



復旦大學
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Synthetic Approaches to Ambiguine Family

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2019.5.10

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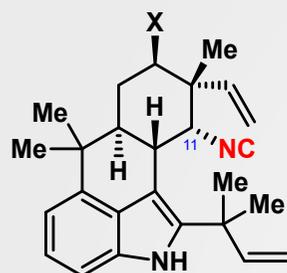


Conclusion

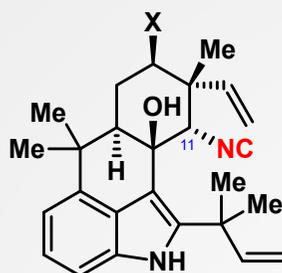


Introduction to ambigunes

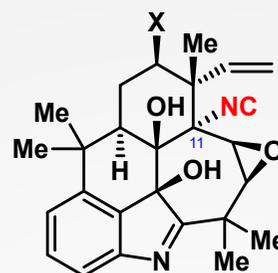
- 17 compounds
- biological activity
- isolation
- structure



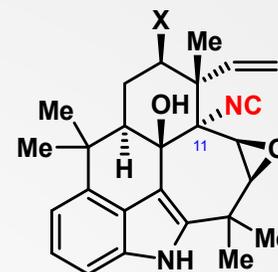
ambiguline A; X=Cl
ambiguline H; X=H



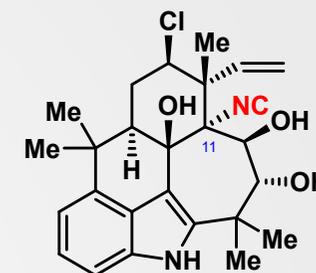
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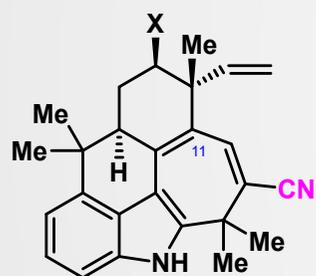
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ambiguline J; X=H



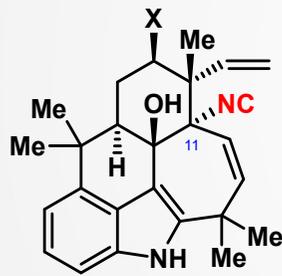
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ambiguline I; X=H



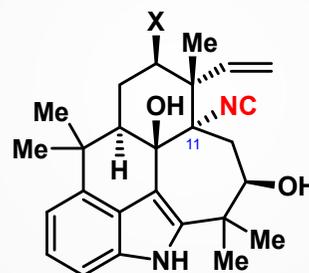
ambiguline F



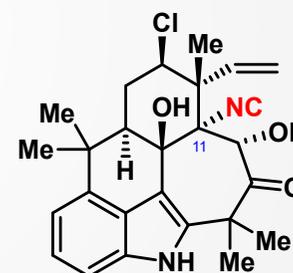
ambiguline G; X=Cl
ambiguline Q; X=H



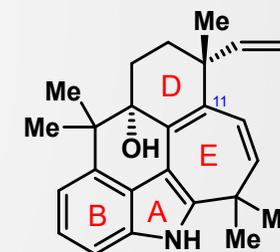
ambiguline K; X=Cl
ambiguline L; X=H



ambiguline M; X=Cl
ambiguline N; X=H



ambiguline O



ambiguline P

The ambiguines were first reported by Smitka and Moore in 1992. Isolated primarily from *Fischerella ambigua*, these alkaloids possess the core structure.

| First Isolated From | Year |
|--|-------------------------|
| <i>Fischerella ambigua</i> (A-F) <i>Hapalosiphon hibernicus</i> (A, E) <i>Westiellopsis prolifica</i> (D, E) | 1992 (Smitka and Moore) |
| <i>Hapalosiphon delicatulus</i> (G) | 1998 (Moore) |
| <i>Fischerella ambigua</i> (H-J) | 2007 (Carmeli) |
| <i>Fischerella ambigua</i> (K-O) | 2009 (Orjala) |
| <i>Fischerella ambigua</i> (P-Q) | 2010 (Orjala) |

Related References:

Smitka, T. A.; Bonjouklian, R.; Doolin, L.; Jones, N. D.; Deeter, J. B.; Yoshida, W. Y.; Prinsep, M. R.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1992**, *57*, 857.

Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1998**, *61*, 1304.

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Mo, S.; Kronic, A.; Chlipala, G.; Orjala, J. *J. Nat. Prod.* **2009**, *72*, 894.

Mo, S.; Kronic, A.; Santarsiero, B. D.; Franzblau, S. G.; Orjala, J. *Phytochemistry* **2010**, *71*, 2116.

目前，研究者只对**ambiguines**进行了初步生物活性研究

| | MIC (mM) | | | | | IC ₅₀ (mM) |
|--------------------|---------------------------|----------------------|---------------------|------------------------|-----------------------|-----------------------|
| | M. tuberculosis 结核分枝杆菌 | B. anthracis 炭疽杆菌 | S. aureus 金色葡萄球菌 | M. smegmatis 耻垢分枝杆菌 | C. albicans 人白色念珠菌 | Vero |
| Ambiguine A | 6.7 | 1.0 | 1.8 | 14.8 | <1.0 | 26.0 |
| Ambiguine B | NT | 3.7 | 10.9 | 27.8 | 1.7 | 58.6 |
| Ambiguine C | 7.0 | 16.1 | 7.4 | 59.6 | <1.0 | 78.3 |
| Ambiguine E | 21.0 | 3.6 | 1.5 | 1.4 | <0.9 | 42.6 |
| Ambiguine F | 61.2 | NT | NT | NT | NT | 57.9 |
| Ambiguine G | 53.7 | >100 | 6.6 | 49.7 | >100 | 40.8 |
| Ambiguine I | 13.1 | >128 | 8.9 | 59.7 | 1.7 | >128 |
| Ambiguine K | 6.6 | 7.4 | 4.6 | 23.7 | <0.9 | 53.2 |
| Ambiguine L | 11.7 | 16.2 | 10.5 | 29.3 | <1.0 | 44.6 |
| Ambiguine M | 7.5 | 28.5 | 4.7 | 25.8 | 1.1 | 79.8 |
| Ambiguine N | 27.1 | 30.9 | 5.5 | 48.8 | <1.0 | 118.4 |
| Ambiguine O | NT | 13.8 | NT | NT | NT | 80.7 |
| Ambiguine P | >100 | NT | >100 | NT | 32.9 | NT |

Related References:

Smitka, T. A.; Bonjouklian, R.; Doolin, L.; Jones, N. D.; Deeter, J. B.; Yoshida, W. Y.; Prinsep, M. R.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1992**, *57*, 857.

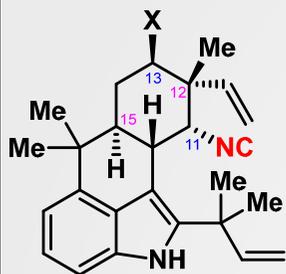
Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1998**, *61*, 1304.

Raveh, A.; Carmeli, S. *J. Nat. Prod.* **2007**, *70*, 196.

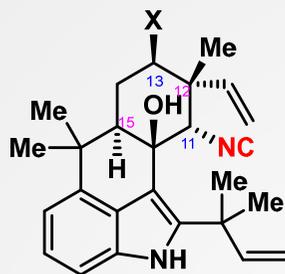
Mo, S.; Kronic, A.; Chlipala, G.; Orjala, J. *J. Nat. Prod.* **2009**, *72*, 894.

Mo, S.; Kronic, A.; Santarsiero, B. D.; Franzblau, S. G.; Orjala, J. *Phytochemistry* **2010**, *71*, 2116.

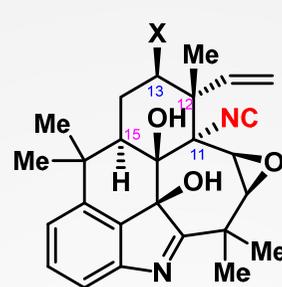
Walton, K.; Gantar, M.; Gibbs, P. D. L.; Schmale, M. C.; Berry, J. P. *Toxins* **2014**, *6*, 3568.



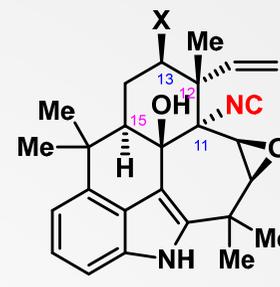
ambiguline A; X=Cl
ambiguline H; X=H



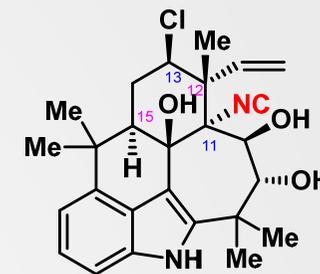
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ambiguline C; X=H



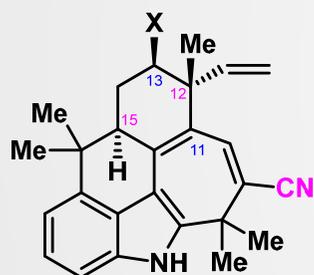
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ambiguline J; X=H



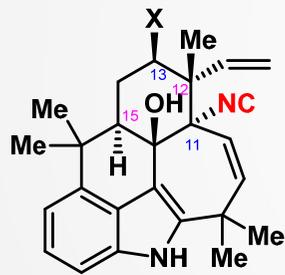
ambiguline E; X=Cl
ambiguline I; X=H



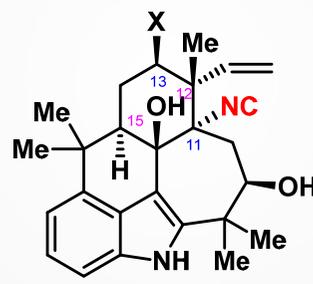
ambiguline F



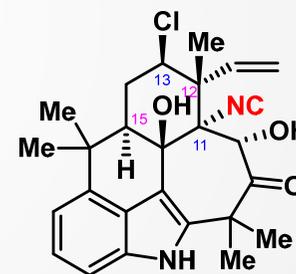
ambiguline G; X=Cl
ambiguline Q; X=H



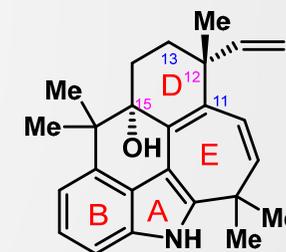
ambiguline K; X=Cl
ambiguline L; X=H



ambiguline M; X=Cl
ambiguline N; X=H



ambiguline O

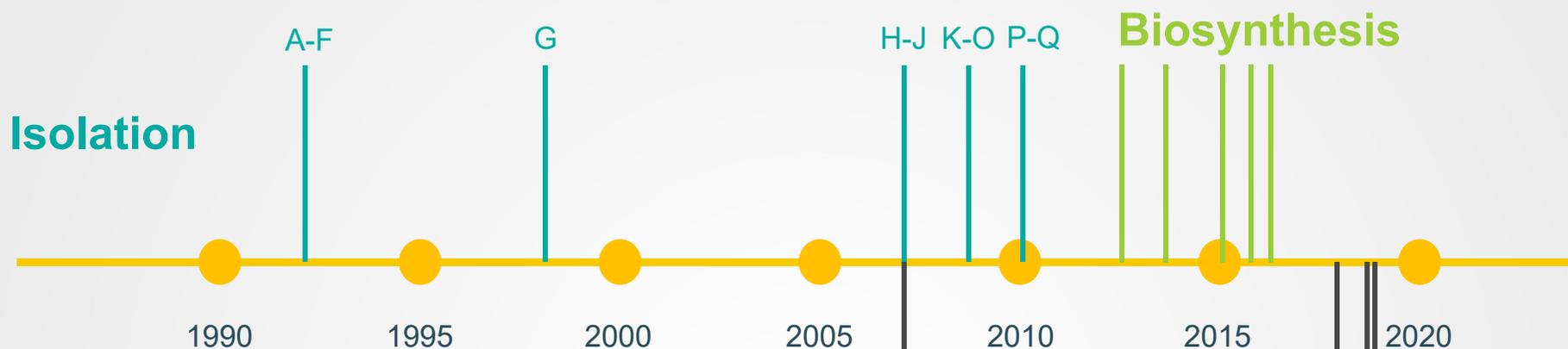


ambiguline P

- 4-rings (A, B, C, H) or 5-rings, C11-NC, C12-vinyl, C12-methyl
- a “reverse prenyl” group at the indole C-2 position (tetracyclic ambigulines) OR seven-membered E-ring (pentacyclic ambigulines)
- the same relative stereochemical configurations at C-10, C-11 (when C10, C-11 is sp³ hybridized), C-12, C-13 (when C-13 bears a chlorine) and C-15
- Dimethyl at ring B C-16 position

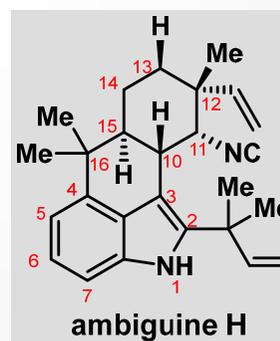


Total synthesis of ambiguines



Total Synthesis:

Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.
 Maimone, T. J.; Ishihara, Y.; Baran, P. S. *Tetrahedron* **2015**, *71*, 3652.
 Sahu, S.; Das, B.; Maji, M. S. *Org. Lett.* **2018**, *20*, 6485.
 Johnson, R. E.; Ree, H.; Hartmann, M.; Lang, L.; Sawano, S.; Sarpong, R. *J. Am. Chem. Soc.* **2019**, *141*, 2233.
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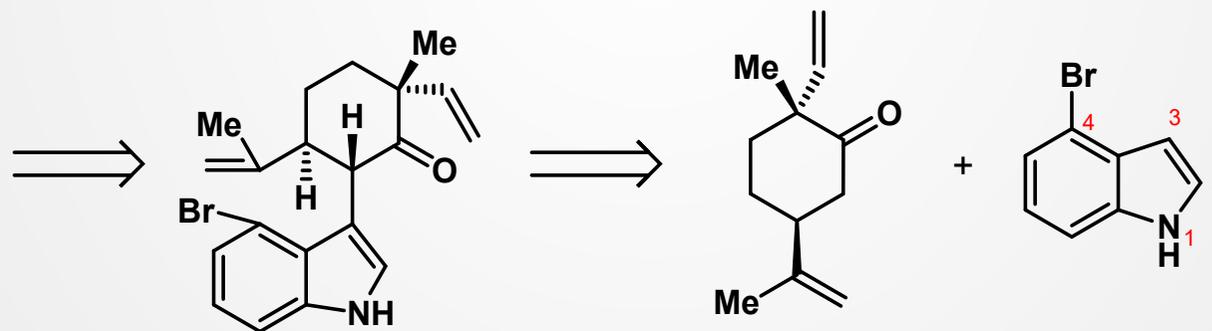
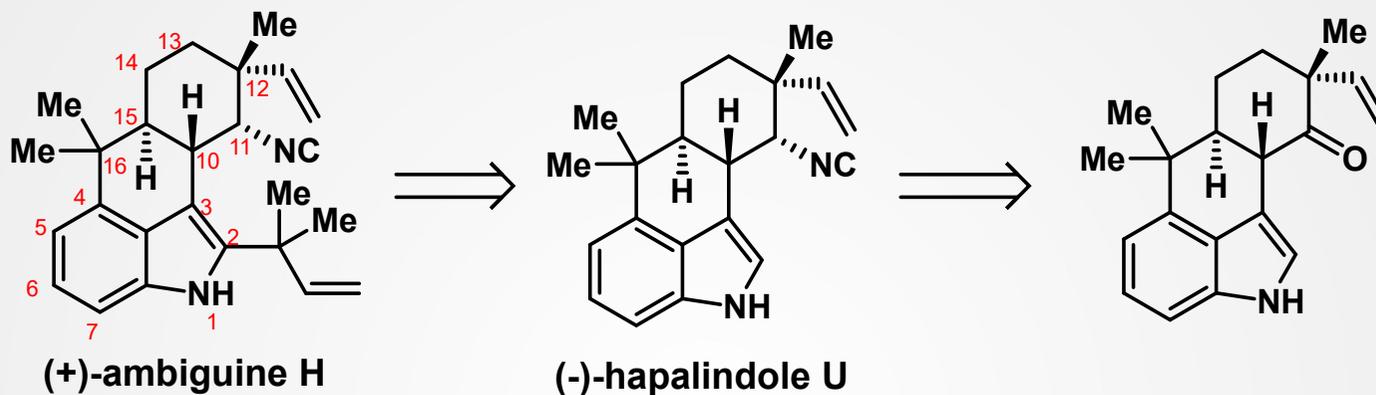
Total Synthesis



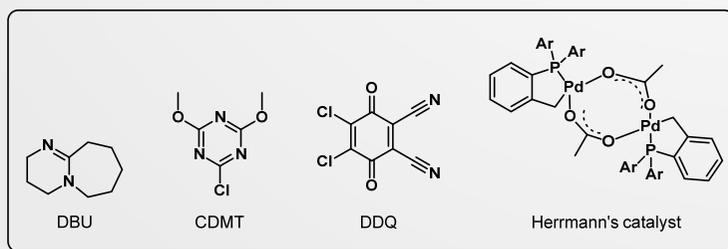
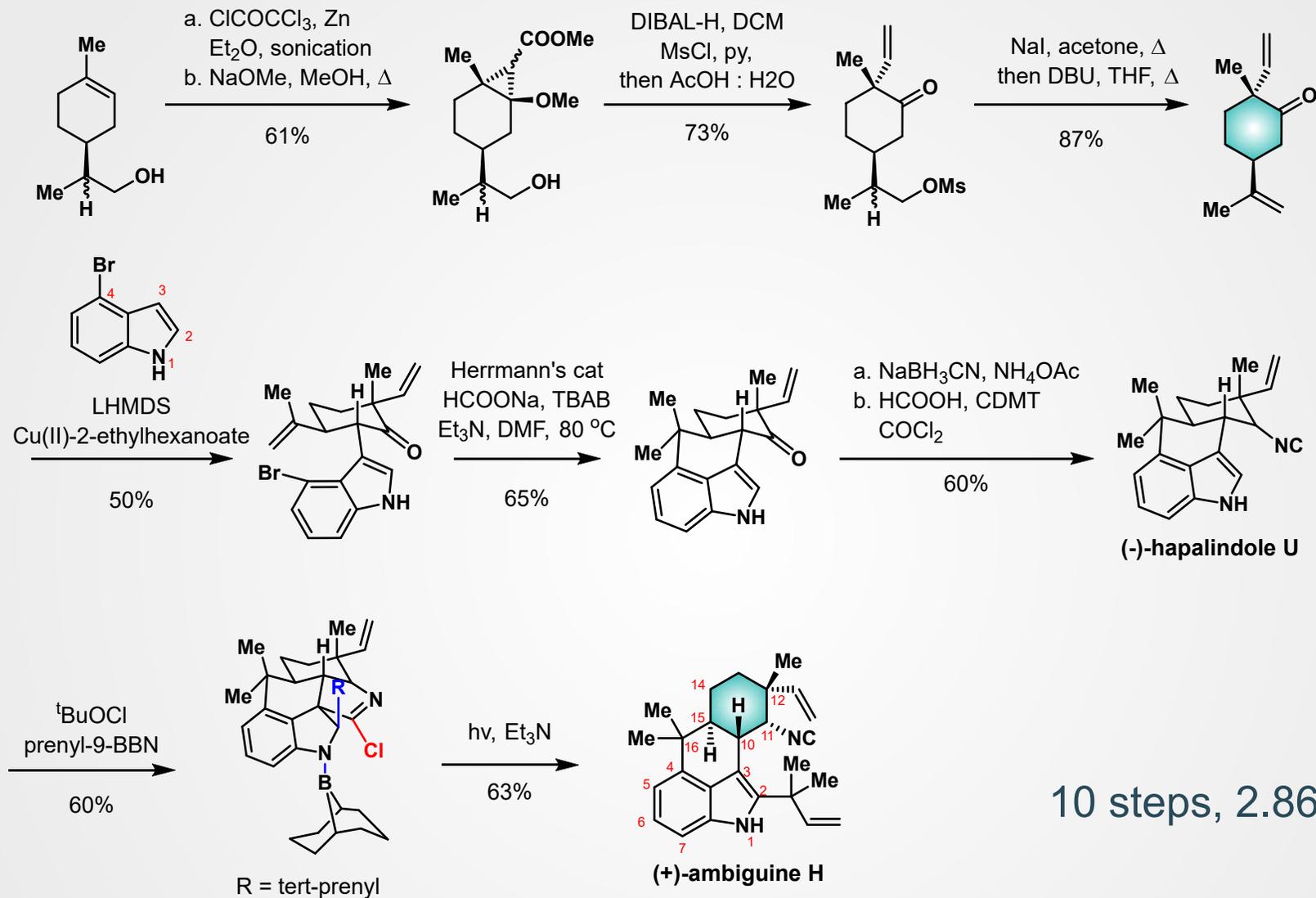
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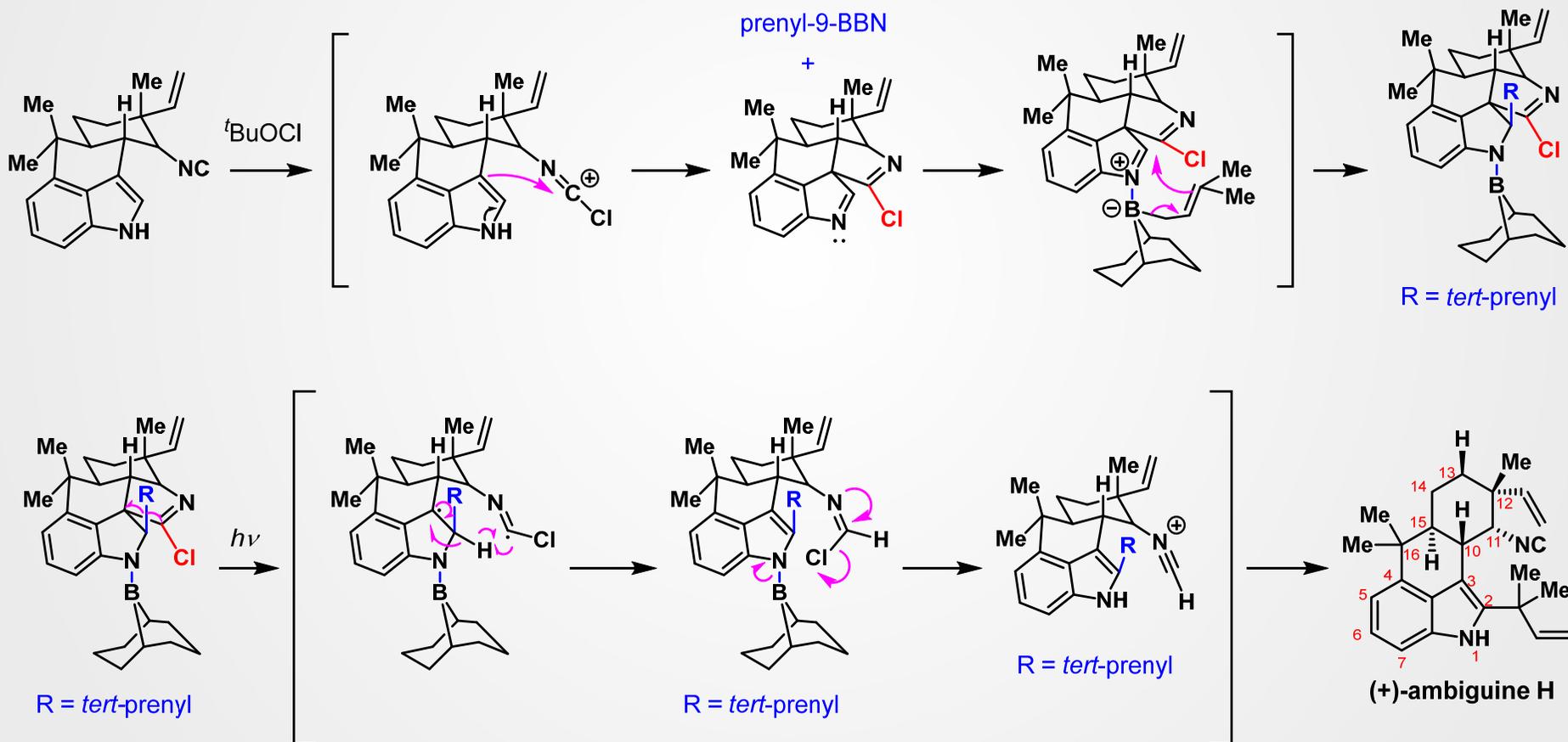
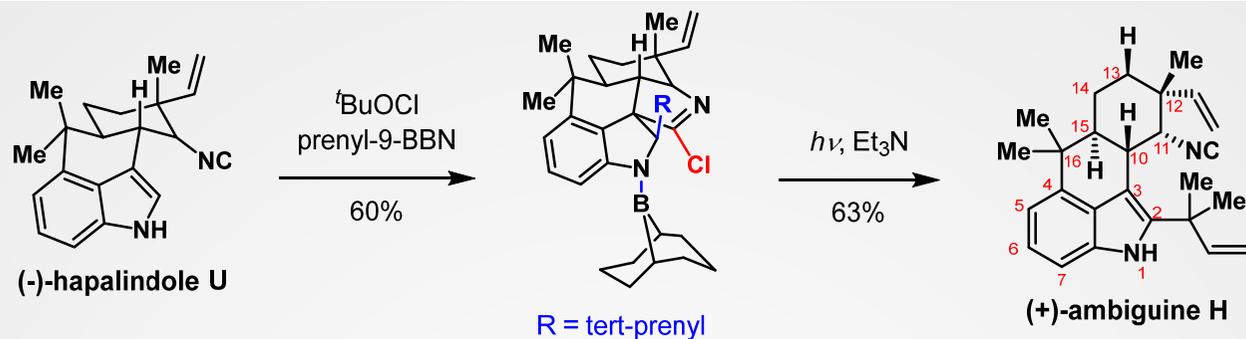
Hillwig, M. L. ; Zhu, Q.; Liu, X. *ACS Chem. Biol.* **2014**, *9*, 372.
 Hillwig, M. L. ; Fuhrman, H. A.; Ittiamornkul, K.; Sevco, T. J.; Kwak, D. H.; Liu, X. *ChemBioChem* **2014**, *15*, 665.
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 Micallef, M.L.; Sharma, D.; Bunn, B.M.; Gerwick, L.; Viswanathan, R.; Moffitt, M.C. *BMC Microbiology*, **2014**, *14*, 213.
 Li, S.; Lowell, A. N.; Yu, F.; Raveh, A.; Newmister, S. A.; Bair, N.; Schaub, J. M.; Williams, R. M.; Sherman, D. H. *J. Am. Chem. Soc.* **2015**, *137*, 15366.
 Liu, X.; Hillwig, M. L.; Koharudin, L. I. M.; Gronenborn, A. M. *Chem. Commun.* **2016**, *52*, 1737.
 Hillwig, M. L. ; Zhu, Q.; Ittiamornkul, K.; Liu, X. *Angew. Chem. Int. Ed.* **2016**, *55*, 5780.

Baran's Retrosynthetic Analysis of (+)-Ambiguine H



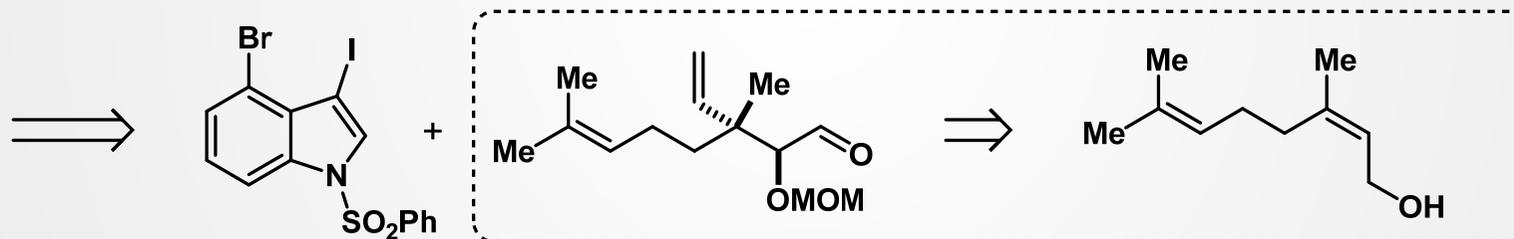
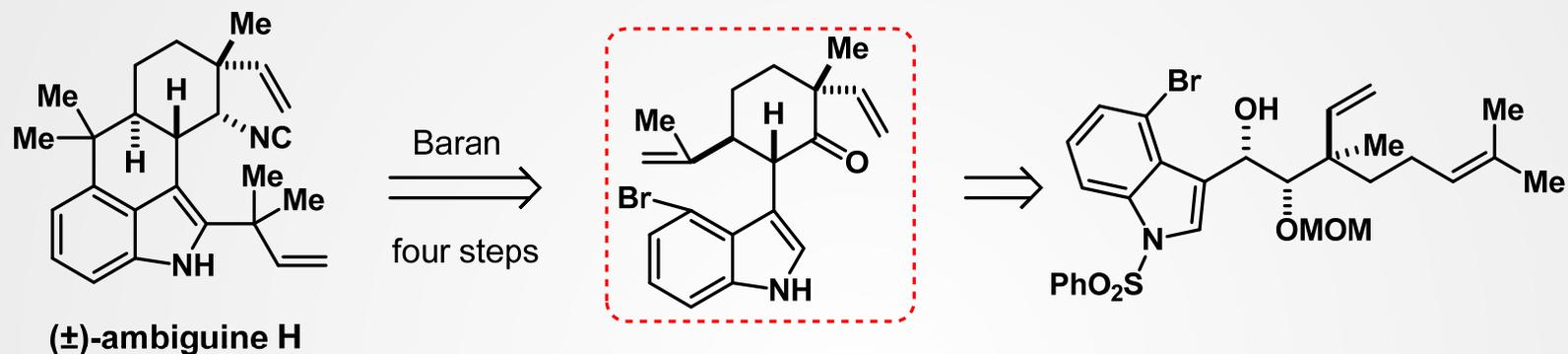
- Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450.
Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394.
Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.
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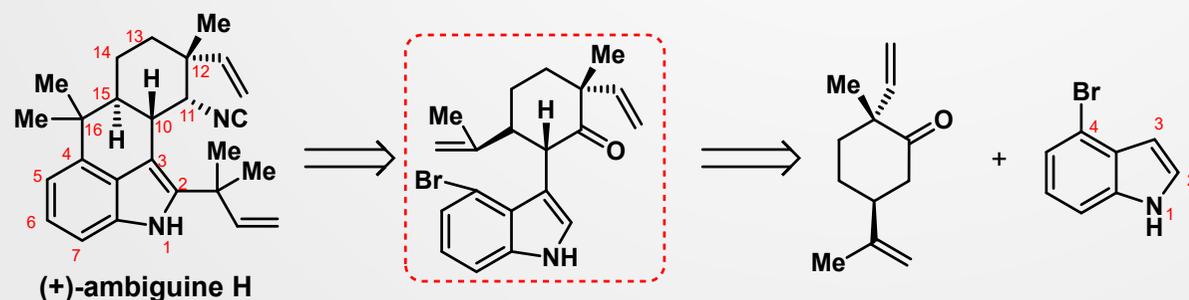


Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.

Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanth, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964.

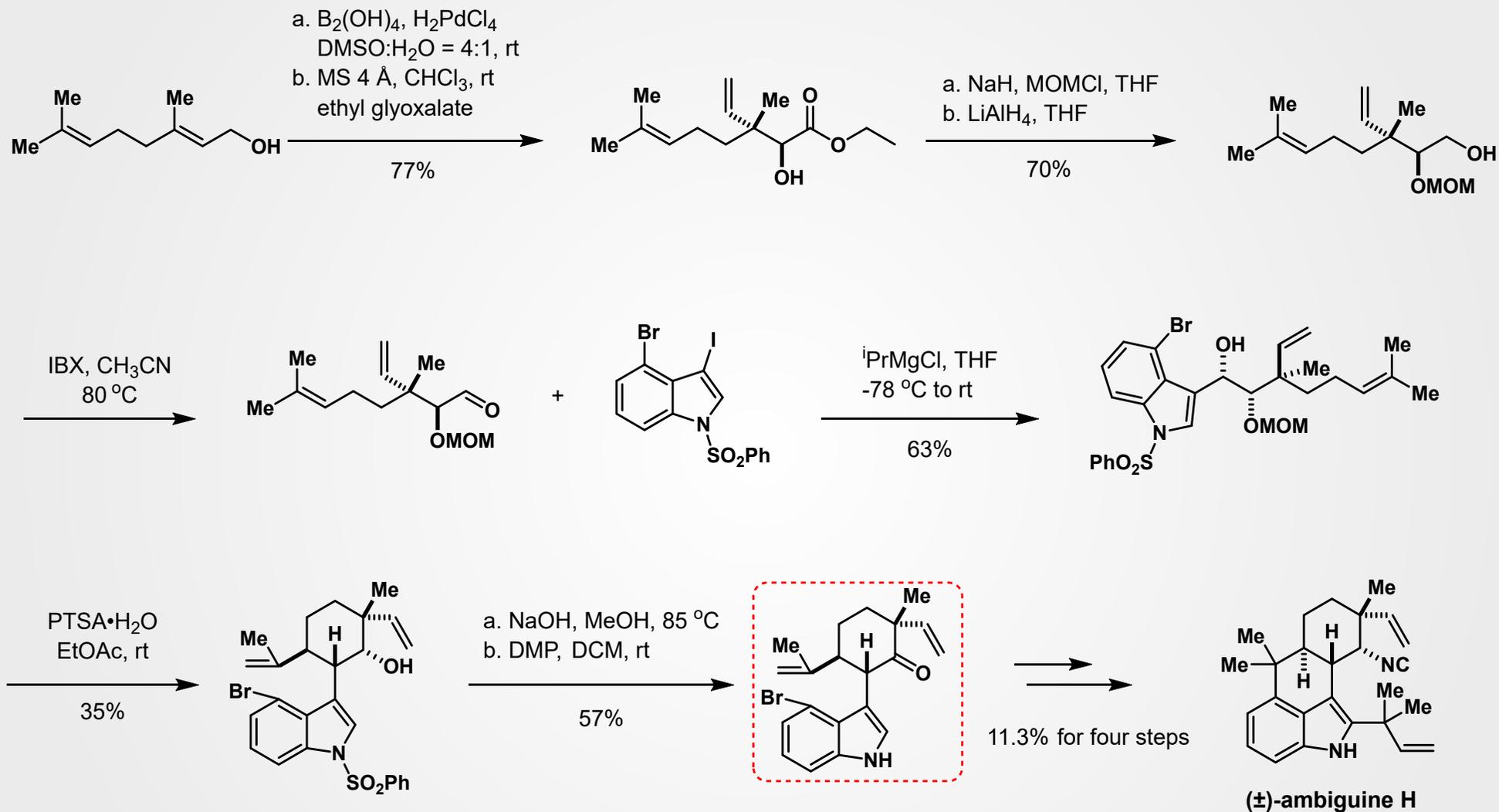
Maji's Retrosynthetic Analysis of (\pm)-Ambiguine H

Baran's Retrosynthetic Analysis of (+)-Ambiguine H

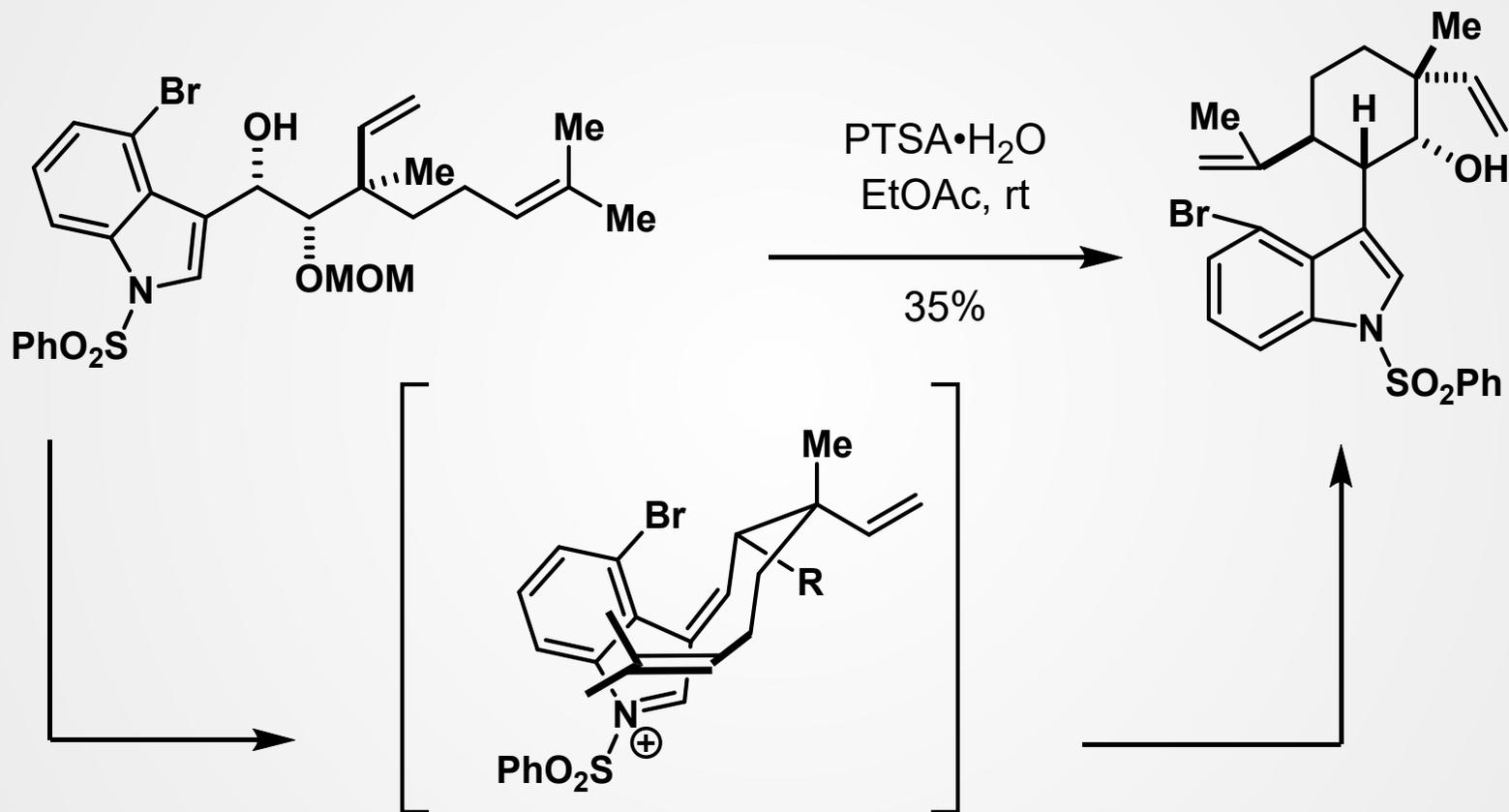


Sahu, S.; Das, B.; Maji, M. S. *Org. Lett.* **2018**, *20*, 6485.

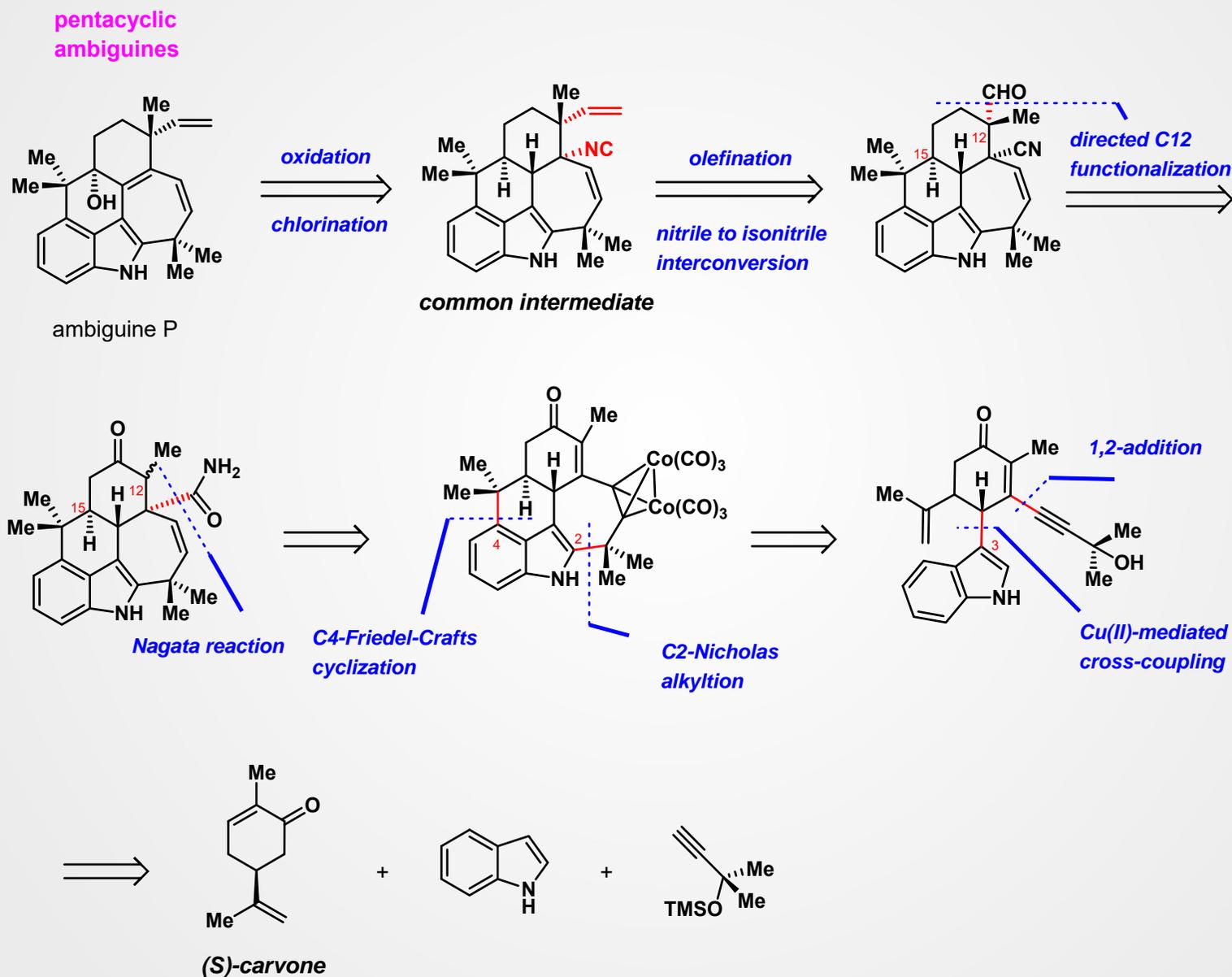
Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.

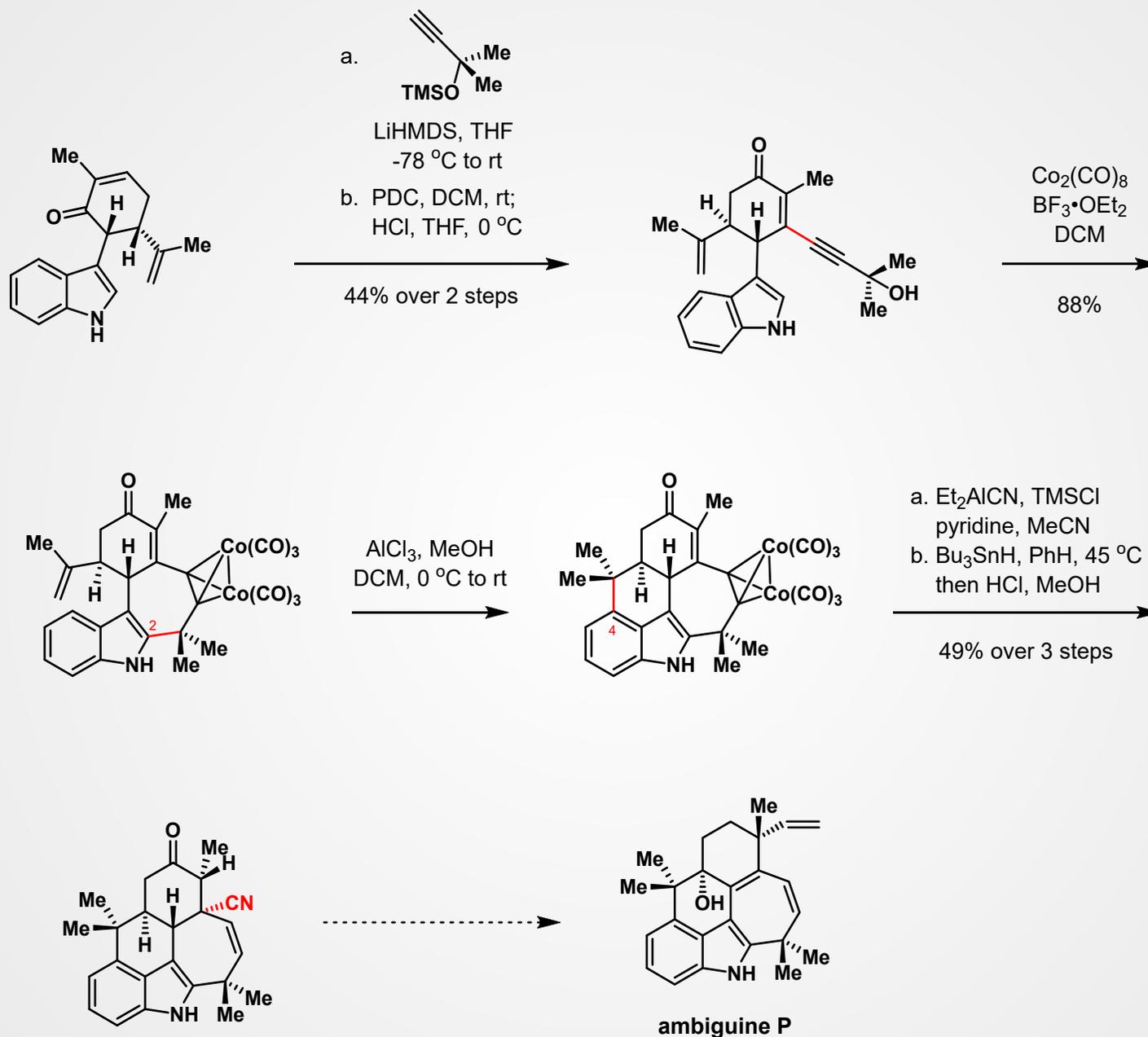


13 steps, 0.77% yield

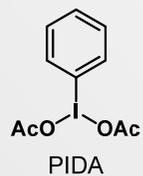
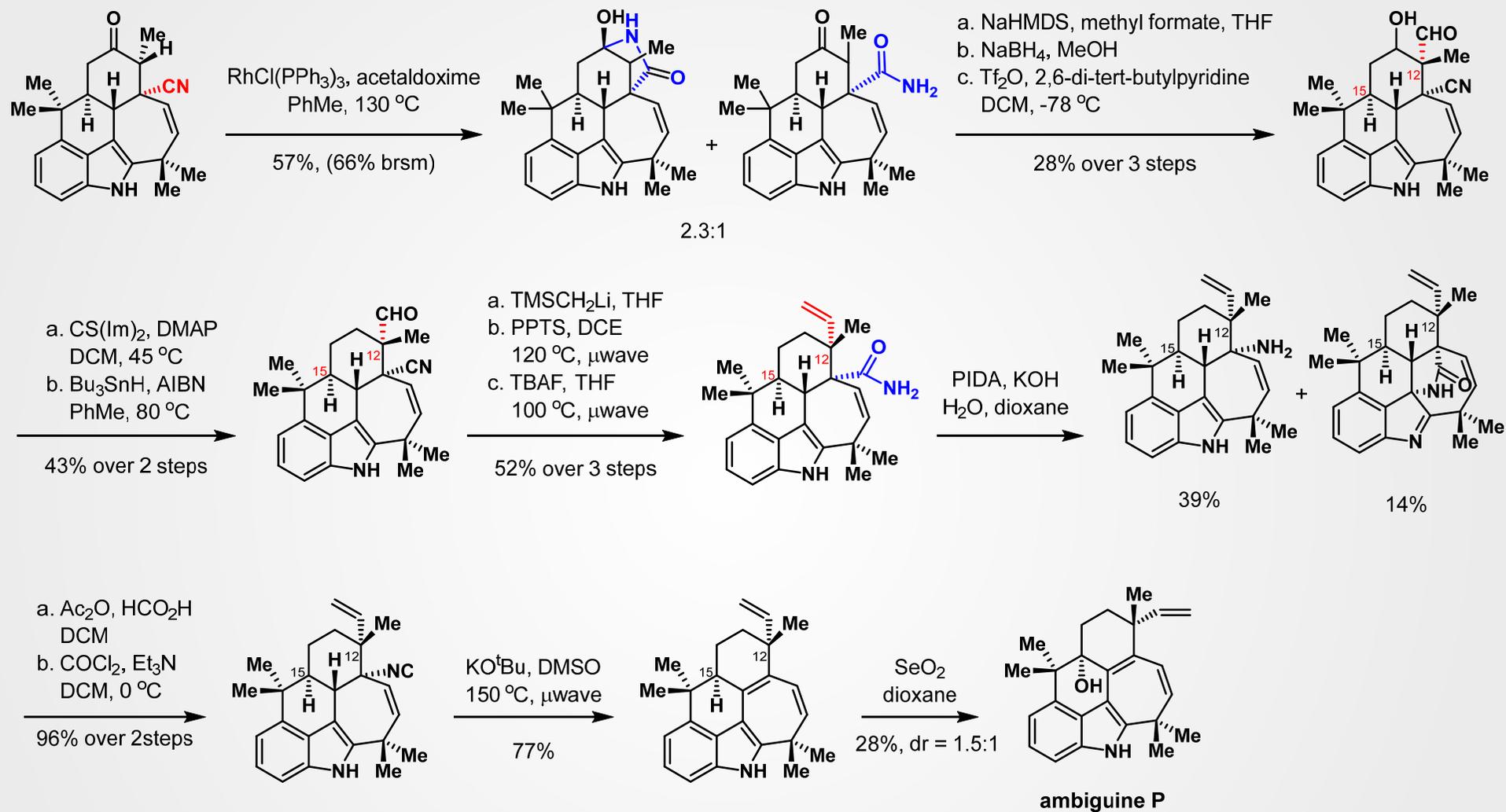


Sarpong's Retrosynthetic Analysis of (-)-Ambiguine P



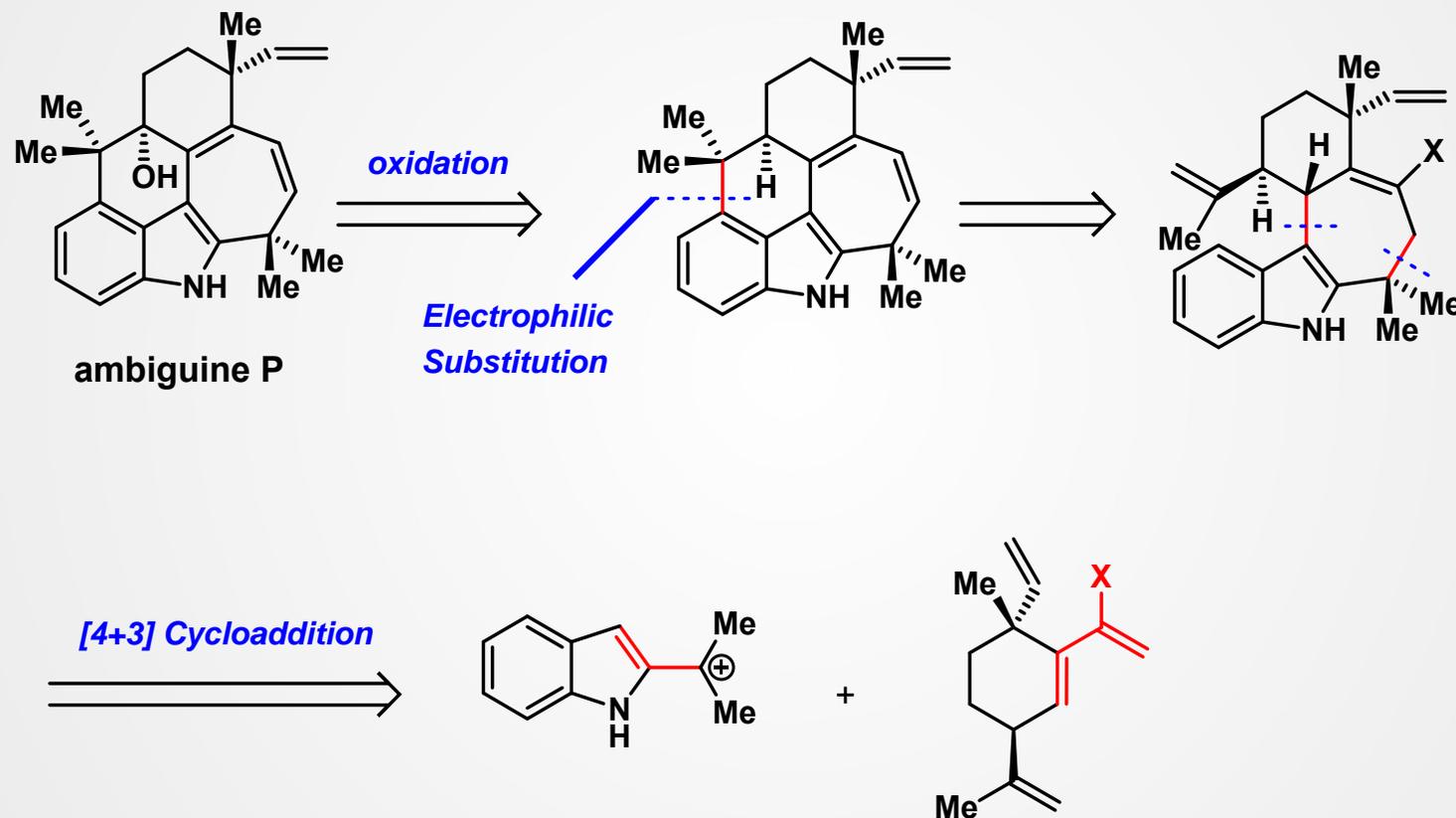


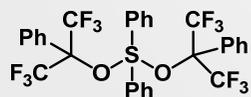
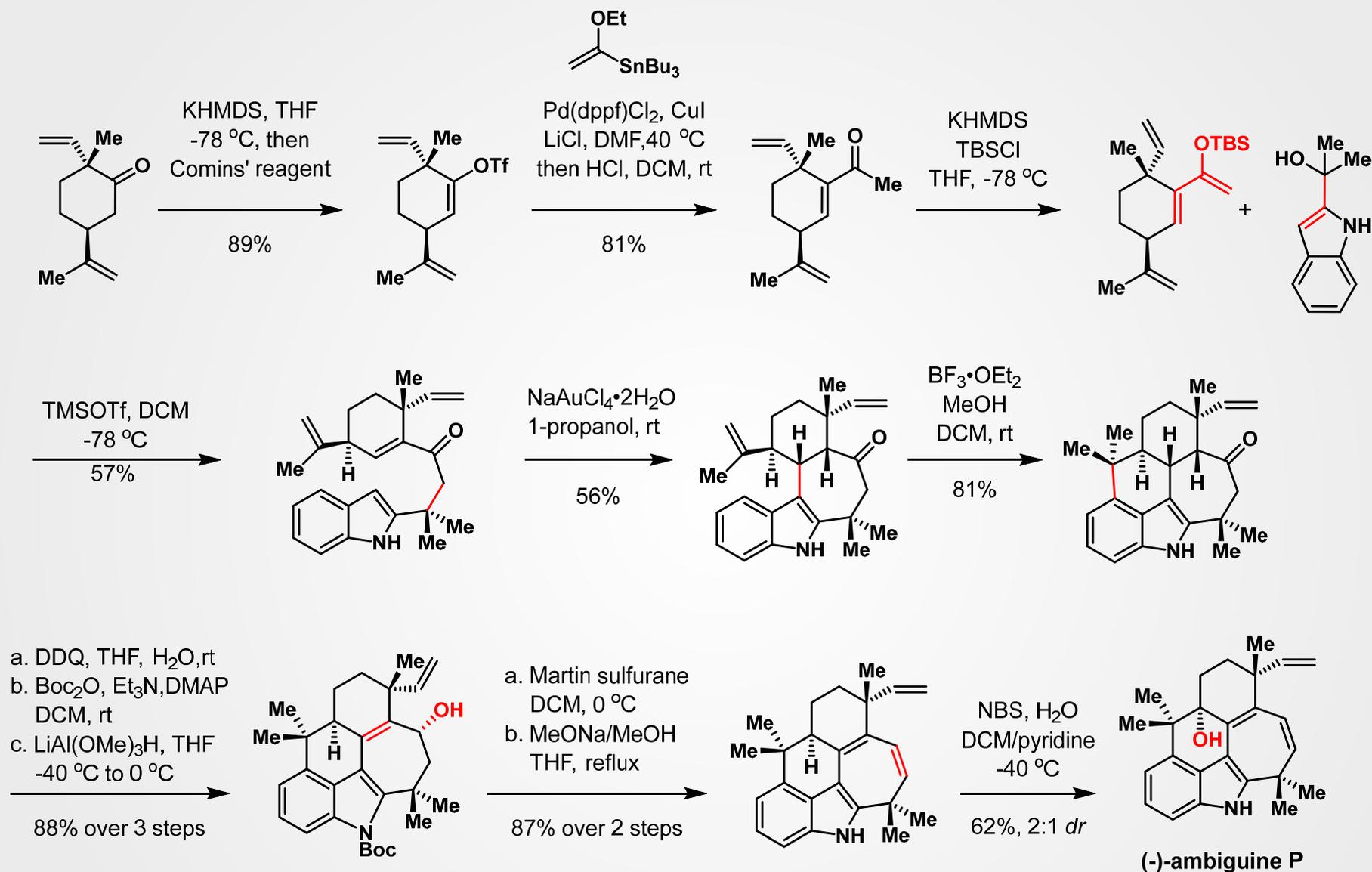
PDC: pyridinium dichromate



22 steps, 0.02% yield

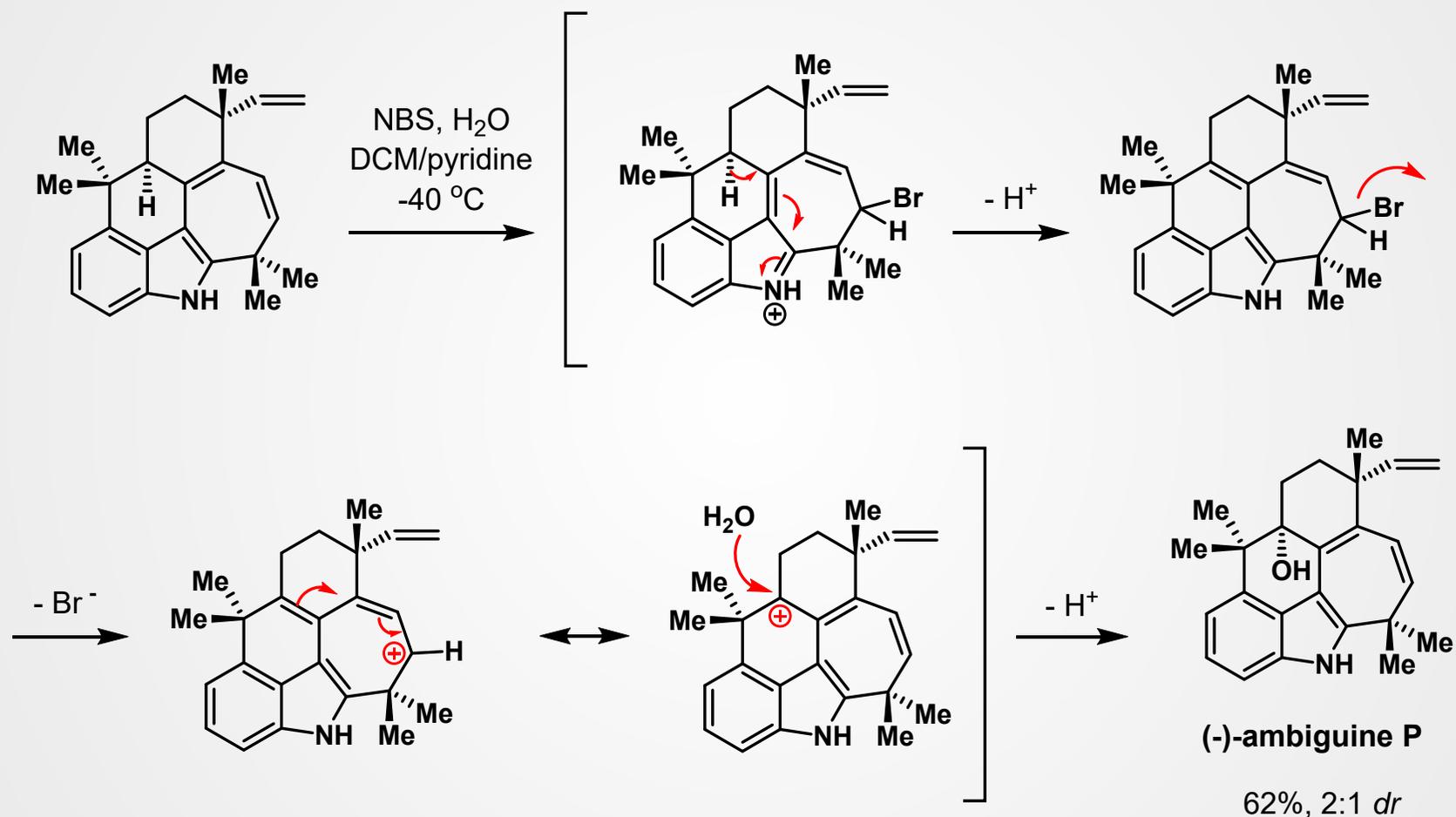
Rawal's Retrosynthetic Analysis of (-)-Ambiguine P





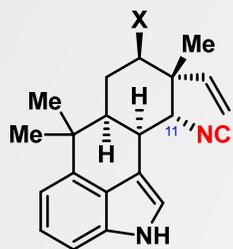
Martin's sulfurane

16 steps, 2.29% yield

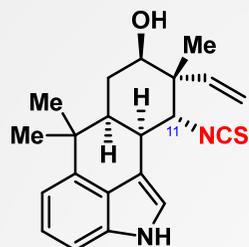




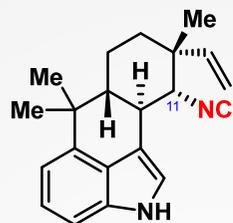
Construction of core skeleton



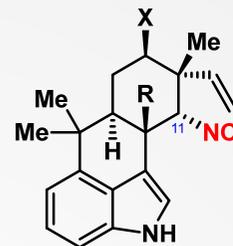
hapalindole J: X=H
hapalindole A: X=Cl



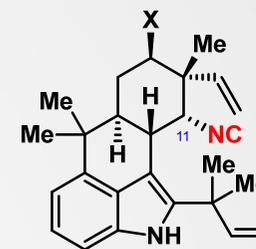
hapalindole O



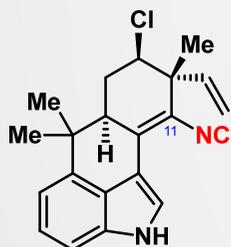
hapalindole H



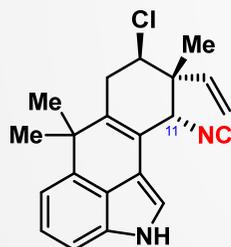
hapalindole G: X=Cl, R=H
hapalindole U: X=H, R=H
hapalindole V: X=Cl, R=OH



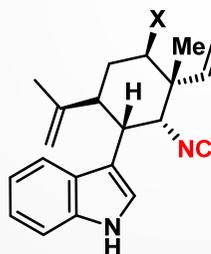
ambiguiene A: X=Cl
ambiguiene H: X=H



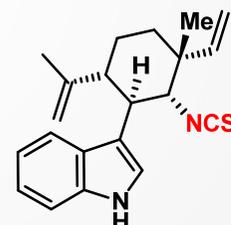
hapalindole I



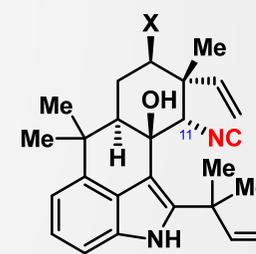
hapalindole K



hapalindole C: X=H
hapalindole E: X=Cl



hapalindole Q



ambiguiene B: X=Cl
ambiguiene C: X=H

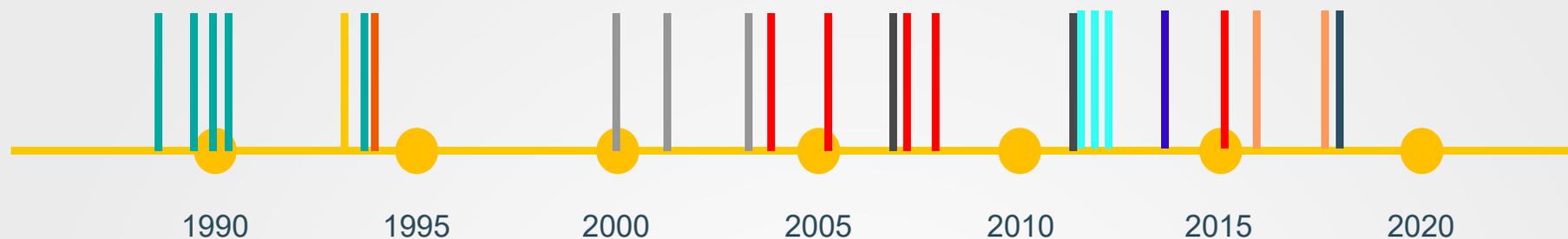
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Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456.

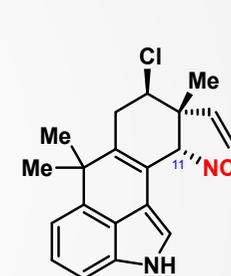
Chang, C. W. *J. Prog. Chem. Org. Nat. Prod.* **2000**, *80*, 186.

Moore, R. E.; Cheuk, C.; Yang, X. Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036.

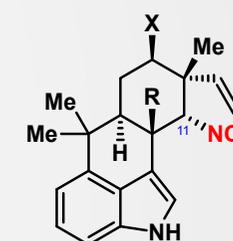
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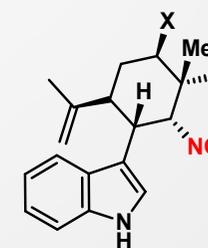
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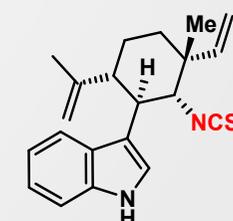
hapalindole K



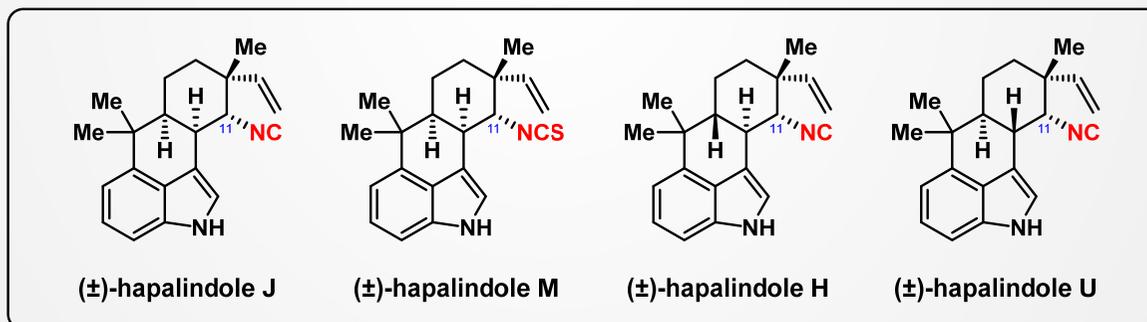
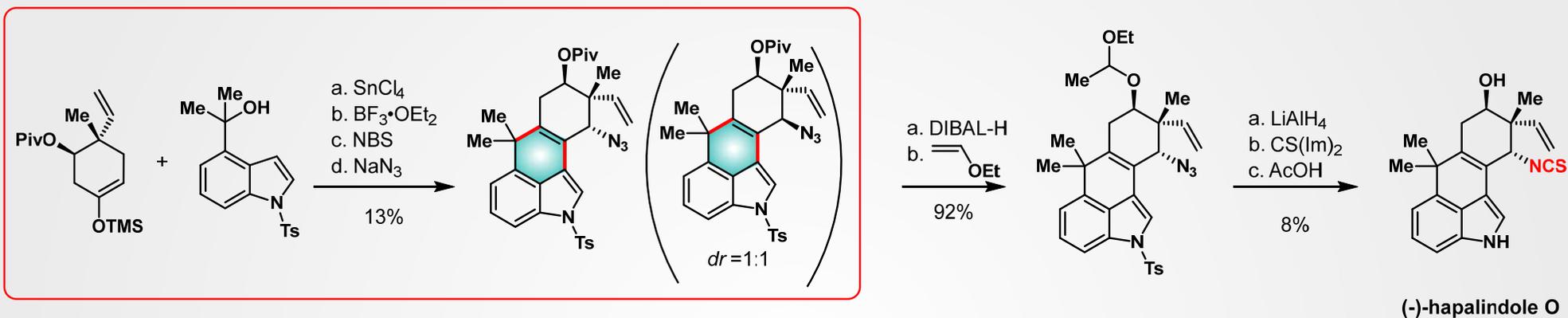
hapalindole G: X=Cl, R=H
 hapalindole U: X=H, R=H
 hapalindole V: X=Cl, R=OH



hapalindole C: X=H
 hapalindole E: X=Cl



hapalindole Q



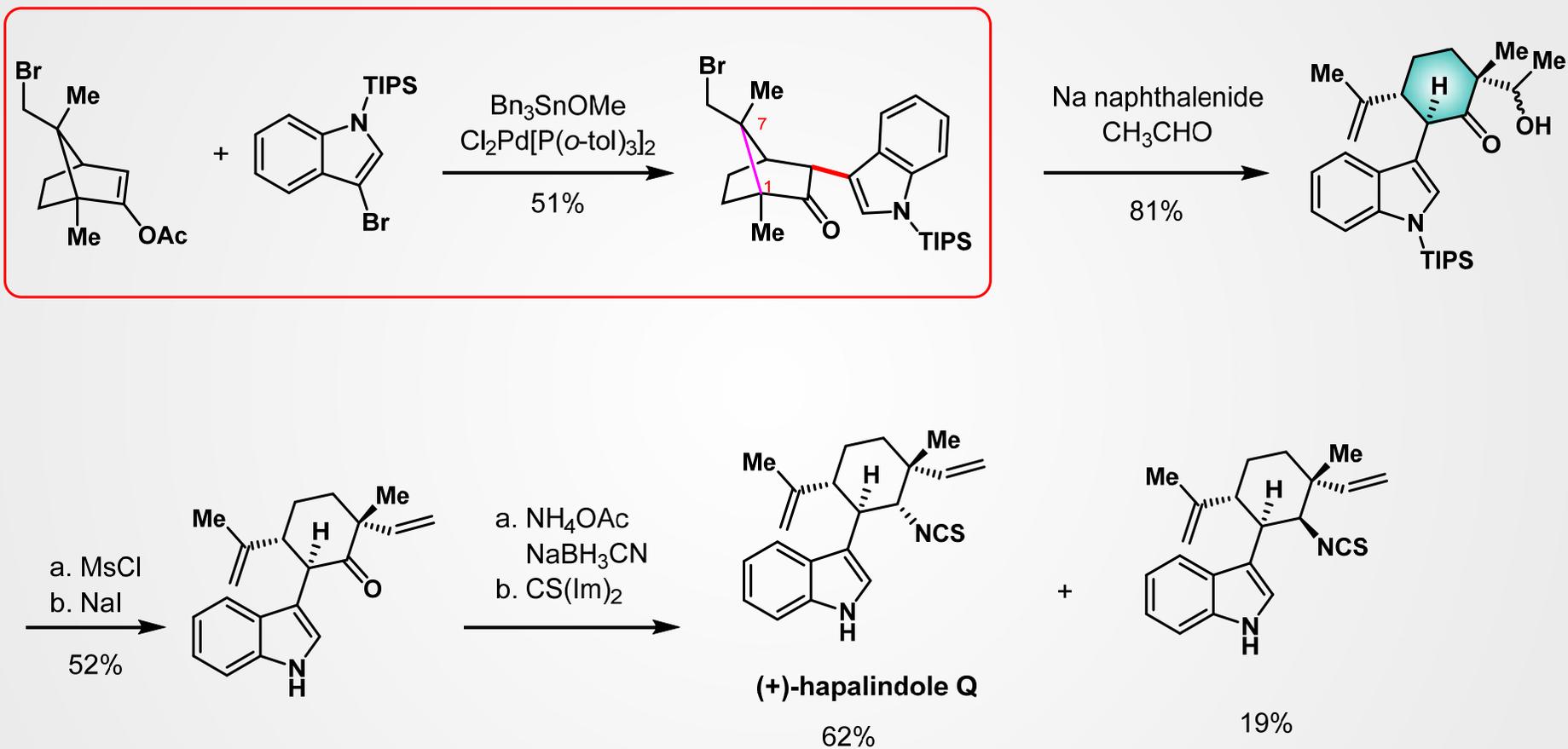
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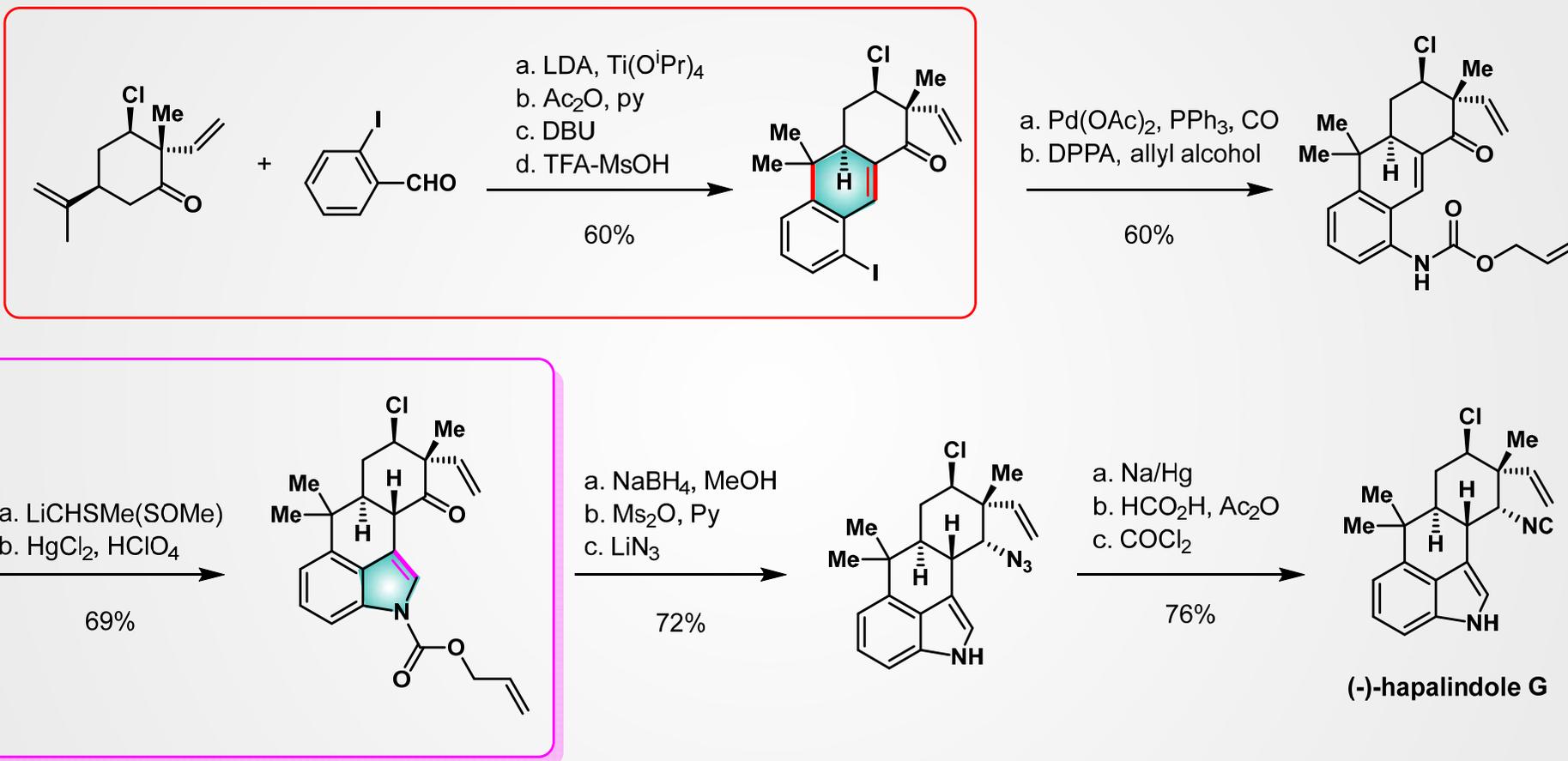
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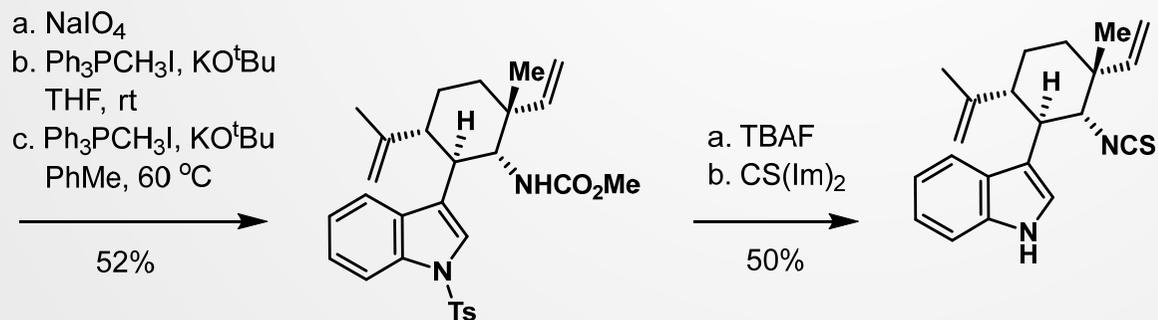
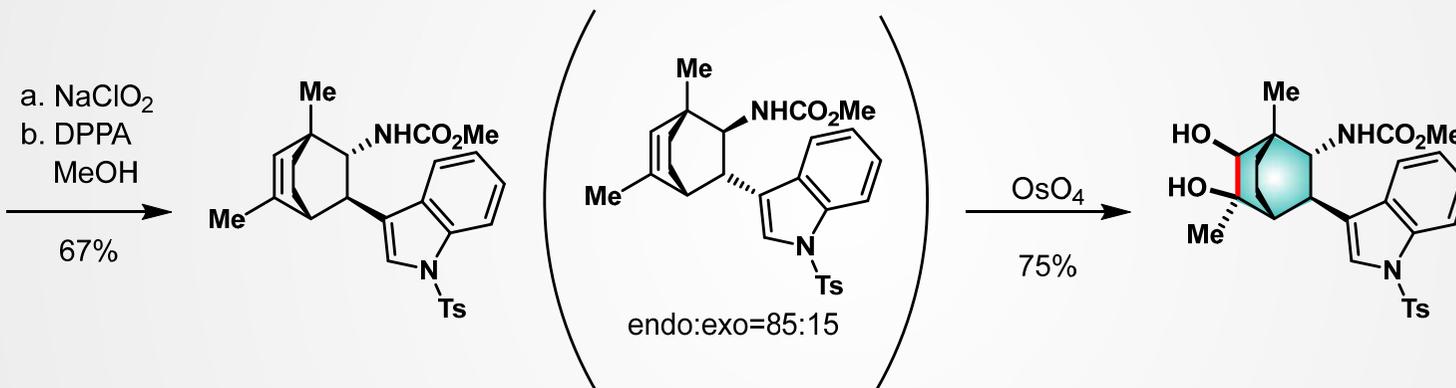
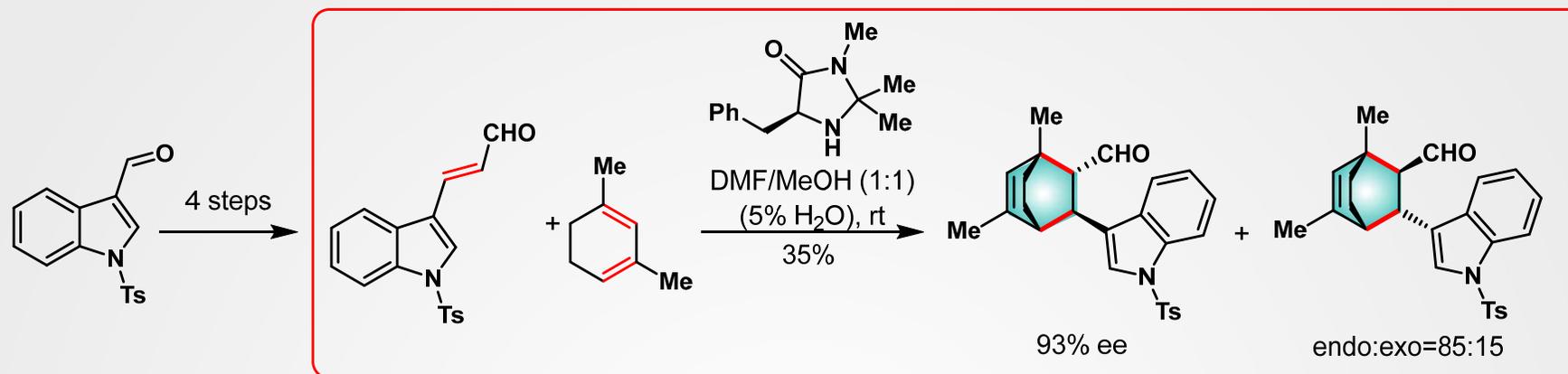
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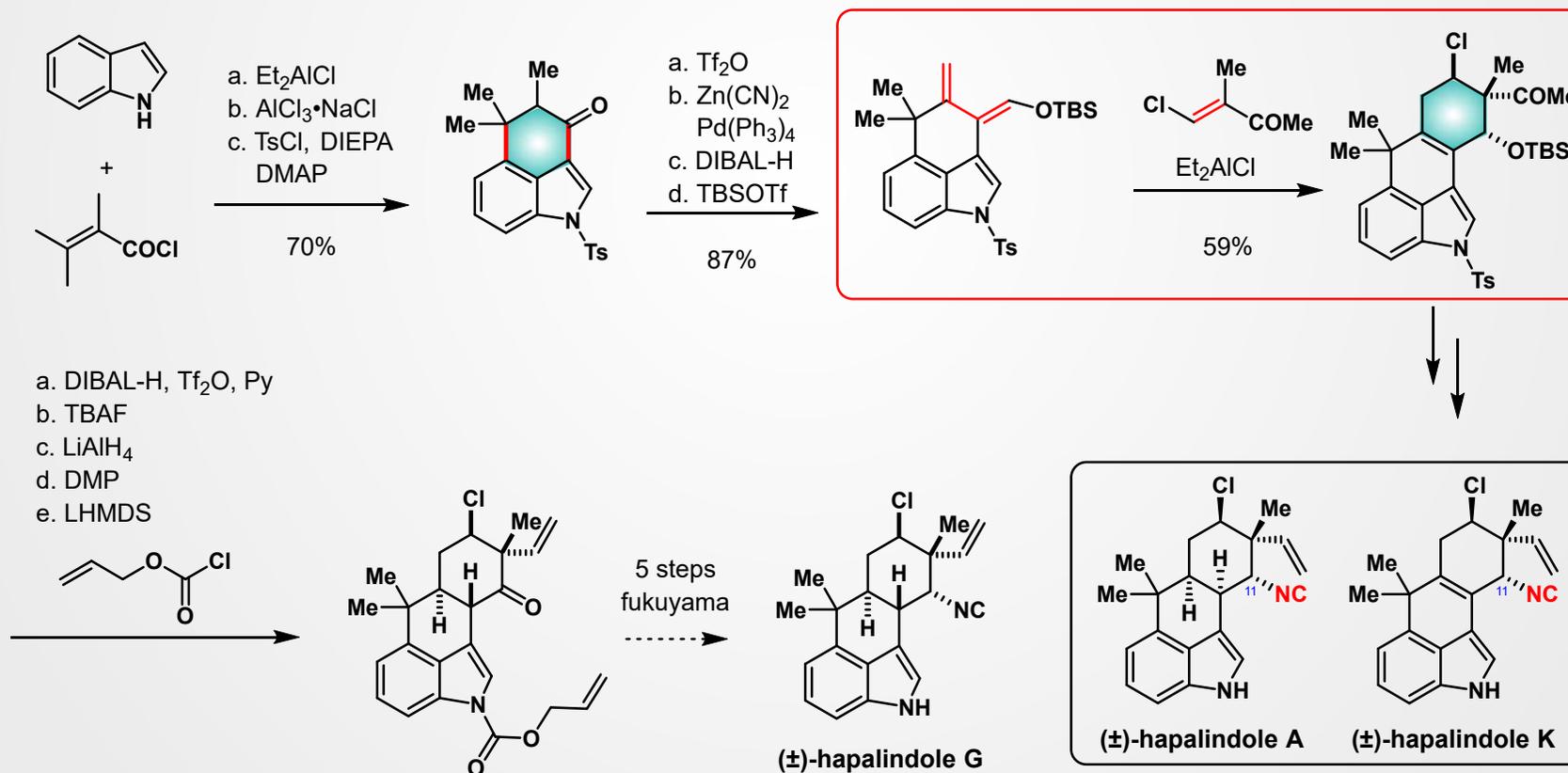
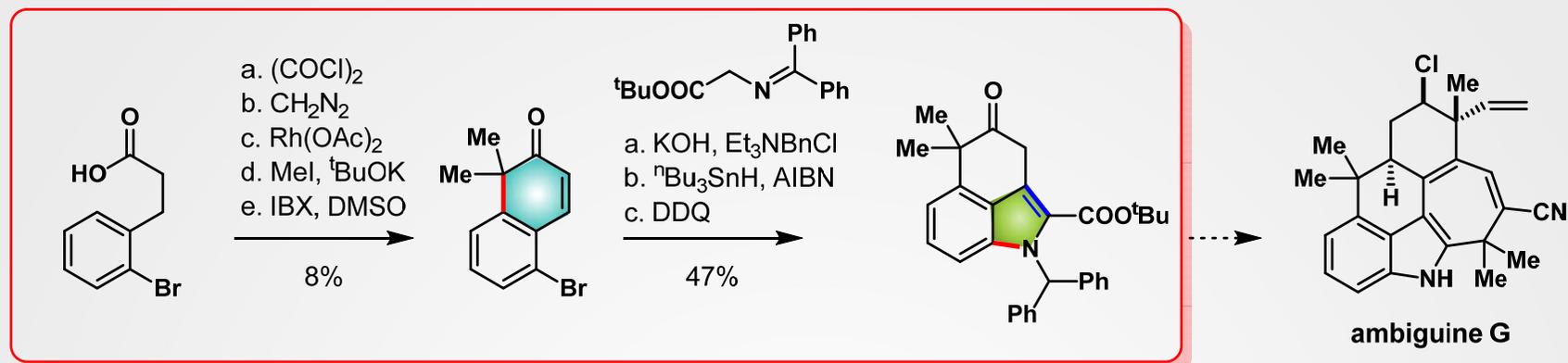
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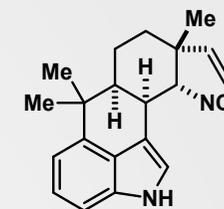
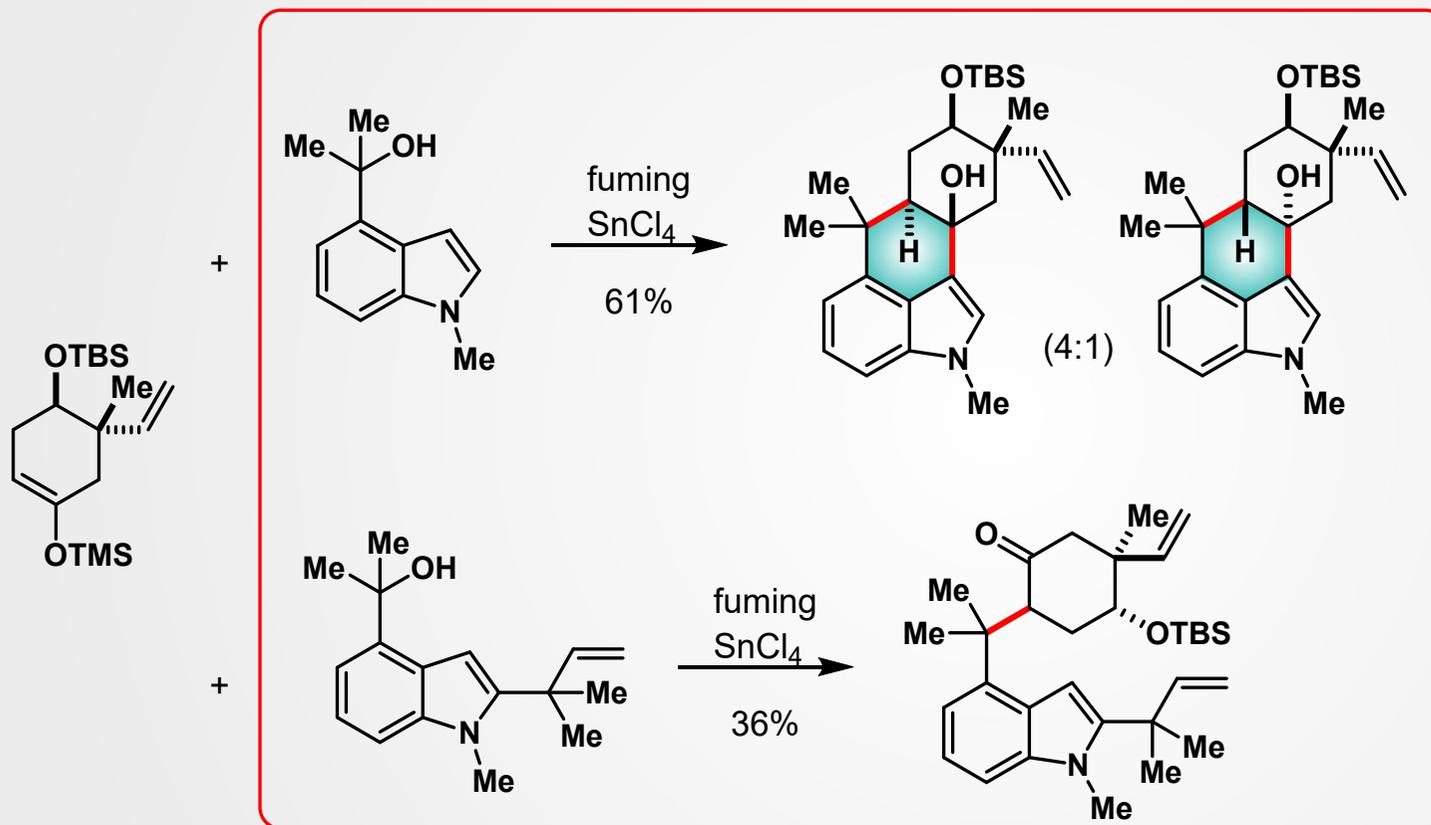
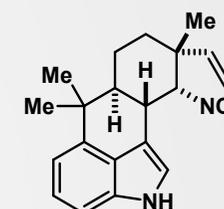
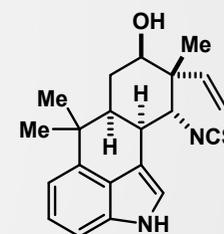
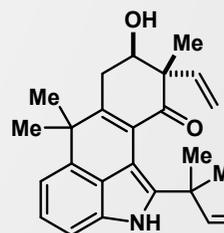


**(+)-hapalindole Q**Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2000**, 2, 3517.Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2001**, 3, 3189.Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, 125, 14120.



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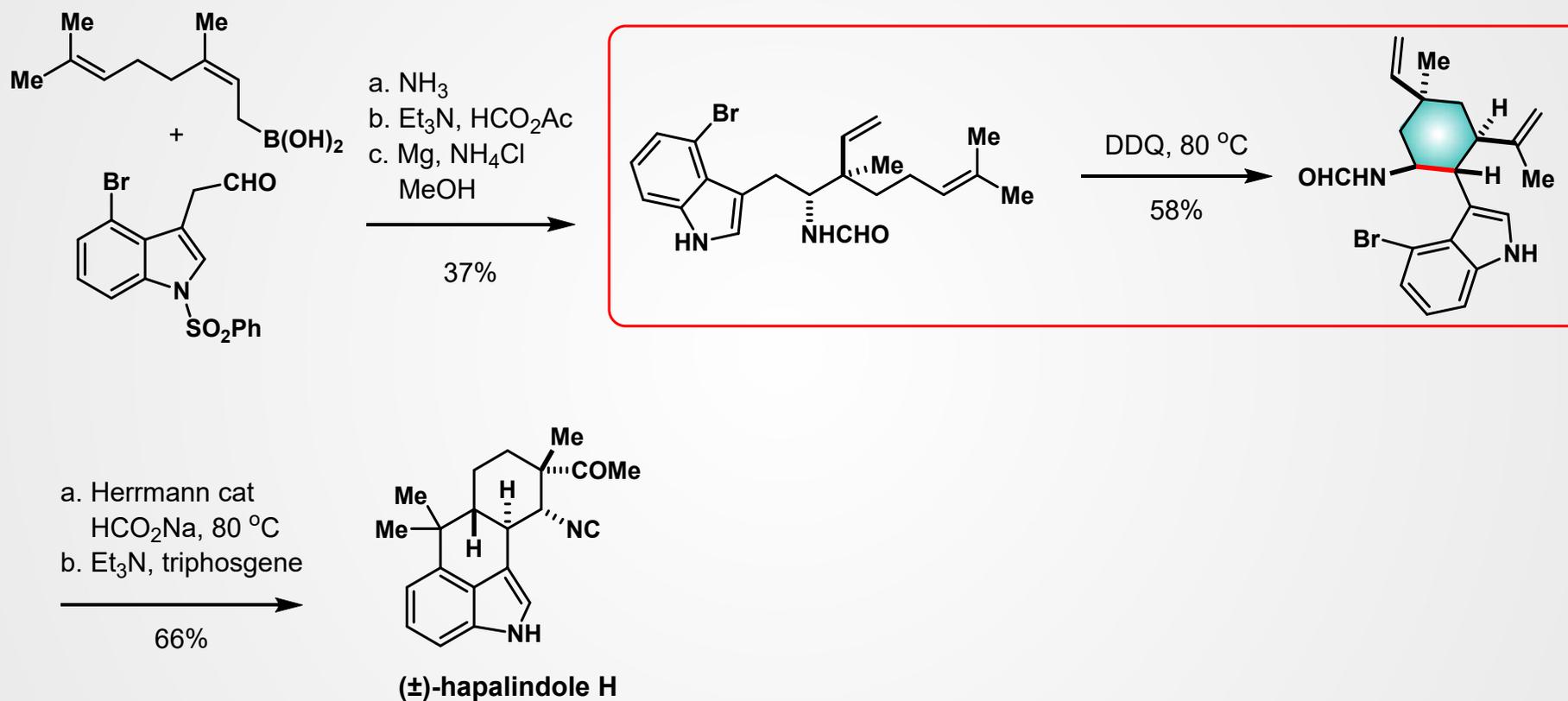
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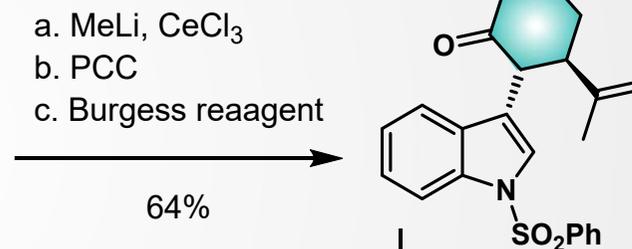
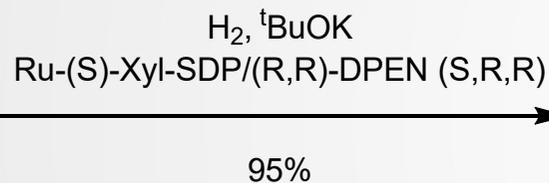
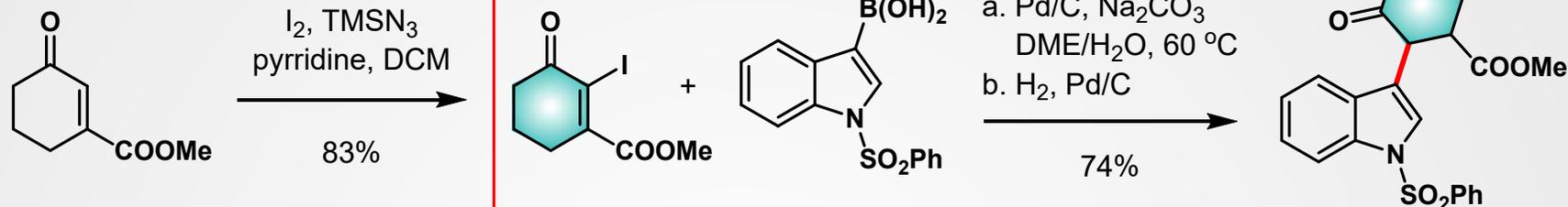
(\pm)-hapalindole J(\pm)-hapalindole U(\pm)-hapalindole Othe core skeleton of
(\pm)-ambiguine A

Rafferty, R. J.; Williams, R. M. *Tetrahedron Lett.* **2011**, 52, 2037.

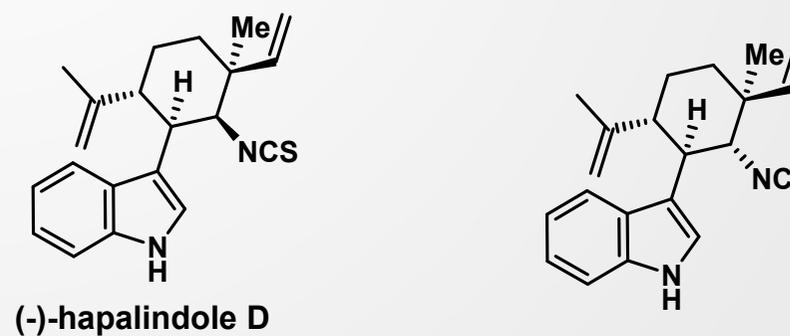
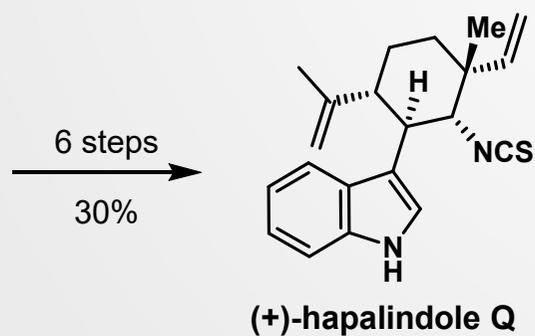
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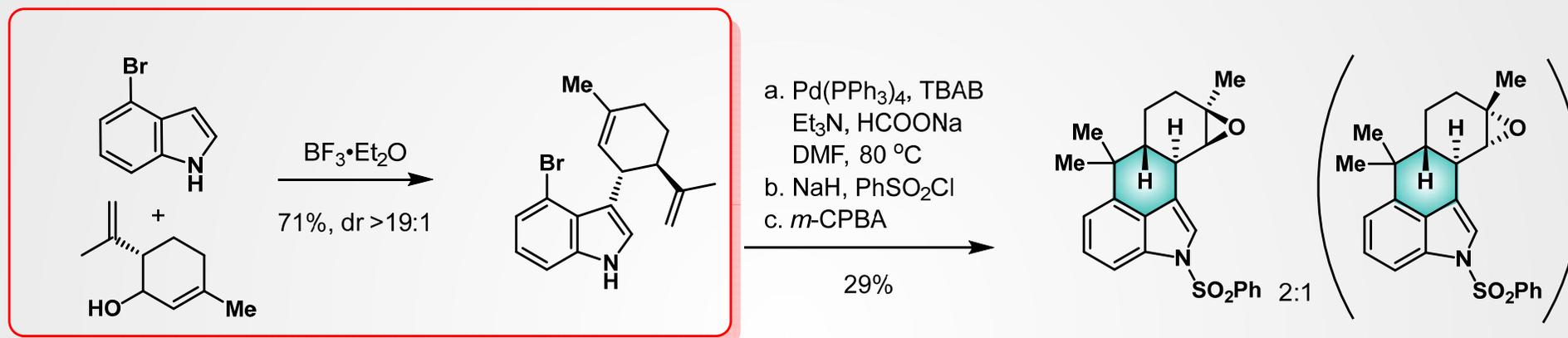
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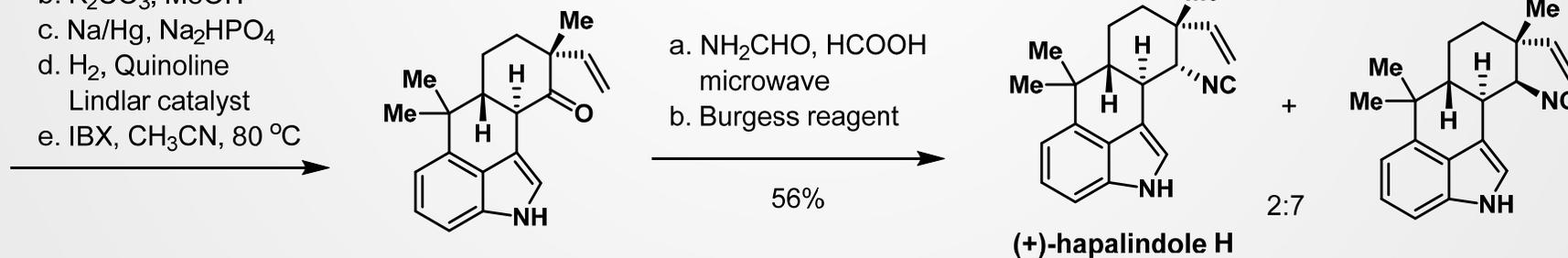
8 steps, 6% 7 steps, 15%





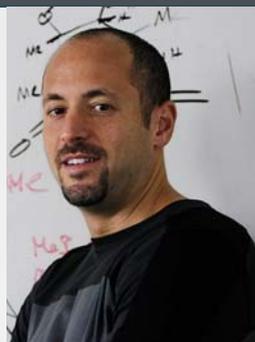
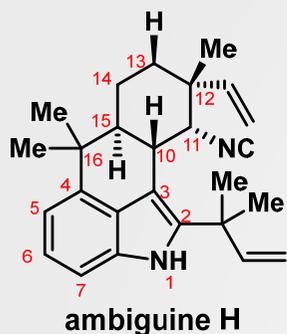
≡—TMS

- nBuLi, AlMe₃
BF₃·Et₂O
- K₂CO₃, MeOH
- Na/Hg, Na₂HPO₄
- H₂, Quinoline
Lindlar catalyst
- IBX, CH₃CN, 80 °C





Conclusion



Baran: **10 steps, 2.86% yield**

without using protecting groups

- ✓ a Cu-mediated coupling reaction
- ✓ Reductive Heck cross coupling
- ✓ Danishefsky protocol



Maji: **13 steps, 0.77% yield**

racemic

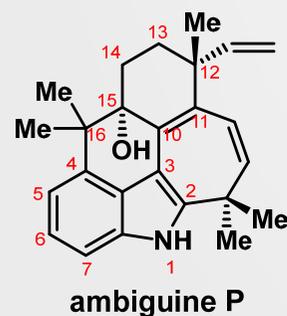
- ✓ Brønsted acid-catalyzed—PTSA·H₂O
- ✓ Cascade Prins-type cyclization



Sarpong: **22 steps, 0.02% yield**

Sequential Indole Functionalizations

- ✓ C2-Nicholas alkylation
- ✓ C4-Friedel-Crafts cyclization
- ✓ directed C-12 functionalization



Rawal: **16 steps, 2.29% yield**

[4+3] cycloaddition reaction-inspired strategy

- ✓ NaAuCl₄·H₂O
- ✓ NBS, H₂O



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感谢批评指正

