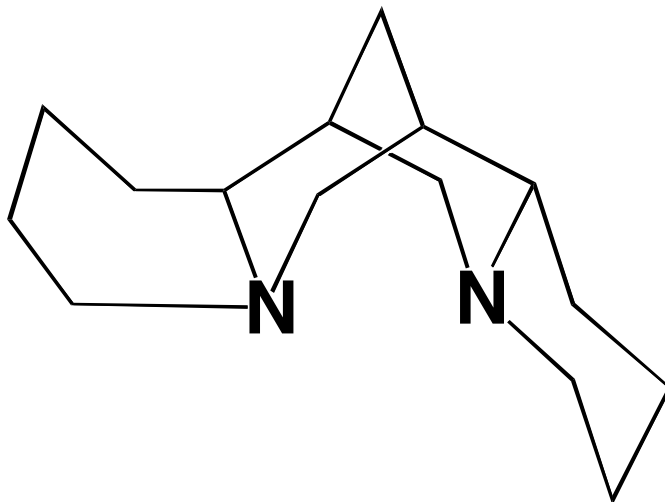


# SPARTEINE -- A lupin alkaloid



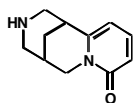
- I. Background
- II. Synthesis
- III. Applications
- IV. Analogs

Raissa Trend  
Stoltz Conference Room  
13 June 2002  
12:00 pm

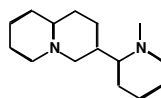
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## General Information

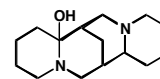
Lupin alkaloids are found in wide variety of plants around the world



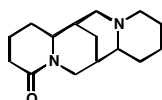
Cytisine



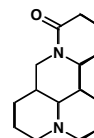
Pusilline



Retamine



Lupanine



Matrine

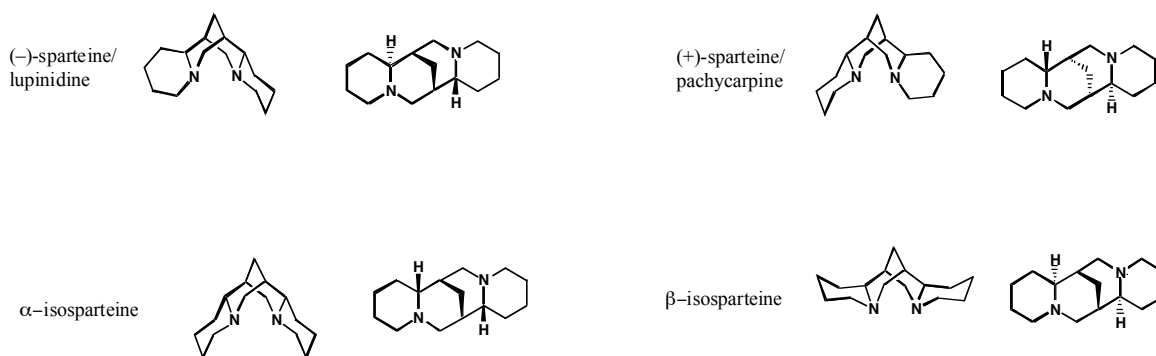
Most contain the quinolizidine ring structure



## General Review

Leonard, N.J. *The Alkaloids, Chemistry and Physiology*, vol. III, R. H. F. Manske and H.L Holmes, Ed., Academic Press, New York, NY, 1953, 119-199.

## Isomers of Sparteine



- (-)-sparteine or lupinidine first isolated in 1851<sup>1</sup>
- (+)-sparteine or pachycarpine is also naturally occurring, but much less abundant
- $\alpha$ -isosparteine isolated after partial and total syntheses<sup>2,3</sup>

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<sup>1</sup> Stenhouse, J. *Annalen*, **1851**, 78, 1.

<sup>2</sup> Marion, L.; Turcotte, F.; Ouellet, J. *Can. J. Chem.* **1951**, 29, 22.

<sup>3</sup> (a) First partial synthesis: Winterfeld, K. *Arch. Pharm.* **1928**, 266, 299. (b) First total synthesis: Leonard, N.J.; Beyler, R.E. *J. Am. Chem. Soc.* **1950**, 72, 1316.

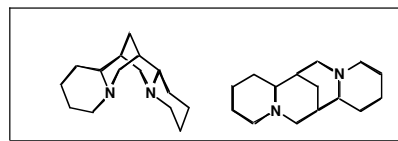
(c) Stereoselective: Oinuma, H.; Dan, S.; Kakisawa, H. *J. Chem. Soc., Chem. Commun.* **1983**, 654.

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## Medical applications of sparteine

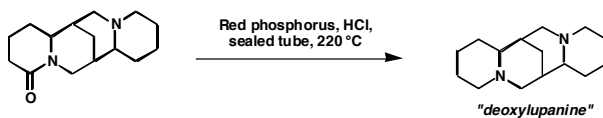
- Lupin alkaloids are generally toxic
- Lupin seeds used as feed must be screened for sparteine levels
- Sparteine is an oxytocic: facilitates childbirth by stimulating contractions of the uterus; induces labor
- Sparteine sulfate marketed as Spartocin injection or Tocosamine sterile solution
- Use was outlawed in 1979 by the FDA due to unpredictable side effects -- associated with uterine rupture and obstetrical complications

## Synthesis -- Early structural issues



• 1851-1929: Formula, reactivity, some structural features assessed

• 1928: First partial synthesis from reduction of ( $\pm$ )-lupanine<sup>1</sup>:

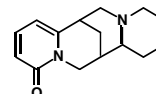


• The most abundant isomer, (–)-sparteine, could not be racemized to corroborate compounds

• At the time, "deoxylupanine" could not be resolved<sup>2</sup>

• 1933: Correct structure proposed<sup>3</sup>, but assignment depended on relation to anagyrene and lupanine

• Step-wise reductions showed relation<sup>4</sup>, but synthesis was key



Anagyrene

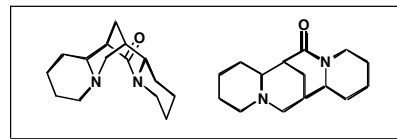
<sup>1</sup> Clemo, G.R.; Leitch, G.C. *J. Chem. Soc.*, **1928**, 1811.

<sup>2</sup> Later resolved by Clemo, G.R.; Raper, R. *Tenniswood, C.R.S. J. Chem. Soc.*, **1931**, 429.

<sup>3</sup> Clemo, G.R.; Raper, R. *J. Chem. Soc.*, **1933**, 644.

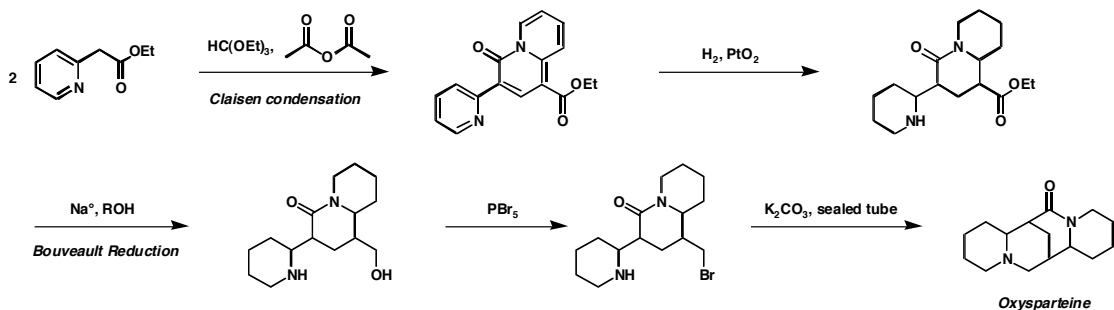
<sup>4</sup> Ing, H.R. *J. Chem. Soc.*, **1933**, 504.

## Early synthetic efforts -- Clemo and coworkers



• Derivatization of sparteine to oxysparteine or "isolupanine" with  $K_3Fe(CN)_6$ <sup>1</sup>

• Total synthesis of a precursor, oxysparteine<sup>2</sup>:



• Confirmed structure of the C<sub>15</sub> lupin alkaloids

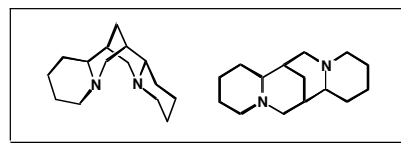
• Oxysparteine could not be reduced by reagents available at the time, but was converted later to sparteine using  $LiAlH_4$ .<sup>3</sup>

<sup>1</sup> Clemo, G.R.; Leitch, G.C. *J. Chem. Soc.*, **1928**, 1811.

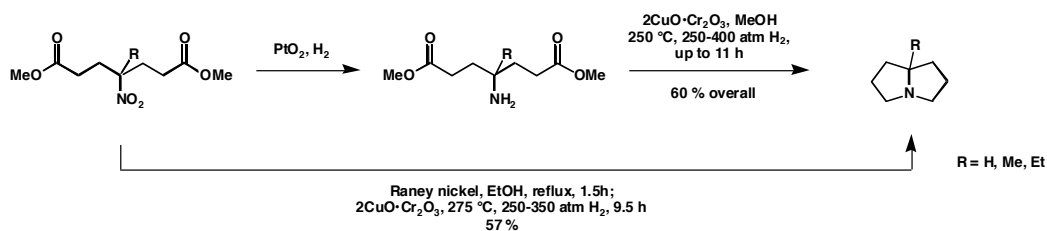
<sup>2</sup> Clemo, G.R.; Morgan, W.McG.; Raper, R. *J. Chem. Soc.*, **1936**, 1025.

<sup>3</sup> Clemo, G.R.; Raper, R.; Short, W.S. *Nature*, **1948**, 162, 296.

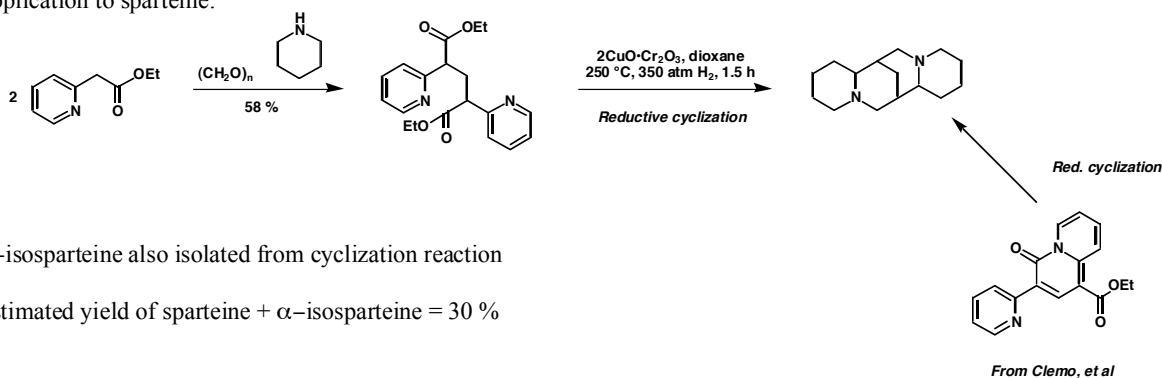
## First total synthesis -- Leonard and coworkers



- Report of a reductive cyclization to form pyrrolizidines:<sup>1</sup>



- Application to sparteine:<sup>2</sup>



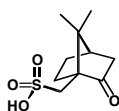
- $\alpha$ -isosparteine also isolated from cyclization reaction
- Estimated yield of sparteine +  $\alpha$ -isosparteine = 30 %

<sup>1</sup> Leonard, N.J.; Hrada, L.R.; Long, F.W.; *J. Am. Chem. Soc.*, **1947**, *69*, 690.

<sup>2</sup> (a) Leonard, N.J.; Beyler, R.E. *J. Am. Chem. Soc.*, **1948**, *70*, 2298. (b) Leonard, N.J.; Beyler, R.E. *J. Am. Chem. Soc.*, **1950**, *72*, 1316

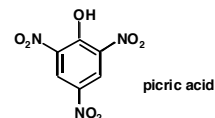
## Resolution -- Leonard and coworkers

- Resolved via  $\beta$ -camphorsulfonic acid<sup>1</sup>

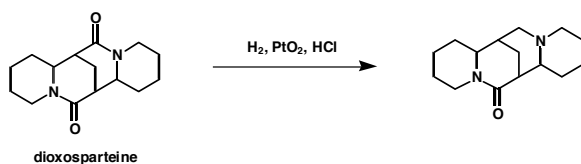


- Characterized and compared with authentic samples via monopicrate, dipicrate and monoperchlorate salts

- $\alpha$ -isosparteine can be separated chromatographically



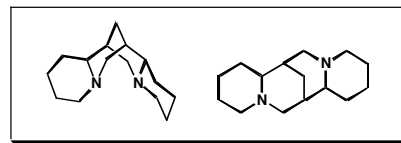
- Early evidence for stereochemistry:<sup>2</sup> $\beta$



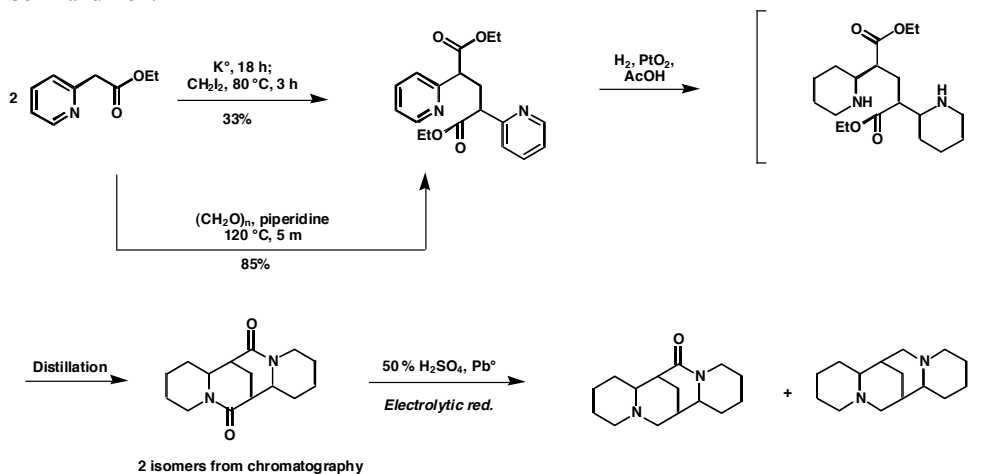
<sup>1</sup> Leonard, N.J.; Beyler, R.E. *J. Am. Chem. Soc.* **1949**, *71*, 757.

<sup>2</sup> Galinovsky, F.; Kainz, G. *Monatsh.*, **1947**, *77*, 137.

## 1948: Year of the sparteine -- Another racemic synthesis

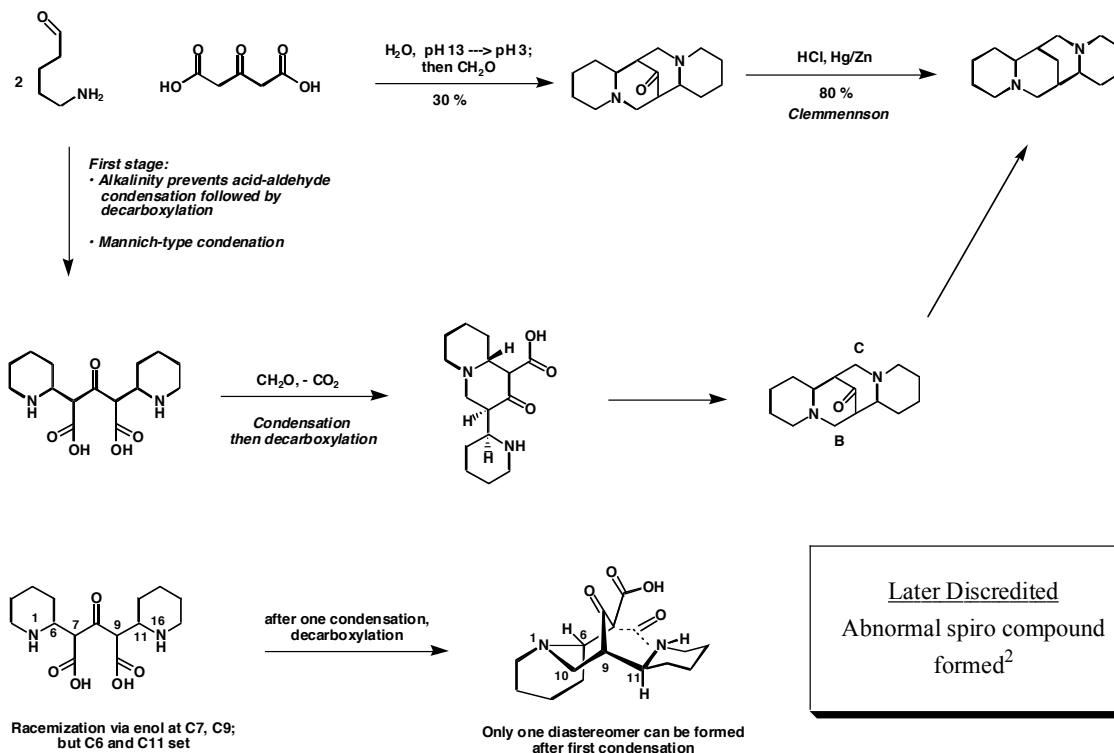


• Sorm and Keil:<sup>1</sup>



<sup>1</sup> (a) Sorm, F.; Keil, B. *Collection Czechoslov. Chem. Commun.* **1947**, *12*, 655. (b) Sorm, F.; Keil, B. *Collection Czechoslov. Chem. Commun.* **1948**, *13*, 544.

## 1950: A proposed bio-related synthesis

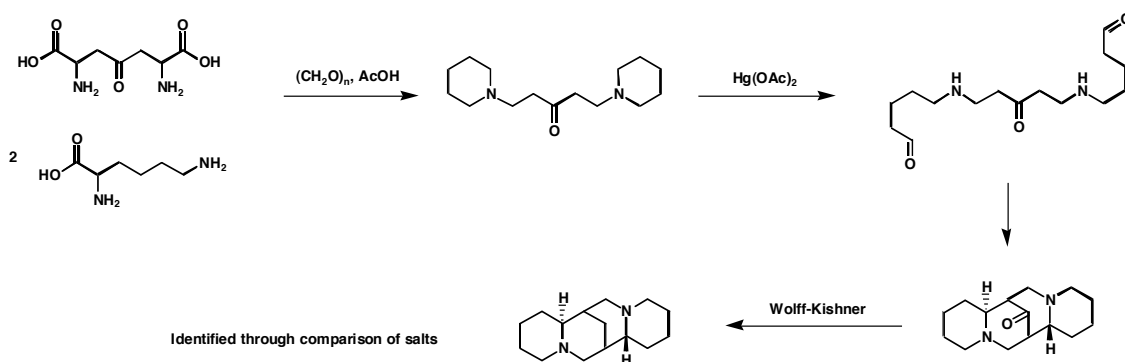


<sup>1</sup> Anet, E.F.L.J.; Hughes, G.K.; Ritchie, E. *Australian J. Sci. Res.* **1950**, *3A*, 635.

<sup>2</sup> Schoepf, C.; Benz, G.; Braun, F.; Hinkel, H.; Rokohol, R. *Angew. Chem.*, **1953**, *65*, 161.

## 1960: Alternative proposed biogenetic synthesis

- Based on current presumptions of the biosynthesis<sup>1,2</sup>

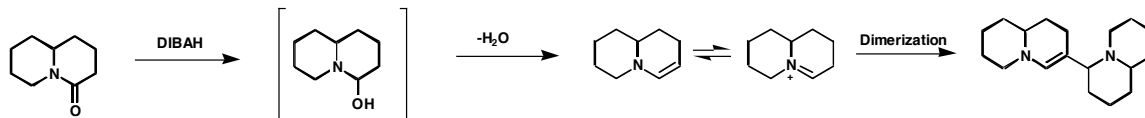


<sup>1</sup>Biosynthesis: Robinson, R. *The Structural Relations of Natural Products*, Oxford University Press, London, 1955, 79.

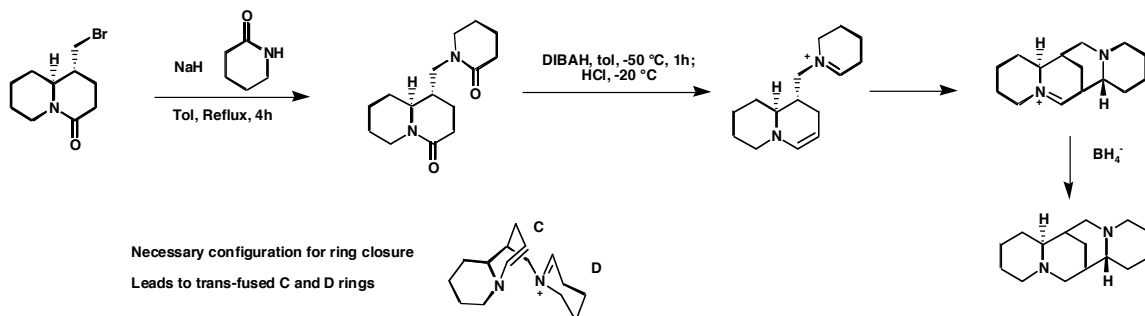
<sup>2</sup> Van Tamelen, E.; Foltz, R.L.; *J. Am. Chem. Soc.*, **1960**, 83, 2400.

## 1973 -- Lactam reduction and condensation approach<sup>1</sup>

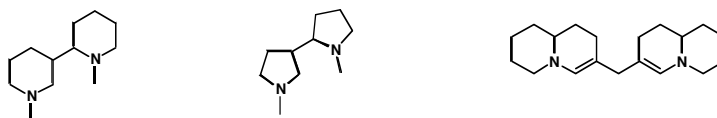
- Principle:



- Applied intramolecularly:

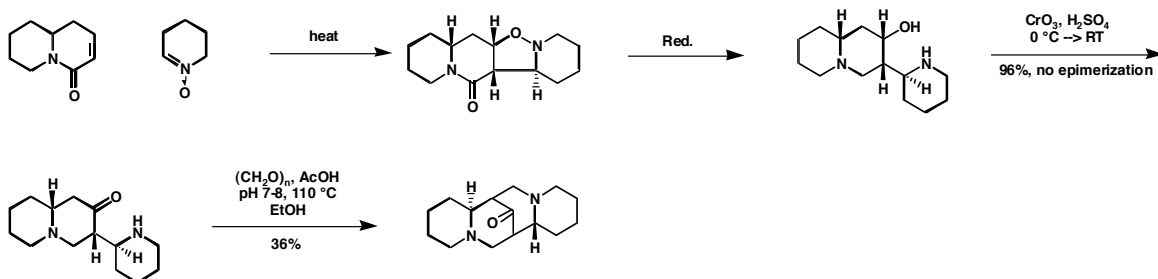


- Applicable to analogs



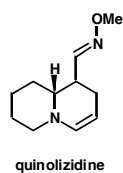
<sup>1</sup>Bohlmann, F.; Mueller, H-J.; Schumann, D. *Chem. Ber.*, 1973, 106, 3026

## 1987 -- Cycloaddition, oxidation, Mannich, reduction<sup>1</sup>

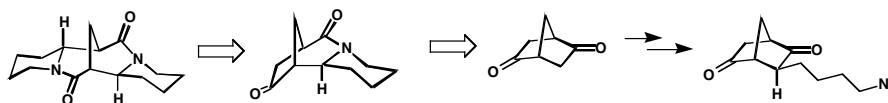


### Further examples:

- Biosynthetic<sup>2</sup>



- Attempted intramolecular Schmidt reaction<sup>3</sup>



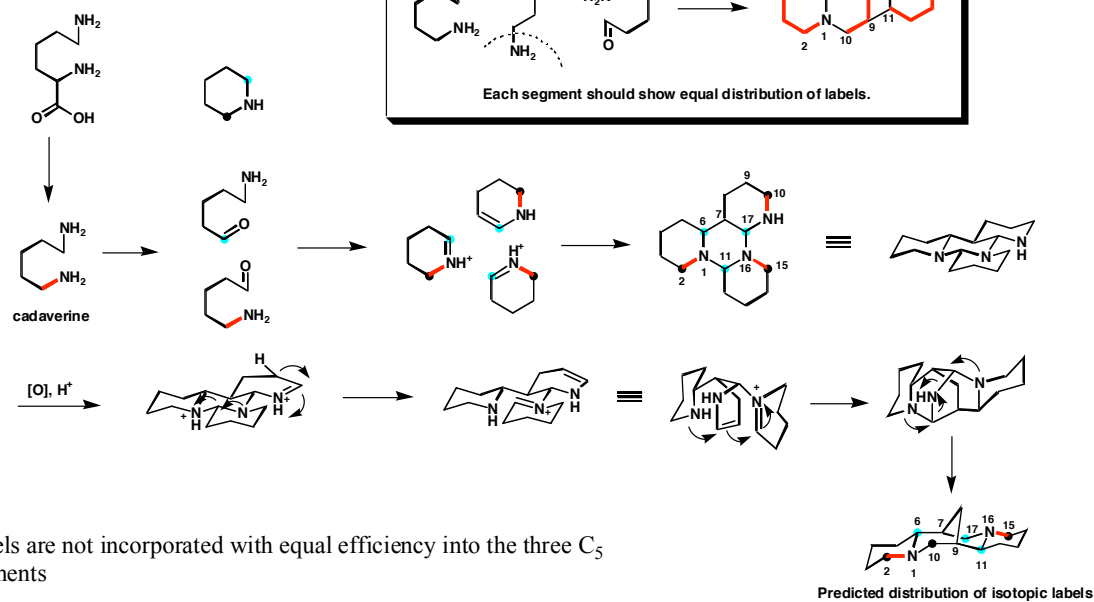
<sup>1</sup>Takatsu, N.; Noguchi, M.; Shigeru, O.; Otomatsu, H. *Chem. Pharm. Bull.*, 1987, 35, 4990

<sup>2</sup>Wanner, M.J.; Koomen, G-J. *J. Org. Chem.*, 1996, 61, 5581.

<sup>3</sup>Wendt, J.A.; Aube, J. *Tet. Lett.*, 1996, 37, 1531.

## A biosynthetic foray

- The piperidine trimer model:<sup>1</sup>

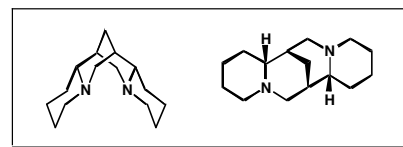


- Labels are not incorporated with equal efficiency into the three C<sub>5</sub> segments

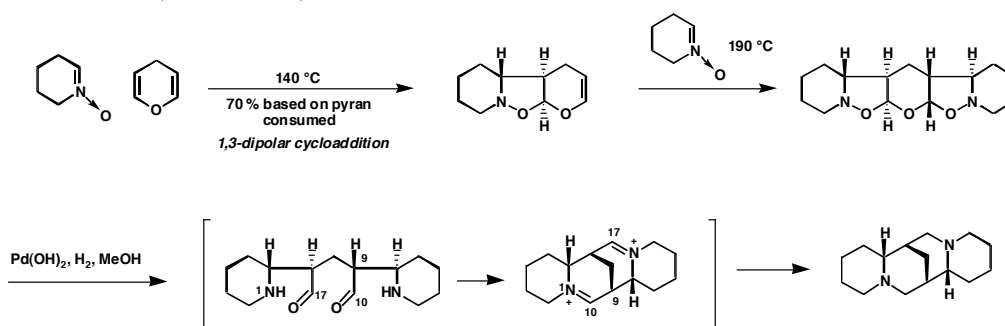
<sup>1</sup> Golebiewski, W.M.; Spencer, I.D. *J. Am. Chem. Soc.*, **1976**, *98*, 6726.

<sup>2</sup> Golebiewski, W.M.; Spencer, I.D. *Can. J. Chem.*, **1987**, *66*, 1734.

## Synthesis $\alpha$ -isosparteine



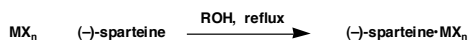
- Stereoselective by successive cycloadditions:<sup>1</sup>



<sup>1</sup> Oinuma, H.; Dan, S.; Kakisawa, H. *J. Chem. Soc. Chem. Commun.*, **1983**, 654.

## Sparteine as ligand -- some examples of transition metal complexes

- Early examples<sup>1</sup>



$\text{MX}_n = \text{CoBr}_2, \text{NiCl}_2, \text{CuCl}_2, \text{CuBr}_2, \text{ZnI}_2, \text{CdCl}_2, \text{etc.}$

Complexes also with  $\alpha$ - and  $\beta$ -isosparteine, sparteine( $\text{H}_2$ )

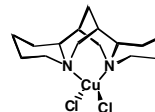
Stable, crystalline salts isolated

V. similar IR spectroscopic properties

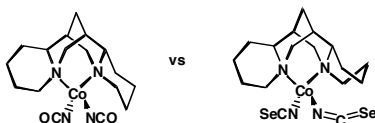
- Effect of different isomers<sup>2</sup>

Rate of hydrolysis varies with degree of physical shielding of the metal by the ligand

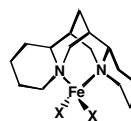
Complex	$10^3 k, \text{s}^{-1}$	$t_{1/2}, \text{min}$
$\beta$ -isosparteine·CuCl <sub>2</sub>	3.85	180
sparteine·CuCl <sub>2</sub>	2.62	264
$\alpha$ -isosparteine·CuCl <sub>2</sub>	2.35	295



- Does the metal or counterion influence conformation of sparteine?<sup>3</sup>



Electronic absorption spectra indicate change in conformation



X = Cl, Br, I

IR data indicates all-chair  
Complexes v. unstable

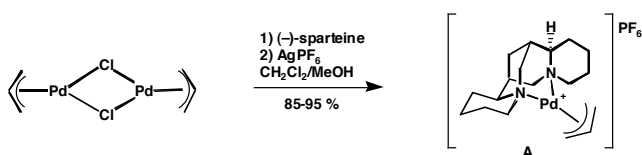
<sup>1</sup> Boschmann, E.; Nypaver, G.A.; Majors, J.P.; Ealy, S.M.; Van Horn, M. *J. Coord. Chem.*, **1978**, *7*, 141.

<sup>2</sup> Boschmann, E.; Weinstock, L.M.; Carmack, M. *Inorg. Chem.*, **1974**, *13*, 1297.

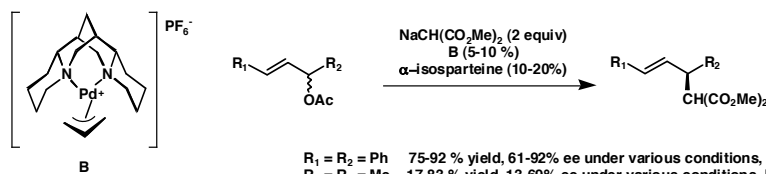
<sup>3</sup> (a) Wroblewski, J.T.; Long, G.J. *Inorg. Chem.*, **1977**, *16*, 704. (b) Wroblewski, J.T.; Long, G.J. *Inorg. Chim. Acta*, **1978**, *30*, 22.

## Sparteine as ligand -- some examples of complexes and applications

- Cationic ( $\eta^3$ -allyl)(sparteine)palladium(II)<sup>1</sup>



- Asymmetric alkylations with A<sup>2</sup> and with (-)- $\alpha$ -isosparteine complex:<sup>3</sup>



R<sub>1</sub> = R<sub>2</sub> = Ph 75-92 % yield, 61-92% ee under various conditions, slightly worse than A  
R<sub>1</sub> = R<sub>2</sub> = Me 17-83 % yield, 13-69% ee under various conditions, better than A

"its pocket depth is deeper than that of sparteine" --> increased stability of B, shorter rxn time

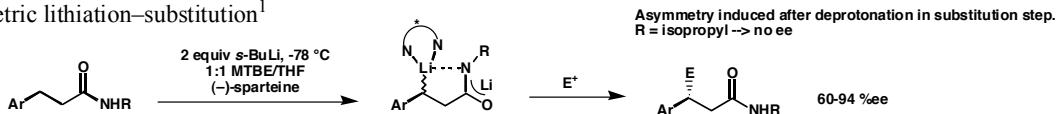
<sup>1</sup> Togni, A.; Rihs, G. *Helv. Chim. Acta*, **1990**, *73*, 723.

<sup>2</sup> Togni, A. *Tet. Asymm.*, **1991**, *2*, 683.

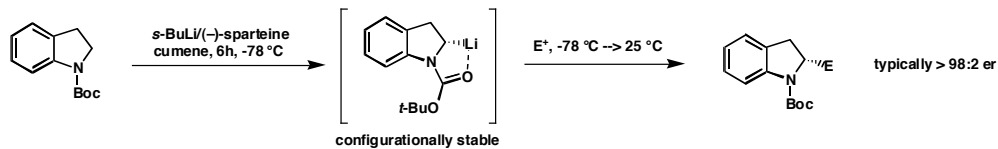
<sup>3</sup> Kang, J.; Cho, W.O.; Won, O.C.; Hyung, G.C. *Tet. Asymm.*, **1994**, 1347.

## Beak applications

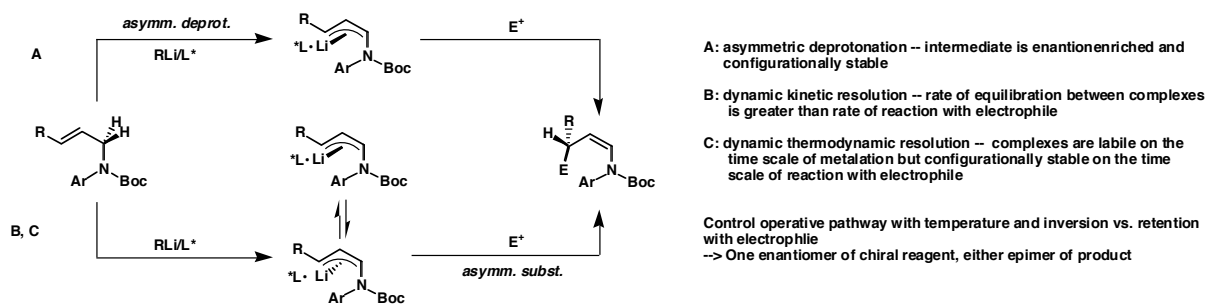
- Asymmetric lithiation–substitution<sup>1</sup>



- Asymmetric lithiation–substitution / deprotonation<sup>2</sup>



- Temperature- and electrophile-dependent stereocontrol<sup>3</sup>



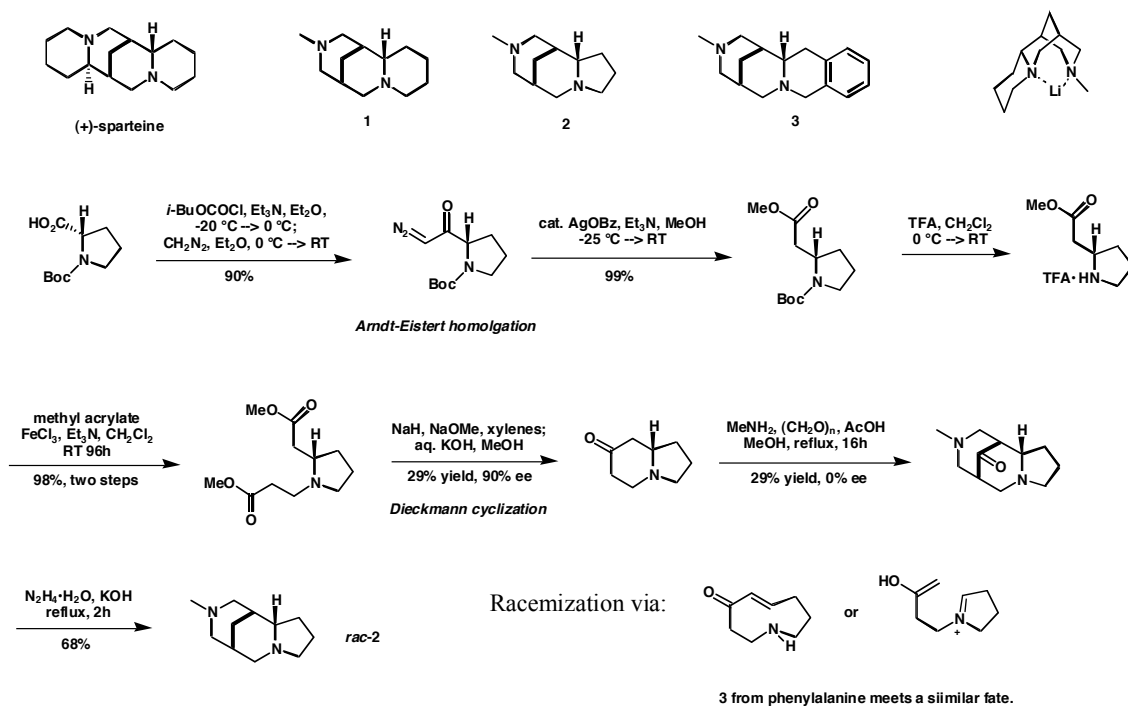
<sup>1</sup> Mechanistic study: Gallagher, D.J.; Du, H.; Long, S.A.; Beak, P. *J. Am. Chem. Soc.*, 1996, 118, 11391.

<sup>2</sup> Bertini Gross, K.M.; Jun, Y.M.; Beak, P. *J. Org. Chem.*, 1997, 62, 7679.

<sup>3</sup> Weisenburger, G.A.; Faibish, N.A.; Pippel, D.A.; Beak, P. *J. Am. Chem. Soc.*, 1999, 121, 9522.

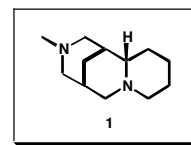
## Efforts towards a suitable substitute...in progress

- O'Brien and coworkers<sup>1</sup>

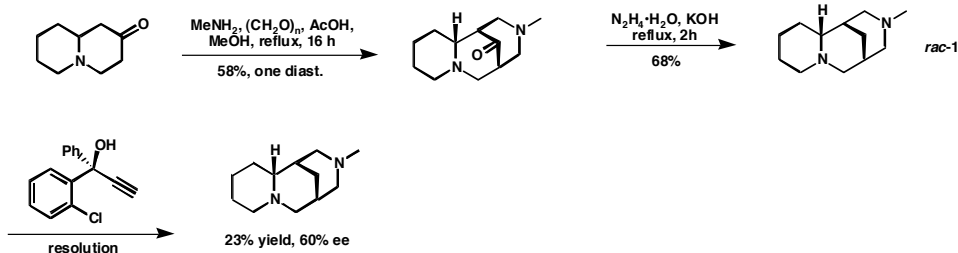


<sup>1</sup> Harrison, J.R.; O'Brien, P.; Porter, D.W.; Smith, N.M. *J. Chem. Soc., Perkin Trans. I.*, 1999, 3623.

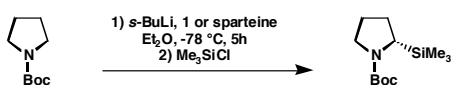
## Efforts towards a suitable substitute...in progress



- O'Brien and coworkers<sup>1</sup>



- Comparison with (-)-sparteine:



Diamine	Yield	% ee
(-)-sparteine	73	95
1 (55% ee)	41	53

Sense of asymmetric induction the same.

- See also Kozlowski, Beak

<sup>1</sup> Harrison, J.R.; O'Brien, P.; Porter, D.W.; Smith, N.M.J. *Chem. Soc., Chem. Commun.*, **2001**, 1202.

## Conclusions

- Sparteine and its isomers remain a synthetic challenge
- Lack of functionality, compact structure, 4 stereocenters, difficult to modify
- Despite limitations, several applications
- Full potential not yet tapped
- Imminent stereoselective syntheses will lead to more extensive application