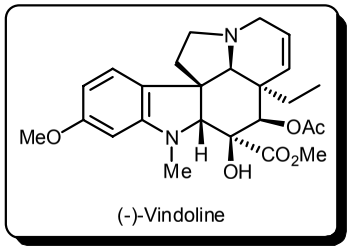
Christos Mitsos

Vindoline

Group Meeting
12/8/2004

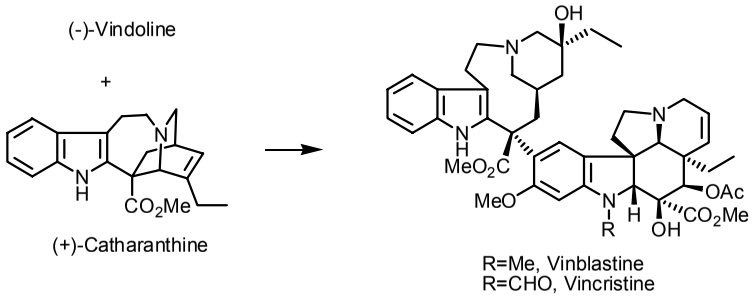


(-)-Vindoline

Major alkaloid of Catharanthus roseus

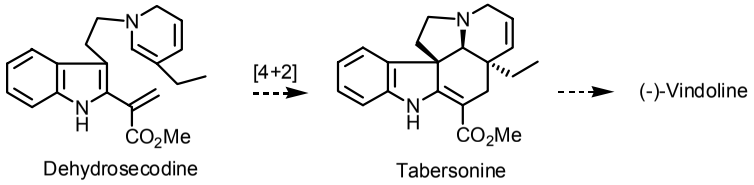
Isolation: Gorman, M. et al. J . Am. Pharm. Assoc., Sci. Ed. 1959, 48, 256.
Structure: Gorman, M. et al. J. Am. Chem. Soc. 1962, 84, 1058-1059.
Crystal structure: Maurin, J. K. et al. Acta Cryst. 2004, C60, 377-380.
Biosynthesis: Scott, A. I. et al. J .Am. Chem. Soc. 1968, 90, 4144-4150.

Vindoline bears no significant biological activities.
However, vinblastine, resulting from the coupling of (-)vindoline with (+)-catharanthine and vincristine, the corresponding N-formyl alkaloid, display significant antitumor activity.
Currently vinblastine and vincristine are used for the treatment of leukemia and lymphoma.



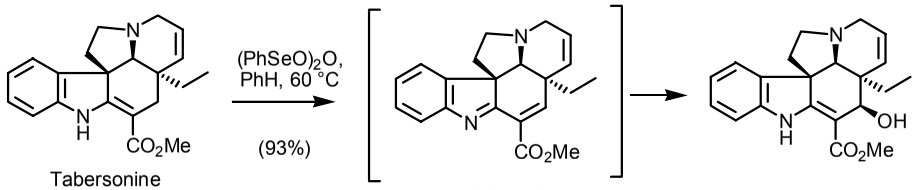
For a review see: Potier, P. J. Nat. Prod. 1980, 43, 72-86.

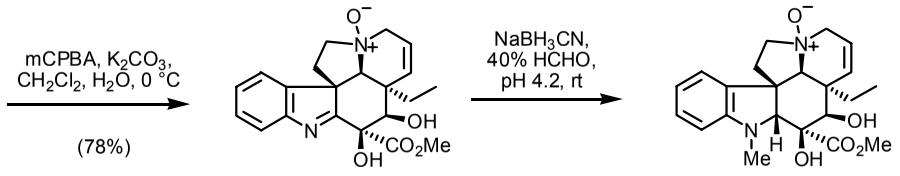
Biosynthetic hypothesis (Wenkert, E. J. Am. Chem. Soc. 1962, 84, 98-102)

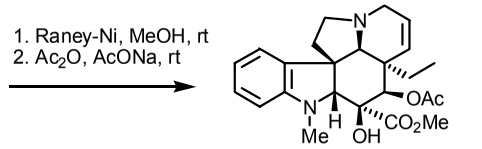


The above hypothesis was supported by the isolation of secodine from natural sources:
Battersby, A. R.; Bhatnagar, A. K. J. Chem. Soc., Chem. Commun. 1970, 193-194.

Bruno Danieli (1984): Hemisynthesis of vindoline from 16-MeO-tabersonine

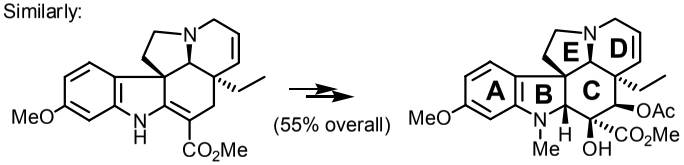






Vindorosine

Similarly:



16-MeO-Tabersonine

Vindoline

Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R. J. Chem. Soc., Chem. Commun. 1984, 909-911.
idem. J. Chem. Soc., Perkin Trans. 1 1987, 155-161.

Scope of presentation

Syntheses of Vindoline: 6 total (3 enantioselective)
4 formal
Through Danieli's 5-step sequence every synthesis of 16-MeO-tabersonine can be extended to vindoline
Several syntheses of 16-MeO-tabersonine have been reported - the most creative of them will be also discussed

Christos Mitsos

George Büchi's total synthesis

Group Meeting
12/8/2004

George H. Büchi (1921-1998)

Born in Baden, Switzerland. Diploma and DSc from Eidgenoss-ische Technische Hoch-schule in Zurich

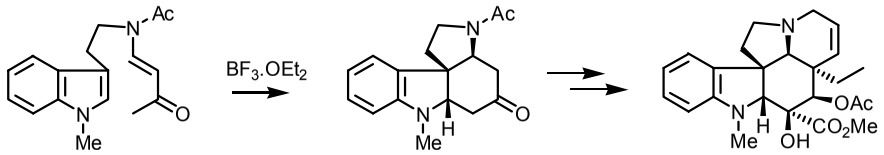
Passed his entire academic career in MIT (1951-1991)

Worked on: organic photochemistry, natural product characterization and natural product total synthesis

A pioneer in organic photochemistry in the 50's
Determined the structure of 55 natural products
Completed the syntheses of 75 natural products

An avid hiker, hunter, skier and fisherman, died of heart failure while hiking in Switzerland

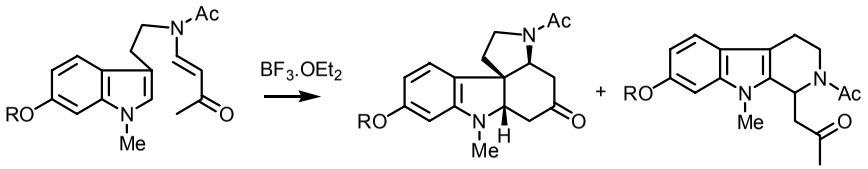
Key step involves a Robinson-type annulation first employed in the synthesis of vindorosine:



Vindorosine

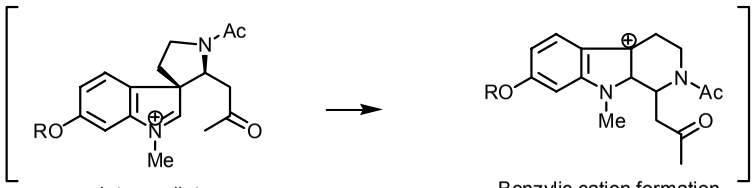
Büchi, G. et al. J. Am. Chem. Soc. 1971, 93, 3299-3300.

Effect of substituent on indole 6-position:



R = Me : 9%
R = Ts : 89%

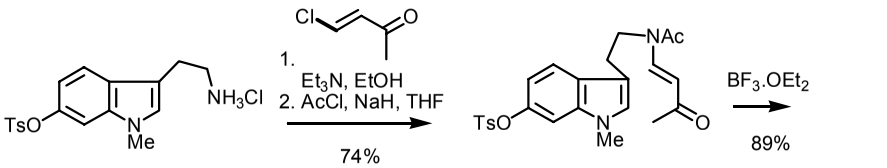
major
2%

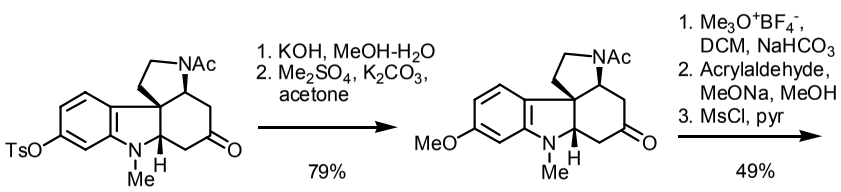


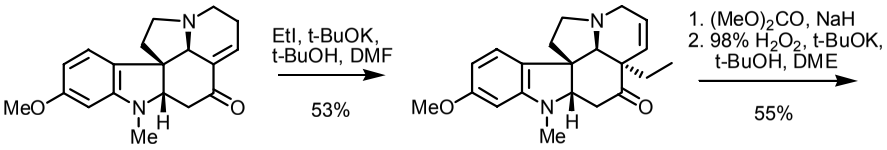
Intermediate indolenium ion

Wagner-Meerwein type rearrangement

Benzylic cation formation favored when para EDG

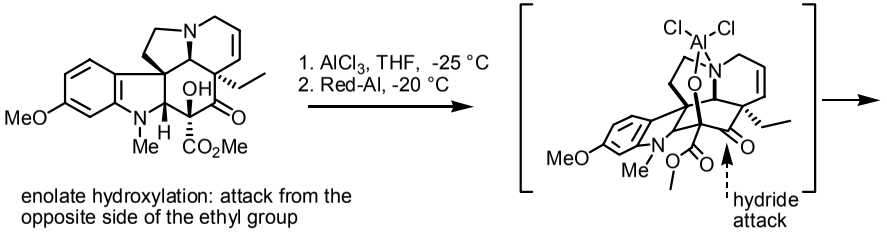






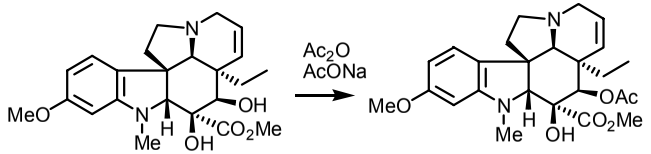
alkylation diastereoselectivity:
CD fused rings need to be cis

'top' face flanked by coordinated LA



enolate hydroxylation: attack from the opposite side of the ethyl group

reduction under other conditions resulted in mixtures of epimeric alcohols



(±)-Vindoline

Ando, M.; Büchi, G.; Ohnuma, T. J. Am. Chem. Soc. 1975, 97, 6880-6881.

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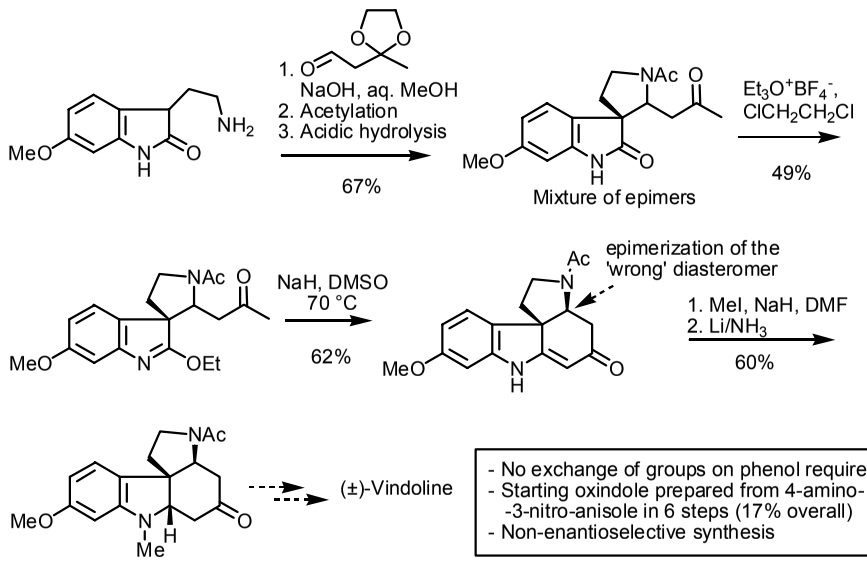
Formal syntheses based on Büchi's route

Group Meeting
12/8/2004

Yoshio Ban (1978): Developed a synthesis of Büchi's ABCE tetracyclic intermediate



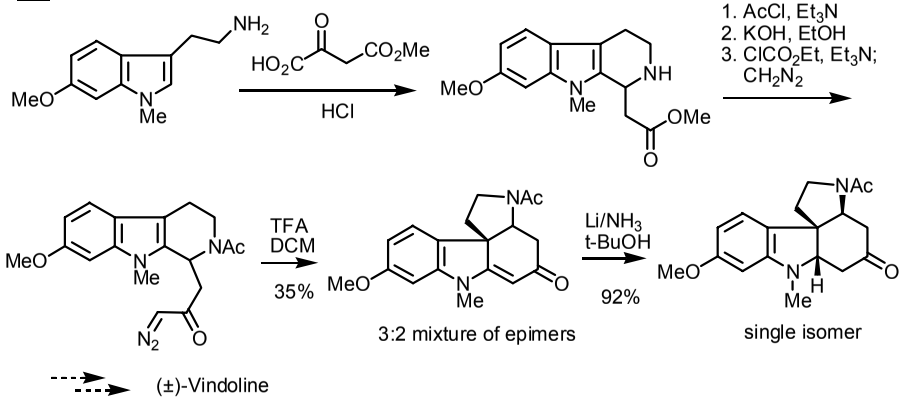
- No exchange of groups on phenol required
- Starting oxindole prepared from 4-amino-3-nitro-anisole in 6 steps (17% overall)
- Non-enantioselective synthesis

Ban Y. et al. Tetrahedron Lett. 1978, 151-154.

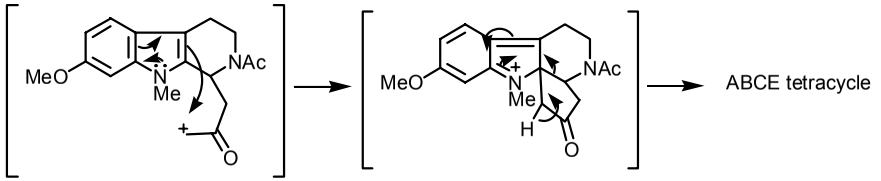
Seiichi Takano (1977): Two syntheses of Büchi's ABCE intermediate

Takano, S. et al. Heterocycles 1977, 6, 1699-1704.
Takano, S. et al. J. Chem. Soc., Chem. Comm. 1978, 943-944.

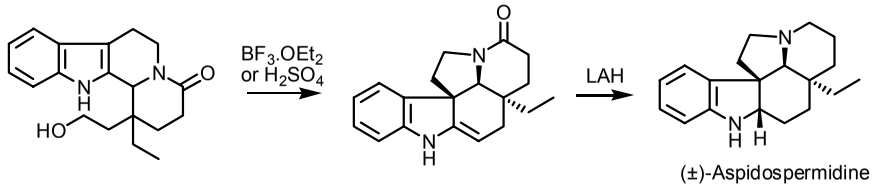
1st:



Mechanism: Diazoketone forms a cationic intermediate which attacks the indole double bond. Rearrangement gives the ABCE tetracycle.



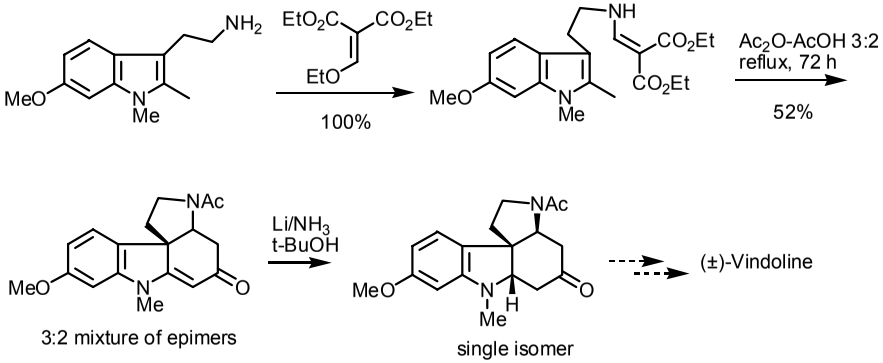
Precedent: Harley-Mason's synthesis of aspidospermidine



Harley-Mason, J.; Kaplan, M. Chem. Comm. 1967, 915-916.

- Mechanistically interesting transformation
- Non-enantioselective route
- Similar transformations adopted by Langlois and Rapoport in their total syntheses of vindoline (vide infra)

2nd:



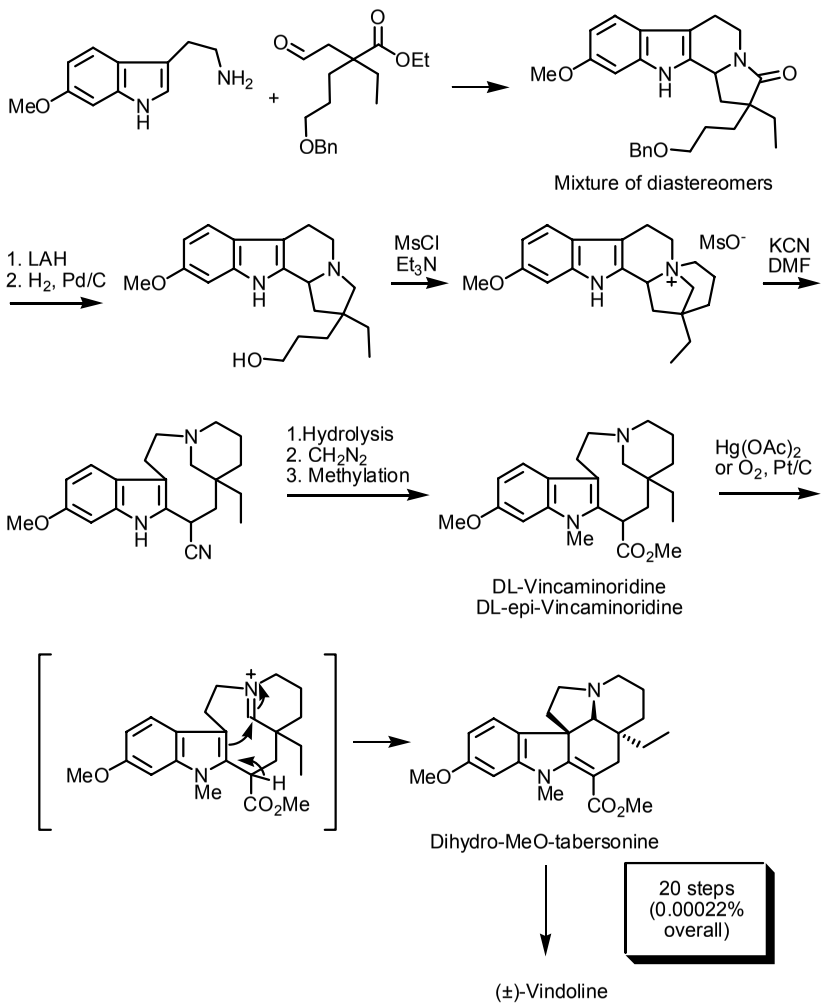
- Tandem 1,4-addition and Dieckmann-type condensation of the enamine
- No reaction in Ac_2O or AcOH alone
- Non-enantioselective synthesis

Christos Mitsos

Kutney's and Langlois' total syntheses

Group Meeting
12/8/2004

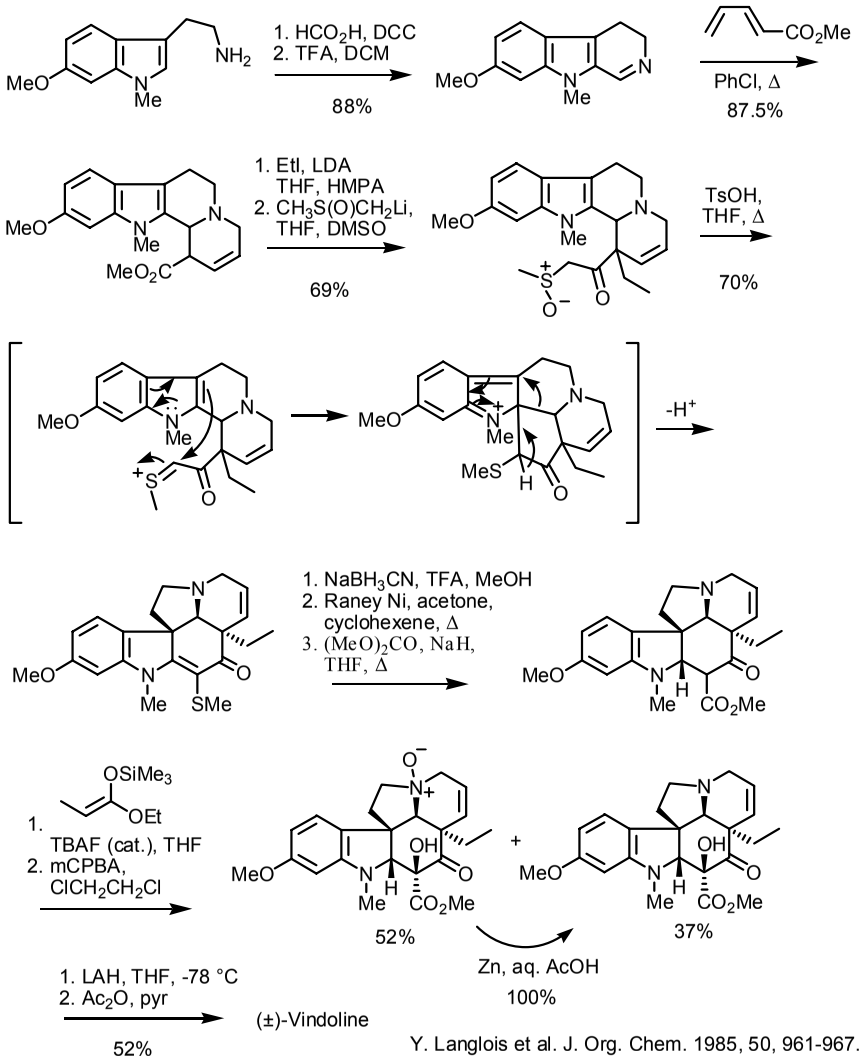
James B. Kutney (1968 and 1978): Second Total synthesis of vindoline



Dihydro-MeO-tabersonine: J. P. Kutney et al. J. Am. Chem. Soc. 1968, 90, 3891-3893.
Vindoline: J. P. Kutney et al. J. Am. Chem. Soc. 1978, 100, 4220-4224.

- Simple and efficient route to 4-ring Aspidosperma alkaloids (Vincaminoridine)
- Transannular cyclization provides diastereoselectively the 5-ring vindoline skeleton

Yves Langlois (1985): Third total synthesis of vindoline

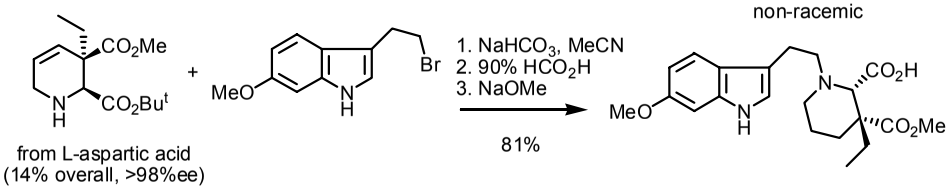


Y. Langlois et al. J. Org. Chem. 1985, 50, 961-967.

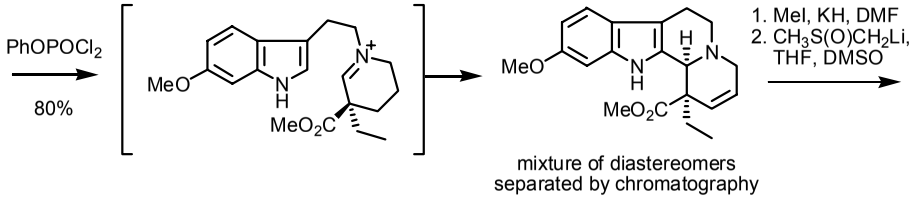
- Elegant synthesis based on Harley-Mason's transformation
- Requisite cationic intermediate formed through a Pummerer rearrangement
- Non-enantioselective synthesis

Henry Rapoport (1987): Enantioselective synthesis

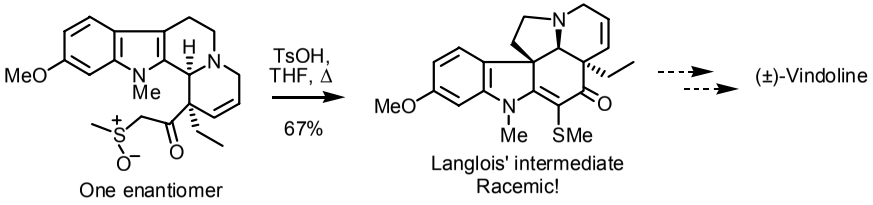
Initial strategy: Enantioselective version of Langlois' total synthesis.
Ring D constructed first from L-aspartic acid and employed in the enantioselective synthesis of Langlois' sulfoxide intermediate.



from L-aspartic acid
(14% overall, >98%ee)



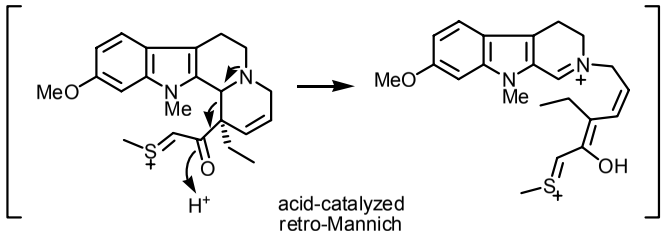
mixture of diastereomers
separated by chromatography



One enantiomer

Langlois' intermediate
Racemic!

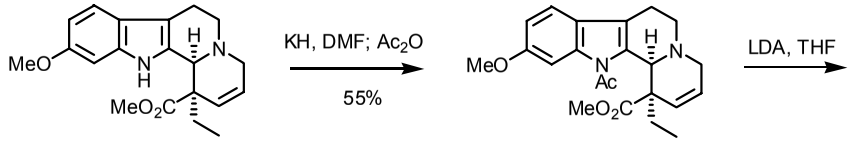
Racemization mechanism:



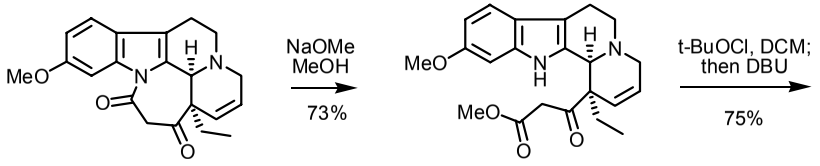
acid-catalyzed
retro-Mannich

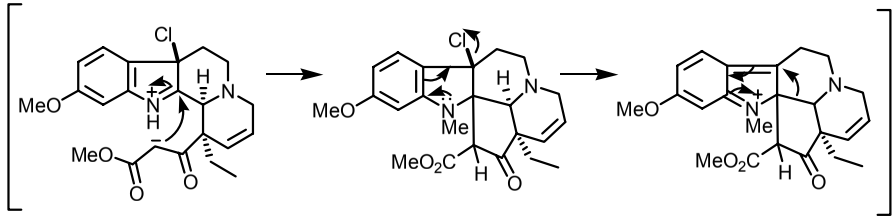
P. L. Feldman, H. Rapoport. J. Org. Chem. 1986, 51, 3882-3890.

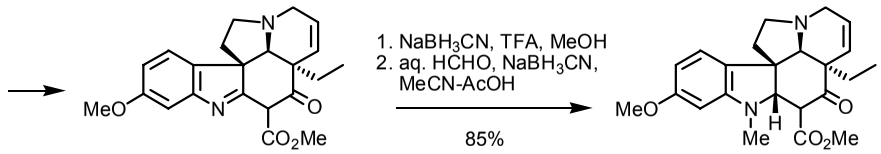
2nd generation strategy: Exchange of roles between indole double bond and side chain.
Instead of attacking a cationic intermediate, indole double bond would be activated to nucleophilic attack by an anionic one.



one diastereomer







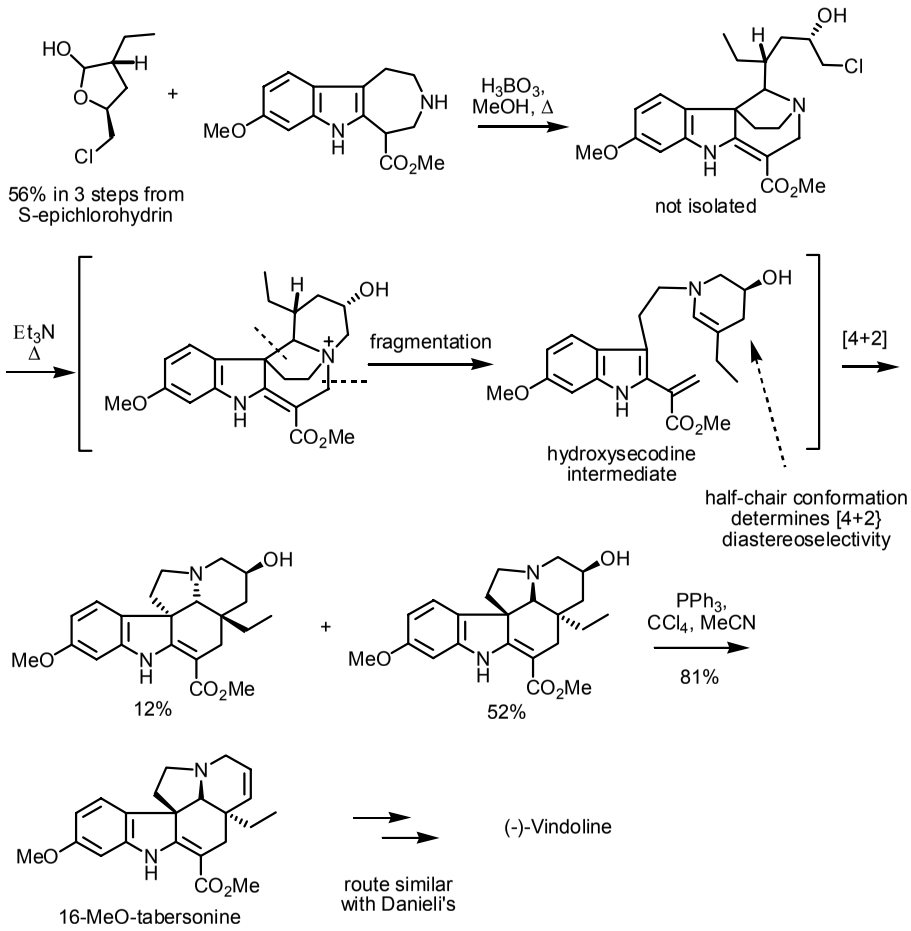
19 steps, 3.6% overall
from L-aspartic acid

1. Rubottom oxidation
2. $AlCl_3$, Red-Al
3. Acetylation

(-)-Vindoline

P. L. Feldman, H. Rapoport. J. Am. Chem. Soc. 1987, 109, 1603-1604.

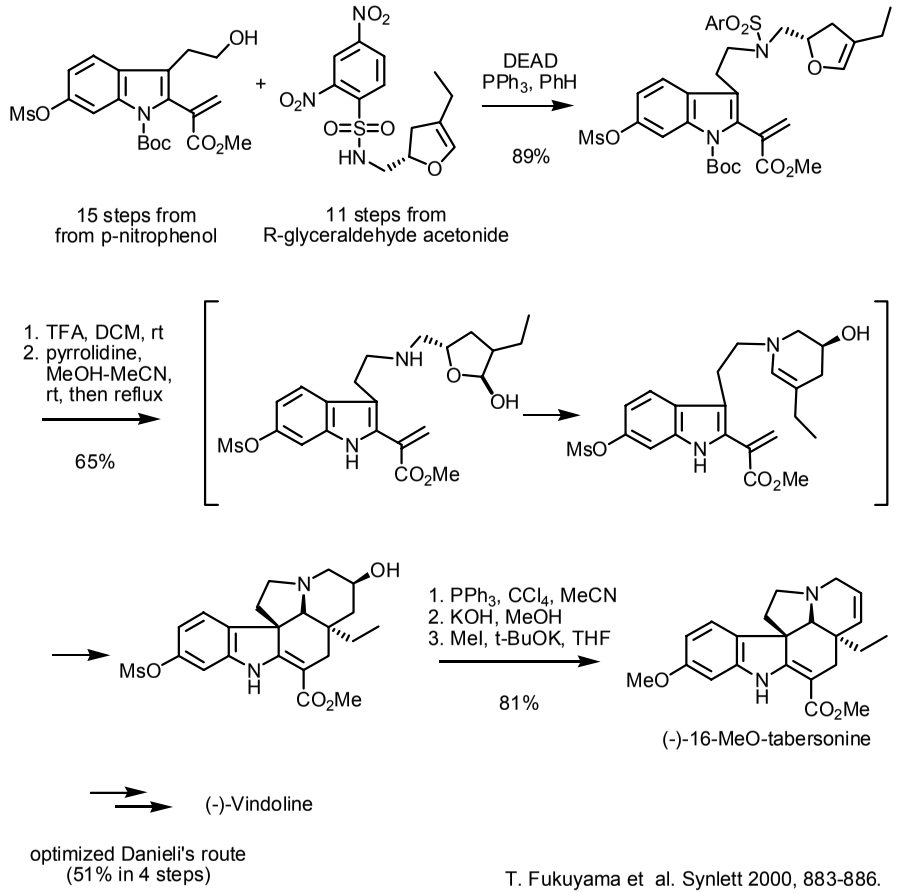
Martin E. Kuehne (1987): First enanntioselective synthesis of vindoline



M. E. Kuehne et al. J. Org. Chem. 1987, 52, 347-353.

- Kuehne was the first to pursue a biomimetic synthesis of vindoline via an intramolecular [4+2] cycloaddition of a secodine intermediate
- The diastereoselectivity of the key transformation is not great, but provides the vindoline skeleton through an one-pot procedure from relatively simple SM
- Diastereoselectivity is based on the preference of the secodine intermediate to adopt a conformation with the OH group in a pseudoequatorial position
- Kuehne completed the first enantioselective synthesis of (-)-vindoline, but also achieved the synthesis of racemic and (+)-vindoline starting from RS- and R-epichlorohydrins

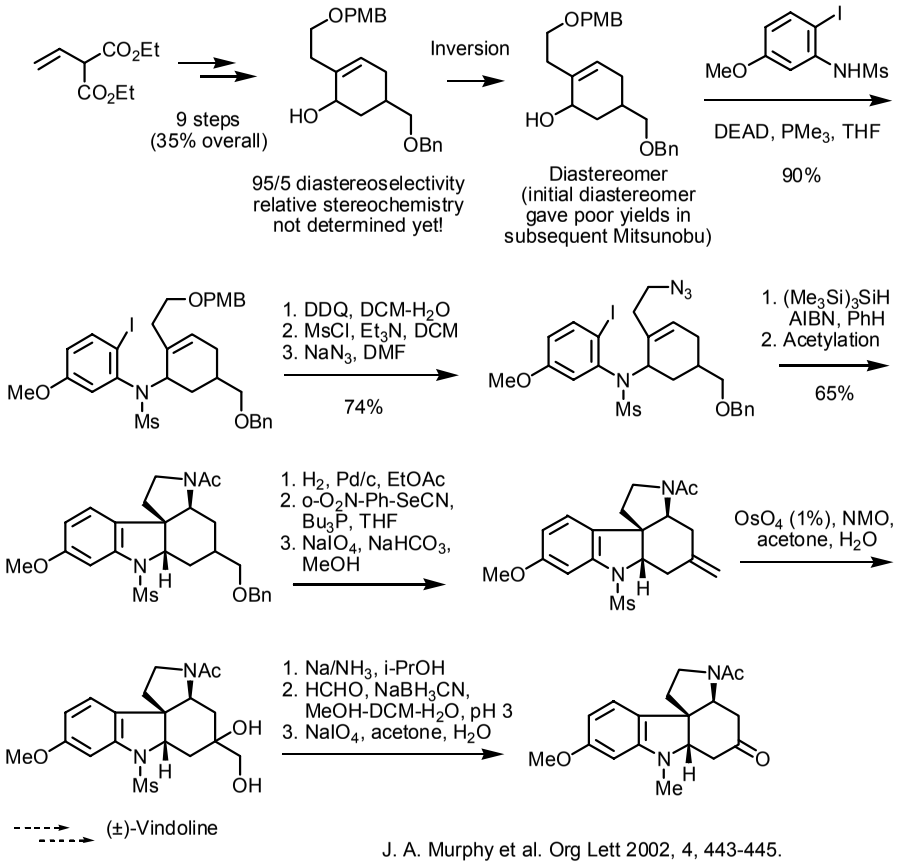
Tohru Fukuyama (2000): Second application of intramolecular [4+2]



T. Fukuyama et al. Synlett 2000, 883-886.

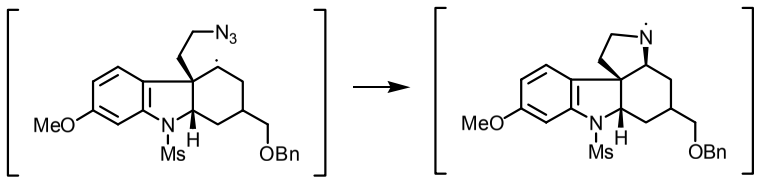
see also vinblastine's synthesis in 'Classics in Total Synthesis', Vol. 2.

John A. Murphy (2002): Construction of B and E rings through tandem radical cyclizations



J. A. Murphy et al. Org Lett 2002, 4, 443-445.

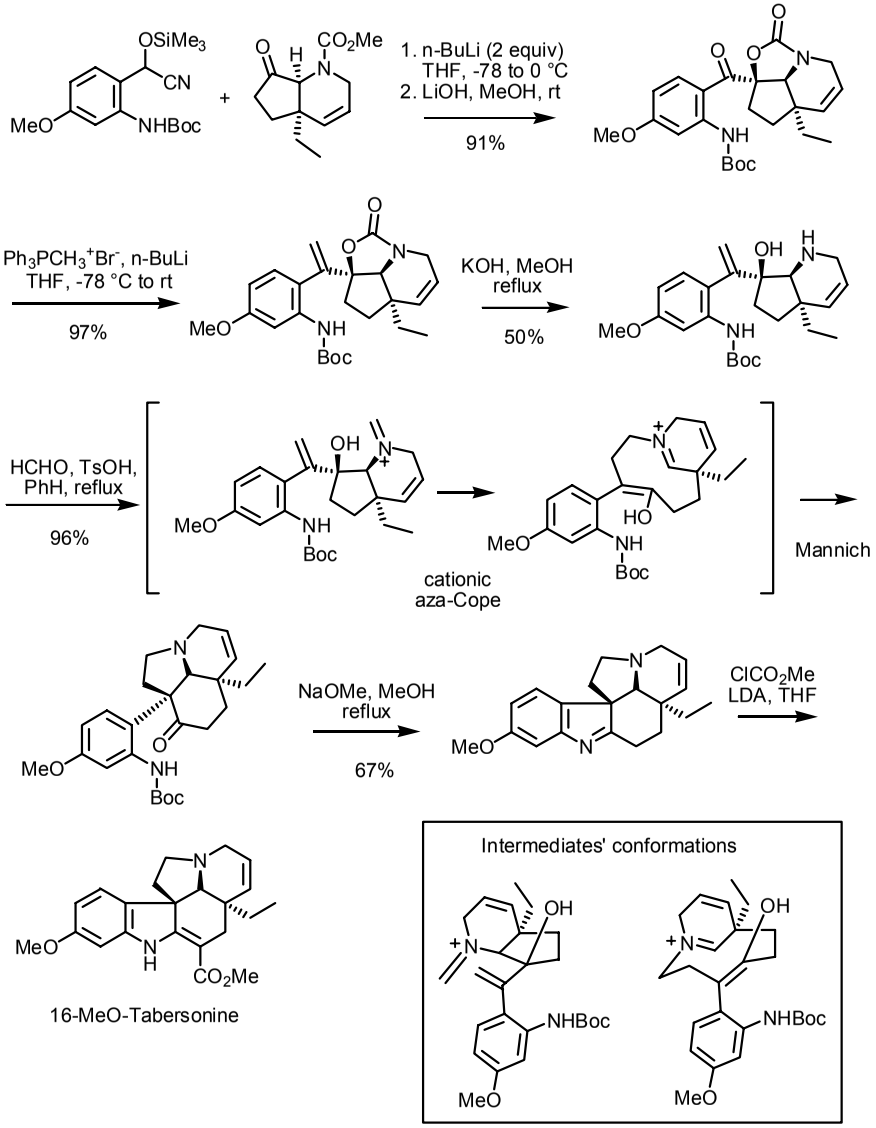
Intermediates:



- Diastereoselectivity based on the necessity of the newly formed rings, B and E, to be cis fused to existing C ring
- Absolute stereochemistry determined by cyclohexanol configuration
- Suitable for enantioselective synthesis of vindoline

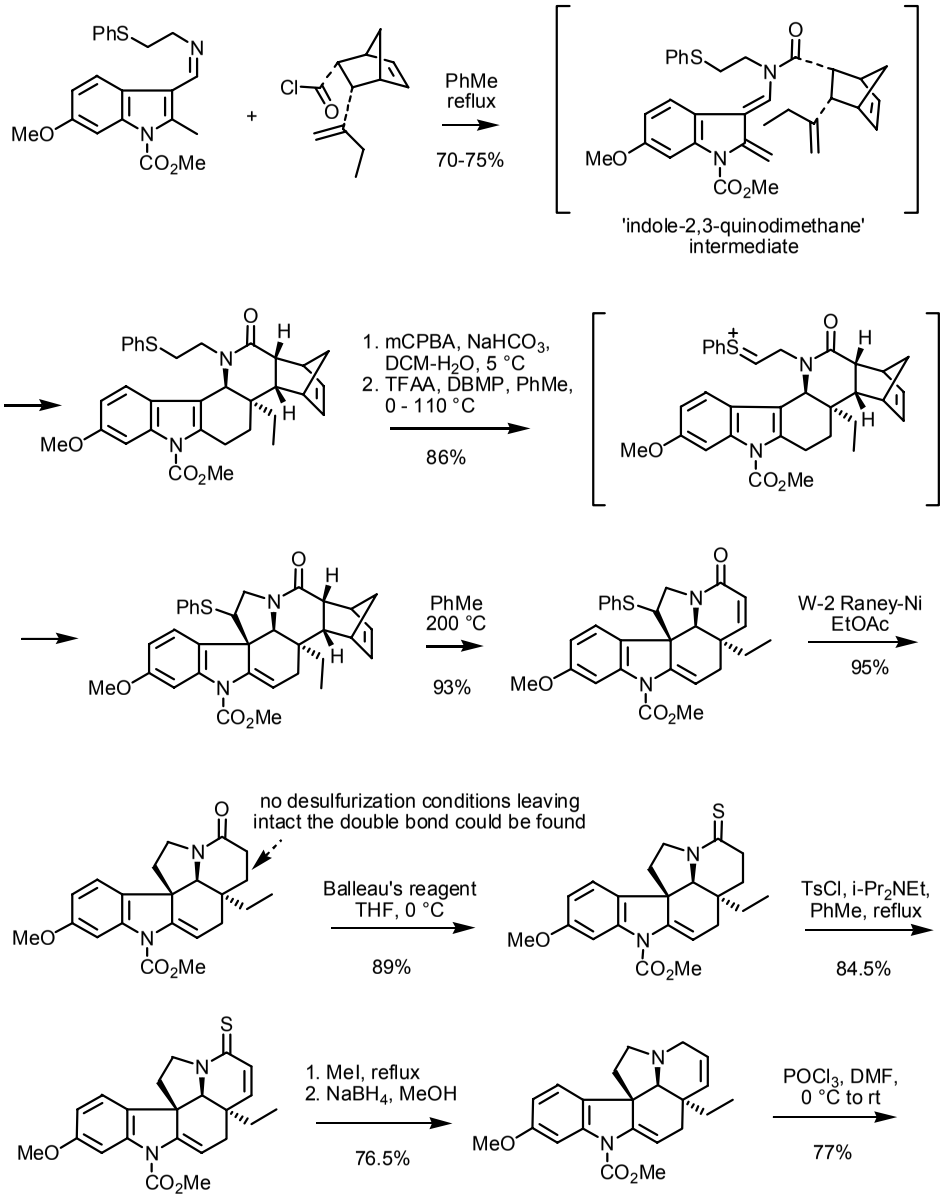
Syntheses of 16-MeO-Tabersonine

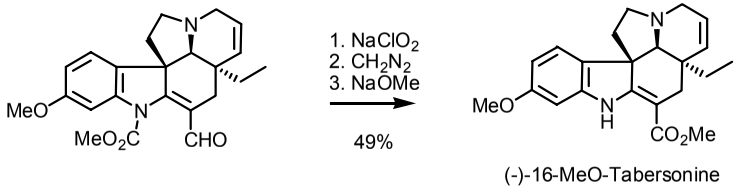
Larry E. Overman (1983): Application of an aza-Cope - transannular Mannich cascade



Intermediates' conformations

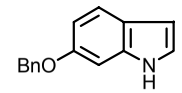
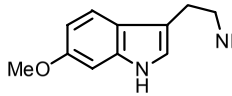
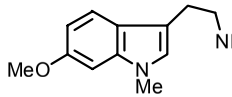
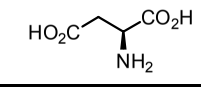
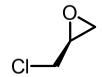
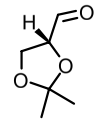
Philip Magnus (1988): Synthesis of 16-MeO-tabersonine via the Indole-quinodimethane strategy





- CD rings formed via an IMDA of a 'quinodimethane' type indole derivative
- Alkene part attached to norbornyl moiety which acts as chiral auxiliary
- E ring formed via Pummerer rearrangement
- Chiral auxiliary removed with retro-DA

In brief:

	SM	Steps	Yield
Büchi		18	< 2.8% (last step not reported)
Kutney		29	< 0.00016% (8 steps not reported)
Langlois		13	< 12% (last step not reported)
Rapoport		22	< 3.6% (last 3 steps not reported)
Kuehne		8	2.0%
Fukuyama		21	13%