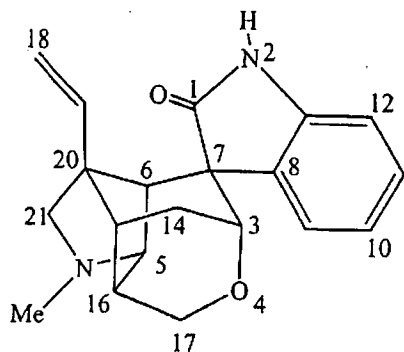


# Total Synthesis of Gelsemine

## 1. Introduction



Gelsemine.

### Isolation

G. sempervirens (Carolina jasmine)

Wormley, T.G. Am. J. Pharm. 1870, 42, 1

### Structure determination

Lovell, F.M. et al. Tetrahedron Lett. 1959, 4, 1

Conroy, H.; Chakrabarti, J.K.

Tetrahedron Lett. 1959, 4, 6

### Bioactivity

analgesic action

	1240 mg/kg	orally
LD <sub>50</sub>	405 mg/kg	intraperitoneally
(mice)	133 mg/kg	intravenously

## Total Synthesis

Johnson, A.P. et al. J. Chem. Soc. Chem. Commun. 1994, 763

Speckamp, W.N. et al. J. Chem. Soc. Chem. Commun. 1994, 767

Hart, D.J. et al. J. Am. Chem. Soc. 1994, 116, 6943

Fukuyama, T. et al. J. Am. Chem. Soc. 1996, 118, 7426 (racemic)

Angew. Chem. Int. Ed. 2000, 39, 4073

Overman, L.E. et al. Angew. Chem. Int. Ed. 1999, 38, 2934

Danishefsky, S.J. et al. Tetrahedron Lett. 2002, 43, 545

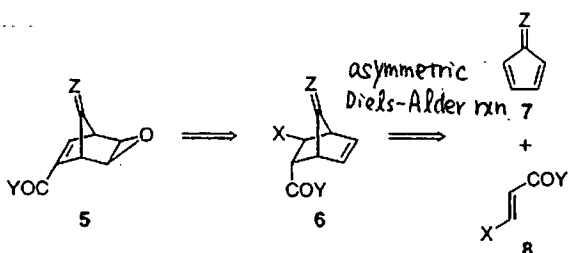
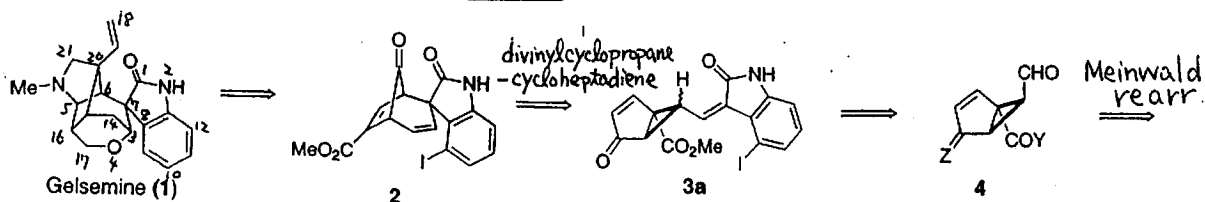
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4. Other Approaches of Constructing Spirooxindole at C17.

## 2. Enantioselective Total Synthesis of (+)-Gelsemine

T. Fukuyama et al.

### 2-1. Retrosynthetic Analysis

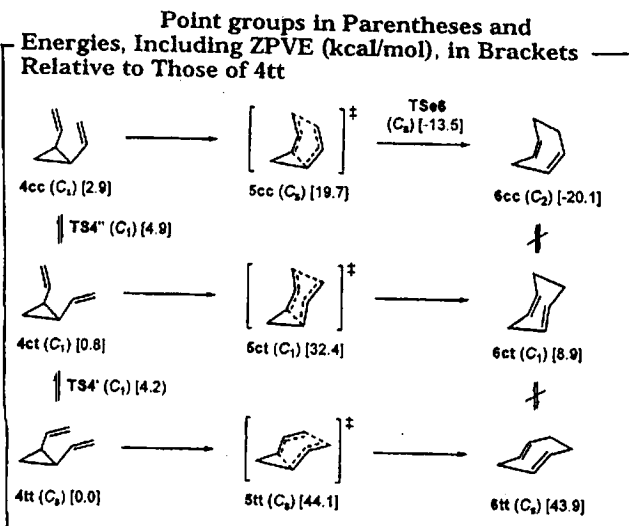


- The stereochemistry at C7 can be controlled by divinylcyclopropane-cycloheptadiene rearrangement.

- Total synthesis commences with asymmetric Diels-Alder reaction.

### 2-2. Key Reaction ~ Divinylcyclopropane-Cycloheptadiene Rearrangement ~

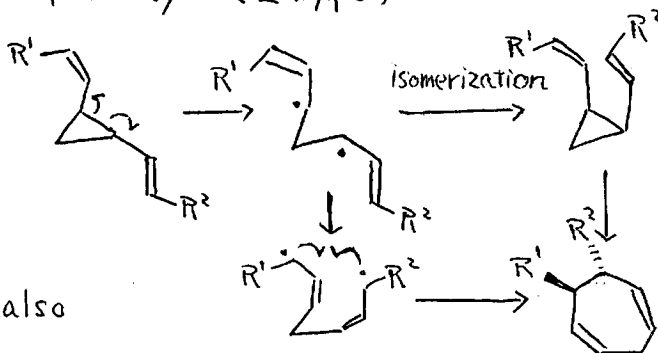
- This reaction is one of the Cope-type rearrangement.



J. Org. Chem. 2003 68 9638

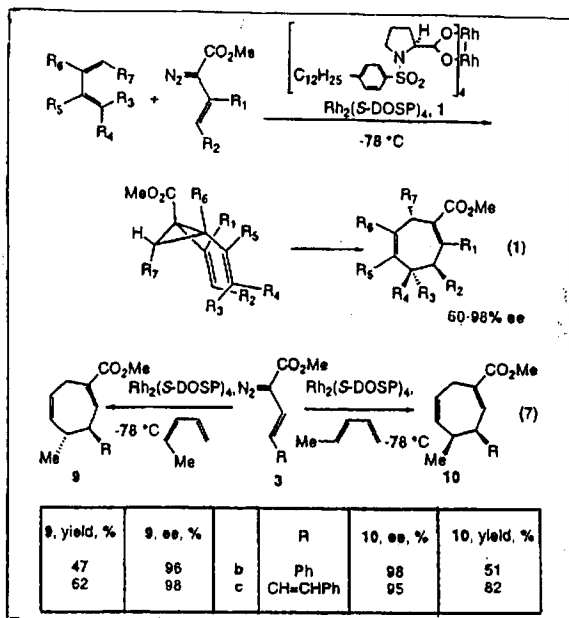
⑨ Preferred transition state is boatlike conformation.

- cis-Divinylcyclopropane rearrangement proceeds via concerted pathway. But trans-divinylcyclopropane is thought to proceed via radicalic pathway. (2 type)



- trans-Divinylcyclopropane rearr. is also highly stereoselective reaction.

So, I think this reaction proceeds via isomerization-concerted pathway.

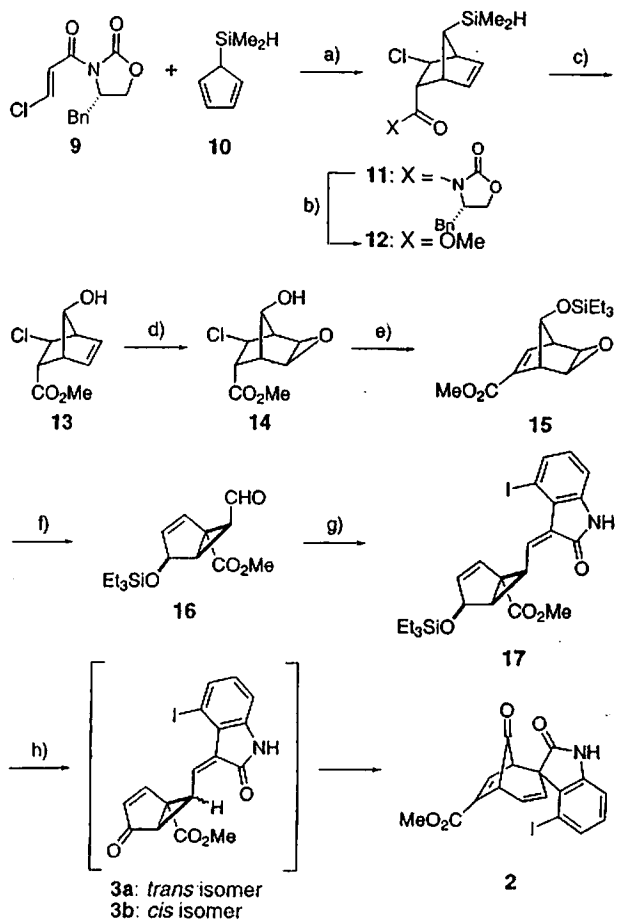


⑤ Combined with asymmetric cyclopropanation, this reaction can be used as a powerful method to construct cycloheptadiene diastereoselectively and enantioselectively.

J. Am. Chem. Soc. 1998, 120, 3326

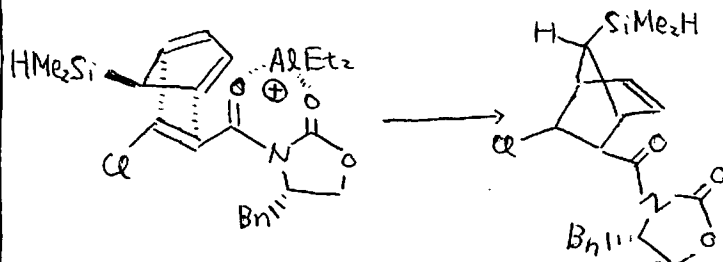
## 2-3. Total Synthesis

### Synthesis of the bicyclo[3.2.1] system



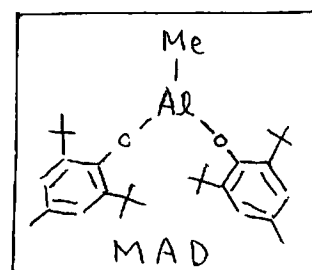
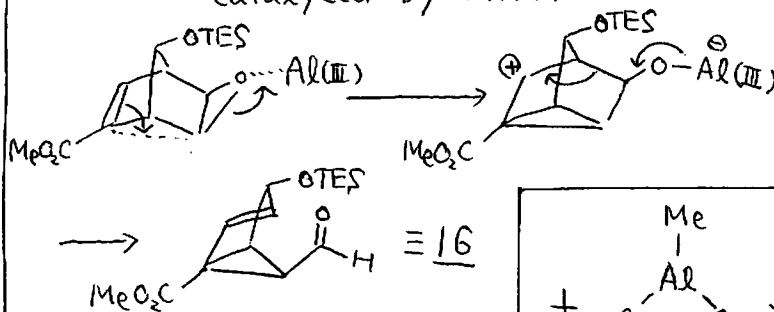
Scheme 2. Synthesis of the bicyclo[3.2.1] system. a)  $\text{Et}_2\text{AlCl}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 88%; b) cat.  $\text{Sm}(\text{OTf})_3$ ,  $\text{MeOH}$ , 99%; c) 30%  $\text{H}_2\text{O}_2$ ,  $\text{KF}$ ,  $\text{KHCO}_3$ ,  $\text{THF}/\text{MeOH}$ , 53%; d)  $\text{VO}(\text{acac})_2$ ,  $t\text{BuOOH}$ , benzene, 100%; e)  $\text{TESOTf}$ , 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ , 97%;  $t\text{BuOK}$ , benzene, 98%; f) MAD, toluene,  $-20^\circ\text{C}$ ; g) 4-iodooxindole, cat. piperidine,  $\text{MeOH}$ , 60% (2 steps); h) TBAF,  $\text{THF}$ , 87%;  $\text{CrO}_3$ ,  $\text{H}_2\text{SO}_4$ , acetone; toluene/ $\text{MeCN}$ ,  $90^\circ\text{C}$ , 83% (2 steps). Bn = Benzyl, Tf = trifluoromethanesulfonyl, acac = acetylacetonate, TES = triethylsilyl, MAD = methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide), TBAF = tetrabutylammonium fluoride.

9+10  $\rightarrow$  11; Chiral auxiliary controlled asymmetric Diels-Alder rxn.



• Optically pure compound was obtained by using Evans's chiral auxiliary.

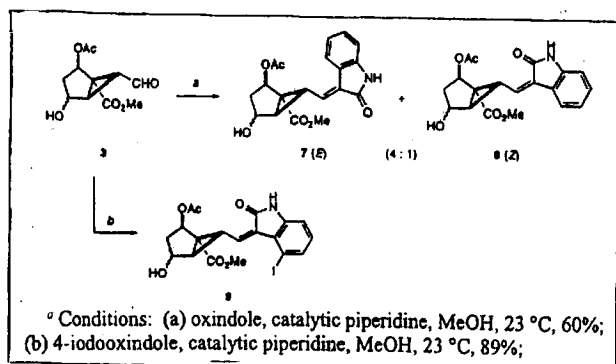
15  $\rightarrow$  16; Meinwald rearrangement catalyzed by MAD.



16 → 17; Knoevenagel condensation.

① The ratio of E/Z is very important at next step.

• They afforded to obtain desired product in racemic case.



J. Am. Chem. Soc. 1996, 118, 7426

② By introducing bulky substituent, (Z)-isomer was obtained as sole product.

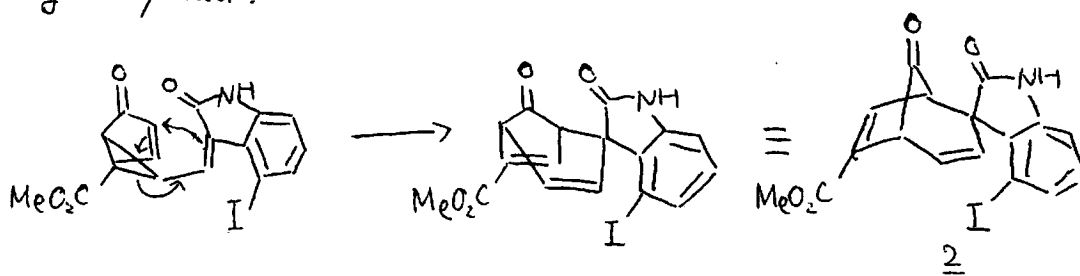
• This strategy worked well, too, on conversion of 16 to 17.

(Z)-isomer is more stable than (E)-isomer by 7.2 kcal·mol<sup>-1</sup>.  
According to PM3 calculation.

17 → 2; Divinylcyclopropane-Cycloheptadiene rearrangement.

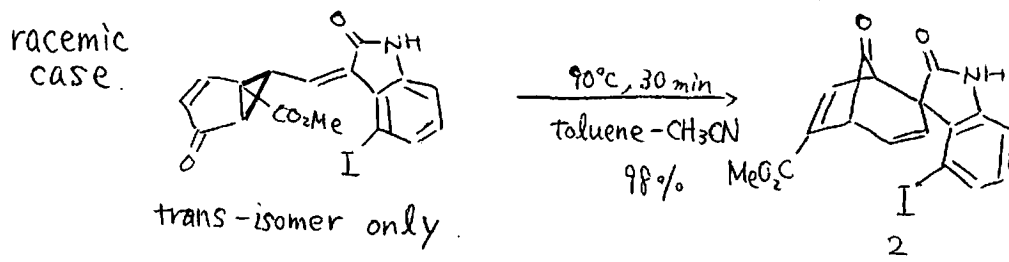
• 3a, b and 2 were in the reaction mixture after Jones' oxidation at r.t..

By heating at 90 °C, these compounds furnished 2 in good yield.

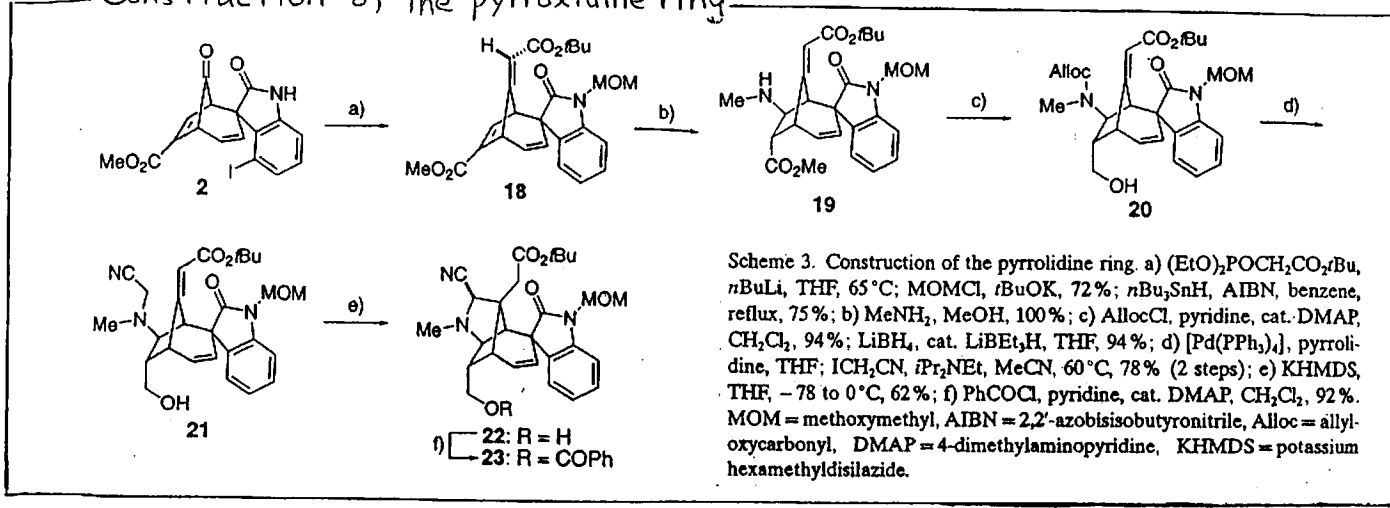


• Trans-isomer also converted to 2 smoothly.

This result is consistent with racemic case.



Construction of the pyrrolidine ring






18  $\rightarrow$  19 ; Michael addition of the methylamine

- Methylamine attacked from less hindered exo side, and protonation also occurred at exo side.

- This stereoselectivity is important to construct desired pyrrolidine ring and tetrahydropyran ring.

19  $\rightarrow$  20 ; Reduction of methyl ester.

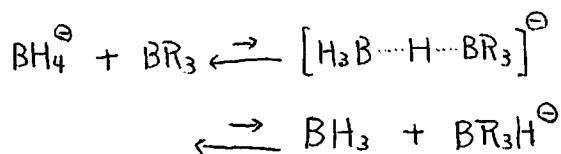
Table I. Rate of Reduction of Ethyl Caproate by  $LiBH_4$  in the Presence of Various Catalysts in Ether at  $25^\circ C^a$ .

catalyst	% reaction					
	0.5 h	1 h	2 h	4 h	8 h	24 h
no catalyst	17	28	41	65	100	100
$LiEt_3BH$	80	100	100			
	100	100				
$LiEt_2BOMe$	83	98	100			
	100	100				
$BF_3 \cdot OEt_2$	21	35	50	73	100	100
$BH_3 \cdot THF$	10	14	18	26	53	62
$n-Bu_3B$	22	98	100			
	100	103				
$n-OctB(OMe)_2$	92	100				
$(MeO)_2B$	52	100				
$(PhO)_2B$	14	30	45	68	98	
$(n-DodO)_2B^b$		26	46		100	

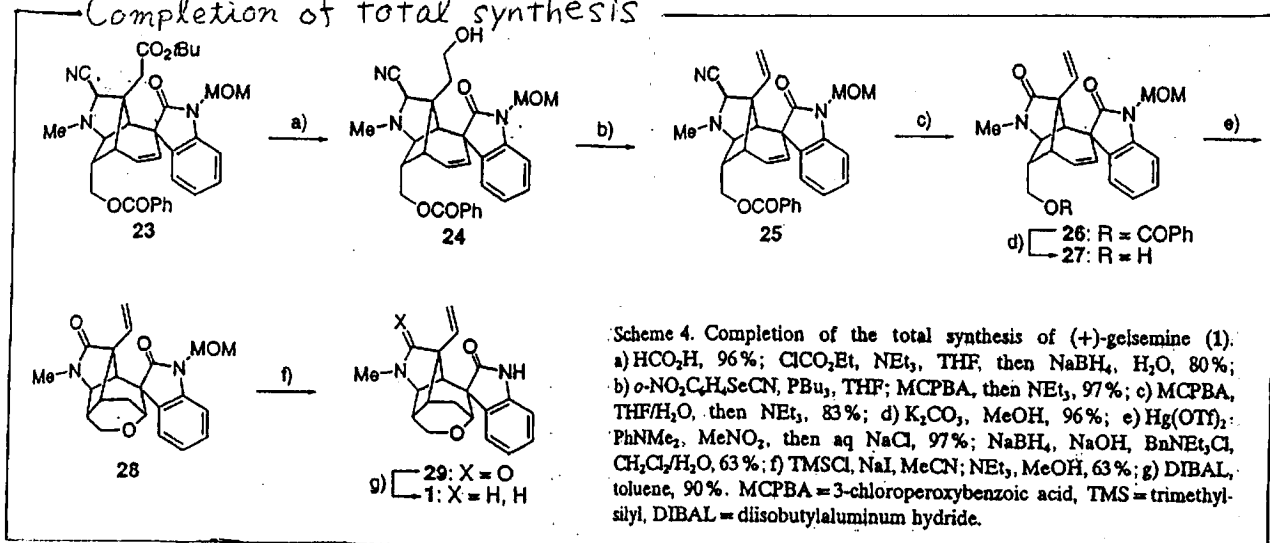
<sup>a</sup> [Ester] = 1.0 M;  $[LiBH_4]$  = 1.0 M; [catalyst] = 0.1 M.

g) Catalytic amount of  $LiBEt_3H$  accelerates the reduction of the ester.

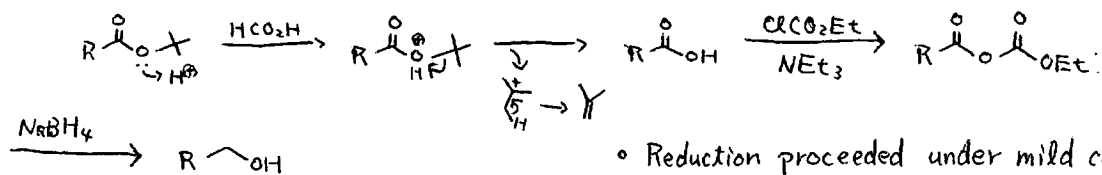
- One possible explanation is a rapid mobile equilibrium that produces a small quantity of the substituted borohydride



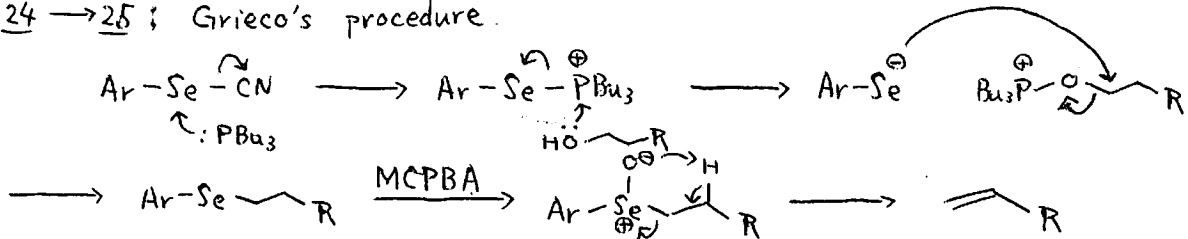
## Completion of total synthesis



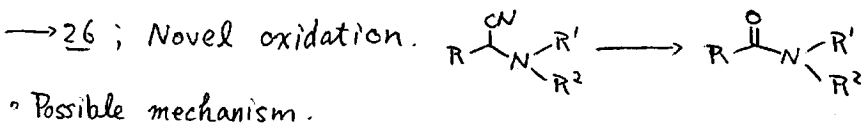
23  $\rightarrow$  24; Reduction of tert-butyl ester via mixed anhydride.



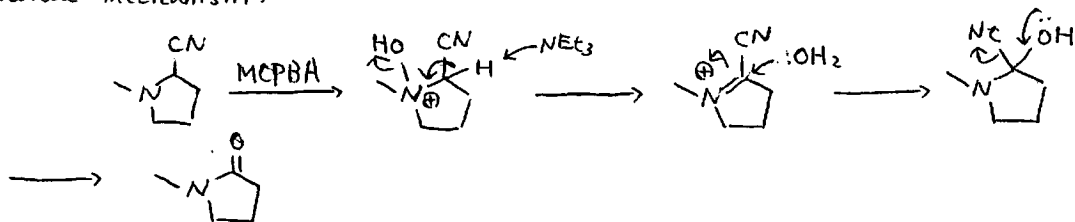
24  $\rightarrow$  25; Grieco's procedure.



25  $\rightarrow$  26; Novel oxidation.

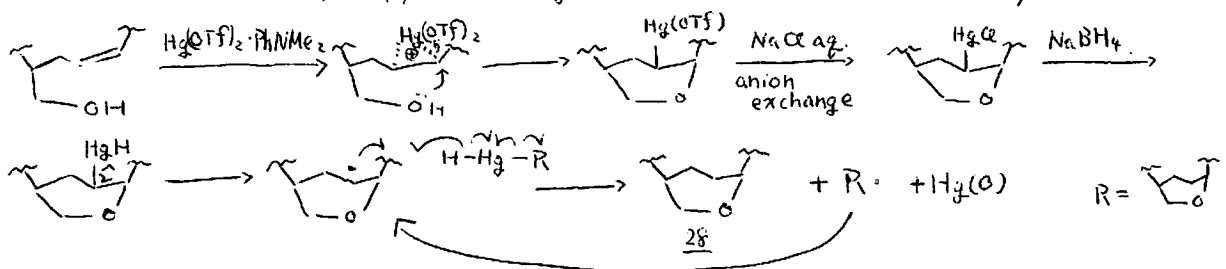


• Possible mechanism.



27  $\rightarrow$  28; Oxymercuration followed by reductive demercuration.

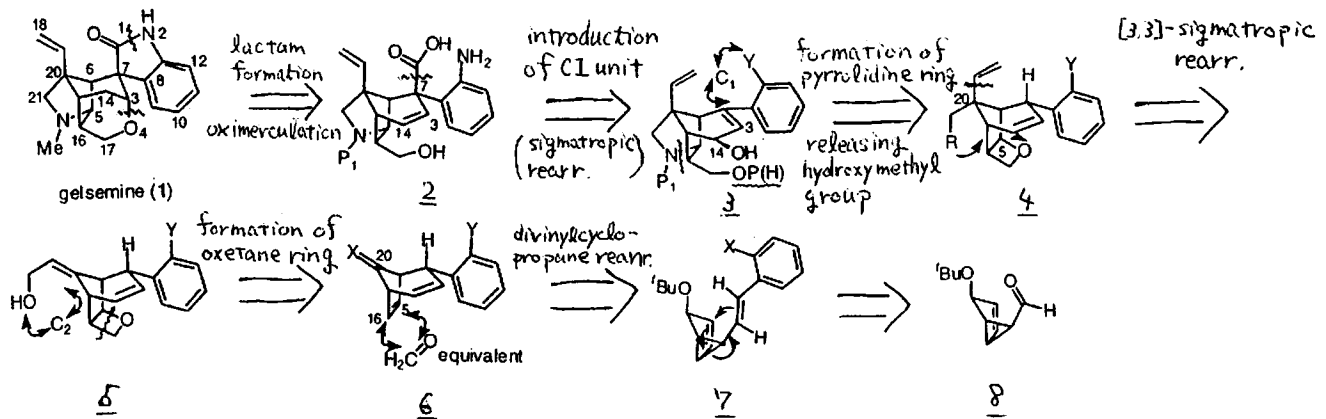
⊙ Desired tetrahydropyran ring was constructed smoothly.



### 3. Total Synthesis of (±)-Gelsemine

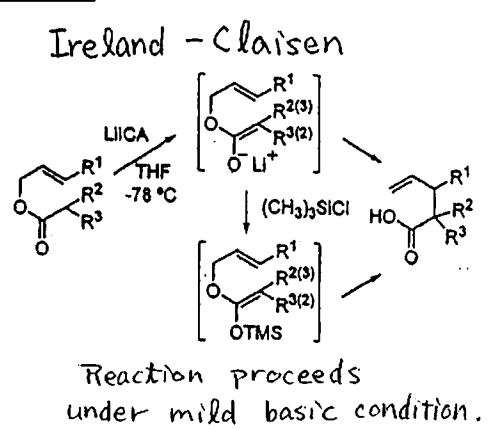
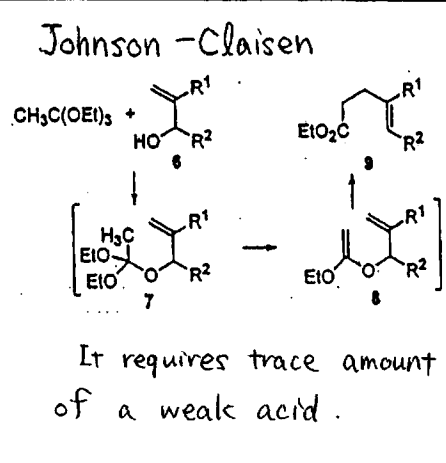
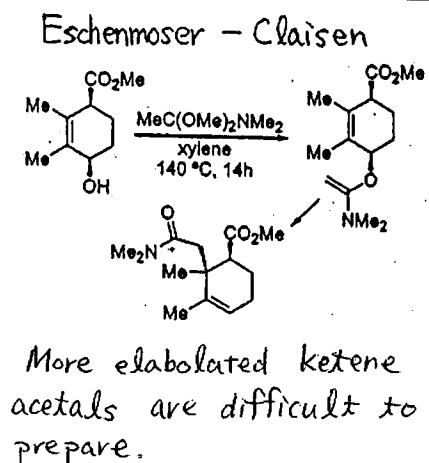
Panishetsky, S.J. et al.

#### 3-1. Retrosynthetic Analysis.

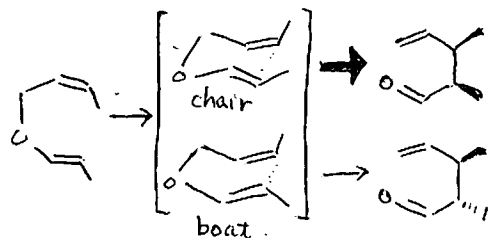


- ① They used divinylcyclopropane rearr., too.
- ② Hydroxymethyl group was released to convex side via oxetane ring.
- ③ Sigmatropic rearr. played important roles.

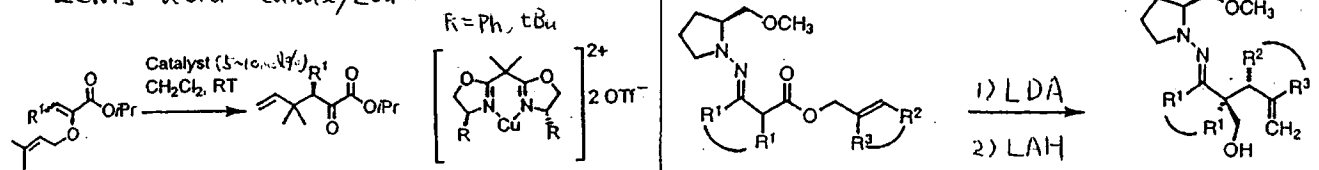
#### 3-2. Key Reaction ~ Claisen rearrangement derivatives ~



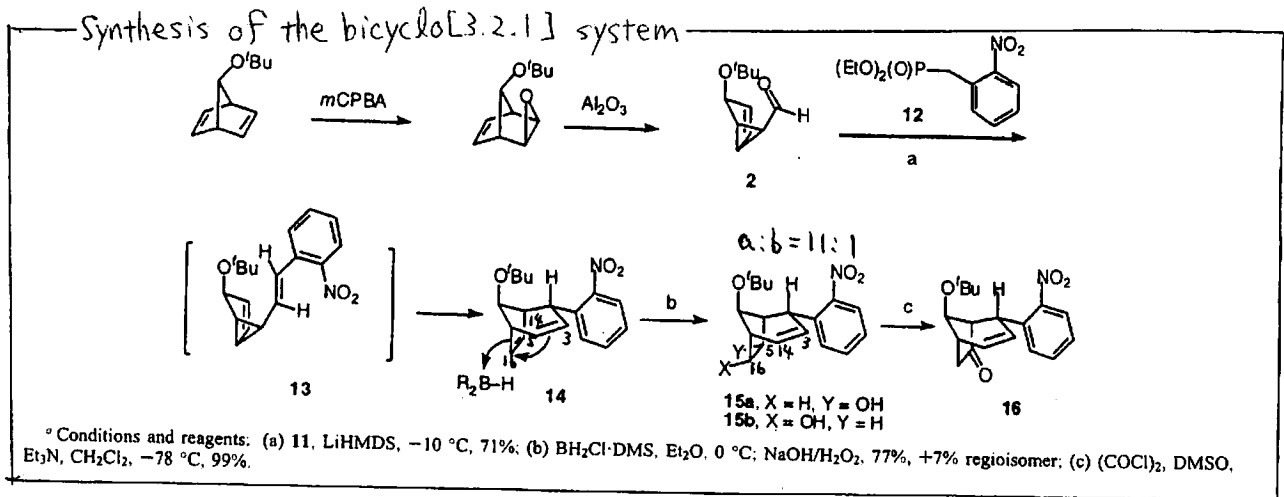
- ① These reactions prefer chairlike transition state to boatlike transition state. (minimizing the repulsive steric interactions)
- ② Stereochemistry of the product is easy to predict because of the chairlike transitionstate.
- ③ Recently enantioselective Claisen rearrangement has developed.



Lewis acid catalyzed.



## 3-3. Total Synthesis



$2 \rightarrow 14$ ; HWE olefination followed by divinylcyclopropane rearr.

• In contrast to Fukuyama's case, 13 was cis-isomer only, so the reaction proceeded smoothly at  $-10^{\circ}\text{C}$ .

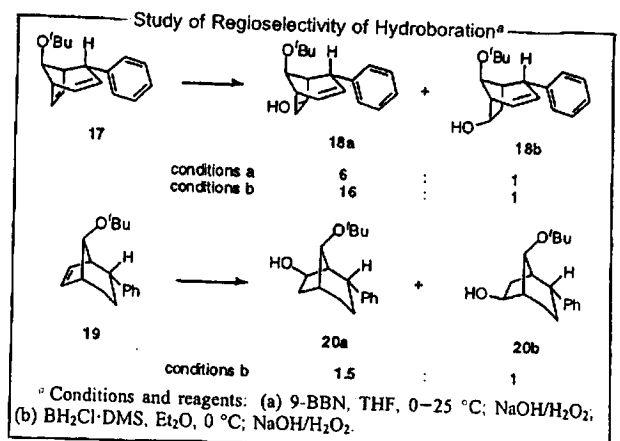
$14 \rightarrow 15a$ ; Chemoselective and regioselective hydroboration-oxidation.

① C5-C16 double bond is more reactive than C3-C14 double bond, because of the greater level of strain.

② Regioselectivity depends on homoallylic effect of C3-C14.

③ More electrophilic boron reagent ( $\text{BH}_2\text{Cl}\cdot\text{DMS}$ ) enhances the electron-deficient transition state, and results in a higher regioselectivity.

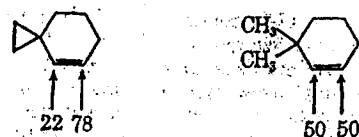
(When 9-BBN was used on 14, the ratio of a:b was 6:1.)



④ Almost no selectivity occurred without homoallylic effect.

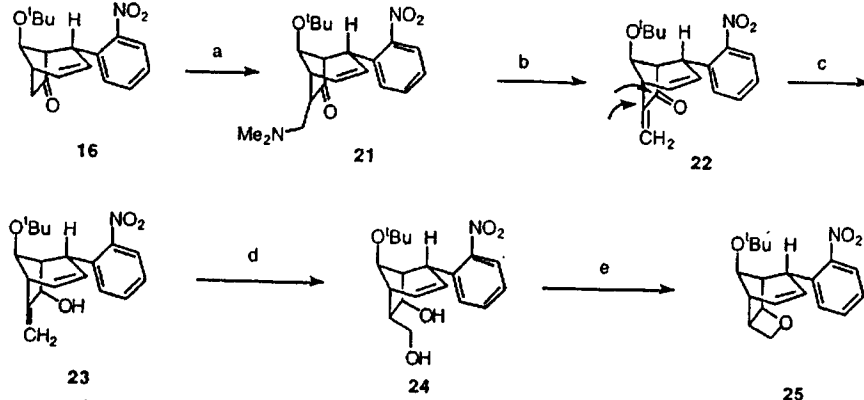
( $19 \rightarrow 20a, b$ )

• Cyclopropyl substitution showed similar effect.



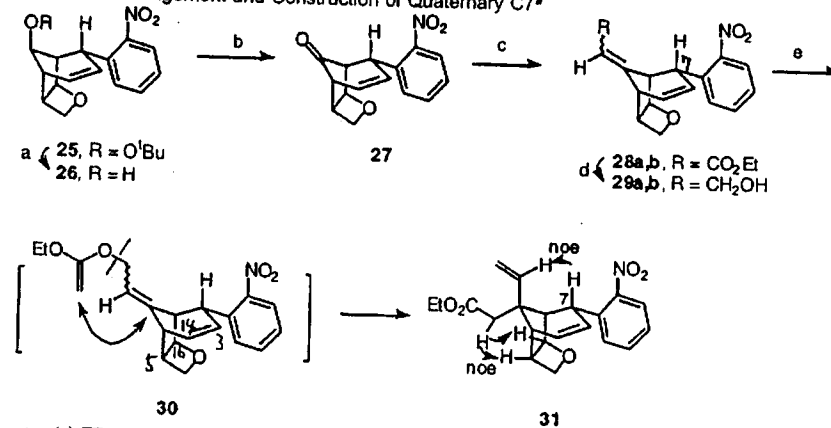


Construction of oxetane ring



<sup>a</sup> Conditions and reagents: (a) LiHMDS, TESCl, Et<sub>3</sub>N, THF, -78 to 0 °C; Eschenmoser's salt, CH<sub>2</sub>Cl<sub>2</sub>, 91%; (b) MeI, CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O; Al<sub>2</sub>O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 95%; (c) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, 99%; (d) 9-BBN dimer, THF; NaOH/H<sub>2</sub>O<sub>2</sub>, 88%; (e) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; NaHMDS, THF, -78 to 0 °C, 91%.

Scheme 8. Johnson-Claisen Rearrangement and Construction of Quaternary C7\*



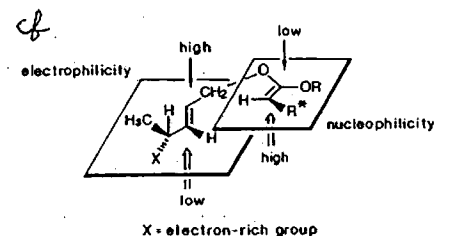
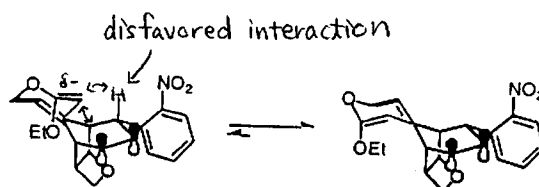
<sup>a</sup> Conditions and reagents: (a) TFA/CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 81%; (b) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 81%; (c) triethyl phosphonoacetate, NaH, THF, 0 °C, 3:2, 92%; (d) DIBAL, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 88%; (e) CH<sub>3</sub>C(OEt)<sub>3</sub>, catalytic propionic acid, toluene, reflux, 64%.

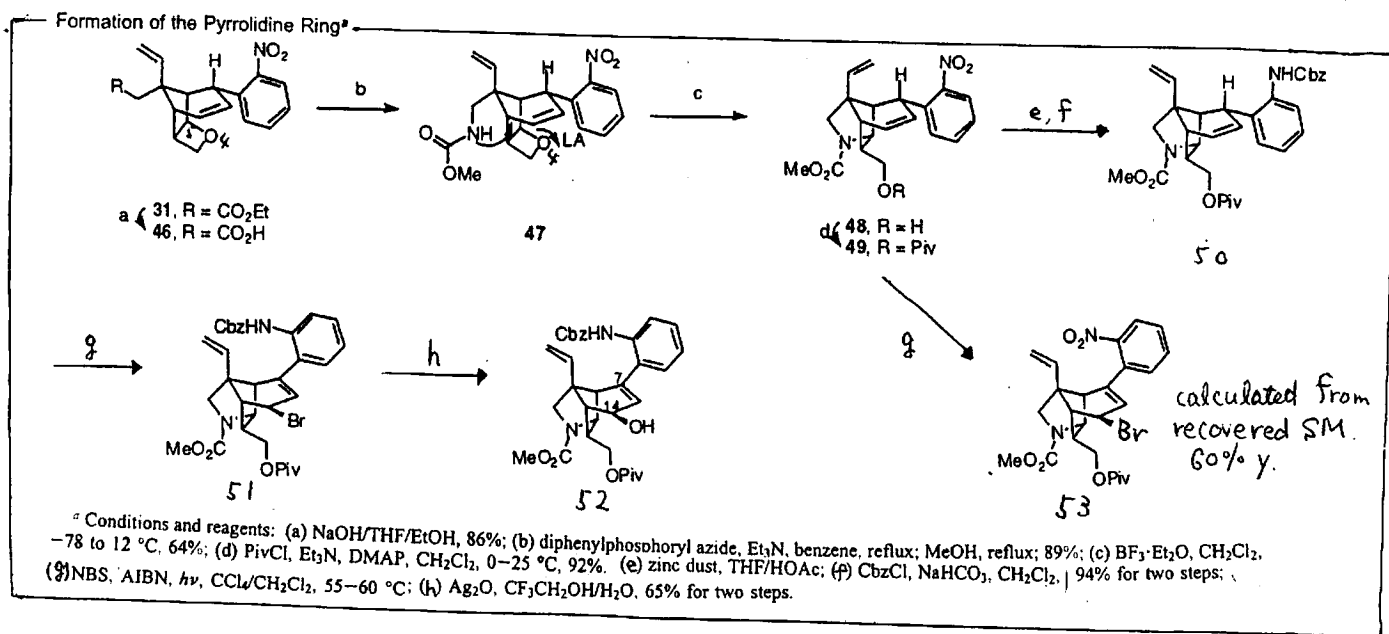
22 → 23 ; Luche reduction

- ⊙ NaBH<sub>4</sub> attacked from exo side, because of the steric hindrance. And next hydroboration also attacked from exo side.

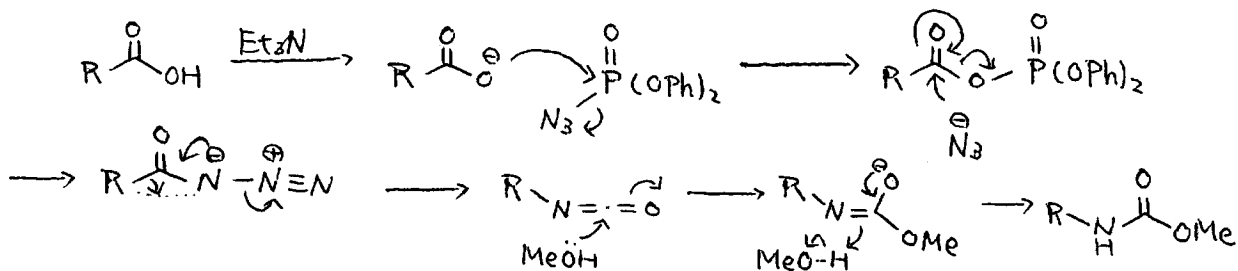
29 → 31 ; Johnson-Claisen rearrangement.

- ⊙ Both isomers (29a,b) was converted to 31.
- ⊙ Several factors lead to this stereochemistry.
  - repulsion between the proton at C7.
  - repulsion between the C3-C14 π-system.
  - attracted to electron withdrawing C5-C16 bond.





46  $\rightarrow$  47 ; Modified Curtius rearrangement.



⊙ This is much more simple and convenient than the original procedure.

⊙ It doesn't require either strong acid or base.  
(Hofmann rearr  $\Rightarrow$  base, Schmidt rearr  $\Rightarrow$  acid).

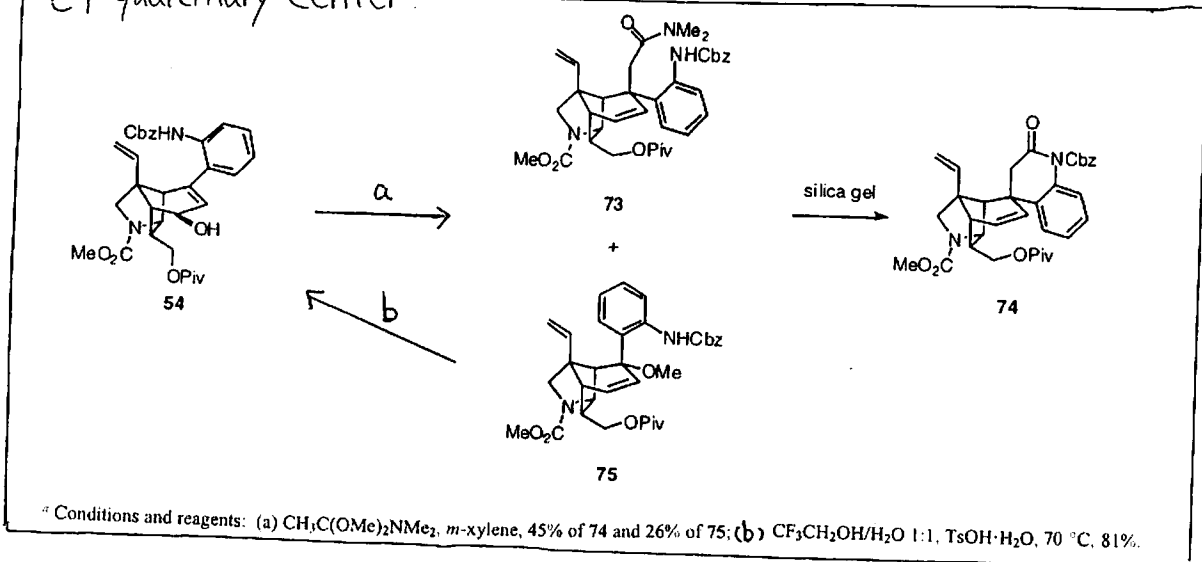
47  $\rightarrow$  48 ; Formation of pyrrolidine ring and releasing hydroxymethyl group to convex side.

⊙ C5-O4 bond is activated by Lewis acid BF<sub>3</sub>·Et<sub>2</sub>O. Intramolecular displacement accomplished desired product 48.

50  $\rightarrow$  51 ; Bromination and allylic transposition.

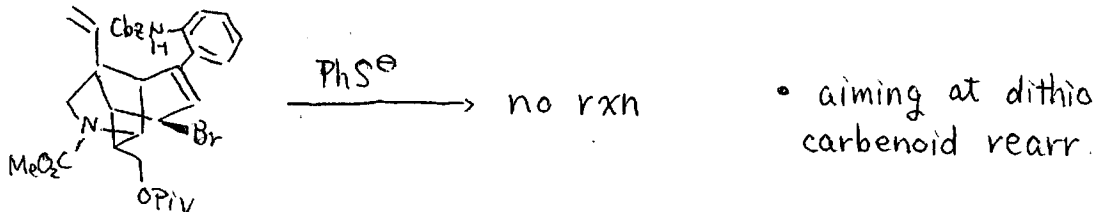
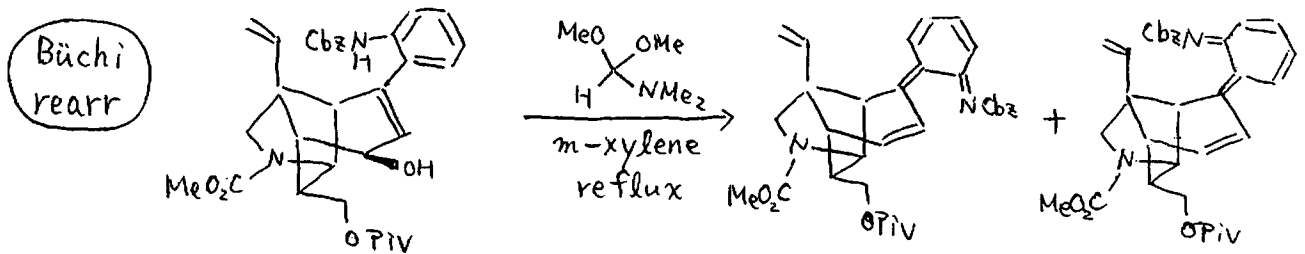
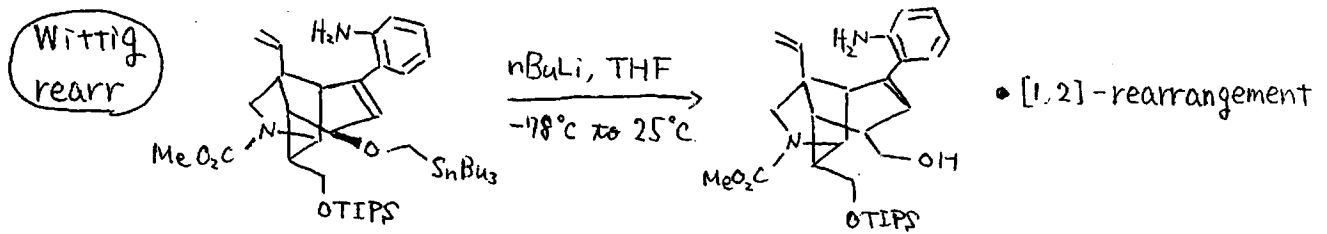
⊙ Reducing the nitro group on 49 made it easy to oxidize benzylic carbon.

C7 quaternary center



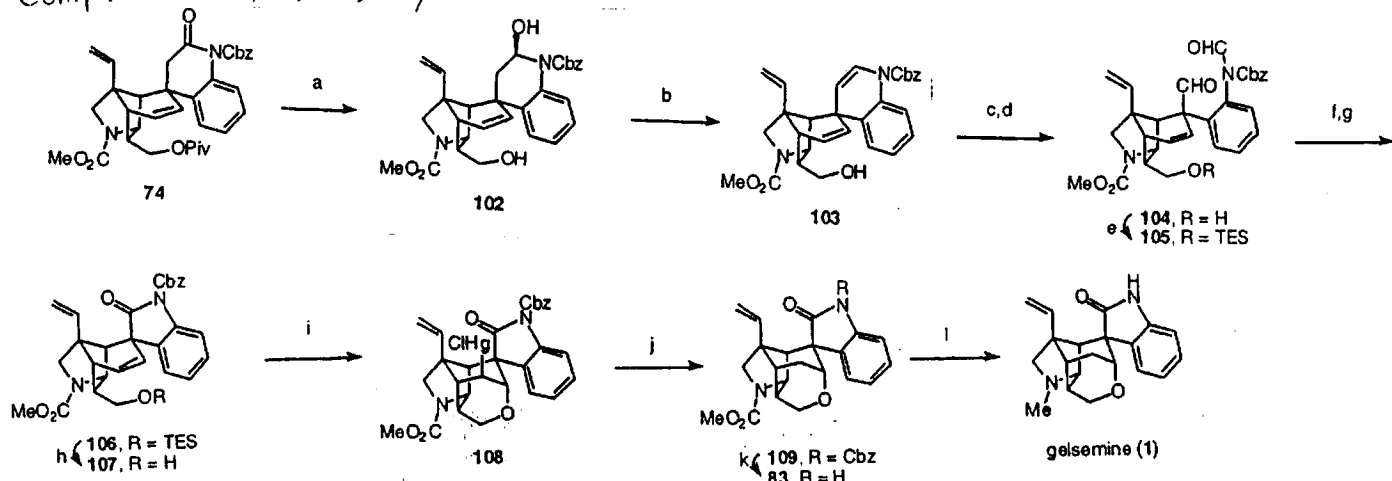
54  $\longrightarrow$  73; Eschenmoser - Claisen rearrangement.

⊙ At first, they attempted to introduce C1-unit to C7 by [2,3]-sigmatropic rearrangement. But all attempts failed.



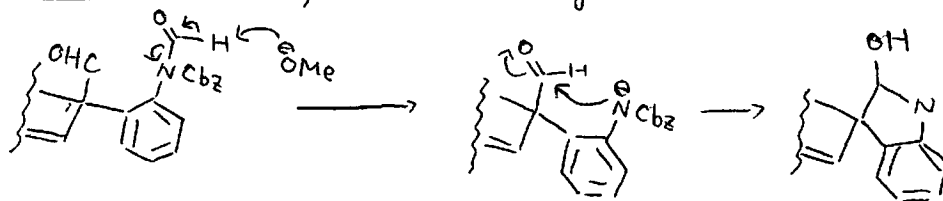
⊙ Other Claisen rearrangement derivatives (Ireland - Claisen, Johnson - Claisen) only recovered SM.

Completion of total synthesis



° Conditions and reagents: (a) DIBAL, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 86%; (b) TsOH·H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 72%; (c) OsO<sub>4</sub>, THF, -25 °C; NaHSO<sub>3</sub> (aqueous), 44% + 33% of starting material; (d) NaIO<sub>4</sub>, THF/H<sub>2</sub>O, 99%; (e) TESOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 52%; (f) K<sub>2</sub>CO<sub>3</sub>, MeOH; (g) TPAP, NMO, CH<sub>2</sub>Cl<sub>2</sub>, 4 Å MS, 78% for two steps; (h) HF·Py, THF, 0 °C, 99%; (i) Hg(OTf)<sub>2</sub>·C<sub>6</sub>H<sub>5</sub>NMe<sub>2</sub>, CH<sub>3</sub>NO<sub>2</sub>, 92%; (j) NaBH<sub>4</sub>, 10% NaOH, EtOH/CH<sub>2</sub>Cl<sub>2</sub>; (k) 10% NaOH, THF, 67% over two steps; (l) LiAlH<sub>4</sub>, THF, 0-25 °C, 81%.

105  $\rightarrow$  106 ; N-Deformylation and ring closure.



• They finally succeeded in obtaining spirooxindole group.

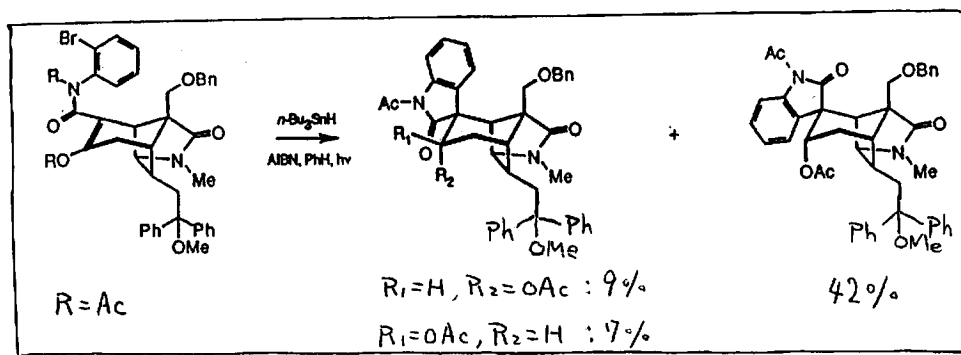
107  $\rightarrow$  108 ; Oxymercuration followed by reductive demercuration.

• The same strategy as Fukuyama's to construct tetrahydropyran ring.

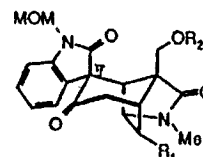
4. Other Approaches in Constructing Spirooxindole at C7.

4-1. Free radical cyclization by Hart and co-workers.

J. Am. Chem. Soc. 1994, 116, 6943

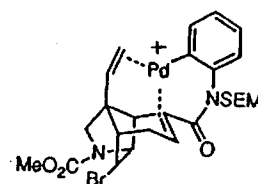
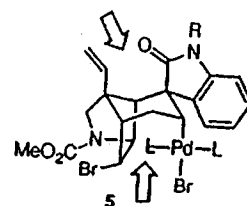
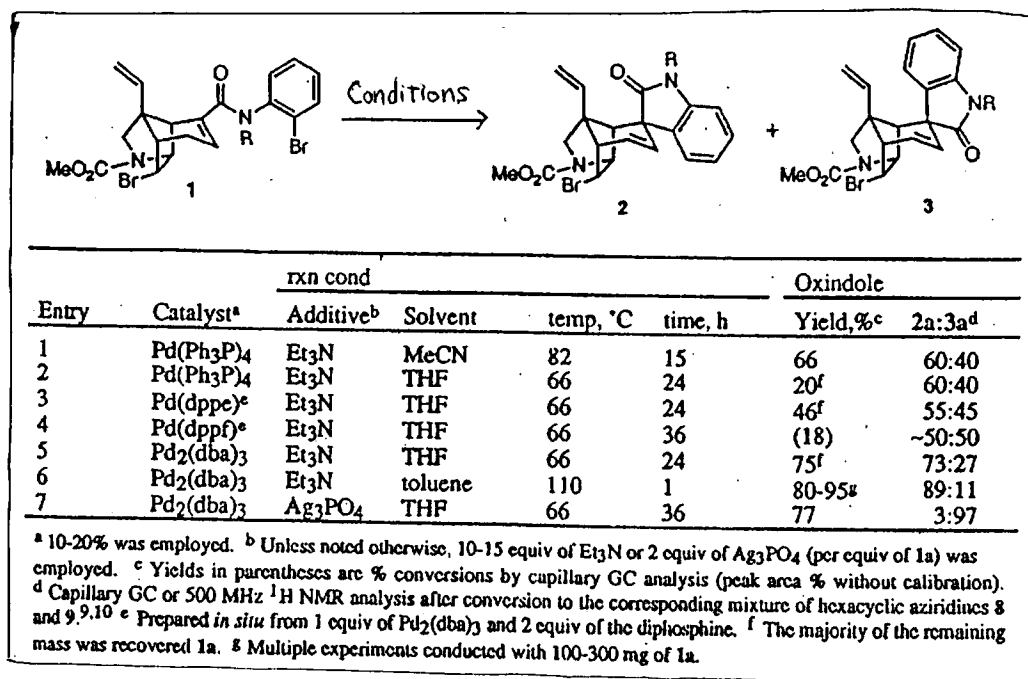


If R = MOM, Bn the main product was



and the C7 isomer.

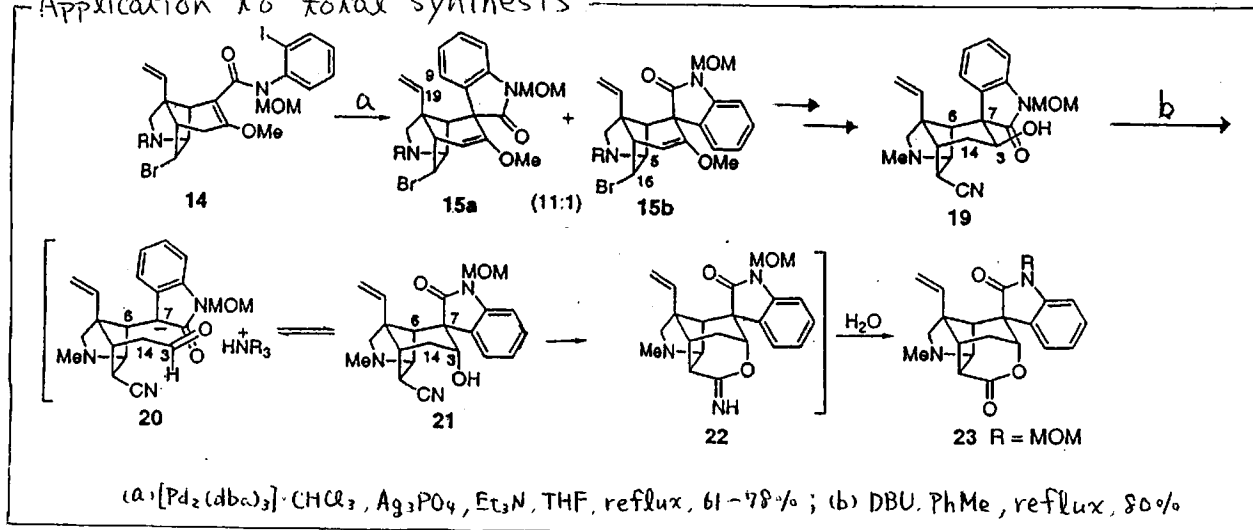
## 4-2, Intramolecular Heck reaction by Overman and co-workers



⑥ At first, they considered to reduce steric interactions between phosphine ligand and the pyrrolidine ring, but failed.

⑥ In cationic condition, palladium coordinated to angular vinyl group.

## Application to total synthesis



⑥ They succeeded intramolecular Heck reaction to tetrasubstituted vinylogous carbamate.

⑥ By refluxing 19 and DBU in toluene, desired epimerization occurred.