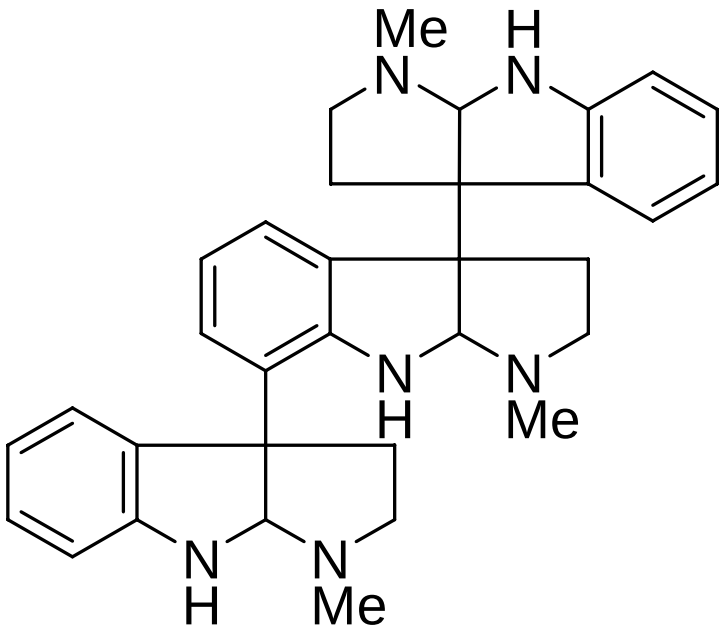
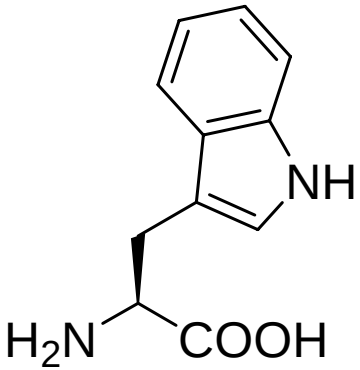
Methodologies for Synthesis of Cyclotryptamine Alkaloids



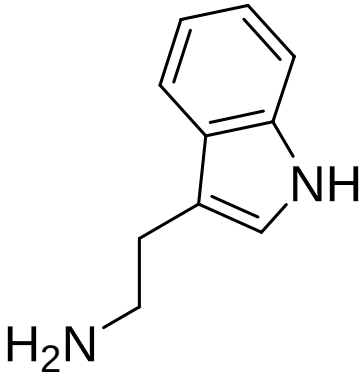
Min Xie

11/20/2007

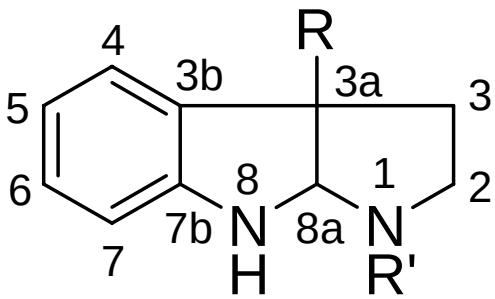
Nomenclature



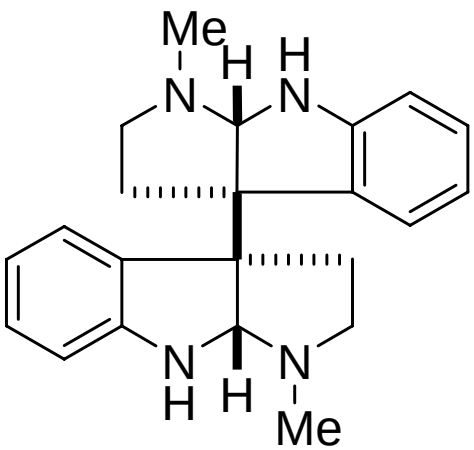
Tryptophan



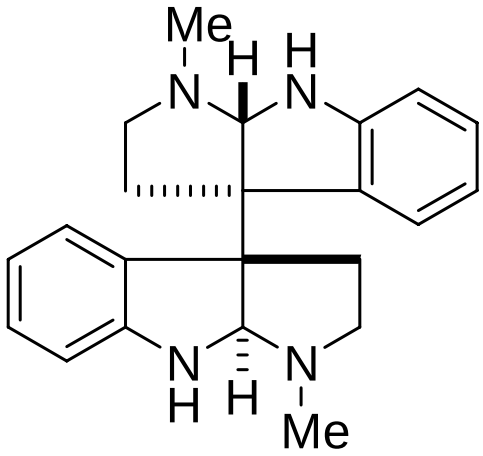
Tryptamine
-**Biosynthetic intermediate**
-**Neurotransmitter**



cyclotryptamine

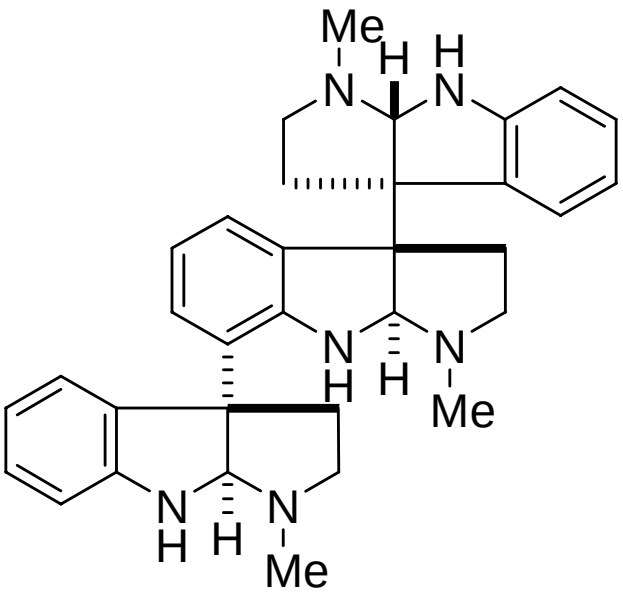


(-)-chimonanthine

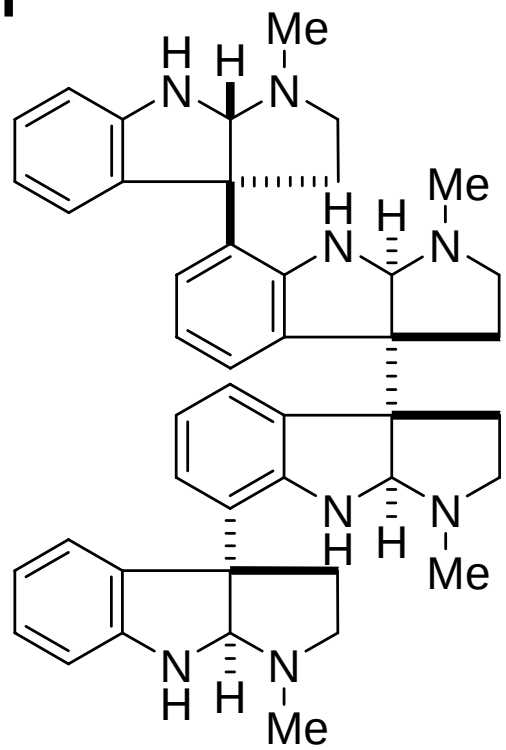


meso-chimonanthine

Higher-order Cyclotryptamine Alkaloids



(-)-hodgkinsine



(-)-quadrigemine C

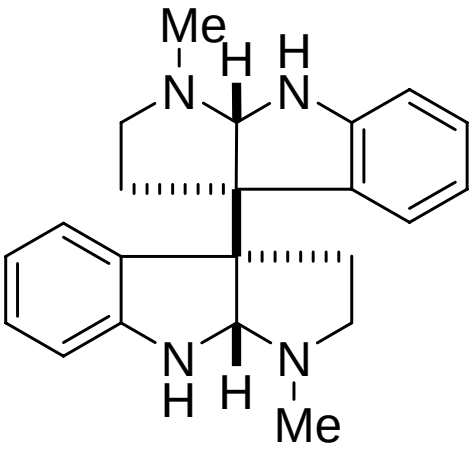
From *Psychotria colorata*
- antibacterial
- analgesic

Non-peptide antagonist of the somatostatin.

Rasolonjanahary, Sevenet, Voegelein, Kordon， *Eur. J. Pharm.* 1995, 285, 19.

Somatostatin: peptide hormone
- regulates the endocrine system
- affects neurotransmission and cell proliferation (wikipedia)

Question



(-)-chimonanthine

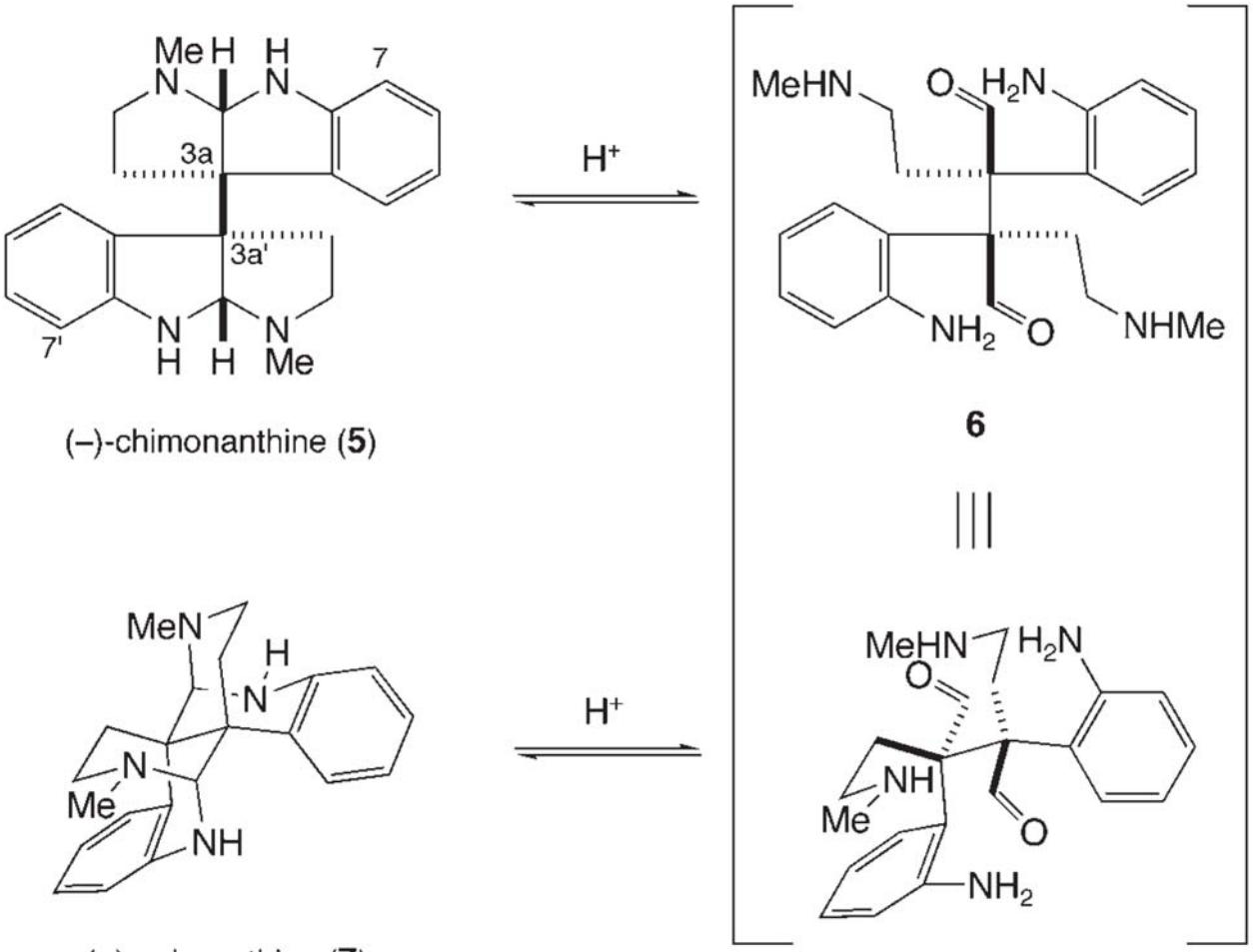
H^+

?

2 H_2O

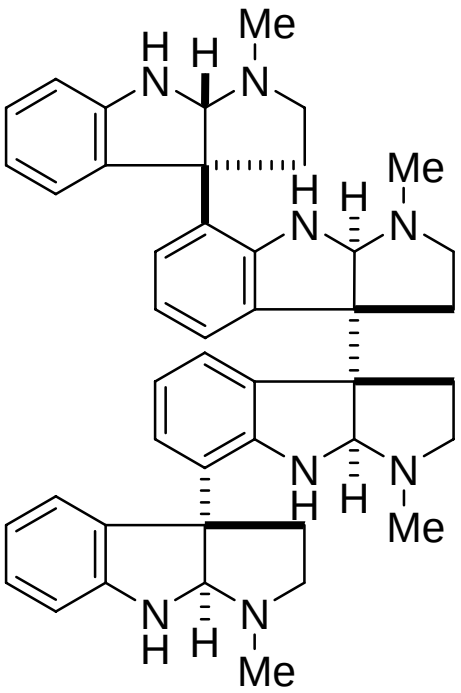
2 H_2O

Isomeric Natural Products



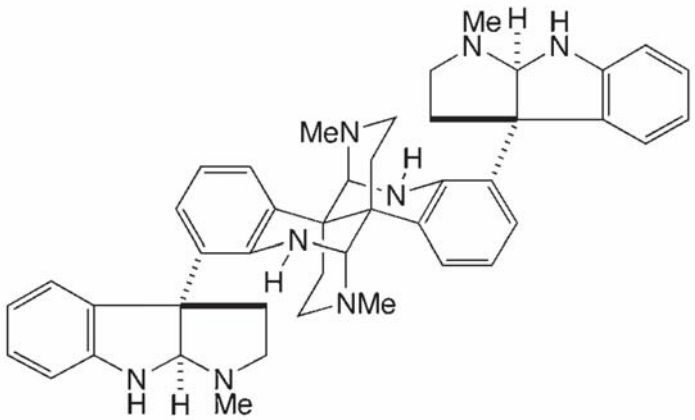
(–)-chimonanthine (**5**)

(+)-calycanthine (**7**)



(-)-quadrigemine C

H^+



psycholeine (**15**)

Structural Features of Cyclotryptamine Alkaloids

- Repeated Pyrollindinoindoline units
- Pyrolidine
  - *Cis* configuration
  - N-methylated
- Vincinal quaternary C centers
- Benzylic-benzylic or C7-benzylic linkage
- Elongated C3a-C3a' σ bond

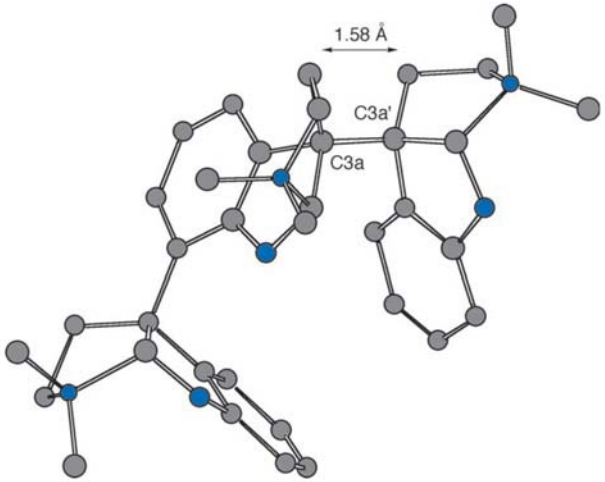
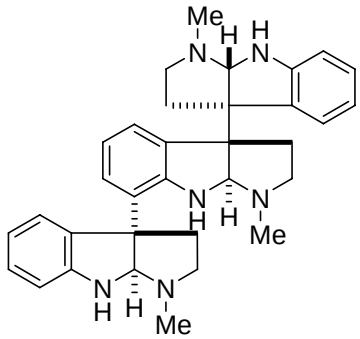


Figure 10. Crystal structure of the trimethiodide derivative of hodgkinsine.[24]

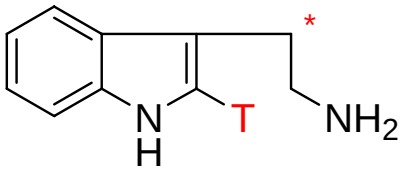


(-)-hodgkinsine

Synthetic challenge:

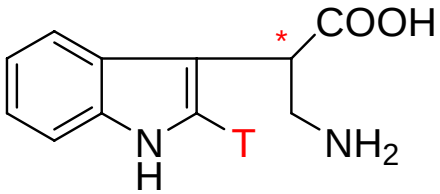
- Stereocontrolled construction of vicinal quarternary carbon centers.
- Construction of diaryl quarternary carbon centers.
- Construction of pyrollindino[2,3-*b*]indoline scaffold.
- Mild conditions to maintain labile C3a-C3a' s bond.

Isotope Labeling Experiment



[β-^{14}C, 2-^{3}H]tryptamine

^{3}H:^{14}C = 4.20

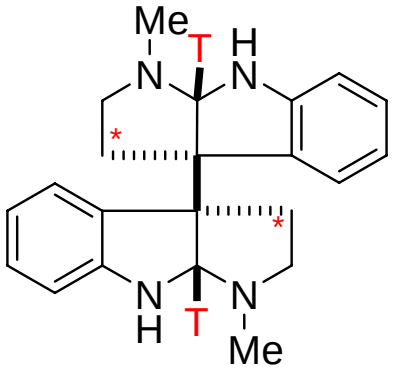


rac

[β-^{14}C, 2-^{3}H]tryptophan

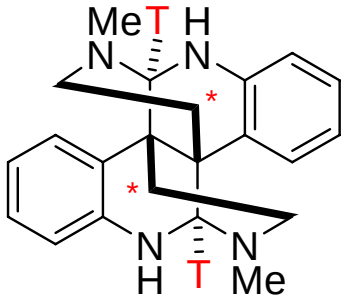
^{3}H:^{14}C = 4.35

Chimonanthus fragrans →



(-)-chimonanthine

↓ AcOH



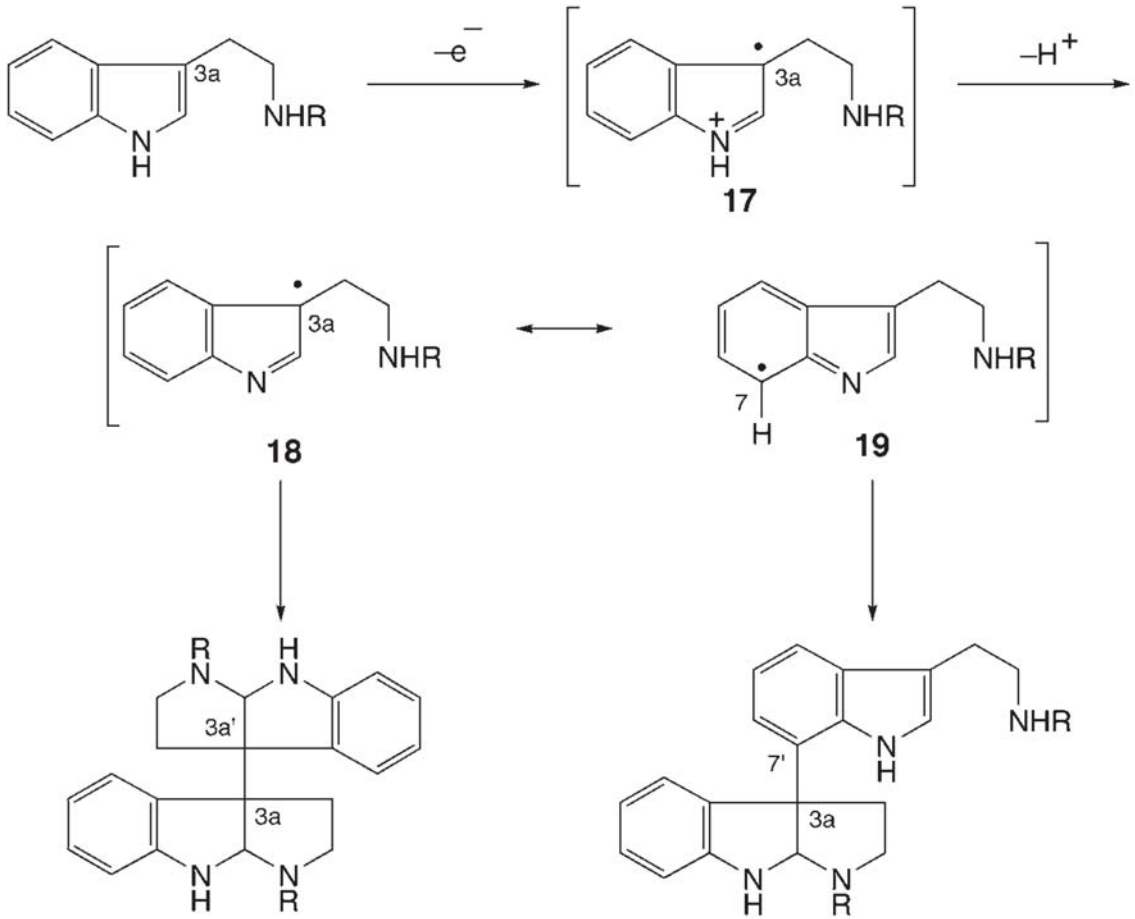
(+)-calycathine

tryptamine incorporation 11.1% ^{3}H:^{14}C = 4.06

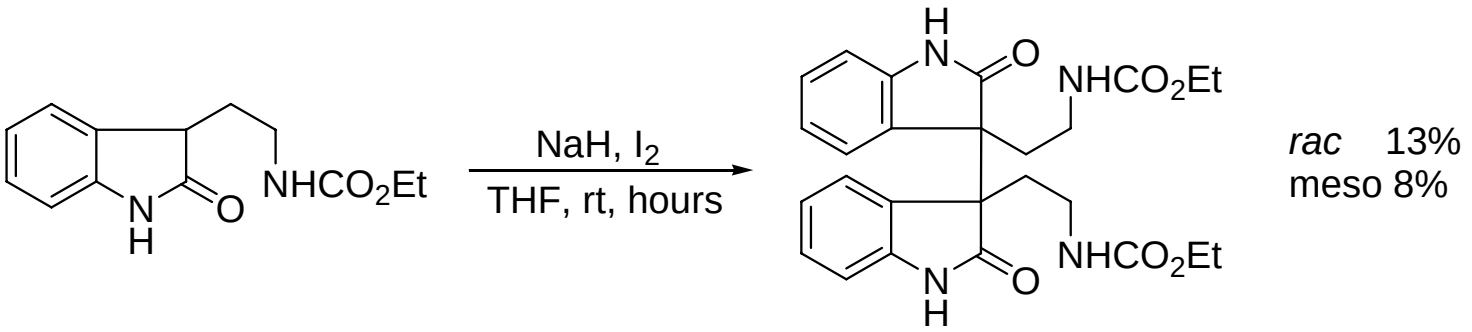
tryptophan incorporation 3.6% ^{3}H:^{14}C = 4.30

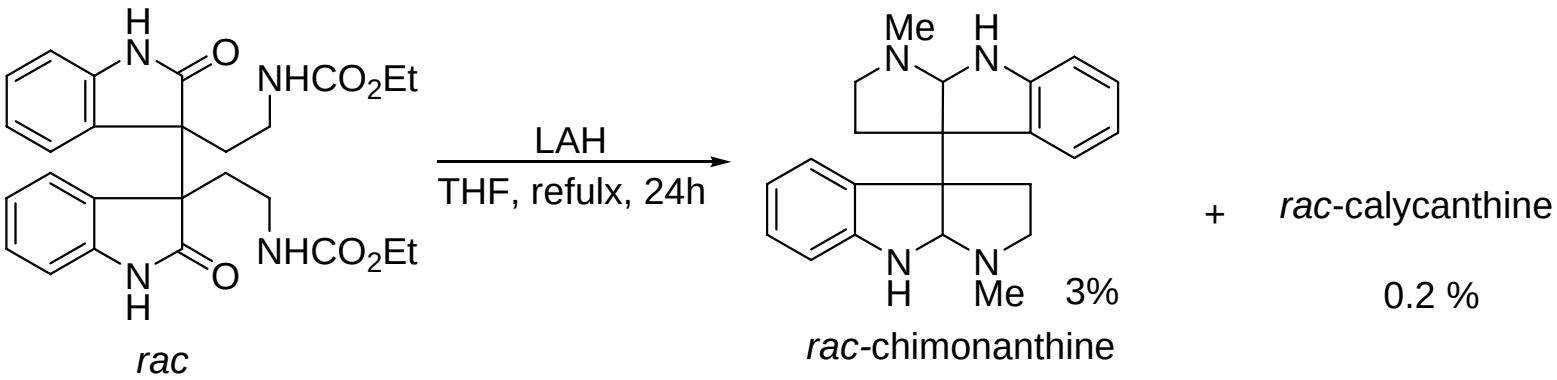
Kirby, Shah, Herbert, *JCS*. 1969, 1916

Proposed Biosynthethic Route



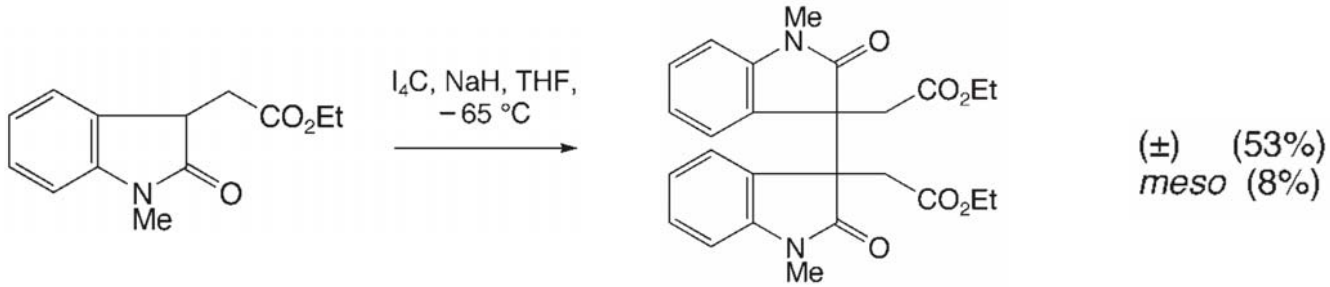
Oxidative Coupling of Oxindoles



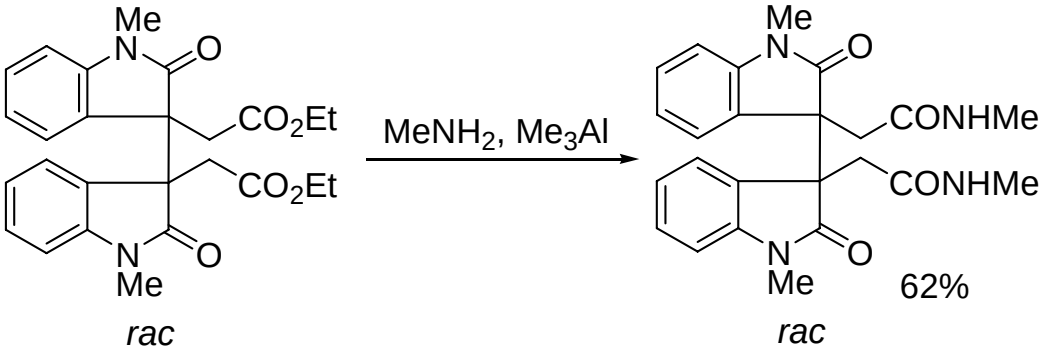


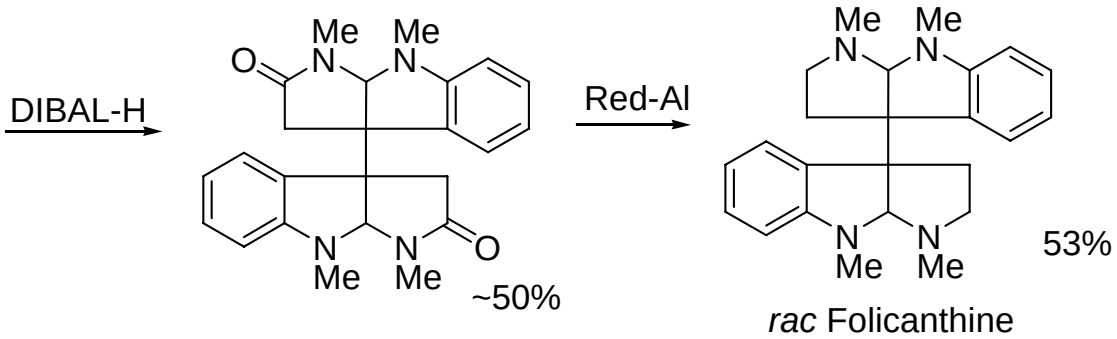
Hendrickson, Goschke, Rees,Tetrahedron 1964, 20, 565

Revised Oxidative Coupling Method



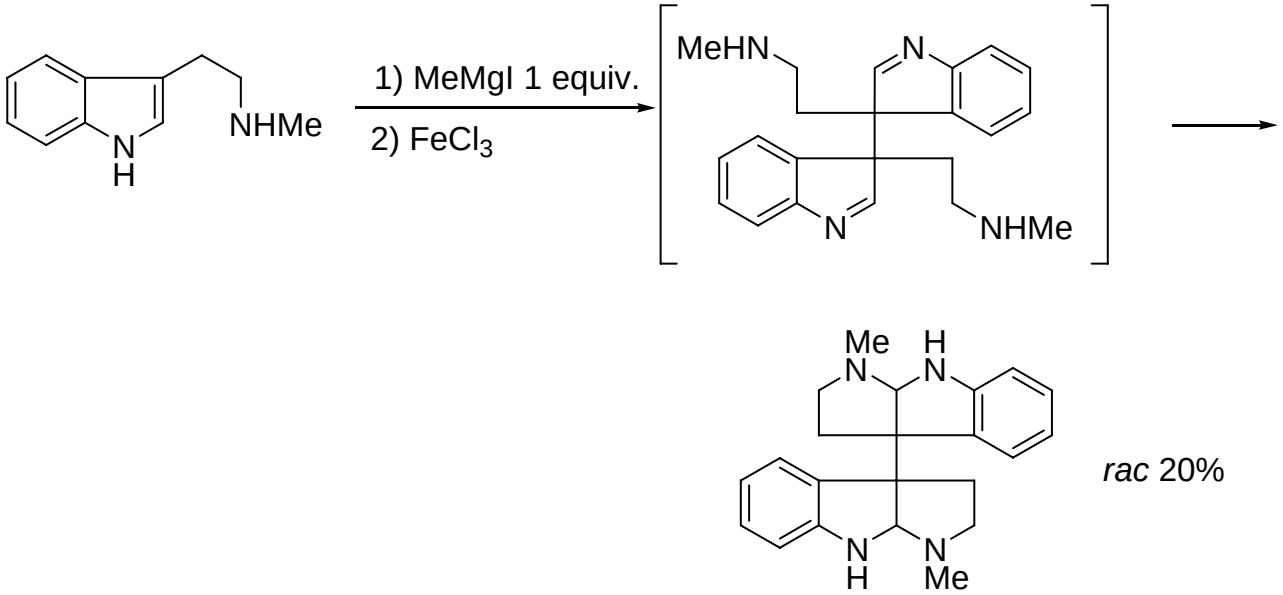
$$R^- + CI_4 \longrightarrow [R^{\bullet}(CI_4^{\bullet -})]$$



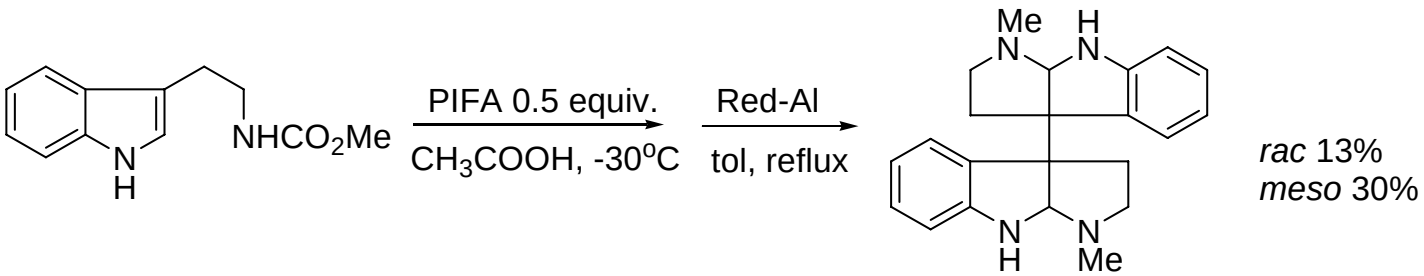


Fang, Horne, Taylor, Rodrigo, JACS. 1994, 116, 9480

Oxidative Coupling of Tryptamines

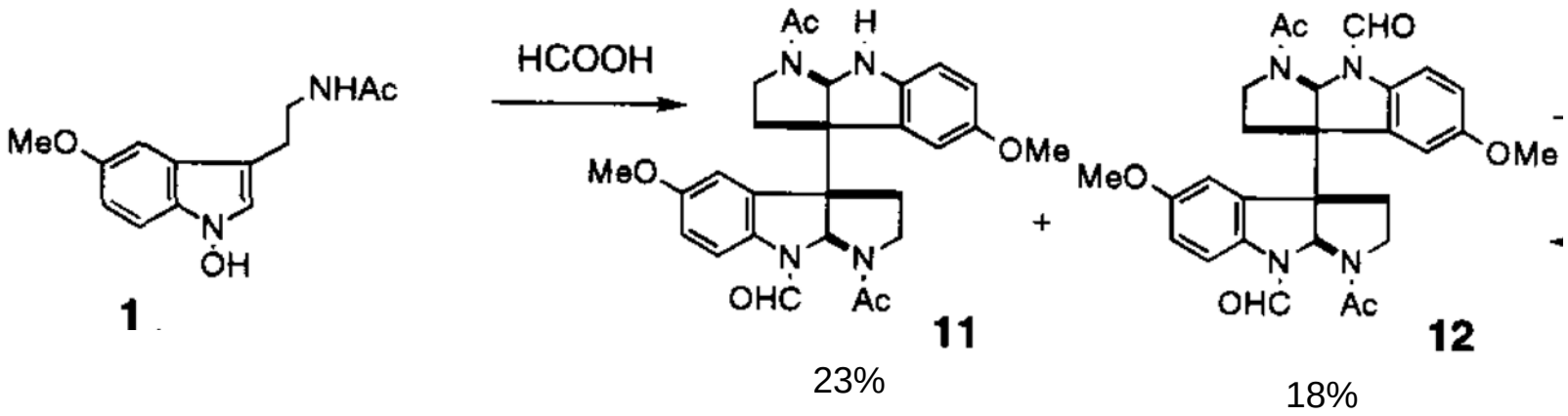


Scott, Hall, McCapra, *JACS*. 1964, 86, 302

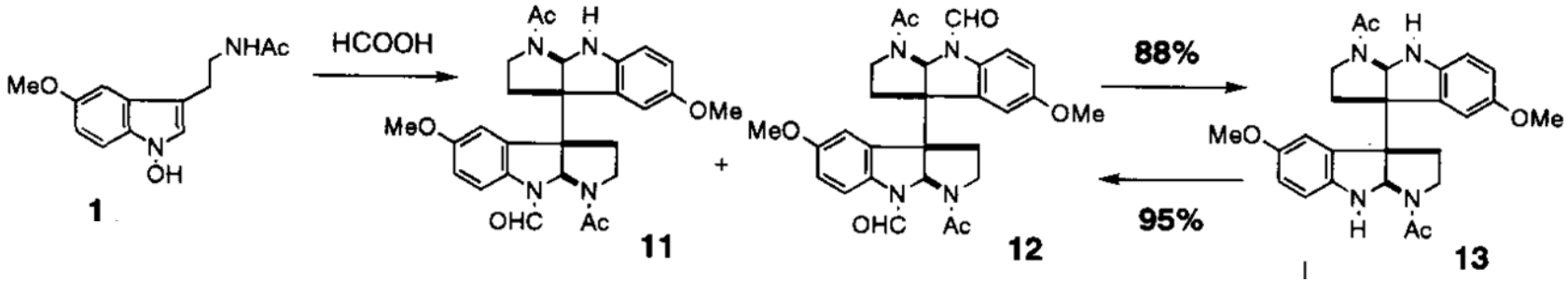


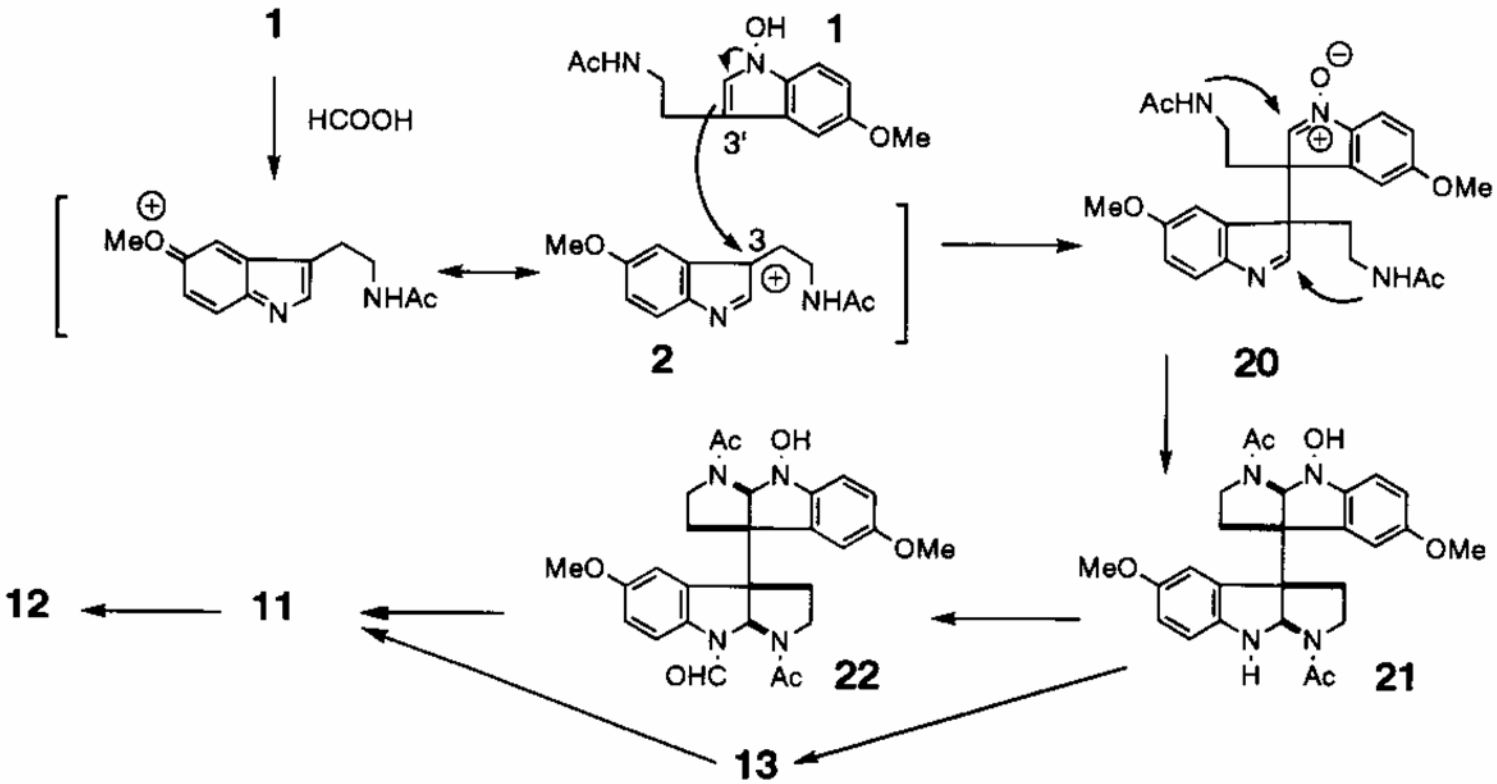
Ishikawa, Takayama, Aimi, TL. 2002, 43, 5637

Cyclization of Hydroxyindole

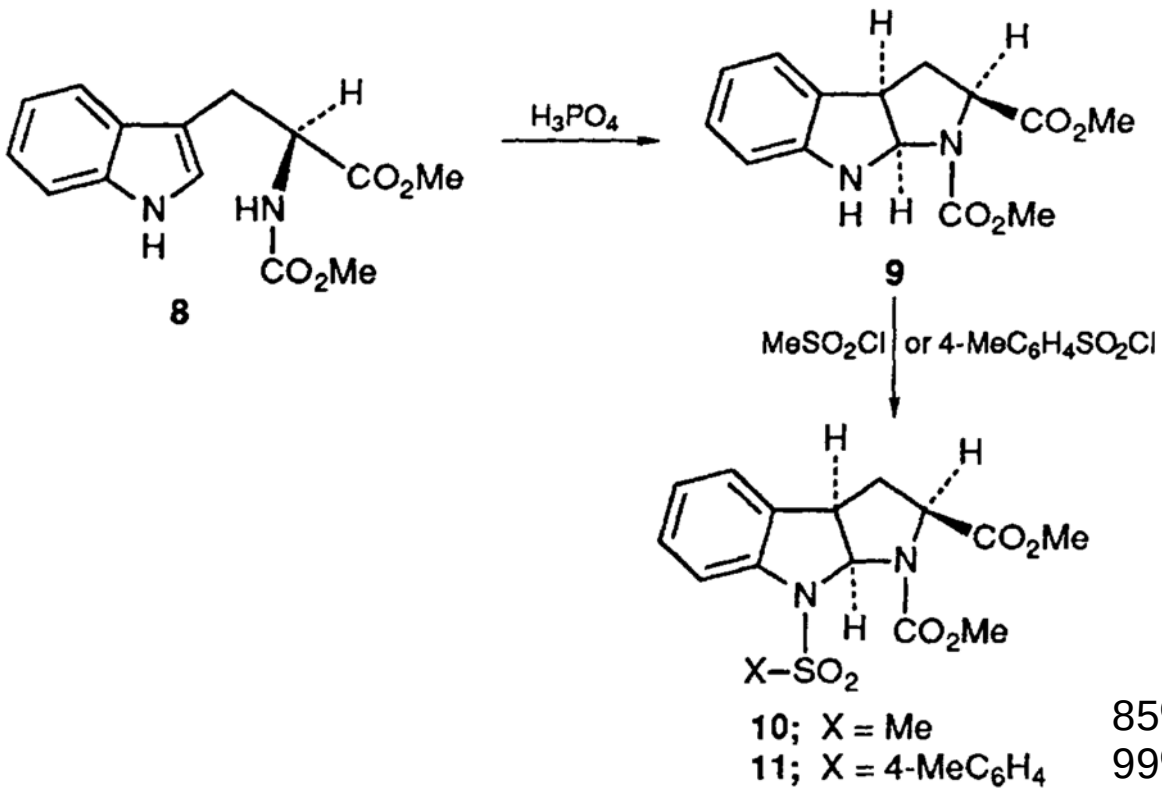


Somei, Oshikiri, Hasegawa, Yamada, *Heterocycles*, 1999, 51, 1237


HCOOH
88%
95%
1
11
12
13


1
HCOOH
2
20
21
22
11
12
13

Trytophan as a Chiral Pool Material

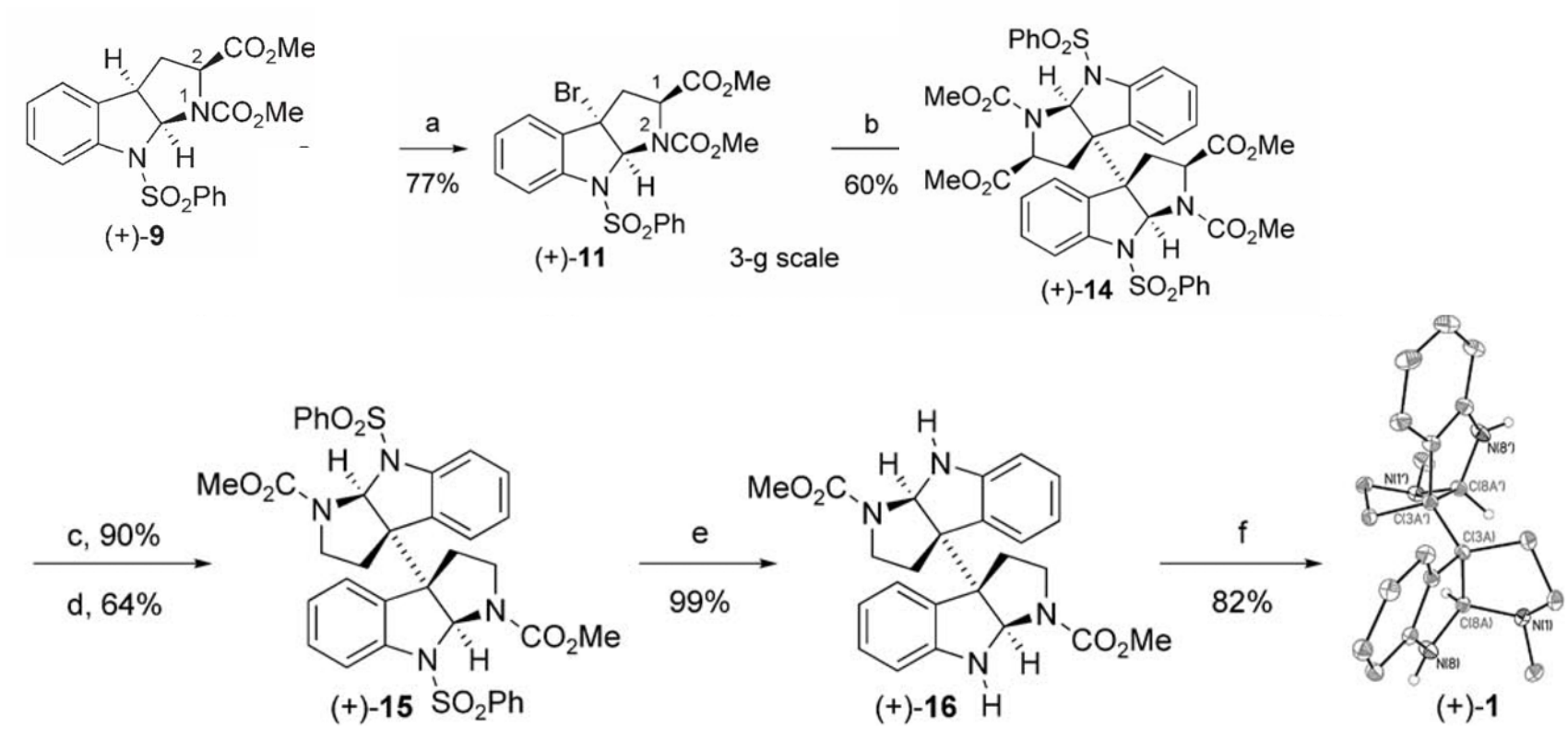


85% yield
99%de
99%ee

Taniguchi, Hino, *Tetrahedron*, 1981,37, 1487.

Crich, Bourne, Davies, Horwell, *J. Chem. Soc., Perkin Trans. 1* 1991, 1693

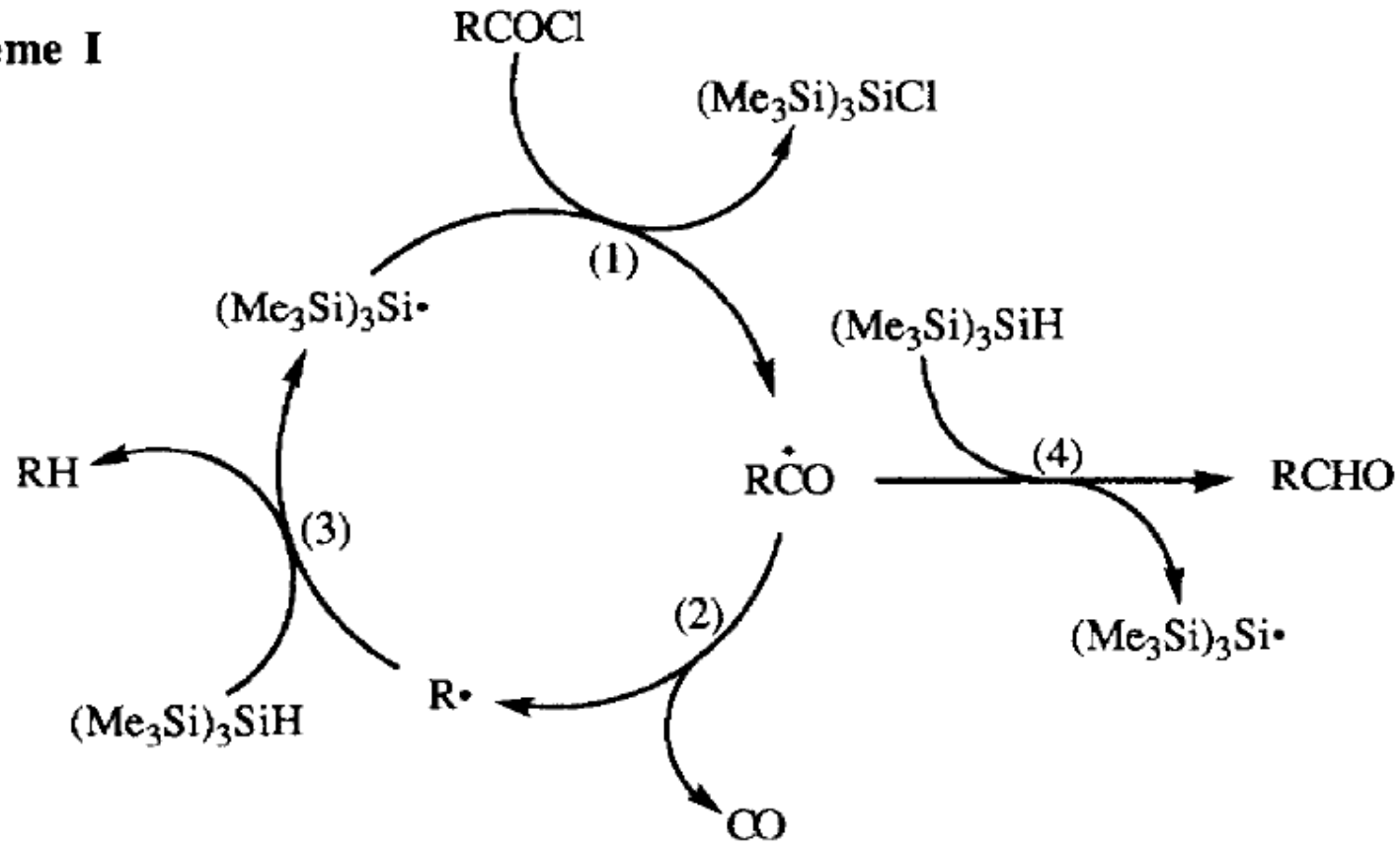
Diastereoselective Reductive Coupling



Scheme 4. Concise total synthesis of (+)-**1**: a) 1,3-dibromo-5,5-dimethylhydantoin, AIBN, CCl_4, 80 °C, 1 h, 77 %. b) $[CoCl(PPh_3)_3]$, acetone, 23 °C, 15 min, 60 %. c) aq KOH/MeOH, 23 °C, 30 min, 90 %. d) oxalyl chloride, DMF, CH_2Cl_2, 23 °C, 1.5 h; $(Me_3Si)_3SiH$, AIBN, toluene, 80 °C, 3.5 h, 64 %. e) Na(Hg), Na_2HPO_4, MeOH, 23 °C, 3.5 h, 99 %. f) Sodium bis(2-methoxyethoxy)aluminum hydride, toluene, 110 °C, 1.5 h, 82 %.

Movassaghi, Schmidt, ACIE. 2007, 46, 3725

Scheme I



Ballestri, ChatgiliaJoglu, *TL*. 1992, 33, 1787

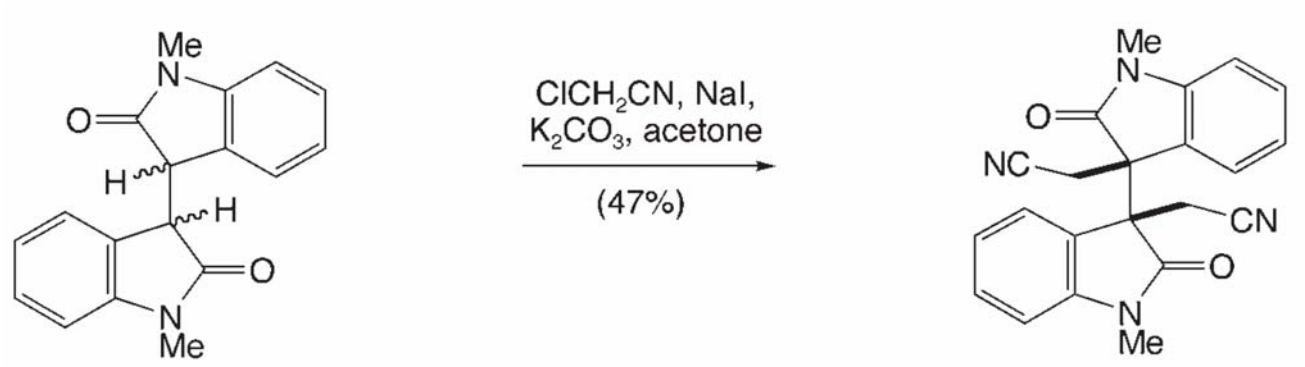
Summary on Homocoupling Approach

- Oxidative coupling
  - Biomemic.
  - Low efficiency.
  - Lack of stereocontrol.

Reductive coupling
  - High stereocontrol.
    - Chiral pool material
    - cis configuration of pyrolidinoindoline

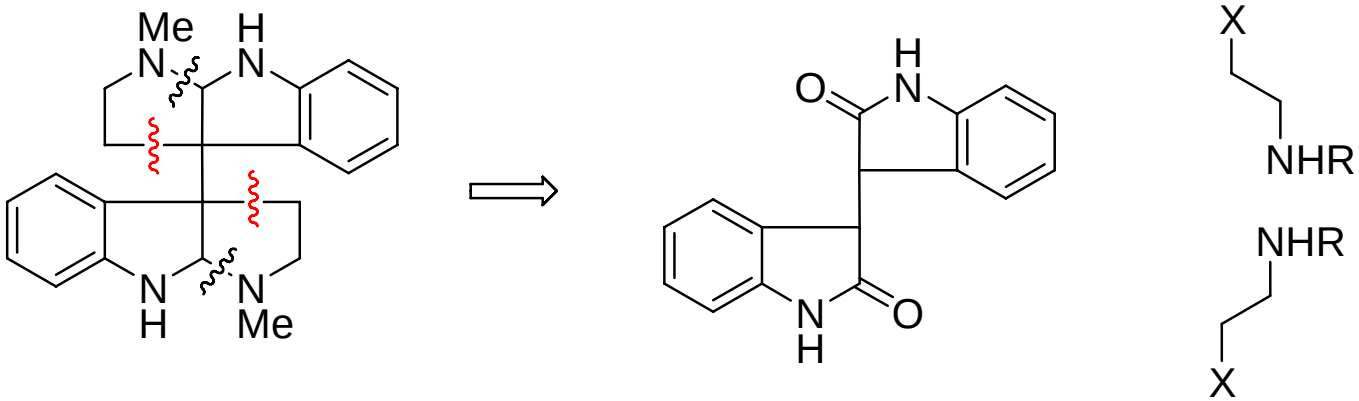
Limited to alkaloids containing 2 pyrolidinoindoline units

Dialkylation as a Potential Stereocontrolled Approach

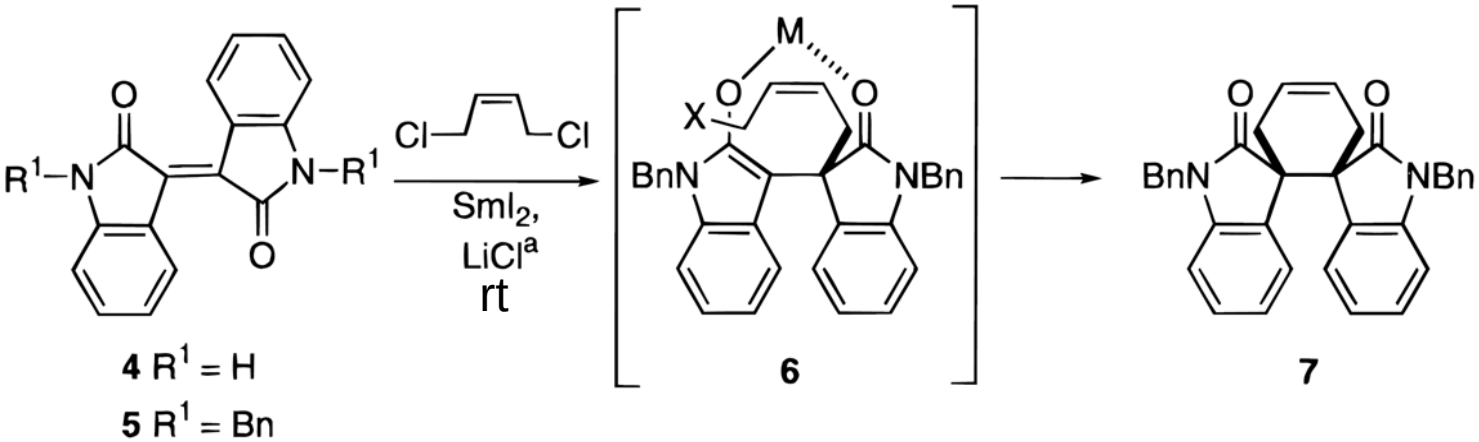


(±)-diastereomer only

T. Hino, *Chem. Pharm. Bull*. 1961, 9, 979



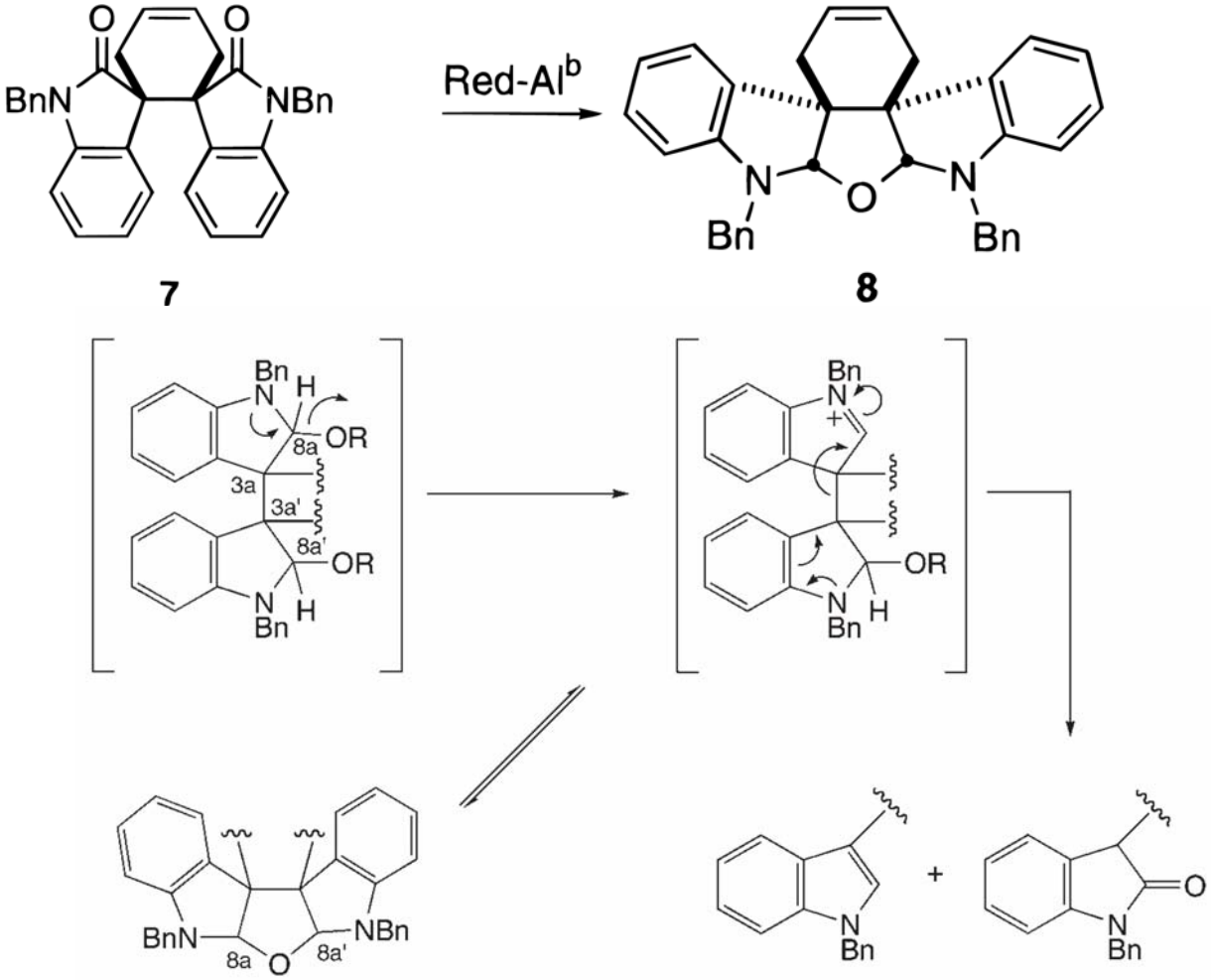
Stereocontrolled Reductive Dialkylation



82%

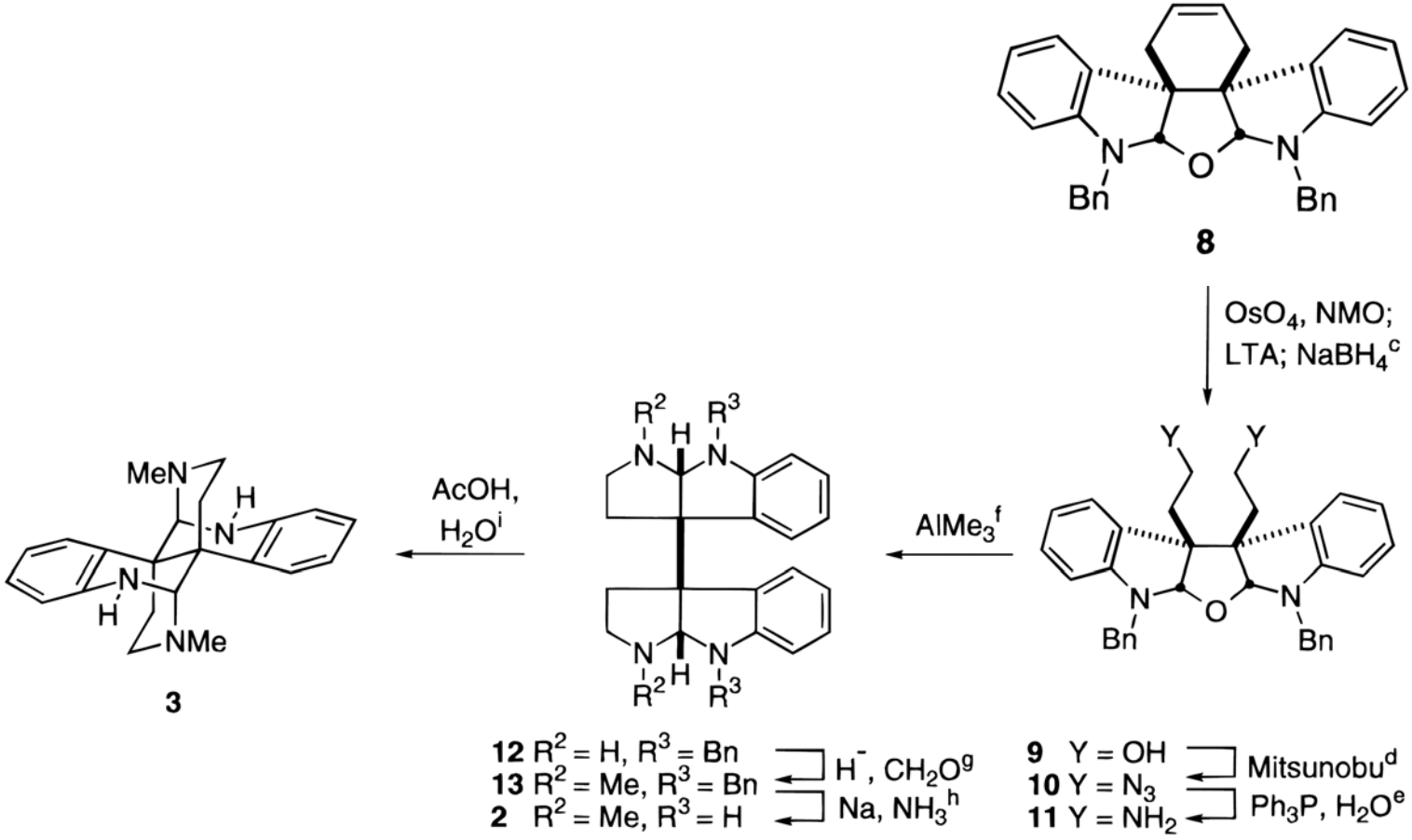
Link, Overman, JACS.1996, 118, 8166

Synthesis of meso-Chimonathine and Calycathine



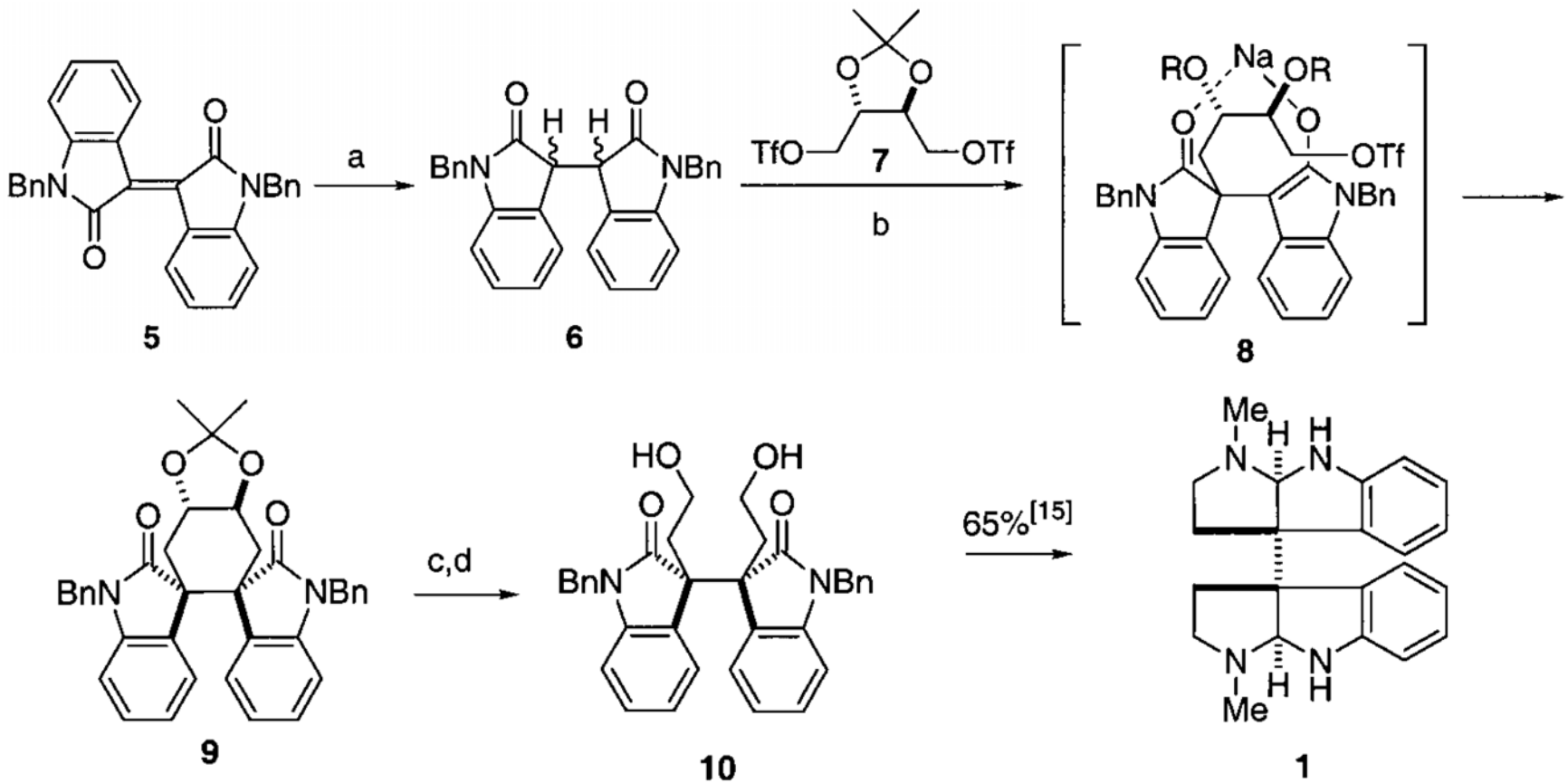
Link, Overman, *JACS*.1996, 118, 8166

Elaboration into meso-Chimonathine and Calycathine



[a] Key: (a) SmI_2, LiCl, THF, rt; *cis*-1,4-dichloro-2-butene, rt, 82%; (b) RedAl, PhH, rt→reflux, 78%; (c) OsO_4, NMO, acetone, H_2O, 96%; $Pb(OAc)_4$, EtOH, PhH, 0 °C; $NaBH_4$, 94%; (d) HN_3, Ph_3P, MeO_2CNNCO_2Me, THF, 0 °C, 87%; (e) Ph_3P, H_2O, THF; (f) Me_3Al, PhH, 68%; (g) CH_2O, $NaCNBH_3$, MeCN, H_2O, 87%; (h) Na, NH_3, THF, −78 °C, 92%; (i) AcOH, H_2O, 100 °C, 25%.

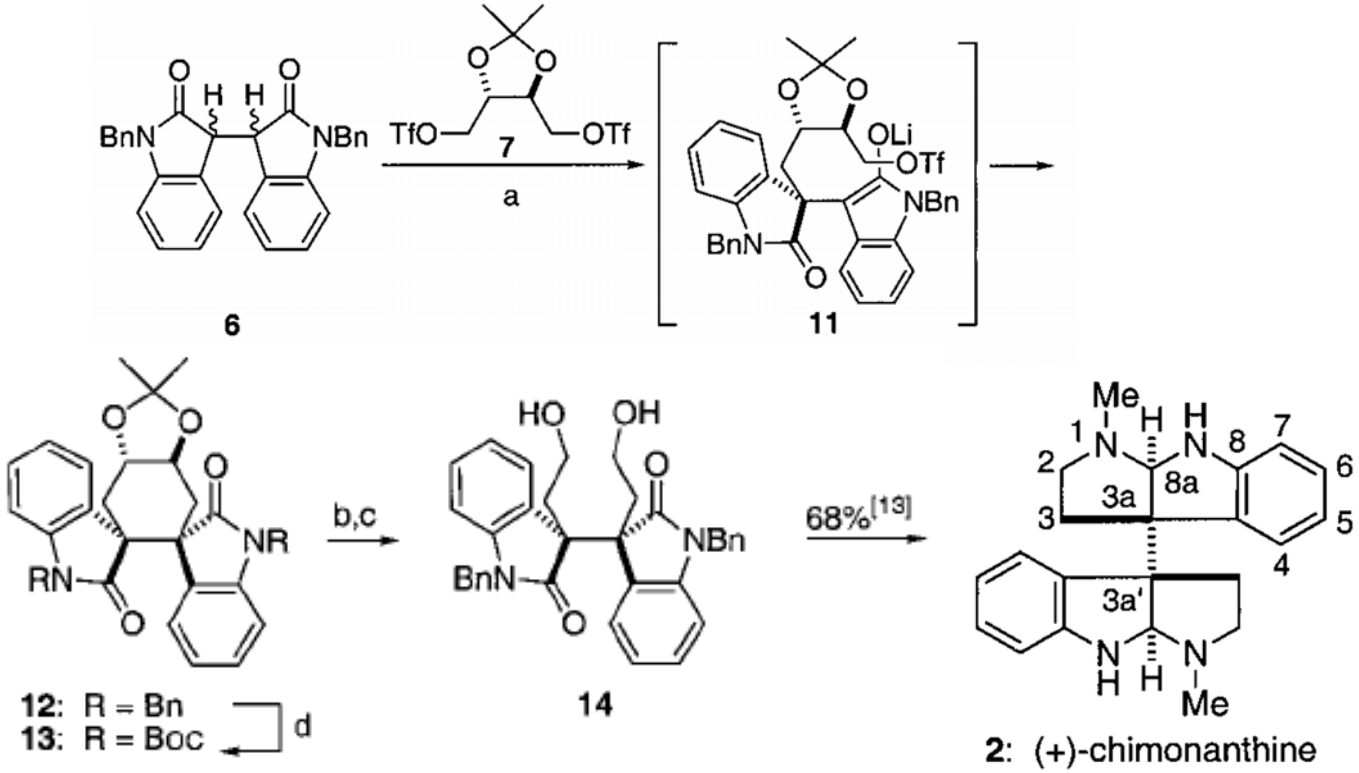
Dialkylation via Enolates



Scheme 1. a) Zn, AcOH, room temperature, 83 %; b) NaHMDS (2.1 equiv), THF, −78 °C, 92 %; c) CSA, MeOH/CH_2Cl_2, 100 %; d) $Pb(OAc)_4$, PhH; $NaBH_4$, MeOH, 92 %. Bn = benzyl, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, OTf = trifluoromethansulfonate (triflate),

Overman, Larrow, Stearns, Vance, ACIE. 2000, 39, 213

Chiral Non-racemic Cyclotryptamine via Dialkylation

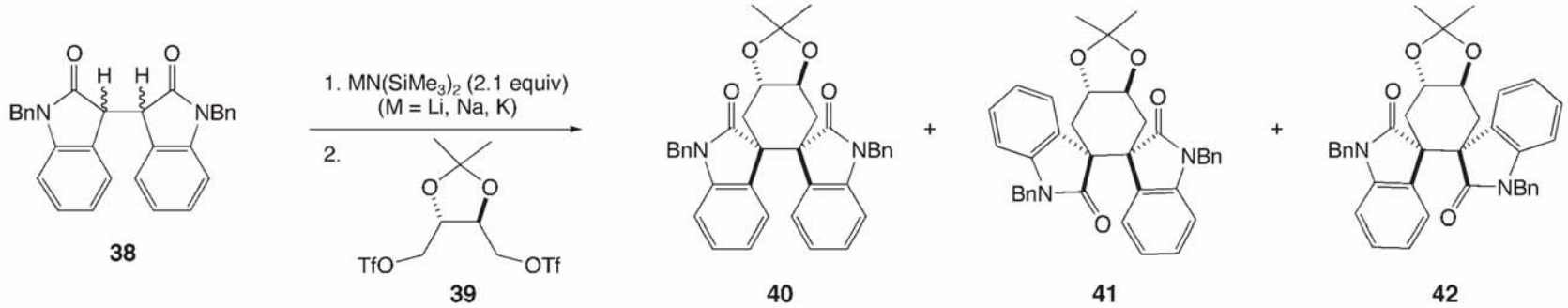


Scheme 2. a) LiHMDS (2.1 equiv), THF/DMPU, −78 °C, 55 %; b) CSA, MeOH/CH_2Cl_2, 100 %; c) $Pb(OAc)_4$, PhH; $NaBH_4$, MeOH, 90 %; d) *t*Bu-Li, Et_2O, −78 °C then O_2; Boc_2O, DMAP, CH_2Cl_2, 61 %. Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, DMPU = 1,3-dimethylhexahydro-2-pyrimidinone.

Overman, Larrow, Stearns, Vance, ACIE. 2000, 39, 213

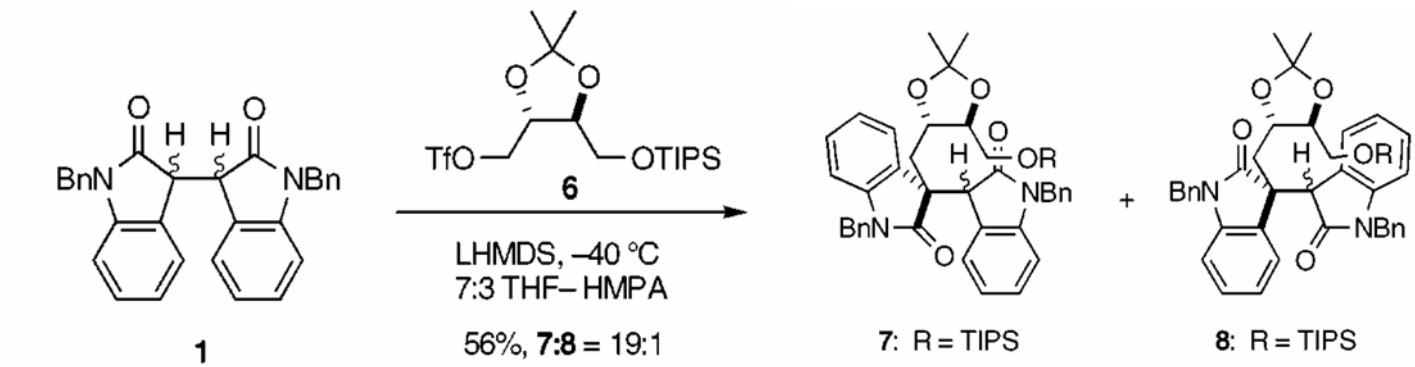
Strong counterion and solvent effects on the stereoselectivity.

Mechanistic Investigation



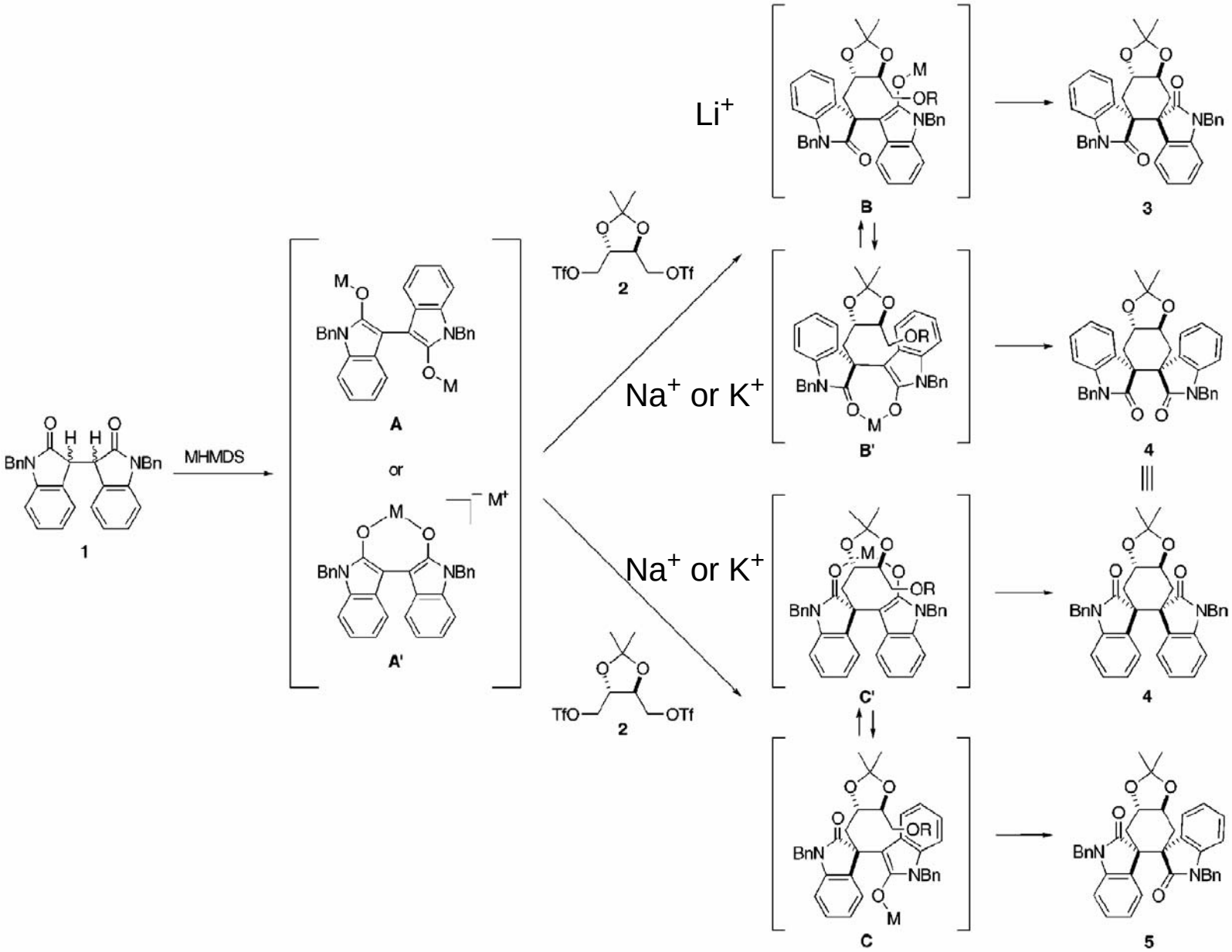
$NaN(SiMe_3)_2$, THF, –78 °C	92%	trace	trace
$LiN(SiMe_3)_2$, THF/DMPU, –78 °C	20%	55%	trace

- Dienolates are formed prior to monoalkylation. → Responsible for stereochemical outcome.
- Na+ or K+ enolates →*meso* major product → Decreased by crown ether additive.
- Li+ enolates → C2 major product → Increased by DMPU or HMPA.
- The monoakylation of Li+ dienolate is highly diastereoselective.

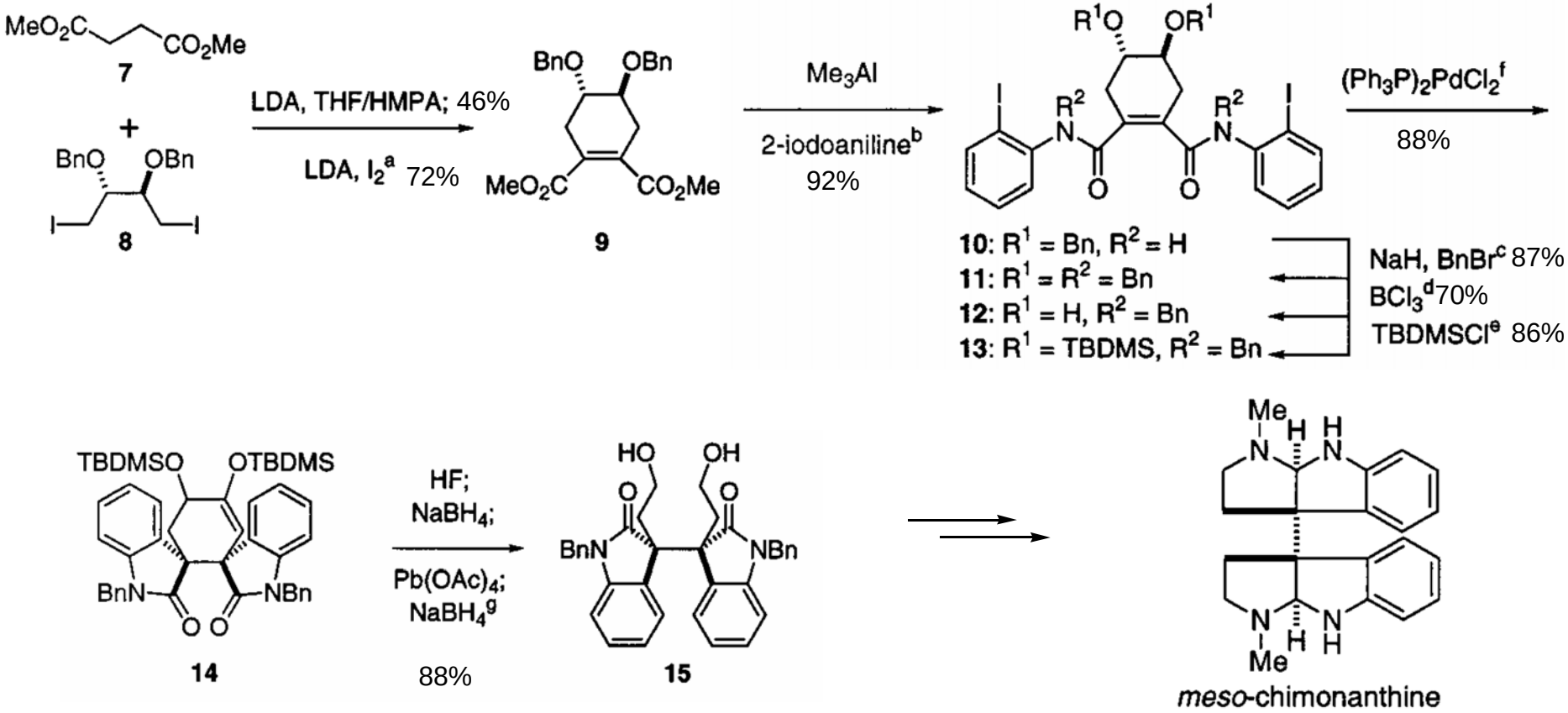


Model for Product Distribution

Scheme 1. Stereoselective Dialkylation Reactions

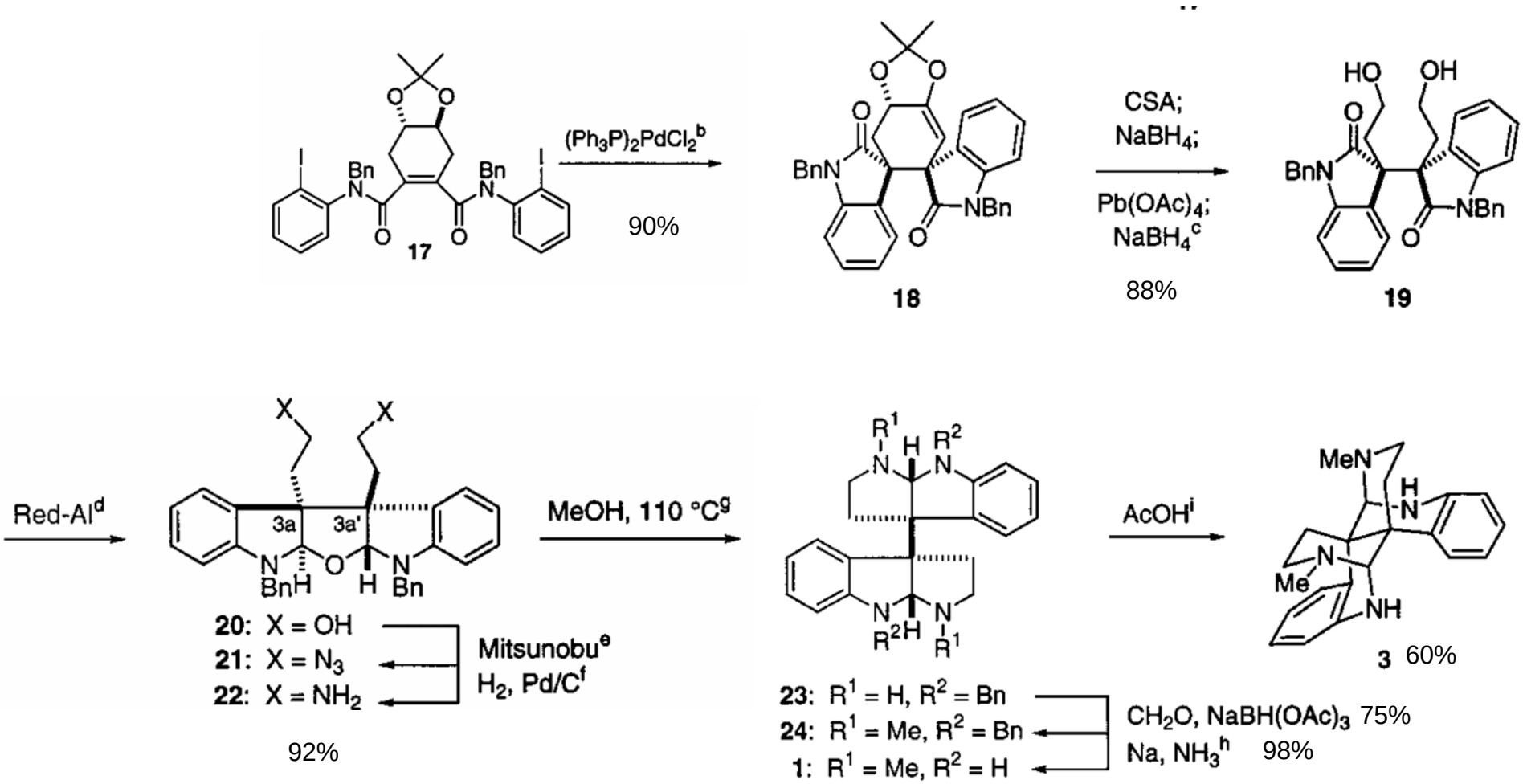


meso-Chinonanthine via Cascade Heck Cyclization



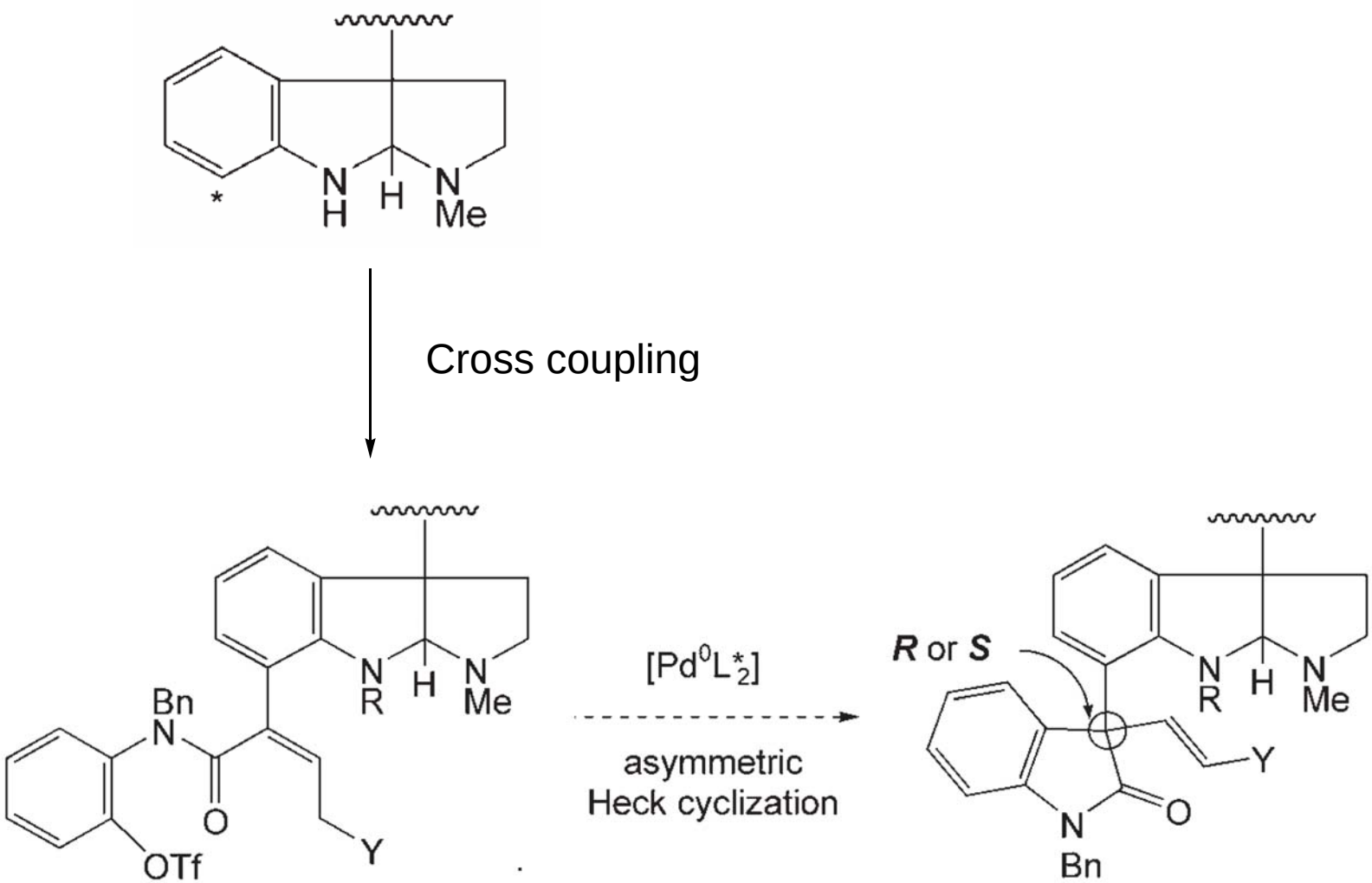
Overman, Paone, Stearns, JACS, 1999, 121, 7702

(-)-Chinonanthine via Cascade Heck Cyclization

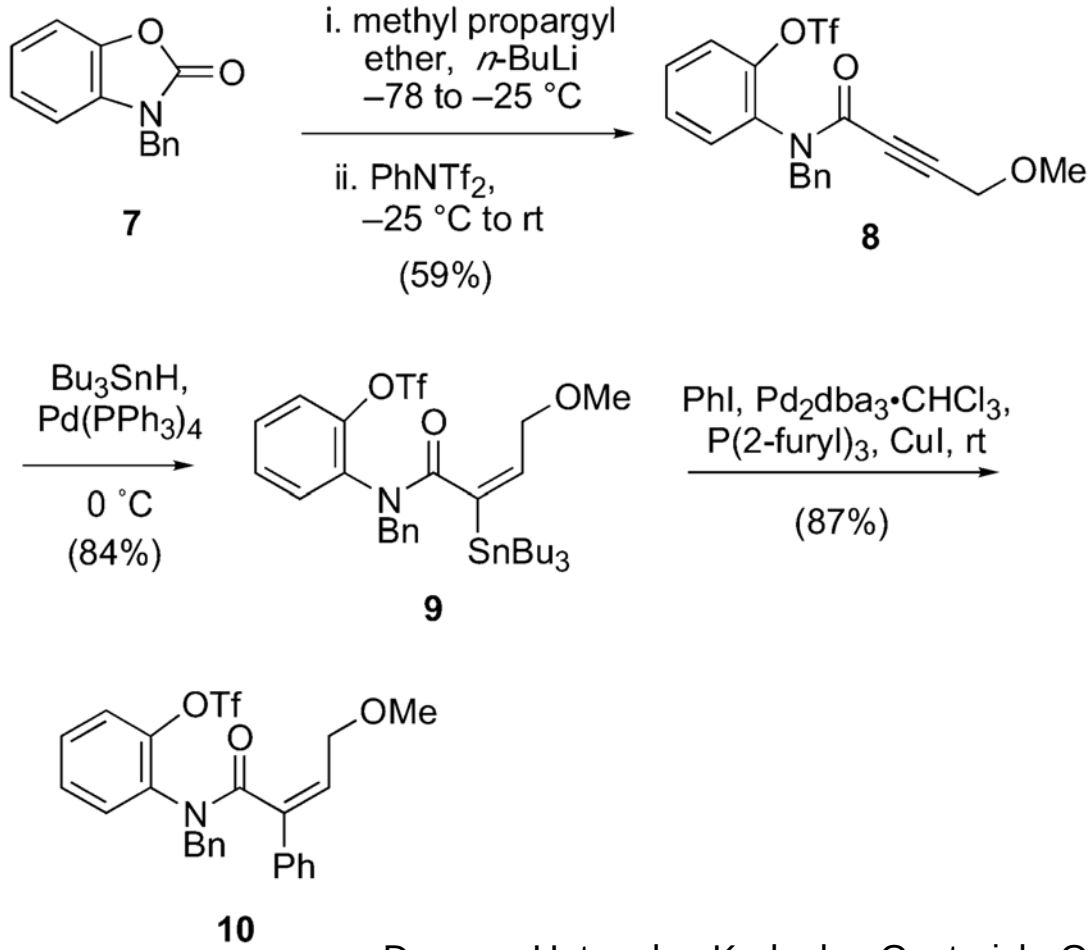


Overman, Paone, Stearns, JACS, 1999, 121, 7702

Diaryl Quarternary Centers via Asymmetric Heck Cyclization

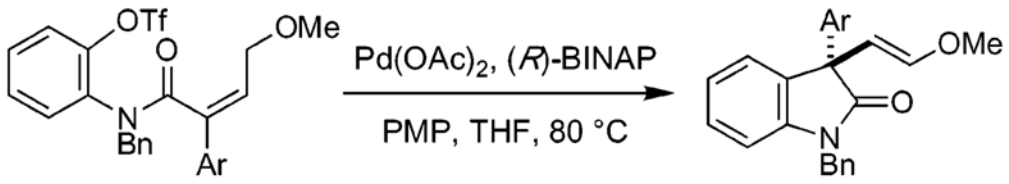


Preparation of Substrate via Stille Coupling

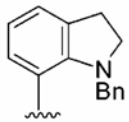
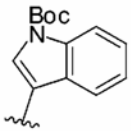


Dounay, Hatanaka, Kodanko, Oestreich, Overman, Pfeifer, Weiss, JACS. 2003, 125, 6261

Enantioselective Heck Cyclization

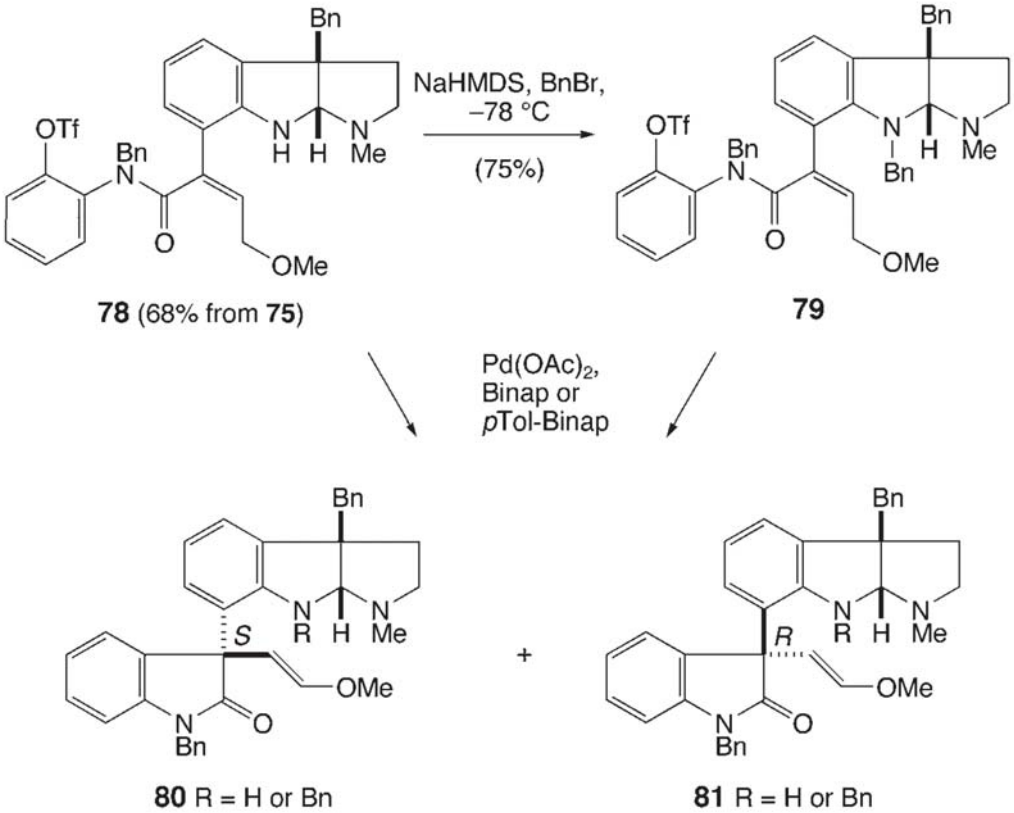


10, 11a–j **12, 18a–j**

entry	Ar	$Pd(OAc)_2$, mol %	(*R*)-BINAP, mol %	[substrate], M	time, h	product	yield, %[a]	ee, %[b]
1	Ph	10	20	0.1	4	**12**	86	84
2		5	10	0.25	6	**12**	86	82
13		10	20	0.1	18	**18g**	86	95[c]
14		10	20	0.1	12	**18h**	86	86[c,e]

Dounay, Hatanaka, Kodanko, Oestreich, Overman, Pfeifer, Weiss, JACS. 2003, 125, 6261

Diastereoselective Heck Cyclization

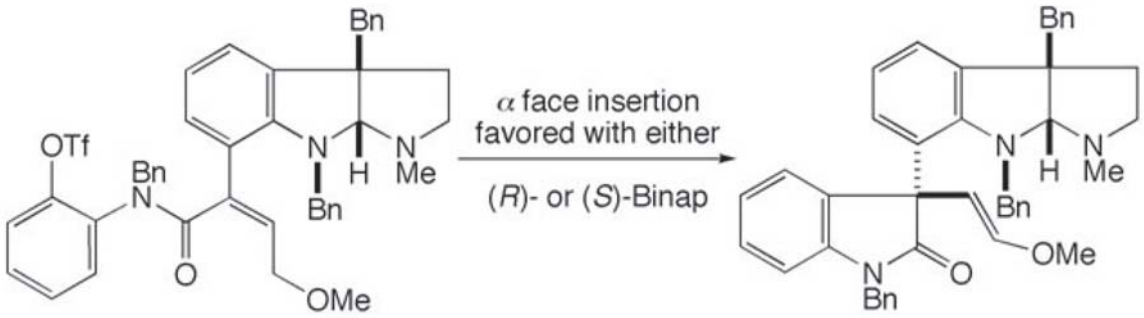


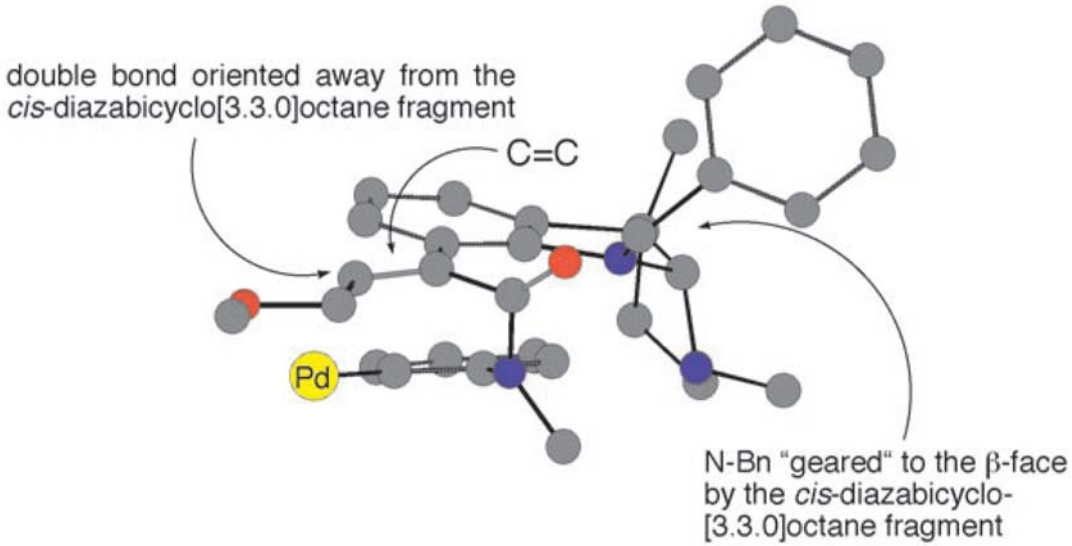
catalyst	R	**80:81**
(*R*)-Binap	Bn	20:1
(*S*)-Binap	Bn	6:1
(*R*)-Binap	H	3:1
(*S*)-Binap	H	1:3

⇦ dominant substrate control

⇦ dominant catalyst control

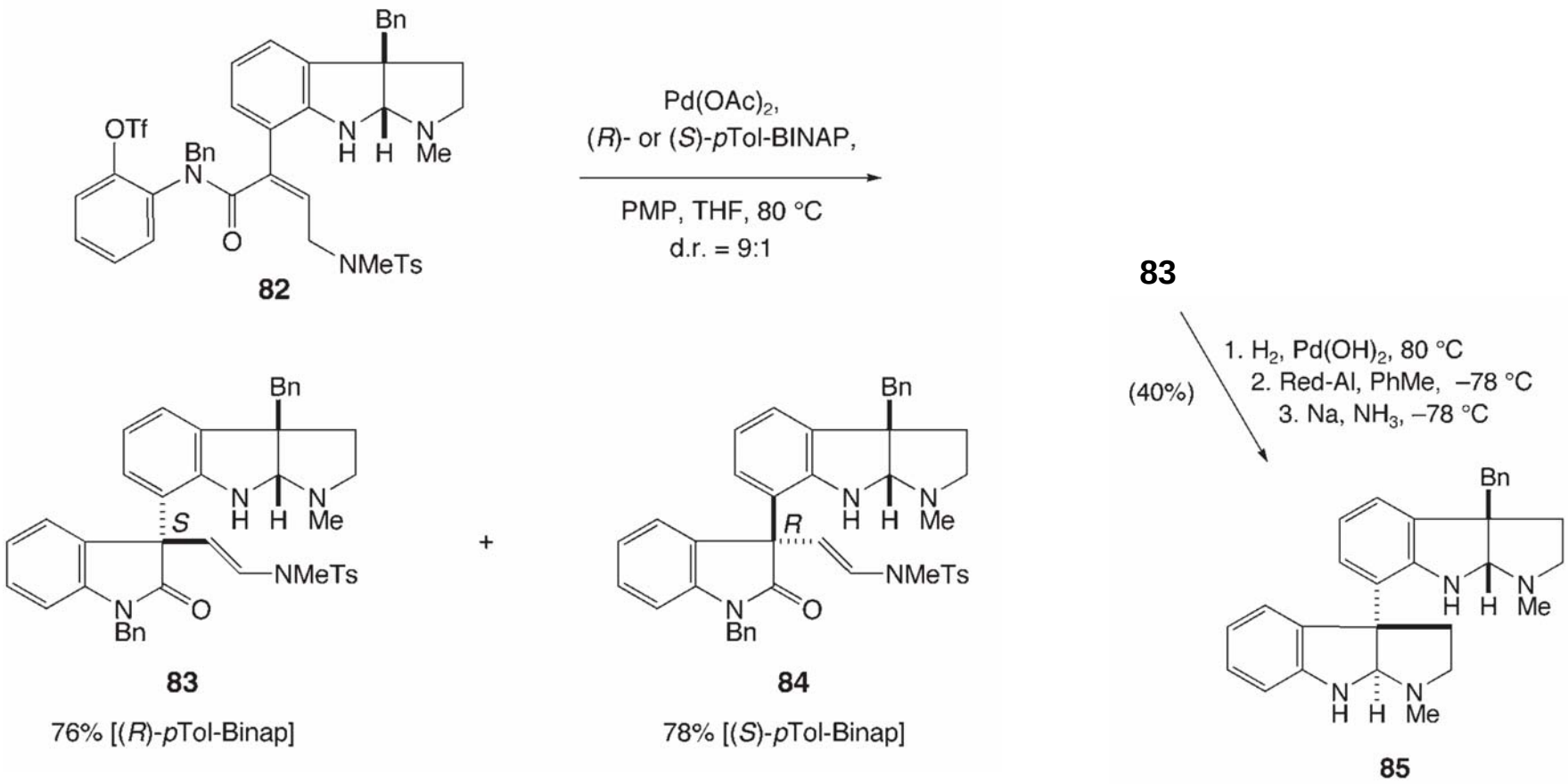
Overman, Steven, ACIE. 2007, 46, 5488





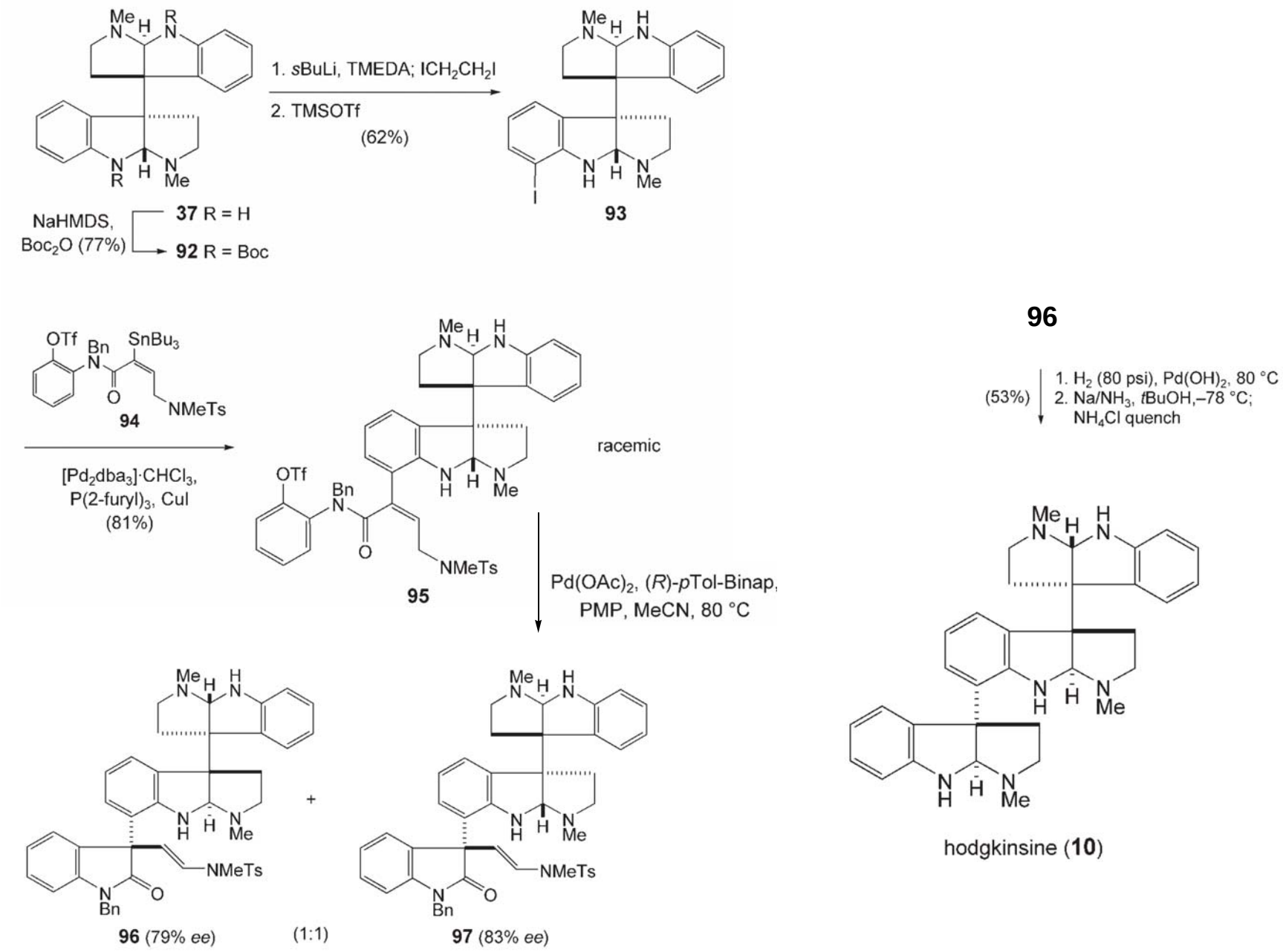
Overman, Steven, ACIE. 2007, 46, 5488

Substrate with Aminovinyl Sidechain

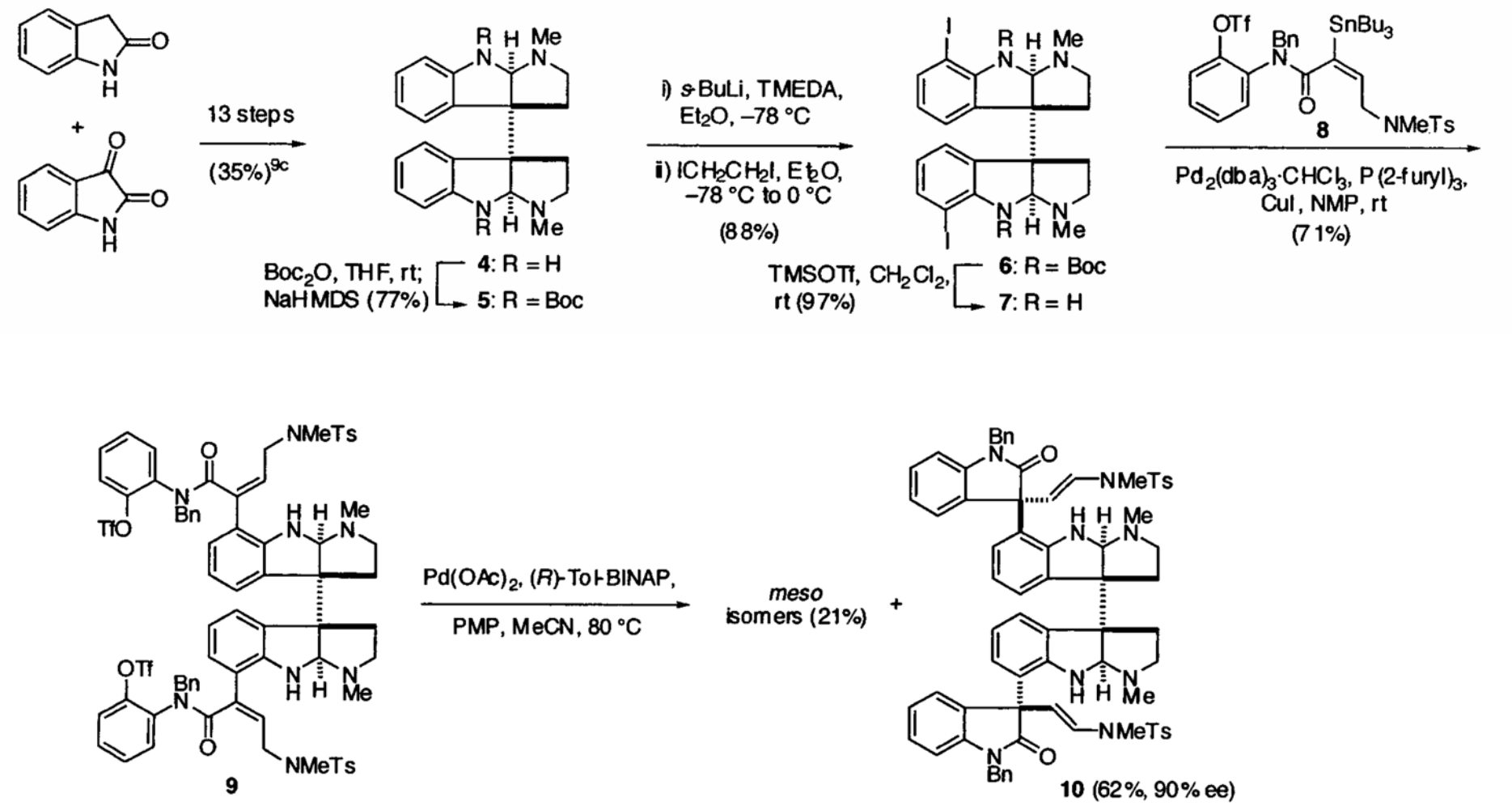


Overman, Steven, ACIE. 2007, 46, 5488

Synthesis of Hodgkinsine

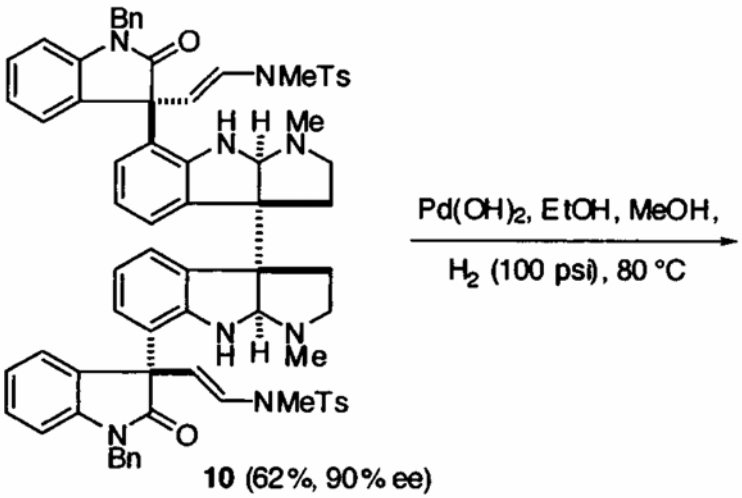


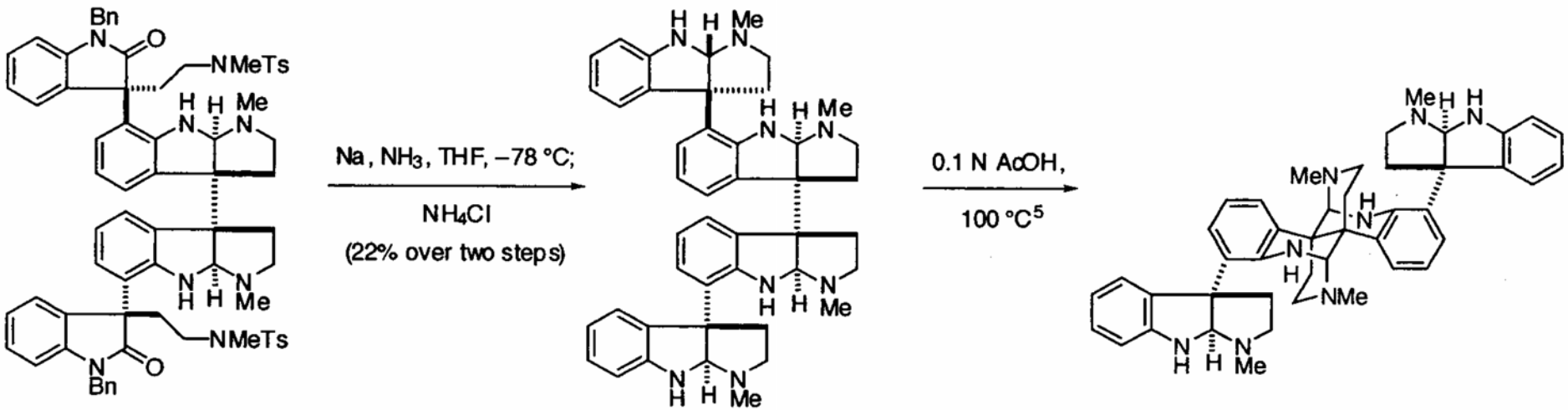
Synthesis of Quadrigemine C



Lebsack, Link, Overman, Stearns, JACS. 2002, 124, 9008

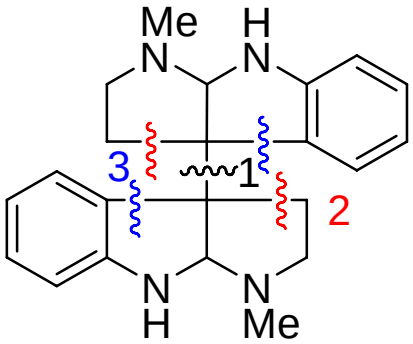
Synthesis of Quadrigemine C





Lebsack, Link, Overman, Stearns, JACS. 2002, 124, 9008

Summary

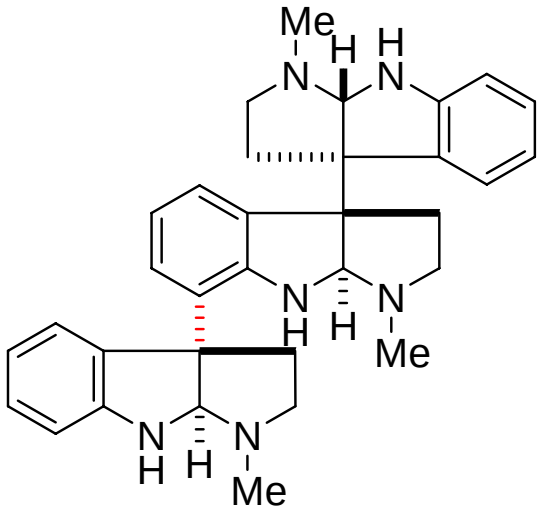


1 Oxidative coupling: *meso*-chimonathine
Reductive coupling: (+)-chimonathine

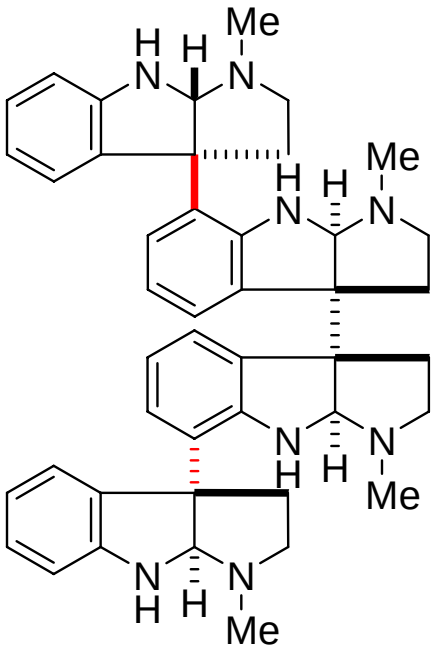
2 Dialkylation
3 Cascade Heck

meso-chimonathine
(+) or (-) - chimonathine

Enantioselective Heck cyclization



(-)-hodgkinsine



(-)-quadrigemine C