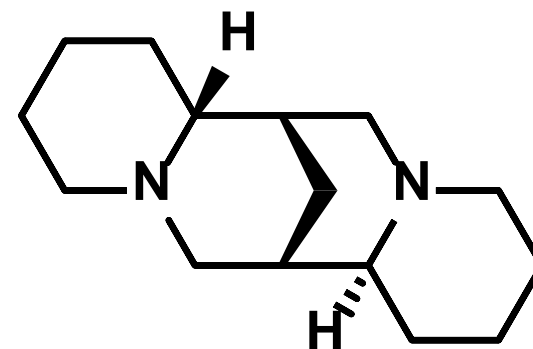


Total syntheses of sparteine

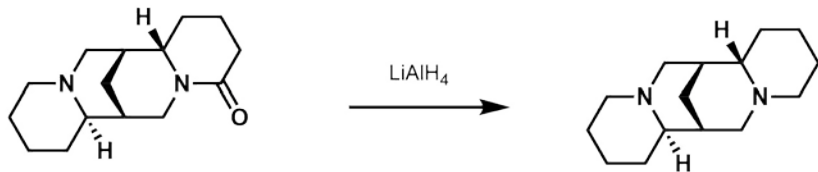
literature talk

M. Sc. Till Vogel

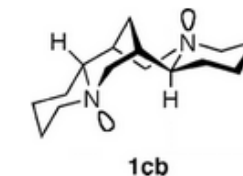
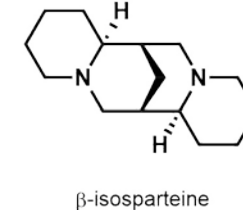
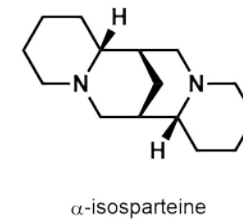
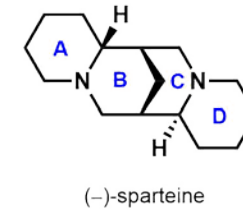


What's special about sparteine?

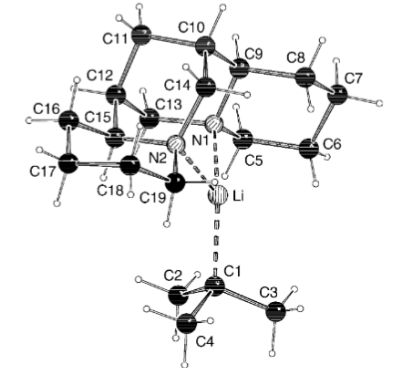
- (-)-sparteine first isolated from scotch broom by Stenhouse from *Cytisus scoparius* in 1851, relative stereochemistry determined in 1951^[1]
- α -isosparteine and β -isosparteine (C_2 -symmetric diastereomers of sparteine) also naturally occurring
- Tetracyclic lupine alkaloids with quinolizidine and bispidine motive
- (+)-sparteine also occurring in plants (extraction more inconvenient) \rightarrow semisynthetic preparation from (-)-lupanine (obtainable by racemate resolution)^[3]



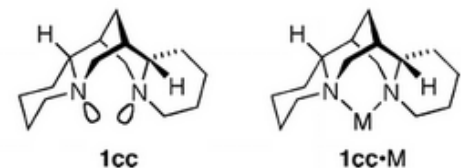
- Certain biological activities, but little medicinal use
- Most significant property: formation of optical active complexes with organolithium species \rightarrow used for asymmetric deprotonation
- Problem: use of sparteine relies on natural product extraction \rightarrow strong variations in price and availability^[5]



Cytisus scoparius (scotch broom).^[2]



Crystal structure of sparteine·BuLi.^[4]

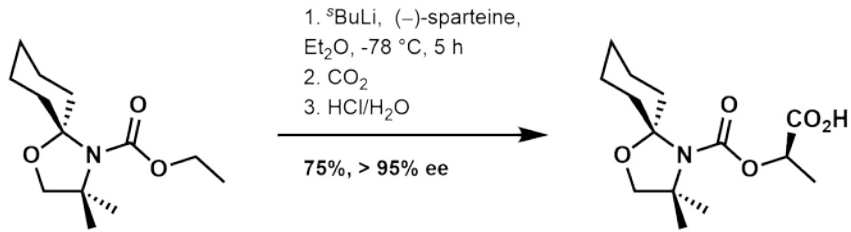


Relevant conformations of sparteine.^[5]

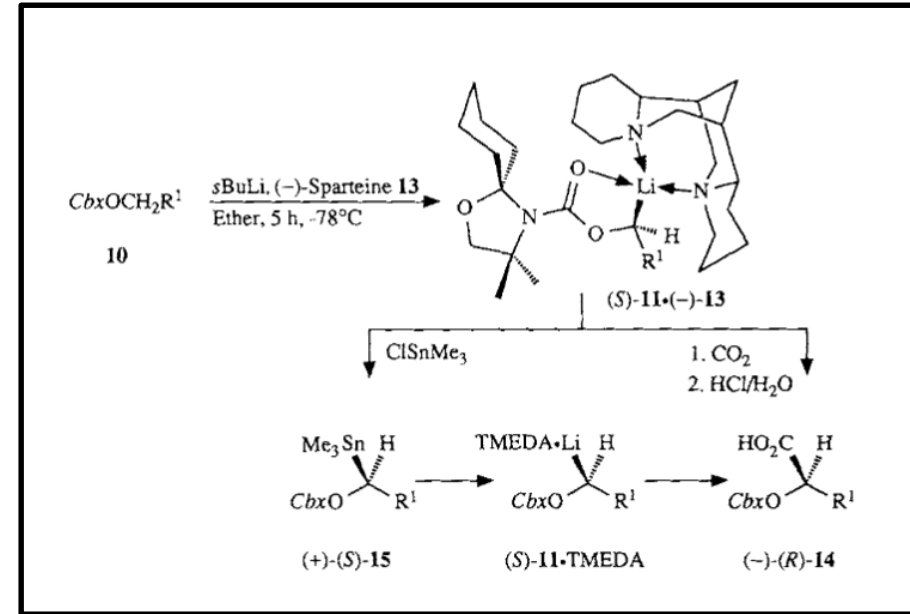
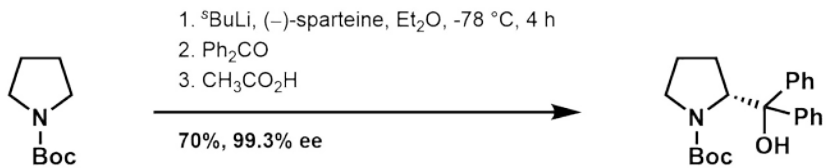
[1] J. Von Stenhouse, *Justus Liebigs Ann. Chem.* **1851**, 78, 1–30. [2] unchanged from: https://en.wikipedia.org/wiki/File:Cytisus_scoparius_by_Danny_S._-001.JPG [3] T. Ebner, M. Eichelbaum, P. Fischer, C. O. Meese, *Arch. Pharm. (Weinheim)*. **1989**, 322, 399–403. [4] C. Strohmann, T. Seibel, K. Strohfeltdt, *Angew. Chemie - Int. Ed.* **2003**, 42, 4531–4533. [5] N. R. Norcross, J. P. Melbardis, M. F. Solera, M. A. Sephton, C. Kilner, L. N. Zakharov, P. C. Astles, S. L. Warriner, P. R. Blakemore, *J. Org. Chem.* **2008**, 73, 7939–7951.

Use of sparteine in asymmetric synthesis:

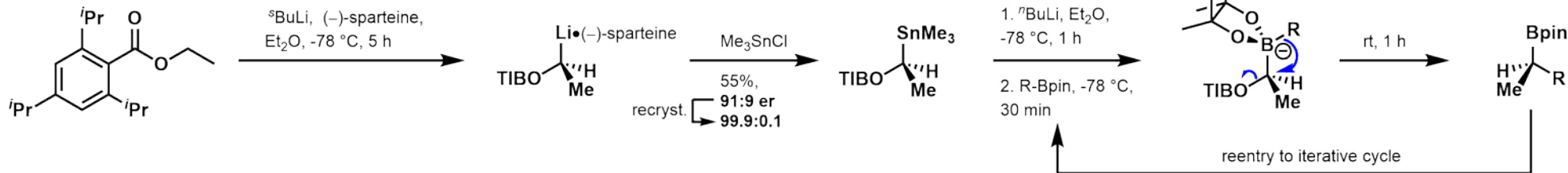
- **Early works by Hoppe^[1]**



- **and Beak^{[2],[3]}**



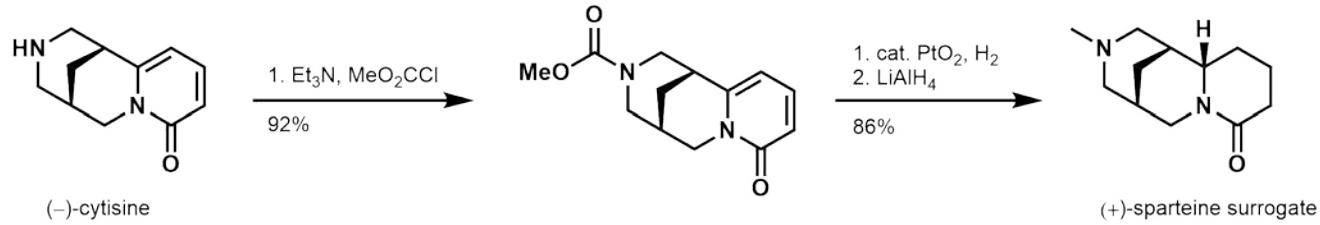
- **More recent work by Aggarwal^[4]**



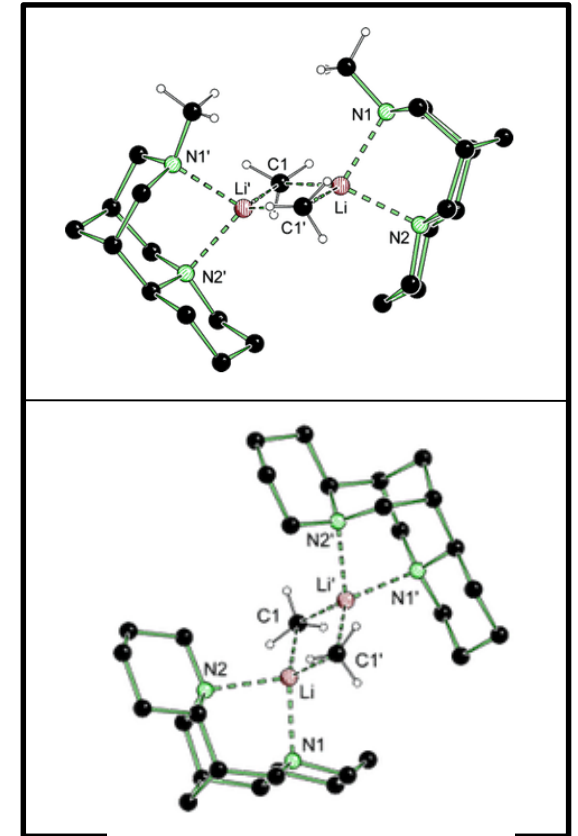
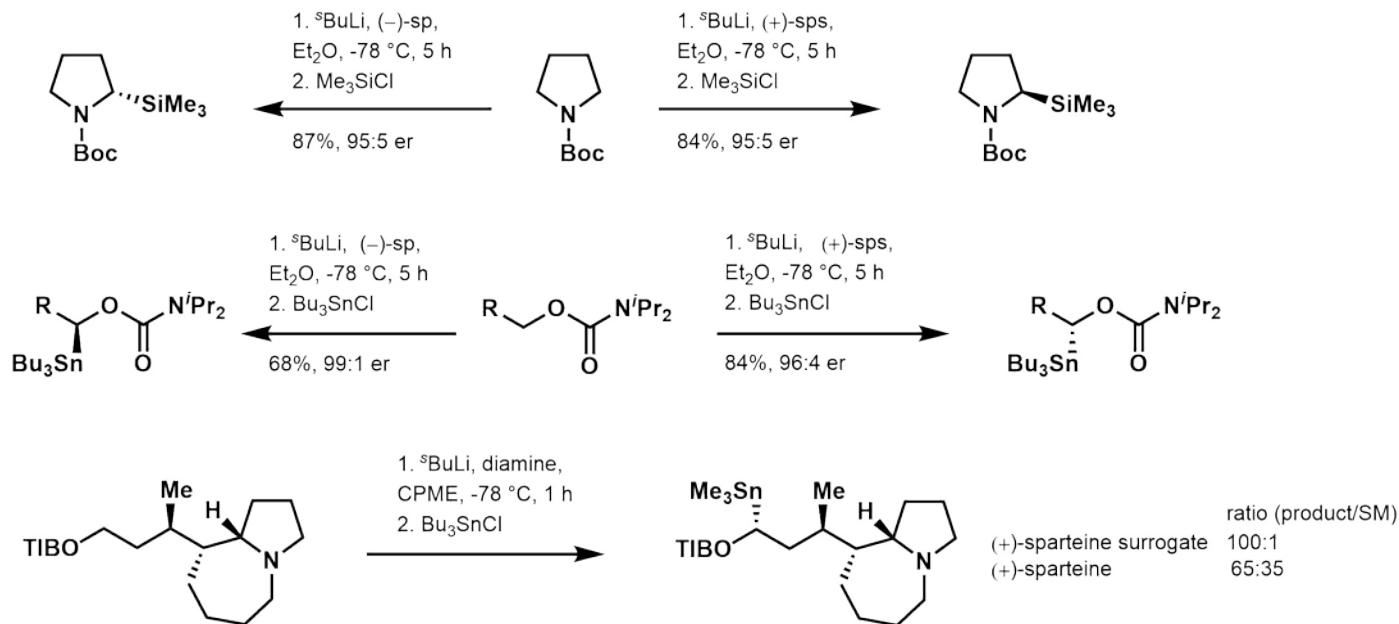
[1] P. Tebben, F. Hintze, D. Hoppe, *Angew. Chem., Int. Ed.* **1990**, *29*, 1422–1424. [2] S. T. Kerrick, P. Beak, *J. Am. Chem. Soc.* **1991**, *113*, 9708–9710. [3] P. Beak, S. T. Kerrick, S. Wu, J. Chu, *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239. [4] M. Burns, S. Essafi, J. R. Bame, S. P. Bull, M. P. Webster, S. Balieu, J. W. Dale, C. P. Butts, J. N. Harvey, V. K. Aggarwal, *Nature* **2014**, *513*, 183–188.

Sparteine surrogates

- Development of (+)-sparteine surrogates ((+)-sps) due to limited availability of (+)-sparteine ((+)-sp) by O'Brien^[1]



- Comparable or even better performance in asymmetric lithiations^{[1],[2]}



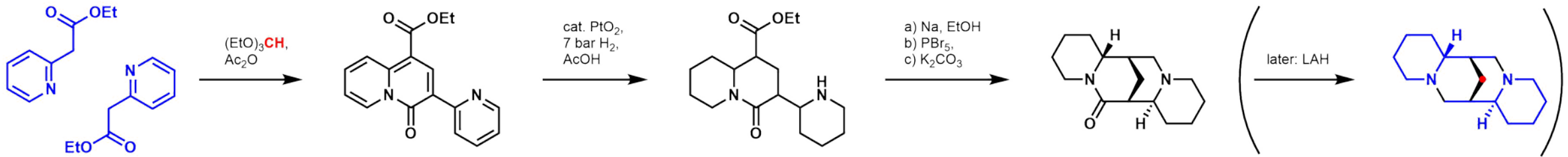
Crystal structures of $[(+)\text{-sps}\cdot\text{MeLi}]_2$ and $[(+)\text{-sp}\cdot\text{MeLi}]_2$.^[3]

[1] M. J. Dearden, C. R. Firkin, J. P. R. Hermet, P. O'Brien, *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871. [2] A. Varela, L. K. B. Garve, D. Leonori, V. K. Aggarwal, *Angew. Chemie - Int. Ed.* **2017**, *56*, 2127–2131.

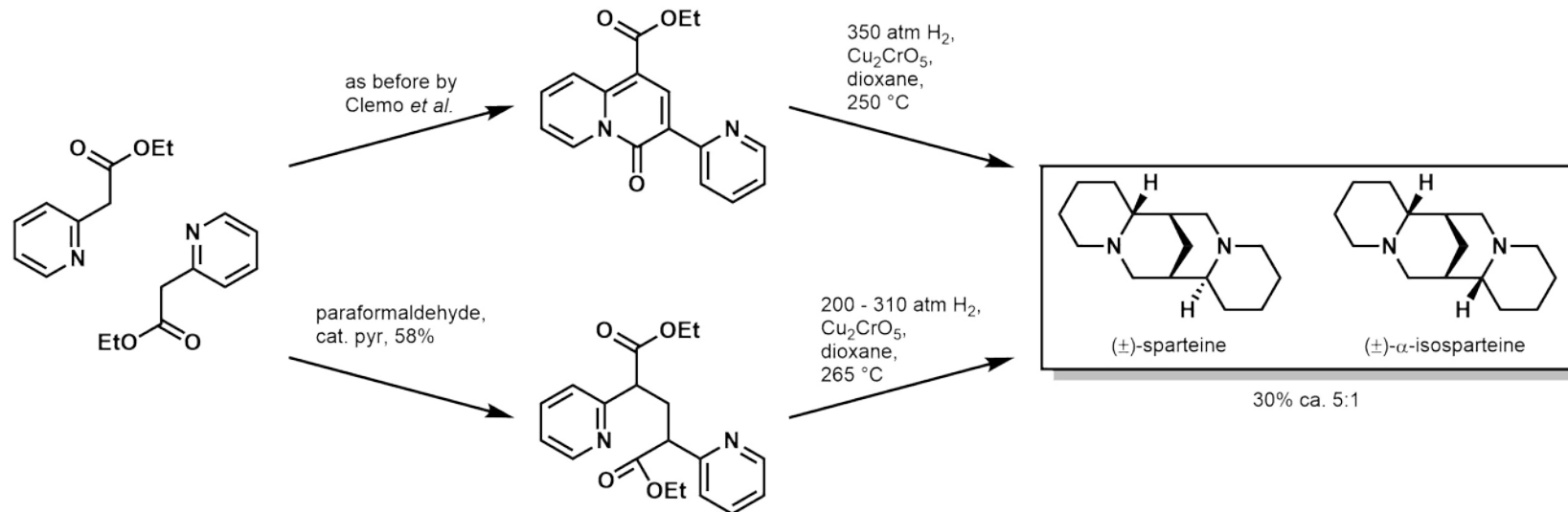
[3] C. Strohmann, K. Strohfeltdt, D. Schildbach, M. J. McGrath, P. O'Brien, *Organometallics* **2004**, *23*, 5389–5391.

Racemic syntheses of sparteine

- First racemic approach, synthesis of 10-oxosparteine (Clemons, Morgan & Raper, **1936**)^[1]

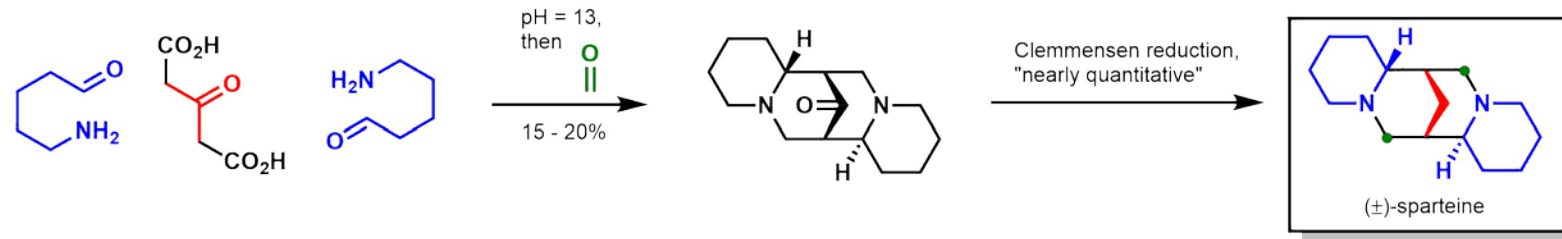


- First racemic synthesis by a reductive cyclization approach (Leonard & Beyler, **1948, 1950**)^{[2],[3]}

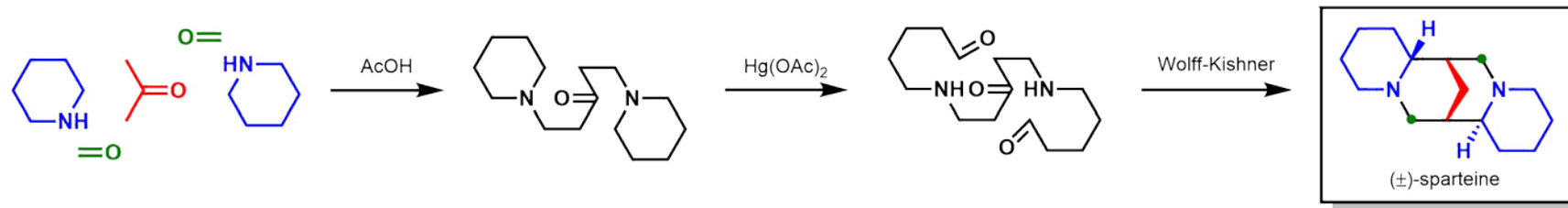


[1] G. R. Clemons, W. M. Morgan, R. Raper, *J. Chem. Soc.*, 1025–1028. [2] N. J. Leonard, R. E. Beyler, *J. Am. Chem. Soc.* **1948**, 70, 2298–2299. [3] N. J. Leonard, R. E. Beyler, *J. Am. Chem. Soc.* **1950**, 72, 1316–1323.

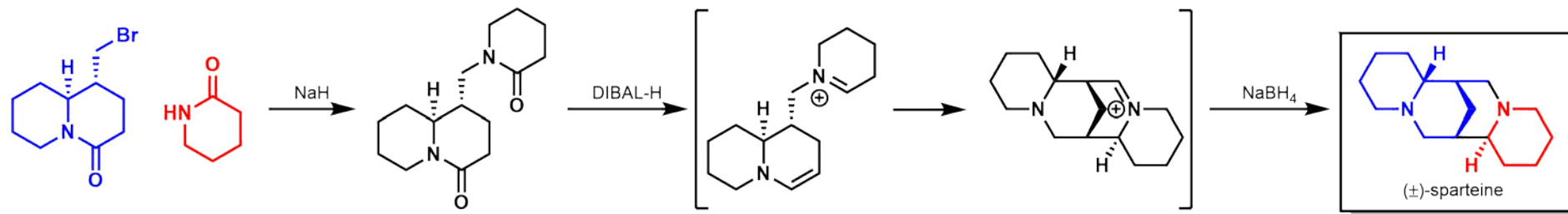
- First „biomimetic“ synthesis of (±)-sparteine (Anet, Hughes, Ritchie, **1950**) – veracity called into question^{[1],[2]}



- Unambiguous biomimetic approach by double Mannich reaction (Tamelen & Foltz, **1960**)^[3]

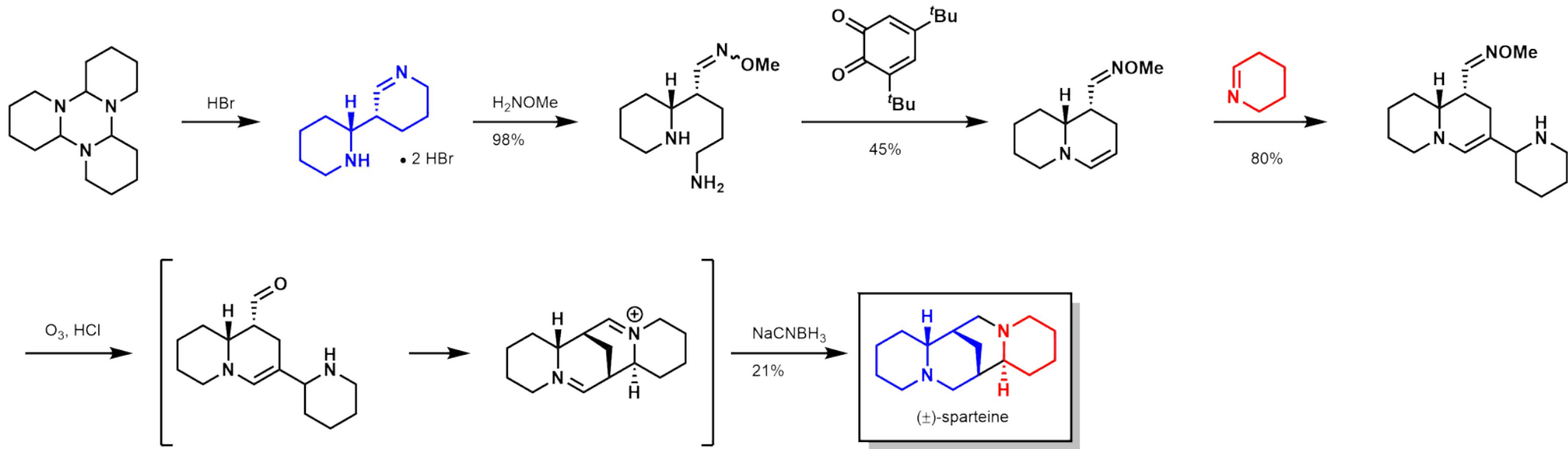


- Another biomimetic approach by enamine-imminium-cyclization (Bohlmann, Müller & Schumann, **1973**)^[4]



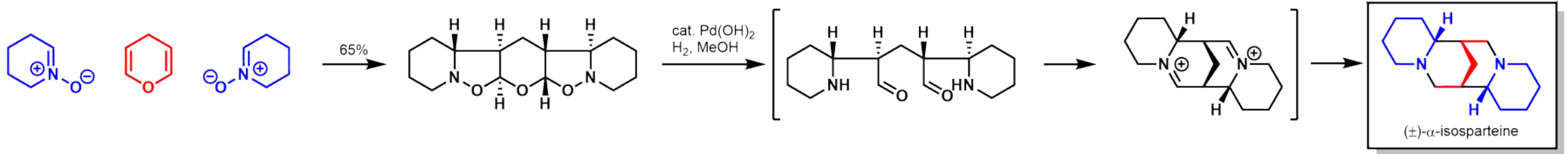
[1] E. Anet, G. K. Hughes, E. Ritchie, *Nature* **1950**, 4184, 35–36. [2] R. Rokohl, H. Hinkel, F. Braun, G. Benz, C. Schöpf, *Angew. Chem.* **1953**, 65, 161–162. [3] E. E. van Tamelen, R. L. Foltz, *J. Am. Chem. Soc.* **1960**, 82, 2400. [4] F. Bohlmann, H. J. Müller, D. Schumann, *Chem. Ber.* **1973**, 106, 3026–3034.

- Most accurate biomimetic approach (Wanner & Koomen, 1996)^[1]

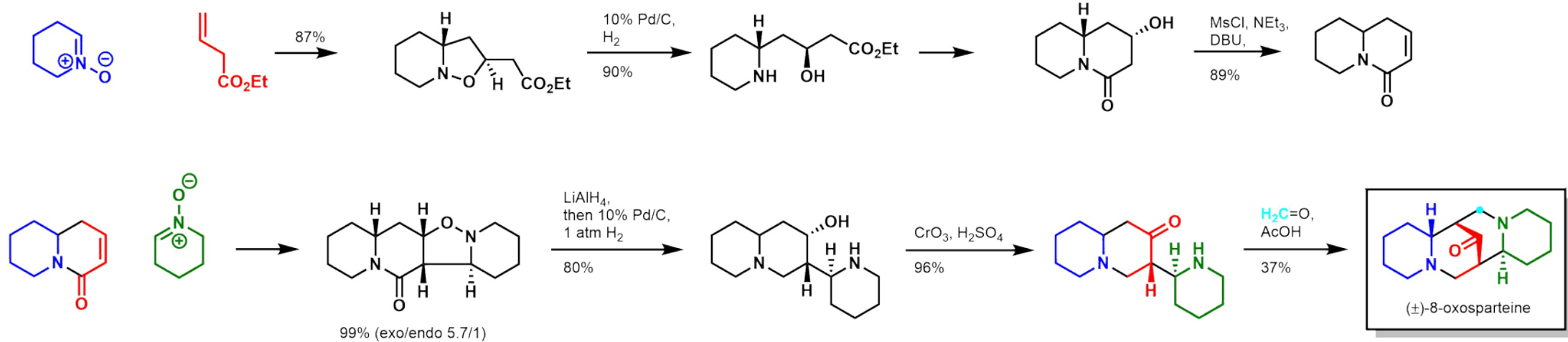


[1] M. J. Wanner, G. J. Koomen, *J. Org. Chem.* **1996**, 61, 5581–5586.

- Synthesis of (±)-α-isosparteine by a 1,3-dipolar cycloaddition approach (Oinuma, Dan, Kakisawa, **1983**)^[1]

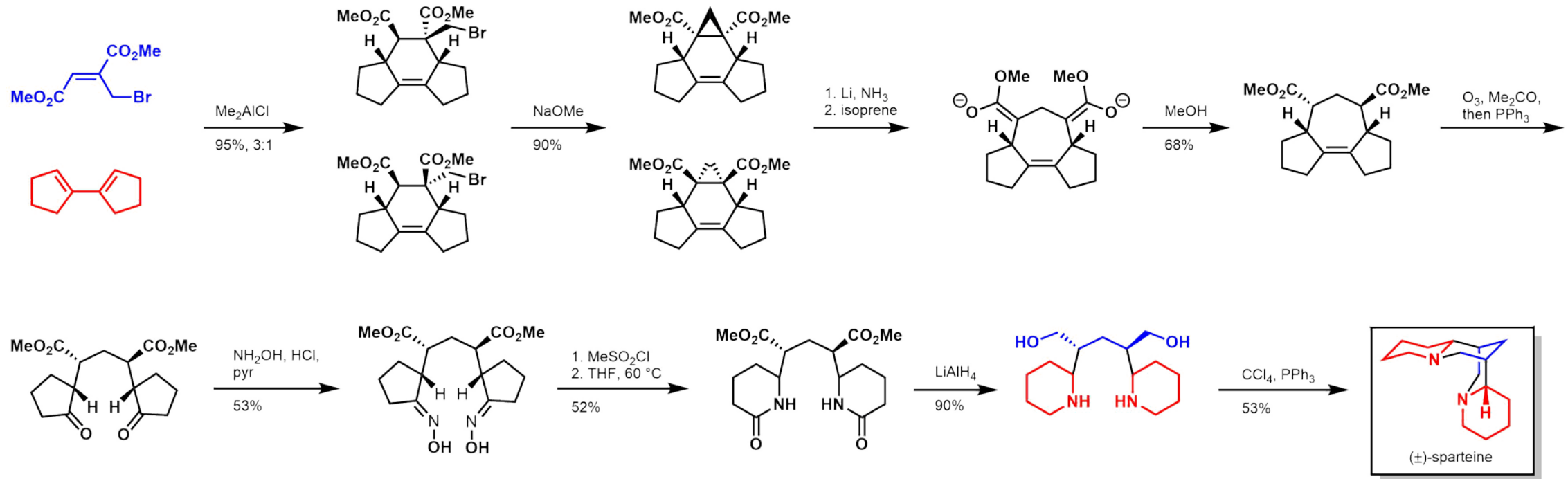


- Formal total synthesis of (±)-sparteine by a 1,3-dipolar cycloaddition approach (Takatsu, Noguchi, Ohmiyata & Otomasu, **1987**)^[2]



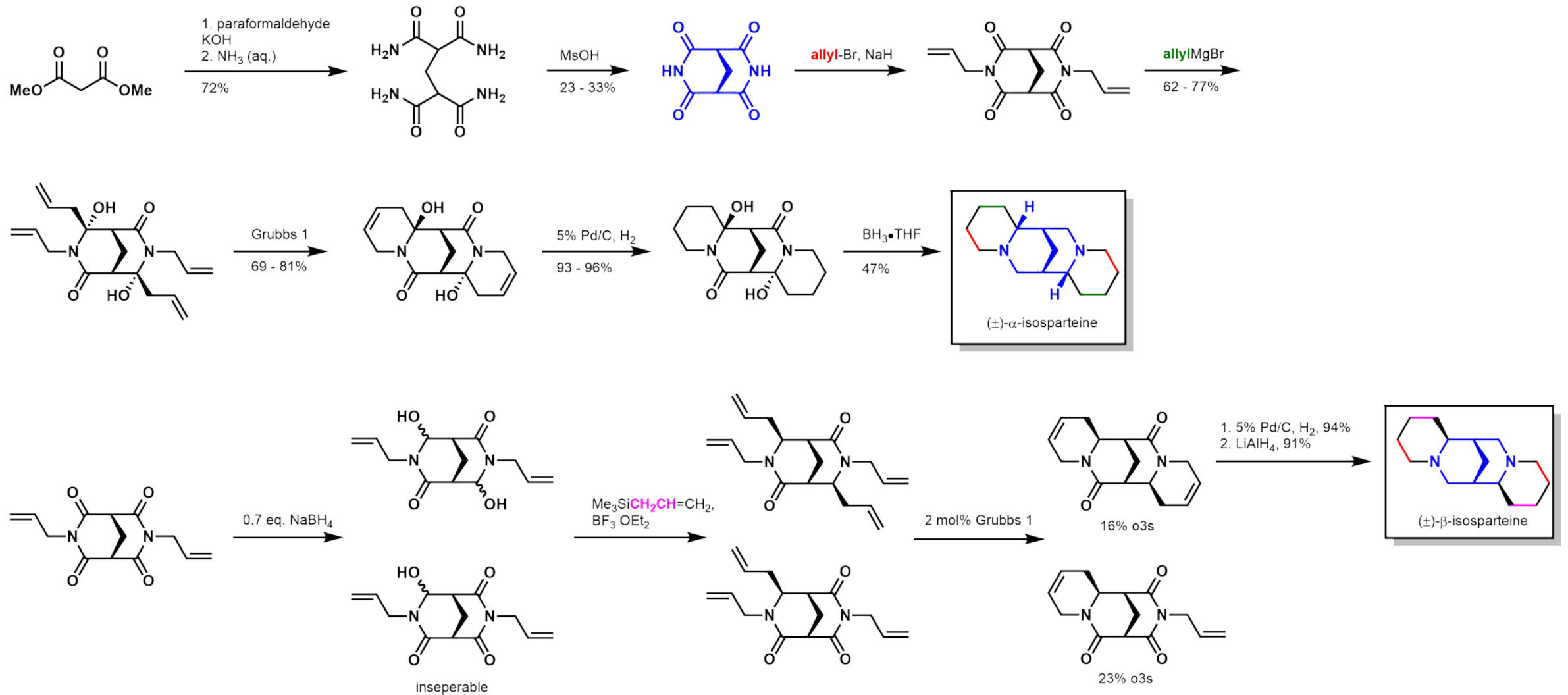
[1] H. Oinuma, S. Dan, H. Kakisawa, *J. Chem. Soc., Chem. Commun.* **1983**, 654–655. [2] N. Takatsu, M. Noguchi, S. Ohmiya, H. Otomasu, *Chem. Pharm. Bull.* **1987**, 35, 4990–4992.

- Synthesis of (±)-sparteine by a sequence of ring-closing and ring-opening events (Fleming *et al.*, 2005)^[1]

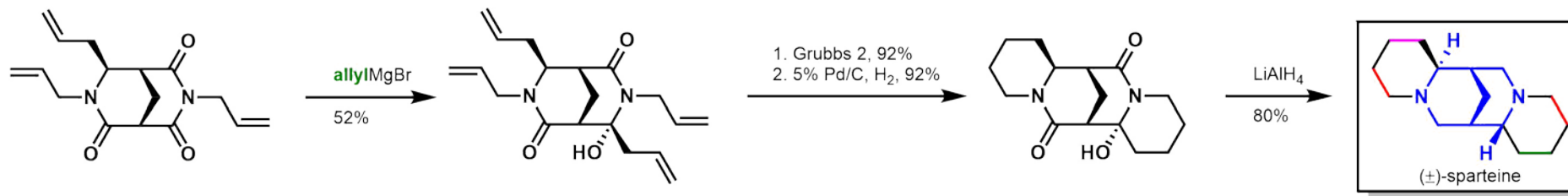


[1] T. Buttler, I. Fleming, S. Gonsior, B. Kim, A. Sung, H. Woo, *Org. Biomol. Chem.* **2005**, 3, 1557–1567.

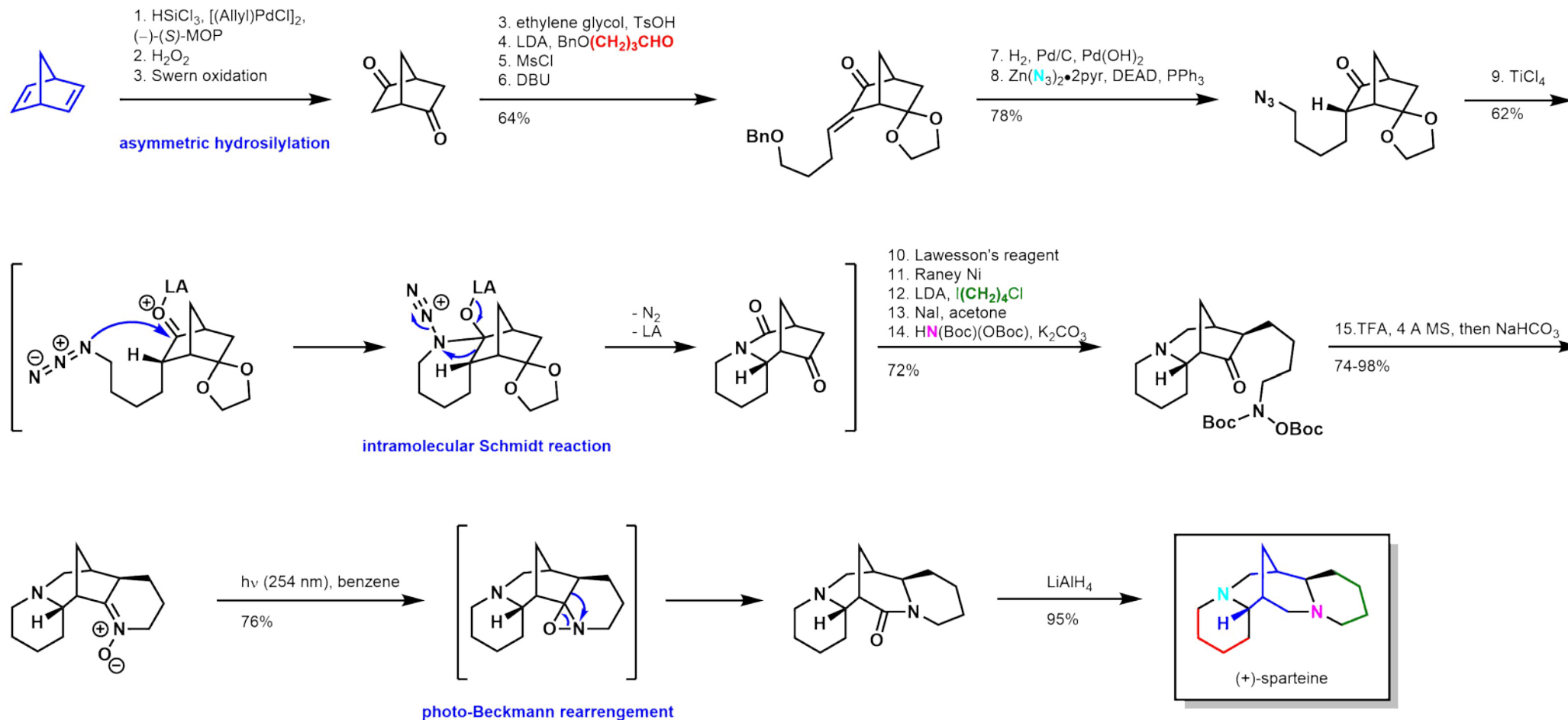
- Unified syntheses of (±)-sparteine, (±)-α-isosparteine and (±)-β-isosparteine (Blakemore, 2008)^[1]



[1] N. R. Norcross, J. P. Melbardis, M. F. Solera, M. A. Sephton, C. Kilner, L. N. Zakharov, P. C. Astles, S. L. Warriner, P. R. Blakemore, *J. Org. Chem.* **2008**, *73*, 7939–7951.



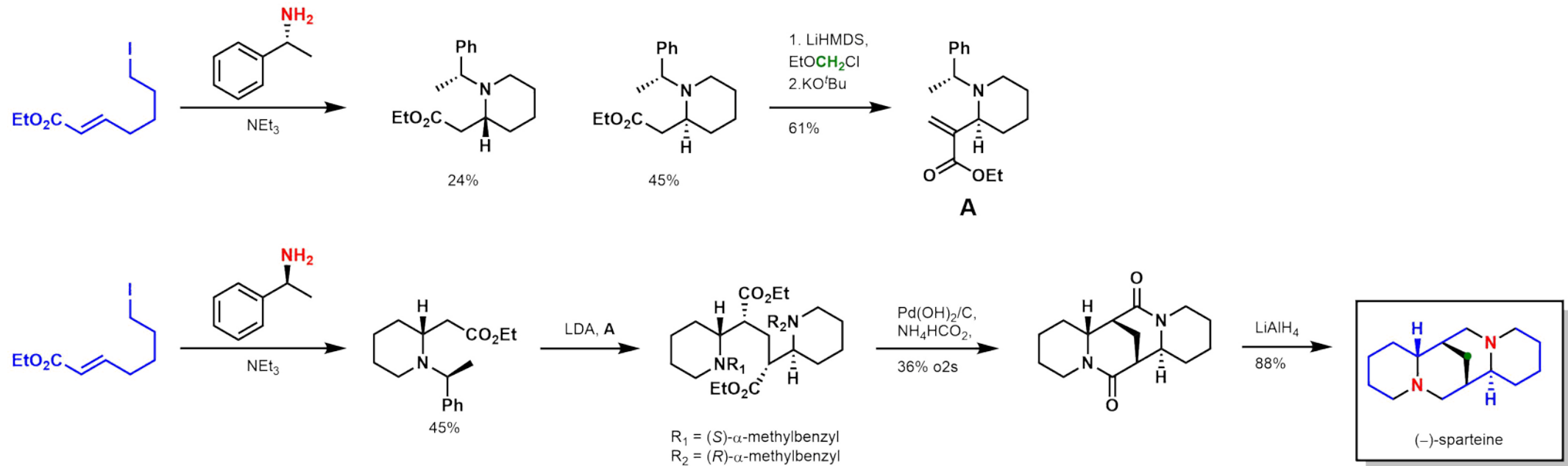
First asymmetric synthesis of (+)-sparteine (Aubé, 2002)^[1]



[1] B. T. Smith, J. A. Wendt, J. Aubé, *Org. Lett.* **2002**, 4, 2577–2579.

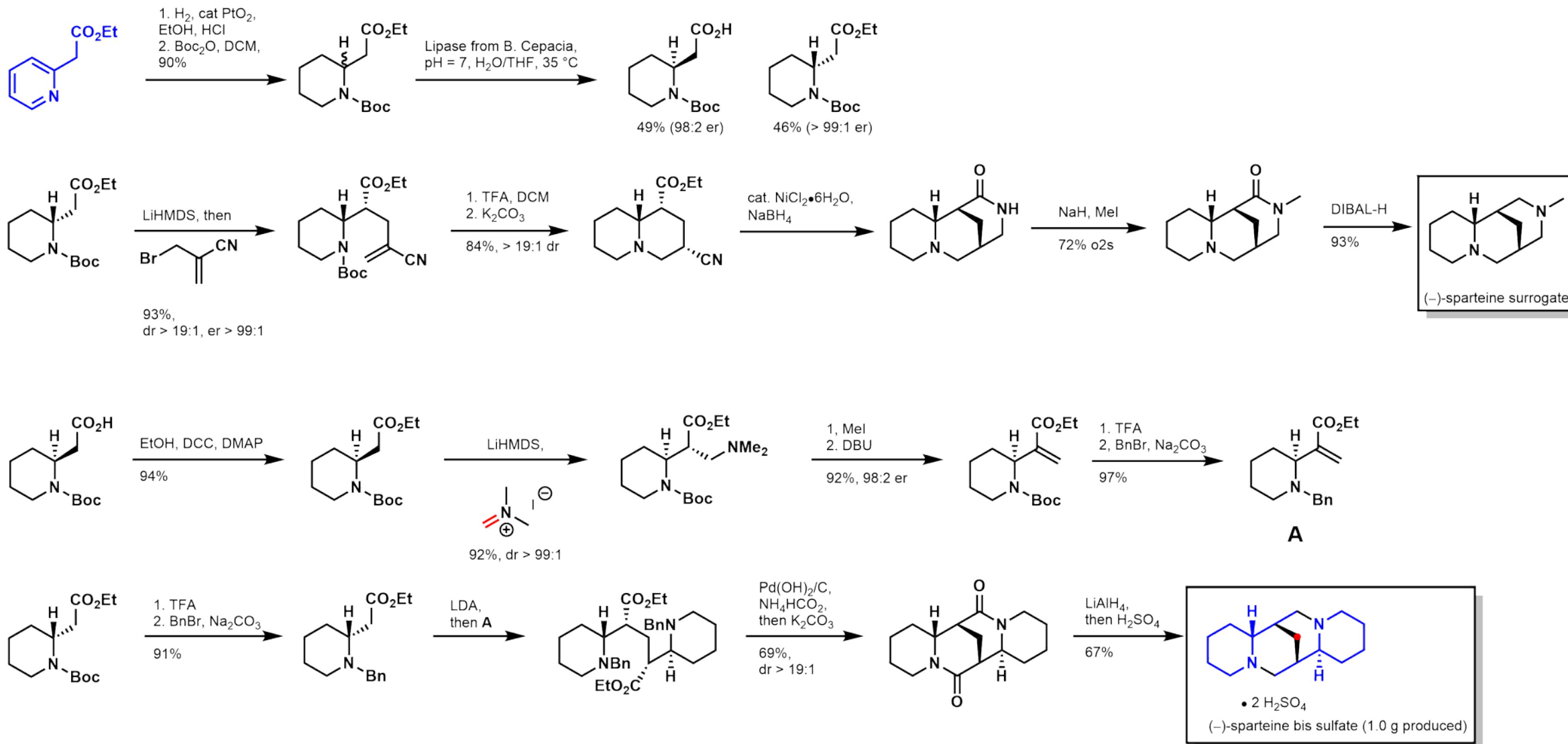
First asymmetric synthesis of (-)-sparteine (O'Brien, 2004)^[1]

- Concise six-step synthesis by use of enantiomerically pure commercially available (*R*)- and (*S*)- α -methylbenzylamine



[1] J. P. R. Hermet, M. J. McGrath, P. O'Brien, D. W. Porter, J. Gilday, *Chem. Commun.* **2004**, 10, 1830–1831.

Gram-scale synthesis of (-)-sparteine and (-)-sparteine surrogate (O'Brien, 2018)^[1]

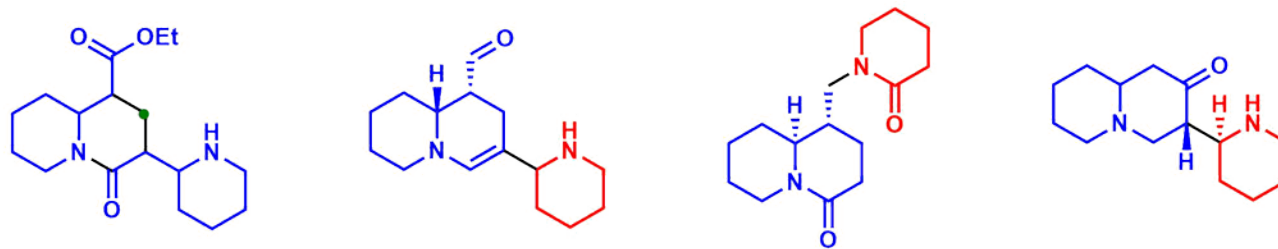


[1] J. D. Firth, S. J. Canipa, L. Ferris, P. O'Brien, *Angew. Chemie - Int. Ed.* **2018**, *57*, 223–226.

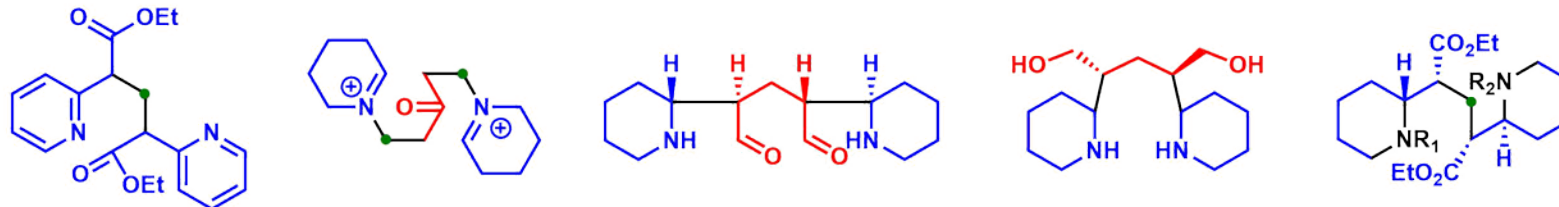
Conclusion

- Several racemic syntheses starting from 1948
- Only one asymmetric synthesis of (+)-sparteine Aubé (2002, enantioselective) and two of (-)-sparteine (O'Brien, 2004 & 2017, both resolution based)^{[1],[2],[3]}
- Basically two general approaches: a) outside-in (A and D ring constructed first or introduced by SM, afterwards cyclization event under formation of B and C ring [sequentially by intermediates A or in one step by intermediates B])

A:



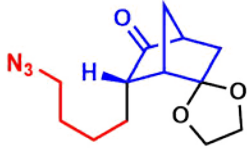
B:



[1] B. T. Smith, J. A. Wendt, J. Aubé, *Org. Lett.* **2002**, 4, 2577–2579. [2] J. P. R. Hermet, M. J. McGrath, P. O'Brien, D. W. Porter, J. Gilday, *Chem. Commun.* **2004**, 10, 1830–1831. [3] J. D. Firth, S. J. Canipa, L. Ferris, P. O'Brien, *Angew. Chemie - Int. Ed.* **2018**, 57, 223–226.

b) inside-out (B and C ring constructed first or introduced by SM, afterwards cyclization events under formation of A and D ring [sequentially by intermediate A or in one step by intermediates B])

A:



B:

