北京大学
PEKING UNIVERSITY

Collective Asymmetric Total Synthesis of C-11 Oxygenated Cephalotaxus Alkaloids

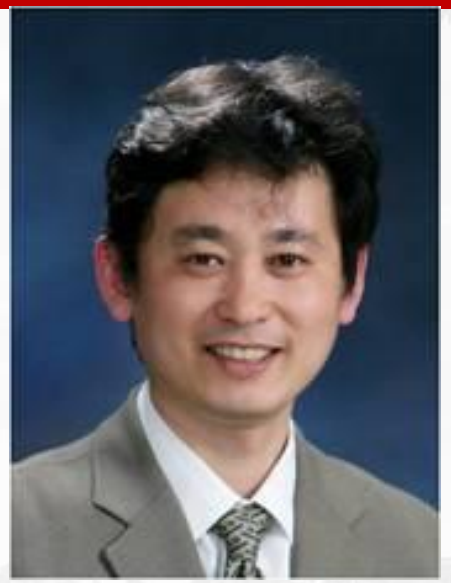
Jae Hyun Kim, Hongjun Jeon, Choyi Park, Soojun Park, and Sanghee Kim*

10.1002/anie.202101766

Reporter: Peng Chen

2021. 4. 1

Sanghee Kim (김 상희)



Education:

1997 – 1998 The Scripps Research Institute Post-doctoral fellow (Advisor: Prof. K.C. Nicolaou)

1992 – 1997 University of Pennsylvania Ph.D., Organic Chemistry (Advisor: Prof. Jeffrey D. Winkler)

1988 – 1990 Seoul National University M.S., Medicinal Chemistry (Advisor: Prof. Deukjoon Kim)

1984 – 1988 Seoul National University B.S., Pharmacy

Professional Experience:

2001 – Present Professor Seoul National University, College of Pharmacy

1999 – 2001 Assistant Professor: Seoul National University, Natural Products Research Institute

1998 – 1999 Senior Research Scientist: Abbott Laboratories, Infectious Diseases, USA

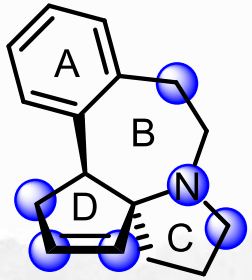
1991 – 1992 Chemistry Research Scientist: Korea Institute of Science and Technology, Korea

Cephalotaxus alkaloids

Isolated From : Cephalotaxus drupacea and Cephalotaxus fortunei

Structural Features:

An azaspiranic tetracyclic scaffold



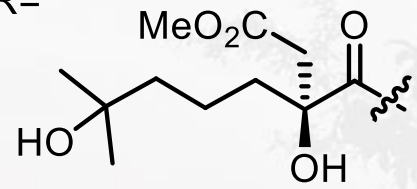
azaspiranic
tetracyclic backbone

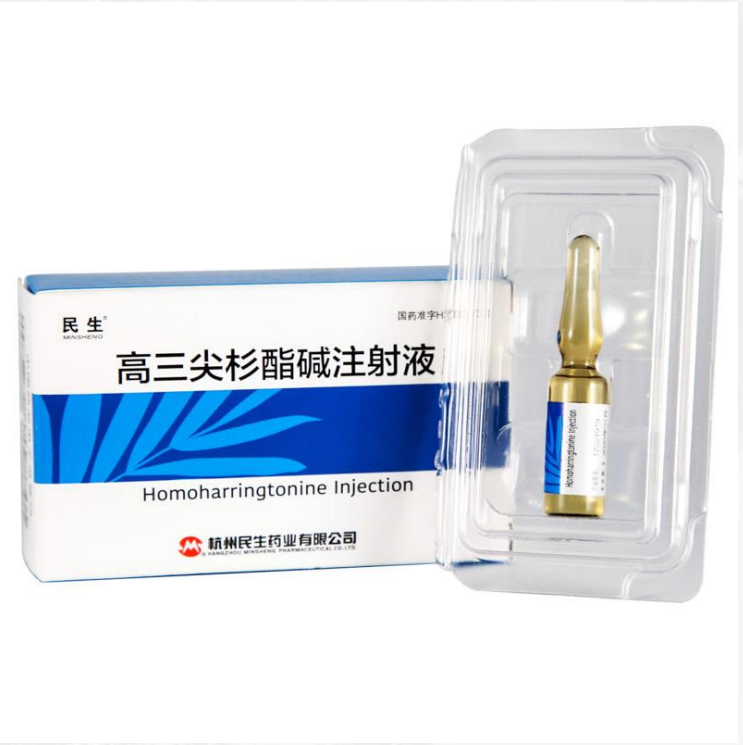
● :sites oxidation
patterns differ

Biological activity: antileukemic and antitumor activities

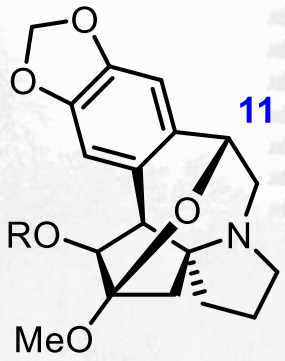
cephalotaxine (**1**): R = H
homoharringtonine (**2**):

R=

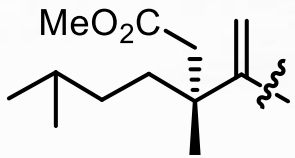




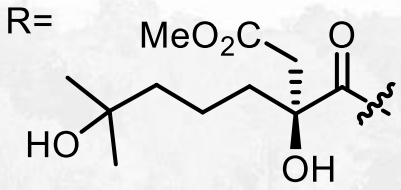
C-11 Oxygenated Cephalotaxus alkaloids



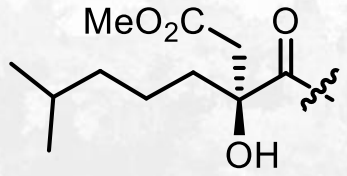
drupacine (**3**): R = H
drupangtonine (**5**): R=



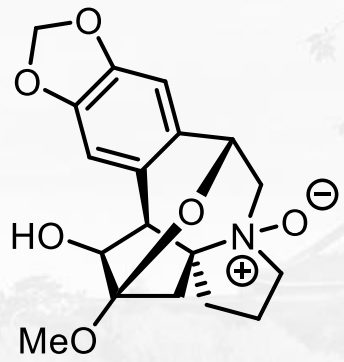
cephalezomine A (**6**):



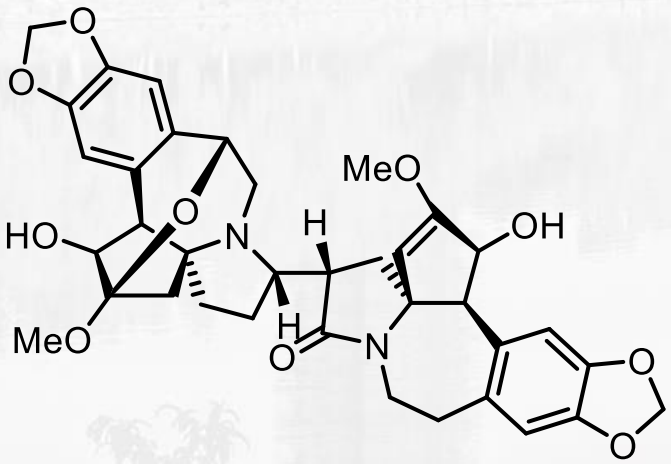
cephalezomine B (**7**):



11-hydroxy-cephalotaxine (**4**)

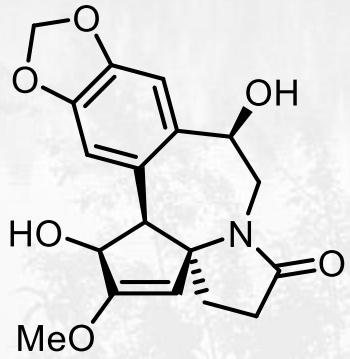


cephalancetine B (**8**)

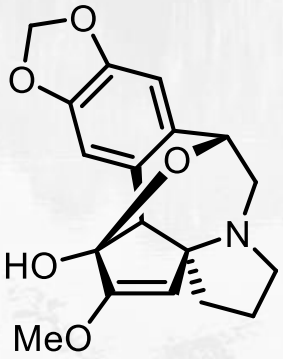


cephalancetine D (**9**)

cephalocyclidin A (**10**)



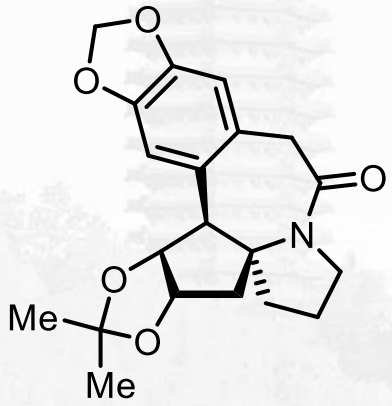
torreyafargesine A (**11**)



11-hydroxycephalotaxinone hemiketal (**12**)

Previous works

(A)



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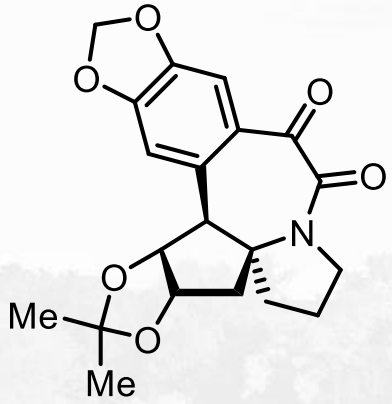
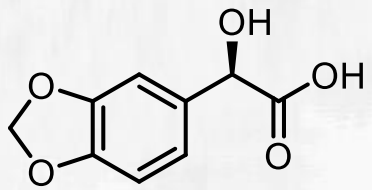


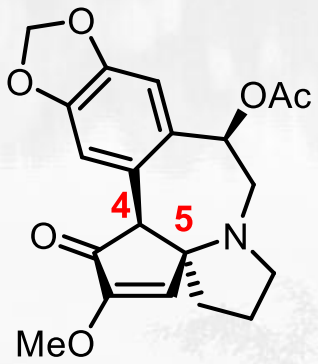
14

P. L. Fuchs, *et al.*
J. Am. Chem. Soc. **1990**, *112*, 9601–9613

(B)



15

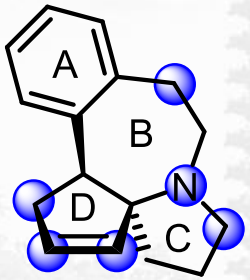


(4*S*, 5*S*): (4*R*, 5*R*) = 2:1

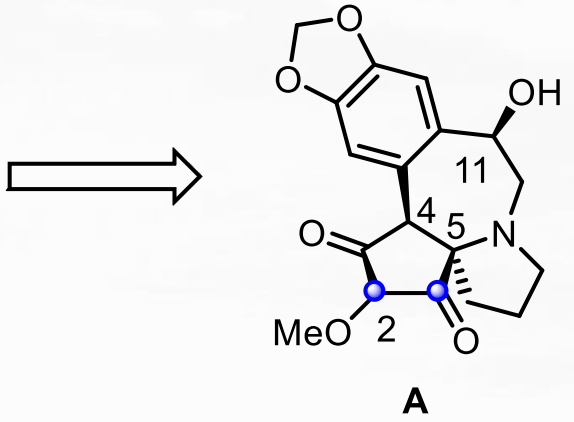
drupacine (**3**)

B. M. Stoltz, *et al.*
J. Org. Chem. **2007**, *72*, 7352–7358.

Retrosynthetic route

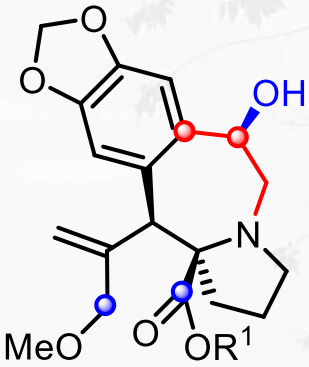


target alkaloids
3, 4, 8, 10-12

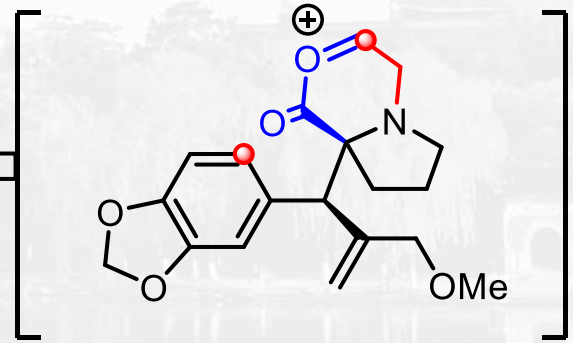


A

Dieckmann

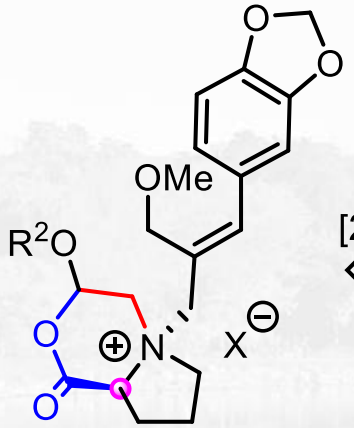


B



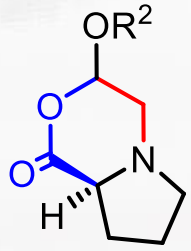
C

[2,3]-Stevens



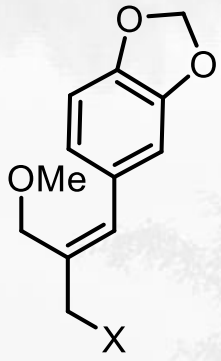
G

D



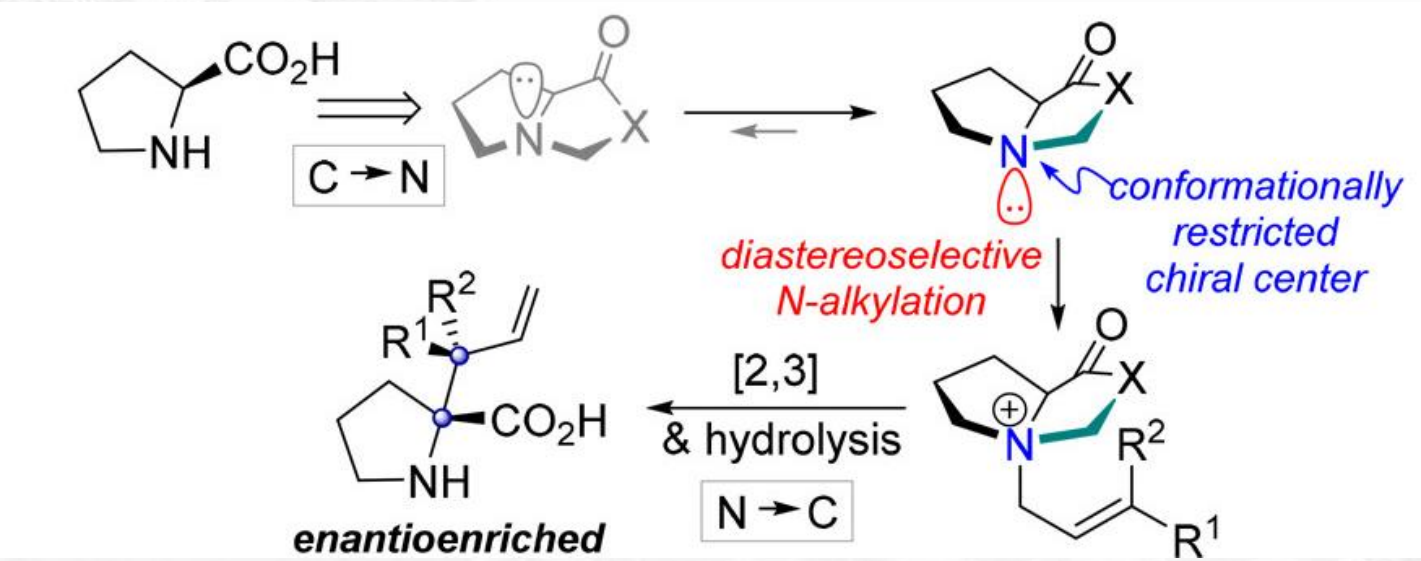
E

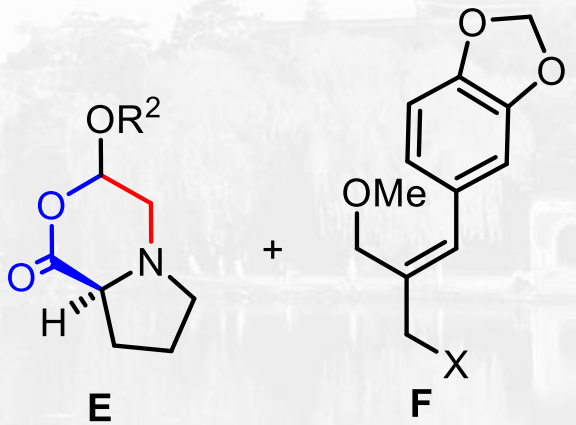
+



F

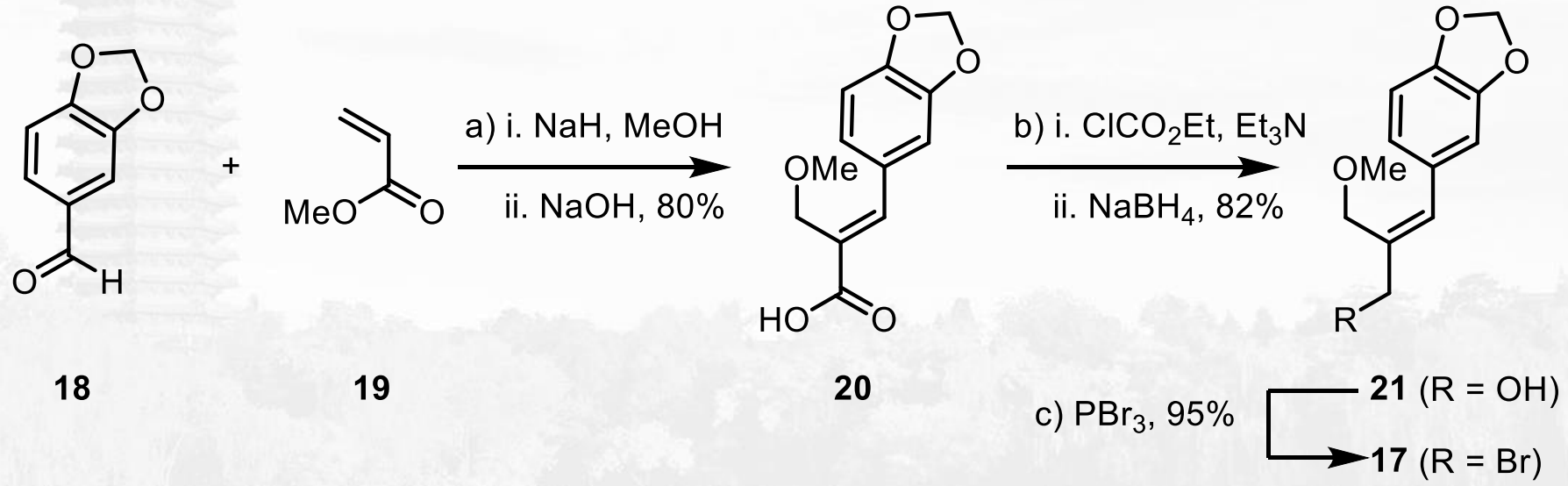
C-N-C chirality transfer

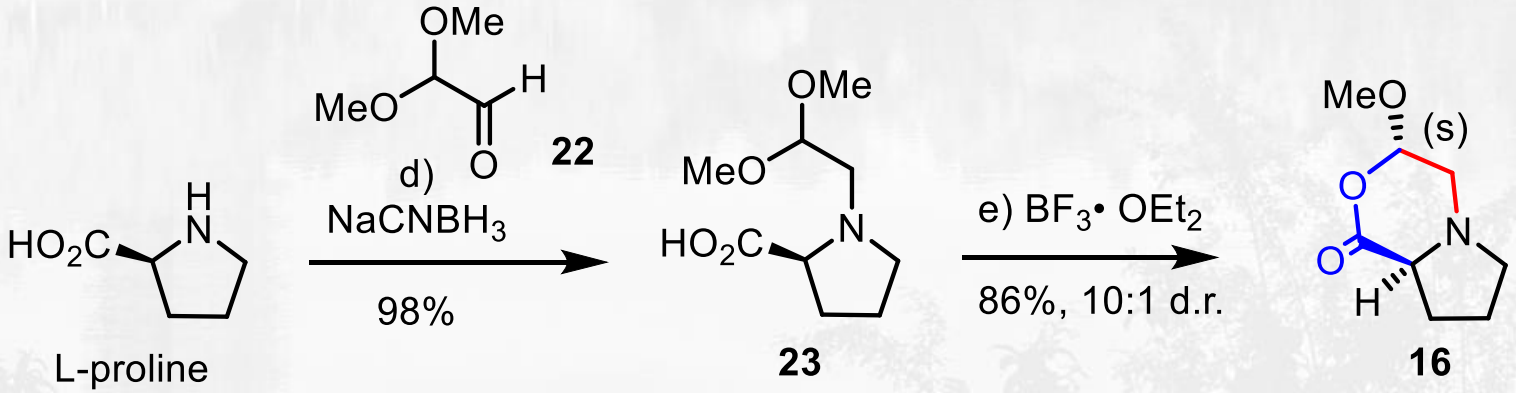




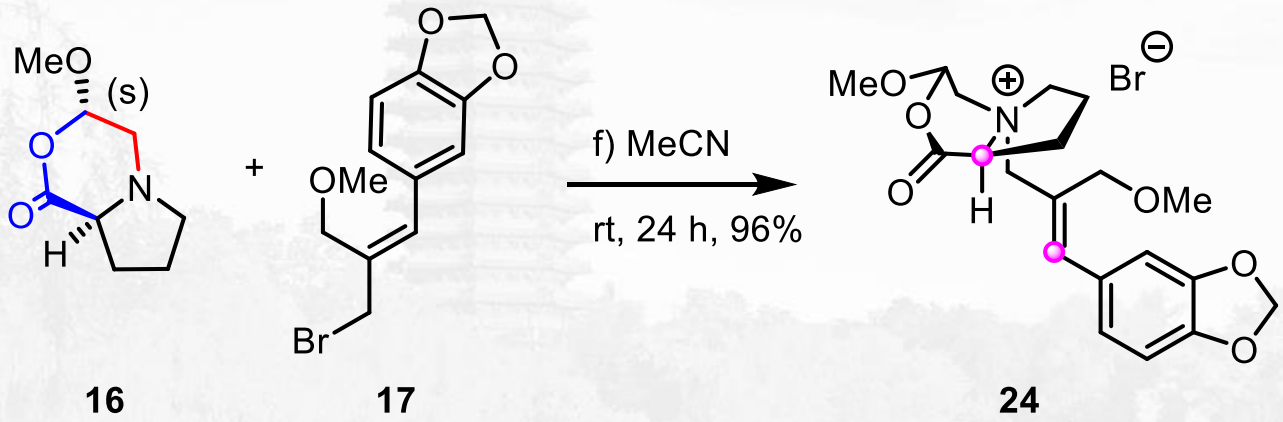
Org. Lett. **2018**, *20*, 6121–6125

Syntheses of fragments 16 and 17

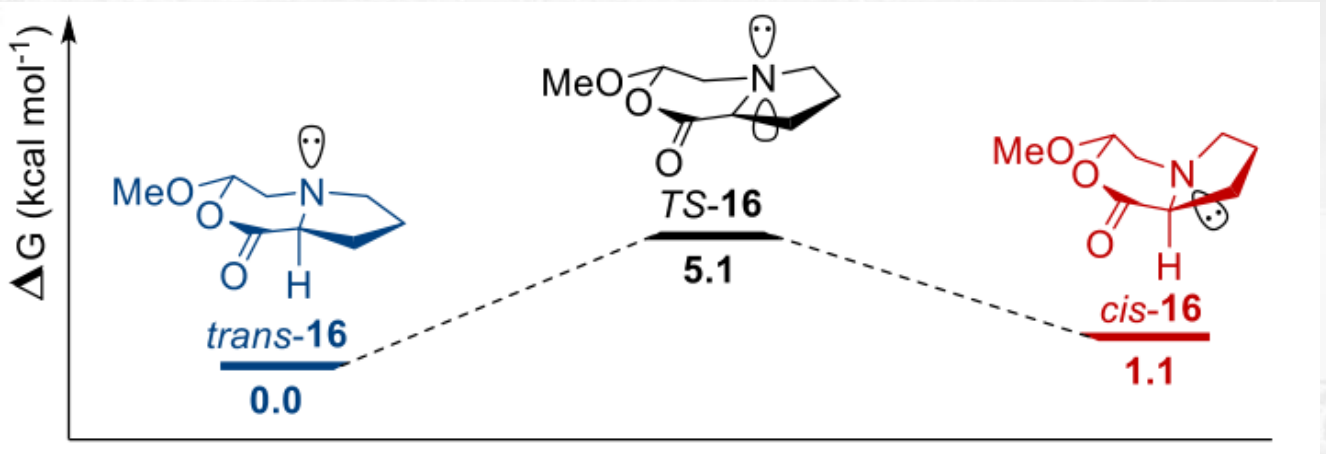


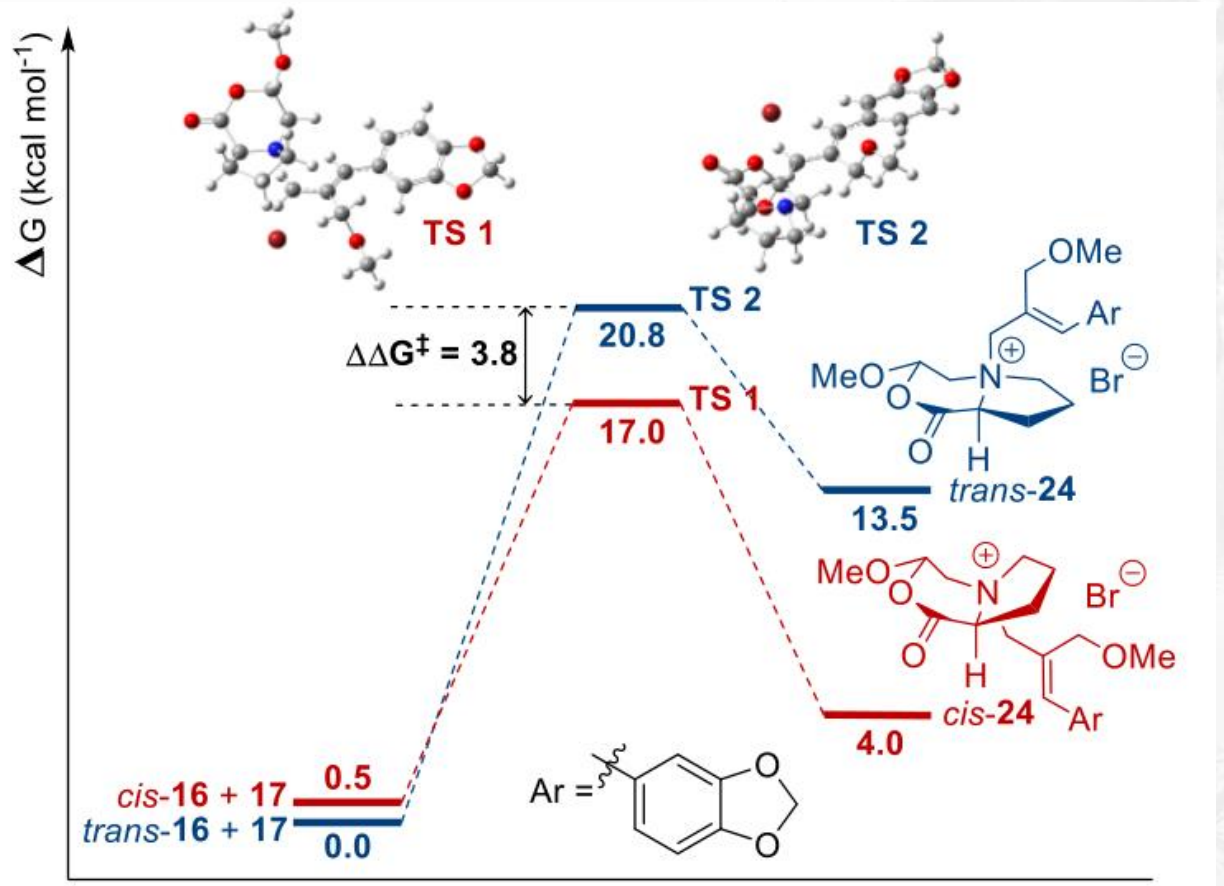


Synthesis of compound 24

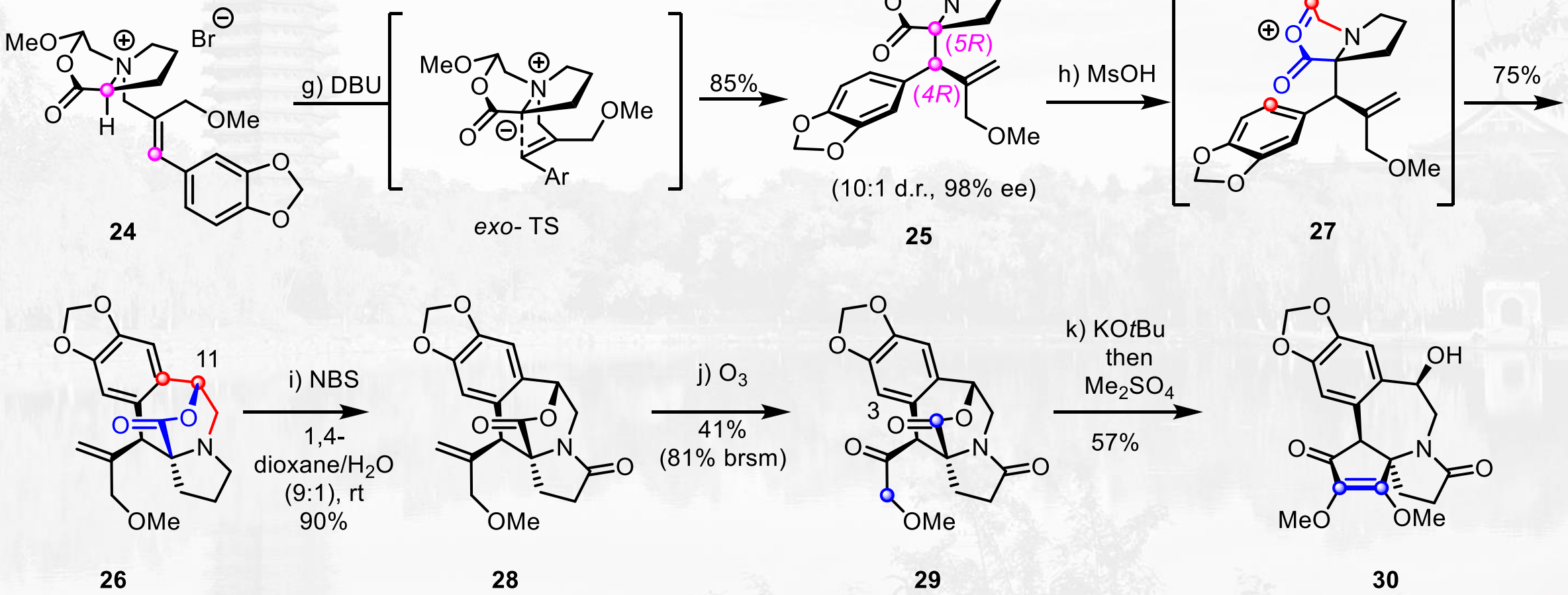


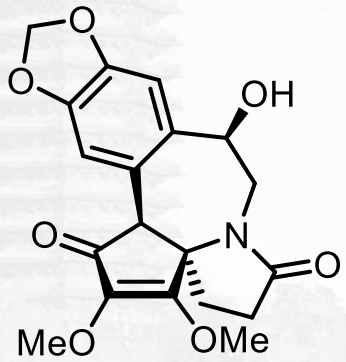
16 17 24





Synthesis of compound 30

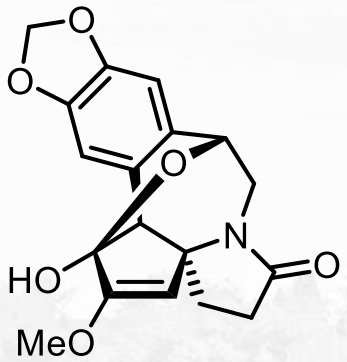




30

a) PtO_2, H_2
b) K_2CO_3

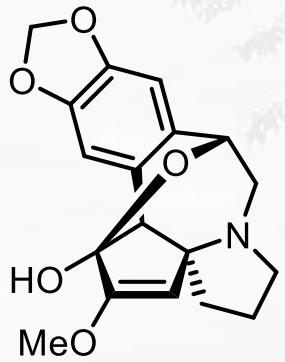
77% for 2 steps



31

c) $RhH(CO)(PPh_3)_3$
$PhSiH_3$

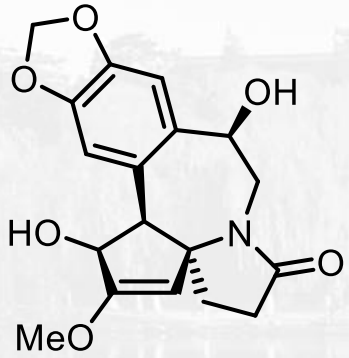
91%



11-hydroxycephalotaxinone hemiketal (**12**)

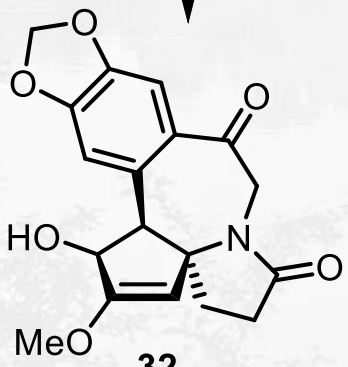
d) $NaBH_4$

89%
10:1 d.r.



torreyafargesine A (**11**)

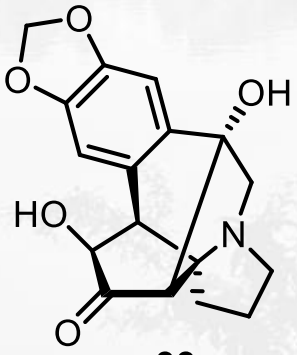
h) PCC 65%



32

i) $RhH(CO)(PPh_3)_3$
$PhSiH_3$
65%

j) HCl
60%

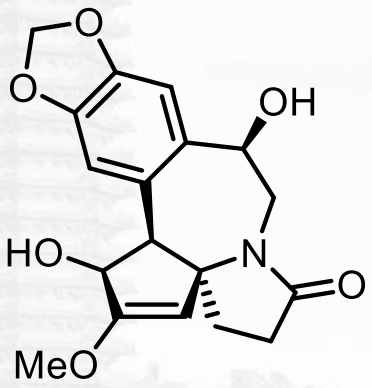


33

k) $LiAlH_4$

76%

cephalocyclidin A (**10**)



torreyafargesine A (**11**)

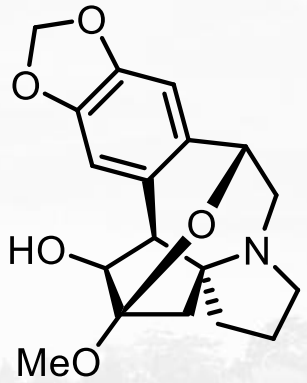
e) $LiAlH_4$

72%

11-hydroxy-cephalotaxine (**4**)

f) HCl

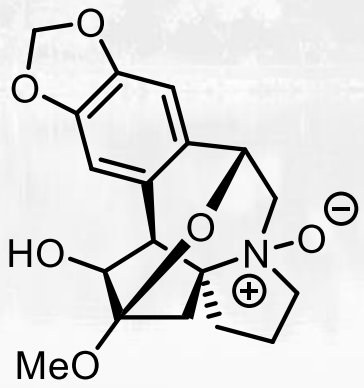
78%



drupacine (**3**)

g) *m*CPBA

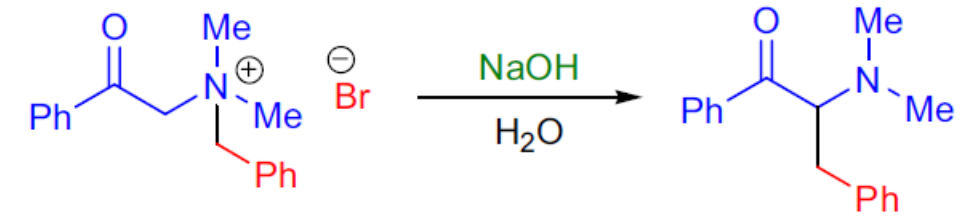
83%



cephalancetine B (**8**)

Mechanism for STEVENS REARRANGEMENT

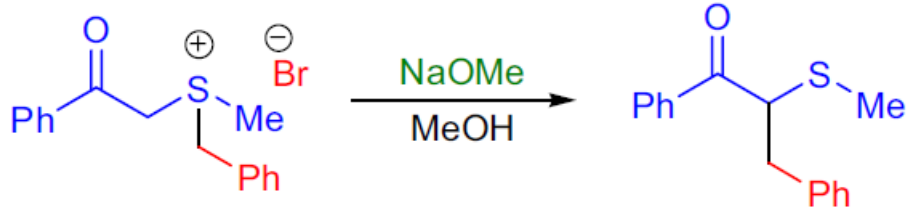
Stevens (1928):



phenacylbenzyldimethyl ammonium bromide

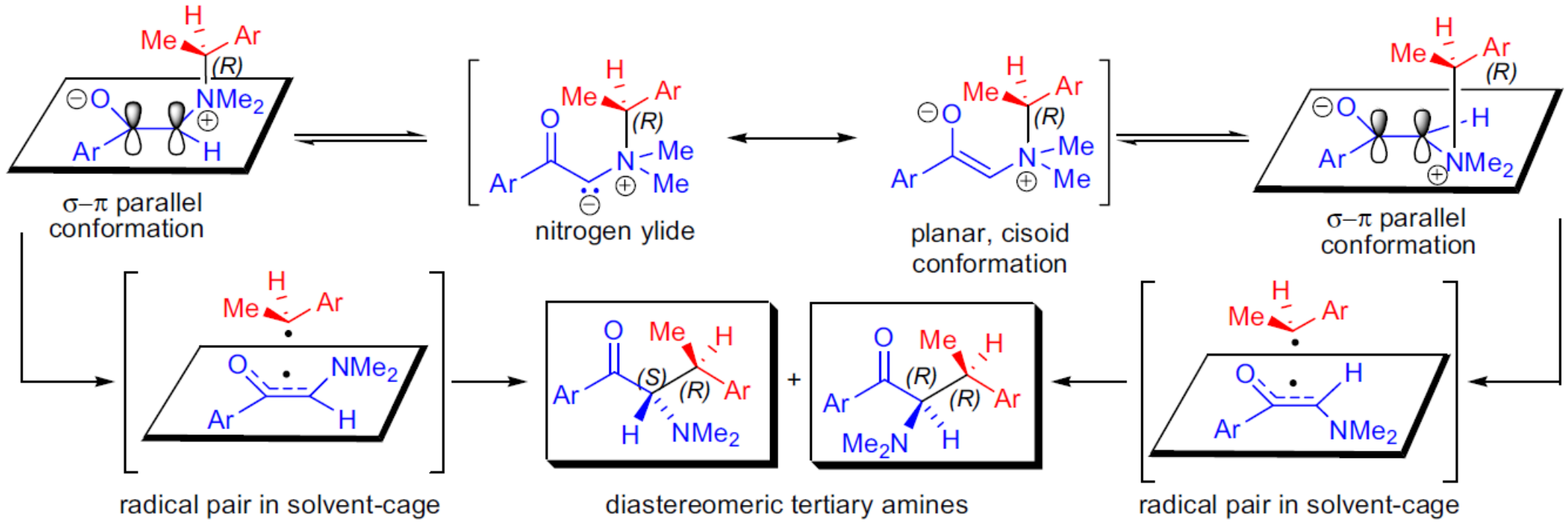
1-benzoyl-2-benzyl dimethylamine

Stevens (1932):

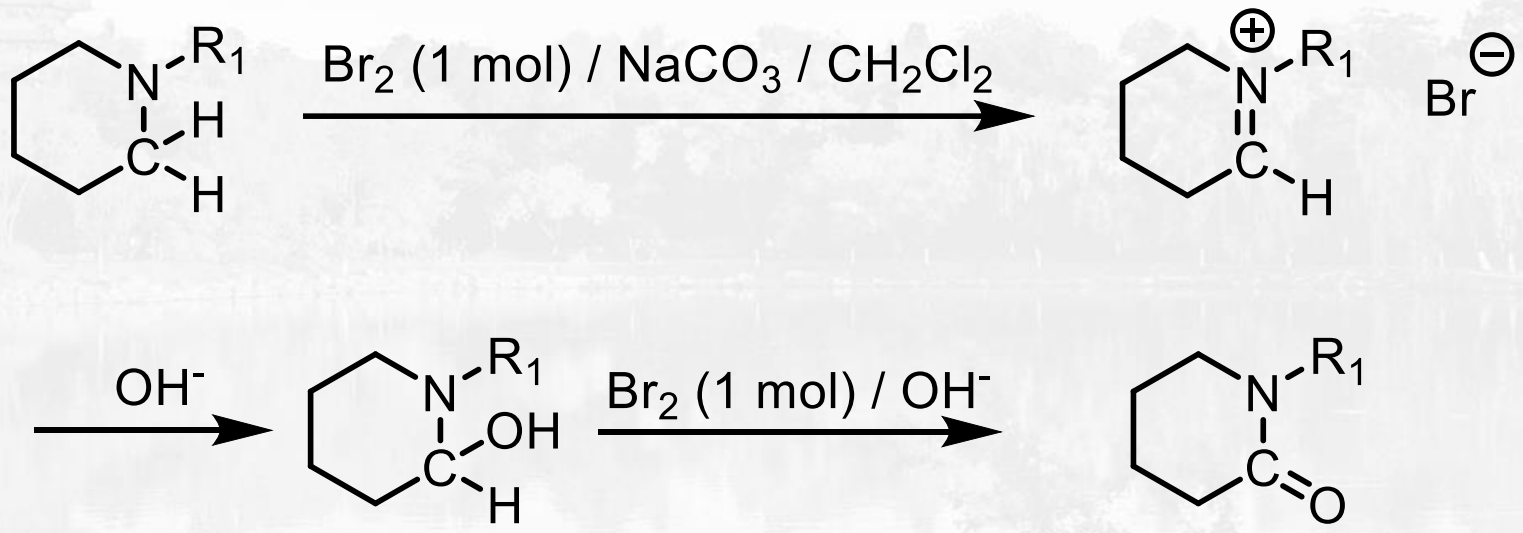


phenacylbenzylmethyl sulfonium bromide

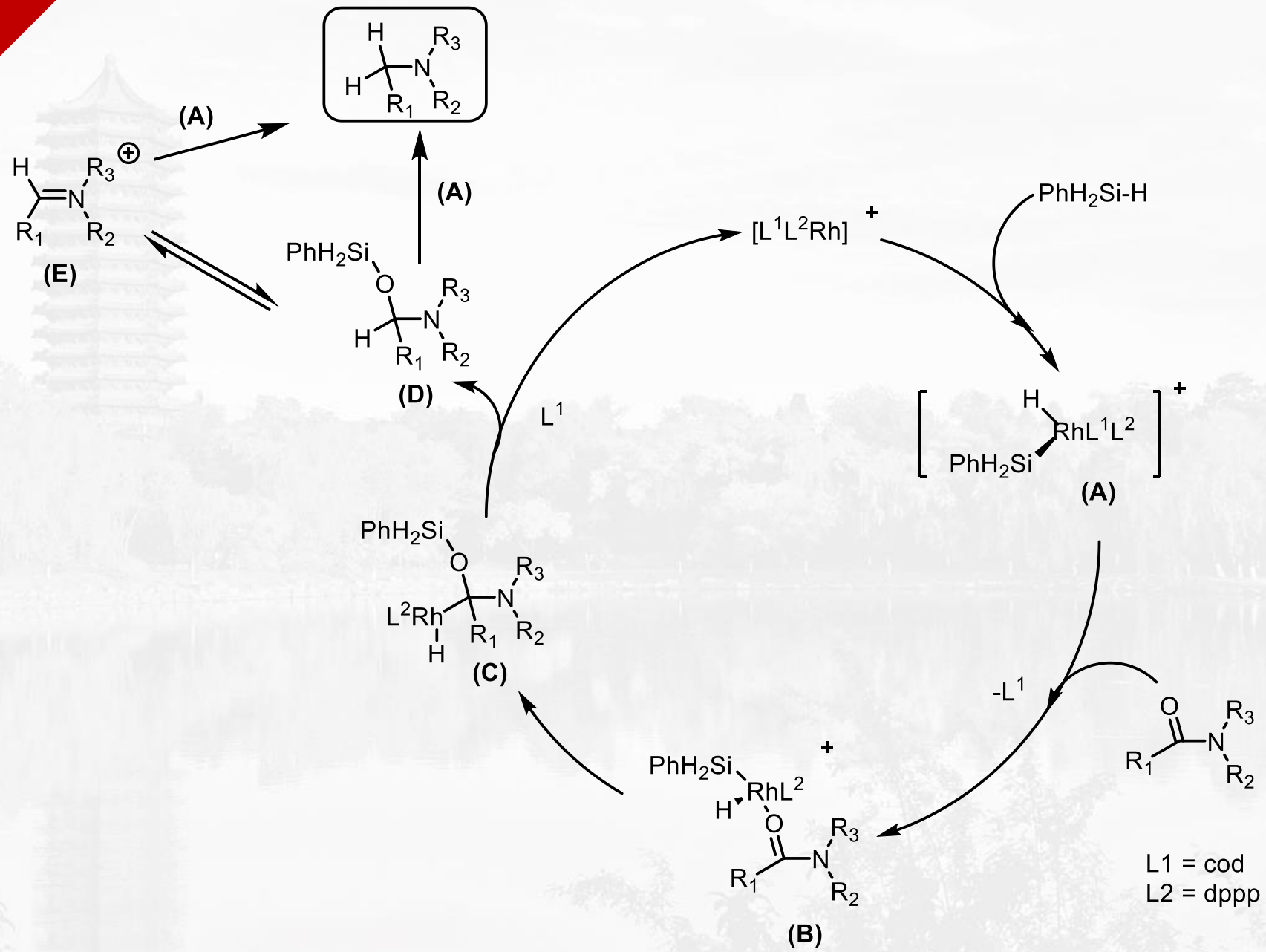
2-methylsulfanyl-1,3-diphenyl-propan-1-one



Mechanism for 26 to 28



Picot, X. Lusinchi, *Synthesis,* **1975**, 109–111



M. Beller, *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 12389–12393