Indole and Oxy-indoles

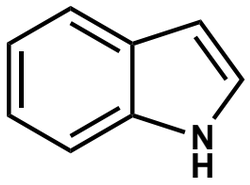
Reactivity and applications in total synthesis

Literature Talk

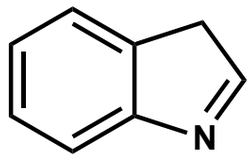
Philipp Gritsch

26th November 2012

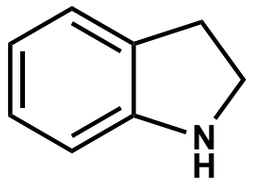
Introduction



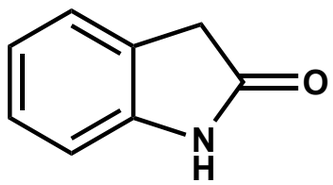
Indol



Indolenine

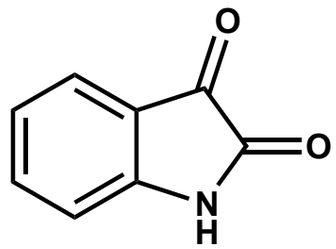


Indoline



Oxindole

Indoxyl



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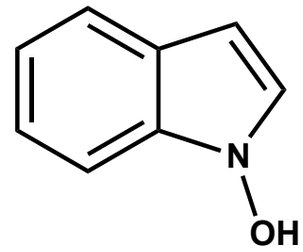
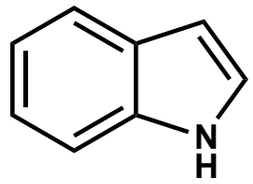
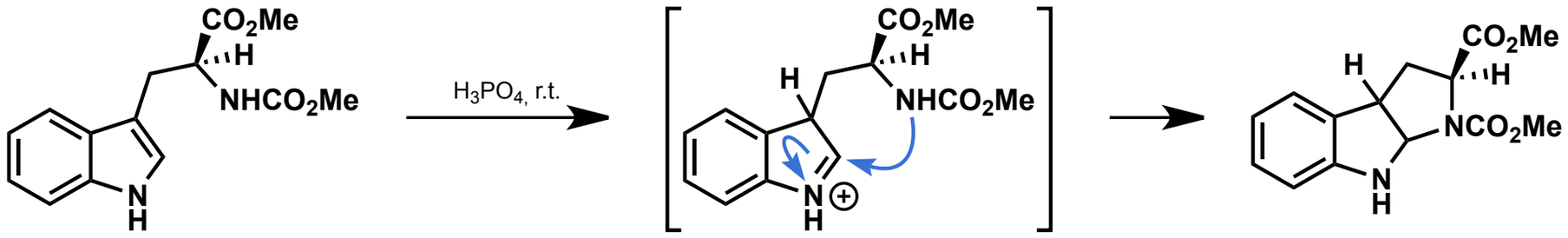


Hydroxyindol

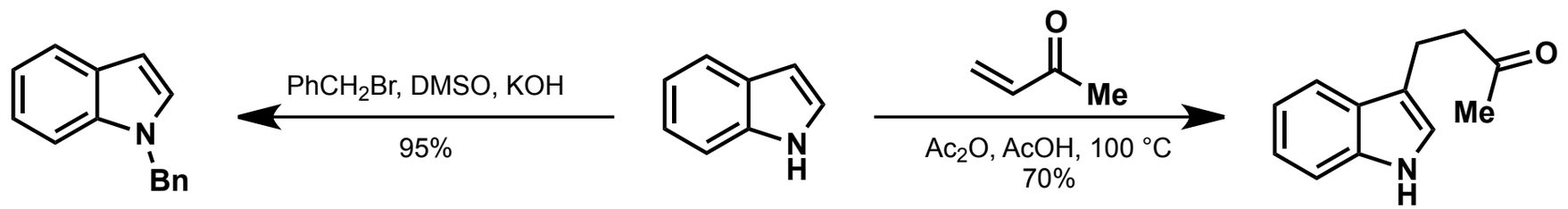
Indol: general



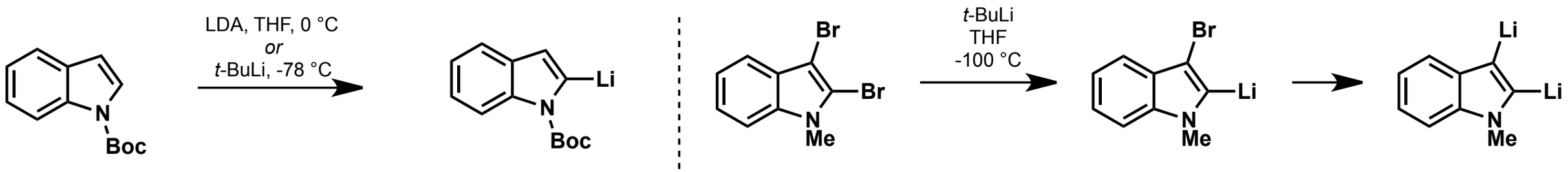
- nucleophilic substitution: only after electronics change eg. protonation



- electrophilic substitution: preferably at C-3, after deprotonation also on N-1

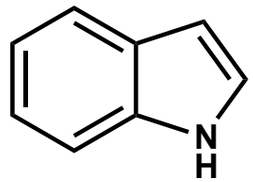


- metalation: if N-1 is substituted, usually C-2 reacts first

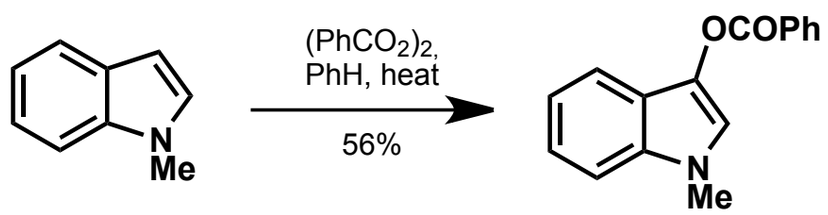


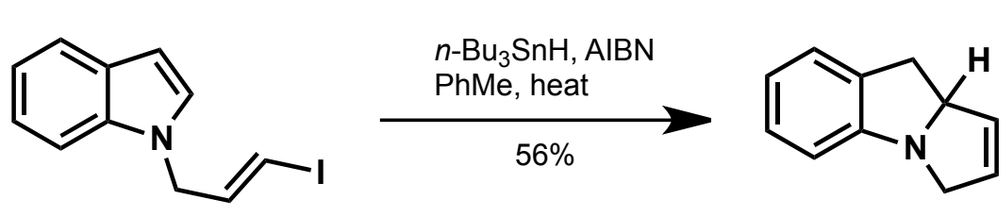
Joule, J.A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley 2010
Sundberg, R.J. *Indoles*, 1st ed.; Elsevier 1995

Indol: general

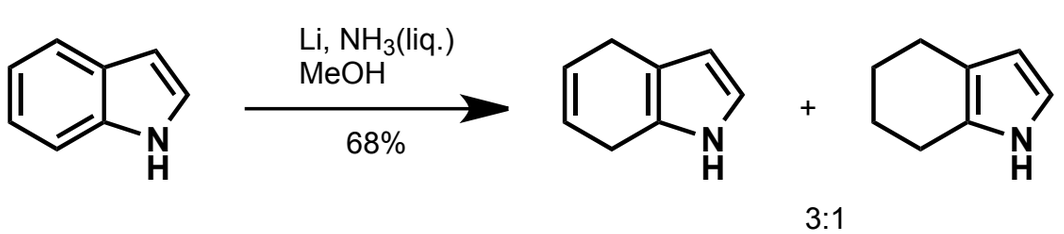


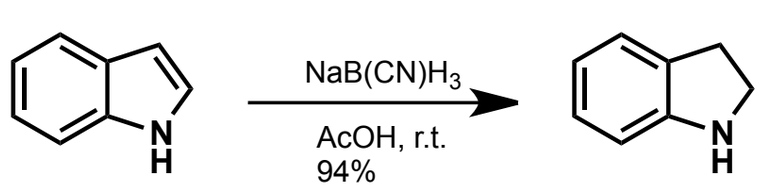
- radical reactions: limited substrate scope





- reducing agents: no reactions with nucleophilic reagents (LAH, $NaBH_4$). Reactions with Li or under acidic conditions





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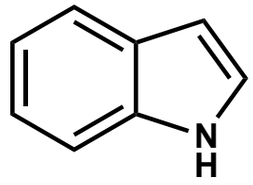
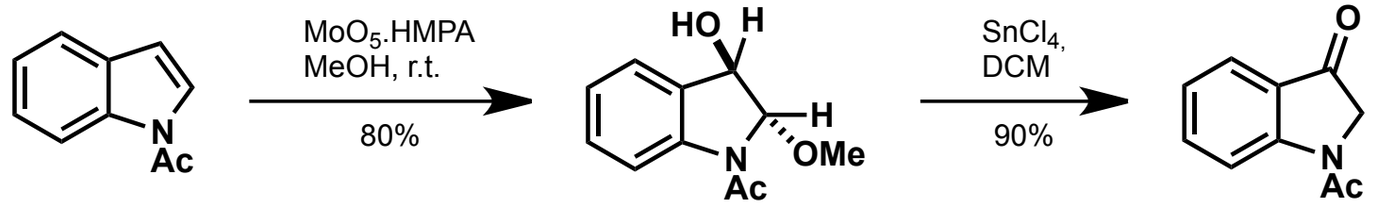
Sundberg, R.J. *Indoles*, 1st ed.; Elsevier 1995

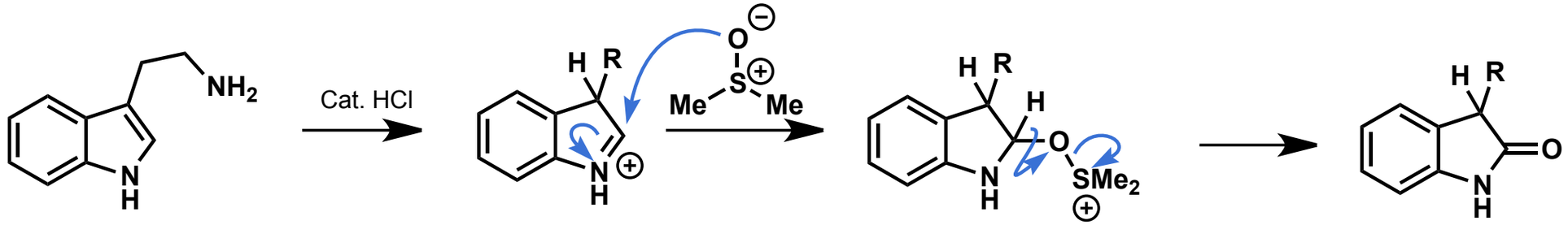
Oxidation of Indole



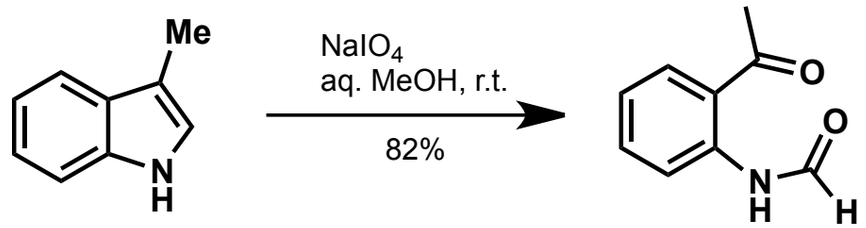
- Oxidation with MoO_5.HMPA



- Swern type oxidation

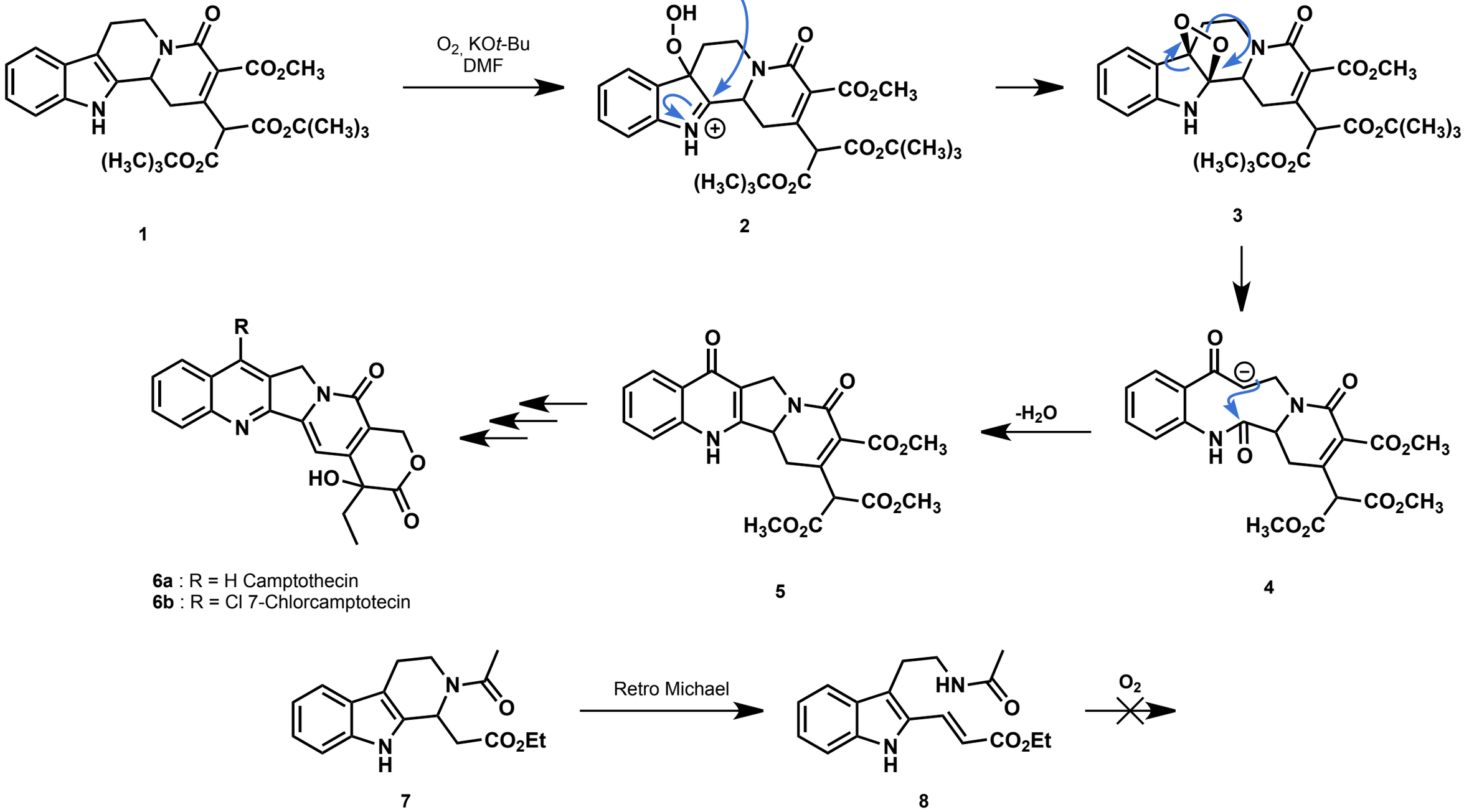


- Cleavage of 2,3-double bond can be achieved with: O_3, $NaIO_4$, KO_2, O_2/EtOH+hν



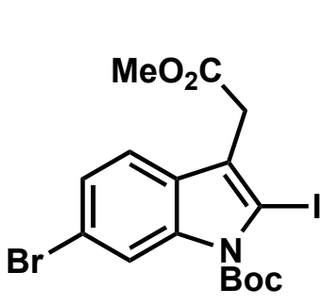
Joule, J.A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.;Wiley 2010
Sundberg, R.J. *Indoles*, 1st ed.; Elsevier 1995

Autoxidation of Indole: Total Synthesis of Camptothecin



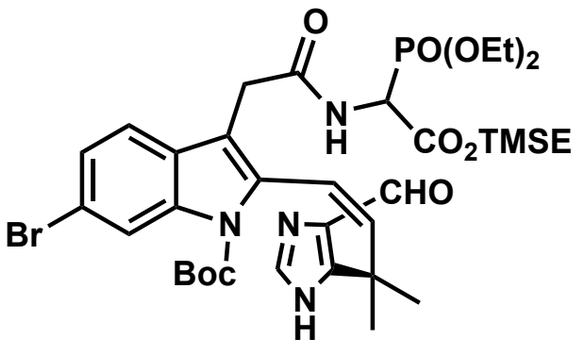
Winterfeldt, E.; Korth, T.; Pike, D.; Boch, M. *Angew. Chem.* **1972**, *84 (6)*, 265-266
Winterfeldt, E. Liebigs Ann. Chem. **1971**, *745*, 23-30

Total Synthesis of (±)-Chartelline C



9

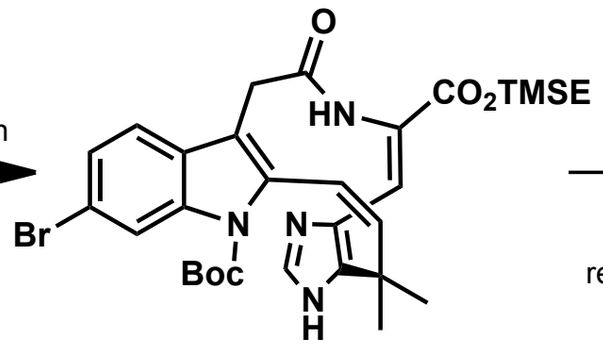
6 steps



10

a) DIPEA, LiCl
MeCN, 70 °C, 6h

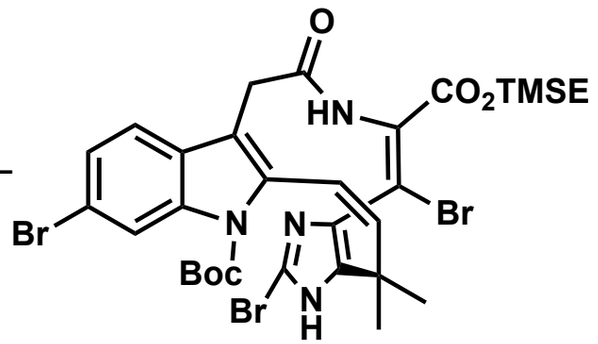
56%



11

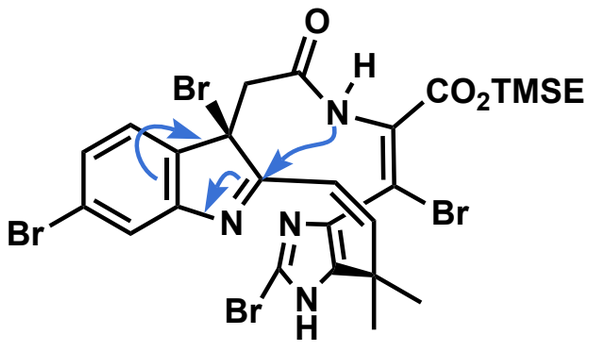
b) Br_2, $CaCO_3$, PhH, r.t. , 6 h
then
NBA, PhH, r.t. 12 h

36%
60% based on
recovered dibrominated
intermediate



12

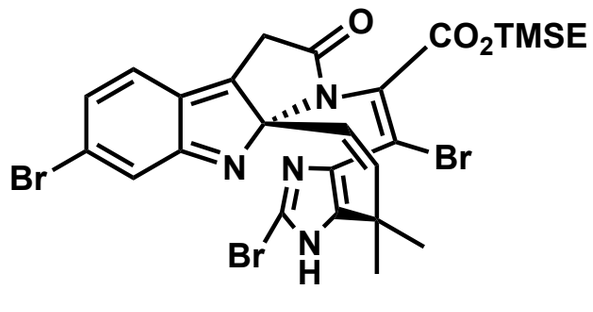
c) NBS, 185 °C,
4x 1.5min



13

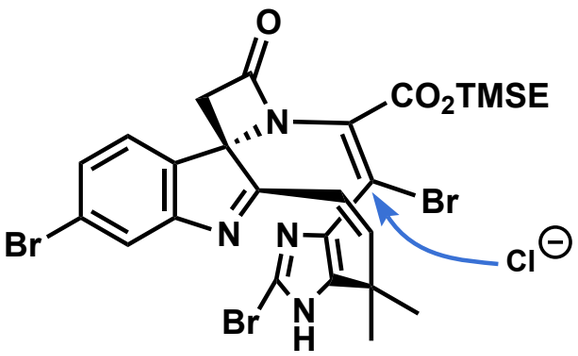
then K_2CO_3,
18-C-6, 20 °C, 1h

[- HBr]



14

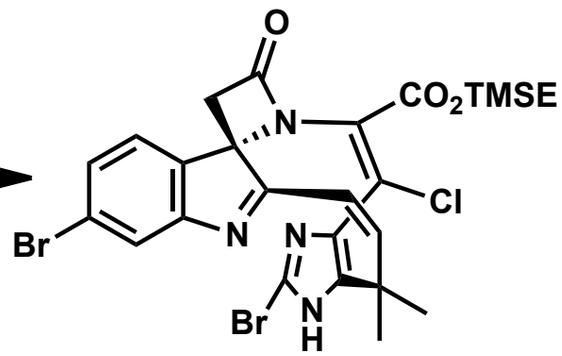
[1,5] shift



15

then $NaHCO_3$,
Brine, 15 min

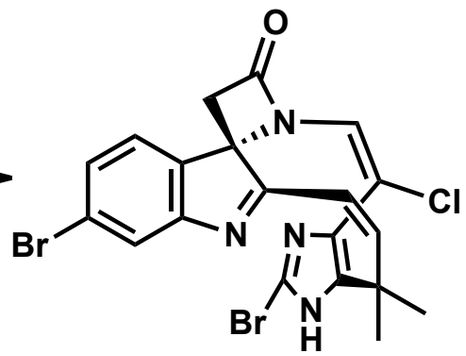
93%



16

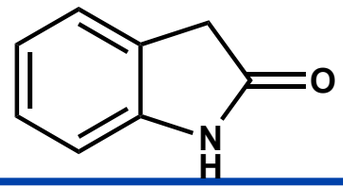
d) TFA, DCE, r.t., 4h

then
o-*DCB,* 200 °C, 5min



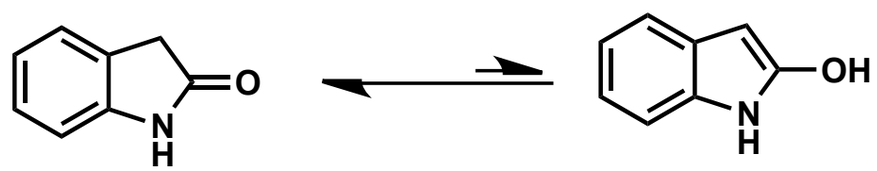
(±)-Chartelline C
17

Oxindole



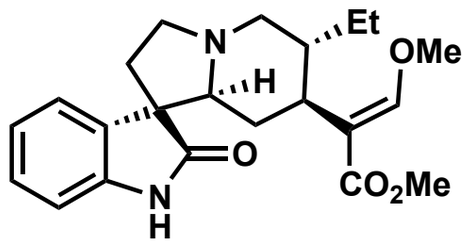
- behaves largely like a 5-membered lactame

  only one tautomer observed

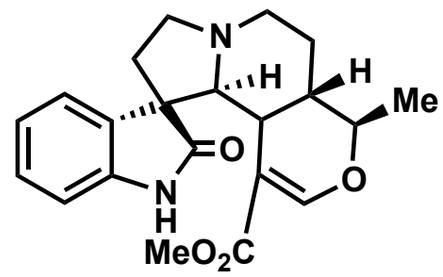


- oxindole alkaloids:

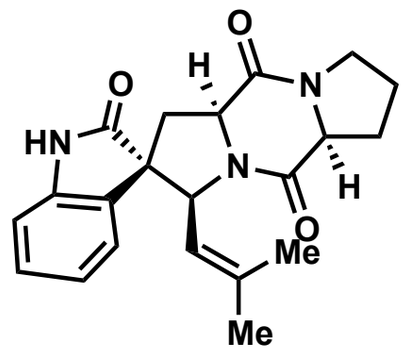
  frameworks derived from tryptamine



rychnophiline
(secoyohimbane skeleton)
tetracyclic
18



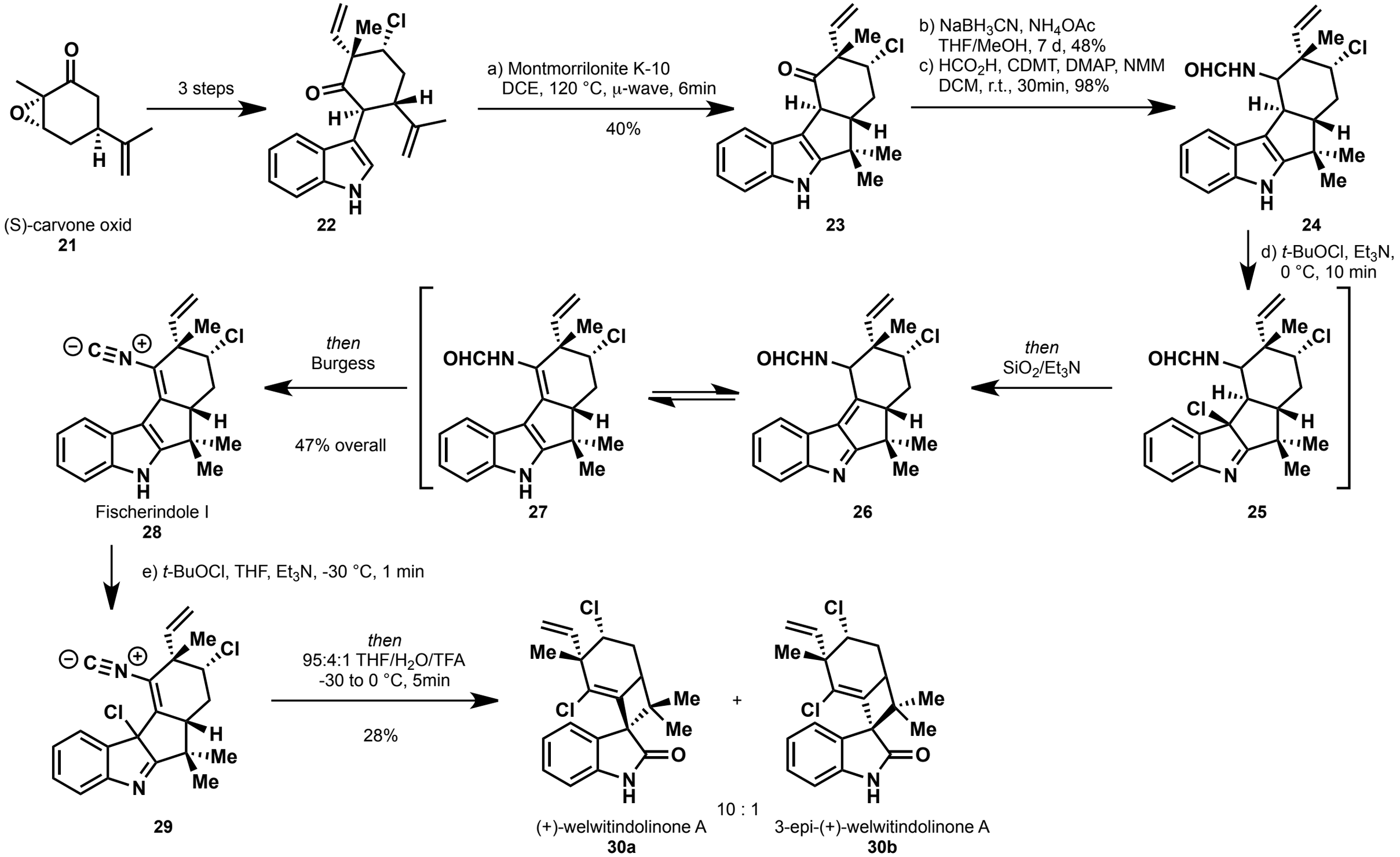
formosamine
(heteroyohimbane skeleton)
pentacyclic
19



spirotryprostatin A
20

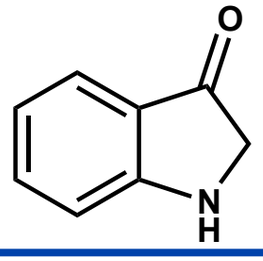
Joule, J.A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.;Wiley 2010
Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209-2219

Total Synthesis Welwitindonlinone A

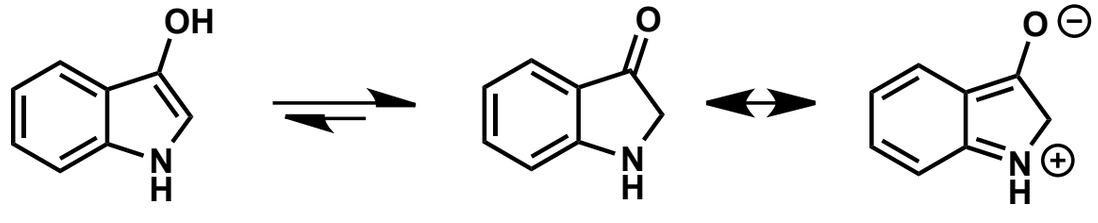


Baran, P. S.; Richter. J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394-15396

Indoxyl: general reactivity



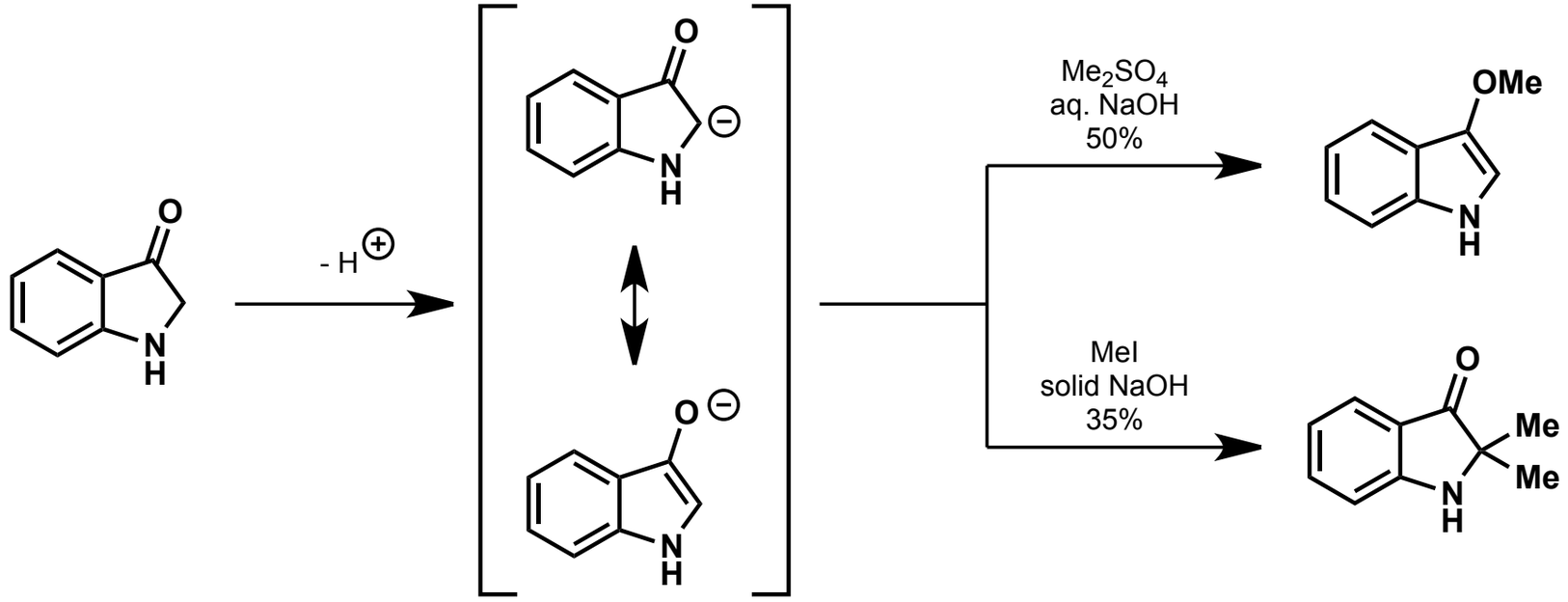
- Tautomeric equilibrium



3-hydroxy inole
minor tautomer

indoxyl

- More acidic than oxindole, reactions at C and at O occur



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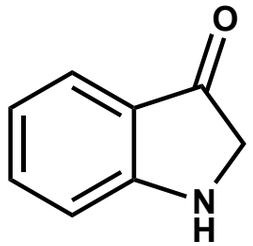
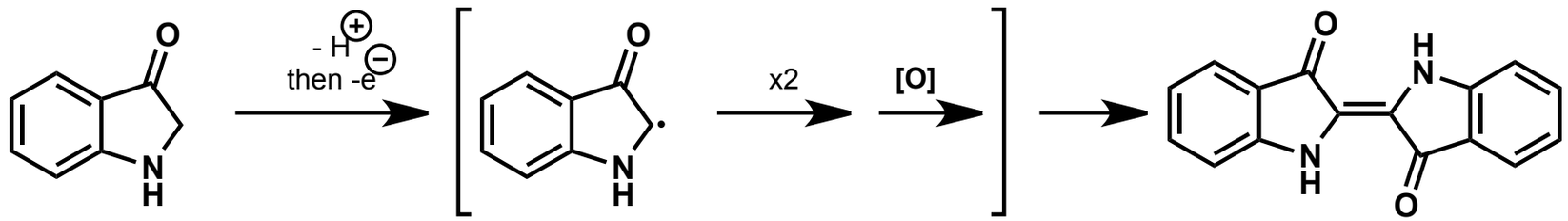
Indoxyl: general reactivity

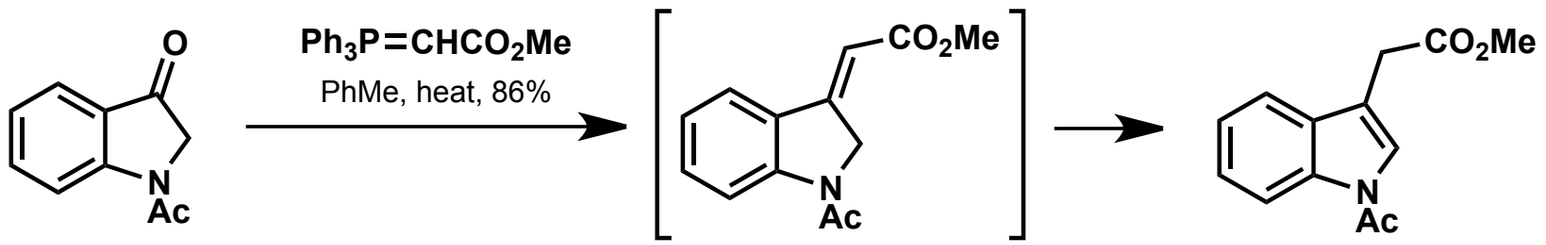


- particularly easily autooxidised



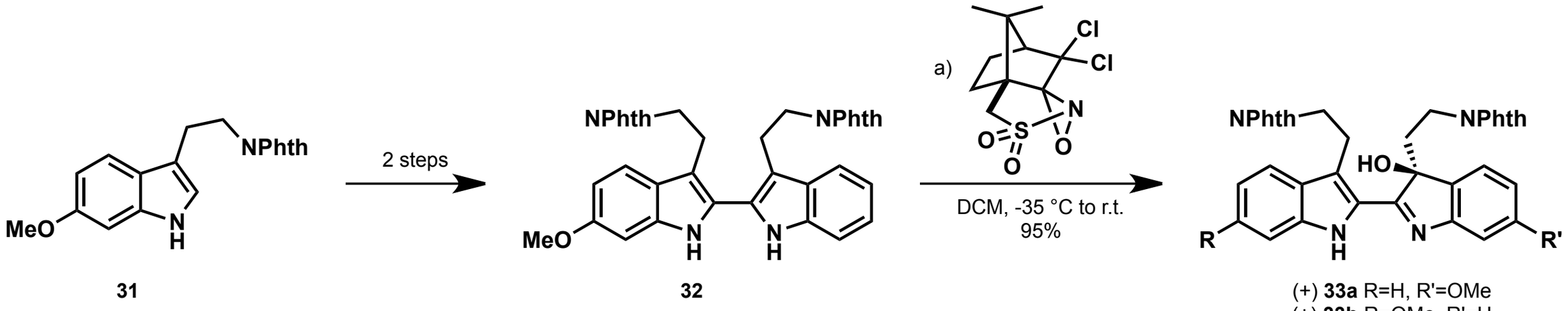
Indigo

- Acetyl groups increase stability



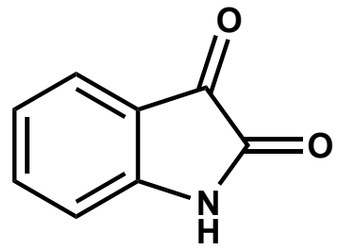
Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley 2010

Total Synthesis of (–)-Trigonolimine C

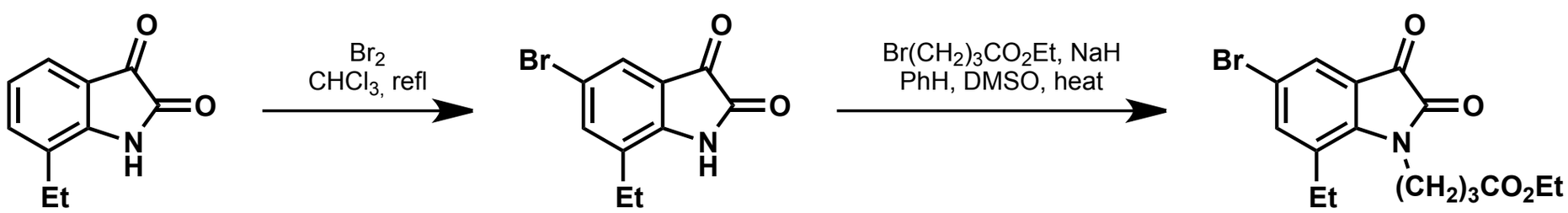


Han, S.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *113*, 10768-10771

Isatin



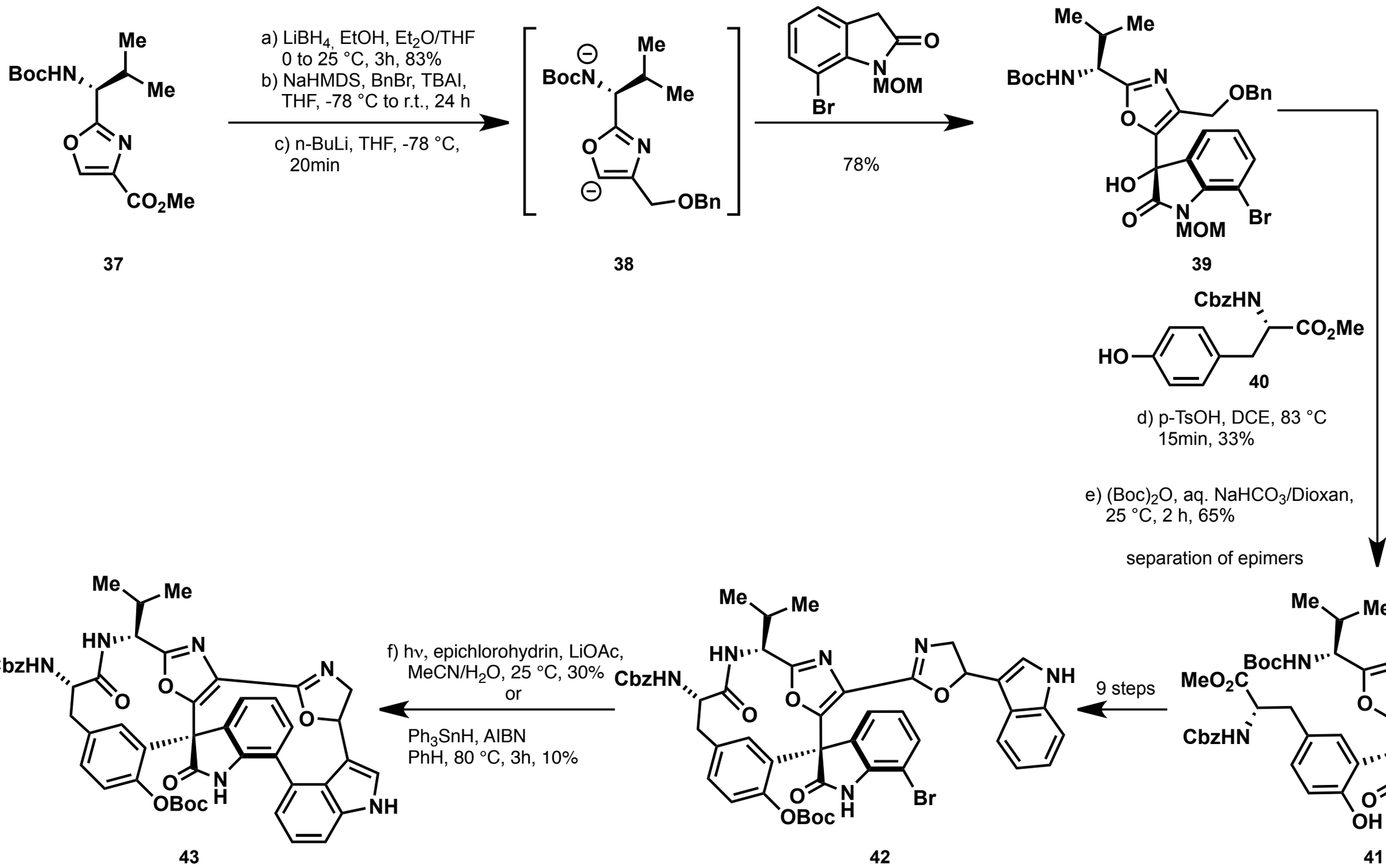
- stable orange compound
- aromatic substitution at C-5, N-Alkylation *via* an anion



- chemoselective derivatisation of C-2 and C-3 carbonyls

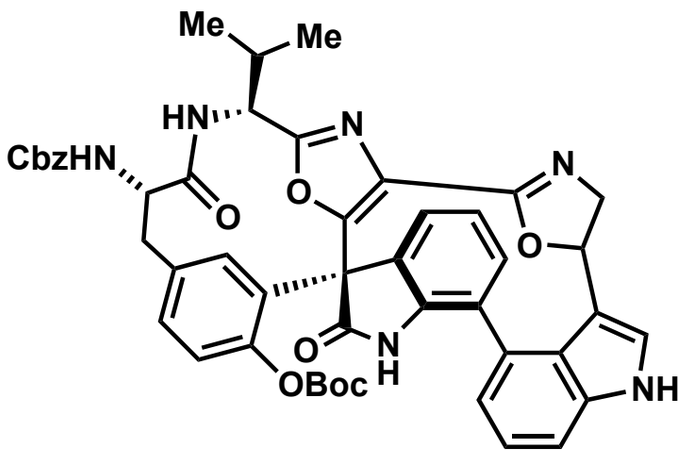
Joule, J.A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley 2010
Sundberg, R.J. *Indoles*, 1st ed.; Elsevier 1995

Total Synthesis of Diazonamide A



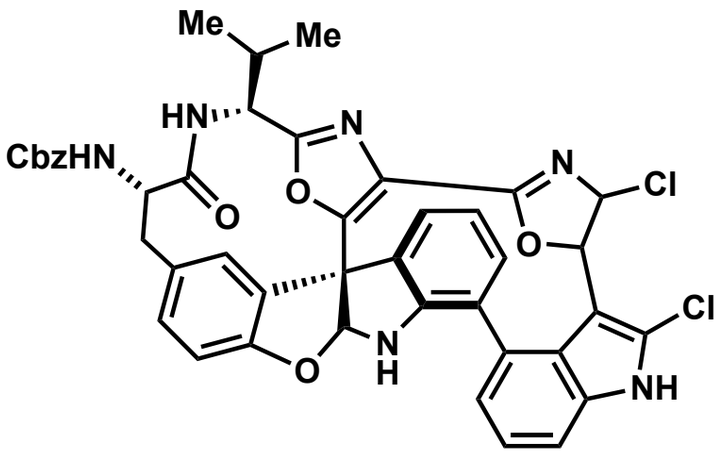
Nicolau, K. N.; Bella, M.; Chen, D.Y.-K.; Huang, X.; Ling, T.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2002**, *41(18)*, 3495-3499

Total Synthesis of Diazonamide A



43

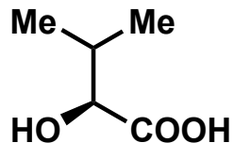
g) NCS, CCl_4/THF, 60 °C, 2 h, 53%
h) TFA, 25 °C, 10 min, 98%
i) DIBAL-H, THF, -78 °C to r.t., 3h, 56%



44

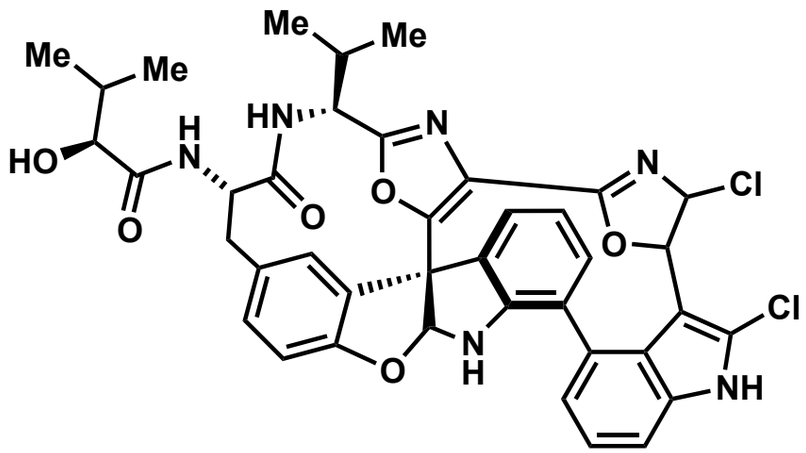
j) H_2, $Pd(OH)_2$/C, EtOH, 25 °C, 2h

k) EDC, HOBt, $NaHCO_3$, DMF, r.t., 12 h



(S)-isovaleric acid

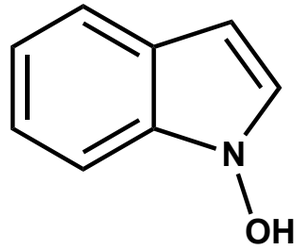
82 %

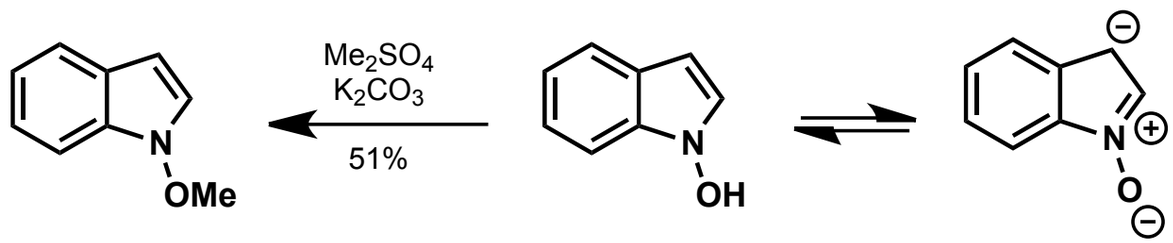


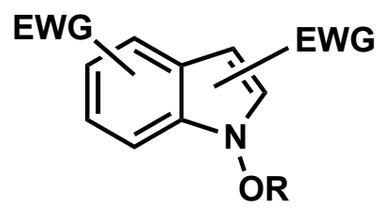
Diazonamide A
45

Nicolau, K. N.; Bella, M.; Chen, D.Y.-K.; Huang, X.; Ling, T.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2002**, *41(18)*, 3495-3499

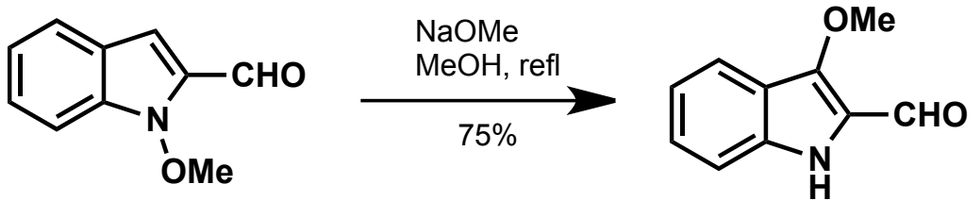
Hydroxyindole

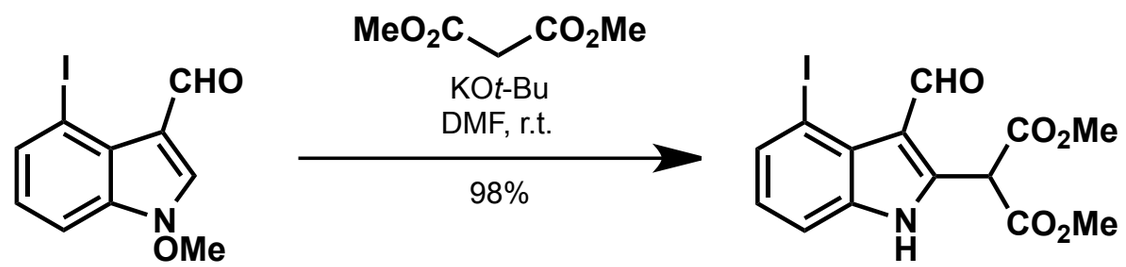




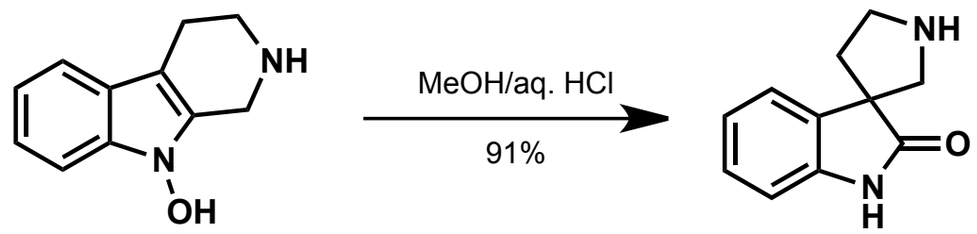


- Hydroxy funtionality is weakly acidic and very nucleophilic
- Selective Lithiation at C-2
- Nucleophilic substitution with departure of 1-substituent





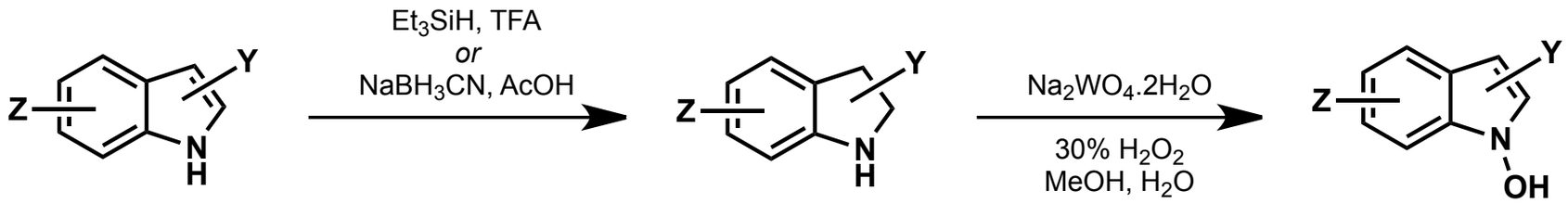
- Rearrangement to Oxindoles



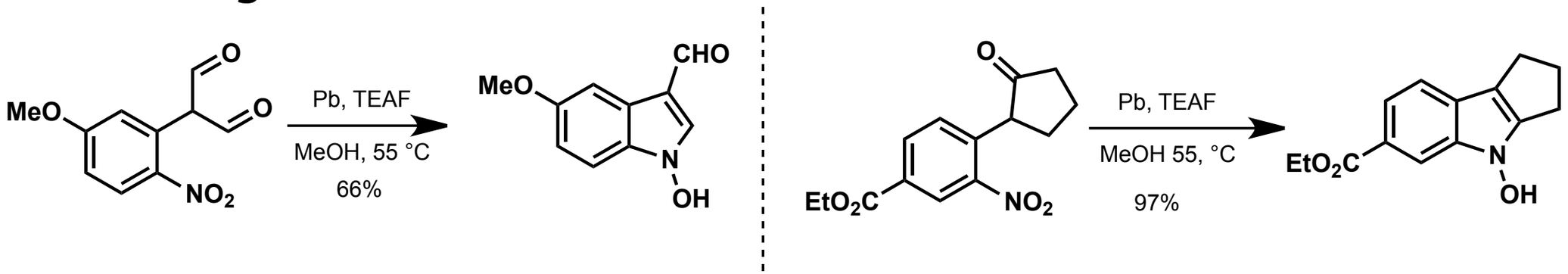
Somei, M. Recent Advances in the Chemistry of 1-Hydroxyindoles, 1-Hydroxytryptophans and 1-Hydroxytryptamines. In *Advances in Heterocyclic Chemistry* Kratitzky, A. R. Elsevier, 2002; Vol. 82, p. 101-155

Synthesis of hydroxyindoles

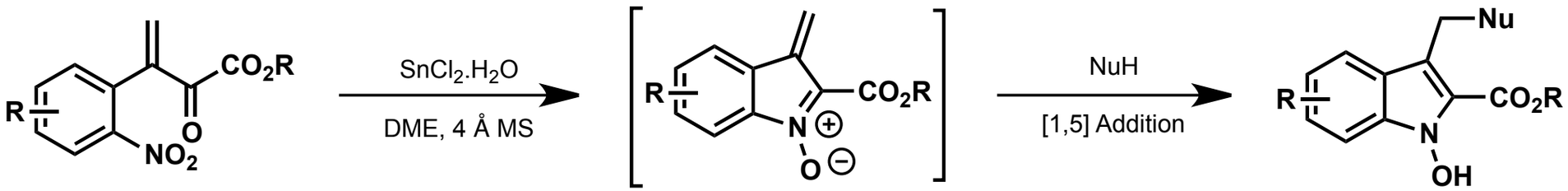
- Somei



- Wong

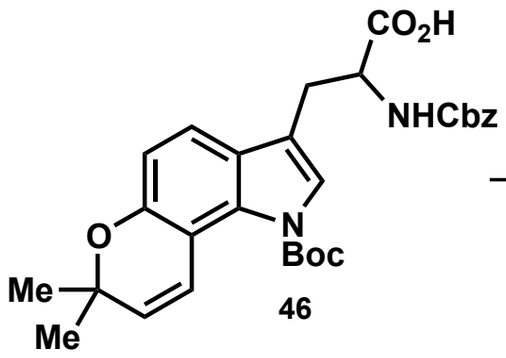


- Nicolaou



Somei, M.; Shoda, T. *Heterocycles*, **1981**, *16*, 1523-1525; Somei, M.; Kawasaki, T. *Heterocycles*, **1989**, 29, 1251-1254
Wong, A.; Kuethe, J.T.; Davies, I.W. *J. Org. Chem.* **2003**, *68*, 9865-9866
Nicolau, K.C.; Lee, S.H.; Estrada, A.A.; Zak, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3736-3740

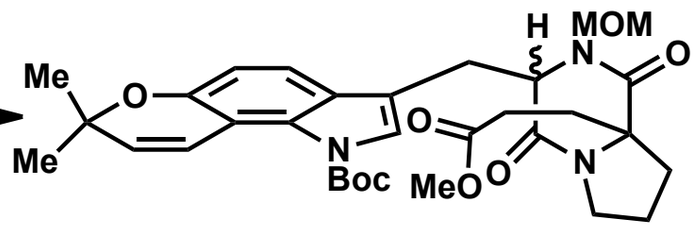
Total Synthesis of Stephacidin B



46

3 steps

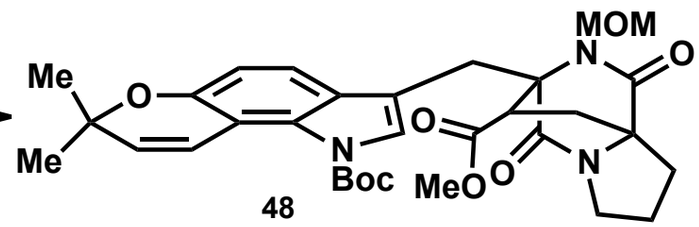
63%



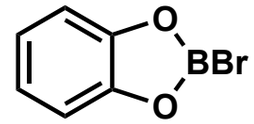
47

a) LDA, THF, -78 °C, 5 min
then $Fe(acac)_2$,
THF, -78 °C to r.t., 1h

61%



48



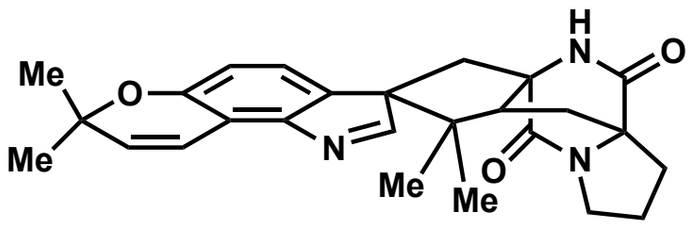
b) CH_2Cl_2, 0 °C, 40min
c) MeMgBr, PhMe, *then* Burgess reagent,
PhH, 50 °C, 30 min

49

d) sufolane, 240°C

50

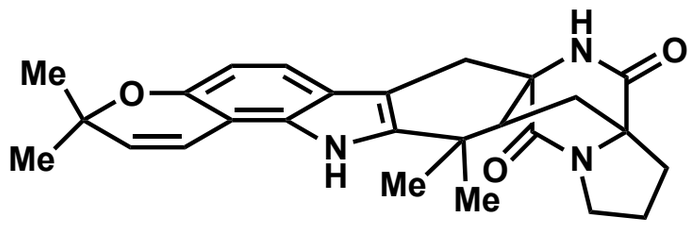
51



52

[1,2] shift

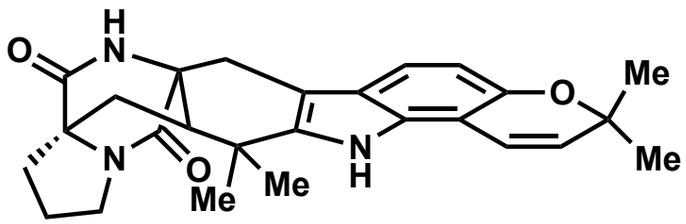
45%



(-)-Stephacidin A
53a

Baran. P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 606-609
Baran. P. S.; Guerrero, C. A.; Hafensteiner, B. D.; Ambhaikar, N. B. *Angew. Chem. Int. Ed.* **2005**, *117*, 3960-3963

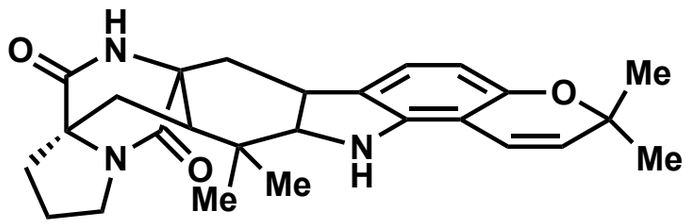
Total Synthesis of Stephacidin B



(+)-Stephacidin A
53b

a) $NaCNBH_4$, AcOH, 24 h

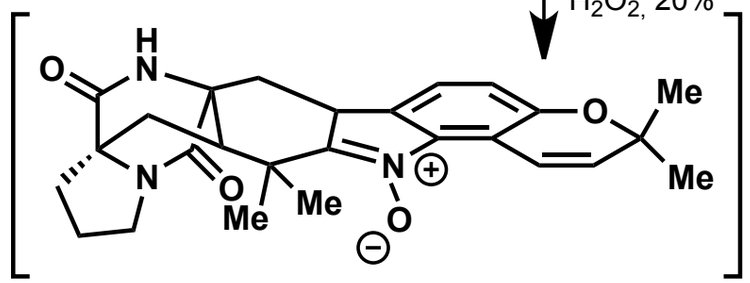
93%



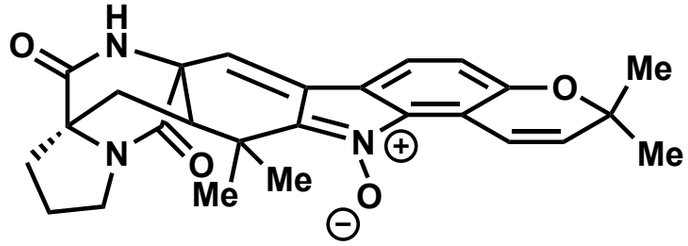
54

b) SeO_2, H_2O_2, dioxane,
25 °C, 40 h
27%, 50% recovered

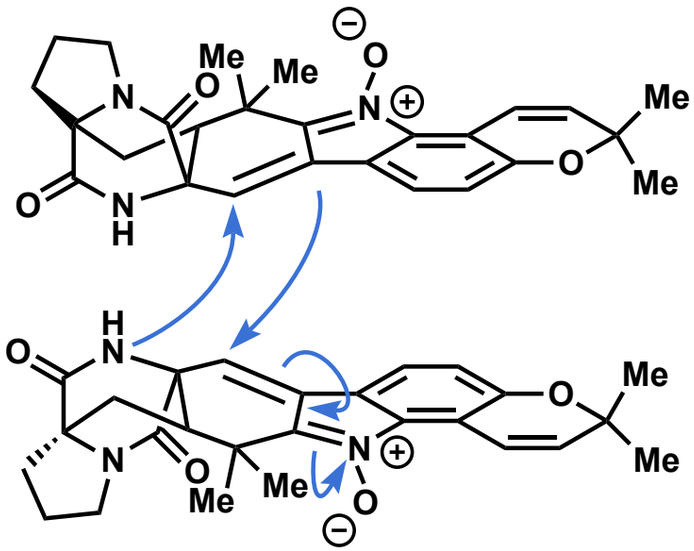
or
$Na_2WO_4.2H_2O$
H_2O_2, 20%



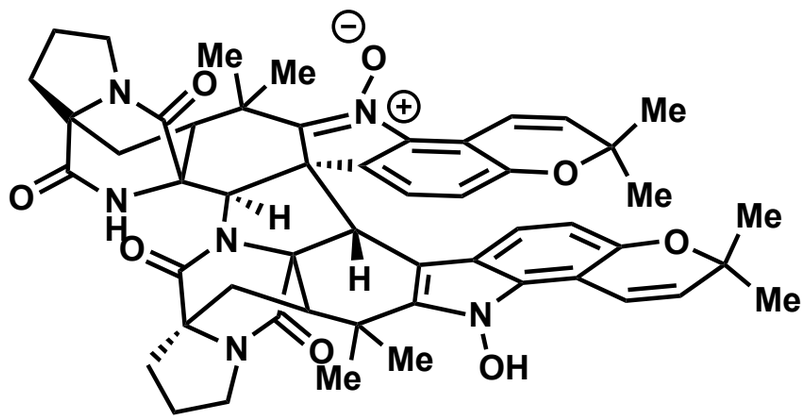
55



(+)-Avrainvillamide
56



c) prep TLC
(SiO_2, EtOAc)
or
Et_3N, MeCN, 25 °C, 1 h
or
DMSO, then conc.



(+)-Stephacidin A
57

Baran. P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 606-609
Baran. P. S.; Guerrero, C. A.; Hafensteiner, B. D.; Ambhaikar, N. B. *Angew. Chem. Int. Ed.* **2005**, *117*, 3960-3963

Thank you for your attention

Questions?