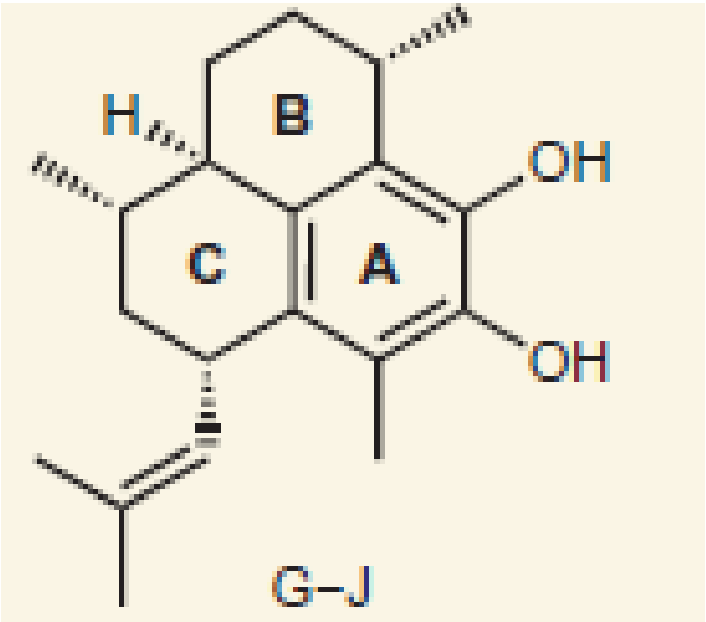
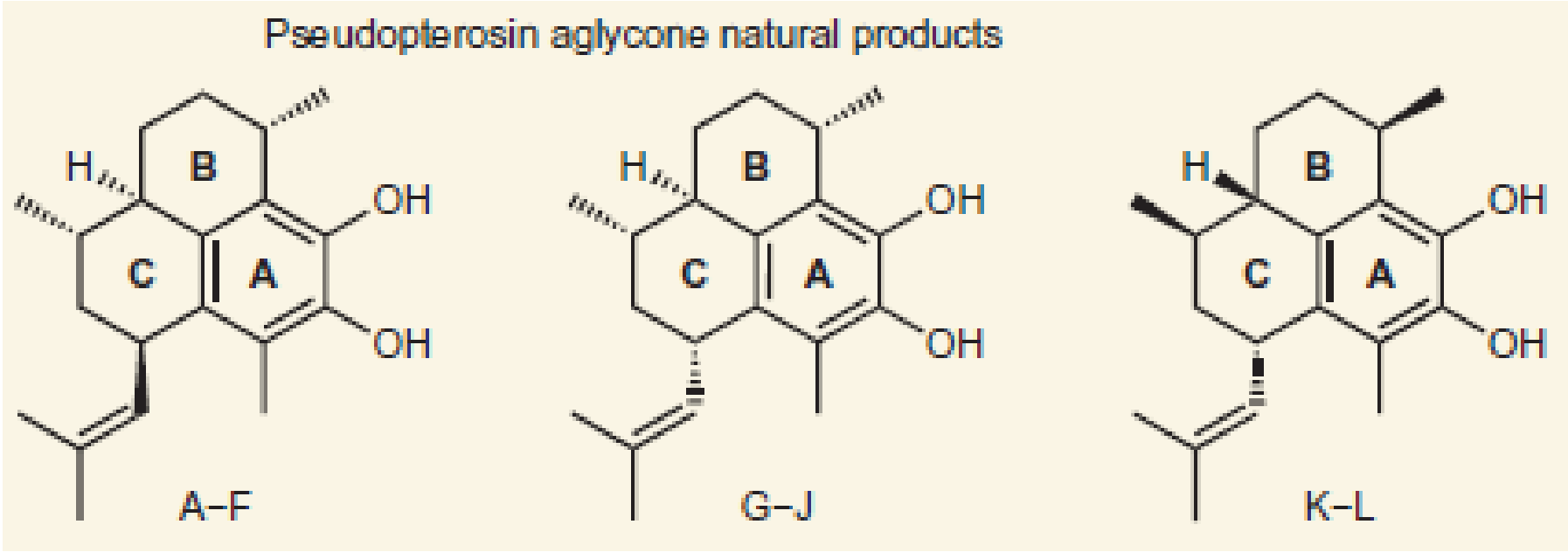
Pseudopterosin synthesis from a chiral cross-conjugated hydrocarbon through a series of cycloadditions



NATURE CHEMISTRY DOI: 10.1038/NCHEM.2112

Wipf group current literature
Zhizhou Yue 01032015

1

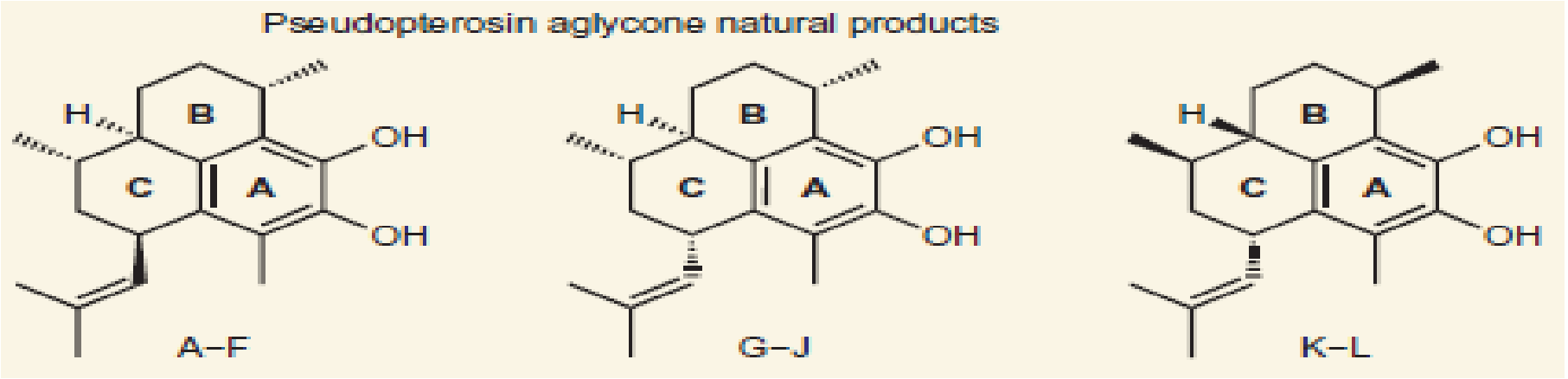


Pseudopterosins: The largest family of **amphilectane diterpenes** (31 members isolated), all of which are derived from one of three stereoisomeric aglycones. The remaining structural diversity arises from the **nature** of the sugar, the **site** of glycosylation and the **extent** of sugar acetylation.

Bioorg. Med. Chem. 19, 6702–6719 (2011).

Wide range of biological activities:
anticancer,
antimalarial,

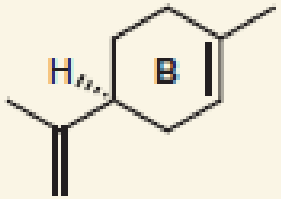
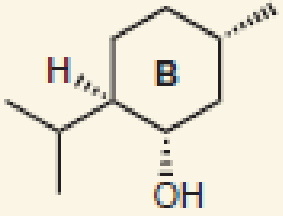
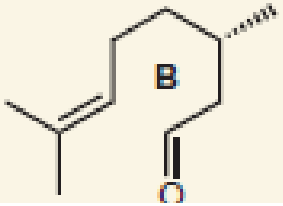
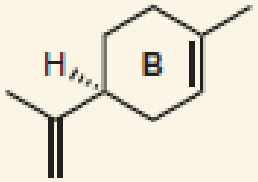
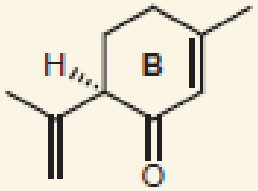
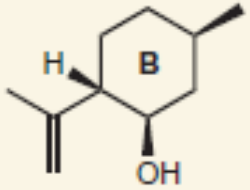
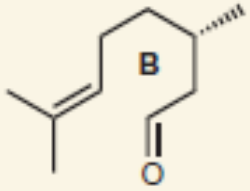
anti-inflammatory properties that exceed the potencies of existing drugs such as indomethacin
.



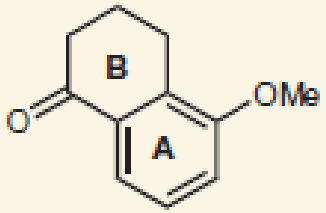
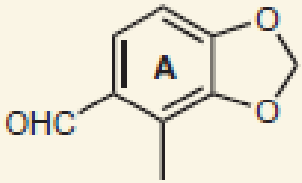
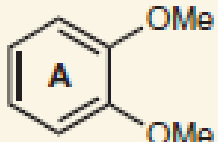
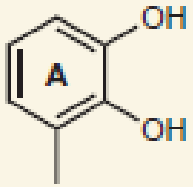
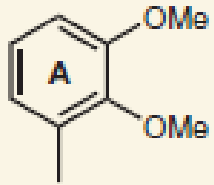
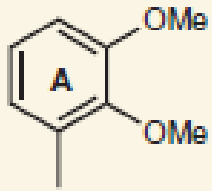
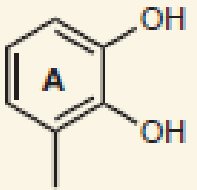
- Chiral tricyclic hexahydro-phenalenes
- Previous synthesis.
- ‘Structure–goal’ strategies
- SM: either chiral monoterpenes or substituted benzenes
- Method: Through sequences of chain extensions and annulations.

Important Synthesis Before

Terpene precursor approaches

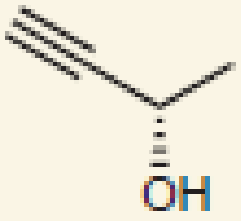
Starting material	Pseudopterosin	Steps	Ref.
Terpene precursor approaches			
	A–F* chiral pool	30	Broka[5] 1988
	A–F chiral pool	21	Corey[6] 1989
	A–F† chiral pool	19	Corey[7] 1990
	A–F chiral pool	16	Corey[13] 1998
	G–J chiral pool	14	Corey[14] 2000
	K–L chiral pool	15	Kocienski[15] 2001
	A–F chiral pool	17	Kocienski[15] 2001

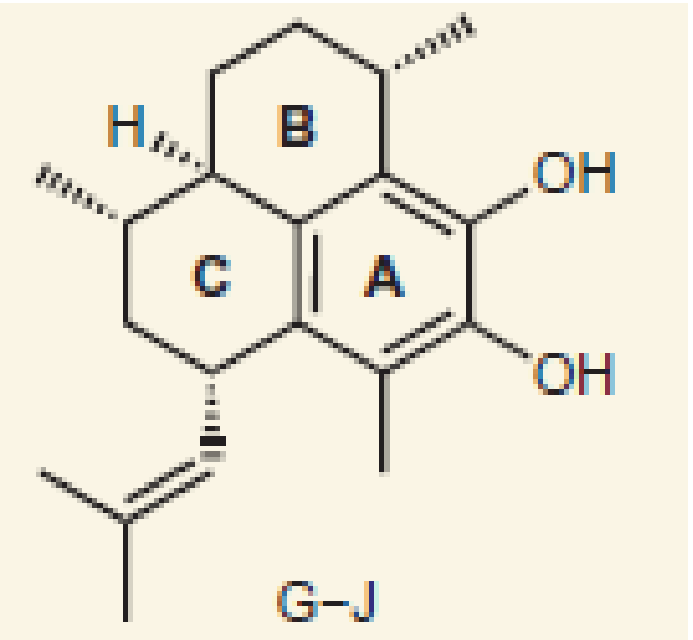
Aromatic precursor approaches

	A–F/K–L racemic	25	McCombie[8–10] 1990–1991
	A–F chiral pool	22	Buszek[11] 1995
	A–F enantioselective	20	Schmalz[12] 1997
	A–F/K–L racemic	14	Harrowven[16] 2004
	A–F† enantioselective	19	RajanBabu[17] 2011
	G–J enantioselective	21	RajanBabu[17] 2011
	A–F enantioselective	24	Cooksey & Kocienski[18] 2012

This work

This work

Starting material	Pseudopterosin	Steps
	(−)-G–J enantioselective	11
	(−)-G–J chiral pool	10



From ‘structure–goal’ strategies to “ ‘**transform-based’ s**

Does not commence with a ‘mappable’ commercial precursor and instead employs a powerful, triple cycloaddition sequence of a highly reactive cross-conjugated precursor to generate the natural product framework in very short order

7

retrosynthetic analysis

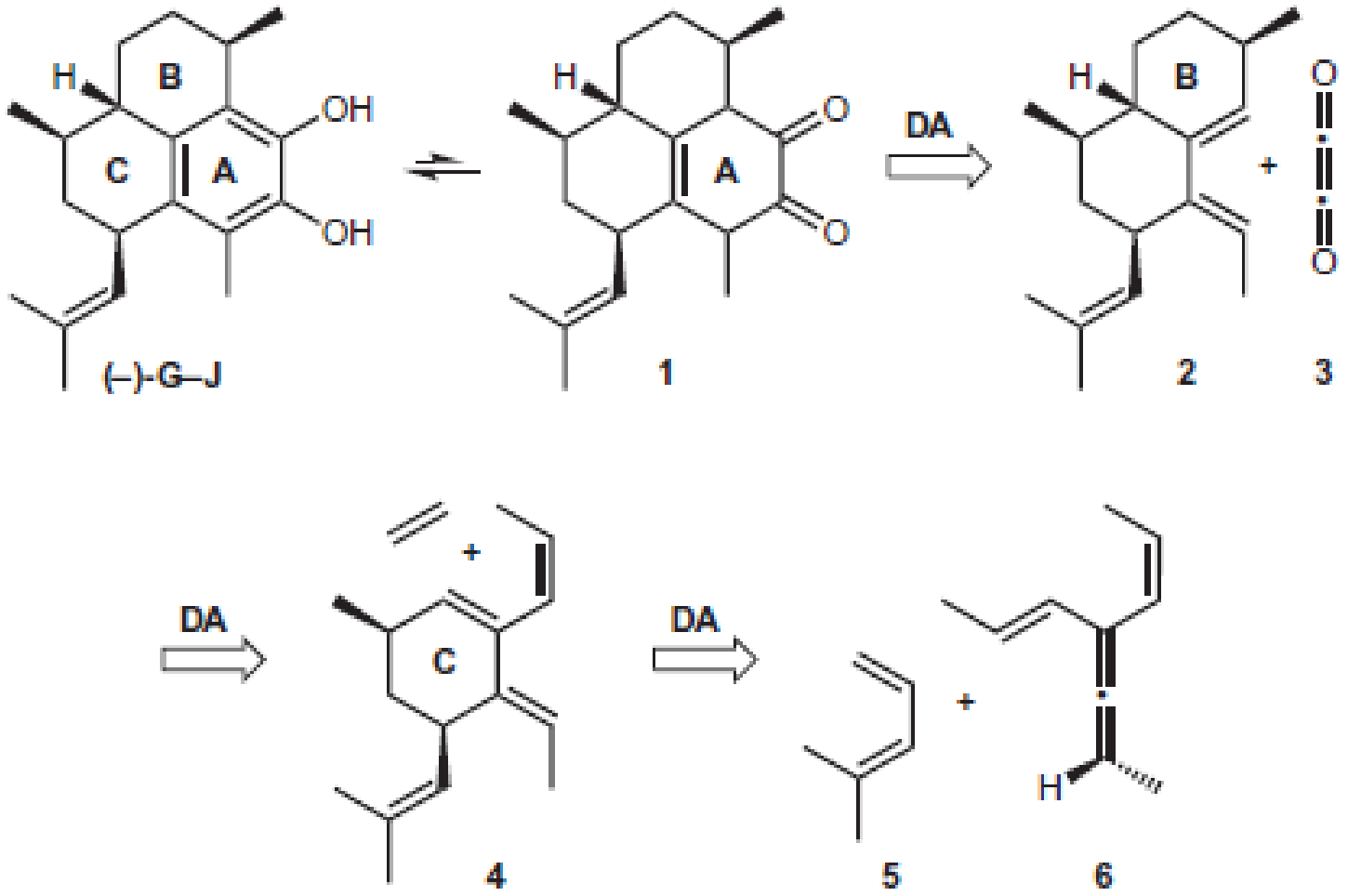


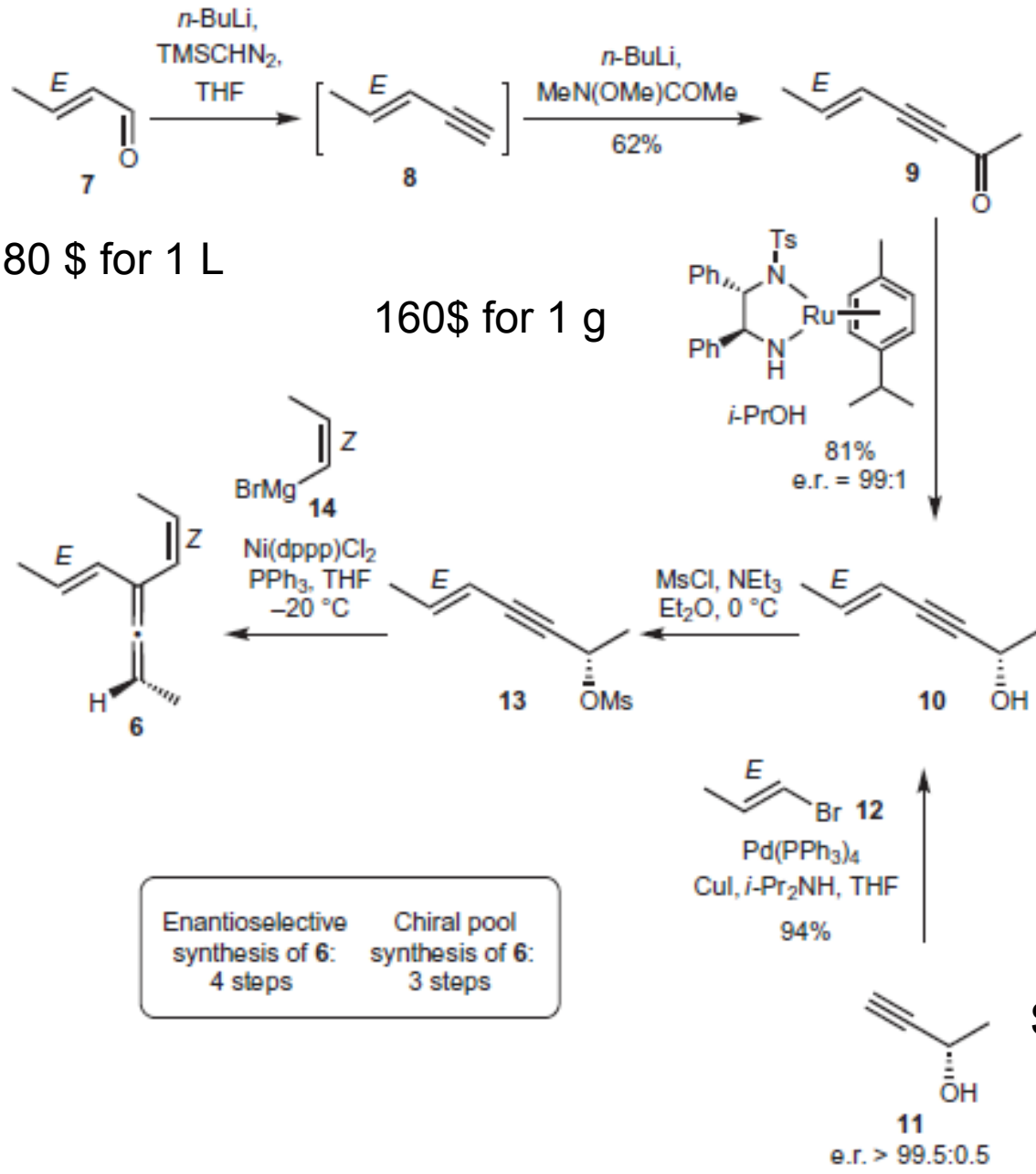
Figure 1 | Strategic bond disconnections pursued in this study.
Retrosynthetic analysis of the pseudopterosin (–)-G–J aglycone reveals the triple DA disconnection to axially chiral 1,1-divinylallene **6**.

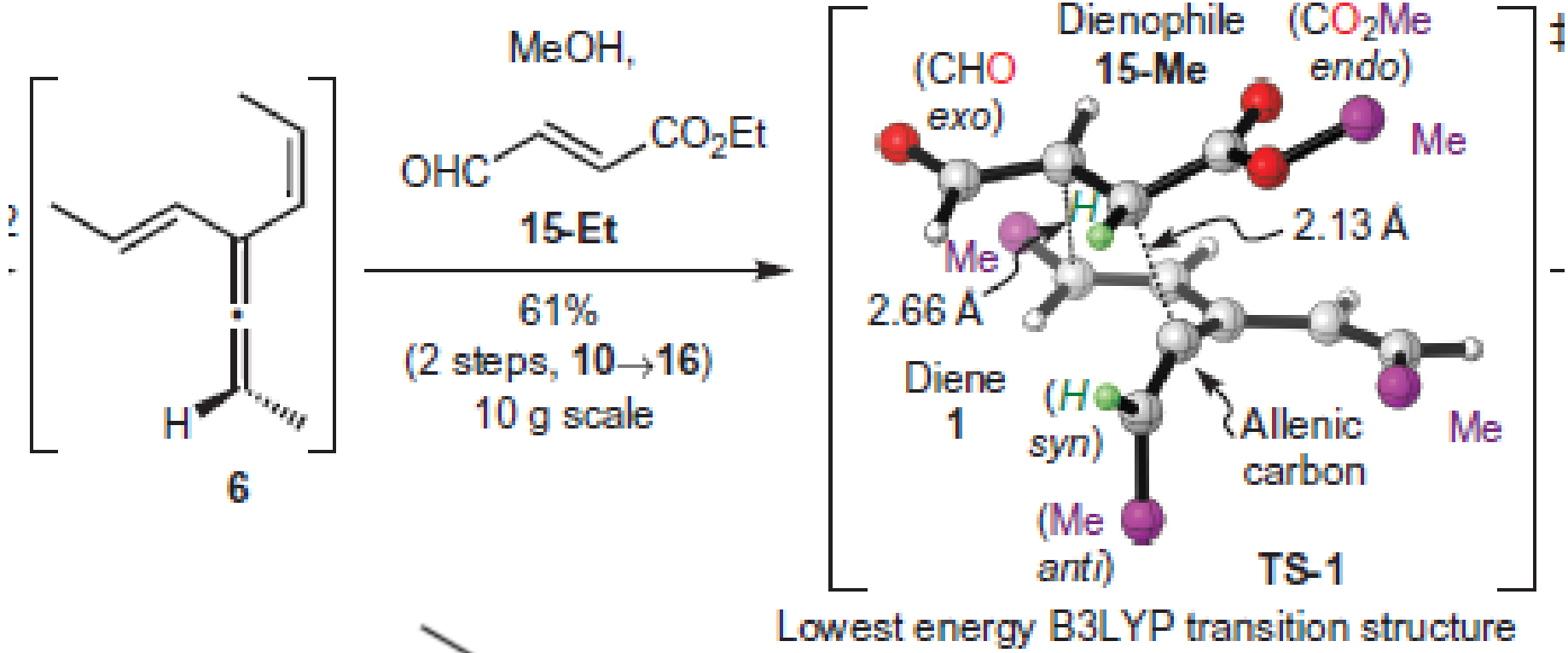
3

Key Problem

- Four acyclic precursors through the consecutive disconnection of three pairs of covalent bonds.
- Chemoselectivity, regioselectivity and stereoselectivity in the three cycloadditions
- Potentially problematic preparation and handling of crossconjugated hydrocarbon.
- The presence of both E- and Z-configured propenyl-substituents in substituted divinylallene confers axial chirality upon the structure
- The possibility of a substrate-controlled stereoselective synthesis.

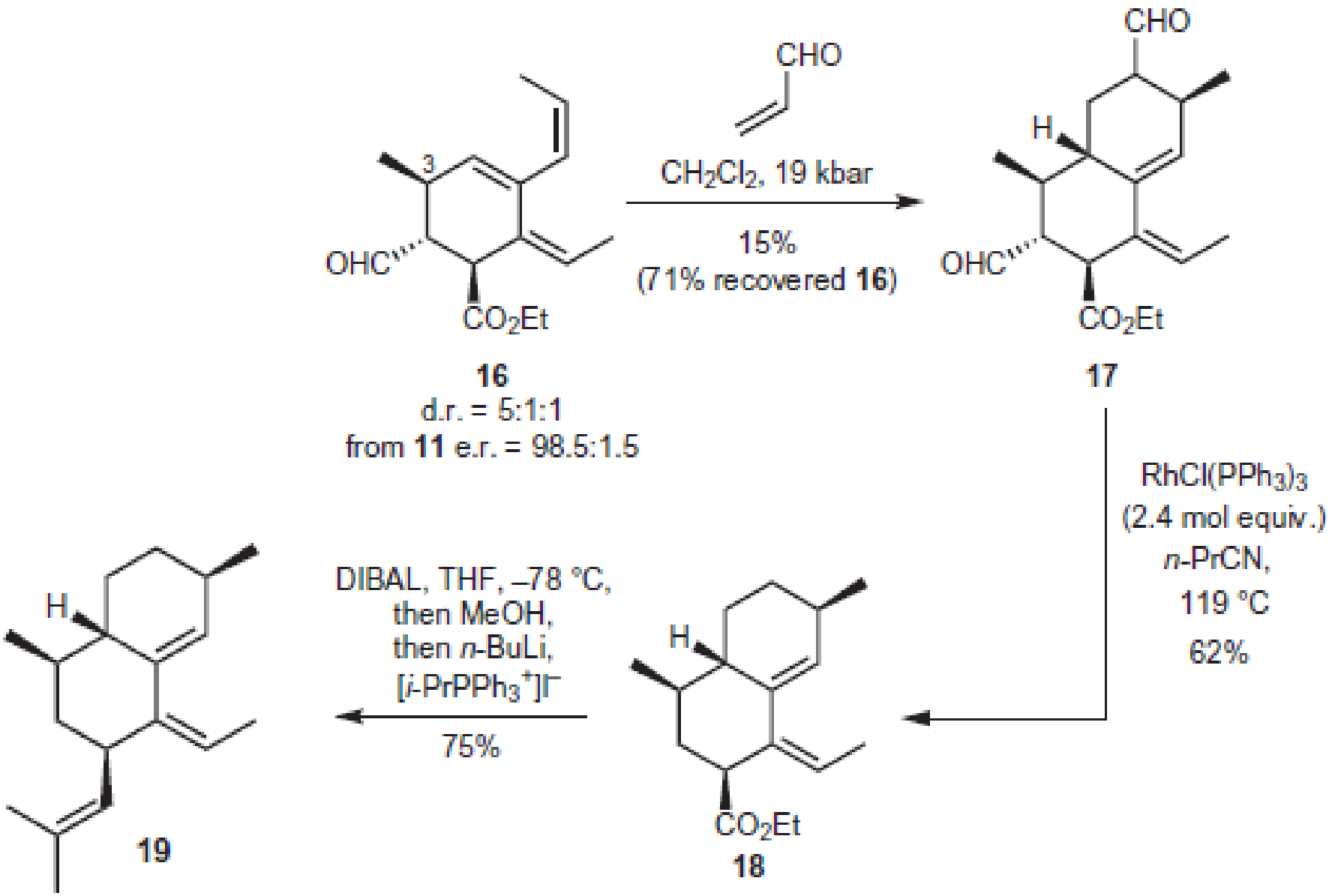
chiral 1,1-divinylallene 6

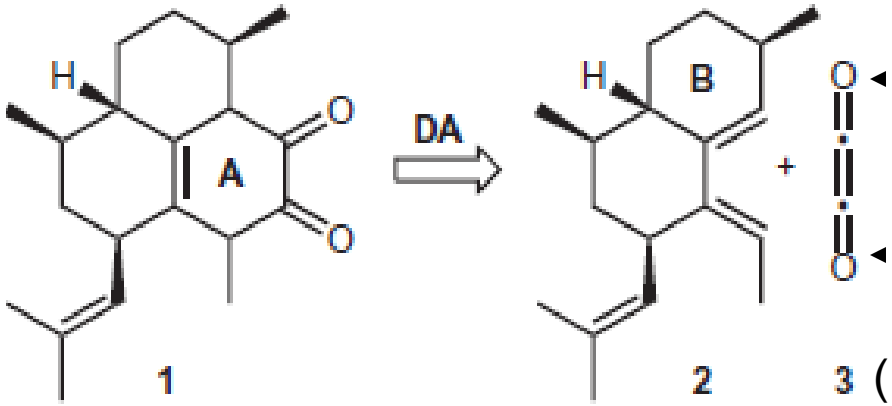




The TS with the opposite orientation to TS-1 lies 4.9 kJ / mol higher in energy. The endo-CO2Me mode of dienophile addition is favoured over the alternative exo mode by 1.1 kJ /mol, and the allenic methyl group’s preference for anti over syn is 8.5 kJ /mol.

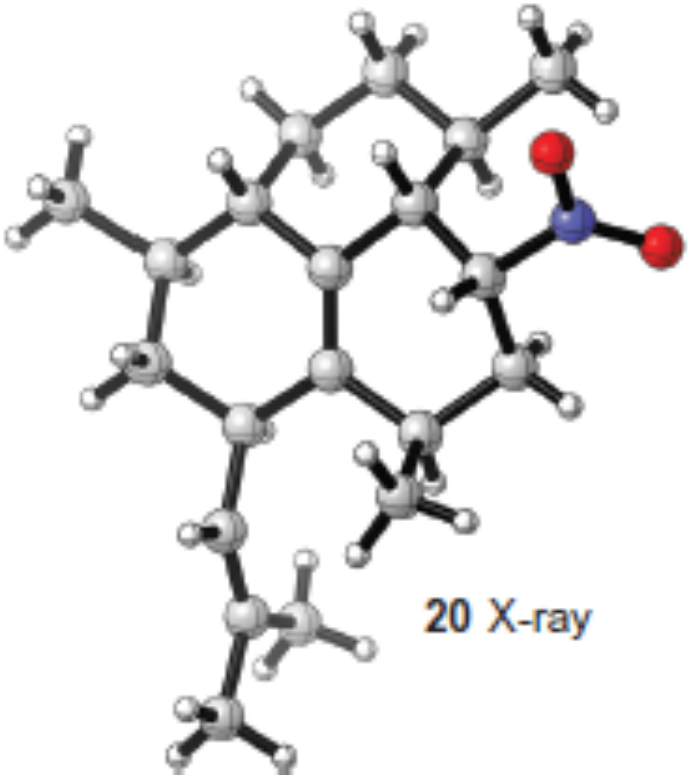
11


CHO
CH2Cl2, 19 kbar
15%
(71% recovered 16)
OHC
CO2Et
16
d.r. = 5:1:1
from 11 e.r. = 98.5:1.5
17
RhCl(PPh3)3
(2.4 mol equiv.)
n-PrCN,
119 °C
62%
18
DIBAL, THF, –78 °C,
then MeOH,
then n-BuLi,
[i-PrPPh3+]I−
75%
19



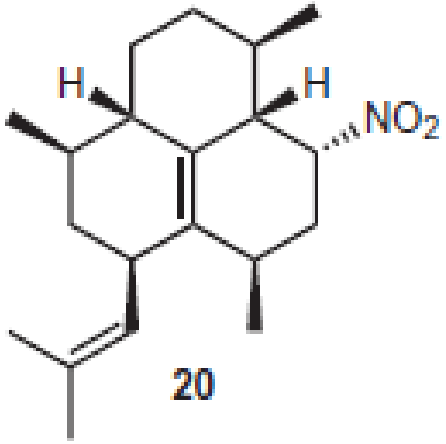
1 2 3 (Fleeting existence)

- NO_2 (equivalent) (Nef reaction)
- Via oxidation



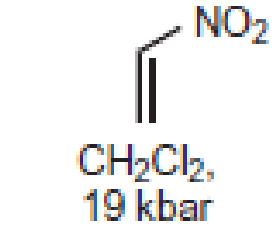
20 X-ray

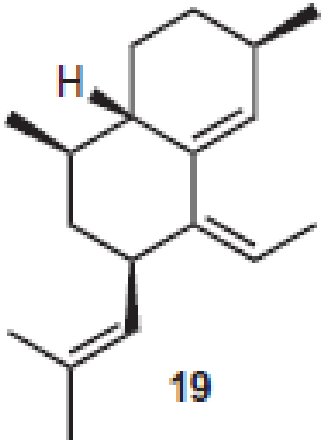
≡



20

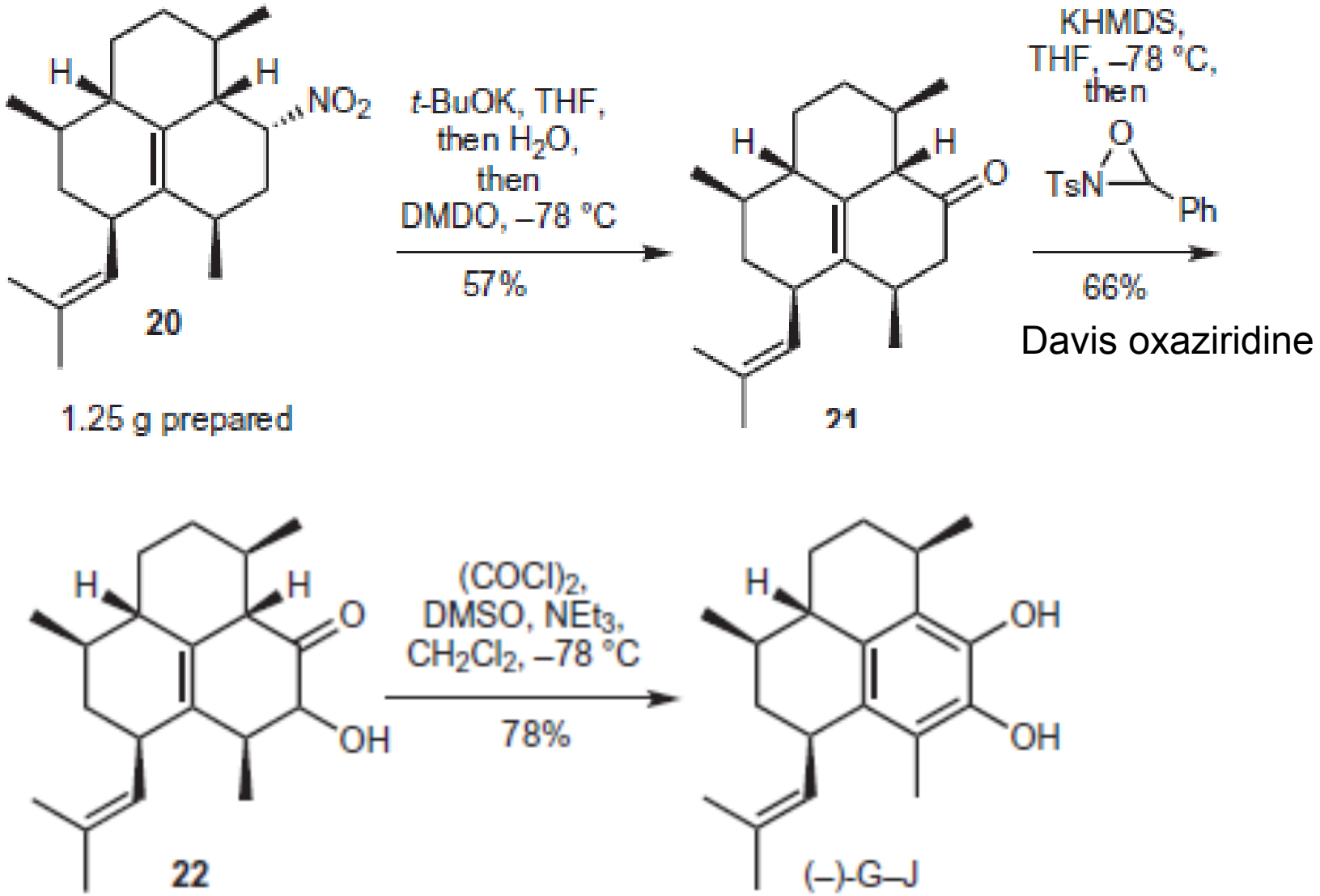
1.25 g prepared





19

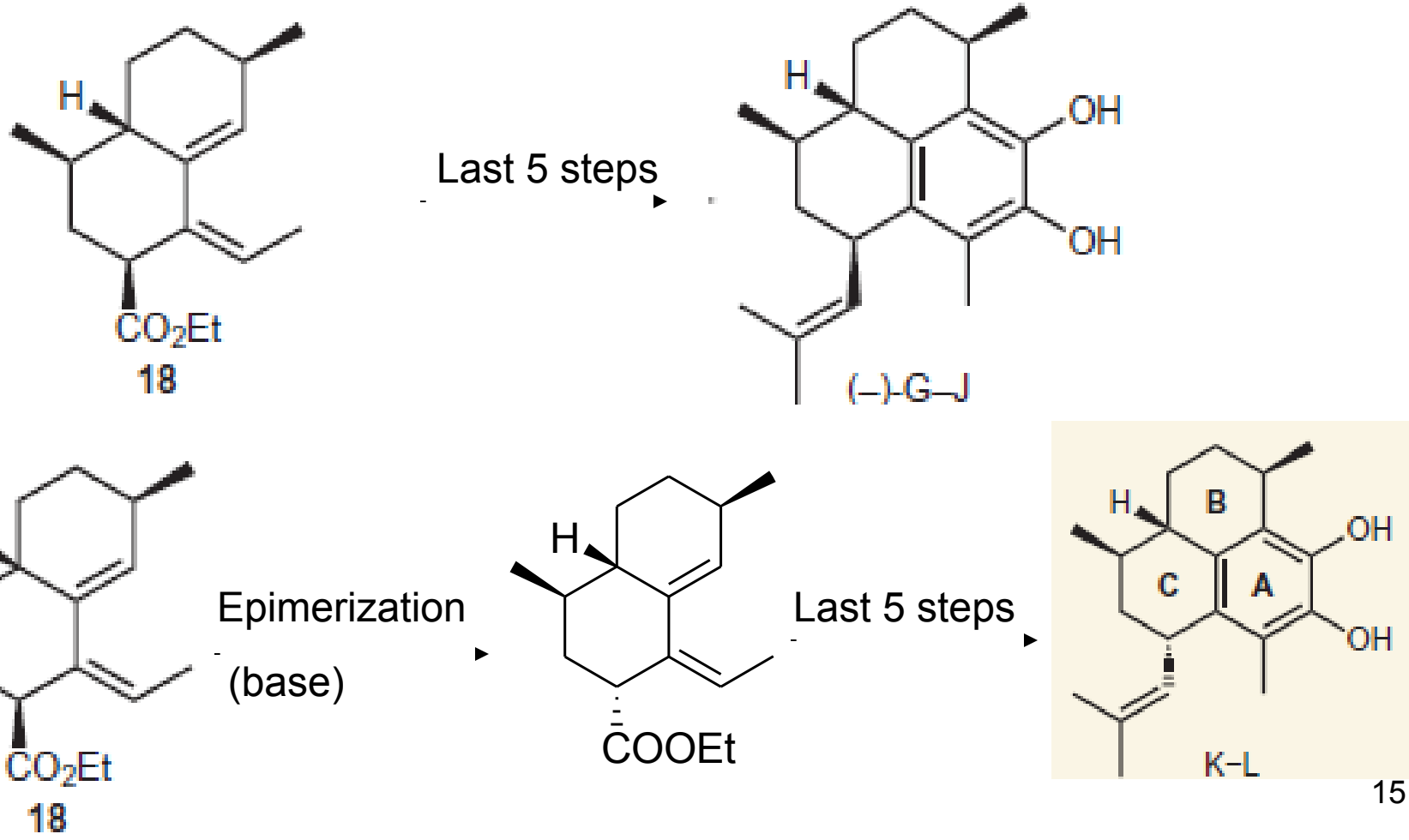
13



Catalytic method: 11 steps 0.51%
Chiral pool: 10 steps 0.96 %

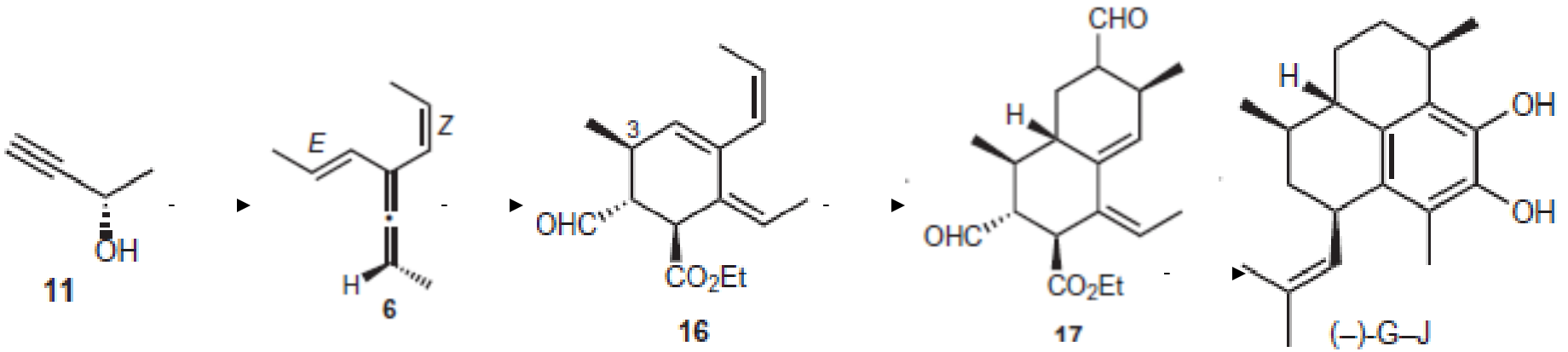
preparation of Pseudopterosin K–L, A-F.

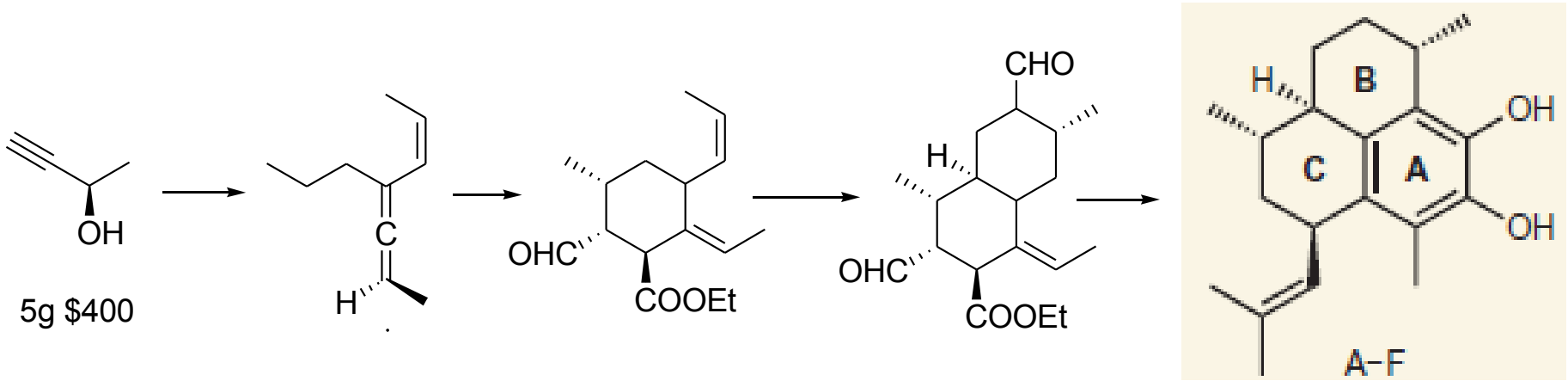
K–L aglycone: Epimerization of ester 18 followed by the same five-stepsequence



15

Pseudopterosin A–F aglycone: employing either the enantiomeric Noyori catalyst or the enantiomer of the chiral pool precursor





16

Conclusion

The pursuit of a transform-based strategy has culminated in the shortest catalytic enantioselective (11 steps) and chiral pool (10 steps) total syntheses of a pseudopterosin natural product.

The synthesis constructs all three rings of the tricyclic natural product via a triple DA reaction sequence commencing with anaxially chiral, substituted 1,1-divinylallene.

Novel and notable features of this highly unorthodox approach include:

(1) a new variation on the cross-coupling theme to prepare hydrocarbon 6;

(2) the stereoselective cycloaddition of axially chiral divinylallene 6;

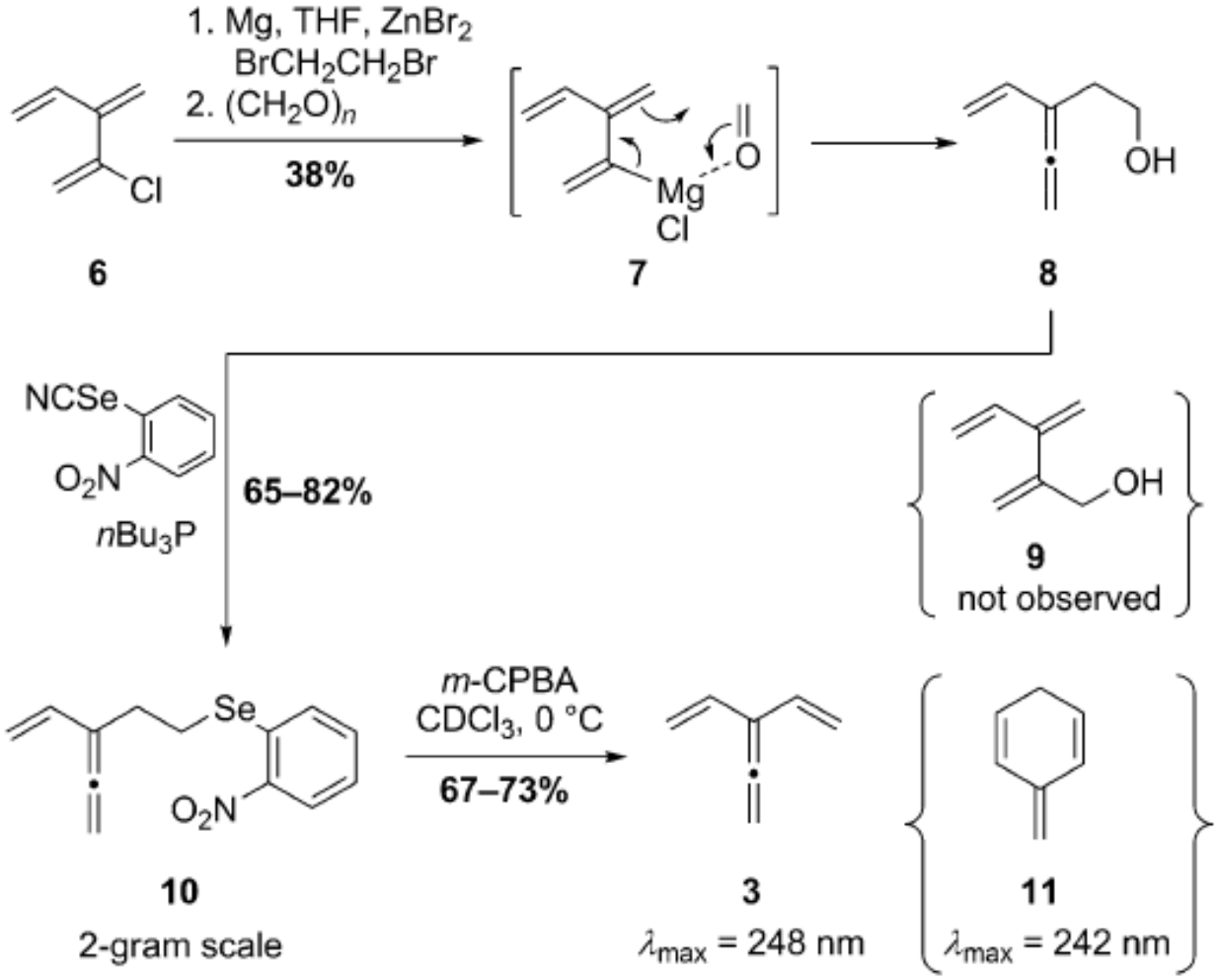
(3) a point-to-axial-topoint chirality manoeuver with retention of enantiopurity;

(4) a novel DA reaction-based catechol synthesis

This work is perhaps the most extreme incarnation yet of the potency of the DA reaction in natural product synthesis, and one that signals the coming of age of cross-conjugated hydrocarbons in this domain.

Thank You

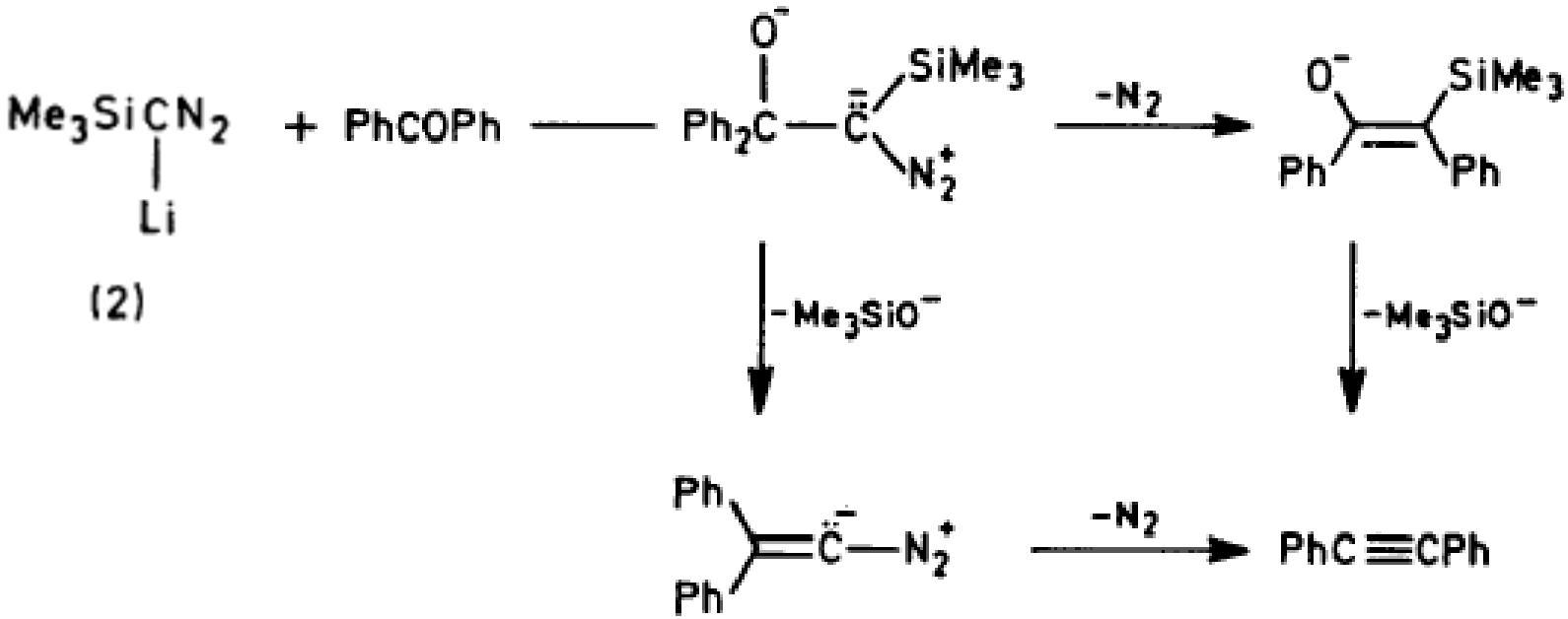
- **Reference 20**
- **Angew. Chem. Int. Ed. 2011, 50, 10425 –10428**



21

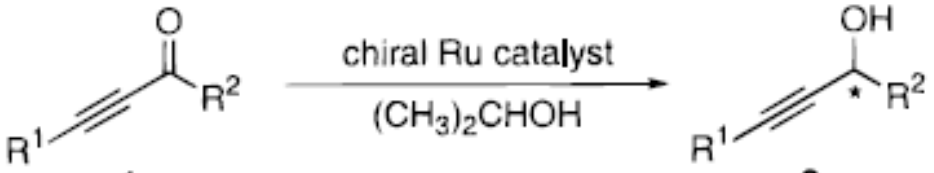
Scheme 2. First synthesis of the parent 1,1-divinylallene **3**.

- **Reference 21,22,23**
- **Colvin–Hamill conditions(*n*-BuLi,TMSCHN2)**
- **From aldehyde to terminal alkyne**
- J. Chem. Soc. Chem. Commun. 151–152 (1973).
- J. Chem. Soc. Perkin Trans. 1869–874 (1977).
- Org. Lett. 6, 2035–2038 (2004).



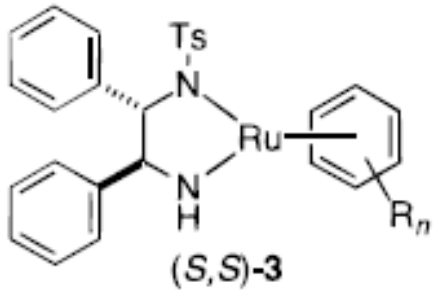
Reference 24 Noyori conditions

J. Am. Chem. Soc. **1997,** *119,* 8738-8739



1 **2**

a: $R^1 = C_6H_5$; $R^2 = CH_3$
b: $R^1 = C_6H_5$; $R^2 = C_2H_5$
c: $R^1 = C_6H_5$; $R^2 = CH(CH_3)_2$
d: $R^1 = C_6H_5$; $R^2 = c\text{-}C_6H_{11}$
e: $R^1 = C_6H_5$; $R^2 = C(CH_3)_3$
f: $R^1 = n\text{-}C_4H_9$; $R^2 = CH_3$
g: $R^1 = n\text{-}C_4H_9$; $R^2 = CH(CH_3)_2$
h: $R^1 = Si(CH_3)_3$; $R^2 = CH_3$
i: $R^1 = Si(CH_3)_3$; $R^2 = n\text{-}C_4H_9$
j: $R^1 = Si(CH_3)_3$; $R^2 = n\text{-}C_5H_{11}$
k: $R^1 = Si(CH_3)_3$; $R^2 = CH(CH_3)_2$



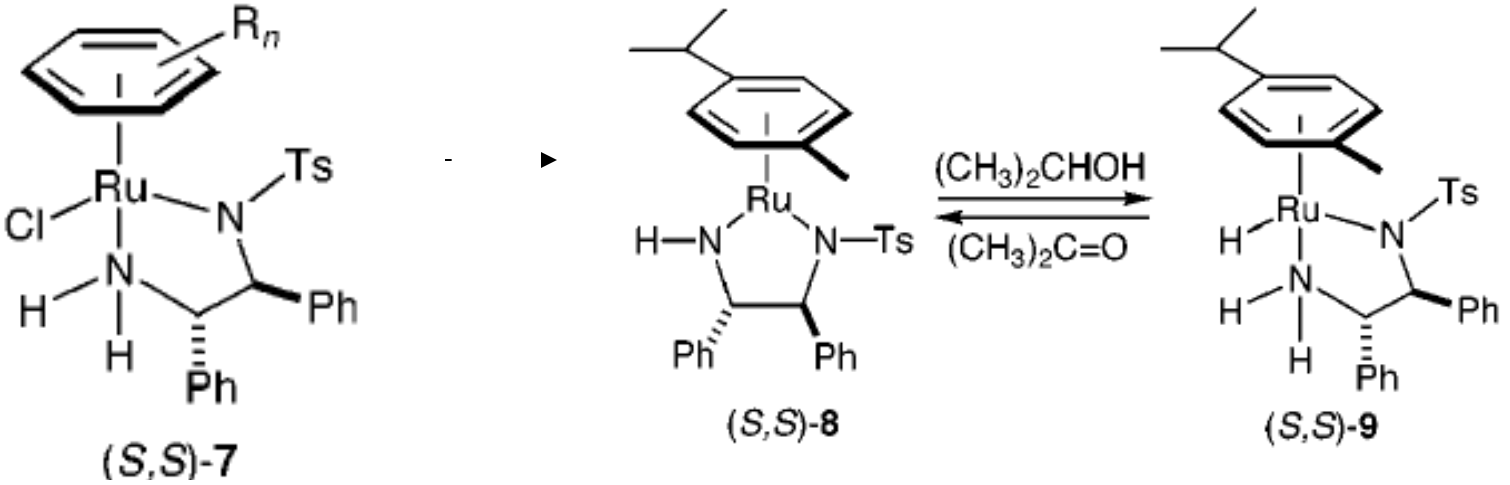
(*S,S*)-**3**

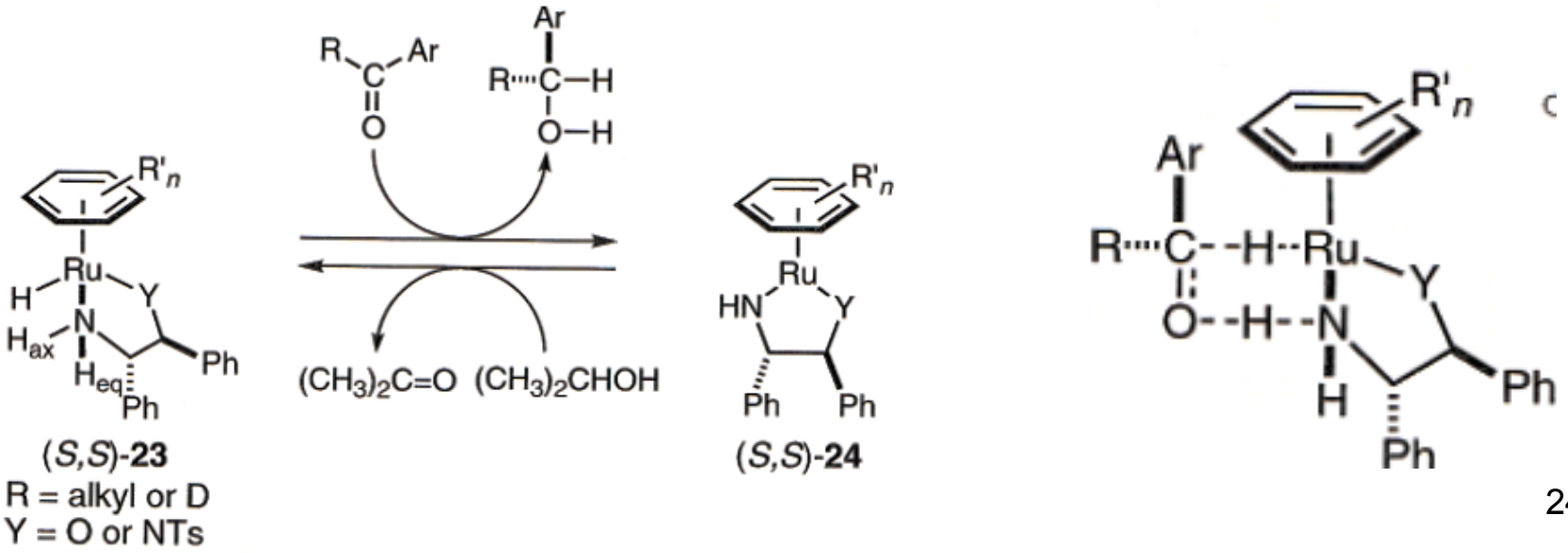
a: η^6-arene = mesitylene
b: η^6-arene = *p*-cymene

				Product 2		
				Yield	ee	config
1e	(*S,S*)-**4a**	B[k]	13	84	98	*S*
1f	(*S,S*)-**4a**	B	6	70	98[l]	*S*
1g	(*S,S*)-**4a**	B	6	90	>99[l]	*S*
1g (1 M)	(*S,S*)-**4a**	B[k]	13	85	99[l]	*S*
1h	(*S,S*)-**3b**	A	12	>99	98[m]	*S*
1h	(*S,S*)-**3b**	A[n]	27	86	98[m]	*S*
1i	(*S,S*)-**3b**	A	12	>99	97[o]	*S*
1j (1 M)	(*S,S*)-**3b**	A[k]	12	99	94[o]	*S*[p]
1j	(*R,R*)-**3b**	A	15	98	99[o]	*R*[p]
1k	(*S,S*)-**3b**	A	12	>99	99[q]	*S*[i]

23

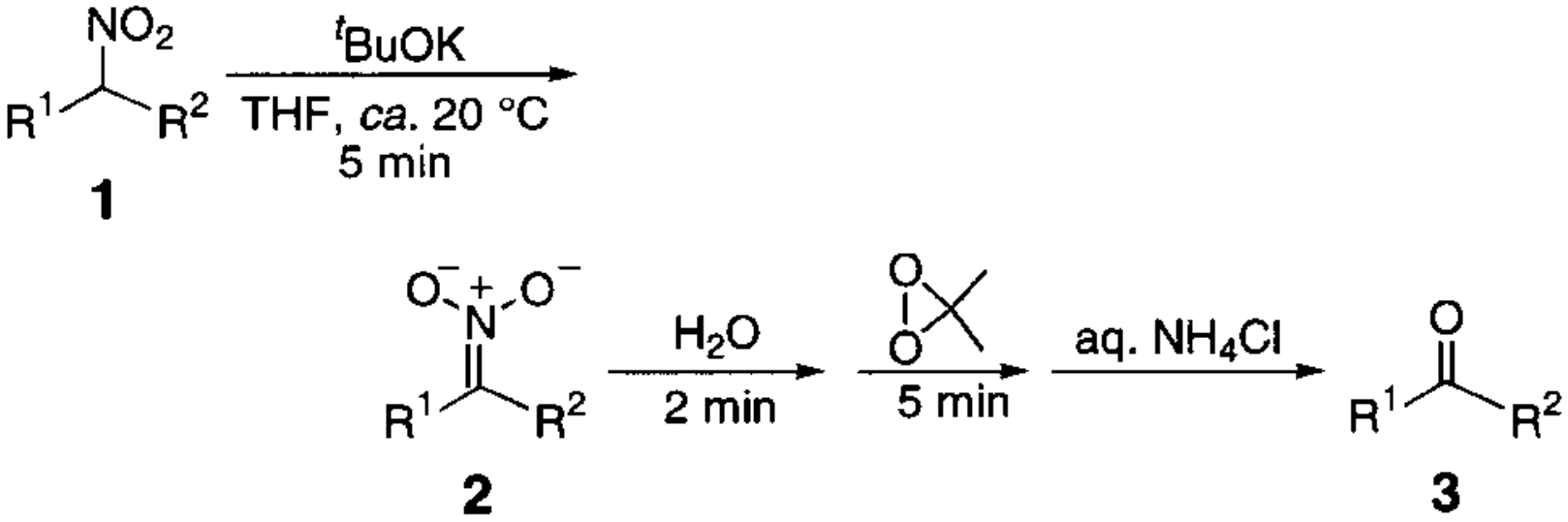
Ref 24-2 JOC 2001, 66, 7931

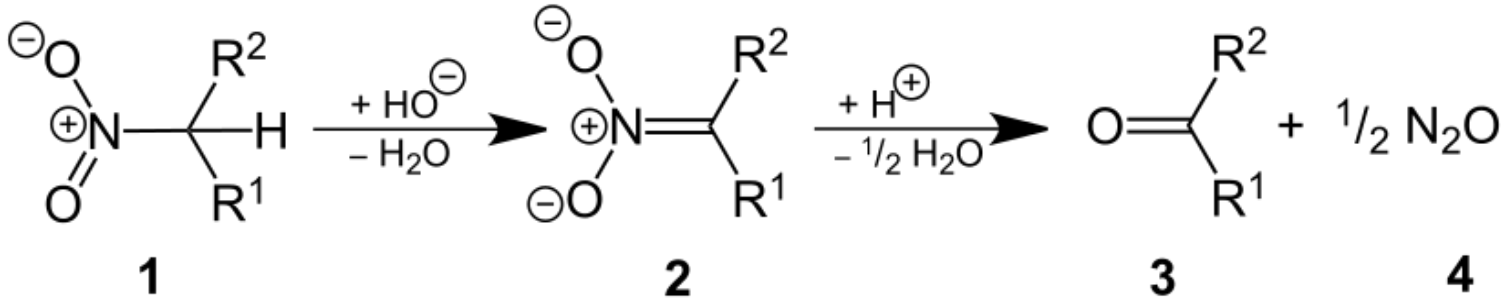


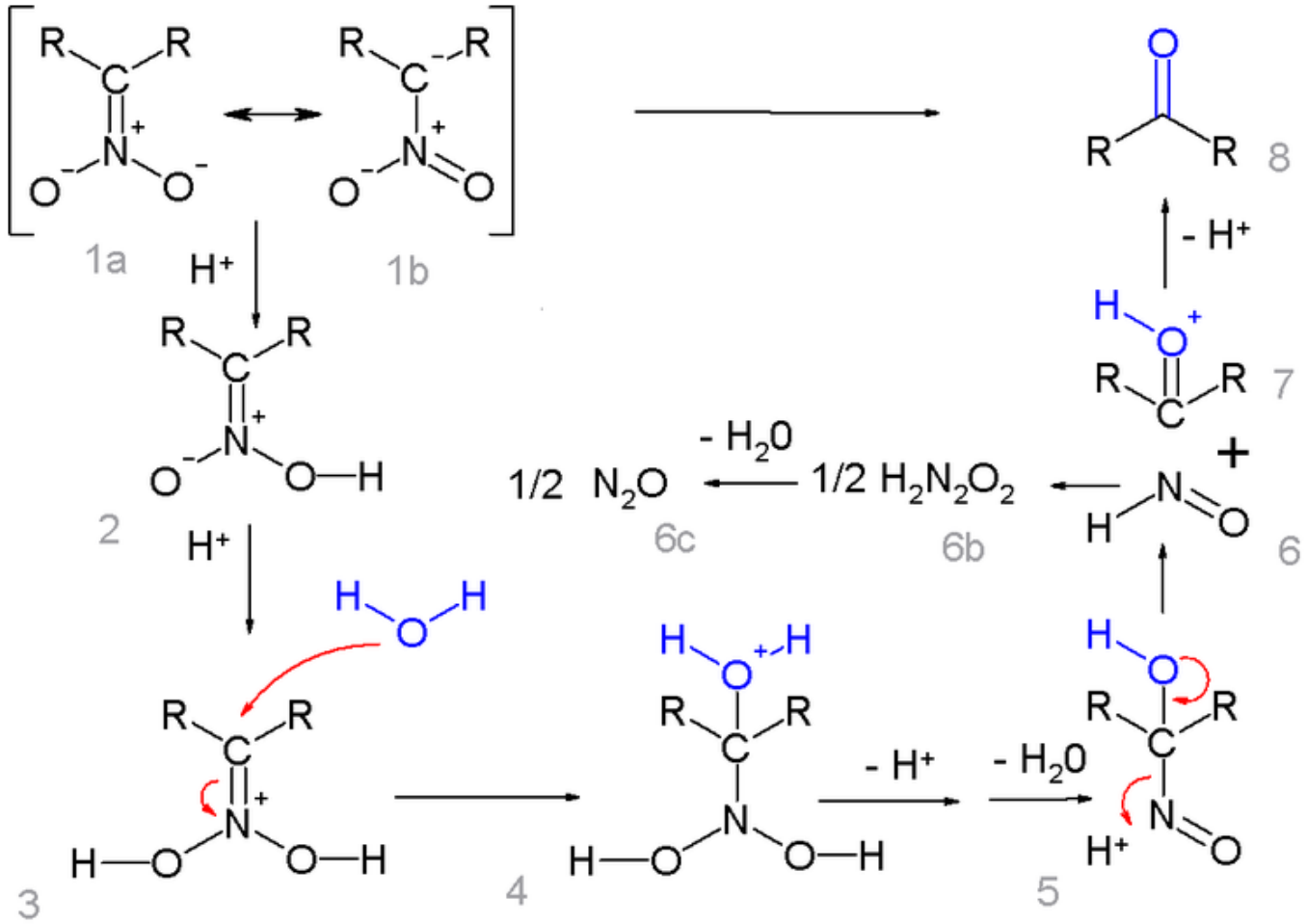


Reference 28 Nef reaction

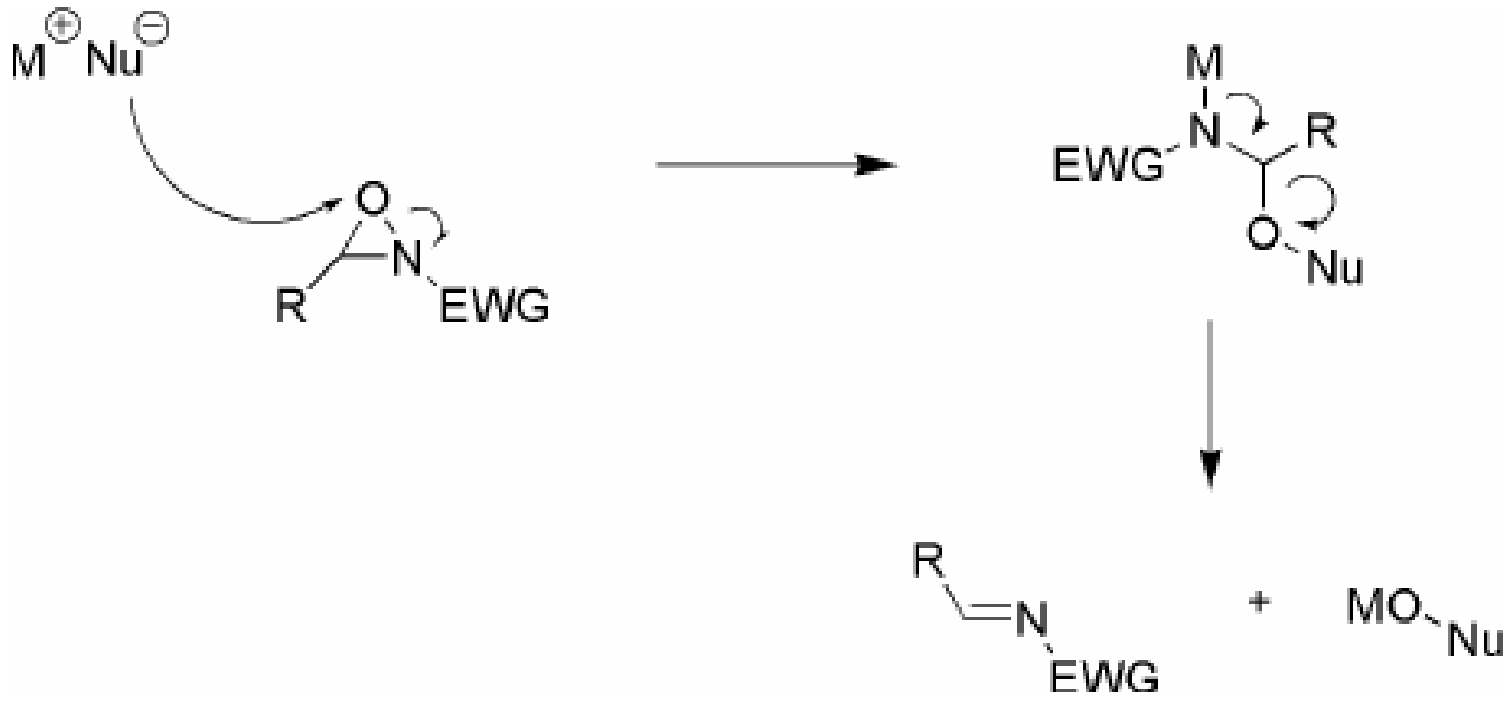
Table 1. DMD Oxidation of Nitronate Anions to Carbonyl Products[a]




+ HO⊖
– H2O
+ H⊕
– 1/2 H2O
+ 1/2 N2O
1
2
3
4


1a
1b
H+
2
H+
3
4
5
- H+
- H2O
6
6b
6c
1/2 H2N2O2
1/2 N2O
- H2O
7
- H+
8

electrophilic oxygenation with Davis' oxaziridine



Scheme 3. General mechanism of oxygenation of nucleophiles.

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Swern Oxidation