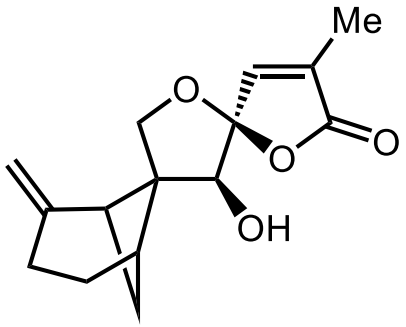
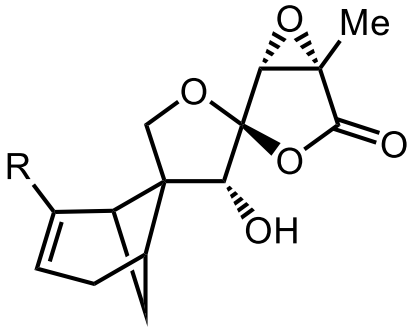
Flow Chemistry-Enabled Divergent and Enantioselective Total Syntheses of Massarinolin A, Purpurolides B, D, E, 2,3- Deoxypurpurolide C, and Structural Revision of Massarinolin A

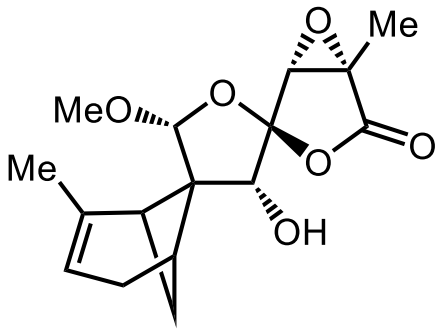
Ye-Cheng Wang,[a][b] Chengsen Cui,[a][b] and Mingji Dai*[a]



Massarinolin A
(**1b**, revised)

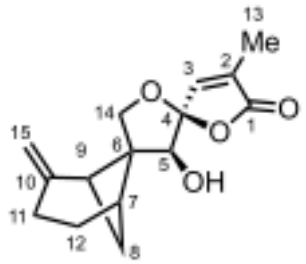


Purpurolide B (R = OAc)
Purpurolide D (R = OH)
Purpurolide E (R = H)



Purpurolide C (8)

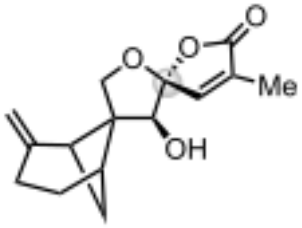
DOI: 10.1002/anie.202109625.



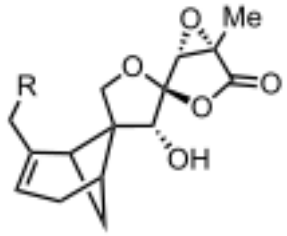
Massarinolin A
(**1a**, originally proposed)
antibacterial activity

bicyclo[3.1.1]heptane
oxaspiro[3.4]octane
dioxaspiro[4.4]nonane

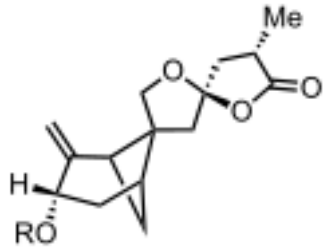
this work:
first total synthesis
structural revision



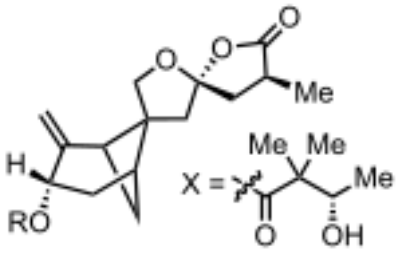
Massarinolin A
(**1b**, revised)



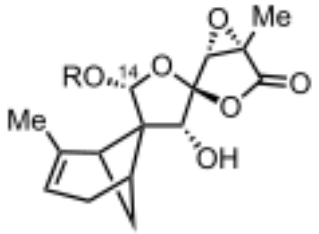
Purpurolide B (**2**, R = OAc)
Purpurolide D (**3**, R = OH)
Purpurolide E (**4**, R = H)
pancreatic lipase inhibition



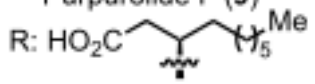
Expansolide A (**5a**, R = Ac)
Expansolide C (**6a**, R = H)
Decipienolide A (**7a**, R = X)



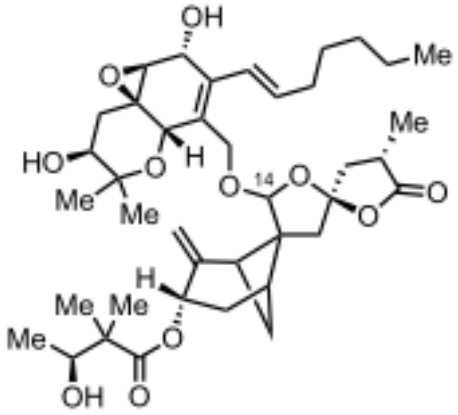
Expansolide B (**5b**, R = Ac)
Expansolide D (**6b**, R = H)
Decipienolide B (**7b**, R = X)



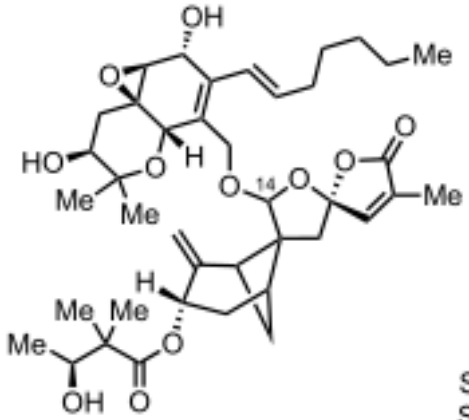
Purpurolide C (**8**, R = Me)
Purpurolide F (**9**)



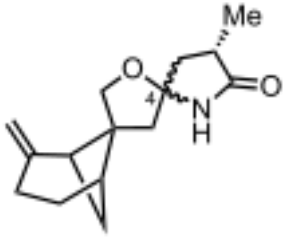
α-glucosidase inhibition activity



Eutypellacytosporin A (**10a**, 14*S*)
Eutypellacytosporin B (**11a**, 14*R*)

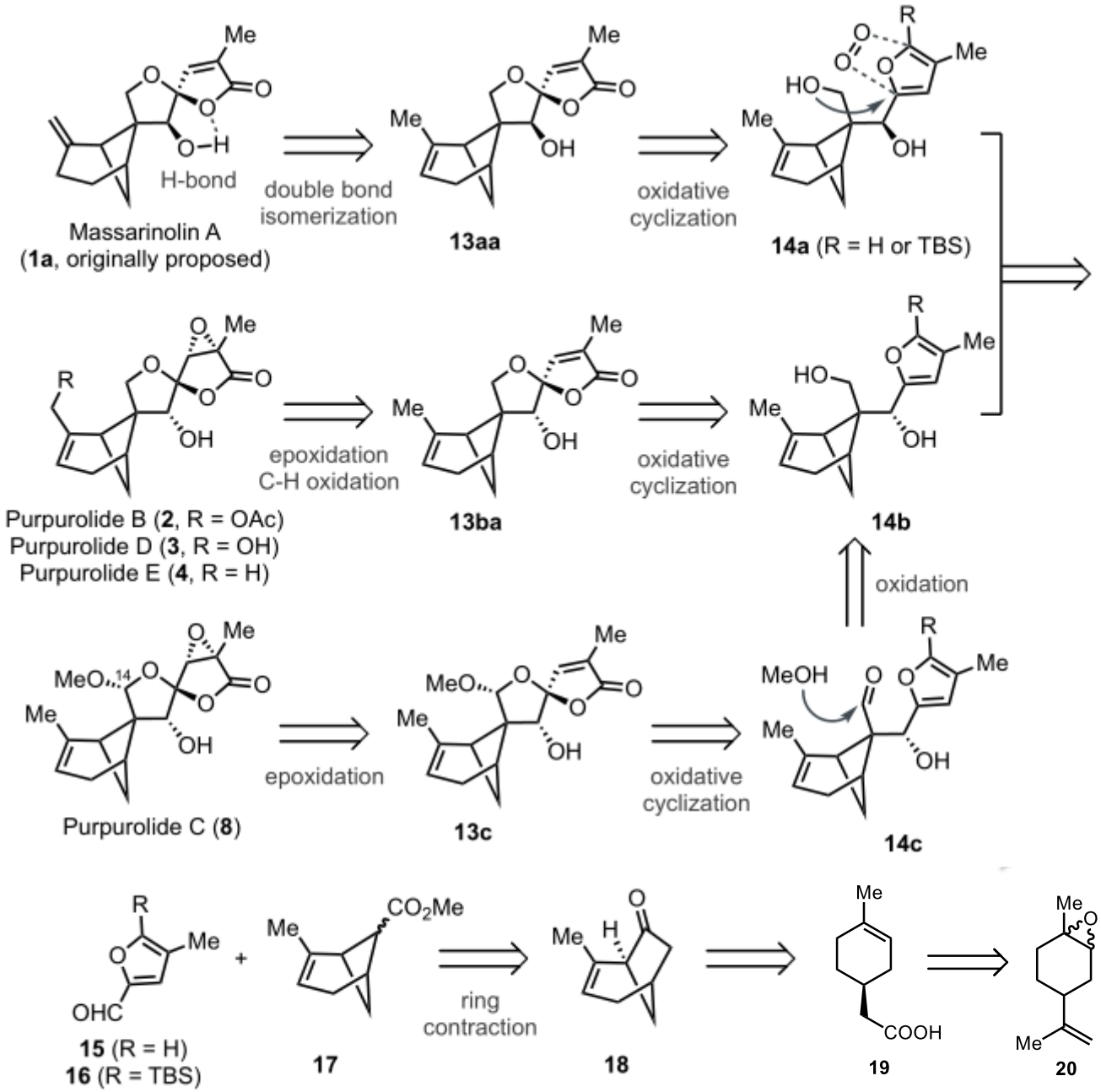


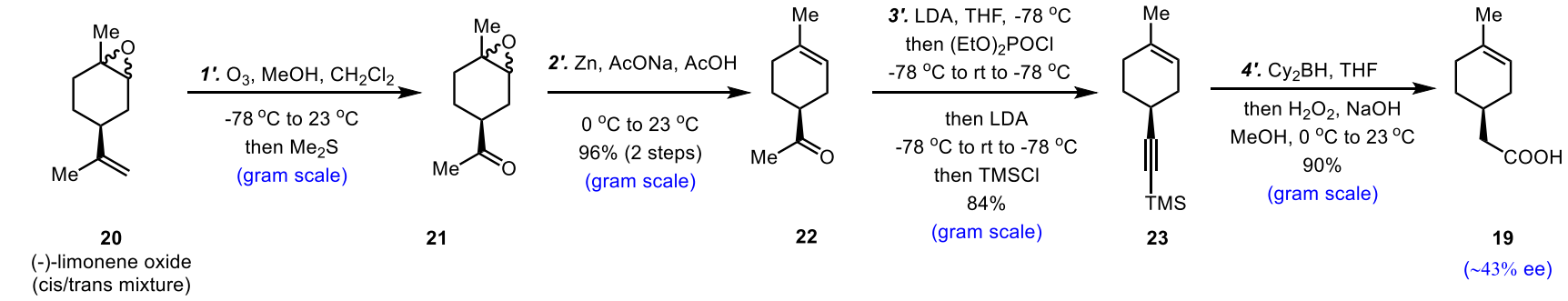
Eutypellacytosporin C (**10b**, 14*S*)
Eutypellacytosporin D (**11b**, 14*R*)

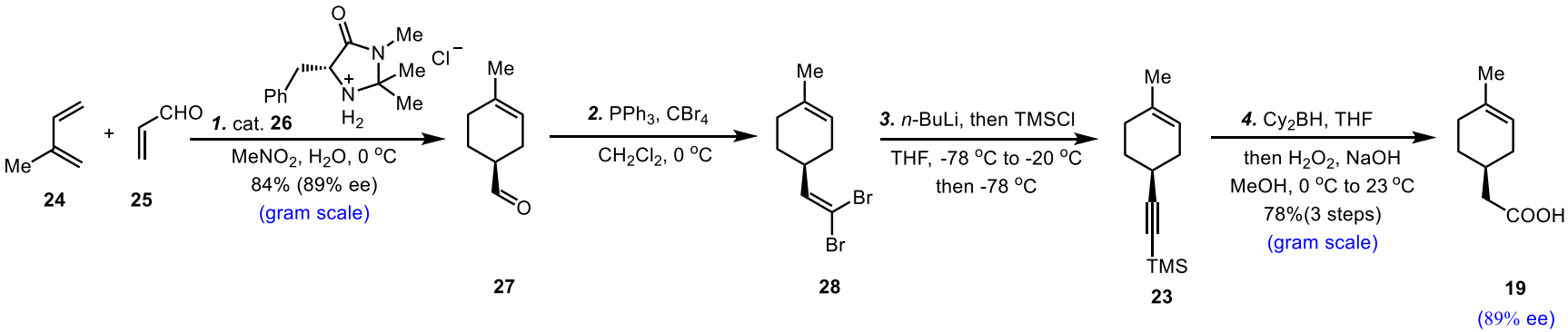


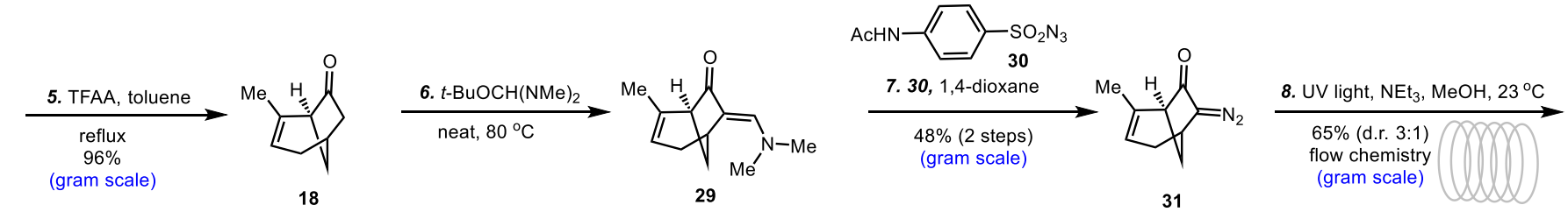
Sporulaminal A (**12a**, 4*R*)
Sporulaminal B (**12b**, 4*S*)

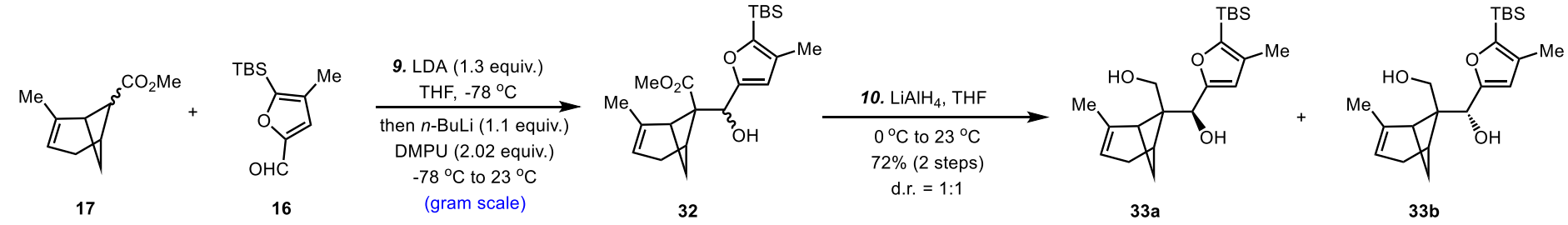
IC_{50}: 4.9 to 17.1 μM against DU145, SW1990, Huh7, and PANC-1

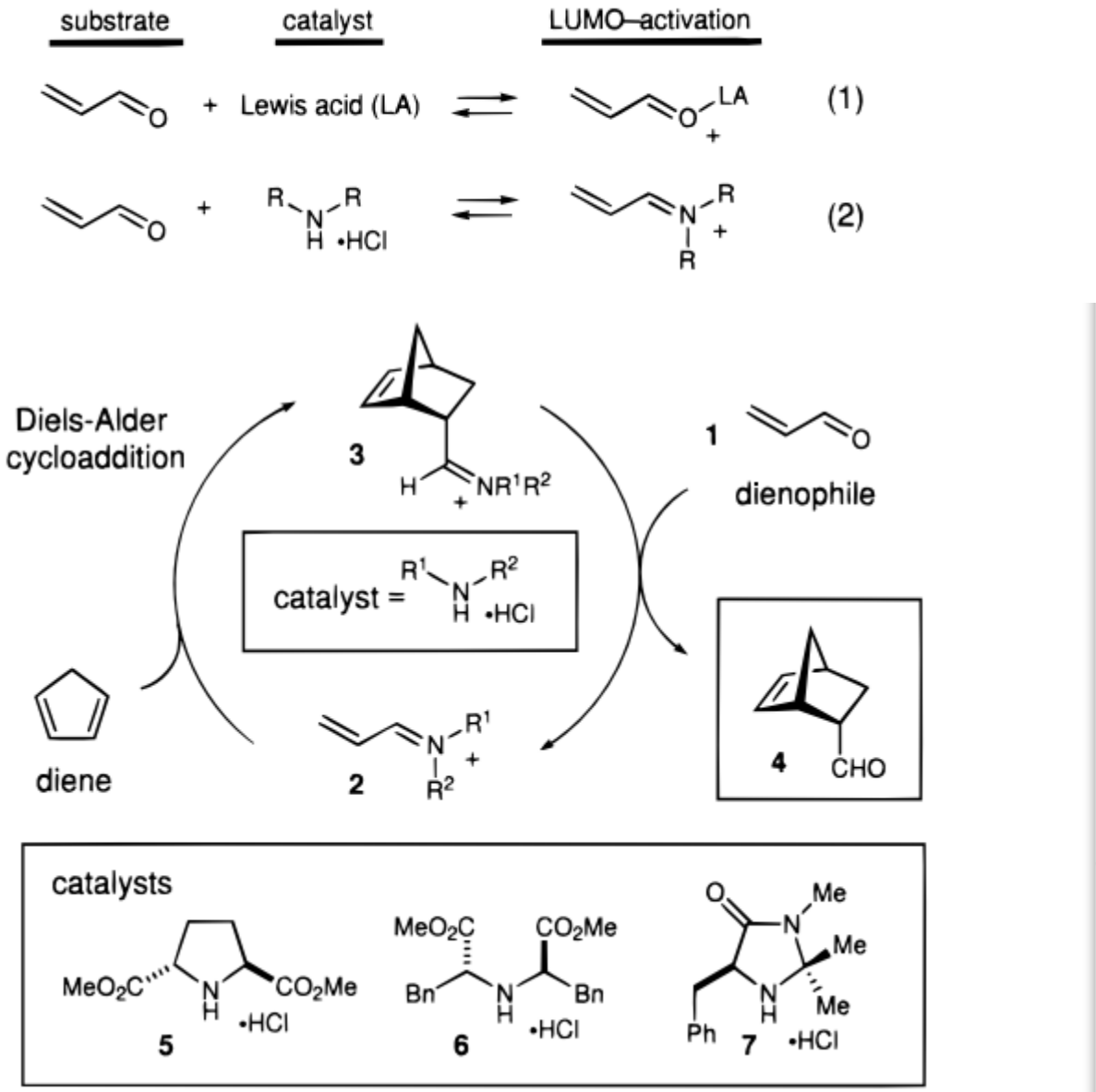

Me
O
O
O
O–H
H-bond
Massarinolin A
(1a, originally proposed)
double bond
isomerization
13aa
oxidative
cyclization
14a (R = H or TBS)
R
HO
OH
epoxidation
C-H oxidation
Purpurolide B (2, R = OAc)
Purpurolide D (3, R = OH)
Purpurolide E (4, R = H)
13ba
14b
oxidation
MeO
Purpurolide C (8)
epoxidation
13c
MeOH
14c
CO2Me
OHC
15 (R = H)
16 (R = TBS)
17
ring
contraction
18
COOH
19
20


1'. O3, MeOH, CH2Cl2
-78 °C to 23 °C
then Me2S
(gram scale)
2'. Zn, AcONa, AcOH
0 °C to 23 °C
96% (2 steps)
(gram scale)
3'. LDA, THF, -78 °C
then (EtO)2POCl
-78 °C to rt to -78 °C
then LDA
-78 °C to rt to -78 °C
then TMSCl
84%
(gram scale)
4'. Cy2BH, THF
then H2O2, NaOH
MeOH, 0 °C to 23 °C
90%
(gram scale)
20
(-)-limonene oxide
(cis/trans mixture)
21
22
23
19
(~43% ee)


24
25
1. cat. 26
MeNO2, H2O, 0 °C
84% (89% ee)
(gram scale)
27
2. PPh3, CBr4
CH2Cl2, 0 °C
28
3. n-BuLi, then TMSCl
THF, -78 °C to -20 °C
then -78 °C
23
4. Cy2BH, THF
then H2O2, NaOH
MeOH, 0 °C to 23 °C
78%(3 steps)
(gram scale)
19
(89% ee)


5. TFAA, toluene
reflux
96%
(gram scale)
18
6. t-BuOCH(NMe)2
neat, 80 °C
29
30
7. 30, 1,4-dioxane
48% (2 steps)
(gram scale)
31
8. UV light, NEt3, MeOH, 23 °C
65% (d.r. 3:1)
flow chemistry
(gram scale)

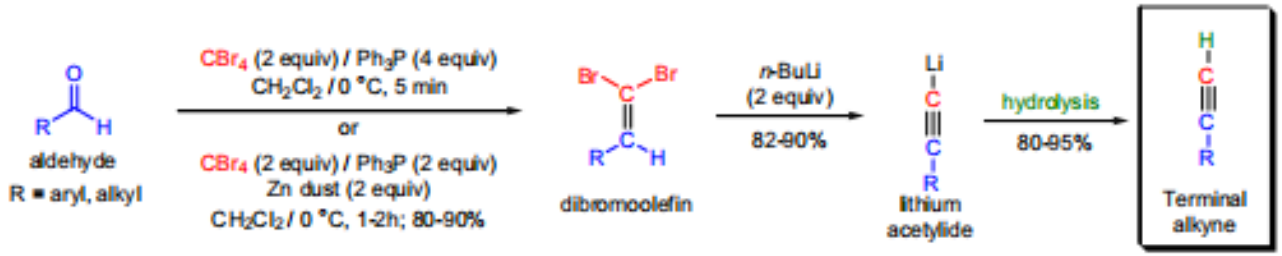

17
16
9. LDA (1.3 equiv.)
THF, -78 °C
then n-BuLi (1.1 equiv.)
DMPU (2.02 equiv.)
-78 °C to 23 °C
(gram scale)
32
10. LiAlH4, THF
0 °C to 23 °C
72% (2 steps)
d.r. = 1:1
33a
33b



J. Am. Chem. Soc. **2000**, *122*, 4243.

COREY-FUCHS ALKYNE SYNTHESIS

(References are on page 566)

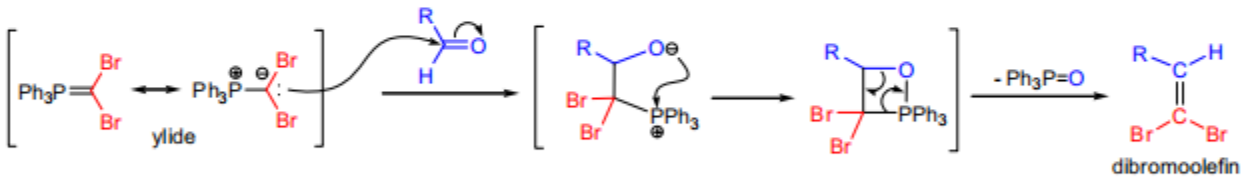


Mechanism: [6,1]

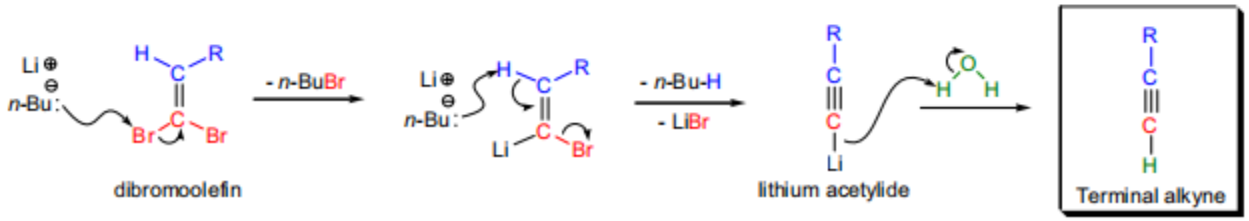
The mechanism of dibromoolefin formation from the aldehyde is similar to the mechanism of the *Wittig reaction*. However, there is very little known about the formation of the alkyne from the dibromoolefin. The mechanism below is one possible pathway to the observed product.

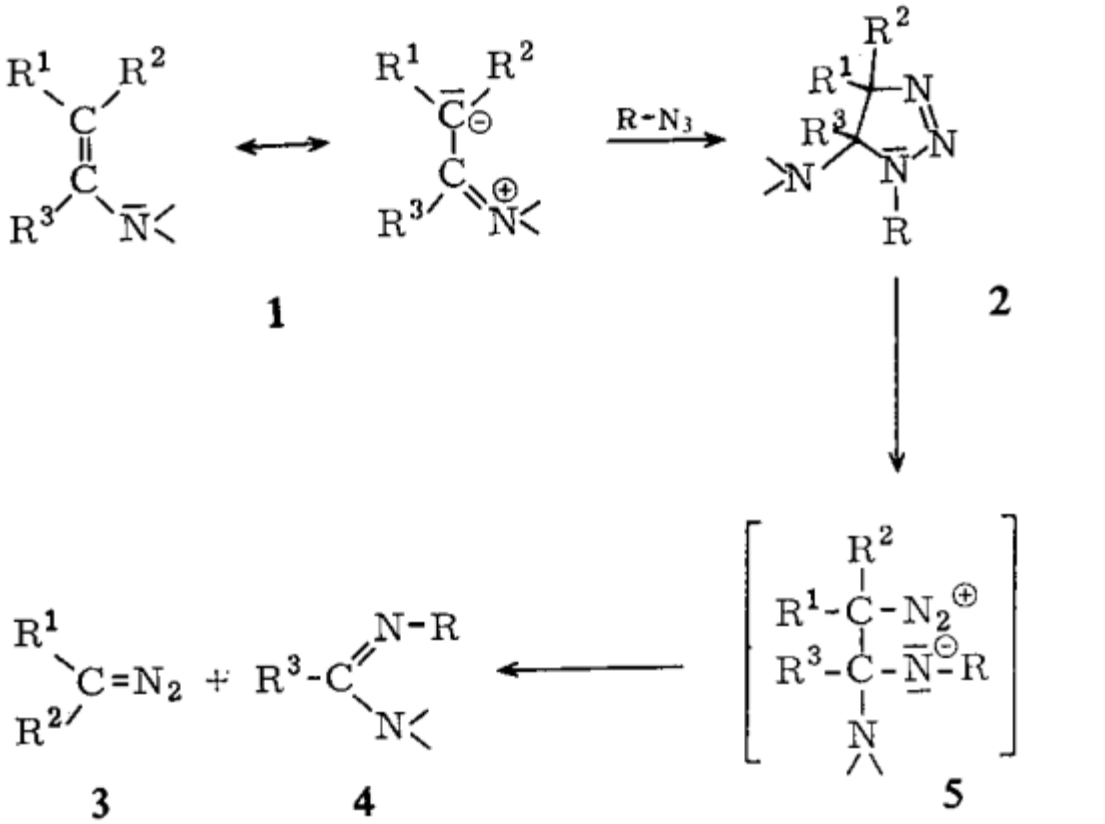
Generation of the phosphorous ylide:

Reaction of the phosphorous ylide with the aldehyde:



Conversion of dibromoolefin to terminal alkyne:



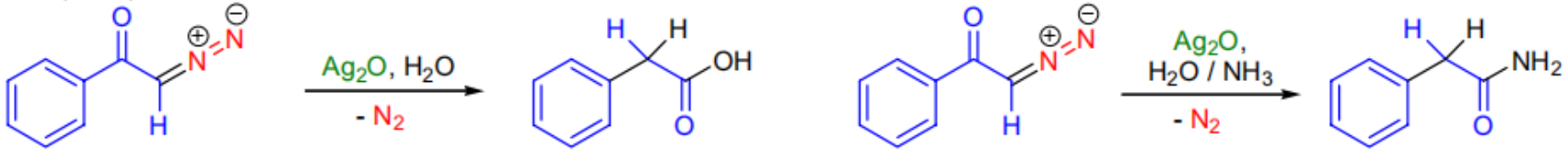


Liebigs Ann. Chem. **1970**, *734*, 70.

WOLFF REARRANGEMENT

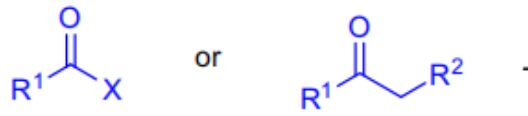
(References are on page 711)

Wolff (1902):



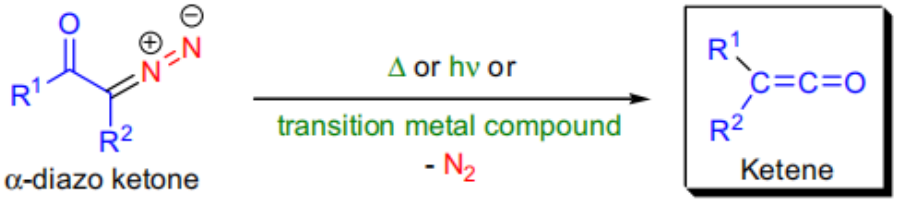
diazoacetophenone — phenylacetic acid — diazoacetophenone — phenylacetamide

Preparation of the α-diazo ketone:



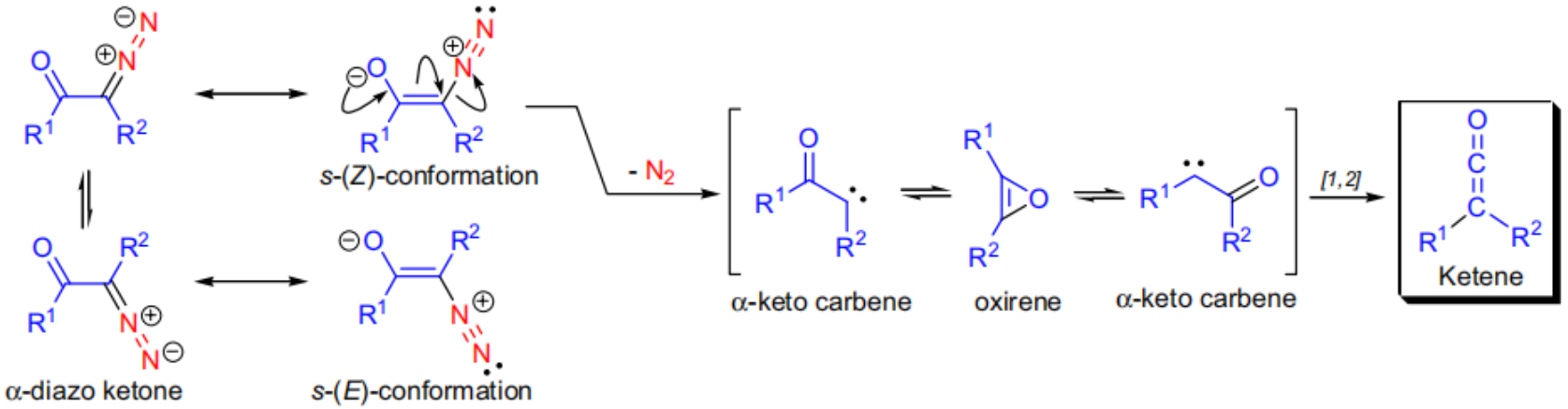
carboxylic acid or acid derivative — ketone or activated methylene compound

Wolff rearrangement:

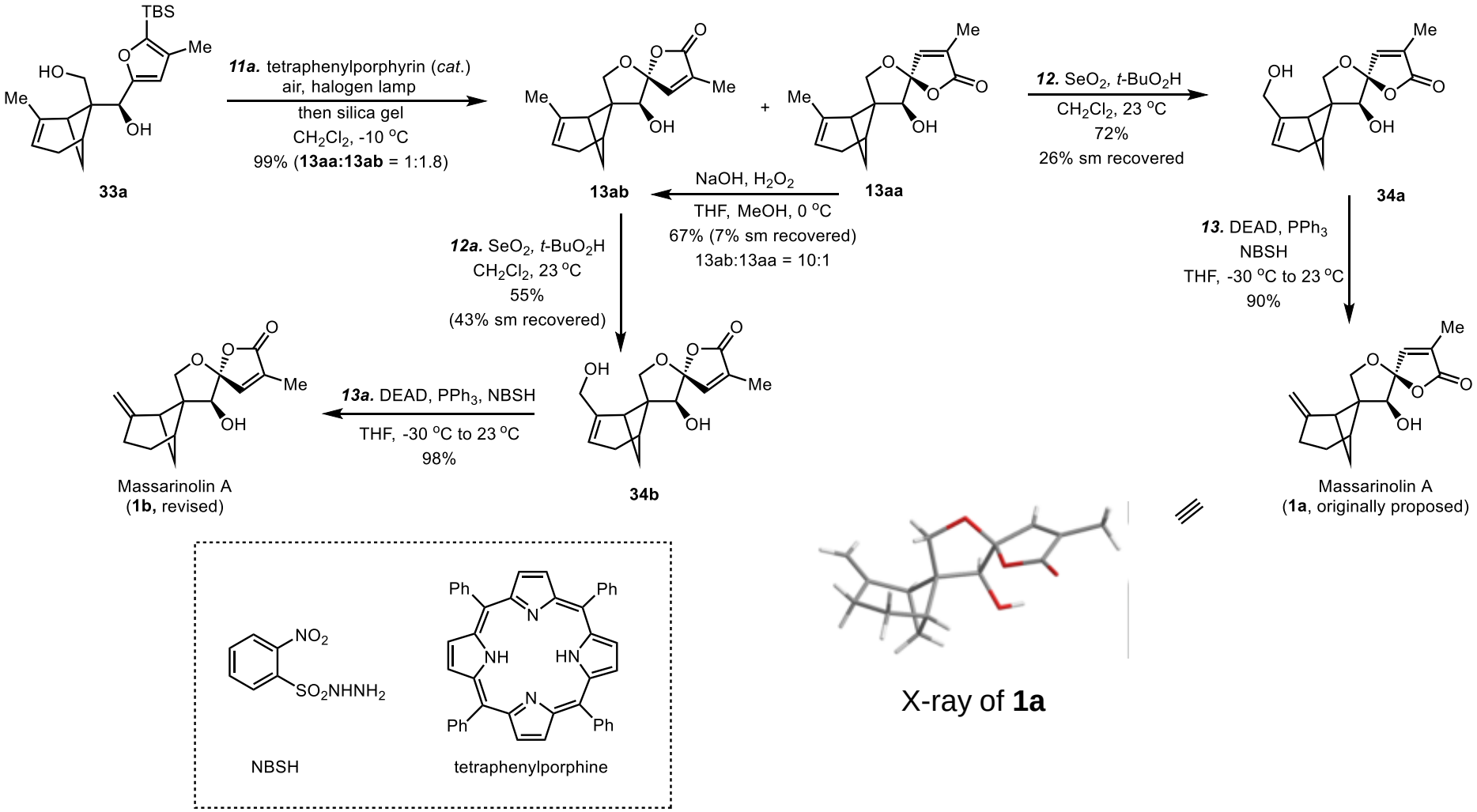


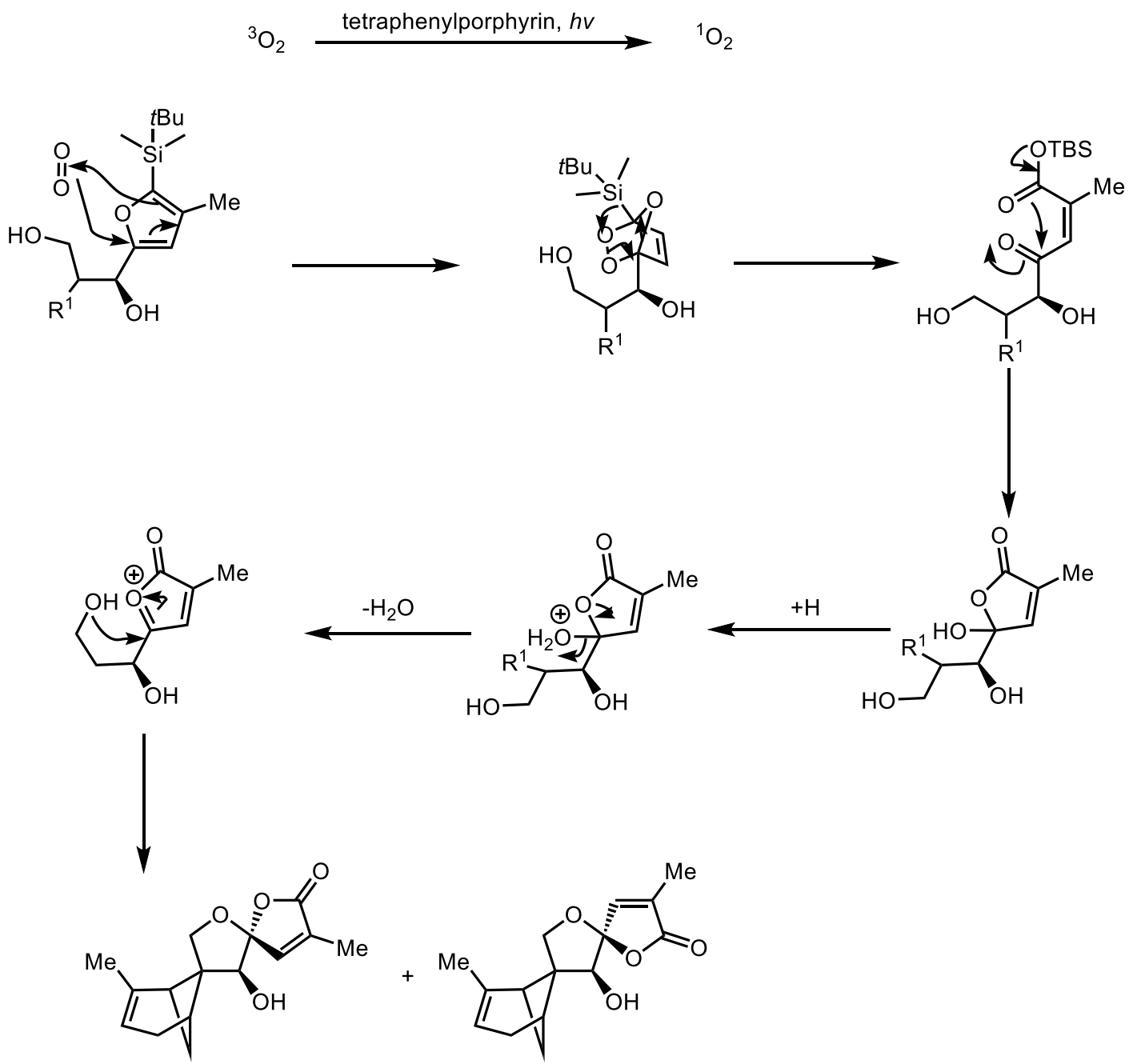
α-diazo ketone

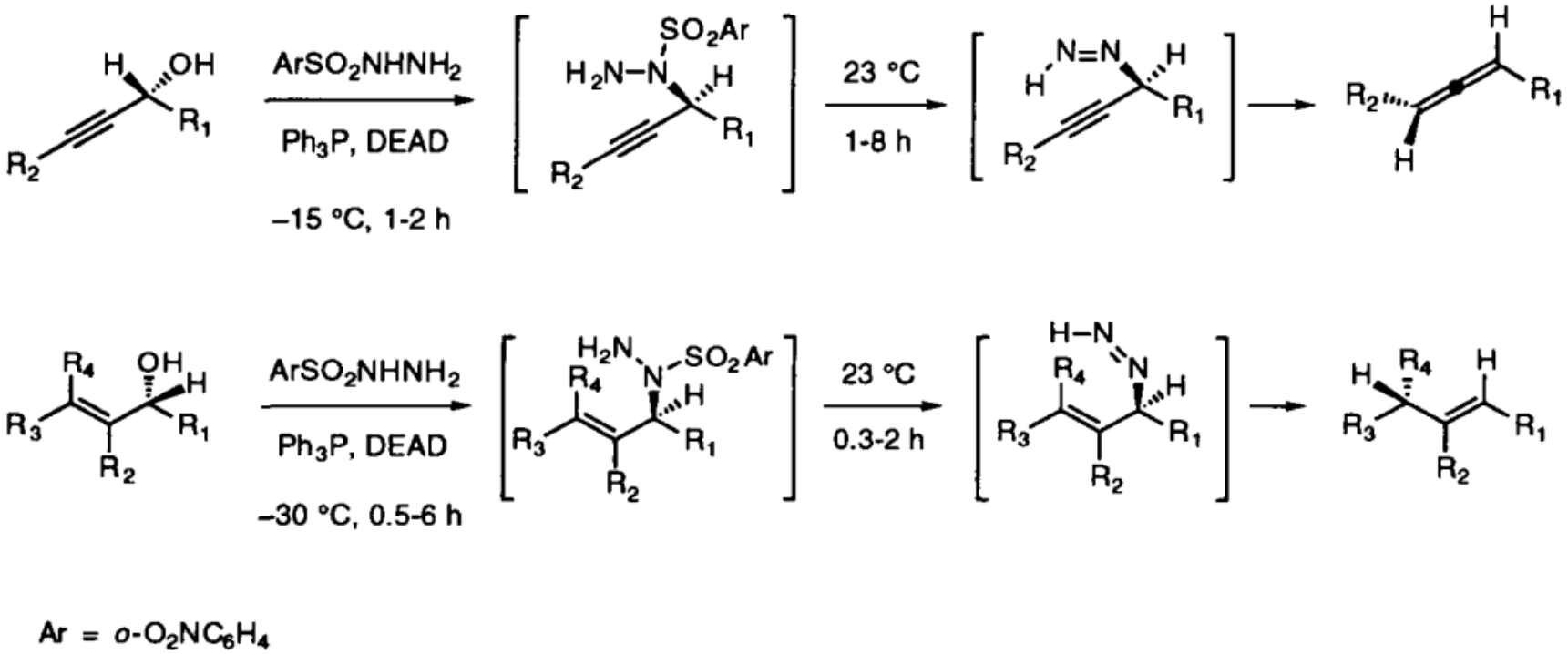
Mechanism: [65,9,13]



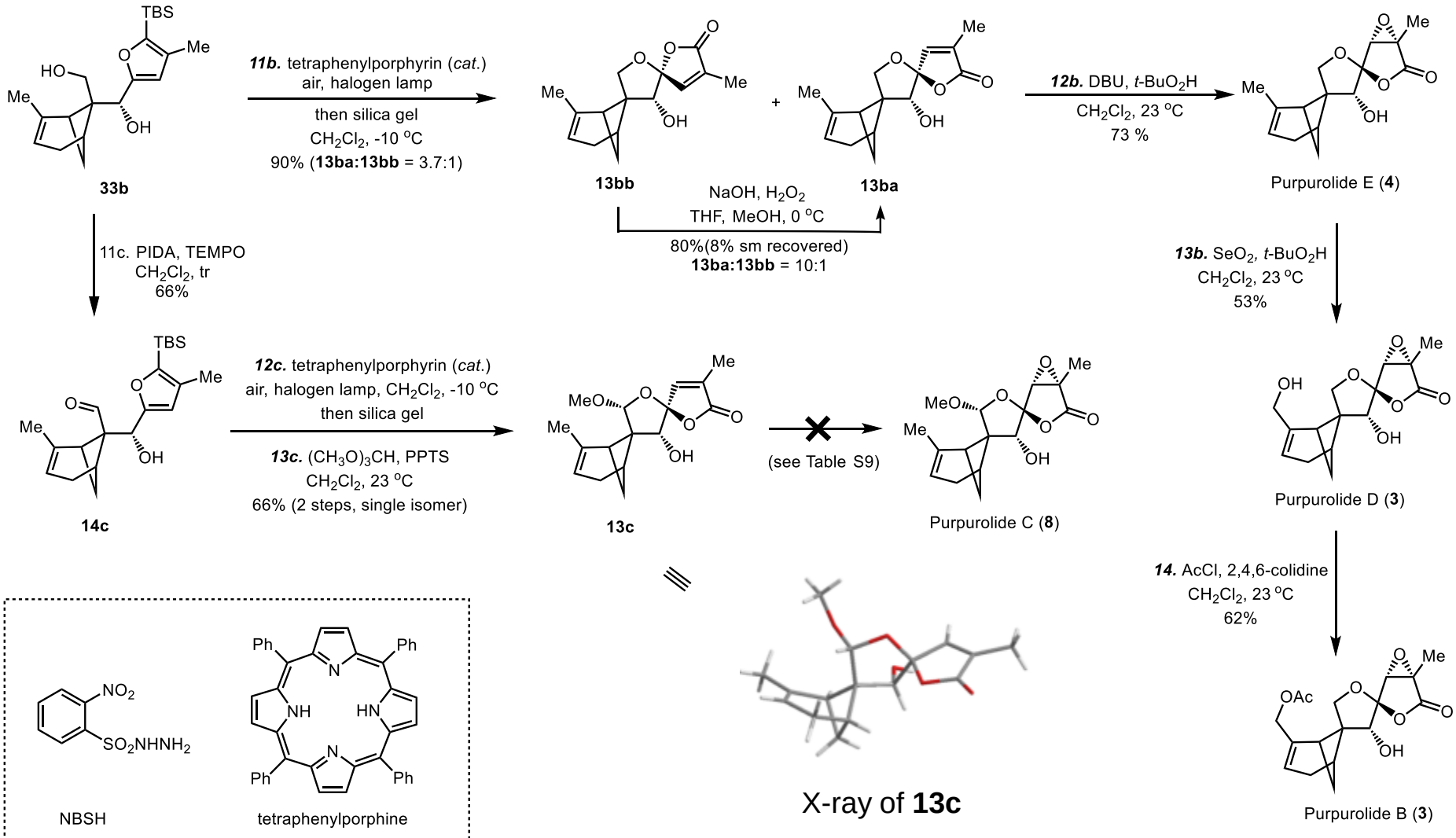
α-diazo ketone — s-(Z)-conformation — s-(E)-conformation — α-keto carbene — oxirene — α-keto carbene

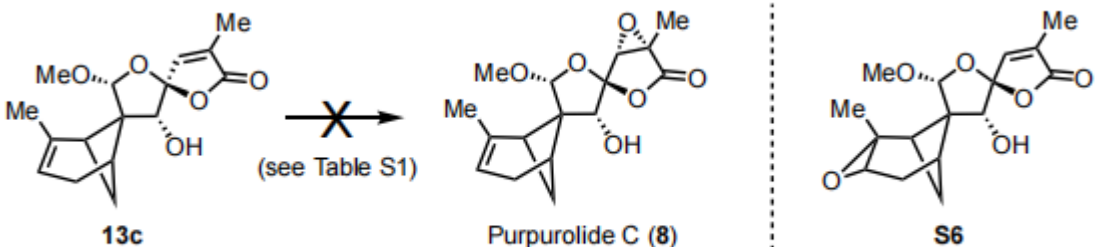

TBS
HO
Me
O
Me
OH
33a
11a. tetraphenylporphyrin (cat.)
air, halogen lamp
then silica gel
CH2Cl2, -10 °C
99% (13aa:13ab = 1:1.8)
13ab
13aa
NaOH, H2O2
THF, MeOH, 0 °C
67% (7% sm recovered)
13ab:13aa = 10:1
12. SeO2, t-BuO2H
CH2Cl2, 23 °C
72%
26% sm recovered
34a
12a. SeO2, t-BuO2H
CH2Cl2, 23 °C
55%
(43% sm recovered)
13. DEAD, PPh3
NBSH
THF, -30 °C to 23 °C
90%
13a. DEAD, PPh3, NBSH
THF, -30 °C to 23 °C
98%
Massarinolin A
(1b, revised)
34b
Massarinolin A
(1a, originally proposed)
NO2
SO2NHNH2
NBSH
Ph
N
NH
HN
tetraphenylporphine
X-ray of 1a


$^3O_2$
tetraphenylporphyrin, *hv*
$^1O_2$
*t*Bu
Si
Me
HO
R^1
OH
OTBS
+H
$-H_2O$
H_2O
+



Tetrahedron Letters, **1996**. 4841.


TBS
HO
Me
O
Me
OH
33b
11b. tetraphenylporphyrin (cat.)
air, halogen lamp
then silica gel
CH2Cl2, -10 °C
90% (13ba:13bb = 3.7:1)
13bb
13ba
NaOH, H2O2
THF, MeOH, 0 °C
80%(8% sm recovered)
13ba:13bb = 10:1
12b. DBU, t-BuO2H
CH2Cl2, 23 °C
73 %
Purpurolide E (4)
11c. PIDA, TEMPO
CH2Cl2, tr
66%
13b. SeO2, t-BuO2H
CH2Cl2, 23 °C
53%
14c
12c. tetraphenylporphyrin (cat.)
air, halogen lamp, CH2Cl2, -10 °C
then silica gel
13c. (CH3O)3CH, PPTS
CH2Cl2, 23 °C
66% (2 steps, single isomer)
13c
(see Table S9)
Purpurolide C (8)
Purpurolide D (3)
14. AcCl, 2,4,6-colidine
CH2Cl2, 23 °C
62%
Purpurolide B (3)
NO2
SO2NHNH2
NBSH
Ph
N
NH
HN
tetraphenylporphine
X-ray of 13c



13c Purpurolide C (**8**) **S6**

Table S9. Epoxidation for **13c**.

Entry	Reagent	Solvent	T (°C)	Time	Result
1	DBU (3 equiv.), TBHP (5 equiv.)	CH_2Cl_2	0 to rt	1 d	NR
2	DBU (3 equiv.), TBHP (5 equiv.)	CH_2Cl_2 (concentrated)	rt	3 d	decompose
3	NaOH (1.2 equiv.), TBHP (5 equiv.)	CH_2Cl_2, H_2O	rt	1 d	NR
4	Triton B (1drop), TBHP (5 equiv.)	CH_2Cl_2	rt	1 min	decompose
5	Bu_4NOH (0.1 equiv.), TBHP (1.4 equiv.)	THF, H_2O	0 to rt	1 d	NR
6	*n*-BuLi (1.1 equiv.), TBHP (1.5 equiv.)	THF	0 to 100	1 d	NR
7	*n*-BuLi (5.5 equiv.), TBHP (7.5 equiv.)	THF	0 to rt	1 d	NR
8	DBU (3 equiv.), TBHP (5 equiv.)	DCE	100	1 d	NR
9	DBN (10 equiv.), TBHP (10 equiv.)	CH_2Cl_2	0 to rt	1 d	NR
10	$VO(acac)_2$ (1 equiv.), TBHP (3 equiv.), 2,6-lutidine (1 equiv.)	toluene	rt	2 d	NR
11	DMDO (2 equiv.)	acetone	0	1 h	13c'
12	NaClO (2 equiv.)	diethyl ether, DMF	0	2 h	13c'
13	NMO (2 equiv.)	dioxane	100	1 d	NR
14	NMO (4 equiv.)	dioxane	100	12 h	decompose
15	DBU (1.5 equiv.), *m*CPBA (3 equiv.)	CH_2Cl_2	rt to 60	1 d	NR
16	DBU (1.5 equiv.), *m*CPBA (6 equiv.)	CH_2Cl_2	60	1 d	SM+**S6**

17	DBU (6 equiv.), *m*CPBA (3 equiv.)	DCE	100	1 d	SM+**S6**
18	K_2CO_3 (2 equiv.), *m*CPBA (2 equiv.)	CH_2Cl_2	rt	1 d	NR
19	KOH (2 equiv.), *m*CPBA (2 equiv.)	CH_2Cl_2	rt	1 d	NR
20	KOH (2 equiv.), *m*CPBA (2 equiv.), 18-C-6 (0.5 equiv.)	CH_2Cl_2	rt	1 d	NR
21	$KHCO_3$ (8 equiv.), *m*CPBA (4 equiv.)	CH_2Cl_2, H_2O	0	10 min	**S6**
22	KHMDS (1 equiv.), *m*CPBA (1 equiv.)	THF	0 to rt	1 d	NR
23	NaOH (10 equiv.), H_2O_2 (50 equiv.)	THF	rt	1 d	decompose
24	NaOH (1.2 equiv.), H_2O_2 (5 equiv.)	THF	rt	1 d	decompose
25	*t*-$BuNH_2$ (0.5 equiv.), H_2O_2 (4 equiv.)	MeOH	rt	1 d	NR
26	LiOH (1 equiv.), H_2O_2 (5 equiv.)	MeOH	rt	16 h	SM+**S6**
27	NaOH (1.2 equiv.), H_2O_2 (5 equiv.)	MeOH	rt	0.5 d	NR