Convergent Strategies in Total Syntheses of ***Complex*** Diterpenoids

Masayuki Inoue*

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Report: Zhe Dong
Advisor: Prof. Guangbin Dong
Apr 1st 2015

Masayuki Inoue
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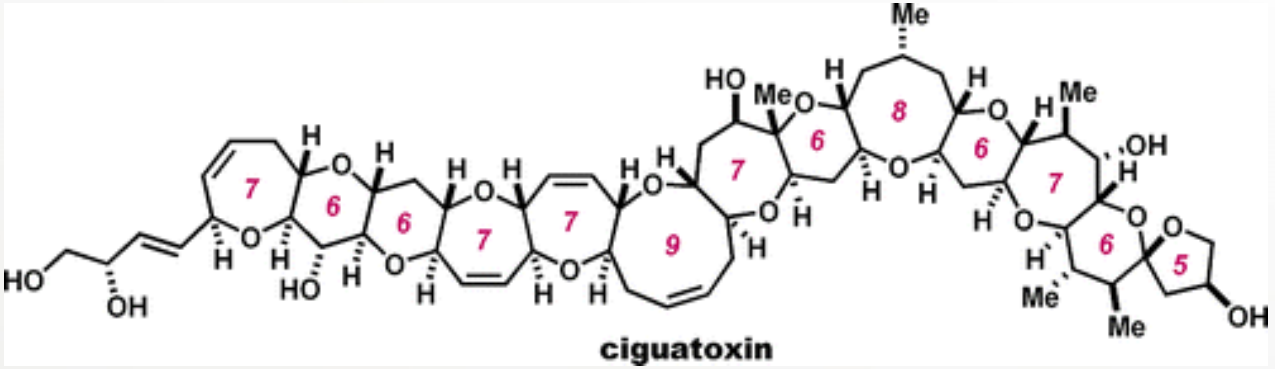
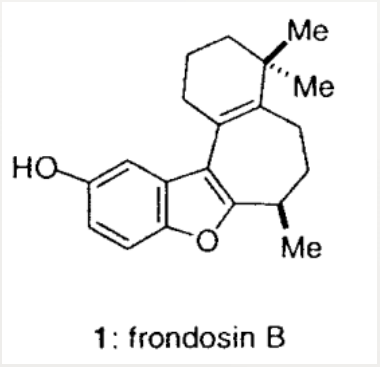
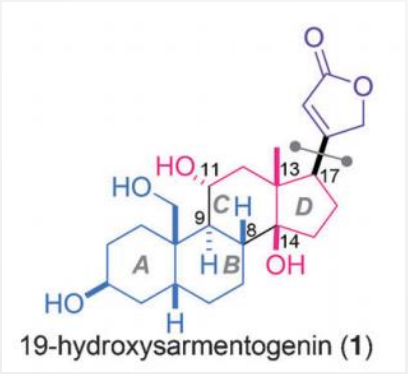
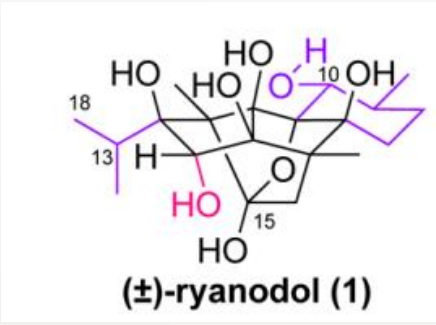
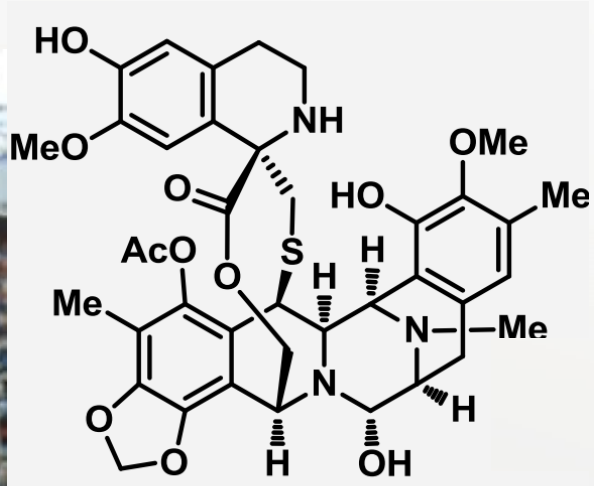




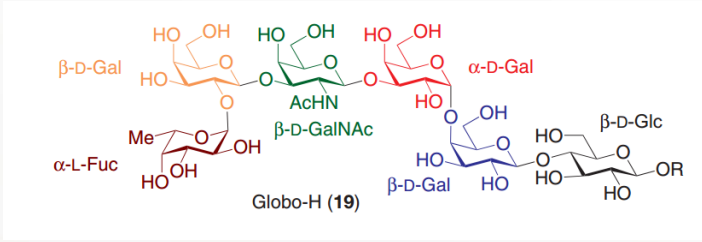


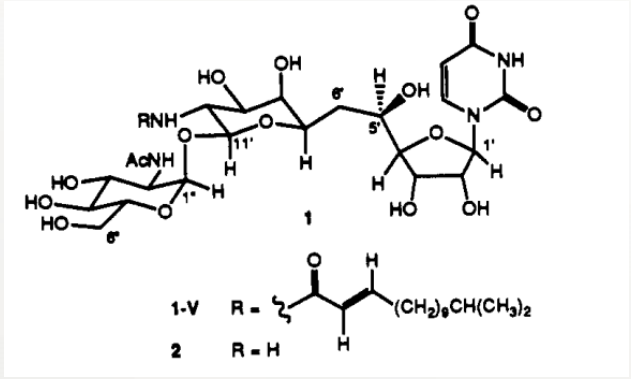


BS in chemistry, Tokyo University 1993
PHD : Prof. Kazuo Tachibana Tokyo University 1993-1998
Postdoc: Samuel. J. Danishefsky 1998-2000
AP in Prof:Masahiro Hirama at Tohoku University 2000-2007
Full Professor in Pharmaceutical Sciences Tokyo University, 2007-now
Become Full Professor when only 36!



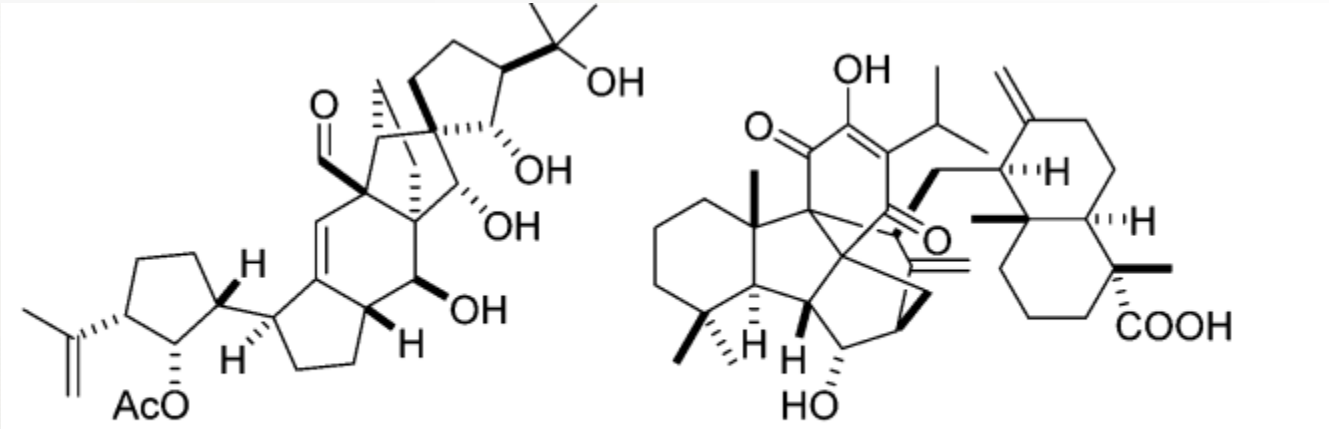
Ecteinascidin 743



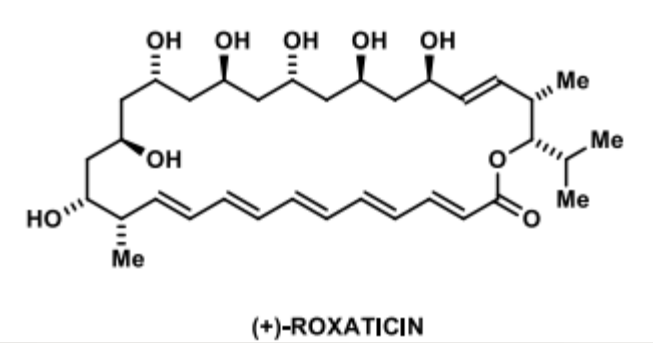


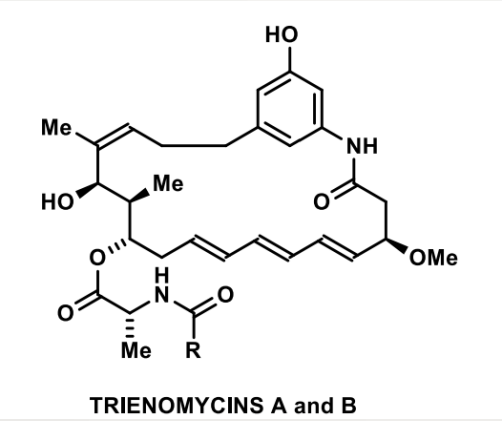
David Gin
(1967-2011)

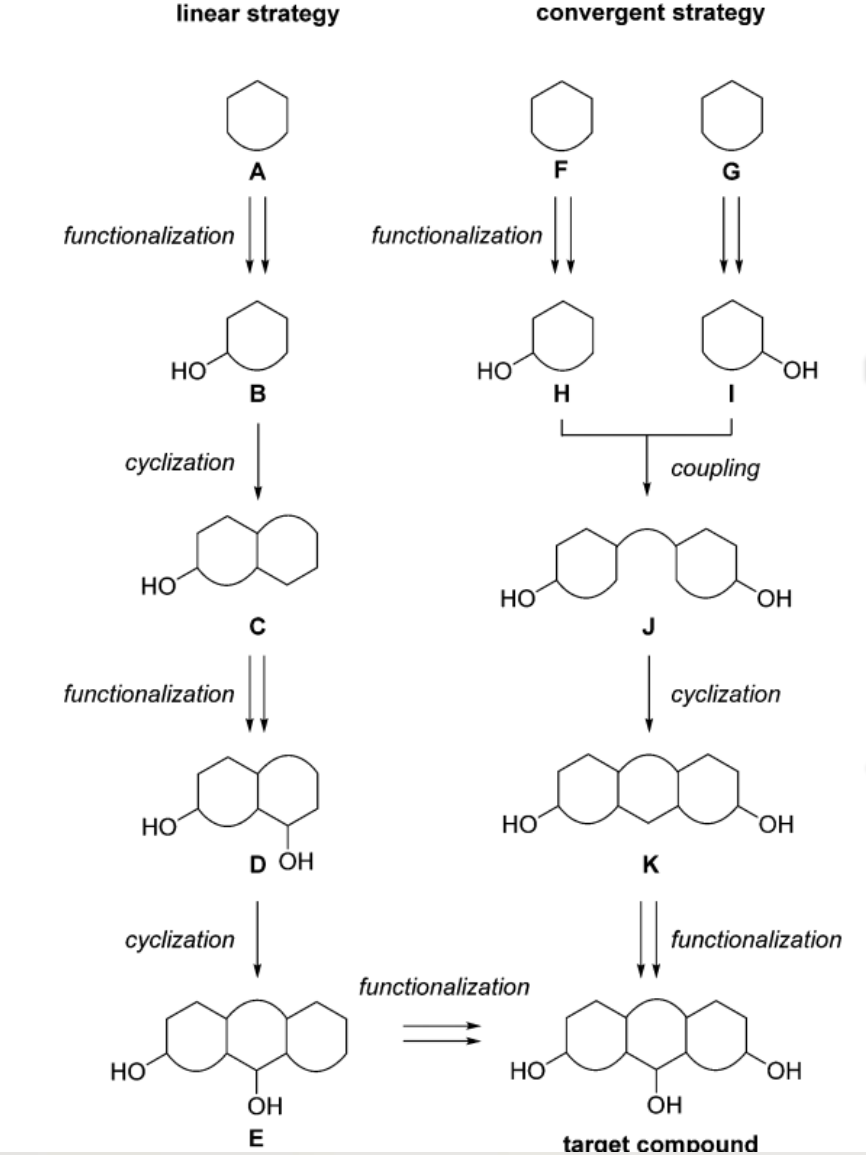
PHD : Prof. Andrew G. Myers 1989-1994
Postdoc: E.J. Corey 1994-1996
Professor UIUC 1996-2006
Memorial Sloan-Kettering Cancer Center 2006-2011



Strategy is more important

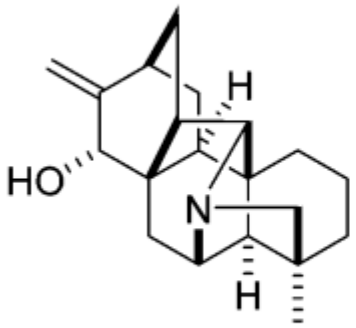






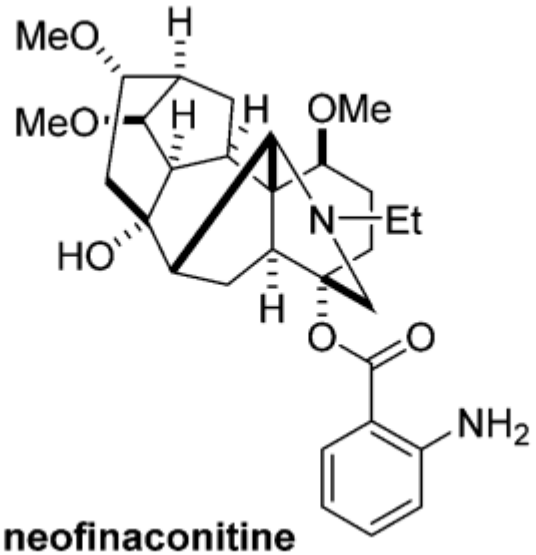
Cycloaddtion:
Diels-Alder Reaction
1,3-dipolar addition
TM catalyzed [M+N+O]
(Seldom used in truly
Complex cage molecule)

Convergent :



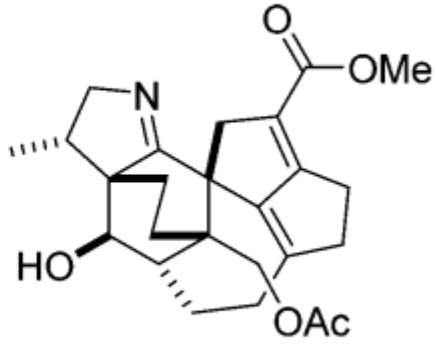
nominine

David Gin 15LLS



neofinaconitine

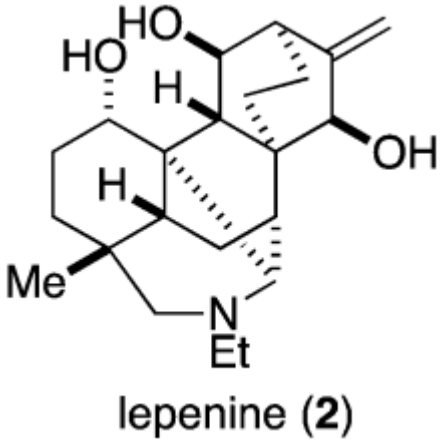
David Gin 27LLS



daphmanidin E

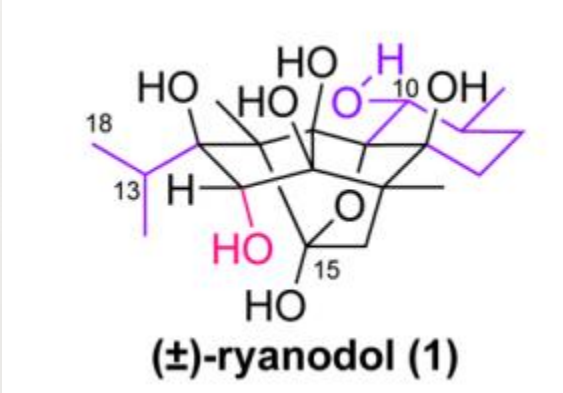
Erick Carreira 30 LLS

Liner :



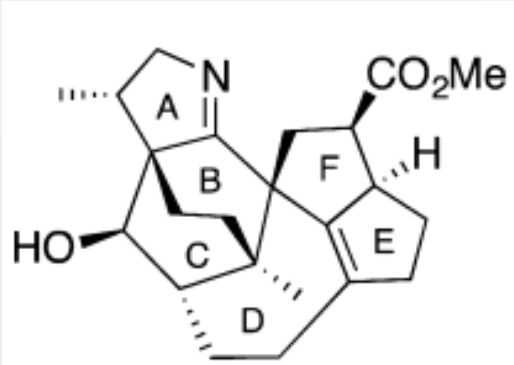
lepenine (**2**)

Fukuyama 35 LLS

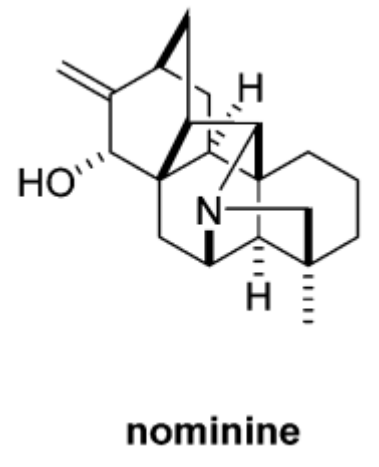


(±)-ryanodol (1)

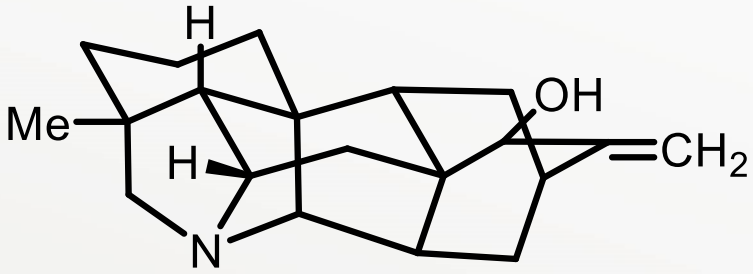
Inoue 35 LLS
Deslongchamps 41 LLS



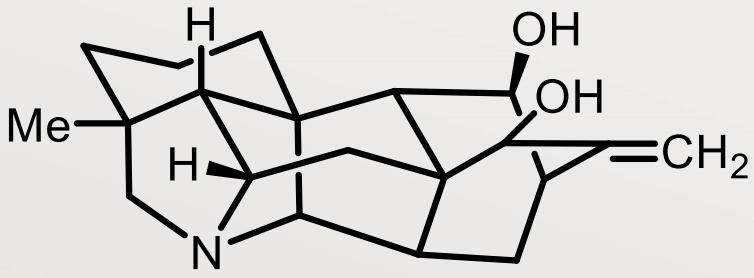
A B Smith 37 LLS



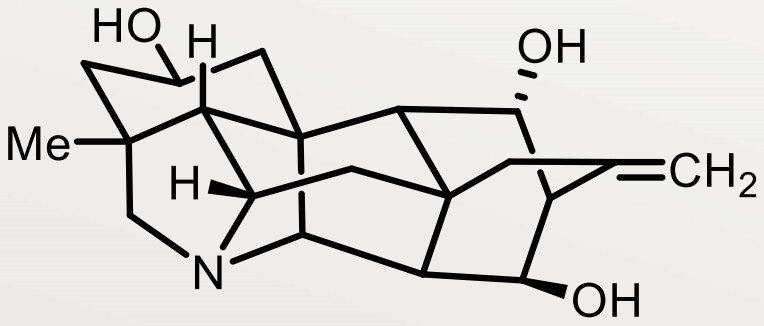
David Gin 15LLS
Nastume 40LLS



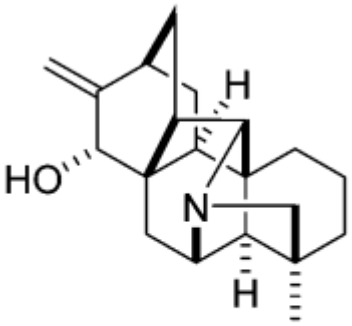
Nominine
Isolated at 1947 by Japanese Group
first synthesized by 2004



Kobusine

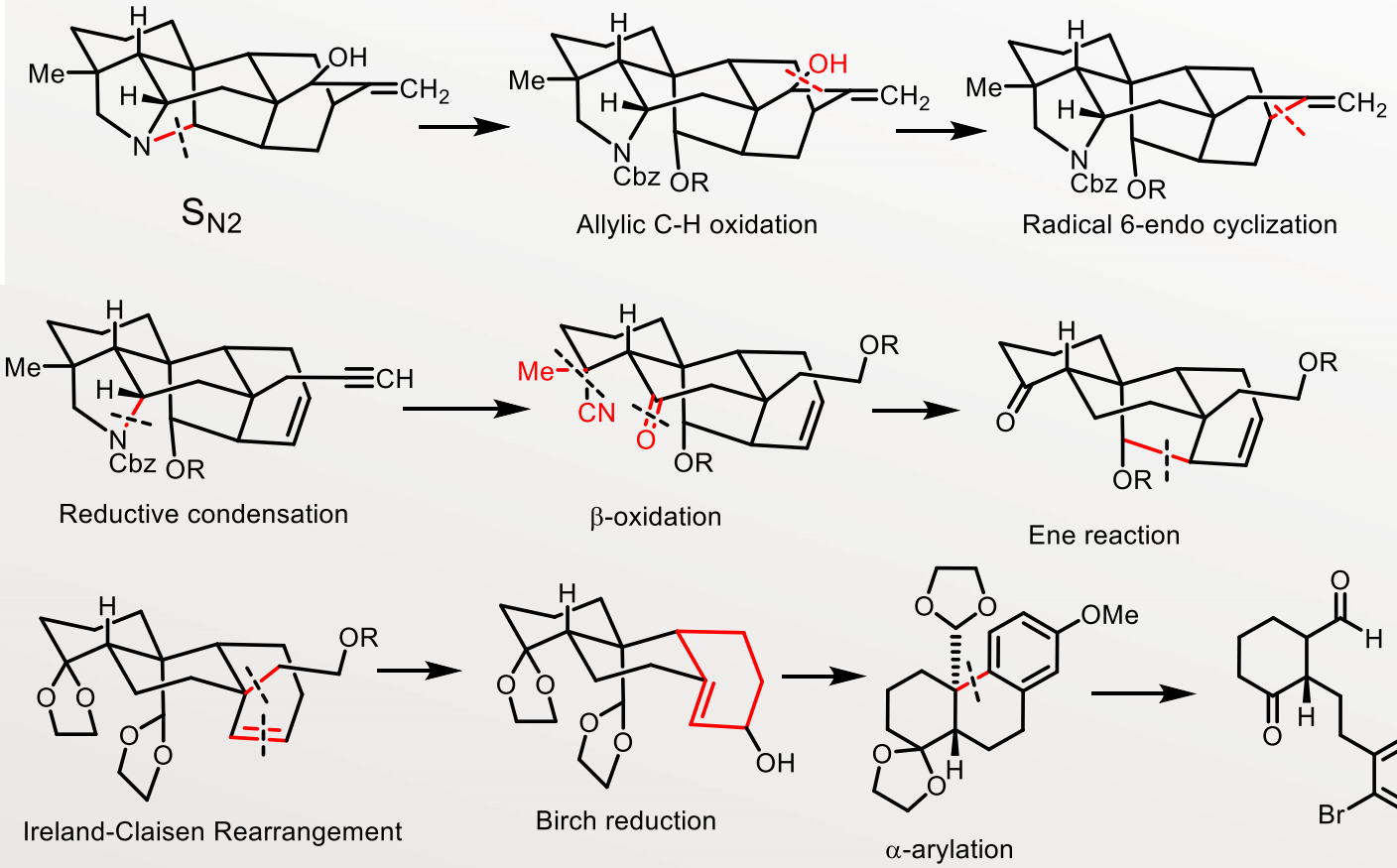


Hetisine



nominine

Nastume 40LLS



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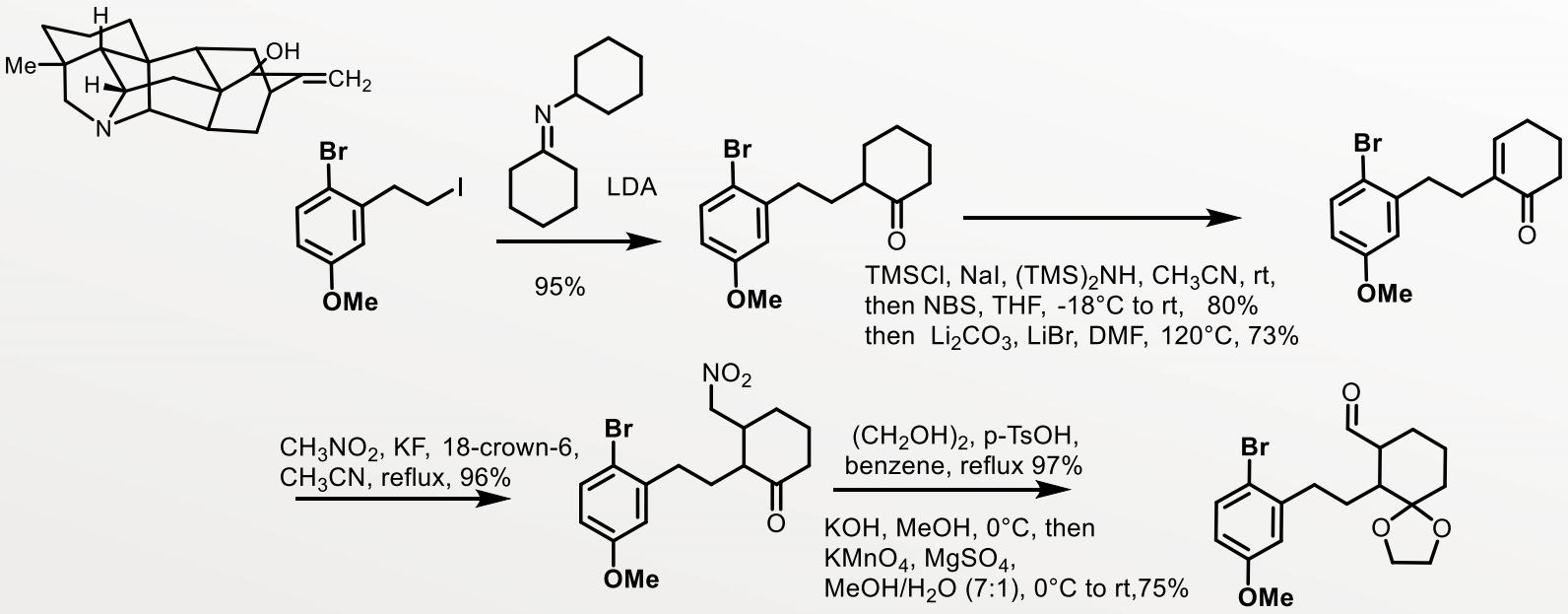

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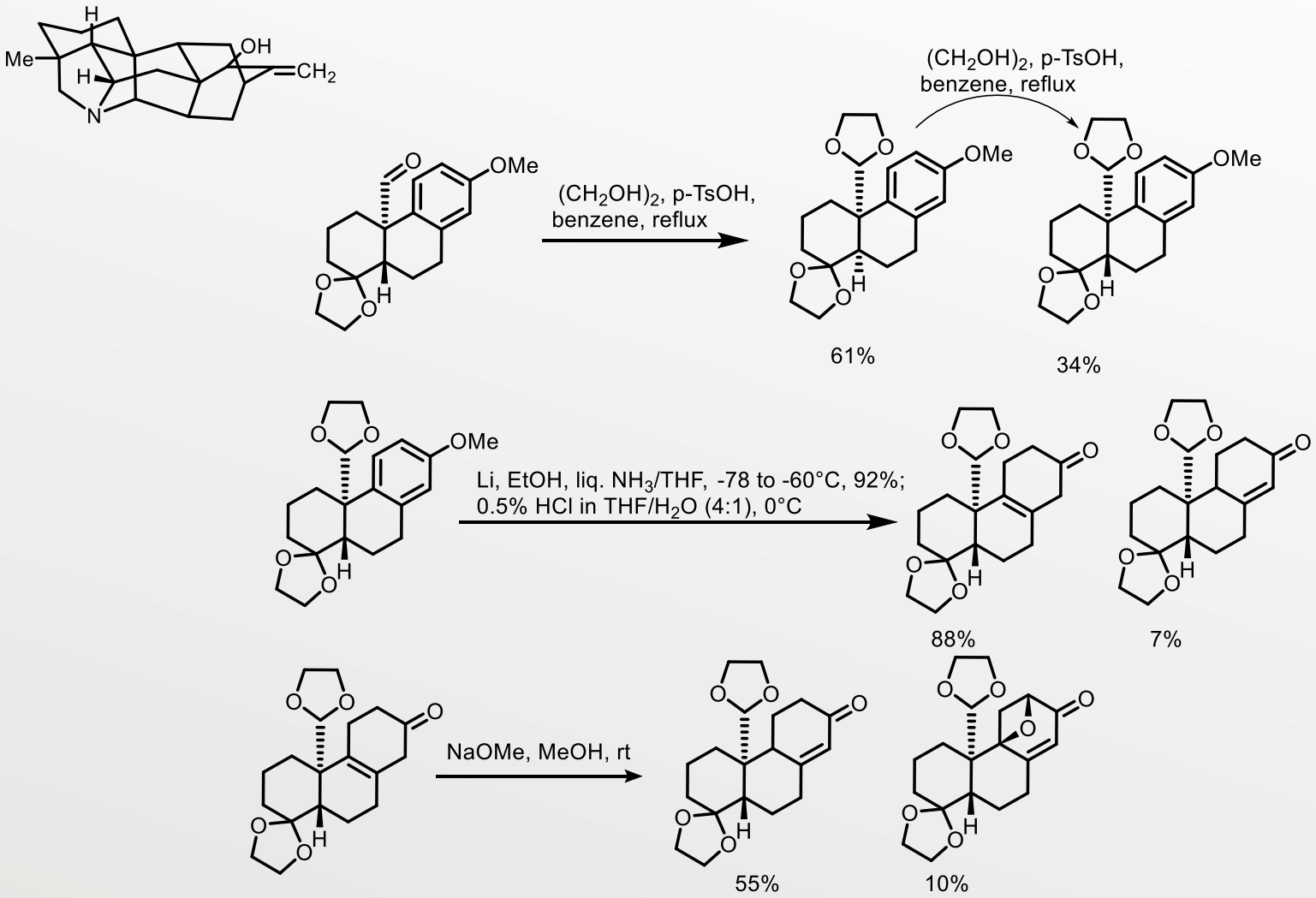

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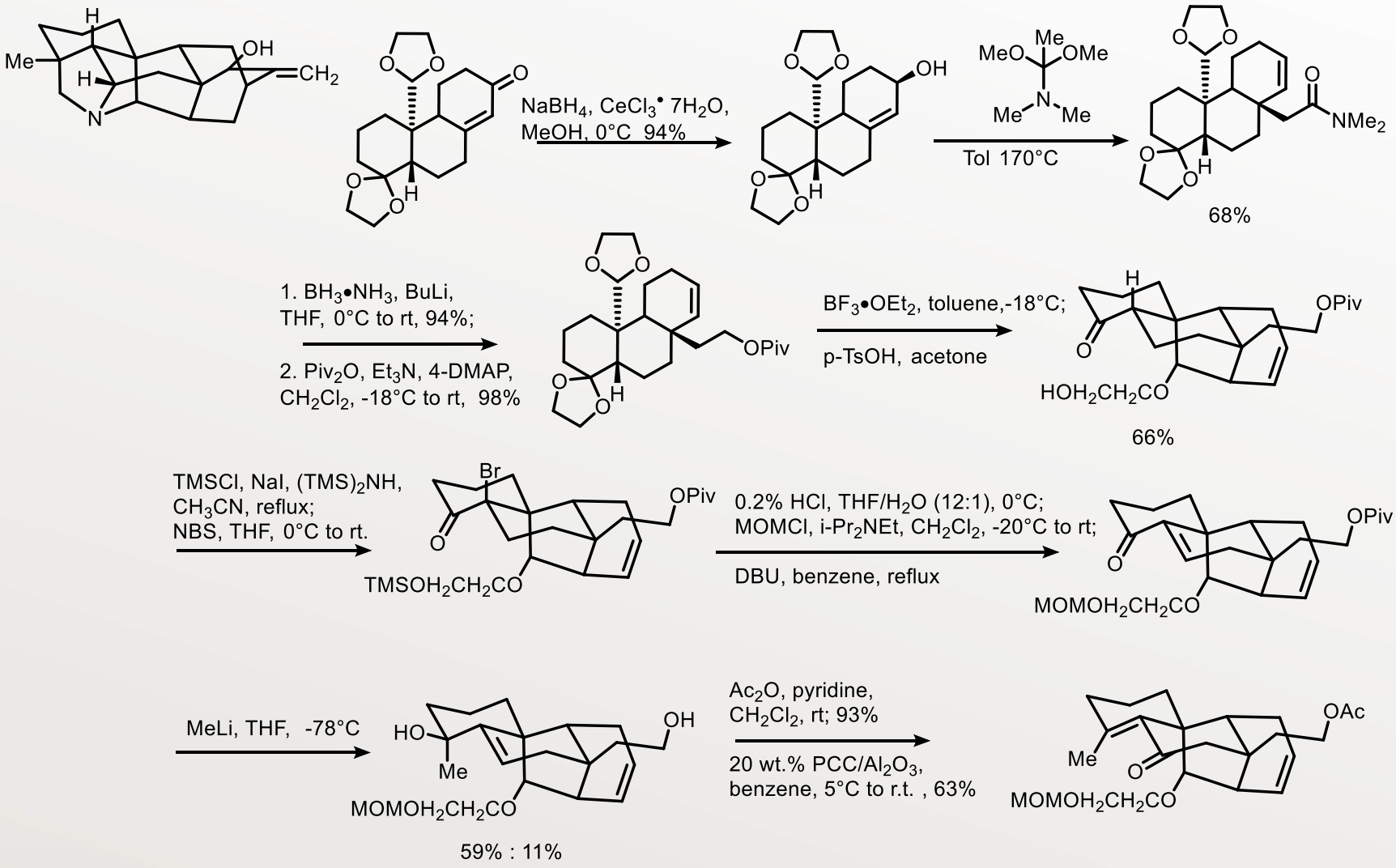

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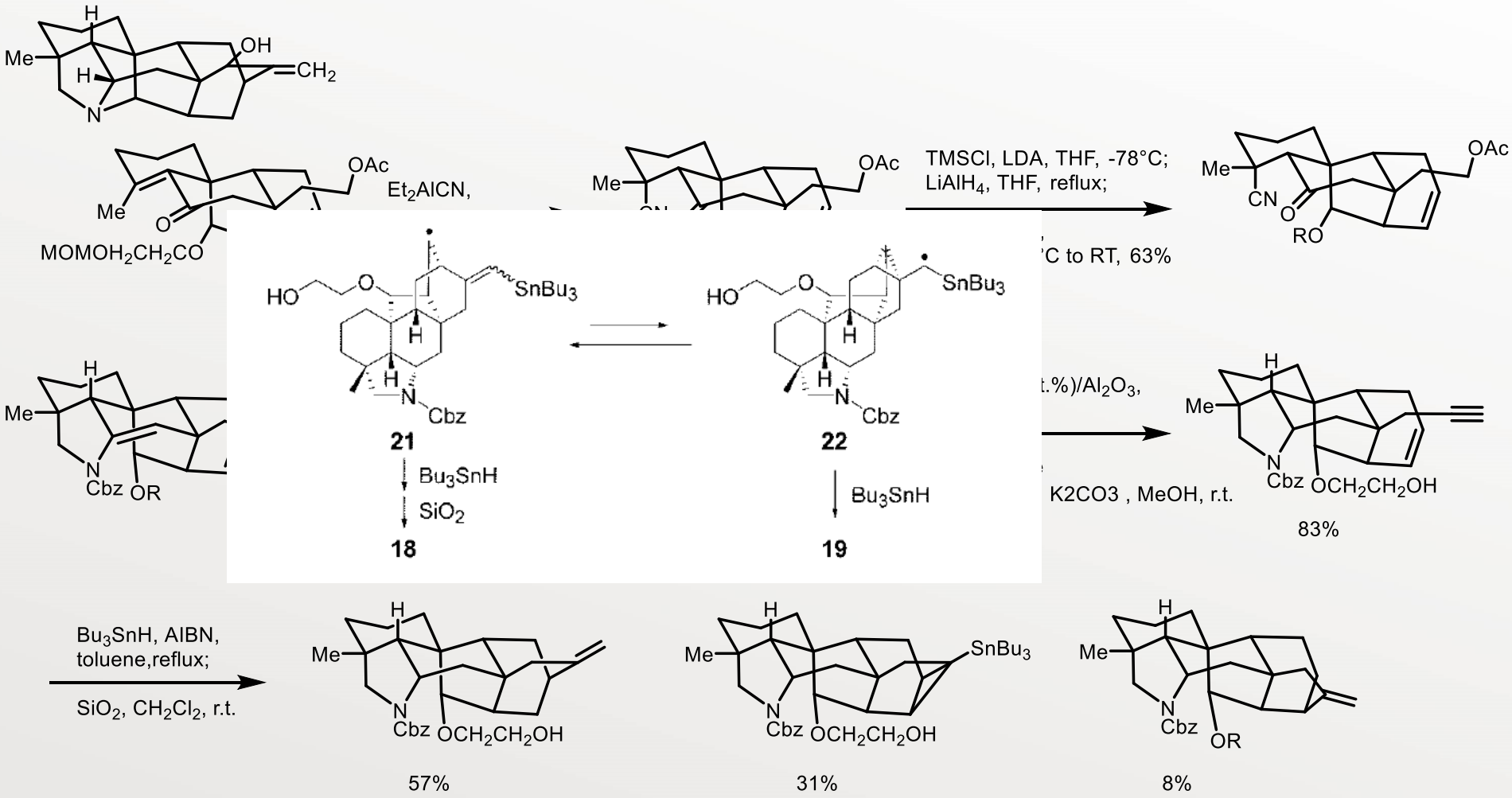

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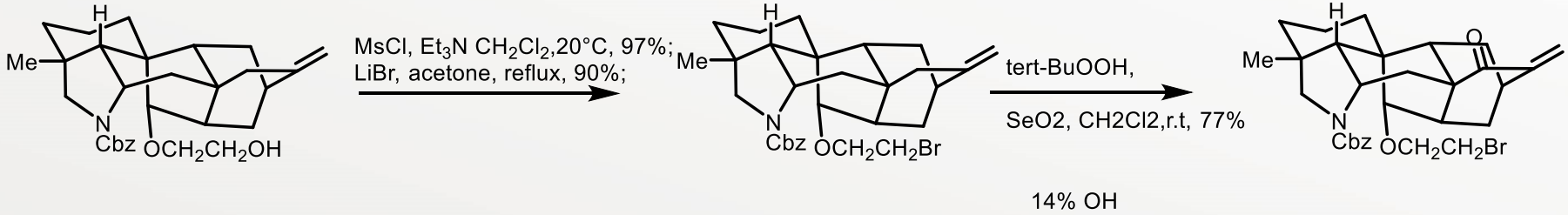

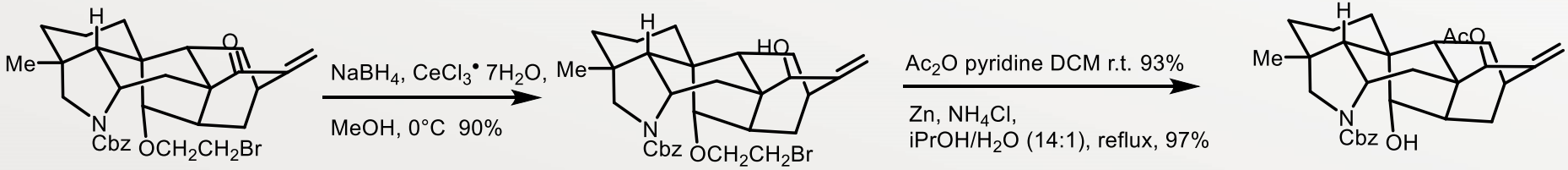

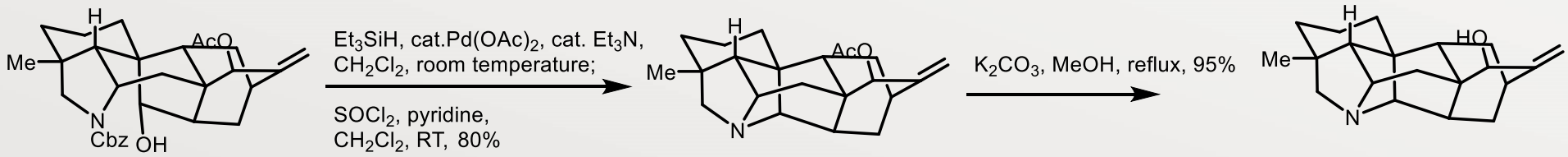

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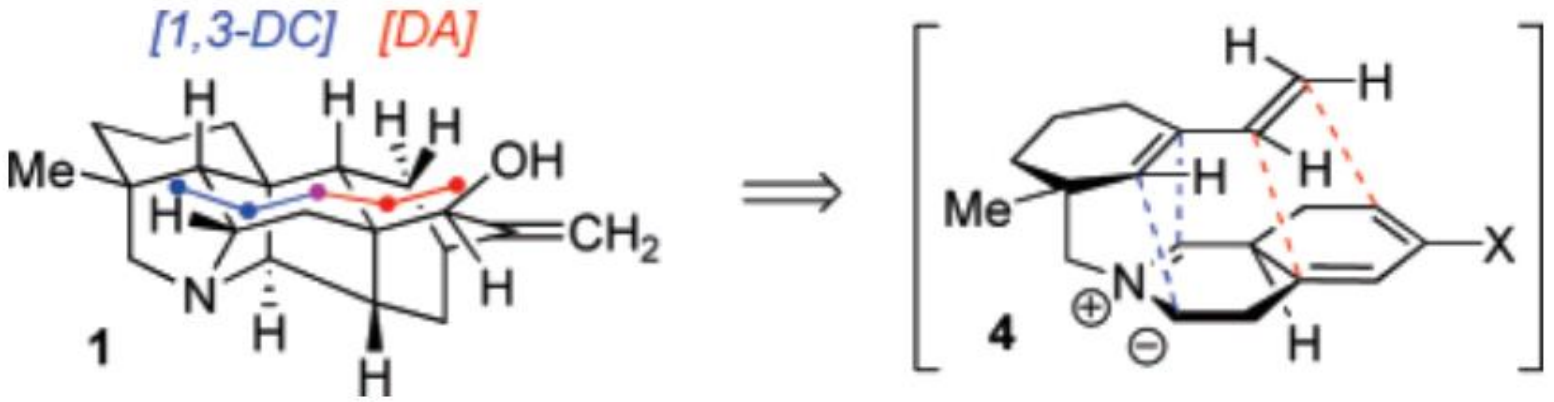
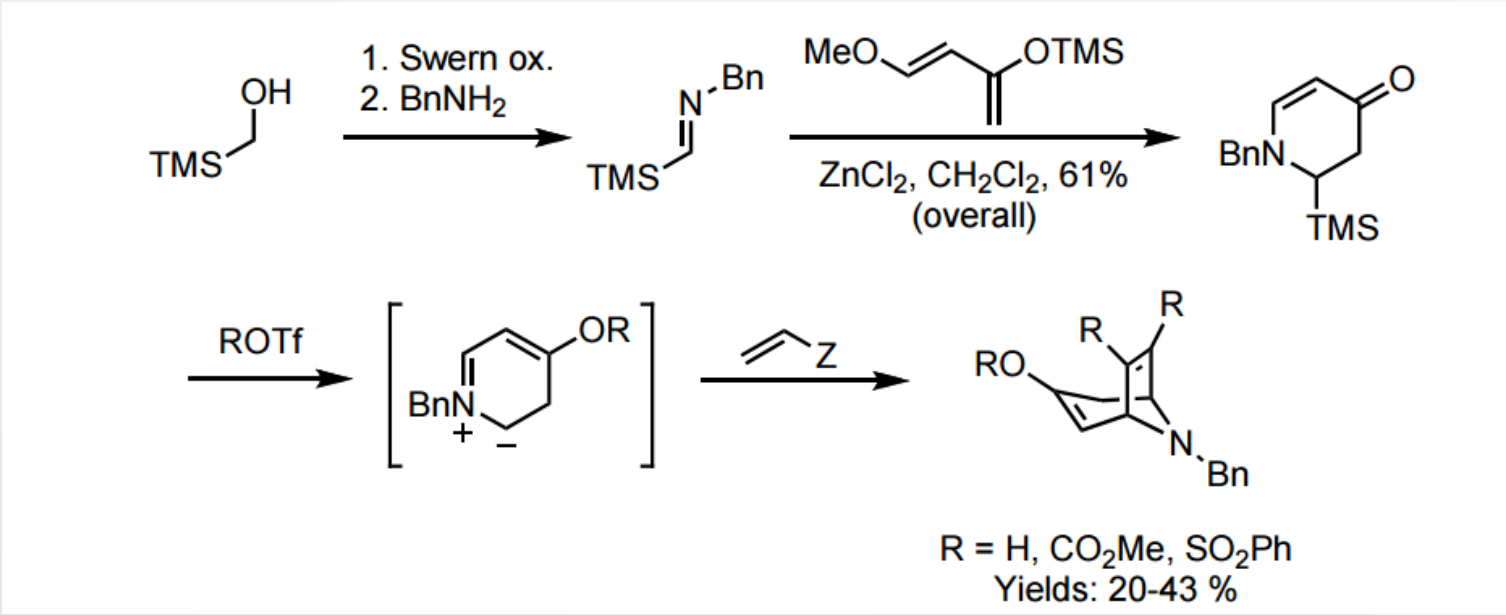
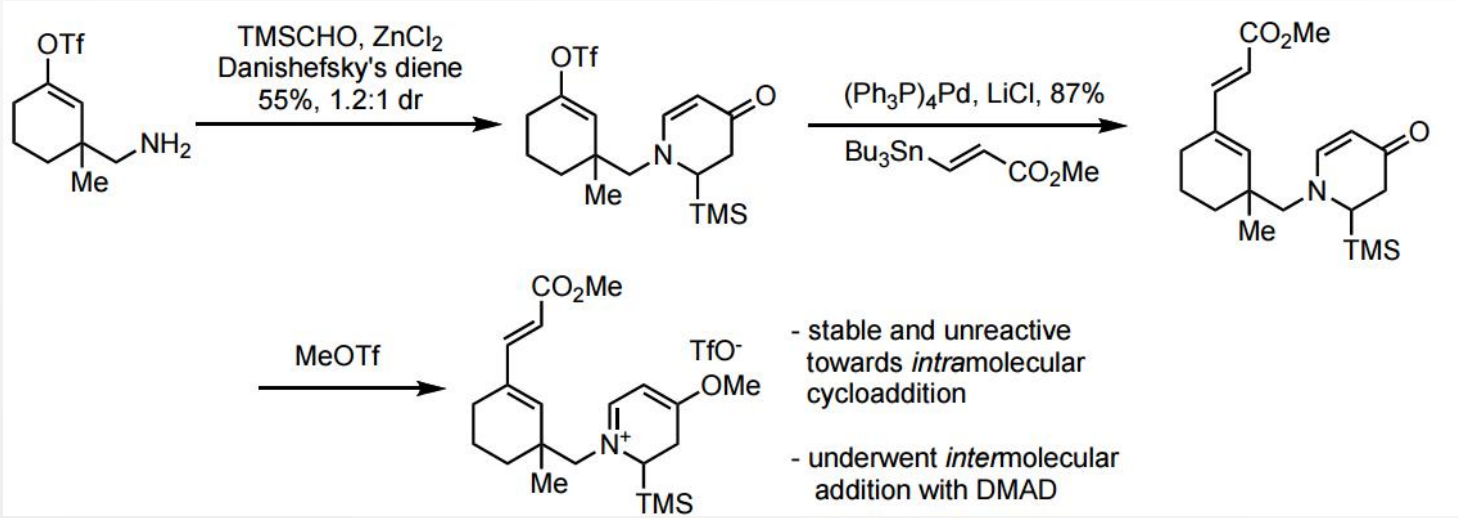
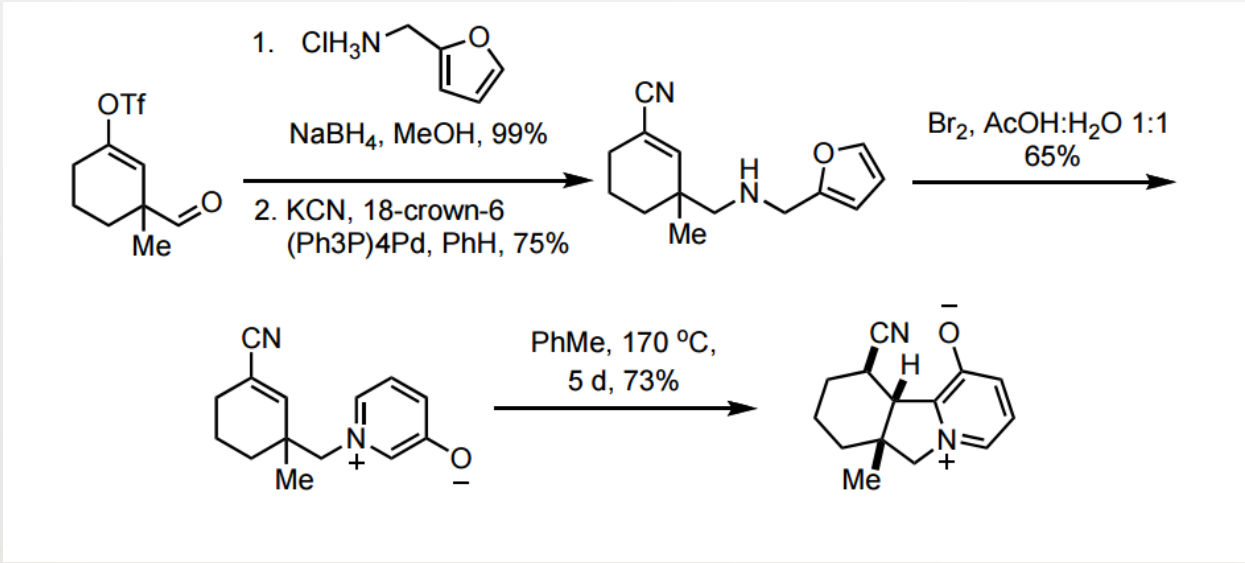




Kevin M. Peese and David Y. Gin *J. Am. Chem. Soc.*, **2006**, *128,* 8734–8735
Kevin M. Peese and David Y. Gin *Chem. Eur. J.* **2008**, 14, 1654 – 1665





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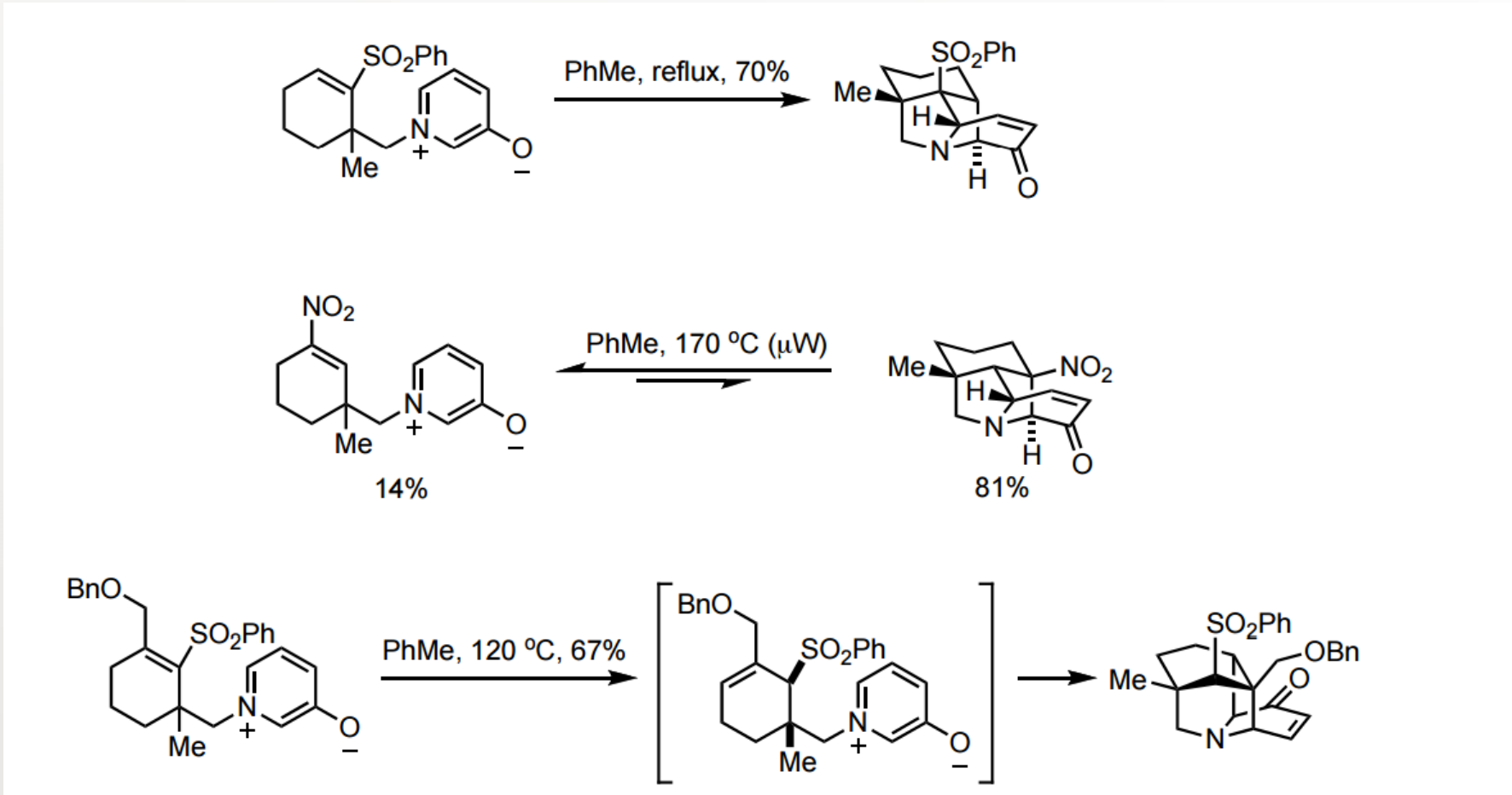

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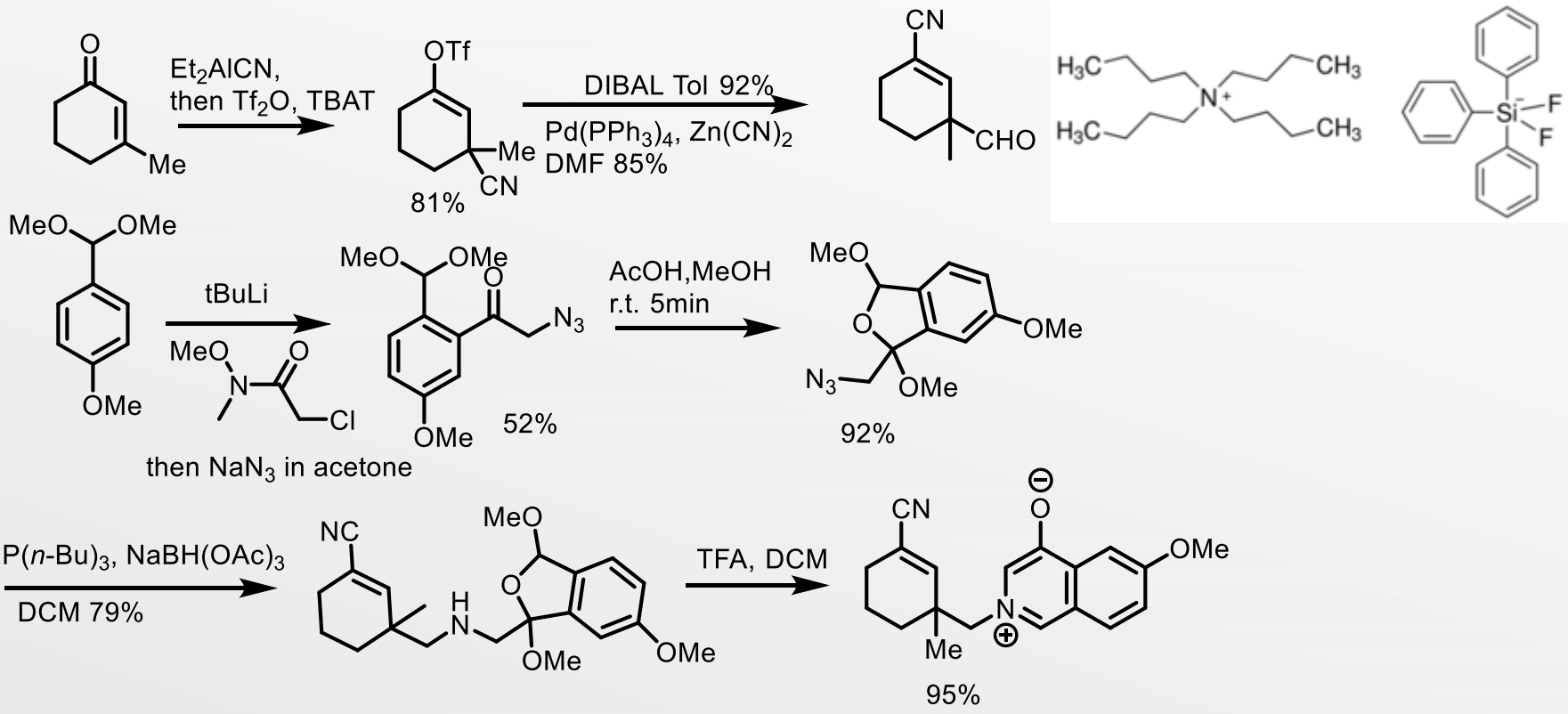

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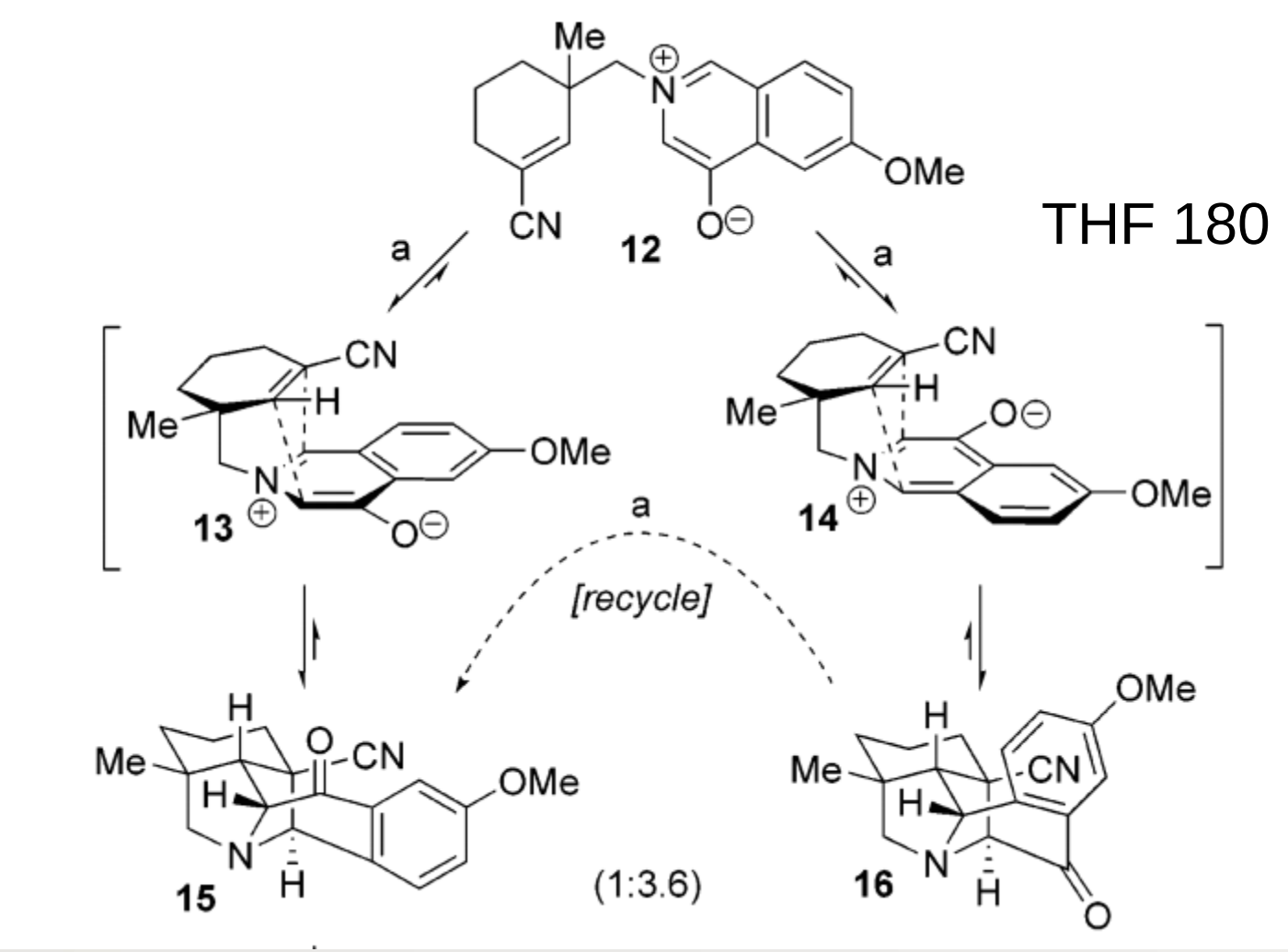

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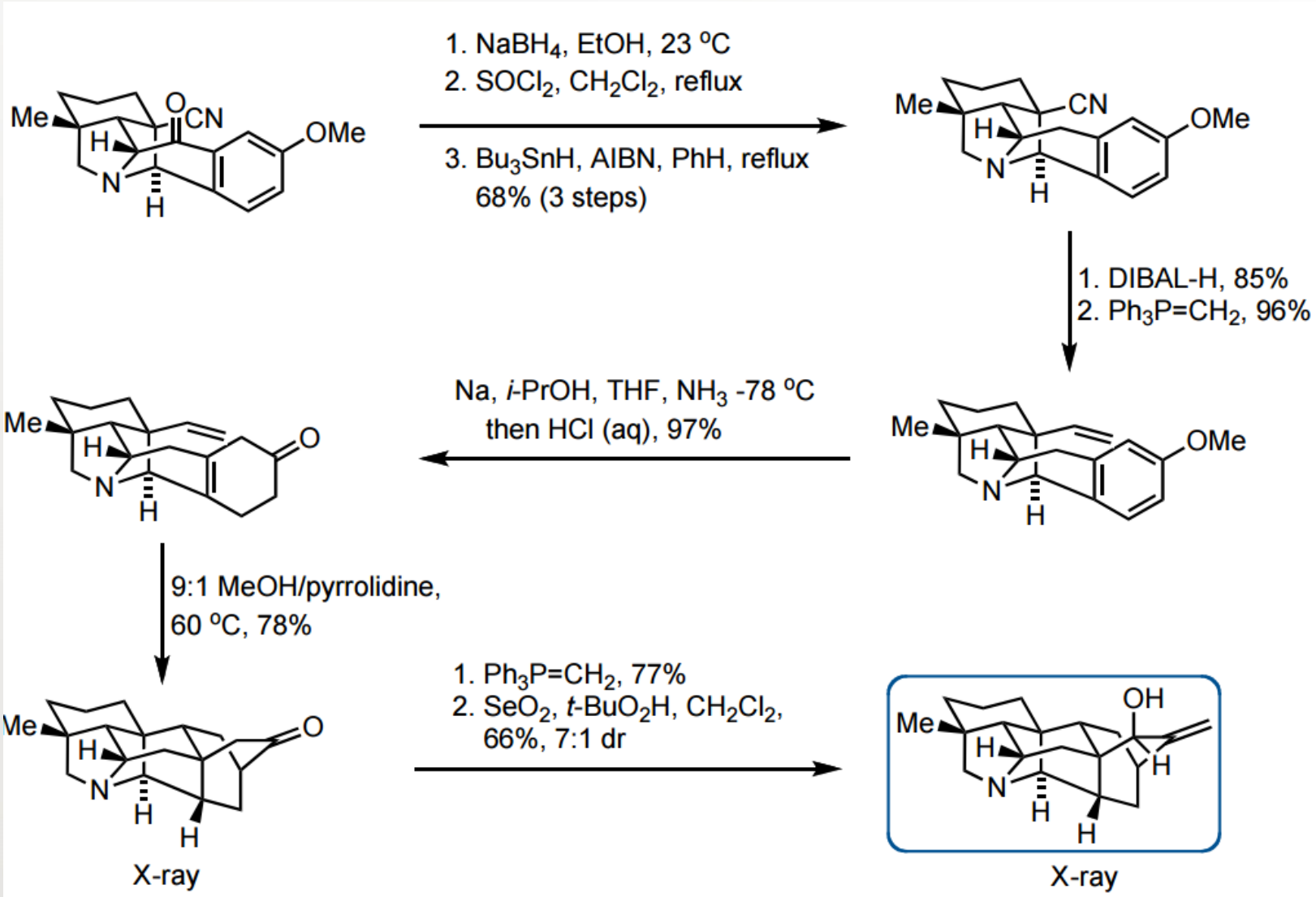

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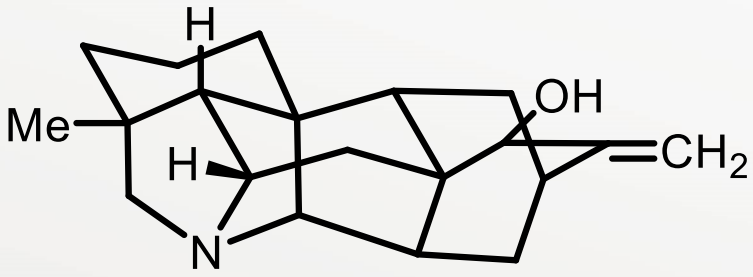
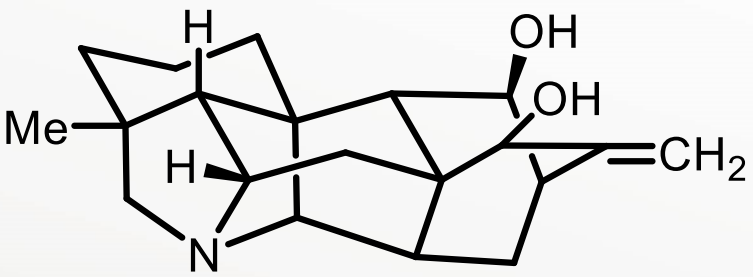
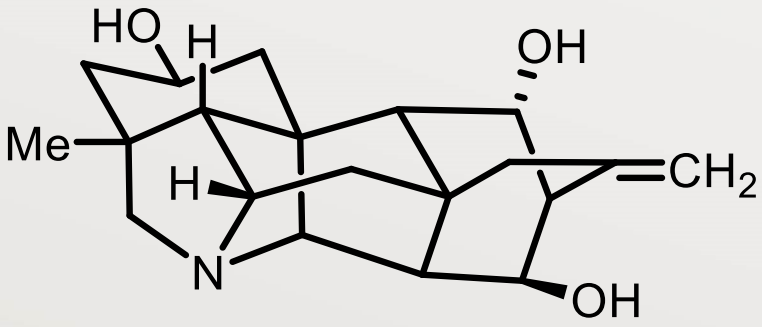


nominine

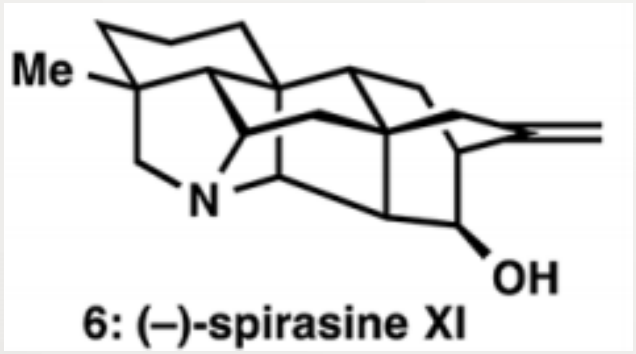


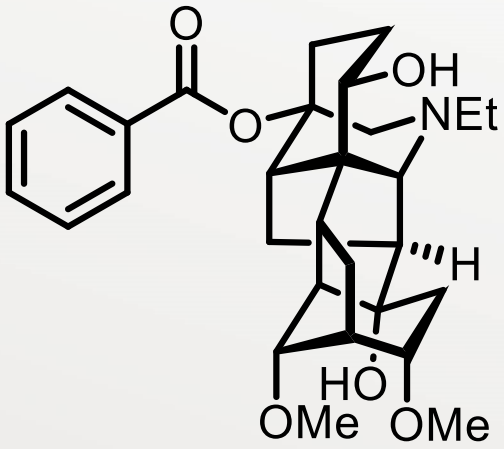
Kobusine

Selective C-H oxidation based on masked-OH?

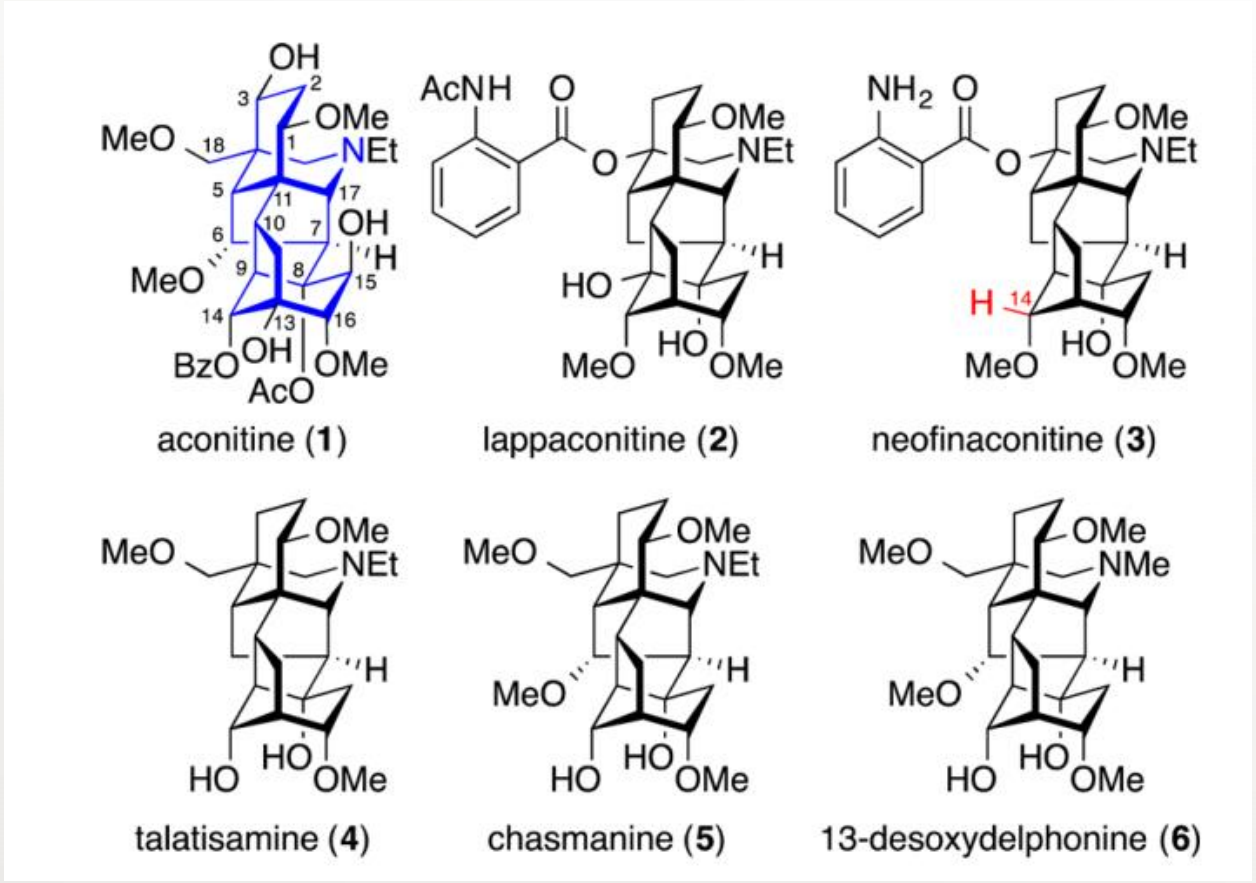


Hetisine

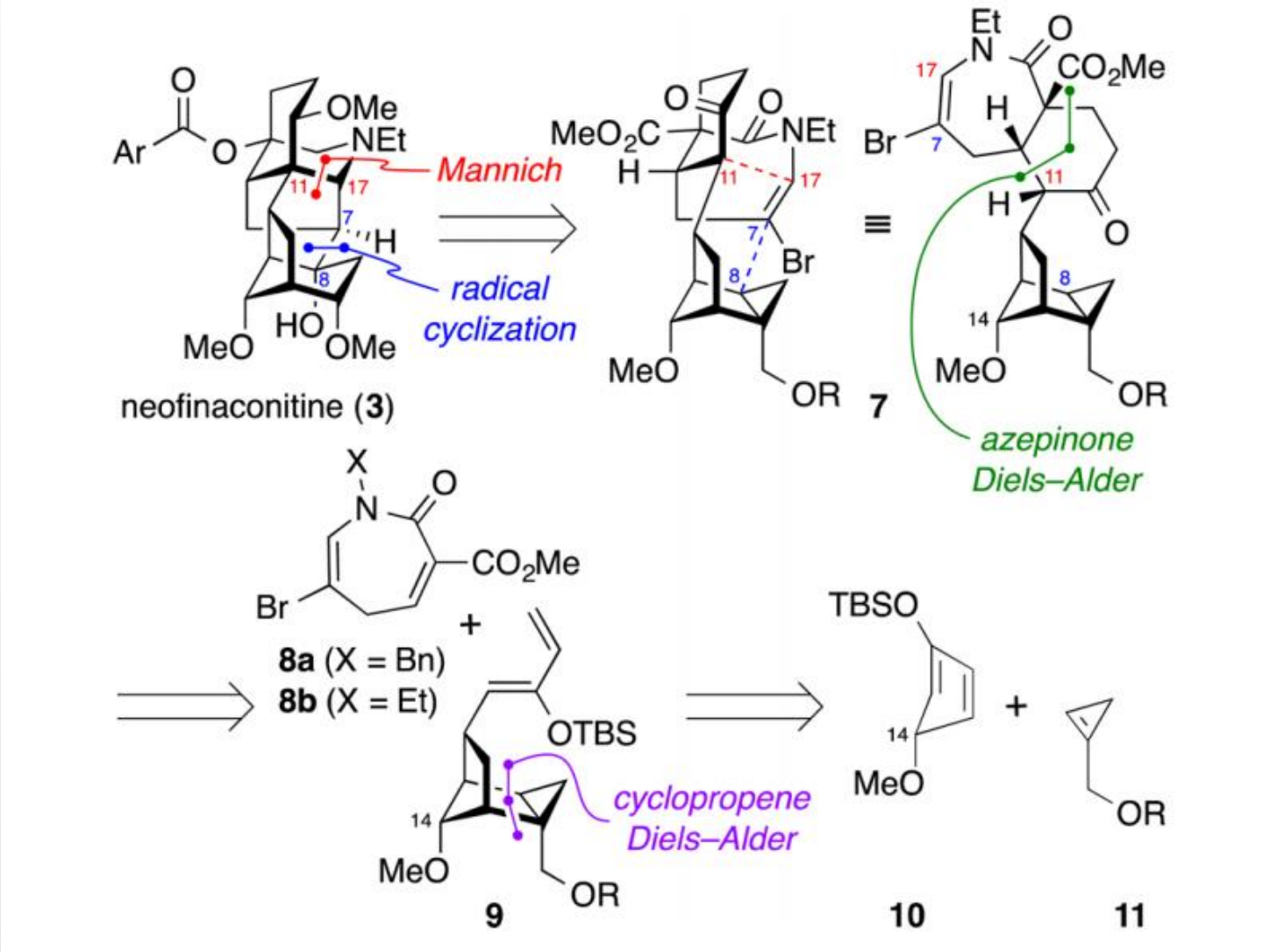




6,6,5,6,5,6
Hexacyclic core



Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y.
J. Am. Chem. Soc. **2013**, 135, 14313−14320.



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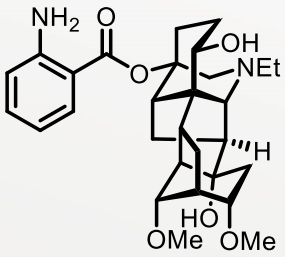

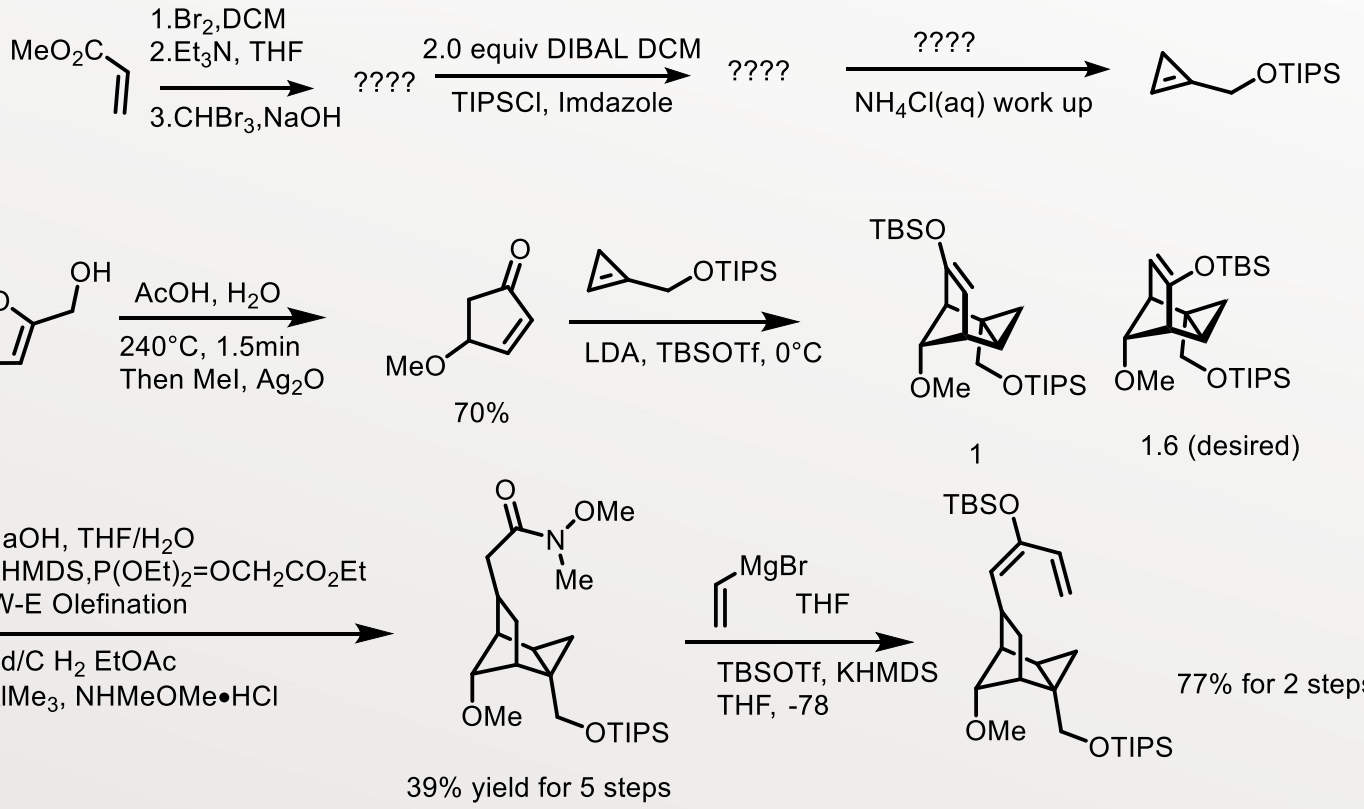

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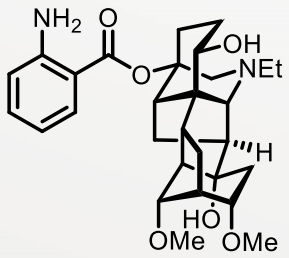

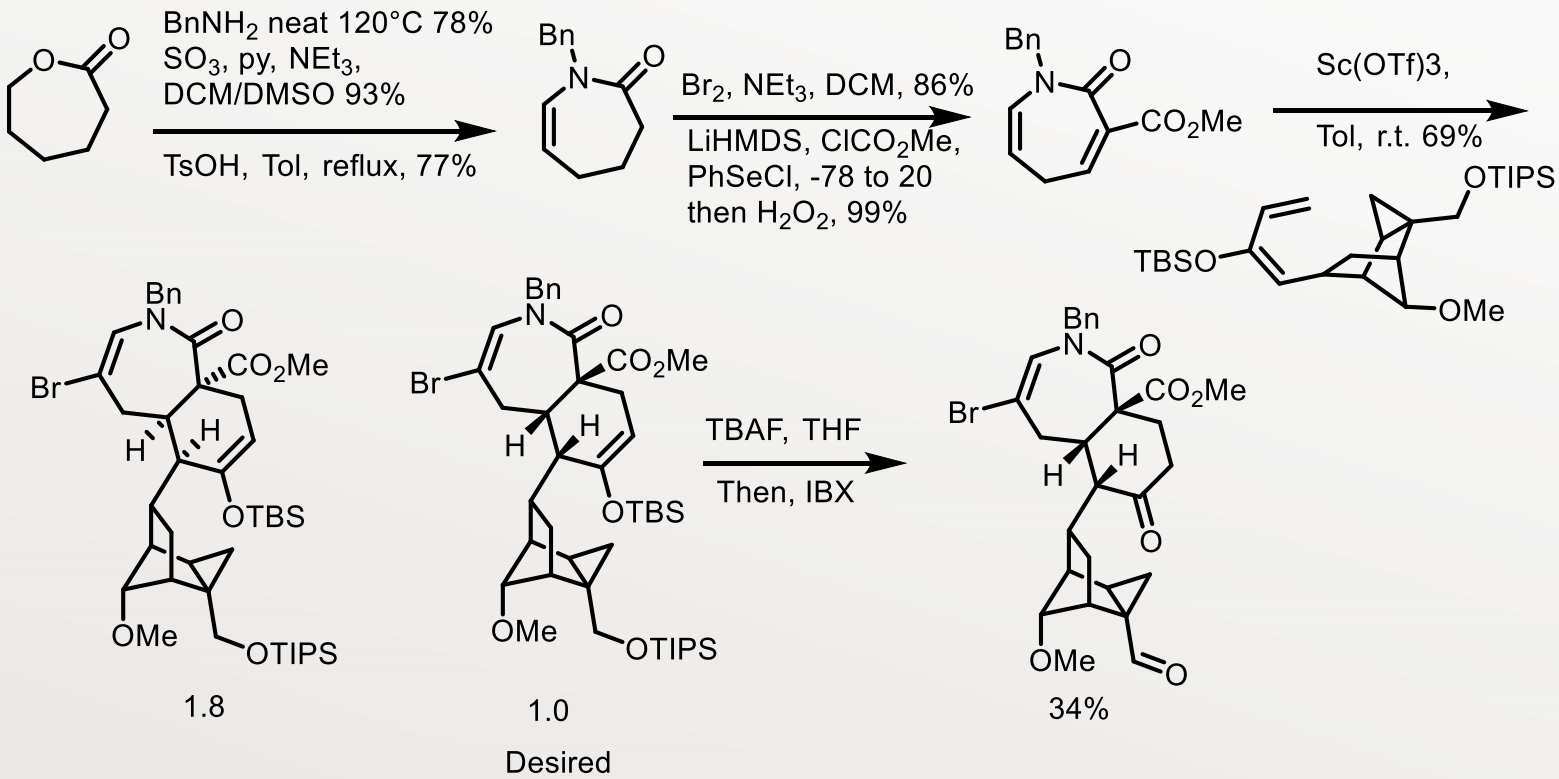

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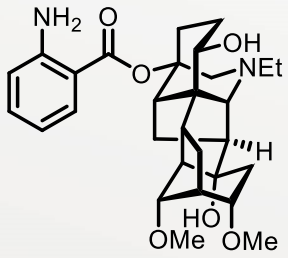
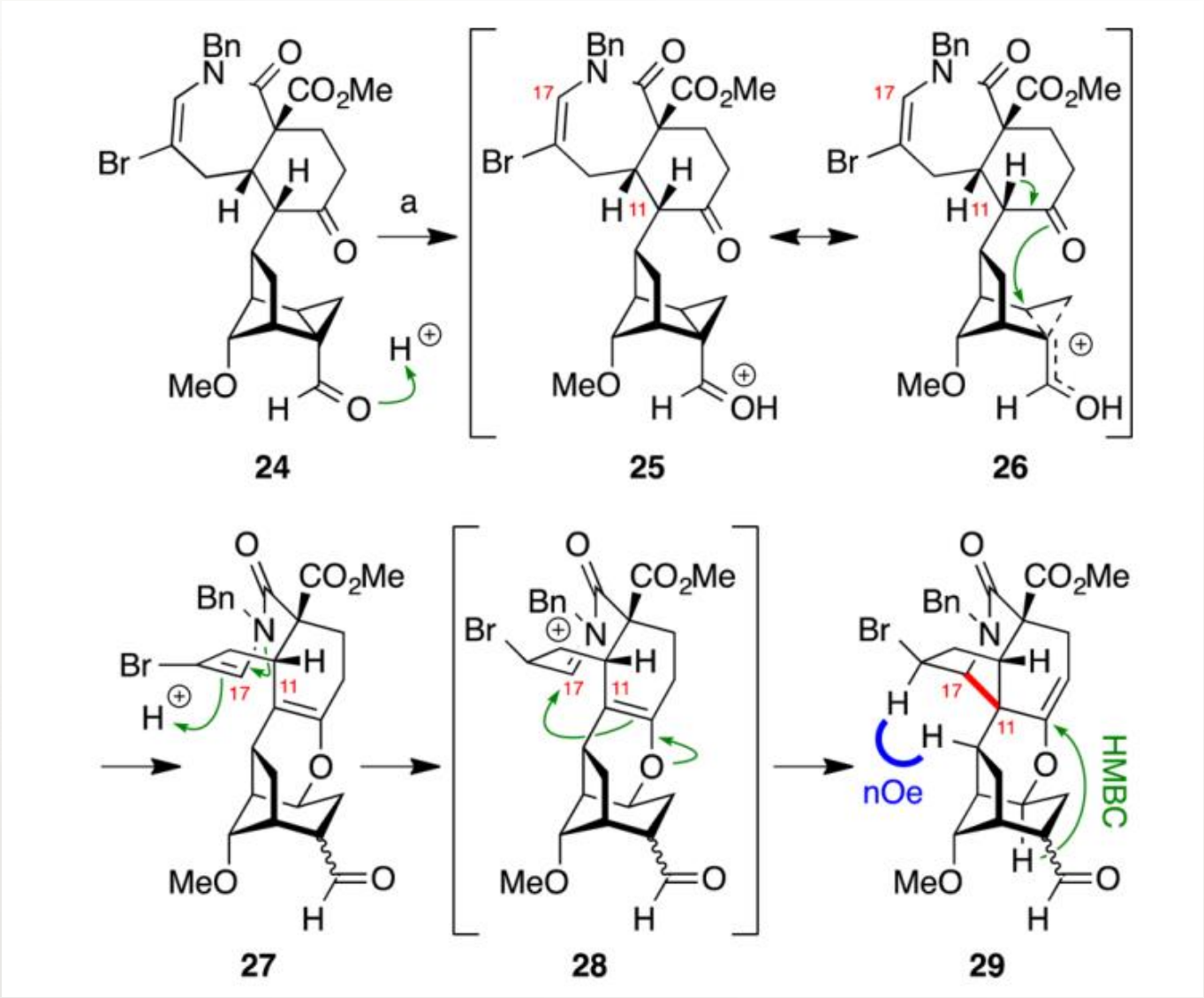


Tf_2NH,
DCM, 0°C



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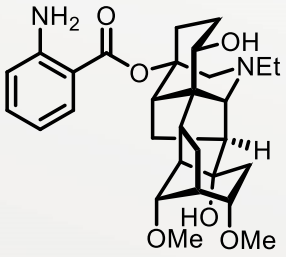
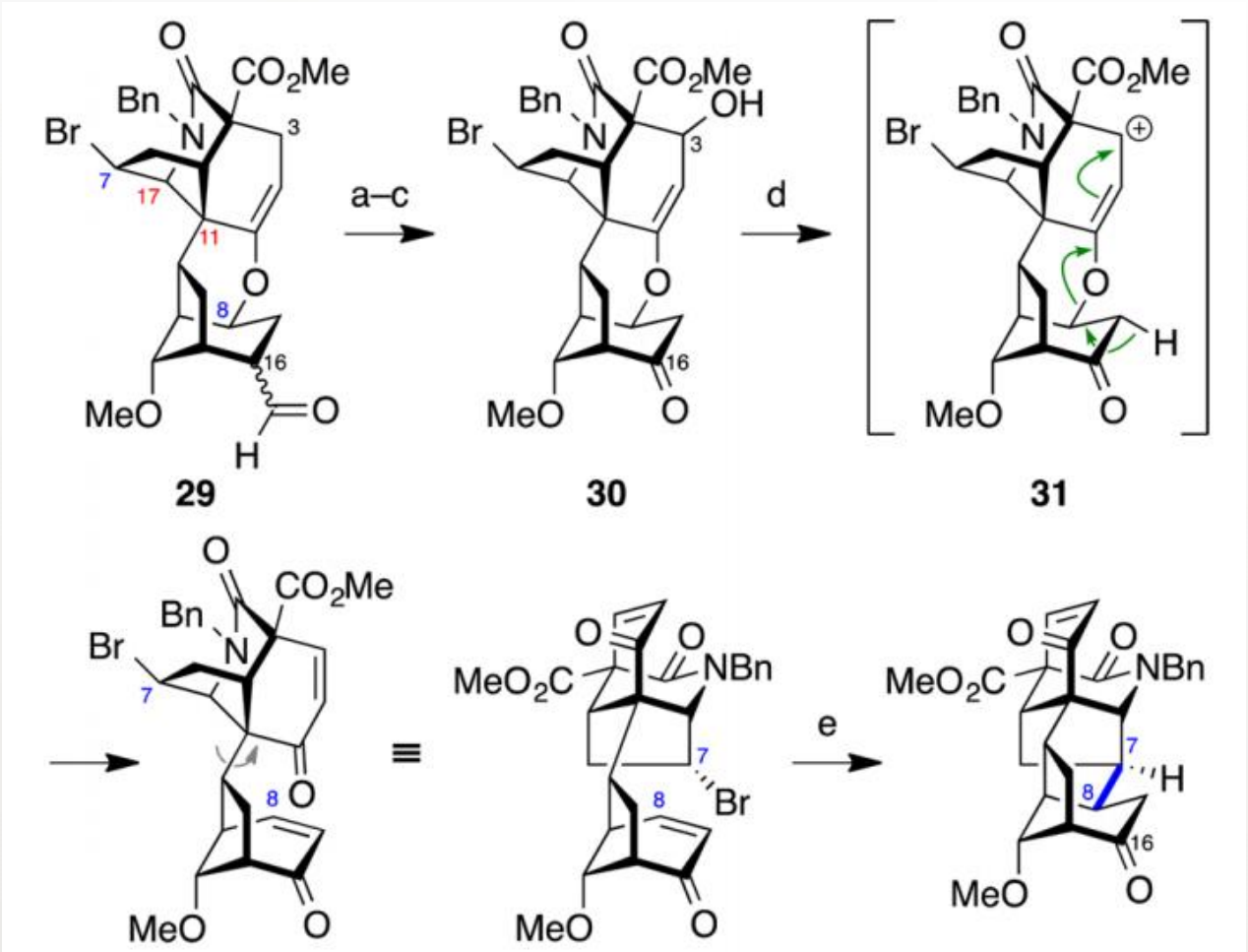
J. Am. Chem. Soc. **2013**, 135, 14313−14320.





C19-norditerpenoid alkaloids **35**. (a) TBSOTf, Et_3N, CH_2Cl_2, 86%. (b) OsO_4, $PhI(OAc)_2$, 2,6-lutidine, THF/H_2O, 74%. (c) $Ce(NH_4)_2(NO_3)_6$, $CH_3CN/CH_2Cl_2/H_2O$, 50 °C. (d) MsCl, Et_3N, CH_2Cl_2, 50 °C, 57% over two steps. (e) Bu_3SnH, AIBN, PhH, 80 °C,

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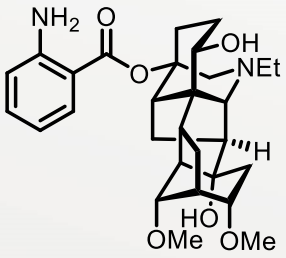

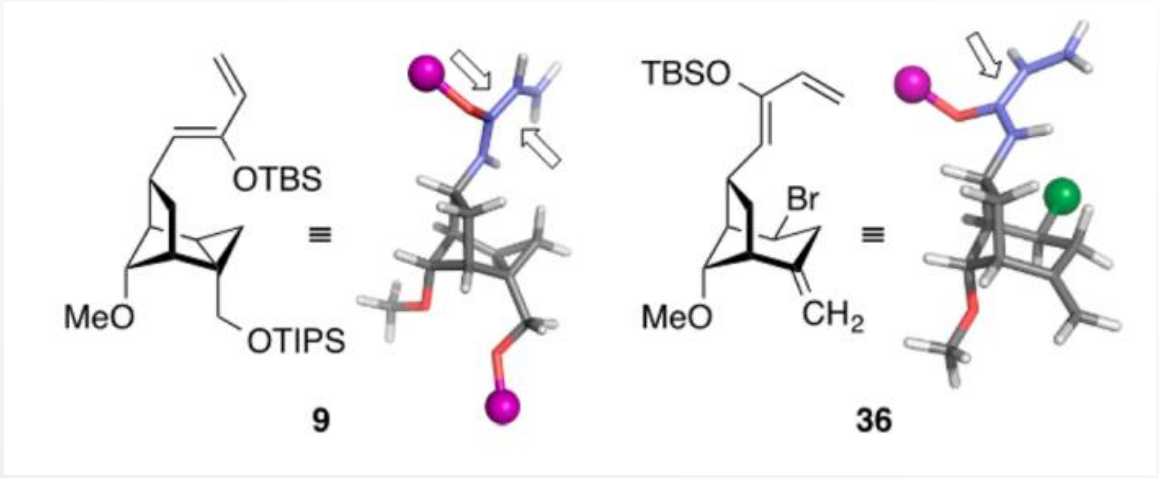

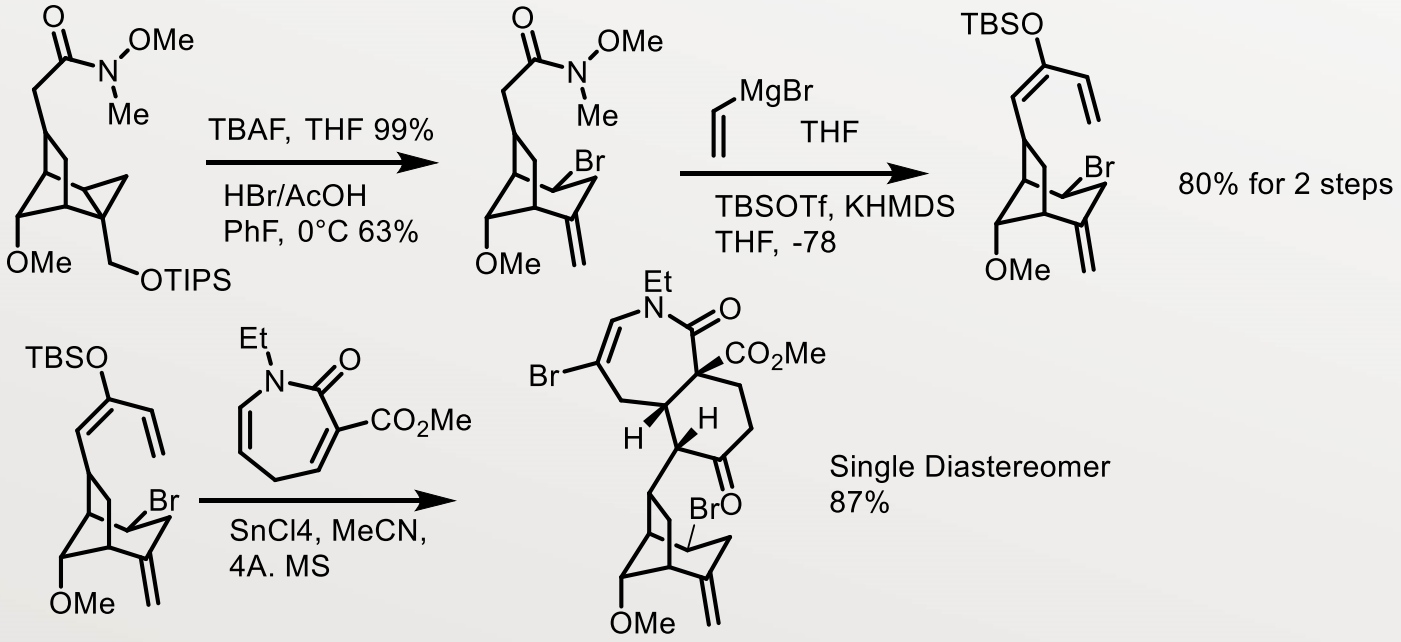

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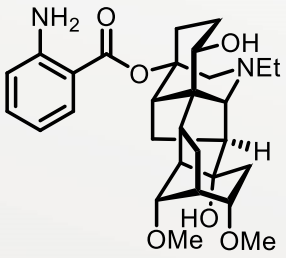
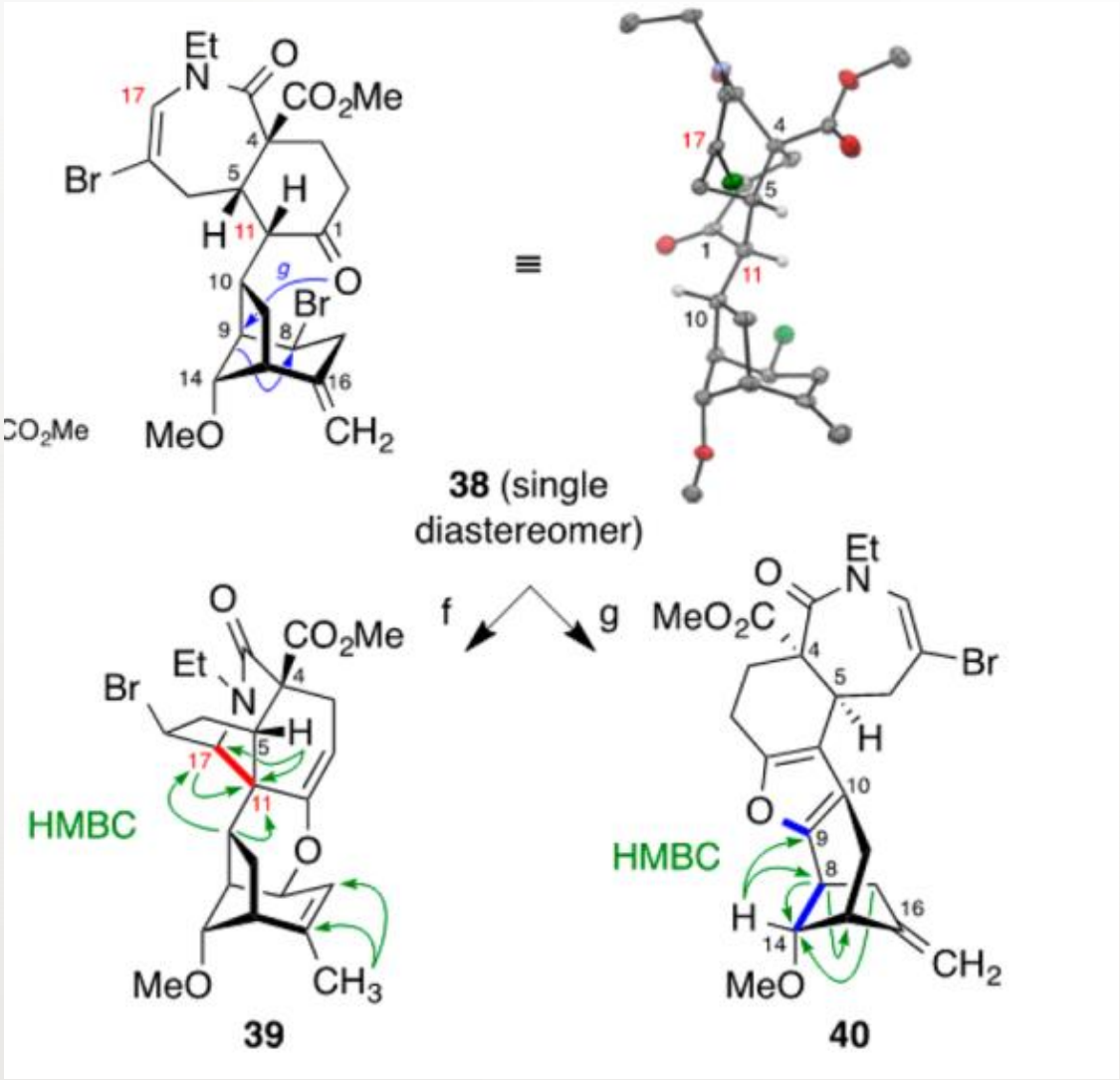
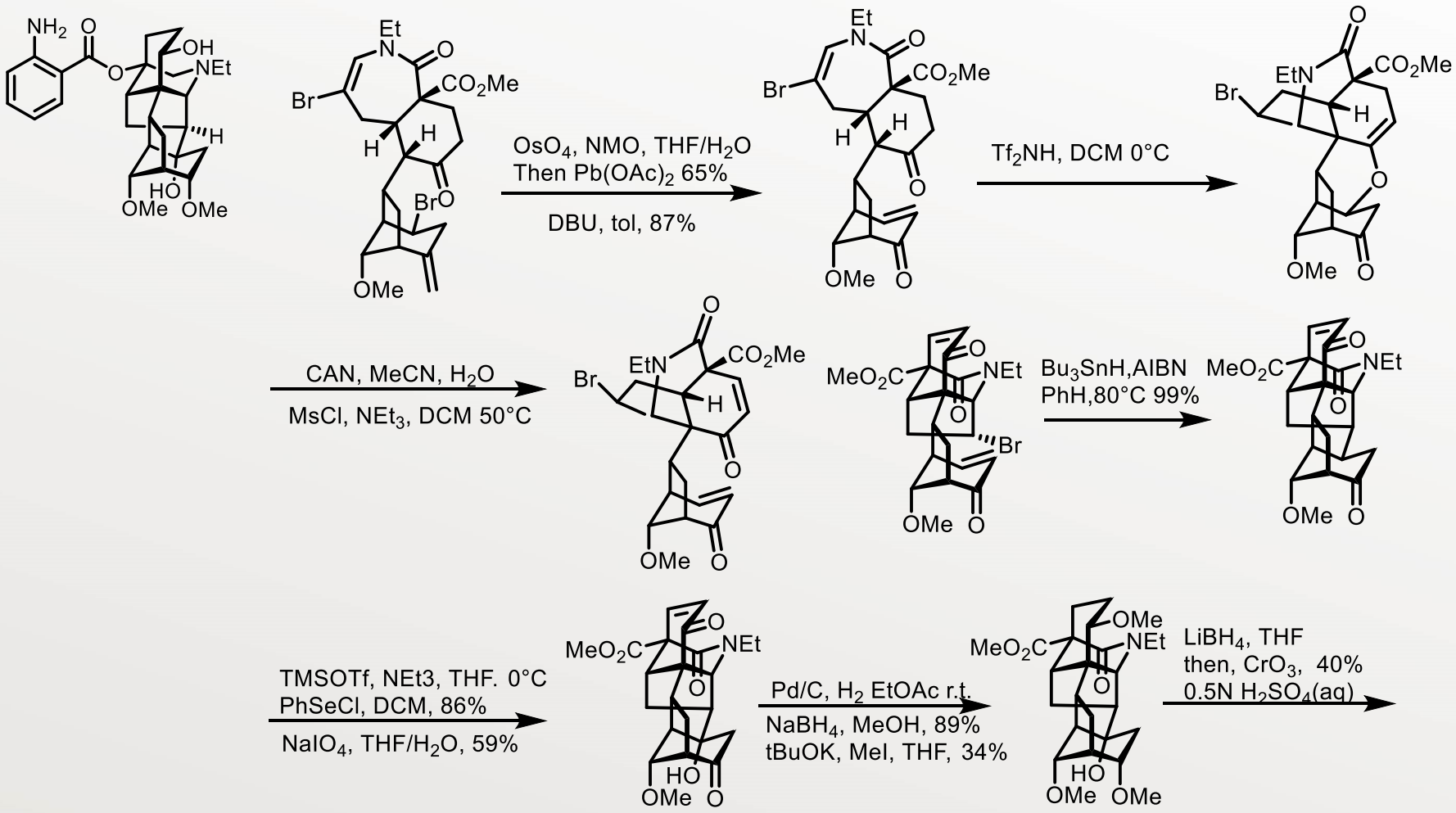


(f) Tf_2NH, CH_2Cl_2, 46%.

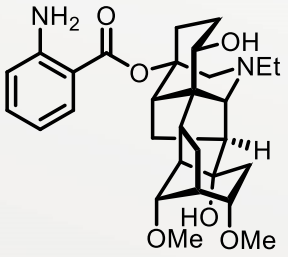
(g) AgO_2CCF_3, CH_2Cl_2, 60%.

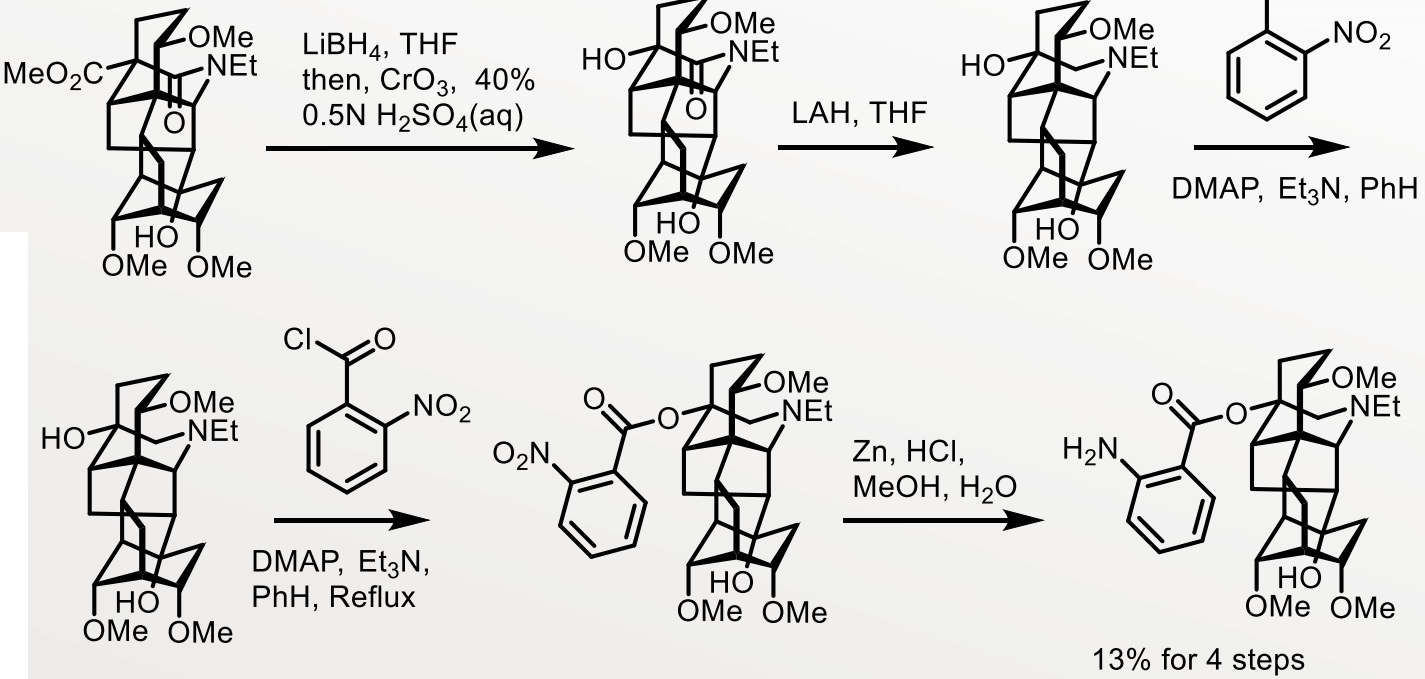


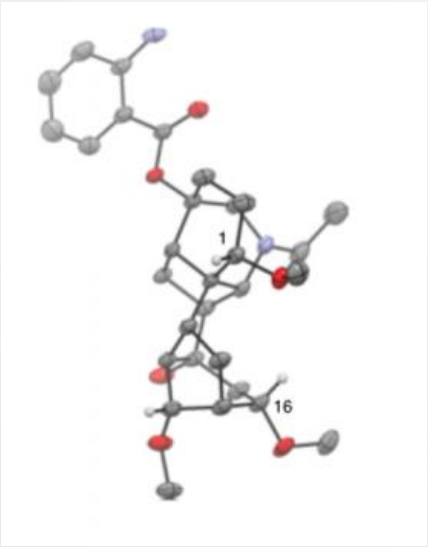
Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc*. **2013**, 135, 14313−14320.



Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc*. **2013**, 135, 14313−14320.







27 LLS, 2 D-A, 1-Manich, radical

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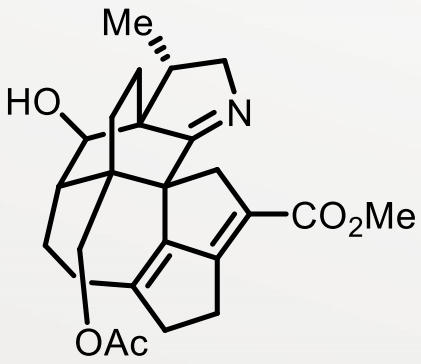
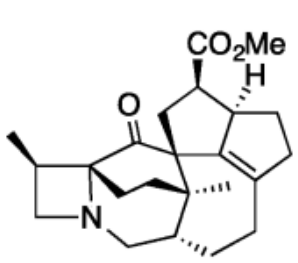
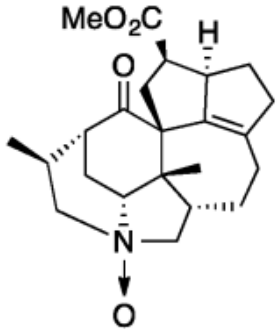
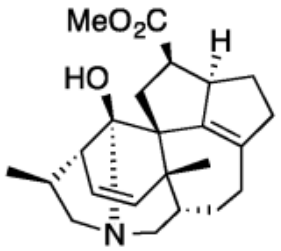




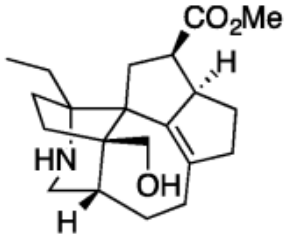
(–)-Calyciphylline C



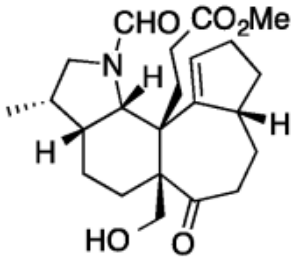
(–)-Calyciphylline A



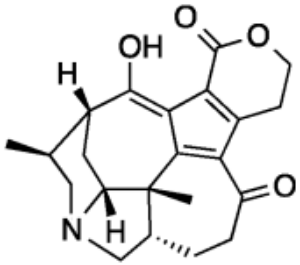
Calyciphylline H



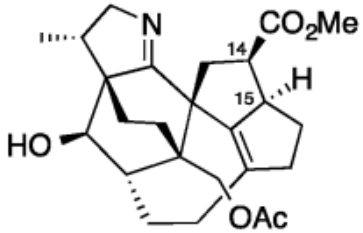
Paxdaphnine B



Daphniglaucin C

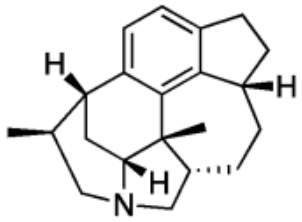


Daphnicyclidin A



(–)-Daphmanidin A

C_{14}-C_{15} dehydro: (+)-Daphmanidin E (Carreira)



Daphenylline (Li)

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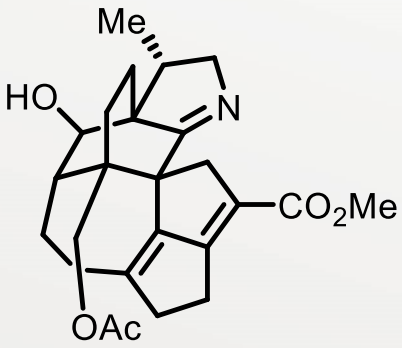

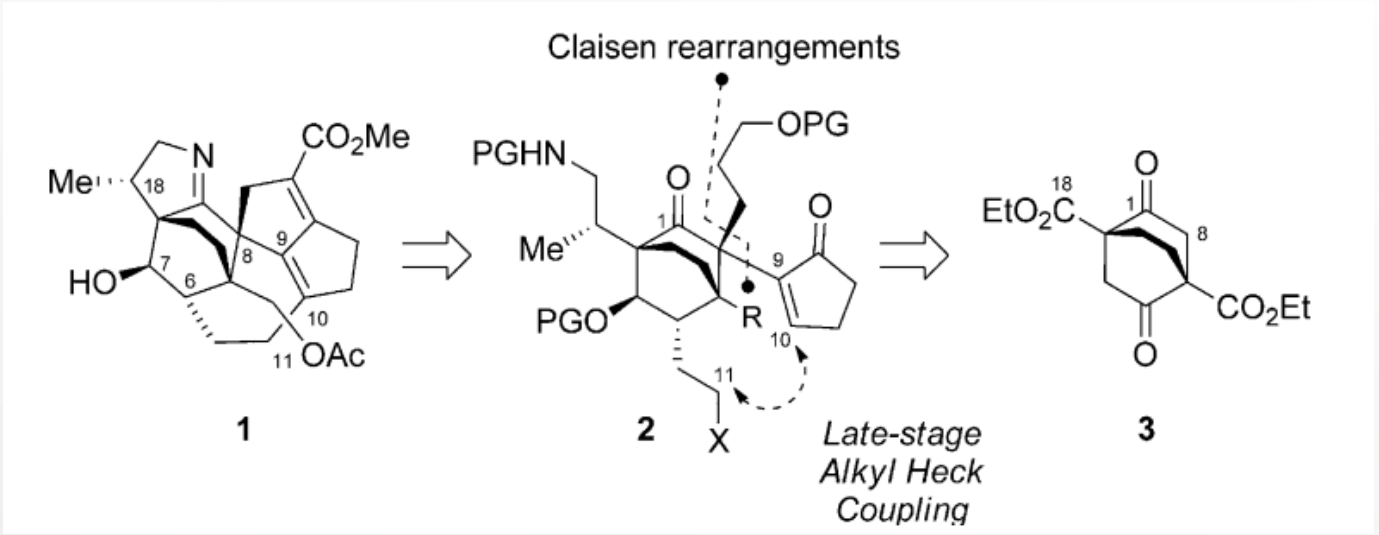

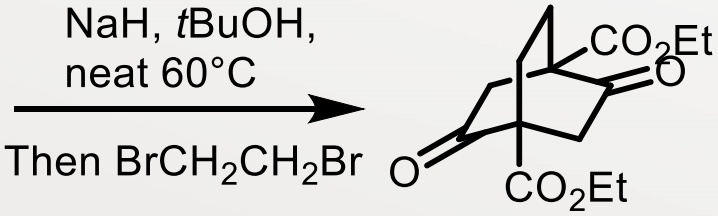

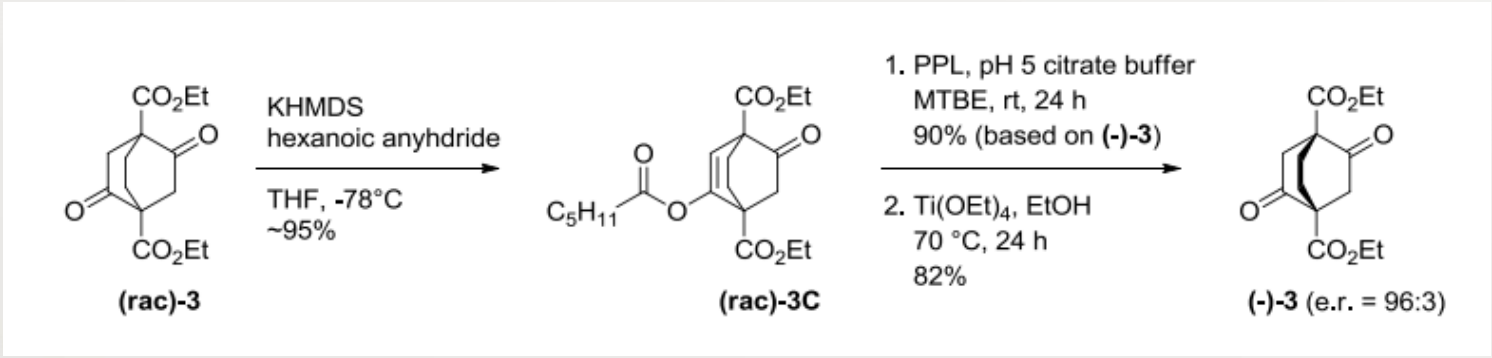

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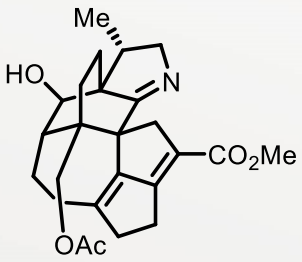

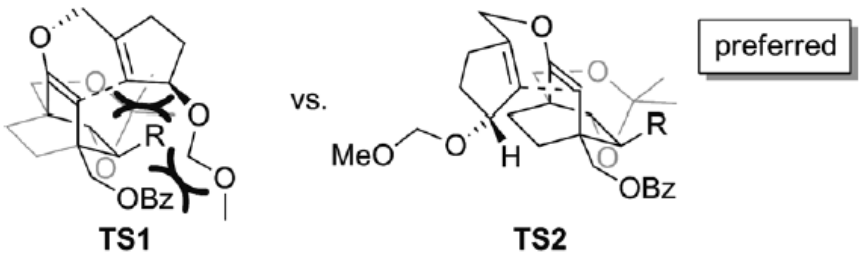

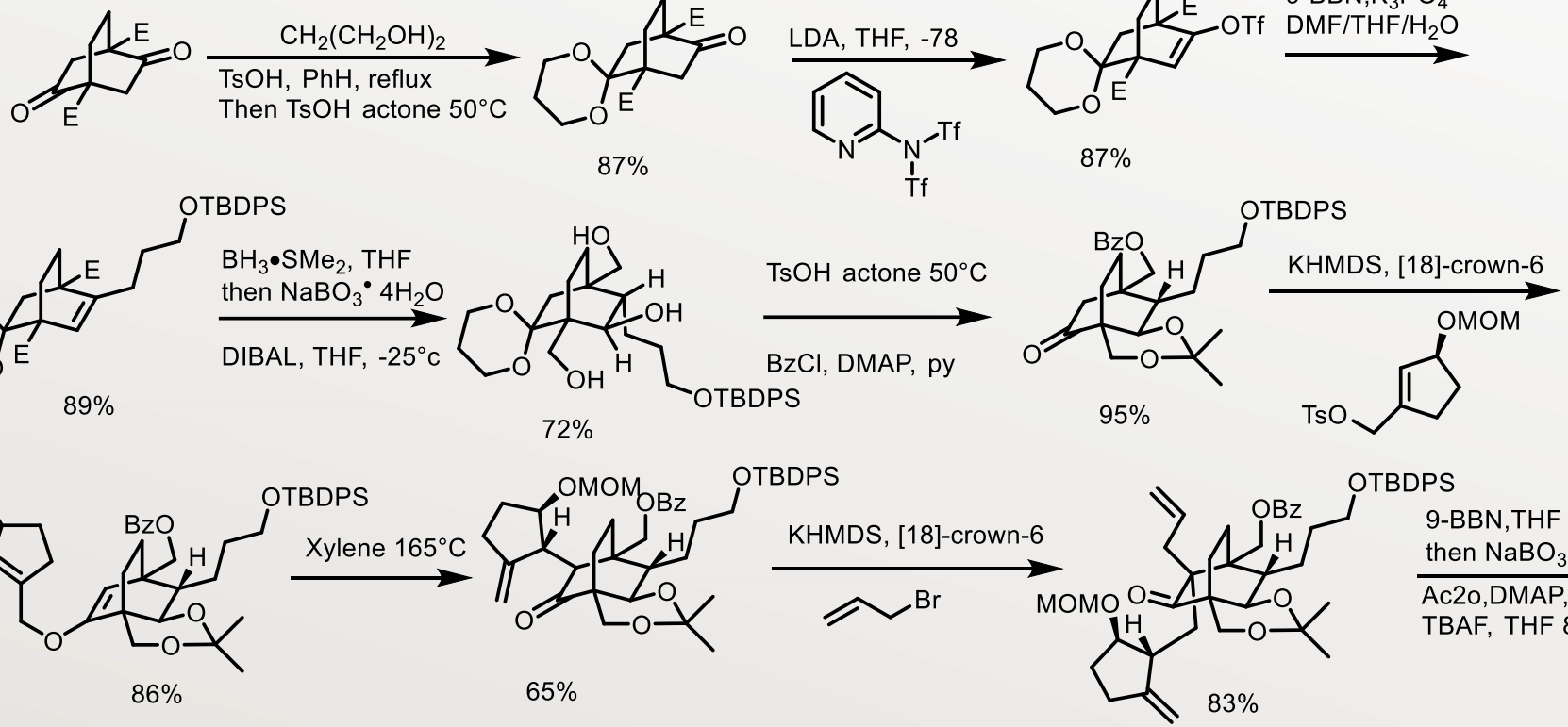

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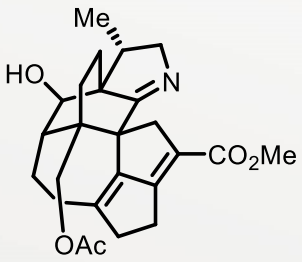

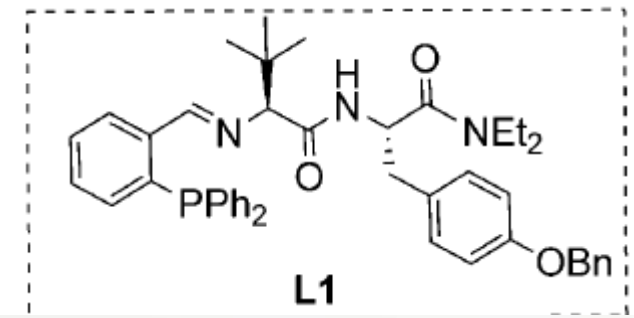

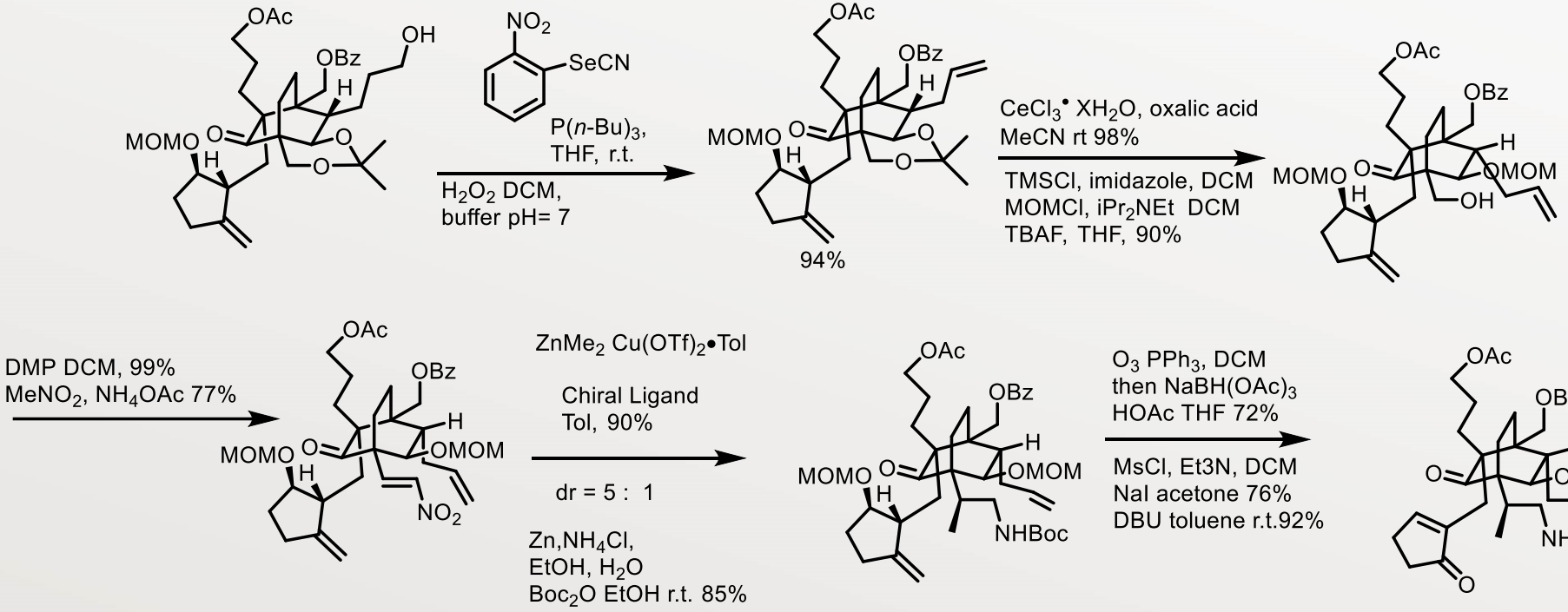

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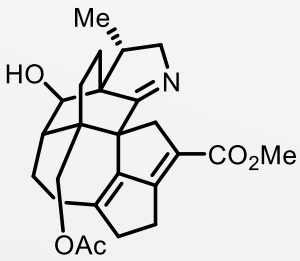

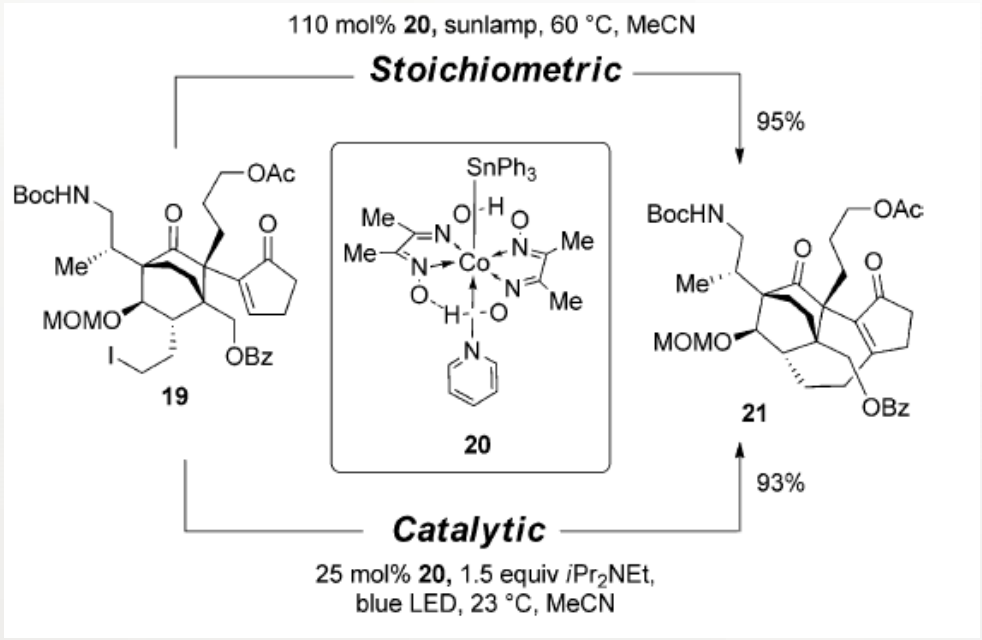

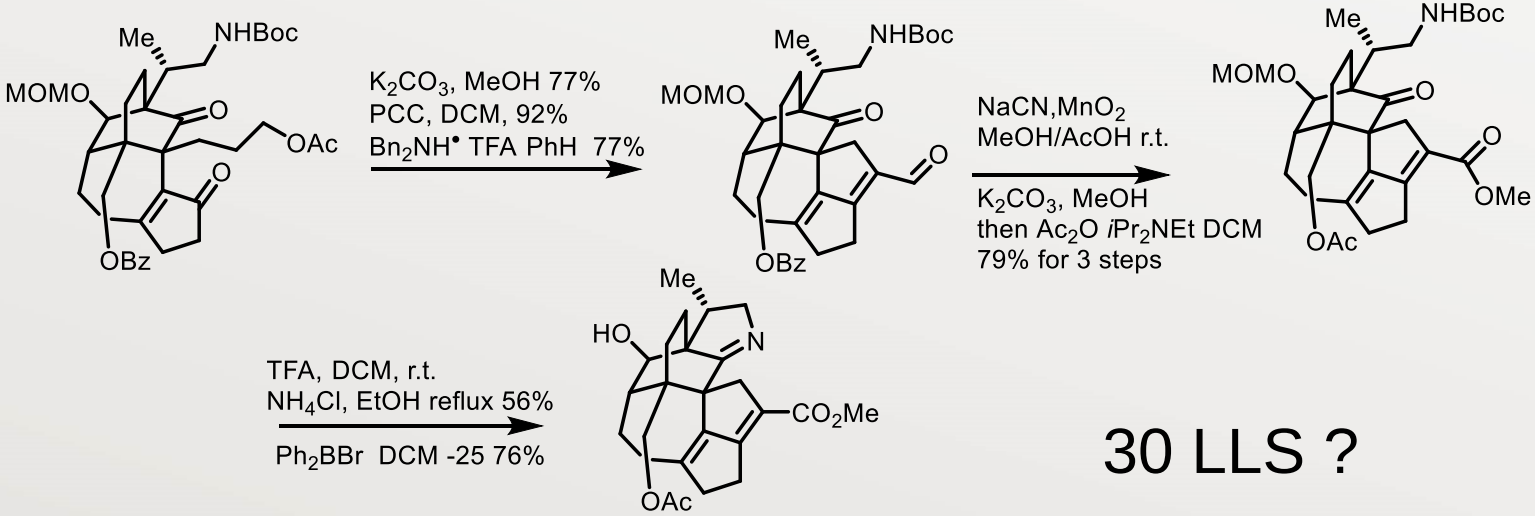

30 LLS ?

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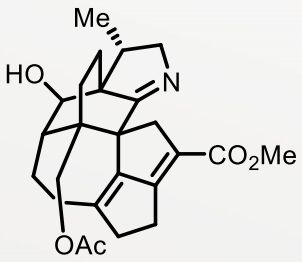

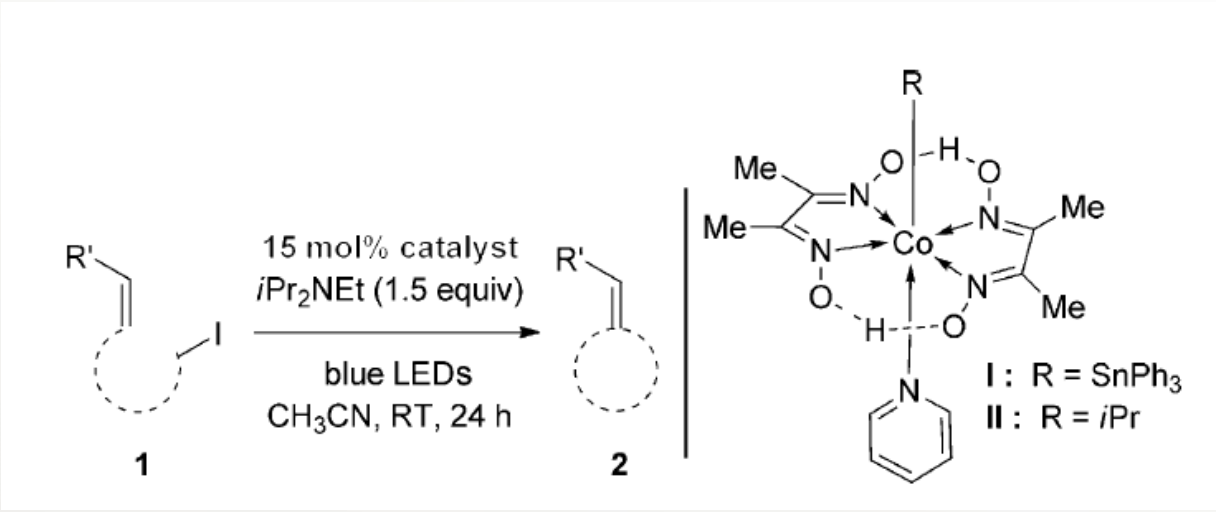

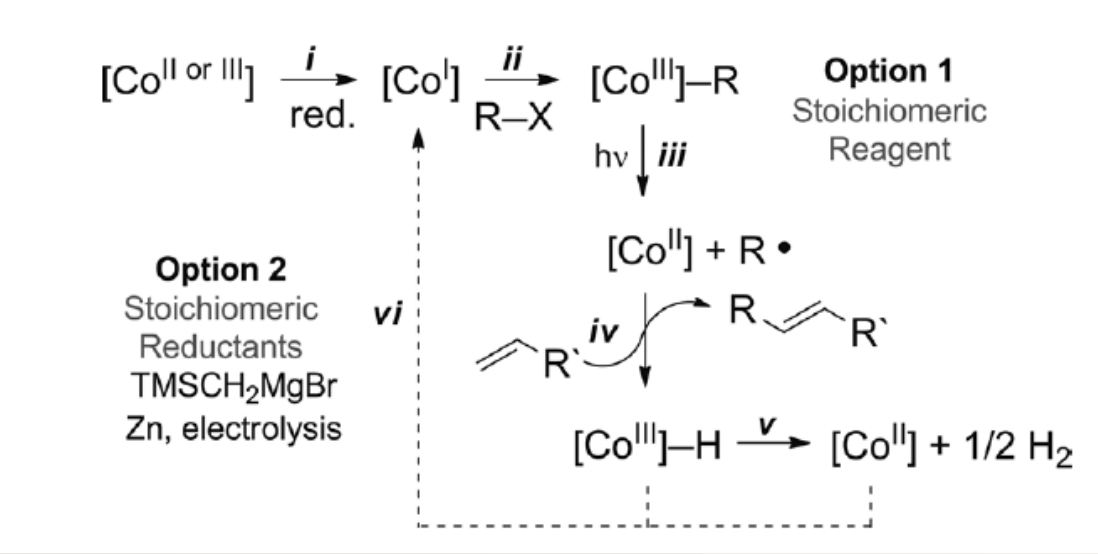

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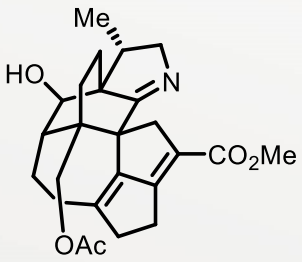
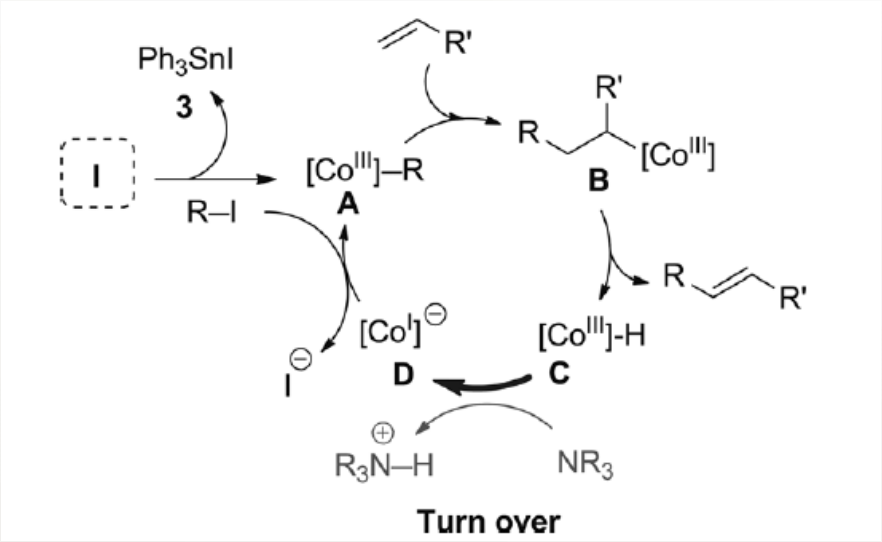
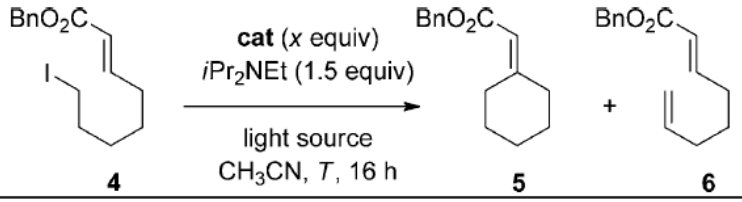
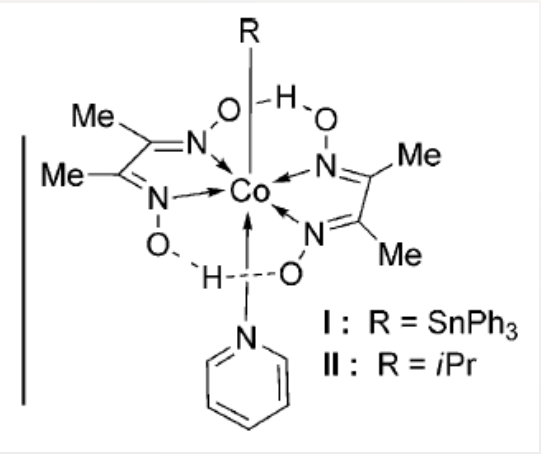






Entry	Cat. (equiv)	Light source	Conversion [%] (5/6)[a]
1	I (0.2)	sunlamp[b]	95 (5:1)
2	I (0.1)	sunlamp[b]	48 (5:1)
3	none	sunlamp	0
4	I (0.1)	no light[c]	<5
5	I (0.1)	blue LEDs	>95 (5:1)
6[d]	I (0.1)	blue LEDs	10
7	II (0.1)	blue LEDs	>95 (1.3:1)



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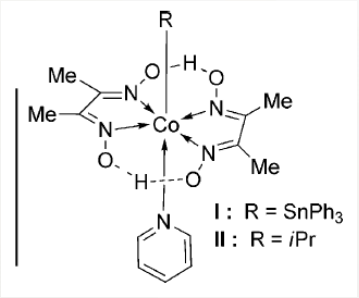
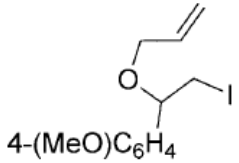
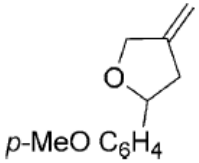
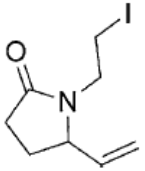
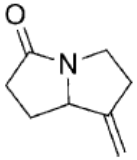
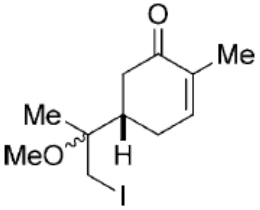
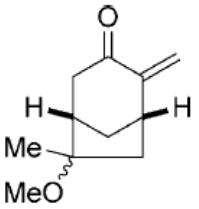
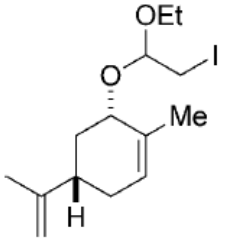
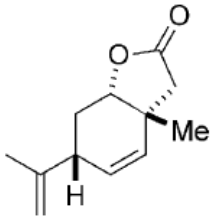
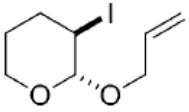
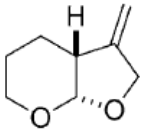
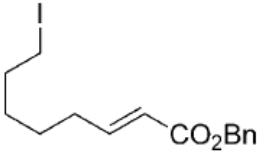
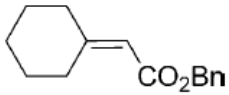
M.E. Weiss, E.M. Carreira, *Angew. Chem. Int. Ed.* **2011**, 50, 11125



1			I: 86 II: 91
2			I: 91 II: 85
3			I: 83 II: 47[a]
4[f]			I: 83[b] II: 50[a]
5[f]			I: 82 II: < 5[a]
6			I: 76[c] II: 52[c]

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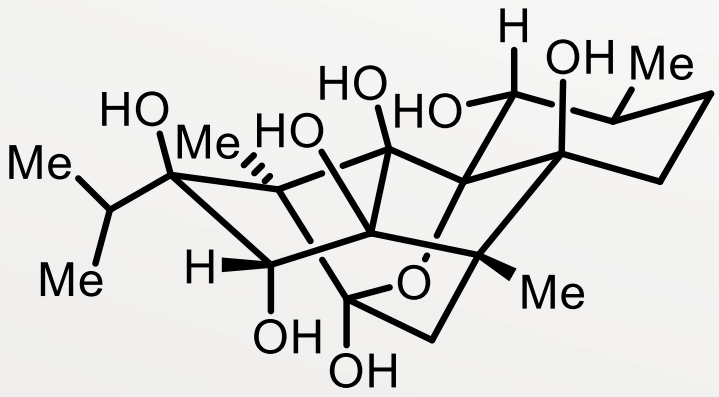
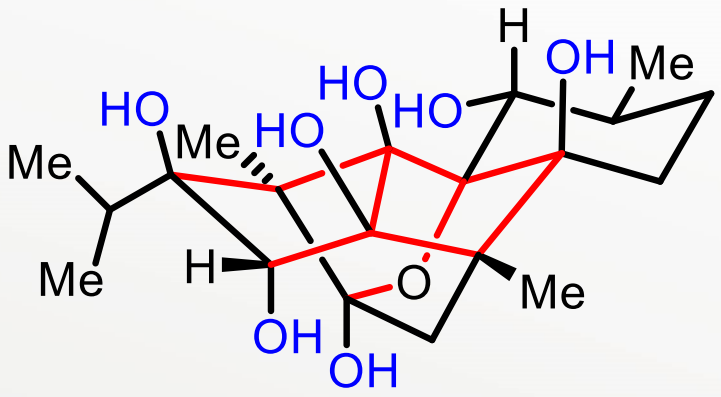
M.E. Weiss, E.M. Carreira, *Angew. Chem. Int. Ed.* **2011**, 50, 11125





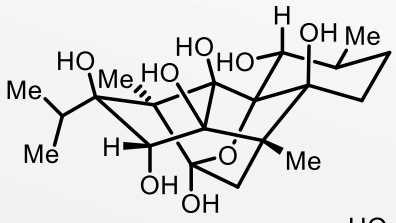
Ryanodol,

8 continuous tetra-substituted carbon,
7 free –OH group in C20, diterpene
5,5,5,6,6 penta-cyclic core

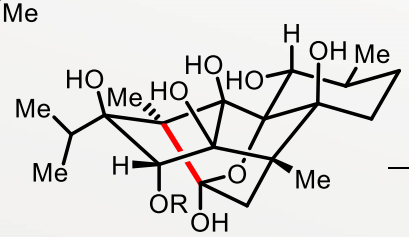
a high-conductance, an intracellular calcium channel
known as the ryanodine receptor

Pierre Deslongchamps *Can. J. Chem.* **1979**, *57*, 3348.

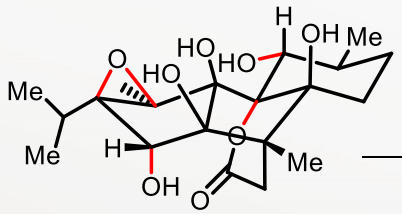
I. Nagatomo, M.; Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M.
J. Am. Chem. Soc. **2014**, 136, 5916.



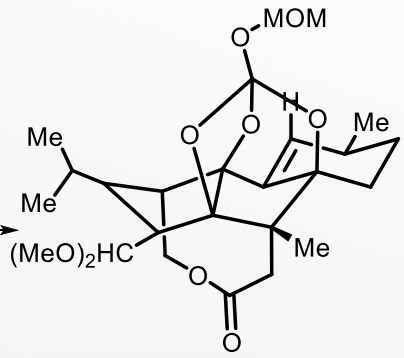
Directly control Ca channel



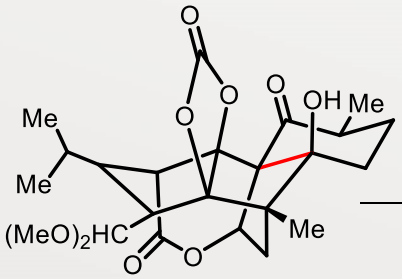
1,2 additon initiated by
Disolving metal reduction



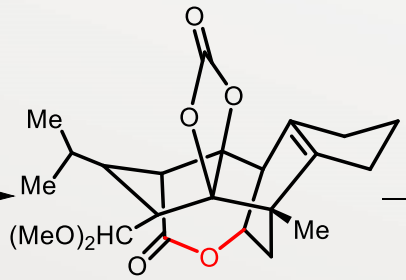
epoxidation and
Arrange the oxidation state



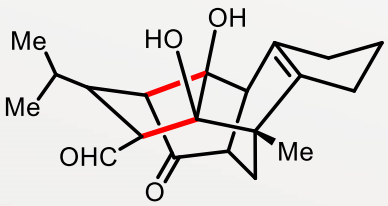
Arrange the oxidation state
C-C bond cleavage



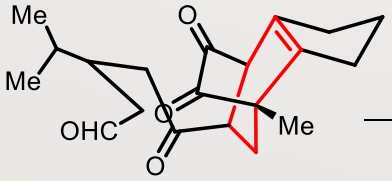
Transannular aldol reaction



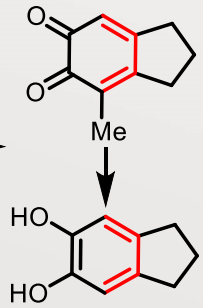
baeyer villiger oxidation

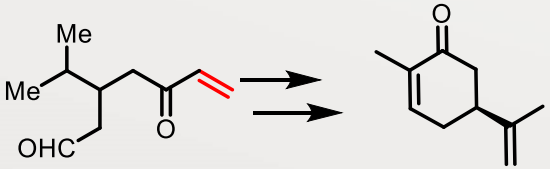


Aldol reaction

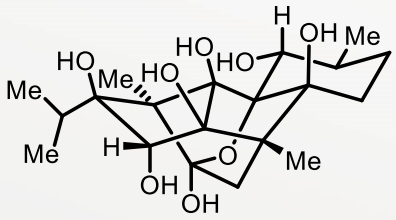


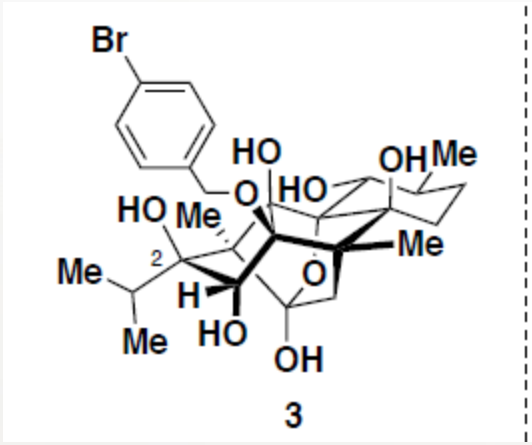
Diels-Alder Reaction

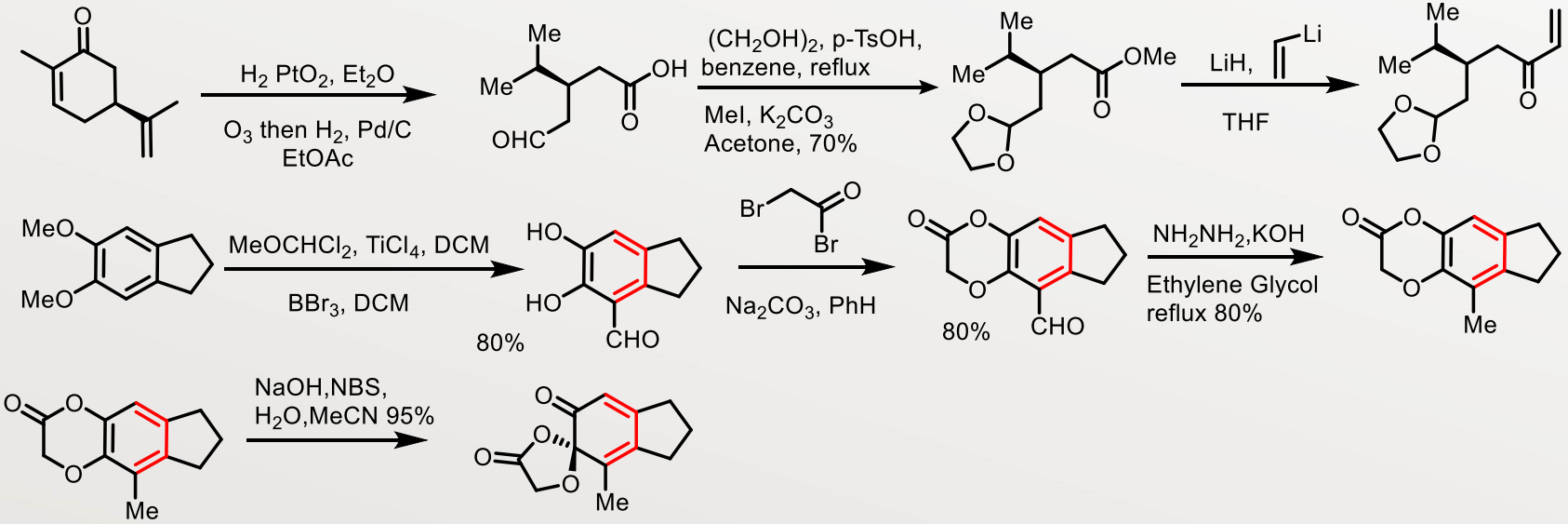




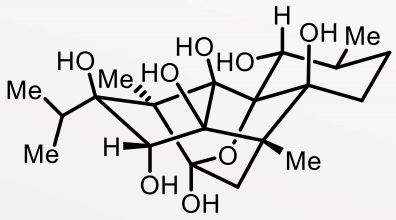
•*Can. J. Chem.* **1979**, *57*, 3348.

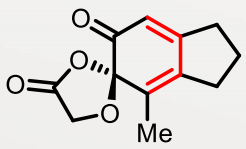


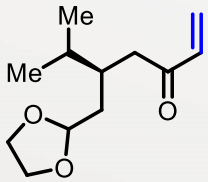




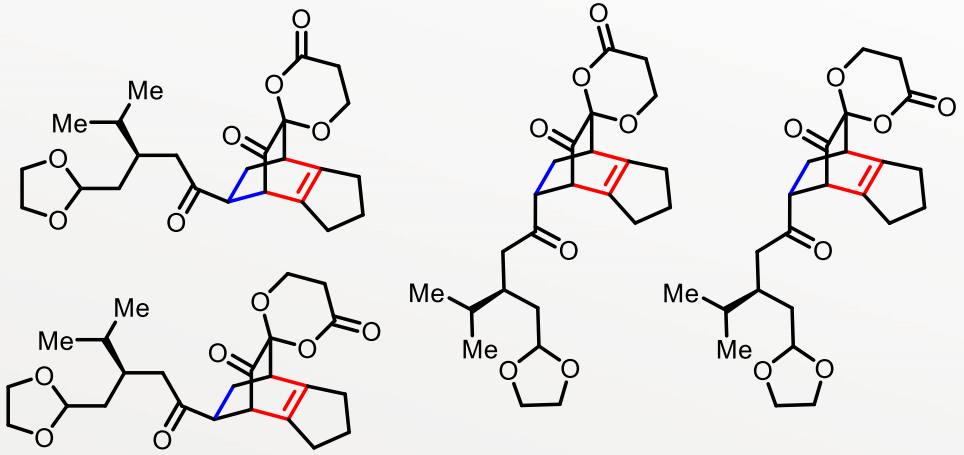
•*Can. J. Chem.* **1979**, *57*, 3348.





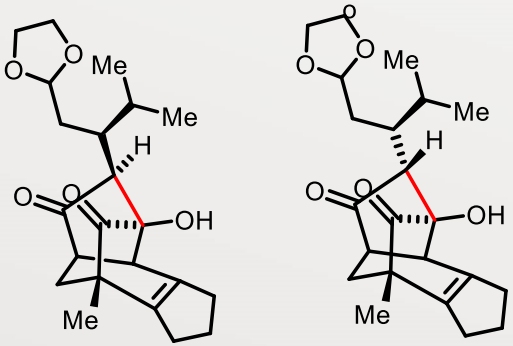


PhH, reflux



end 1 : 1 exo

1N NaOH THF, r.t

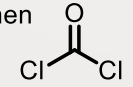


endo 3 : 1 exo

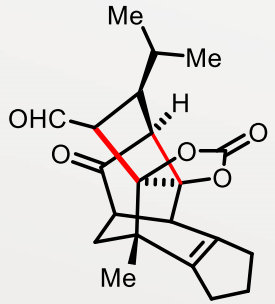
27% yield for five steps

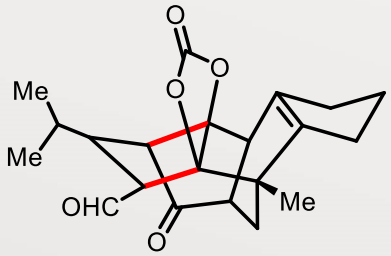
AcOH : H_2O= 7:3
75°C 2 hour

1N NaOH THF, r.t
then

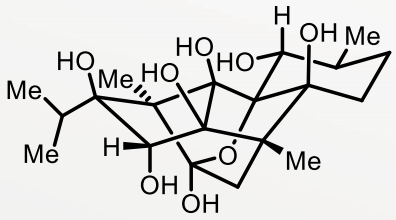


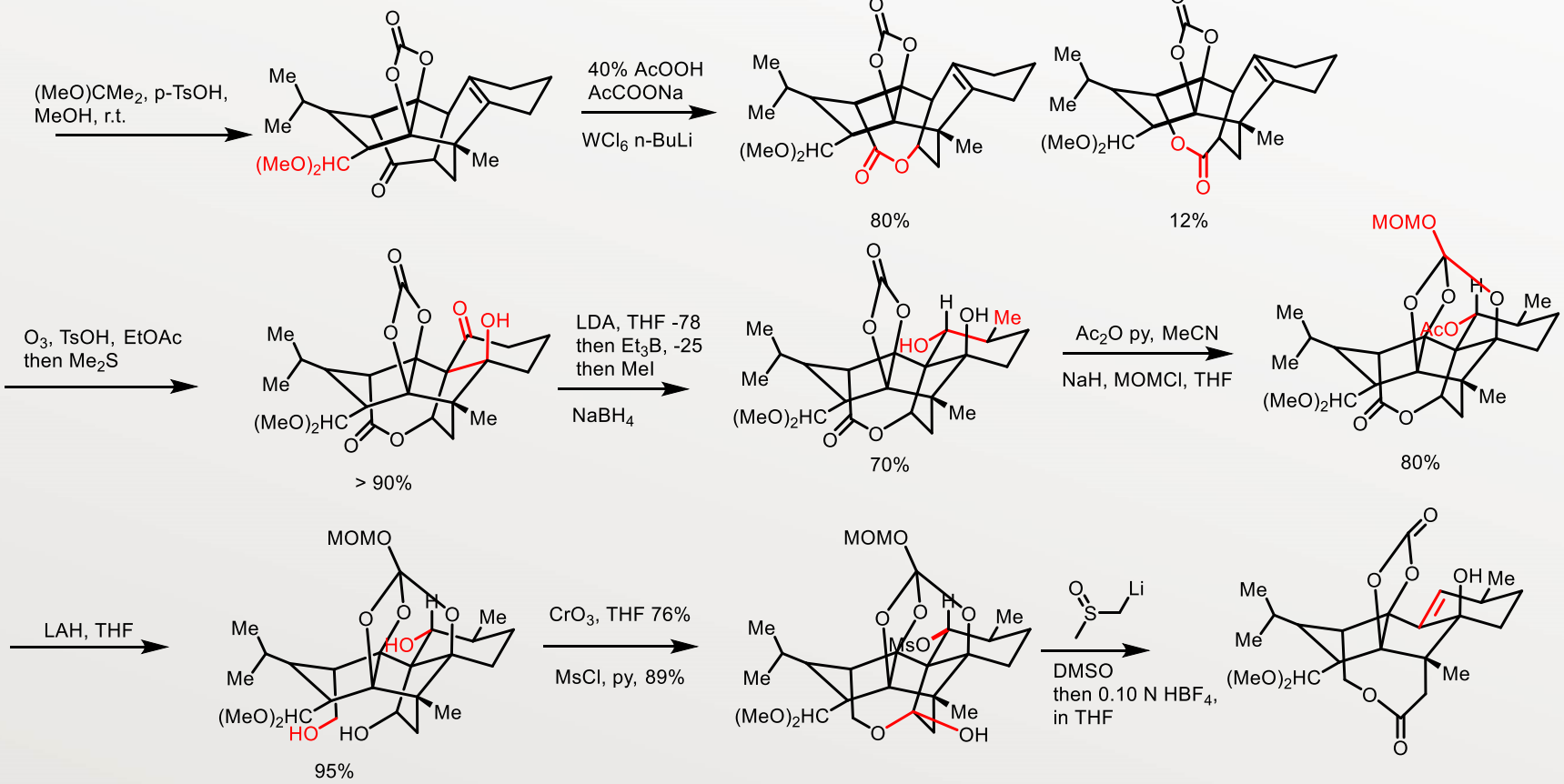
pyridine, PhH



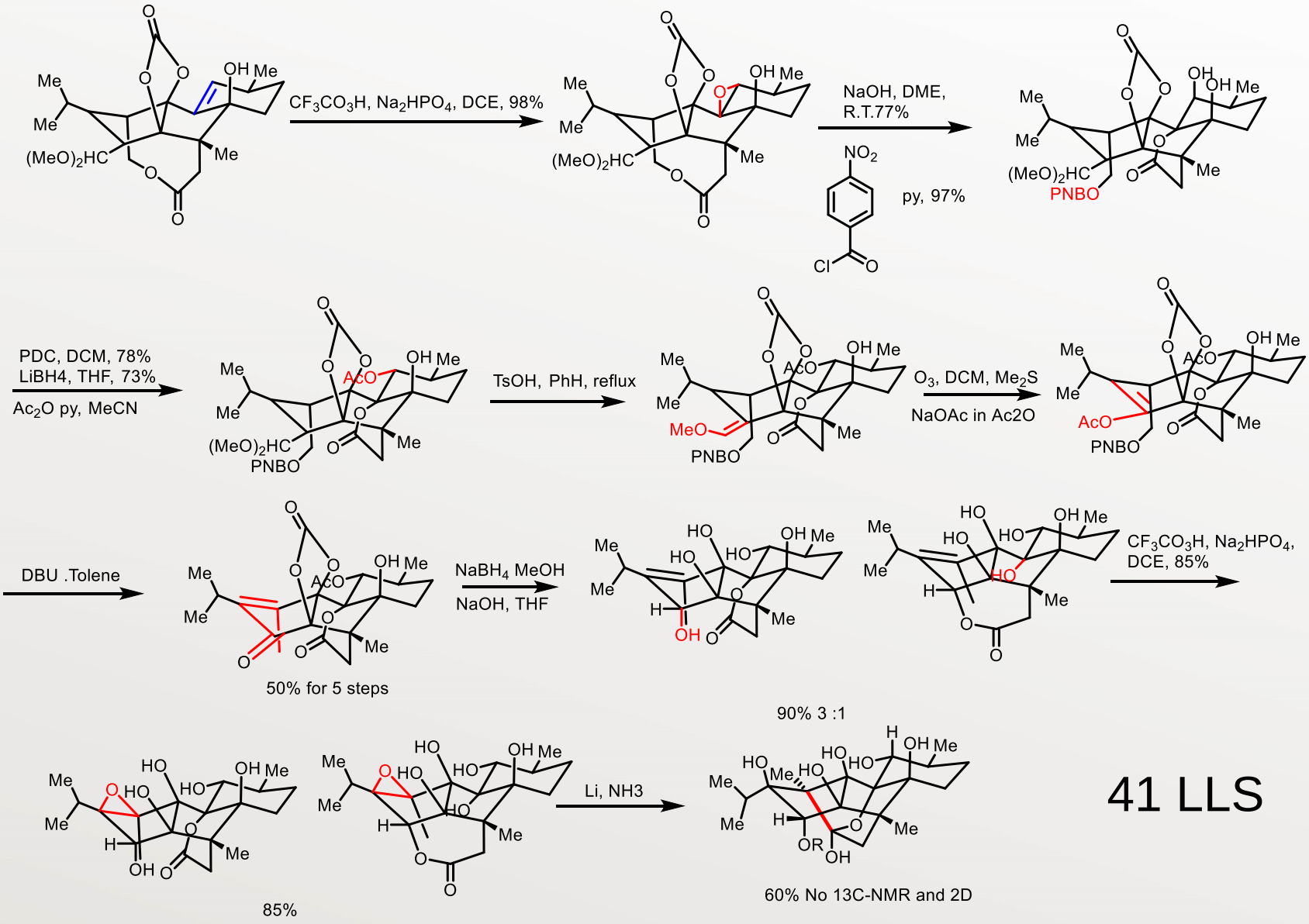


•*Can. J. Chem.* **1979**, *57*, 3348.



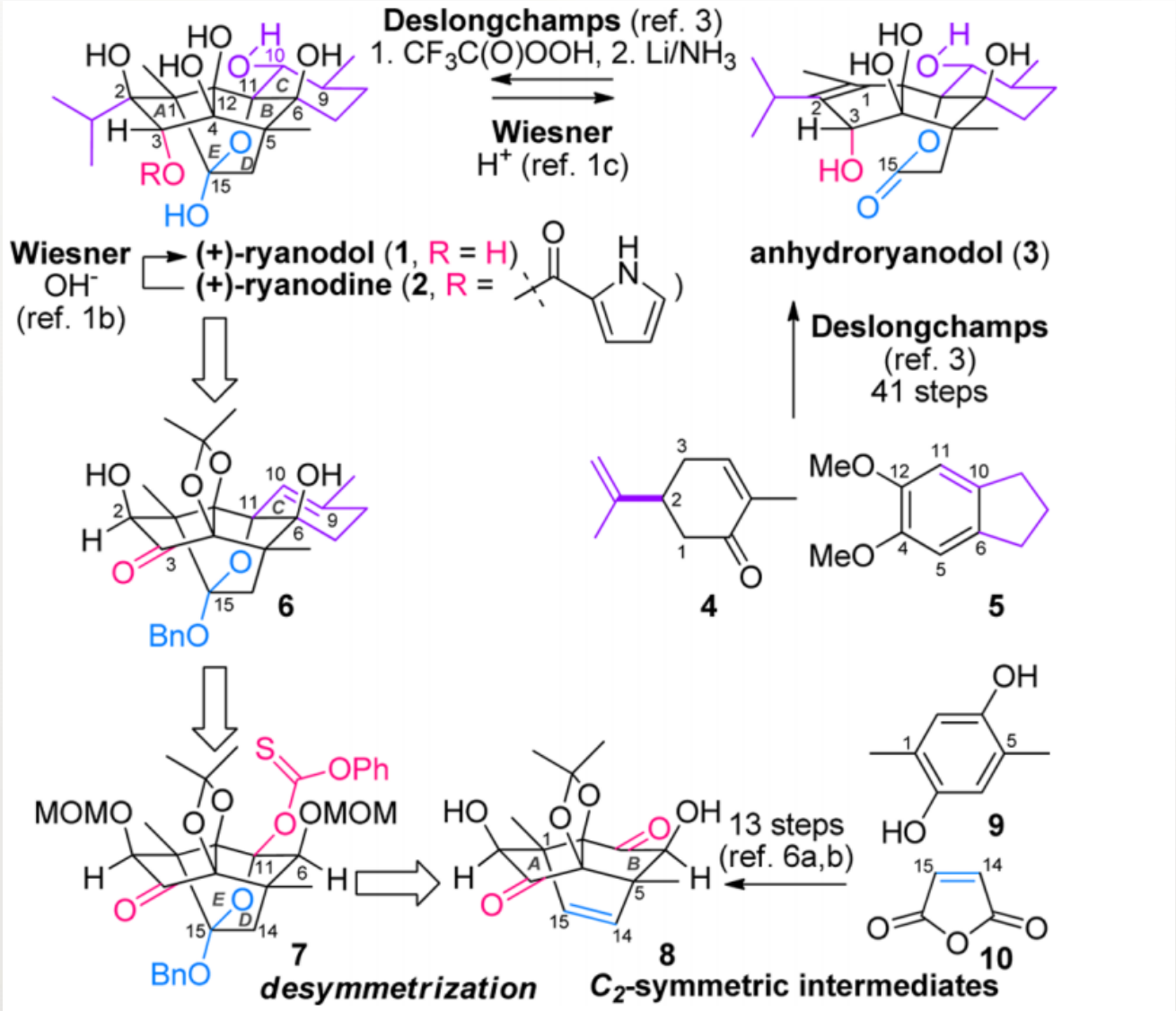


- *Can. J. Chem.* **1979**, *57*, 3348.

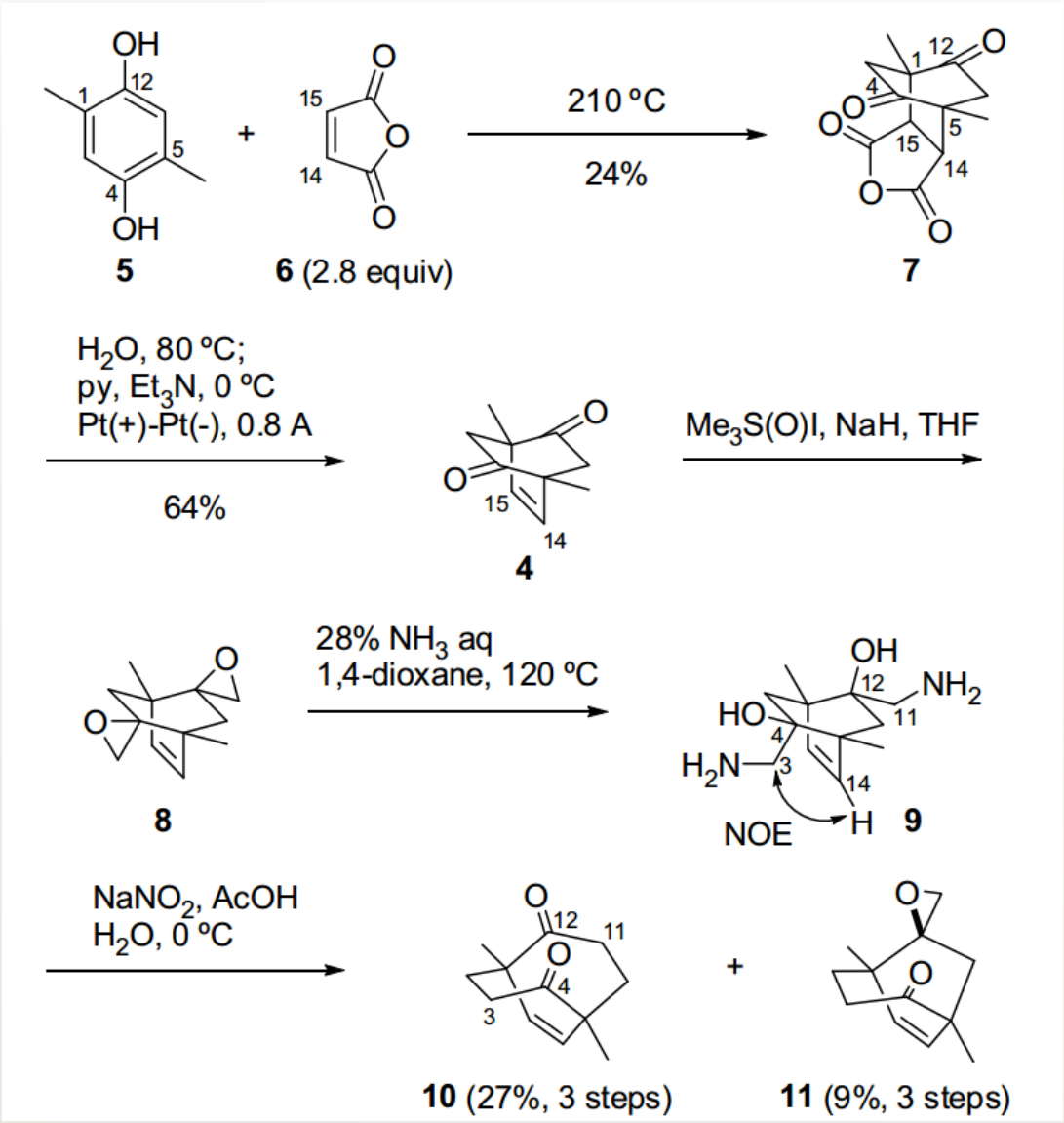


41 LLS

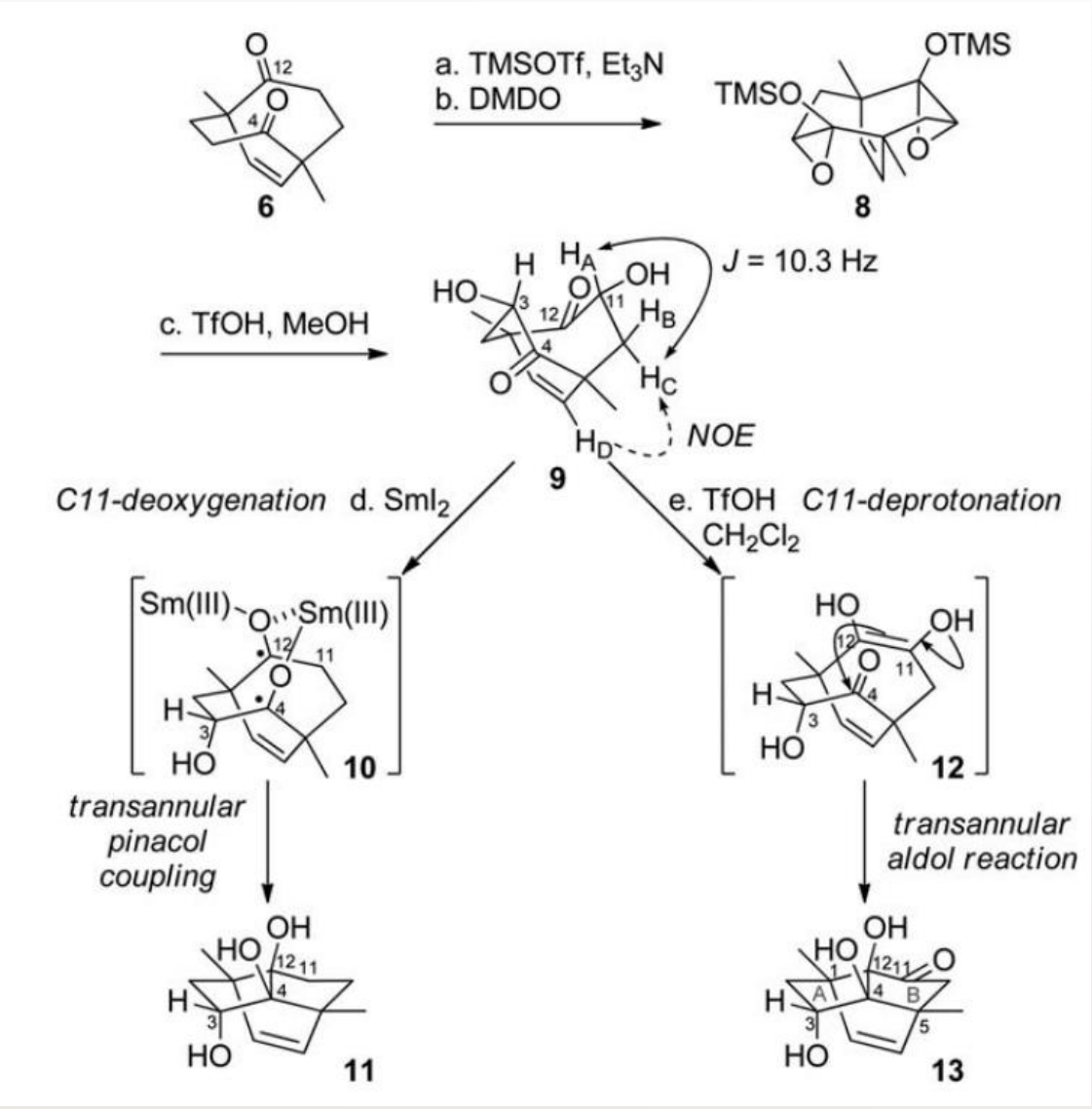
- *Can. J. Chem.* **1979**, *57*, 3348.



l. Nagatomo, M.; Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2014**, 136, 5916.



Hagiwara, K.; Himuro, M.; Hirama, M.; Inoue, M. *Tetrahedron Lett*. **2009**, 50, 1035



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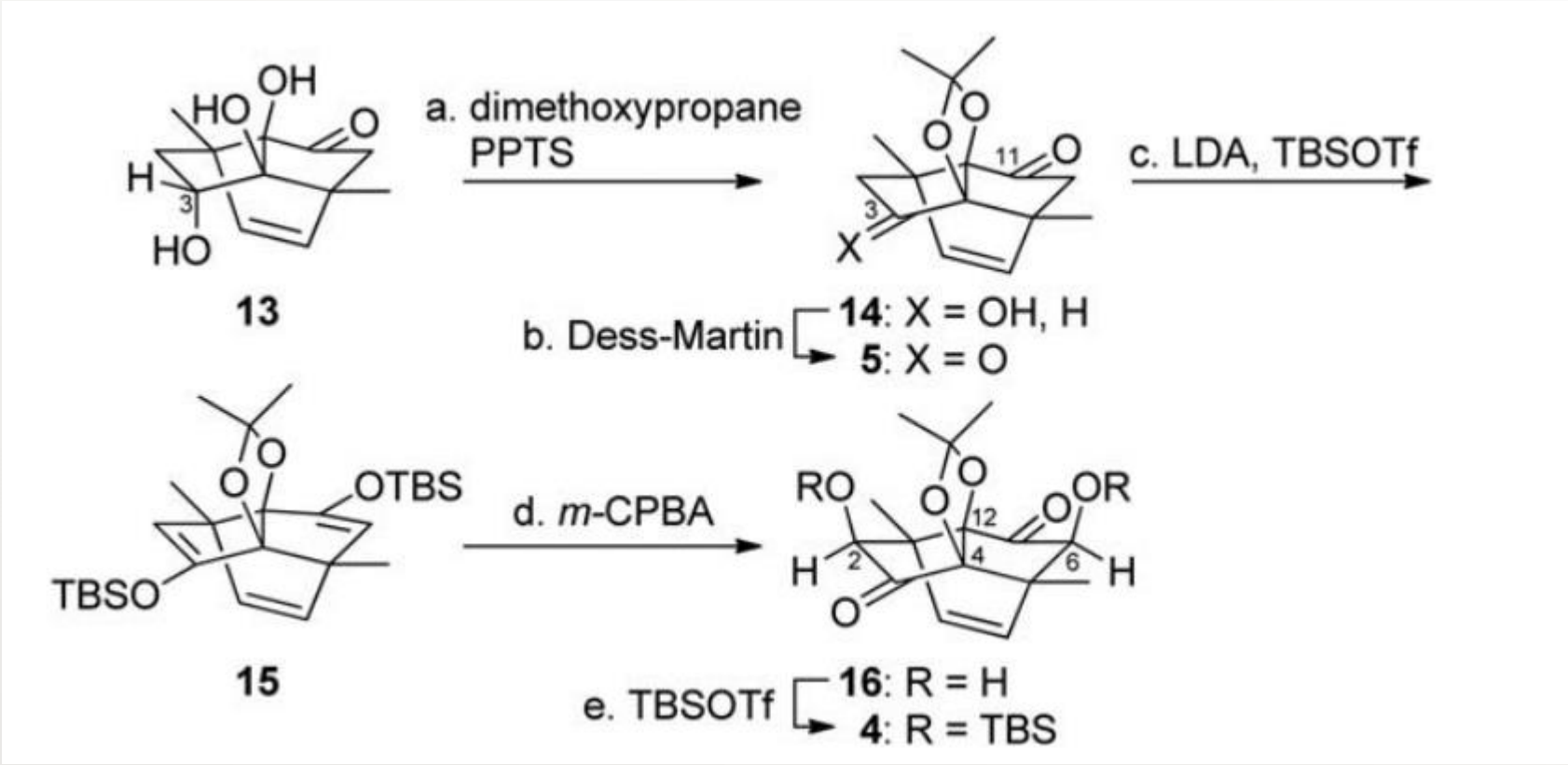

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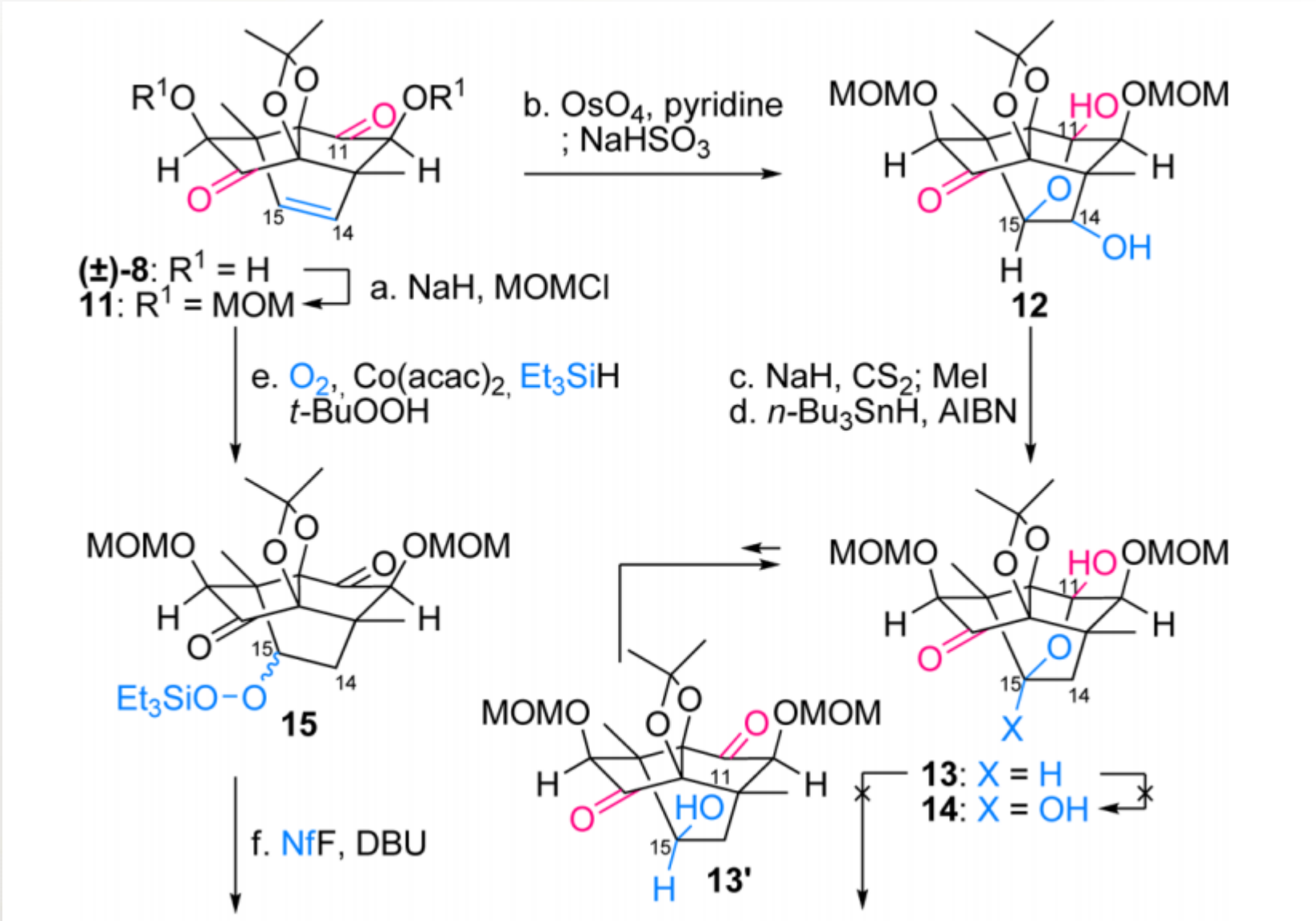
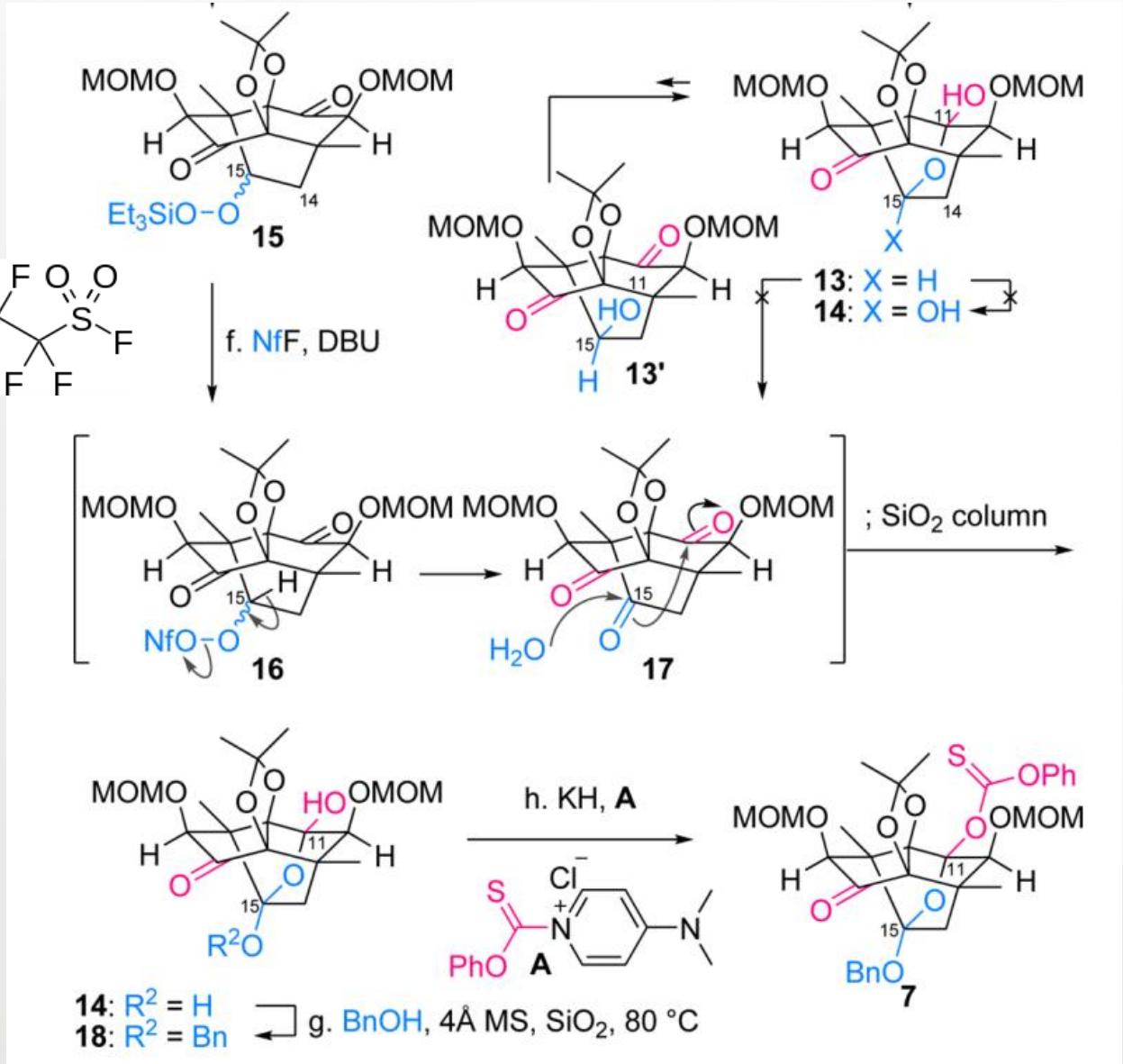
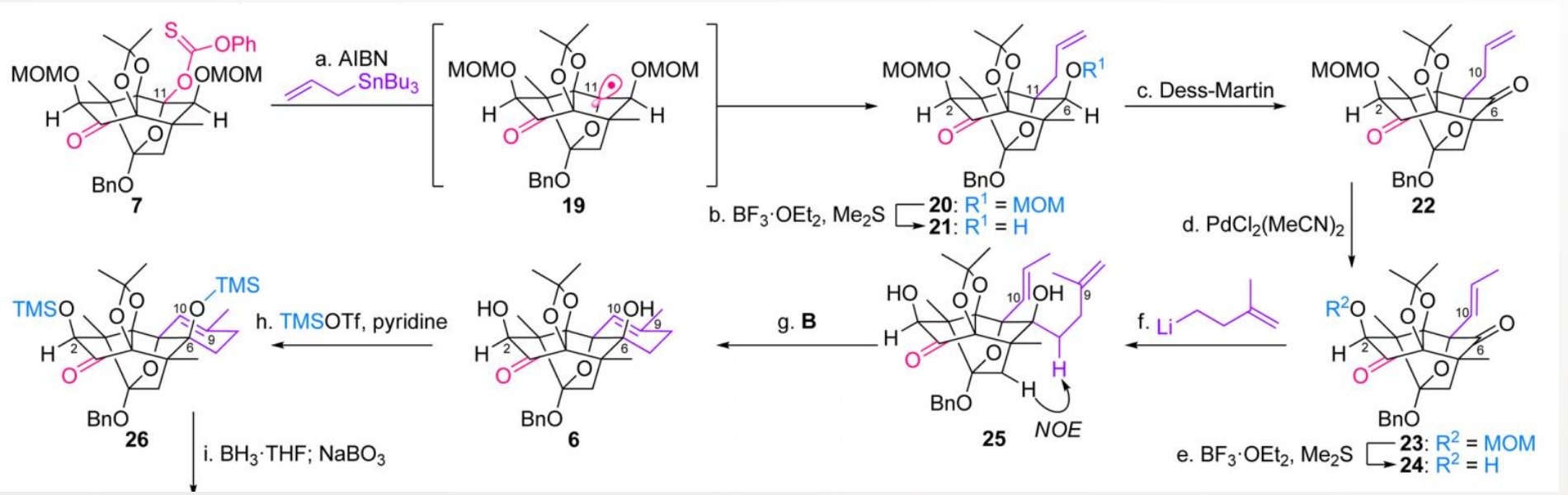
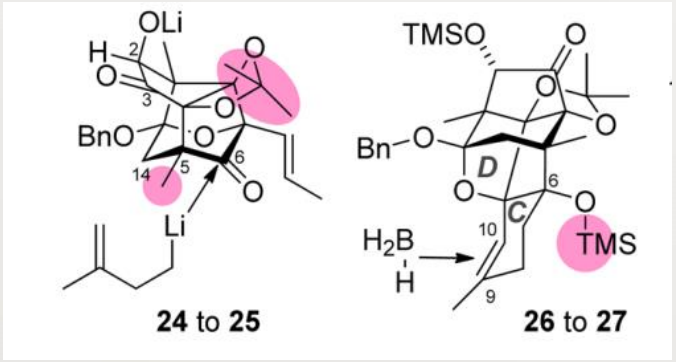


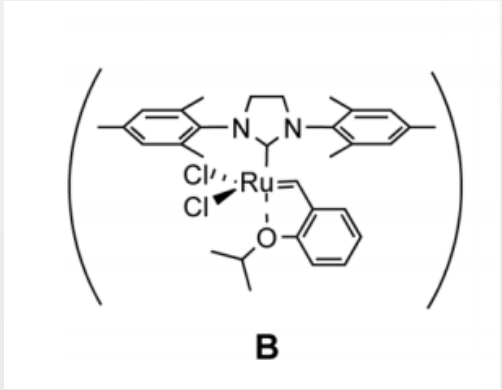
l. Nagatomo, M.; Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2014**, 136, 5916.



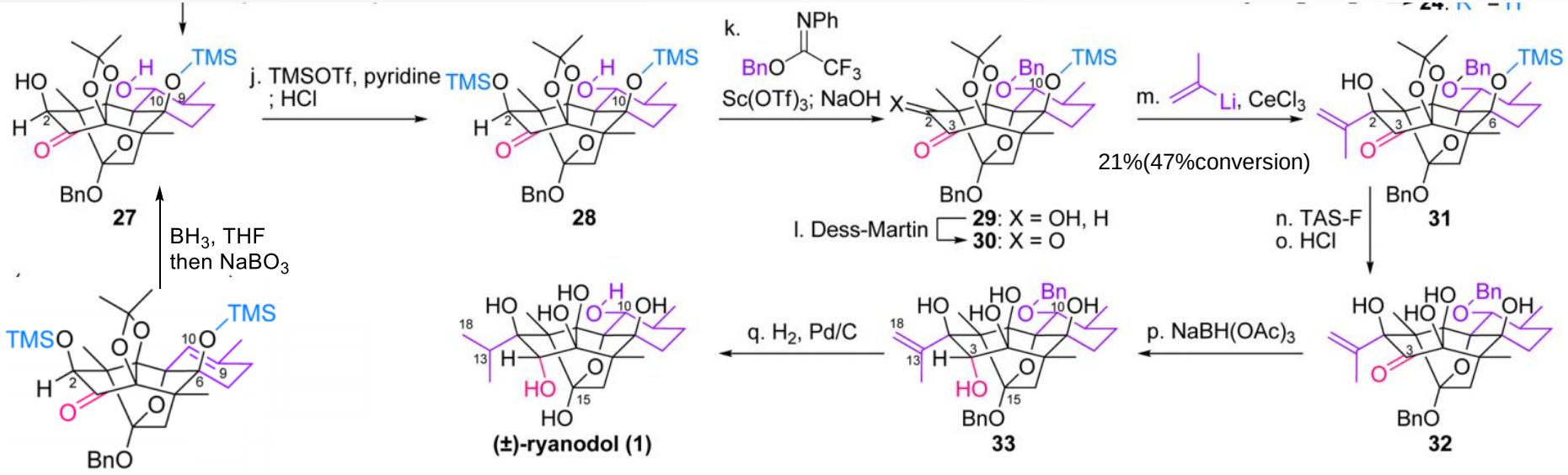
l. Nagatomo, M.; Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2014**, 136, 5916.





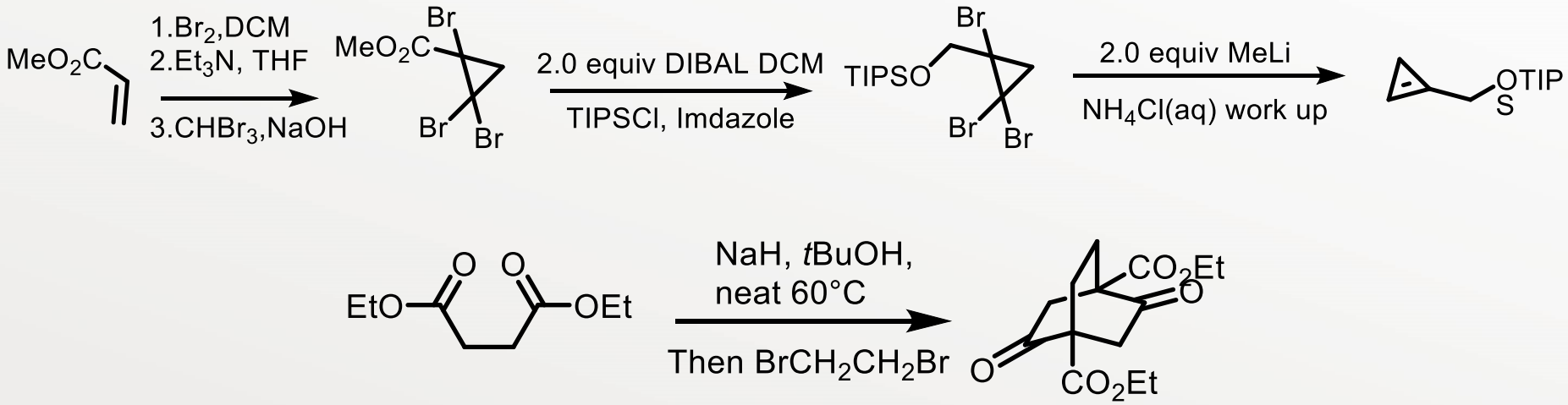


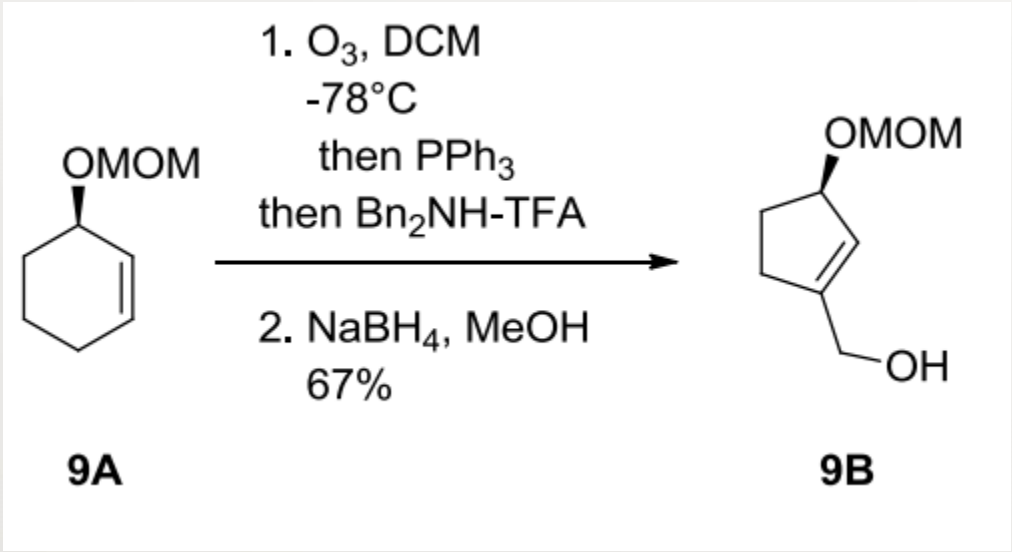
I. Nagatomo, M.; Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2014**, 136, 5916.

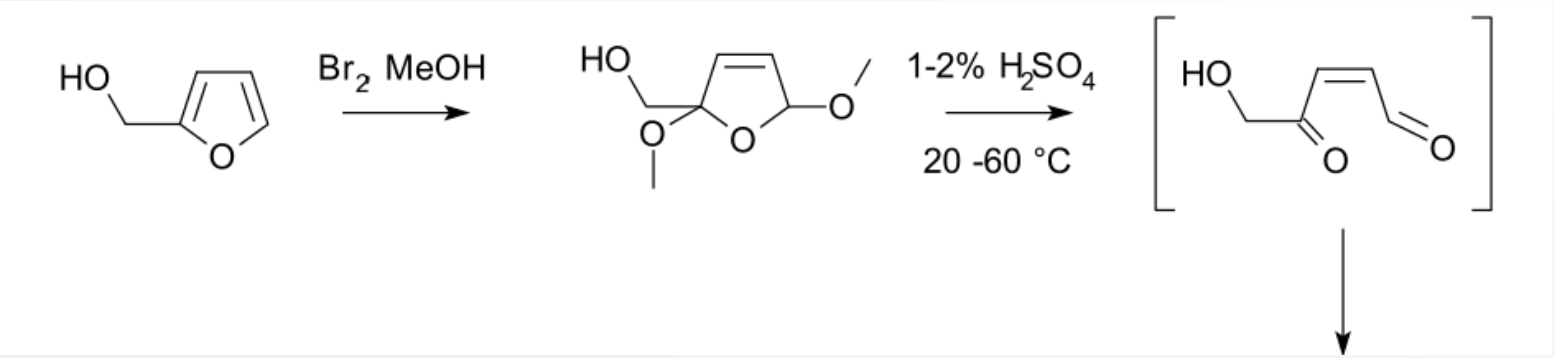


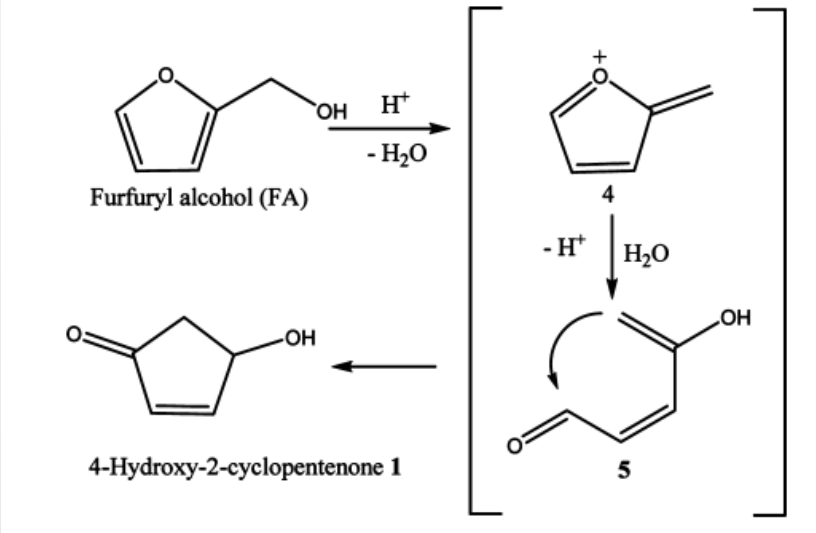
Compounds **32**, **33**, **1** and **2** have a propensity to form the corresponding borates with B_2O_3 leached from borosilicate glassware (Pyrex glass). Therefore, these reactions were carried out in quartz glass flask, and soda-lime glassware was used for the purification, and quartz glass tube was used for the NMR experiments. For a related example, see: A. Kawamura, J. Guo, Y. Itagaki, C. Bell, Y. Wang, G. T. Haupert, Jr., S. Magil, R. T. Gallagher, N. Berova and K. Nakanishi, *Proc. Natl. Acad. Sci. USA*, **1999**, ***96***, 6654.

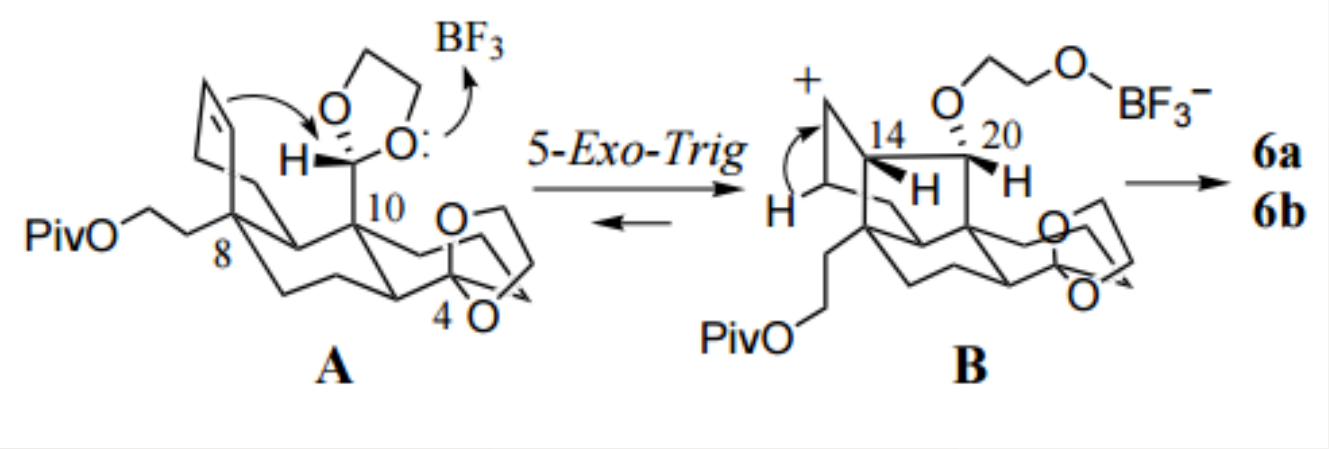
Thank you for your attention


MeO2C
1.Br2,DCM
2.Et3N, THF
3.CHBr3,NaOH
Br
MeO2C
Br
Br
2.0 equiv DIBAL DCM
TIPSCl, Imdazole
TIPSO
Br
Br
Br
2.0 equiv MeLi
NH4Cl(aq) work up
OTIP
S
EtO
O
O
OEt
NaH, tBuOH,
neat 60°C
Then BrCH2CH2Br
CO2Et
O
O
CO2Et


OMOM
1. O3, DCM
-78°C
then PPh3
then Bn2NH-TFA
2. NaBH4, MeOH
67%
OMOM
OH
9A
9B


HO
O
Br2 MeOH
HO
O
O
O
1-2% H2SO4
20 -60 °C
HO
O
O


O
OH
H+
- H2O
Furfuryl alcohol (FA)
+
O
4
- H+
H2O
OH
O
O
OH
4-Hydroxy-2-cyclopentenone 1
5



$$\mathrm{ArSeCN + Bu_3P \rightarrow ArSe\overset{+}{P}Bu_3\ CN^-} \qquad (6)$$

$$\mathrm{ArSe\overset{+}{P}Bu_3\ CN^- + RCH_2OH \rightarrow RCH_2O\overset{+}{P}Bu_3 + HCN + ArSe^-} \qquad (7)$$

$$\mathrm{RCH_2O\overset{+}{P}Bu_3 + ArSe^- \rightarrow RCH_2SeAr + Bu_3P{=}O} \qquad (8)$$