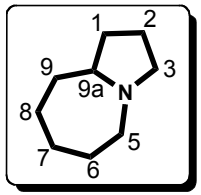
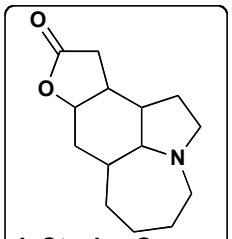
Stemona Alkaloids

Tom Maimone

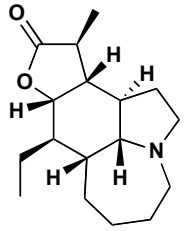
I. Introduction



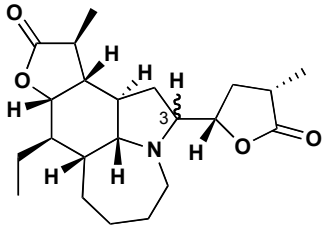
- **The *Stemonaceae* plant family, which comprises over 30 species, produces a large class of structurally diverse alkaloids featuring a conserved pyrrolo [1,2-a] azepine = perhydroazaazulene = 4-azazaulene nucleus**
- **Their roots have been used for centuries in traditional chinese medicince for a variety of purposes including (but not limited to): treatment of bronchitis, tuberculosis, pertussis, as well as anti-parasitic agents**
- **Over 80 members have been discovered and many more are likely to be isolated (restriction is limited to only 8 species, mostly from the *Stemona* genus)**



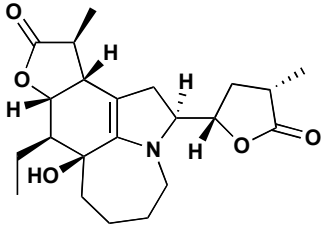
I. *Stenine Group*



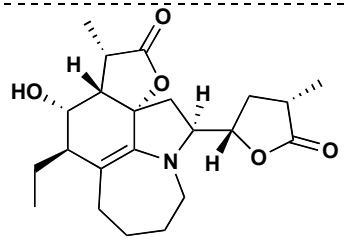
stenine



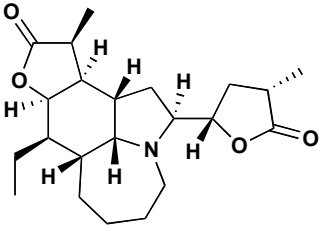
tuberostemonine (H_3 = α)
tuberostemonine A (H_3 = β)



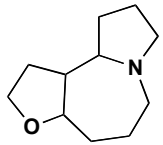
tuberostemonol



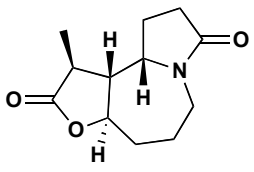
oxotuberostemonine



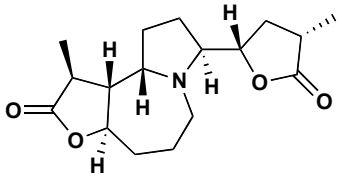
neotuberostemonine



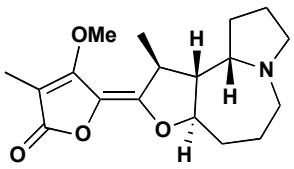
II. *Stemoamide Group*



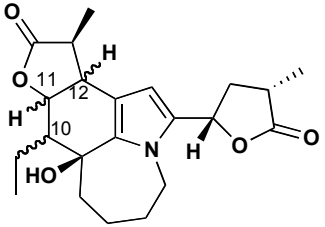
stemoamide



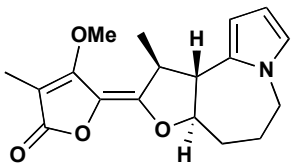
stemonine



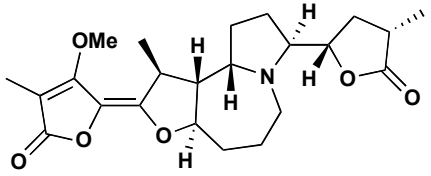
neostemonine



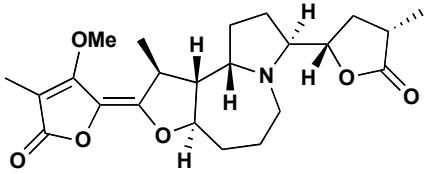
didehydrotuberostemonine (H_{11} = β, H_{12} = β, Et = β)
bisdehydroneotuberostemonine (H_{11} = α, H_{12} = α)



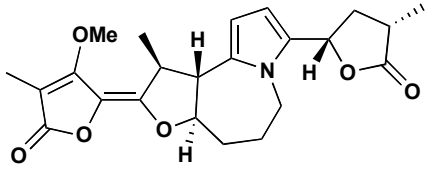
bisdehydroneostemonine



protostemonine



protostemonine



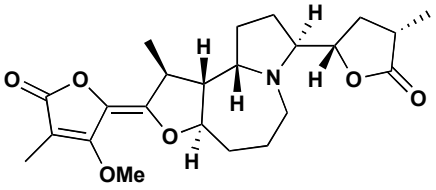
didehydroprotostemonin

For excellent reviews see (and references therein): Pilli *et al*. *Nat. Prod. Rep.,* **2000**, *17,* 117-127. Seger *et al. Chemistry & Biodiversity*. **2004**. *1, 265-279.*

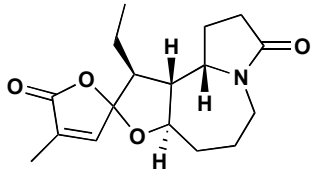
Stemona Alkaloids

Tom Maimone

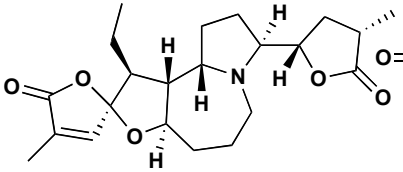
II. *Stemoamide Group (Con't)*



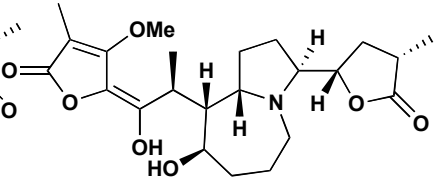
isoprotostemonine



tuberstemoamide

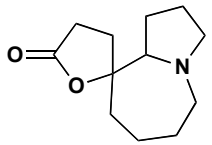


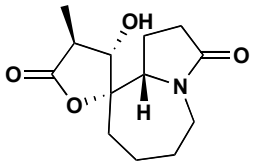
stemoninine



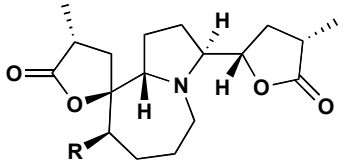
stemodiol

III. Tuberostemospironine Group

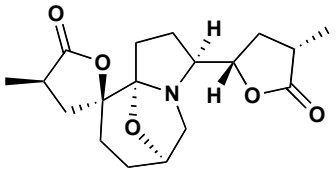




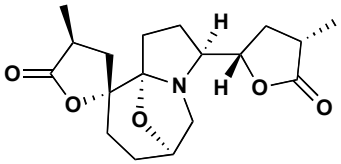
tuberstemospironine



croomine (R = H)
stemospironine (R = OMe)

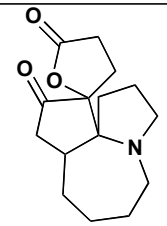


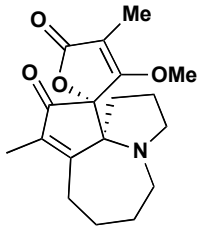
stemotinine



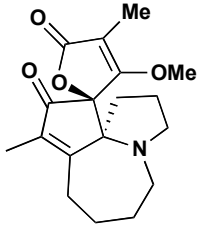
isostemotinine

IV. Stemonamine (maistemonine) Group

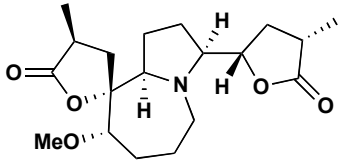




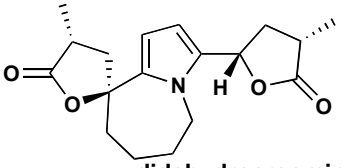
stemonamine



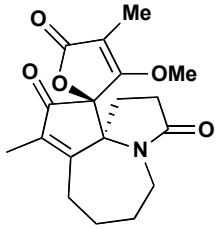
isostemonamine



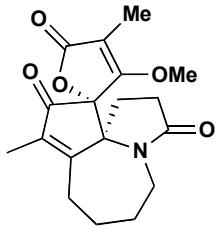
stemonidine



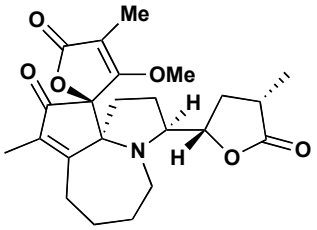
didehydrocroomine



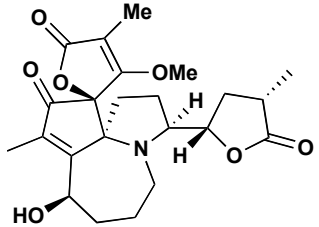
isostemonamide



stemonamide



maistemonine

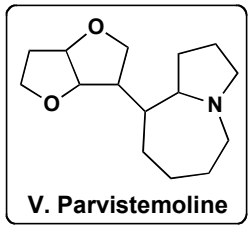


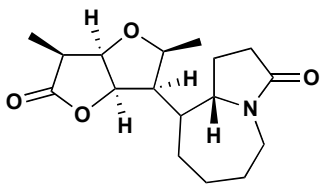
oxymaistemonine

Pilli *et al*. *Nat. Prod. Rep.,* **2000**, *17,* 117-127.

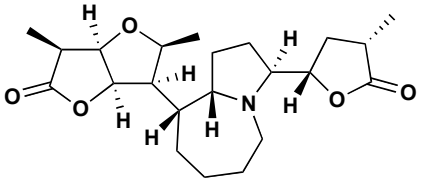
Stemona Alkaloids

Tom Maimone

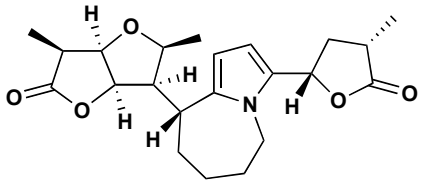




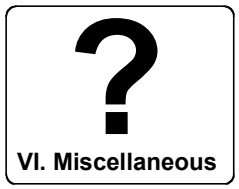
parvistemoline

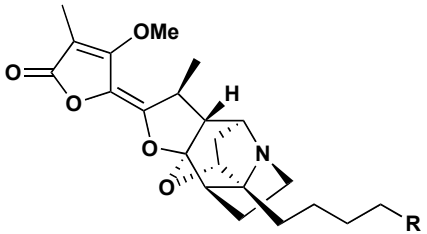


parvistemonine

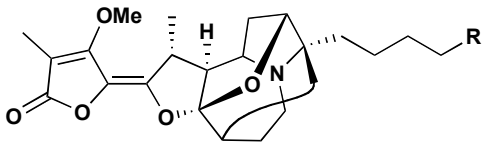


didehydroparvistemonine

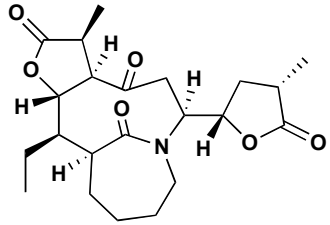




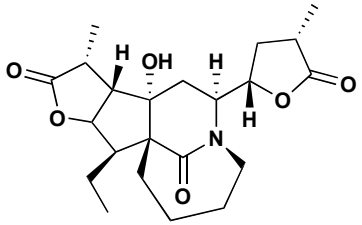
stemofoline (R = H)
oxystemofoline (R = OH)
methoxystemofoline (R = OMe



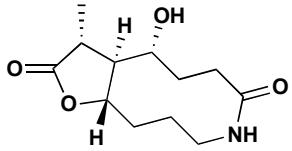
parvistemoninine (R = H)
parvistemoninol (R = OH)



tuberostemonone



tuberostemoninol



parvistemoamide

Pilli *et al*. *Nat. Prod. Rep.,* **2000**, *17,* 117-127.

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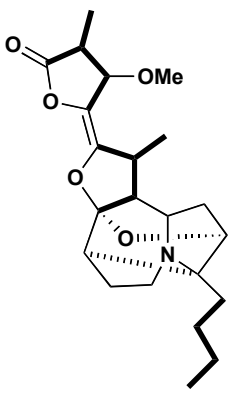
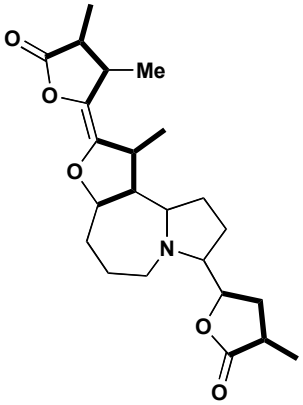
II. Biosynthetic Considerations

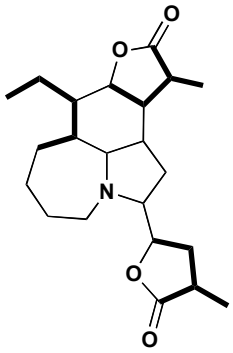
Consider the following carbocyclic skeletons where the C_5 units of presumed terpene origin are drawn in bold:



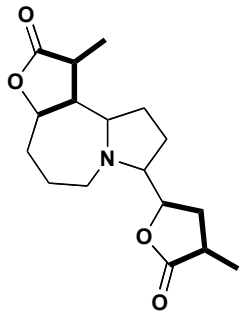
Stemofoline



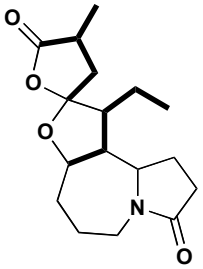
protostemonine



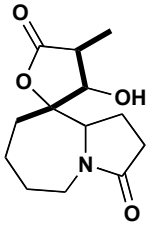
tuberostemonine



stemonine

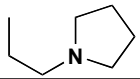


tuberstemonamide

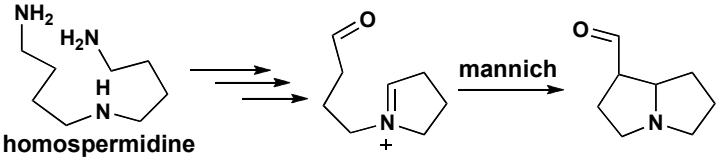


tuberostemospironine

This leaves the following fragment unaccounted for:

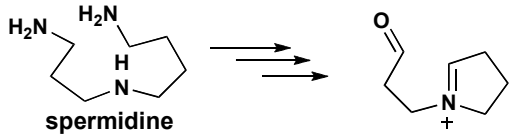


Recall pyrrolizidine biosynthesis:



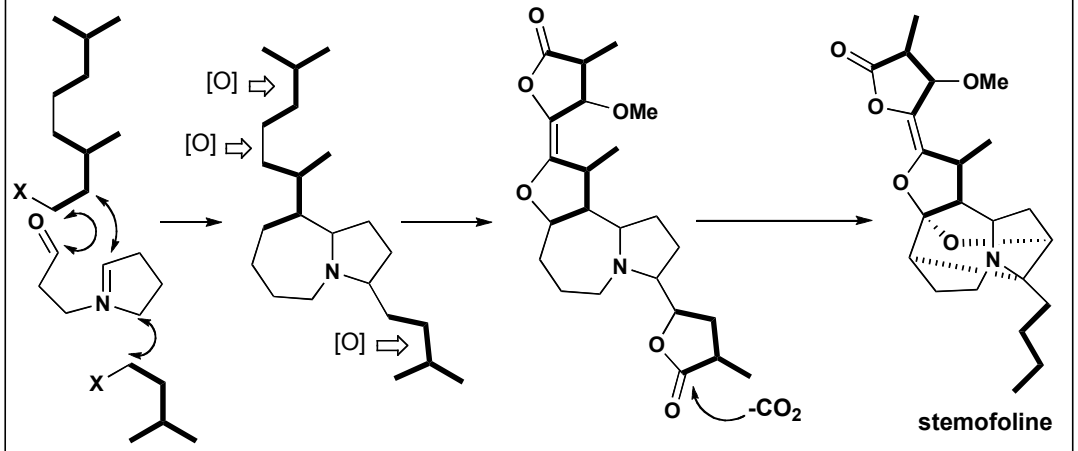
homospermidine

An analagous pathway could produce the stemona alkaloids



spermidine

Thus the following biosynthetic picture emerges:

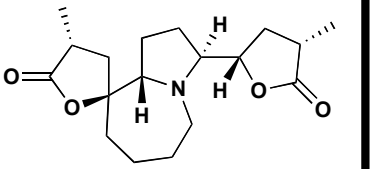


stemofoline

Stemona Alkaloids

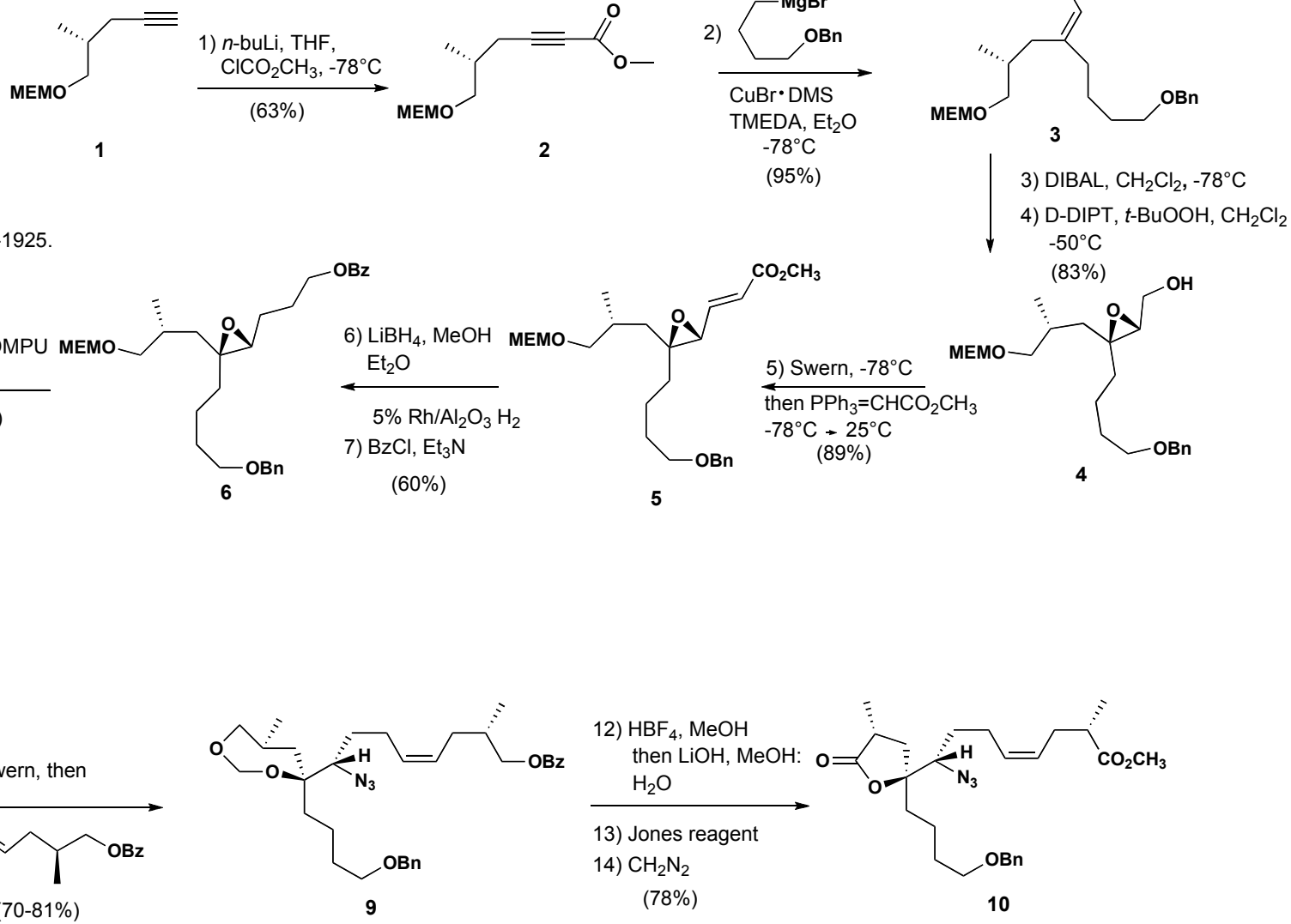
Tom Maimone

III. Synthesis



Croomine
(D.R. Williams *et al*, 1989)

J. Am. Chem. Soc. **1989**, *111*, 1923 -1925.



Stemona Alkaloids

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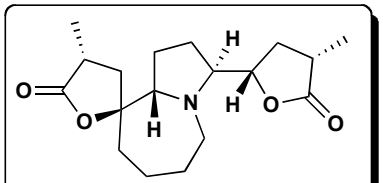
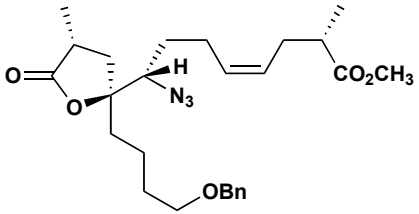


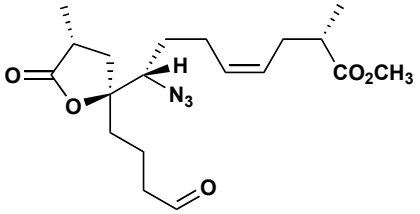
Croomine
(D.R. Williams *et al*, 1989)



10

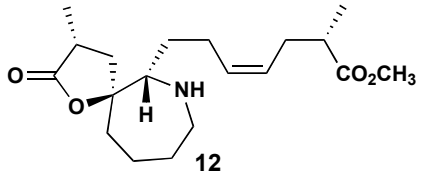
15) BCl_3, CH_2Cl_2, -78°C

16) swern
(71%)



11

17) PPh_3, 25°C
then $NaBH_4$, MeOH
(90%)

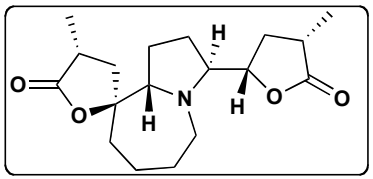


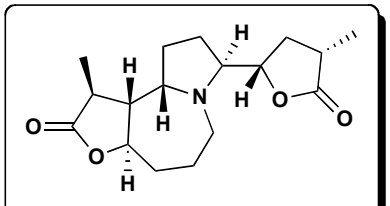
12

18) I_2, Et_2O, CH_2Cl_2
25°C

(25°C)

mechanism ?

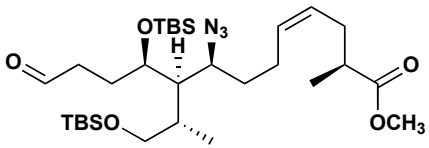




Stemonine
(D.R. Williams *et al*, 2003)

Org. Lett. **2003**, *5*, 3361-3364

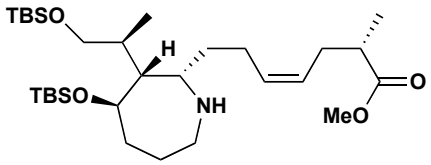
A Similar iodination cascade was used here as well



prepared in many steps

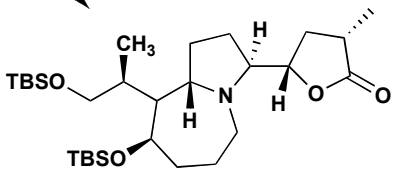
1) $EtPPh_2$, PhH,
18h, 25°C, then
$NaBH_4$, MeOH

(70%)



13

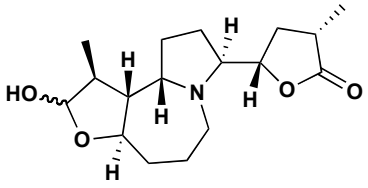
2) I_2, Et_2O:CH_2Cl_2, 48 h, 25°C
42%



14

4) TBAF
5) DMP

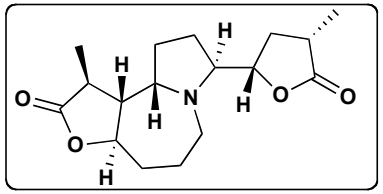
(69%)



15

6) Jones Reagent

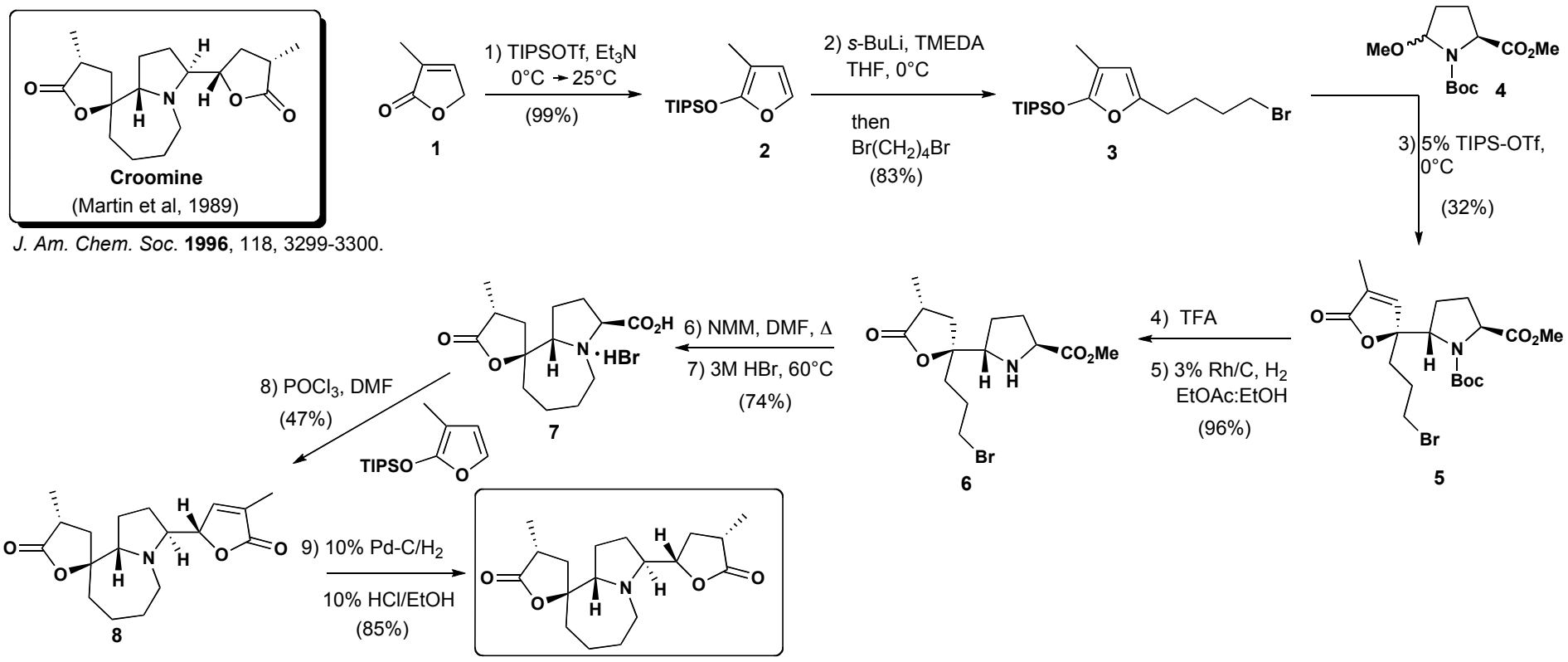
(68%)

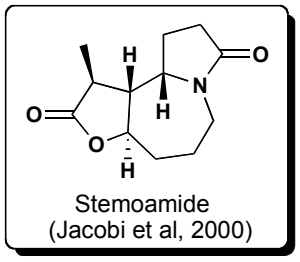


Stemona Alkaloids

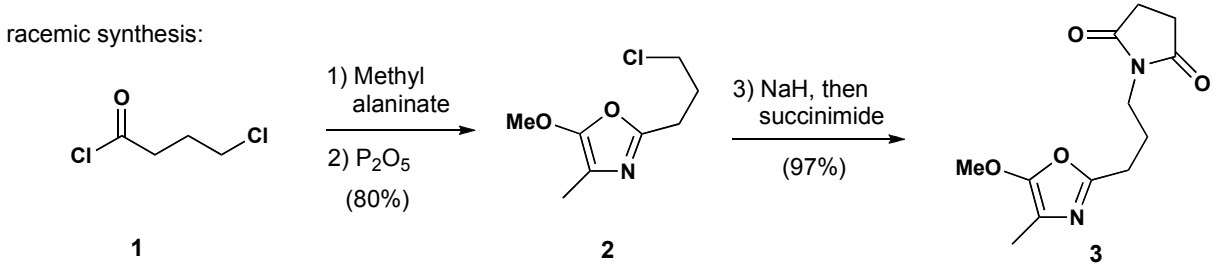
Tom Maimone

J. Am. Chem. Soc. **1996**, 118, 3299-3300.





J. Am. Chem. Soc. **2000**, 122, 4295-4303



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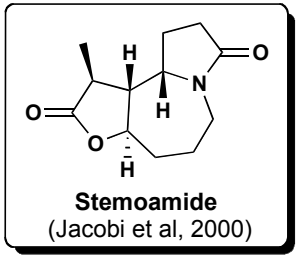
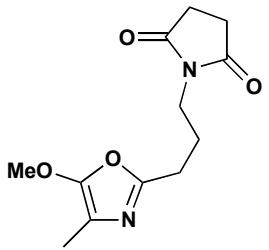
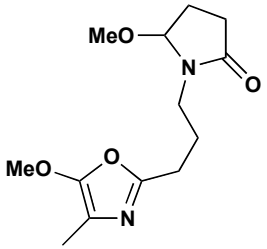
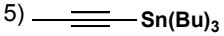




4) $NaBH_4$, MeOH, H^+

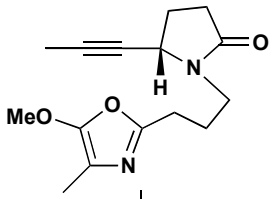
(72%)



5) 

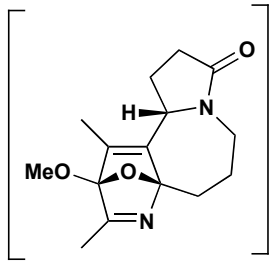
$BF_3 \cdot OEt_2$

(92%)

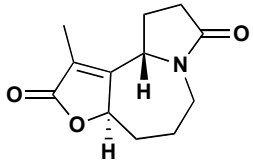


6) Diethylbenzene reflux

(55%)

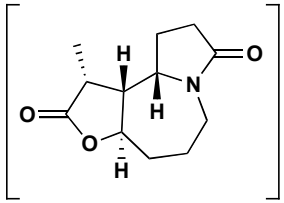


H^+

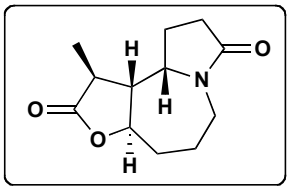


$NaBH_4$

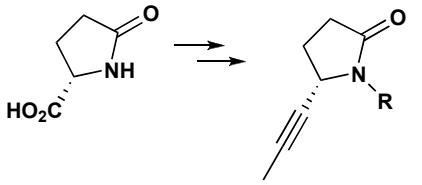
$NiCl_2$



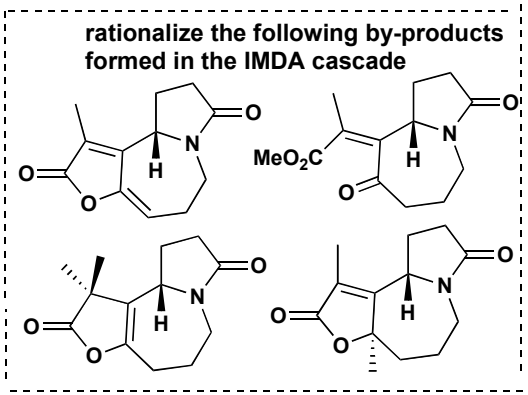
73%



an enantioselective route was also developed using L-pyroglutamic acid



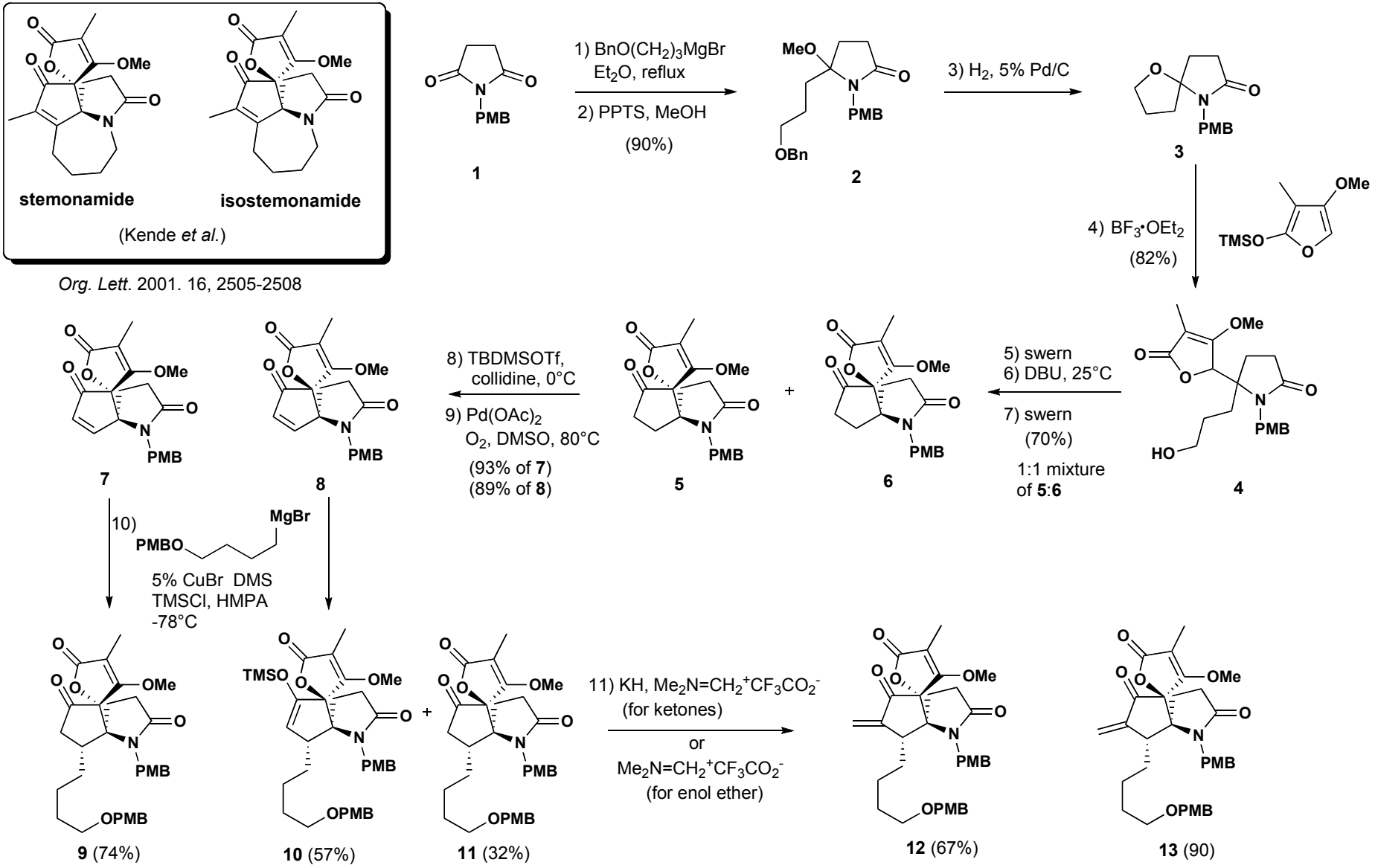
rationalize the following by-products formed in the IMDA cascade



Stemona Alkaloids

Tom Maimone

Org. Lett. 2001. 16, 2505-2508



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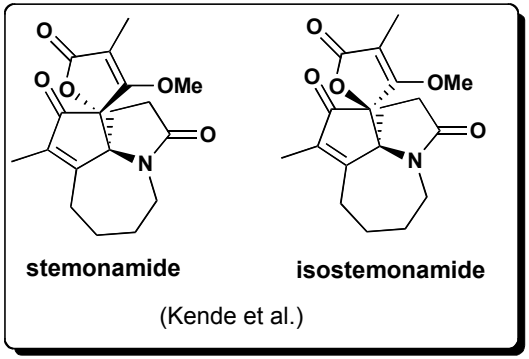

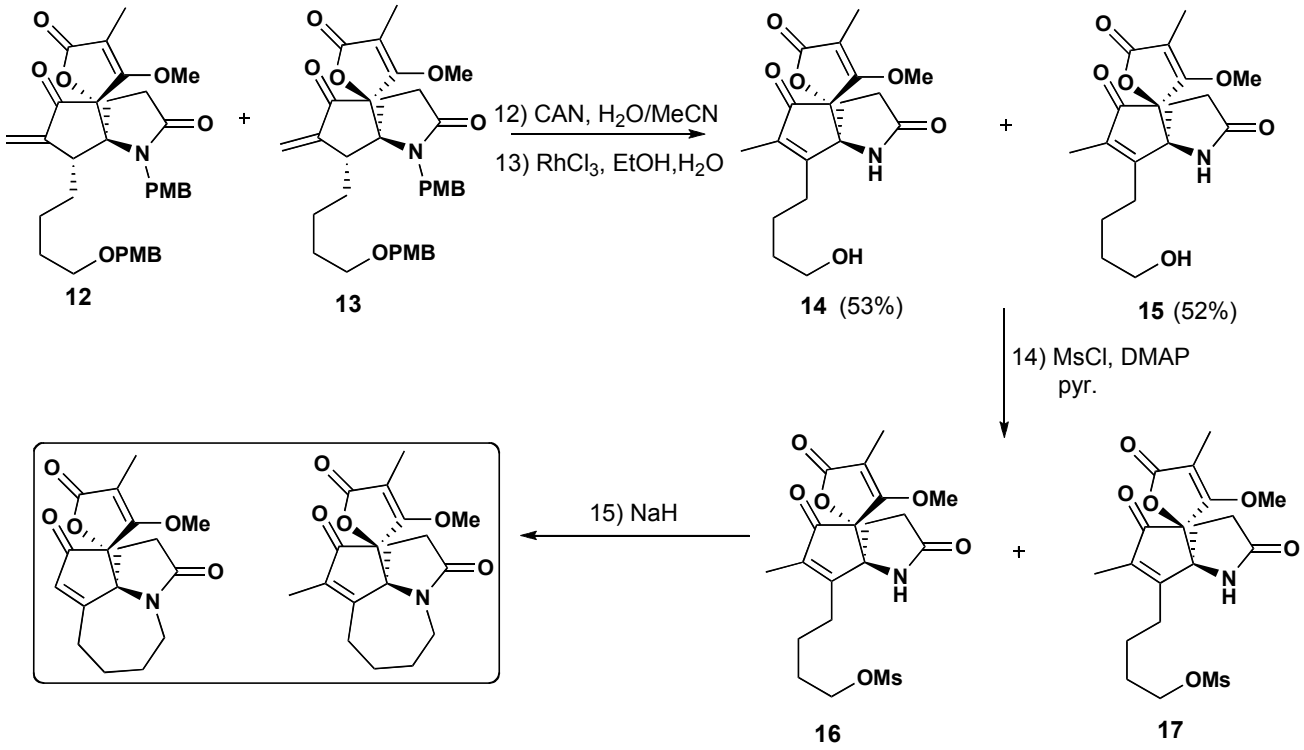

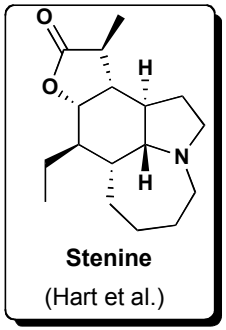

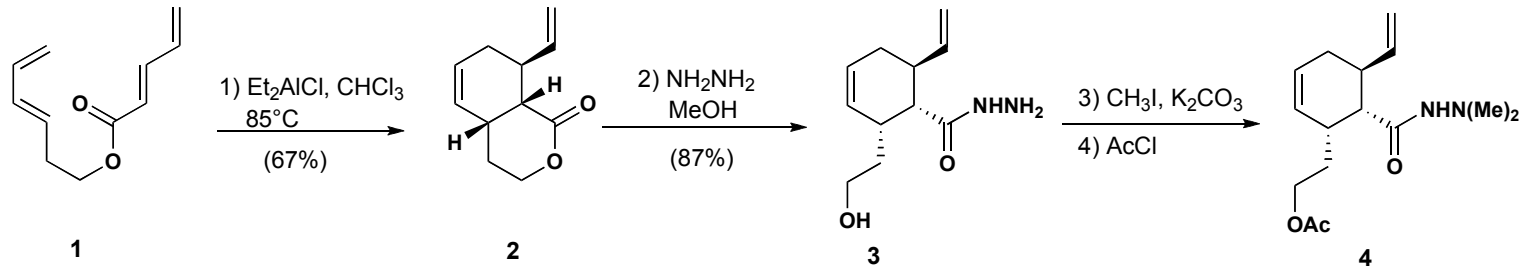

J. Org. Chem. 1990. 55, 6236-6240

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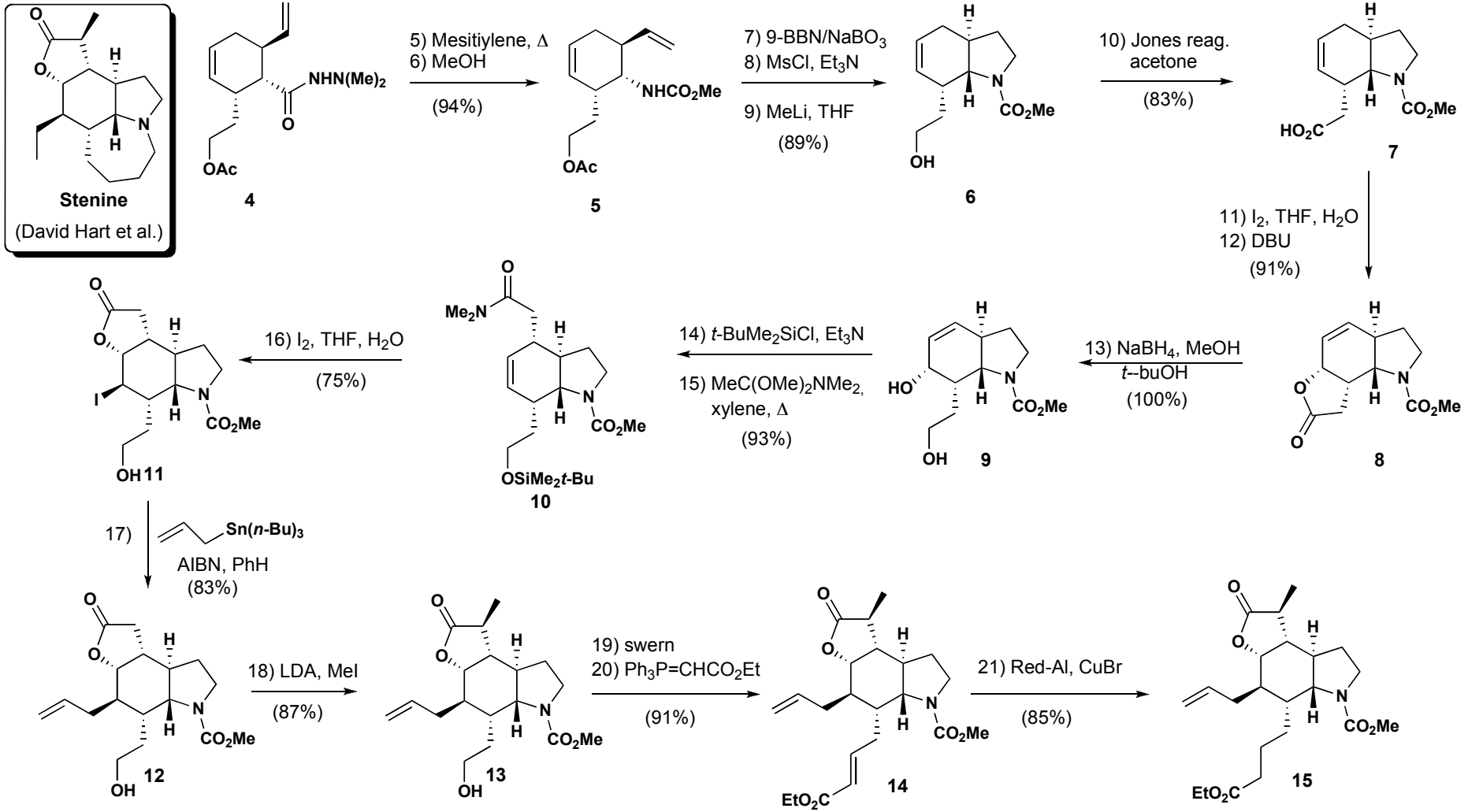
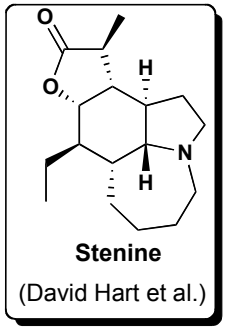
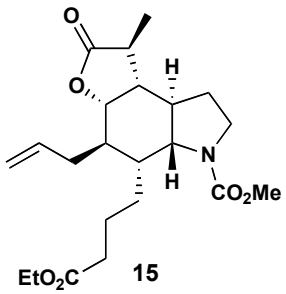


Stemona Alkaloids

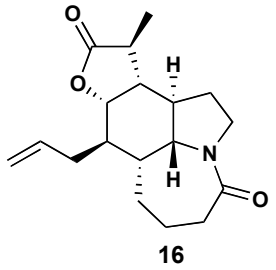
Tom Maimone





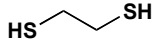
22) TMSI, then PhMe, Δ

(85%)

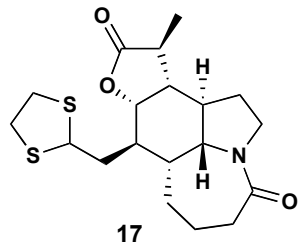


23) OsO_4 (cat) $NaIO_4$

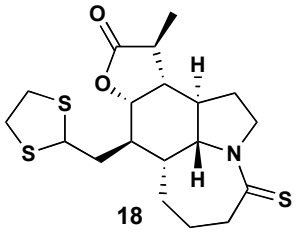
24)



$SiO_2/SOCl_2$



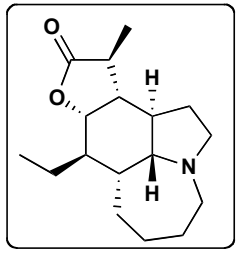
25) Lawesson's reagent (84%)



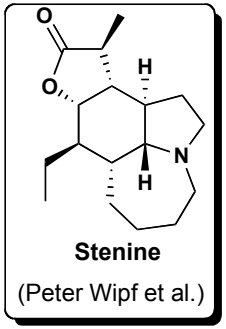
26) Raney Ni

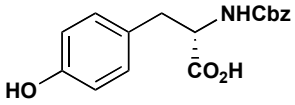
EtOH

(75%)



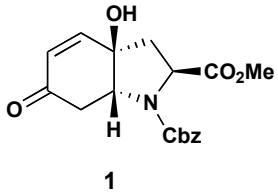
for a similar synthesis with an asymmetric Diels-Alder see Morimoto et al. Angew. Chem. Int. Ed. Engl. 1996, 35, 904-906.





1) $PhI(OAc)_2$, $NaHCO_3$ MeOH, 21 40°C

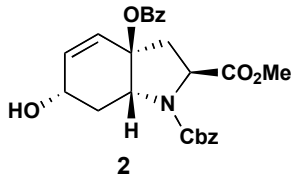
(55%)



2) Bz_2O

3) $NaBH_4$, $CeCl_3$

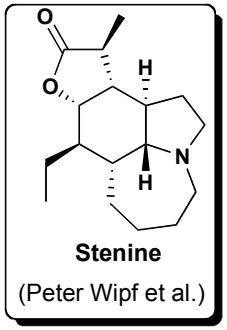
(89%)



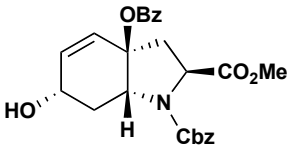
J. Am. Chem. Soc. 1995, 117, 11106-11112

Stemona Alkaloids

Tom Maimone

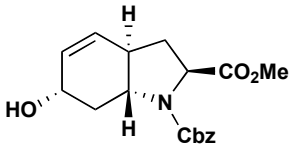


Stenine
(Peter Wipf et al.)



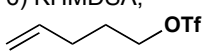
2

4) $Pd_2(dba)_3 \cdot CHCl_3$
Bu_3P, HCO_2H,
Et_3N
(68%)

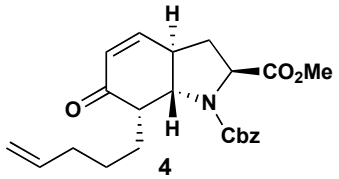


3

5) TPAP, NMO
6) KHMDSA,

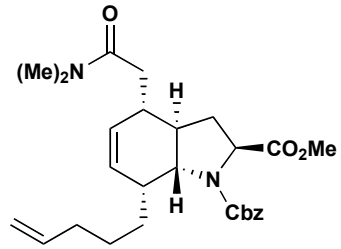


(46%)



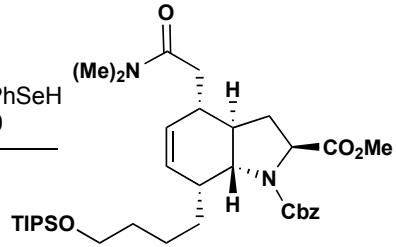
4

7) $NaBH_4$, $CeCl_3$
8) $H_3CC(OMe)_2NMe_2$,
130°C
(77%)



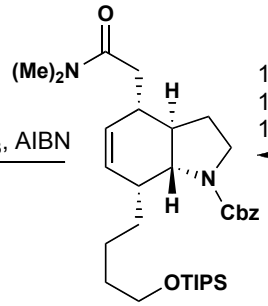
5

9) AD-mix β, $NaIO_4$
10) $NaBH_4$
11) TIPS-Cl, DMAP
(76%)



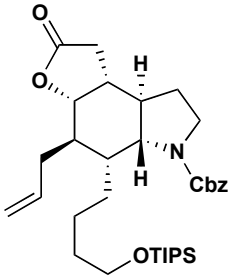
6

12) LiOH, H_2O/THF
13) $PhOPOCl_2$, NEt_3, PhSeH
14) Bu_3SnH, AIBN, 130
(70%)



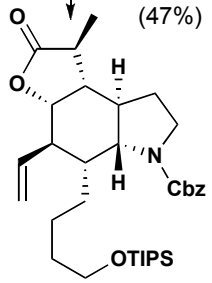
7

15) I_2, pH 5.5
16) Allyl-$SnBu_3$, AIBN



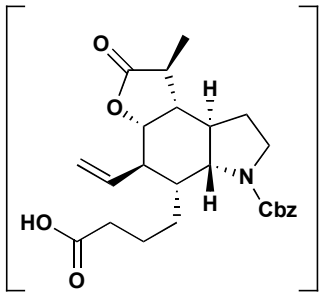
8

17) LDA, HMPA, MeI
18) OsO_4, $NaIO_4$
19) $NaBH_4$, -40°C
20) *o*-(NO_2)PhSeCN, Bu_3P, H_2O_2
(47%)

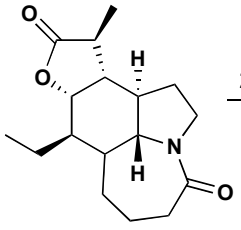


9

21) HF, MeCN
22) DMP, $NaClO_2$

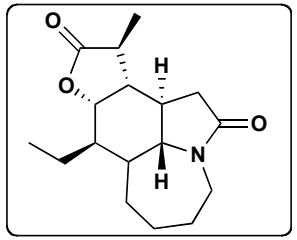


23) $Pd(OH)_2$, H_2
24) FDPP
(71%)



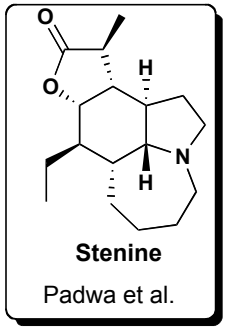
10

25) Lawesson's
26) Raney-Ni
(73%)



Stemona Alkaloids

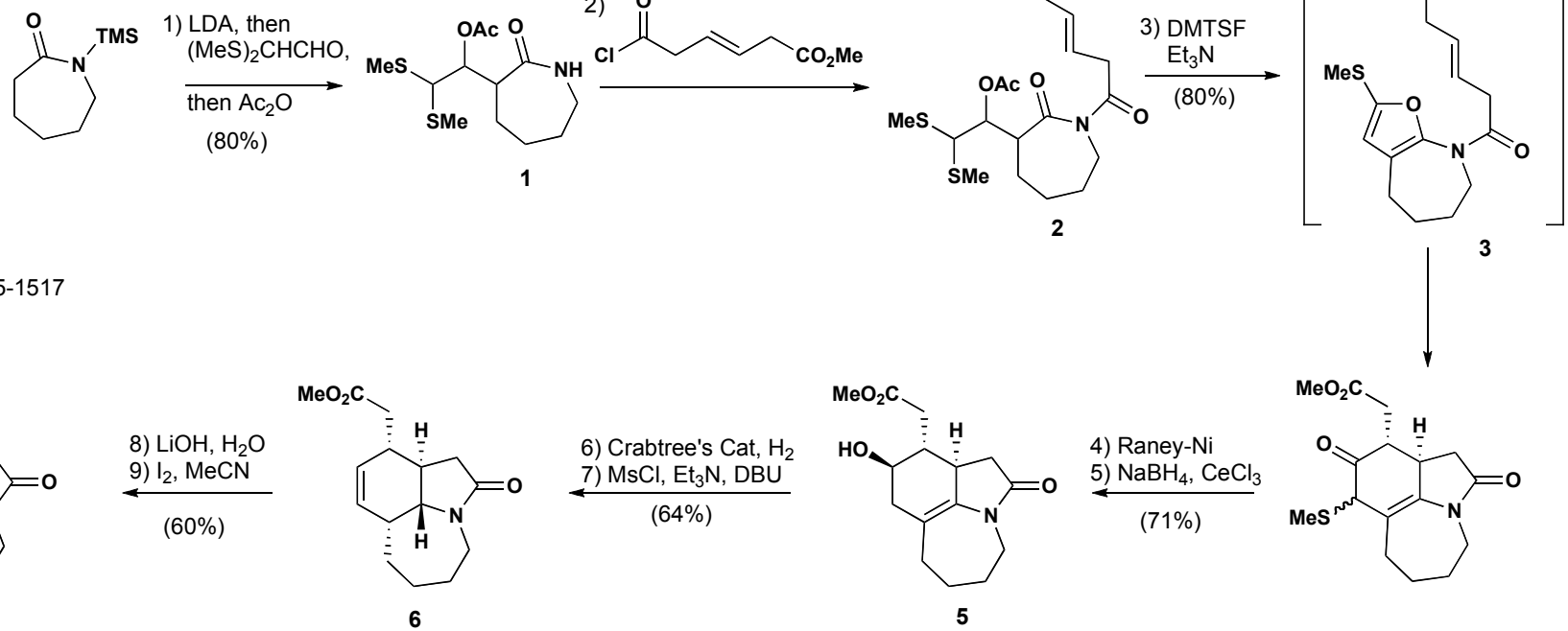
Tom Maimone



Stenine

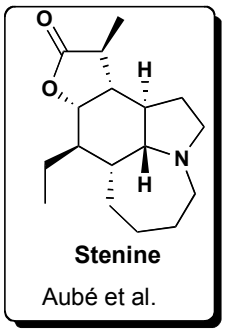
Padwa et al.

Org. Lett. 2002, 4, 1515-1517

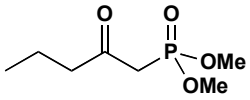


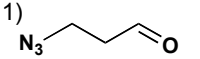
Stemona Alkaloids

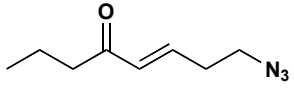
Tom Maimone



Stenine
Aubé et al.

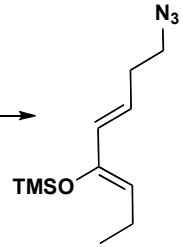


1) 
NaH/ THF
(92%)

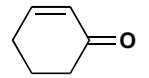


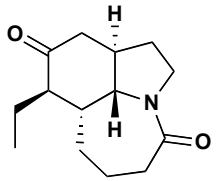
1

2) TMSOTf
(95%)



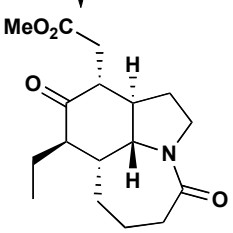
2

3) 
$SnCl_4$
(70% 3:1 dr)

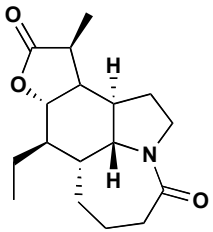


3

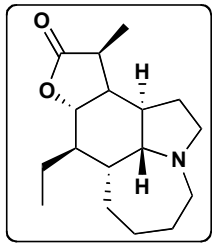
4) LHMDS, then $BrCH_2CO_2Me$
(73%)



5) $NaBH_4$
6) LHMDS, MeI
(51%)

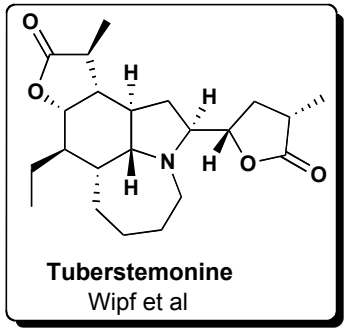


7) Lawesson's
8) Raney Ni
(83%)

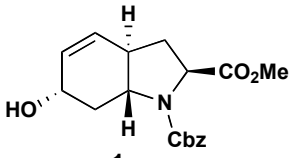


8 Steps
19% Yield
No PG's

J. Am. Chem. Soc. 2005, 127, 15712-15713



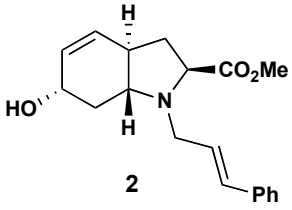
Tuberstemonine
Wipf et al



1

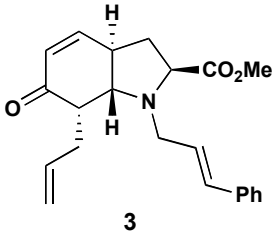
from the oxidative tyrosine cyclization

1) TBDMS-Cl, imidazole
DMAP
2)Et_3SiH, $Pd(OAc)_2$, NEt_3
3) cinnamyl bromide
4) TBAF
(80%)



2

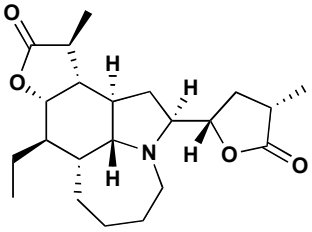
5) TPAP, NMO
6) KHMDS, allyl iodide
(58%)



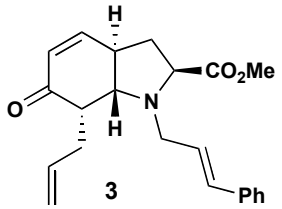
3

Stemona Alkaloids

Tom Maimone



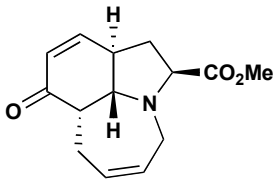
Tuberstemonine
(Wipf et al.)



3

7) Grubbs

(92%)

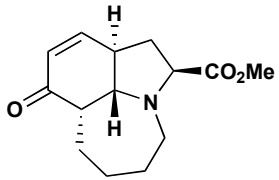


4

8) PhSH, Et_3N
9) $(PPh_3)_3RhCl$, H_2

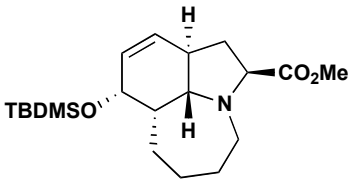
10) DBU

(81%)



5

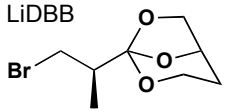
11) $NaBH_4$, $CeCl_3$
12) TBDMS-Cl, imid.
DMAP
(56%)



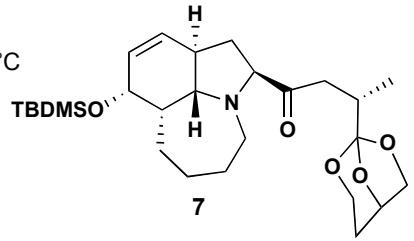
6

13) (Me)(OMe)NH HCl
Me_2AlCl

14) LiDBB



(89%)

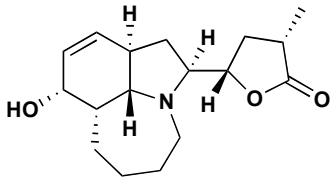


7

15) L-selectride, -78°C

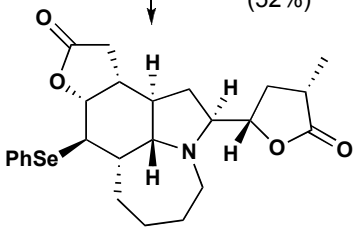
16) TsOH, MeOH

(56%)



8

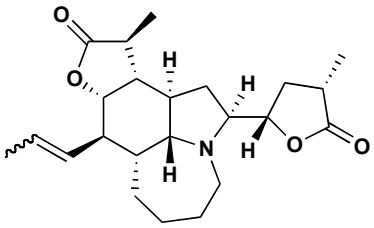
17) $MeC(OMe)_2NMe_2$,
xylene, Δ
18) PhSeCl, $MeCN/H_2O$
(52%)



9

19) allyl-$SnPh_3$
20) LDA, HMPA, MeI

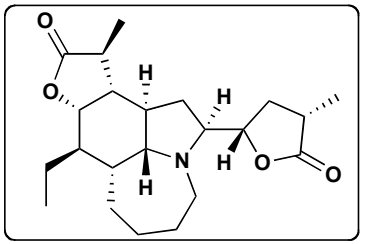
21) allyltritylamine, DIEA,
toluene, 110°C
(45%)



10

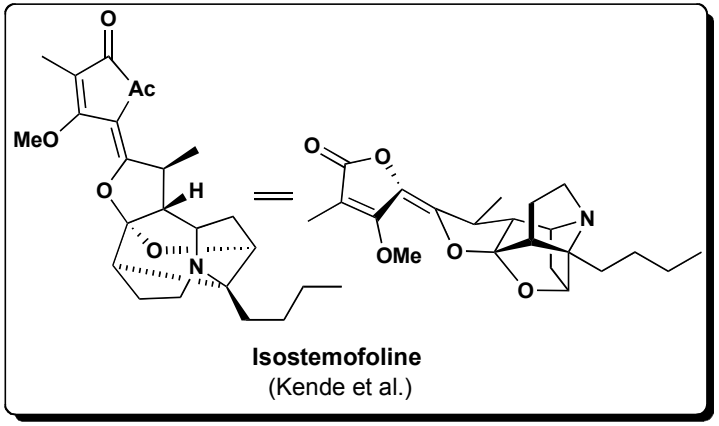
22) Grubbs, TsOH,
ethylene

23) Pd/C, H_2



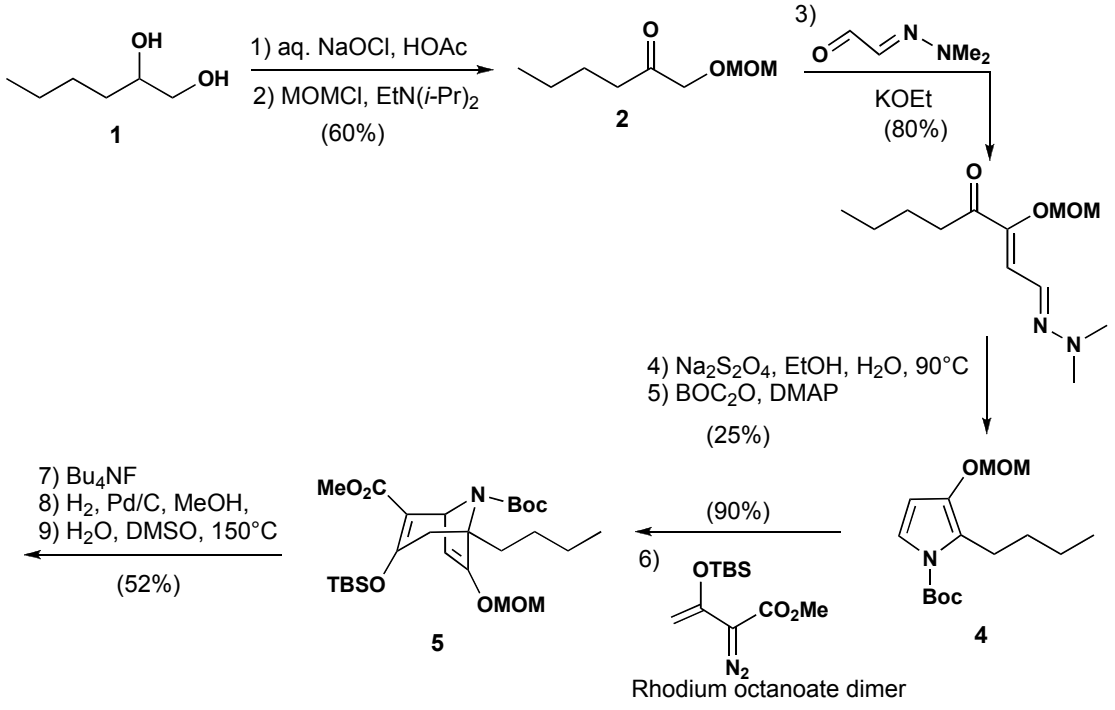
Stemona Alkaloids

Tom Maimone



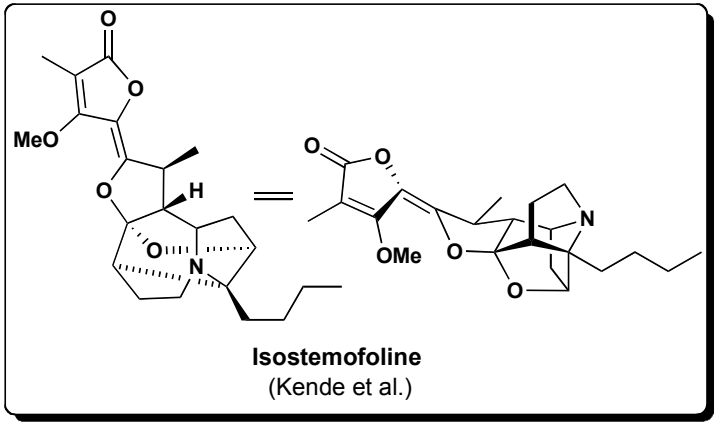
Isostemofoline
(Kende et al.)

J. Am. Chem. Soc. 1999. 121, 7431-7432

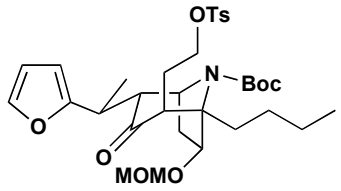


Stemona Alkaloids

Tom Maimone



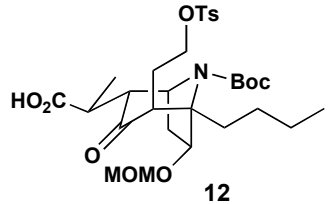
Isostemofoline
(Kende et al.)



11

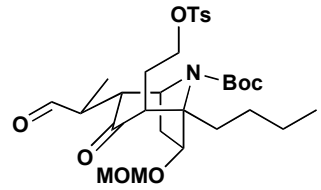
18) O_3, DMS

(65%)



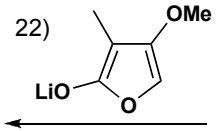
12

19) *i*-BuOCOCl, NMM
20) $NaBH_4$, MeOH
21) DMP

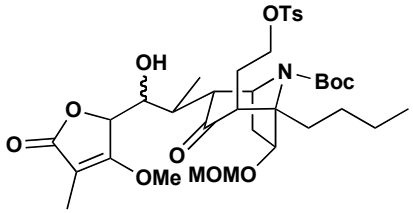


13

22)



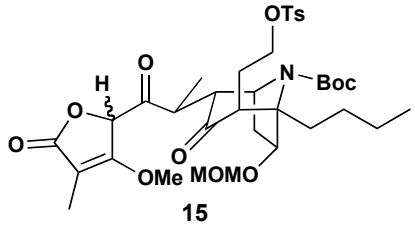
(56%)



14

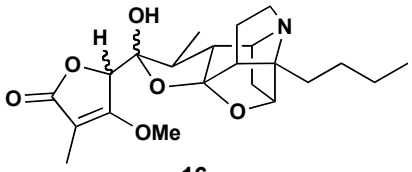
23) DMP, CH_2Cl_2

(61%)



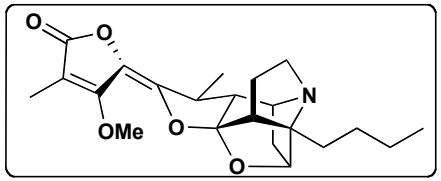
15

24) CF_3CO_2H
then $NaHCO_3$
(67%)



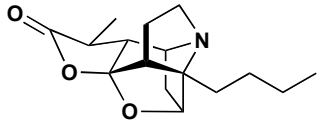
16

25) Tf_2O



(12%)

\+

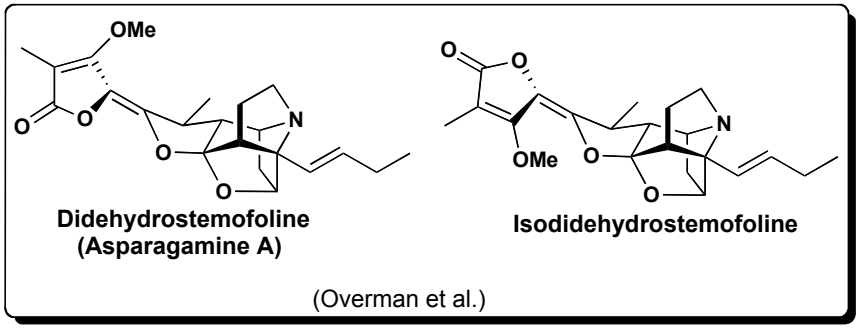
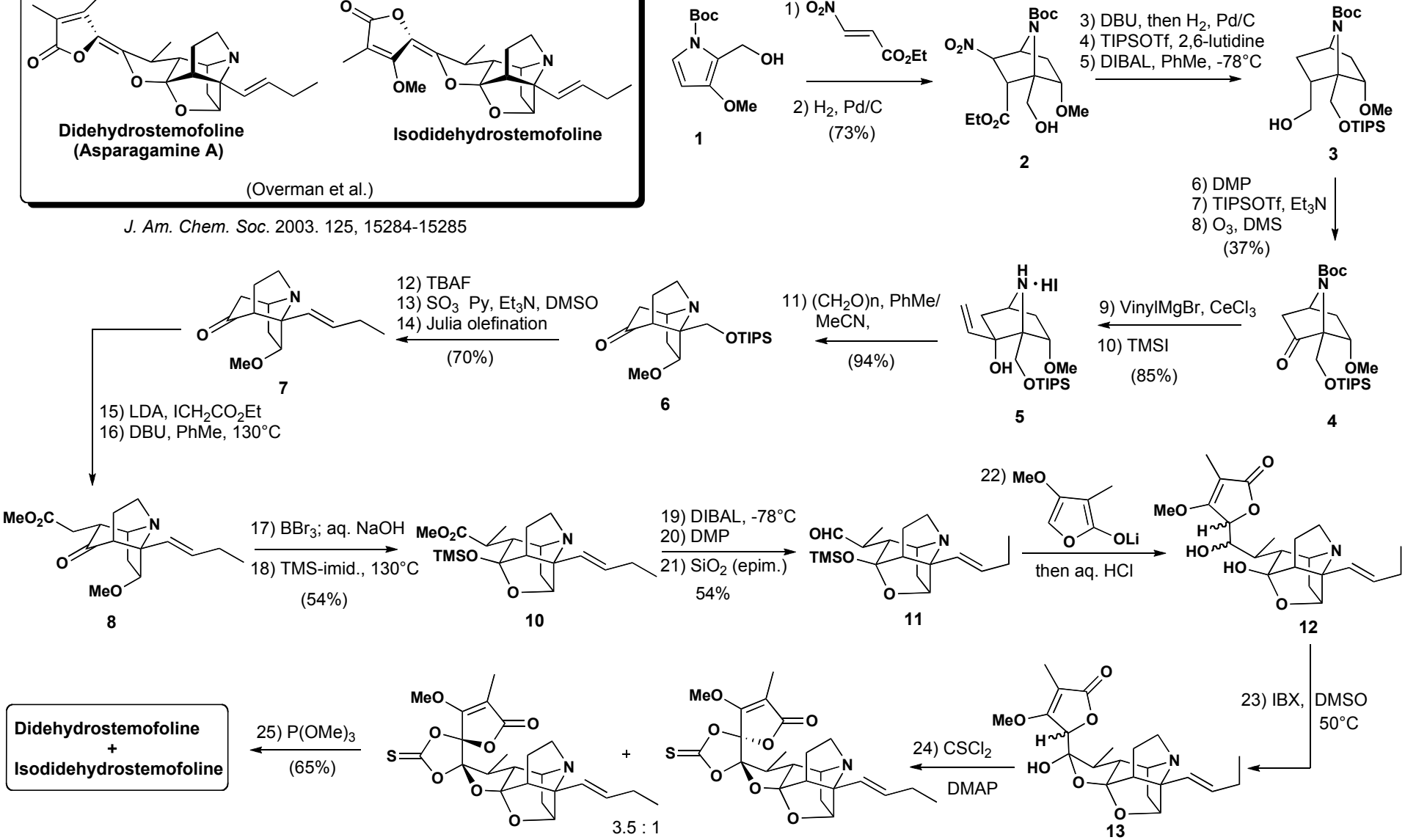


(14%)

\+ ?

Stemona Alkaloids

Tom Maimone



J. Am. Chem. Soc. 2003. 125, 15284-15285