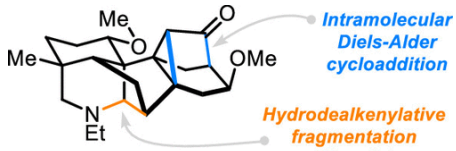


Vilmoraconitine

Total Synthesis of Vilmoraconitine: Jiujian Ji, Jiajun Chen, Sixun Qin, Wanye Li, Jun Zhao, Guozhao Li, Hao Song, Xiao-Yu Liu*, and Yong Qin* **Cite this:** J. Am. Chem. Soc. 2023, 145, 7, 3903–3908

Scheme 2. Total Synthesis of Vilmoraconitine (3)[a]

key reations

1:1dr

a) *n*-BuLi, 91%

b) $Ph(OAc)_2$, MeOH
c) mesitylene, 180 °C
62% overall yield of **11a** based on recycling of **11b**

NOE

d) NaH, MeI, 85%
e) TBAF, 93%
f) IBX, 90%

4:1dr

1) DMP
2) $NaBH(OMe)_3$
11a (1-α-OH, 40%)
11b (1-β-OH, 41%)

8 (R = TBS) — decagram scale

9

10 (R = TBS) — coupling

12

OD/DA cascade

OD:oxidative dearomatization

endo-selective: retro DA/IMDA cascade

g) *t*-BuOK, MeI, 89%

13

h) $EtNH_2$•HCl, $NaBH_3CN$; NaOH, $(Boc)_2O$, 90%

14

i) $LiAlH_4$
j) *p*-TsOH
k) SmI_2
62% (3 steps)

7

unprotected ketone compatible

l) O_3; $FeSO_4$•$7H_2O$
4-methoxybenzenethiol
77% [1.5 gram scale]

6

hydrodealkenylative fragmentation

m) TFA, 90%

Mannich cyclization

simultaneous formation of B/E/F rings

7 ->5 in one pot: low yield

5

n) LDA, $NCCO_2Me$
o) Cs_2CO_3, MVK
62% (2 steps)

15

p) KHMDS, 85%

Robinson annulation

16

q) $TiCl_4$, MeOH, 80% (93% brsm)
r) $LiAlH_4$
s) AZADO, CuCl, bpy, DMAP
88% (2 steps)

17

t) $(EtO)_2P(O)CH_2CN$, LDA, 93%
u) TMSOTf, 92%

18

v) I_2, $NaHCO_3$, 80%

20

w) TMP, TBSOTf

21

mesitylene
150 °C; *p*-TsOH
75%

22 + 20(12%)
"unusual regioselectivity"

IMDA

x) $NaBH_4$
y) *t*-BuOK, MeI
67% (2 steps)

23

oxidative decyanation

z) LDA, O_2; $SnCl_2$
aq. Na_2CO_3
80%

24

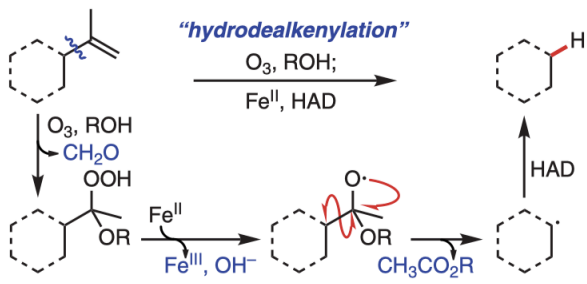
aa) $LiAlH_4$
ab) AZADO, CuCl
bpy, DMAP
68% (2 steps)

one step selective reduction unsuccessful

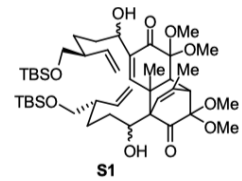
vilmoraconitine (3)

Enol silane formation; IMDA

19

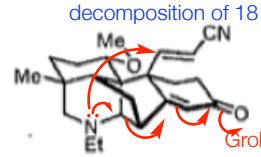


retro DA/IMDA cascade intermediate



S1

decomposition of 18



protection as nitrogen-boran complex unsuccessful

Grob-type or Michael