Literature Report VII

Enantioselective Total Synthesis of the Marine Macrolides Salarins A and C

Reporter: Gao-Wei Wang
Checker: Li-Xia Liu
Date: 2024-4-22

Wilson, D. M.; Britton, R. *J. Am. Chem. Soc.* **2024**, *146*, 8456-8463

CV of Prof. Robert Britton

Background:

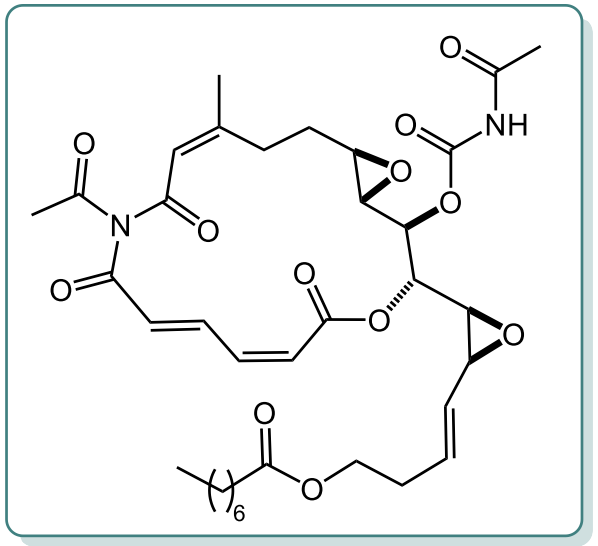
- **1996** B.S., University of Waterloo
- **2002** Ph.D., University of British Columbia
- **2002-2004** Postdoctoral Fellow, University of Cambridge
- **2004-2005** Senior Research Chemist, Merck Frosst Canada
- **2005-now** Assistant Prof., Associate Prof., Full Prof., Simon Fraser University

Research:

Natural product chemistry total synthesis, method development, *J*-based configuration /conformation analysis, structure activity relationship studies

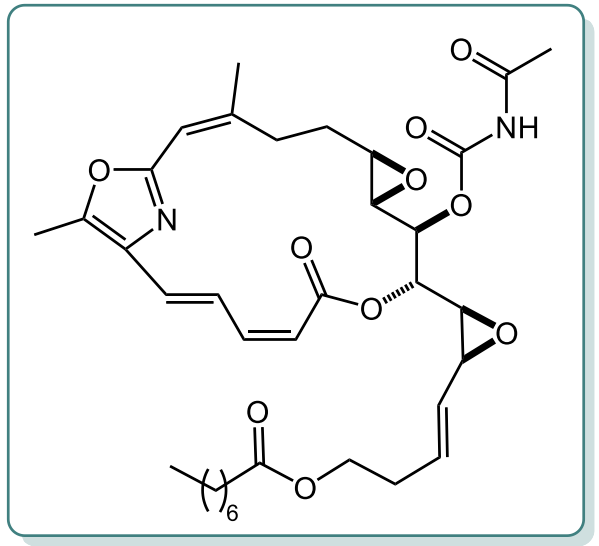
Contents

Introduction



Salarin A

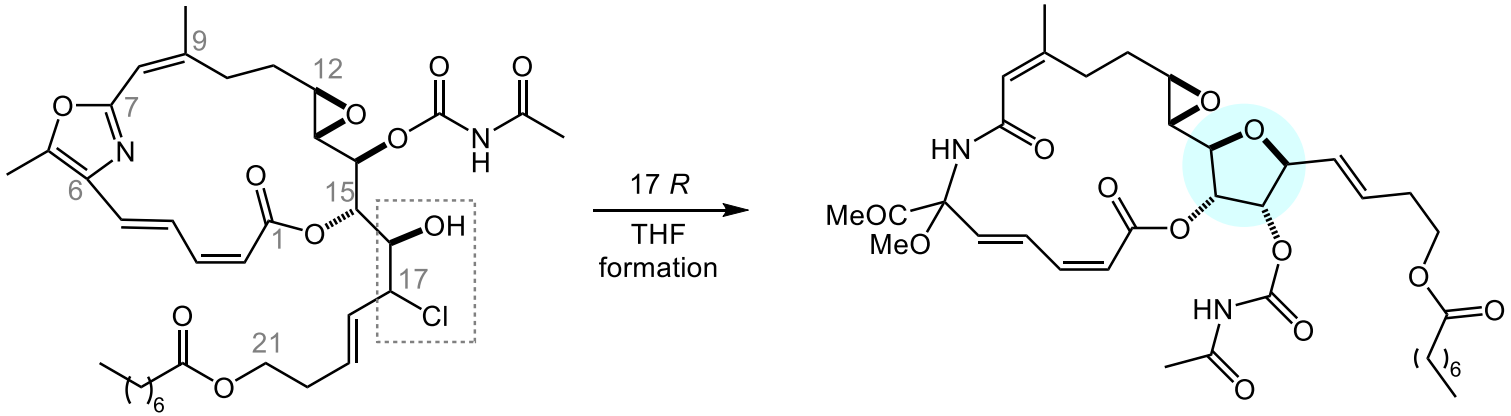
Fascaplysinopsis sp. sponge



Salarin C

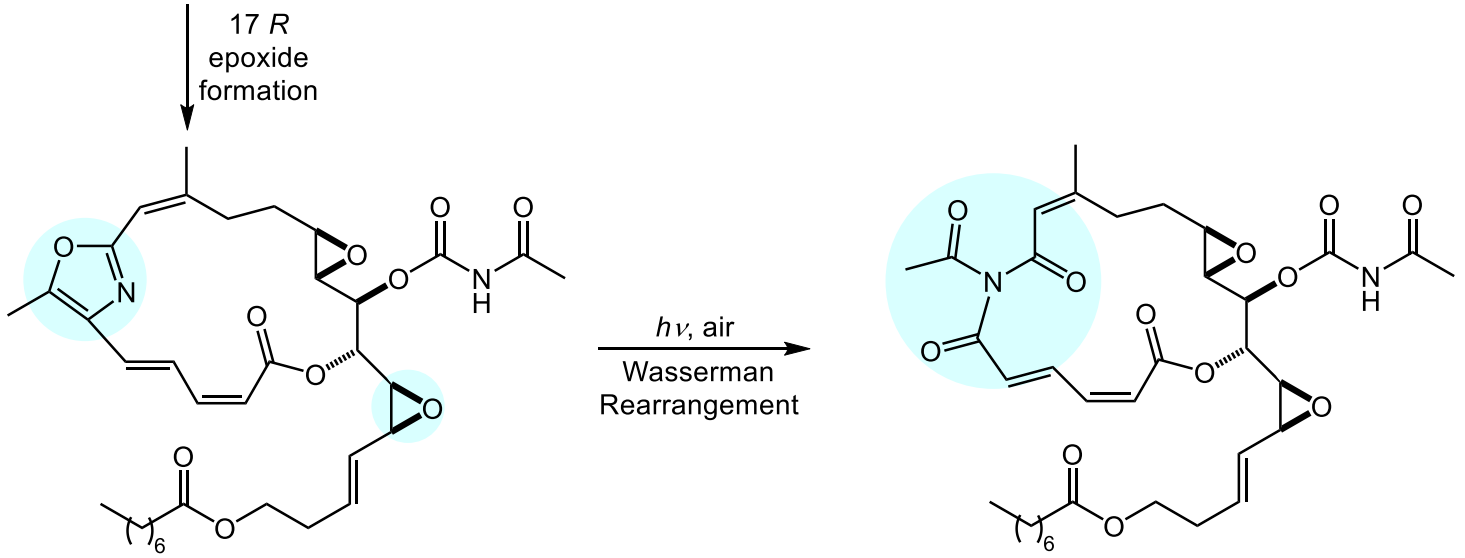
- An unusual *N*-acetyl carbamate and caprylic ester side chain
- The presence of either a strained triene oxazole or triacyl amine within the macrocycle
- The isolation and elucidation by Kashman and co-workers in 2008

Introduction



salarin F (3), IC_{50} > 1μM

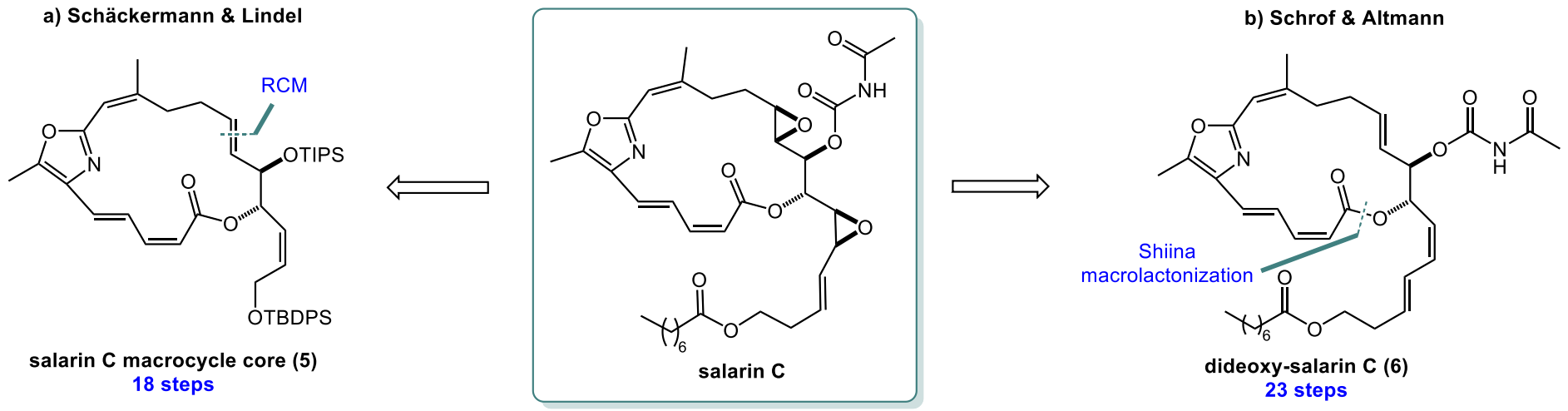
salarin B (4), IC_{50} ~ 1μM



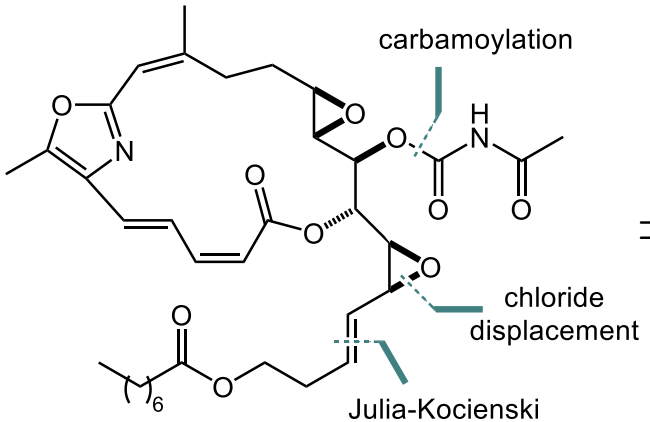
salarin C (1), IC_{50} = 5 nM

salarin A (2), IC_{50} > 1μM

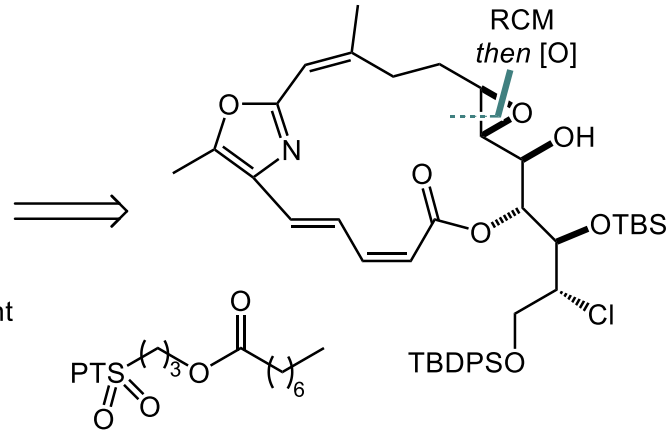
Synthetic Precedent for the Construction of Salarin C



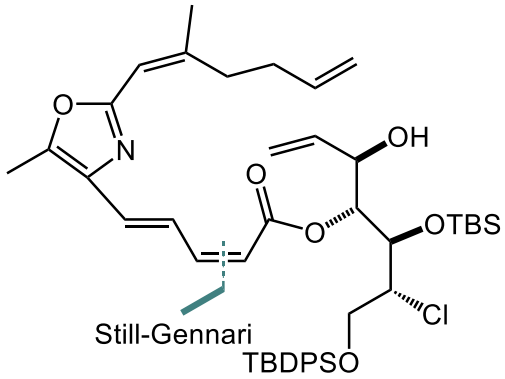
Retrosynthetic Analysis of Salarin C



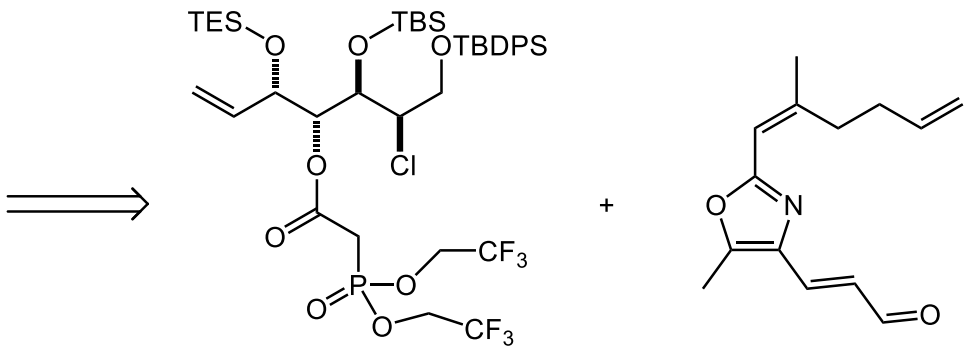
salarin C (1)
24 steps



8 **9**



10

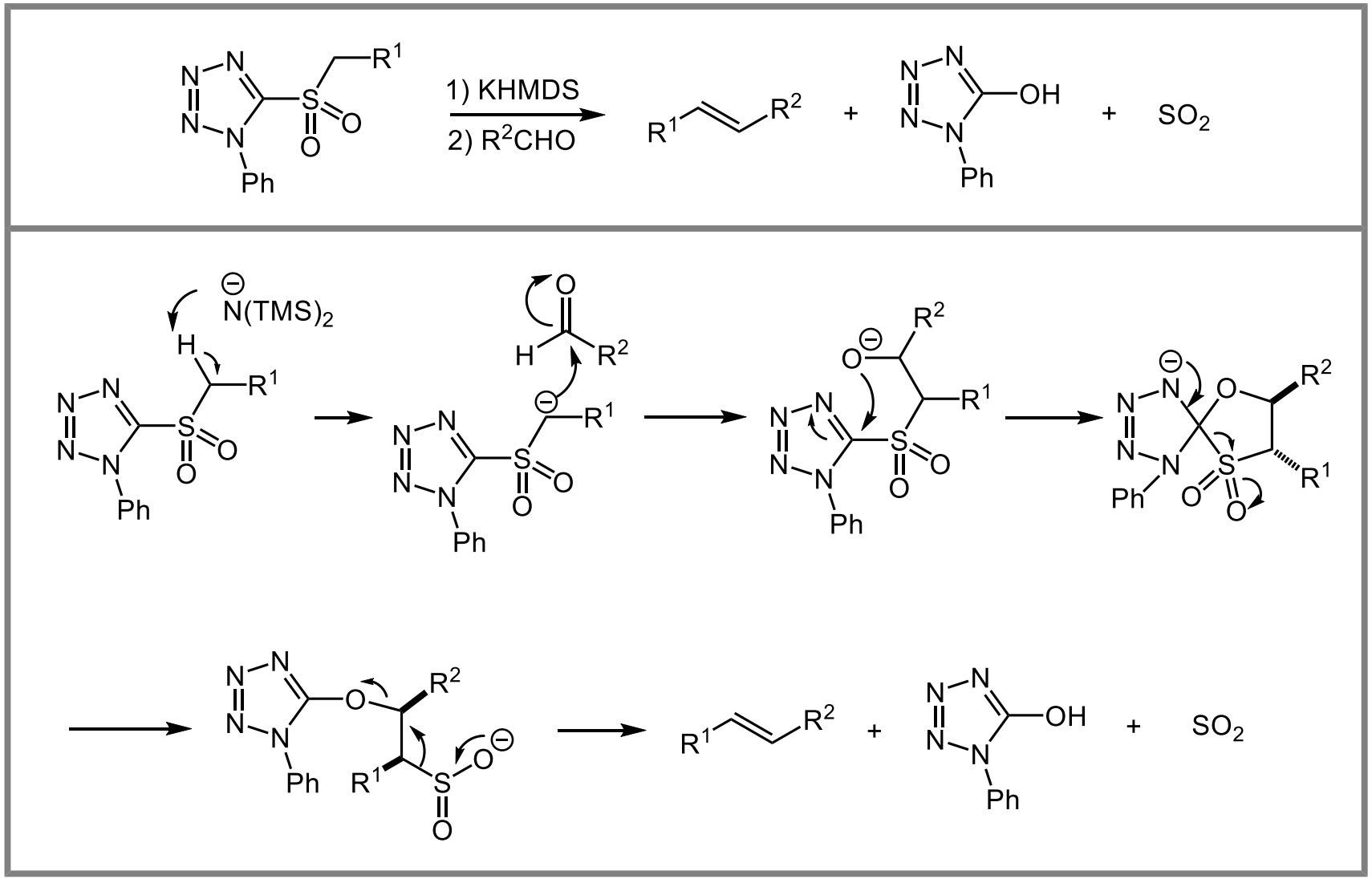


11

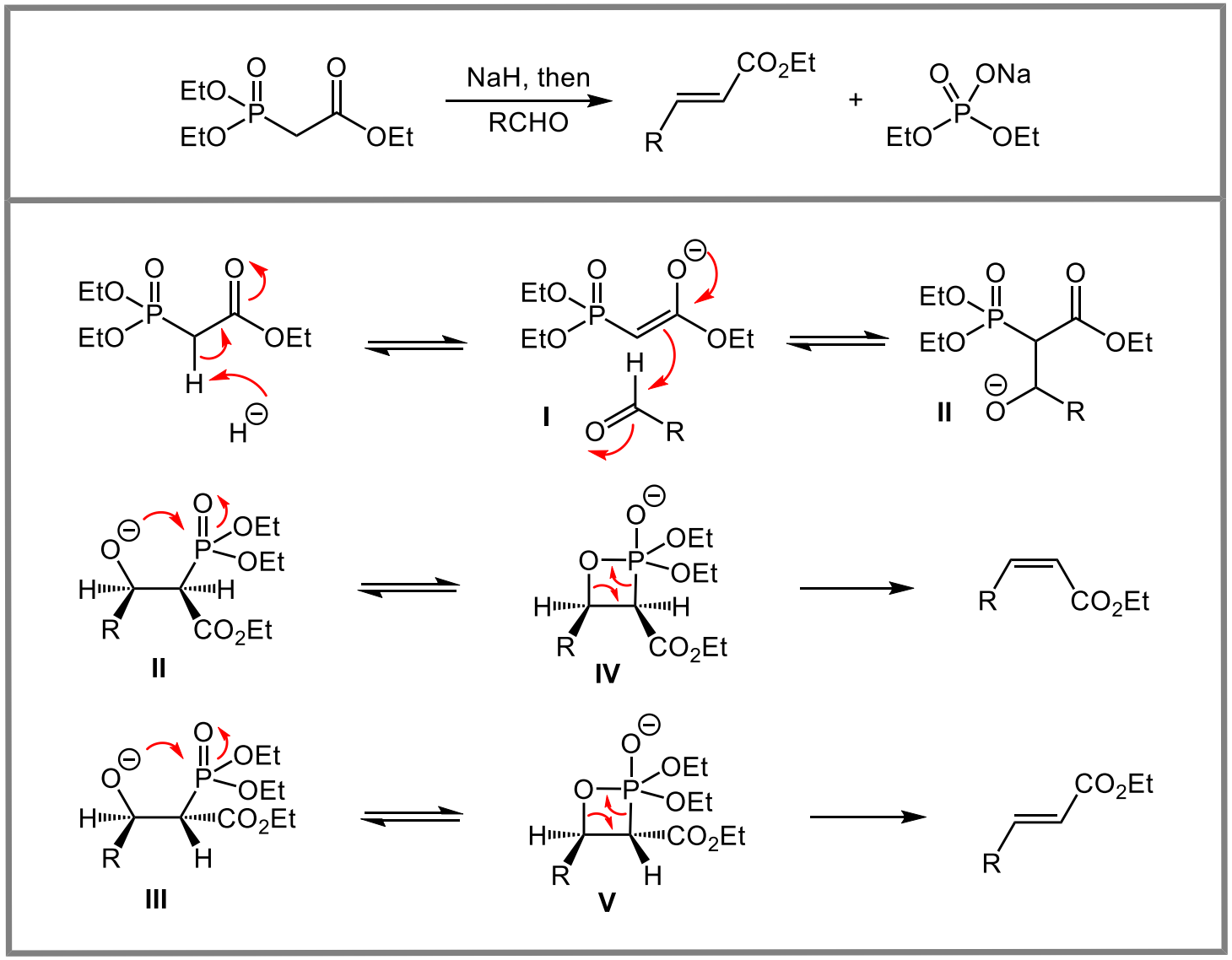
+

12

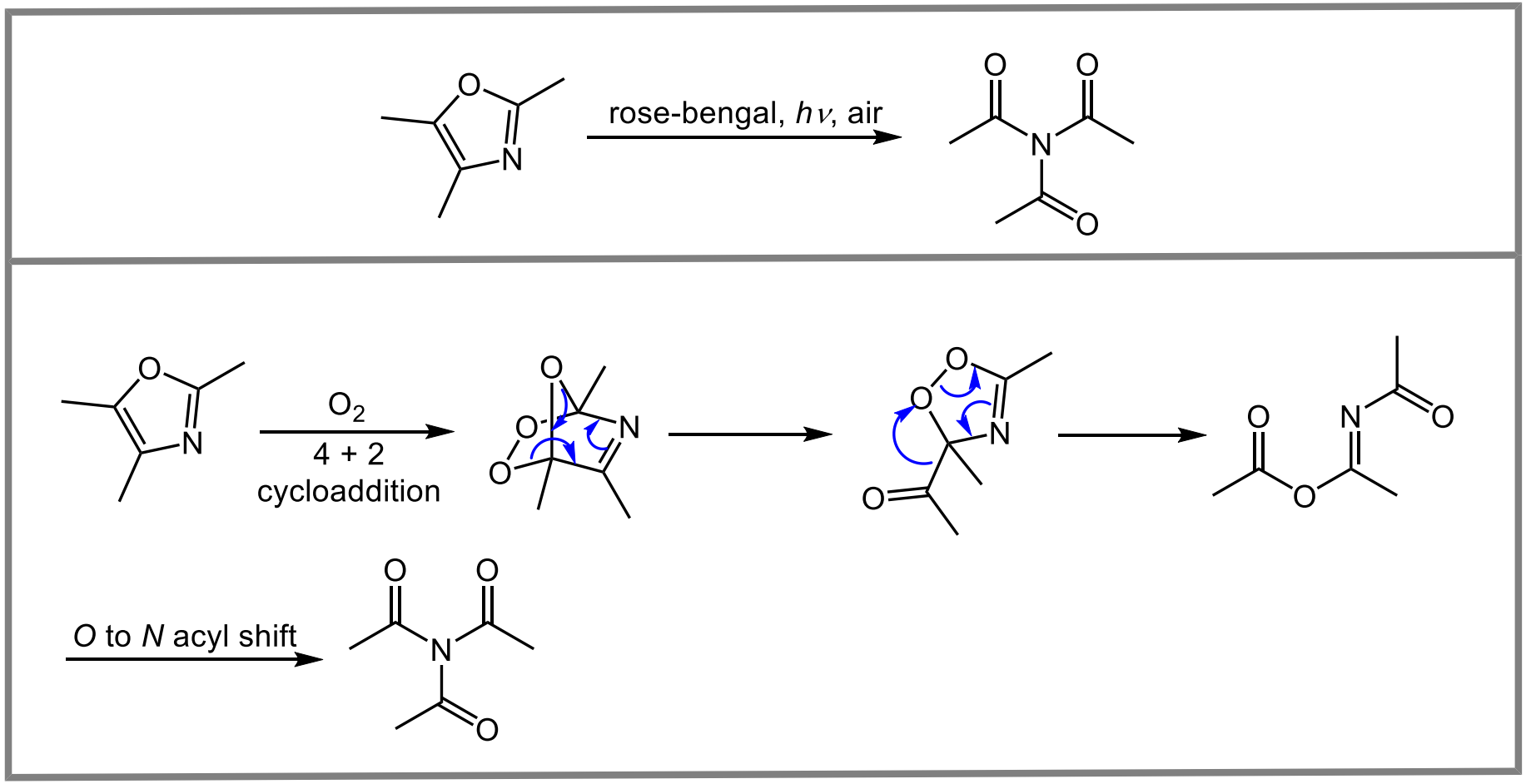
Julia–Kocienski Olefination



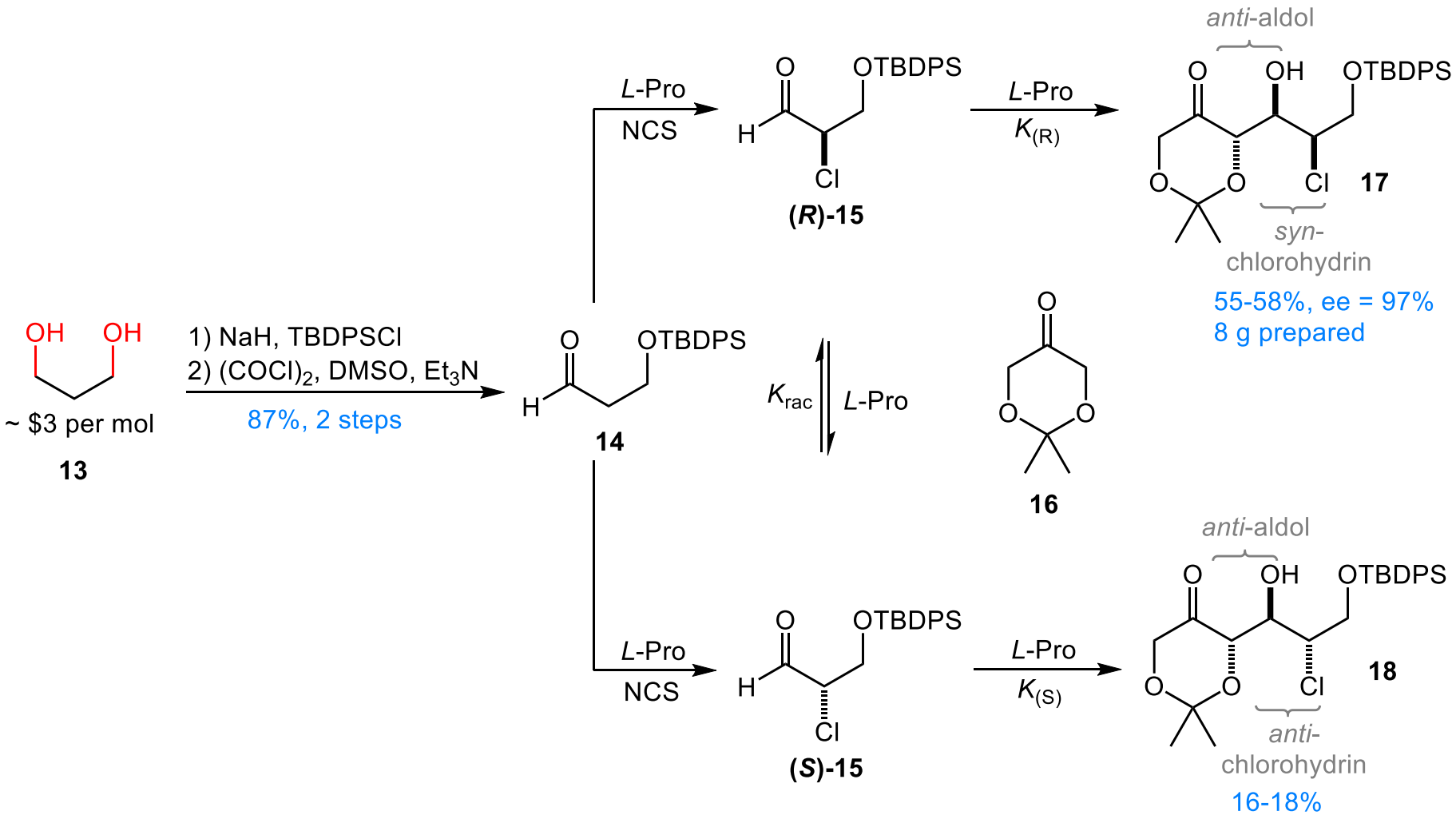
HWE Olefination



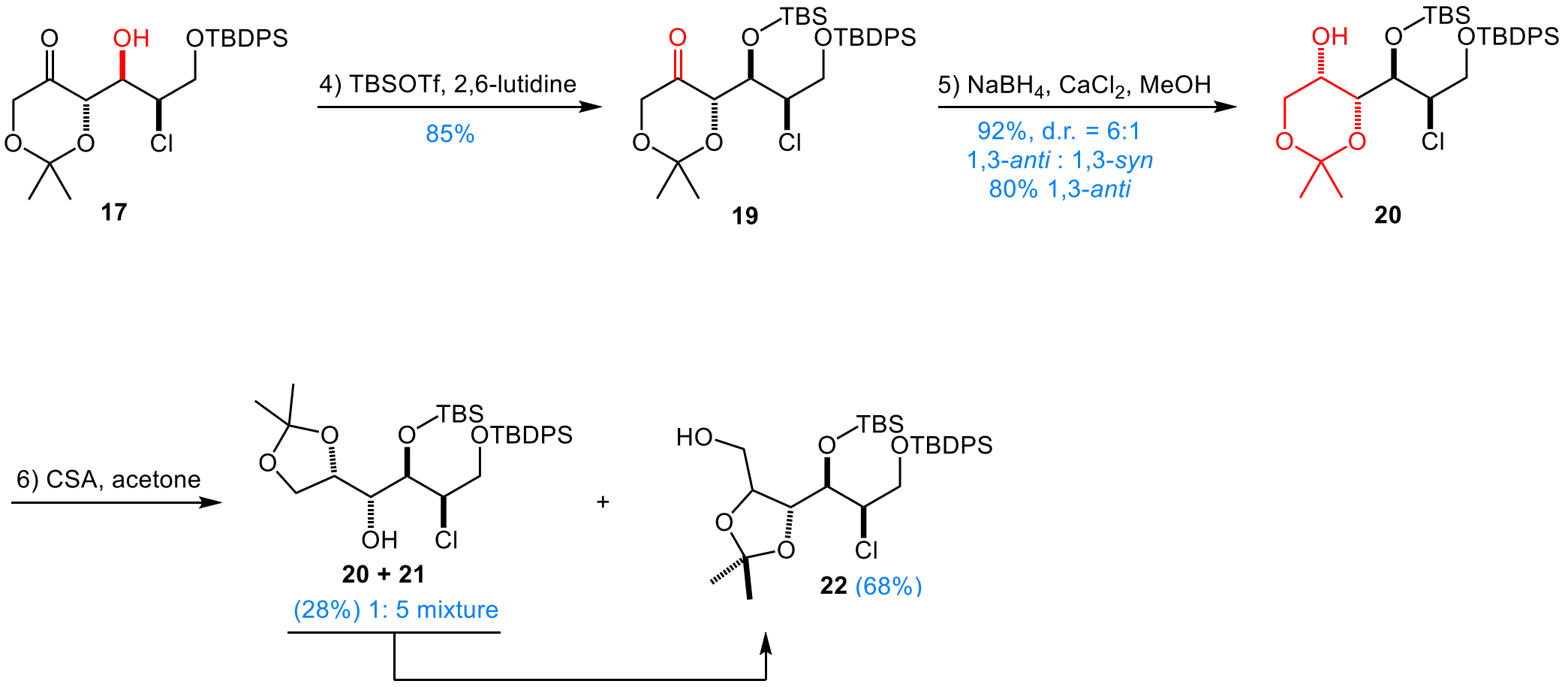
Wasserman Rearrangement



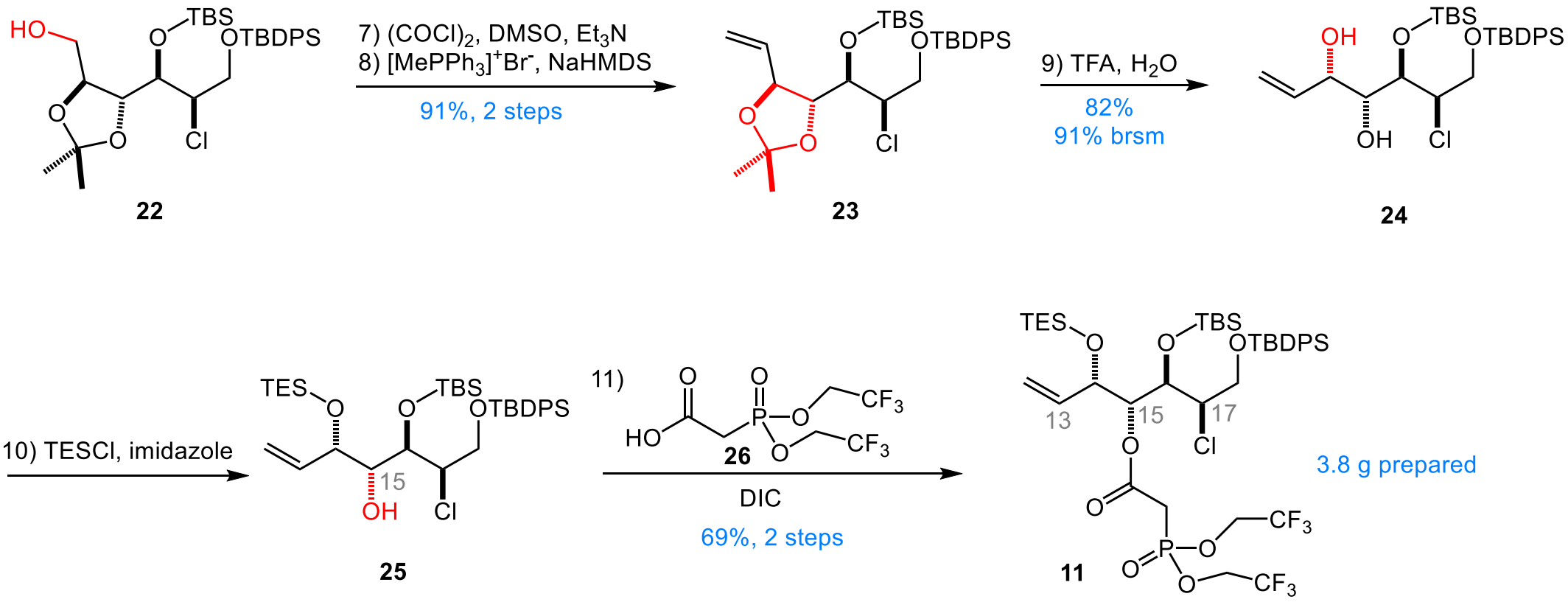
Synthesis of Intermediate 17



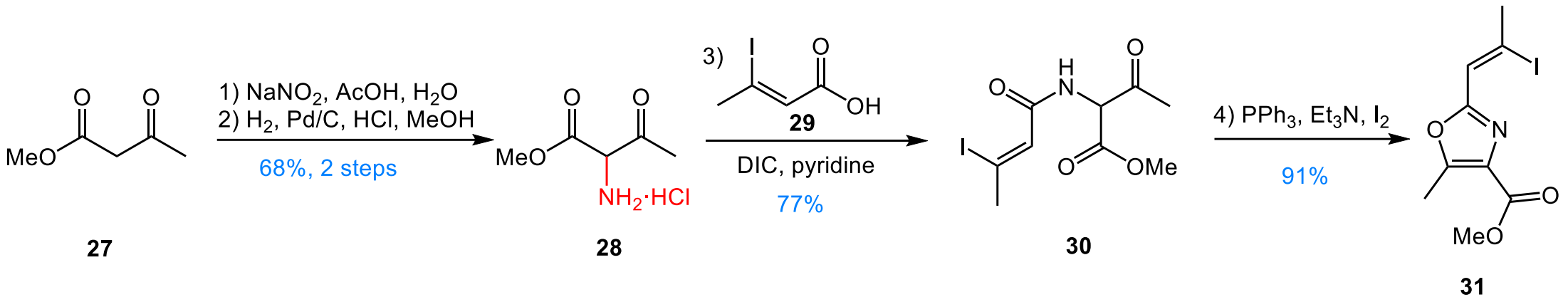
Synthesis of Intermediate 22

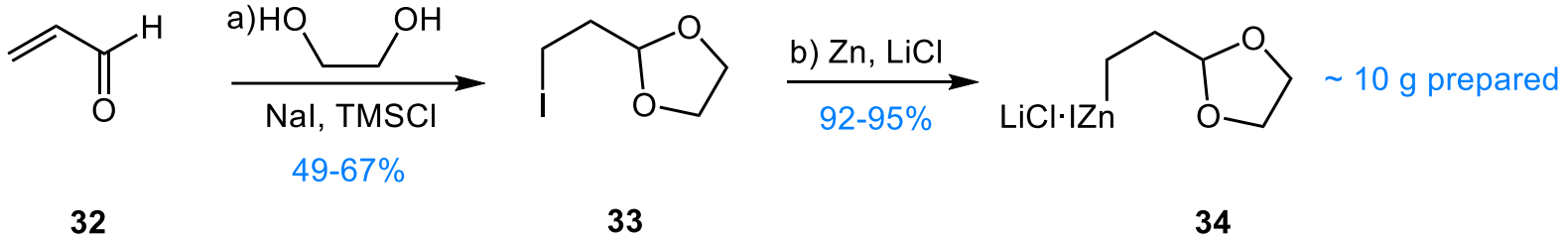


Synthesis of Intermediate 11

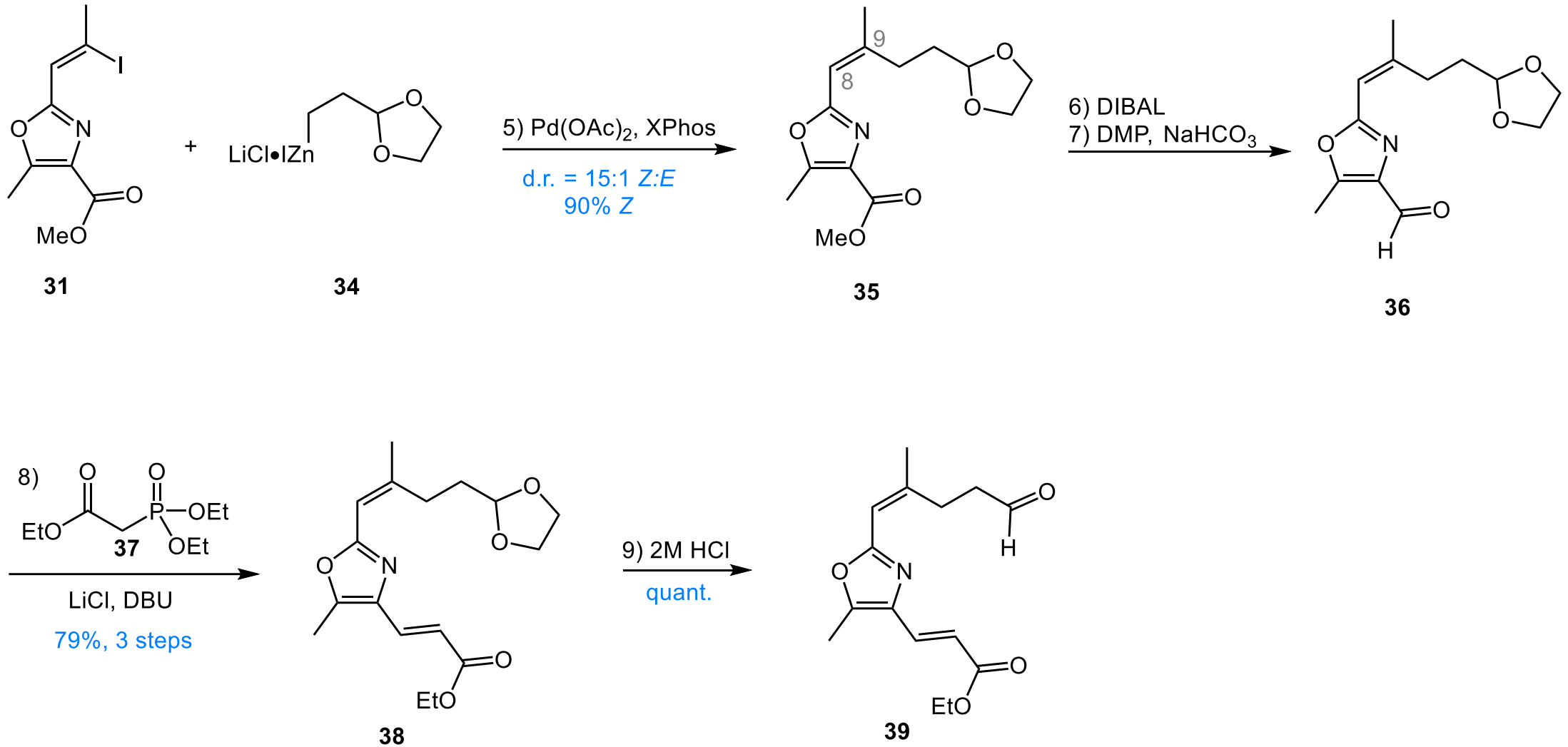


Synthesis of Intermediates 31 and 34

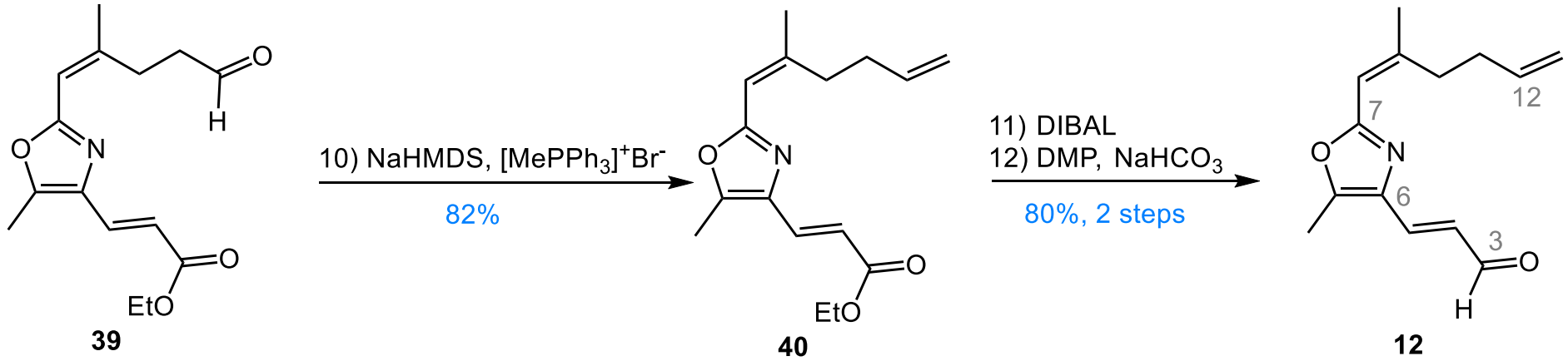


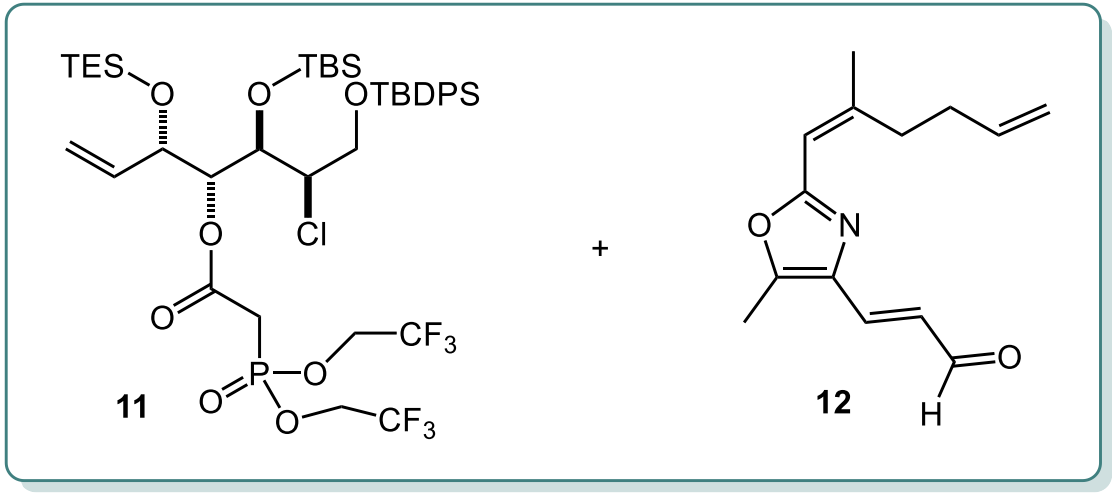


Synthesis of Intermediate 39

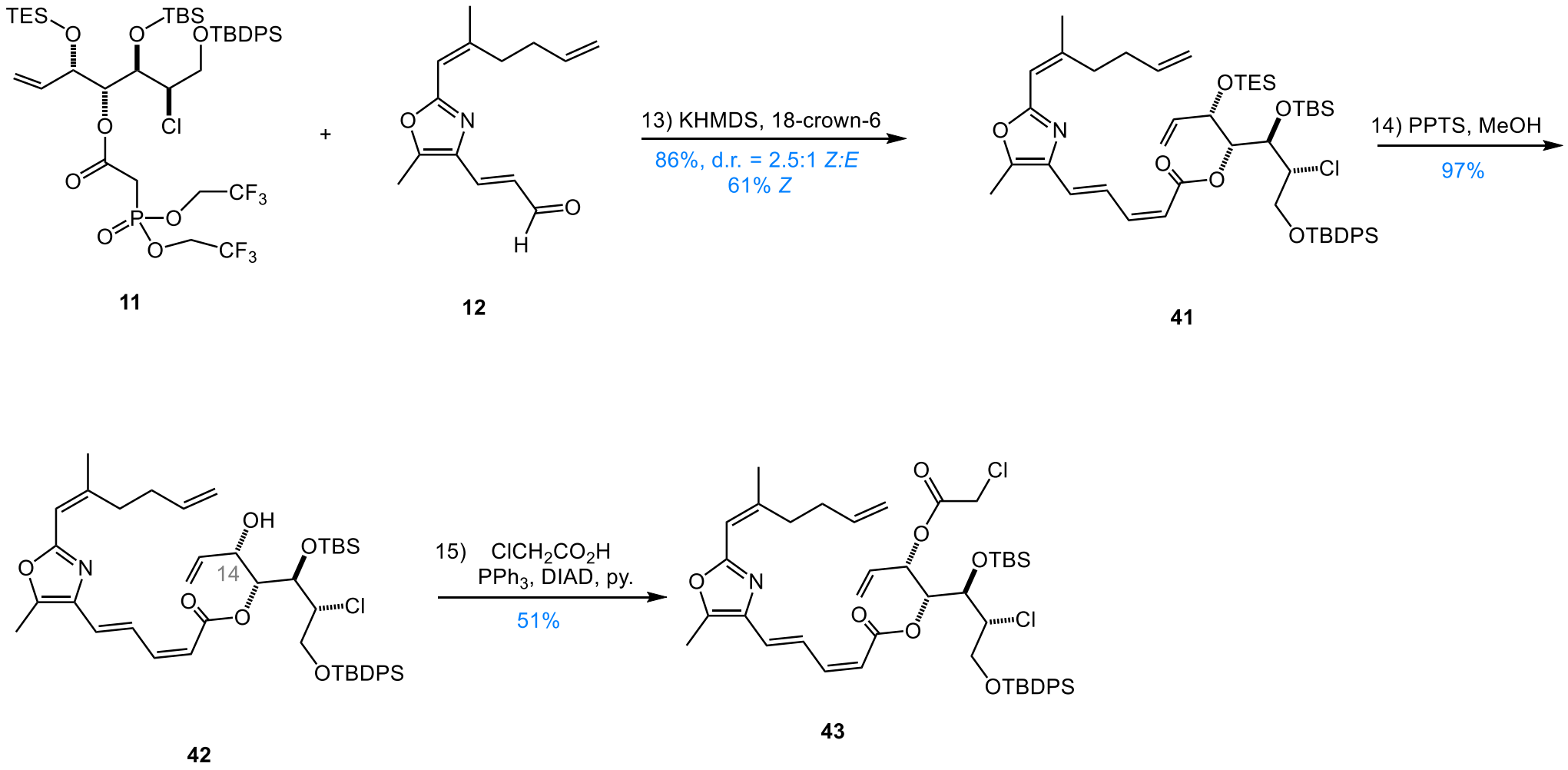


Synthesis of Intermediate 12

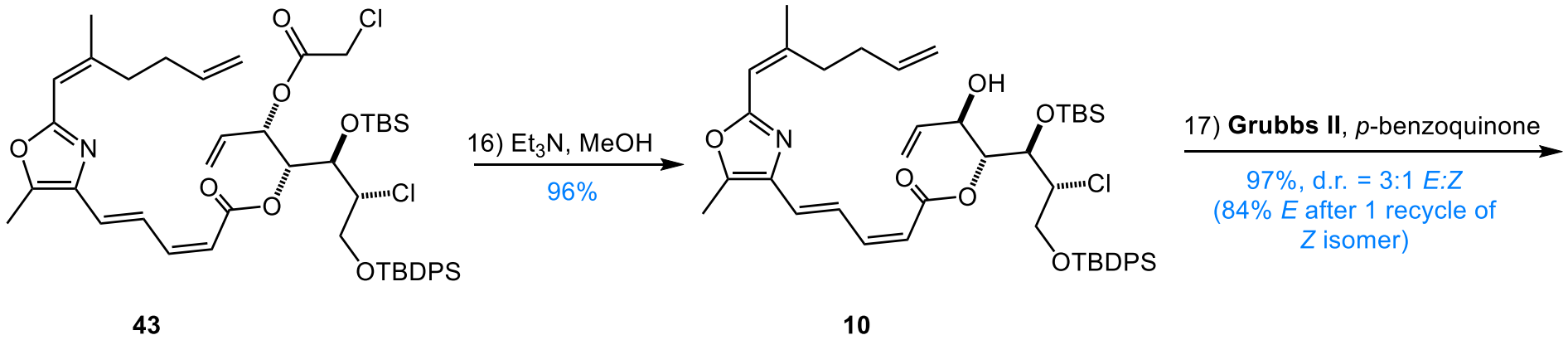




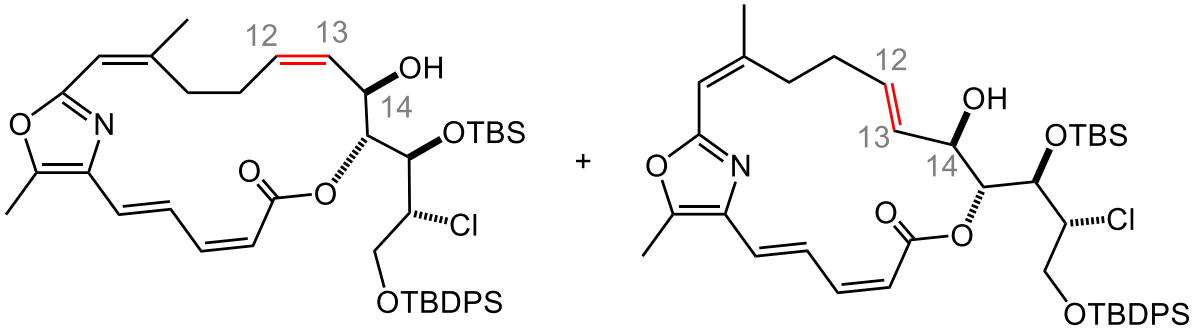
Synthesis of Intermediate 43



Synthesis of Intermediate 45



43 **10**

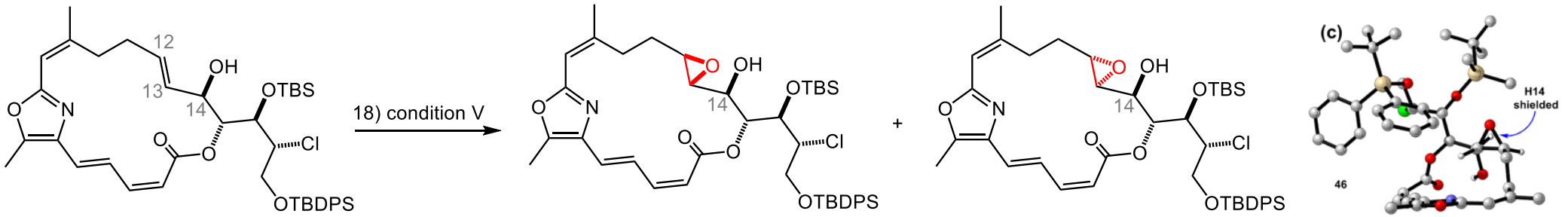


44 **45**

Grubbs II, *p*-benzoquinone

48%

Reaction Conditions for the Epoxidation of 45



45

9

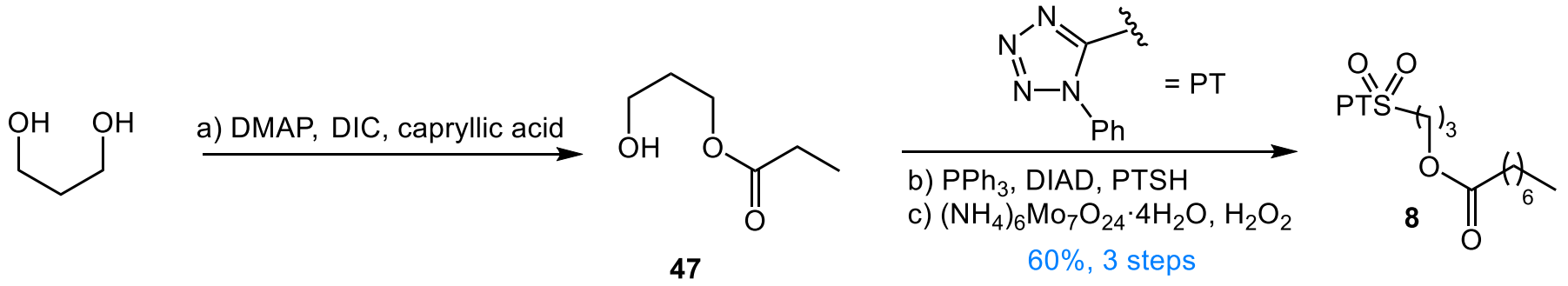
δ (H14) = 4.84 ppm

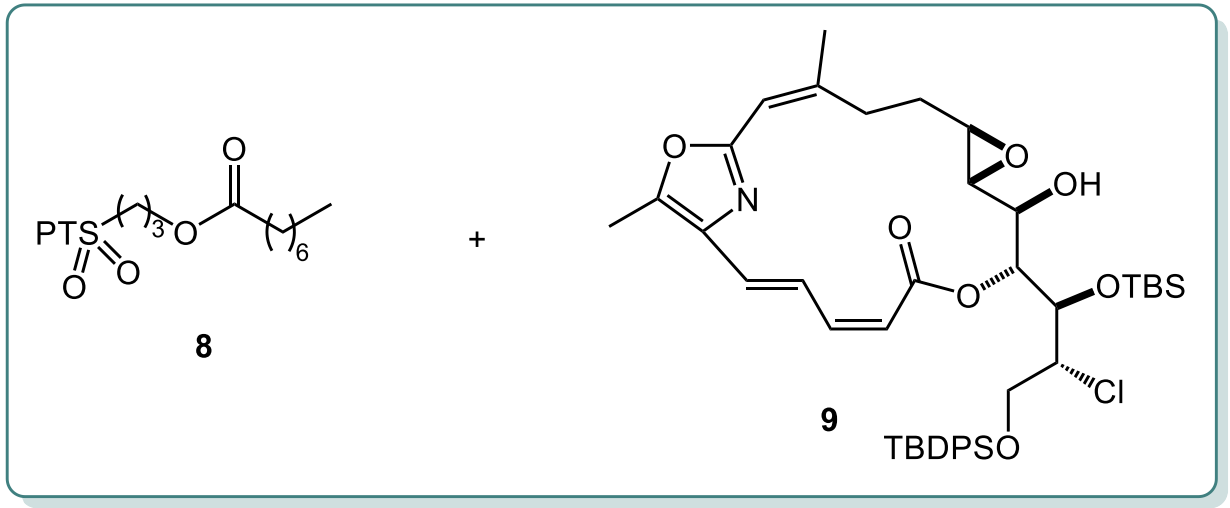
46

δ (H14) = 3.70 ppm

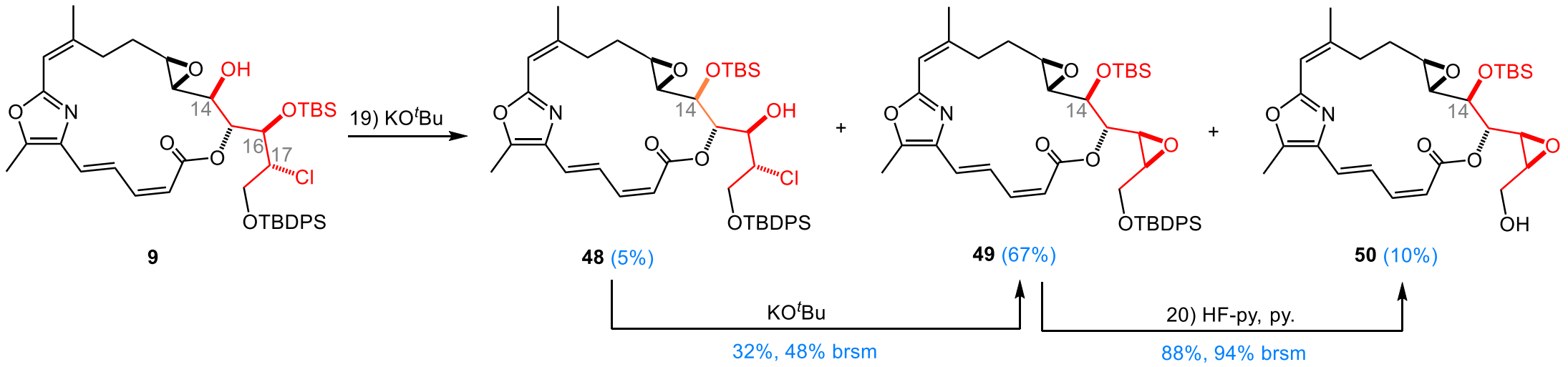
Entry	Reagent	Solvent	T (°C)	t (h)	d.r.	Yield of 9
I	$VO(acac)_2$ (10 mol%), ^tBuOOH	C_6H_6	rt	3	1:1	65%
II	$VO(acac)_2$ (10 mol%), ^tBuOOH	CH_2Cl_2	-20	24	3:1	42%
III	$VO(acac)_2$ (10 mol%), ^tBuOOH, 3Å MS	CH_2Cl_2	rt	1	2.5:1	74%
IV	$Ti(O^iPr)_4$ (1.2 eq.), ^tBuOOH, 3Å MS	CH_2Cl_2	rt	1	11:1	89%
V	**$Ti(O^iPr)_4$ (1.2 eq.), ^tBuOOH, 3Å MS**	**CH_2Cl_2**	**-20 to -5**	**1**	**19:1**	**96%**

Synthesis of Intermediate 8

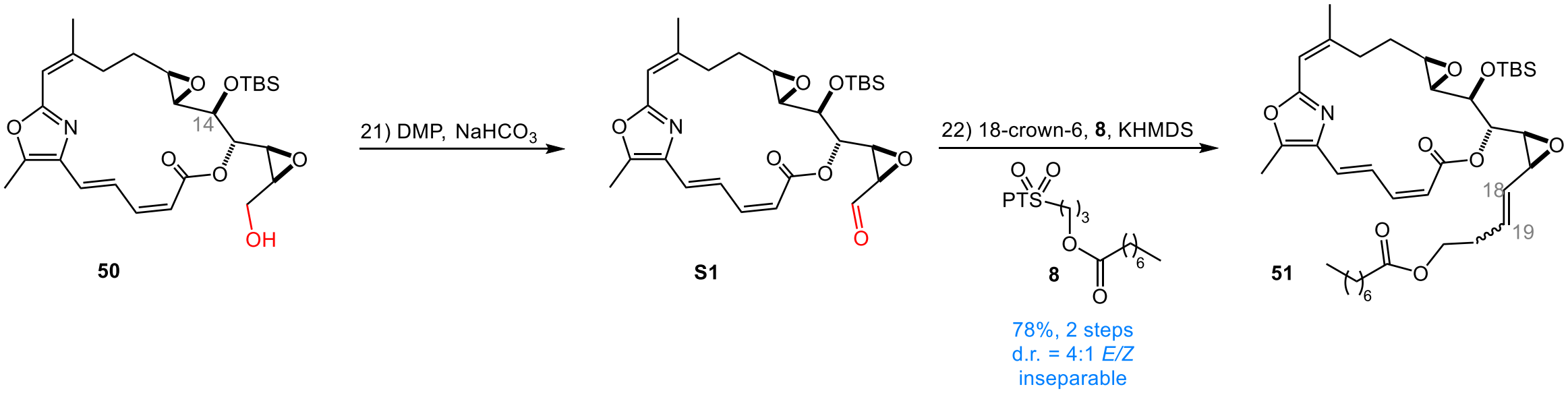




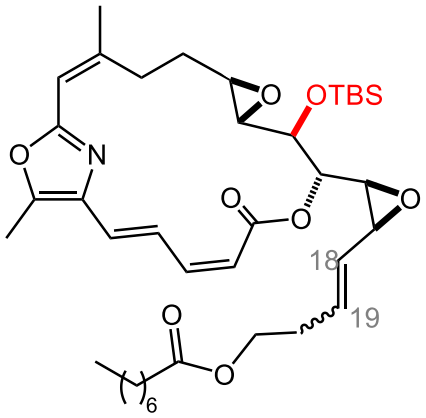
Synthesis of Intermediate 50



Synthesis of Intermediate 51



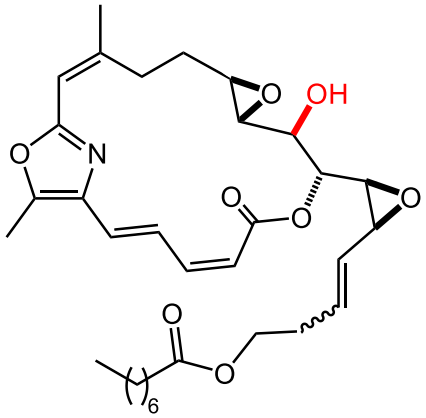
Synthesis of Salarin C



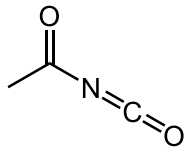
51

23) TBAF, NH_4Cl

75%

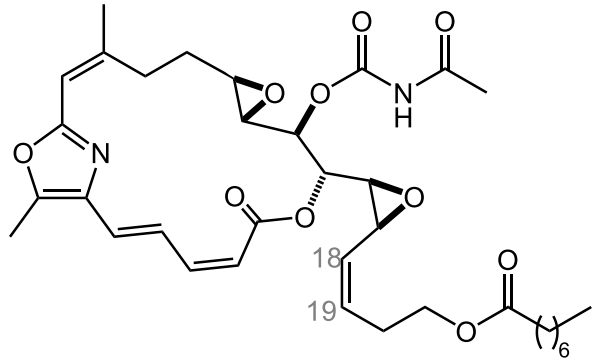


52



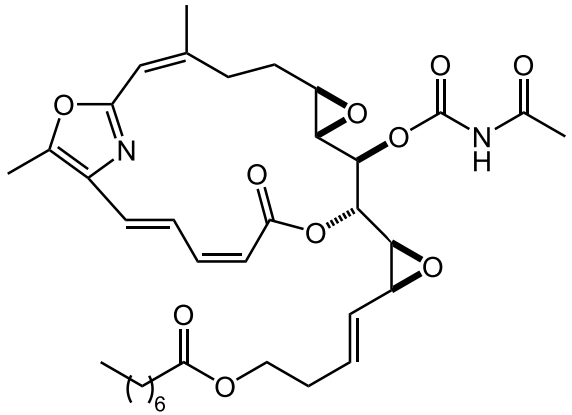
24) 2,6-lutidine

84% *E/Z* isomers separable



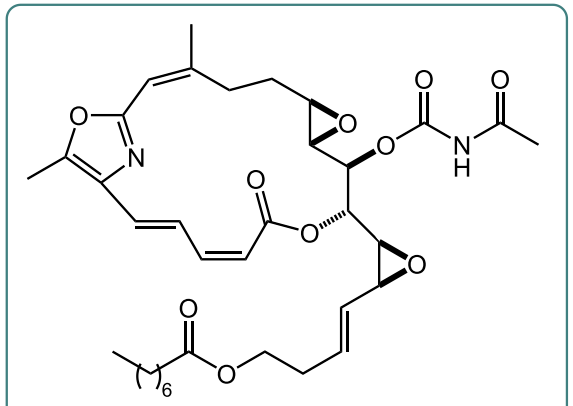
C17,C18-*Z* salarin C (53) (12%)

+



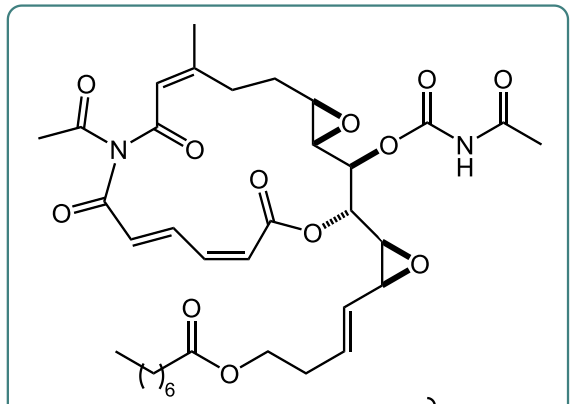
salarin C (1) (72%)
1.4%, 24 steps
from methylacetoacetate

Synthesis of Salarin A



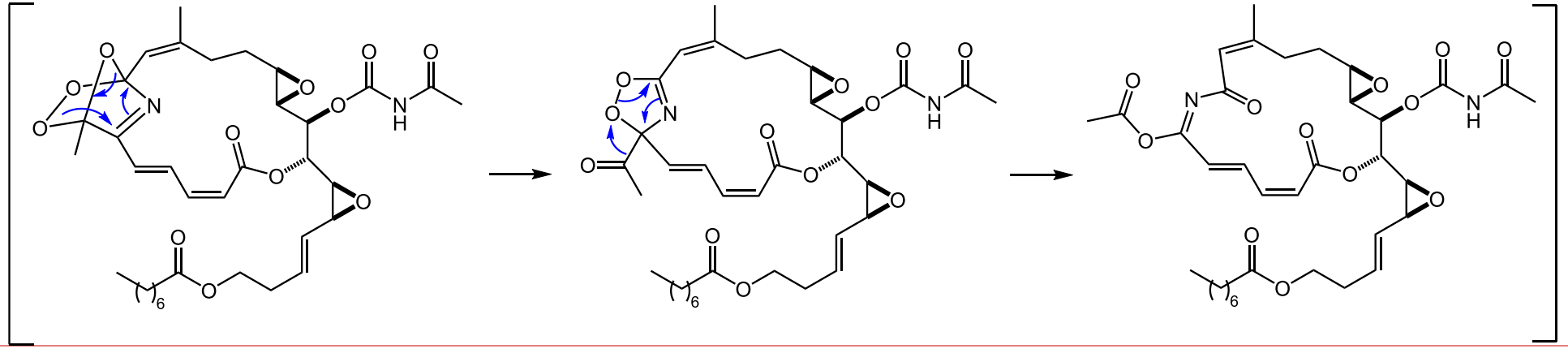
salarin C (1) (72%)
1.4%, 24 steps
from methylacetoacetate

25) rose-bengal, *hν*, air, $CDCl_3$



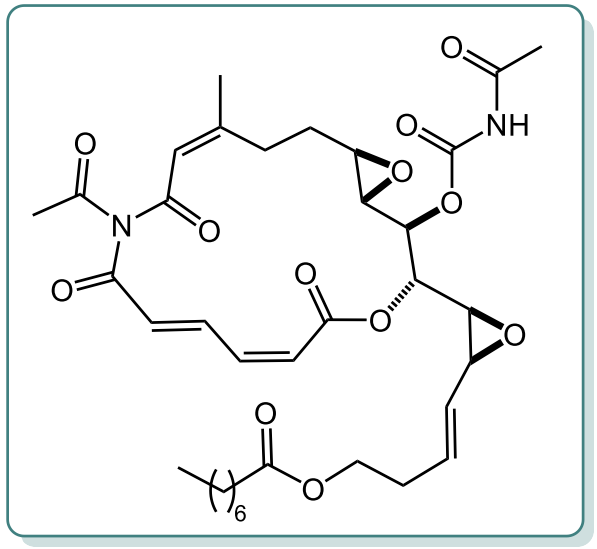
salarin A (2) (24%) + ***Z,Z*-dienoate** + ***E,E*-dienoate** + ***E,Z*-dienoate** } 38%

4 + 2
cycloaddition



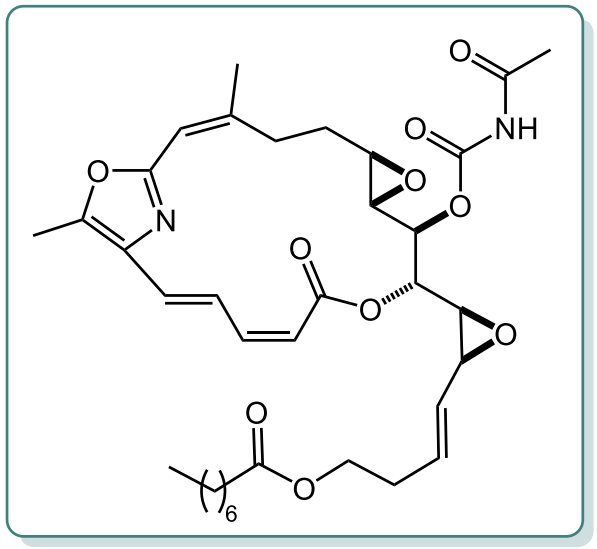
O to *N*
acyl shift

Summary



Salarin A

1.0%, 23 steps from 1,3-propanediol



Salarin C

1.4%, 24 steps from methyl acetoacetate

- ✓ **Macrocycle formation *via* ring-closing metathesis**
- ✓ **Macrocyclic substrate-controlled epoxidation of the C12−C13 allylic alcohol**
- ✓ **A late-stage Julia−Kocienski olefination to install the side chain**

Writing strategy

☐ The First Paragraph

沙拉素家族天然产物的来源

沙拉素的药物活性

介绍本文合成策略

✓ **Salarins are a small family of cytotoxic nitrogenous marine macrolides isolated from a spicule-less *Fascaplysinopsis sp*. sponge collected off the coast of Madagascar. Beginning with the isolation and elucidation of the planar structures of salarins A, B, and C by Kashman and co-workers in 2008, salarins have been the subject of sustained research.**

✓ **Following the initial disclosure of their structures, salarins were screened against a chronic myelogenous leukemia (CML) cell line (K562).**

✓ **A brief summary of our synthetic strategy is presented in retrosynthetic form in Figure 1d. Thus, salarin C could be prepared from the protected chlorohydrin and salarin F analogue 9 *via* epoxide formation, Julia−Kocienski olefination with 8, and carbamoylation. ...**

Writing Strategy

☐ The Last Paragraph

总结工作

↓

本文亮点

↓

展望

- ✓ In conclusion, we report the first total synthesis of salarin C in 1.4% yield over 24 steps from methyl acetoacetate or 1.0% yield in 23 steps from 1,3-propanediol.
- ✓ Additionally, we have demonstrated the biomimetic Wasserman rearrangement of salarin C to salarin A in the presence of sunlight/air. Notably, in our hands, all macrocyclic intermediates were stable provided they were kept away from sunlight.
- ✓ Studies are ongoing in our laboratory to biologically evaluate these fascinating compounds and create synthetic derivatives to support structure−activity relationship studies.

Representative examples

- ✓ We were wary of the noted instability of both the natural product and the synthetic precursors. (警惕)
- ✓ Heading into the final stages of the synthesis we anticipated that several protecting group manipulations would be required before formation of the C16−C17 epoxide. (进入最后阶段)
- ✓ At this juncture, primary alcohol 50 was oxidized with Dess−Martin periodinane47 in the presence of $NaHCO_3$. (在这个节骨眼上)

Acknowledgment

Thanks
for your attention !