Total Synthesis of (-)-*Lepadiformine*

JACS Asap Chihiro Kibayashi

Acc. Chem. Res. **2003**, *36*, 59-65 Weinreb

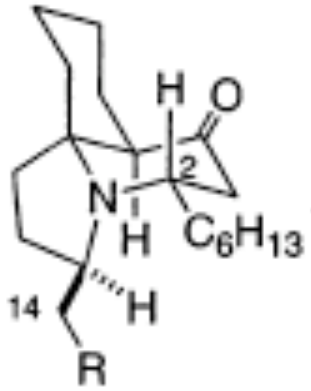
OL **2001**, *3*, 3507-3510 Weinreb

Chunrui Wu

Jan 20, 2005

Background

Azatricyclic ring
Cis- BC ring



2 R=Cl cylindricine A
3 R=OH cylindricine C
4 R=OMe cylindricine D
5 R=OAc cylindricine E
6 R=SCN cylindricine F

Cylindricines

Isolated from the marine ascidians *Clavelina cylindrica*

Structures were established by x-ray of their picrate salts.

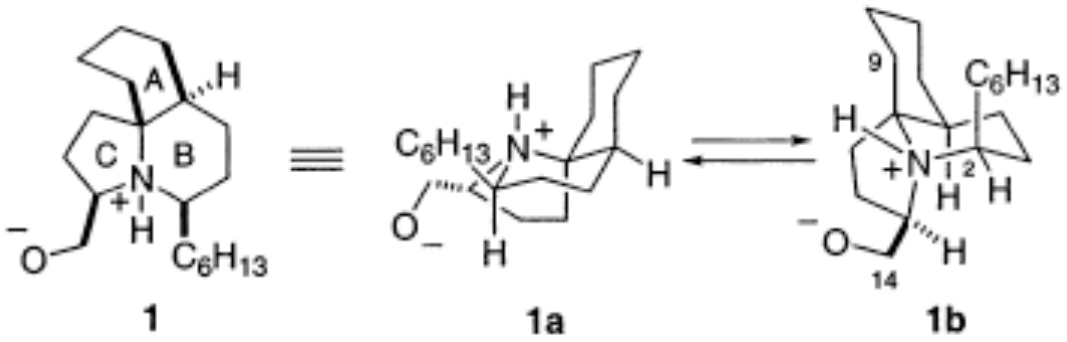
Blackman, A. J. *Tet* **1993**, *49*, 1355-1361.

Background of Lepadiformine

- Isolation: HCl extraction of marine tunicate
  Clavelina lepadiformis, 1994

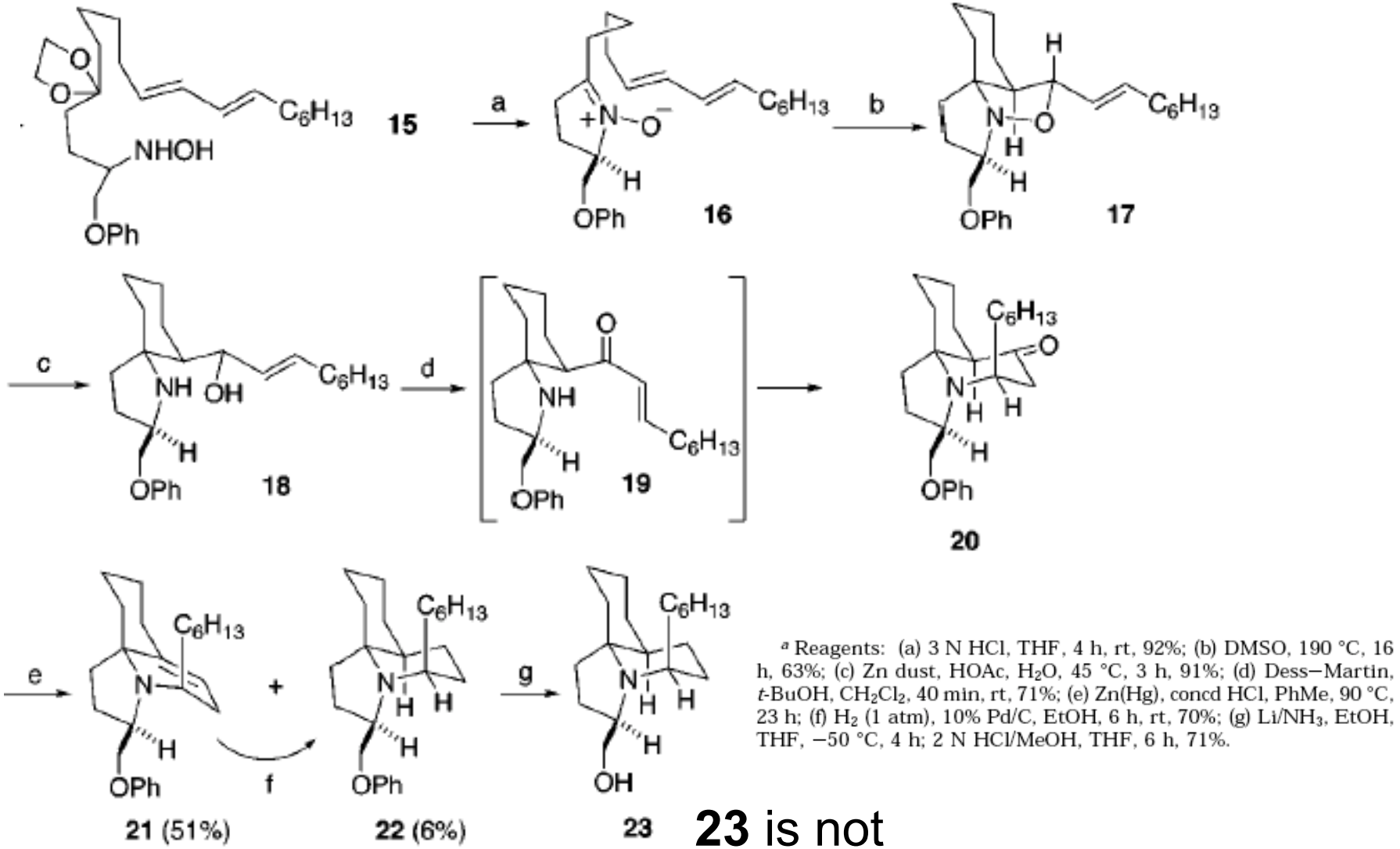
- Bioactivity: moderate cytotoxic activity
  cardiovascular effect

Structure: putative



Biard, J. F. *Tet.Lett.* **1994**, *35*, 2691-2694

Disproof of Biard *Lepadiformine* Structure via Synthesis--*Weinreb*

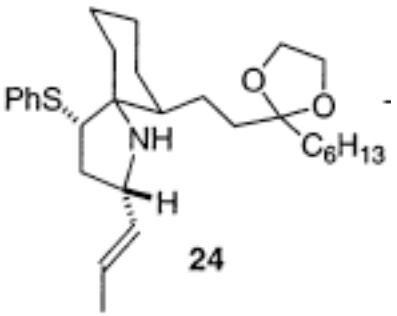


[a] Reagents: (a) 3 N HCl, THF, 4 h, rt, 92%; (b) DMSO, 190 °C, 16 h, 63%; (c) Zn dust, HOAc, H_2O, 45 °C, 3 h, 91%; (d) Dess–Martin, *t*-BuOH, CH_2Cl_2, 40 min, rt, 71%; (e) Zn(Hg), concd HCl, PhMe, 90 °C, 23 h; (f) H_2 (1 atm), 10% Pd/C, EtOH, 6 h, rt, 70%; (g) Li/NH_3, EtOH, THF, −50 °C, 4 h; 2 N HCl/MeOH, THF, 6 h, 71%.

23 is not lepadiformine

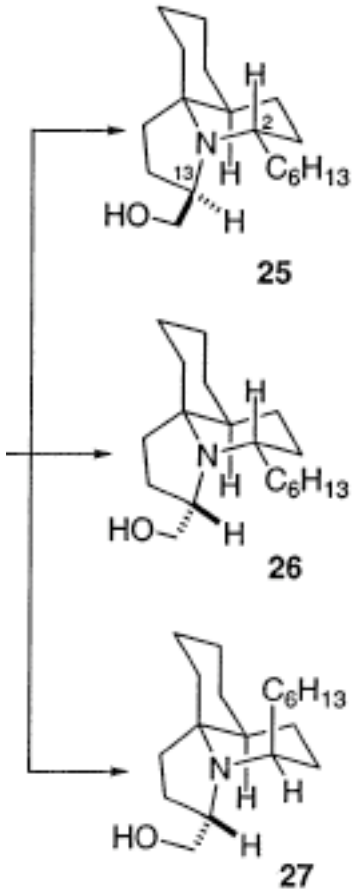
Weinreb, S. M. JOC **1999**, *64*, 686-687

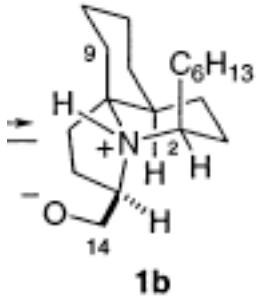
Disproof of Biard *Lepadiformine* Structure via Synthesis--*Pearson*



24

Incorrect C10-C13
Relative stereochemistry





1b

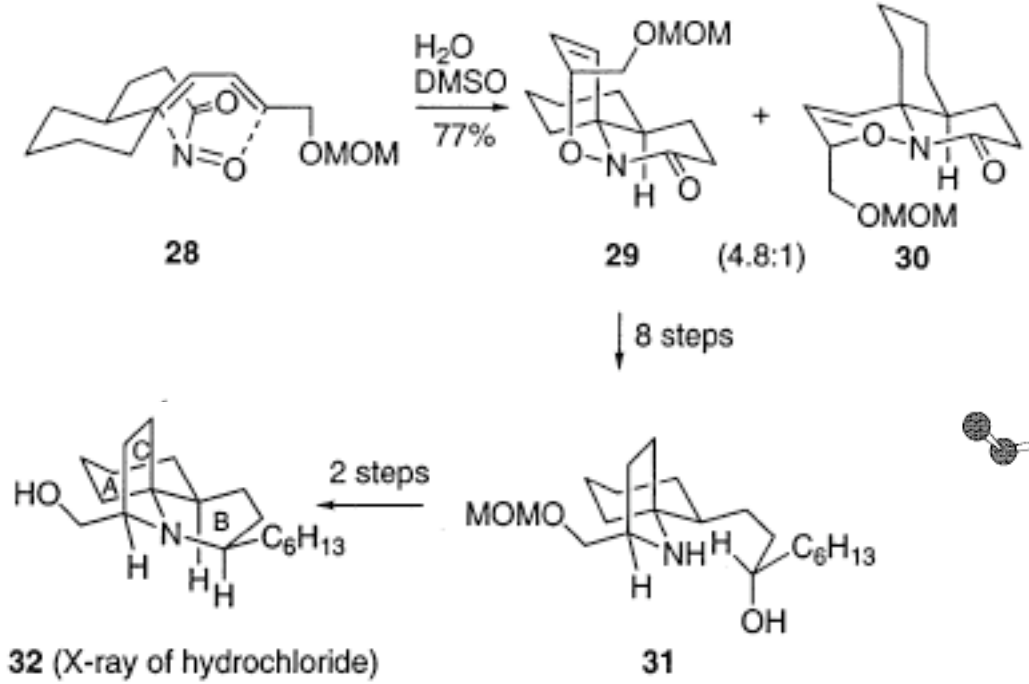
Wrong atomic connection
Epimer of **1** at C10

None of the those compounds nor hydrochlorides was identical of natural alkaloid. *Lepadiformine* is not epimer of **1** at C2 or C13

Pearson, W. H., *JOC* **1999**, *64*, 688-689.

Disproof of Biard *Lepadiformine* Structure via Synthesis--Kibayashi

Intramolecular acylnitroso Diels-Alder strategy



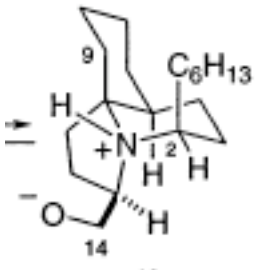
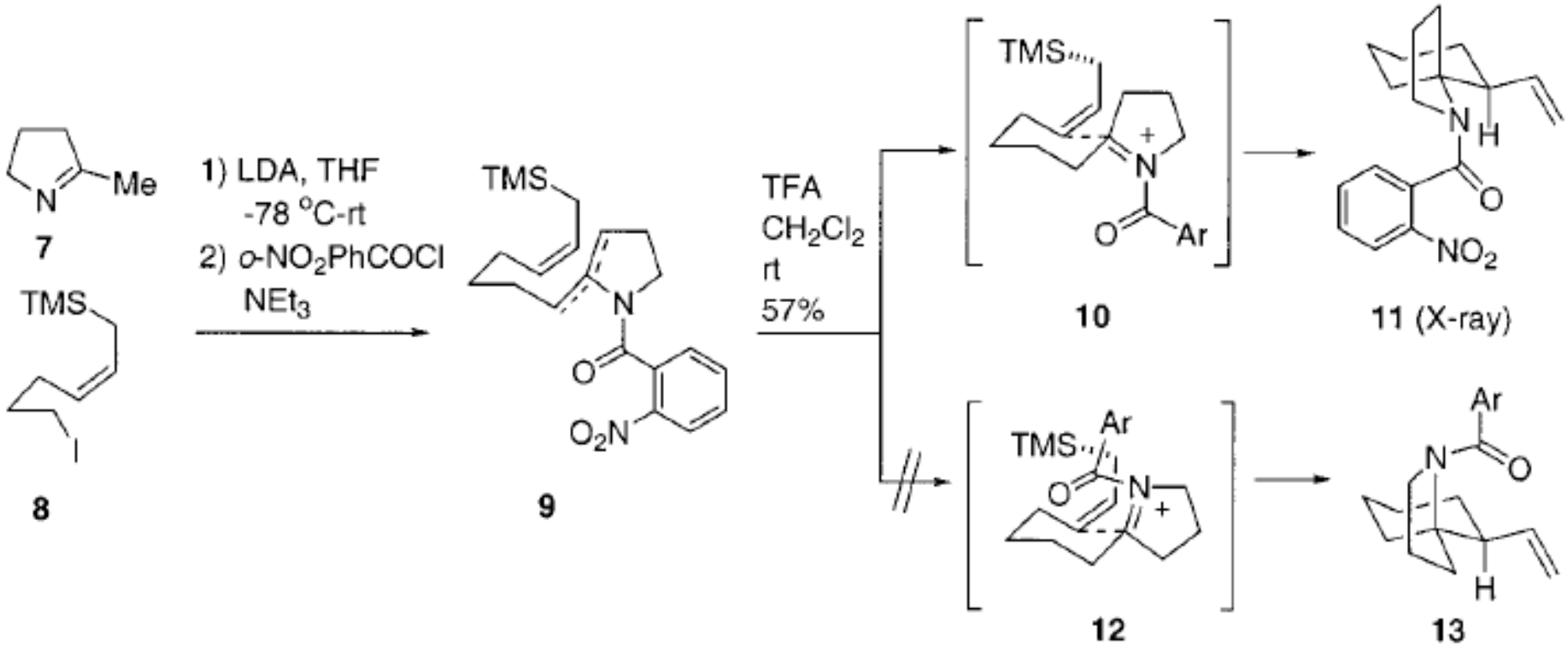


Figure 2. The X-ray structure (Chem3D representation) of synthetic (±)-lepadiformine hydrochloride [**5**·HCl].

Kibayashi, C. *JACS* **2000**, *122*, 4583-4592

New Synthesis of *Lepadiformine* *--Weinreb*

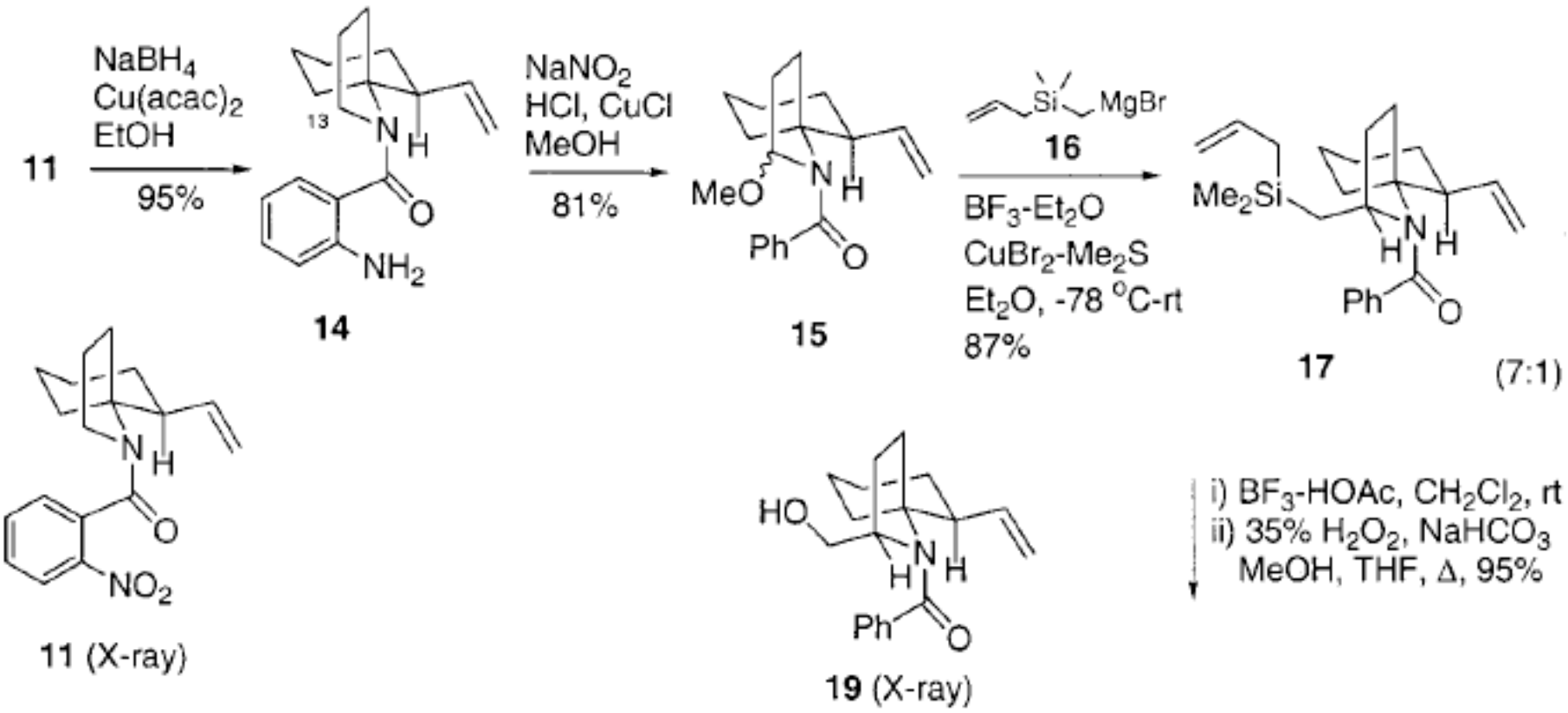
Intramolecular allysilane/N-acyliminium ion spirocyclization strategy



Weinreb, S. M. *OL.* **2001**, *3*, 3507-3510;*JOC*, **2002**, *67*, 4337

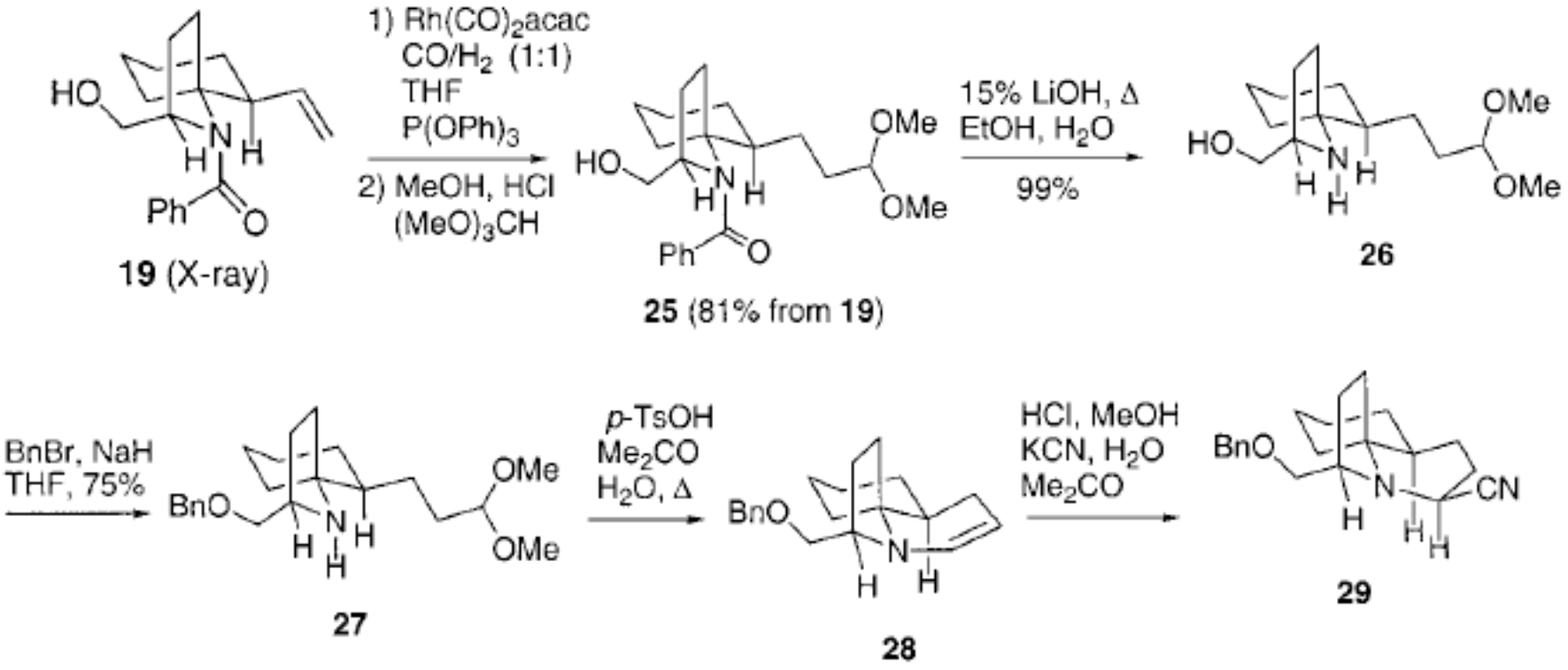
New Synthesis of *Lepadiformine* --*Weinreb*

Oxidative remote fuctionalization of *o*-aminobenzamide



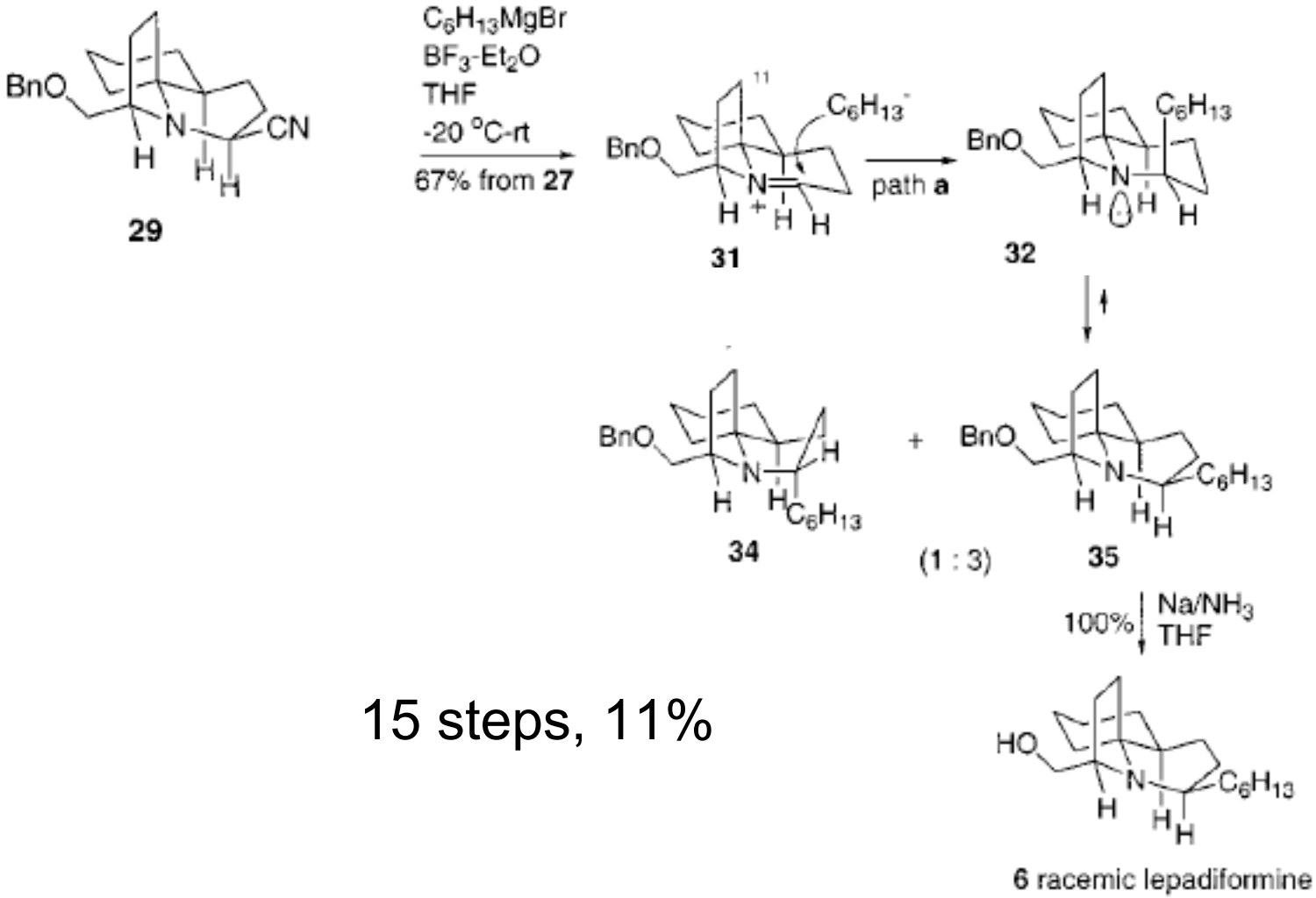
Weinreb, S. M. *OL.* **2001**, *3*, 3507-3510;*JOC*, **2002**, *67*, 4337

New Synthesis of *Lepadiformine* *--Weinreb*



Weinreb, S. M. *OL.* **2001**, *3*, 3507-3510;*JOC*, **2002**, *67*, 4337

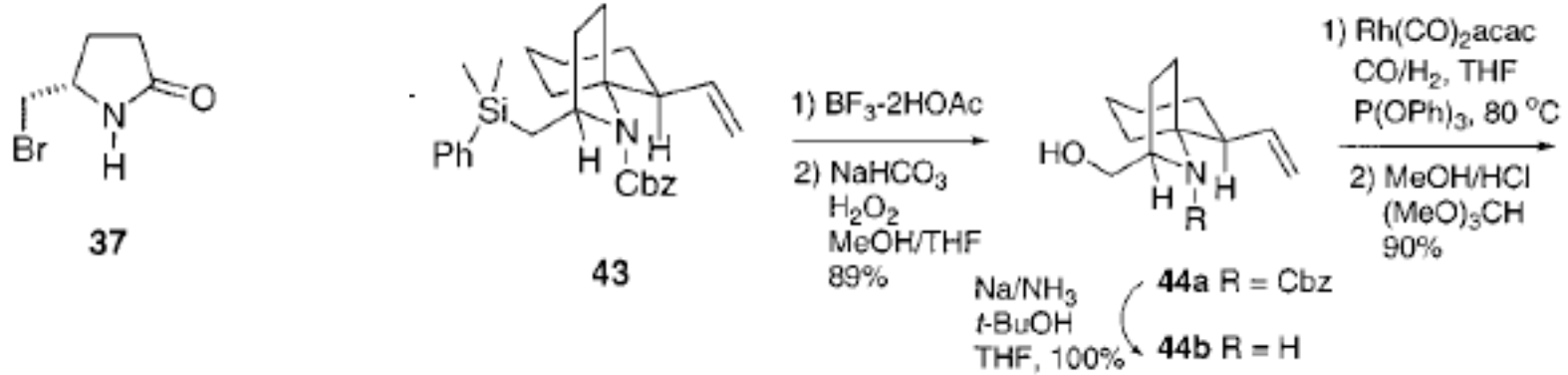
New Synthesis of *Lepadiformine* -- *Weinreb*

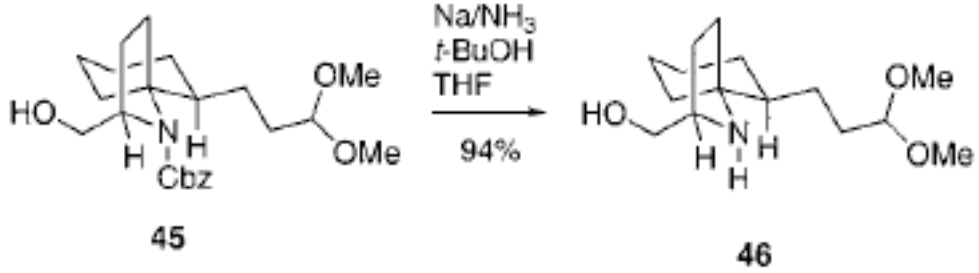


15 steps, 11%

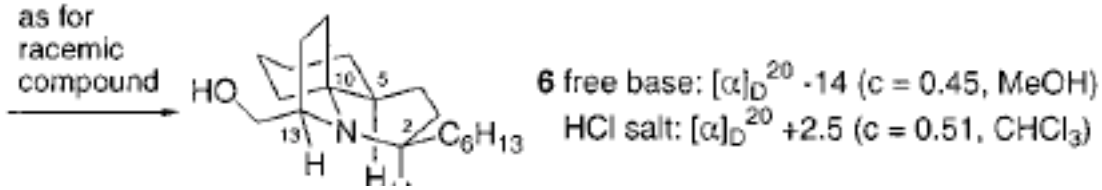
Weinreb, S. M. *OL.* **2001**, *3*, 3507-3510;*JOC*, **2002**, *67*, 4337

Determination of Absolute Configuration



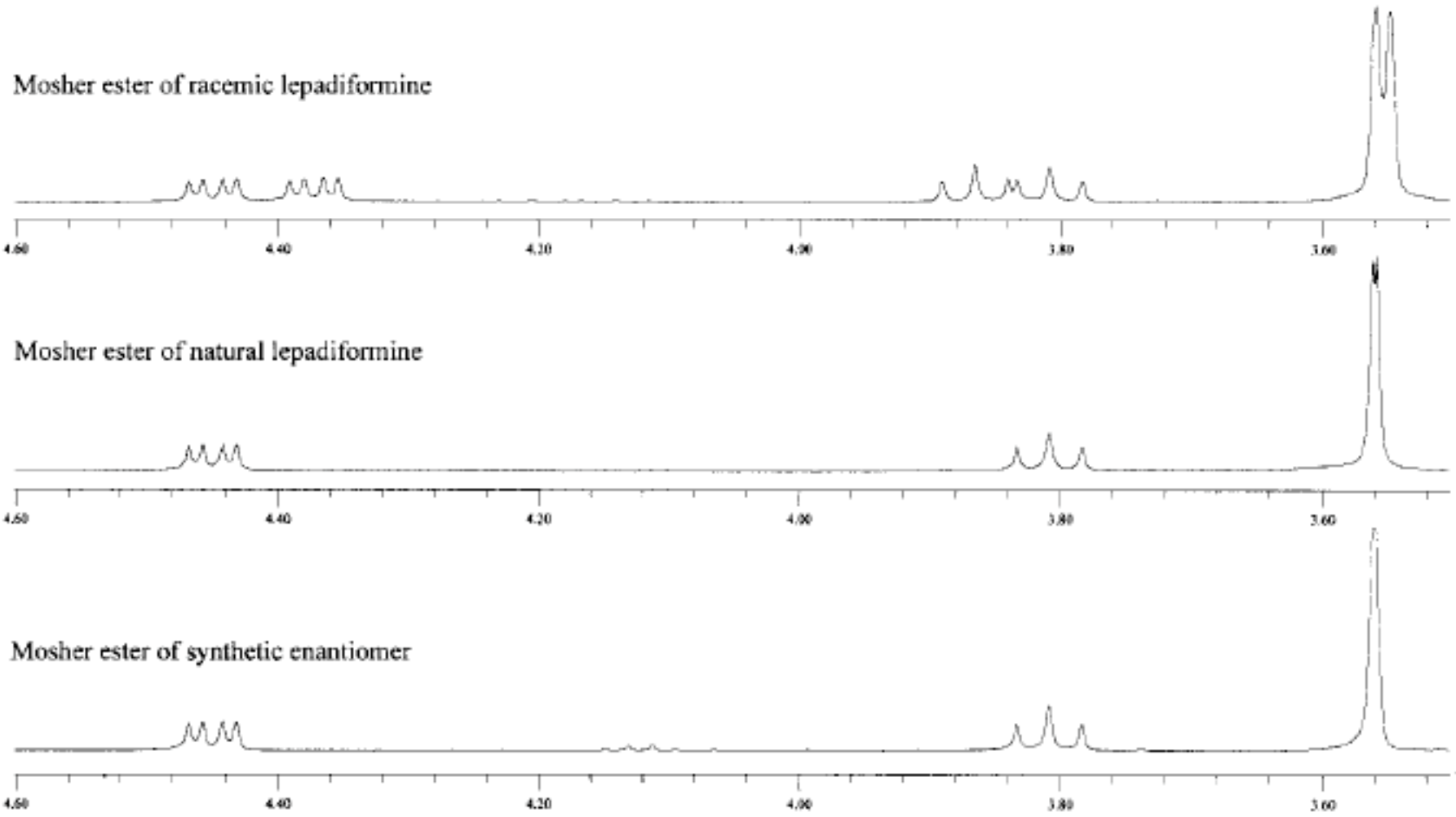


2 (*R*), 5 (*S*), 10 (*S*), 13 (*S*)

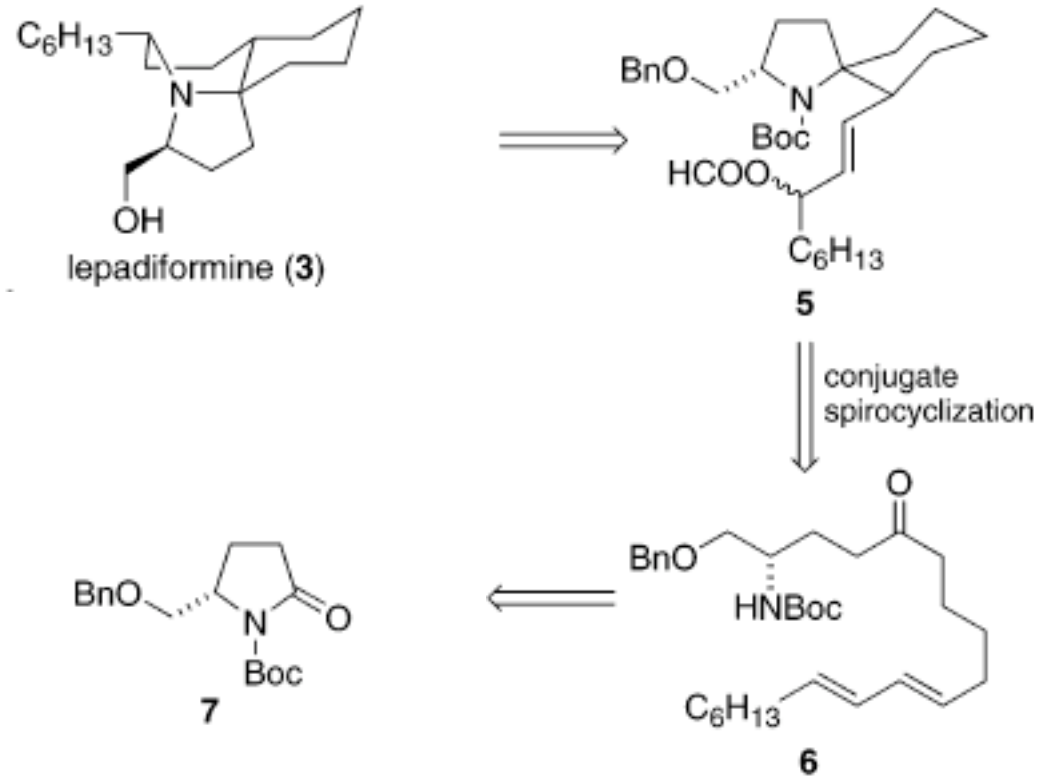


Weinreb, S. M. *JOC*, **2002**, *67*, 4337

Determination of Absolute Configuration

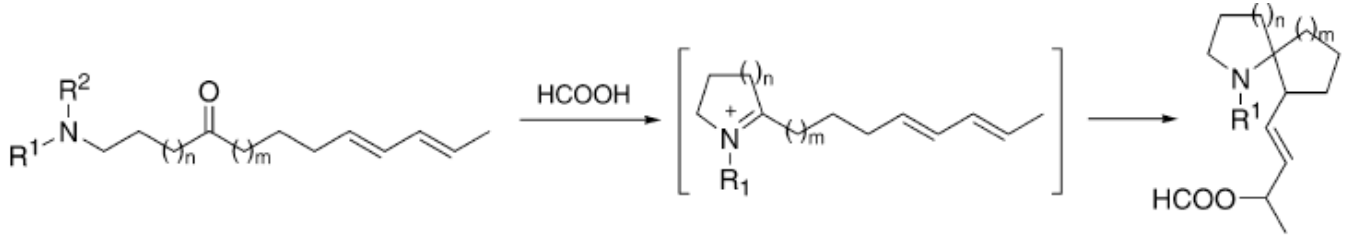


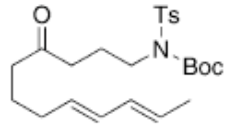
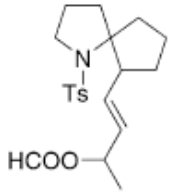
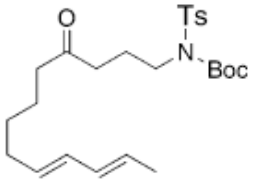
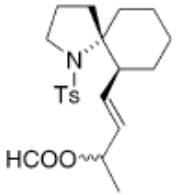
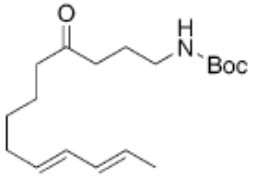
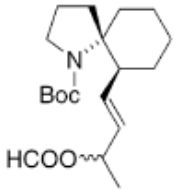
New Synthesis of (-)-Lepadiformine -*-Kibayashi*



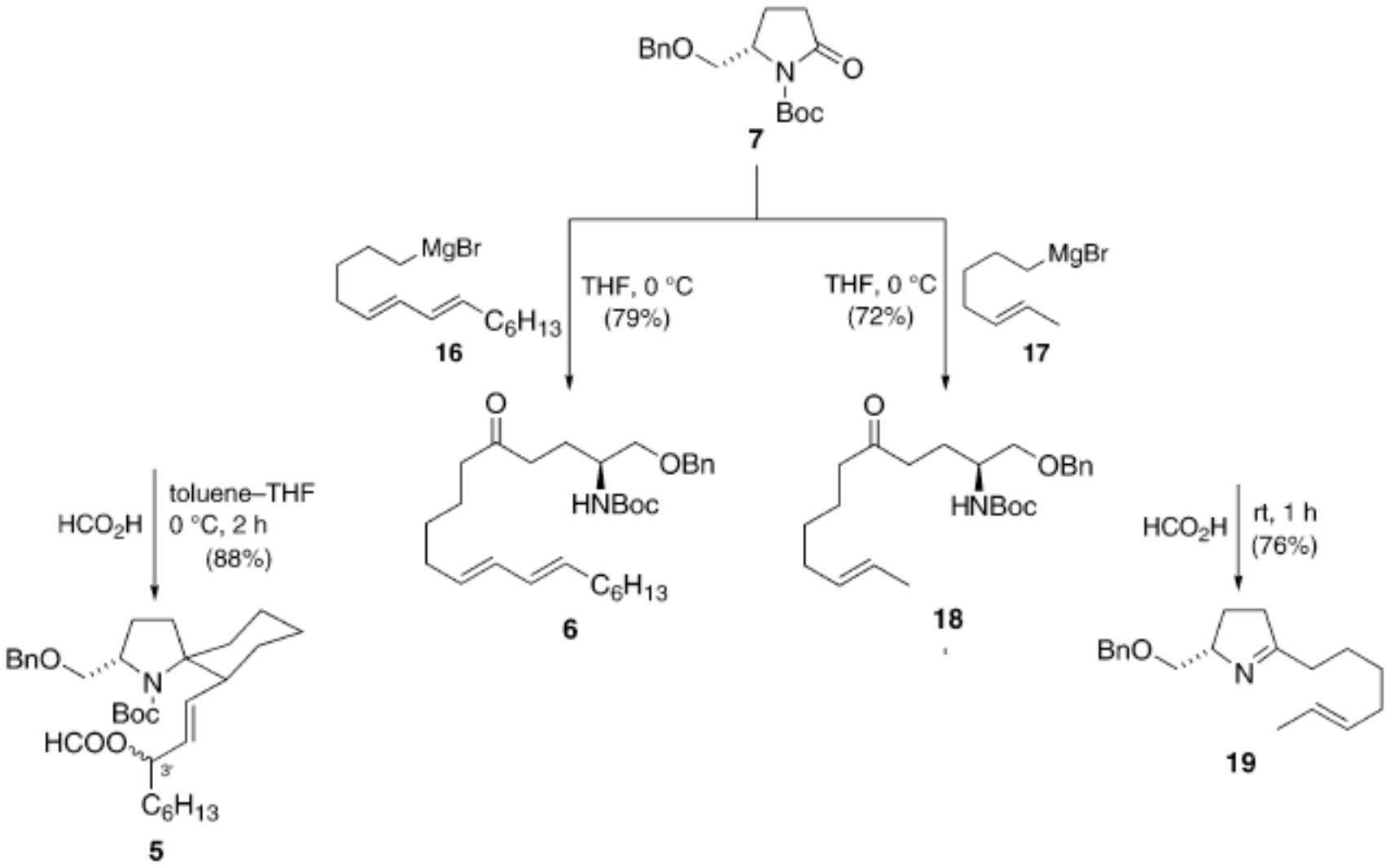
Kibayashi, C. *JACS*, *asap*

New Synthesis of (-)-Lepadiformine - *-Kibayashi*

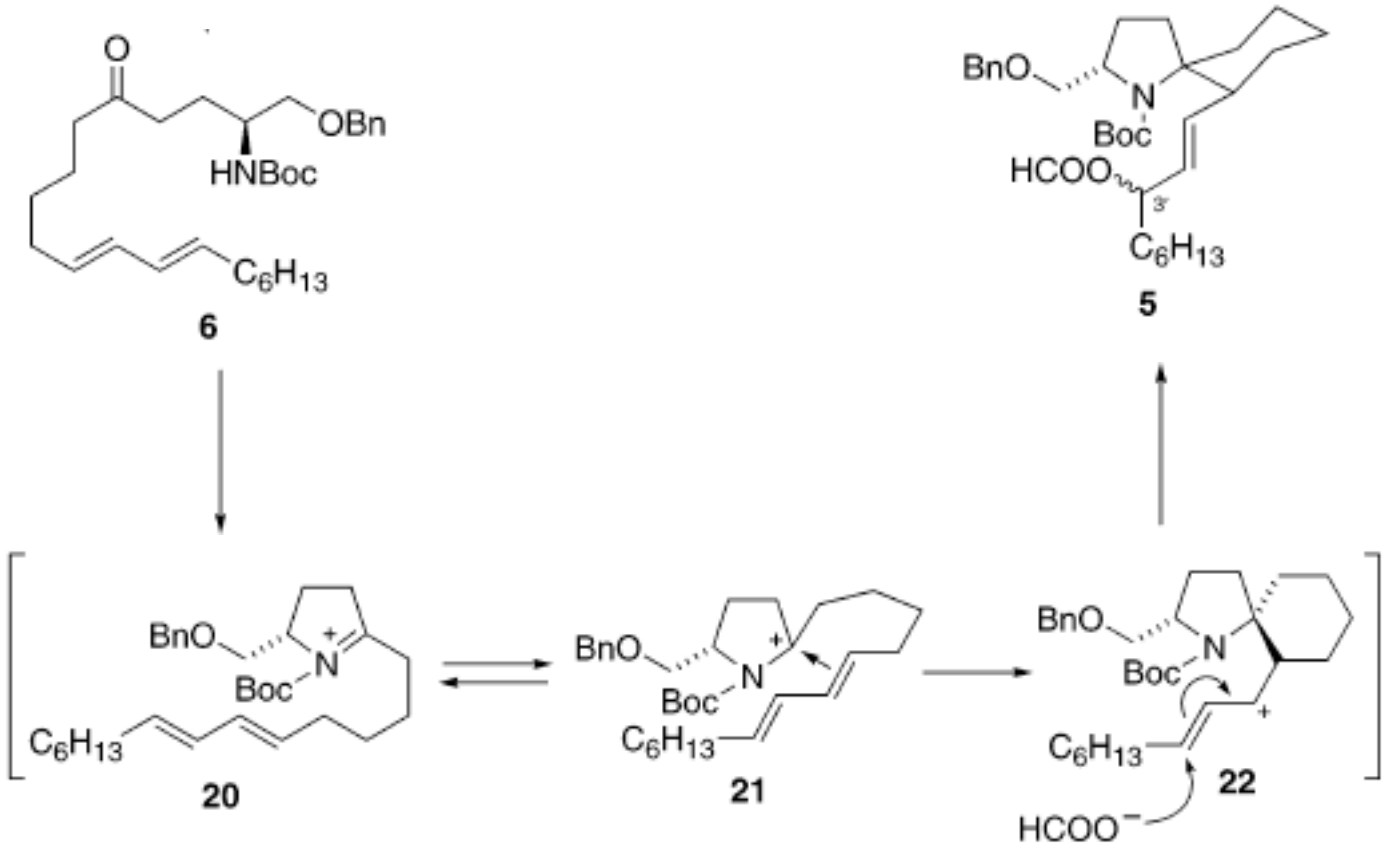


entry	compound	solvent	temp.	time (h)	product	yield (%
1	 **8**	CH_2Cl_2	rt	40	 **12**	43[c]
2	 **9**	CH_2Cl_2	rt	40	 **13**	55
3	 **10**	CH_3CN	0 °C	2	 **14**	54
4	**10**	toluene–THF	0 °C	1	**14**	66

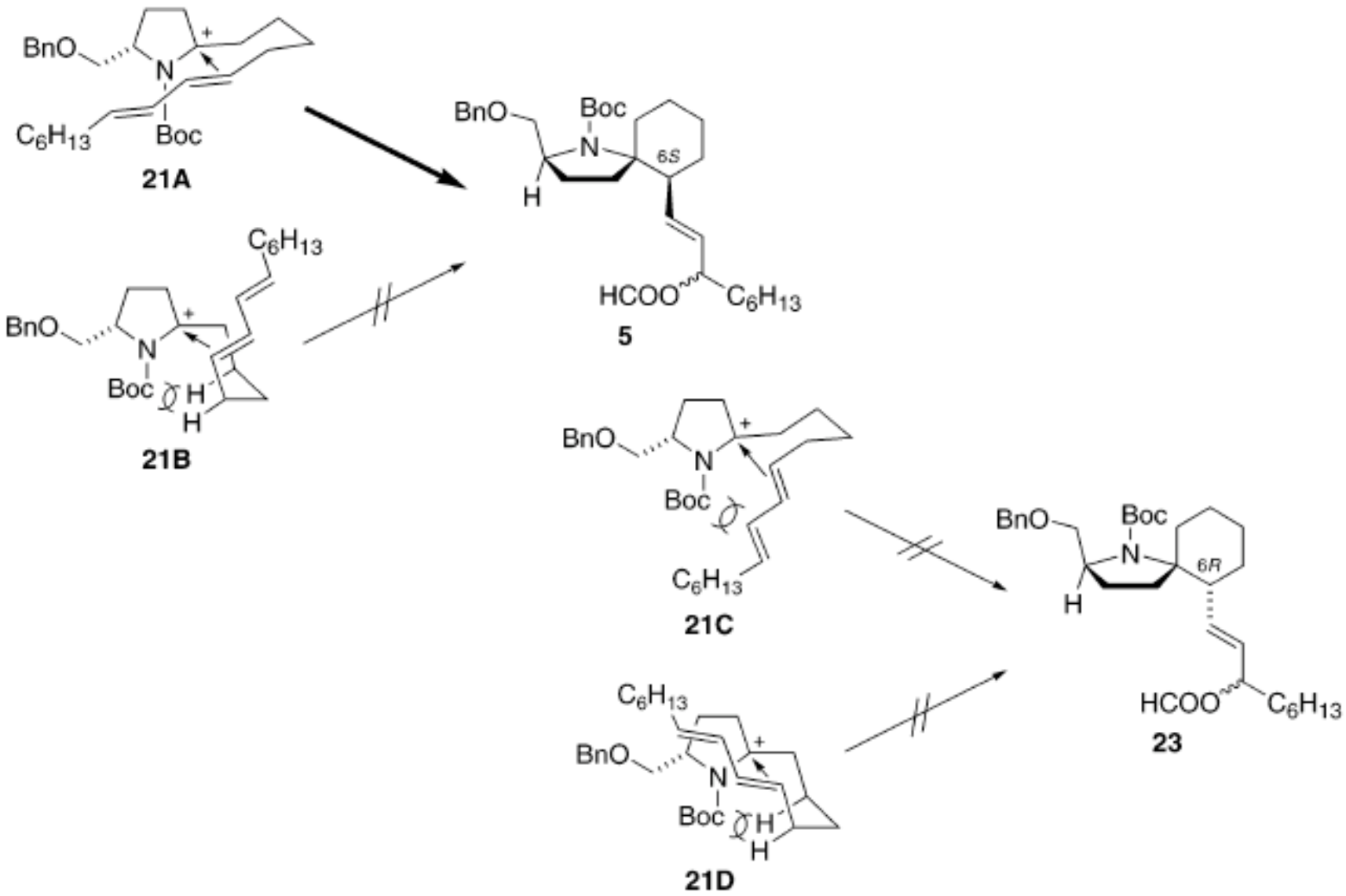
New Synthesis of (-)-Lepadiformine - -*Kibayashi*

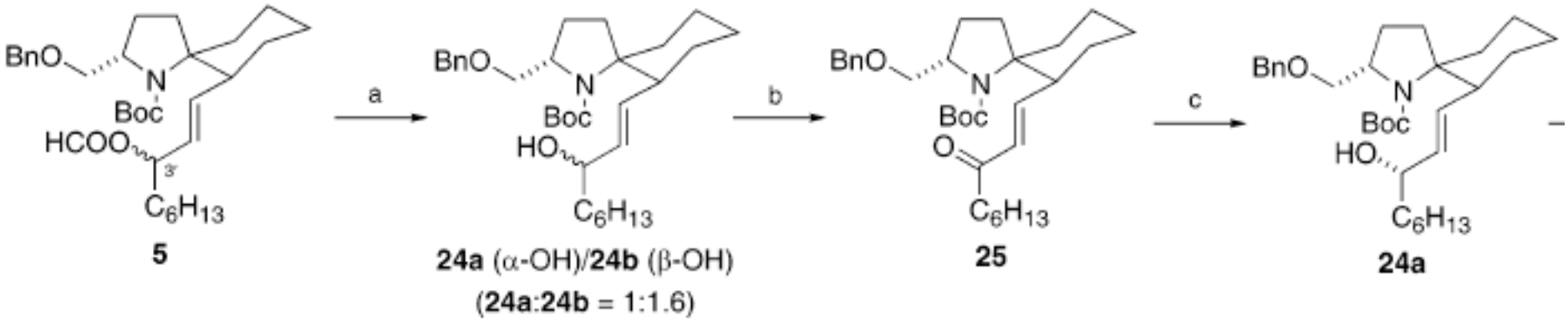


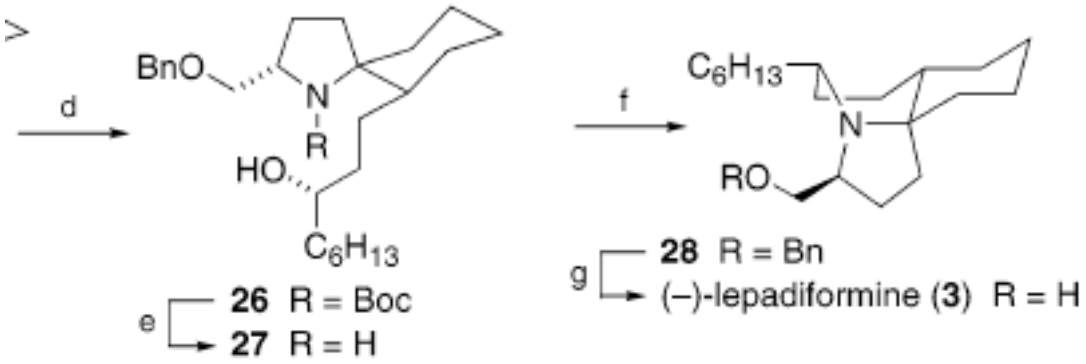
Stereoselective Formation of **5**



Stereoselective Formation of **5**



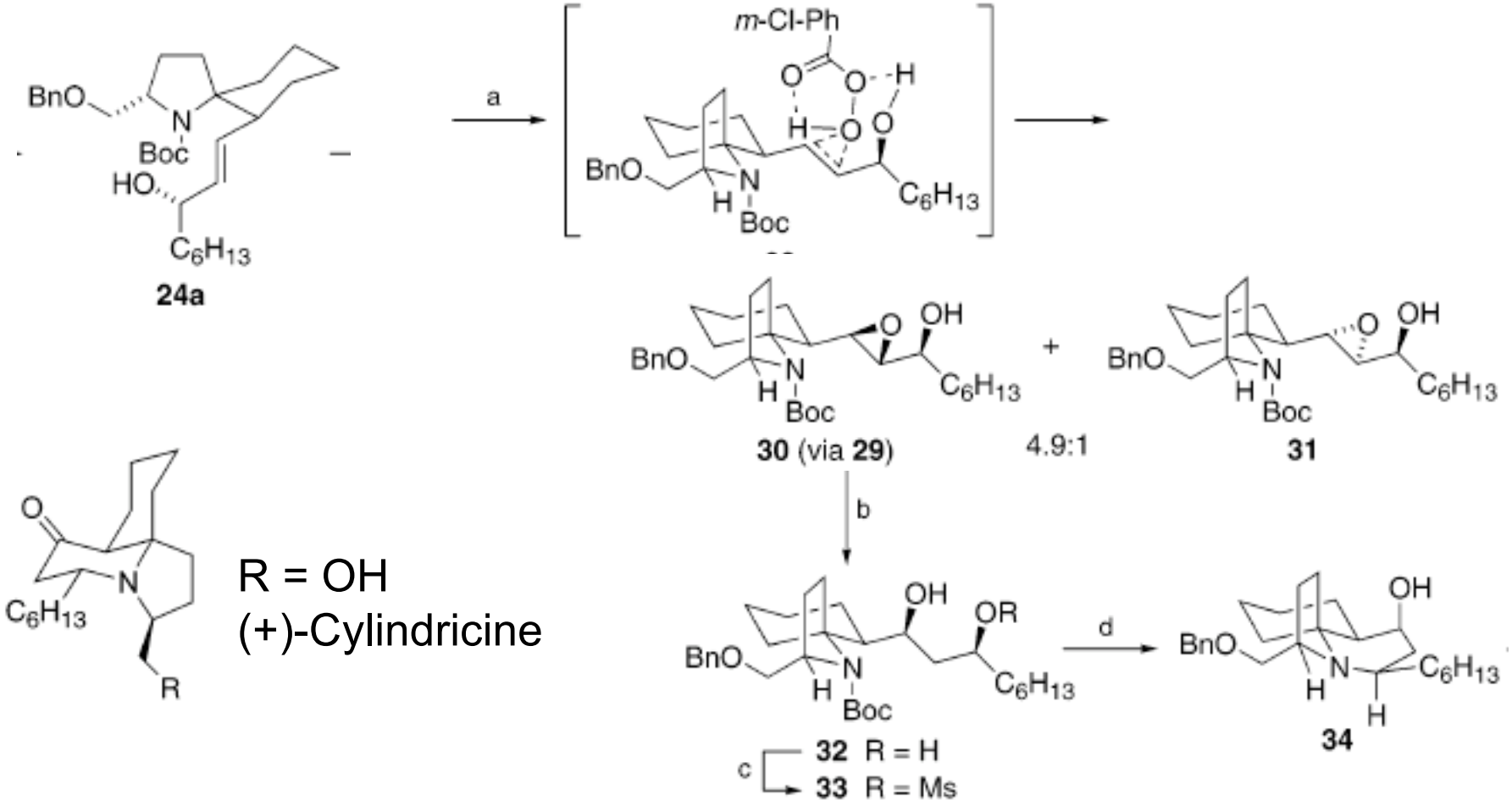




9 steps from **7** (pyrrolidinone), 31% yield

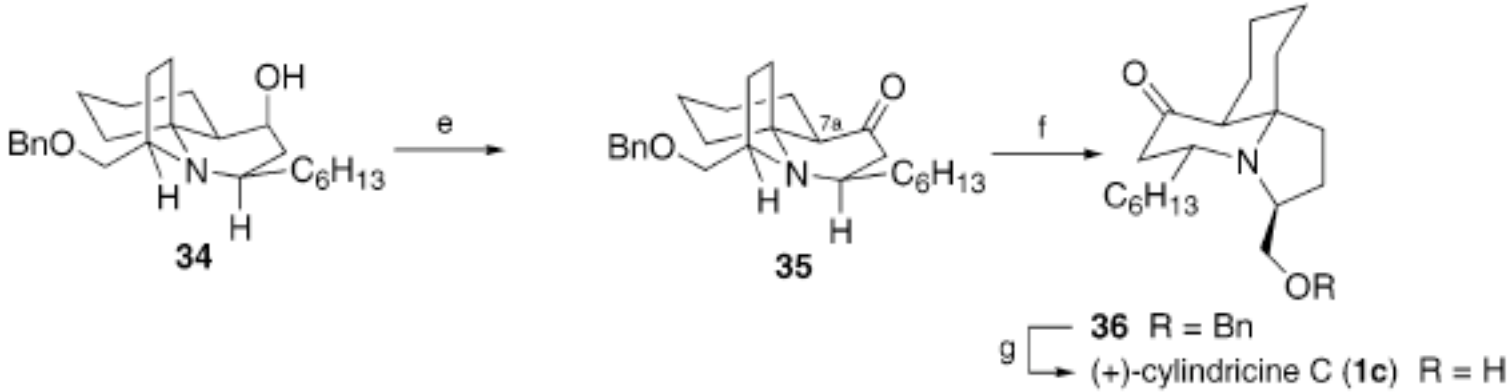
[a] Reagents and conditions: (a) K_2CO_3, MeOH−H_2O, room temperature, 98%; (b) MnO_2, CH_2Cl_2, room temperature, 91%; (c) method A: (*R*)-oxazaborolidine, BH_3·THF, 0 °C, 77% (60% de); method B: (*S*)-BINAL-H, THF, −78 °C, 92% (97% de); (d) H_2, PtO_2, AcOEt, 86%; (e) CF_3CO_2H, CH_2Cl_2, room temperature, 91%; (f) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, room temperature, 82%; (g) H_2, $Pd(OH)_2$−C, MeOH, 87%.

Synthesis of (+)-*Cylindricine*



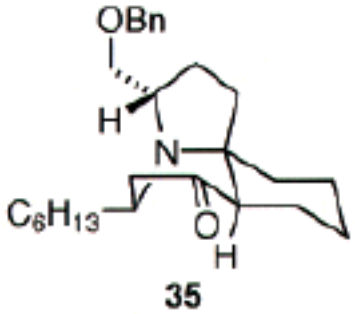
[a] Reagents and conditions: (a) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 0 °C, 68% for **30**; (b) $LiAlH_4$, Et_2O, room temperature, 84%; (c) MsCl (1 equiv), Et_3N, DMAP, CH_2Cl_2, room temperature, 73%; (d) CF_3CO_2H, CH_2Cl_2, room temperature, then $NaHCO_3$ aq, room temperature, 30 min, 84%; (e) Swern

Synthesis of (+)-*Cylindricine*



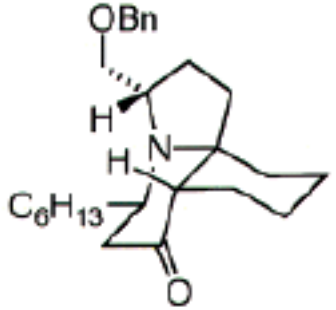
ox; (f) K_2CO_3 aq, MeOH, room temperature, 2 h, 86% over two steps; (g) H_2, $Pd(OH)_2$−C, MeOH, 73%.

38.3 kcal/mol



35

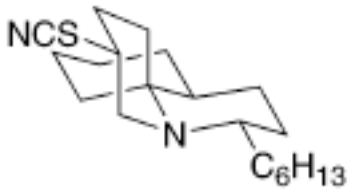
32.8 kcal/mol



36

MM2 calculation:
B ring of **35** is in boat conformation
epimer **36** with chair-chair conformation is more stable than **35**.

Synthesis of (-)-Fasicularin

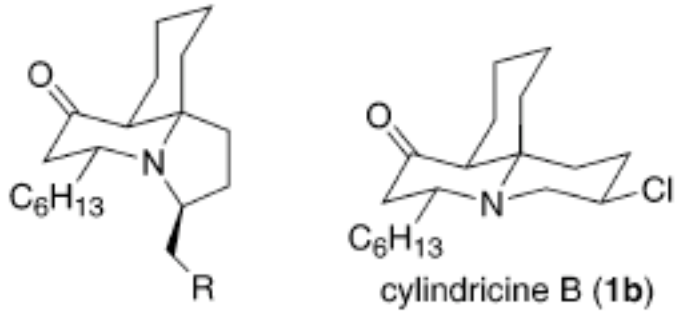


fasicularin (**4**)

Isolated in 1997 from the micronesian ascidian *Nephteis fasicularis*,

Trans-fused BC ring

Cytotoxic to Vero cells,
Selective activity against DNA repair-deficient organism

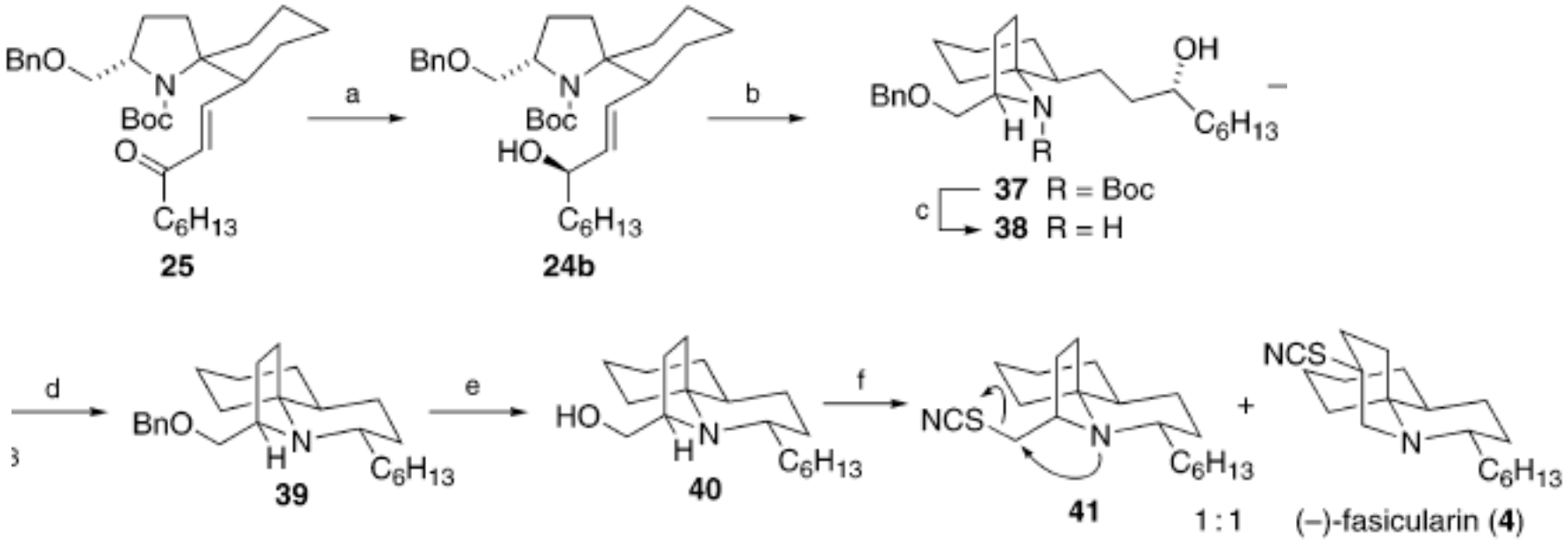


cylindricine A (**1a**) R = Cl
C (**1c**) R = OH

cylindricine B (**1b**)

1a <=>**1b** via aziridinium ion intermediate

Synthesis of (-)-*Fasicularin*



11 steps and 28% yield from **7**

[a] Reagents and conditions: (a) (*R*)-BINAL-H, THF, −78 °C, 84%, (80% de); (b) H_2, PtO_2, AcOEt, room temperature, 81%; (c) CF_3CO_2H, CH_2Cl_2, room temperature, 99%; (d) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, room temperature, 88%; (e) H_2, $Pd(OH)_2$−C, MeOH, 95%; (f) method A: HSCN, Ph_3P, DEAD, toluene, room temperature, 24 h, 20%; method B: NH_4SCN, Ph_3P, DEAD, CH_2Cl_2, room temperature, 15 min, 94%; (g) CH_3CN, room temperature, 72 h, 91%.

Remote functionalization of *o*-aminobenzamide

Scheme 2