New Synthetic Routes to Tamiflu

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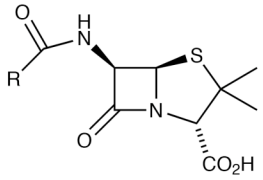
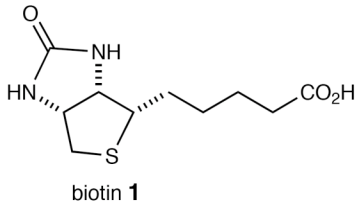
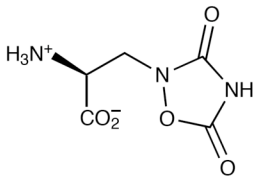
Chiral 1,2 Diamines

Natural Products

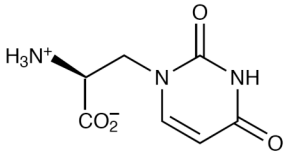




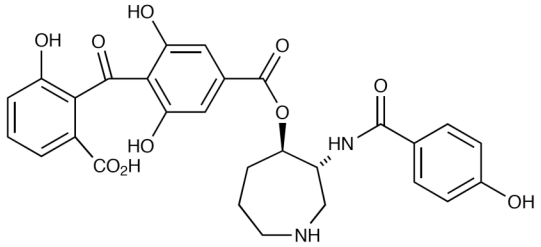
biotin **1**



L-quisqualic acid **3**

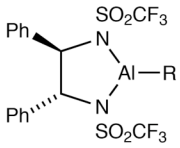


willardiine **4**



balanol **13**

Chiral Ligands



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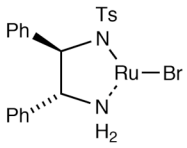

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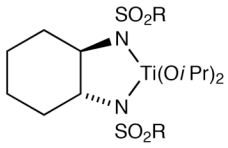

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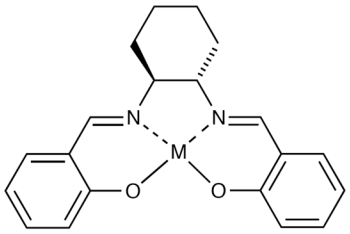

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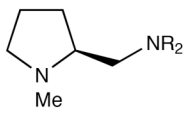

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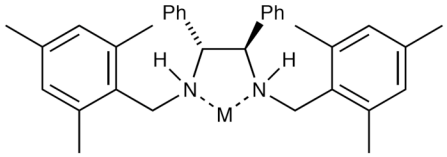
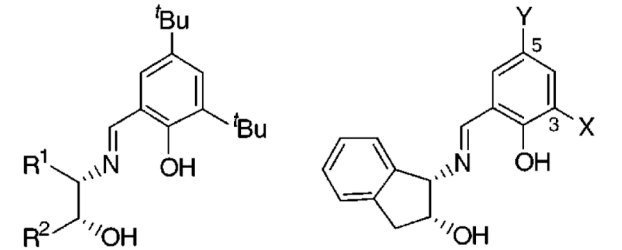


69

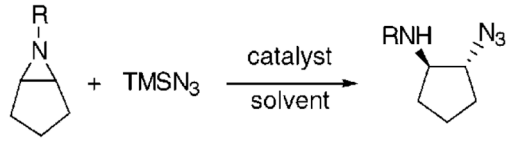
T. Gall, *Angew. Chem. Int. Ed.,* **1998,** 2580

Early Example of Desymmetrization of Aziridines



4: R^1= Ph, R^2= H
5: R^1= R^2= Ph
6: R^1, R^2= $CH_2(CH_2)_2CH_2$

7: X= Y= ^{t}Bu
8: X= Adamantyl, Y= Me
9: X= $SiMe_3$, Y= H
10: X= $SiMe(Ph)_2$, Y= H



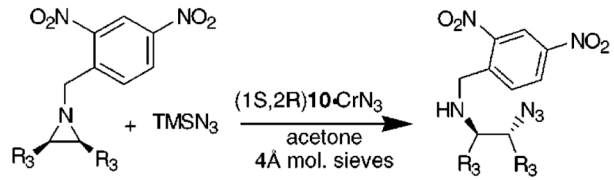
2 R = 2,4-dinitrobenzyl **3**

Table 1. Asymmetric Ring Opening of *N*-2,4-Dinitrobenzyl Cyclopentene Imine (**2**) Catalyzed by Cr(III) Complexes of Ligands **4**−**10**[a]

ligand	**4**	**5**	**6**	**7**	**8**	**9**	**10**
ee (%)[b]	4	7	24	66	64	69	70
convn (%)[c]	30	50	60	100	100	100	100

[a] Reactions were carried out at room temperature in acetone with 5 mol % of catalyst. [b] Enantiomeric excesses were determined by HPLC analysis of crude reaction mixtures. [c] Reaction time was 24 h for **4**−**6** and 3 h for **7**−**10**.

Table 2. Enantioselective Ring Opening of Meso *N*-2,4-Dinitrobenzyl Aziridines Catalyzed by **10**·CrN_3[a]



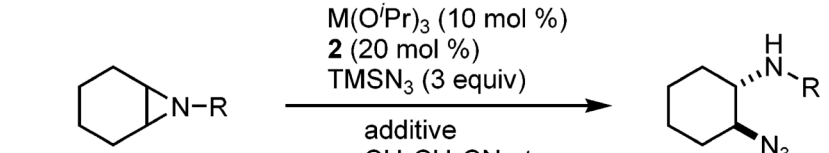
entry	R_3	R_3	temp (°C)	time (h)	isolated yield (%)	ee (%)[b]
1	-$(CH_2)_4$-		−30	48	95	94
2	-CH_2CH=$CHCH_2$-		−30	100	75	88
3	-$(CH_2)_3$-		−30	72	87	87
4	-CH_2OCH_2-		−15	90	73	90
5	Me	Me	−30	96	80	83

[a] Reactions were carried out with 10 mol % catalyst and 4 Å molecular sieves (ca. 1:1 w/w relative to the aziridine substrate). [b] Enantiomeric excesses were determined by HPLC analysis of crude reaction mixtures.

E. Jacobsen, *Org. Lett.* **1999**, 1611

Desymmetrization of *meso*-Aziridines with $TMSN_3$

Table 1. Optimization of Reaction Conditions

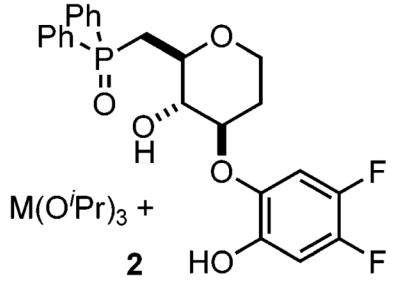


3a: R = 4-nitrobenzoyl
3b: R = 3,5-dinitrobenzoyl

4a or **4b**

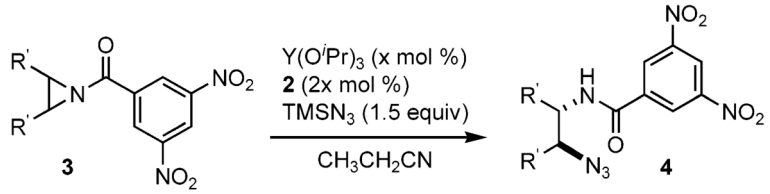
entry	M	substrate	additive[a]	time (h)	yield (%)[b]	ee (%)[c]
1	Gd	**3a**	DMP, TFA	20	>99	46
2	Gd	**3a**	DMP	20	>99	64
3	Gd	**3a**	none	20	>99	66
4	Gd	**3b**	none	16	90	85
5	Dy	**3b**	none	16	93	90
6	Er	**3b**	none	16	89	89
7	Yb	**3b**	none	16	91	82
8	Sc	**3b**	none	16	90	63
9	Y	**3b**	none	1	90	92

[a] DMP = 2,6-dimethylphenol (1 equiv was used). TFA = trifluoroacetic acid (5 mol % was used). [b] Isolated yield. [c] Determined by chiral HPLC.



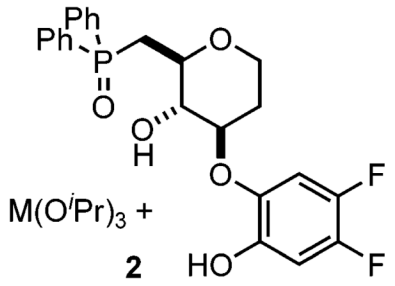
Desymmetrization of *meso*-Aziridines with $TMSN_3$

Table 2. Catalytic Enantioselective Desymmetrization of *meso*-Aziridines with $TMSN_3$



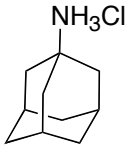
entry	substrate (R = 3,5-$(NO_2)_2$-Bz)		temp. (°C)	catalyst (x mol %)	time (h)	yield (%)[a]	ee (%)[b]
1[c]	NR	**3b**	0	1	36	97	92[d]
2	NR	**3c**	r.t.	5	36	>99	94
3	NR	**3d**	40	10	20	94	86
4			40	5	48	93	83
5	NR	**3e**	r.t.	2	48	96	91[d]
6	NR	**3f**	r.t.	2	48	98	91
7	O NR	**3g**	40	10	18	>99	96
8	CbzN NR	**3h**	r.t.	5	48	>99	94
9	Me NR Me	**3i**	r.t.	1	48	94	95[d]
10	*n*-Pr NR *n*-Pr	**3j**	r.t.	5	48	>99	87
11	Ph NR Ph	**3k**	r.t.	2	48	>99	93

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Three equivalents of $TMSN_3$ was used. [d] The absolute configuration was determined as shown.

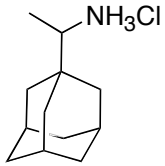


The Importance of Tamiflu

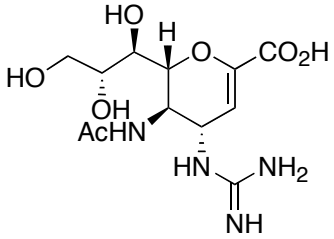
- There are currently 4 drugs for the treatment of influenza infections.



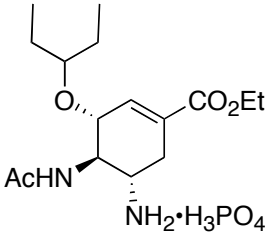
Amantadine



Rimantadine



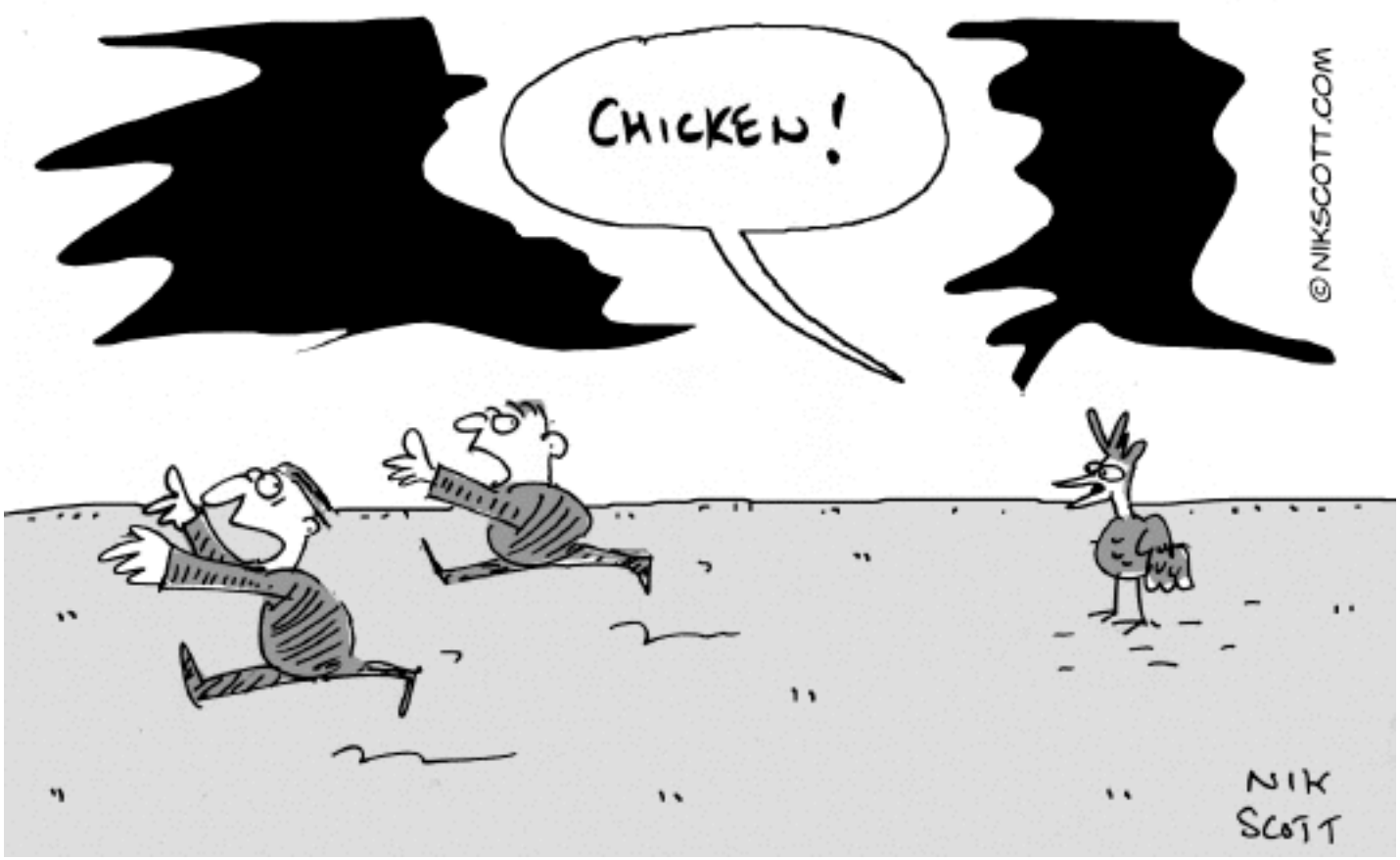
Zanamivir
(Relenza)



Oseltamivir
(Tamiflu)

- The neuraminidase inhibitors, Zanamivir (Relenza) and Oseltamivir (Tamiflu), have little toxicity and do not promote drug resistance.
- If the H5N1 virus becomes readily transmitted through human-human contact, the treatment of choice would be Tamiflu.

A. Moscona, *N. Eng. J. Med.*, **2005**, 353


CHICKEN!
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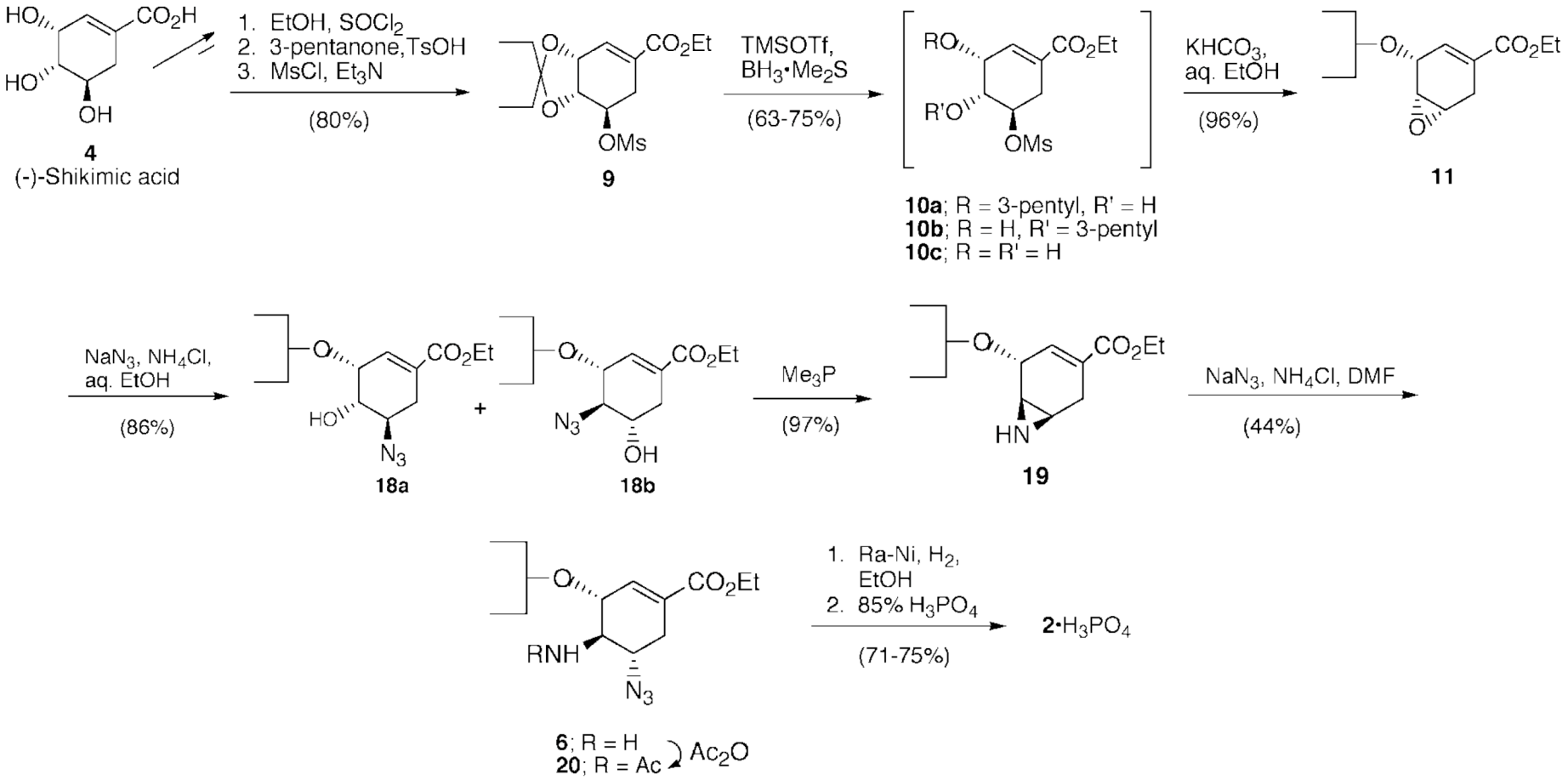
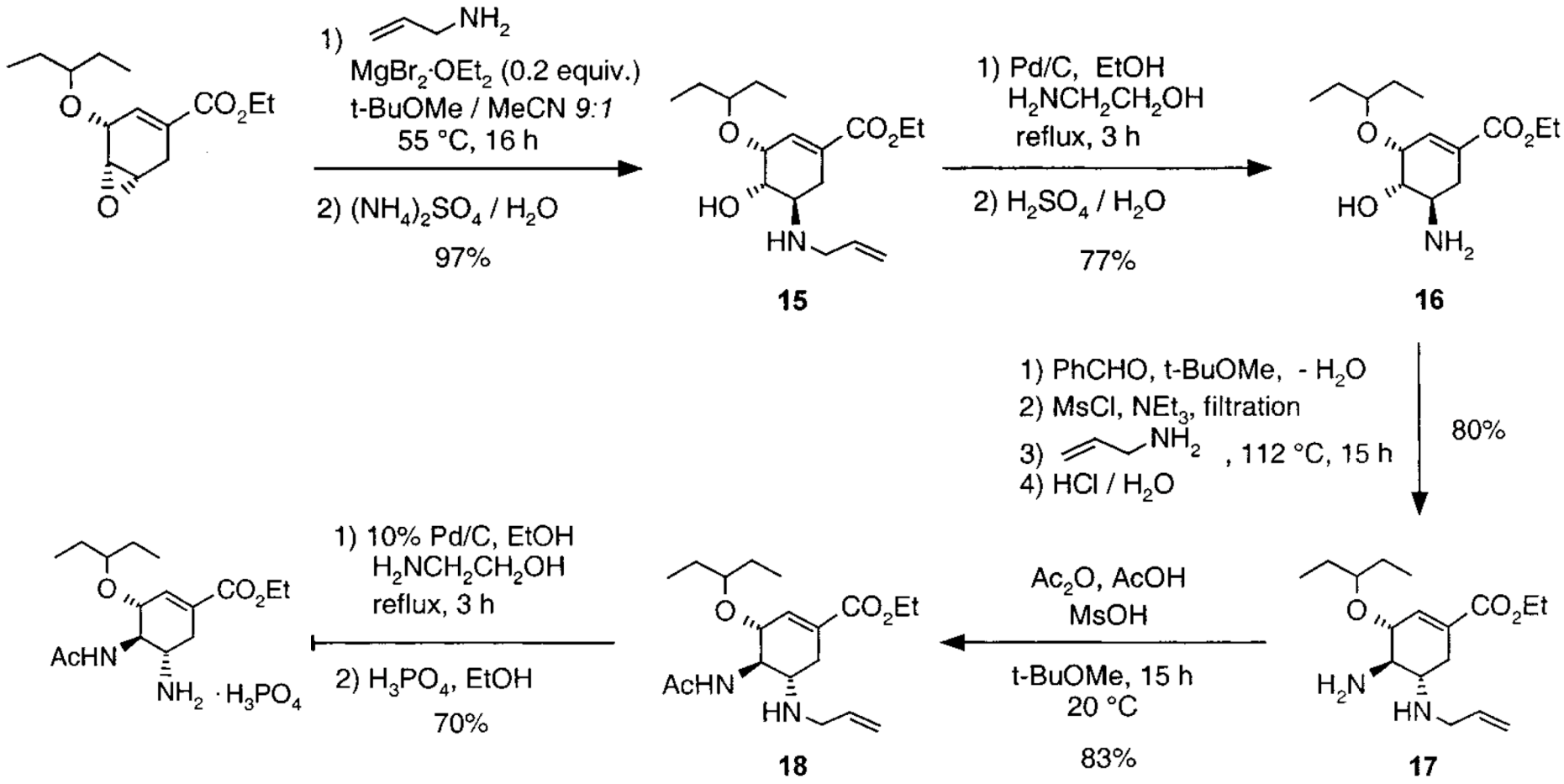
First Route to Tamiflu



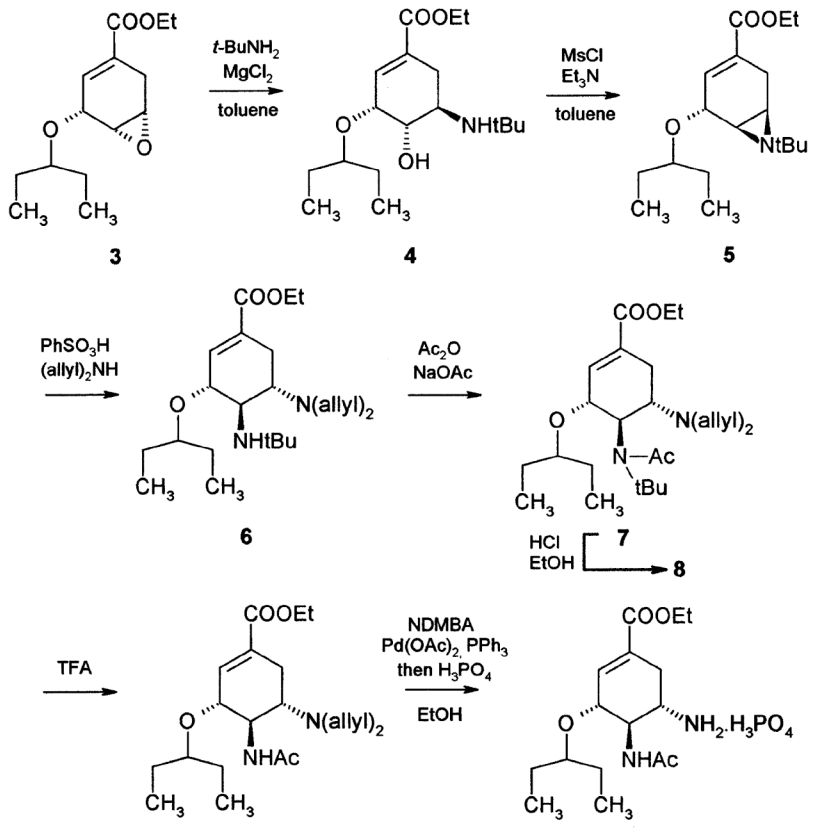
J. Rohloff, *J. Org. Chem.* **1998**, 4545

Second Route to Tamiflu



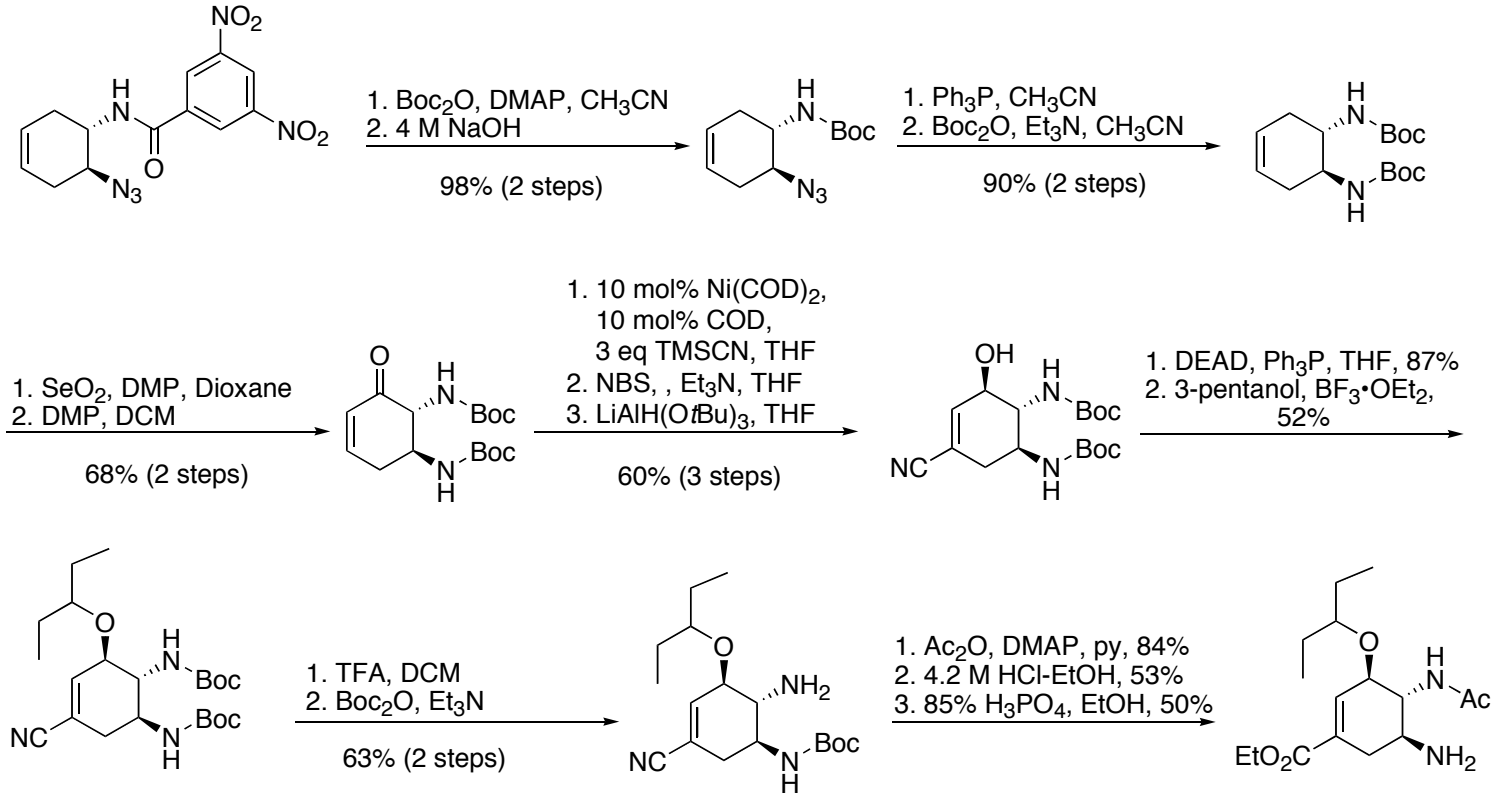
M. Karpf, *J. Org. Chem.,* **2001,** 2044

Third Route to Tamiflu

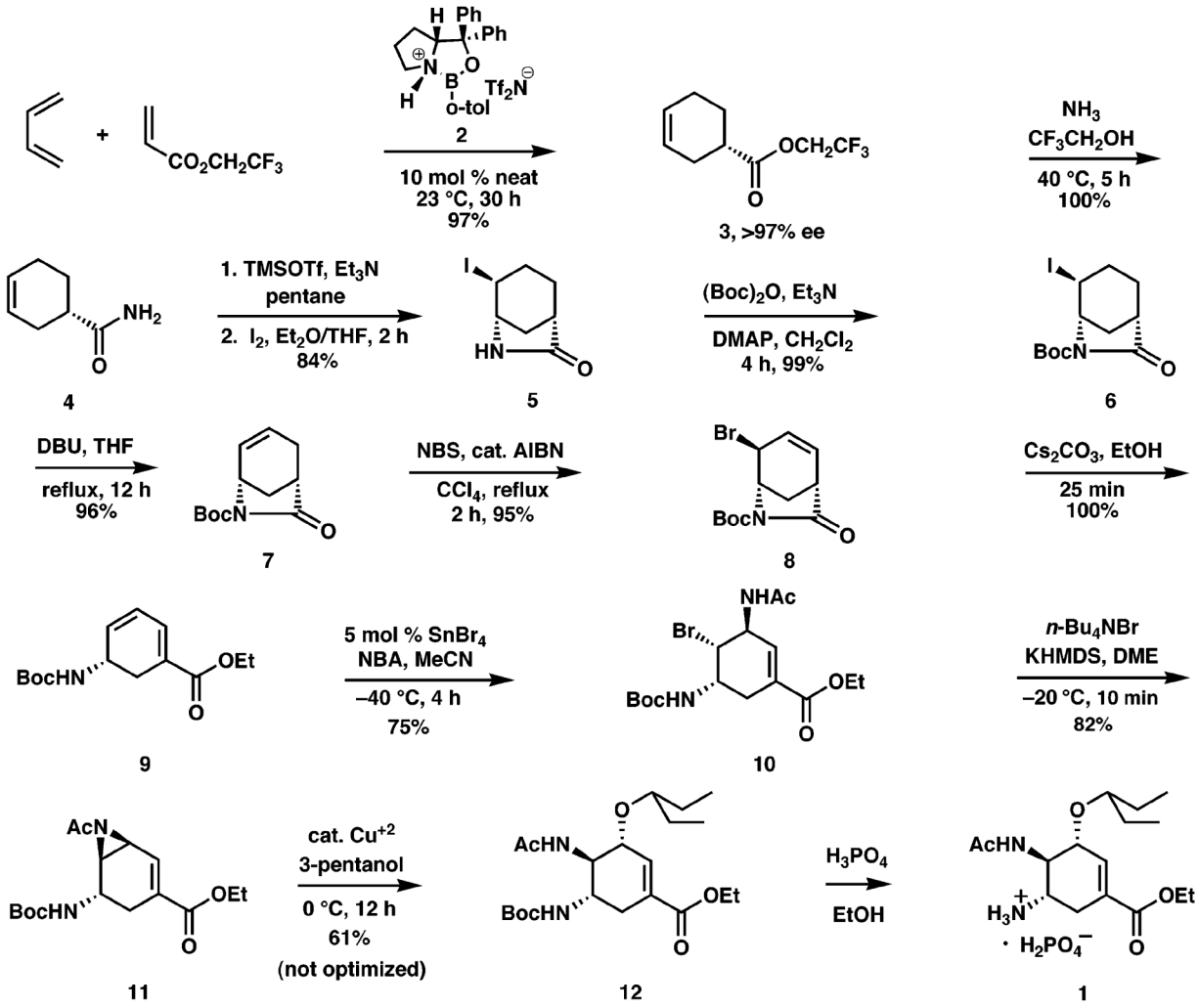


P. Harrington, *Org. Pro. Res. Dev.* **2004,** 86

Shibasaki Route to Tamiflu



Corey Route to Tamiflu



Conclusion

- The key step in the Shibasaki synthesis are a catalytic enantioselective desymmetrization of a *meso*-aziridine.
- The key steps in the Corey route are a enantioselective Diels-Alder, iodo-lactamization and bromoacetamidation.
- Both routes offer a new way to access Tamiflu that does not require the use of shikimic acid or quinic acid.
- "Although our route is already very efficient, it's conceivable that when you put new developments together, you'll have an even better and cheaper process. I think the Tamiflu supply problem is solved" E.J. Corey C&E News May 5th, 2006

Though the possibility does exist that each route could be modified, currently due to scalability issues with reagents, neither route offers a viable alternative to process route.