Total Synthesis of Saxitoxin and Its Analogues

2016/06/25

M1 Akira Hirose

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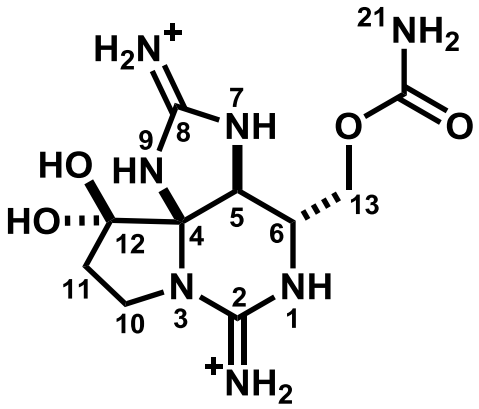
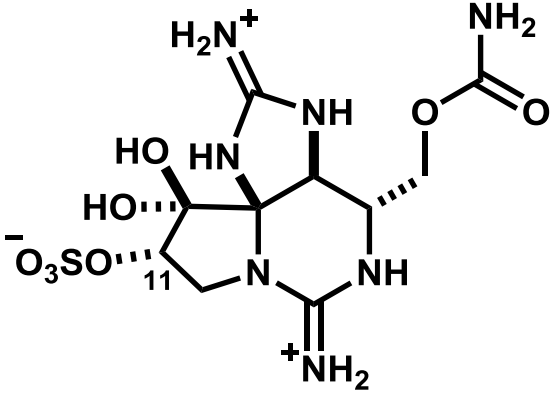
Introduction (1) – Saxitoxin and Its Analogues



(+)-saxitoxin (STX)



(+)-gonyautoxin 3 (GTX 3)
GTX 2: epimer at C11

Isolation

- by Schantz, in 1957 from Alaskan butter clams *Saxidomus giganteus*

-> belonging to paralytic shelfish poisons (PSPs)

- >50 related analogues have been isolated.

Structual Determination

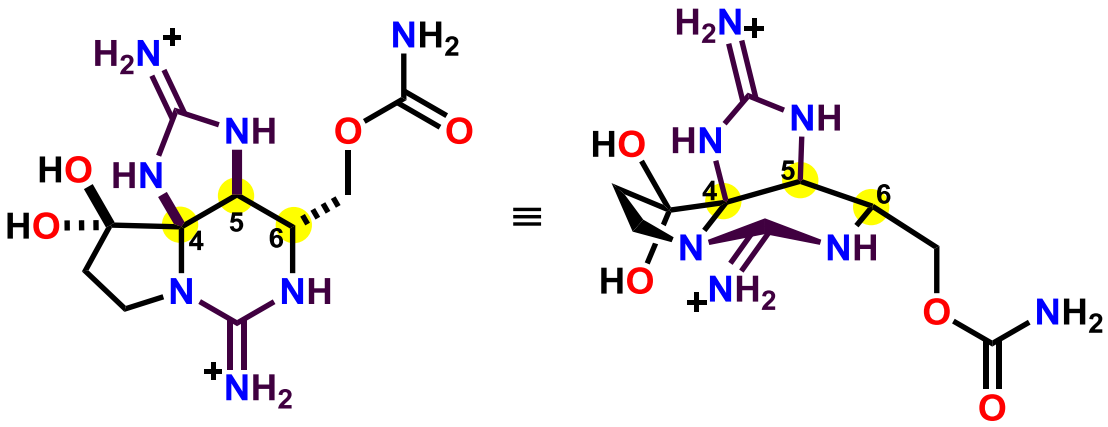
- X-ray cristal structures were published in 1975, by Shantz/Clardy and Rapoport
- finally confirmed by Kishi's first total synthesis in 1977

Biological activity

- Na_v (the voltage gated Na^+ ion channel)-selective blocker

-> reversibly binding with the outer pore of Na_v and inhibiting Na^+ ion flux

Introduction (2) – Problems in synthesis of STX



Structual features

- high polarity due to bis-guanidinium functional groups
  -> bad solubility and great difficulty of isolation and purification
- the number of heteroatoms > that of carbon (molecular formula: $C_{10}H_{19}N_7O_4$)
  -> Side reactions would occur without proper control of functional groups.
- tricyclic skeleton, including three contiguous asymmetric carbon centers (C4, C5, C6)
- unusual hemiaminal moiety at C4

Total syntheses

- saxitoxin

(a) Kishi, Y. et al. *J. Am. Chem. Soc.* **1977**, *99*, 2818-2819.
(b) Jacobi, P. A. et al. *J. Am. Chem. Soc.* **1984**, *106*, 5594-5598.
(c) Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, *128,* 3926-3927.; Du Bois, J. et al. *J. Am. Chem. Soc.* **2007**, *129,* 9964-9975.*
(d) Nagasawa, K. et al. *Chem. - Asian J.* **2009**, *4*, 277-285.
(e) Sawayama, Y.; Nishikawa, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 7176-7178.
(f) Bhonde, V. R.; Looper, R. E. *J. Am. Chem. Soc.* **2011**, *133*, 20172-20174.**

- gonyautoxin

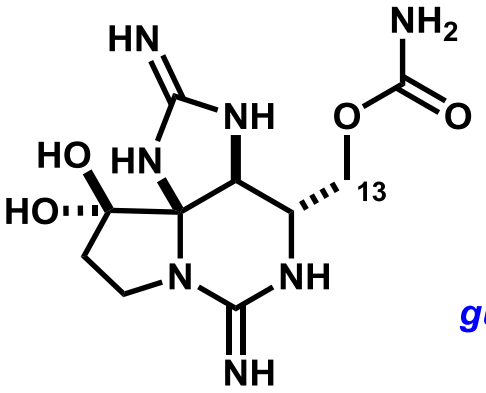
(a) Mulcahy, J. V.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 12630-12631.*
(b) Iwammoto, O.; Nagasawa, K. *Org. Lett*. **2010**, *12*, 2150-2153.

*** Please refer to LS by Amaoka-san in 2008.**

**** Please refer to LS by Sakata-san in 2012.**

Contents

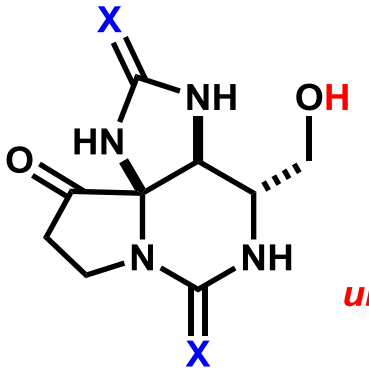
Retrosynthetic Analysis by Kishi



saxitoxin

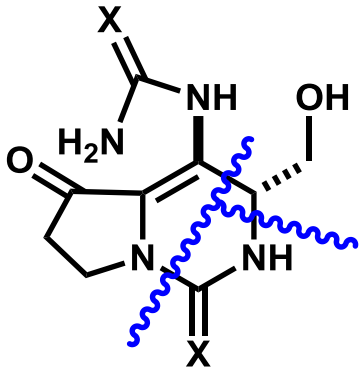
carbamoylation of 13-OH

introduction of guanidinum groups in the late stage

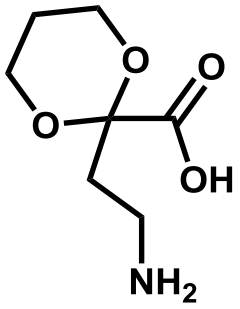


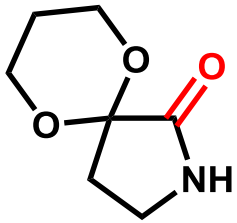
X = O or S

the second urea (or thiourea) cyclization

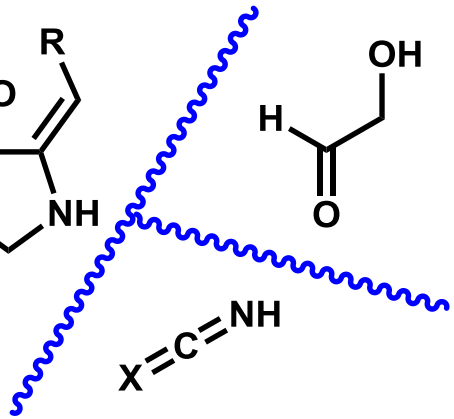


three components urea (or thiourea) construction

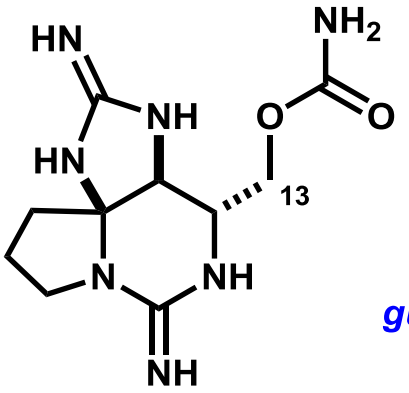




Eschenmoser's[1)] *procedure*



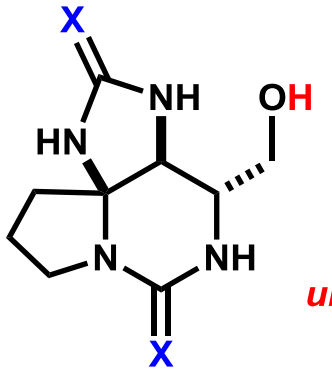
Model Experiment – Synthesis of C12 Deoxo Series[1)]



12-deoxosaxitoxin

carbamoylation of 13-OH

introduction of guanidinum groups in the late stage



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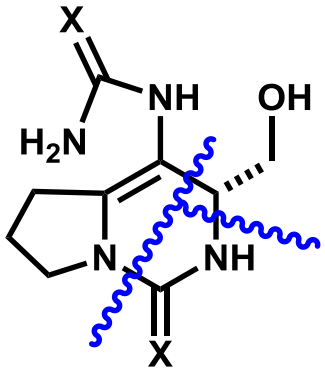
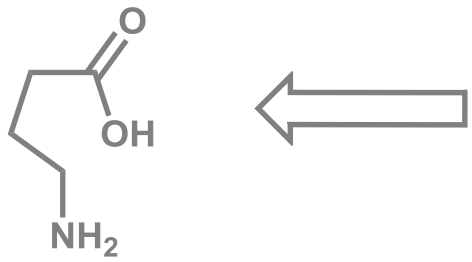
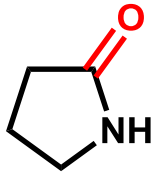
the second urea (or thiourea) cyclization



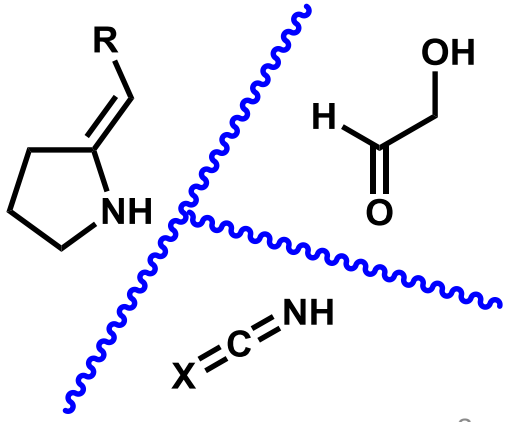
three component urea (or thiourea) construction





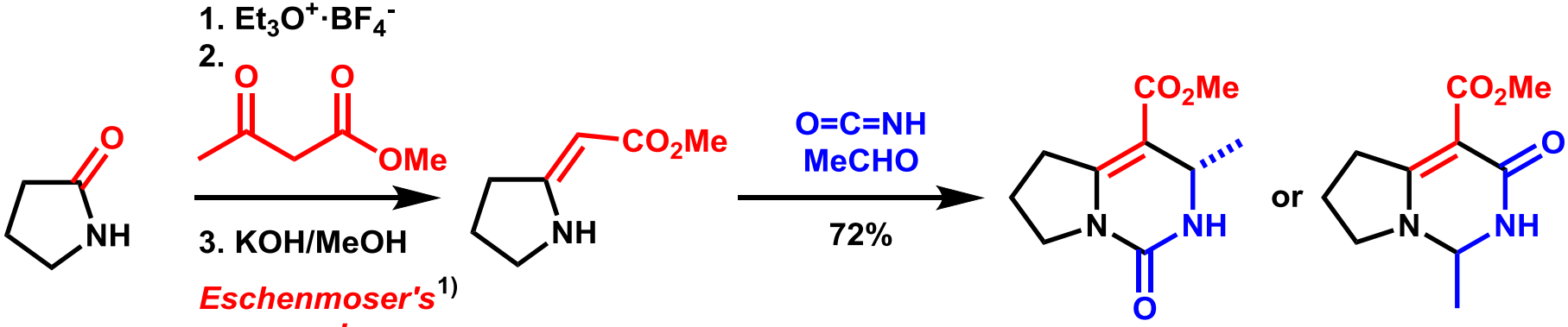
2-pyrrolodonone
commercially available

Eschenmoser's[1)] procedure



1. Taguchi, H.; Yazawa, H.; Arnett, J. F.; Kishi, Y. *Tetrahedoron Lett.* **1977**, *7*, 627.

Model Experiment (1) – the First Urea Construction –



2-pyrrolodonone

A (desired)

B

Two experiments to determin structure (A or B?)

1. Ecshenmoser, A. *Quart. Rev.* **1970**, *24*, 366.
2. Schuett, W.; Rapoport. *J. Am. Chem. Soc.* **1962**, *84*, 2266.

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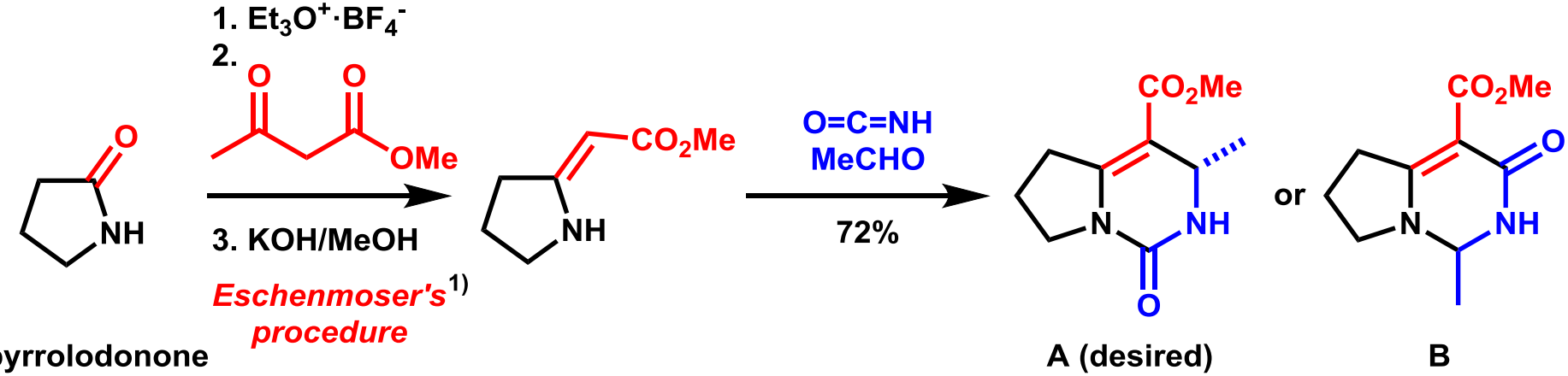

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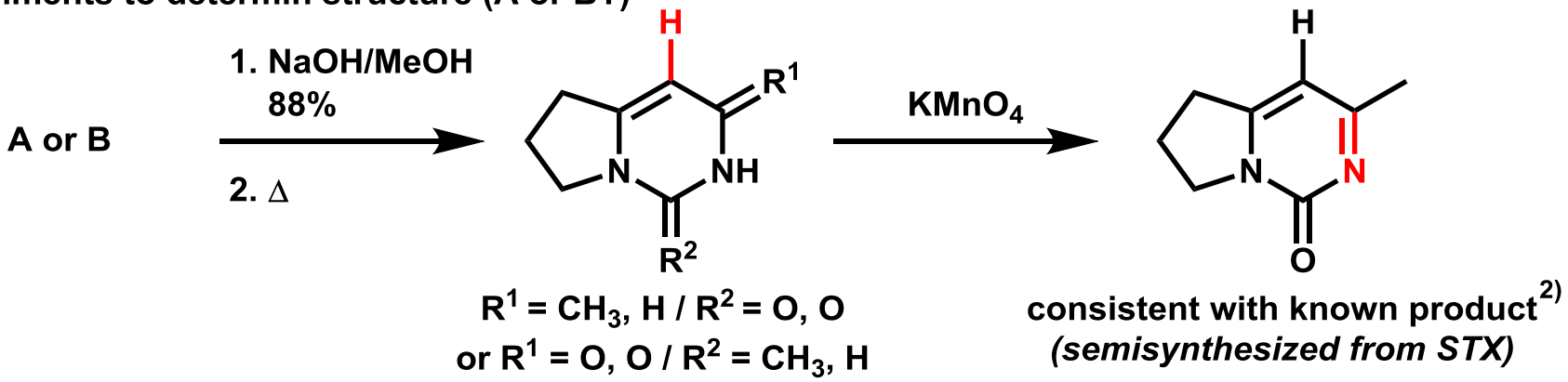

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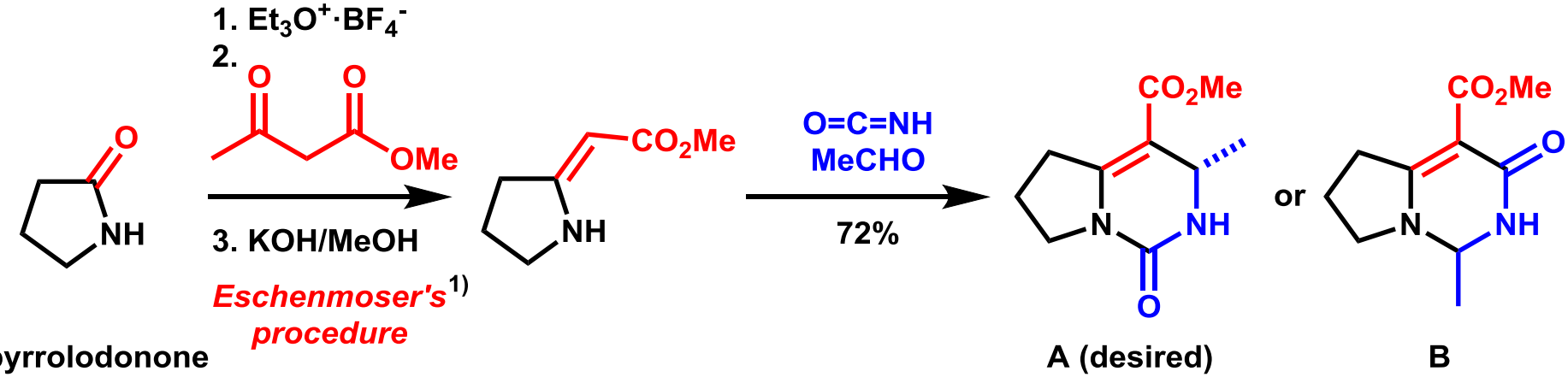

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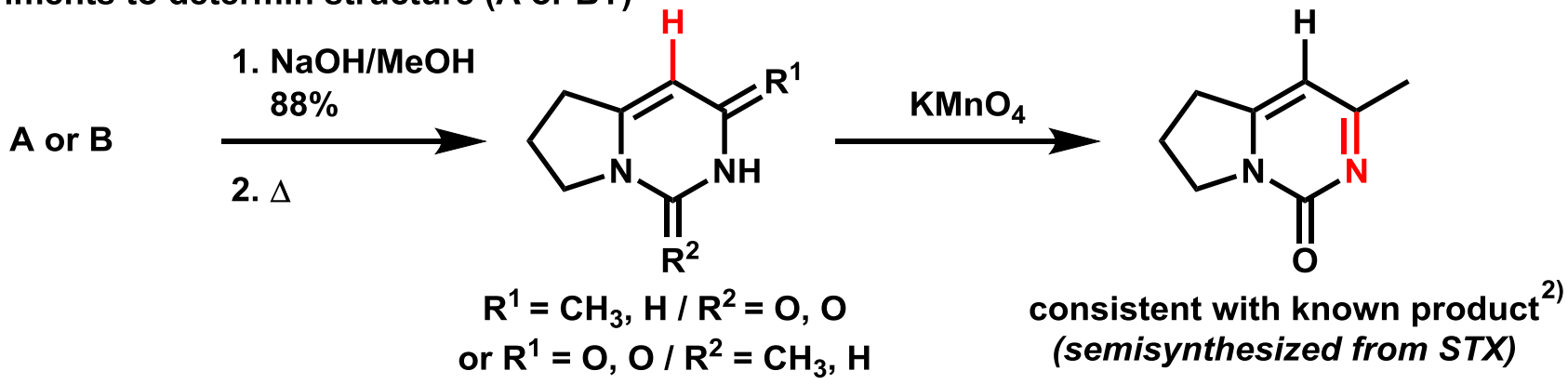

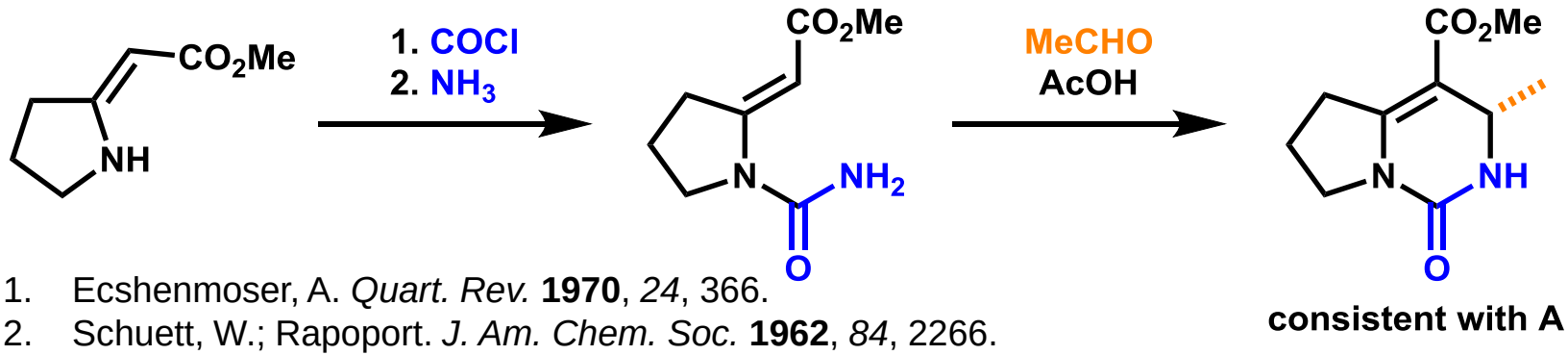

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2. Schuett, W.; Rapoport. *J. Am. Chem. Soc.* **1962**, *84*, 2266.

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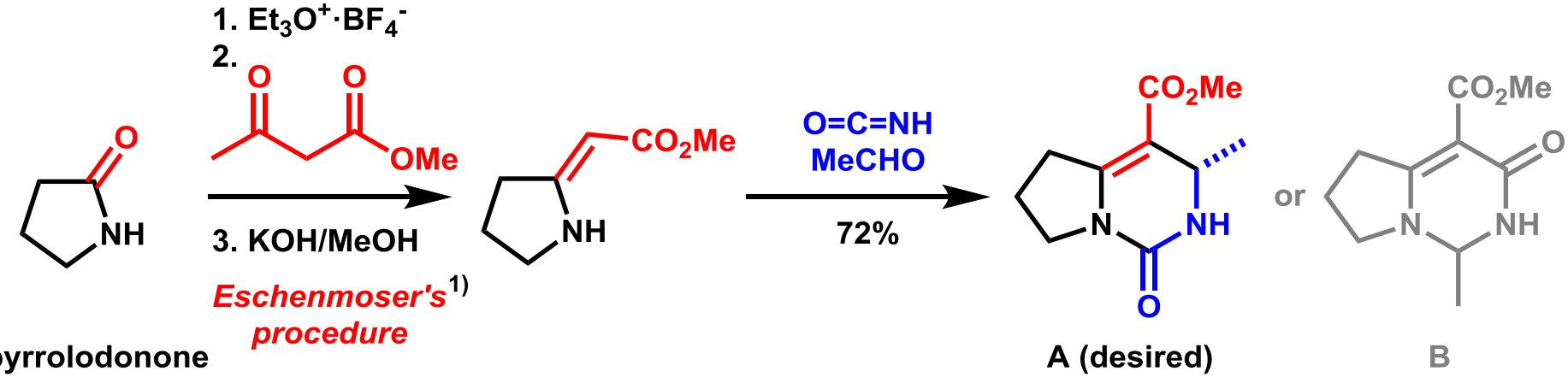

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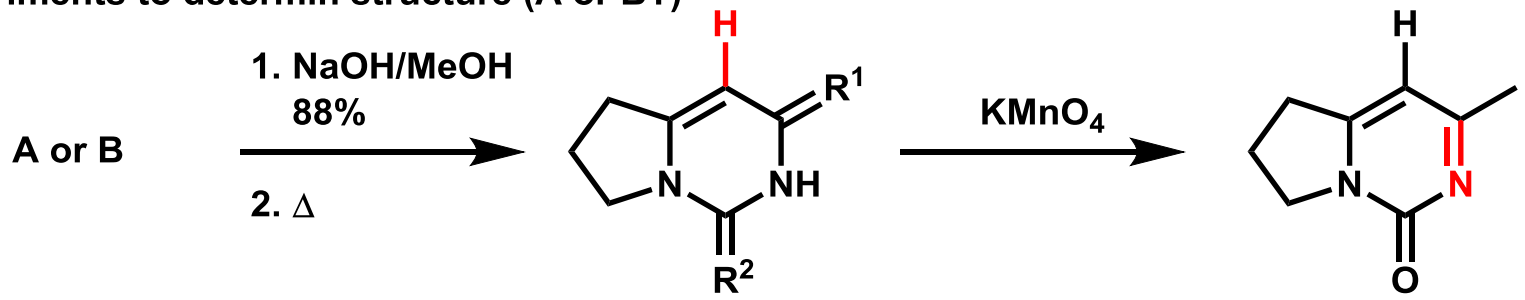
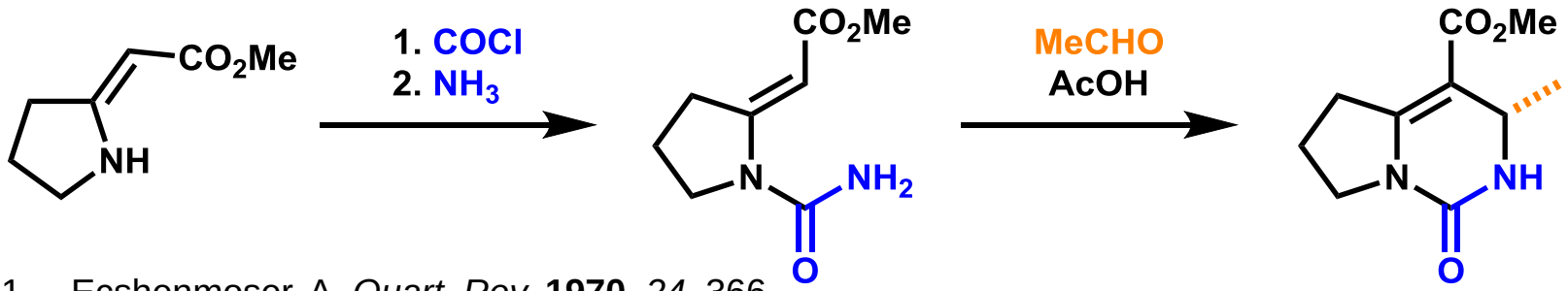
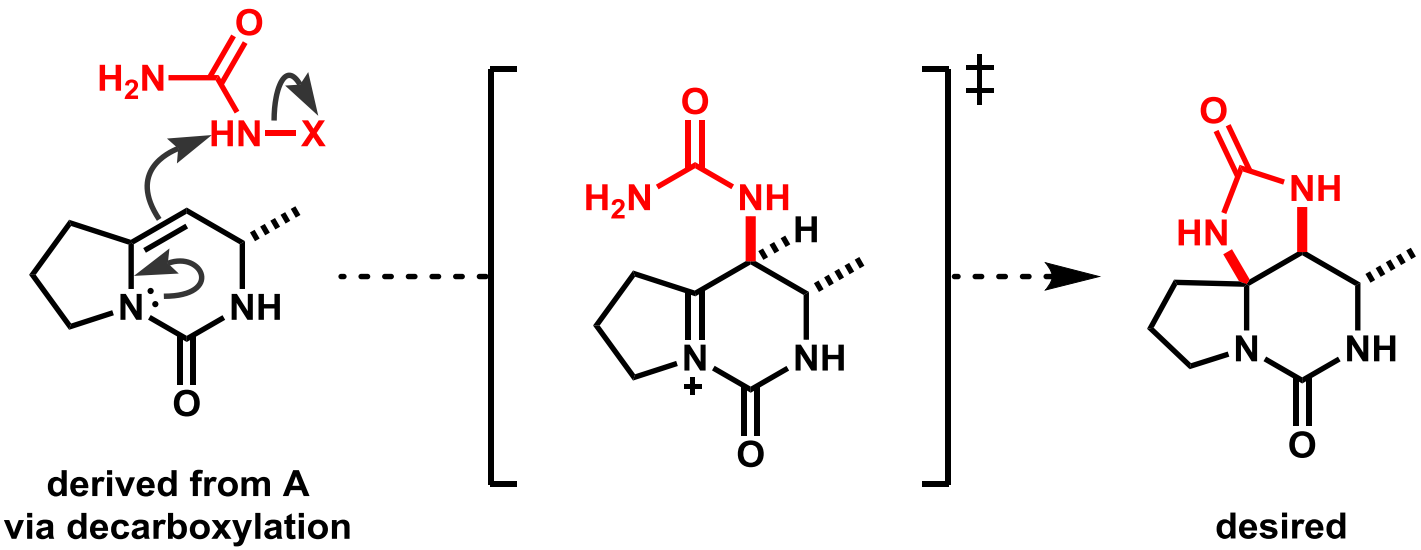




1. Ecshenmoser, A. *Quart. Rev.* **1970**, *24*, 366.
2. Schuett, W.; Rapoport. *J. Am. Chem. Soc.* **1962**, *84*, 2266.

Model Experiment (2) – Two ways of Urea Cyclization

the 1st way: amination with a properly protected and functionalized urea

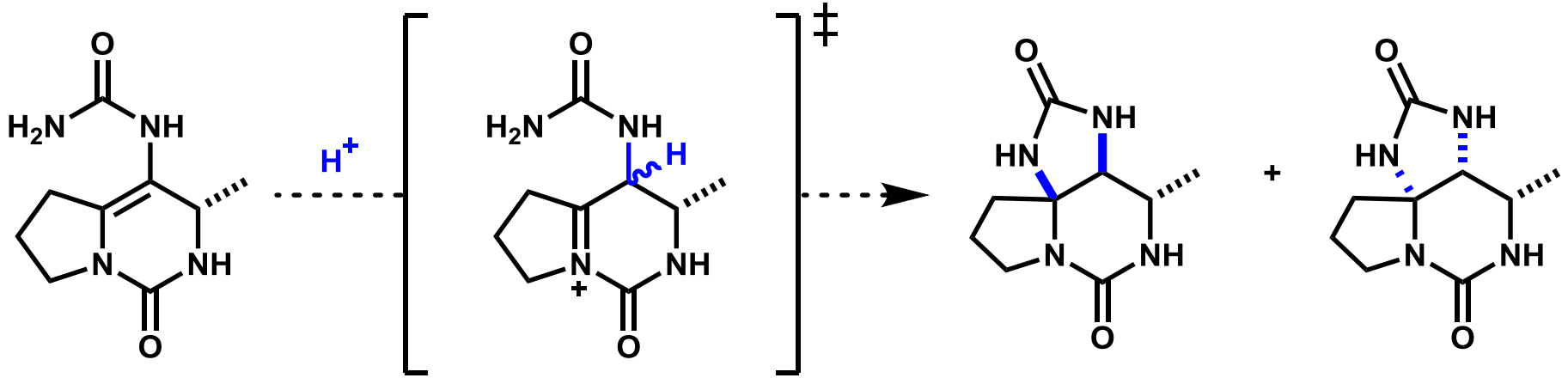


derived from A
via decarboxylation

desired

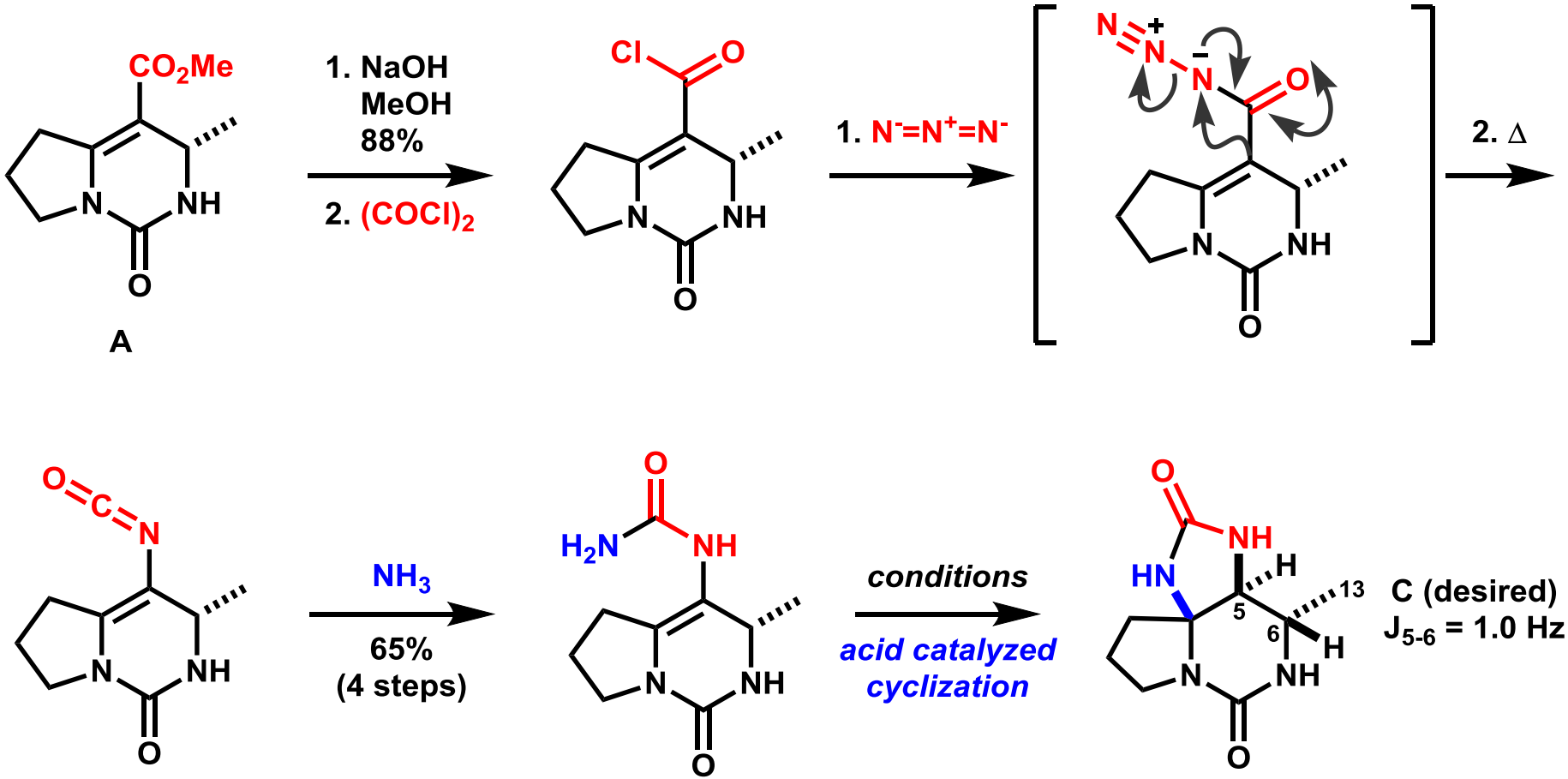
Decarboxylated compound turned out to be unstable.
-> This route was not feasible.

the 2nd way: acid catalyzed cyclization



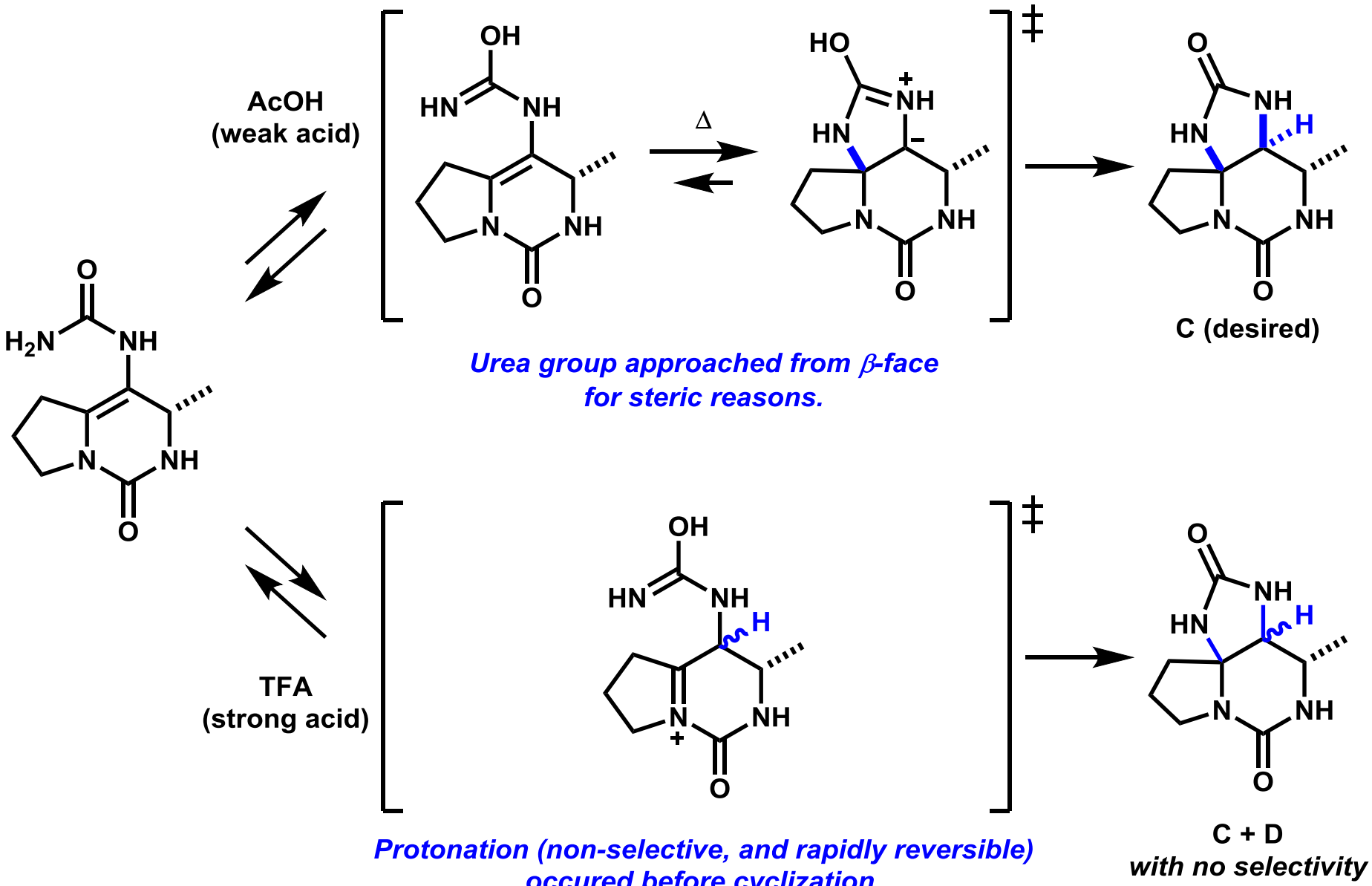
desired

Model Experiment (3) – Investigation of Cyclization –

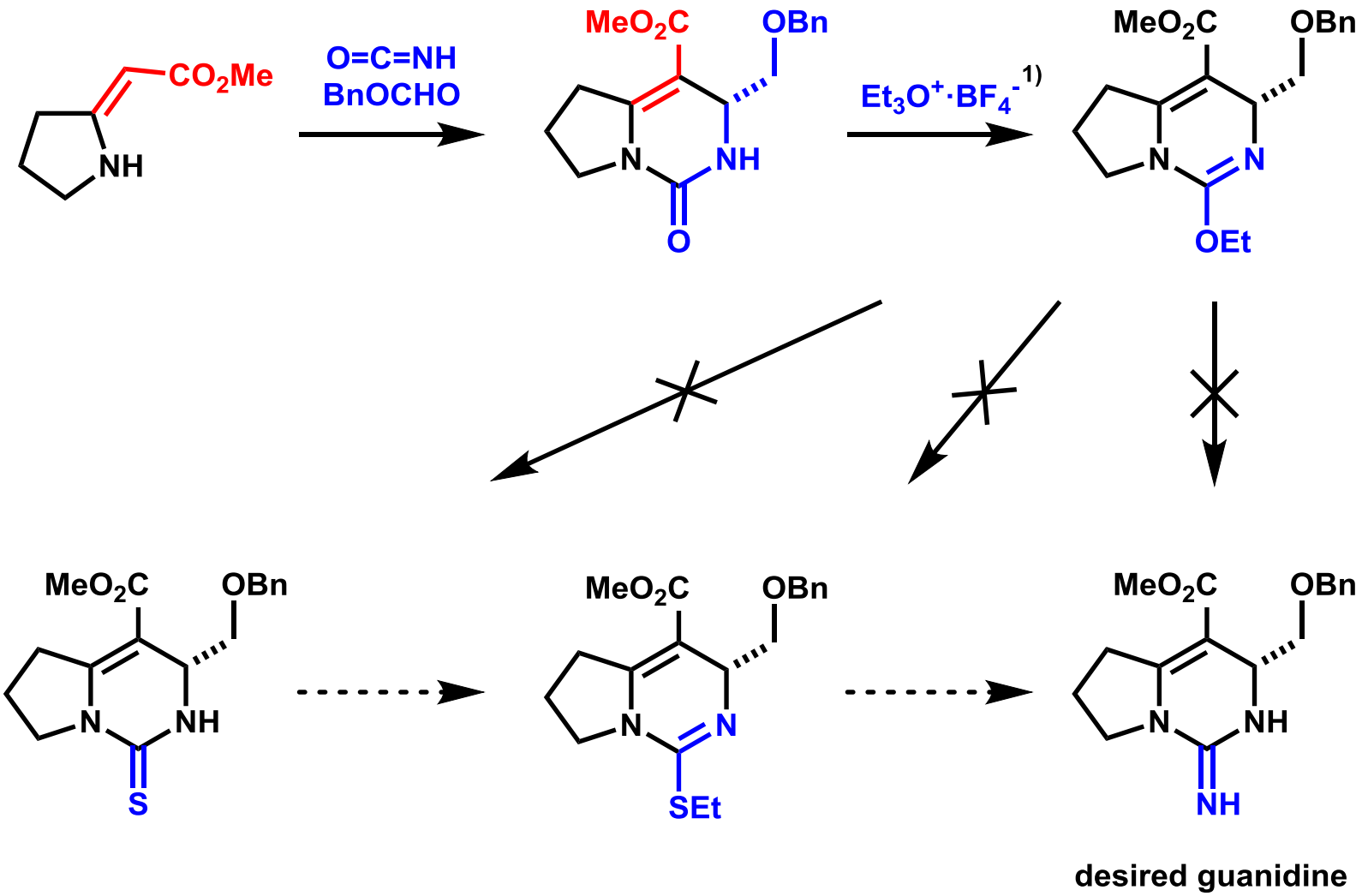


entry	conditions	result		
		C	D	C/D
1	AcOH, 50 °C	93%	-	>>20 : 1
2	CF_3CO_2H, rt.	30%	45%	2 : 3

Stereoselectivity of Cyclization

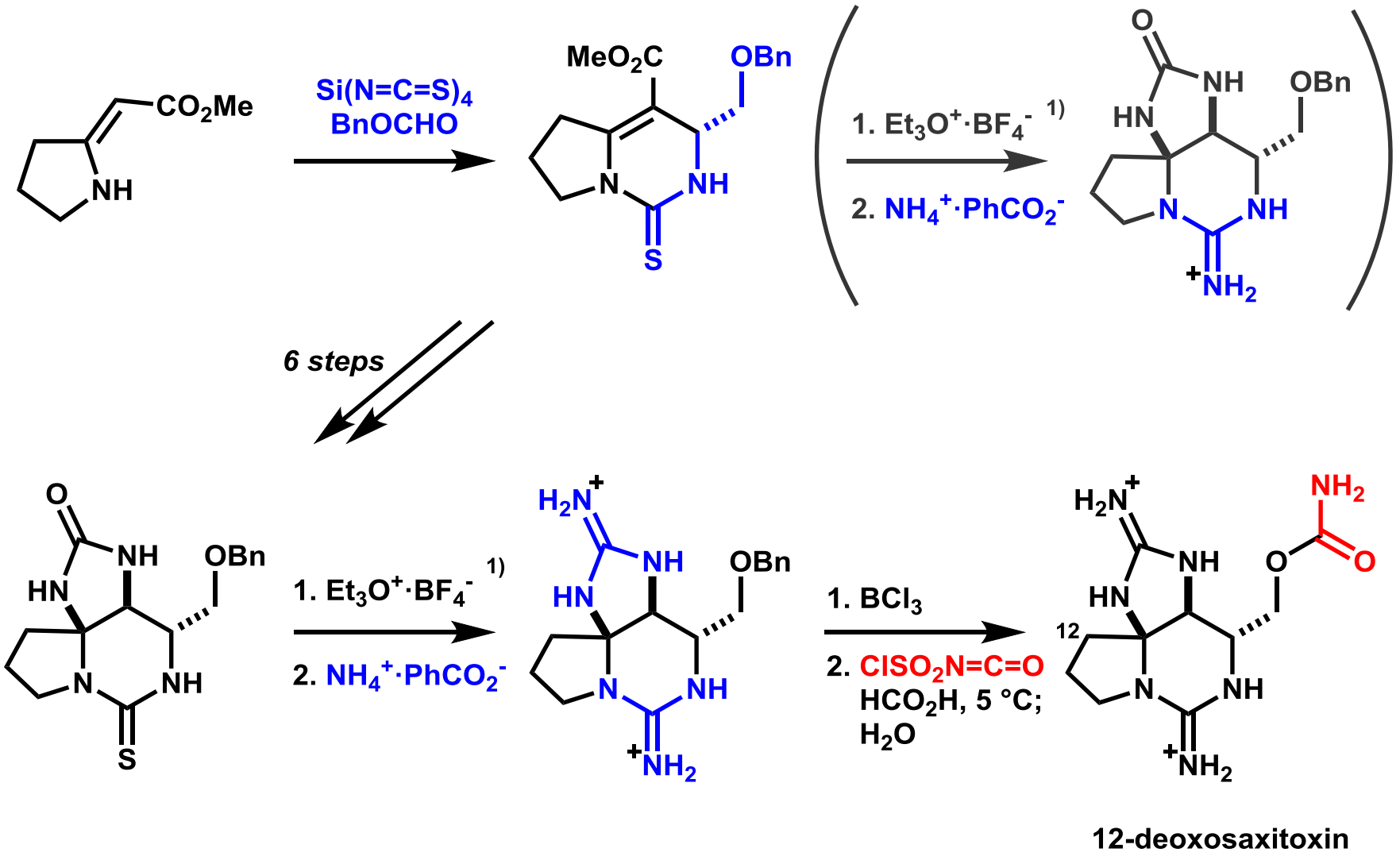


Model Experiment (4)
– Attempts to transform Urea to Guanidine –



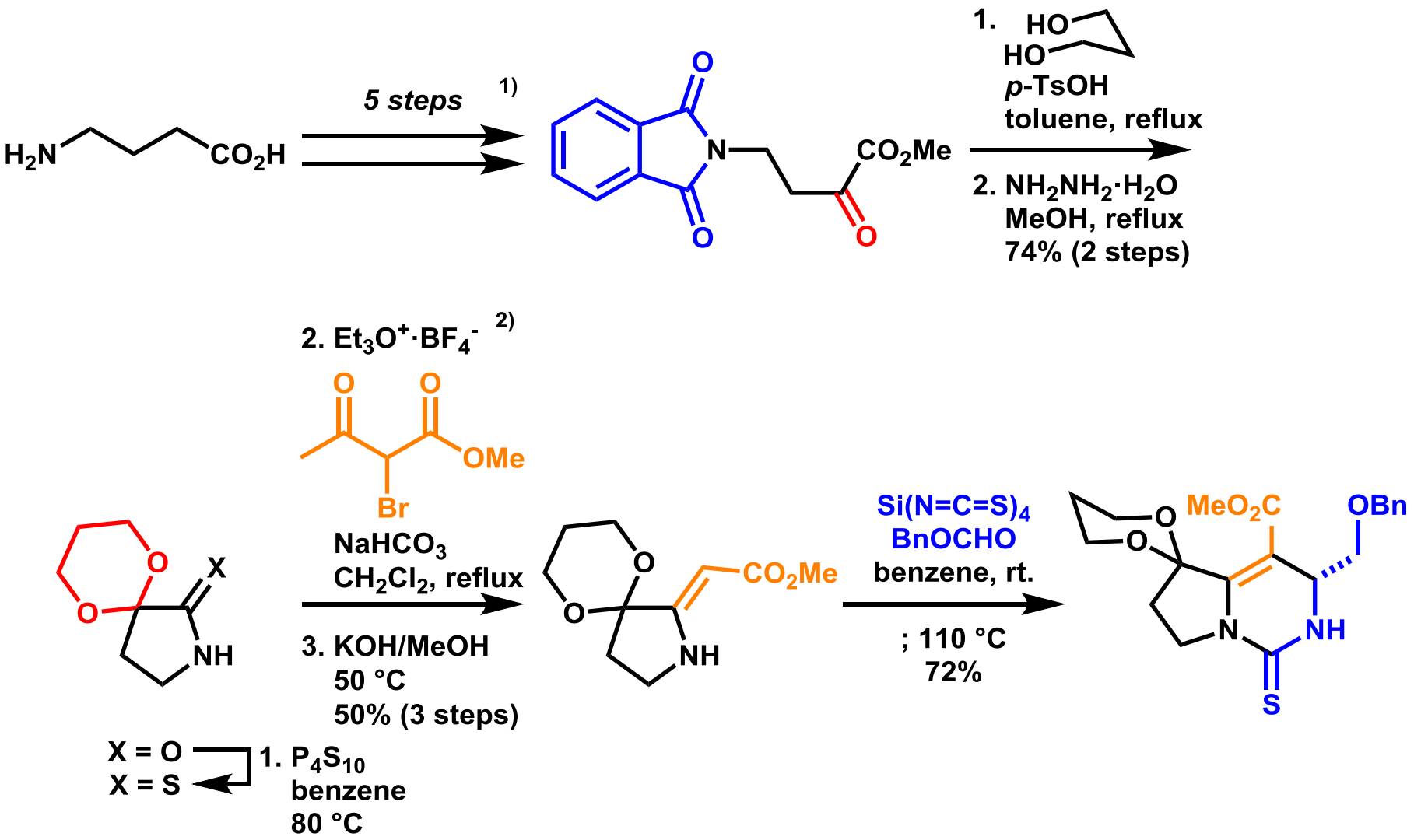
1. Roth, M.; Dubs, P.; Götschi, E.; Ecshenmoser, A. *Helv. Chim. Acta.* **1970**, *54*, 710.

Model Experiment (4) – Construction of Bis-Guanidines and Total Synthesis of 12-DeoxoSTX –



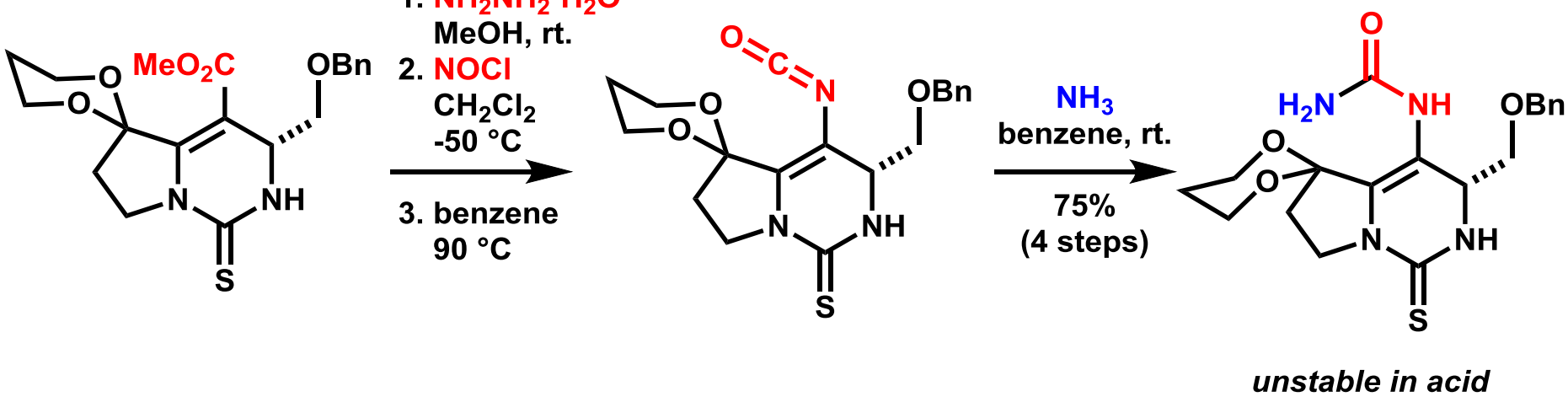
1. Roth, M.; Dubs, P.; Götschi, E.; Ecshenmoser, A. *Helv. Chim. Acta.* **1970**, *54*, 710.

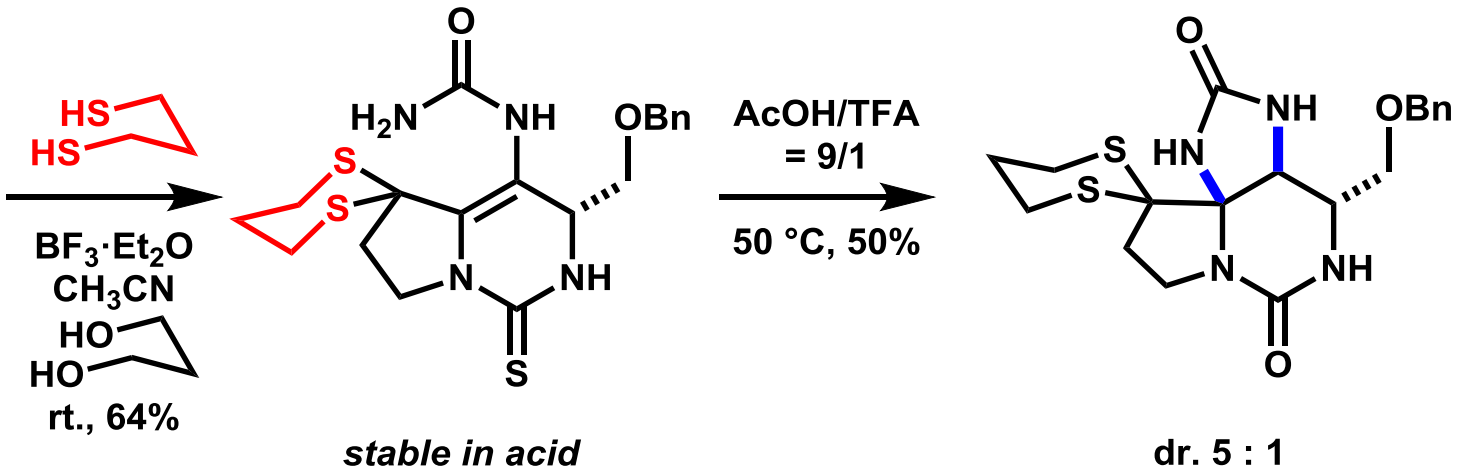
Total Synthesis of (±)-STX (1)



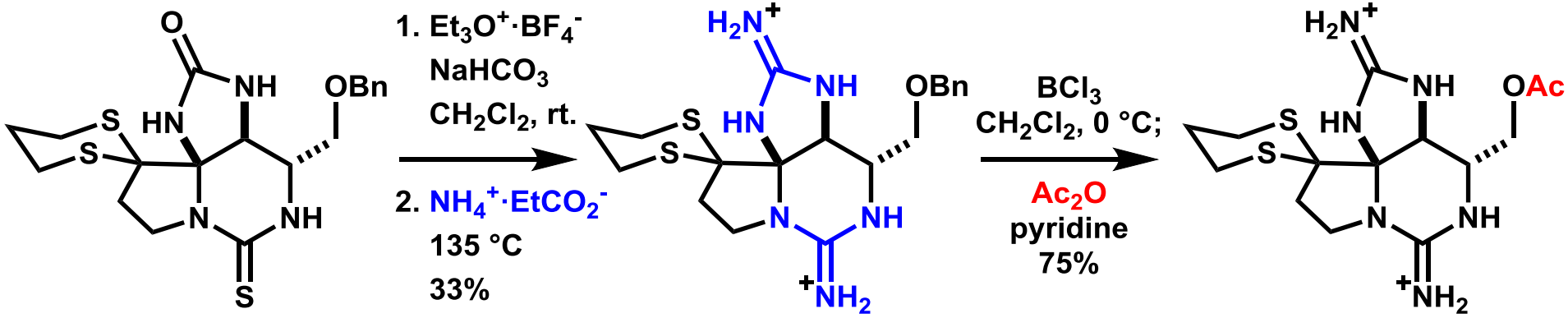
1. Busby, G. W. *Ph. D. Dissertation, Harnard Univercity*, **1974**.
2. Ecshenmoser, A. *Quart. Rev.* **1970**, *24*, 366.

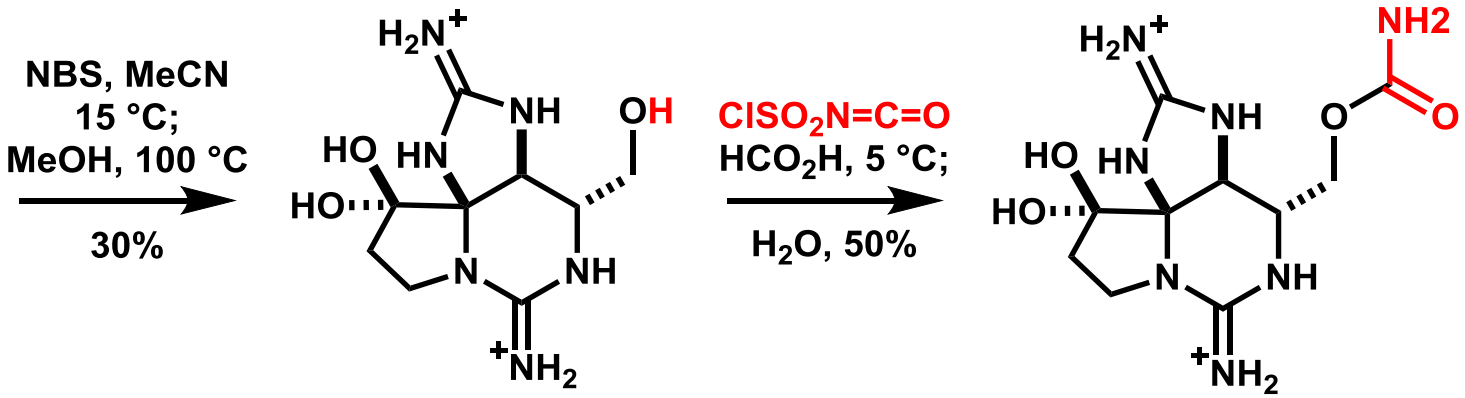
Total Synthesis of (±)- STX (2)





Total Synthesis of (±)- STX (3)



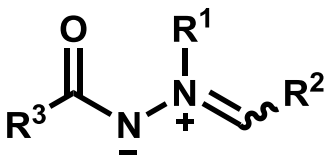


decarbamoylsaxitoxin

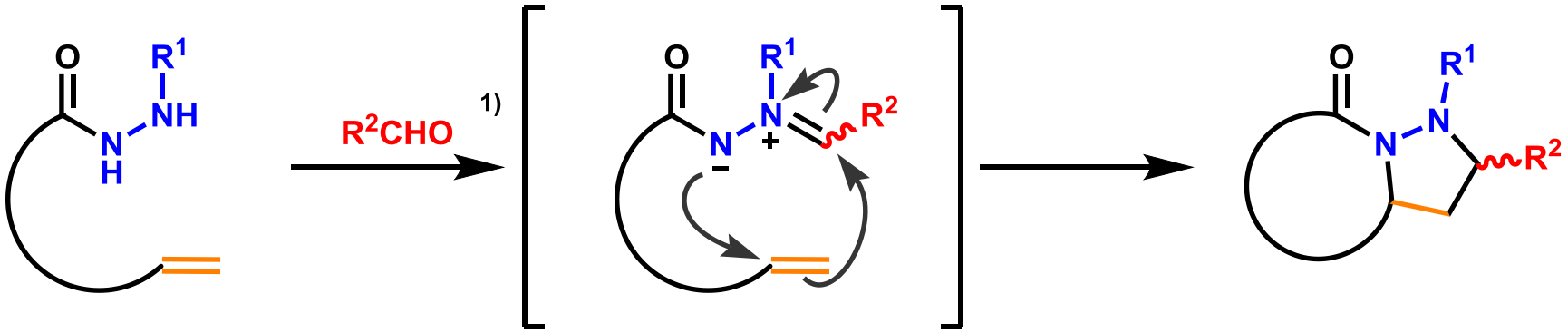
(±)-saxitoxin

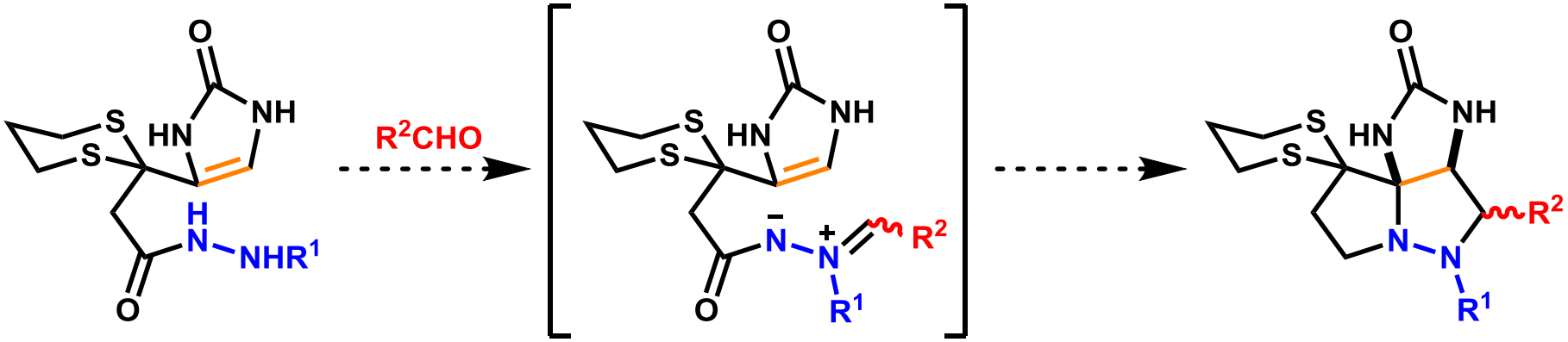
Contents

[3+2]-Cycloaddition of Azomethine Imine[1-3)]



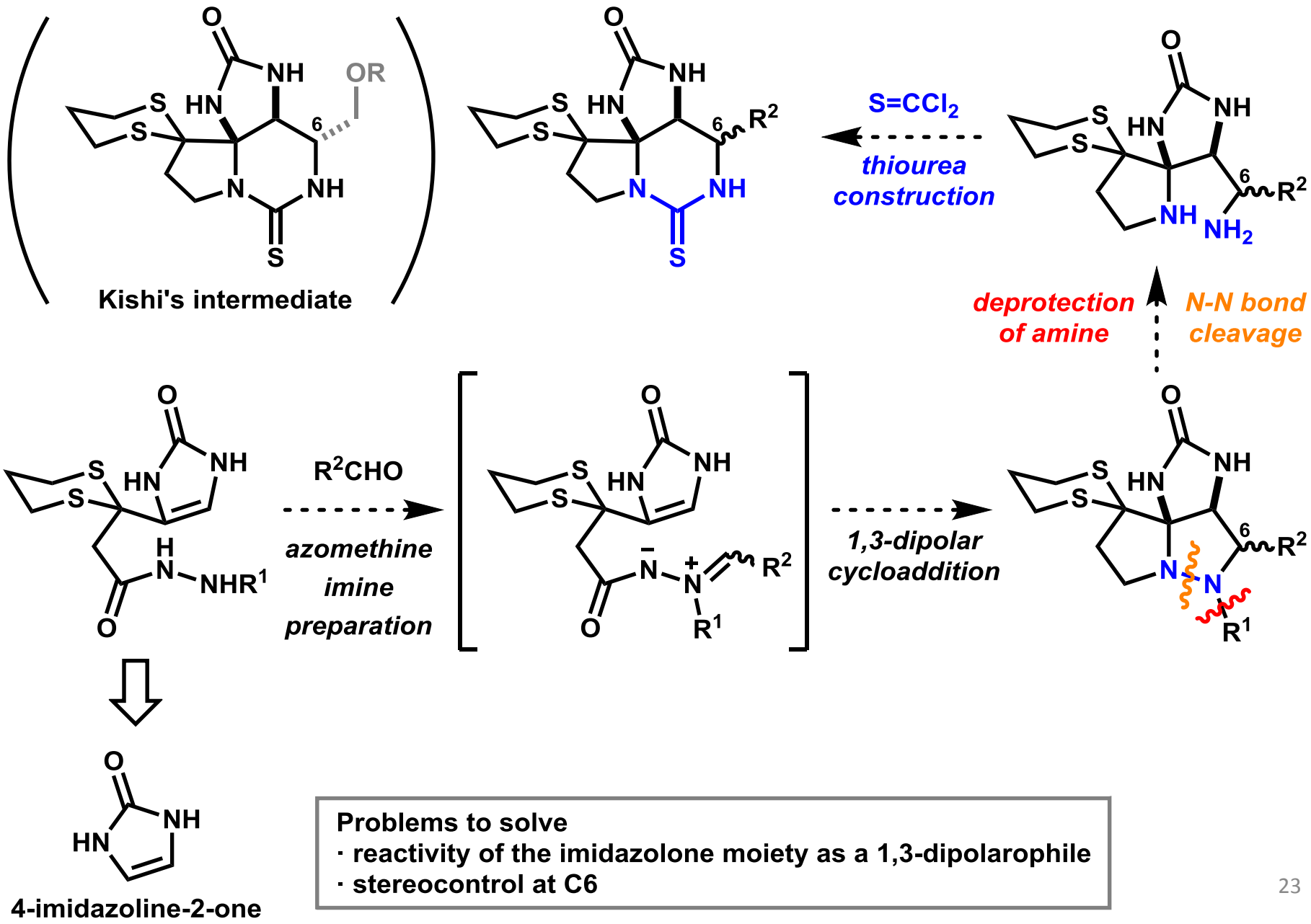
azomethine imine:
· behaving as 1,3-dipole
· unstable
· obtained *in situ*





1. Oppilzer, W. *Tetrahedoron Lett*. **1970**, 2199.
2. Oppilzer, W.; Weber, H. P. *Tetrahedoron Lett*. **1972**, 1711.
3. Oppilzer, W. *Angwe. Chem, Int. Ed.* **1977**, *16*, 10.

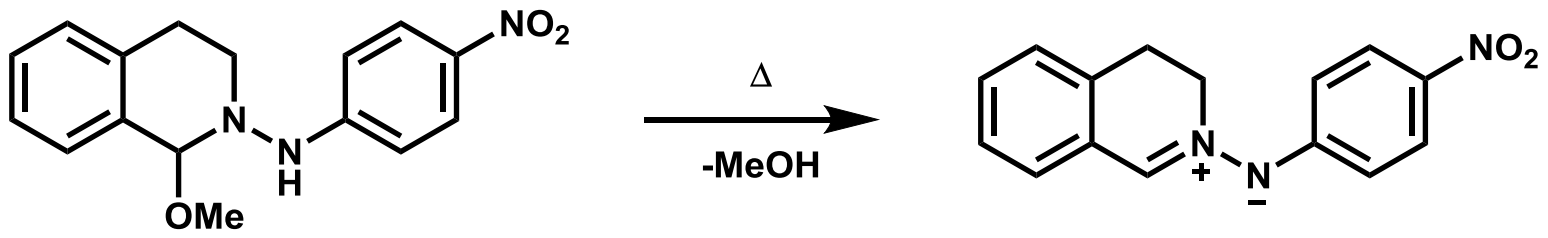
Synthetic Approach to STX by Jacobi



Problems to solve
- reactivity of the imidazolone moiety as a 1,3-dipolarophile
- stereocontrol at C6

Investigation of cycloaddition with imidazolone

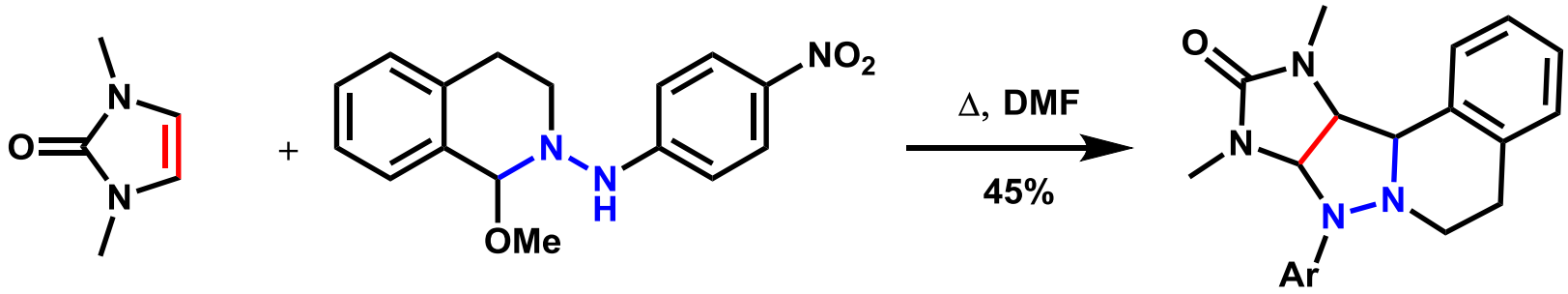
preparation of azomethine imine

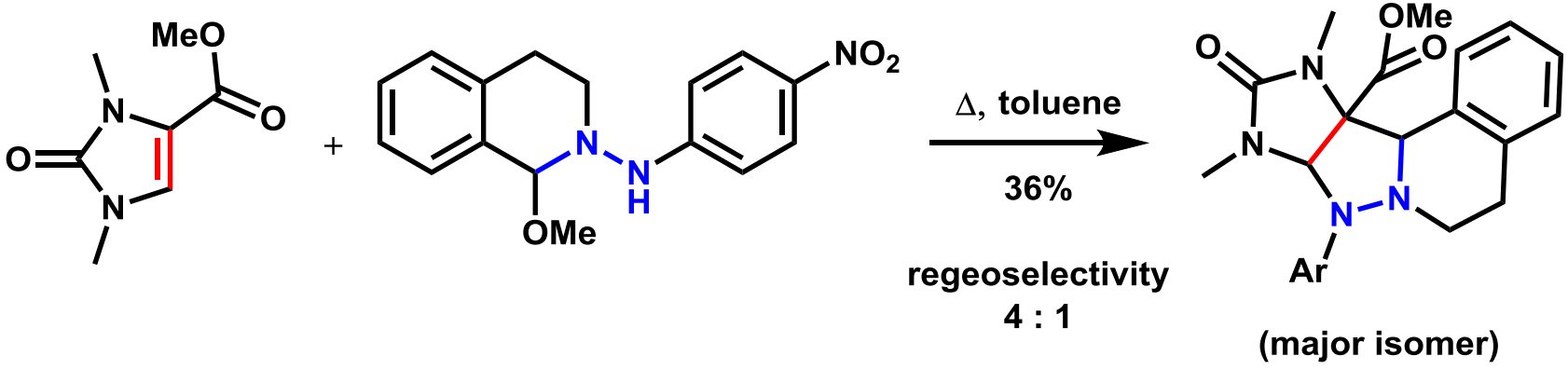


dihydroisoquinoline

azomethine imine

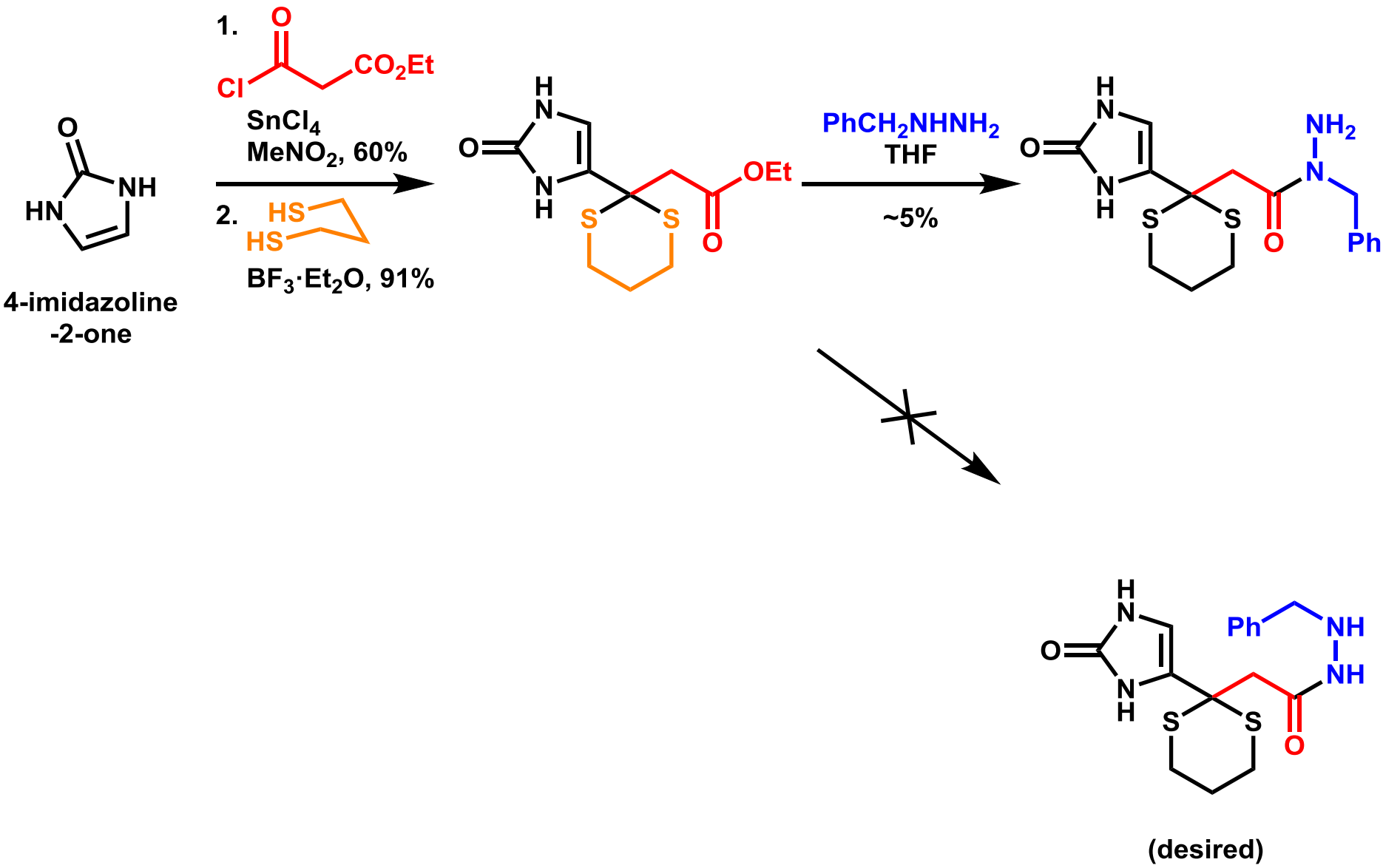
cycloaddition with *N,N*-dimethyl-4-imidazolin-2-one series



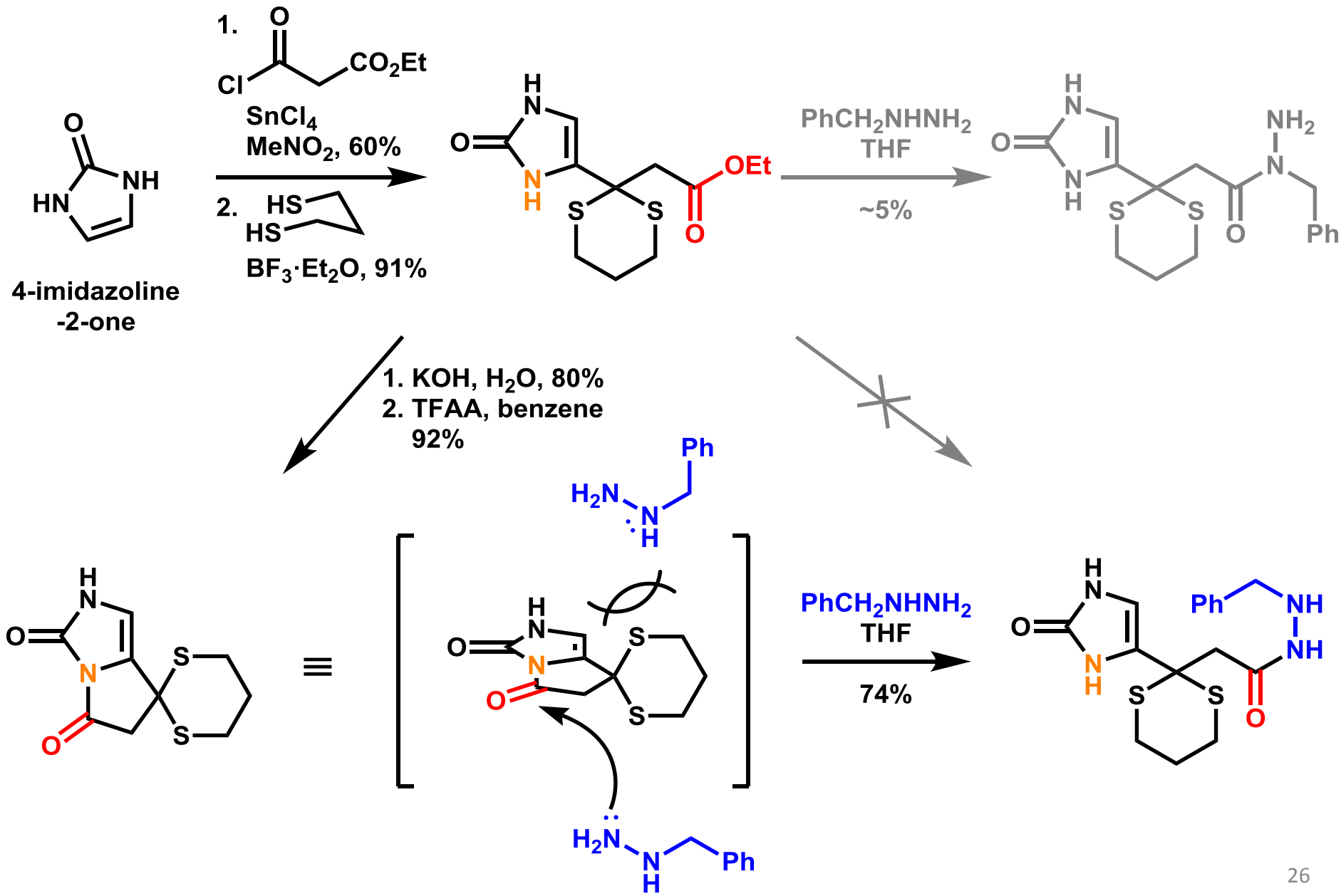


-> Imidazolone moieties can function as 1,3-dipolarophiles with azomethine imine.

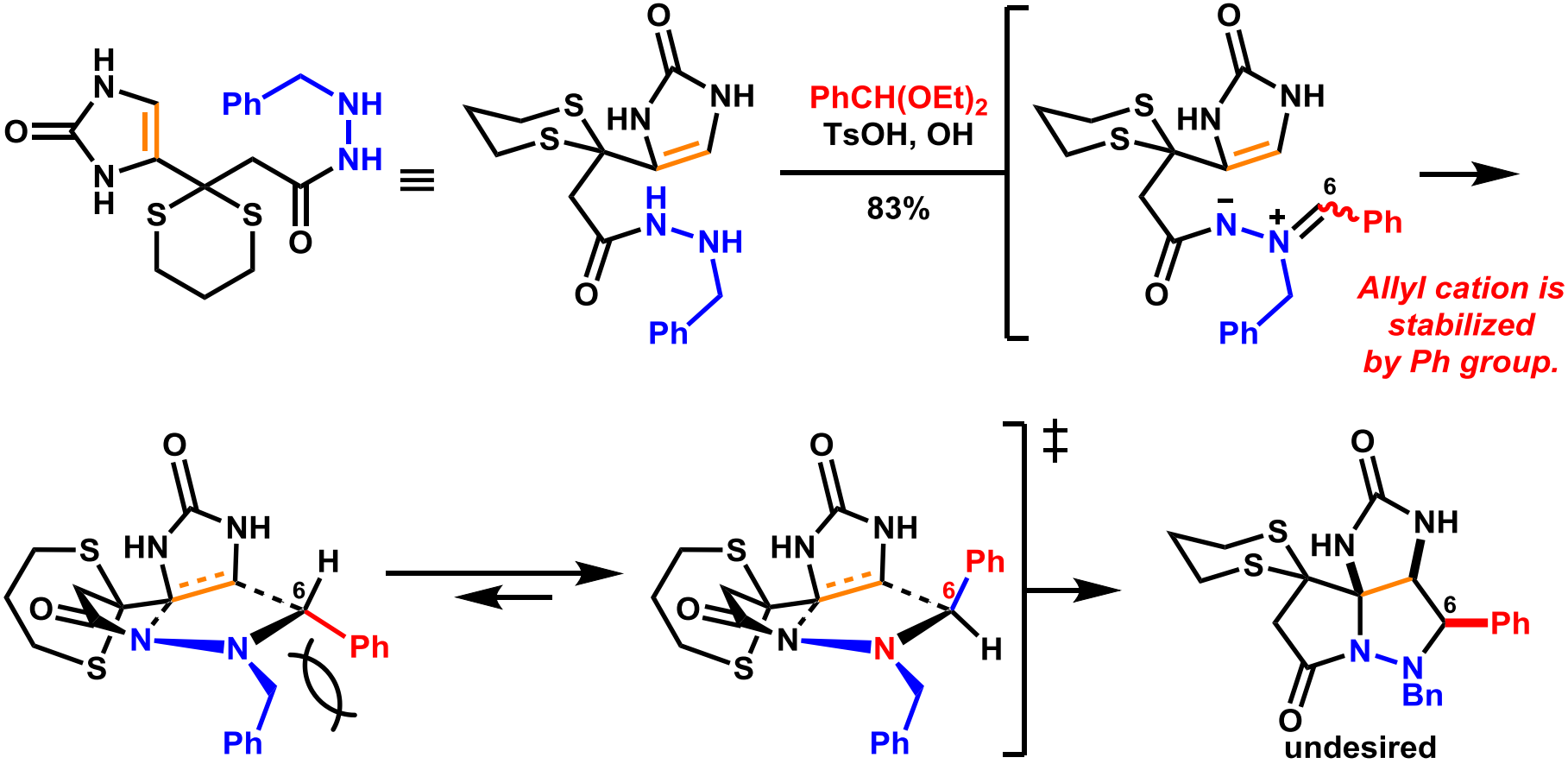
Synthesis of Precursor of Cycloaddition



Synthesis of Precursor of Cycloaddition

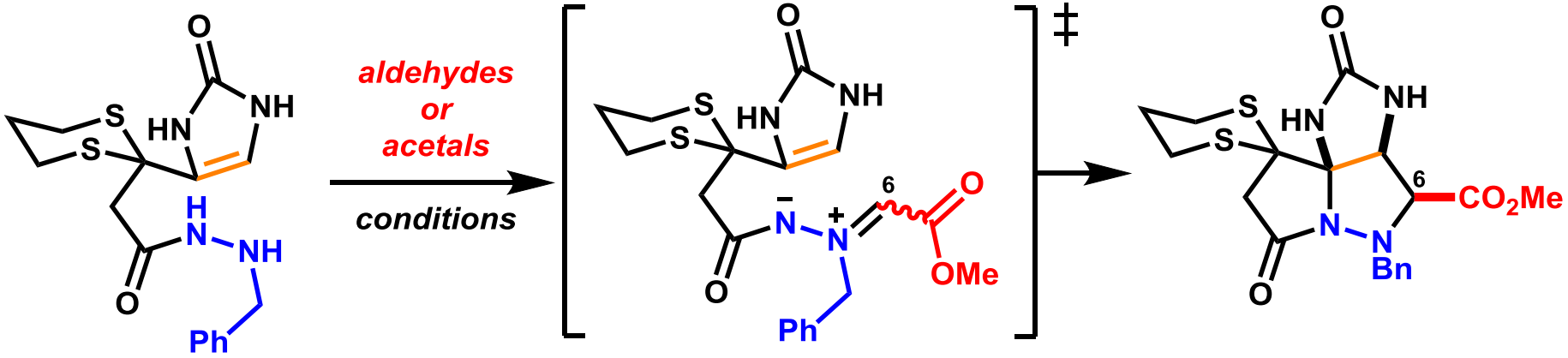


Kinetic Controlled 1,3-Dipolar Cycloaddition

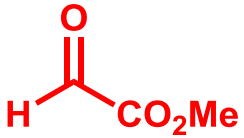
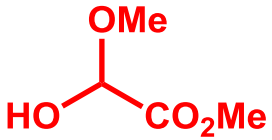
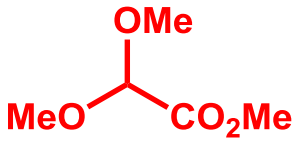
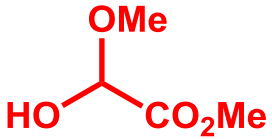


Modifications of *kinetic* stereoselectivity of cycloaddition were all failed.
-> The conditions of *thermodynamic* equilibration were explored.

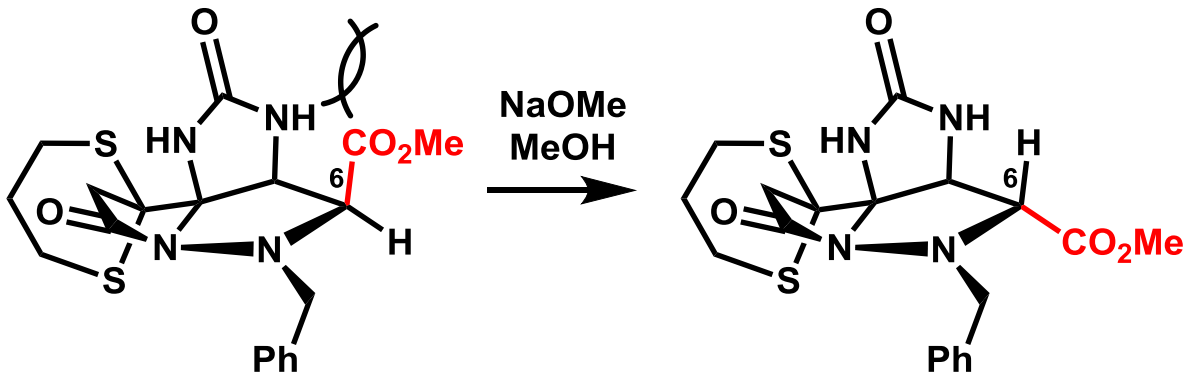
Attempts to Epimerize at C6 Stereochemistry (1)

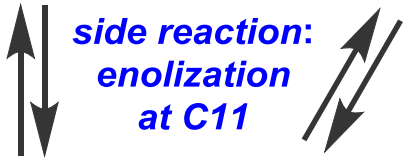


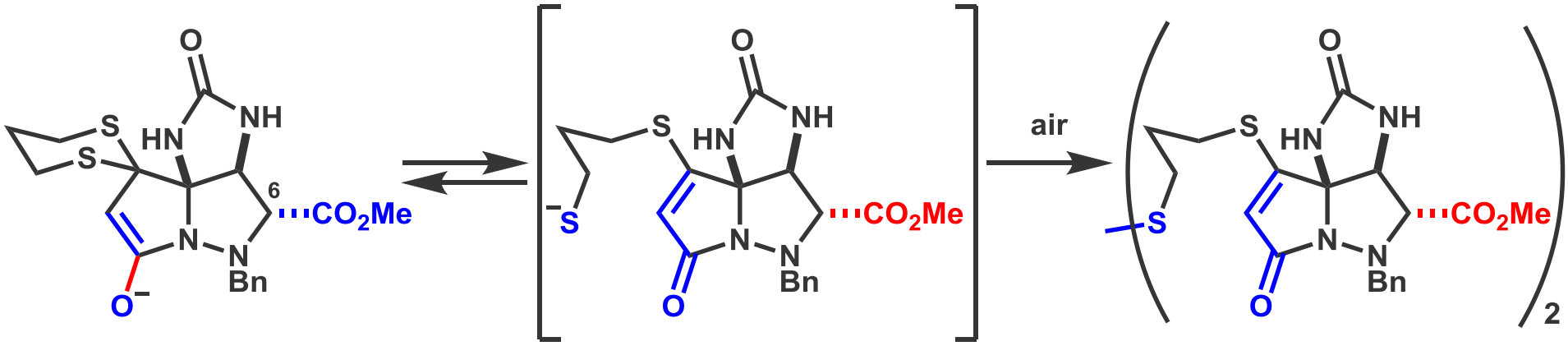
Cation of dipole was unstabilized by -CO_2Me (electron-withdrawing group)?

entry	*aldehydes/acetals*	*conditions*	result
1		TsOH, DMF 80 °C	decomposed
2		TsOH, DMF 80 °C	no reaction
3		TsOH, DMF 80 °C	no reaction
4		$BF_3{\cdot}Et_2O$ MeCN, reflux	67%

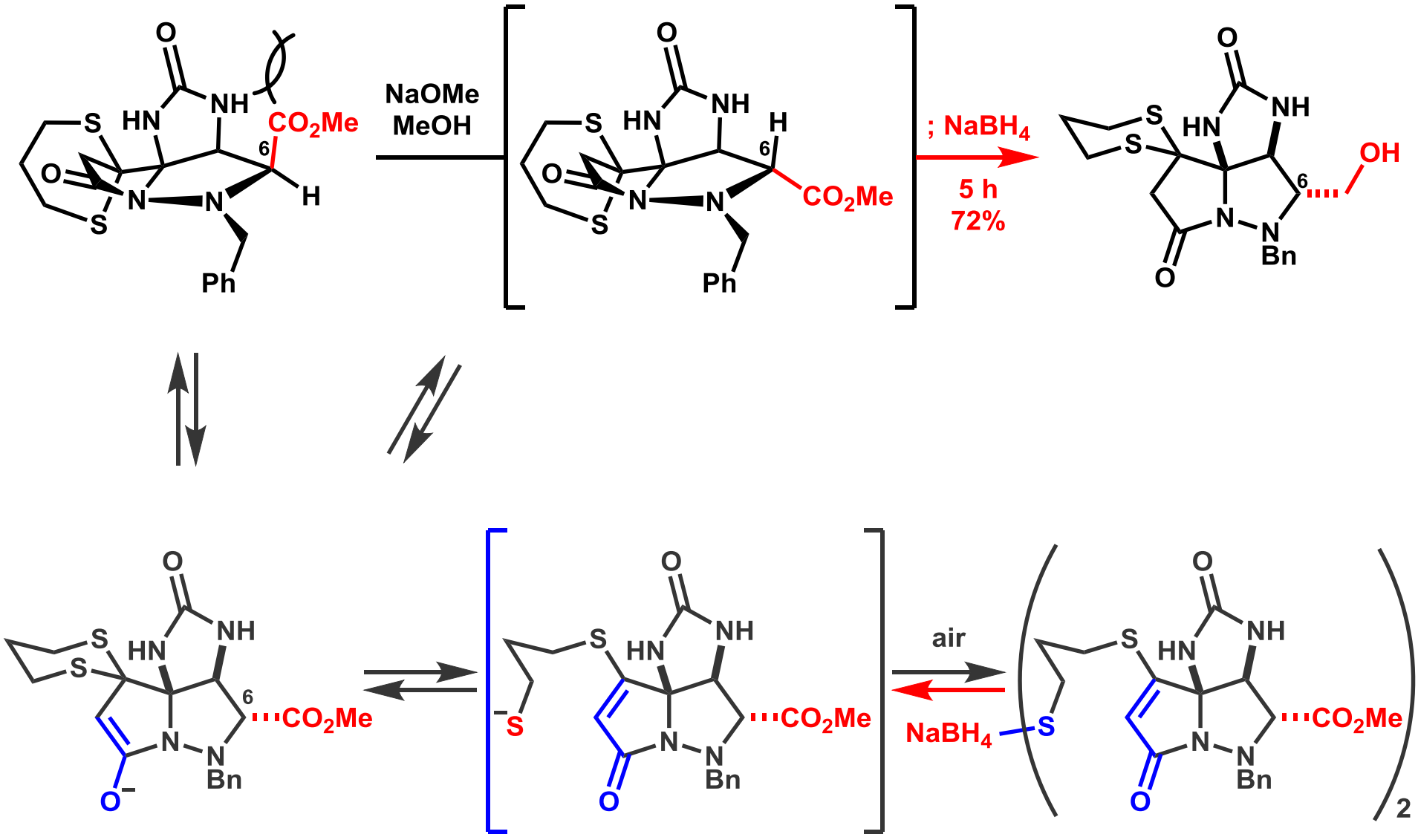
Attempts to Epimerize at C6 Stereochemistry (2)



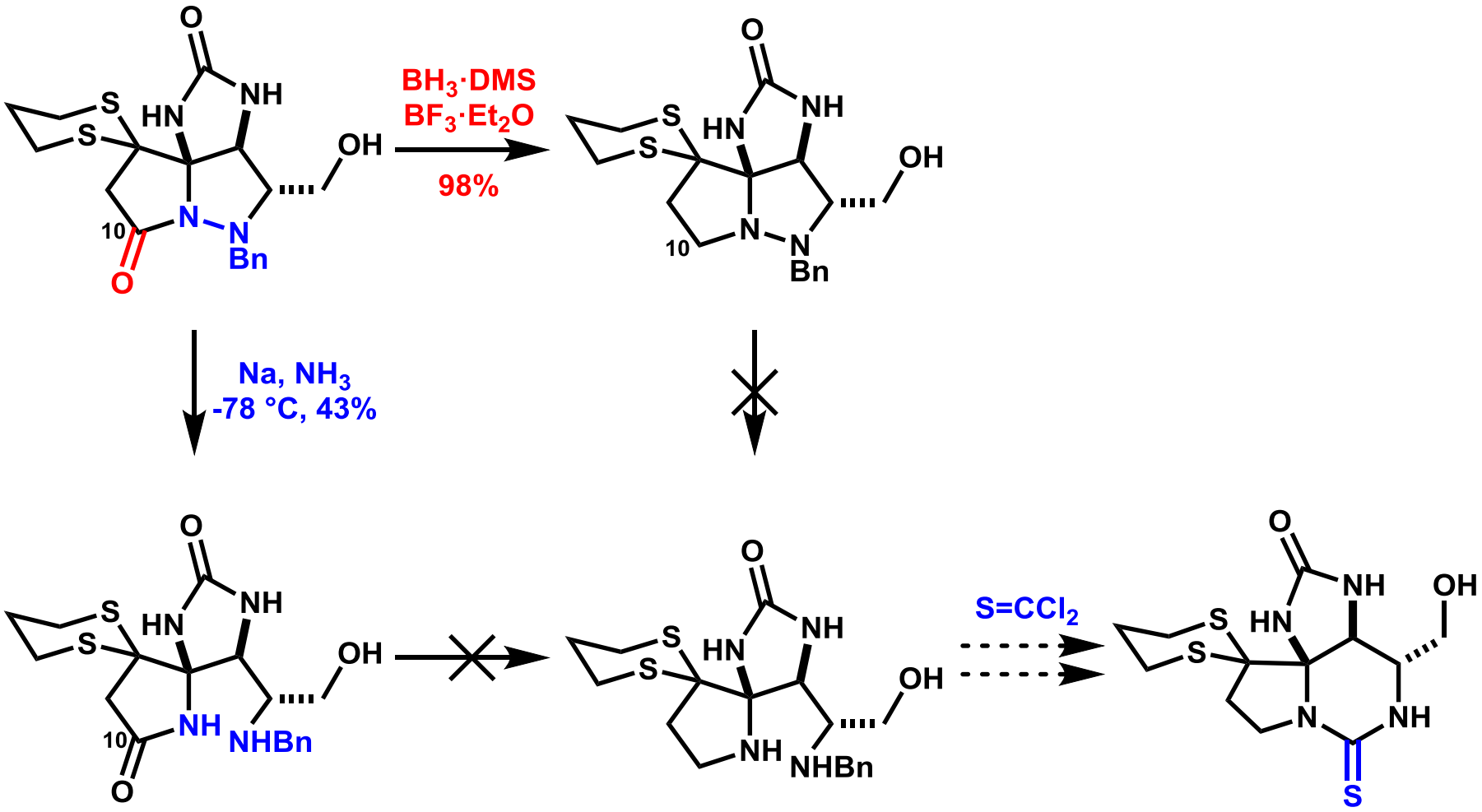




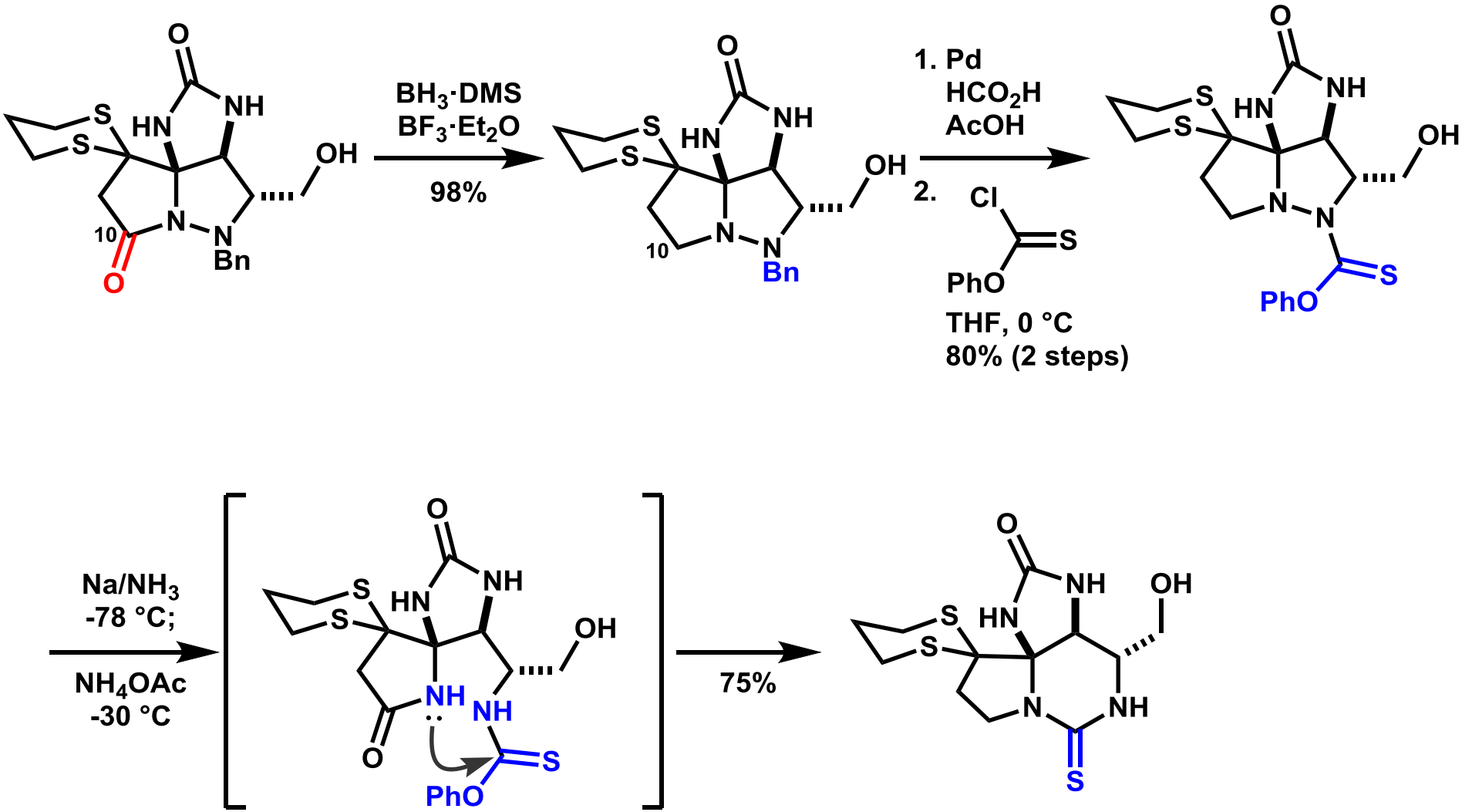
Attempts to Epimerize at C6 Stereochemistry (2)



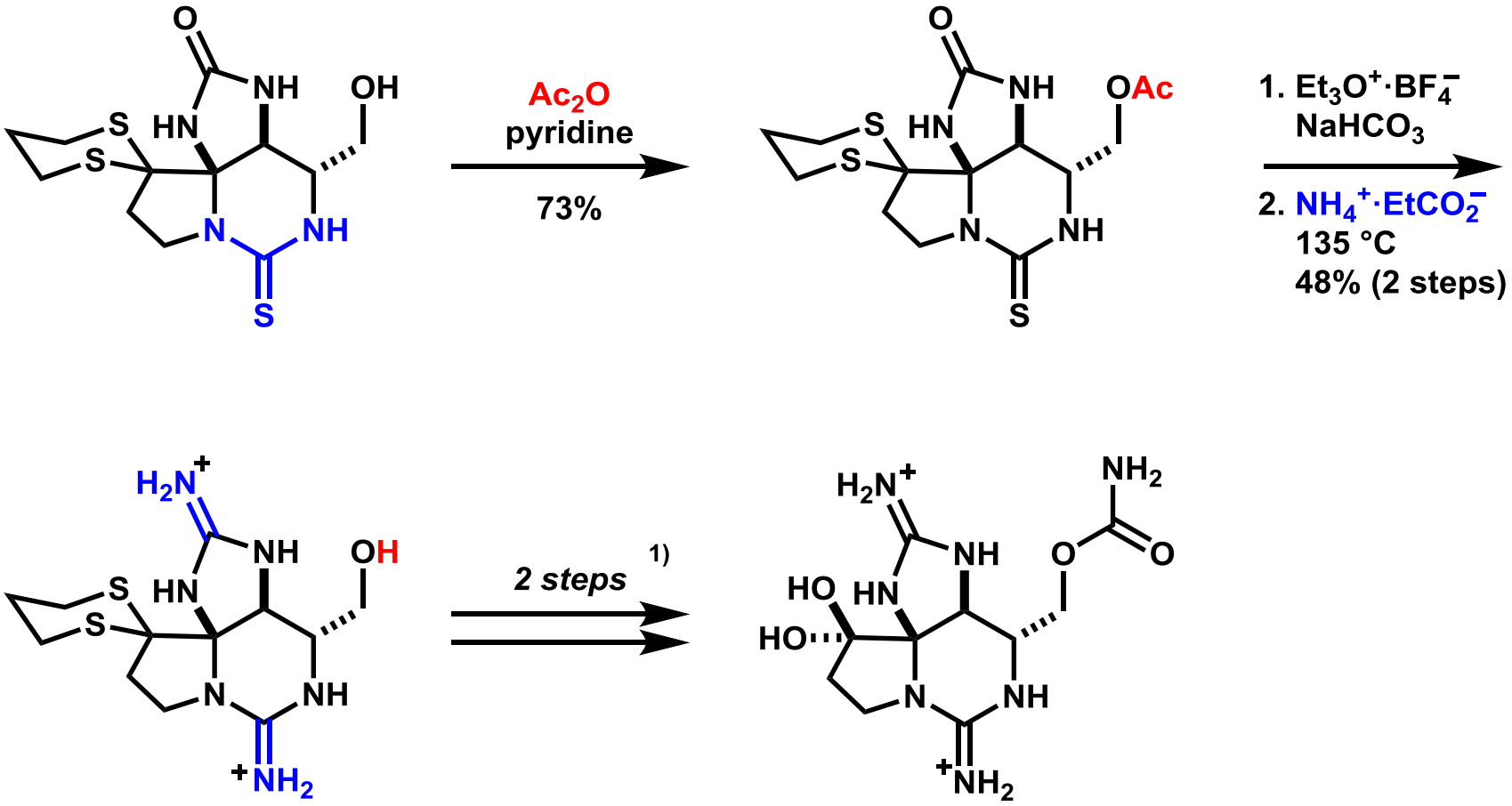
N-N bond Cleavage and Thiourea Construction (1)



N-N bond Cleavage and Thiourea Construction (2)



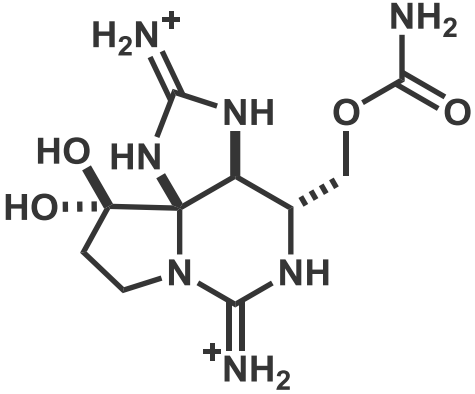
Completion of Formal Synthesis of (±)-STX



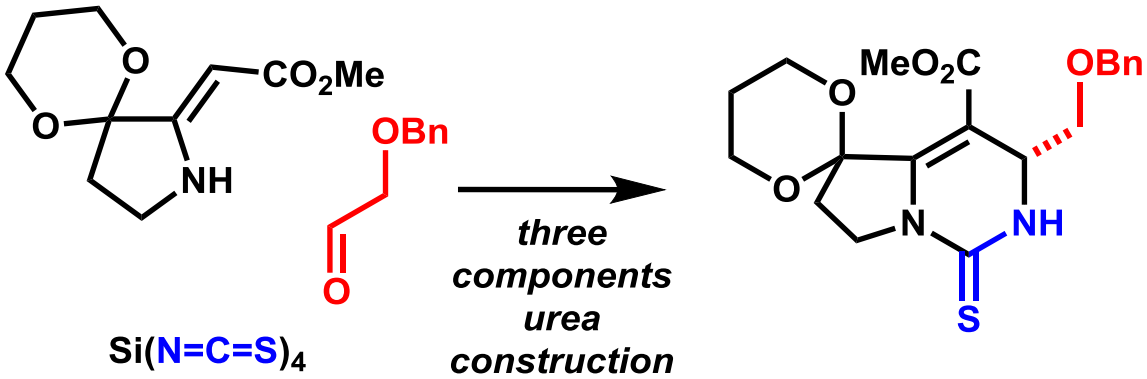
1. Tanino, H.; Nakata,T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 2818.

Contents

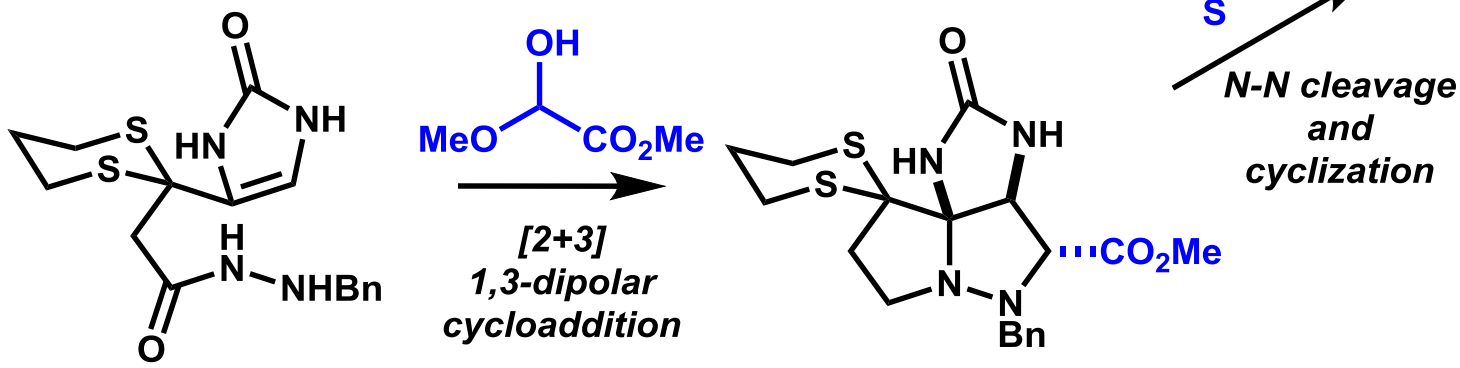
Brief Summary



Kishi's route (17 steps, total 0.35%)*

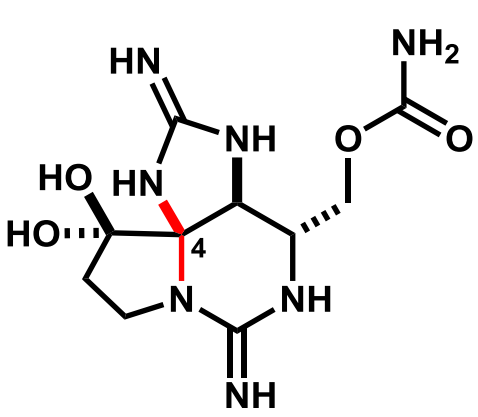


Jacobi's route (16 steps, total 0.44%)



* **Kishi achieved synthesis of (-)-STX, unnatural form, adding more 5 steps to previous route.;** Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 7001.

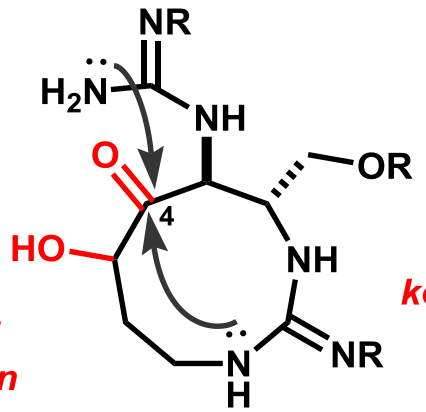
Synthetic Approach to (+)-STX by Du Bois



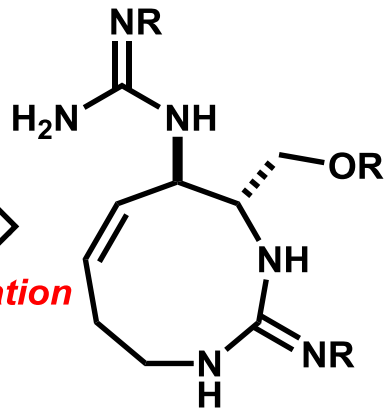
(+)-saxitoxin

deprotection of guanidine

transformation of nine-membered ring to STX skeleton

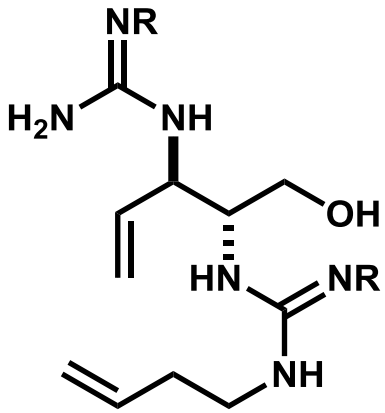


ketohydroxylation



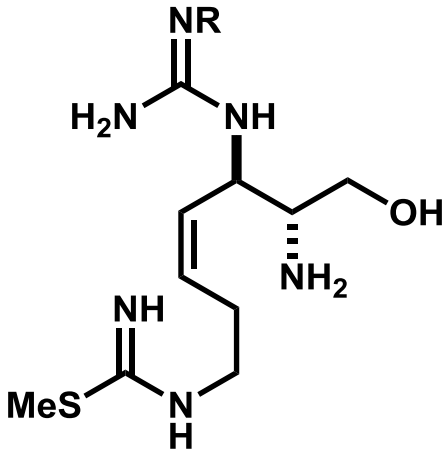
Ring Closing Metathesis

or isothiourea condensation



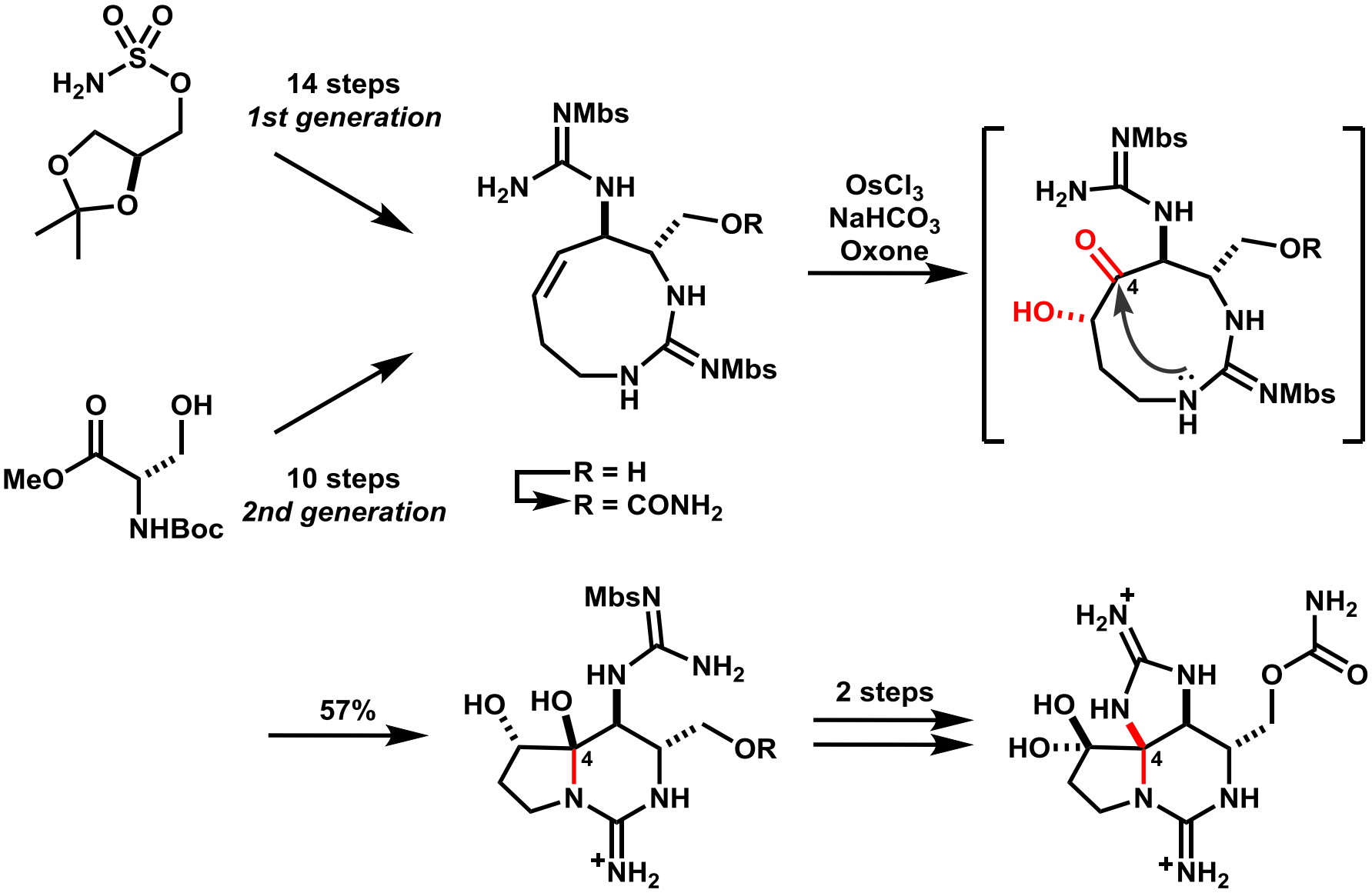
Ring Closing Metathesis precursor

or



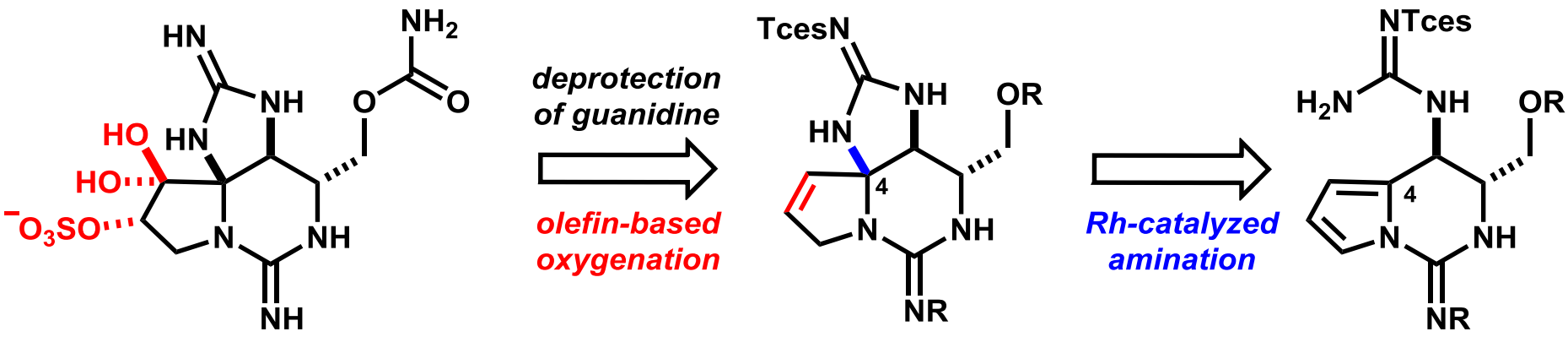
isothiourea condensation precursor

Total Synthesis of (+)-STX



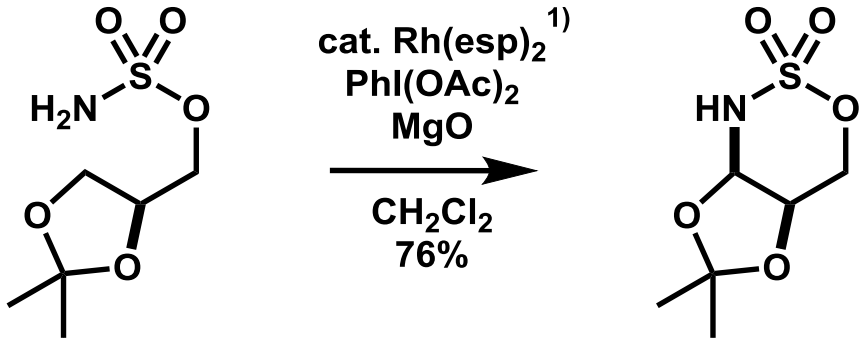
-> GTX could not be synthesized with this route.
New *route suited for functionalized analogues is needed.*

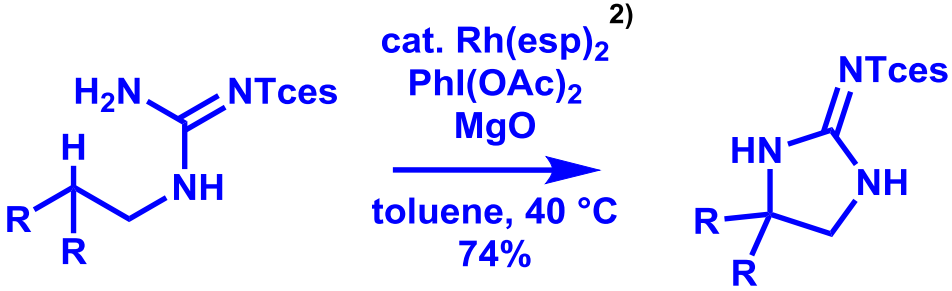
Synthetic Approach to (+)-GTX by Du Bois (1)

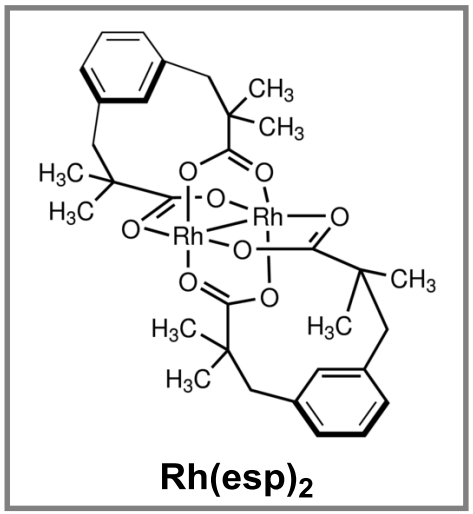


(+)-gonyautoxin 3

Rh-catalized C-H amination reaction



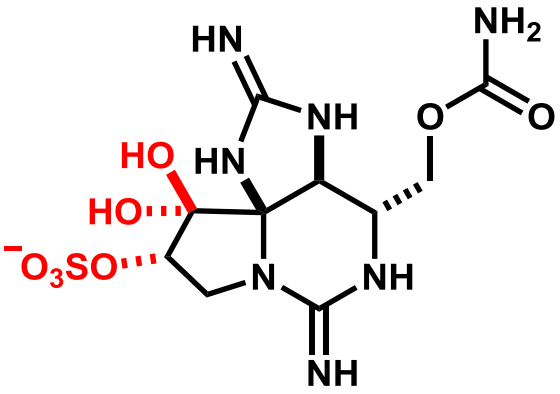




-Tces = $-SO_3CH_2CCl_3$

1. Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc*. **2006**, *128*, 3926.
2. Du Bois, J. et al. Org. Lett. **2006**, *8*, 1073.

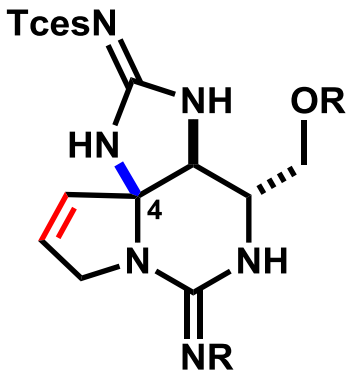
Synthetic Approach to (+)-GTX by Du Bois (2)



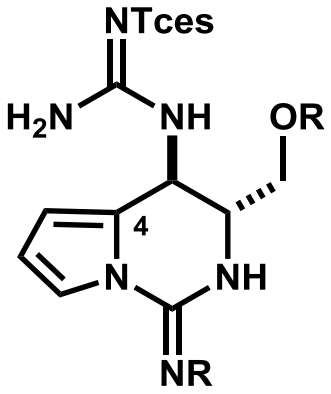
(+)-gonyautoxin 3

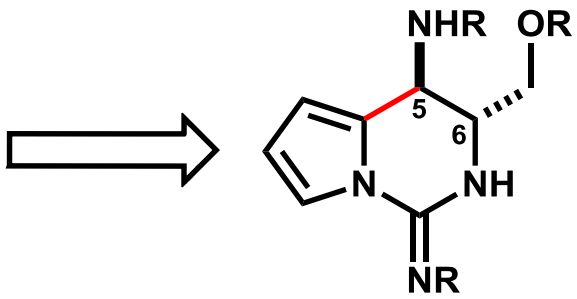
deprotection of guanidine

olefin-based oxygenation

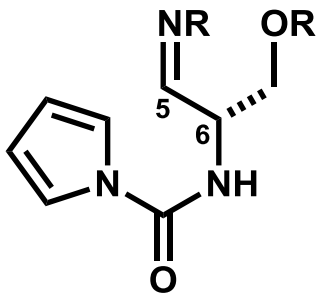


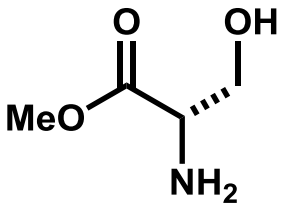
Rh-catalyzed amination





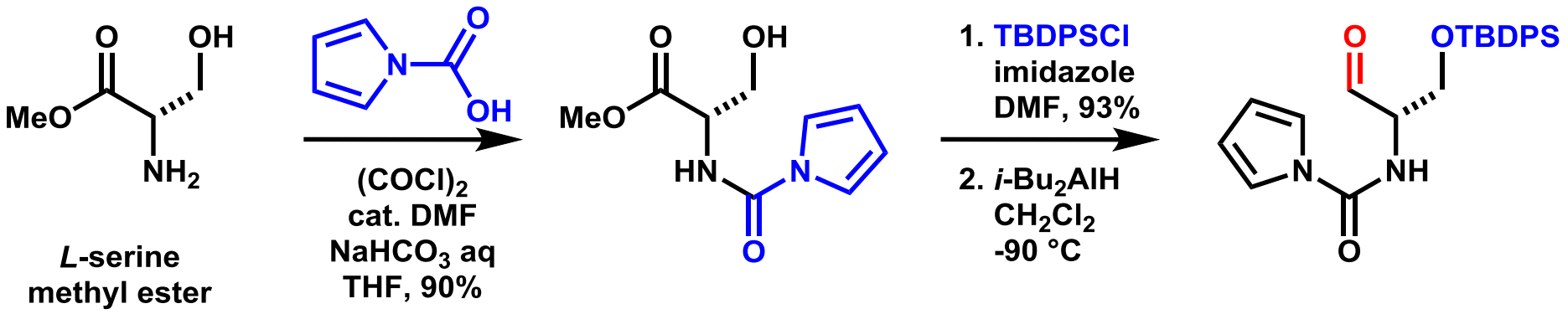
Pictet-Spengler reaction

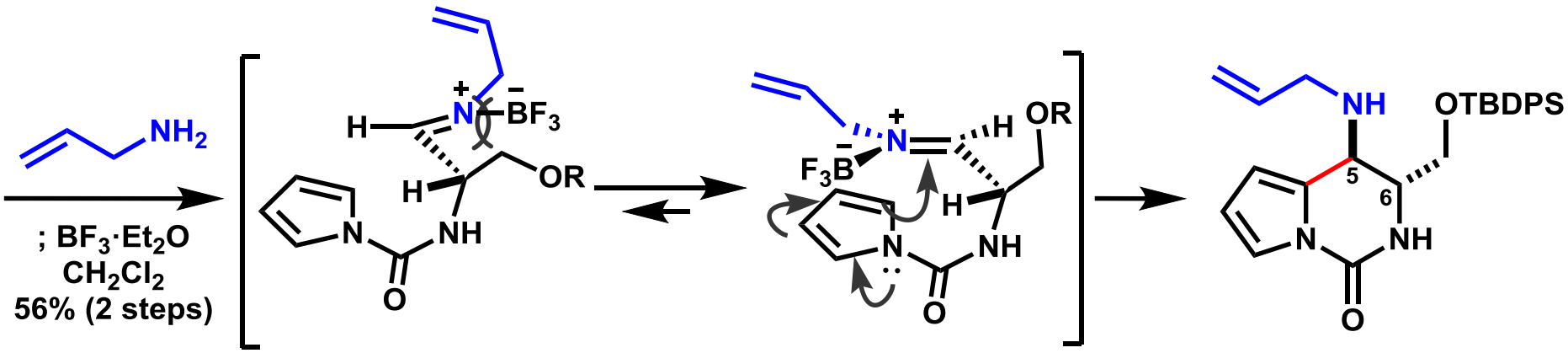




L-serine methyl ester

Total Synthesis of (+)-GTX (1)
– Stereocontrolled Pictet-Spengler Reaction –

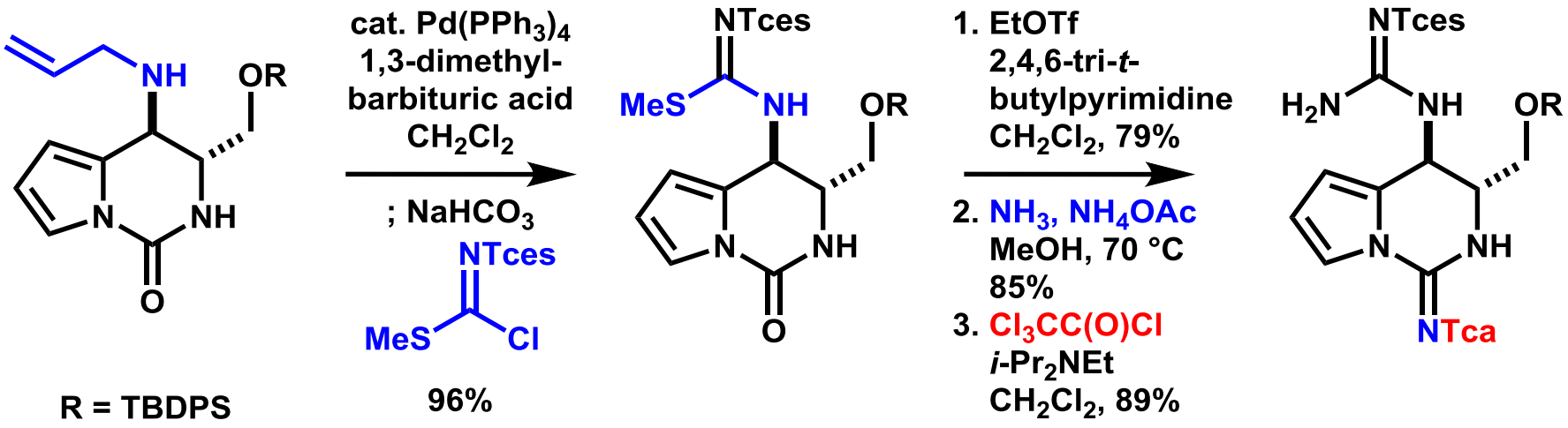


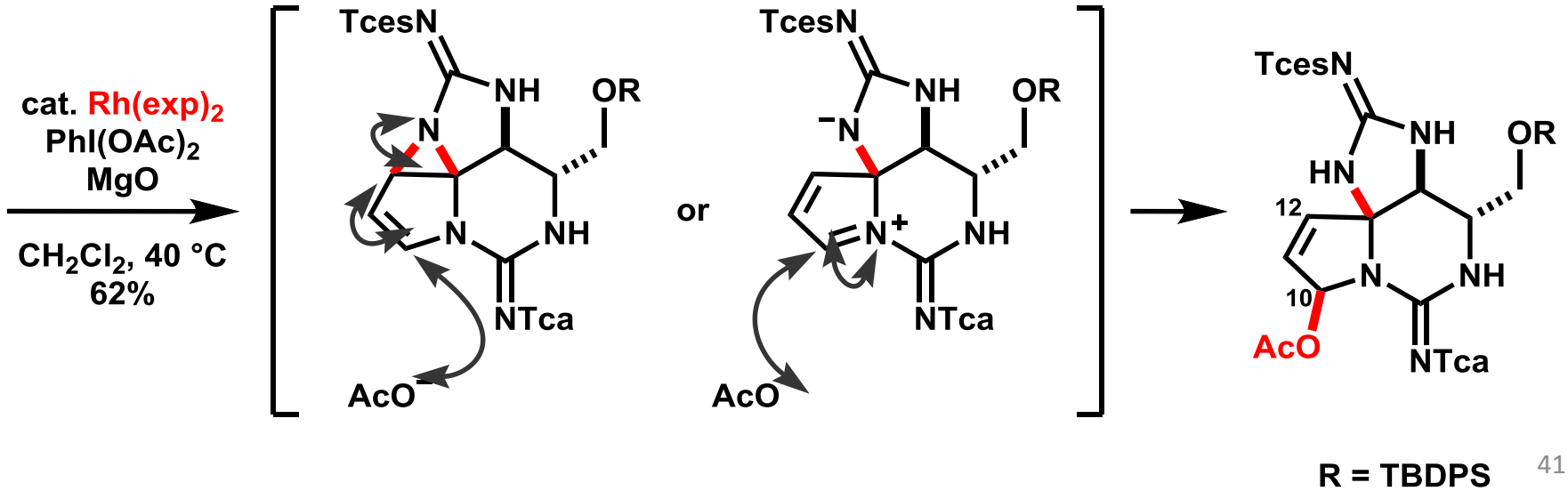


TS of Pictet-Spengler reaction
(1,3-allylic strain is minimized)

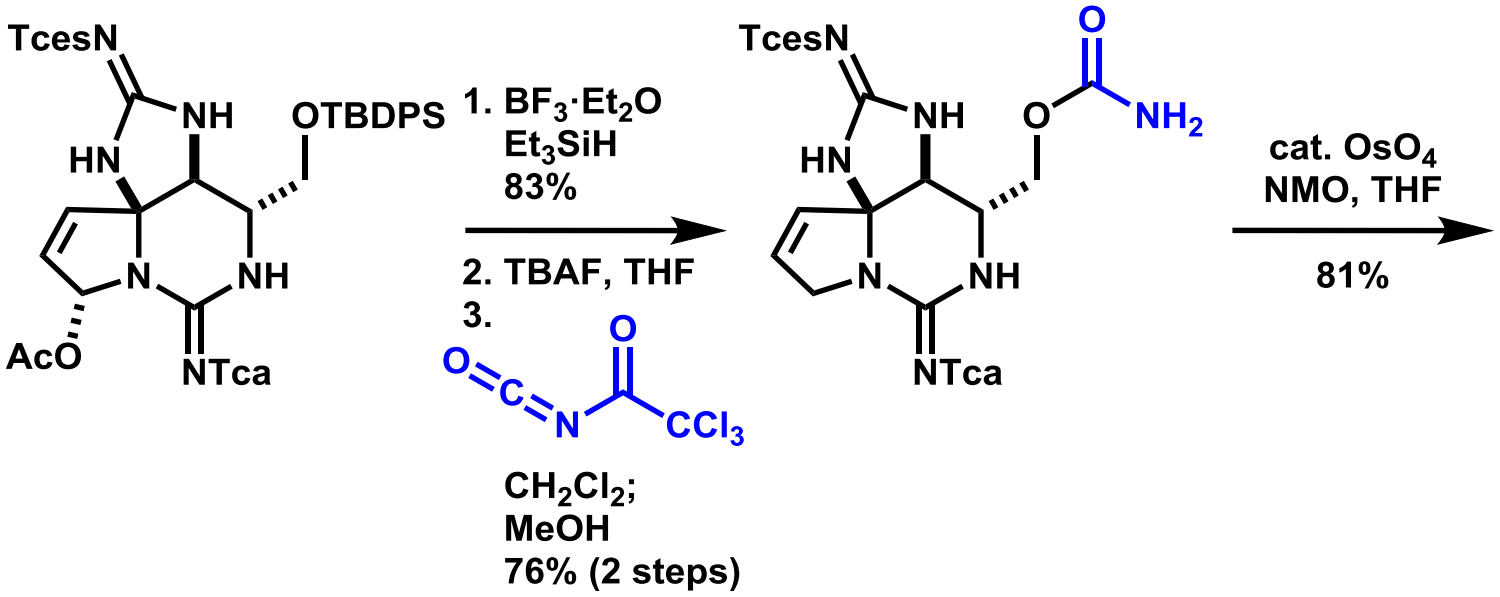
trans **selectivity (>20:1)**

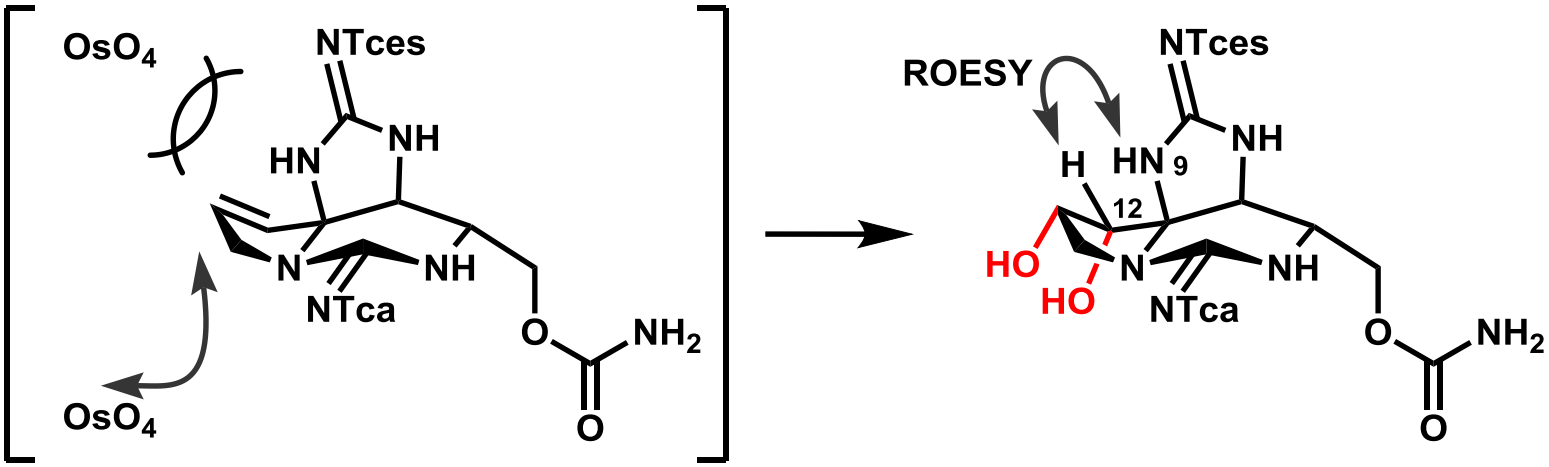
Total Synthesis of (+)-GTX (2)
– Aminal Construction by Rh-catalyzed Amination –



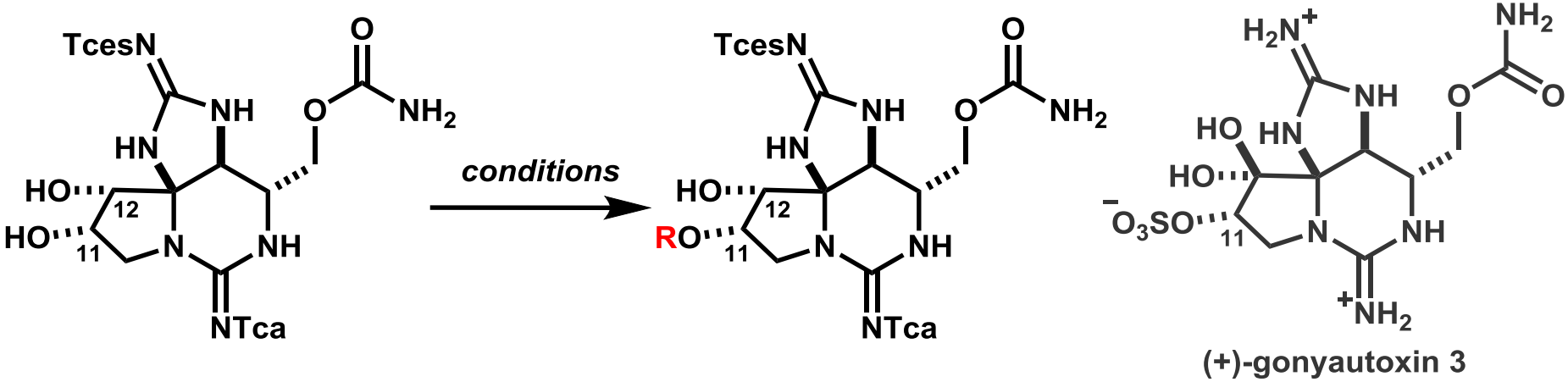


Total Synthesis of (+)-GTX (3) – Dihydroxylation –



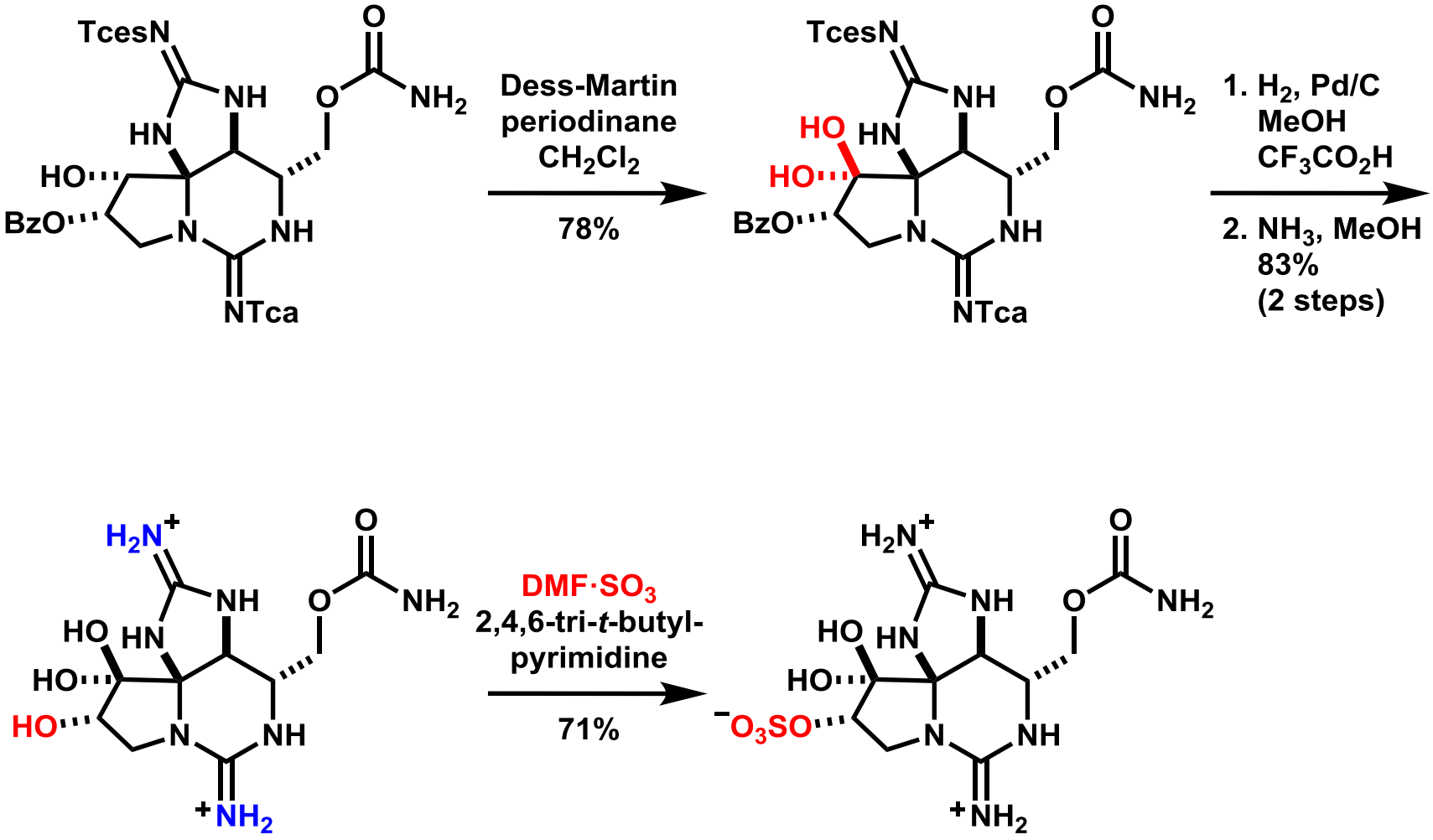


Total Synthesis of (+)-GTX (4) – Protection of 11-OH –



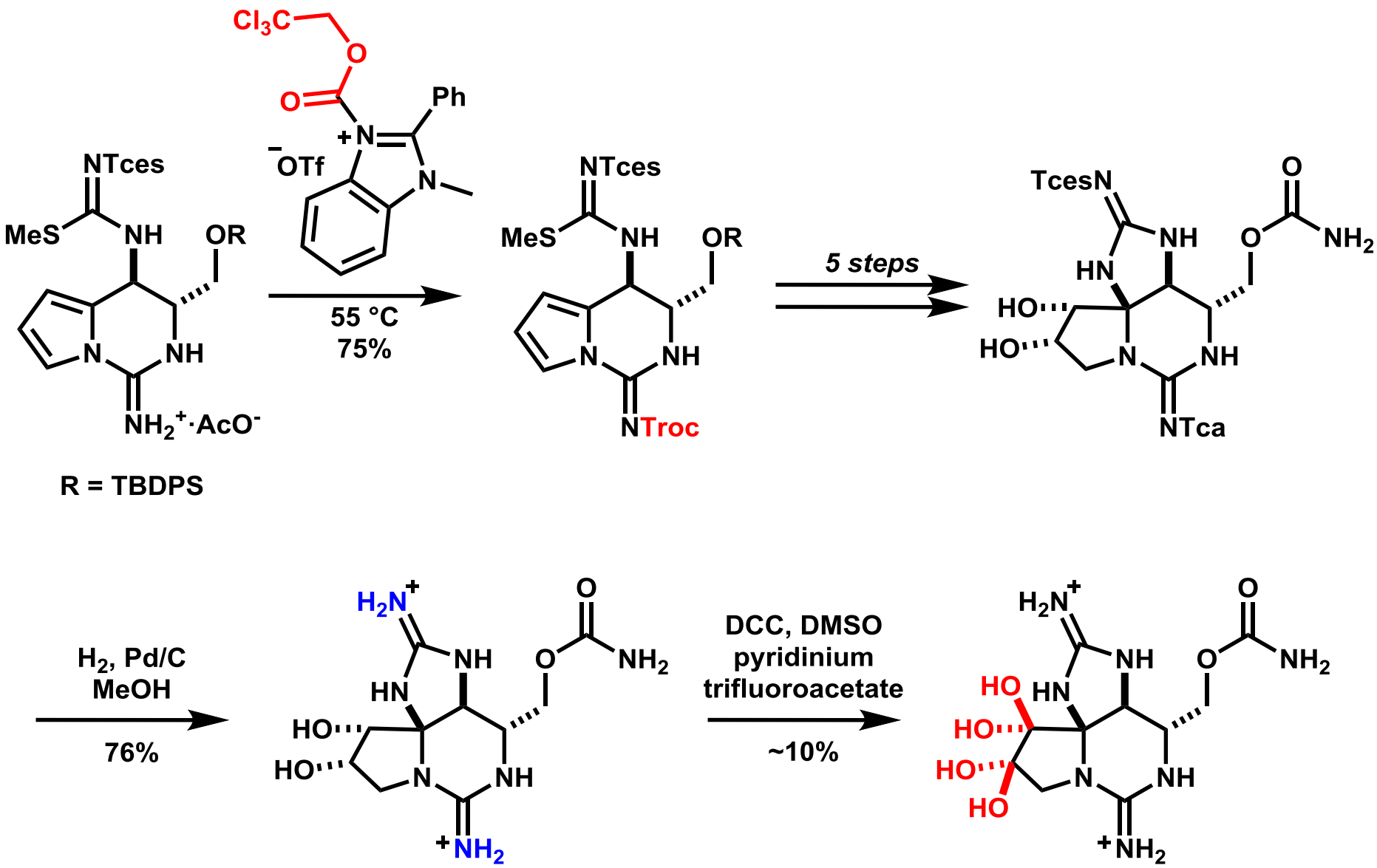
entry	electrophile	Base	temperature[°C]	yield
1	TcesCl	NEt_3, DMAP	23	-
2	TcesN-Me-imidazolium$^+$·OTf-	N-Me-imidazole	23	-
3	TESSI	TESSI	23	30-50
4	Ac_2O	2,6-lutidine	23	-
5	Ac_2O	2,4,6-tri-*t*-butylpyrimidine	40	trace
6	(*n*-PrCO)$_2$O	2,4,6-tri-*t*-butylpyrimidine	66	40
7	$(PhCO)_2O$	2,4,6-tri-*t*-butylpyrimidine, DMAP	0	40
8	PhC(O)CN	DMAP	-78	69

Total Synthesis of (+)-GTX (5)



(+)-gonyautoxin 3

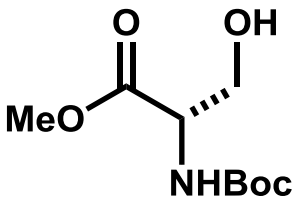
Access to (+)-11,11-Dihydroxysaxitoxin



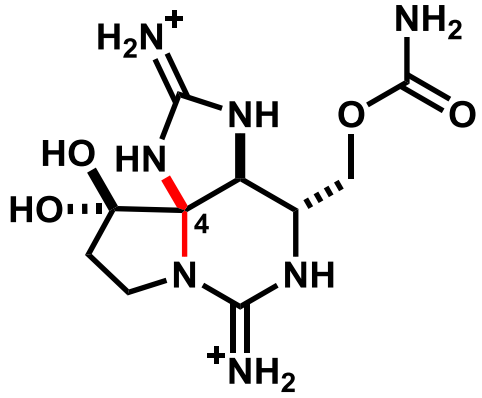
R = TBDPS

(+)-11,11-dihydroxySTX

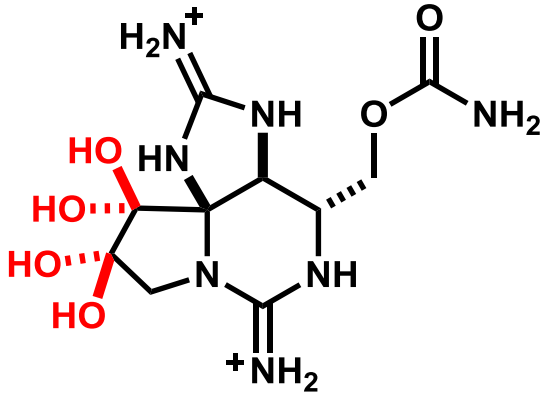
Summary



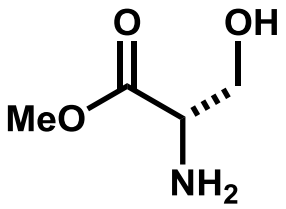
N-Boc-*L*-serine
methyl ester



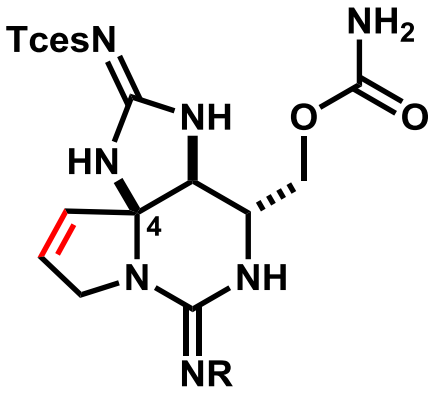
(+)-saxitoxin
14 steps, total 1.73%



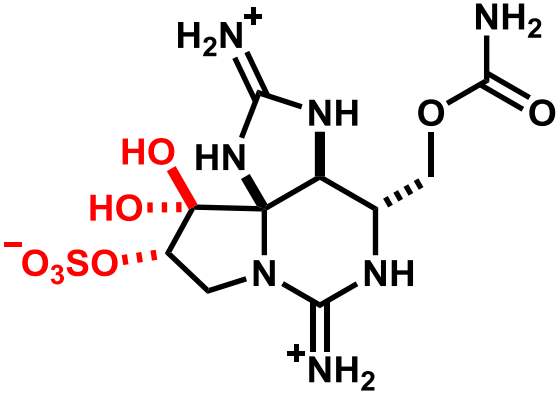
(+)-11,11-dihydroxySTX



L-serine methyl ester



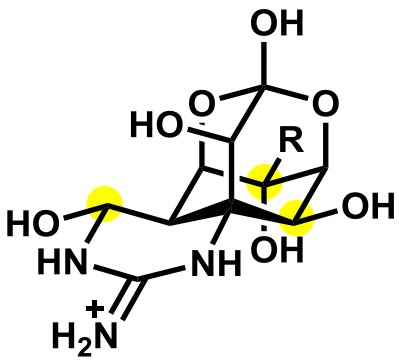
olefin intermediate



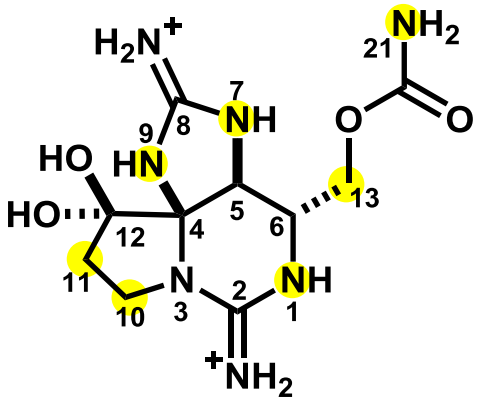
(+)-gonyautoxin 3
18 steps, total 2.70%

Appendix

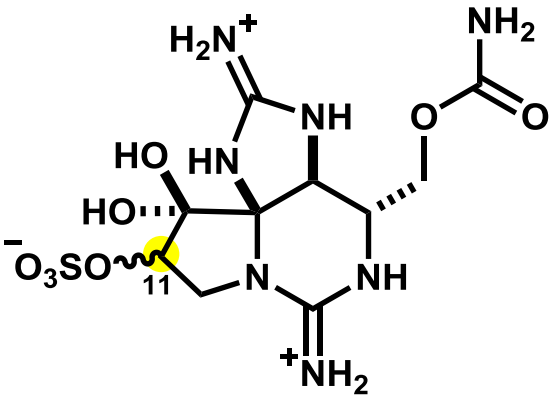
Why Saxitoxin?



(-)-tetrodotoxin (TTX)
R = CH_2OH



(+)-saxitoxin (STX)



(+)-gonyautoxin (GTX)

Why synthesis of (+)-STX is needed?

· STX is an important tool in ion channel research.

-> The concise and scalable synthetic route to STX is needed for biological assay.

Why not other blockers of Na^+ ion channels (tetrodotoxin/TTX), but STX?

- tetrodotoxin
  · few carbon atoms unmodified
  · Na^+ channels inhibition of deoxygenated TTX analogues is lower than that of TTX.
- saxitoxin
  · 7 unfunctionalized carbon/nitorogen atoms (yellow highlighted)
  · comparable potency of STX analogues to STX

-> existence of various structural analogues

Final purpose of Du Bois

· new Na^+ channel blockers with designed function