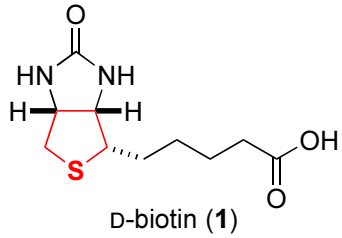
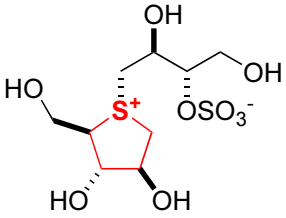
Problem Session

Sep. 24, 2016 Hiroaki Itoh

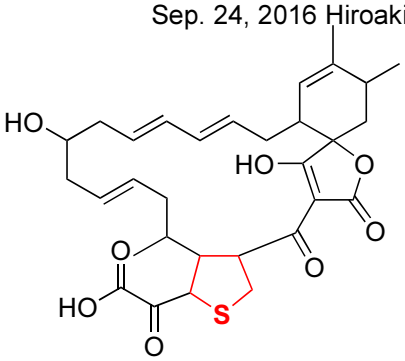
0. Natural products containing tetrahydrothiophene



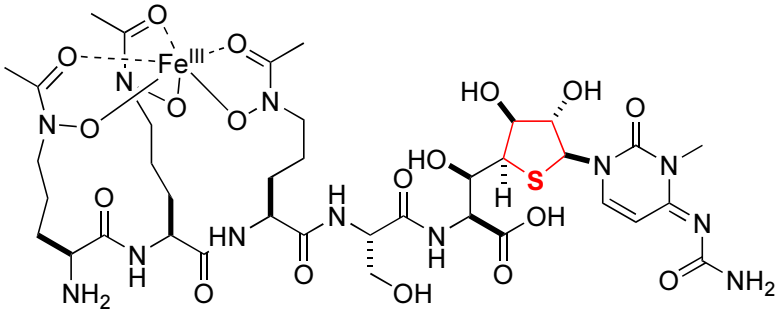
D-biotin (**1**)
vitamin B_7
(problem 1)



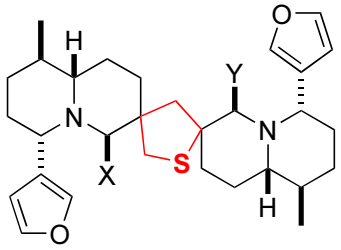
salacinol (**2**)
α-glucosidase inhibitor



tetronothiodin (**3**)
cholecystokinin type-B receptor antagonist



albomycin δ_2 (**4**)
antibiotic activity

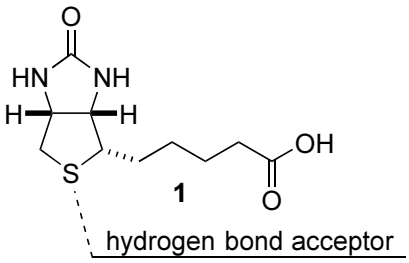


Nuphar dimers
immunosuppressive activity
apoptosis promoter, antimetastatic activity
(problem 2)

1. D-Biotin

1-1. Interaction of D-biotin

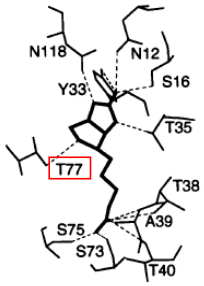
Biotin/avidin interaction are one of the most strong noncovalent and specific interaction (biotin $K_d = 10^{-15}$ M).
application -> tagging for pull-down assay etc.



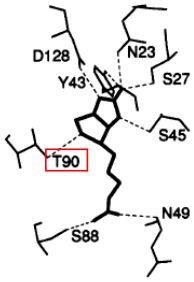
1

hydrogen bond acceptor

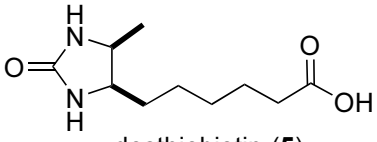
avidin



streptavidin



interaction of sulfur atom: Thr-77 (avidin) and Thr-90 (streptavidin)



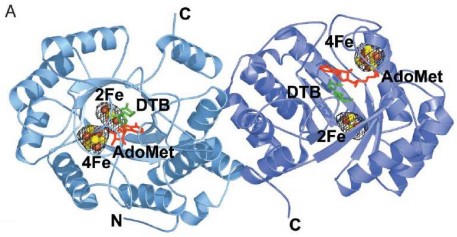
desthiobiotin (**5**)

biotin: $K_d = 10^{-15}$ M
desthiobiotin: $K_d = \mathbf{10^{-11}}$ M

elutable or reversible avidin-biotin affinity systems after pull down

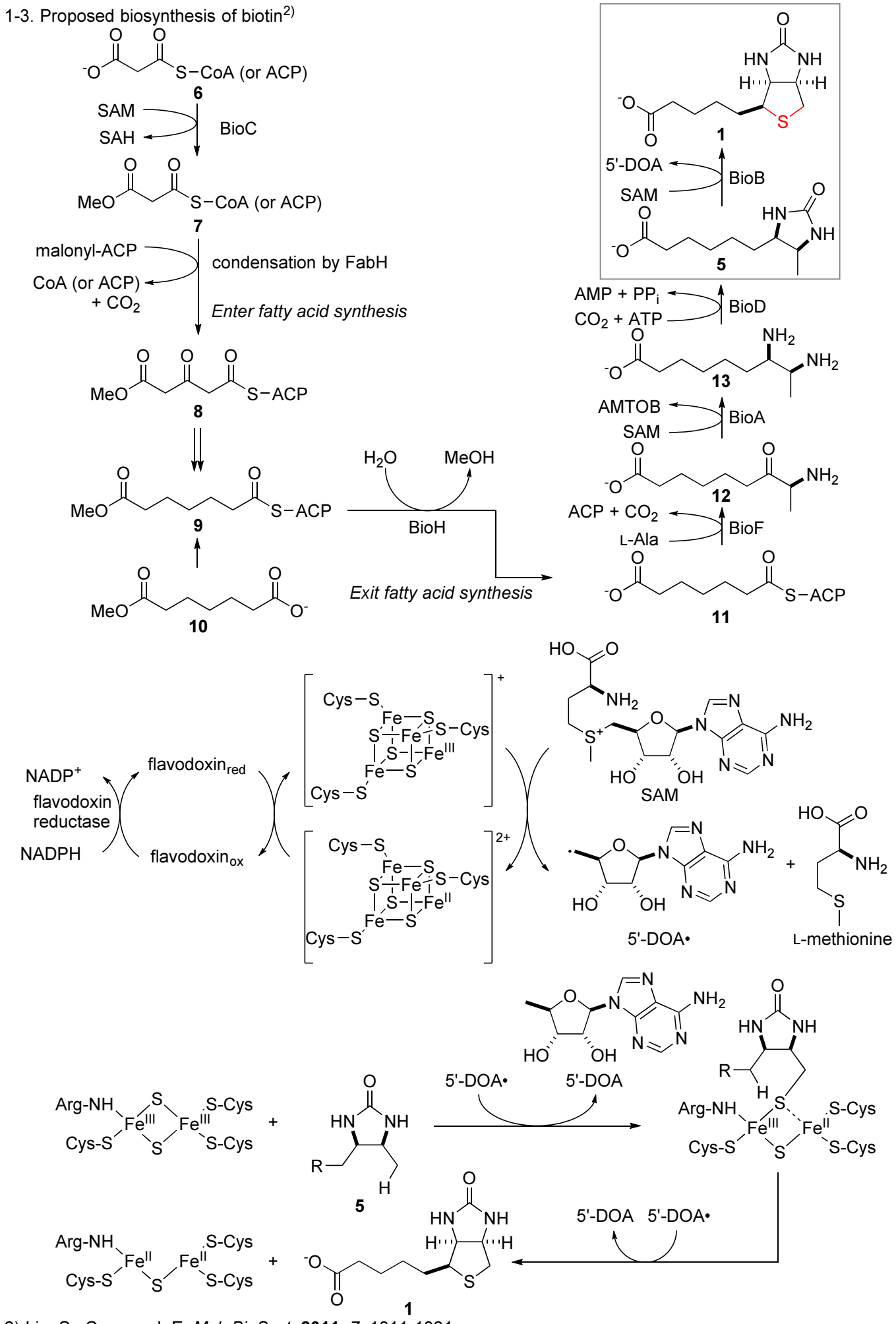
1-2. Biotin synthase (BioB)[1)]

biotin synthase (BioB): radical SAM enzyme
$[4Fe\text{-}4S]^{2+}$ cluster and $[2Fe\text{-}2S]^{2+}$ cluster



1) Berkovitch, F.; Nicolet, Y.; Wan, J. T.; Jarrett, J. T.; Drennan, C. L. *Science* **2004**, *303*, 76-79.

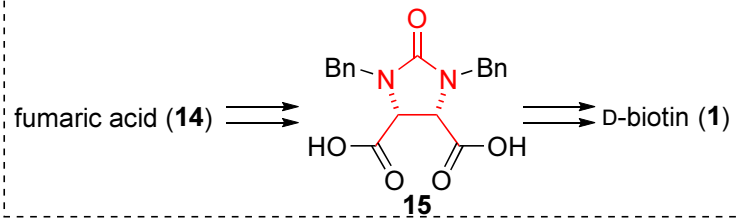
1-3. Proposed biosynthesis of biotin[2)]



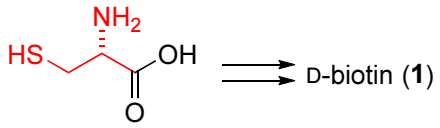
2) Lin, S.; Cronan, J. E. *Mol. BioSyst.* **2011**, *7*, 1811-1821.

1-4. Synthesis of D-biotin from L-cysteine

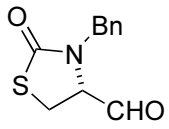
First synthesis of D-biotin
(Goldberg and Sternbach, Hoffmann-La Roche)[3]



Synthesis from L-cysteine[3,4]



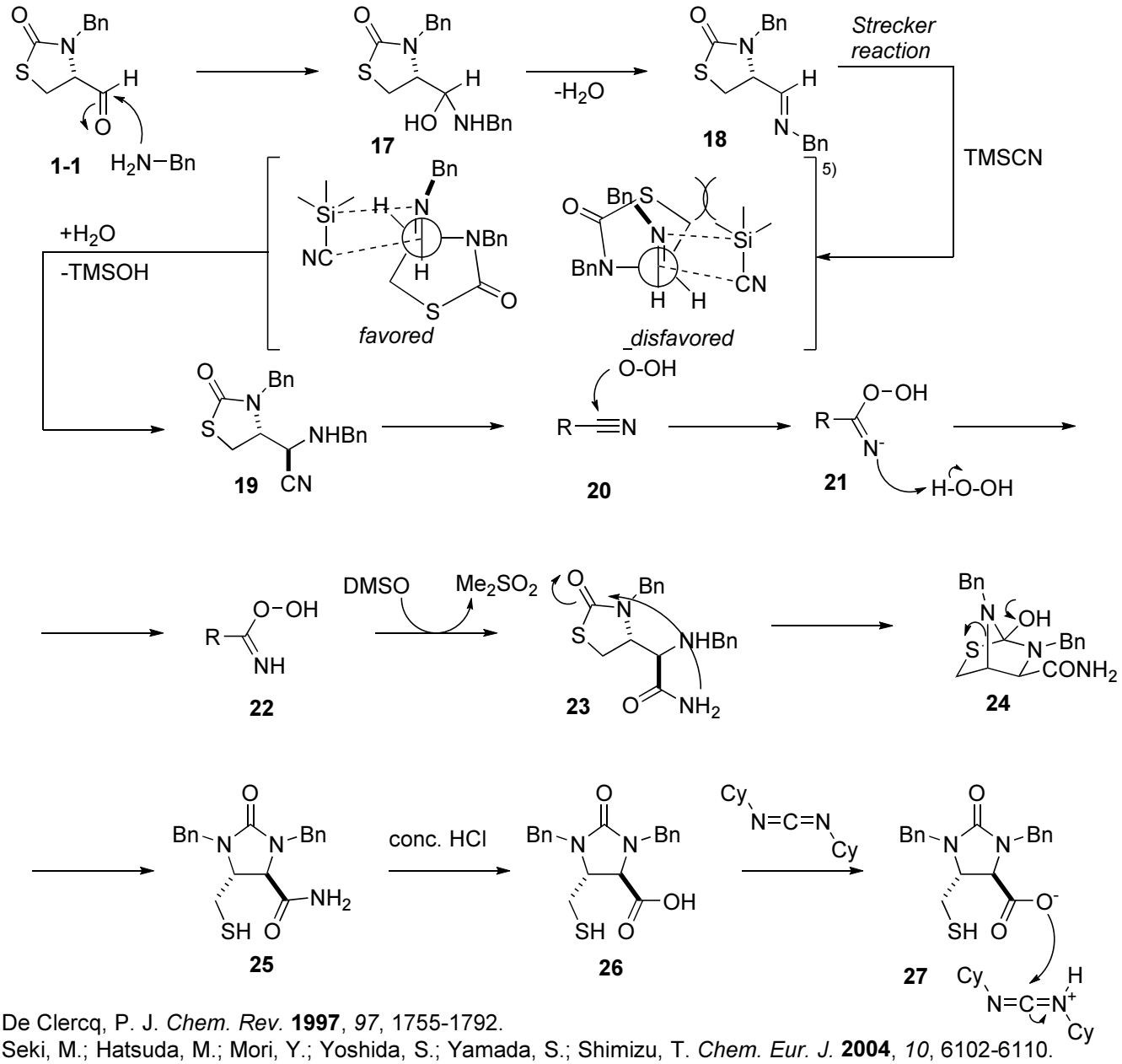
1.



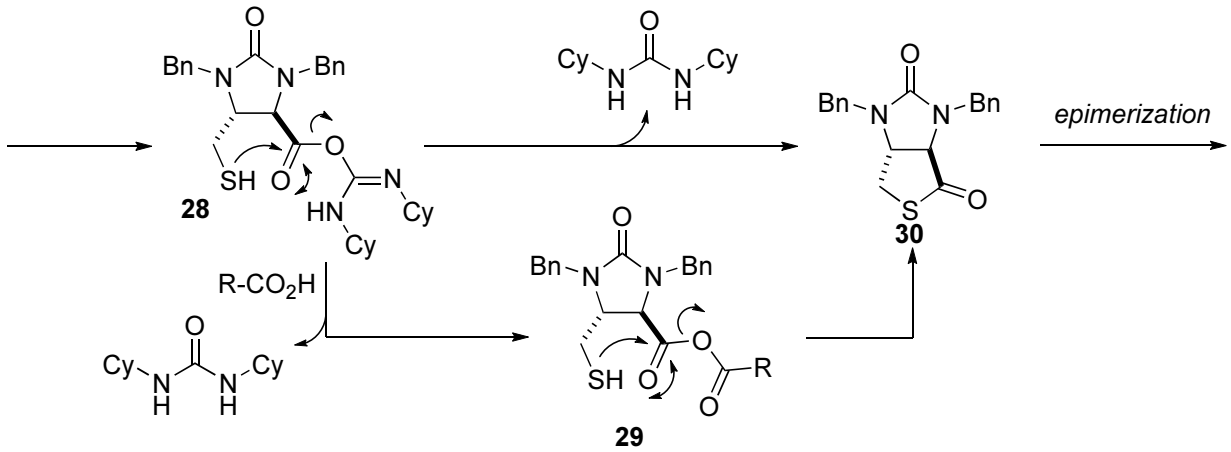
1-1

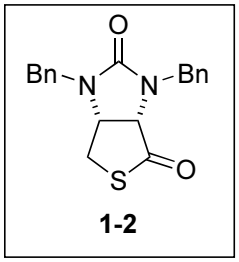
1. $BnNH_2$ (1.0 eq), $MgSO_4$ (1.0 eq), toluene, 5 to 25 °C, 2 h;
   TMSCN (2.1 eq), -5 to 20 °C, 15 h, 96%
2. H_2O_2 (2.9 eq), K_2CO_3 (0.14 eq), DMSO, CH_2Cl_2
   20 °C, 6 h, 93%
3. DMF, 90 °C, 3 h;
   conc. HCl, 90 °C, 3 h, 95%
4. DCC (1.5 eq), TFA (0.4 eq), pyridine (1.4 eq), $CHCl_3$
   0 °C to reflux, 7 h, 80%

1-2
bicyclic compound



3) De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755-1792.
4) Seki, M.; Hatsuda, M.; Mori, Y.; Yoshida, S.; Yamada, S.; Shimizu, T. *Chem. Eur. J.* **2004**, *10*, 6102-6110.
5) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1996**, *61*, 9028-9032.





D-biotin (**1**)

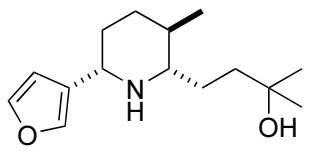
well-known[3)]
synthetic intermediate
for D-biotin

2. Nuphar alkaloids

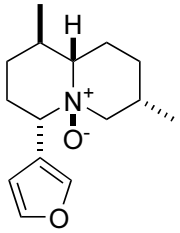
Class of alkaloids isolated from aquatic plants of th genus *Nuphar*

2-1. Selected *Nuphar* alkaloids

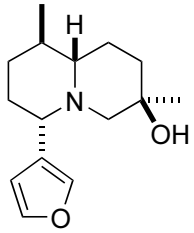
C_{15}



nupharamine (**31**)

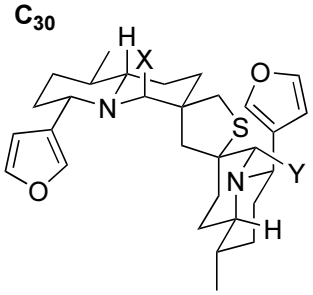


nupharidine (**32**)

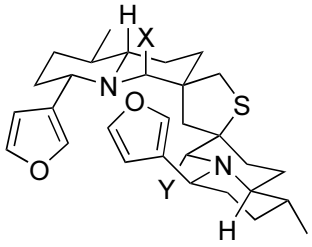


nupharolutine (**33**)

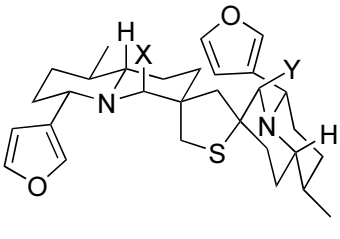
C_{30}



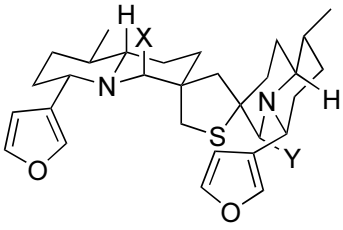
34a-d
thiobinupharidine



35a-d
thionuphlutine

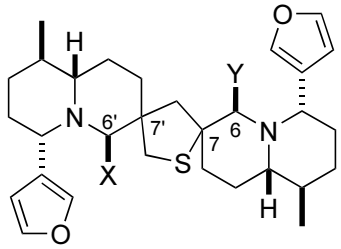


36a-d
neothiobinupharidine



37a-d
neothionuphlutine

(not isolated from natural sources)



a: X = Y = OH
b: X = H, Y = OH
c: X = OH, Y = H
d: X = Y = H

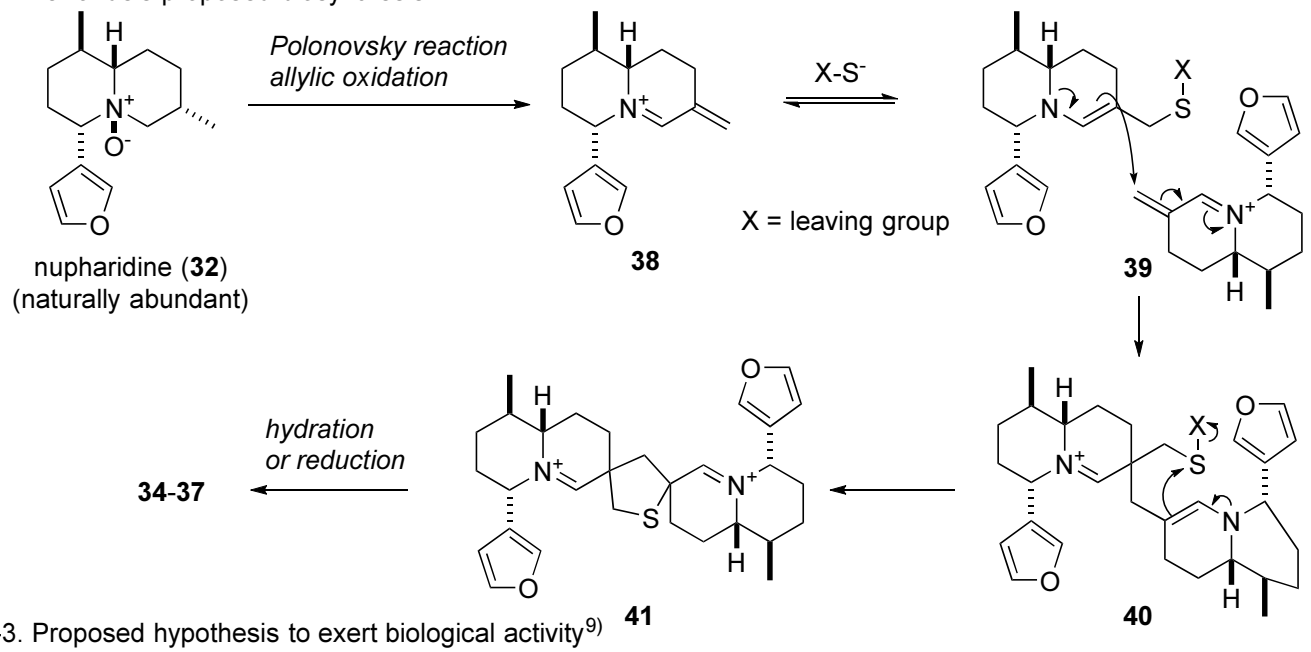
] potent biological activity (induction of apoptosis, inhibition of invasion of collagen matrix by melanoma)

total synthesis of *Nuphar* dimer: Shenvi (2013)[6)]
Wu (2015)[7)]

7) Korotkov, A.; Li, H.; Chapman, C.; Xue, H.; MacMillan, J. B.; Eastman, A.; Wu, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 10604-10607.

6) Jansen, D. J.; Shenvi, R. A. *J. Am. Chem. Soc.* **2013**, *135*, 1209-1212.

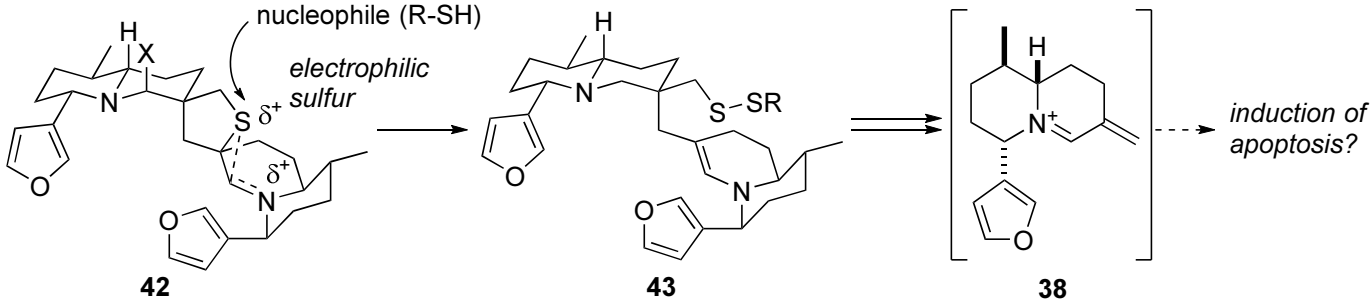
2-2. LaLonde's proposed biosynthesis[8)]



nupharidine (**32**)
(naturally abundant)

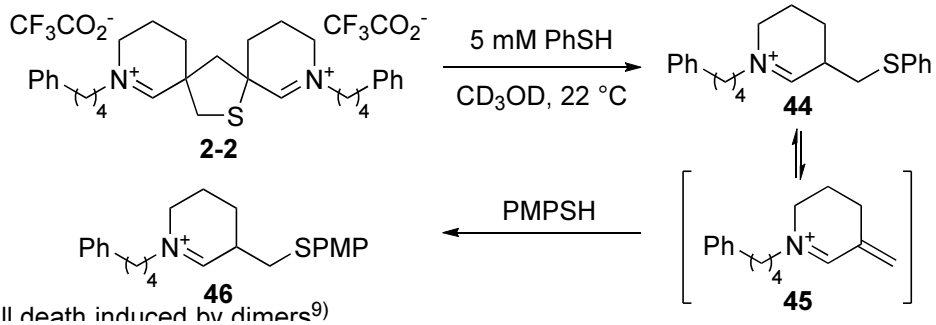
38 **39** **40** **41**

2-3. Proposed hypothesis to exert biological activity[9)]



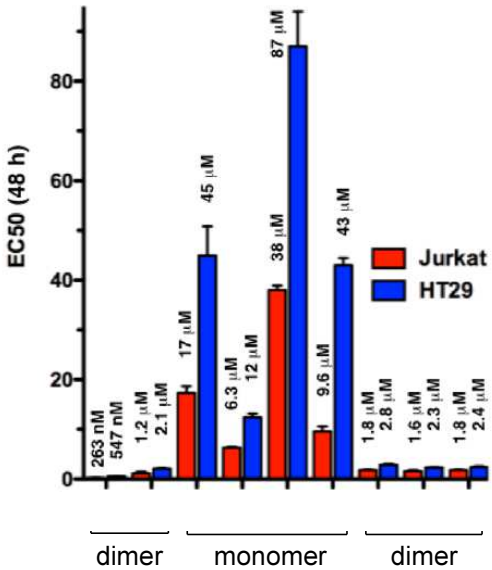
42 **43** **38**

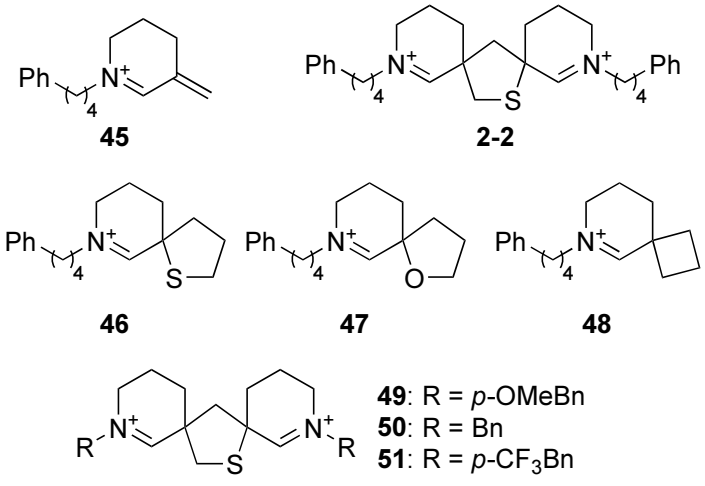
2-4. Retrodimerization of model compound by thiol[9)]



2-2 **44** **45** **46**

2-5. Rapid cell death induced by dimers[9)]



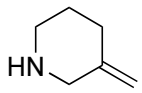


45 **2-2** **46** **47** **48**

49: R = *p*-OMeBn
50: R = Bn
51: R = *p*-CF_3Bn

8) Wong, C. F.; LaLonde, R. T. *Experientia* **1975**, *31*, 15-16.
9) Tada, N.; Jansen, D. J.; Mower, M. P.; Blewett, M. M.; Umotoy, J. C.; Cravatt, B. F.; Wolan, D. W.; Shenvi, R. A. *ACS Cent. Sci.* **2016**, *2*, 401-408.

2.

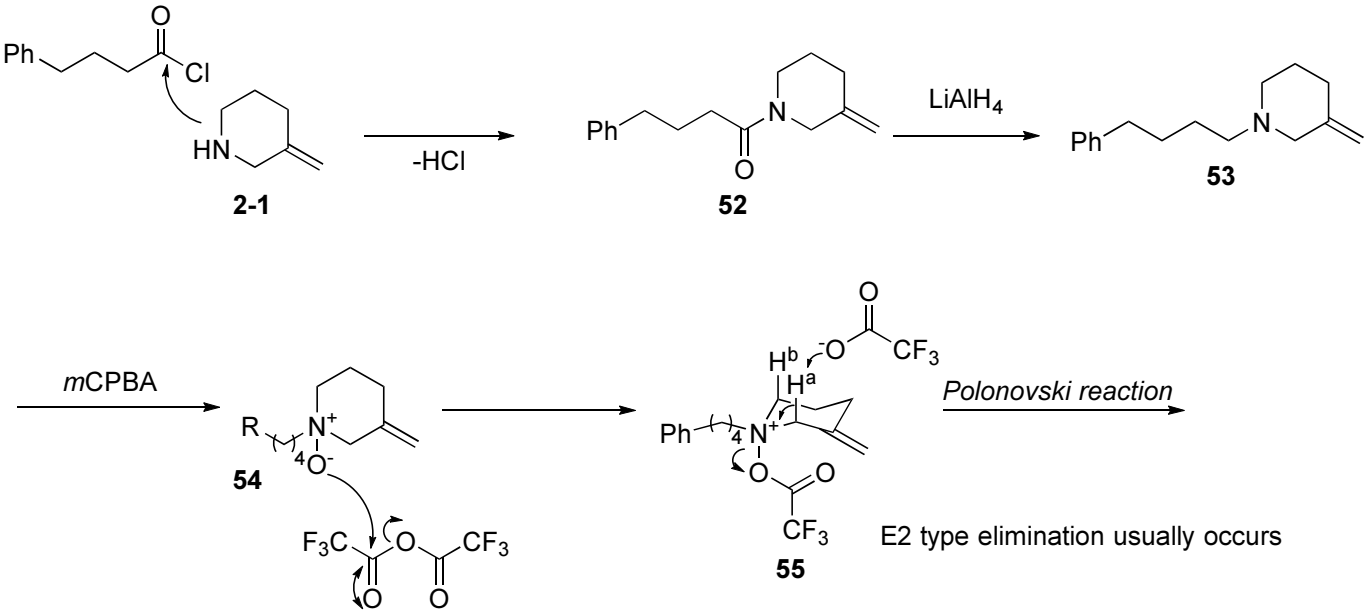


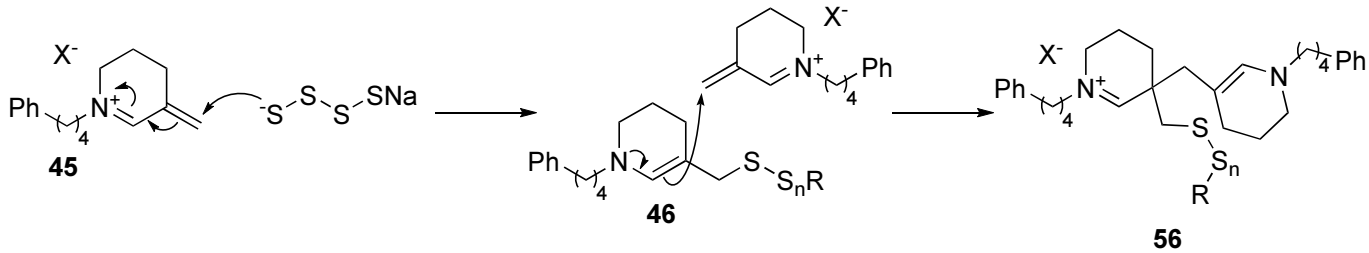
2-1

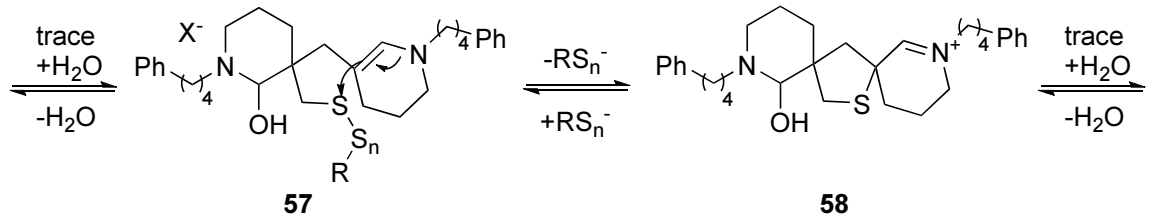
1. $Ph(CH_2)_3COCl$ (1.6 eq), Me_3N (1.6 eq), CH_2Cl_2 0 °C to rt, 35 min, 99%
2. $LiAlH_4$ (2.0 eq), Et_2O, 0 °C, 1 h, 82%
3. *m*CPBA (1.0 eq), CH_2Cl_2, 0 °C, 10 min, 50%
4. $(CF_3CO)_2O$ (10 eq), CH_2Cl_2, 0 °C, 2 h
5. Na_2S_4 (0.51 eq), THF, rt, 6 h; TFA (>2 eq), 34% (2 steps)

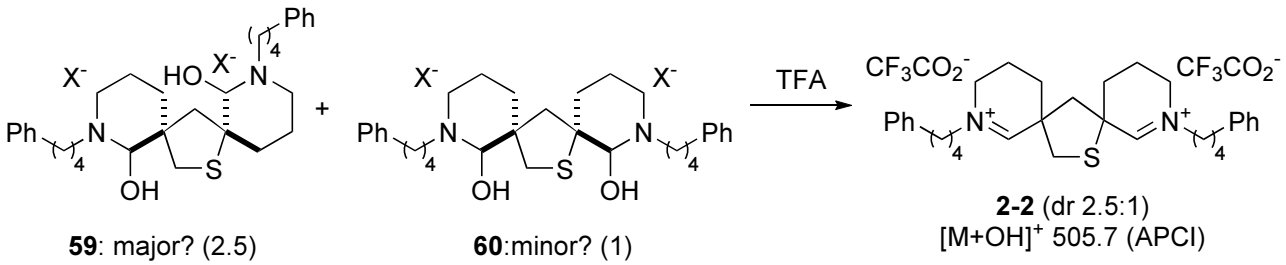
2-2

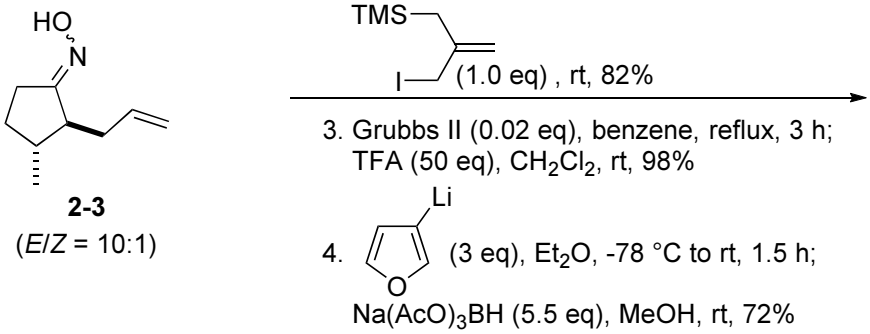
dr 2.5:1
MS spec. *m/z* = 505.7 (APCI)

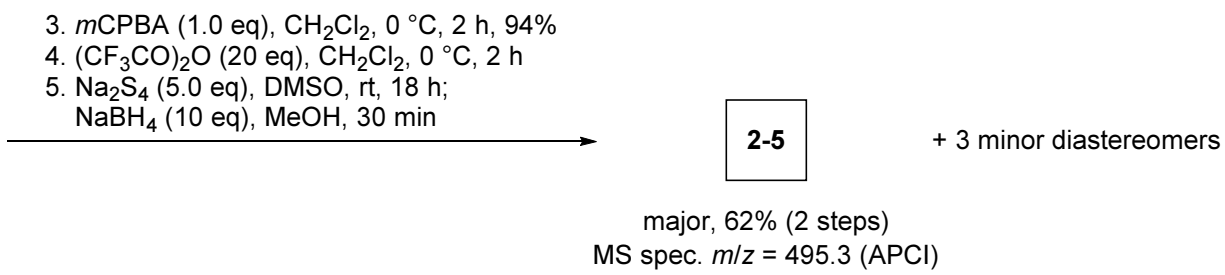




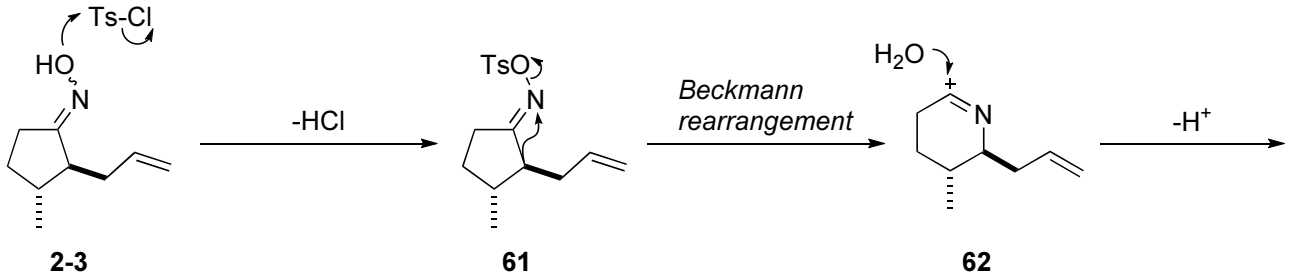


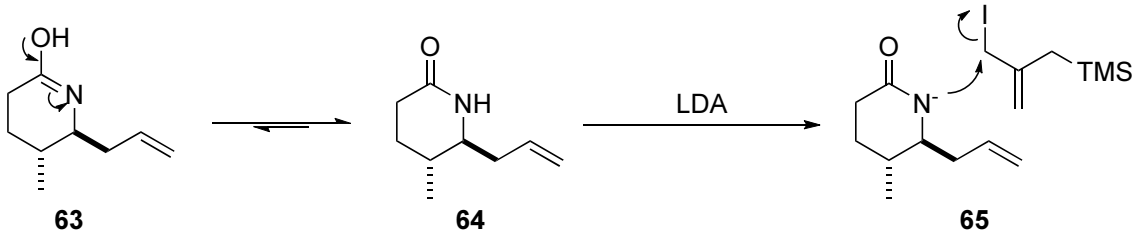


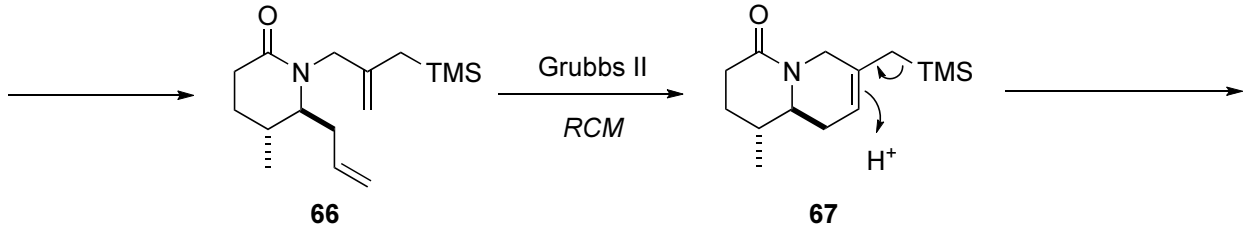


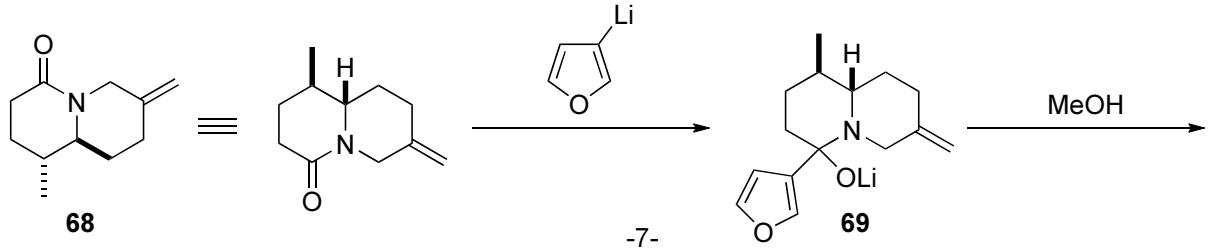


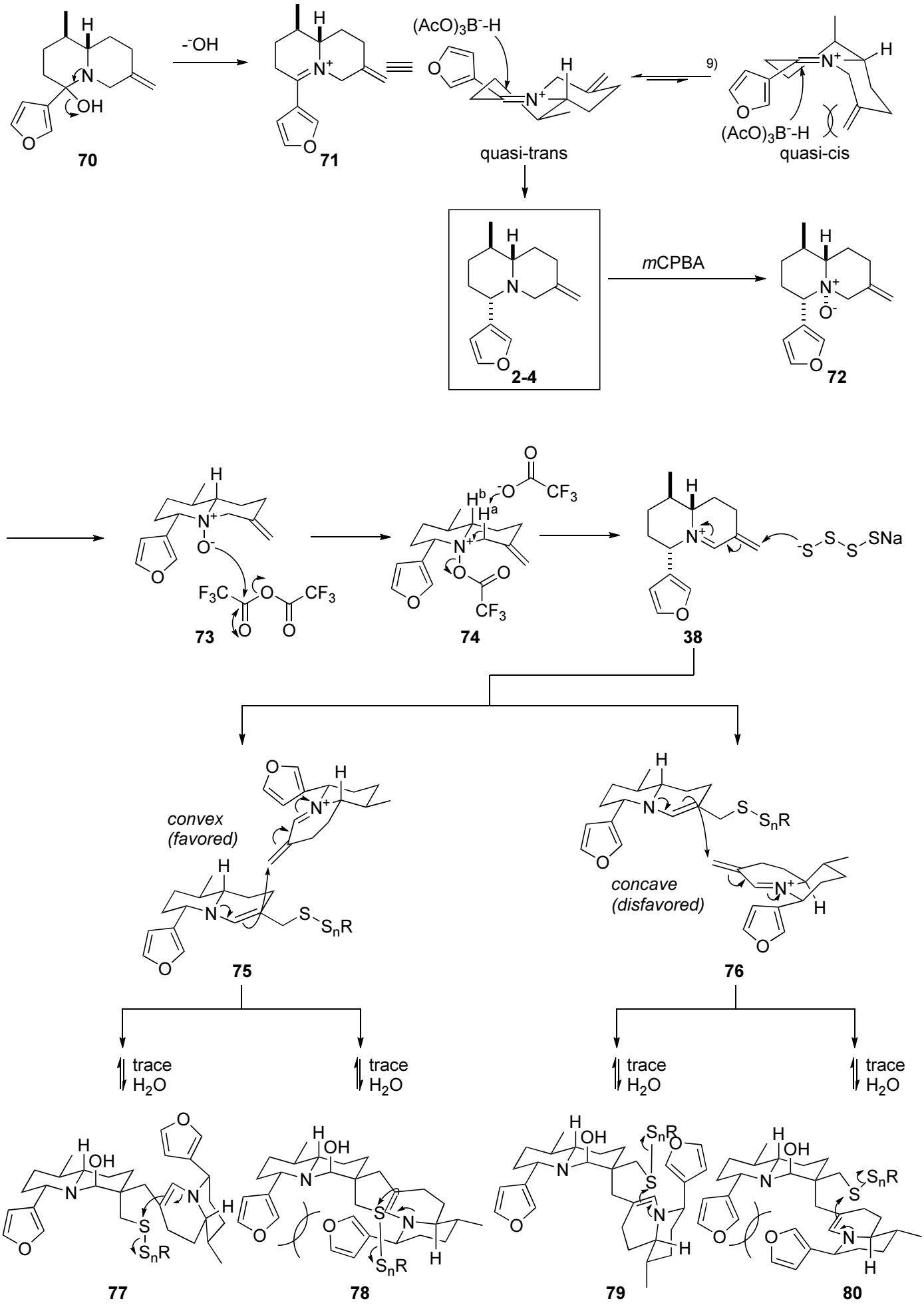
major, 62% (2 steps)
MS spec. *m*/*z* = 495.3 (APCI)



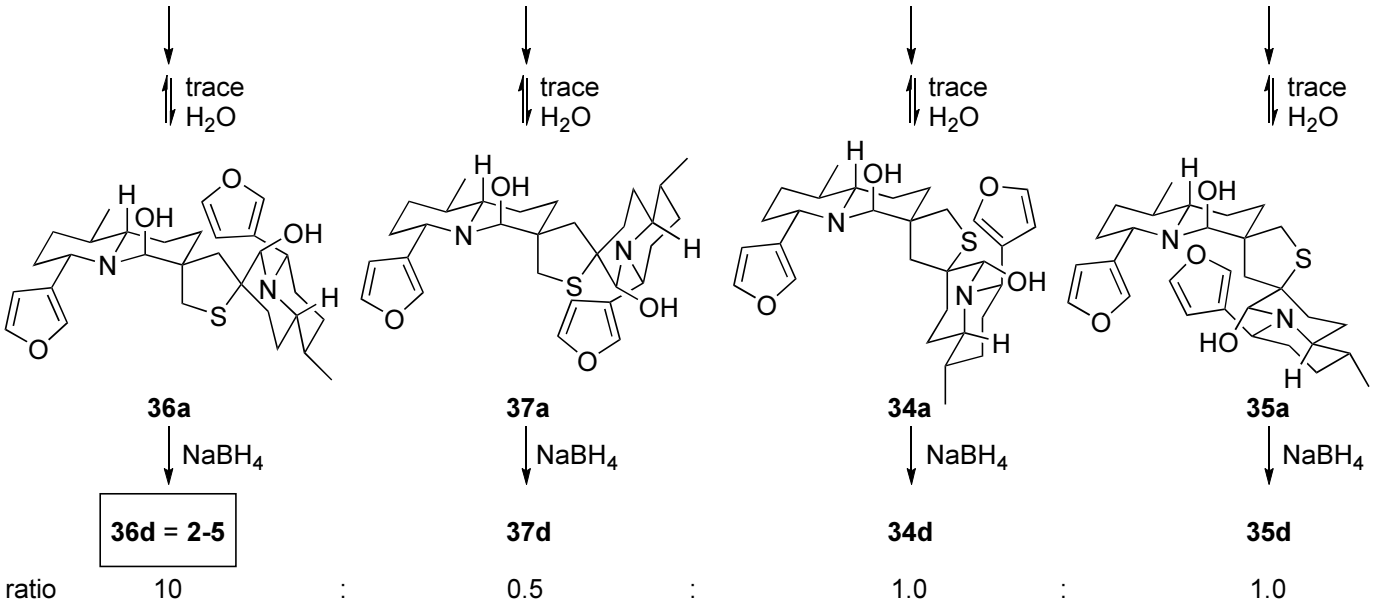








9) Hwang, Y.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 3885-3890.


trace
H2O
trace
H2O
trace
H2O
trace
H2O
36a
37a
34a
35a
NaBH4
NaBH4
NaBH4
NaBH4
36d = 2-5
37d
34d
35d
ratio
10
:
0.5
:
1.0
:
1.0