2009/10/21
Furutachi Makoto (M2)

Total synthesis of (+)-Haplophytine

contents

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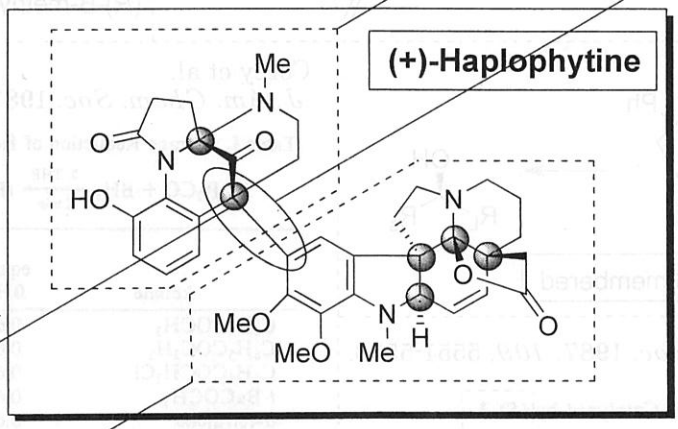
1. Introduction

>>the left-half segment possesses a bicyclo[3.3.1]skeleton that includes bridged ketone and aminal functionalities.

>>highly congested C-C bond adjoining the two distinct halves of the molecule



>>anticockroach / insecticidal powder
>>ten rings
>>six stereocenters (five of which are tetrasubstituted)

>>connected by a quaternary carbon center

>>the right-half segment is a hexacyclic aspidosperma class of alkaloid, named **aspidophytine**

History

1) Haplophytine was first isolated by Snyder and co-workers in 1952.

2) Yates, Cava, and co-workers determined its structure by X-ray crystallography in 1973.

3) Total synthesis of Aspidophytine

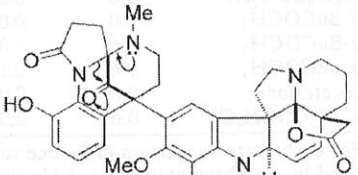
- E. J. Corey ---------- 1999 (*J. Am. Chem. Soc.*)
- T. Fukuyama & H. Tokuyama --- 2003 (*Org. Lett.*)
- A. Padwa ---------- 2006 (*Org. Lett.*)
- J. P. Marino ---------- 2006 (*Tetrahedron Lett.*)
- K. C. Nicolaou ---------- 2007 (*Angew. Chem. Int. Ed.*)
- T. Fukuyama & H. Tokuyama --- 2007(*Synlett*)
- K. C. Nicolaou ---------- 2008 (*J. Am. Chem. Soc.*)

4) Total synthesis of (+)-Haplophytine

- T. Fukuyama & H. Tokuyama --- 2009 (*Angew. Chem. Int. Ed.*)
- K. C. Nicolaou ---------- 2009 (*Angew. Chem. Int. Ed.*)

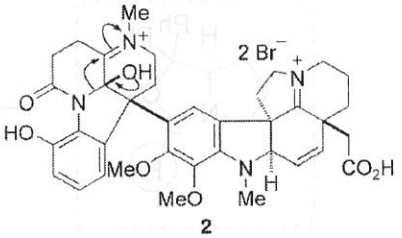
Now(2009)

Structure of (+)-haplophytine (1) and its rearrangement.



(+)-haplophytine (1)

aq $NaHCO_3$ ↑ ↓ HBr

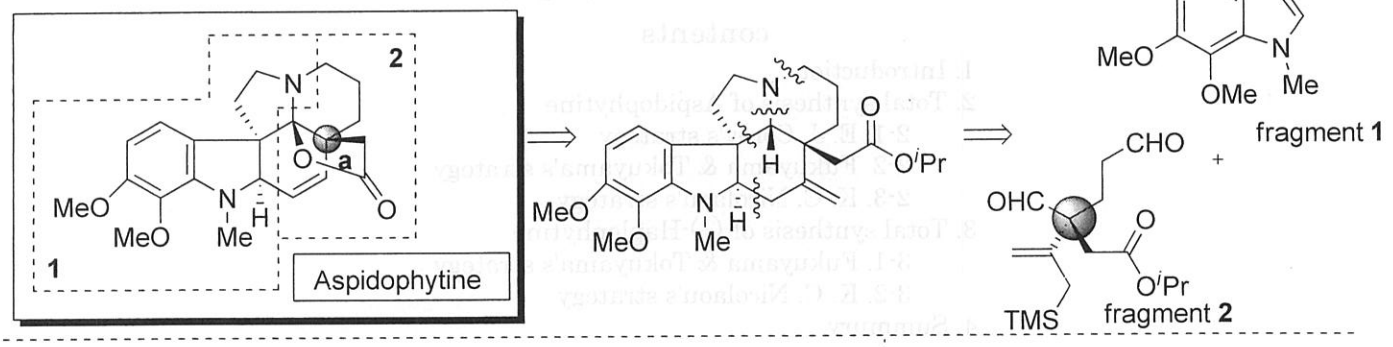


2

2. Total synthesis of Aspidophytine

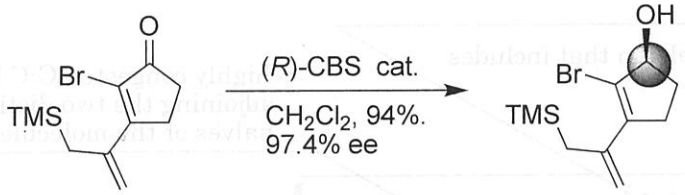
2-1. E. J. Corey's strategy

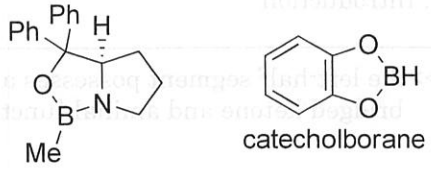
J. Am. Chem. Soc. **1999**, *121*, 6771.



Construction of chiral center a

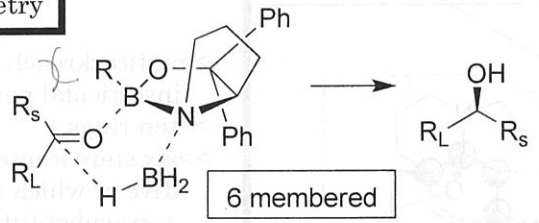
CBS reduction





(*R*)-B-methyloxazaborolidine

asymmetry



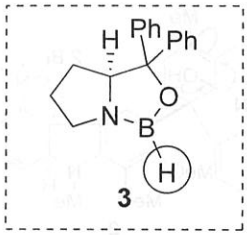
Corey et al. *J. Am. Chem. Soc.* 1987, *109*, 5551-5553.

Table I. Borane Reduction of Ketones Catalyzed by (*S*)-**3**

$$2R_1R_2CO + BH_3 \xrightarrow[1\text{ min, }25\text{ °C}]{3,\ THF} (R_1R_2CH\text{-}O)_2BH \rightarrow R_1R_2CHOH$$

ketone	equiv BH_3	equiv **3**	config of prod.[a] (% ee)[b]
$C_6H_5COCH_3$	2	1	*R* (97)
$C_6H_5COCH_3$	1	0.1	*R* (97)[d]
$C_6H_5COCH_3$	1.2	0.025	*R* (95)
$C_6H_5COCH_3$	1.2	0.005	*R* (80)
$C_6H_5COC_2H_5$	1.2	0.05	*R* (86)
$C_6H_5COC_2H_5$	1	0.05	*R* (88)
$C_6H_5COC_2H_5$	0.6	0.05	*R* (90)[d]
t-$BuCOCH_3$	1.0	0.05	*R* (81)
t-$BuCOCH_3$	0.6	0.05	*R* (88)
t-$BuCOCH_3$	0.6	0.1	*R* (92)[c,d]
α-tetralone	0.6	0.05	*R* (89)[d]
$C_6H_5COCH_2Cl$	0.6	0.05	*S* (97)[d]

[a] For each entry conversion of ketone to alcohol was >99.7% as determined by gas chromatography. [b] Absolute configuration determined by isolation and measurement of rotation; ee determined by gas chromatographic analysis.[5] [c] Borane added over 5 min to a mixture of ketone and **3** at −10 °C. [d] Entries refer to optimal conditions for that substrate.



air and moisture sensitive

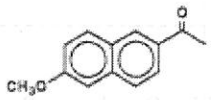
improved !!

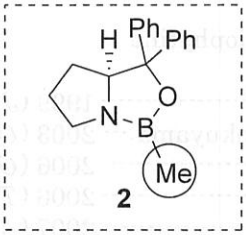
Corey et al.

J. Am. Chem. Soc. 1987, *109*, 7925-7926.

Table I. Borane Reduction of Ketones Catalyzed by (*S*)-**2**

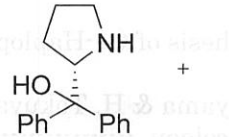
$$2R_1R_2CO + BH_3 \xrightarrow[2\text{ min}]{2,\ THF} (R_1R_2CH\text{-}O)_2BH \rightarrow R_1R_2CHOH$$

ketone	equiv BH_3	equiv **2**	reaction temp, °C	config of product[a] (% ee)[b]
$C_6H_5COCH_3$	0.6	0.1	2	*R* (96.5)
$C_6H_5COC_2H_5$	0.6	0.1	−10	*R* (96.7)
$C_6H_5COCH_2Cl$	0.6	0.1	32	*S* (95.3)
t-$BuCOCH_3$	0.6	0.1	−10	*R* (97.3)
α-tetralone	0.6	0.1	−10	*R* (83.3)
α-tetralone	0.6	0.25	−10	*R* (86.0)
c-$C_6H_{11}COCH_3$	0.6	0.1	−10	*R* (84)
	0.6	0.1	23	*R* (91)[c,d,e]
	0.6	0.1	23	*R* (97.6)[f]
$C_6H_5CO(CH_2)_2CO_2CH_3$	0.6	0.1	0	*R* (94)[f,g]
$C_6H_5CO(CH_2)_3CO_2CH_3$	0.6	0.1	0	*R* (96.7)[f,g]



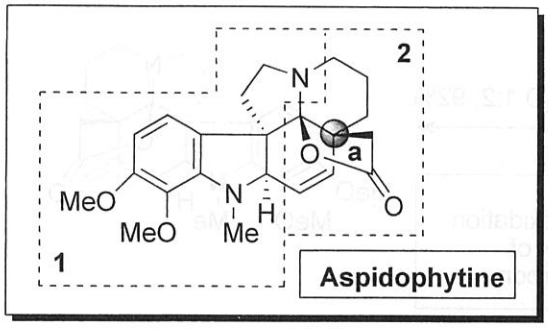
air and moisture tolerance

much more easily prepared than **3**

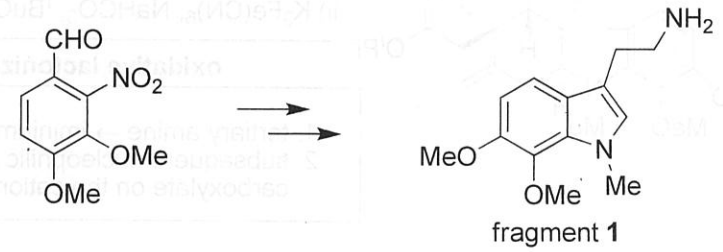


(S)-(-)-2-(diphenylhydroxymethyl) pyrrolidine

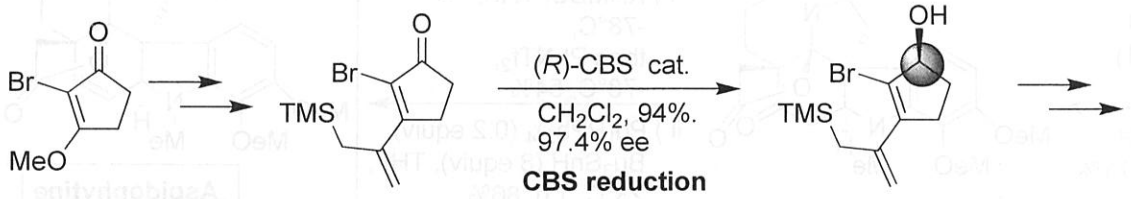
methylboronic acid

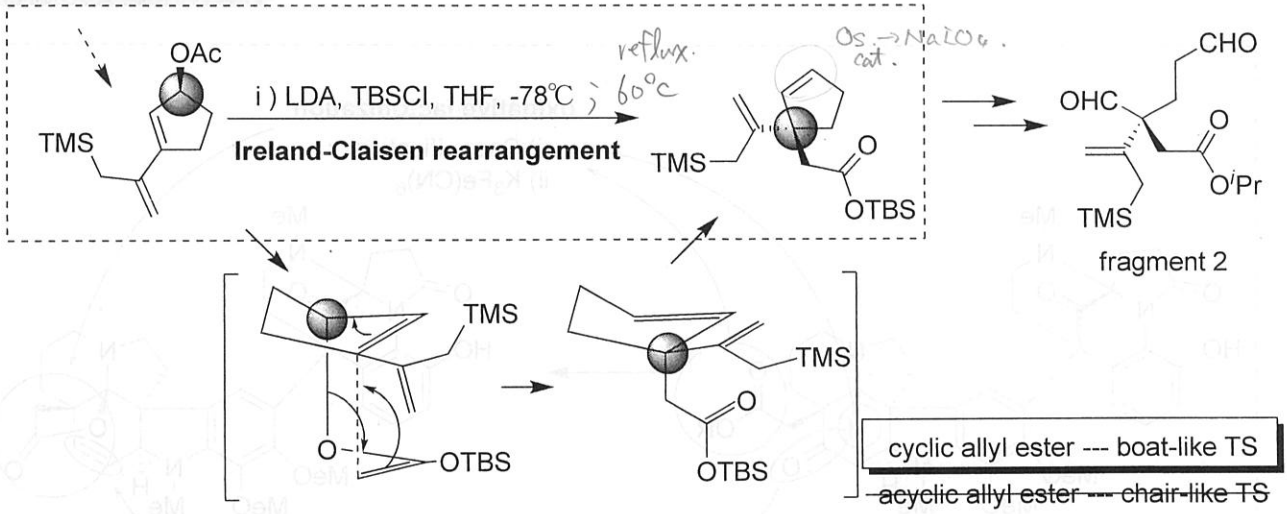


Construction of fragment 1



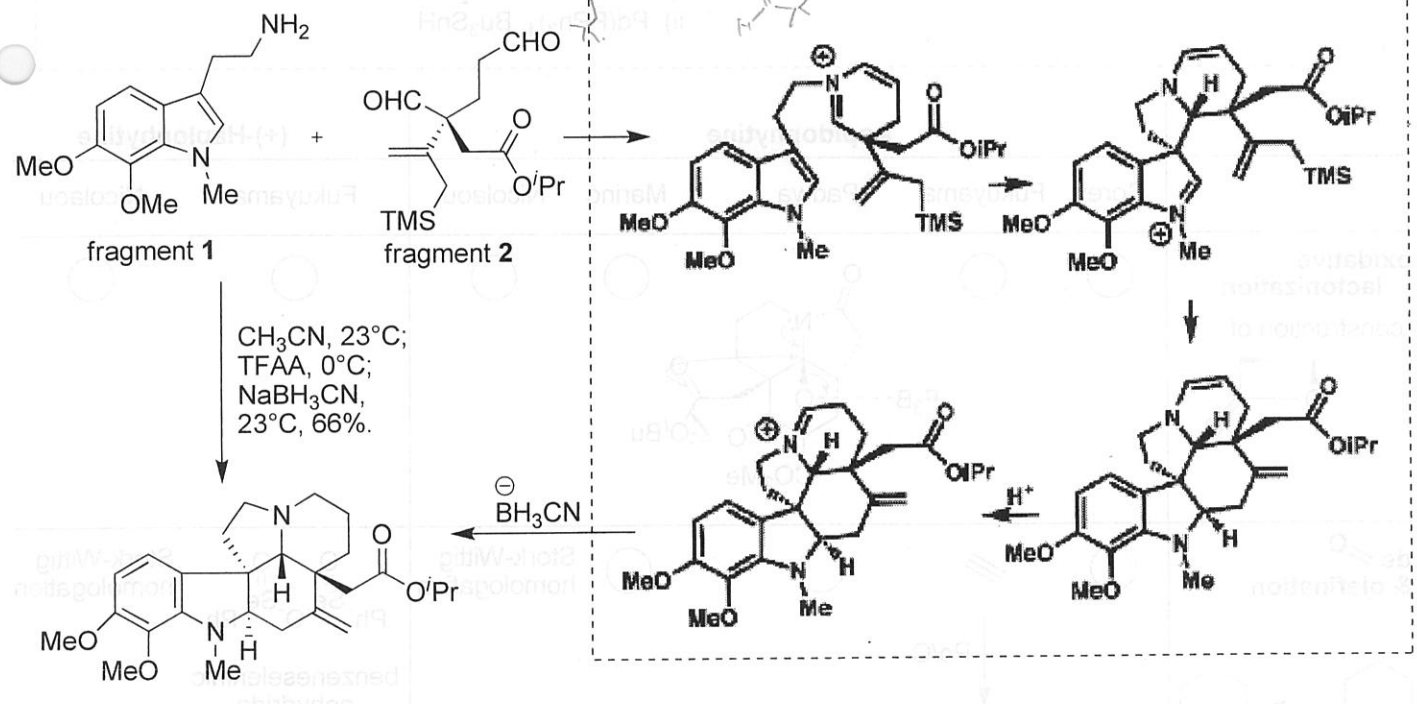
Construction of fragment **2** containing chiral center a



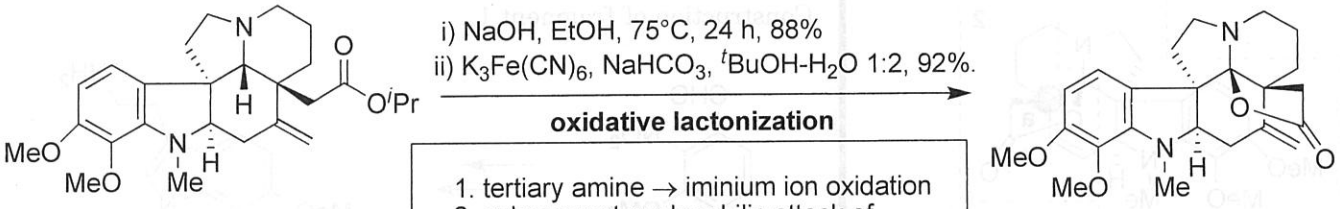


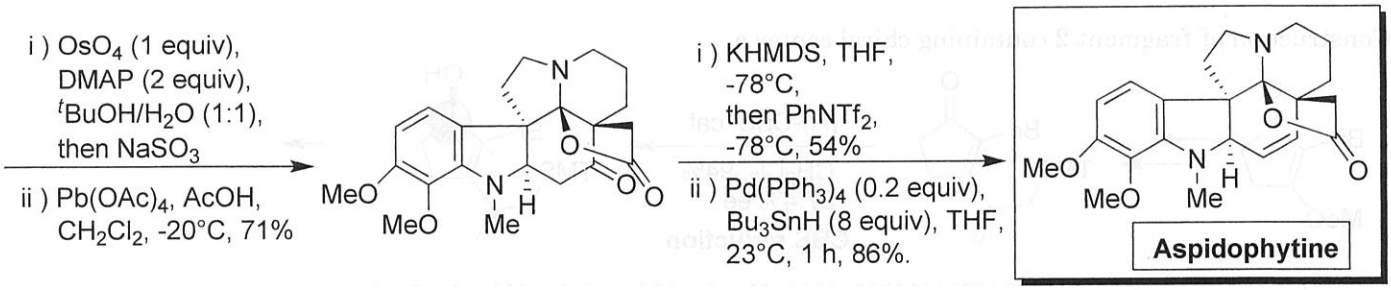
1+2 formation

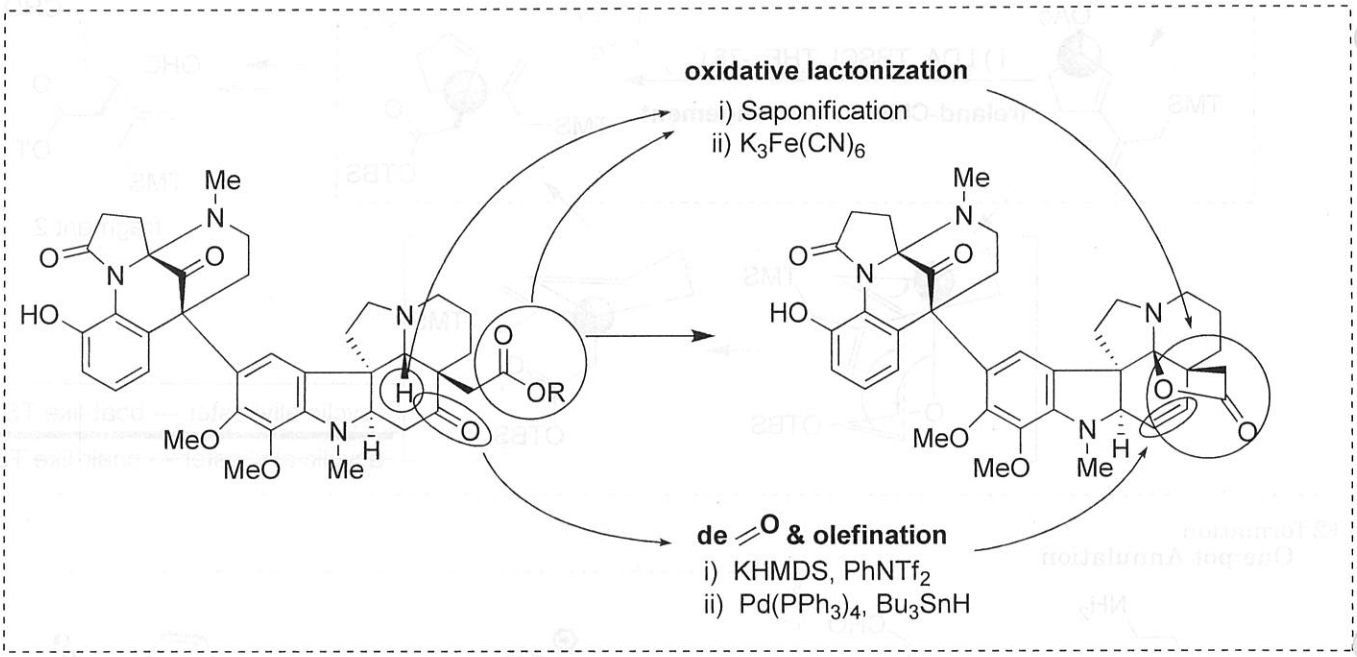
One-pot Annulation

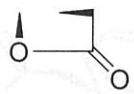
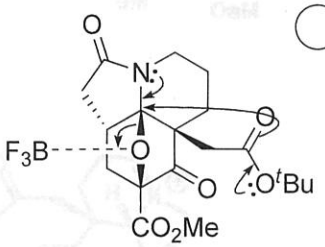
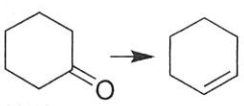
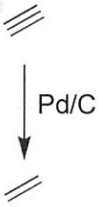
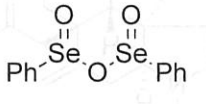


Completion of the total synthesis of **Aspidophytine**



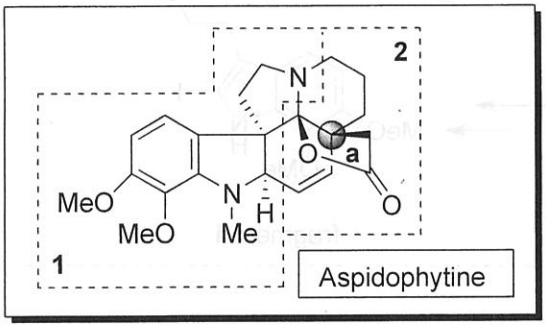


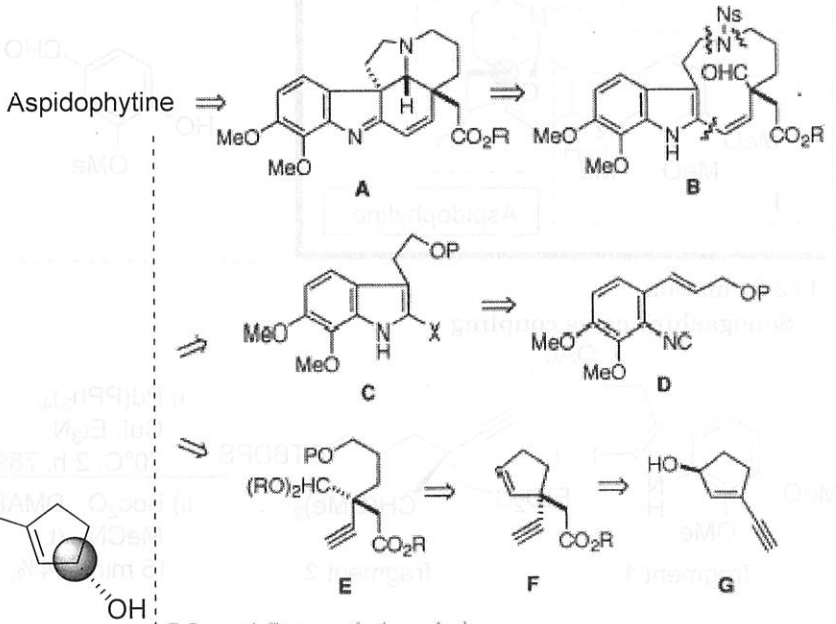


	Aspidophytine					(+)-Haplophytine	
	Corey	Fukuyama	Padwa	Marino	Nicolaou	Fukuyama	Nicolaou
oxidative lactonization construction of 	○	○		○	○	○	○
de =O & olefination 	○		○	○	Stork-Wittig homologation	 benzeneseleninic anhydride	Stork-Wittig homologation

2-2. Fukuyama & Tokuyama's strategy

Org. Lett. **2003**, *5*, 1891. & *Tetrahedron* **2003**, 59, 8571-8587.

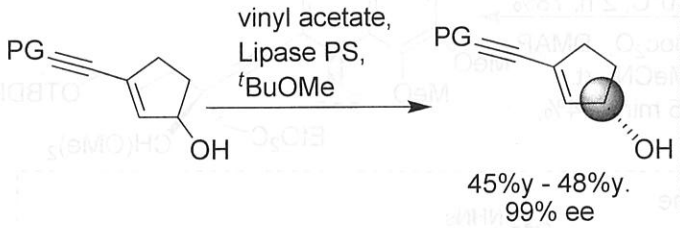




Scheme 1. Retrosynthetic analysis.

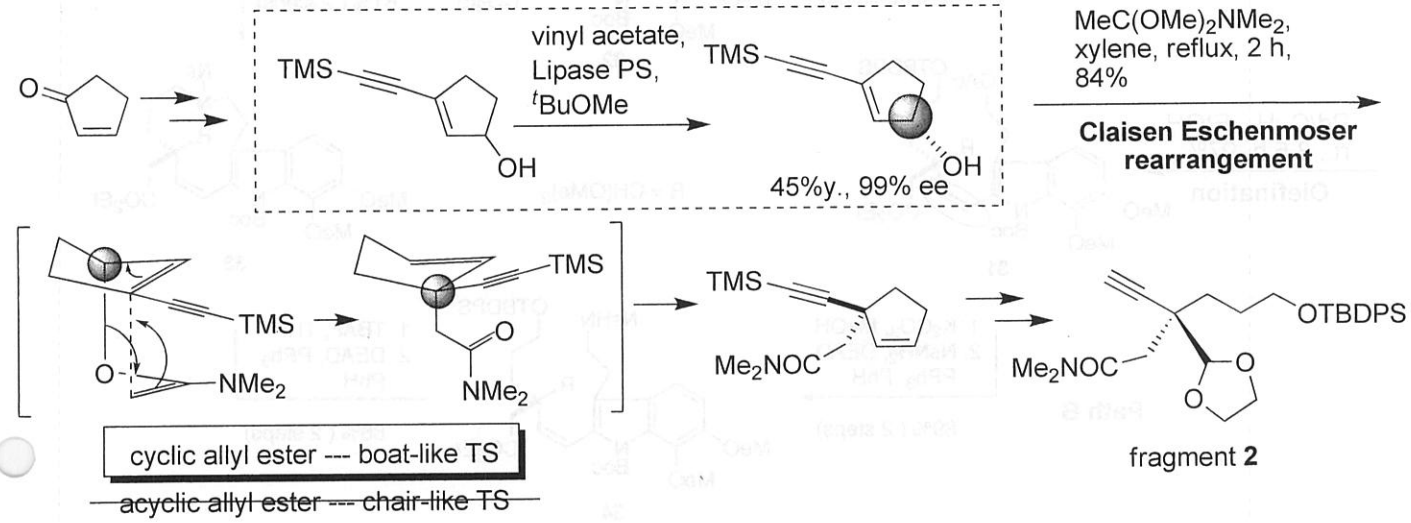
Construction of chiral center a

enzyme (kinetic resolution)

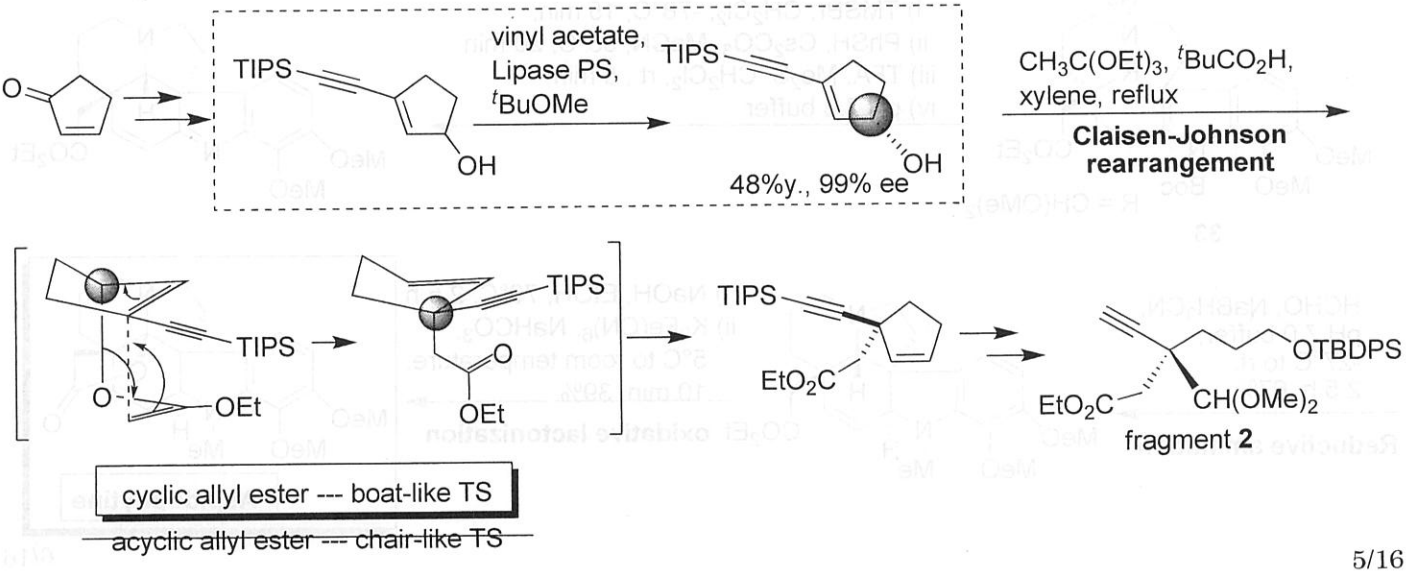


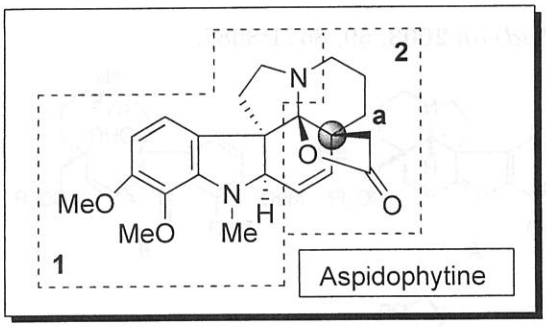
construction of **2** & Construction of chiral center a

First generation total synthesis

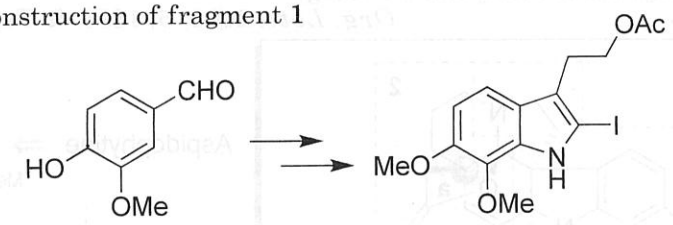


A second generation total synthesis by improved route





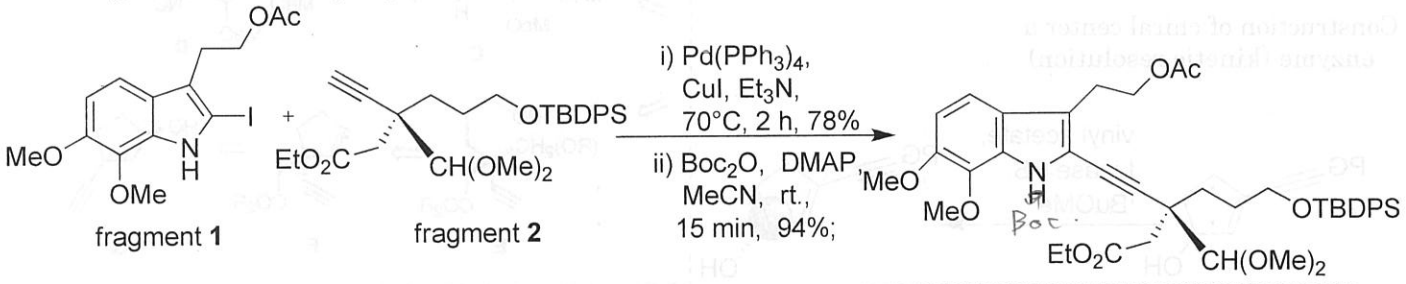
Construction of fragment 1



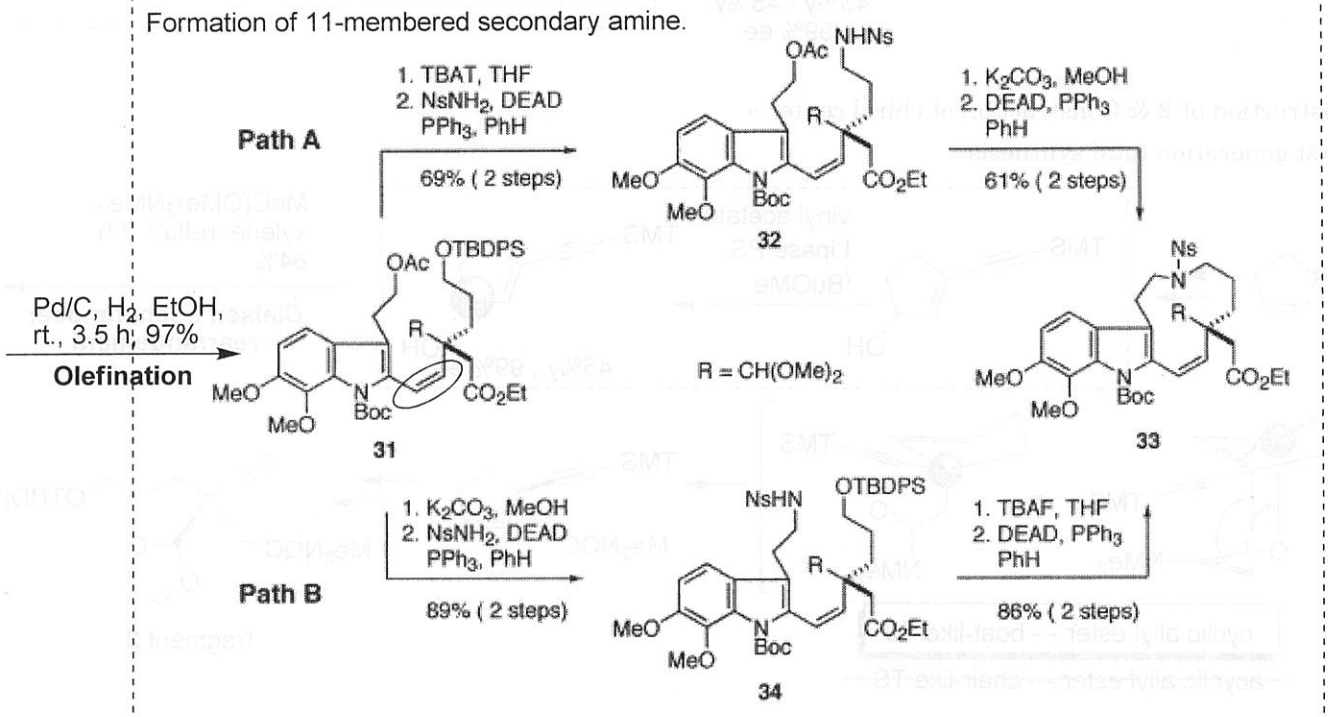
fragment **1**

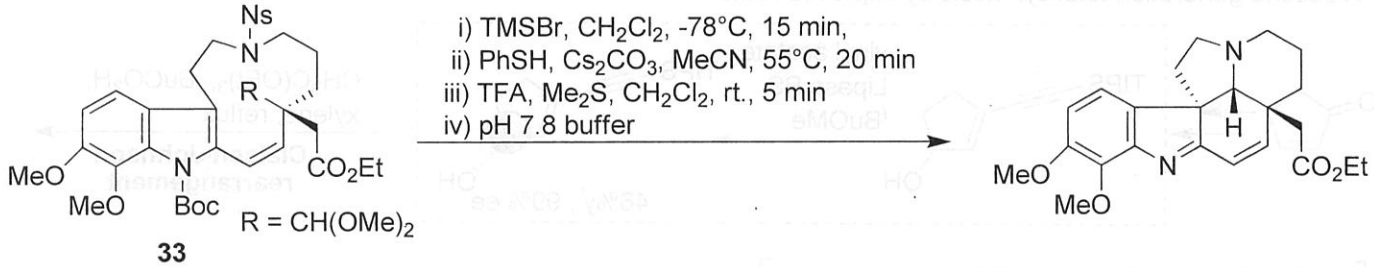
1+2 formation

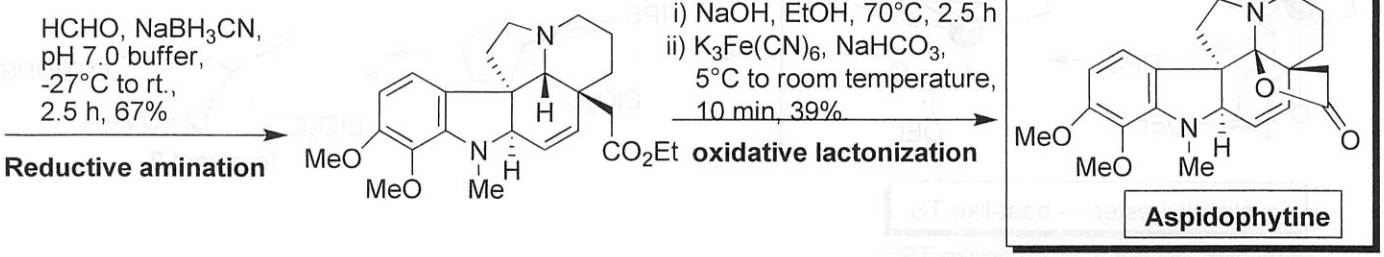
Sonogashira cross coupling



Formation of 11-membered secondary amine.

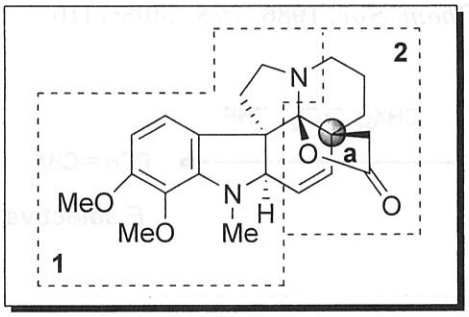




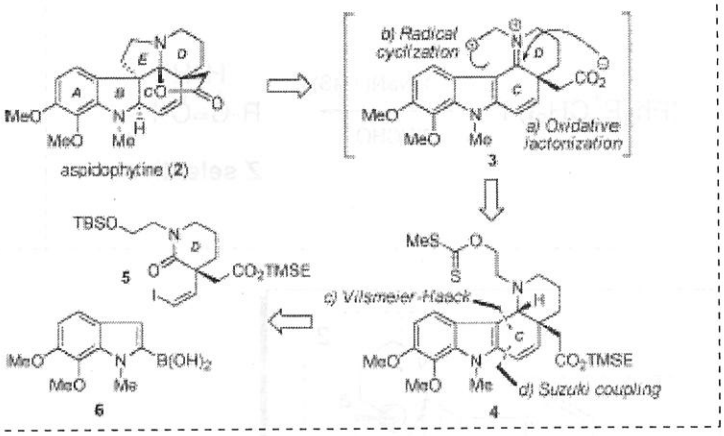


2-5. K. C. Nicolaou's strategy

J. Am. Chem. Soc. **2008**, *130*, 14942.

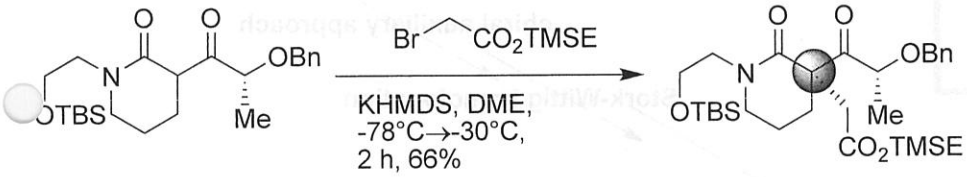


Scheme 1. Retrosynthetic Analysis of Aspidophytine

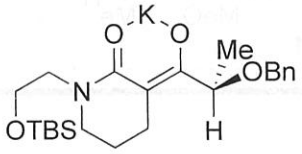


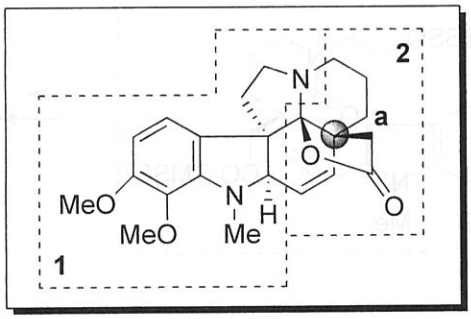
Construction of chiral center a

Chiral auxiliary approach

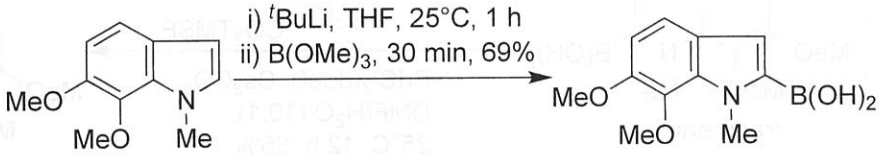


TS

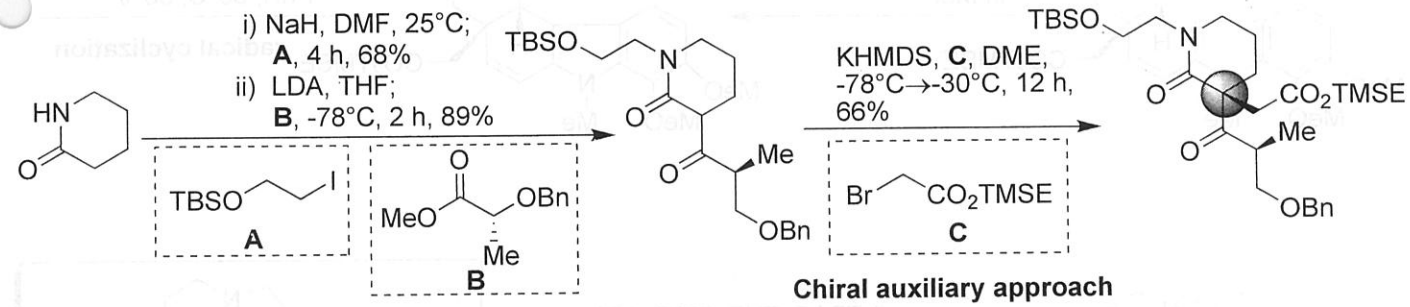




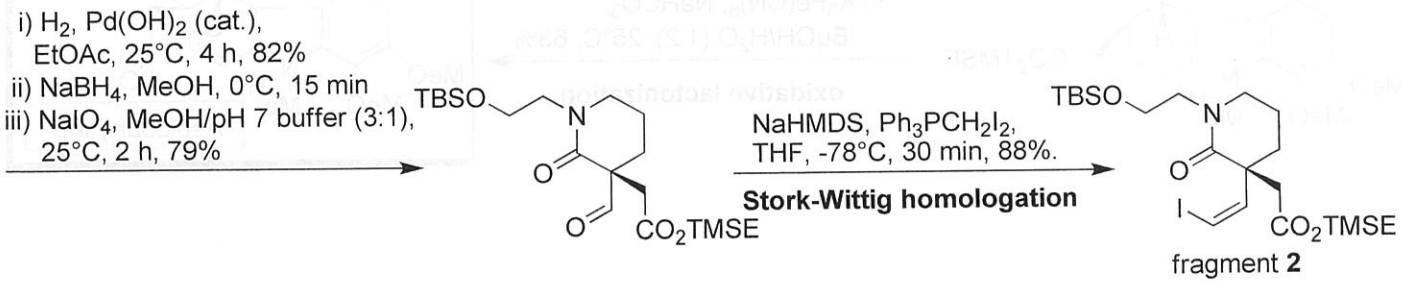
Construction of fragment **1**



Construction of fragment **2** & chiral center a

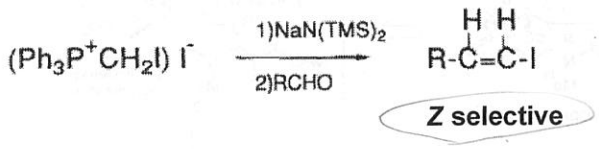


Chiral auxiliary approach

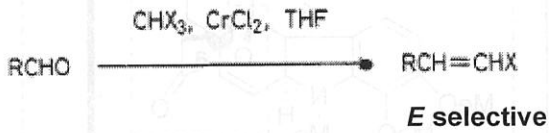


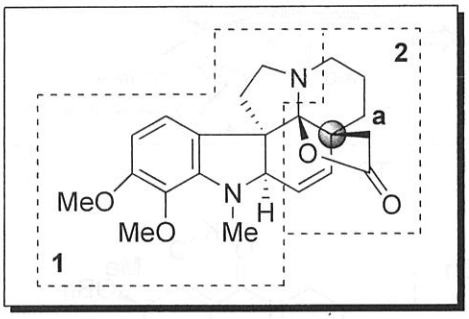
Stork-Wittig homologation

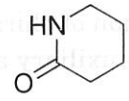
Stork et al.
Tetrahedron Lett. **1989**, *30*, 2173-2174.



Takai et al.
J. Am. Chem. Soc. **1986**, *108*, 7408-7410.



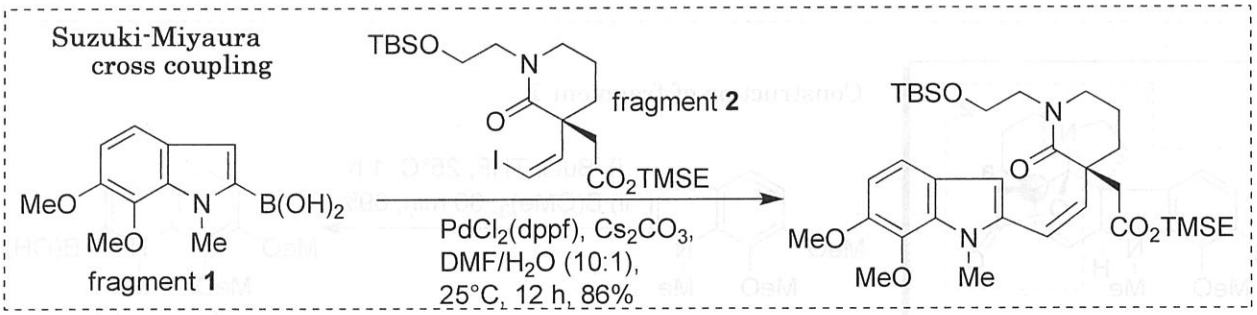


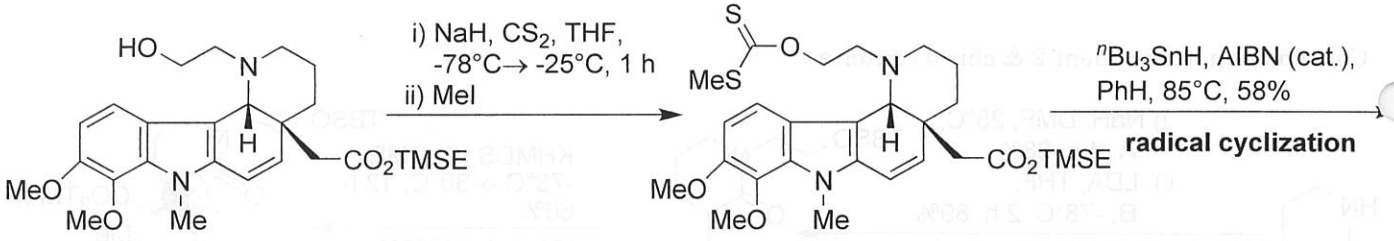


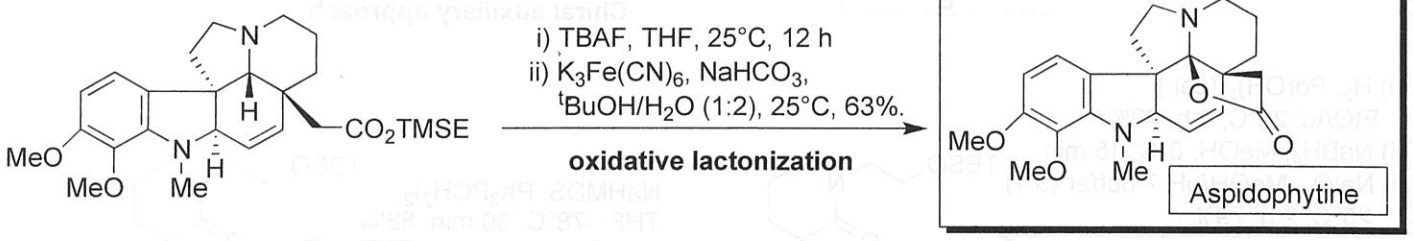
chiral auxiliary approach

Stork-Wittig homologation

1+2 formation



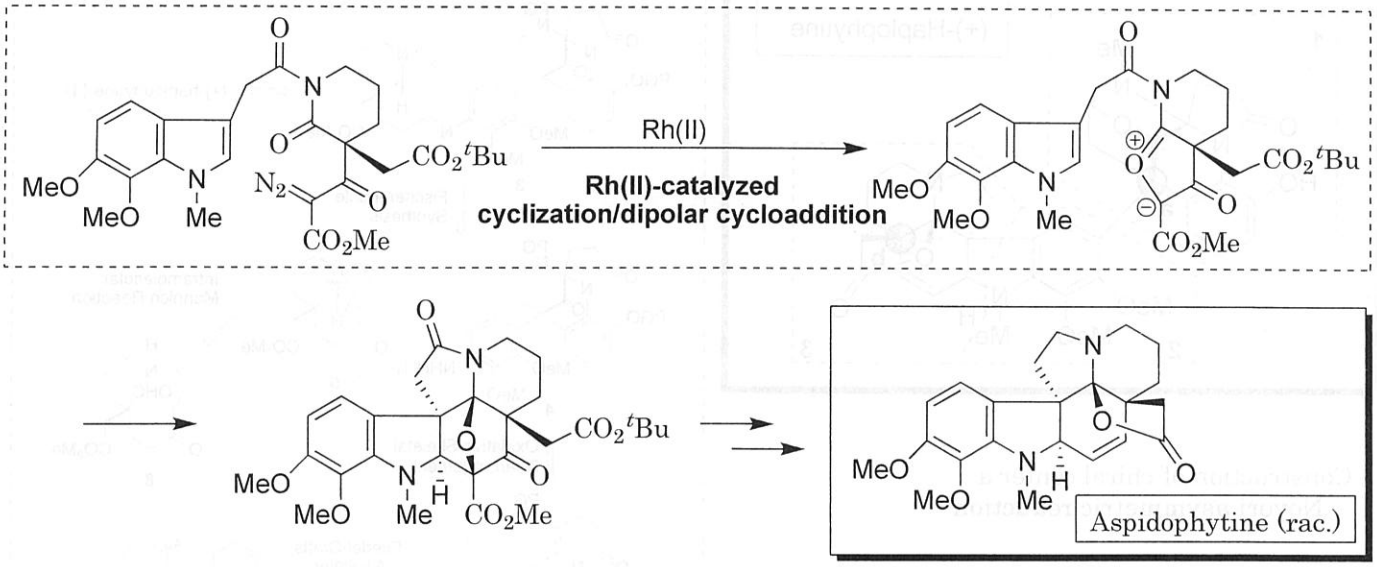




Other works toword Aspidophytine

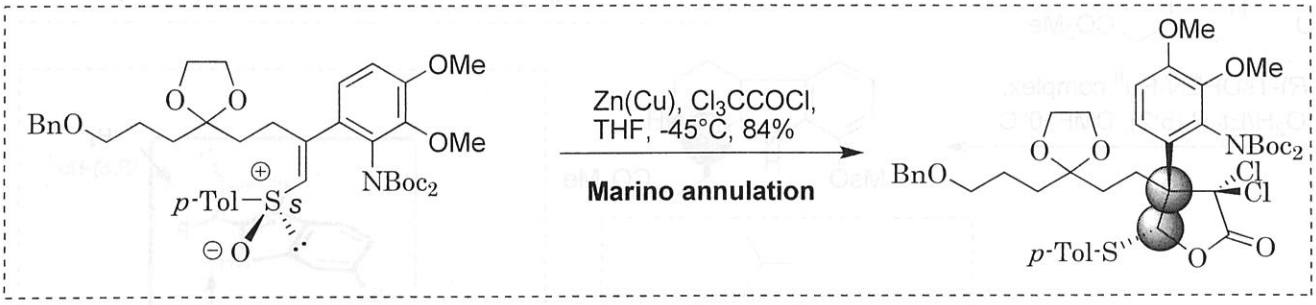
Padwa's strategy ⟶ rac.

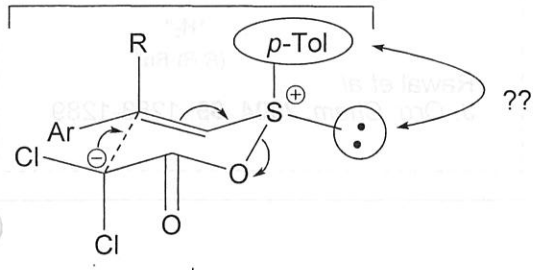
Org. Lett. **2006**, *8*, 3275.

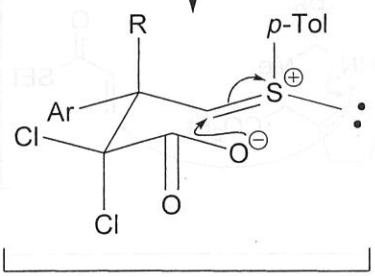


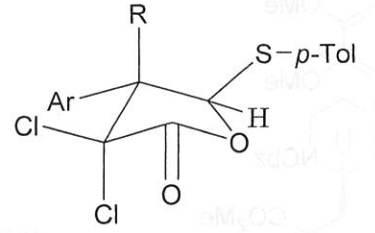
Marino's strategy

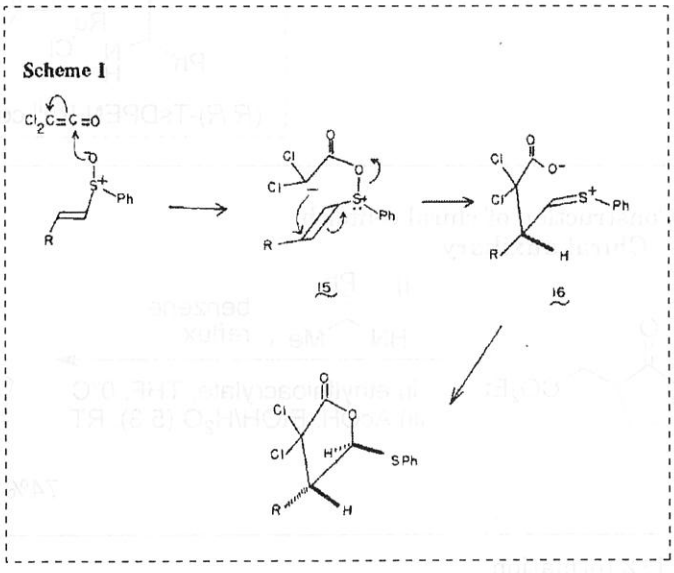
Tetrahedron Lett. **2006**, *47*, 7711.

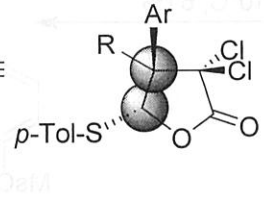


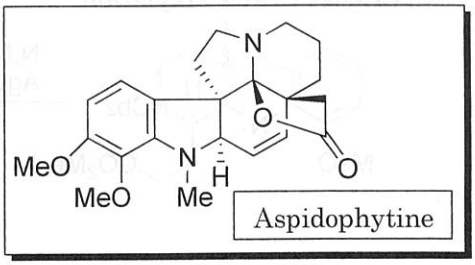








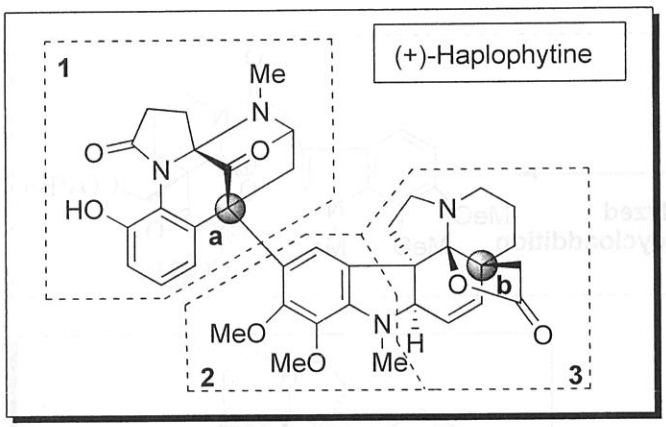


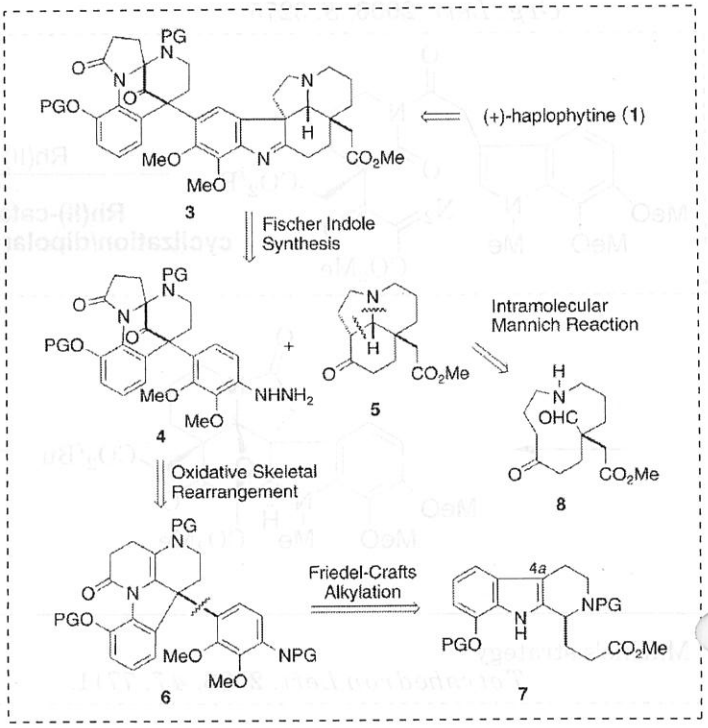


3. Total synthesis of (+)-Haplophytine

3-1. Fukuyama & Tokuyama's strategy

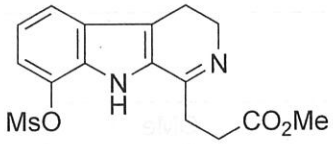
Angew. Chem. Int. Ed. **2009**, DOI: 10.1002/anie.200902192.



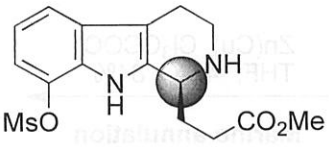


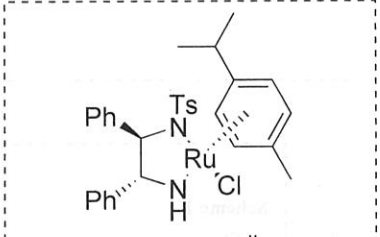
Construction of chiral center **a**

Noyori asymmetric reduction

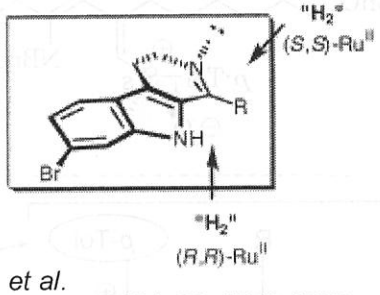


(*R*,*R*)-TsDPEN-Ru^{II} complex,
HCO_2H/Et_3N (5:2), DMF, 0°C





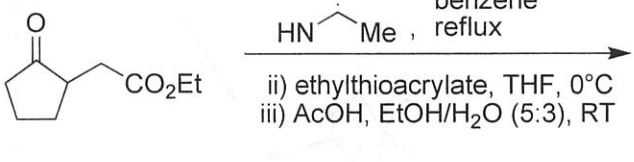
(*R*,*R*)-TsDPEN-Ru^{II} complex

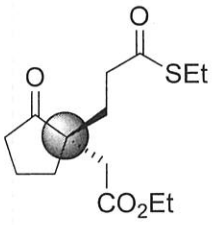


Rawal *et al.*
J. Org. Chem. **2004**, **69**, 1283-1289

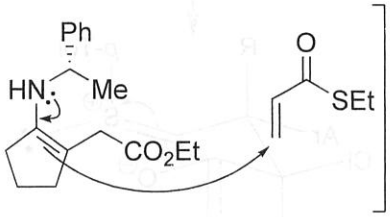
Construction of chiral center **b**

Chiral auxiliary



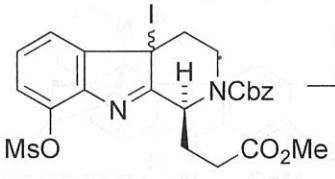


74% (2 steps), 97.8% ee

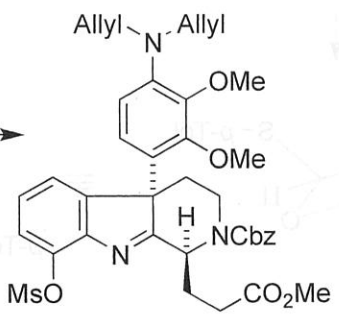


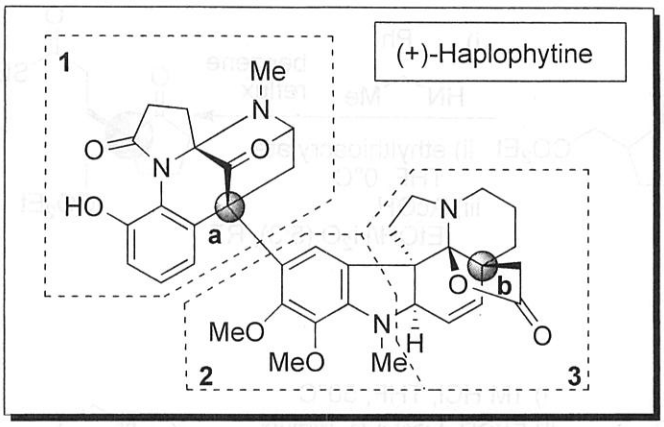
1+2 formation

Friedel-Crafts alkylation

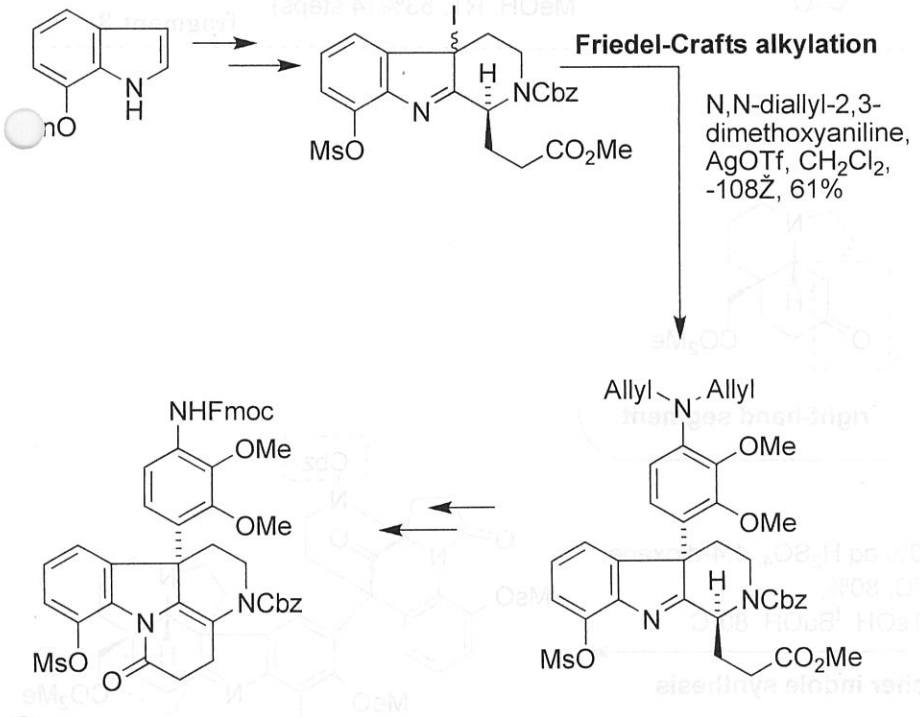


N,N-diallyl-2,3-dimethoxyaniline,
AgOTf, CH_2Cl_2, -10°C, 61%

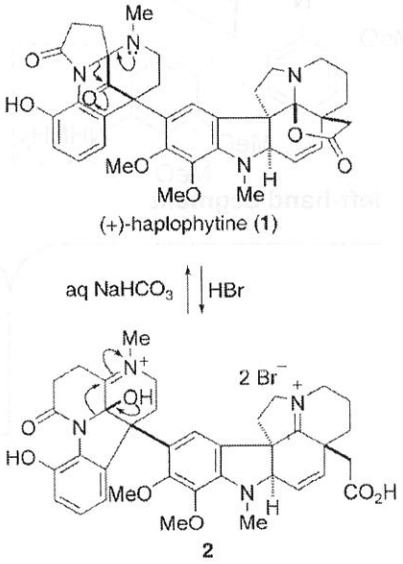


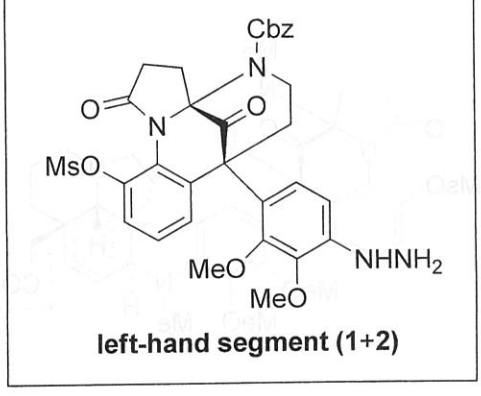


1+2 formation

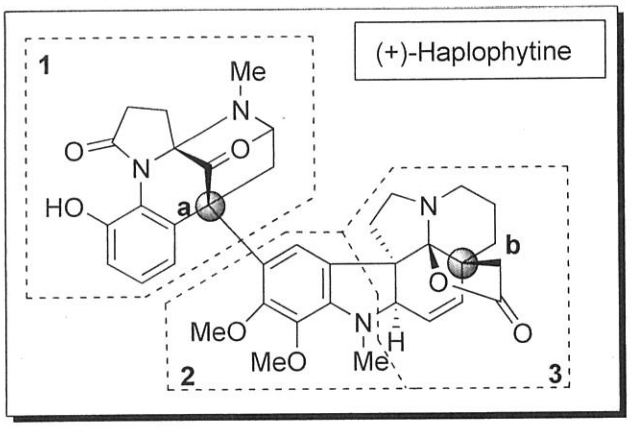


Structure of (+)-haplophytine (1) and its rearrangement.

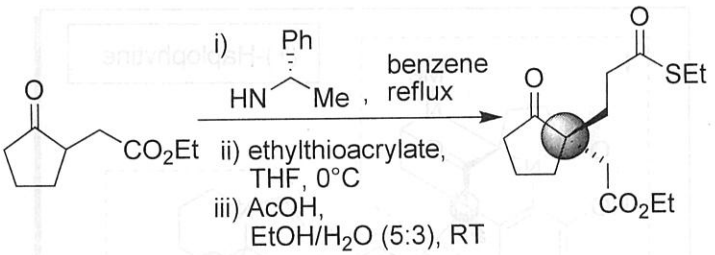


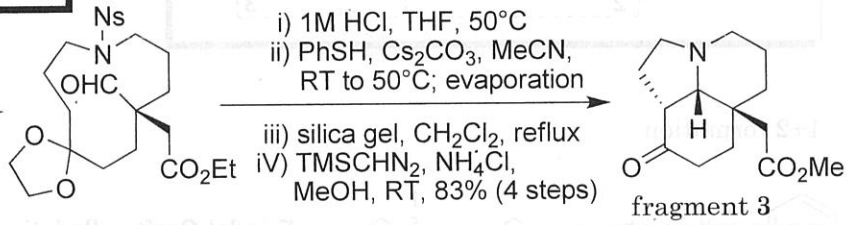


Nsだと
こっちがSN
おしだしでおかしなことがおこる

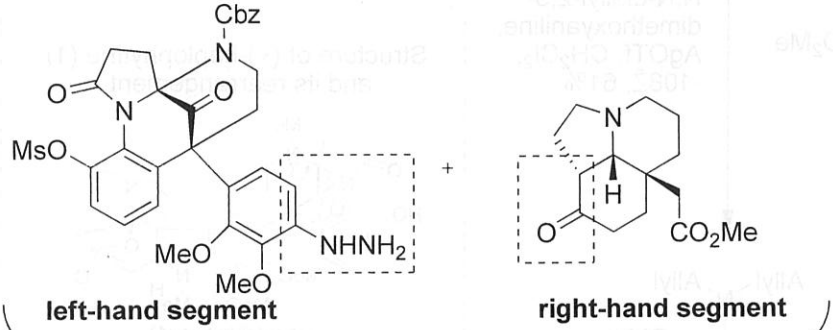


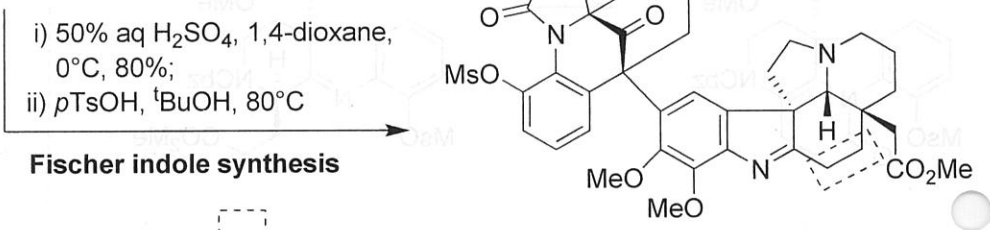
Construction of chiral center **a** & fragment 3

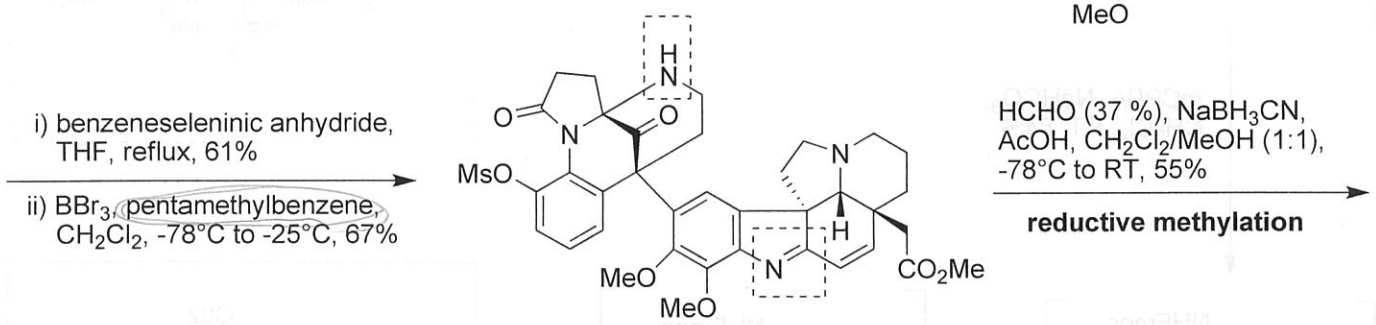


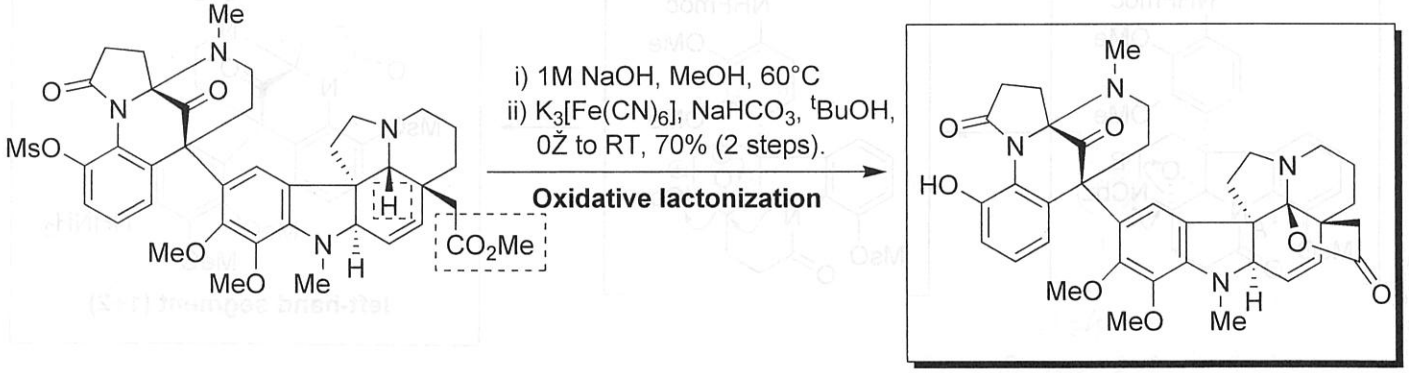


(1+2)+3 formation



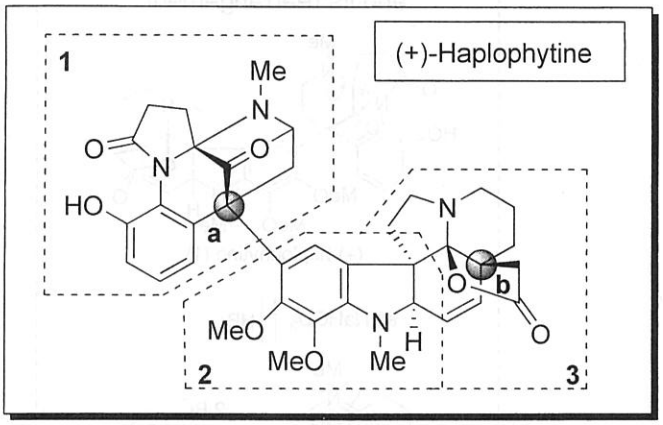


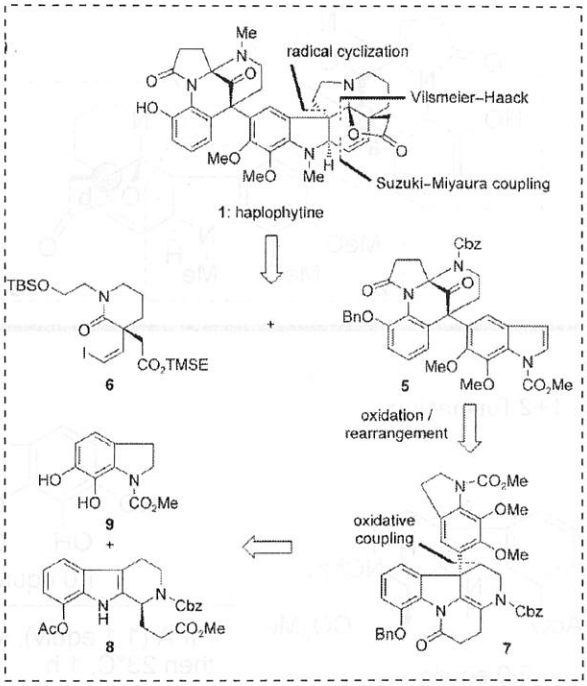




3-2. K. C. Nicolaou's strategy

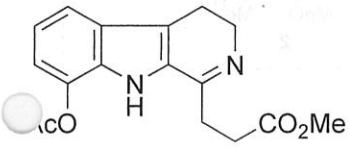
Angew. Chem. Int. Ed. **2009**, *48*, DOI: 10.1002/anie.200904588.

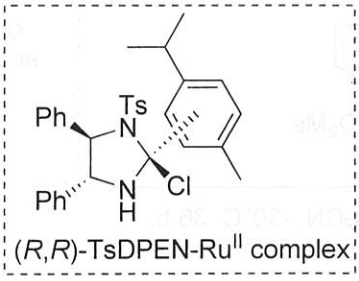




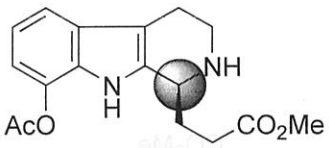
Construction of chiral center a

Noyori asymmetric reduction



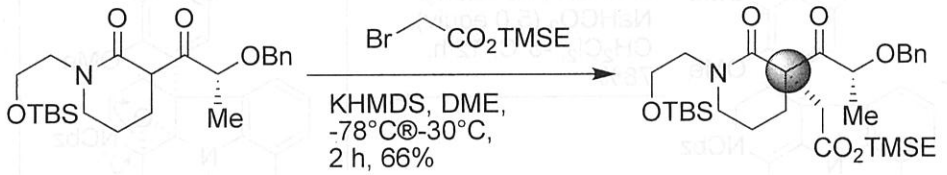


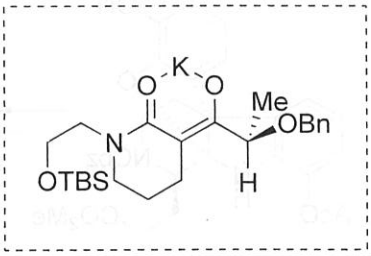
(R,R)-TsDPEN-Ru^{II} complex (0.03 equiv),
HCO_2H/Et_3N (5:2), DMF, 23°C, 0.5 h



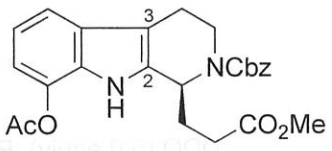
Construction of chiral center b

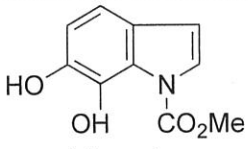
Chiral auxiliary



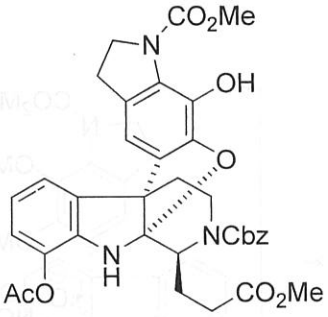


1+2 formation



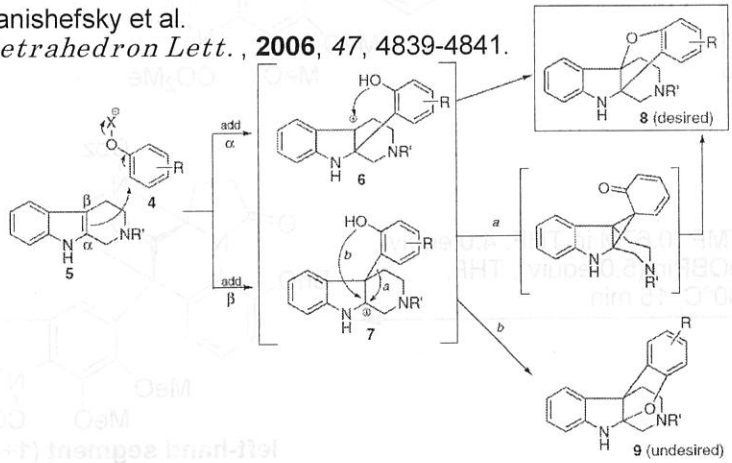


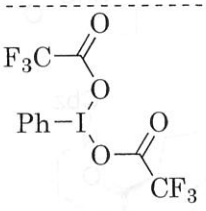
PIFA (1.1 equiv), MeCN, -30°C, 36 h,
then 23°C, 1 h



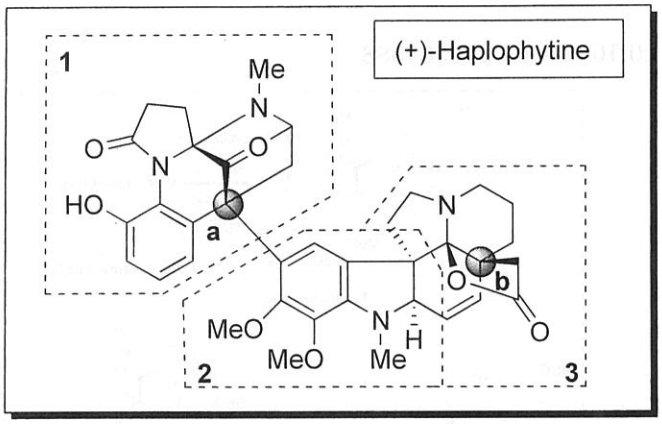
Danishefsky et al.

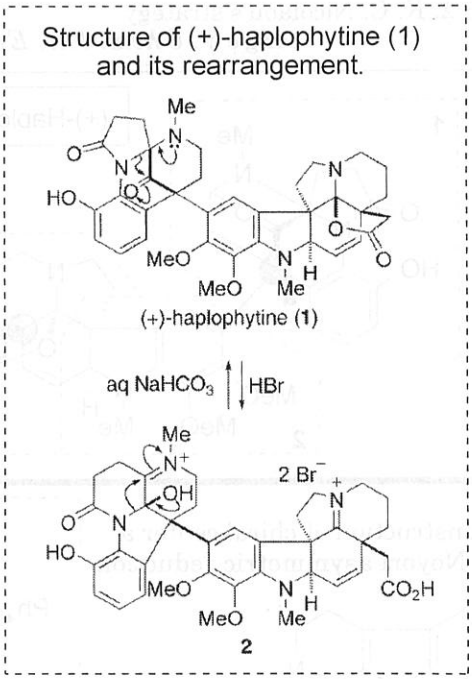
Tetrahedron Lett., **2006**, *47*, 4839-4841.



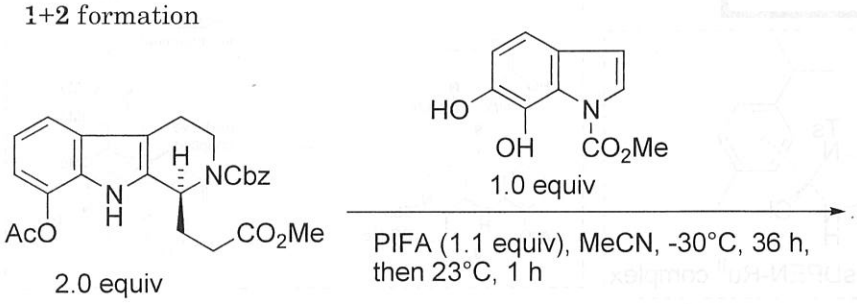


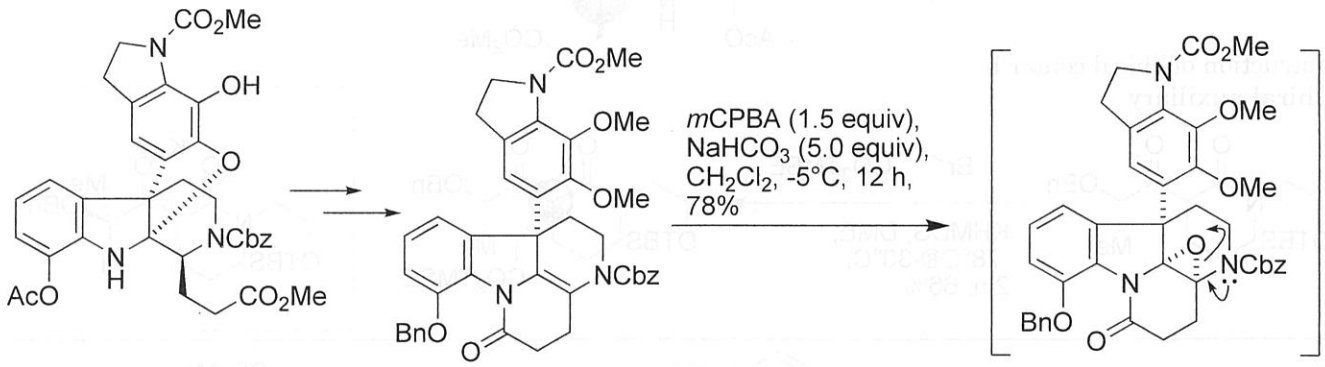
PIFA =
phenyliodium bis (trifluoroacetate)

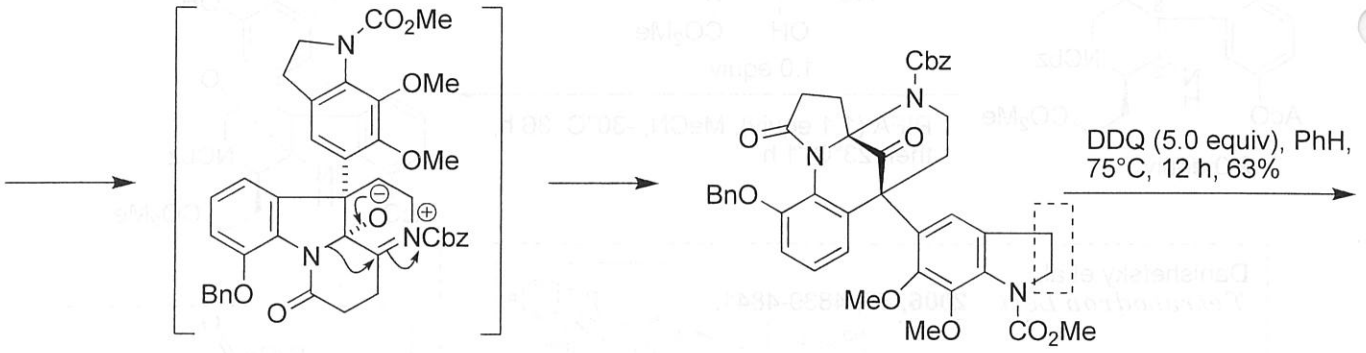


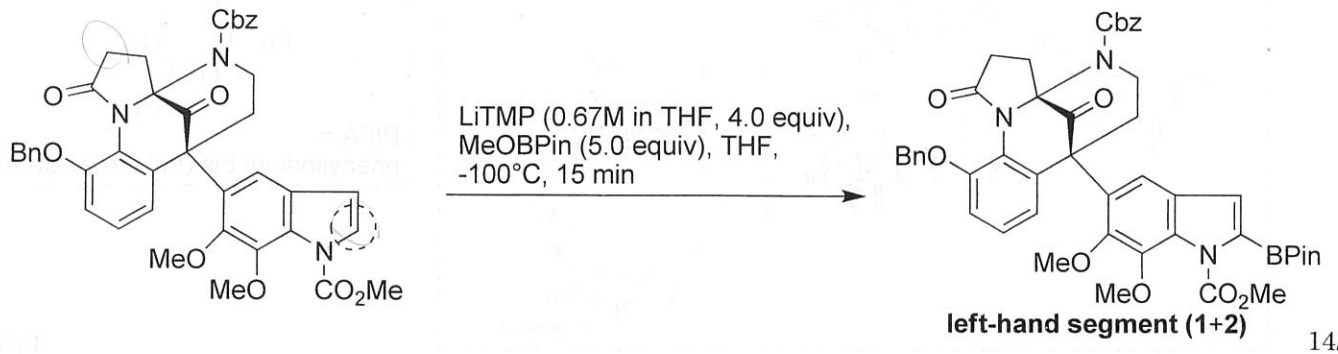


1+2 formation

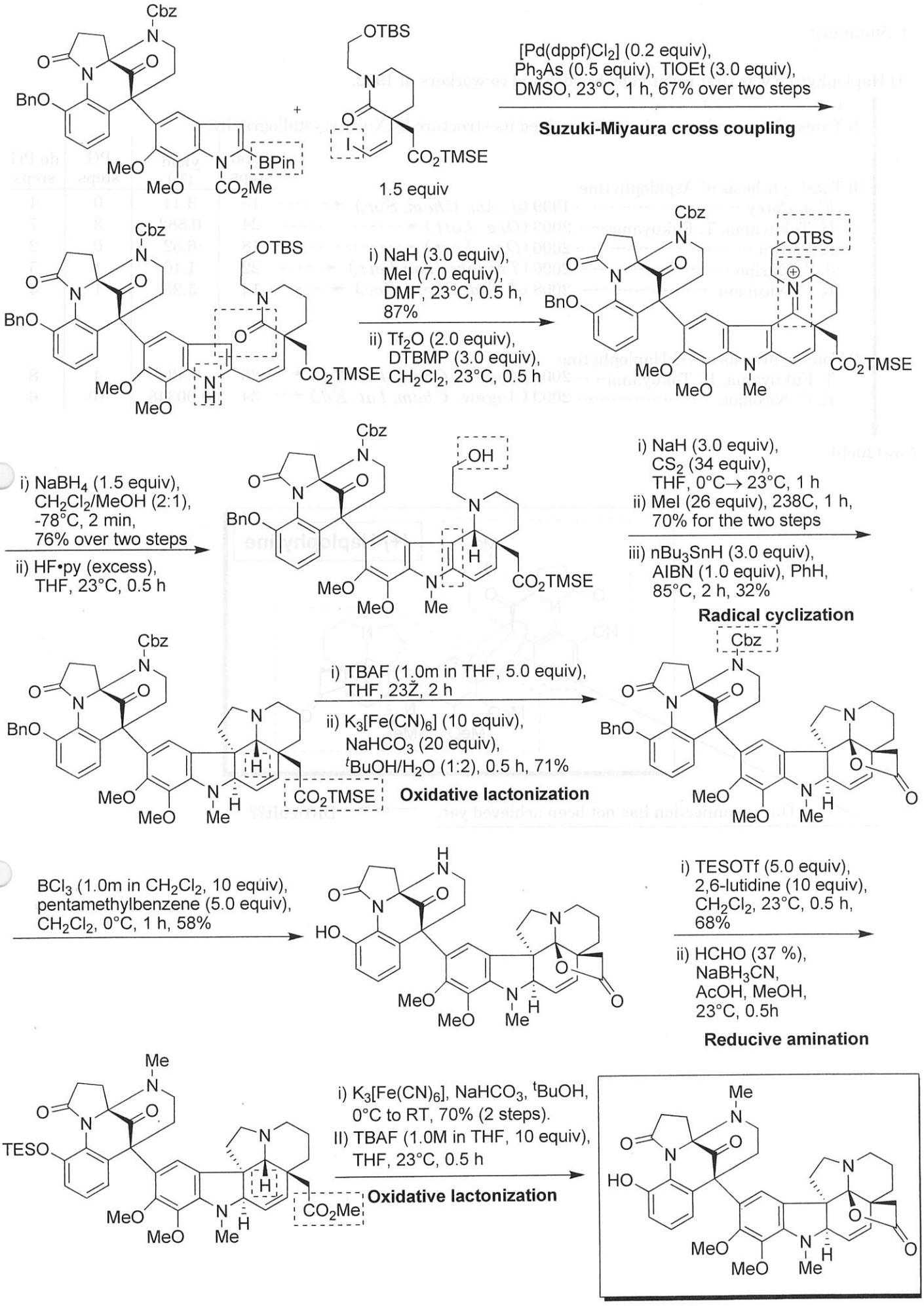








left-hand segment (1+2)


Cbz
BnO
MeO
MeO
BPin
CO2Me
OTBS
I
CO2TMSE
1.5 equiv
[Pd(dppf)Cl2] (0.2 equiv),
Ph3As (0.5 equiv), TlOEt (3.0 equiv),
DMSO, 23°C, 1 h, 67% over two steps
Suzuki-Miyaura cross coupling
i) NaH (3.0 equiv),
MeI (7.0 equiv),
DMF, 23°C, 0.5 h,
87%
ii) Tf2O (2.0 equiv),
DTBMP (3.0 equiv),
CH2Cl2, 23°C, 0.5 h
Me
i) NaBH4 (1.5 equiv),
CH2Cl2/MeOH (2:1),
-78°C, 2 min,
76% over two steps
ii) HF•py (excess),
THF, 23°C, 0.5 h
OH
i) NaH (3.0 equiv),
CS2 (34 equiv),
THF, 0°C→ 23°C, 1 h
ii) MeI (26 equiv), 238C, 1 h,
70% for the two steps
iii) nBu3SnH (3.0 equiv),
AIBN (1.0 equiv), PhH,
85°C, 2 h, 32%
Radical cyclization
i) TBAF (1.0m in THF, 5.0 equiv),
THF, 23Ž, 2 h
ii) K3[Fe(CN)6] (10 equiv),
NaHCO3 (20 equiv),
tBuOH/H2O (1:2), 0.5 h, 71%
Oxidative lactonization
BCl3 (1.0m in CH2Cl2, 10 equiv),
pentamethylbenzene (5.0 equiv),
CH2Cl2, 0°C, 1 h, 58%
HO
i) TESOTf (5.0 equiv),
2,6-lutidine (10 equiv),
CH2Cl2, 23°C, 0.5 h,
68%
ii) HCHO (37 %),
NaBH3CN,
AcOH, MeOH,
23°C, 0.5h
Reducive amination
TESO
i) K3[Fe(CN)6], NaHCO3, tBuOH,
0°C to RT, 70% (2 steps).
II) TBAF (1.0M in THF, 10 equiv),
THF, 23°C, 0.5 h
Oxidative lactonization

4. Summury

1) Haplophytine was first isolated by Snyder and co-workers in 1952.

2) Yates, Cava, and co-workers determined its structure by X-ray crystallography.

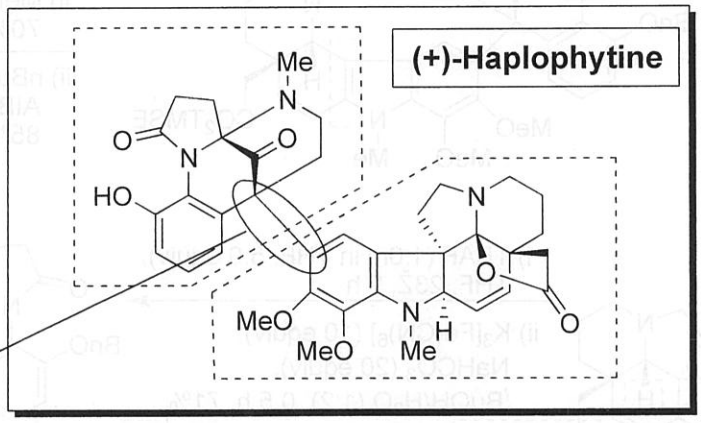
3) Total synthesis of Aspidophytine

		Total steps	yield (%)	PG steps	de PG steps
E. J. Corey	1999 (*J. Am. Chem. Soc.*)	15	3.44	0	4
H. Tokuyama, T. Fukuyama	2003 (*Org. Lett.*)	24	0.882	3	7
A. Padwa	2006 (*Org. Lett.*)	18	6.52	0	2
J. P. Marino	2006 (*Tetrahedron Lett.*)	22	1.16	1	5
K. C. Nicolaou	2008 (*J. Am. Chem. Soc.*)	14	**5.23**	1	4

4) Total synthesis of (+)-Haplophytine

T. Fukuyama, H. Tokuyama	2009 (*Angew. Chem. Int. Ed.*)	26	0.434	4	8
K. C. Nicolaou	2009 (*Angew. Chem. Int. Ed.*)	34	0.00348	10	6

Now(2009)



Direct connection has not been achieved yet. → Difficult??