Literature Report (3)

Light-Mediated Total Synthesis of 17-Deoxyprovidencin

Reporter: Yue Ji
Checker: Xian-Feng Cai
Date: 2014/06/17

Mulzer, J. *et al*.
Angew. Chem. Int. Ed. **2014**, *53*, 3859.

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- Introdunction
- Retrosynthesis of 17-deoxyprovidencin
- Total Synthesis of 17-deoxyprovidencin
- The first generation approach to 17-deoxyprovidencin
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Introduction

Education

1974	PhD in Organic Chemistry, Supervisor Professor Rolf Huisgen, University of Munich
1974-1975	Postdoctoral fellow Harvard University (Supervisor Professor E. J. Corey)
1984-1995	Free University of Berlin
1996-	University of Vienna

Prof. Dr. Johann Mulzer
University of Vienna

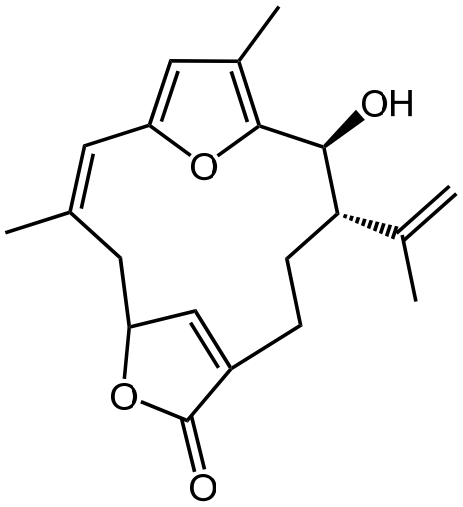
Research Interests

Asymmetric Synthesis of Natural Products (Macrolides, Alkaloids, Terpenes, Peptides and Amino Acids);

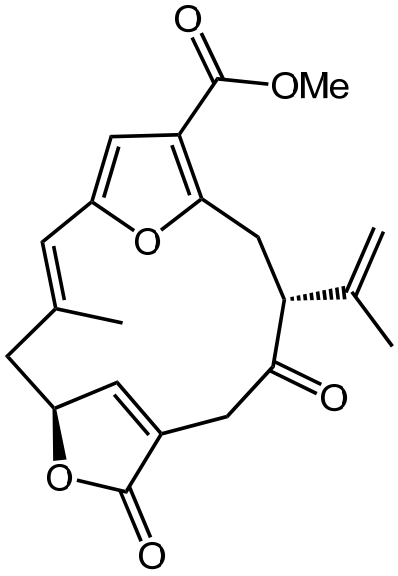
Development of Synthetic Methodology (among aldol additions, β-lactone chemistry, olefinations, ring enlargements, sigmatropic rearrangements);

Elucidation of Organic Reaction Mechanisms

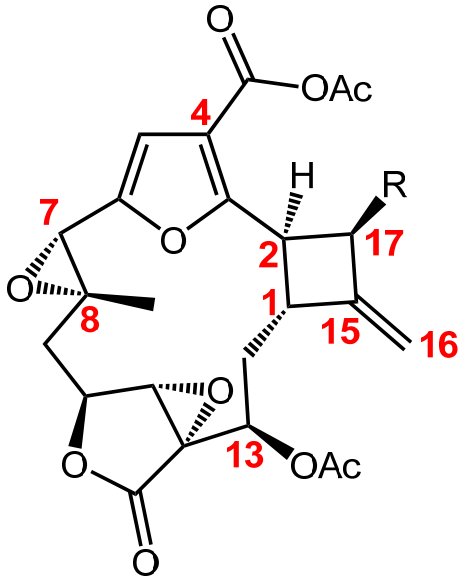
Introduction



bipinnatin J

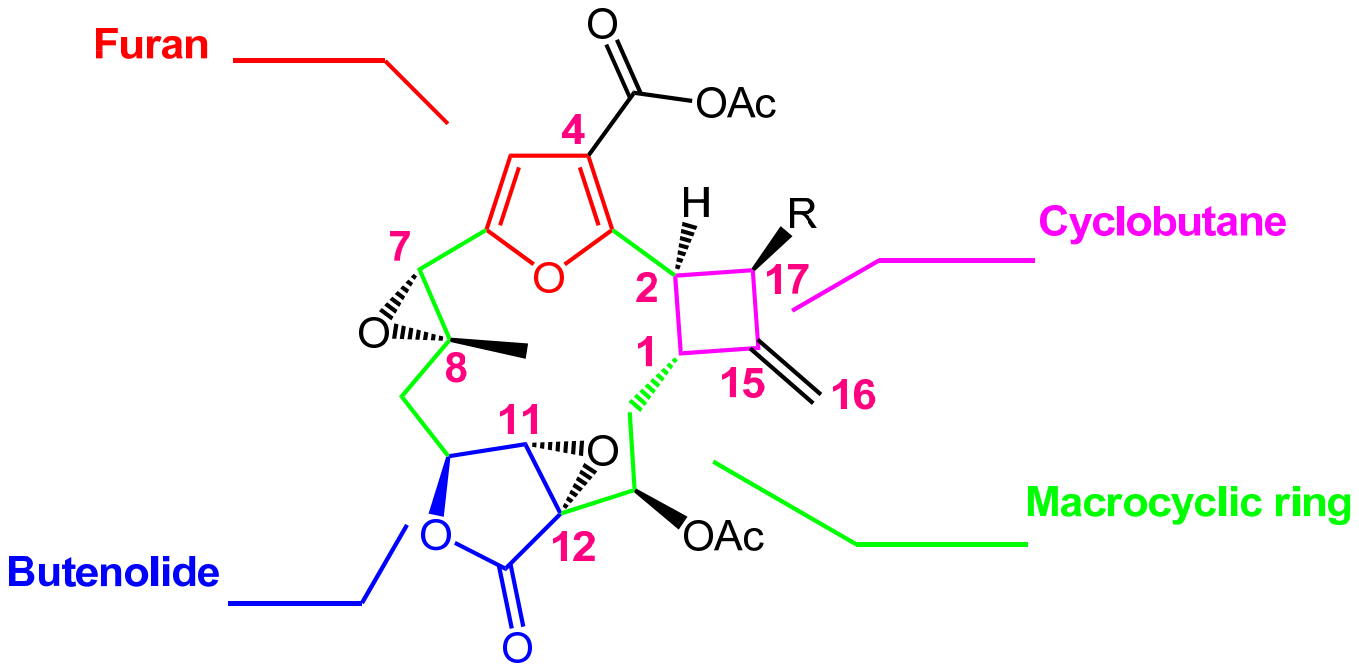


acerosolide



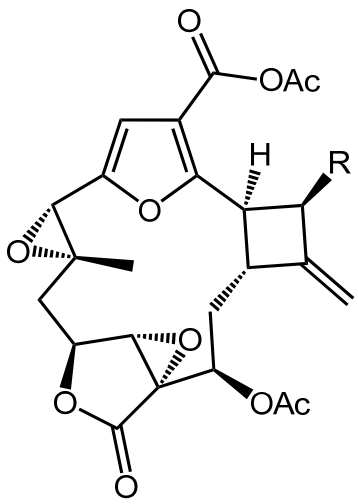
R = OH; providencin (**1**)
R = H; 17-deoxyprovidencin (**2**)

Introduction



R = OH; providencin (**1**)
R = H; 17-deoxyprovidencin (**2**)

Introduction



First generation approach

Synthesis of the cyclobutane moiety

Synthesis of vinylfuran via Wipf cyclization

Ring closure via Horner-Wadsworth-Emmons olefination

Construction of Butenolide

Second generation approach

Synthesis of the cyclobutane moiety

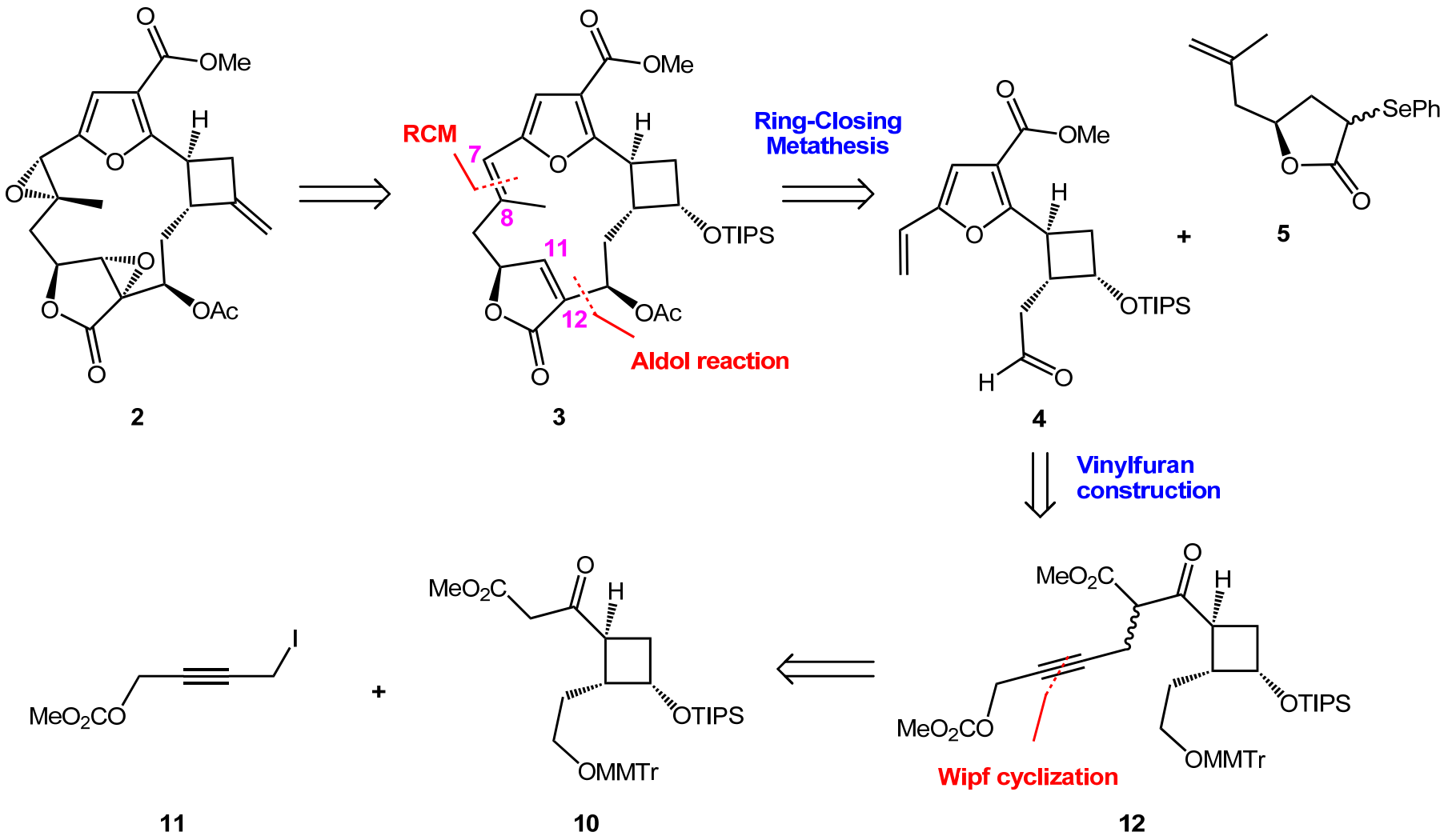
Synthesis of phenylseleno-substituted lactone

Synthesis of vinylfuran via Wipf cyclization

Ring-closing metathesis

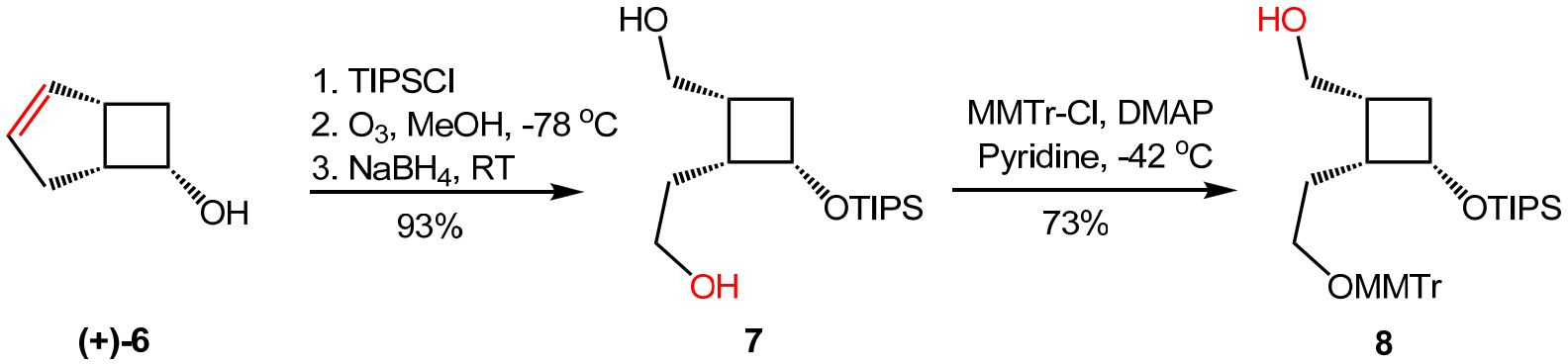
Mulzer, J. *et al*. *Synlett* **2009**, *9*,1357.
Mulzer, J. *et al*. *Angew. Chem. Int. Ed.* **2014**, *53*, 3859.

Retrosynthetic analysis of 17-deoxyprovidencin

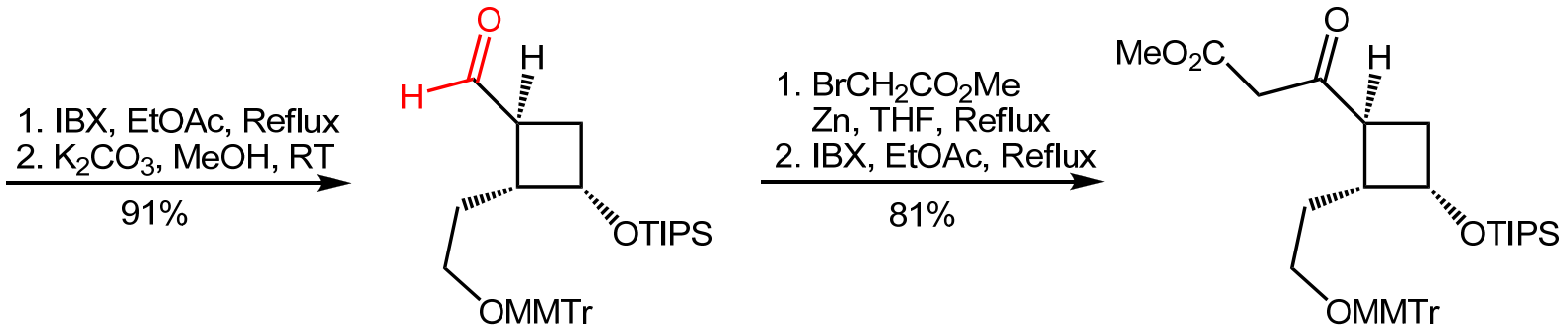


The second generation approach

Synthesis of Cyclobutane Moiety



(+)-6 **7** **8**

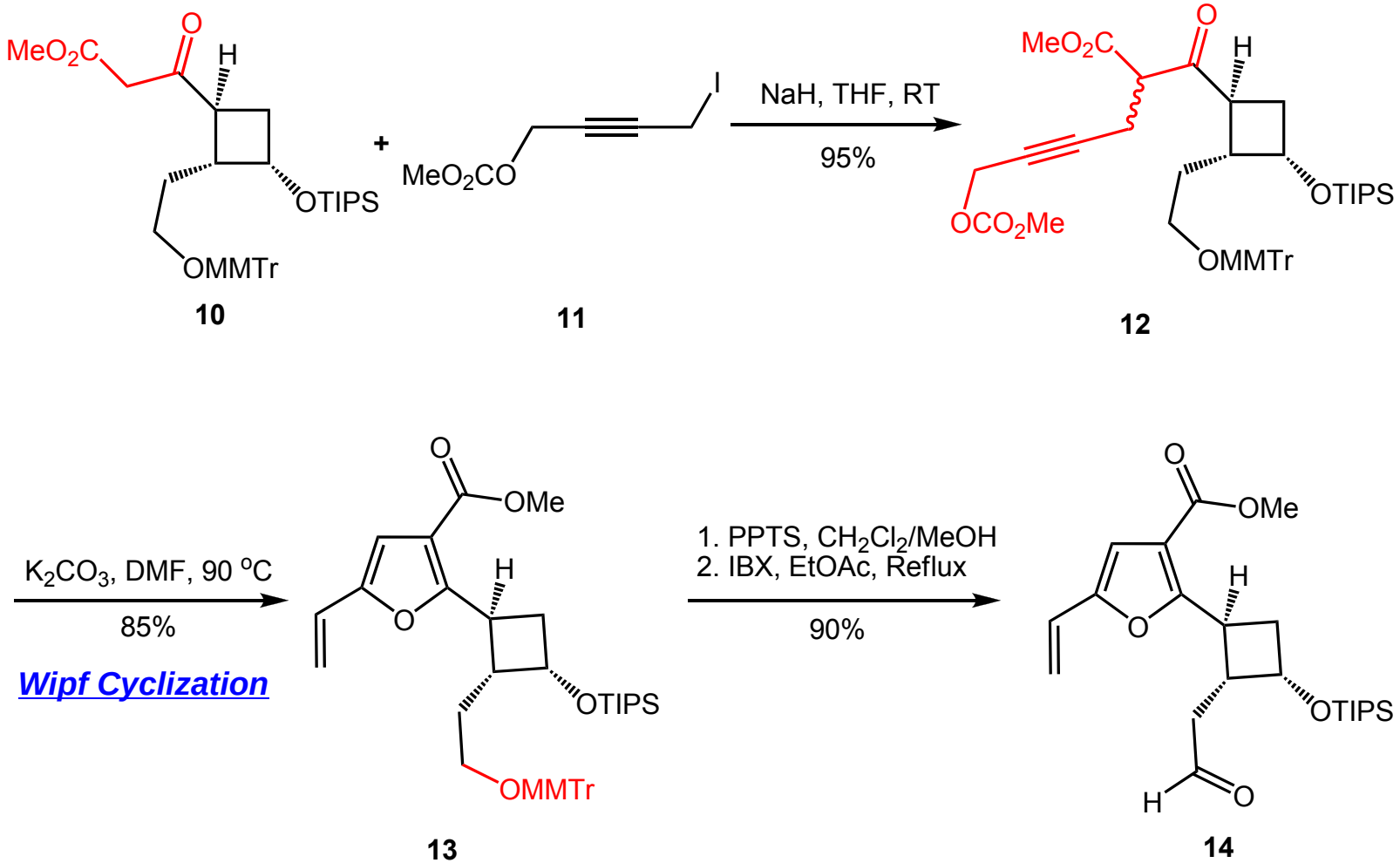


9 **10**

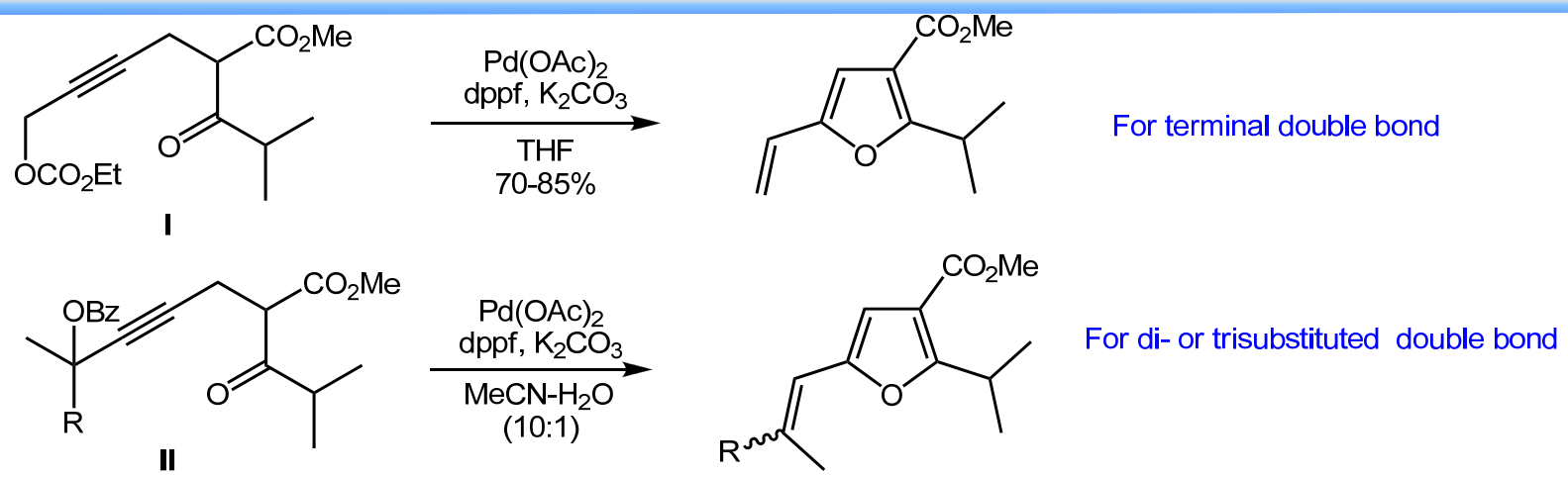
Mulzer, J. *et al*. *Angew. Chem. Int. Ed.* **2014**, *53*, 3859.

The second generation approach

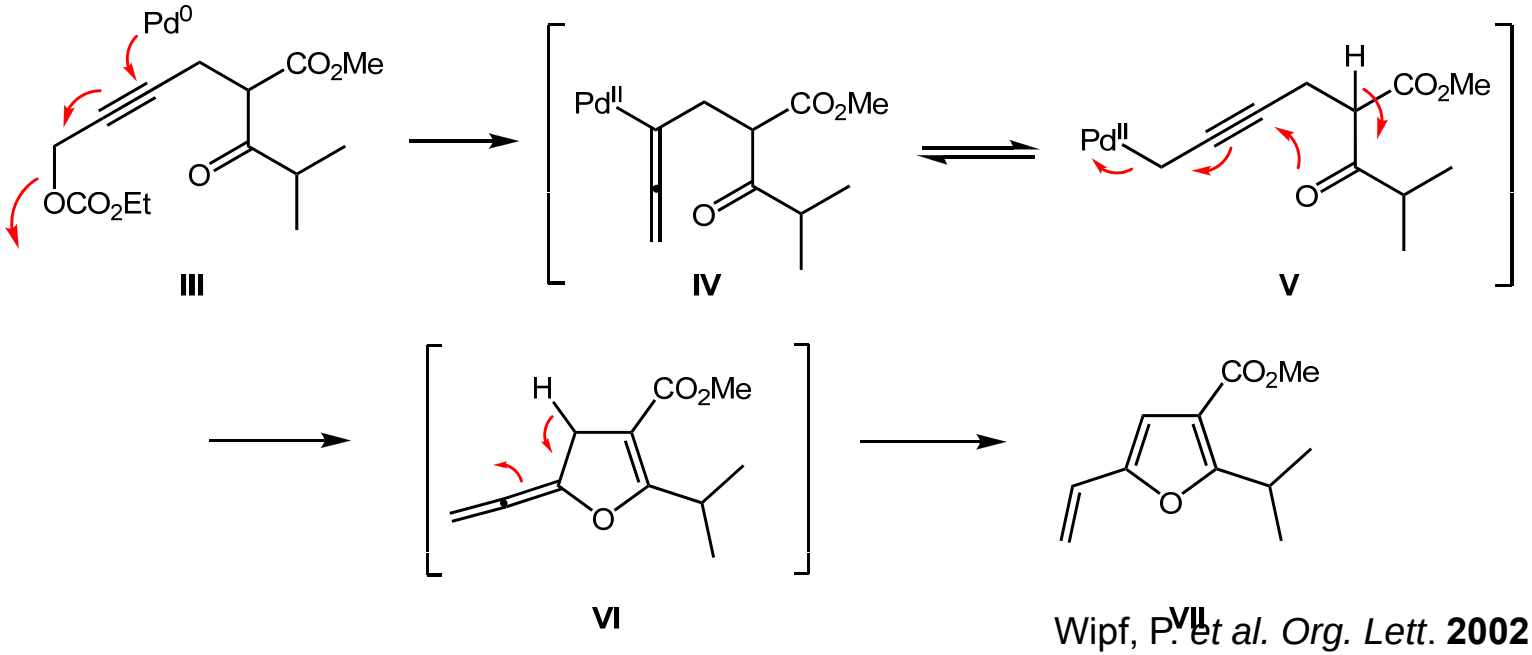
Synthesis of Furancarboxylate



Wipf cyclization



Mechanism

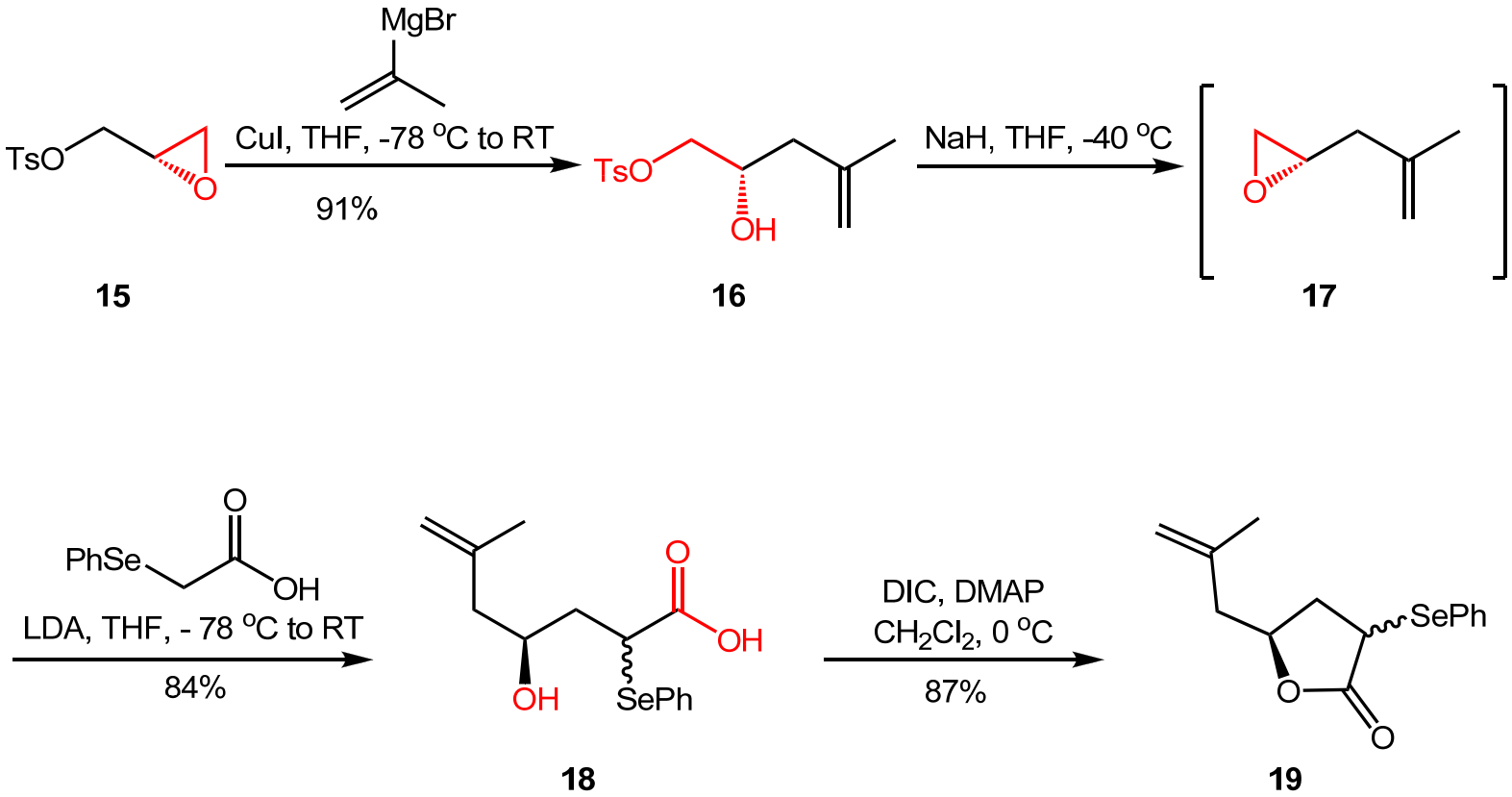


Wipf, P. *et al. Org. Lett*. **2002**, *4*, 1787.

Back

The second generation approach

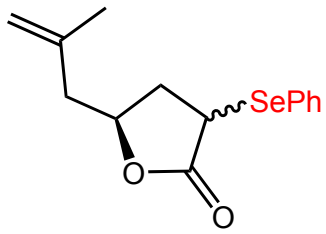
Synthesis of phenylseleno-substituted lactone



Mulzer, J. *et al*. *Synlett* **2009**, *9*,1357.

The second generation approach

Ring-closing metathesis



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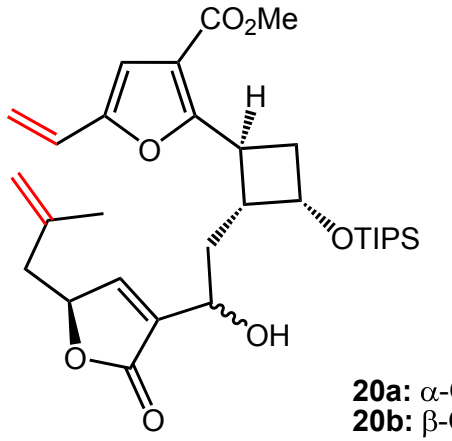
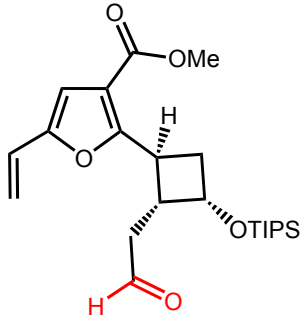
1. LDA, THF, -78 °C
2. **14**, THF, -78 °C
3. CH_2Cl_2, H_2O_2, sat. NH_4Cl

57%



20a: α-OH
20b: β-OH

Grubbs II cat.
Benzene, 80 °C



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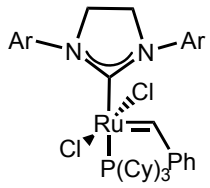
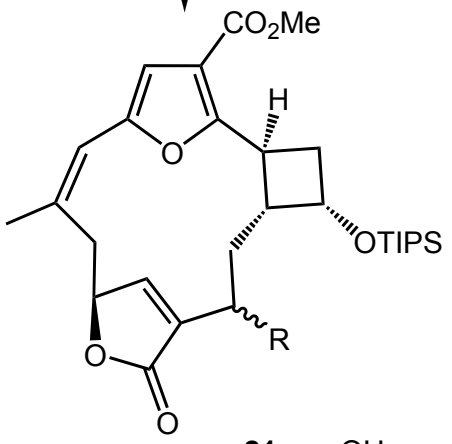


Hoveyda-Grubbs Catalyst



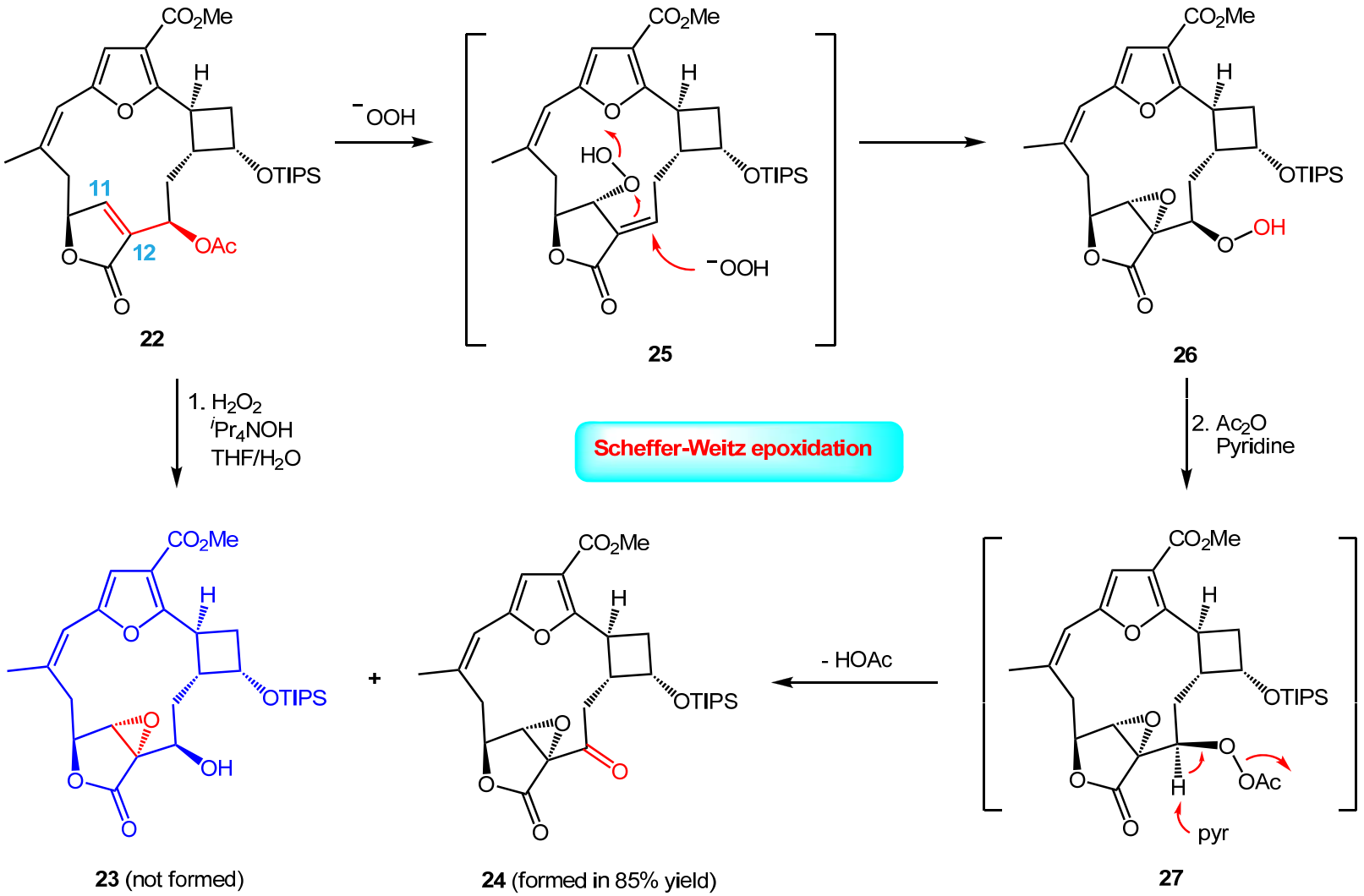
Ac_2O, DIPEA
DMAP, 0 °C

>95%

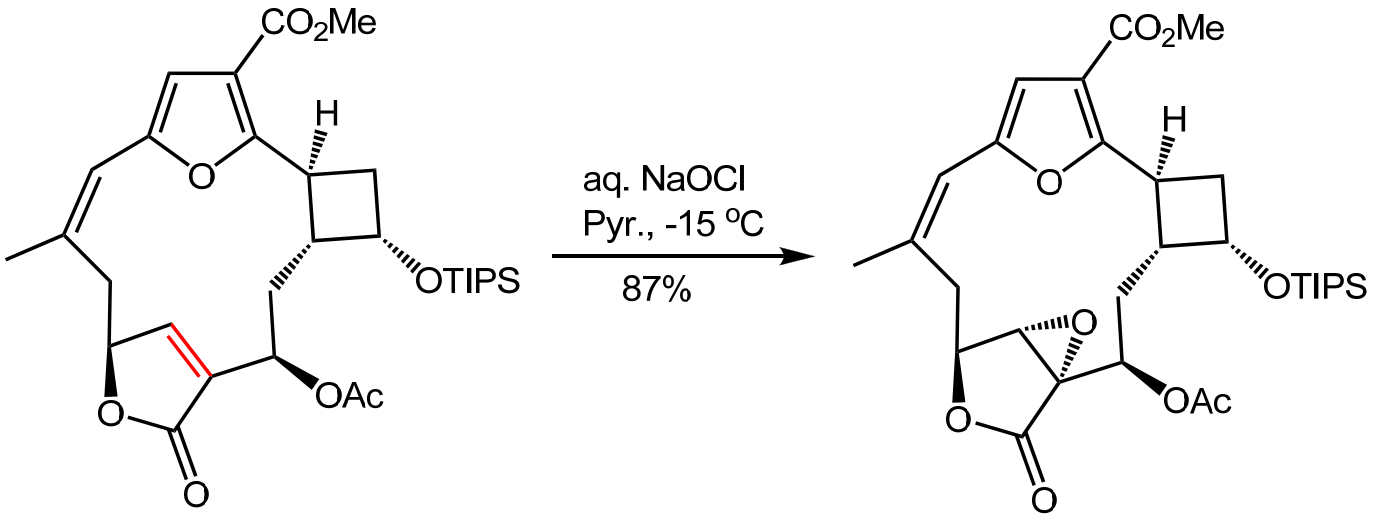
21a: α-OH
21b: β-OH
(**21a**:**21b** = 1.5:1)

22: α-OAc

Δ-11,12-epoxide

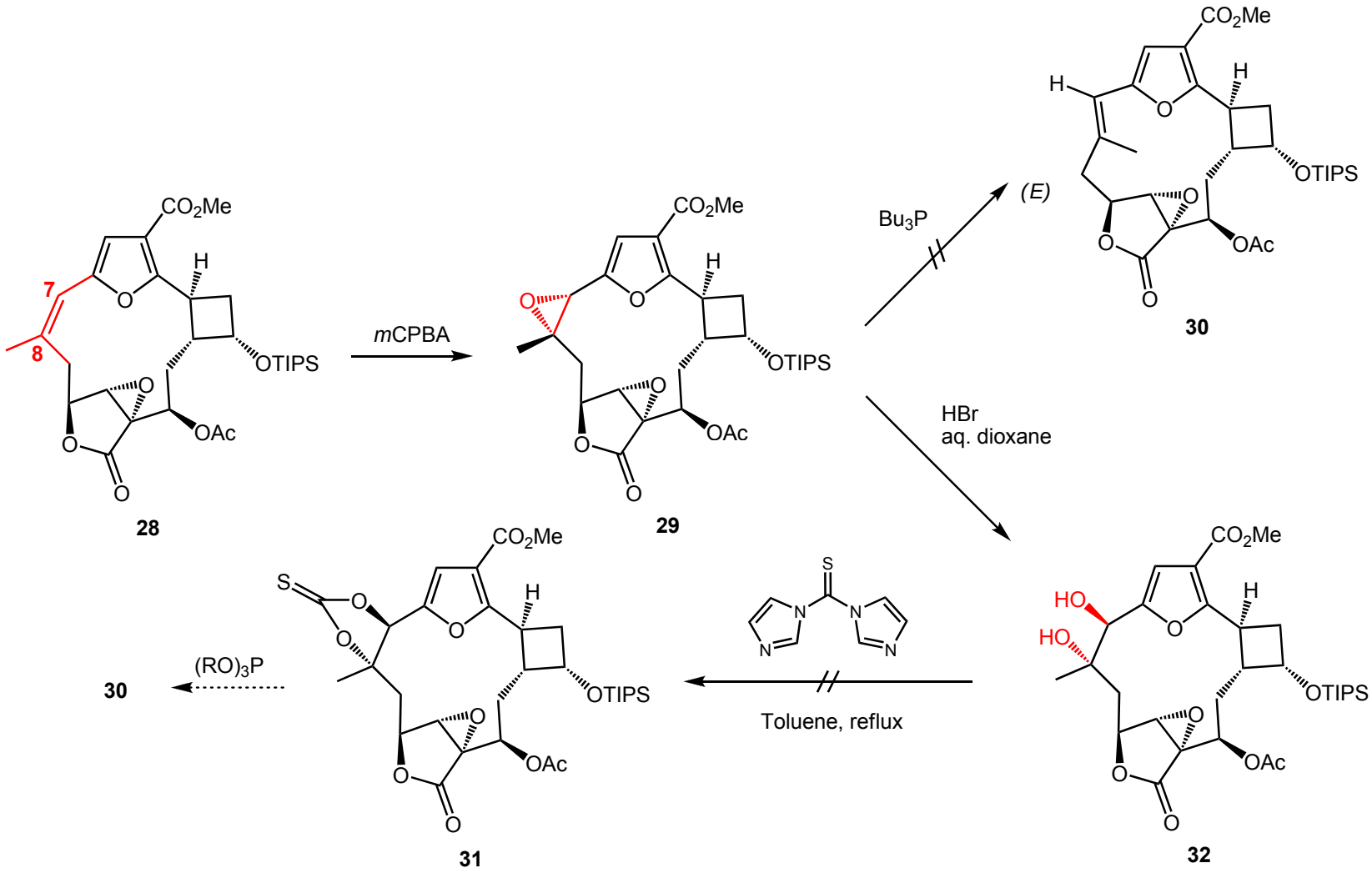


Δ-11,12-epoxide

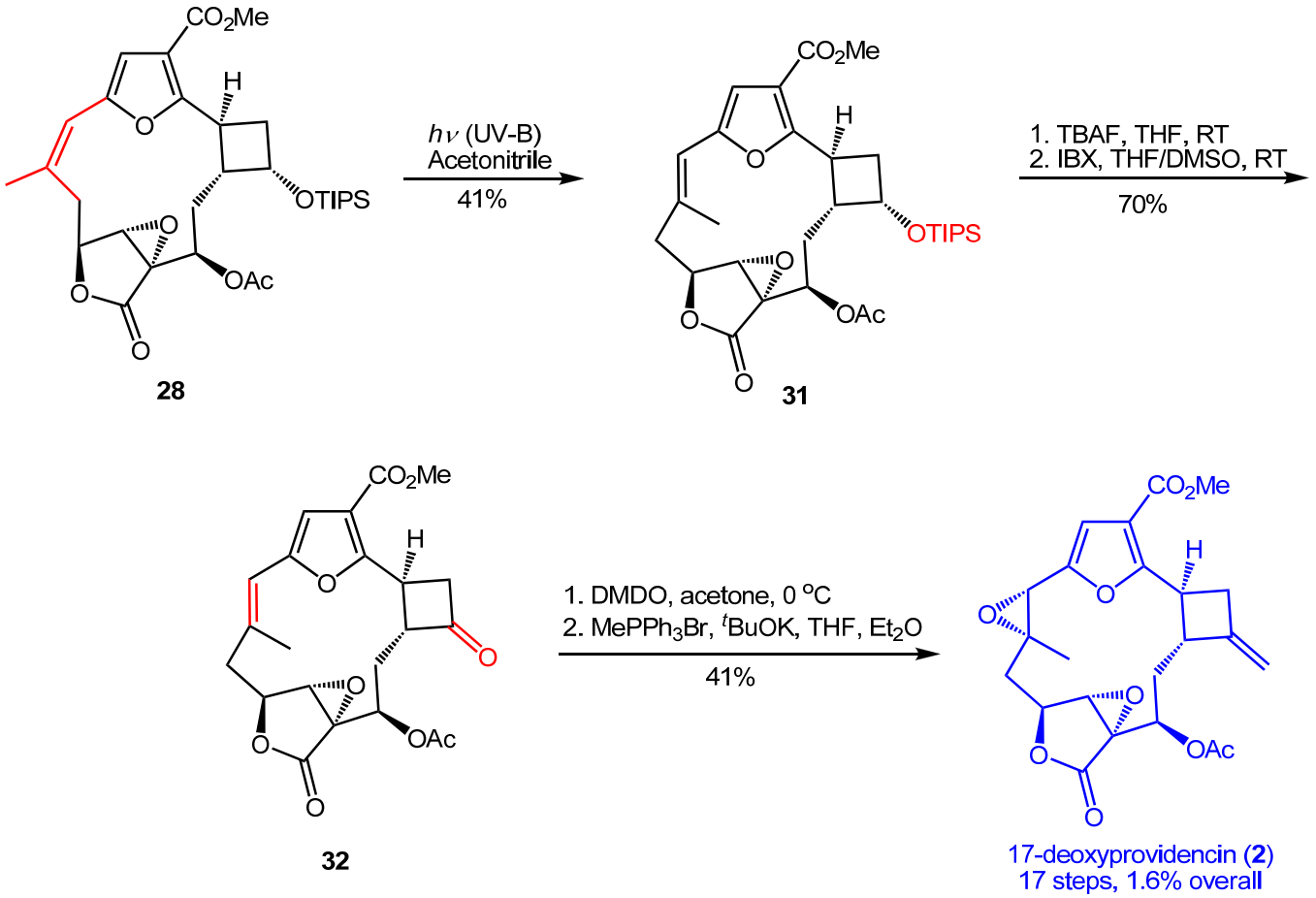


22 **28**

Δ-7,8-epoxide

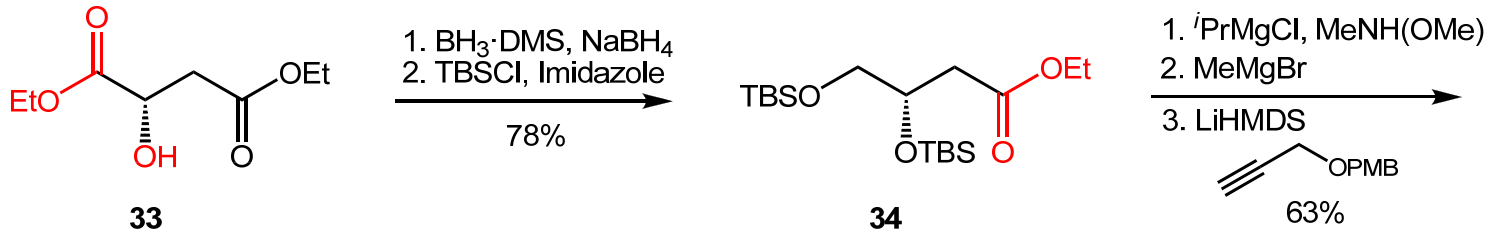

CO2Me
H
7
8
O
OTIPS
OAc
28
mCPBA
29
Bu3P
(E)
30
HBr
aq. dioxane
32
HO
HO
S
N
Toluene, reflux
31
(RO)3P
30

Synthesis of 17-deoxyprovidencin

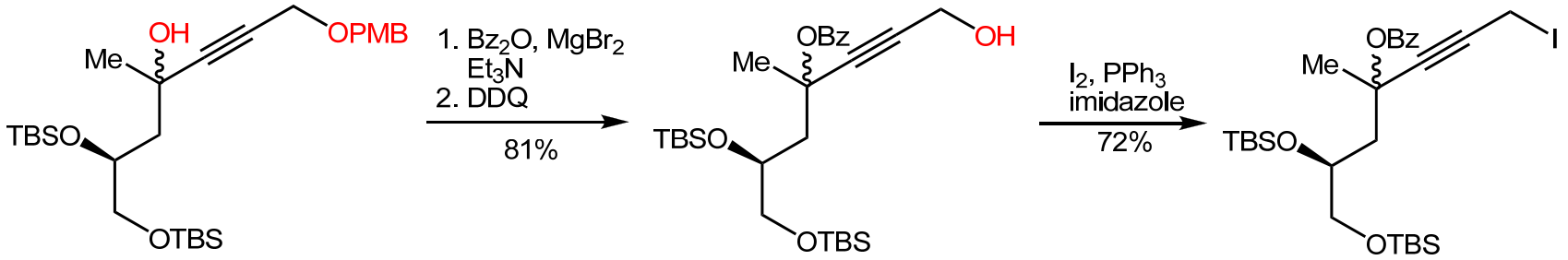


The first generation approach

Synthesis of the Western fragement



33 **34**

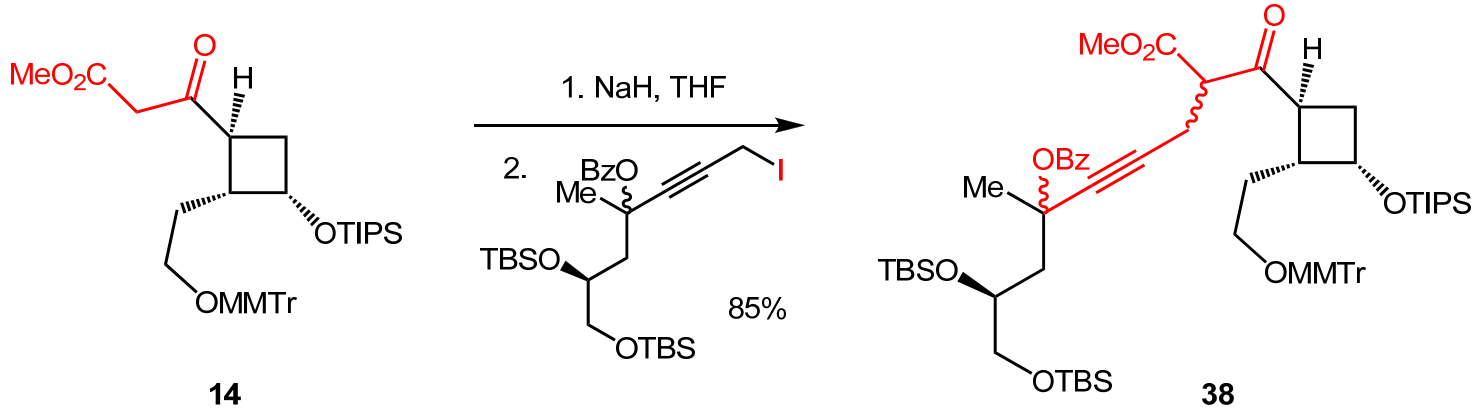


35 **36** **37**

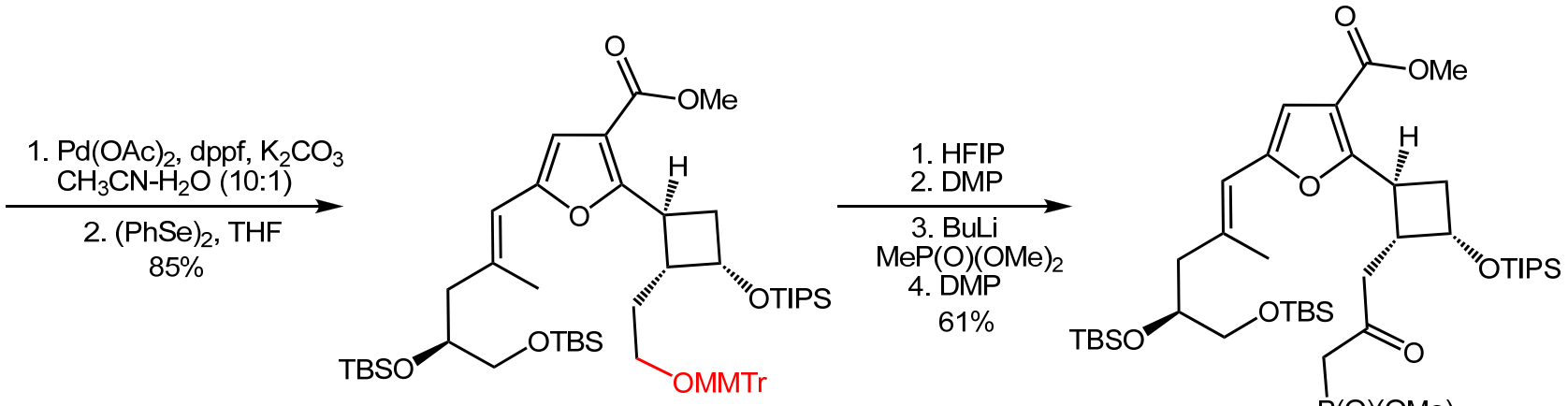
Mulzer, J. *et al*. *Synlett* **2009**, *9*,1357.

The first generation approach

Synthesis of vinylfuran via Wipf cyclization



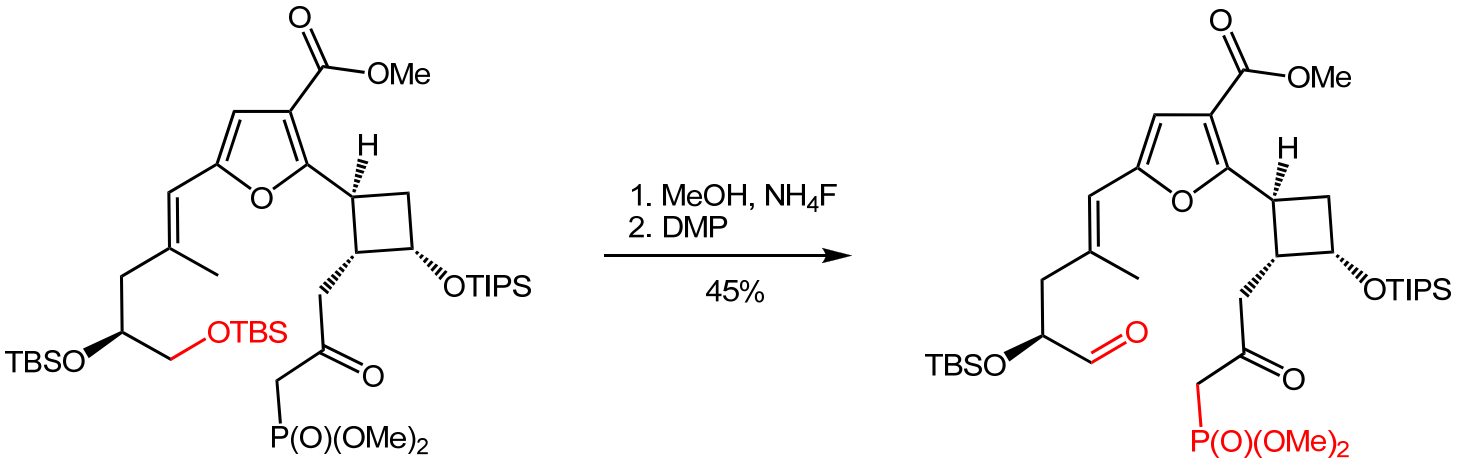
14 **38**



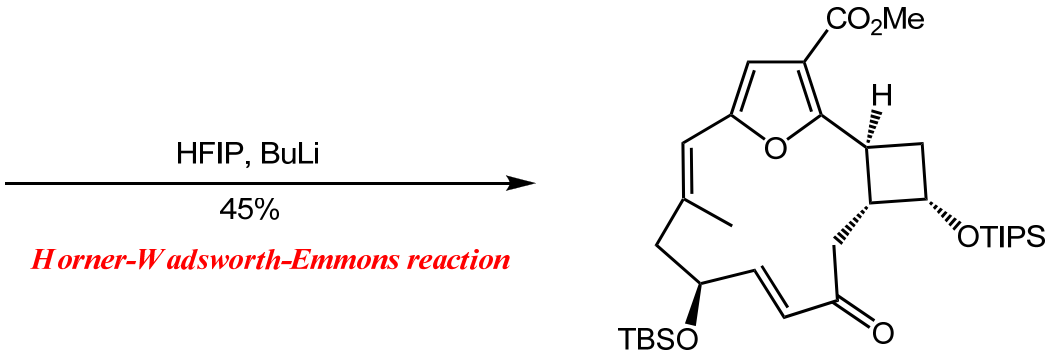
39 **40**

The first generation approach

Ring closure *via* Horner-Wadsworth-Emmons olefination



40 **41**



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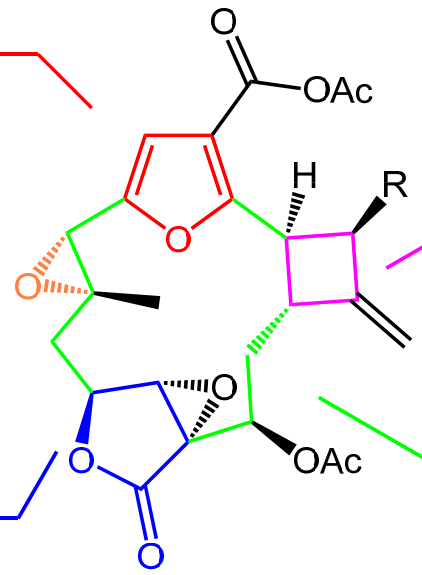
Summary

vinylfuran:
via a Wipf cyclization

***Z/E* isomerization:**
via photo-induced

Butenolide:
via a Steglich condition



Cyclobutane

Macrocyclic ring:
Z-selective RCM macrocyclization

R = OH; providencin (**1**)
R = H; 17-deoxyprovidencin (**2**)

17 steps, 1.6% yield

The class of furanocembranoids offers a diverse range of structurally and biologically interesting natural compounds. In 2003, a highly oxygenated furanobutenolide-based cembrane named providencin (**1**) was isolated from the Caribbean sea plume *Pseudopterogorgia kallos* (Bielschowsky, 1918) by the Rodriguez group. The biosynthesis of **1** is unknown, even though bipinnatin J has been shown to be a plausible precursor. In terms of its biological properties, **1** exhibits moderate activity against human breast cancer and lung and CNS cancer cell lines. The relative configuration was determined by single-crystal X-ray analysis, but the absolute configuration has remained unknown.

Compared to other members of the furanocembranoid family, **1** contains two unusual structural features: a cyclobutanol moiety and a Δ-7,8 *trans* epoxide in the macrocyclic ring. The crystal structure of **1** reveals a perpendicular arrangement of butenolide and furan in the macrocycle; the high ring strain of this macrocycle makes it impossible to build a Dreiding model without breaking any bonds. Evidently, the ring strain is mainly due to the *trans* arrangement of the Δ-7,8 epoxide and the rigid angle of 144^{o} between the C7 and C2 appendages around the furan ring.

In conclusion, we have presented a synthesis of 17-deoxyprovidencin (**2**) in 17 steps along the longest linear sequence with an overall yield of 1.6 %. Key steps include an aldol addition with subsequent oxidative elimination of selenide, a *Z*-selective RCM macrocyclization, a photo-induced *Z*/*E* isomerization to a highly strained conformationally restricted ring system, and a stereoselective epoxidation of the *E* olefin. To corroborate our biosynthetic hypothesis, various allylic oxidations at the C17 position, including enzymatic hydroxylations, remain to be performed.