Total Synthesis of (+)-Herpotrichones A–C

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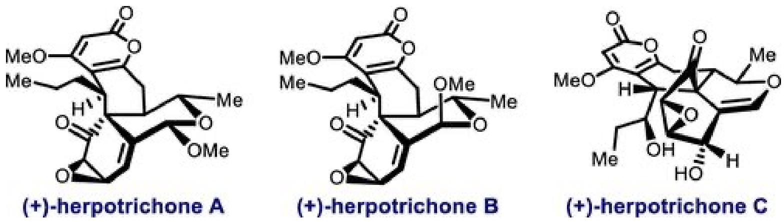
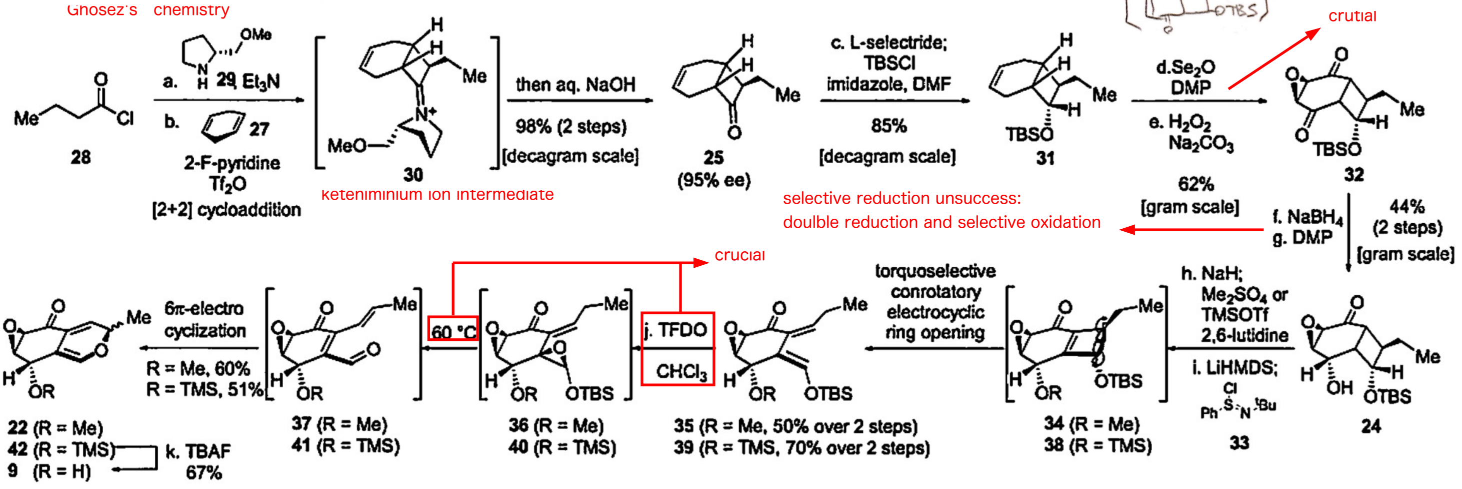
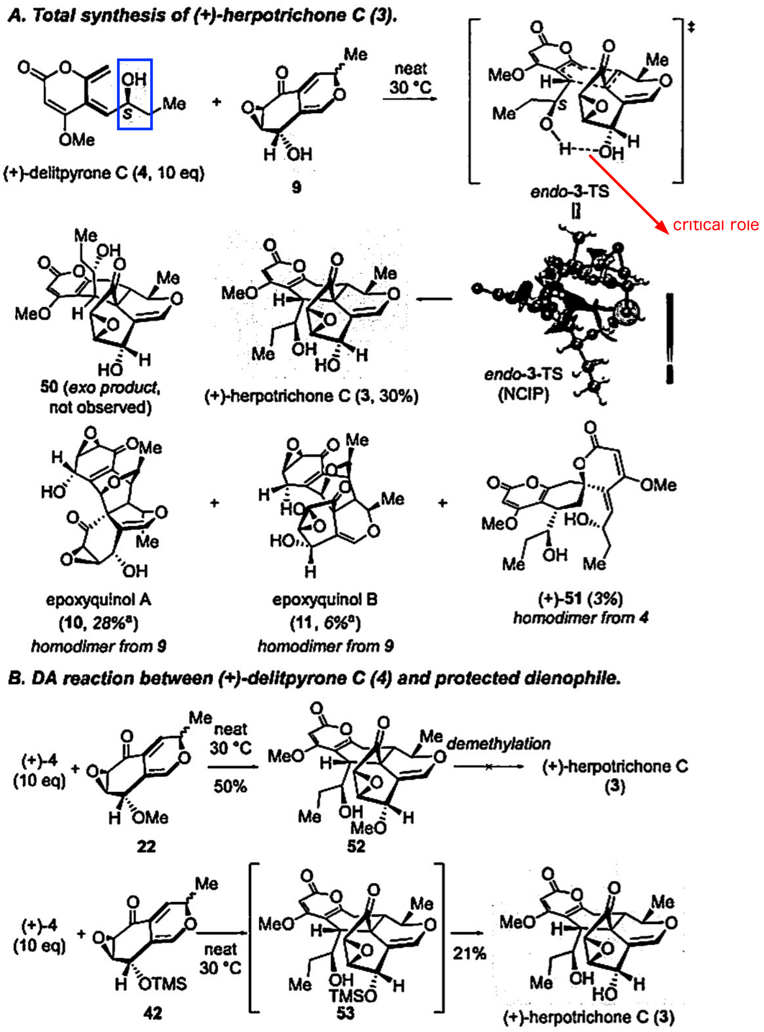

(+)-herpotrichone A
(+)-herpotrichone B
(+)-herpotrichone C

Epoxyquinoids

Scheme 3. Synthesis of Dienophiles 9 and 22ª


Ghosez's chemistry
a. 29, Et3N
b. 27
2-F-pyridine
Tf2O
[2+2] cycloaddition
28
30
keteniminium ion intermediate
then aq. NaOH
98% (2 steps)
[decagram scale]
25
(95% ee)
c. L-selectride;
TBSCl
imidazole, DMF
85%
[decagram scale]
31
d.Se2O
DMP
e. H2O2
Na2CO3
62%
[gram scale]
crutial
32
selective reduction unsuccess:
double reduction and selective oxidation
f. NaBH4
g. DMP
44%
(2 steps)
[gram scale]
24
h. NaH;
Me2SO4 or
TMSOTf
2,6-lutidine
i. LiHMDS;
33
34 (R = Me)
38 (R = TMS)
torquoselective
conrotatory
electrocyclic
ring opening
35 (R = Me, 50% over 2 steps)
39 (R = TMS, 70% over 2 steps)
j. TFDO
CHCl3
crucial
36 (R = Me)
40 (R = TMS)
60 °C
37 (R = Me)
41 (R = TMS)
6π-electro
cyclization
R = Me, 60%
R = TMS, 51%
22 (R = Me)
42 (R = TMS)
9 (R = H)
k. TBAF
67%

Scheme 6. Total Synthesis of Herpotrichone C (3)



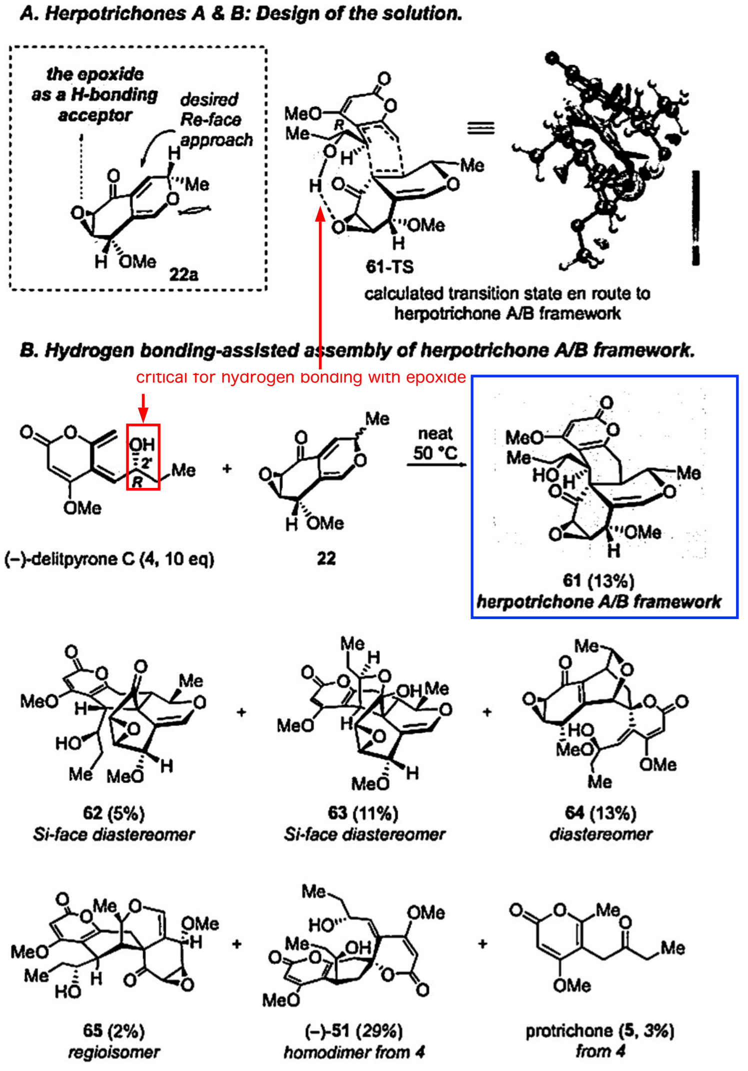
A. Total synthesis of (+)-herpotrichone C (3).

(+)-delitpyrone C (4, 10 eq)
9
neat
30 °C
endo-3-TS
critical role
50 (exo product, not observed)
(+)-herpotrichone C (3, 30%)
endo-3-TS
(NCIP)
epoxyquinol A
(10, 28%ª)
homodimer from 9
epoxyquinol B
(11, 6%ª)
homodimer from 9
(+)-51 (3%)
homodimer from 4

B. DA reaction between (+)-delitpyrone C (4) and protected dienophile.

(+)-4
(10 eq)
22
neat
30 °C
50%
52
demethylation
(+)-herpotrichone C
(3)
(+)-4
(10 eq)
42
neat
30 °C
53
21%
(+)-herpotrichone C (3)

Scheme 7. Assembly of the Herpotrichone A/B Framework (61)ª



A. Herpotrichones A & B: Design of the solution.

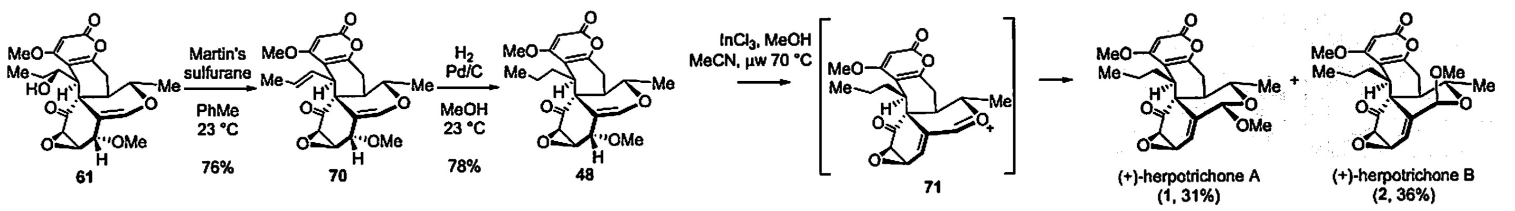
the epoxide
as a H-bonding
acceptor
desired
Re-face
approach
22a
61-TS
calculated transition state en route to
herpotrichone A/B framework

B. Hydrogen bonding-assisted assembly of herpotrichone A/B framework.

critical for hydrogen bonding with epoxide
(−)-delitpyrone C (4, 10 eq)
22
neat
50 °C
61 (13%)
herpotrichone A/B framework
62 (5%)
Si-face diastereomer
63 (11%)
Si-face diastereomer
64 (13%)
diastereomer
65 (2%)
regioisomer
(−)-51 (29%)
homodimer from 4
protrichone (5, 3%)
from 4

Both (-) and (+)-deliptyrone C (4) were accessed by adapting Enomoto's synthetic route with slight modifications.

Scheme 8. Completion of the Total Synthesis of Herpotrichones A (1) and B (2)


Ferrier rearrangement
61
Martin's
sulfurane
PhMe
23 °C
76%
70
H2
Pd/C
MeOH
23 °C
78%
48
InCl3, MeOH
MeCN, μw 70 °C
71
(+)-herpotrichone A
(1, 31%)
(+)-herpotrichone B
(2, 36%)