Analogues Preparation of (±)-Meloscine Using Radical Cascade Reaction

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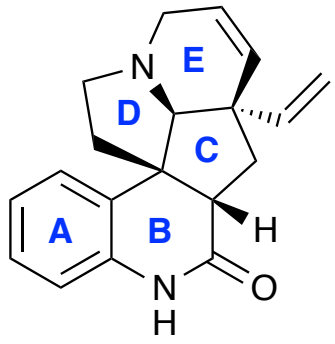
Wipf Group Research Topic Seminar

May-25-2013

Outline

- Background of Meloscine
- Previous Synthetic Studies
  (±)-Meloscine – Overman, Mukai, Feldman, and Curran
  (+)-Meloscine – Bach
- Radical Reactions
- Analogues Preparation
- Conclusion

Meloscine



meloscine

A representative member of *Melodinus* alkaloids.

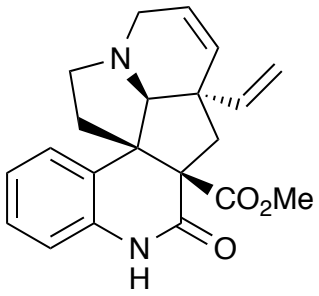
Meloscine was isolated from the New Caledonian plant *Melodinus Scandens Forst* in1969.

Extracts of some *Melodinus* species are traditional Chinese folk medicines to treat meningitis and rheumatic heart disease.

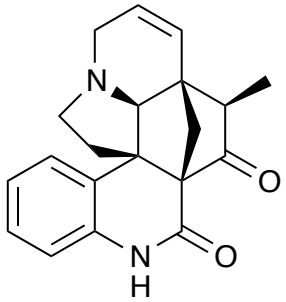
Structure features
- Pentacyclic system
- Dihydroquinolin-2-one moiety (rings A/B)
- Cyclopentane ring containing 4 stereogenic centers (ring C)

Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. *Helv. Chim. Acta*. **1969**, *52*, 1886–1905.
Oberhaensli, W. E. *Helv. Chim. Acta.* **1969**, *52*, 1905–1911.
Plat, M.; Hachem-Mehri, M.; Koch, M.; Scheidegger, U.; Potier, P. *Tetrahedron Lett*. **1970**, *11*, 3395–3398

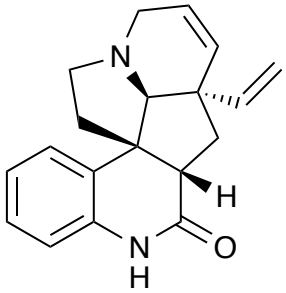
Representative Examples of the Melodinus Alkaloids



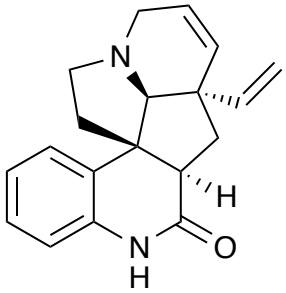
(+)-Scandine



(+)-Meloscandonine



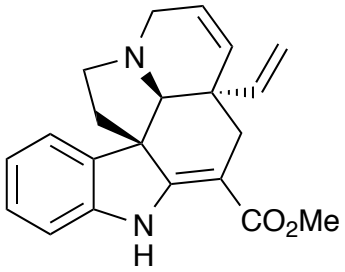
(+)-Meloscine



(+)-Epimeloscine

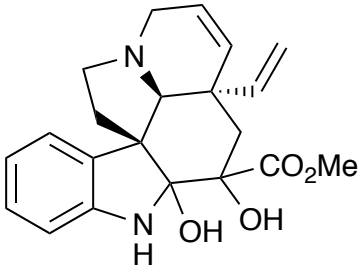
Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. *Helv. Chim. Acta* **1969**, *52*, 1886–1905.
Plat, M.; Hachem-Mehri, M.; Koch, M.; Scheidegger, U.; Potier, P. *Tetrahedron Lett.* **1970**, *11*, 3395–3398.

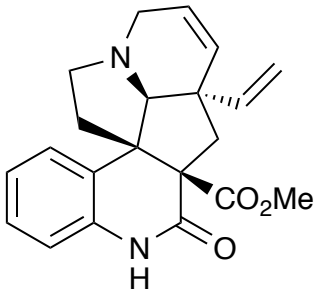
Biosynthesis of the Melodinus Alkaloids



18,19-Dehydrotabersonine

[O]

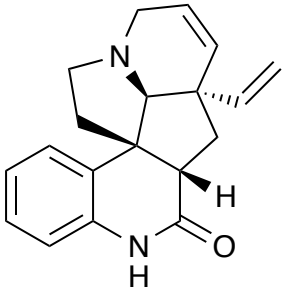




Scandine

hydrolysis

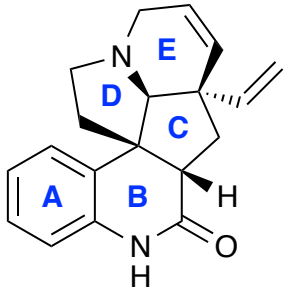
decarboxylation



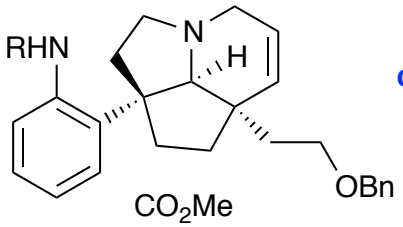
Meloscine

biomimetic semisynthesis of (+)-scandine and (+)-meloscine from 18,19-dehydrotabersonine: Palmisano, G.; Danieli, B.; Lesma, G.; Riva, R.; Riva, S. Demartin, F.; Masciocchi, N. *J. Org. Chem.* **1984**, *49*, 4138–4143. Hugel, G.; Levy, J. *J. Org. Chem.* **1986**, *51*, 1594–1595.

Retrosynthetic Analysis of (±)-Meloscine (Overman)

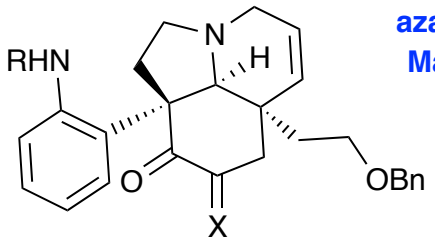


meloscine



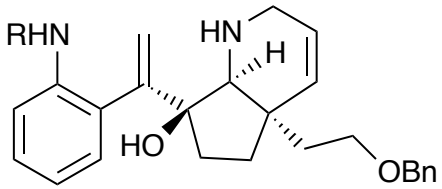
1

Wolff ring contraction



2

aza-Cope-Mannich



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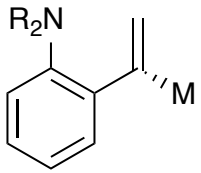
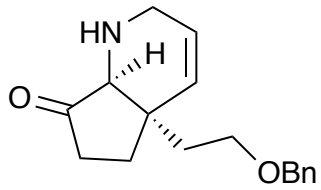


4

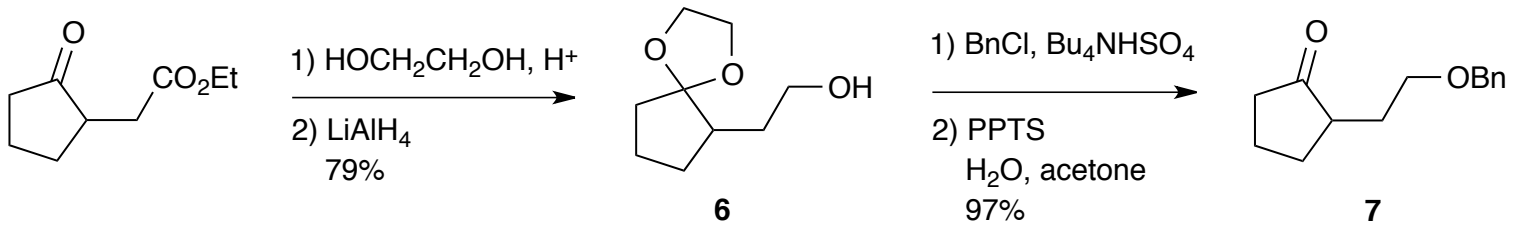
+

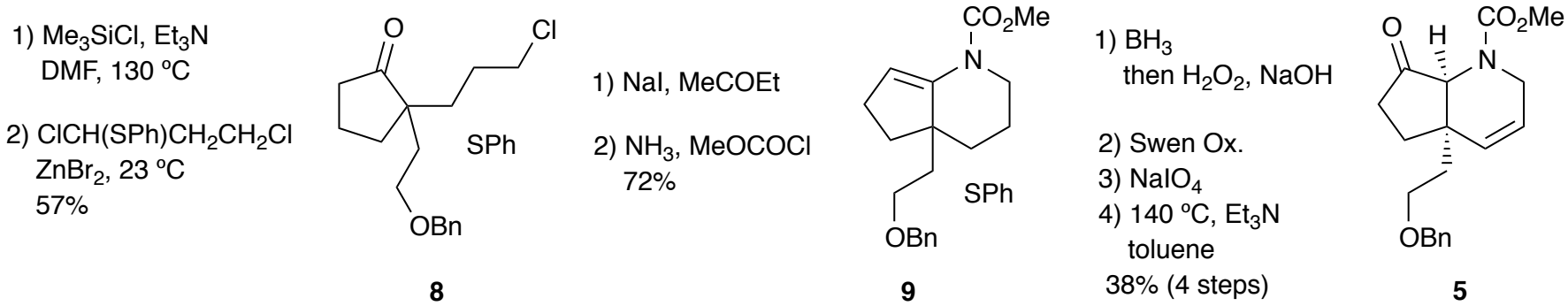


5

Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Org. Chem.* **1989**, *54*, 1236–1238.
Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610.

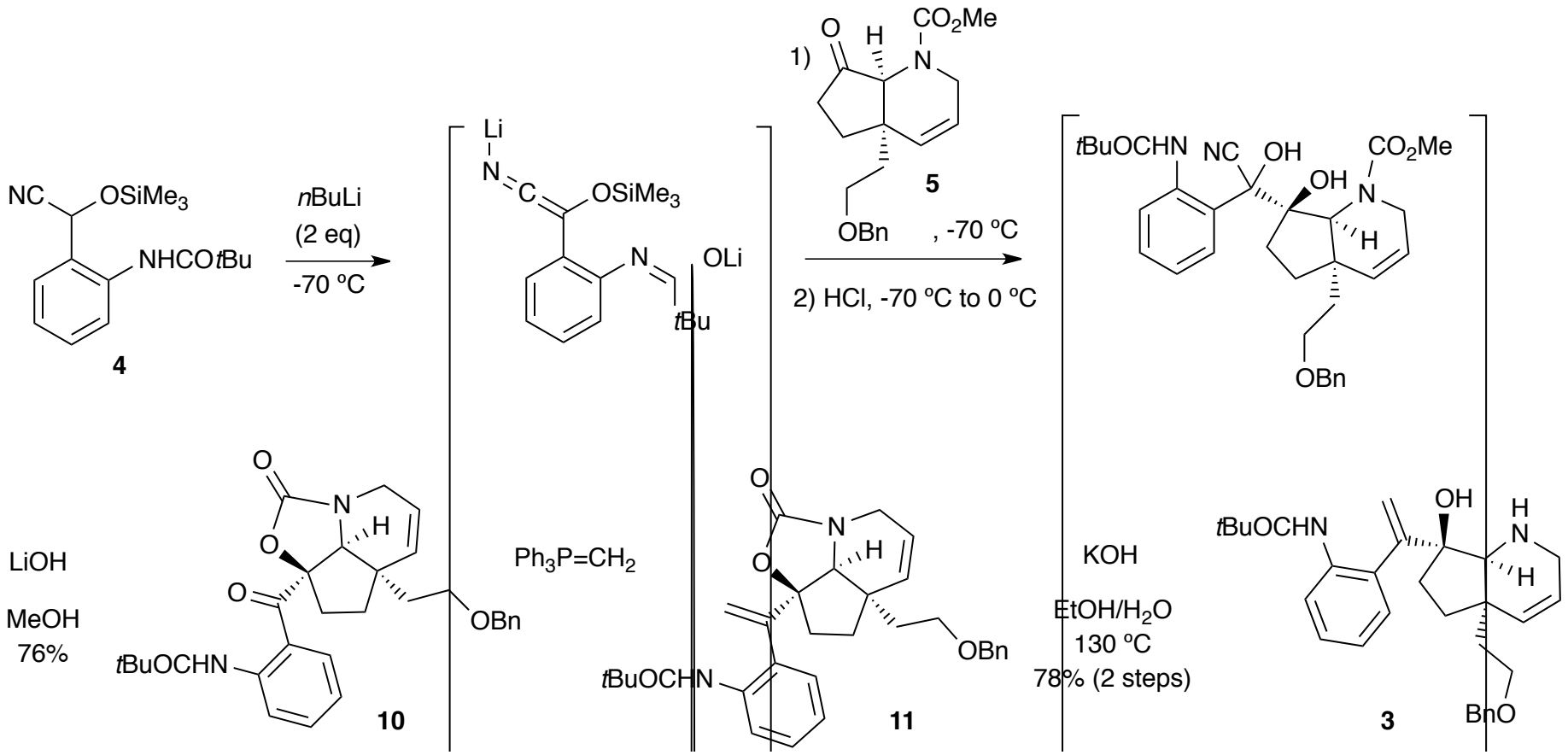
Preparation of cis-Pyrindinone





Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Org. Chem.* **1989**, *54*, 1236–1238.
Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610.

Conversion to Aza-Cope-Mannich Rearrangement Precursor



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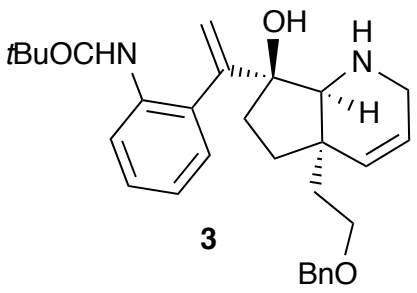
Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610.

Aza-Cope-Mannich Rearrangement and End Game

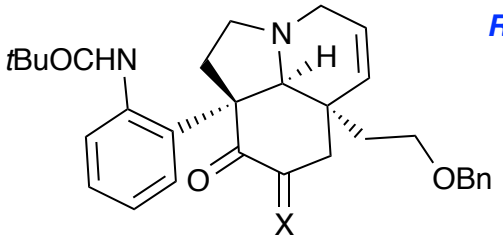


3

aza-Cope-Mannich

HCHO
camphorsulfonic acid

benzene, reflux
82%



Wolff Rearrangement

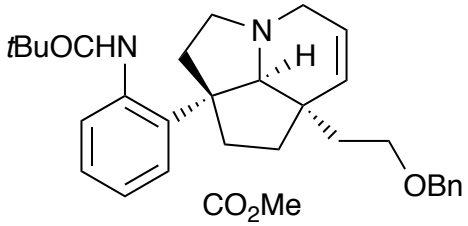
hv

MeOH

12, X = H, H

2,4,6-triisopropylbenzene-sulfonyl azide, 98%

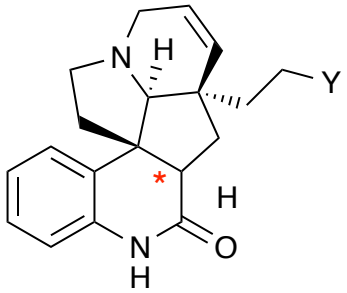
13, X = N_2



14, 94%

KOH

0 °C to 150 °C
95%



β-H/α-H 10:1

1) Na/NH_3
-70 °C
2) TsCl, pyridine
96% (2 steps)

15, Y = OBn

16, Y = OTs

(*o*-nitrophenyl)seleno-cyanate
$NaBH_4$, EtOH
23 °C, 20 h, 58%

17, Y = Se(*o*-NO_2)C_6H_4

*m*CPBA, -70 °C

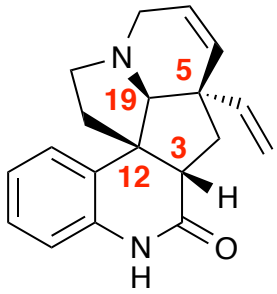
then Me_2S, Et_3N
warm up to rt

meloscine (81%)
epimeloscine (69%)

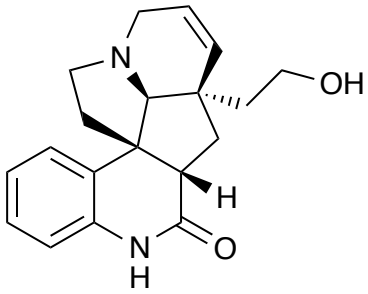
26 steps

Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Org. Chem.* **1989**, *54*, 1236–1238.
Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610.

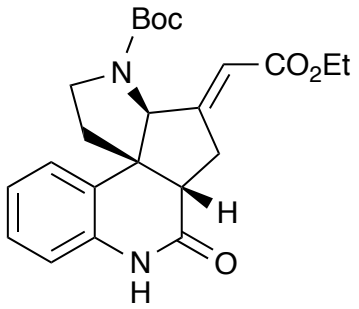
Retrosynthetic Analysis of (+)-Meloscine (Bach)



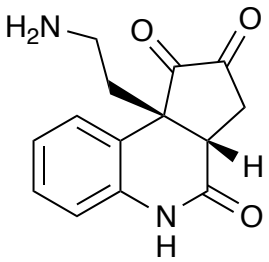
(+)-meloscine



18

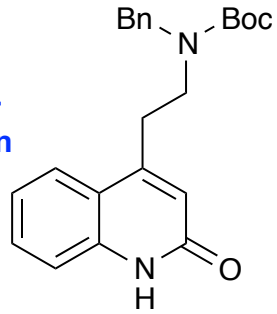


19

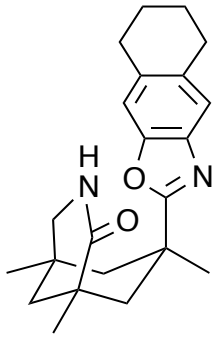


20

[2+2] photo-cycloaddition



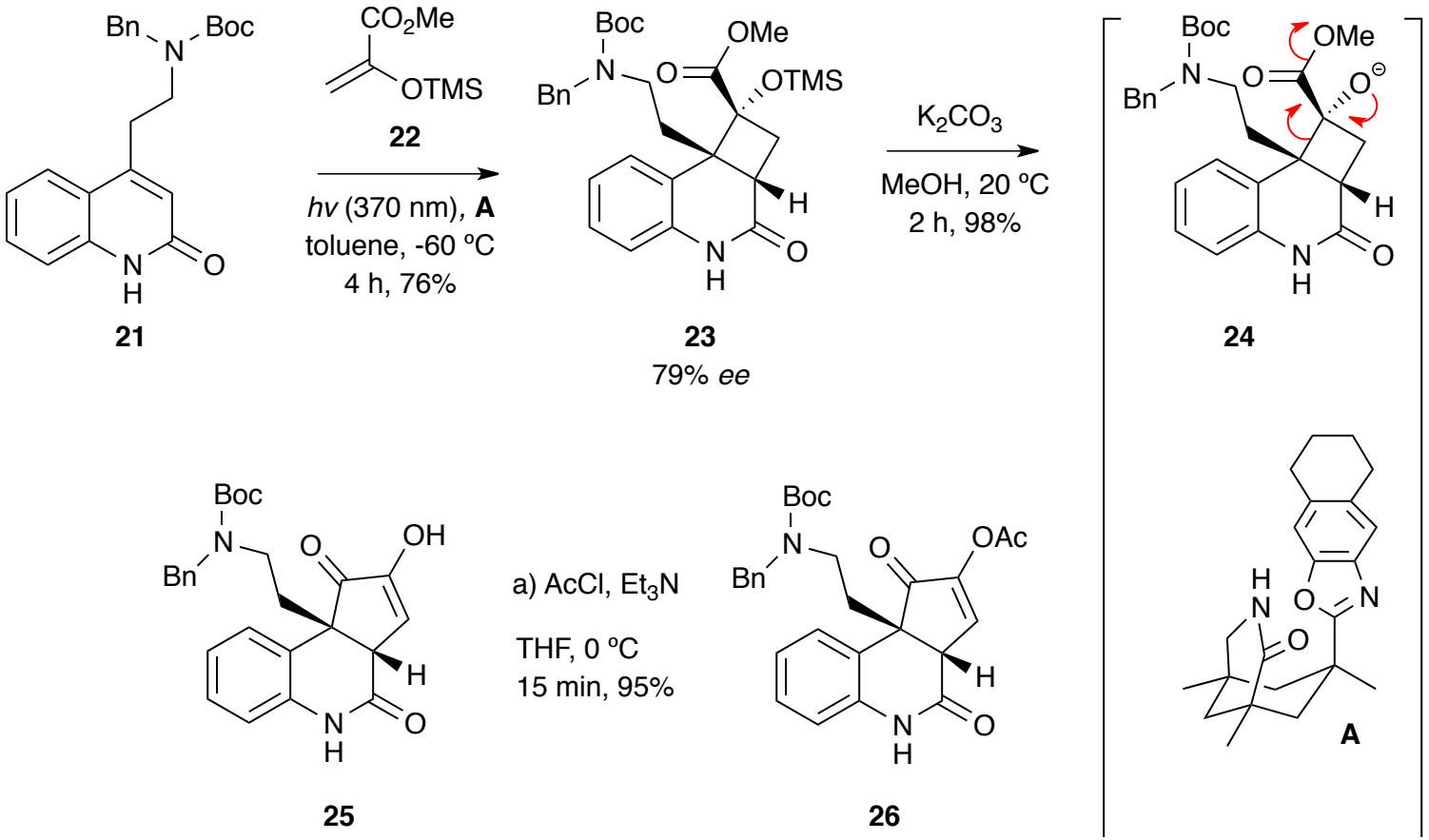
21
quinolone



chiral complexing agent **A**

Selig, P.; Bach, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5082–5084.

Synthesis of the Tricyclic Intermediate



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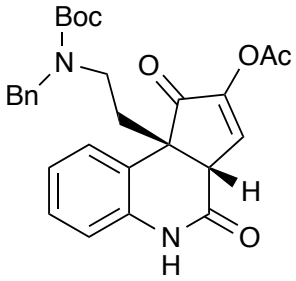
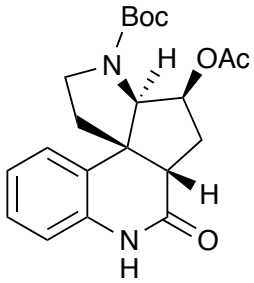
Completion of the Total Synthesis of (+)-Meloscine



26

b) TFA, CH_2Cl_2
20 ºC, 1h
c) H_2 $Pd(OH)_2/C$
MeOH, 0 ºC to 20 ºC

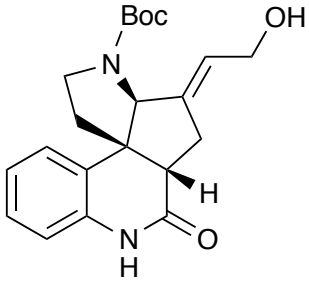
d) Boc_2O, Et_3N, CH_2Cl_2
20 ºC, 1 h
78% (3 steps)



27

e) K_2CO_3, MeOH
20 ºC, 3.5 h, 94%
f) IBX, DMSO
20 ºC, 18 h, 94%

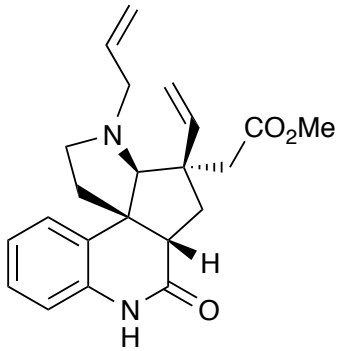
g) Ph_3PCHCO_2Et
THF, reflux, 22 h, 84%
h) DIBAL-H, CH_2Cl_2
-45 ºC, 30 min, 81%



28

i) $MeC(OMe)_3$
hydroquinone, 135 ºC
16 h, 85% (*d.r.* 70:30)

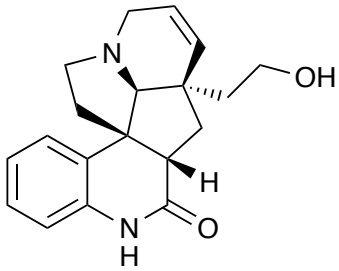
j) TFA, CH_2Cl_2
20 ºC, 1 h
k) allyl bromide
K_2CO_3, MeCN
20 ºC, 20 h
65% (2 steps)



29

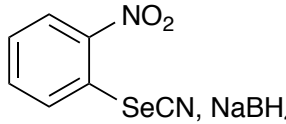
l) Grubbs-II
toluene, 65 ºC
18 h, 95%

m) DIBAL-H, CH_2Cl_2
-78 ºC, 30 min
n) $NaBH_4$, EtOH
0 ºC, 20 min
70% (2 steps)



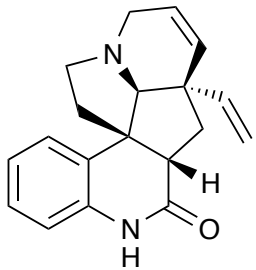
18

o) TsCl, Et_3N
CH_2Cl_2, 20 ºC
18 h, 72%

p)


EtOH, 20 ºC, 80 h, 98%

q) TFA, mCPBA
CH_2Cl_2, -78 ºC to 20 ºC
4 h, 86%

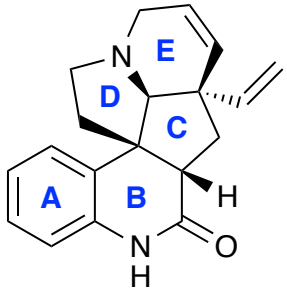


meloscine

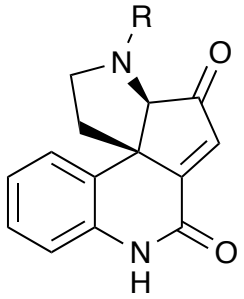
25 steps

Selig, P.; Bach, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5082–5084.

Retrosynthetic Analysis of (±)-Meloscine (Mukai)

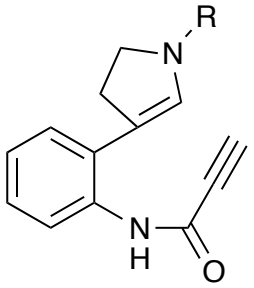


meloscine



30

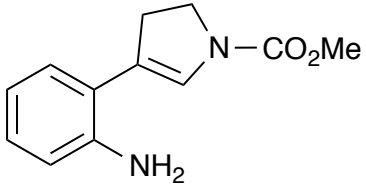
Pauson-Khand



31

Hayashi, Y.; Inagaki, F.; Mukai, C. *Org. Lett.* **2011**, *13*, 1778–1780.

Construction of A, B, C, and D Rings

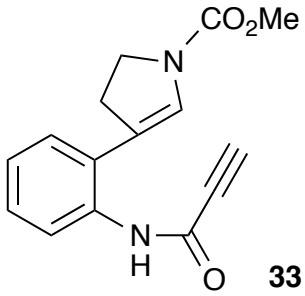


32

5 steps from (2-nitrophenyl)-acetonitrile

propiolic acid
EDC•HCl

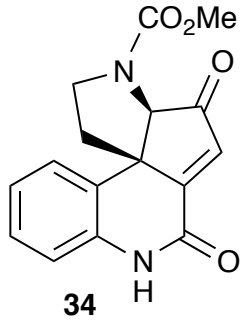
CH_2Cl_2, rt
83%



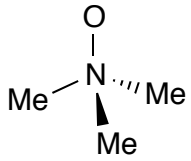
33

$Co_2(CO)_8$
MeCN, rt

then
TMANO•$2H_2O$
rt, 56%



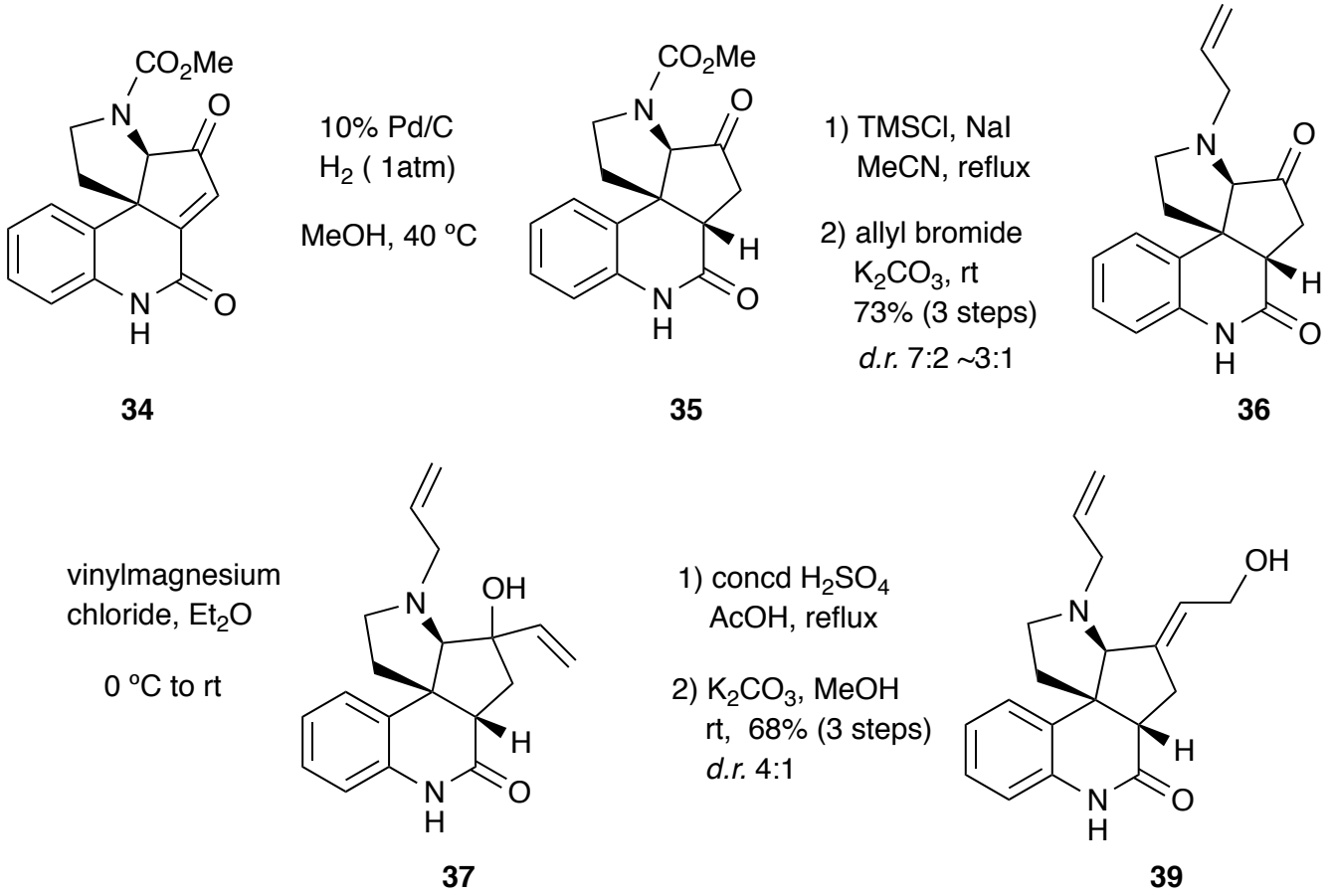
34



TMANO:
trimethylamine *N*-oxide

Hayashi, Y.; Inagaki, F.; Mukai, C. *Org. Lett*. **2011**, *13*, 1778–1780.
Dihydropyrrole-aniline derivative: Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Soc. Chem*. **1993**, *115*, 3030–3031.

Synthesis of Hydroxyethylidene Derivative

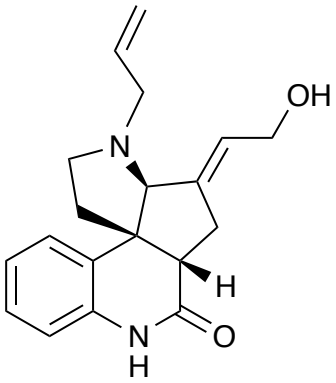


34 **35** **36**

37 **39**

Hayashi, Y.; Inagaki, F.; Mukai, C. *Org. Lett*. **2011**, *13*, 1778–1780.

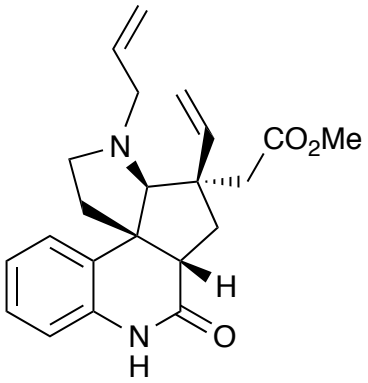
Completion of Total Synthesis of (±)-Meloscine



38

$MeC(OMe)_3$
hydroquinone

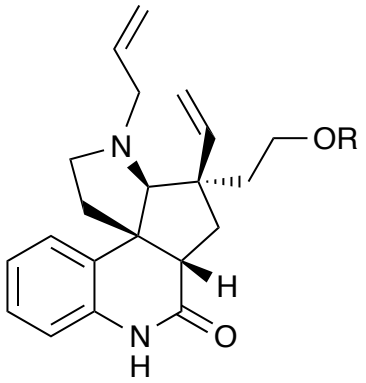
microwave
irradiation
200 °C
73% (*d.r.* 3:1)



39

LAH, THF

0 °C to rt
65%



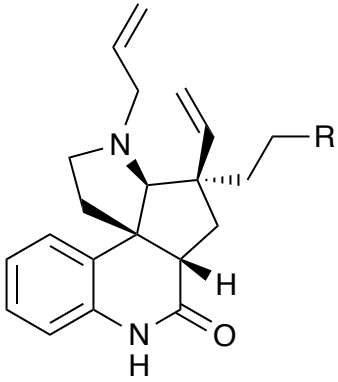
39, R = H

TsCl, Et_3N
CH_2Cl_2, rt

40, R = Ts

PhSeSePh
$NaBH_4$, EtOH

0 °C to rt



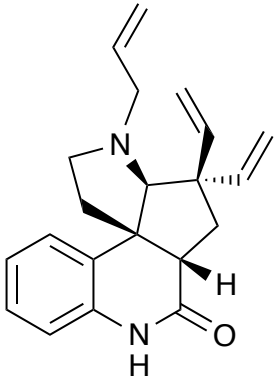
41, R = SePh

42, R = Se(O)Ph

NCS
$MeOH/CH_2Cl_2$
0 °C

benzene, 70 °C

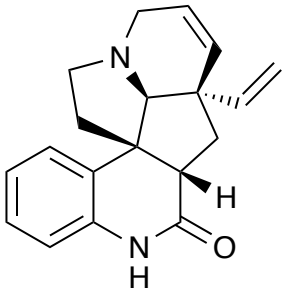
71% (4 steps)



43

Hoveyda-
Grubbs II

toluene, 60 °C
99%



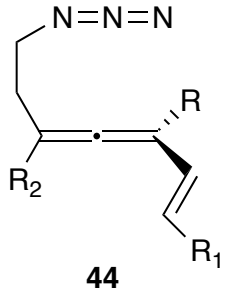
meloscine

20 steps

Hayashi, Y.; Inagaki, F.; Mukai, C. *Org. Lett.* **2011**, *13*, 1778–1780.

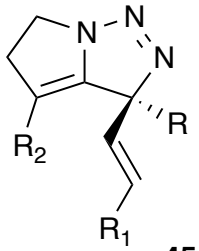
Retrosynthetic Analysis of (±)-Meloscine (Feldman)

Allenyl azide cyclization cascade



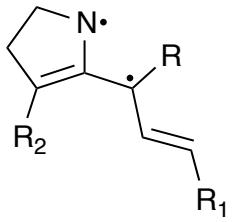
44

heat



45

-N_2



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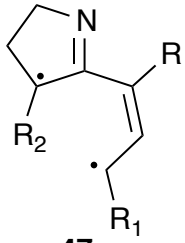
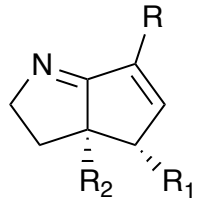


47



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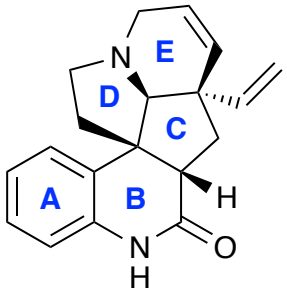
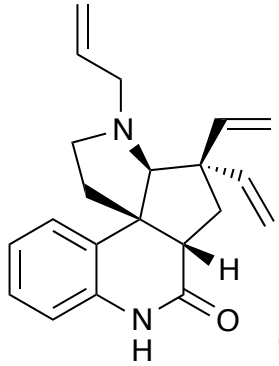


meloscine



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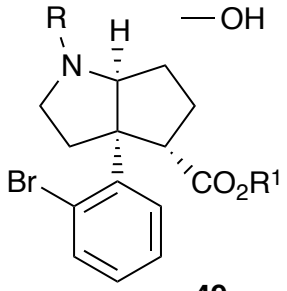

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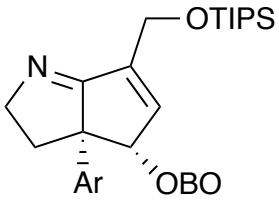

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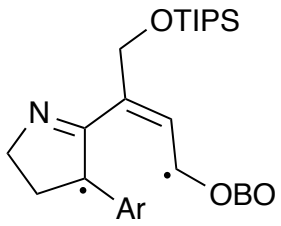

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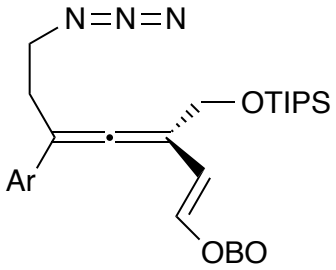

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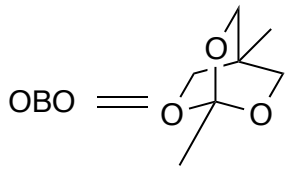
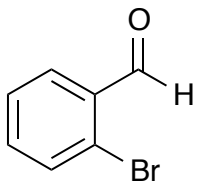


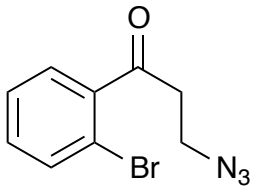
Feldman, K. S.; Antoline, J. F. *Org. Lett.* **2012**, *14*, 934–937.

Synthesis and Cyclization of the Allenyl Azide Sbustrate

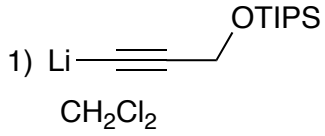


1) CH_2=CHMgBr
THF
2) Jones Ox

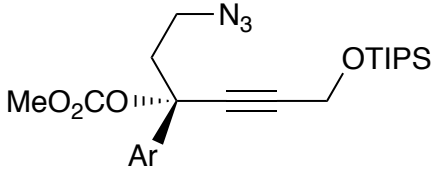
3) NaN_3, H_2O
AcOH
70% (3 steps)



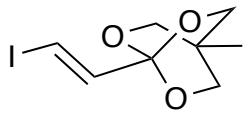
53



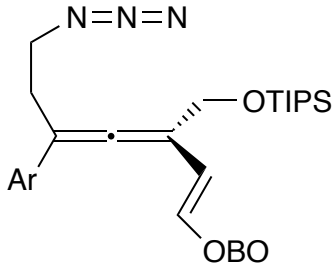
2) $ClCO_2Me$
CH_2Cl_2
84% (2 steps)



54, Ar = 2-BrC_6H_4



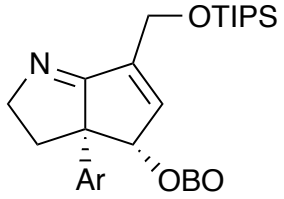
*t*BuLi, $ZnCl_2$
cat. $Pd(PPh_3)_4$
THF, Et_2O, rt



52

toluene
110 °C

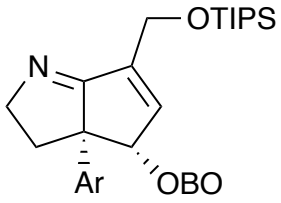
55%



50

Feldman, K. S.; Antoline, J. F. *Org. Lett.* **2012**, *14*, 934–937.

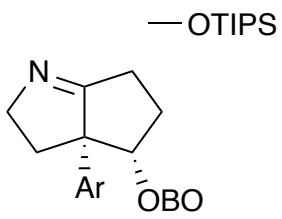
Completion of the Synthesis of (±)-Meloscine



50

1400 psi H_2
Pt/C, Et_3N

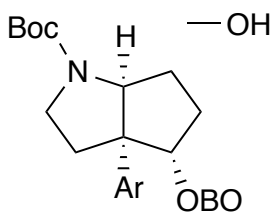
80%



55

1) $LiEt_3BH$, THF
2) Boc_2O, Et_3N
H_2NOH•HCl

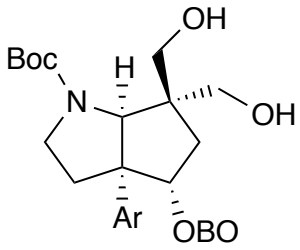
3) Bu_4NF, THF
59% (3 steps)



56

1) Dess-Martin Ox.
2,6-lutidine
microwave

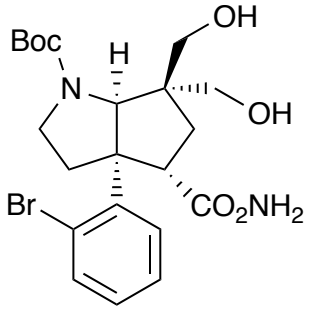
2) HCOH, KOH
CH_2Cl_2, $(CH_2OH)_2$
84% (2 steps)



57

1) 10% H_3PO_4
THF

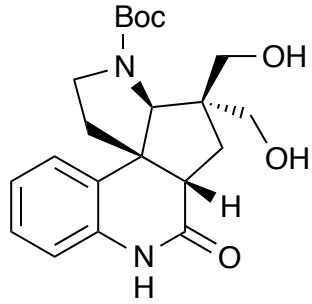
2) 100 psi NH_3
*i*PrOH, THF
68% (2 steps)



58

CuI, Cs_2CO_3
1,10-phenanthroline

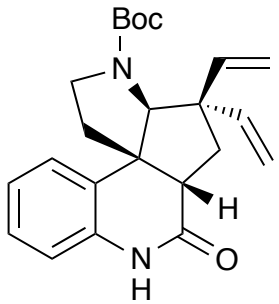
DMSO
microwave
78%



69

1) Dess-Martin Ox.
2,6-lutidine
H_2O sat. CH_2Cl_2
microwave

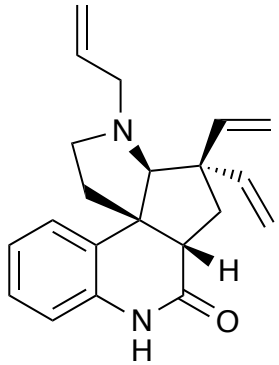
2) Ph_3PCH_3Br
$NaNTMS_2$, THF



60

1) TFA, CH_2Cl_2

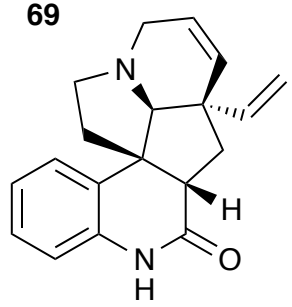
2) allyl bromide
K_2CO_3, MeCN
57% (4 steps)



43

Hoveyda-
Grubbs II

toluene
76%



meloscine

19 steps

Feldman, K. S.; Antoline, J. F. *Org. Lett.* **2012**, *14*, 934–937.

Radical Reactions

Synthetic advantages of radical reactions

- Carbon-centered radicals are extremely reactive.

- Radical additions to C=C bonds are usually exothermic and irreversible, with early, reactant-like transition state.

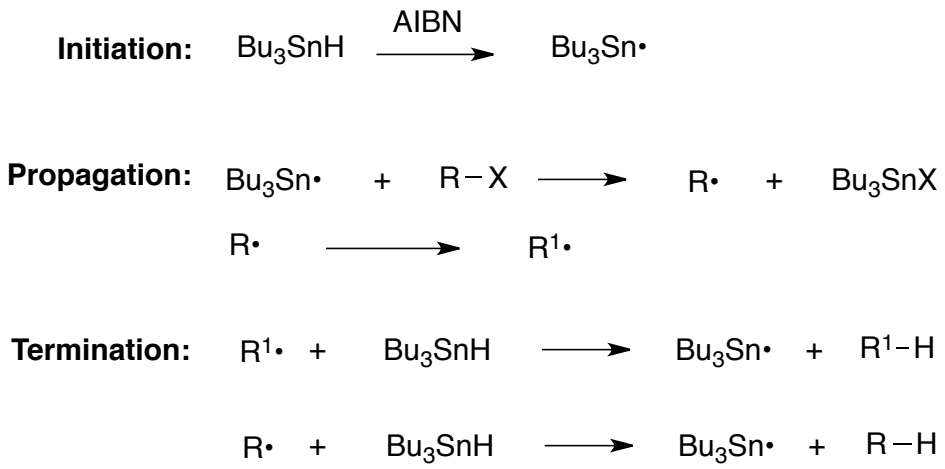
- Radical intermediates are ideally suited for the synthesis of crowded bonds.

- Carbon-centered radicals are inert toward OH or NH groups.

- Radical centers do not usually retain stereochemistry.

Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev*. **1991**, *91*, 1237–1286.

Radical Reactions: Tin Hydride Method



- Common reagent for free-radical reaction.
- Mild and selective reagent, so that carbonyl groups and alcohols do not need to be protected.

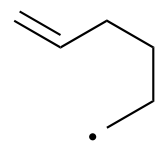
- A limitation of the method is that tin hydride is by nature a reducing agent.

Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev*. **1991**, *91*, 1237–1286.

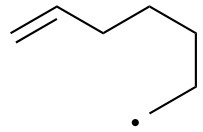
5-Memered Ring Formation

- Cyclizations are usually faster for the formation of 5-membered rings than for any other ring size.

  The 5-hexenyl radical cyclizes 20 times faster than does the 6-heptenyl radical.



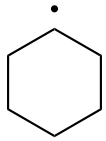
5-hexenyl radical



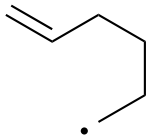
6-heptenyl radical

- The regioselectivity for 5-*exo* cyclizations is often outstanding.

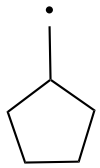
  For the 5-hexenyl radical, 5-*exo* cyclization is 50 times faster than 6-*endo* cyclization



6-endo



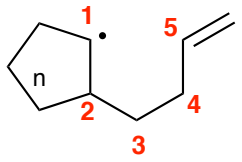
5-*exo*

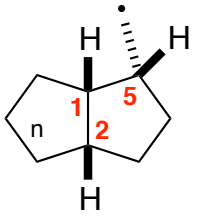


Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev*. **1991**, *91*, 1237–1286.
Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett*. **1985**, *26*, 373–376.

5-Memered Ring Formation

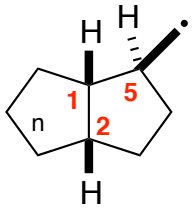
- Radical cyclizations giving 5-membered rings can be highly stereoselective.





1,5-*cis*

+

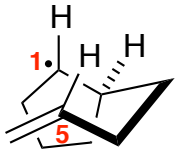


1,5-*trans*

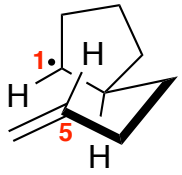
n = 1, cyclopentyl	8.3	1
n = 2, cyclohexyl	3.5	1

Beckwith's Transition-State Model

1,5-*cis*

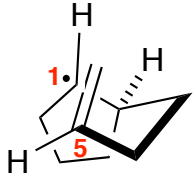


chair-like



chair-like

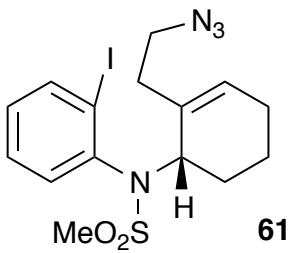
1,5-*trans*



boat-like

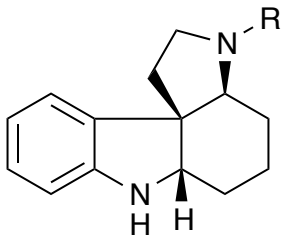
Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev*. **1991**, *91*, 1237–1286.
Rajanbabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139–145.
Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett*. **1985**, *26*, 373–376.

Radical Reactions: Efficient Synthesis of the ABCE Ring System of Aspidospermidine



61

TMS_3SiH, AIBN
C_6H_6, 80 °C, 5 h



65, R = $Si(TMS)_3$

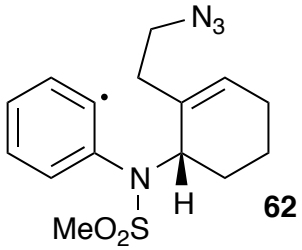
66, R = H

H_2O
95% (2 steps)

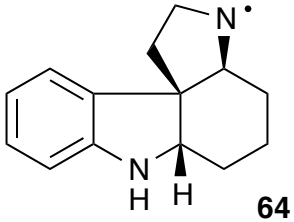
$Si(TMS)_3$—I

•$Si(TMS)_3$

$Si(TMS)_3$—H



62



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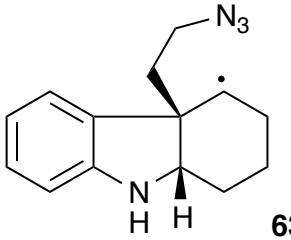
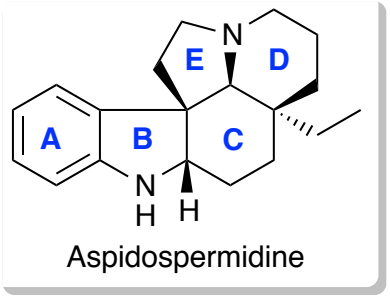


63

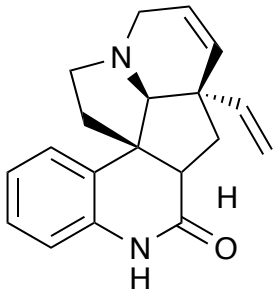
-N_2



Aspidospermidine

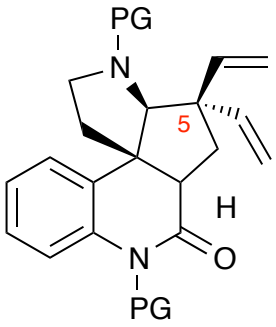
Kizil, M.; Murphy, J. A. *J. Chem. Soc. Chem. Commun.* **1995**, 1409–1410.

Retrosynthetic Analysis of (±)-Meloscine (Curran)



meloscine

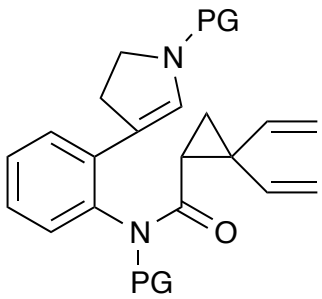
RCM



66

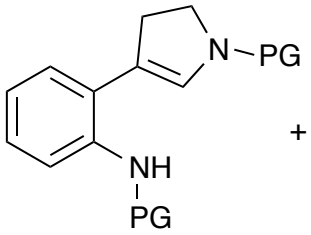
radical cascade

PG = protecting group



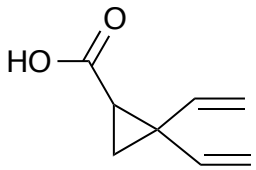
67

acylation



68

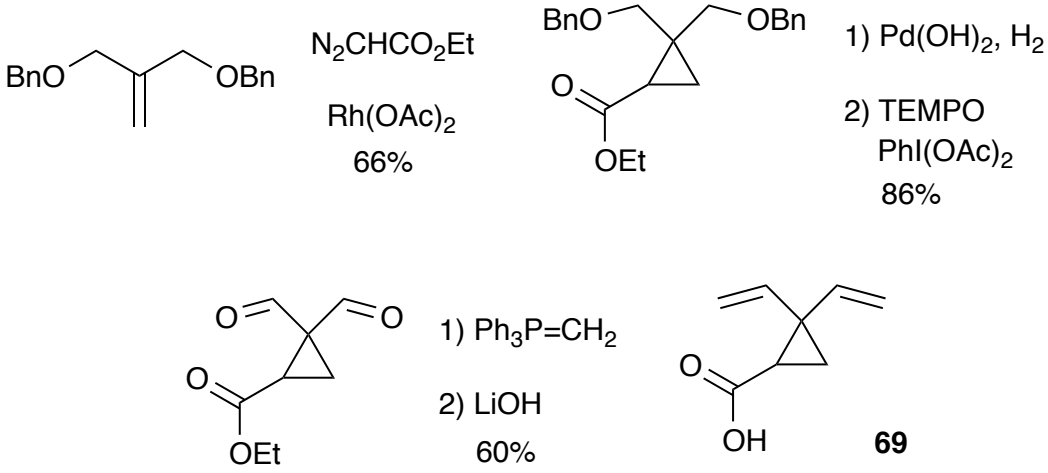
+

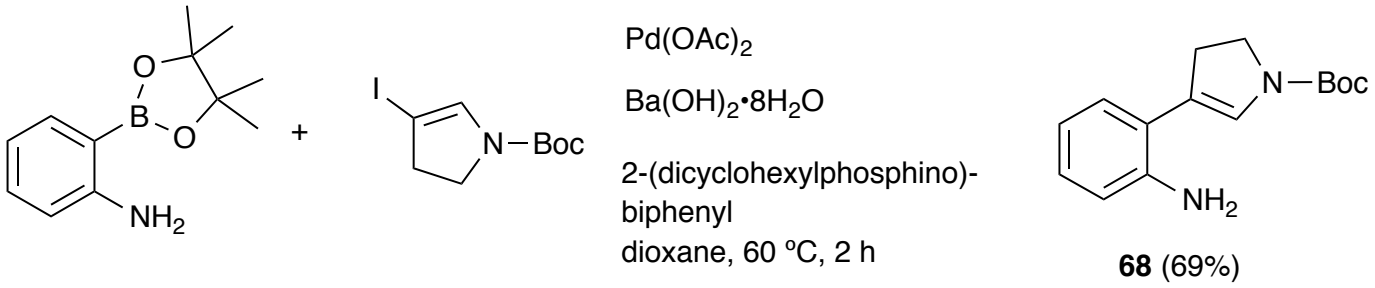


69

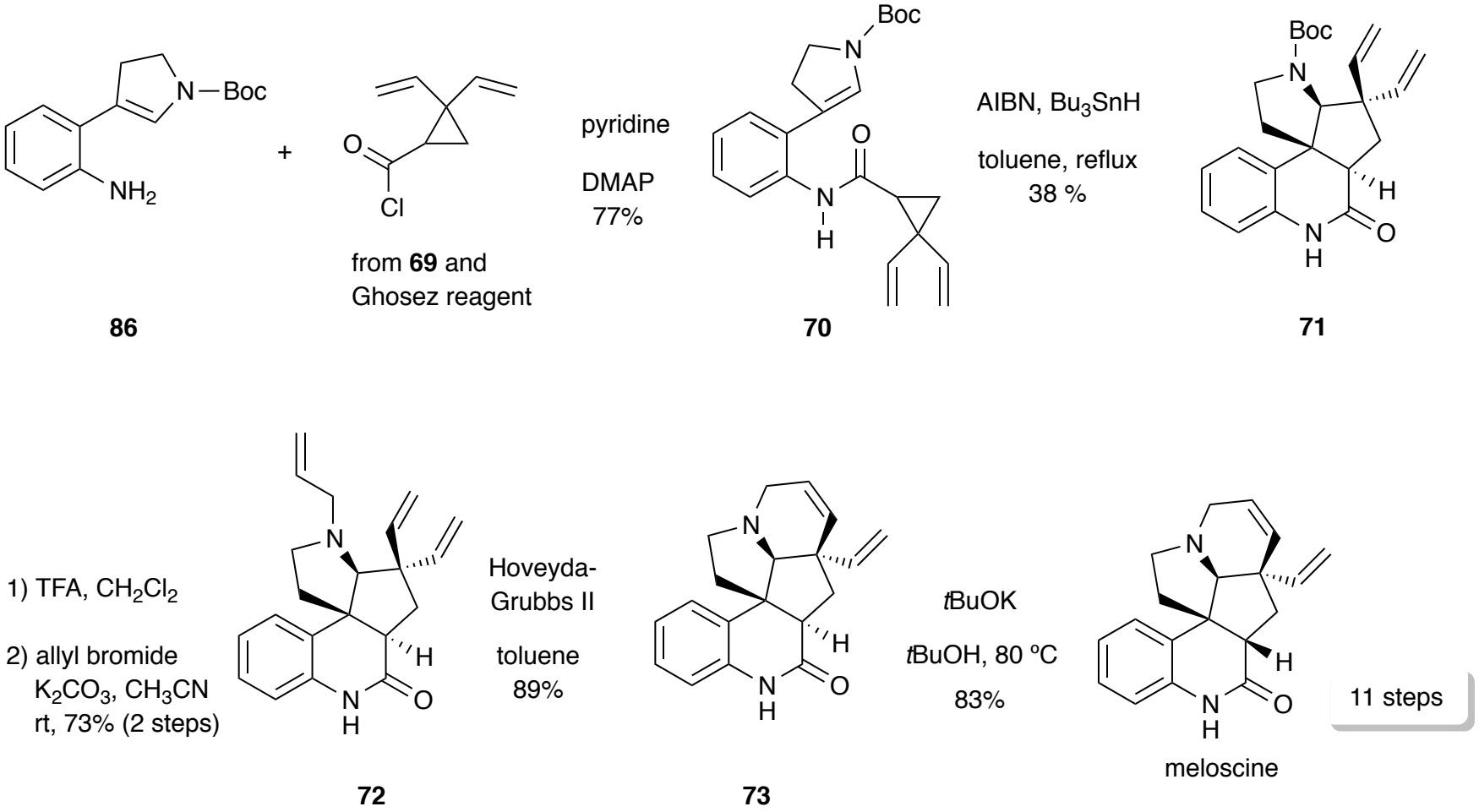
Zhang, H.; Curran, D. P. *J. Am. Chem. Soc.* **2011**, *133*, 10376–10378.

Preparations of Starting Materials



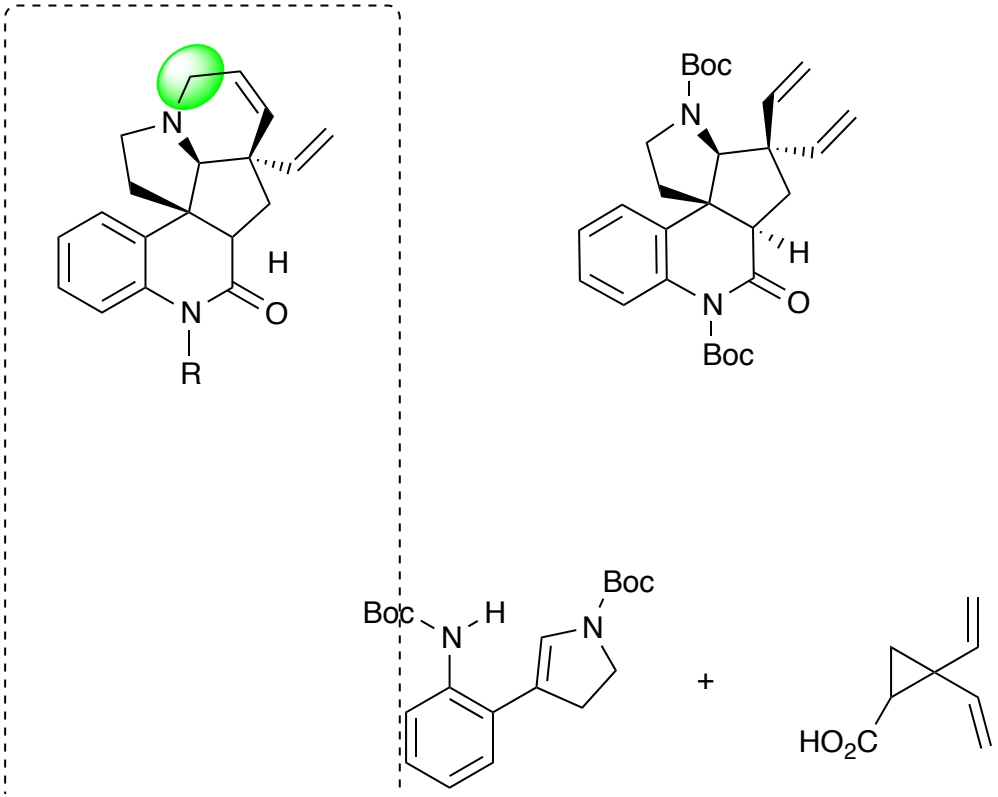


Syntheses of (±)-Epimeloscine and (±)-Meloscine

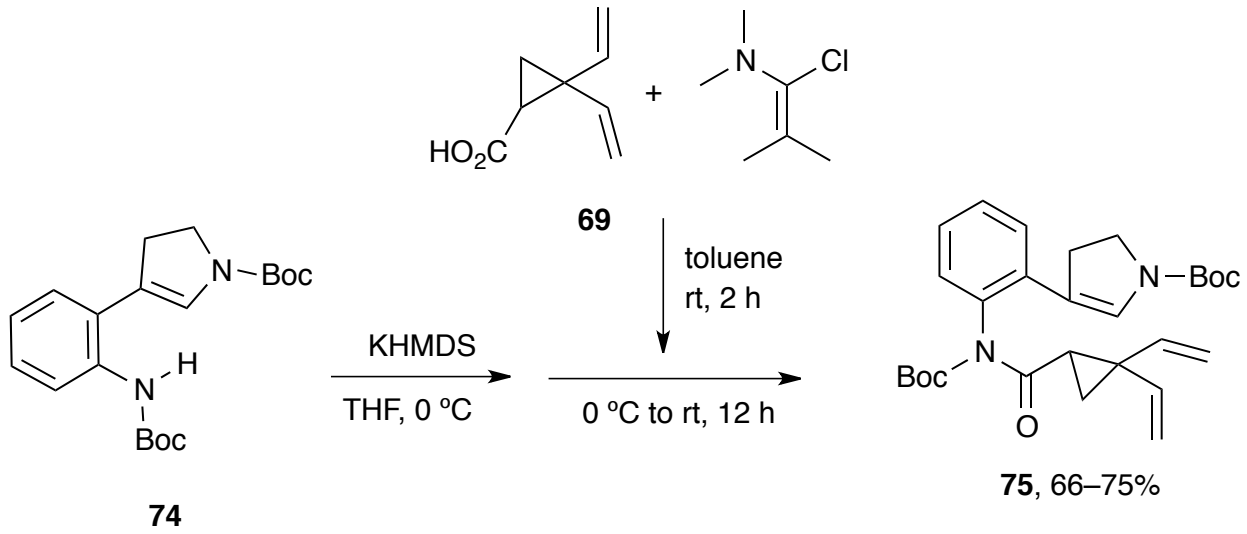


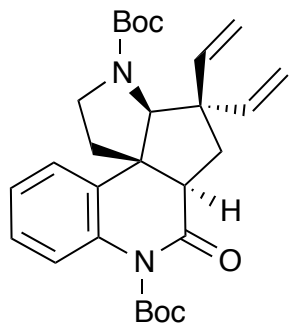
Zhang, H.; Curran, D. P. *J. Am. Chem. Soc*. **2011**, *133*, 10376–10378.

Strategy for Analogues Preparation



Radical Reaction: Tetracyclic Intermediate



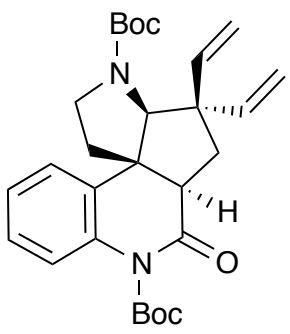


AIBN, Bu_3SnH

toluene, reflux

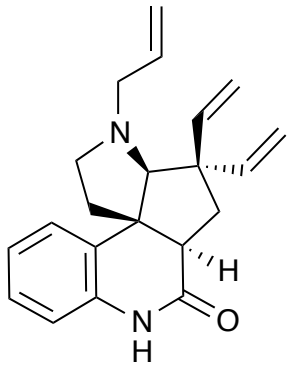
76, 22–43%

(±)-Epimeloscine and (±)-Meloscine



76

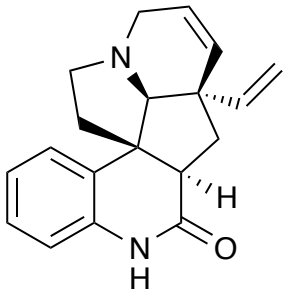
1. TFA, CH_2Cl_2
   rt, 3 h
2. allyl bromide
   K_2CO_3, CH_3CN
   rt, 12 h



77
45–79% (2 steps)

Hoveyda-
Grubbs II

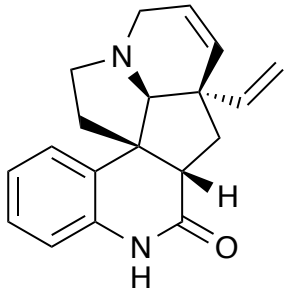
toluene
83 °C



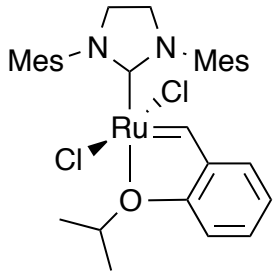
Epimeloscine
63–71%

*t*BuOK

*t*BuOH, 83 °C
12 h

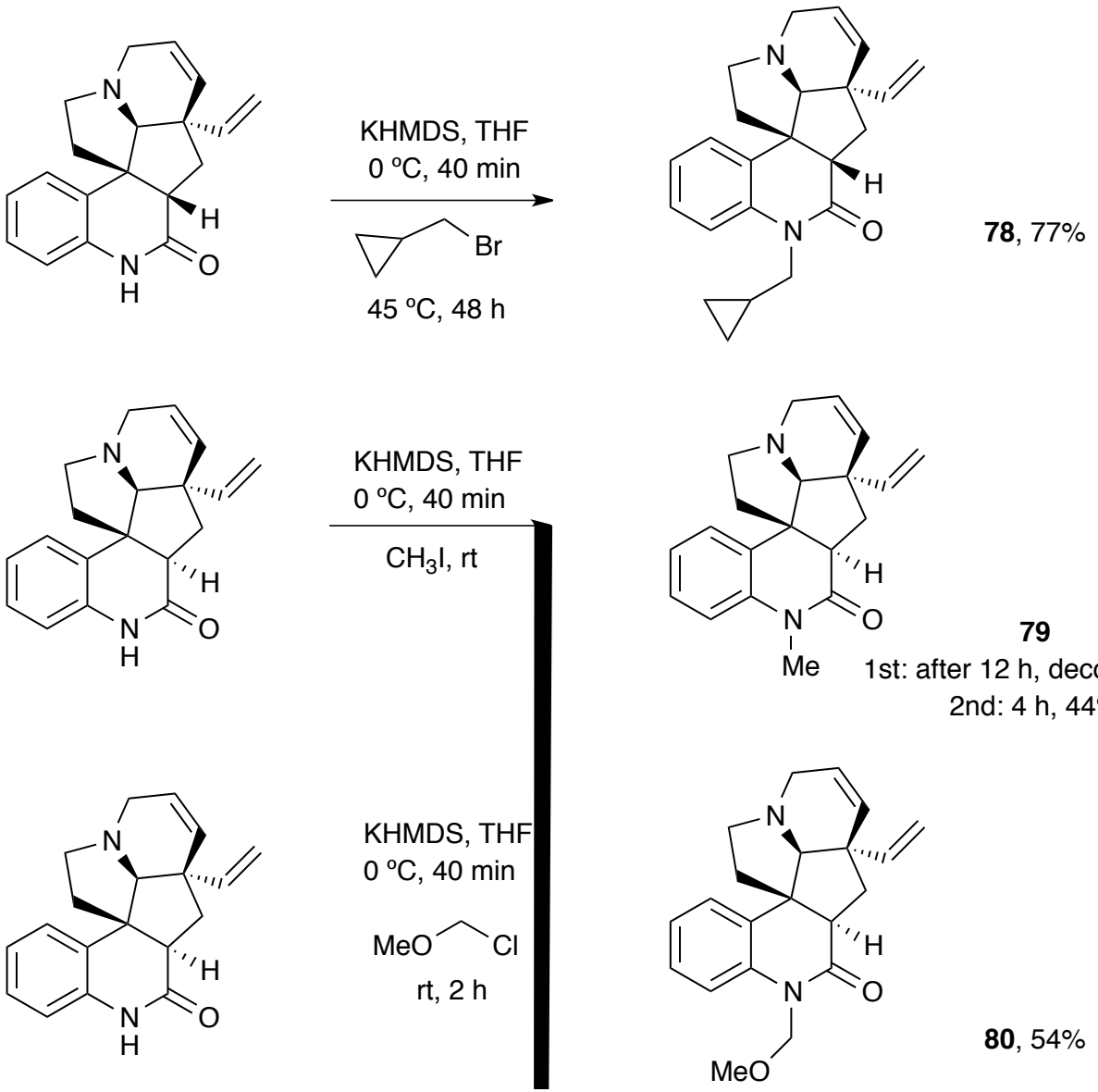


Meloscine
71–92%

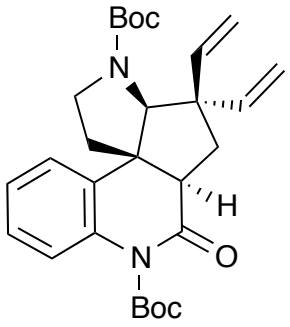


Hoveyda-Grubbs II
Generation Catalyst

Alkylation Reactions



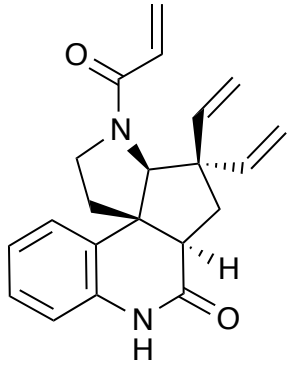
Preparation of Amide Derivatives



76

1. TFA, CH_2Cl_2
   rt, 3 h

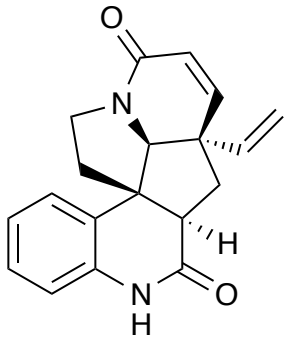
2. acryloyl chloride
   iPr$_2$NEt, CH_2Cl_2
   rt, 12 h



81, 26–53% (2 steps)

Hoveyda-
Grubbs II

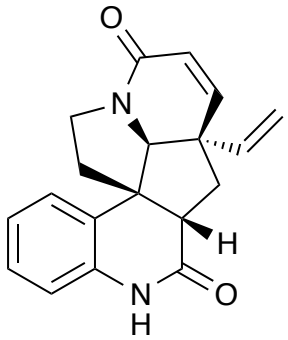
toluene
83 °C



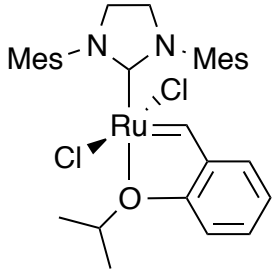
82, 78–85%

*t*BuOK

*t*BuOH, 83 °C

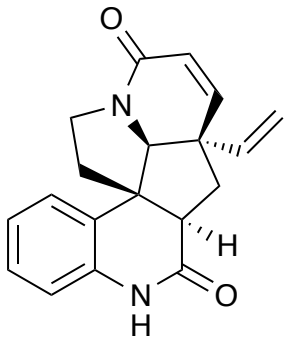


83



Hoveyda-Grubbs II
Generation Catalyst

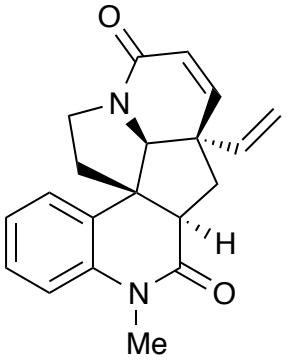
Amide and Sulfonamide Derivatives



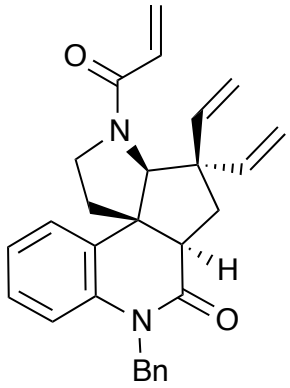
82

KHMDS, THF
0 °C, 40 min

CH_3I, rt



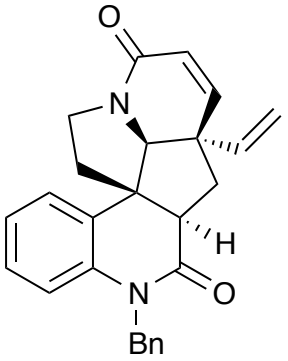
84, 61%



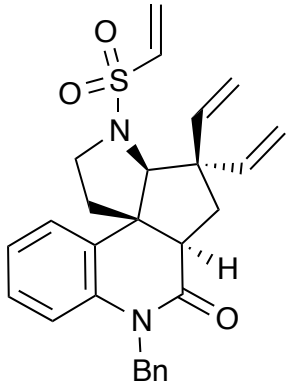
85

Hoveyda-
Grubbs II

toluene
83 °C



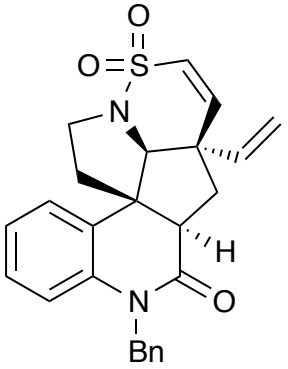
86, 44%



87

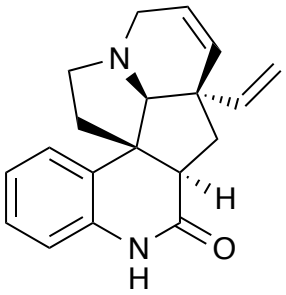
Hoveyda-
Grubbs II

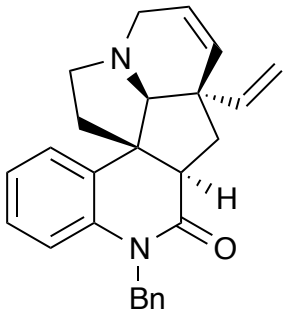
toluene
95 °C

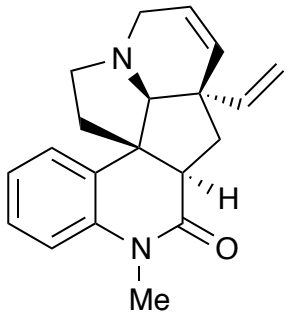


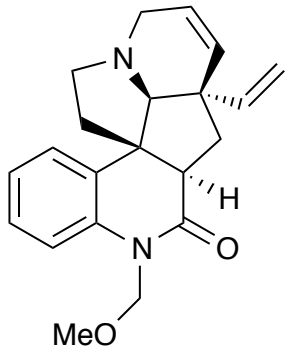
88, 77%

Conclusion


N
H
N
H
O


N
H
N
O
Bn


N
H
N
O
Me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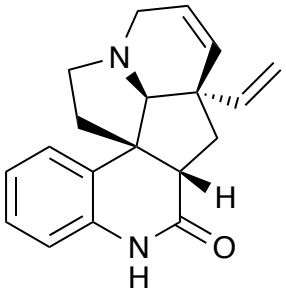
H
N
O
MeO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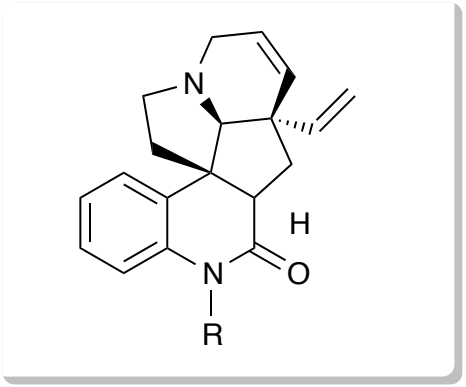
H
N
H
O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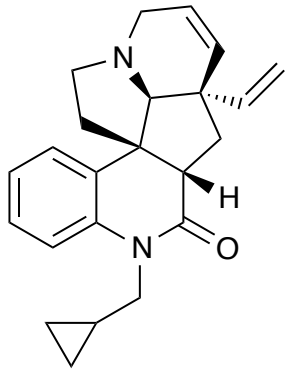
H
N
O
R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N
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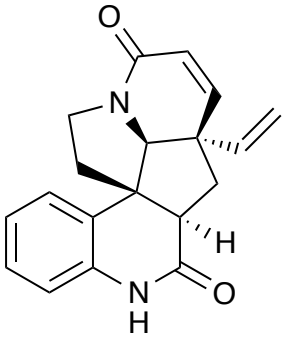
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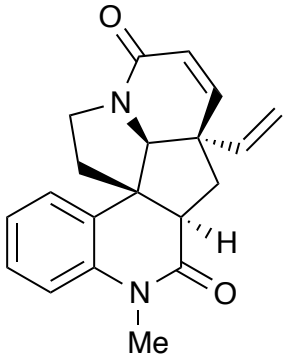
N
H
N
H
O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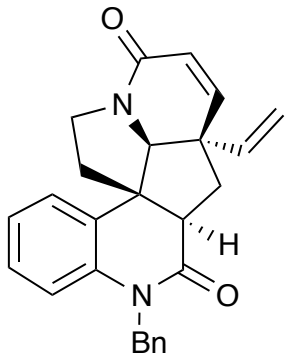
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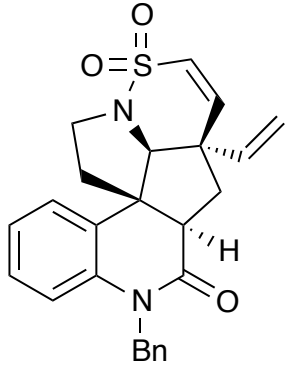
O
O=S
N
H
N
O
Bn

Acknowledgement

- Dr. Peter Wipf
- Dr. Dennis P Curran

  Hanmo Zhang, Ben Hay
- Dr. Matthew G LaPorte
- Mr. Pete Chambers (LC-MS)
- Wipf group members past & present