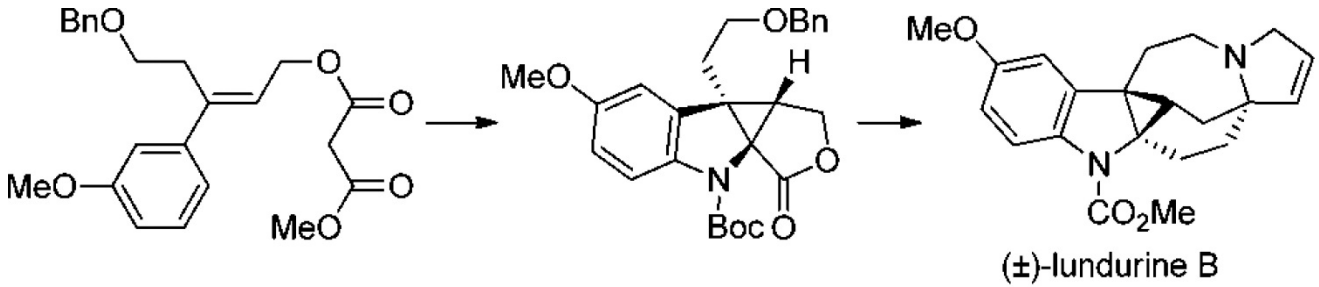
Total Synthesis of (±)-Lundurine B

Masaki Hoshi , Osamu Kaneko , Masaya Nakajima , Shigeru Arai , and Atsushi Nishida.
Org. Lett., **2014**, *16* (3), 768–771



(±)-lundurine B

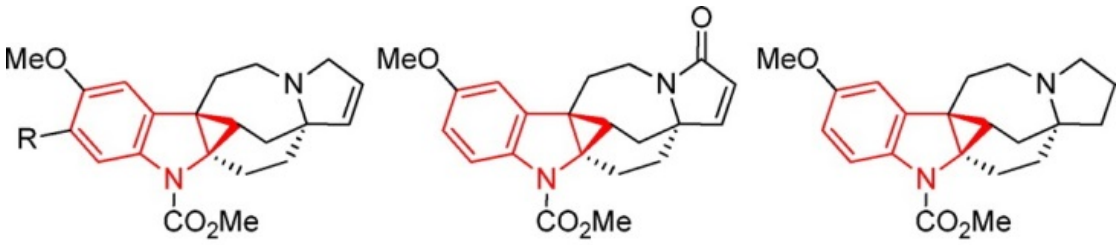
Liming Cao

Wipf Group Current Literature

2/15/2014

Lundurine B

- Plants of genus *Kopsia* are a rich sources of novel alkaloids with intriguing carbon skeletons and interesting biological activities.
- Lundurine B were first isolated from *Kopsia tenuis* in Malaysia by Kam and co-workers in 1995.
- The intriguing hexacyclic framework includes an unprecedented cyclopropane-fused indoline skeleton.
- The structures of Ludurine A-C reflect the progressive stages in the oxidation level.



R = H: lundurine B
R = OMe: lundurine D

lundurine A

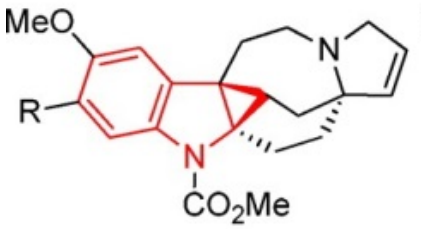
lundurine C

J. Nat. Prod. **1993**, 56, 1134
J. Nat. Prod. **2011**, 74, 1309
Tetrahedron Lett. **1995**, 36, 759
*Tetrahedron***2004**, 60, 10739

Cytotoxic Effects

Compound	IC_{50} value (μg/ml)			
	B16 melanoma	KB/S[a]	KB/VJ300[a]	KB/VJ300[b]
Lundurine A	>25	>25	>25	8.8
Lundurine B	2.8	19	15.5	4.6
Lundurine C	>25	>25	>25	14.2
Lundurine D	7.2	>25	>25	4.6

a. KB/S and KB/VJ300 are vincristine-sensitive and -resistant human oral epidermoid carcinoma cell line, respectively.
b. With added vincristine 0.1 μg/ml.



R = H: lundurine B
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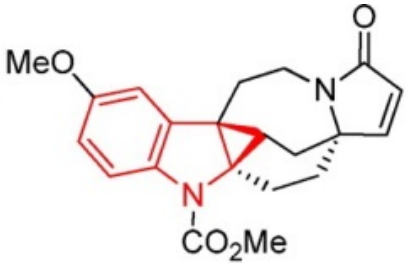
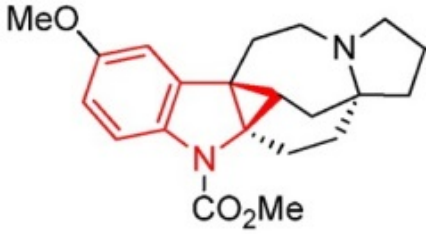


lundurine A



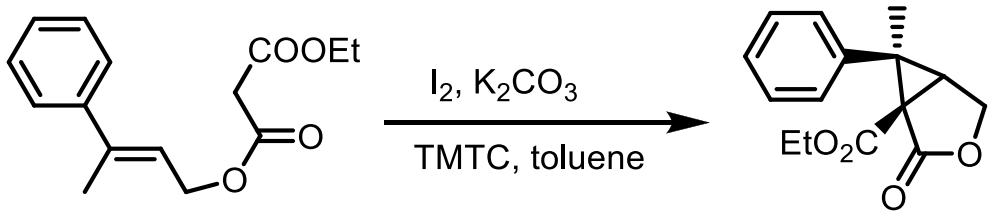
lundurine C

- Lundurines B and D showed appreciable in vitro cytotoxicity towards B16 melanoma cells.
- Surprisingly, lundurines B and D did not display appreciable cytotoxicity towards KB cells, but were found instead to be effective in circumventing multidrug-resistance (MDR) in vincristine-resistant KB cells.

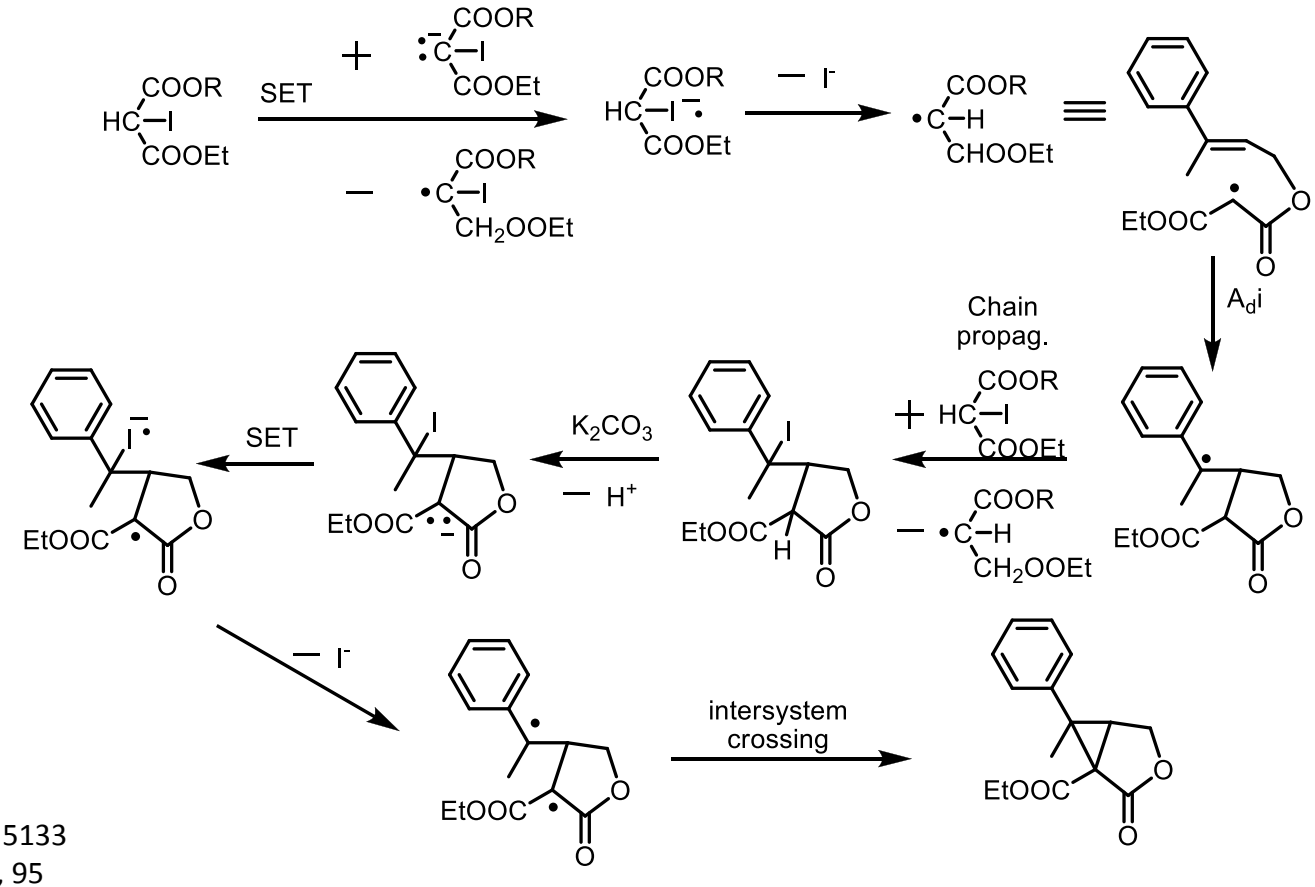
Tetrahedron **2004**, 60, 10739

Preparation of Cyclopropanes

Töke:

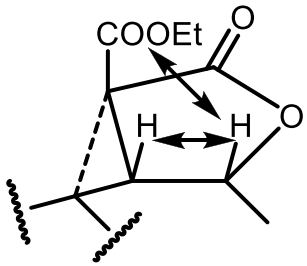


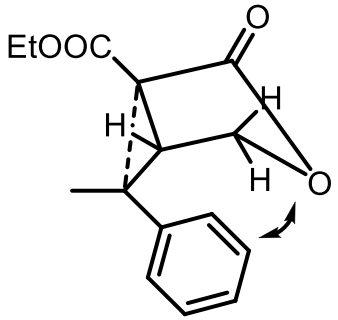
Mechanism:



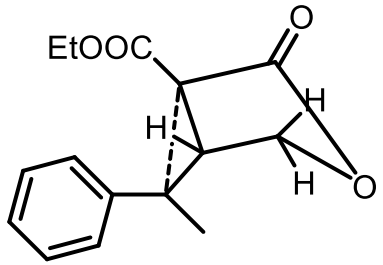
Tetrahedron **1993**, 49, 5133
THEOCHEM **1997**, 392, 95
Tetrahedron **1999**, 55,1367

Preparation of Cyclopropanes





endo

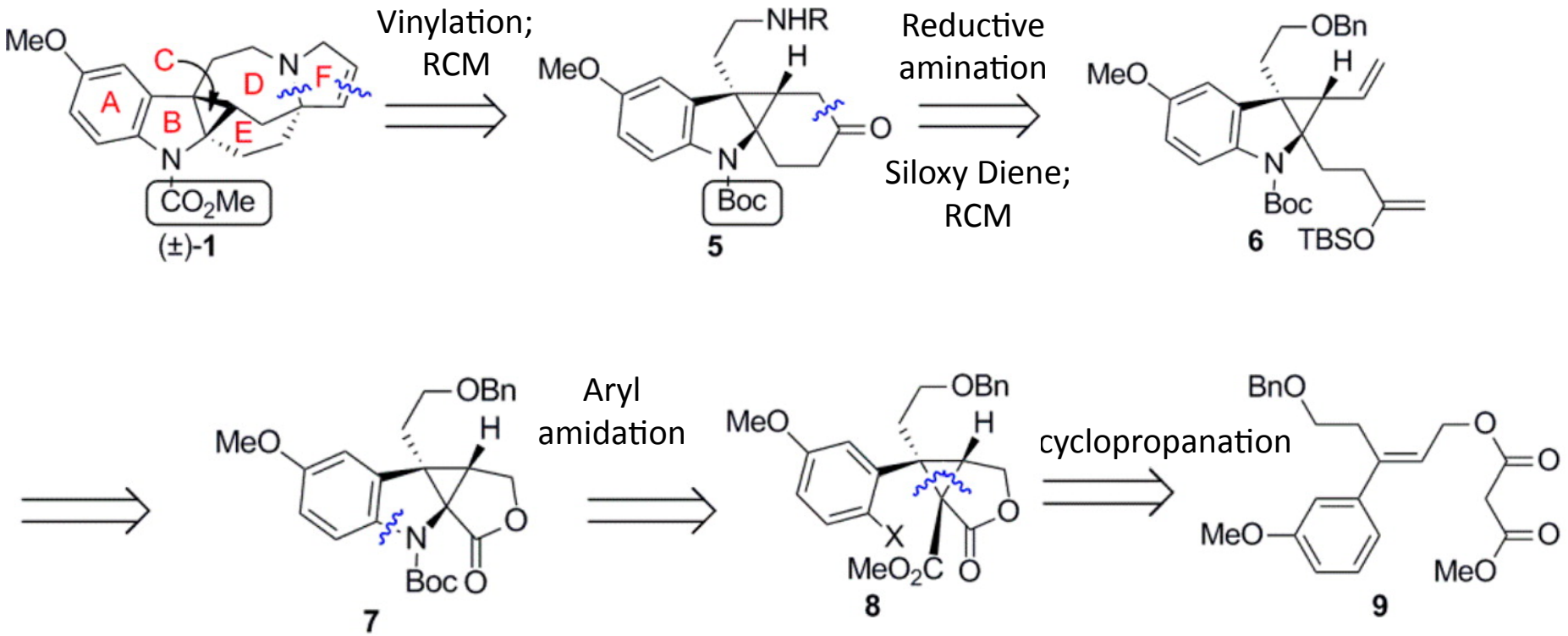


exo

- Steric interactions diminished if the lactone moiety in an envelope-like conformation
- The repulsive force between the lactone-oxygen and the phenyl group in the *endo* position increased, making the *exo* conformation more favorable

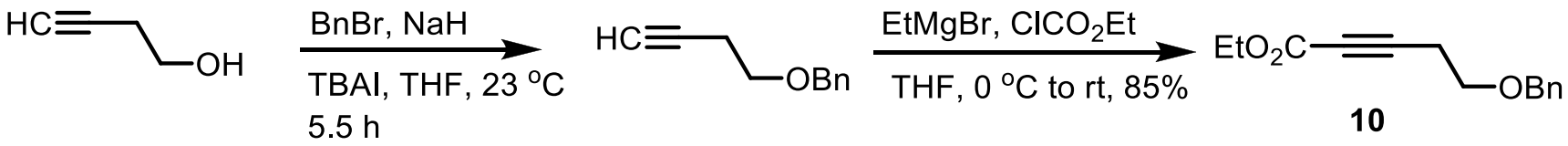
Tetrahedron **1999**, 55,1367

Retrosynthesis



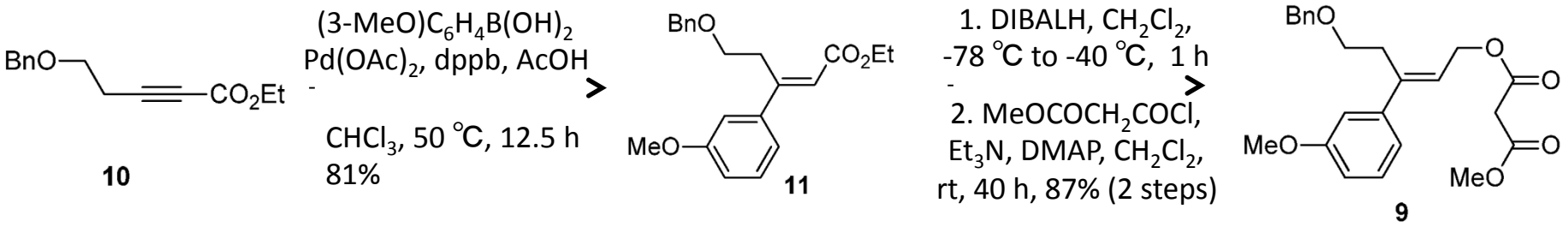
Org. Lett. **2014**, *16* , 768–771

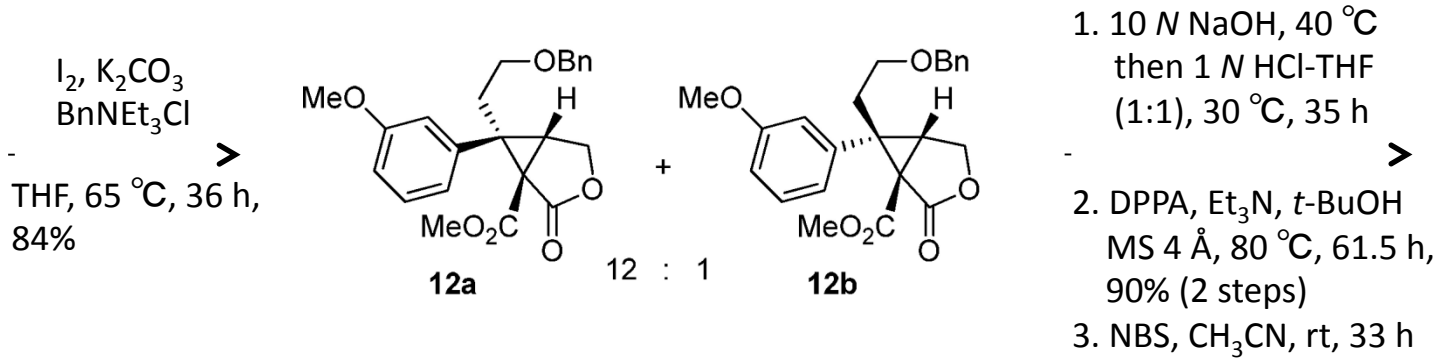
Starting Material



Tetrahedron Lett **2004** , *45*, 7855
Tetrahedron: Asymmetry **2004**, 15, 81

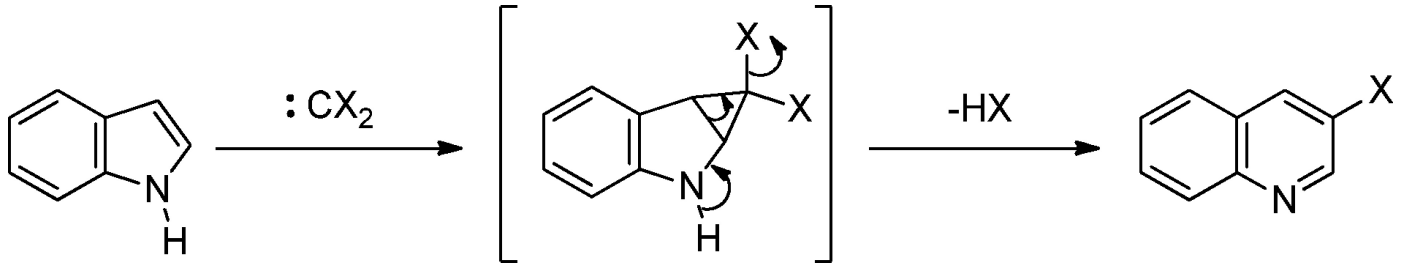
Synthesis of Cyclopropane-Fused Indoline





Org. Lett. **2014**, *16* , 768–771

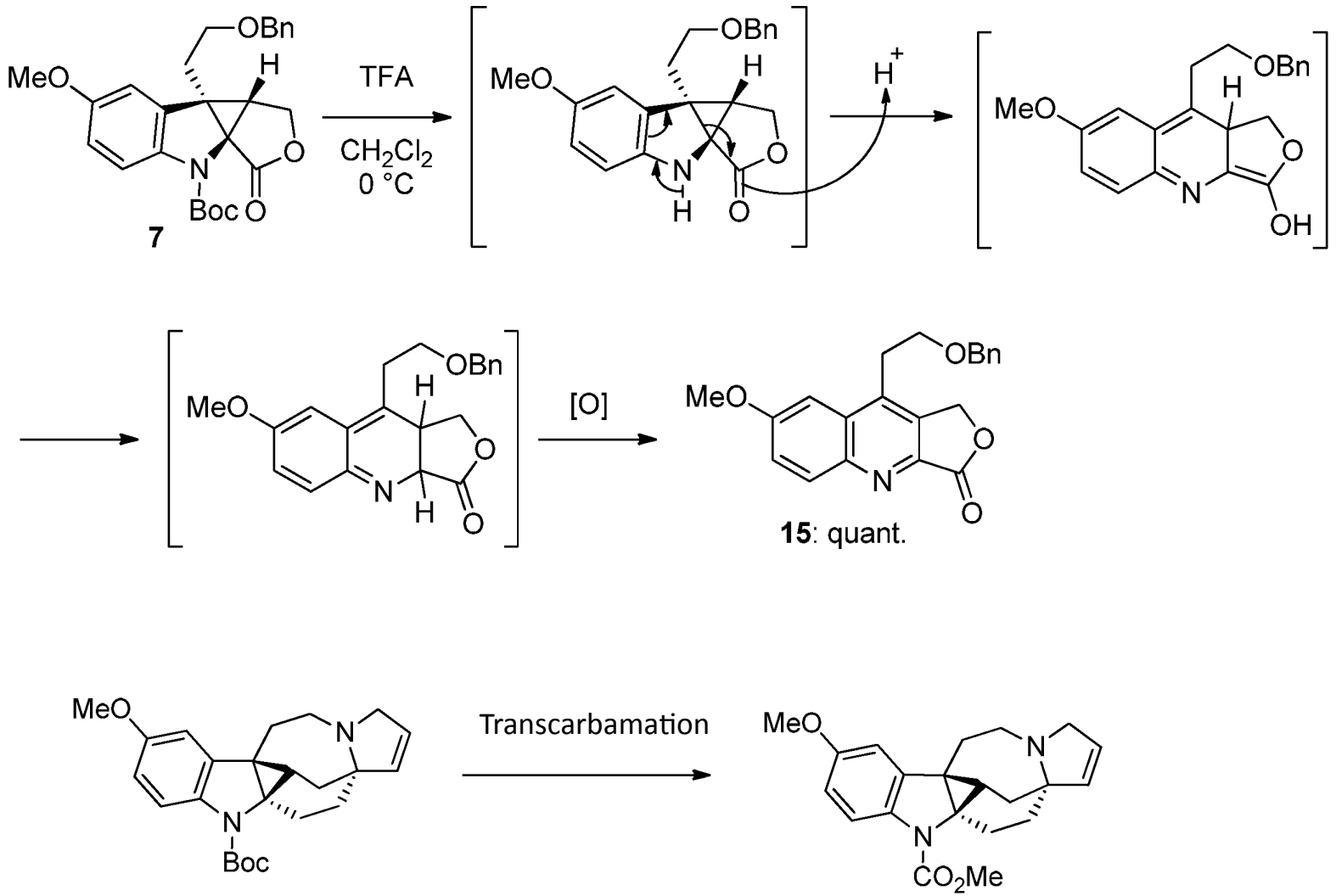
Rearrangement of Cyclopropane-Fused Indolines



- The old rearrangement of cyclopropane-fused indolines prepared by the reaction of indole and dihalocarbene gives a quinoline skeleton with a release of strain energy.

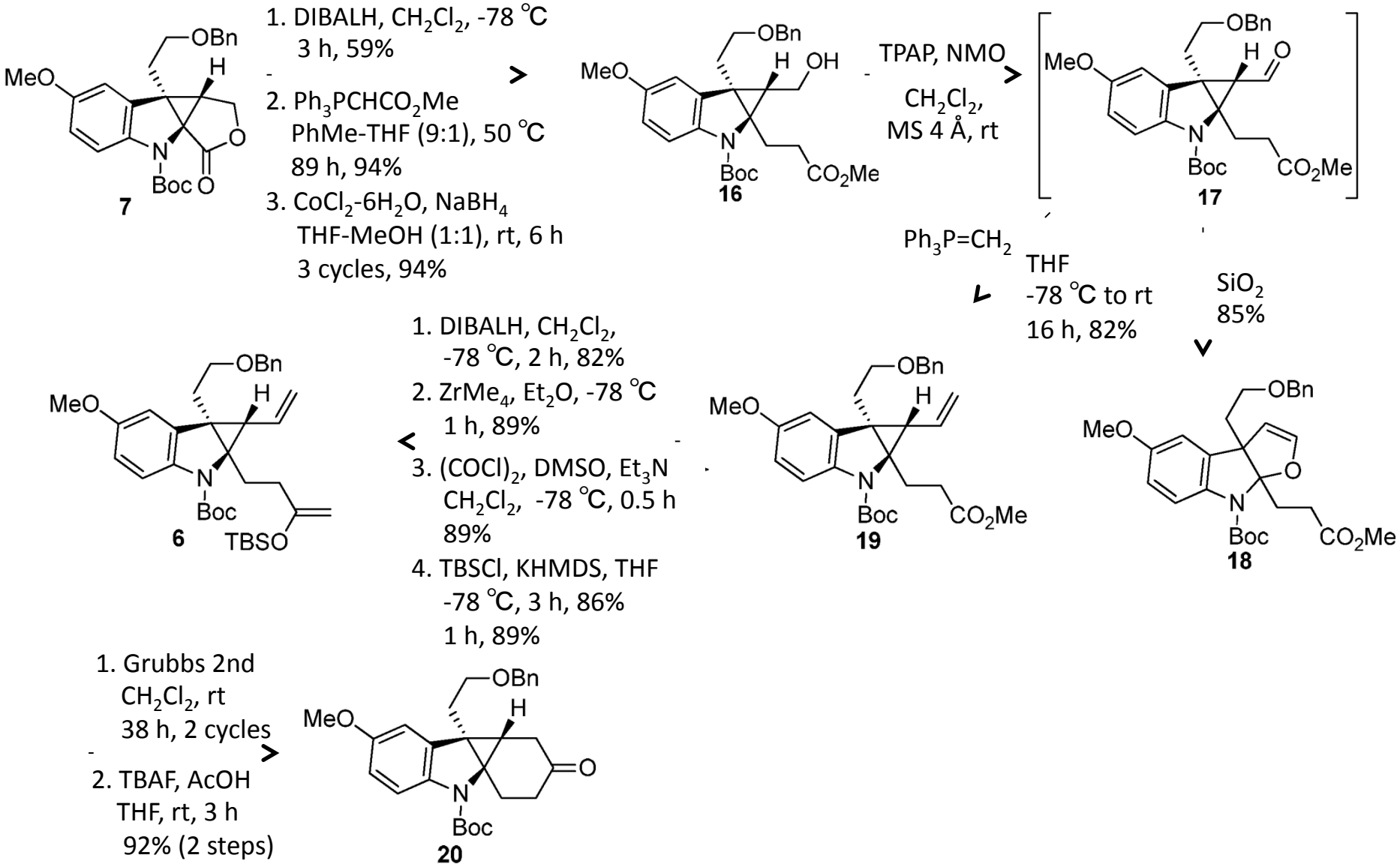
Ber **1906**, 39,2515
Ber **1906**, 39, 4388
Org. Lett. **2014**, *16* , 768–771

Acid-Promoted Rearrangement of Cyclopropane-Fused Indoline to Quinoline



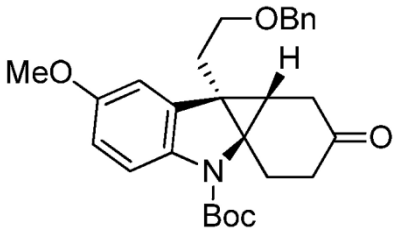
Org. Lett., **2014**, *16*, 768–771
J. Org. Chem. **1990**, 55, 870

Synthesis of ABCE Core Skeleton



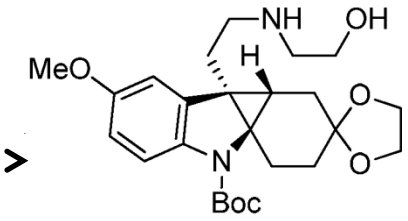
Org. Lett. **2014**, *16*, 768–771

Total Synthesis of (±)-Lundurine B



20

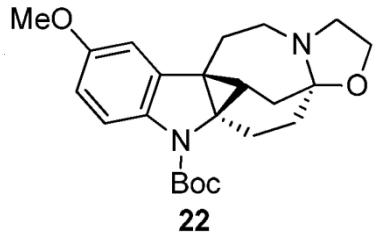
1. $TMSOCH_2CH_2OTMS$ $TMSOTf$, CH_2Cl_2 -78 °C, 22 h
2. H_2, $Pd(OH)_2/C$, EtOH, rt, 1.5 h
3. $(COCl)_2$, DMSO, Et_3N CH_2Cl_2, -78 °C, 0.5 h 83% (3 steps)
4. 2-aminoethanol, MeOH, rt 3.5 h, then $NaBH_4$, rt, 26 h



21

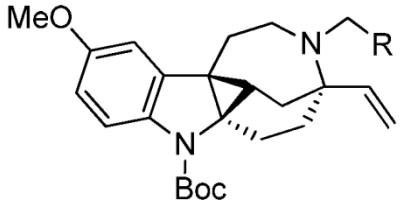
$AcOH\text{-}THF\text{-}H_2O$ (3:1:1), 40 °C, 32 h

then $CHCl_3$, MS 4 Å 62 °C, 8 h, 81% (2 steps)



22

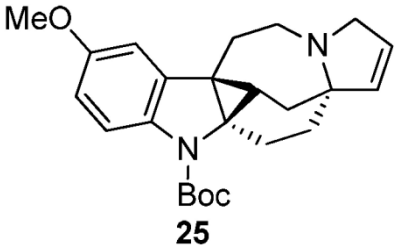
1. vinylMgBr, $AlCl_3$, $Et_2O\text{-}CH_2Cl_2$ (20:1), rt, 3 h, 86%
2. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1.5 h, 80%
3. Ph_3PCH_3Br, *n*-BuLi , THF, rt, 2.5 h 63%



23: R = CH_2OH
24: R = $CH{=}CH_2$

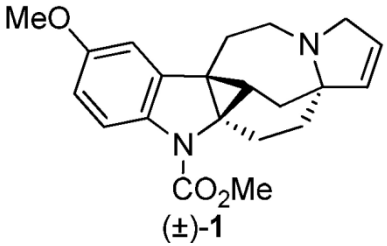
Grubbs 2nd

CH_2Cl_2, rt, 31 h 97%



25

1. $TMSOTf$, TMEDA CH_2Cl_2, rt, 16 h
2. MeI, TBAF, THF MS 4 Å, 0 °C, 0.5 h 31% (2 steps)



(±)-**1**

Org. Lett. **2014**, *16* , 768–771

Conclusion

- A total synthesis of (±)-Lundurine B was achieved from known material in 29 steps.
- This synthesis features:
  - A highly efficient and stereoselective synthesis of cyclopropane-fused indoline
  - Siloxy-diene RCM for a fused cyclohexanone,
  - Bridgehead vinylation
  - Transcarbamation of a hindered N-boc group