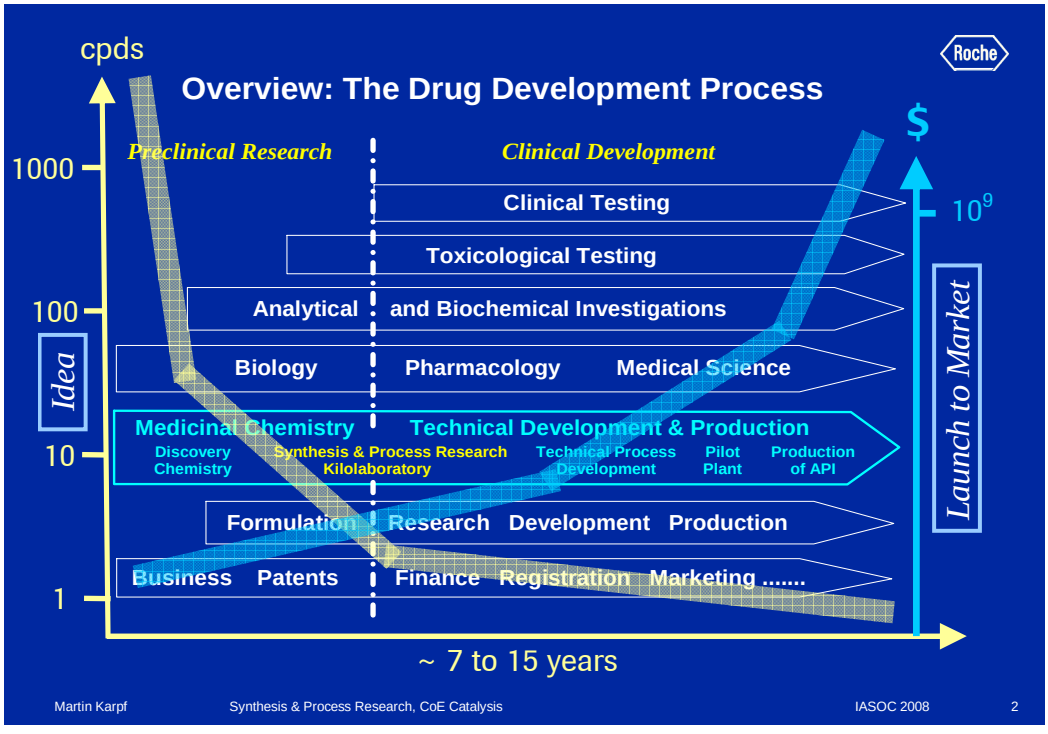
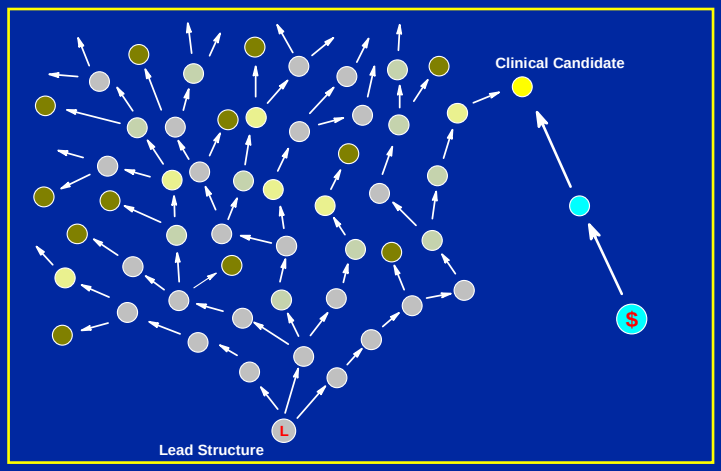
From Milligrams to Tons: The Importance of Synthesis & Process Research in the Development of New Drugs

Martin Karpf *Synthesis & Process Research*
CoE Catalysis



Why Synthesis & Process Research ?

Synthetic Strategies: **Discovery Chemistry** *Diversity* **vs.** *vs.* **Synthesis & Proc. Research** *Target Orientation*



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Prof. Ryoji Noyori
Nobel Laureate 2001

"chemical synthesis with practical elegance"

key requirements:

- **absolute efficiency using perfect chemical reactions**
  ► 100% selectivity & 100% yield
- **economical processes ► no unwanted wastes**
- **environmentally friendly ► resource and energy-saving**

"The need for efficient and practical synthesis remains one of the greatest intellectual challenges with which chemists are faced in the 21st Century"

R. Noyori, *Adv. Synth. Catal.* **2001**, *343*, 1

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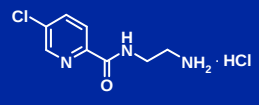
Synthesis & Process Research at Roche

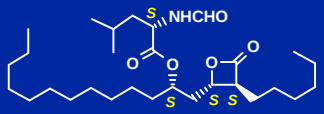
"comparing" number of synthetic steps and overall yield :

Tempium™ (Alzheimers D.)
Lazabemide:



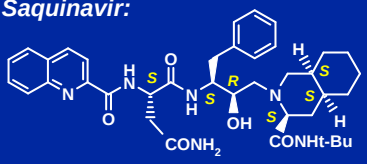
Discovery Chemistry: 9 (8%)
Synth. & Proc. Research: 1 (75%)

Xenical™ (Obesity)
Tetrahydrolipstatin:



12 (2%)
8 (22%)

Invirase™ (HIV)
Saquinavir:



Discovery Chemistry: 25 (5%)
Synth. & Proc. Research: 10 (50%)

Tamiflu™ (Influenza)
Oseltamivir Phosphate:

16 (5%)
10 (35%)

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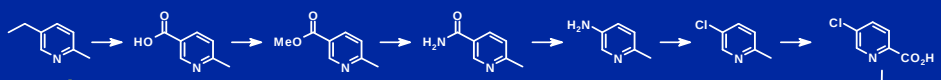
Tempium™ (Lazabemide): MAO-B-Inhibitor => Alzheimer's Disease

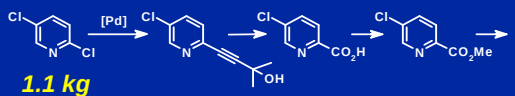


~ 26 kg

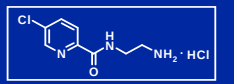
Discovery Chemistry Synthesis
Drug Discovery
9 Steps
overall yield 2 - 8%

R. Imhof, E. Kyburz,
Patent CH 1984-4132 **(1984)**

Synthesis Research & Catalysis
Alkynylation
4 Steps
overall yield 58%



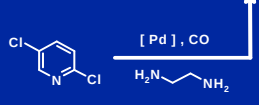
1.1 kg



1 kg

M. Scalone, P. Vogt,
Patent EP385210 **(1990)**

Synthesis Research & Catalysis
(2nd Generation Synth.):
Carbonylation
1 Step
overall yield 75%



0.8 kg

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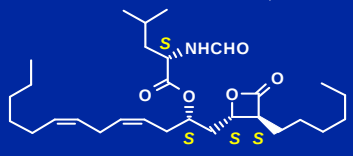
Xenical™: Pancreatic Lipase Inhibitor => Obesity

Tetrahydrolipstatin

H_2 / Pd(C)

fermentation:
streptomyces toxytricini



Lipstatin

Linoleic Acid

E.K. Weibel et al., *J. Antibiotics* **1987**, *40*, 1081

W. Weber et al., *EP 803576* (**1997**)

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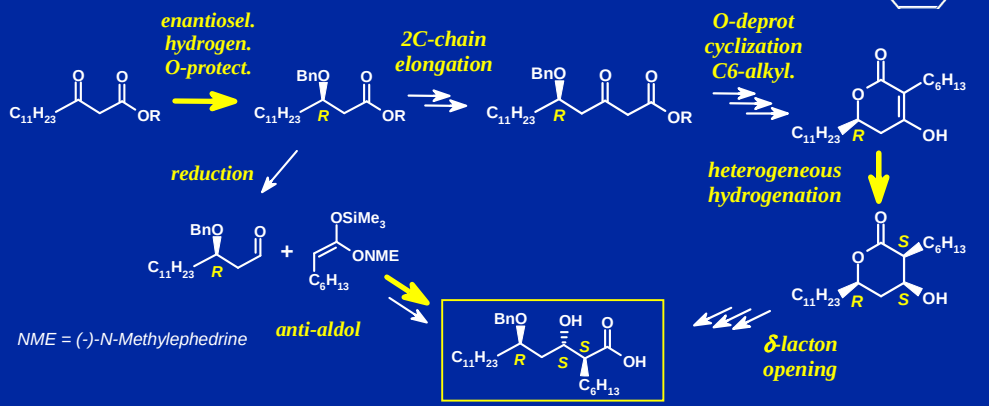
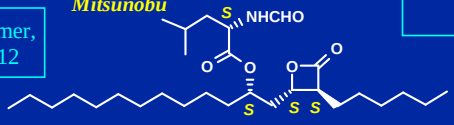
Tetrahydrolipstatin: Control of Configuration



β-lactone form. O-deprot. Mitsunobu



Tetrahydrolipstatin

P. Barbier, F. Schneider, U. Widmer, *Helv. Chim. Acta* **1987**, *70*, 1412

U. Zutter, M. Karpf, EP 443449 (**1991**)

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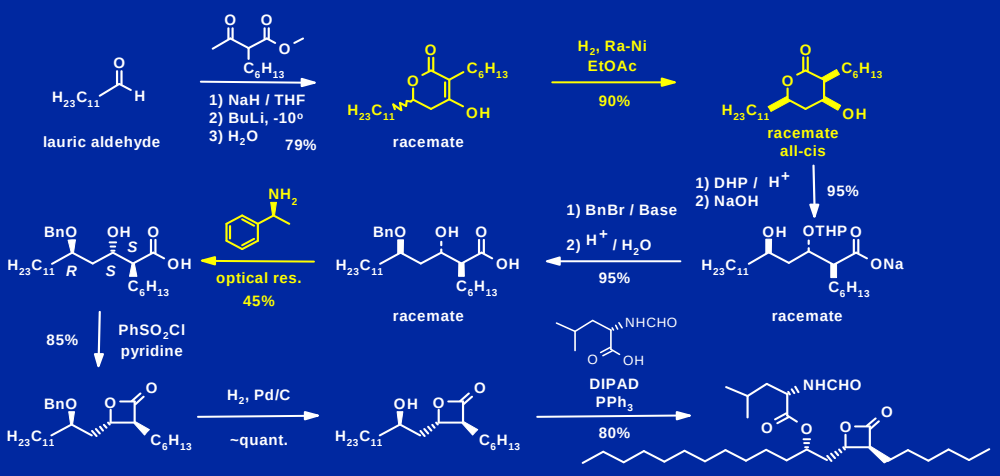
Current Technical Synthesis of Tetrahydrolipstatin

via rac.-Dihydropyrone and Optical Resolution



U. Zutter, M. Karpf, EP 443449 (**1991**)

number of steps: 8
overall yield: 20 - 22%

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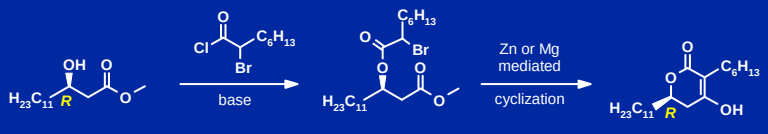
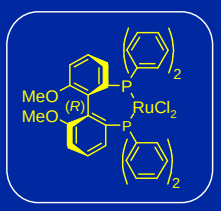
Enantioselective Approach to the (*R*)-Dihydropyrone



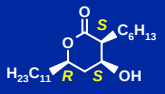
Hydrogenation Conditions:

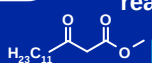
catalyst:	**[Ru(OAc)$_2$((*R*)-MeOBIPHEP)]**
S/C:	**50'000**
H$_2$ pressure:	**40 bar**
solvent:	**MeOH**
conc:	**40 wt.-%**
temp:	**80°C**
reaction	**4 to 22 h (<99.9% conv)**



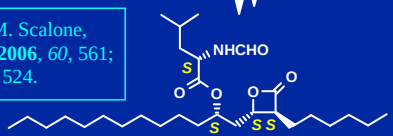
H$_2$, Ra-Ni 90%

99%
>99% ee





R. Birk, M. Karpf, K. Püntener, M. Scalone, M. Schwindt, U. Zutter, *Chimia* **2006**, *60*, 561; Org. Proc. Res. & Dev. **2007**, *11*, 524.



number of steps: 9
overall yield: 38 - 40%

Tetrahydrolipstatin

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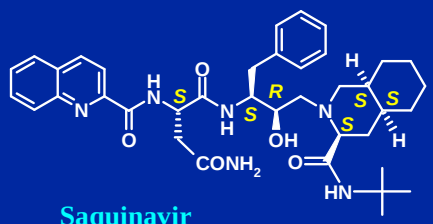
Invirase™ (Saquinavir): HIV-Protease Inhibitor => Aids



Saquinavir
INVIRASE™

Basler Zeitung

"..... the molecule has an extremely complicated structure and its synthesis requires 21 steps: experts doubt if Roche or anybody else will ever be in the position to produce enough material even if it will ever reach the market ....."

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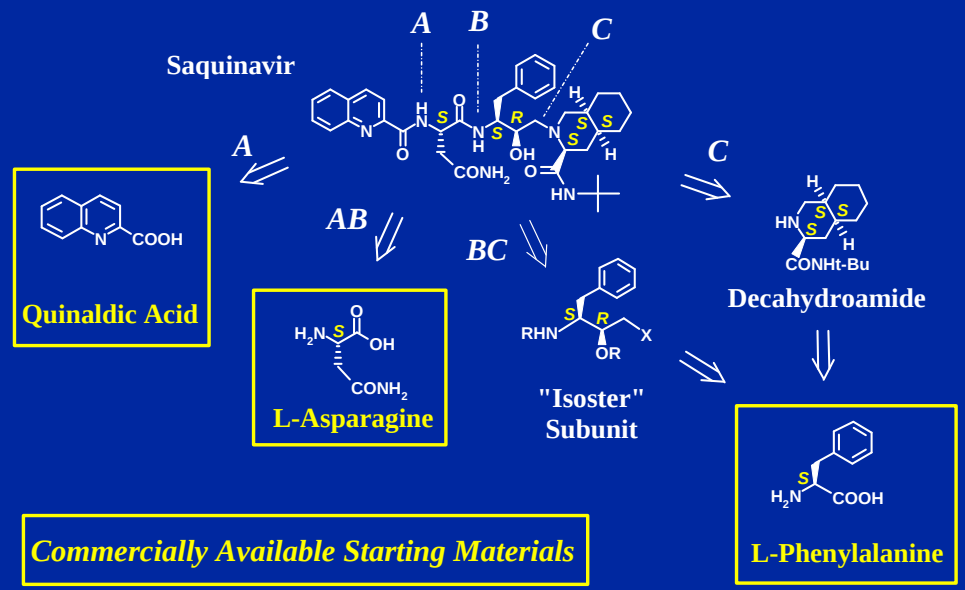
Saquinavir: The Starting Materials



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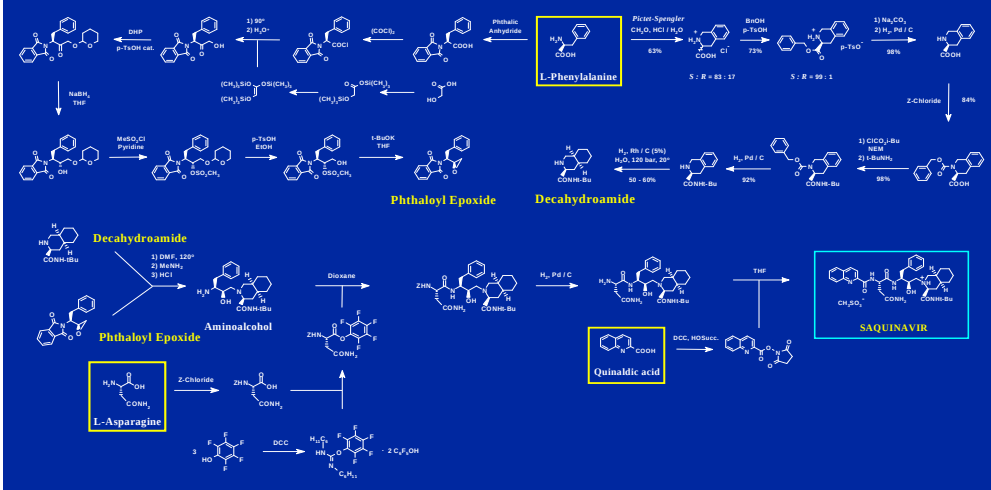
Discovery Chemistry Synthesis of Saquinavir



S. Redshaw et al. :
Science **1990**, *248*, 358;
J. Org. Chem. **1994**, *59*, 3656

- steps 25
- overall yield 5%

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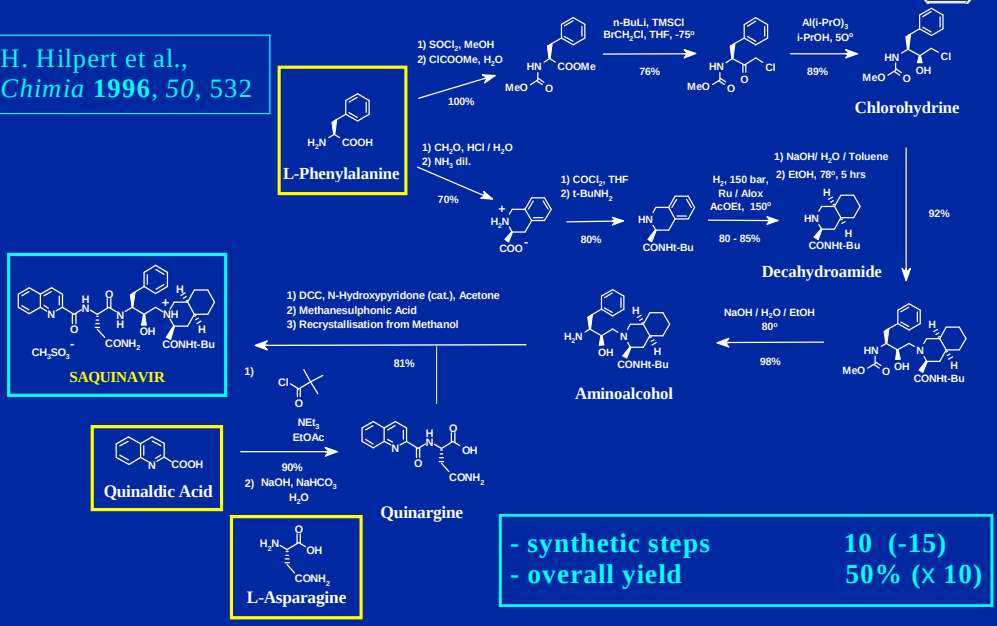
Commercial Synthesis of Saquinavir

H. Hilpert et al.,
Chimia **1996**, *50*, 532



- synthetic steps 10 (-15)
- overall yield 50% (x 10)

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The Synthetic-Technical Development of Invirase™

Synthesis	*Steps*	*overall yield*	*required for* **1 T on** active drug	
			Reagents	**Solvents**
Discovery Route	25	5%	700 T	176
Trouble Shooting	25	20%	88 T	23
Scalable Synthesis	16	26%	80 T	17
Commercial Synthesis	**10**	**50%**	**13 T**	**3**

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Marketed Anti-Influenza Neuraminidase Inhibitors

TAMIFLU™ (Oseltamivir Phosphate)

Ro 64-0796 / GS-4104 — *oral Bioavail. ~ 80%*, *IC_{50} ~1 nM (Acid)*, *$t_{1/2}$ ~ 2.6 h*

Use Oral Treatment and Prevention of Influenza Virus Infections (Viral Flu)

Originator Gilead Sciences, California, Kim et al.
Patent February 1995
NDA April 1999
Launch November 1999

Competitor: GlaxoSmithKline

RELENZA™ (Zanamivir)

GG-167 — *oral Bioavail. ~ 4%*, *IC_{50} ~1 nM*, *$t_{1/2}$ ~ 18 min*

Use Topical Treatment of Influenza Application via Disk Inhaler

Originator Biota Holdings, Australia, von Itzstein, Monash University
Patent April 1990
NDA November 1998
Launch July 1999

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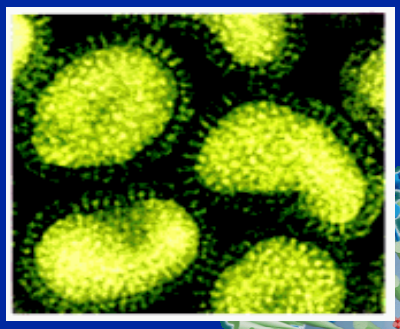
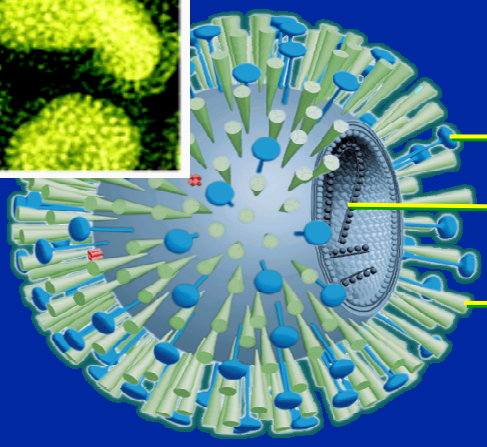
The Influenza Virus





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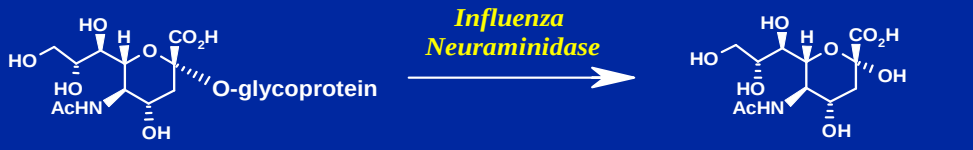
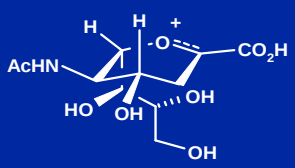
Role of Neuraminidase in Influenza Virus Replication

Cleavage of terminal sialic acid end groups of the glycoproteins on the infected cell surface allowing for the release of the newly formed viruses to infect new host cells



N-Acetyl-Neuraminic Acid
sialic acid

transition state



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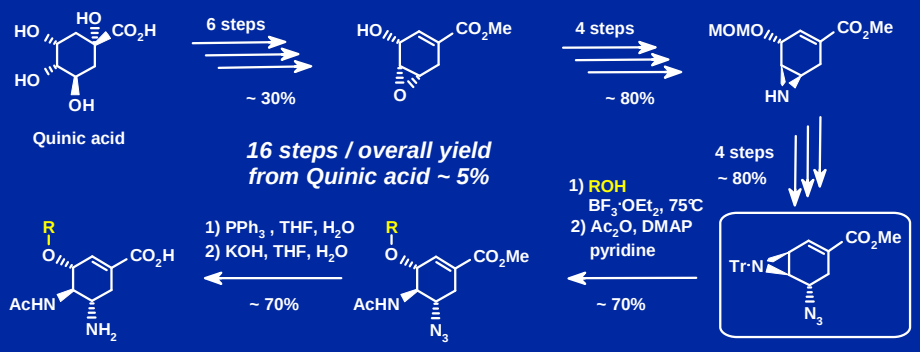
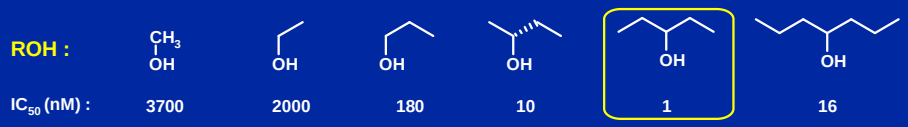
GILEAD Drug Discovery Synthesis





Kim et al., *J. Am. Chem. Soc.* **1997**, *119*, 681 & *J. Med. Chem.* **1998**, *41*, 2451

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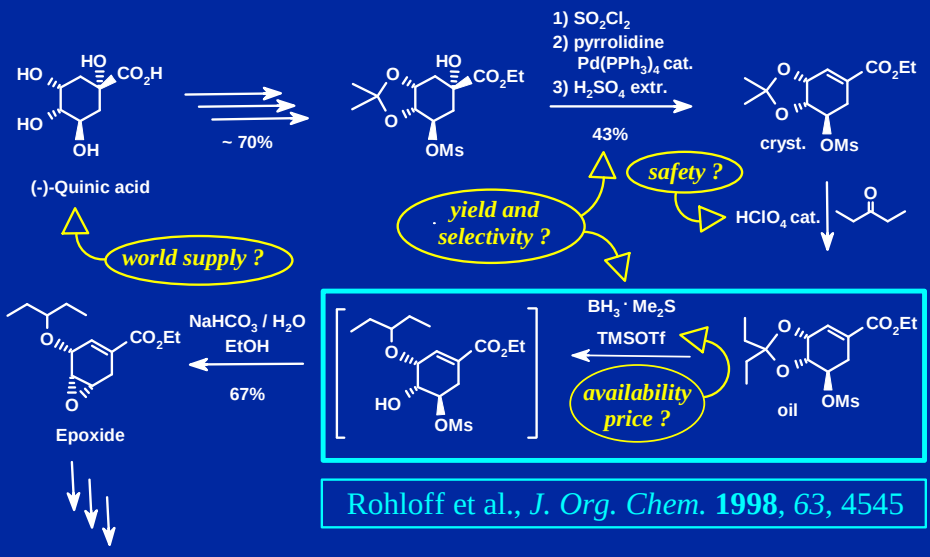
GILEAD Process Chemistry Synthesis of Oseltamivir Phosphate



Rohloff et al., *J. Org. Chem.* **1998**, *63*, 4545

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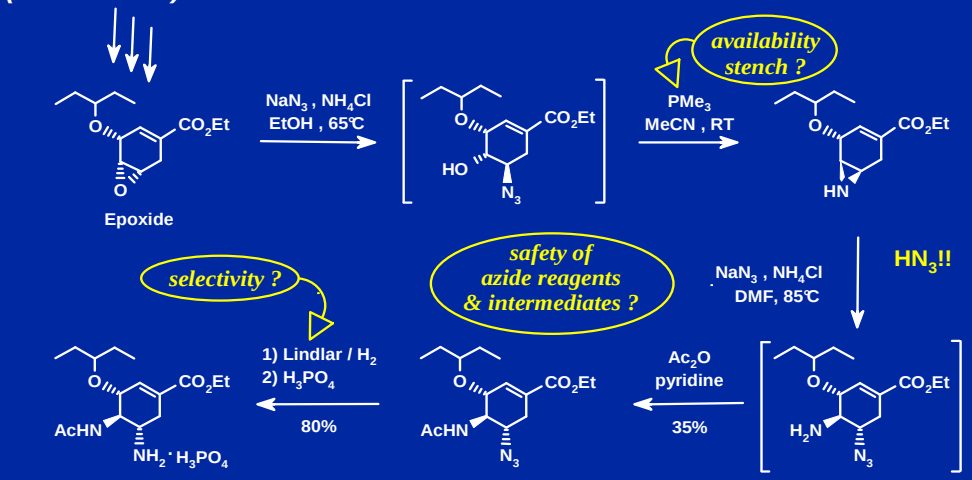
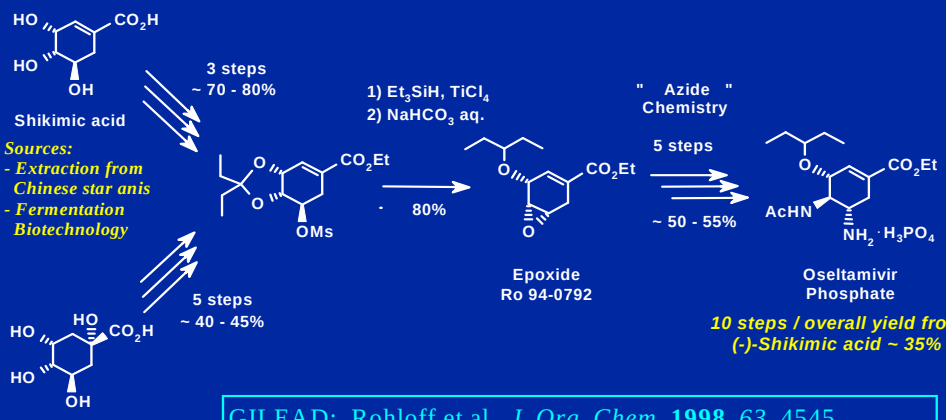
GILEAD Process Chemistry Synthesis of Oseltamivir Phosphate *(continued…)*



13 steps / overall yield from (-)-Quinic acid ~ 0 - 6%

Rohloff et al., *J. Org. Chem.* **1998**, *63*, 4545

Current Commercial Synthesis of Oseltamivir Phosphate



Sources:
- *Extraction from Chinese star anis*
- *Fermentation Biotechnology*

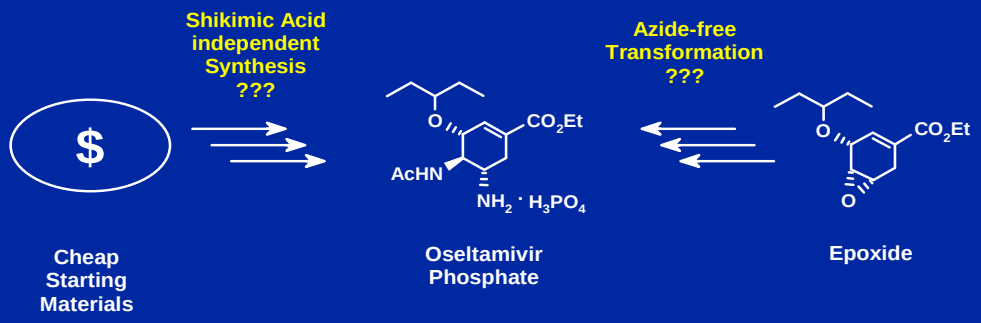
Source:
- *Extraction from the bark of Cinchona tree*

10 steps / overall yield from (-)-Shikimic acid ~ 35%

GILEAD: Rohloff et al., *J. Org. Chem.* **1998**, *63*, 4545
ROCHE : Karpf et al., *Chimia* **2007**, *61*, 93
(-)-SA : Frost, Weber et al., *Biotechnol. Prog.* **2003**, *19*, 808

Current Production Capacity: 400 metric Tons/Year

Early Questions for Synthesis & Process Research



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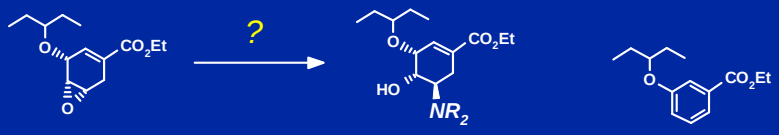
How to Replace Azide Reagents and Intermediates ?

Attempted Epoxide Ring Opening — **René Trussardi**



Selection of nitrogen nucleophiles tested:

CH_3CONH_2 $CH_3C(=NH)NH_2$ NH_3 $(NH_4)_2SO_4$ $NaN(CN)_2$ CH_3CN H_2NCN

$H_2NNH_2 \cdot HCl$ $EtO_2CNHNHCO_2Et$ H_2N–O–Bn / $SiMe_3$ Me_3Si–N(H / Li / K)–$SiMe_3$

Problems: aromatization, decomposition, no or non-selective reaction

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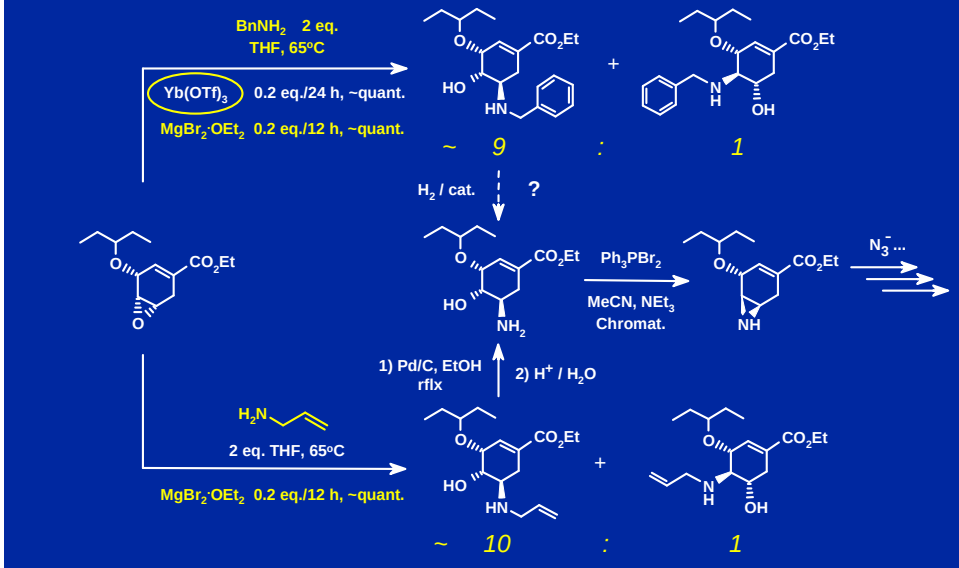
New Catalyst for Epoxide Ring Opening



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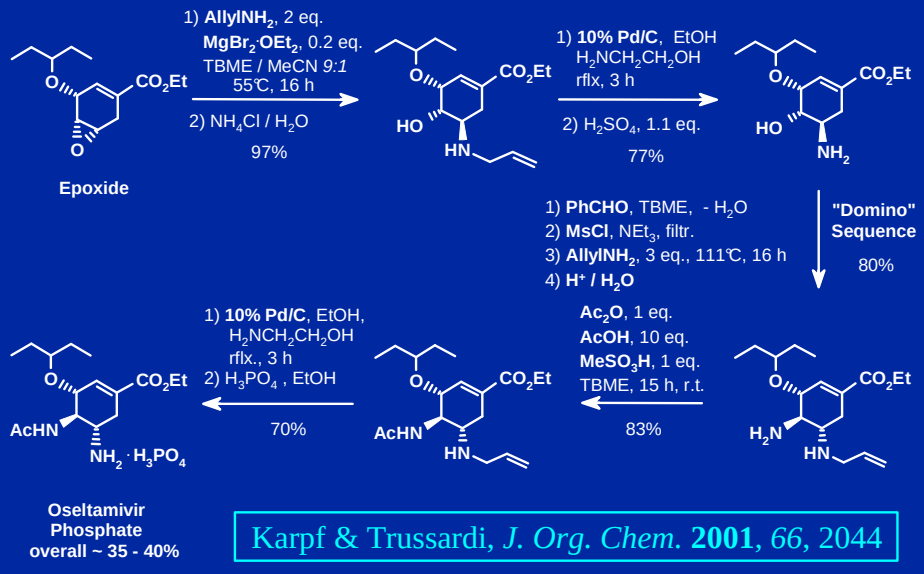
The "Allylamine Synthesis" of Oseltamivir Phosphate



Karpf & Trussardi, *J. Org. Chem.* **2001**, *66*, 2044

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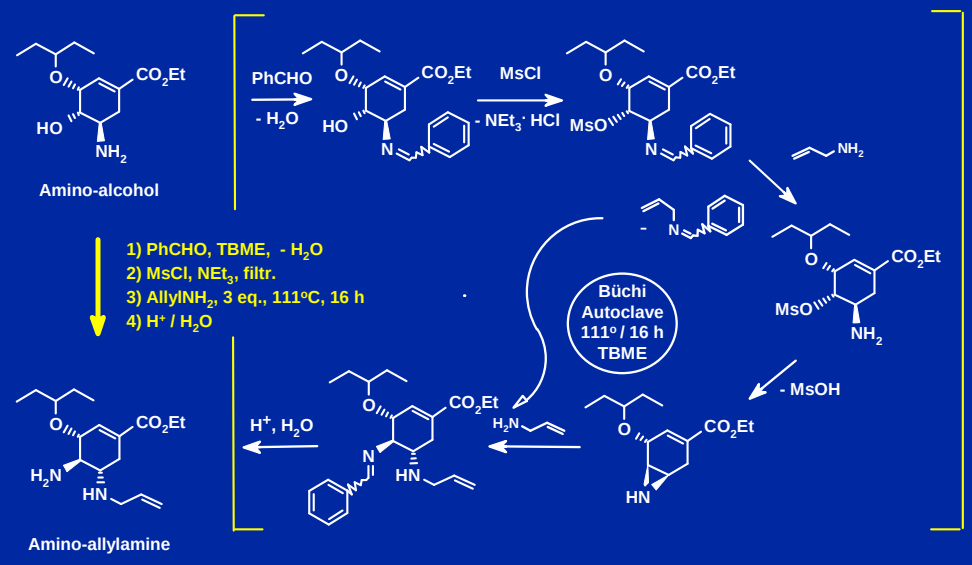
The "Domino" Sequence



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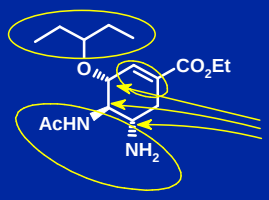
Evaluation of Shikimic Acid Independent Syntheses

The Key Problems:



- Efficient Induction of 3 Stereogenic Centers
- Regioselective Introduction of the 1,2-Double Bond
- Introduction of the 4,5-Amino Substituents
- Formation of the 3-Pentylether

Conceivable Solutions and Starting Materials:

- Diels-Alder Approaches
- Starting from Aromatic Rings & Transformation
- Ring Construction & Transformations
- Starting from Chiral Pool

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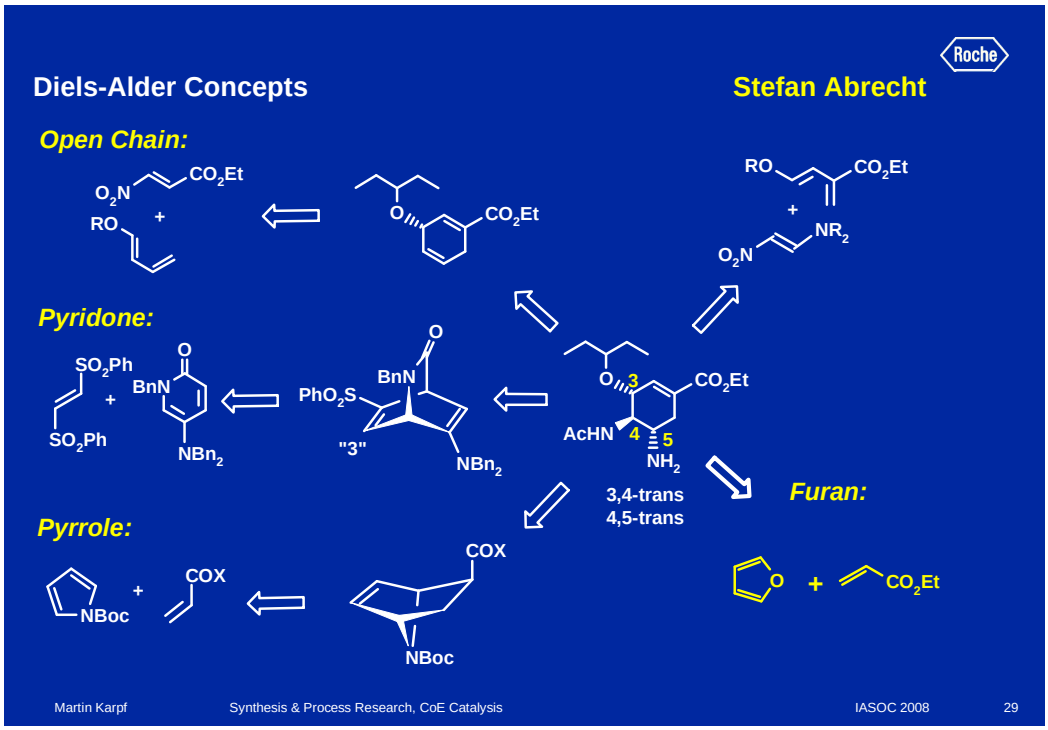
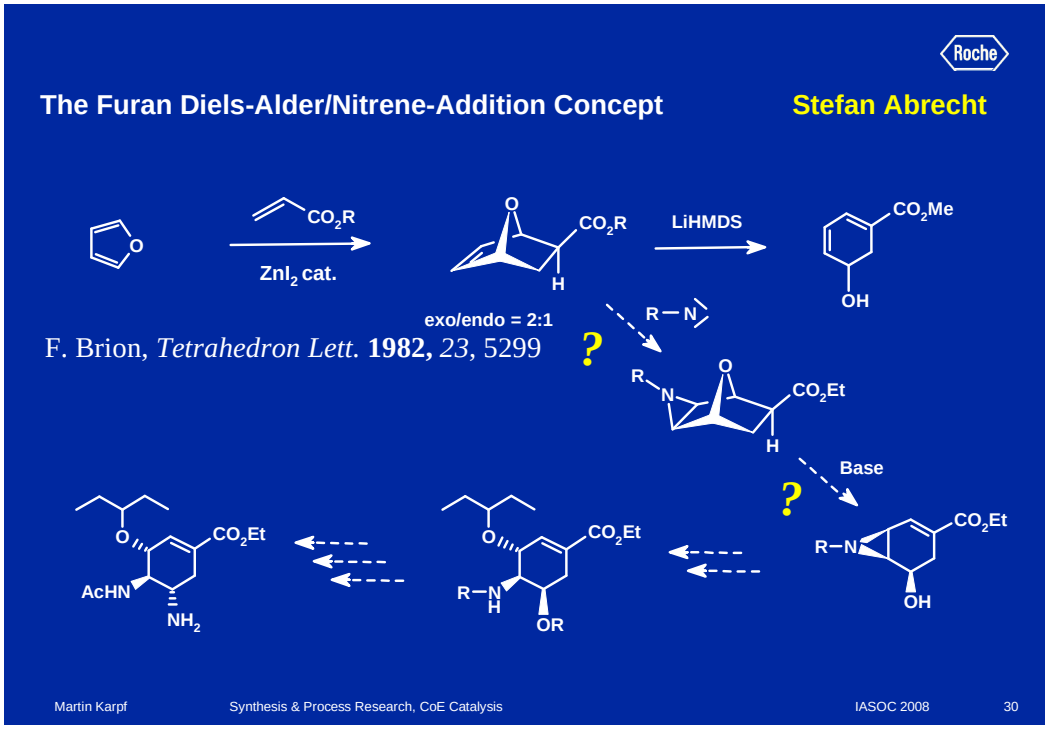
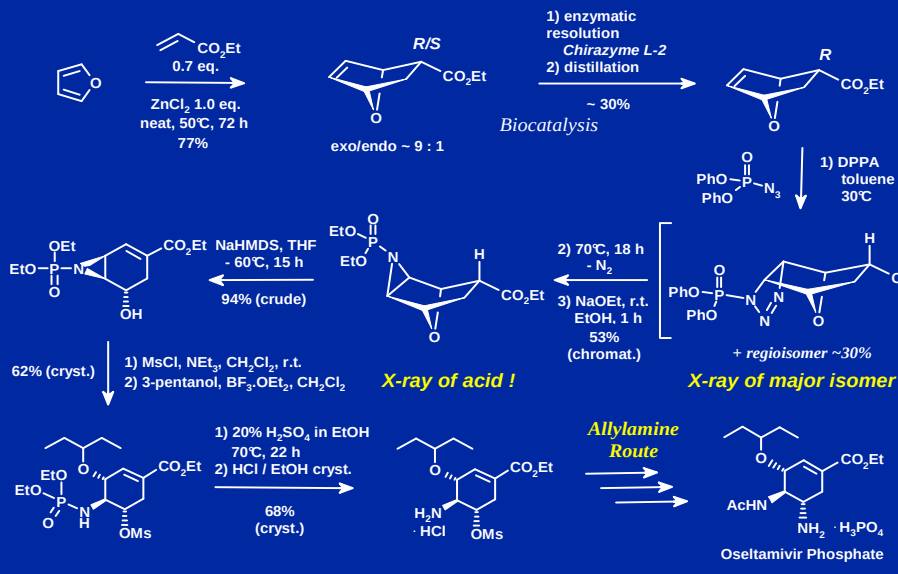

Roche
Diels-Alder Concepts
Stefan Abrecht
Open Chain:
Pyridone:
Pyrrole:
Furan:
3,4-trans
4,5-trans
Martin Karpf
Synthesis & Process Research, CoE Catalysis
IASOC 2008
29

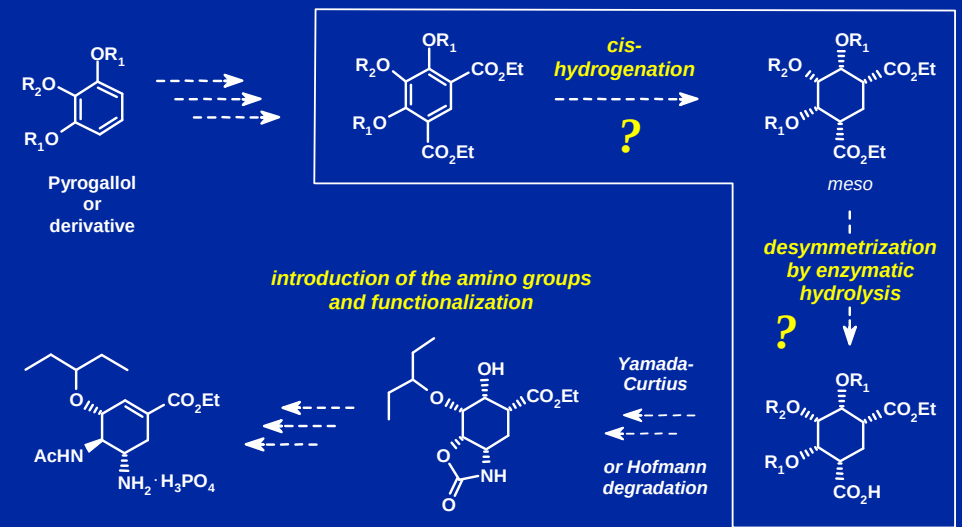

Roche
The Furan Diels-Alder/Nitrene-Addition Concept
Stefan Abrecht
ZnI2 cat.
LiHMDS
exo/endo = 2:1
F. Brion, Tetrahedron Lett. 1982, 23, 5299
Base
Martin Karpf
Synthesis & Process Research, CoE Catalysis
IASOC 2008
30

Furan Diels-Alder / Diphenylphosphoryl Azide Approach

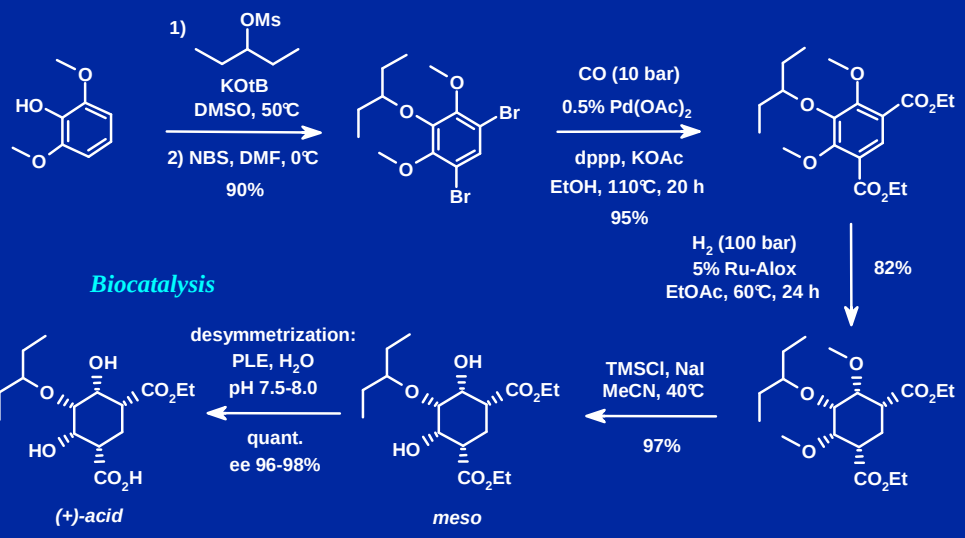


The Desymmetrization Concept

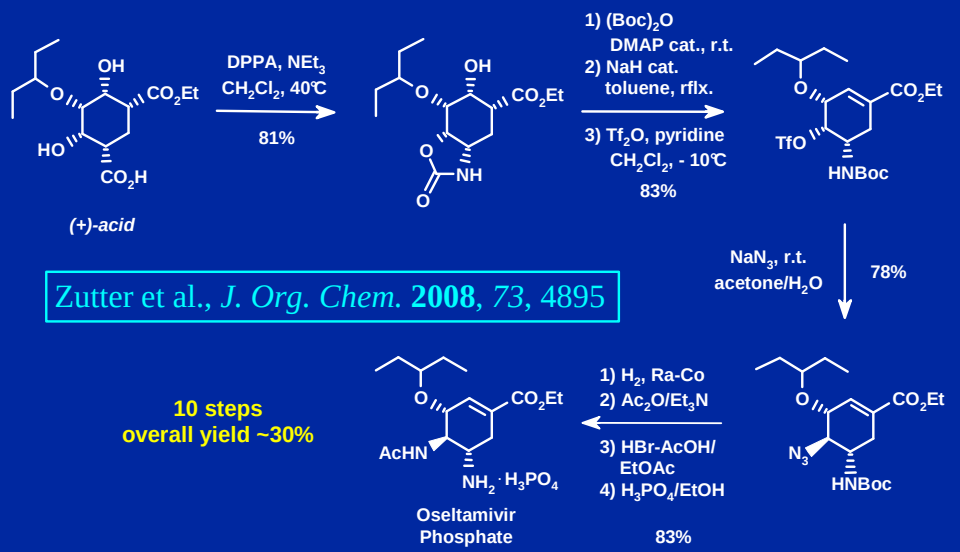
Ulrich Zutter



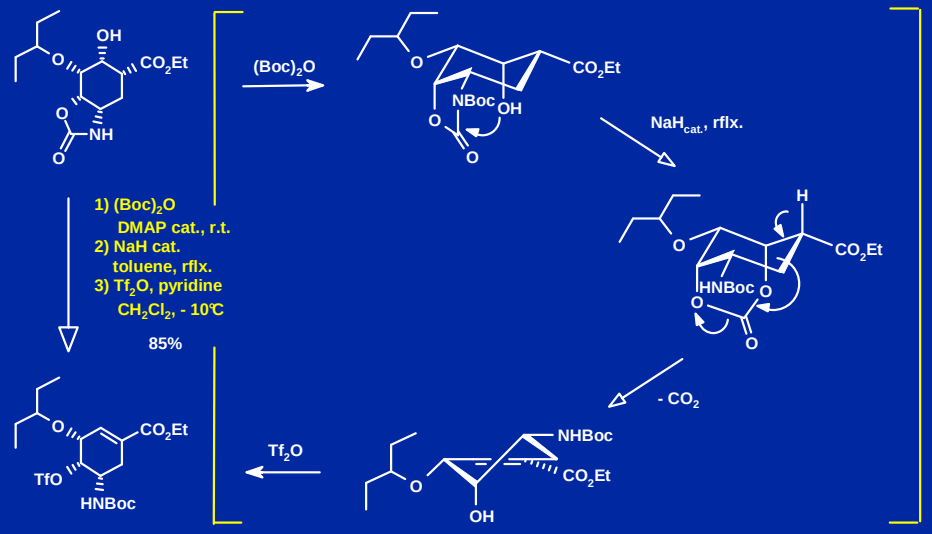
meso-Diester Synthesis and Desymmetrization



The Endgame: Introducing the Amino Functions



The Oxazolidinone Shortcut



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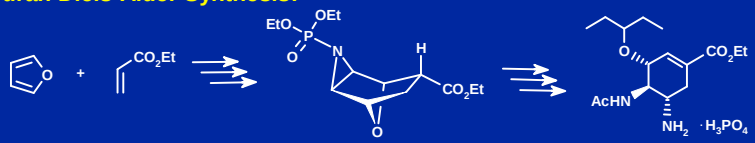
Results of

Synthesis & Process Research on Oseltamivir Phosphate

Azide-free Allylamine Synthesis:

Furan Diels-Alder Synthesis:



Oseltamivir Phosphate

Desymmetrization Approach:

M. Karpf et al.,
Chimia **2004**, *58*, 621;
Chimia **2007**, *61*, 93

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