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Total Synthesis of (+)-Kalmanol

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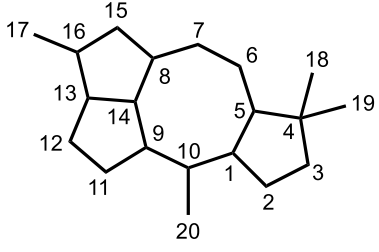
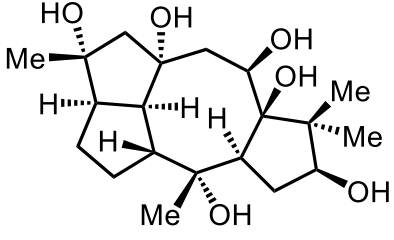


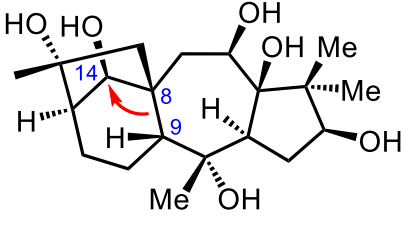
kalmane skeleton

- Unique 5/5/8/5 tetracyclic
- 9-11 contiguous stereocenters
- Highly oxidative decoration
- Analgesic effects and cardiotoxic properties



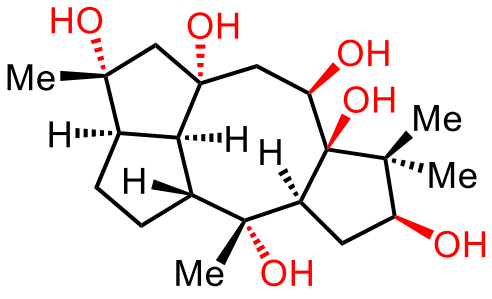
kalmanol (**1**)

1,2-migration
biosynthetic relation



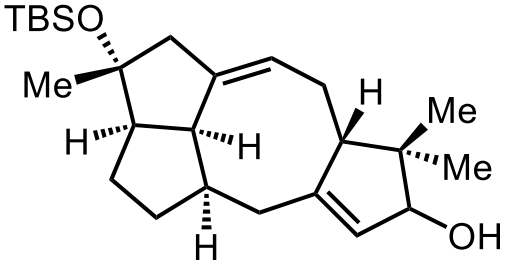
grayanotoxin III (**2**)

Retrosynthetic Analysis



kalmanol (**1**)

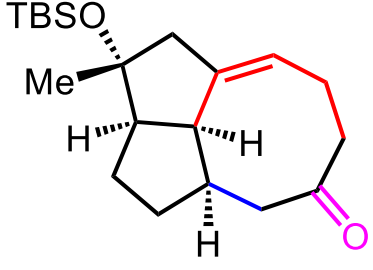
FGT/[O]



3

alkylation

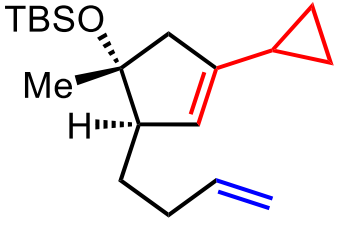
aldol



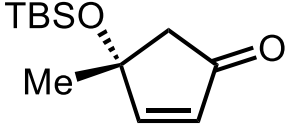
4

CO

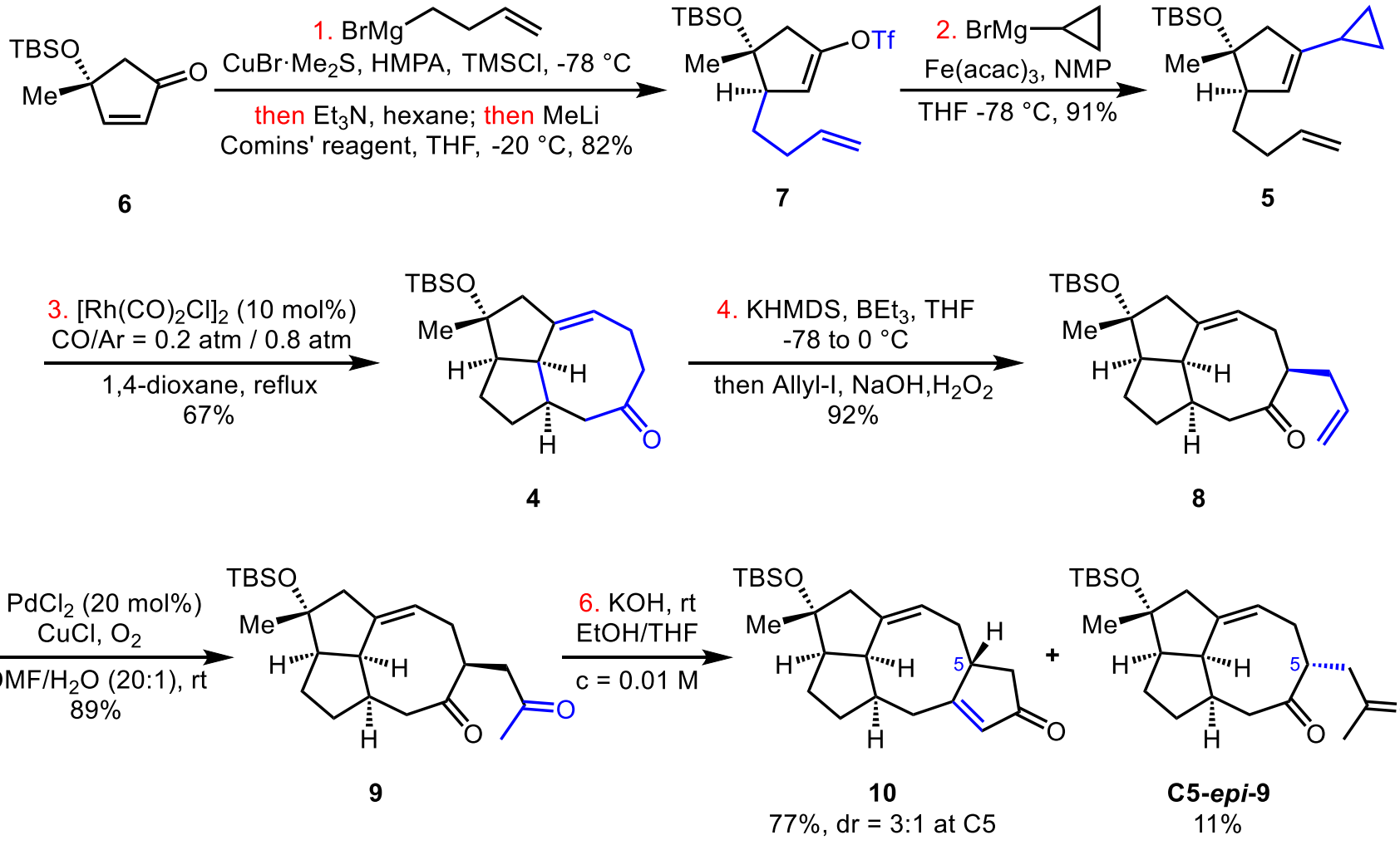
Rh-Cat.
[5+2+1]

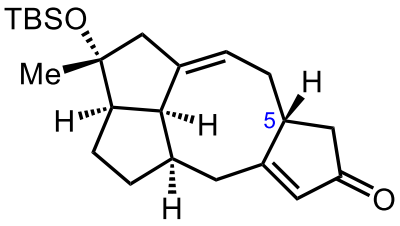


5



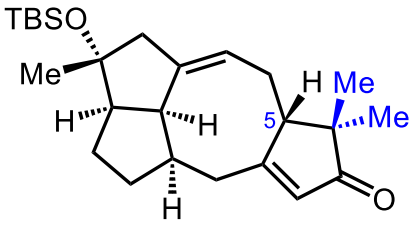
6


TBSO
Me
O
6
1. BrMg
CuBr·Me2S, HMPA, TMSCl, -78 °C
then Et3N, hexane; then MeLi
Comins' reagent, THF, -20 °C, 82%
TBSO
Me
H
OTf
7
2. BrMg
Fe(acac)3, NMP
THF -78 °C, 91%
TBSO
Me
H
5
3. [Rh(CO)2Cl]2 (10 mol%)
CO/Ar = 0.2 atm / 0.8 atm
1,4-dioxane, reflux
67%
TBSO
Me
H
H
H
O
4
4. KHMDS, BEt3, THF
-78 to 0 °C
then Allyl-I, NaOH,H2O2
92%
TBSO
Me
H
H
H
O
8
5. PdCl2 (20 mol%)
CuCl, O2
DMF/H2O (20:1), rt
89%
TBSO
Me
H
H
H
O
O
9
6. KOH, rt
EtOH/THF
c = 0.01 M
TBSO
Me
H
H
H
5
O
10
77%, dr = 3:1 at C5
+
TBSO
Me
H
H
H
5
O
O
C5-epi-9
11%



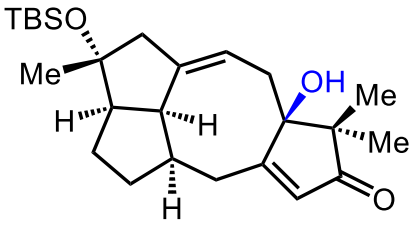
10 (dr = 3:1 at C5)

7. NaH, MeI
DME, 60 °C
92%



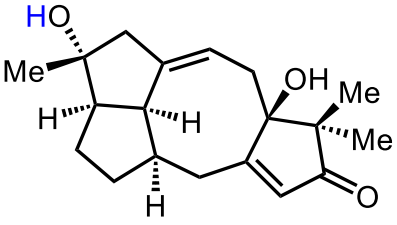
3 (dr = 3:1 at C5)

8. DBU, $P(OEt)_3$, O_2
MW, DMSO, 50 °C
31% (25% SM)



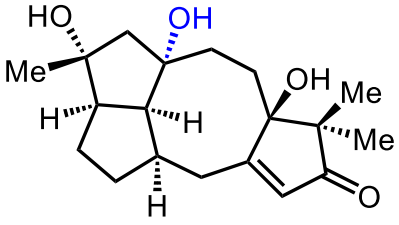
11

9. H_2SO_4 (2 M)
1,4-dioxane, rt
96%



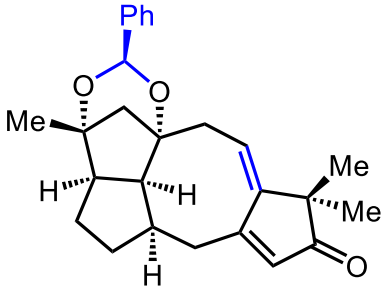
12

10. $Fe(acac)_3$, $NaHCO_3$
p-NsOMe, $PhSiH_3$
MeOH, 0 °C to rt
63%



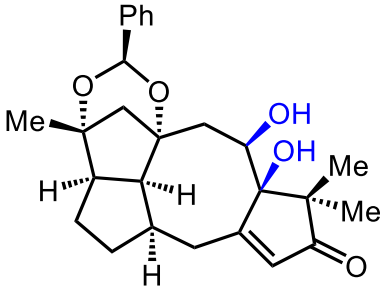
13

11. $PhCH(OMe)_2$
CSA, DCM
then Martin Sulfurane
95%



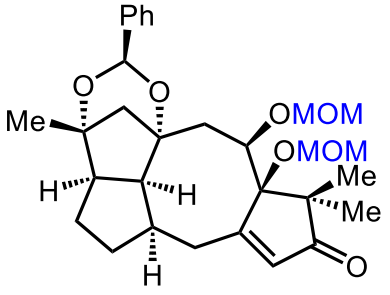
14

12. K_2OsO_4, NMO, critic acid
t-BuOH/H_2O (1:1), rt
then Na_2SO_3 (aq.), 40 °C
89%



S-1

13. MOMBr, DIPEA
TBAI, 75 °C
toluene/DCM (10:1)
95%



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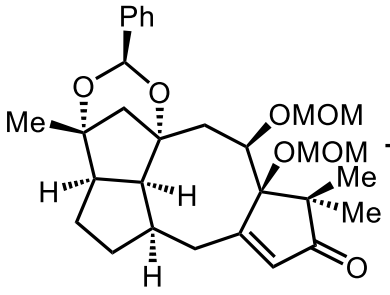
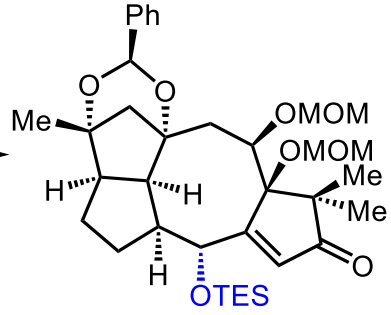


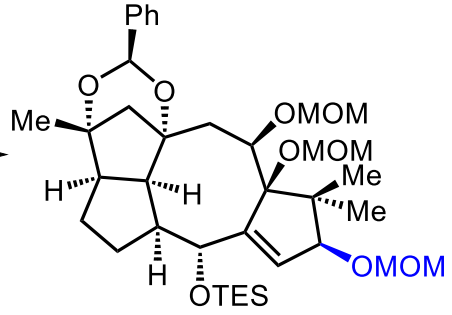
15

14. *t*-BuOK, $P(OEt)_3$
O_2, DMSO, rt
then TESCl
imidazole, 72%



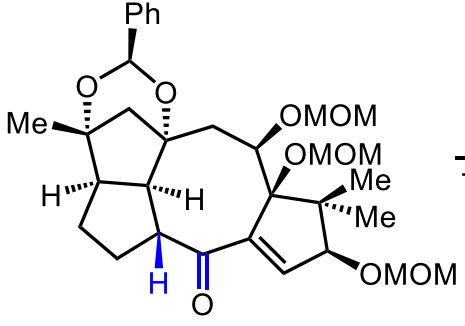
16

15. DIBAL-H, THF, -78 °C
16. MOMBr, DIPEA
toluene/DCM (10:1), rt
95% for 2 steps



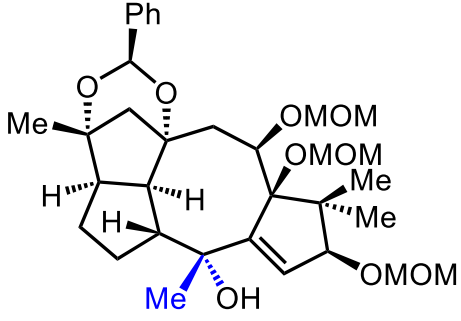
17

17. TBAF, THF, 0 °C to rt
18. DMP, DCM, then DBU
81% for 2 steps



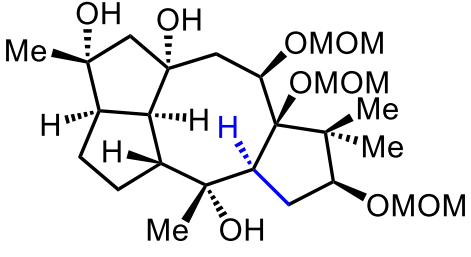
18

19. $MeCeCl_2$
THF, 0 °C, 99%



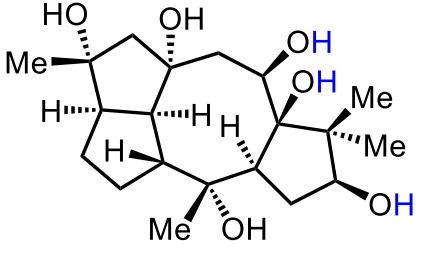
19

20. $Pd(OH)_2/C$
H_2 (4 atm), MeOH
99%



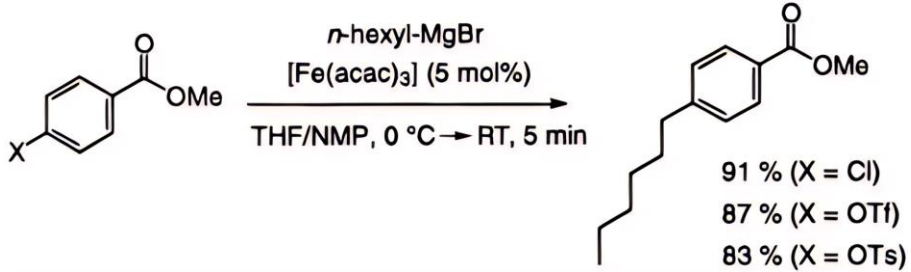
20

21. RuO_4, rt
$CCl_4/MeCN/H_2O$ (2:2:3)
22. KOH, MeOH, 65 °C
75% for 2 steps



kalmanol (**1**)

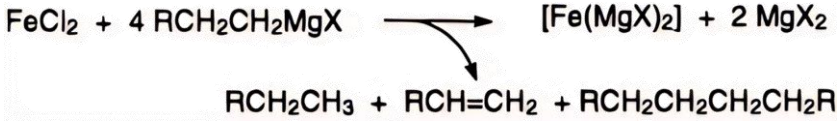
Step 2 Iron-Catalyzed Cross-Coupling Reactions

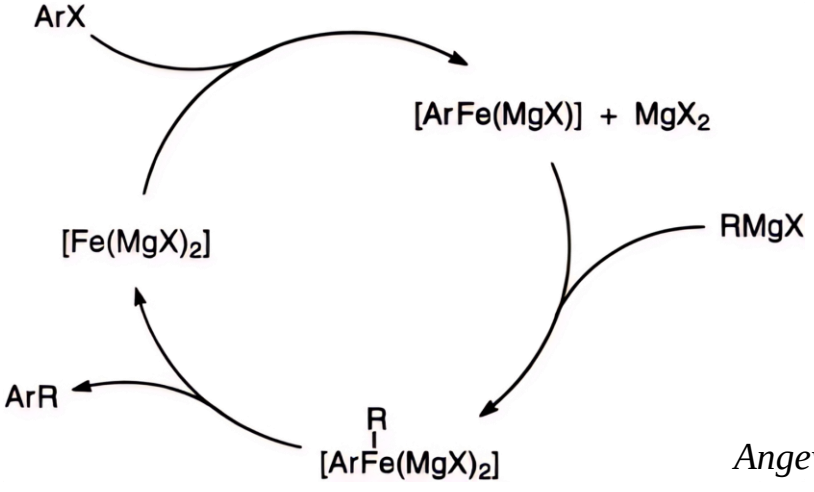


- 使用廉价易得的铁盐代替贵金属催化剂，反应速度快，不需要配体
- 更适合于氯代和磺酸酯底物，溴代物和碘代物易被直接还原

Mechanism:

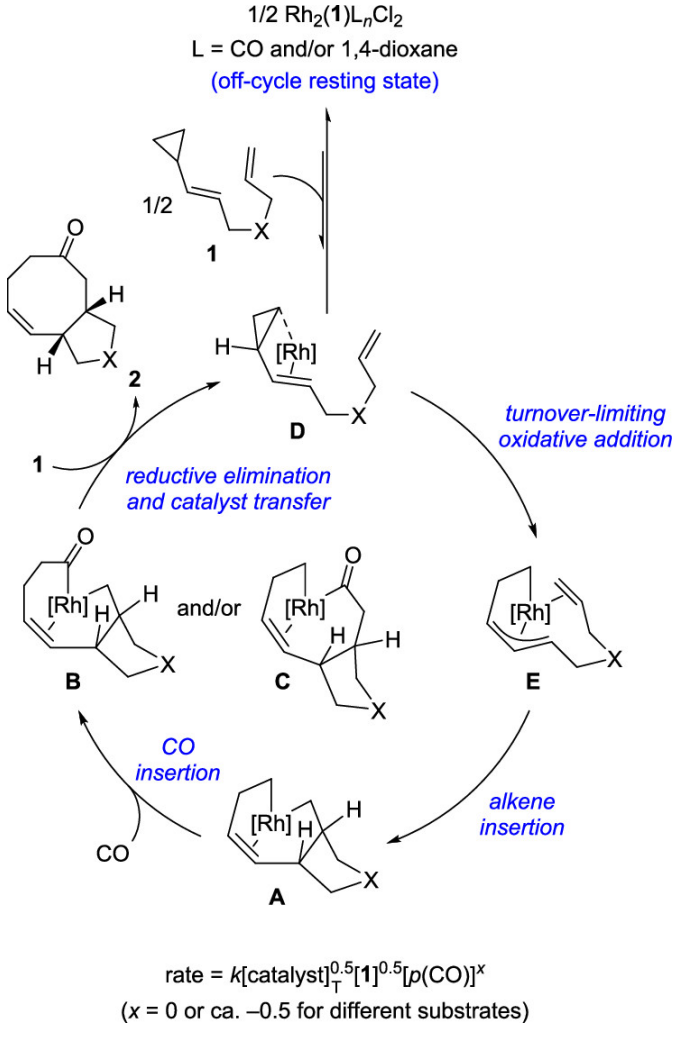
- 主要催化物种为负价态铁化合物

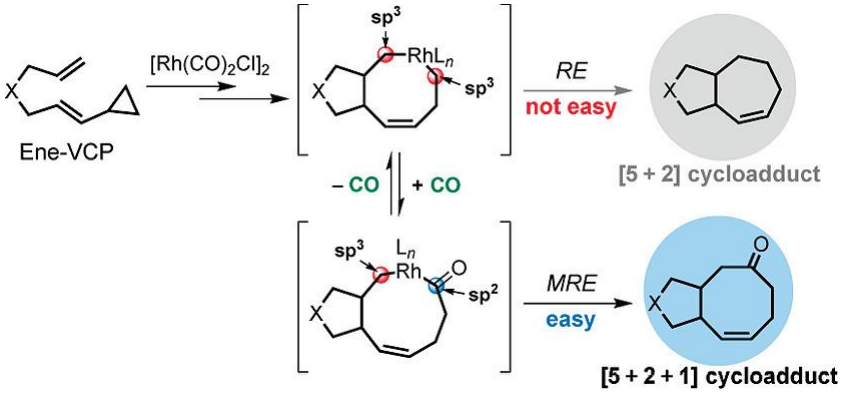




Angew. Chem. Int. Ed., **2002**, *41*, 609.

Step 3 Rhodium-Catalyzed [5+2+1] Cycloaddition

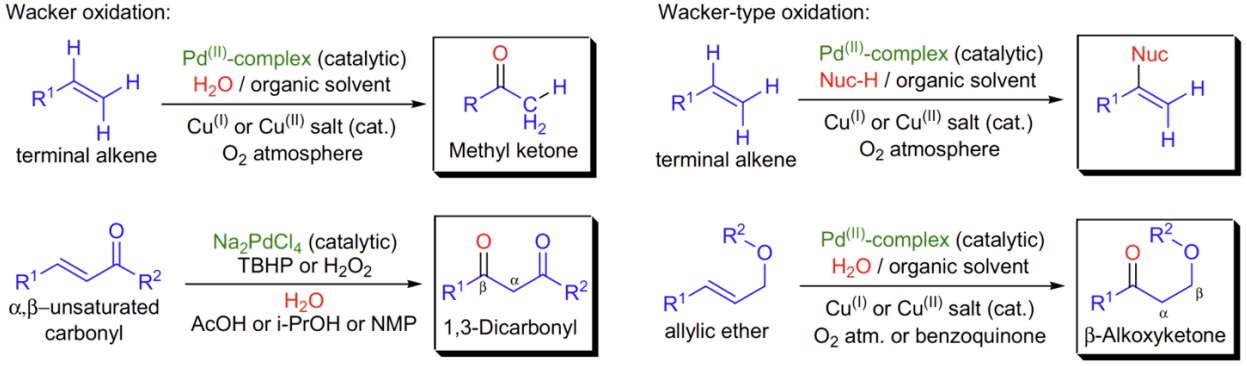




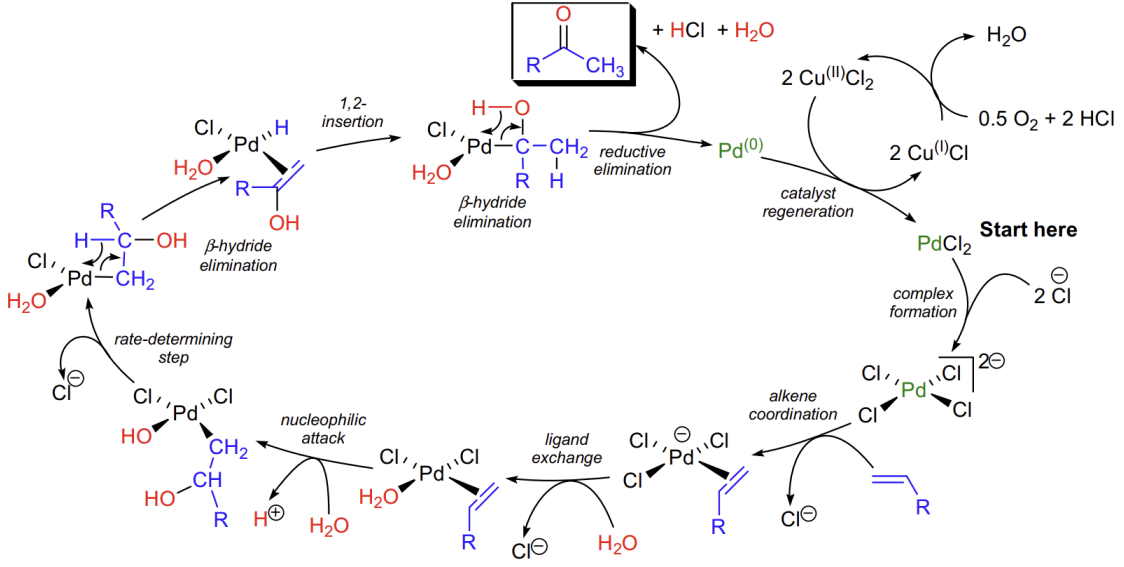
- 计算设计的多组分环化反应
- 也能得到反式并环产物
- 相比直接还原消除得到**[5+2]**产物，插羰后消除具有能量优势
- 决速步为**C-C**活化（环丙烷开环）过程
- 对**CO**表观反应级数为**-0.5**，可能原因为催化剂二聚体解聚时释放**CO**，从而**CO**分压升高不利于反应

J. Am. Chem. Soc., **2007**, *129*, 10060.
J. Am. Chem. Soc., **2022**, *144*, 2624.

Step 5 Wacker Oxidation

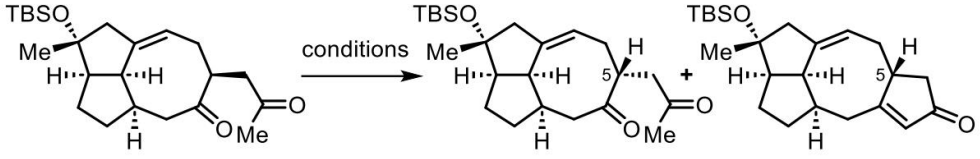


Mechanism:



Step 6 Aldol Condensation Cyclization of Diketone 9

Section 1.1 Attempts to aldol/elimination reaction and control experiments.



9 **C5-*epi*-9** **10**

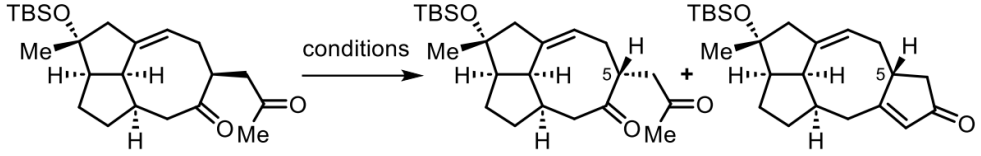
entry	conditions	Product	yield (%)[a]	dr[b]
1	NaHMDS, THF, −78 °C to rt	**10**	35	-[c]
2	*t*-AmOH, NaH, toluene/*t*-AmOH = 5:1, 60 °C	**10**	15	2:1
3[d]	LiTMP, HMPA, THF, −78 °C	-	-	-
4[e]	Zn(TMP)Cl·LiCl, THF, 0 °C to rt	-	-	-
5	MeONa, MeOH, 0 °C to rt	**C5-*epi*-9**	63	-
6	Pyrrolidine, AcOH, MTBE, 60 °C	**C5-*epi*-9**	43	-
7[d]	PTSA, toluene, 60 °C	-	-	-
8	MeOLi, *i*-PrOH, 0 °C to rt	**C5-*epi*-9**	20	-
9	NaOH, *i*-PrOH, rt	**10**	15	2.3:1
10[e]	H_3PO_4, toluene, reflux	-	-	-
11[d]	*n*-Bu_4NOH, THF, rt	-	-	-
12	NaH, toluene, 80 °C	**10**	65	1:5
13[d]	NaH, DMF, rt	-	-	-
14	NaH, heptane, 80 °C	**10**	45	1:6
15	**KOH, EtOH/THF, 0 °C to rt**	**10**	**77**	**3:1**

[a]Isolated yield. [b]Ratio of dr was determined by ^{1}H NMR of the pure isolated product.

[c]Single isomer. [d]decomposed. [e]No reaction.

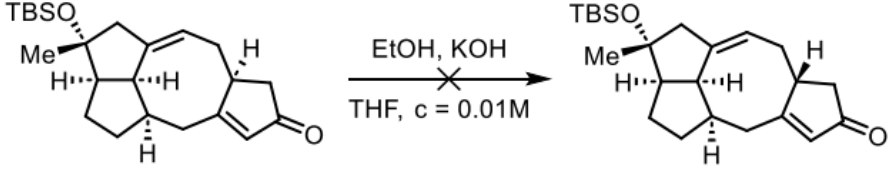
Step 6 Aldol Condensation Cyclization of Diketone 9

Section 1.1 Attempts to aldol/elimination reaction and control experiments.



9 **C5-*epi*-9** **10**

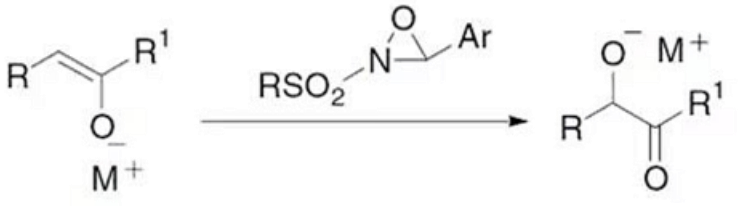
entry	conditions	Product	yield (%)[a]	dr[b]
15	**KOH, EtOH/THF, 0 °C to rt**	**10**	**77**	**3:1**



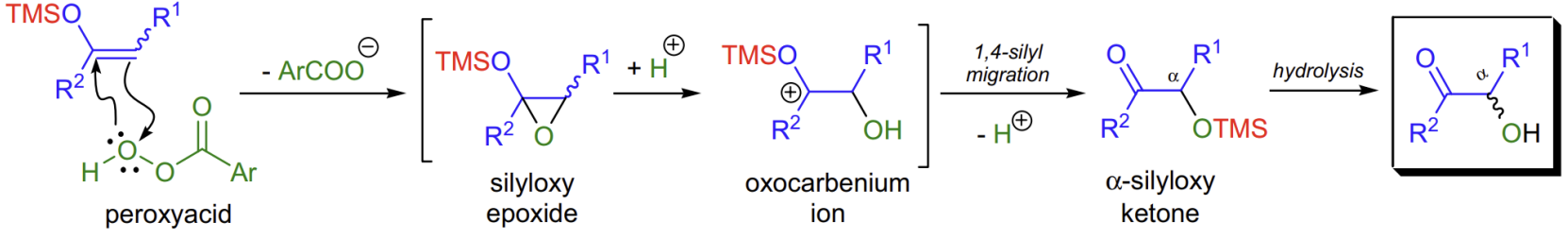
C5-*epi*-10 (single isomer) **10**

Step 8 Convert Carbonyl Compounds to Acyloins

- **Davis Oxaziridine**
  - 高活性，高选择性
  - 可能发生Mannich副反应
  - Davis试剂还原生成的胺有时难以除去

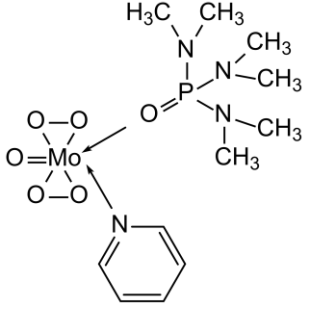


- **Rubottom Oxidation**
  - 室温或低于室温的温和条件
  - 部分烯醇硅醚易水解影响反应

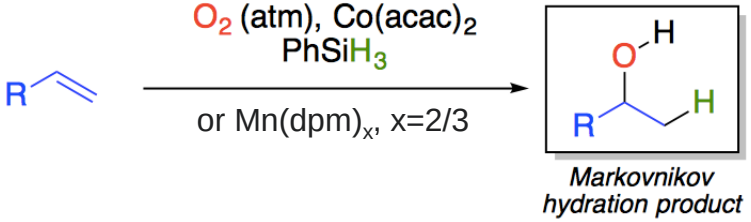


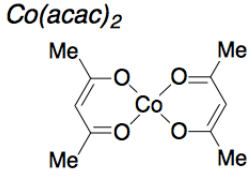
- **O_2/P(OMe)$_3$**
  - 强碱性、低温反应
  - 经历过氧化物中间体

- 过氧化钼 **MoOPH (MoO_5-Pyr-HMPA)**
  - 强碱性、低温反应
  - 优先从小位阻一侧进攻

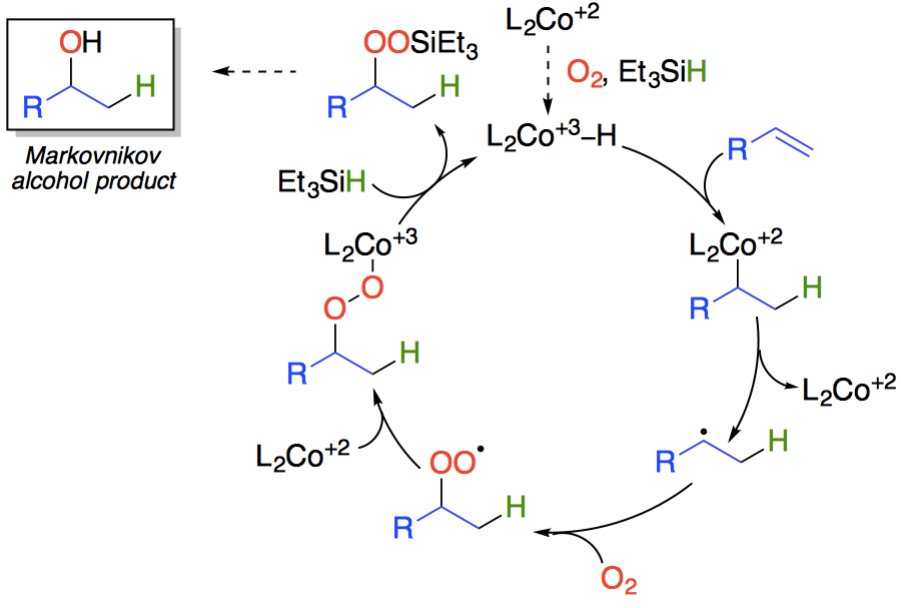


Step 10 Mukaiyama Hydration



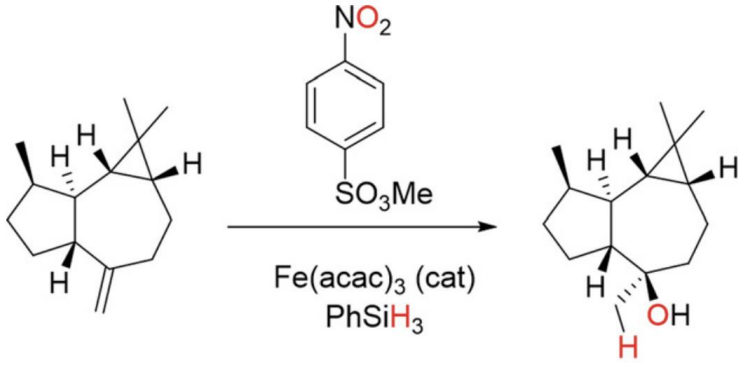


Mechanism:

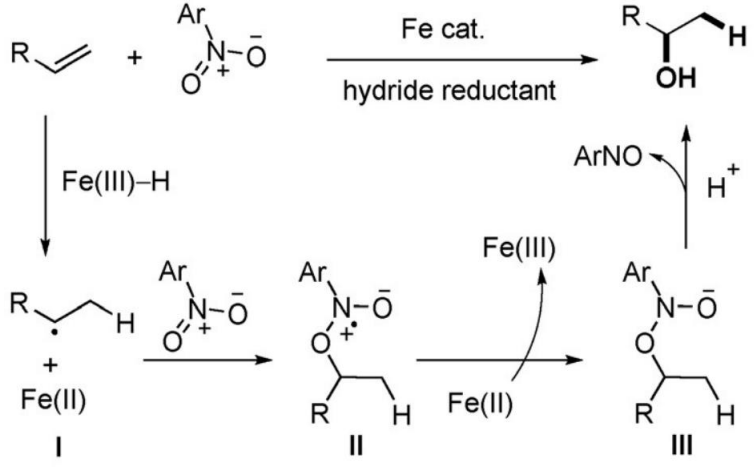


Org. Lett., **2002**, *4*, 3595.

Step 10 Mukaiyama Hydration Using *p*-NsOMe as Oxidant



Mechanism:



Advantages:

- 不需要氧气氛围，条件相对温和
- 不需要气-液两相反应，速率加快
- 更易控制非对映选择性

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