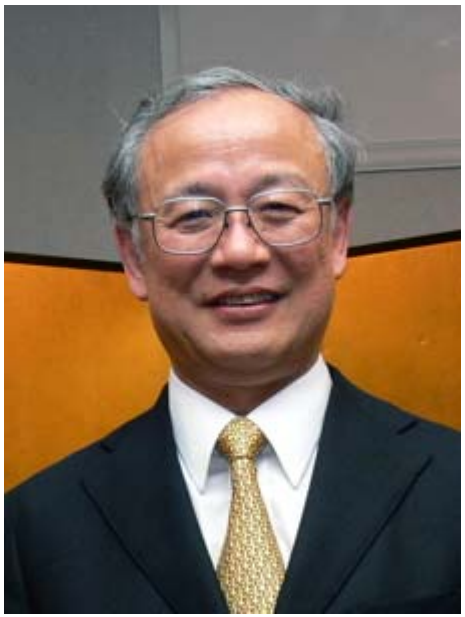
Tohru Fukuyama, Ph.D.



1948 Born in Anjo, Aich, Japan
1971 B.A. Nagoya University, Japan
1973 M.A. Nagoya University, Japan
1977 Ph.D Harvard University (Professor Y. Kishi)
1978-1979 Postdoctoral Study Harvard University
(Professor Y. Kishi)
1979 Assistant Professor, Rice University
1988 Full Professor, Rice University
1995 Professor of Pharmaceutical Sciences
University of Tokyo

Awards

ACS Arthur C. Cope Scholar Award (1993)
Synthetic Organic Chemistry Award, Japan (2002)
ISHC Senior Award in Heterocyclic Chemistry (2003)
ACS Award for Creative Work in Synthetic Organic Chemistry (2004)
The PSJ Award (Pharmaceutical Society of Japan Award, 2006)

Top 5 cited paper

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2-NITROBENZENESULFONAMIDES AND 4-NITROBENZENESULFONAMIDES - EXCEPTIONALLY VERSATILE MEANS FOR PREPARATION OF SECONDARY-AMINES AND PROTECTION OF AMINES
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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 101 (1): 259-260 1979
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PARA-ANISYL GROUP - A VERSATILE PROTECTING GROUP FOR PRIMARY ALCOHOLS
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2,4-dinitrobenzenesulfonamides: A simple and practical method for the preparation of a variety of secondary amines and diamines.
TETRAHEDRON LETTERS 38 (33): 5831-5834 AUG 18 1997

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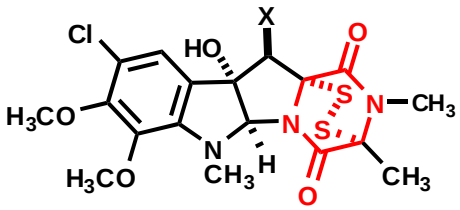
FACILE REDUCTION OF ETHYL THIOL ESTERS TO ALDEHYDES - APPLICATION TO A TOTAL SYNTHESIS OF (+)-NEOTHRAMYCIN-A METHYL-ETHER
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 112 (19): 7050-7051 SEP 12 1990
Times Cited: 118

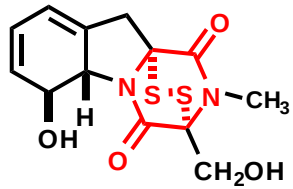
Ph.D and Postdoctoral Work



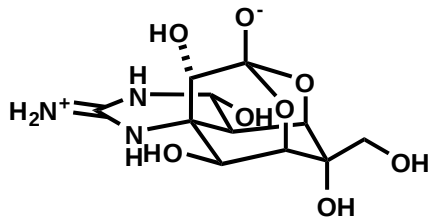
Sporidesmin A: X = OH
Sporidesmin B: X = H

Epidithiapiperazinedione

JACS 1973, 95, 6490; 6492; 6493;
JACS 1976, 98, 6723;
TL 1974, 1549; 1971,4657; 1976, 3393;
JCS CC 1975, 543.

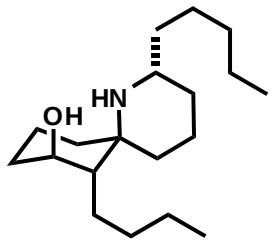


Gliotoxin

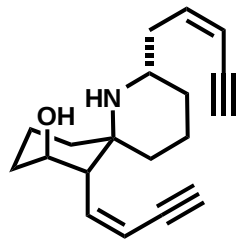


Tetrodotoxin

JACS 1972, 94, 9217; 9219
JCS CC1972, 64.

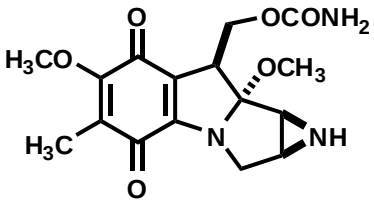


Perhydrohistrionicotoxin



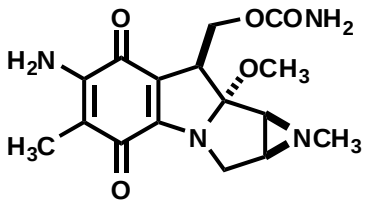
histrionicotoxin

JOC 1975, 40, 2009; 2011

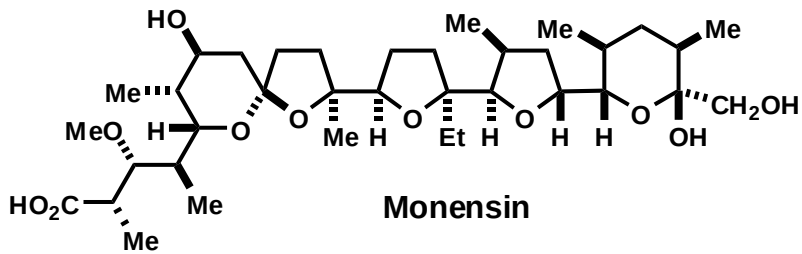


Mitomycin A

JACS 1977, 99, 8115
TL 1977, 4295



Porfiromycin



Monensin

JACS 1979, 101, 259; 260; 262

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Part IV: Fukuyama Indole Synthesis

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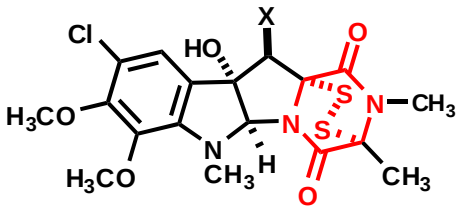
Ph.D and Postdoctoral Work



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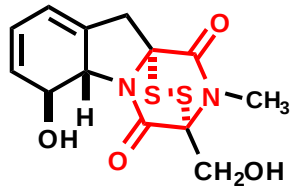
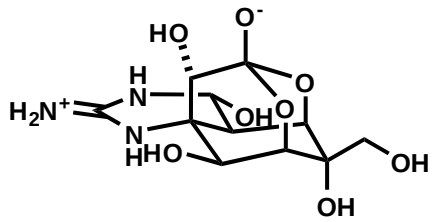


Gliotoxin



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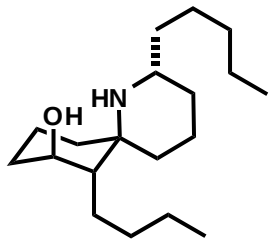
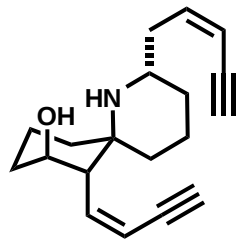


Perhydrohistrionicotoxin



histrionicotoxin

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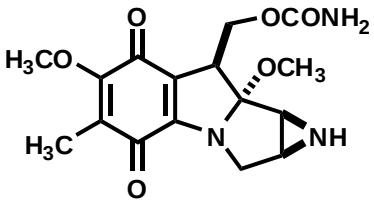

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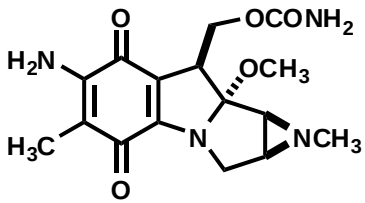
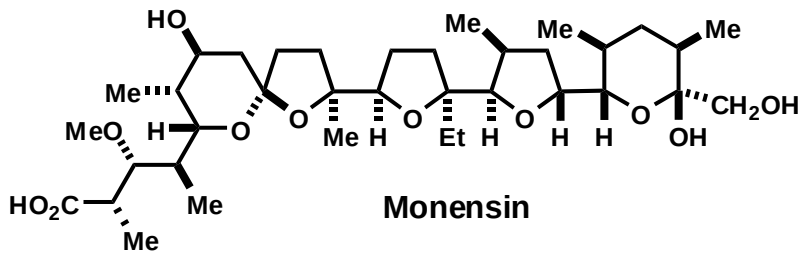


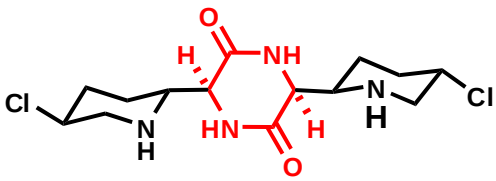
Porfiromycin



Monensin

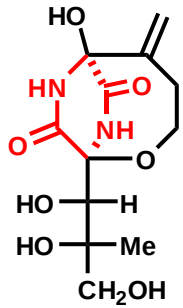
JACS 1979, 101, 259; 260; 262

Part I: Synthesis of Piperazine-derived Natural Product



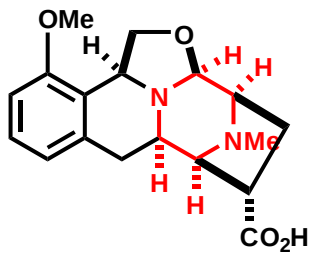
Antibiotic 539A

JACS 1980, 102, 2122



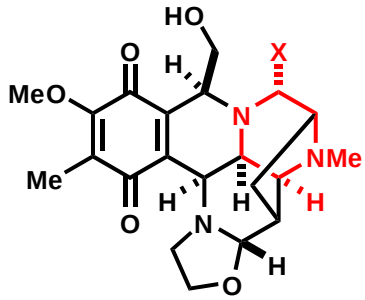
Bicyclomycin

TL 1981, 4155



Quinocarin

JACS 1988, 5196

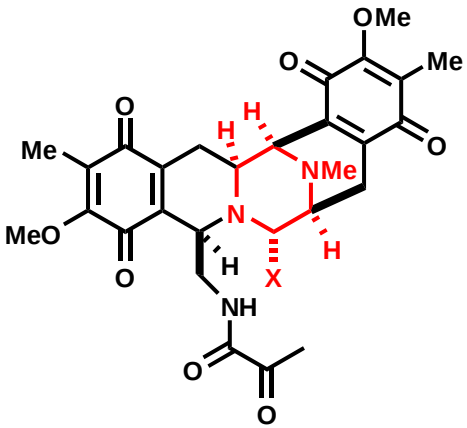


Cyanocycline A: X = CN

JACS, 1987, 1587

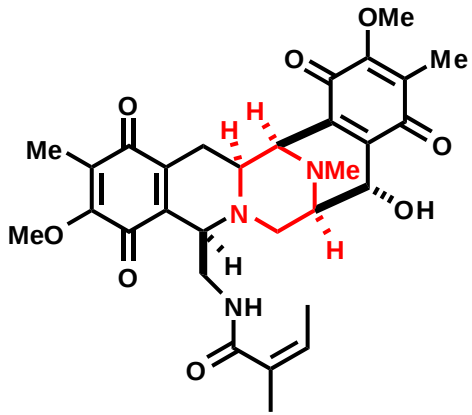
naphthyridinomycin X = OH

TL 1986, 6173; OL 2004, 3095



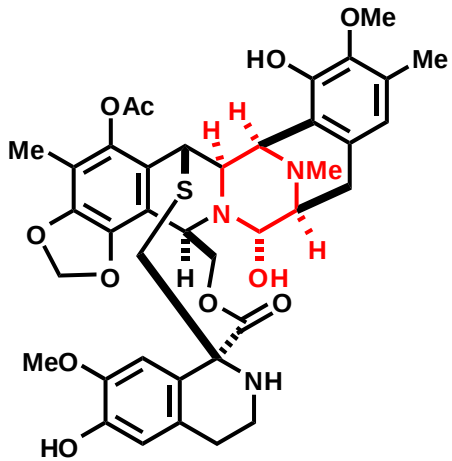
Saframycin B: X = H JACS, 1982, 4957

Saframycin A: X = CN JACS, 1990, 3712



Renieramycin A

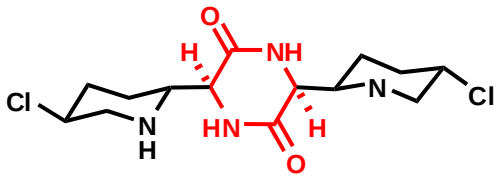
TL 1990, 5989



Ecteinascidin 743

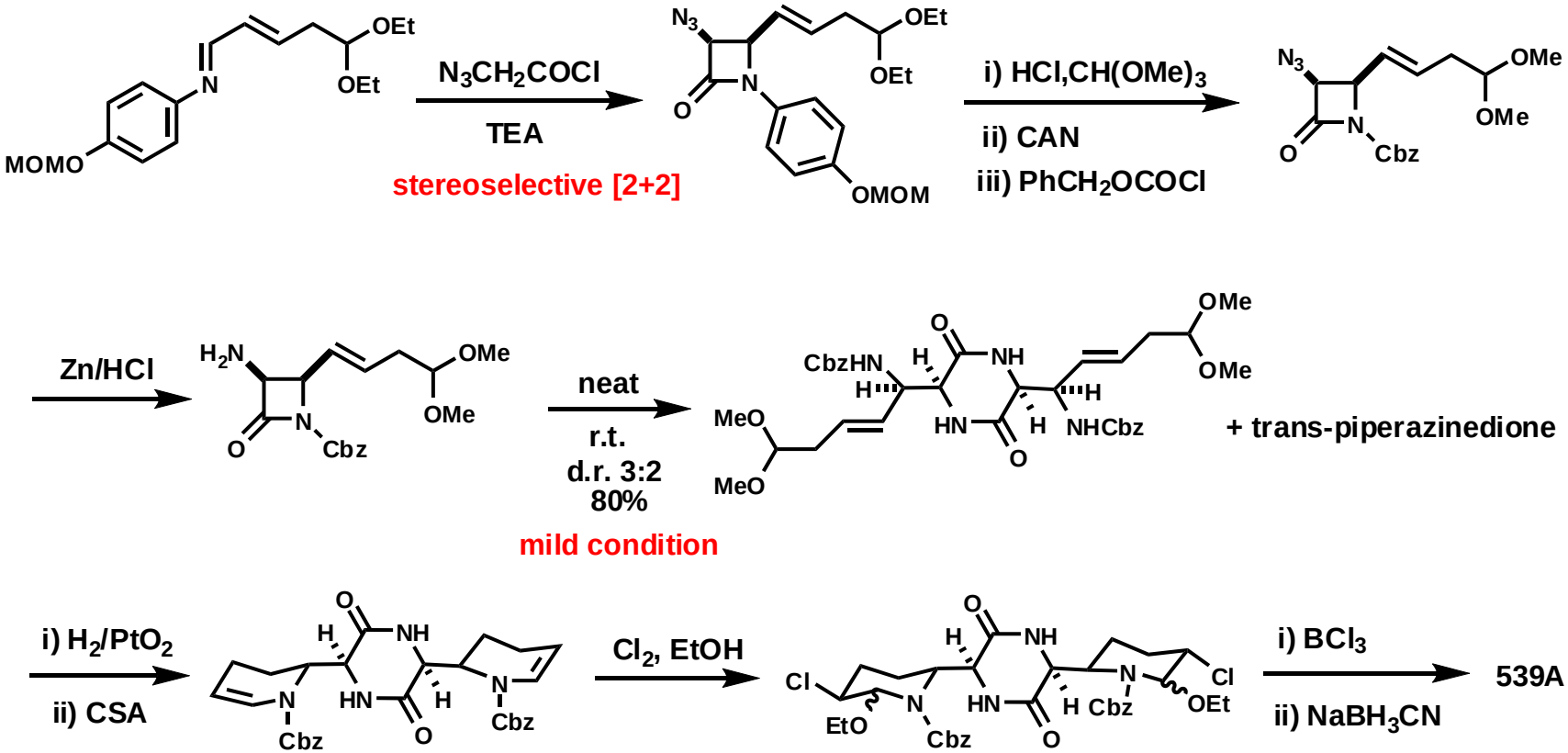
JACS 2002, 6552

First independent paper

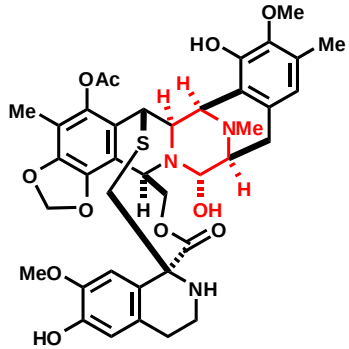


Antibiotic 539A

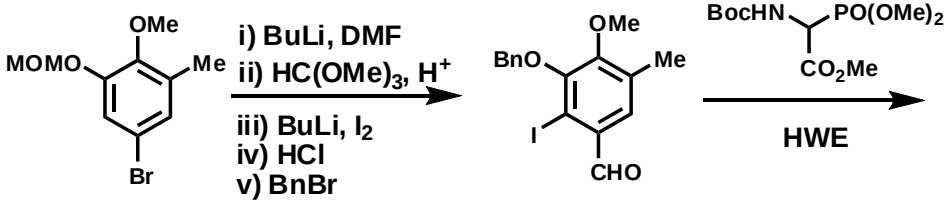
JACS 1980, 102, 2122

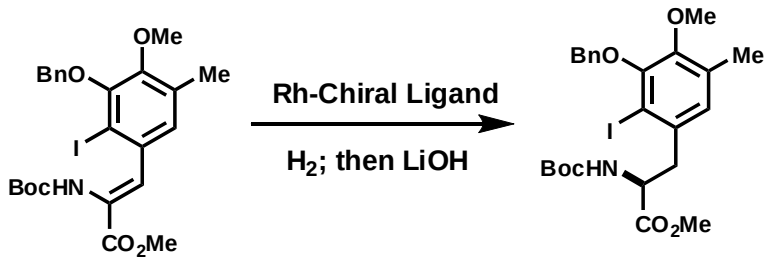


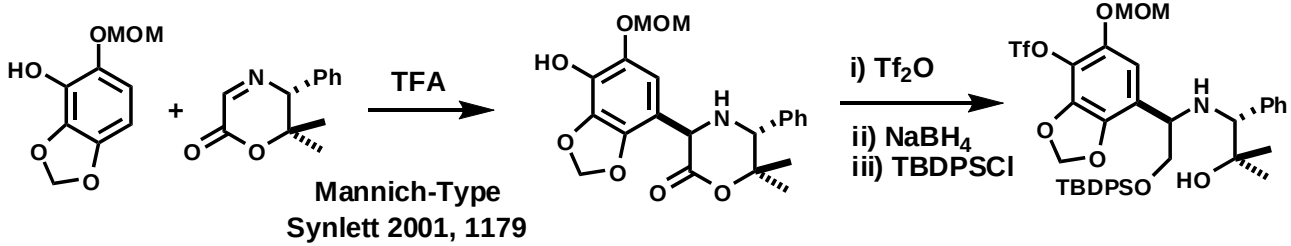
Total Synthesis of ET 743

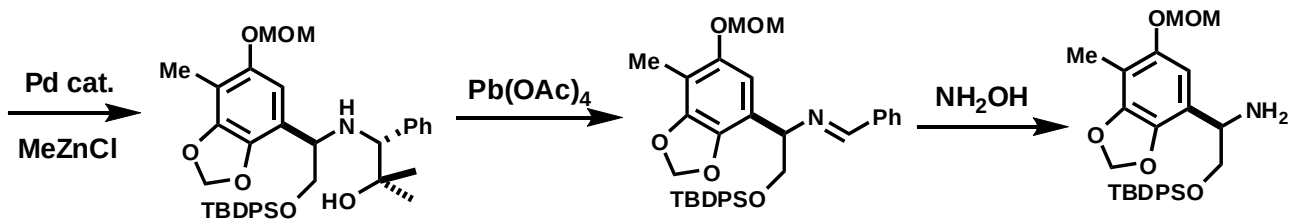


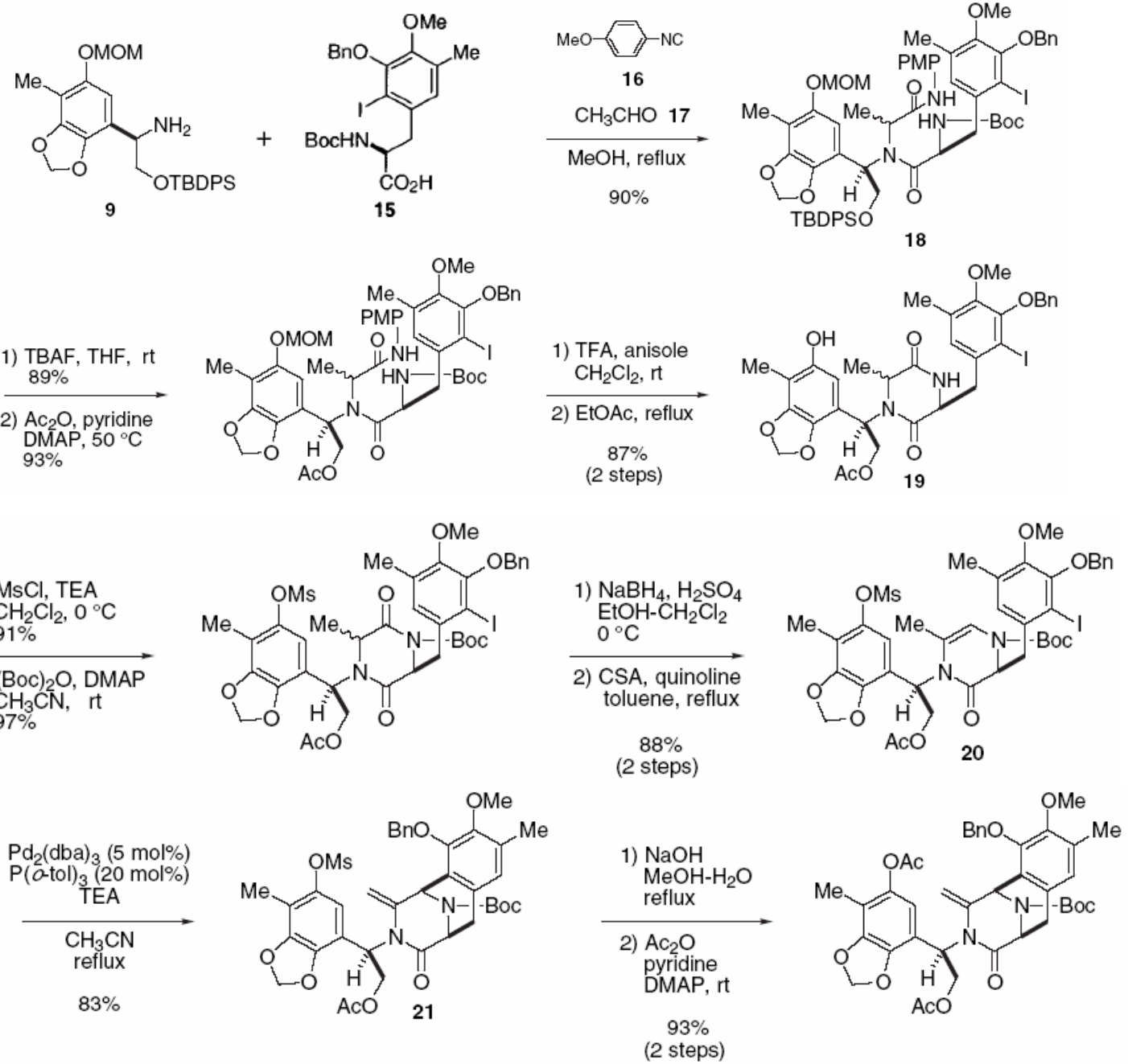
Ecteinascidin 743
JACS 2002, 6552

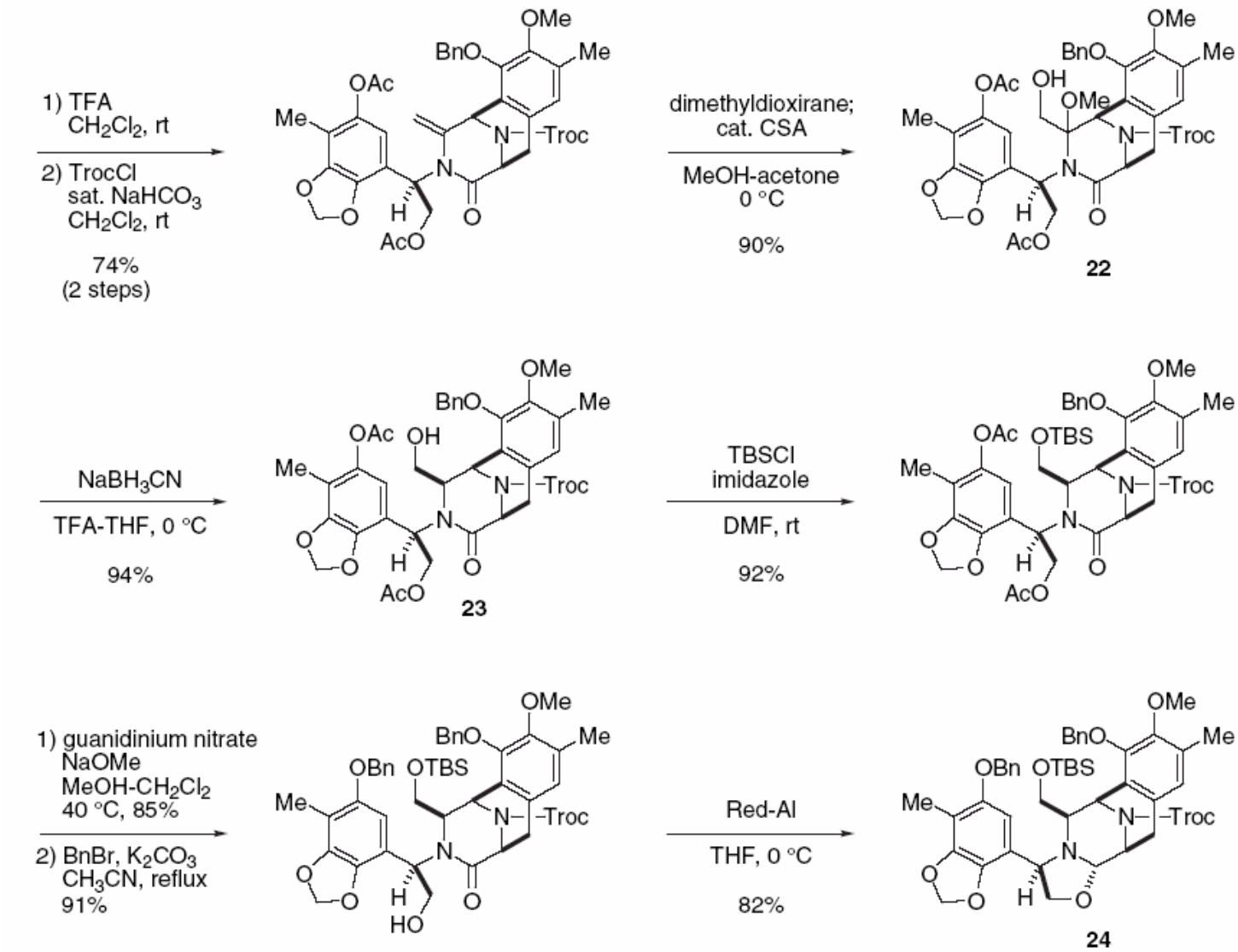


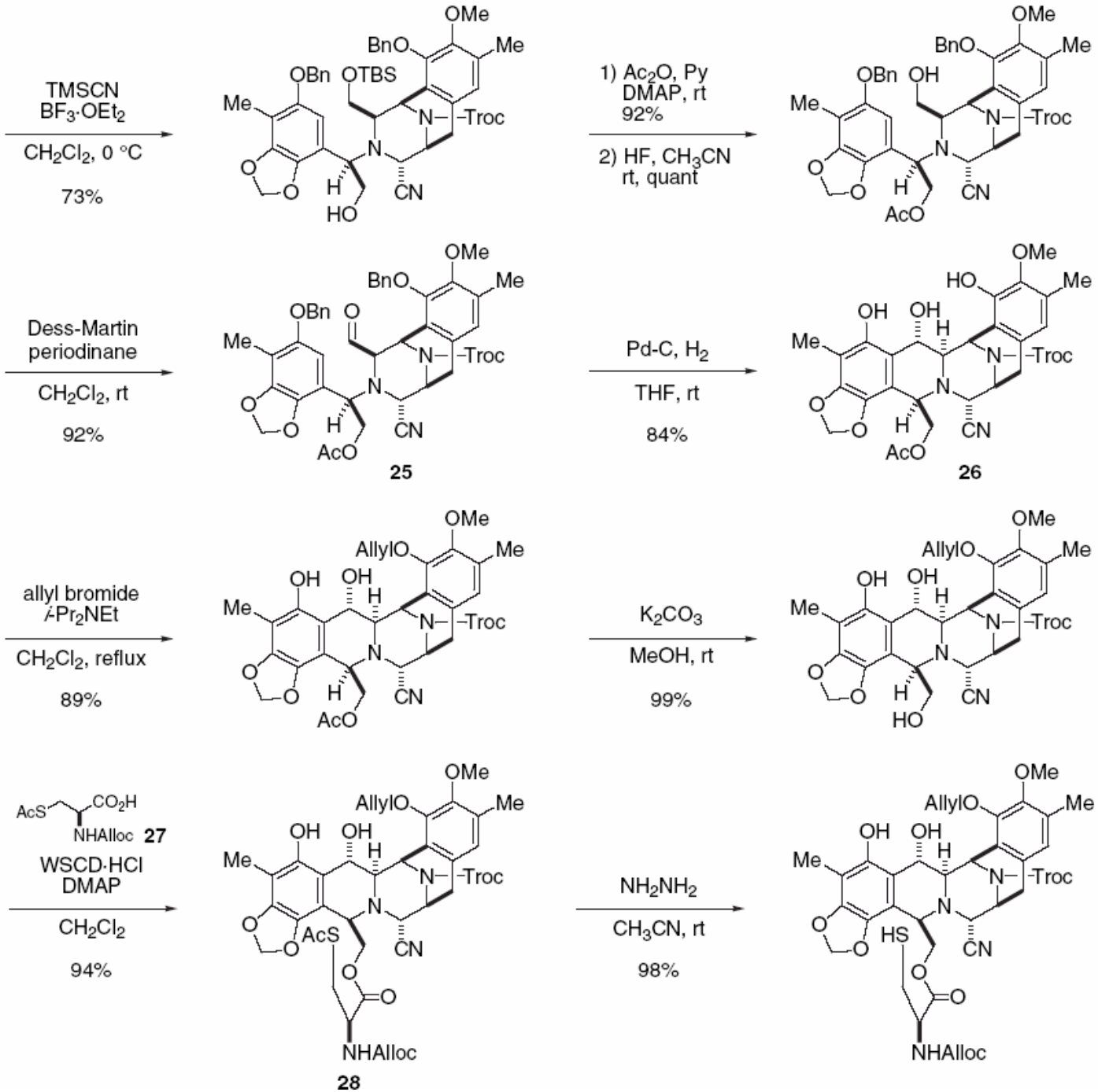




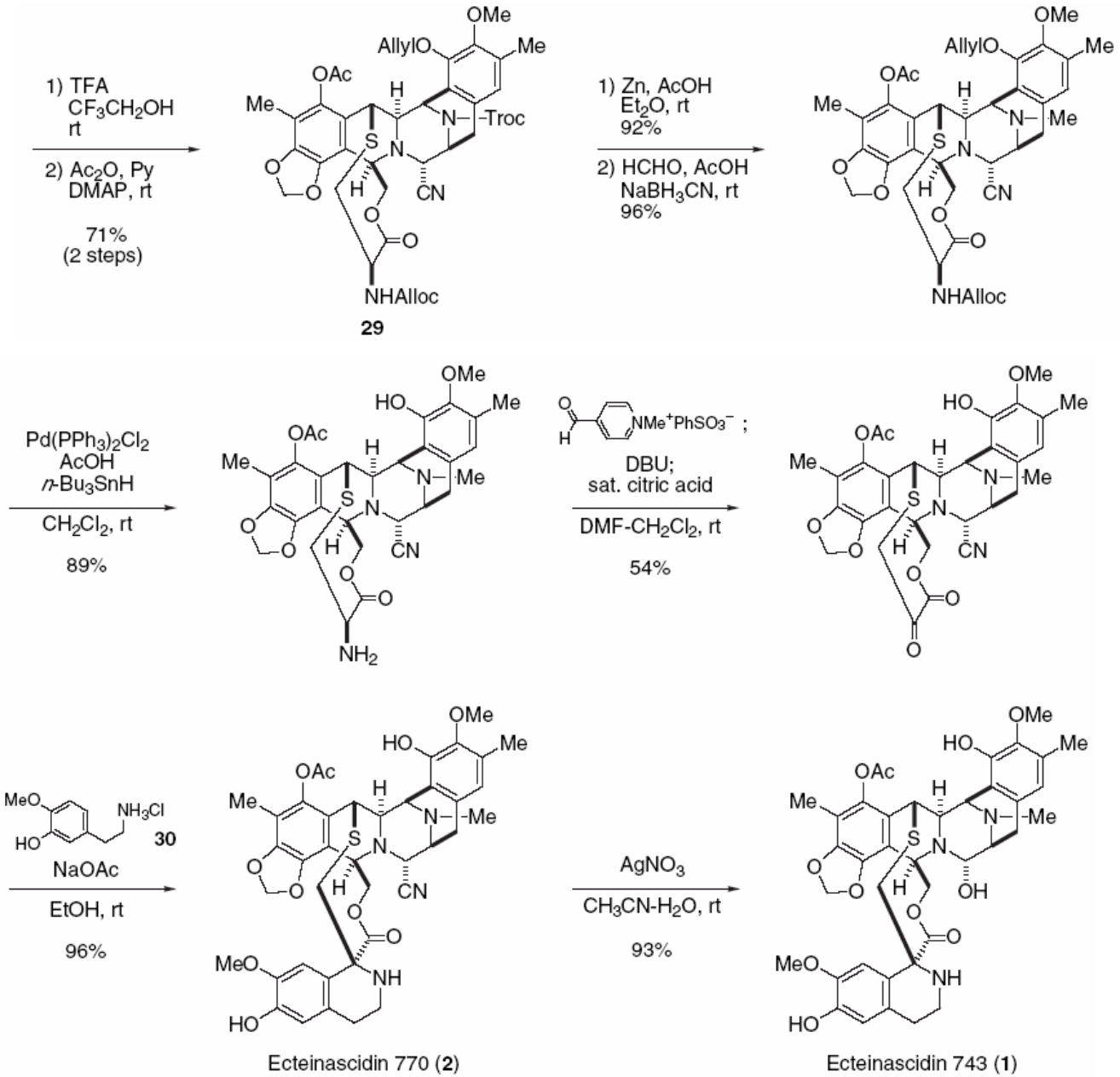



9
15
16
CH3CHO 17
MeOH, reflux
90%
18
1) TBAF, THF, rt
89%
2) Ac2O, pyridine
DMAP, 50 °C
93%
1) TFA, anisole
CH2Cl2, rt
2) EtOAc, reflux
87%
(2 steps)
19
1) MsCl, TEA
CH2Cl2, 0 °C
91%
2) (Boc)2O, DMAP
CH3CN, rt
97%
1) NaBH4, H2SO4
EtOH-CH2Cl2
0 °C
2) CSA, quinoline
toluene, reflux
88%
(2 steps)
20
Pd2(dba)3 (5 mol%)
P(o-tol)3 (20 mol%)
TEA
CH3CN
reflux
83%
21
1) NaOH
MeOH-H2O
reflux
2) Ac2O
pyridine
DMAP, rt
93%
(2 steps)


1) TFA
CH_2Cl_2, rt
2) TrocCl
sat. $NaHCO_3$
CH_2Cl_2, rt
74%
(2 steps)
dimethyldioxirane;
cat. CSA
MeOH-acetone
0 °C
90%
22
$NaBH_3CN$
TFA-THF, 0 °C
94%
23
TBSCl
imidazole
DMF, rt
92%
1) guanidinium nitrate
NaOMe
$MeOH-CH_2Cl_2$
40 °C, 85%
2) BnBr, K_2CO_3
CH_3CN, reflux
91%
Red-Al
THF, 0 °C
82%
24


TMSCN
BF3·OEt2
CH2Cl2, 0 °C
73%
1) Ac2O, Py
DMAP, rt
92%
2) HF, CH3CN
rt, quant
Dess-Martin
periodinane
CH2Cl2, rt
92%
25
Pd-C, H2
THF, rt
84%
26
allyl bromide
iPr2NEt
CH2Cl2, reflux
89%
K2CO3
MeOH, rt
99%
AcS
CO2H
NHAlloc 27
WSCD·HCl
DMAP
CH2Cl2
94%
28
NH2NH2
CH3CN, rt
98%

Total Synthesis of ET 743



Outline of Fukuyama's research

Part I: Synthesis of Piperazine-derived Natural Product

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Part III: Nitrobenzensulfonamides Chemistry

Part IV: Fukuyama Indole Synthesis

Part V: Others

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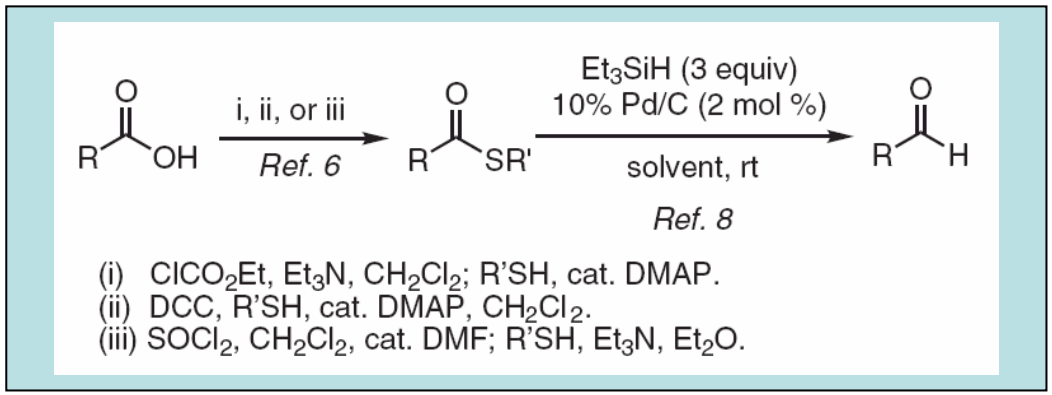
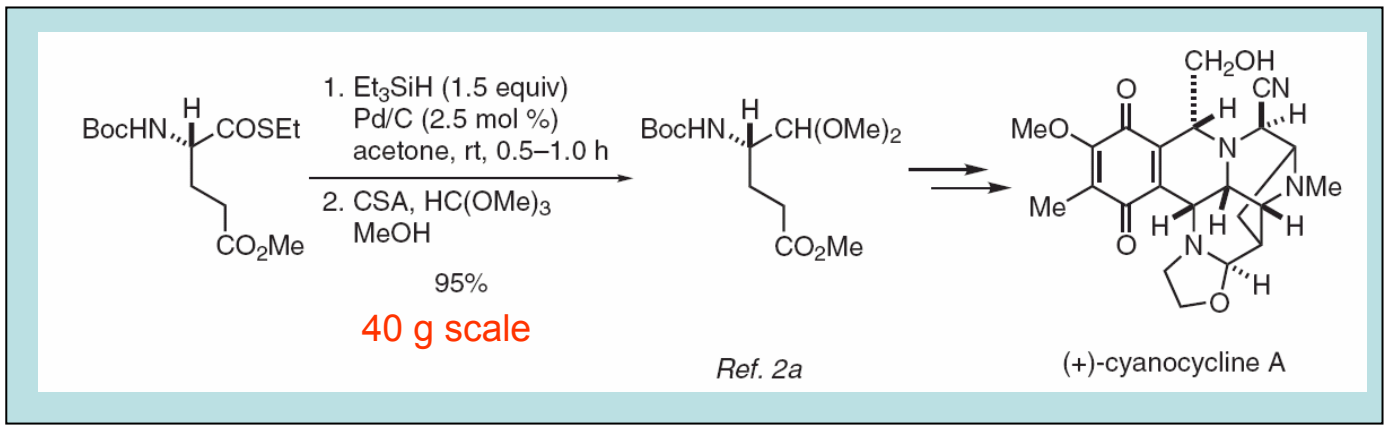
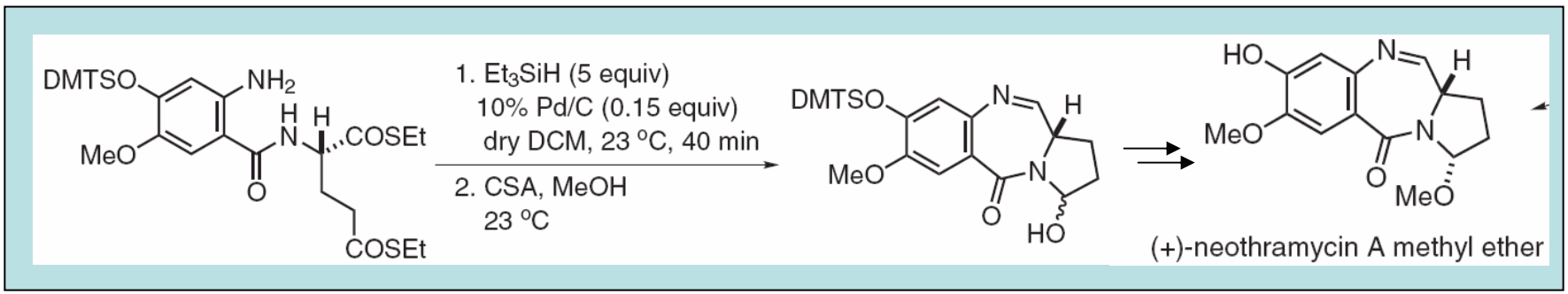


JACS 1990, 112, 7050
Review: Aldrichimica Acta 2004, 87





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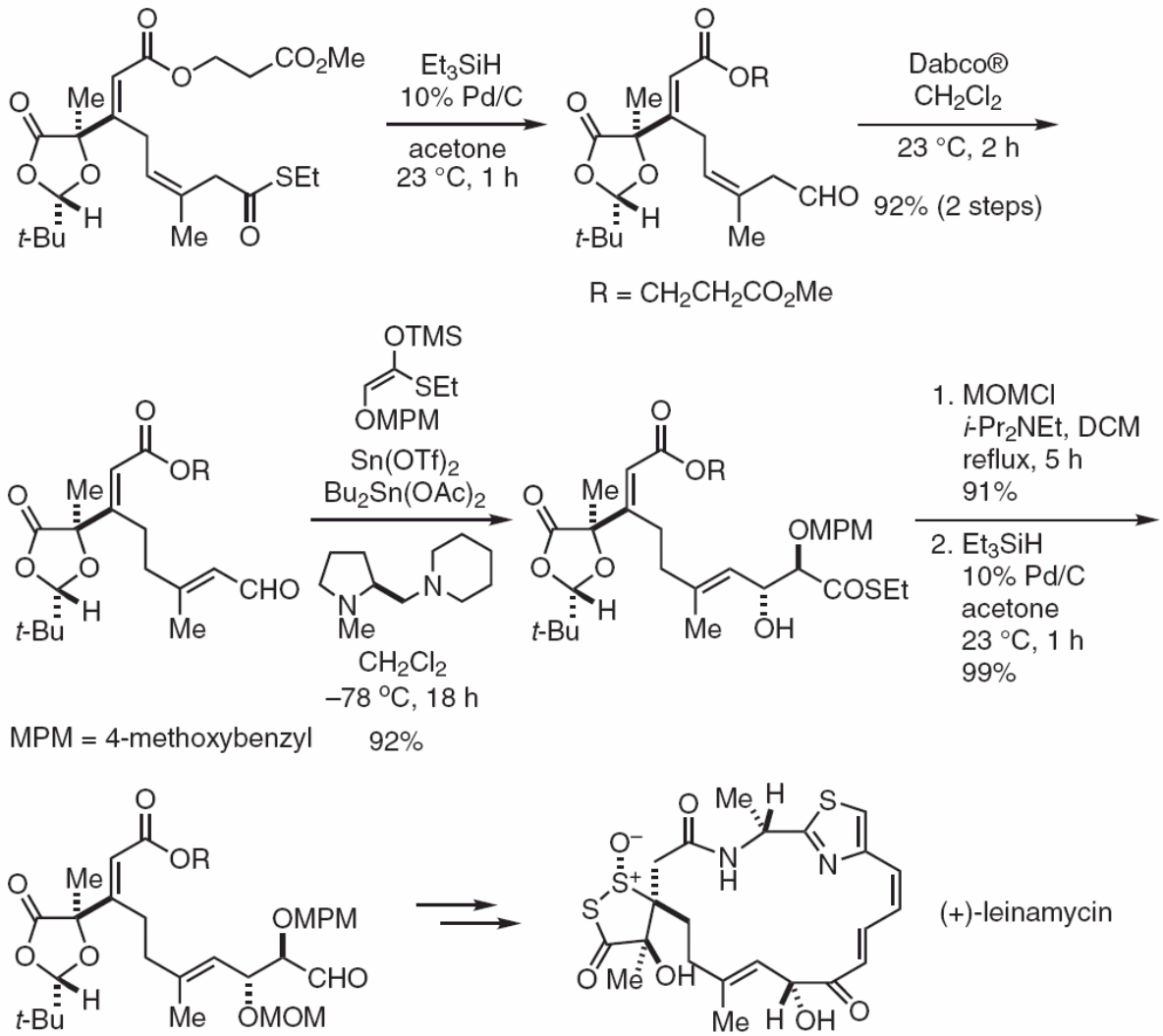

TL 1992, 5701

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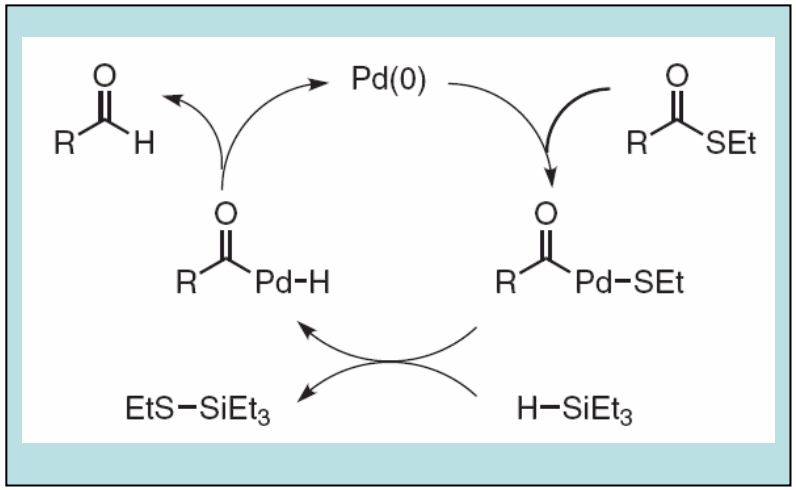
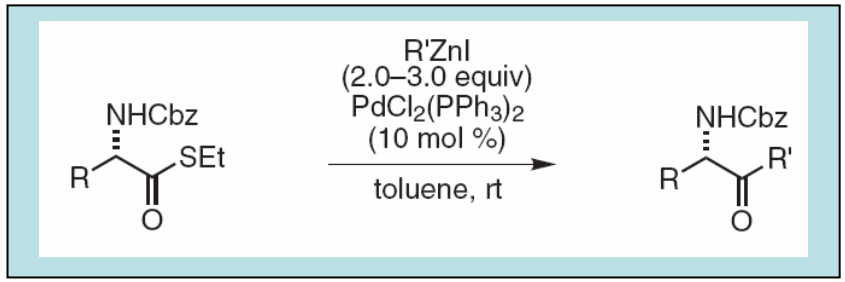
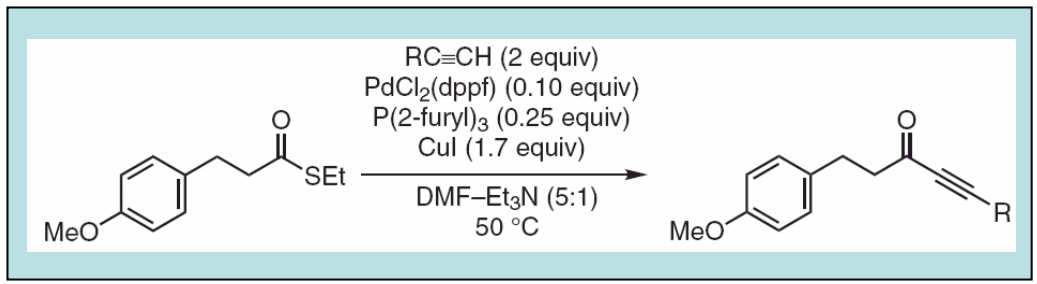
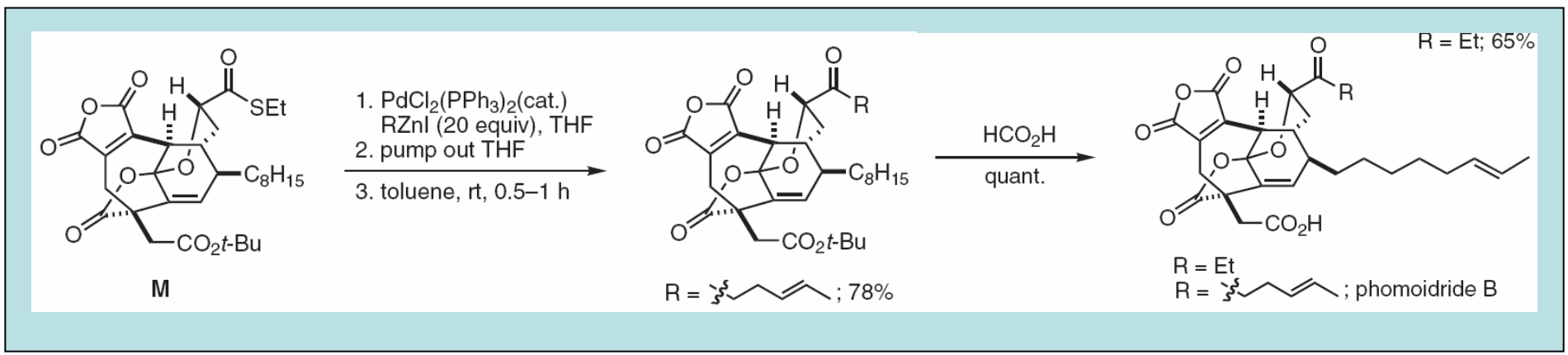




TL 1998, 3189



Synlett 2003, 1512



OL 2003, 2235

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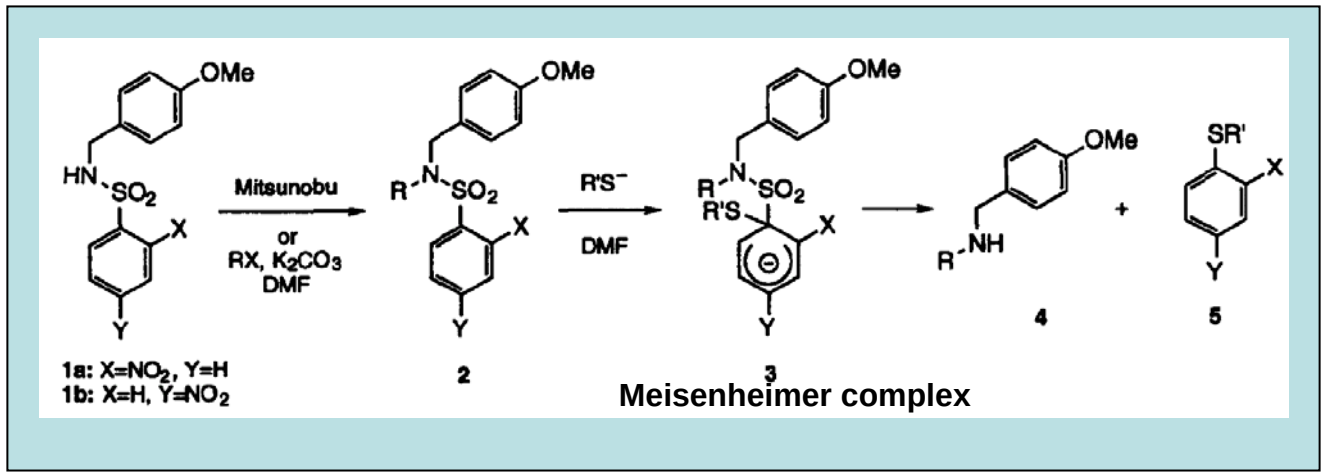
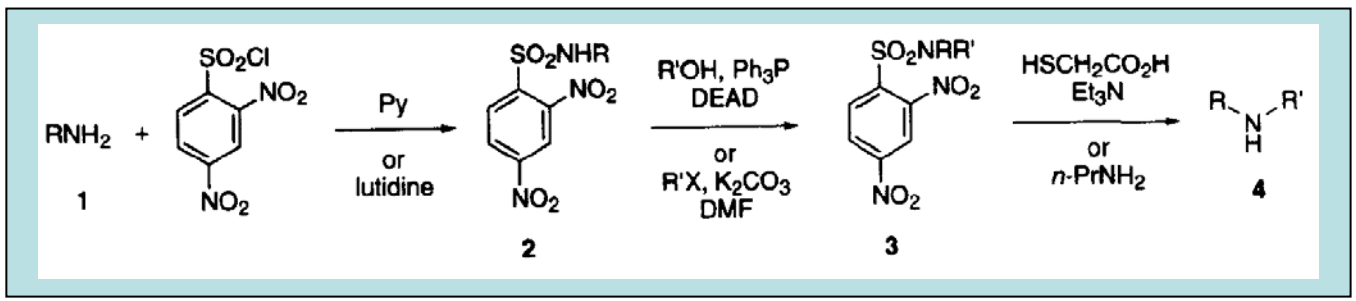
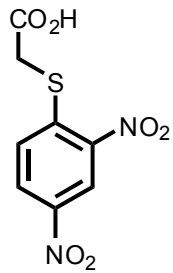
A simple and practical method for the preparation of a variety of amines and diamine

TL 1995, 36, 6373; TL 1997, 38, 583; Synlett 1999, 1301

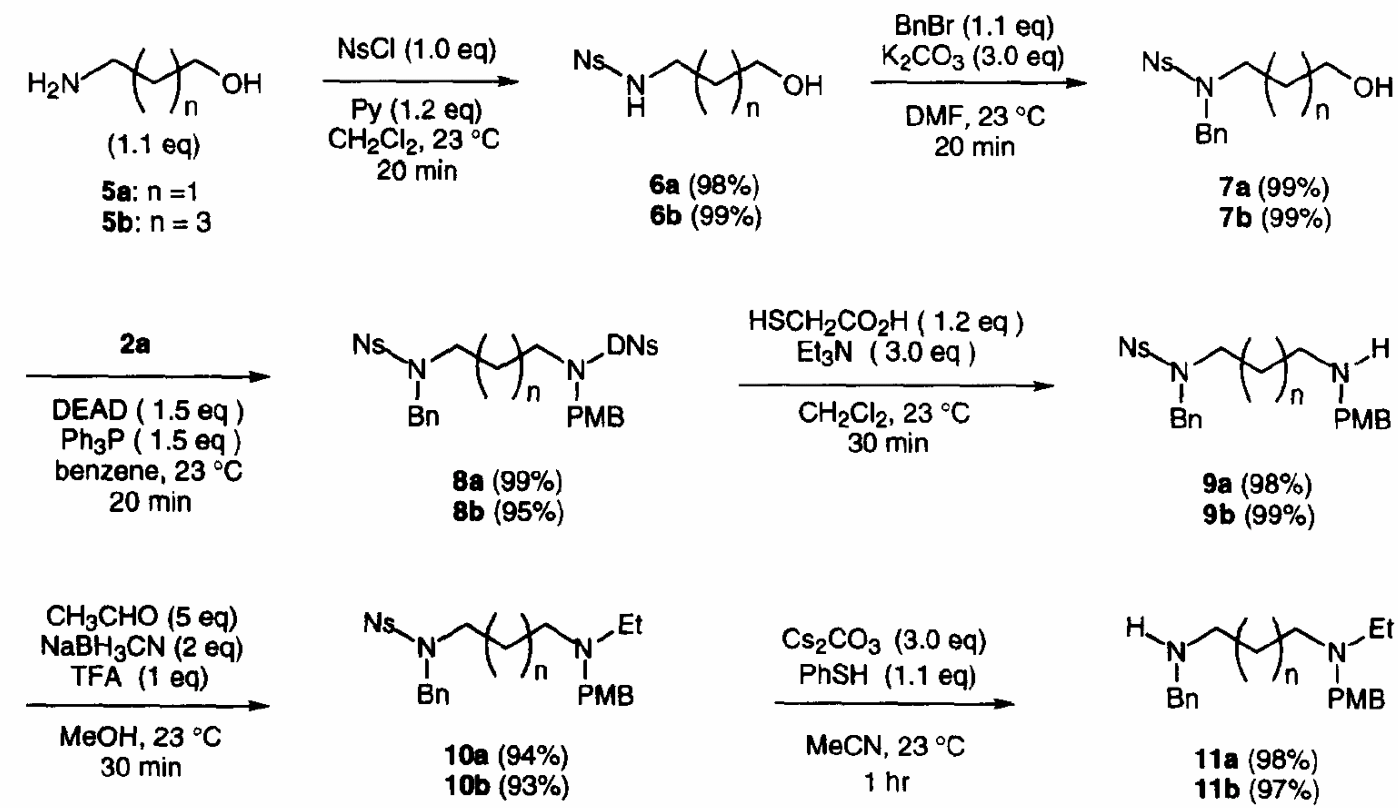






wash away by $NaHCO_3$(aq.)

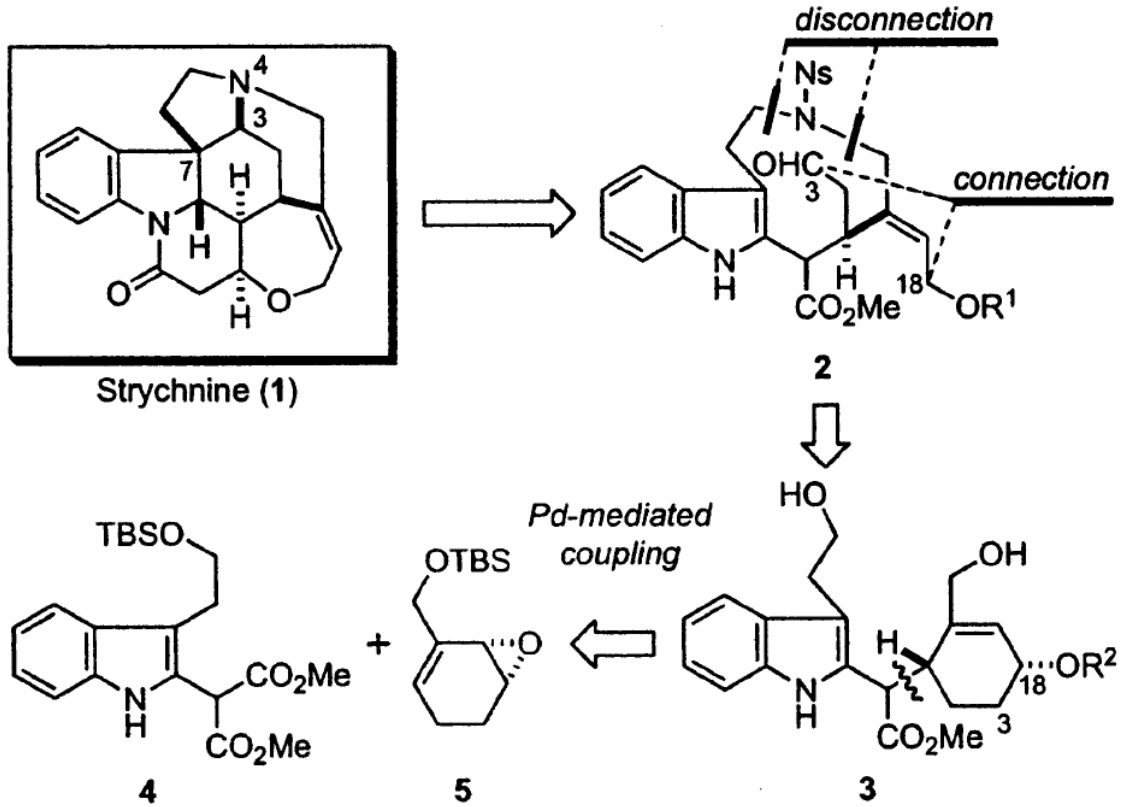
Part III: Nitrobenzensulfonamides Chemistry



Ns = 2-nitrobenzenesulfonyl, DNs = 2,4-dinitrobenzenesulfonyl

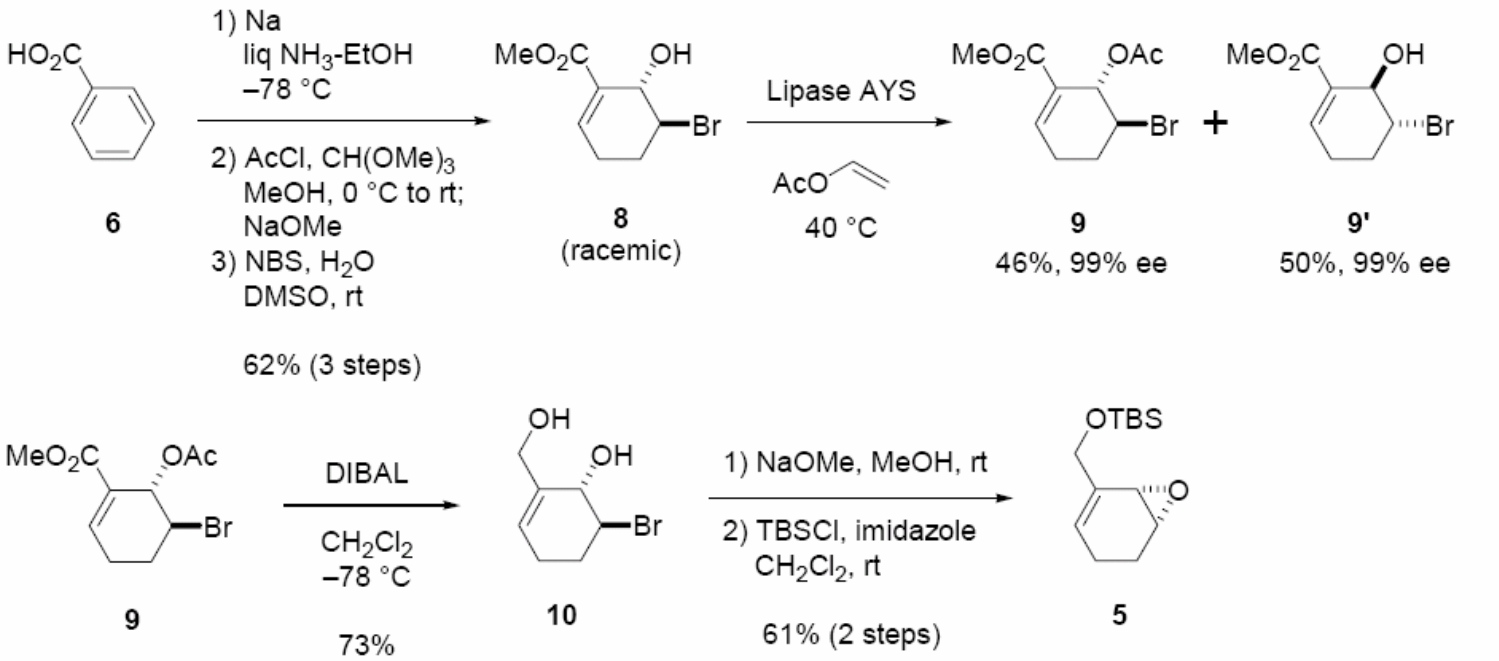
Nitrobenzensulfonamides: Application in Strychnine Synthesis

Scheme 1. Retrosynthetic Analysis

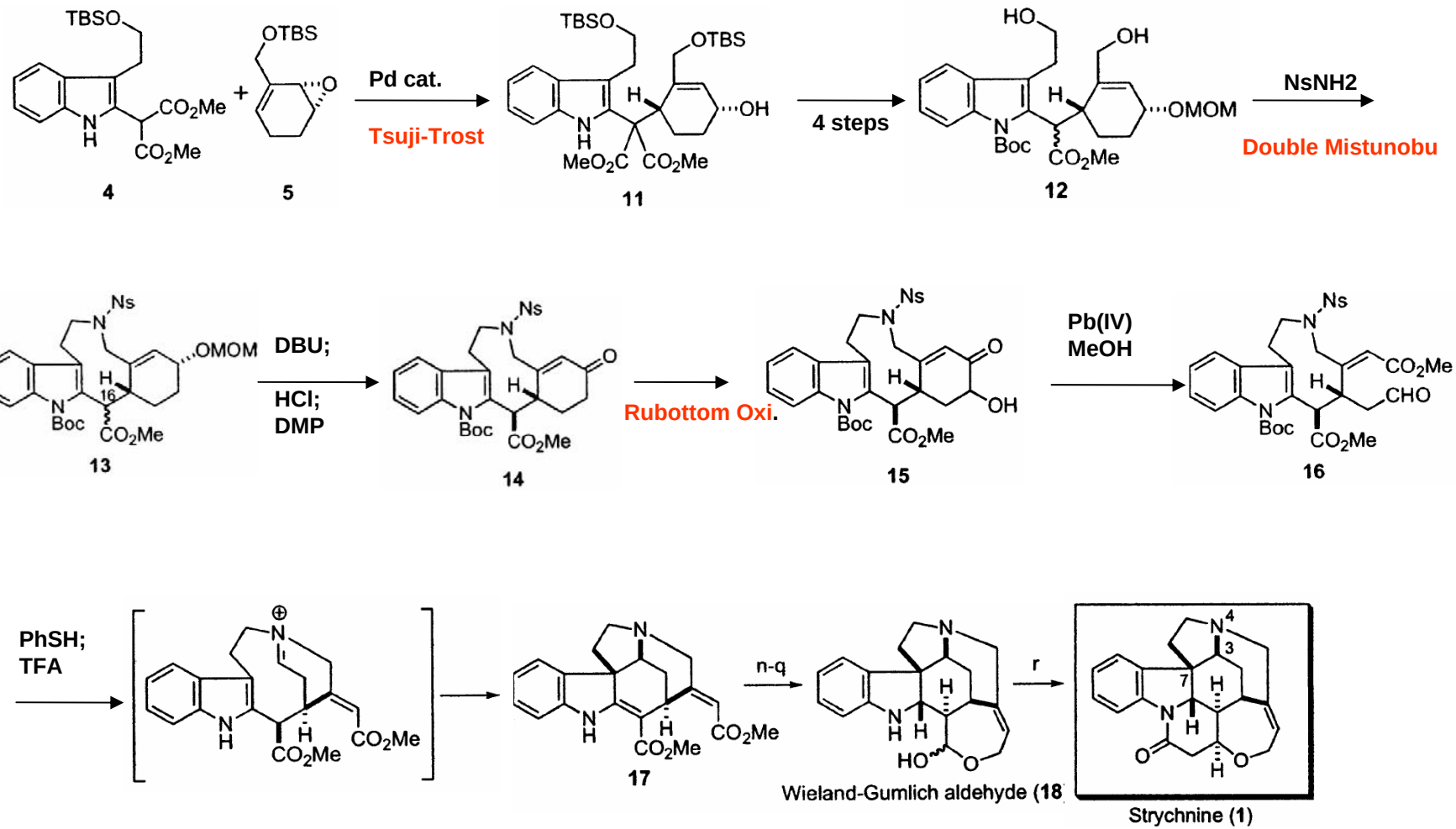


Nitrobenzensulfonamides: Application in Strychnine Synthesis

Synthesis of Vinyl Epoxide 5



Nitrobenzensulfonamides: Application in Strychnine Synthesis



Outline of Fukuyama's research

Part I: Synthesis of Piperazine-derived Natural Product

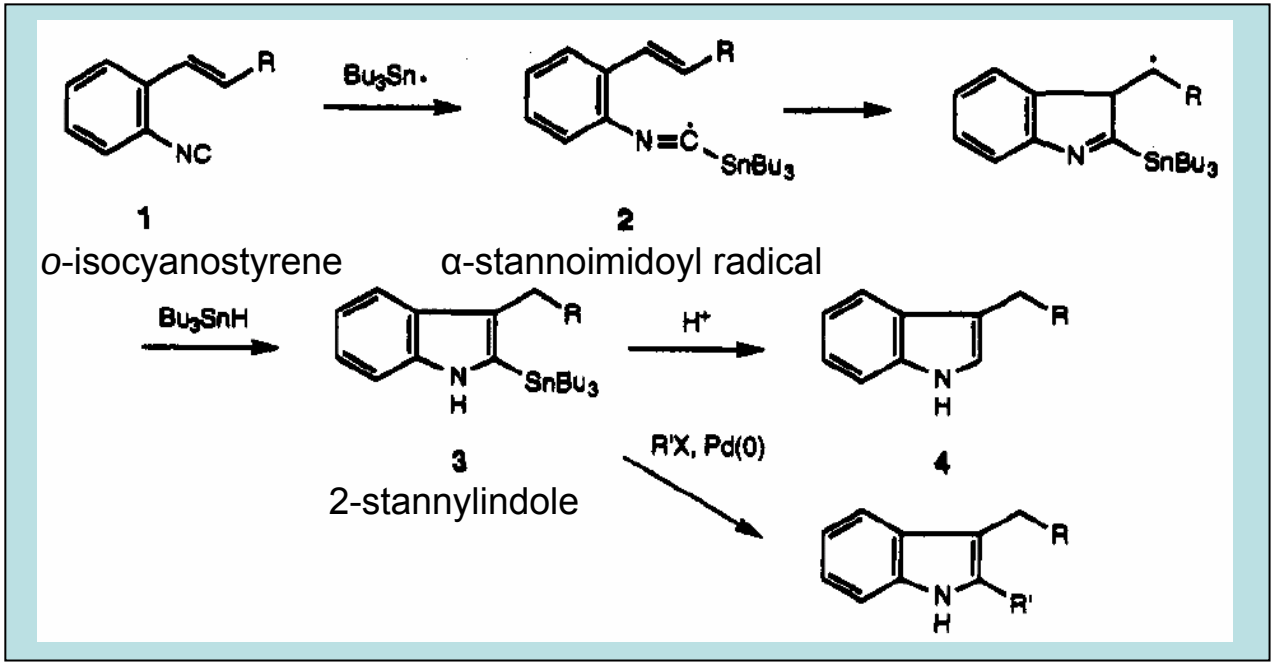
Part II: Pd-catalyzed Synthesis of Aldehydes and Ketones from Thiol Esters

Part III: Nitrobenzensulfonamides Chemistry

Part IV: Fukuyama Indole Synthesis

Part V: Others

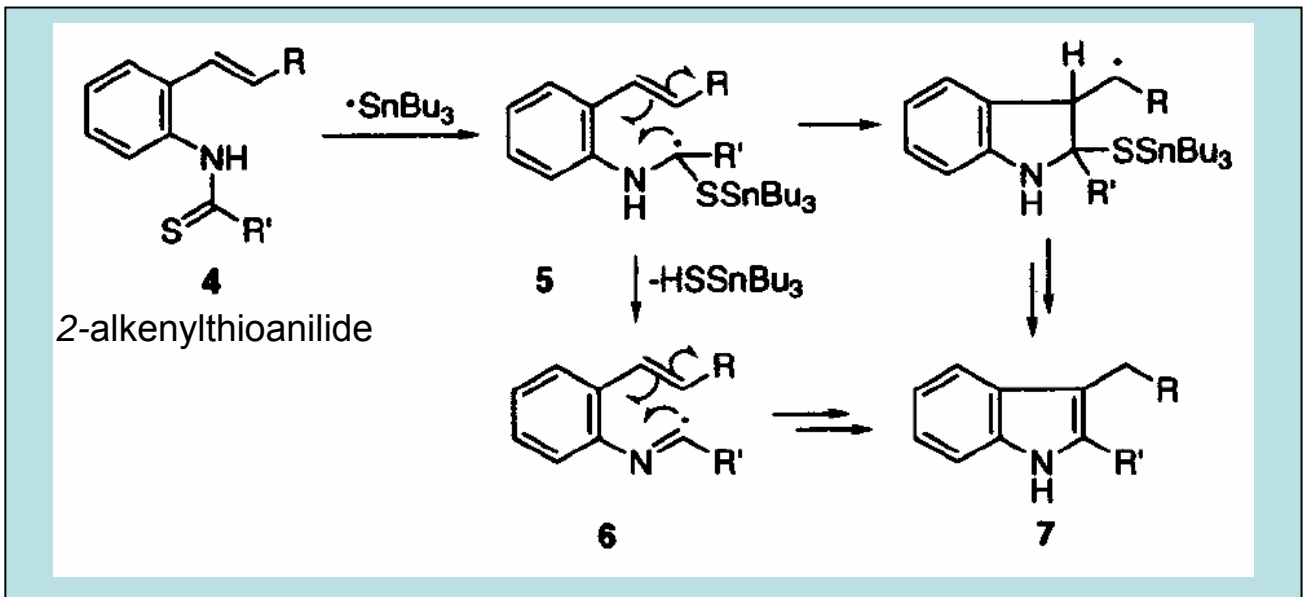
Part IV: Fukuyama Indole Synthesis



JACS 1994, 116, 3127

3-substituted indole

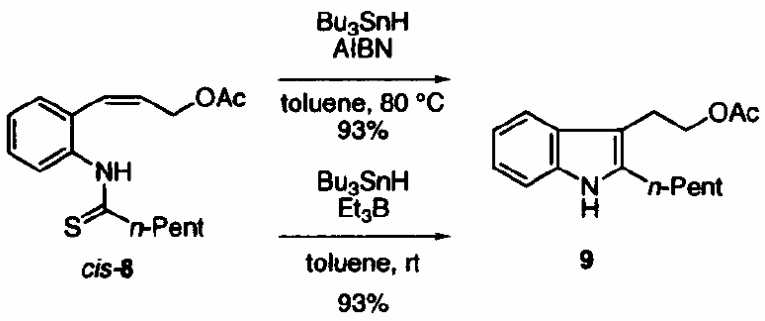
2,3-disubstituted indole



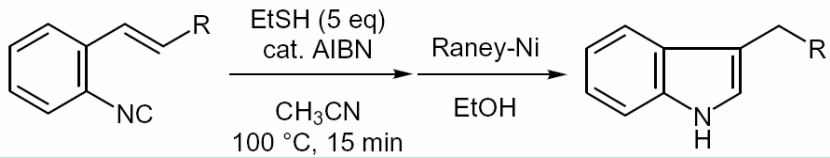
JACS 1999, 121, 3791

2,3-disubstituted indole

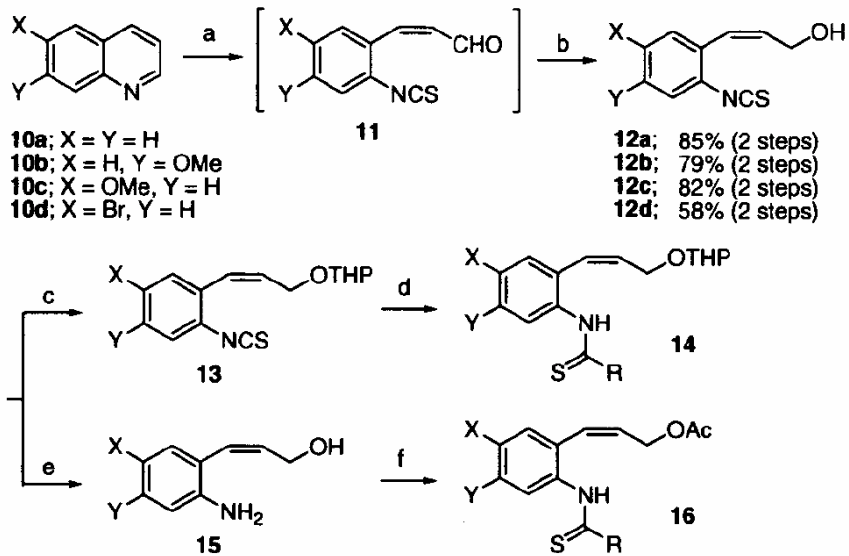
Part IV: Fukuyama Indole Synthesis



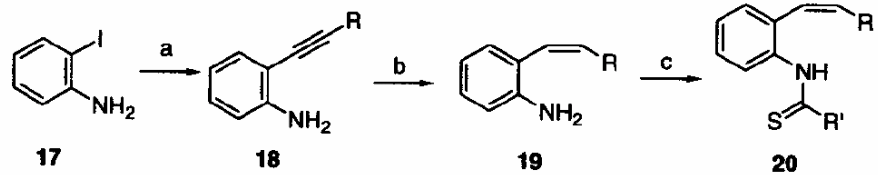
Tin free indole synthesis: Synlett 2001, 1403



2-alkenylthioanilides synthesis

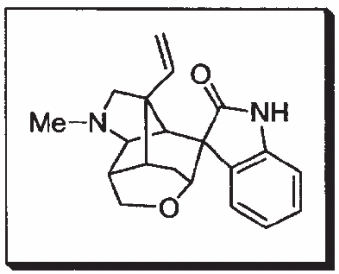


[a] (a)$CSCl_2$ (1.0 equiv), $BaCO_3$ (1.5 equiv), CH_2Cl_2/H_2O. (b) $NaBH_4$, CH_2Cl_2/MeOH. (c) DHP, CSA, CH_2Cl_2, 90%. (d) RMgX or Li enolate. (e) 5 M KOH, *t*-BuOH/H_2O, reflux, 80%. (f) RCOCl, $PhNEt_2$; Ac_2O, pyridine; Lawesson's reagent, toluene, 110 °C.



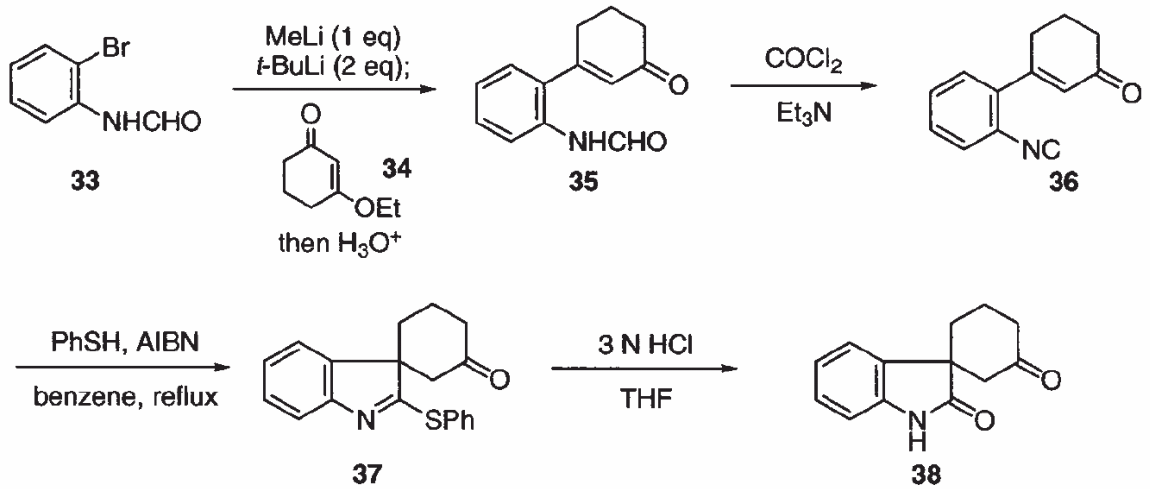
[a] (a) HC≡CR, $PdCl_2(PPh_3)_2$, CuI, Et_2NH. (b) Activated Zn, $BrCH_2$-CH_2Br, (CuBr, LiBr), EtOH. (c) 1. $CSCl_2$, $CaCO_3$. 2. RMgBr or 1. RCOCl, pyridine. 2. Lawesson's reagent, toluene, 110 °C.

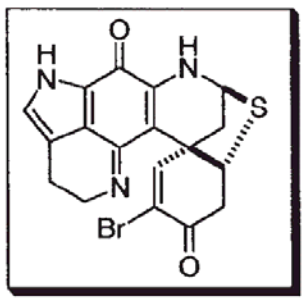
Application of Fukuyama Indole Synthesis



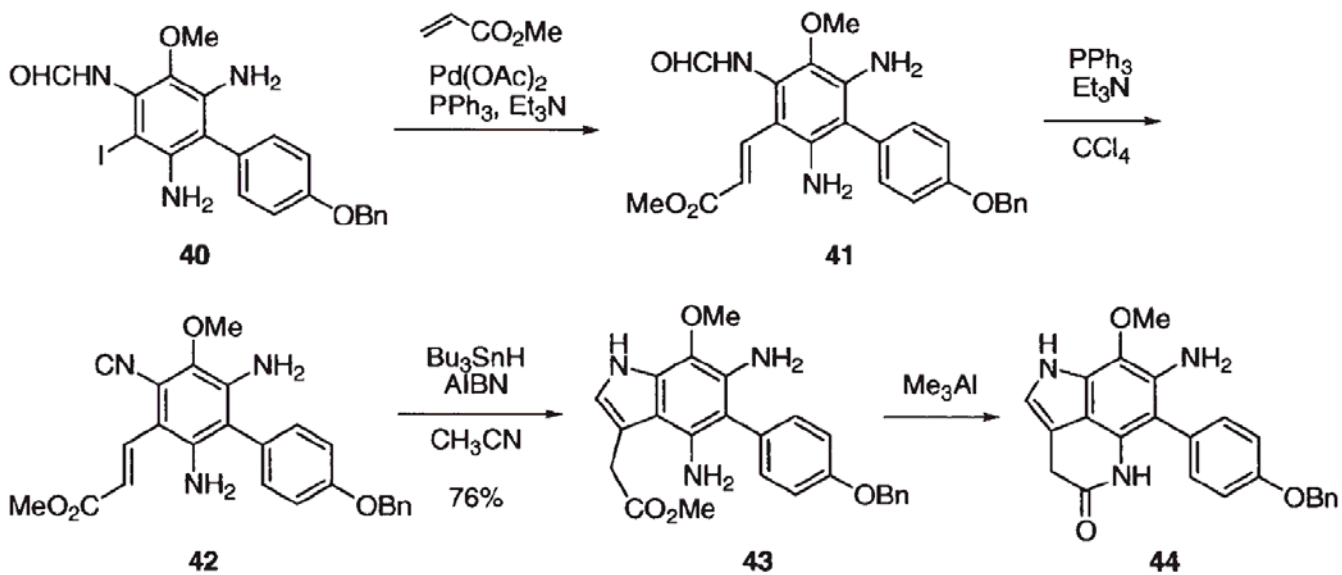
Gelsemine (**32**)

Spiroindolinone

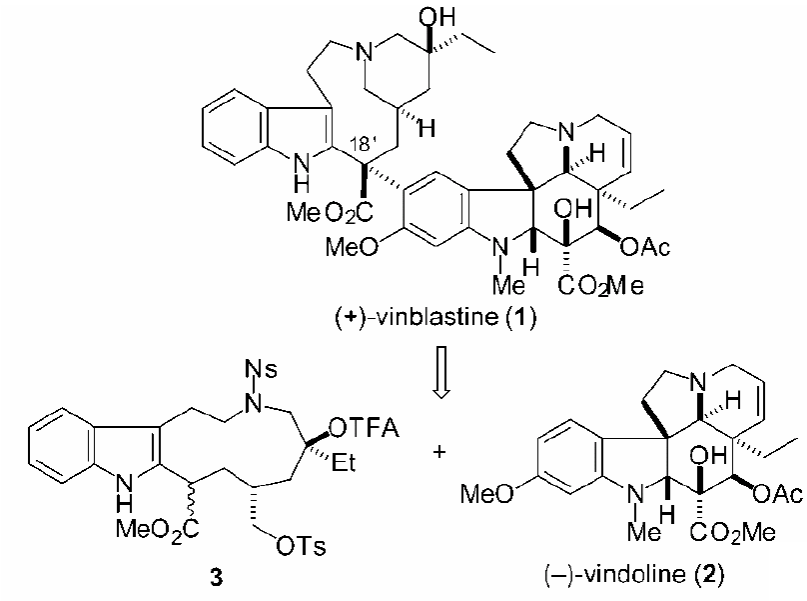


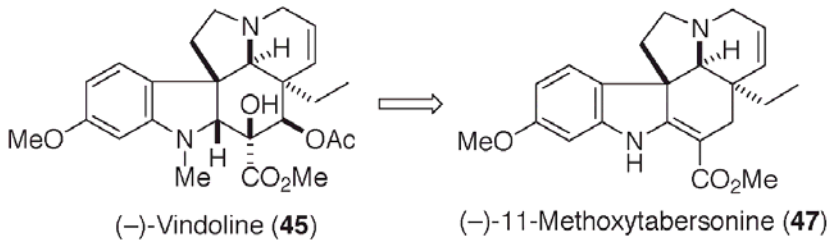


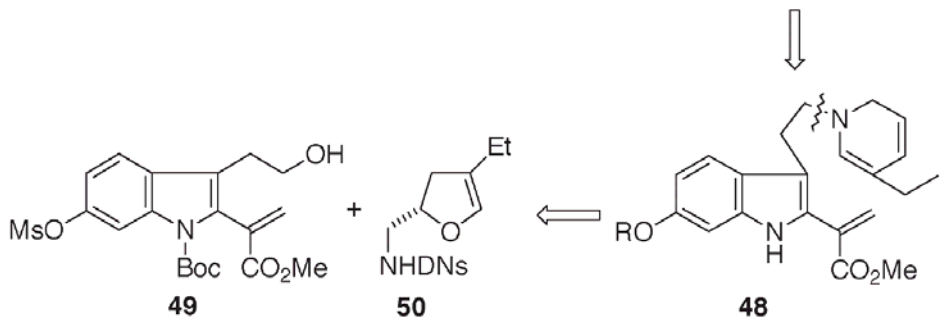
Discorhabdin A (**39**)



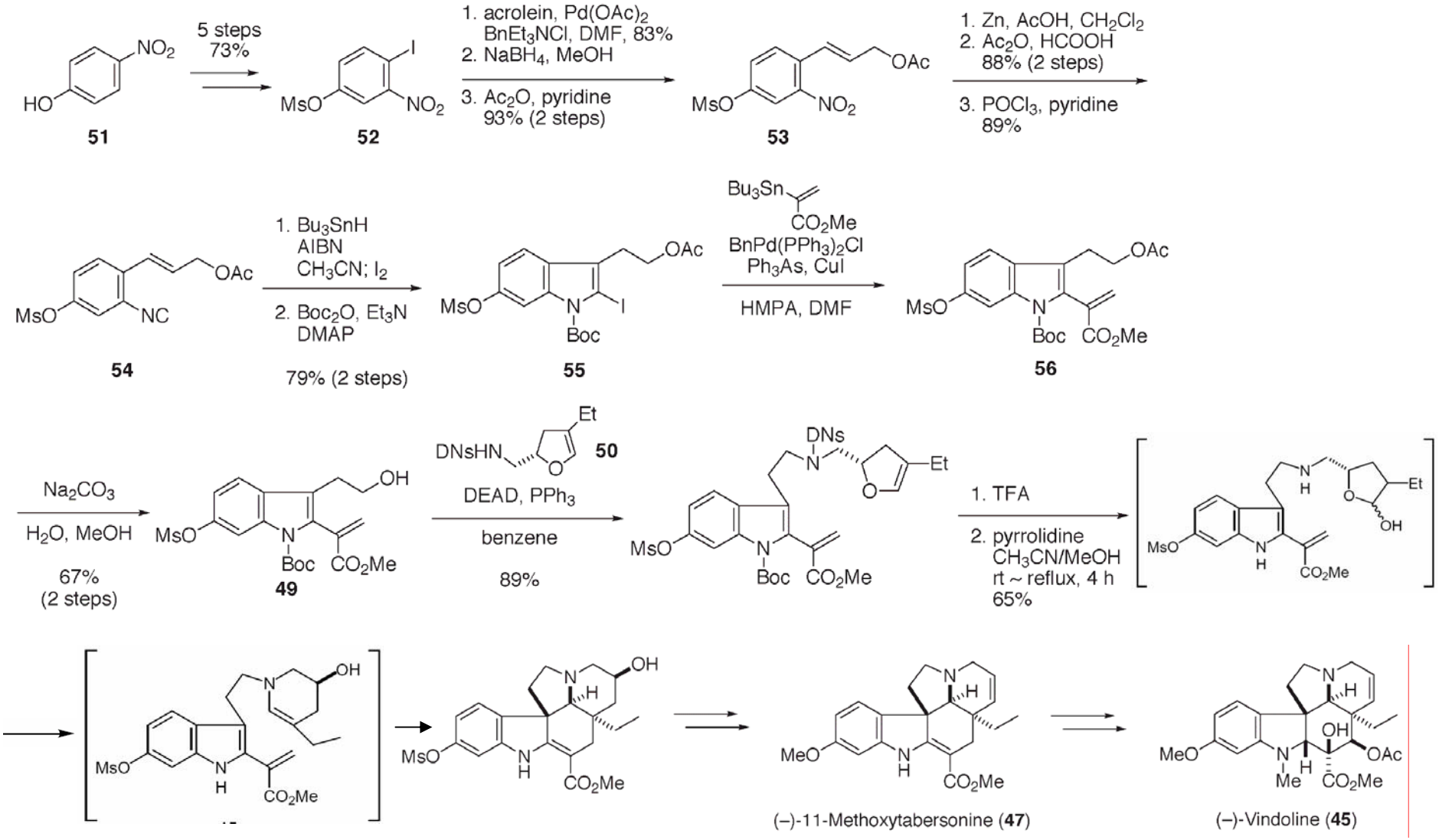
Part IV: Indole Synthesis—Application in Vinblastine synthesis



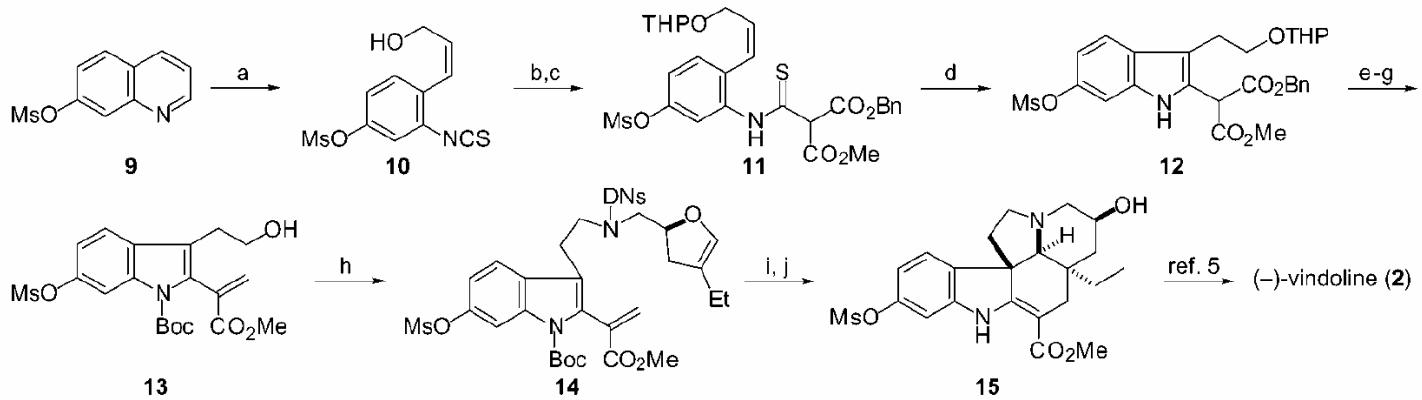




Part IV: Indole Synthesis—Application in Vindoline synthesis

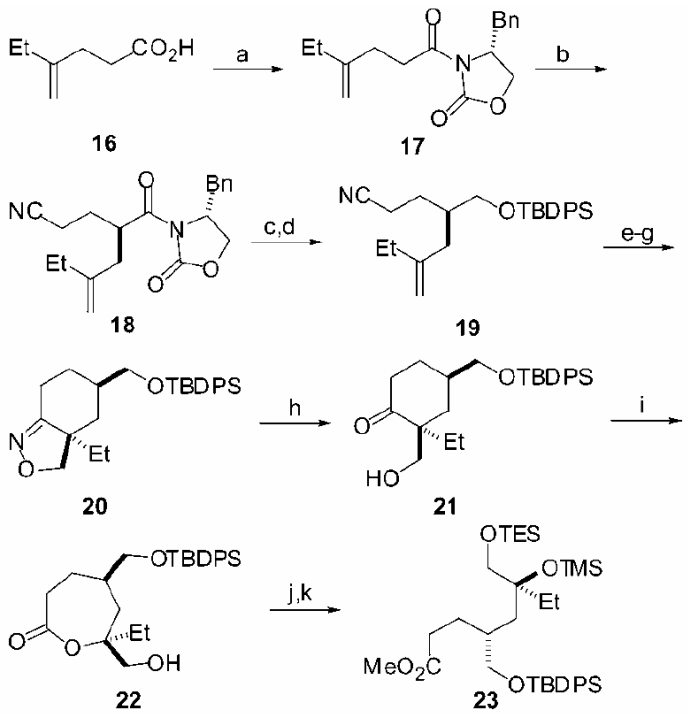


Part IV: Indole Synthesis—Application in Vindoline synthesis

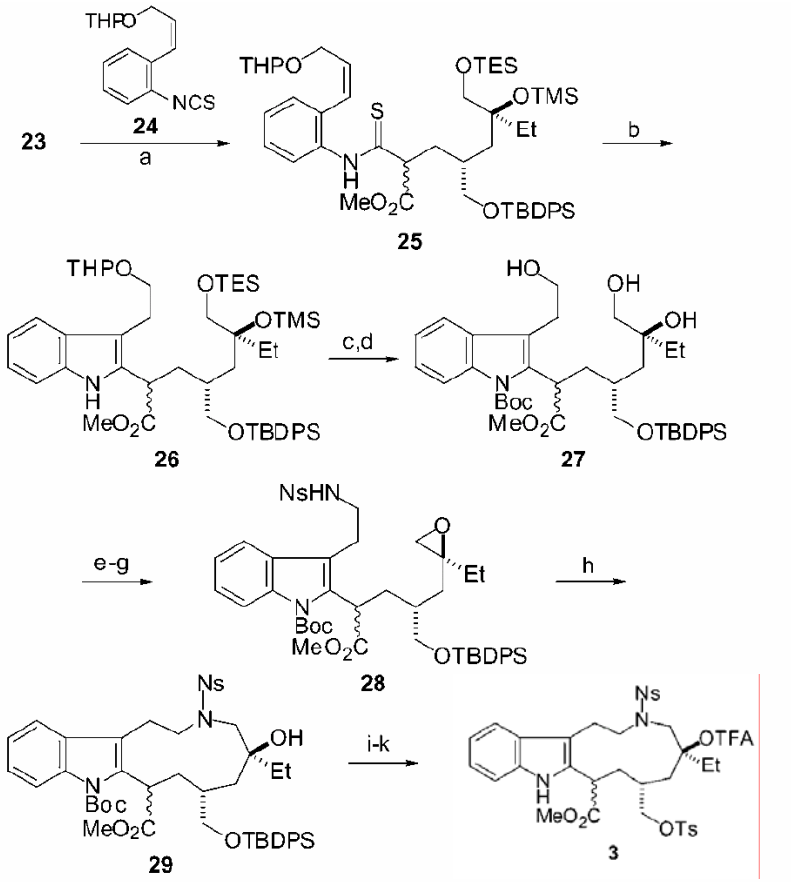


[a] Reagents and conditions: (a) thiophosgene, Na_2CO_3, THF−H_2O, 0 °C; $NaBH_4$, MeOH, 0 °C; (b) DHP, CSA, CH_2Cl_2, room temperture, 65% (2 steps); (c) benzyl methyl malonate, NaH, THF, 0 °C; (d) AIBN, Bu_3SnH, toluene, 110 °C; (e) Boc_2O, Et_3N, DMAP, CH_2Cl_2, room temperature, 60% (3 steps); (f) H_2, Pd/C, EtOH, room temperature; Me_2NH·HCl, HCHO, AcONa, AcOH-EtOH, room temperature, 72% (2 steps); (g) CSA, MeOH, room temperature, 99%; (h) **8**, DEAD, Ph_3P, benzene, 79%; (i) TFA, Me_2S, CH_2Cl_2, room temperature; (j) pyrrolidine, MeOH−CH_3CN, 0 °C to 50 °C, 73% (2 steps).

Part IV: Indole Synthesis—Application in Vinblastine synthesis

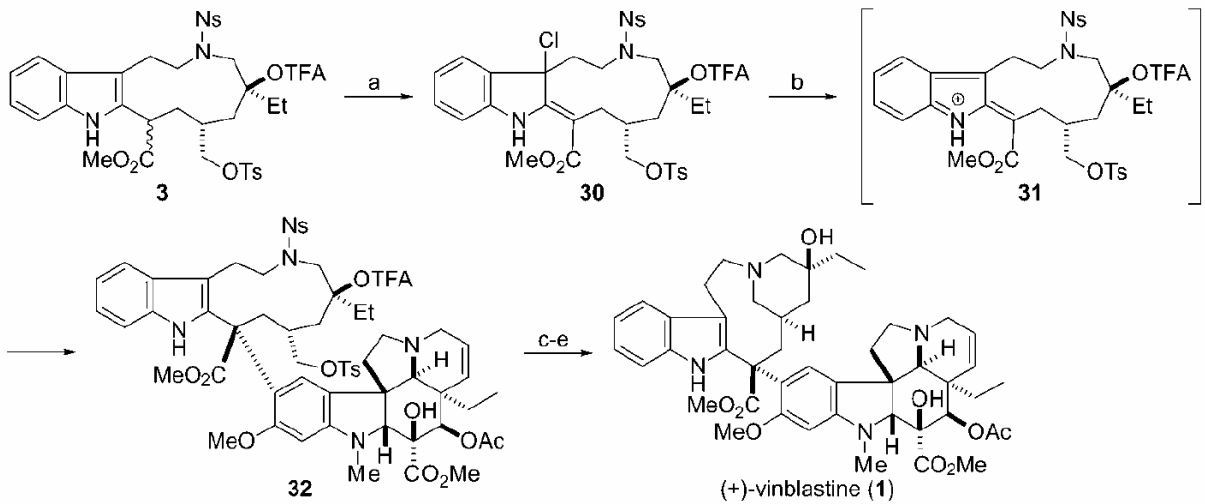


[a] Reagents and conditions: (a) PivCl, Et_3N, Et_2O, 0 °C; *n*-BuLi, (*R*)-4-benzyl-2-oxazolidinone, THF, −78 °C, 89%; (b) (*i*-PrO)$TiCl_3$, *i*-Pr_2NEt, acrylonitrile, CH_2Cl_2, 0 °C, 82%; (c) $NaBH_4$, THF−H_2O, room temperature, 92%; (d) TBDPSCl, imidazole, DMF, room temperature, 92%; (e) DIBAL, CH_2Cl_2, −78 °C; (f) $H_2NOH{\cdot}HCl$, NaOAc, EtOH, room temperature; (g) NaClO aqueous, CH_2Cl_2, room temperature, 59% (3 steps); (h) Zn, AcOH, 66%; (i) *m*CPBA, AcOH, room temperature; (j) K_2CO_3, MeOH, room temperature, 80% (2 steps); (k) TESCl, imidazole, DMF, room temperature; TMSCl, room temperature, 92%.

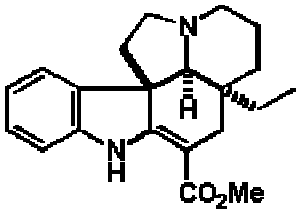


[a] Reagents and conditions: (a) LDA, THF, −78 °C; **24**, −78 to 0 °C, 76%; (b) Bu_3SnH, Et_3B, THF, room temperature, 67%; (c) Boc_2O, Et_3N, DMAP, CH_2Cl_2, room temperature, 87%; (d) AcOH−H_2O (95:5), 80 °C, 71%; (e) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, room temperature, 84%; (f) $NaHCO_3$, DMF, 80 °C, 90%; (g) $NsNH_2$, DEAD, Ph_3P, toluene, room temperature, 88%; (h) K_2CO_3, DMF, 90 °C, 82%; (i) TFA, CH_2Cl_2, room temperature, 85%; (j) TsCl, $Me_2N(CH_2)_3NMe_2$, CH_3CN-toluene, room temperature, 88%; (k) TFAA, pyridine, CH_2Cl_2, room temperature, 90%.

Part IV: Indole Synthesis—Application in Vinblastine synthesis

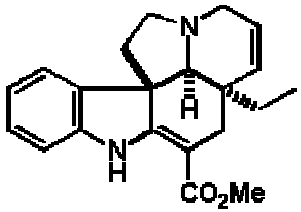


[a] Reagents and conditions: (a) *t*-BuOCl, CH_2Cl_2, 0 °C; (b) (−)-vindoline (**2**), TFA, CH_2Cl_2, 0 °C to room temperature, 97%; (c) Et_3N, MeOH, room temperature, quantitative; (d) $HSCH_2CH_2OH$, DBU, CH_3CN, room temperature, 76%; (e) $NaHCO_3$, *i*-PrOH−H_2O, room temperature, 66%.

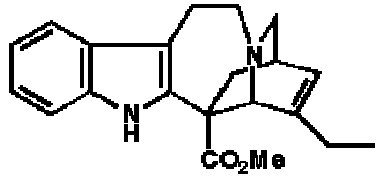


(±)-Vincadifformine

TL **1999**, 1519

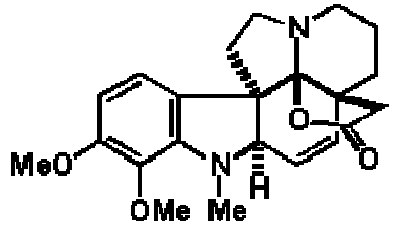


(-)-Tabersonine



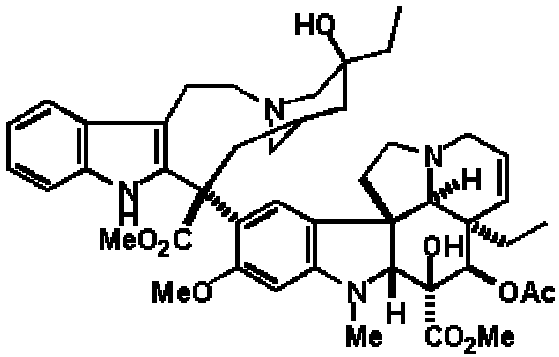
(±)-Catharanthine

OL **1999**, 973



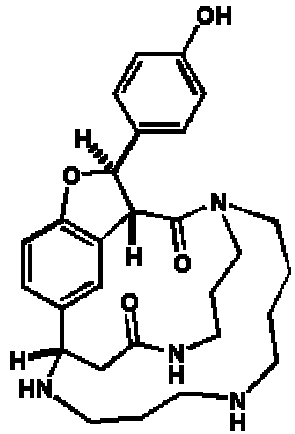
Aspidophytine

OL **2003**, 1891



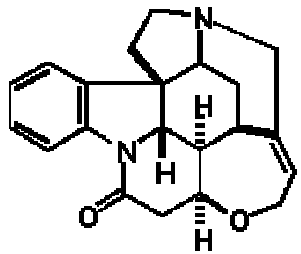
Vinblastine

JACC **2002**, 2137



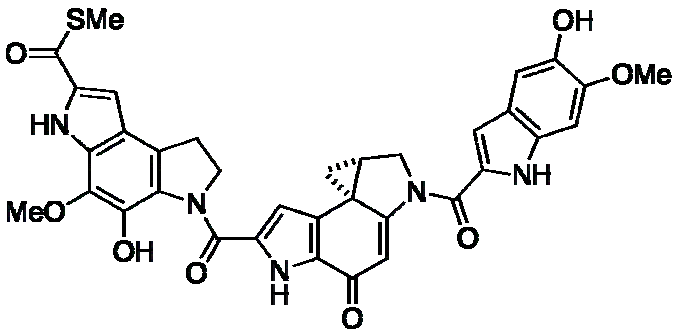
Ephedradine A

JACS **2003**, 8112



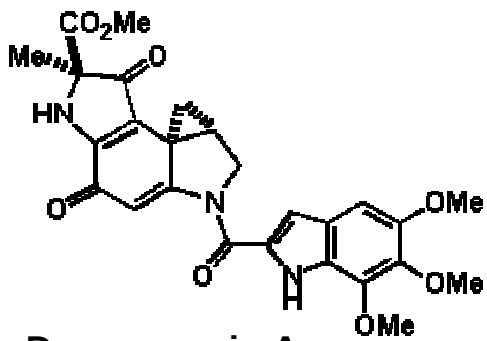
Strychnine

JACS **2004**, 10246



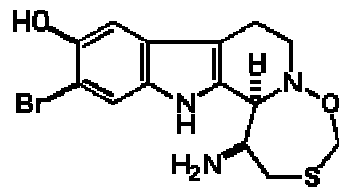
Yatakemycin

JACS **2006**, 7136



Duocarmycin A

JACS **2003**, 6630



Eudistomin C

JACS **2005**, 15038

Outline of Fukuyama's research

Part I: Synthesis of Piperazine-derived Natural Product

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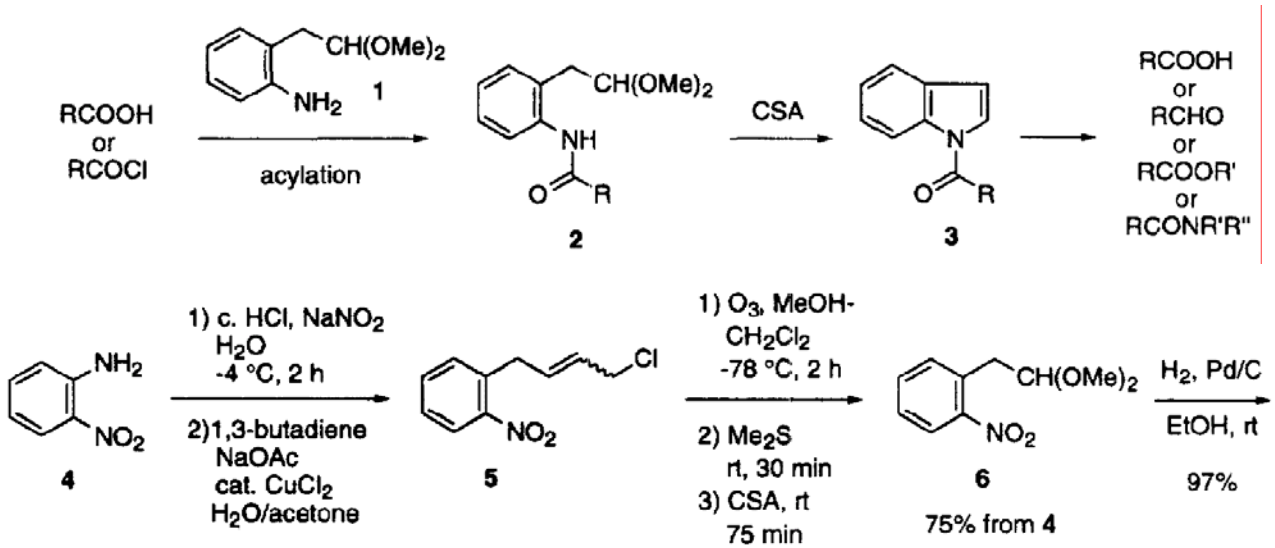
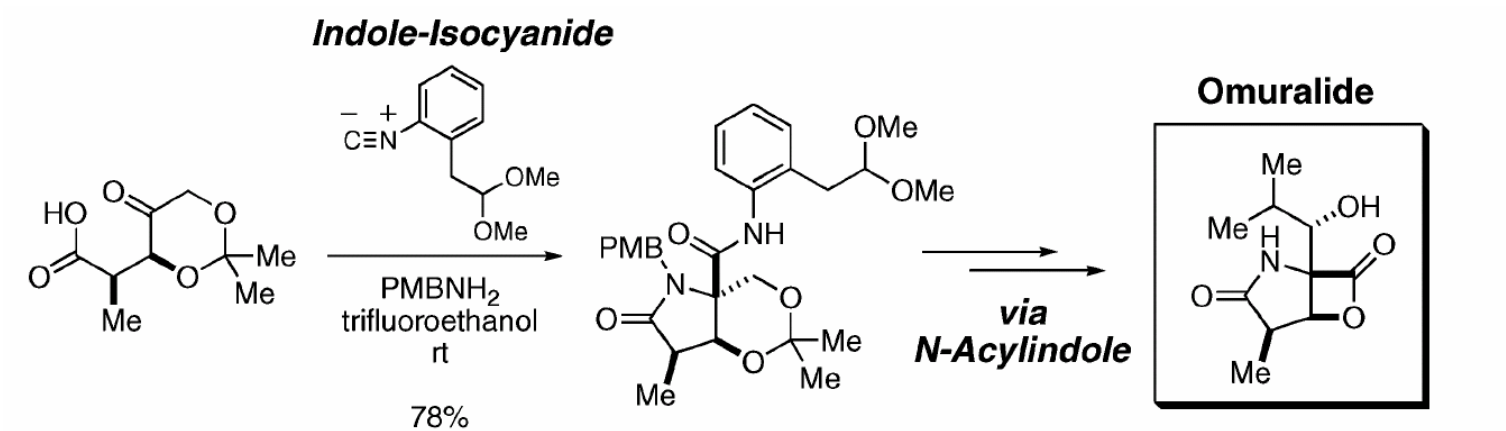
Part IV: Fukuyama Indole Synthesis

Part V: Others

2-(2-aminophenyl)-acetaldehyde Dimethyl Acetal

Protection of Carboxylic acids TL 1998, 39, 71

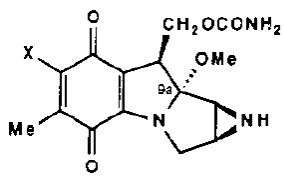




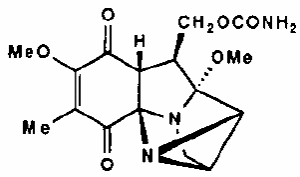
Yoshihisha Kobayashi et al OL 2007, ASAP

Total synthesis Mitomycin C

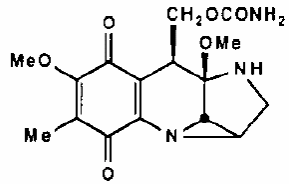
JACS 1987, 7881 and 1989, 8303
TL 1986, 6299



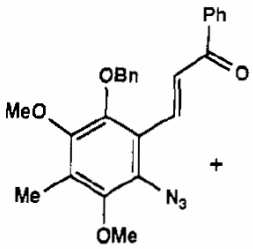
1: X = NH_2 Mitomycin C
2: X = OMe Mitomycin A



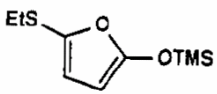
3: Albomitomycin A



4: Isomitomycin A

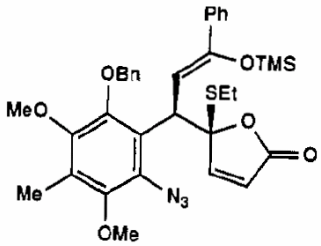


3



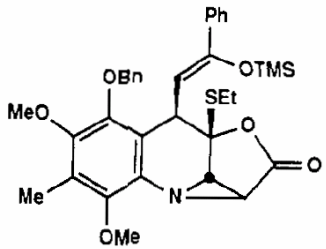
4

SnCl4
a
95%



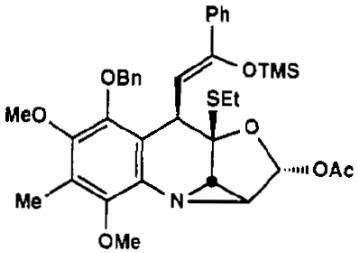
5

Tol. reflux
b
86%



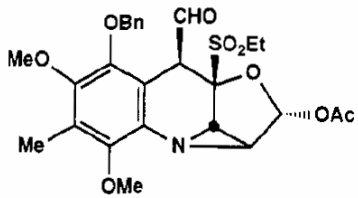
6

DIBAL-H;
Ac2O
c, d
99%



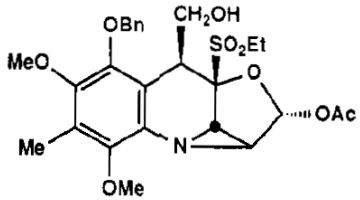
7

RuO2, NaIO4
e
84%



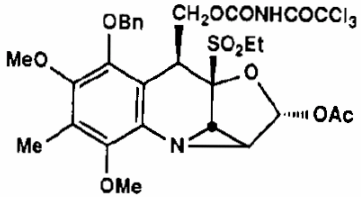
8

NaBH4
f
97%



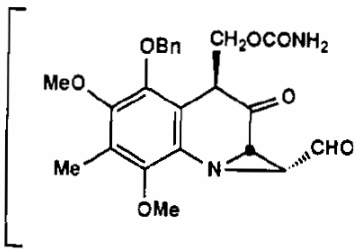
9

CCl3CONCO
g

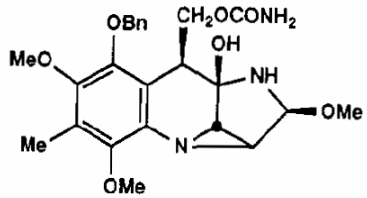


10

h
NH3, MeOH



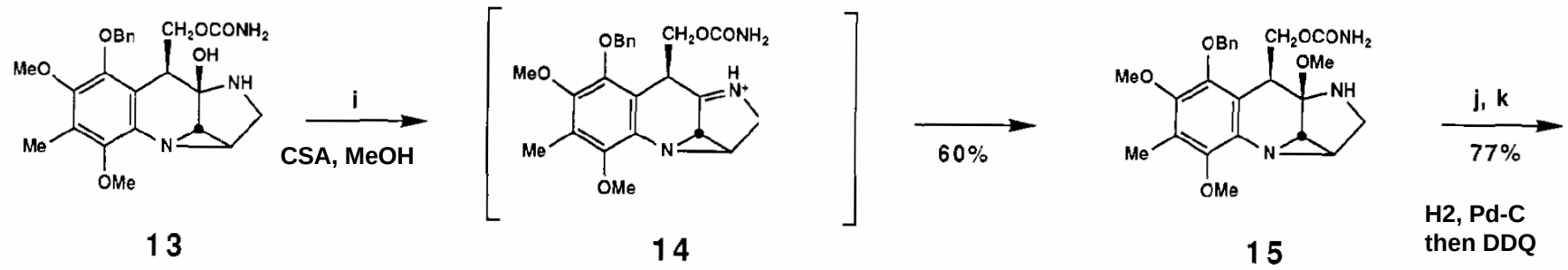
11

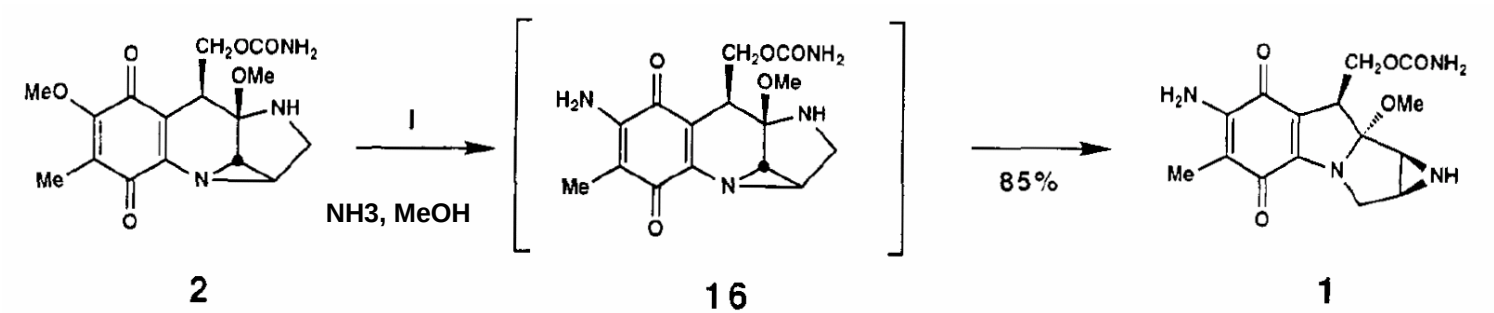


12

NaBH4
61%

Total synthesis Mitomycin C

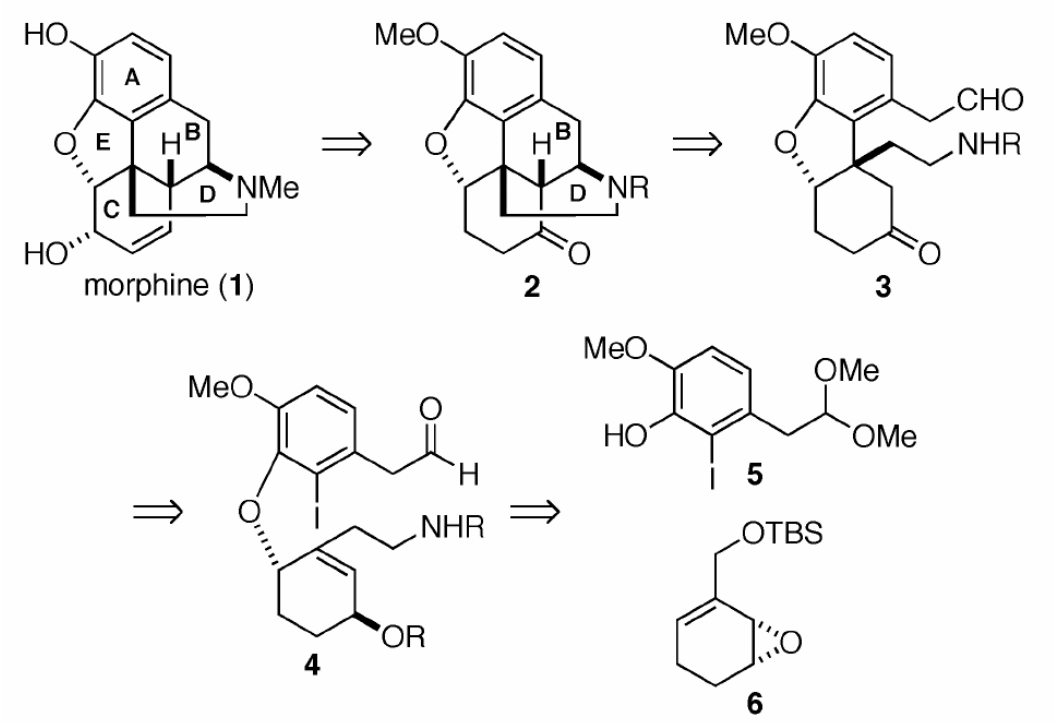




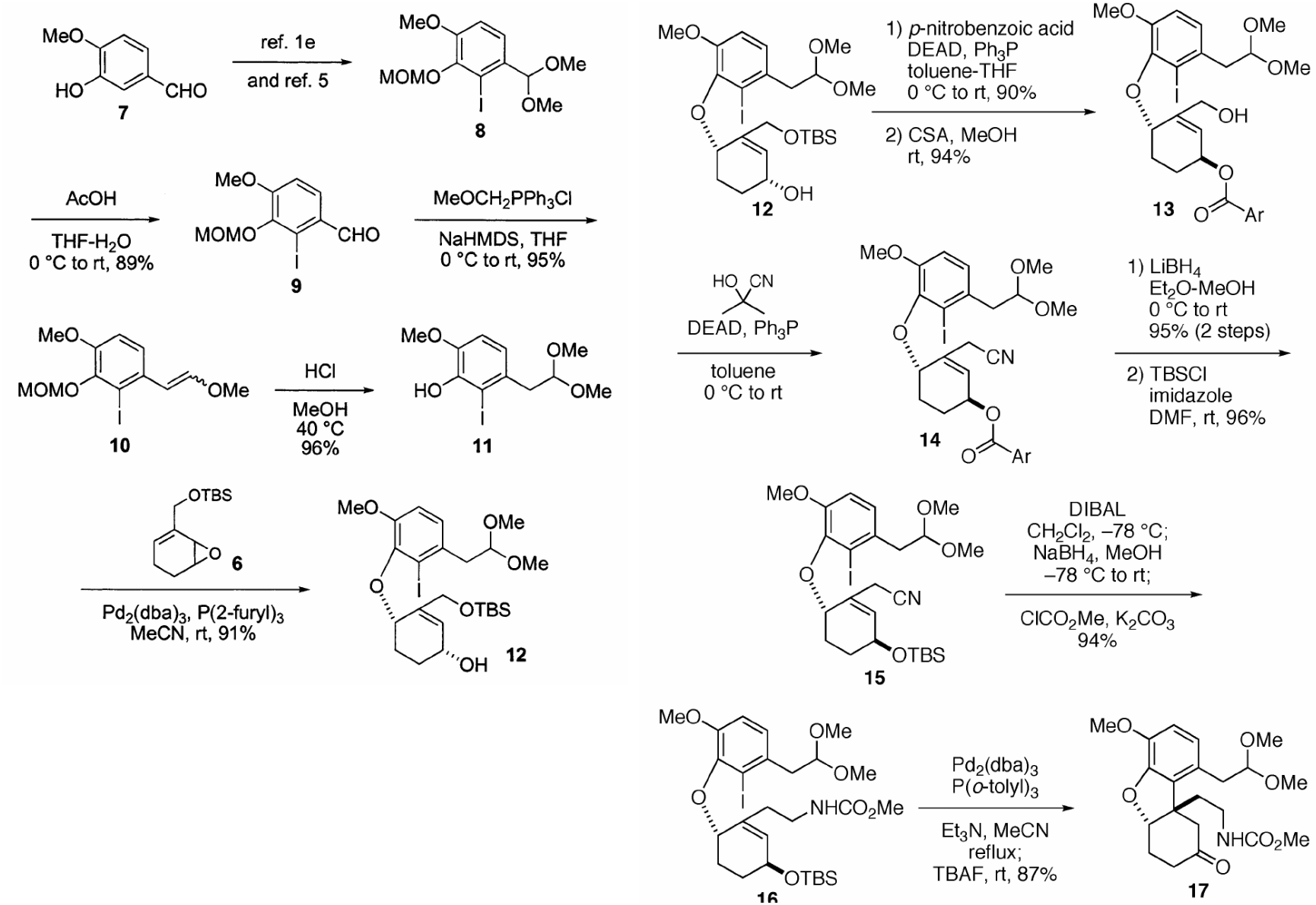
Mitomycin C

Total synthesis Morphine

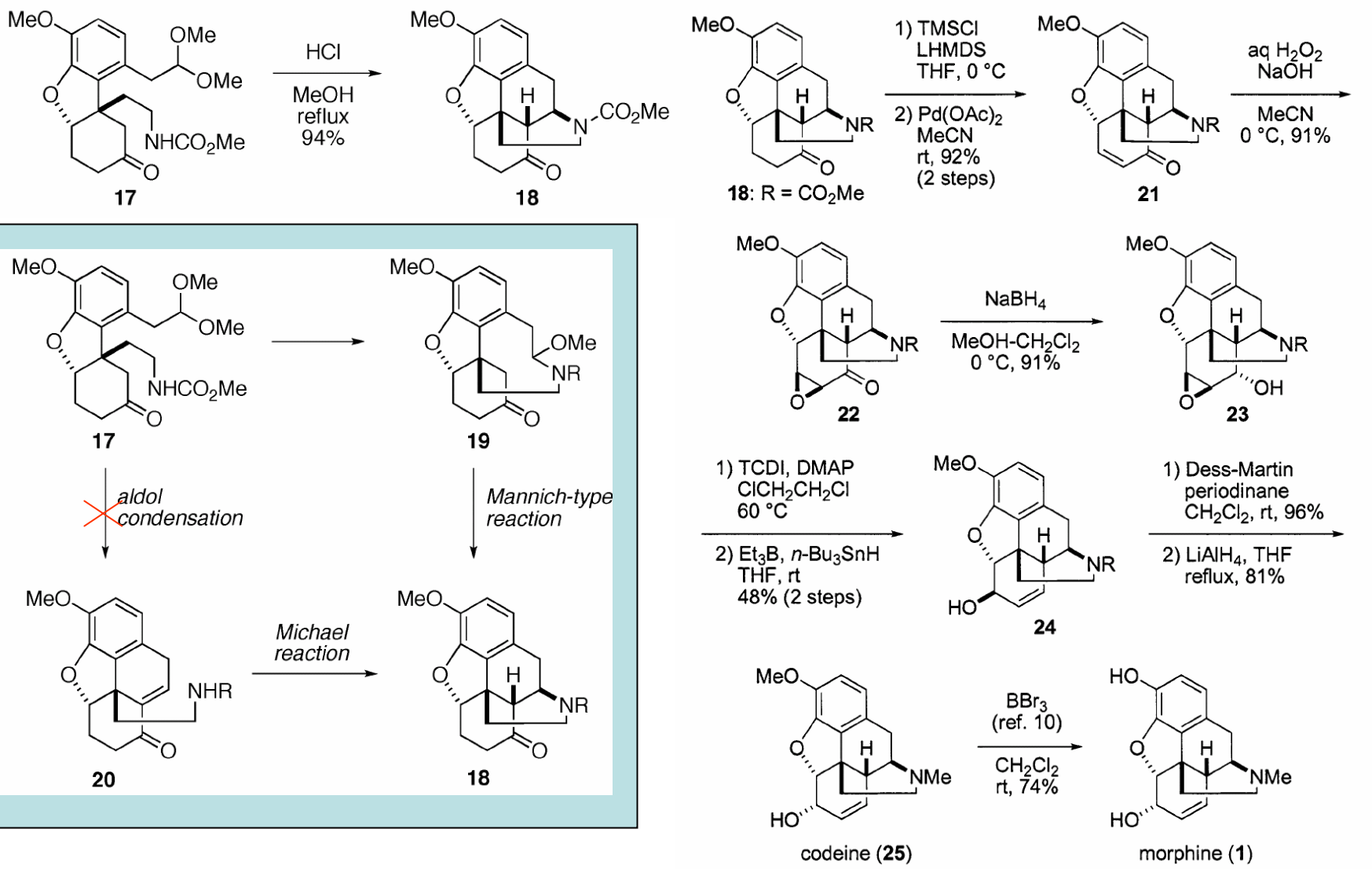
OL 2006, 5311



Total synthesis Morphine

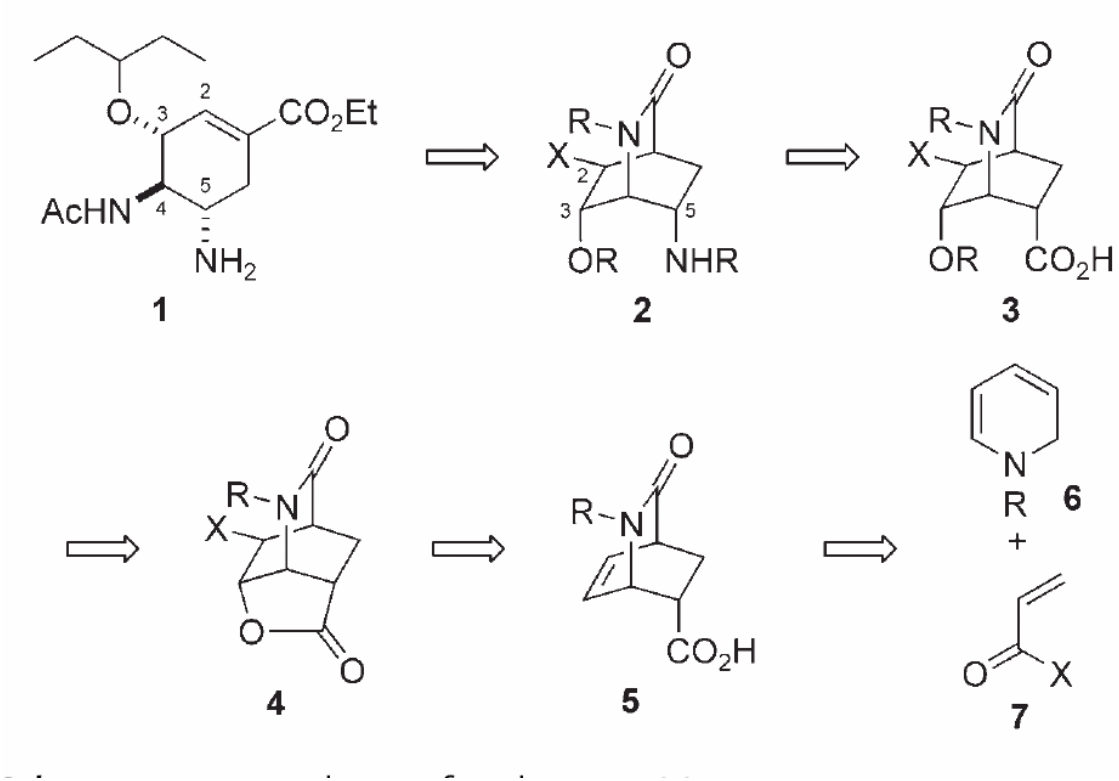


Total synthesis Morphine

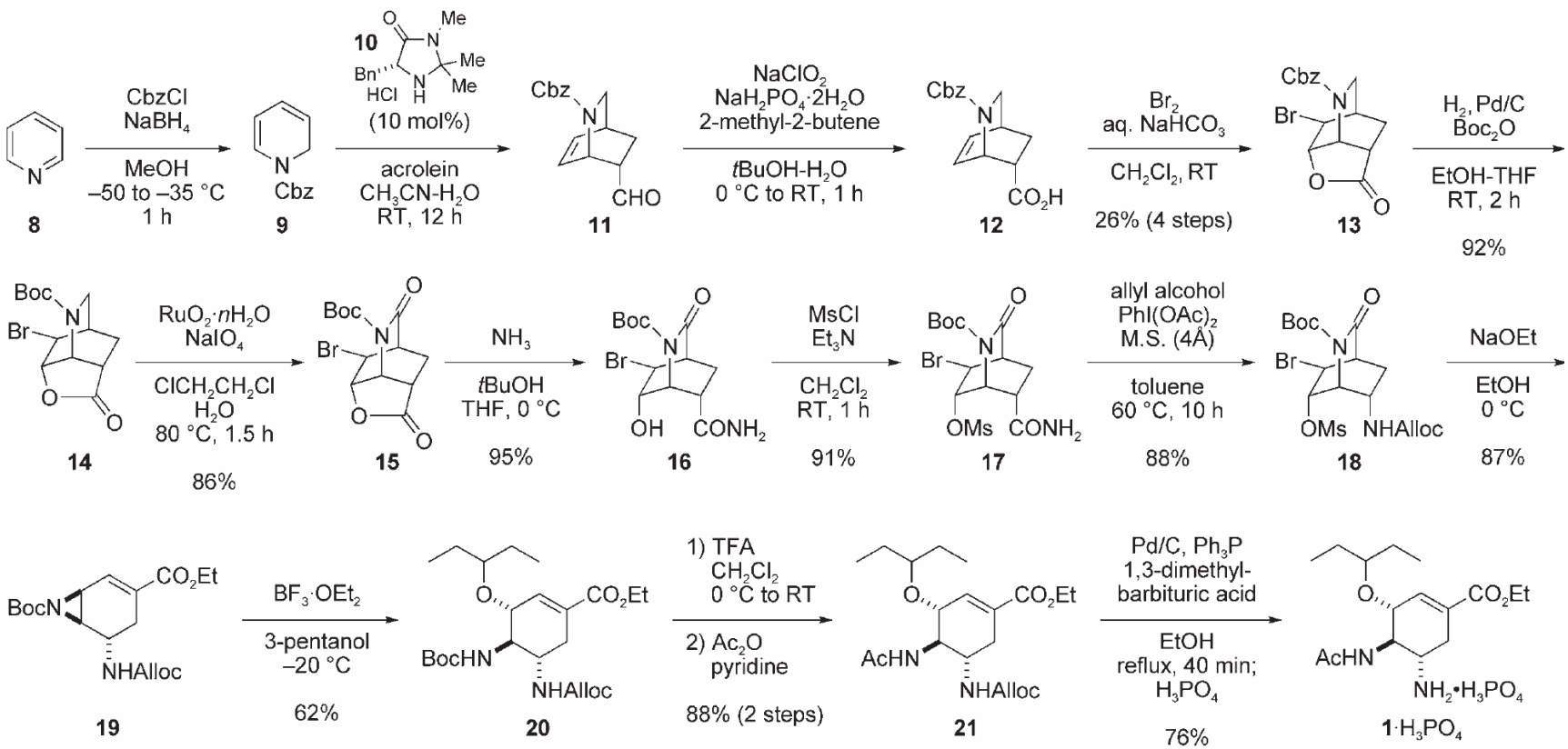


Total synthesis Tamiflu

ACIEE 2007, 5734



Total synthesis Tamiflu



Scheme 2. Synthesis of oseltamivir phosphate (**1**·H_3PO_4). Alloc = allyloxycarbonyl, Bn = benzyl, Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, Ms = methanesulfonyl, M.S. = molecular sieves, TFA = trifluoroacetic acid.