Total Synthesis of Prostaglandins

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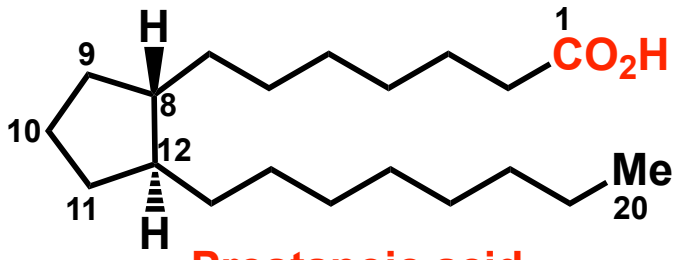
CH-588 Course on Organic Synthesis

Prostaglandins & its classifications



Prostanoic acid

The prostaglandins were discovered in the early 1930's by von Euler

The structures of the first family of prostaglandins were known in 1966

They are carbocyclic oxygenated C-20 molecules having the framework of prostanoic acid

Numbering and nomenclature for all the prostaglandins is based on this parent skeleton

Various members of prostaglandins were distinguished by the nature of functionalities present

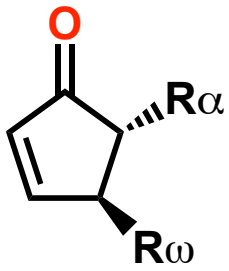
a. In the 5-membered ring

b. Number of unsaturation in the two side-chain appendages

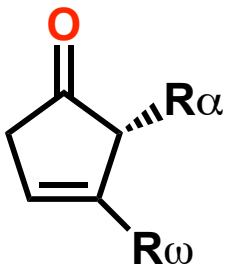
PGA
PGB
PGC
PGD
PGE
PGF

PG-Prostaglandin

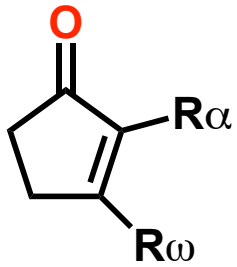
Prostaglandins & its classifications



PGA

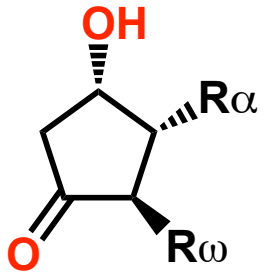


PGB

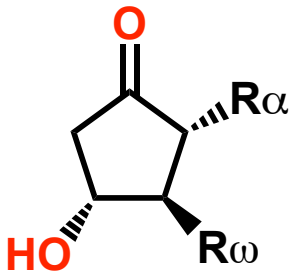


PGC

PGA, PGB and PGC have one double bond in the cyclopentenone ring

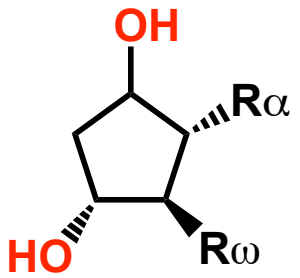


PGD

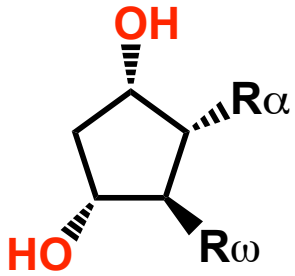


PGE

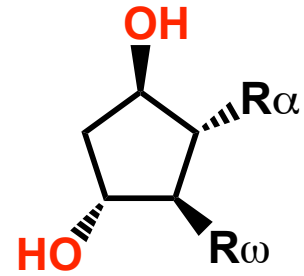
PGD, PGE- one hydroxyl & one keto-group in the cyclopentane ring



PGF



PGF_{α}



PGF_{β}

PGF – Two hydroxyl groups in the cyclopentane ring

PGF_{α}- the hydroxyl group at C_9 is α

PGF_{β}- the hydroxyl group at C_9 is β

The subscripts 1,2 in $PGF_{1\alpha}$, $PGF_{2\alpha}$ represents the number of double bonds in the side chain

Synthetic Challenges and Corey's Approach

Members of 'F series' have 5 chiral centers and 4 are contiguous

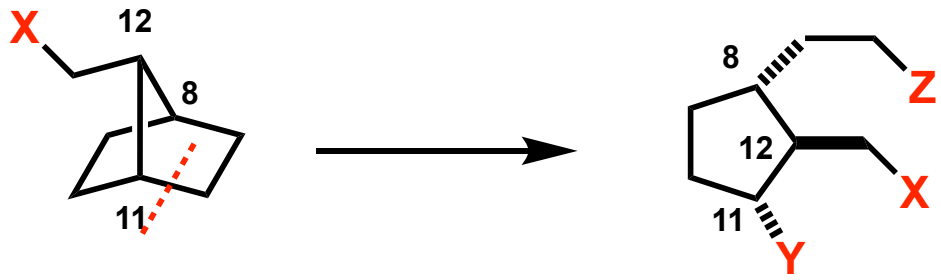
Hydroxyl bearing C15 center is away from the cyclopentane ring

The presence of '*cis*' and '*trans*' double bonds in the side chains

The presence of β-hydroxyketones make those PGs unstable towards acid and base

Due to the presence of diols and β-hydroxyketones suitable protecting groups and mild deprotection strategies are required

Bicycloheptane Approach

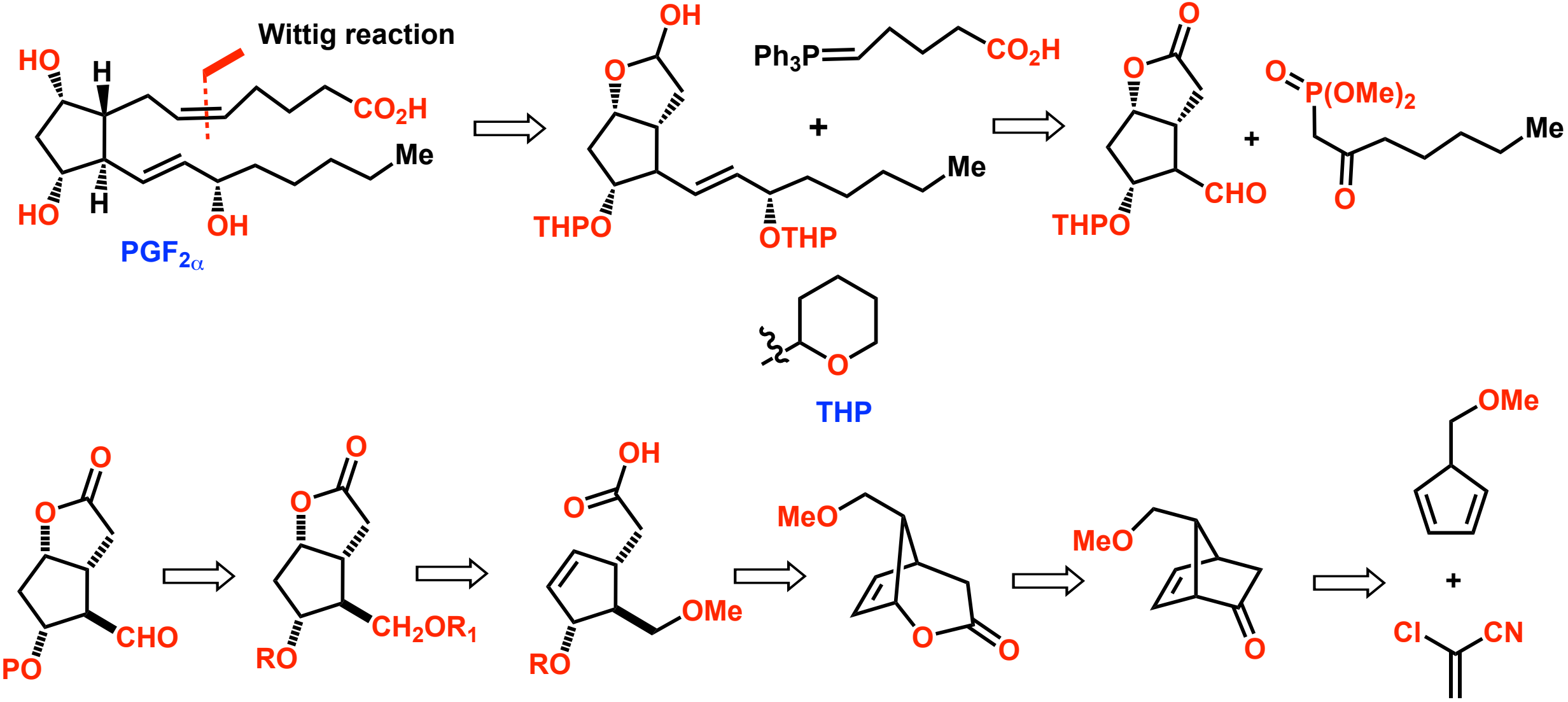


The cleavage of the substituted bicycloheptane would provide trisubstituted cyclopentane with correct stereochemistry

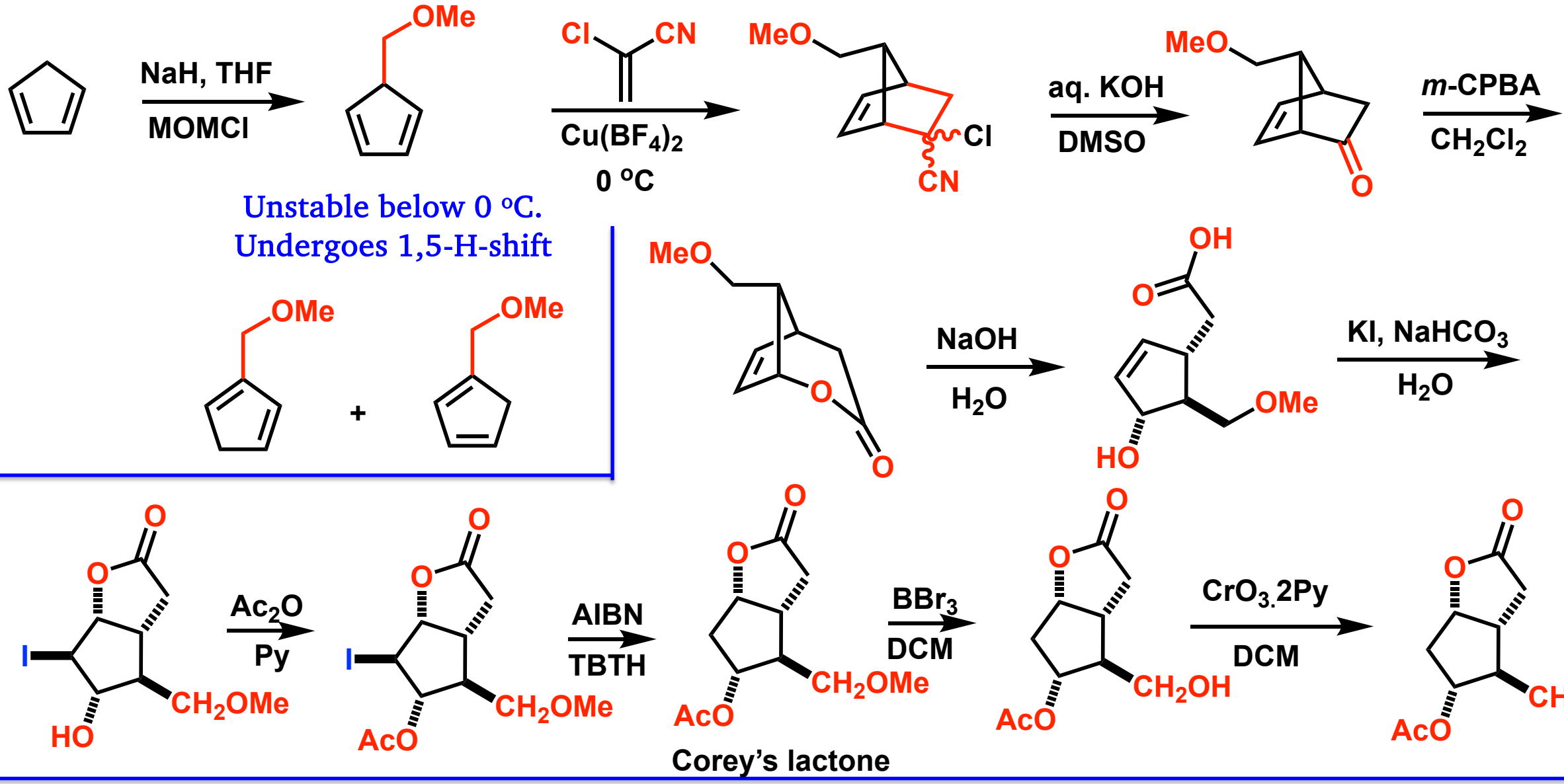
Key reactions involved in this synthesis are

1. Diels-Alder reaction
2. Baeyer-Villiger oxidation
3. Iodolactonization

Corey's Bicycloheptane Approach

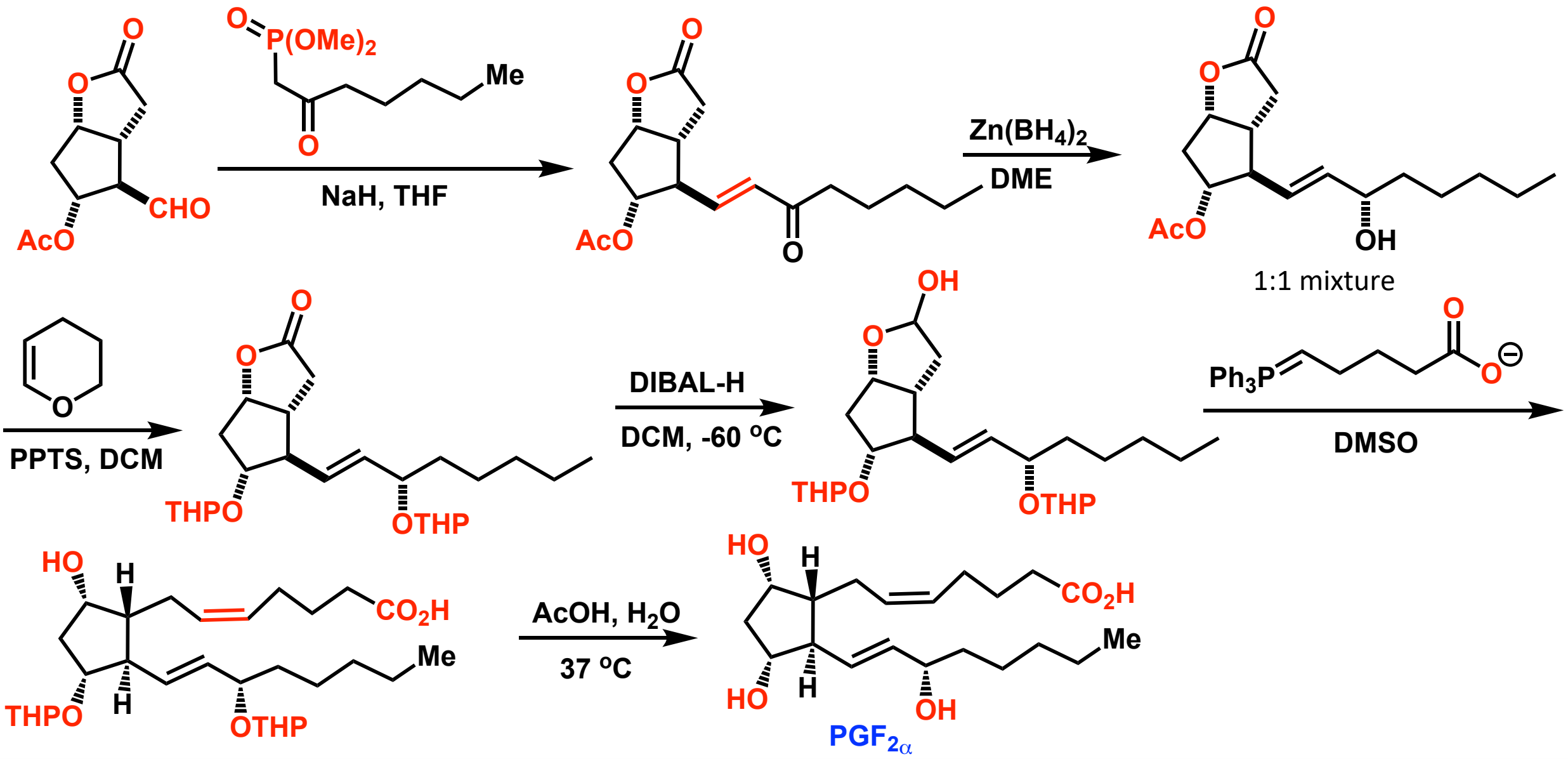


Corey's Total Synthesis

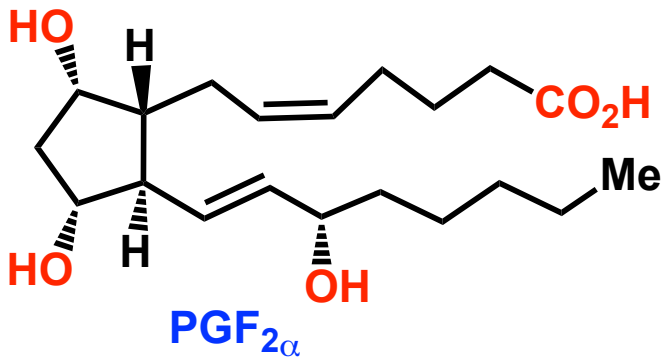


Corey's lactone

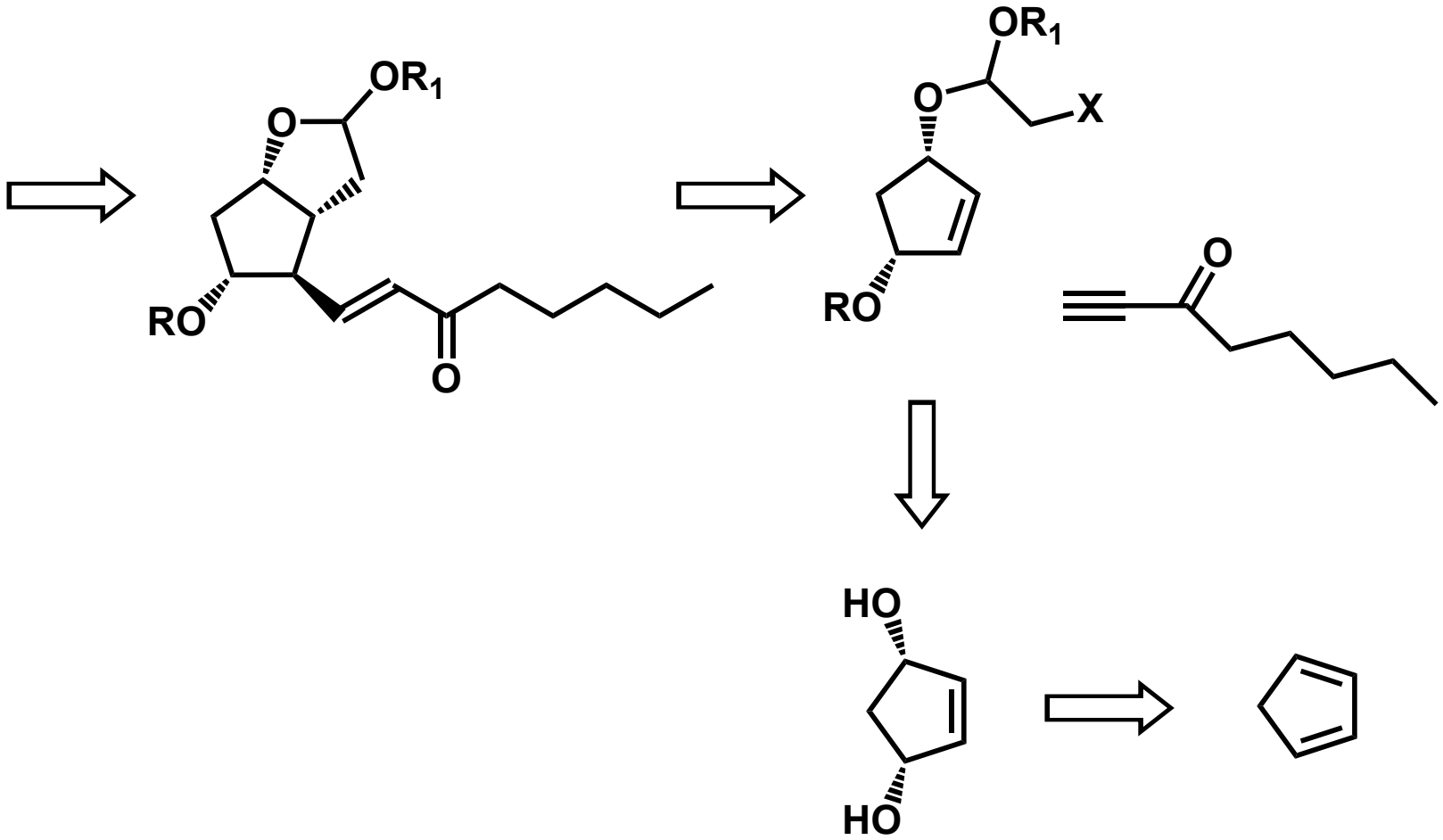
Corey's Total Synthesis



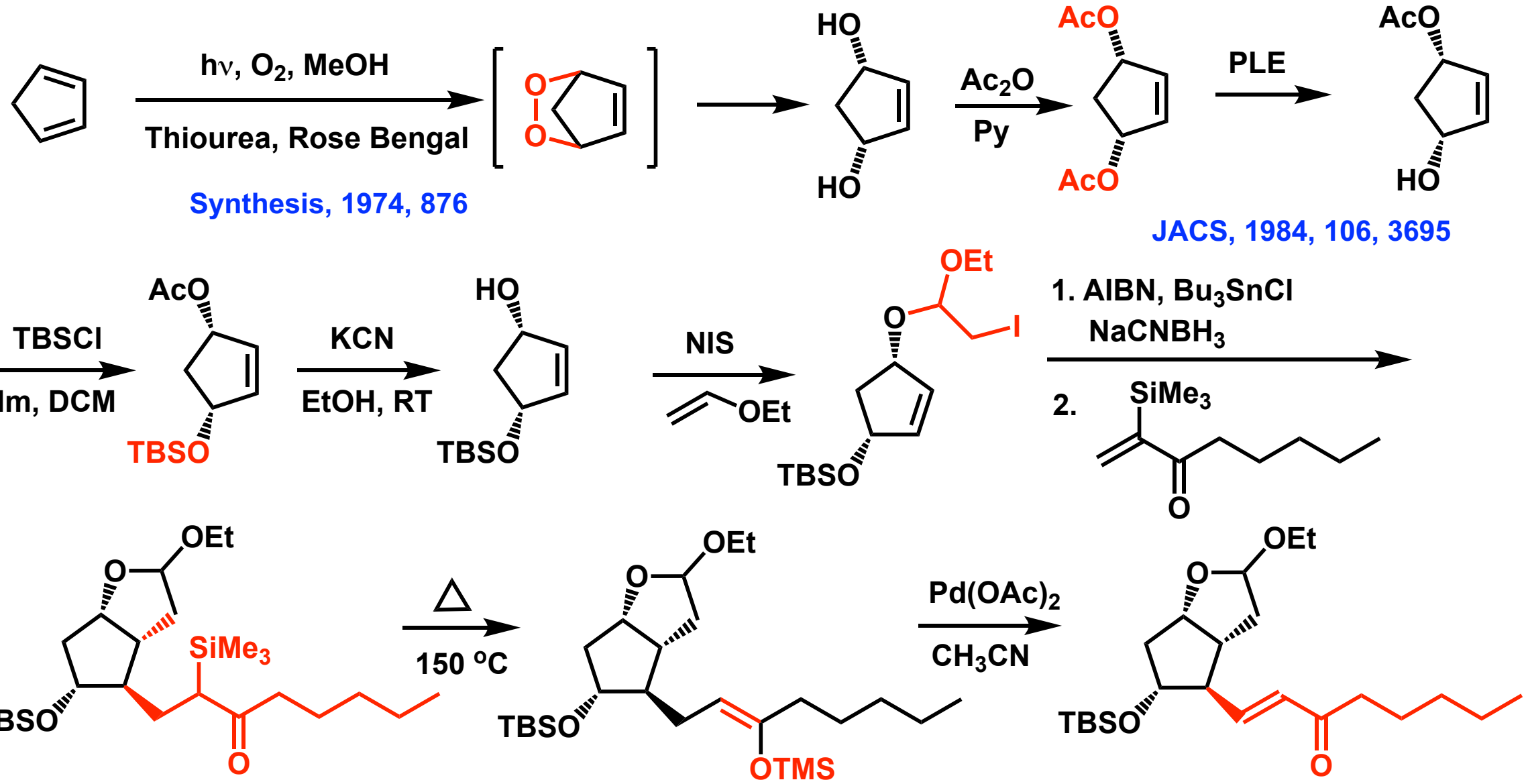
Stork's Total Synthesis



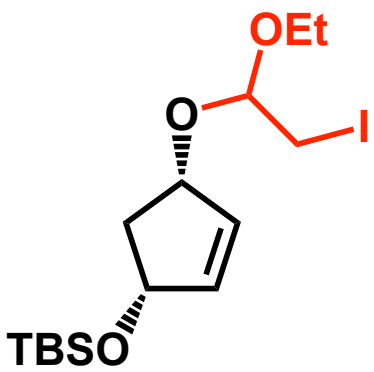
Stork, G.; Sher, P. M.; Chen, H.-L..,
J. Am. Chem. Soc., **1986,** *108*, 6384-85

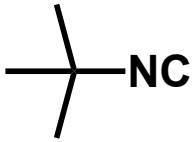


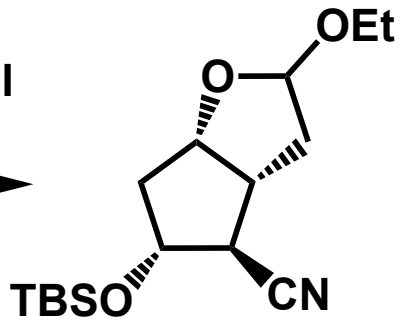
Total Synthesis of $PGF_{2\alpha}$



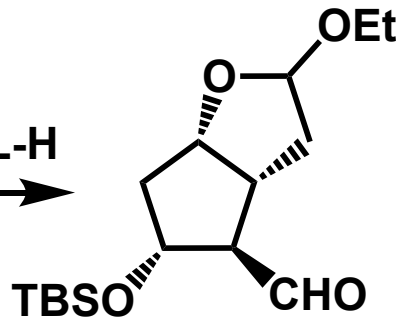
Total Synthesis of $PGF_{2\alpha}$

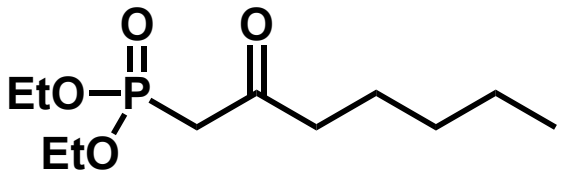


1. AIBN, Bu_3SnCl
   $NaCNBH_3$
2. 

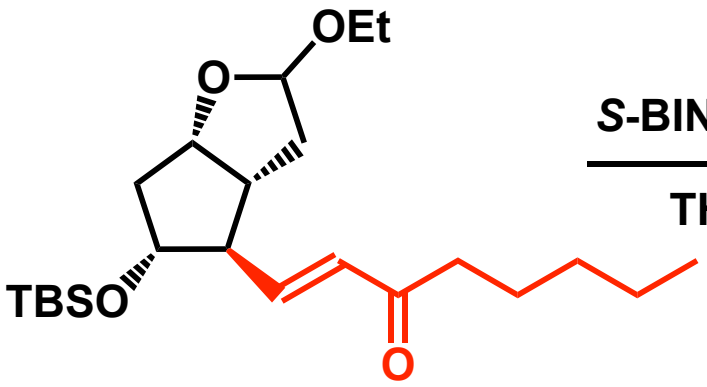


DIBAL-H
THF

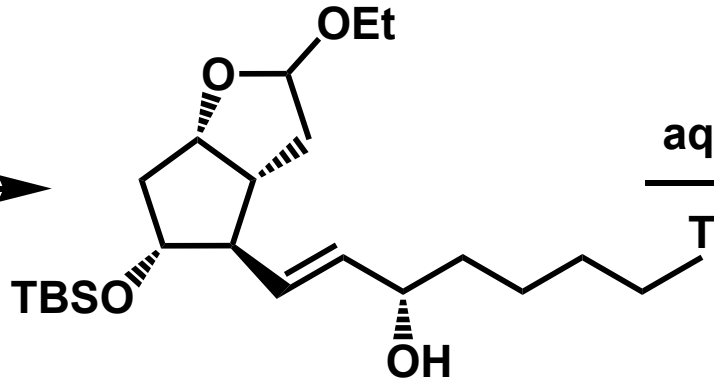




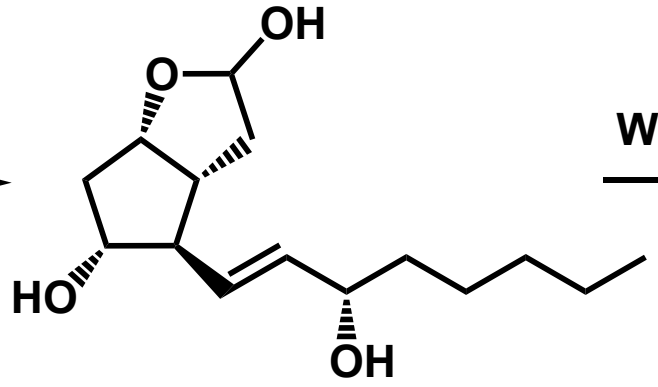
$^{n}BuLi$, THF



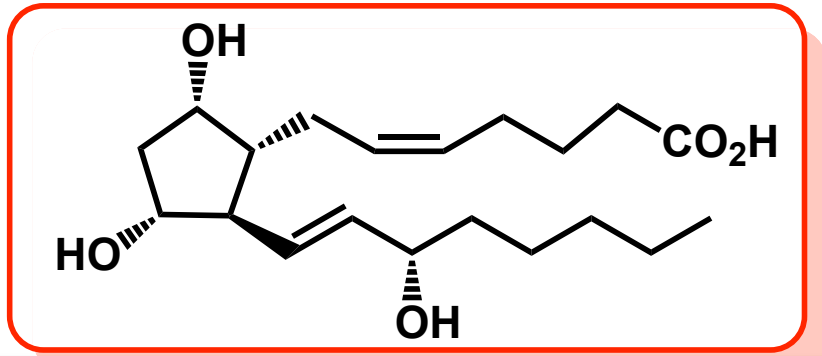
S-BINAL-H
THF



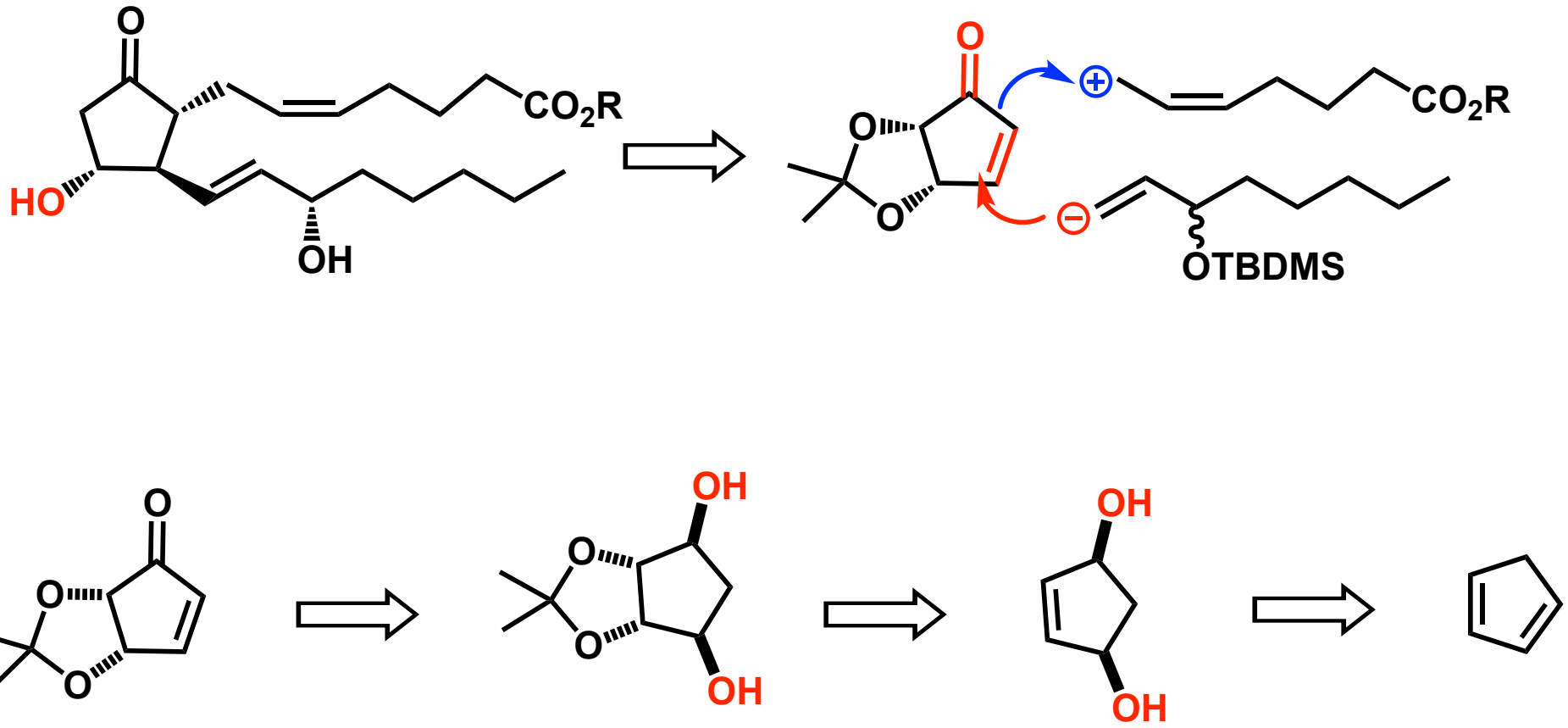
aq. HCl
THF



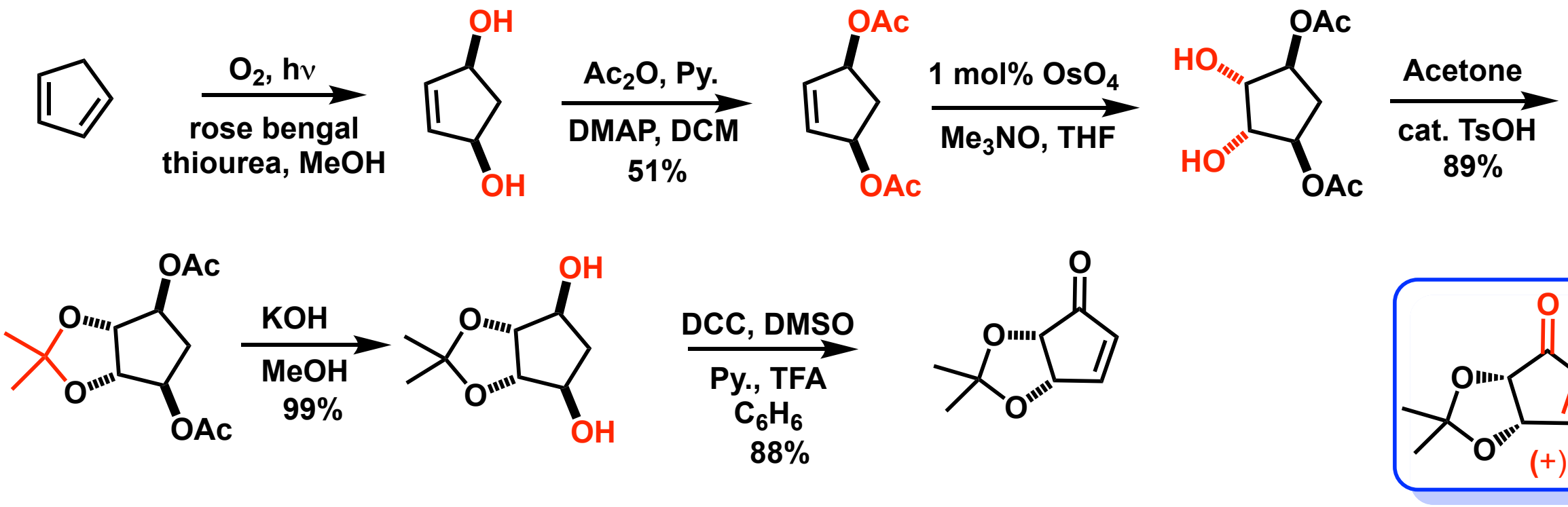
Wittig



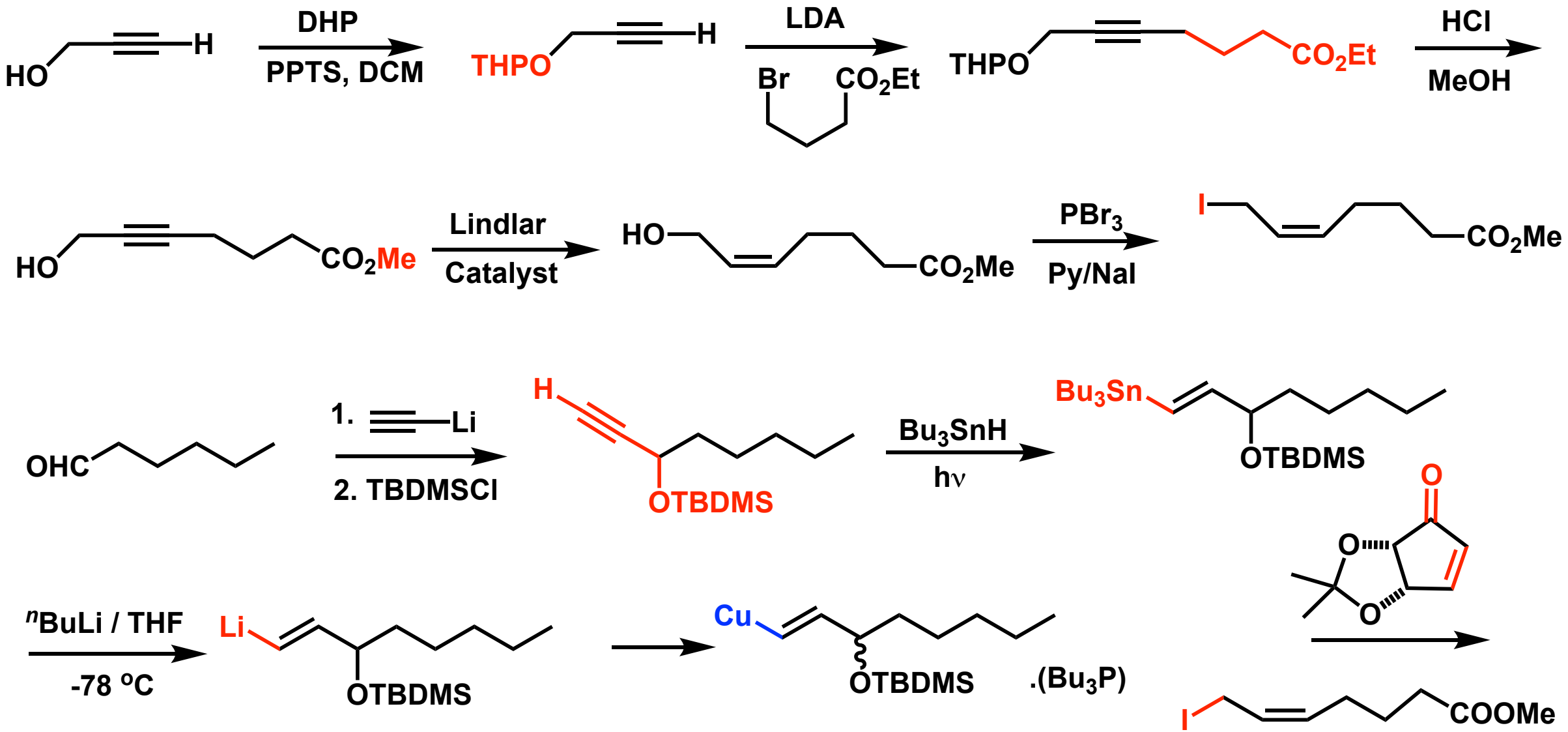
Johnson's Total Synthesis of PGE



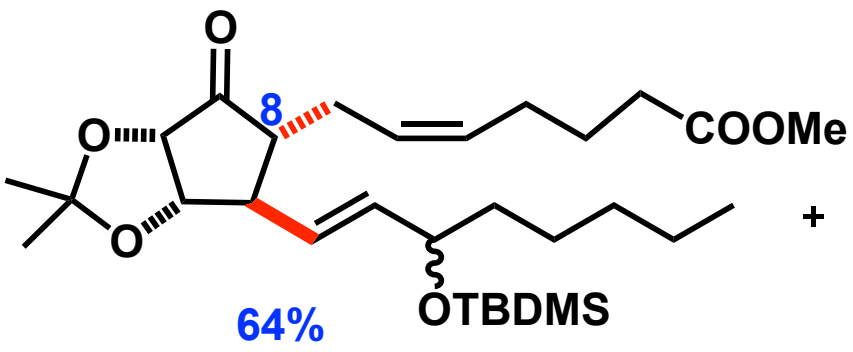
Johnson's Total Synthesis of PGE



Synthesis of Side Chains

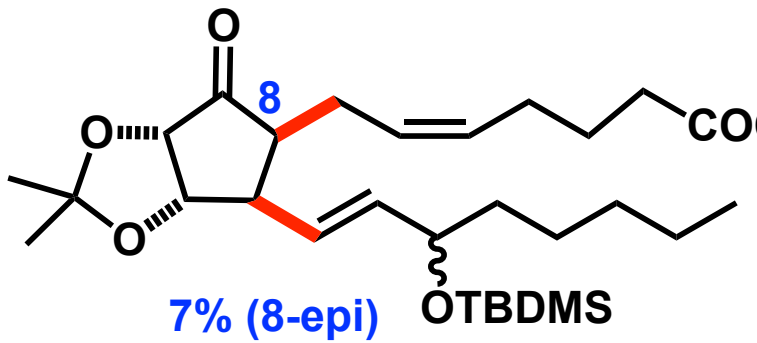


Johnson's Total Synthesis of PGE



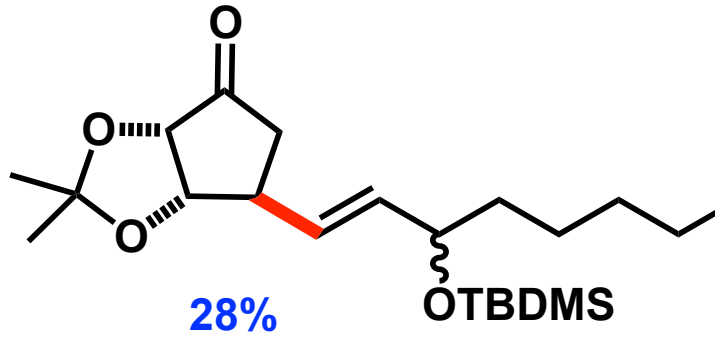
64%

+



7% (8-epi)

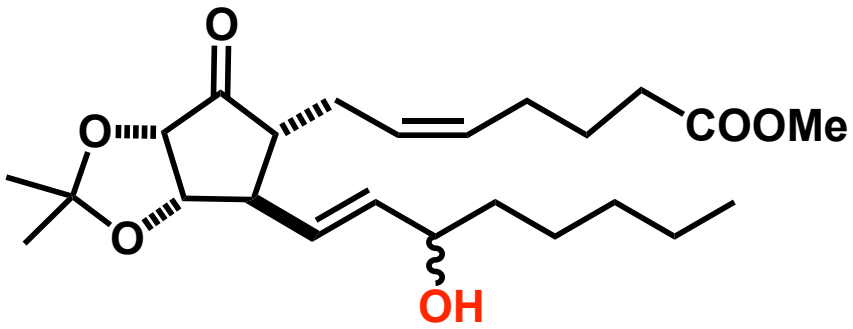
+



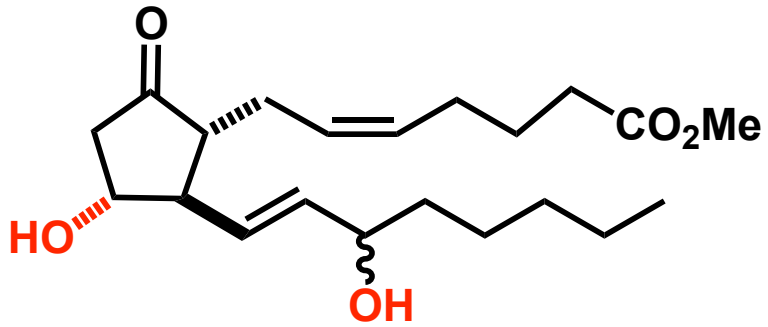
28%

HF, Py

95%



Al(Hg)
THF
H_2O



(±)-PGE_2, methyl ester

(±)-15-epi-PGE_2, methyl ester