Total Synthesis of Gelsemine

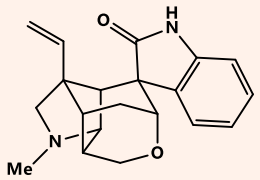
6 of 9 approaches to synthesize Gelsemine

Pan Group
Xue Shangfei
2024.04.03

Bioactivity

- **钩吻碱，具有抗伤害和促进睡眠活性,可有效缓解慢性疼痛。**

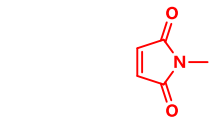
- **斑马鱼幼虫 LC50 = 1.54 mM（496.5 mg/kg）**



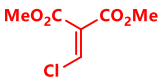
Gelsemine

• 没有活性

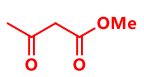
Review: Lin, H. and Danishefsky, S.J. (2003), Gelsemine: A Thought-Provoking Target for Total Synthesis†. Angewandte Chemie International Edition, 42: 36-51. https://doi.org/10.1002/anie.200390048



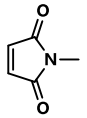
Speckamp, 1994
Racemic
19 steps, 0.83%



Johnson, 1994
Racemic
29 steps, 0.58%

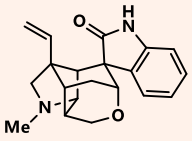


Fukuyama, 1996
Racemic
32 steps, 0.25%



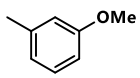
Hart, 1997
Racemic
23 steps, 0.25%

J. Am. Chem. Soc. 1997, 119, 27, 6226–6241



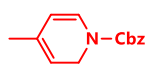
Gelsemine

Overman, 1999
Racemic
26 steps, 1.2%



J. Am. Chem. Soc. 2005, 127, 51, 18046–18053
J. Am. Chem. Soc. 2005, 127, 51, 18054–18065

Qiu, Zhai, 2015
Asymmetric
12 steps, 5%

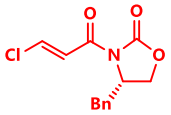


Qin, 2012
Asymmetric
25 steps, 1%

Danishefsky, 2002
Racemic
32 steps, 0.019%

F. W. Ng, H. Lin, Q. Tan, S. J. Danishefsky, Tetrahedron Lett. 2002, 43, 545–548
H. Lin, F. W. Ng, S. J. Danishefsky, Tetrahedron Lett. 2002, 43, 549–551.

Fukuyama, 2000
Asymmetric
31 steps, 0.86%



A. Peter Johnson Group 1994

J. CHEM. SOC., CHEM. COMMUN., 1994 765

A Total Synthesis of Gelsemine: Oxindole Spiroannelation

Jonathan K. Dutton, Robert W. Steel, Andrew S. Tasker, Velimir Popsavin and A. Peter Johnson*
School of Chemistry, University of Leeds, Leeds, UK LS2 9JT

Photolysis of alkoxy-substituted-1-alkenylbenzotriazoles provides a new route to spiro-oxindoles which has been utilised in a total synthesis of gelsemine.

J. CHEM. SOC., CHEM. COMMUN., 1994 765

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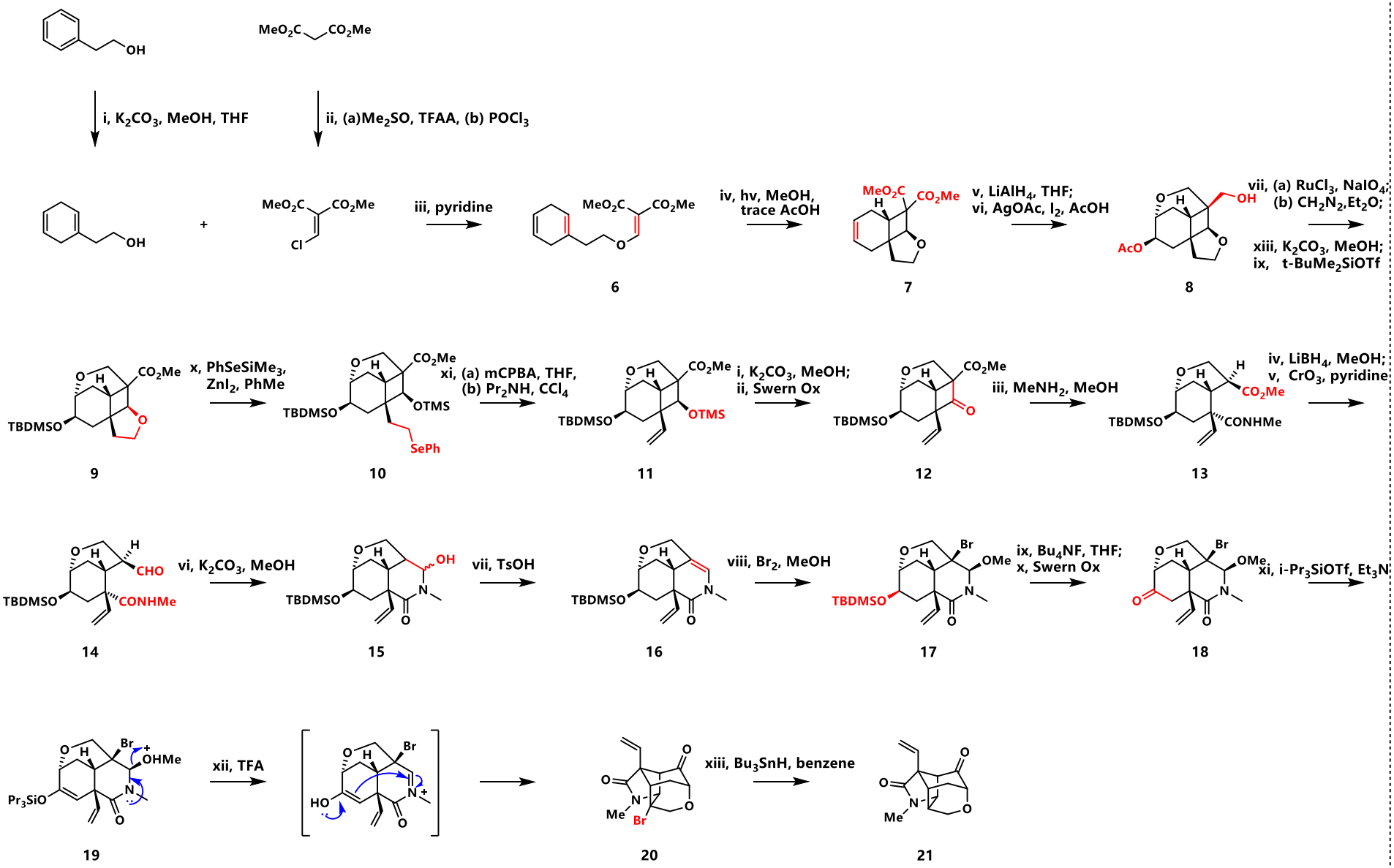
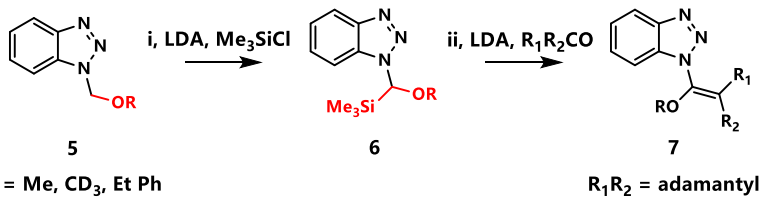
Photolysis of alkoxy-substituted-1-alkenylbenzotriazoles provides a new route to spiro-oxindoles which has been utilised in a total synthesis of gelsemine.

Synthesis of a Key Tetracyclic Intermediate



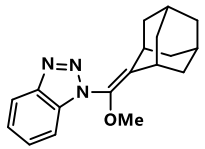
Model Reaction & Mechanism



5 6 7

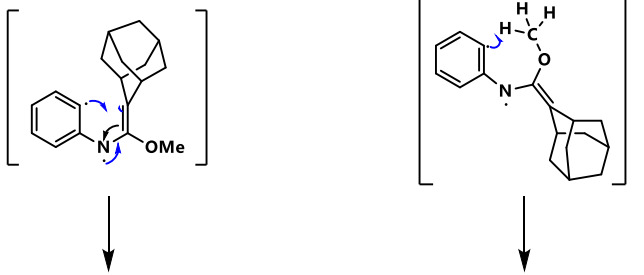
R = Me, CD_3, Et Ph

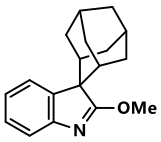
R_1R_2 = adamantyl



8

i, hv, MeCN





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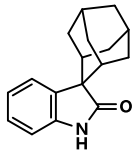

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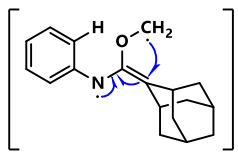
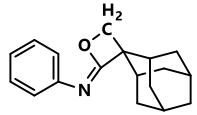
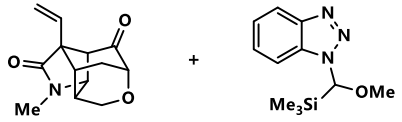




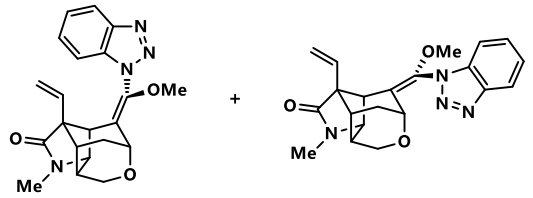
10

Completion of the total synthesis of gelsemine



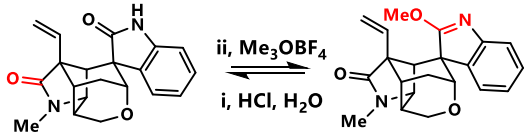
3

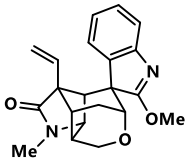
i, LDA (2 eq.);
ii, BunLii (2 eq.);
iii, 3;



12 13

iv, hv, MeCN



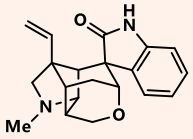


3 14 15

21 -oxogelsemime

iii, DEAD;
iv, MeOH;
v, CrO_3;

vi, DIBALH



2

natural gelsemine

W. Nico Speckamp Group 1994

J. CHEM. SOC., CHEM. COMMUN., 1994 767

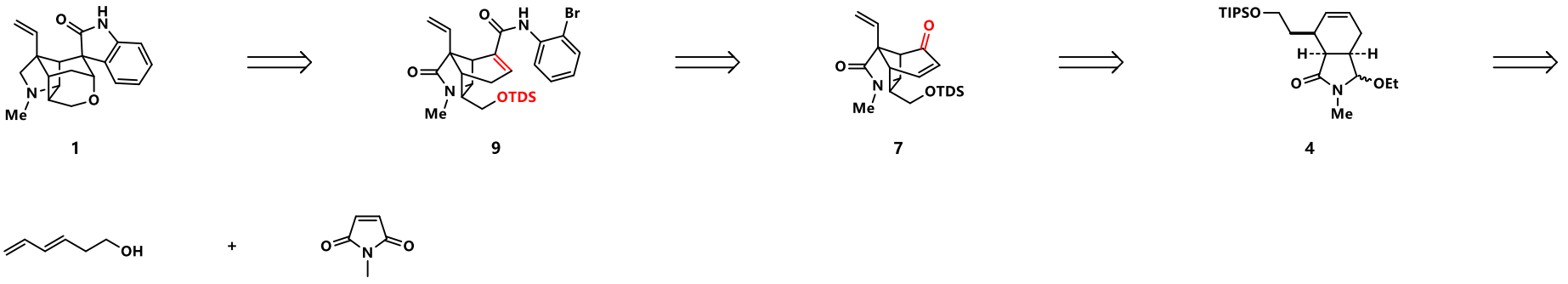
The Total Synthesis of (±)-Gelsemine

Nicholas J. Newcombe, Fang Ya, Robert J. Vijn, Henk Hiemstra* and W. Nico Speckamp*

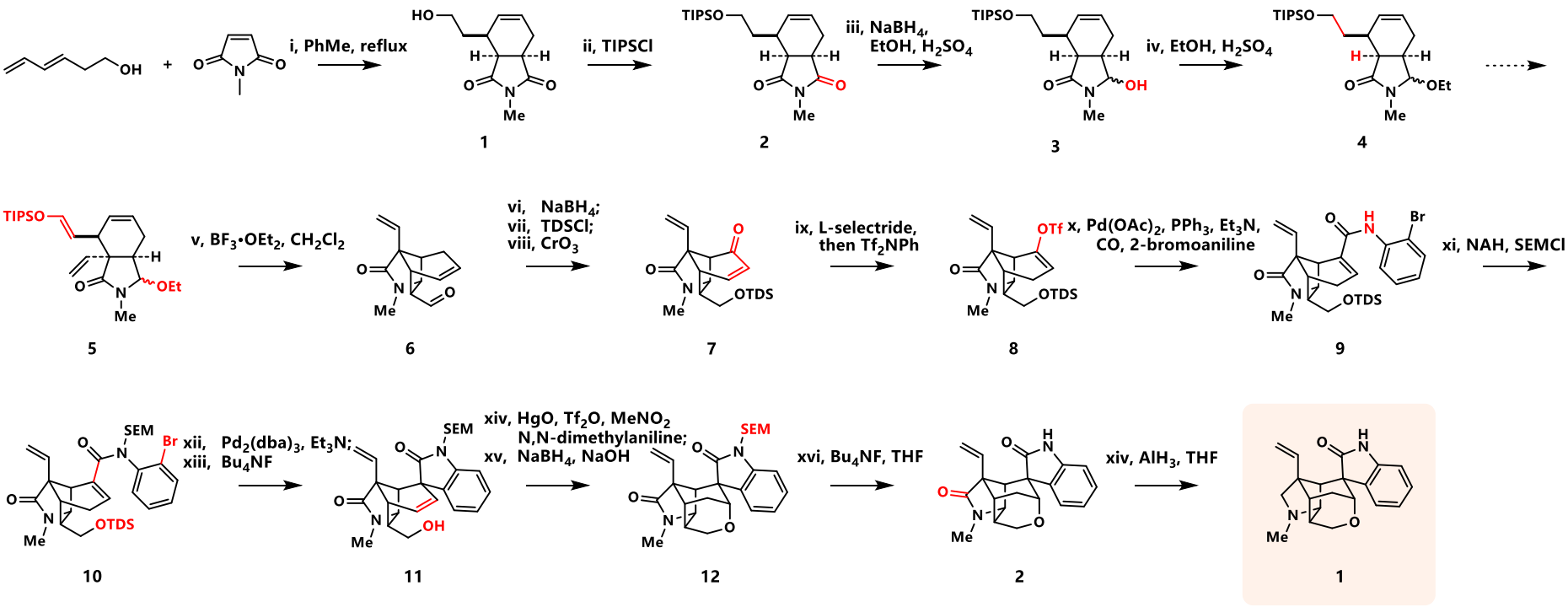
Laboratory of Organic Chemistry, University of Amsterdam Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Oxindole alkaloids gelsemine and 21-oxogelsemine in racemic form are synthesised from sorbic acid.

Retrosynthesis



Synthesis of Gelsemine



Tohru Fukuyama Group 1996

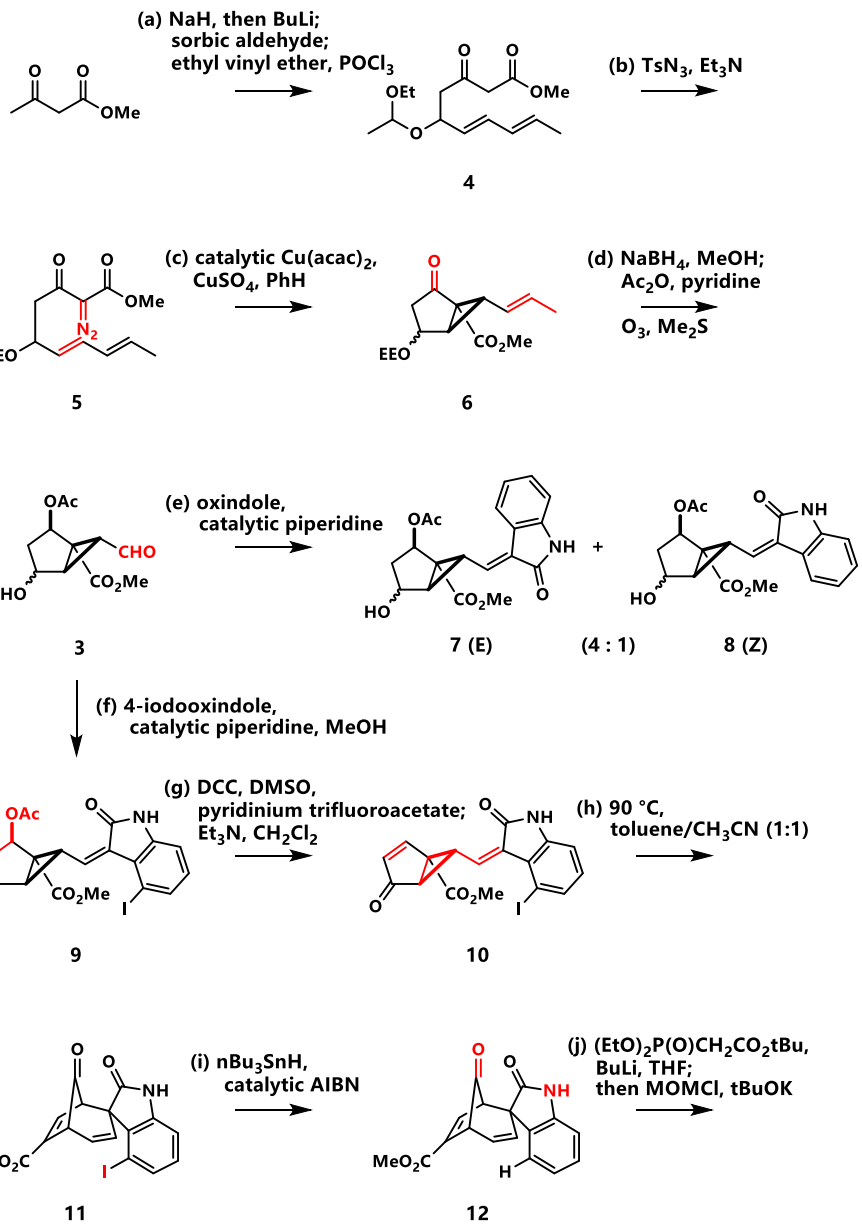
Stereocontrolled Total Synthesis of (±)-Gelsemine

Tohru Fukuyama* and Gang Liu[1]

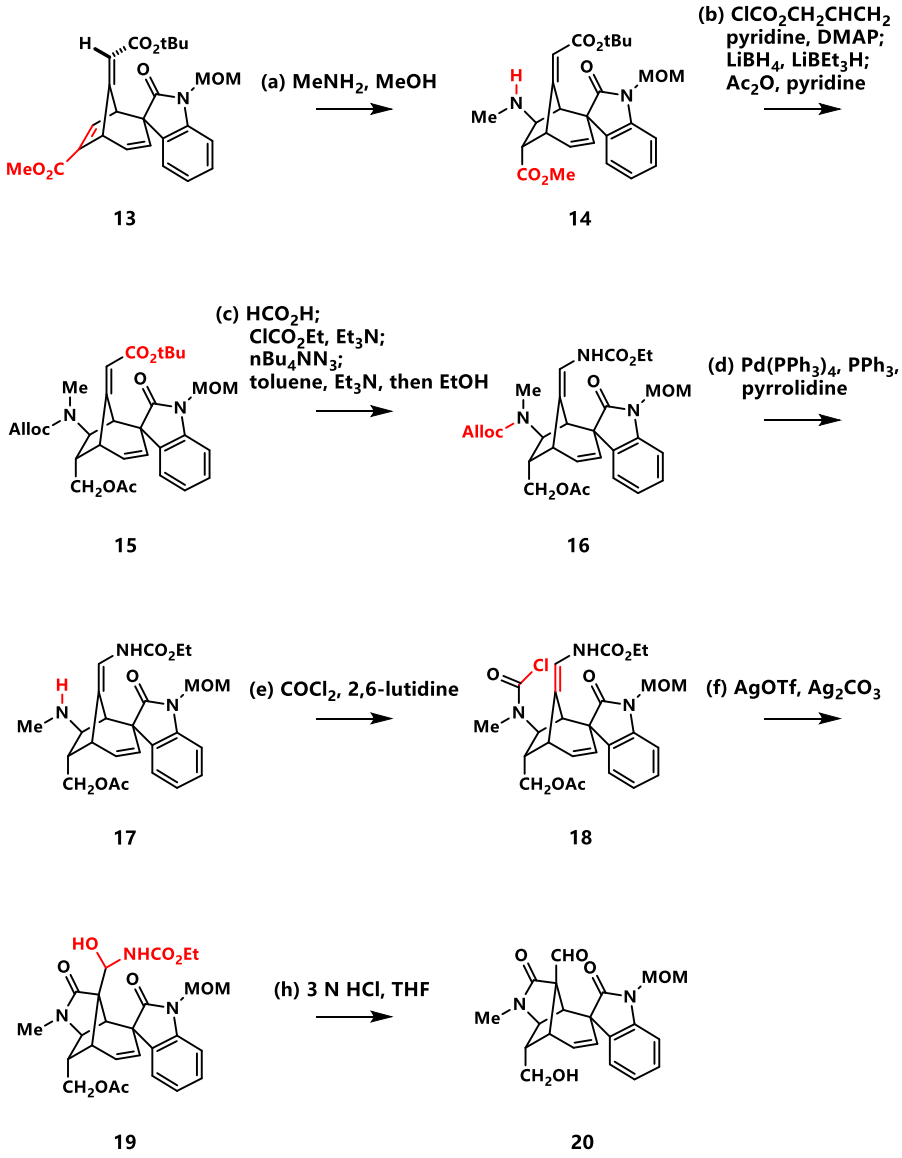
Department of Chemistry, Rice University
Houston, Texas 77005-1892
Faculty of Pharmaceutical Sciences
University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113, Japan

Received May 20, 1996

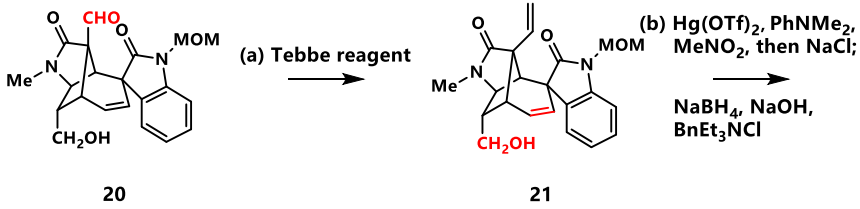
Synthesis of 12



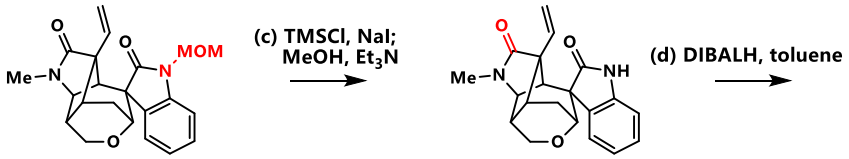
Synthesis of 20



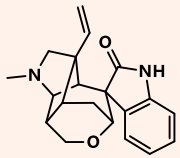
Synthesis of Gelsemine



20 21



22 2



Gelsemine (1)

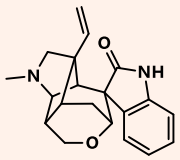
Tohru Fukuyama Group 2000

Enantioselective Total Synthesis of (+)-Gelsemine: Determination of Its Absolute Configuration**

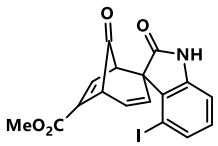
Satoshi Yokoshima, Hidetoshi Tokuyama, and Tohru Fukuyama*

Angew. Chem. Int. Ed. **2000**, *39*, No. 22

Retrosynthesis of gelsemine

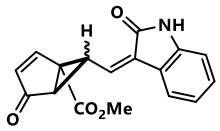


Gelsemine (1)

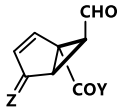


2

stereochemistry controlled thermal rearrangement



3a



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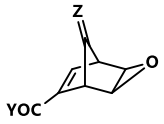

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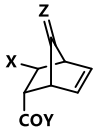


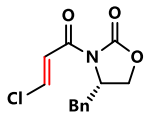
6

Diels – Alder Reaction

7

8

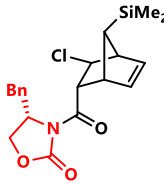
Synthesis of the bicyclo[3.2.1] system



9

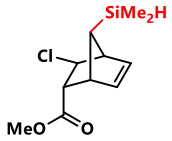
10

a) Et_2AlCl, DCM



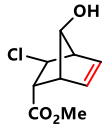
11

b) cat. $Sm_4(OTf)_3$, MeOH



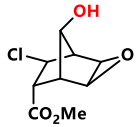
12

c) 30% H_2O_2, KF, $KHCO_3$, THF/MeOH



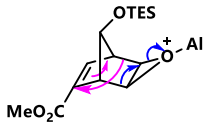
13

d) $VO(acac)_2$, tBuOOH



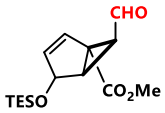
14

e) TESOTf, 2,6-lutidine



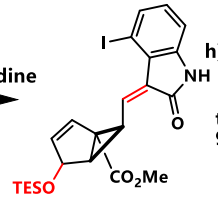
15

f) MAD, toluene



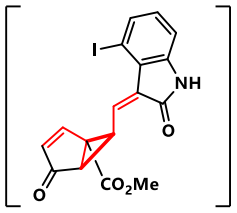
16

g) 30, piperidine

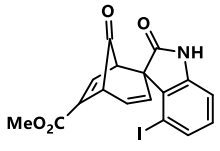


17

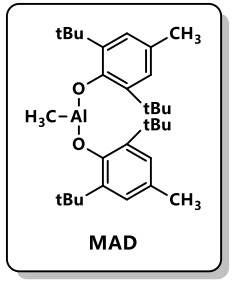
h) TBAF, THF; CrO_3, H_2SO_4; toluene/MeCN 90℃



3a: trans isomer
3b: cis isomer

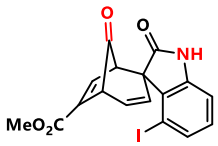


2



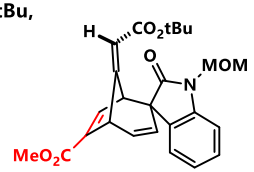
MAD

Construction of the pyrrolidine ring



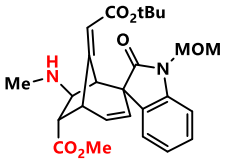
2

a) $(EtO)_2POCH_2CO_2tBu$, nBuLi; MOMCl, tBuOK; nBu_3SnH, AIBN



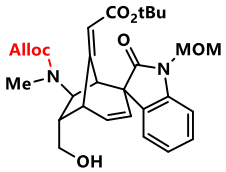
18

b) $MeNH_2$, MeOH



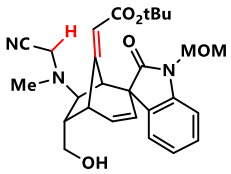
19

c) AllocCl, pyridine; $LiBH_4$, cat. $LiBEt_3H$



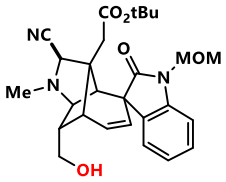
20

d) $[Pd_4PPh_3)_4]$, pyrrolidine; ICH_2CN, iPr_2NEt



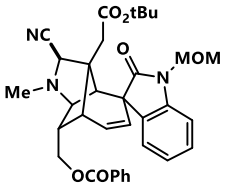
21

e) KHMDS, THF



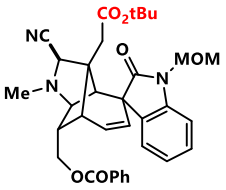
22

f) PhCOCl, pyridine, DMAP



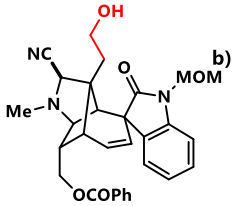
23

Completion of the total synthesis of (+)-gelsemine (1)



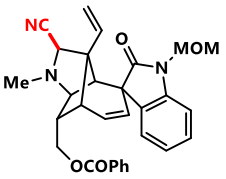
23

a) HCO_2H; $ClCO_2Et$, NEt_3, THF then $NaBH_4$, H_2O



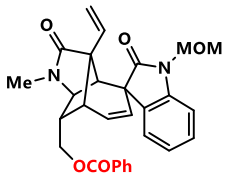
24

b) $o\text{-}NO_2C_6H_4SeCN$, PBu_3; mCPBA, then NEt_3



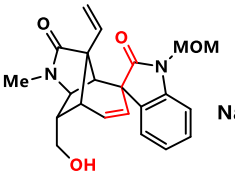
25

c) mCPBA, then NEt_3



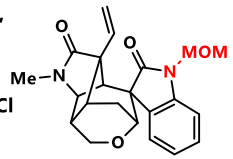
26

d) K_2CO_3, MeOH



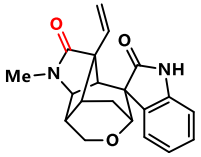
27

e) $Hg(OTf)_2 \cdot PhNMe_2$, $MeNO_2$ then aq NaCl; $NaBH_4$, NaOH, $BnNEt_3Cl$



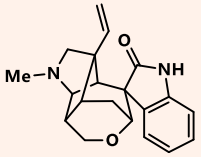
28

f) TMSCl, NaI, MeCN; NEt_3, MeOH



29

g) DIBAL, toluene



1

秦勇课题组 2012

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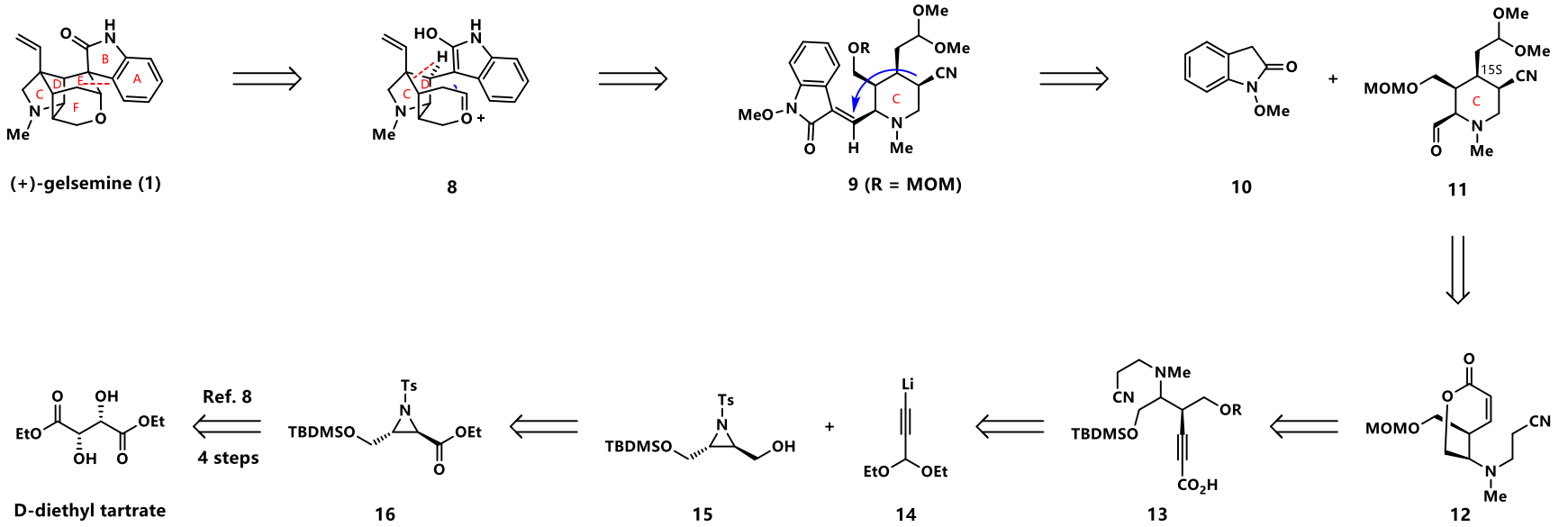
Natural Products

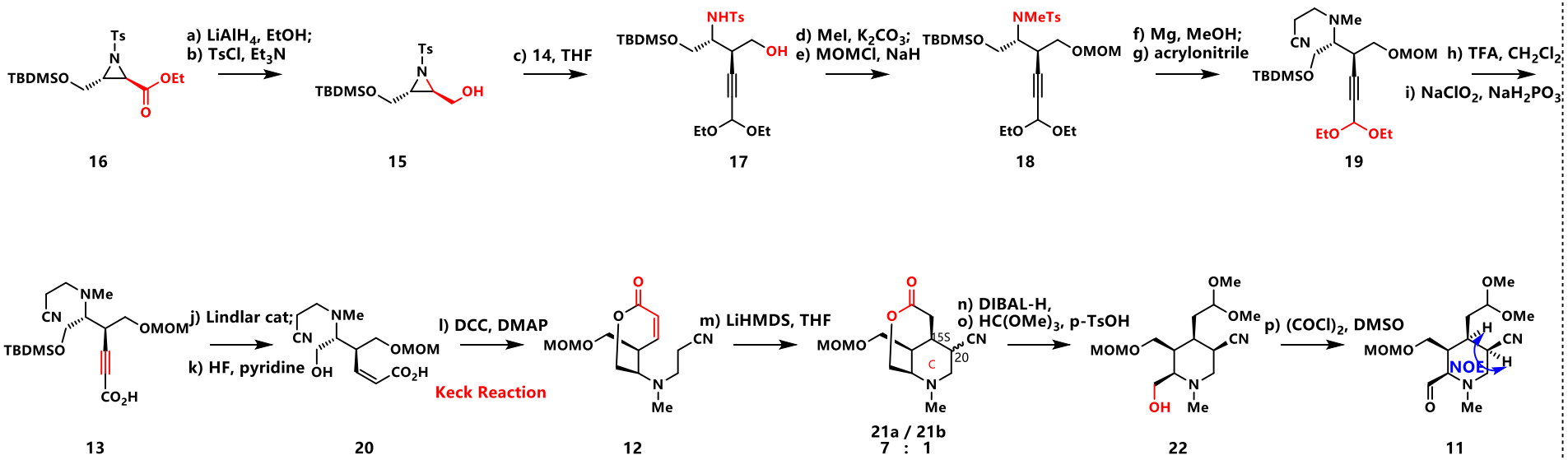
Biomimetic Total Synthesis of (+)-Gelsemine**

*Xuan Zhou, Tao Xiao, Yusuke Iwama, and Yong Qin**

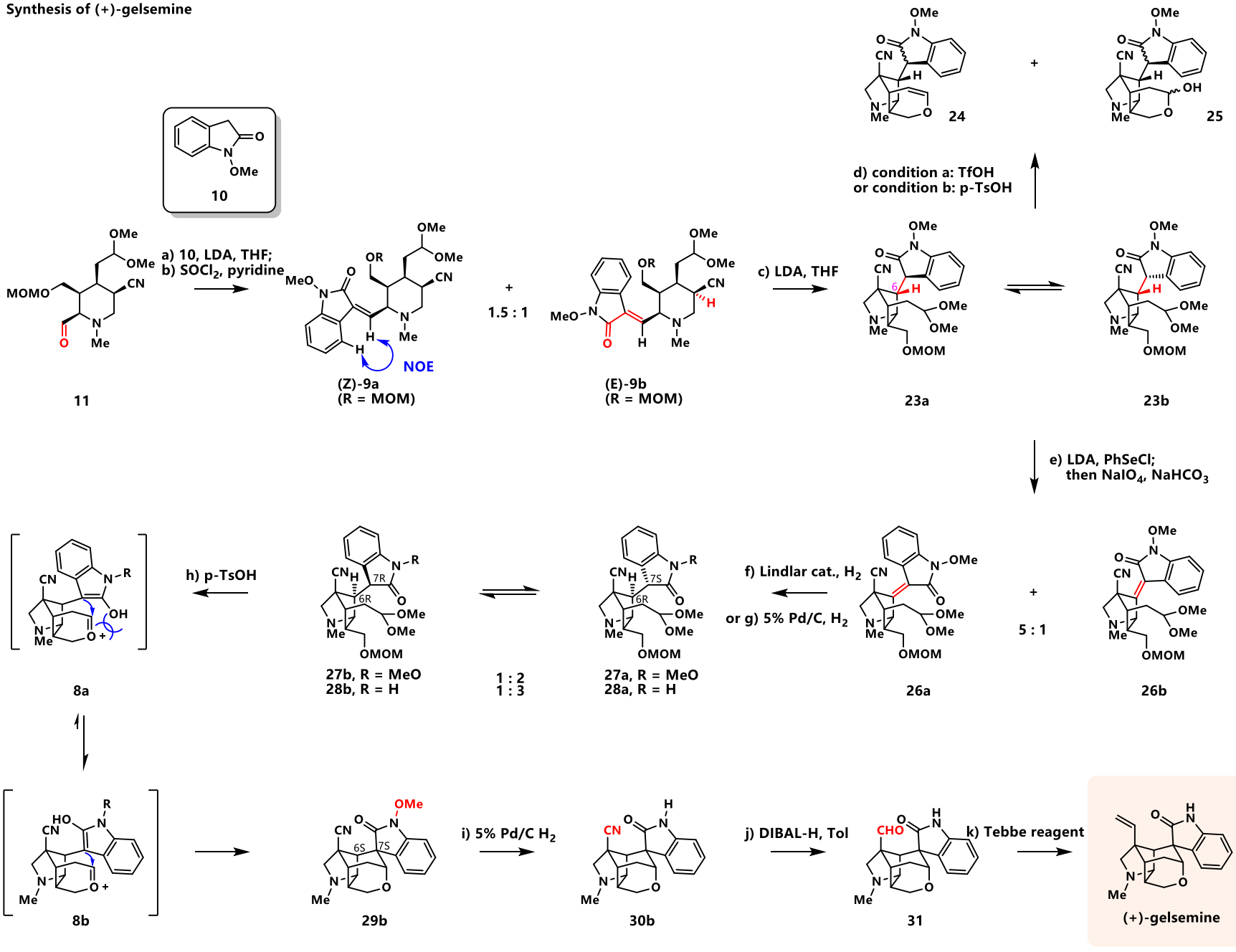
Retrosynthetic analysis of (+)-gelsemine



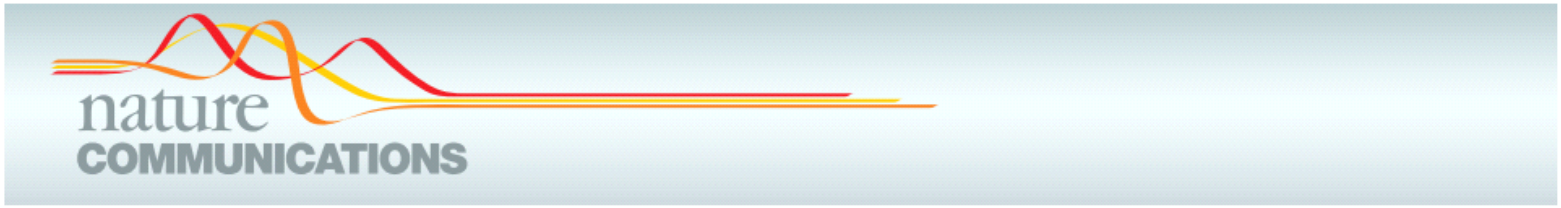
Preparation of the chiral cis tetra-substituted piperidine ring



Synthesis of (+)-gelsemine



邱发洋、翟宏斌等 2015



ARTICLE

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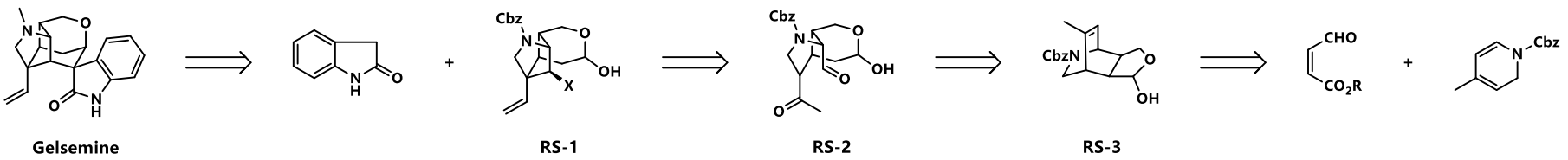
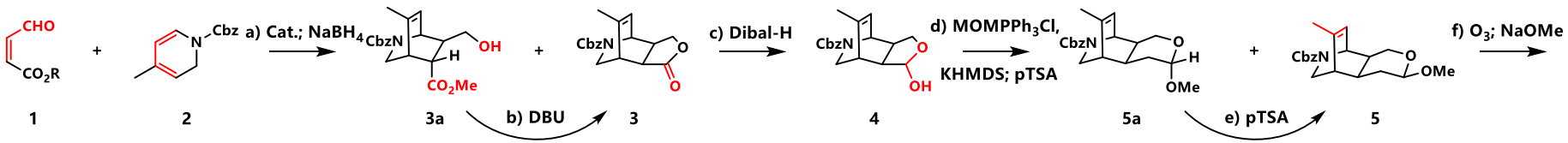
Total synthesis of (+)-gelsemine via an organocatalytic Diels–Alder approach

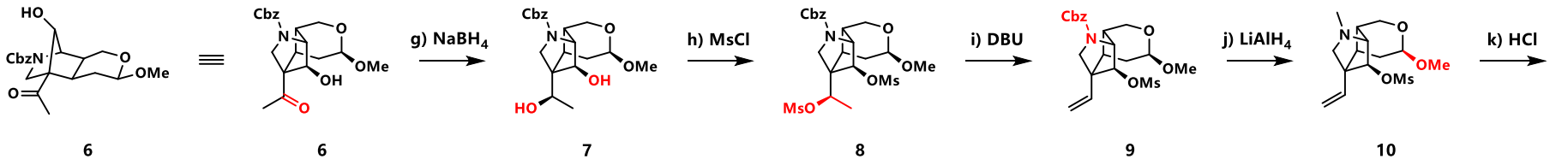
Xiaoming Chen[1,2], Shengguo Duan[1,2], Cheng Tao[1], Hongbin Zhai[1] & Fayang G. Qiu[2]

Retrosynthetic analysis of gelsemine

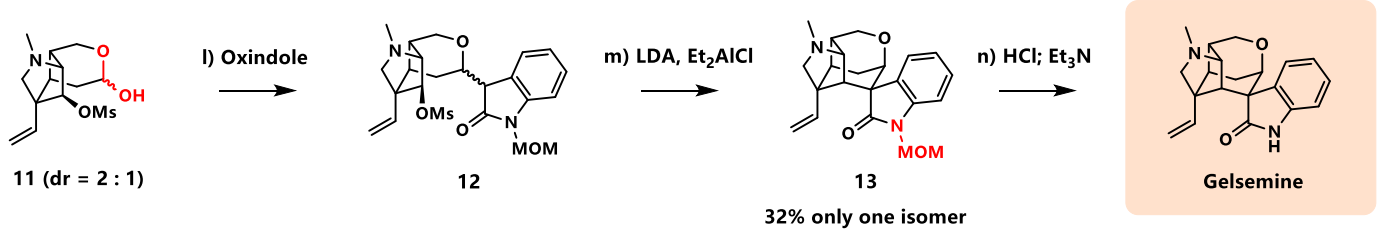


The synthesis of (þ)-gelsemine



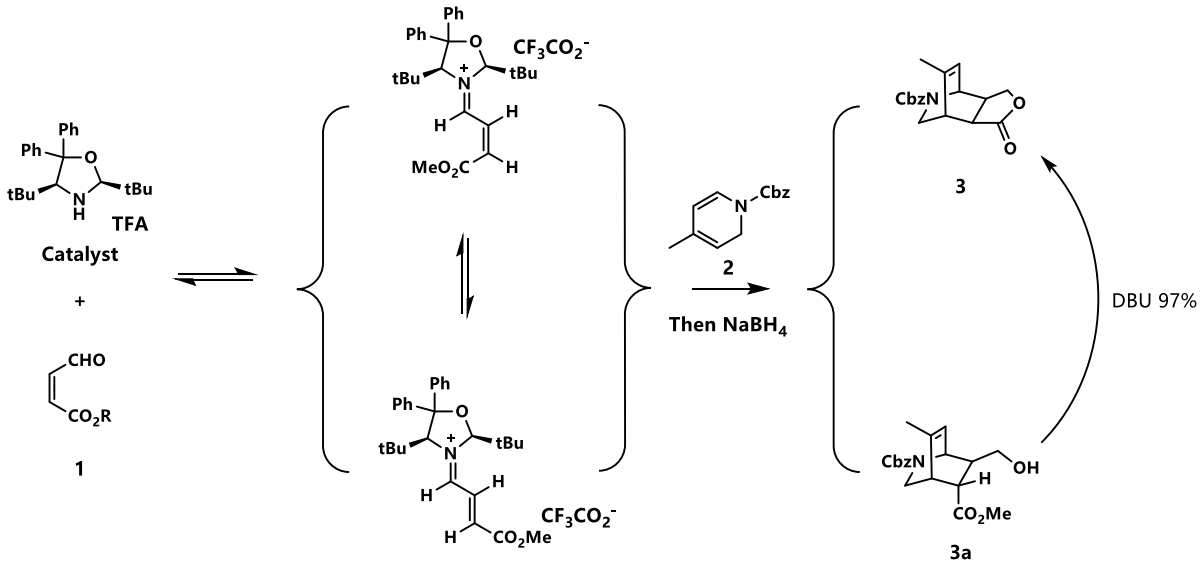


1.1 g in one sequence

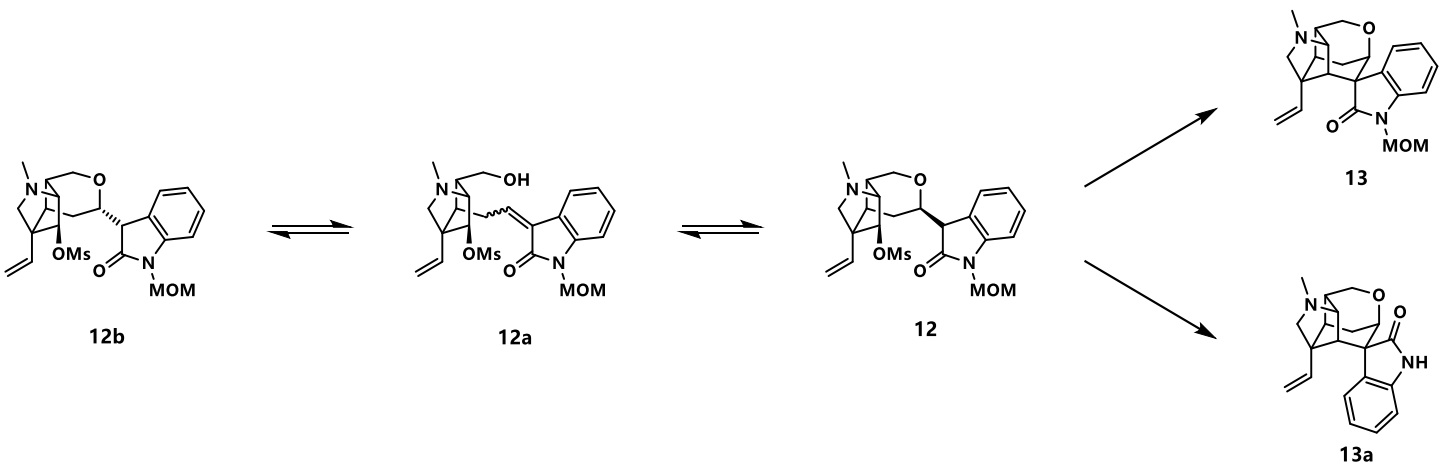


32% only one isomer

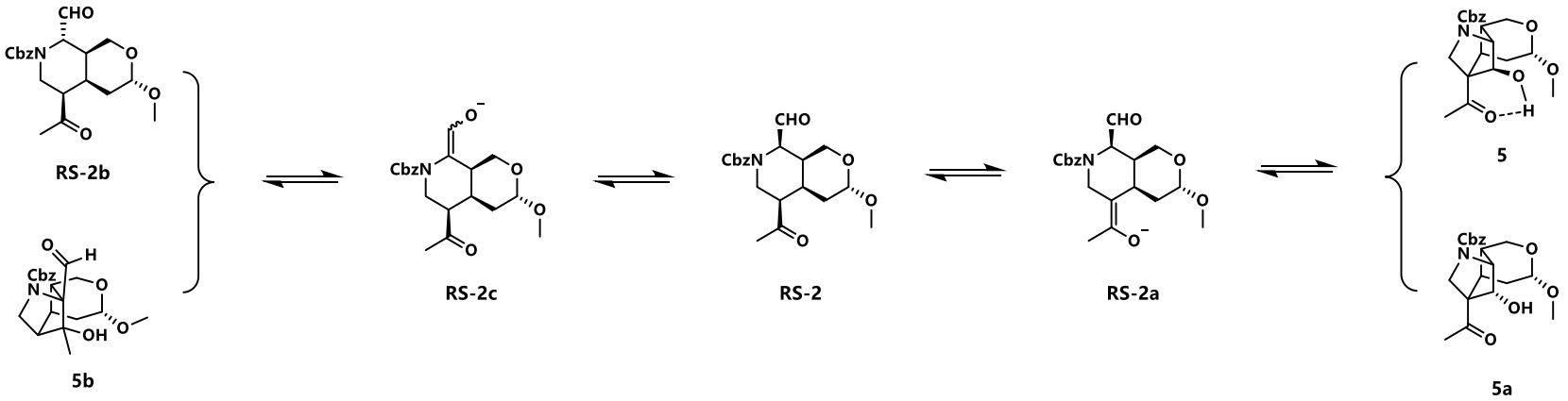
Intermediates leading to the formation of 3 and 3a



Cyclization of intermediate 9 to form the gelsemine framework



The aldol condensation and possible complications



Thanks!