Shikimic Acid – A Synthetic Star

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March 12th, 2019

Medicine

Process

Biosynthesis

Total Synthesis

Production

Applications

Outline

Introduction

Production

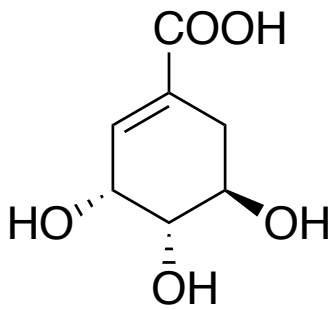
- Chemical Syntheses
- Biosynthesis
- Extraction from plant sources
- Fermentation

Synthetic Applications

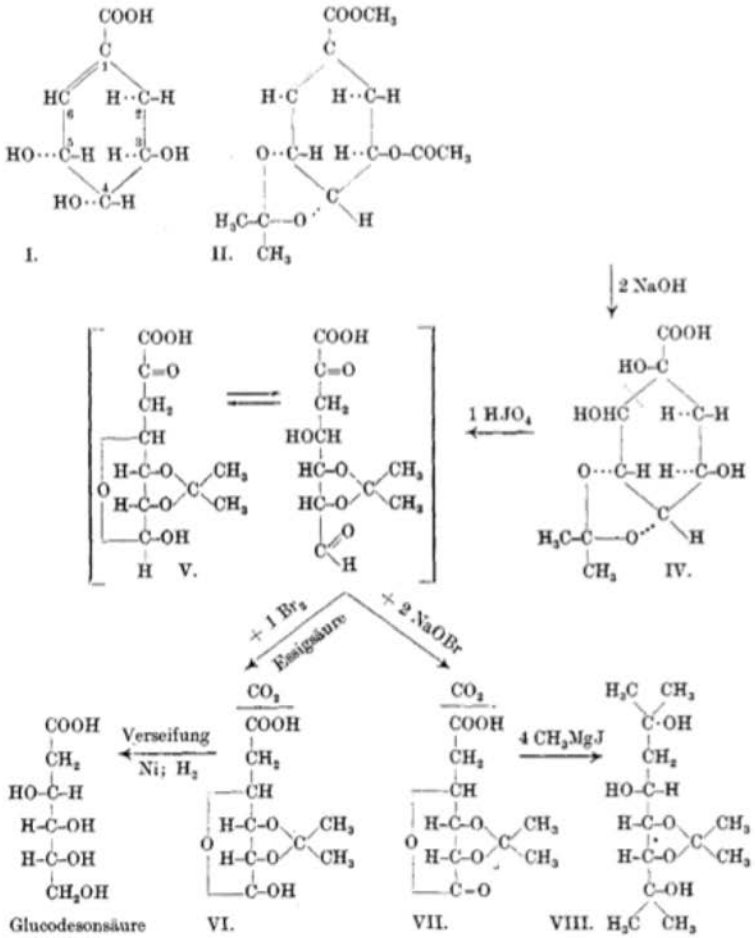
- Oseltamivir
- Total Synthesis
- Other Synthetic applications

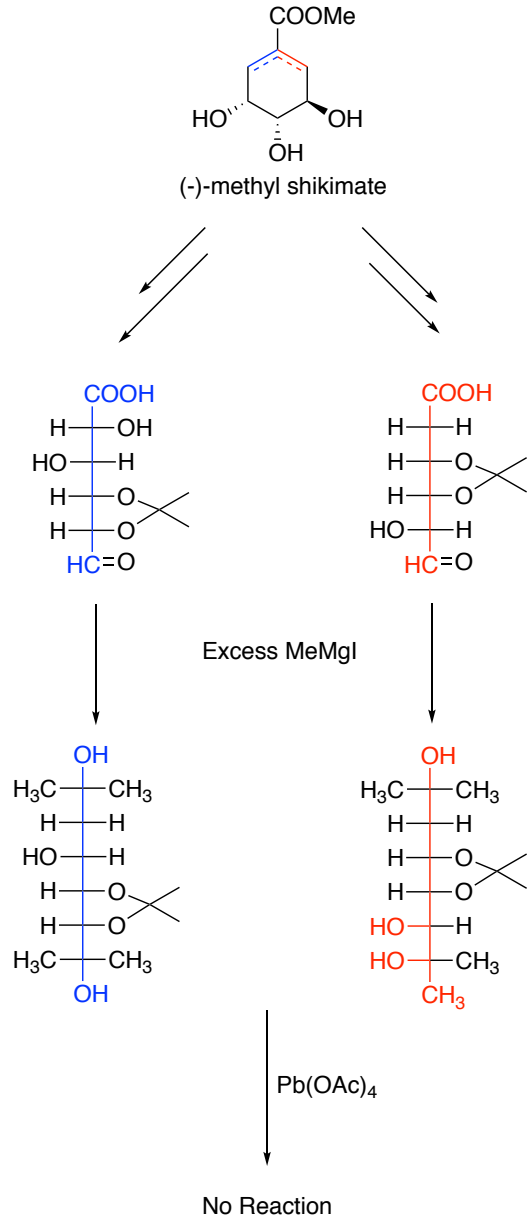
Shikimic Acid

- First isolated from *Illicium anisatum (Japanese Star Anise)* by Johan Fredrik (Eykman) Eijkman (1885)
- Structure first elucidated by H.O.L. Fischer and G. Dangschat (1932-1938)
- Plays a crucial role in aromatic amino acid biosynthesis
- Main precursor chemical of oseltamivir (Tamiflu)
- Produced on multi-hundred ton scale annually



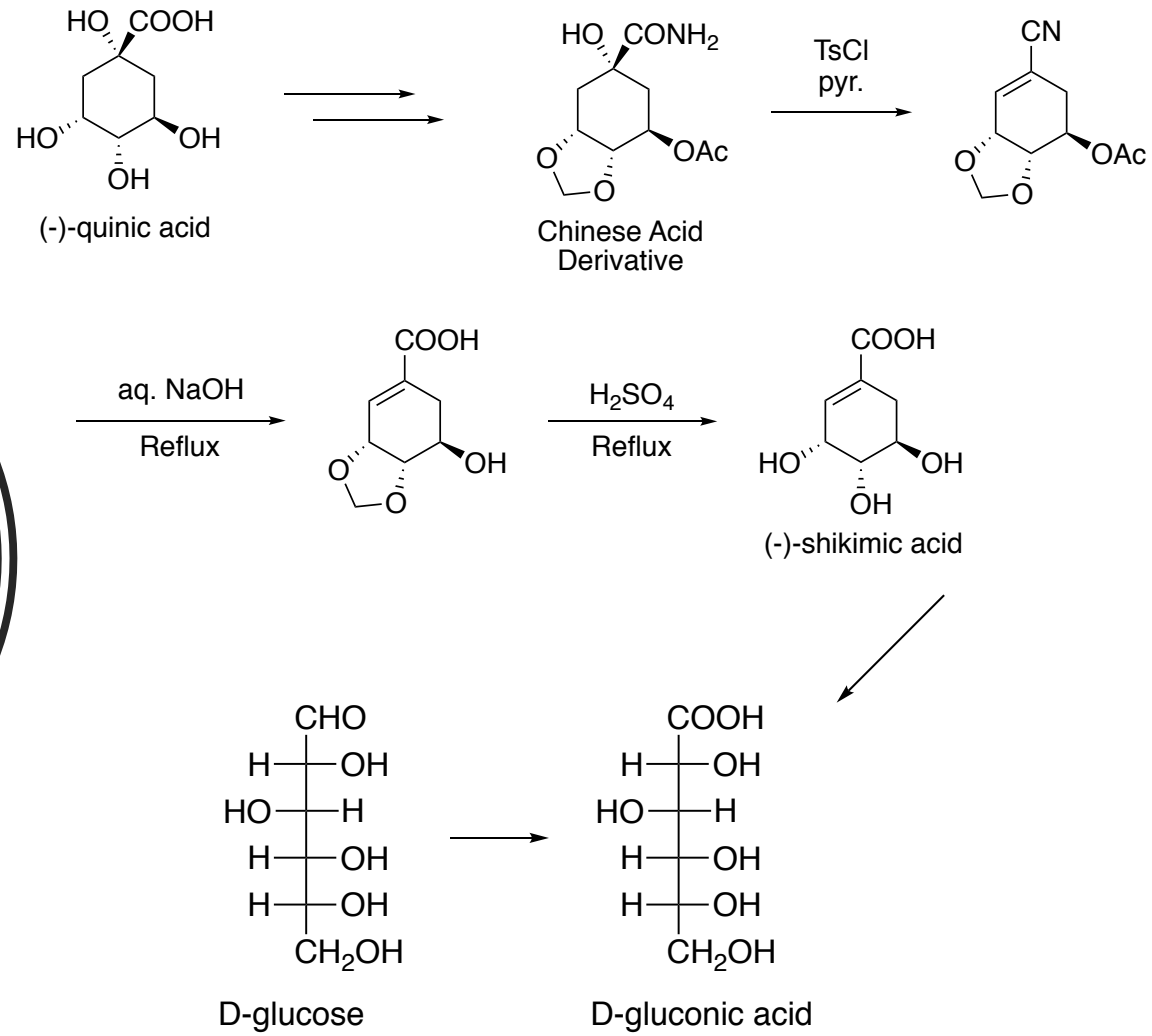
Elucidation of Structure





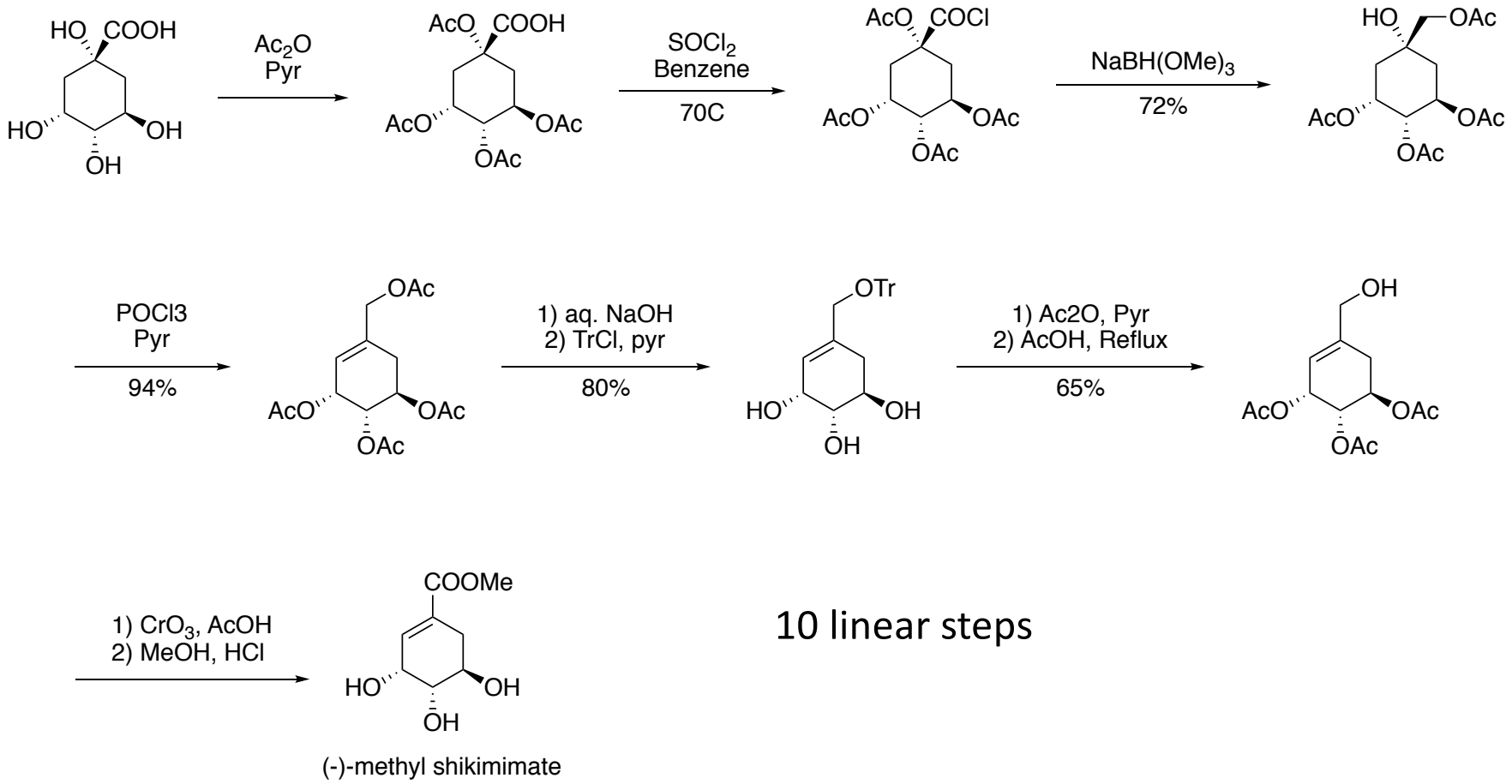
Fischer, H. O. and Dangschat, G. (1937), Über die Konfiguration der Shikimisäure und ihren Abbau zur Glucodensonsäure. HCA, 20: 705-716.

First Chemical Synthesis – Dangschat and Fischer (1938)



Dangschat, G. & Fischer, H.O.L. Naturwissenschaften (1938) 26: 562. https://doi.org/10.1007/BF01774350

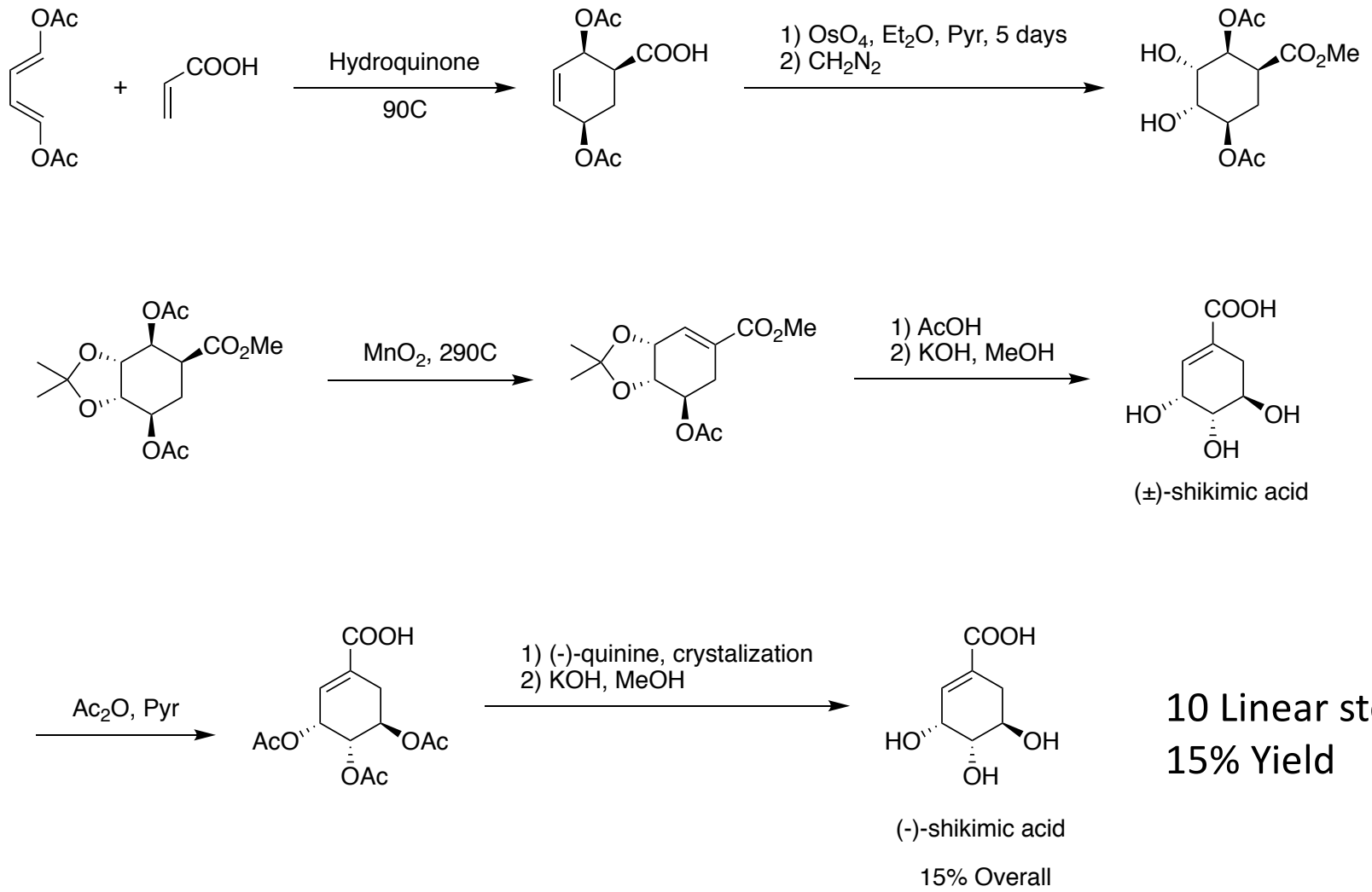
Grewe Synthesis From Quinic Acid (1957)



10 linear steps

Grewe, R. , Büttner, H. and Burmeister, G. (1957), Überführung der Chinasäure in ungesättigte Verbindungen vom Typ der Shikimisäure. Angewandte Chemie, 69: 61-61.

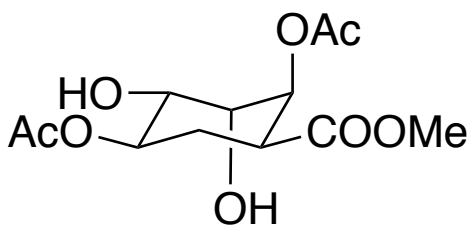
First Method Utilizing Non-Chiral Pool Reagents (1960)



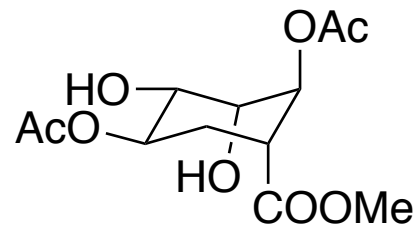
10 Linear steps
15% Yield

J. Chem. Soc., 1960,0, 1560-1565

Structural Dispute

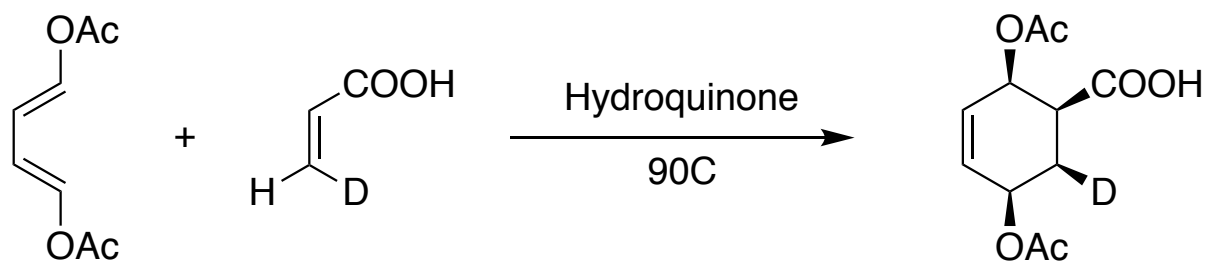


Overmann



Smissman

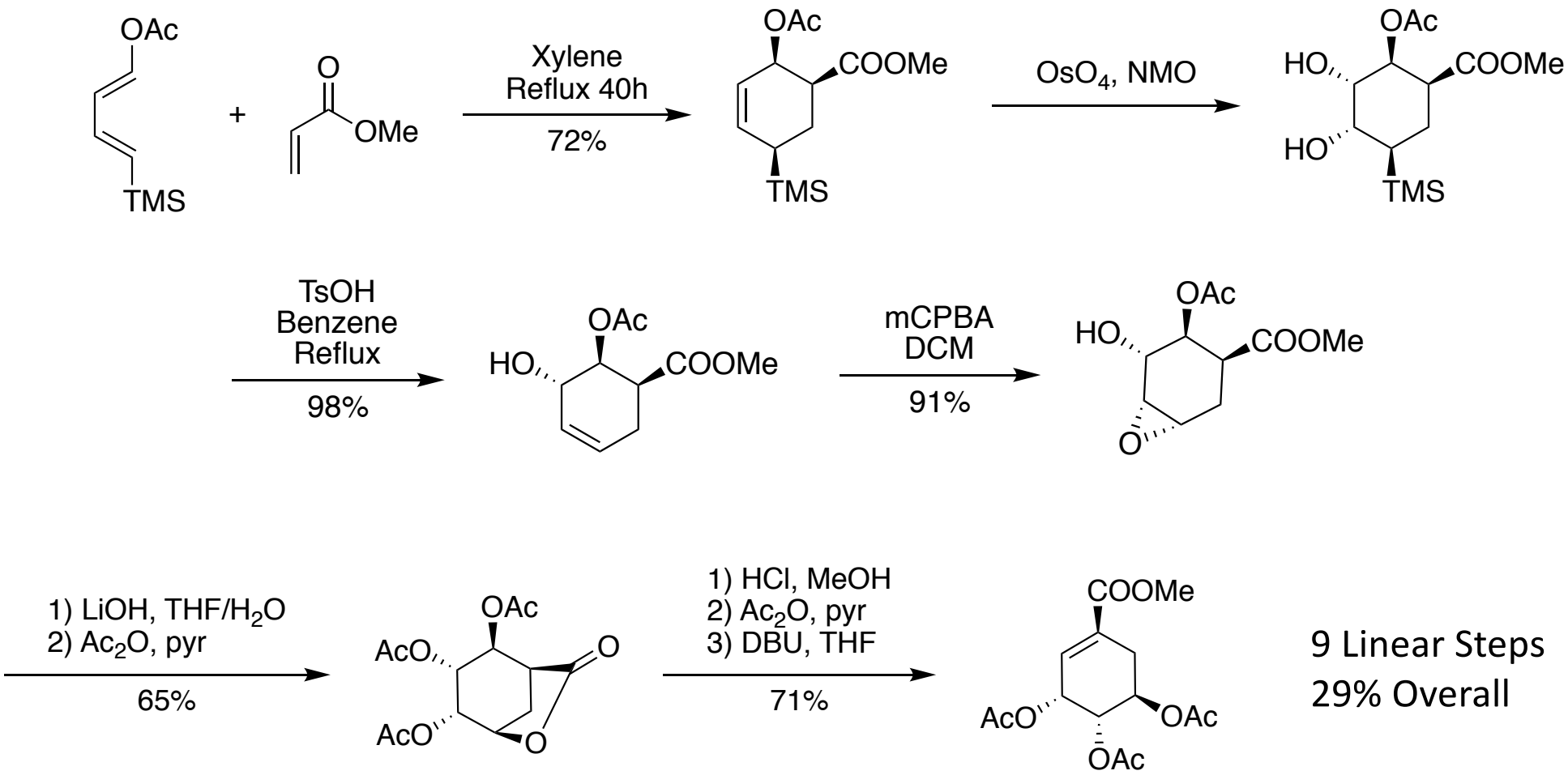
Chris Abell:



The reaction yields primarily the endo product as reported by Overmann

Shankar Balasubramanian, Chris Abell, The synthesis of (6R)-[6-2H]- and (6S)-[6-2H]5 enolpyruvylshikimate-3-phosphate, Tetrahedron Letters, 32, 7, 1991, 963-966

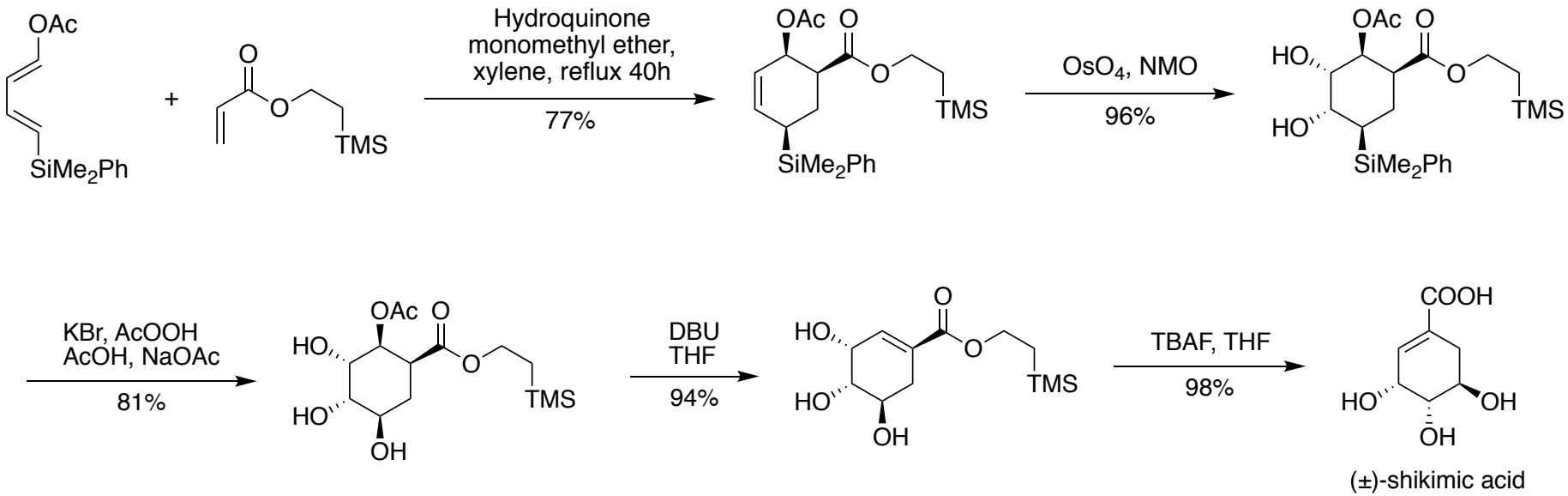
First Koreeda Synthesis (1981)



9 Linear Steps
29% Overall

J. Am. Chem. Soc. 1982, 104, 8, 2308-2310

Koreeda Synthesis Utilizing Fleming-Tamao Oxidation (1990)



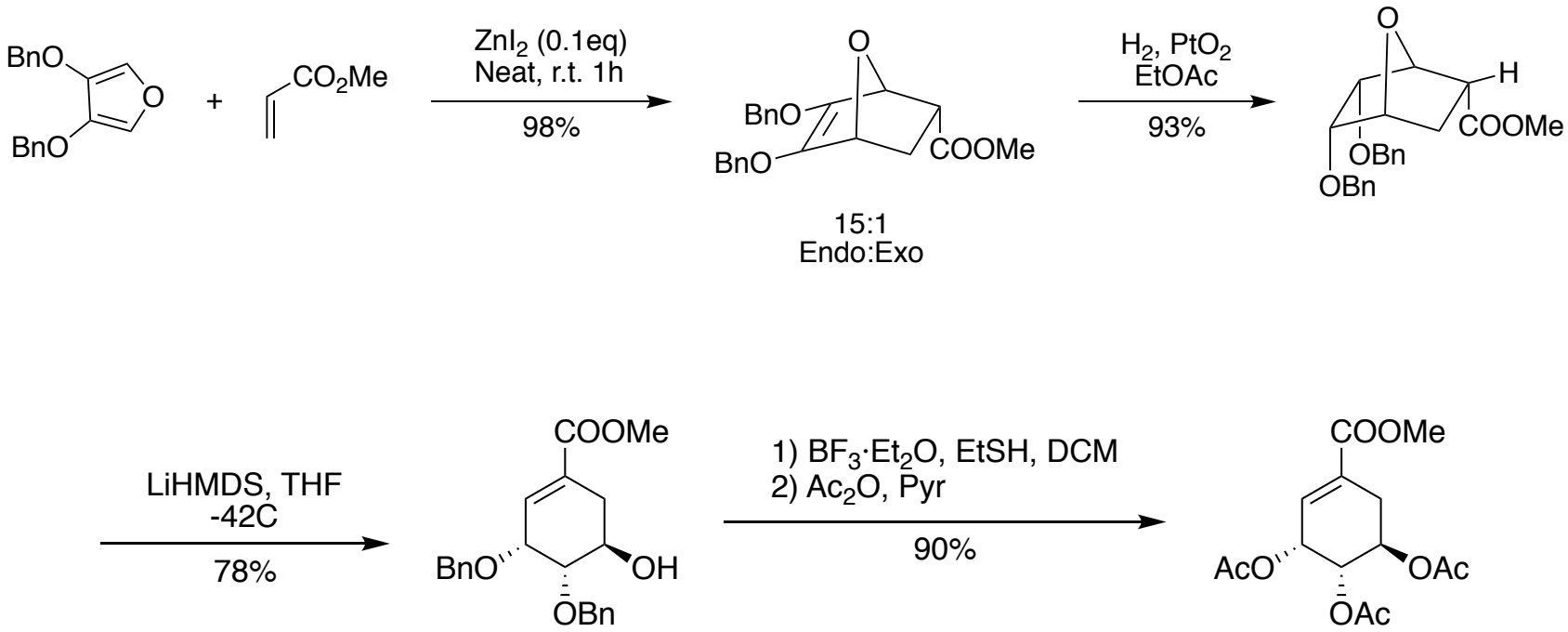
9 Linear steps
29% Overall

5 Linear steps
55% overall

5 Linear steps
64% overall yield

Tetrahedron Letters Volume 31, Issue 42, 1990, Pages 5997-6000

Koreeda Furan Based Diels-Alder Synthesis (1989)



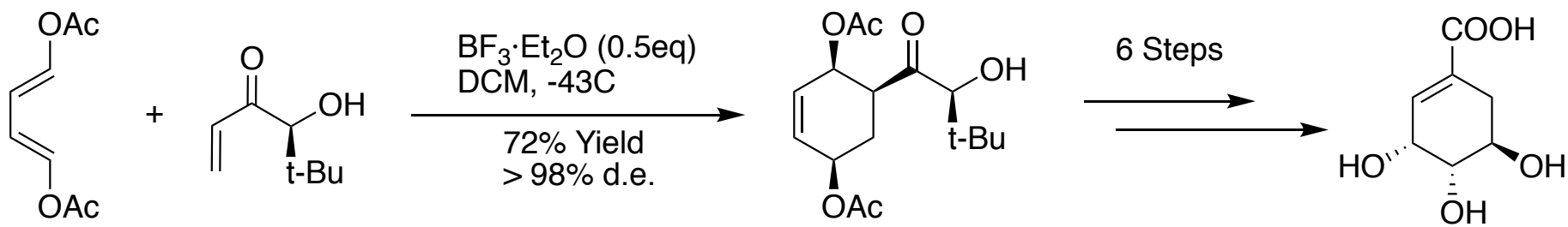
9 Linear steps
29% Overall

5 Linear steps
55% overall

5 Linear steps
64% overall yield

J. Chem. Soc., Perkin Trans. 1, 1989,0, 2129-2131

First Fully Synthetic Enantioselective Synthesis (Masamune 1983)

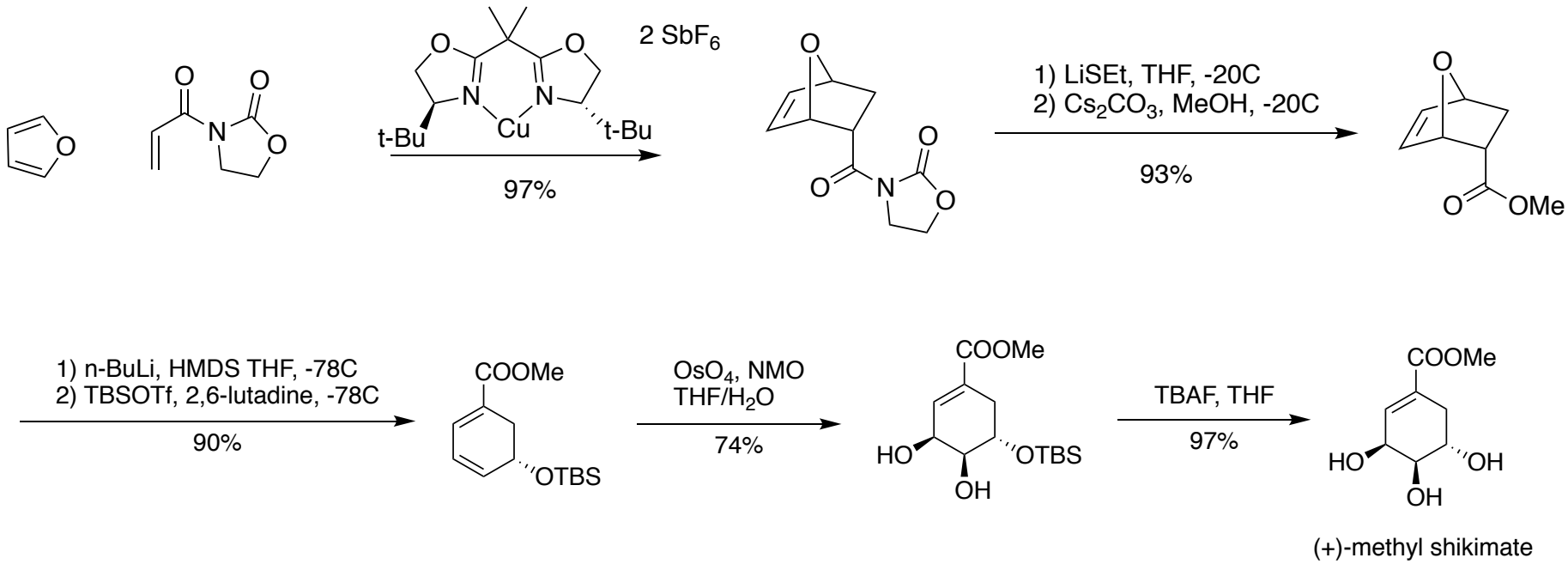


(9) A detailed account of this synthesis will be prepared for publication.

…and it never was

J. Org. Chem. 1983, 48, 23, 4441-4444

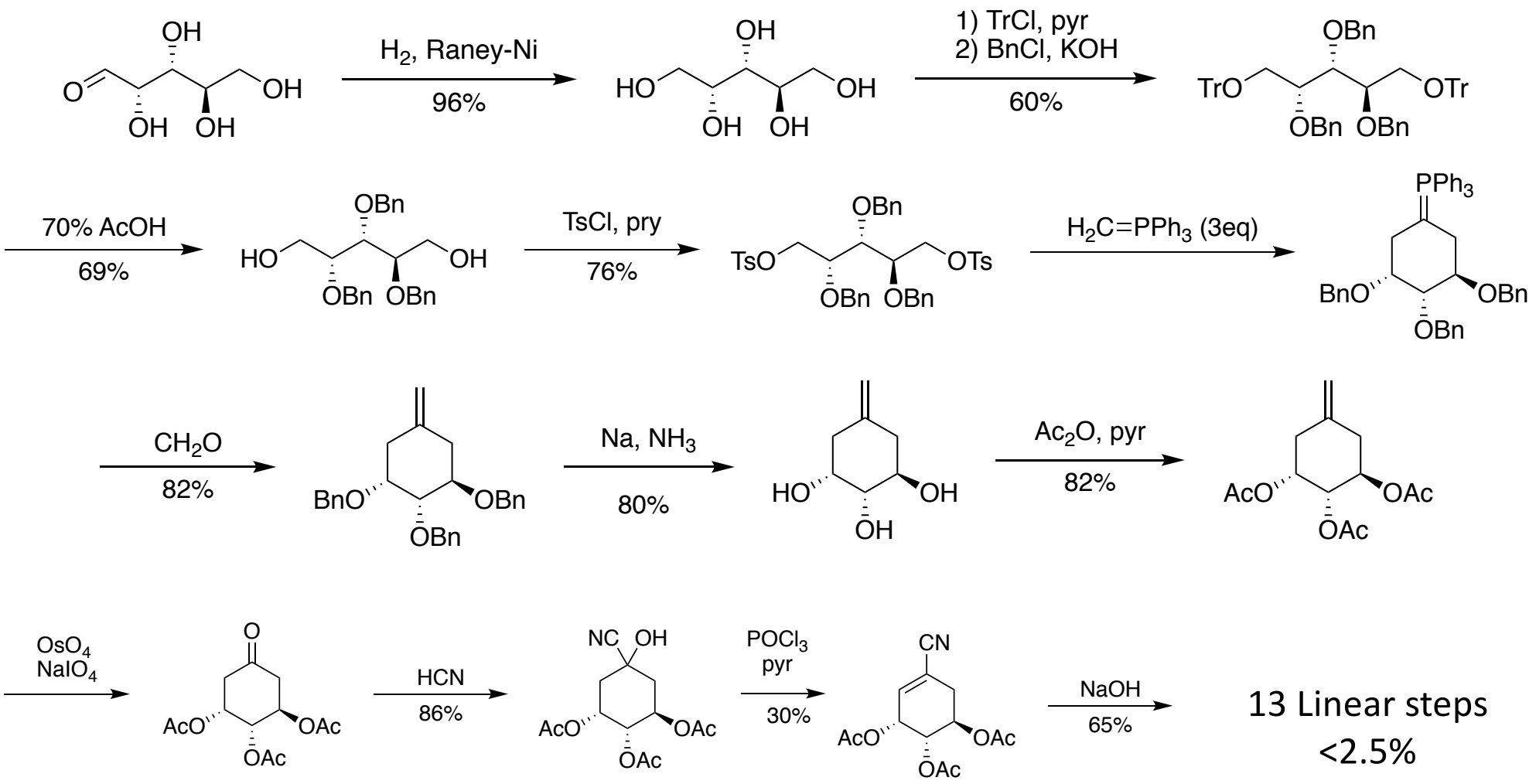
Evans and Barnes Asymmetric Synthesis (1996)



6 Linear steps
40% Overall

Tetrahedron Letters, Vol. 38, No. 1, pp. 57-58, 199

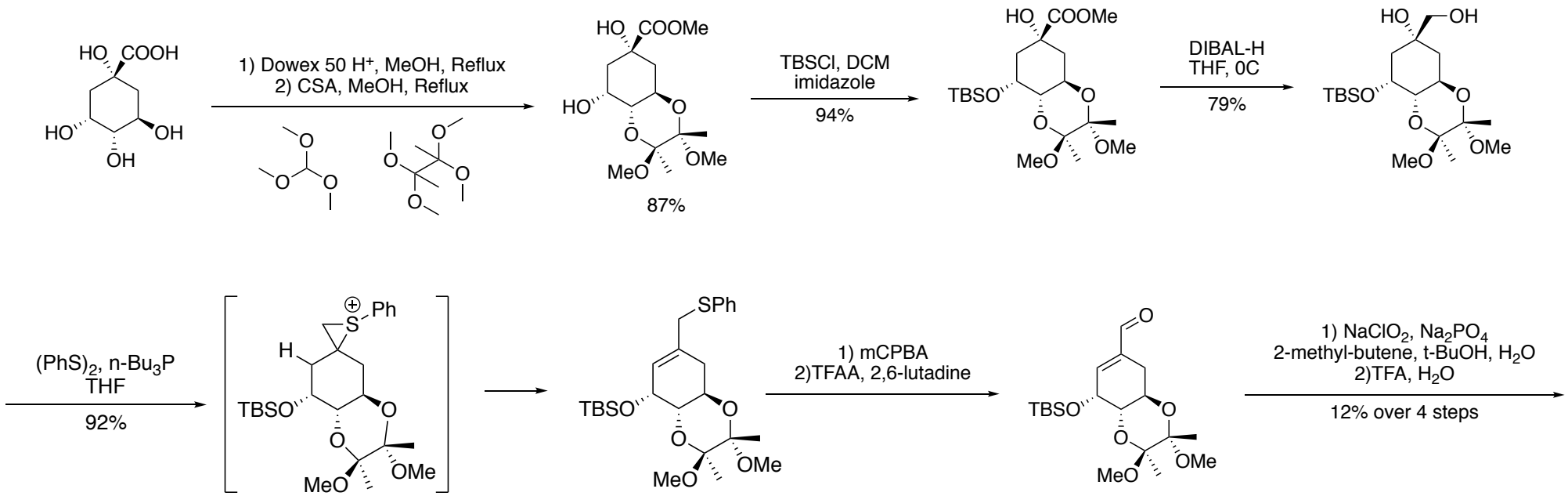
First Synthesis From a Sugar (Bestman 1971)

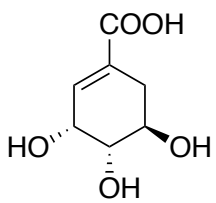


13 Linear steps
<2.5%

Angew. Chem. internat. Edit. J Vol. 10 (1971) No. 5, 336

(-)-shikimic Acid via Thiiranium Ion Intermediate (1998)





(-)-shikimic acid

9 Linear steps
7% overall yield

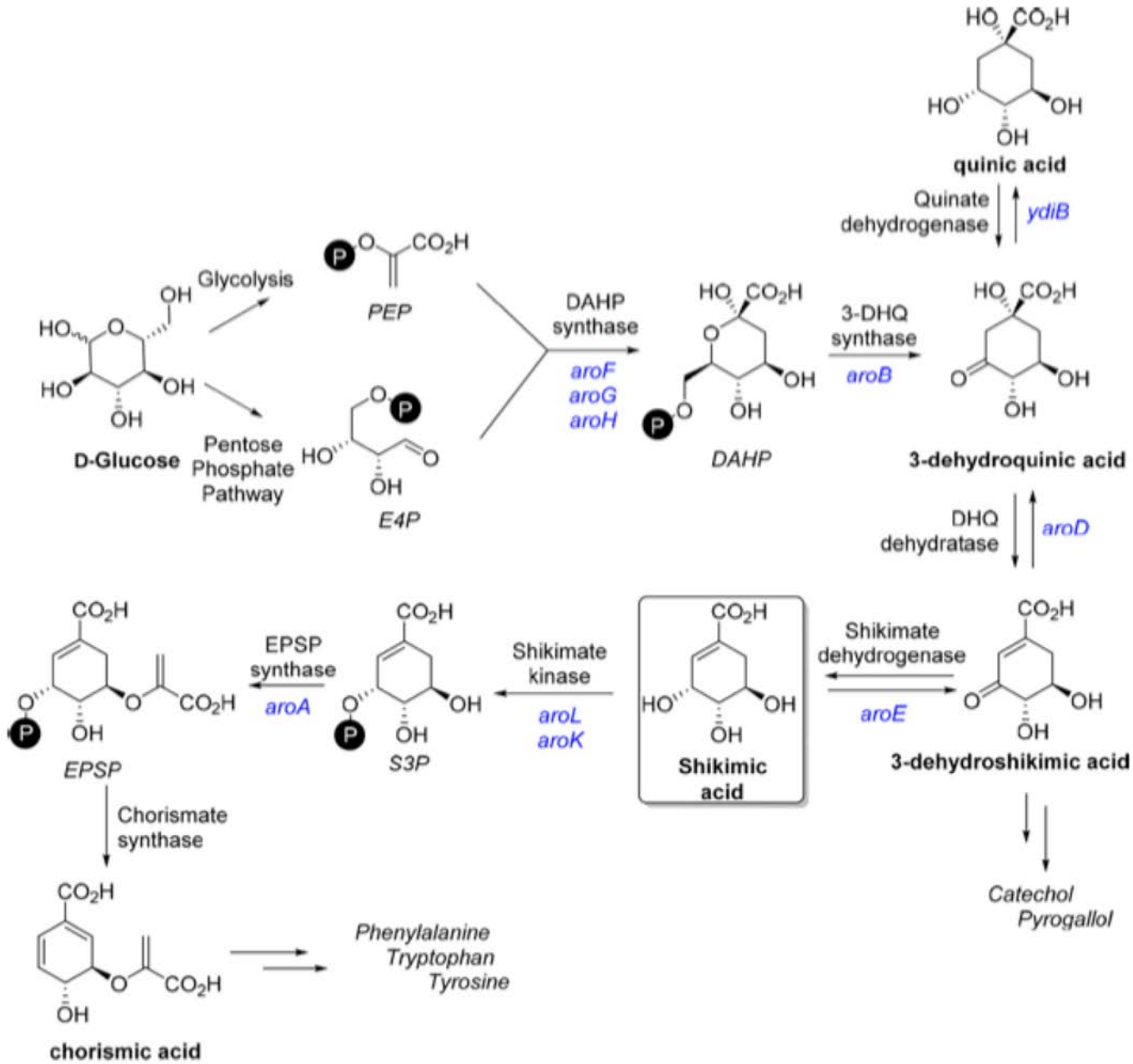
T. Shinada;Y. Yoshida; Y. Ohfune Tetrahedron Letters Volume 39, Issue 33, 13 August 1998, Pages 6027-6028

Synthetic Summary

- Elaboration of natural metabolites
- Diels-Alder chemistry
- From natural and unnatural sugars

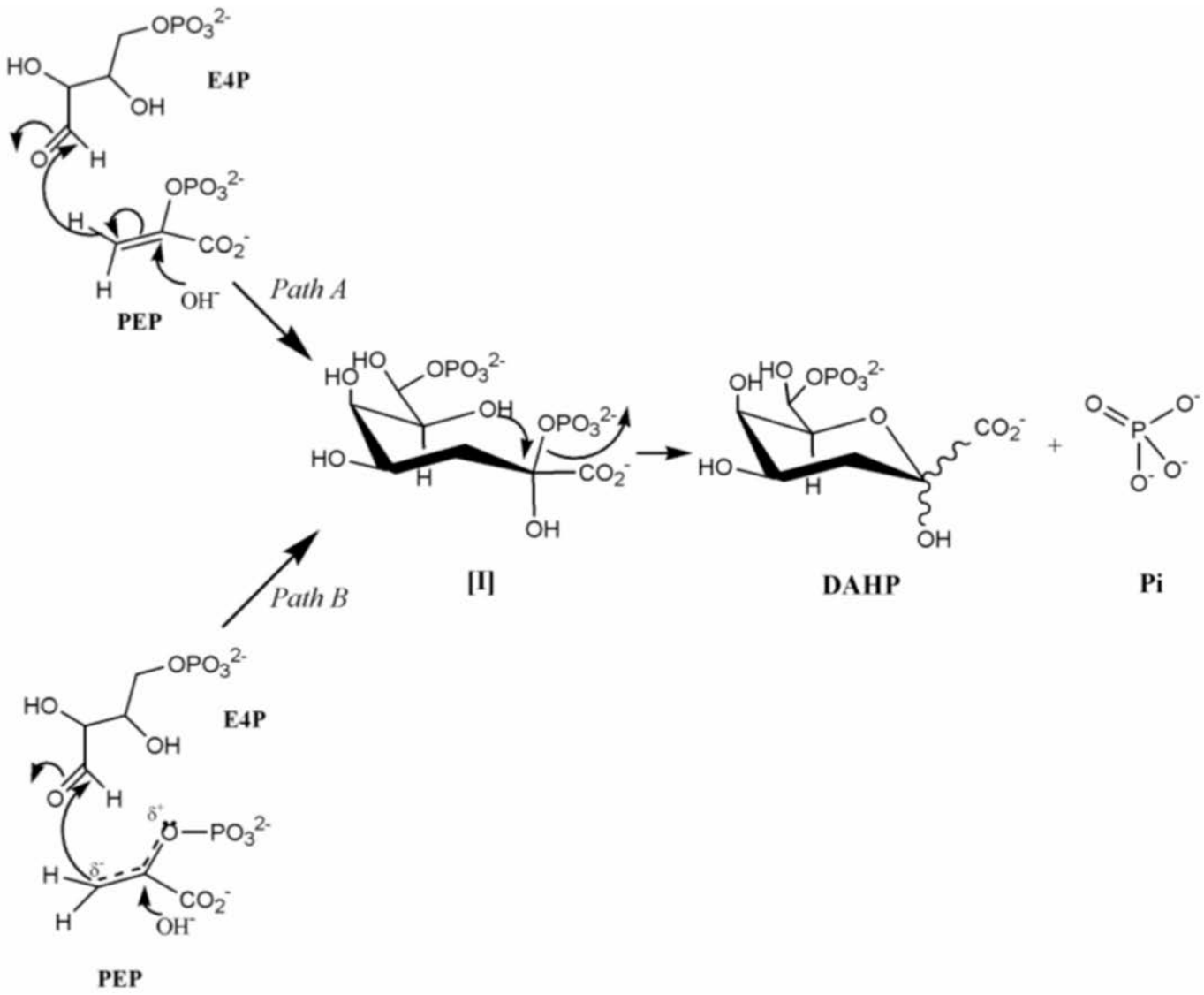
Author	Step count	Yield
Koreeda	5	64% (Racemic)
Koreeda	5	55% (Racemic)
Evans	6	40%
Grewe	9	41% (Racemic)
Rodrigo	6	31%

Biosynthesis



Chem. Rev. 2018, 118, 20, 10458-10550

DAHP Synathase

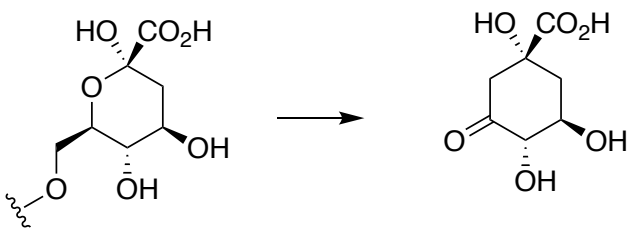


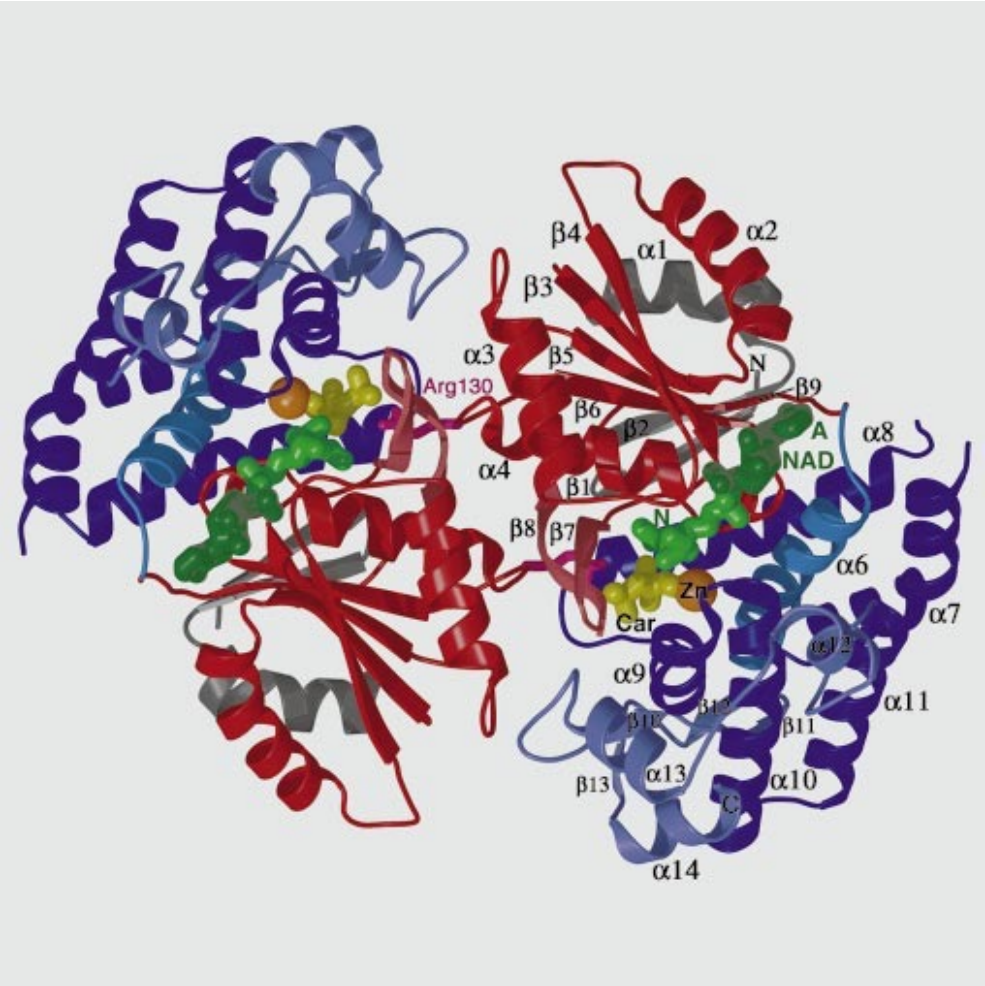
The Journal of Biological Chemistry279, 45618-45625.

DHQ Synthase

5 Synthetic Operations at a single site:

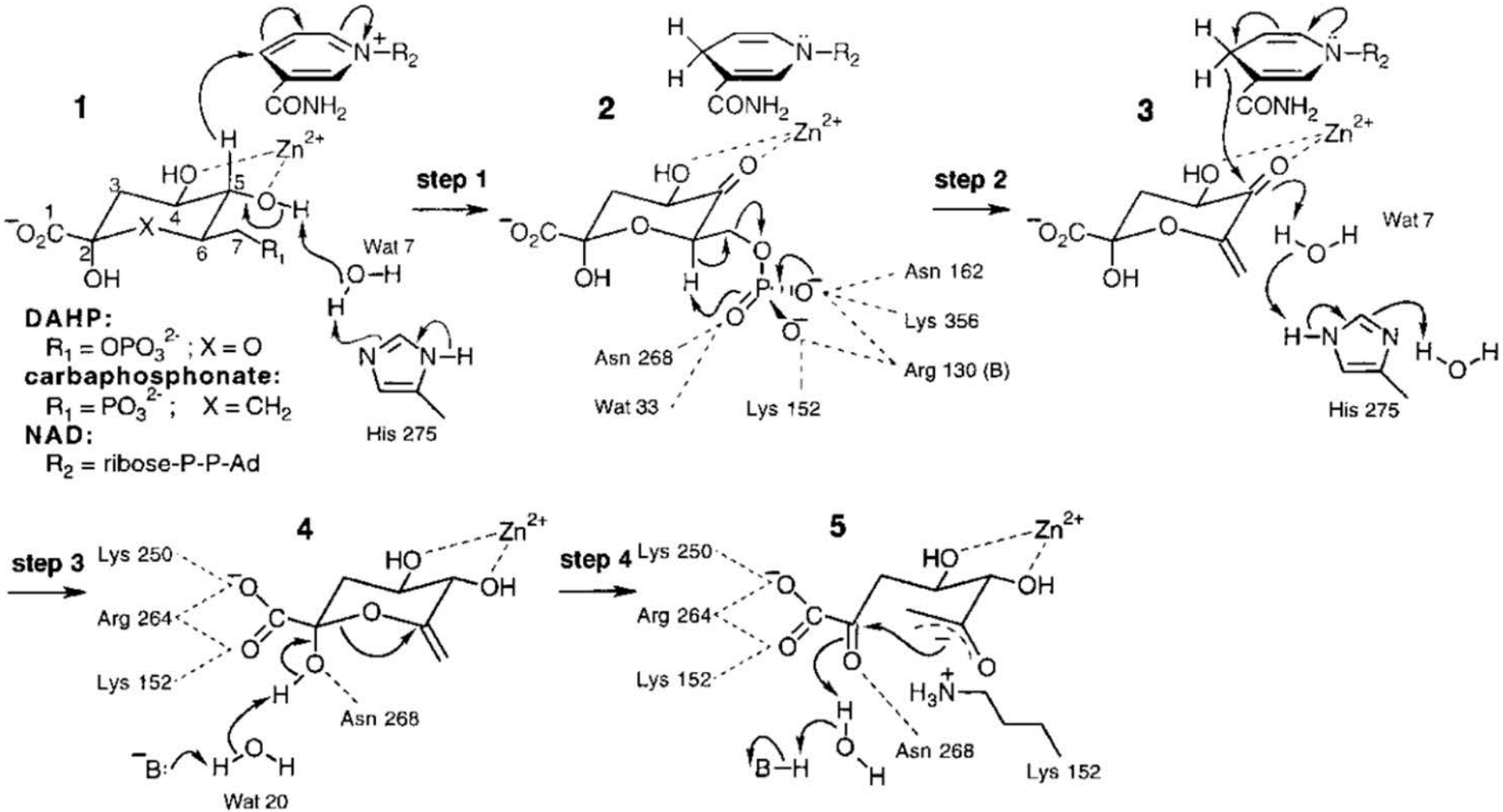
1. Oxidation
2. B-elimination
3. Reduction
4. Ring opening
5. Intramolecular Aldol





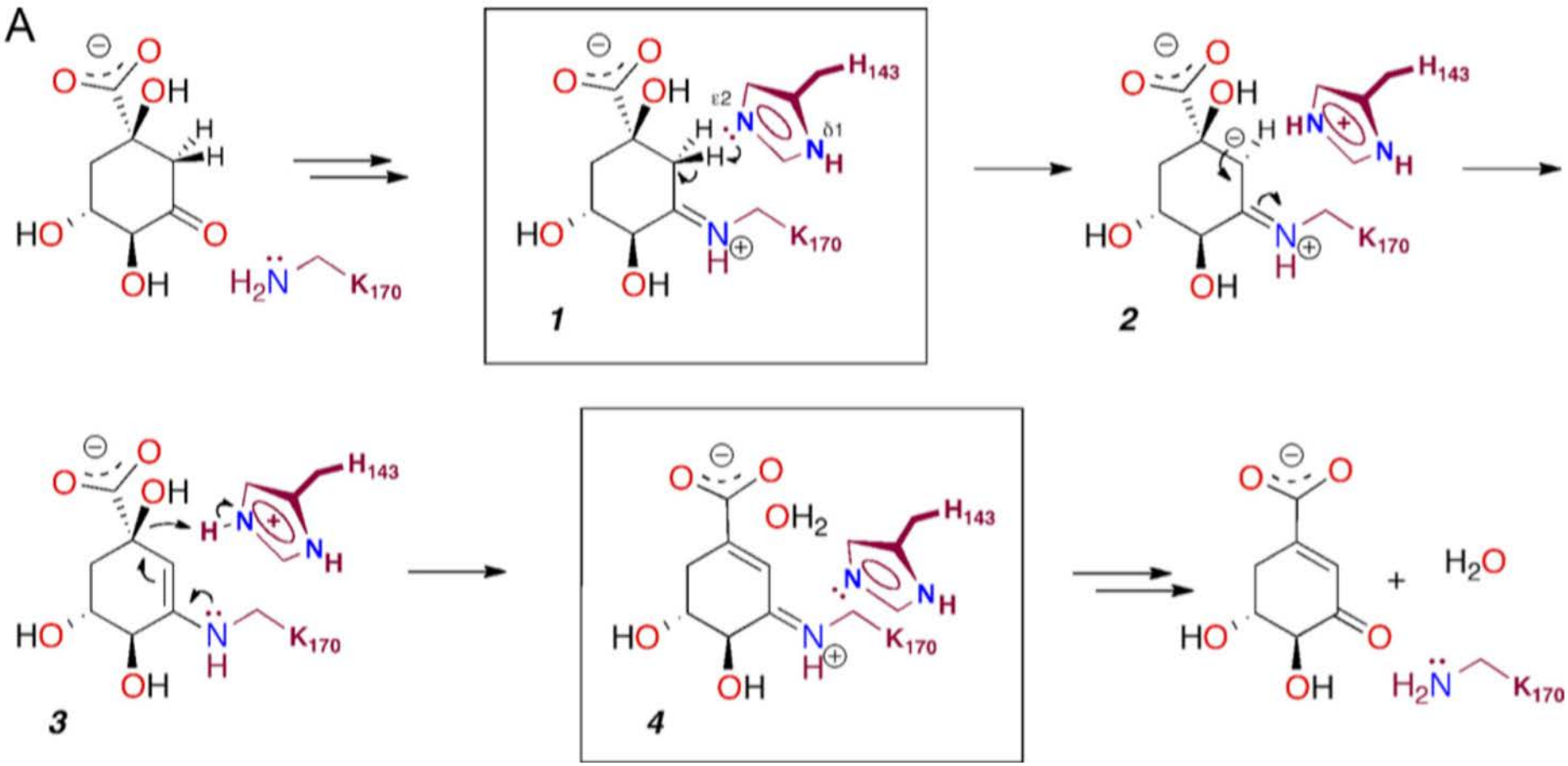
Nature **volume 394**, pages 299–302 (16 July 1998)

DHQS Mechanism



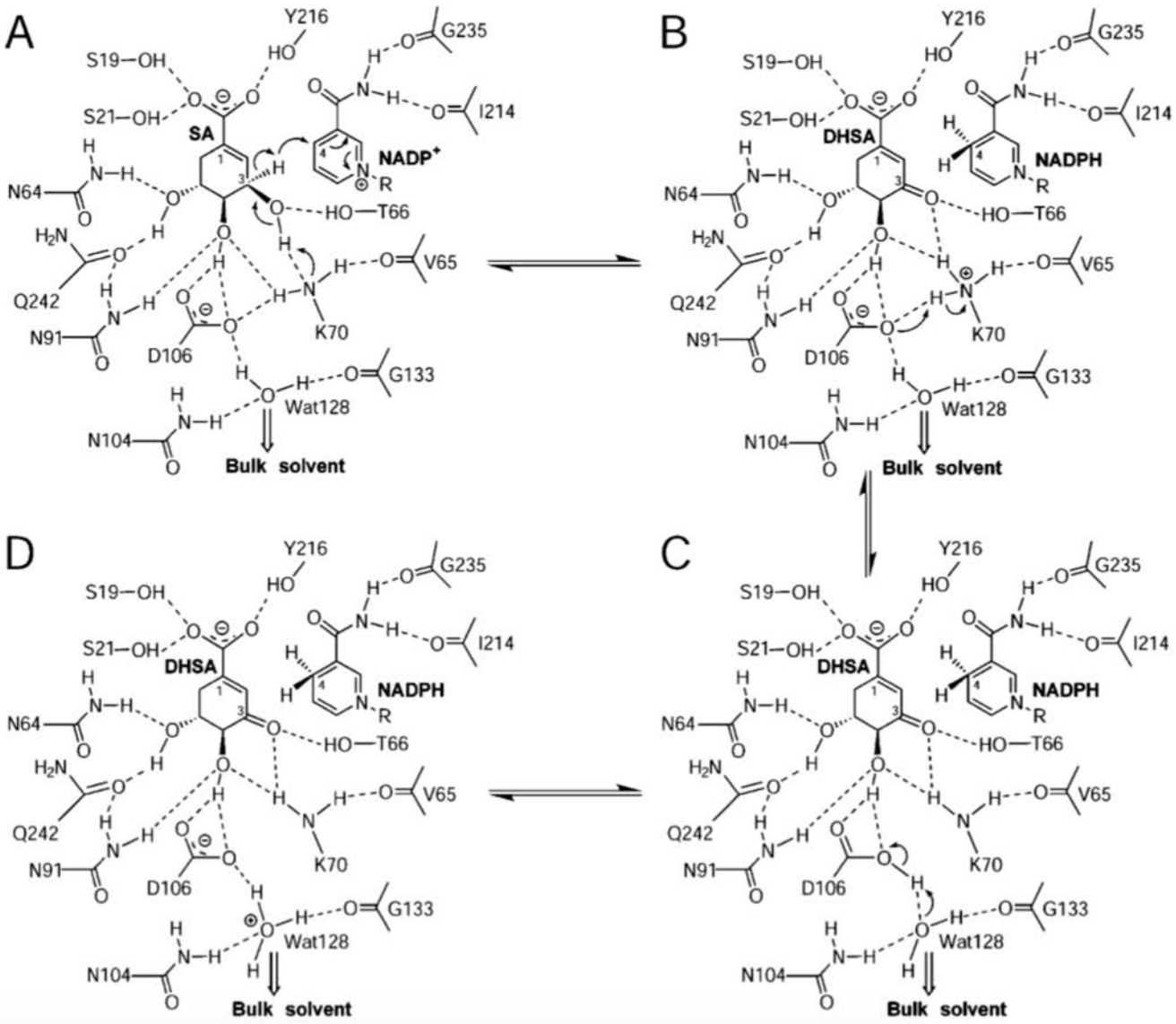
Nature **volume 394**, pages 299–302 (16 July 1998)

DHQ Dehydrase Mechanism



THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL.286,NO.5,pp.3531–3539,February4,2011

Shikimate Dehydrogenase



Biochemistry 2007, 46, 33, 9513-9522

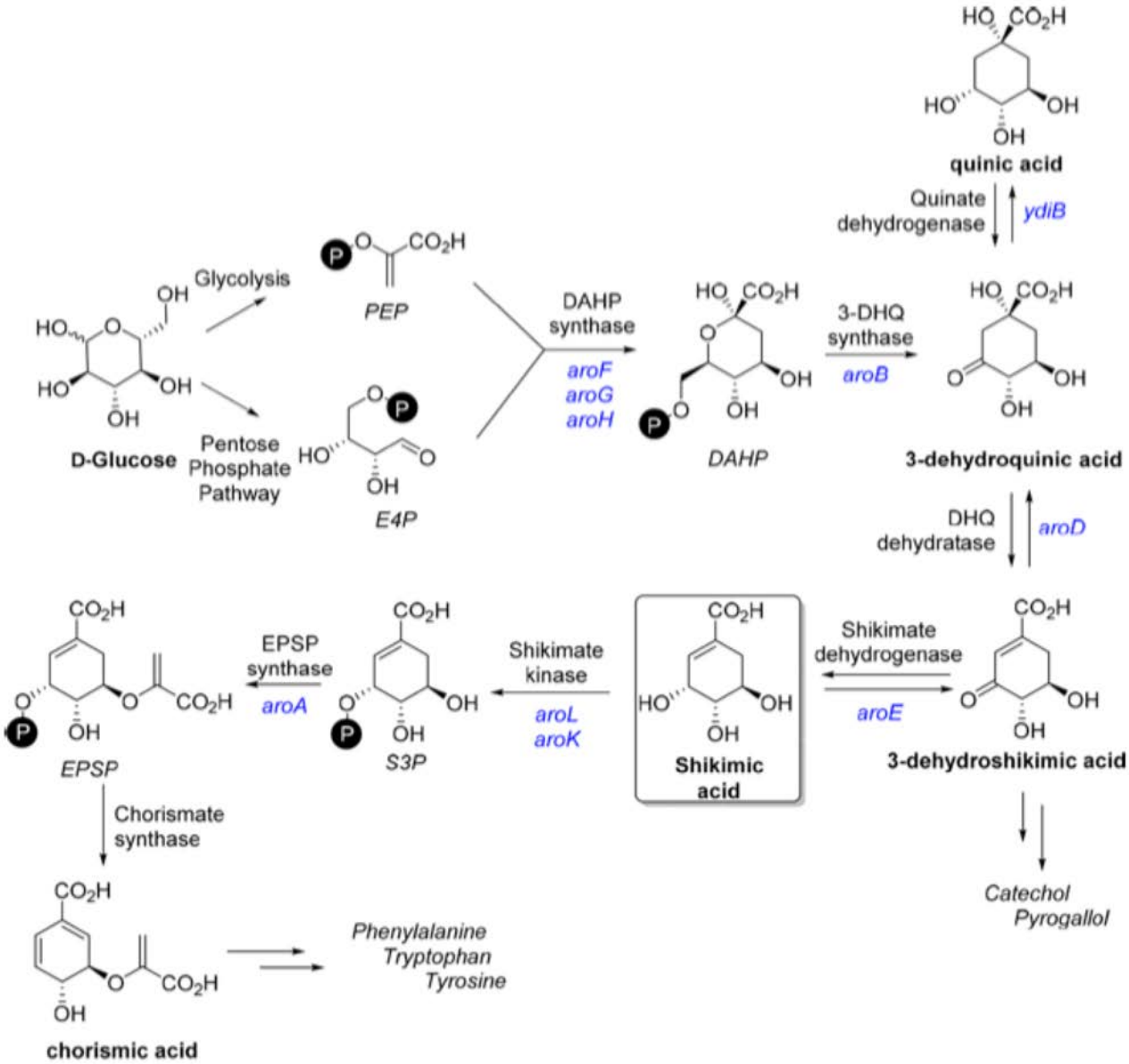
Extraction From Plants

1[75]	*I. religiosum*	27 g	four extractions (20 min) with refluxing EtOH (70 mL)	4.44 g, 16.5%
2[76]	*I. verum* seeds and carpels	900 g	Soxhlet extraction with 95% EtOH (4 L) for 24 h	50–60 g, 6–7%
3[77]	*I. verum* seeds	25 g	Soxhlet extraction with 95% EtOH (125 mL) for 2 h	0.6–1.74 g, 2.4–7%
4[78]	*I. verum* seeds	400 g	refluxed over 6 h in 2 L of 95% aq *i*-PrOH; residual seeds again refluxed for 4 h in 95% aq *i*-PrOH	20 g, 5%
5[80]	*I. verum* seeds	40 g	ground star anise (20 g) packed in the portafilter (sample compartment) of an espresso machine and extracted (approximately 2 min) with a 30% EtOH/water solution (200 mL)	2.21 g, 5.5%
6[81]	*I. griffithii* dried fruits	54 g	powdered fruits extracted with 150 mL of hexane with a Soxhlet apparatus; defatted plant material then extracted with 150 mL of $CHCl_3$; defatted plant material extract in $CHCl_3$ again extracted with 150 mL of MeOH	10 g, 18.5%
7[82]	*L. styraciflua* seeds	35 g	stirred overnight in 400 mL of deionized water at 65 °C	1.1 g, 3.23%
8[41]	Scots pine (*P. sylvestris*) dry needles	1.0 kg	three separate water extractions (5 L each) at 45 °C for 2	*b*

2[76]	*I. verum* seeds and carpels	900 g	Soxhlet extraction with 95% EtOH (4 L) for 24 h	50–60 g, 6–7%
5[80]	*I. verum* seeds	40 g	ground star anise (20 g) packed in the portafilter (sample compartment) of an espresso machine and extracted (approximately 2 min) with a 30% EtOH/water solution (200 mL)	2.21 g, 5.5%

Chem. Rev. 2018, 118, 10458–10550

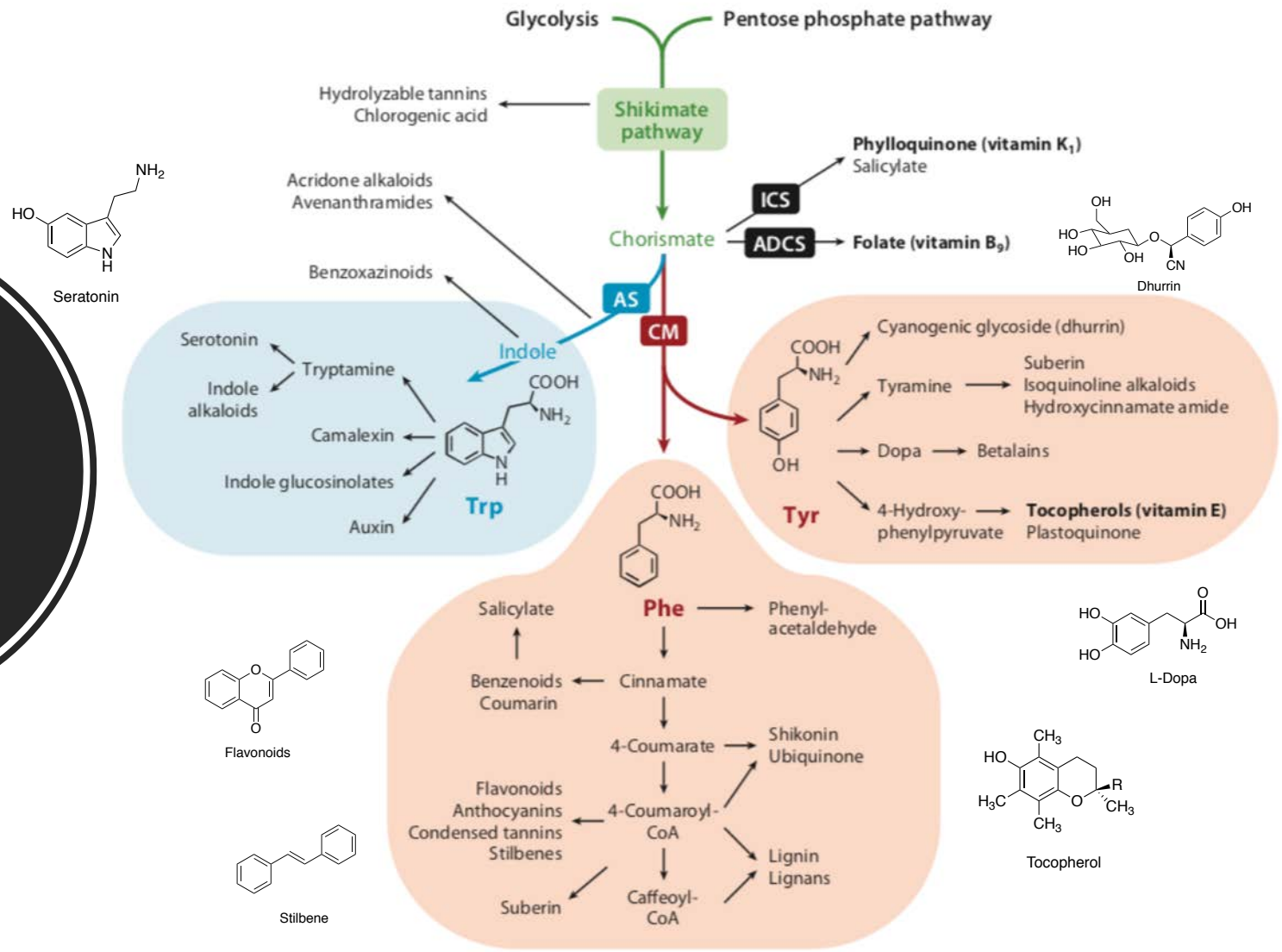
Beneficial Modifications for Shikimic Acid Synthesis in E. Coli



The most efficient batch fed fermentation reactors can produce over 5g/L·H at a cost of 40g/H of glucose

Chem. Rev. 2018, 118, 10458−10550

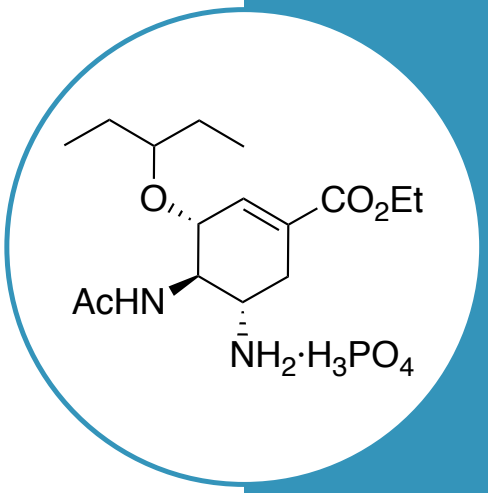
Synthesis of Aromatic Amino Acids



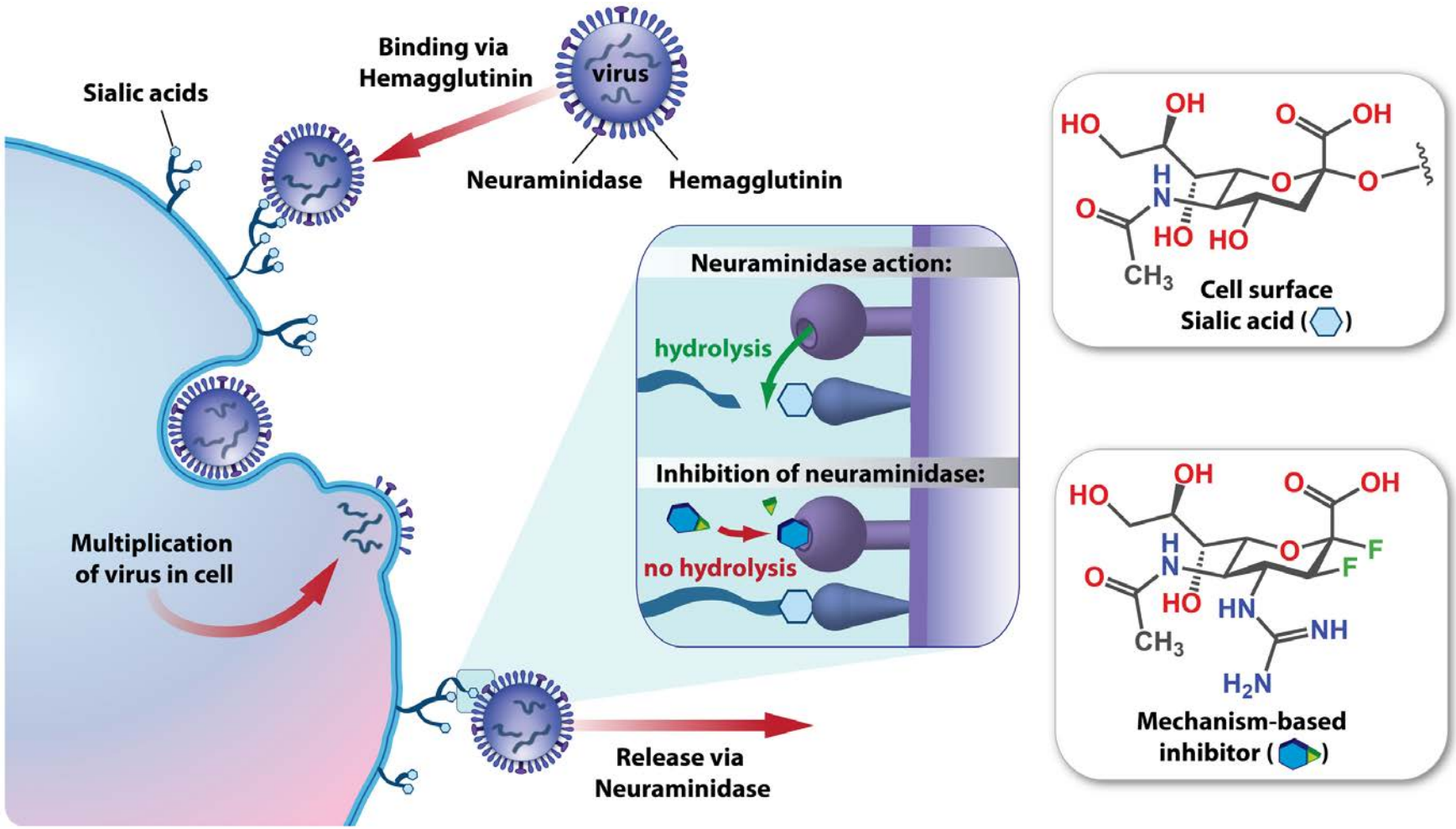
Chem. Rev. 2018, 118, 10458−10550

Oseltamivir (Tamiflu)

- Discovered by Gilead (1995)
- Licensed to Roche in 1996
- FDA approval granted in 1999
- Over $18bn in sales
- WHO list of essential medicines (not currently)

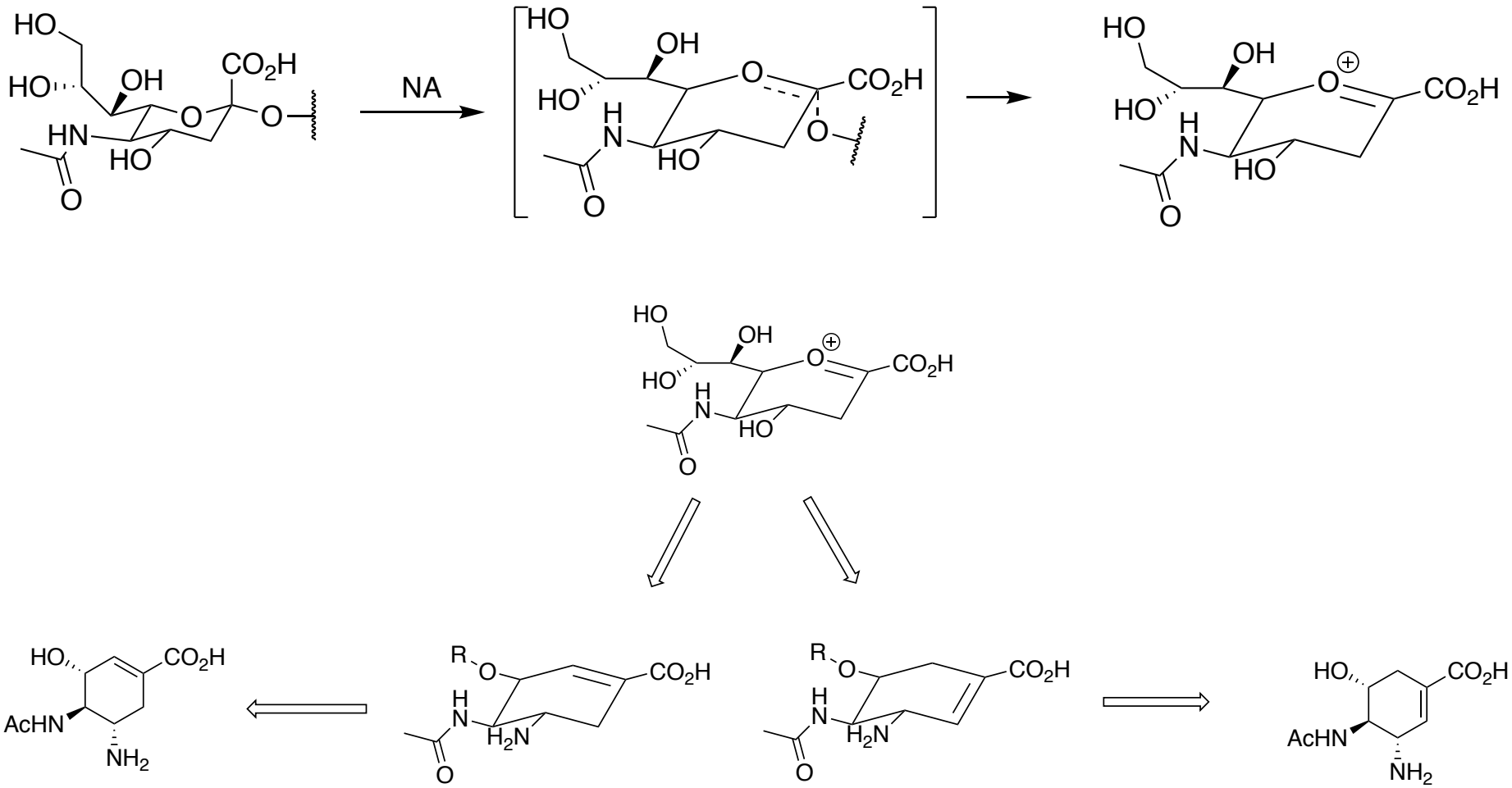


Mechanism of Action



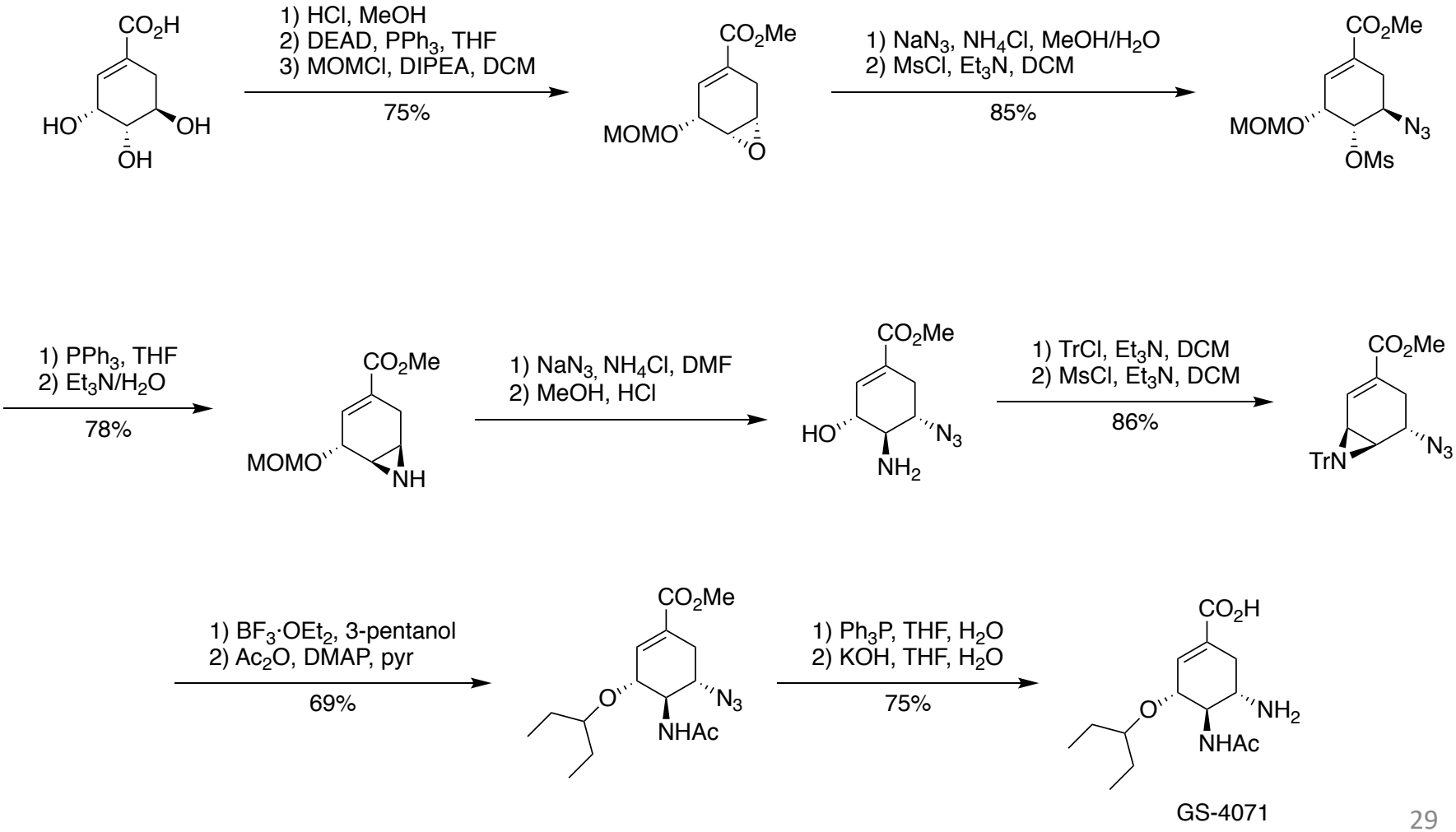
Science 05 Apr 2013: Vol. 340, Issue 6128, pp. 71-75 DOI: 10.1126/science.1232552

Discovery at Gilead



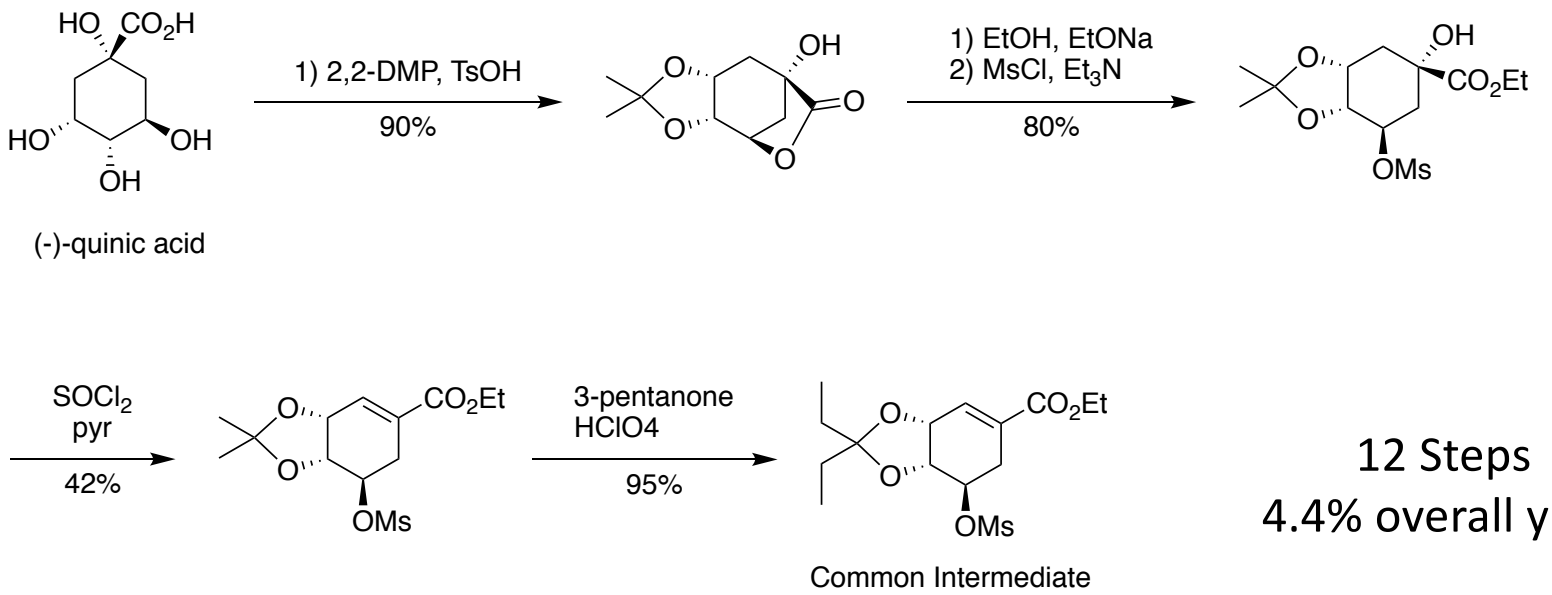
J. Am. Chem. Soc. **1997,** *119,* 681-690

Medicinal Chemistry Route



J. Am. Chem. Soc. **1997,** *119,* 681-690

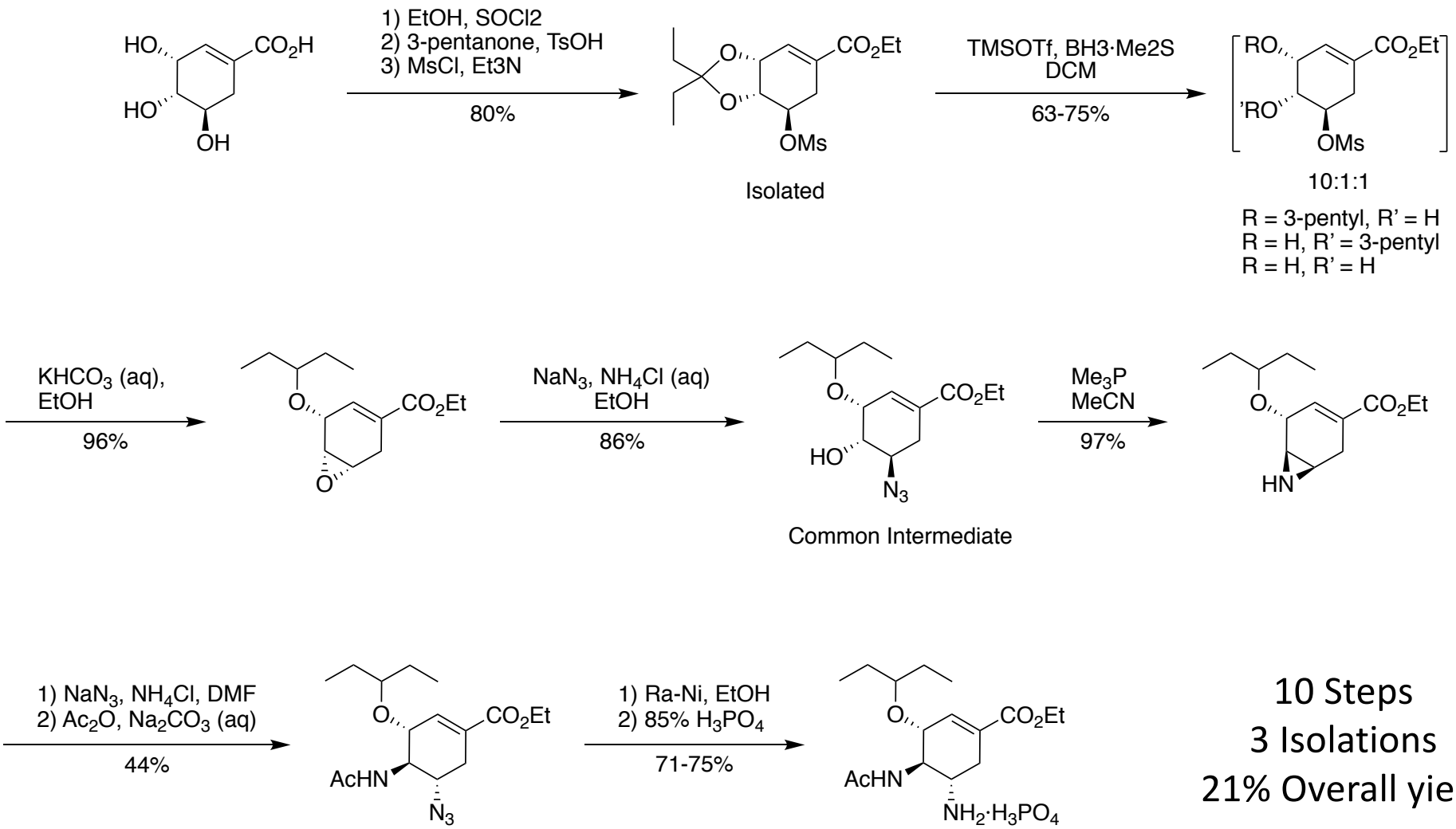
Pre-Clinical Scale-Up (Gilead)



12 Steps
4.4% overall yield

J. Org. Chem. 1998, 63, 13, 4545-4550

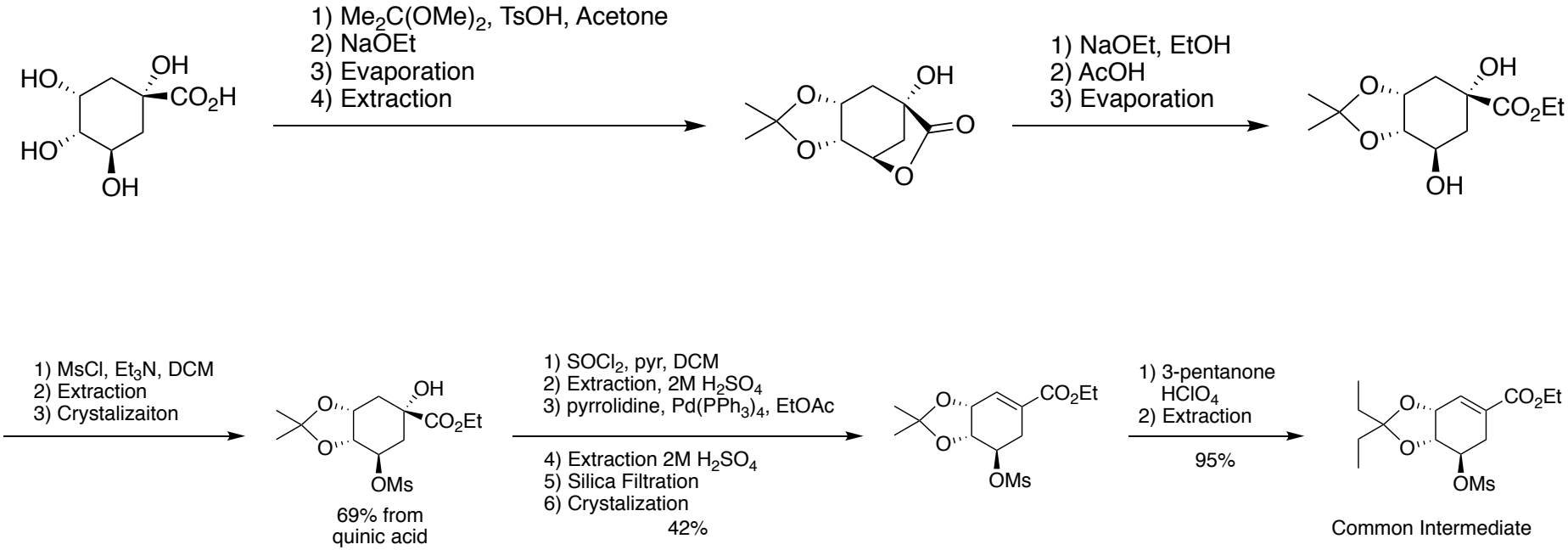
Pre-Clinical Scale-Up (Gilead)



10 Steps
3 Isolations
21% Overall yield

J. Org. Chem. 1998, 63, 13, 4545-4550

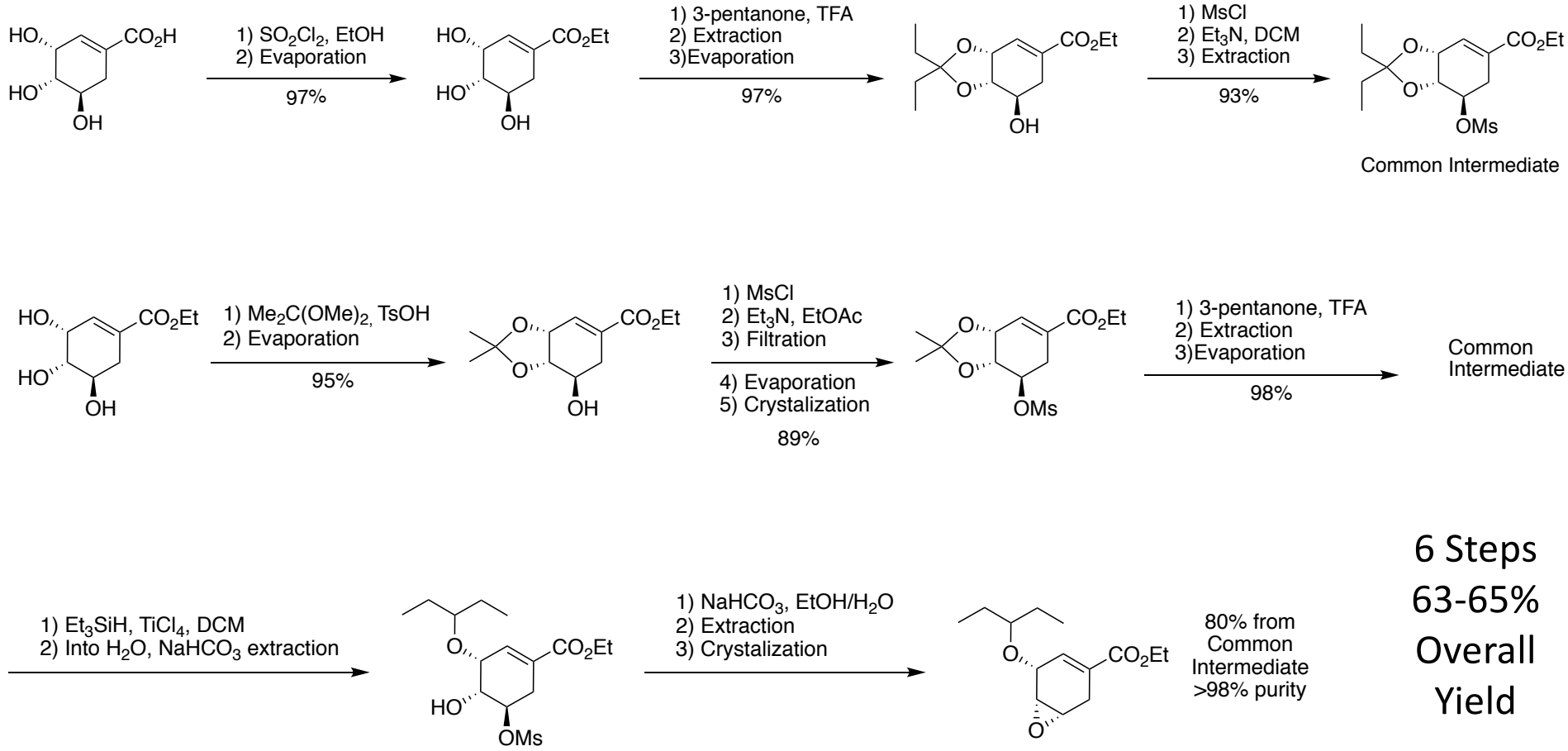
Industrial Synthesis of Epoxide Intermediate



7 Steps to Tamiflu
35-38% Overall yield

Org. Proc. Res. Dev. 1999, 3, 4, 266-274

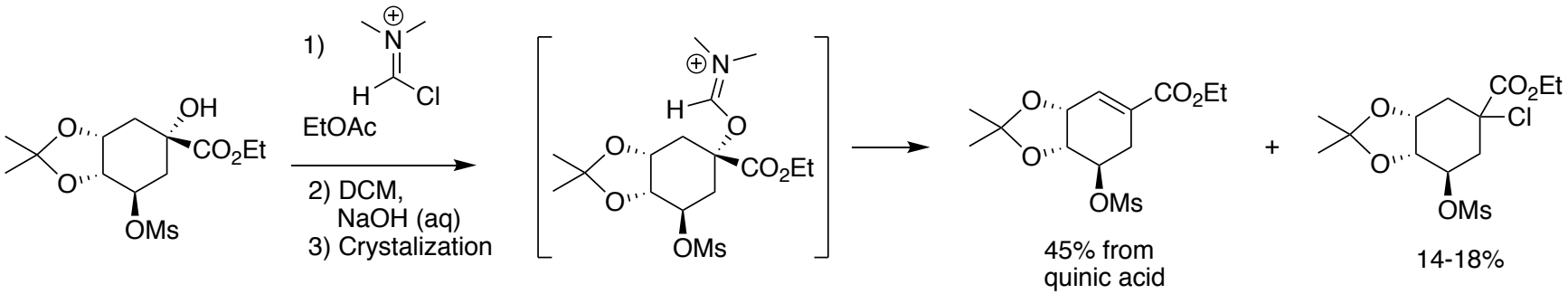
Industrial Synthesis of Epoxide Intermediate

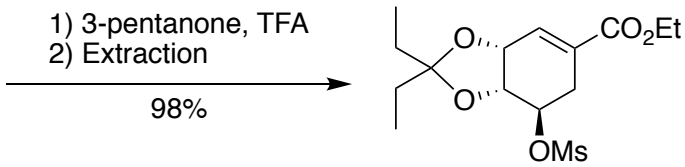


6 Steps
63-65%
Overall
Yield

Org. Proc. Res. Dev. 1999, 3, 4, 266-274

Attempted Synthesis of (-)-Shikimic Acid via Quinic Acid (Roche)

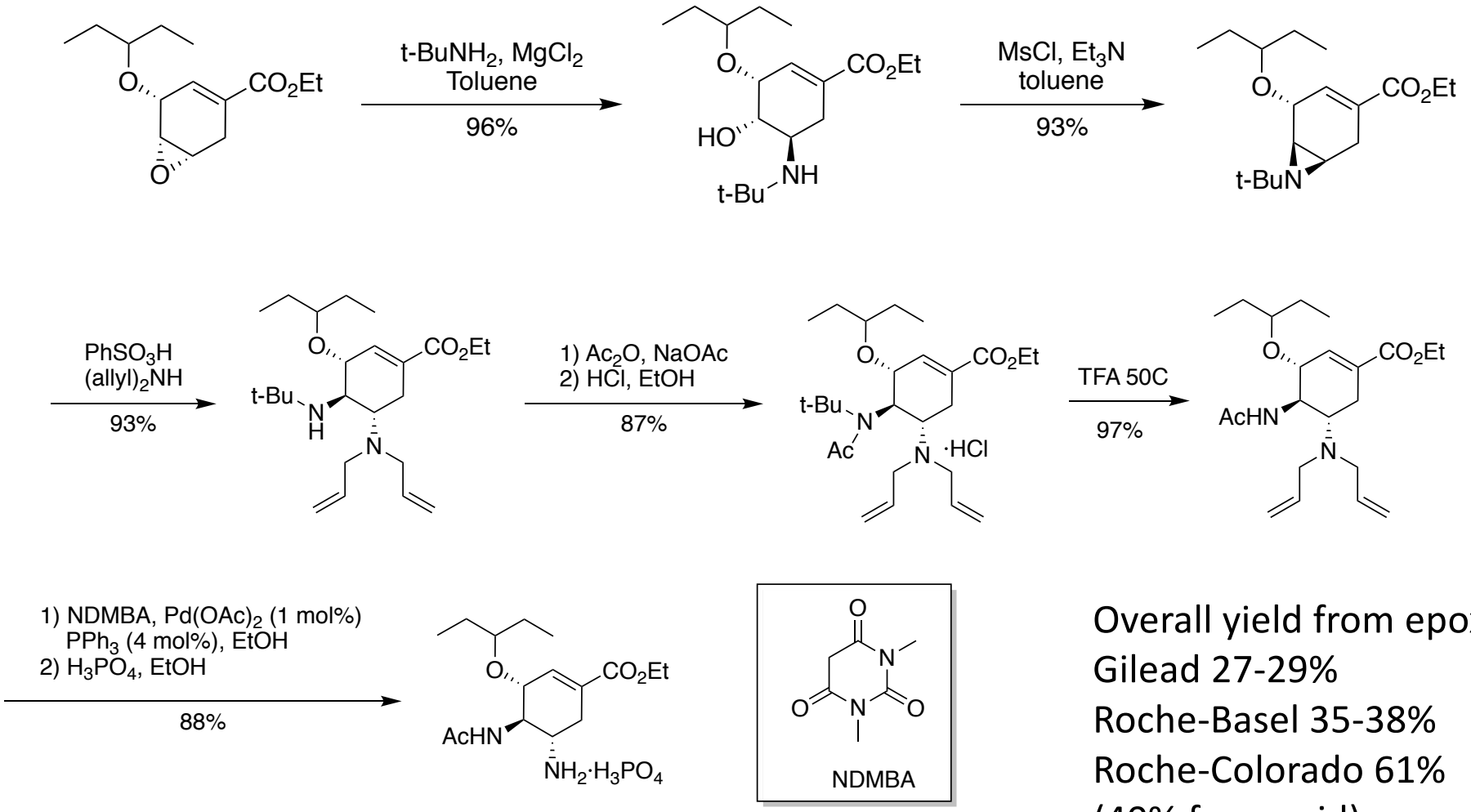




44.1% from (-)-quinic acid
Highest reported yield
Kg scale

Org. Proc. Res. Dev. 1999, 3, 4, 266-274

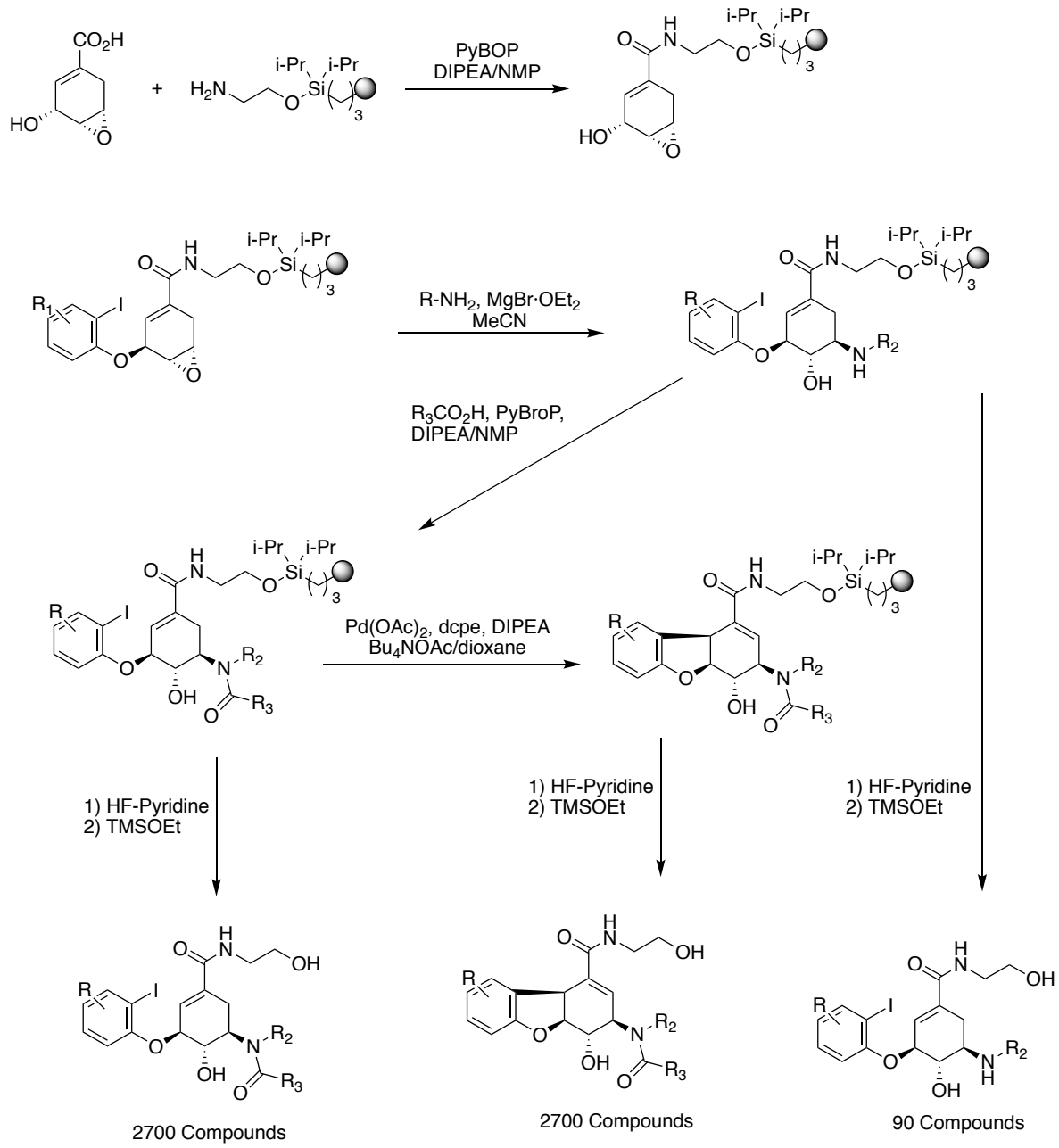
Roche-Colorado Azide Free Synthesis



Overall yield from epoxide:
Gilead 27-29%
Roche-Basel 35-38%
Roche-Colorado 61%
(40% from acid)

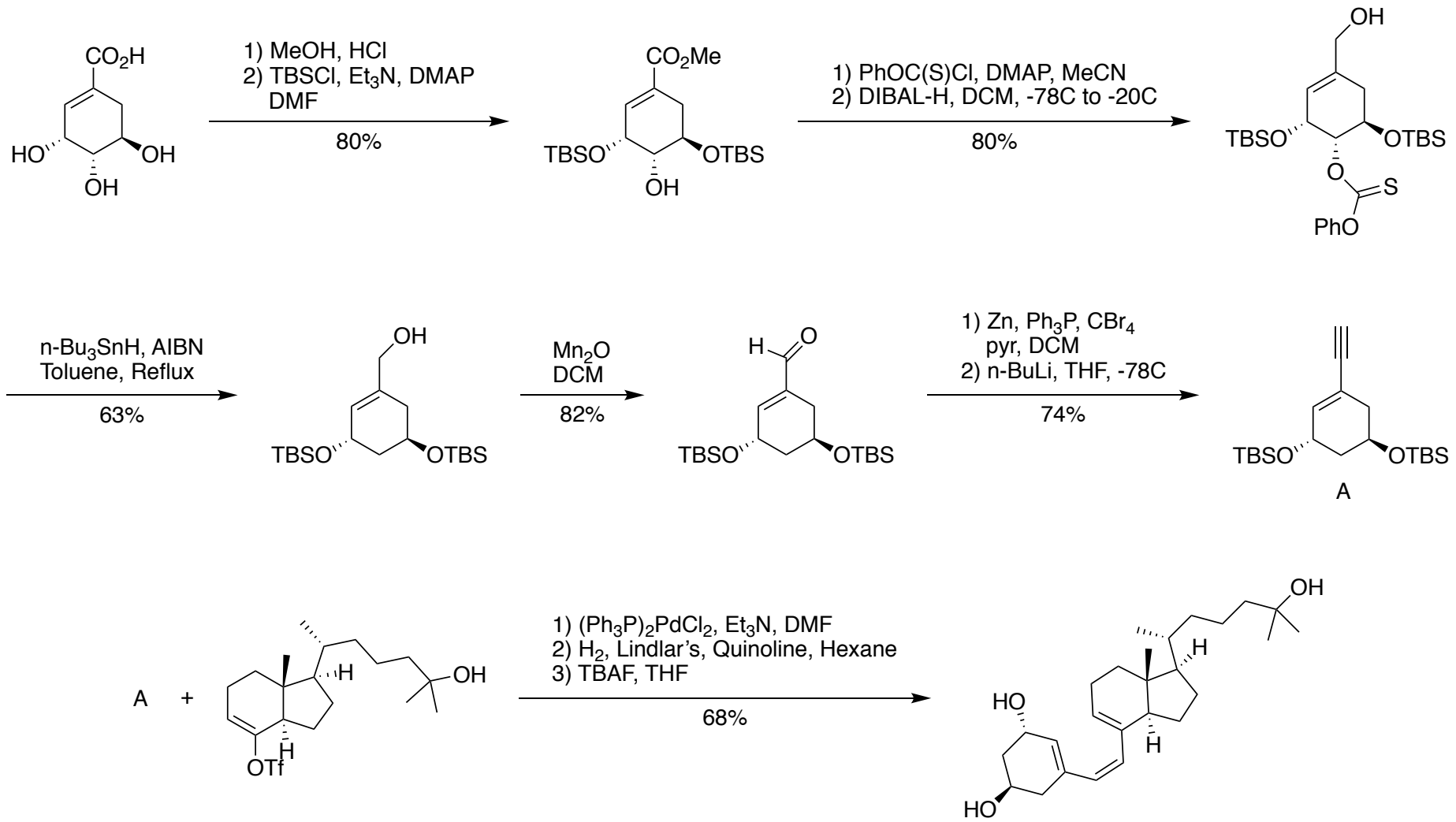
Org. Proc. Res. Dev. 2004, 8, 1, 86-91

Library Synthesis



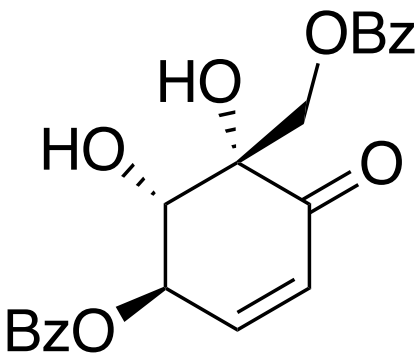
J. Comb. Chem. 2007, 9, 245–253.

Synthesis of Pre-Vitamin D3

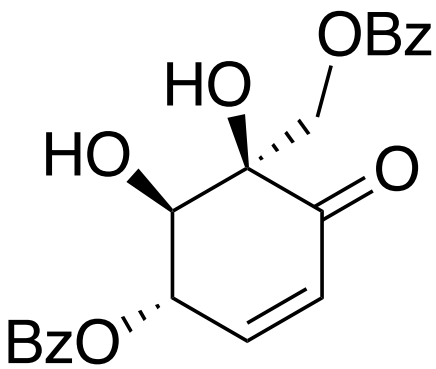


Eur. J. Org. Chem. 2017, 2017, 504–513.

Synthesis of Anti-Cancer Agents (+)-Zeylenone and (-)-Zeylenone



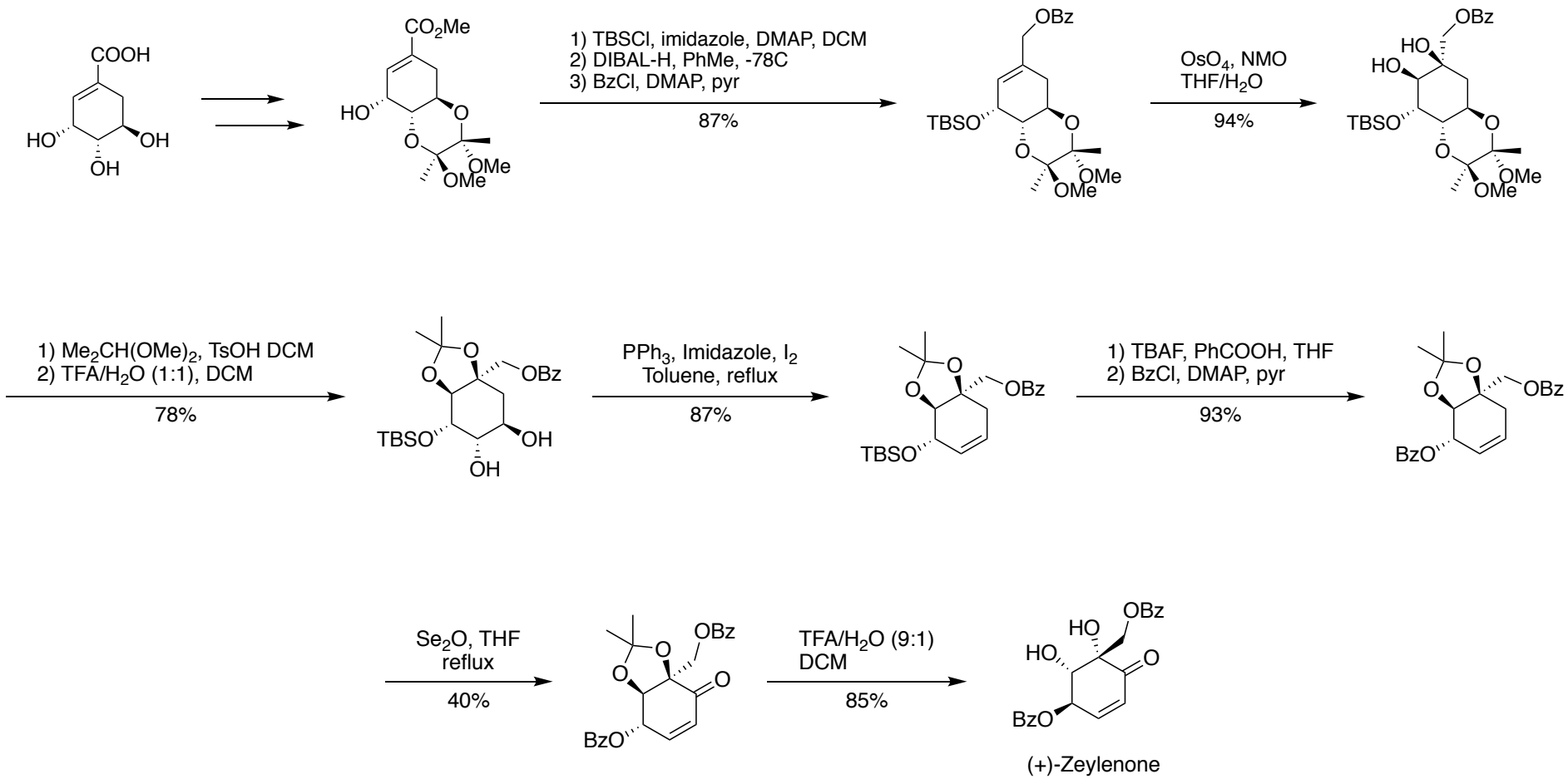
(+)-Zeylenone



(-)-Zeylenone

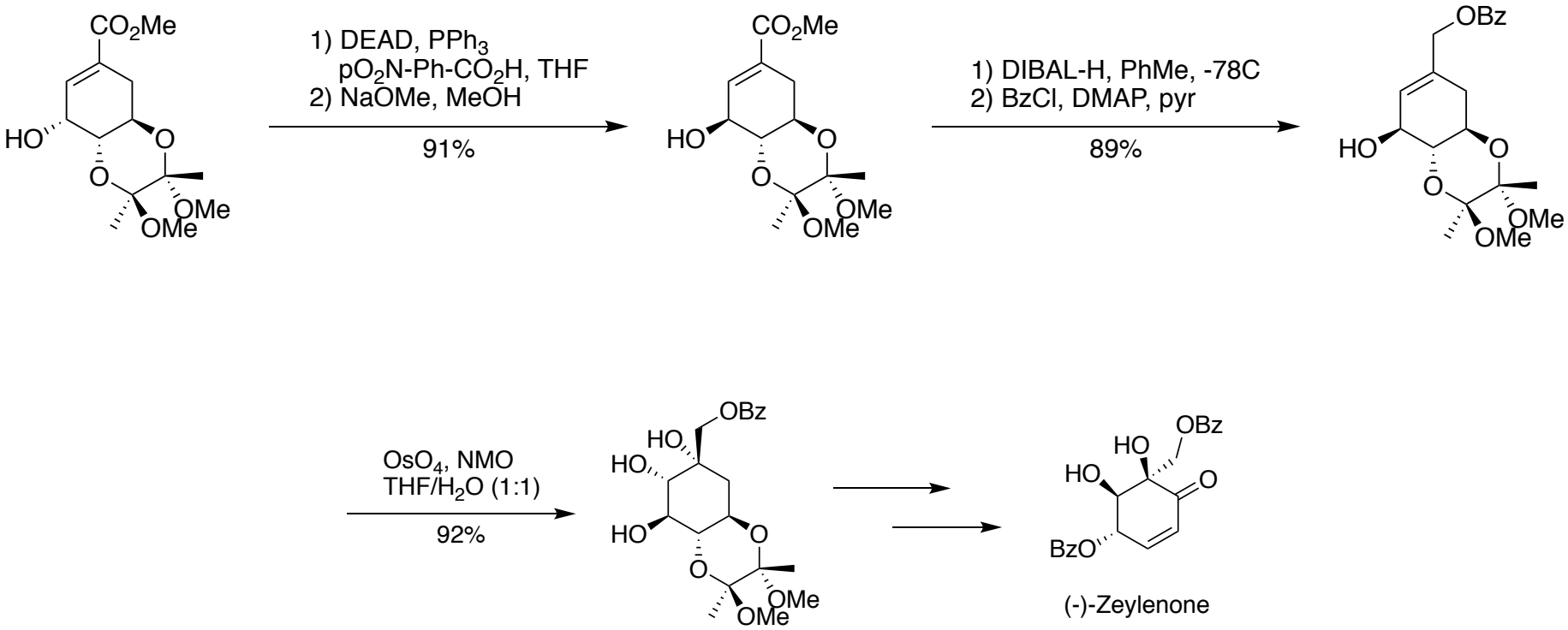
Scientific Reports | 7: 1669 | DOI:10.1038/s41598-017-01804-2

Synthesis of (+)-Zeylenone



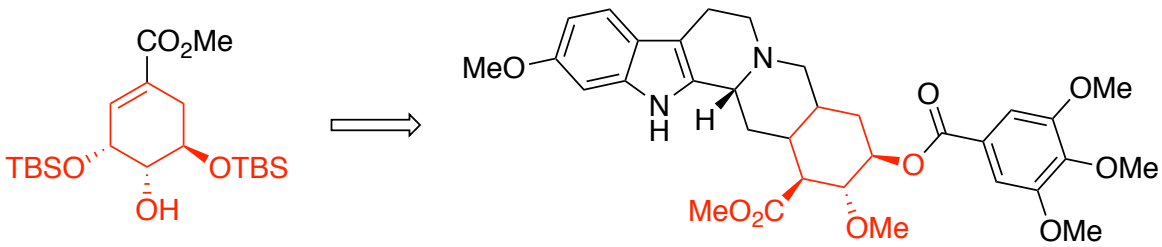
Tetrahedron, Volume 60, Issue 29, 12 July 2004, Pages 6233

Synthesis of (-)-Zeylenone



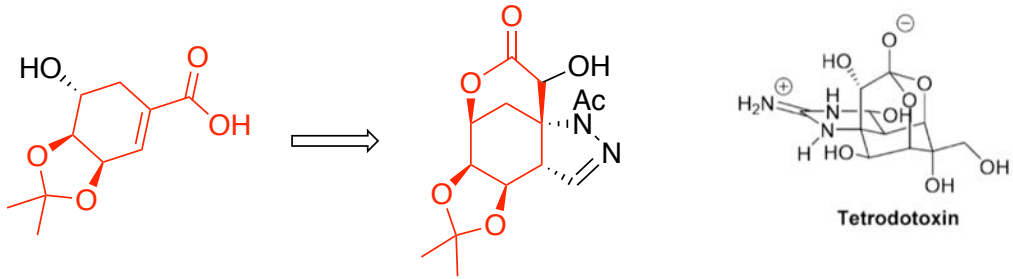
Tetrahedron, Volume 60, Issue 29, 12 July 2004, Pages 6233

Honorable Mentions



(-)-Reserpine

Helv. Chim. Acta 2007, 90, 1366–1372.



J. Org. Chem. 1970, 35, 1093–1096.

Conclusions

- Shikimic acid is a versatile and valuable precursor for a wide variety of stereochemically rich products
- The synthetic challenges associated with forming very small, but functionally rich natural products highlights synthetic organic shortcomings that still exist

Questions?