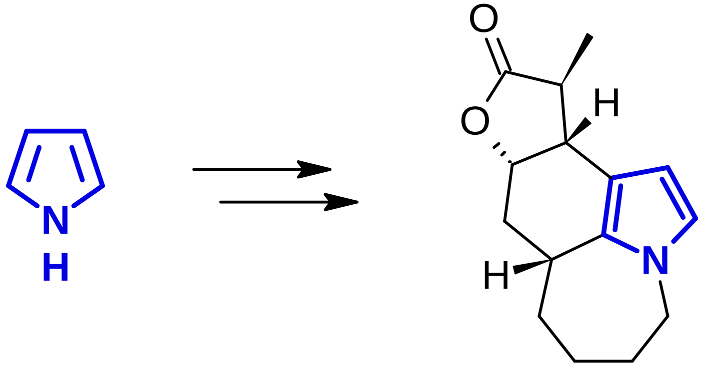
Igor Opsenica
06/18/2011

Synthesis of the Stenine Ring System from Pyrrole



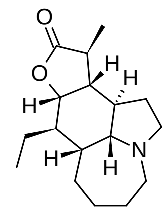
Bates, R. W.; Sridhar, S.
J. Org. Chem., **2011,** *76,* 5026–5035

The Stemonaceae family is still the only source of the *Stemona* alkaloids

The *Stemona* alkaloids are:

•structurally characterized by the presence
    pyrrolo[1,2-*a*]azepine core
    pyrido[1,2-*a*]azepine core

•currently comprises 139 alkaloids

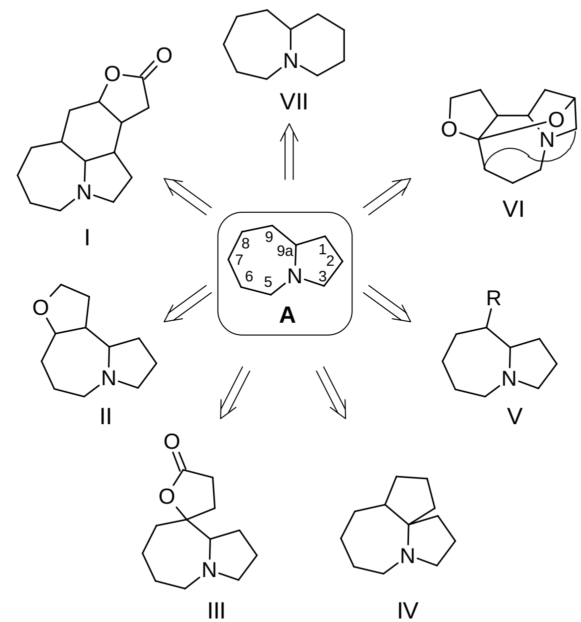


Stenine

Stemona sessilifolia

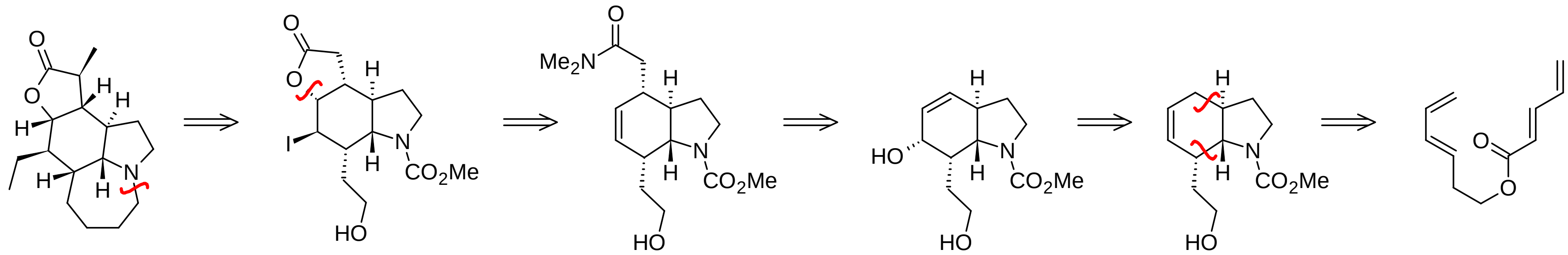
The *Stemona* alkaloids can be organize into eight groups:
•stenine (I),
•stemoamide (II),
•tuberostemospironine (III),
•stemonamine (IV),
•parvistemoline (V),
•stemofoline (VI) (all of which contain the pyrrolo[1,2-*a*]azepine core)

•stemocurtisine (VII) displaying the pyrido[1,2-*a*]azepine nucleus,
•miscellaneous group

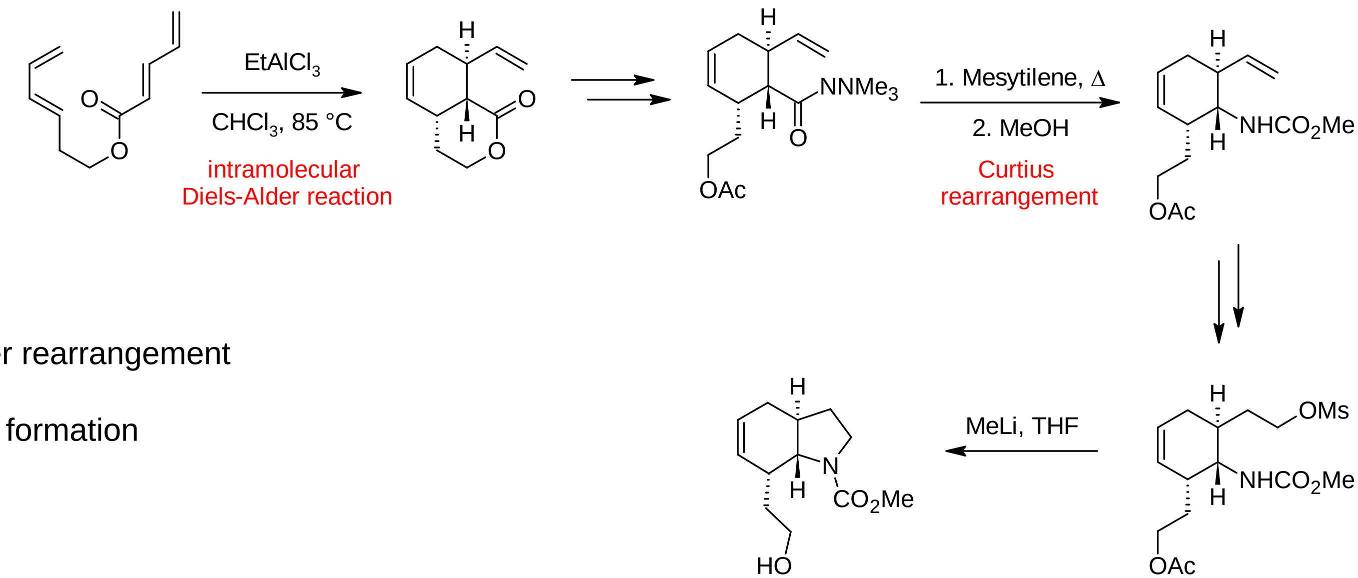


Nat. Prod. Rep., **2010,** *27,* 1908

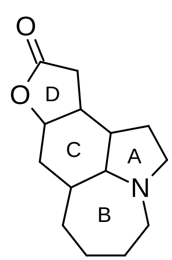
Chen, C.; Hart, D. J. *J. Org. Chem.*, **1990,** *55,* 6236



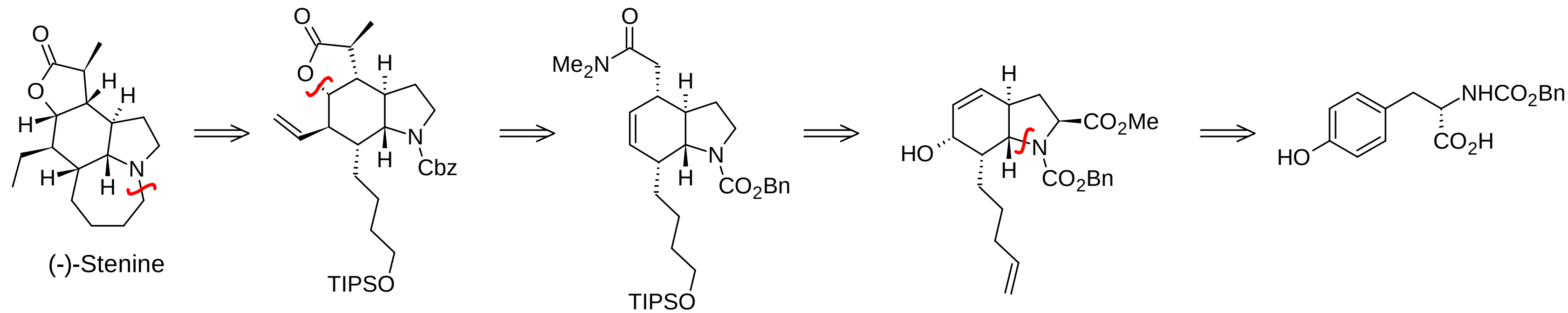
(±)-Stenine

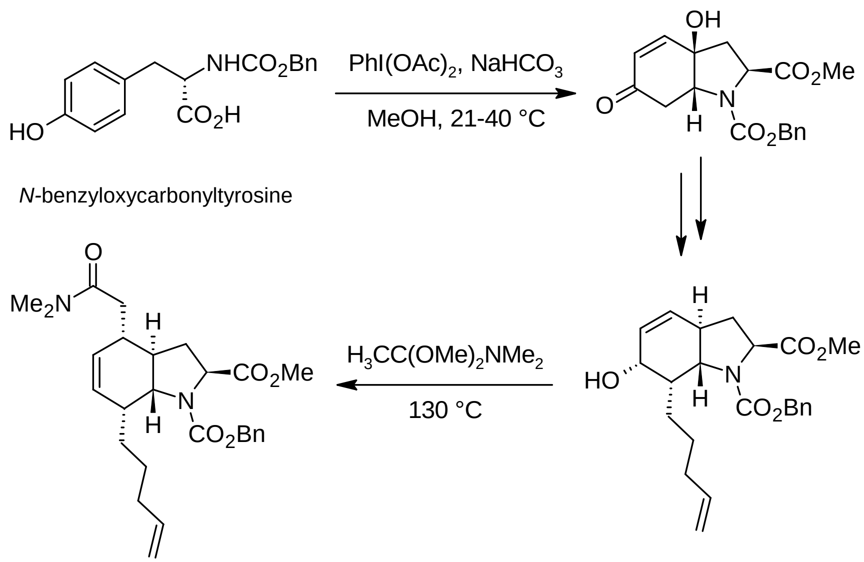


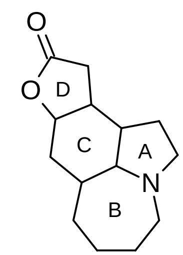
ring D: Claisen–Eschenmoser rearrangement
and iodolactonization
ring B: intramolecular lactam formation



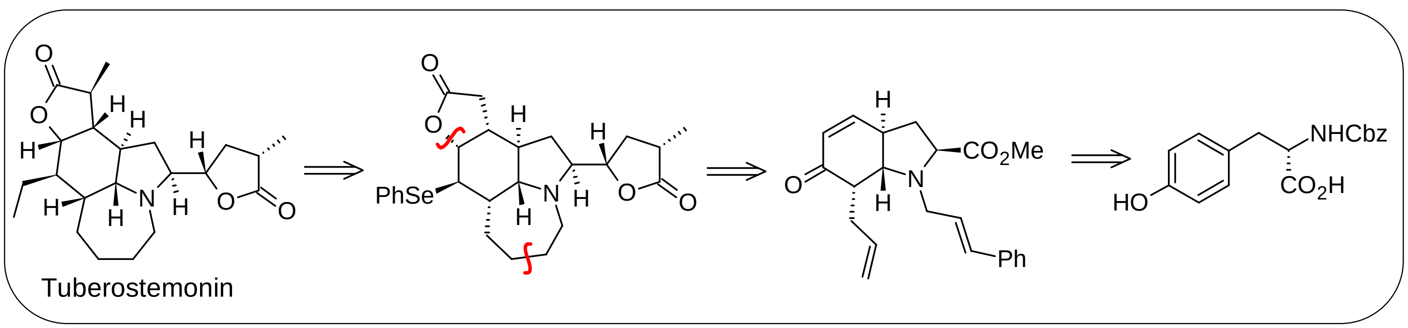
Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995,** *117,* 11106
Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005,** *127,* 225



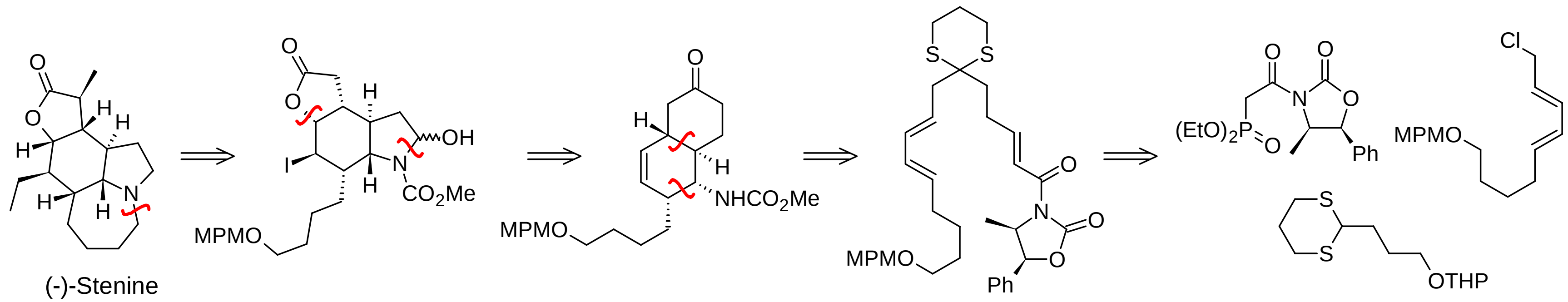


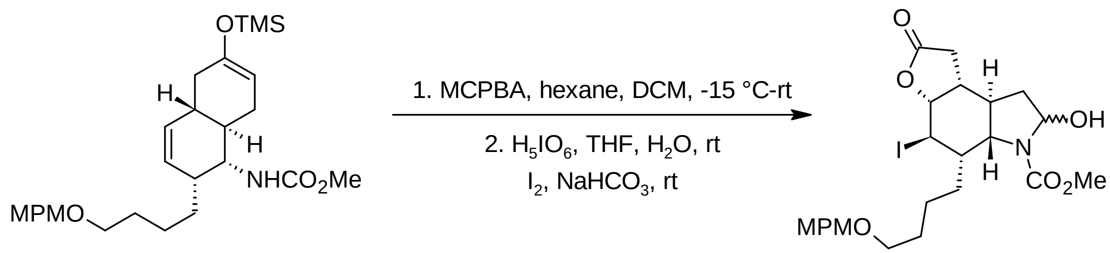


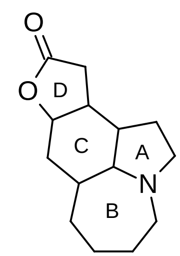
ring D: Claisen–Eschenmoser rearrangement and iodolactonization
ring B: intramolecular lactam formation



Morimoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem. Int. Ed. Engl.,* **1996,** *35,* 904

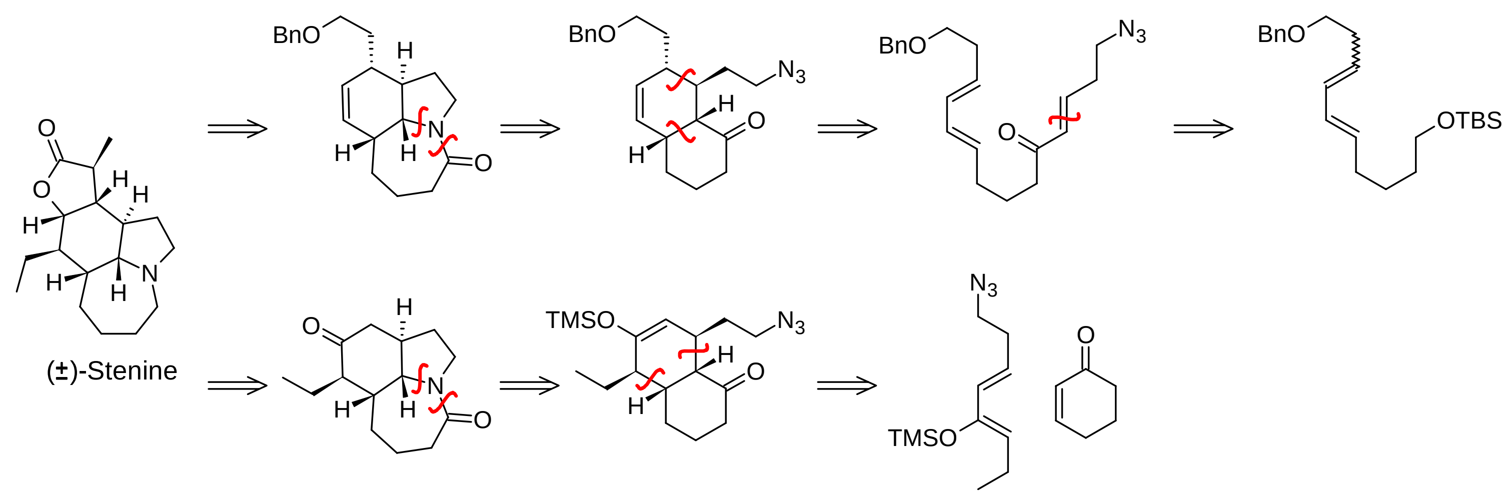


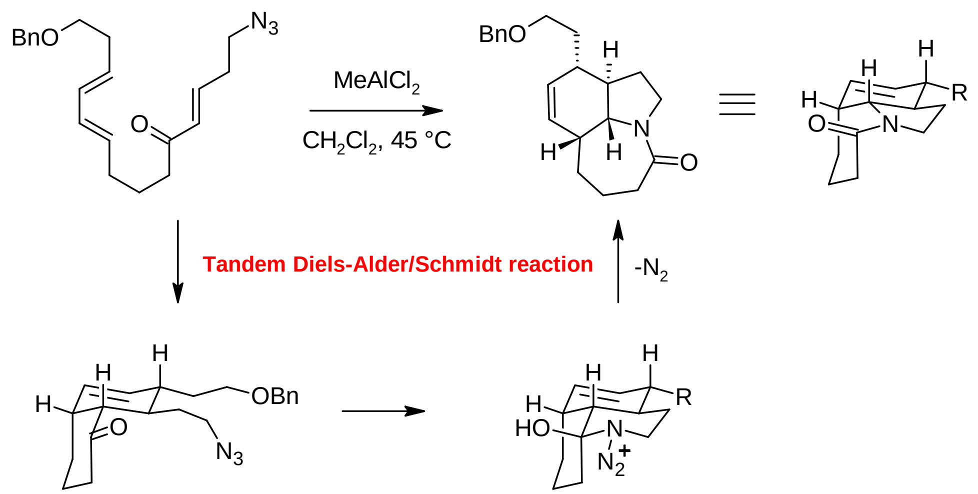


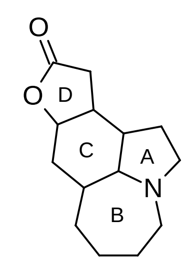


ring B: intramolecular nitrogen alkylation

Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aube, J. *J. Am. Chem. Soc.* **2008,** *130,* 6018

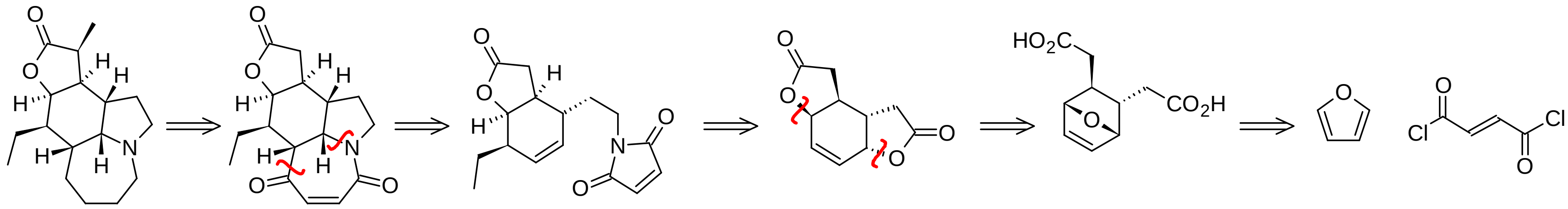






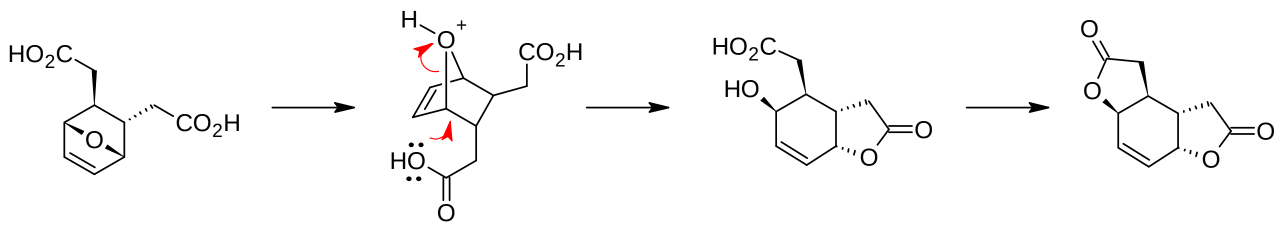
ring D: iodolactonization

Lainchbury, M. D.; Medley, M. I.; Taylor, P. M.; Hirst, P.; Dohle, W.; Booker-Milburn, K. I. *J. Org. Chem.,* **2008,** *73,* 6497

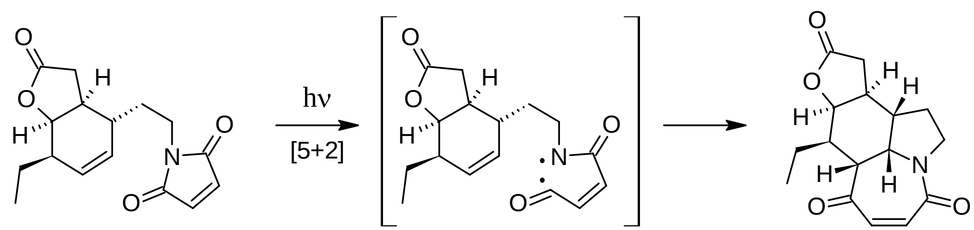


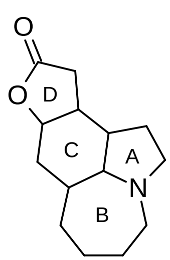
(±)-Neostenine

ring C / D:

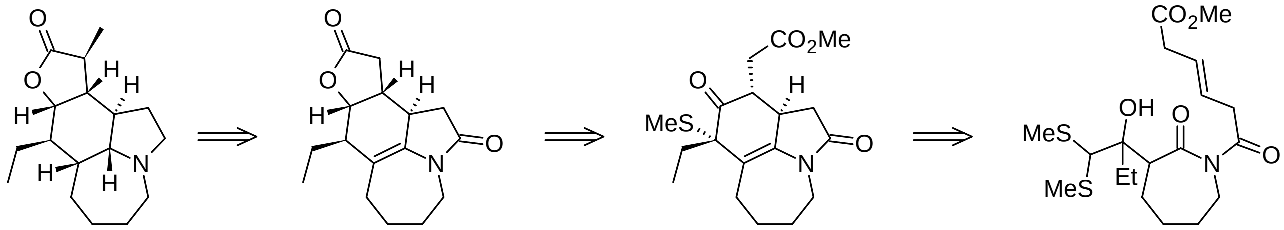


ring A / B:

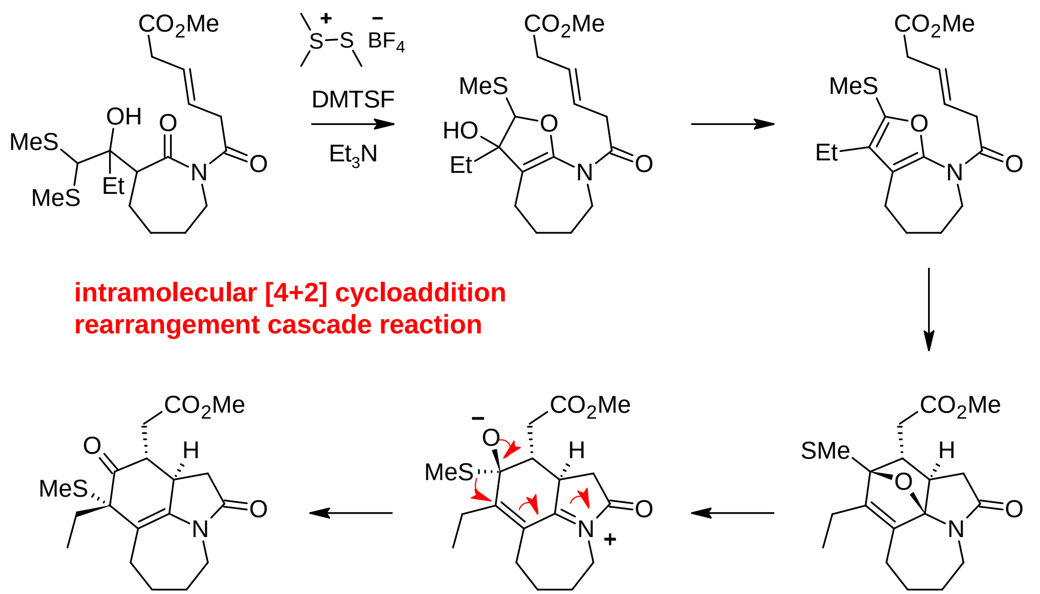


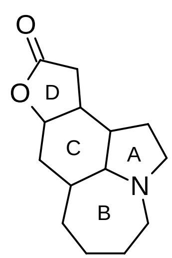


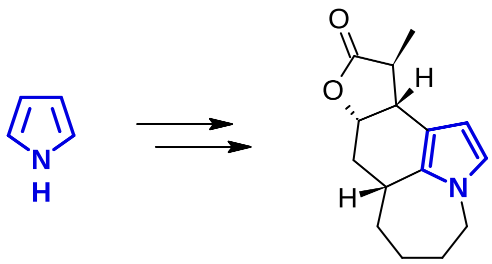
Padwa, A.; Ginn. J. D. *J. Org. Chem.* **2005,** *70,* 5197



(±)-Stenine







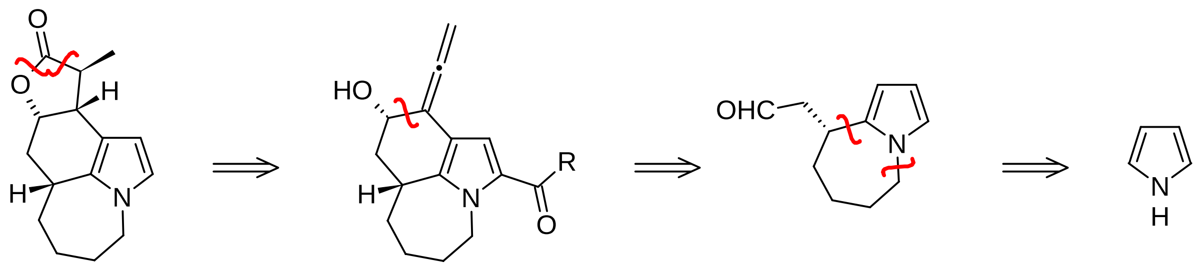
Bates, R. W.; Sridhar, S.
J. Org. Chem., **2011,** *76,* 5026–5035

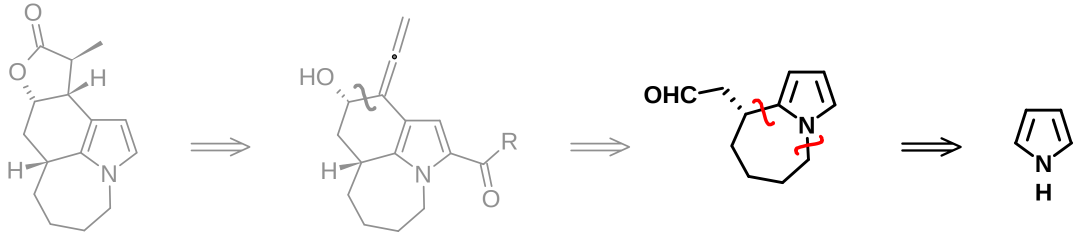
The *Stemona* alkaloids are attractive synthetic targets
due to the diversity of structures found in this family of alkaloids

Recently, it has been reported that neostenine, a stereoisomer of stenine,
has antitussive activity comparable to that of codeine

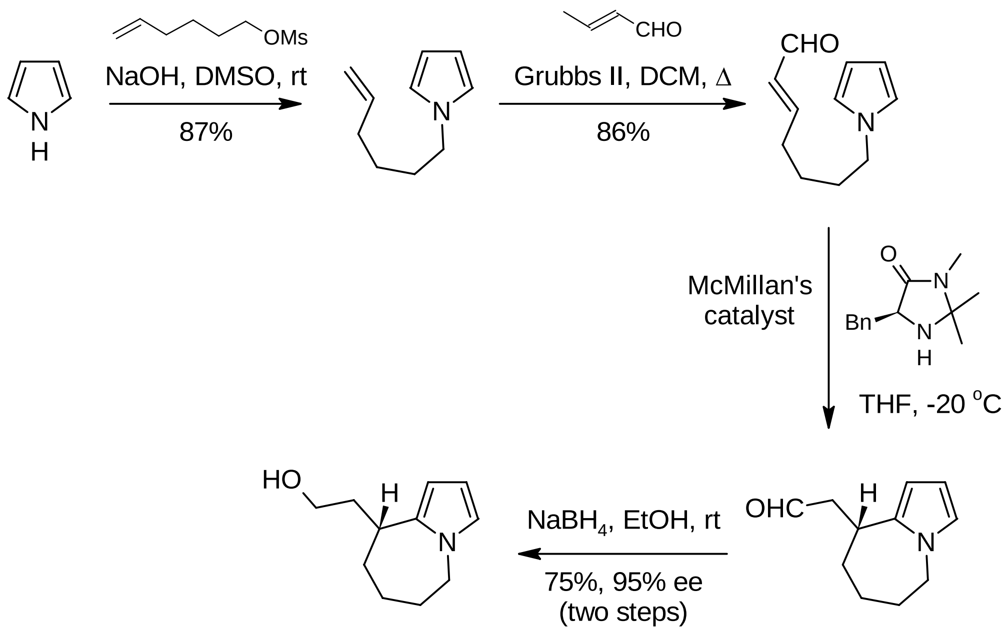
Using pyrroles in natural product synthesis is challenging:
•highly electron-rich nature of the pyrrole ring promote certain productive reactions,
but it can also cause some problems

Additional synthetic strategies has been used to
construct the pyrrole moiety in pyrrole-containing natural products

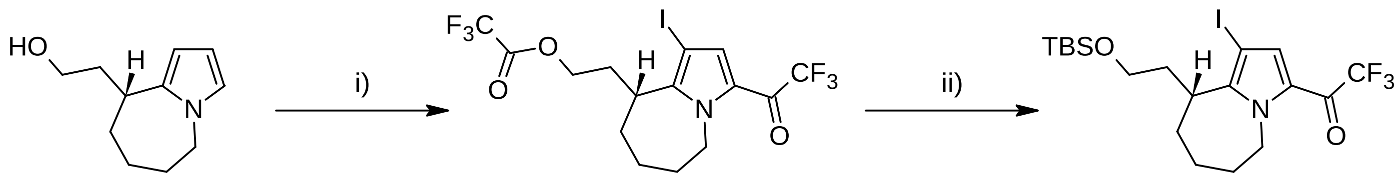




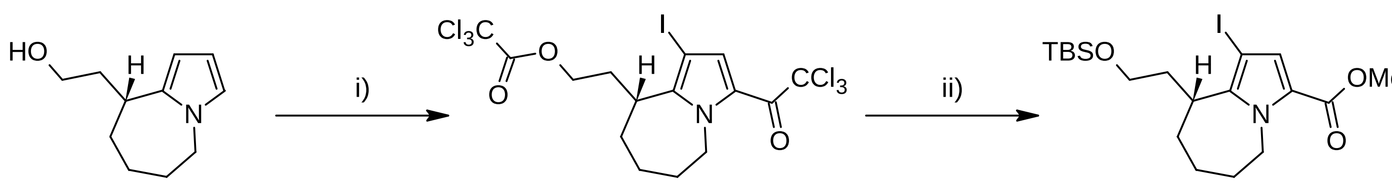
HO
R
OHC
N
H



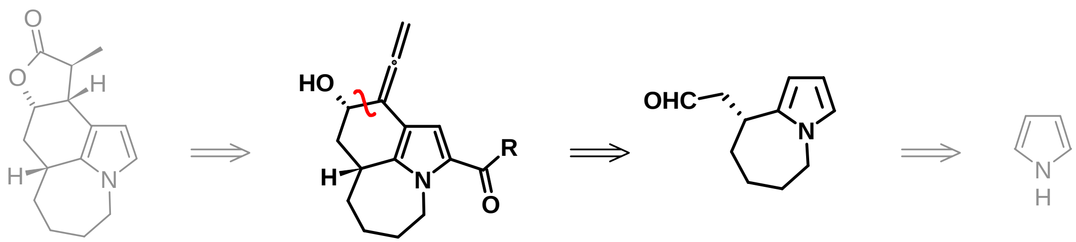
OMs
NaOH, DMSO, rt
87%
CHO
Grubbs II, DCM, Δ
86%
CHO
McMillan's catalyst
Bn
THF, -20 °C
NaBH4, EtOH, rt
75%, 95% ee
(two steps)
OHC
HO

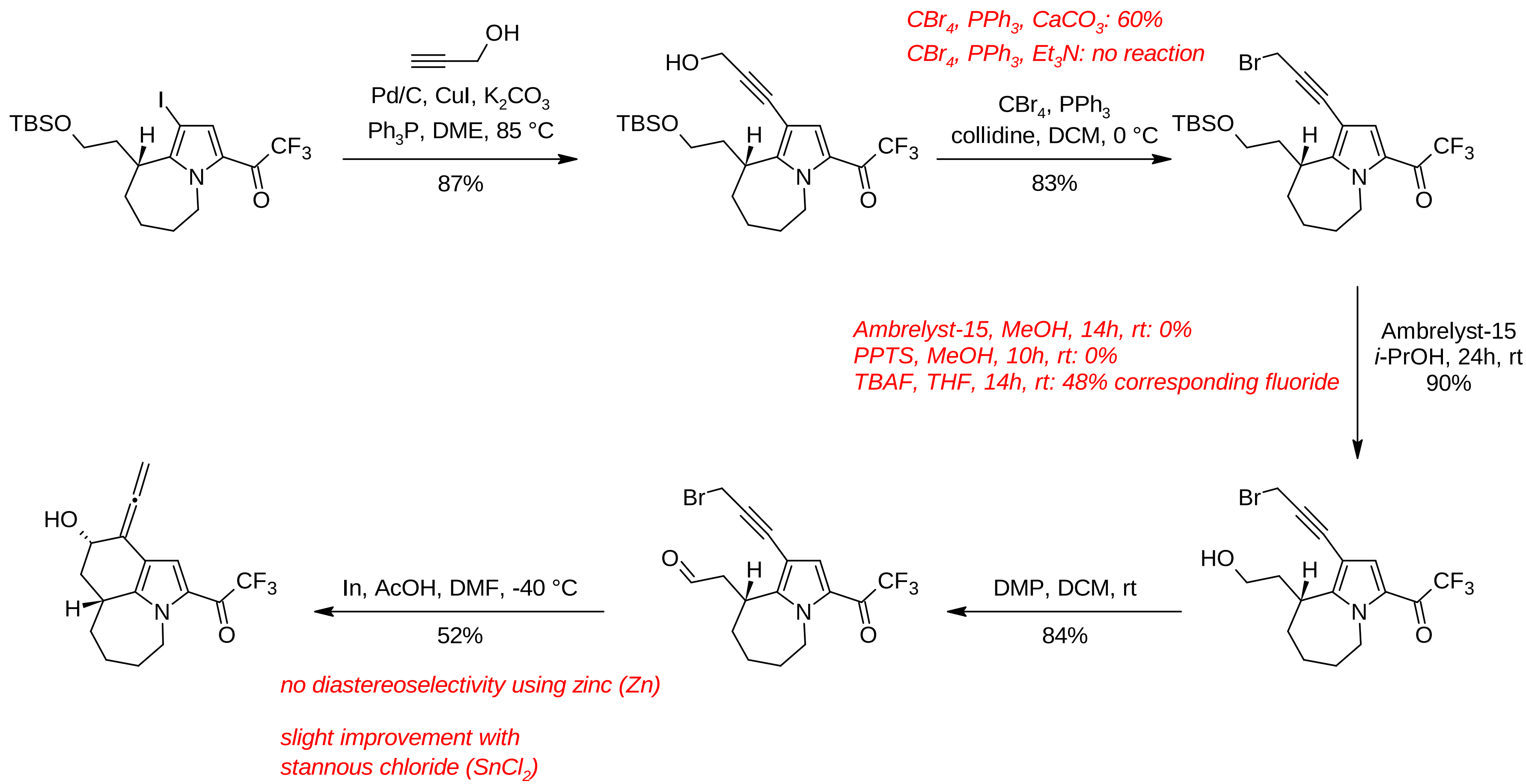


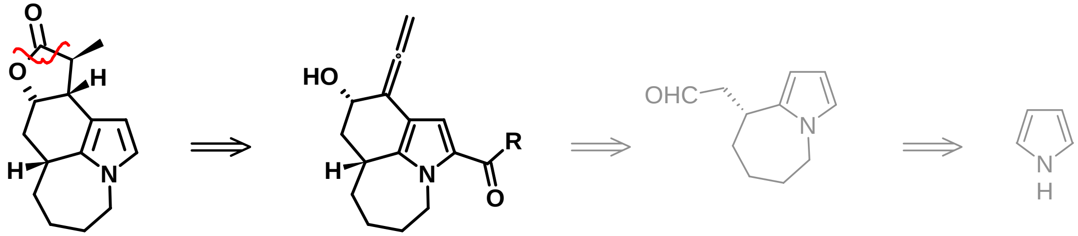
i) 1) $(CF_3CO)_2O$, Et_2O, rt, 83%; 2) ICl, DCM, rt, 88%
ii) 1) PVP, MeOH, rt, quant.; 2) TBSCl, imidazole, DCM, rt, quant.

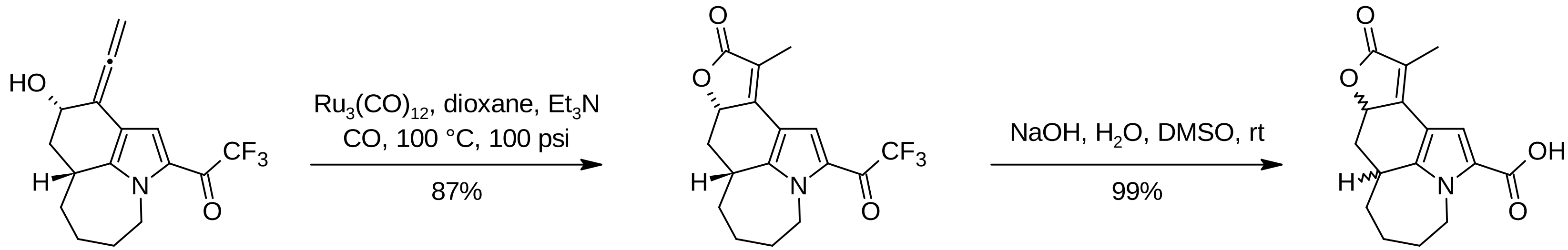


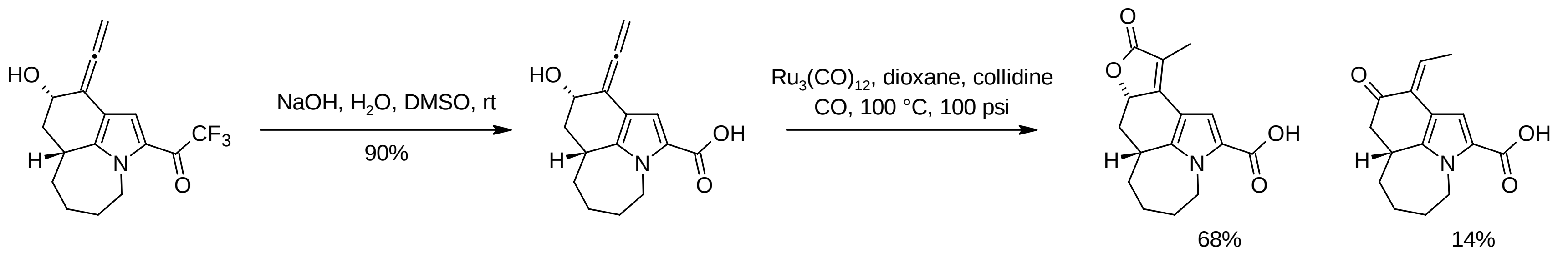
i) 1) CCl_3COCl, Et_2O, rt, 95%; 2) ICl, DCM, rt, 90%
ii) 1) NaOMe, MeOH, rt, 90%.; 2) TBSCl, imidazole, DCM, rt, 80%

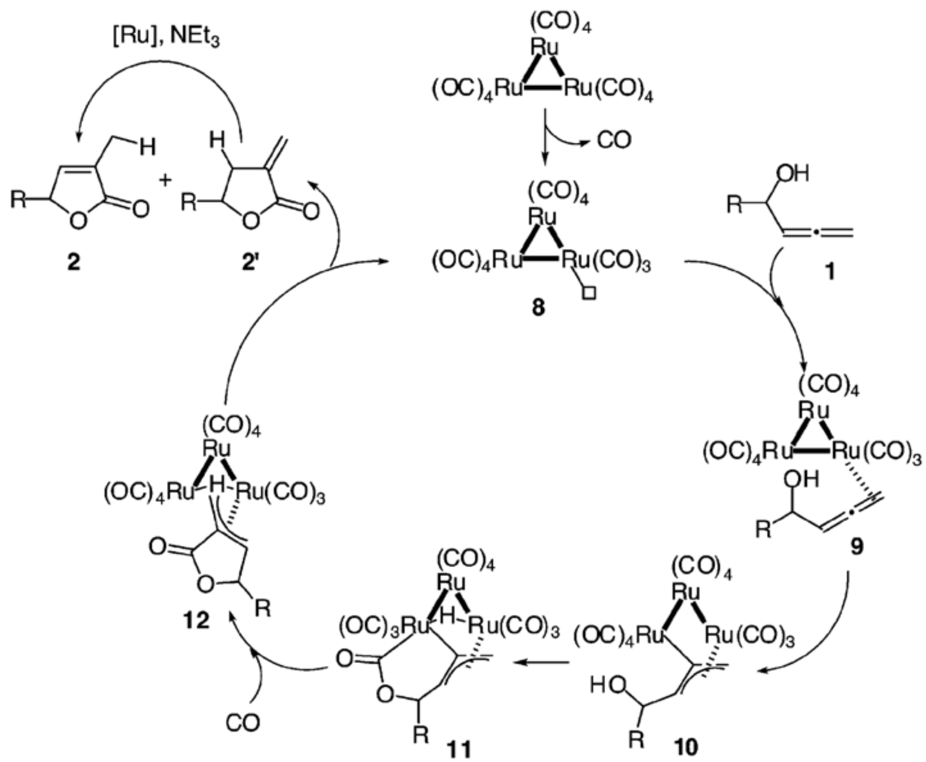

HO
R
H
O
OHC
N
H


TBSO
I
H
N
CF3
O
OH
Pd/C, CuI, K2CO3
Ph3P, DME, 85 °C
87%
HO
CBr4, PPh3, CaCO3: 60%
CBr4, PPh3, Et3N: no reaction
CBr4, PPh3
collidine, DCM, 0 °C
83%
Br
Ambrelyst-15, MeOH, 14h, rt: 0%
PPTS, MeOH, 10h, rt: 0%
TBAF, THF, 14h, rt: 48% corresponding fluoride
Ambrelyst-15
i-PrOH, 24h, rt
90%
DMP, DCM, rt
84%
In, AcOH, DMF, -40 °C
52%
no diastereoselectivity using zinc (Zn)
slight improvement with
stannous chloride (SnCl2)


O
O
H
H
N
HO
H
N
R
O
OHC
N
N
H


HO
H
N
CF3
O
Ru3(CO)12, dioxane, Et3N
CO, 100 °C, 100 psi
87%
O
O
H
N
CF3
O
NaOH, H2O, DMSO, rt
99%
O
O
H
N
OH
O



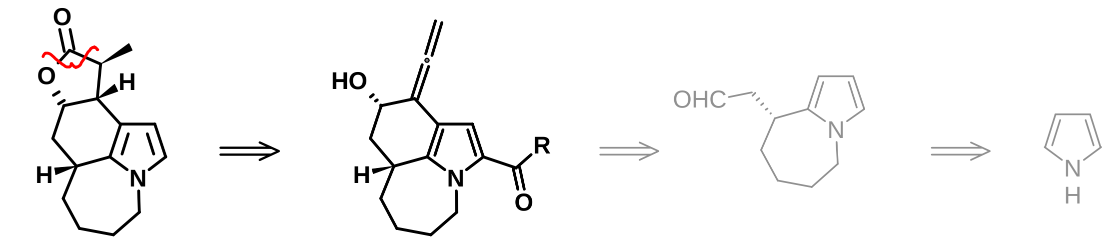


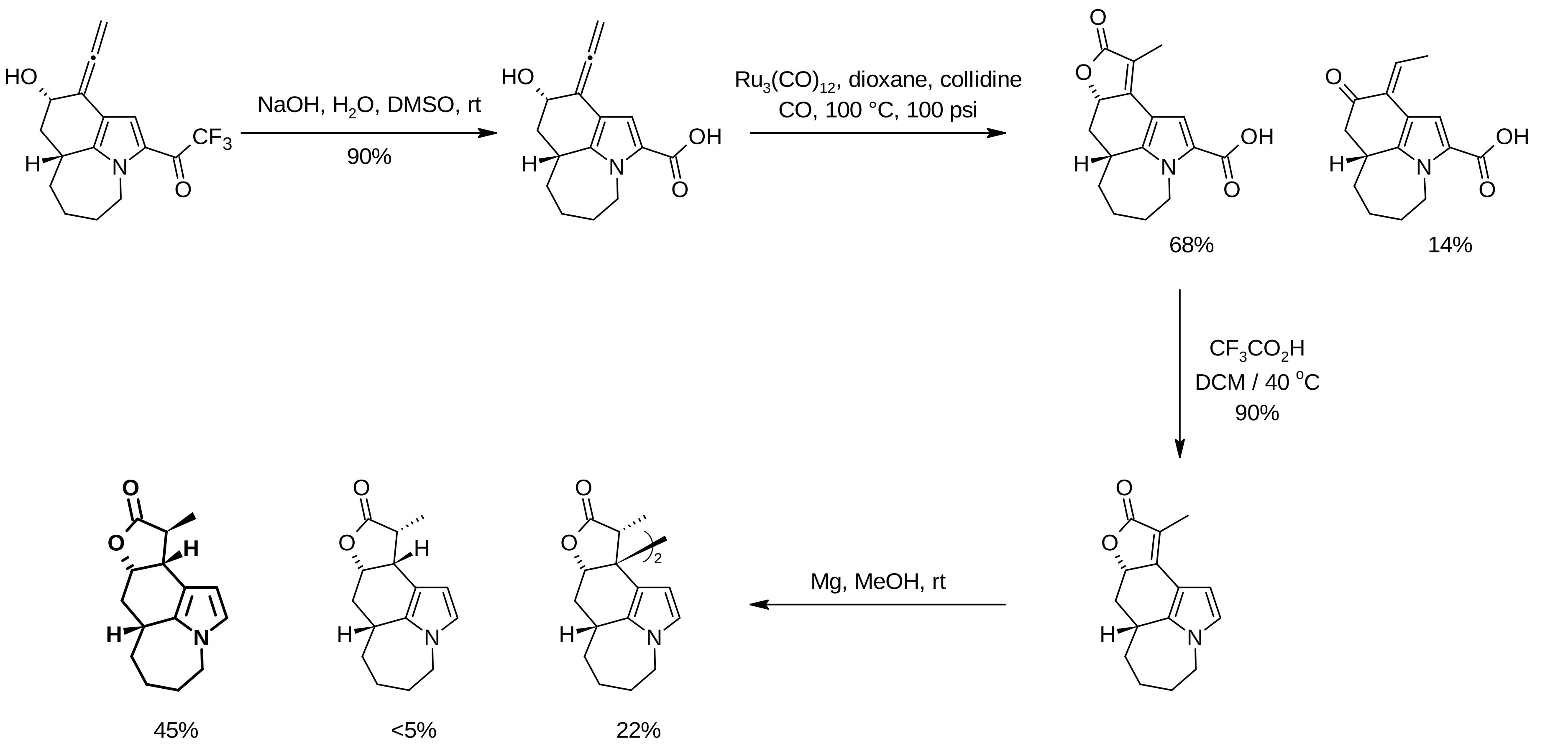
Possible Mechanism of
Ruthenium-Catalyzed Cyclocarbonylation
J. Org. Chem. **2003,** *68,* 8571-8576

Cyclocarbonylation of Allenol - $Ru_3(CO)_{12}$, CO

reagent and solvent	catalyst loading / mol%	yield of butenolid (%)	yield of enone (%)
dioxane, Et_3N (6 eq)	4	40	30[a]
Et_3N (neat)	4	20	40[b]
2,4,6-collidine (neat)	4	50	5[c]
dioxane, collidine (6 eq)	4	68	14[c]

[a] A ca. 2:1 mixture of *E*/*Z* isomers. [b] A ca. 10:1 mixture.
[c] One isomer.


OHC
R
N
H


HO
CF3
NaOH, H2O, DMSO, rt
90%
OH
Ru3(CO)12, dioxane, collidine
CO, 100 °C, 100 psi
68%
14%
CF3CO2H
DCM / 40 °C
90%
Mg, MeOH, rt
45%
<5%
22%

CONCLUSION

Additional contribution to the synthesis of the stemona alkaloids using an new synthetic approach

The high electron density of the pyrrole ring can complicate some reactions but can be controlled by using the trifluoroacetyl group, that can easily and rapidly be removed