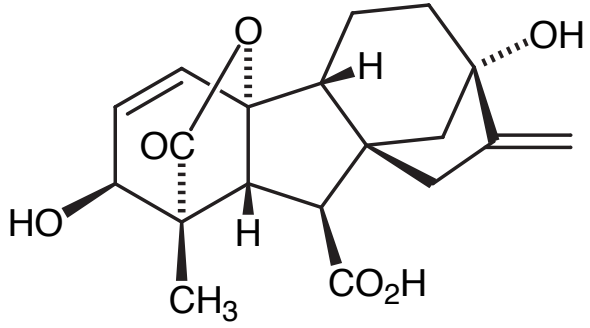
Highlights from the Synthesis of Gibberellins:

a 30 Year Odyssey

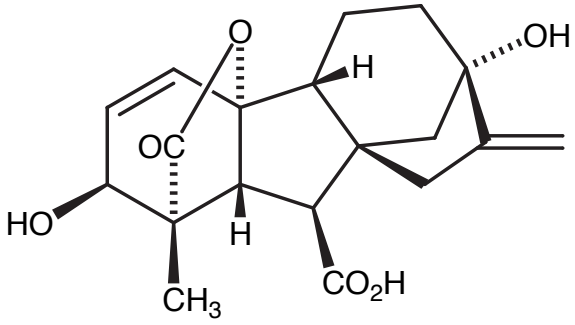


A Friday Afternoon Seminar

6 February 2004

Jonathan R. Scheerer

Highlights from the Synthesis of Gibberellins:



Outline of Presentation:

I. Introduction to Gibberellins: History, Ubiquity, and Biology

II. Biosynthesis

III. Gibberellic Acid: Structure and Reactivity

IV. Conversion of Gibberellic Acid into other Gibberellins

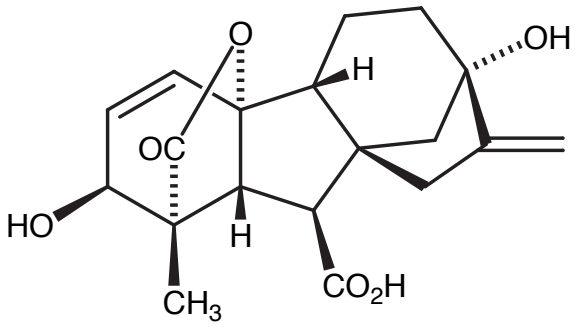
V. Total Synthesis

VI. Partial Synthesis / Stragedy

Relvant Reviews:

Mander, *Chem. Rev.* **1992**, 573-612.
Mander, *Nat. Prod. Rep.* **2003**, 49-69.
MacMillan, *Nat. Prod. Rep.* **1996**, 229.
Crozier, A. Ed. *The Biochemistry and Physiology of Gibberellins.* Praeger: New York, 1983. (vol 1 and 2)

A Brief History of Gibberellin Research:



1828 - first reports of "bakanae" disease in rice plants (foolish seedling; stupid rice crop)

1898 - first research paper, links disease to fungal infection

1912 - Kurosawa found that filtrates from infected dried rice seedlings also causes disease
Concludes that bakanae is caused by discrete chemical

1935 - First use of term "gibberellin" in scientific literature

1938 - Crystalline compound (mix of three gibberellins) isolated from fungal filtrate

1945 - Research expands to U.S. and U.K.

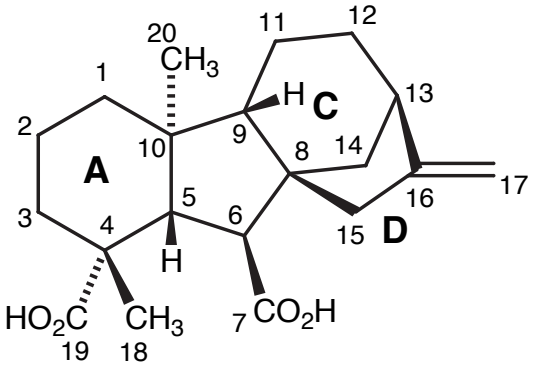
1955 - compound isolated. termed "gibberellic acid"

1958 - correct structure proposed (stereochemical ambiguities remain)

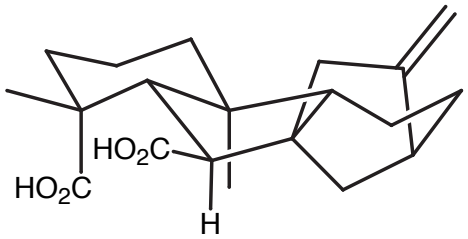
1961 - structure verified by X-ray

1978 - First total synthesis (Corey)

C_{20} and C_{19} Gibberellins: Structure and Nomenclature

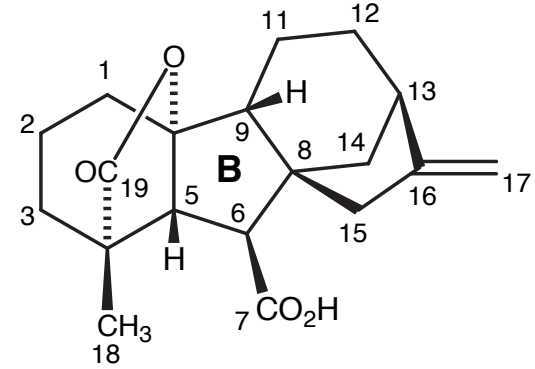


C_{20}-Gibberellin Skeleton

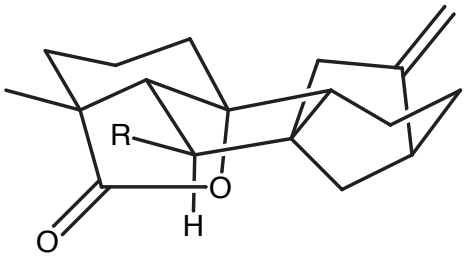


GA_{12}

ent-gibberell-16-ene-7,19-dioic acid



C_{19}-Gibberellin Skeleton

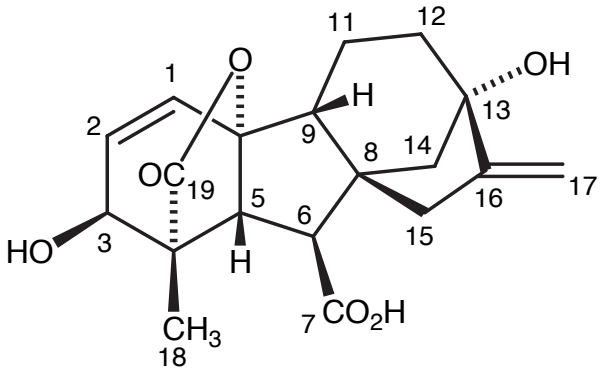


R = CO_2H

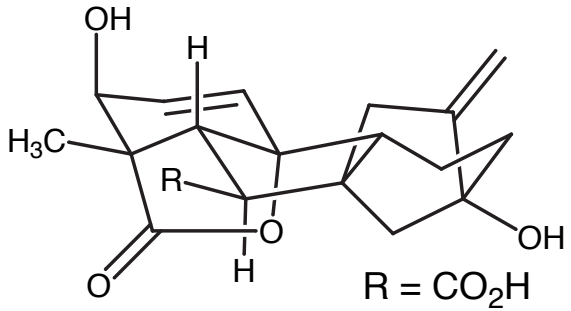
GA_9

ent-norgibberell-16-ene-7,19-dioic acid 19,10-lactone

Gibberellic Acid (GA_3)



GA_3



Fermented from *Gibberellia fujikuroi* (a fungus) on ton scale

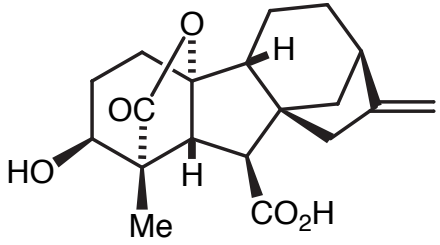
Bioactive at low concentrations ((sub-nanomolar common for applications)

Widely investigated and applied for commercial uses

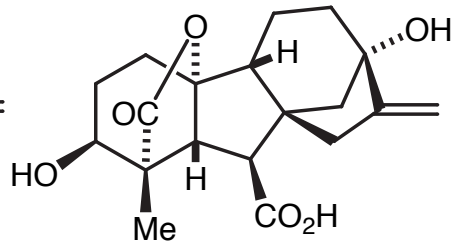
Retail prices: $10 / g

Current yields: 15-30 g / L culture

Also bio-available in decent quantity:

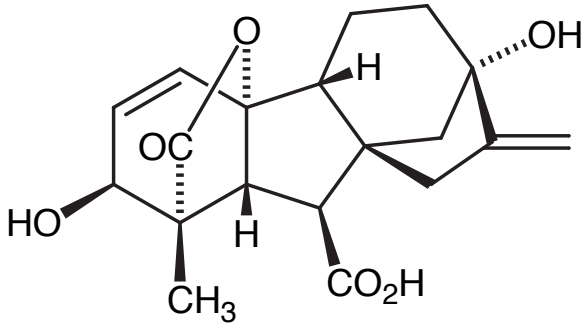


GA_4



GA_1

A Brief History of Gibberellins:



Representative Biological Functions of Gibberellins:

– Stimulate stem elongation by stimulating cell division elongation

– Breaks seed dormancy in plants which require winter freezing

– Stimulates flowering/budding in response to lengthening days

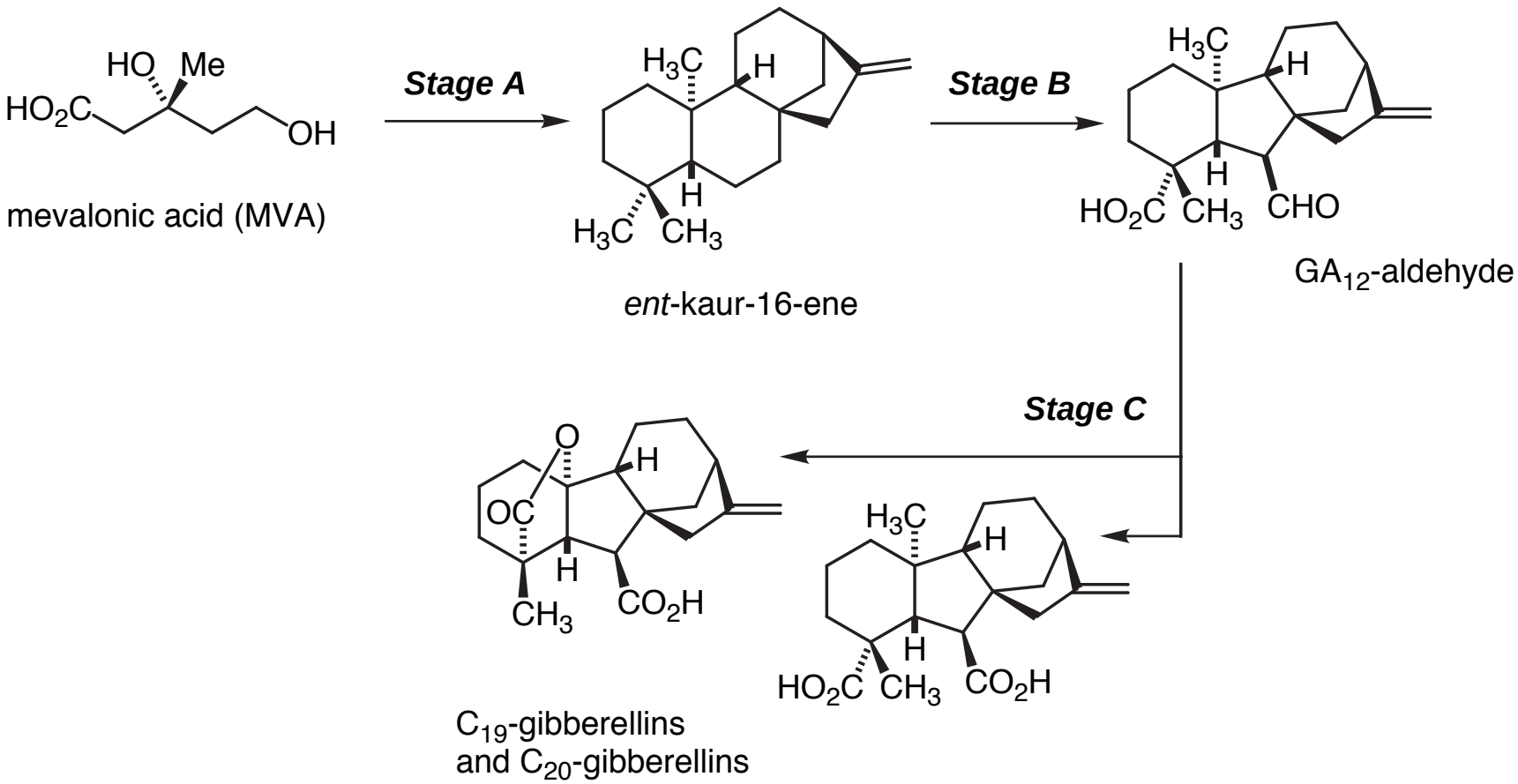
– Can induce seedless fruit development (parthenocarpic)

– Can delay senescence (ripening) in leaves and fruit

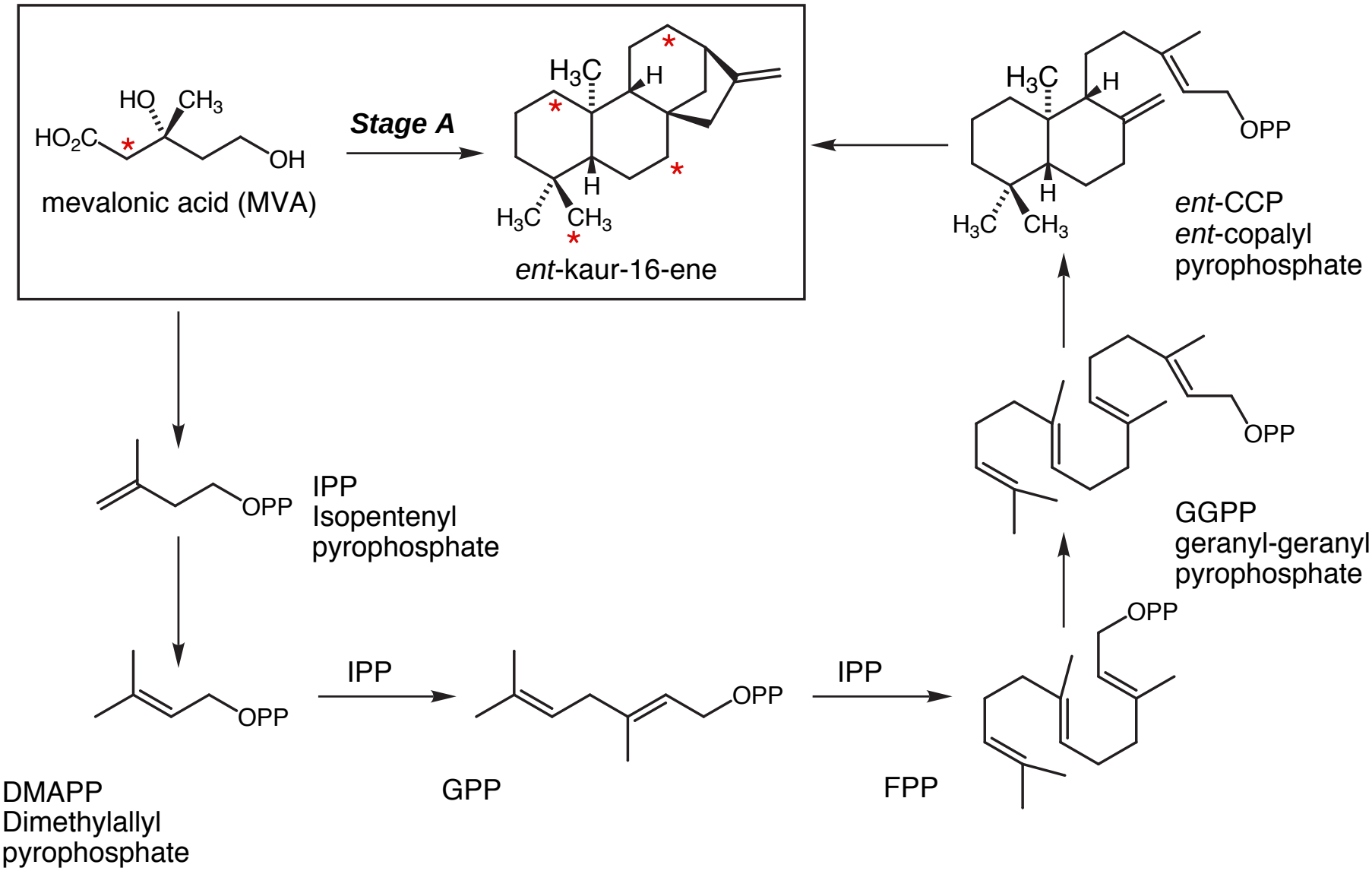
– Induces maleness (sex expression) in dioecious flowers

– Other growth effects on fruit and budding

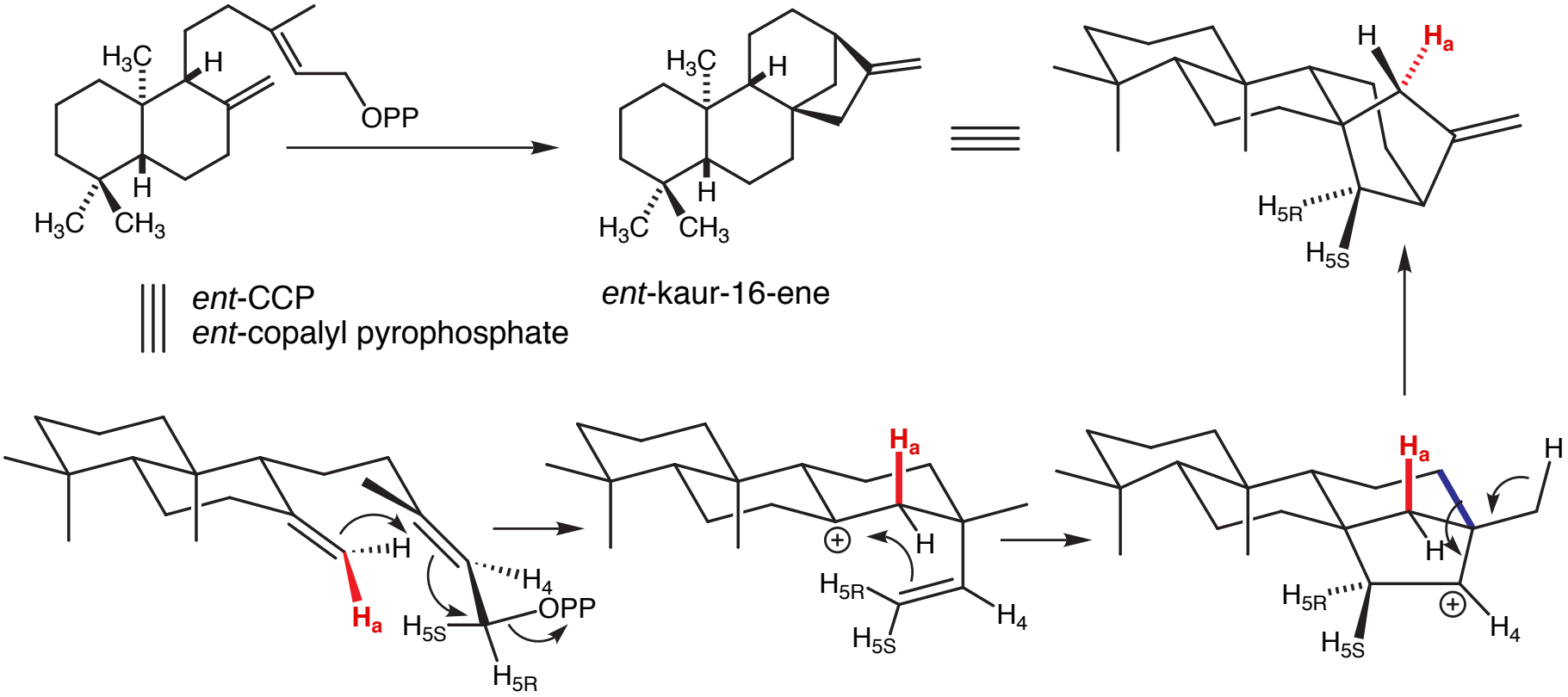
Gibberellin Biosynthesis: Three Stages



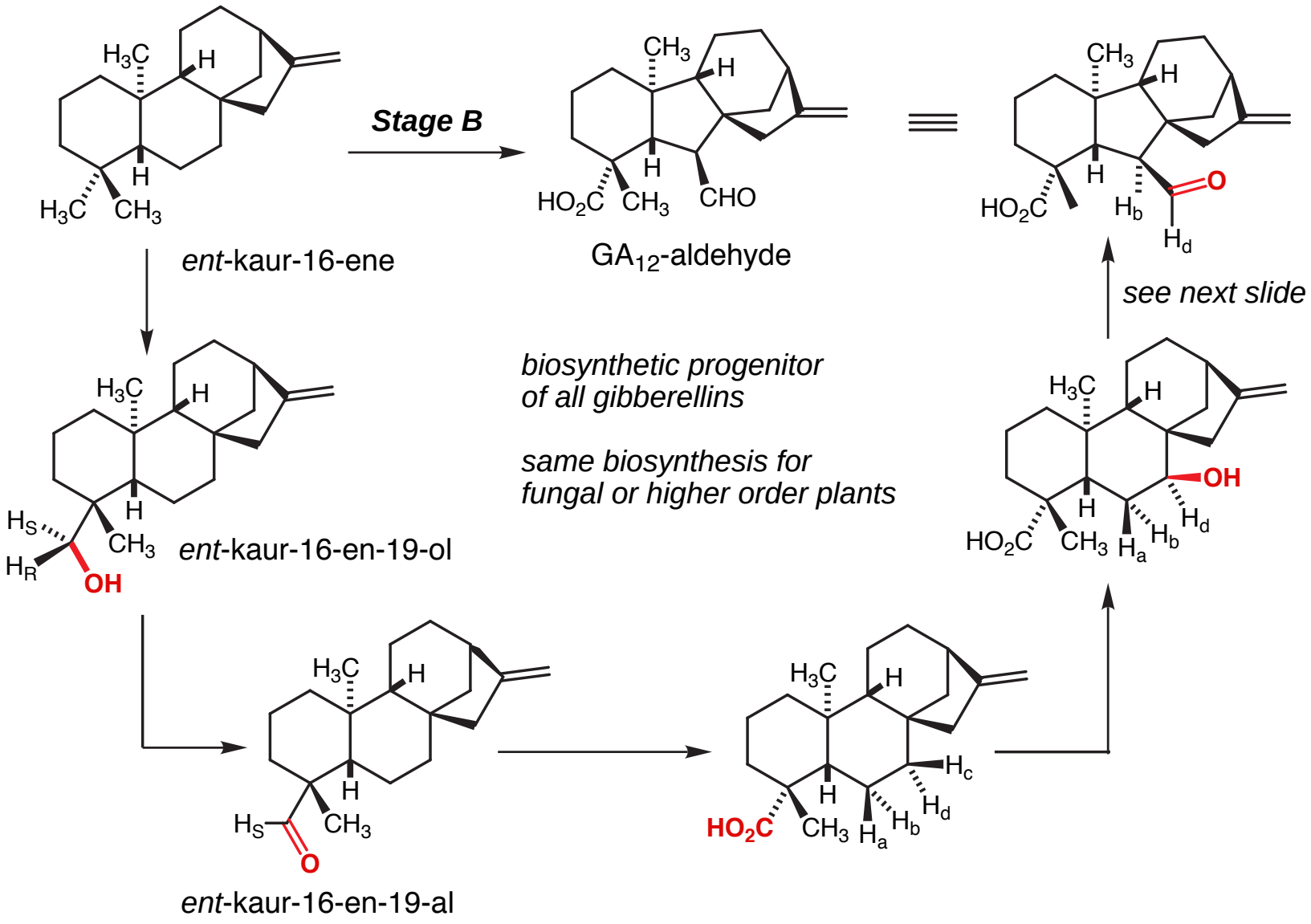
Gibberellin Biosynthesis: Stage A



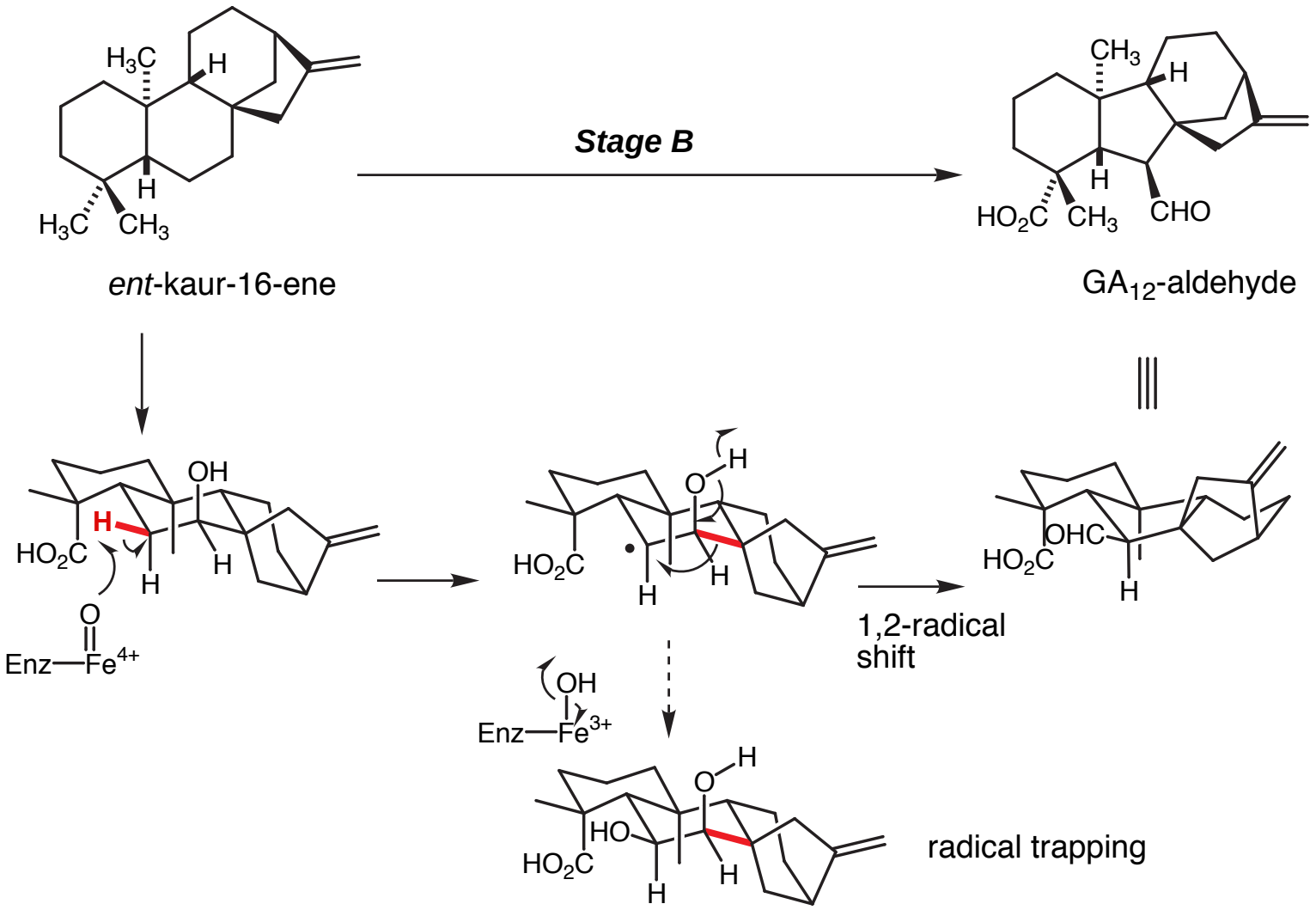
Gibberellin Biosynthesis: ent-*CCP to* ent-*kaurene*



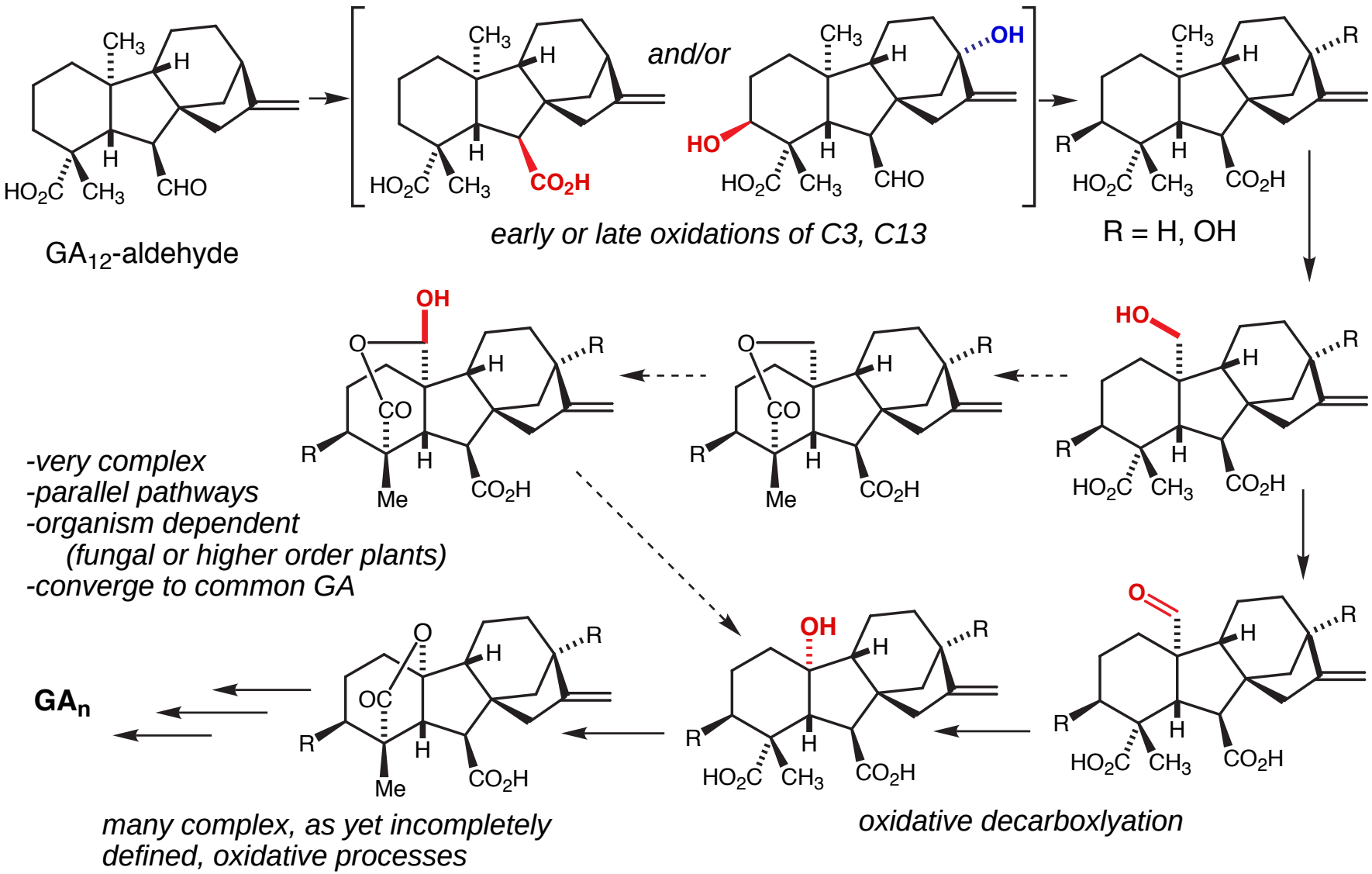
Gibberellin Biosynthesis: Stage B



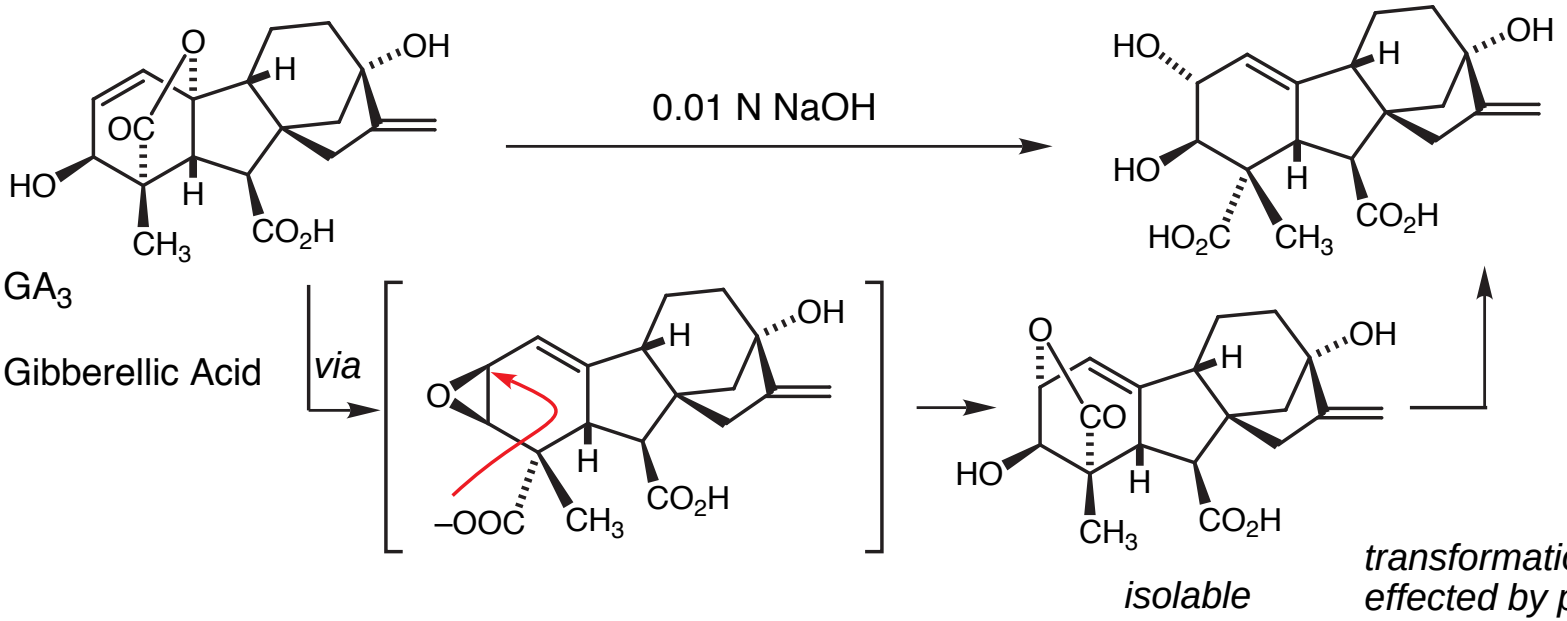
Gibberellin Biosynthesis: Ring Contraction

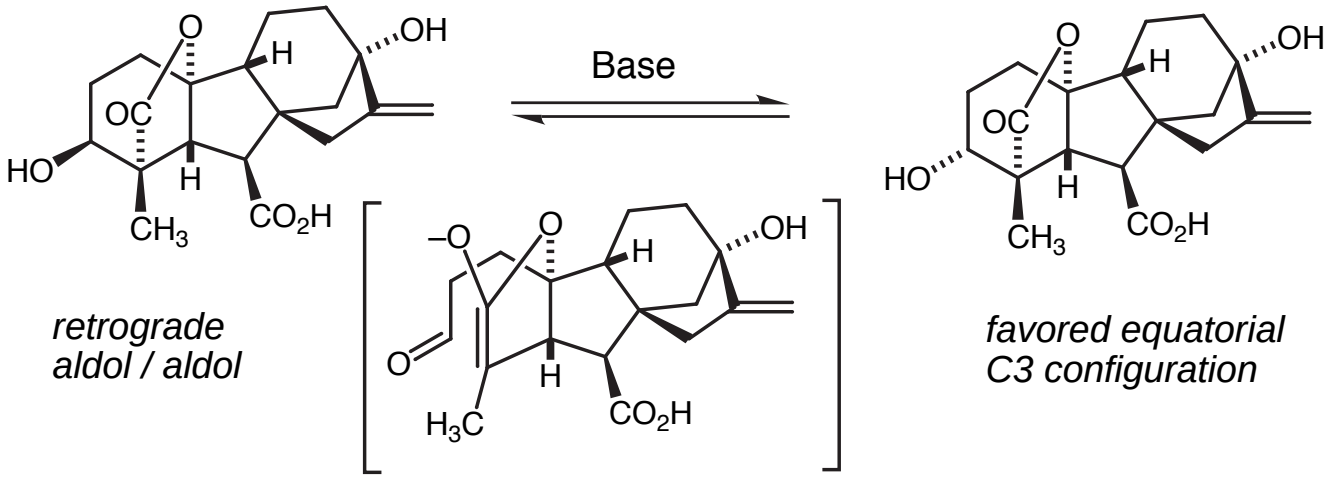


Gibberellin Biosynthesis: Stage C

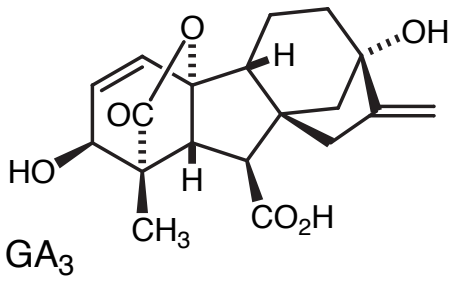


Rearrangements of Gibberellic Acid in Basic Media





Rearrangements on Gibberellic Acid in Acidic Media

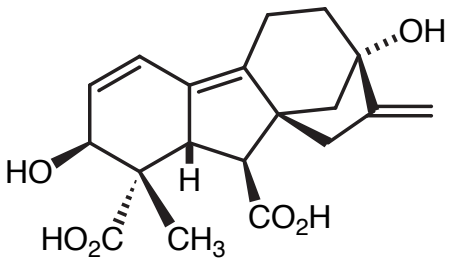


GA_3

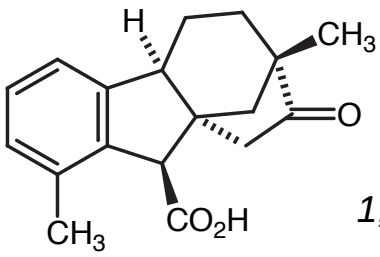
Gibberellic Acid

H^+

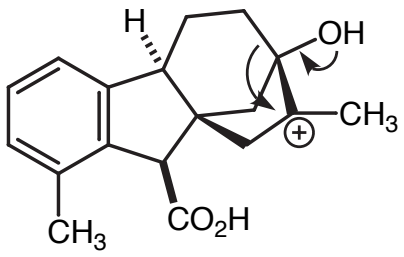
(or H_2NNH_2)

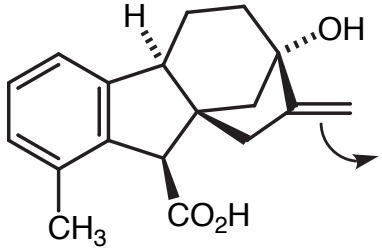


Gibberellenic Acid



1,2 shift



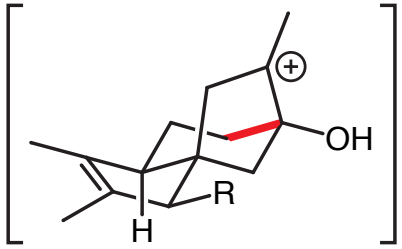


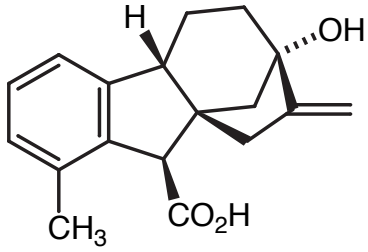
H^+

H^+

H_2NNH_2

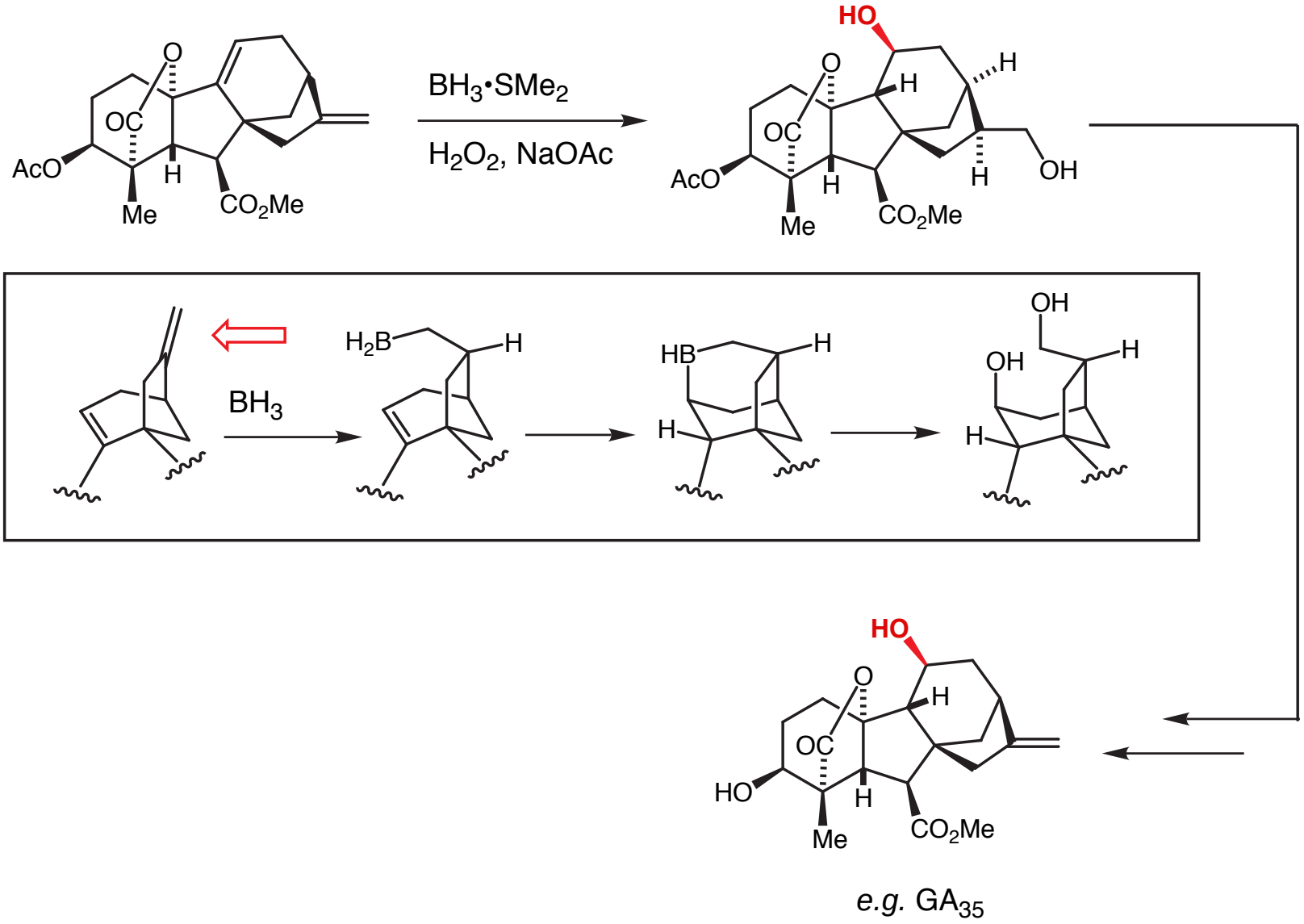
Thermodynamically more stable C9 epimer



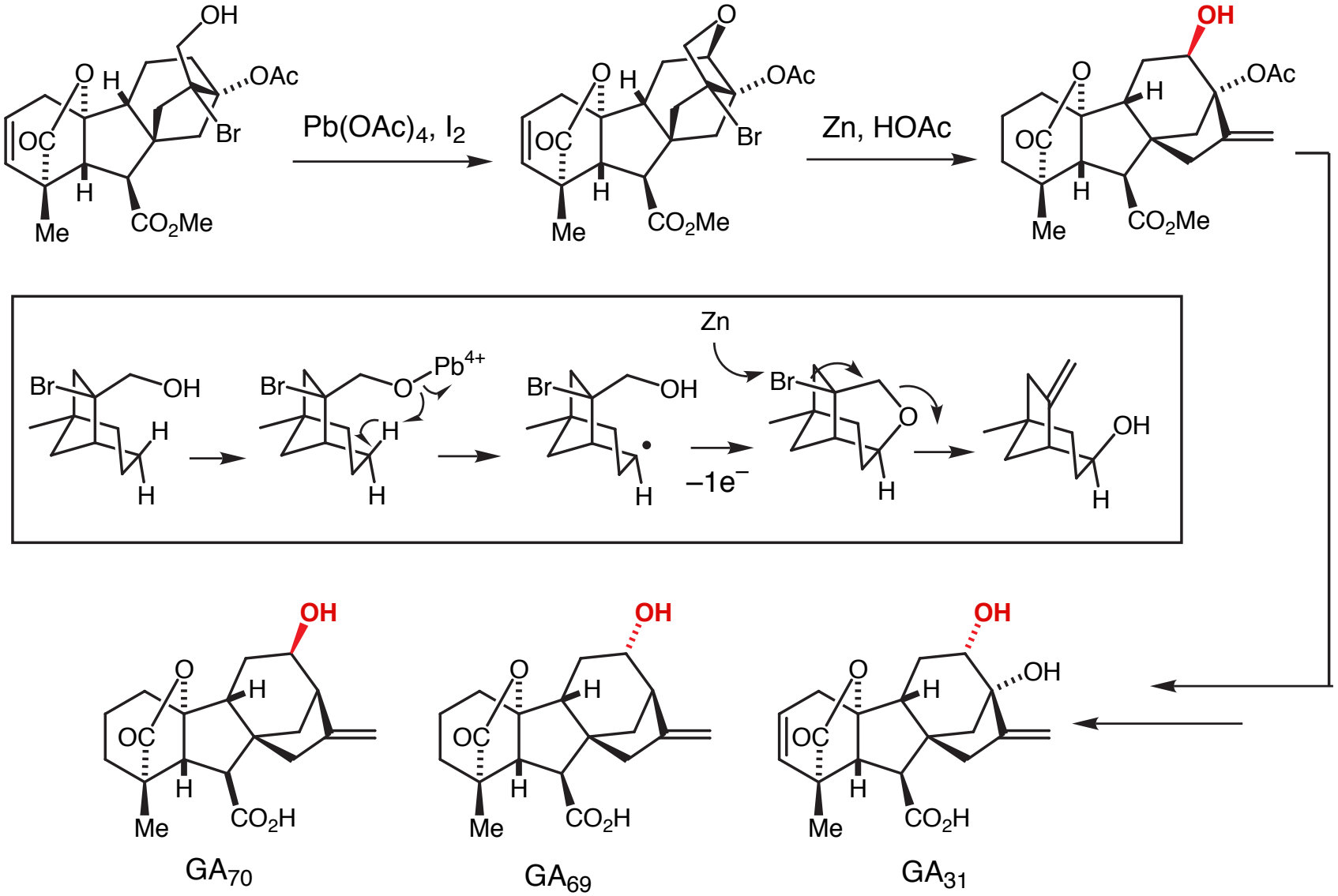


"...gibberellic acid has enjoyed a significant notoriety for instability and rearrangement. This view appears to be exagerated." L.Mander

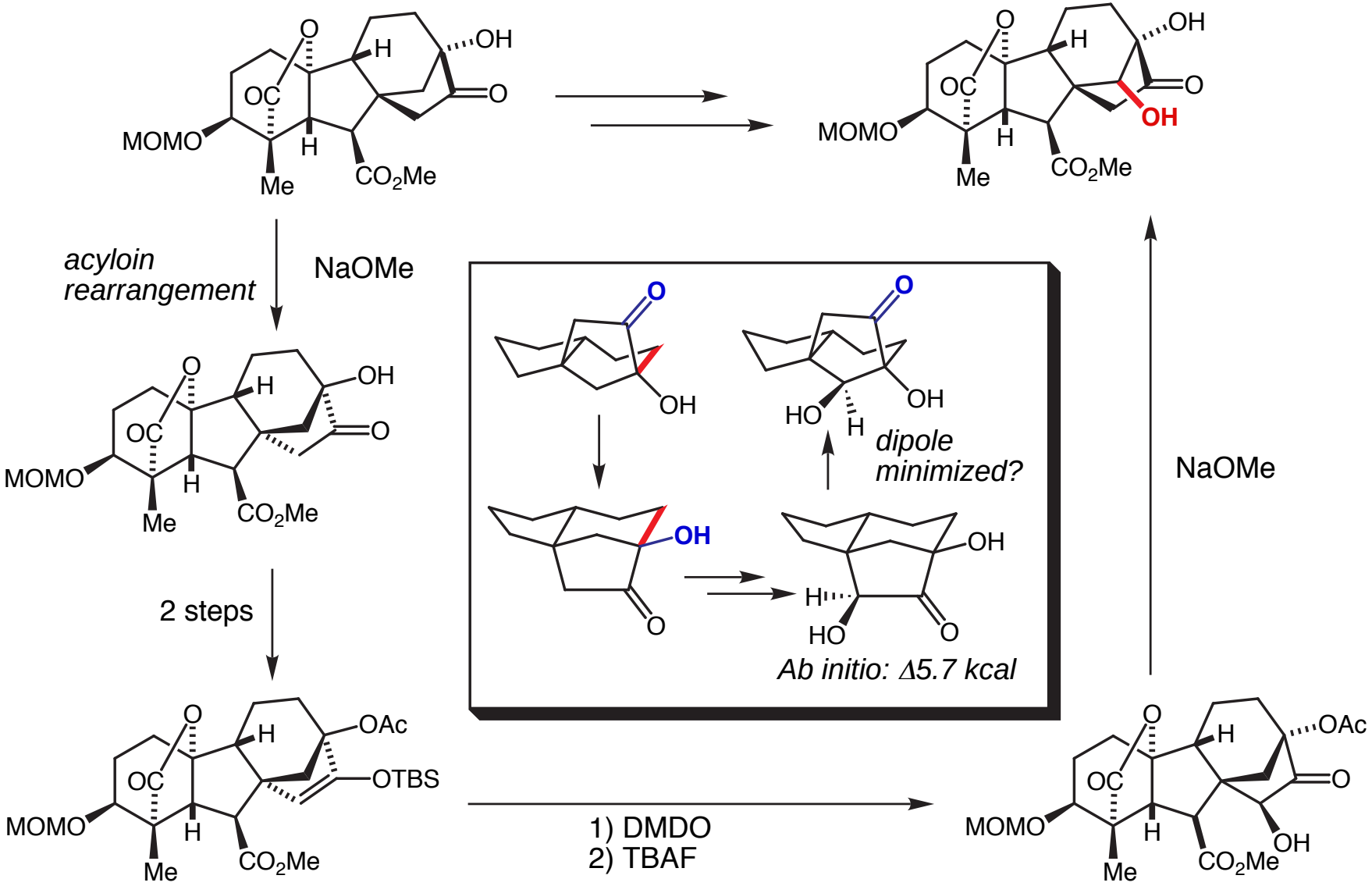
C11 oxidation: Bishydroboration



C12 oxidation of Gibberellin Skeleton

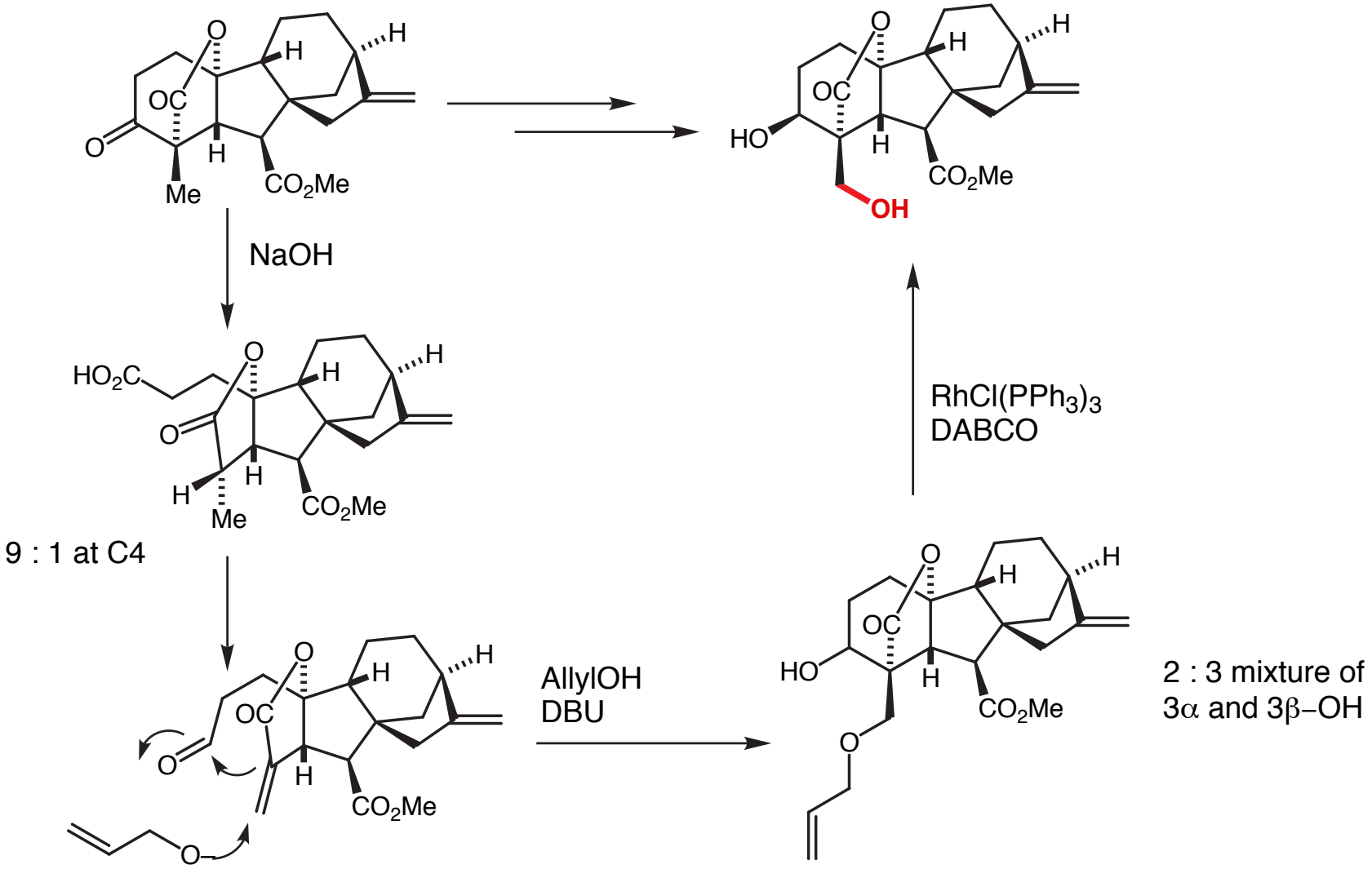


C14 Hydroxylation of Gibberellin Skeleton



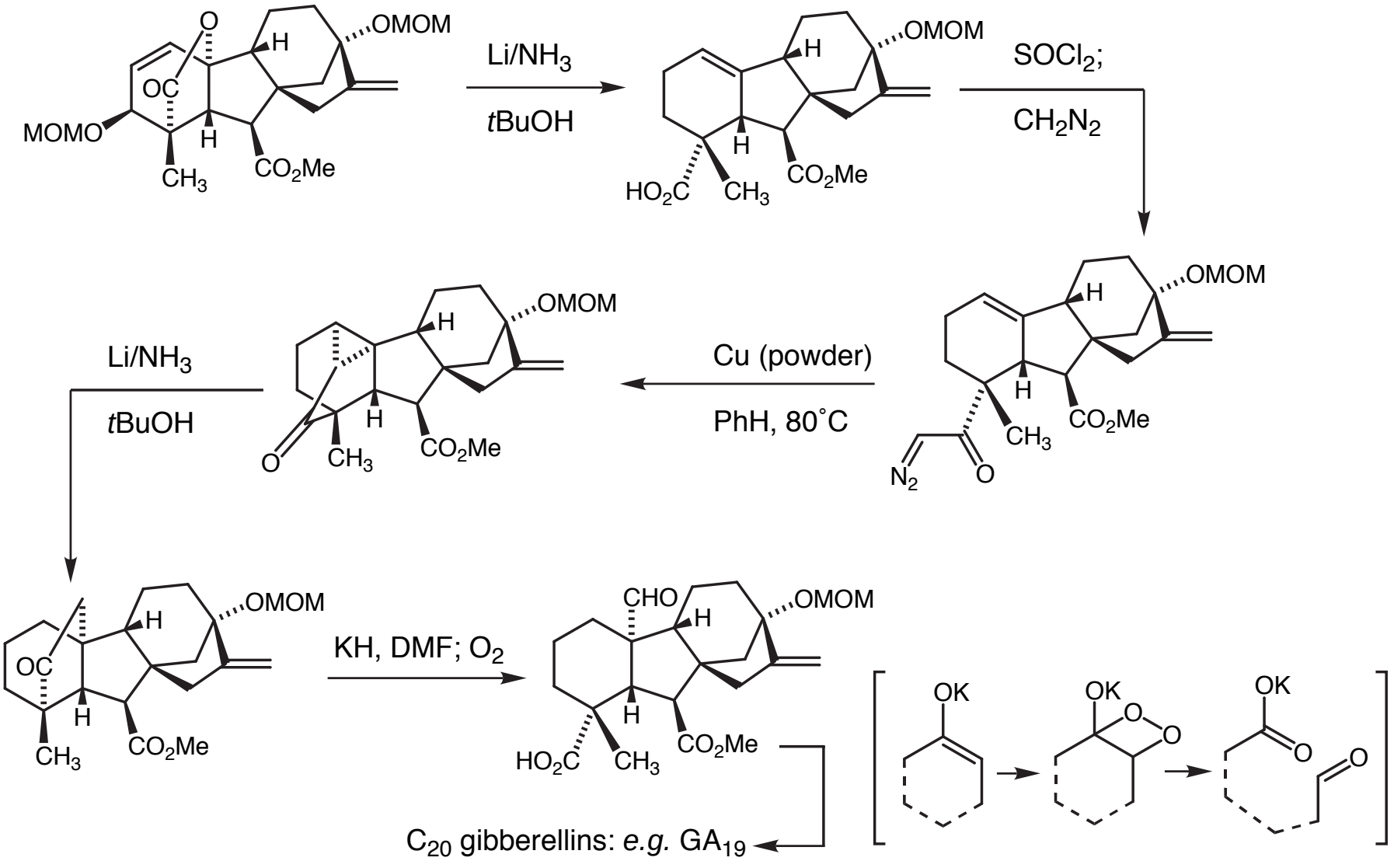
Mander, *Tetrahedron,* **1998**, 11637.

C18 Hydroxylation of Gibberellin Skeleton



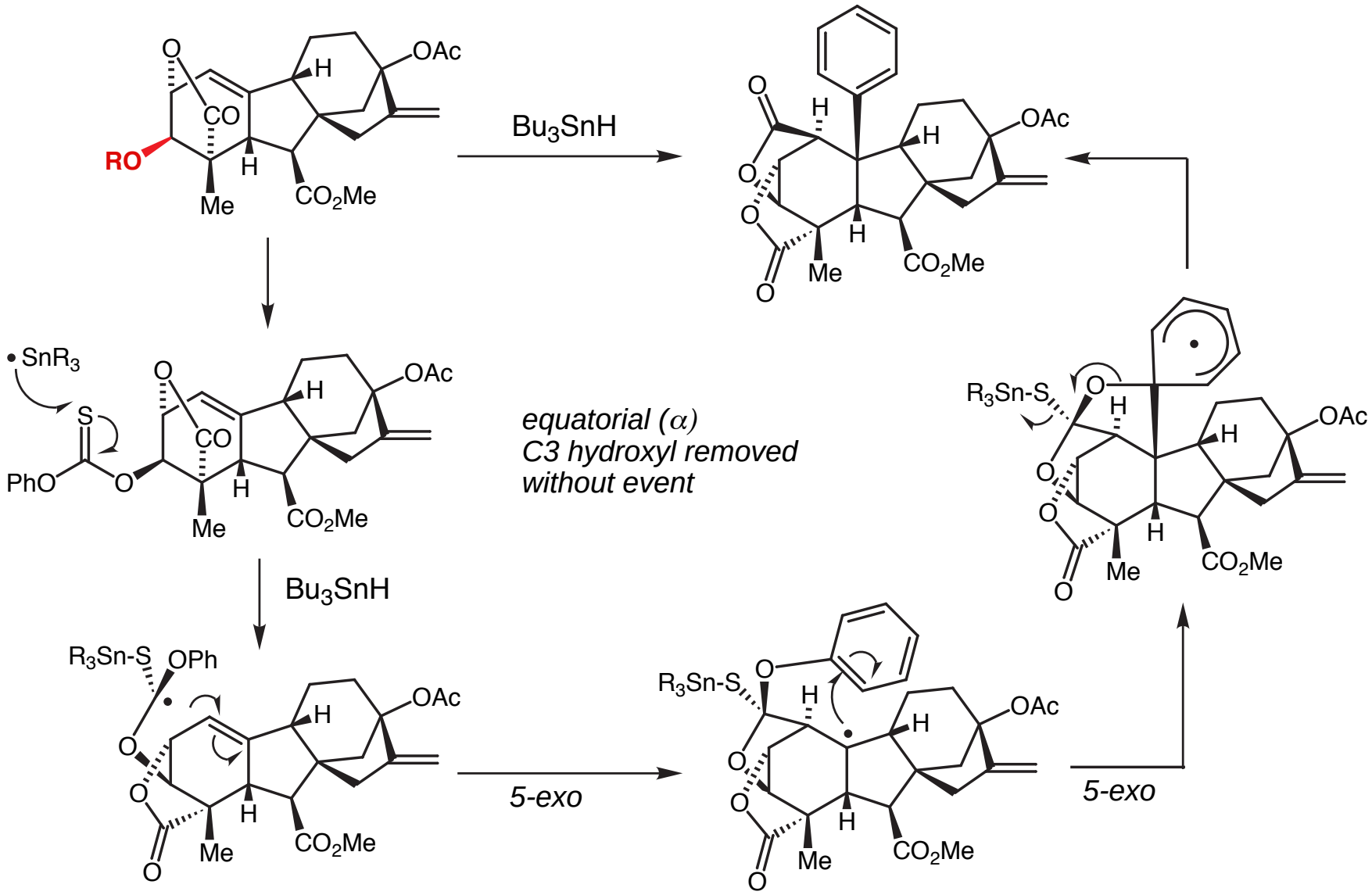
Thomson, Mander, *JCS Perkin I,* **2000**, 2893.

Conversion of C_{19} Gibberellins into C_{20} Variants



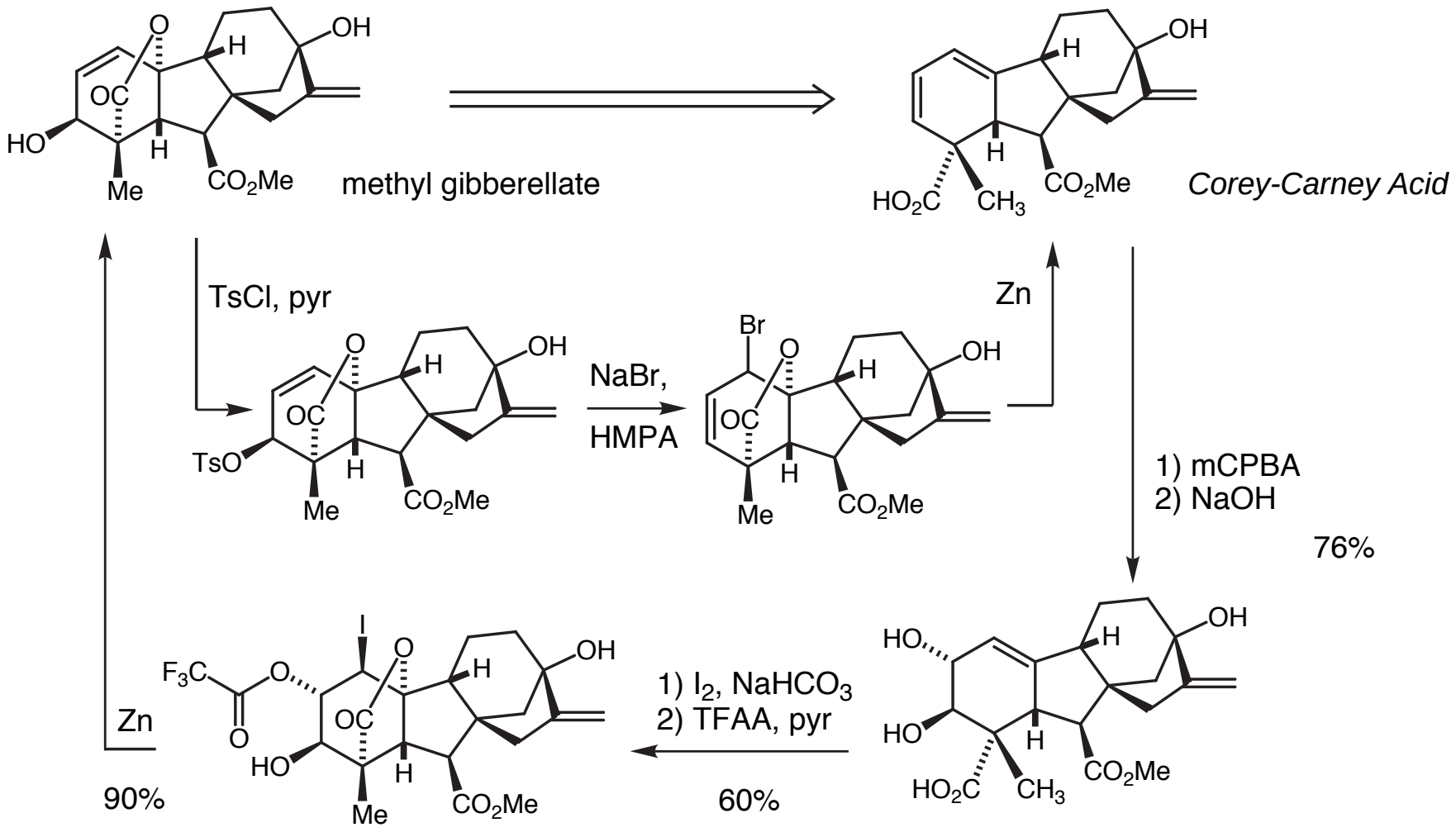
Mander, Tet. Lett. **1985**, 5725.

Radical Cascade: Attempted Deoxygenation at C3



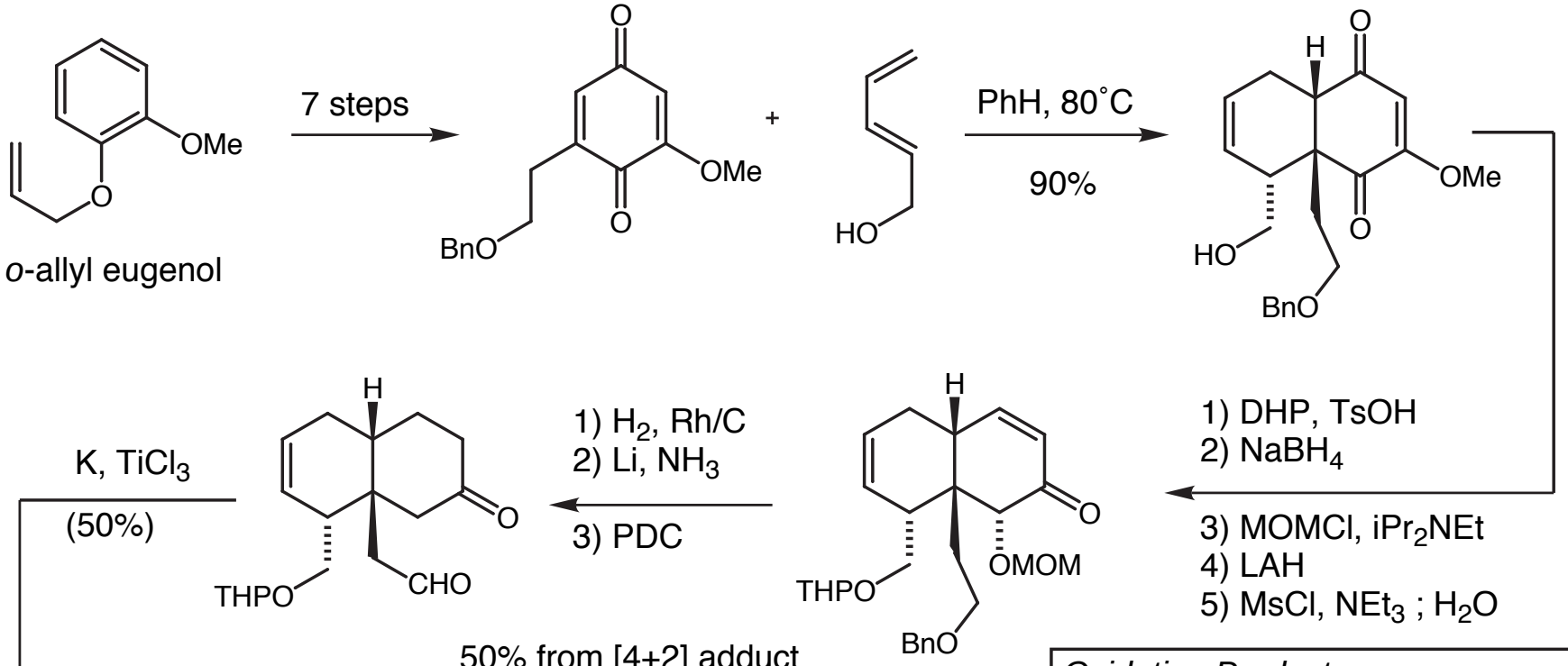
Barton, McCombie, *JCS Perkin I,* **1975**, 1574.
Mander,*TL,* **1996**, 4255.
synthetic application:* Sherburn,*JACS,* **2003, 12108.

Dismantling and Reconstituting the A-Ring

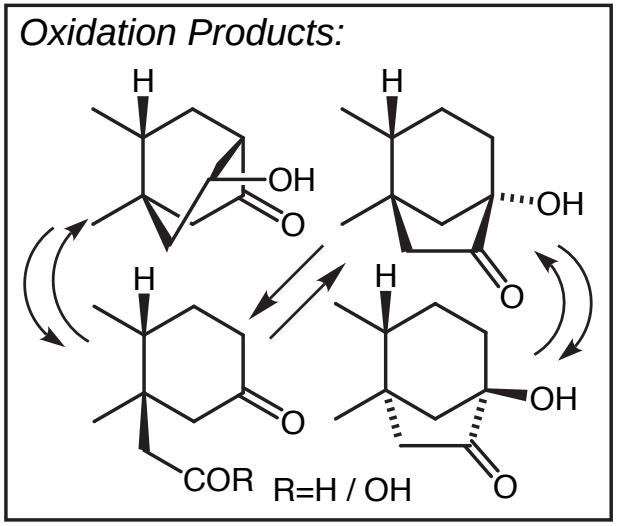


Danheiser, *Strategies and Tactics in Organic Synthesis*. Ed. Lindberg **1984**, 22-65.

Corey Synthesis of GA_3: Hydronaphthalene Approach

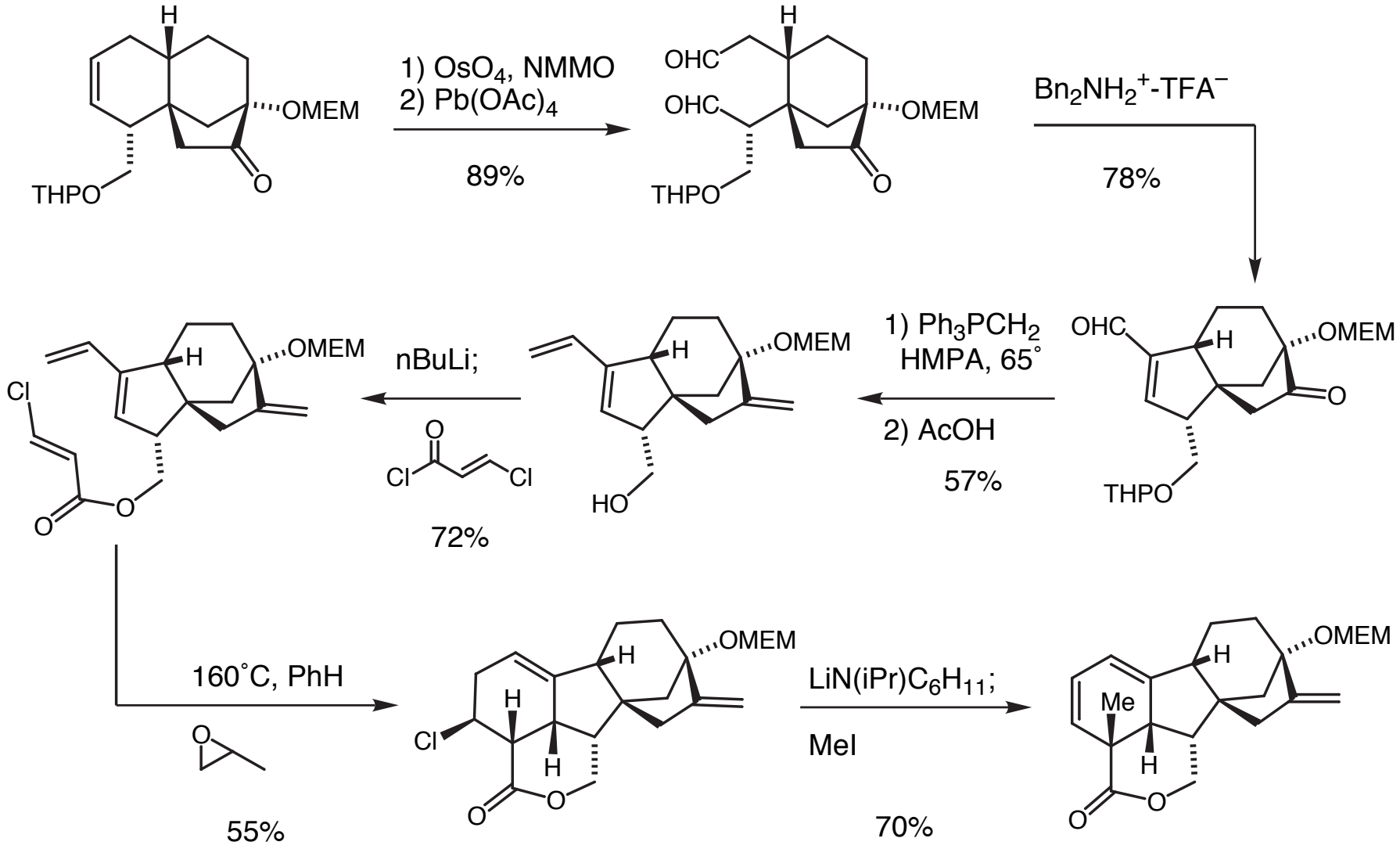


"...quenching reactions involving 50g of potassium can provide moments of great drama, as well as piquant stimulation for the experimentalist."



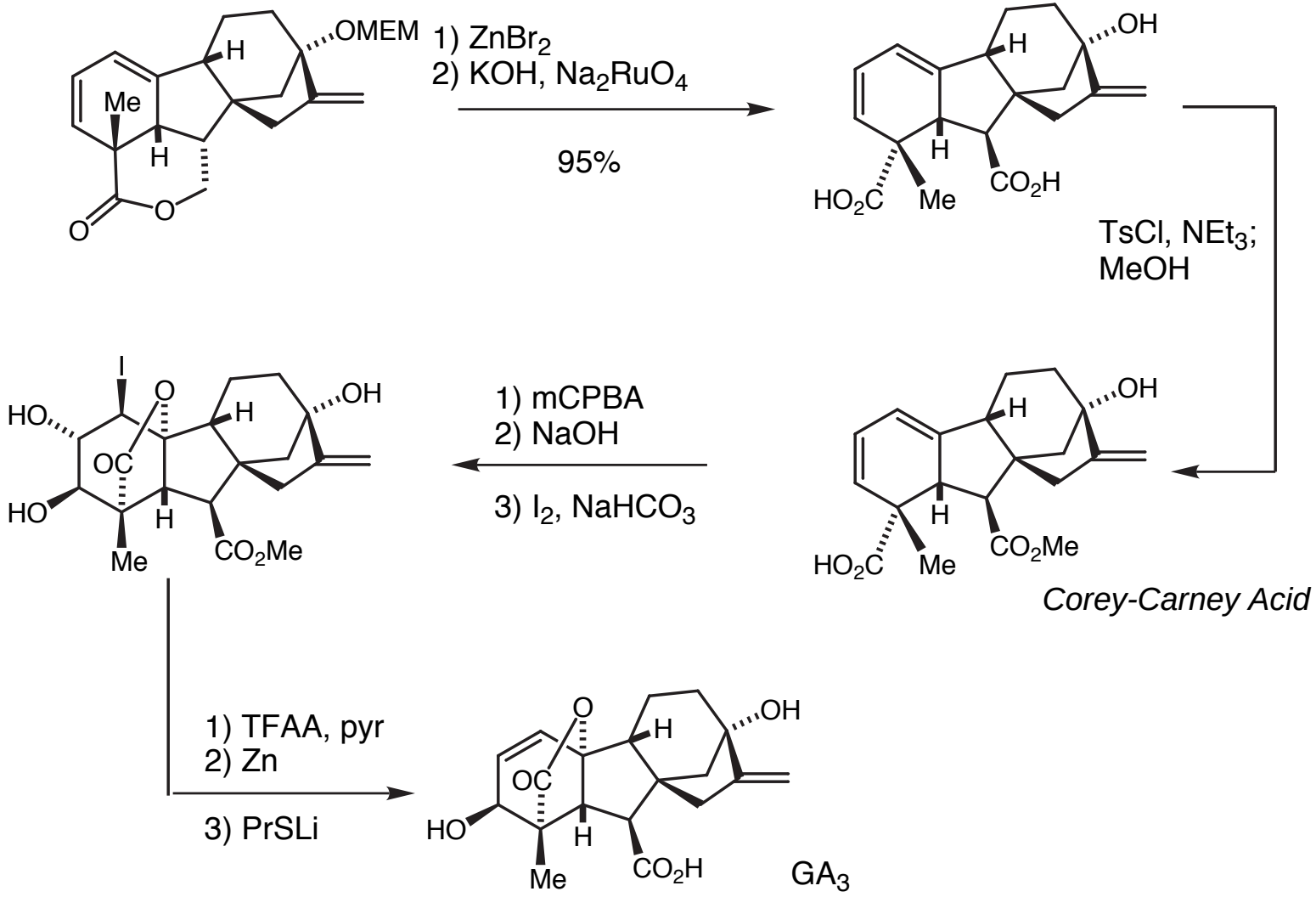
Corey, *JACS*, **1978**, 8034.

Contraction of B-Ring; A-Ring Formation through Cycloaddition



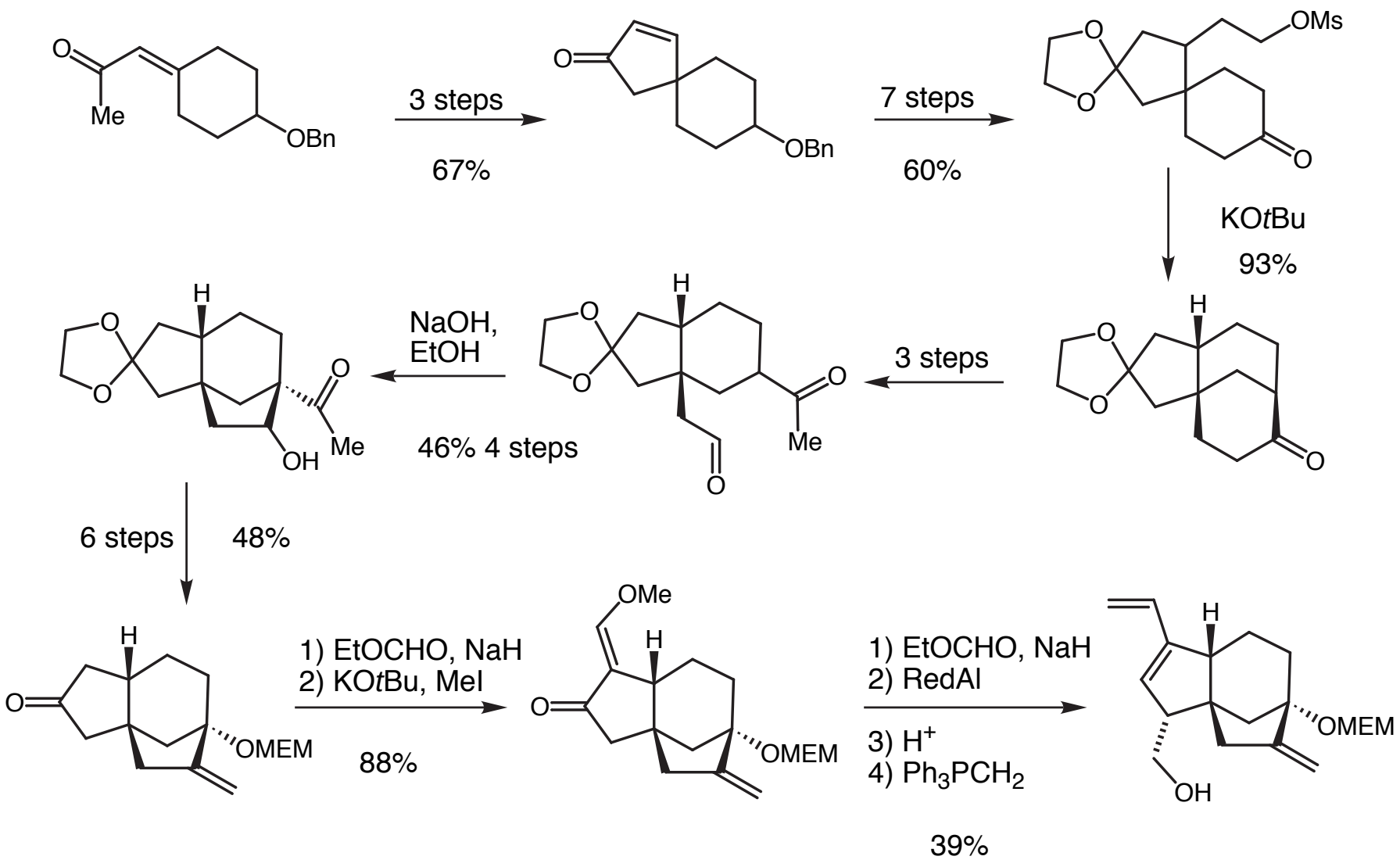
Corey, *JACS*, **1978**, 8034.

Gibberellic Acid Endgame: Corey



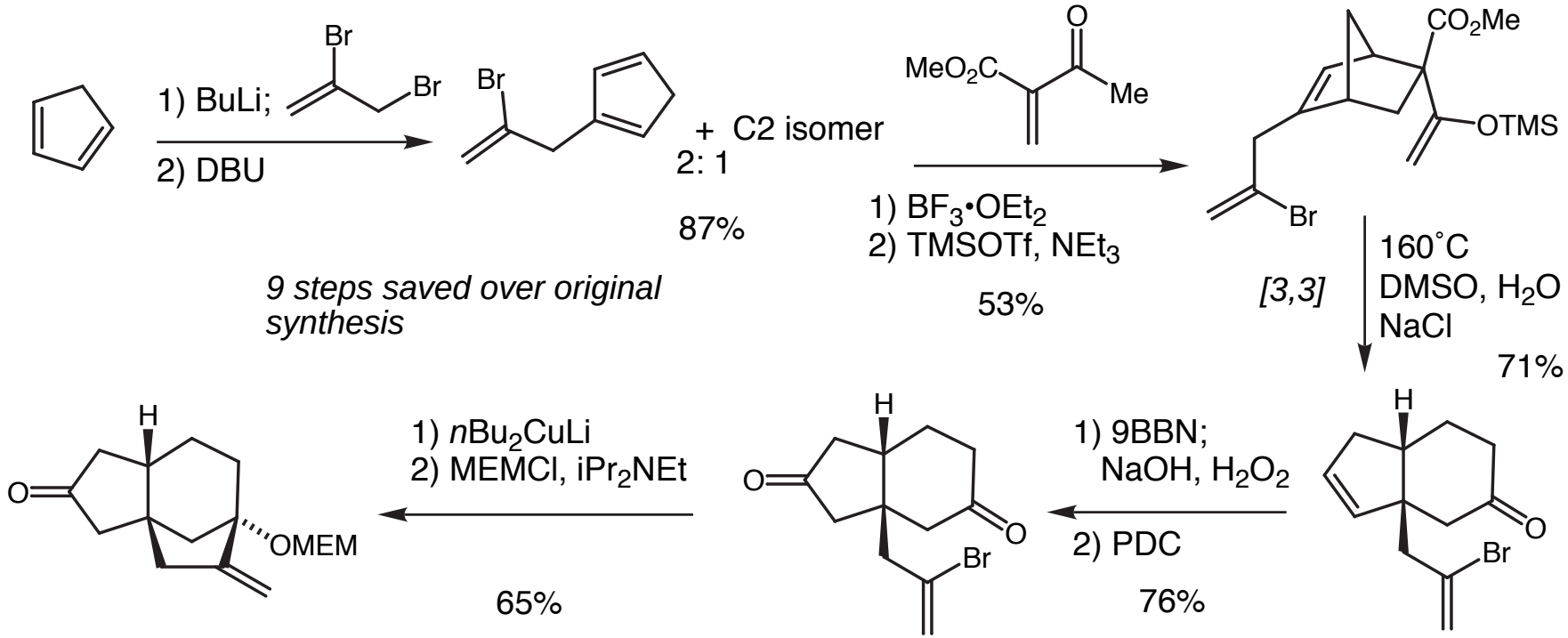
Corey, *JACS,* **1978**, 8034.

Alternative Route to Key Tricyclic Intermediate: *The Hammer and Tongs Approach*



Corey, *JACS,* **1978**, 8034.

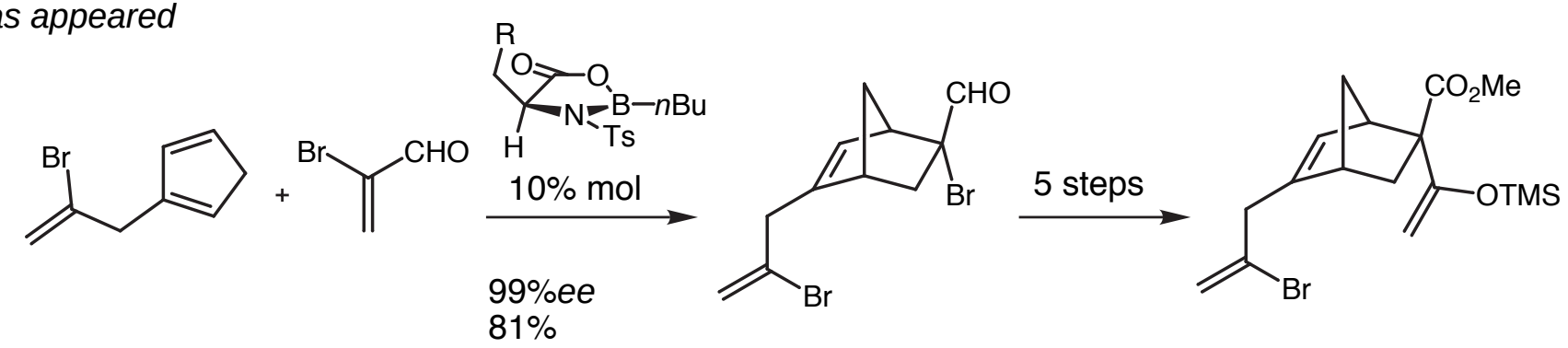
Cope Rearrangement for B/C Ring Junction



9 steps saved over original synthesis

---

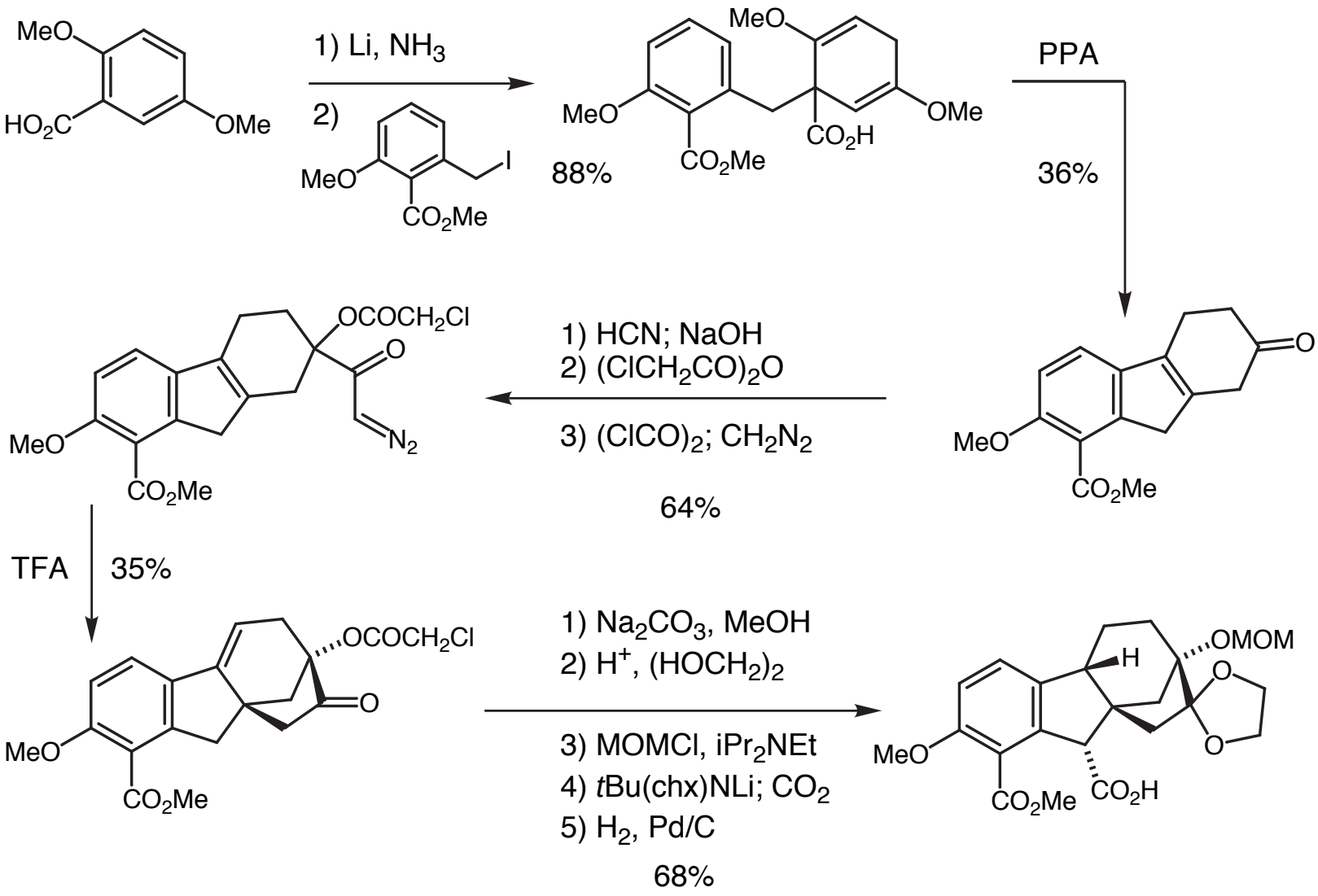
enantioselective variant has appeared



R = 3-indole

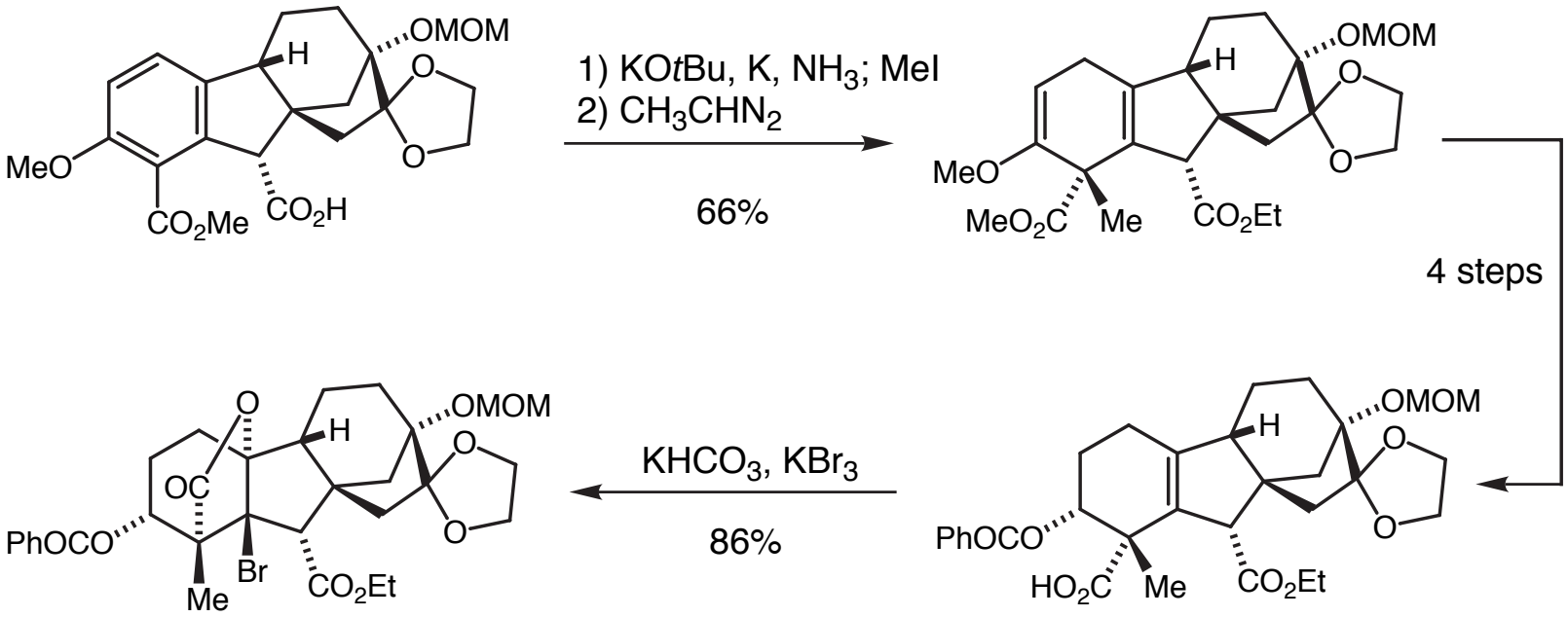
Corey, *JACS,* **1982**, 6129.
Corey, *JACS,* **1994**, 3611.

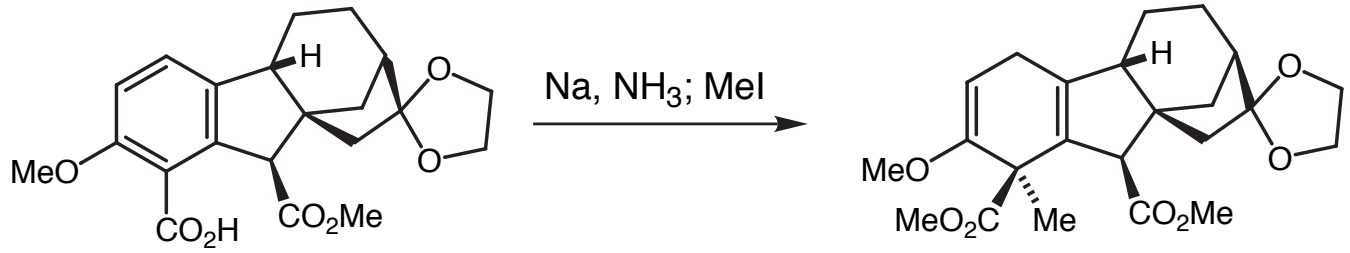
Mander: Fluorene Approach



Mander, *JACS*. **1980**, 6626.

Mander: A-Ring Assembly through Birch Reduction/Alkylation

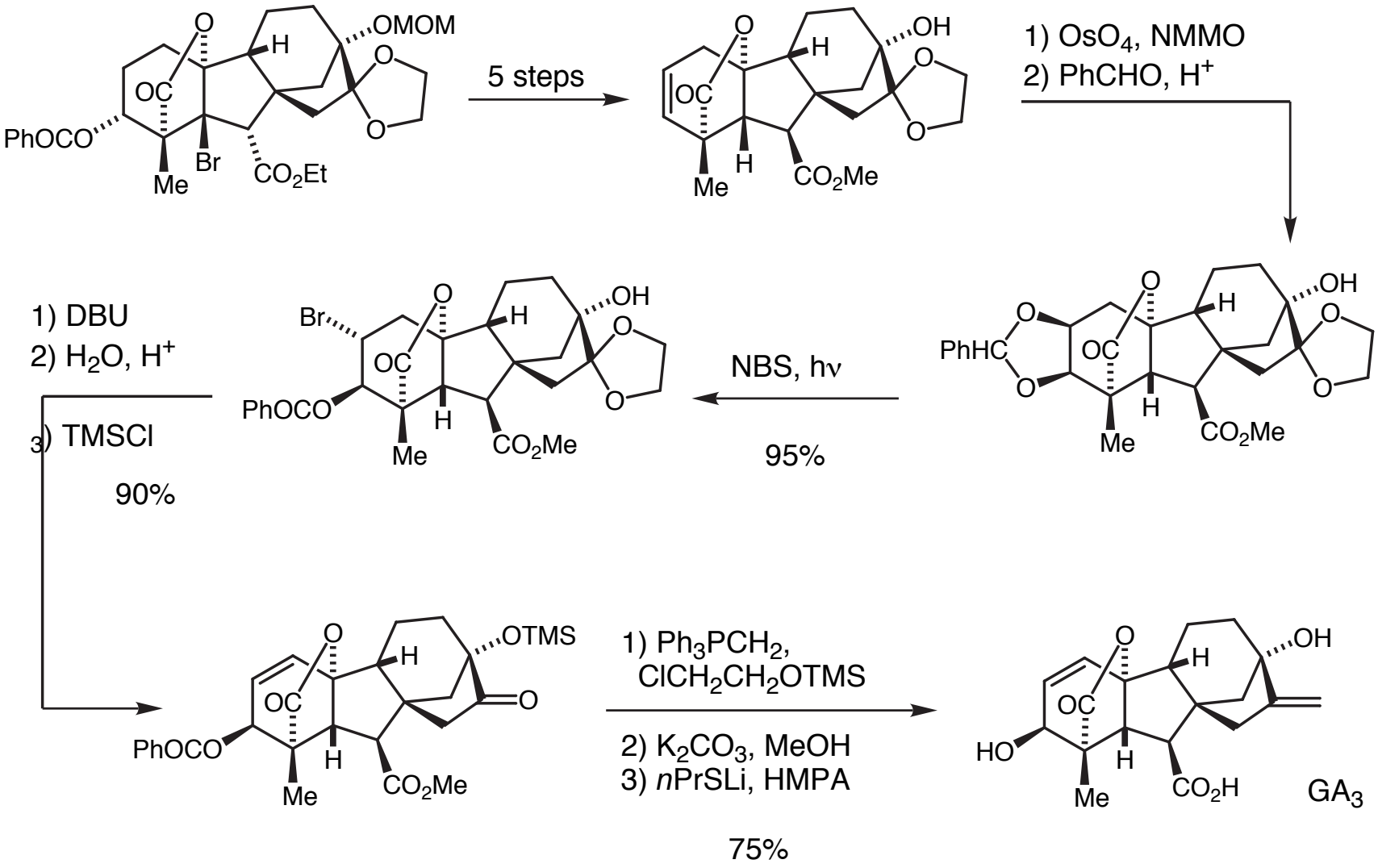




C7 ester controls alkylation

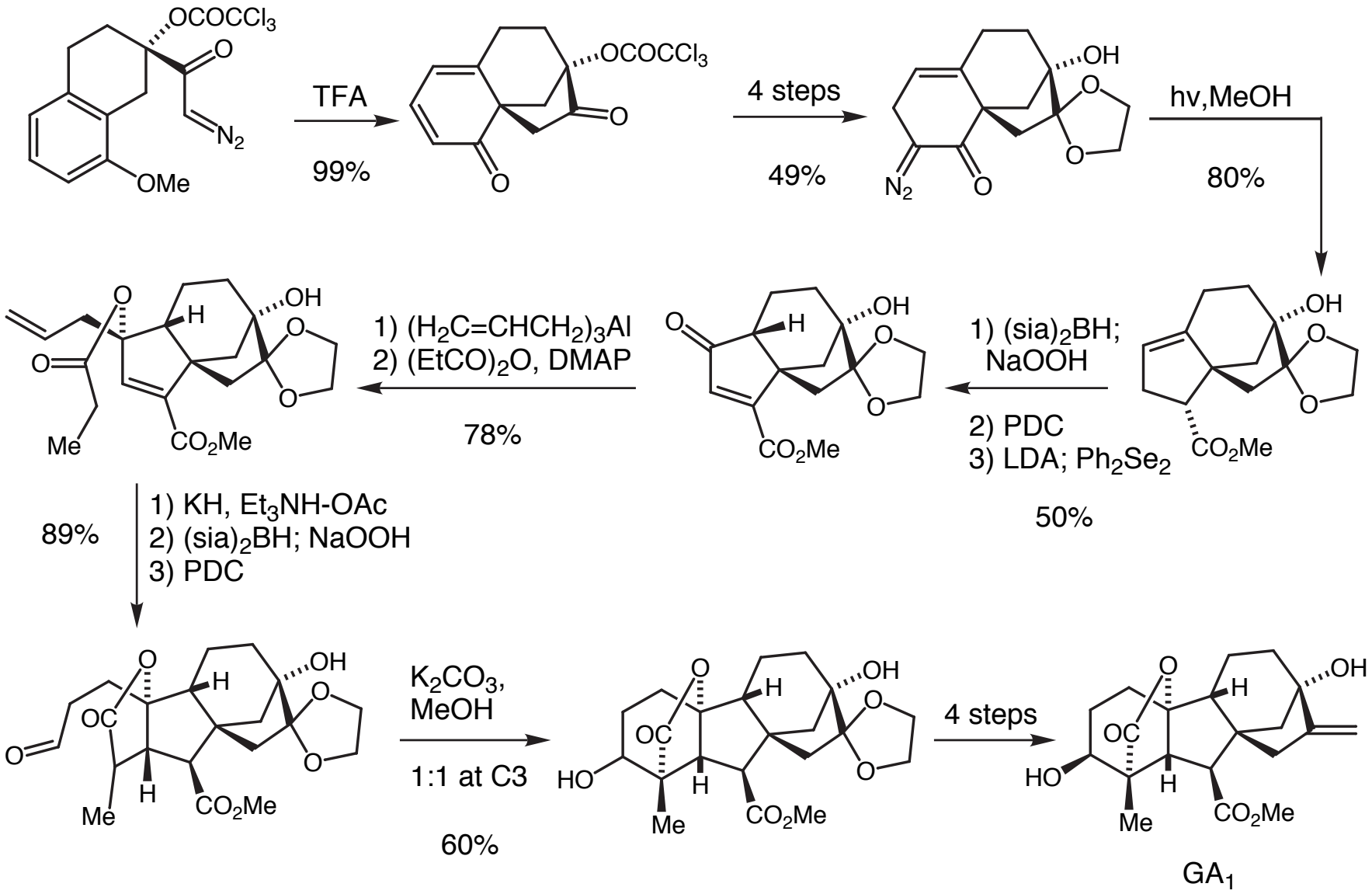
Mander, *JACS*. **1980**, 6626.
Baker, *Chem. Com.* **1972**, 951.

Mander: Gibberellic Acid



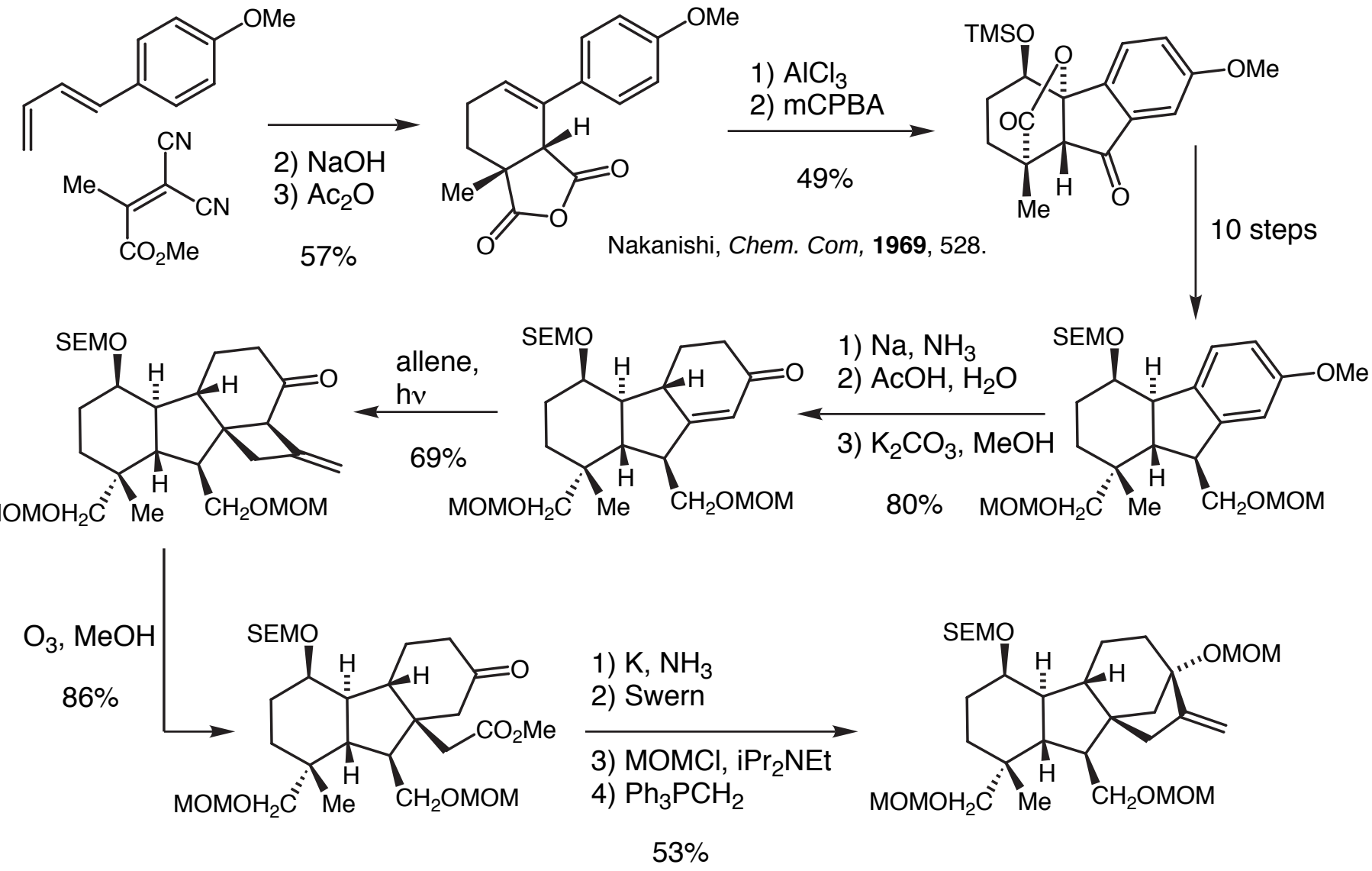
Mander, *JACS*. **1980**, 6626.

Mander: A-ring Aldol Approach (GA_1)



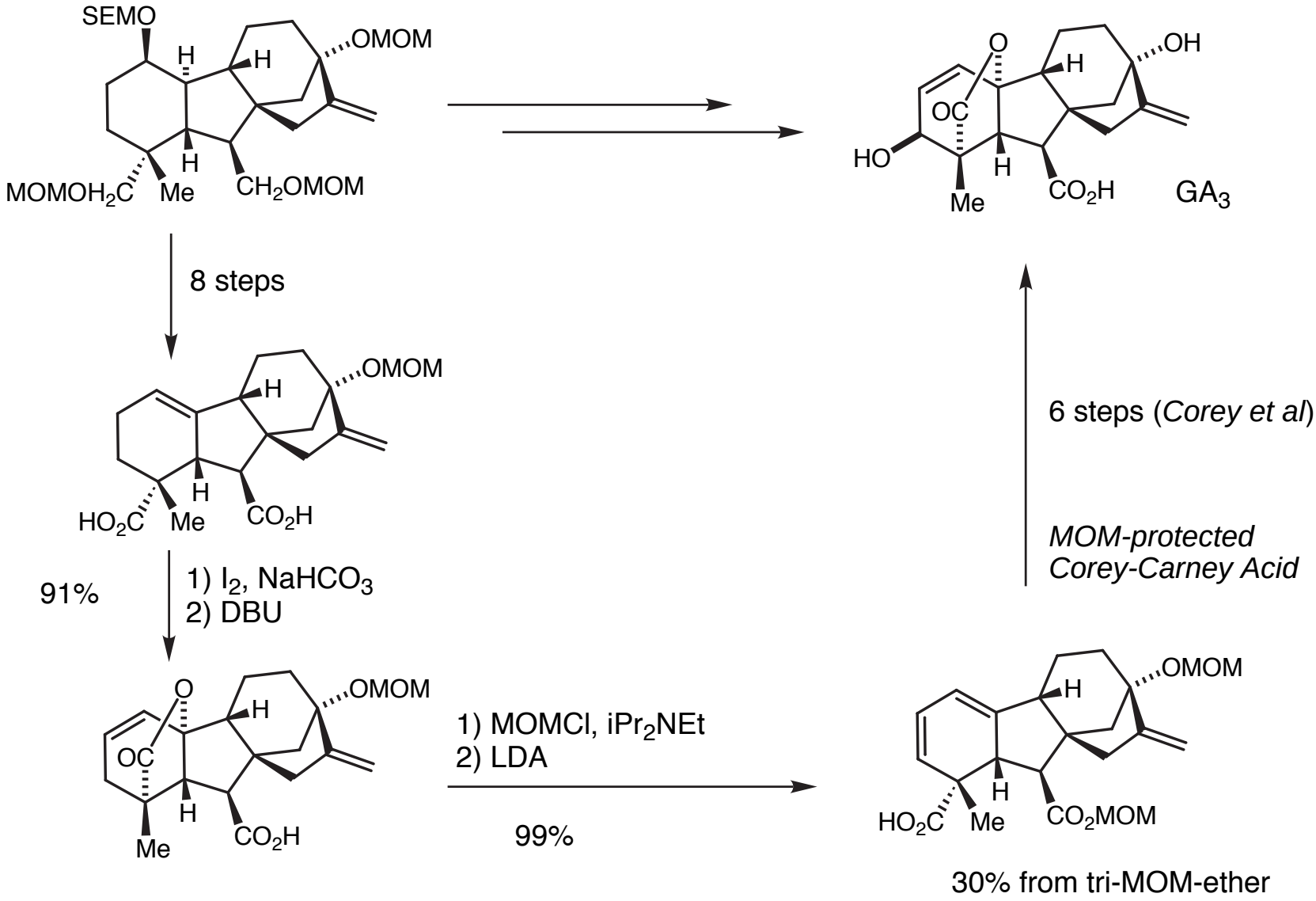
Mander, *JACS*. **1980**, 6626.

Yamada: Intermolecular [4+2] Ring A Construction



Yamada, *TL,* **1989**, 971.

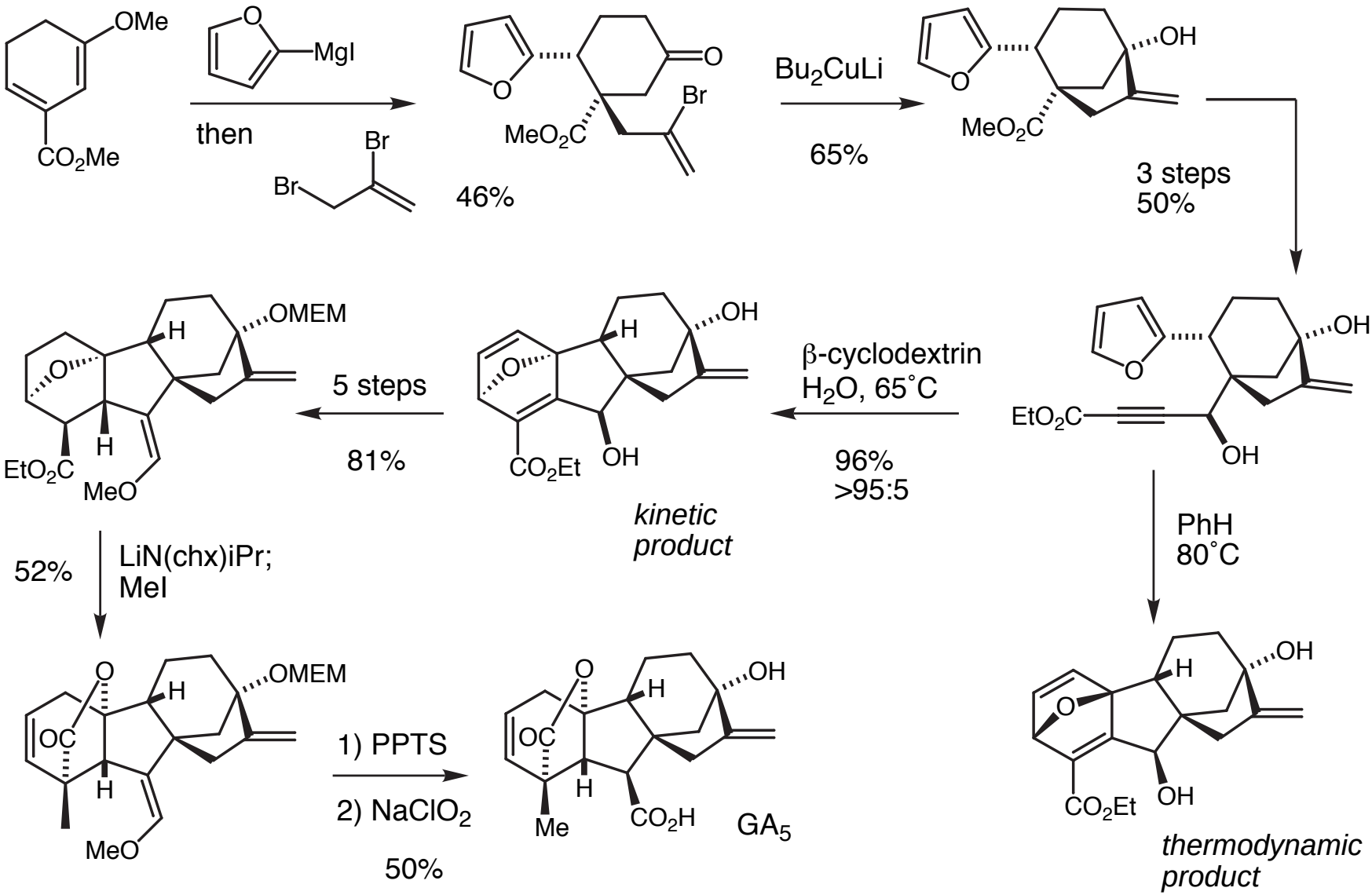
Yamada: Synthesis of Gibberellic Acid



34-GA3-yamadatotal2.cdx 2/5/04 2:50 PM

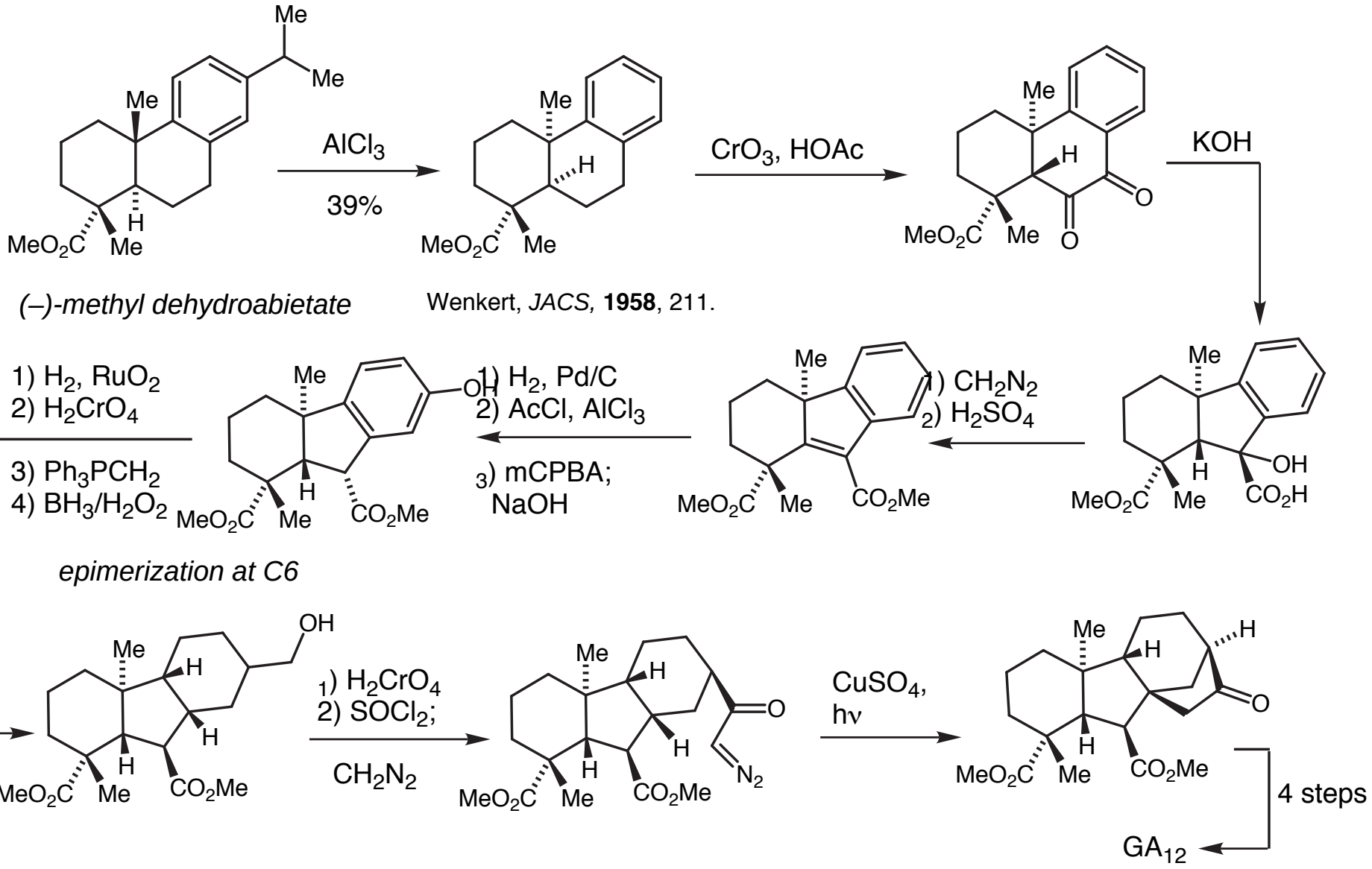
Yamada, *TL,* **1989**, 971.

Synthesis of GA_5 via Furan [4+2]: DeClercq



DeClercq, *Tet. Lett*. **1986**, 1731.

GA_{12} Synthesis from Dehydroabiatate: Tahara

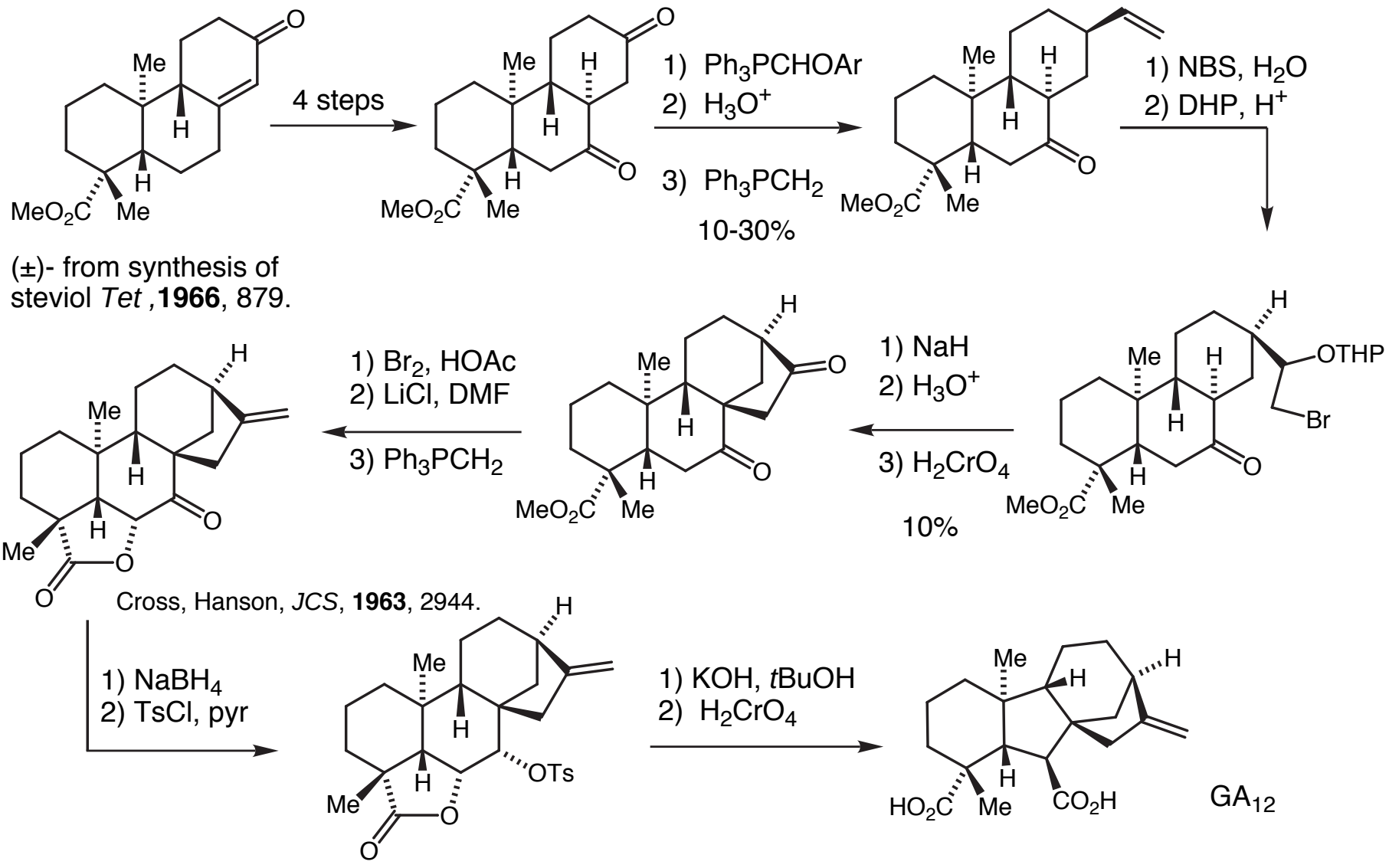


(–)-methyl dehydroabietate

Wenkert, *JACS,* **1958**, 211.

Tahara, *JCS Perkin I,* **1972**, 320.
Tahara, *TL,* **1976**, 1515.

GA_{12} Formal Synthesis: Mori

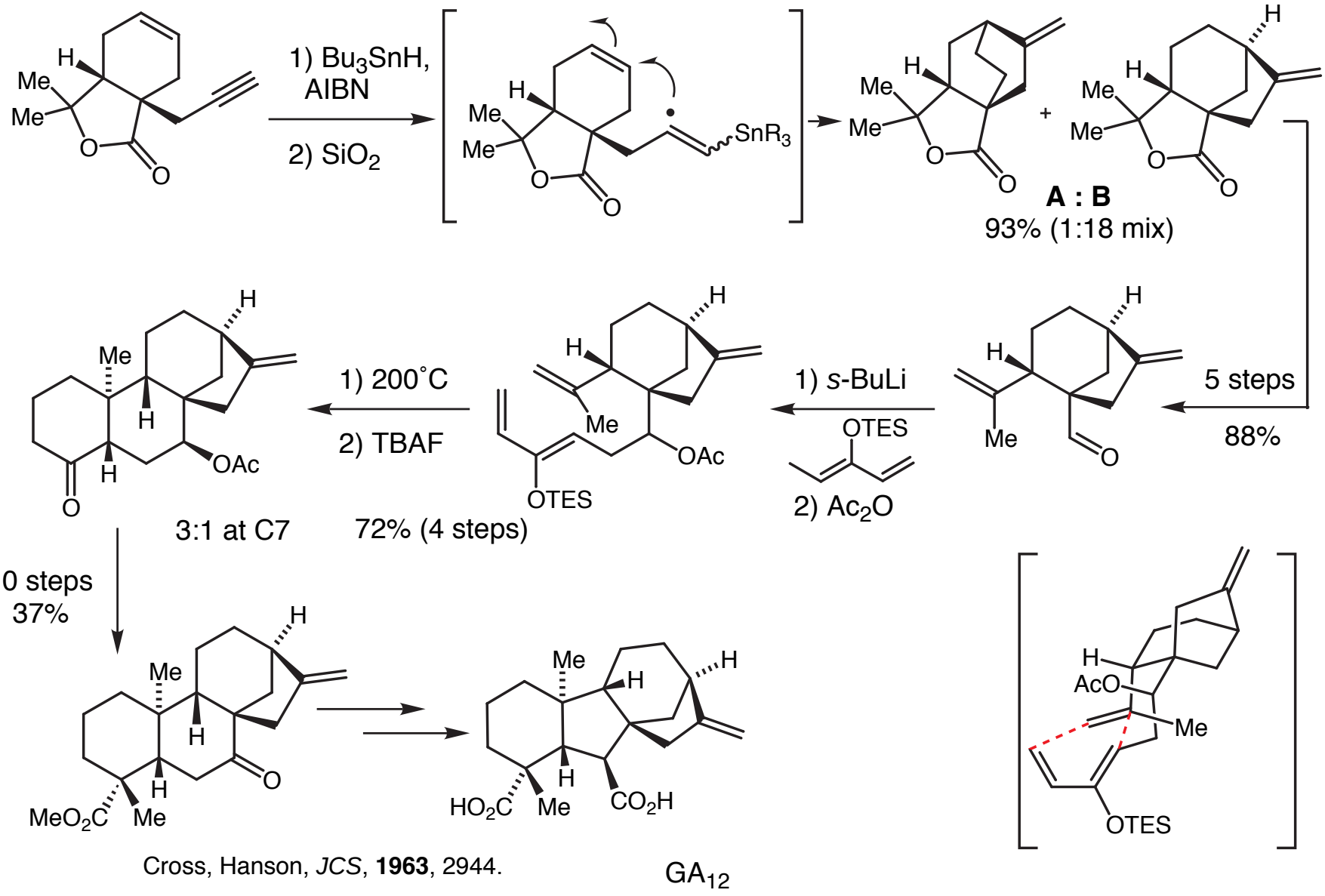


(±)- from synthesis of steviol *Tet* ,**1966**, 879.

Cross, Hanson, *JCS*, **1963**, 2944.

Mori, *Tet,* **1976**, 1497.

GA_{12} Formal Synthesis: Ihara

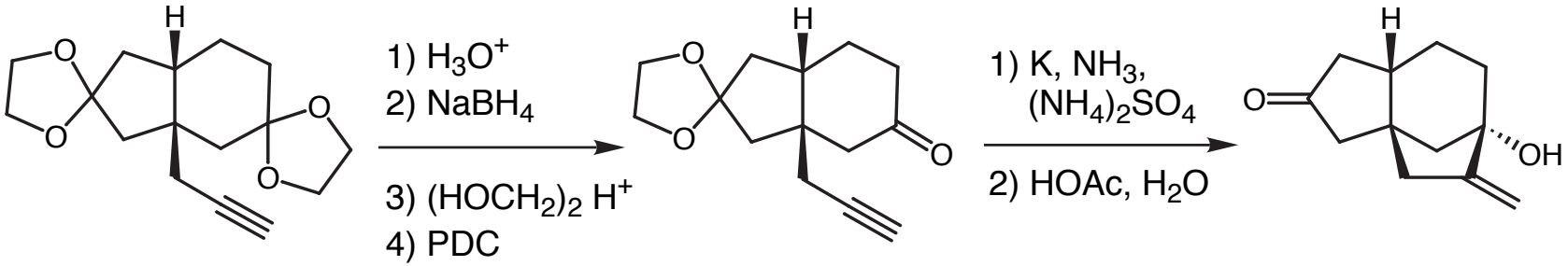


Cross, Hanson, *JCS*, **1963**, 2944.

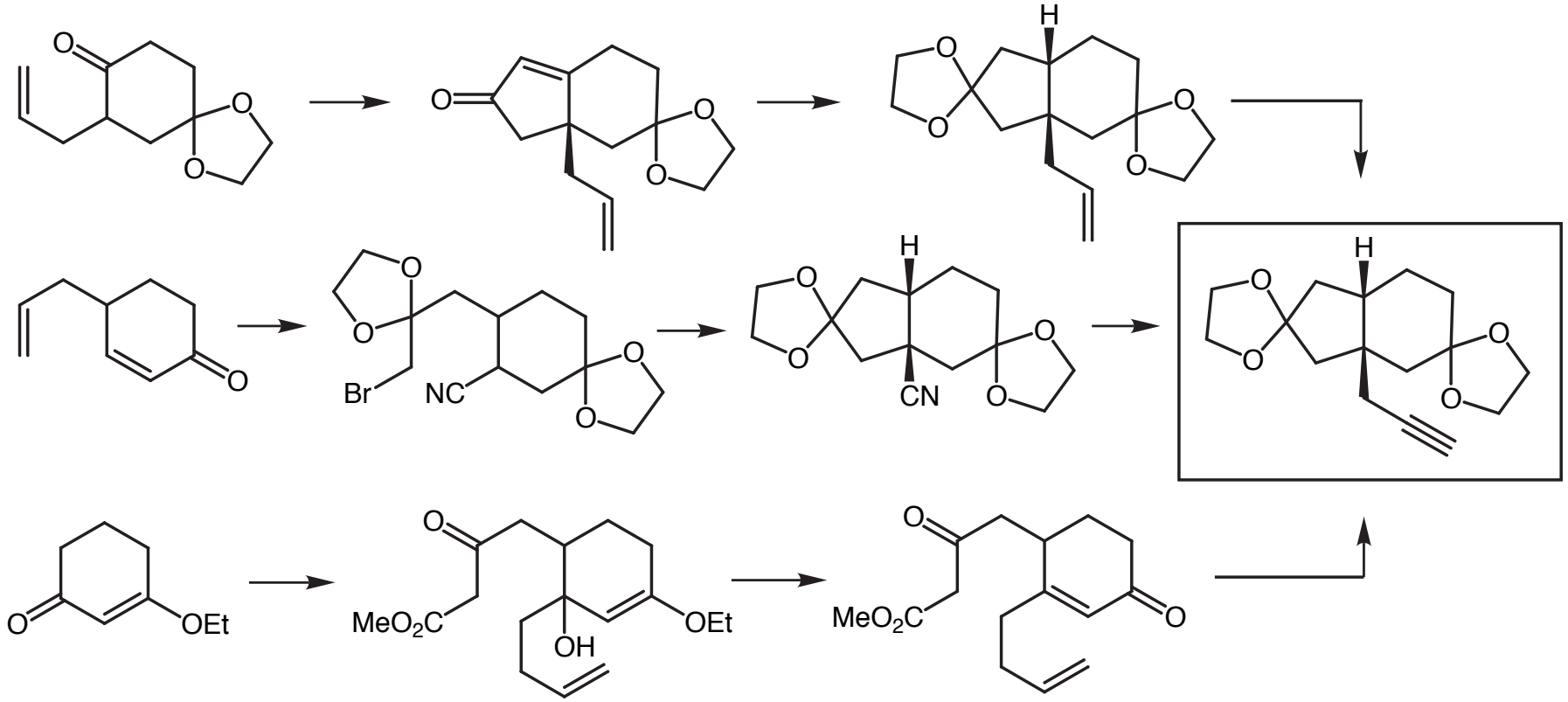
GA_{12}

Ihara, *JACS*, **2001**, 1856.

Stork D-ring Approach: Reductive Cyclization

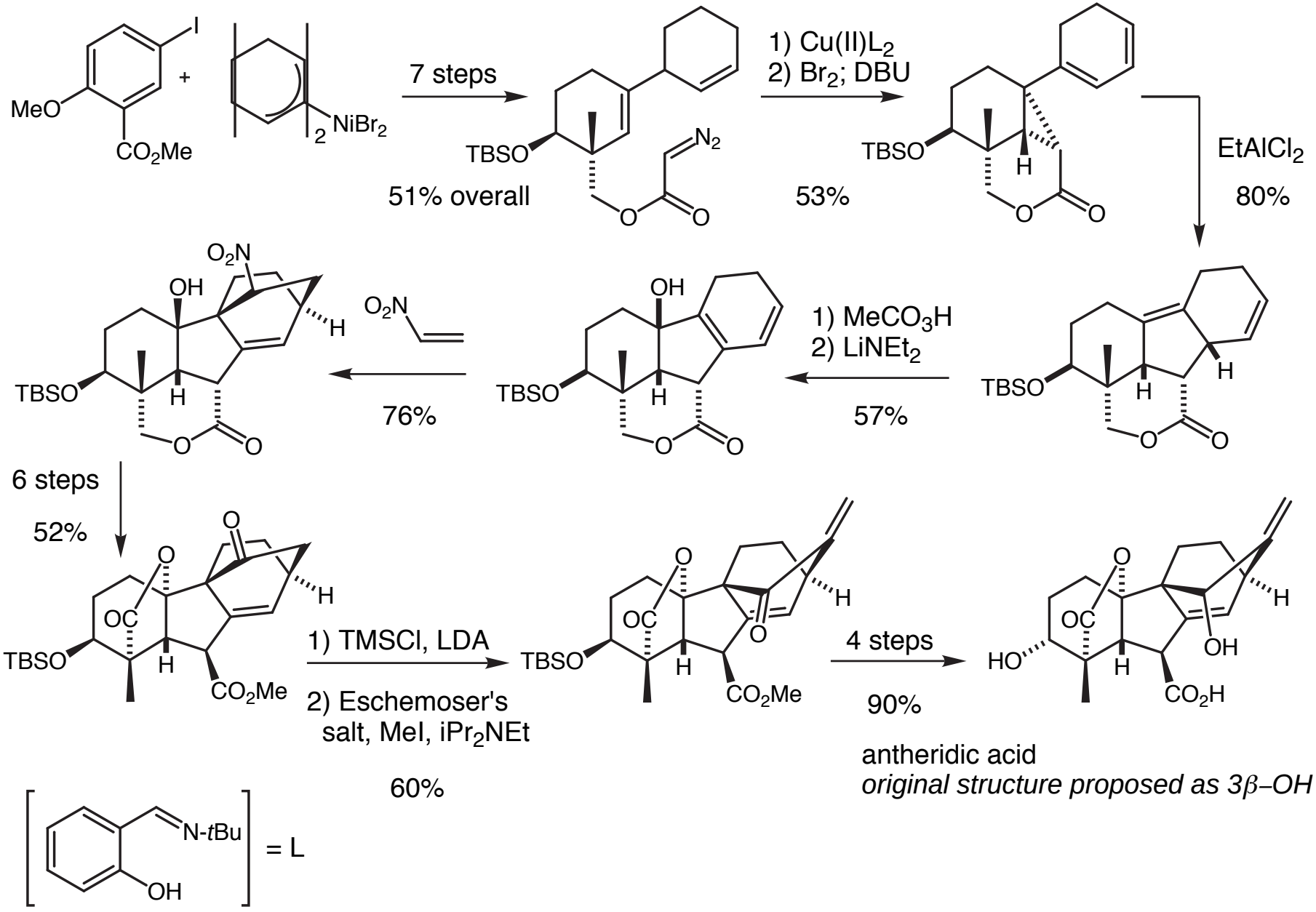


Three Routes to Bicycle:



Stork, *JACS,* **1979**, 7107.
Stork, *JACS,* **1965**, 1148.

Total Synthesis of Antheridic Acid: Corey

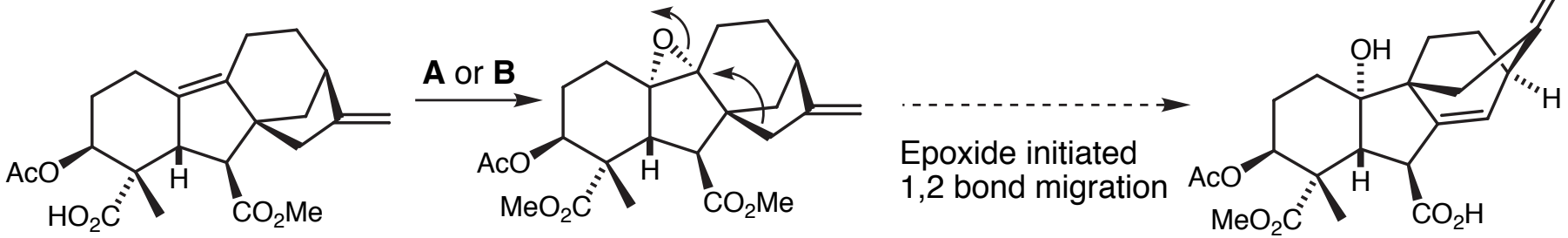


41-anteridiogens3-Corey.cdx 2/5/04 3:31 PM

Corey, Myers, *JACS,* **1985**, 5574.

Proposed Biomimmetic Synthesis of Antheridic Acid Investigated

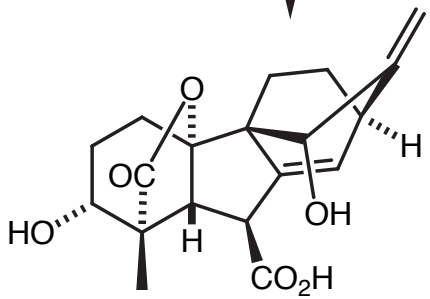
C9,10-epoxygibberellin



Desired Bond Migration could not beEffected

A) Im_2CO, H_2O_2 *intramolecular delivery*

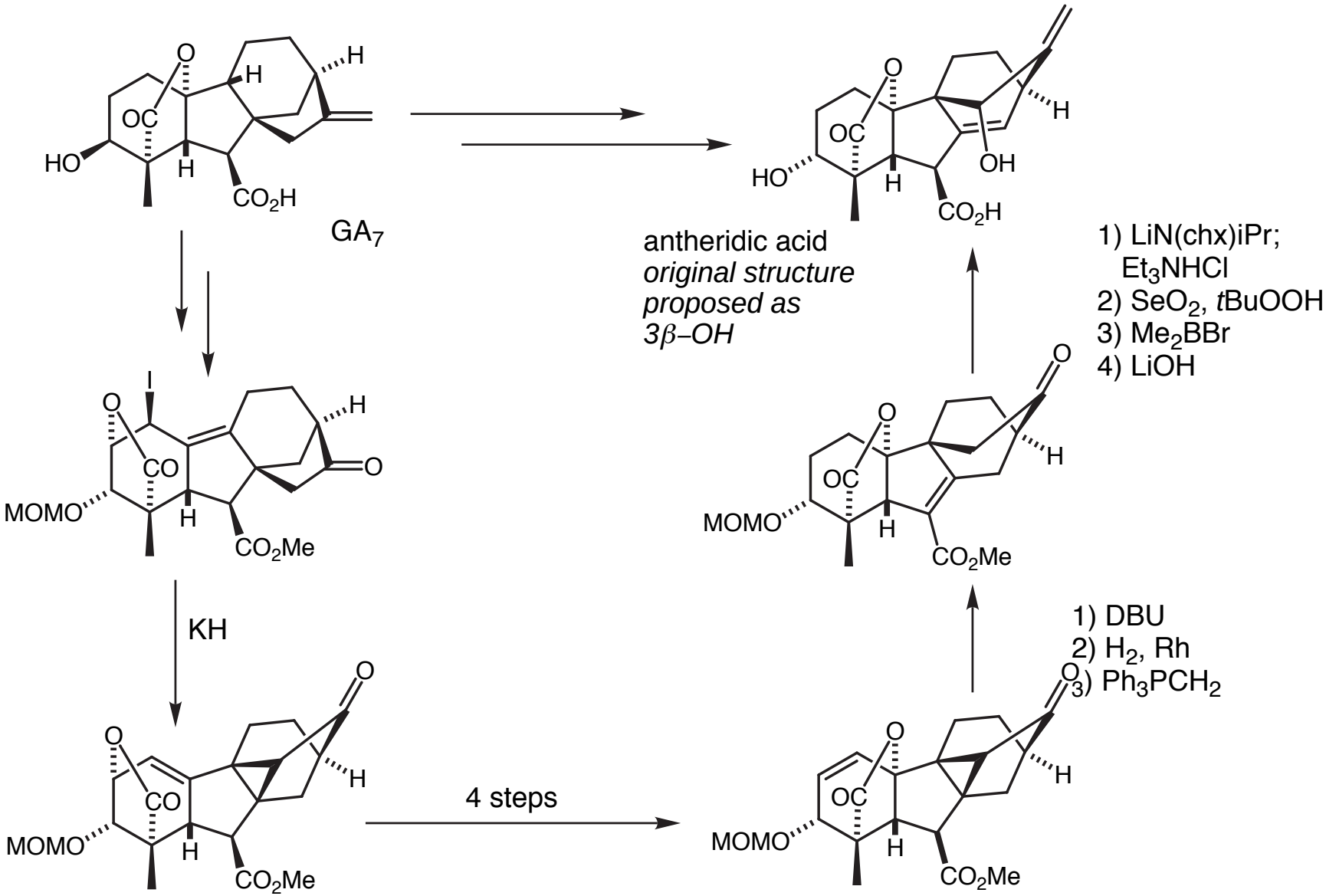
B) mCPBA ($k_{rel} < 10^{-2}$) *intermolecular*



antheridic acid
original structure proposed as 3β–OH

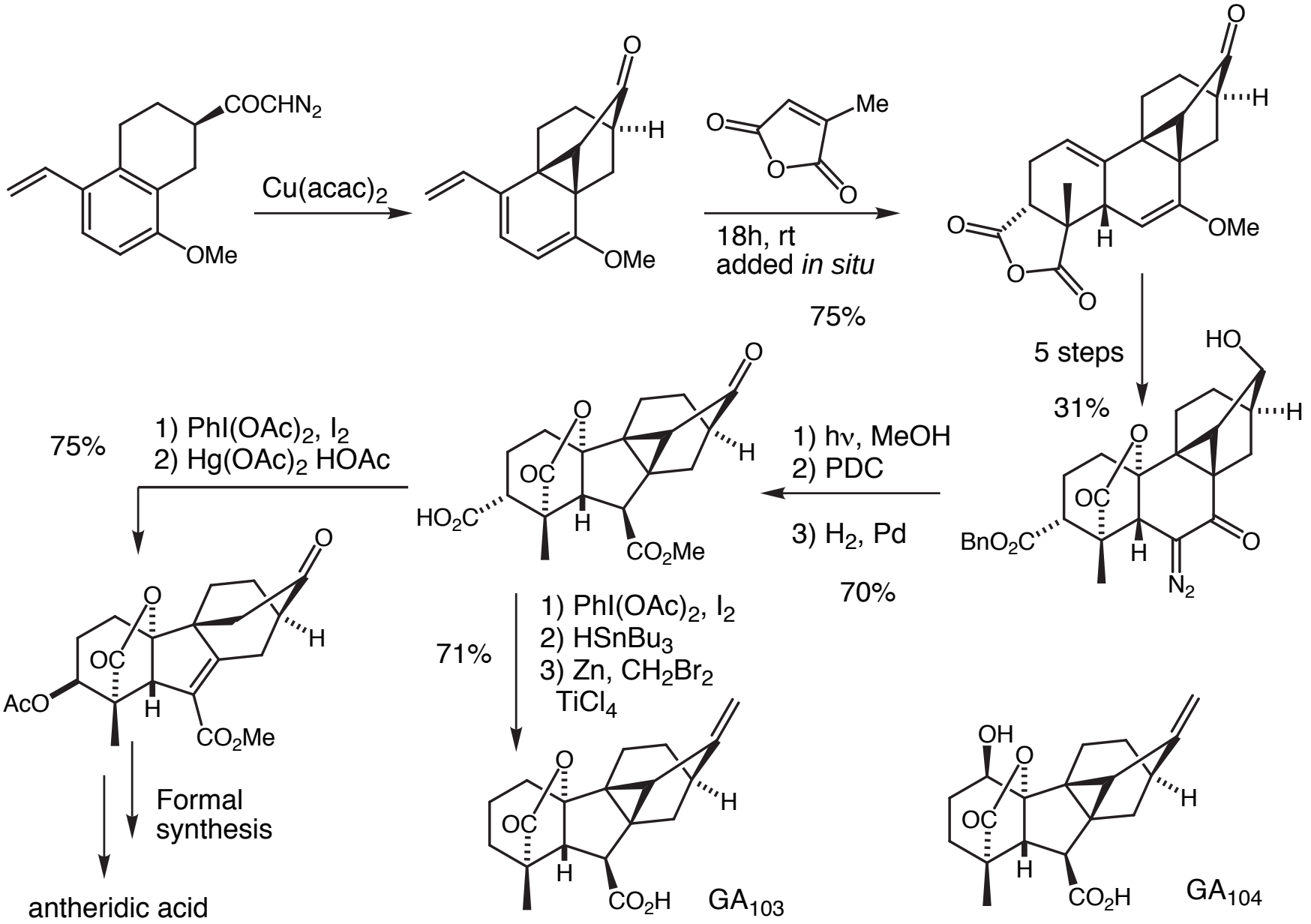
Mander, *JACS,* **1987**, 6839.

Conversion of GA_7 into Antheridic Acid



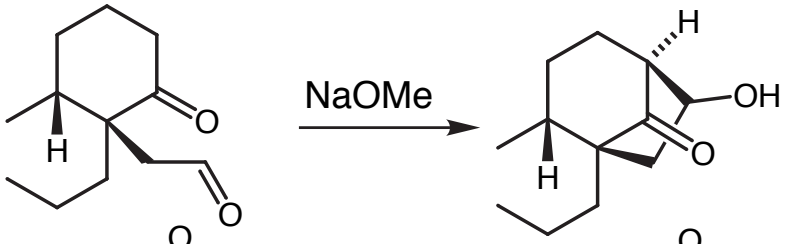
Mander, *JACS*, **1987**, 6839.

Synthesis of Antheridiogens: Mander

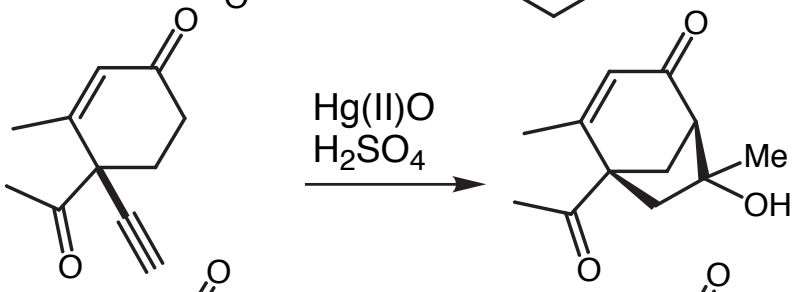


Mander, *JACS,* **1997**, 3828.

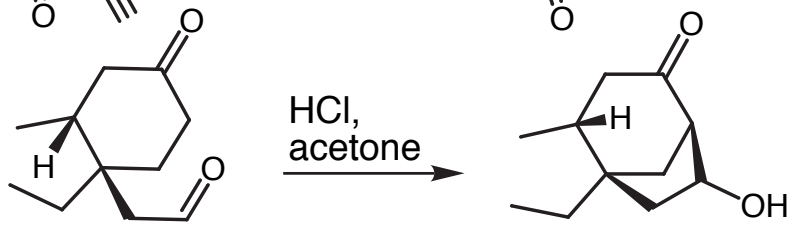
Aldol C/D Ring Strategies Not Discussed



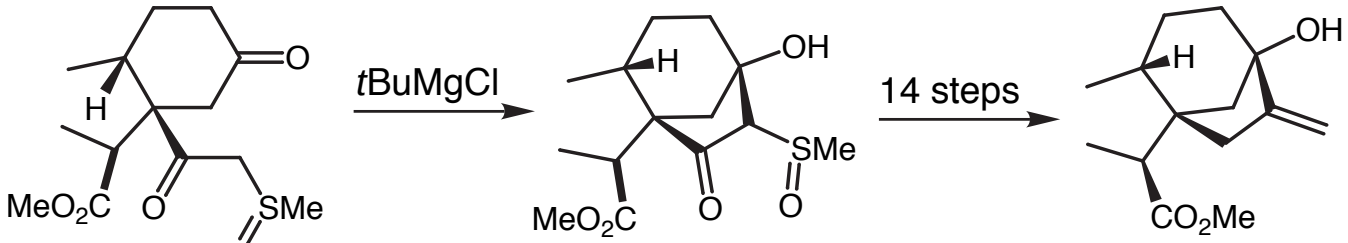
Ireland, *JOC,* **1966**, 2530. (toward kaurenes)



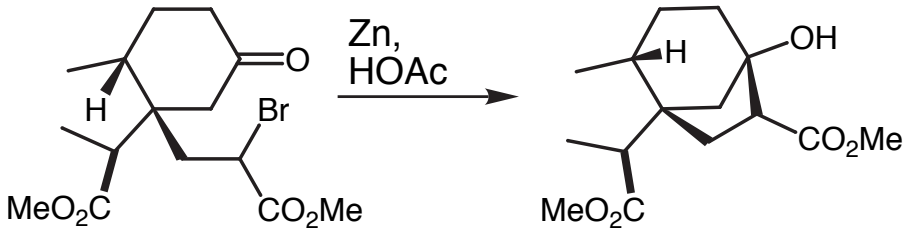
Takano, Ogasawara, *Chem. Com.,* **1981**, 635.



Takano, Ogasawara, *Chem. Com.,* **1981**, 637.

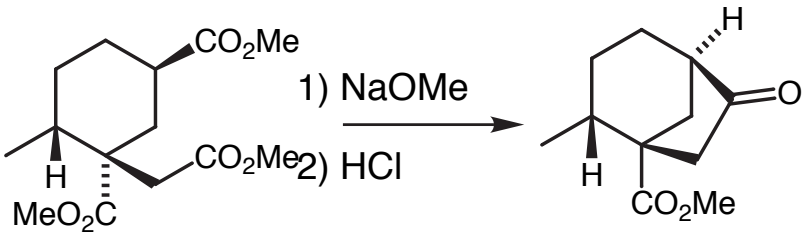


House, *JOC,* **1973**, 1398.

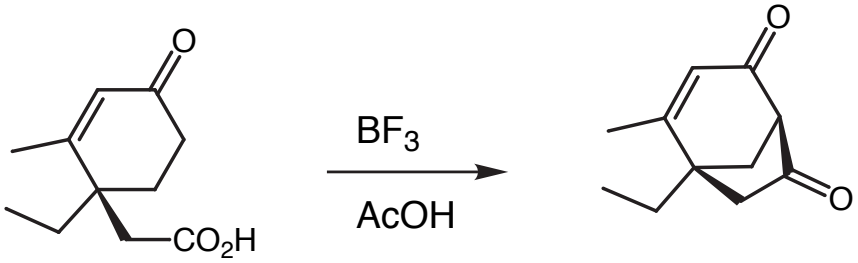


Ziegler, *JOC,* **1971**, 3707. (model system)

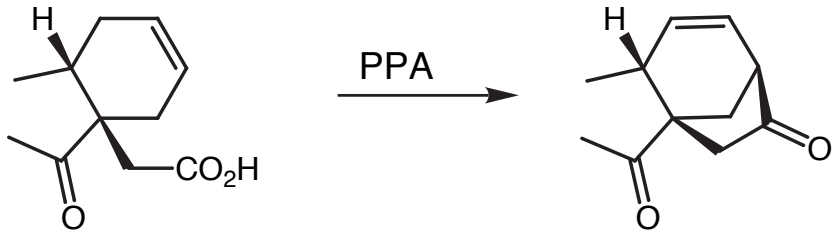
Acylation C/D Ring Strategies Not Discussed



Baker, *Chem. Com.,* **1971**, 180.

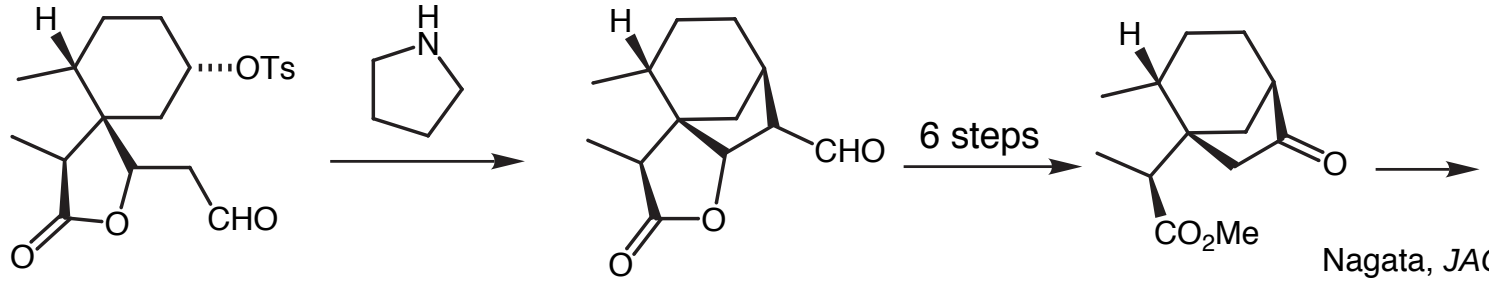


Lowenthal, *JCS Perkin I,* **1976**, 944.

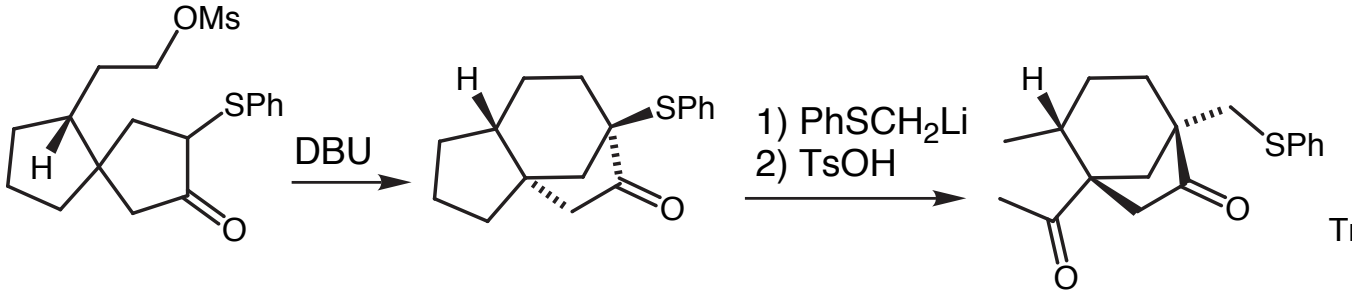


Jammaer, *Tet.,* **1975**, 2293.

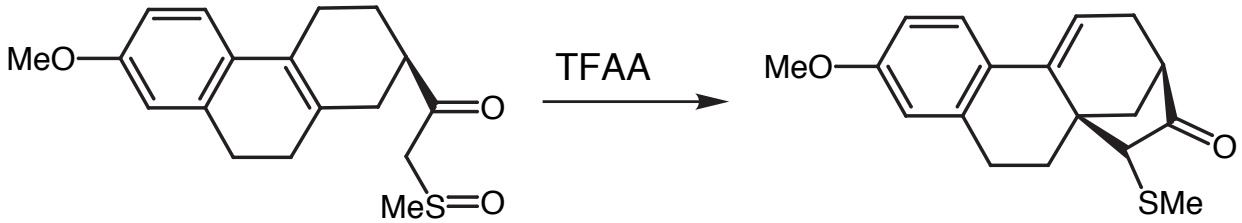
Alkylation C/D Ring Strategies Not Discussed



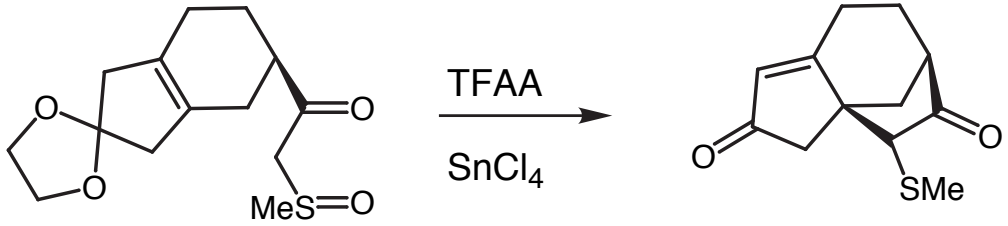
Nagata, *JACS,* **1972**, 4654.



Trost, *JOC,* **1978**, 1031.

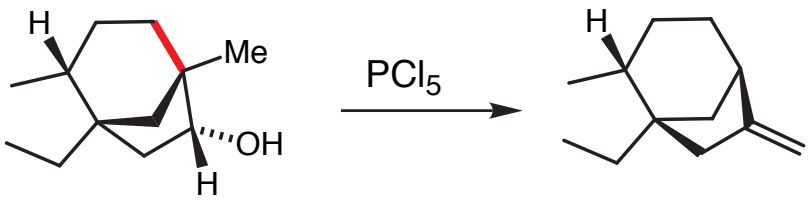


Mander, *Synthesis,* **1981**, 620.

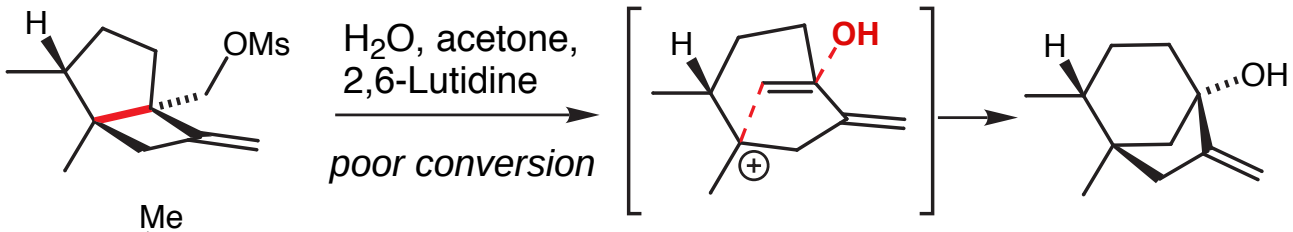


Barco, *Tet.,* **1989**, 3935.

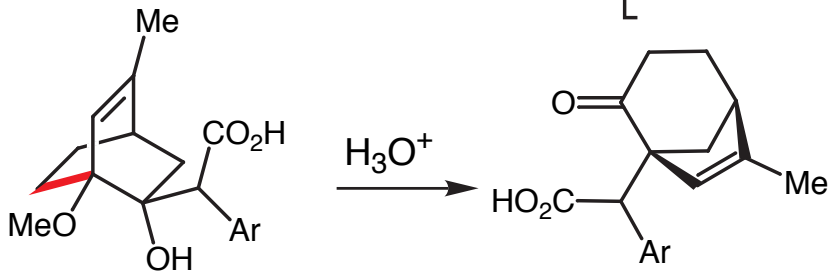
Rearrangement C/D Ring Strategies Not Discussed



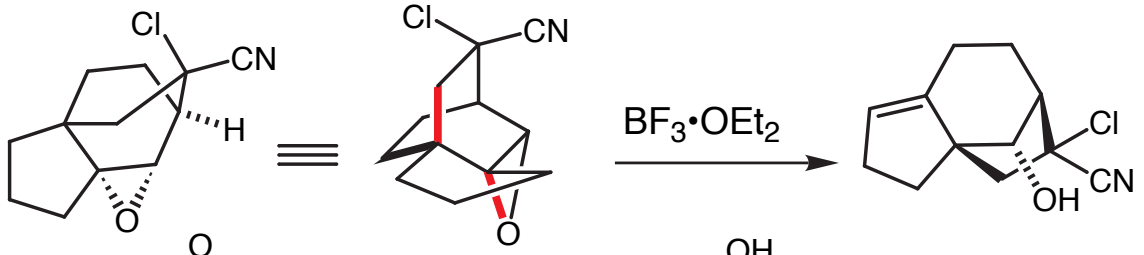
Cross, MacMillan, *JCS,* **1958**, 2520.



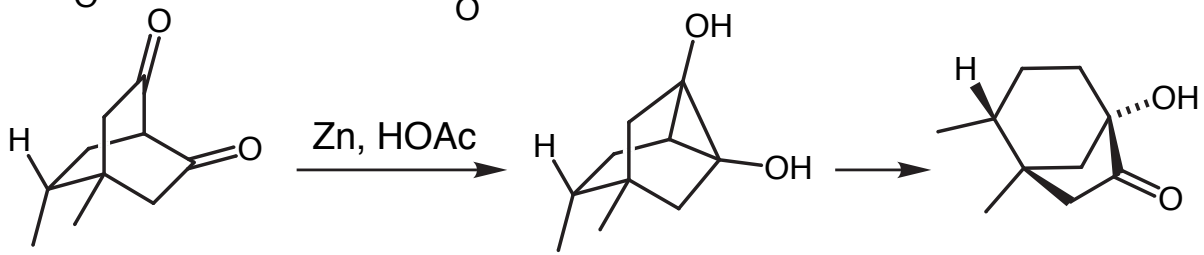
Ziegler, *Tet.,* **1977**, 373.



Monti, *JOC,* **1978**, 4062.

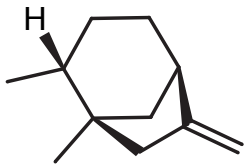


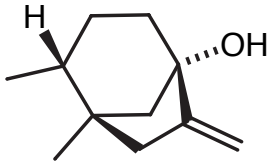
Yamada, *Synthesis,* **1977**, 581.

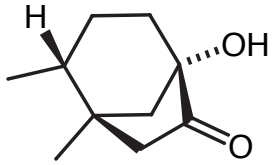


Mori, *Tet.,* **1972**, 3217.

A Summary of General C/D Ring Strategies







I) Reductive Ring Closure

II) Alkylation / Acylation

III) Aldol

IV) Carbenoid

V) Rearrangement / Fragmentation

"The problem of the synthesis of gibberellic acid has provided the impetus for the development of many new synthetic methods . . . " Corey