UNIVERSITÄT
BERN

Prostaglandins synthesis: a review

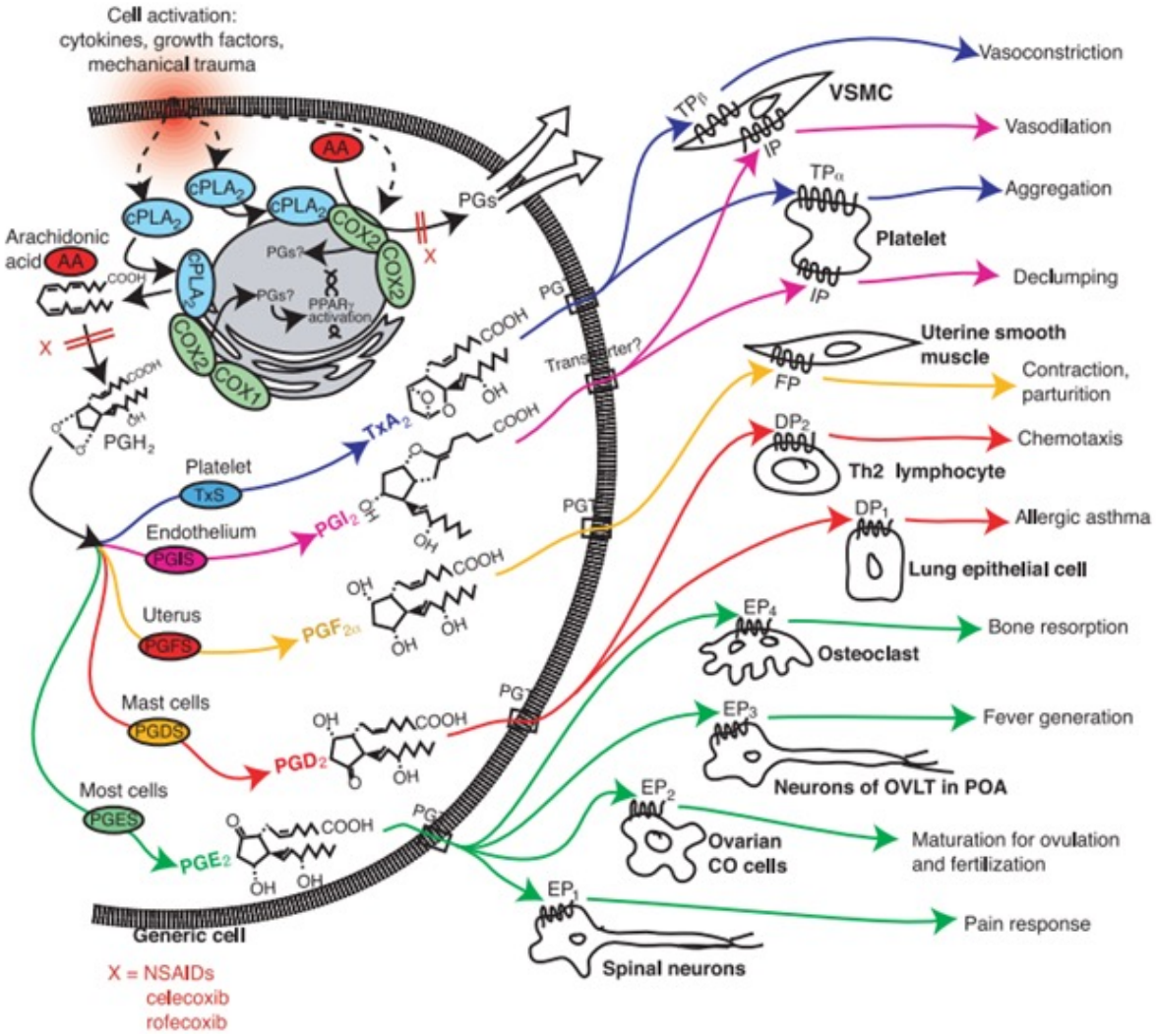
Journal Club Renaud Group – Gaetano Geraci – 03.11.2021

Table of contents

- Prostaglandins
  - Biological role
  - Biosynthesis
- Interest of prostaglandins in pharmaceutical chemistry
- Structural analysis of prostaglandins
- Corey's synthesis of $PGF_{2\alpha}$ and PGE_2 (1969)
- Woodward's synthesis of $PGF_{2\alpha}$ (1973)
- Aggarwal's synthesis of $PGF_{2\alpha}$ (2012)
- Baran's synthesis of $PGF_{2\alpha}$ (2017)
- Zhang's synthesis of $PGF_{2\alpha}$ and PGE_2 (2021)
- Discussion and conclusion

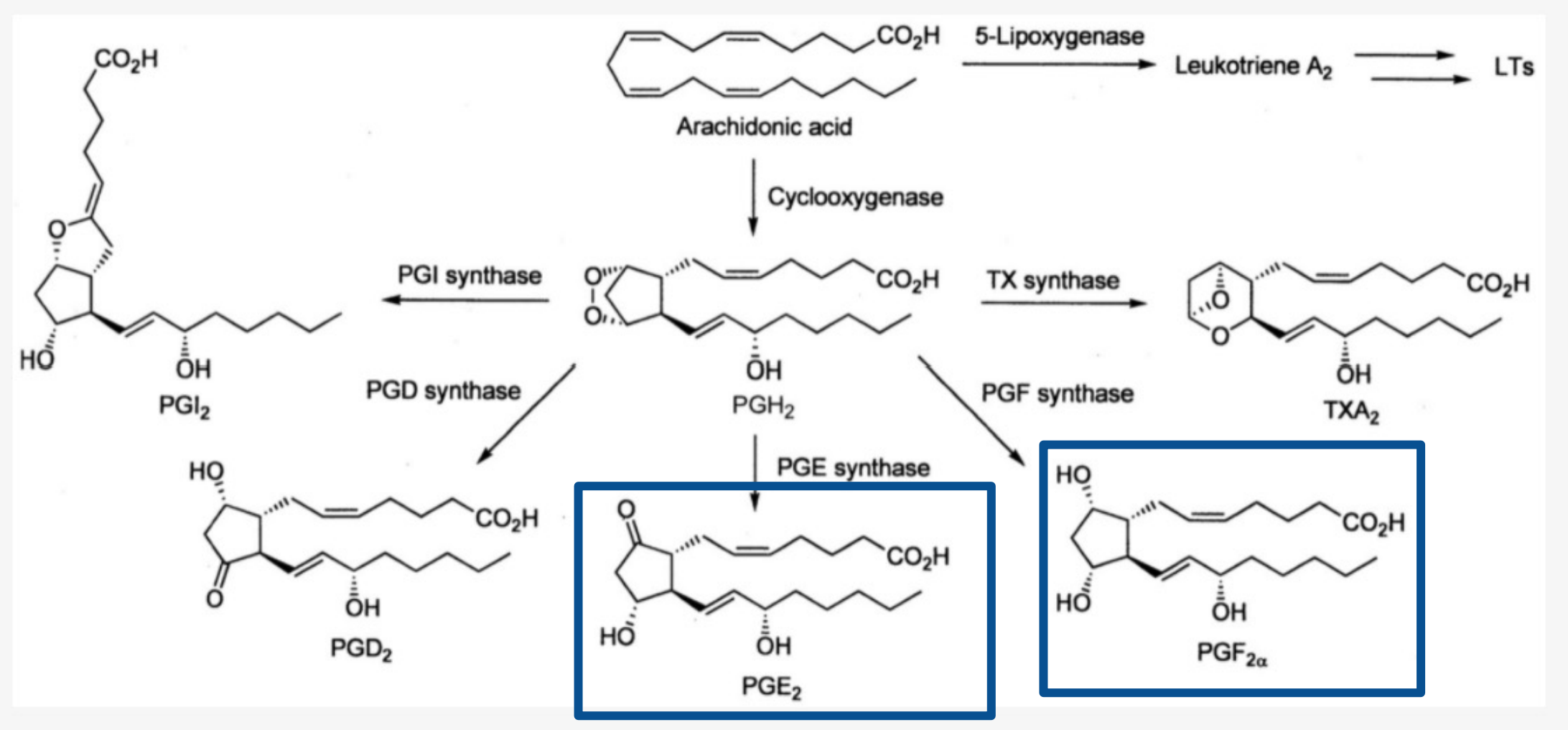
Prostaglandins

- A group of physiologically active lipid compounds called eicosanoids having diverse hormone-like effects in animals
- Sune K. Bergström, Bengt I. Samuelsson and John R. Vane got the Nobel prize in 1982 for their contribution on prostaglandins studies
- Display different arrays of physiological responses (locally-acting vasodilators, inhibition of the aggregation of blood platelets, inflammation cascade…)



https://www.creative-proteomics.com/services/prostaglandins-analysis-service.htm

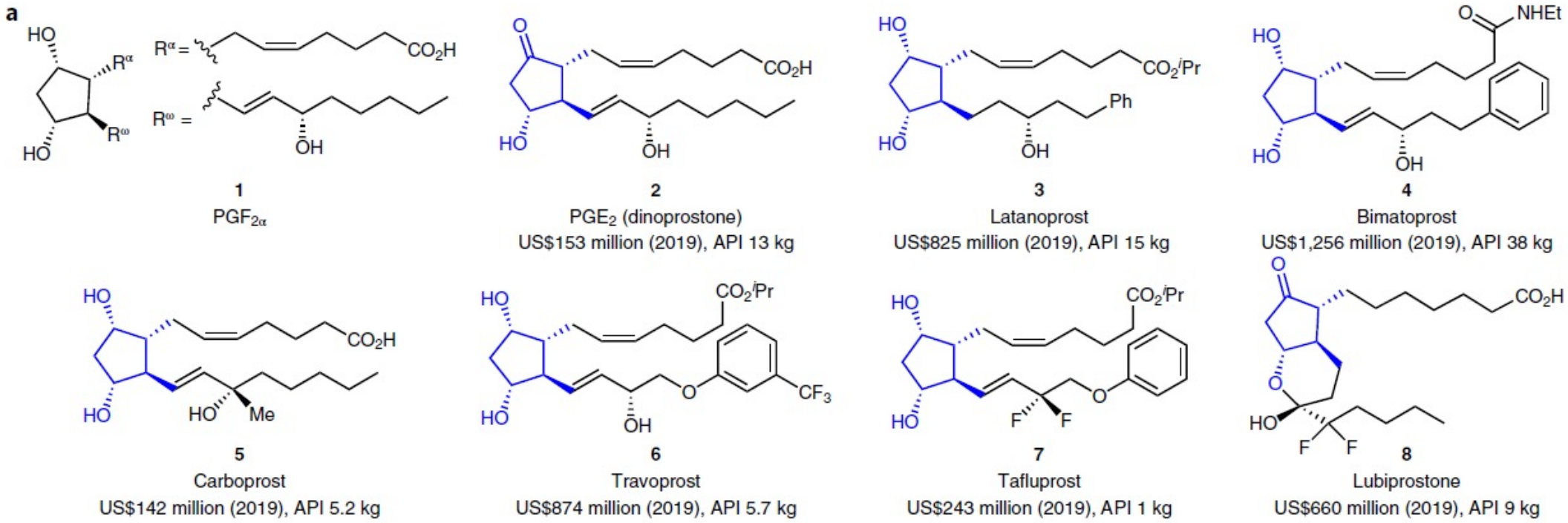
Biosynthesis



Molecules **2019**, *24*(22), 4019

Interest in pharmaceutical chemistry

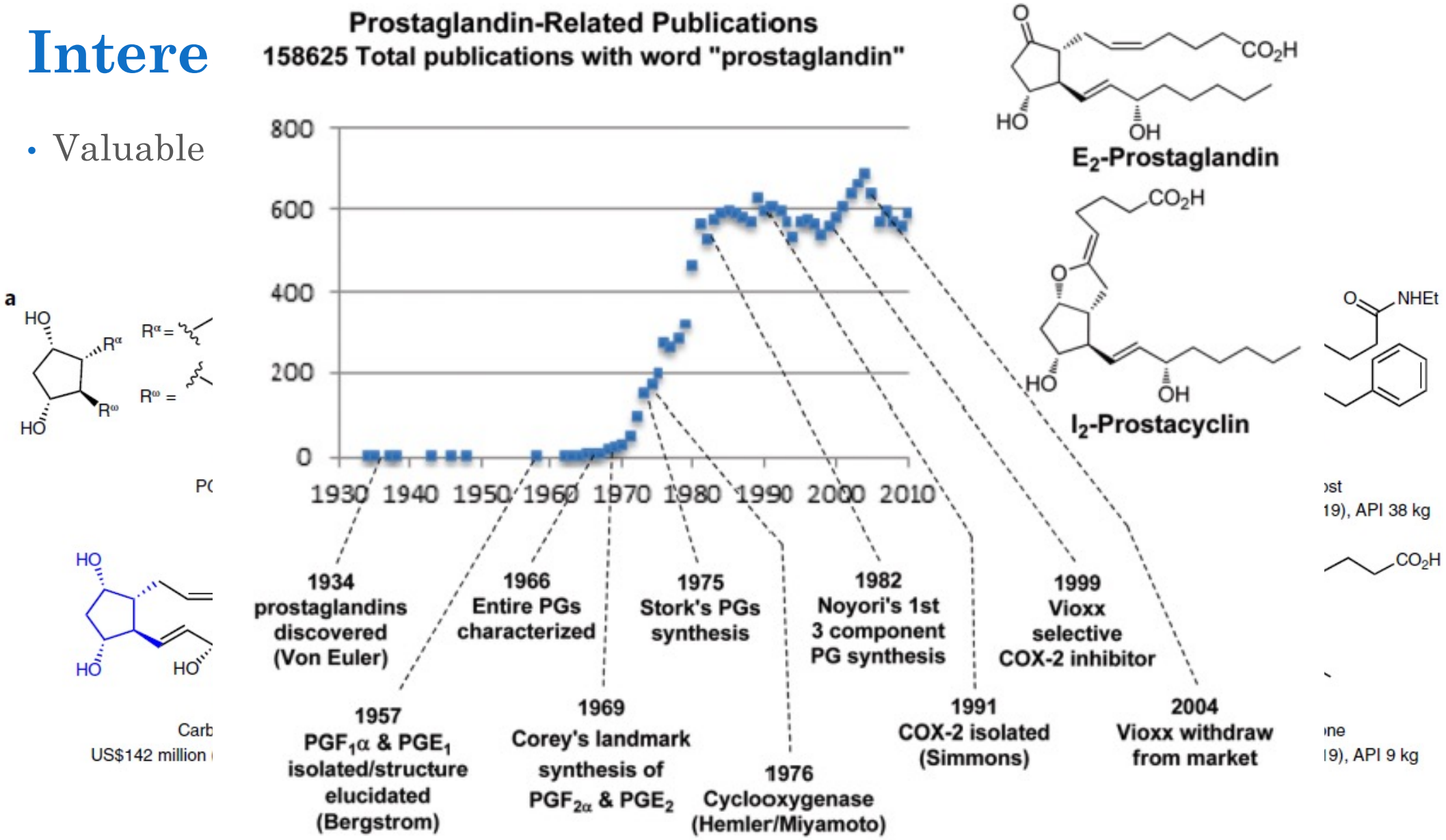
- Valuable drug candidates



For more drug candidates: *Org. Biomol. Chem.*, **2017**, 15, 6281–6301

Intere

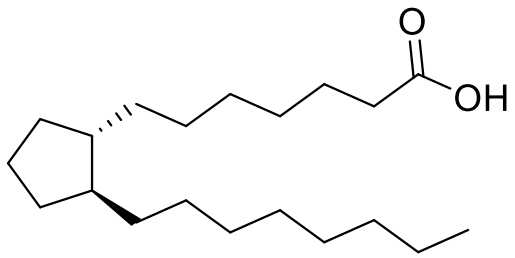
- Valuable



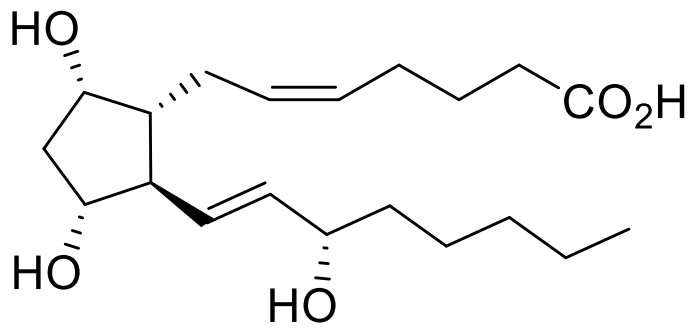
Org. Biomol. Chem., **2017**, 15, 6281–6301

Structural analysis of prostaglandins

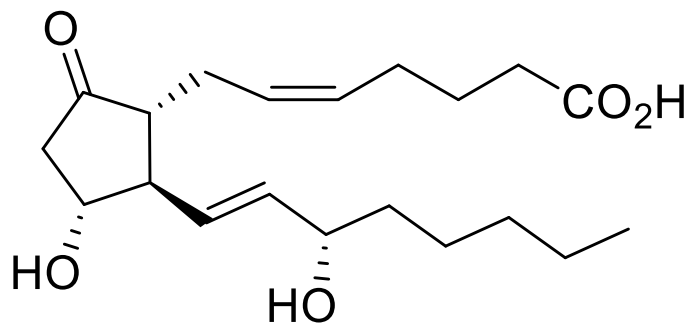
- Skeleton of prostanoic acid



- Different substituents on the five-membered ring
- Different degree of unsaturation in the side chains



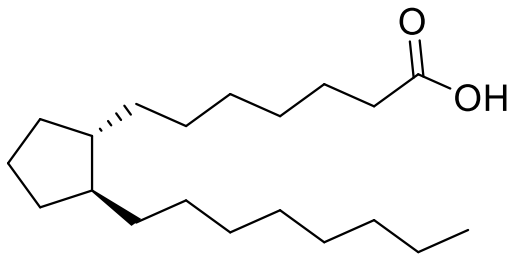
$PGF_{2\alpha}$



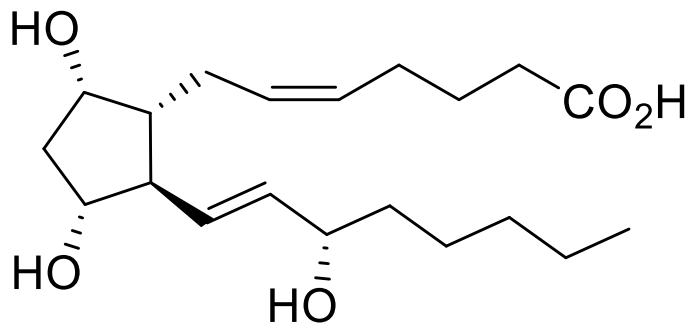
PGE_2

Structural analysis of prostaglandins

- Skeleton of prostanoic acid



- Different substituents on the
- Different degree of unsaturati

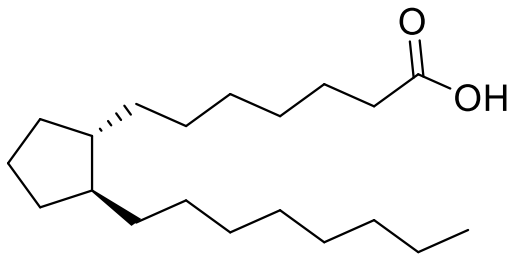


$PGF_{2\alpha}$

- Five asymmetric carbon atoms (four contiguous on a cyclopentane ring)
- Control of the stereochemistry of C15
- Stereoselective construction of *cis*- and *trans*-disubstituted olefins with complementary methods

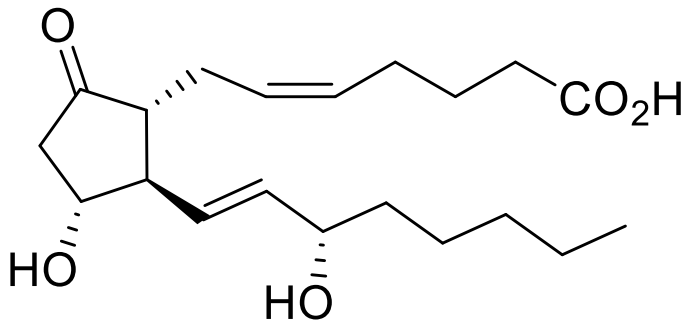
Structural analysis of prostaglandins

- Skeleton of prostanoic acid



- Different substituents on the five-membered ring
- I on in the side chains

- Lability in acidic or basic media of the ß-hydroxyketo moiety
- Control of the stereochemistry of C15
- Stereoselective construction of *cis*- and *trans*-disubstituted olefins with complementary methods

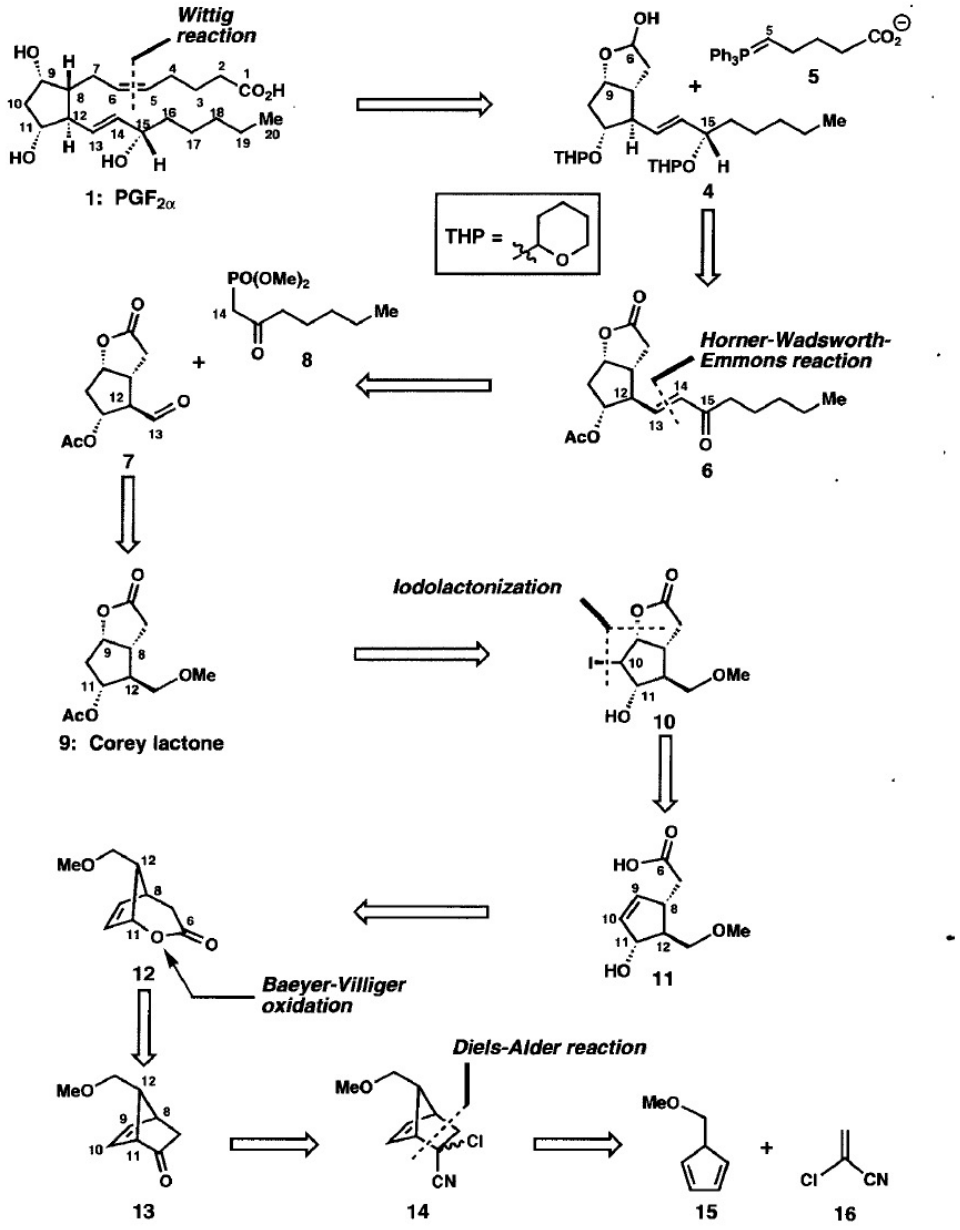


PGE_2

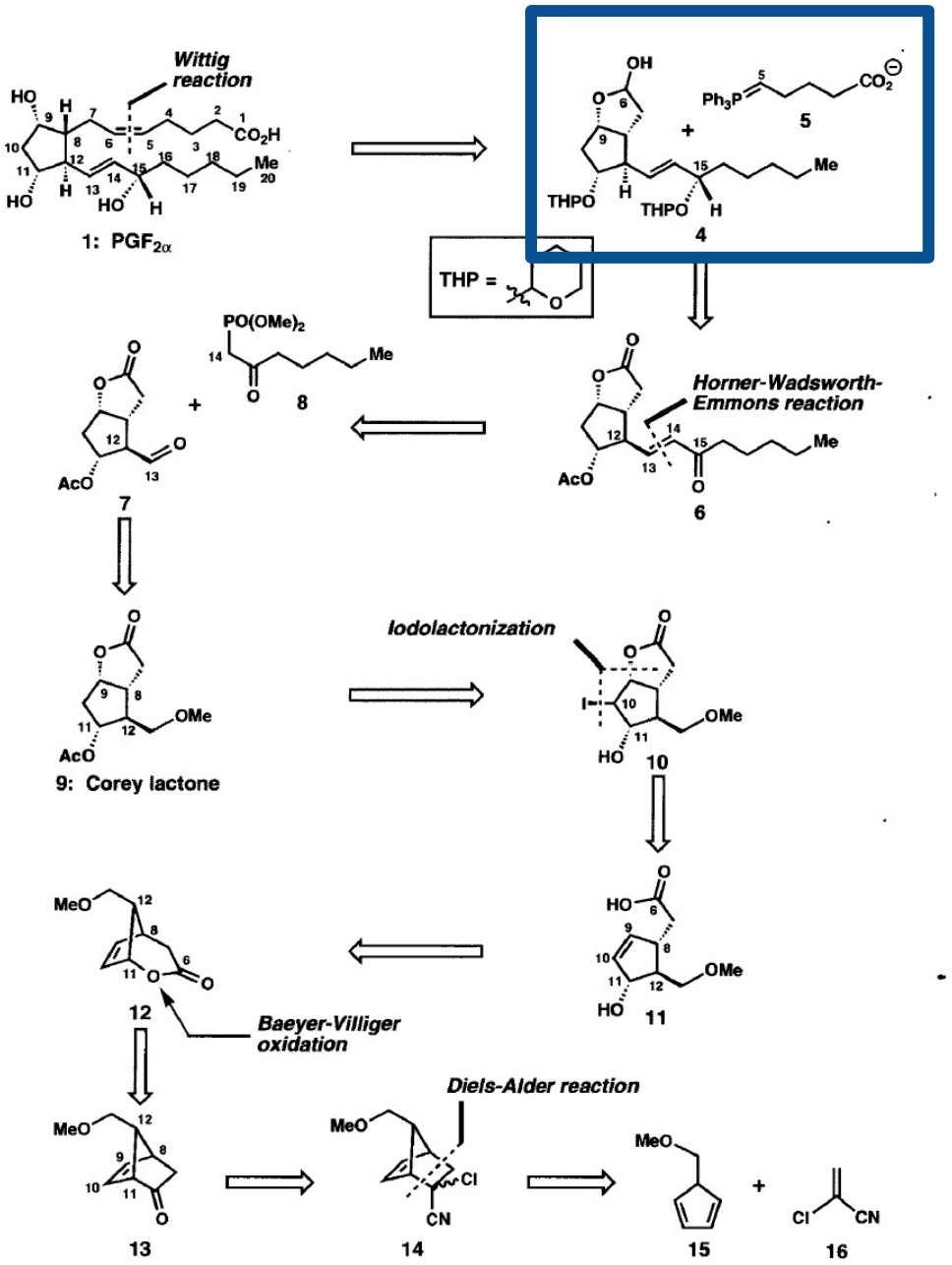
Corey's synthesis of $PGF_{2\alpha}$ and PGE_2

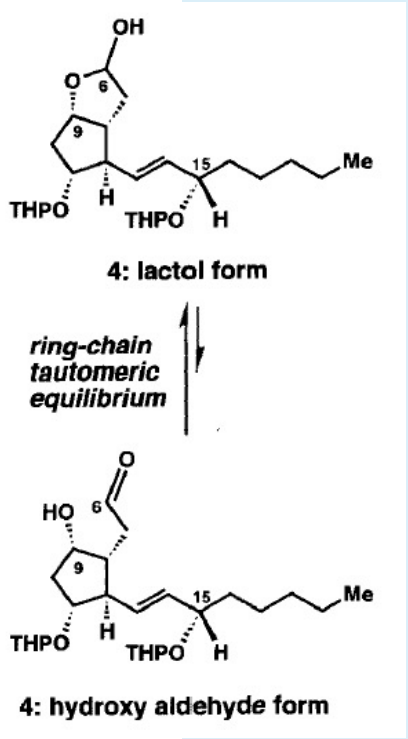
K. C. Nicolaou and E. J. Sorensen, Classics in Total Synthesis, VCH, Weinheim, 1996, p. 65-81

J. Am. Chem. Soc. **1969**, 91, 5675; *J. Am. Chem. Soc.* **1970**, 92, 397; *J. Am. Chem. Soc.* **1970**, 92, 2586; *N. Y. Acad. Sci.* **1971**, 180, 24



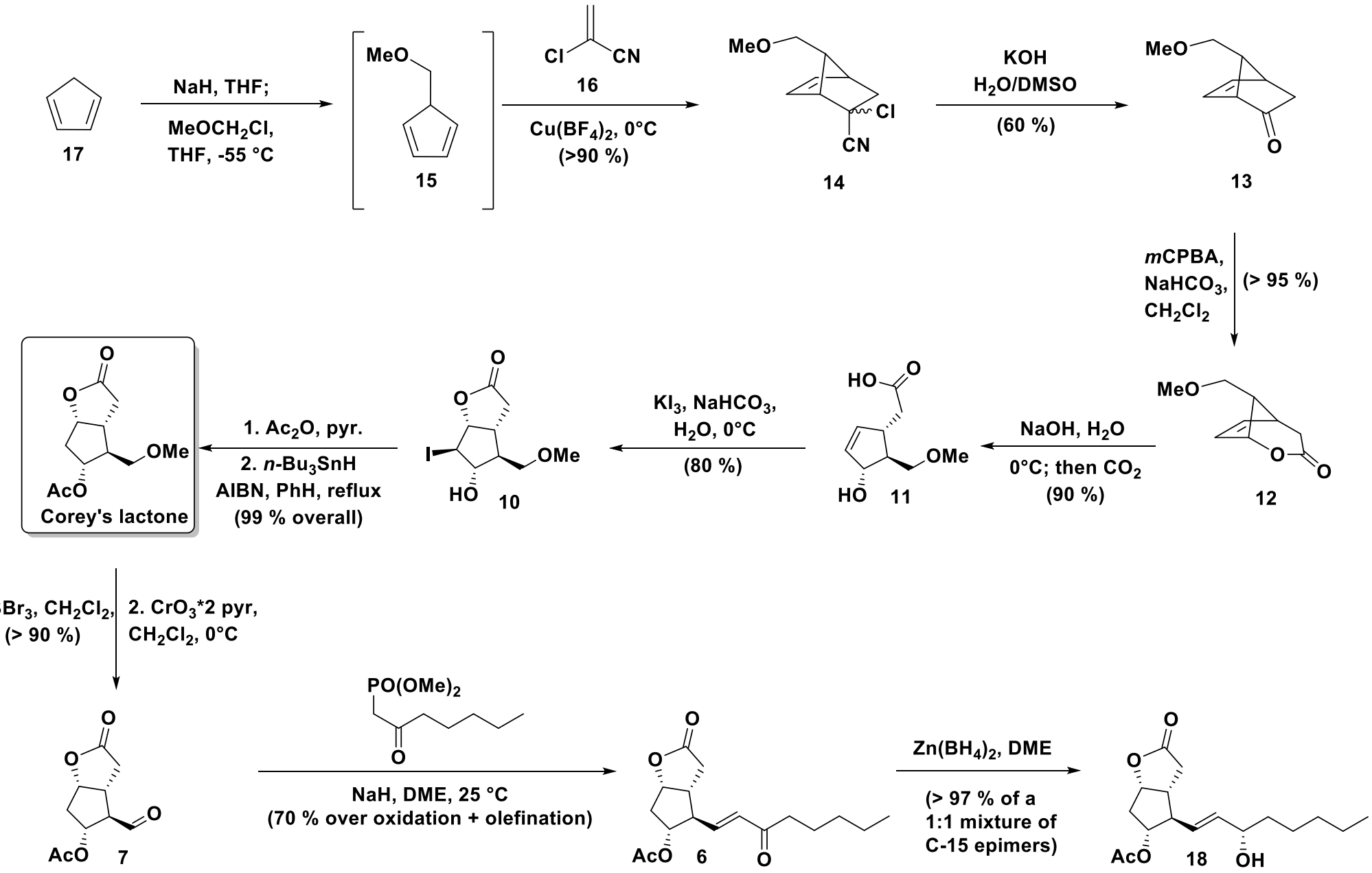
Retrosynthetic approach



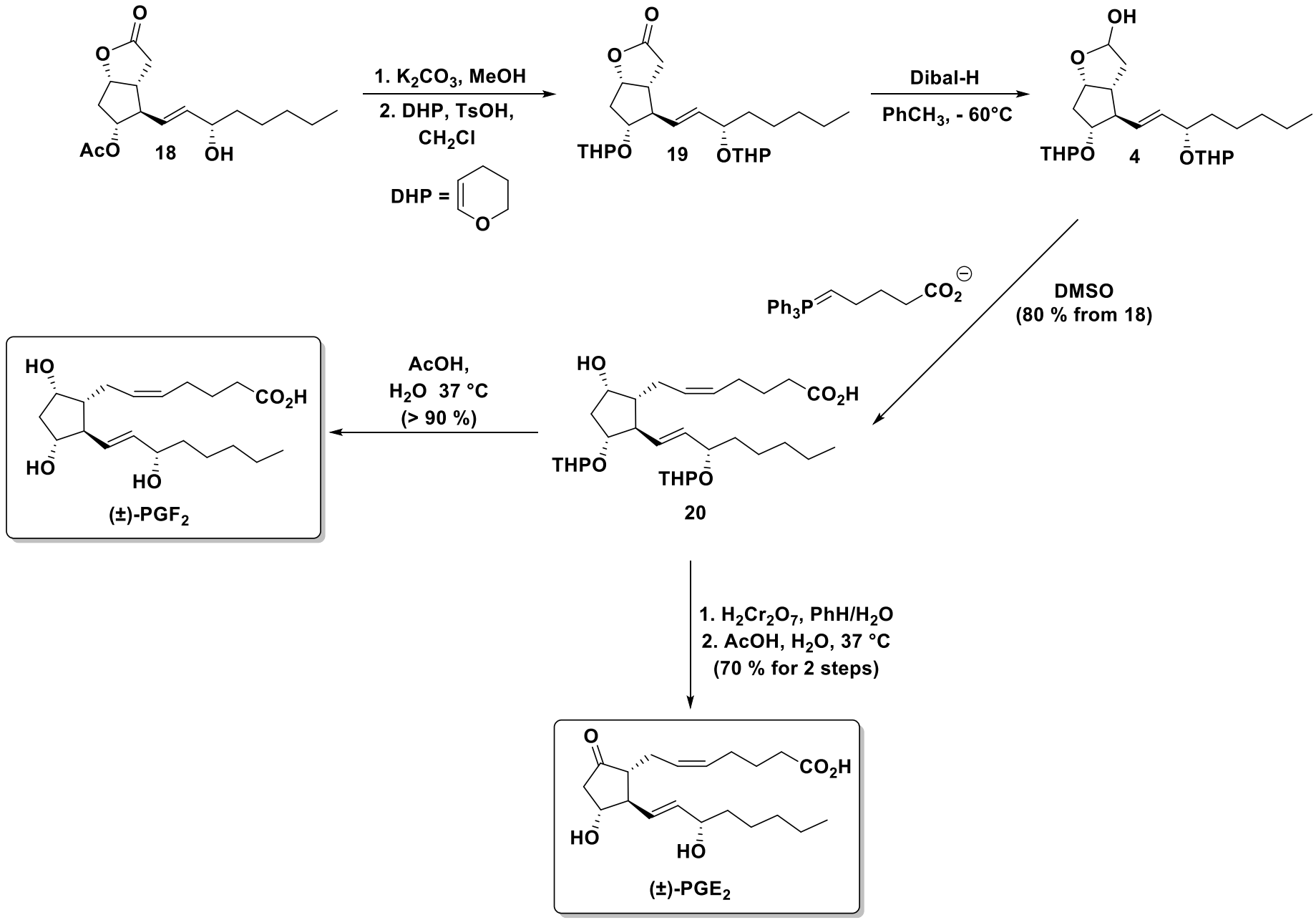


Retrosynthetic approach

Total synthesis (1)

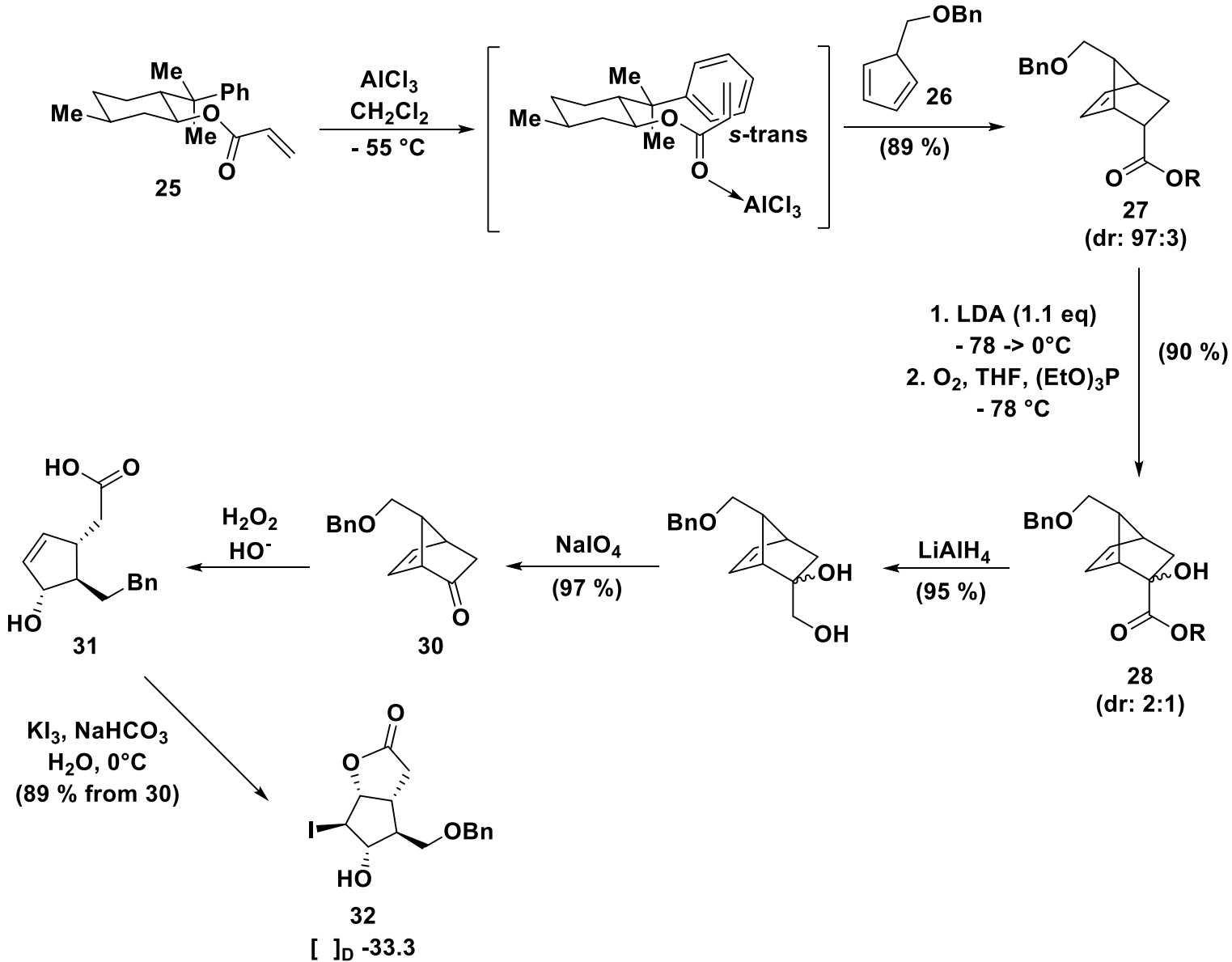


Total synthesis (2)



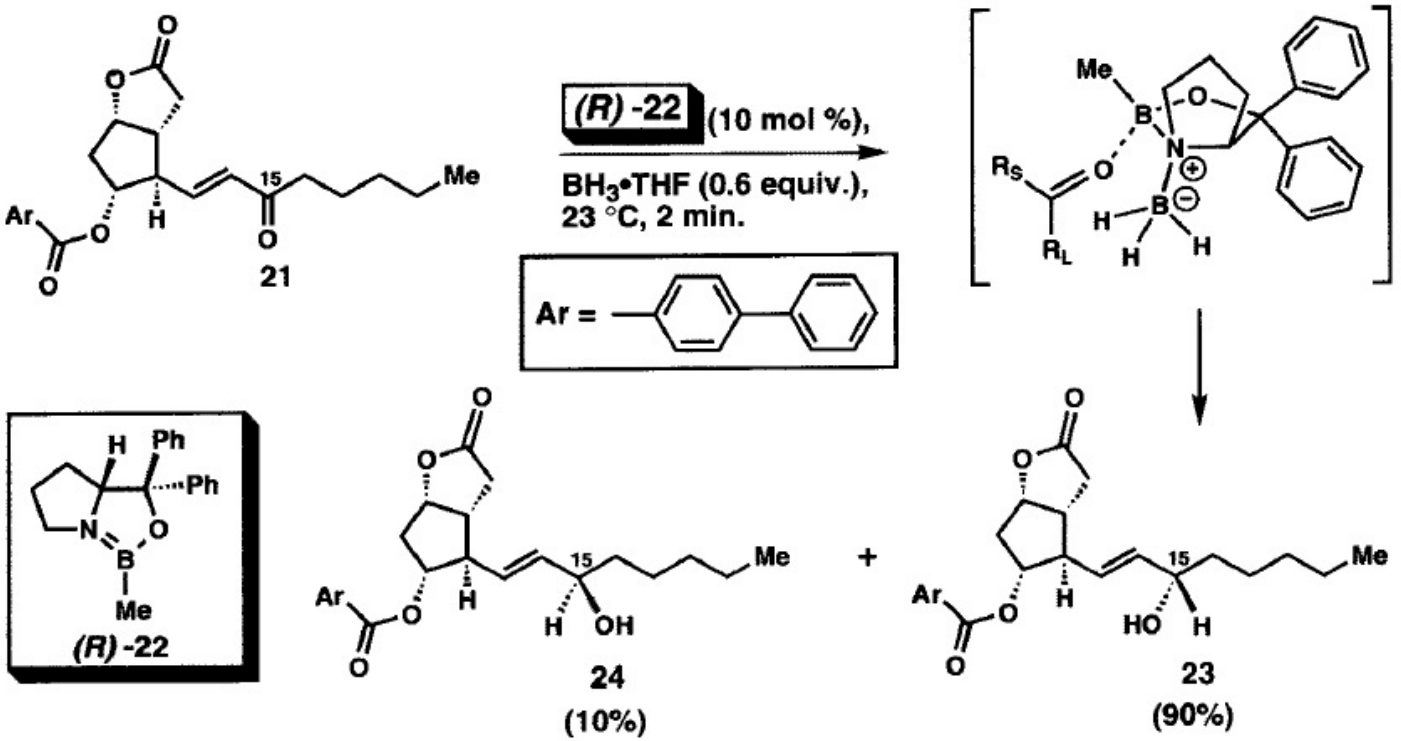
Further developments

1. Asymmetric Diels-Alder reaction (1975)



Further developments

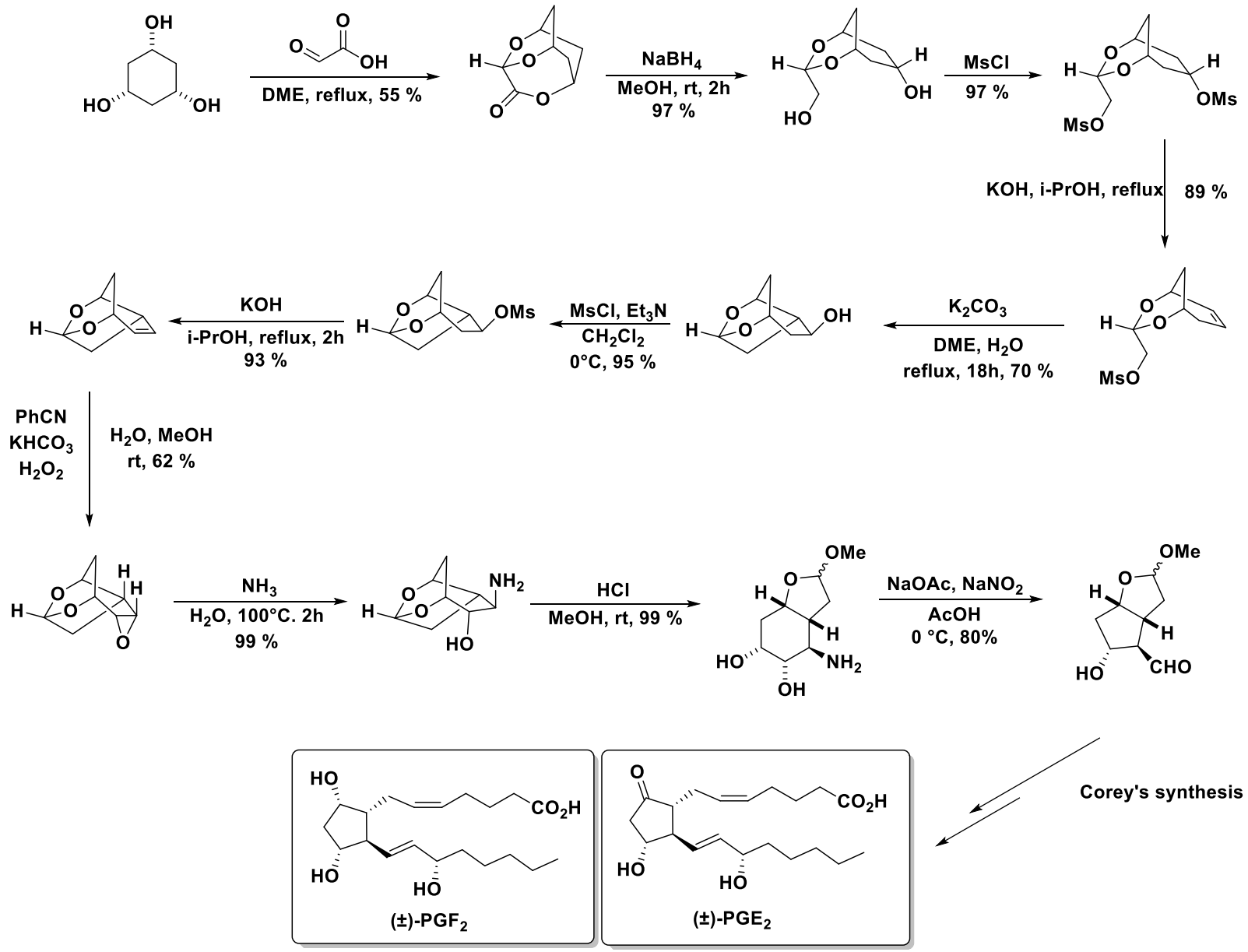
2. Enantioselective reduction of unsaturated ketones (1987)



Woodward's synthesis of $PGF_{2\alpha}$

J. Am. Chem. Soc. **1973**, 95, 20, 6853–6855

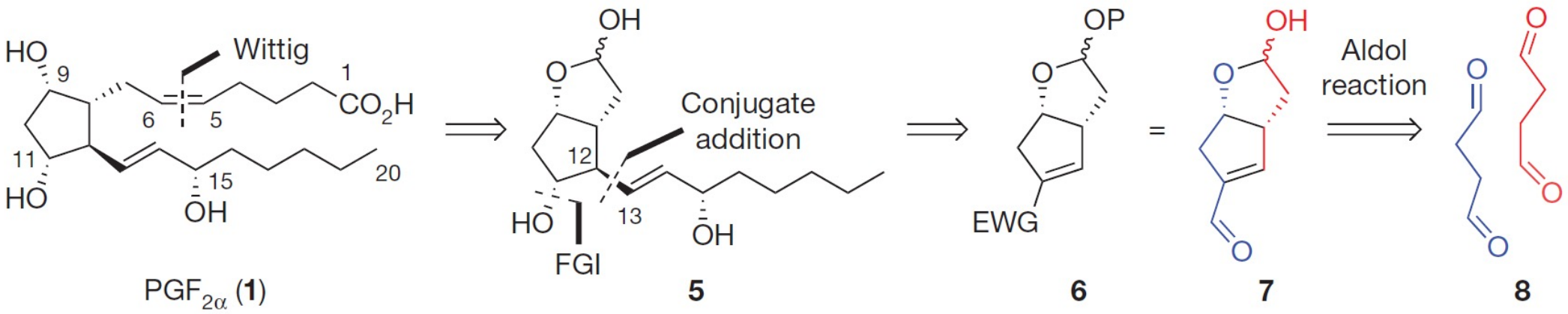
Total synthesis



Aggarwal's synthesis of $PGF_{2\alpha}$

Nature **2012,** 489, 278-281

Retrosynthetic approach



- The upper side-chain is introduced via a Wittig reaction (same as Corey's synthesis)
- The lower side-chain is introduced via 1,4-addition to an enone
- The enone is synthesized via an asymmetric (proline catalyzed) aldol reaction

Total synthesis

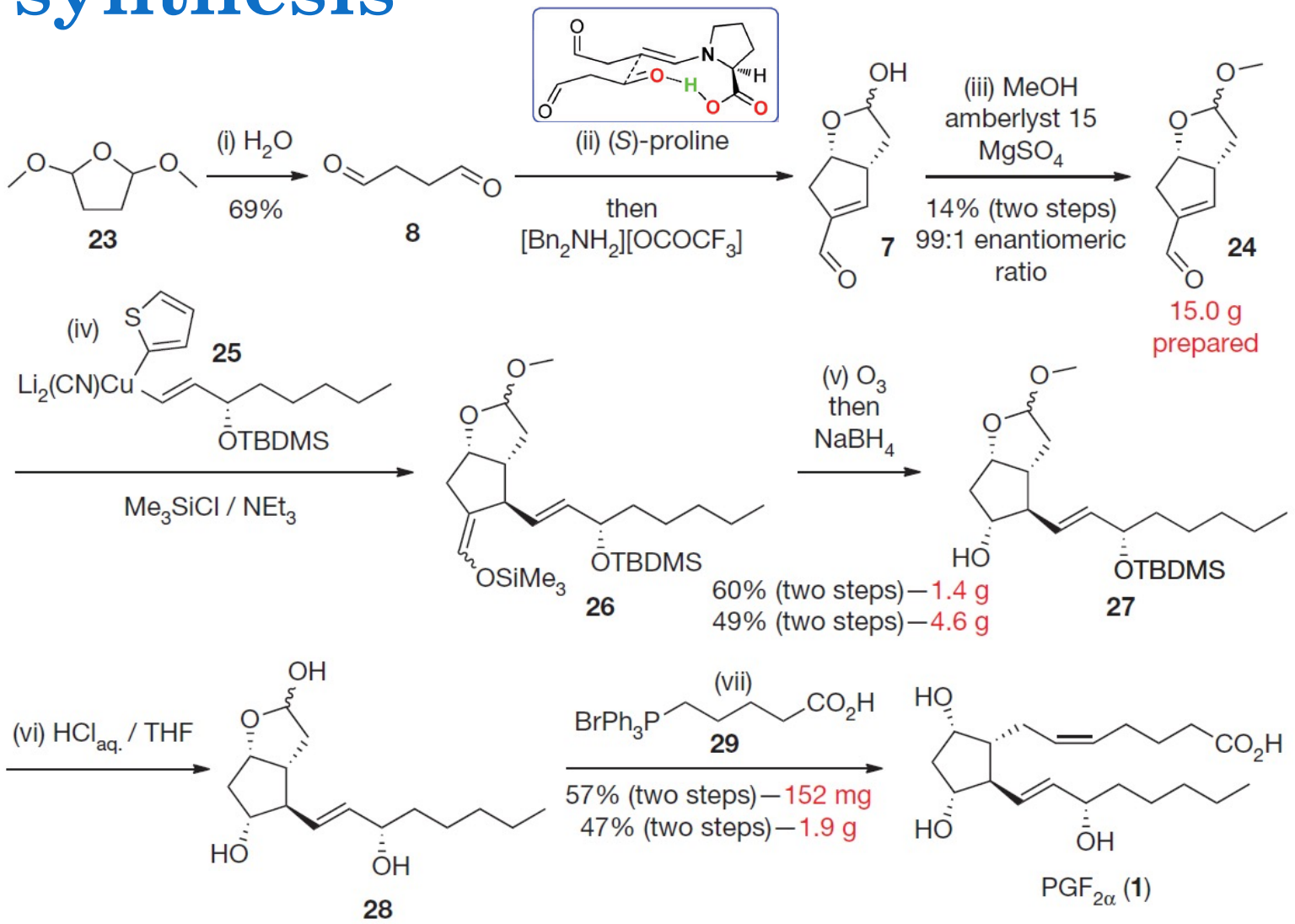
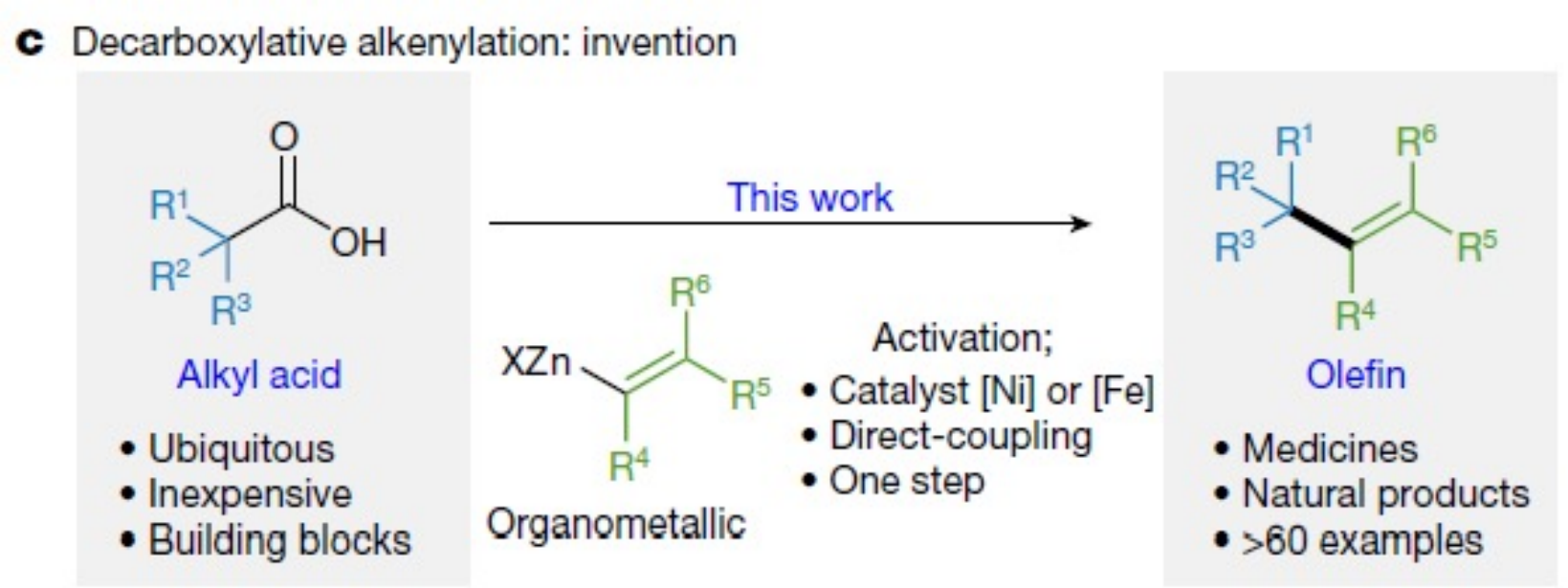


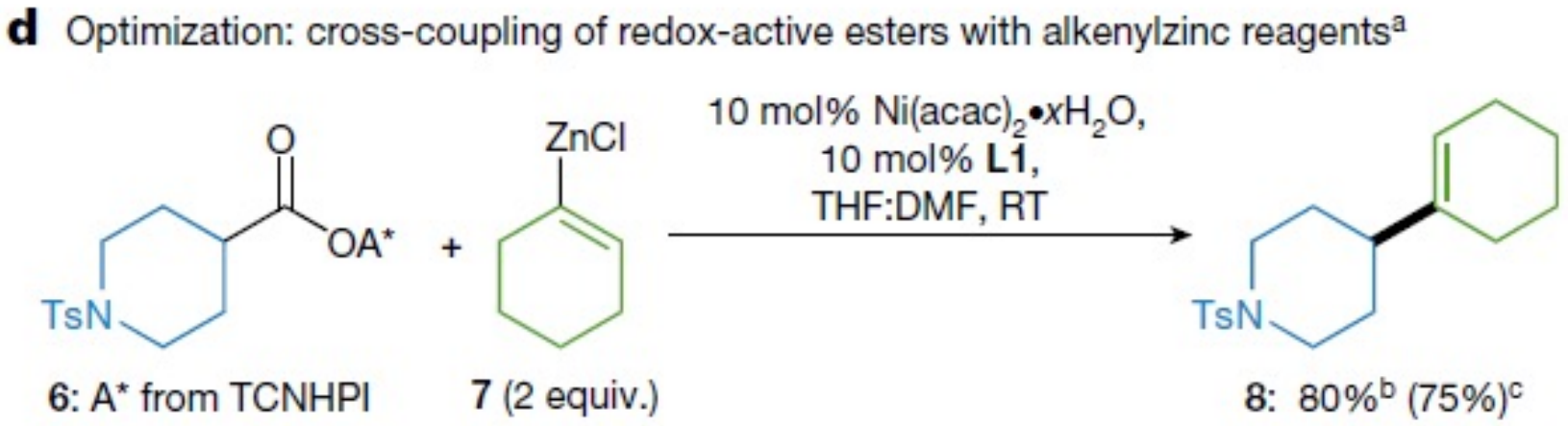
Figure 4 | A concise asymmetric synthesis of $PGF_{2\alpha}$ (1). Reaction conditions are as follows (see the Supplementary Information for full details). (i), H_2O, at 75 °C for 4 h, then at 115 °C to distil MeOH and H_2O. (ii), (*S*)-proline (2 mol.%), THF (2 M), at room temperature for 20 h, then $[Bn_2NH_2][OCOCF_3]$ (2 mol.%), THF (1 M), at room temperature for 14 h. (iii), MeOH (2.0 equivalents), amberlyst 15, $MgSO_4$, CH_2Cl_2, at room temperature for 14 h. (iv), **25** (1.1 equivalents), THF, then Me_3SiCl, Et_3N. (v), O_3, CH_2Cl_2/MeOH (3:1), −78 °C, then $NaBH_4$ (3 equivalents), at −78 °C to room temperature. (vi), 1.5% aqueous HCl/THF (3:2), at room temperature for 16 h. (vii), (4-carboxybutyl)(triphenyl)phosphonium bromide (6 equivalents), potassium *tert*-butoxide (12 equivalents), THF, at 0 °C to room temperature. TBDMS, *tert*-butyldimethylsilyl.

Baran's synthesis of $PGF_{2\alpha}$

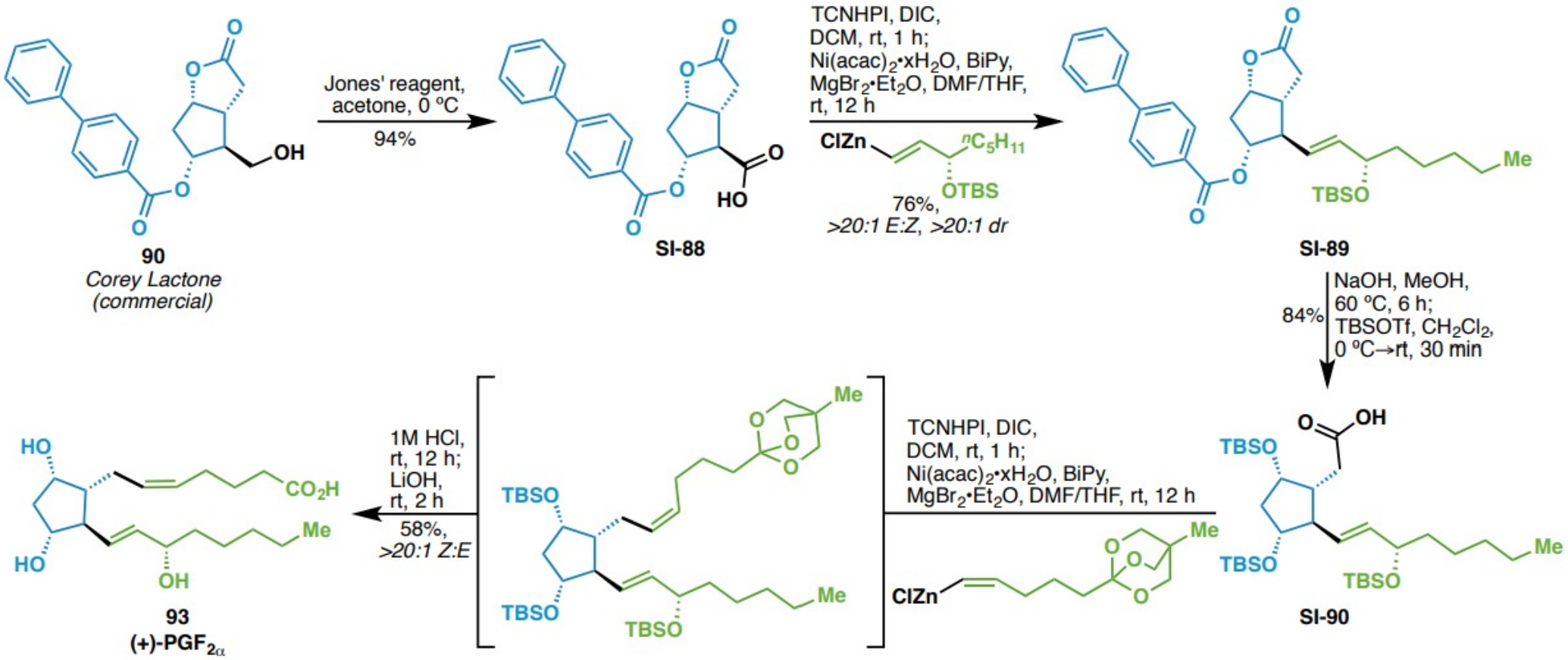
Nature **2017,** 545, 213-219

Strategy


c Decarboxylative alkenylation: invention
Alkyl acid
• Ubiquitous
• Inexpensive
• Building blocks
This work
Organometallic
Activation;
• Catalyst [Ni] or [Fe]
• Direct-coupling
• One step
Olefin
• Medicines
• Natural products
• >60 examples

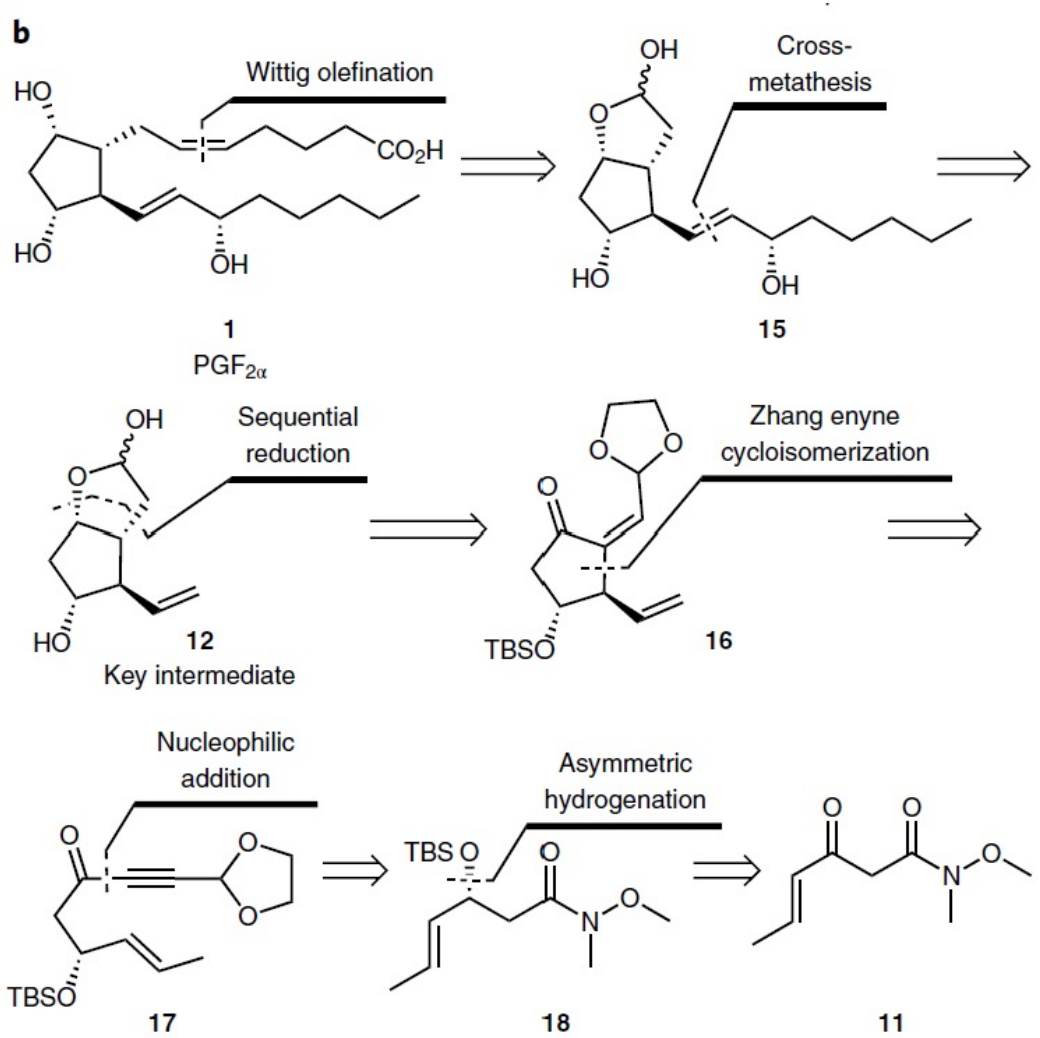

d Optimization: cross-coupling of redox-active esters with alkenylzinc reagents[a]
10 mol% Ni(acac)2•xH2O,
10 mol% L1,
THF:DMF, RT
6: A* from TCNHPI
7 (2 equiv.)
8: 80%[b] (75%)[c]

Application to $PGF_{2\alpha}$ synthesis



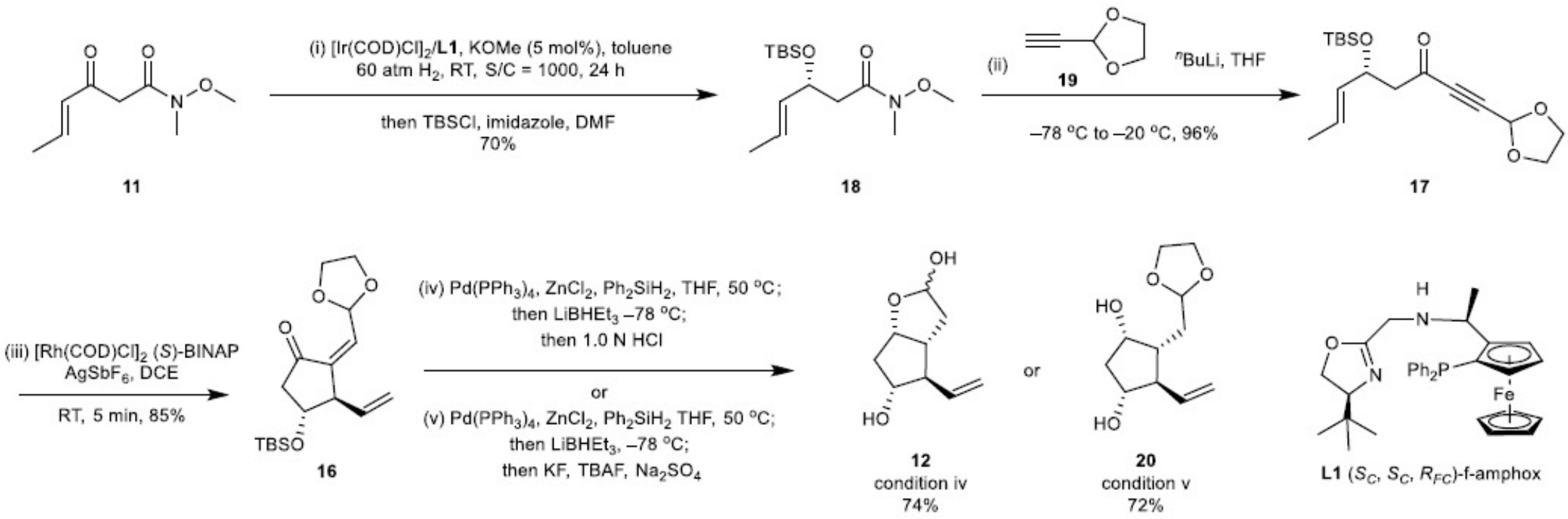
Zhang's synthesis of $PGF_{2\alpha}$ and PGE_2

Nature **2021,** 13, 692-697

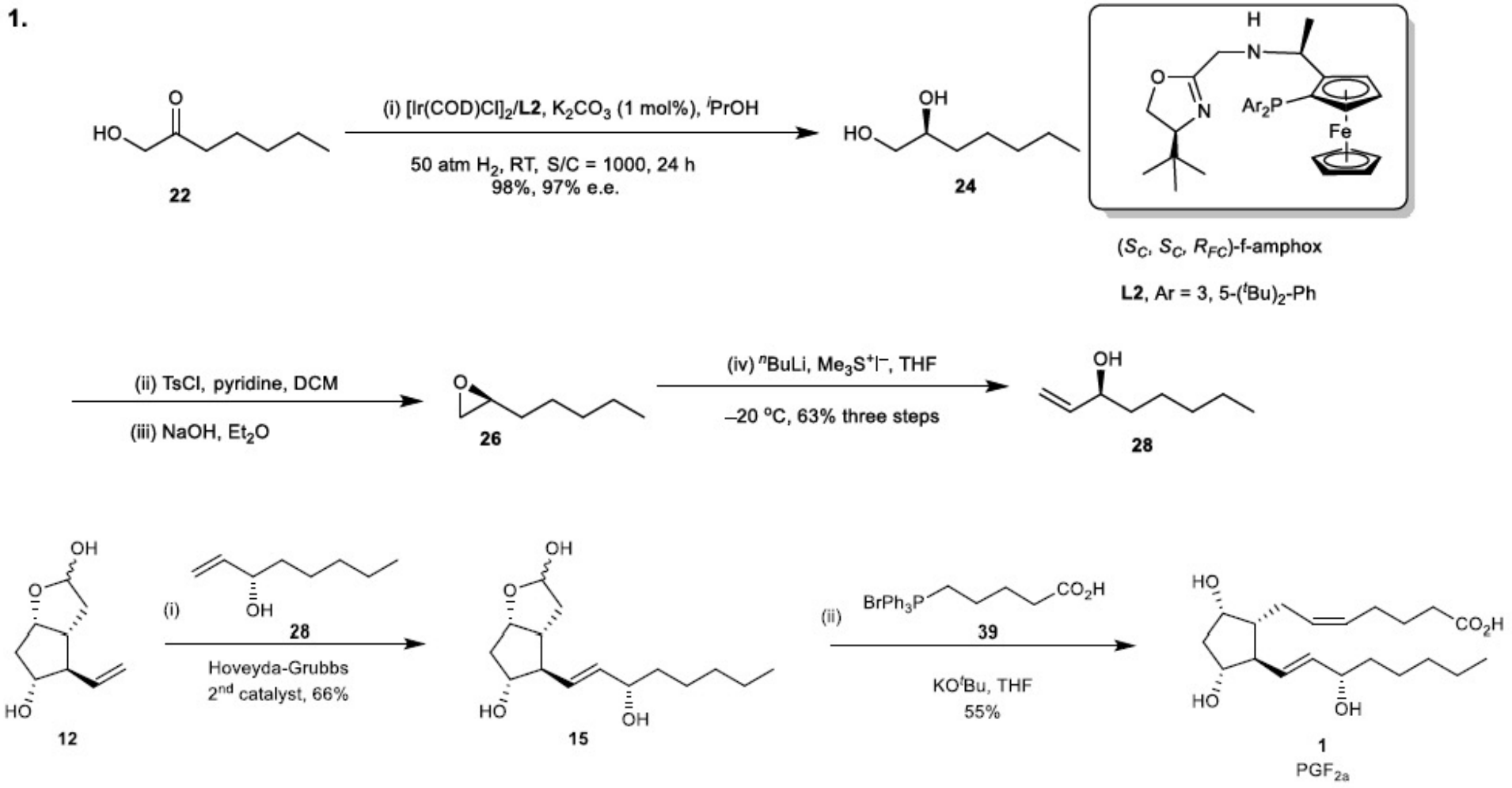


Retrosynthetic approach

Synthesis of $PGF_{2\alpha}$ (1)

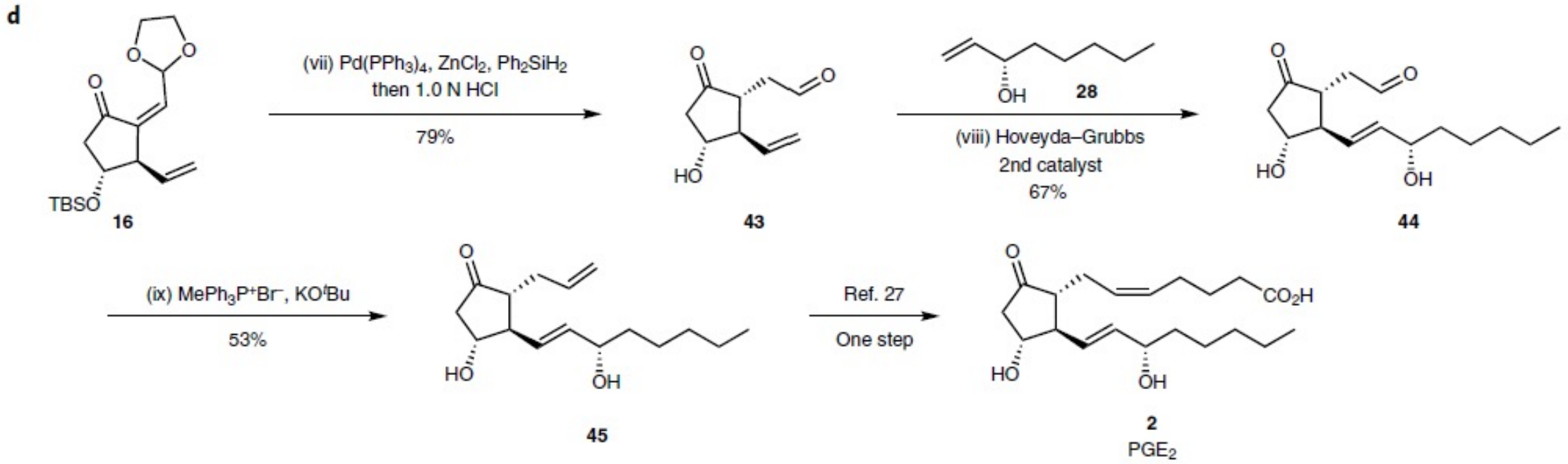


Synthesis of $PGF_{2\alpha}$ (2)

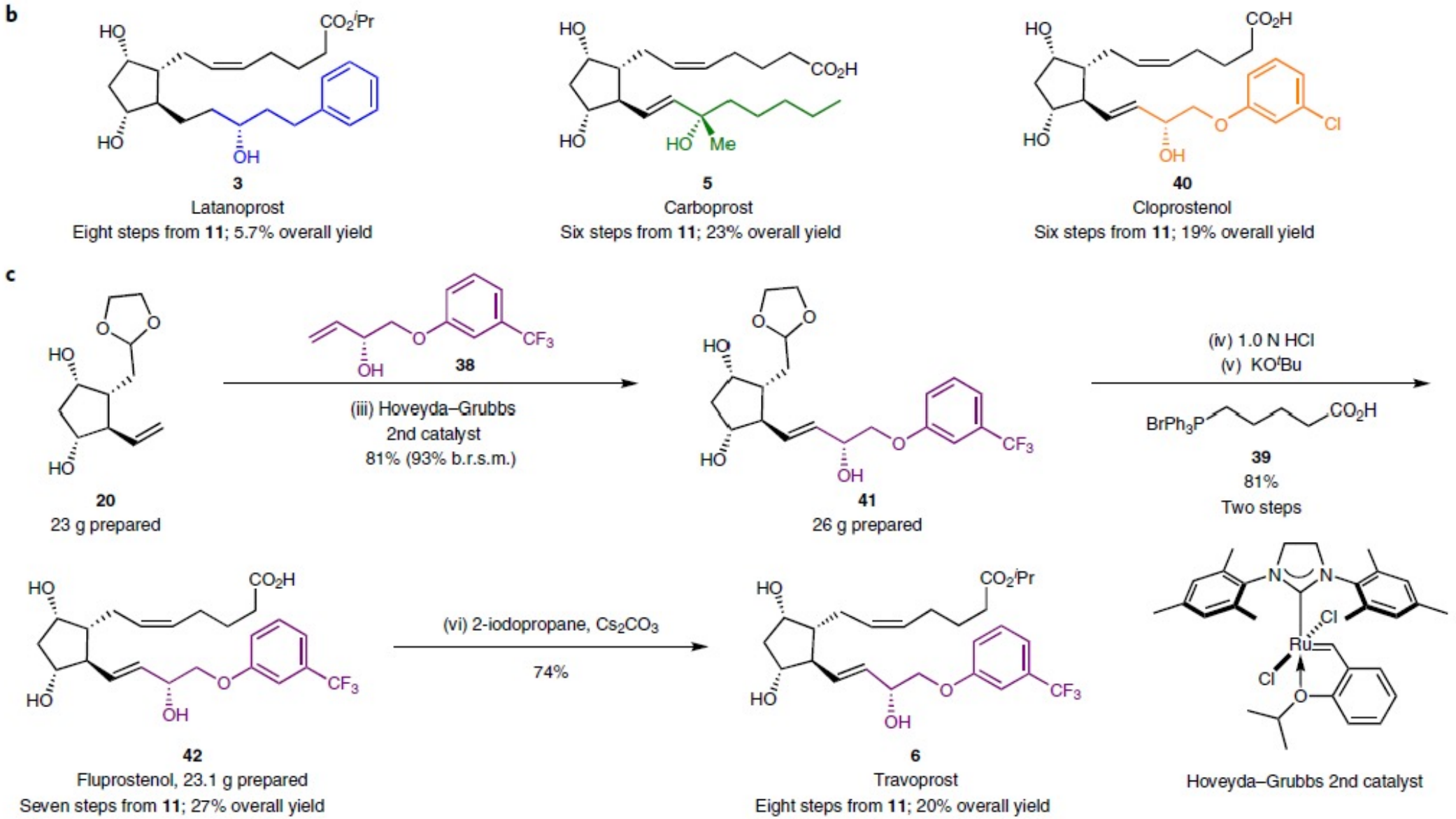


Six steps from 11;
15 % overall yield

Synthesis of PGE_2



Access to other related compounds



Discussion and conclusion

- Corey's and Woodward's synthesis -> easy chemistry, hard to scale up
- Aggarwal's synthesis -> elegant approach, scale-up possible, **low yield**
- Baran's synthesis -> high AE for the addition of the side chains
- Zhang's synthesis –> high control of the stereochemistry, **scalable,** catalytical reactions, access to different prostaglandins derivatives

ARTICLES
https://doi.org/10.1038/s41557-021-00706-1
nature chemistry

Check for updates

Concise, scalable and enantioselective total synthesis of prostaglandins

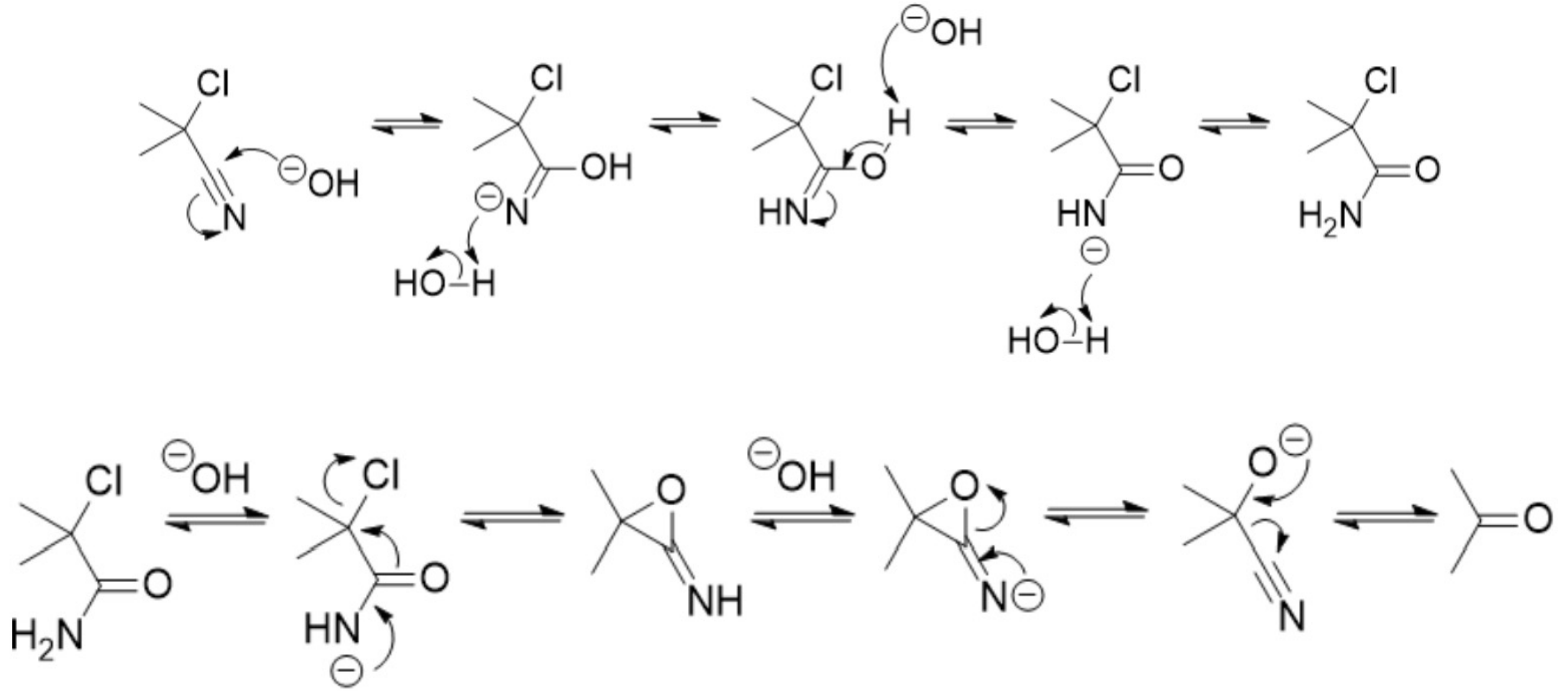
Fuhao Zhang[1,2], Jingwen Zeng[1], Mohan Gao[1], Linzhou Wang[1], Gen-Qiang Chen[1,3] ✉, Yixin Lu[2] and Xumu Zhang[1,3] ✉

Thank you for your attention !

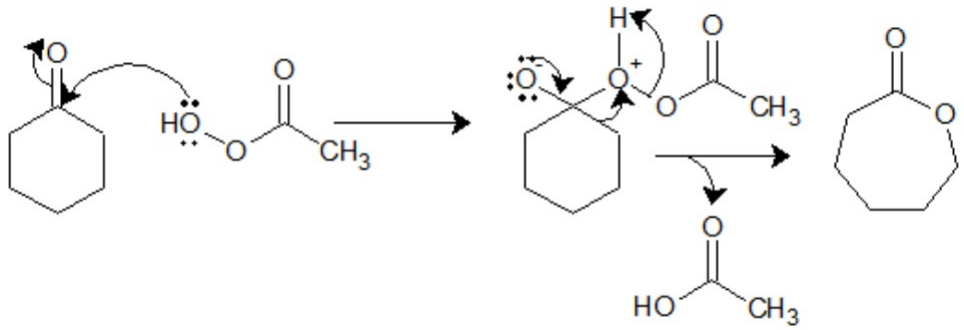
Mechanisms of reactions

A Corey's approach

1 Hydrolysis of chloronitriles (*Tetrahedron Lett.* **1983,** *24* (51), 5687–5690.)

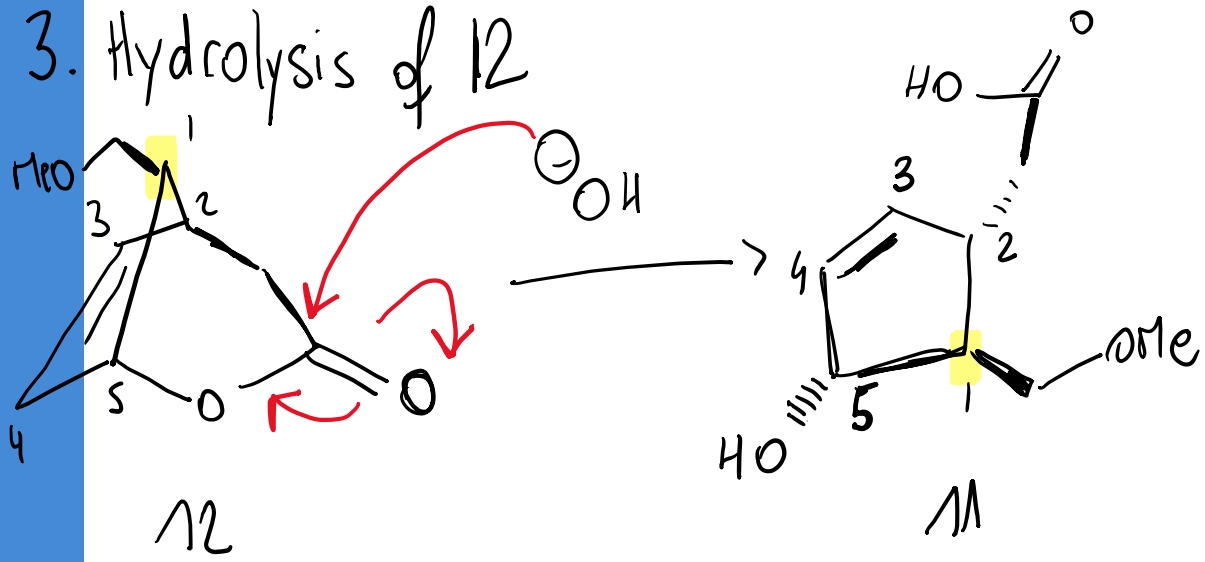


2. Baeyer-Villiger oxidation (https://www.organicchemistrytutorials.com/baeyer-villiger-oxidation/)



- regioselective
- no epoxidation of double bond

3. Hydrolysis of 12

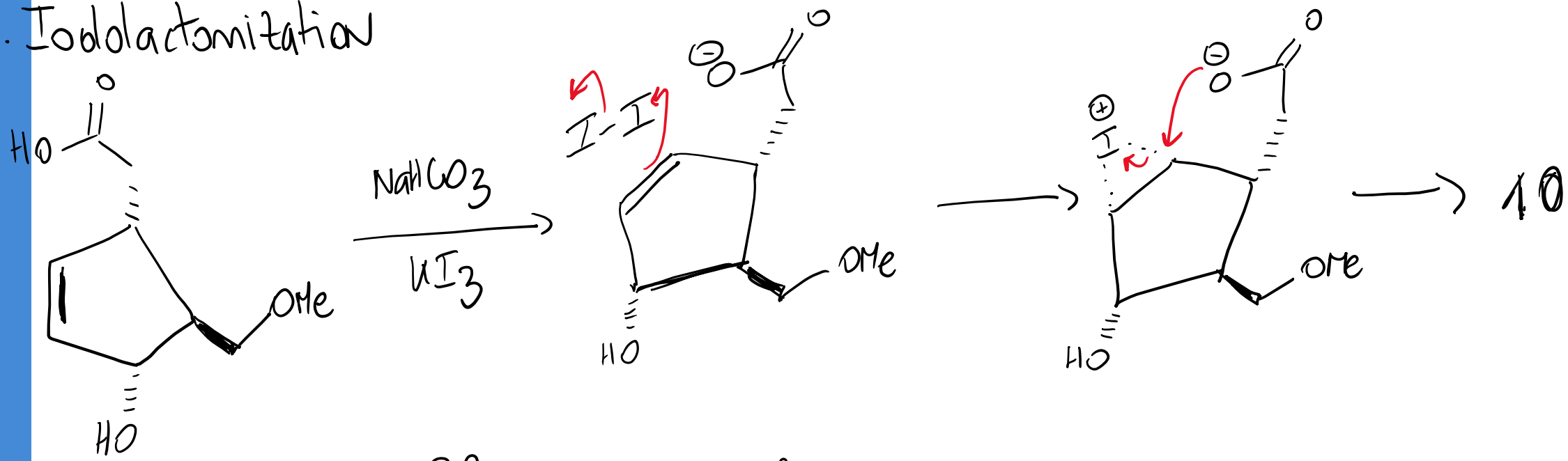


12

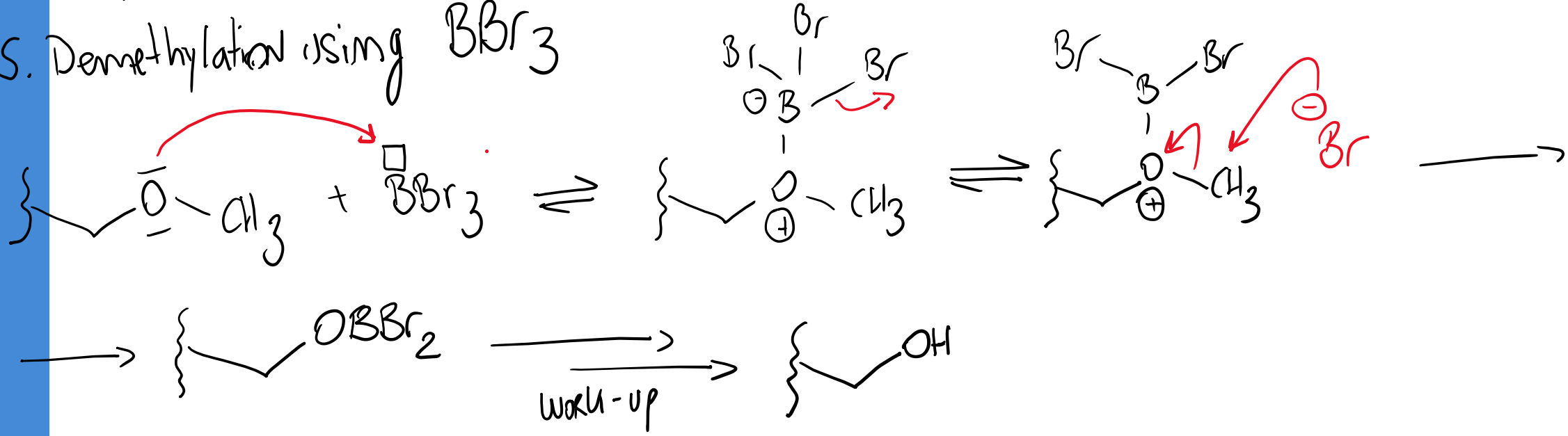
11

CO_2: neutralization of the mixture

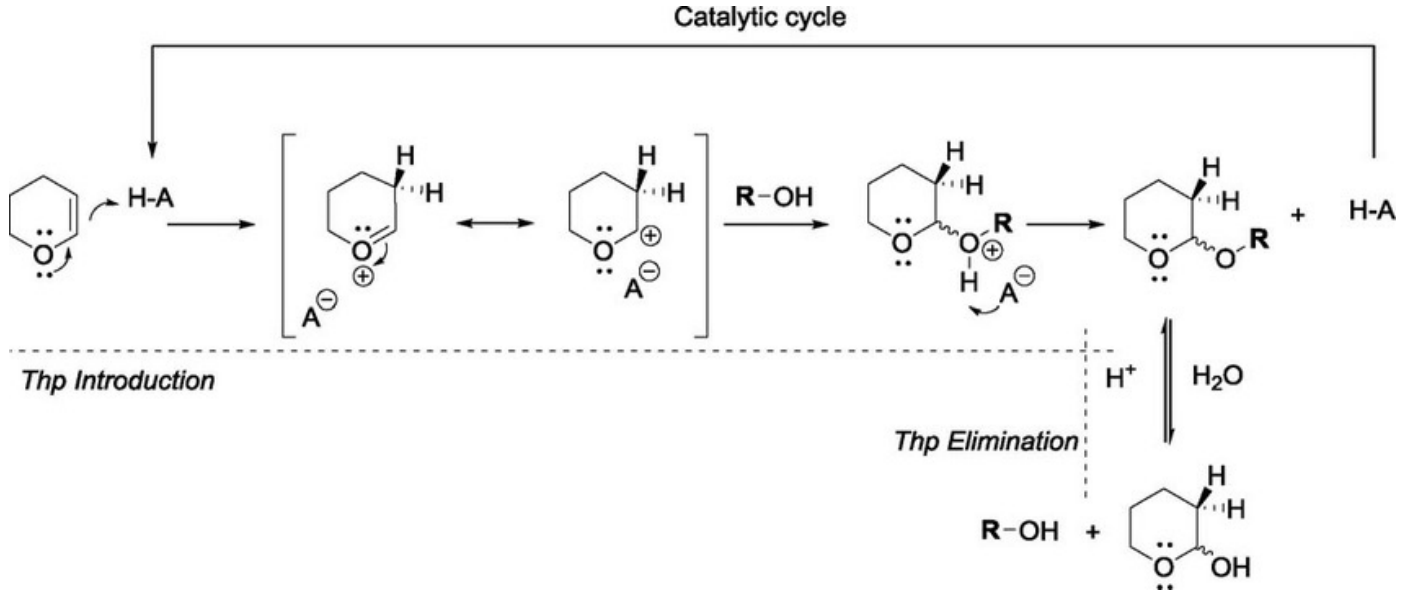
4. Iodolactonization



5. Demethylation using BBr_3

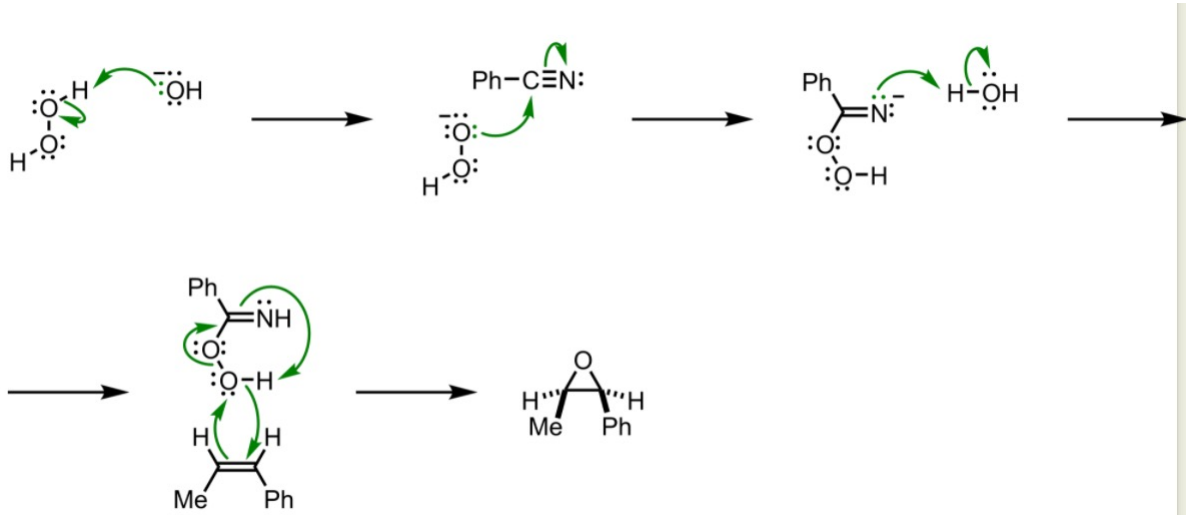


6. PROTECTION OF ALCOHOLS WITH DHP & TSOH cat.

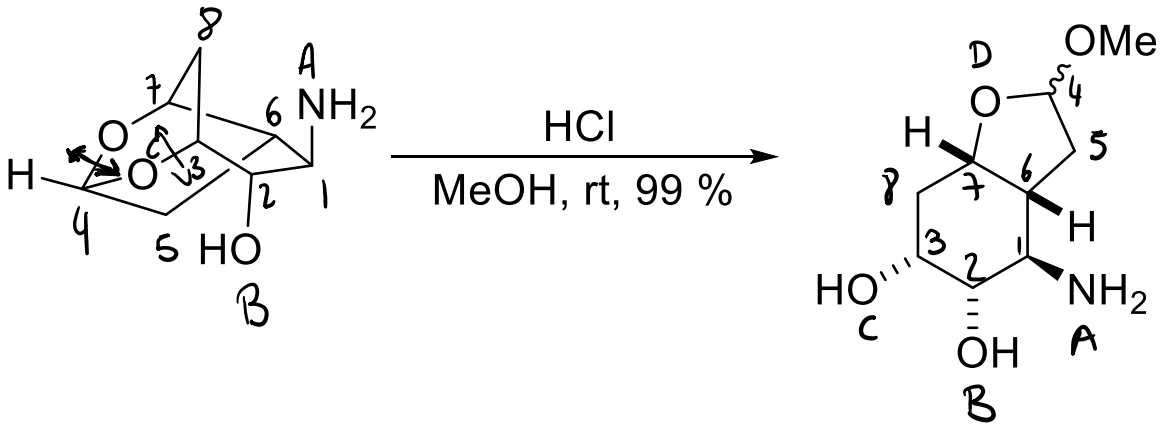


B Woodward's approach

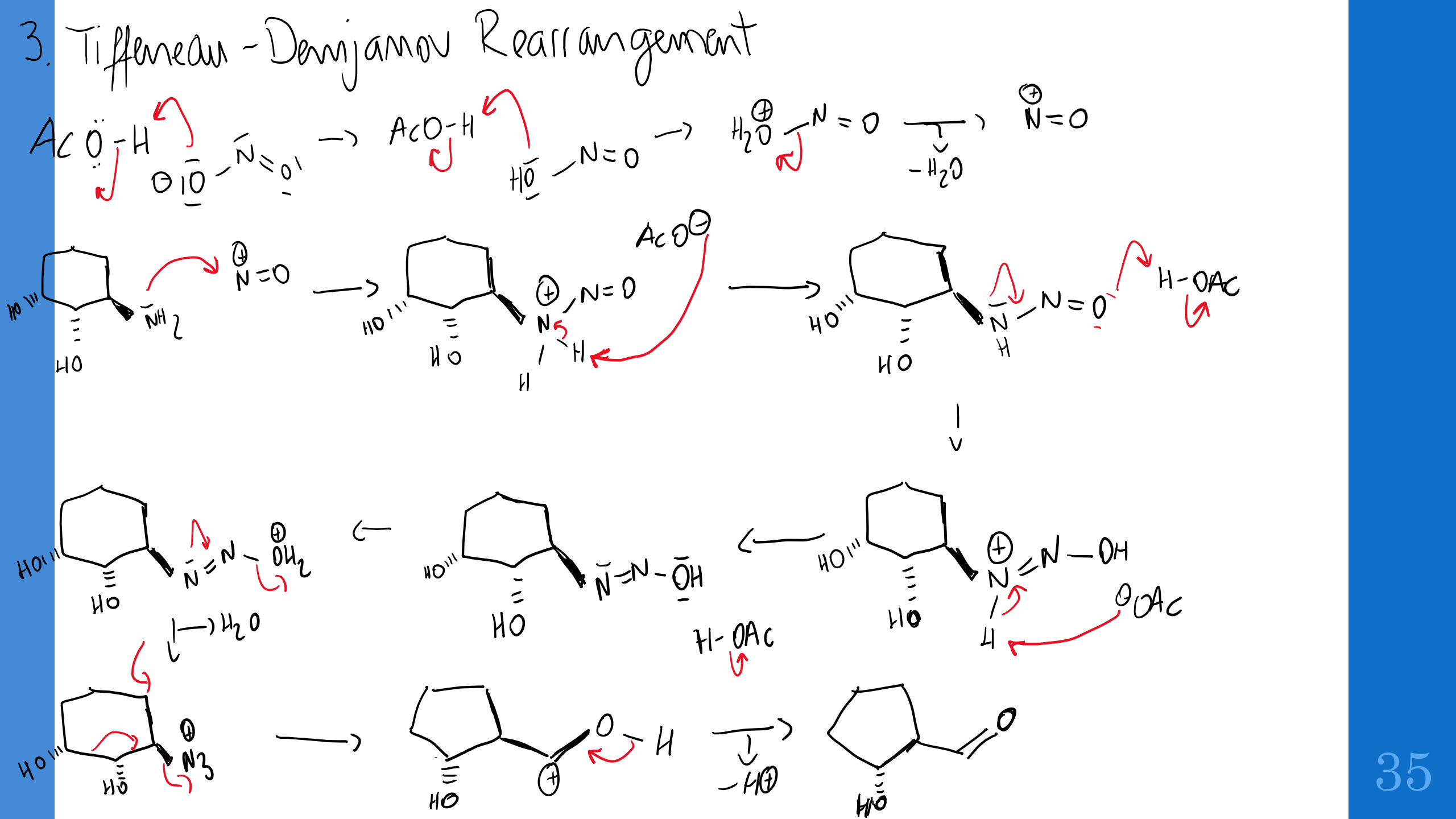
1. Payne Epoxidation (https://synarchive.com/named-reactions/payne-epoxidation)



2. Hydrolysis



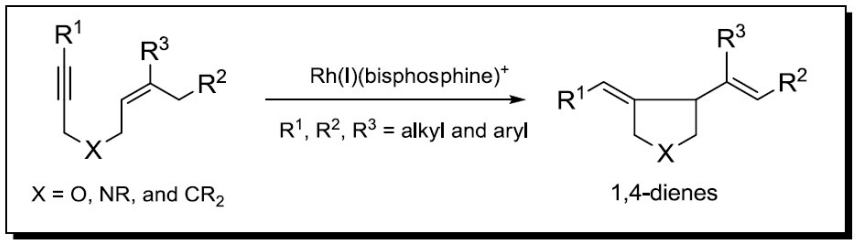
3. Tiffeneau-Demjanov Rearrangement

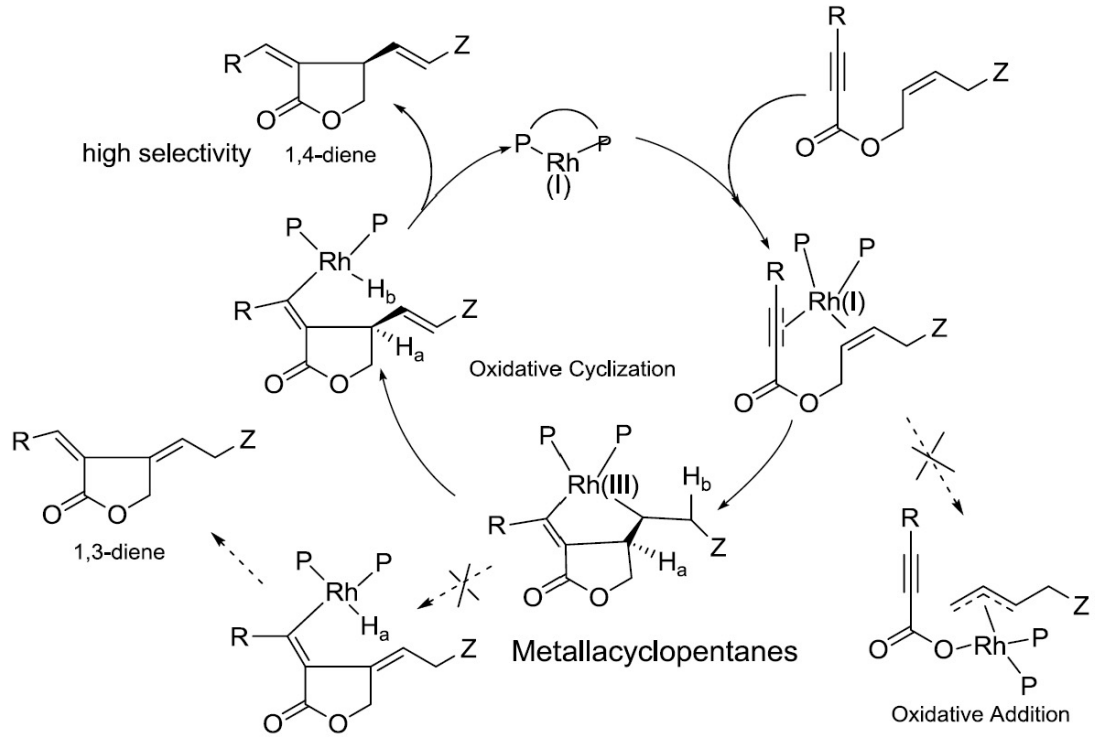


5 Zhang's approach

1. Cycloisomerization (Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000,** *122*, 6490–6491)

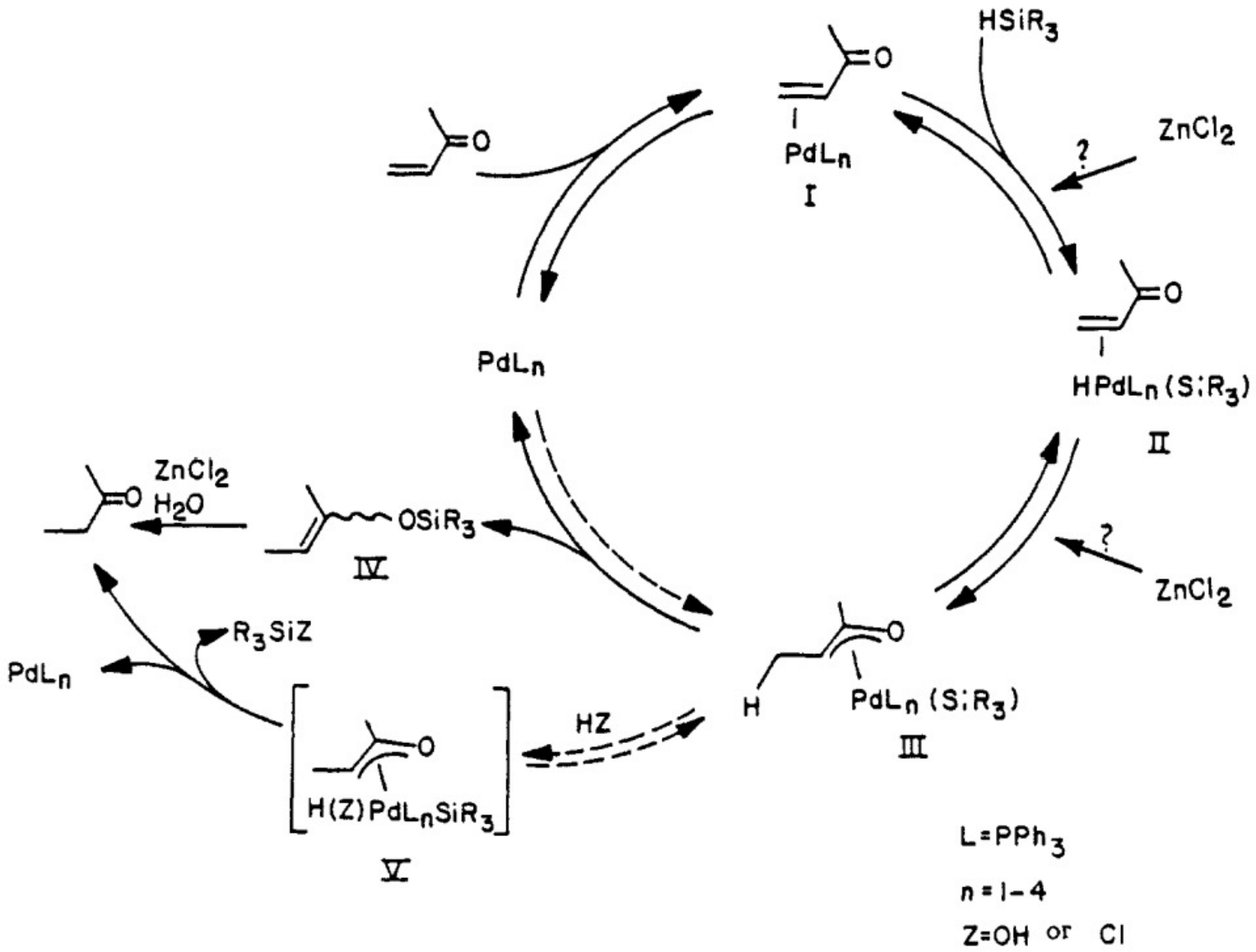
Enynes are cycloisomerized regio- and enantio-selectively with a Rh complex with phosphine ligands.



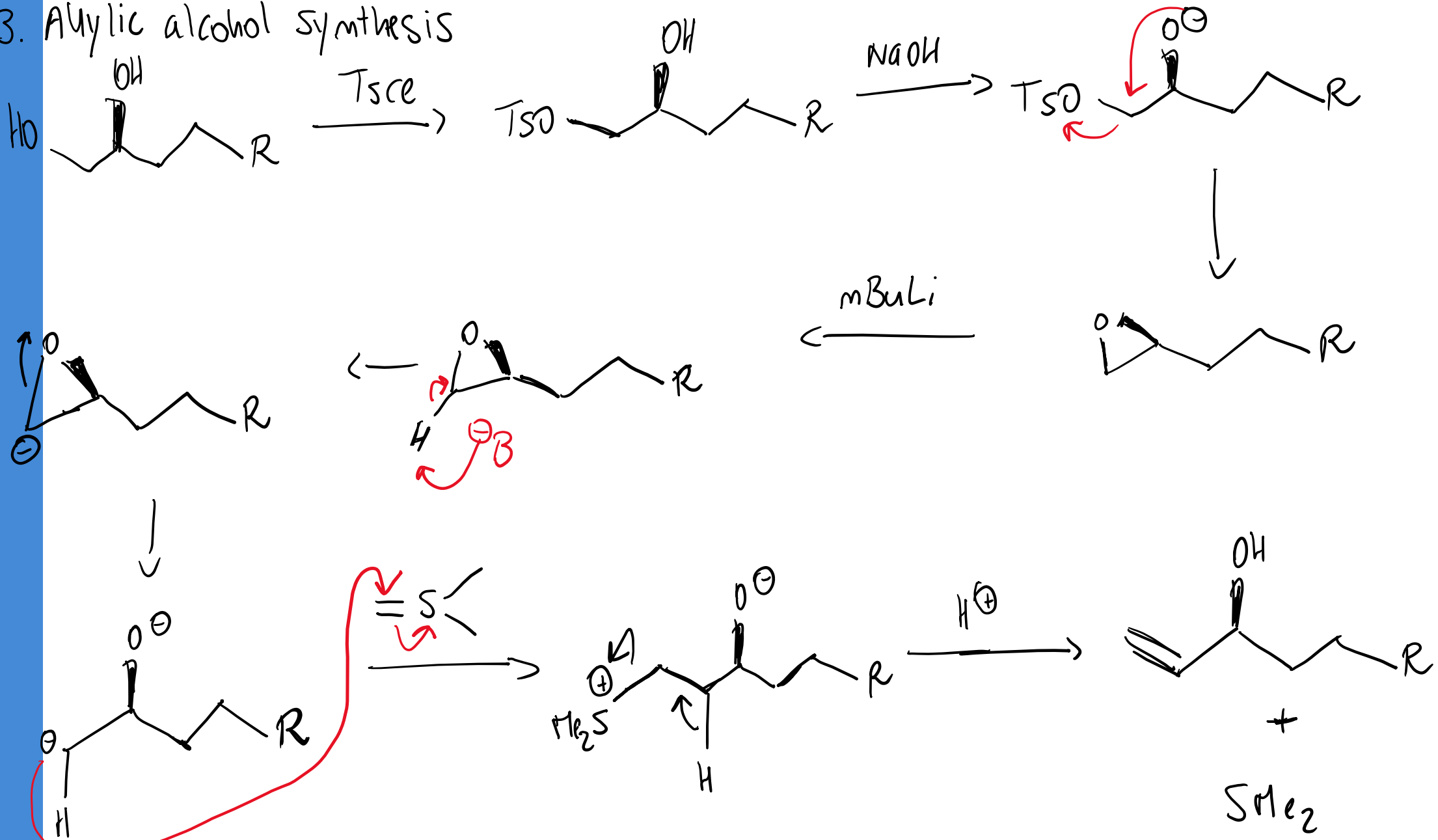


2. Conjugate 1,4 - reduction (*J. Am. Chem. Soc.* **1986**, 108, 7314-7325)

Scheme II



3. Allylic alcohol synthesis



Ref : *Tetrahedron Letters* **1994**, Vol. 35, No. 30. pp. 5449-5452