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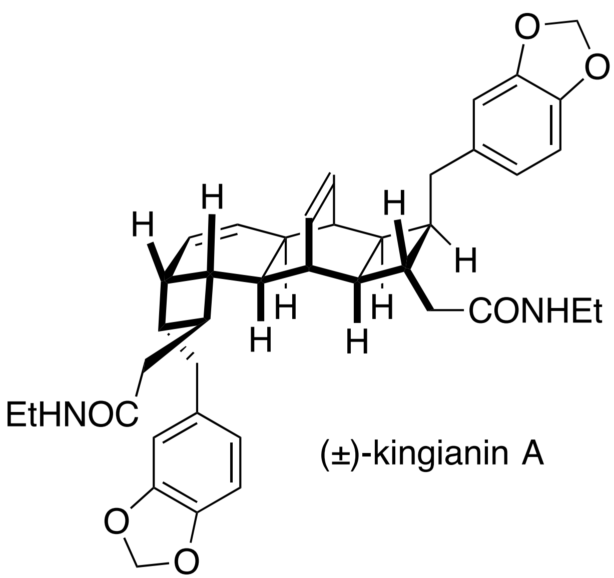
Universität Bern

Journal Club/ Literature Presentation

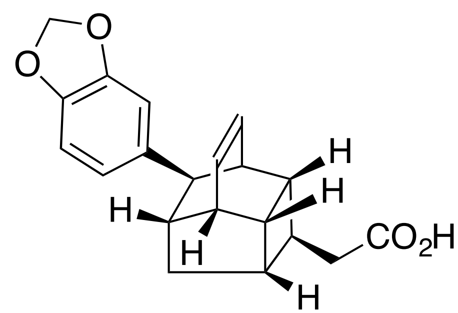
December 3rd 2015

UNIVERSITÄT BERN

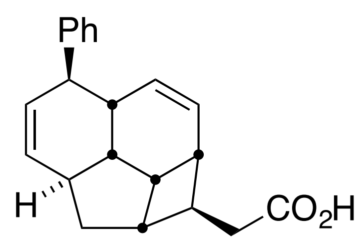
Unified total synthesis of the natural products endiandric acid A, kingianic acid E, and kingianins A, D, and F



(±)-kingianin A



(±)-kingianic acid E

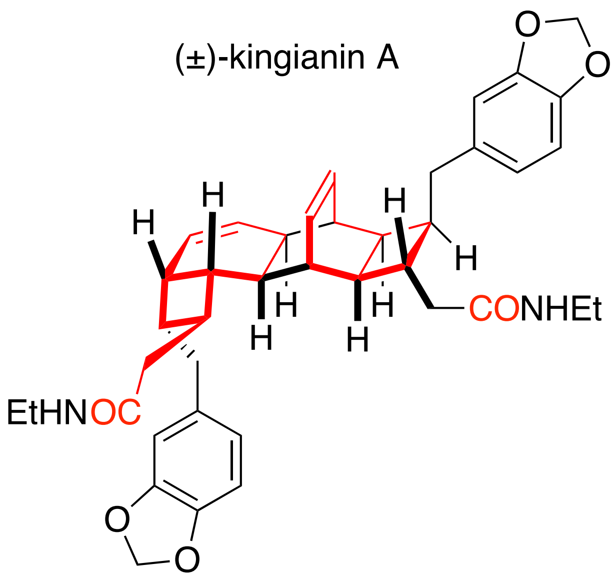


(±)-endiandric acid A

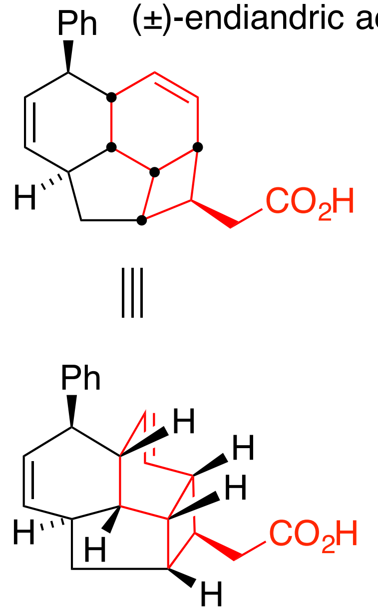
Drew, S. L.; Lawrence, A. L.; Sherburn, M. S. *Chem. Sci.* **2015**, *6* (7), 3886–3890.
Drew, S. L.; Lawrence, A. L.; Sherburn, M. S. *Angew. Chem. Int. Ed.* **2013**, *52* (15), 4221–4224.

Common structural motifs

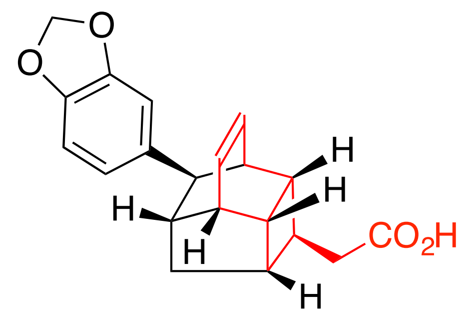
(±)-kingianin A



(±)-endiandric acid A



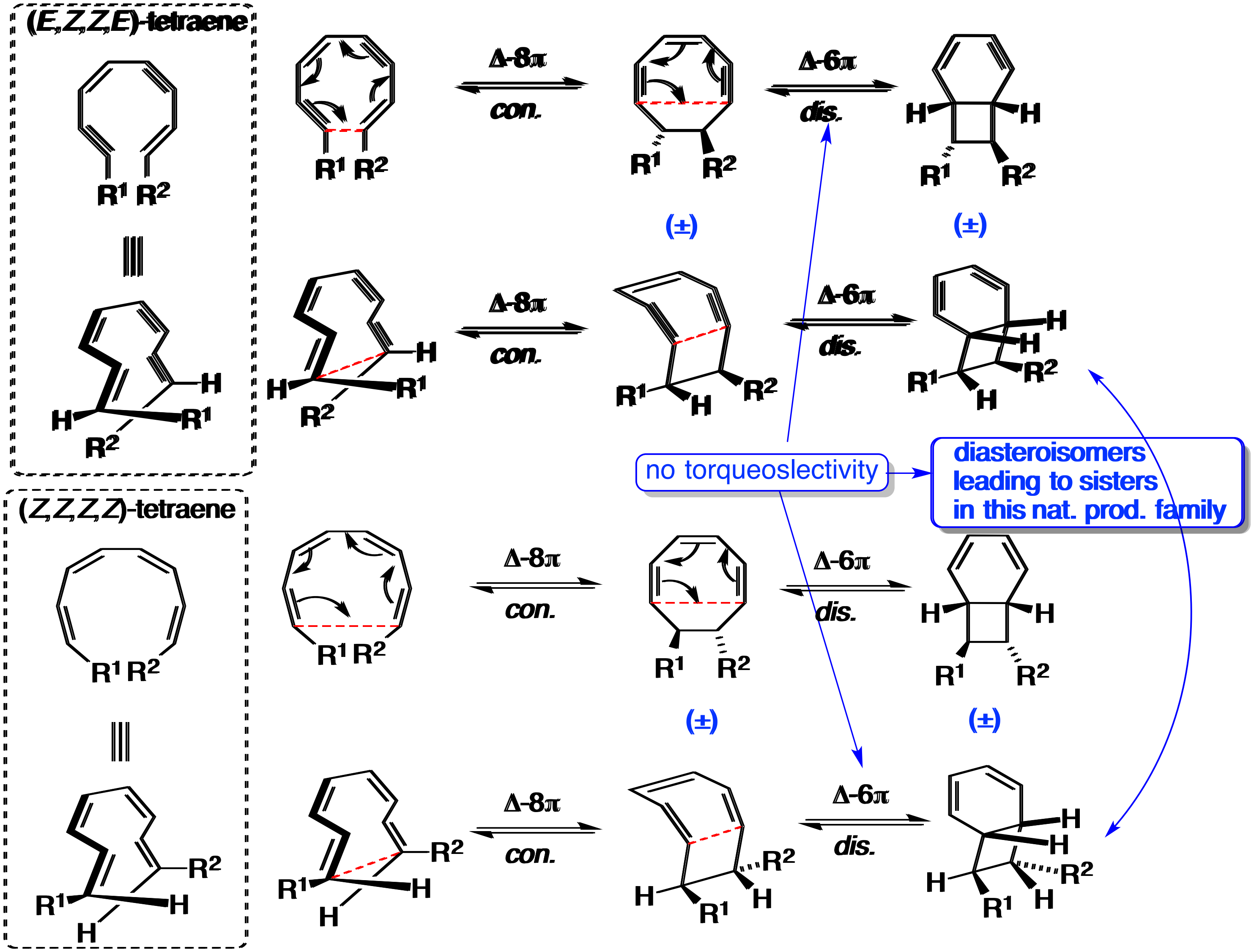
(±)-kingianic acid E



- Very packed *fused polycyclic* system: think high *DBE*: think *electrocyclization*

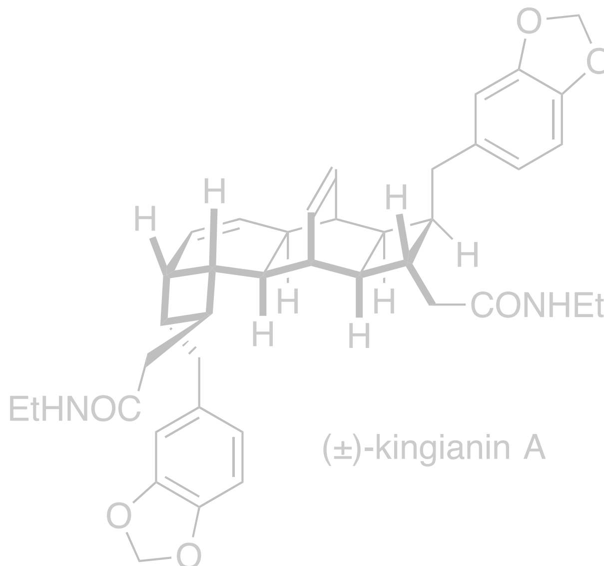
- Identified common structural element, bicyclo[4.2.0]octene,
for a unified total synthesis

Postulated biosynthesis: cascade electrocyclization/ Black-Banfield hypothesis

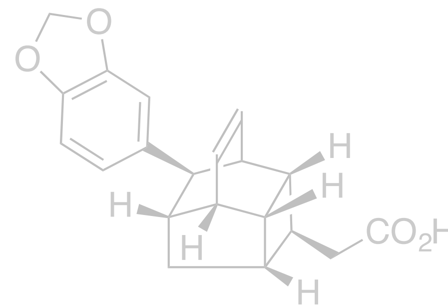


Bandaranayake, W. M.; Banfield, J. E.; Black, D. S. C. *J. Chem. Soc., Chem. Commun.* **1980**, No. 19, 902–903.
And refs [5b-5f] in ACIE paper.

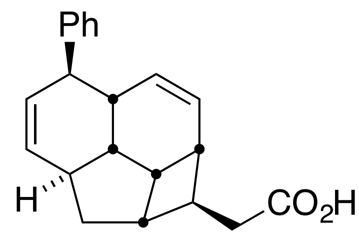
Endiandric acids



(±)-kingianin A

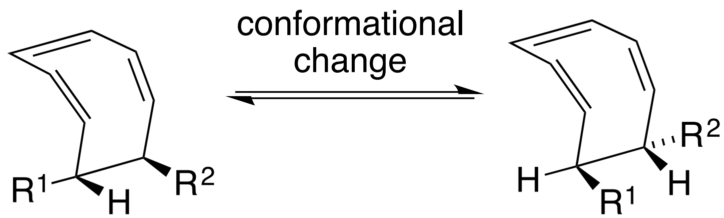


(±)-kingianic acid E



(±)-endiandric acid A

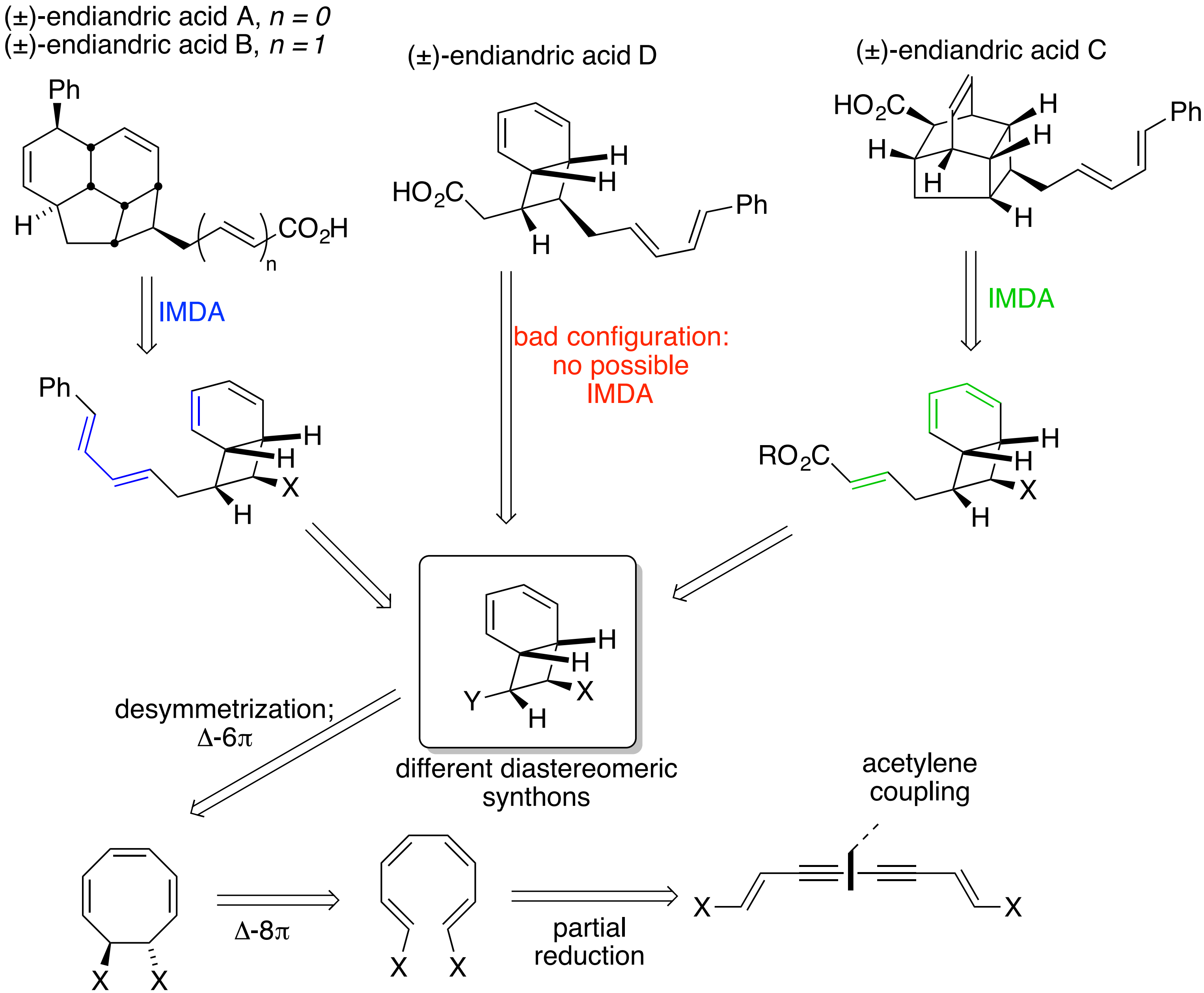
Exploring the cascade: exploiting lack of selectivity



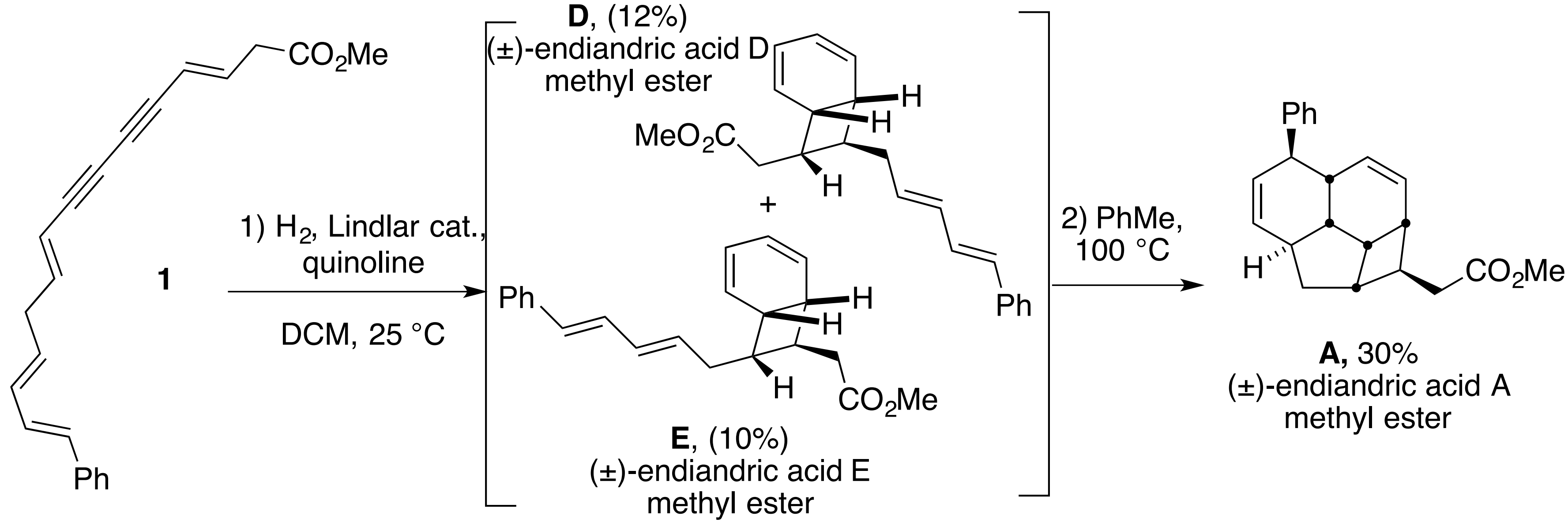
Energy to ringflip lower than pericyclic reaction and reversible.
No way to control diastereoselectivity using a biomimetic pathway (except tethers, etc.)

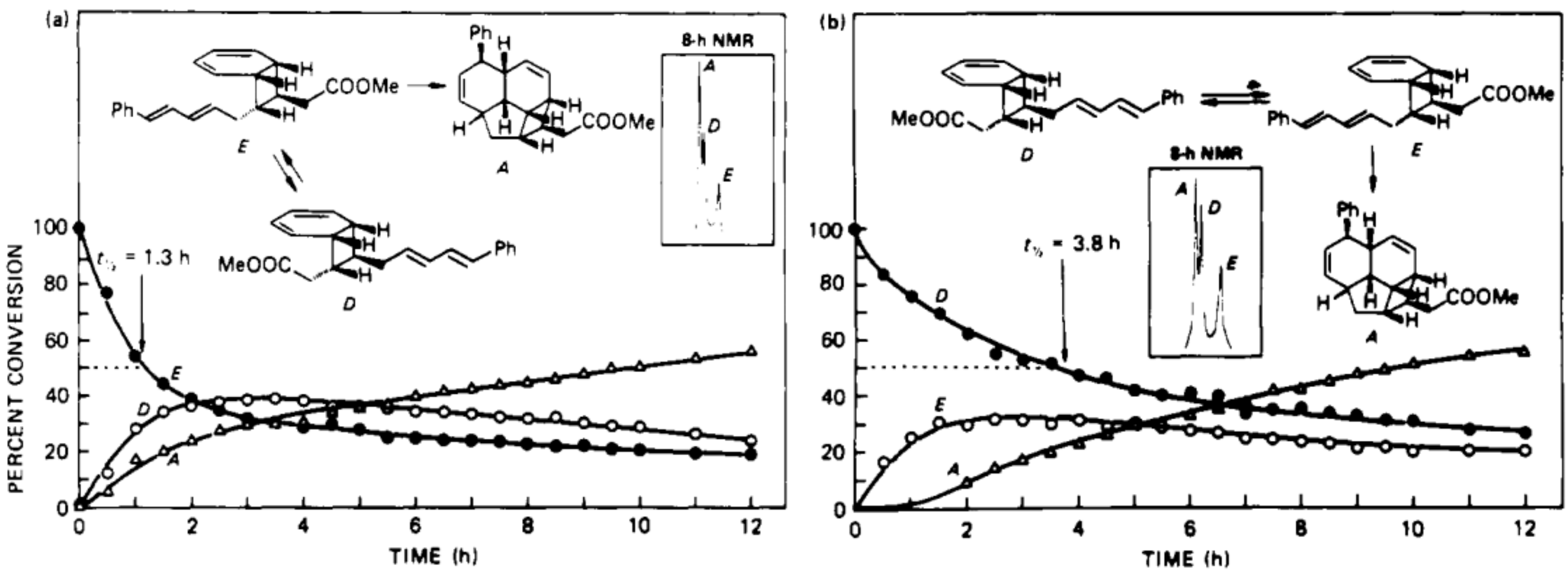
Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104* (20), 5555–5557.
Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104* (20), 5557–5558.
Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.* **1982**, *104* (20), 5558–5560.
Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104* (20), 5560–5562.

Nicolaou's Biomimetic Retrosynthesis

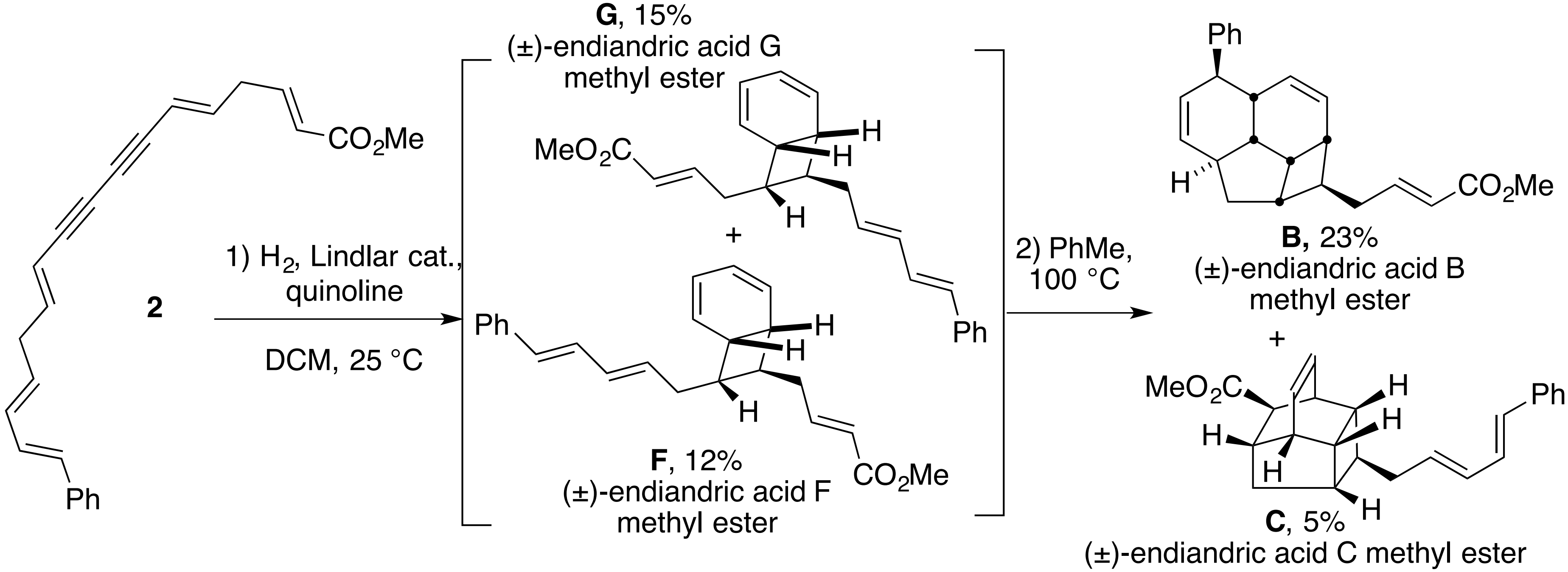


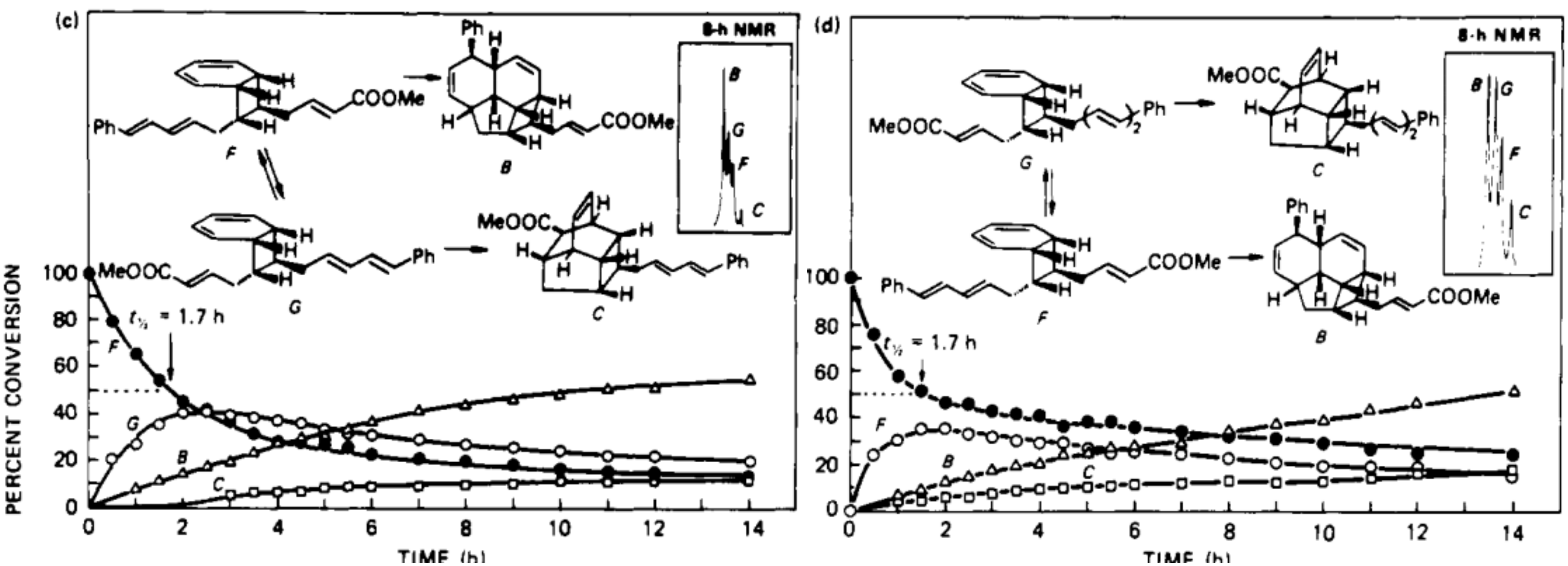
Nicolaou's one-pot hydrogenation/8π/6π/IMDA of 1



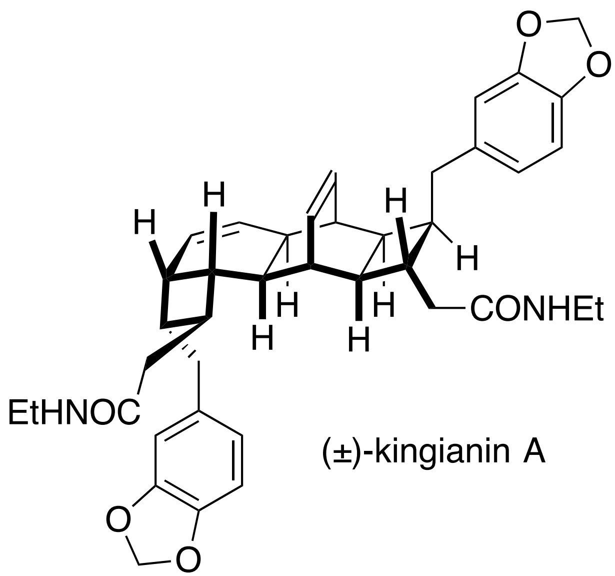


Nicolaou's one-pot hydrogenation/8π/6π/IMDA of 2

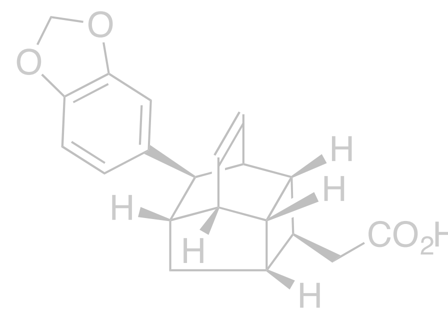




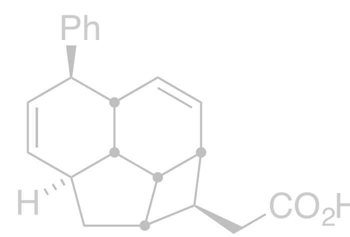
Kingianins



(±)-kingianin A

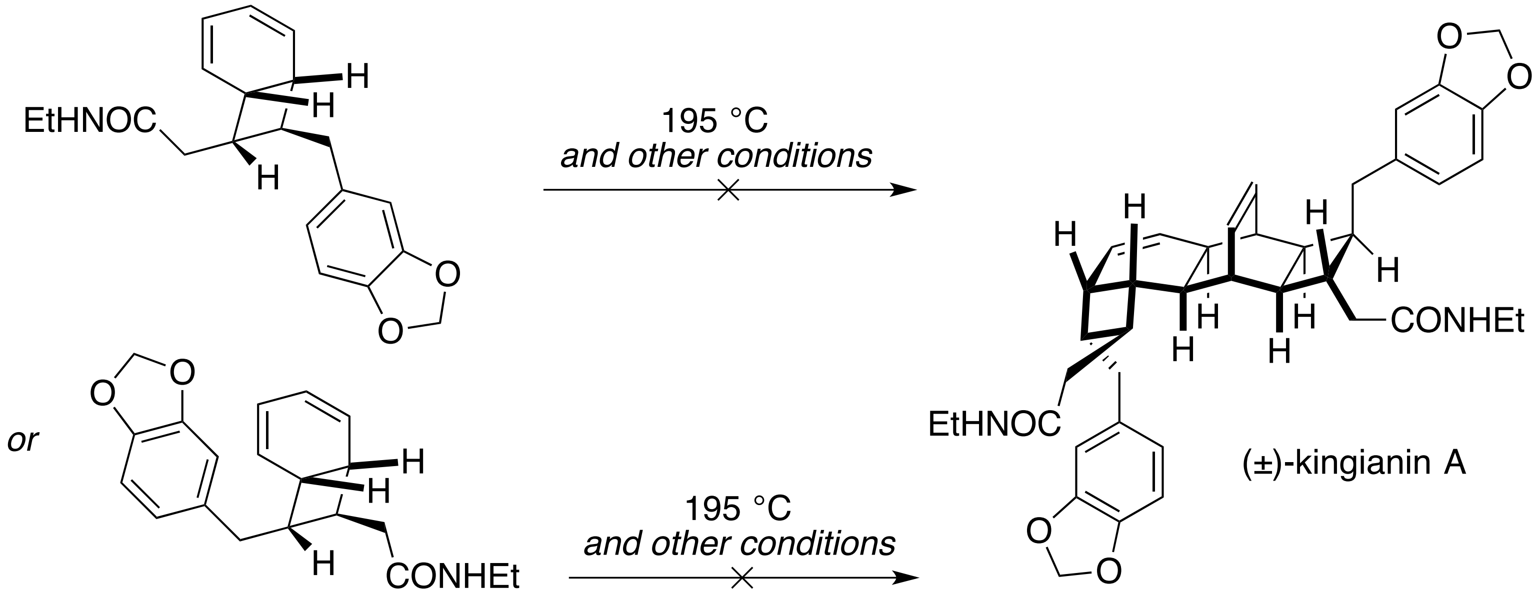


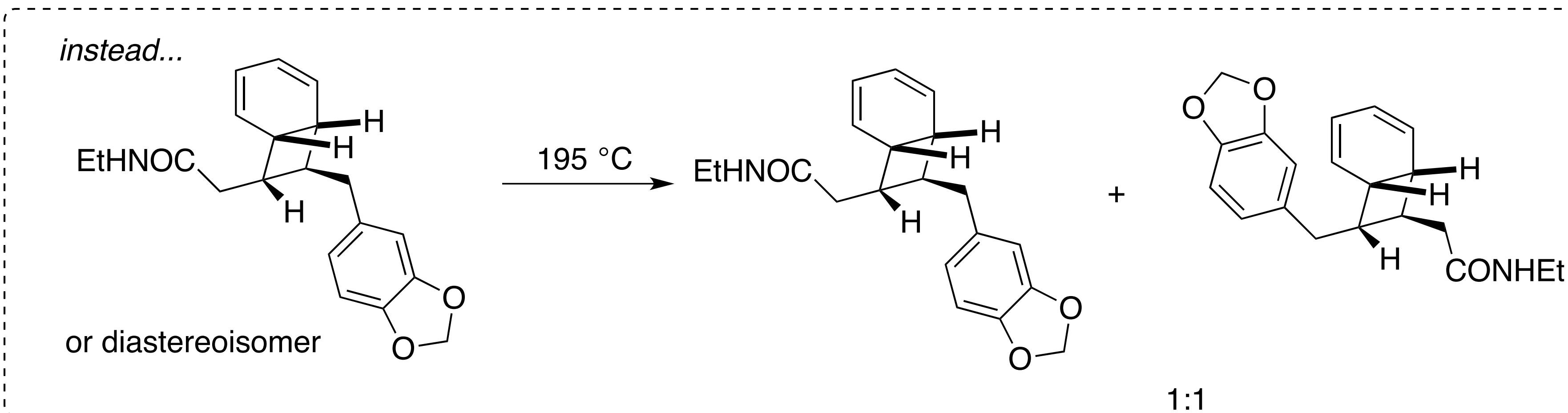
(±)-kingianic acid E



(±)-endiandric acid A

Moses' studies towards kingianins: not thermal DA dimerization

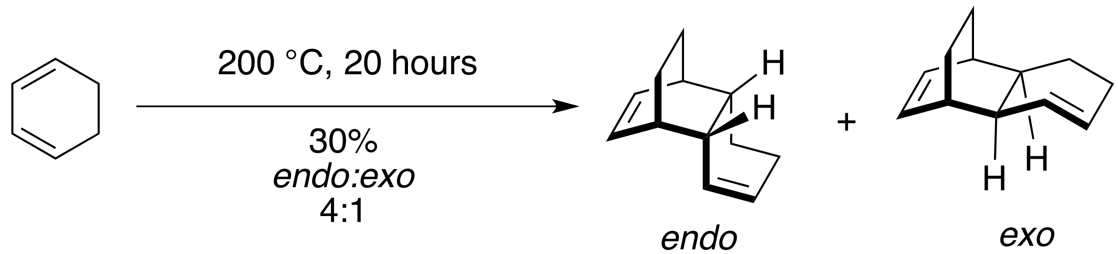




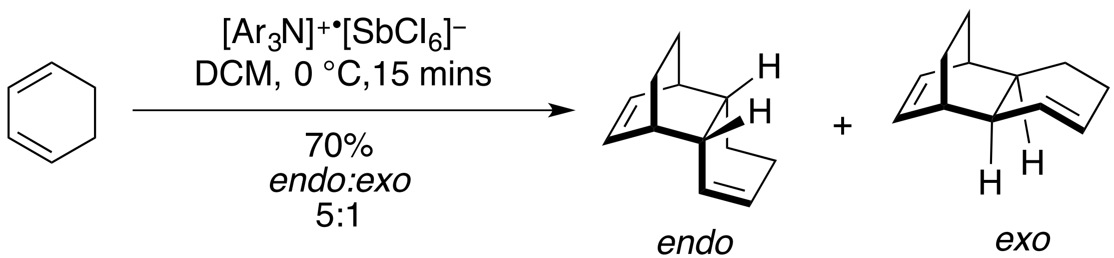
Equilibrating mix via retro-6π electrocyclization, ringflip, and 6π electrocyclization

Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem. Commun.* **2011**, *47* (38), 10605.

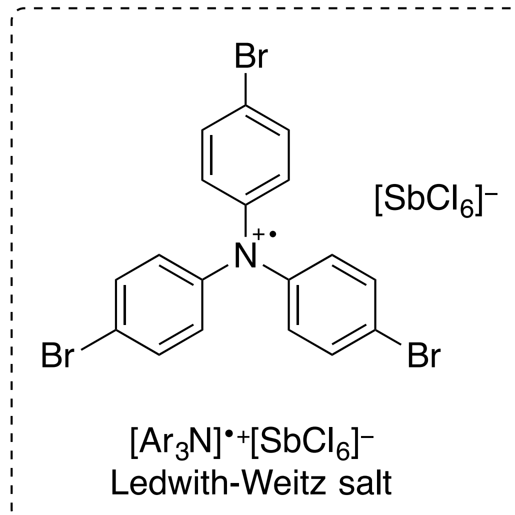
Bauld's radical cation hexadiene dimerization



Valentine, D.; Turro, N. J.; Hammond, G. S. *J. Am. Chem. Soc.* **1964**, *86* (23), 5202–5208.

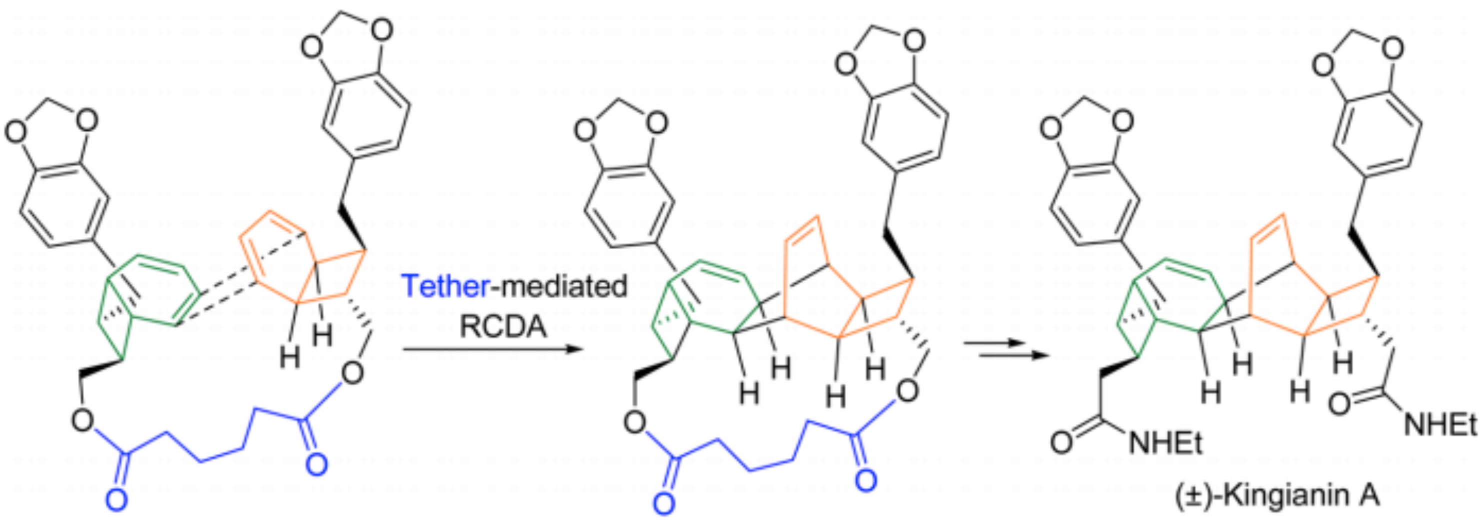


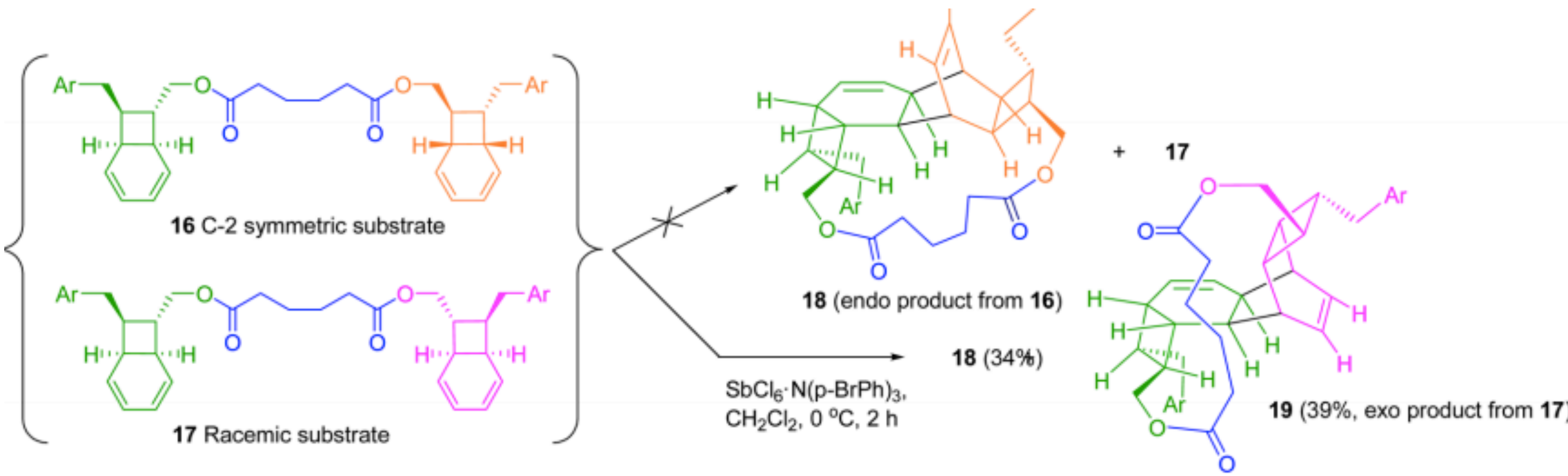
Bellville, D. J.; Wirth, D. W.; Bauld, N. L. *J. Am. Chem. Soc.* **1981**, *103* (3), 718–720.



Bell, F. A.; Ledwith, A.; Sherrington, D. C. *J. Chem. Soc., C* **1969**, 2719.

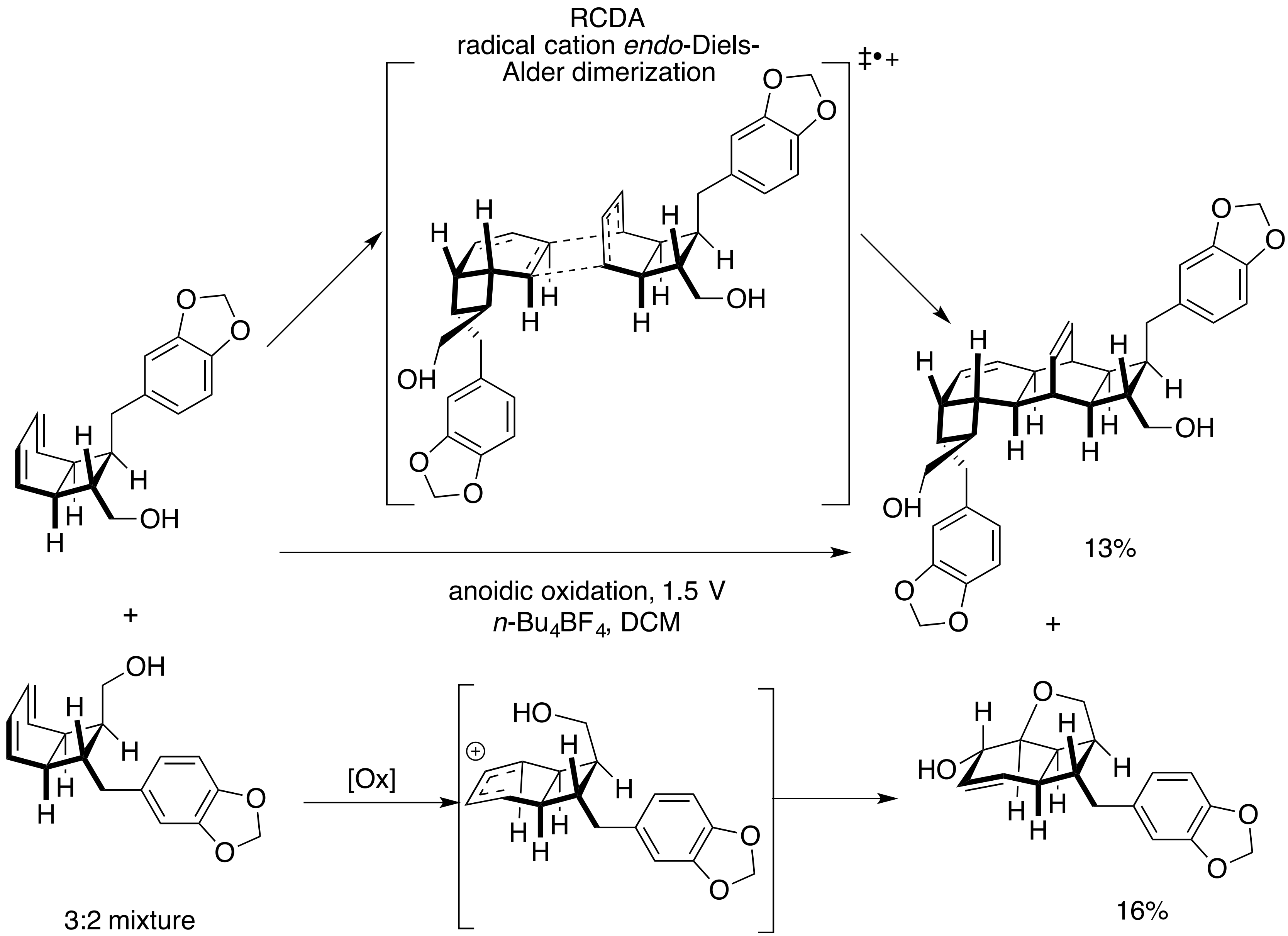
Parker's tethered-RCDA approach





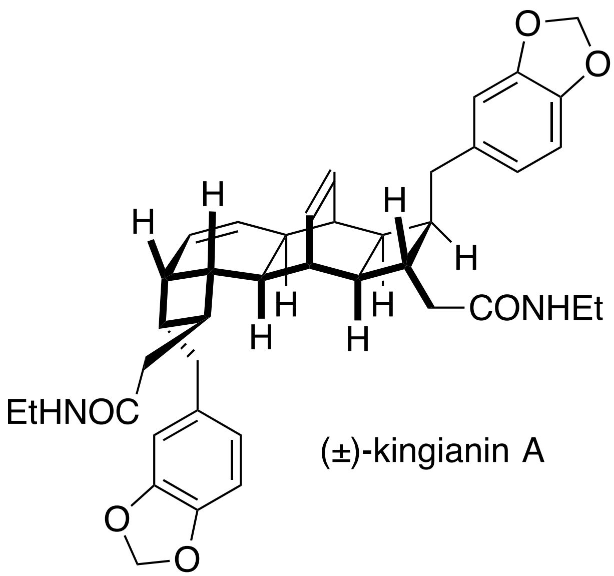
Lim, H. N.; Parker, K. A. *Org. Lett.* **2013**, *15* (2), 398–401.
Lim, H. N.; Parker, K. A. *J. Org. Chem.* **2014**, *79* (3), 919–926.

Moses’ take two

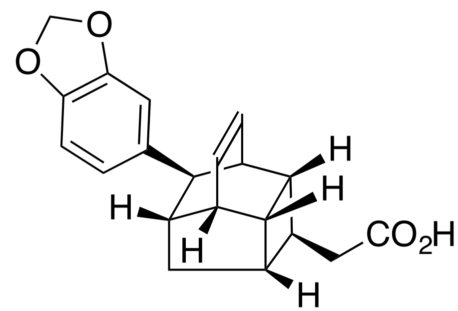


Moore, J. C.; Davies, E. S.; Walsh, D. A.; Sharma, P.; Moses, J. E. *Chem. Commun.* **2014**, *50* (83), 12523–12525.

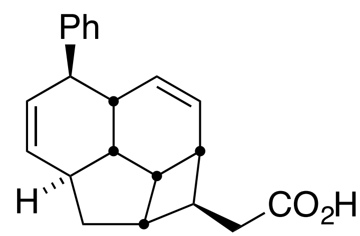
The three families: Sherburn



(±)-kingianin A

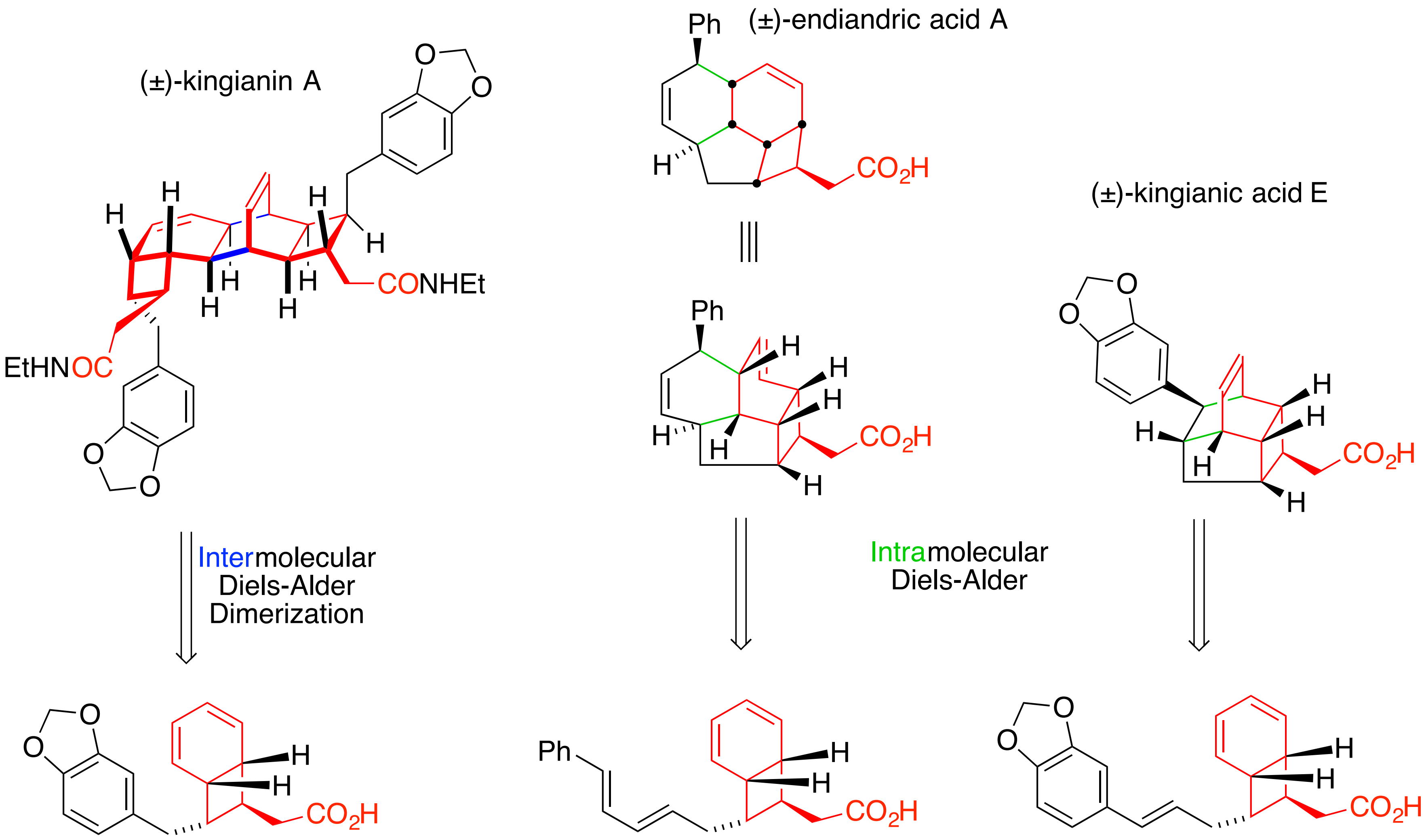


(±)-kingianic acid E

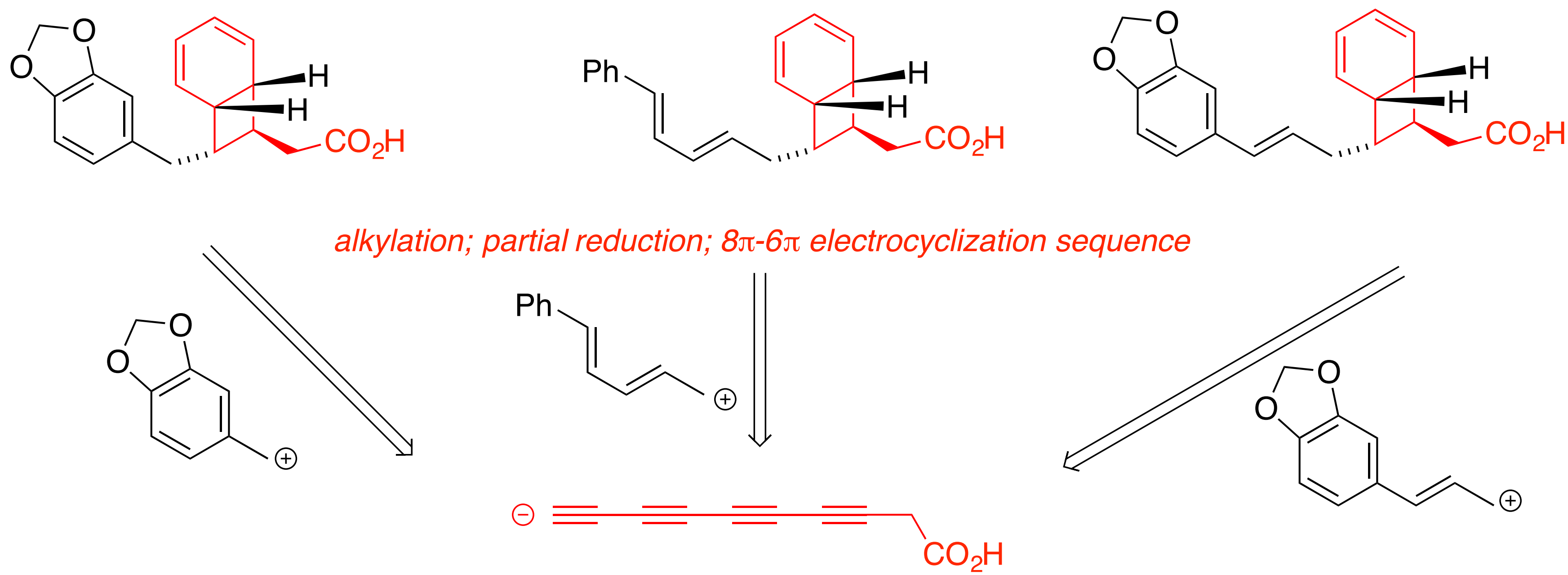


(±)-endiandric acid A

Retrosynthetic analysis: revealing the motif



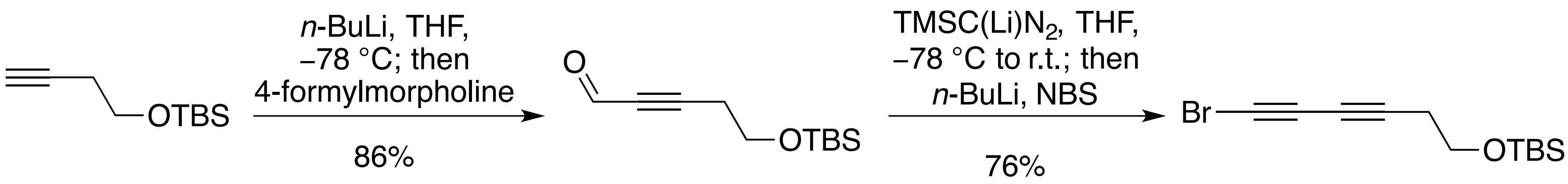
Retrosynthetic analysis: finding the common intermediate

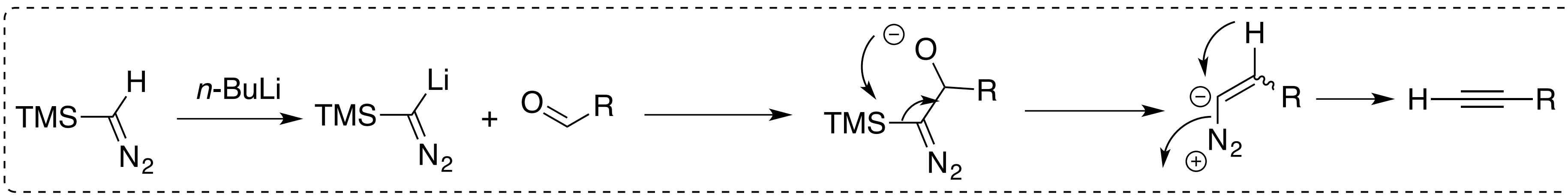


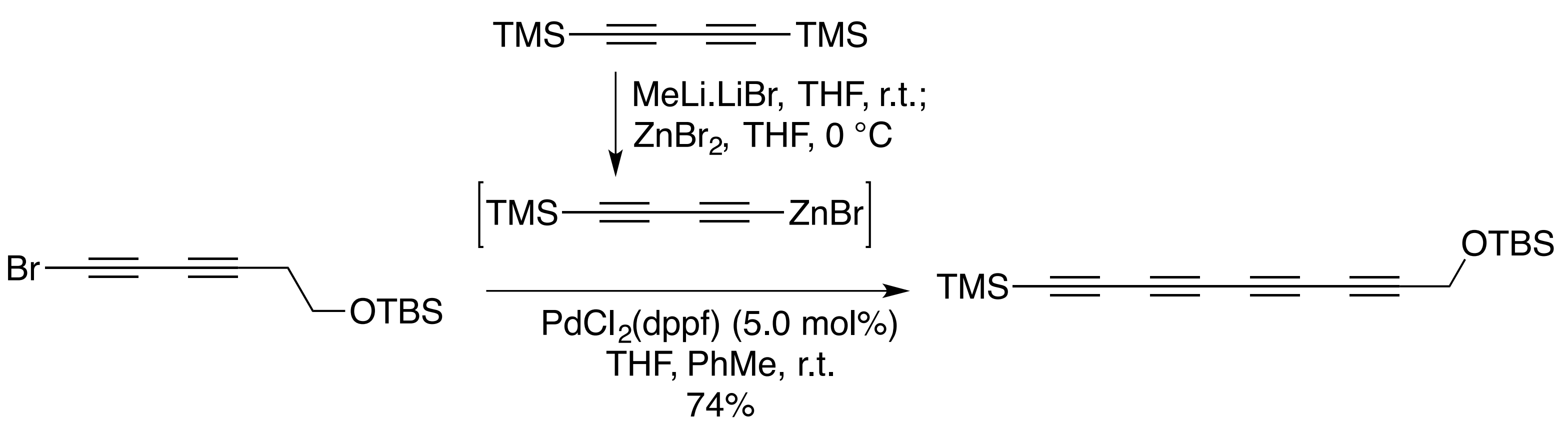
- Very packed *fused polycyclic* system: think high *DBE*: think *electrocyclization*

- Identified common structural element, bicyclo[4.2.0]octene, for a unified total synthesis

Sherburn: forward synthesis

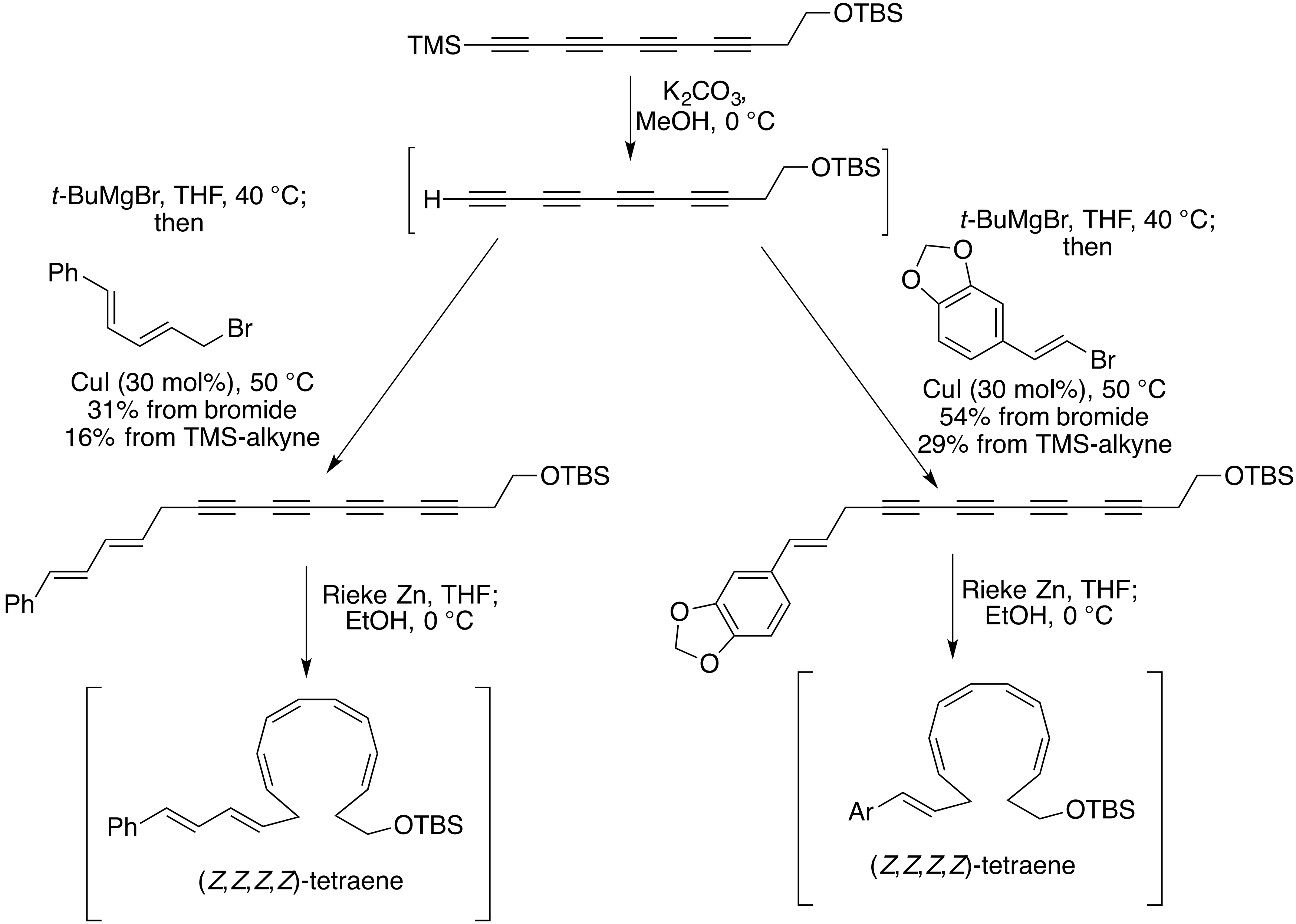




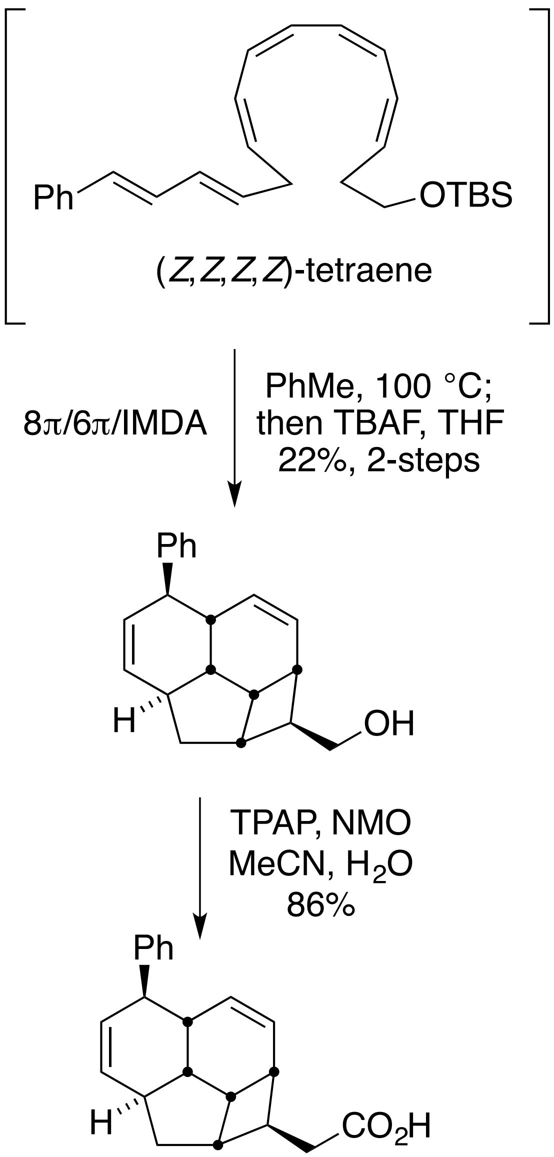


Formylation of alkynes via lithium acteylides using a) DMF: Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**., or b) N-formylmorpholine: Sneddon, H. F.; Gaunt, M. J.; Ley, S. V. *Org. Lett.* **2003**, *5* (7), 1147–1150. Colvin alkyne homologation: Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869–874.

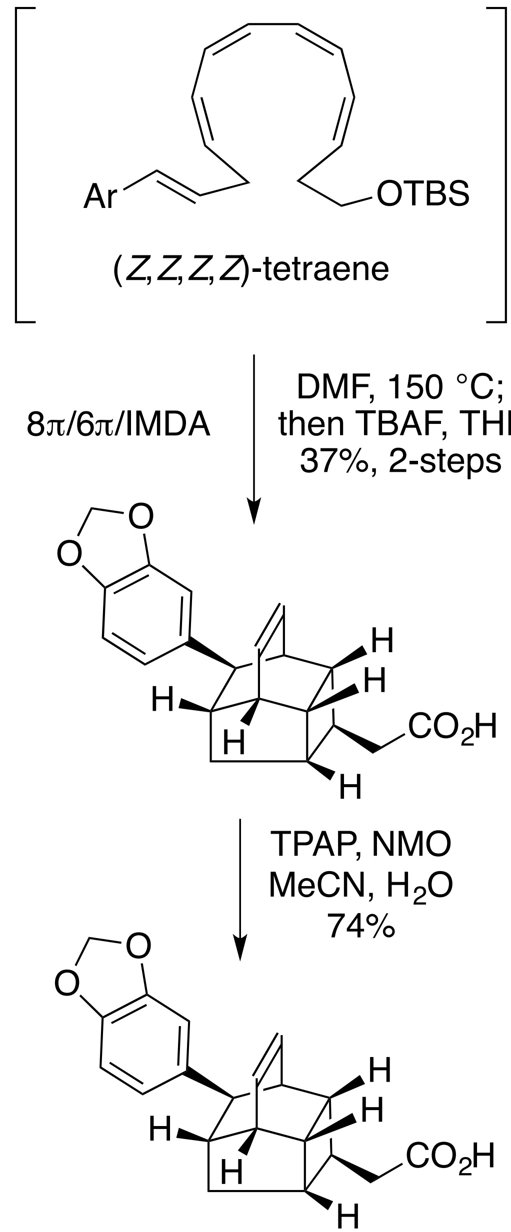
Sherburn: forward synthesis



Sherburn: forward synthesis

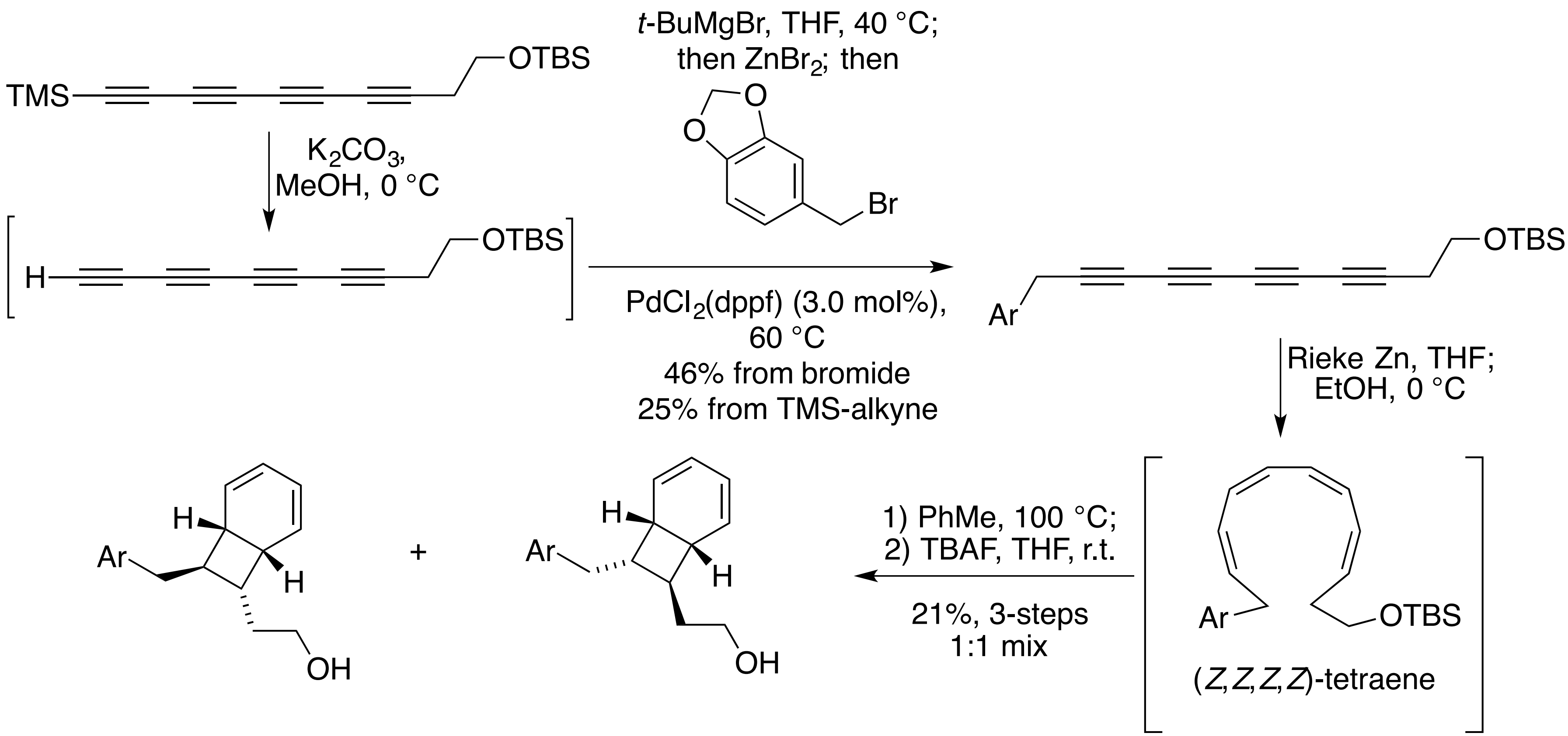


(±)-endiandric acid A

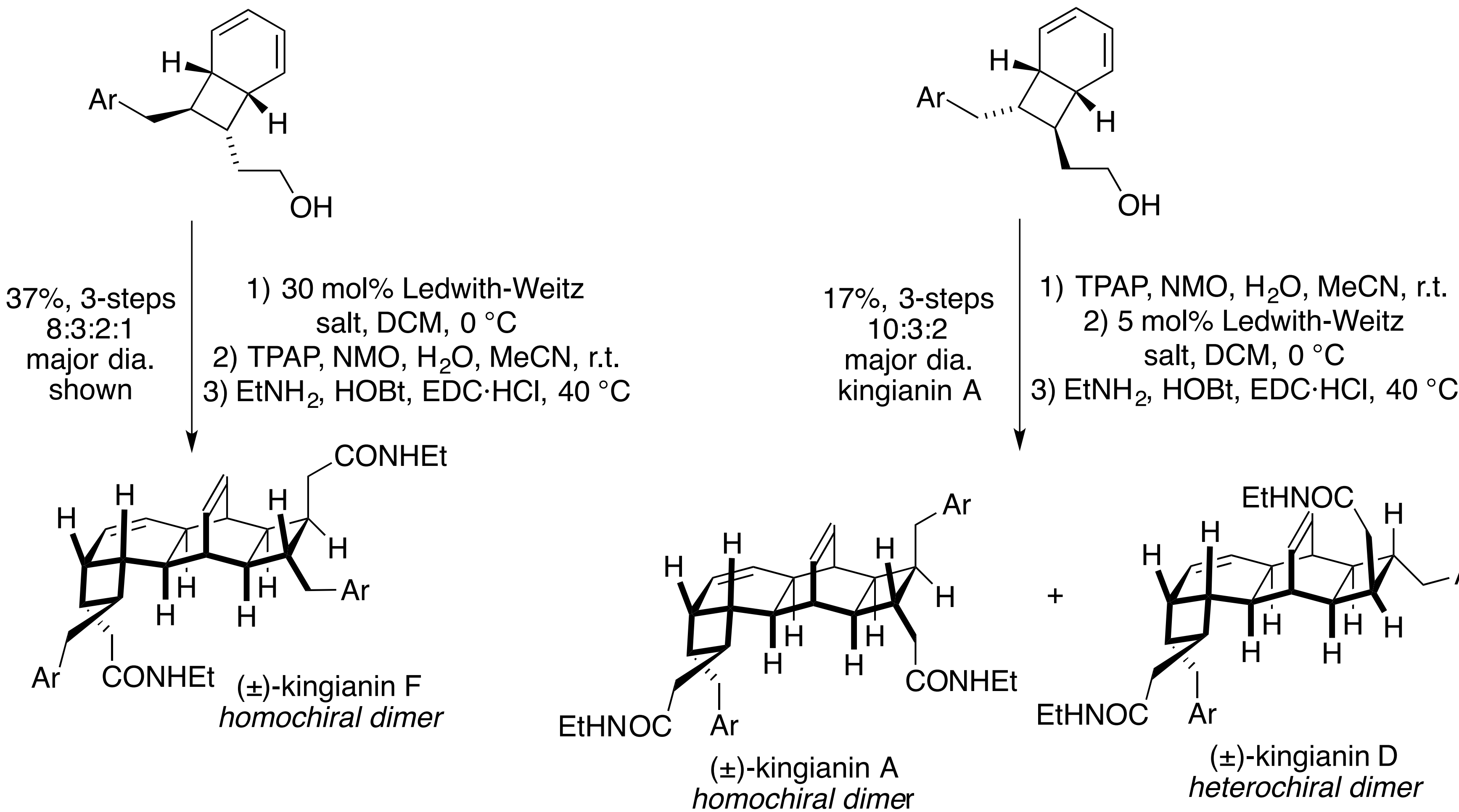


(±)-kingianic acid E

Sherburn: forward synthesis



Sherburn: forward synthesis

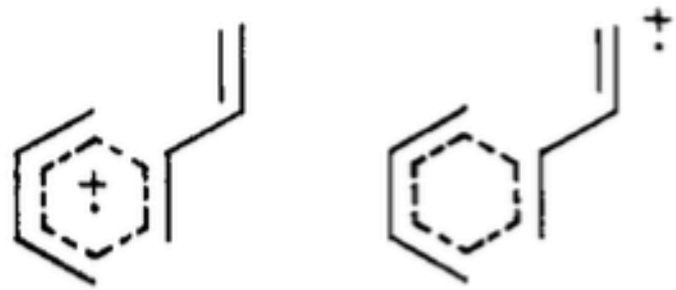


Conclusions

- Sherburn's strategy gives controlled access to 3 different families of nat. prods. from a common intermediate
- Unusal and unprecedented *Z,Z,Z,Z*-tetraene synthesized from
- Unusual tetrayne which can undergo some unprecedented tramsofrmations
- *Z,Z,Z,Z*-tetraene requires relatively high T for cascade
- Black/ Banfield hypothesis for *E,Z,Z,E*-tetraene seems most likely (c.f. r.t. /Nicolaou)
- Controlling different diastereoisomers from cascade not possible (like Nature)
- RCDA dimerization gives mostly the *endo*-homodimer, reasons not understood

Thanks for your attention!

Back-up slide: mechanism of radical cation dimerization of hexadiene



12
[4 + 1]

13
$[4 + 2]^{+\cdot}$

double bond (**13**). The complete proposed mechanism follows:

$$DP + Ar_3N^{+\cdot} \rightleftharpoons Ar_3N: + DP^{+}$$

$$\left.\begin{array}{l} DP^{+\cdot} + D \rightarrow A^{+\cdot} \\ A^{+\cdot} + DP \rightarrow A + DP^{+\cdot} \end{array}\right\} \text{propagation}$$

D = diene, DP = dienophile, A = adduct

Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem. Commun.* **2011**, *47* (38), 10605.