Tamiflu

: still needs

total synthesis?

Group Meeting
Literature Talk
12-19-2013
Hee Nam Lim
Prof. Guangbin Dong Group

http://commons.wikimedia.org/wiki/File:Tamiflu_75mg_german_closeup.jpg

In 1918 Influenza in Spain (H1N1) pandemic
Infected 500 million people
killed 50-100 million people

In 1957 and 1968 Asian flu (H2N2)
Killed about 70,000 people

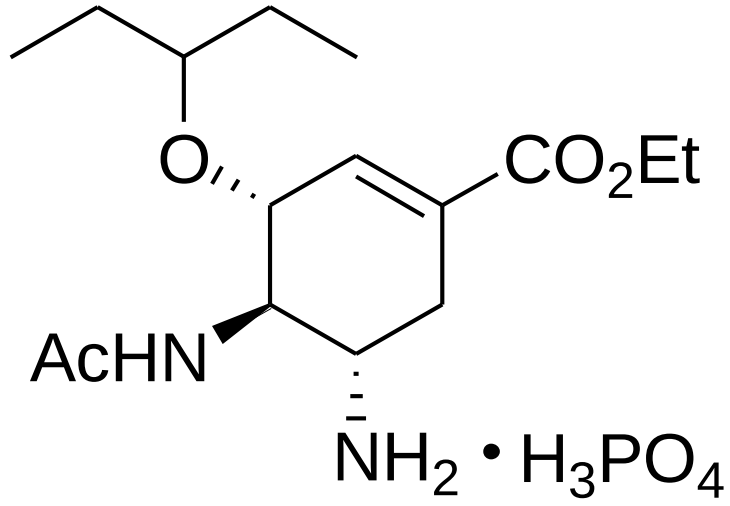
In 1997, Hongkong Avian flu (H5N1)
Infected over 100 people, half died.

Kills 20,000 – 40,000 Americans
US Healthcare - $12 billion dollors

New viruses are being reported (e.g. H7N9, Swine influenza…)

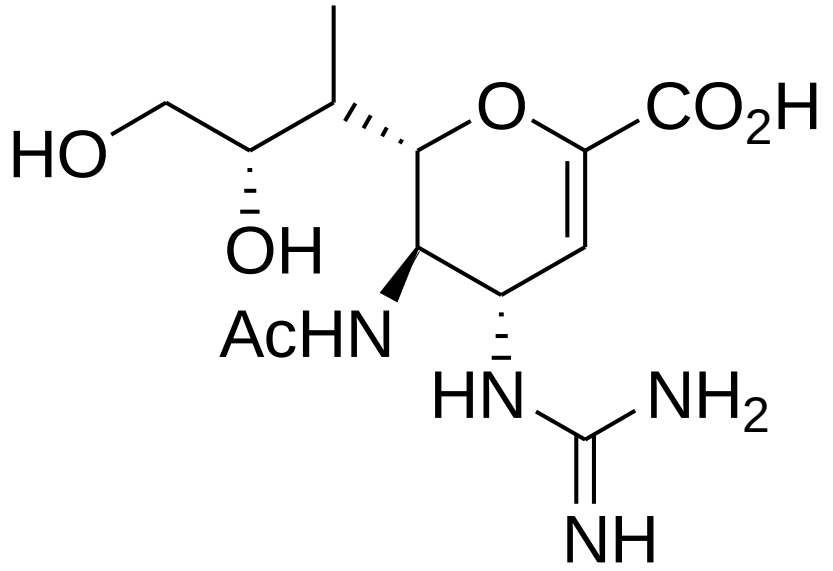
http://www.flu.gov/pandemic/history/

http://kansasheart.com/2012/09/tis-the-seasonits-time-for-your-flu-shot/



Oseltamivir (Tamiflu™)
- Treatment for Influenza A and B virus
- Neuroaminidase Inhibitor: reduce symptoms and prevents the spread and infection to other cells.
- Effective to H5N1 (AI) and H1N1 viruses

- First developed by Gilead Sciences in 1995 and commercialized by F. Hoffman-La Loche Ltd in 1999.
- The patent will be expired in 2016.



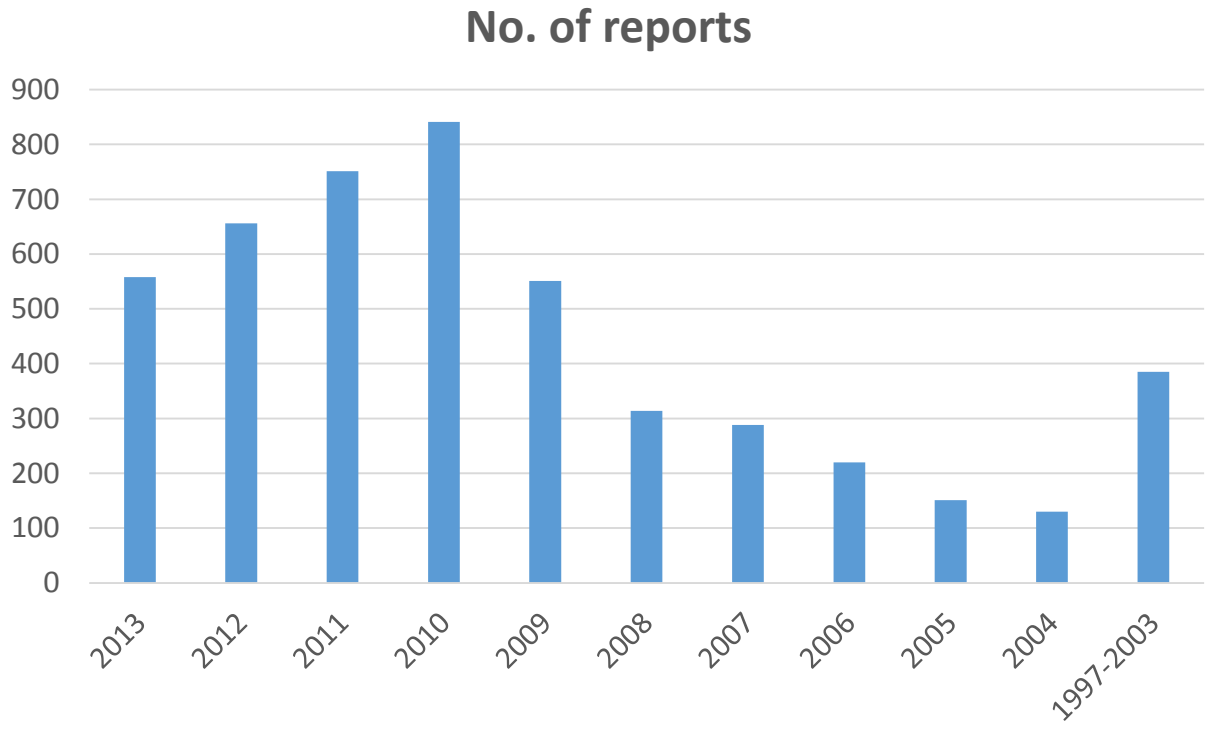
Zanamivir (Relenza™)

Limitation:
Must be administered by inhalation

Javier Magano *Tetrahedron* **2011**, *67*, 7875-7889.

Stats. for Tamiflu Research

"Oseltamivir" - **4850** hit in SCI Finder



About 60 research papers related to the synthesis of Oseltamivir have been published. (total synthesis, modification, formal synthesis)

Pros and Cons

What's good?

- Proactive drug, water soluble -> orally available
- Still best drug in the treatment of influenza viruses
- Mildness -> allow administration to infants <1 year

What are issues?

- Side effects (nausea, vomiting, diarrhea, abdominal pain, and headache, etc..)
- Production shortage - limited source of starting material

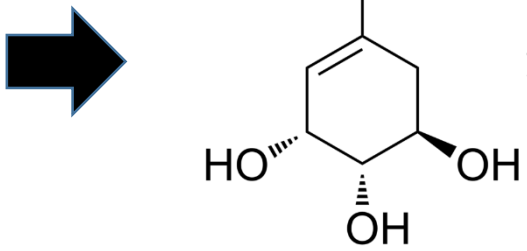
(dose – twice a day/ 75 mg, every year, 400 million packs are produced)

- Mutants resistant to the current drug
- No other effective alternative drugs except Zanamivir

http://en.wikipedia.org/wiki/Oseltamivir

From current industrial process

13 G
(Star Anise)



Shikimic acid

1.3 G

10 capsules of Tamiflu (75mg)

Synthesis Issue:

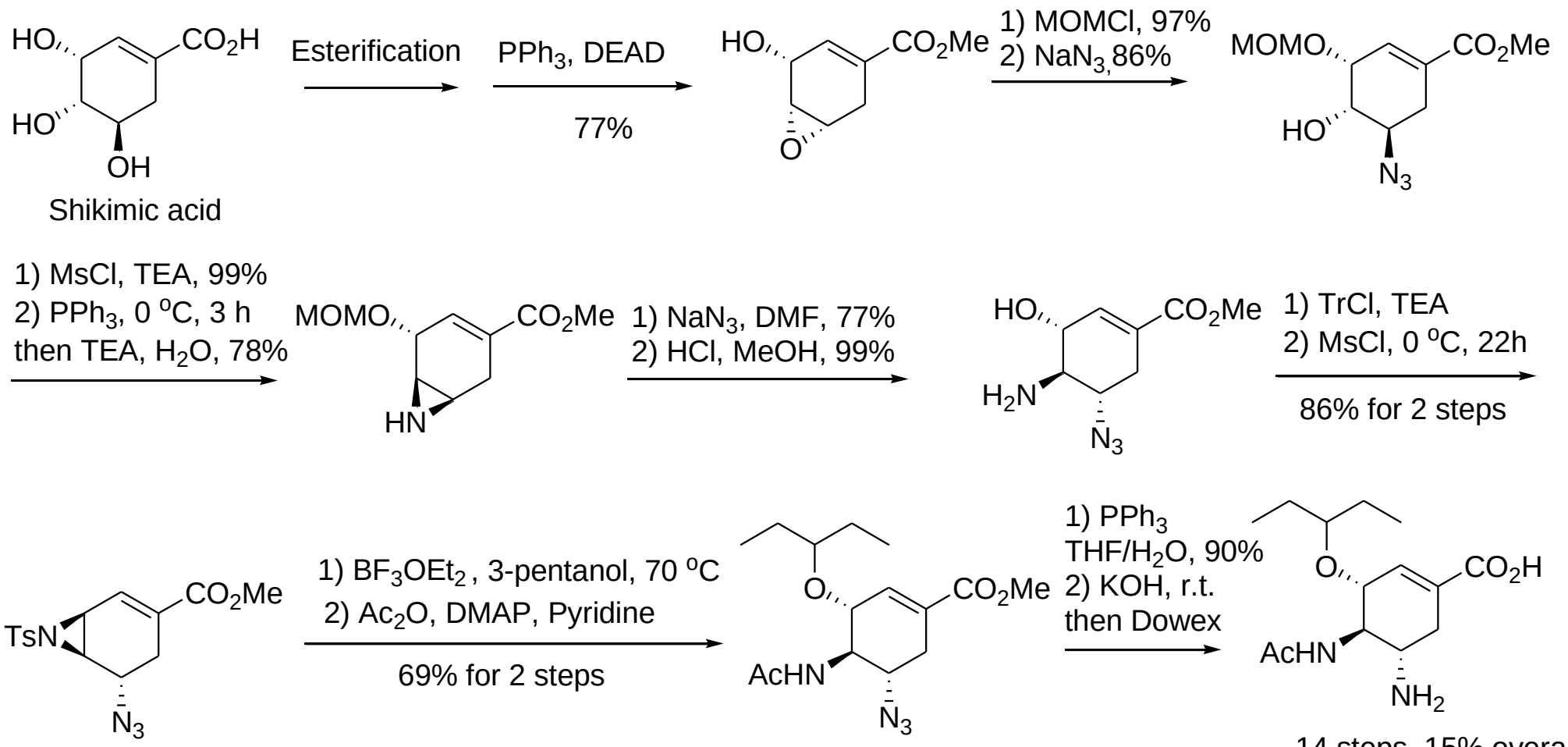
1) Streamlining synthesis

2) Greener synthesis

3) Large-Scale manufacturing - overall steps, cost, starting material availability , protecting group, halogenated solvents, hazardous and toxic reagents, chromatography, etc..

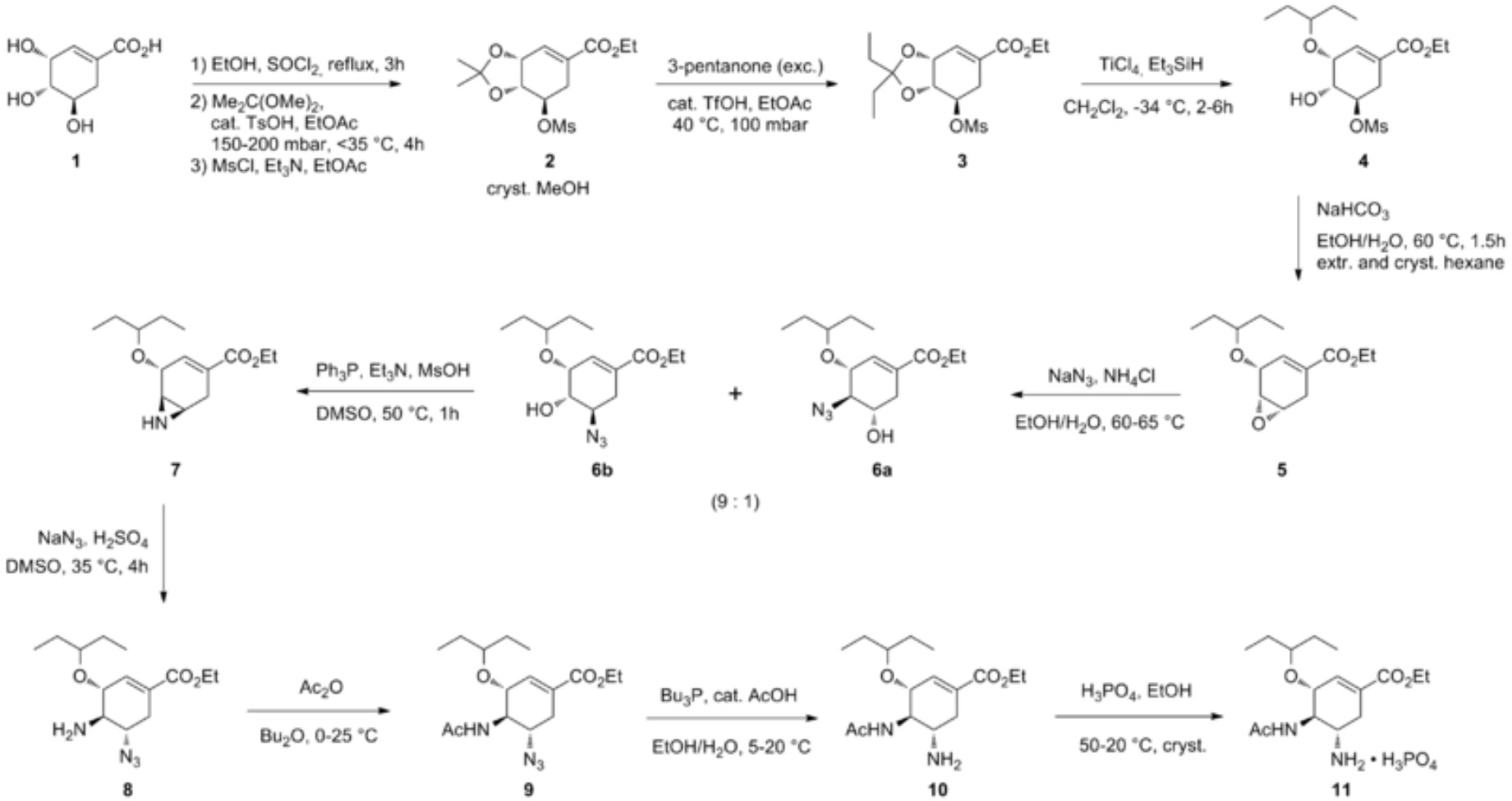
http://en.wikipedia.org/wiki/Star_anise

Gilead Science's First Total Synthesis: the use of (–)-Shikimic acid



Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc*. **1997**, *119*, 681.

F. Hoffman-La Loche's current process

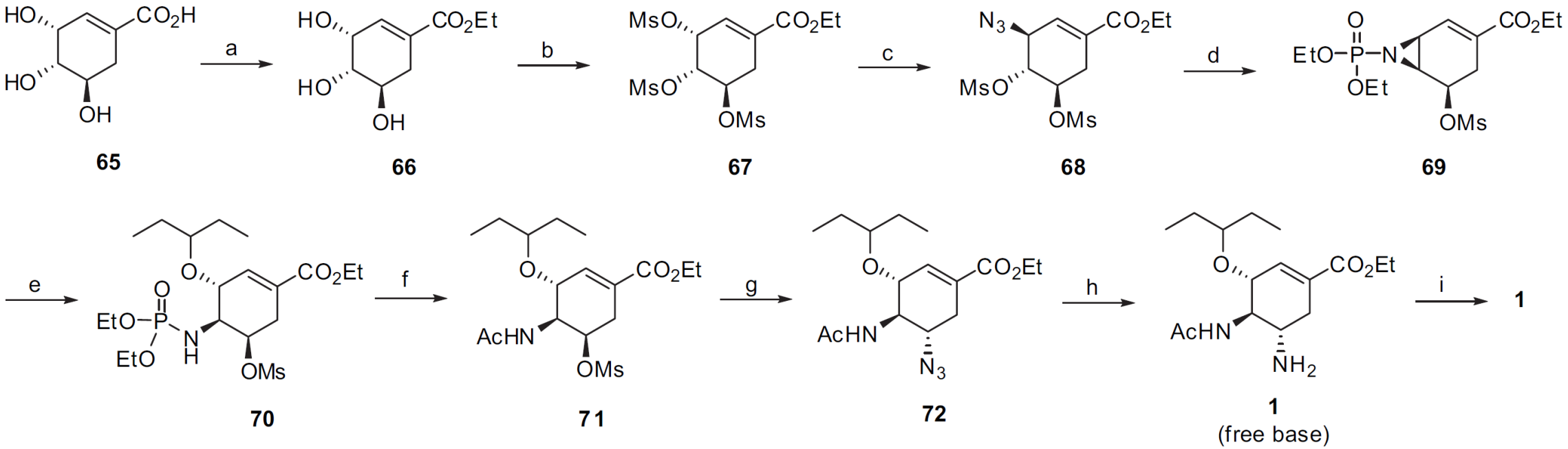


Federspiel M., Fischer R., Hennig M., Mair H.-J., Oberhauser T., Rimmler G., Albiez T., Bruhin J., Estermann H. et al. *Org. Process Res. Dev.* **1999**, *3*, 266–274.

Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia* **2004**, *58*, 621.

F. Hoffman-La Loche Ltd.: new method

8 Steps, 20% overall



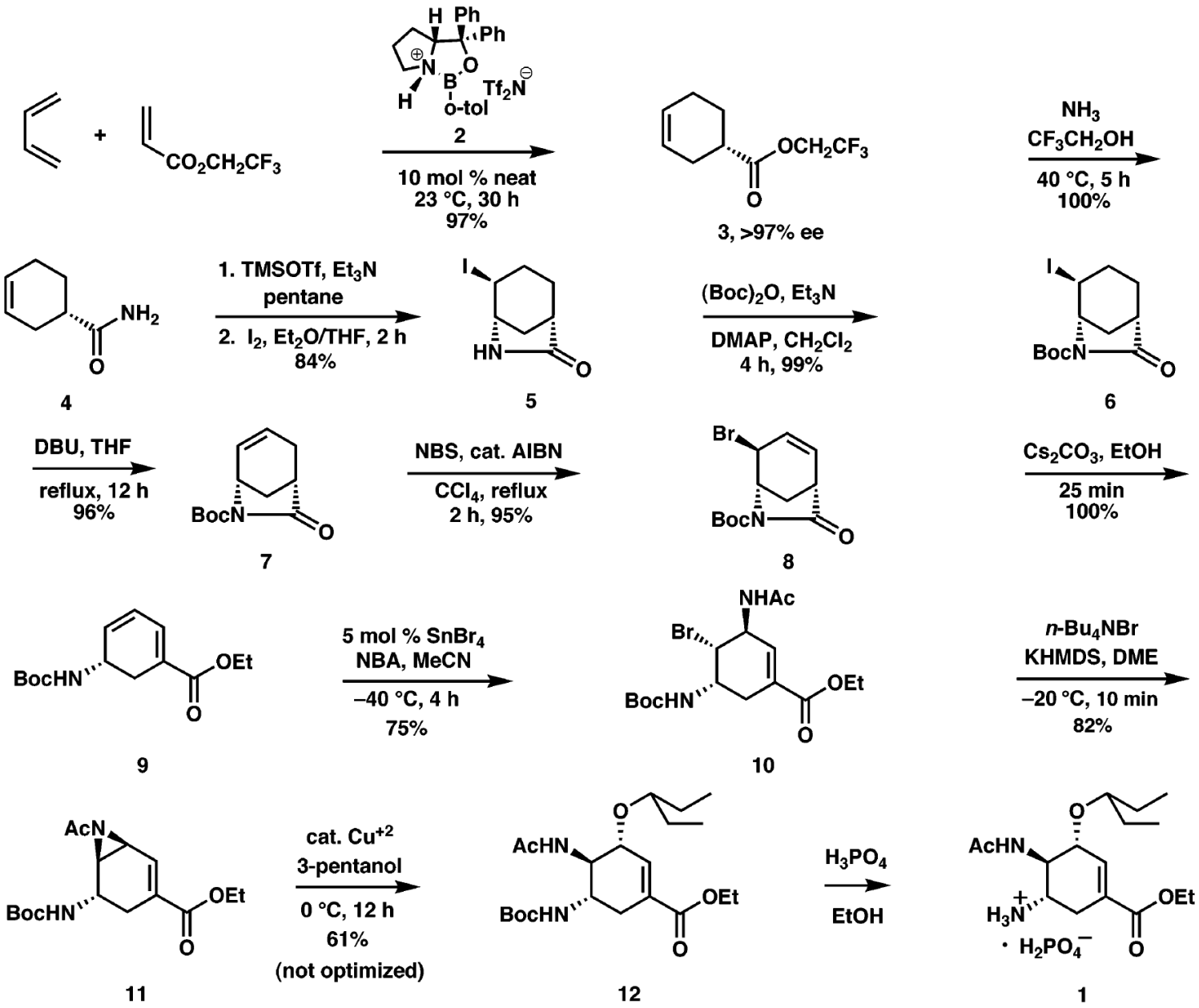
65 66 67 68 69 70 71 72 **1** (free base)

Reagents and conditions: (a) Cl_2SO, EtOH, reflux, 2 h. (b) $MeSO_2Cl$, TEA, EtOAc, 0-5 °C to rt, 20 h. (c) NaN_3, DMSO, rt, 3 h. (d) $(EtO)_3P$, PhMe, reflux, 5 h. (e) 3-Pentanol, BF_3•OEt_2, rt, 16 h, 45% from **65**. (f) (i) H_2SO_4, EtOH, reflux, 16 h; (ii) Ac_2O, EtOAc, rt, 1 h, 73% (2 steps). (g) NaN_3, DMSO, EtOH, 90 °C, 20 h, 66%. (h) *n*-Bu_3P, EtOH, rt, 5 h. (i) H_3PO_4, acetone, 92% (2 steps).

1) Two azide substitution 2) operational simplicity, inexpensive route, no protecting group

Karpf, M.; Trussardi, R. *Angew. Chem., Int. Ed*. **2009**, *48*, 5760.

Corey's Approach : Enantioselective Diels-Aler Reaction



Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc*. **2006**, *128*, 6310

Shibasaki's First Approach: Y-catalyzed asymmetric opening of aziridine

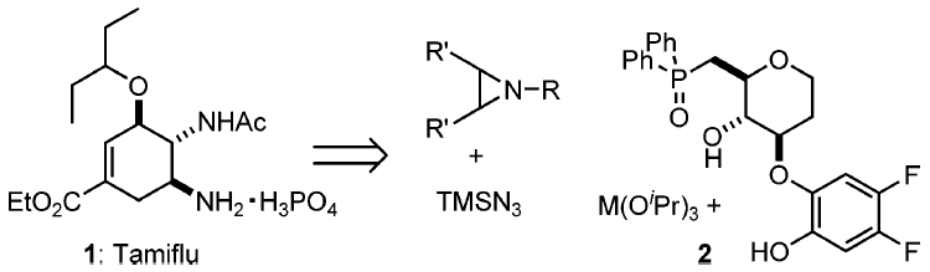
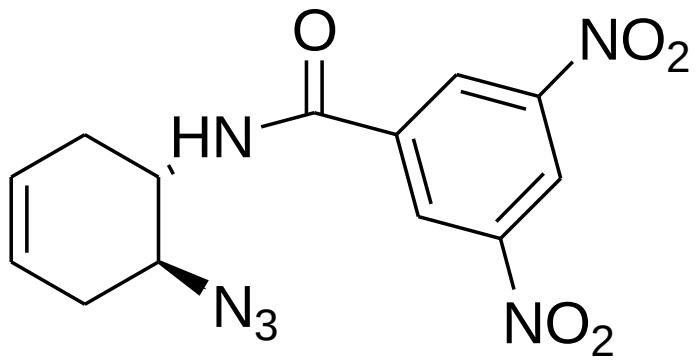


Table 1. Optimization of Reaction Conditions

3a: R = 4-nitrobenzoyl
3b: R = 3,5-dinitrobenzoyl

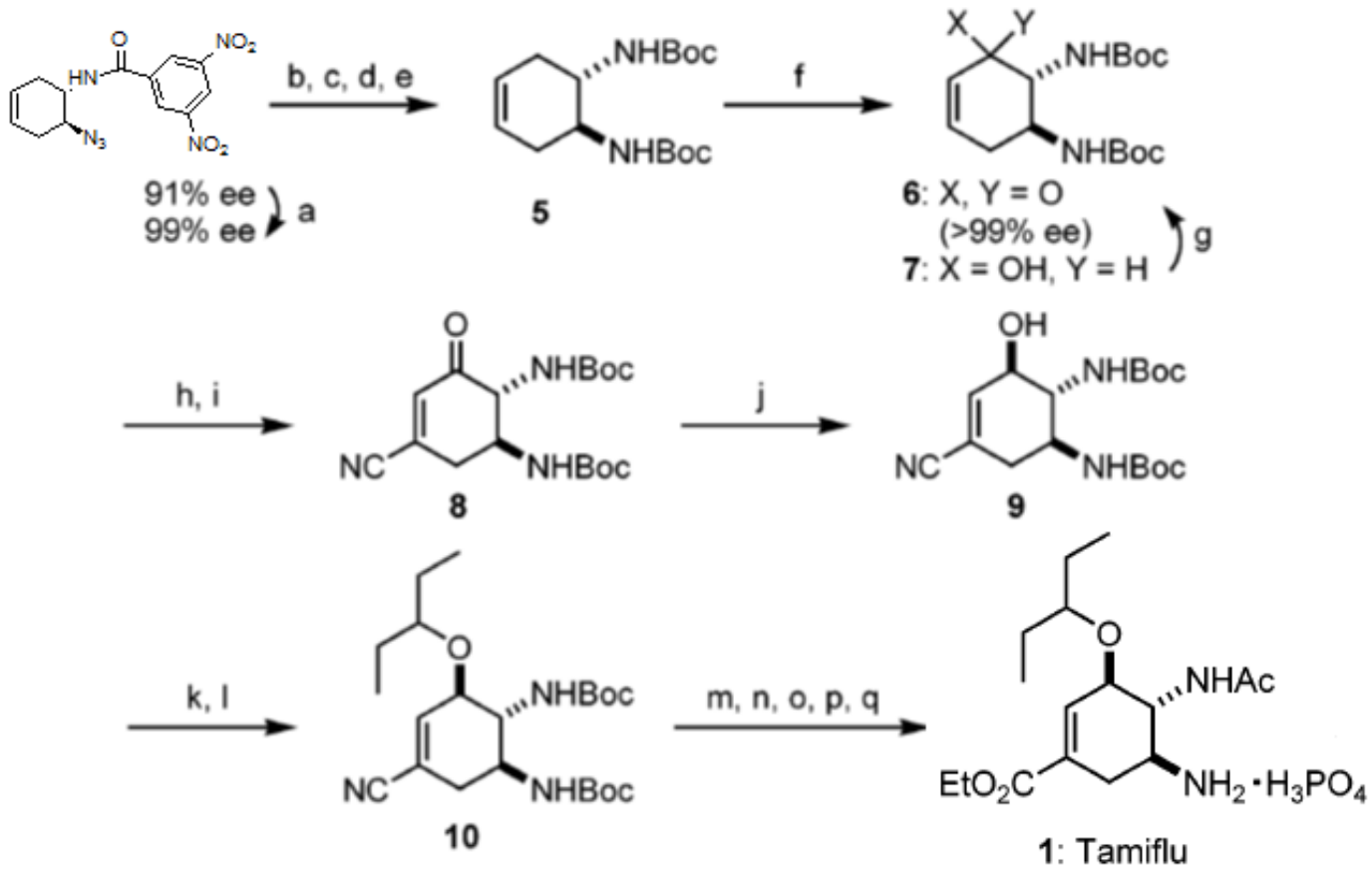
4a or **4b**

entry	M	substrate	additive[a]	time (h)	yield (%)[b]	ee (%)[c]
1	Gd	**3a**	DMP, TFA	20	>99	46
2	Gd	**3a**	DMP	20	>99	64
3	Gd	**3a**	none	20	>99	66
4	Gd	**3b**	none	16	90	85
5	Dy	**3b**	none	16	93	90
6	Er	**3b**	none	16	89	89
7	Yb	**3b**	none	16	91	82
8	Sc	**3b**	none	16	90	63
9	Y	**3b**	none	1	90	92



96 %, 91 % ee

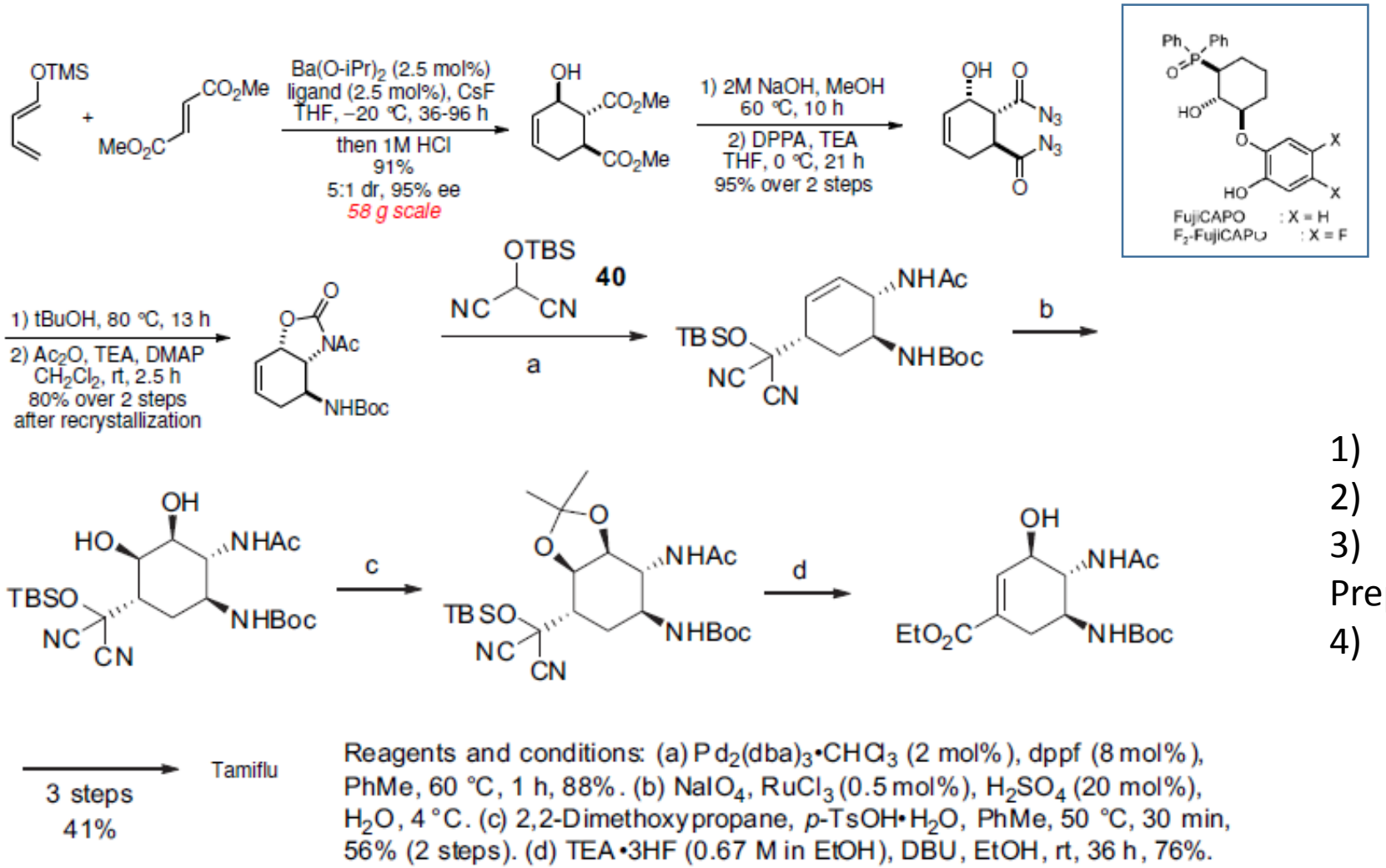
Y. Fukuta, T. Mita, N. Fukuda, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc*. **2006**, *128*, 6312.



1) Catalytic asymmetric introduction of 1,2-diamine functionality
2) Relatively long overall steps, low overall yield
3) Protection/ Deprotection
4) Mitsunobu reaction
5) Toxicity of SeO_2

[a] Reagents and conditions: (a) recrystallized from ^{i}PrOH, 72%; (b) Boc_2O (1.5 equiv), DMAP (0.5 equiv), CH_3CN, rt, 3 h; (c) 4 M NaOH, rt, 2 h, 98% (2 steps); (d) Ph_3P (1.1 equiv), CH_3CN, 50 °C, 3 h; H_2O, 40 °C, 2 h; (e) Boc_2O (2 equiv), Et_3N (5 equiv), CH_2Cl_2, rt, 2 h, 90% (2 steps); (f) SeO_2 (1 equiv), Dess−Martin periodinane (1.5 equiv), dioxane, 80 °C, 12 h; (g) Dess−Martin periodinane (1.5 equiv), CH_2Cl_2, 4 °C, 68% (2 steps); recrystallized from $^{i}Pr_2O$−hexane, >99% ee, 62%; (h) $Ni(COD)_2$ (10 mol %), COD (10 mol %), TMSCN (3 equiv), THF, 60 °C, 65 h; (i) NBS (1.05 equiv), THF, 20 min; Et_3N (14 equiv), 4 °C, 40 min; (j) $LiAlH(O^{t}Bu)_3$ (5 equiv), THF, 4 °C, 30 min, 60% (>20:1) (3 steps); (k) DEAD (2.5 equiv), Ph_3P (2.5 equiv), THF, 4 °C, 1 h, 87%; (l) 3-pentanol, BF_3·OEt_2 (1.5 equiv), 4 °C, 1 h, 52%; (m) TFA (20 equiv), CH_2Cl_2, 4 °C to rt, 3 h; (n) Boc_2O (1.1 equiv), Et_3N (5 equiv), CH_2Cl_2, 4 °C, 30 min, 63% (2 steps); (o) Ac_2O (2 equiv), DMAP (0.5 equiv), py, rt, 1 h, 84%; (p) 4.2 M HCl−EtOH, 60 °C, 4 h; H_2O, 4 °C, 3 h, 53%; (q) 85% H_3PO_4 (1 equiv), EtOH; cryst, 50%.

Shibasaki's second Approach: Diels-Alder reaction



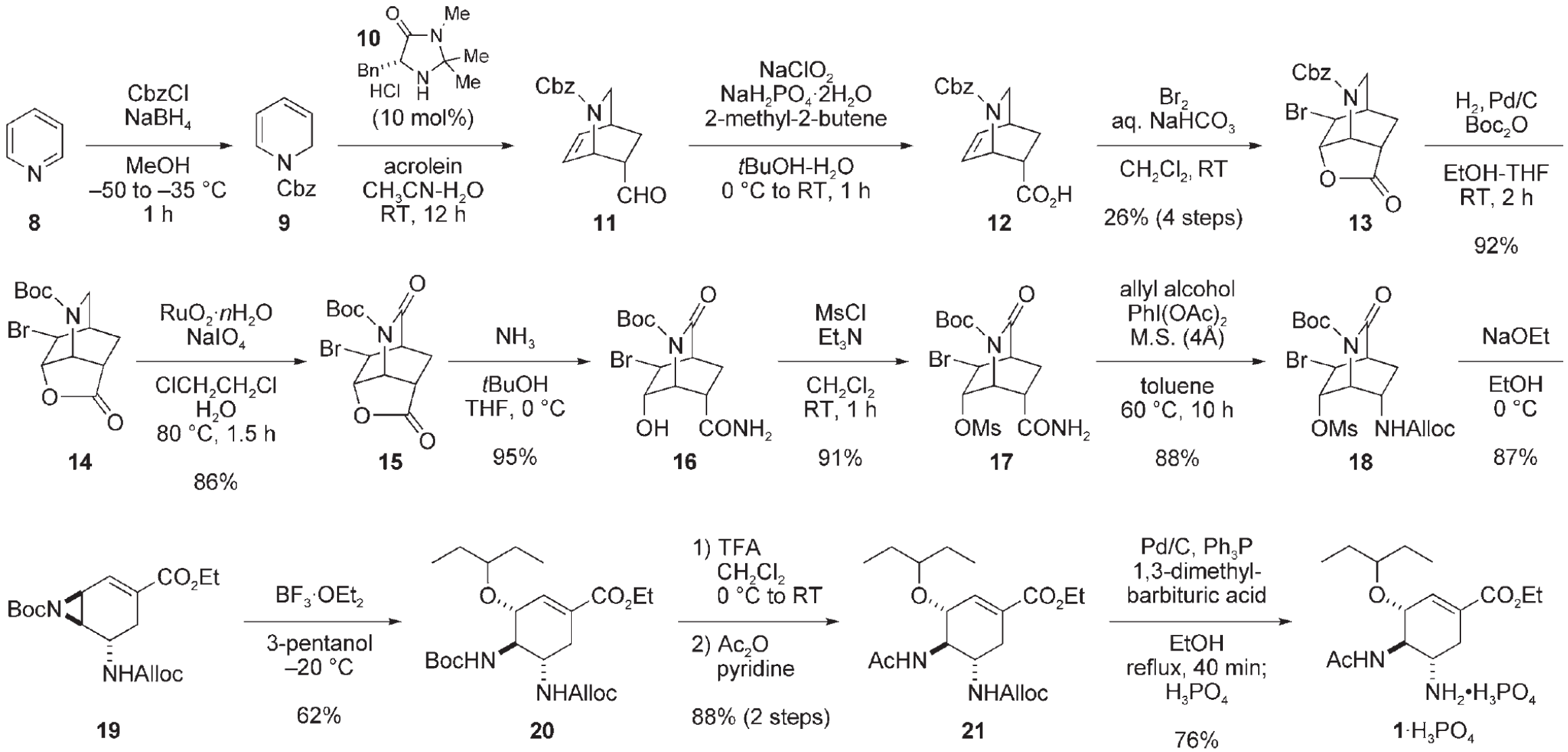
Reagents and conditions: (a) $Pd_2(dba)_3 \cdot CHCl_3$ (2 mol%), dppf (8 mol%), PhMe, 60 °C, 1 h, 88%. (b) $NaIO_4$, $RuCl_3$ (0.5 mol%), H_2SO_4 (20 mol%), H_2O, 4 °C. (c) 2,2-Dimethoxypropane, *p*-TsOH•H_2O, PhMe, 50 °C, 30 min, 56% (2 steps). (d) TEA•3HF (0.67 M in EtOH), DBU, EtOH, rt, 36 h, 76%.

1) Scalable
2) Curtius rearrangement
3) Several chromatography including Prep-TLC
4) Overall 13%, 11 steps

Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed*. **2009**, *48*, 1070.

Yamatsugu, K.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2009**, *65*, 6017.

Fukuyama's approach: Enantioselective Diels-Alder reaction



5.6%, 14 steps

Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed*. **2007**, *46*, 5734

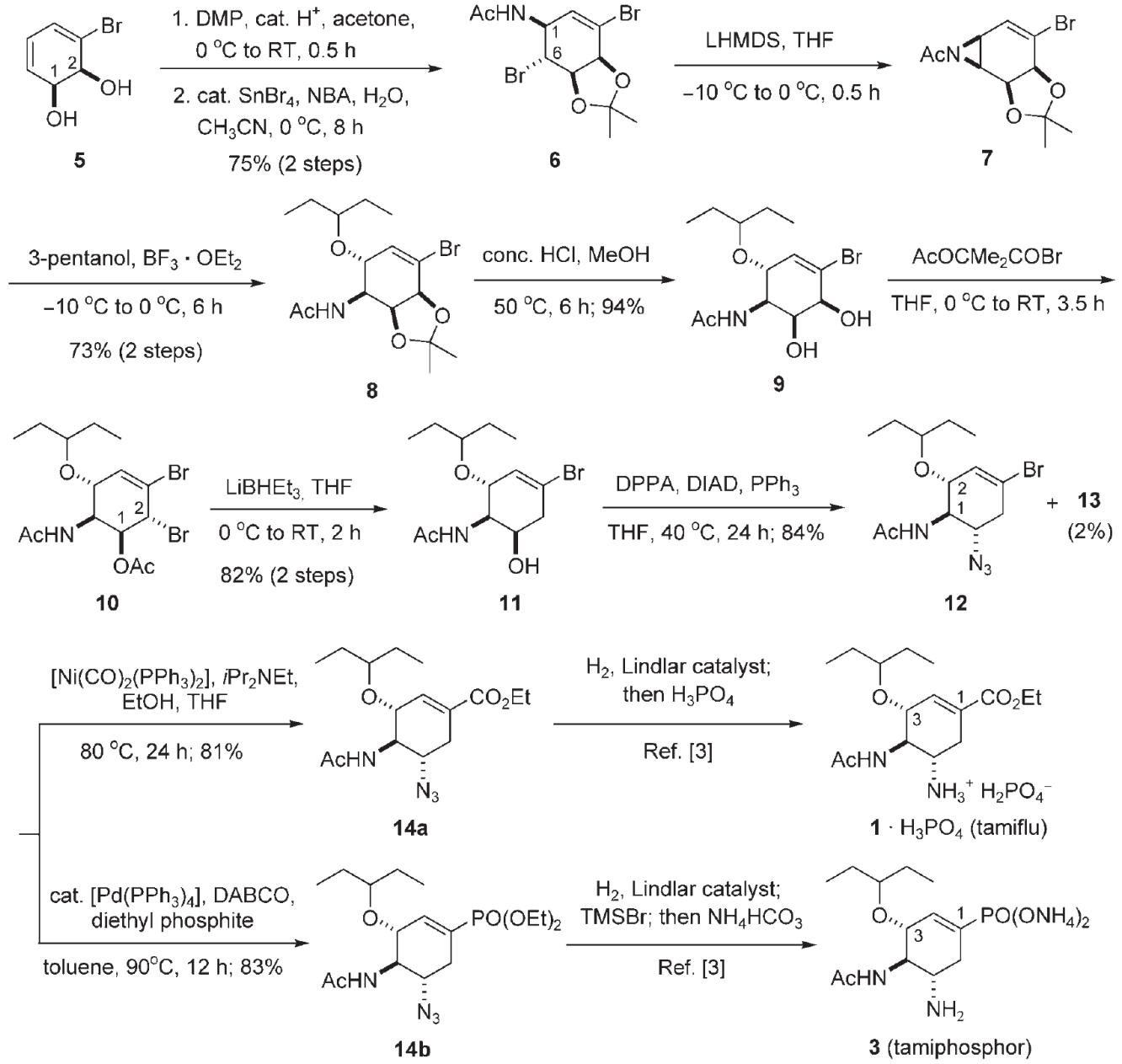
Wong's synthesis

Chemoenzymatric oxidation
Of bromobenzene

Use of strong base

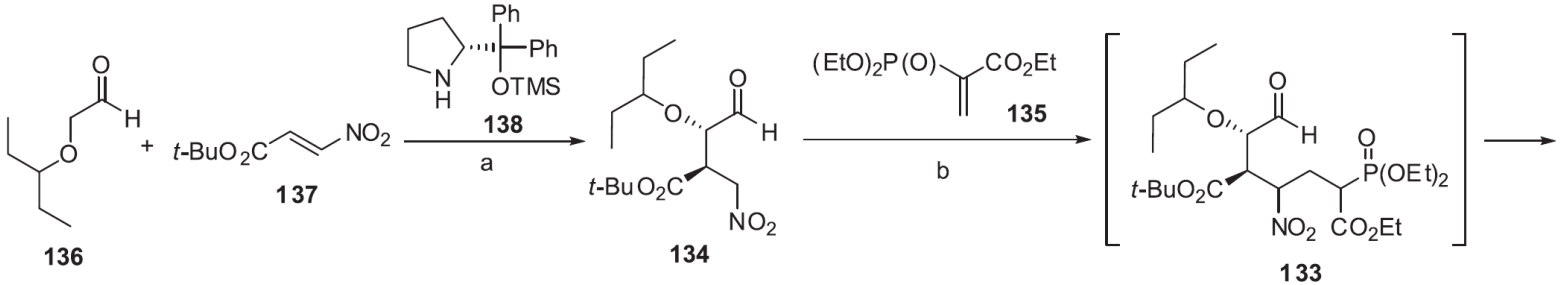
Mitsunobu

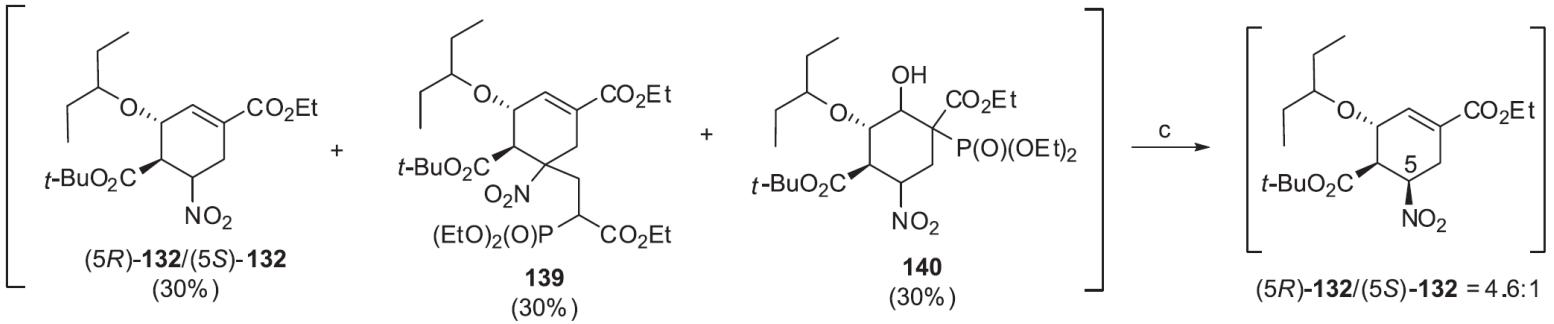
11steps, 21-26%

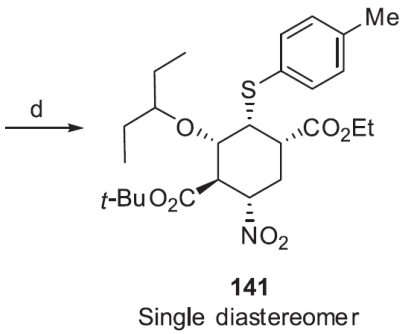


Shie, J.-J.; Fang, J.-M.; Wong, C.-H.
Angew. Chem., Int. Ed. **2008**, *47*, 5788

Hayashi's approach: two "one-pot" sequence







One pot from **134**

Use of equimolar **136** and **137**

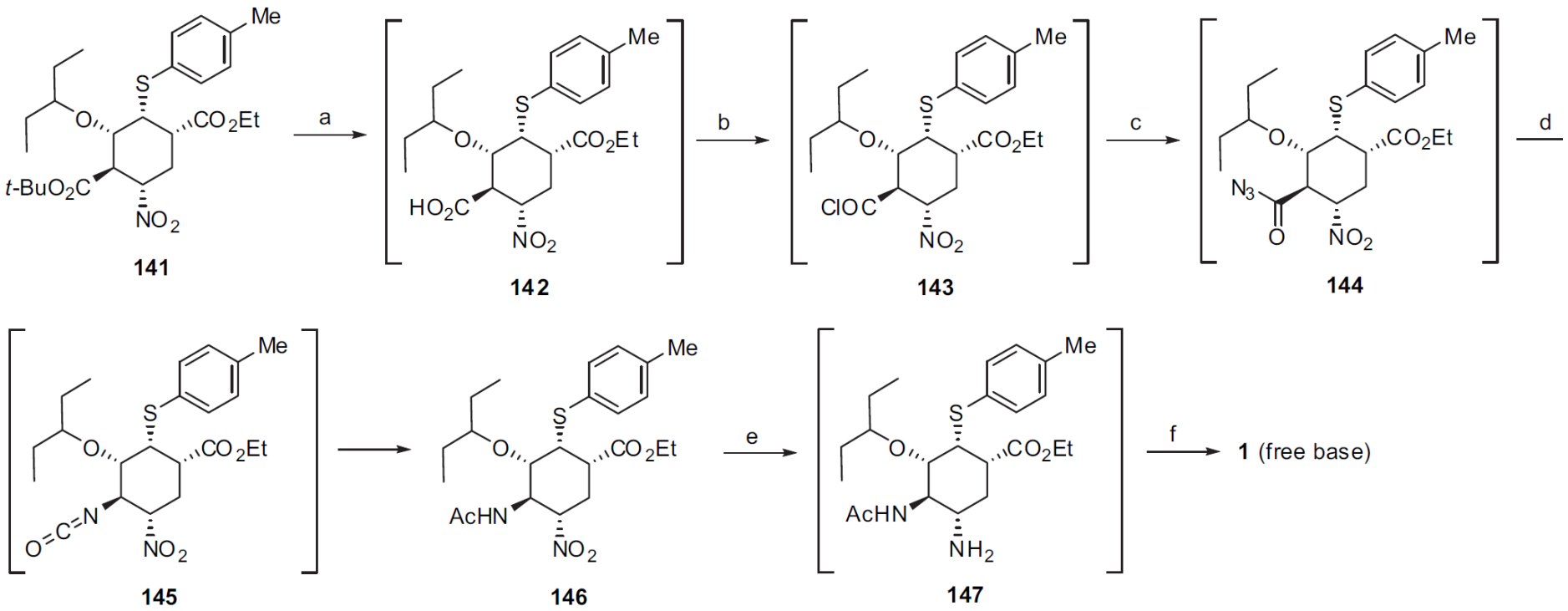
The formation of single diastereomer **141**

Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304

Ishikawa, H.; Suzuki, T.; Orita, H.; Uchimaru, T.; Hayashi, Y. *Chem. Eur. J.* **2010**, *16*, 12616.

Reagents and conditions: (a) **138** (1 mol%), $ClCH_2CO_2H$ (20 mol%), PhMe, rt, 6 h, dr = 7.8:1, ee = 97%. (b) Cs_2CO_3, PhMe, 0 °C to rt, 4 h. (c) EtOH, rt, 10 min. (d) *p*-MeC_6H_4SH, Cs_2CO_3, EtOH, -15 °C, 36 h, 74% (4 steps).

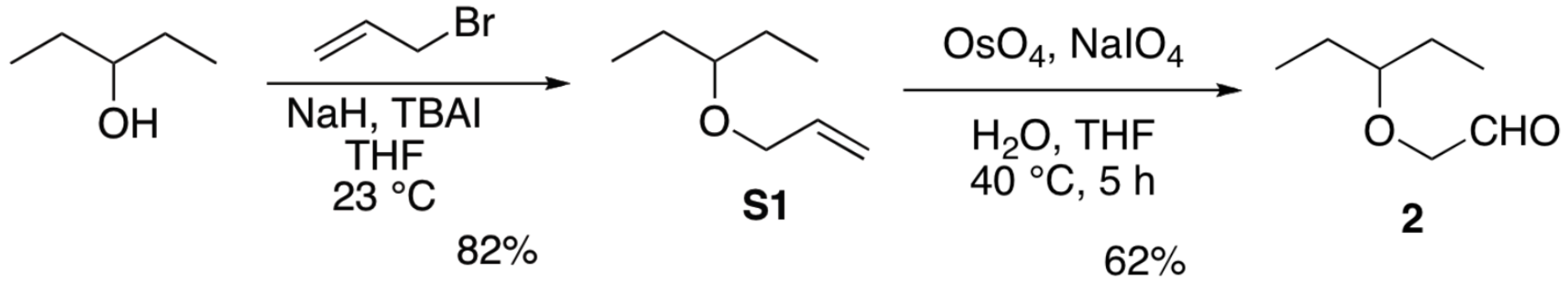
Hayashi's approach: two "one-pot" sequence (cont'd)

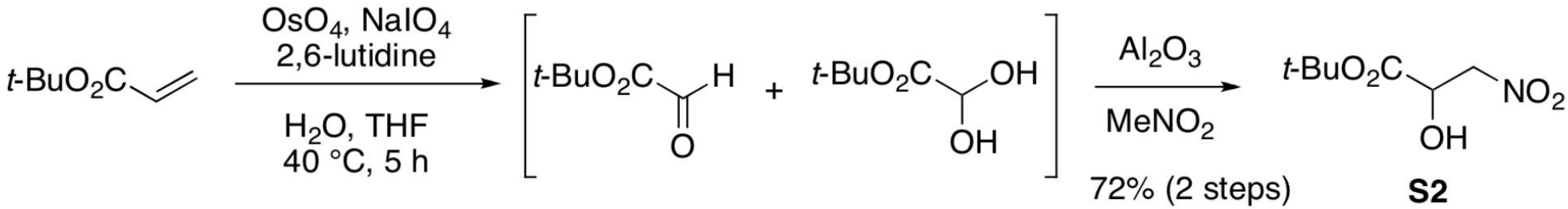


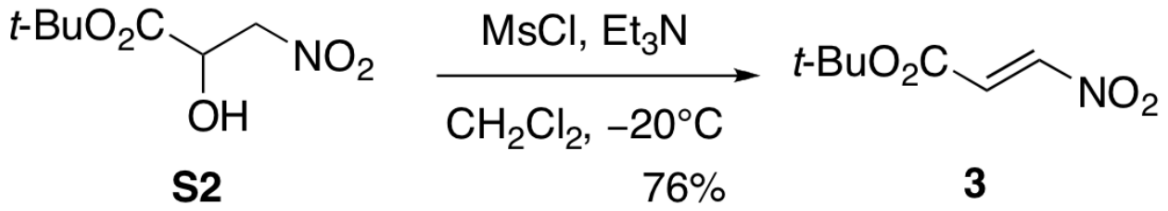
Reagents and conditions: (a) TFA, PhMe, 23 °C, 4 h. (b) $(COCl)_2$, DMF, PhMe, 23 °C, 30 min. (c) $TMSN_3$, pyridine, PhMe, 0 to 23 °C. (d) Ac_2O, HOAc, 0 to 23 °C, 48 h. (e) (i) Zn (powder), TMSCl, EtOH, 70 °C, 2 h; (ii) NH_3 (gas), 0 °C, 10 min. (f) K_2CO_3, EtOH, 23 °C, 9 h, 81% (6 steps).

1) 10 overall steps, 60% overall yield, deomstrated on gram-scale
2) Protecting group free, base free, no chromatography, no purification of intermediates

Hayashi's approach: Preparation of Starting materials

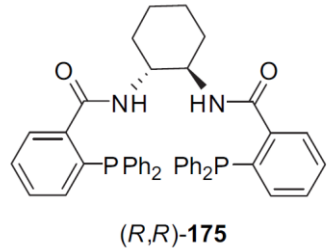




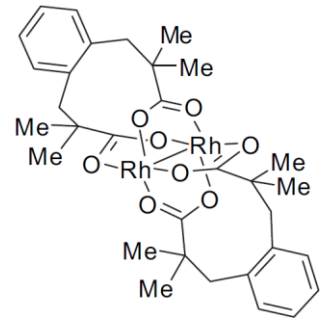


Patented!!

Trost's Synthesis: AAA chemistry



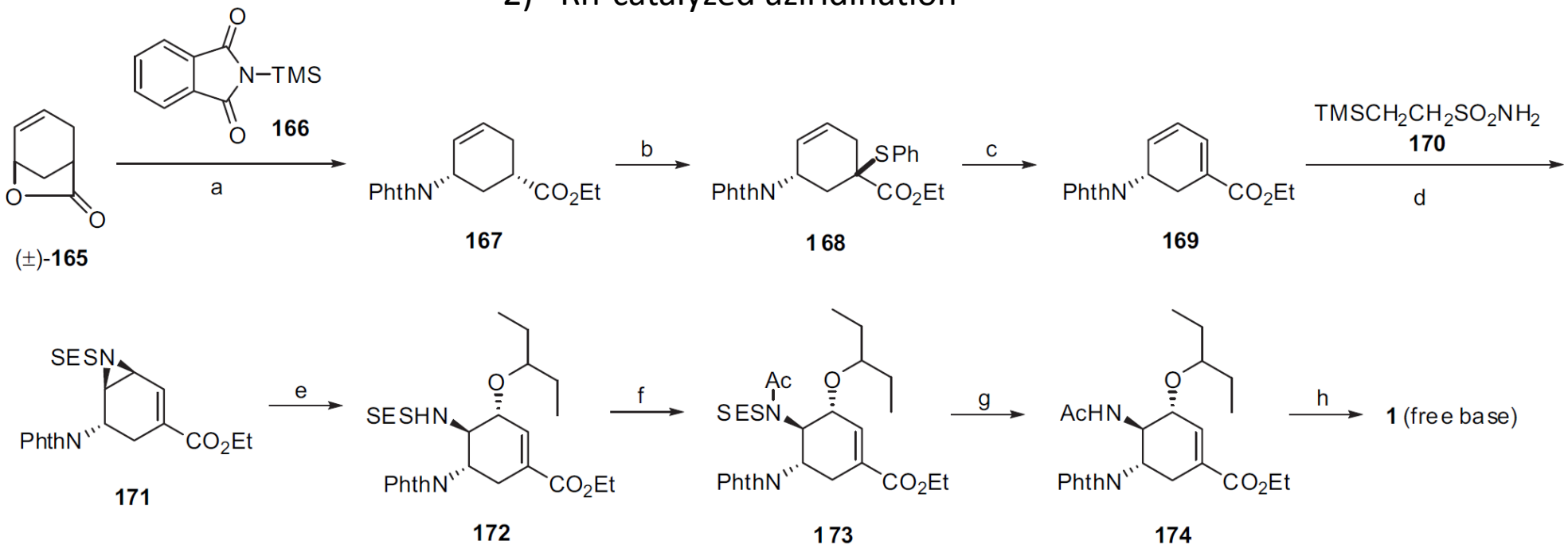
(*R*,*R*)-**175**



176

Two Trasition metal catalyzed transformation

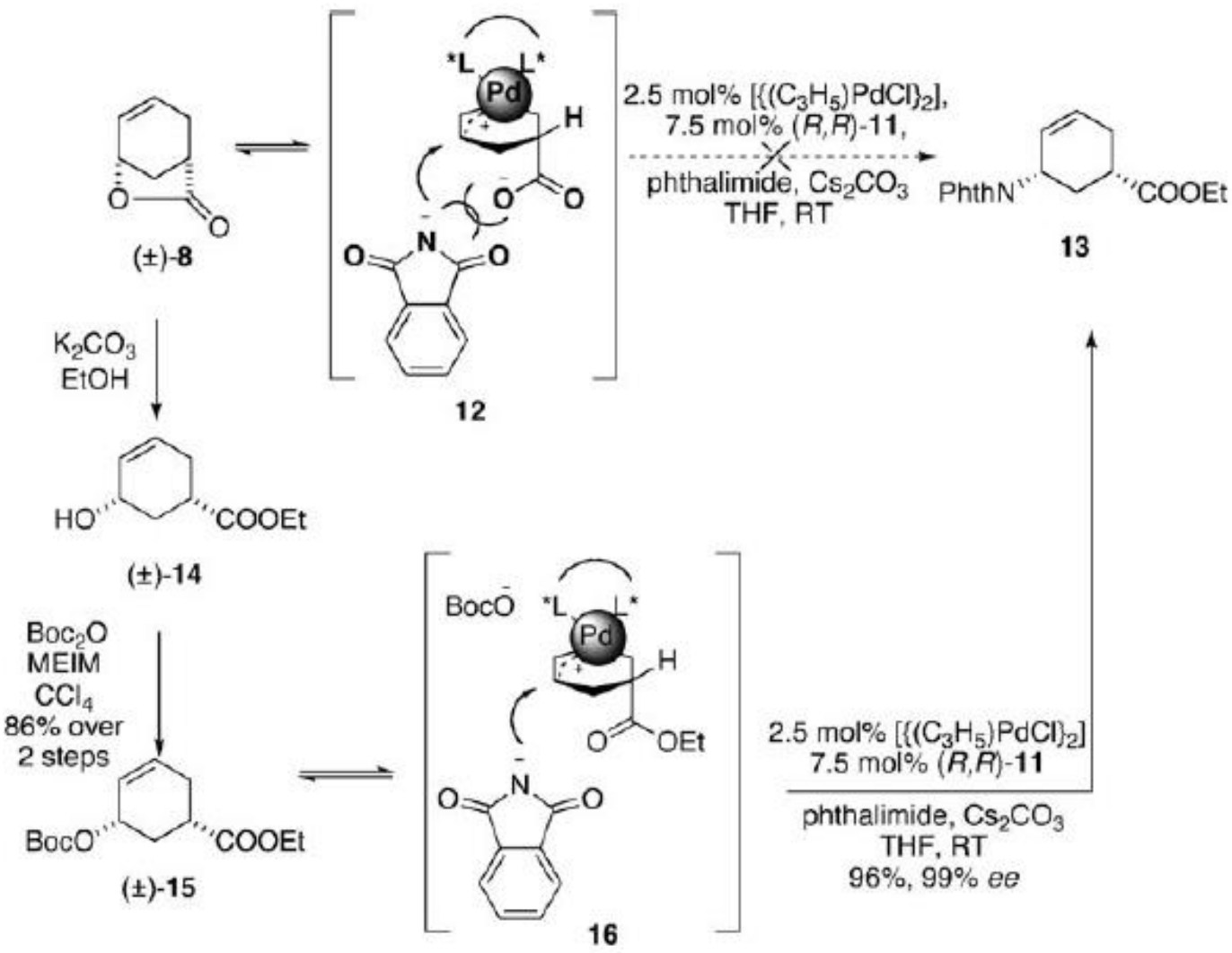
1) Pd-catalyzed AAA
2) Rh-catalyzed aziridination

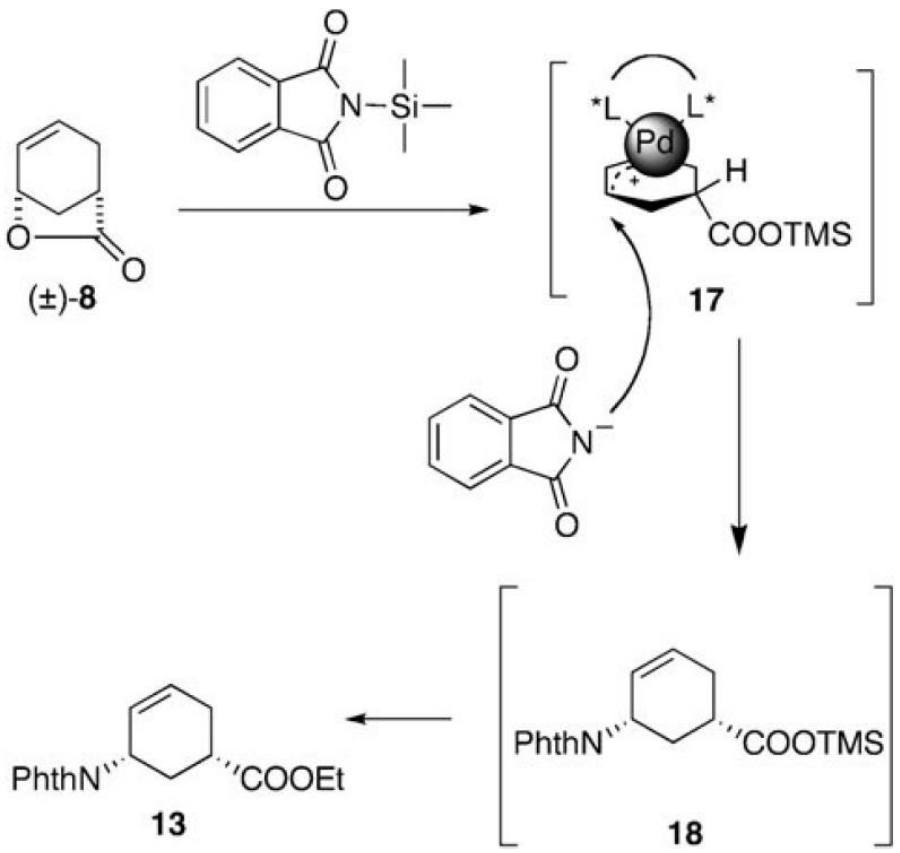


Reagents and conditions: (a) (i) [{Pd(C_3H_5)Cl}$_2$] (2.5 mol%), **175** (7.5 mol%), THF, 40 °C; (ii) TsOH•H_2O, EtOH, reflux, 84%, 98% ee. (b) KHMDS, $PhSSO_2Ph$, THF, -78 °C to rt, 94%. (c) (i) *m*-CPBA, $NaHCO_3$, 0 °C; (ii) DBU, PhMe, 60 °C, 85%. (d) **176** (2 mol%), $PhI(O_2CCMe_3)_2$, MgO, PhCl, 0 °C to rt, 86%. (e) 3-Pentanol, BF_3•Et_2O, 75 °C, 65%. (f) DMAP, py, Ac_2O, MW, 150 °C, 1 h, 84%. (g) TBAF, THF, rt, 95%. (h) NH_2NH_2, EtOH, 68 °C, 100%.

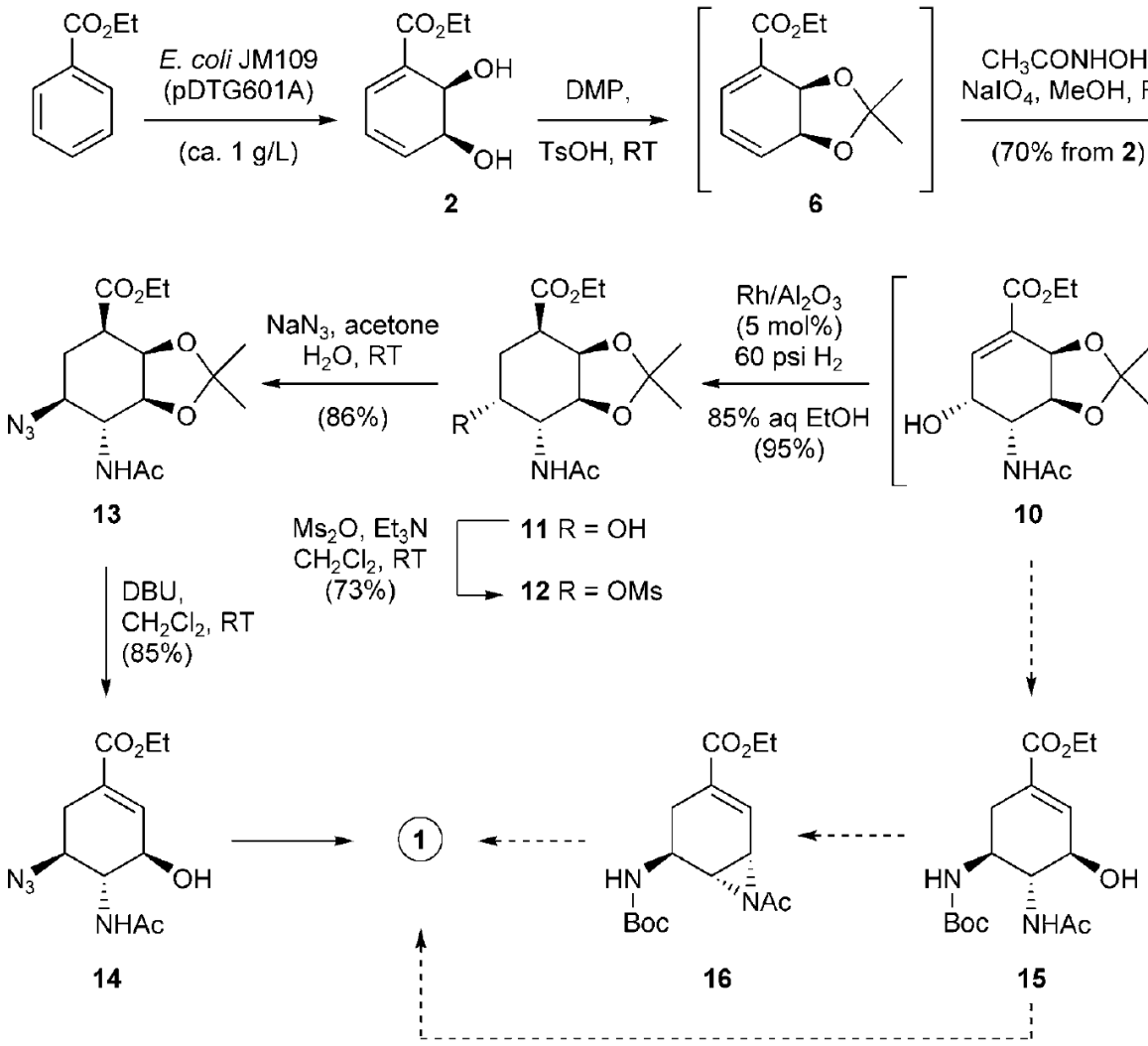
Trost, B. M.; Zhang, T. *Angew. Chem., Int. Ed*. **2008**, *47*, 3759

Trost's Synthesis: AAA of lactone





Hudlicky's First Approach using ethyl benzoate



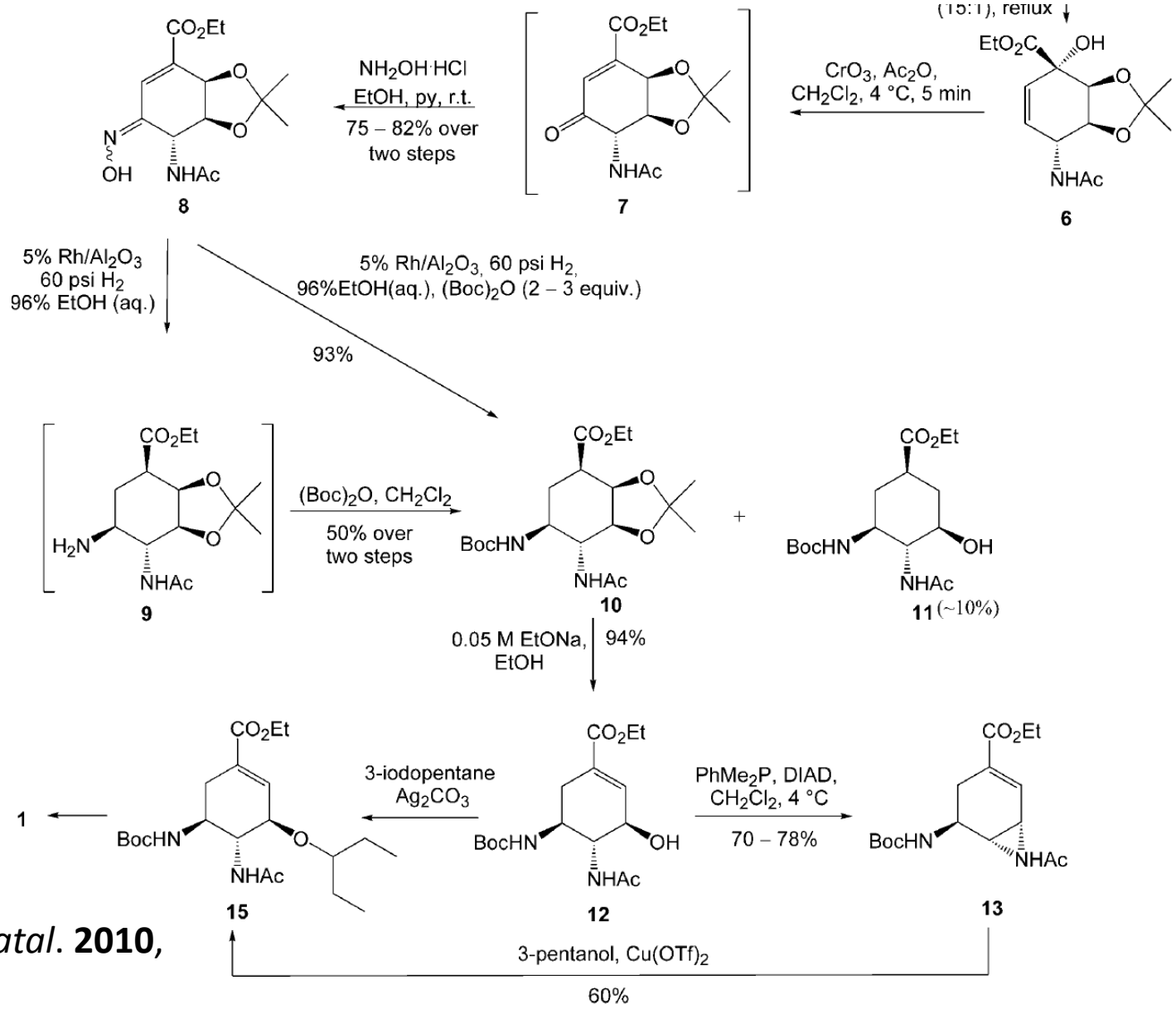
1) Chemoenzymatic Approach from readily available ethyl benzoate ($30/1Kg)
2) Diels-Alder reaction to introduce amino group at C4
3) The use of azide, low yielding enzymatic oxidation, overall 10% to the compound **14**

Sullivan, B.; Carrera, I.; Drouin, M.; Hudlicky, T. *Angew. Chem., Int. Ed*. **2009**, *48*, 4229.

Hudlicky's Second Approach using ethyl benzoate

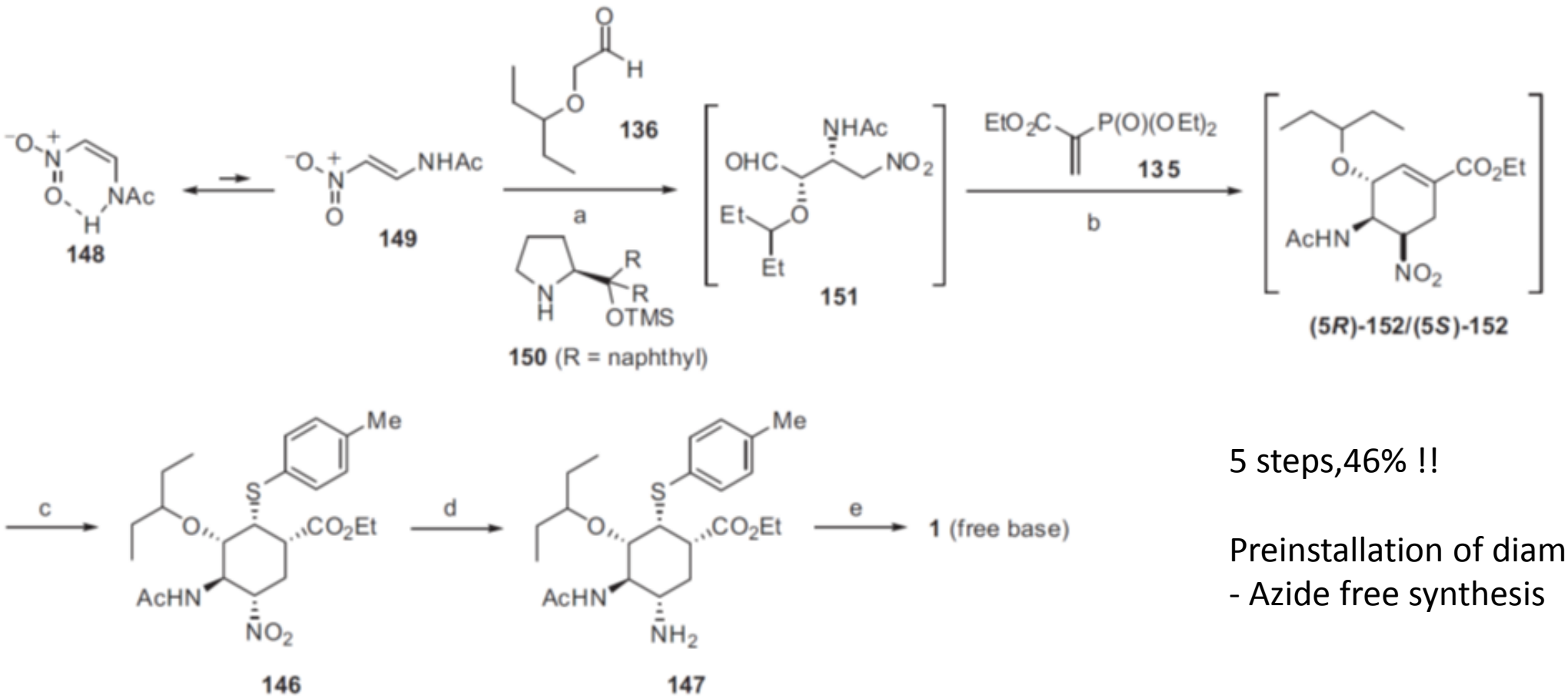
1) Azide Free synthesis
2) Safty concern: NH_2OH-HCl
3) Scalability of Mitsunobu?
4) Several chromatography and mg scale

Synthesis in the experimental procedure.



Werner, L.; Machara, A.; Hudlicky, T. *Adv. Synth. Catal*. **2010**, *352*, 195−200.

Ma's approach: Organocatalysis



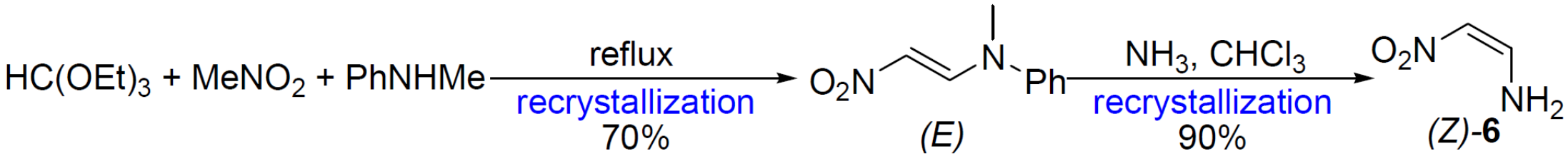
5 steps,46% !!

Preinstallation of diamine moiety
- Azide free synthesis

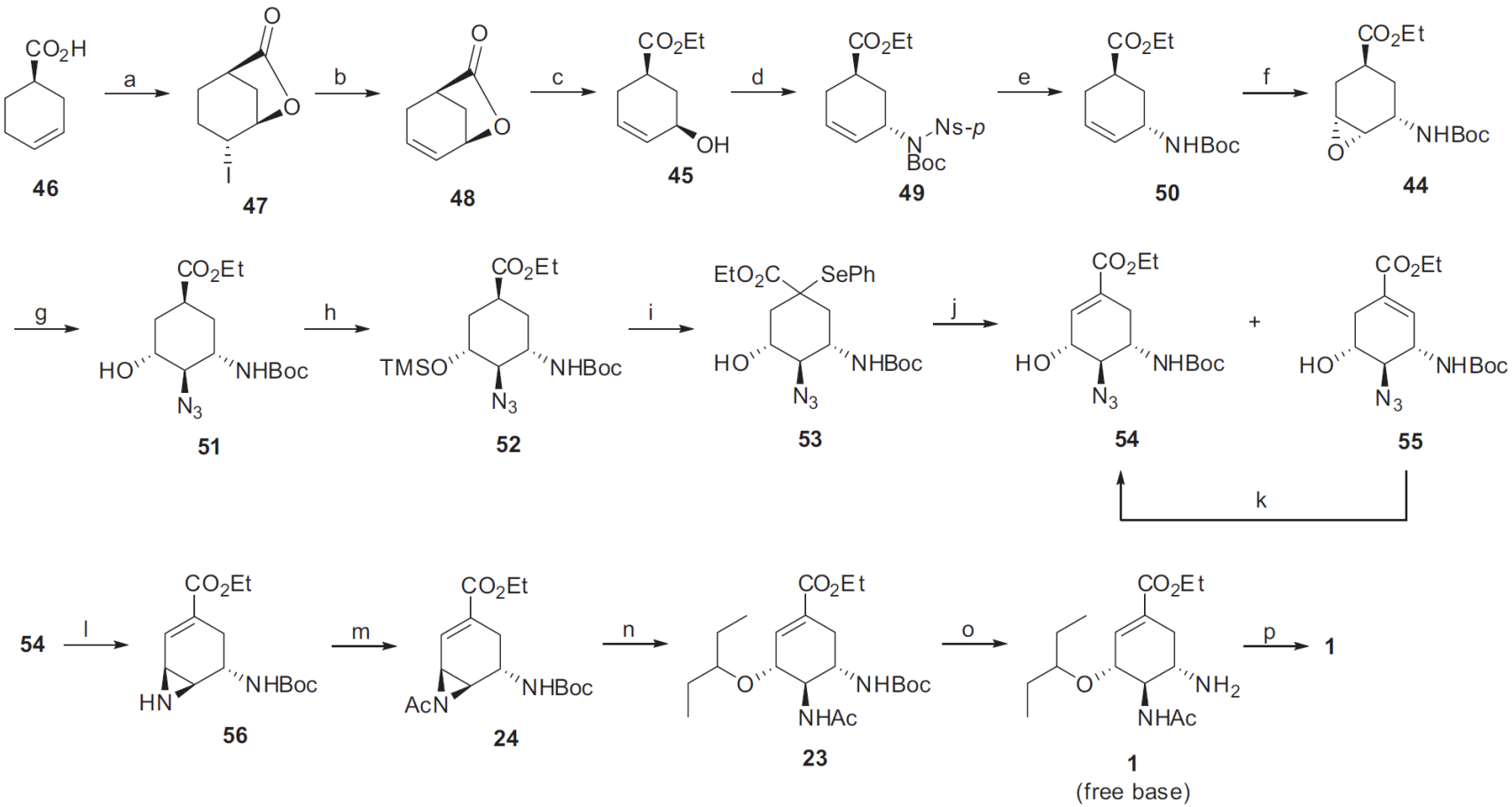
Reagents and conditions: (a) **150** (10 mol%), $PhCO_2H$ (30 mol%), $CHCl_3$, 4 Å molecular sieves, –5 °C, *syn*/*anti* ratio: 5:1. (b) Cs_2CO_3, 0 °C, 3 h. (c) *p*-MeC_6H_4SH, –15 °C, 48 h, 54% (3 steps), 96% ee. (d) Zn, TMSCl, EtOH. (e) K_2CO_3, MeOH, 85% (2 steps).

Zhu, S.; Yu, S.; Wang, Y.; Ma, D. Angew. Chem., Int. Ed. **2010**, *49*, 4656.

Ma’s approach: Preparation of 2-aminonitroolefin



Raghavan's asymmetric Diels-Alder approach



Reagents and conditions: (a) I_2, KI, $NaHCO_3$, H_2O, rt, 20 h, 93%. (b) DBU, PhMe, reflux, 6 h, 92%. (c) K_2CO_3, EtOH, rt, 5 h, 90%. (d) BocNHNs-*p*, DEAD, Ph_3P, PhMe, –20 °C, 6 h, 89%. (e) 2-Mercapto ethanol, DBU, acetone, rt, 3 h, 91%. (f) *m*-CPBA, CH_2Cl_2, 0 °C, 6 h, 84%. (g) $TMSN_3$, $Ti(Oi\text{-}Pr)_4$, benzene, 5 to 0 °C, 2 h, 86%, **51**/**59** ratio: 3:1 (Scheme 6). (h) TMSCl, TEA, CH_2Cl_2, 0 °C, 95%. (i) LDA, PhSeSePh, –78 °C, 30 min, 74%. (j) 30% H_2O_2 pyridine, CH_2Cl_2, rt, 30 min, 76%, **54**/**55** ratio: 1:1.5. (k) DBU, PhMe, 36 h, 65%, **54**/**55** ratio: 3:1. (l) Ph_3P, PhMe, reflux, 3 h, 83%. (m) Ac_2O, DMAP, TEA, CH_2Cl_2, 0 °C to rt, 30 min, 87%. (n) 3-Pentanol, $BF_3 \cdot OEt_2$, –20 °C, 30 min, 70%. (o) TFA, CH_2Cl_2, rt, 1 h. (p) H_3PO_4 (1M in EtOH), rt to 50 °C; then 4 °C, 71% (2 steps)

Starting from the chiral acid

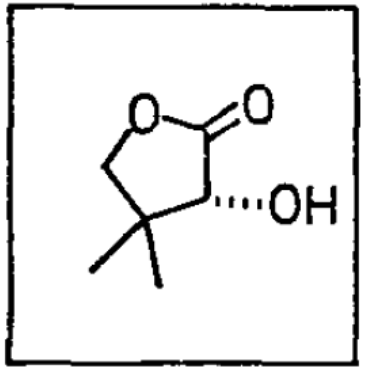
Mitsunobu to install C3-amino group

Carbamate-directed Epoxidation

16 Steps, 4.3%

Raghavan, S.; Babu, V. S. *Tetrahedron* **2011**, *67*, 2044.

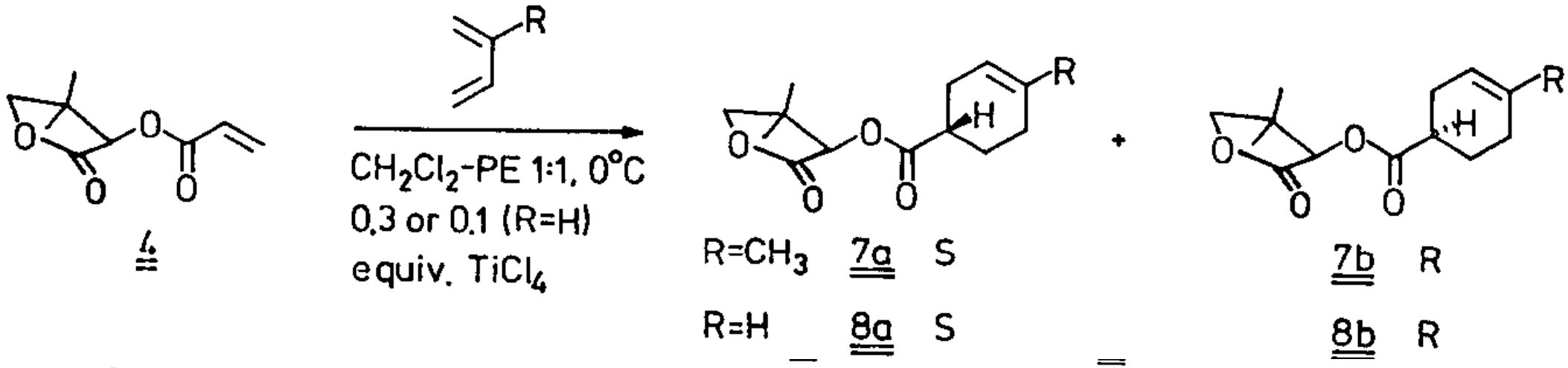
100 G/ $ 274
recyclable



D-pantolactone

Asymmetric Diels-Alder reaction

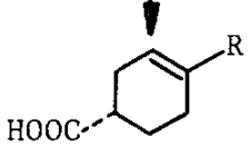
Poll, T.; Sebezak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett*. **1985**, *26*, 3095.



4

R=CH_3 7a S 7b R

R=H 8a S 8b R

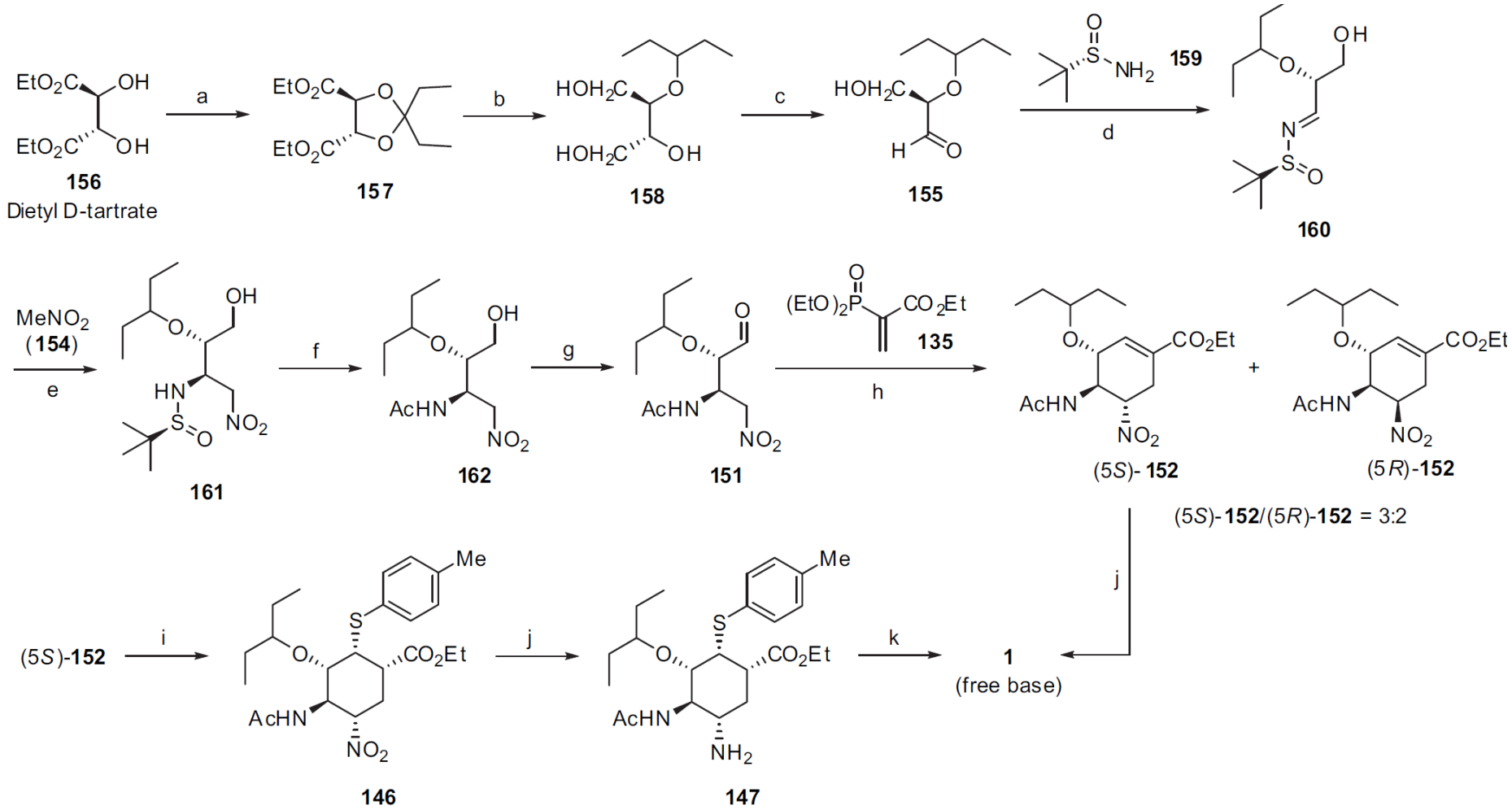
diastereoselectivity	7a : 7b = 97 : 3 8a : 8b = 93 : 7		
recrystallized material (3 cryst.)	7a : 7b > 99.5 : 0.5 8a : 8b > 99.5 : 0.5	Y.: 76 % Y.: 73 %	
$LiOH/THF,H_2O$	mp(7a) = 56 °C, mp(8a) = 38 °C		
 (S)-9 R = CH_3	ep ≥ 99.7 %	$[\alpha]_D^{20}$ -107 (c 4, 95 % EtOH)	Y.: 97 %
(S)-10 R = H	ep ≥ 99.5 %	$[\alpha]_D^{22}$ - 95 (c 7, CH_3OH)	Y.: 97 %

Lu's approach: D-Tartrate

1) Use of Chiral Sulfinamide to install diastereoselective amine functionality

2) 11 steps
21% overall

D-tartrate: $213/ 100G



Reagents and conditions: (a) 3,3-Dimethoxypentane, *p*-TsOH, PhMe, reflux, 3 h, 96%. (b) (i) LAH, $AlCl_3$, Et_2O/CH_2Cl_2 (1:1), –30 °C, 30 min; then 0 °C; (ii) rt, 1 h; then, reflux, 2 h, 88%. (c) $NaIO_4$, THF/H_2O (1:1), 95%. (d) $CuSO_4$, CH_2Cl_2, rt, 3 days, 73%. (e) $MeNO_2$, NaOH, 4 Å molecular sieves, rt, 24 h, 86%, dr = 10:1. (f) (i) HCl, MeOH, rt, 2 h; (ii) Ac_2O, MeOH, rt, 30 min, 83%. (g) IBX, EtOAc, reflux, 3 h, 100%. (h) DBU, LiCl, MeCN, –15 °C, 14 h; then 0 °C, 2 h, 61%, dr = 3:2. (i) *p*-MeC_6H_4SH, Cs_2CO_3, EtOH, –15 °C, 48 h, 95%. (j) (i) Zn (powder), TMSCl, EtOH, 70 °C, 2 h; (ii) NH_3 (gas), 0 °C, 15 min; (iii) K_2CO_3, rt, 6 h, 86%.

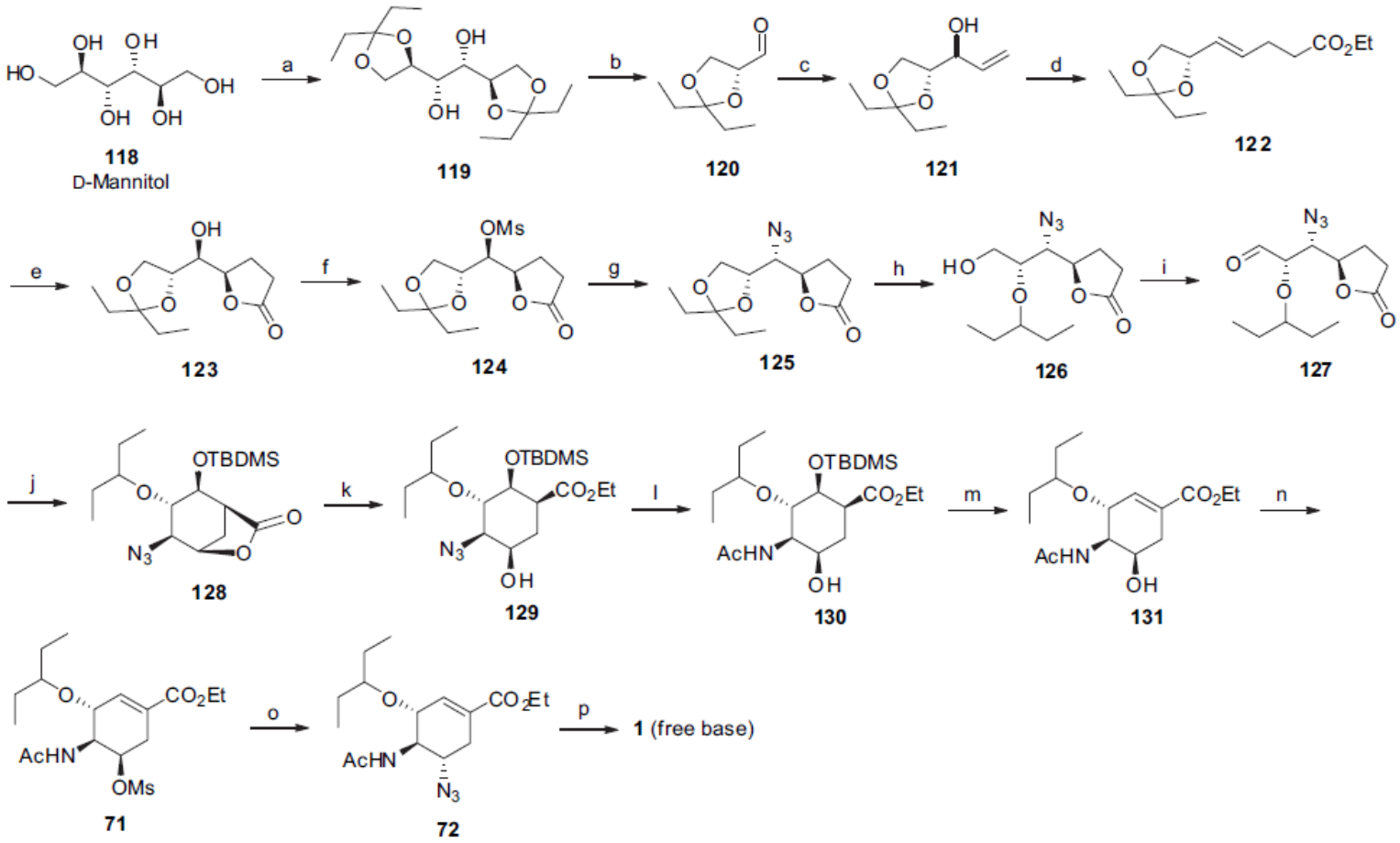
Weng, J.; Li, Y.-B.;Wang, R.-B.; Li, F.-Q.; Liu, C.; Chan, A. S. C.; Lu, G. *J. Org. Chem.* **2010**, *75*, 3125.

Ko's approach: D-mannitol

1) Sharpless dihydroxylation
Azide chemistry in hight temp.
Chromatographic separation
Protecting group

2) 16 steps/ 7% overall

D-mannitol: $163/ 3 KG
- attractive starting material



Reagents and conditions: (a) 3,3-Dimethoxypentane, CSA, DMF, 40 °C, 4 h. (b) KIO_4, $KHCO_3$, H_2O/THF (2.5:1), rt, 4 h. (c) Vinylmagnesium bromide (1 M in THF), 0 °C, 5 h, 43% (3 steps). (d) $MeC(OEt)_3$, propionic acid, 132 °C, 25 h, 85%. (e) AD-mix-β, *t*-BuOH/H_2O (1:1), $MeSO_2NH_2$, 0 °C, 6 h, 93%. (f) MsCl, TEA, CH_2Cl_2, 0 °C, 4 h, 100%. (g) NaN_3, DMF, 120 °C, 49 h, 73%. (h) BH_3•Me_2S (2 M in THF), TMSOTf, CH_2Cl_2, –50 °C, 30 min; then –20 to –30 °C, 22 h, 94%. (i) $(COCl)_2$, DMSO, CH_2Cl_2, TEA, –68 °C, 1 h, 92%. (j) TBDMSOTf, DIPEA, CH_2Cl_2, 0 °C, 25 min; then rt, 2 h, 76%. (k) LiBr, DBU, EtOH, 0 °C, 1 h, 96%. (l) H_2 (balloon), 10% Pd/C, Ac_2O, TEA, EtOAc, rt, 22 h, 96%. (m) DBU, $LiClO_4$, EtOH, reflux, 2.5 h, 62%. (n) MsCl, TEA, CH_2Cl_2, 0 °C, 1.5 h, 97%. (o) LiN_3, DMF, 90 °C, 7 h, 78%. (p) Ph_3P, THF/H_2O (5:1), 50 °C, 19 h, 98%.

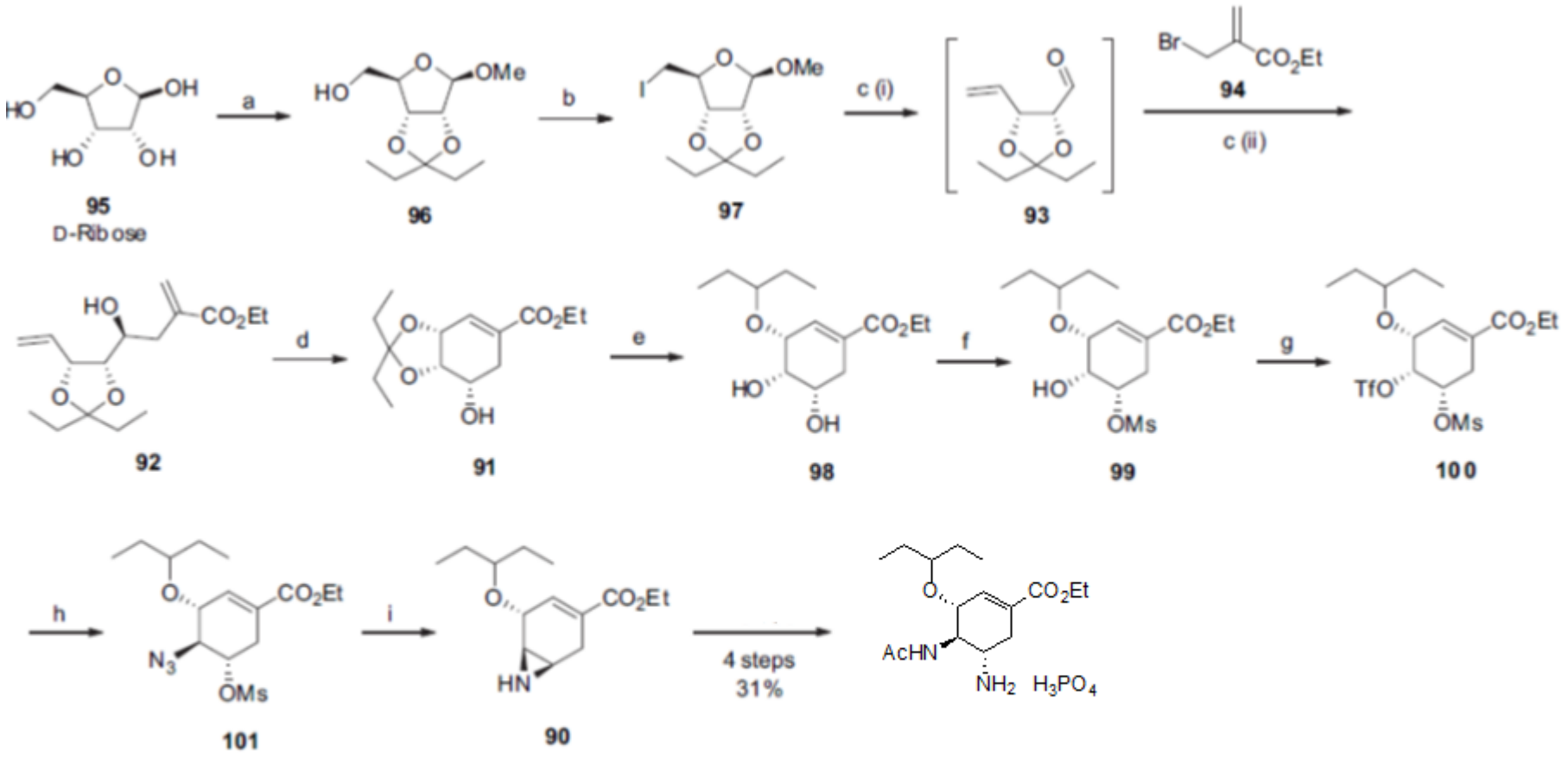
Ko, J. S.; Keum, J. E.; Ko, S. Y. *J. Org. Chem*. **2010**, *75*, 7006.

Chen and Chai's Formal synthesis: D-Ribose

1) Protecting group free ,but halogenated solvent chromatography

2) 12 steps/ 9% overall

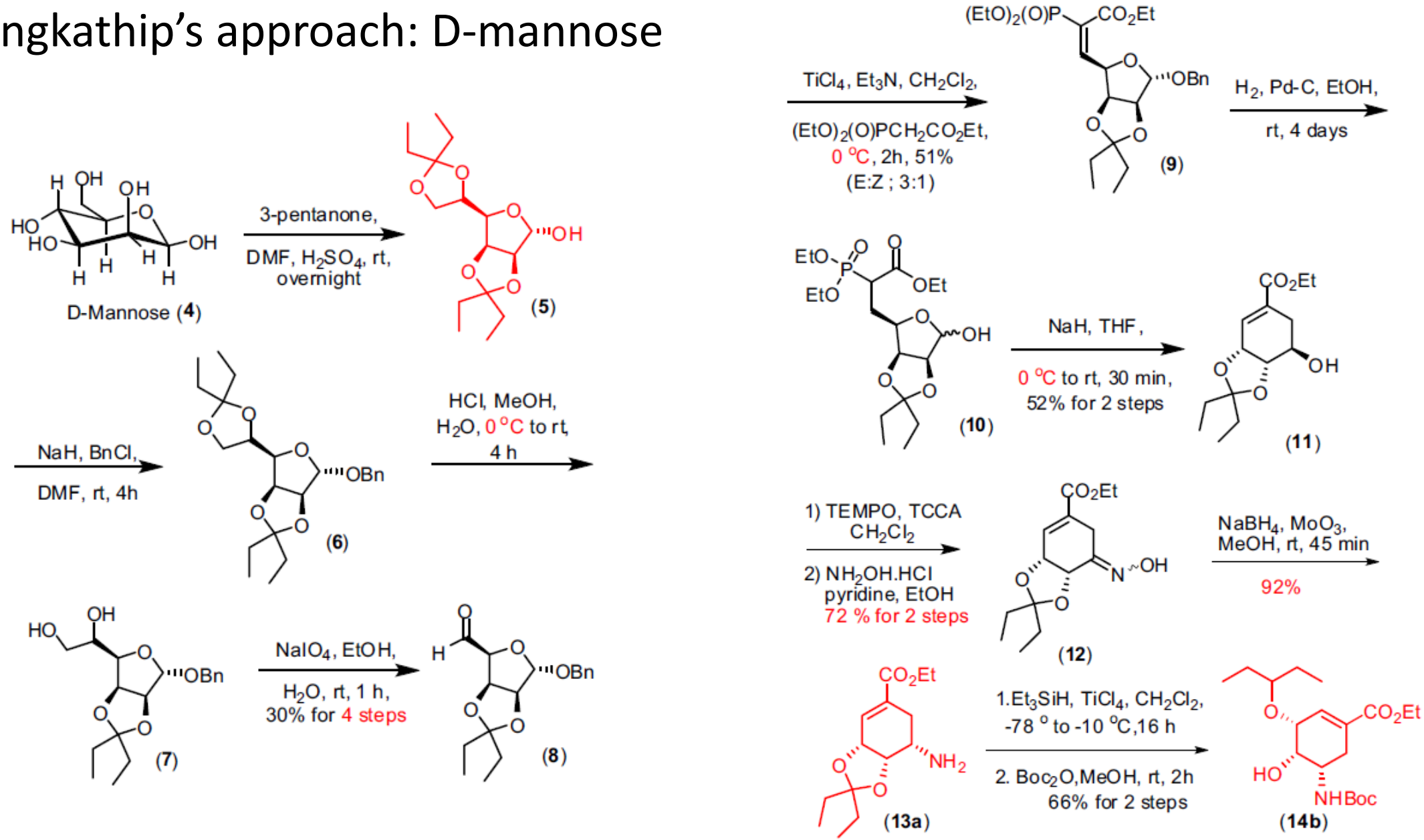
D-Ribose: $250/ 0.5 KG



Reagents and conditions: (a) 3-Pentanone, HCl (1 M in MeOH), $HC(OMe)_3$, reflux, 6 h, 89%. (b) I_2, Ph_3P, PhMe/MeCN (1:1), reflux, 5 min, 90%. (c) (i) Zn, THF/H_2O (2:1), reflux, 3 h; (ii) reflux, 4 h, 78%, dr = 5.2:1. (d) **102** (2 mol%), DCE, reflux, 2 h, 99%. (e) (i) $AlCl_3$, $CHCl_3$, sonication, 0 °C; (ii) Et_3SiH, -50 °C, 4 h; then 0 °C, 16 h, 67%. (f) MsCl, TEA, CH_2Cl_2, –20 °C, 40 min; then rt, 1 h, 92%. (g) Tf_2O, py, CH_2Cl_2, -10 °C, 30 min; then 0 °C, 20 min. (h) NaN_3, acetone/H_2O (9:1), rt, 4 h, 86% (2 steps). (i) Ph_3P, TEA, THF, rt, 17 h, 84%.

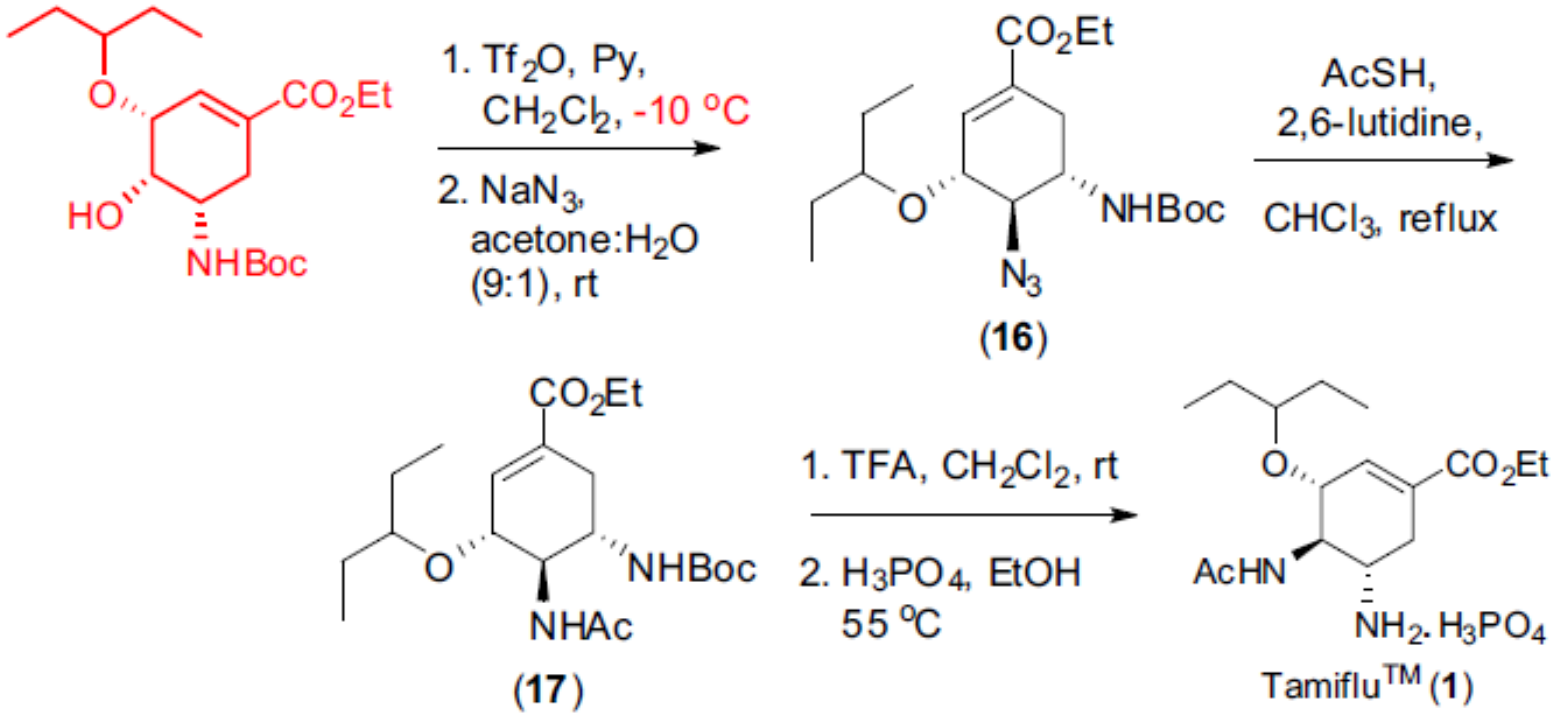
Osato, H.; Jones, I. L.; Chen, A.; Chai, C. L. L. Org. Lett. **2010**, *12*, 60.

Kongkathip's approach: D-mannose



Chuanopparat, N.; Kongkathip, N.; Kongkathip, B. *Tetrahedron* **2012**, *68*, 6803-6809

Kongkathip's approach: D-mannose (cont'd)



(16)

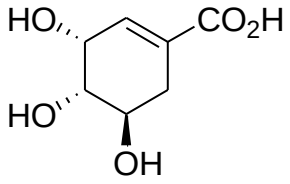
(17)

Tamiflu™ (1)

11 steps, 2.9% overall

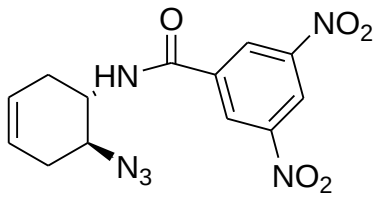
D-mannose: $312/ 0.5 KG

SUMMARY

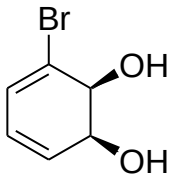


Shikimic acid

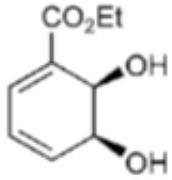
Hoffman-La Loche



Shibasaki



Wong



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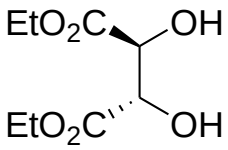
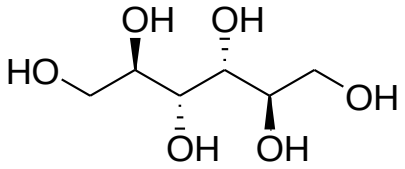


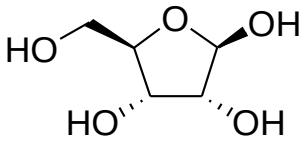
D-tartrate

Lu



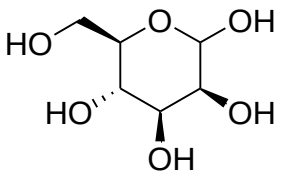
D-mannitol

Ko



D-ribose

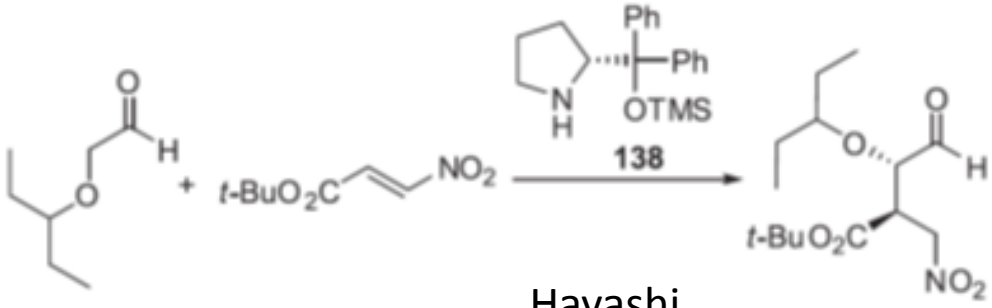
Chen and Chai



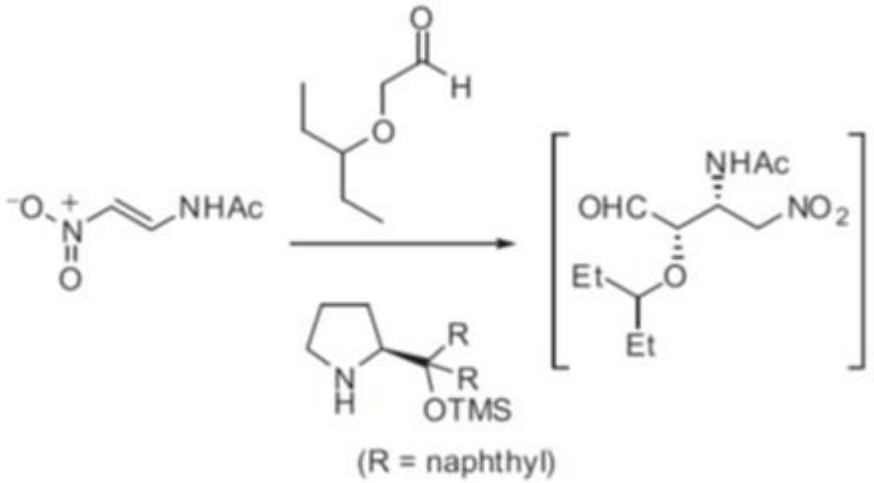
D-mannose

Kongkathip

Asymmetric Organocatalysis



Hayashi

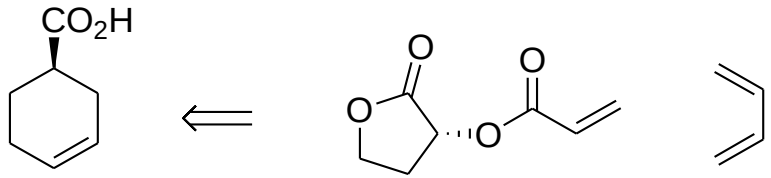


(R = naphthyl)

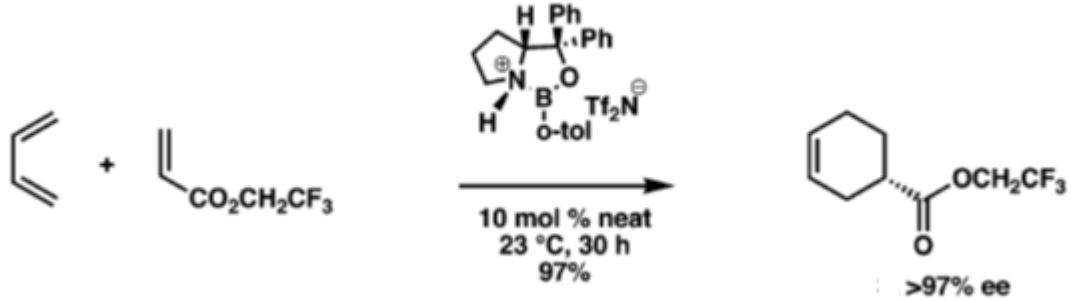
Ma

SUMMARY (cont'd)

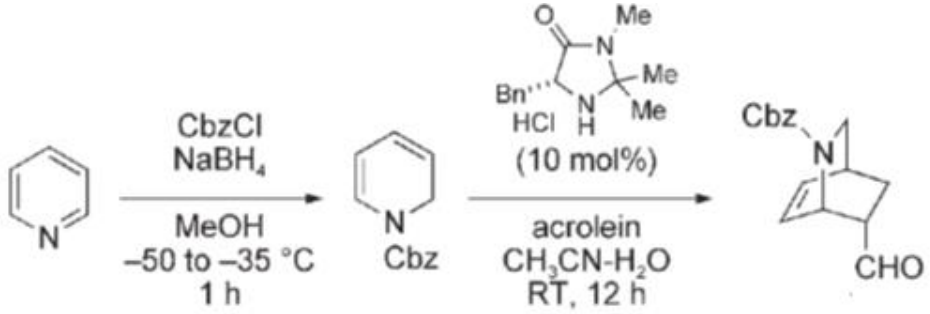
Asymmetric Diels-Alder Strategy



Raghavan



Corey



Fukuyama

Shibasaki

SUMMARY (cont'd)

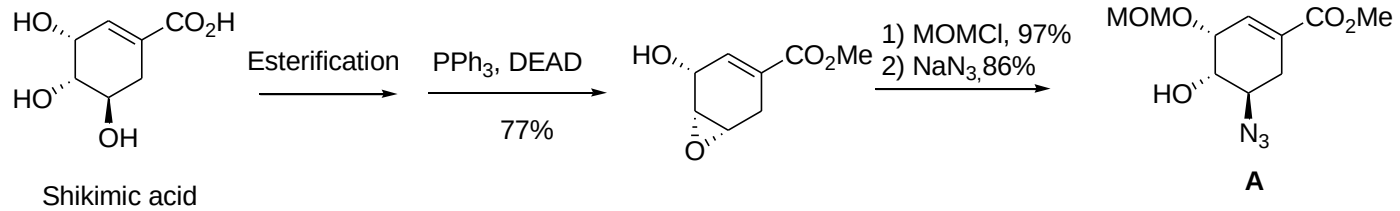
Need to keep developing total synthesis?

Yes. The mutation of influenza virus (e.g. H5N1) is probable to make a global pandemic in the future. New drug development for the alternative of Oseltamivir also required for drug-resistant viruses.

New and economic process to manufacture this drug may help decrease the price, which ultimately helps people in developing countries.

The patent expires in 2016, thus efficient and inexpensive production of this drug will determine the market price.

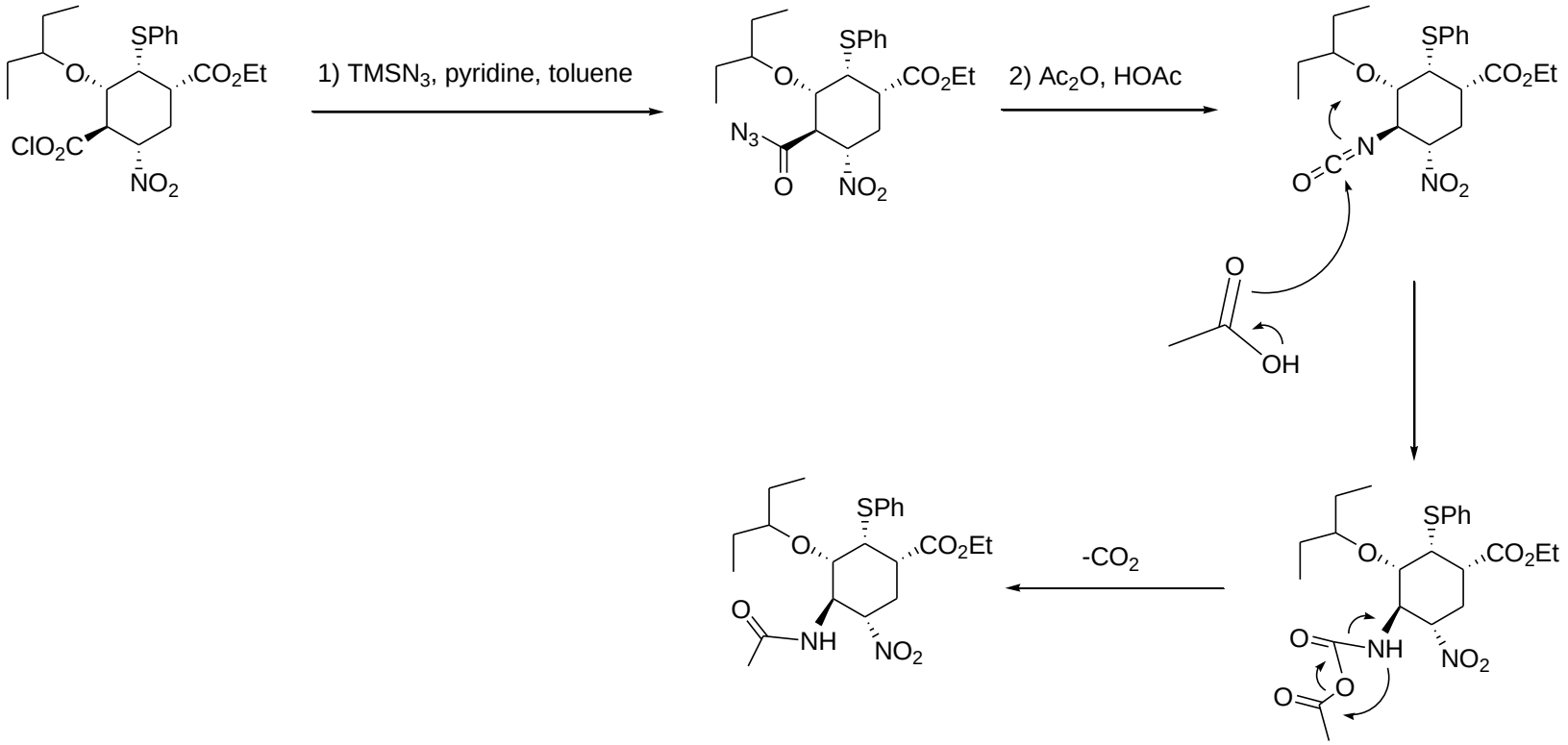
1)



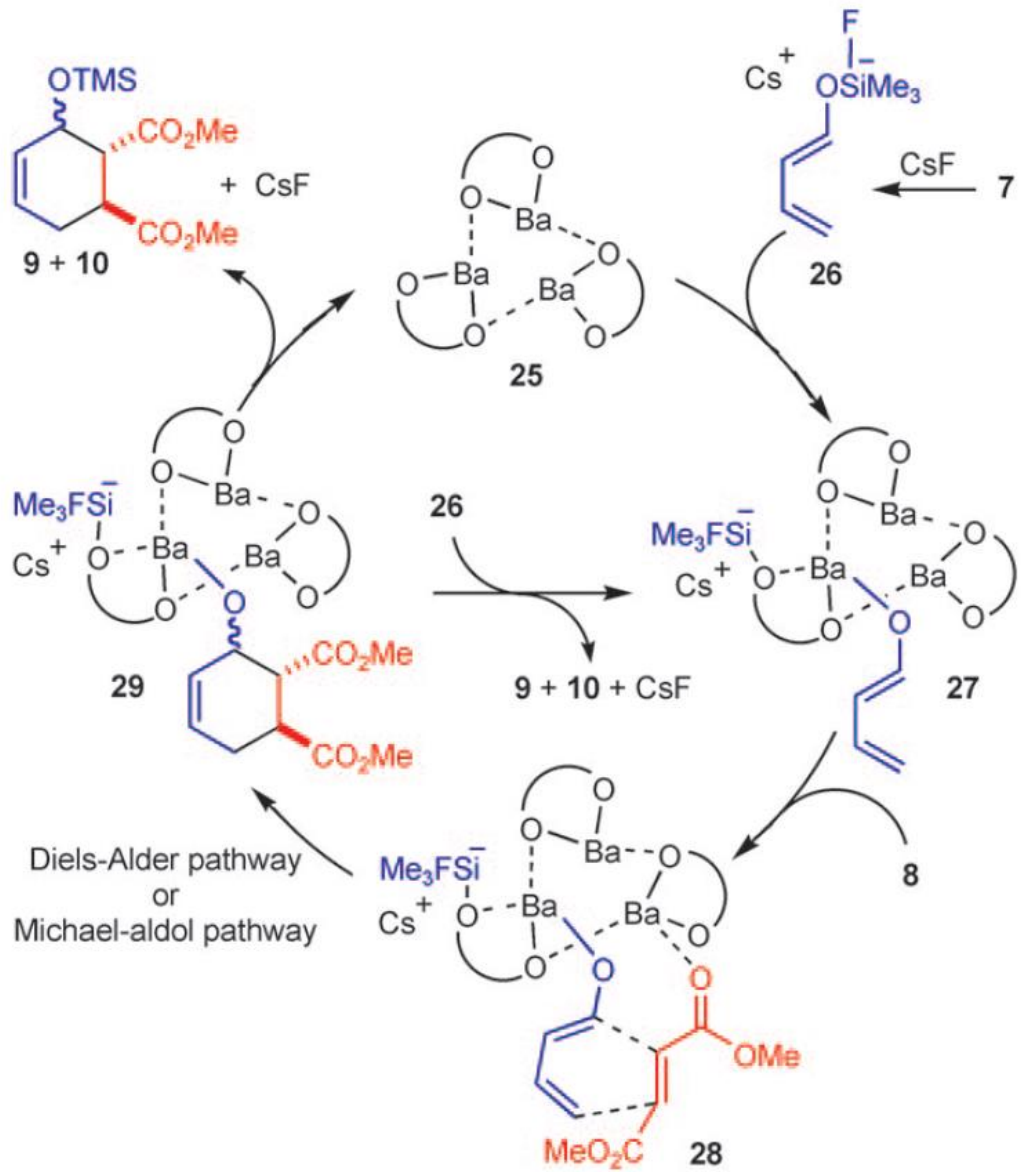
Shikimic acid

A

2)



3) Proposed catalytic cycle



Hoffman rearrangement