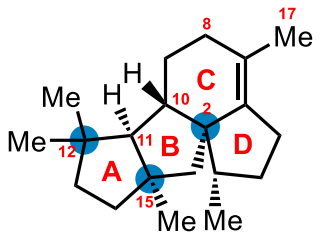
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

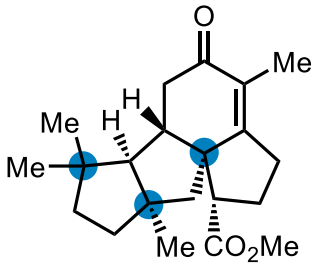
Total Syntheses of Polycyclic Diterpenes Phomopsene, Methyl Phomopsenonate, and *iso*-Phomopsene via Reorganization of C–C Single Bonds

Jun-Jie Yin, Yun-Peng Wang, Jun Xue, Feng-Fan Zhou, Xing-Qian Shan, Rong Zhu, Kun Fang, Lei Shi,* Shu-Yu Zhang, Si-Hua Hou,* Wujiong Xia, and Yong-Qiang Tu*

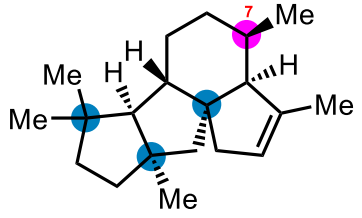
J. Am. Chem. Soc., **2023**, *145*, 21170.



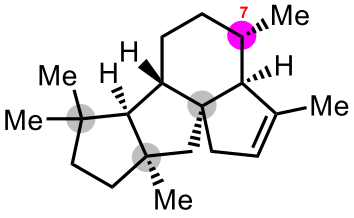
phomopsene (1)



methyl phomopsenonate (2)

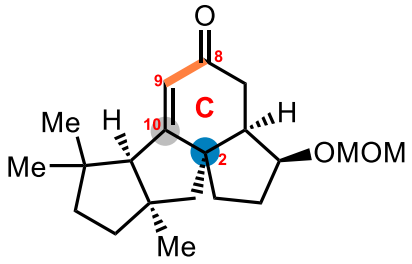


***iso*-phomopsene (3a)**
originally proposed structure



***iso*-phomopsene (3)**
revised structure (this work)

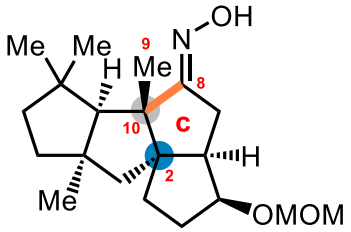
late-stage diversification



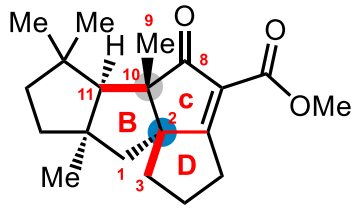
4
(5/5/6/5 tetracycle)

unusual fragmentation/ reconstruction

c-to-C



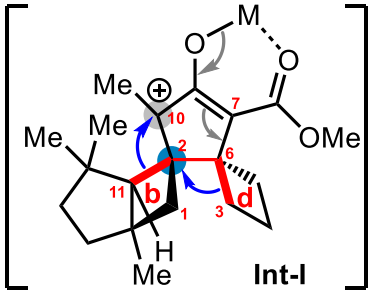
5
(5/5/5/5 tetracycle)



6

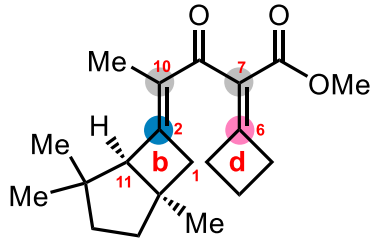
stereospecific cascade ring expansions

b-to-B
d-to-D



Int-I

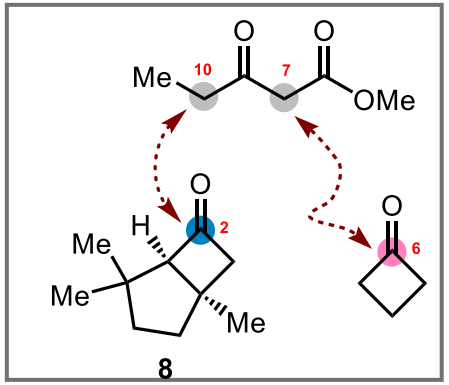
Nazarov cyclization



7

Aldol condensation

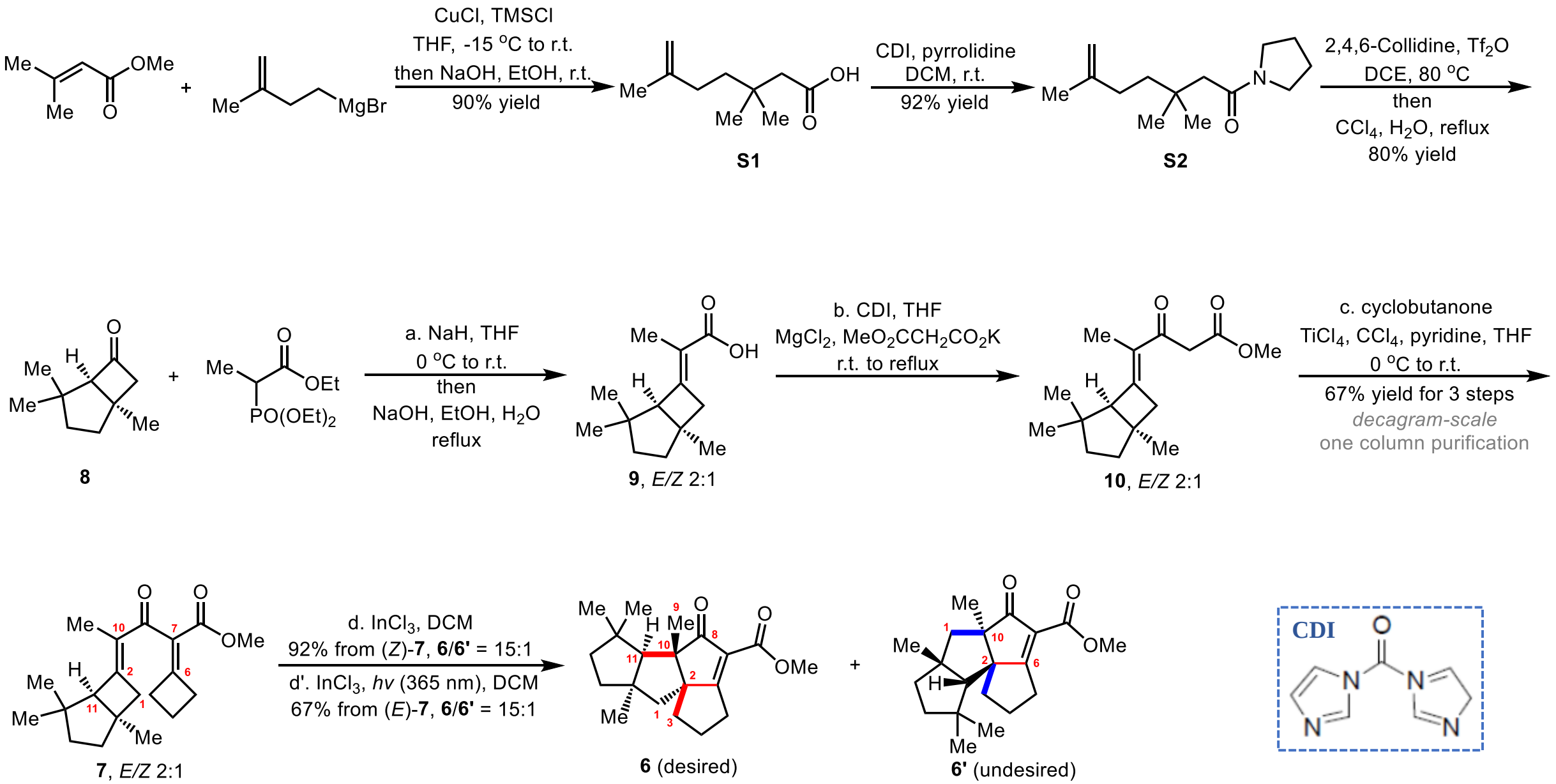
Simple building blocks



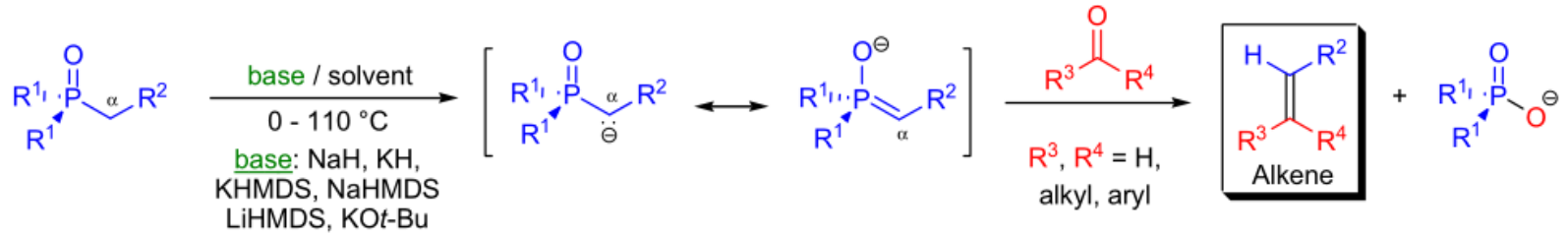
8

- 5/5/6/5 tetracycles
- 3 quaternary centers
- 5-6 contiguous stereocenters
- no synthesis reported

Scheme 2. Preparation of 5/5/5/5 Tetracycle via Tandem Nazarov Cyclization/Double Ring Expansions Reaction



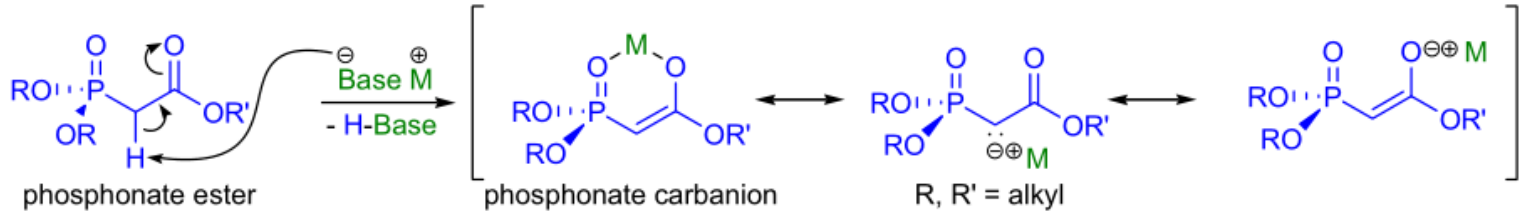
HORNER-WADSWORTH-EMMONS OLEFINATION

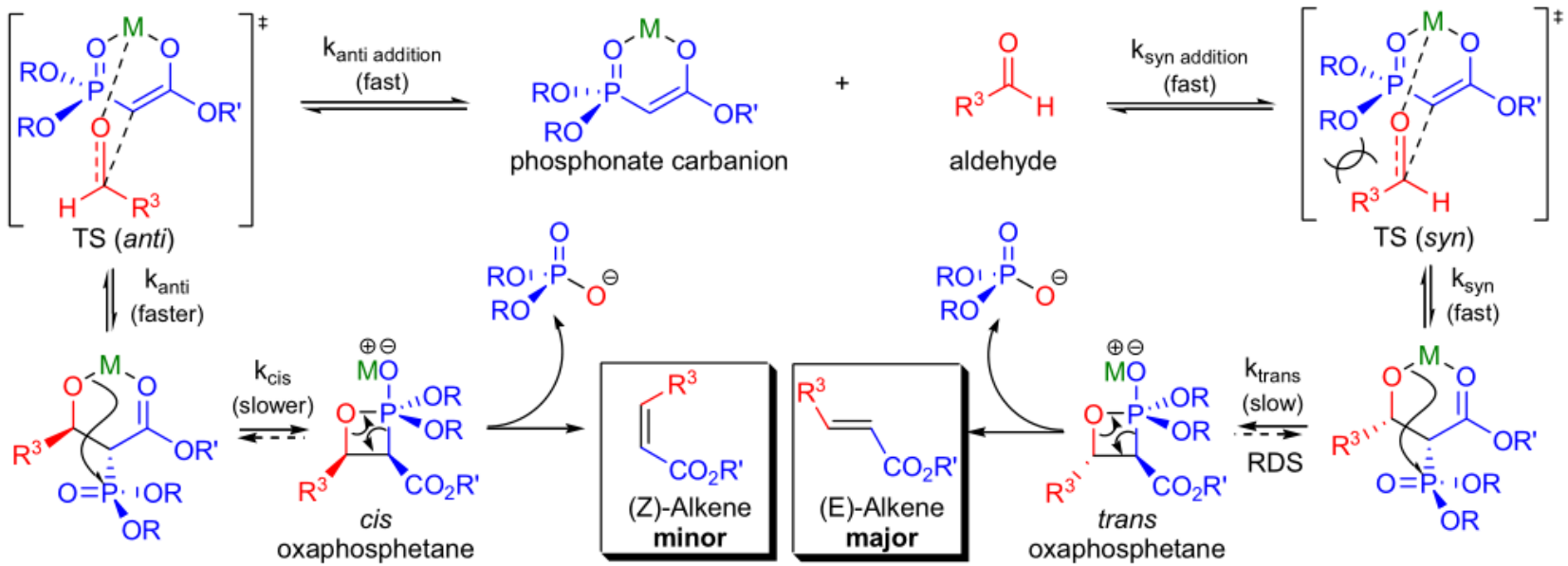


R^1 = aryl, alkyl; R^2 = alkyl, aryl, COR, CO_2R, CN, SO_2R ⟹ *Horner-Wittig reaction*

R^1 = O-aryl, O-alkyl, NR_2; R^2 = aryl, alkenyl, COR, CO_2R, CN, SO_2R ⟹ *Wadsworth-Emmons reaction*

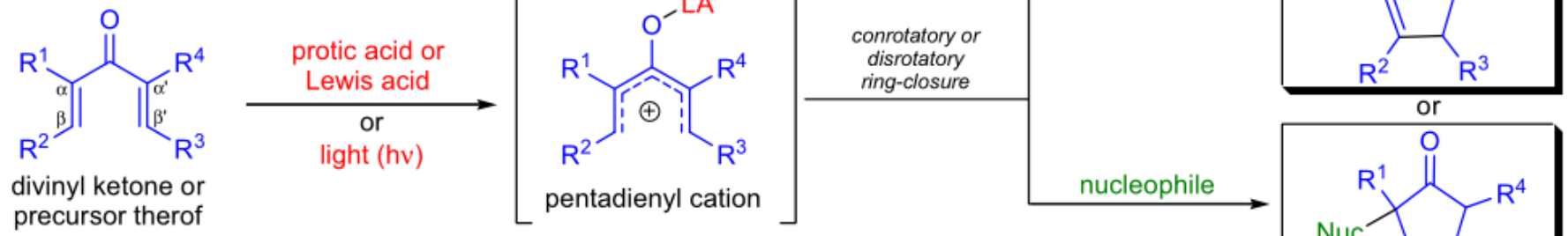
Mechanism: [47,9,48,11]



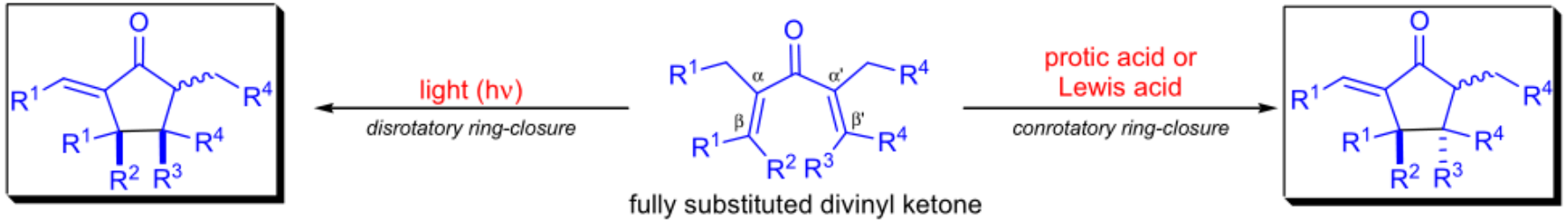


NAZAROV CYCLIZATION

General scheme for Nazarov cyclization:



Thermal and photochemical Nazarov cyclization:



Mechanism: [32-37,15,10]

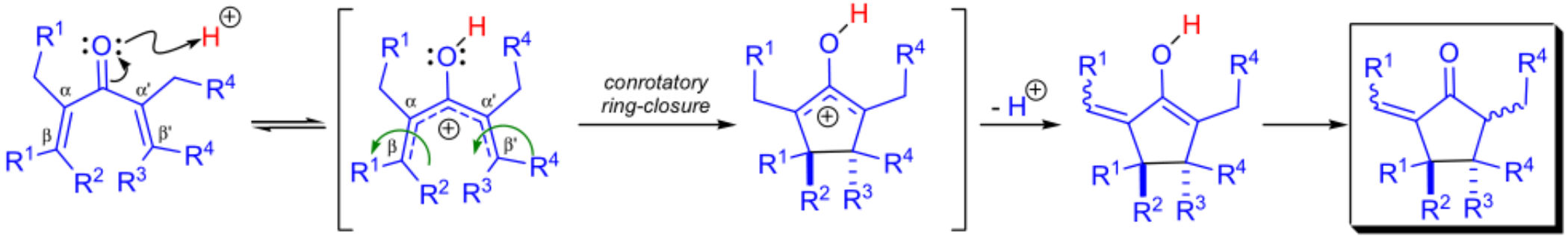
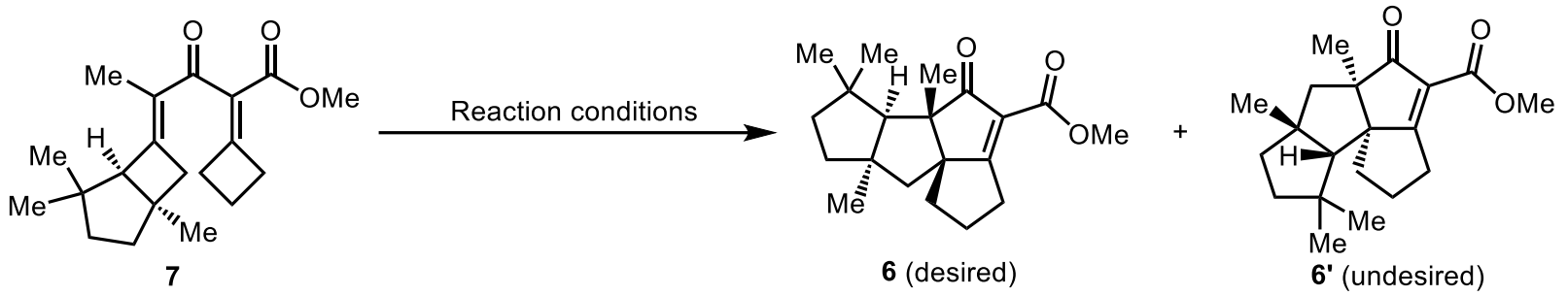


Table S1. Optimization of the Tandem Nazarov Cyclization/Double Ring Expansions Reaction with Compound **7** [a]

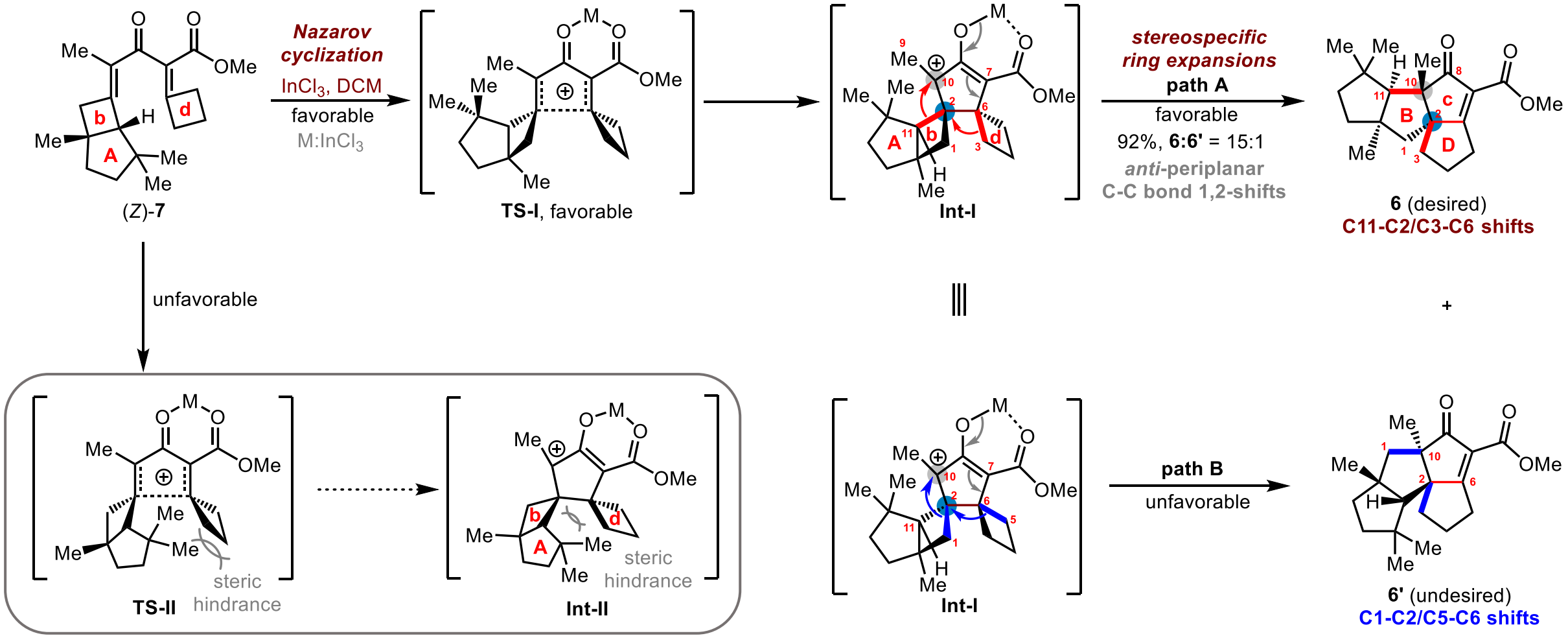


7 **6** (desired) **6'** (undesired)

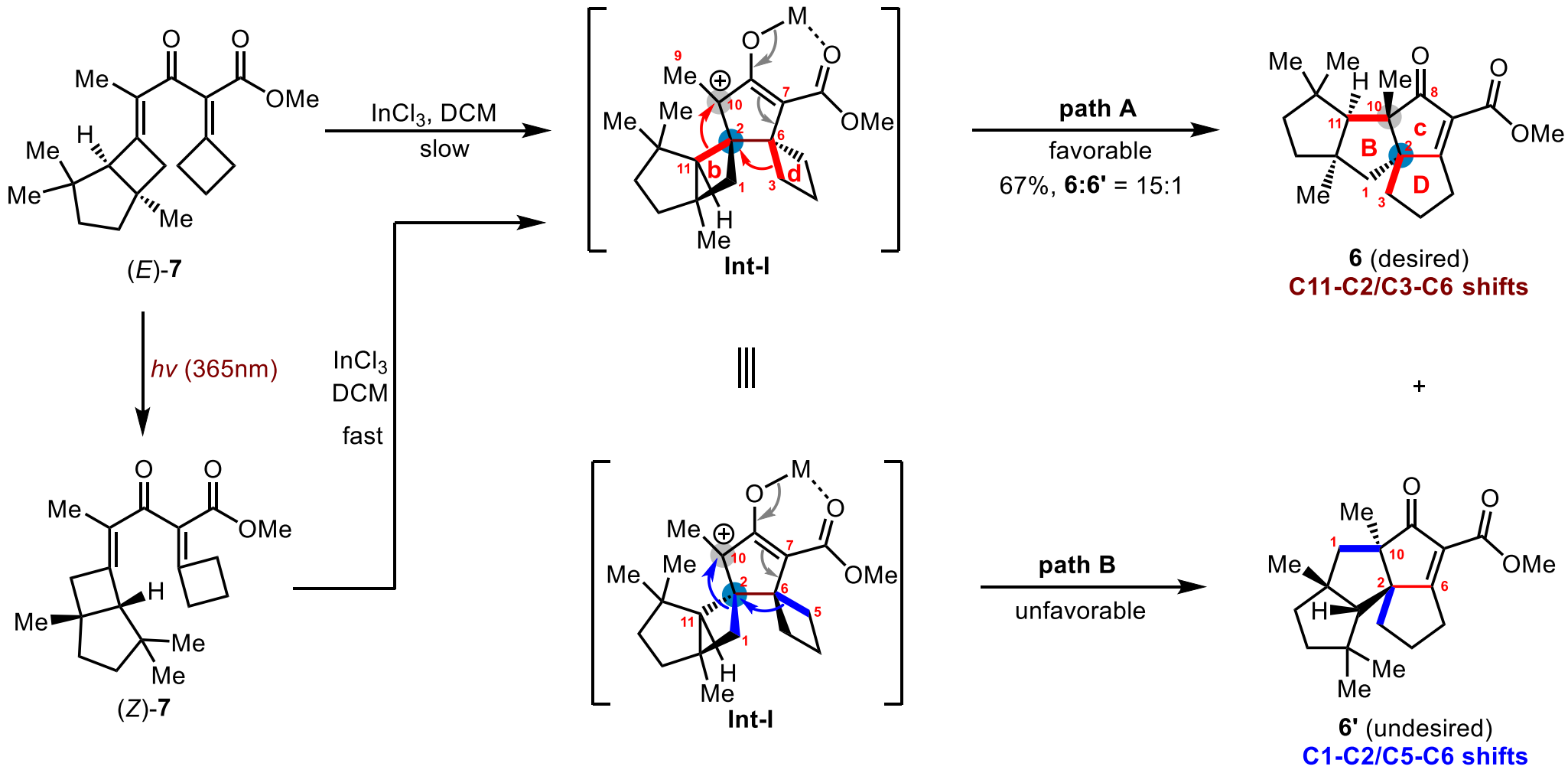
Entry	Substrate	Reaction conditions	Conversion	Yield and ratio of **6**:**6'**
1	**7**, *E*/*Z* 2:1	$Al(OTf)_3$ (0.1 equiv.), DCM, RT		33%, 4.1:1
2	**7**, *E*/*Z* 2:1	$Sc(OTf)_3$ (0.1 equiv.), DCM, RT		42%, 3.2:1
3	**7**, *E*/*Z* 2:1	$Zn(OTf)_2$ (0.1 equiv.), DCM, RT		n.d.
4	**7**, *E*/*Z* 2:1	$Cu(OTf)_2$ (0.1 equiv.), DCM, RT		11%, 1.7:1
5	**7**, *E*/*Z* 2:1	$Fe(OTf)_3$ (0.1 equiv.), DCM, RT		49%, 2:1
6	**7**, *E*/*Z* 2:1	$Sn(OTf)_2$ (0.1 equiv.), DCM, RT		18%, 2.6:1
7	**7**, *E*/*Z* 2:1	$In(OTf)_3$ (0.1 equiv.), DCM, RT		52%, 4.3:1
8	**7**, *E*/*Z* 2:1	$InCl_3$ (0.1 equiv.), DCM, RT		31%, 9.5:1
9	**7**, *E*/*Z* 2:1	$InCl_3$ (0.1 equiv.), $AgBF_4$ (0.3 equiv.), DCM, RT		44%, 4.6:1
10	**7**, *E*/*Z* 2:1	$InCl_3$ (0.1 equiv.), $AgSbF_6$ (0.3 equiv.), $CHCl_3$, RT		72%, 3:1
11	**7**, *E*/*Z* 2:1	$InCl_3$ (0.1 equiv.), $AgNTf_2$ (0.3 equiv.), DCM, RT		79%, 2.5:1
12	**7**, *E*/*Z* 2:1	$InCl_3$ (0.1 equiv.), DCE, RT		40%, 9.6:1
13	**7**, *E*/*Z* 2:1	$InCl_3$ (0.1 equiv.), $CHCl_3$, RT		47%, 7.4:1
14	**7**, *E*/*Z* 2:1	$InCl_3$ (0.1 equiv.), CCl_4, RT		n.d.
15	**7**, *E*/*Z* 2:1	$InCl_3$ (0.1 equiv.), DCM, reflux		53%, 15:1
16	**7**, E/Z 2:1, 2.0 g	$InCl_3$ (0.3 equiv.), DCM (0.5 M), 80°C, 46 h	48%	40%, 15:1
17	(*Z*)-**7**	$InCl_3$ (0.1 equiv.), DCM, reflux	100%	87%,15:1
18	**(*Z*)-7, 1.0 g**	**$InCl_3$ (0.3 equiv.), DCM (0.5 M), 80°C, 12 h**	**100%**	**92%, 15:1**
19	(*E*)-**7**	$InCl_3$ (0.1 equiv.), DCM, reflux	50%	43%, 15:1
20	(*E*)-**7**, 2.0 g	$InCl_3$ (0.3 equiv.), DCM (0.5 M), 80°C, 46 h	35%	20%, 15:1
21	(*E*)-**7**	$InCl_3$ (0.1 equiv.), PTSA (0.1 equiv.) DCM, RT	100%	20%, 1.9:1
22	(*E*)-**7**	$InCl_3$ (0.1 equiv.), $(PhO)_2PO_2H$ (0.1 equiv.), DCM, RT	92%	46%, 2.5:1
23	(*E*)-**7**	$FeCl_3$ (0.1 equiv.), DCM, reflux	81%	29%, 4.4:1
24[b]	(*E*)-**7**, 1.0 g	*hν* (365 nm), DCM (0.2 M), RT, 10 h		n.d.
25[c]	(*E*)-**7**, 1.0 g	*hν* (254 nm), DCM (0.2 M), RT, 10 h		n.d.
26	(*E*)-**7**, 0.24 g	$InCl_3$ (0.3 equiv.), DCM (0.05 M), *hν* (365 nm), 80°C, 24 h	75%	58%, 15:1
27	**(*E*)-7, 1.0 g**	**$InCl_3$ (0.3 equiv.),DCM (0.21 M), *hν* (365 nm), 80°C, 48 h**	**71%**	**67%, 15:1**

[a] The reaction was run on a 0.2 mmol scale in solvent (1.0 mL) for 12 hours. All yields were isolated yields, while the ratio of 6:6' was determined by ^1H NMR. [b] (*E*)-**7** was recycled in 54% yield, (*Z*)-**7** was isolated in 45% yield. [c] (*E*)-**7** was recycled in 31% yield, (*Z*)-**7** was isolated in 58% yield. n.d. = not detected.

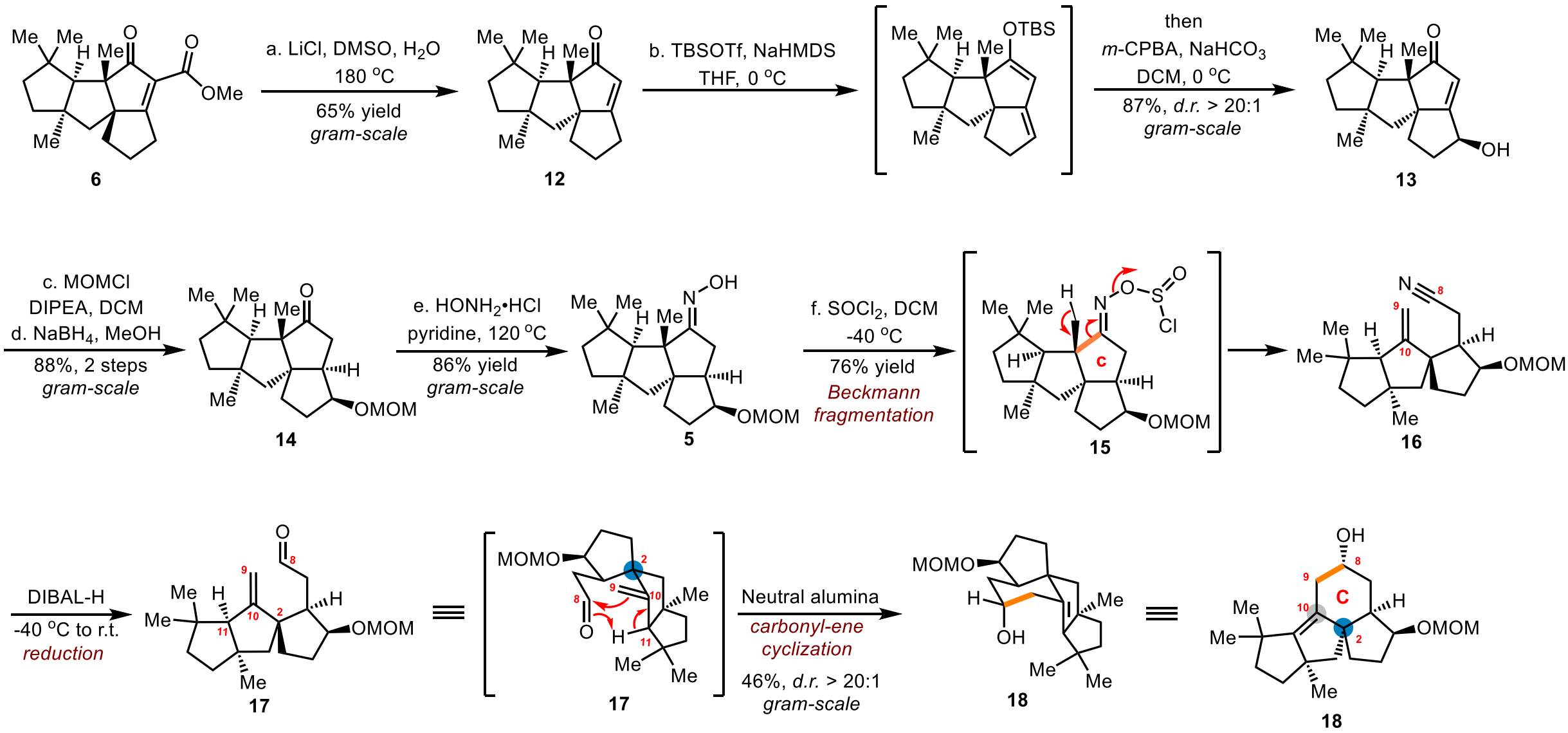
Scheme S1. Proposed Mechanism for Formation of 6 and 6′ from (*Z*)-7



Scheme S2. Proposed Mechanism for Formation of 6 and 6′ from (E)-7

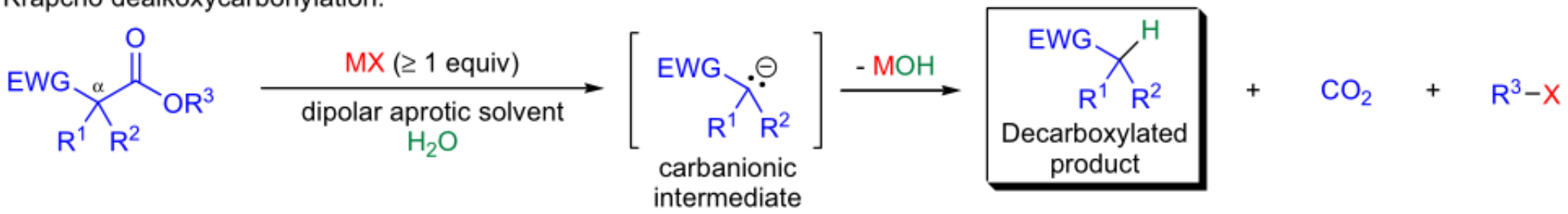


Scheme 3. Total Synthesis and Structure Revision of *iso*-Phomopsene



KRAPCHO DEALKOXYCARBONYLATION

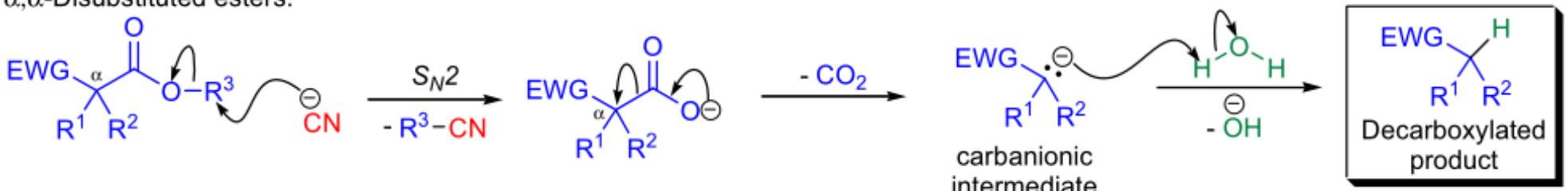
Krapcho dealkoxycarbonylation:



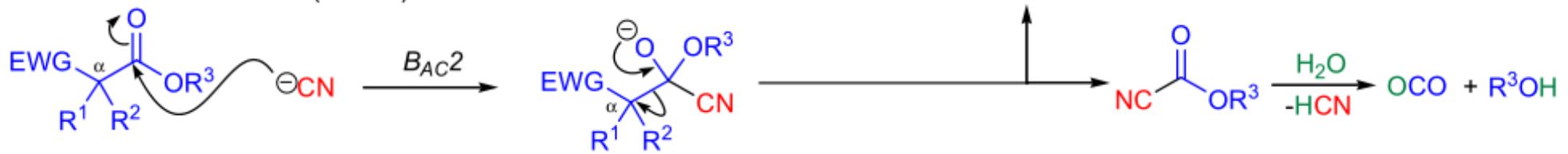
EWG = CO_2-alkyl, CO_2-aryl, CN, CO-alkyl, SO_2-alkyl, SO_2-aryl; $R^{1\text{-}2}$ = H, alkyl, aryl; R^3 = Me, Et; MX = NaCN, KCN, LiCl, NaCl, NaBr, NaI, LiI·H_2O, Na_2CO_3·H_2O, Na_3PO_4·$12H_2O$, Me_4NOAc ; solvent: DMSO, DMF, DMA, HMPT

Mechanism: [16,17,9,18,19]

α,α-Disubstituted esters:

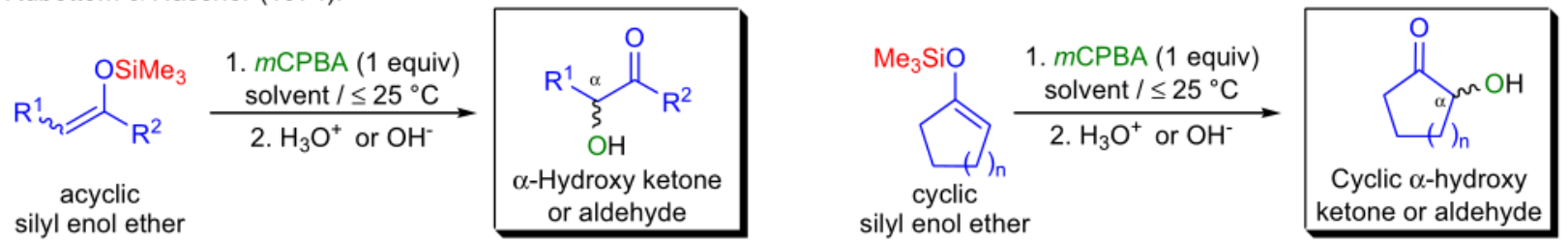


α-Monosubstituted esters (R^2 = H):

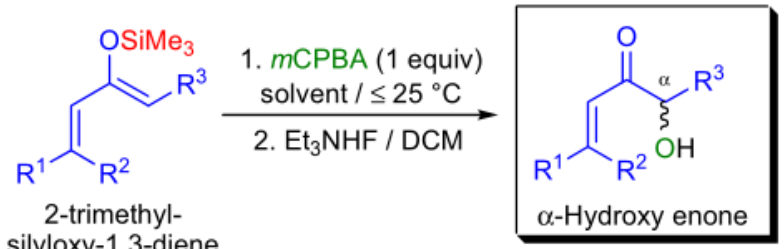


RUBOTTOM OXIDATION

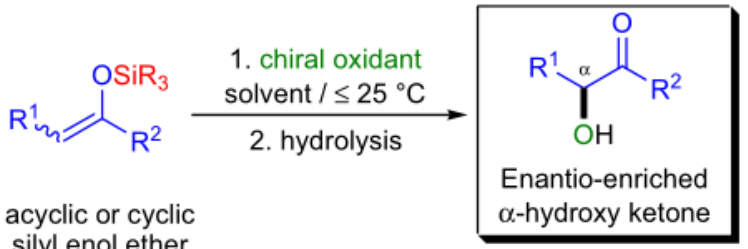
Rubottom & Hassner (1974):



Oxidation of 2-trimethylsilyloxy-1,3-dienes:

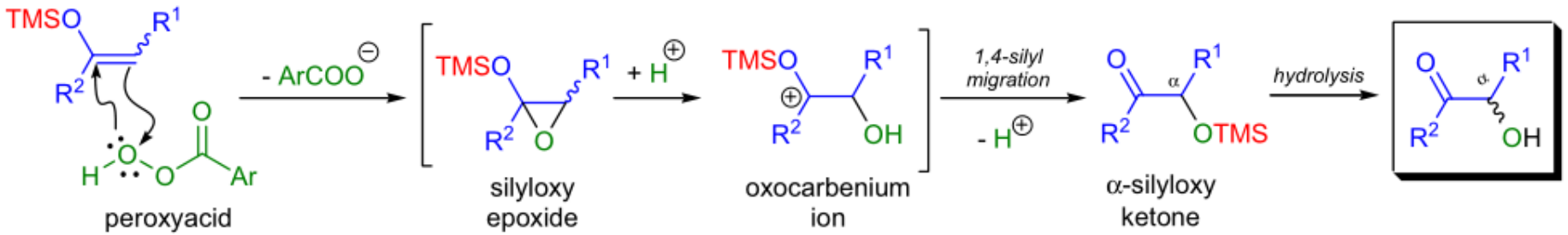


Asymmetric modification:

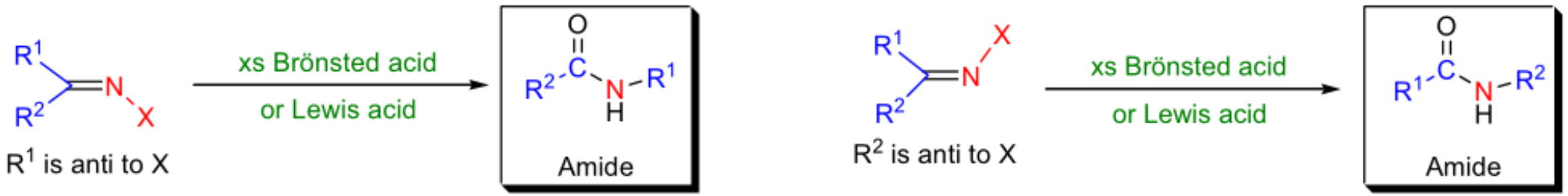


R^{1-3} = H, alkyl, aryl, substituted alkyl and aryl; SiR_3 = $SiMe_3$, $SiMe_2$(t-Bu), $SiEt_3$; solvent: CH_2Cl_2, pentane, toluene; n = 1-3;
chiral oxidant: Davis' chiral oxaziridine, Shi's D-fructose derived ketone/Oxone, (Salen)manganese(III)-complexes/NaOCl or PhIO

Mechanism: [18,1,19]



BECKMANN REARRANGEMENT



R^1, R^2 = alkyl, aryl, heteroaryl; X = OH, OTs, OMs, Cl

Mechanism: [28,19,22-24,29-31]

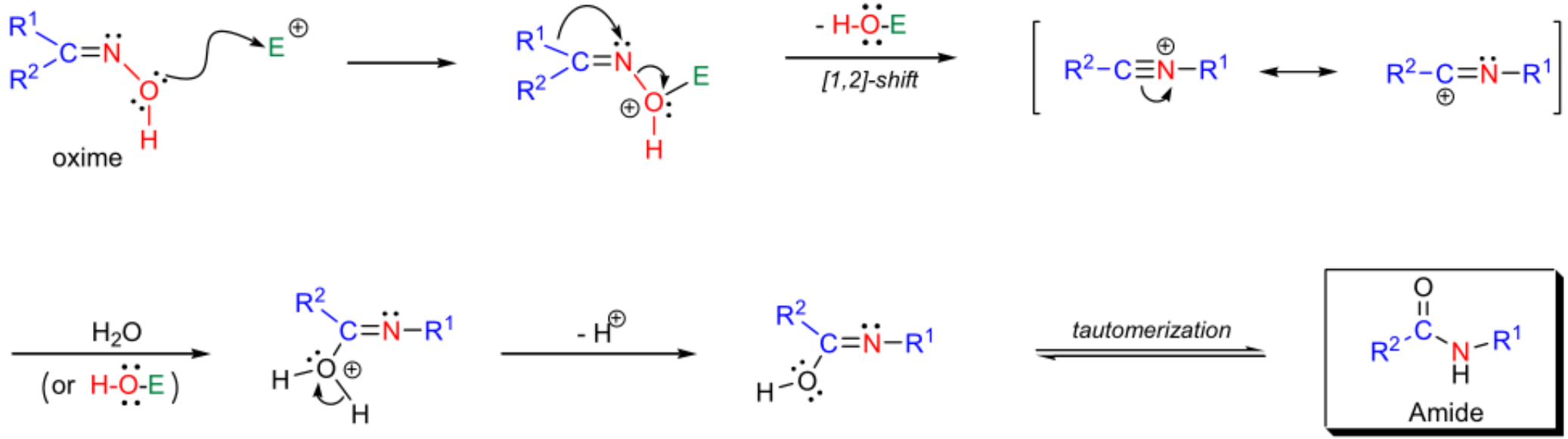
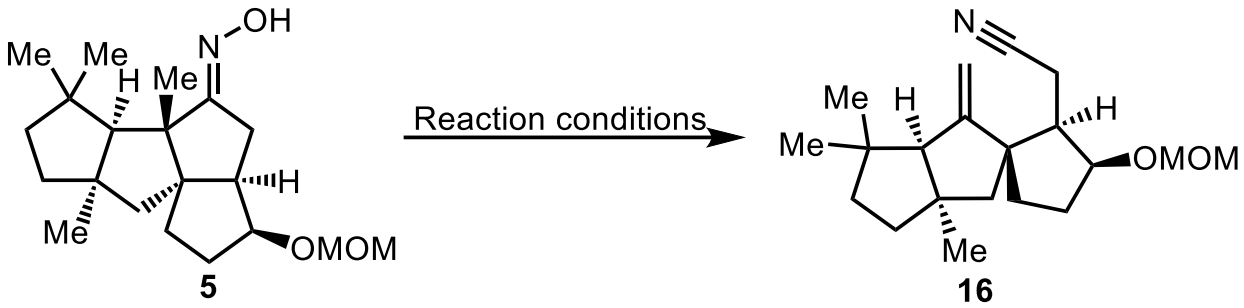
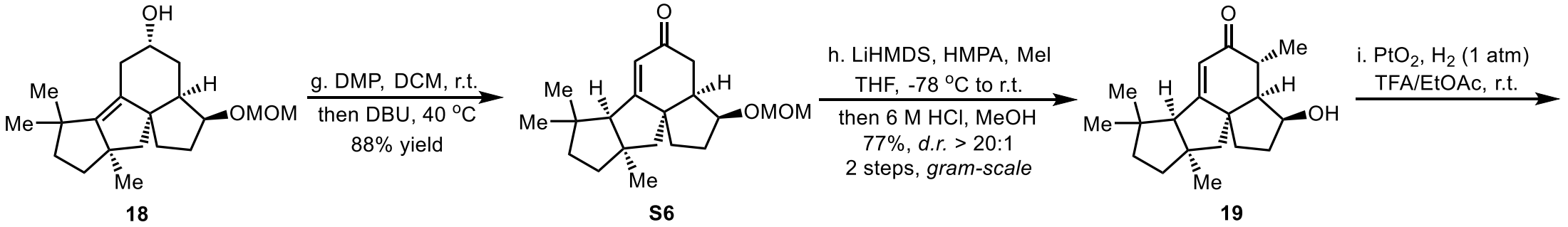


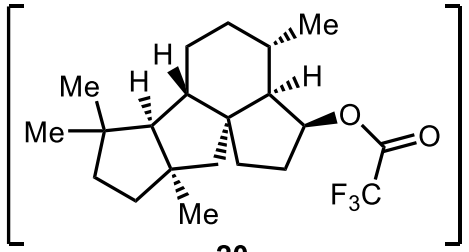
Table S2. Optimization of the Beckmann Fragmentation with Compound 5 [a]



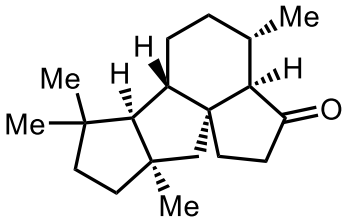
Entry	Reaction conditions	Yield of 16
1	TsCl (2.0 equiv), pyridine (0.5 M) 80 °C, 2 h	37%
2	H_2SO_4 (8.0 M, 3.0 equiv), 120 °C, 1 h	n.d.
3	TFA (1.0 equiv), DCC (3.0 equiv) DMSO/Benzene(1:1 0.1M), RT, 12 h	31%
4	TFA (1.0 equiv), $CH(OMe)_3$ (2.0 equiv) THF (0.2 M), reflux, 12 h	22%
5	Ac_2O (1.5 equiv), PTSA (1.5 equiv) MeCN (0.2 M), 60°C, 12 h	n.d.
6	$SOCl_2$ (1.0 eq), $CHCl_3$ (0.1M), RT, 1 h	40%
7	$SOCl_2$ (1.0 eq), DCM (0.1M), RT, 1 h	46%
8	$SOCl_2$ (1.0 eq), DCM (0.1M), 0°C, 1 h	44%
9	$SOCl_2$ (1.0 eq), DCM (0.1M), -40°C, 1 h	71%
10 [b]	**$SOCl_2$ (0.7 eq), DCM (0.1M), -40°C, 1 h**	**73%**
11	$SOCl_2$ (0.5 eq), DCM (0.1M), -40°C, 1 h	65%

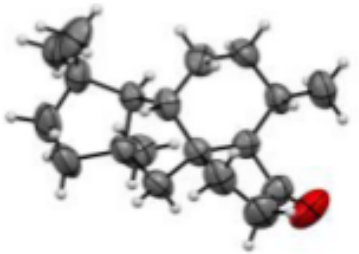
[a] The reaction was run on a 0.2 mmol scale, all yields were isolated yields. n.d. = not detected. b The reaction was run on a 2.0 mmol scale.





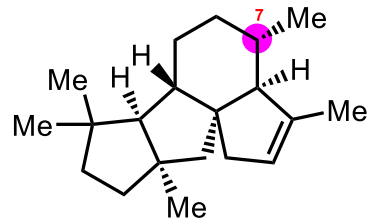
Li_2CO_3, MeOH
DMP, DCM
63%, *d.r.* > 20:1
280 mg-scale



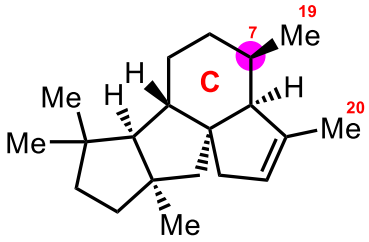


X-ray structure of **21**

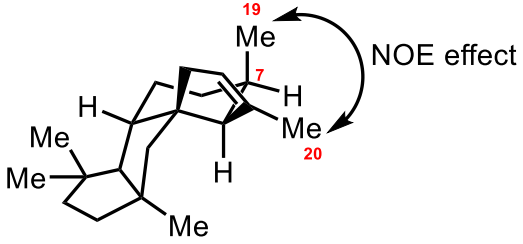
j. LiHMDS, $PhNTf_2$
THF, -78 °C to r.t.
then $Pd(PPh_3)_4$
MeMgBr, r.t.
66% yield

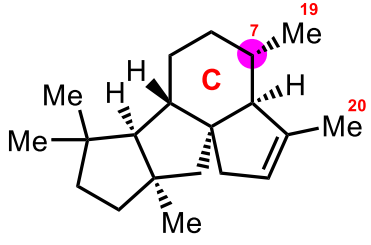


***iso*-phomopsene (3)**
revised structure

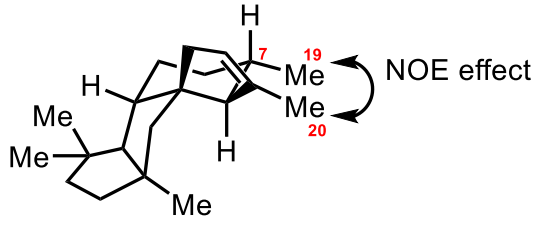


***iso*-phomopsene (3a)**
originally proposed structure

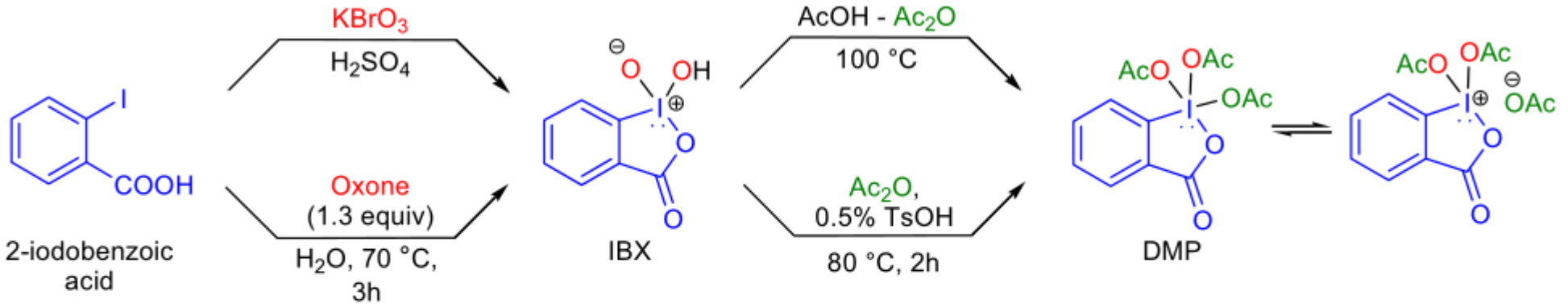


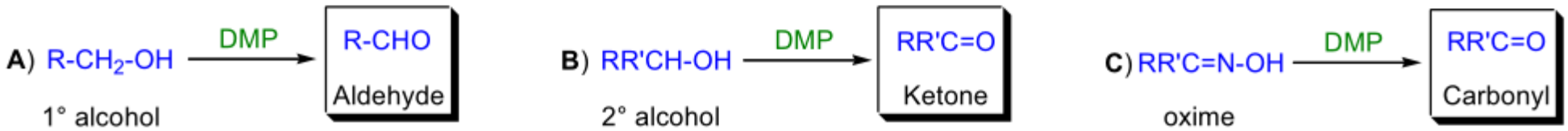


***iso*-phomopsene (3)**
revised structure

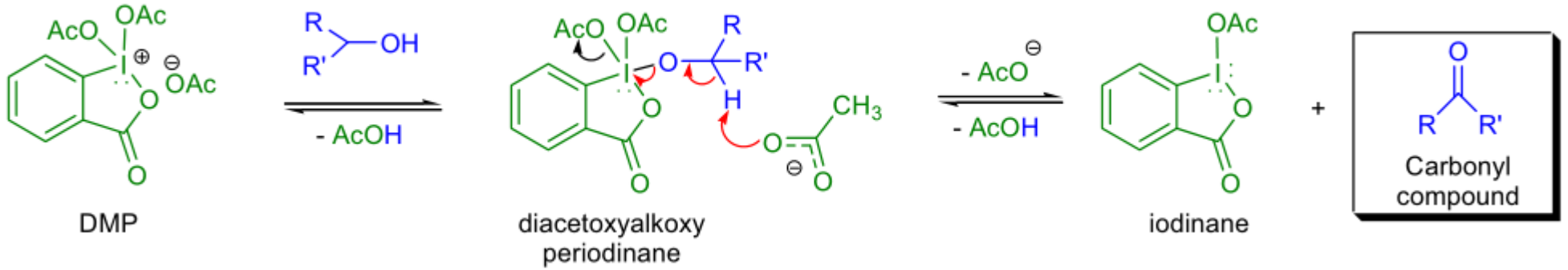


DESS-MARTIN OXIDATION

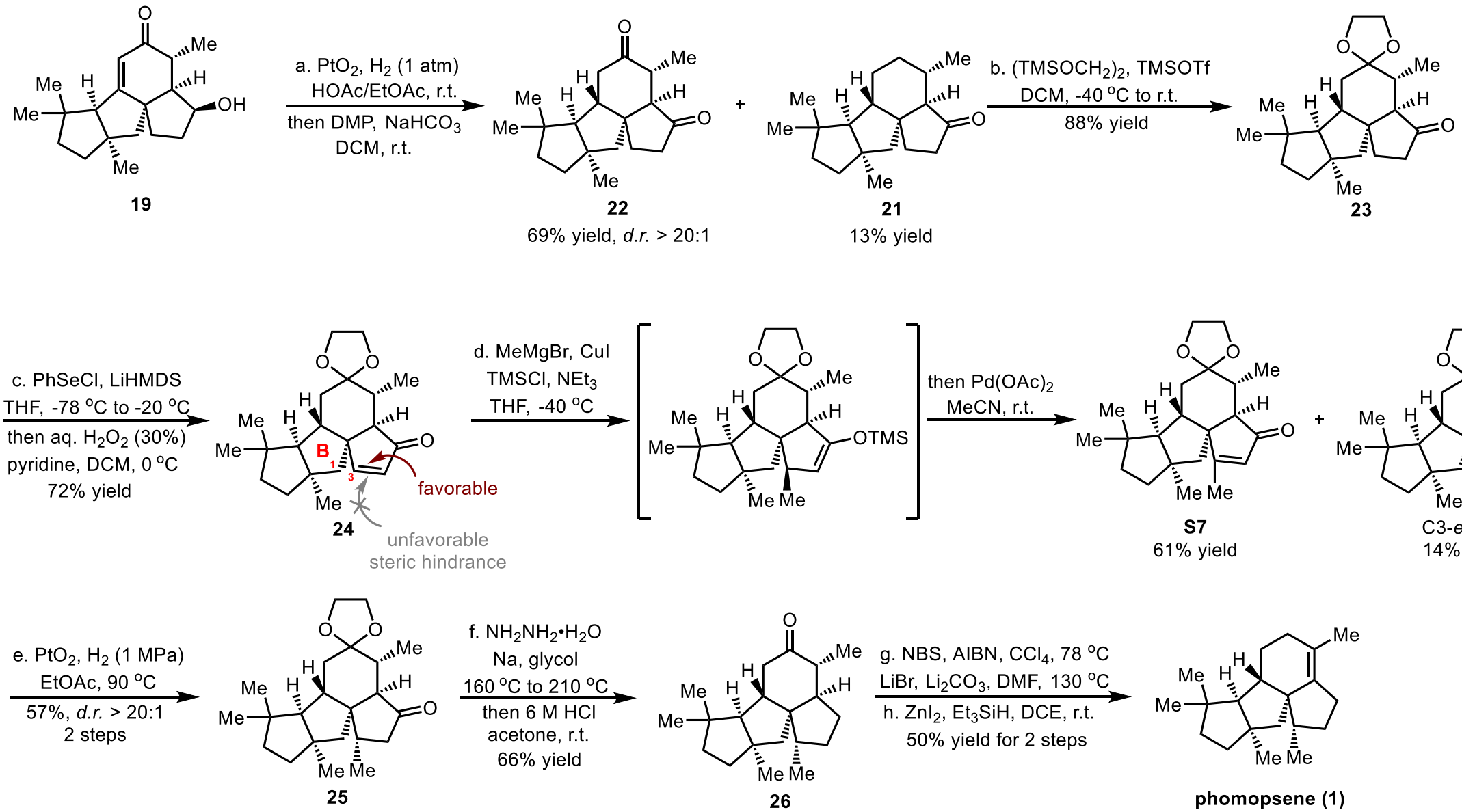




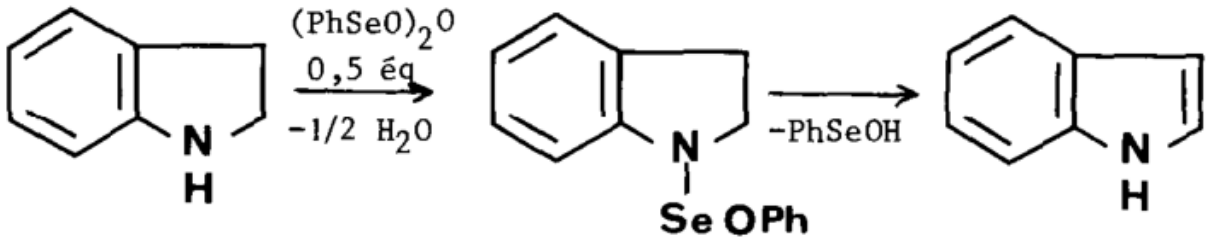
Mechanism: [9,11,27,28]



Scheme 4. Total Syntheses of Phomopsene and Methyl Phomopsenonate



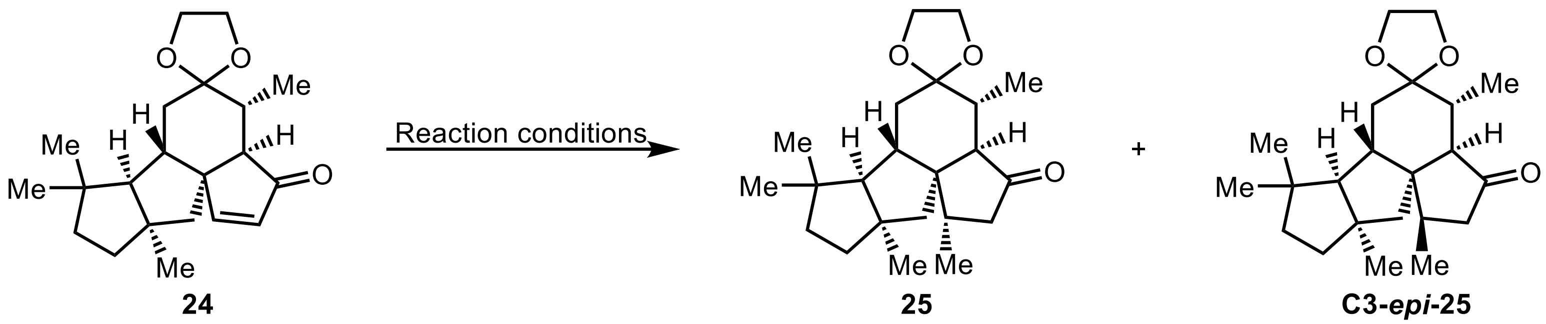
23-24



(1) (6)

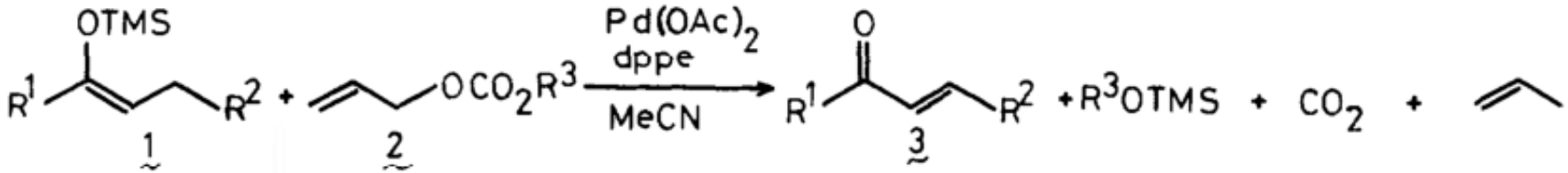
Tetrahedron Lett., **1982**, *23*, 4949.

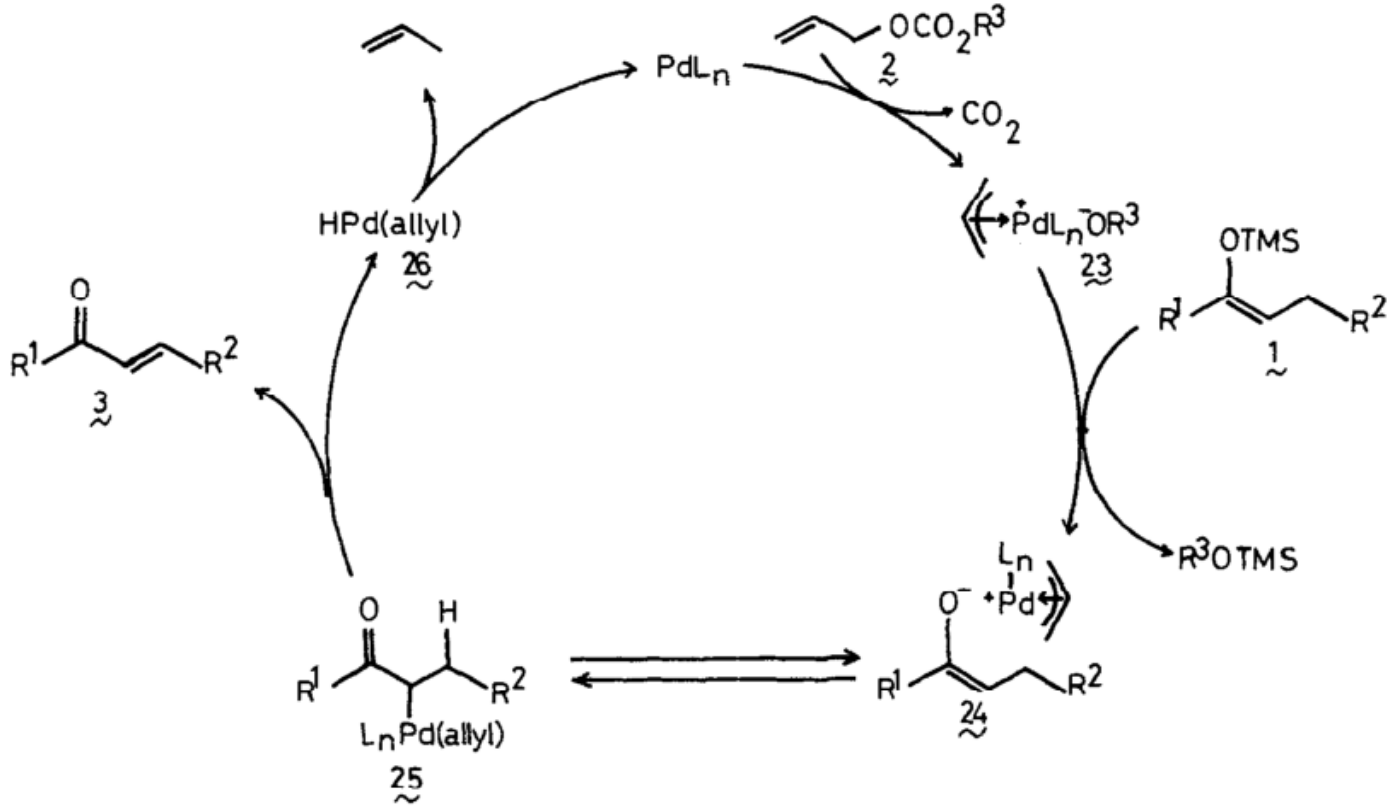
Table S3. Optimization of the 1,4-Addition with Compound 24 [a]



Entry	Reaction conditions	Yield 25	Yield C3-*epi*-25
1	CuI (3.0 equiv) MeMgBr (3.0 M in Et_2O, 6.0 equiv)	n.d.	79%
2	$Cu(OTf)_2$ (3.0 equiv) MeMgBr (3.0 M in Et_2O, 6.0 equiv)	n.d.	44%
3	CuTc (3.0 equiv) MeMgBr (3.0 M in Et_2O, 6.0 equiv)	n.d.	57%
4	$CuBr{\cdot}Me_2S$ (3.0 equiv) MeMgBr (3.0 M in Et_2O, 6.0 equiv)	n.d.	n.d.
5	$Ni(acac)_2$ (3.0 equiv) MeMgBr (3.0 M in Et_2O, 6.0 equiv)	n.d.	68%
6	CuI (3.0 equiv) $AlMe_3$ (1.0 M in toluene, 6.0 equiv)	n.d.	61%
7	CuI (3.0 equiv) Me_2Zn (1.0 M in hexane, 6.0 equiv)	n.d.	n.d.

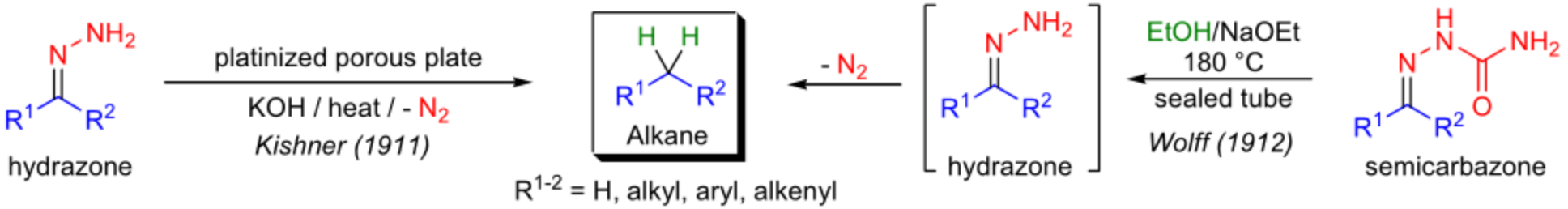
[a] The reaction was run on a 0.2 mmol scale in THF (1.0 mL) at 0 °C for 12 hours, all yields were isolated yields. n.d. = not detected.





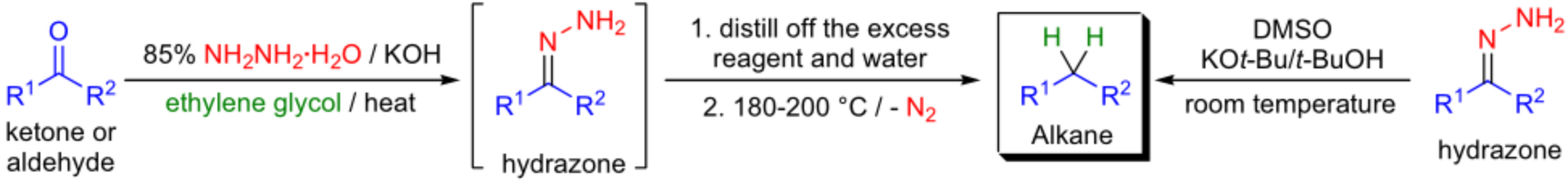
Tetrahedron Lett., **1983**, *23*, 5635.

WOLFF-KISHNER REDUCTION



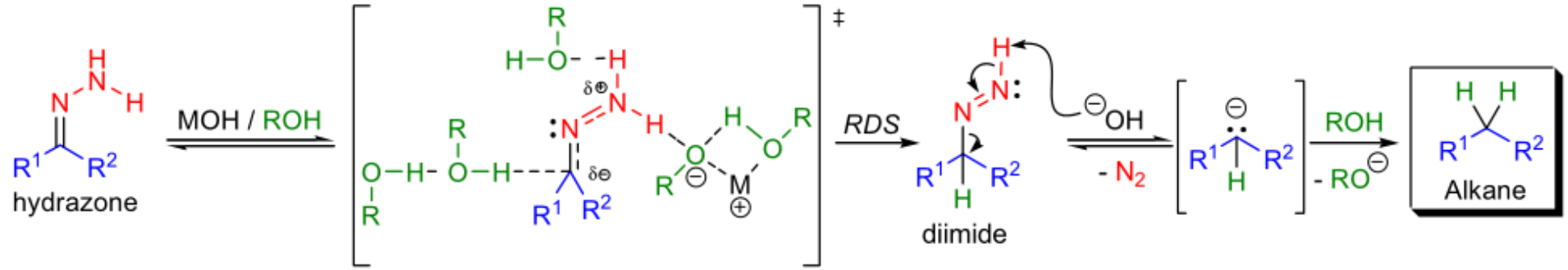
Huang-Minlon modification (1946):

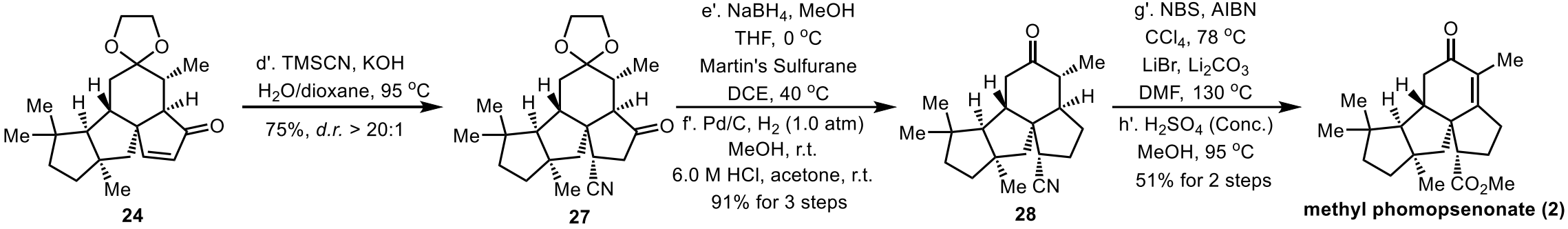
Cram modification (1962):



Mechanism: [25-32]

The rate-determining step is the proton capture at the carbon terminal. This process takes place in a concerted fashion with the solvent-induced proton abstraction at the nitrogen terminus to form a diimide that undergoes a loss of N_2.





Scheme 5. Enantioselective Syntheses of 1−3

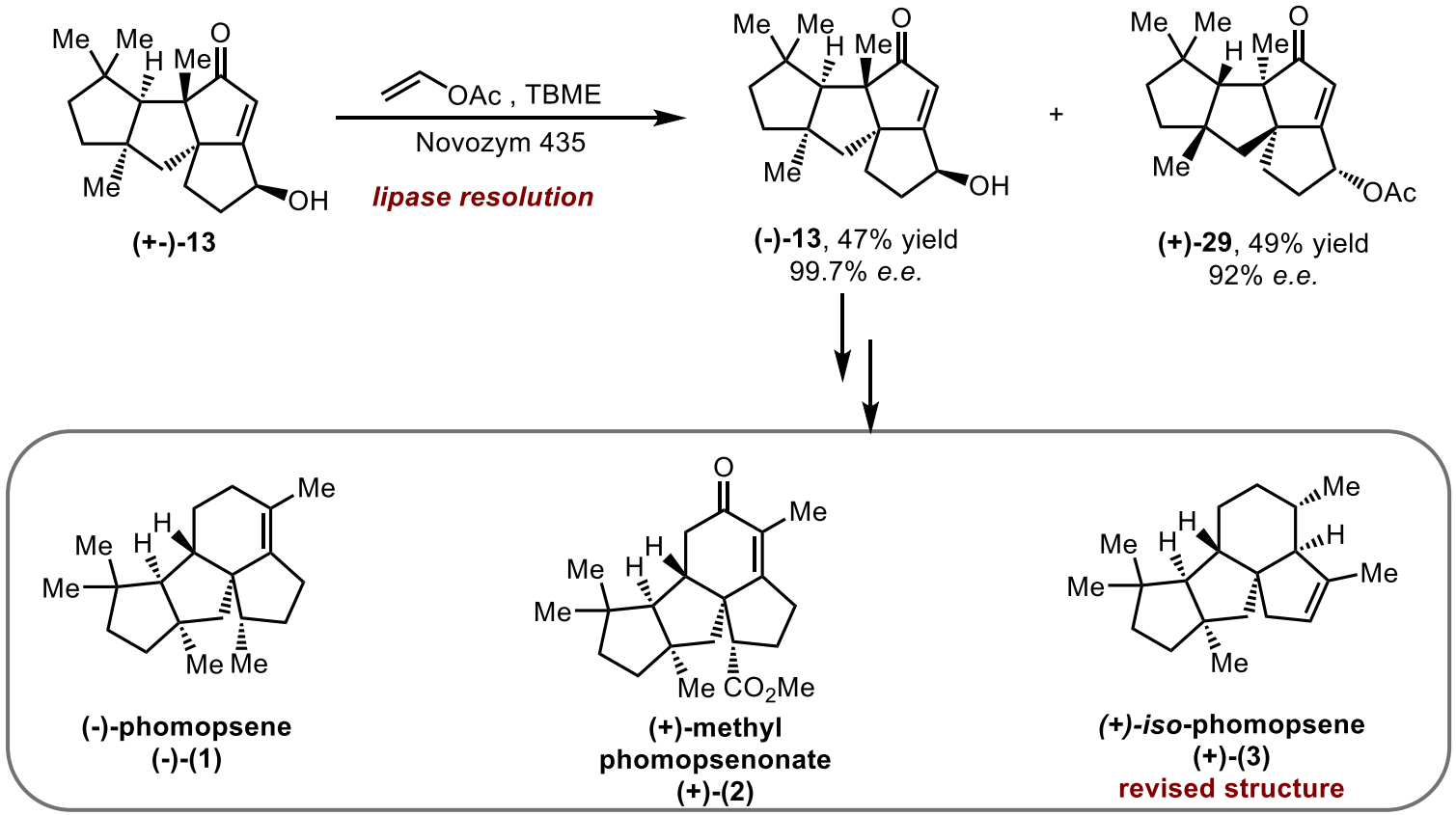
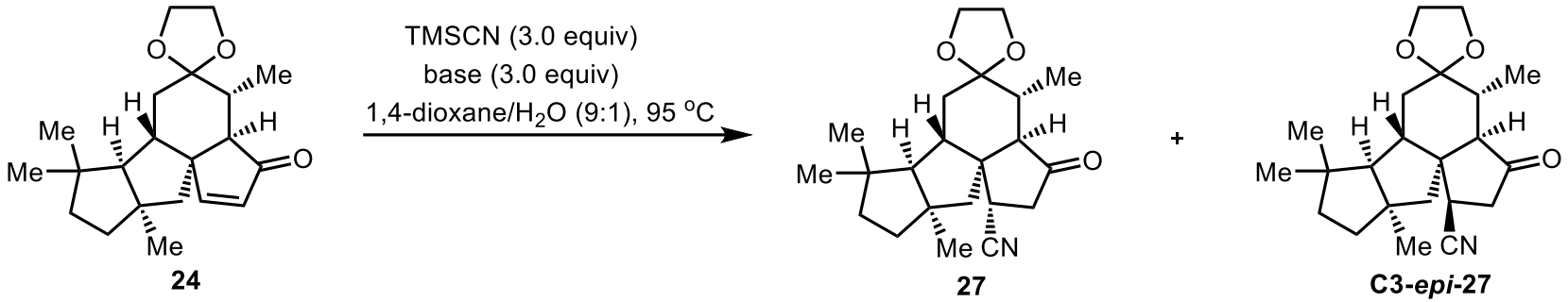


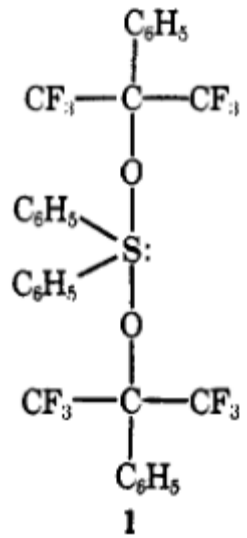
Table S4. Condition Screening for Cyanogenation of Compound 24 [a]



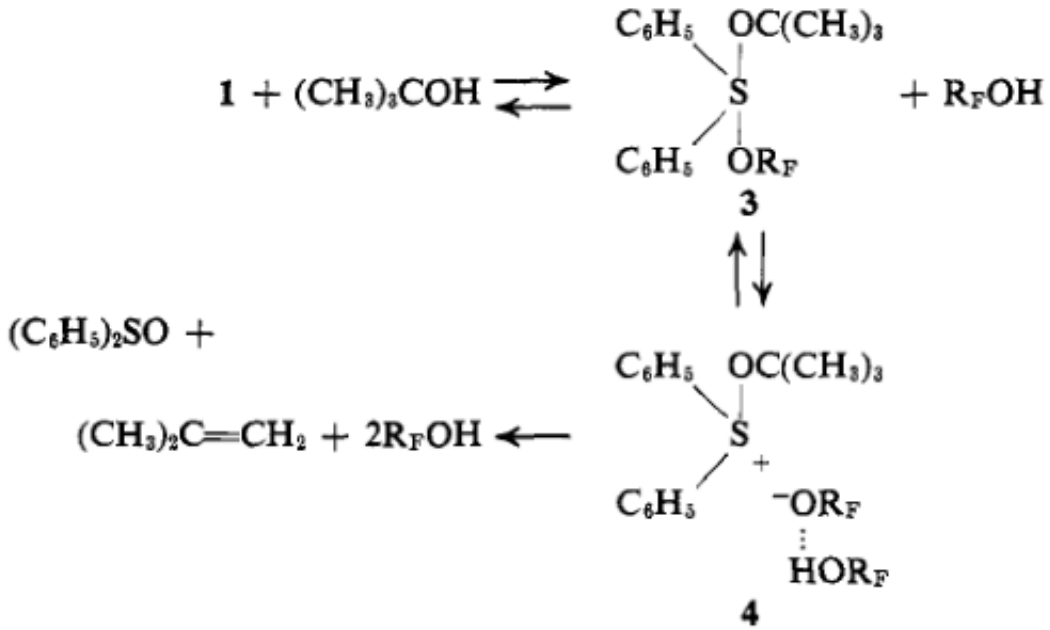
Entry	Base	Yield	
		27	C3-*epi*-27
1	NaF	n.d.	32%
2	KF	n.d.	<5%
3	CsF	<5%	65%
4	TBAF	n.d.	12%
5	NaOH	71%	<5%
6	KOH	75%	<5%
7	Na_2CO_3	<5%	66%
8	K_2CO_3	<5%	78%
9	Cs_2CO_3	<5%	72%
10	CsOAc	n.d.	<5%

[a] The reaction was run with **24** (0.1 mmol, 1.0 equiv.), TMSCN (0.3 mmol, 3.0 equiv.) and base (0.3 mmol, 3.0 equiv.) in1,4-dioxane/H_2O (9:1, 0.5 mL) at 95 ℃ for 6 hours, all yields were isolated yields. n.d. = not detected.

Martin's Sulfurane



1



J. Am. Chem. Soc., **1971**, 5003.