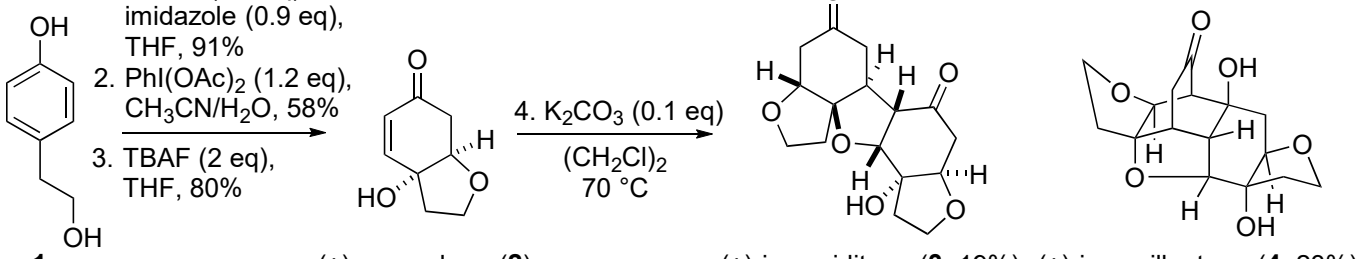
Problem Session No.2 9th, July, 2016 Kai Kitamura

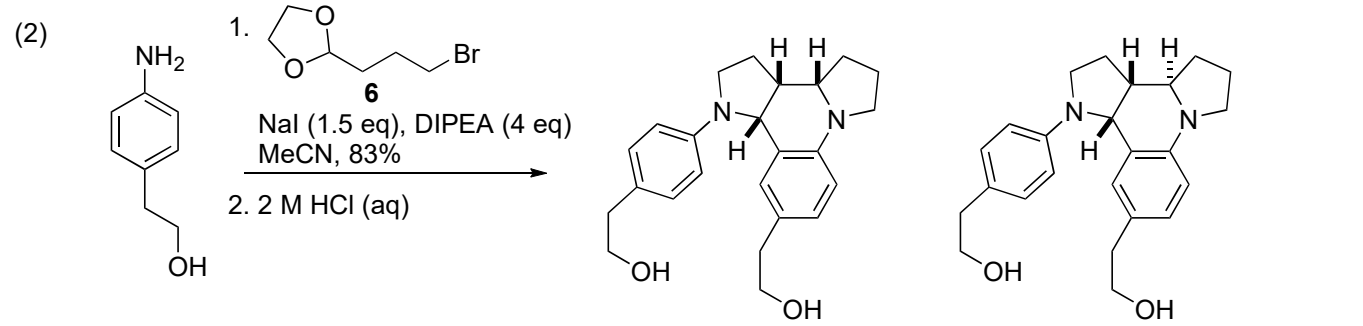
Please fill in the blank [**A**] and provide mechanisms of the reactions (1)-(4).

(1)



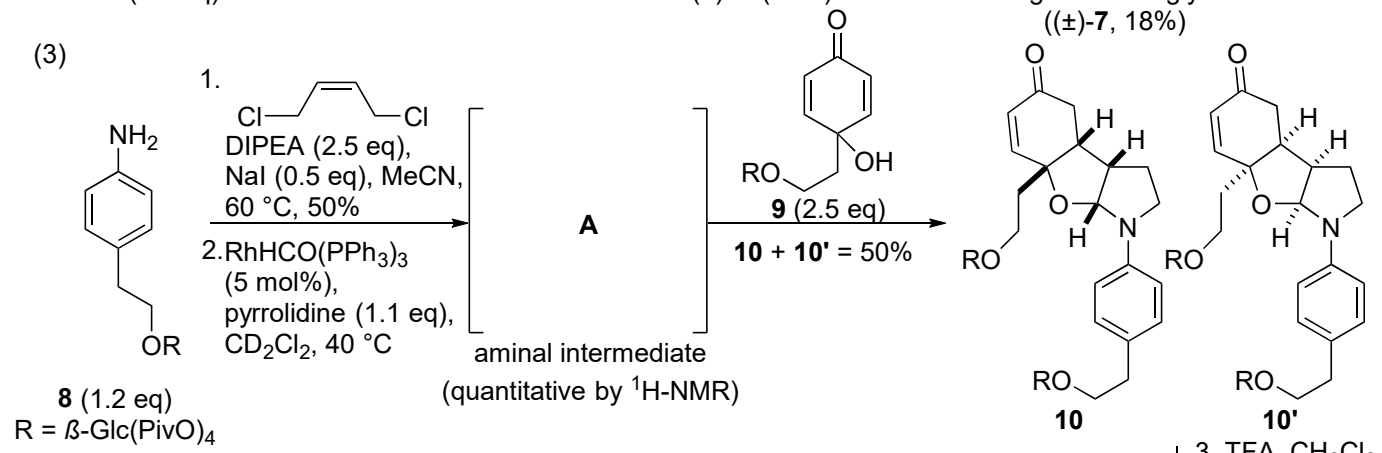
1 (±)-rengyolone (**2**) (±)-incarviditone (**3**, 19%) (±)-incarvilleatone (**4**, 23%)

(2)



5 (2.5 eq) (±)-**7'** (32%) incargranine B aglycone ((±)-**7**, 18%)

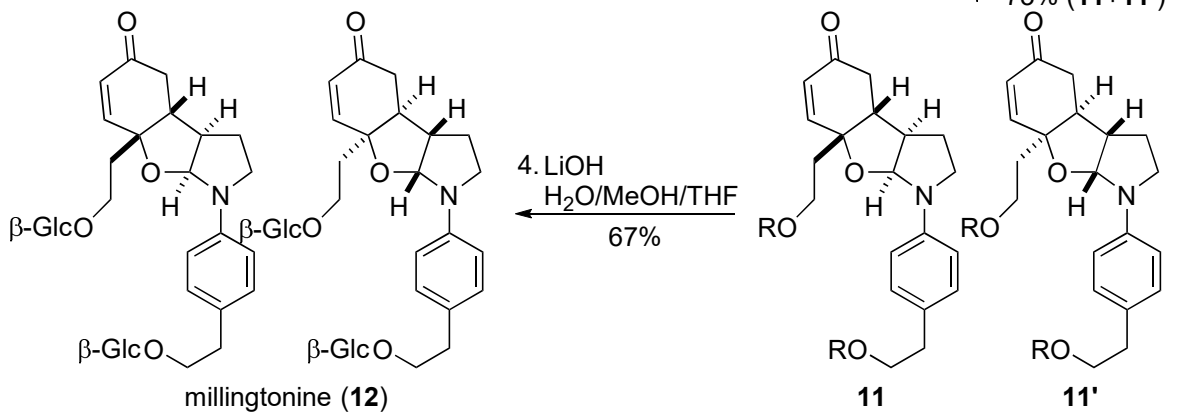
(3)



8 (1.2 eq)
R = ß-Glc(PivO)4

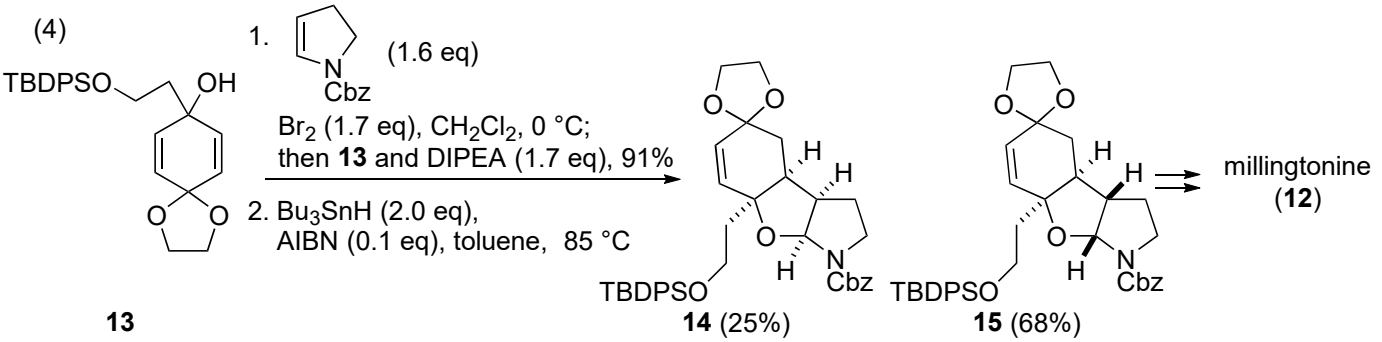
10 **10'**

3. TFA, CH_2Cl_2
73% (**11**+**11'**)



millingtonine (**12**) **11** **11'**

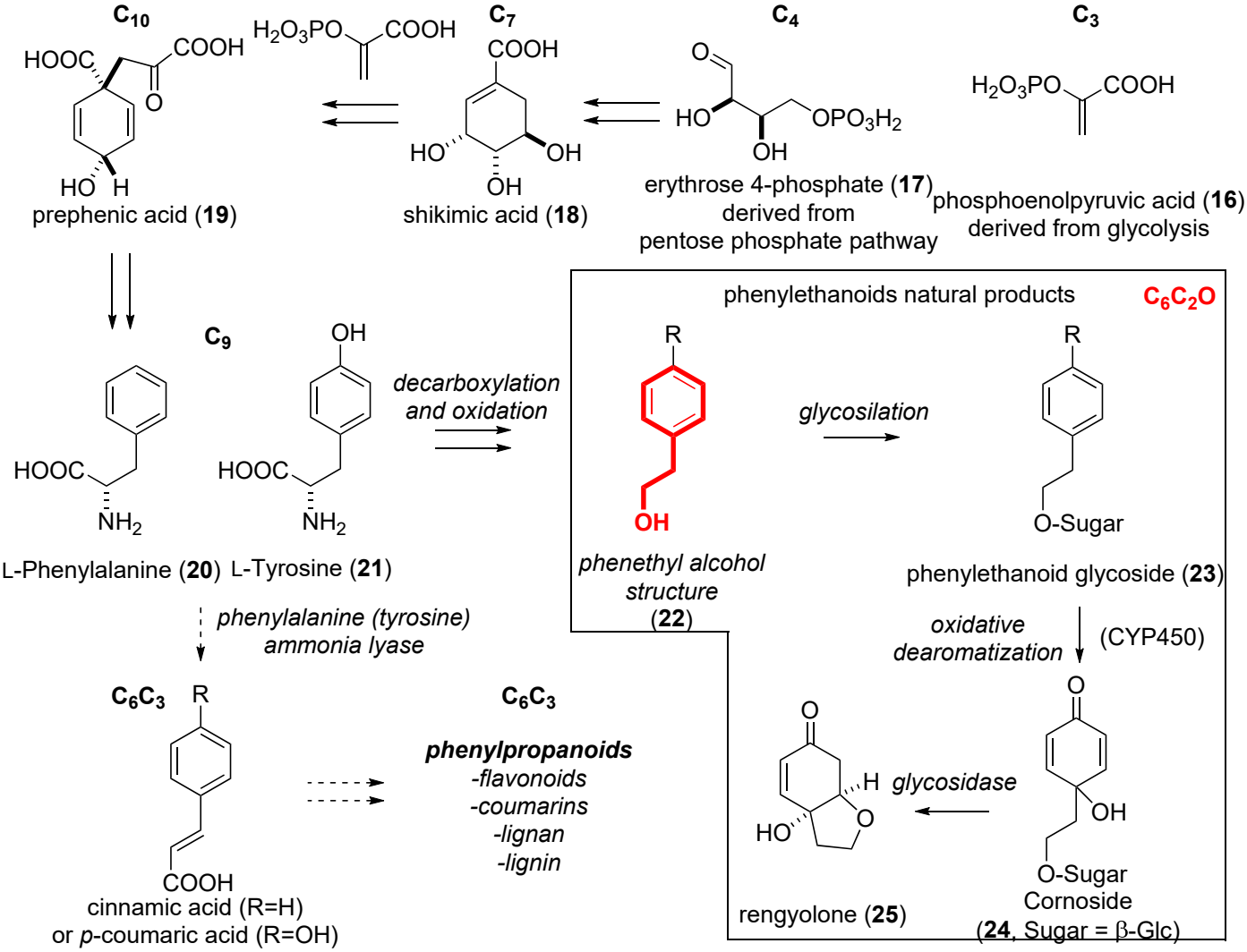
(4)



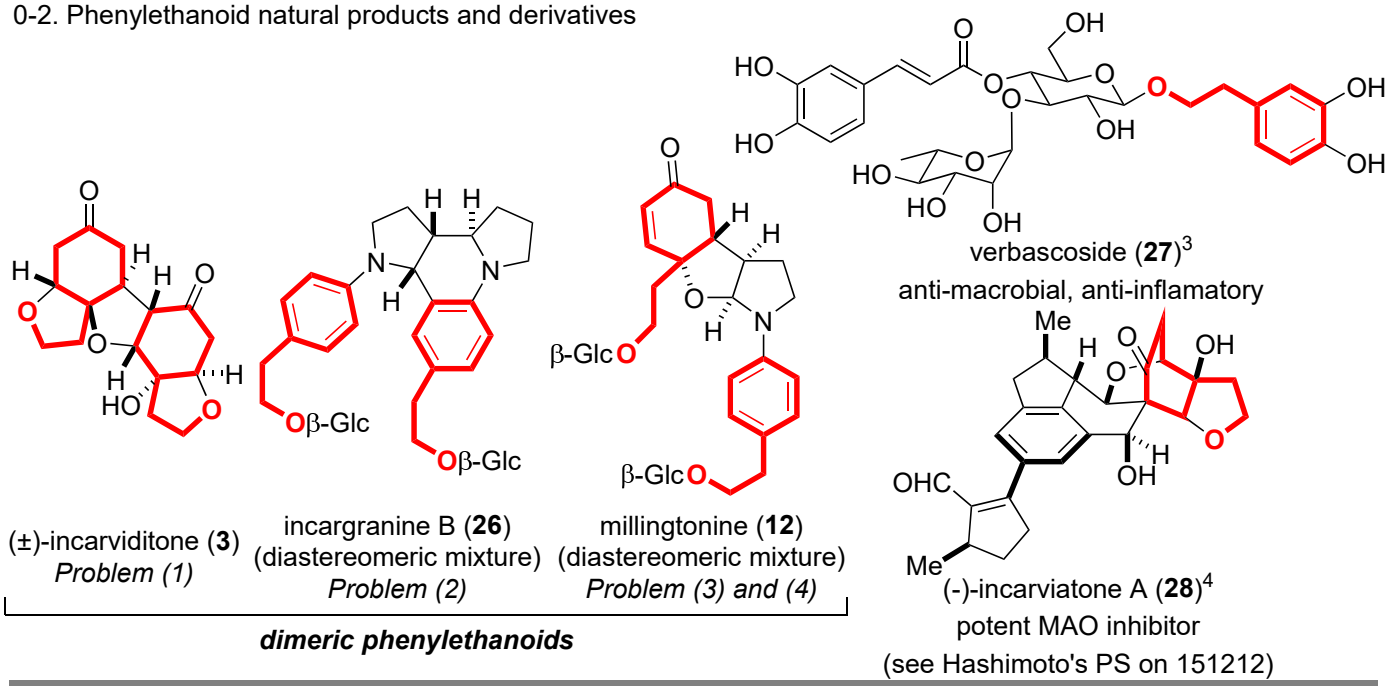
13 **14** (25%) **15** (68%)

Biomimetic Total Synthesis of Dimeric Phenylethanoids

0-1. Biosynthesis of phenylethanoids[1, 2]



0-2. Phenylethanoid natural products and derivatives

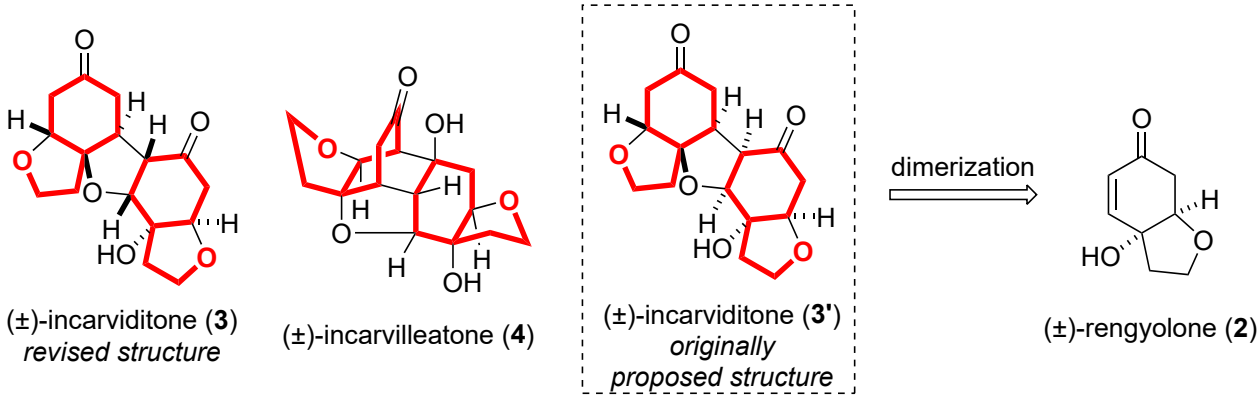


1. Inoue, K *YAKUGAKU ZASSHI* **2005**, *125*, 31.
2. Jiménez, C and Riguerab, R *Nat. Prod. Rep.* **1994**, *11*, 591
3. Alipieva, K; Korkina, L; Orhan, IE; Georgiev MI *Biotechnol. Adv.* **2014**, *32*, 1065.
4. Hong, B; Li, C; Wang, Z; Chen, J; Li, H; Lei, X *J. Am. Chem. Soc.* 2015, *137*, 11946.

Problem 1. Total Synthesis of Incarvilleatone and Incarviditone
(5. Brown, PD; Willis, AC; Sherburn, MS and Lawrence, AL *Org. Lett.* **2012**, *14*, 4537).

1-1. Introduction

Biosynthetic hypothesis:



(±)-incarviditone (**3**) *revised structure*

(±)-incarvilleatone (**4**)

(±)-incarviditone (**3'**) *originally proposed structure*

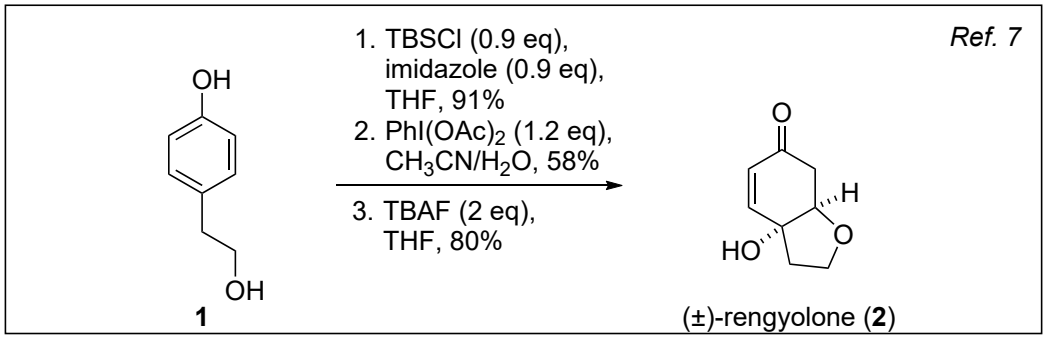
(±)-rengyolone (**2**)

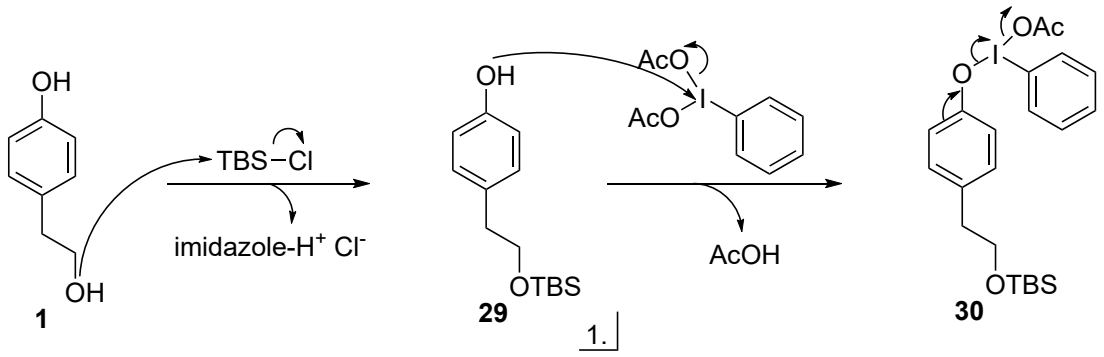
Isolation[6]**:** In 2009, from chinese plant (*Incarvillea delavayi.*), with (±)-rengyolone (**2**).

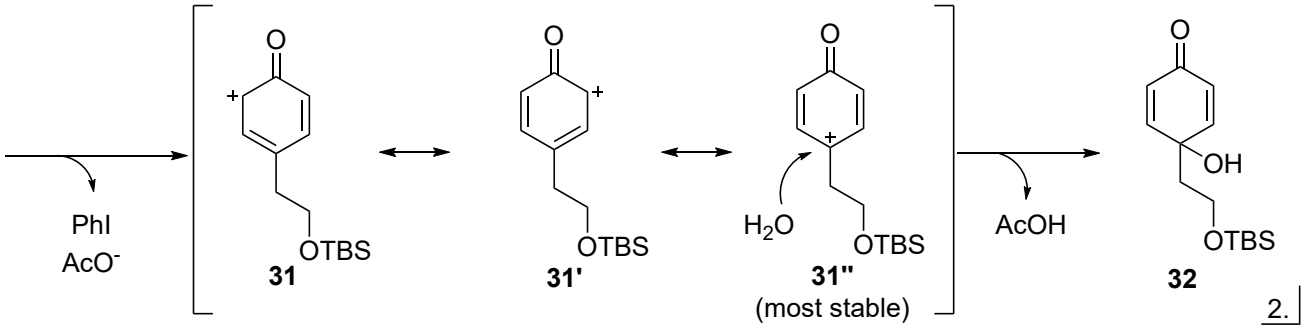
Biological Activity[6]: Cytotoxicity against HL-60 and 6T-CEM cell line. (GI_{50} = 48 μM and 72 μM, respectively).

Another total synthesis: By Tang, Y *et al* (Ref. 9 in page 5)

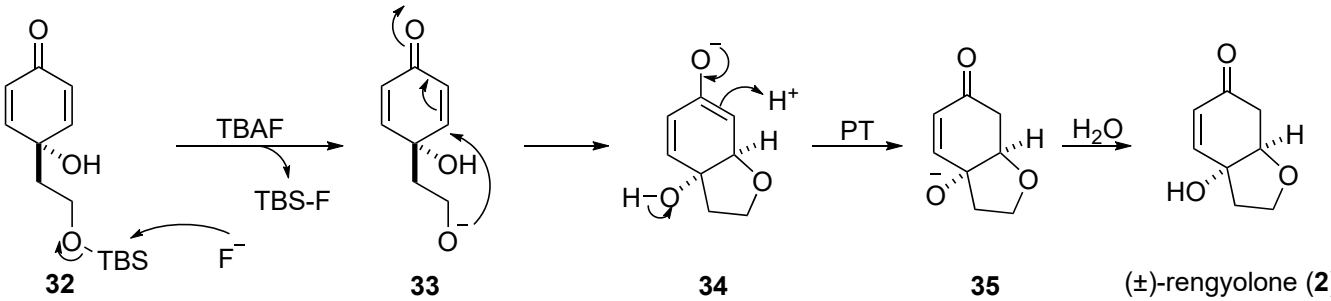
1-2. Reaction mechanisms





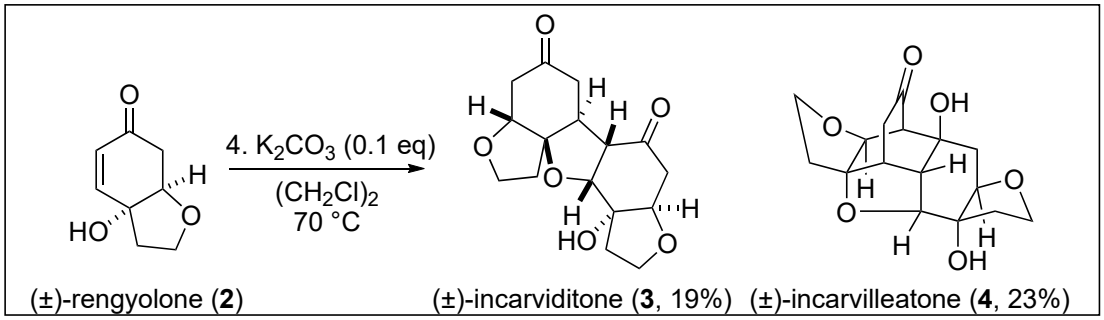


6. Chen, Y-Q; Shen, Y-H; Su, Y-Q; Kong, L-Y and Zhang, W-D *Chem. Biodiversity* **2009**, *6*, 779.
7. Felpin, F-X *Tetrahedron Lett.* **2007**, *48*, 409.



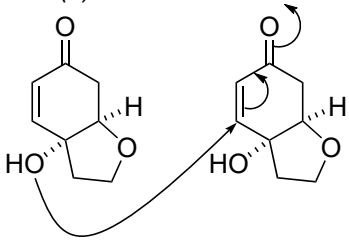
32 (racemic) **33** **34** **35** (±)-rengyolone (**2**)

3.



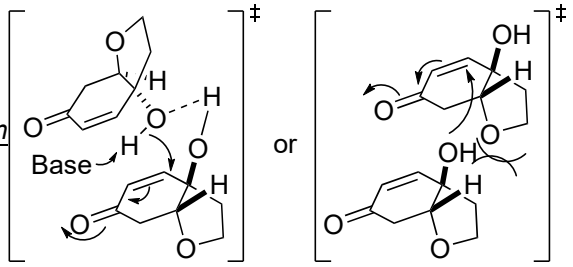
(±)-rengyolone (**2**) (±)-incarviditone (**3**, 19%) (±)-incarvilleatone (**4**, 23%)

Toward (±)-incarviditone



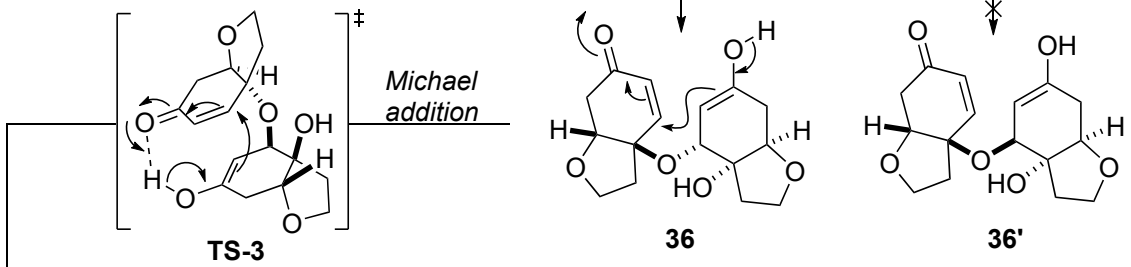
(±)-rengyolone (**2**)

homochiral oxa-Michael addition

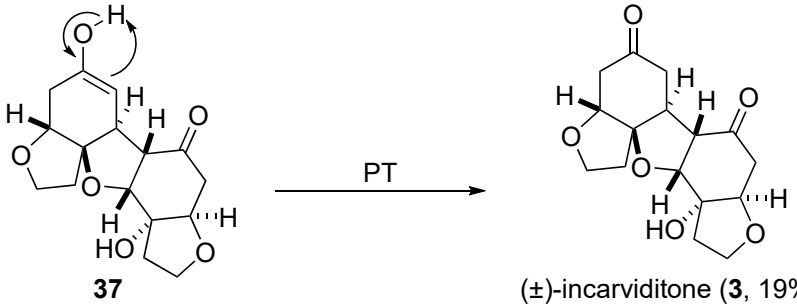


TS-1 *convex/convex transition state (favored)*

TS-2 *convex/concave transition state (disfavored)*

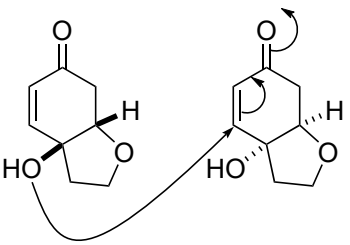


TS-3 **36** **36'**



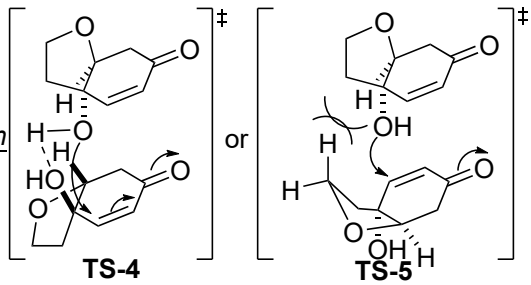
37 (±)-incarviditone (**3**, 19%)

Toward (±)-incarvilleatone



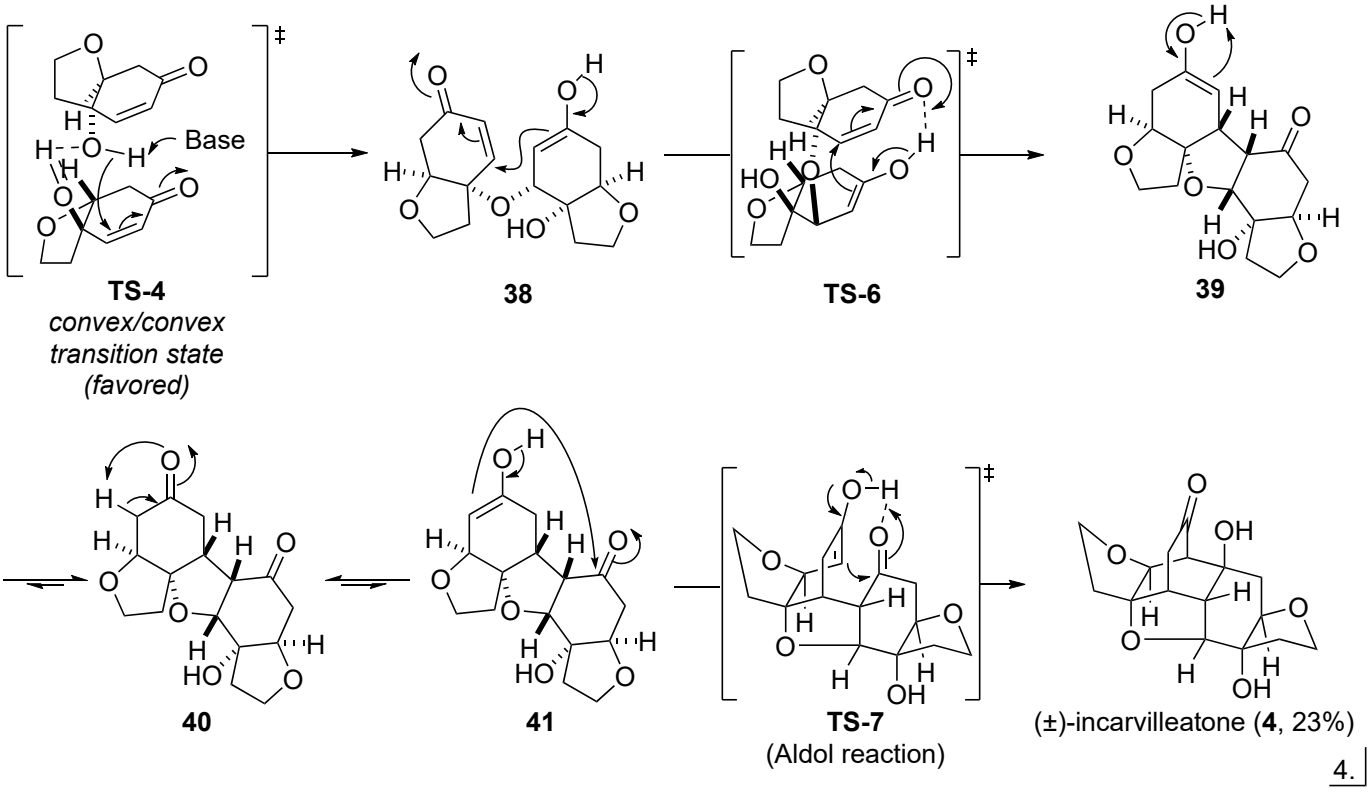
(±)-rengyolone (**2**)

heterochiral oxa-Michael addition



TS-4 *convex/convex transition state (favored)*

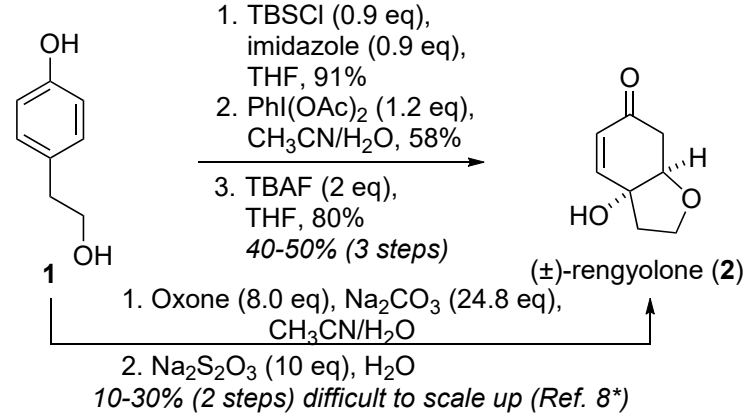
TS-5 *convex/concave transition state (disfavored)*



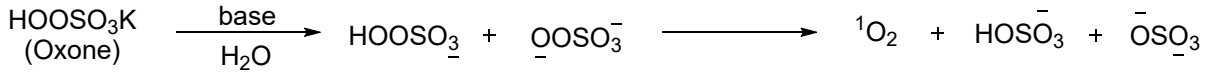
4.

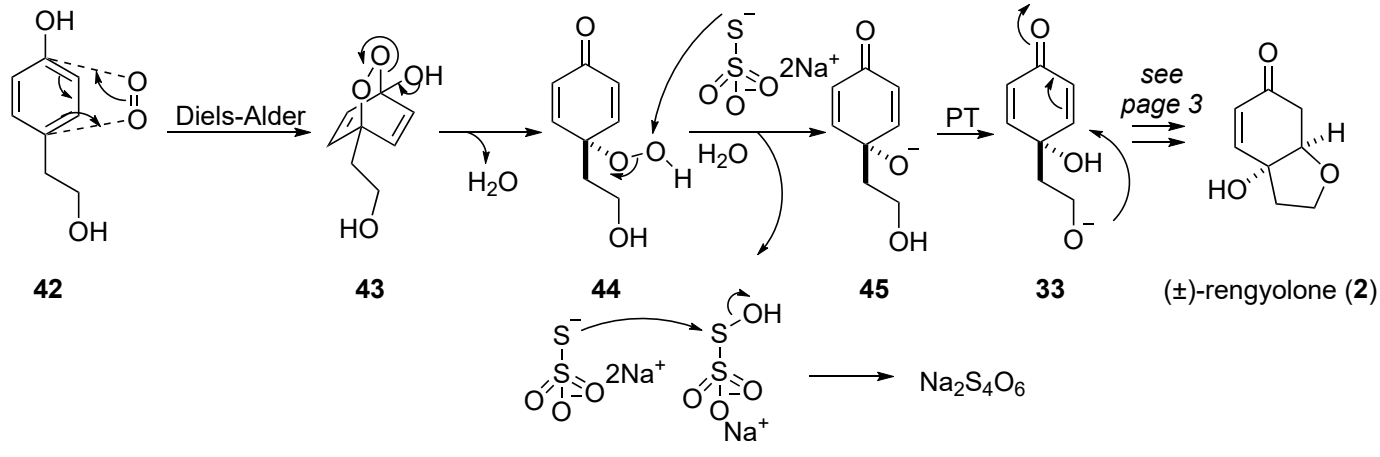
1-3. Discussion

1-3-1. Another method[8] for preparation of (±)-rengyolone (**2**)



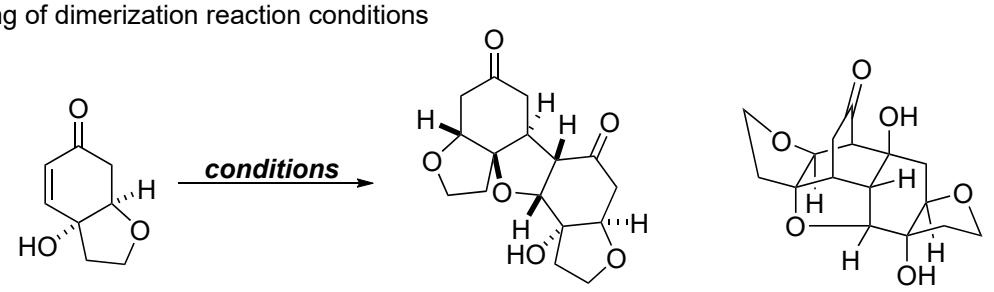
*proposed mechanism





8. You, Z; Hoveyda, A and Snapper, ML *Angew. Chem. Int. Ed.* **2009**, *48*, 547.

1-3-2. Screening of dimerization reaction conditions



(±)-rengyolone (**2**) (±)-incarviditone (**3**) (±)-incarvilleatone (**4**)

entry*	base	solvent	temp	**3**	**4**
1	K_2CO_3 (0.1 eq)	$(CH_2Cl)_2$	70 °C	19%	23%
2	DABCO (excess)	dioxane/H_2O	rt	NR	NR
3	DBU (excess)	CH_2Cl_2	rt	NR	NR
4	*t*-BuOK	THF	rt	15%	17%
5	NaHMDS (2.0 eq)	THF	rt	0%	7%
6	NaH (2.0 eq)	THF	rt	0%	0%
7	NaH (2.0 eq)	CH_2Cl_2	rt	25%	30%
8	NaH (1.0 eq)	CH_2Cl_2	rt	38%	40%
9	NaH (0.5 eq)	CH_2Cl_2	rt	30%	35%

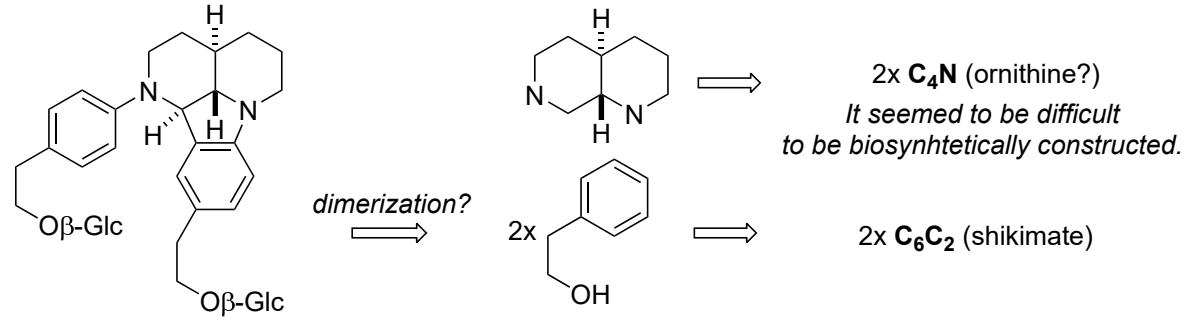
*For entry 1 and 2-9, see Ref. 5 and 9, respectively.
**Dimerizations using acid catalysis were unsuccessful. (data not shown.)

Hydrogen bond or metal chelation seem to be important.

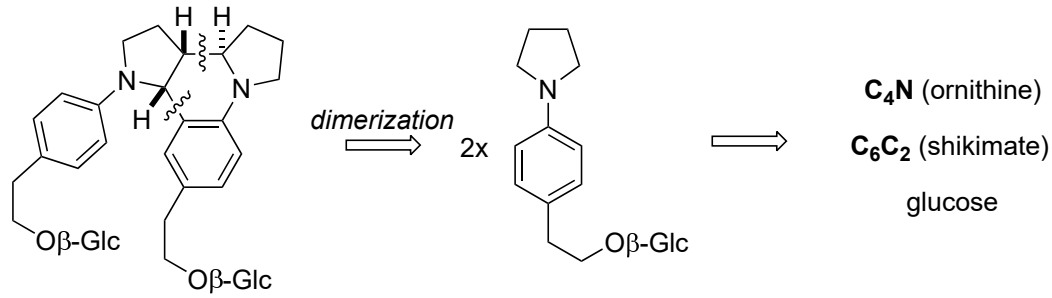
Problem 2. Total Synthesis and Structural Revision of the Alkaloid Incargranine B
(10. Brown, PD; Willis, AC; Sherburn, MS and Lawrence, AL *Angew. Chem. Int. Ed.* **2013**, *52*, 13273).

2-1. Introduction

Biosynthetic hypothesis:



Incargranine B (**46**)
originally proposed structure (Ref. 11)
(diastereomeric mixture)

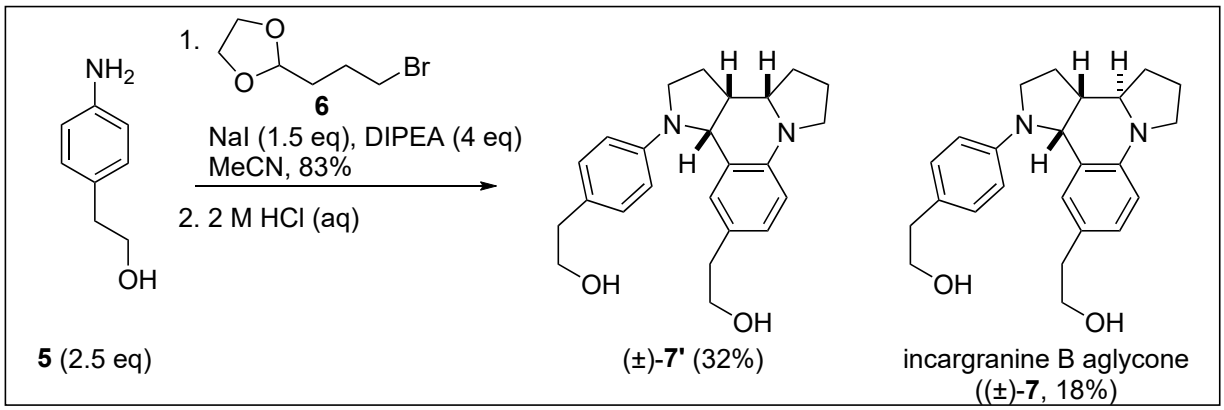


Incargranine B (**47**)
reviced structure
(diastereomeric mixture)

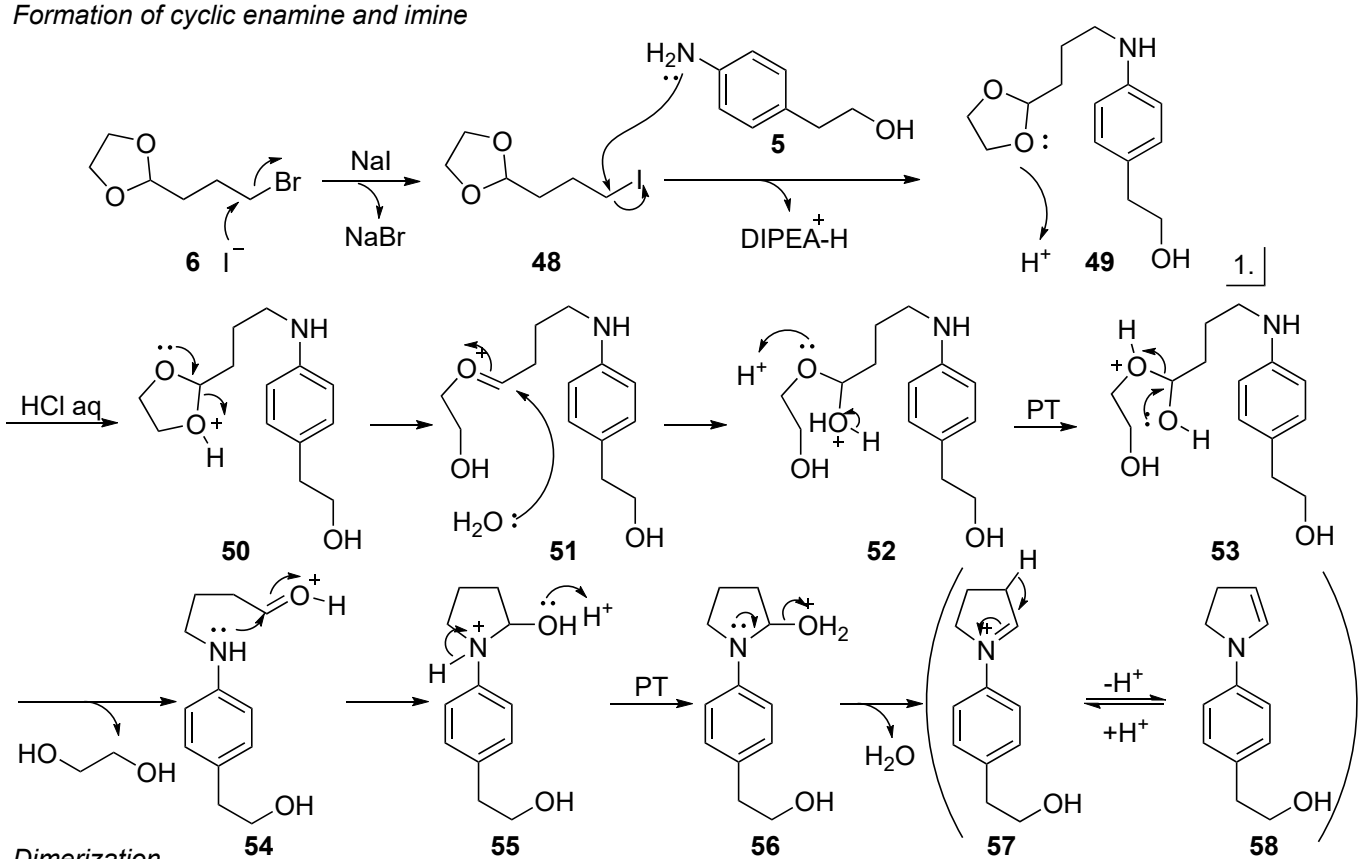
Isolation[11]**:** In 2010, from a chinese plant (*Incarvillea mairei var. grandiflora*).
Biological activity: Not reported.
Another total synthesis[12]: By Liu, X-Y *et al* in 2016. (aglycone)

9. Xhao, K; Cheng, G-J; Yang, H; Shang, H; Zhang, X; Wu, Y-D and Tang, Y *Org. Lett* **2012**, *14*, 4878.
11. Shen, Y-H; Su, Y-Q; Tian, J-M; Lin, S; Li, H-L; Tang, J and Zhang, W-D *Helv. Chim. Acta* **2010**, *93*, 2393.
12. Ma, CL; Li, X-H; Yu, X-L; Zhu, X-L; Hu, Y-Z; Dong, X-W; Tan, B; and Liu X-Y *Org. Chem. Front.* **2016**, *3*, 324.

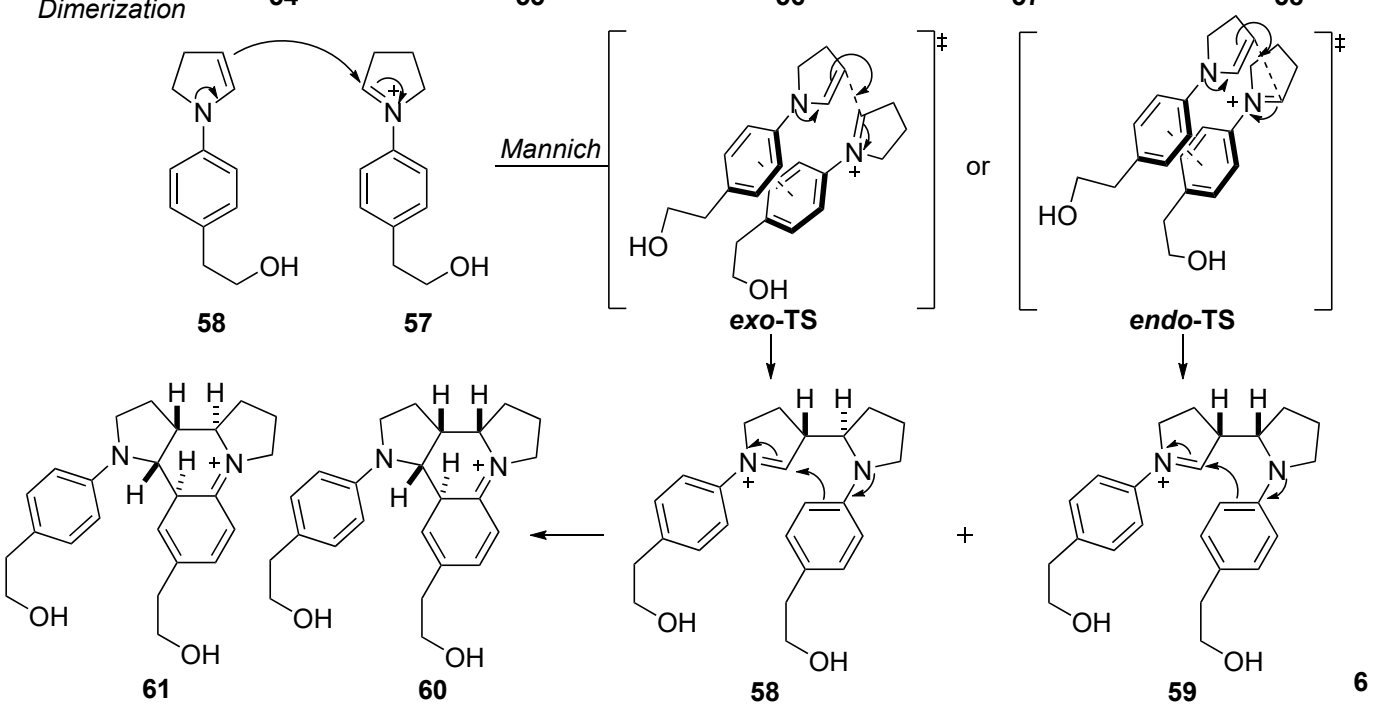
2-2. Reaction mechanisms

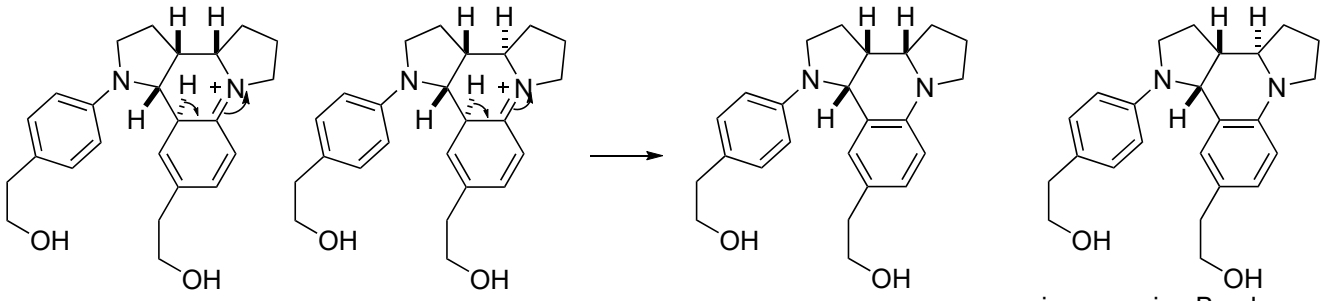


Formation of cyclic enamine and imine



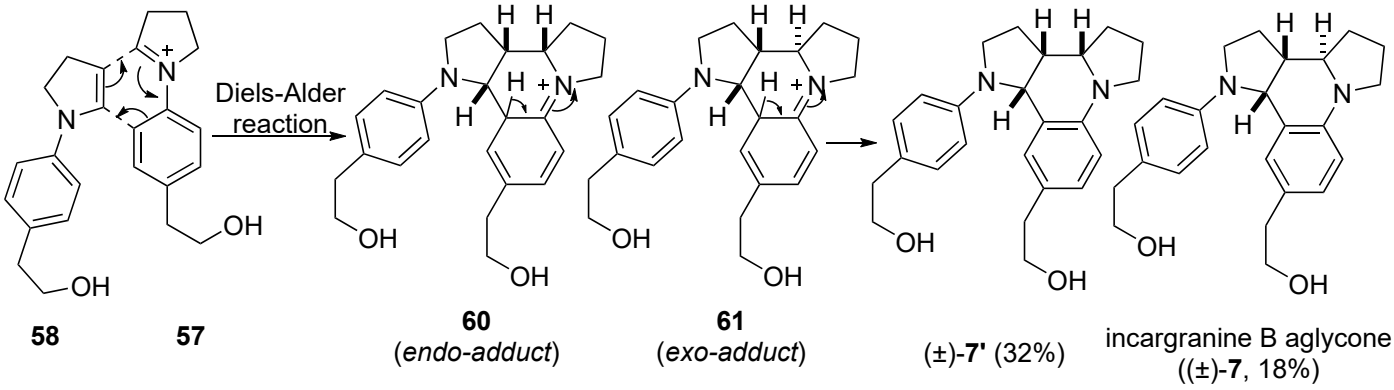
Dimerization





2-3. Discussion

2-3-1. Another possibility of the dimerization mechanism

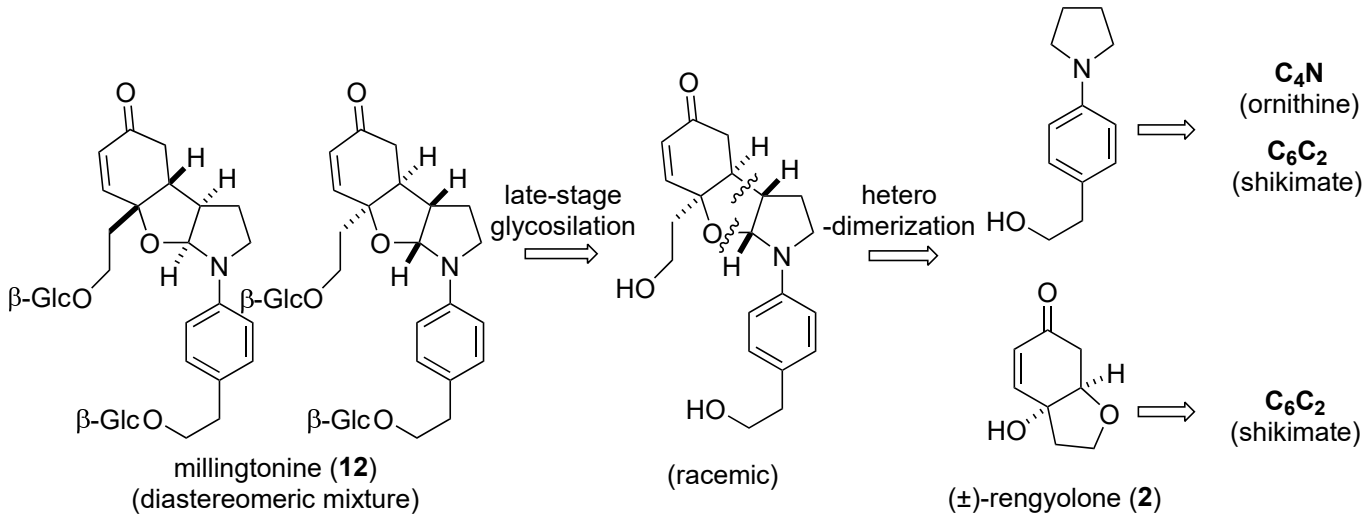


Problem 3. Total Synthesis of Millingtonine

(13. Brown, PD and Lawrence, AL *Angew. Chem. Int. Ed.* **2016**, *Early View*)

3-1. Introduction

Biosynthetic hypothesis



Isolation[13]**:** In 1996, from indian cork tree (*Millingtonia hortensis*).

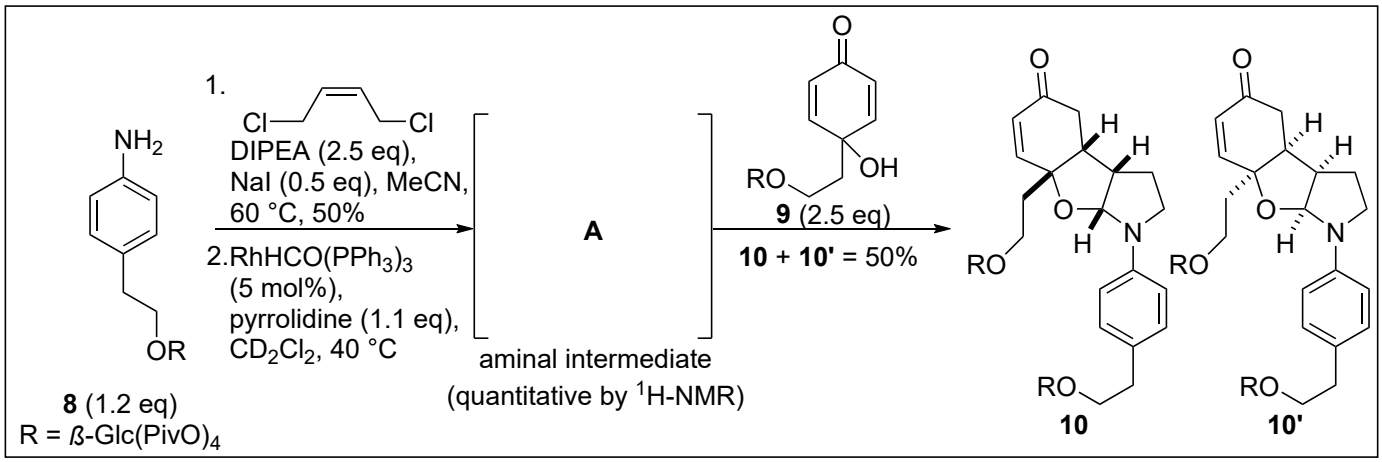
Biological activity: Not reported.

Another total synthesis[15]: By Wegner J, Ley SV, Baxendale IR *et al* in 2011. (*Problem 4, see page 11)*)

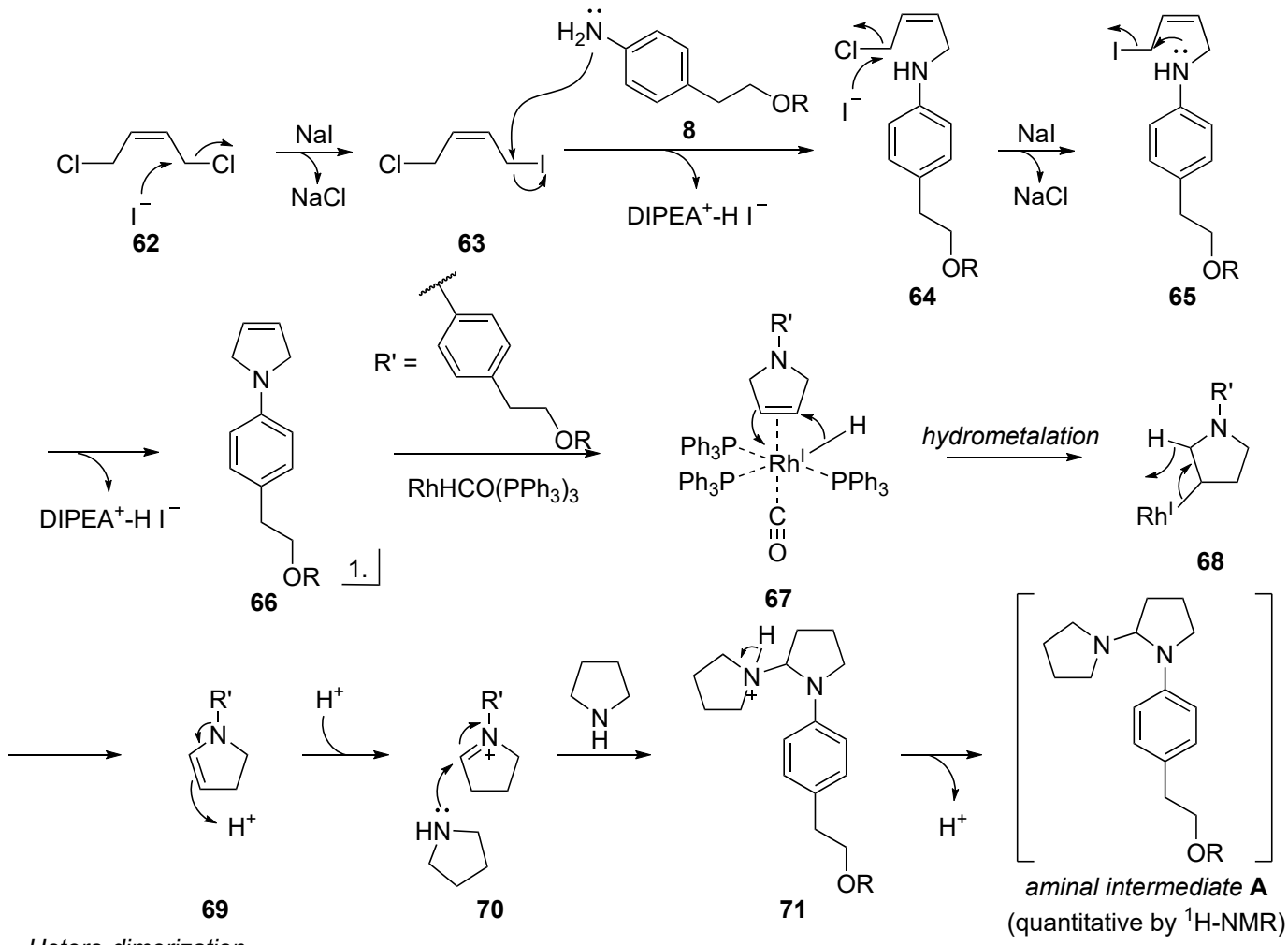
Steps and yield : 7 steps/7% (longest linear, total 10 steps)

14. Hase, T; Ohtani, K; Kasai, R; Yamasaki, K and Picheansoonthon, C *Phytochemistry* **1996**, *41*, 317.

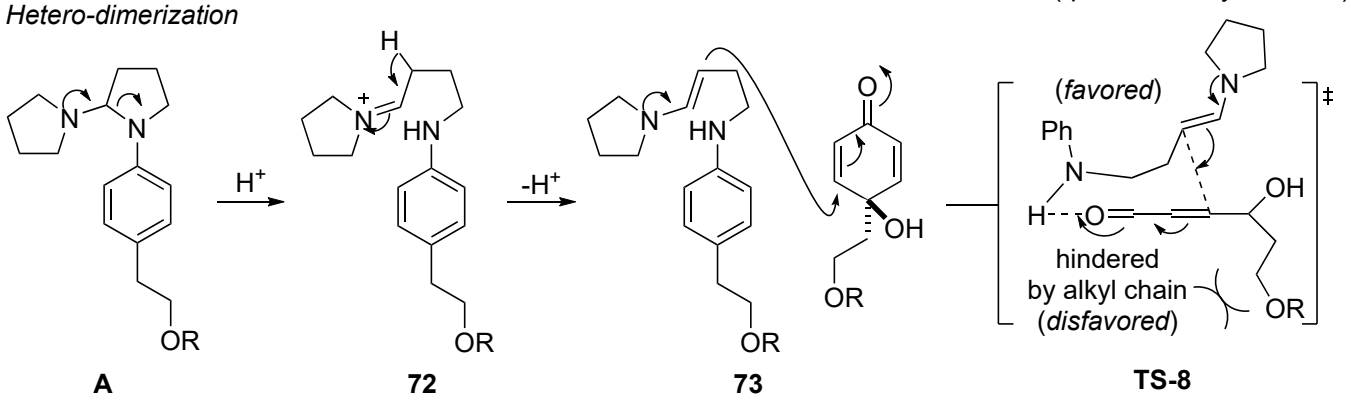
3-2. Reaction mechanisms



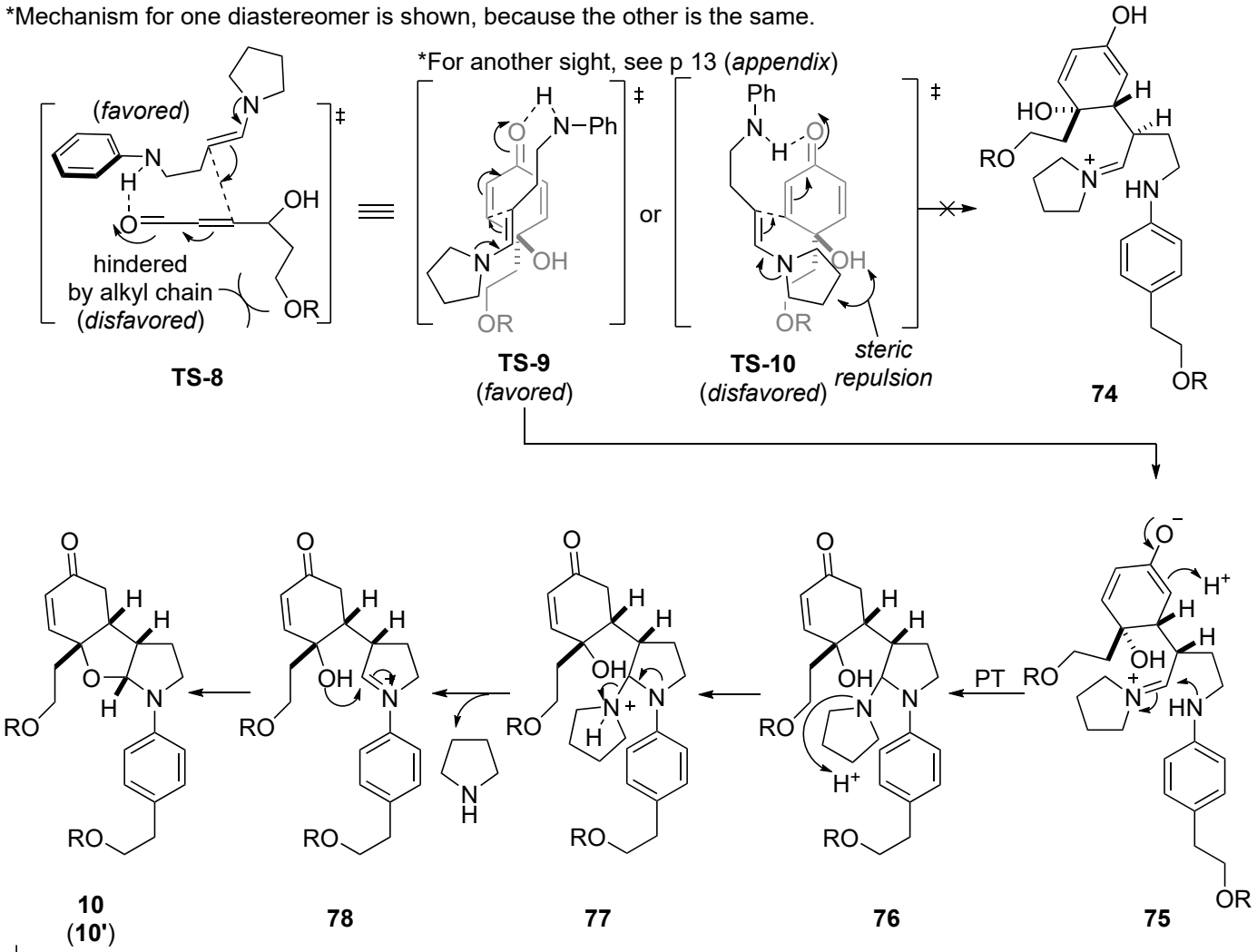
Formation of aminal intermediate



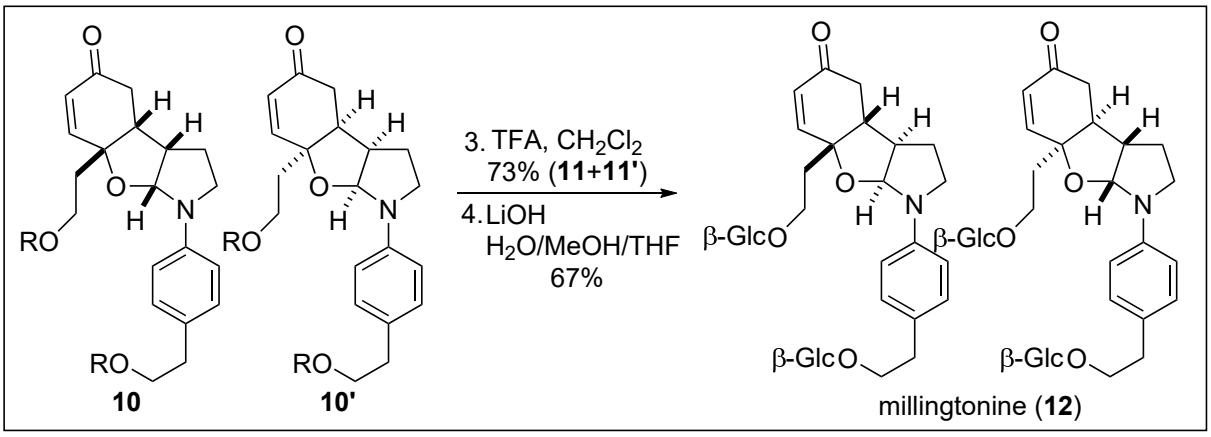
Hetero-dimerization



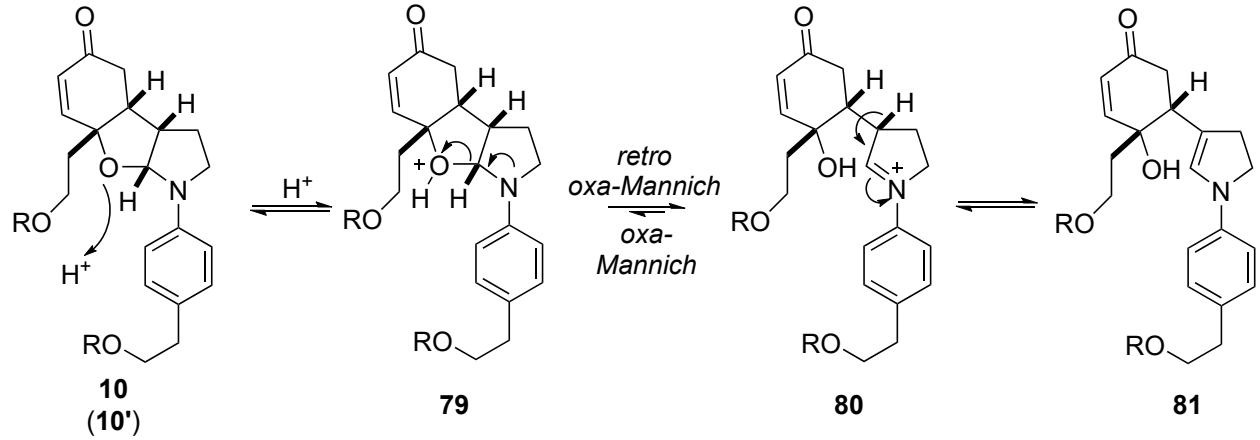
*Mechanism for one diastereomer is shown, because the other is the same.



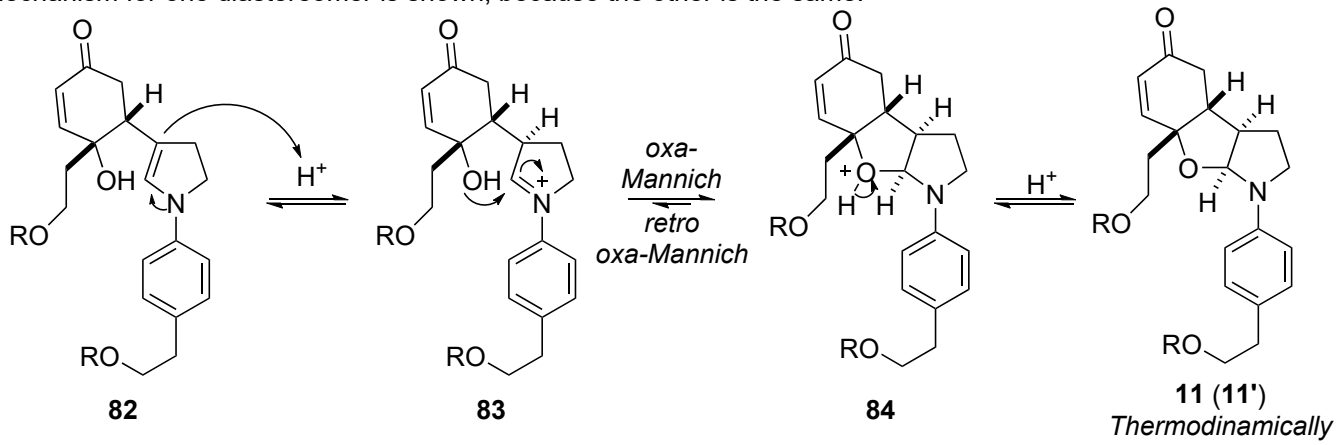
2.



Acid-catalysed isomerization



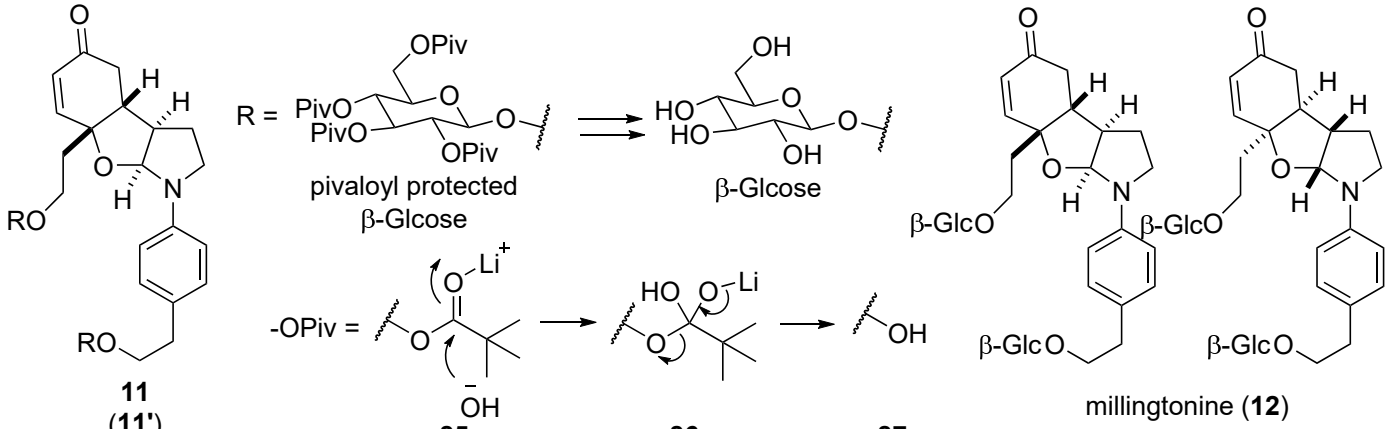
*Mechanism for one diastereomer is shown, because the other is the same.



82 **83** **84** **11** (**11'**)

Thermodinamically stable structure
**see discussion*

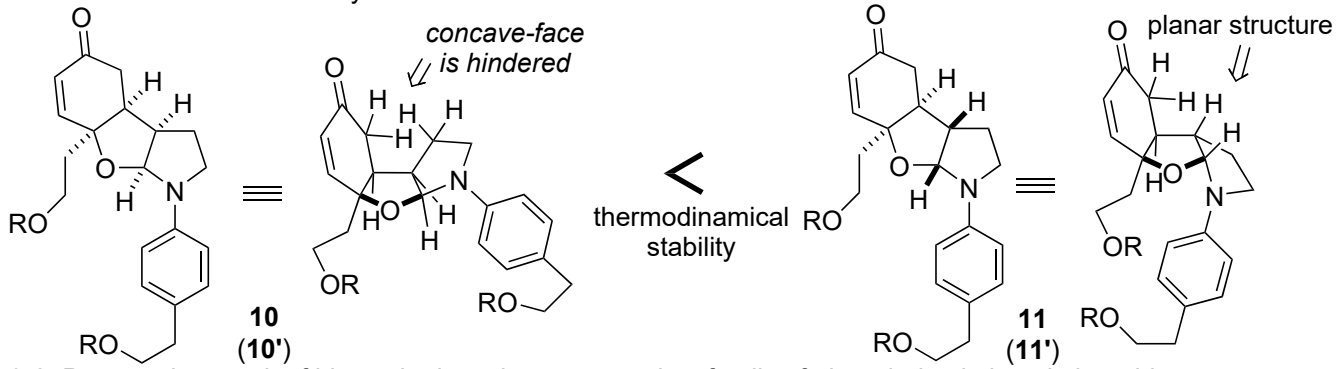
Removal of pivaloyl groups



11 (**11'**) **85** **86** **87**

3-3. Discussion

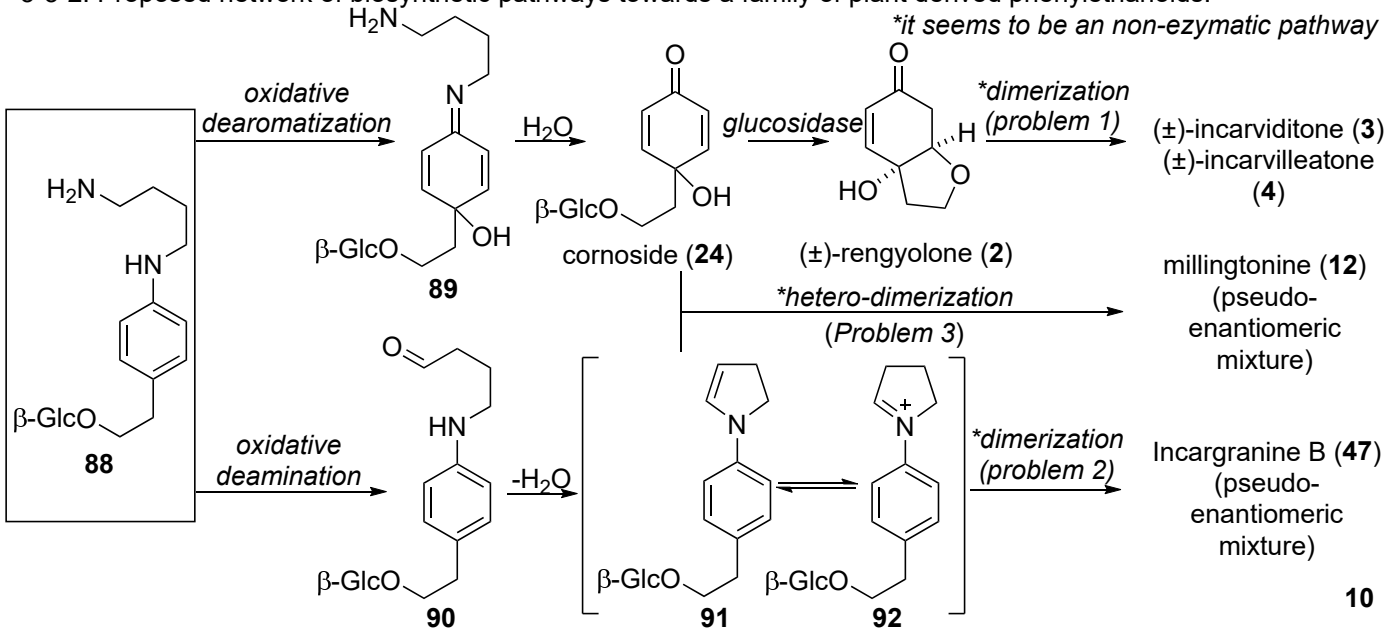
3-3-1. Thermodinamical stability in isomerization reaction.



10 (**10'**) **11** (**11'**)

3-3-2. Proposed network of biosynthetic pathways towards a family of plant derived phenylethanoids.

**it seems to be an non-ezymatic pathway*

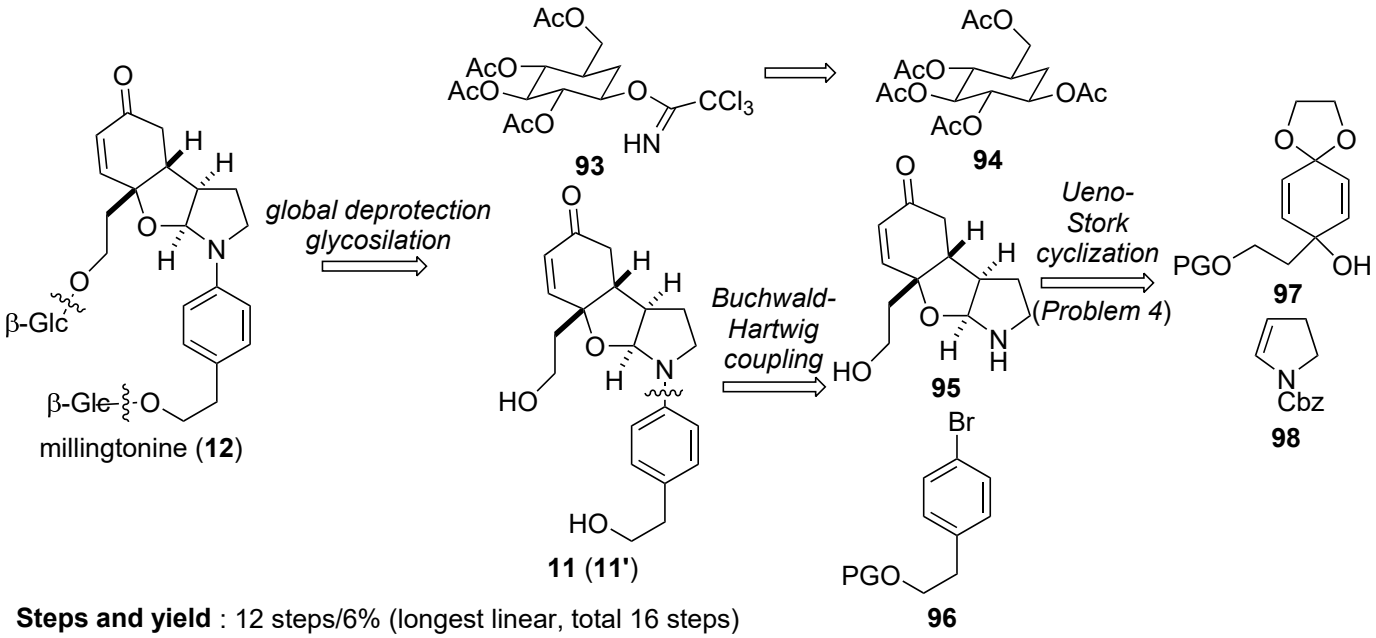


89 **88** **90** **91** **92**

Problem 4. Total Synthesis of Millingtonine
(15. Wegner, J; Ley, SV; Kirschning, A; Hansen, A-L; Garcia, JM and Baxendale, IR *Org.Lett.* **2012**, *14*, 696.)

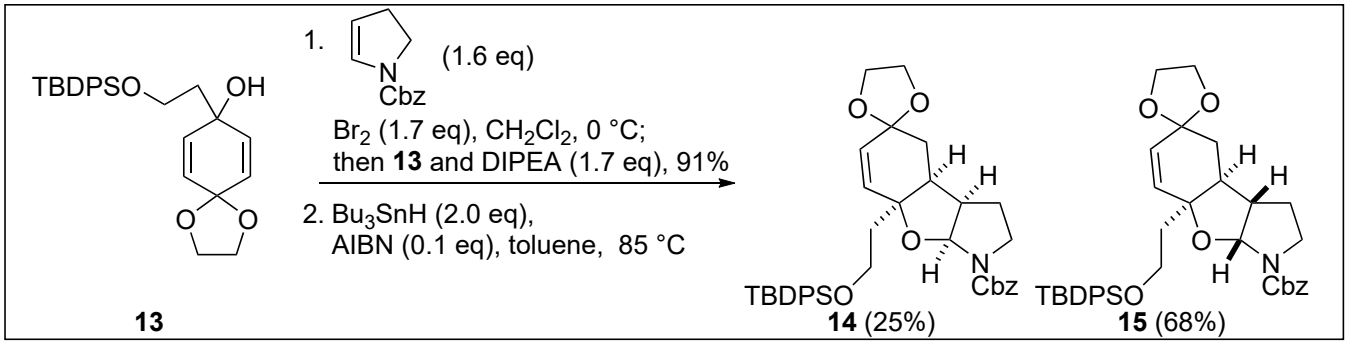
4-1. Introduction (For biosynthesis, isolation and bioactivity, see *page 7*.)

Retrosynthetic analysis:

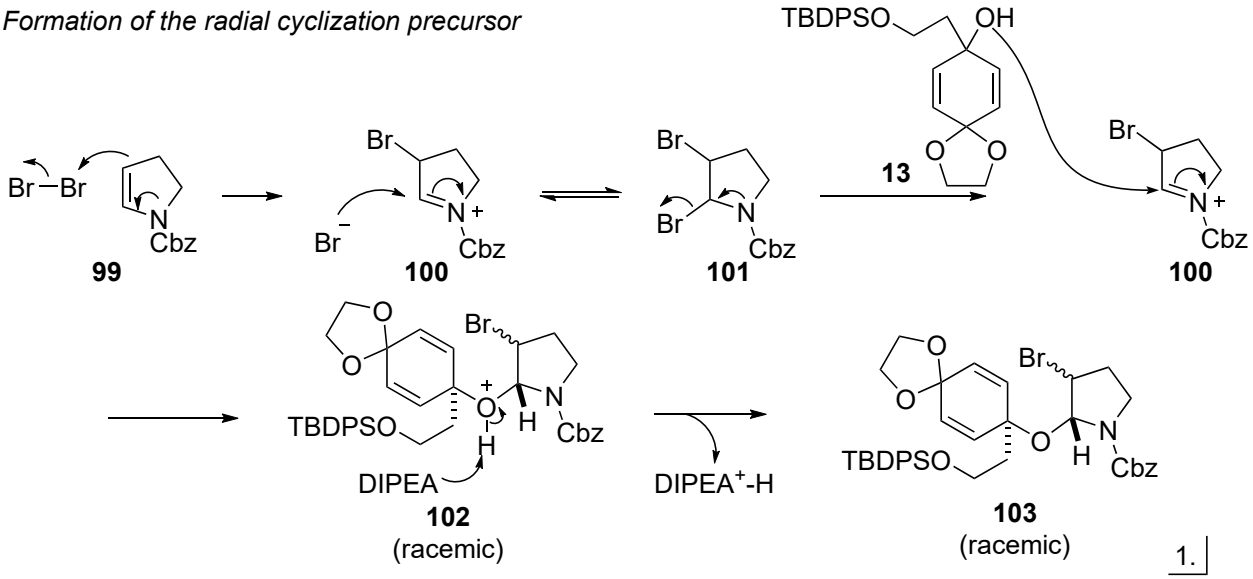


Steps and yield : 12 steps/6% (longest linear, total 16 steps)

4-2. Reaction mechanisms

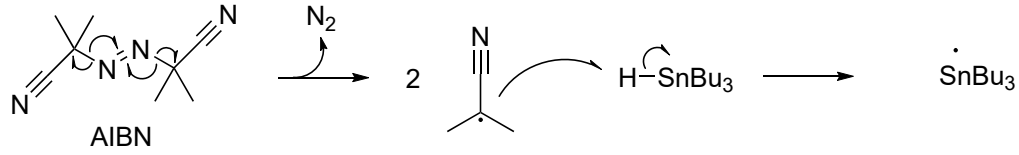


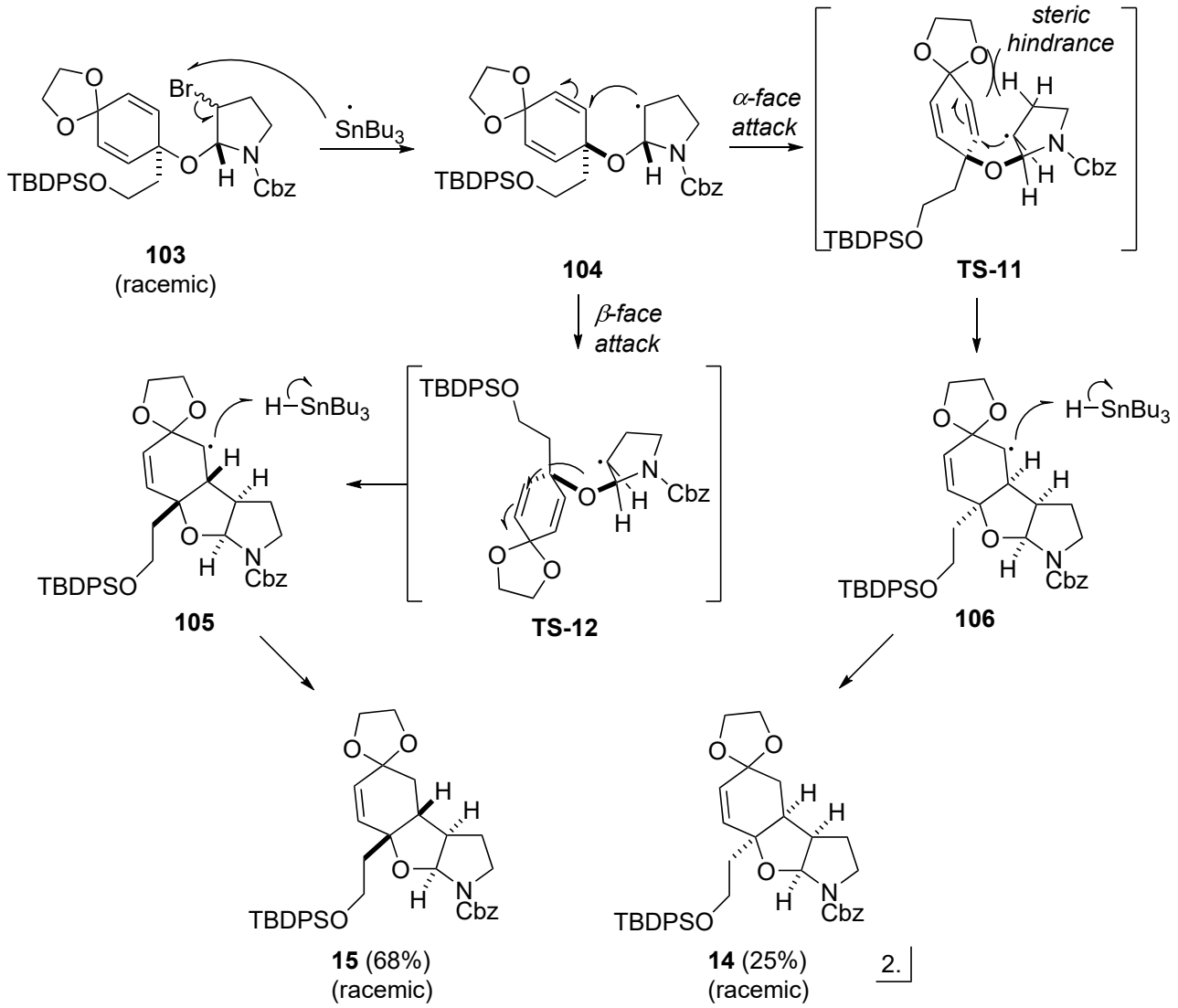
Formation of the radial cyclization precursor



1.

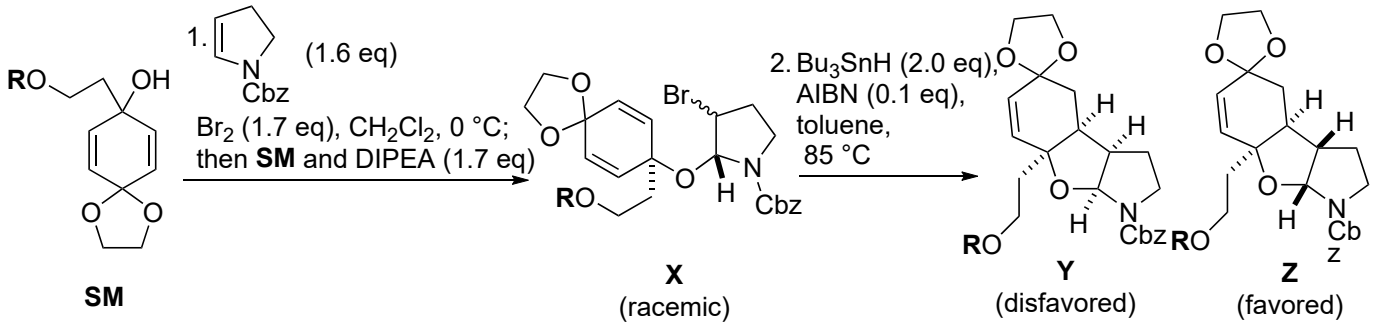
Ueno-Stork cyclization reaction





4-3. Discussion

4-3-1. Effect of protecting group on stereoselectivity of Ueno-Stork cyclization

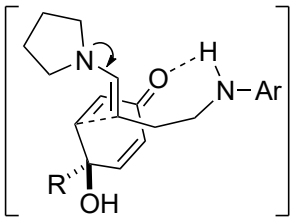


R	X	Y*	Z*	ratio (Y:Z)
TBDPS	91%	25% (27%)	68% (75%)	1:2.7
Trityl	52%	10% (19%)	24% (46%)	1:2.4
TBS	60%	24% (40%)	31% (52%)	1.1.3

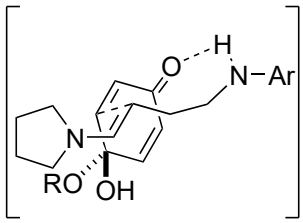
*two step yield (one step yield)

Larger or phenyl-containing protecting group seems to be preferable.

Appendix:



TS-9
(*favored*)



TS-10
(*disfavored*)