Michael N. Paddon-Row, Michael S. Sherburn et. al.

Nature Chemistry **2015**, *7*, 82—86

Pseudopterosin Synthesis

From a cross-conjugated hydrocarbon and through a series of cycloadditions

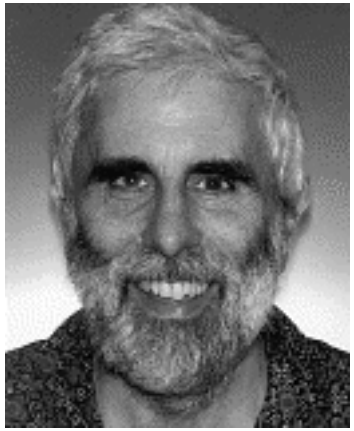
5th March 2015, Renaud Group meeting/ journal club, Nick Tappin

Who

Mick Sherburn

ANU in Canberra, Australia

- 91, PhD from Nottingham under supervision of John Murphy
- 94-97, Lecturer Massey University, NZ
- 97-02, Lecturer University of Sydney
- 02--, Research School of Chemistry (ANU in Canberra)
- AB of Synthesis, Synlett, Nat Prod Rep, Chem: Asia; EB of Asian JOC and Nat Sci Rep
- "Next Generation Chem Syn", hydrocarbons, Drug Delivery



Michael Paddon-Row

Emeritus Professor University of New South Wales, Australia

- 67, PhD from ANU
- 67-68, RA Princeton
- Many positions held around world including EAB of Journal of Structural Chemistry

- Phys Org Chem, Comp Chem, Syn of theoretically curious molecules

Outline

- Premise
  - isolation, activity, biosynthesis
  - structure
  - other syntheses, starting points
- Retrosynthesis
  - method justification
  - comparison to others' work
- Forward synthesis

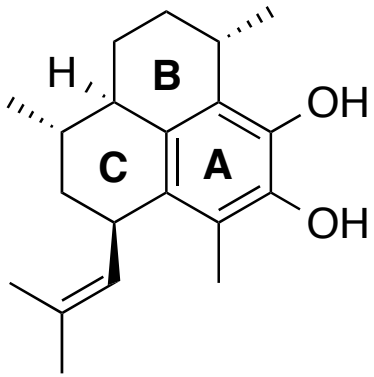
Isolation

- Purple sea whip
- pseudopterogorgia elisabethae
- Carribean, Bahamas

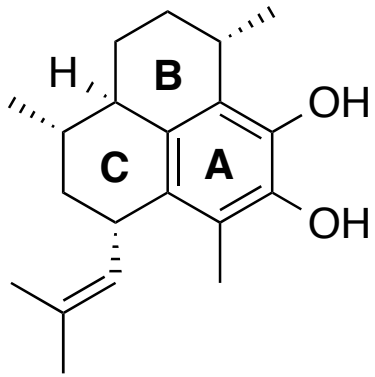
Activity

- Commercially interesting for skin care treatments
- More potent anti-inflammatory than clinically used drug indomethacin
- Low acute toxicity to mice
- Passed Phase I and II clinical trials
- Stunted development due to supply issues
- Total synthesis has important role

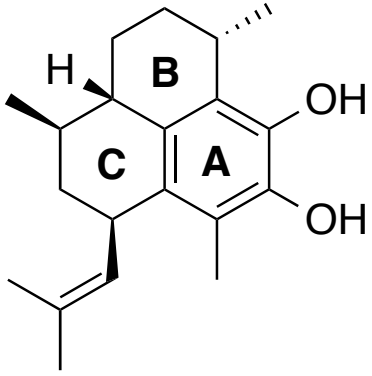
Structure: pseudoptersins



A--F



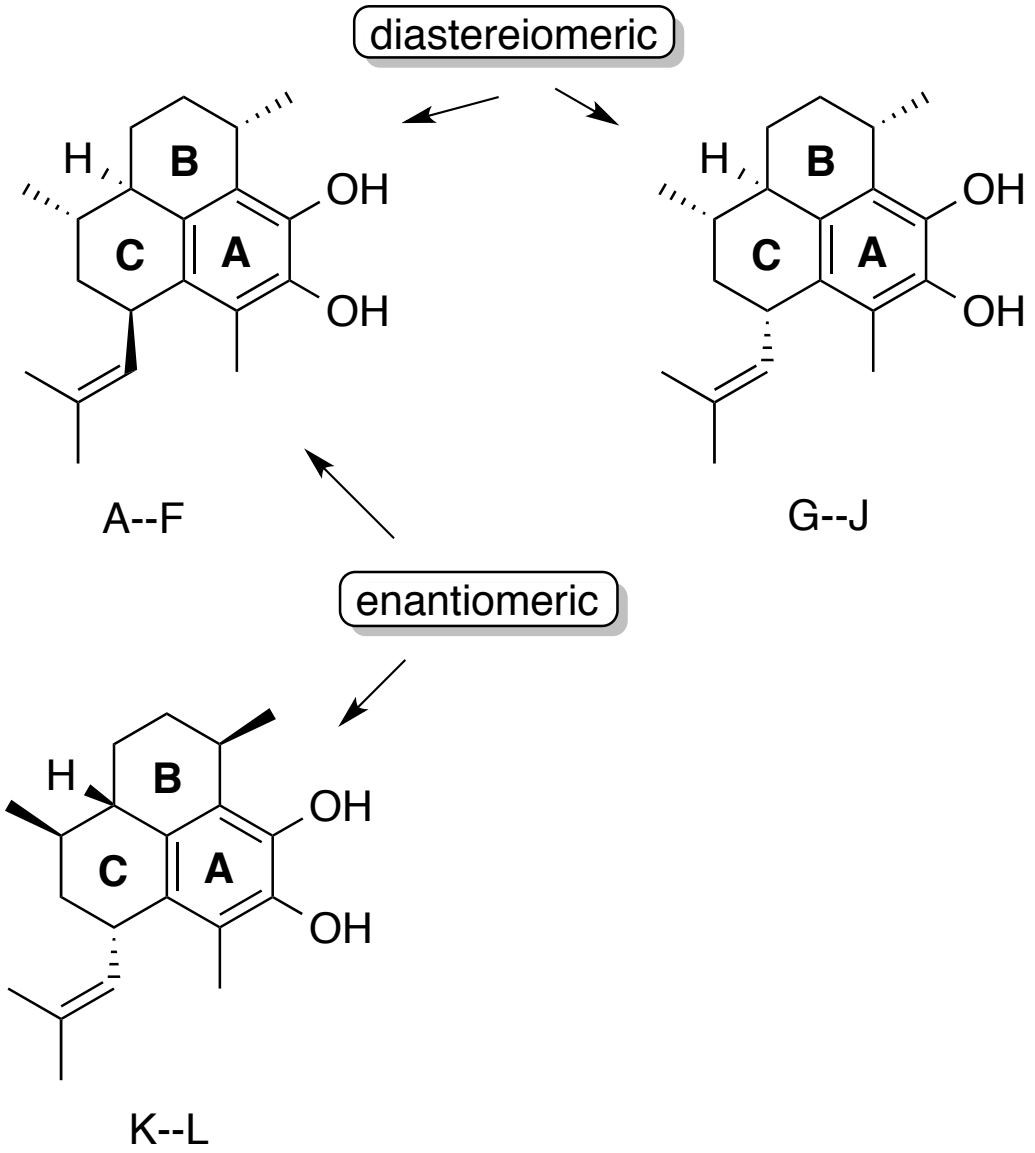
G--J



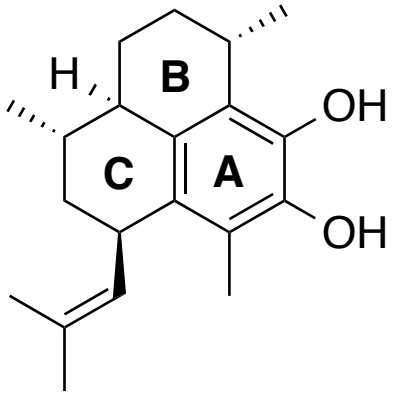
K--L

- largest family of amphilectane diterpenes
- 31 memebers, varity comes from nature of sugar:
  - site of glycosylation
  - extent of acetylation
- 3 stereoisomeric aglycones

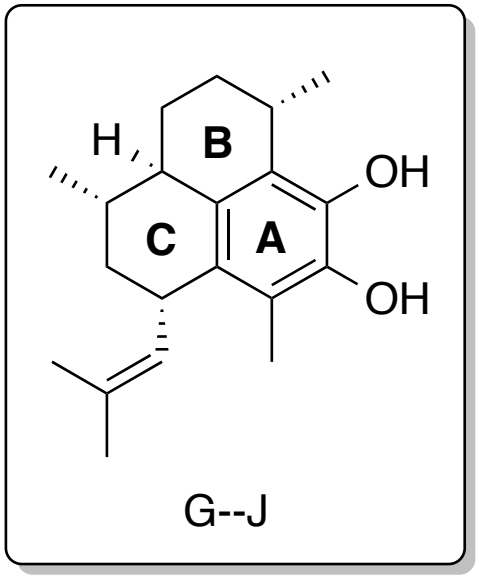
Structure: pseudoptersins



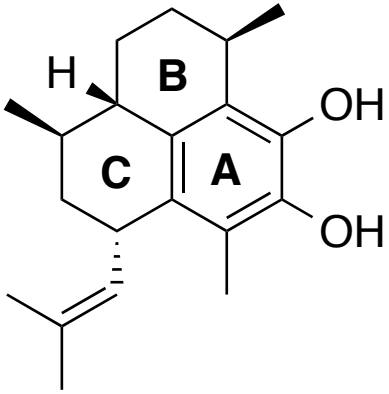
Structure: pseudoptersins



A--F



G--J

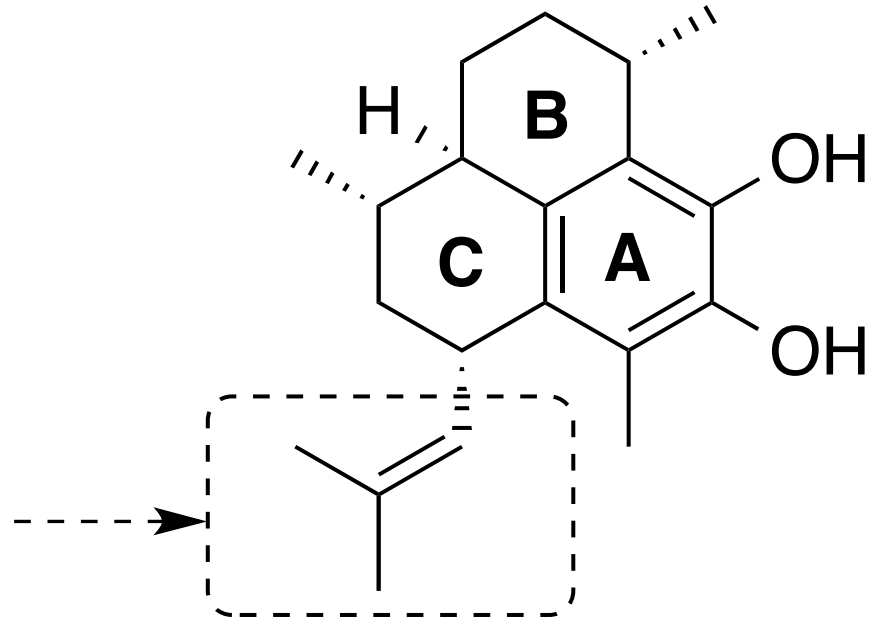


K--L

Pertinent Structural Features

- Fully substituted benzene ring
- Fully fused 6,6,6-tricycle (A, B, and C share a common C-atom)
- Fatty, i.e., no easy FG handle

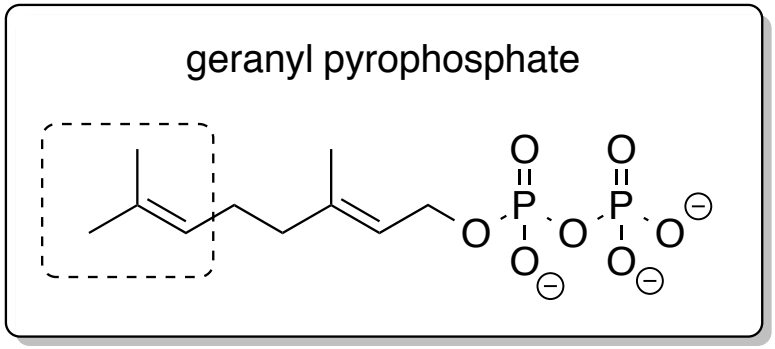
Quick question

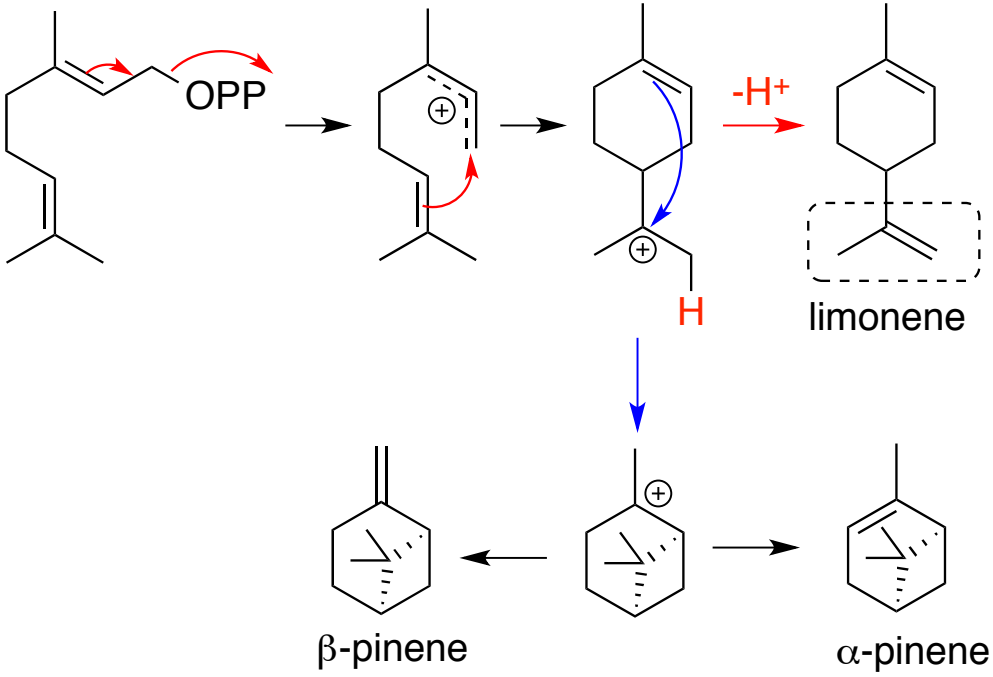


What does this tell us about the molecule? What other common compounds have structures related to this?

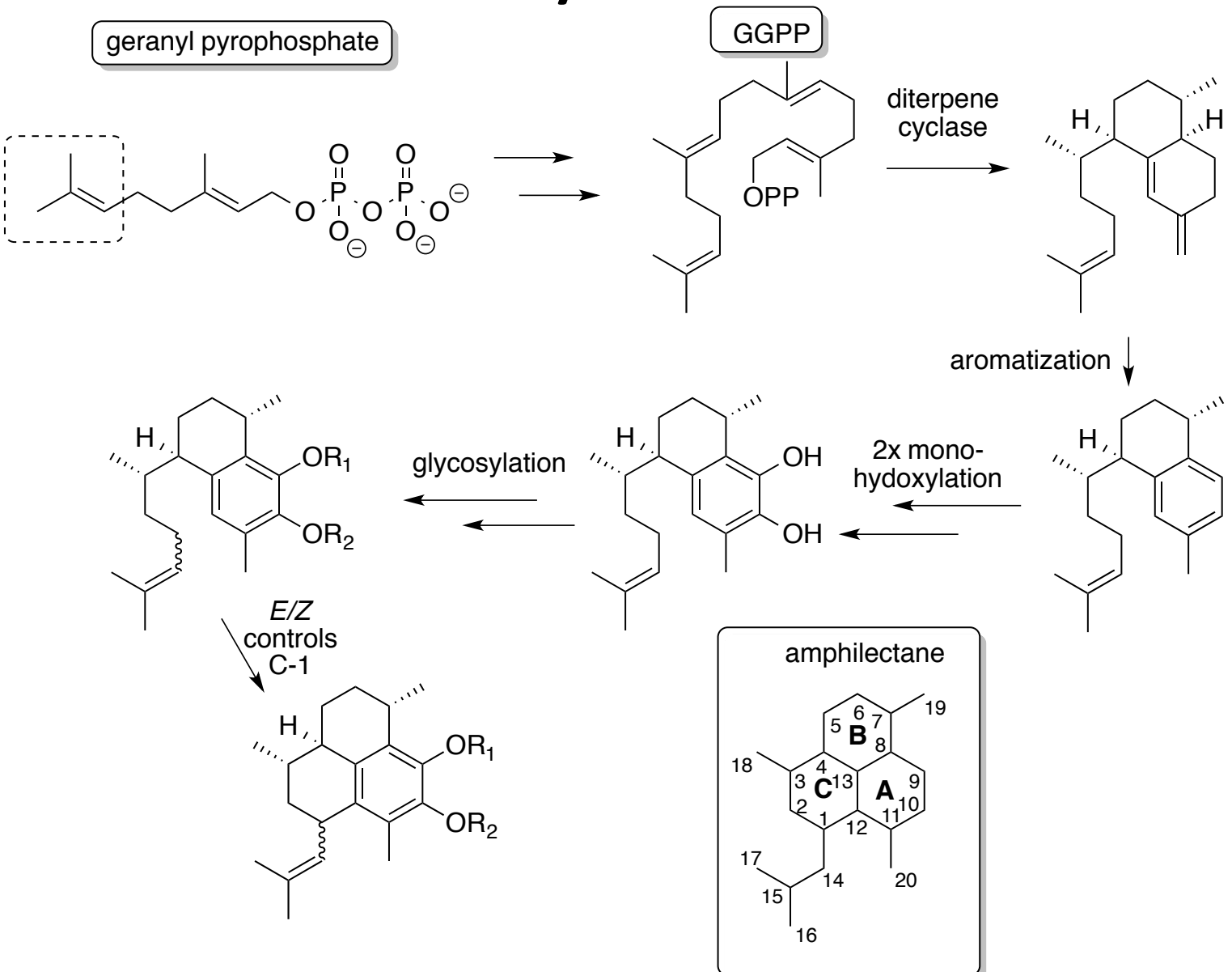
Answer

$C_{10}H_{16}$ a monoterpene, i.e., 2x isoprene (C5-rule)



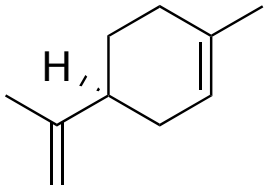


Biosynthesis

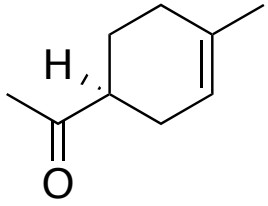


Other syntheses: ‘mapable’

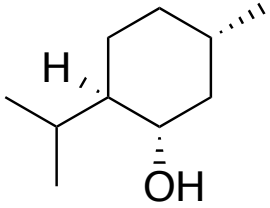
Terpene precursors



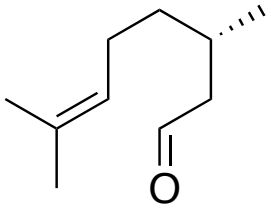
Broka, '88
Corey, '98



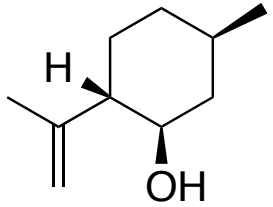
Corey, '00



Corey, '89

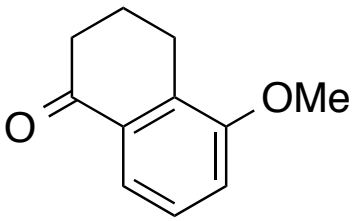


Corey, '90
Kocienski, '01

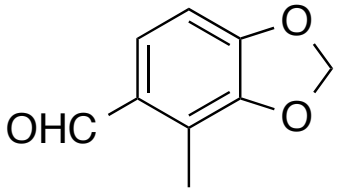


Kocienski, '01

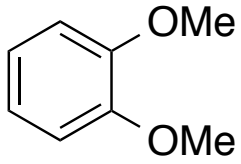
Aromatic precursors



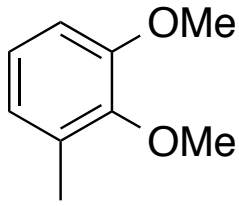
McCombie '90--91



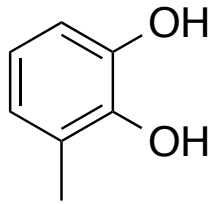
Buzek '95



Schmalz '97

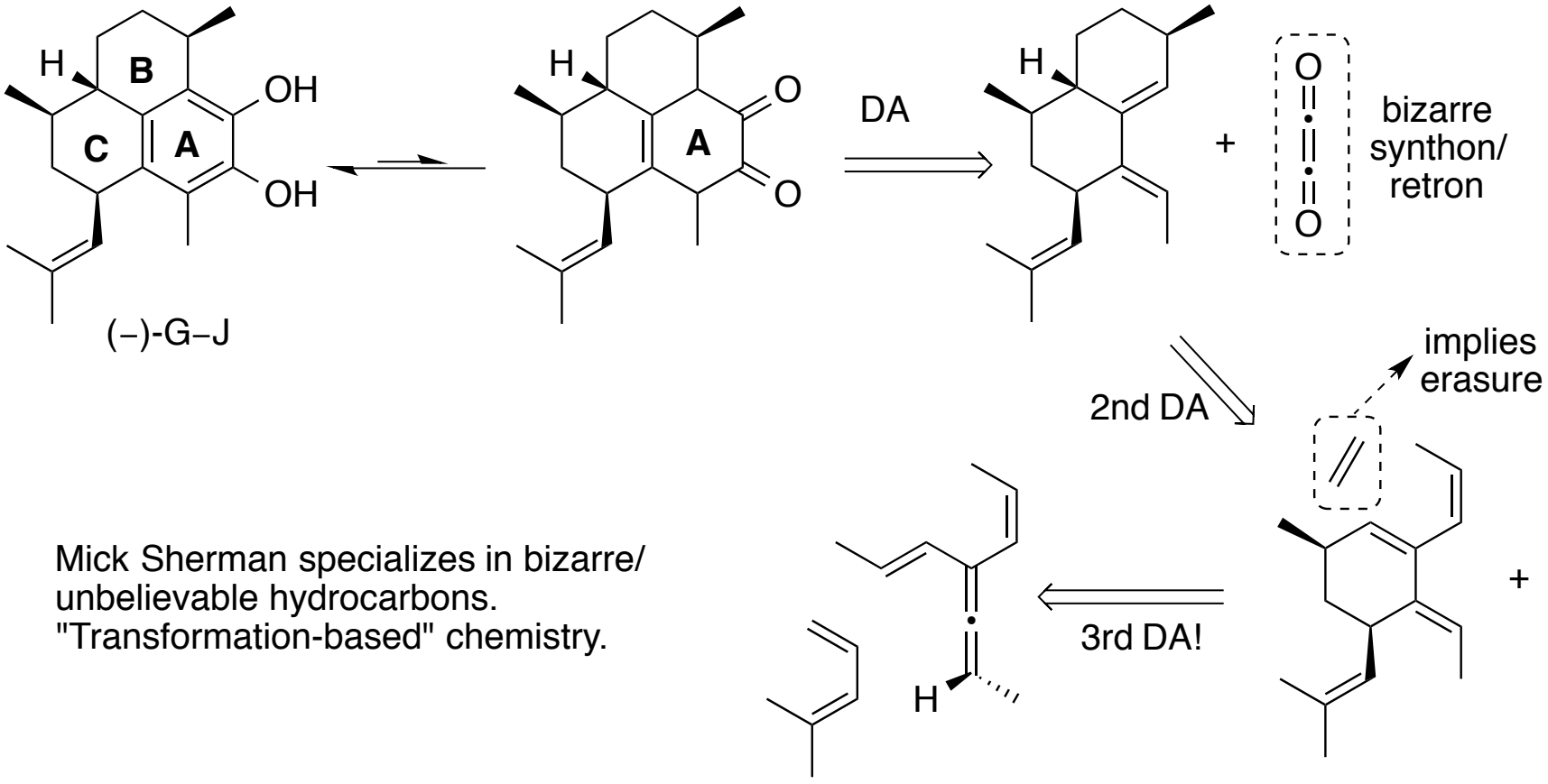


RajanBabu '11



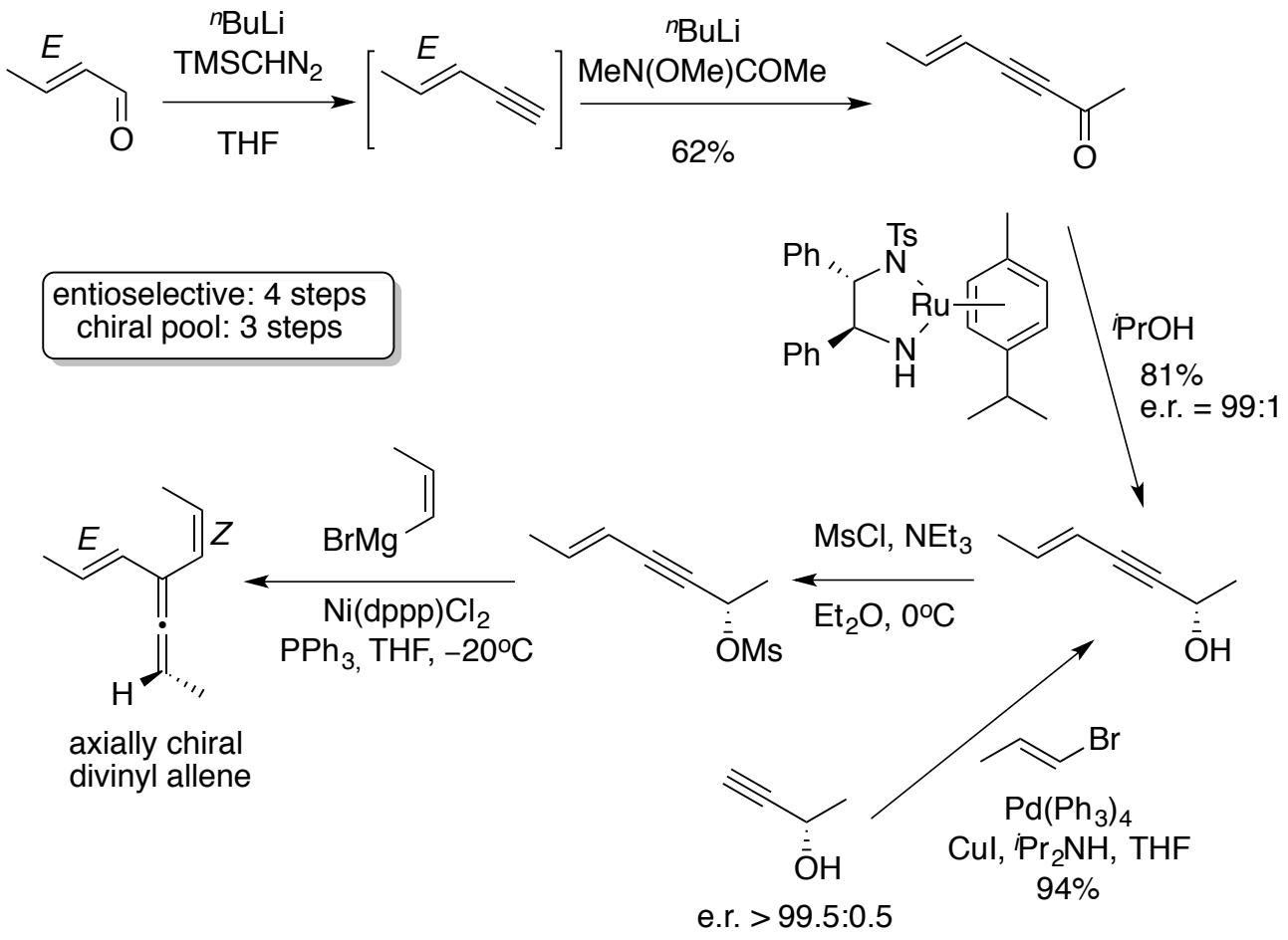
Harrowven '04
Cooksey and
Kocienski '12

Retrosynthesis

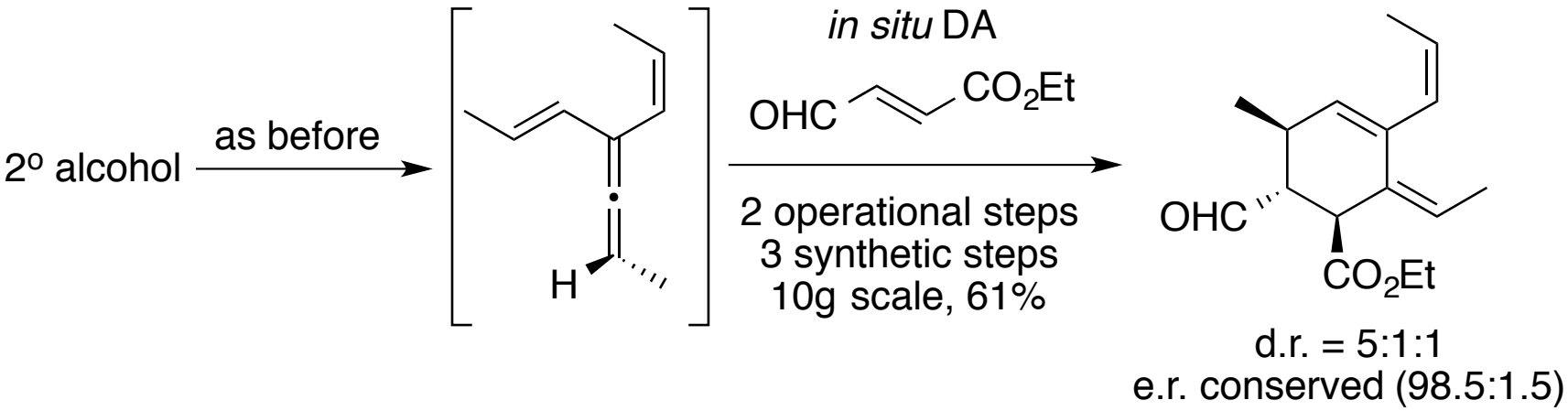


Mick Sherman specializes in bizarre/ unbelievable hydrocarbons.
"Transformation-based" chemistry.

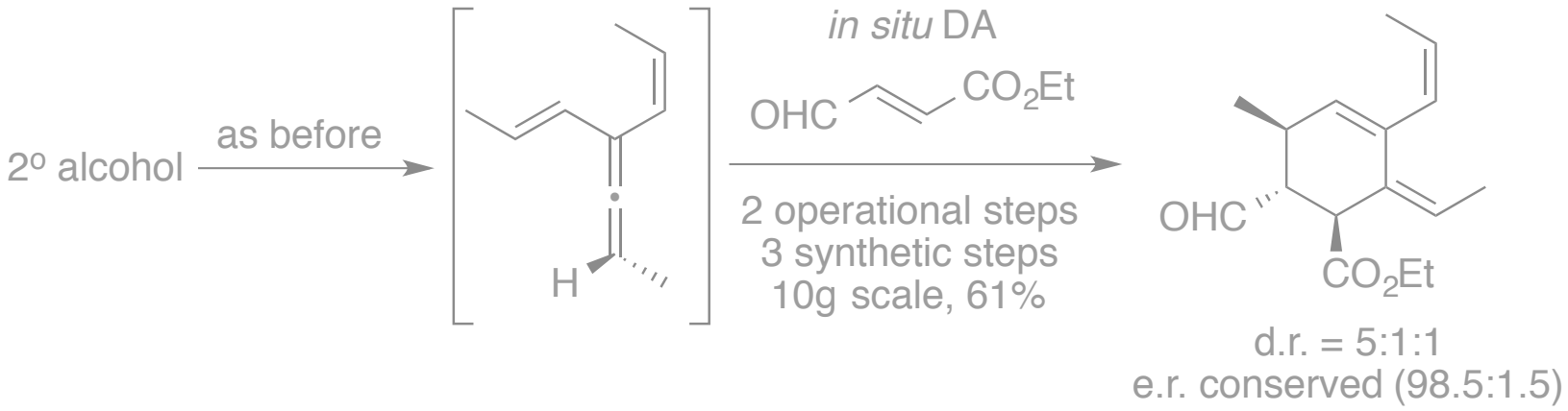
Forward Synthesis

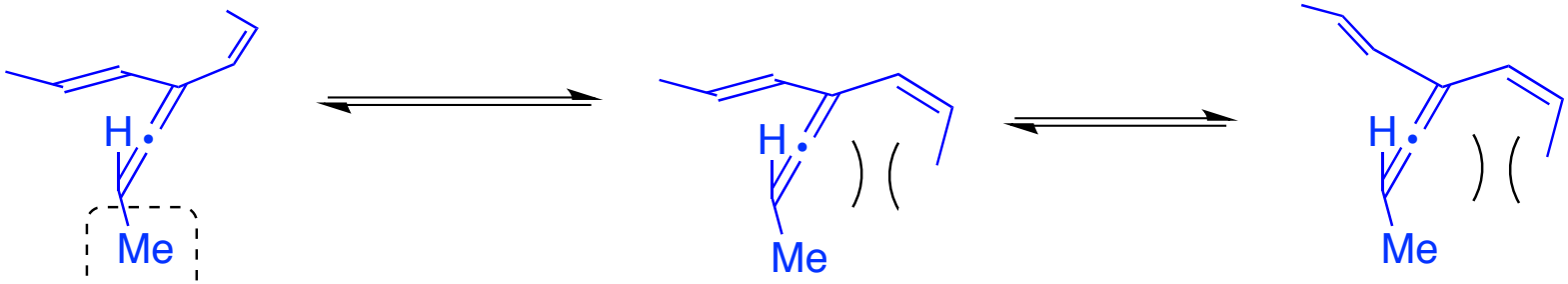


Forward Synthesis: remarkable DA(s)



Forward Synthesis: remarkable DA(s)

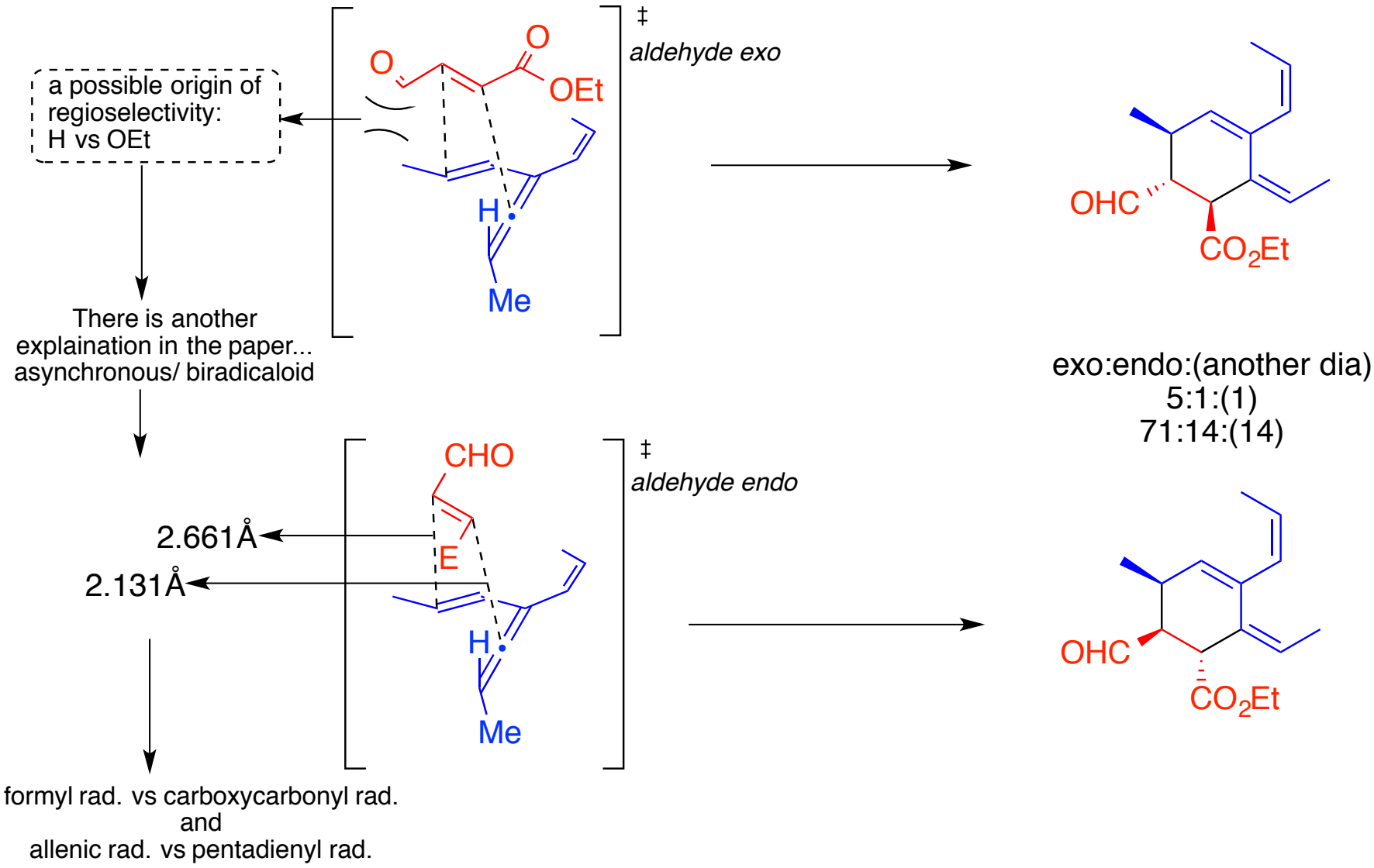




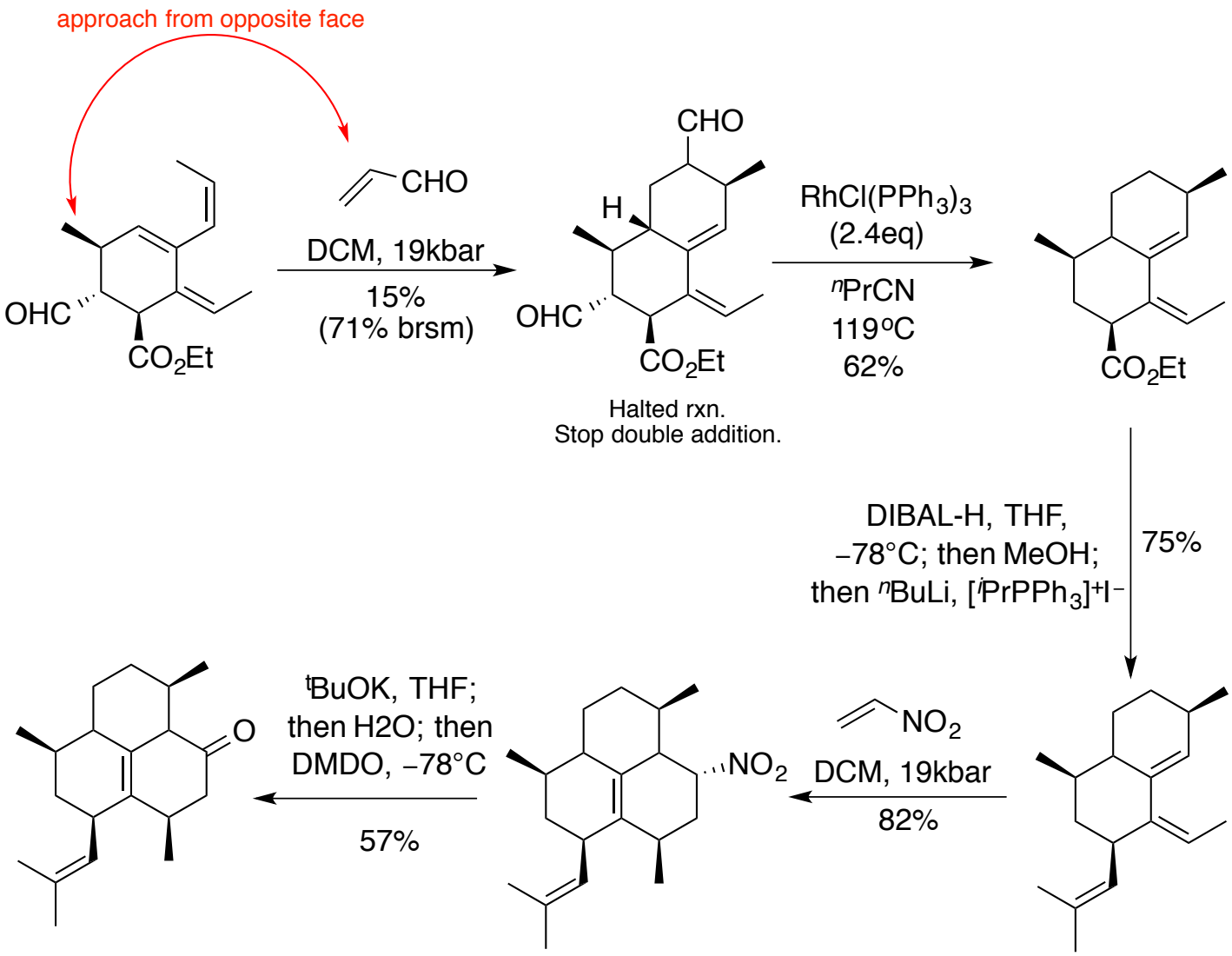
blocks face below
(axial to point chirality transfer, thus entioselective)

presumably disfavoured *s-cis* conformation, thereby no free rotation around σ-bond

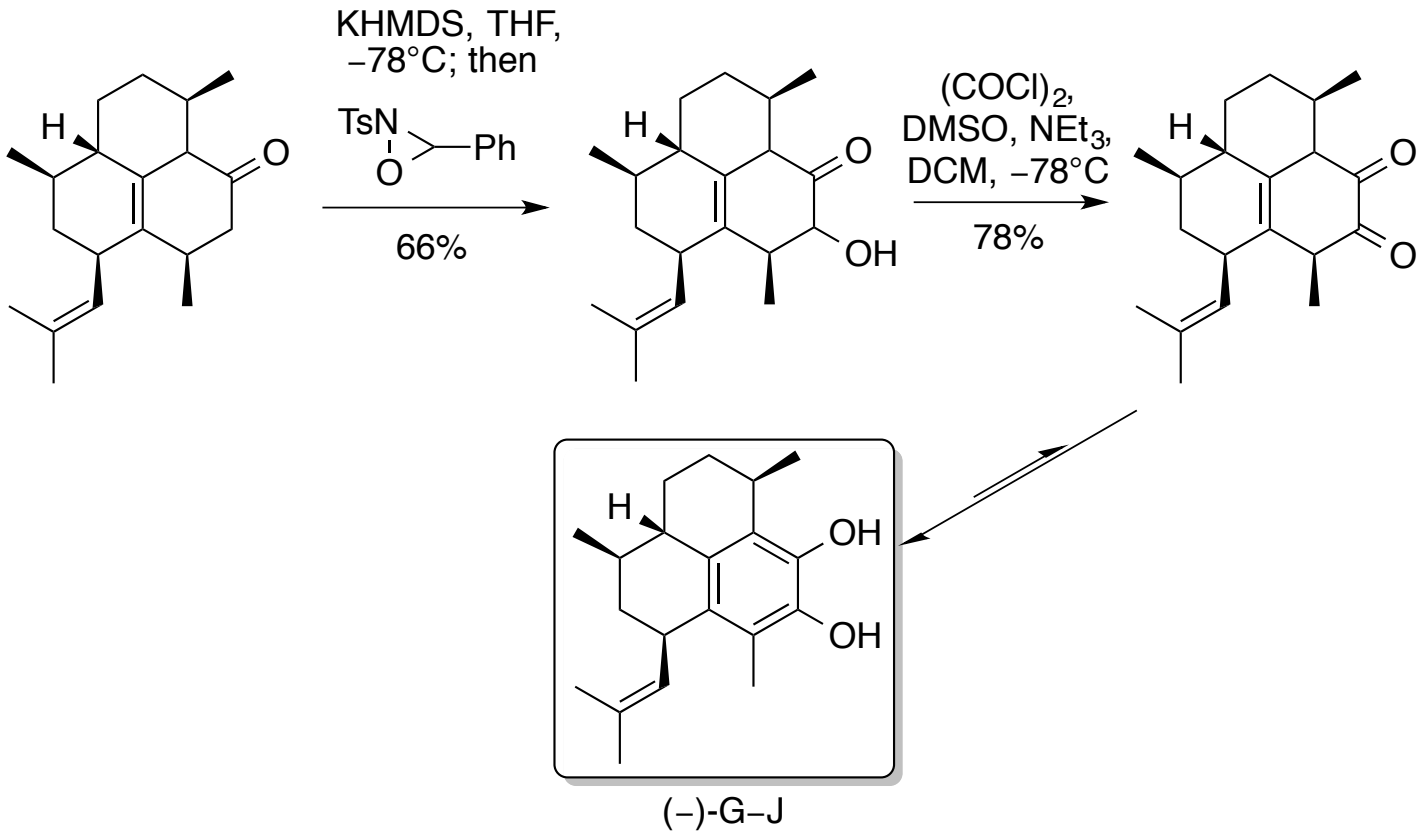
Forward synthesis: remarkable DA(s)



Forward synthesis: Middle game



Forward synthesis: Endgame



Conclusion

- Demonstrated 3 powerful and sequential DAs
- Retrosynthesis is more ‘intellectual/ conceptual’ than previous syntheses beginning with skeletally superposable SMs
- Allene in DA
- Unique hydrocarbon ‘units’ for
- ‘Transformation based’ disconnections