Synthetic methodology for Tetrodotoxin

Literature Seminar

2017/9/30

Takahiro Watanabe

Contents

Contents

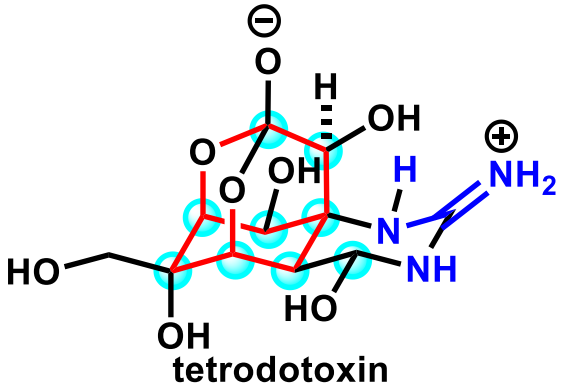
Introduction: Tetrodotoxin

Isolation

from pufferfish (*Spheroides rubripes*)

Biological activity

potent inhibitor of voltage-gated sodium channels (Na_vs)



tetrodotoxin

Structure

polyfunctionalized dioxaadamantane skeleton with nine contiguous stereogenic centers

cyclic guanidine containing a hemiaminal moiety

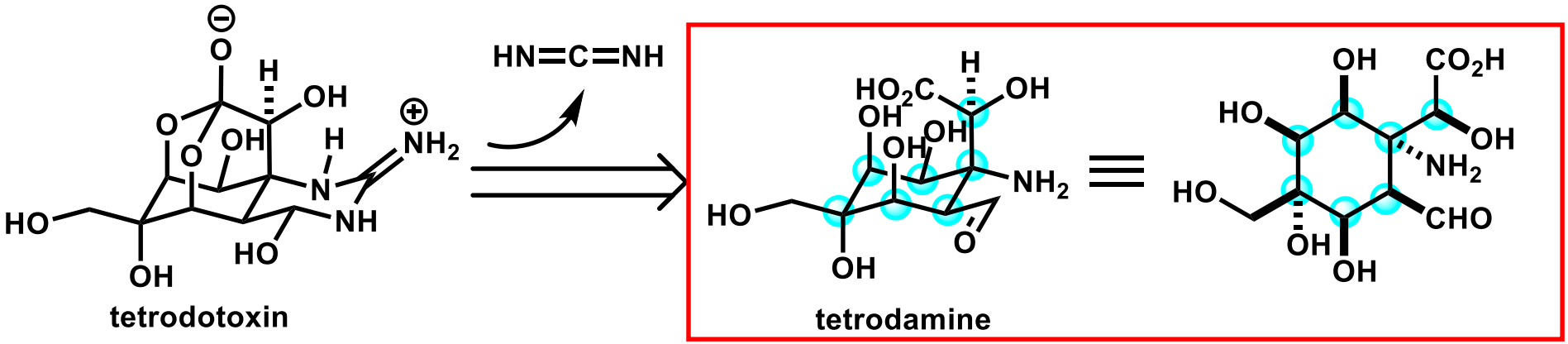
Total synthesis (five group)

racemic: Kishi (1972), Sato (2005)

enantioselective: Isobe (2003, 2004), Du Bois (2003), Sato (2008, 2010), Fukuyama (2017)

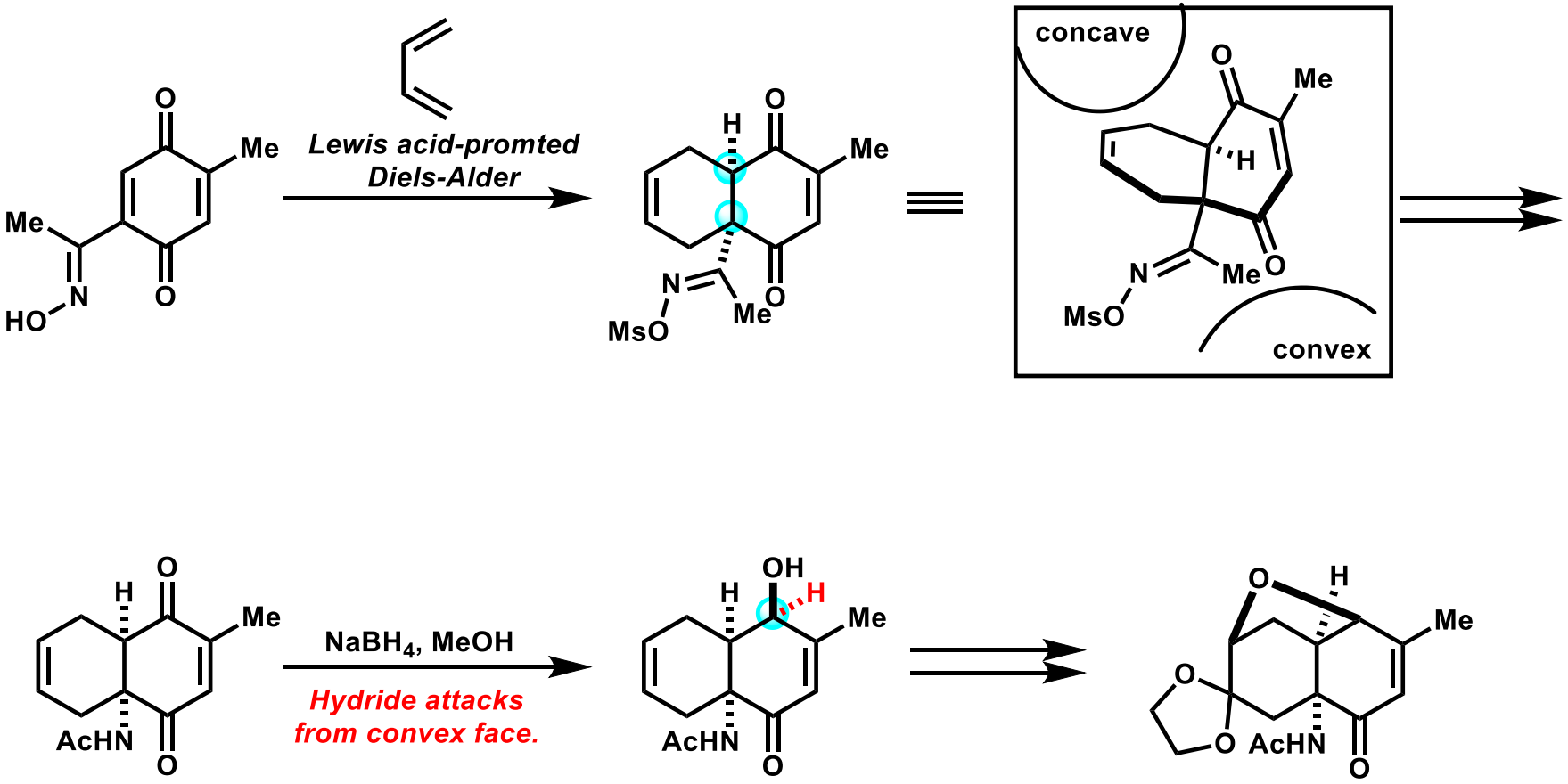
Kishi, Y.; Nakatsubo, F.; Aratani, M.; Goto, T.; Inoue, S.; Kakoi, H.; Sugiura, S. *Tetrahedron Lett*. **1970**, *11*, 5127.
Kishi, Y.; Nakatsubo, F.; Aratani, M.; Goto, T.; Inoue, S.; Kakoi, H. *Tetrahedron Lett*. **1970**, *11*, 5129.
Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217.
Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219.
Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798.
Nishikawa, T.; Urabe, D.; Isobe, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4782.
Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.
Sato, K.; Akai, S.; Sugita, N.; Ohsawa, T.; Kogure, T.; Shoji, H.; Yoshimura, J. *J. Org. Chem.* **2005**, *70*, 7496.
Sato, K.; Akai, S.; Shoji, H.; Sugita, N.; Yoshida, S.; Nagai, Y.; Suzuki, K.; Nakamura, Y.; Kajihara, Y.; Funabashi, M.; Yoshimura, J. *J. Org. Chem.* **2008**, *73*, 1234.
Akai, S.; Seki, H.; Sugita, N.; Kogure, T.; Nishizawa, N.; Suzuki, K.; Nakamura, Y.; Kajihara, Y.; Yoshimura, J.; Sato, K. *Bull. Chem. Soc. Jpn*. **2010**, *83*, 279.
Maehara, T.; Motoyama, K.; Toma, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2017**, *56*, 1549.

Common conceptual target



Contents

Kishi's approach



Kishi, Y.; Nakatsubo, F.; Aratani, M.; Goto, T.; Inoue, S.; Kakoi, H.; Sugiura, S. *Tetrahedron Lett.* **1970**, *11*, 5127.

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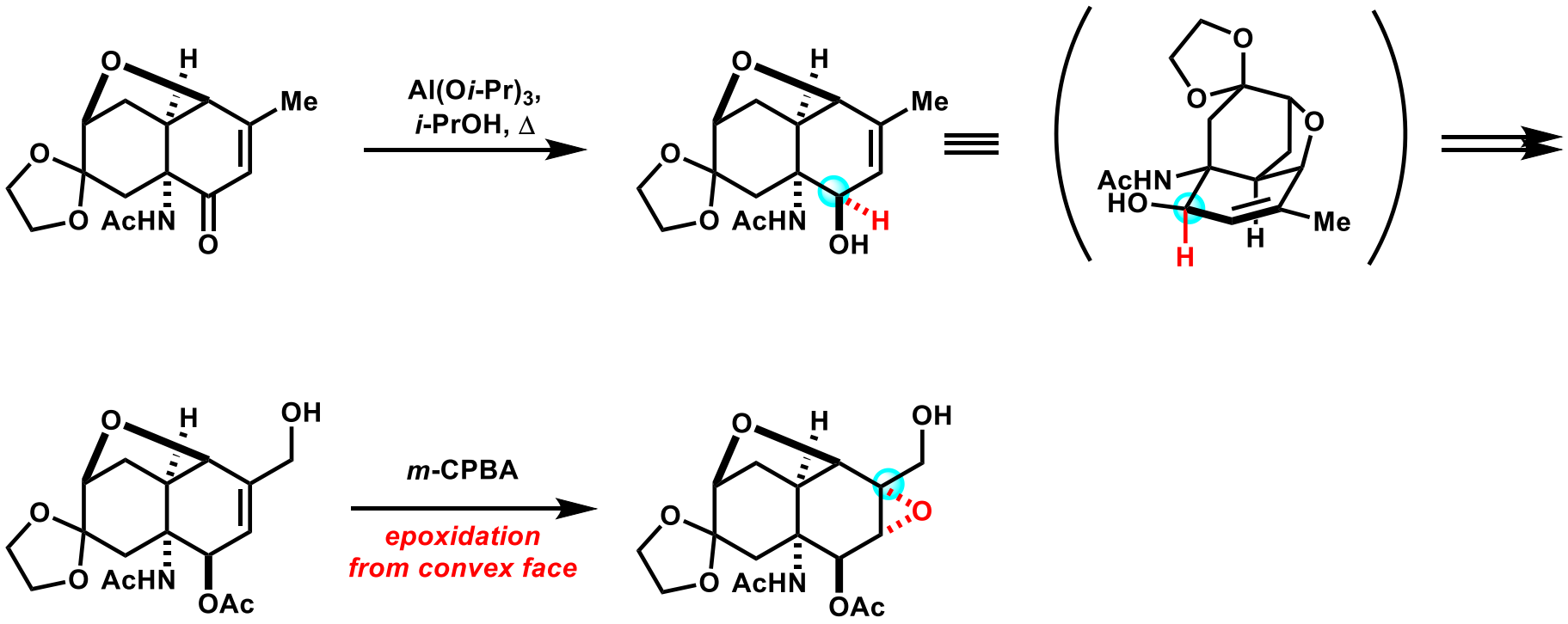

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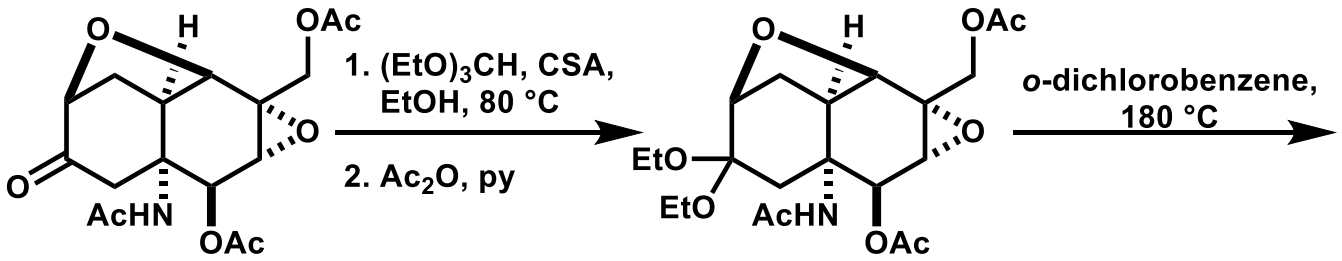
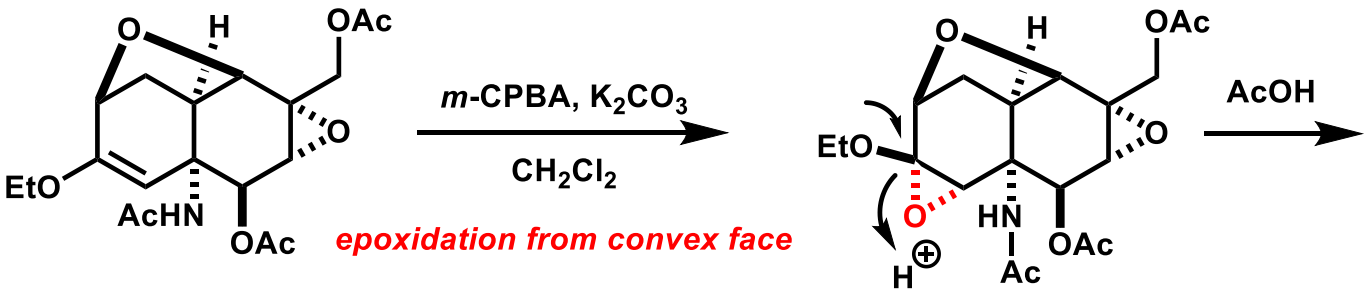
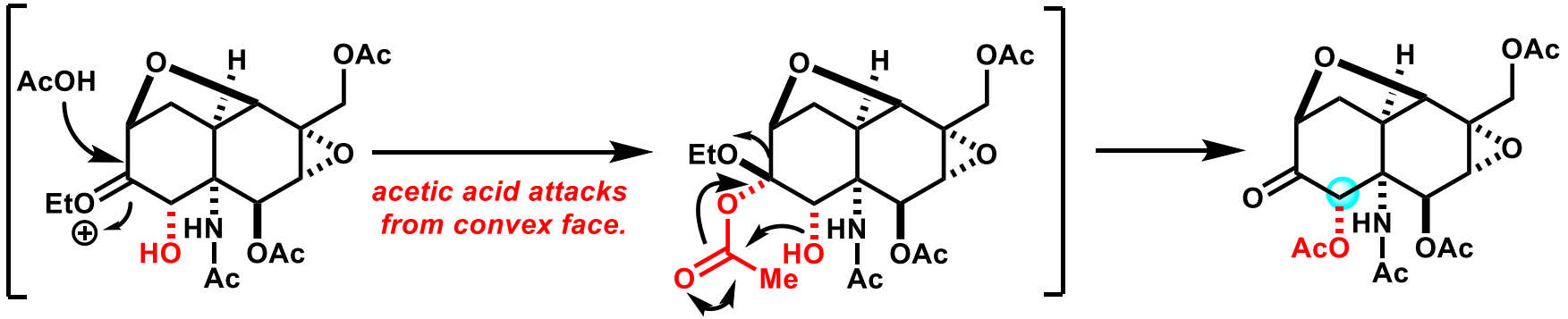
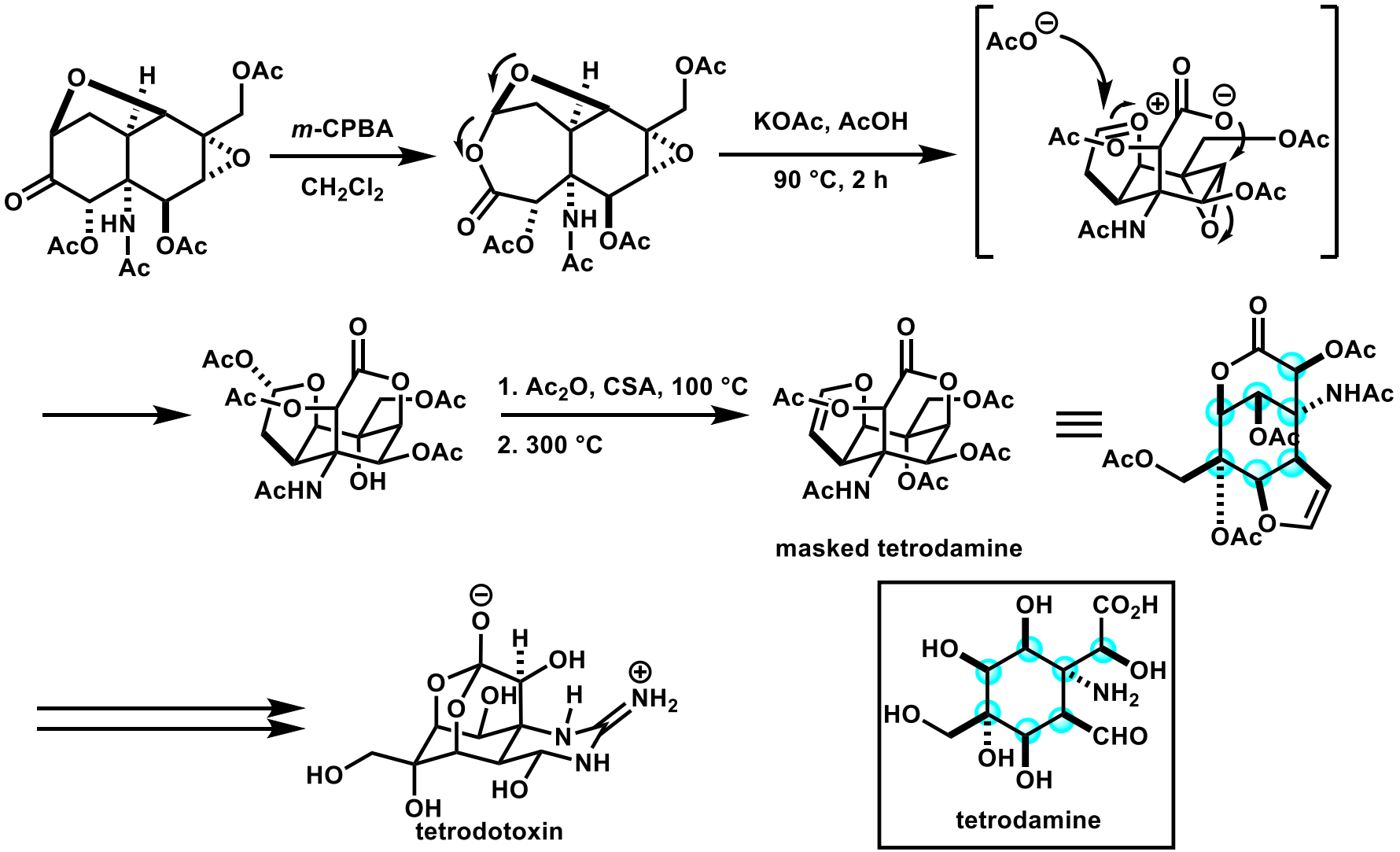






Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217.

Kishi's approach



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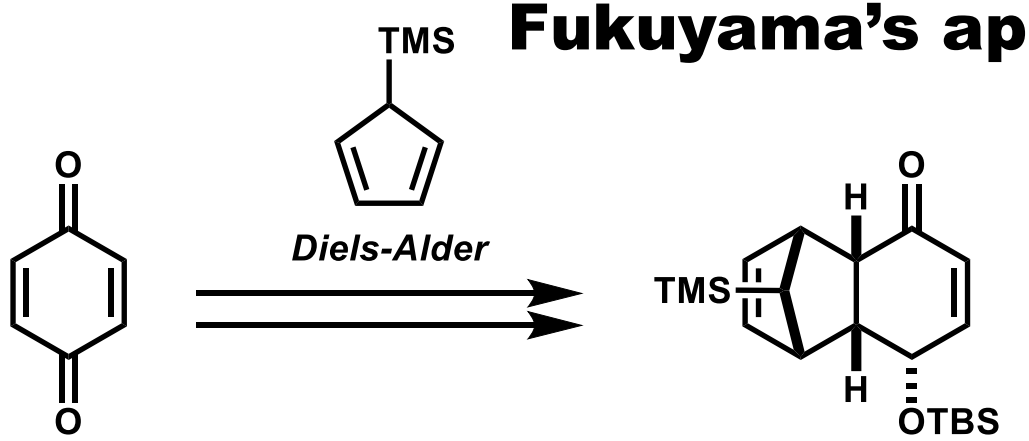
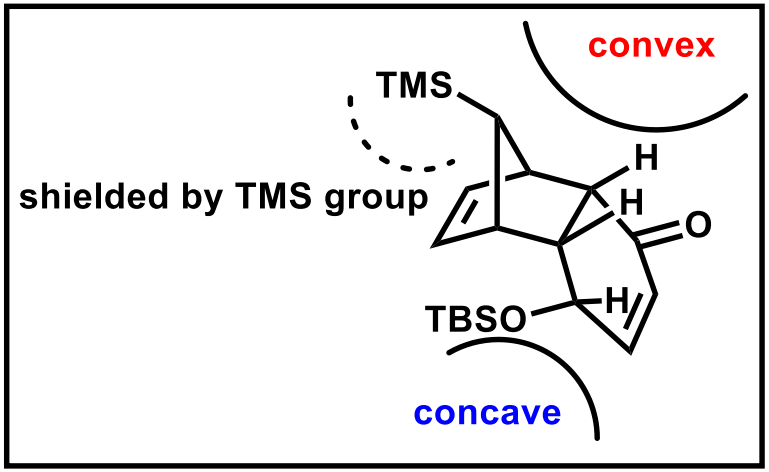
Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219.

Contents

Fukuyama's approach

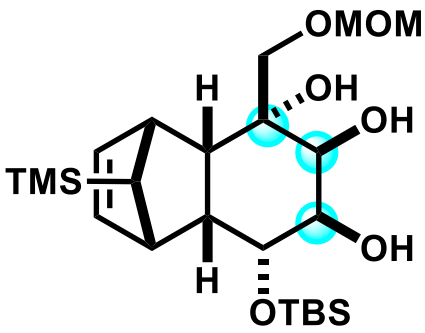


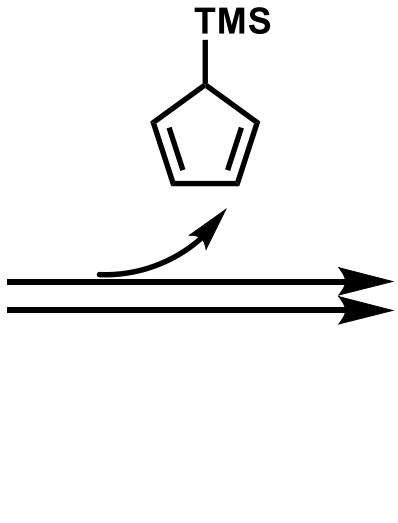


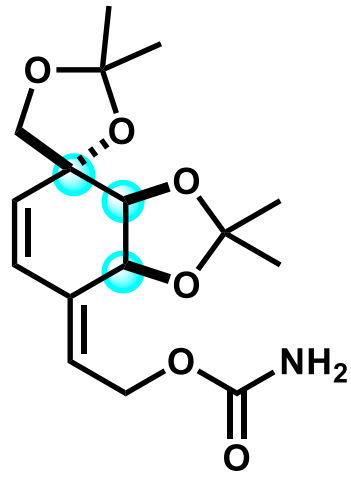
1,2-addition of hydroxymethyl equivalent

dihydroxylation

from convex face

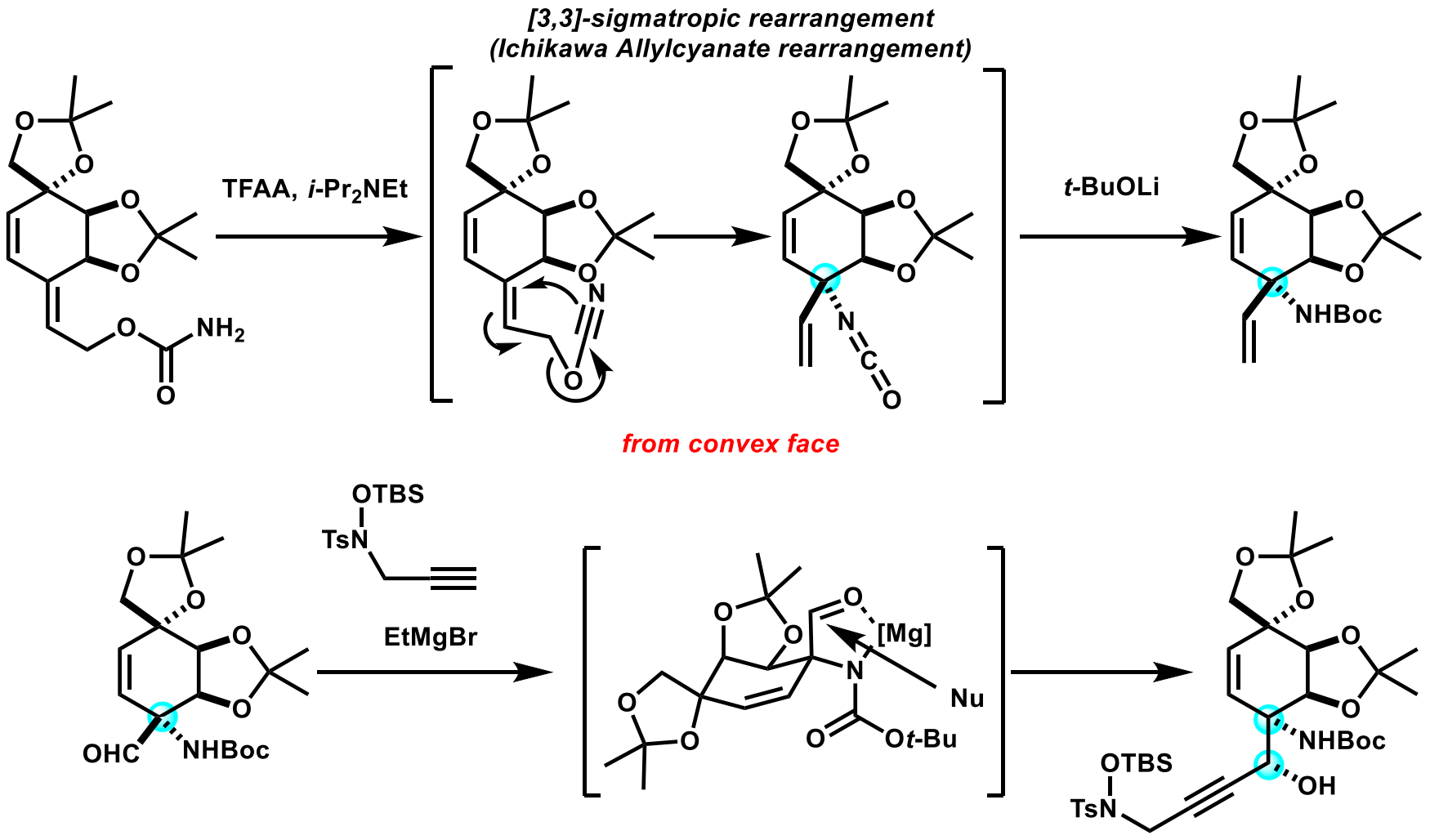






Maehara, T.; Motoyama, K.; Toma, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2017**, 56, 1549.

Fukuyama's approach



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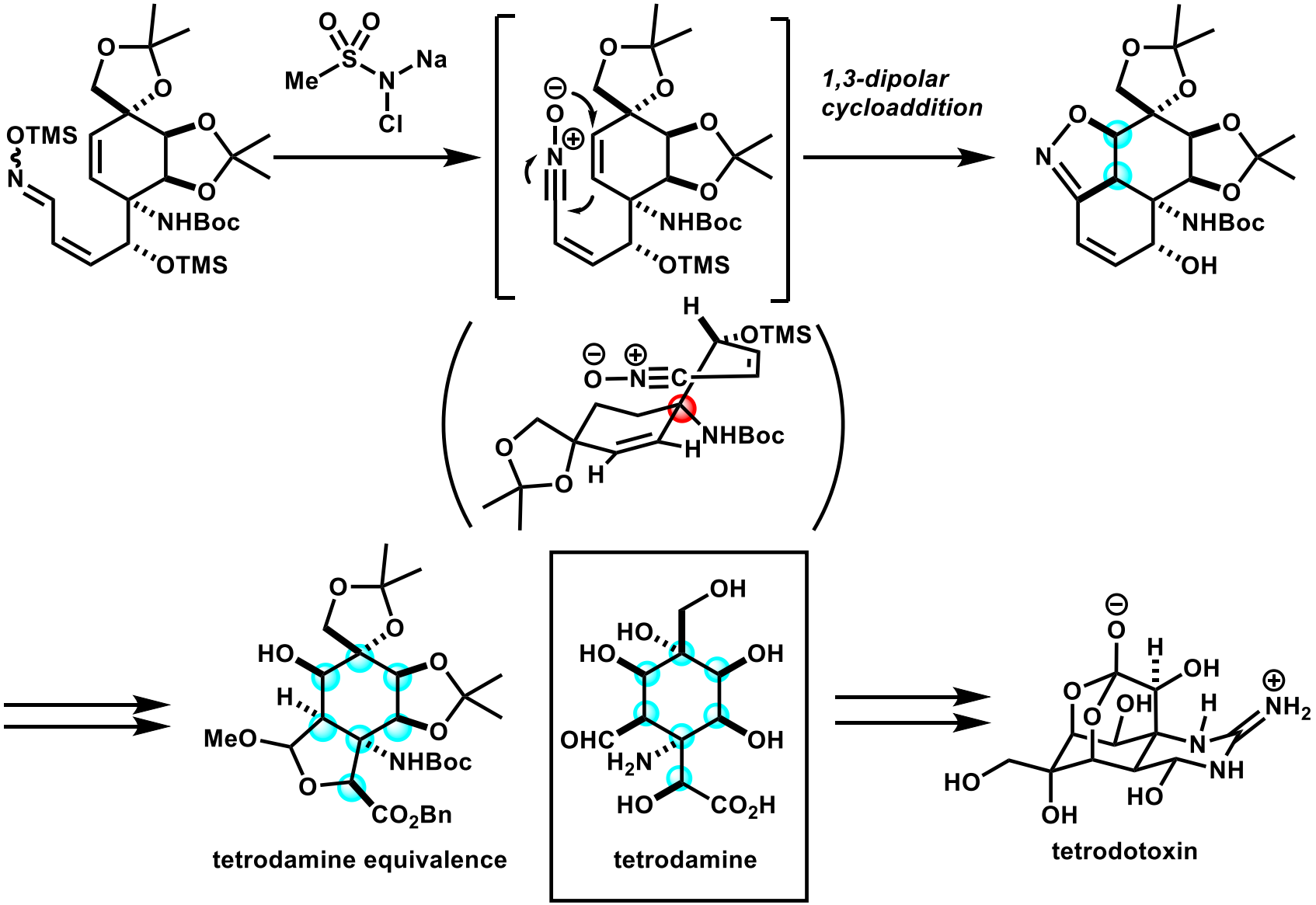
Fukuyama's approach



Maehara, T.; Motoyama, K.; Toma, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2017**, 56, 1549.

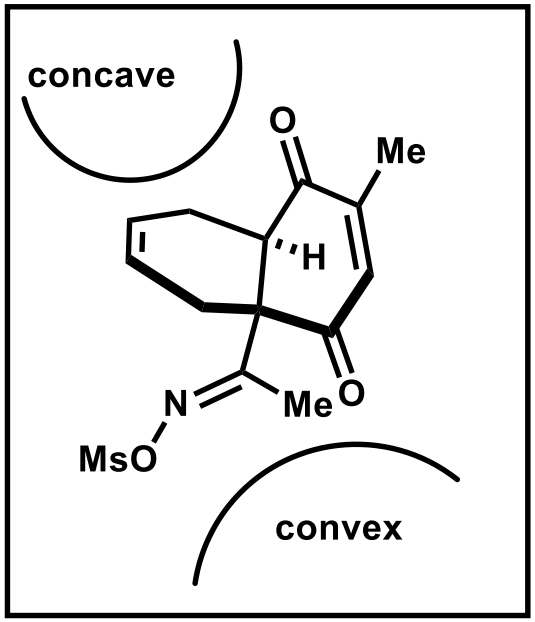
Short summary

Kishi

- Use of Diels-Alder reaction in the early stage

-> determine convex/concave face

- introduction of stereocenters one by one



Fukuyama

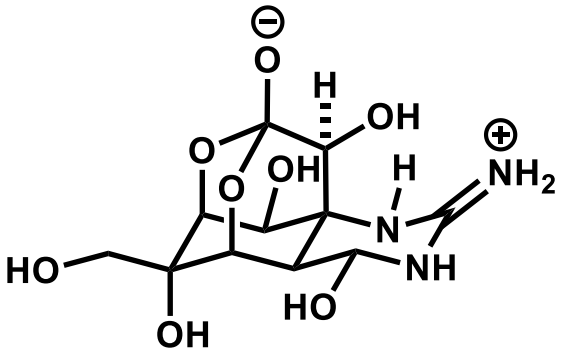
- Diels-Alder -> [3,3]-sigmatropic rearrangement (rearrangement occurs from convex face.)

  -> 1,3-dipolar cycloaddition

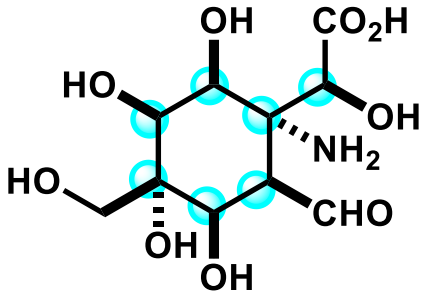
- Introduction of two stereocenters at once by dihydroxylation and 1,3-dipolar cycloaddition (total four stereocenters)

Contents

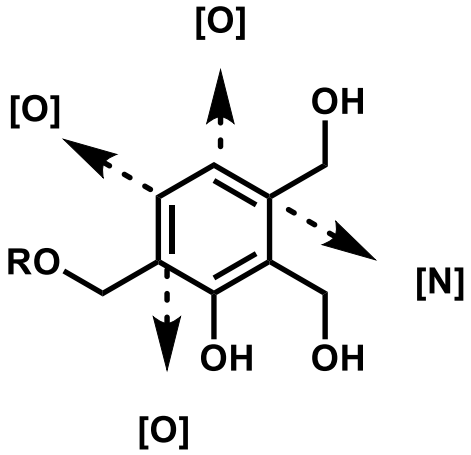
Johnson's strategy



tetrodotoxin



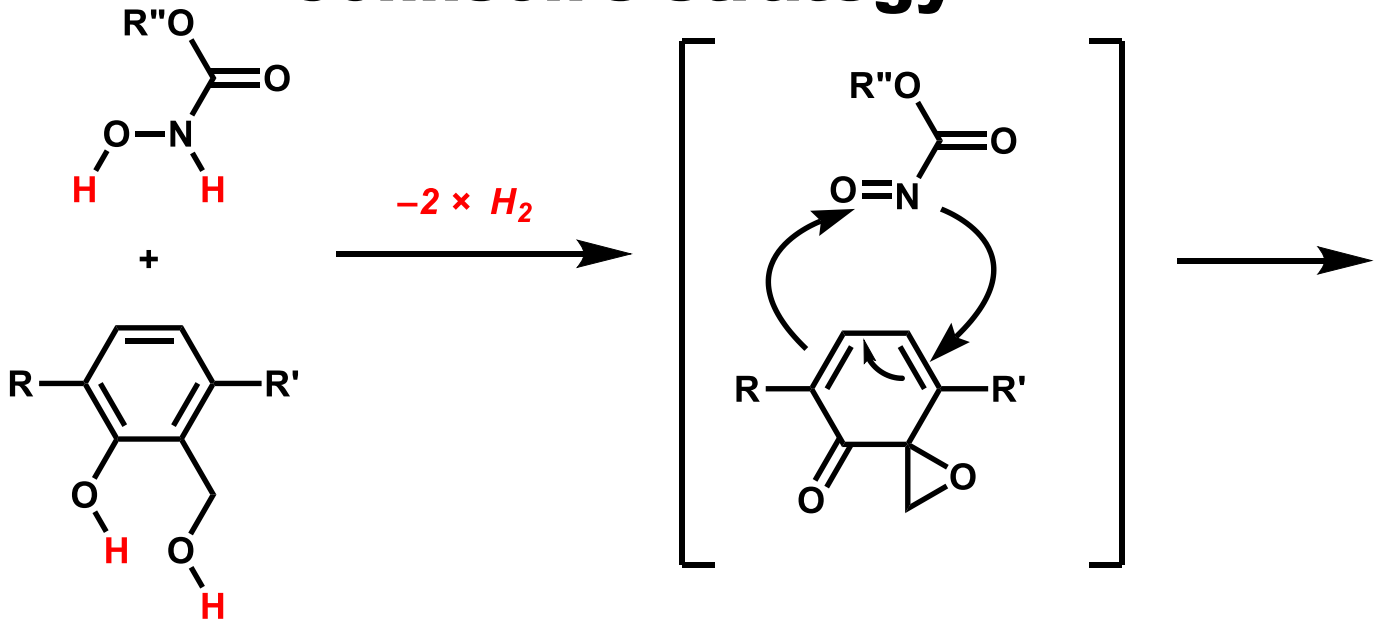
tetrodamine

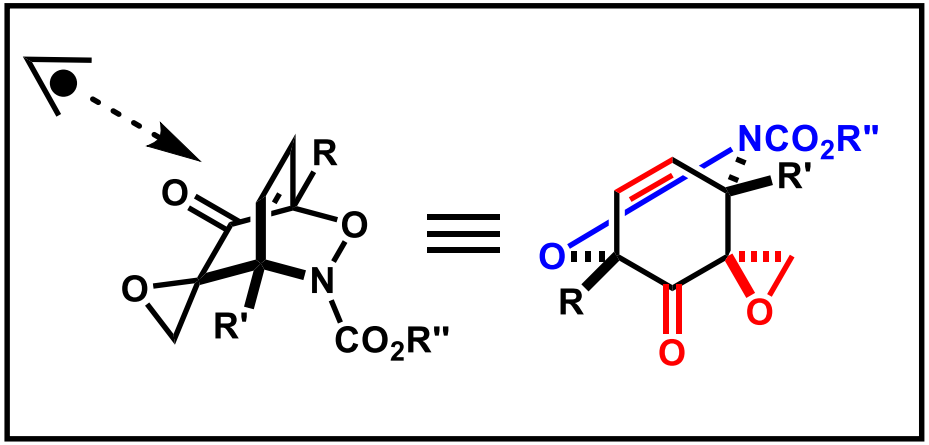


benzenoids —*dearomtization*→ chiral, functionalized cyclohexanes

Good, N, S.; Sharpe, J, R.; Johnson, S, J. *J. Am. Chem. Soc.* **2017**, *139*, 12422.

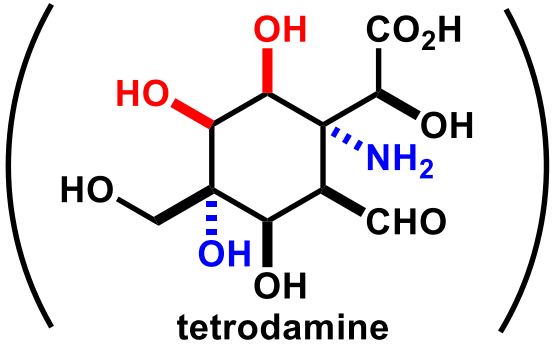
Johnson's strategy





four addressable functional groups

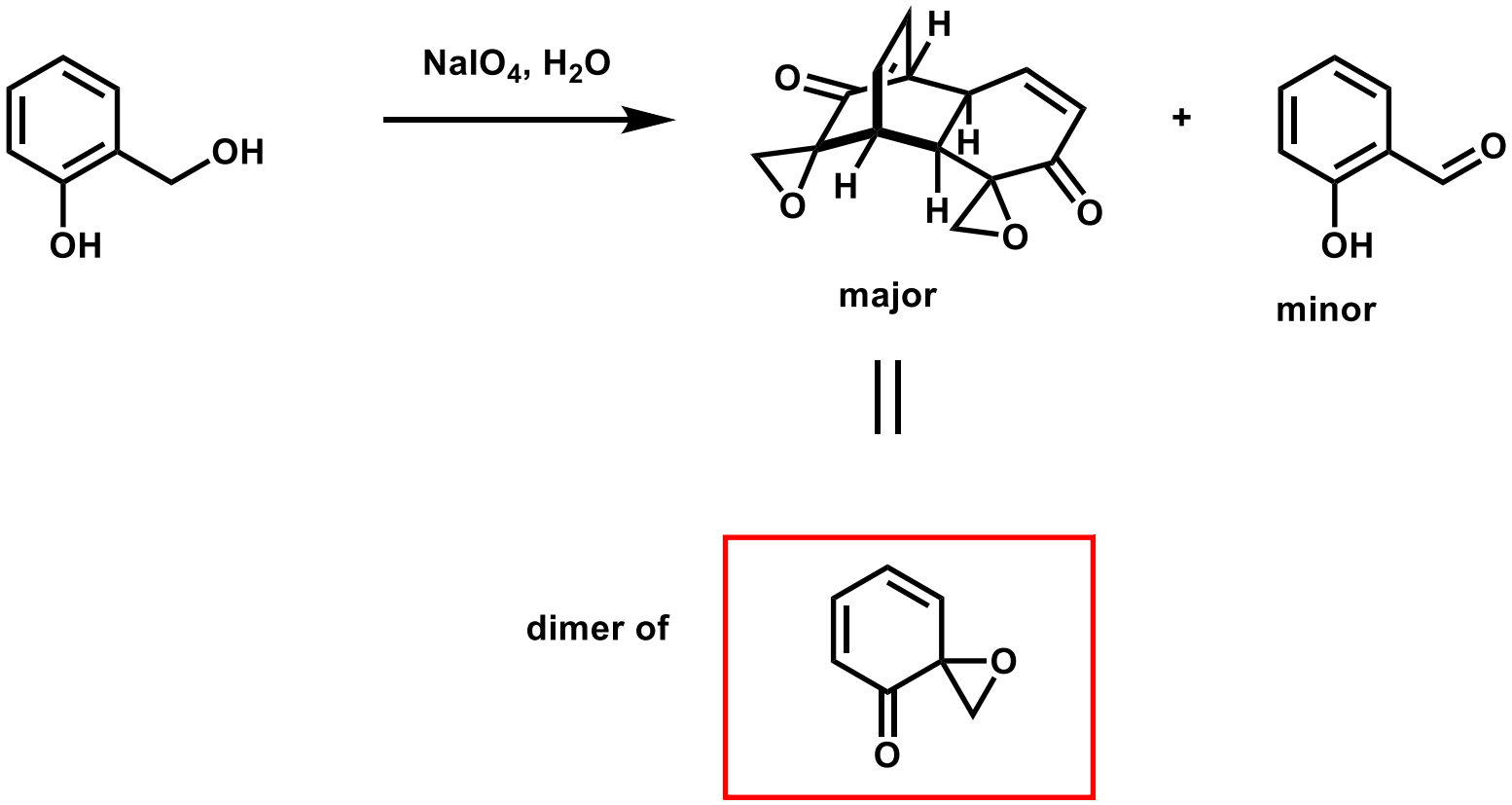
alkene, oxadinane **(latent amino alcohol),** ***epoxide, ketone***



tetrodamine

Good, N, S.; Sharpe, J, R.; Johnson, S, J. *J. Am. Chem. Soc.* **2017**, *139*, 12422.

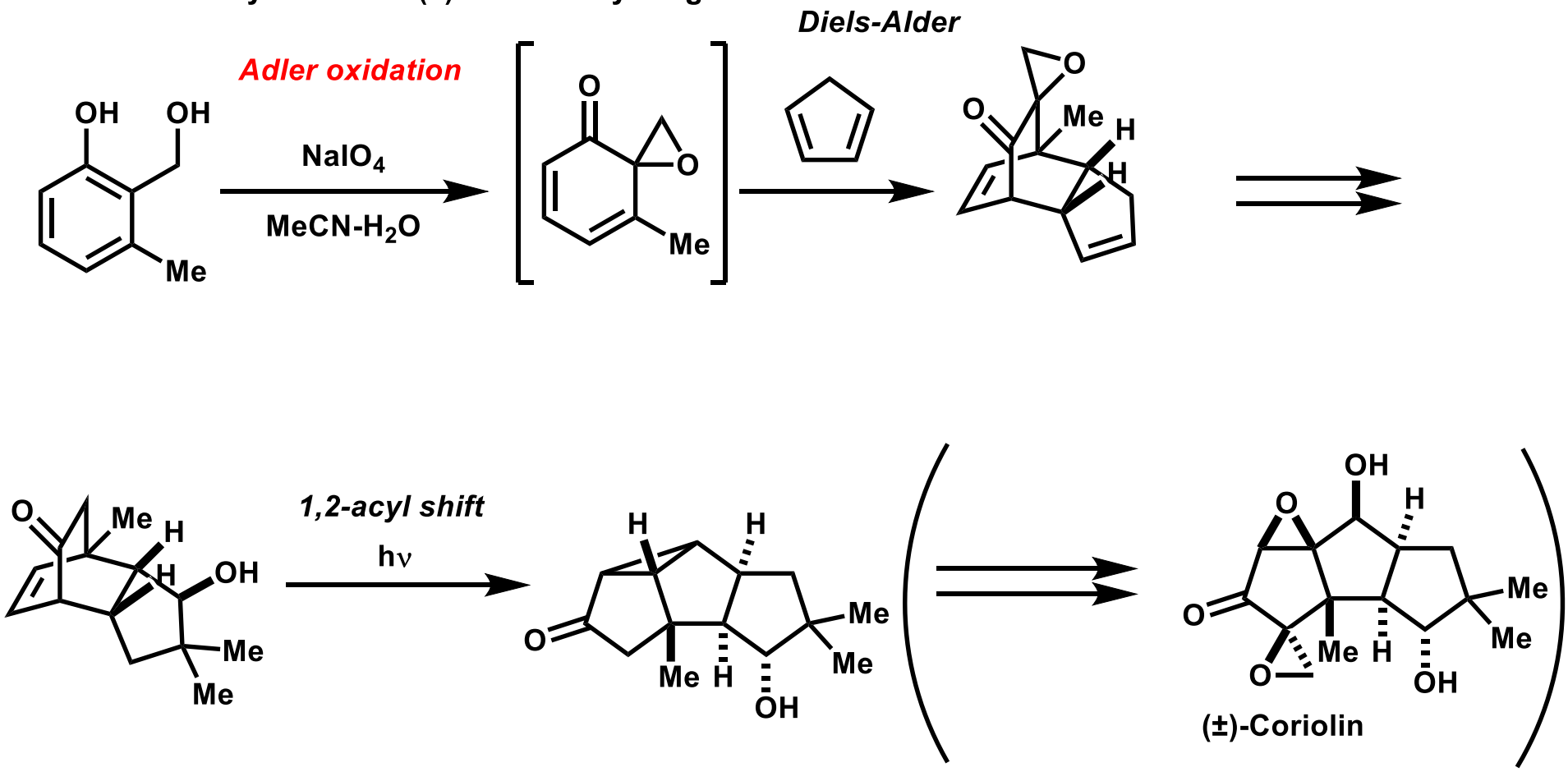
Adler oxidation



Adler, E.; Brasen, S.; Miyake, H. *Acta Chem. Scand.* **1971**, *25*, 2055.

Application of Adler oxidation

Formal total synthesis of (±)-Coriorin by Singh

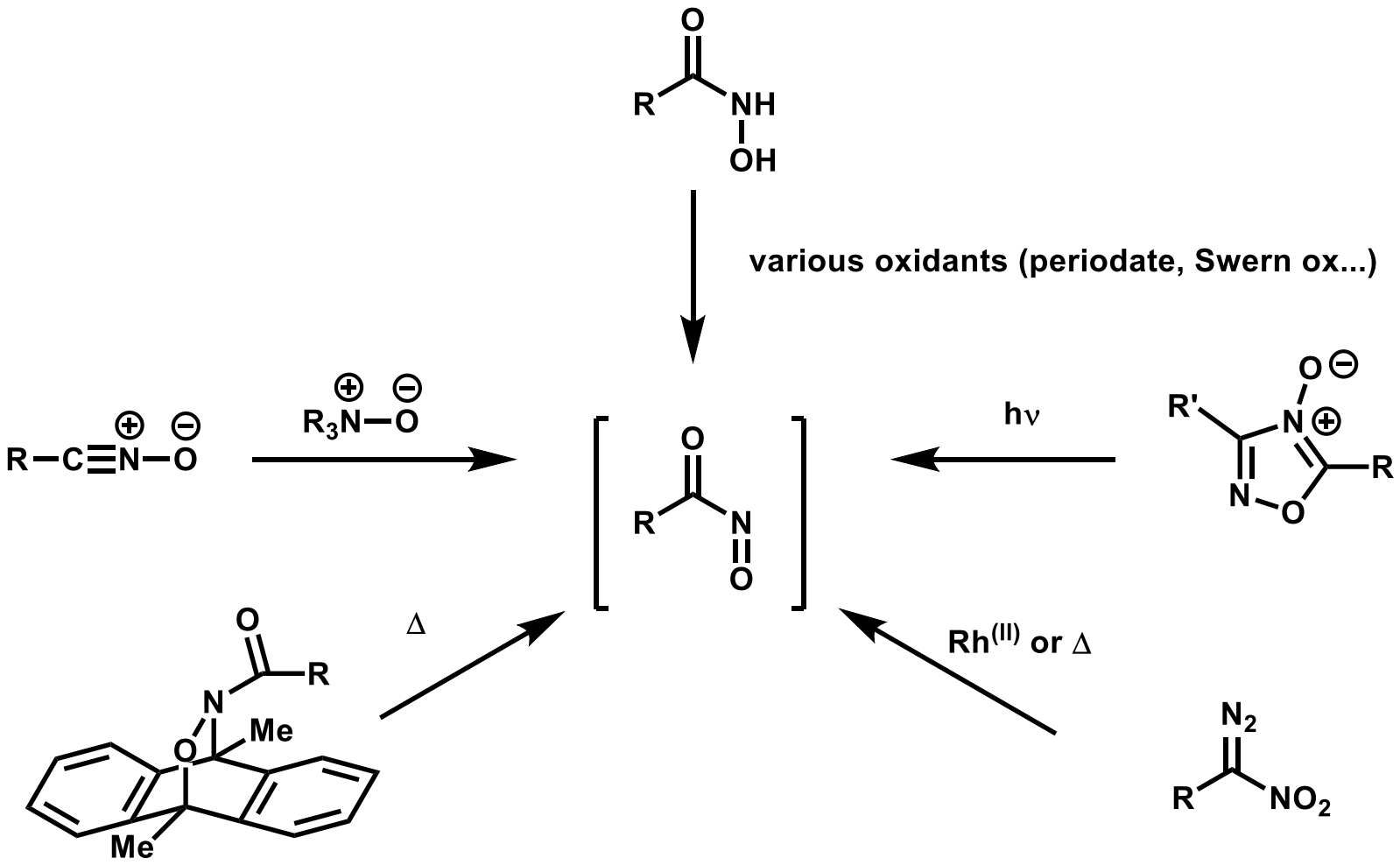


Singh, V.; Samanta, B.; Kane, V, V. *Tetrahedron*, **2000**, *56*, 7785.

Preparation of acylnitroso compounds

Acilnitroso compounds are very reactive. (lifetime: 1 ms order)

-> They are prepared and used in situ in chemical reactions.



Optimization of conditions (sequential)

1 2 3 4

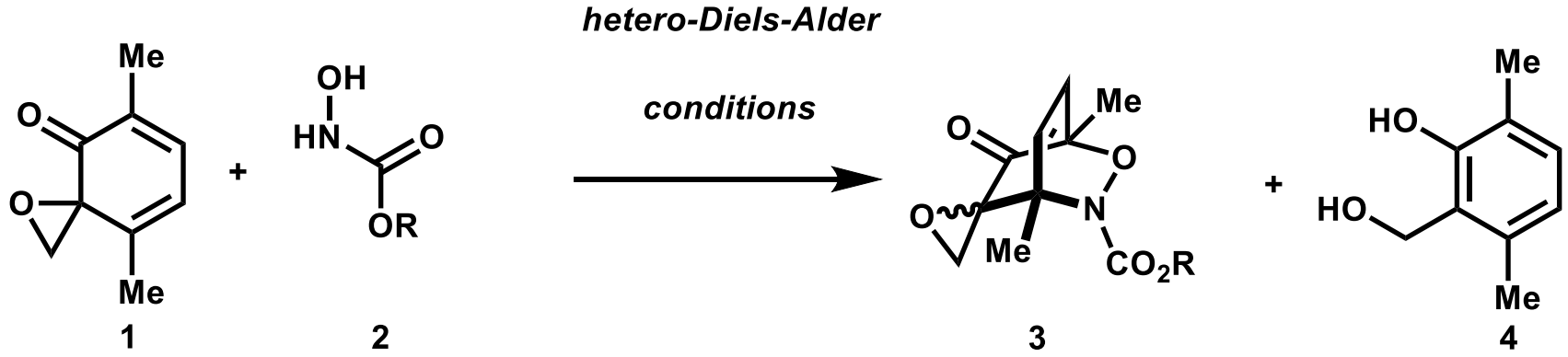
entry	R	oxidant	equiv. of 2 and oxidant (ox.)	solvent	temp.(°C)	conv. of 1 (ratio of 2/3)	dr
1	^{t}Bu	$CuCl_2$(10 mol %), L*, O_2	2: 1.5 eq.	MeOH	rt	85% (1.5:1)	5.3:1
2	^{t}Bu	$^{n}Bu_4NIO_4$	2: 2.0 eq. ox.: 2.0 eq.	CH_2Cl_2	rt-35	30%	2.2:1
3	^{t}Bu	$^{n}Bu_4NIO_4$	2: 2.0+2.0**eq. ox: 2.0+2.0**eq.	$CDCl_3$	45	57%	3.2:1
4	^{t}Bu	$^{n}Bu_4NIO_4$	2: 2.0 eq. ox.: 2.0 eq.	$CDCl_3$	45	58%	2.1:1
5	^{t}Bu	$^{n}Bu_4NIO_4$	2: 2.0 eq. ox.: 2.0 eq.	$CHCl_3$ (with EtOH as stabilizer)	45	100% (4:1)	2.1:1

*** L = 2-ethyloxazoline (20 mol %)**

**** Additional 2.0 eq. of 2 was added for 2 hours.**

Good, N, S.; Sharpe, J, R.; Johnson, S, J. *J. Am. Chem. Soc.* **2017**, *139*, 12422.

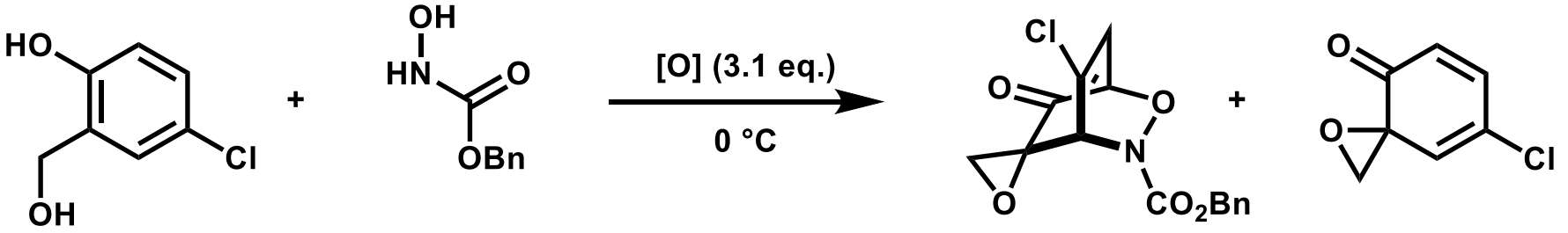
Optimization of conditions (sequential)



entry	R	oxidant	equiv. of 2 and oxidant (ox.)	solvent	temp.(°C)	conv. of 1 (ratio of 3/4)	dr (yield)
6	Bn	$^{n}Bu_4NIO_4$	2: 2.0 eq. ox.: 2.0 eq.	$CDCl_3$	45	68%	2.7:1 (12%)
7	Bn	$^{n}Bu_4NIO_4$	2: 2.0 eq. ox.: 2.0 eq.	$CDCl_3$	30	87%	4.0:1 (51%)
8	Bn	$^{n}Bu_4NIO_4$	2: 2.0 eq. ox.: 2.0 eq.	$CDCl_3$	rt	91%	4.3:1 (74%)

Good, N, S.; Sharpe, J, R.; Johnson, S, J. *J. Am. Chem. Soc.* **2017**, *139*, 12422.

Optimization of conditions (one-pot)

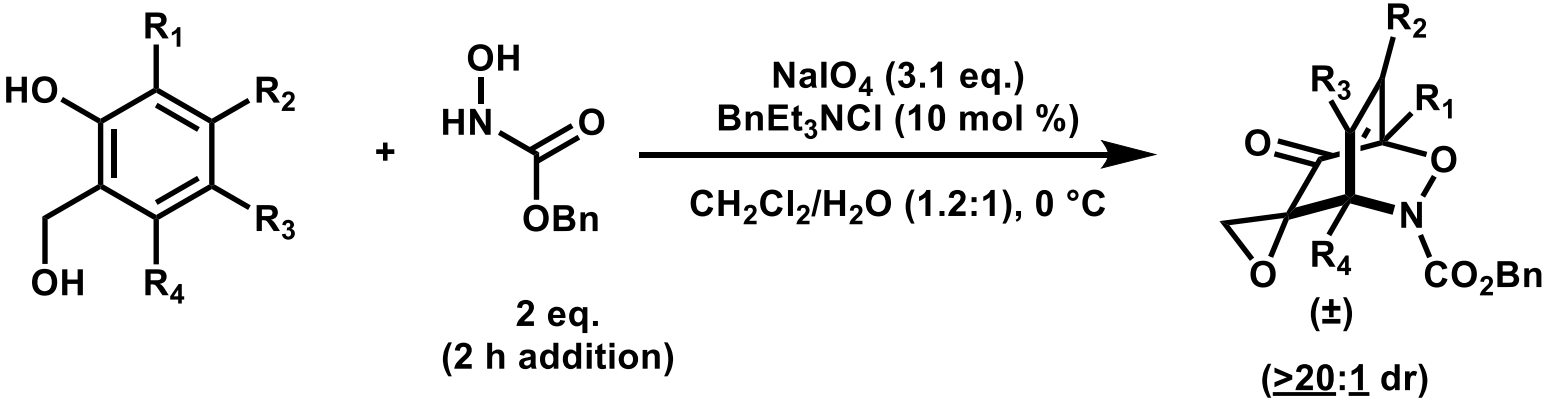


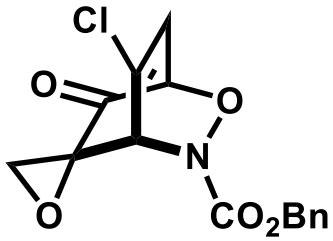
5 (2 h addition) 6 >20:1 dr 7

entry	oxidant	solvent	catalyst	conv. of 5	product
1	$NaIO_4$	MeOH/water	–	100%	5
2	$NaIO_4$	THF/water	–	100%	5
3	$^nBu_4NIO_4$	MeOH/water	–	100%	5
4	$^nBu_4NIO_4$	THF/water	–	100%	5
5	$^nBu_4NIO_4$	THF	–	20%	6/7 (10:1)
6	$NaIO_4$	$CDCl_3$/water	$BnEt_3NCl$ (10 mol %)	100% (*60%)	6/7 (10:1)
7	$NaIO_4$	CH_2Cl_2/water	$BnEt_3NCl$ (10 mol %)	100% (*76%)	6/7 (20:1)

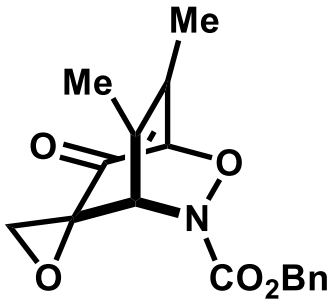
Good, N, S.; Sharpe, J, R.; Johnson, S, J. *J. Am. Chem. Soc.* **2017**, *139*, 12422. * isolated yields

Scope of the One-pot procedure

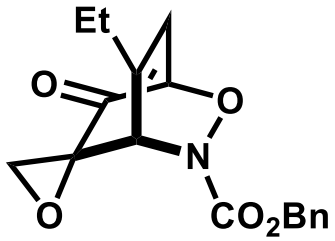




75%



70%



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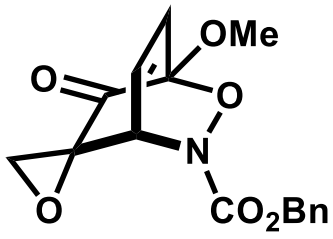
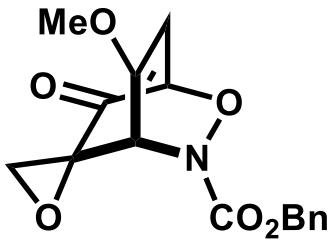
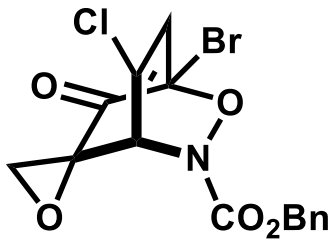


43%



16%



67%

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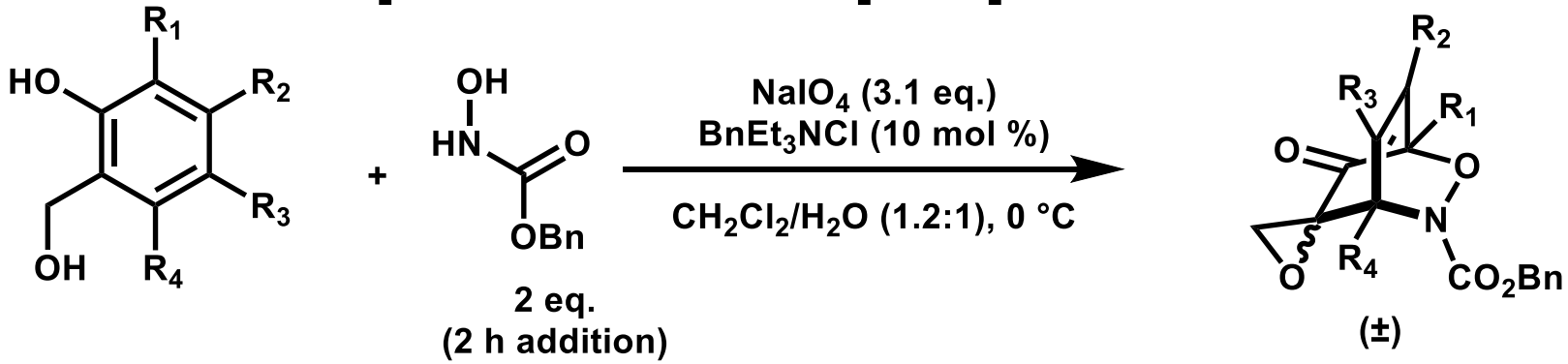
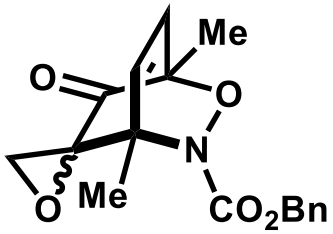
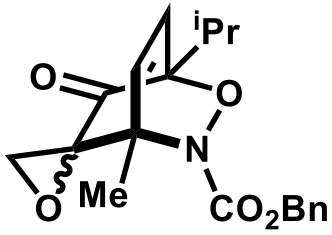
Scope of the One-pot procedure

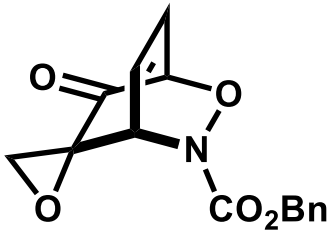




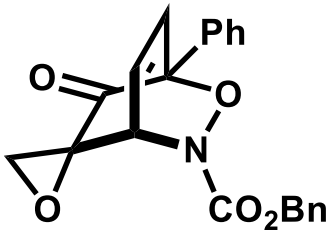
44% (4.0:1 dr)



50% (3.2:1 dr)



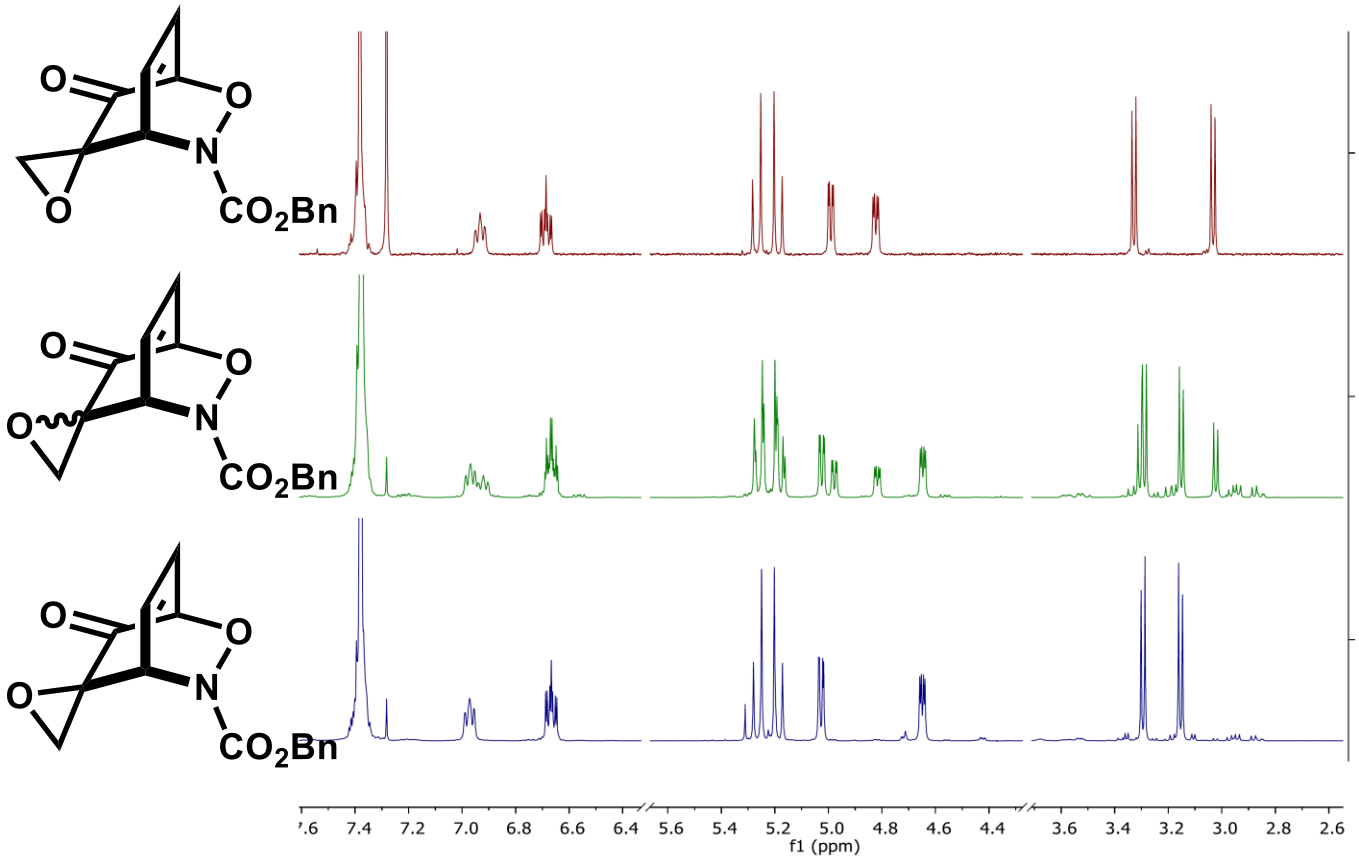
76 % (>20:1 dr)
(Thermal isomerization occurs 40 °C and over.)



52 % (>20:1 dr)
(Isomerization is observed after standing at rt.)

Good, N, S.; Sharpe, J, R.; Johnson, S, J. *J. Am. Chem. Soc.* **2017**, *139*, 12422.

Kinetically or thermodynamically products



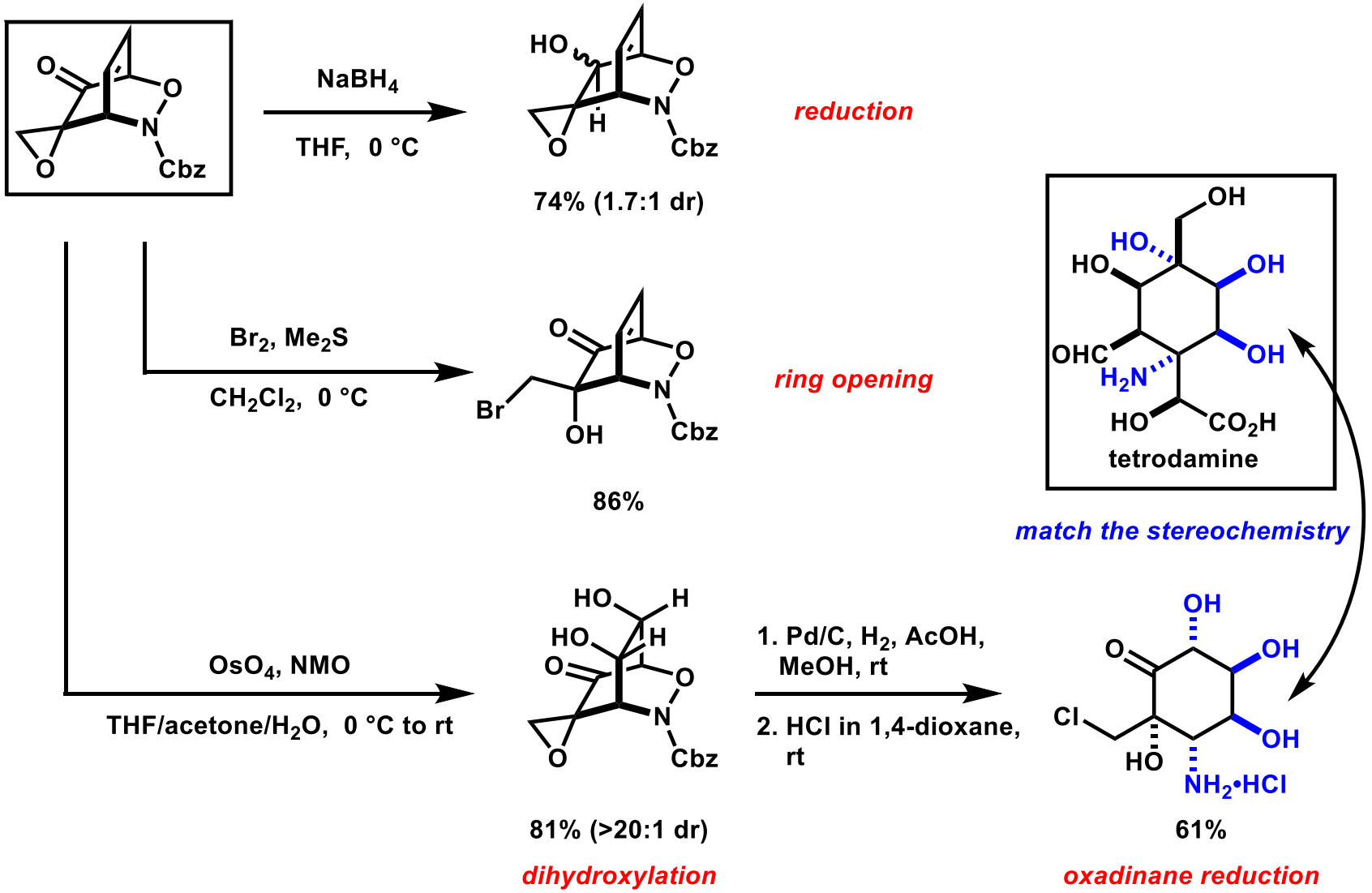
Initially isolated kinetic diastereomer

After heating at 40-65 °C for 50 h

Isolated thermodynamic diastereomer

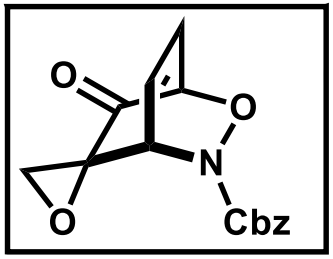
Good, N, S.; Sharpe, J, R.; Johnson, S, J. *J. Am. Chem. Soc.* **2017**, *139*, 12422.

Chemoselective reactions of heterocycloadducts



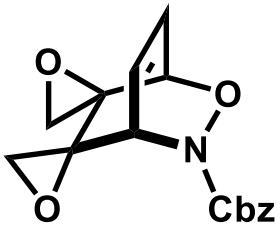
Good, N, S.; Sharpe, J, R.; Johnson, S, J. *J. Am. Chem. Soc.* **2017**, *139*, 12422.

Chemoselective reactions of heterocycloadducts



NaH, Me_3SO-I

THF, 0 °C



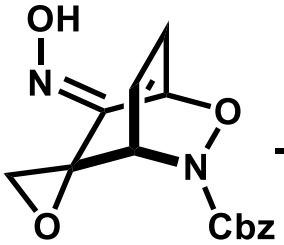
59%

epoxidation

NH_2OH, HCl, NaOAc

THF, rt

condensation

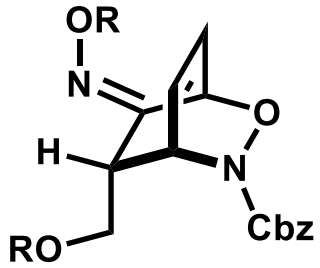


71%

$NaBH_4$

MeOH, 0 °C

reductive fragmentation

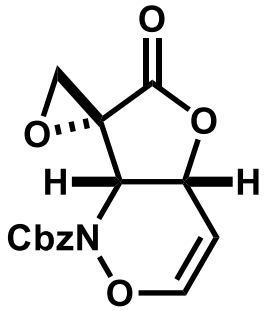


45% (R=H) (>20:1 dr)

56% (R=*p*$O_2NC_6H_4CO$)

*m*CPBA, $NaHCO_3$

CH_2Cl_2, rt

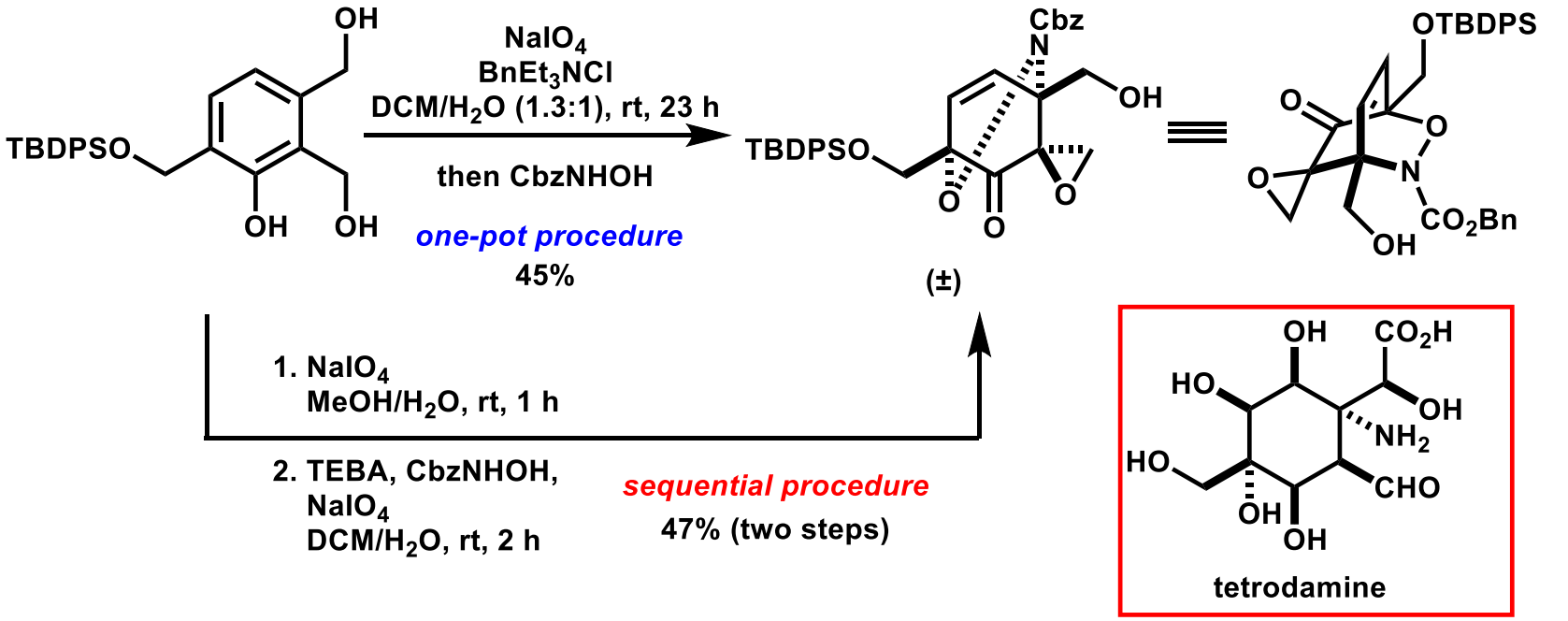


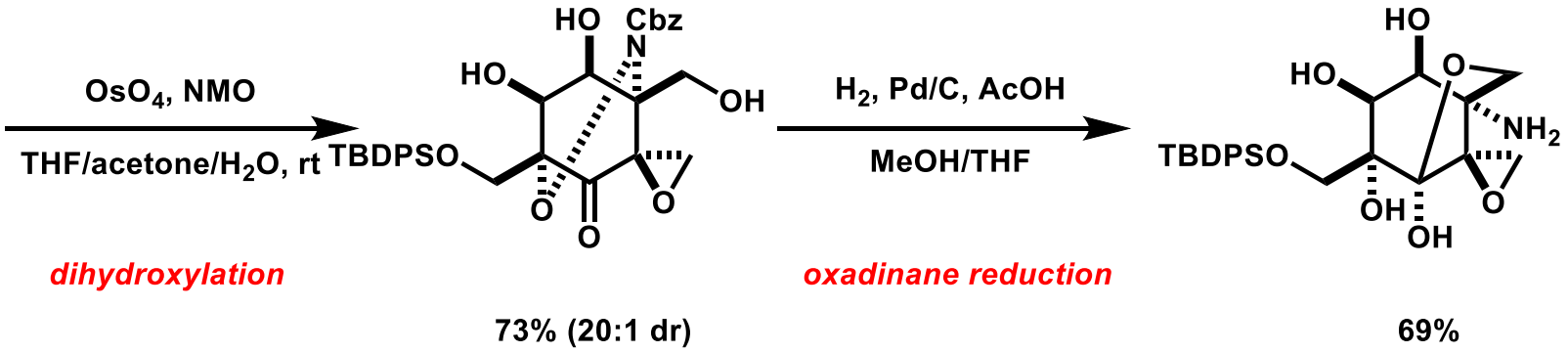
50%

vinylogous Bayer-Villiger oxidation

Good, N, S.; Sharpe, J, R.; Johnson, S, J. *J. Am. Chem. Soc.* **2017**, *139*, 12422.

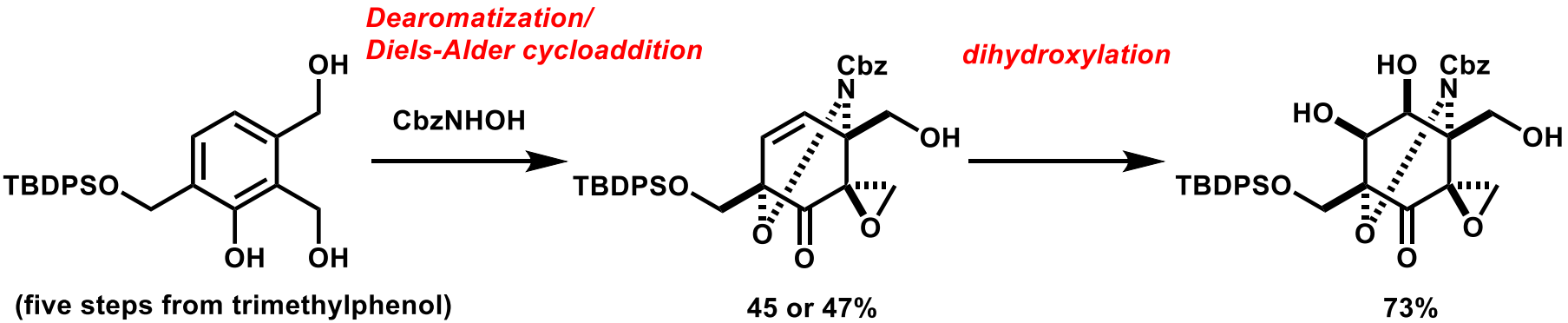
Application of the Oxidation/Cycloaddition cascade procedure towards the TTX core structure

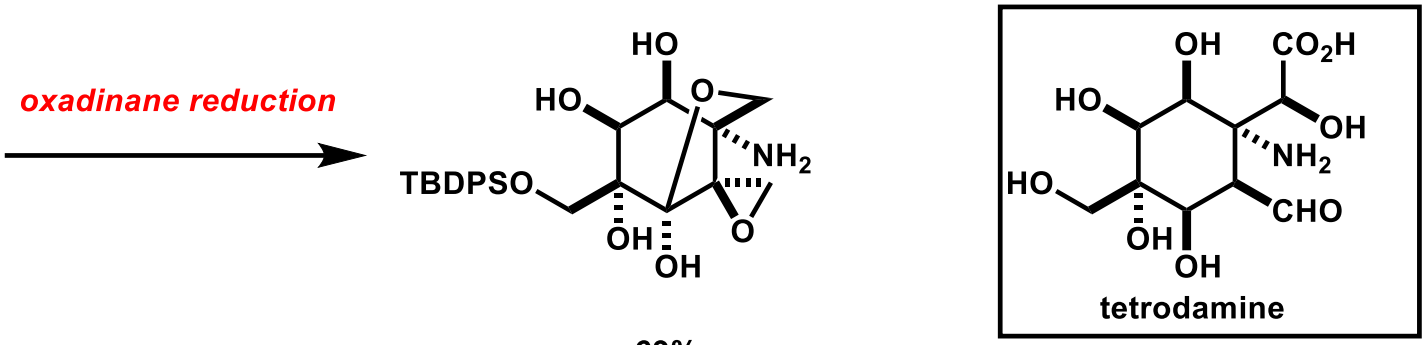




Good, N, S.; Sharpe, J, R.; Johnson, S, J. *J. Am. Chem. Soc.* **2017**, *139*, 12422.

Summary





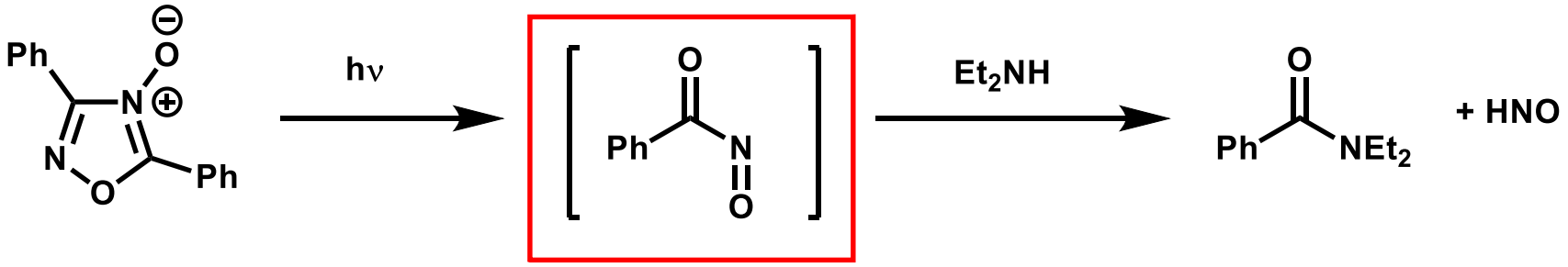
[2,2,2]-bicyclic products bearing four orthogonal functional groups from simple, aromatic feedstocks

-> Enable to introduce highly substituted stereocenters to cyclohexane ring

Good, N, S.; Sharpe, J, R.; Johnson, S, J. *J. Am. Chem. Soc.* **2017**, *139*, 12422.

Appendix

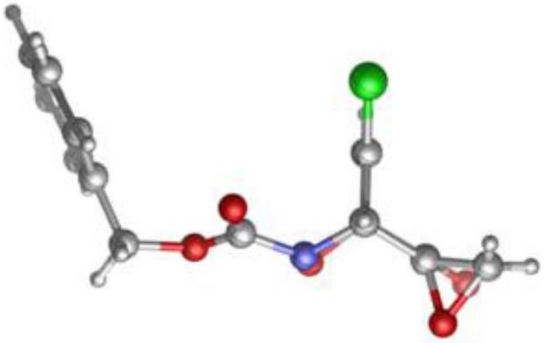
The lifetime of acylnitroso compounds



the lifetime of acylnitroso compounds is on the order of 1 ms.
(observeded by time-resolved IR spectroscopy)

Cohen, A. D.; Zeng, B. B.; King, S. B.; Tosano, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 1444.

Crystal Structures



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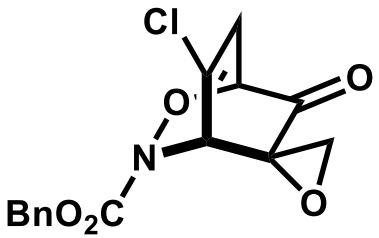

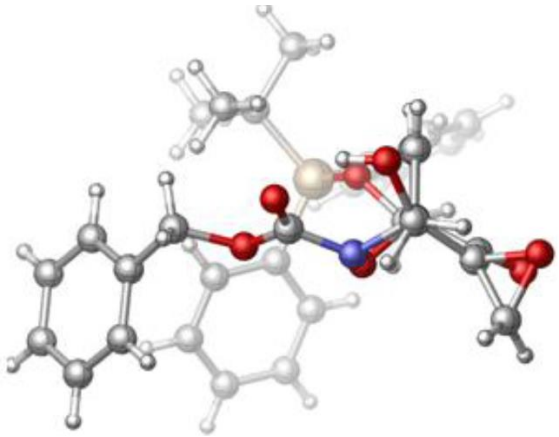

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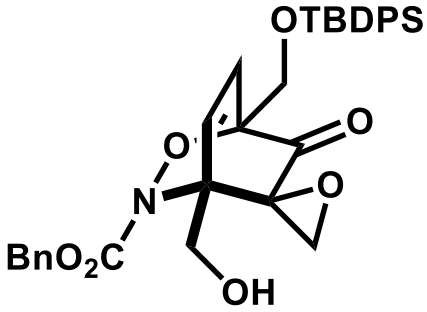
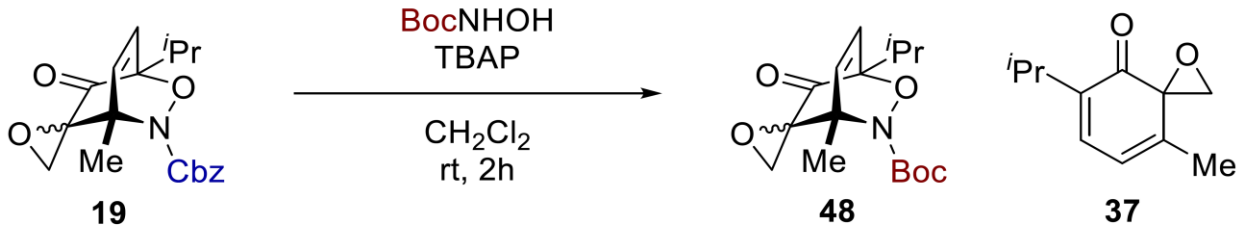


(TBDPS= Si^tBuPh_2)

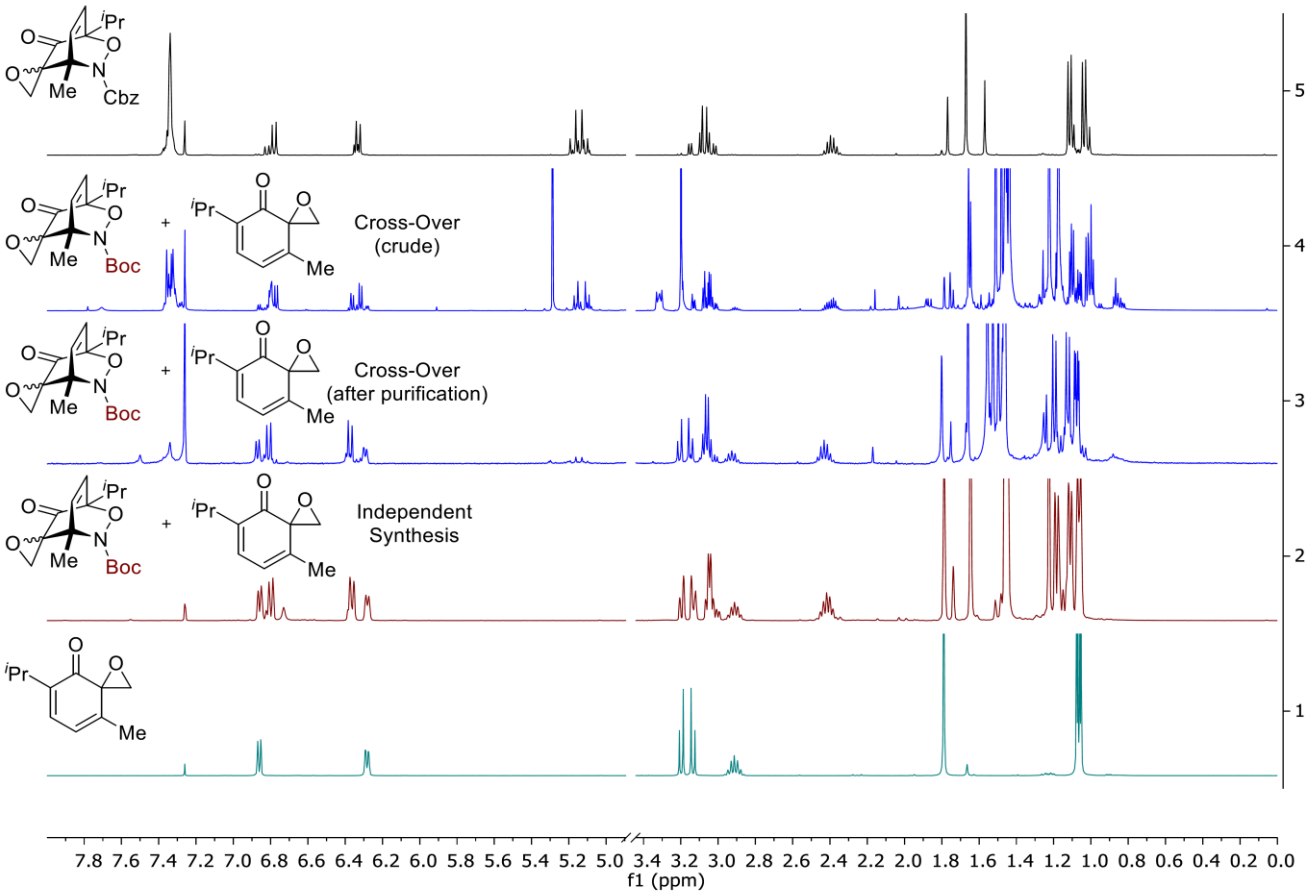
Cross-over experiment

Cross-over experiment:



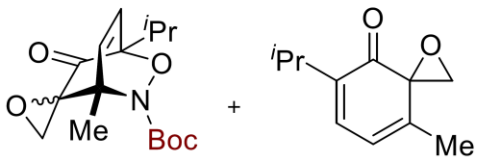
A solution of *t*BuO_2CNHOH (77 mg, 0.58 mmol) in CH_2Cl_2 (1 mL) was added via syringe pump over 2 h to a mixture of **19** (3.4:1 dr, 20 mg, 0.06 mmol) and *n*Bu_4NIO_4 (252 mg, 0.58 mmol) in CH_2Cl_2 (1 mL) at rt. After complete addition, the reaction was diluted with MTBE (4 mL) and the mixture was filtered through a plug of Celite®. The filtrate was concentrated by rotary evaporation and the crude residue was purified by flash chromatography on silica gel (EtOAc:hexanes 10:90 to 20:80) to afford an inseparable mixture of **37** and **48** (mixture of diastereomers, no yield recorded). The ^{1}H NMR spectrum of the mixture of products matched an independently synthesized mixture of **37** and **48** (prepared using a modified General Procedure A in which BnO_2CNHOH is exchanged for *t*BuO_2CNHOH). The ^{1}H spectrum of the independently prepared mixture of **37** and **48** is included below the stacked spectra.

Cross-over experiment



Cross-over experiment

Independent synthesis



48

\+

37

1H NMR (400 MHz, $CDCl_3$)