Application of Cross-Conjugated Heteroaromatic Betaines to the Synthesis of the Schizozygane Alkaloid (±)-Strempeliopine

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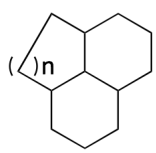
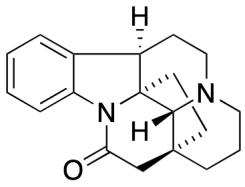
JOC, ASAP, DOI: 10.1021/jo901336z

Gary Davis Current Lit. 9-12-2009

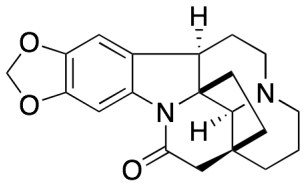
Basic Family Members



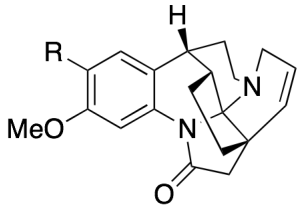
Cyclopentaquinolizine (n = 1)
Hexahydrojulolidine (n = 2)



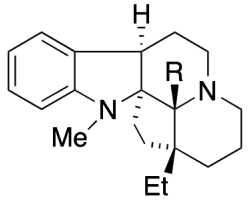
Strempeliopine



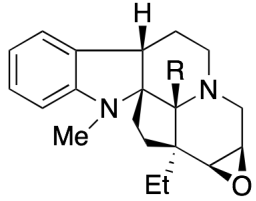
Schizozygine



Isoschizogaline (R = H)
Isoschizogamine (R = OMe)



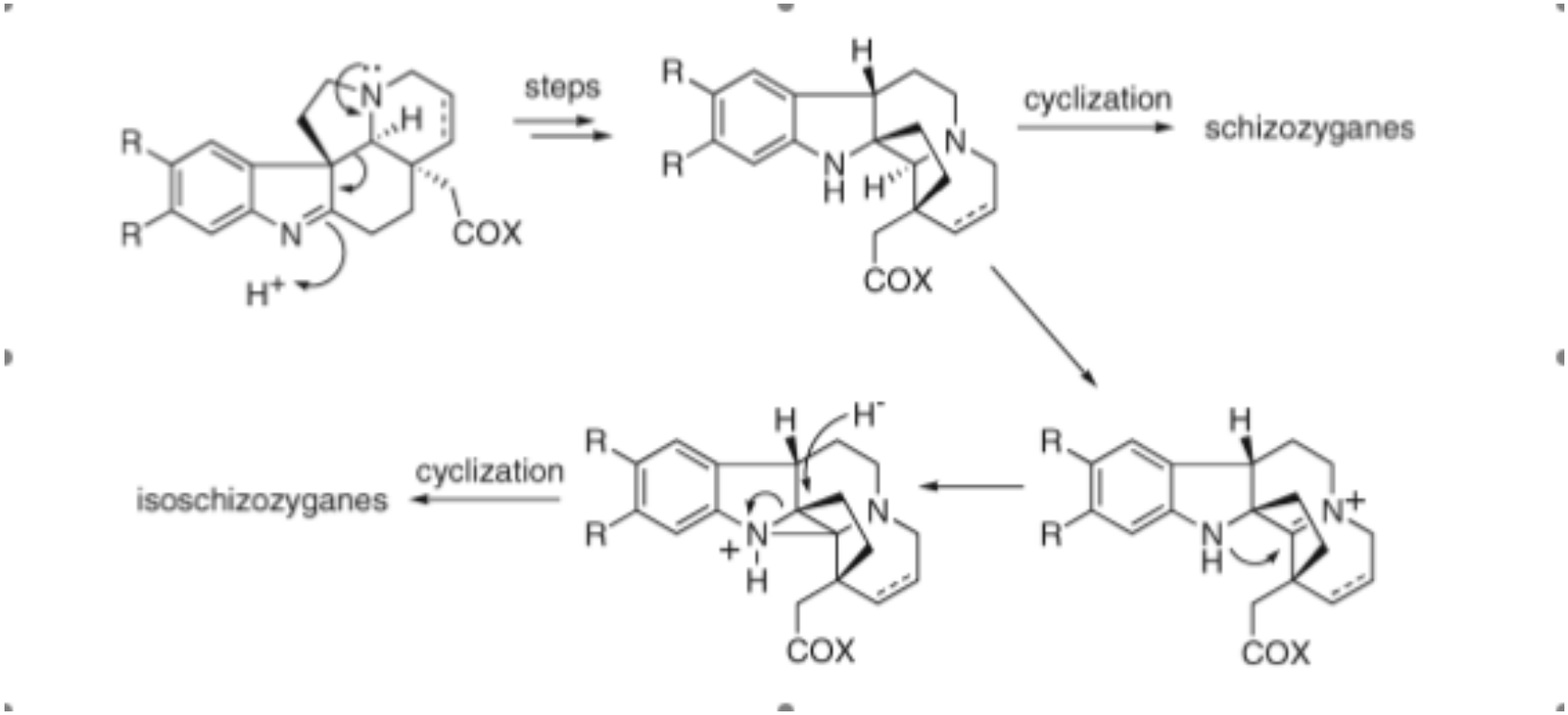
Vallesamidine



Andrangine

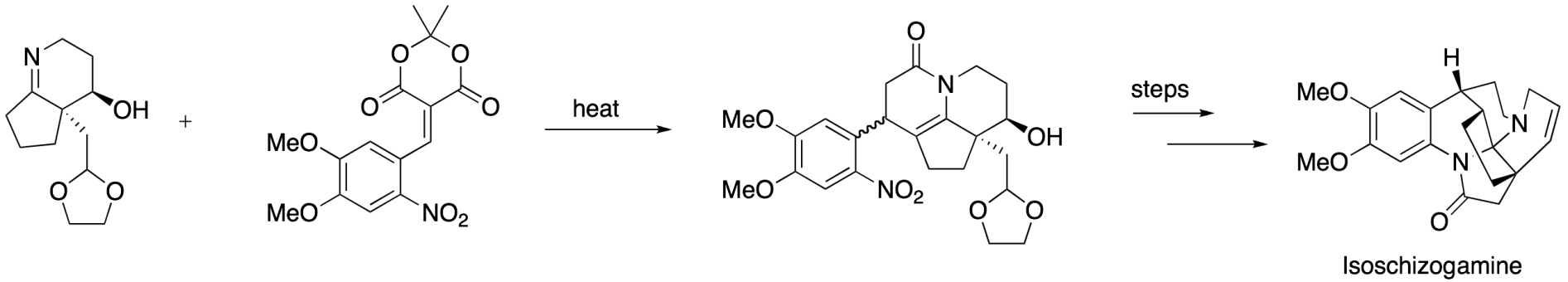
- Isolated from Cuban species *Strempeliopis strempelioides* K. Schum and East-African shrub *Schizozygia coffaeoides* (Boj.) Baill.
- Traditional medicine for variety of skin diseases.
- Some exhibit antifungal and antimicrobial activity.

Proposed Biosynthesis



Hájícek, J.; Tamir, J.; Budësinsky, M. *Tet. Lett*. **1998**, *39*, 505.

Synthesis of (±)-Isoschizogamine

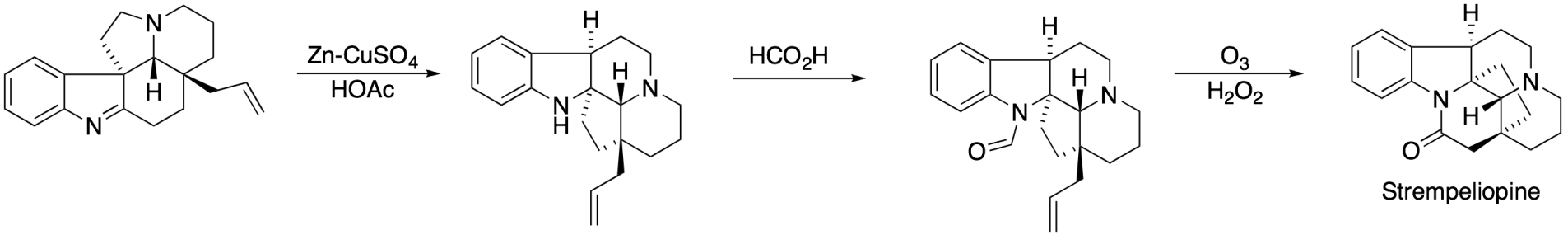


Key Points

- First concise total synthesis of isoschizogamine
- Based on proposed biosynthetic pathway
- Michael addition of enamine tautomer
- Cyclization expunges acetone and CO_2

Hubbs, J. L.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 1315.

Synthesis of Strempeliopine

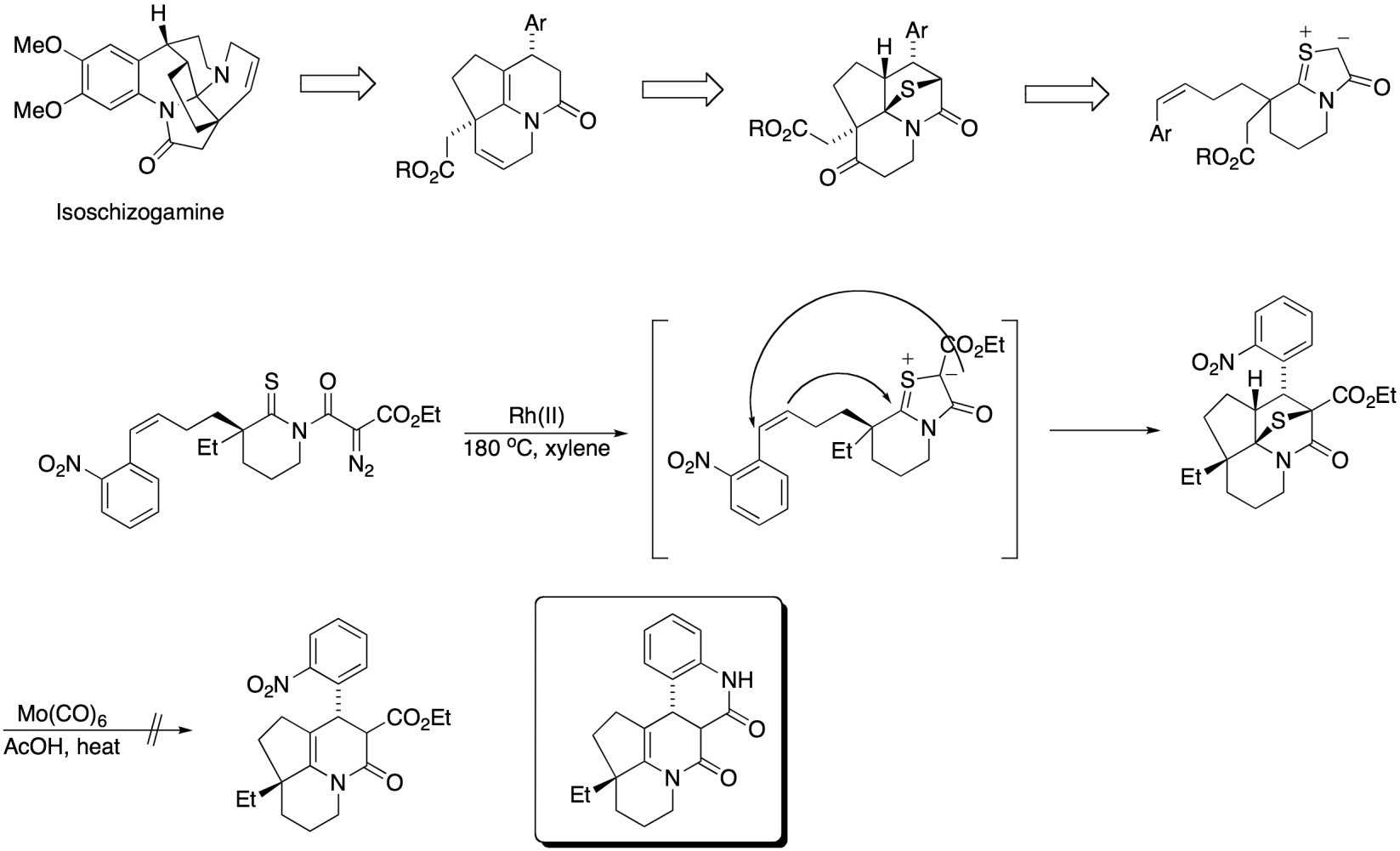


Key Points

- First and only synthesis prior to title paper
- Key step: reductive rearrangement of indolenine using Zn-$CuSO_4$

Mauperin, P.; Levy, J.; Le Men, J. *Tet. Lett*. **1971**, 999.

1,3-Dipolar Addition Approach

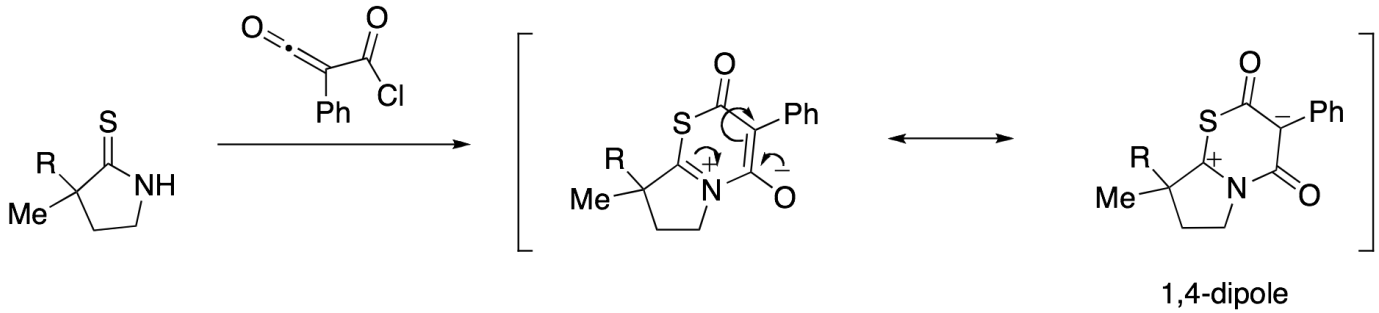


1,4-Dipolar Addition

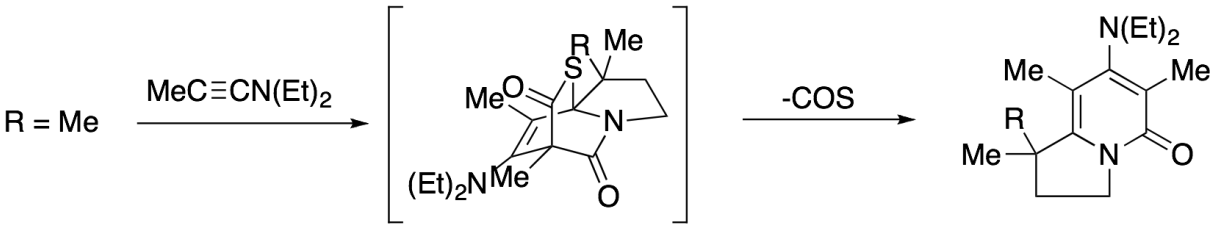
- Existence first postulated in 1967
- Incorporated in cross-conjugated heteroaromatic betaines in ‘82 & ’85
- Cycloadditions give bi- and tricyclic heterocycles not easy accesible by other routes
- Obstacle: cycloadducts can be difficult to convert to useful structures

Topics in Heterocyclic Chemistry, **1969**, Chap. 8.
Heterocycles **1982**, *19*, 1083.
Tetrahedron **1985**, *41*, 2239.
JOC **1972**, *37*, 1422.
JOC **1989**, *54*, 1077.

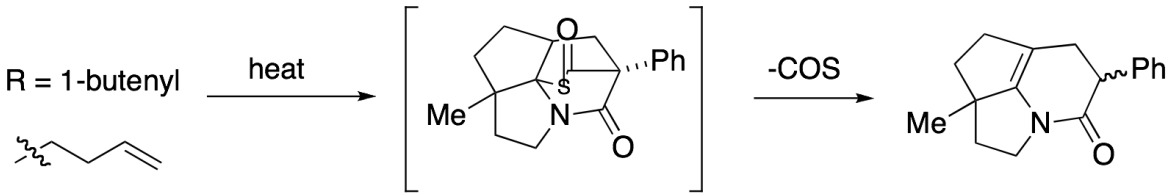
Padwa's Earlier Work



Intermolecular Cyclization Elimination

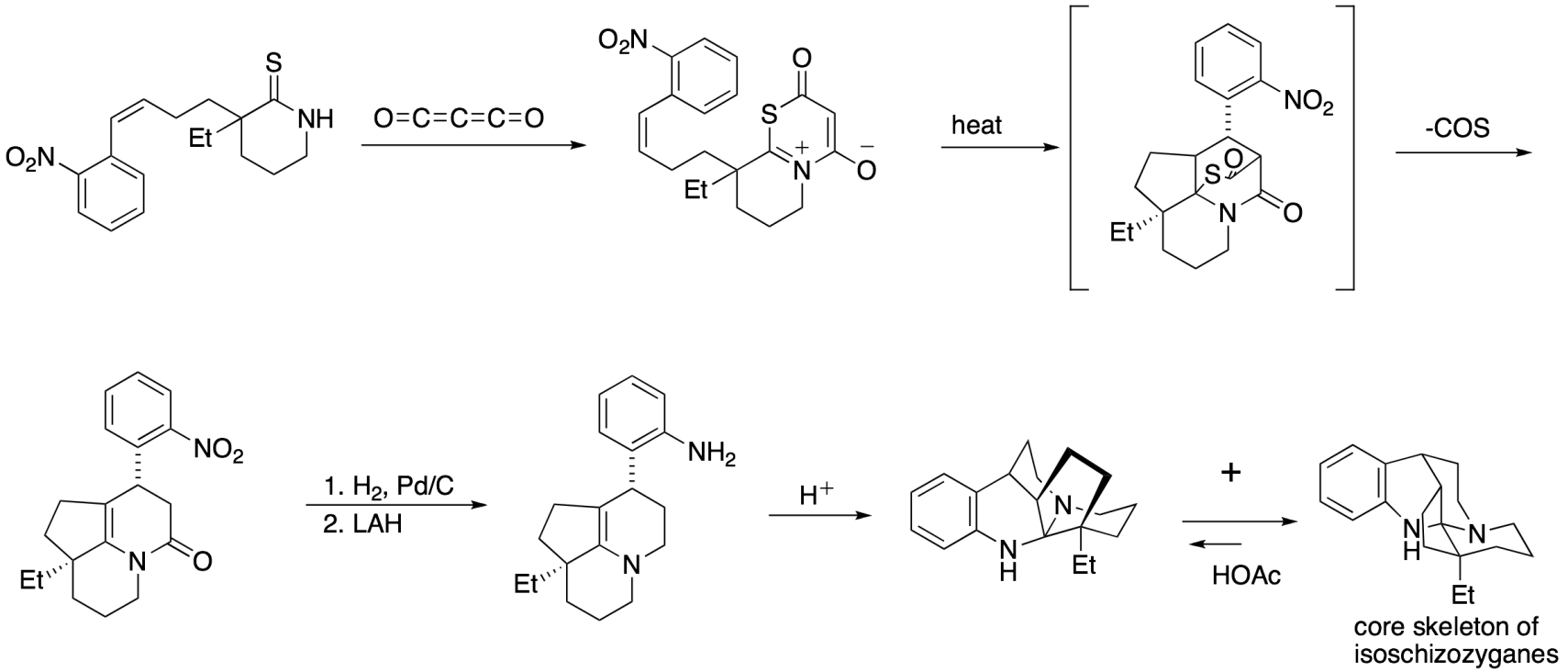


Intramolecular Cyclization Elimination



Padwa, A.; Coats, S. J.; Semones, M. A. *Tetrahedron* **1995**, *51*, 6651.

Application to Isoschizozygane Core

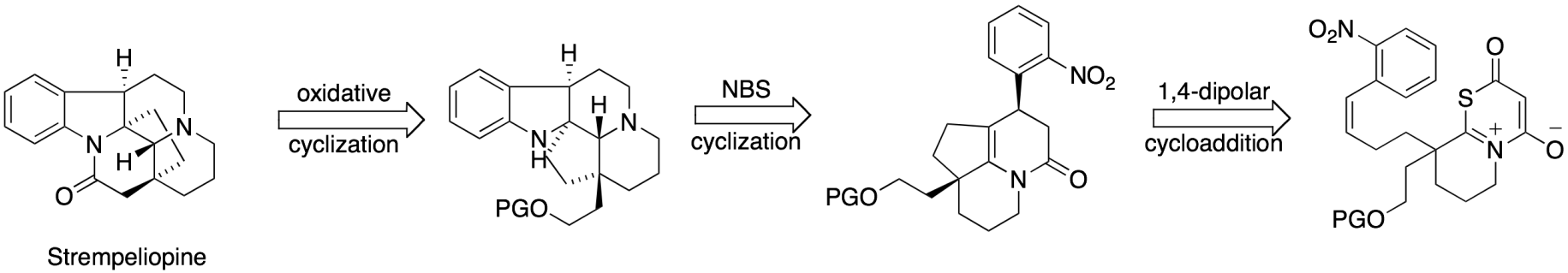


Keys

Constructing appropriately substituted 1,4-dipoles

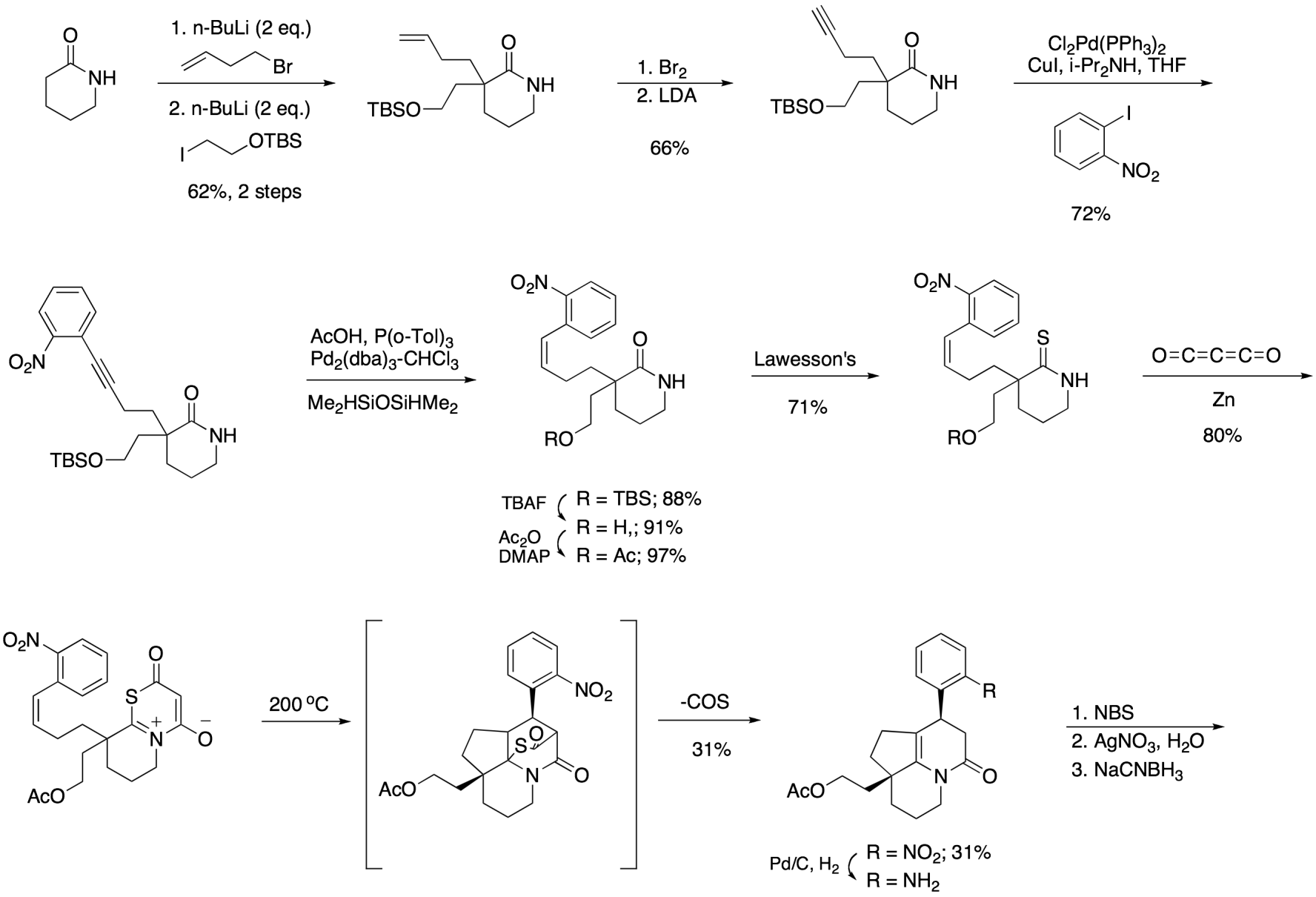
Allow for the elimination of a small stable fragment (ie COS, CO_2, HOCN)

Retrosynthesis

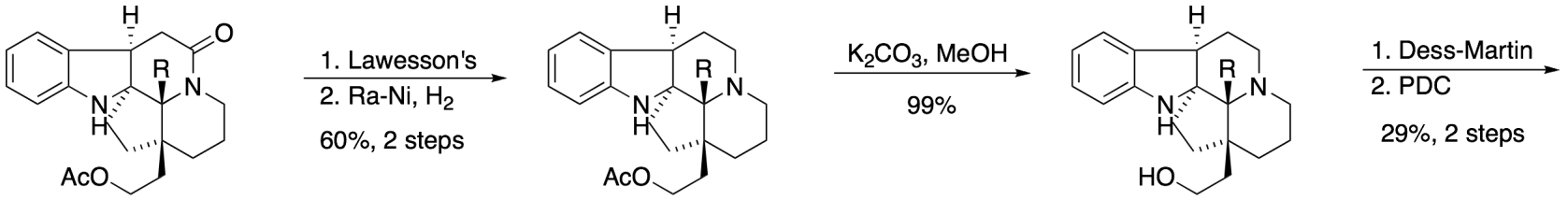


Strempeliopine

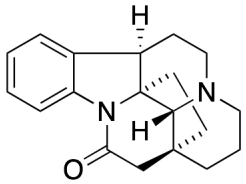
Title Paper Synthesis



Title Paper Synthesis



R = OH; 21% 3 steps
R = H; 69%



Strempeliopine

Summary & Future Work

- Successfully synthesized both the isoschizozygane skeleton and (±)-strempeliopine.
- (±)-Strempeliopine was synthesized in 14 steps from δ-valerolactam.
- Expands the use of 1,4-dipolar additions.
- Method could potentially be used to access other members of this family.