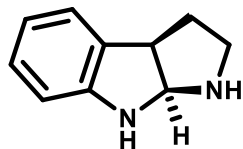
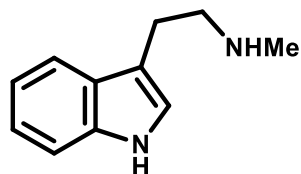


"cyclotryptamine alkaloids"
or "polypyrroloindoline alkaloids"



(3aR,8aS)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole



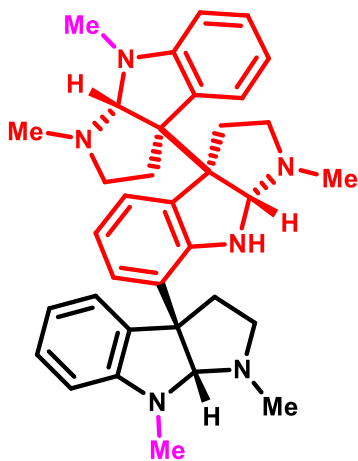
N-methyltryptamine



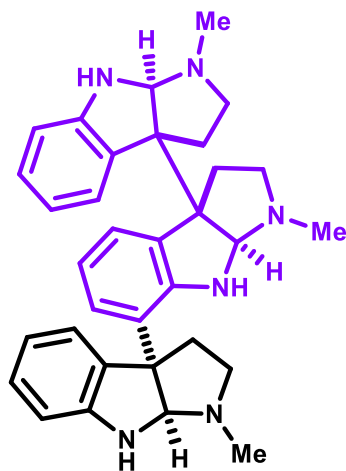
https://commons.wikimedia.org/wiki/File:Psychotria_punctata.jpg

Psychotria spp.

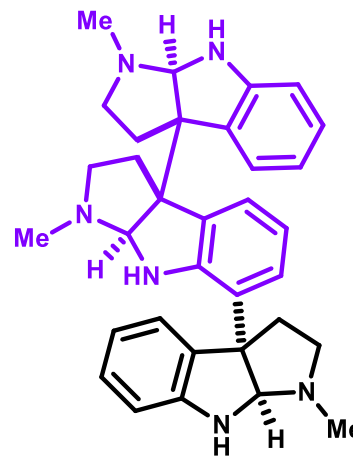
N-methyltryptamine trimers:



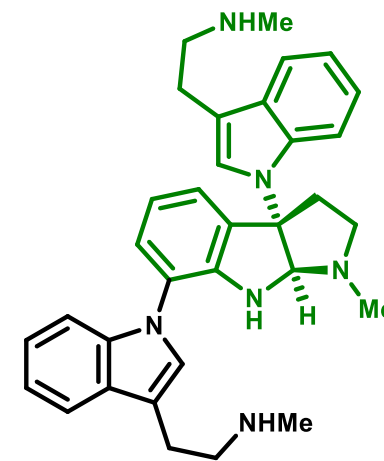
(-)-idiospermuline



(-)-hodgkinsine



(-)-hodgkinsine B



(+)-psychotrimine

Steven, A.; Overman, L. E. *Angew. Chem. Int. Ed.* **2007**, *46*, 5488. (review)

Hodgkinsine: Kodanko, J. J.; Overman, L. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 2528.

Snell, R. H.; Woodward, R. L.; Willis, M. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 9116.

Idiospermuline: Overman, L. E.; Peterson, E. A. *Tetrahedron* **2003**, *59*, 6905.

Psychotrimine: Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125.

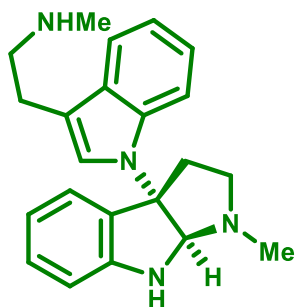
Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886.

Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119.

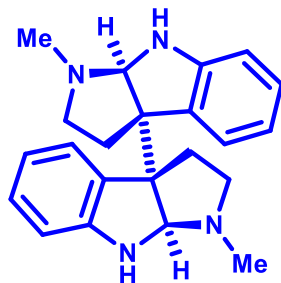
Takahashi, N.; Ito, T.; Matsuda, Y.; Kogure, N.; Kitajima, M.; Takayama, H. *Chem. Commun.* **2010**, *46*, 2501.

Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 2716.

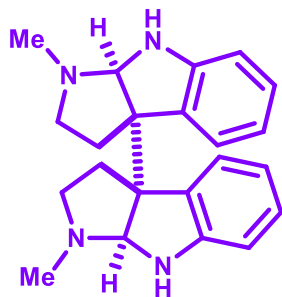
lower order species:



(+)-psychotriazine

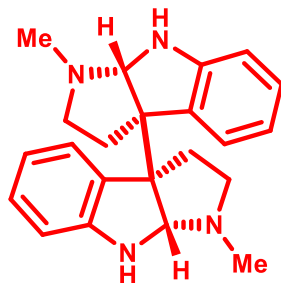


(+)-chimonanthine



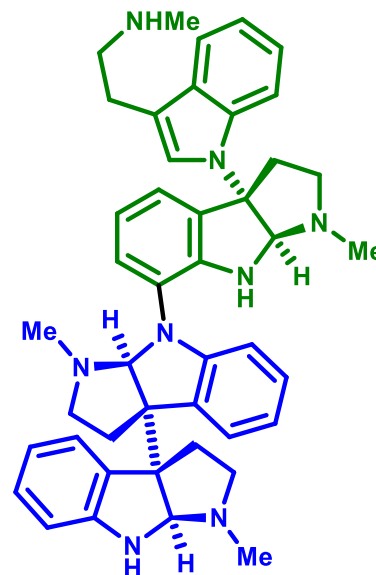
meso-chimonanthine

+ several others



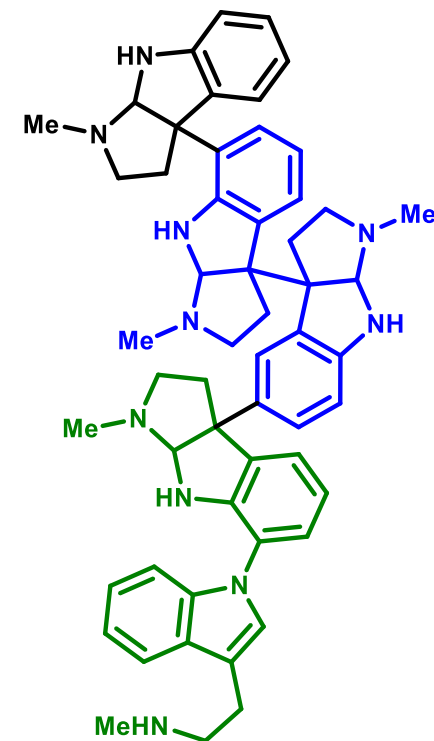
(-)-chimonanthine

higher order species:



(+)-psychotretamine

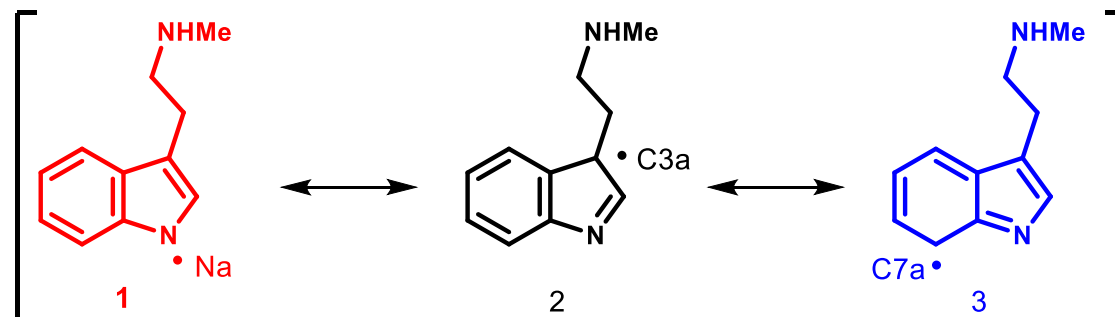
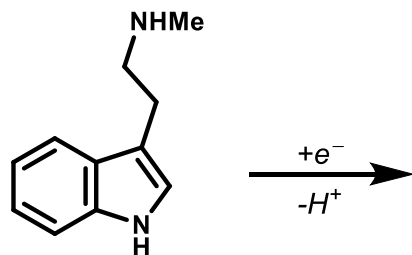
+ many others



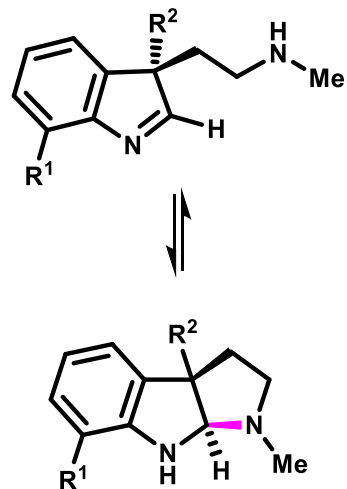
(+)-psychopentamine

(stereochemistry
not fully elucidated)

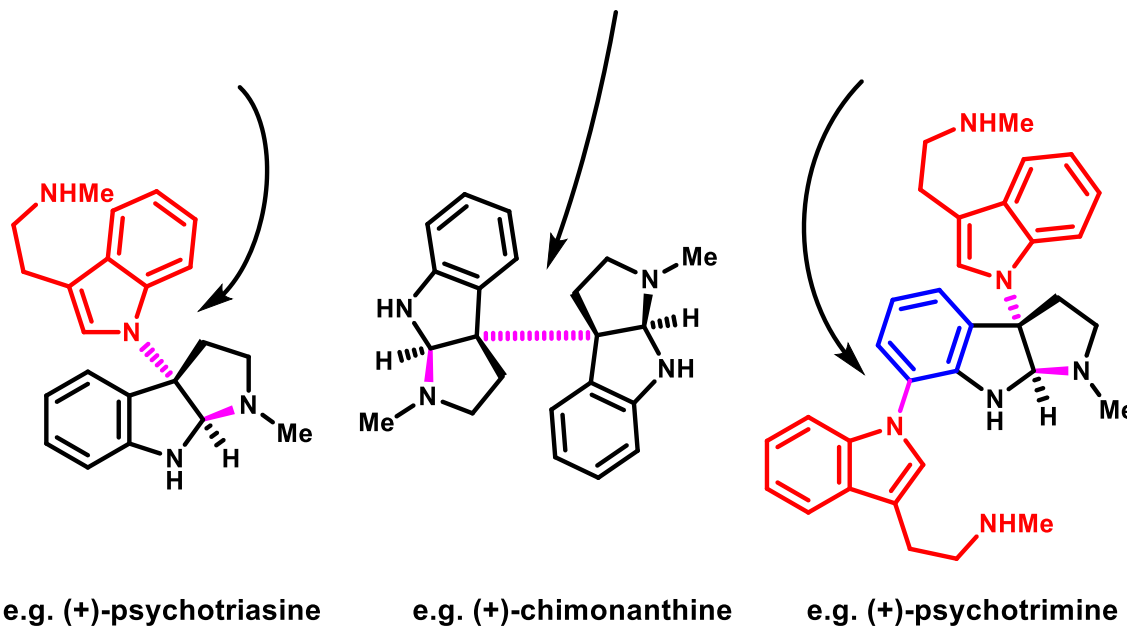
Biosynthesis:

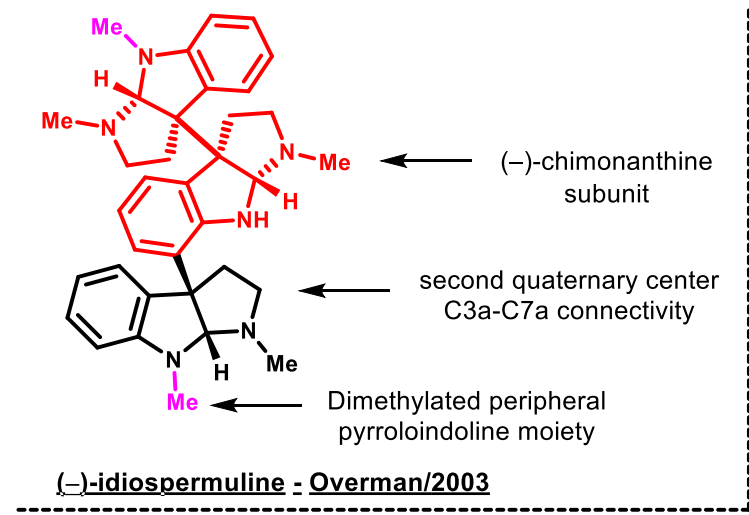


ring-chain tautomerization

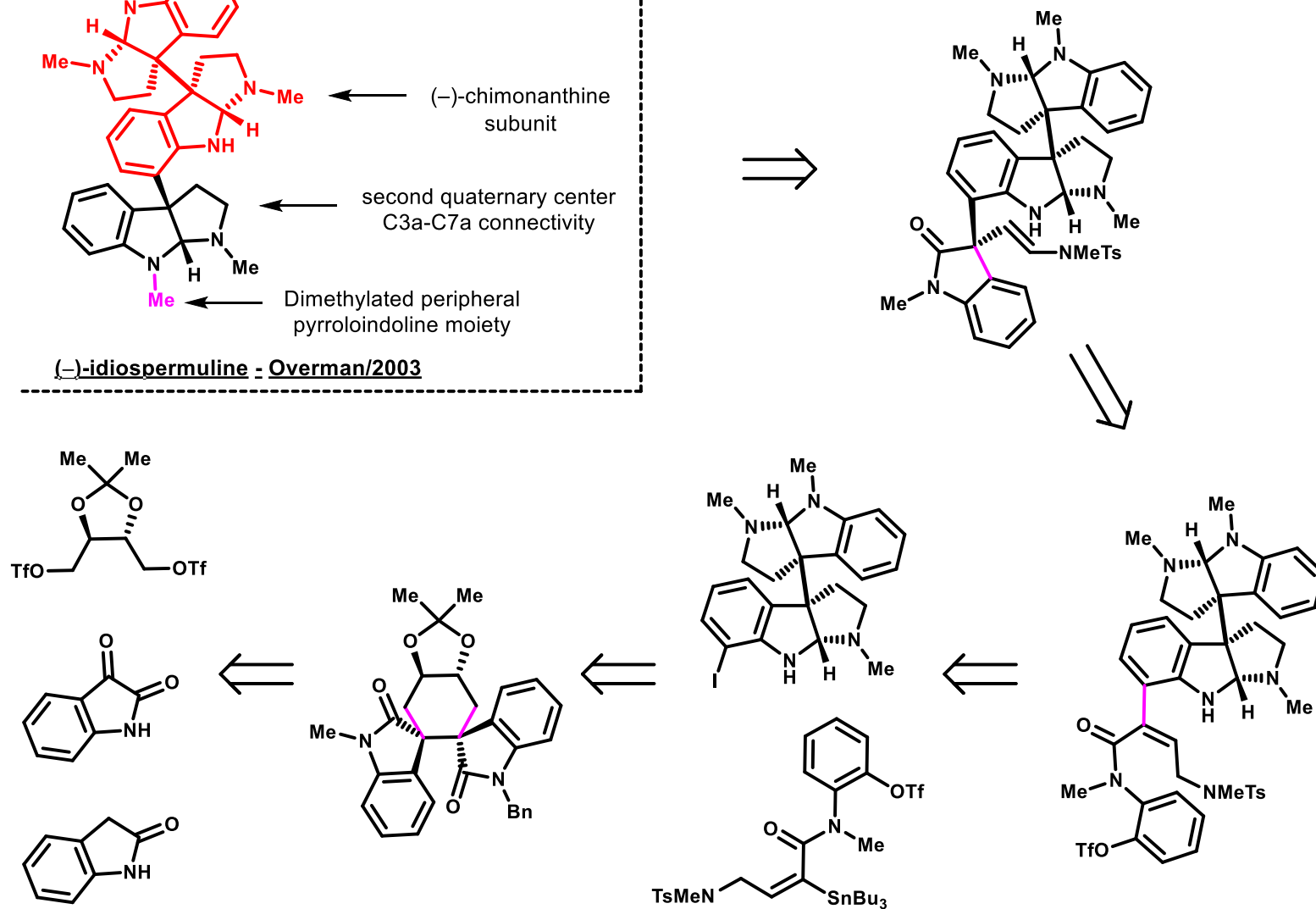


cis closed form predominant

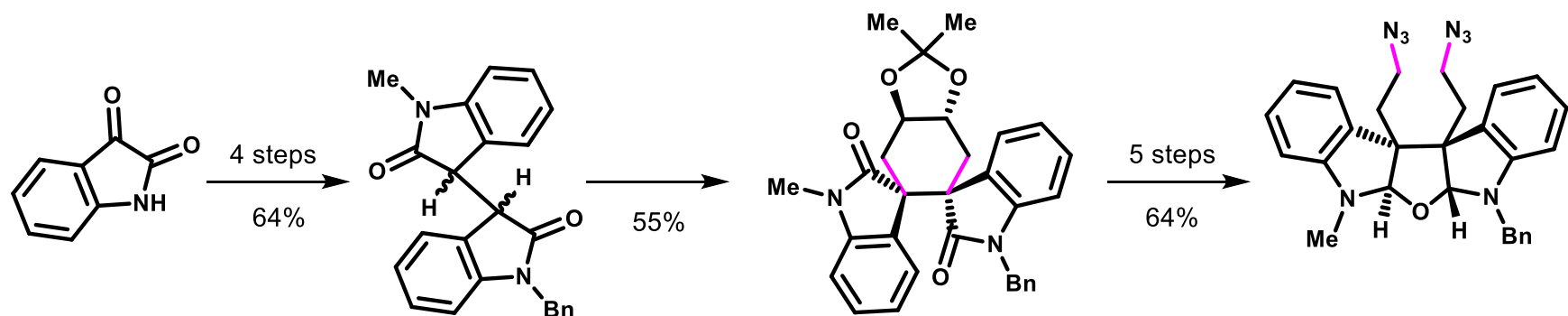




Overman's retrosynthesis:



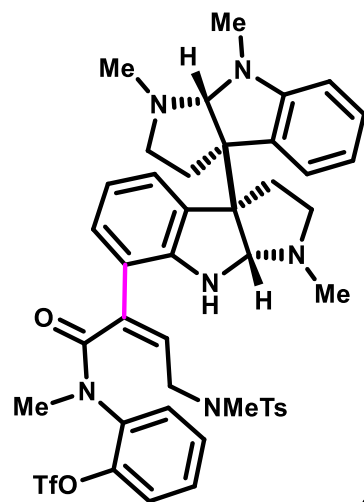
Overman's forward:



(1) benzylation (2) condensation with
oxindole (3) N-methylation (4) hydrogenation
/ PtO₂

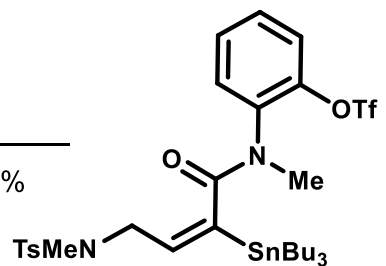
Li-dienolate
dialkylation

deprotection
oxidative diol cleavage
2x reductions
azide mitsunobu



Stille coupling

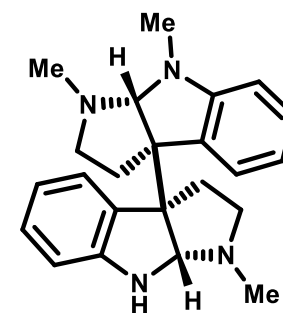
94%



Boc installation,
directed metallation/iodination (CH₂I)₂,
de-Boc (TMSOTf)

3 steps

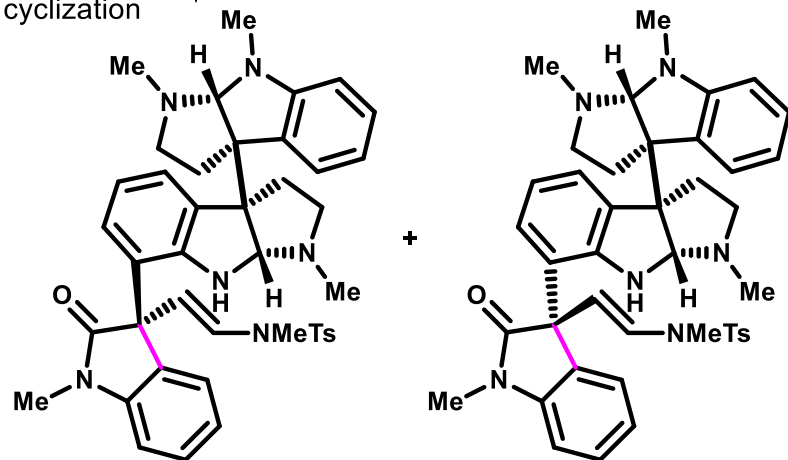
63%



Staudinger,
dehydration,
reductive methylation,
debenzylation

asymmetric
Heck
cyclization

97%

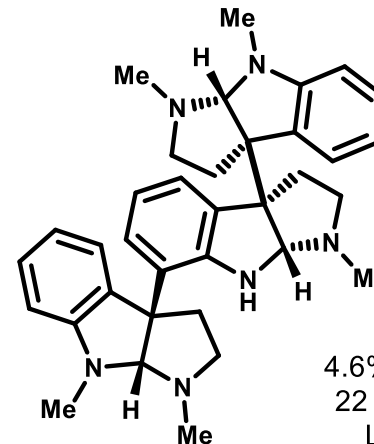


6:1 dr with (S)-Tol-Binap (1:18 with R)

1) hydrogenation
2) RedAl
3) Na, NH₃

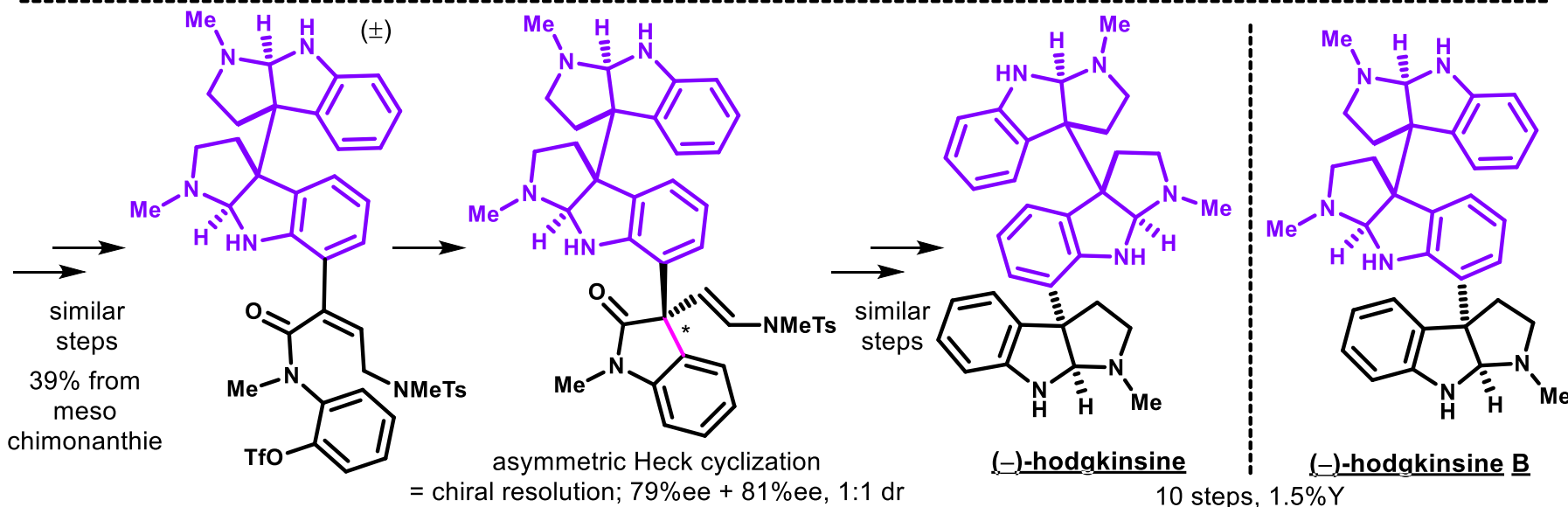
(prep HPLC)

47%



4.6% over
22 steps
LLS

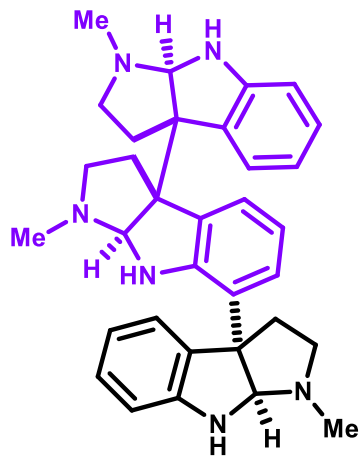
(-)-idiospermuline



(-)-hodgekinsine

(-)-hodgekinsine B

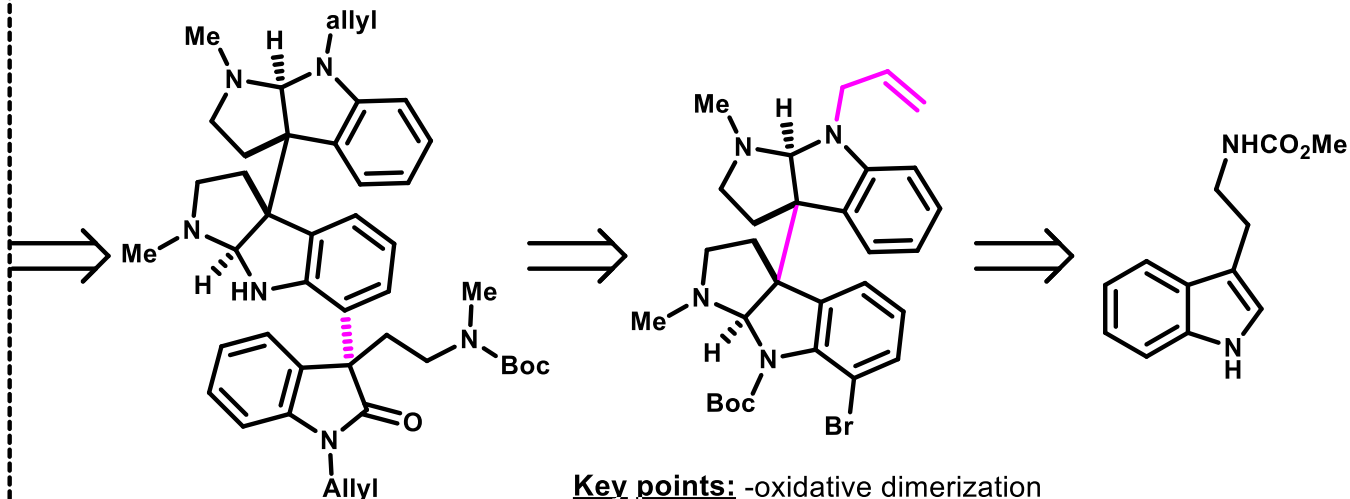
10 steps, 1.5%Y



(-)-hodgkinsine B

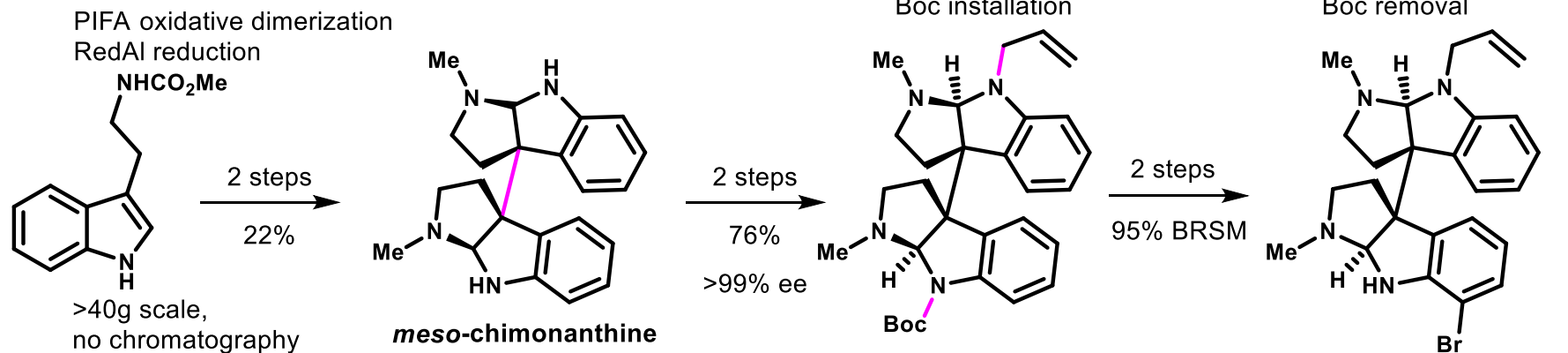
Overman 2003, Willis 2011

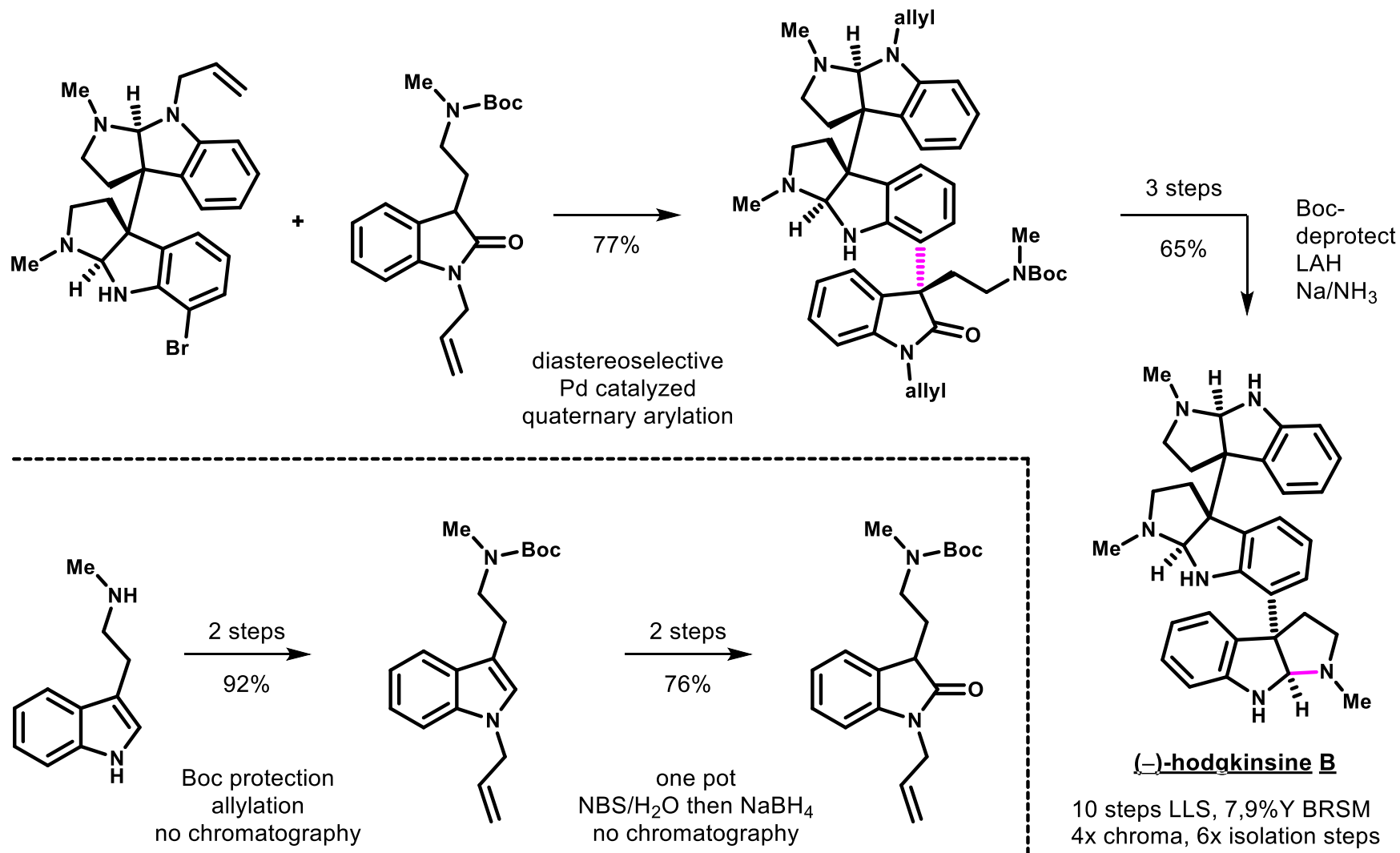
Willis' retrosynthesis:

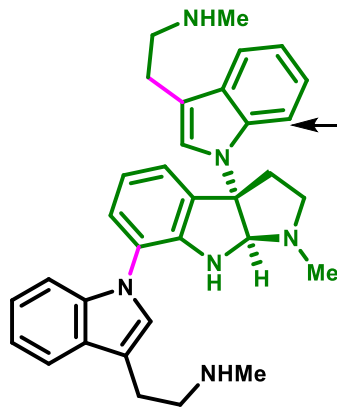


Key points: -oxidative dimerization
-Trost allylative desymmetrization
-diastereoselective quaternary arylation

Willis' forward:







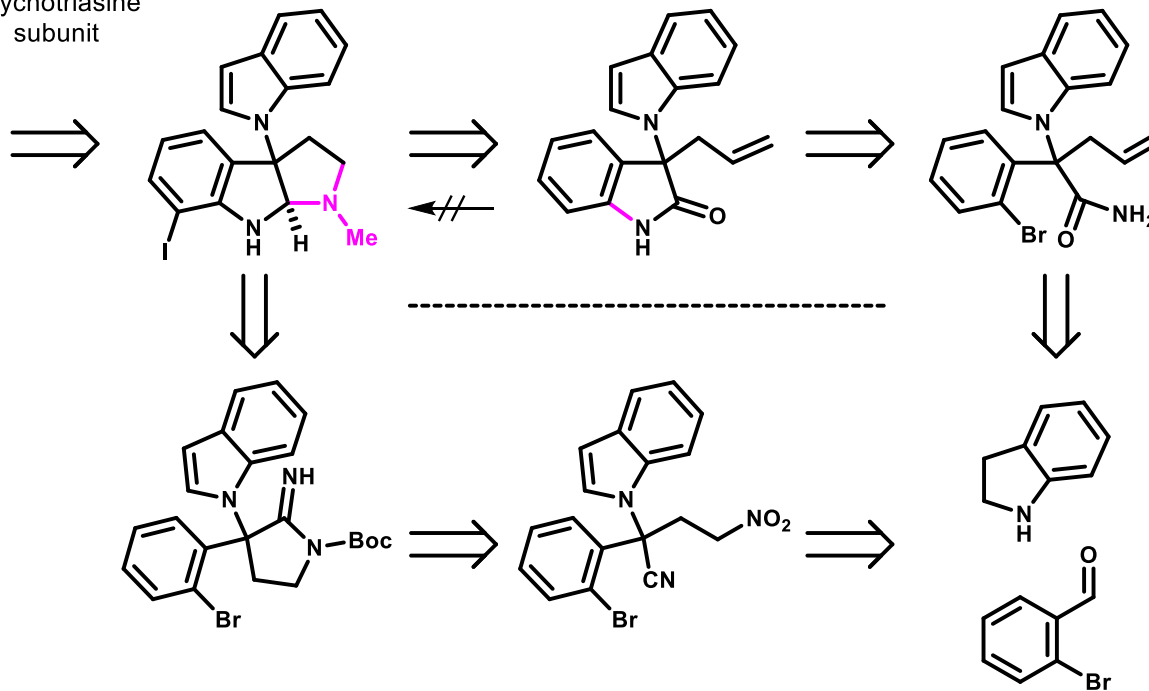
(+)-psychotrimine

- (±) - Takayama, 2008
- (±) - Baran, 2008
- (+) - Takayama, 2010
- (+) - Baran/Takayama, 2011

Takayama (±): 16 steps, 13%Y
Baran (±): 5 steps, 45%Y
Takayama (+): 26 steps, 7.8%Y
Collaboration (+): 9 steps, 7%Y

Takayama's rac-retrosynthesis

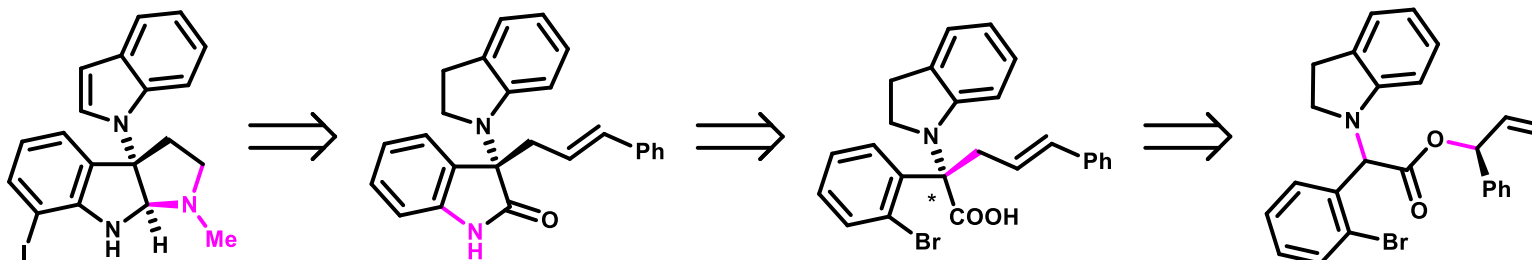
psychotriazine subunit

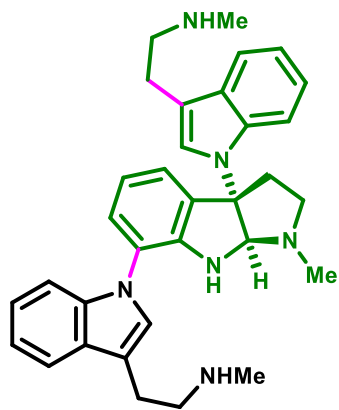


Key points: -pyrrolindoline aminative cyclization

Takayama's (+) retrosynthesis:

Key points: -Ireland-Claisen stereochemical transfer





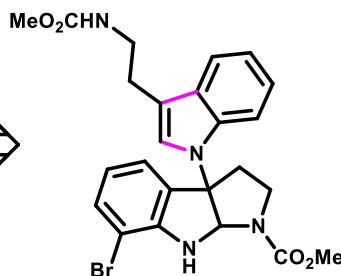
(+)-psychotrimine

- (±) - Takayama, 2008
- (±) - Baran, 2008
- (+) - Takayama, 2010
- (+) - Baran/Takayama, 2011

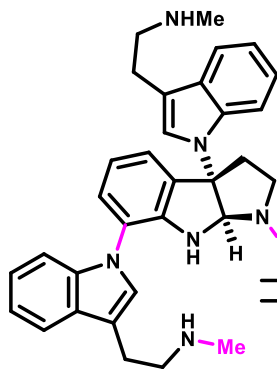
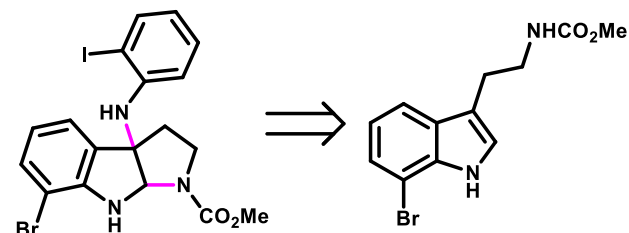
Takayama (±): 16 steps, 13%Y
Baran (±): 5 steps, 45%Y
Takayama (+): 26 steps, 7.8%Y
Collaboration (+): 9 steps, 7%Y

Baran's retrosynthesis:

rac-psychotrimine

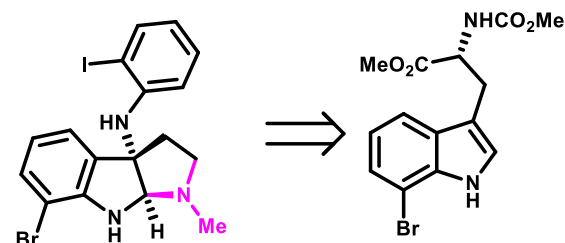
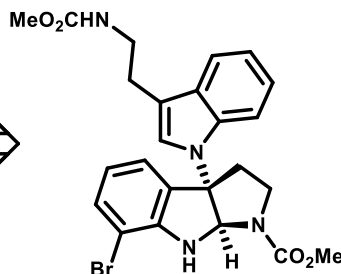


Key points: -tryptamine oxidative amination-cyclization
-LaRock indole synthesis

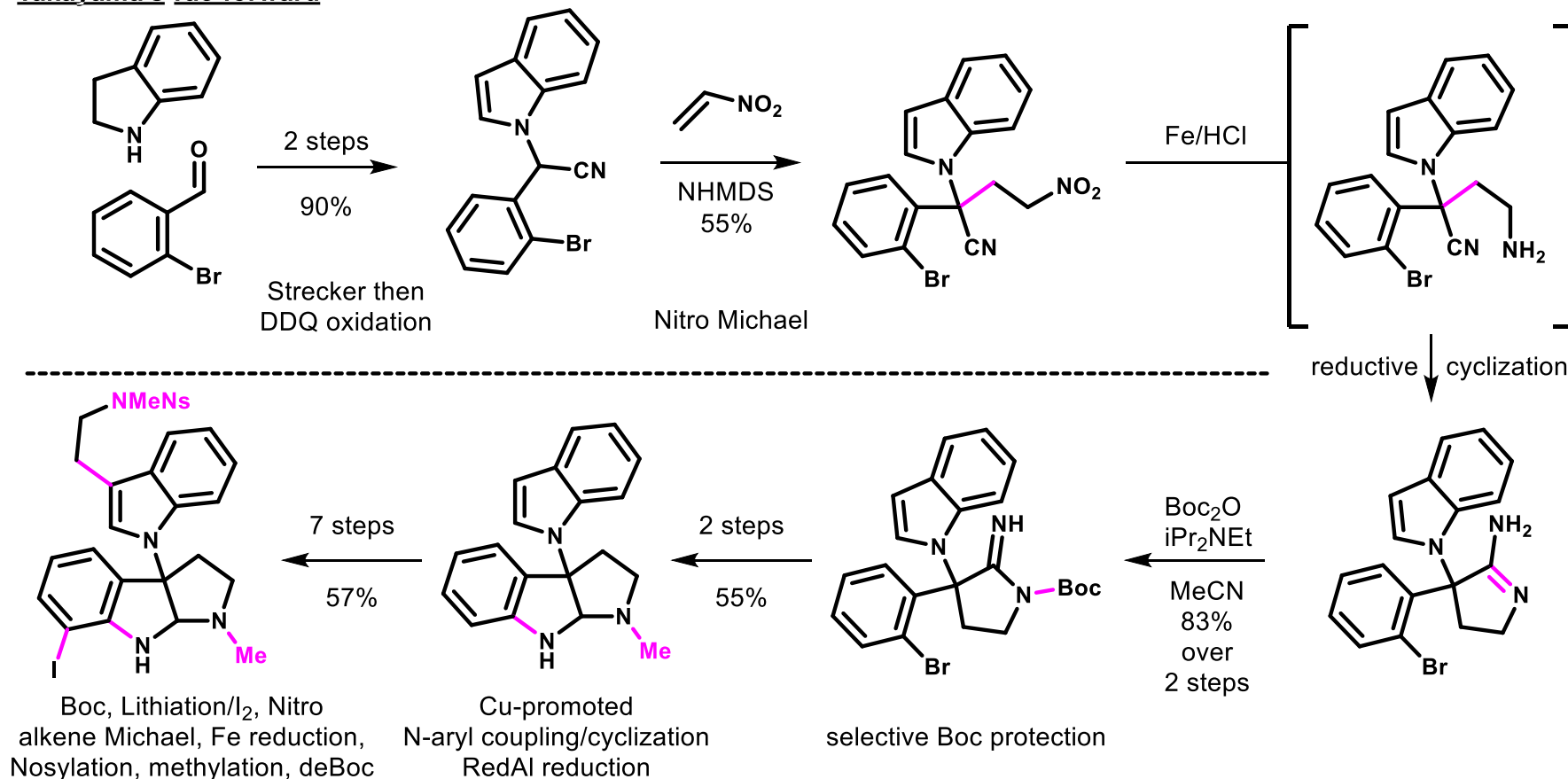


(+)-psychotrimine

Key points: -diastereoselective oxidative amination-cyclization



Takayama's rac-forward



Psychotrimine: Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125.

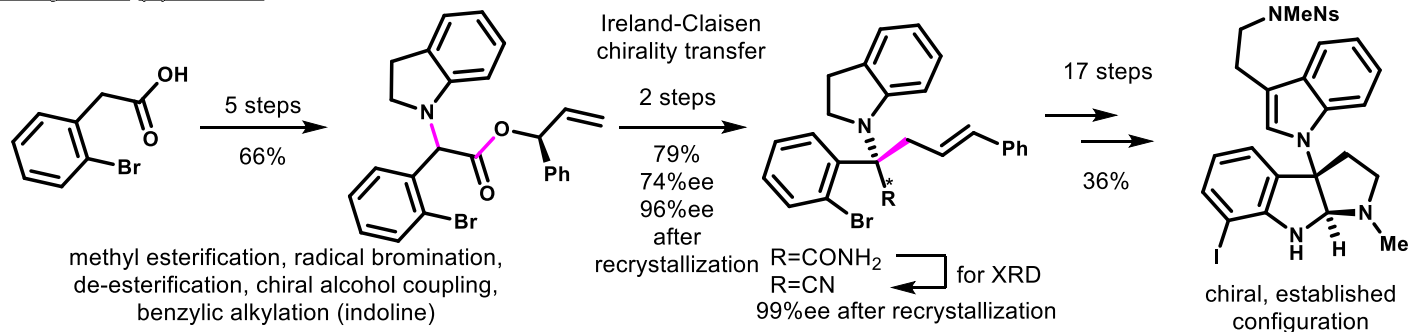
Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886.

Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119.

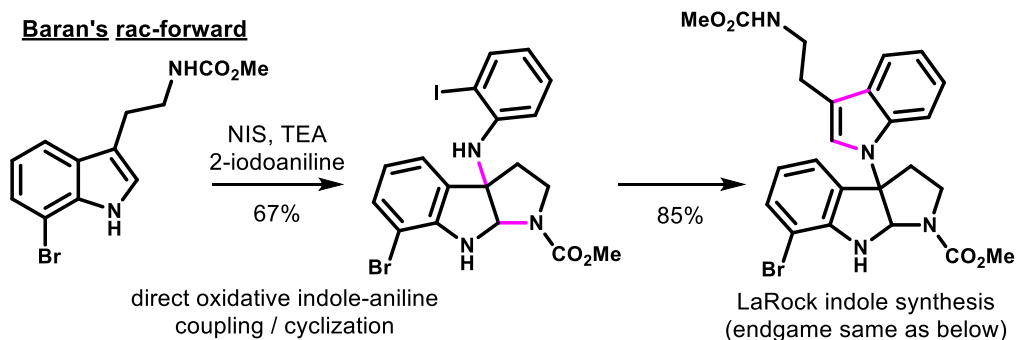
Takahashi, N.; Ito, T.; Matsuda, Y.; Kogure, N.; Kitajima, M.; Takayama, H. *Chem. Commun.* **2010**, *46*, 2501.

Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 2716.

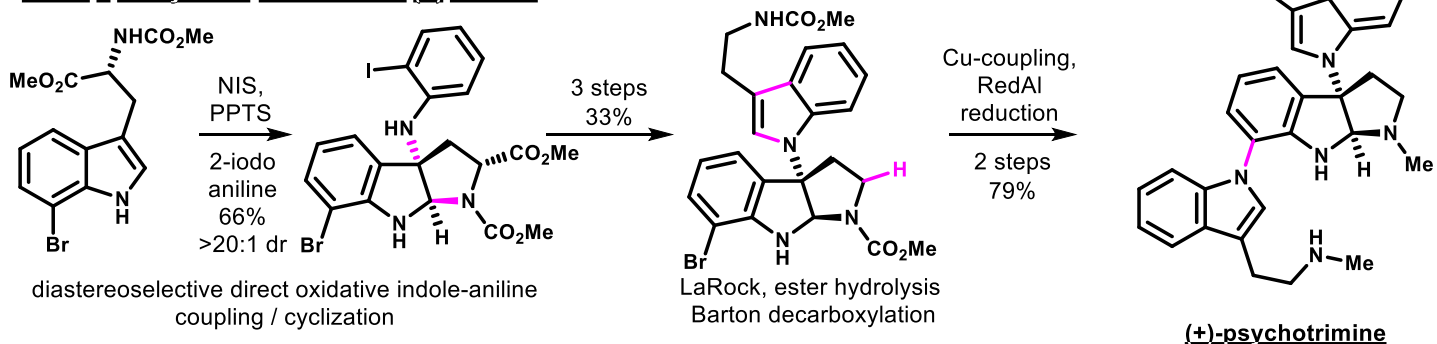
Takayama's (+)-forward



Baran's rac-forward



Baran + Takayama's collaborative (+) forward



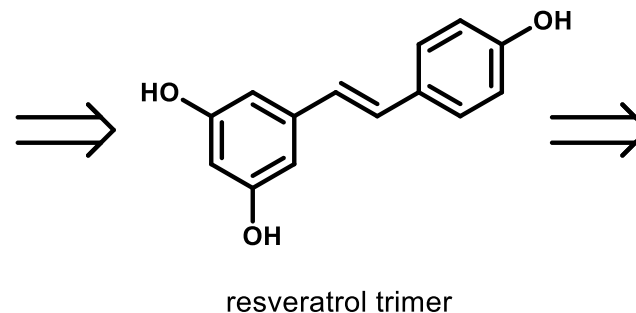
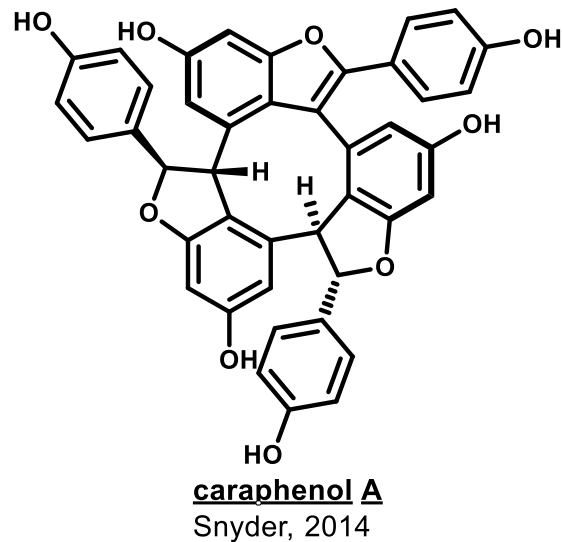
Psychotrimine: Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125.

Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886.

Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119.

Takahashi, N.; Ito, T.; Matsuda, Y.; Kogure, N.; Kitajima, M.; Takayama, H. *Chem. Commun.* **2010**, *46*, 2501.

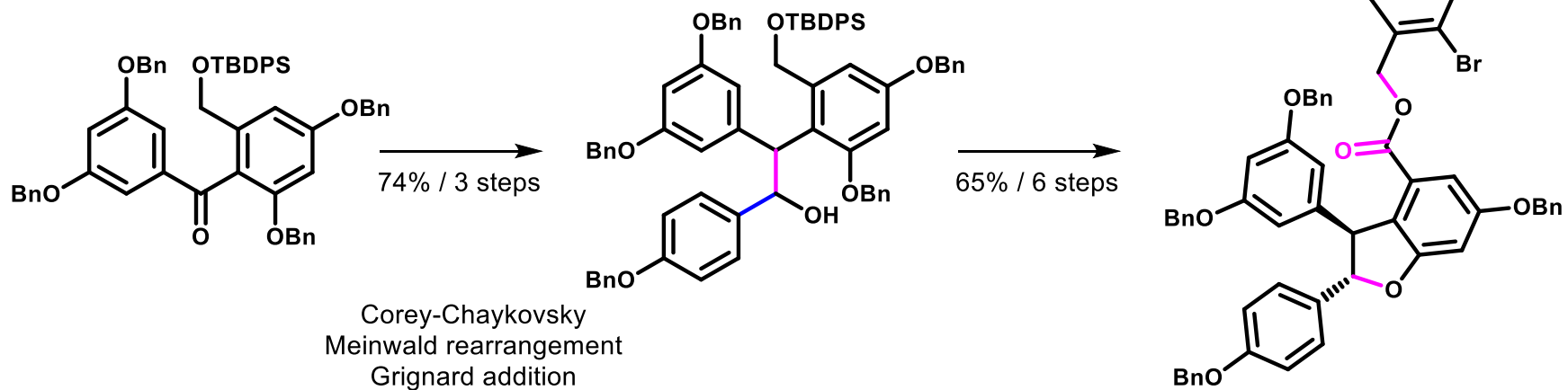
Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 2716.

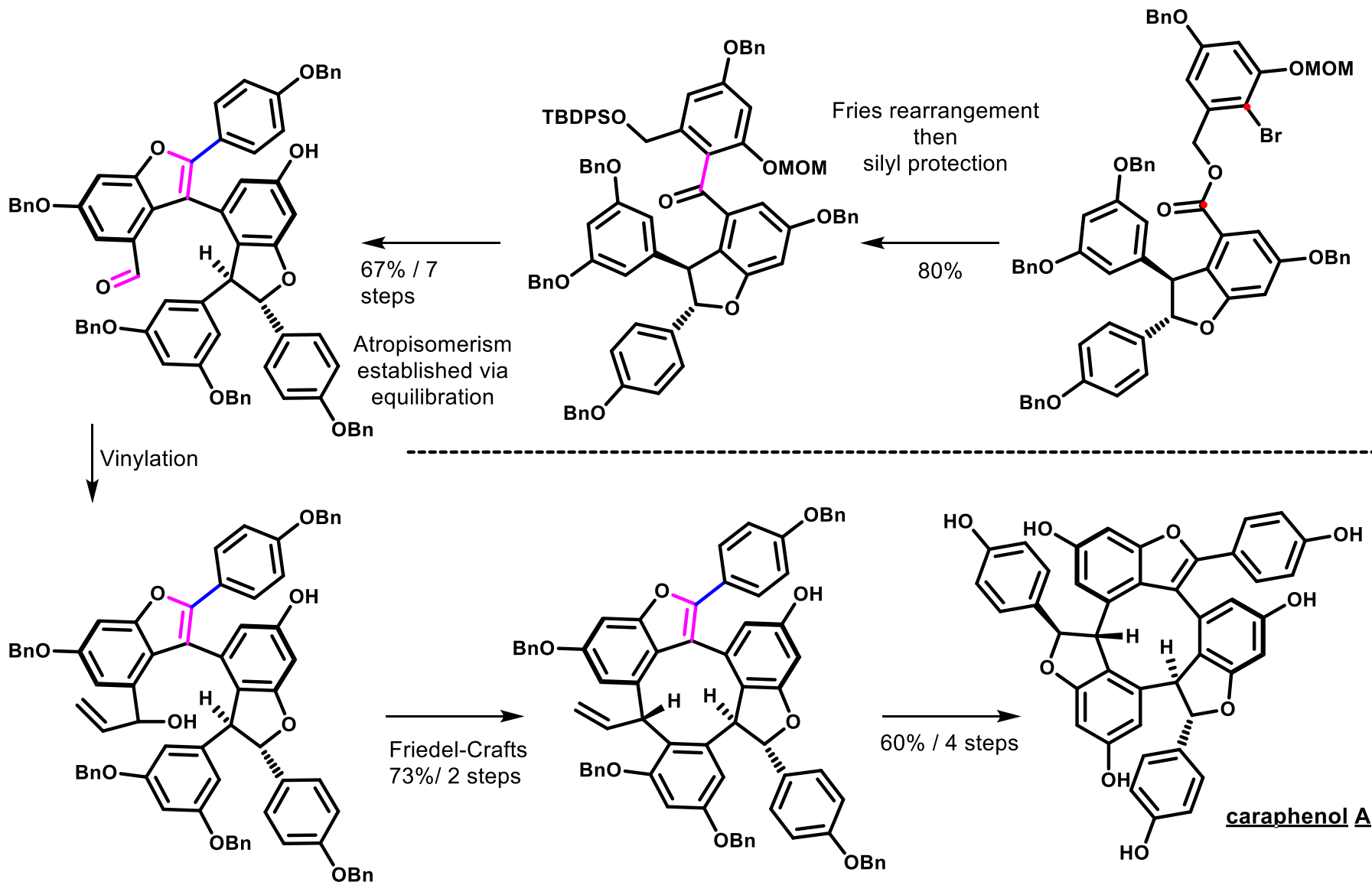


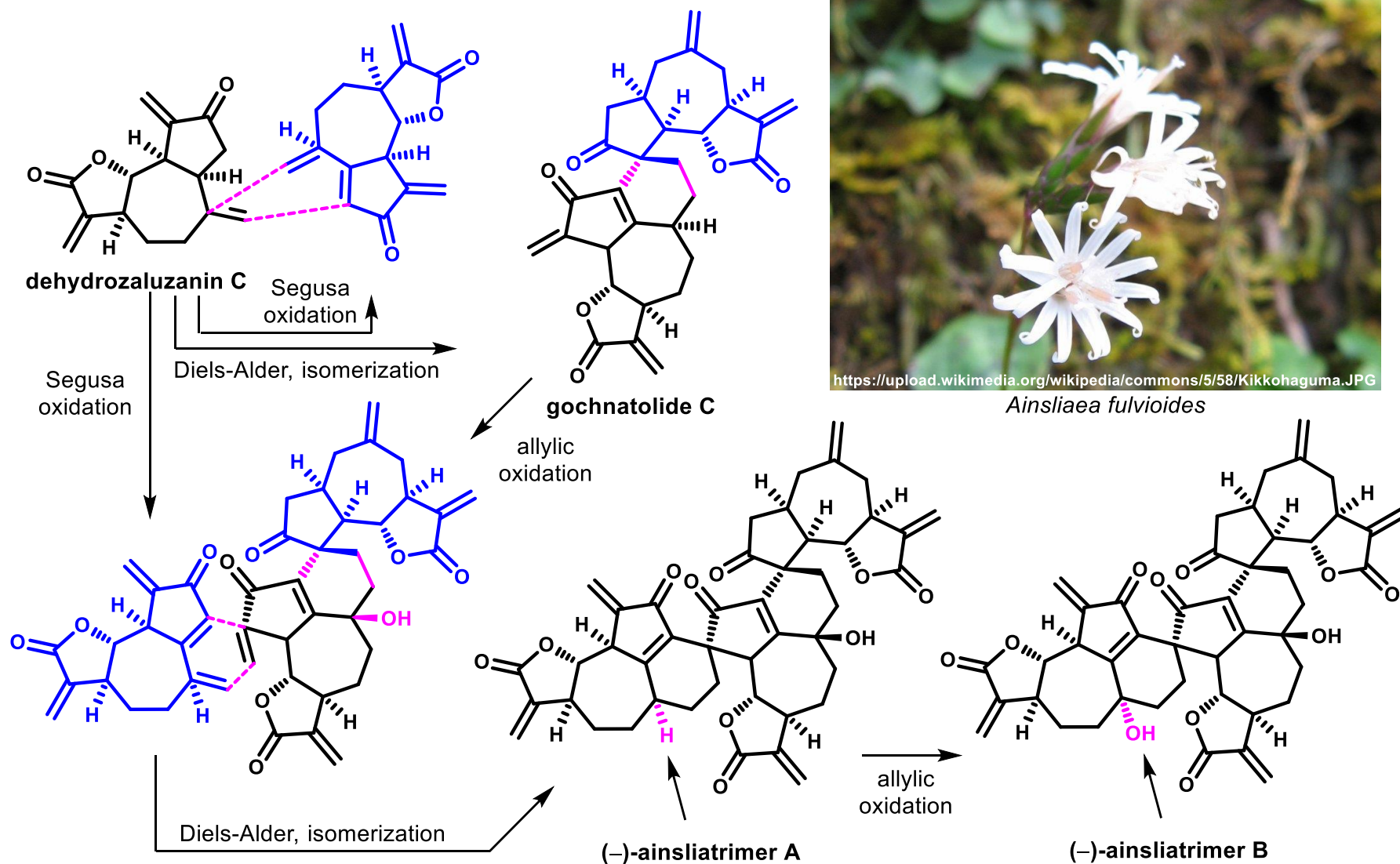
https://en.wikipedia.org/wiki/Red_wine#/media/File:Pouring_a_glass_of_red_wine.tiff

Snyder's Total Synthesis

- Key points:**
- iterative strategy
 - takes advantage of multiple skeletal rearrangements
 - 9-member ring established using Friedel-Crafts cyclization



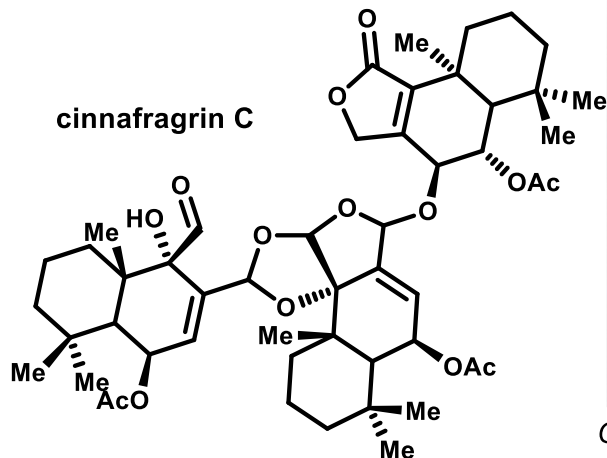




Ainsliaea fulvioides

Lei, 2013

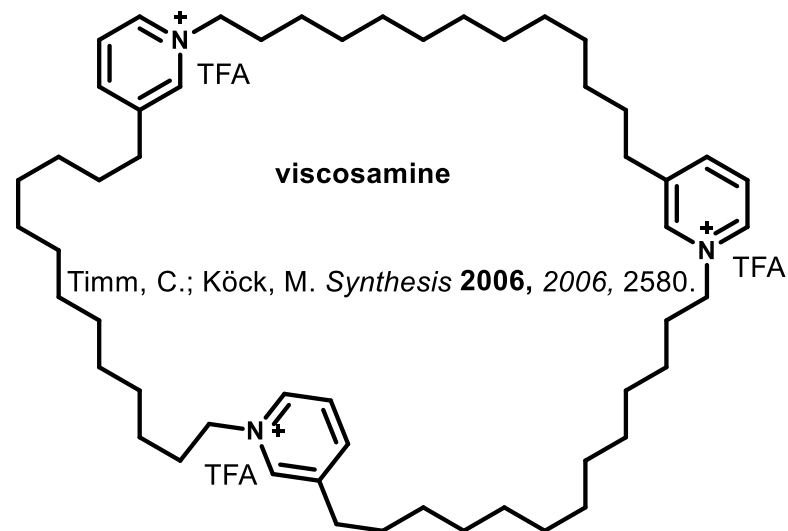
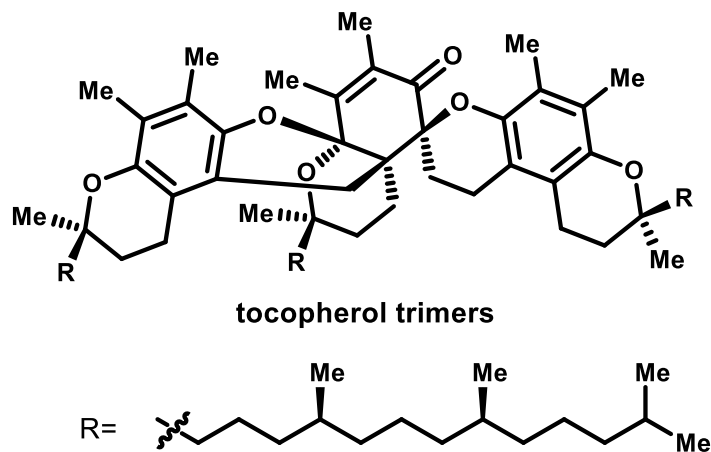
Harinantenaina, L.; Takaoka, S. *J. Nat. Prod.* **2006**, *69*, 1193.



Cinnamomum fragrans

"It is noteworthy that this is the first drimane sesquiterpene trimer found in nature"

Liao, D.; Li, H.; Lei, X. *Org. Lett.* **2012**, *14*, 18.



Liu, Y.; Wray, V.; Abdel-Aziz, M. S.; Wang, C.-Y.;
Lai, D.; Proksch, P. *J. Nat. Prod.* **2014**, *77*, 1734.

