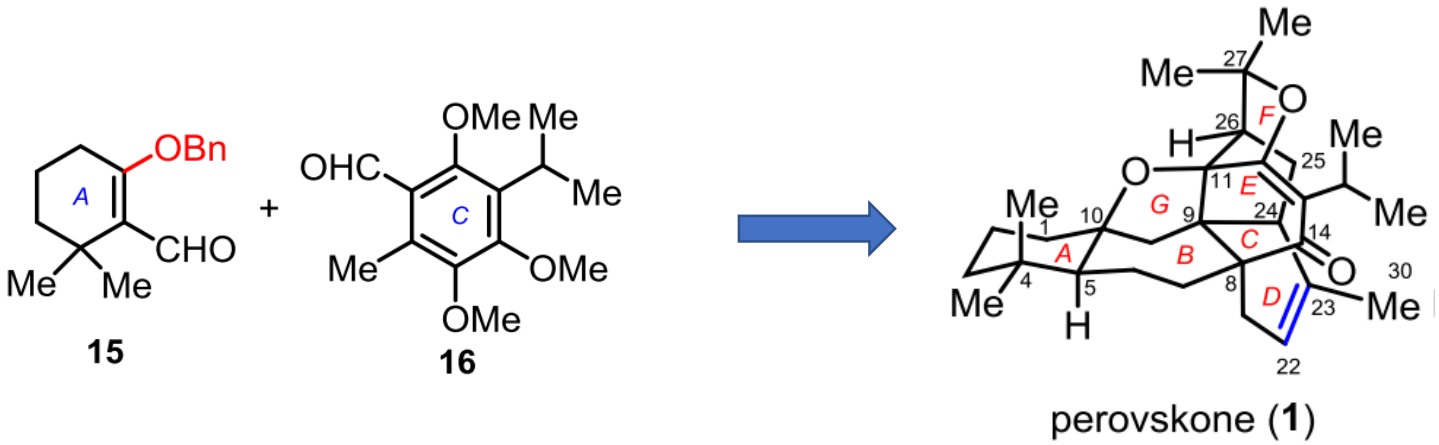
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

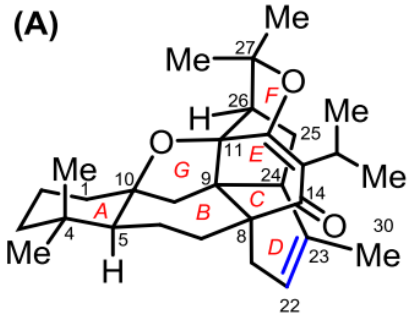
Asymmetric Total Synthesis and Biosynthetic Implications of Perovskones, Hydrangenone, and Hydrangenone B

Baochao Yang, Guoen Wen, Quan Zhang, Min Hou, Haibing He, and Shuanhu Gao*

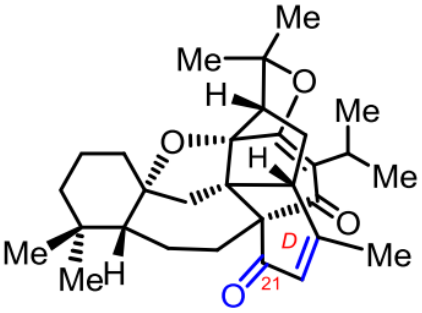
DOI: 10.1021/jacs.1c02674.



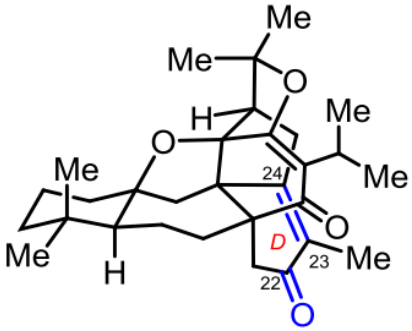
(A)



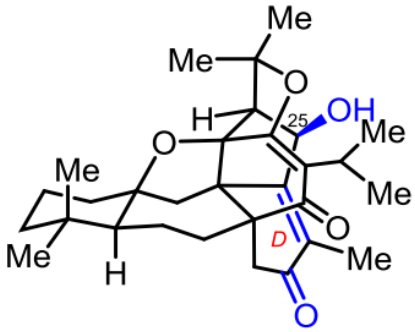
perovskone (**1**)



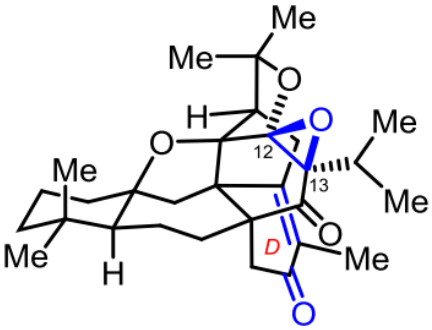
perovskone B (**2**)



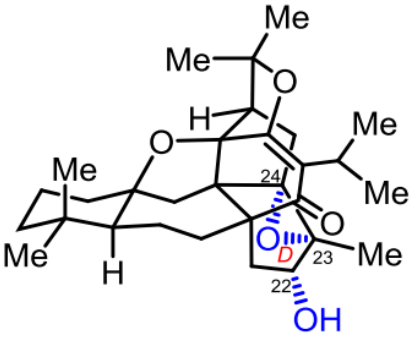
perovskone C (**3**)



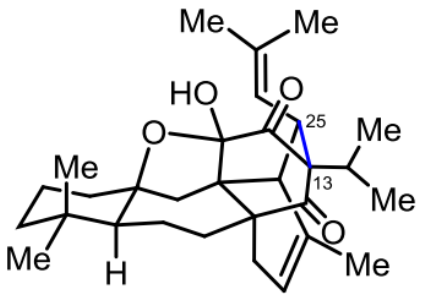
perovskone D (**4**)



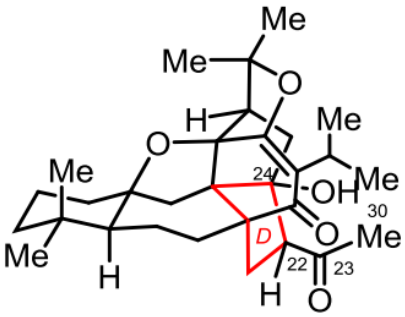
perovskone E (**5**)



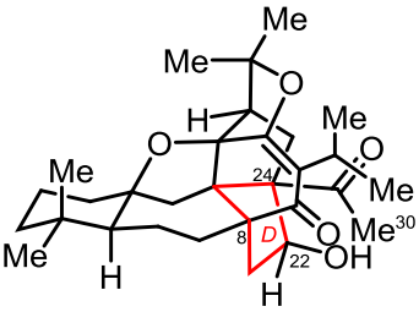
perovskone F (**6**)



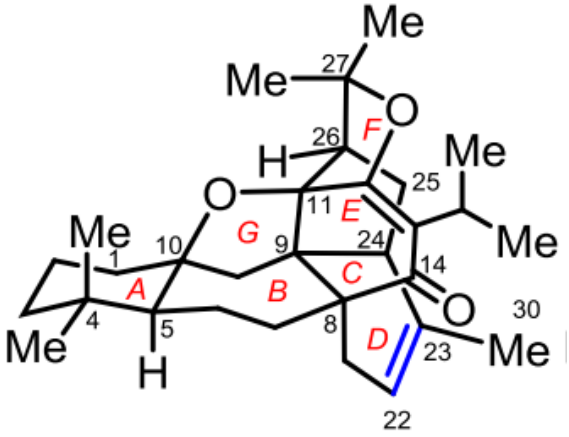
salvadione A (**7**)



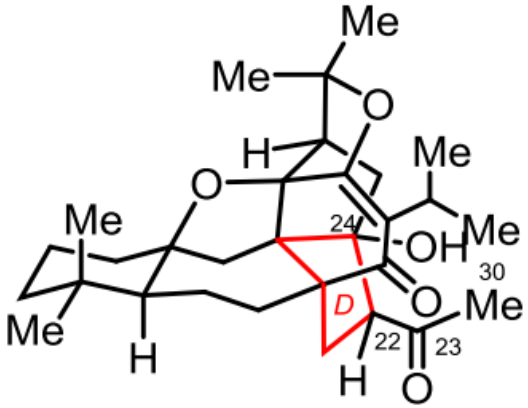
hydrangenone (**8**)



hydrangenone B (**9**)



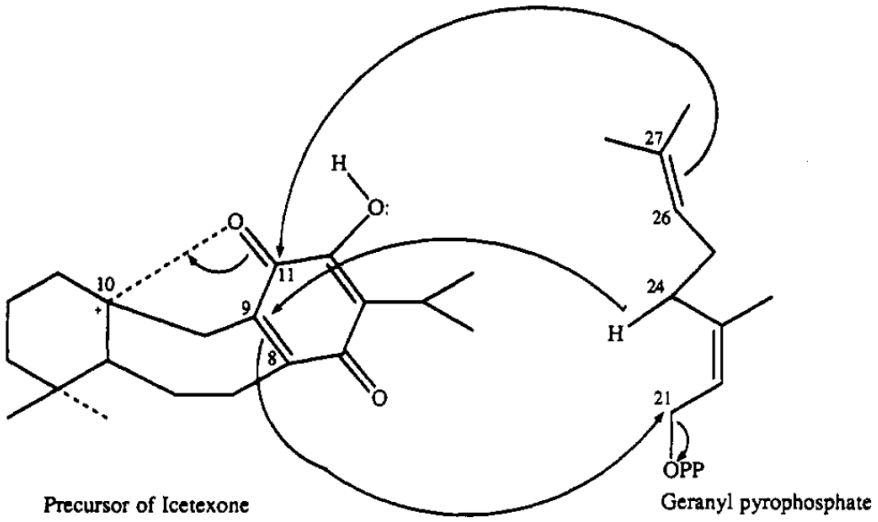
perovskone (**1**)



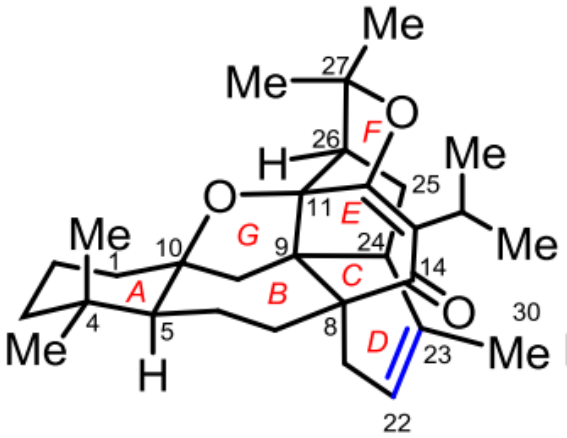
hydrangenone (**8**)

- isolated from the genus *Salvia* plants
- a complex heptacyclic framework
- eight adjacent stereocenters
- antiplasmodial activity

Scheme I. Proposed Biosynthesis of Perovskone (1)



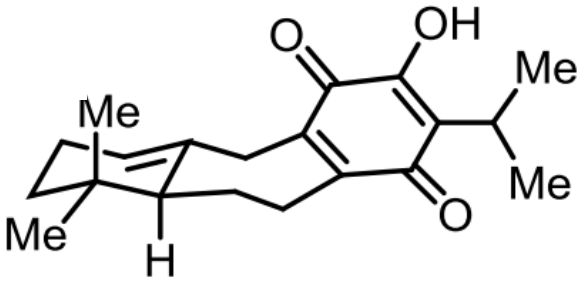
J. Org. Chem. **1992**, *57*, 4339.



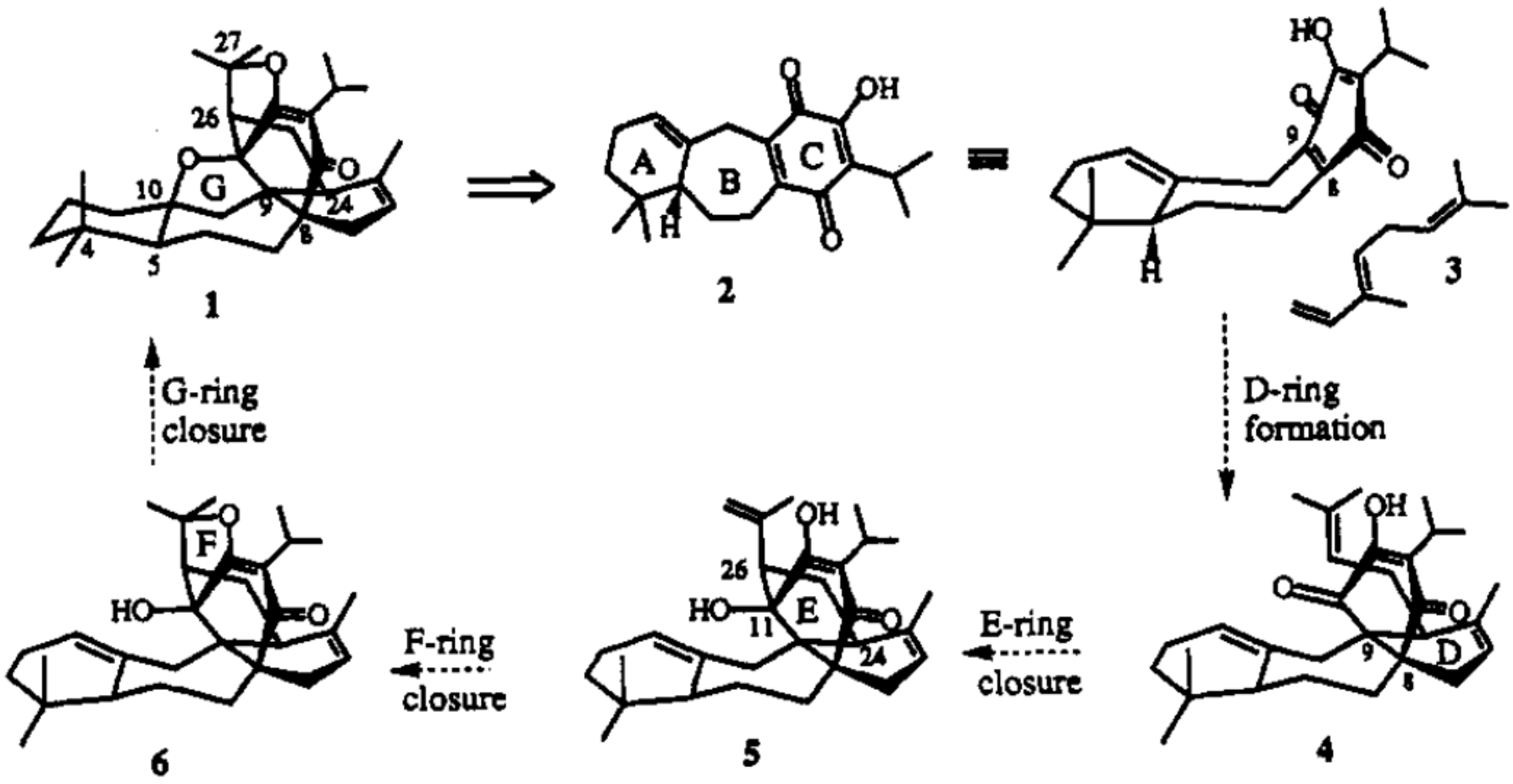
perovskone (**1**)

Further Oxidation

perovskones B-F

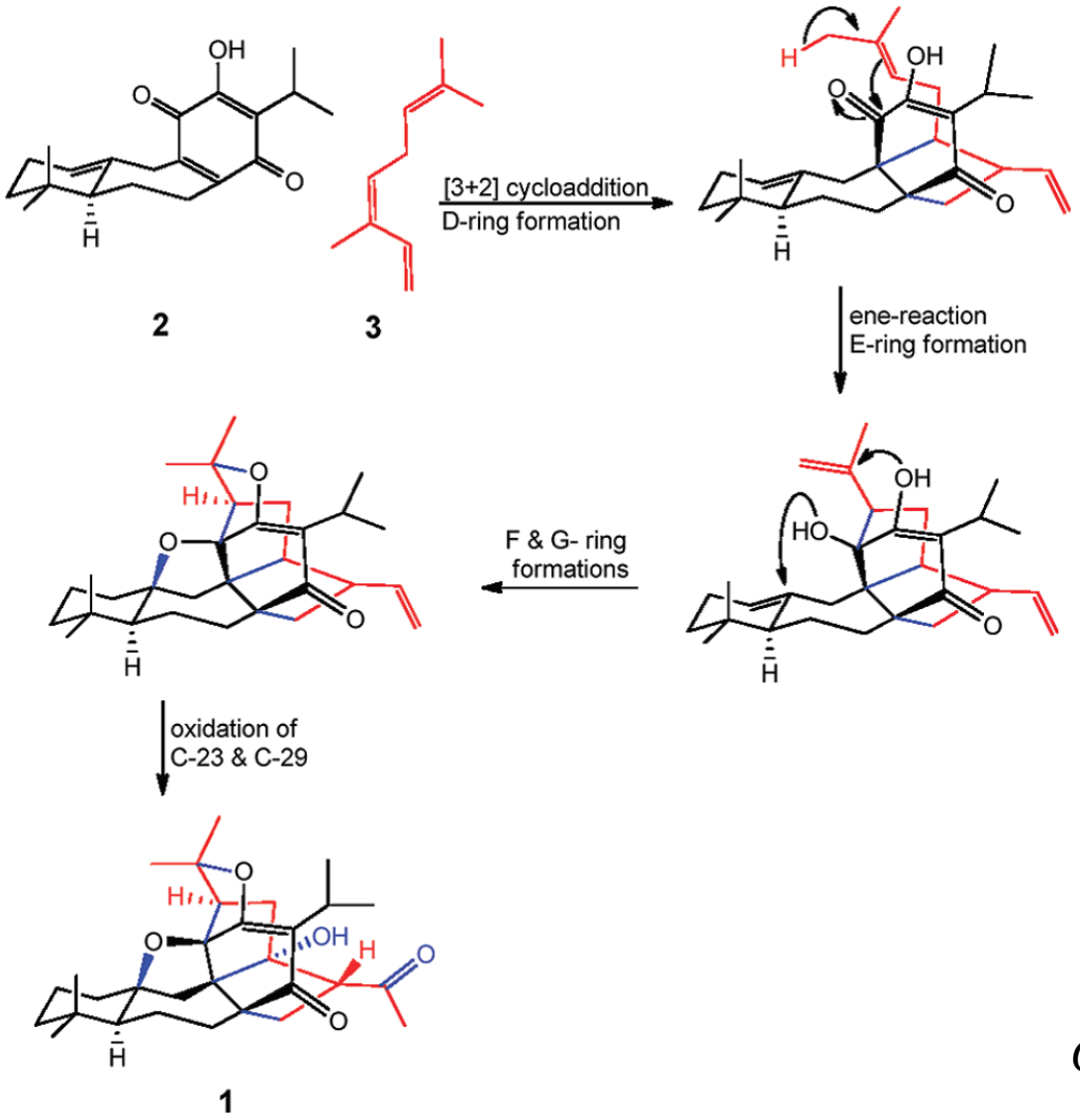


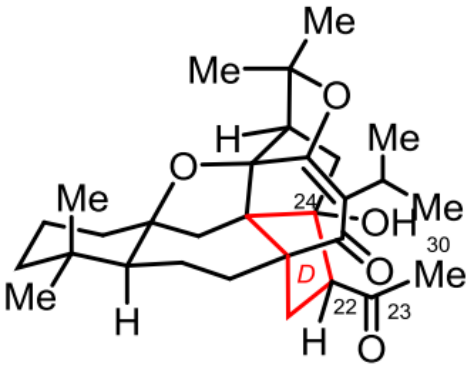
putative icetexane precursor (**10**)



J. Am. Chem. Soc. **1994**, *116*, 4979.

Scheme 1. Plausible Biogenetic Pathway of **1**

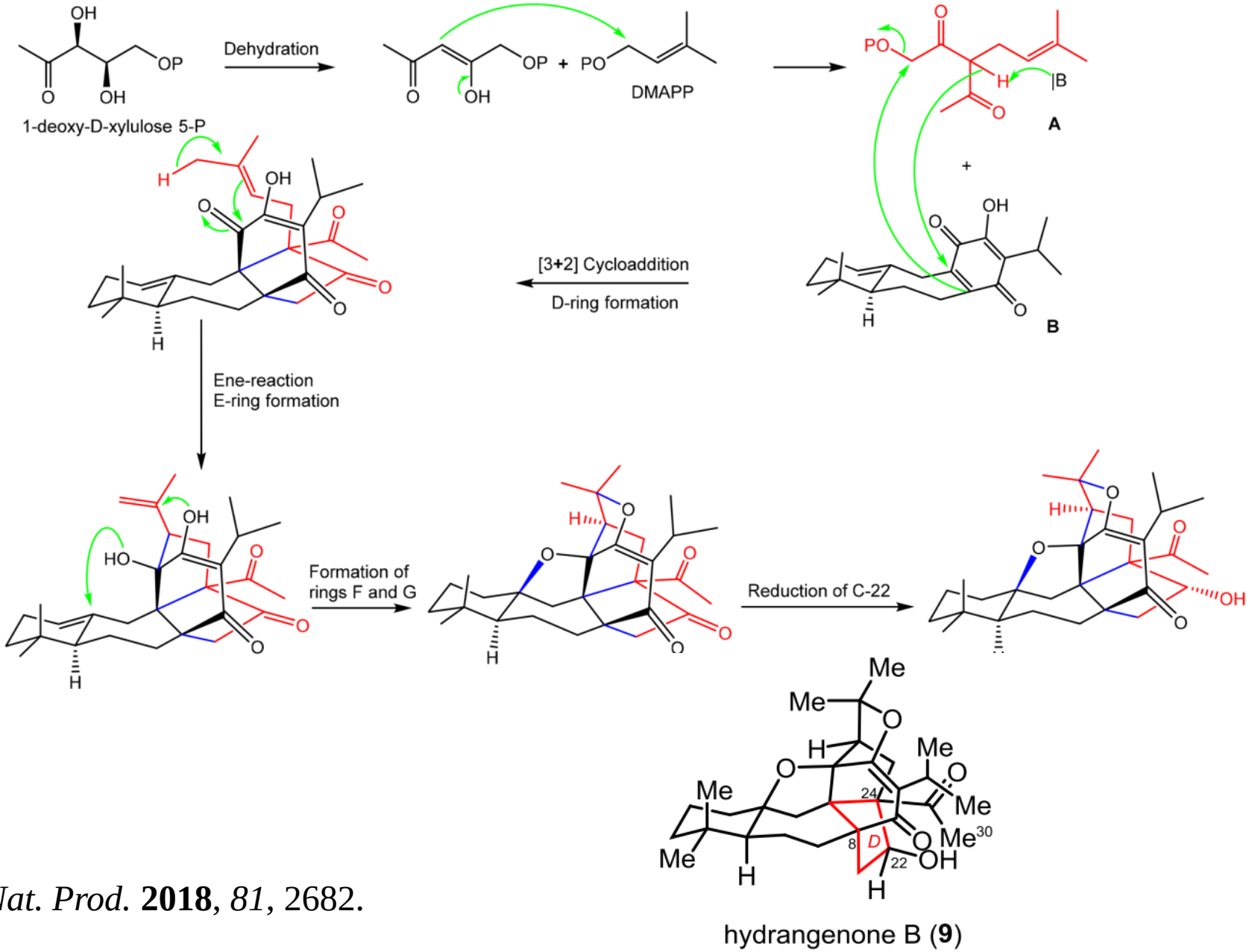




hydrangenone (**8**)

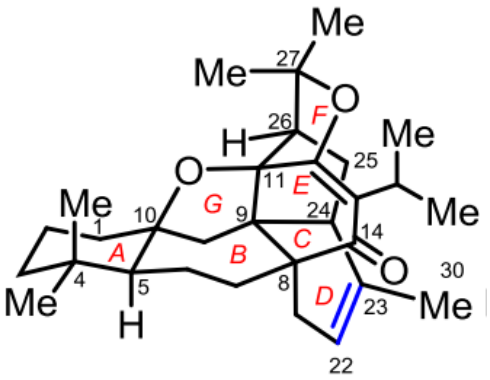
Org. Lett. **2012**, *14*, 166.

Scheme 1. Proposed Biosynthetic Pathway of Compound 1



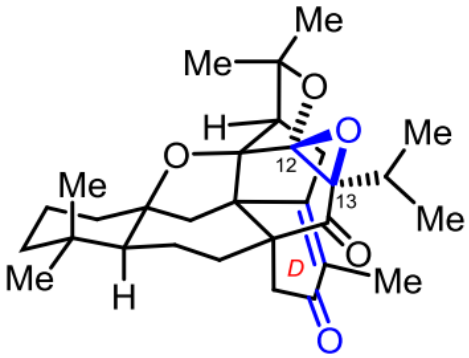
J. Nat. Prod. **2018**, *81*, 2682.

We tried to answer two questions during this study: (1) Is there any natural occurring biosynthetic precursor for the biosynthesis of perovskones? (2) Is there any other biosynthetic pathway, except the proposed [3 + 2] cycloaddition, for the formation of hydrangenone (**8**) and hydrangenone B (**9**) containing five-membered ring.

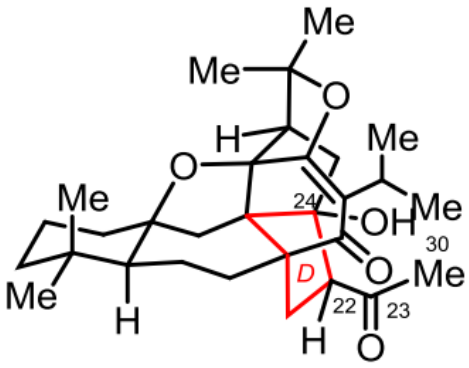


perovskone (**1**)

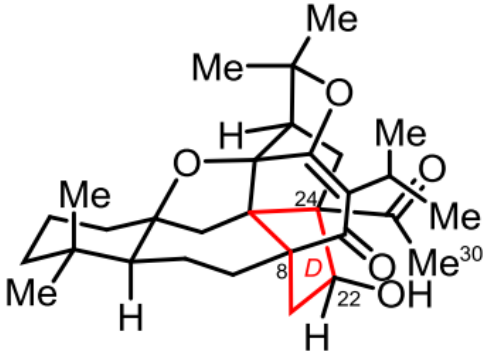
- **A complex heptacyclic skeleton**
  - fused A-B-C-D ring
  - oxo-bridged furan F-G rings
- **Eight contiguous stereocenters**
  - two all-carbon quaternary centers
  - three oxo-quaternary centers
- **A highly oxidized C-D-E ring**
  - enones and the labile epoxides



perovskone E (**5**)

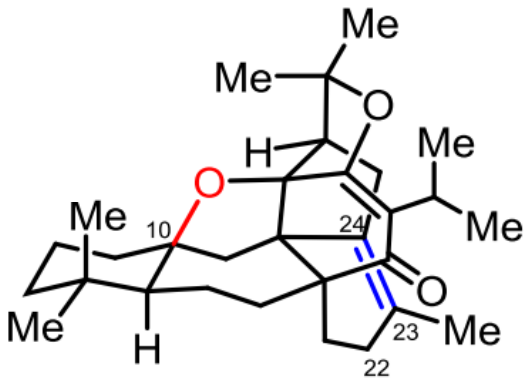


hydrangenone (**8**)



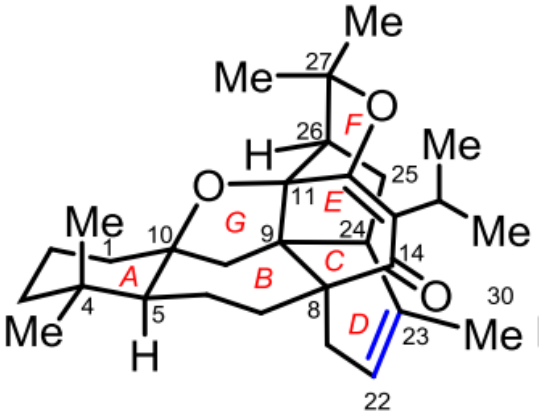
hydrangenone B (**9**)

- **A β-hydroxy ketone motif**
- **Intramolecular aldol reaction**



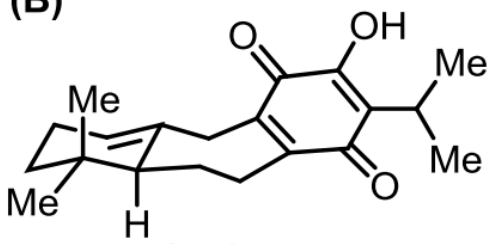
$\Delta^{23,24}$- perovskone (**14**)

Olefin Migration

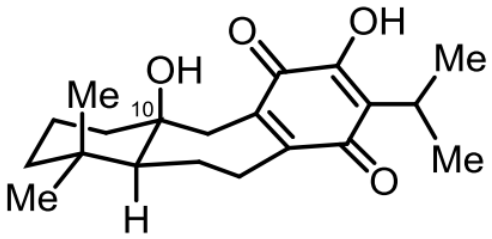


perovskone (**1**)

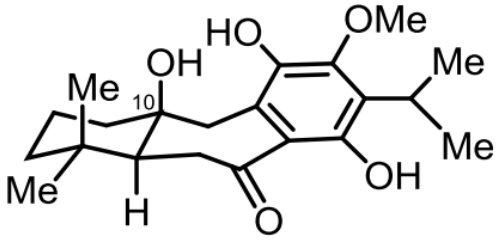
(B)



putative icetexane precursor (**10**)



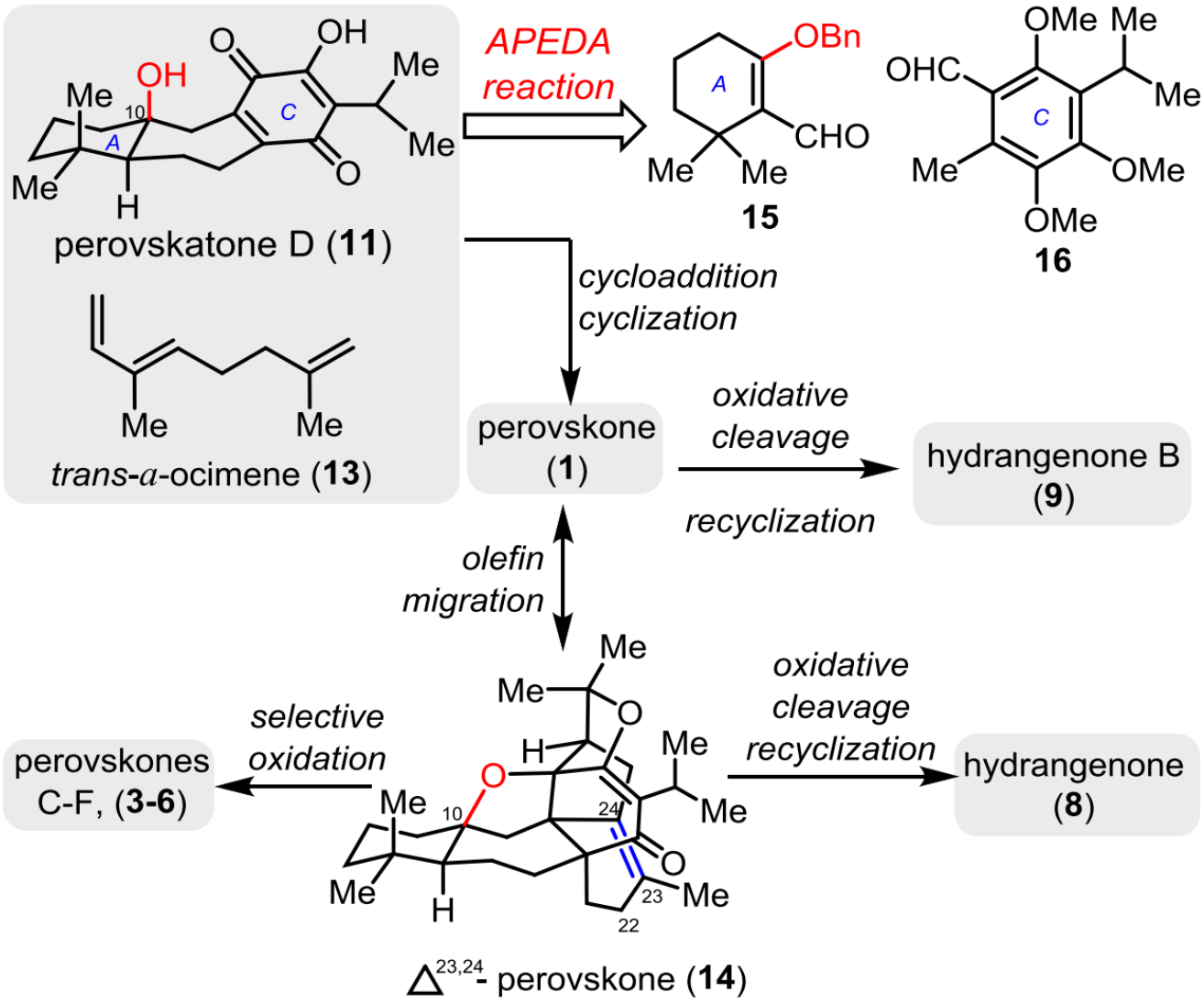
perovskatone D (**11**)

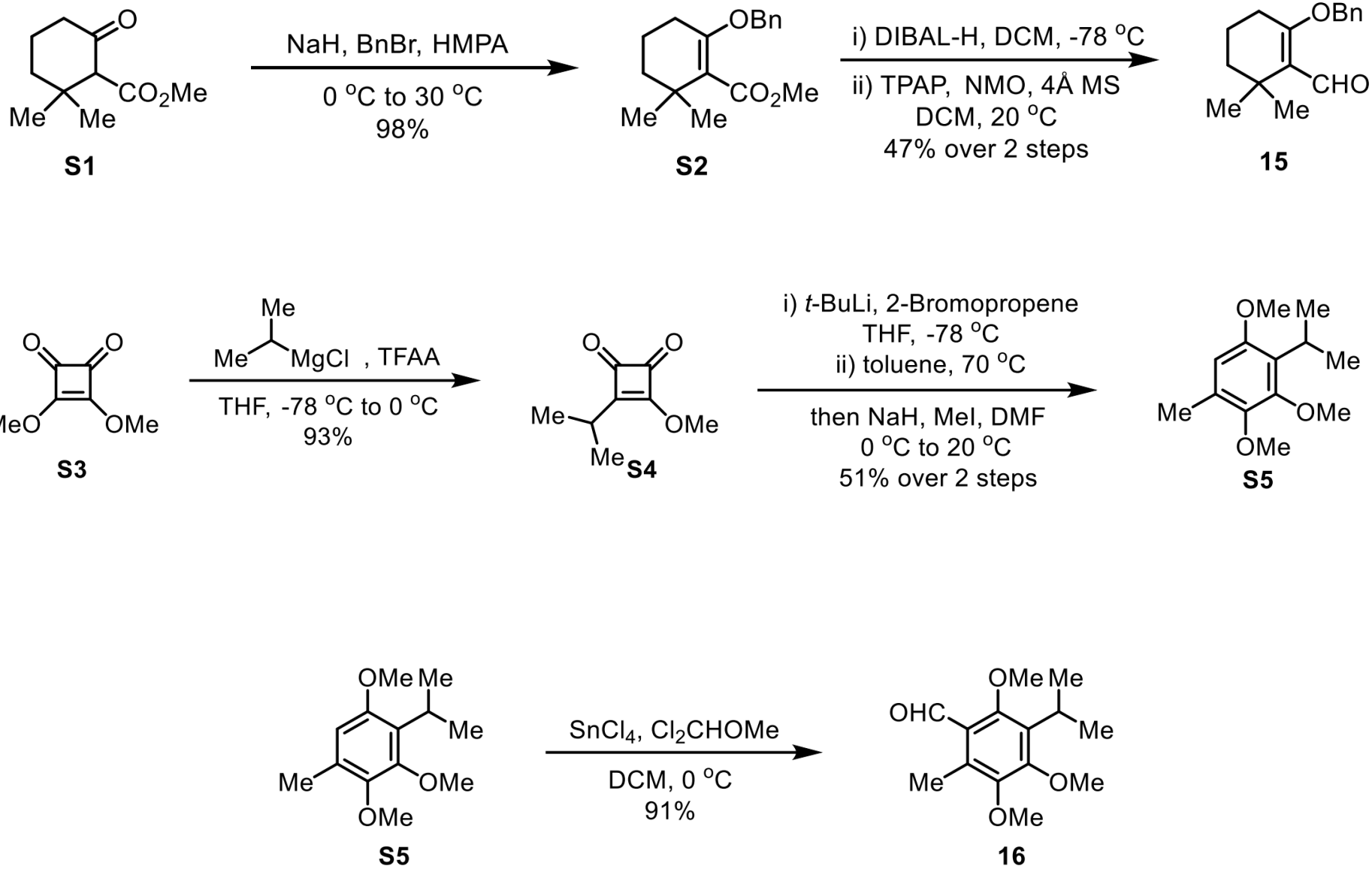


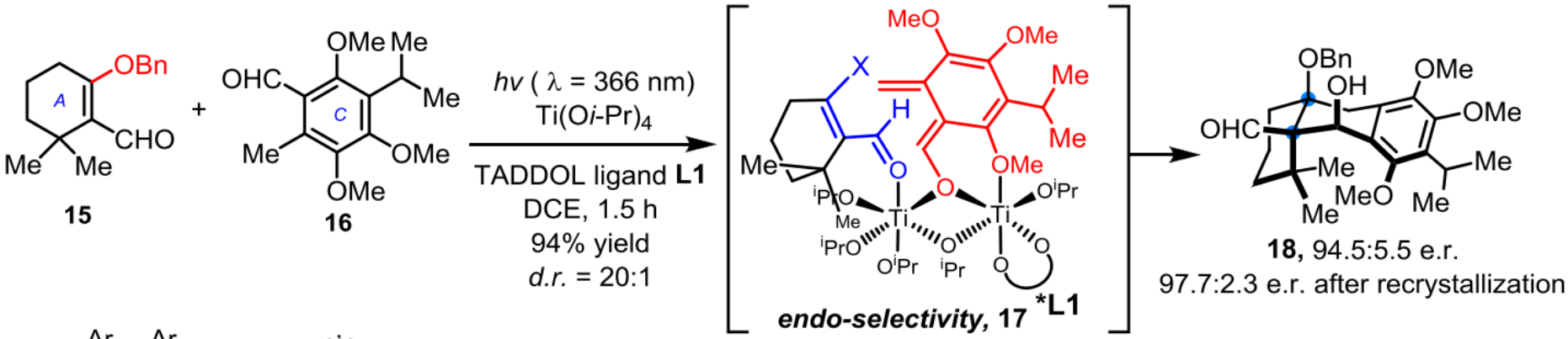
coulterone (**12**)

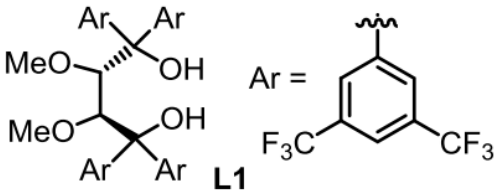
- **Icetexanes diterpenoids**
- **Containing a hydroxyl group at C-10**
- **Discovered from the same natural sources**

Scheme 1. Synthetic Plan

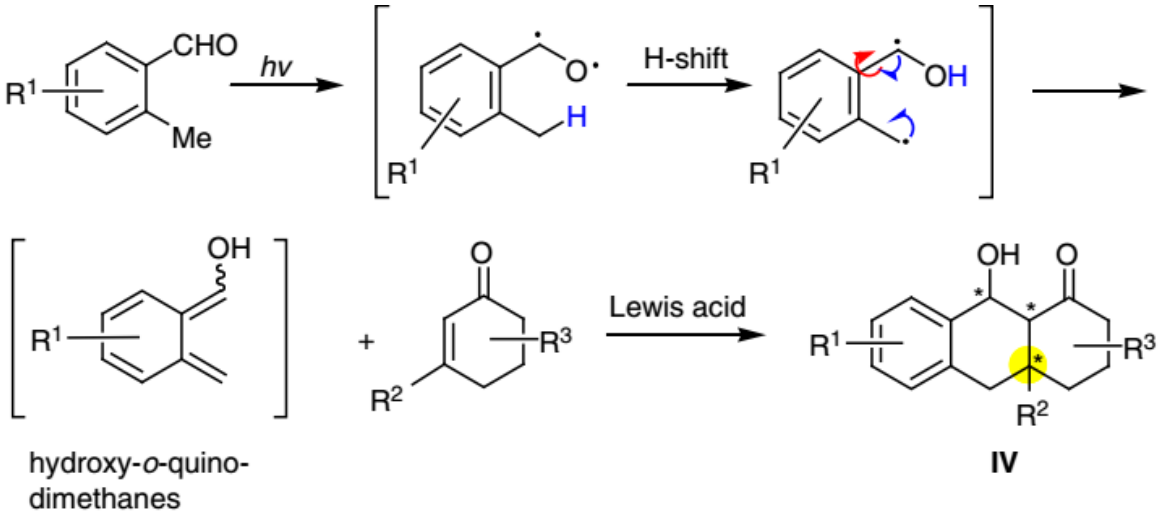



NaH, BnBr, HMPA
0 °C to 30 °C
98%
i) DIBAL-H, DCM, -78 °C
ii) TPAP, NMO, 4Å MS
DCM, 20 °C
47% over 2 steps
Me, MgCl , TFAA
THF, -78 °C to 0 °C
93%
i) t-BuLi, 2-Bromopropene
THF, -78 °C
ii) toluene, 70 °C
then NaH, MeI, DMF
0 °C to 20 °C
51% over 2 steps
SnCl4, Cl2CHOMe
DCM, 0 °C
91%
S1
S2
15
S3
S4
S5
S5
16

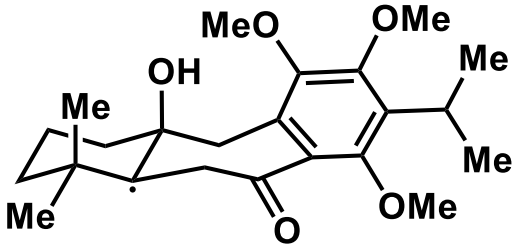


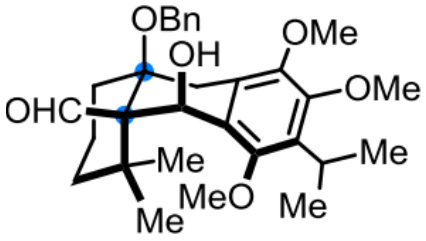


Asymmetric photoenolization/Diels-Alder (PEDA) reaction



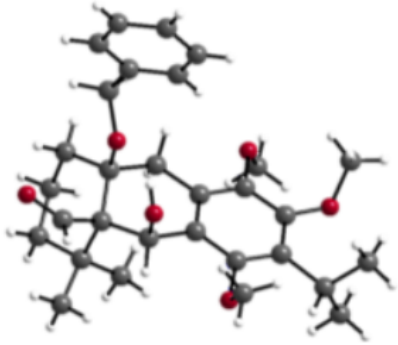
Nat. Commun. **2017**, *8*, 622.





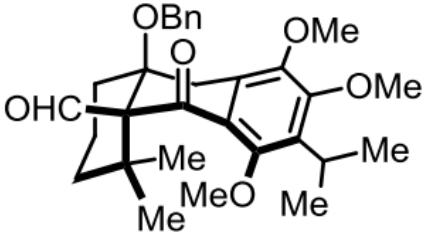
18, 94.5:5.5 e.r.
97.7:2.3 e.r. after recrystallization

≡



18, X-ray

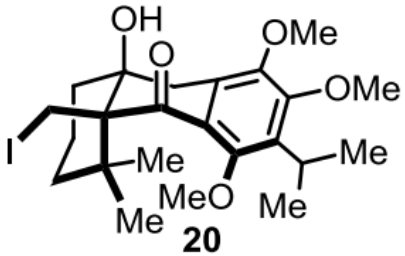
IBX DMSO
73%



19

1) $PdCl_2$, H_2 balloon
EtOH/DCM (1:1)
2) Li(*t*-BuO)$_3$AlH

THF, 92% over 2 steps
3) PPh_3, I_2, quinoline
toluene (dry), 91%

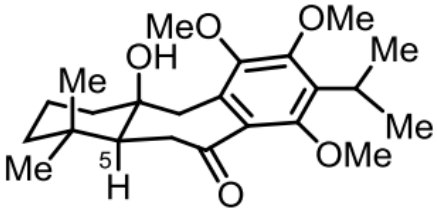


20

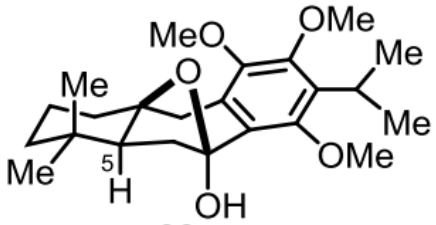
AIBN, Bu_3SnH

68%

toluene
(dry and
degassed)



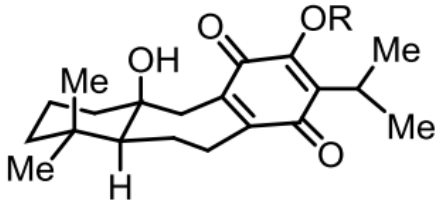
21



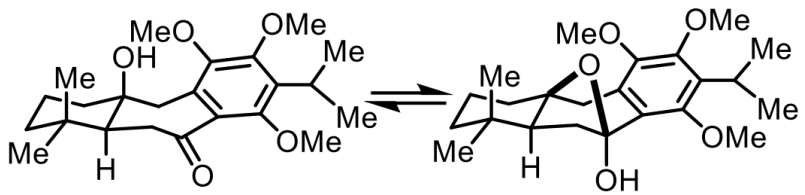
22

1) Li, NH_3/THF(1:1)
2) DDQ, 47% (2 steps)
d.r. = 4.7:1

3) AgO, dioxane/HNO_3
69% combined yield
ratio of **11**:**23** = 1:6.7

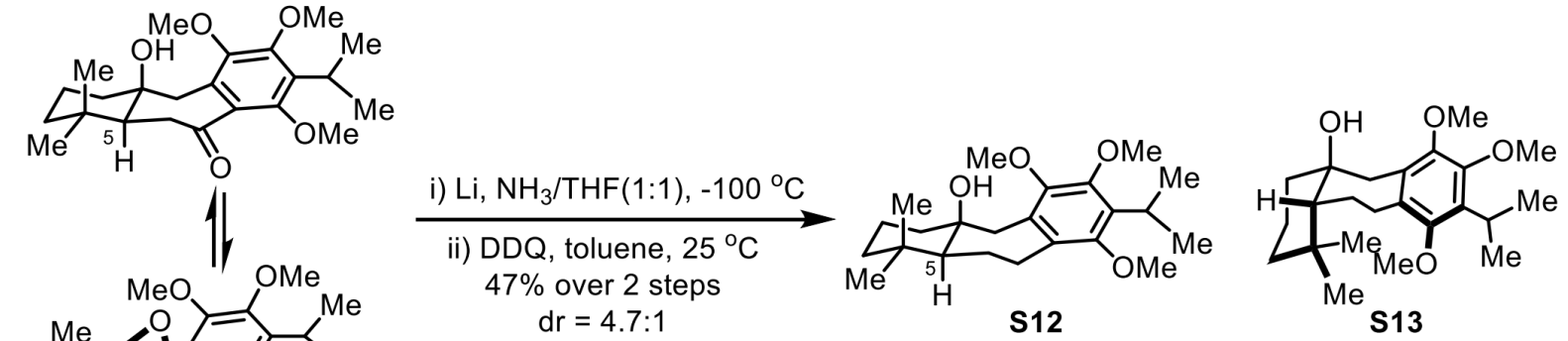


R=Me, methyl-perovskatone D (**23**)
R=H, perovskatone D (**11**)

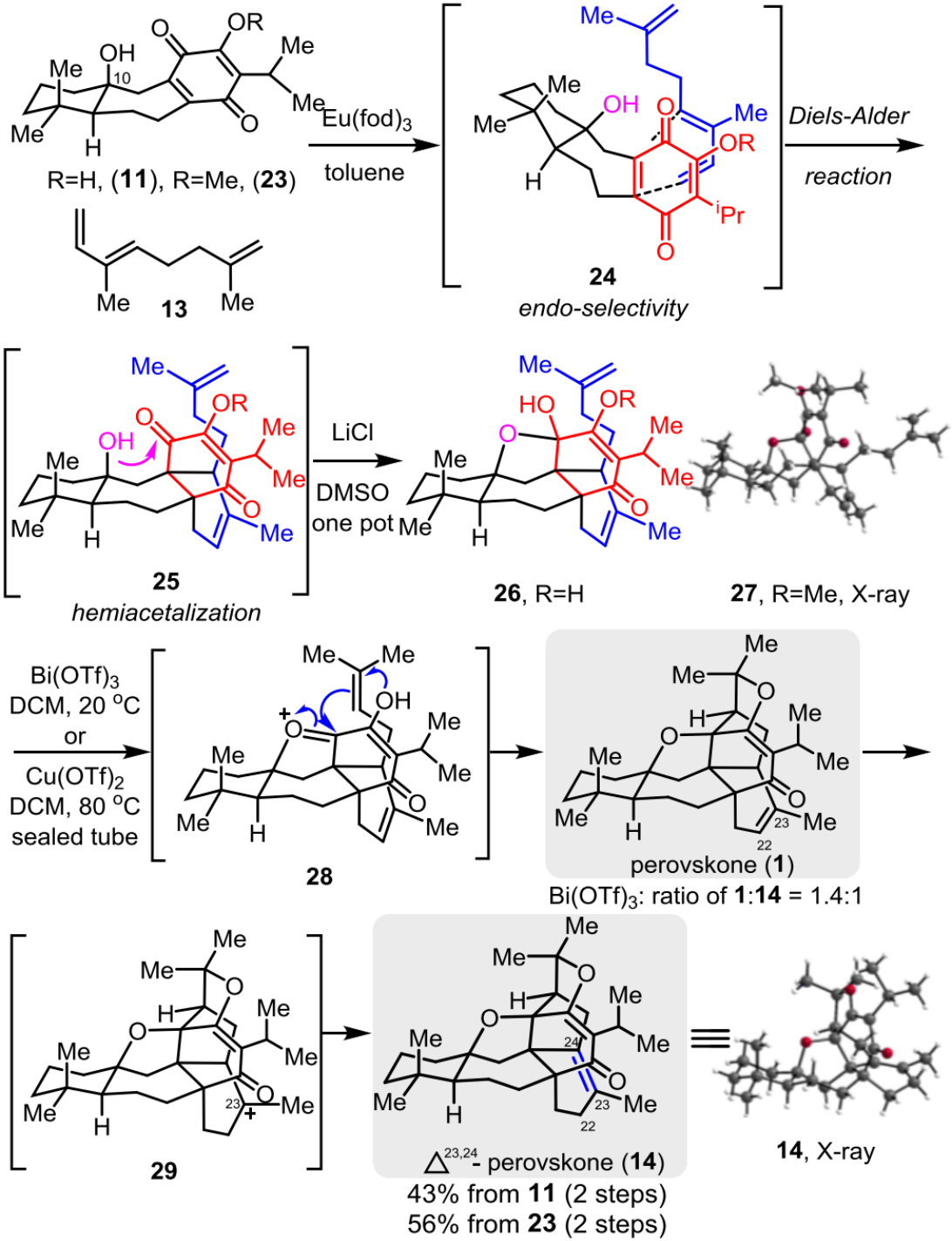


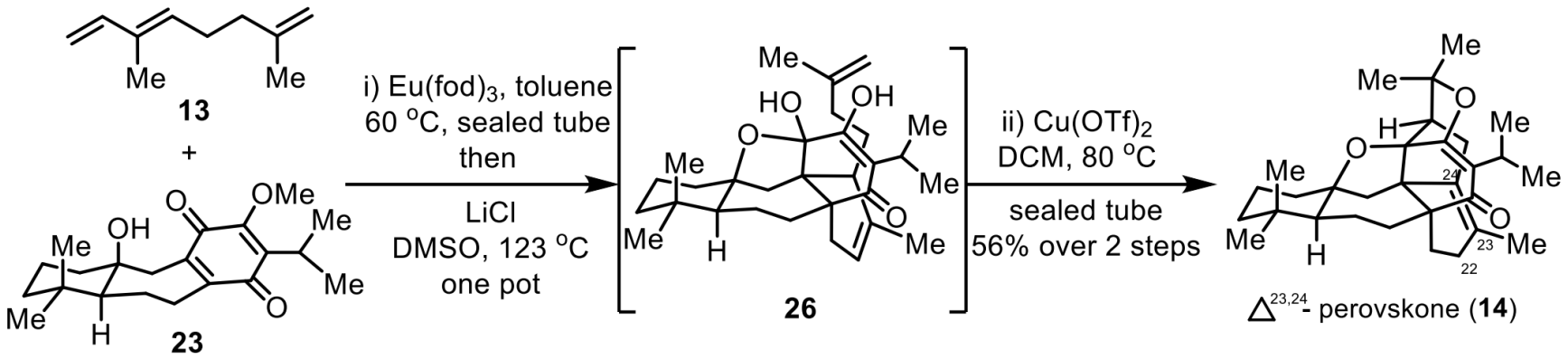
21 22

An inseparable mixture of ompound 21 and 22: R_f = 0.58 (crawled three times with 10% ethyl acetate-petroleum ether); $[\alpha]_D^{20}$ = –12.1 (c = 0.14, $CHCl_3$); IR ν_{max} 3487, 2935, 2870, 1687, 1578, 1456, 1412, 1341, 1122, 1030, 779, 736 cm^{-1}; HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{23}H_{34}O_5$, 390.2406; found, 390.2413. NOTICE: There is a pair of diastereomers in NMR, as well as the interconversion of ketones and hemiketals. So it is difficult to mark the NMR data. Please refer to the attached ^1H NMR and ^{13}C NMR spectrum for details.



21, 22 S12 S13


R=H, (11), R=Me, (23)
Eu(fod)3
toluene
13
24
endo-selectivity
Diels-Alder
reaction
25
hemiacetalization
LiCl
DMSO
one pot
26, R=H
27, R=Me, X-ray
Bi(OTf)3
DCM, 20 °C
or
Cu(OTf)2
DCM, 80 °C
sealed tube
28
perovskone (1)
Bi(OTf)3: ratio of 1:14 = 1.4:1
29
Δ23,24- perovskone (14)
43% from 11 (2 steps)
56% from 23 (2 steps)
14, X-ray


13
+
23
i) Eu(fod)3, toluene
60 °C, sealed tube
then
LiCl
DMSO, 123 °C
one pot
26
ii) Cu(OTf)2
DCM, 80 °C
sealed tube
56% over 2 steps
Δ23,24- perovskone (14)

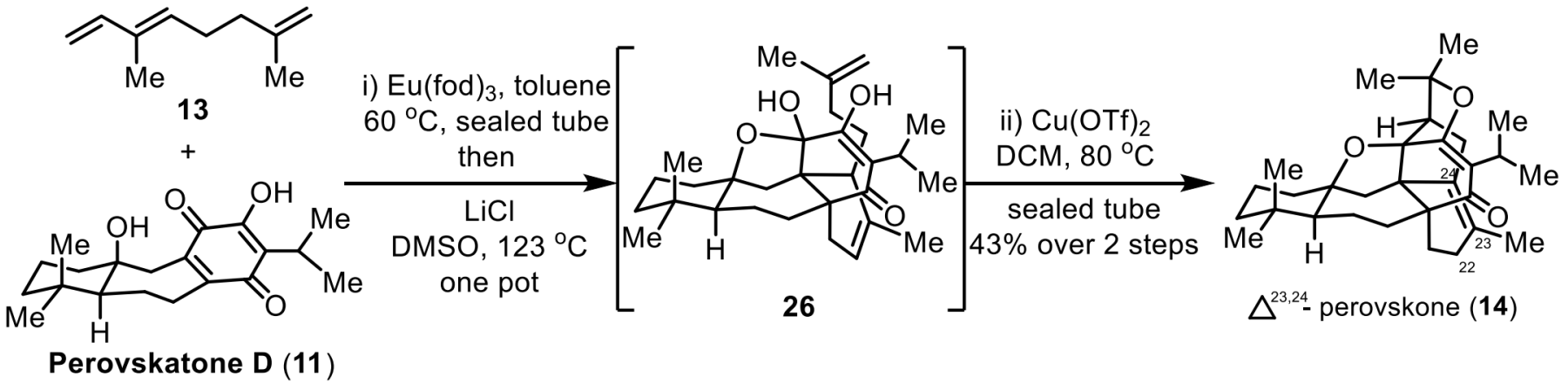
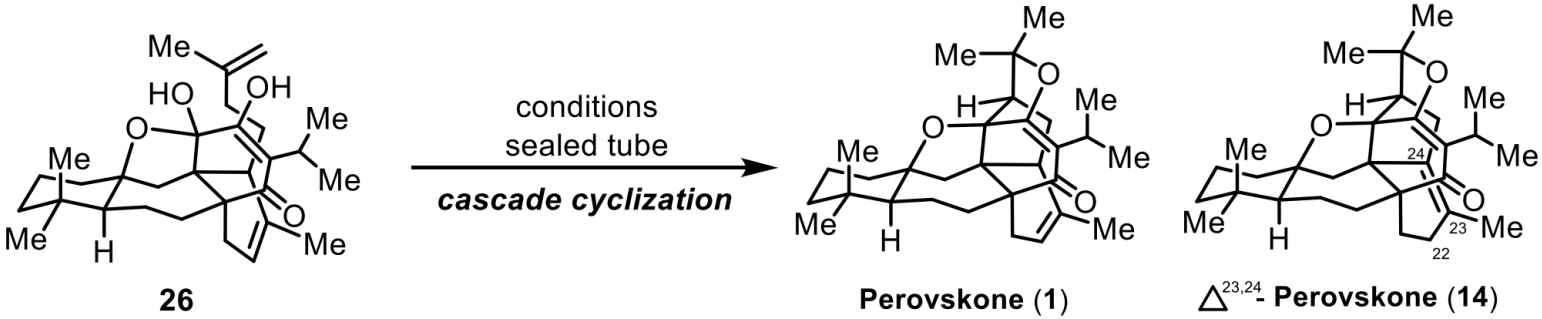

13
+
Perovskatone D (11)
i) Eu(fod)3, toluene
60 °C, sealed tube
then
LiCl
DMSO, 123 °C
one pot
26
ii) Cu(OTf)2
DCM, 80 °C
sealed tube
43% over 2 steps
Δ23,24- perovskone (14)

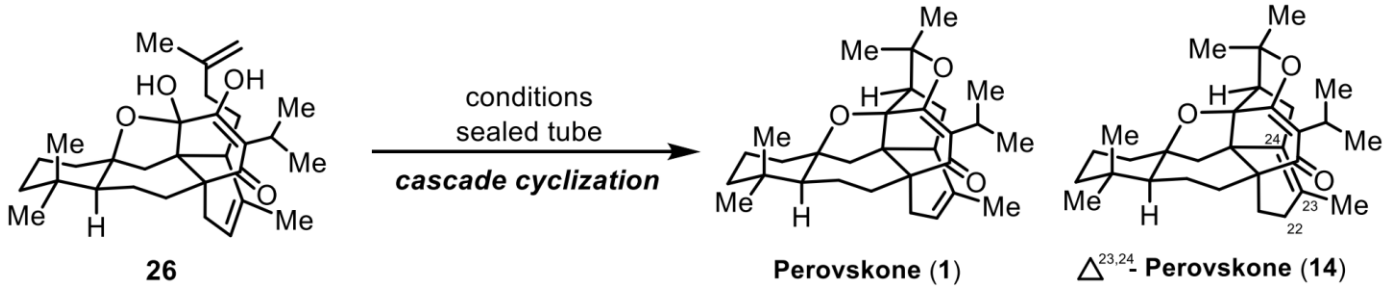
Table S4-1 Screening acid for cascade cyclization



26 **Perovskone (1)** **$\Delta^{23,24}$- Perovskone (14)**

entry	scale	acid	solvent (dry)	T (^{o}C) & time	results[a]
1	1~2 mg	$Eu(fod)_3$ (0.3 equiv.)	toluene	110 ^{o}C (2.5 h) to 120 ^{o}C (19 h)	NR
2	3 mg	$Eu(fod)_3$ (2.5 equiv.)	toluene	120 ^{o}C (52.25 h)	decomposed
3	3 mg	$Er(OTf)_3$ (2.5 equiv.)	toluene	120 ^{o}C (52.25 h)	NR
4	5 mg	Amberlyst ®15-ion (3 equiv.)	DCM	60 ^{o}C (88.5 h)	**14**
5	1.4 mg	PPTS (3 equiv.)	toluene	30 ^{o}C (13 h) to 80 ^{o}C (4 h) to 130 ^{o}C (20 h)	NR
6	~2.5 mg	$BF_3.Et_2O$ (3 equiv.)	DCM	-78 ^{o}C (1.17 h) to 0 ^{o}C (1.5 h) to rt (20 h) to 60 ^{o}C (11.3 h)	trace **14**
7	2.2 mg	$BF_3.Et_2O$ (3 equiv.)	DCM	0 ^{o}C (2 h) to 20 ^{o}C (19.5 h)	trace **1** + ND (**14**)
8	~2.5 mg	$SnCl_4$ (3 equiv.)	DCM	-78 ^{o}C (1.17 h) to 0 ^{o}C (2 h)	ND
9	~2.5 mg	TMSOTf (3 equiv.)	DCM	-78 ^{o}C (1.17 h) to 0 ^{o}C (6.5 h) to 25 ^{o}C (40.3 h)	**14** + trace **1**
10	3.2 mg	TMSOTf (5 + 5 equiv.)	Et_2O	-78 ^{o}C (1.25 h) to 0 ^{o}C (1.3 h) to 28 ^{o}C (97.5 h)	**14**
11	3.2 mg	TMSOTf (5 + 5 equiv.) TMSOAc (7.5 + 7.5 equiv.)	Et_2O	-78 ^{o}C (1.25 h) to 0 ^{o}C (1.3 h) to 28 ^{o}C (97.5 h)	**14**

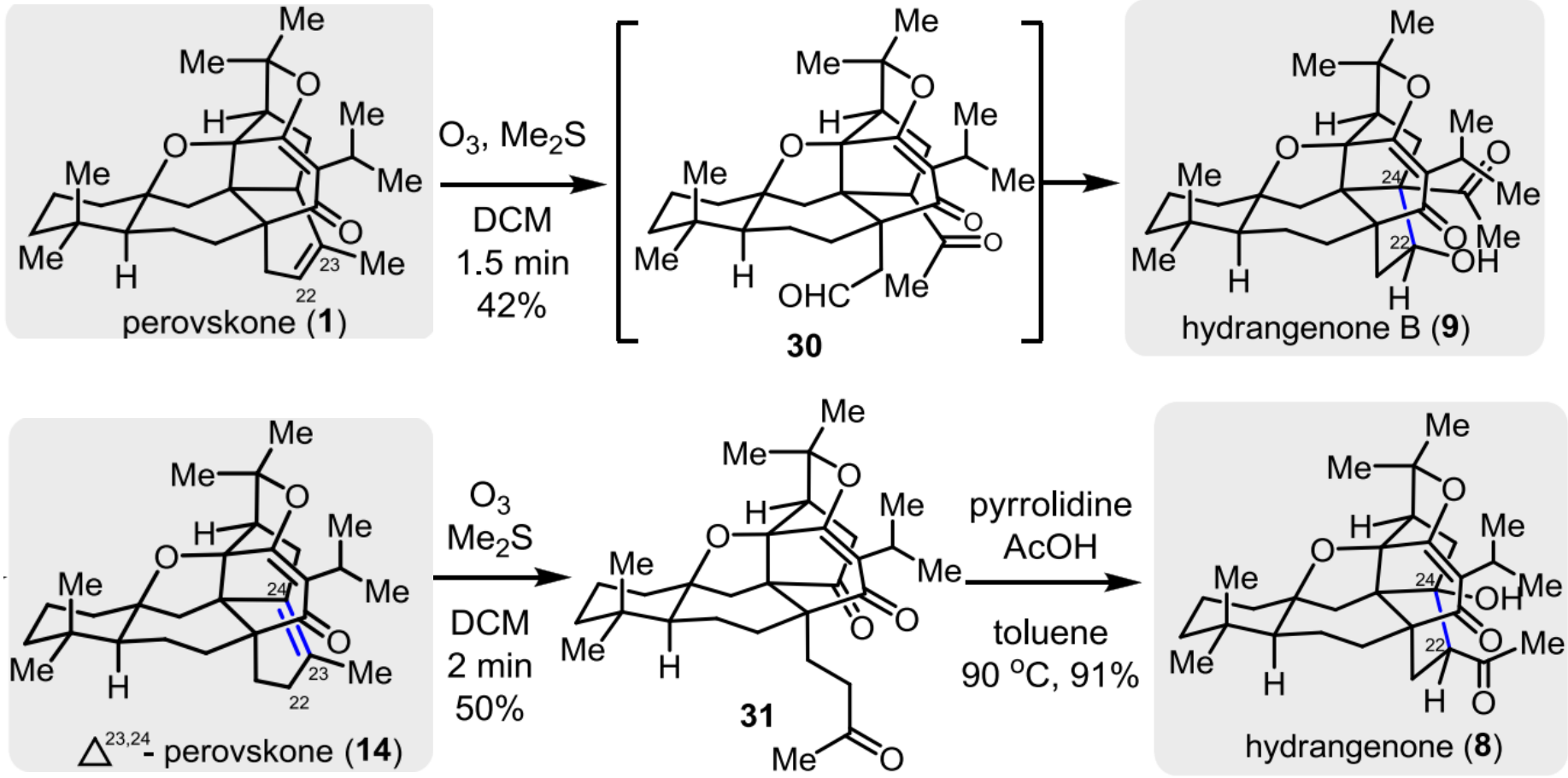
Table S4-1 Screening acid for cascade cyclization



26 **Perovskone (1)** **$\Delta^{23,24}$- Perovskone (14)**

entry	scale	acid	solvent (dry)	T (^{o}C) & time	results[a]
12	2.2 mg	PTSA·H_2O (3 equiv.)	toluene	0 ^{o}C (1.5 h) to rt (1 h) to 60 ^{o}C (17.5 h)	**14**
13	2 mg	PTSA·H_2O (0.5 equiv.)	toluene	50 ^{o}C (18 h) to 60 ^{o}C (47.3 h) to 80 ^{o}C (47.7 h)	**26 + 14**
14	2.2 mg	$InCl_3$ (3 equiv.)	DCE	0 ^{o}C (1.5 h) to rt (43.25 h) to 60 ^{o}C (7.5 h)	messy
15	2.2 mg	TFA (3 + 3 equiv.)	DCM	0 ^{o}C (2 h) to rt (21.25 h) to 45 ^{o}C (3 h) to 60 ^{o}C (38.75 h)	ND
16	3.2 mg	$MeSO_3H$ (3 + 2.3 equiv.) $MgSO_4$ (10 equiv.)	DCM	-78 ^{o}C (1 h) to 0 ^{o}C (1.17 h) to rt (13.5 h) to 50 ^{o}C (1.5 h) to 60 ^{o}C (27 h)	**14**
17	3.2 mg	TfOH (3 + 2.6 equiv.) $MgSO_4$ (10 equiv.)	DCM	-78 ^{o}C to 27 ^{o}C (44.17 h)	**14**
18	3.2 mg	CSA (3 equiv.) $MgSO_4$ (10 equiv.)	DCM	-78 ^{o}C (1 h) to 0 ^{o}C (1.17 h) to rt (13.5 h) to 50 ^{o}C (1.5 h) to 60 ^{o}C (27.5 h) to 80 ^{o}C (7.25 h)	NR
19	3.2 mg	$Eu(fod)_3$ (0.3 equiv.)	toluene	120 ^{o}C (32.75 h)	NR
20	3.2 mg	TMSOTf (4 equiv.)	MeCN	31 ^{o}C (2.67 h)	**14**
21	3.2 mg	$In(OTf)_3$ (1.5 equiv.)	DCM	rt (18.5 h) to 60 ^{o}C (3.5 h) to 80 ^{o}C (5 h)	**14**
22	3.2 mg	$Bi(OTf)_3$ (1.5 equiv.)	DCM	31 ^{o}C (3 h)	**1+14** (1:2.7)

[a] determined by crude ^{1}H NMR

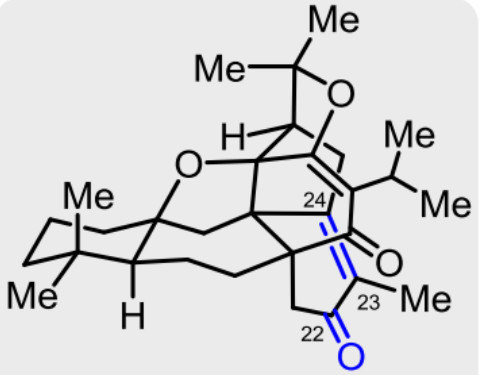

perovskone (1)
O3, Me2S
DCM
1.5 min
42%
30
hydrangenone B (9)
Δ23,24- perovskone (14)
O3
Me2S
DCM
2 min
50%
31
pyrrolidine
AcOH
toluene
90 °C, 91%
hydrangenone (8)

(B)

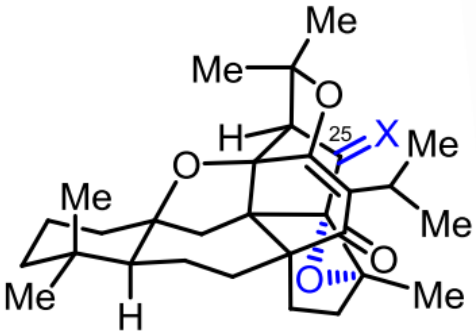
14

Na_2CrO_4
NaOAc, 60 °C

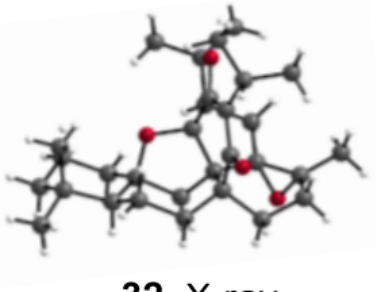
toluene
$AcOH/Ac_2O$



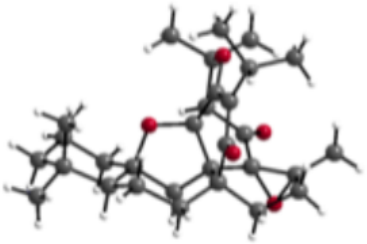
perovskone C (**3**), 17%



32, X=H, H, 26%
33, X=O, 24%

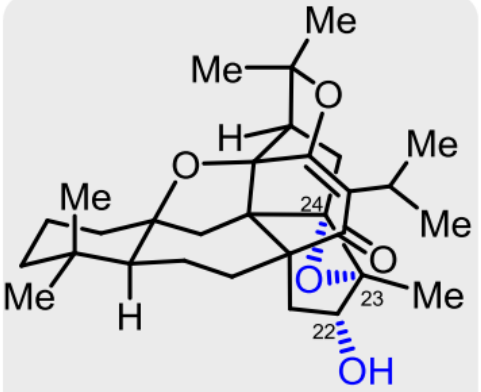


32, X-ray

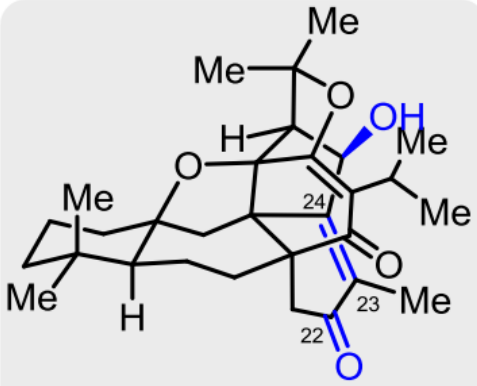


33, X-ray

1) $NaBH_4$, $CeCl_3$, MeOH,
82%, (d.r. = 1.8:1)
2) *m*-CPBA, $NaHCO_3$, DCM, 67%



perovskone F (**6**)



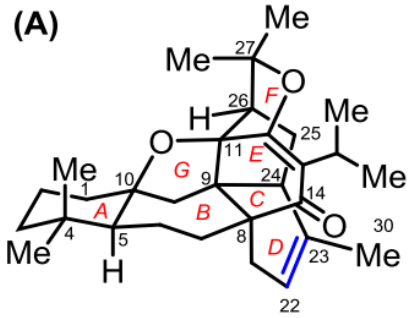
Perovskone D (**4**)

1) SeO_2
dioxane
100 °C

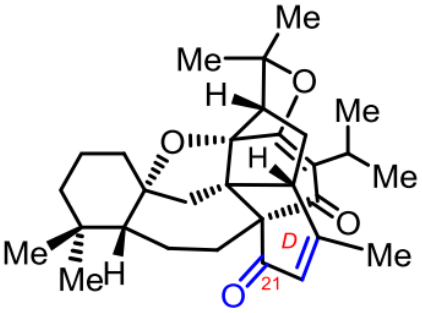
2) DMP, DCM
19% over
2 steps

14

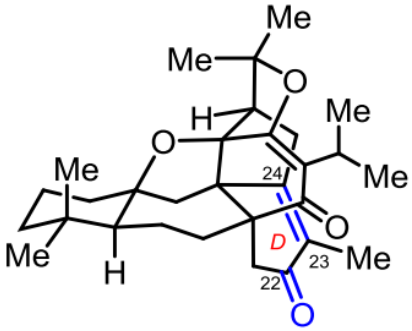
(A)



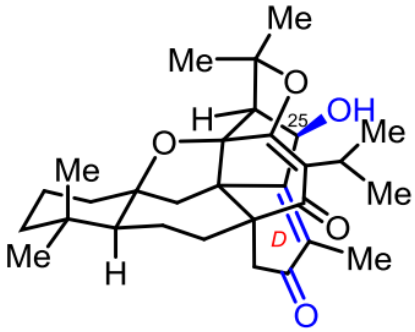
perovskone (**1**)



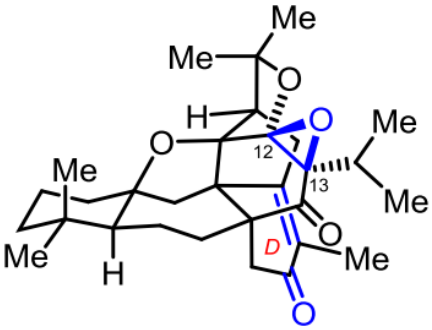
perovskone B (**2**)



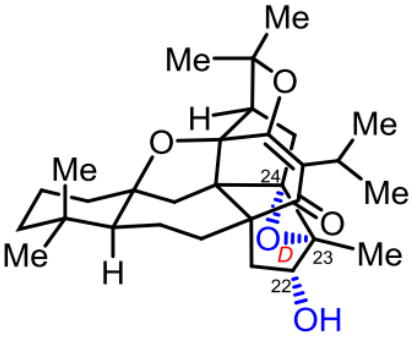
perovskone C (**3**)



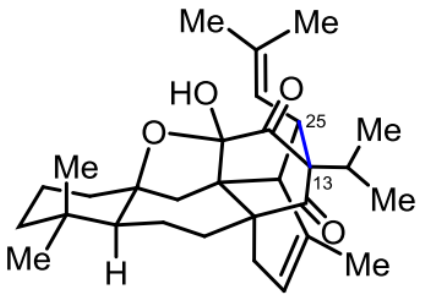
perovskone D (**4**)



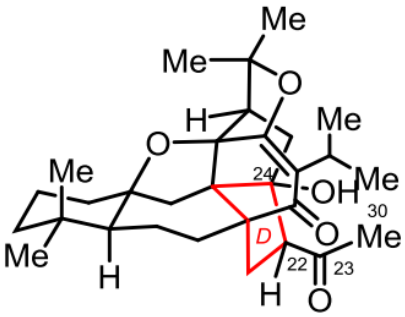
perovskone E (**5**)



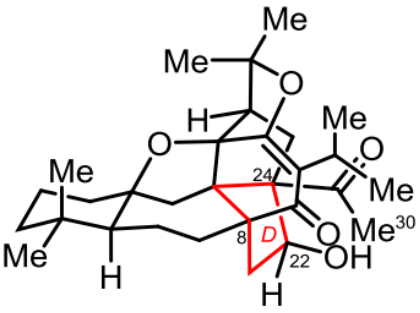
perovskone F (**6**)



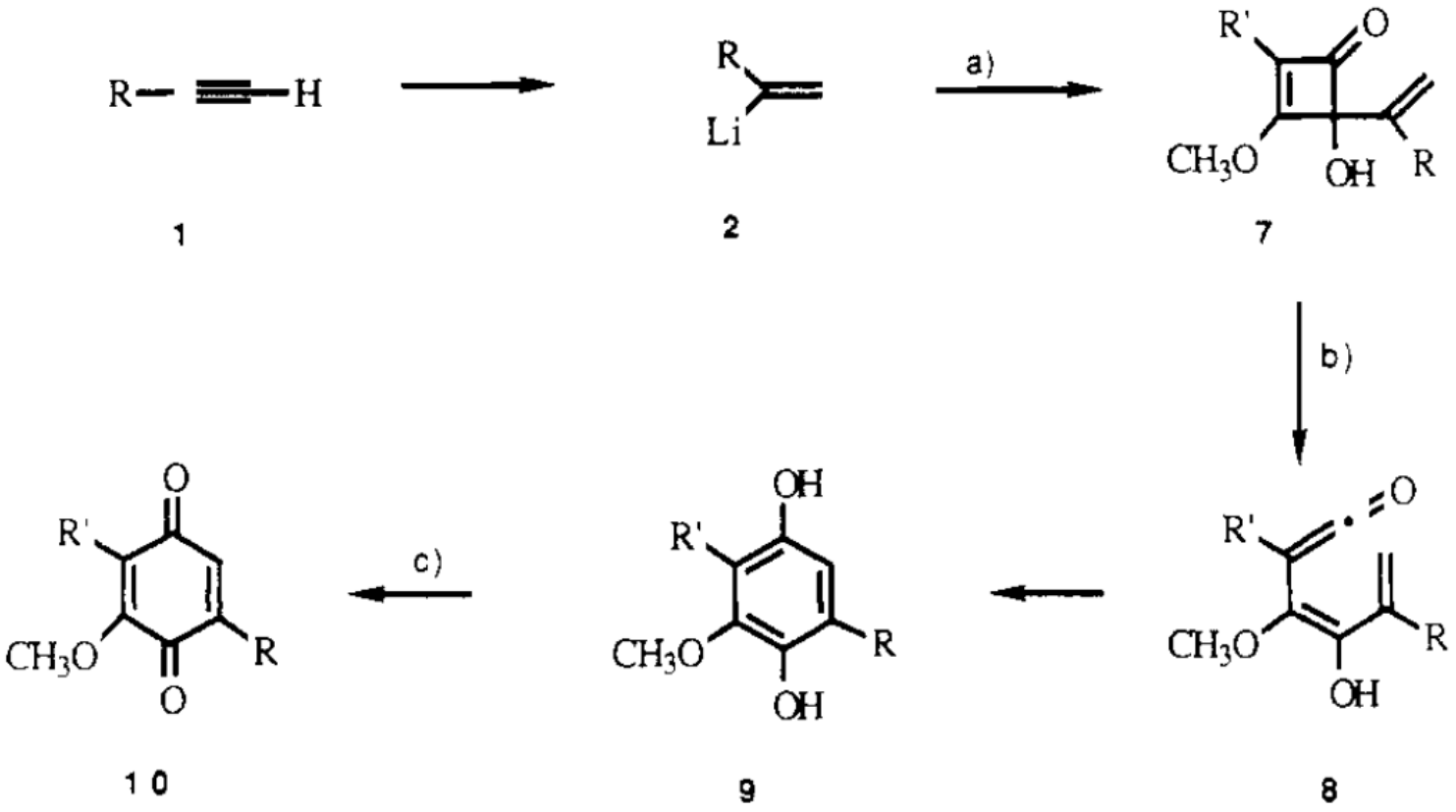
salvadione A (**7**)



hydrangenone (**8**)



hydrangenone B (**9**)



[a] Reagents: (a) a cyclobutenedione; (b) *p*-xylene, 138 °C; (c) oxidation.