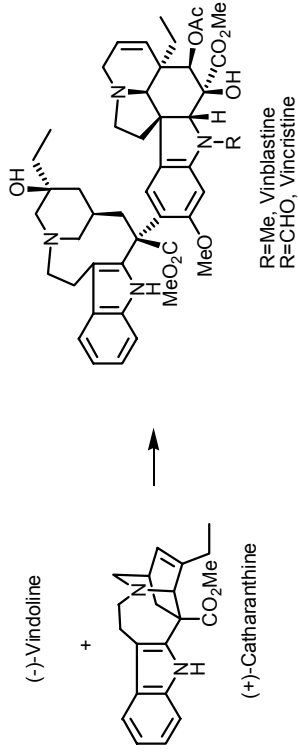


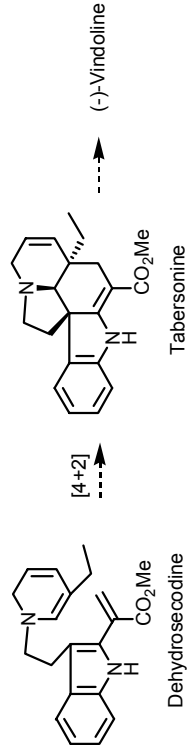
Major alkaloid of *Catharanthus roseus*

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.



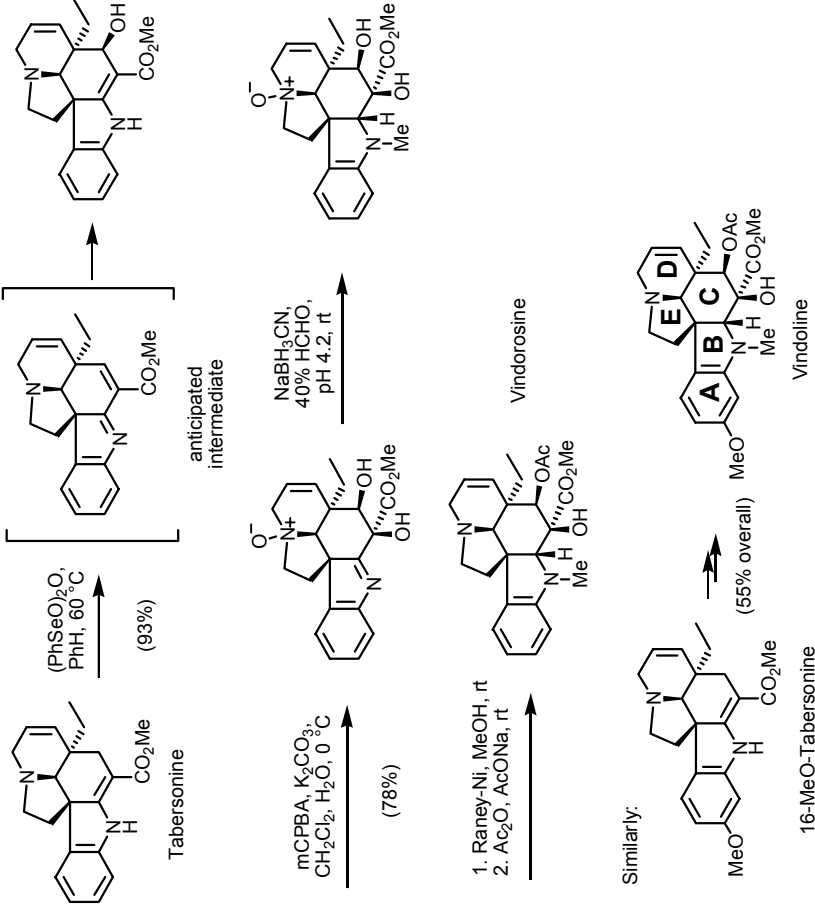
For a review see: Potier, P. J. *Nat. Prod.* 1980, 43, 72-86.

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




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

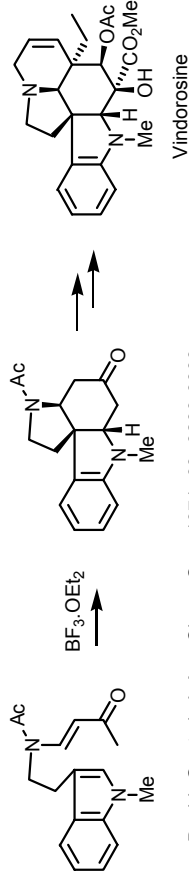
Syntheses of Vindoline: 6 total (3 enantioselective)
4 formal

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



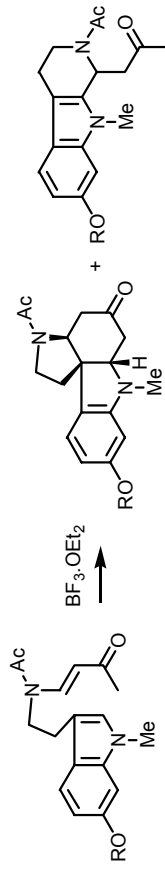
George H. Büchi (1921-1998)
 Born in Baden, Switzerland. Diploma and DSc from Eidgenössische Technische Hochschule in Zurich
 Passed his entire academic career in MIT (1951-1991)
 Worked on: organic photochemistry, natural product characterization and natural product total synthesis
 A pioneer in organic 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:

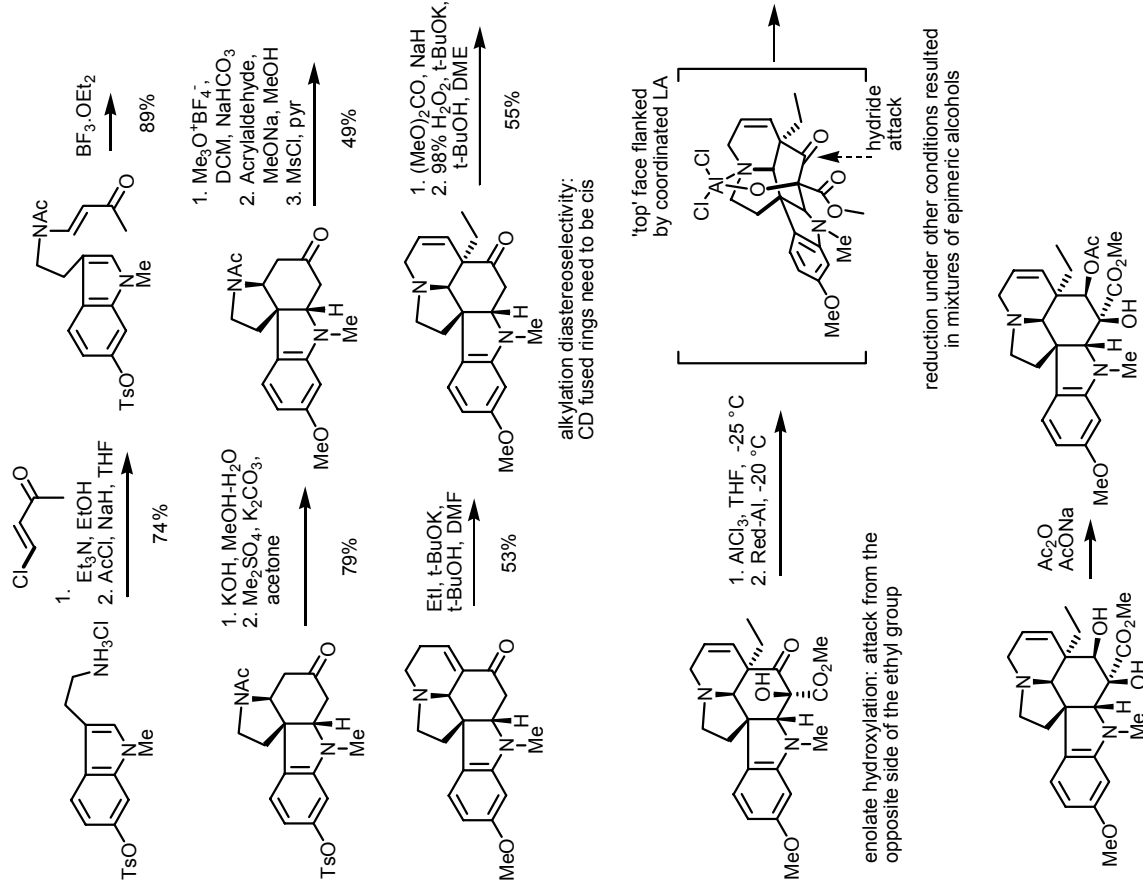
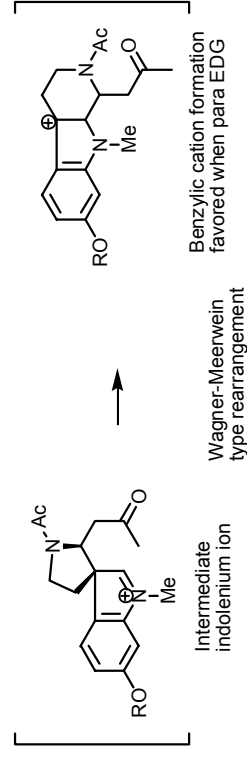


Büchi, G. et al. J. Am. Chem. Soc. 1971, 93, 3299-3300.

Effect of substituent on indole 6-position:



major 2%

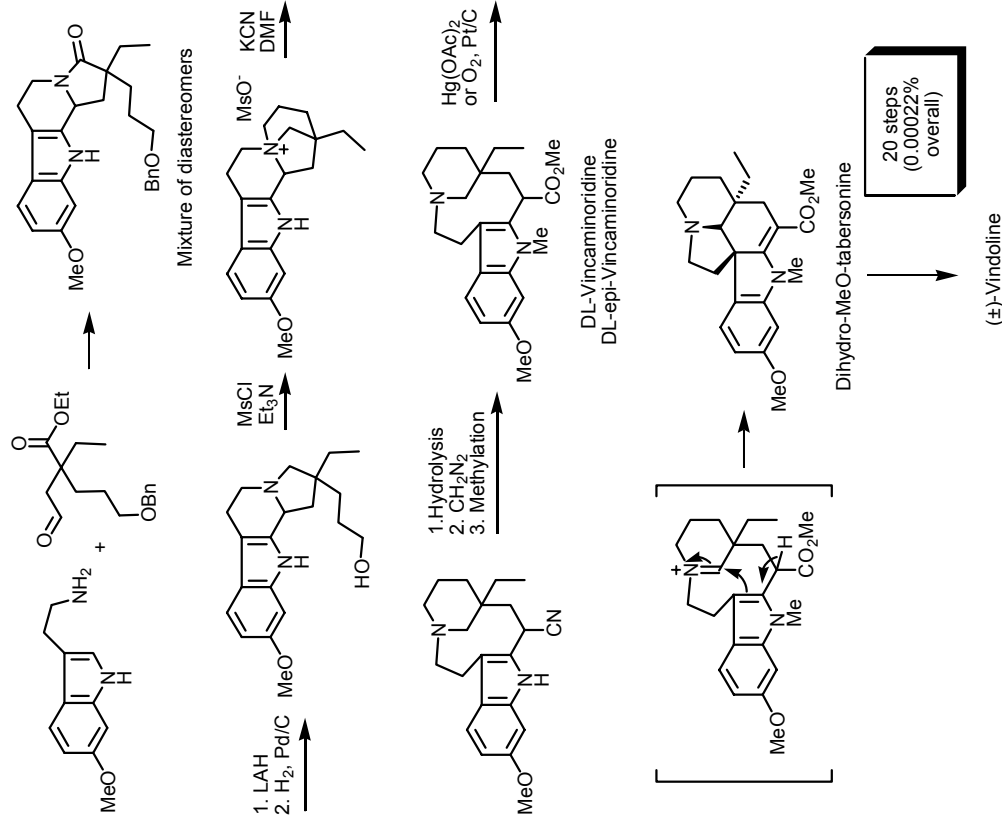


Ando, M.; Büchi, G.; Ohnuma, T. J. Am. Chem. Soc. 1975, 97, 6880-6881.

Kutney's and Langlois' total syntheses

Christos Mitsos

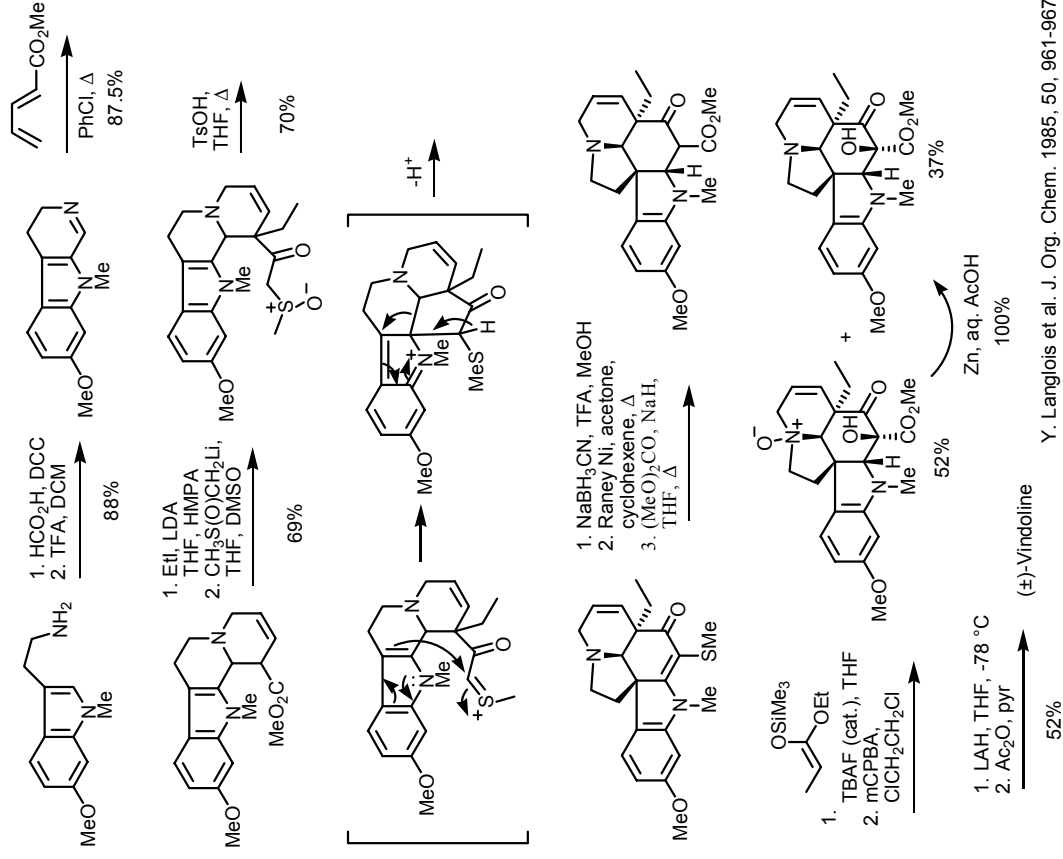
James B. Kutney (1968 and 1978): Second Total synthesis of vindoline



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.

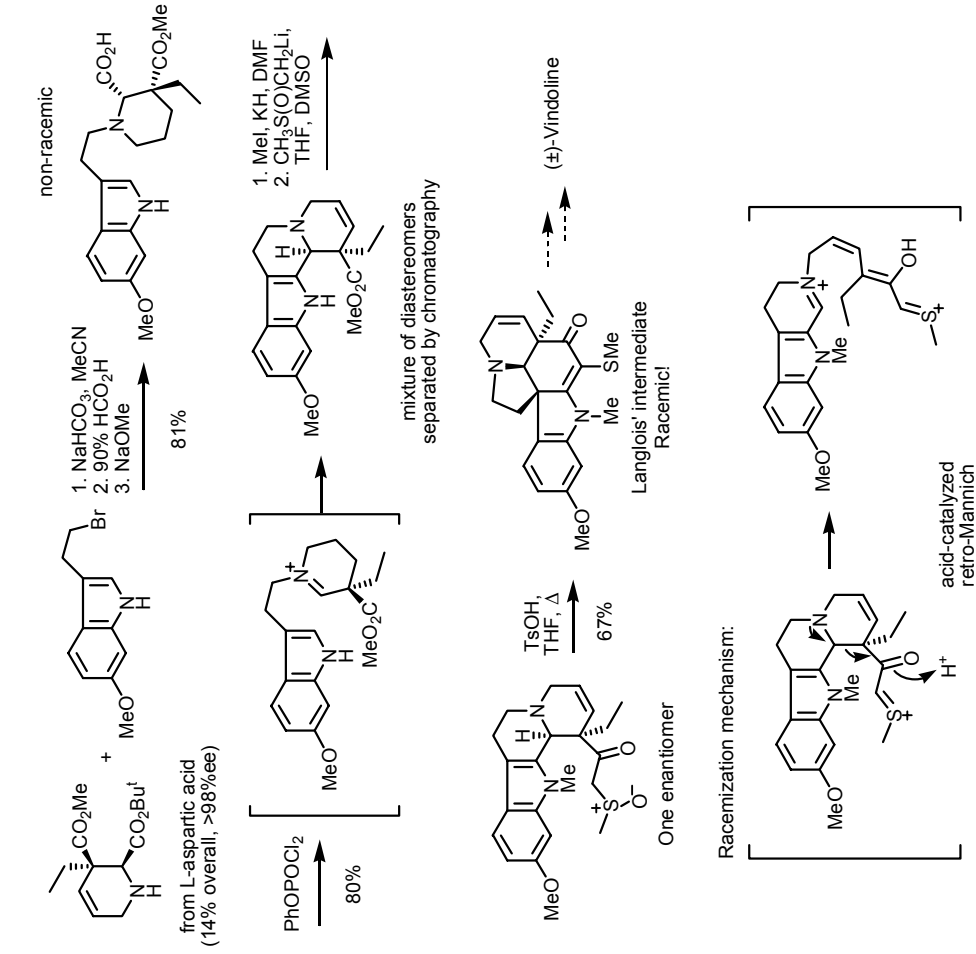
- Elegant synthesis based on Harley-Mason's transformation
- Requisite cationic intermediate formed through a Pummerer rearrangement
- Non-enantioselective synthesis

Rapoport's total synthesis

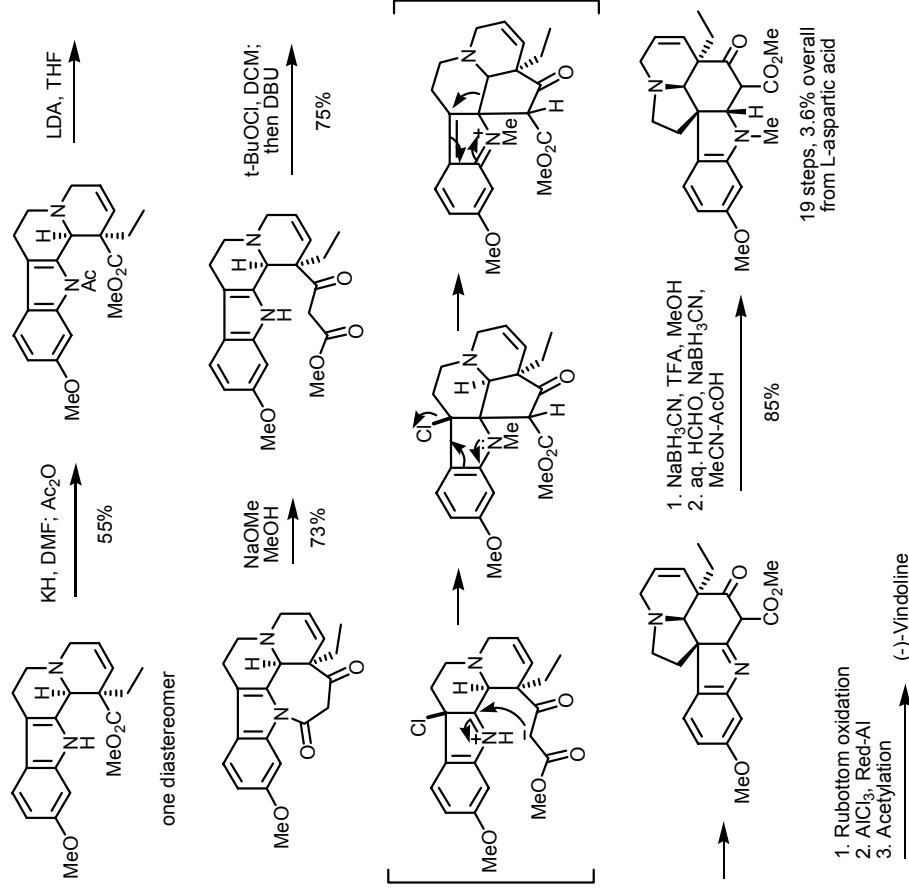
Christos Mitsos

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' sulfonide intermediate.



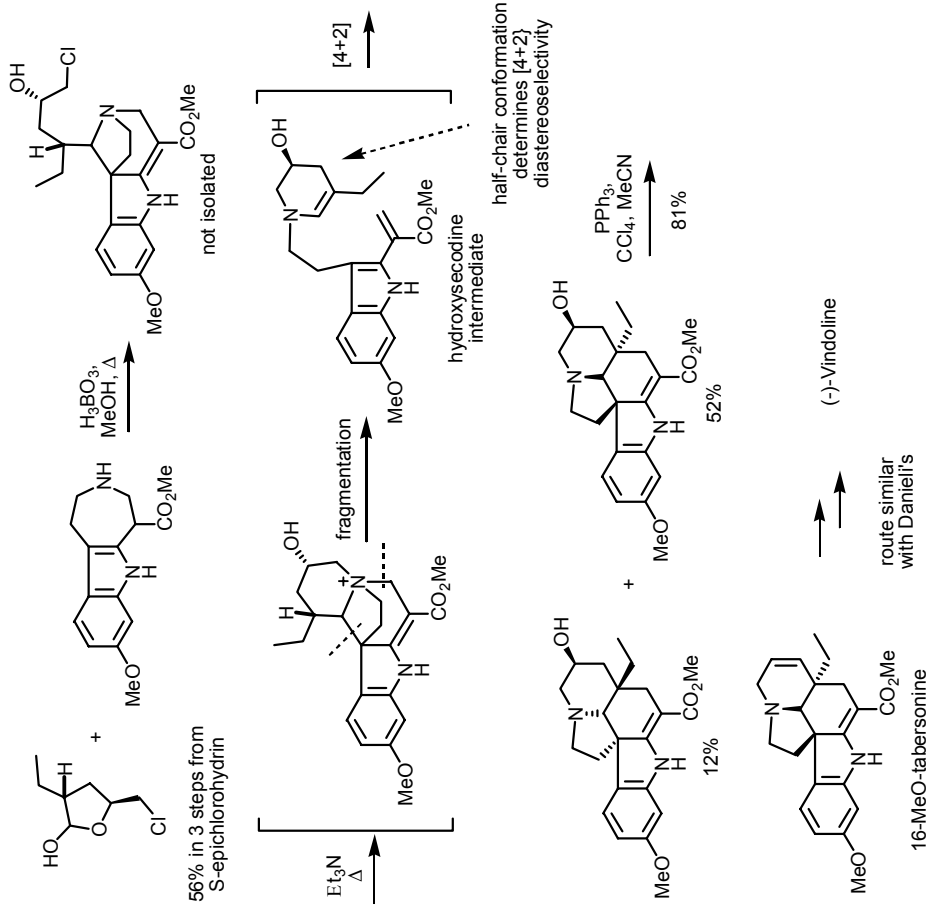
2nd generation strategy: Exchange of roles between indole double bond and side chain. Instead of attacking a cationic intermediate, indole double bond would be activated to nucleophilic attack by an anionic one.



Biomimetic syntheses

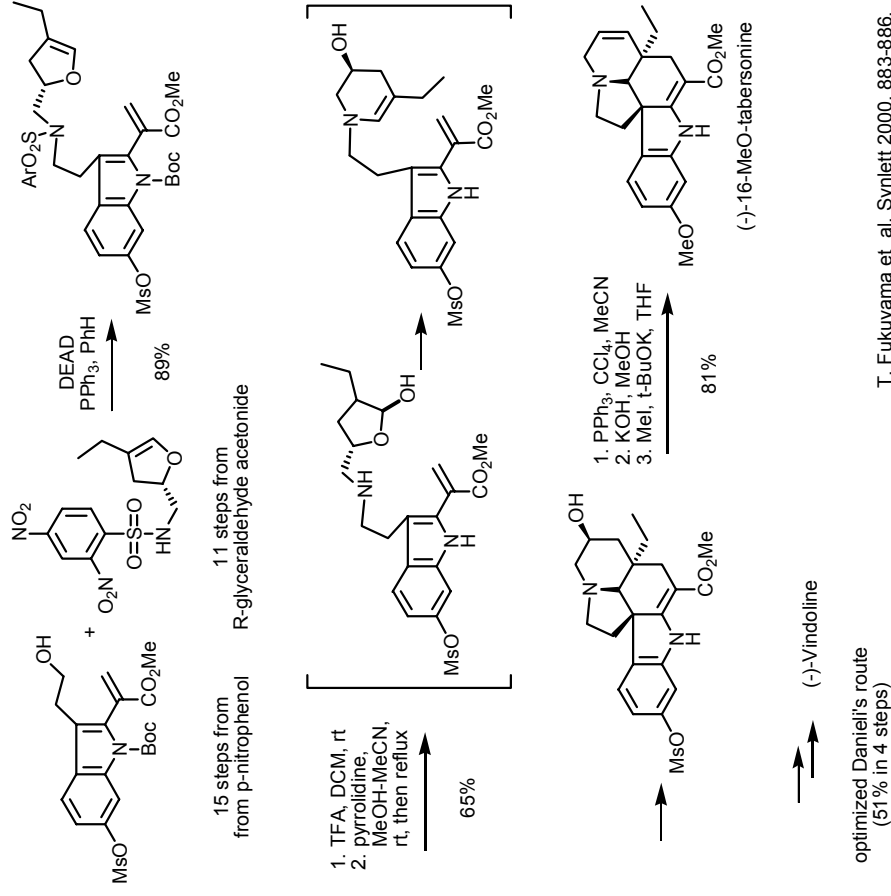
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Martin E. Kuehne (1987): First enantioselective synthesis of vindoline



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

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



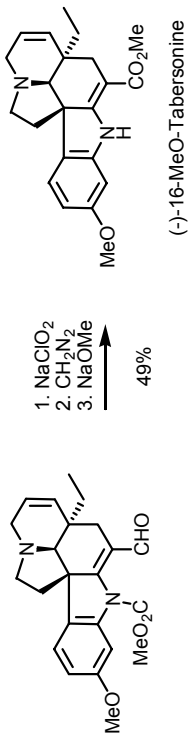
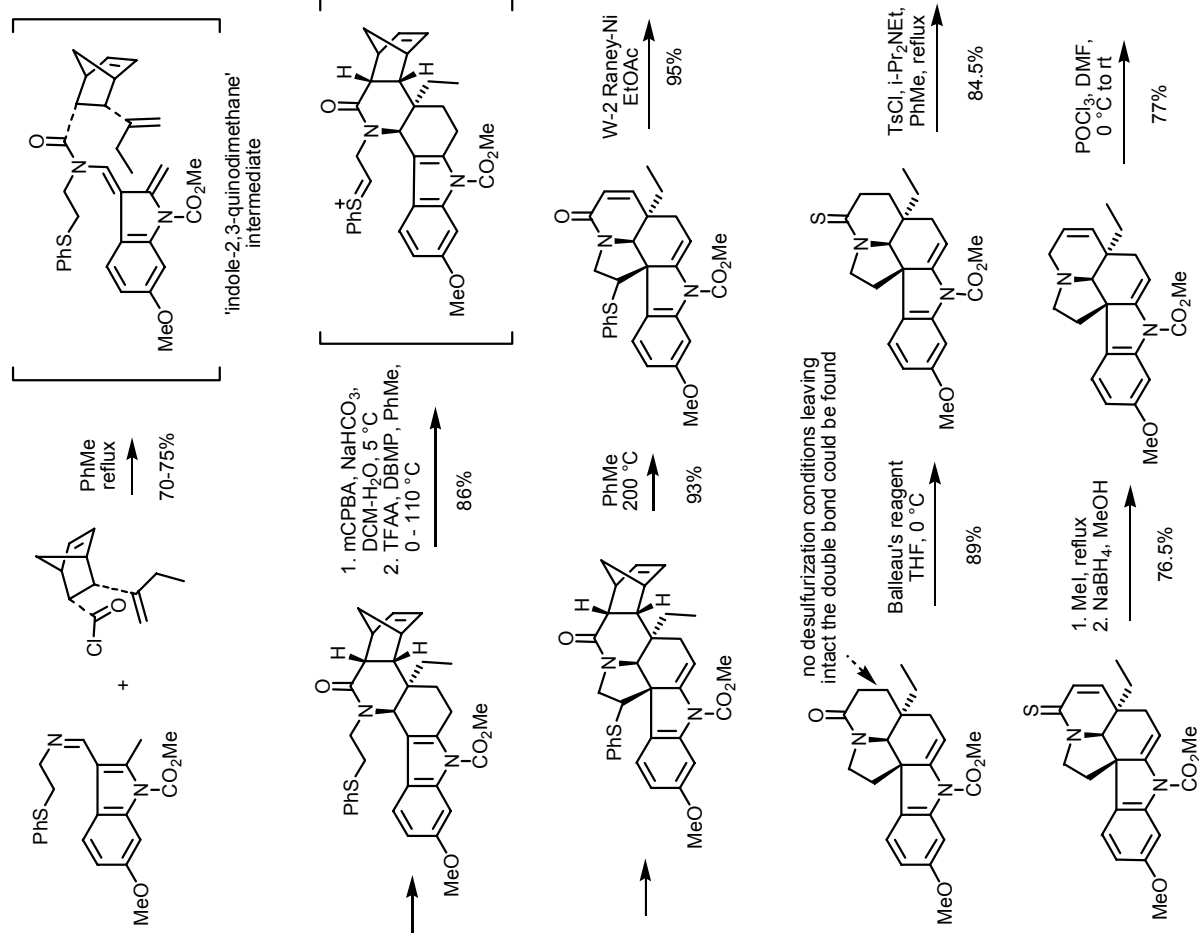
T. Fukuyama et al. Synlett 2000, 883-886.
see also vinblastine's synthesis in 'Classics in Total Synthesis', Vol. 2.

- 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

Magnus Indole-2,3-quinodimethane strategy

Christos Mitsos

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	<chem>Brc1ccc2c(c1)c3c(nc2)C(=O)OCC3</chem>	18	< 2.8% (last step not reported)
Kutney	<chem>COc1ccc2c(c1)c3c(nc2)C(=O)OCC3</chem>	29	< 0.00016% (8 steps not reported)
Langlois	<chem>COc1ccc2c(c1)c3c(nc2)C(=O)OCC3</chem>	13	< 12% (last step not reported)
Rapopot	<chem>COc1ccc2c(c1)c3c(nc2)C(=O)OCC3</chem>	22	< 3.6% (last 3 steps not reported)
Kuehne	<chem>COc1ccc2c(c1)c3c(nc2)C(=O)OCC3</chem>	8	2.0%
Fukuyama	<chem>COc1ccc2c(c1)c3c(nc2)C(=O)OCC3</chem>	21	13%