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Efficient Access to the Core of the *Strychnos*, *Aspidosperma* and *Iboga* Alkaloids. A Short Synthesis of Norfluorocurarine

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1102 Natural Sciences II, Department of Chemistry, The University of California, Irvine, California 92697-2025

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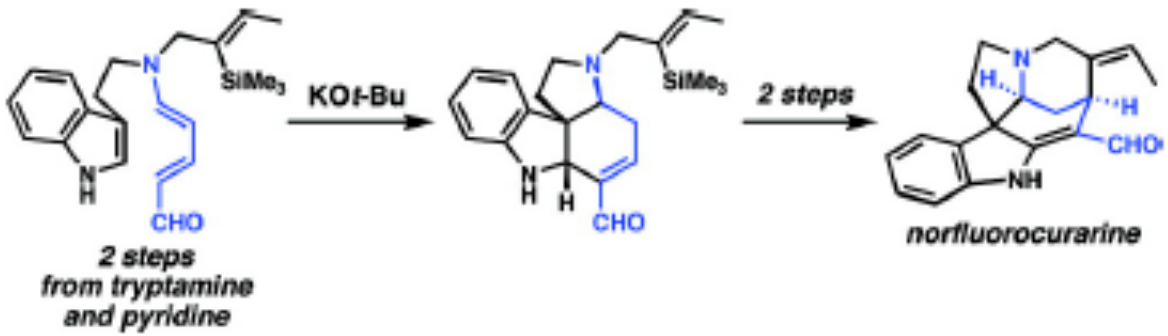
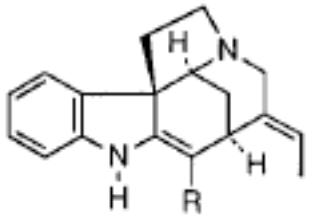
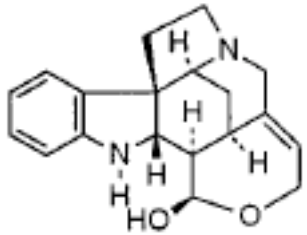


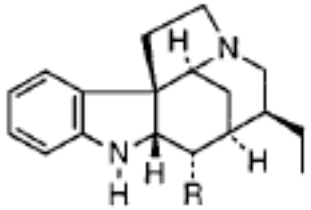
Intramolecular Cycloadditions to Indole Monoterpene Alkaloids - The Curan Skeleton



5 Norfluorocurarine, R = CHO
6 Fluorocurarine, R = CHO (N_b-methyl)
7 Akuammicine, R = CO_2Me
8 Mossambine, R = CO_2Me (14*S*-OH)

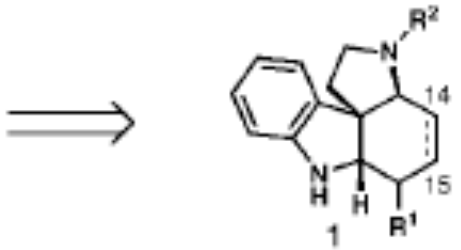


14 Wieland-Gumlich aldehyde



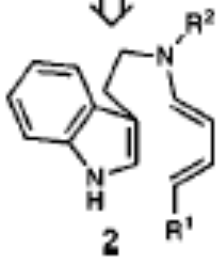
1 Tubifolidine, R = H
2 Tubifoline, R = H (1,2-didehydro)
3 Geissoschizoline, R = CH_2OH
4 19,20-Dihydroakuammicine, R = CO_2Me (2,16-didehydro)

Strychnos, Iboga and Aspidosperma alkaloids



1

Diels–Alder?



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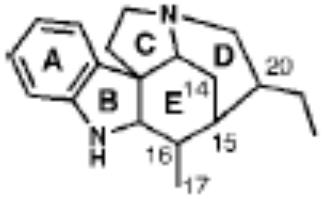


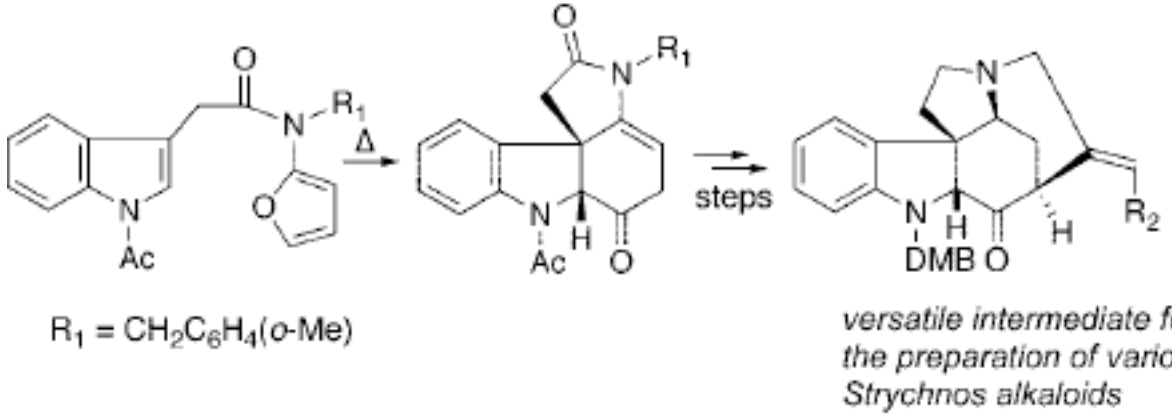
3: ***curan skeleton***

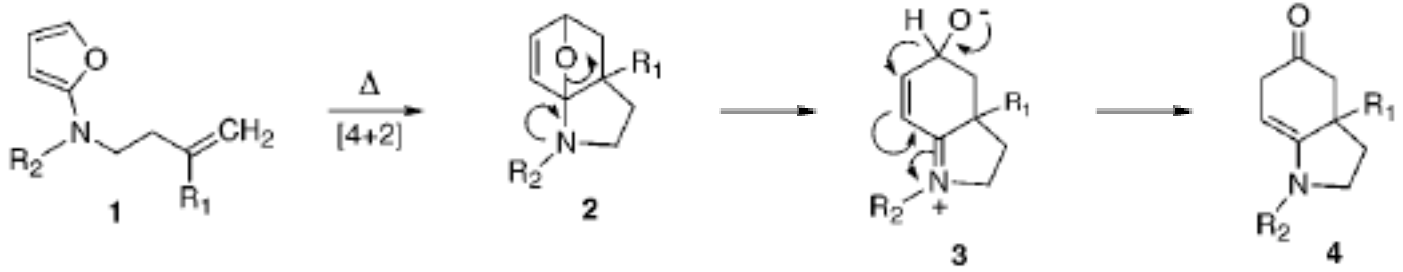
Synthetic Challenge in Diels-Alder

- Indoles are poor dienophiles
- Aminodiens are generally electron-rich

Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131,* 3472-3473
Bonjoch, J.; Sol, D.; Cgarca-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119,* 7230-7240

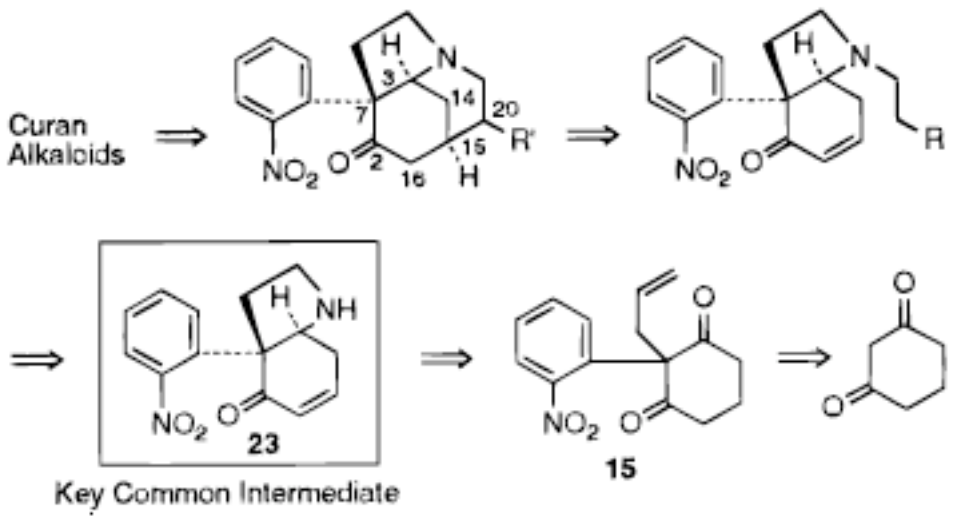
Reported Diels-Alder/Rearrangement of Indole Synthesis of Strychnos Alkaloids

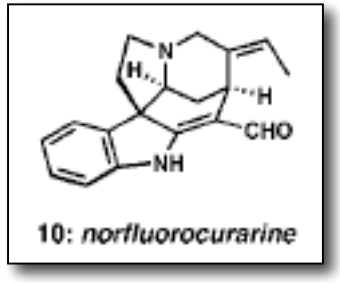




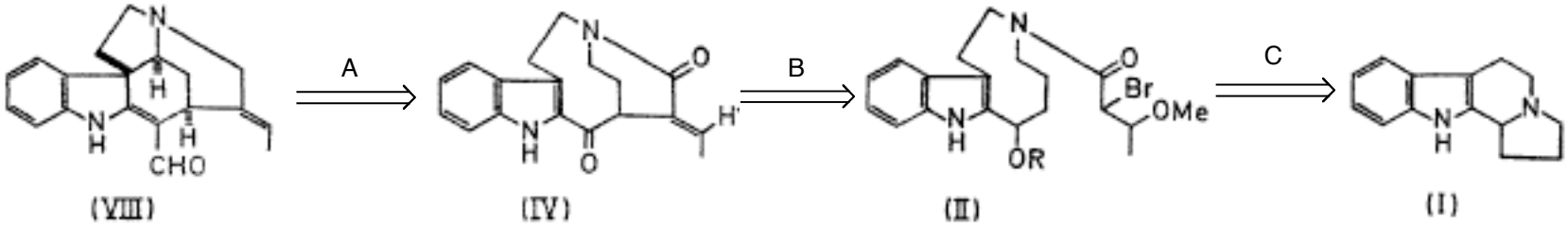
Boonsombat, J.; Zhang, H.; Chughtai, M. J.; Hartung, J.; Padwa, A., *J. Org. Chem.* **2008**, *73*, 3539-3550.
Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 530-5305.

Previous Synthesis of Norfluorocurarine





Bonjoch, J.; Sol, D.; C Garca-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119,* 7230-7240



Crawley, G. C.; Harley-Mason, J. *Chem. Comm.* **1971**, 685-686

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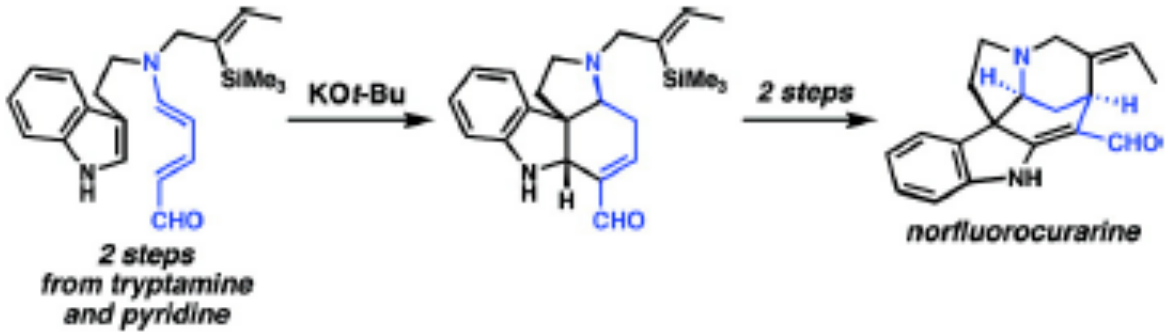
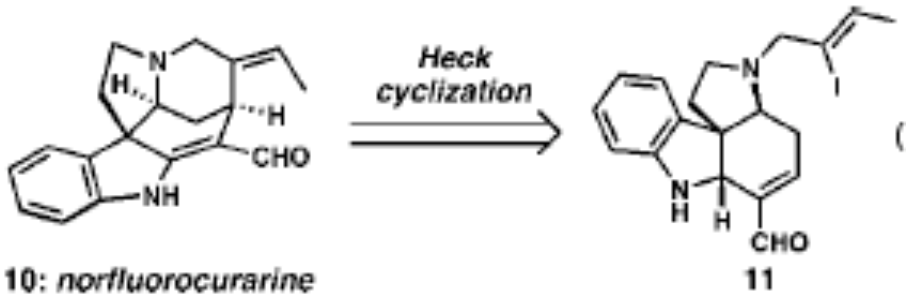
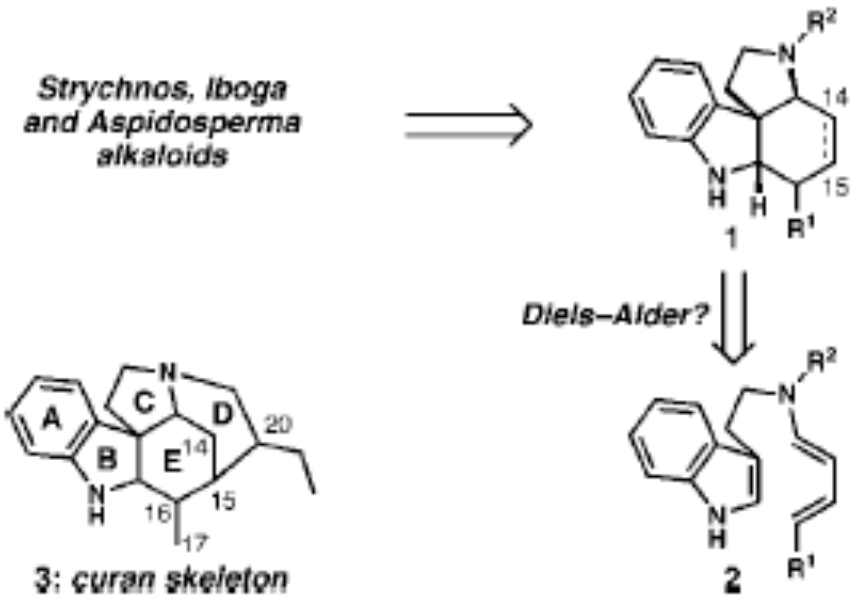


Retrosynthesis of Norfluorocurarine — Key step

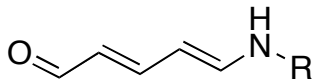




Synthetic Challenge in Diels-Alder

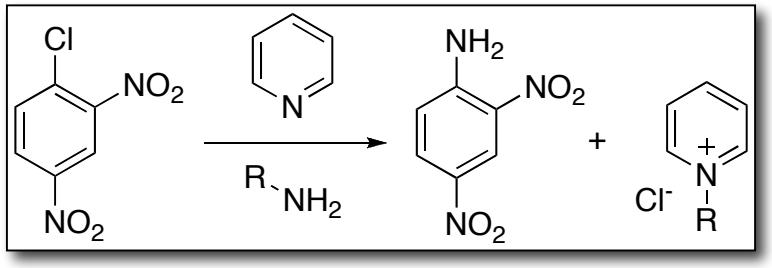
- Indoles are poor dienophiles
- Aminodiens are generally electron-rich

Solution ⇒ Zincke aldehyde

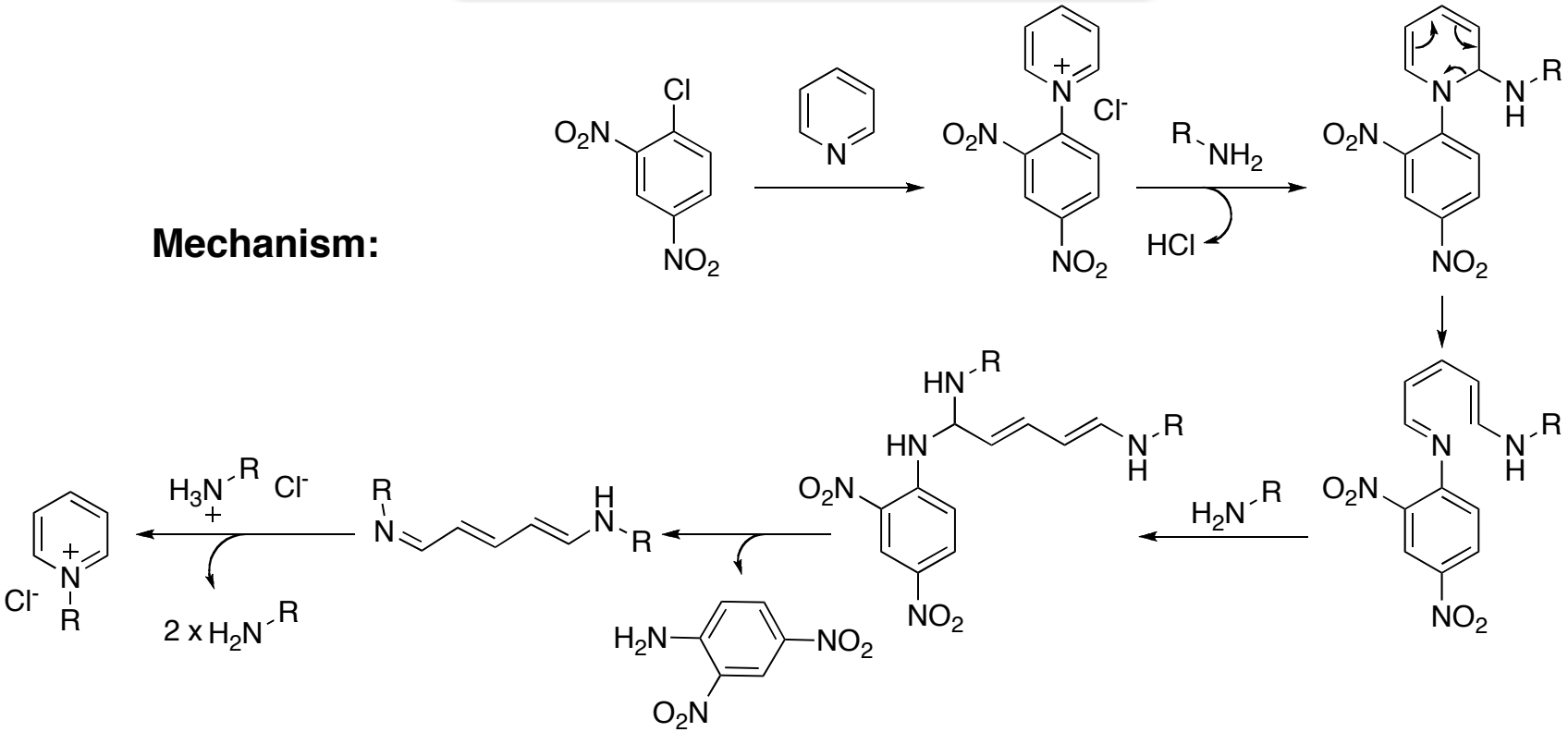


Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131,* 3472-3473

The Zincke Reaction
Ipso-like Substitution of Aryl Chlorides to Anilines

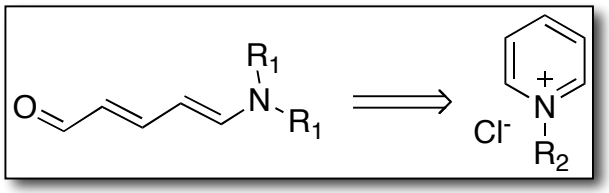


Mechanism:

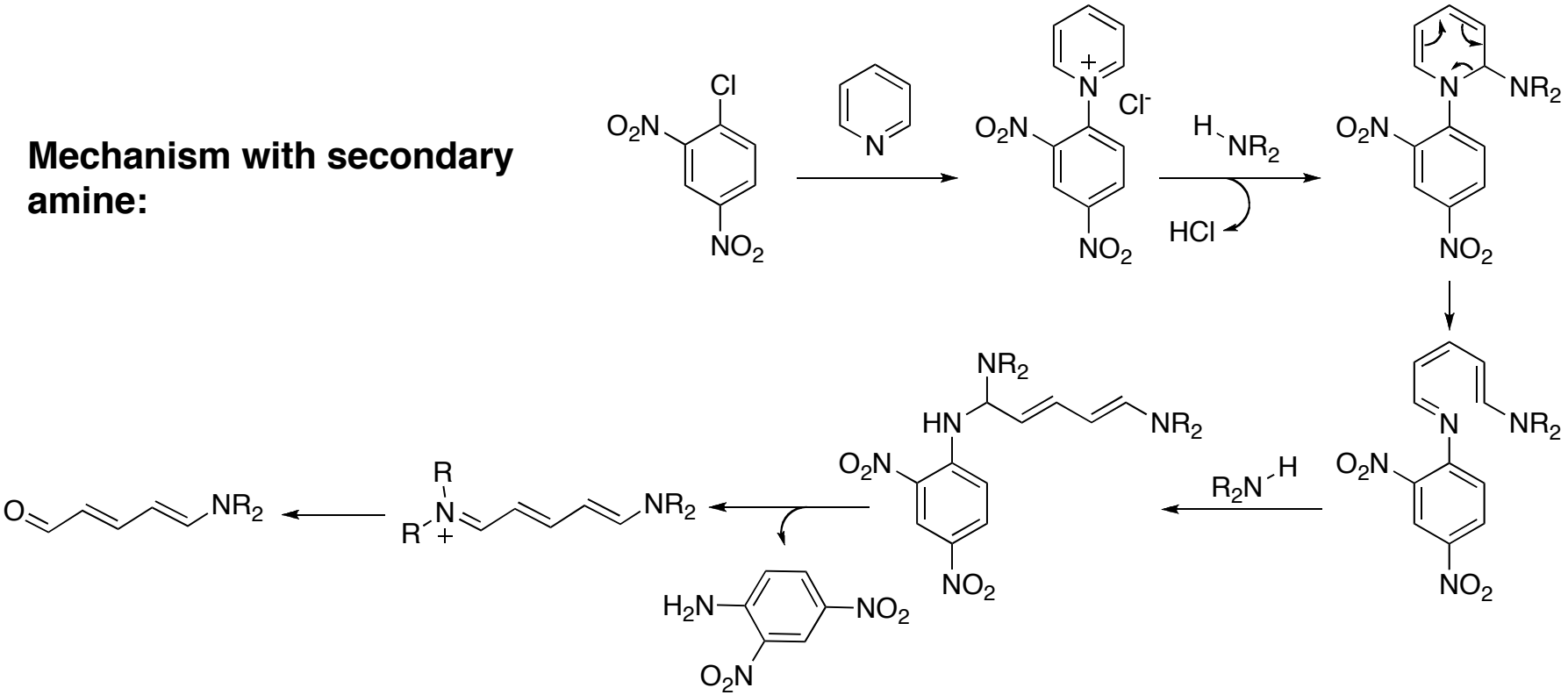


Zincke, T. *Liebigs Ann. Chem.* **1903**, *330,* 361-374
Li, J. J. *Name reactions*, Springer-Verlag: Berlin Heidelberg, Germany, 2003

The Zincke Aldehyde
5-amino-2,4-pentadienal

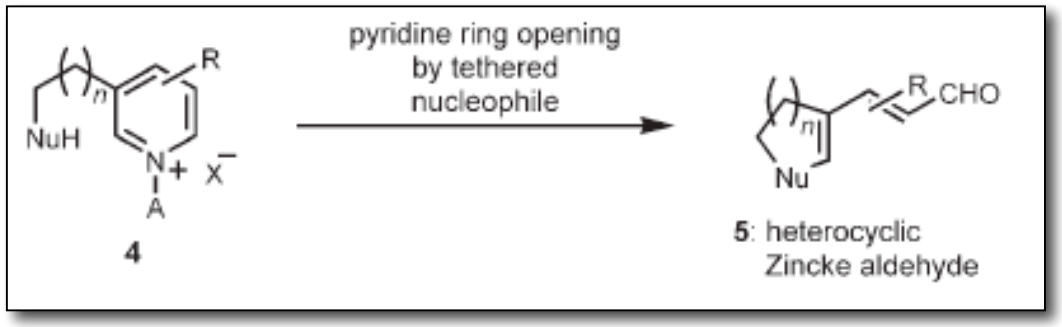


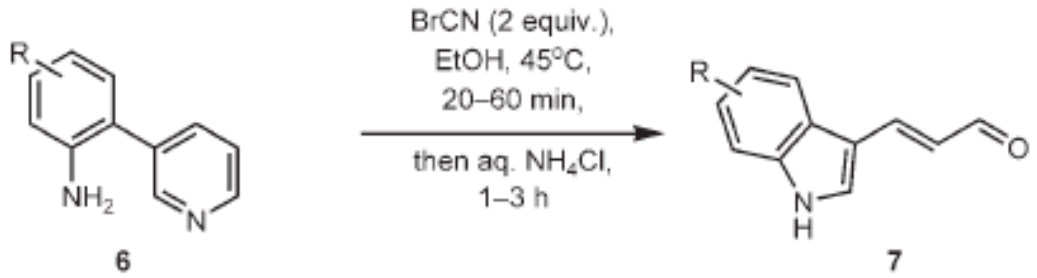
Mechanism with secondary amine:



Zincke, T,; Wurker, W. *Liebigs Ann. Chem.* **1905**, *338,* 107-141
Li, J. J. *Name reactions*, Springer-Verlag: Berlin Heidelberg, Germany, 2003

Zincke Aldehydes in Indole Synthesis





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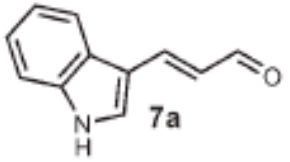
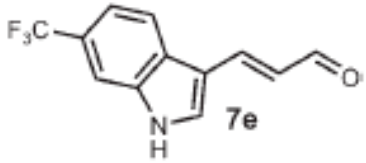
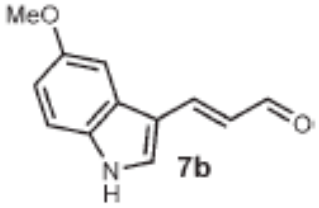
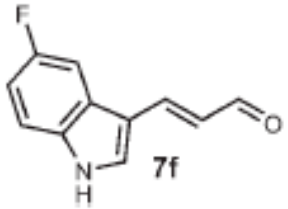
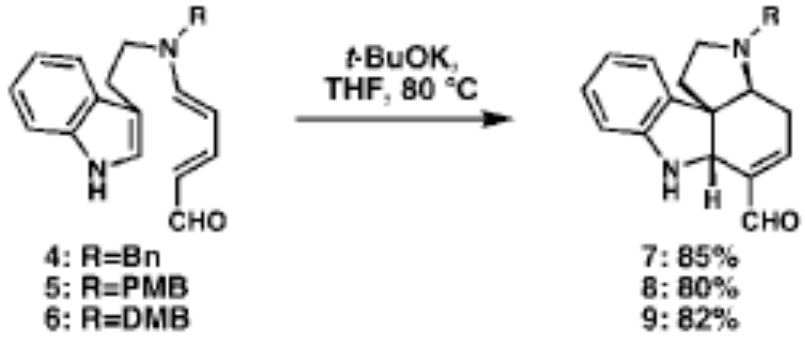
1	 7a	78[a]	5	 7e	78
2	 7b	73[b]	6	 7f	65

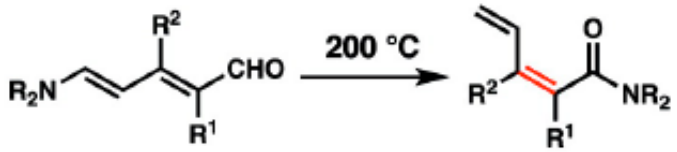
Kearney, A. M.; Vanderwal, C. D. *Angew. Chem.* **2006**, *45,* 7803-7806.

“Diels-Alder” of the Zincke Aldehyde of Tryptamine Anionic 2+4 Cyclization



Traditional Diels-Alder Conditions

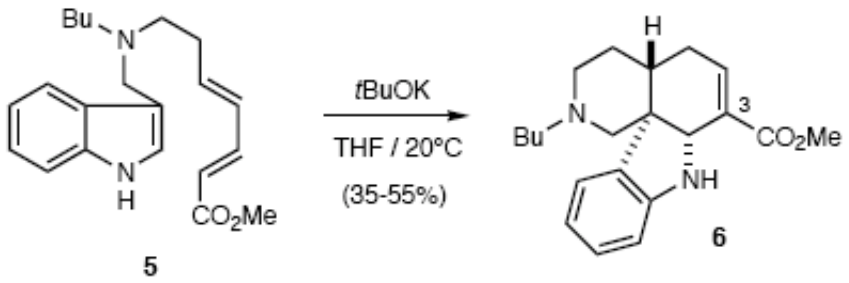
- Thermal Diels-Alder condition failed - pericyclic rearrangement to amide was observed.



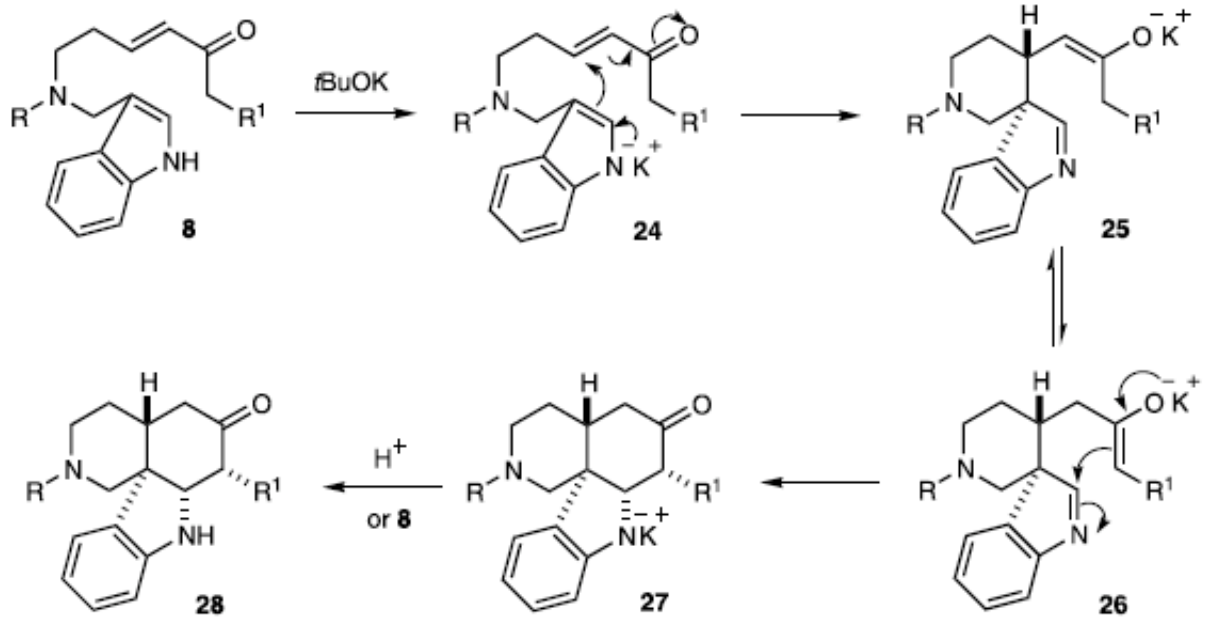
- Acidic conditions caused indole decomposition or Pictet-Spengler like reactions.

Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131,* 3472-3473
Steinhardt, S. E.; Silverston, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130,* 7560-7561

Anionic Polycyclisation Cascade

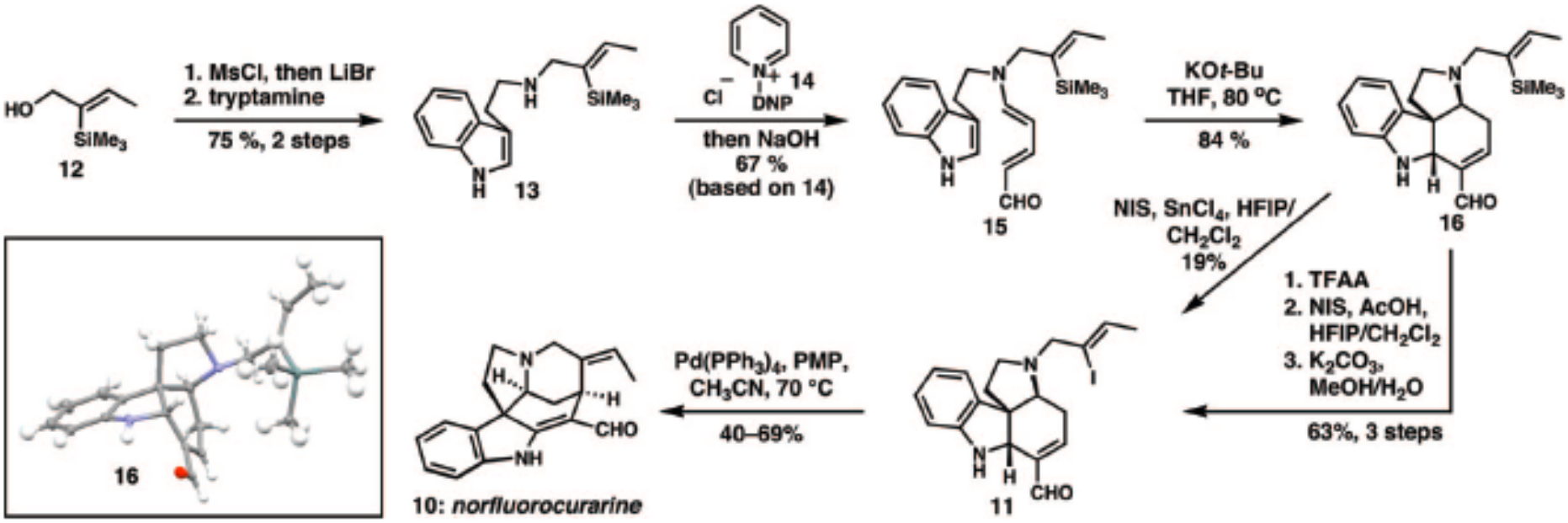


Mechanism:



Turet, L.; Marko, I. E.; Tinant, B.; Declercq, J. P.; Touillaux, R. *Tetrahedron Lett.* **2002**, *43,* 6591-6595

Total Synthesis of Norfluorocurarine



Summary:

- The ABCE core can be generated in three steps from tryptamine.
- Key step: diastereo-selective base-mediated anionic bicyclization

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