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Enantioselective Total Synthesis of Dysiherbols A, C, and D

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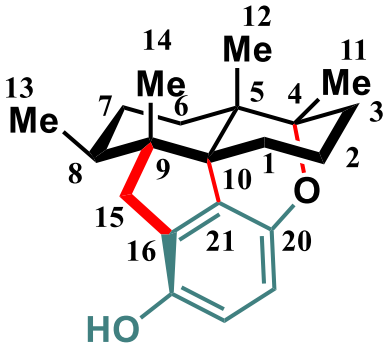
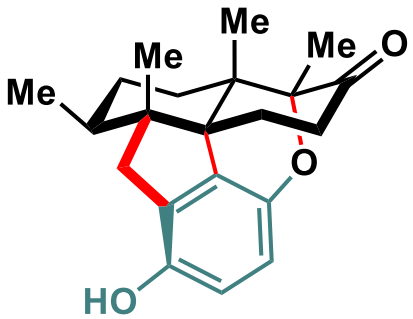
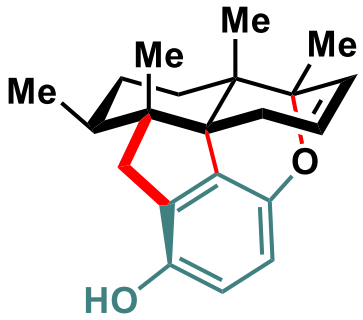


4: Dysiherbol A



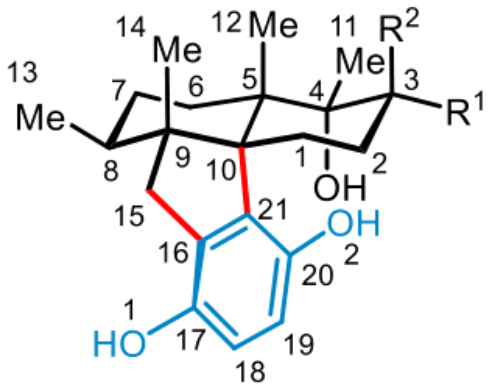
34: Dysiherbol C



30: Dysiherbol D

DOI:10.1021/jacs.2c08435.

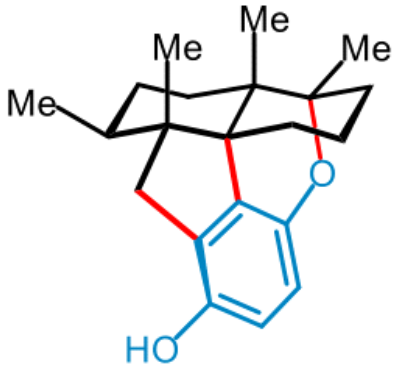
Representative polycyclic Q/HS



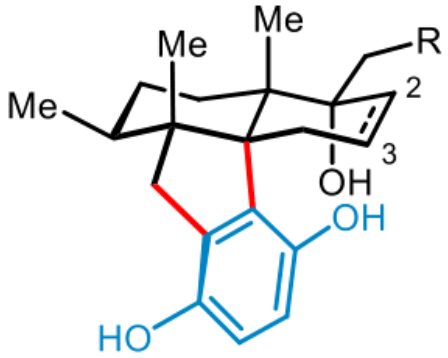
dysiherbol A (**1**): $R^1 = R^2 = H$ *

dysiherbol B (**2**): $R^1 = OH$, $R^2 = H$ ***

dysiherbol C (**3**): $R^1 = R^2 = O$ ***

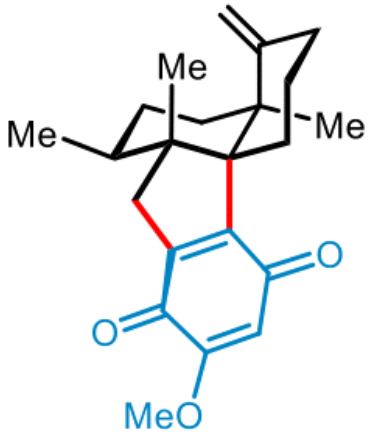


dysiherbol A (**4**) **

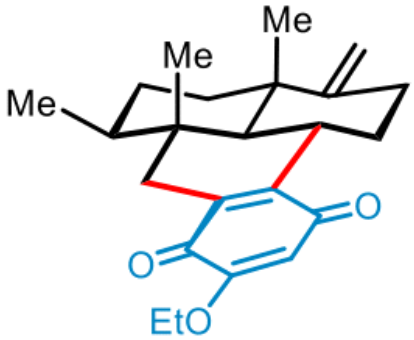


dysiherbol D (**5**): R = H, $\Delta^{2,3}$ ***

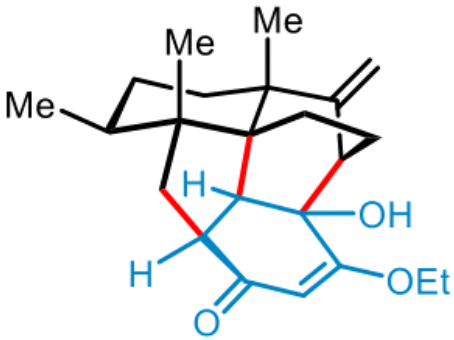
dysiherbol E (**6**): R = OH ***



cycloaurenone C (**7**)

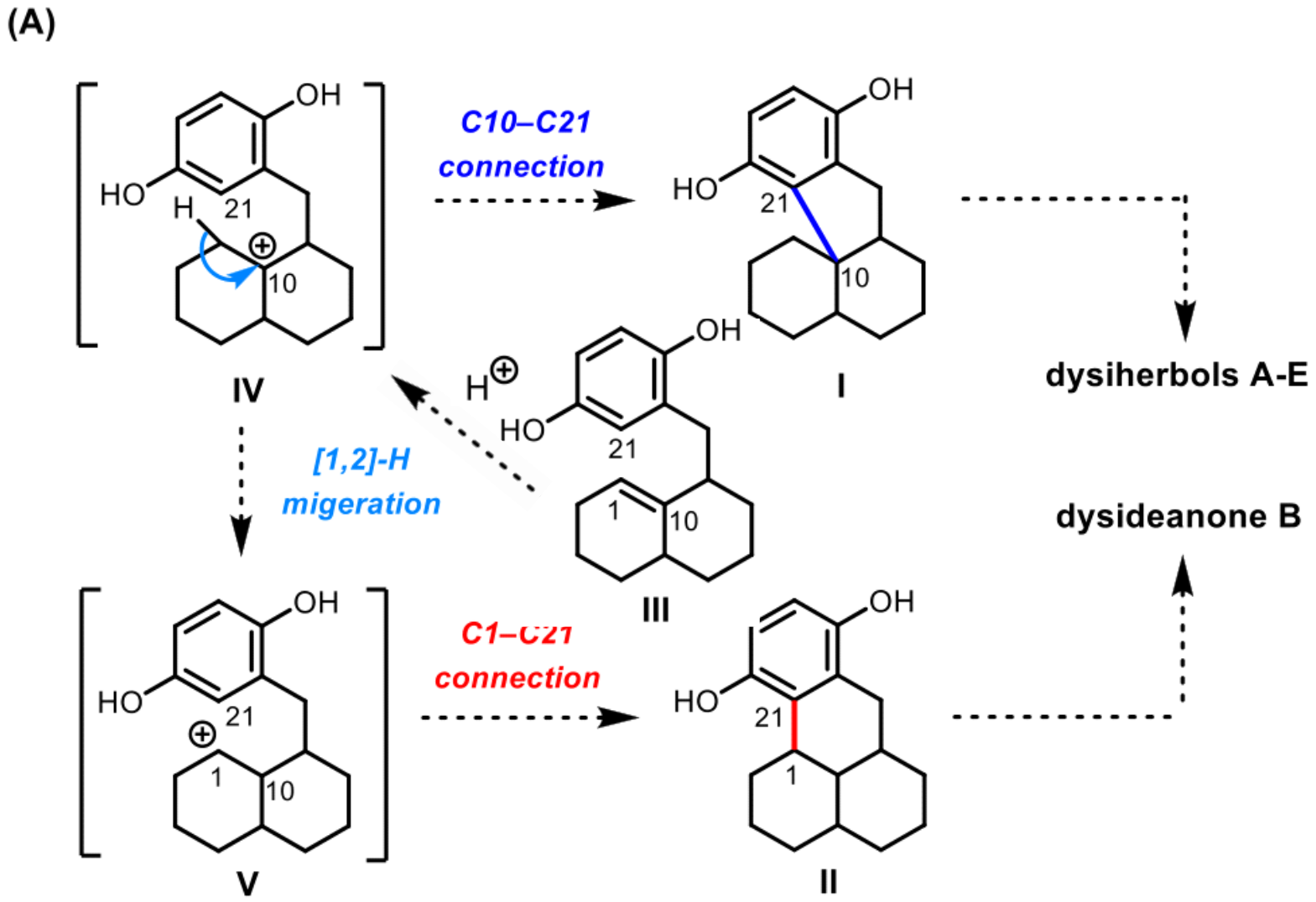


dysideanone B (**8**)

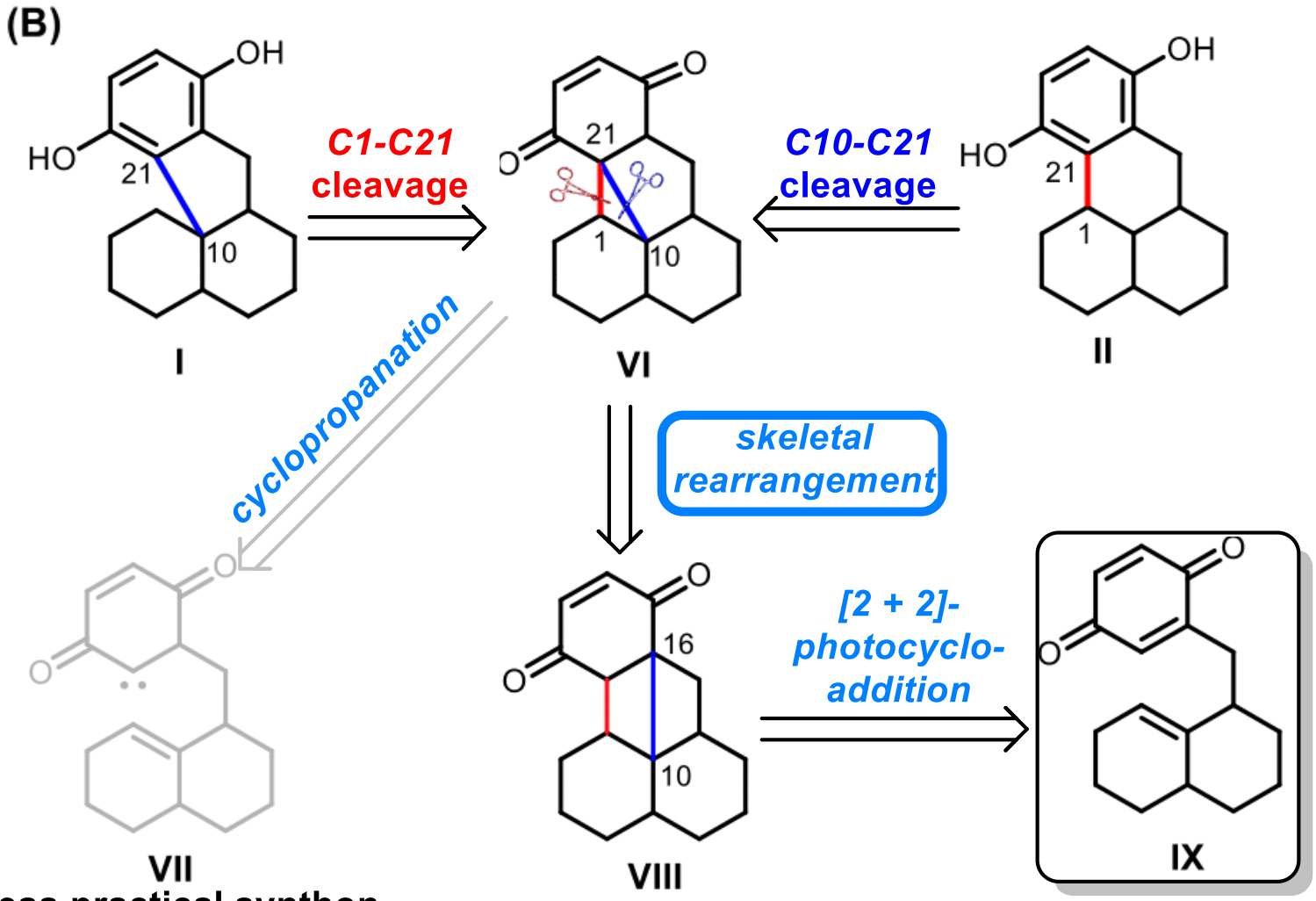


septosone A (**9**)

* originally proposed structure ** revised structure *** yet-to-be-validated structure

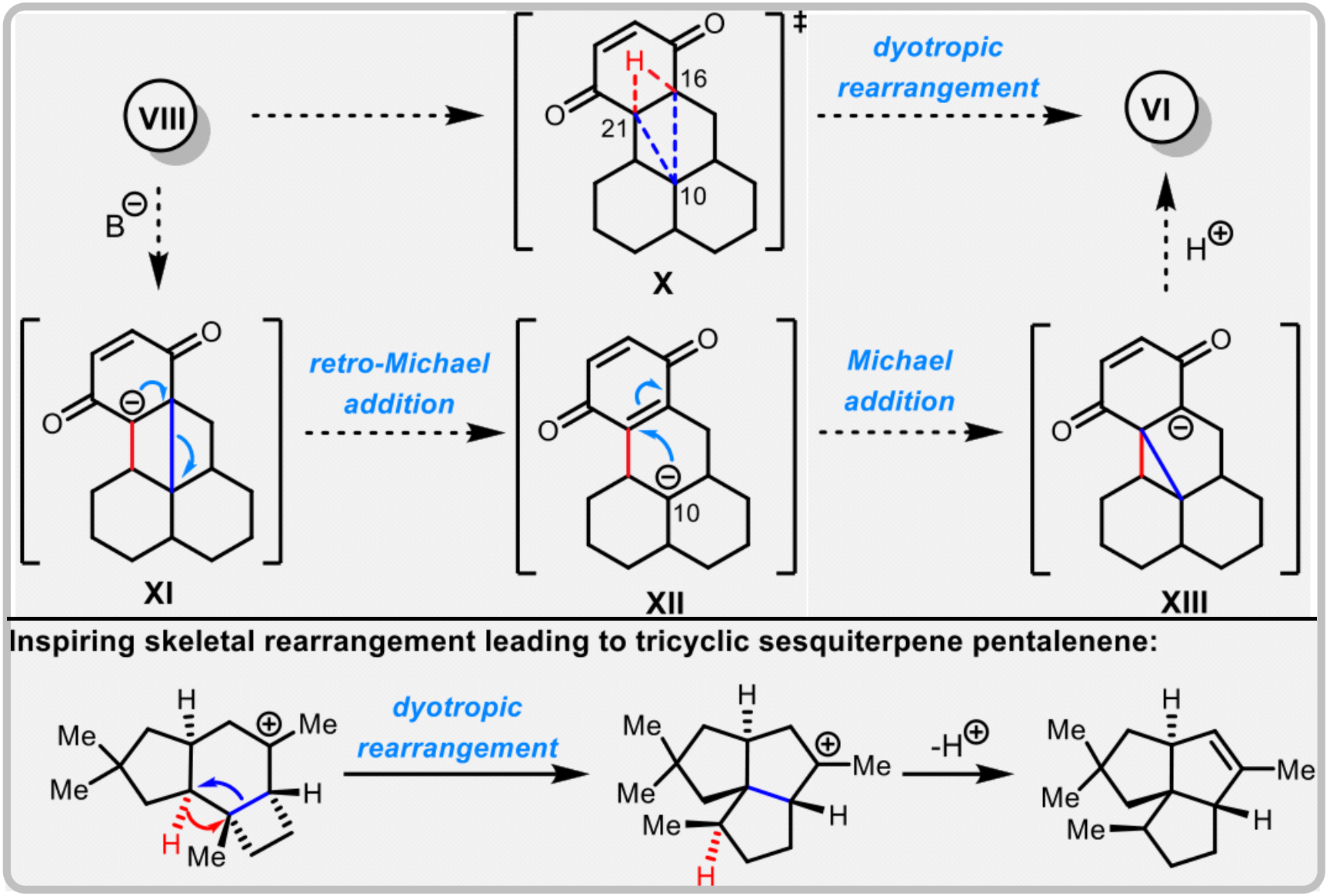


(A) Bioinspiration: diverted synthesis of 6/6/5/6 and 6/6/6/6 tetracyclic Q/HS via a selective C−C bond formation.



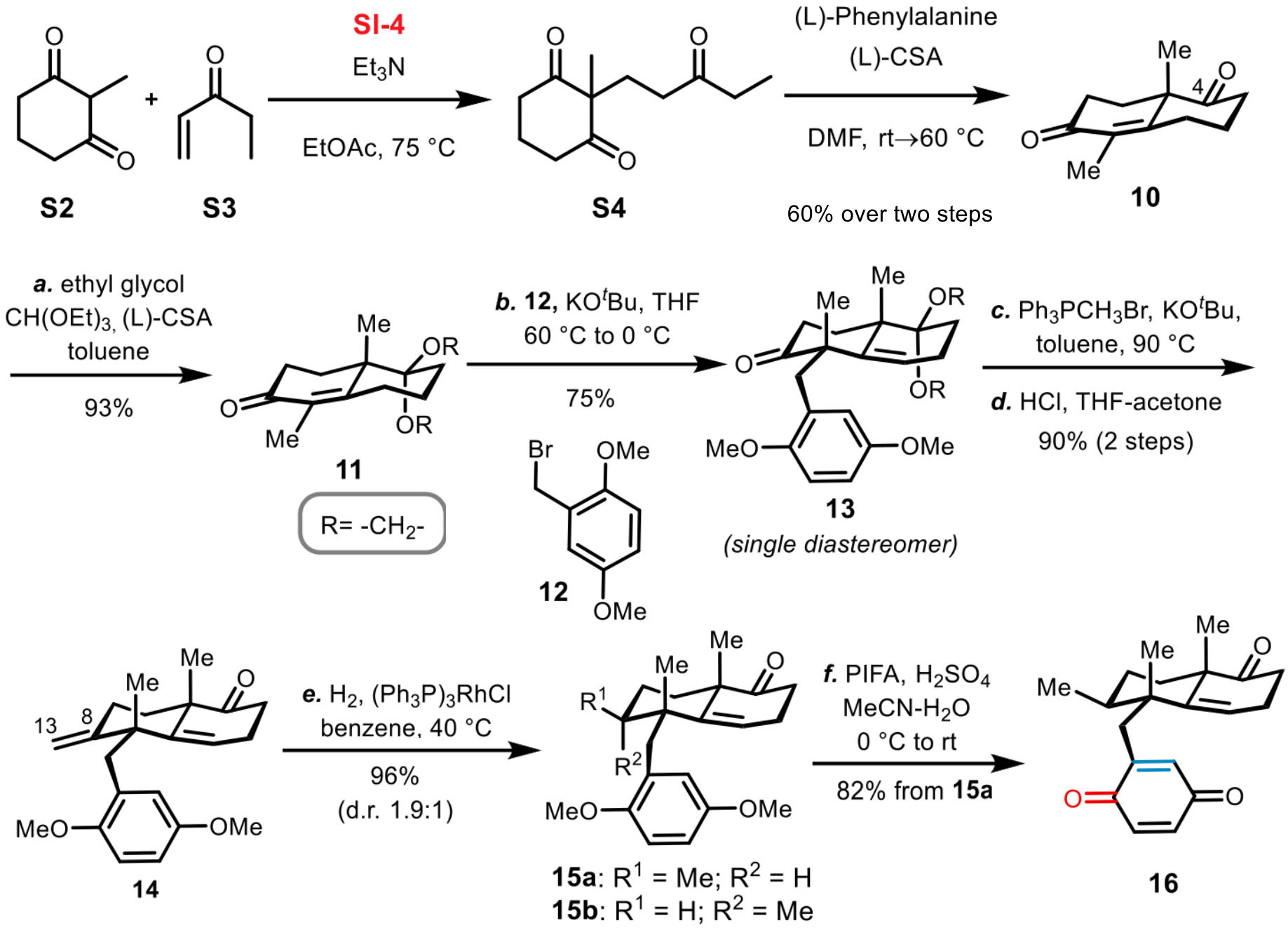
(B) Rational design: diverted synthesis of 6/6/5/6 and 6/6/6/6 tetracyclic Q/HS via a selective C−C bond cleavage.

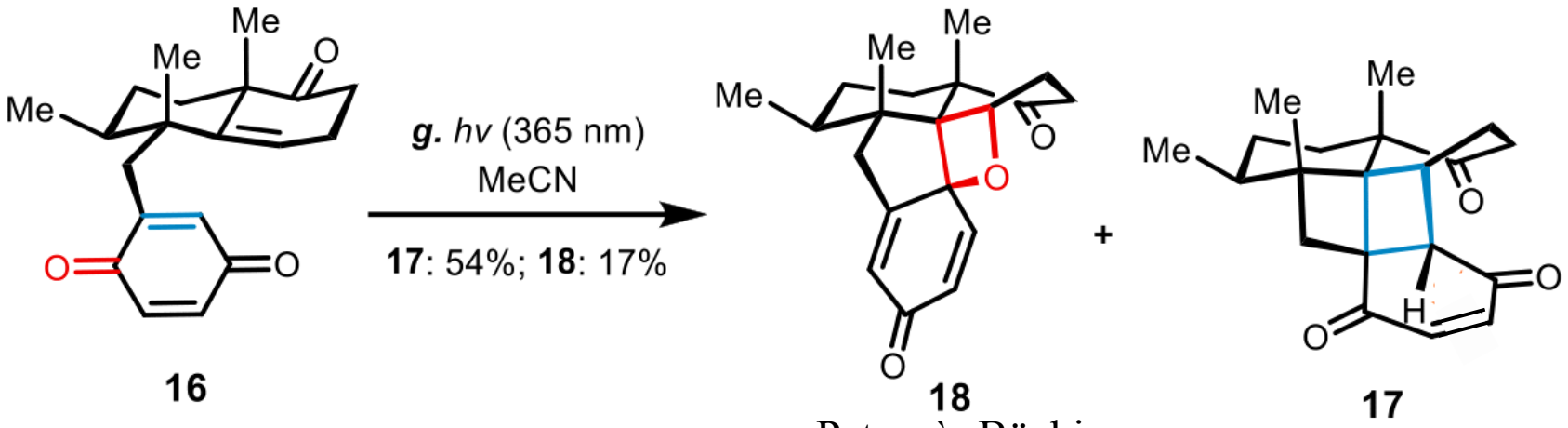
(C)



(C) Proposed reaction pathways of the skeletal rearrangement from VIII to VI.

Scheme 1. Initial Studies toward the Total Synthesis of Dysiherbol A (4)



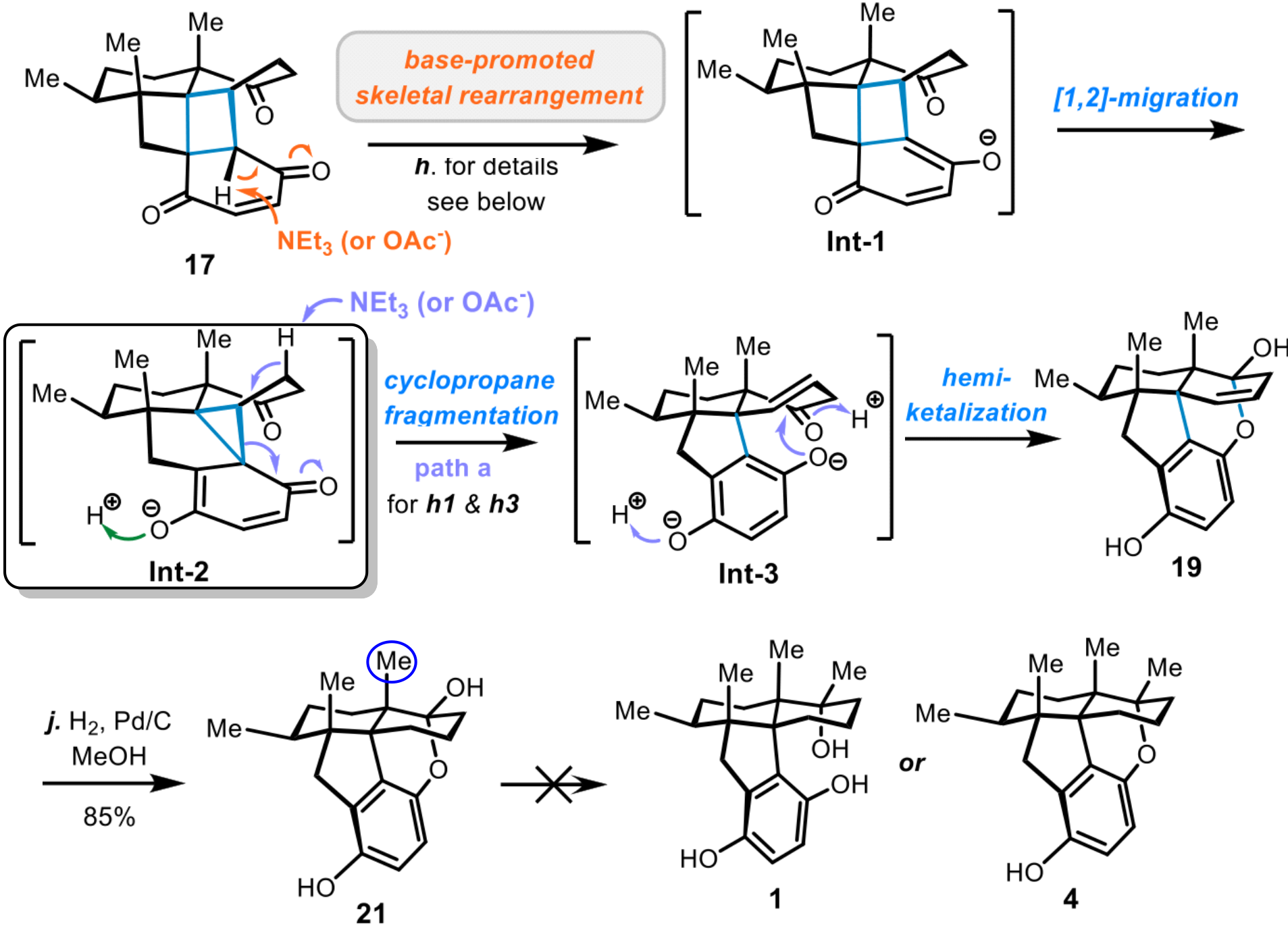


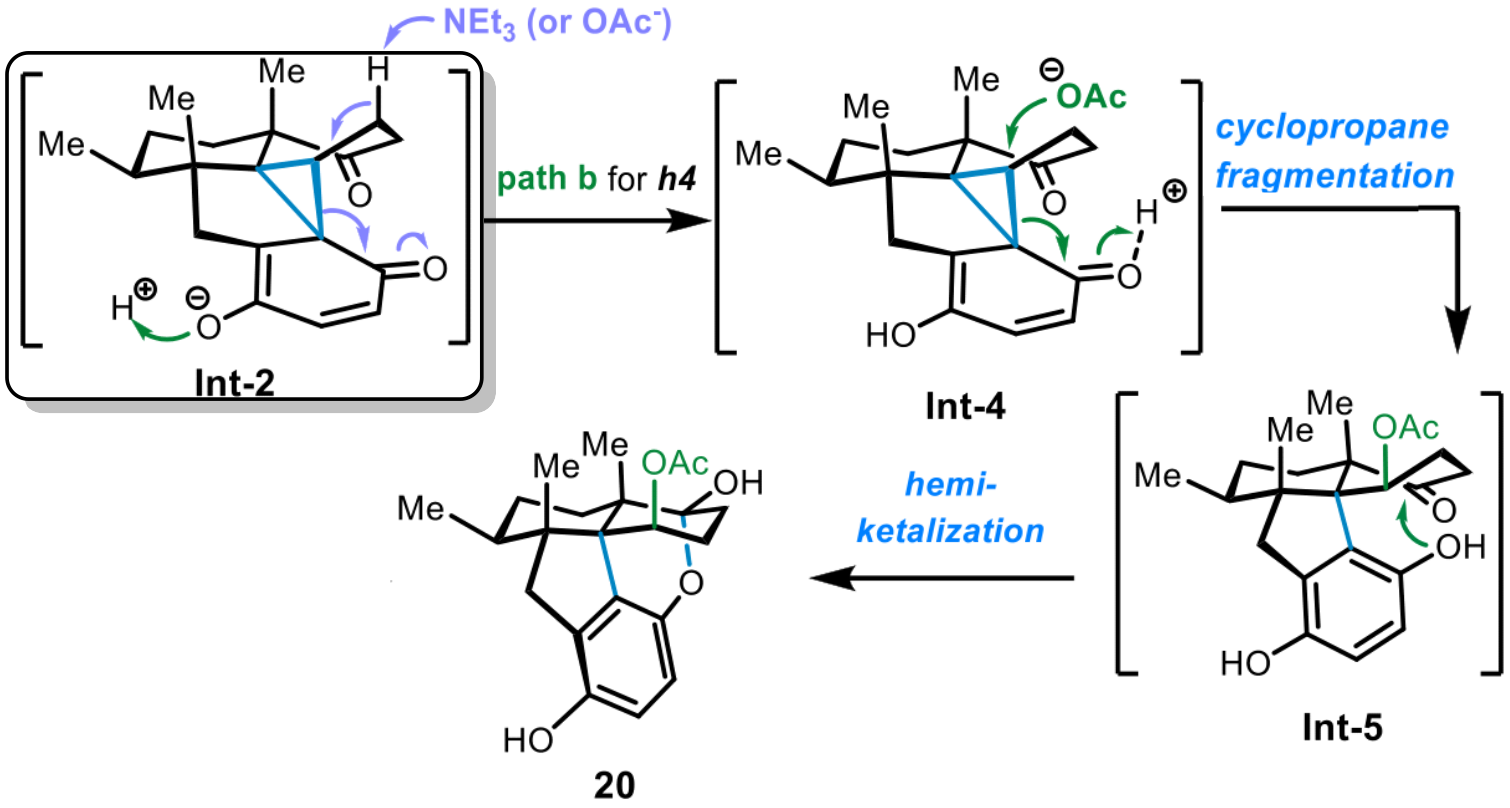
16 18 17

Paternò–Büchi reaction

step g Solvent	17 : 18 (ratio, 5 min)
benzene (0.01M)	1.8:1
acetone (0.01M)	2.3:1
MeCN (0.01M)	2.5:1
MeCN (0.001M)	3.0:1

当使用254 nm的光源时，同样以化合物**17**为主产物，遗憾的是化合物17在此条件下易发生光解。

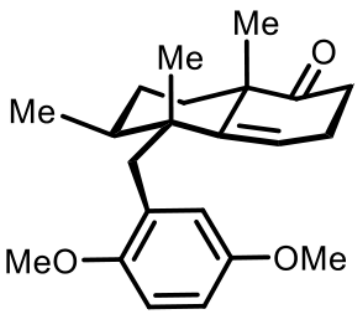

base-promoted skeletal rearrangement
h. for details see below
NEt3 (or OAc-)
17
Int-1
[1,2]-migration
NEt3 (or OAc-)
Int-2
cyclopropane fragmentation
path a
for h1 & h3
Int-3
hemi-ketalization
19
j. H2, Pd/C
MeOH
85%
21
1
or
4



step h

Conditions	Product: yield
1. acetone, 14 days	**19**: ca. 15%
2. Et_3N, MeOH	**19**: 42%
3. $Bu_4N^+AcO^-$, MeCN	**19**: 63%
4. $Bu_4N^+AcO^-$, MeCN-AcOH	**20**: 50%

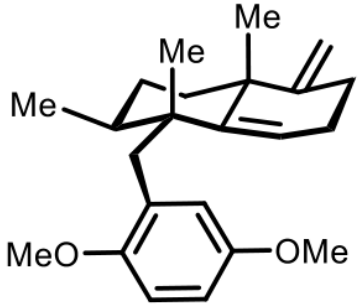
Completion of the Total Synthesis of Dysiherbols A, C, and D



15a

a. Ph_3PCH_3Br
KO^tBu
toluene, 80 °C

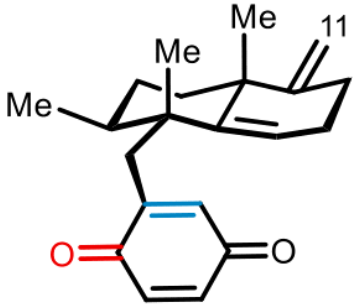
98%



24

b. $PhI(OPiv)_2$
PTSA
$MeCN\text{-}H_2O$

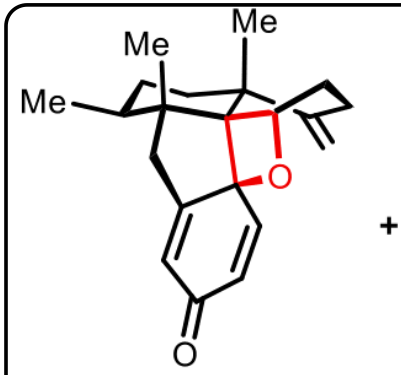
48% (83% brsm)



25

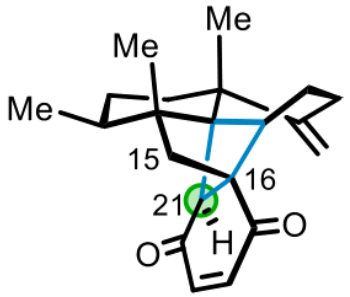
c. *hv* (365 nm)
acetone

26: 29% (41% brsm)
27: 19% (27% brsm)
28: 15% (20% brsm)



28

+



27

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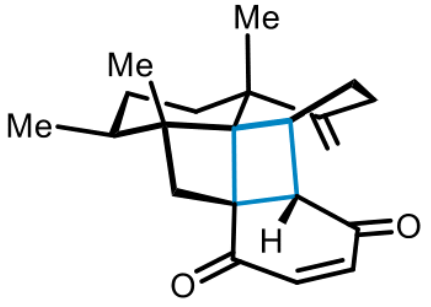
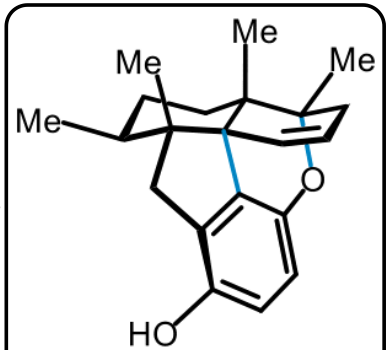


26

d. $Bu_4N^+AcO^-$
then $BF_3{\bullet}Et_2O$
MeCN

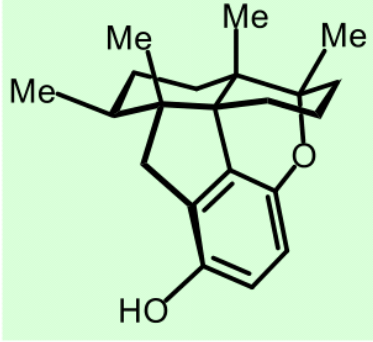
84% from **26**



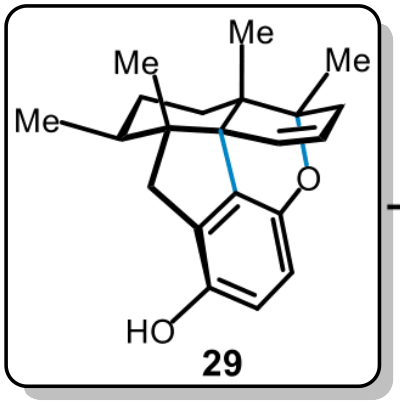
29

e. H_2, Pd/C
MeOH

83%

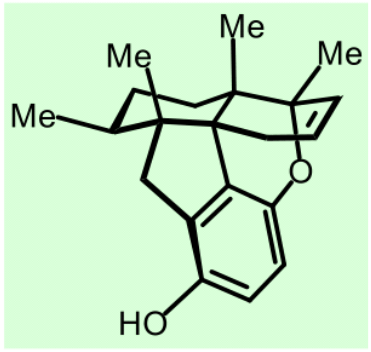


4: dysiherbol A
(revised structure)

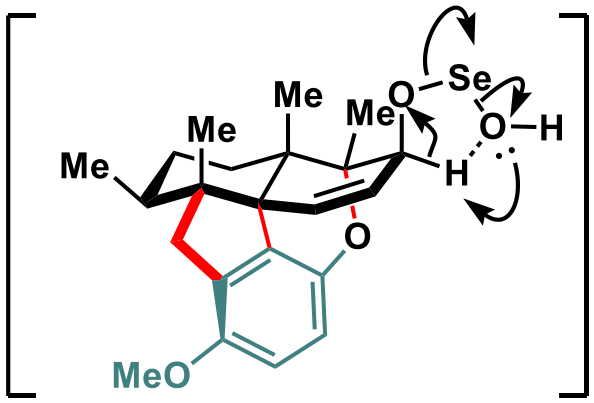


29

f. $RhCl_3 \cdot 3H_2O$
EtOH, 100 °C
66%

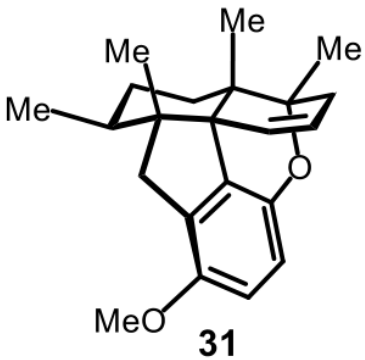


30: dysiherbol D
(revised structure)



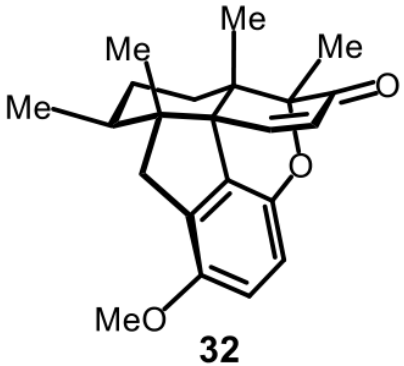
RILEY SELENIUM DIOXIDE OXIDATION
31 to **32**

97%
g. NaOH, MeI
THF



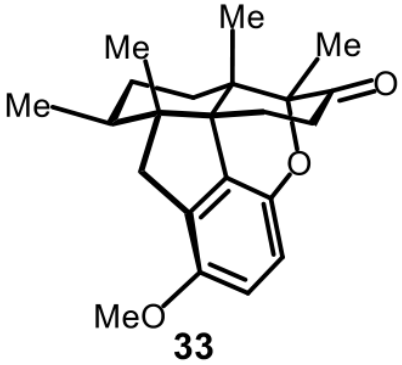
31

h. SeO_2
chlorobenzene
150 °C
56%



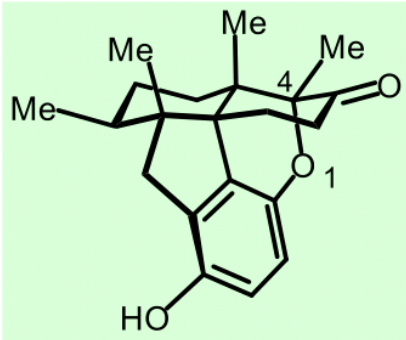
32

i. H_2, Pd/C
MeOH
98%



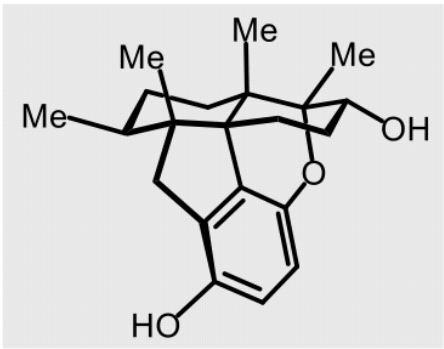
33

j. BBr_3/H_2O
DCM, 0 °C
62%
(86% brsm)



34: dysiherbol C
(revised structure)

various
conditions

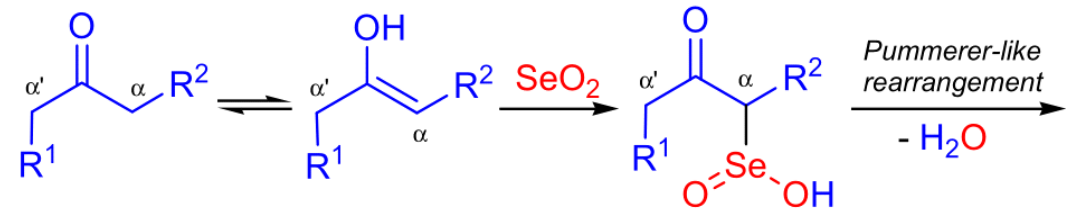


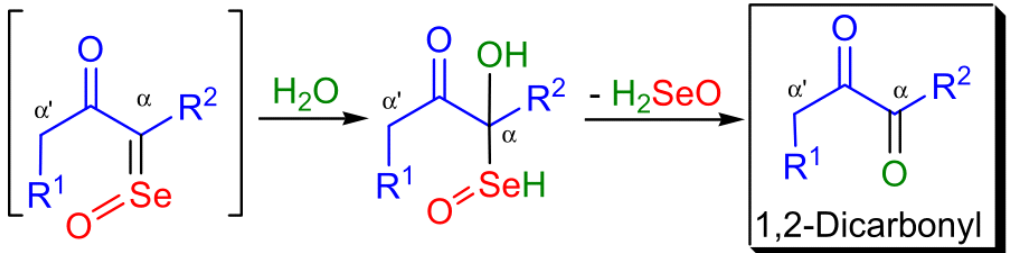
35: dysiherbol B
(revised structure)

RILEY SELENIUM DIOXIDE OXIDATION

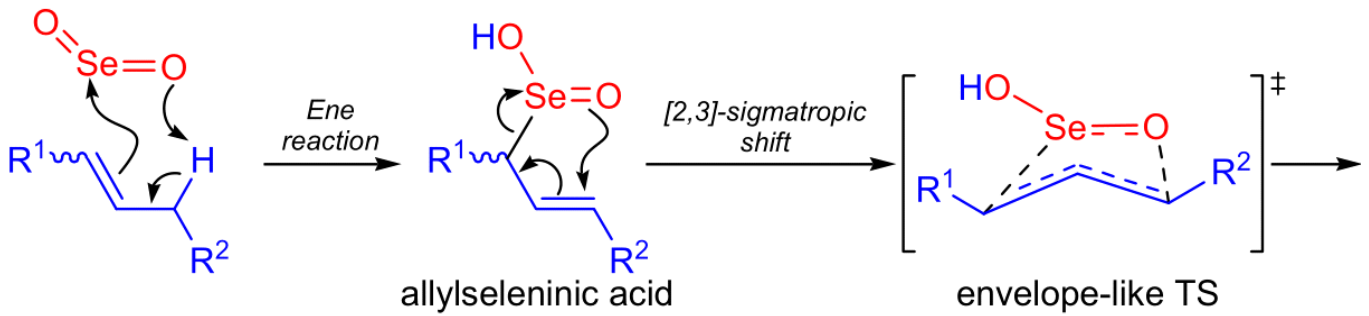
(References are on page 663)

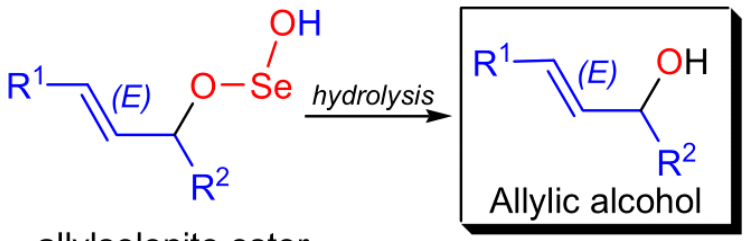
Oxidation of carbonyl compounds:



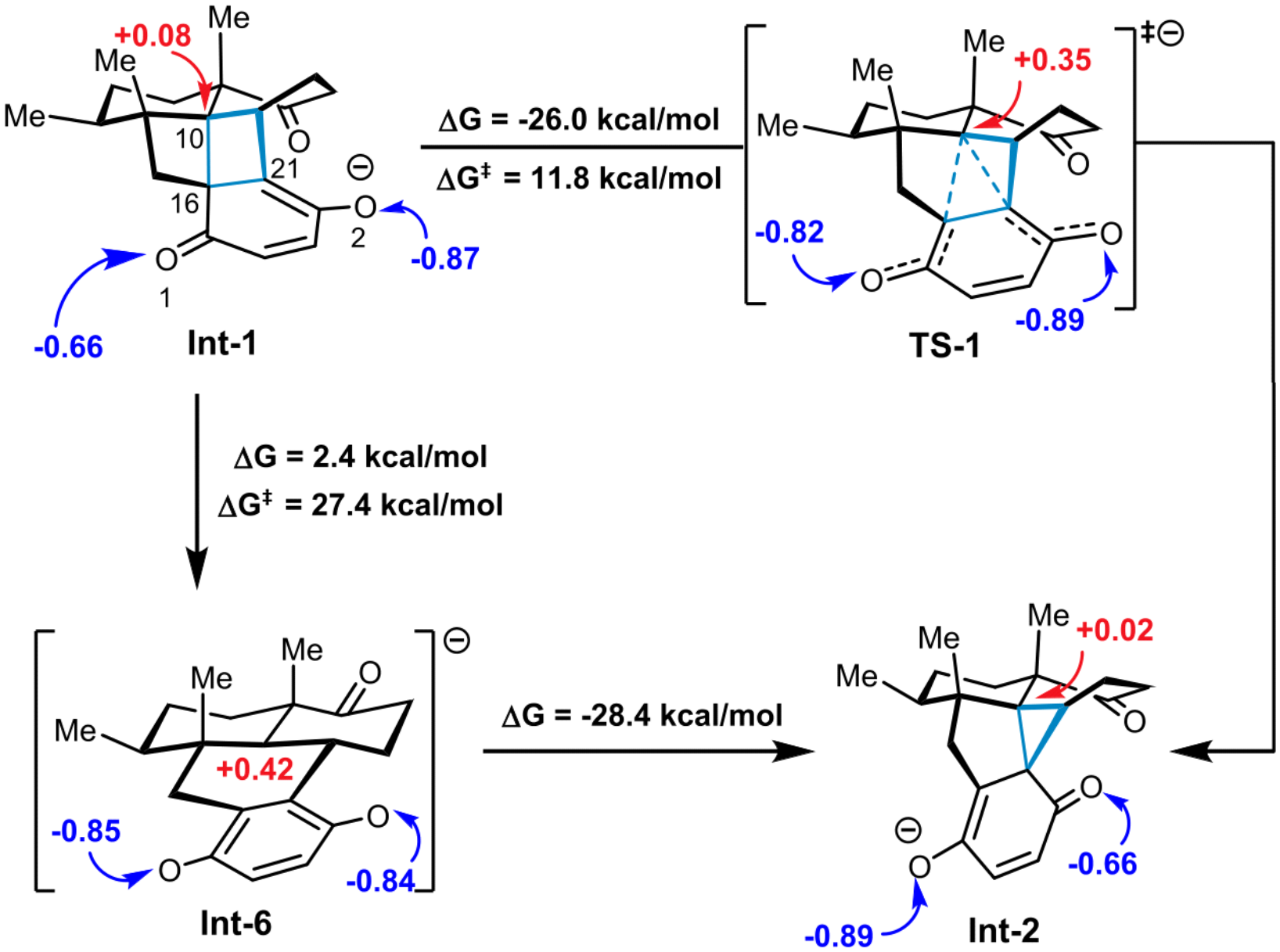


Oxidation of alkenes:

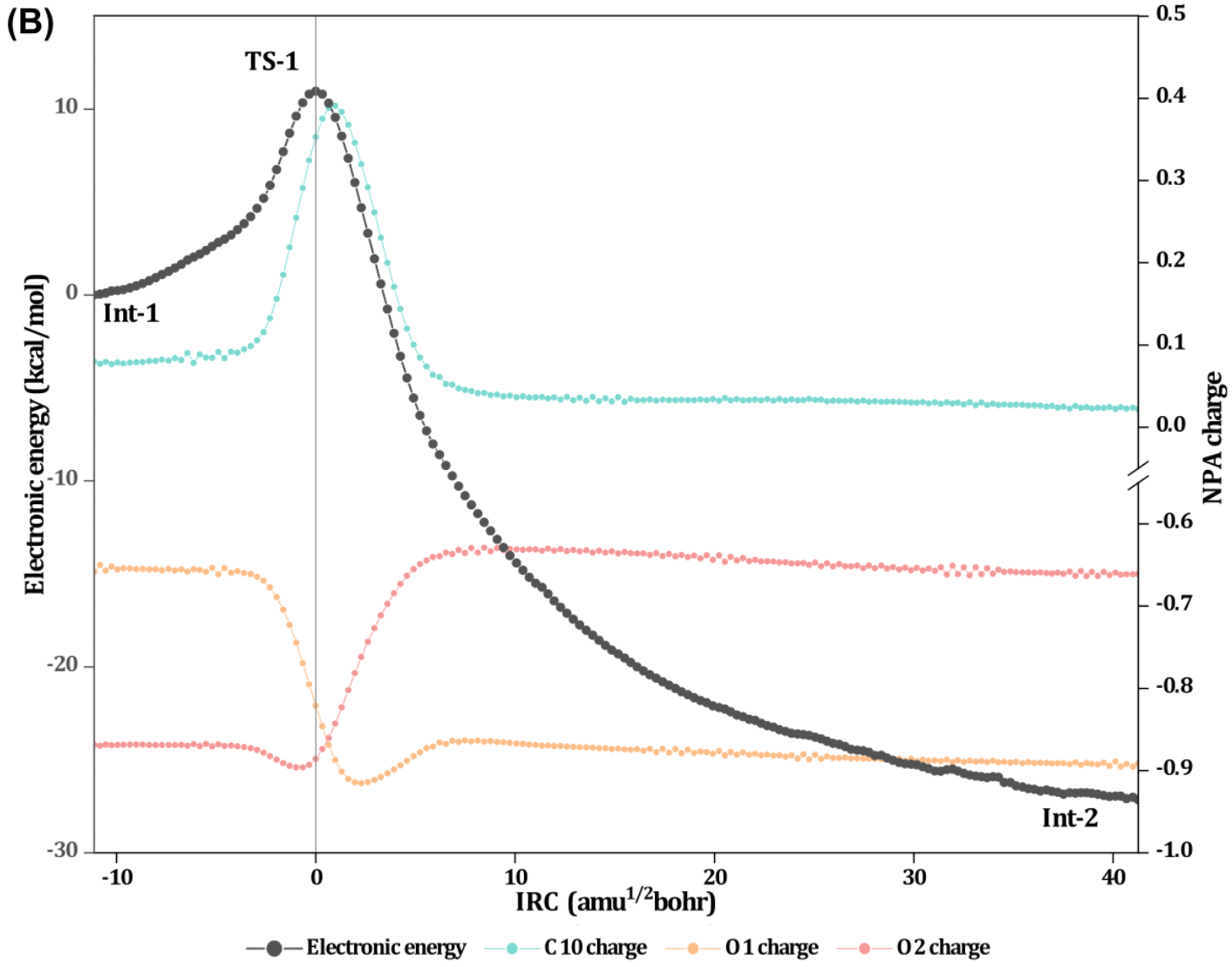


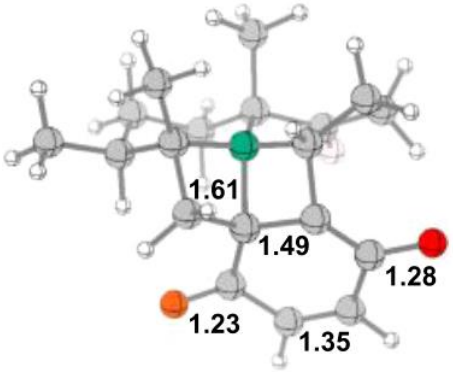


Mechanistic analysis of the [1,2]-migration process

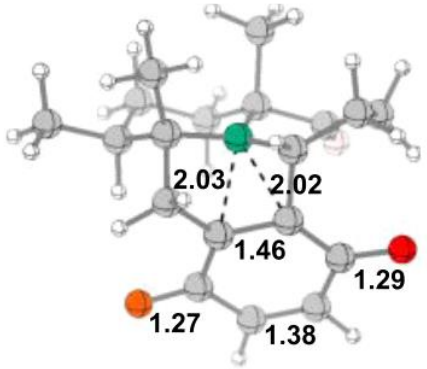


DFT calculation of the presumed intermediates and TS. The selected NPA charges are shown in red and blue.

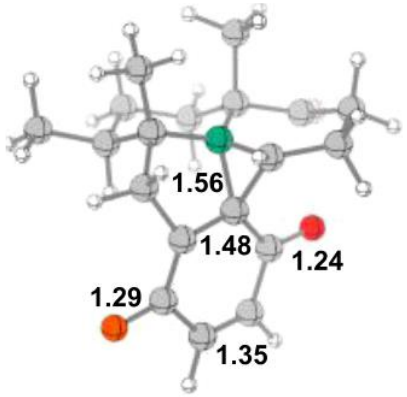




Int-1



TS-1

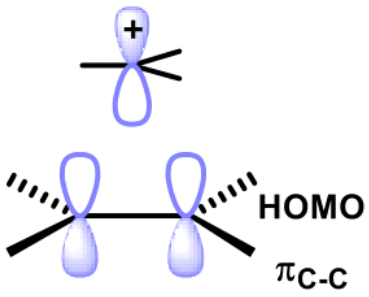


Int-2

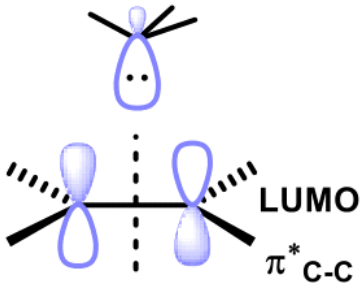
(B) Electronic energy and NPA charge for selected atoms along the IRC. The interatomic distances are shown in angstroms. Calculated at M06-2X/6-311+G(d,p), SMD(MeCN) level of theory. The same level was applied in the following calculations unless otherwise mentioned.

Interpretation of the favored and disfavored factors in the [1,2]-migration

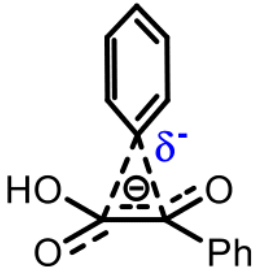
(A)



TS-2



TS-3



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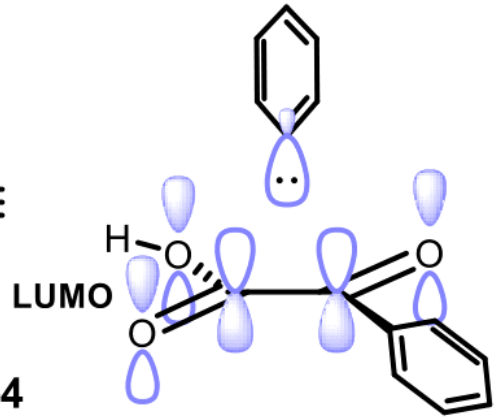
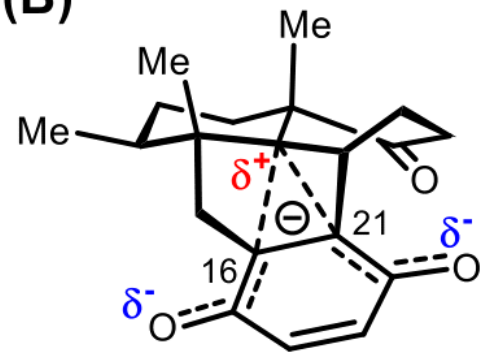


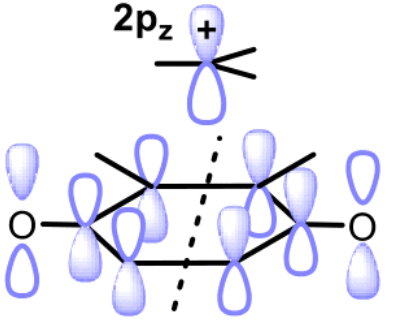
TS-4

Orbital interactions in cationic and anionic [1,2] rearrangement (left) and benzilic acid rearrangement (right).

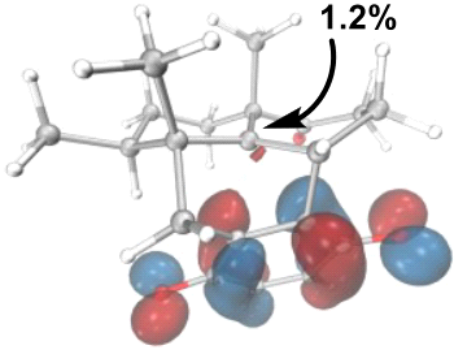
(B)



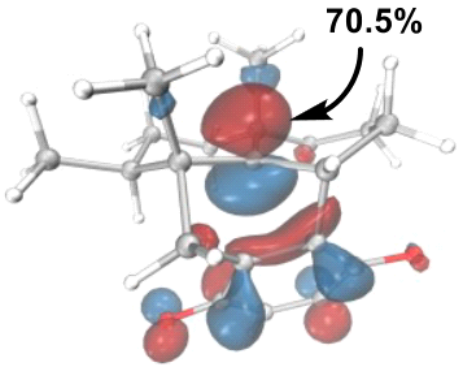
TS-1



HOMO of hydroquinone

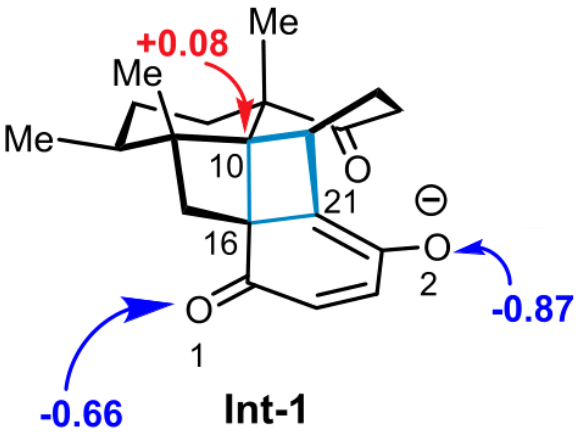


$TS\text{-}1_{HOMO}$

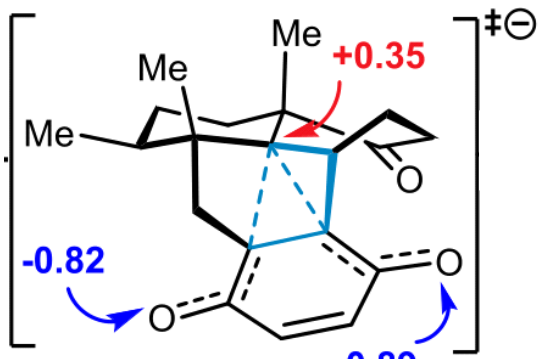


$TS\text{-}1_{LUMO}$

Pictorial representation of orbital interaction and frontier molecular orbitals of **TS-1**. Isovalue = 0.05 a.u.

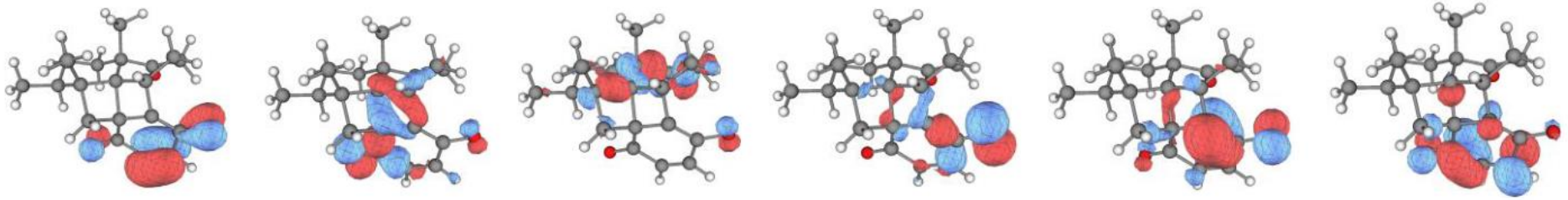


Int-1



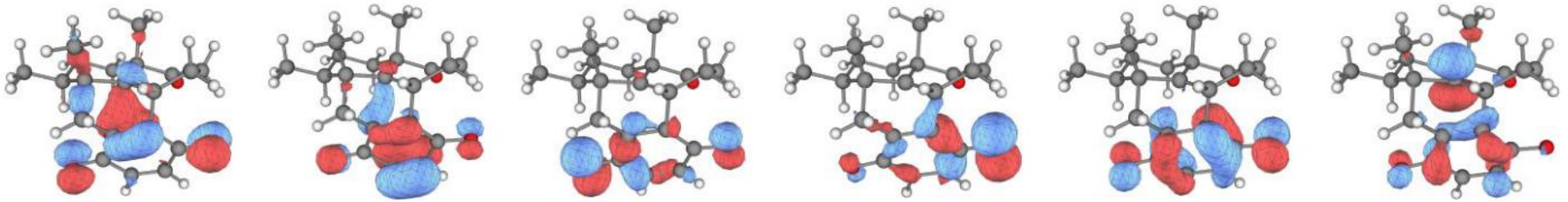
TS-1

MOs of Int-1:



HOMO-4	HOMO-3	HOMO-2	HOMO-1	HOMO	LUMO
-8.54 eV	-8.06 eV	-7.97 eV	-7.16 eV	-5.45 eV	-0.59 eV

MOs of TS-1:

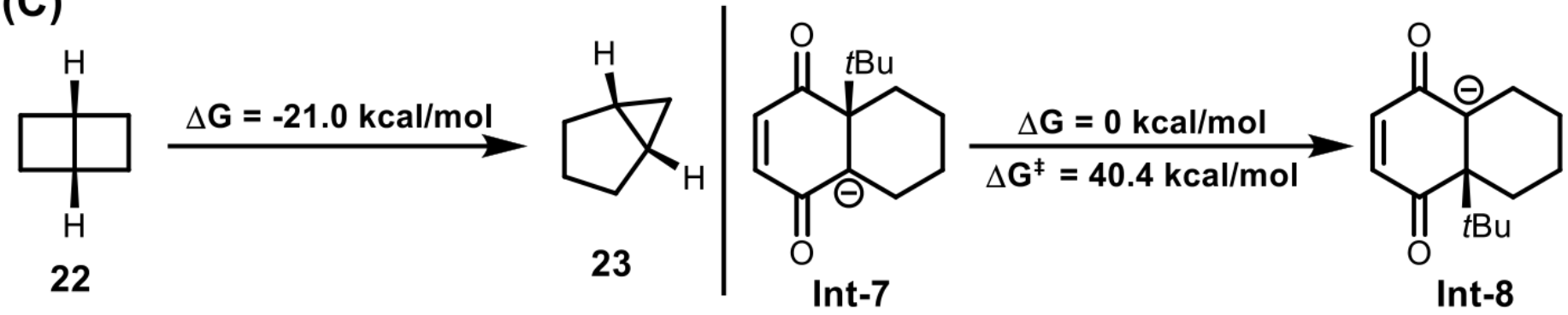


HOMO-4	HOMO-3	HOMO-2	HOMO-1	HOMO	LUMO
-8.17 eV	-7.95 eV	-7.55 eV	-7.15 eV	-4.81 eV	-0.62 eV

Figure S9. MOs of **Int-1** and **TS-1.** Negative charge ignored. Isovalue = 0.05 a.u.

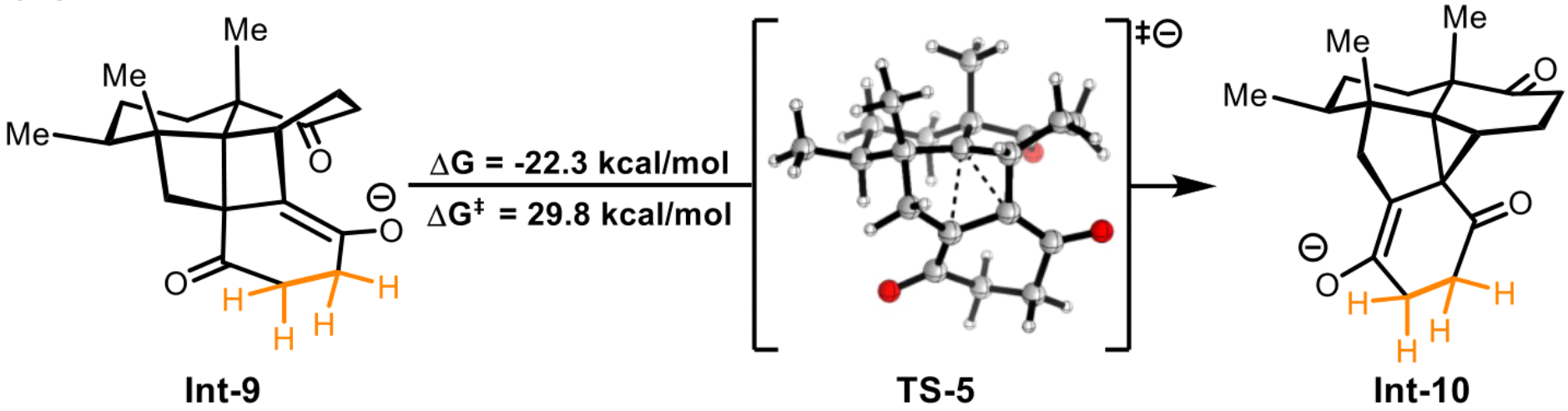
Interpretation of the favored and disfavored factors in the [1,2]-migration

(C)



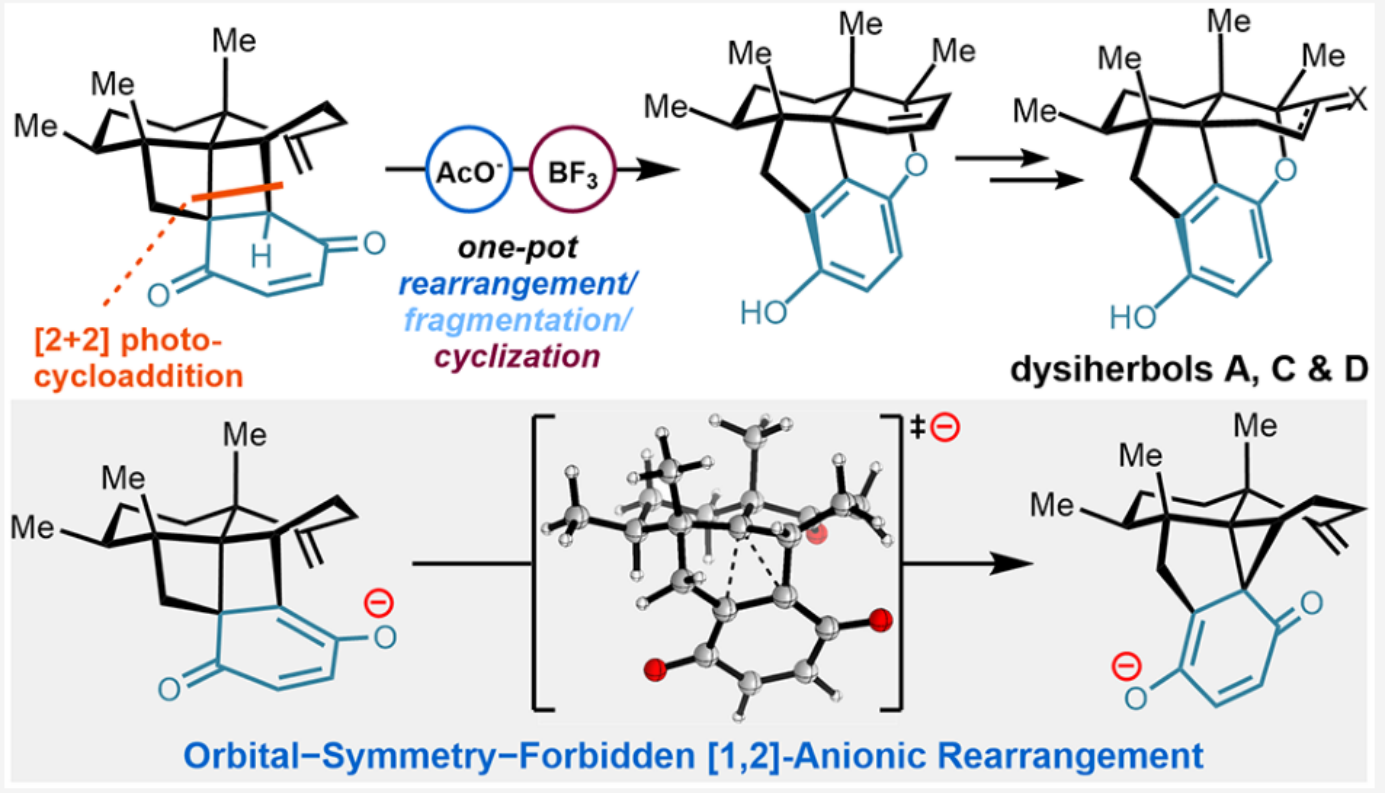
Effect of strain energy release. Left: M06-2X/def2-TZVPP level of theory

(D)



Effect of local aromaticity in transition states

Summary



1） we have accomplished the collective syntheses of dysiherbols A, C, and D, a group of pentacyclic quinone/hydroquinone sesquiterpenes, in a concise and enantioseletive manner.

2） The key features of our total synthesis of dysiherbols include a rarely seen quinone−alkene [2 + 2]-photocycloaddition and an unprecedented [1,2]-anionic rearrangement.