Stereocontrolled organocatalytic synthesis of prostaglandin $PGF_{2\alpha}$ in seven steps

Graeme Coulthard, William Erb, Varinder K. Aggarwal
Nature. August 15, 2012.
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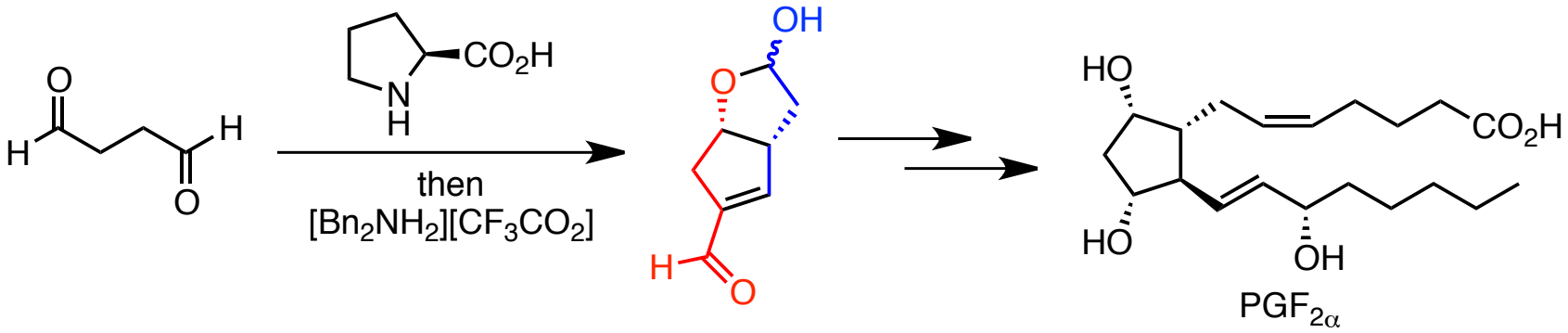
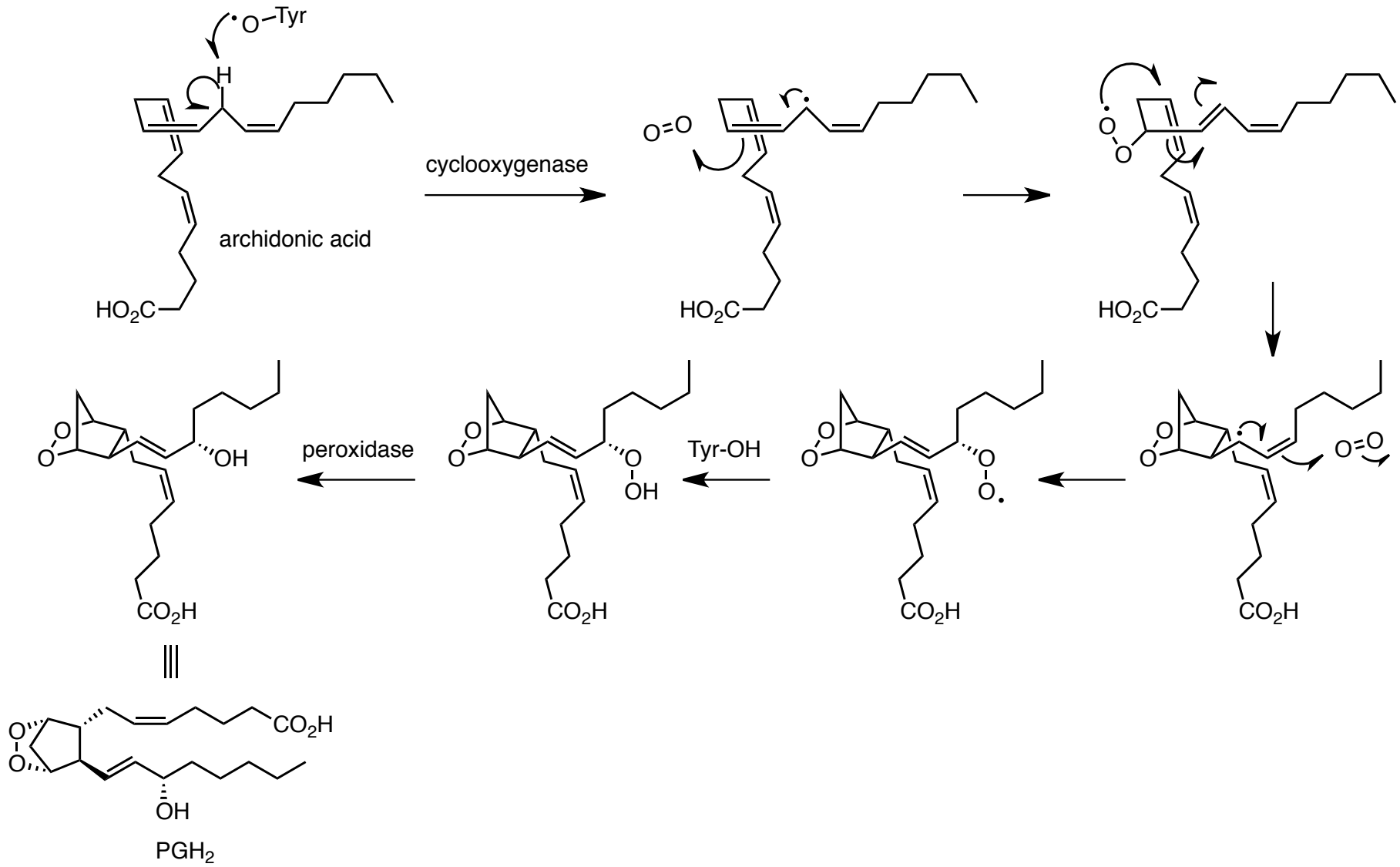


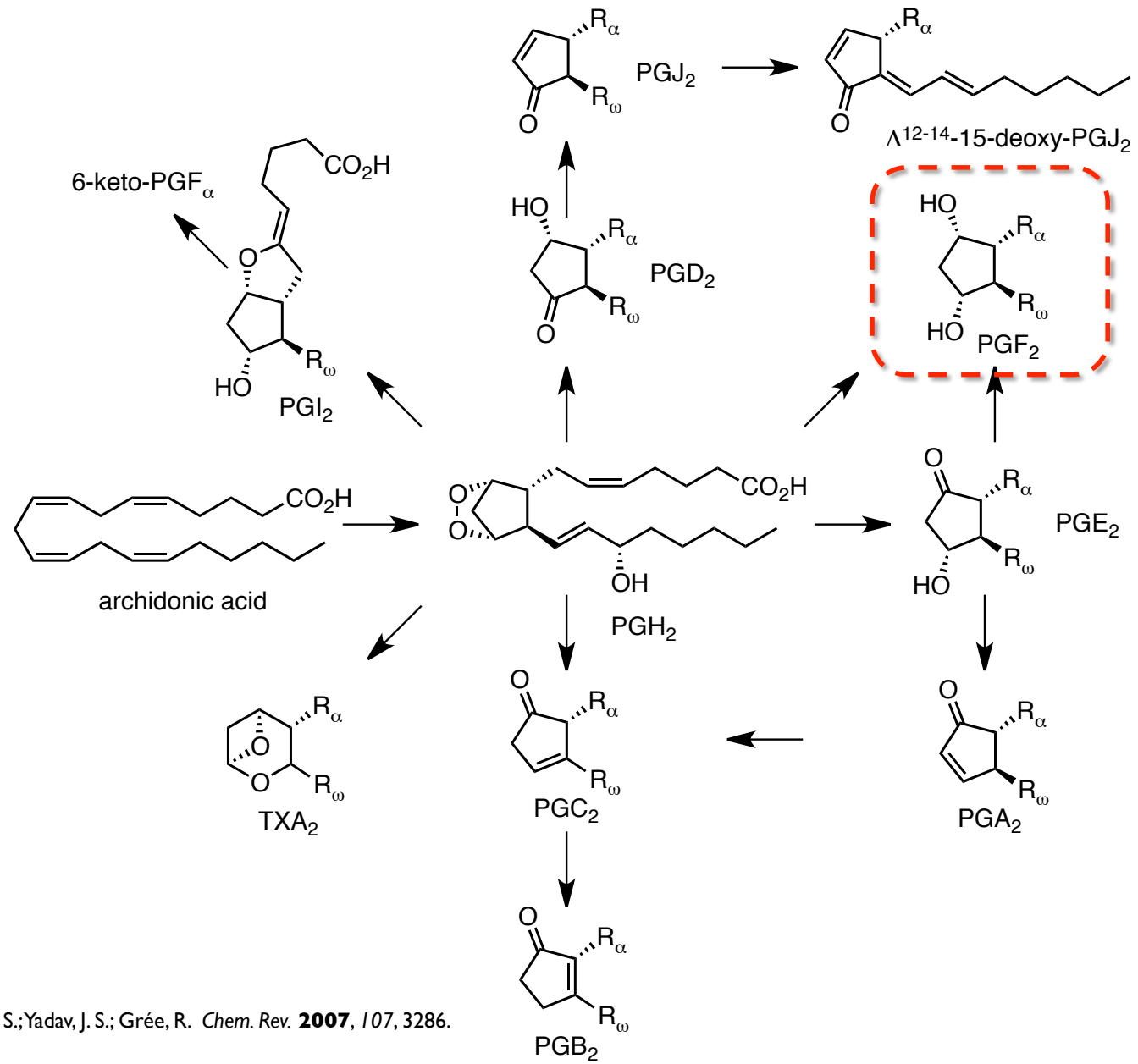
Christopher Rosenker
Wipf Group - Current Literature
August 25, 2012

Biosynthetic Pathway to Prostaglandins



Rouzer, C.A.; Marnet, L. J. *Chem. Rev.* **2003**, *103*, 2239.

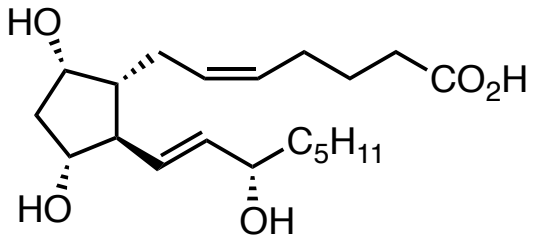
Biosynthetic Pathway to Prostaglandins



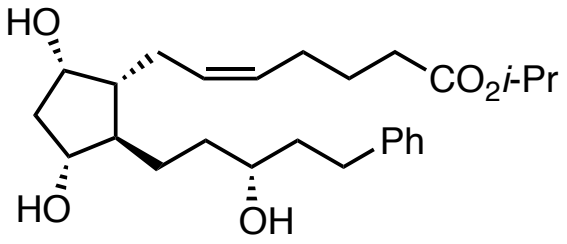
Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Rev.* **2007**, *107*, 3286.

Biological Properties of Prostaglandins

- Implicated in a variety of biological processes:
  - Sleep, pain, fever, inflammation, menstruation, birth, blood vessel constriction, and blood clotting
- Synthesized immediately in response to stimuli
- Lantanoprost is used for treatment of glaucoma
  - $1.75 billion sales in 2010
  - 20 step synthesis based on Corey's original synthetic strategy



$PGF_{2\alpha}$



Lantanoprost

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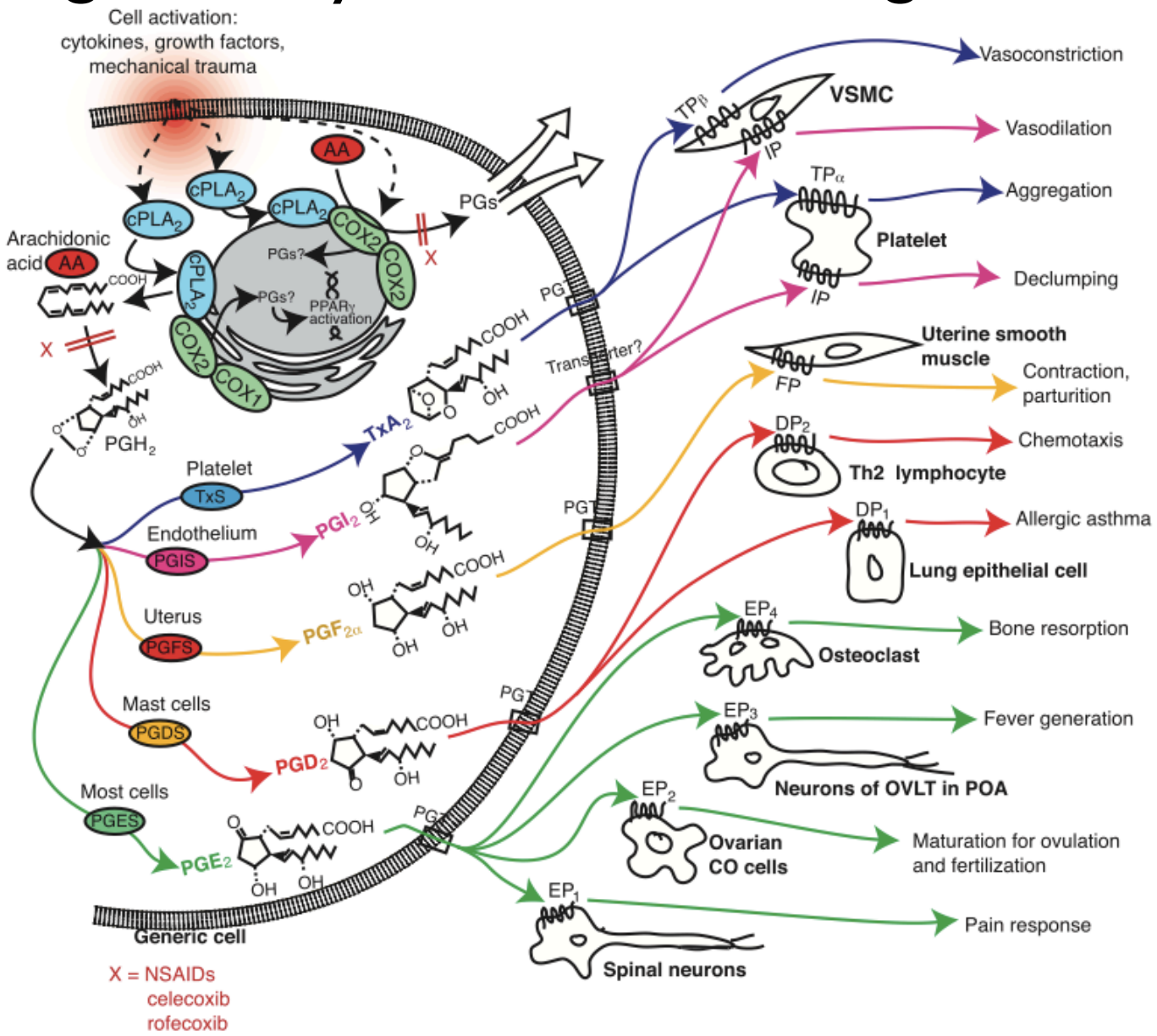
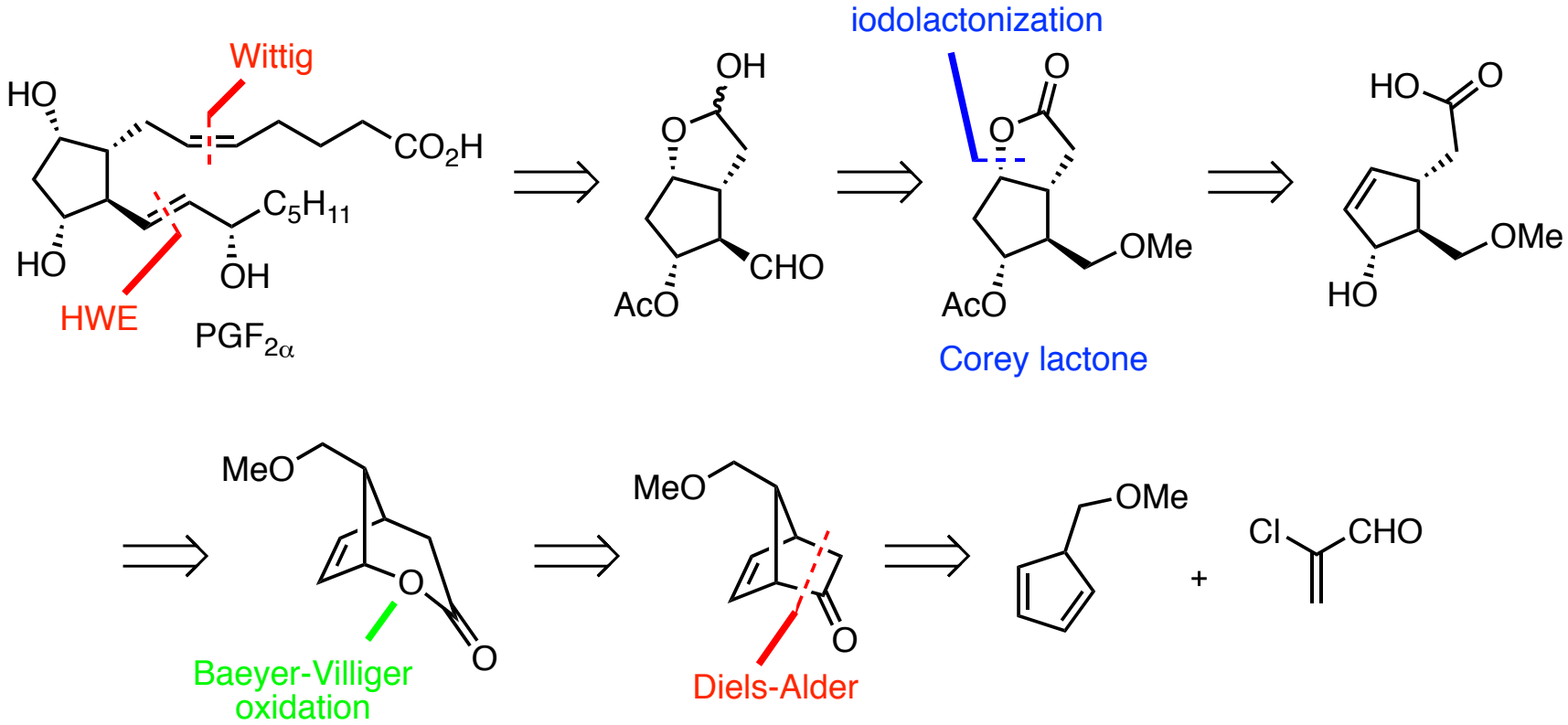
Prostoglandin Synthesis and Biological Actions



Funk, C. D.; *Science* **2001**, *294*, 1871.

Previous Prostaglandin Syntheses

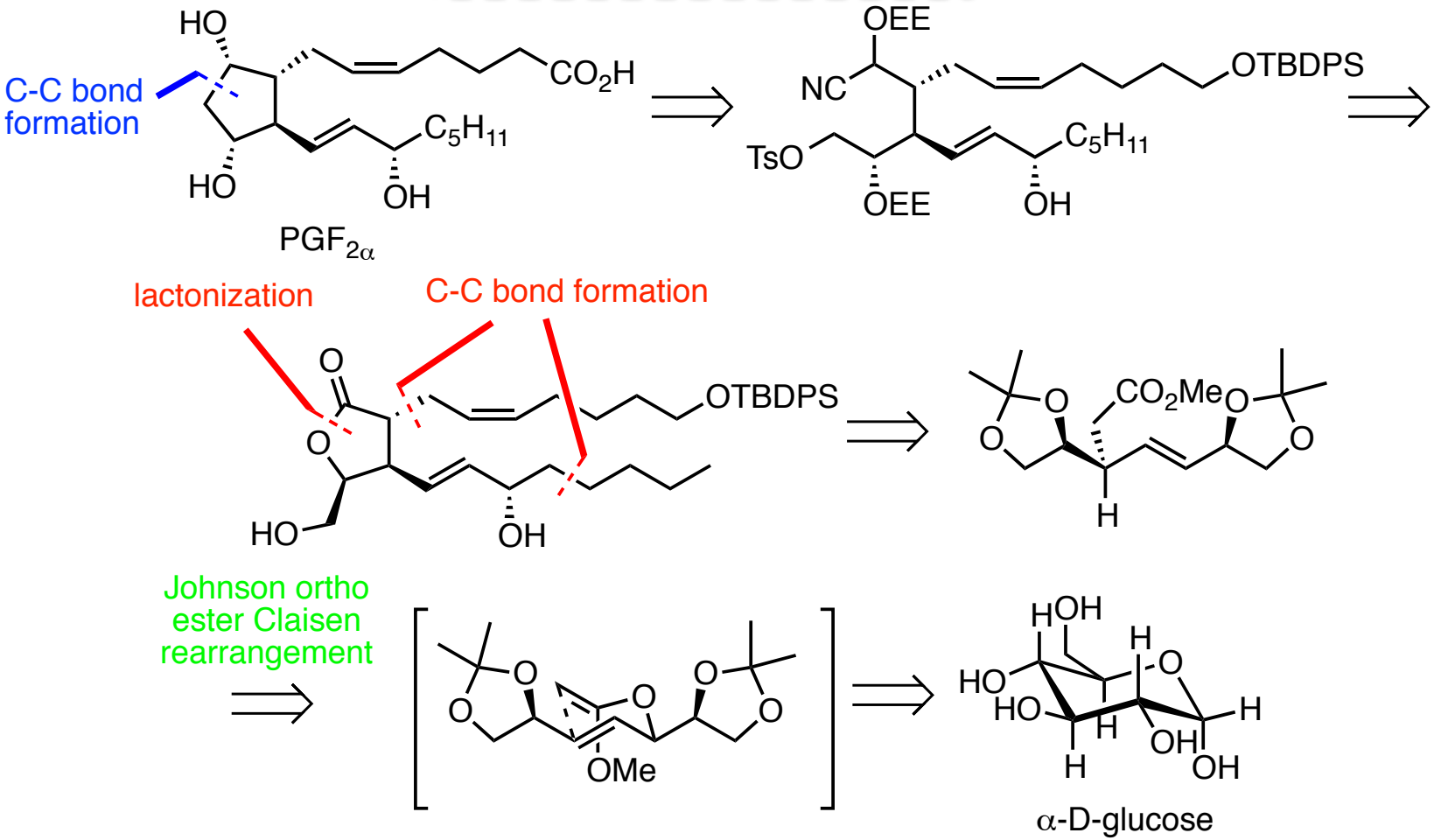


Corey: 17 steps; ~24% yield; >90% per step

Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.
Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996, p 65-81.

Previous Prostaglandin Syntheses

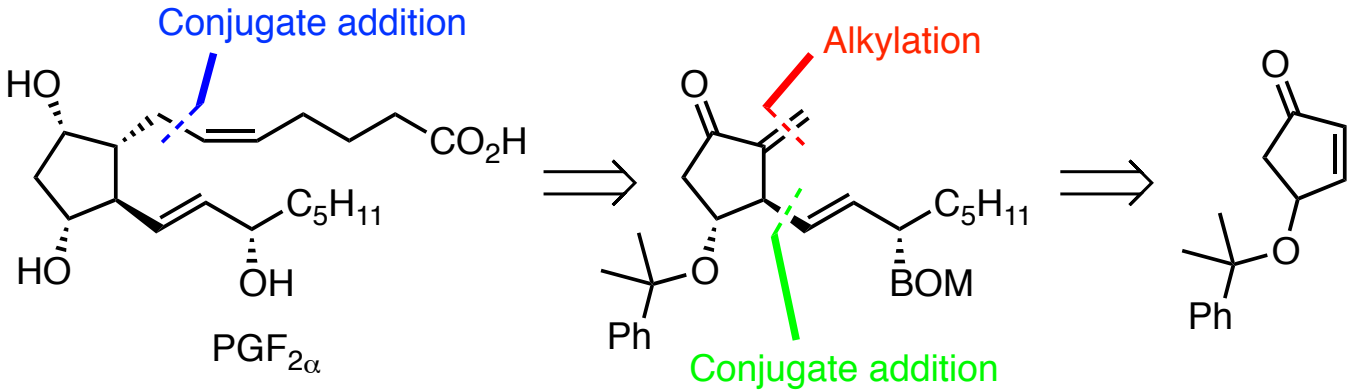
Stork: 30 steps; 0.002% yield



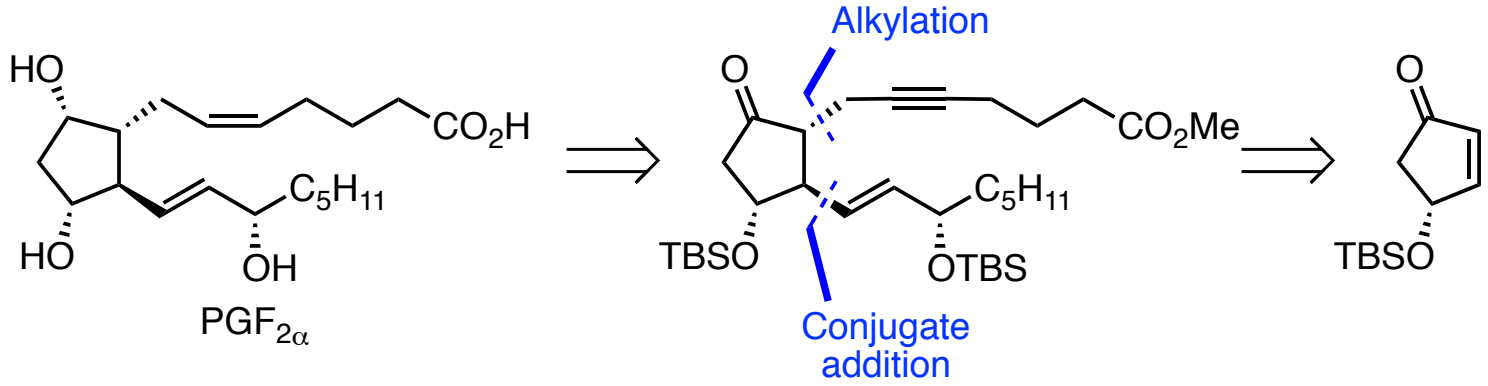
Stork, G.; Takahashi, T.; Kawamoto, I.; Suzuki, T. *J. Am. Chem. Soc.* **1978**, *100*, 8272.
Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996, p 137-151.

Previous Prostaglandin Syntheses

Stork: 11 steps; 15% yield; 84% per step



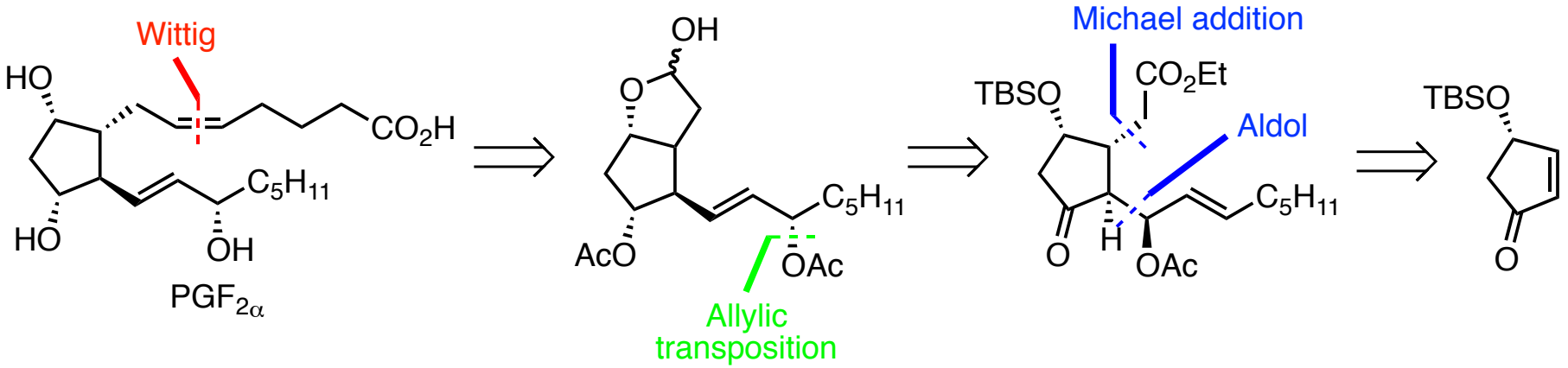
Noyori: 8 steps



Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745.
Stork G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.
Suzuiki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718.

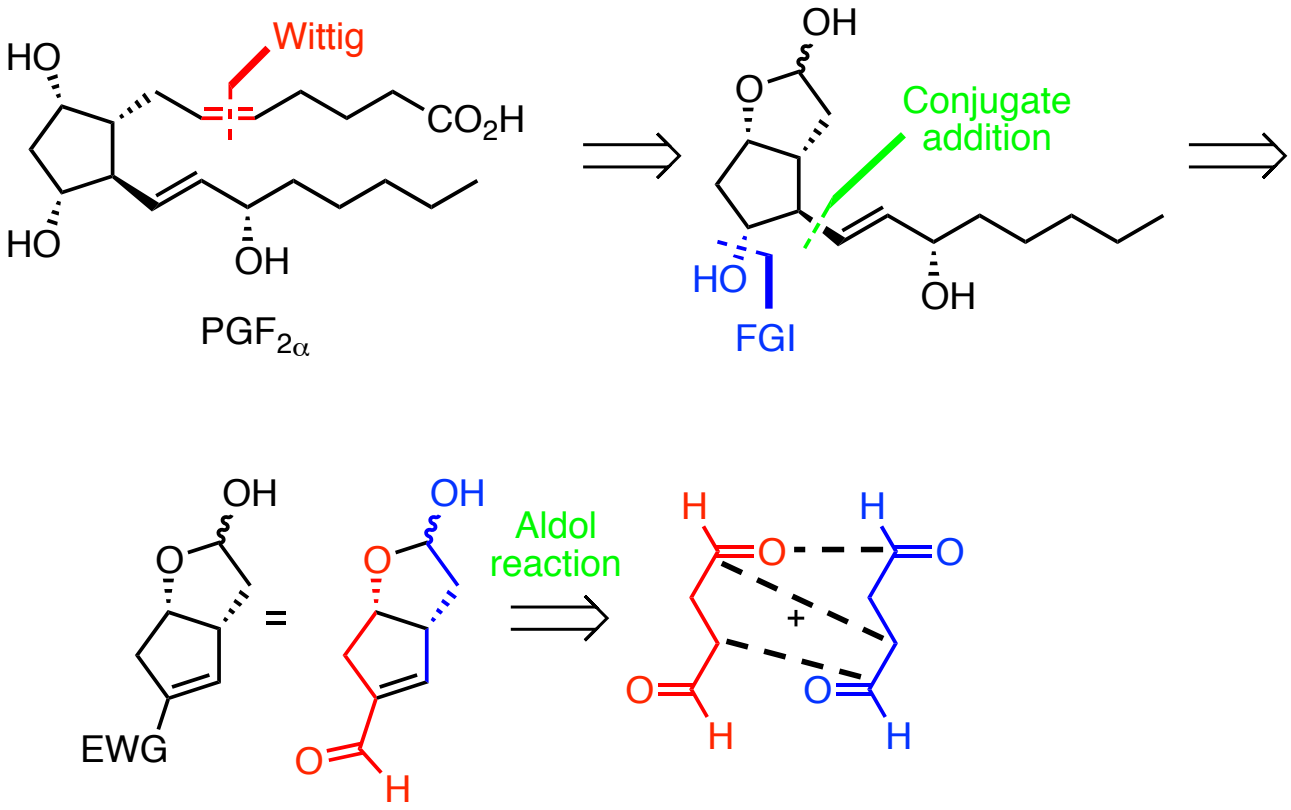
Previous Prostaglandin Syntheses

Danishefsky: 8 steps



Danishefsky, S. J.; Cabal, M. P.; Chow, K. *J. Am. Chem. Soc.* **1989**, *111*, 3456.

Retrosynthesis of $PGF_{2\alpha}$



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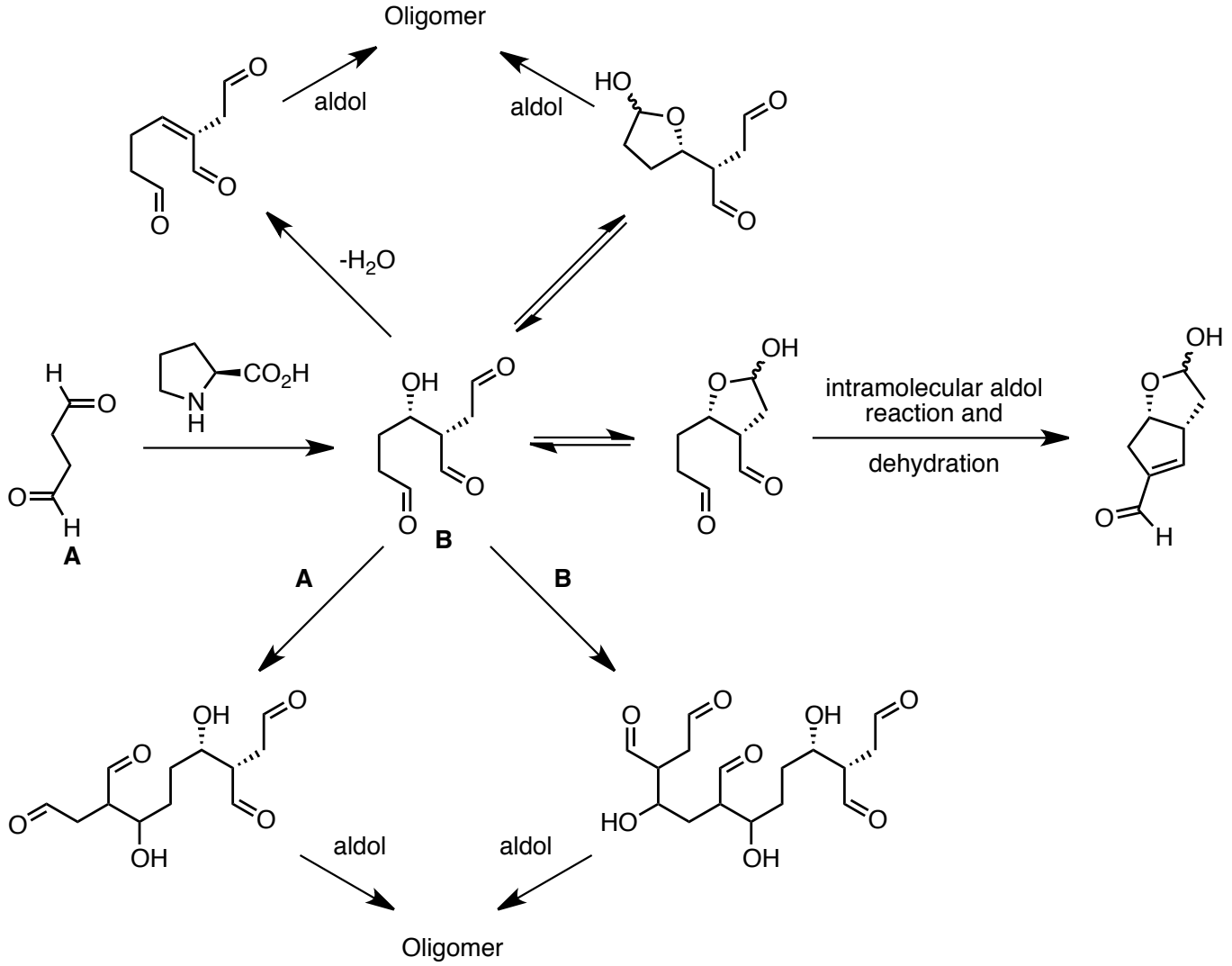
Proline Catalyzed Aldol Dimerization



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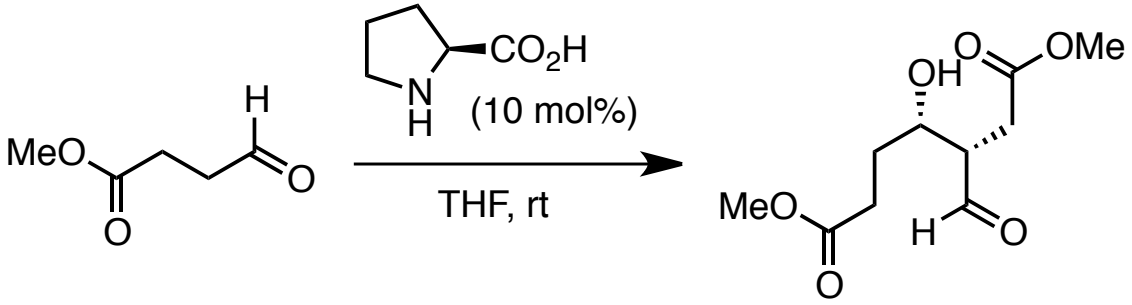
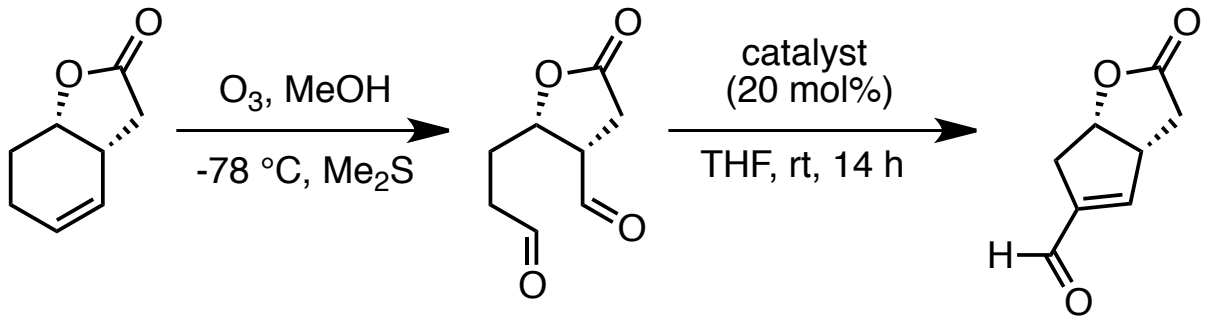
Test Reactions for Aldol Reaction



61%, 3.6:1 *dr*



Catalyst A: (*S*)-Proline - 5%
Catalyst B: $[Bn_2NH_2][CO_2CF_3]$ - 51%

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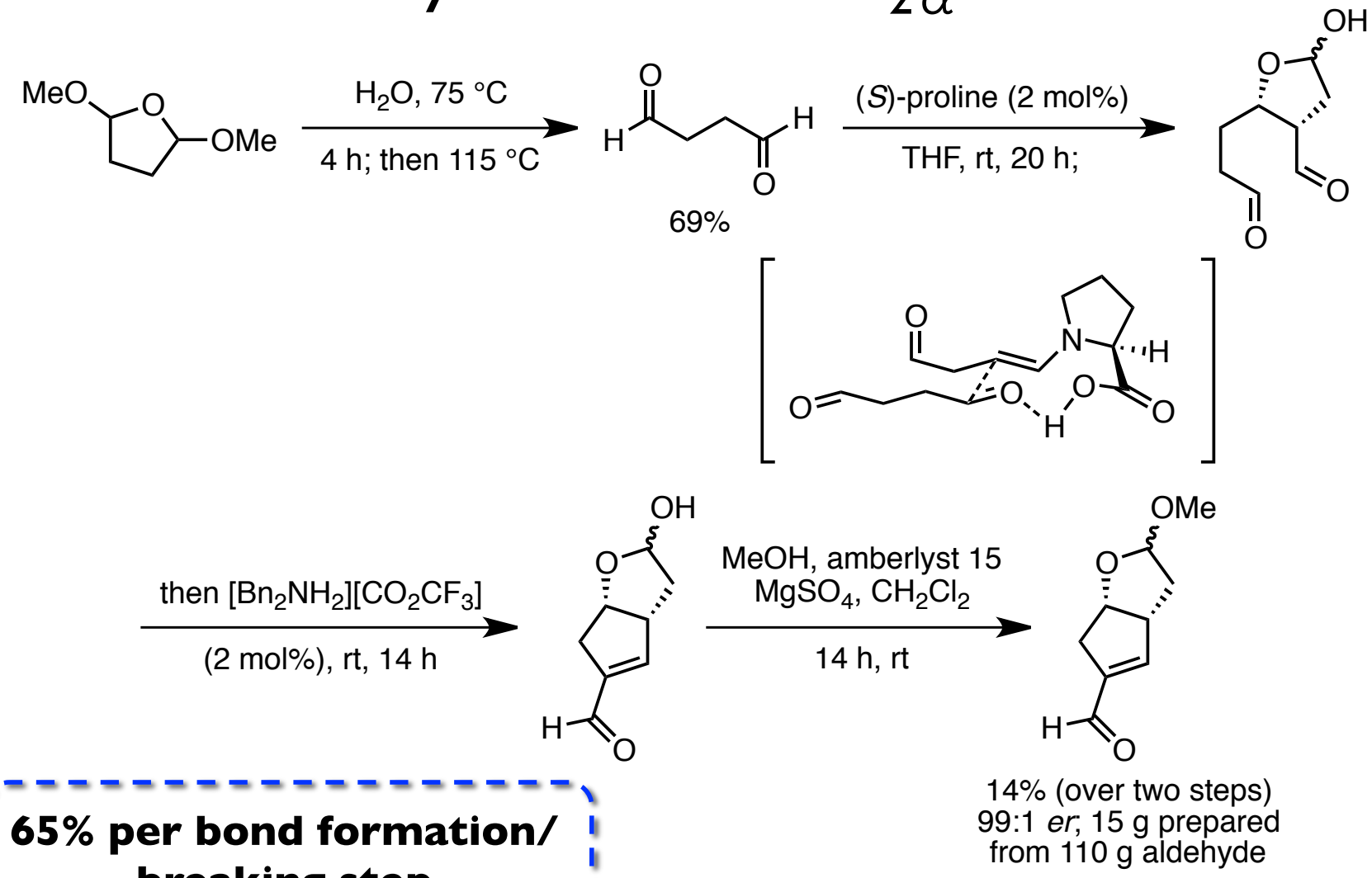
Synthesis of $PGF_{2\alpha}$



65% per bond formation/ breaking step

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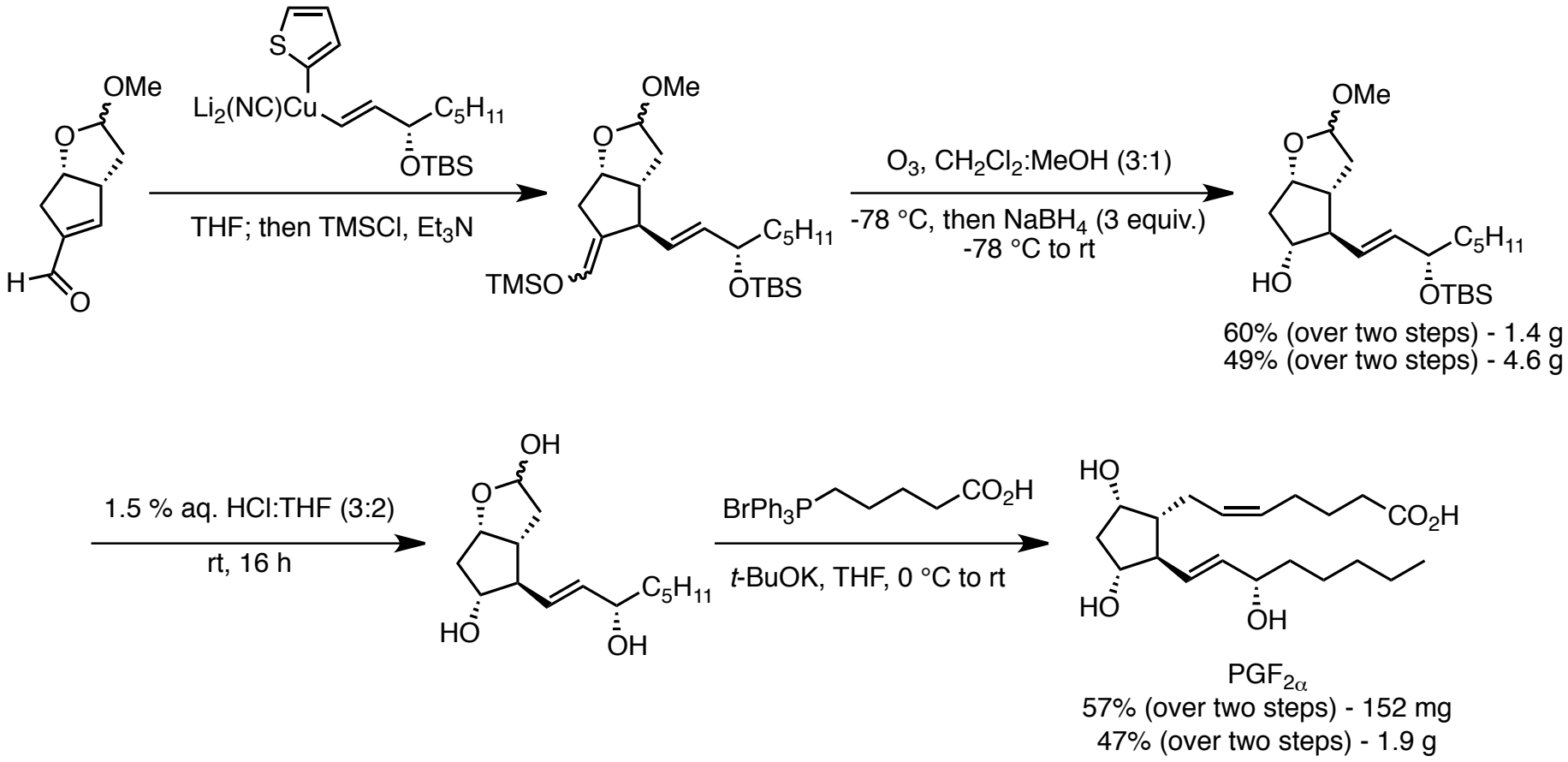
Synthesis of $PGF_{2\alpha}$



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Conclusion

- Seven step synthesis of prostaglandin $PGF_{2\alpha}$ from 2,5-dimethoxytetraydrofuran
  - Total yield 2.2-3.3% (58-61% per step)
  - Synthesis is shorter than the state of the art.
- Key organocatalytic aldol dimerization reaction in high enantiomeric purity (99:1 *er*)
  - 4 bond forming/breaking reactions during process (~65% per rxn)
  - Can be performed on +100 g scale
- Bicyclic enal is a useful intermediate for exploring prostaglandin derivatives.