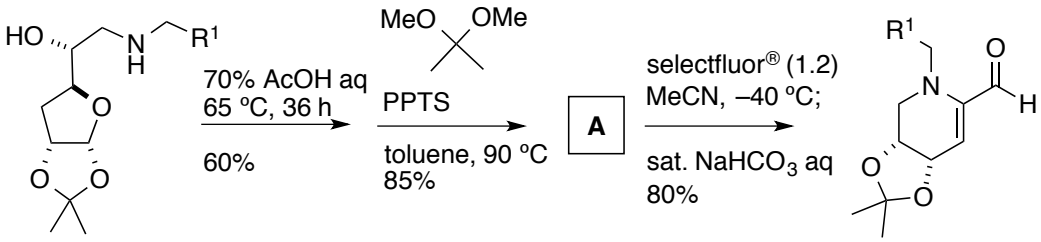
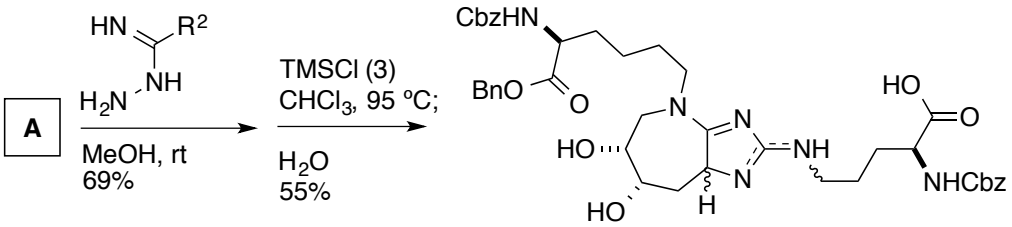
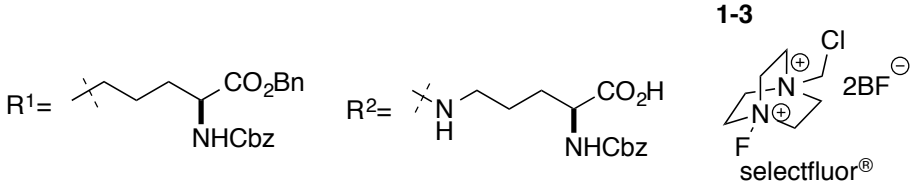
Problem Session (5)

16/04/30 Takuya Kaji

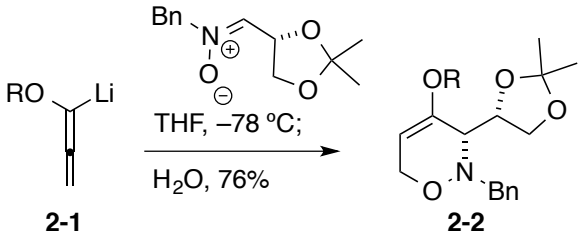
1. Please fill in the blank **A** and provide reaction mechanisms

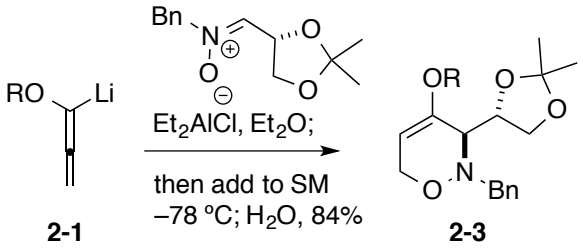


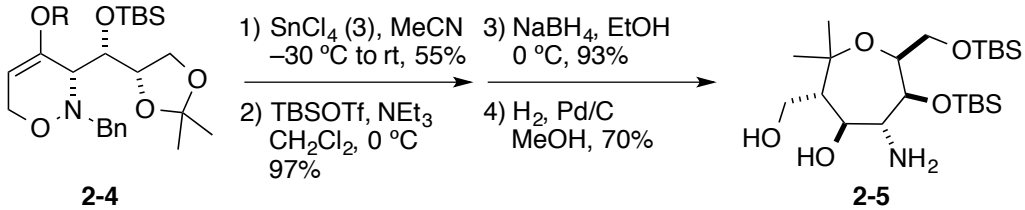


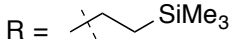


2. Please provide reaction mechanisms and explain selectivities









Problem Session (5) Answer

16/04/30 Takuya Kaji

1. Concise total synthesis of glucosepane (Draghici, C.; Wang, T.; Spiegel, D. A. *Science* **2015**, *350*, 294.)

Background:

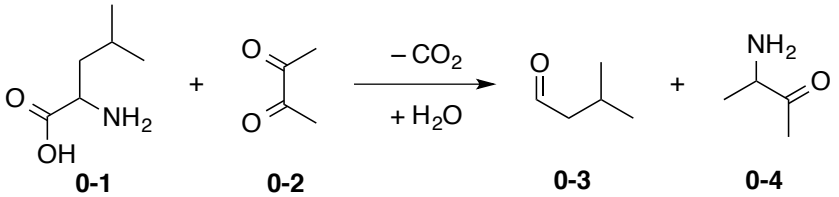
Maillard reaction (for review *Angew. Chem. Int. Ed.* **2014**, *53*, 10316.)

total reaction process between reducing carbohydrates with amino compound

⟶ food science (aroma, taste-active compound, food-degradation), protein glycation

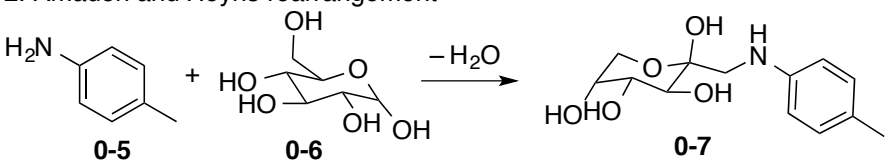
example of reaction involved

1. Strecker degradation

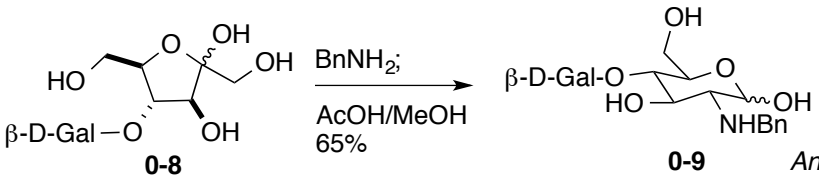


0-1 **0-2** **0-3** **0-4**

2. Amadori and Heyns rearrangement

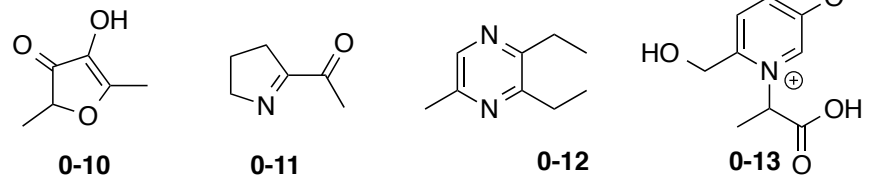


0-5 **0-6** **0-7**



0-8 **0-9** *Angew. Chem. Int. Ed.* **1999**, *38*, 827.

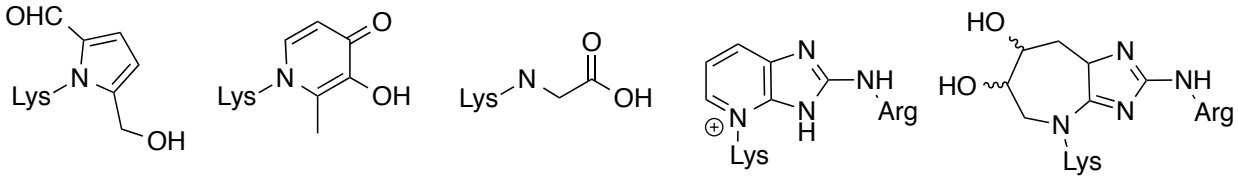
example of Mailllard reaction or caramelization products



0-10 **0-11** **0-12** **0-13**

"strawberry note" "popcorn aroma"

example of Maillard reaction on protein (advanced glycation endproducts)



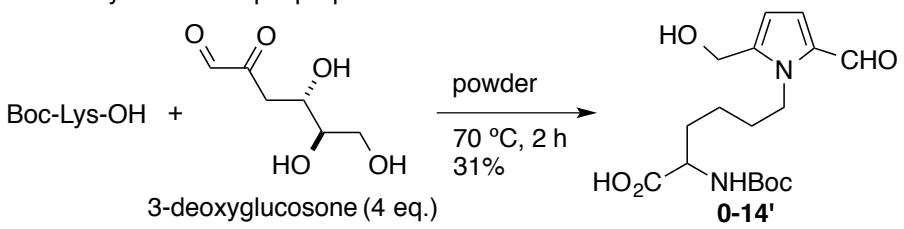
0-14 pyrraline **0-15** **0-16** CML **0-17** pentosidine **0-18** **glucosepane**

Table 1: Content of selected Maillard reaction products in foods.

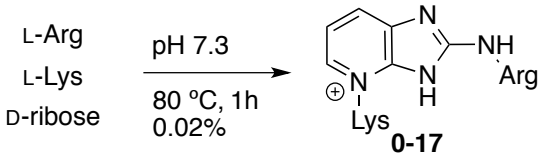
Food	ARP[83,84] [g kg^{-1}][a]	CML[85,86] [mg kg^{-1}]	Pyrraline[87] [mg kg^{-1}]	Pentosidine[88] [mg kg^{-1}]
milk, pasteurized	ca. 0.1	0.2–0.5	n.d.	n.d.
evaporated milk	7–18	46	0.4–3.2	0.02–0.04
pasta	1–19	2.4–3.0	n.d.–12	–
bread	6–7	3–40	6–69	–
bread crusts	–	37–46	60–240	0.03–0.18
meat, roasted	–	2–20	–	–
butter	–	0.3–0.4	–	–
coffee, roasted	–	–	–	1.0–4.0

[a] Amadori product calculated as fructoselysine. [b] Type of heat treatment not given.

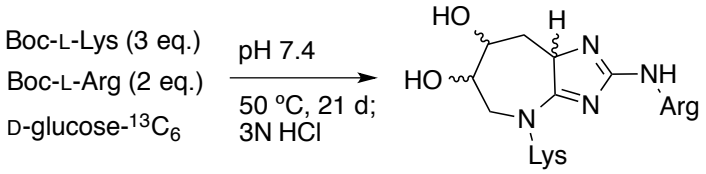
previous synthetic sample preparation



Zeitschrift für Lebensmittel-Untersuchung und Forschung **1996**, *202*, 72.



J. Biol. Chem. **1989**, *264*, 21597.



0-18-a-d (4 diastereomers)
(1.41%, 0.93%, 0.32%, 0.27%) *J. Biol. Chem.* **2002**, *277*, 24907.

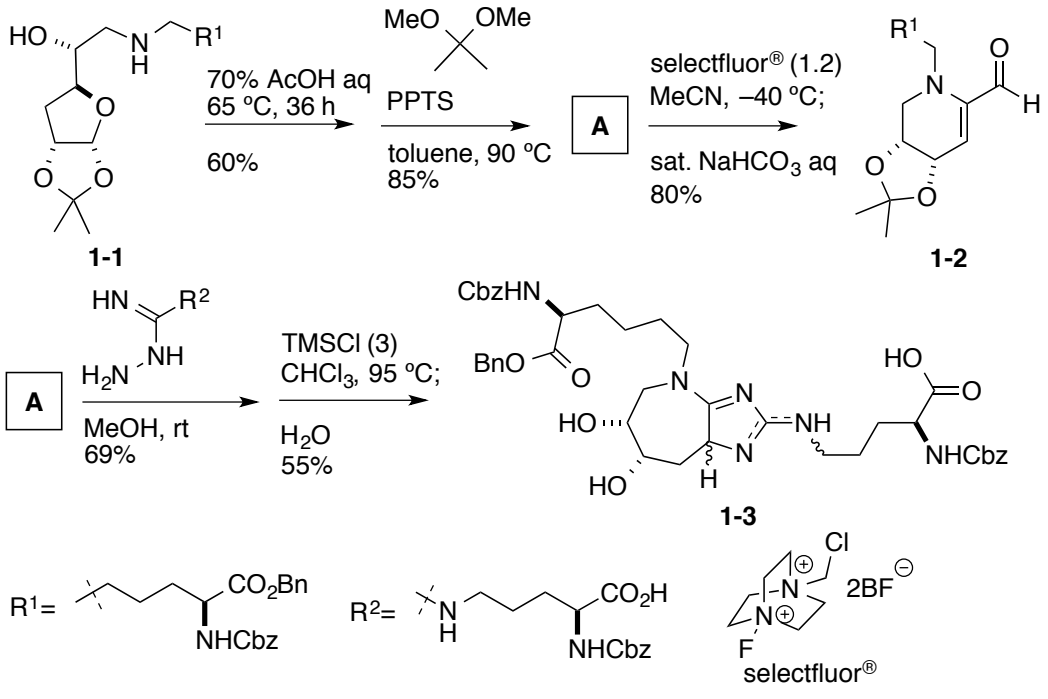
Prof. David A. Spiegel

focuses on developing new synthetic approaches that will help enable our understanding and treatment of human disease.

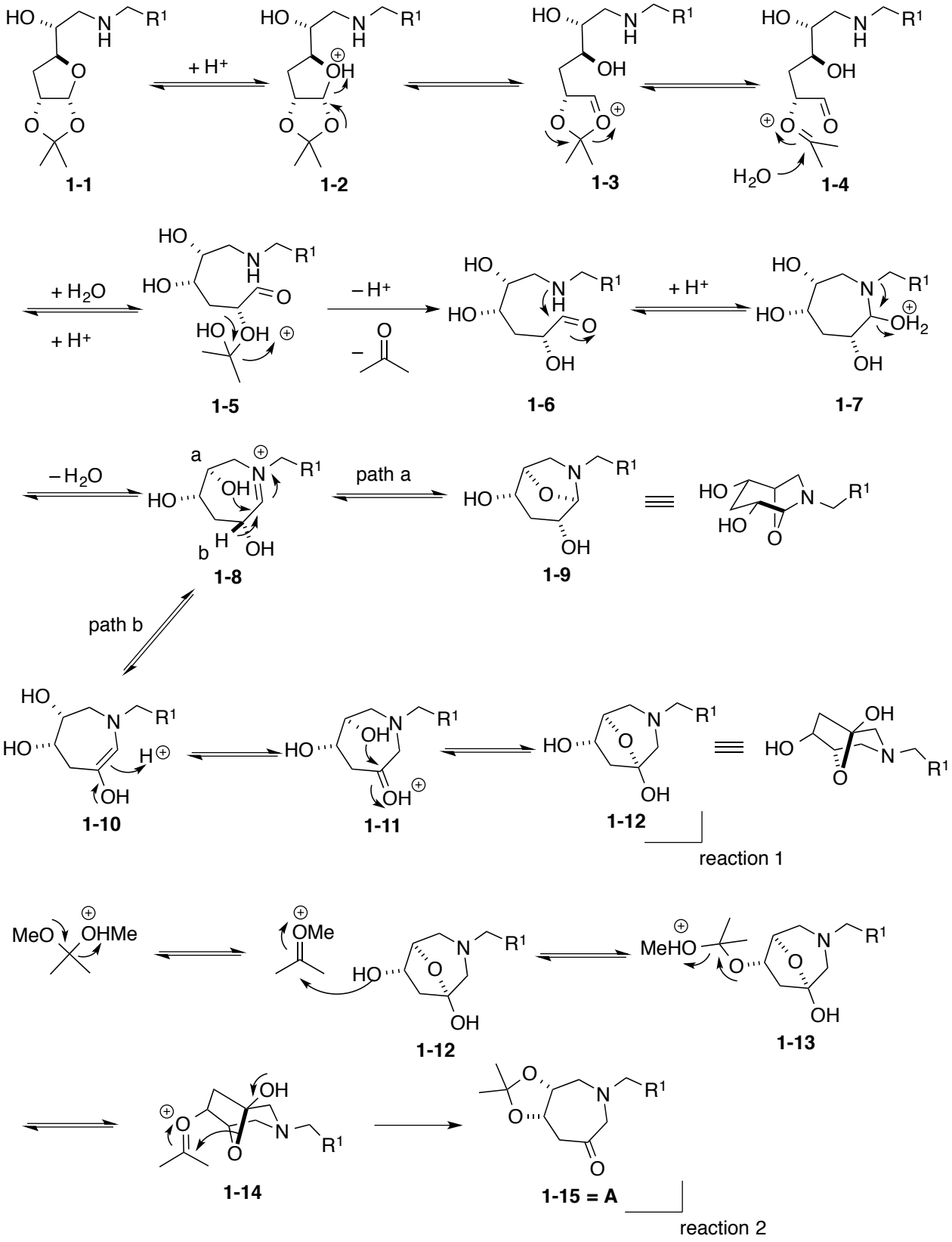
for example, Asaba-san's LS_150926 main paper

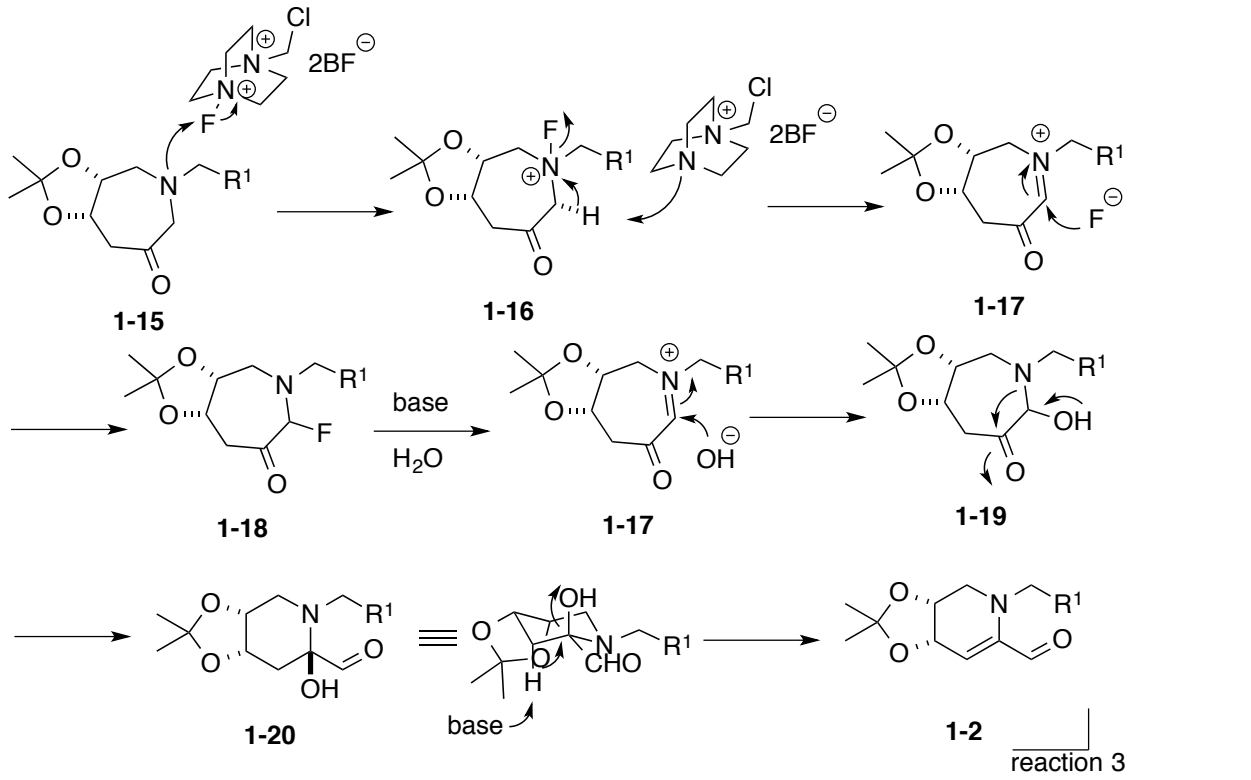
problem

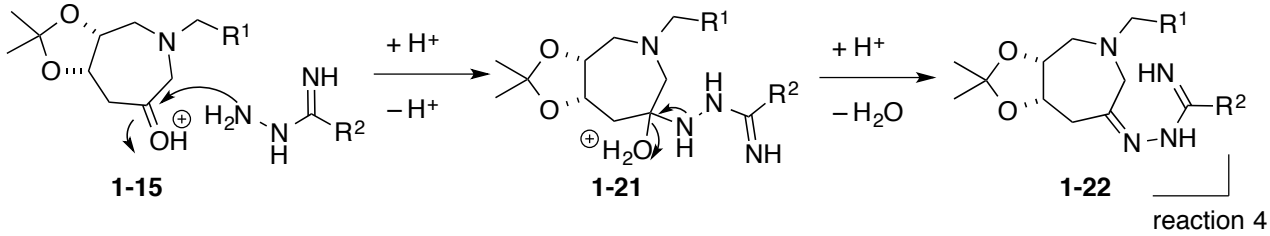
1. Please fill in the blank **A** and provide reaction mechanisms

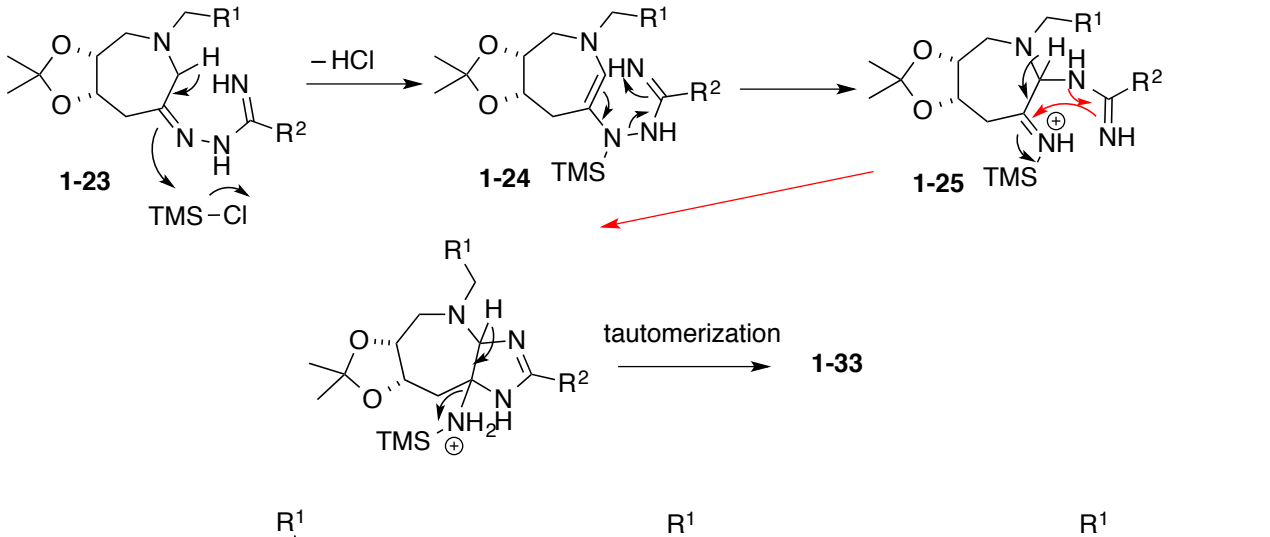


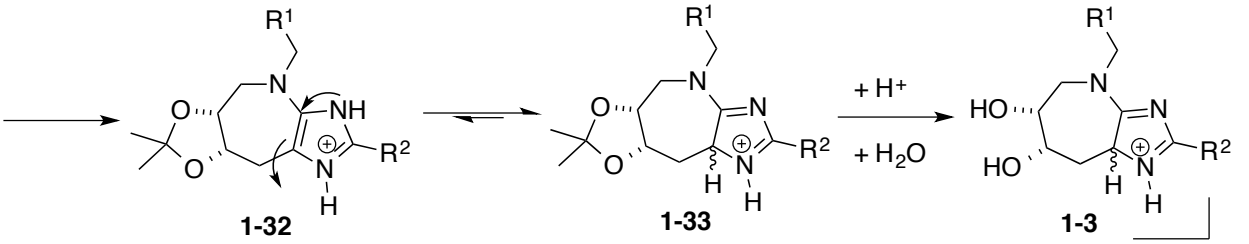
proposed mechanism




Cl
2BF
F
R1
O
N
H
1-15
1-16
1-17
base
H2O
OH
1-18
1-19
1-20
CHO
1-2
reaction 3

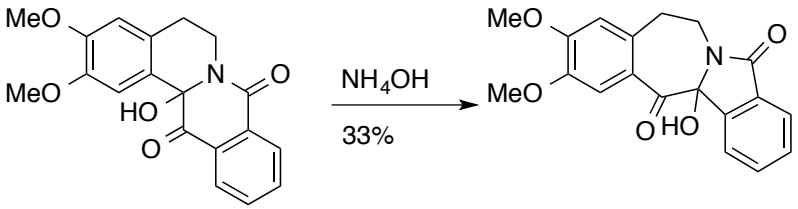

+ H+
– H+
– H2O
NH
R2
H2N
OH
1-15
1-21
1-22
reaction 4


– HCl
HN
TMS – Cl
TMS
1-23
1-24
1-25
tautomerization
1-33
NH2
1-29
1-30
1-31
– NH3
H2O



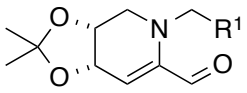
discussion for problem 1

1. similar example of ring contraction



B. E. Piko et al. *Tetrahedron Lett.* **2011**, *52*, 1981.

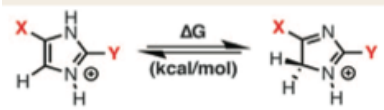
2. reactivity of **1-2**



1-2

+ various protected Arg ⟶ decomposition of **1-2** + recovery of Arg

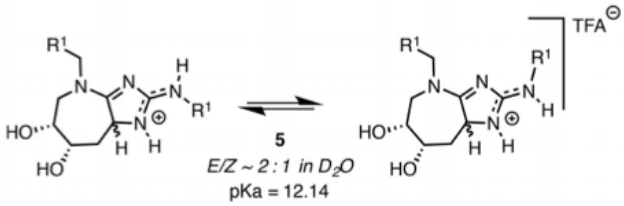
3. tautomerization states of protonated imidazoles



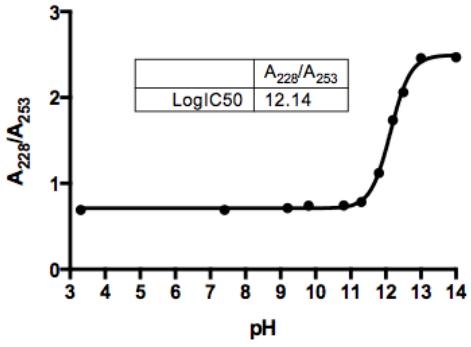
Entry	X	Y	ΔG (kcal/mol)*
1	H	H	26.7
2	H	NHMe	10.5
3	NMe_2	H	-1.5
4	NMe_2	NHMe	-14.8

*All calculations were performed using the Gaussian 09 program suite using the CBS-QB3 method. All calculations implemented a continuum model to account for the effects of water solvent.

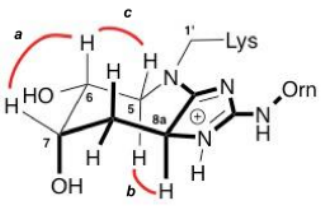
4. *E/Z* isomerization in D_2O



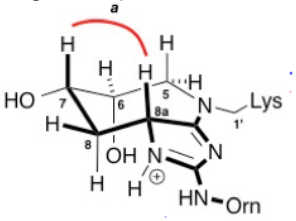
glucosepane - pKa



5. observed NOE for synthesized glucosepane



major 8a-(*S*) isomer



minor 8a-(*R*) isomer

2. Reißig's work related to 1,2-oxazines

Prof. Hans-Ulrich Reißig (Freie univerisität Berlin):

research focus is to design new methods to synthesis of natural products

Total synthetic works by Reißig:

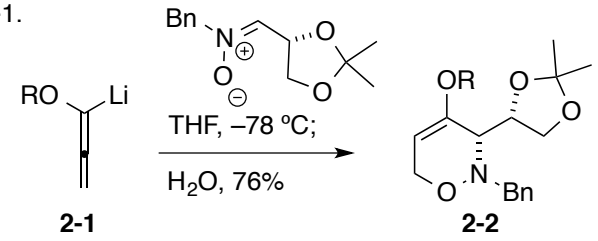
- formal total synthesis of strychnine *Angew. Chem. Int. Ed.* **2010**, *49*, 8021. (for detail, see 110625_LS_ Kengo_Masuda)
- Total synthesis of gamma-rubromycin *Angew. Chem. Int. Ed.* **2014**, *53*, 4332.

Problem 2:
taken from series of research related to 1,2-oxazine synthesis
Synlett **2002**, 817.
Synlett **2005**, 1152.
Angew. Chem. Int. Ed. **2005**, *44*, 6227. –> **problem**
Eur. J. Org. Chem. **2005**, 1003.
Synlett **2006**, 3498.
Synlett **2008**, 2965.
Angew. Chem. Int. Ed. **2009**, *48*, 3169.
Acc. Chem. Res. **2009**, *42*, 45. (review)

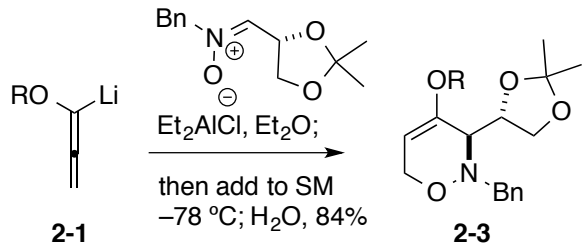
Problem

2. Please provide reaction mechanisms and explain selectivities

2-1.

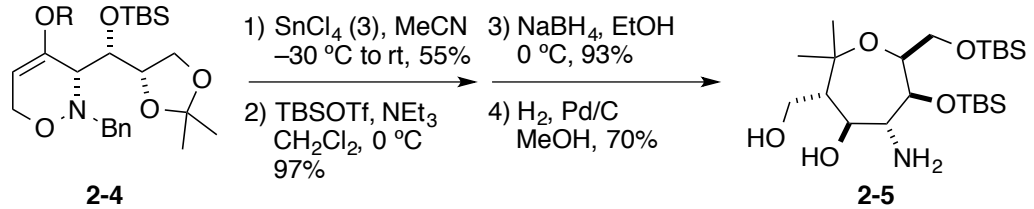


2-1 **2-2**

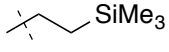


2-1 **2-3**

2-2.

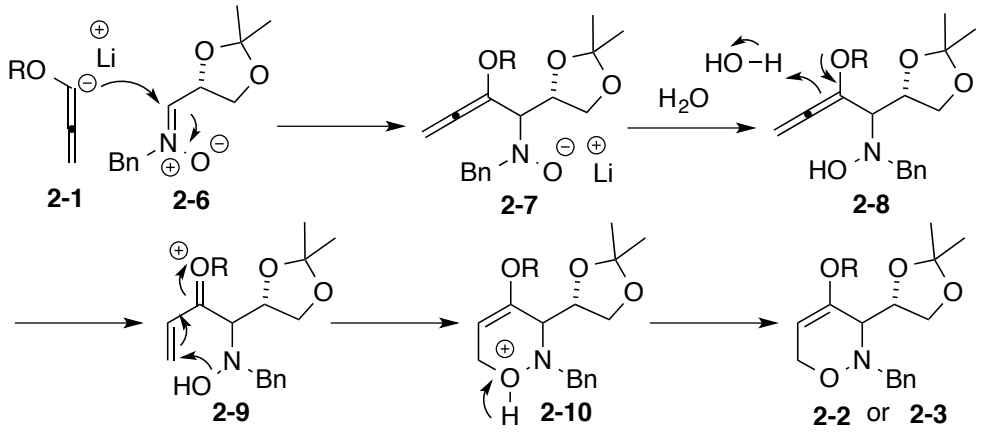


2-4 **2-5**

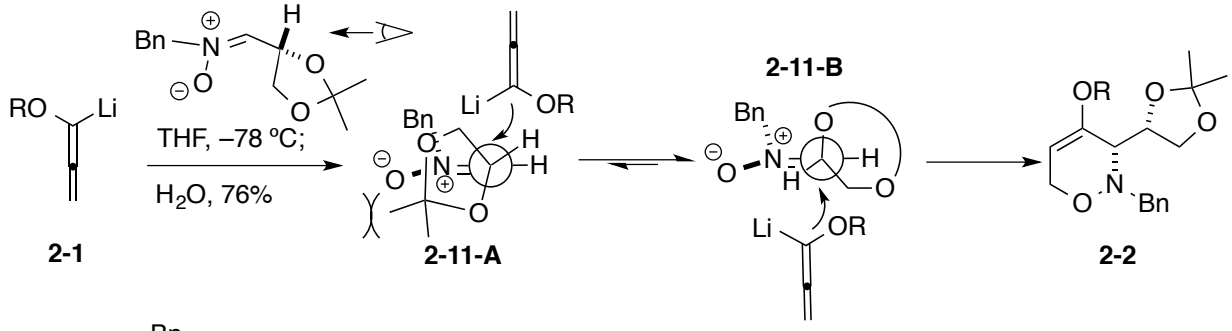
R = 

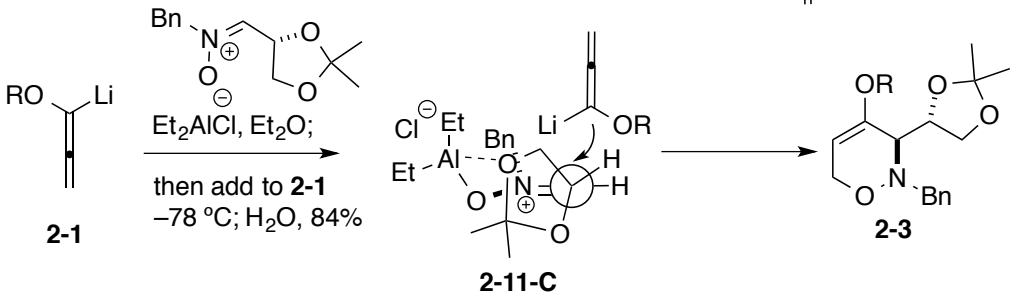
proposed mechanism

2-1.

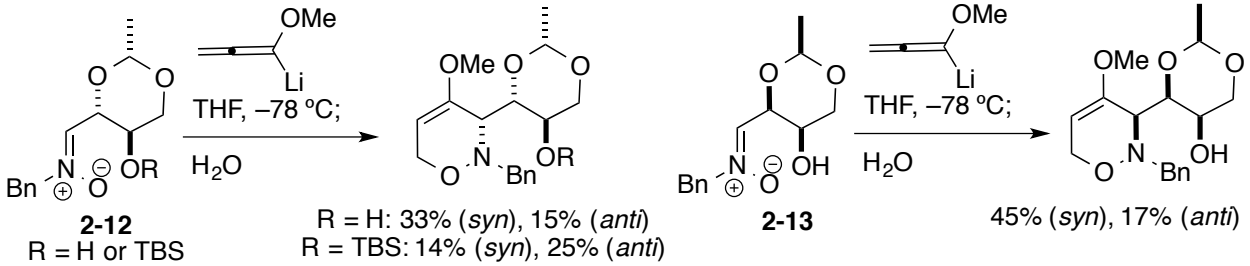


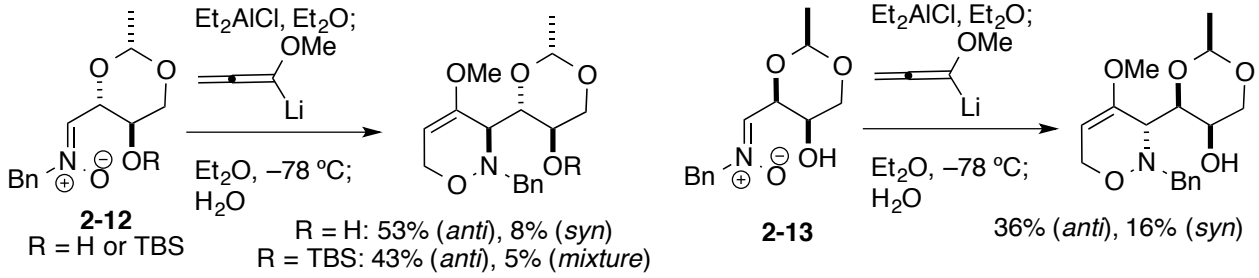
explanation of selectivity





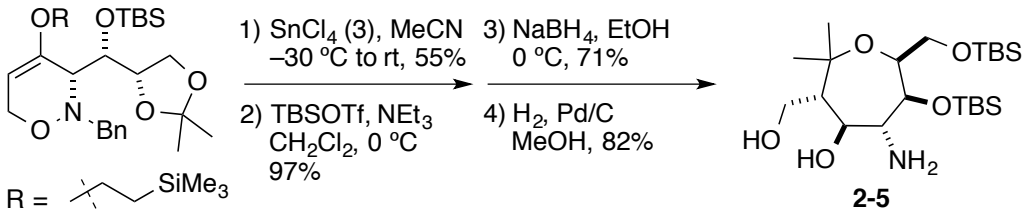
example of other substrate:





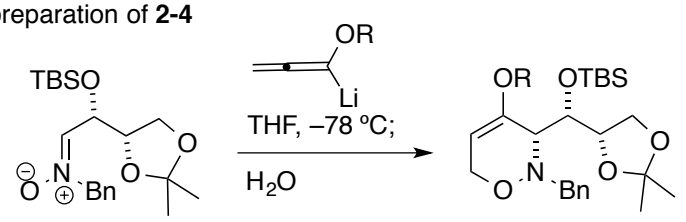
Eur. J. Org. Chem. **2005**, 1003.

2-2.



2-4 **2-5**

preparation of **2-4**



2-14 **2-4**

71% (*syn/anti* > 97:3)

proposed mechanism