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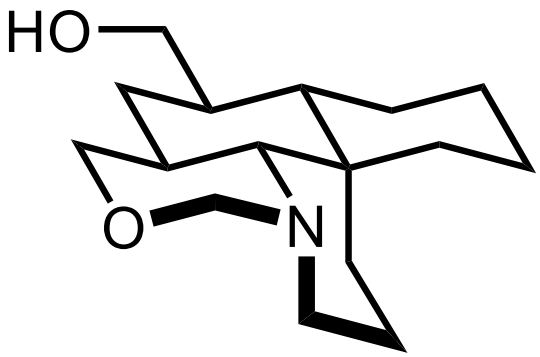
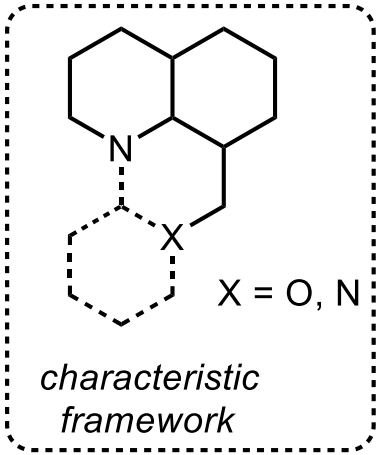
# Symmetry-Driven Total Synthesis of Myrioneurinol

Jake M. Aquilina and Myles W. Smith*

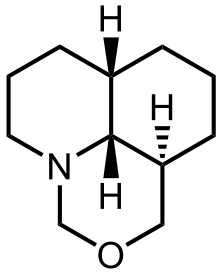



(-)-myrioneurinol

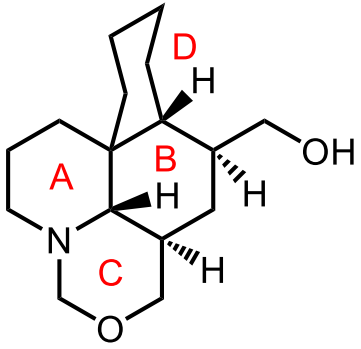
# (A) Representative Myrioneuron alkaloids

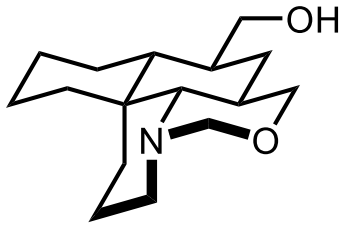



*characteristic framework*

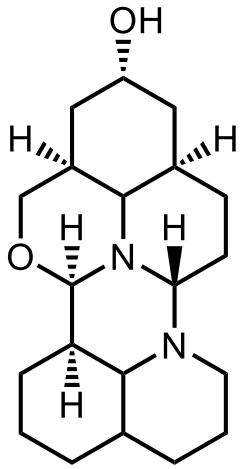


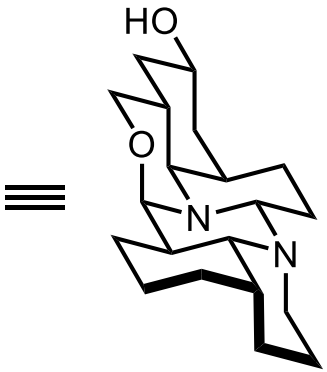
**1:** *myrioxazine A*



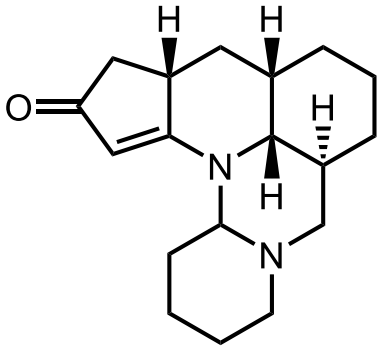




**2:** *(+)-myrioneurinol*

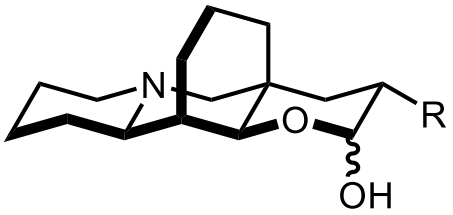



**3:** *myrobotinol*



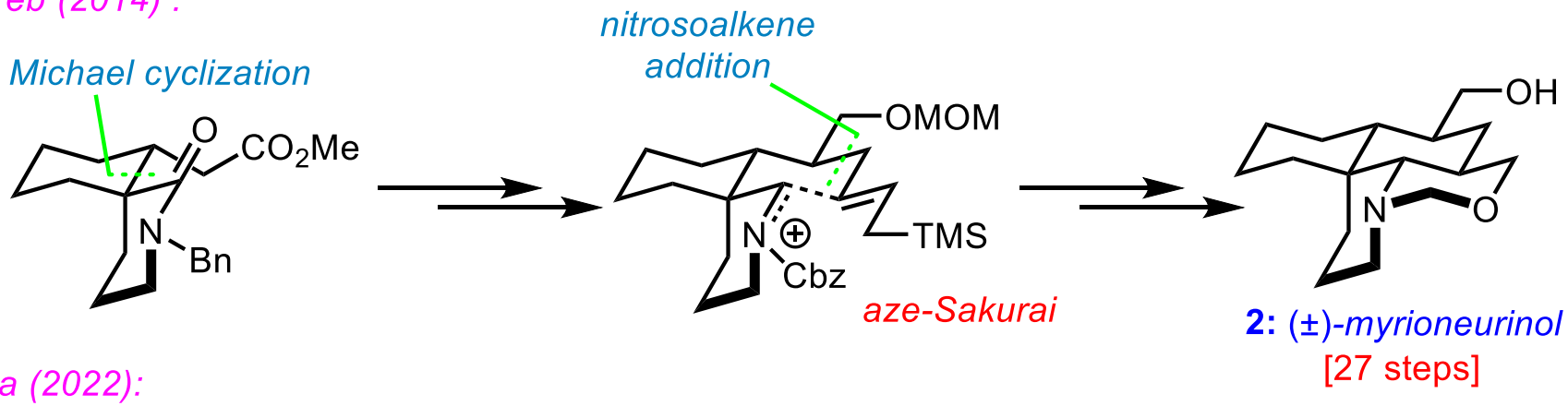

**4:** *myriberine A*




***5:*** *myrifabral A [R = H]*
***6:*** *myrifabral A [R = $CH_2NEt_3$]*

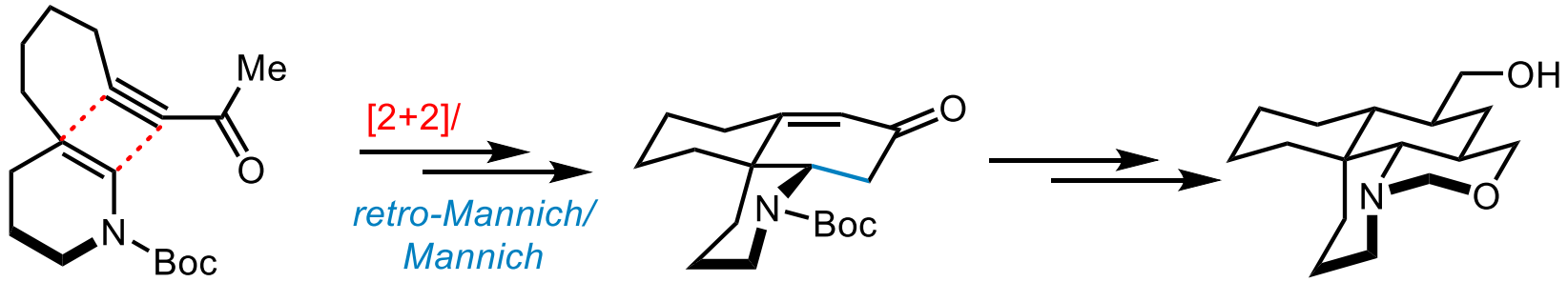
# (B) Prior racemic total syntheses of myrioneurinol

*Weinreb (2014) :*



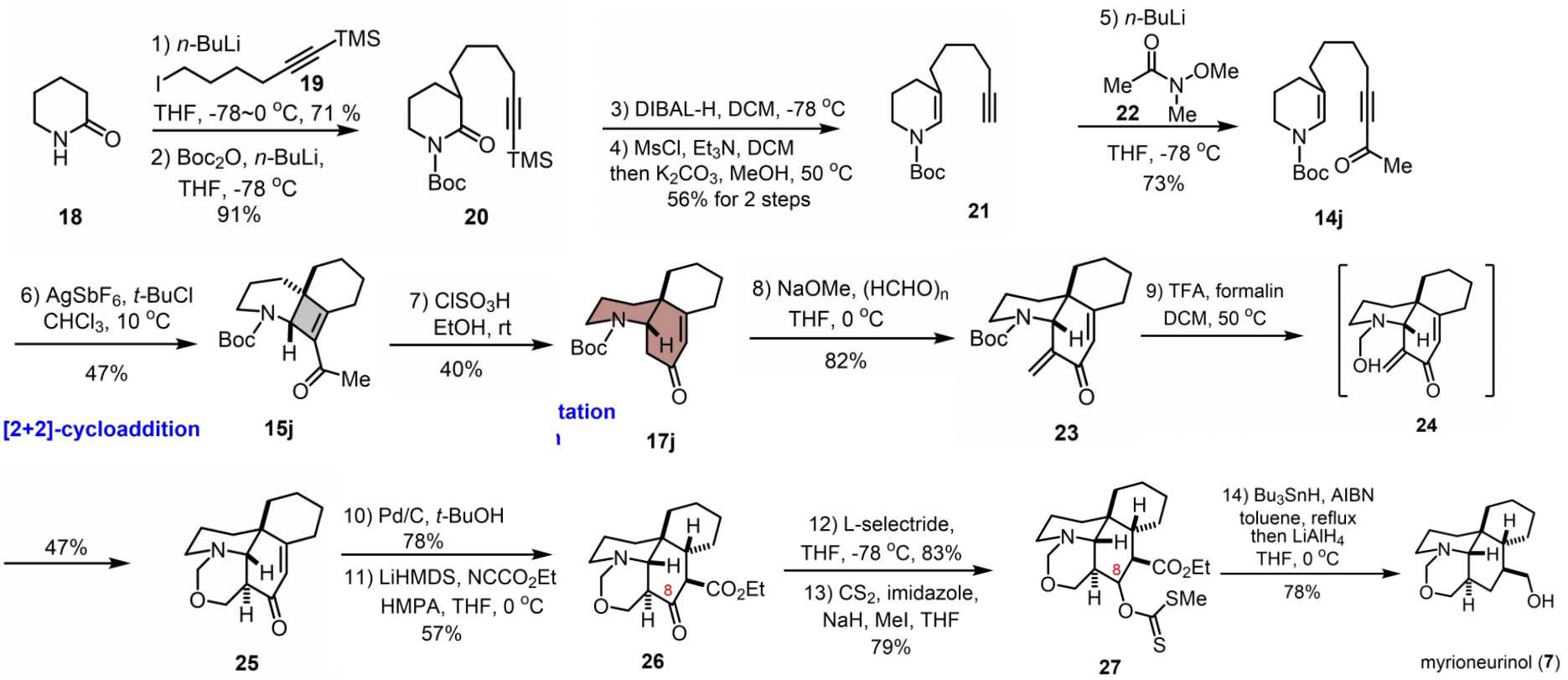

**2:** (±)-*myrioneurinol*
[27 steps]

*Ma (2022):*



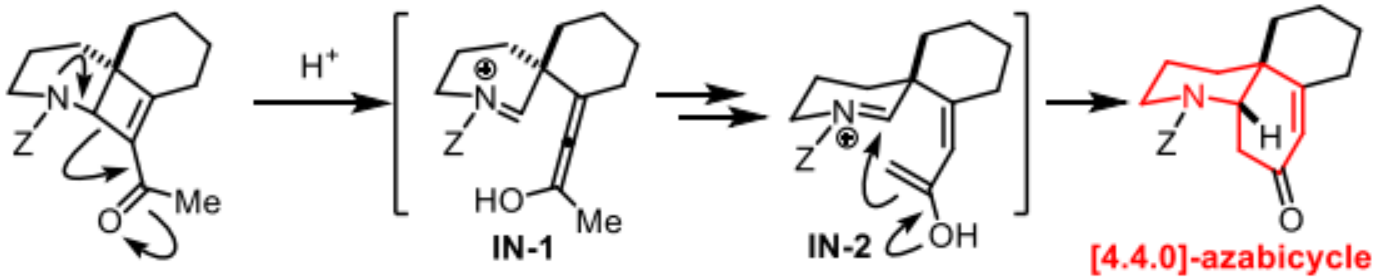

**2:** (±)-*myrioneurinol*
[14 steps]

# Ma's work

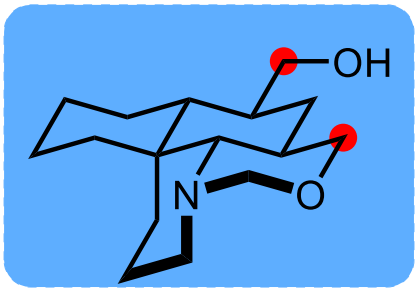



*Angew. Chem. Int. Ed.*, **2022**, *61*, e202200085.

**Proposed mechanism of retro-Mannich fragmentation/Mannich reaction**



# (C)Our symmetry-driven approach to myrioneurinol

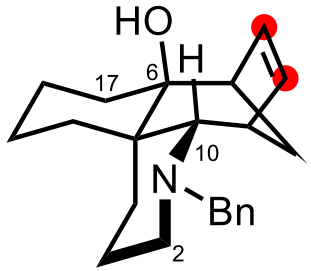



**2:** (+)-myrioneurinol

- *Antimalarial alkaloid*
  *($IC_{50}$ = 41 $\mu$M)*

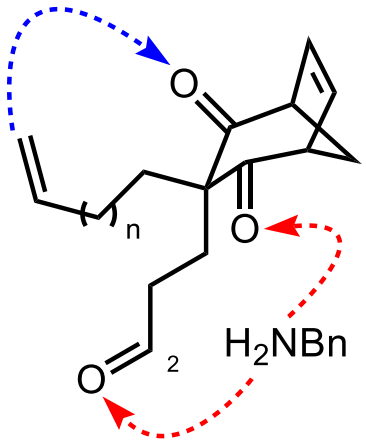
*Oxidative Cleavage/*

*Cyclization*

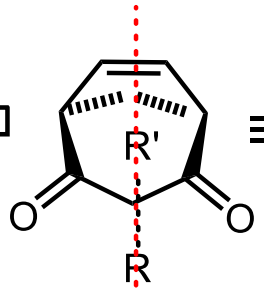



*Cyclohexane Formation*

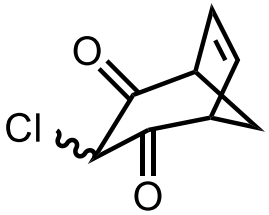
*Desymmetrizing Reductive Amination*



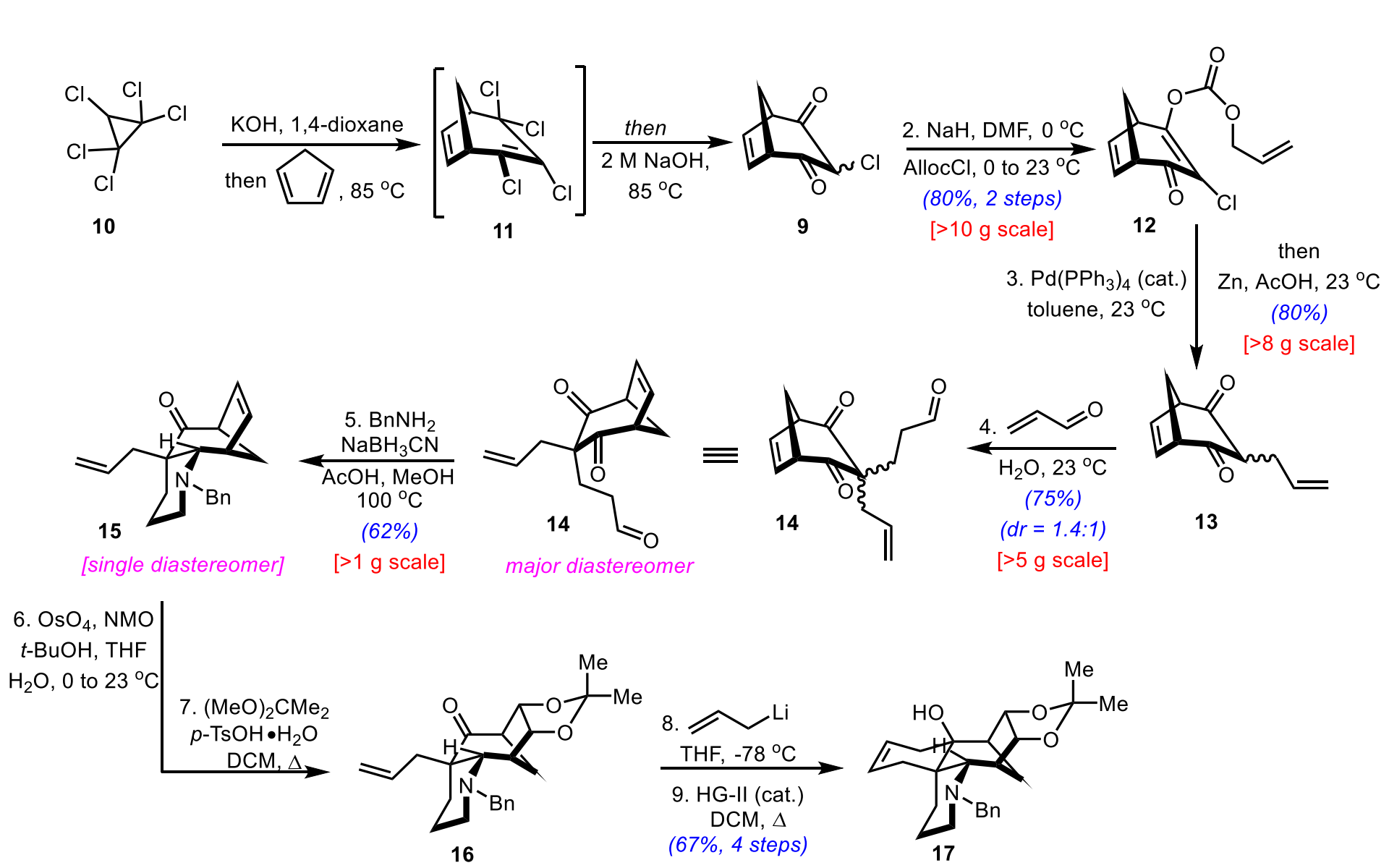

≡



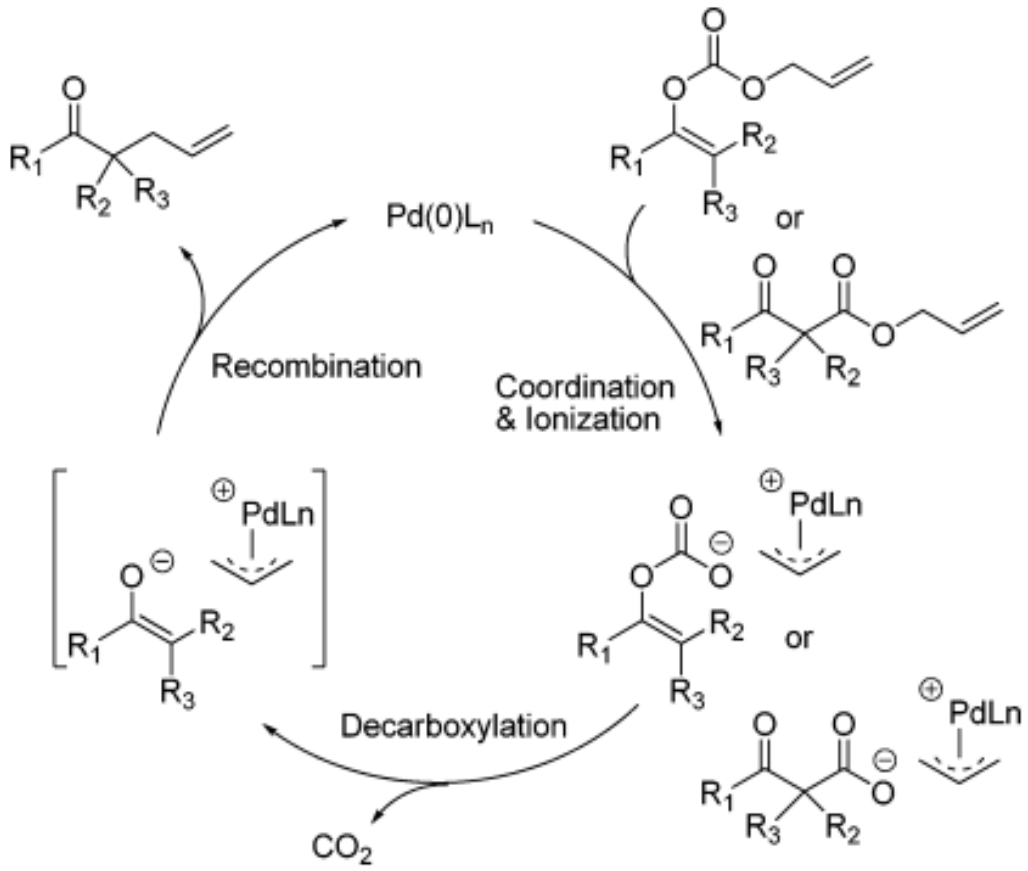

*Sequential Alkylation*




9 *[known]*

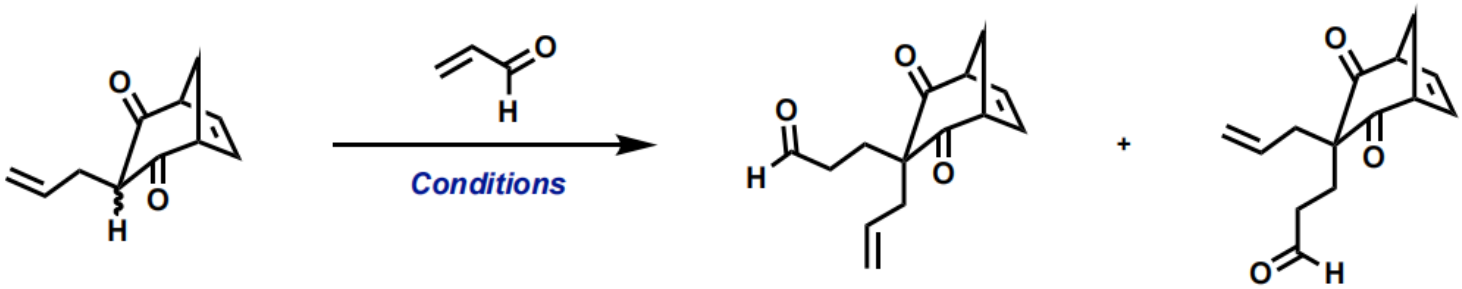


# decarboxylative Tsuji−Trost allylation




*J. Am. Chem. Soc.*, **2009**, *131*, 18343.

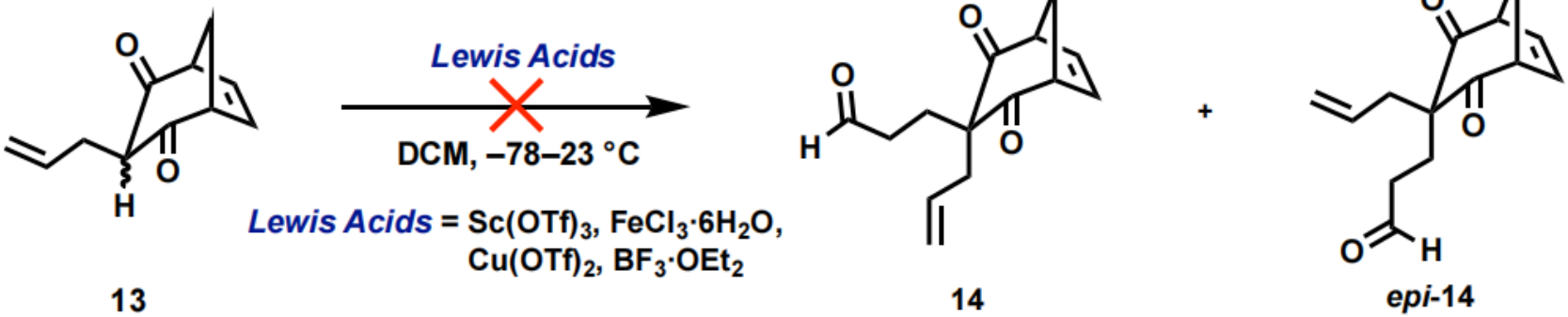
*(i) Attempts to improve diastereoselectivity in Michael addition of **13**:*

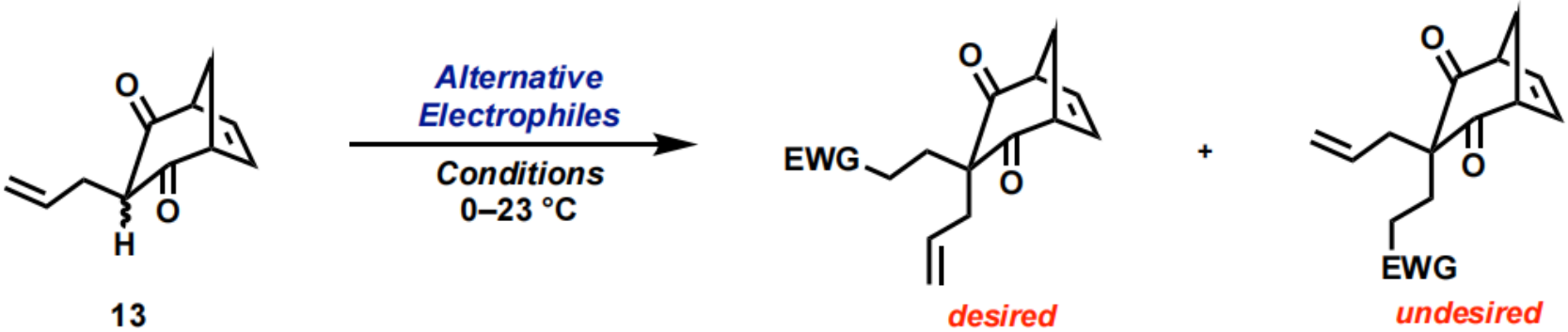


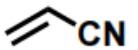
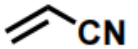
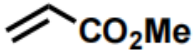
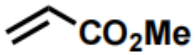

**13** **14** ***epi*-14**

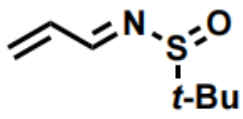
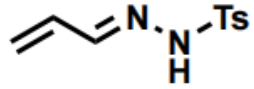
| Entry | Solvent | Base | dr (14:*epi*-14) | Entry | Solvent | Base[c] | dr (14:*epi*-14) |
|---|---|---|---|---|---|---|---|
| 1 | $H_2O$ | – | 1.4:1.0 | 12 | $H_2O$/dioxane (9:1) | – | 1.3:1.0[b] |
| 2 | DCM | – | NR[a] | 13 | $H_2O/CH_3CN$ (9:1) | – | 1.3:1.0[b] |
| 3 | THF | – | NR[a] | 14 | $H_2O/MeNO_2$ (9:1) | – | 1.4:1.0[b] |
| 4 | $CH_3CN$ | – | NR[a] | 15 | $H_2O/MeNO_2$ (1:1) | – | 1.4:1.0[b] |
| 5 | PhMe | – | NR[a] | 16[d] | *t*-BuOH:THF (1:5) | KO*t*Bu | 0.7:1.0 |
| 6 | DMF | – | 1.3:1.0 | 17[d] | THF | KHMDS | 0.8:1.0 |
| 7 | Ether | – | NR[a] | 18[d] | THF | LiHMDS | 0.8:1.0 |
| 8 | IPA | – | 1.2:1.0 | 19 | DMF | $NEt_3$ | 1.0:1.0 |
| 9 | Neat | – | NR[a] | 20 | DMF | DBU | 1.0:1.0 |
| 10 | $H_2O$/DMF (9:1) | – | 1.3:1.0 | 21 | DMF | $Cs_2CO_3$ | 1.0:1.0 |
| 11 | $H_2O$/DMF (1:1) | – | 1.1:1.0 | 22[e] | DMF | – | 0.8:1.0 |

[a]NR = No reaction; [b]Byproduct formation; [c]Typically 0.1 equiv; [d]–78 to 0 °C; [e]–50 °C

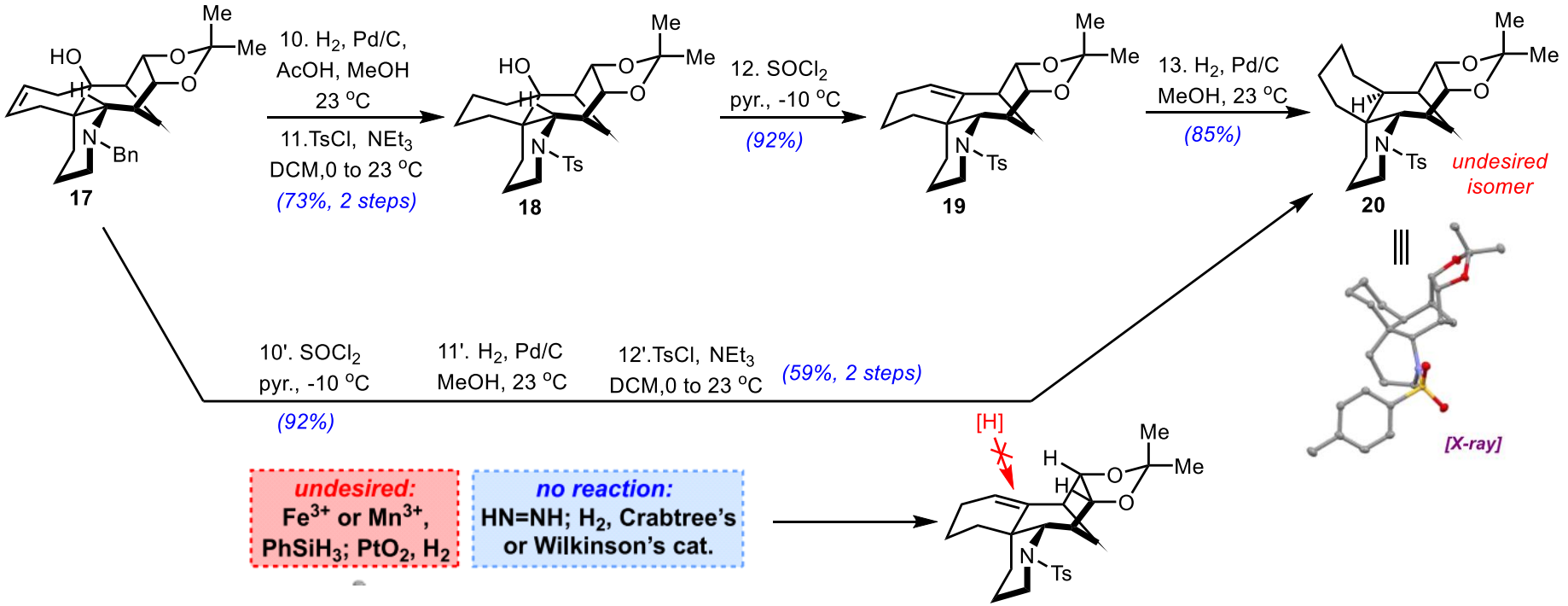


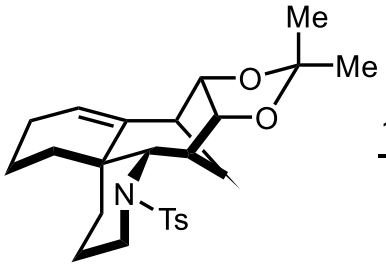




| Entry | Solvent | Electrophile | Base[c] | Result |
|---|---|---|---|---|
| 1 | $H_2O$ |  | – | NR[a] |
| 2 | THF |  | $NEt_3$ | NR[a] |
| 3 | $H_2O$ |  | – | NR[a] |
| 4 | THF |  | $NEt_3$ | NR[a] |

| Entry | Solvent | Electrophile | Base[c] | Result (des:undes) |
|---|---|---|---|---|
| 5 | DMF |  | $Cs_2CO_3$ | 1.3:1.0 |
| 6 | DMF |  | $Cs_2CO_3$ | CM[b] |

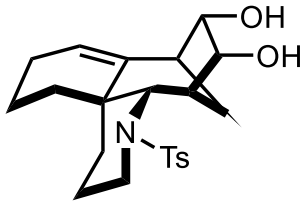
[a]NR = No reaction; [b]CM = Complex mixture; [c]Typically 0.1 equiv.


Me
HO
O
Me
O
H
N
Bn
17
10. $H_2$, Pd/C,
AcOH, MeOH
23 °C
11.TsCl, $NEt_3$
DCM,0 to 23 °C
(73%, 2 steps)
Ts
18
12. $SOCl_2$
pyr., -10 °C
(92%)
19
13. $H_2$, Pd/C
MeOH, 23 °C
(85%)
20
undesired
isomer
[X-ray]
10'. $SOCl_2$
pyr., -10 °C
(92%)
11'. $H_2$, Pd/C
MeOH, 23 °C
12'.TsCl, $NEt_3$
DCM,0 to 23 °C
(59%, 2 steps)
[H]
undesired:
$Fe^{3+}$ or $Mn^{3+}$,
$PhSiH_3$; $PtO_2$, $H_2$
no reaction:
HN=NH; $H_2$, Crabtree's
or Wilkinson's cat.



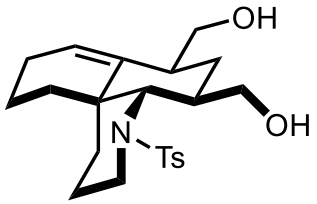

**19**

13. $CeCl_3 \bullet 7H_2O$, $(CO_2H)_2$
$H_2O$, $CH_3CN$, 70 °C



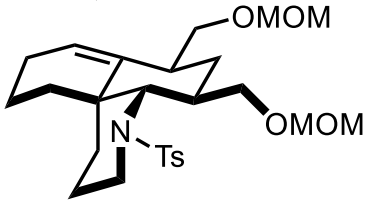

**21**

14. $PhI(OAc)_2$,
DCM, 0 °C
then $NaBH_4$
MeOH, 0 °C



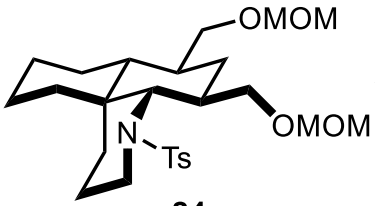

**22**

15. MOMCl, *i*-$Pr_2NEt$
DCM, 0 to 23 °C
*(86%, 2 steps)*



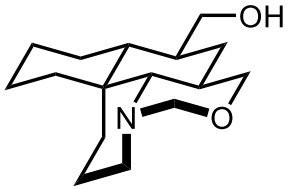

**23**

16. $PhSiH_3$, $Fe(acac)_3$
EtOH, 40 °C
*(64%, dr = 12:1)*



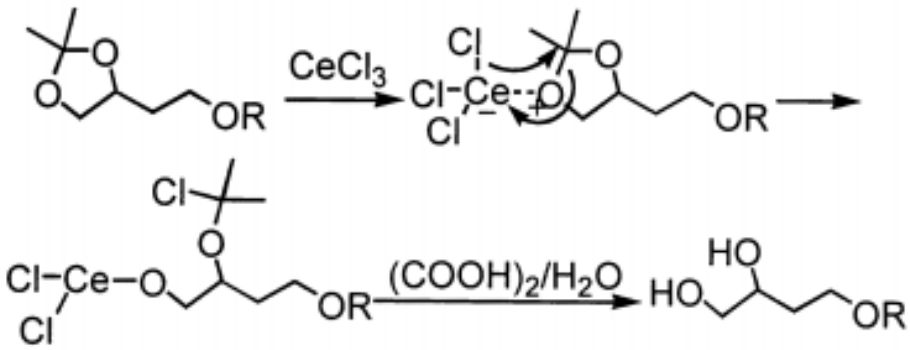

**24**

17. Li $NH_3$, $Et_2O$, -78 °C
18. 6 N HCl, THF, 50 °C
*(35%, 2 steps)*

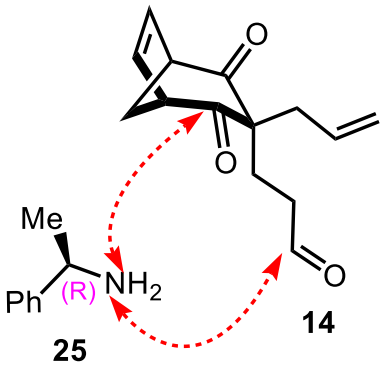



**2:** (±)-*myrioneurinol*
18 steps (~1% yield)

| *Entry* | *Conditions* | *dr* (24:epi-24) | *Yield* (%) |
|---|---|---|---|
| 1 | $H_2$, Pd/C, 23 °C | 1.1:1 | – |
| 2 | $Co(acac)_3$, $Et_3SiH$, 23 °C | 1:1 | – |
| 3 | $Fe(acac)_3$, $PhSiH_3$, 60 °C | 4:1 | 69 |
| 4 | $Fe(acac)_3$, $PhSiH_3$, 40 °C | 12:1 | 64 |




*Synlett*, **2001**, *4*, 535.



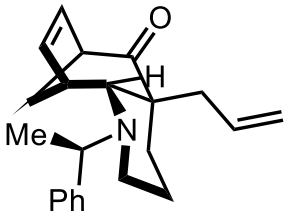

**25**

**14**

5. $NaBH_3CN$, AcOH
MeOH, 100 °C

*(30% pure isomer)*
*(crude dr = 4:1)*

*Asymmetric desymmetrization*

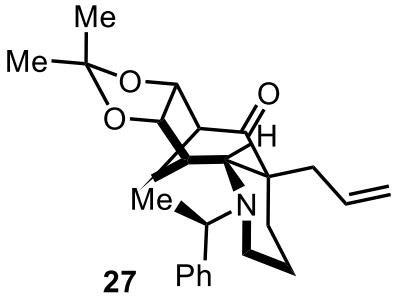



**26**

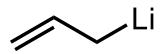
6. $OsO_4$, NMO
*t*-BuOH, THF,
$H_2O$,0 to 23 °C

7. $(MeO)_2CMe_2$
*p*-TsOH•$H_2O$
DCM, Δ

*(57%, 2 steps)*

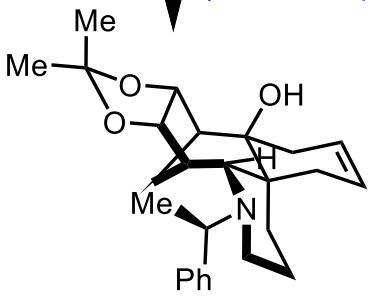



**27**

8. 


THF, -78 °C
9. HG-II (cat.)
DCM, Δ

*(99%, 2 steps)*

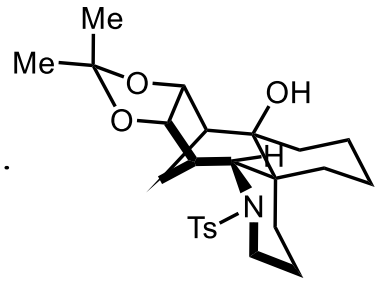



**28**

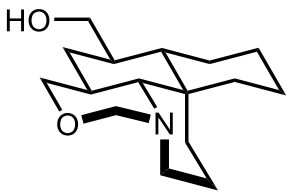
10. $H_2$, Pd/C,
AcOH, MeOH
23 °C

11.TsCl, $NEt_3$
DCM,0 to 23 °C

*(64%, 2 steps)*




**(-)-18**
(>99% ee)




**2:** (-)-*myrioneurinol*

First asymmetric approach to 2