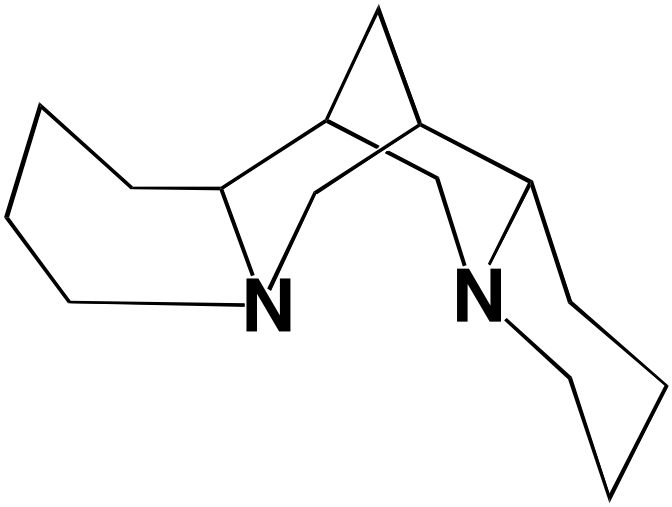
SPARTEINE -- A lupin alkaloid

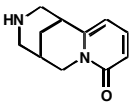


I. Background
II. Synthesis
III. Applications
IV. Analogs

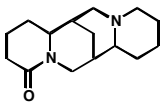
Raissa Trend
Stoltz Conference Room
13 June 2002
12:00 pm

General Information

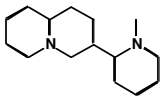
Lupin alkaloids are found in wide variety of plants around the world



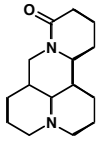
Cytisine



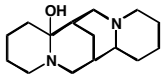
Lupanine



Pusilline



Matrine



Retamine

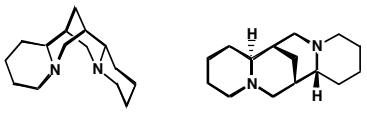
Most contain the quinolizidine ring structure

General Review

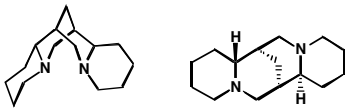
Leonard, N.J. *The Alkaloids, Chemistry and Physiology,* vol. III, R. H. F. Manske and H.L Holmes, Ed., Academic Press, New York, NY, 1953, 119-199.

Isomers of Sparteine

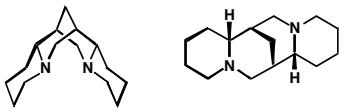
(–)-sparteine/
lupinidine



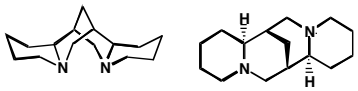
(+)-sparteine/
pachycarpine



α–isosparteine



β–isosparteine



- (–)-sparteine or lupinidine first isolated in 1851[1]
- (+)-sparteine or pachycarpine is also naturally occurring, but much less abundant
- α–isosparteine isolated after partial and total syntheses[2,3]

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[1] Stenhouse, J. *Annalen*, **1851,** *78*, 1.

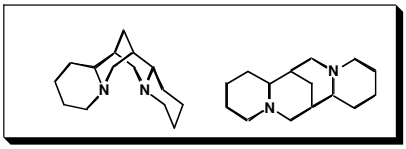
[2] Marion, L.; Turcotte, F.; Ouellet, J. *Can. J. Chem.* **1951**, *29*, 22.

[3] (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.

Medical applications of sparteine

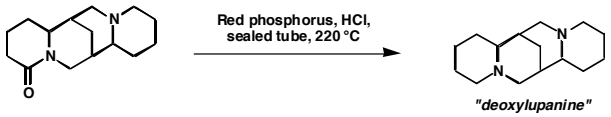
- Lupin alkaloids are generally toxic
- Lupin seeds used as feed must be screened for sparteine levels
- Sparteine is an oxytocic: facilitates childbirth by stimulating contractions of the uterus; induces labor
- Sparteine sulfate marketed as Spartocin injection or Tocosamine sterile solution
- Use was 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 (±)-lupanine[1]:

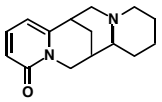


• The most abundant isomer, (–)-sparteine, could not be racemized to corroborate compounds

• At the time, "deoxylupanine" could not be resolved[2]

• 1933: Correct structure proposed[3], but assignment depended on relation to anagyrine and lupanine

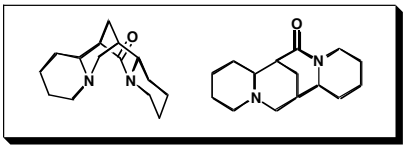
• Step-wise reductions showed relation[4], but synthesis was key



Anagyrine

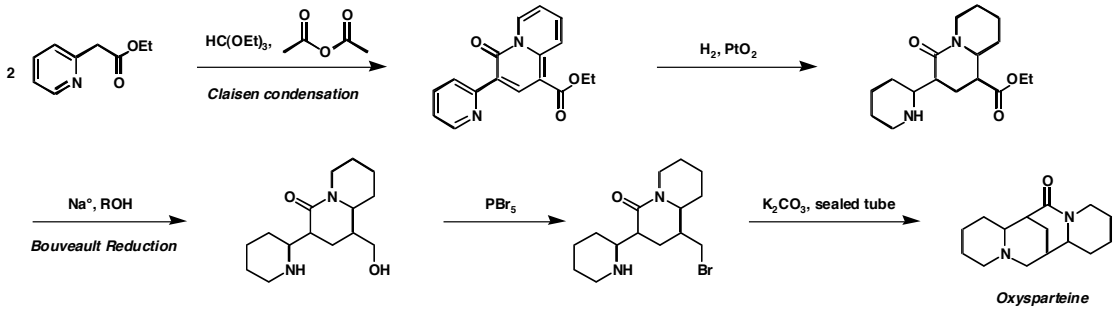
[1] Clemo, G.R.; Leitch, G.C. *J. Chem. Soc,* **1928**, 1811.
[2] Later resolved by Clemo, G.R.; Raper, R. Tenniswood, C.R.S. *J. Chem. Soc.*, **1931**, 429.
[3] Clemo, G.R.; Raper, R. *J. Chem. Soc.*, **1933**, 644.
[4] Ing, H.R. *J. Chem. Soc.*, **1933**, 504.

Early synthetic efforts -- Clemo and coworkers



• Derivatization of sparteine to oxysparteine or "isolupanine" with $K_3Fe(CN)_6$[1]

• Total synthesis of a precusor, oxysparteine[2]:

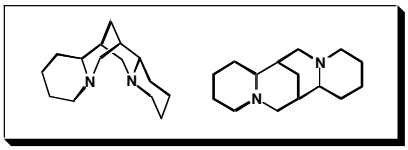


• Confirmed structure of the C_{15} lupin alkaloids

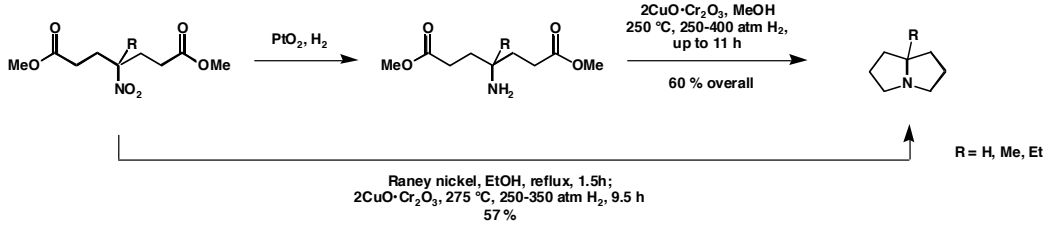
• Oxysparteine could not be reduced by reagents available at the time, but was converted later to sparteine using $LiAlH_4$.[3]

[1] Clemo, G.R.; Leitch, G.C. *J. Chem. Soc.*, **1928**, 1811.
[2] Clemo, G.R.; Morgan, W.McG.; Raper, R. *J. Chem. Soc.,* **1936**, 1025.
[3] Clemo, G.R.; Raper, R.; Short, W.S. *Nature*, **1948**, *162*, 296.

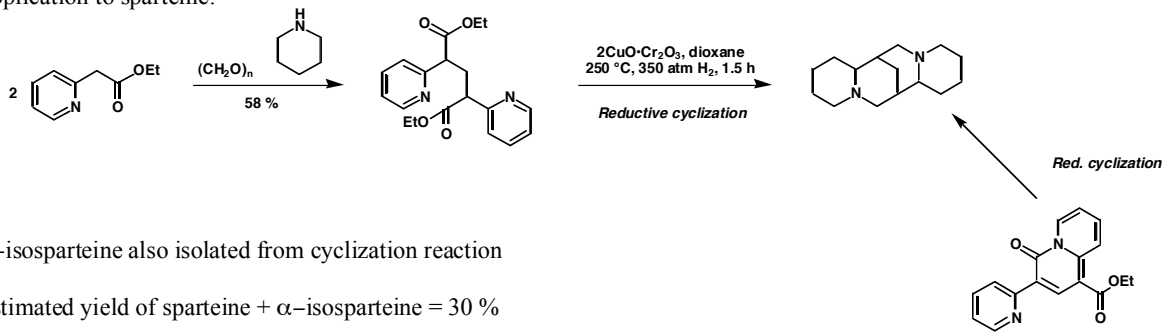
First total synthesis -- Leonard and coworkers



• Report of a reductive cyclization to form pyrrolizidines:[1]



• Application to sparteine:[2]



• α–isosparteine also isolated from cyclization reaction

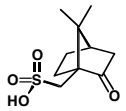
• Estimated yield of sparteine + α–isosparteine = 30 %

From Clemo, et al

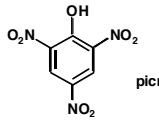
[1] Leonard, N.J.; Hruda, L.R.; Long, F.W.; *J. Am. Chem. Soc.*, **1947**, *69*, 690.
[2] (a) Leonard, N.J.; Beyler, R.E. *J. Am. Chem. Soc.*, **1948**, *70*, 2298. (b) Leonard, N.J.; Beyler, R.E. *J. Am. Chem. Soc.*, **1950**, *72*, 1316

Resolution -- Leonard and coworkers

• Resolved via β–camphorsulfonic acid[1]



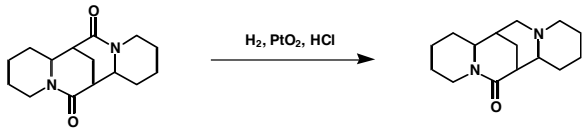
• Characterized and compared with authentic samples via monopicrate, dipicrate and monoperchlorate salts



picric acid

• α–isosparteine can be separated chromatographically

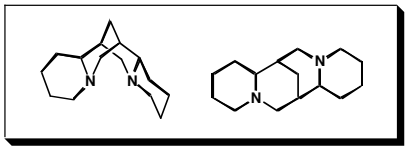
• Early evidence for stereochemistry:[2]ß



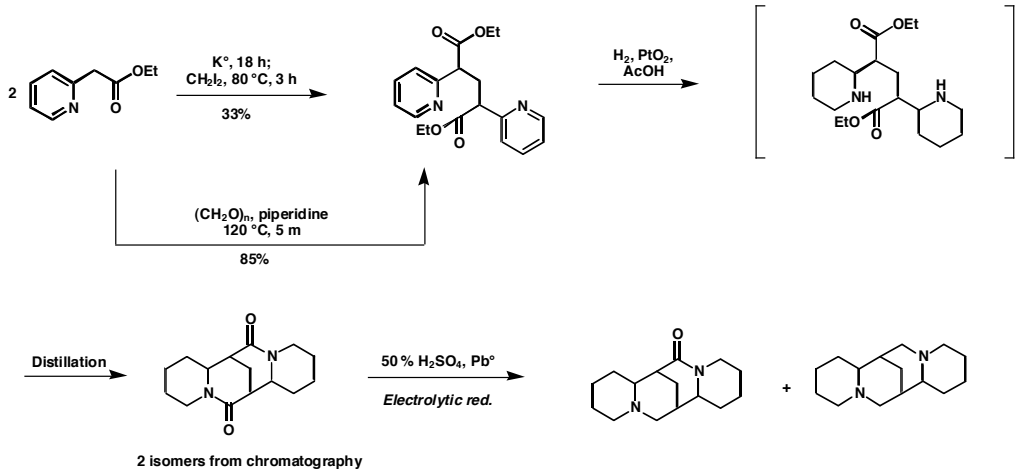
dioxosparteine

[1] Leonard, N.J.; Beyler, R.E. *J. Am. Chem. Soc.* **1949**, *71, 757.*
[2] Galinovsky, F.; Kainz, G. *Monatsh.*, **1947**, *77*, 137.

1948: Year of the sparteine -- Another racemic synthesis

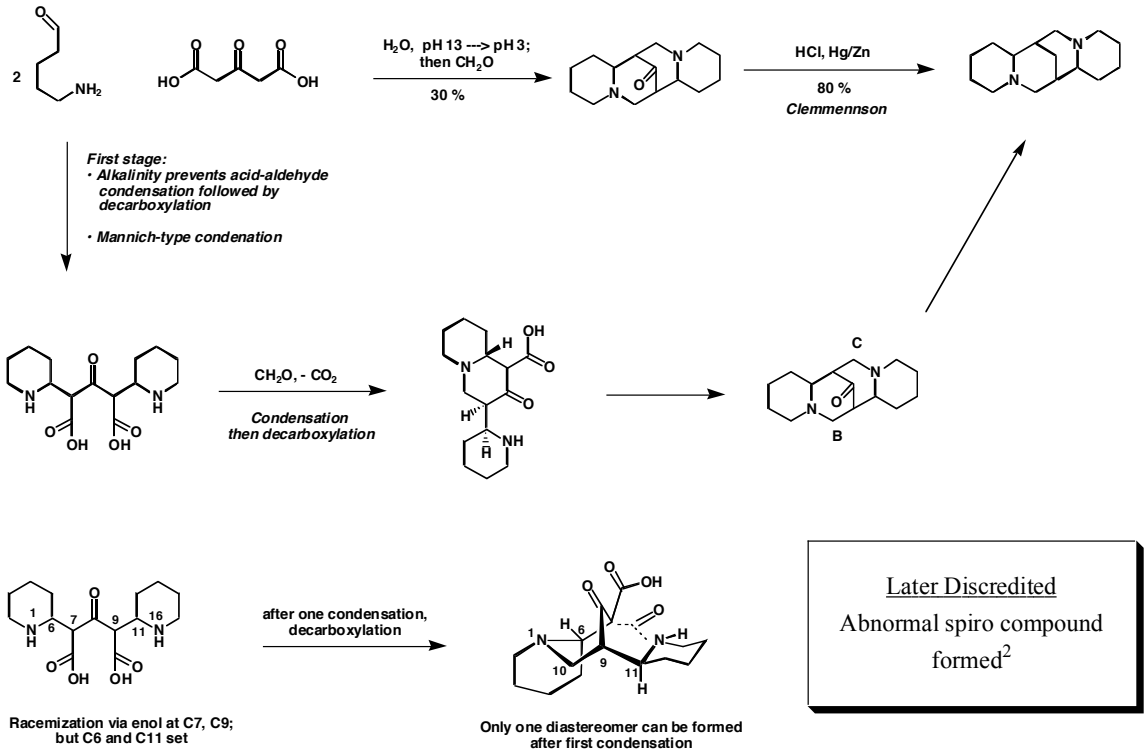


- Sorm and Keil:[1]



[1] (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



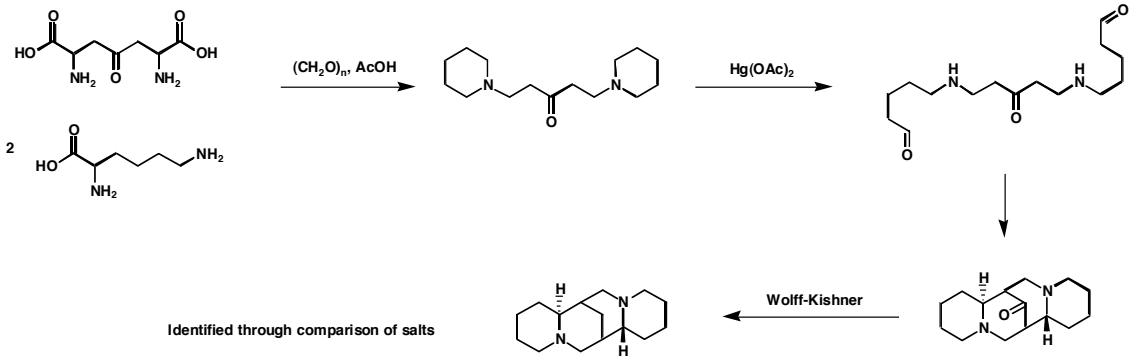
Later Discredited
Abnormal spiro compound formed[2]

[1] Anet, E.F.L.J.; Hughes, G.K.; Ritchie, E. *Australian J. Sci. Res.,* **1950**, *3A*, 635.

[2] Schoepf, C.; Benz, G.; Braun, F; Hinkel, H,; Rokohol, R. *Angew. Chem.*, **1953**, *65*, 161.

1960: Alternative proposed biogenetic synthesis

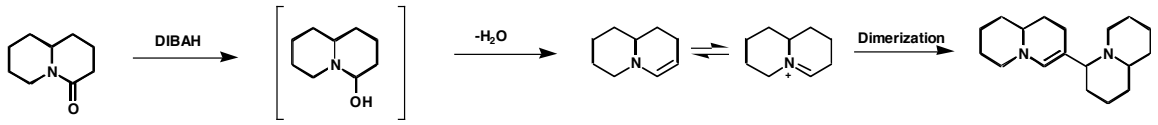
• Based on current presumptions of the biosynthesis[1, 2]



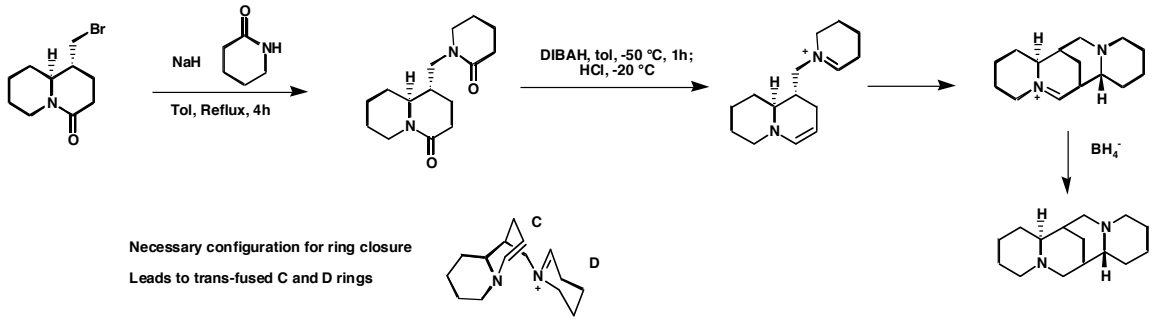
[1]Biosynthesis: Robinson, R. *The Structural Relations of Natural Products*, Oxford University Press, London, 1955, 79.
[2] Van Tamelen, E.; Foltz, R.L.; *J. Am. Chem. Soc.*, **1960,** *83*, 2400.

1973 -- Lactam reduction and condensation approach[1]

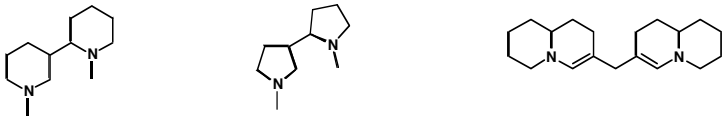
• Principle:



• Applied intramolecularly:

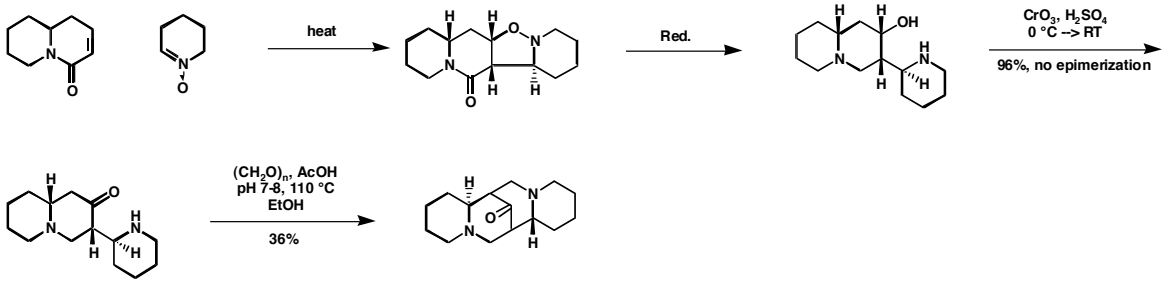


• Applicable to analogs



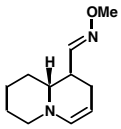
[1]Bohlmann, F.; Mueller, H-J.; Schumann, D. *Chem. Ber.*, **1973**, *106*, 3026

1987 -- Cycloaddition, oxidation, Mannich, reduction[1]



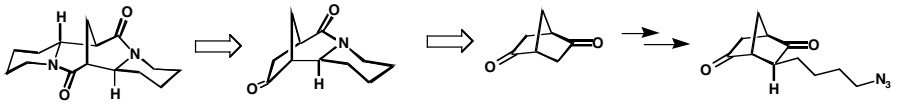
Further examples:

• Biosynthetic[2]



quinolizidine

• Attempted intramolecular Schmidt reaction[3]



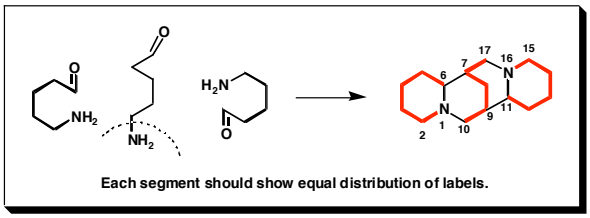
[1] Takatsu, N.; Noguchi, M.; Shigeru, O.; Otomatsu, H. *Chem. Pharm. Bull.*, **1987**, *35*, 4990

[2] Wanner, M.J.; Koomen, G-J. *J. Org. Chem.*, **1996**, *61*, 5581.

[3] Wendt, J.A.; Aube, J. *Tet. Lett.*, **1996**, *37*, 1531.

A biosynthetic foray

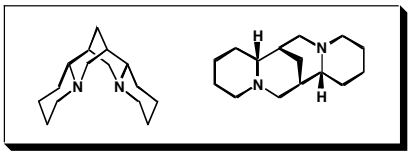
• The piperidine trimer model:[1]



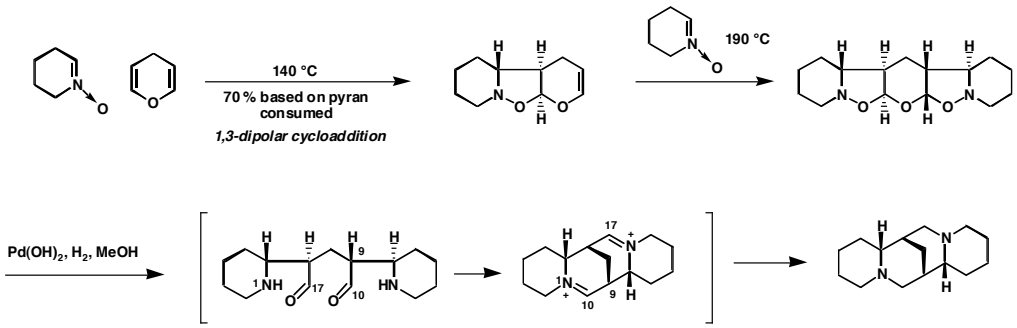
• Labels are not incorporated with equal efficiency into the three C_5 segments

[1] Golebiewski, W.M.; Spencer, I.D. *J. Am. Chem. Soc.*, **1976**, *98*, 6726.
[2] Golebiewski, W.M.; Spencer, I.D. *Can. J. Chem.*, **1987**, *66*, 1734.

Synthesis α–isosparteine



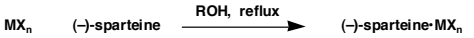
• Stereoselective by successive cycloadditions:[1]



[1] Oinuma, H.; Dan, S.; Kakisawa, H. ***J. Chem. Soc. Chem. Commun.***, **1983**, 654.

Sparteine as ligand -- some examples of transition metal complexes

• Early examples[1]



MX_n = $CoBr_2$, $NiCl_2$, $CuCl_2$, $CuBr_4$, ZnI_2, $CdCl_2$, etc.

Complexes also with α– and β–isosparteine, sparteine(H_2)

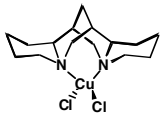
Stable, crystalline salts isolated

V. similar IR spectroscopic properties

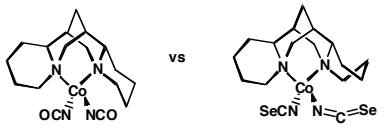
• Effect of different isomers[2]

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

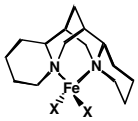
Complex	10^3k, s^{-1}	$t_{1/2}$, min
β–isosparteine·$CuCl_2$	3.85	180
sparteine·$CuCl_2$	2.62	264
α–isosparteine·$CuCl_2$	2.35	295



• Does the metal or counterion influence conformation of sparteine?[3]



Electronic absorption spectra indicate change in conformation



X = Cl, Br, I

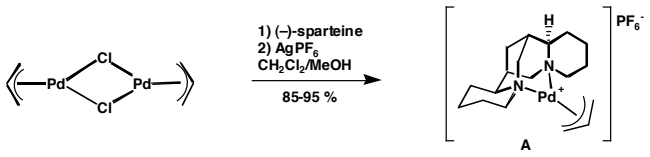
IR data indicates all-chair

Complexes v. unstable

[1] Boschmann, E.; Nypaver, G.A.; Majors, J.P.; Ealy, S.M.; Van Horn, M. *J. Coord. Chem.*, **1978**, *7*, 141.
[2] Boschmann, E.; Weinstock, L.M.; Carmack, M. *Inorg. Chem.*, **1974**, *13*, 1297.
[3] (a) Wrobelski, J.T.; Long, G.J. *Inorg. Chem.*, **1977**, *16*, 704. (b) Wrobelski, J.T.; Long, G.J. *Inorg. Chim. Acta*, **1978**, *30*, 22.

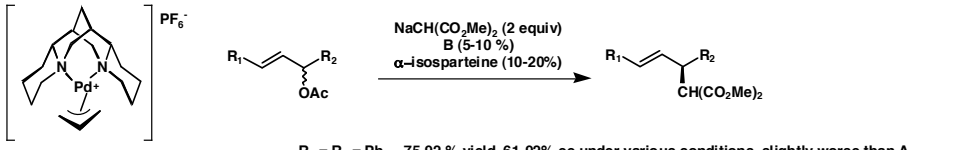
Sparteine as ligand -- some examples of complexes and applications

• Cationic (η^3-allyl)(sparteine)palladium(II)[1]



A

• Asymmetric alkylations with A[2] and with (–)-α-isosparteine complex:[3]



B

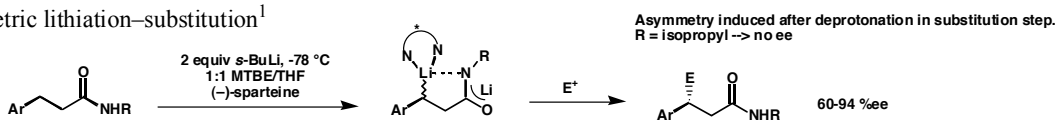
$R_1 = R_2$ = Ph 75-92 % yield, 61-92% ee under various conditions, slightly worse than A
$R_1 = R_2$ = Me 17-83 % yield, 13-69% ee under various conditions, better than A

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

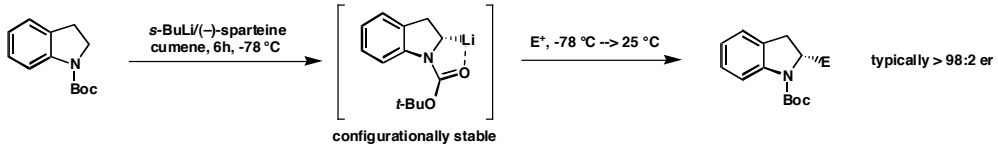
[1] Togni, A.; Rihs, G. *Helv. Chim. Acta*, **1990**, *73*, 723.
[2] Togni, A. *Tet. Asymm.*, **1991**, *2*, 683.
[3] Kang, J.; Cho, W.O.; Won, O.C.; Hyung, G.C. *Tet. Asymm.*, **1994**, 1347.

Beak applications

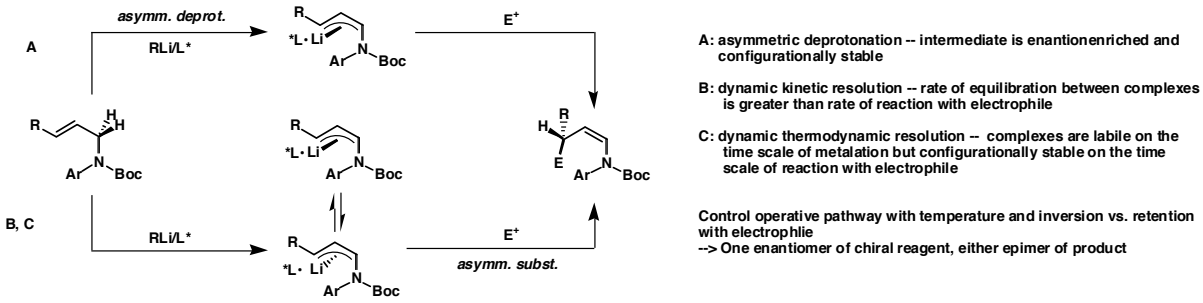
• Asymmetric lithiation–substitution[1]



• Asymmetric lithiation–substitution / deprotonation[2]



• Temperature- and electrophile-dependent stereocontrol[3]



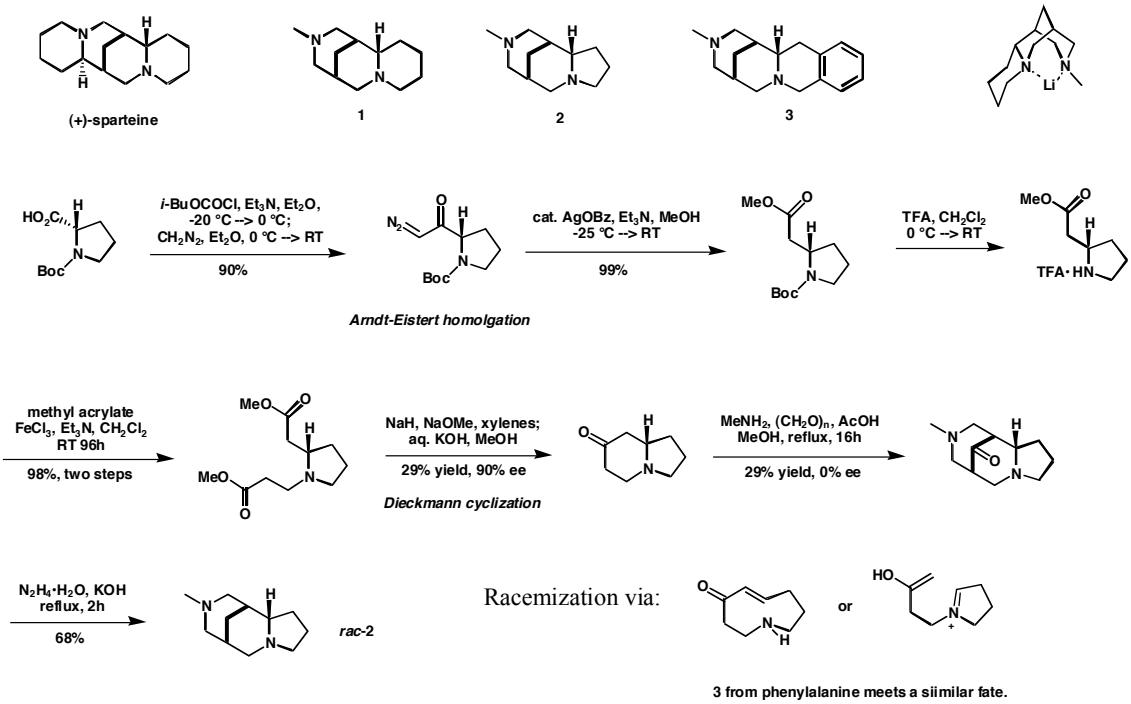
[1] Mechanistic study: Gallagher, D.J.; Du, H.; Long, S.A.; Beak, P. *J. Am Chem. Soc.,* **1996**, *118*, 11391.

[2] Bertini Gross, K.M.; Jun, Y.M.; Beak, P. *J. Org. Chem.,* **1997**, *62*, 7679.

[3] Weisenburger, G.A.; Faibish, N.A.; Pippel, D.A.; Beak, P. *J. Am. Chem. Soc.*, **1999**, *121*, 9522.

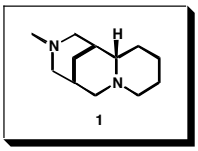
Efforts towards a suitable substitute...in progress

• O'Brien and coworkers[1]

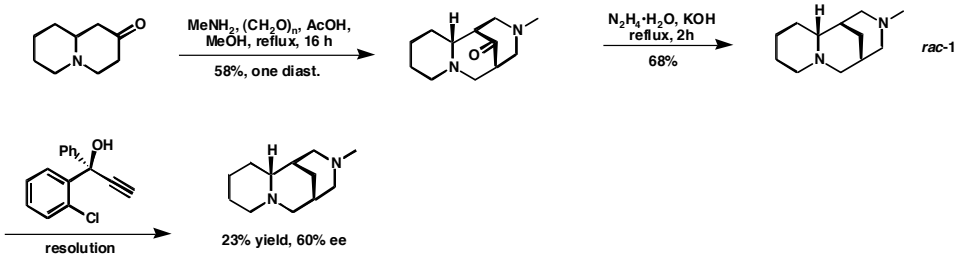


[1] Harrison, J.R.; O'Brien, P.; Porter, D.W.; Smith, N.M. *J. Chem. Soc., Perkin Trans. I.*, **1999**, 3623.

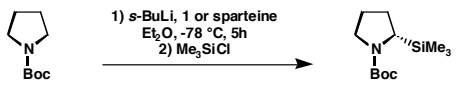
Efforts towards a suitable substitute...in progress



• O'Brien and coworkers[1]



• Comparison with (–)-sparteine:



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

Sense of asymmetric induction the same.

• See also Kozlowski , Beak

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[1] 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