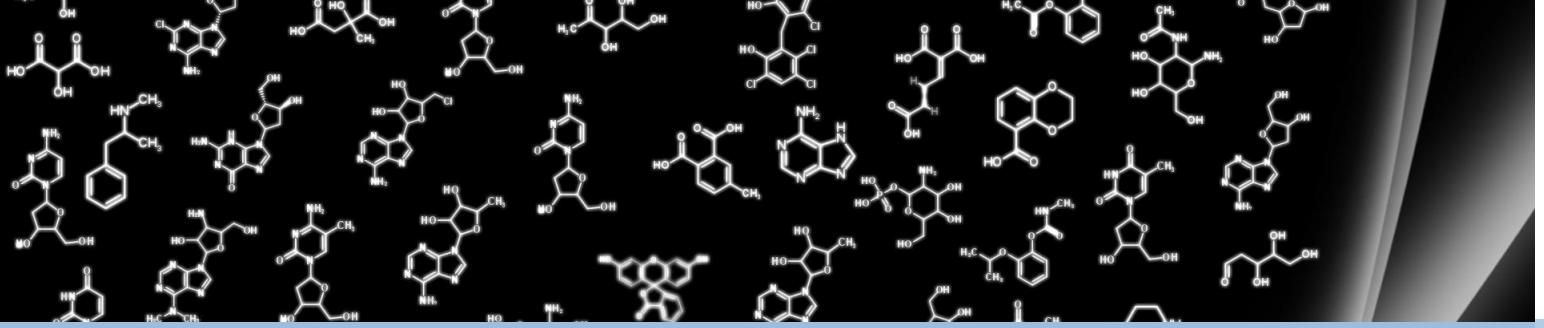

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Gram-Scale Synthesis of the (–)-Sparteine Surrogate and (–)-Sparteine

James D. Firth, Steven J. Canipa, Leigh Ferric and Peter O'Brien
Angew. Chem. Int. Ed. **2018**, *57*, 223-226

Manuel Gnägi
Department of Chemistry and Biochemistry
University of Bern

Journal Club Group Renaud

01.02.2018

Peter O'Brien (York University)

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- PhD at Prof. Stuart Warren
  (University of Cambridge, 1995)
- York University ever since
  (Research fellow, lecturer, reader)
- Professor at the York University, 2007 – present

- <u>Research</u>:
  Contemporary organic synthesis, in particular asymmetric synthesis
  - Organolithium methodology for synthesis of nitrogen heterocycles
  - Design, Synthesis and biological screening of 3-D-fragments
  - Synthetic tools for chemical biology

(–)-Sparteine and Surrogate

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- "Go-to" chiral ligands for organolithium bases such as s-BuLi
- Antiarrhythmic agent (Na-Channel blocker, not FDA approved)

- Sparteine is a natural product, extracted from *Scotch Broom* (central Europe) and *Lupinus mutabilis* (Andes)
- Sparteine (both enantiomers) is commercially available, 60:-/500mg at Sigma-Aldrich
- The Sparteine Surrogate is more efficient for control but also more expensive: 290.-/100mg
- Price variability "prevented" it's use in the process-scale synthesis of Telaprevir (Vertex)

Org Process Res. Dev. **2014**, *18,* 1234-1244

Previous Sparteine syntheses

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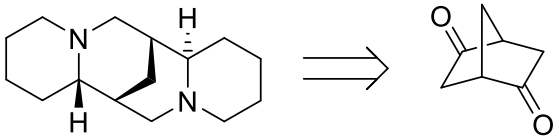
- Only two successful enantioselective routes
- Aubé, (+)-Sparteine:



(+)-Sparteine

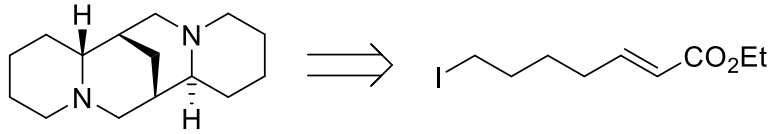
- 15 Steps, 15.7% overall yield; key steps: intramolecular Schmidt and photo-Beckmann rearrangement

B.T. Smith, J. A. Wendt, J. Aubé, *Org. Lett..* **2002**, *4,* 2577-2579
J.-P. R. Hermet, M. J. McGrath, P. O'Brien, D. W. Porter, J. Gilday, *Chem. Commun.* **2004,** 1830-1831

Previous Sparteine syntheses

UNIVERSITÄT BERN

- Only two successful enantioselective routes
- Peter O'Brien, (–)-Sparteine:



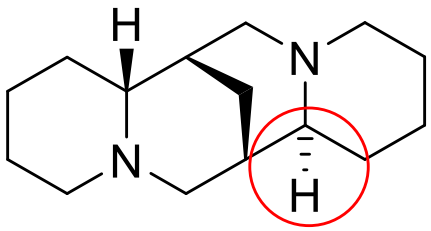
(-)-Sparteine

- 6 Steps, 2% overall yield; key: Michael Addition

B.T. Smith, J. A. Wendt, J. Aubé, *Org. Lett..* **2002**, *4,* 2577-2579
J.-P. R. Hermet, M. J. McGrath, P. O'Brien, D. W. Porter, J. Gilday, *Chem. Commun.* **2004,** 1830-1831

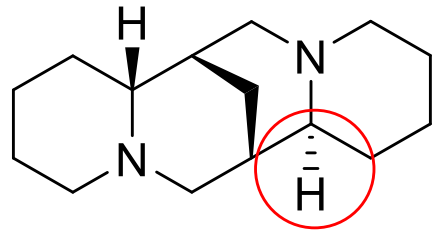
The drawing discussion

> How should we show the stereochemistry?



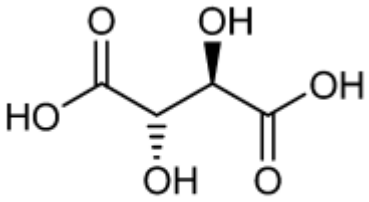
(-)-Sparteine

This Journal

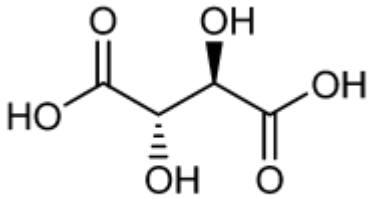


(-)-Sparteine

IUPAC recommended



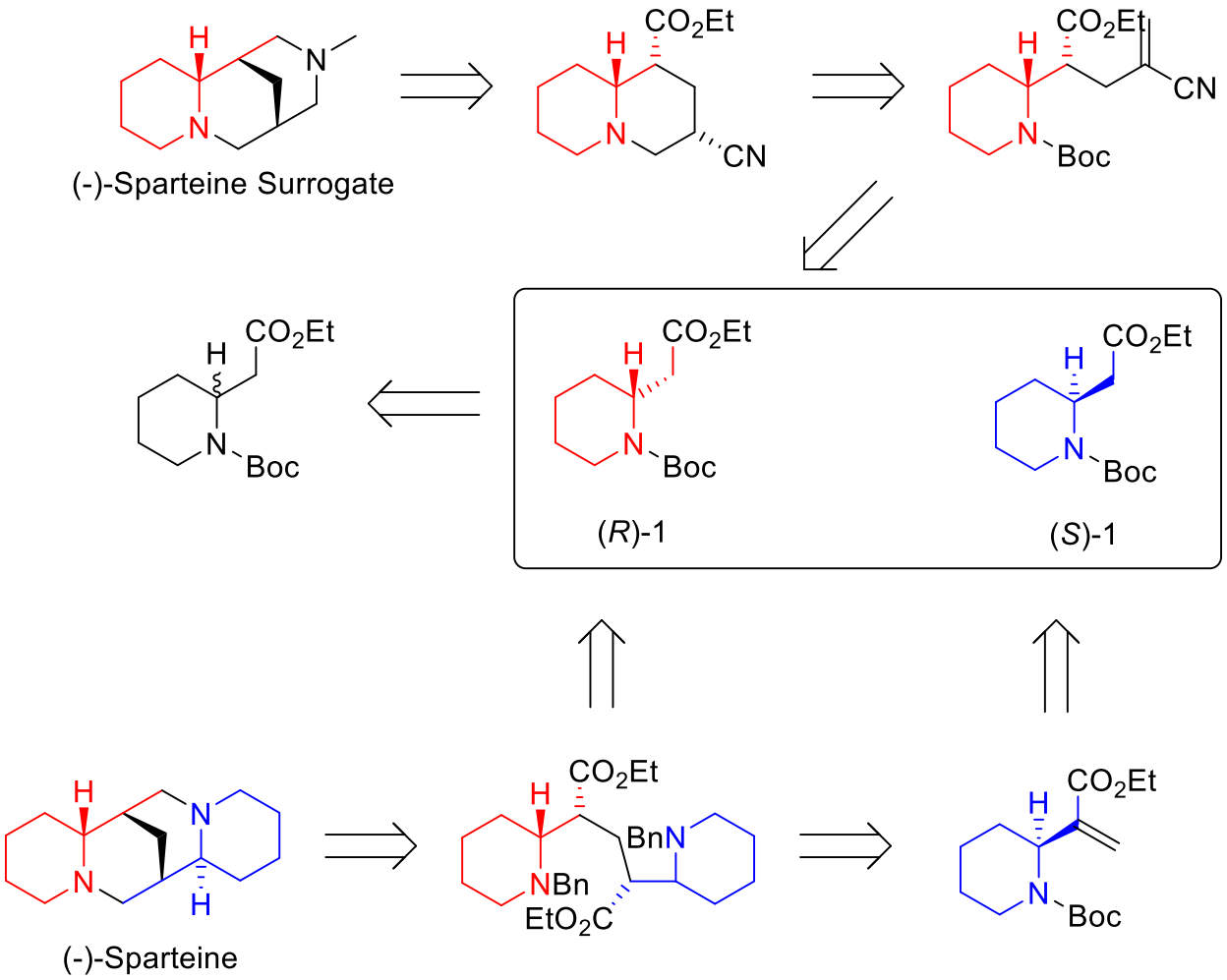
Acceptable



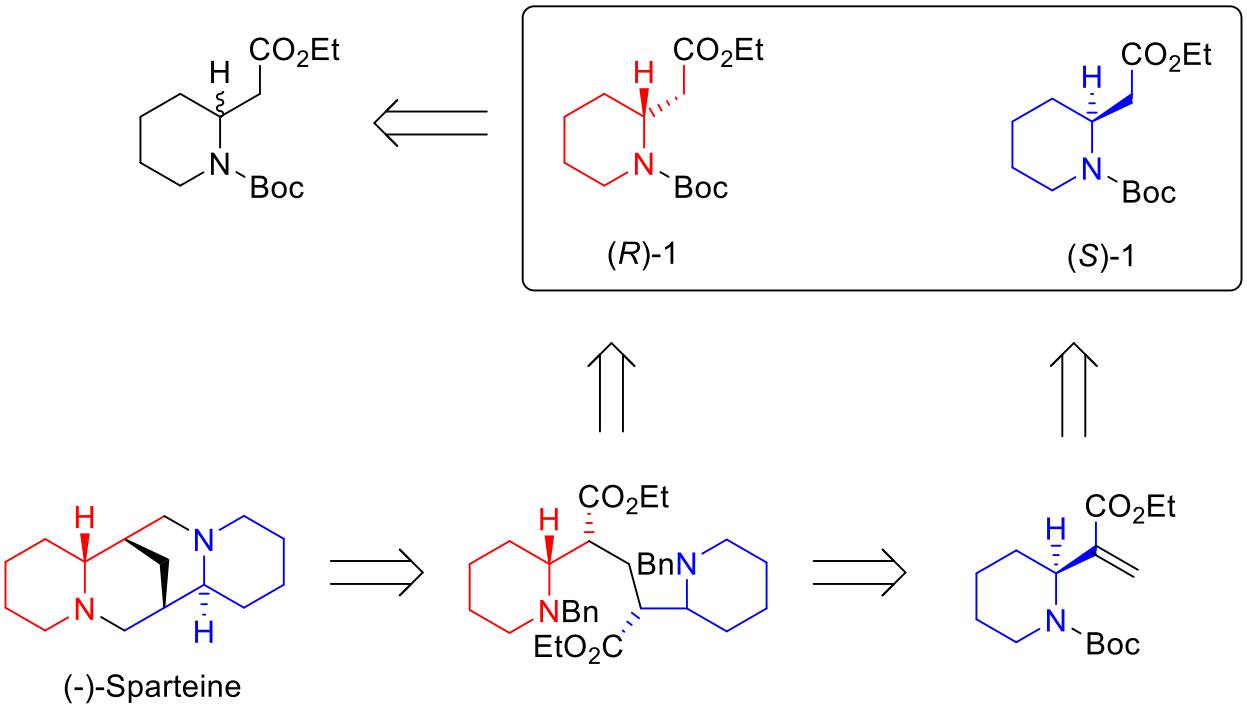
Preferred

IUPAC recommendation:
Pure Appl. Chem., **2006**, *78*, 1897–1970, 2006; doi:10.1351/pac200678101897

Retrosynthetic approach

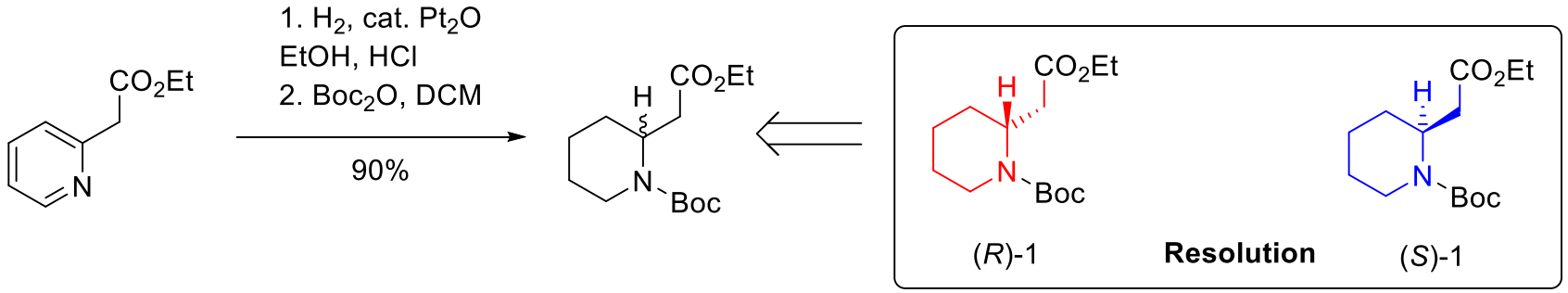


Retrosynthetic approach - Sparteine



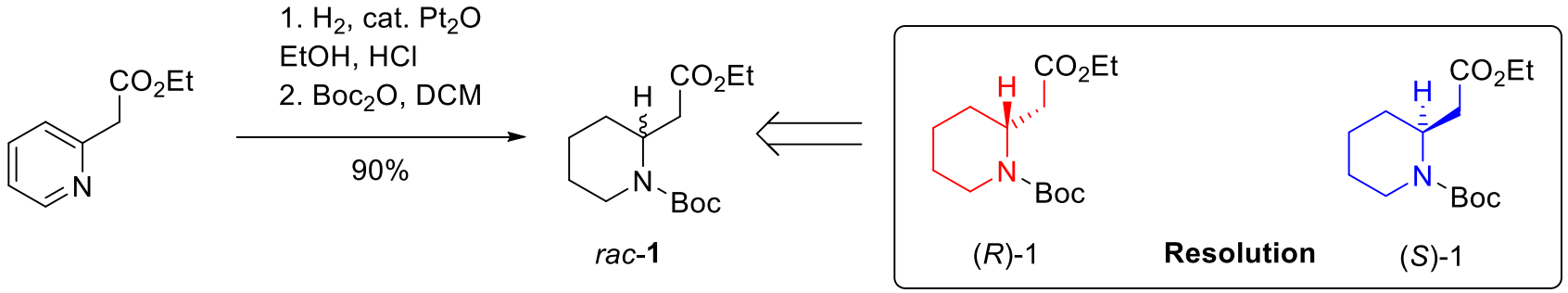
> Only one C-atom and 4 bonds left to introduce!

Forward synthesis – key step

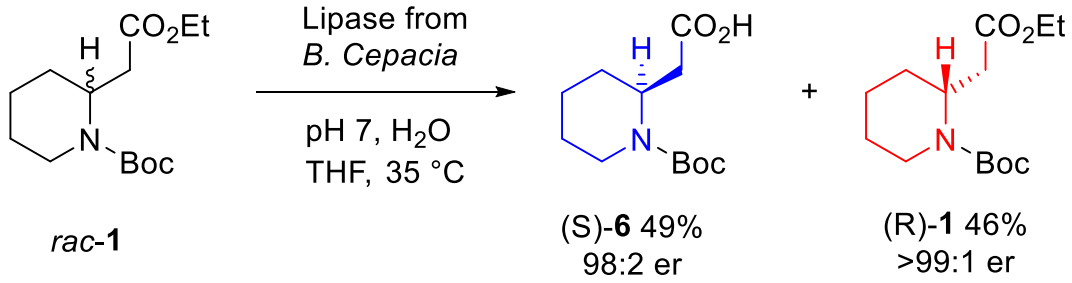


> The key step for both syntheses is the resolution of the starting material:

Forward synthesis – key step



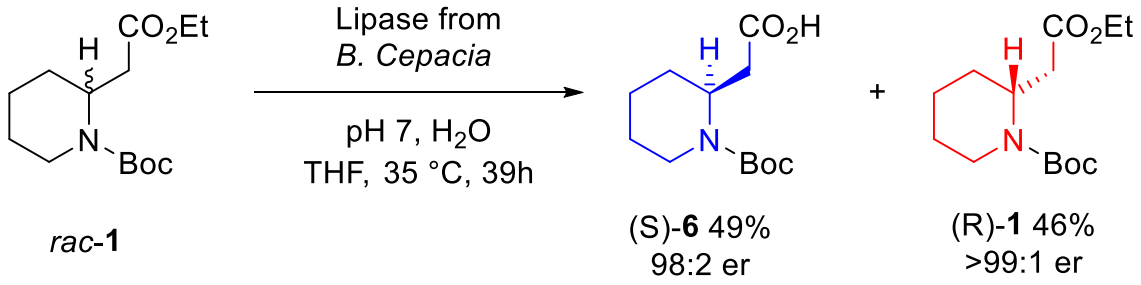
> The key step for both syntheses is the resolution of the starting material: kinetic resolution by *Burkholderia Cepacia* lipase (previously reported)



Tetrahedron Asymmetry.. **2004**, *15,* 3407-3412

Forward synthesis – key step

The key step for both syntheses is the resolution of the starting material: kinetic resolution by *Burkholderia Cepacia* lipase (previously reported)



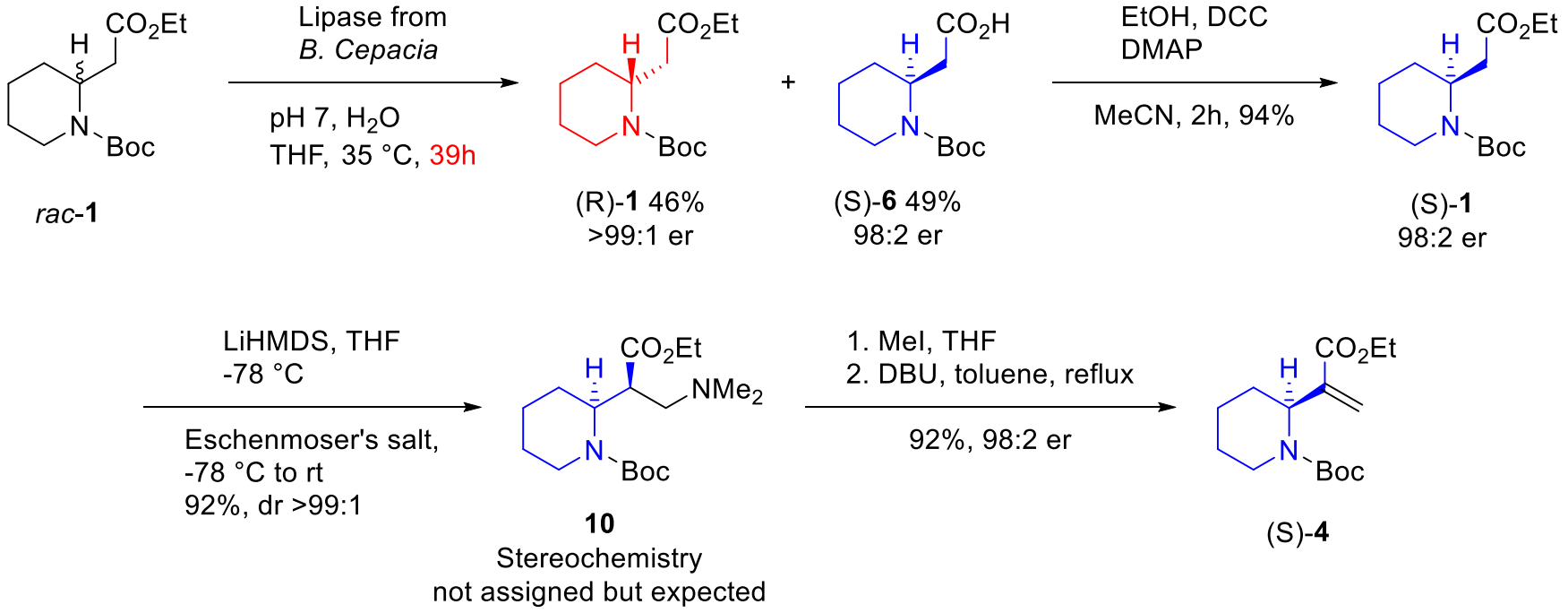
Amount [g] of SM = amount of lipase, but the lipase is incredibly cheap:

226.-/ 50g at Sigma-Aldrich.

B. Cepacia is quite dangerous: naturally resistant to a broad range of antibiotics, 35% mortality rate upon infection

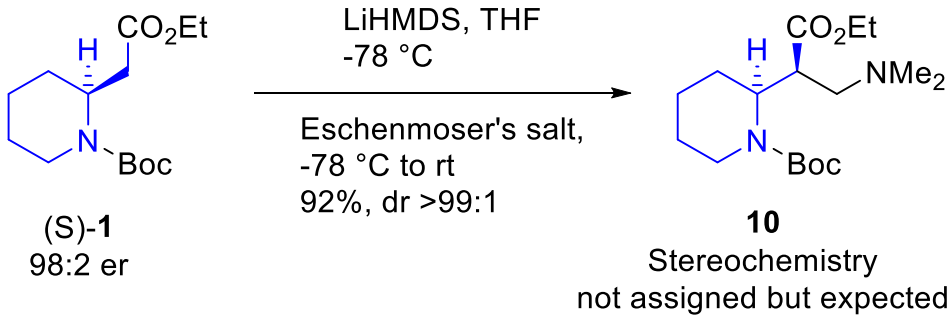
Tetrahedron Asymmetry.. **2004**, *15,* 3407-3412

Forward synthesis II – Sparteine



Stereochemistry of 10

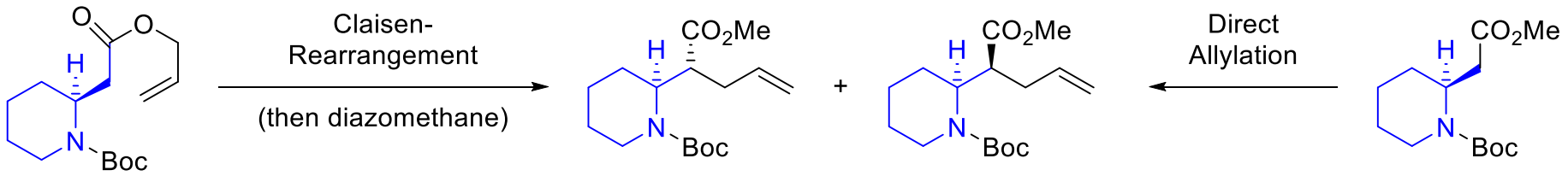
> Stereochemistry of **10** was not assigned but thought to be like:



(S)-**1**
98:2 er

10
Stereochemistry
not assigned but expected

> The literature they cite has two strategies:



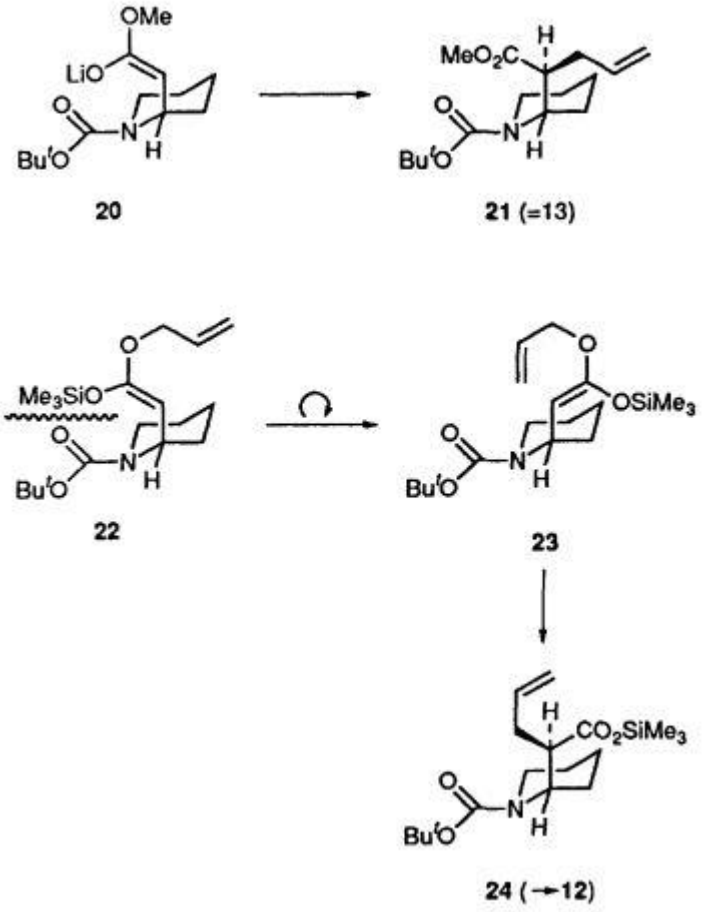
Claisen: 94:6 ("wrong")
Direct: 16:84 ("right")

C. Morley, D. W. Knight, A. C. Share, *J. Chem. Soc., Perkin Trans.* **1994**, 0, 2903-2907

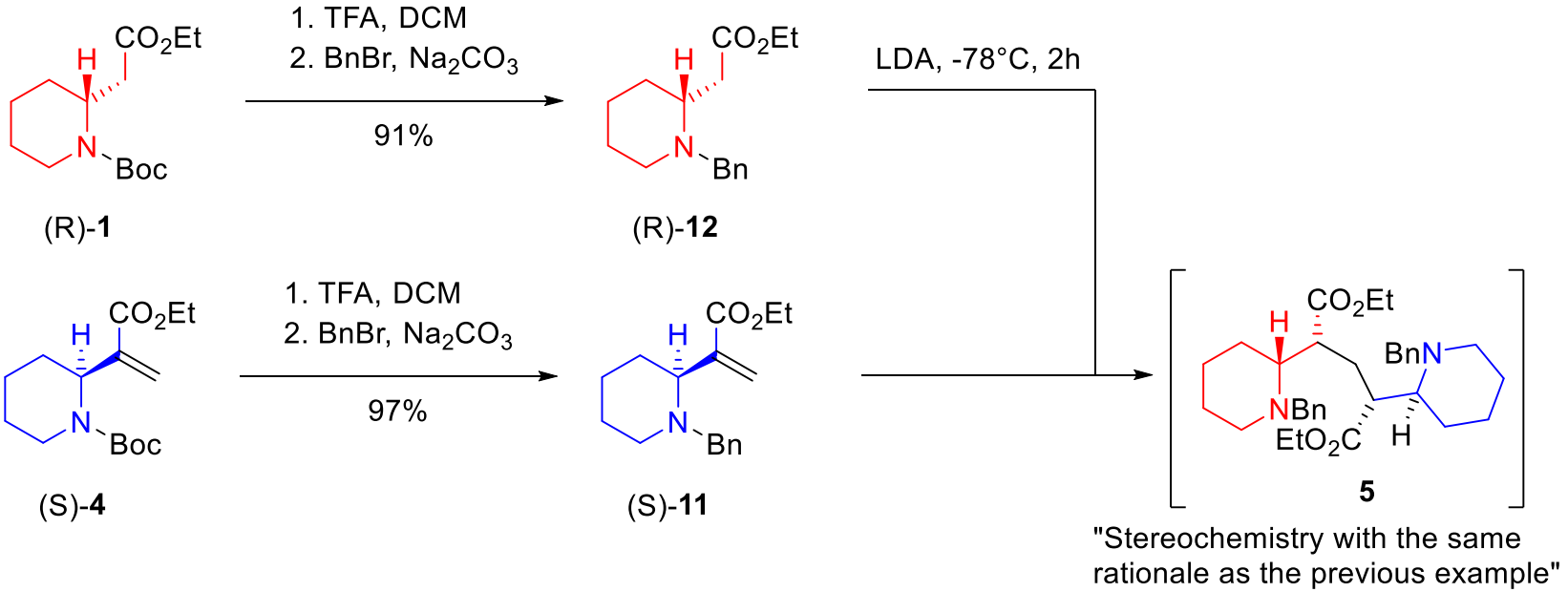
Stereochemistry of 10

The E-enolate is formed in both situations: In the direct allylation example a complex with the PG is formed, attack from the front should give the (S)-center

Reaction via bulky TMS-protection (in the claisen-rearrangement) results in rotation, opposite outcome

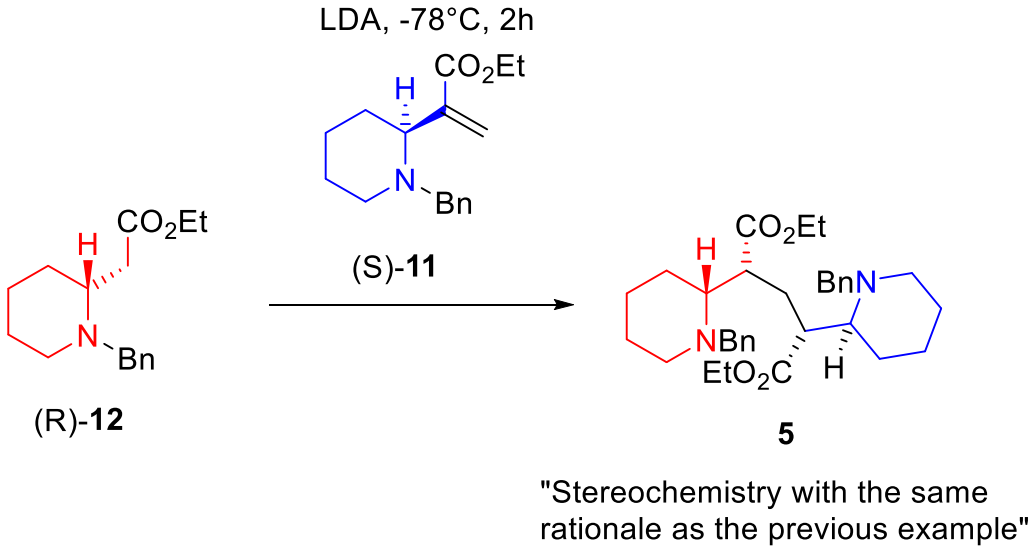


Forward synthesis II – Sparteine



Stereochemistry II – 5

> The stereochemistry should follow the same rationale but:

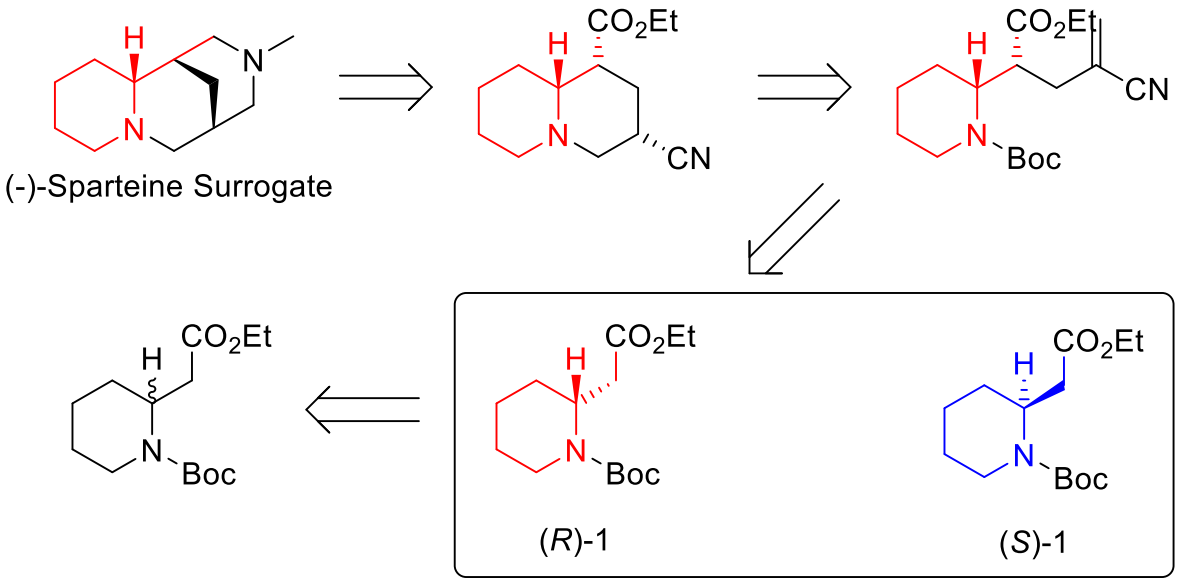


The protecting group is now Bn and not Boc anymore – complexation with nitrogen alone seems to work as well but not as efficient (>19:1 instead of 84:16)

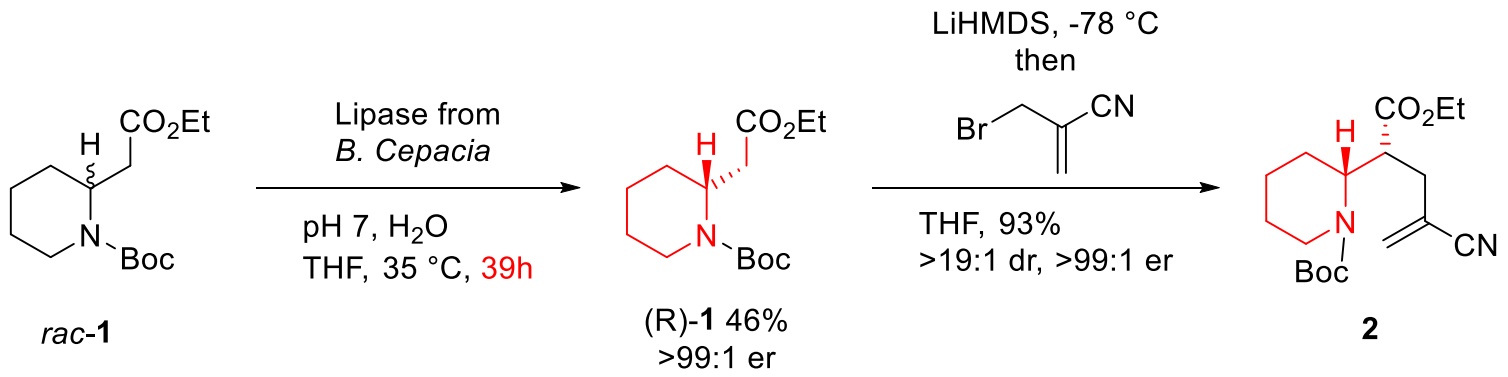
Conclusion Sparteine

- Quite atom economic synthesis
- Key step: Resolution of the racemic starting material
- Key step 2: Diastereoselective Michael Addition (coupling) of the two “hands”
- 10 steps longest linear sequence, 31% yield

Retrosynthetic approach



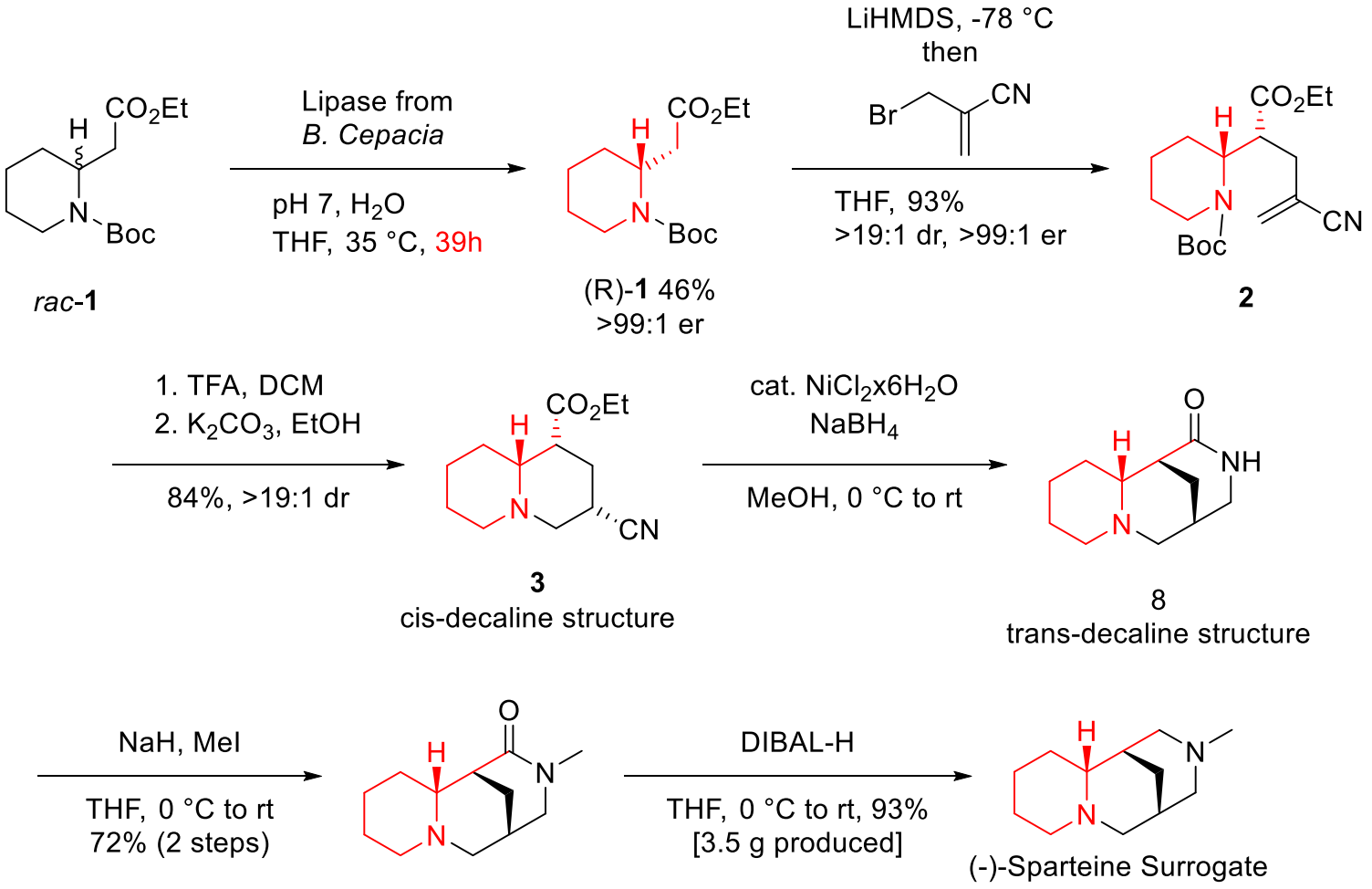
Forward synthesis - Surrogate



Axial protonation from the less sterically hindered face results in equatorial conformation in **3**.

However, ring flipping enables the two groups to be axial, required for lactamization

Forward synthesis II - Surrogate



Conclusion Sparteine Surrogate

- Gram-scale synthesis of Sparteine Surrogate
- Both enantiomers should be achieveable
- 8 steps, 22% overall yield