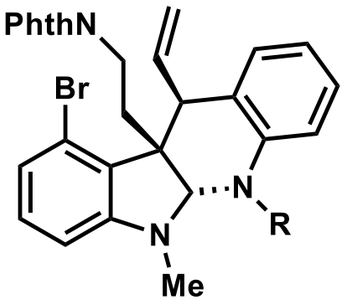


Heck

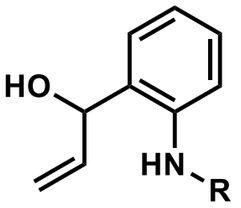
S_n2'

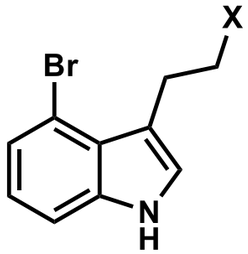


Lemieux-Johnson ox. (x2)
Pinnick ox.
lactamization



Ir-cat.
asymmetric
cyclization

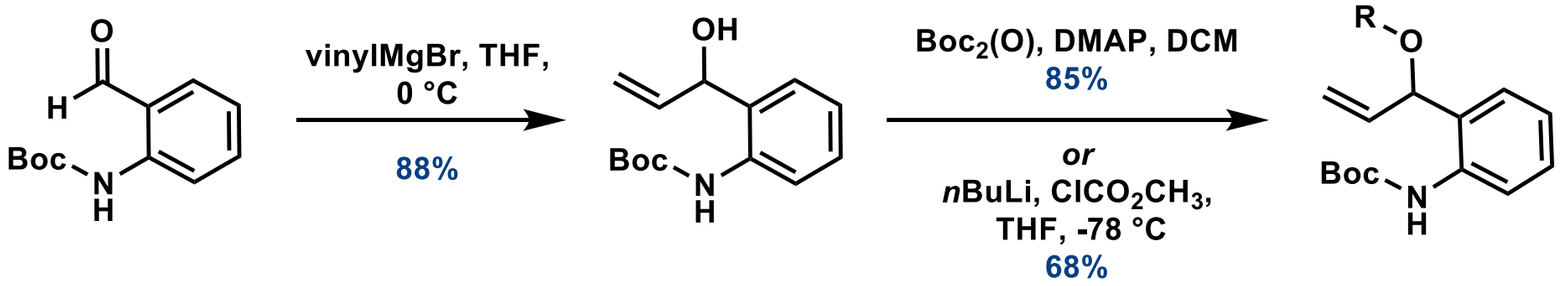




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Synthesis of (-) Communesin F – Yang (2017)

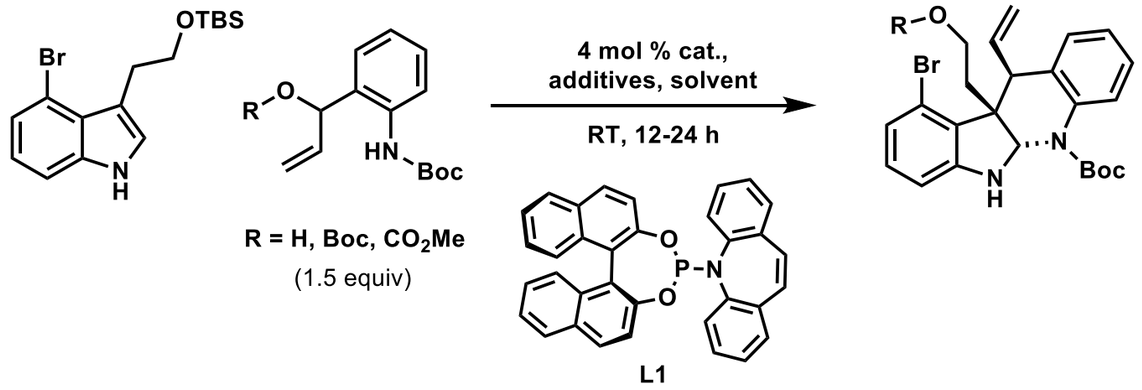
Reaction Development – Starting Material Preparation



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Reaction Development – Optimization



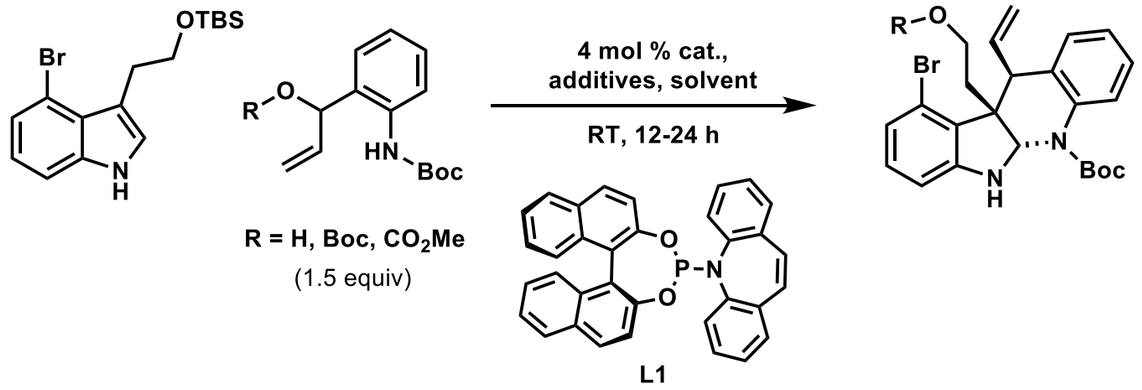
R	catalyst	additives	solvent	ee (%)	yield (%)
H	$Pd(PPh_3)_4$	Et_3B	THF	-	81
H	$Pd(PPh_3)_4$	Et_3B, DBU	CH_2Cl_2	-	75
Boc	$[Ir(cod)Cl]_2$ (S)-L1	Et_3B, KOtBu	1,4-dioxane	92	68
CO_2Me	$[Ir(cod)Cl]_2$ (S)-L1	Et_3B, KOtBu	1,4-dioxane	80	35
Boc	$[Ir(cod)Cl]_2$ (S)-L1	Et_3B, KOtBu	CH_2Cl_2	91	60
Boc	$[Ir(cod)Cl]_2$ (S)-L1	Et_3B, KO*t*Bu	THF	91	52
Boc	$[Ir(cod)Cl]_2$ (S)-L1	Et_3B, KO*t*Bu	PhMe	92	65
Boc	$[Ir(cod)Cl]_2$ (S)-L1	Et_3B, KO*t*Bu	PhMe	83	65
Boc	$[Ir(cod)Cl]_2$ (S)-L1	Ph_3B, KO*t*Bu	PhMe	-	trace
Boc	$[Ir(cod)Cl]_2$ (S)-L1	9-BBN-*n*C_6H_{13}, KO*t*Bu	PhMe	99	55
Boc	$[Ir(cod)Cl]_2$ (S)-L1	9-BBN-*n*C_6H_{13}, KO*t*Bu	PhMe	93	56

undesired pdt

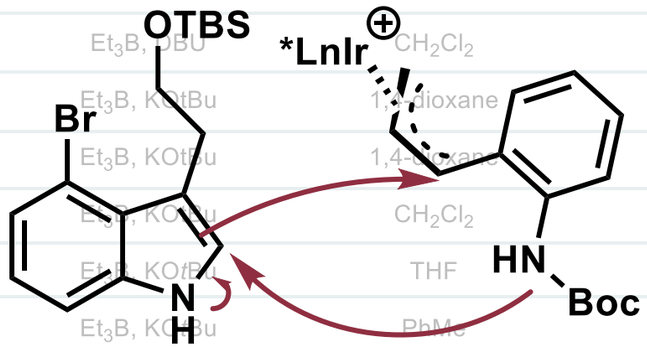
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Synthesis of (-) Communesin F – Yang (2017)

Reaction Development – Optimization



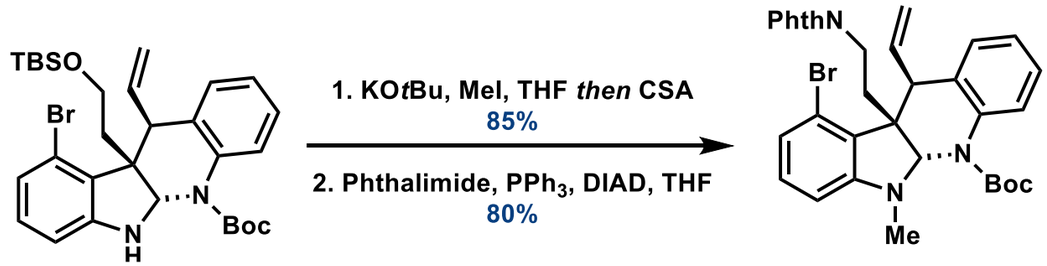
R	catalyst	additives	solvent	ee (%)	yield (%)
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H	$Pd(PPh_3)_4$	Et_3B, *t*BuOH	CH_2Cl_2	-	75
Boc	$[Ir(cod)Cl]_2$ (S)-L1	Et_3B, KO*t*Bu	1,4-dioxane	92	68
CO_2Me	$[Ir(cod)Cl]_2$ (S)-L1	Et_3B, KO*t*Bu	1,4-dioxane	80	35
Boc	$[Ir(cod)Cl]_2$ (S)-L1	Et_3B, KO*t*Bu	CH_2Cl_2	91	60
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Boc	$[Ir(cod)Cl]_2$ (S)-L1	Et_3B, KO*t*Bu	PhMe	83	65
Boc	$[Ir(cod)Cl]_2$ (S)-L1	Ph_3B, KO*t*Bu	PhMe	-	trace
Boc	$[Ir(cod)Cl]_2$ (S)-L1	9-BBN-nC_6H_{13}, KO*t*Bu	PhMe	99	55
Boc	$[Ir(cod)Cl]_2$ (S)-L1	9-BBN-nC_6H_{13}, KO*t*Bu	PhMe	93	56



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Synthesis of (-) Communesin F – Yang (2017)

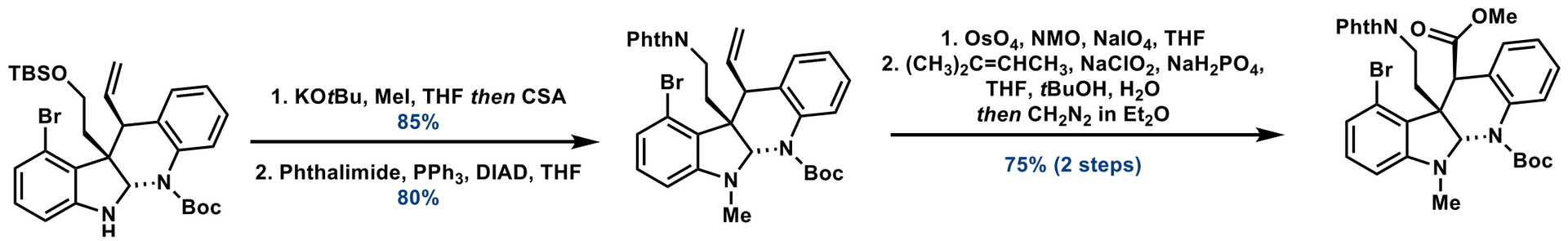
Forward Synthesis



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Synthesis of (-) Communesin F – Yang (2017)

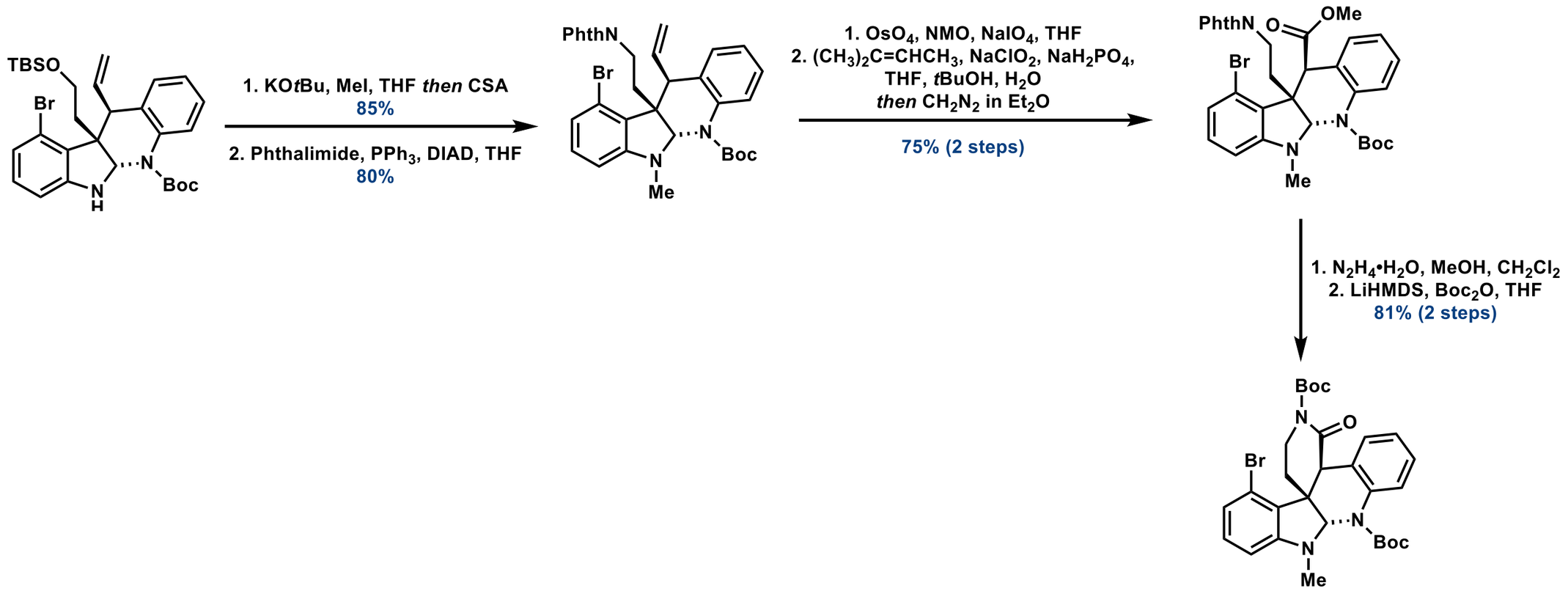
Forward Synthesis



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Synthesis of (-) Communesin F – Yang (2017)

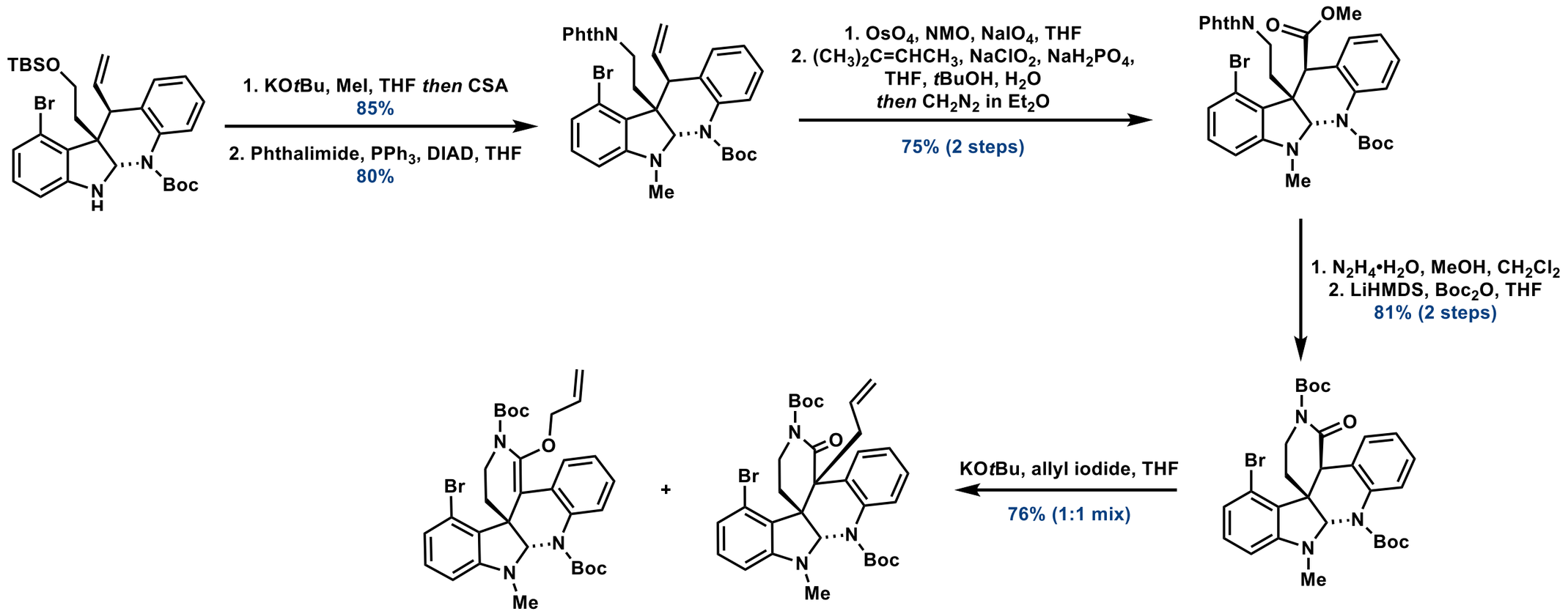
Forward Synthesis



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Synthesis of (-) Communesin F – Yang (2017)

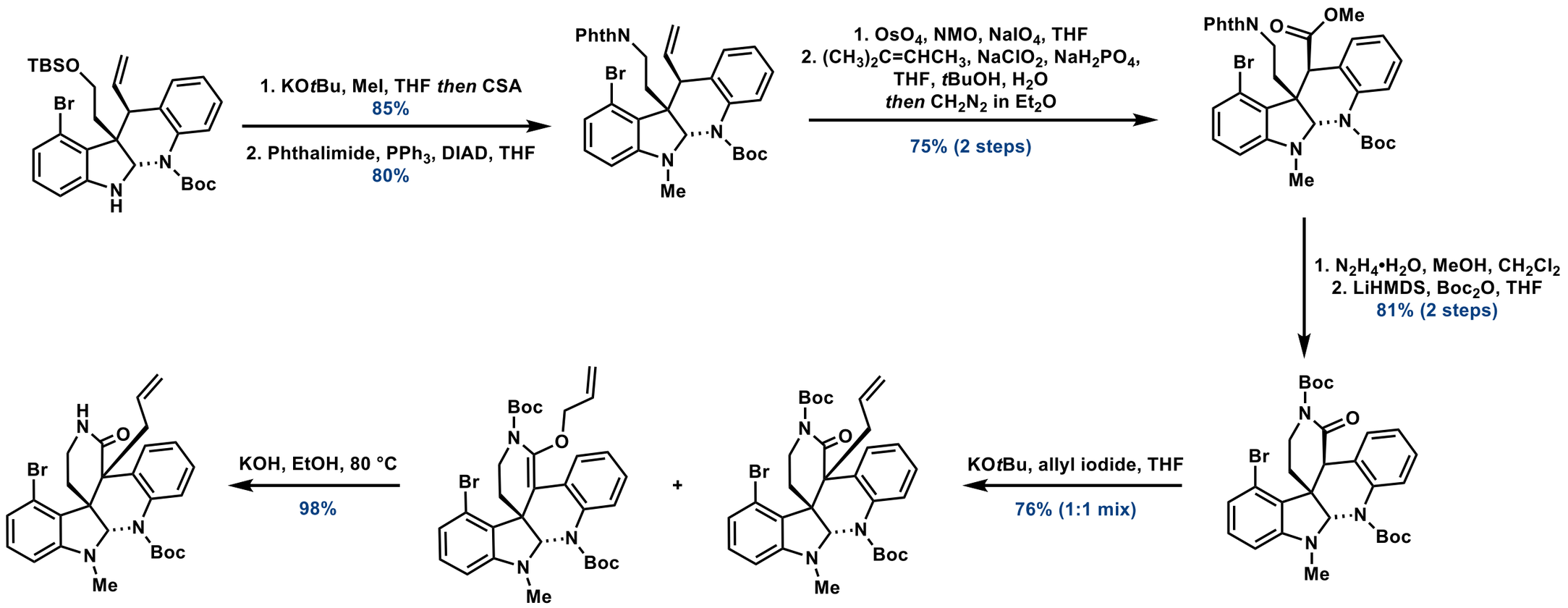
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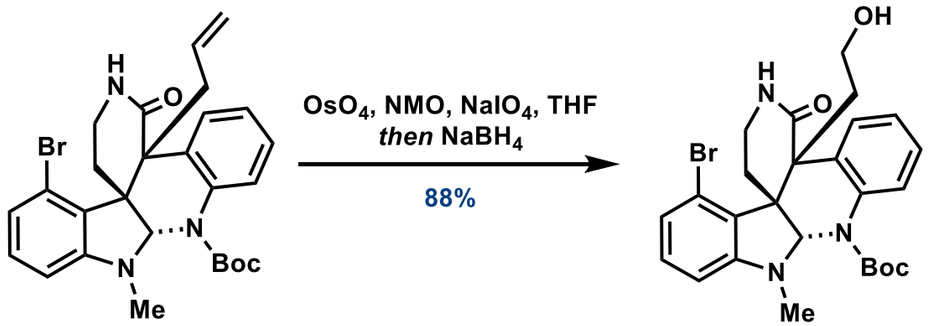
Forward Synthesis



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Synthesis of (-) Communesin F – Yang (2017)

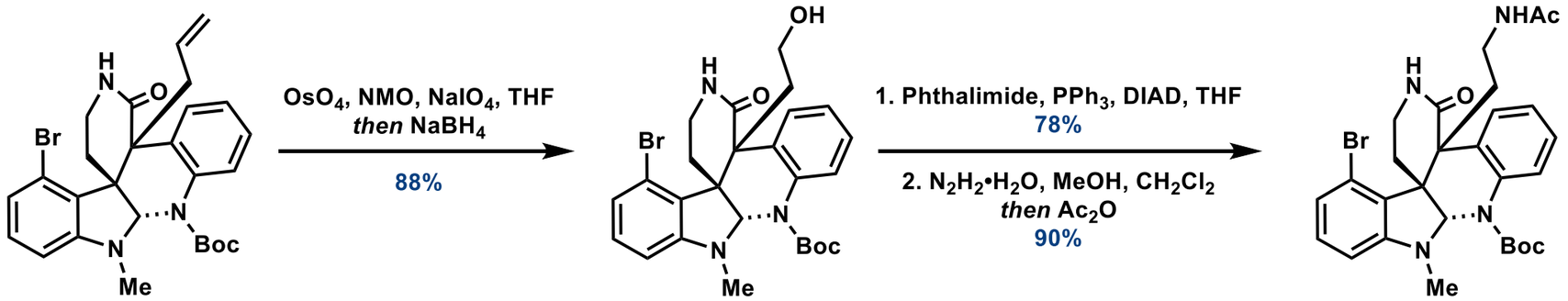
Forward Synthesis



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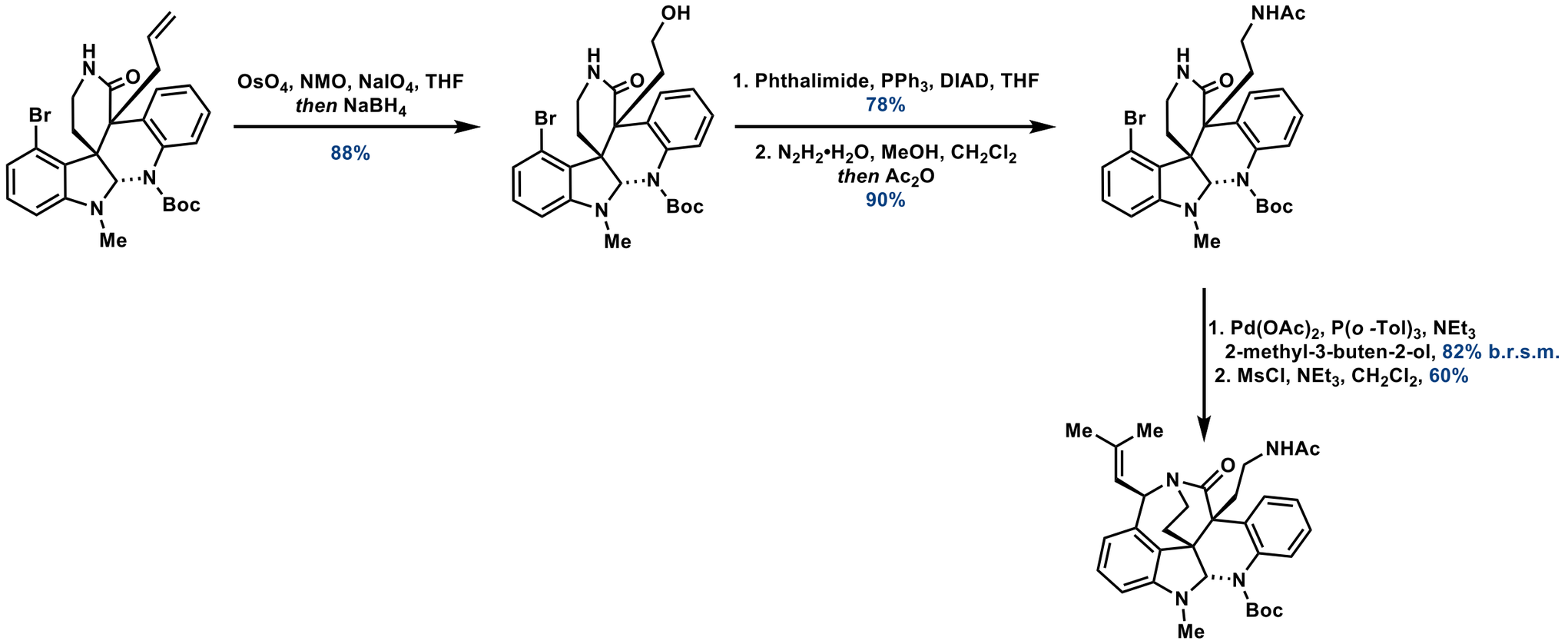
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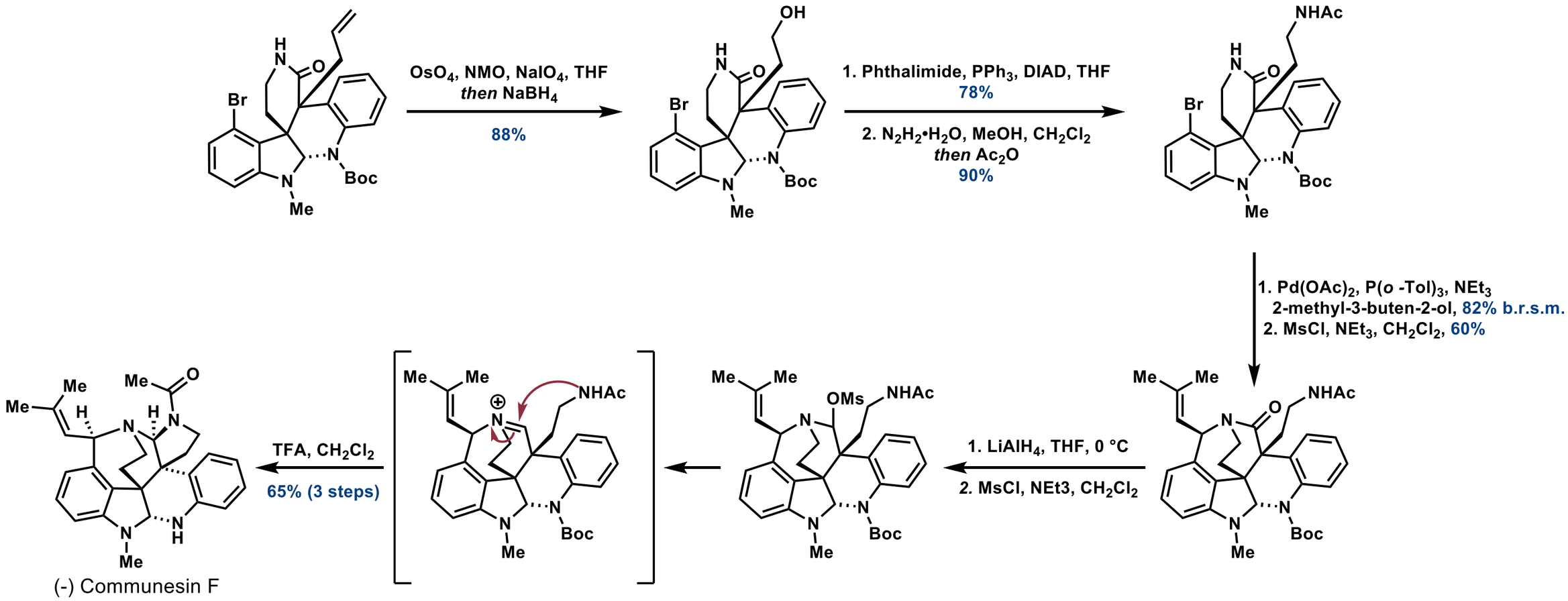
Forward Synthesis



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Synthesis of (-) Communesin F – Yang (2017)

Forward Synthesis



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