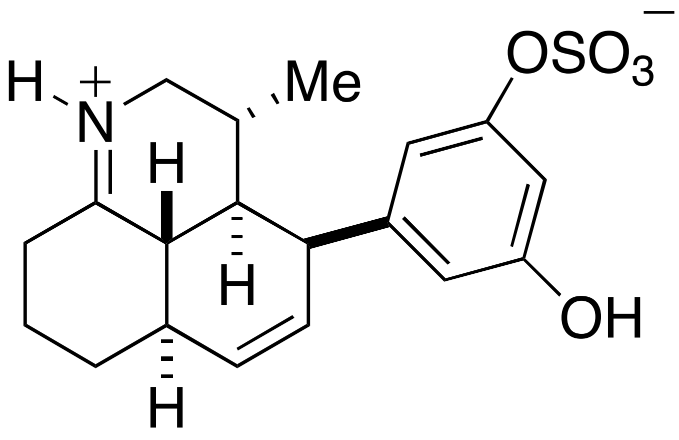
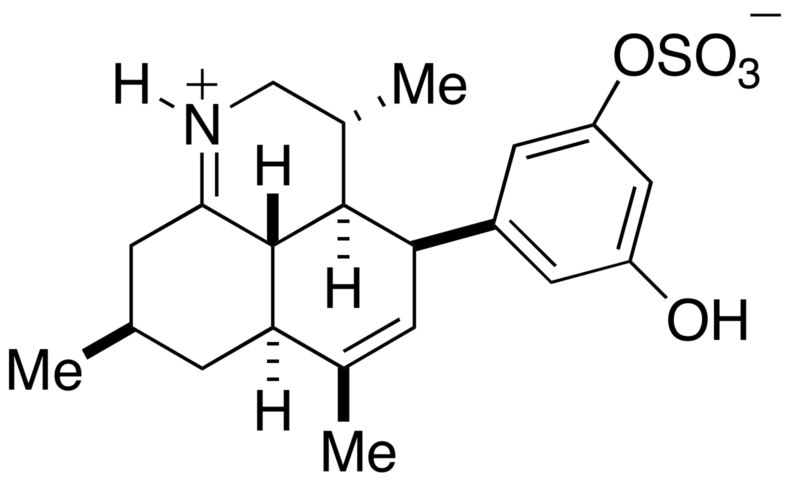
Enantioselective Total Synthesis of the Osteoclastogenesis Inhibitor (+)-Symbioimine



Symbioimine



Neosymbioimine

Kim, J.; Thomson, R. J. *Angew. Chem. Int. Ed.* ASAP

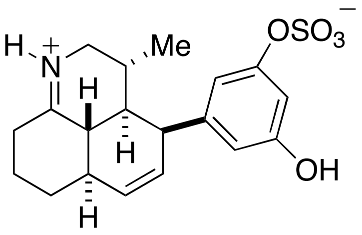
Kalyani Patil@ Wipf group

07 Apr 2007

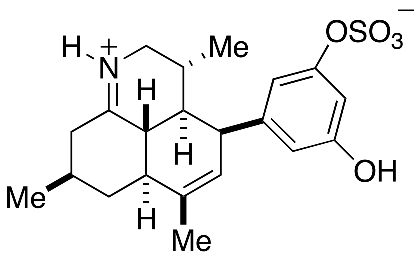
Outline

- Biological Activity
- Synthesis of Symbioimine and Neosymbioimine (Uemura, Maier, and Snider)
- Title Paper
- Summary

Isolation and Biological Activitity of Symbioimines



Symbioimine

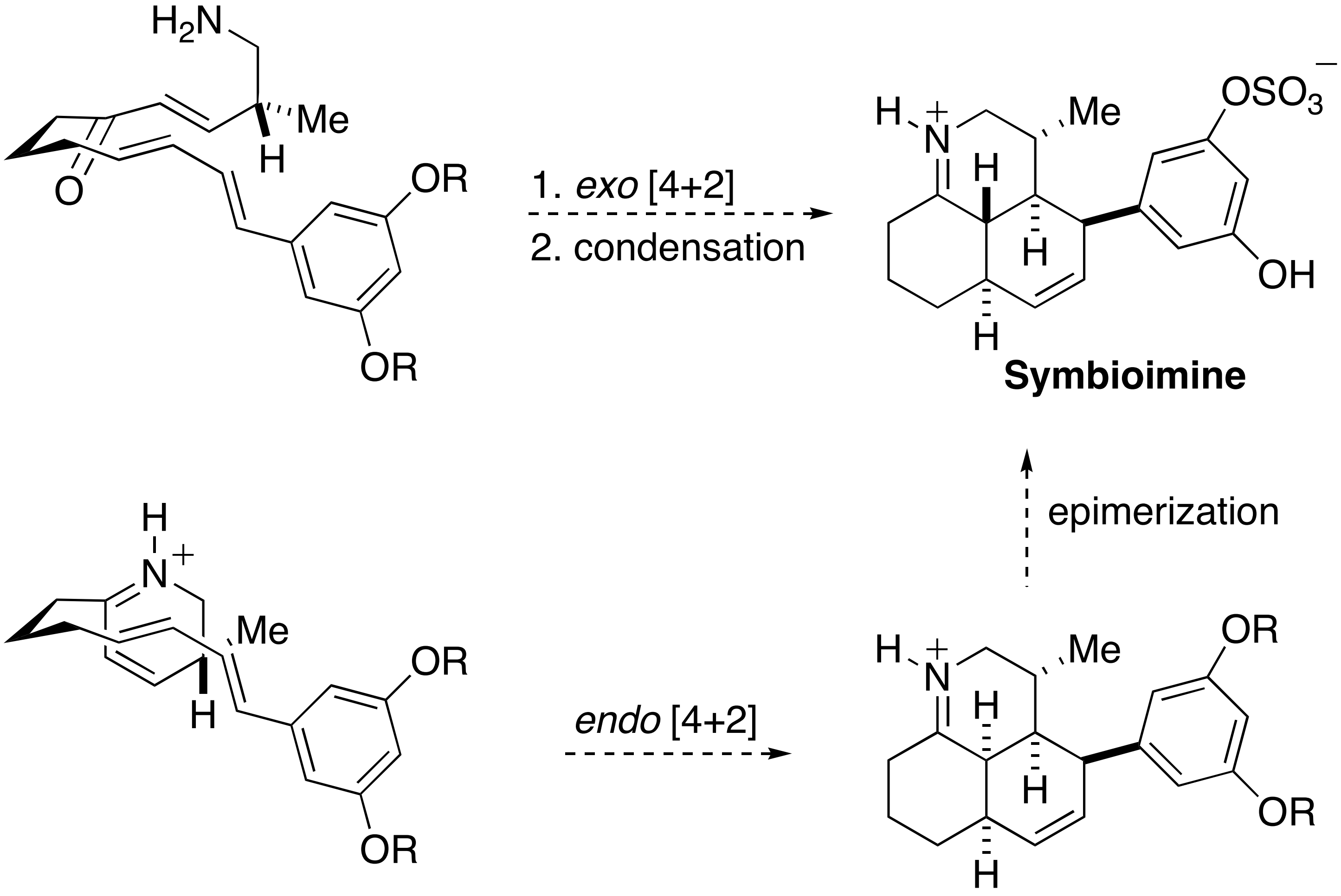


Neosymbioimine

- Isolated by Uemura in 2004 from cultured marine dinoflagellate Symbiodinium sp.
- Tetracyclic alkaloid-zwitterionic tricyclic iminium sulfate
- Inhibits differentiation of RAW 264 cells into osteoclasts (EC_{50}) = 44μg/mL) - antiosteoporosis drug
- Inhibits cyclooxygenase-2 activity at 10μM - antiinflammatory drug

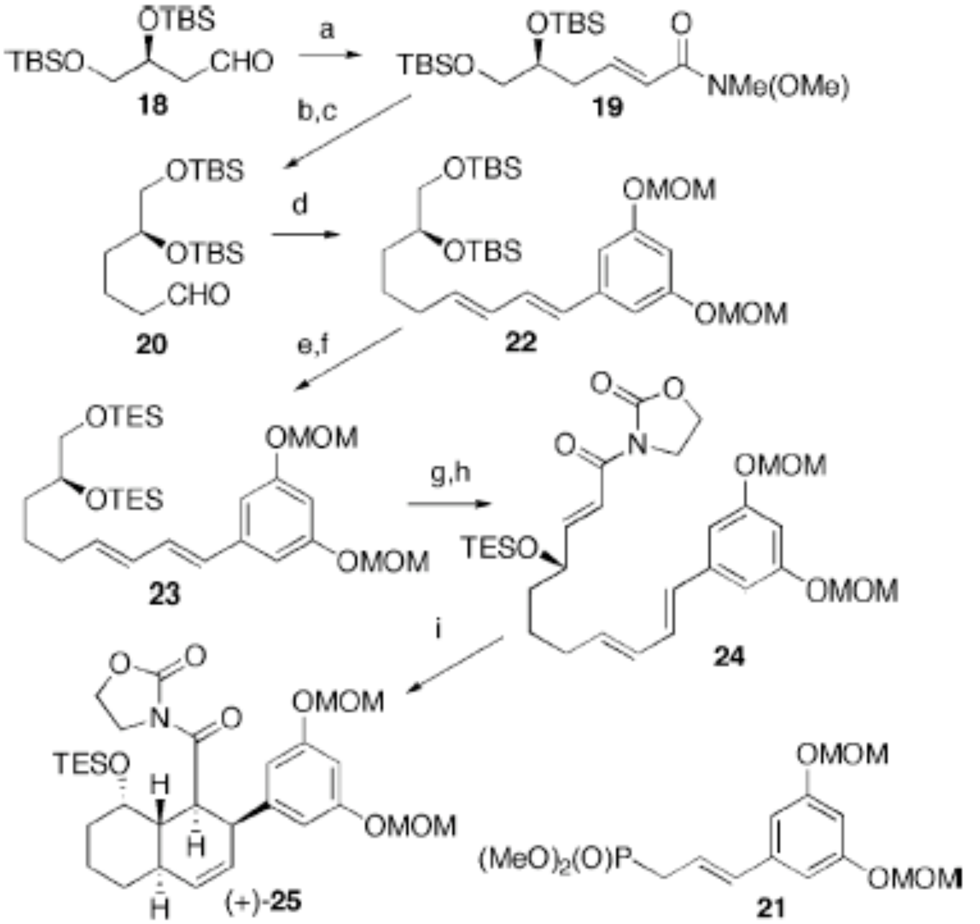
Uemura et al. *J. Am. Chem. Soc.* **2004**, *126*, 4794-4795.

Plausible Biogenetic Pathways to Symbioimines



Uemura et al. *Bioorg*. *Med*. *Chem*. **2005**, *126*, 5253-5258.
Uemura et al. *Chem*. *Lett*. **2005**, *34*, 454-459.

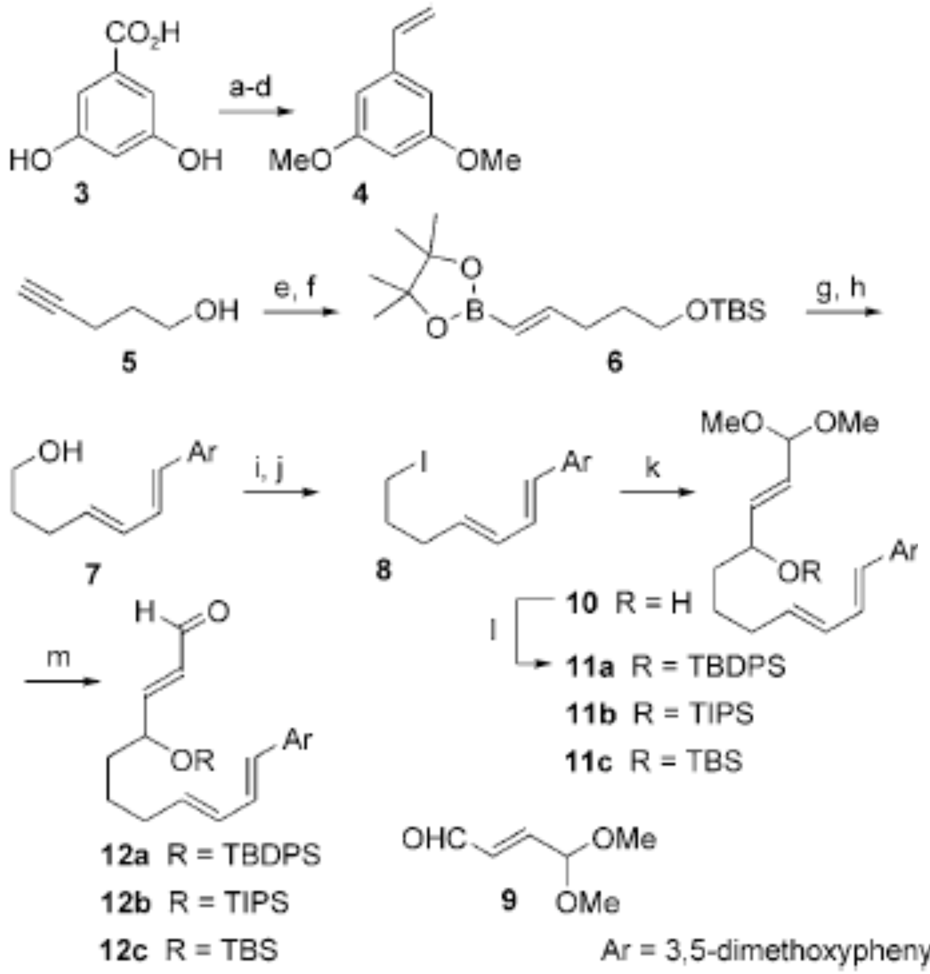
Asymmetric Synthesis of the Octalin Unit of Symbioimine - Uemura



Scheme 4. Synthesis of (+)-**25**. Reagents and conditions: (a) $Ph_3P{=}CHC(O)NMe(OMe)$, CH_2Cl_2, rt, 88%; (b) H_2, Pd–C, EtOAc, rt, 96%; (c) DIBALH, THF, −30 °C to rt, 92%; (d) **21**, ^{n}BuLi, HMDS, THF, −78 °C to rt, 80%; (e) TBAF, THF, rt; (f) TESCl, imidazole, DMAP, rt, 86% (two steps); (g) $(COCl)_2$, DMSO, CH_2Cl_2, −78 to −40 °C, then Et_3N, −78 °C to rt; (h) **10**, Et_3N, LiCl, CH_3CN, rt, 60% (two steps); (i) toluene, 80 °C, quant.

Uemura et al. *Tetrahedron Lett*. **2006**, *47*, 6343-6345.

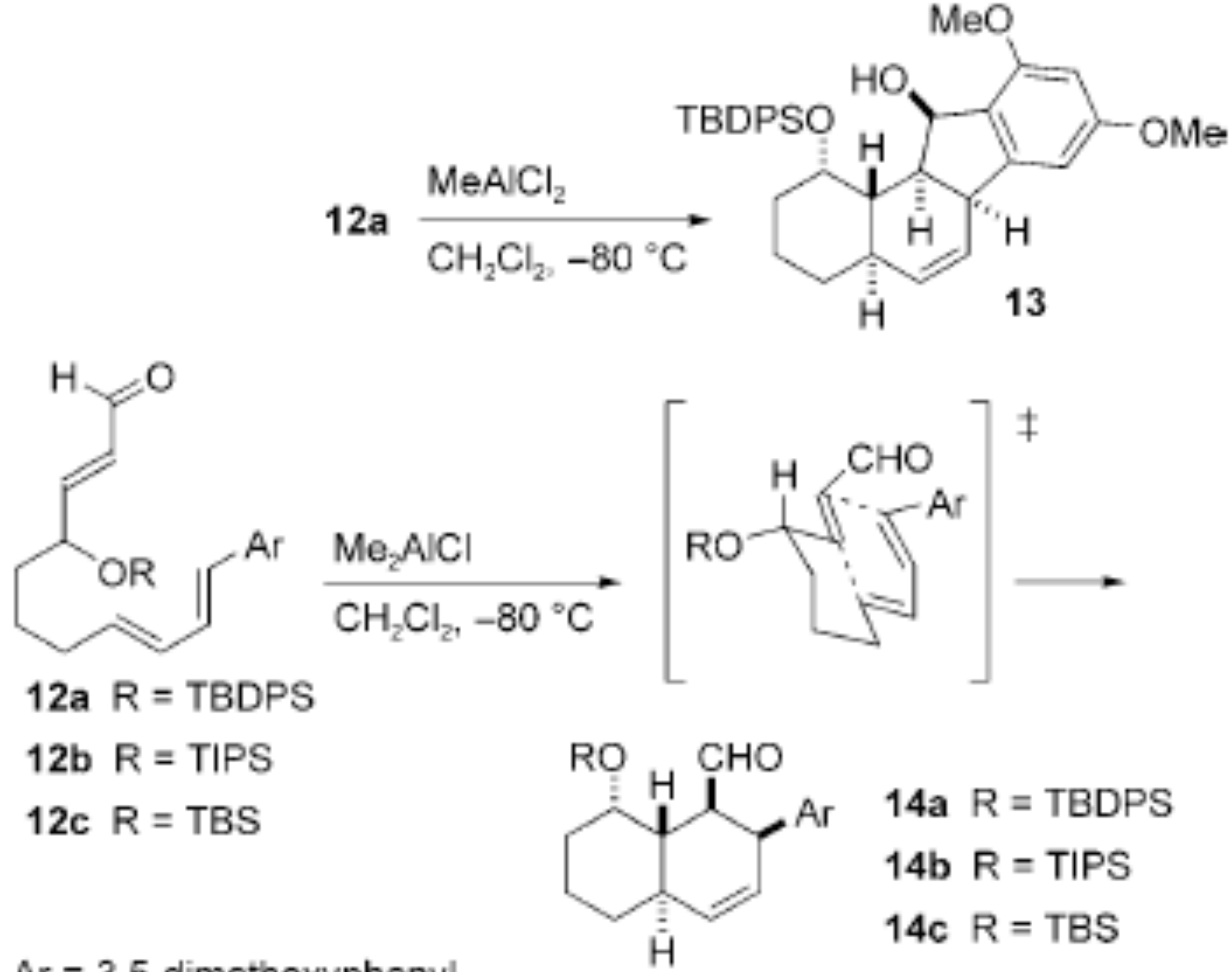
Total Synthesis of (±)-Symbioimine - Maier



Scheme 4. Synthesis of the Diels–Alder substrates **12**. a) $(CH_3O)_2SO_2$ (3.5 equiv), K_2CO_3, acetone, reflux, 4 h (96%); b) $NaBH_4$ (5 equiv), DME, MeOH, reflux, 1 h (99%); c) CrO_3/pyridine (1.2 equiv), CH_2Cl_2, RT, 24 h (81%); d) $Ph_3PCH_3^+Br^-$ (1.2 equiv), KO*t*Bu (1.4 equiv), THF, −65 °C to RT (96%); e) TBSCl, imidazole, CH_2Cl_2, RT, 24 h (99%); f) catechol borane (1.1 equiv), 70 °C, 12 h, then pinacol (1.2 equiv), 23 °C, 3 h (85%); g) **4** (2 equiv), $Pd(OAc)_2$ (0.1 equiv), Na_2CO_3, DMF, 60 °C, **6** (1 equiv), 24 h; h) HCl, MeOH, 23 °C, 0.5 h (68% from **6**); i) MsCl (1.3 equiv), NEt_3, CH_2Cl_2, −30°, 1 h (98%), j) NaI, acetone, 23 °C, 24 h (93%); k) *t*BuLi (2.5 equiv), then **9** (1.2 equiv), Et_2O, −80 °C, 1 h (60%); l) R_3SiCl (2 equiv), imidazole, CH_2Cl_2, RT, 24 h; m) amberlyst 15, acetone, RT, 40 min (**12a**: 80%, 2 steps; **12b**: 75%;

Varseev, G. N.; Maier, M. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 4767-4771.

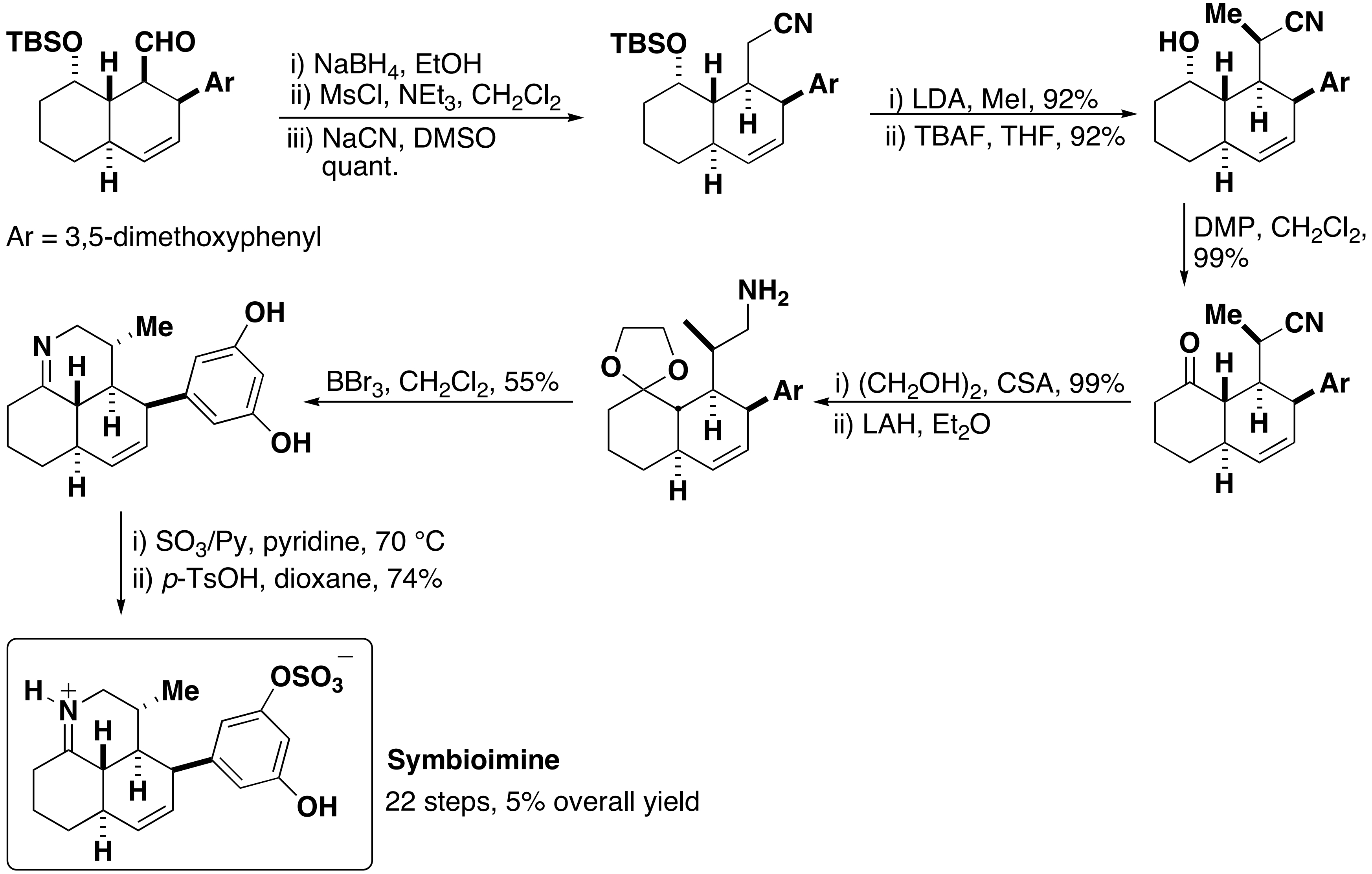
Total Synthesis of (±)-Symbioimine - Maier



Ar = 3,5-dimethoxyphenyl

Varseev, G. N.; Maier, M. E. *Angew*. *Chem*. *Int*. *Ed*. **2006**, *45*, 4767-4771.

Total Synthesis of (±)-Symbioimine - Maier



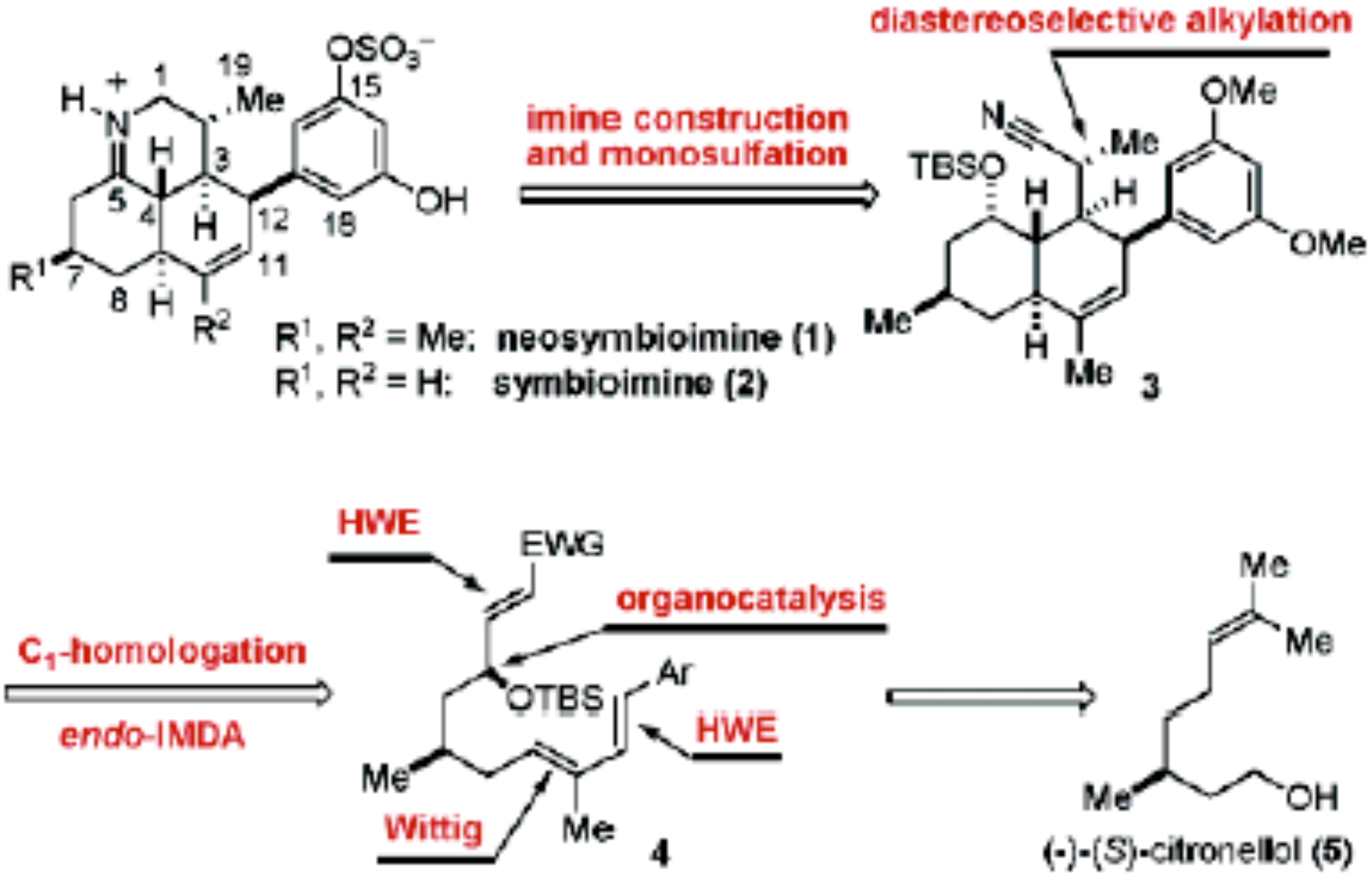
Ar = 3,5-dimethoxyphenyl

Symbioimine

22 steps, 5% overall yield

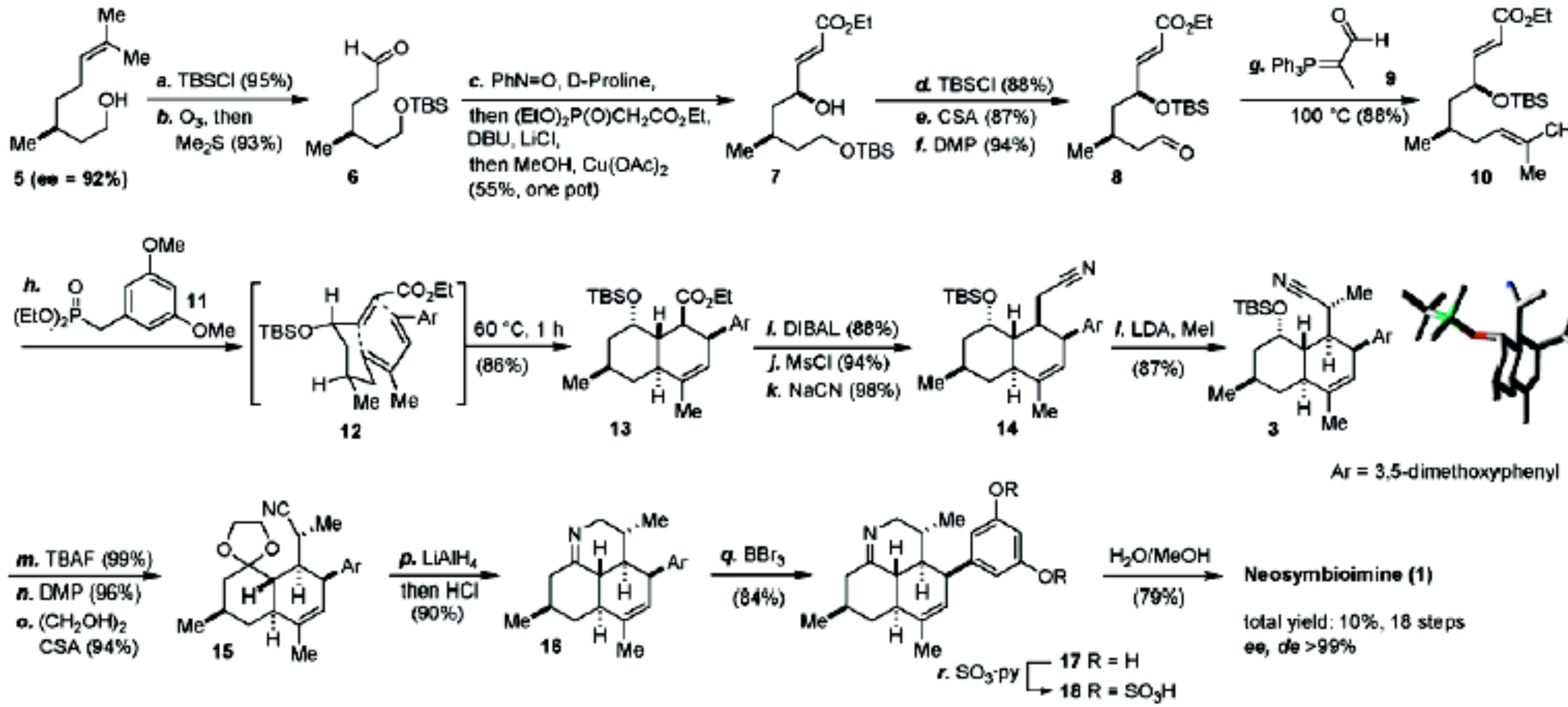
Varseev, G. N.; Maier, M. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 4767-4771.

Retrosynthesis of (+)-Neosymbioimine - Maier



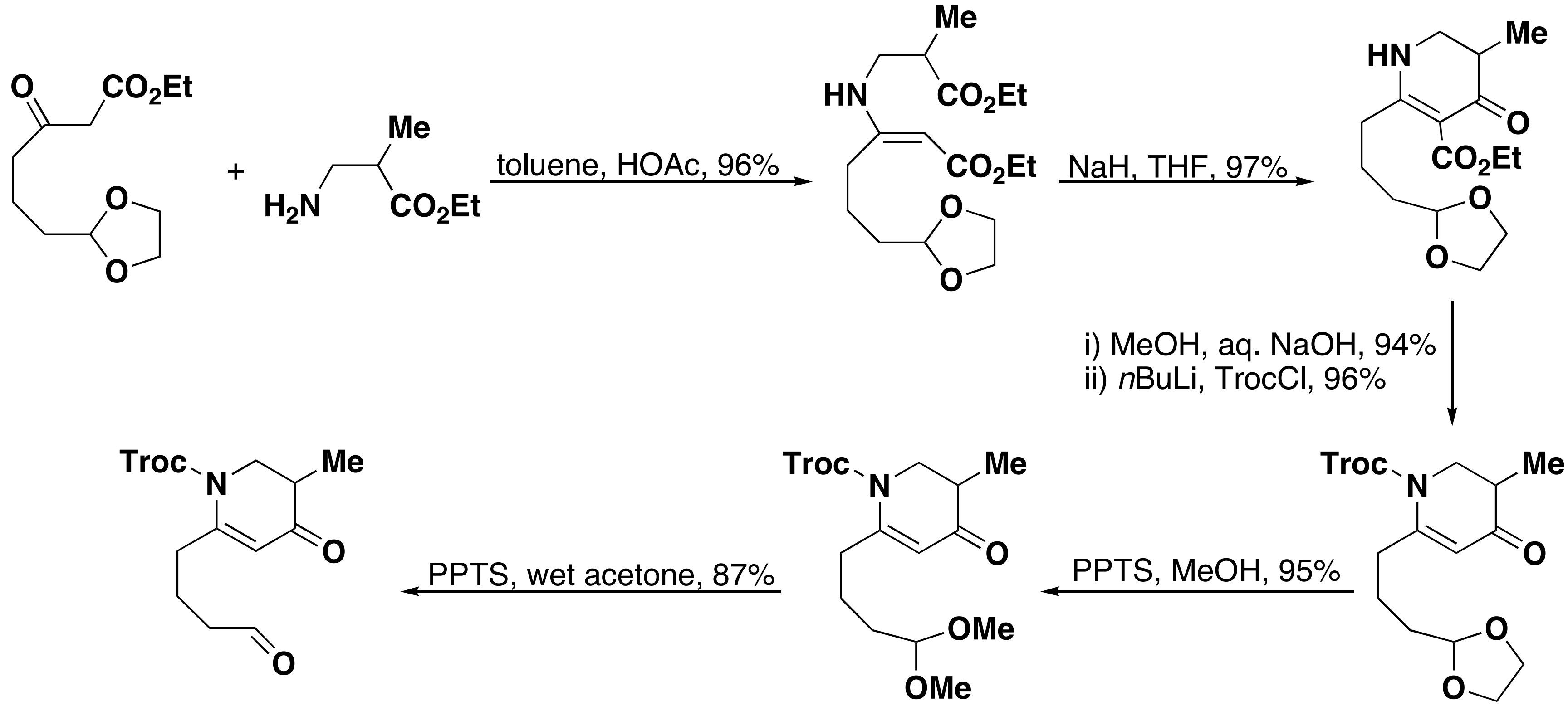
Varseev, G. N.; Maier, M. E. *Org*. *Lett*. **2007**, *9*, 1461-1464.

Synthesis of (+)-Neosymbioimine - Maier



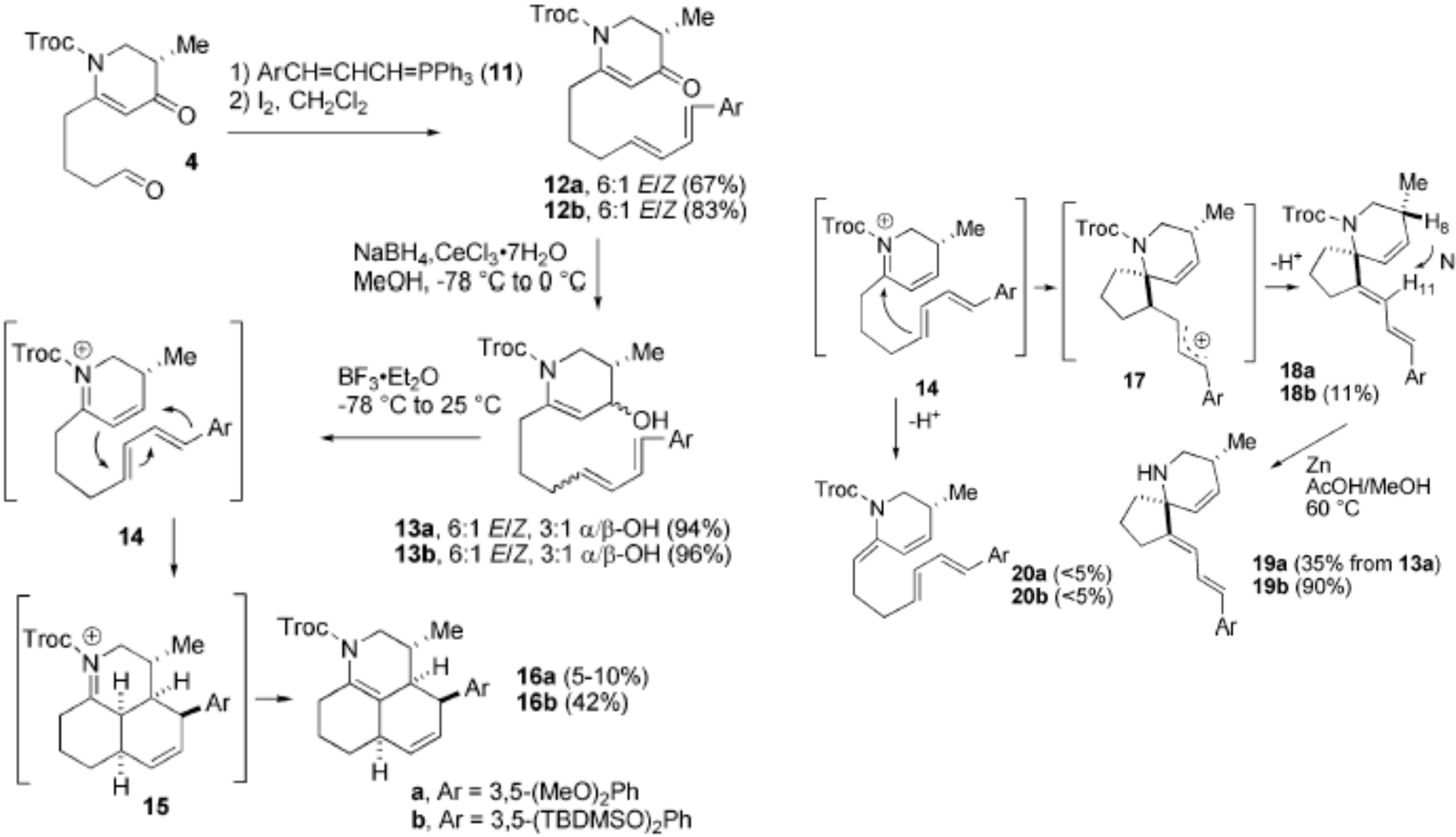
Varseev, G. N.; Maier, M. E. *Org. Lett.* **2007**, *9*, 1461-1464.

Total Synthesis of (±)-Symbioimine - Snider



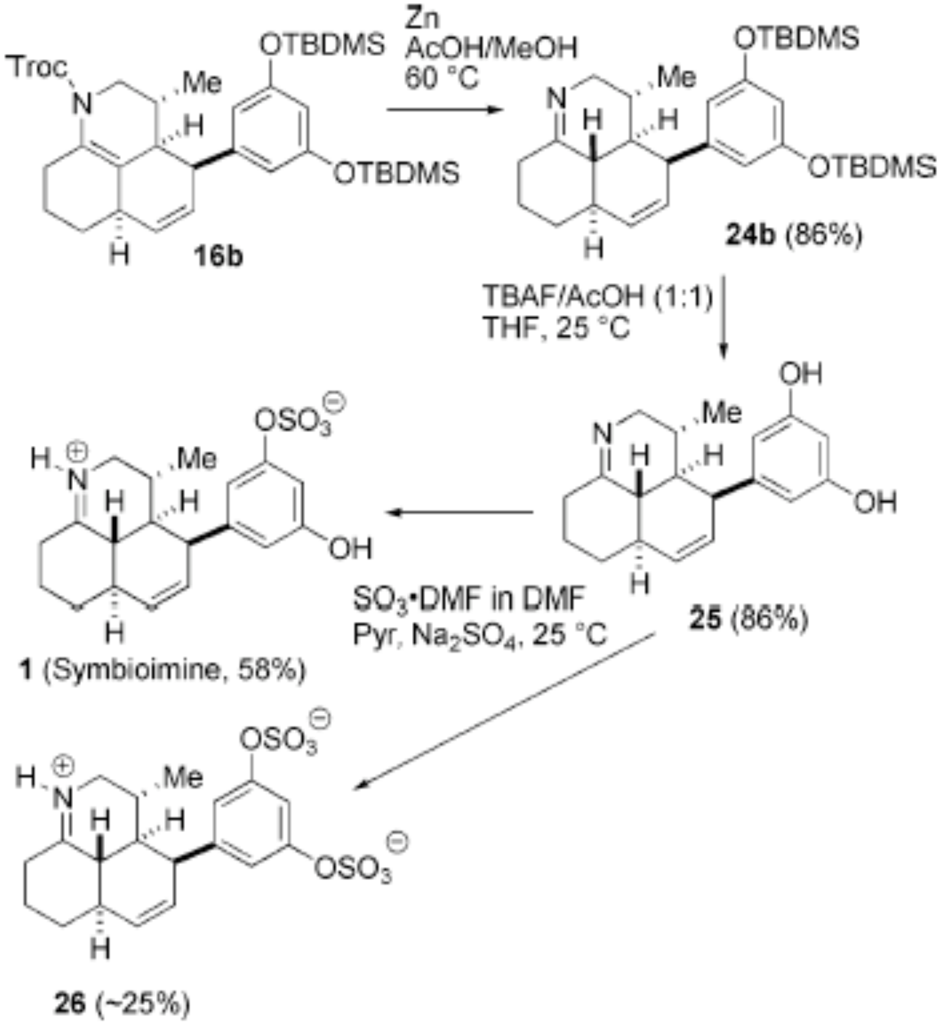
Snider, B. B.; Che, Q. *Angew. Chem. Int. Ed.* **2006**, *45*, 932-935.

Total Synthesis of (±)-Symbioimine - Snider



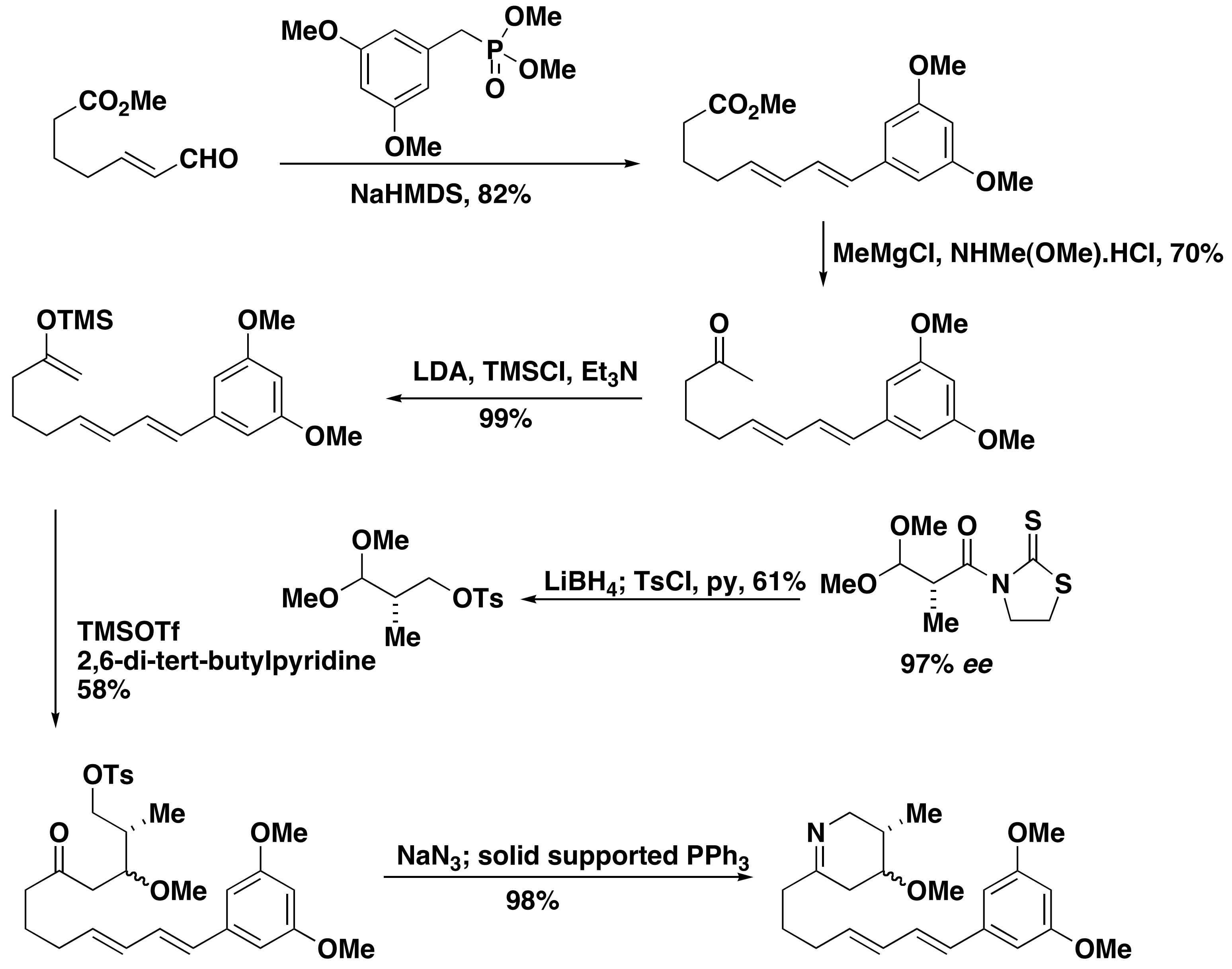
Snider et al. *Org*. *Lett*. **2006**, *8*, 5605-5608.

Total Synthesis of (±)-Symbioimine - Snider



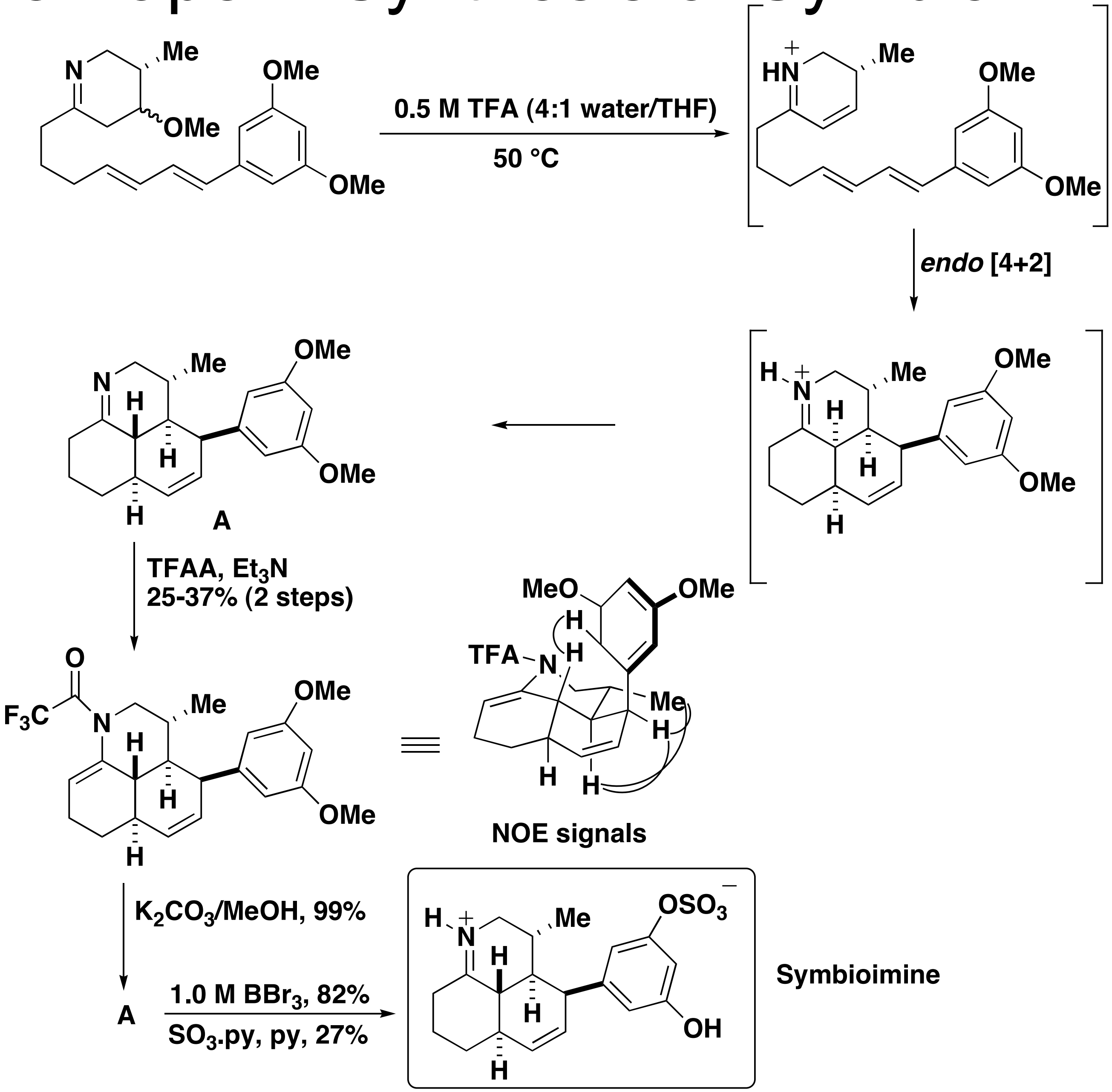
Snider et al. *Org*. *Lett*. **2006**, *8*, 5605-5608.

Title Paper - Synthesis of Symbioimine by Thomson



Kim, J.; Thomson, R. J. *Angew. Chem. Int. Ed.* **2007**, *46*, ASAP.

Title Paper - Synthesis of Symbioimine



Kim, J.; Thomson, R. J. *Angew. Chem. Int. Ed.* **2007**, *46*, ASAP.

Summary

- First asymmetric synthesis of Symbioimine - 10 steps
- *Endo* Diels-Alder reaction *via* iminium ion intermediate
- Diastereoselective formation of two new rings and four stereocenters from a single methyl substituent