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Communication

Asymmetric Total Synthesis of Clionastatins A and B

Wei Ju,‡ Xudong Wang,‡ Hailong Tian, and Jinghan Gui*

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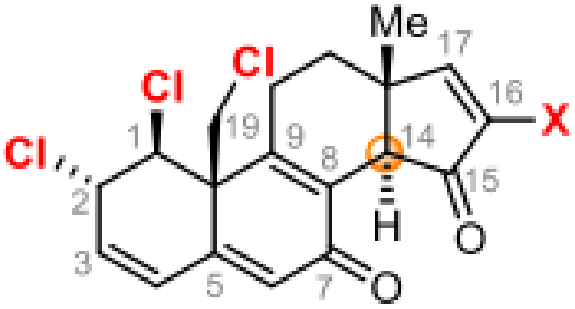
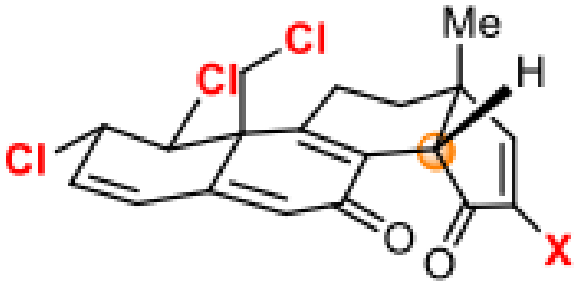


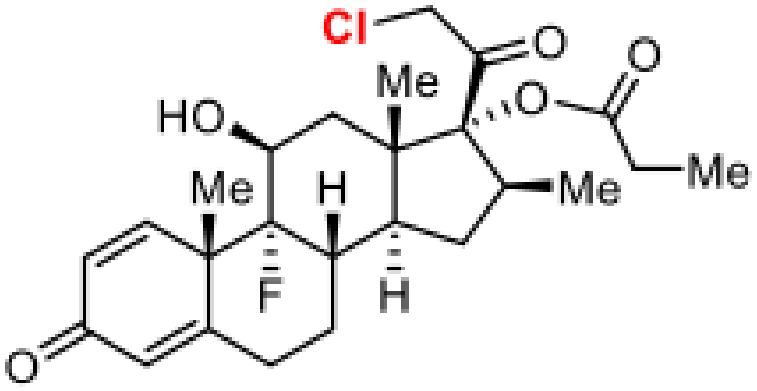
X = H, clionastatin A (**1a**)
X = Cl, clionastatin B (**2a**)
(originally proposed structures)



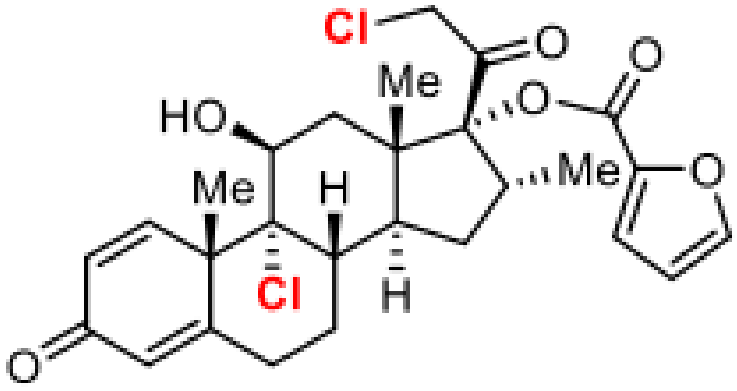
X = H, clionastatin A (**1**)
X = Cl, clionastatin B (**2**)
(revised structures)

- first polyhalogenated steroids in nature;
- highly unsaturated androstane framework;
- C1, C2-pseudoequatorial dichlorides;
- no total synthesis reported.

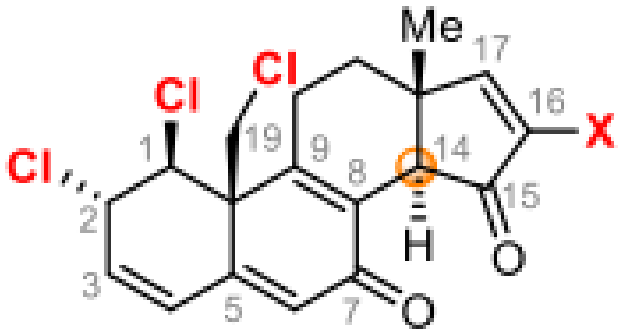
chlorinated steroid drugs



Temovate (clobetasol propionate)



Nasonex (mometasone furoate)



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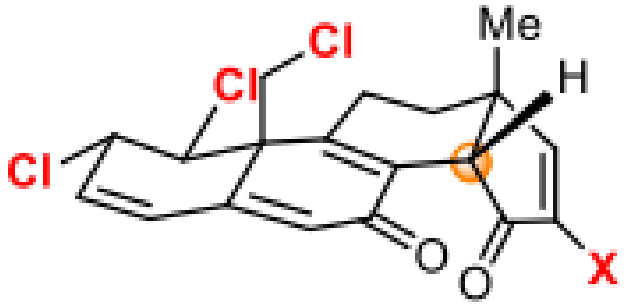
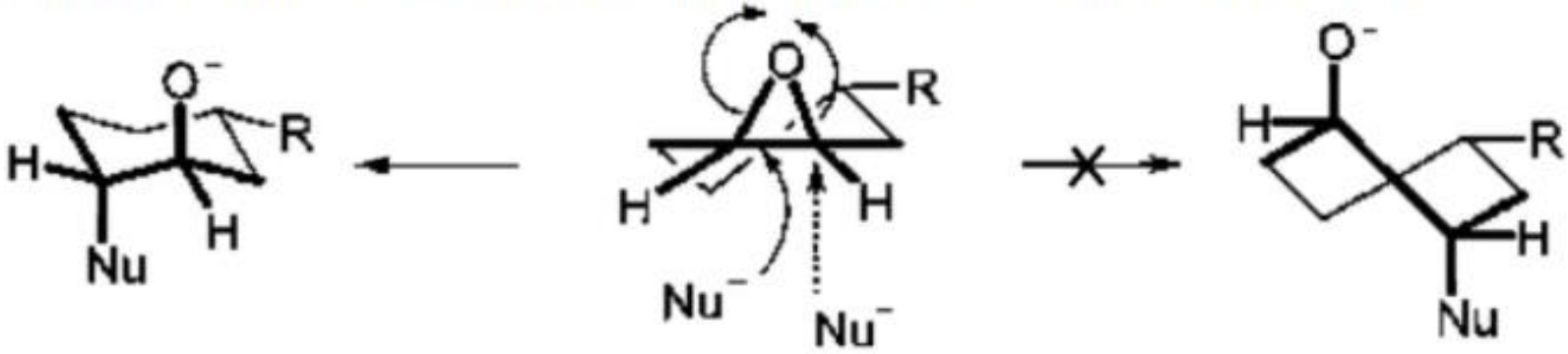


X = H, clionastatin A (**1**)
X = Cl, clionastatin B (**2**)
(revised structures)

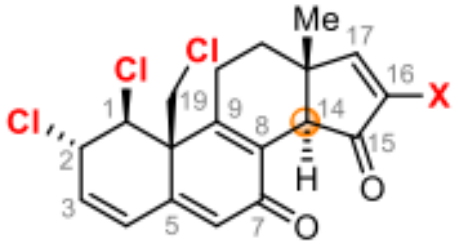
Furst-Plattner规则

有机合成 2020-10-08

环氧环己烷经亲核试剂可区域选择性的开环得到双直立键产物，这一现象源于开环反应的的半椅式构象过渡态倾向于得到环己烷椅式构象产物而非扭型构象产物。



竖键进攻



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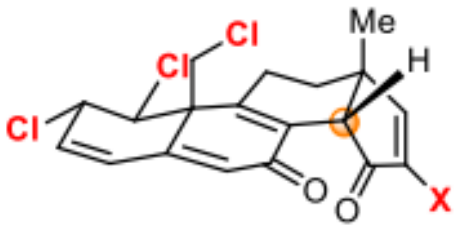
(originally proposed structures)



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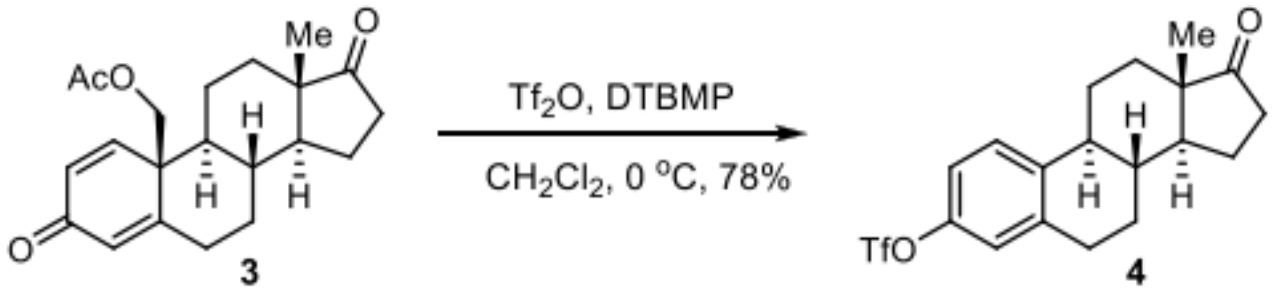
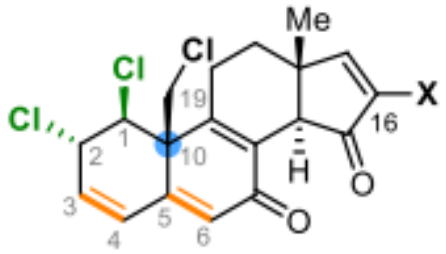
X = Cl, clionastatin B (**2**)
(revised structures)

- first polyhalogenated steroids in nature;
- highly unsaturated androstane framework;
- C1, C2-pseudoequatorial dichlorides;
- no total synthesis reported.

A. Facile aromatization of the C19-hydroxyl dienone compound



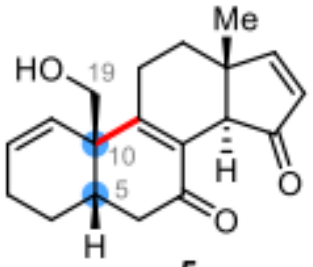
B. Retrosynthetic analysis of clionastatins A and B



X = H, clionastatin A (**1a**)
X = Cl, clionastatin B (**2a**)

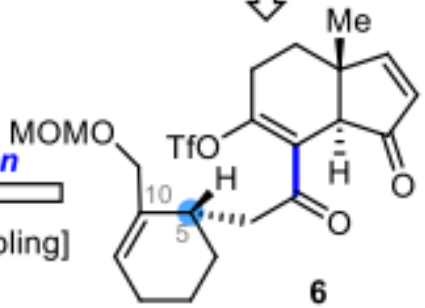
[late-stage desaturation]

[olefin dichlorination]



5

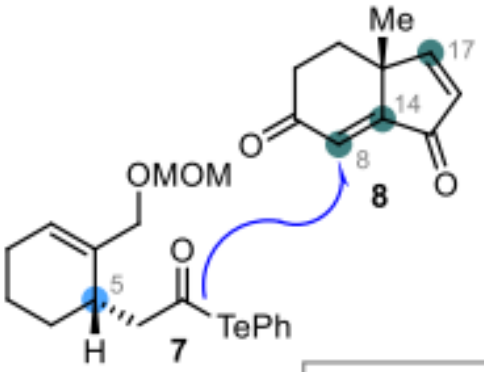
intramolecular Heck reaction



6

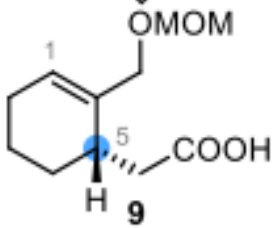
regioselective acyl radical conjugate addition

[radical fragment coupling]



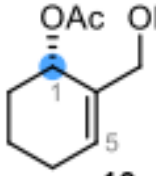
8 **7**

- possible reaction sites of **8** for radical addition
- traceless stereochemical relay: **10**→**9**→→**6**→**5**→**1a** or **2a**



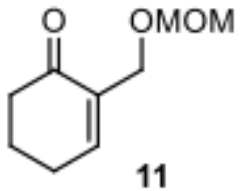
9

Ireland-Claisen rearrangement

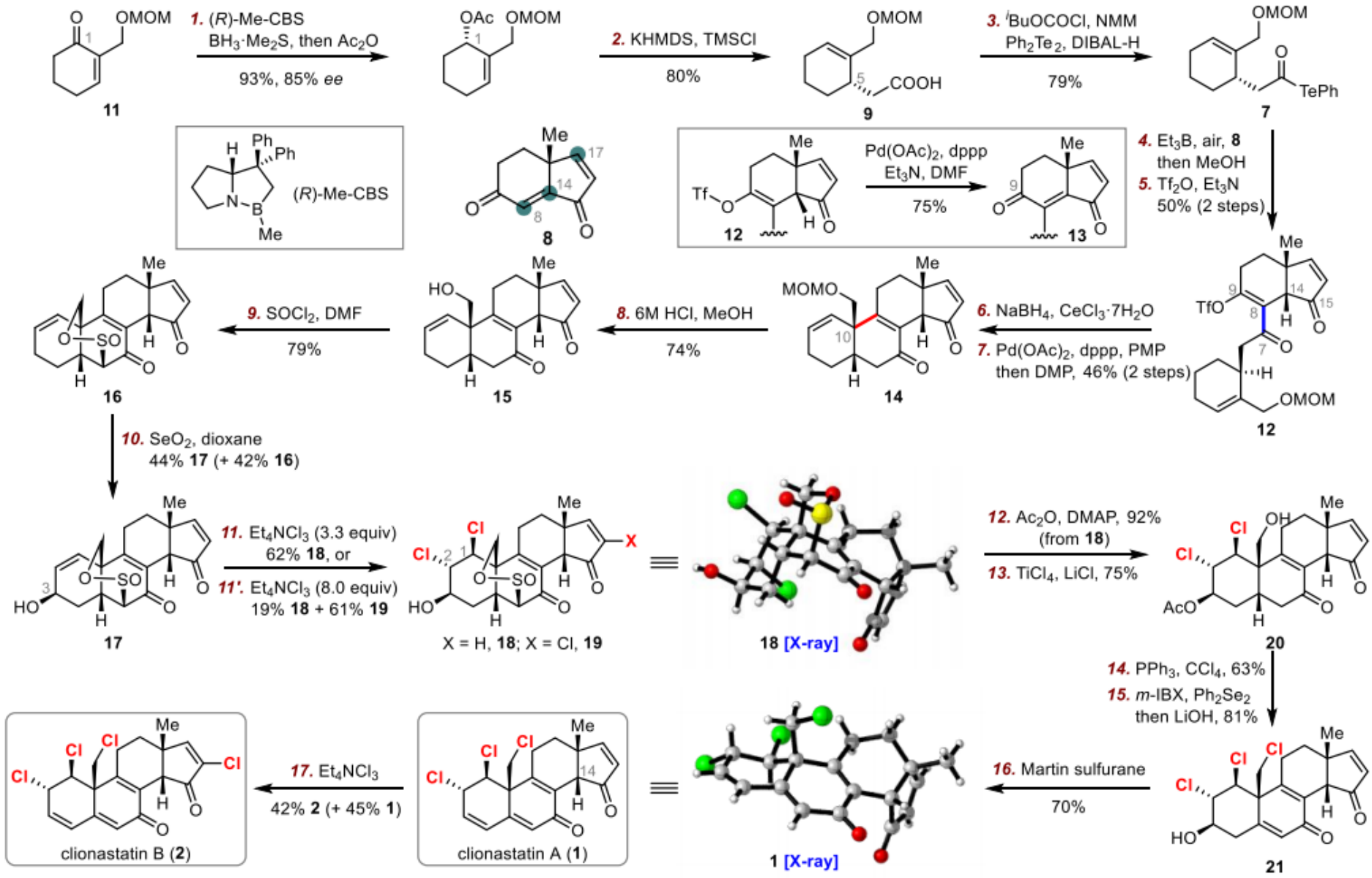


10

CBS reduction

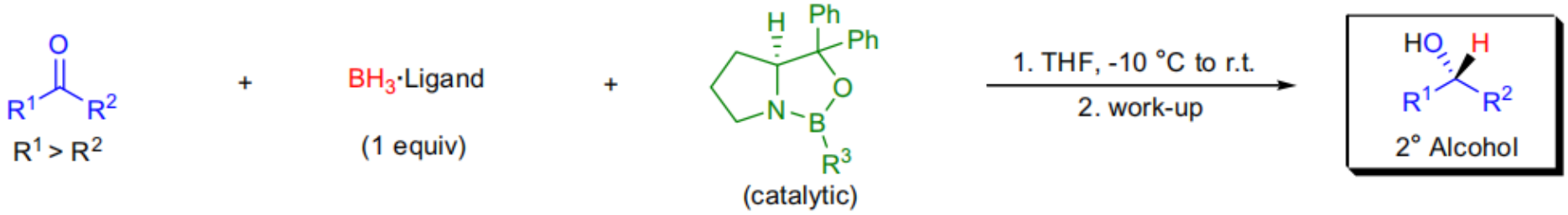


11

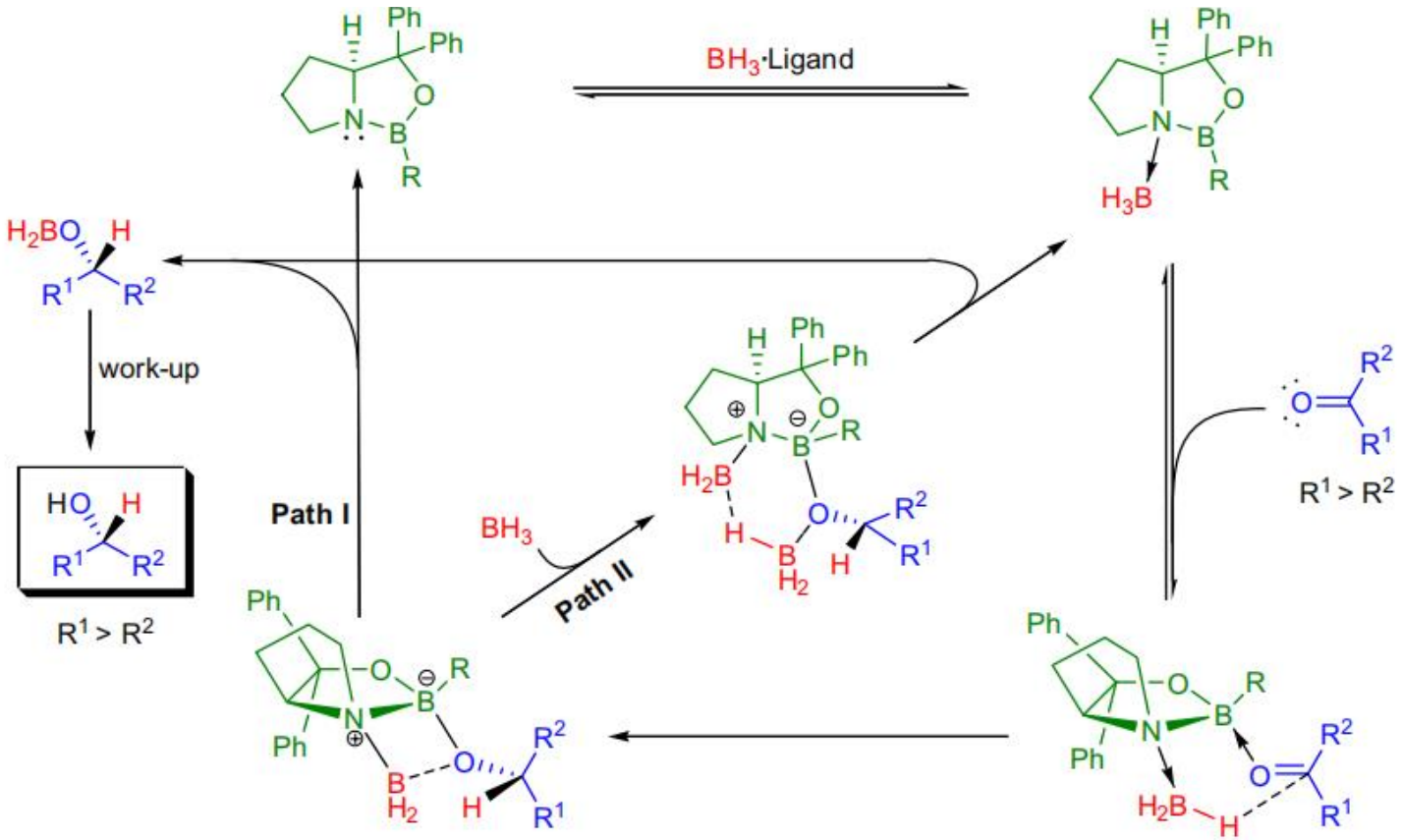

11
1. (R)-Me-CBS
BH3·Me2S, then Ac2O
93%, 85% ee
2. KHMDS, TMSCl
80%
9
3. tBuOCOCl, NMM
Ph2Te2, DIBAL-H
79%
7
(R)-Me-CBS
8
12
Pd(OAc)2, dppp
Et3N, DMF
75%
13
4. Et3B, air, 8
then MeOH
5. Tf2O, Et3N
50% (2 steps)
12
6. NaBH4, CeCl3·7H2O
7. Pd(OAc)2, dppp, PMP
then DMP, 46% (2 steps)
14
8. 6M HCl, MeOH
74%
15
9. SOCl2, DMF
79%
16
10. SeO2, dioxane
44% 17 (+ 42% 16)
17
11. Et4NCl3 (3.3 equiv)
62% 18, or
11'. Et4NCl3 (8.0 equiv)
19% 18 + 61% 19
X = H, 18; X = Cl, 19
18 [X-ray]
12. Ac2O, DMAP, 92%
(from 18)
13. TiCl4, LiCl, 75%
20
14. PPh3, CCl4, 63%
15. m-IBX, Ph2Se2
then LiOH, 81%
21
16. Martin sulfurane
70%
1 [X-ray]
17. Et4NCl3
42% 2 (+ 45% 1)
clionastatin A (1)
clionastatin B (2)

COREY-BAKSHI-SHIBATA REDUCTION (CBS REDUCTION)

(References are on page 565)

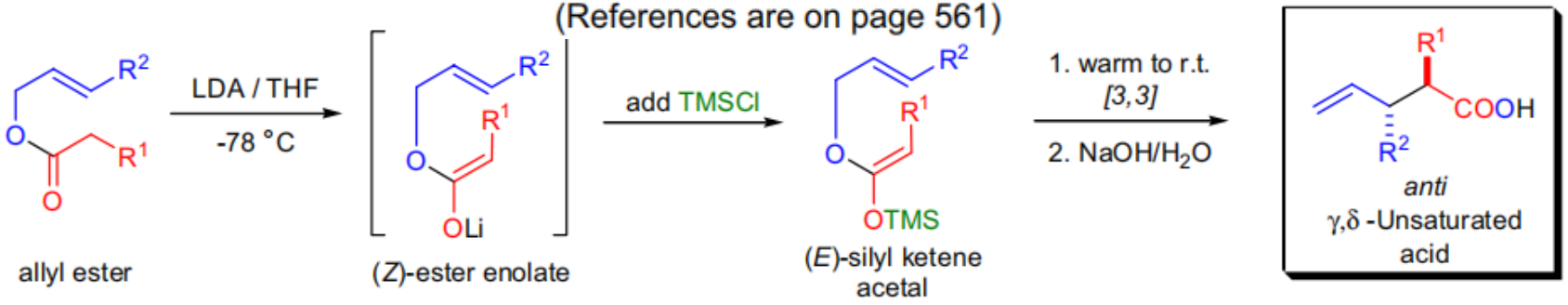


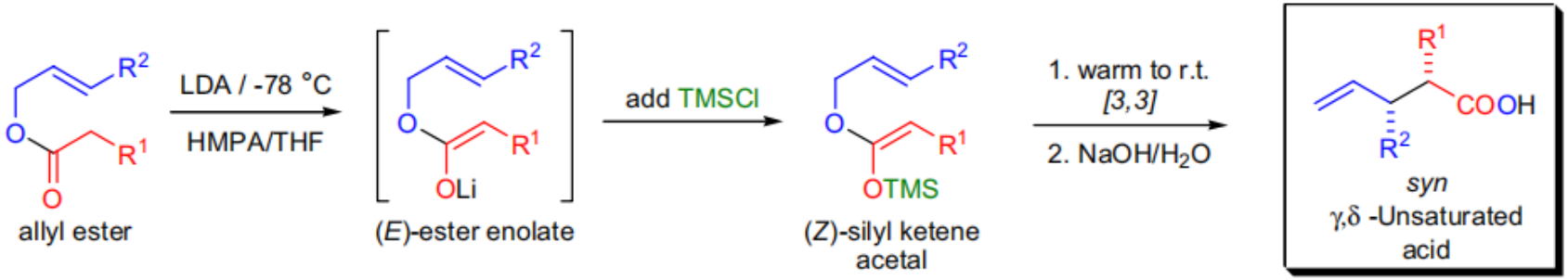
$R^{1\text{-}2}$ = alkyl, aryl; Ligand: THF, Me_2S, 1,4-thioxane, diethylaniline; R^3 = H, alkyl

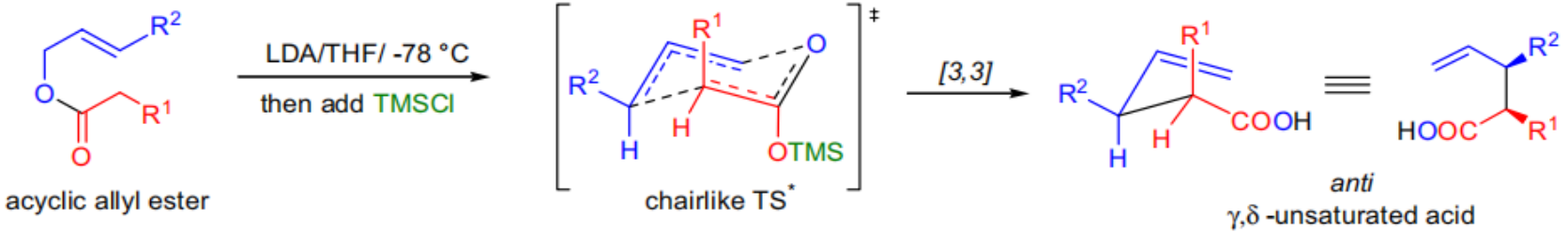


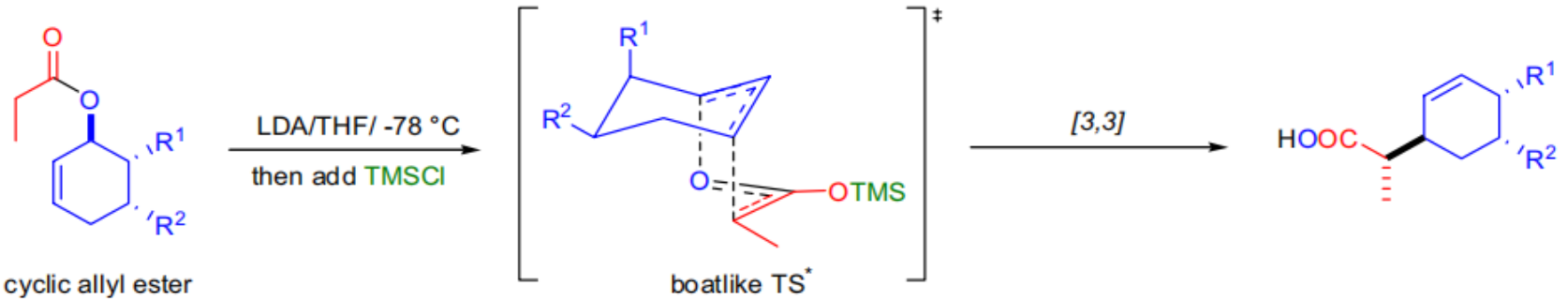
CLAISEN-IRELAND REARRANGEMENT

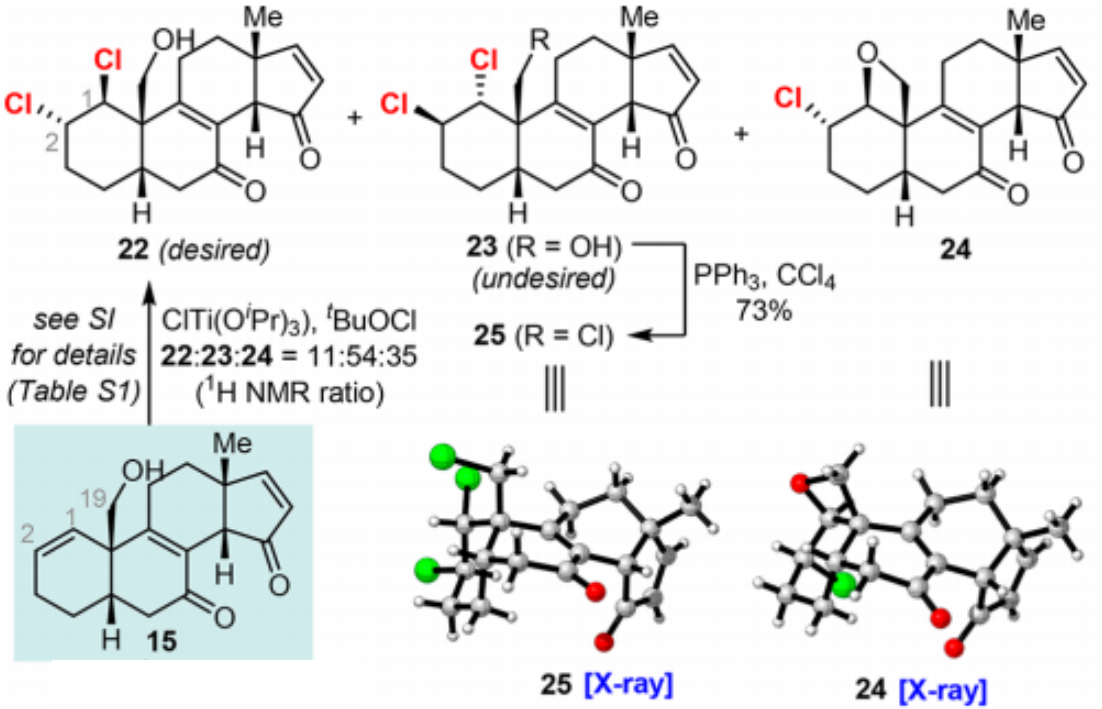
(References are on page 561)





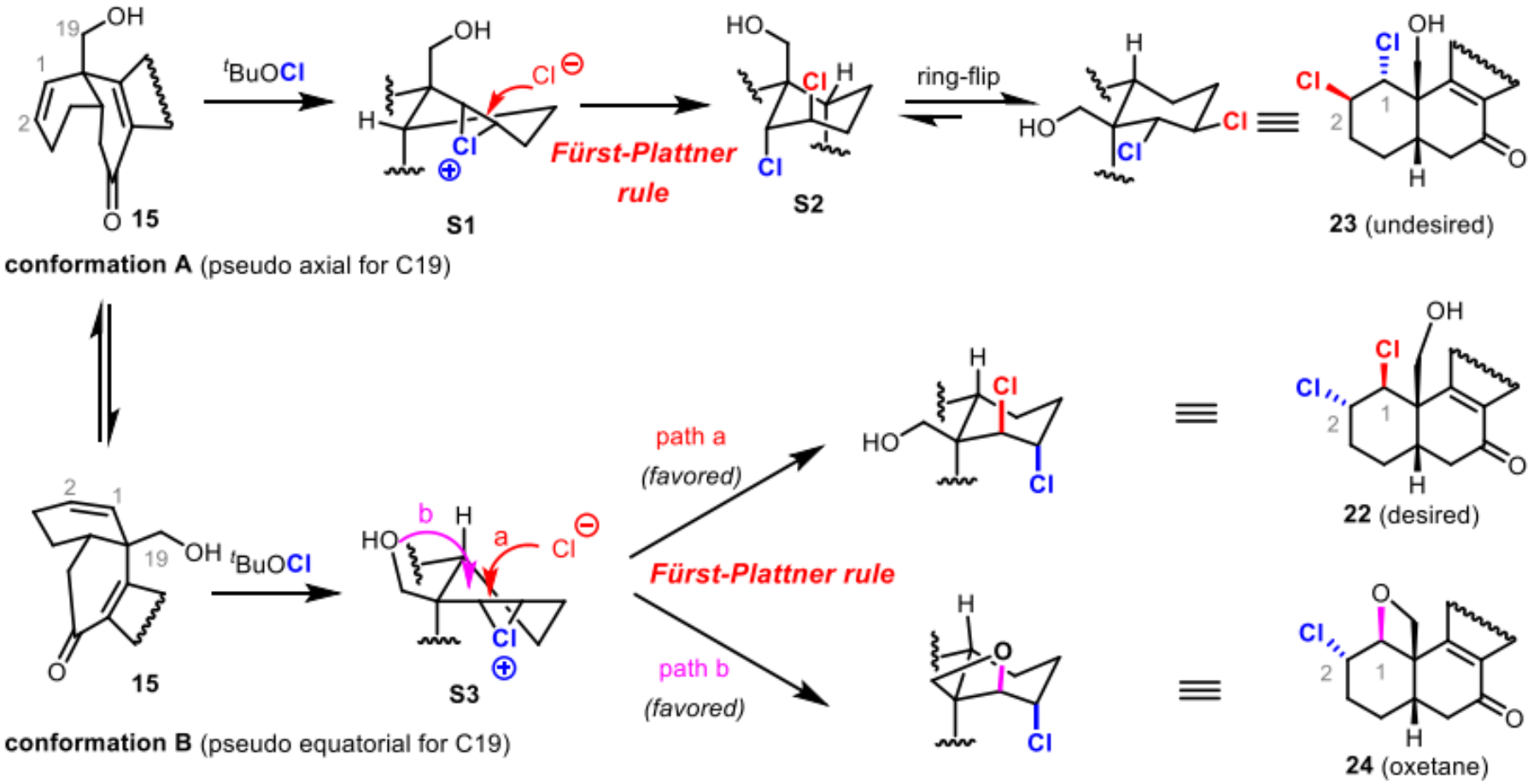


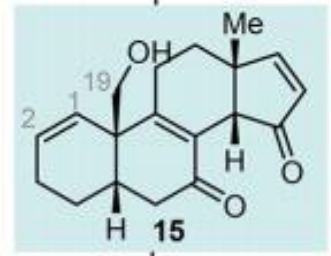




entry	conditions[a]	^{1}H NMR ratio			
		15	**22**	**23**	**24**
1	Et_3NCl_3 (2.0), –78 °C	0	40	50	10
2	$ClTi(O^iPr)_3$ (1.5), ^{t}BuOCl (1.5), rt	0	11	54	35
3	$ClTi(O^iPr)_3$ (1.5), ^{t}BuOCl (1.5), (1*S*,2*R*)-**L** (0.3), rt	42	25	10	23
4	$ClTi(O^iPr)_3$ (1.5), ^{t}BuOCl (1.5), (1*R*,2*S*)-**L** (0.3), rt	30	13	13	44
5	$ClTi(O^iPr)_3$ (1.5), ^{t}BuOCl (1.5), $Ti(O^iPr)_4$ (0.2), rt	0	10	40	50
6	$Cl_2Ti(O^iPr)_2$ (1.2), ^{t}BuOCl (1.2), rt	0	14	59	27
7	$ZrCl_4$ (1.5), ^{t}BuOCl (1.5), rt	0	12	48	40
8	$SnCl_4$ (1.5), ^{t}BuOCl (1.5), rt	(42)[b]	-[c]	(32)[b]	-[c]
9	$SnCl_4$ (3.0), ^{t}BuOCl (2.5), 0 °C	(0)[b]	(6)[b]	(44)[b]	-[c]
10	$SnCl_4$ (3.0), ^{t}BuOCl (2.5), 0 °C, then $BF_3{\cdot}Et_2O$ (2.0)	(0)[b]	-[c]	(60)[b]	-[c]

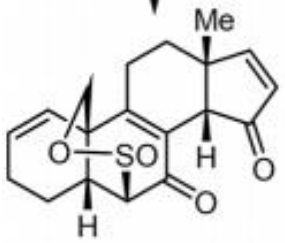
A. Possible pathways for dichlorination of 15 to afford 22, 23 and 24 (without conformational lock):





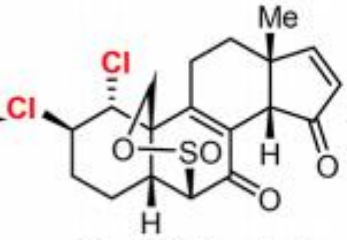
15

$SOCl_2$, DMF
79%

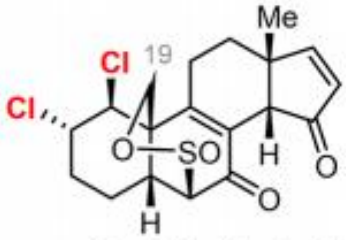


16

Et_4NCl_3



26, 20% *(undesired)*

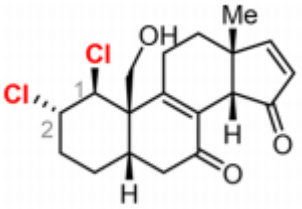


27, 61% *(desired)*

desulfination (**27**→**22**)	Yield (%)
10% HCl/THF (1:10, v/v)	54
conc. HCl/THF (1:5, v/v)	68
LiOH, THF/H_2O (1:1, v/v)	70

$TiCl_4$, LiCl
DMF, 79%

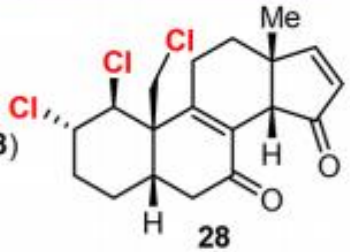
22



22 *(desired)*

PPh_3, CCl_4

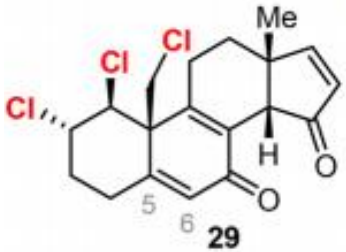
35%



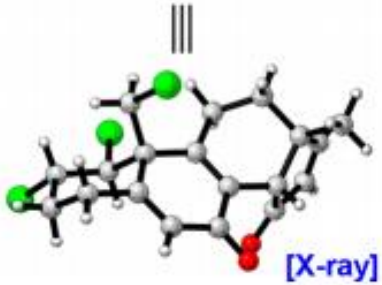
28

m-IBX, Ph_2Se_2

48% **29** (+ 32% **28**)



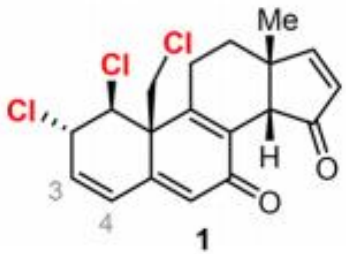
29



[X-ray]

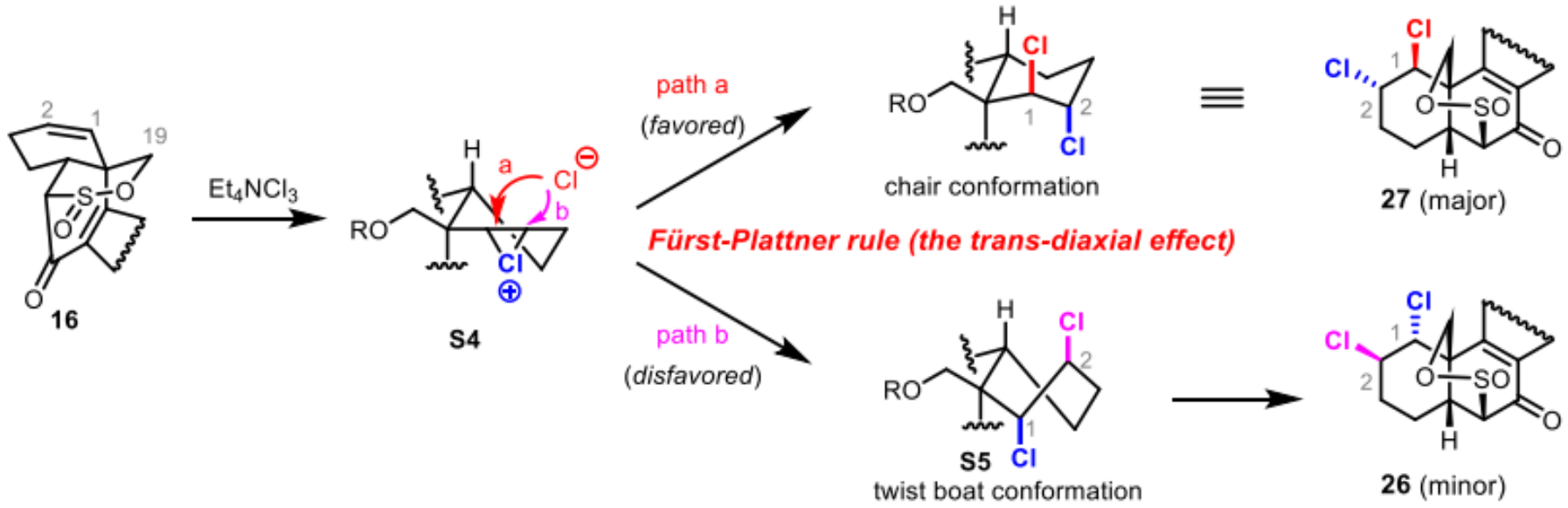
introduction of the C3-C4 olefin

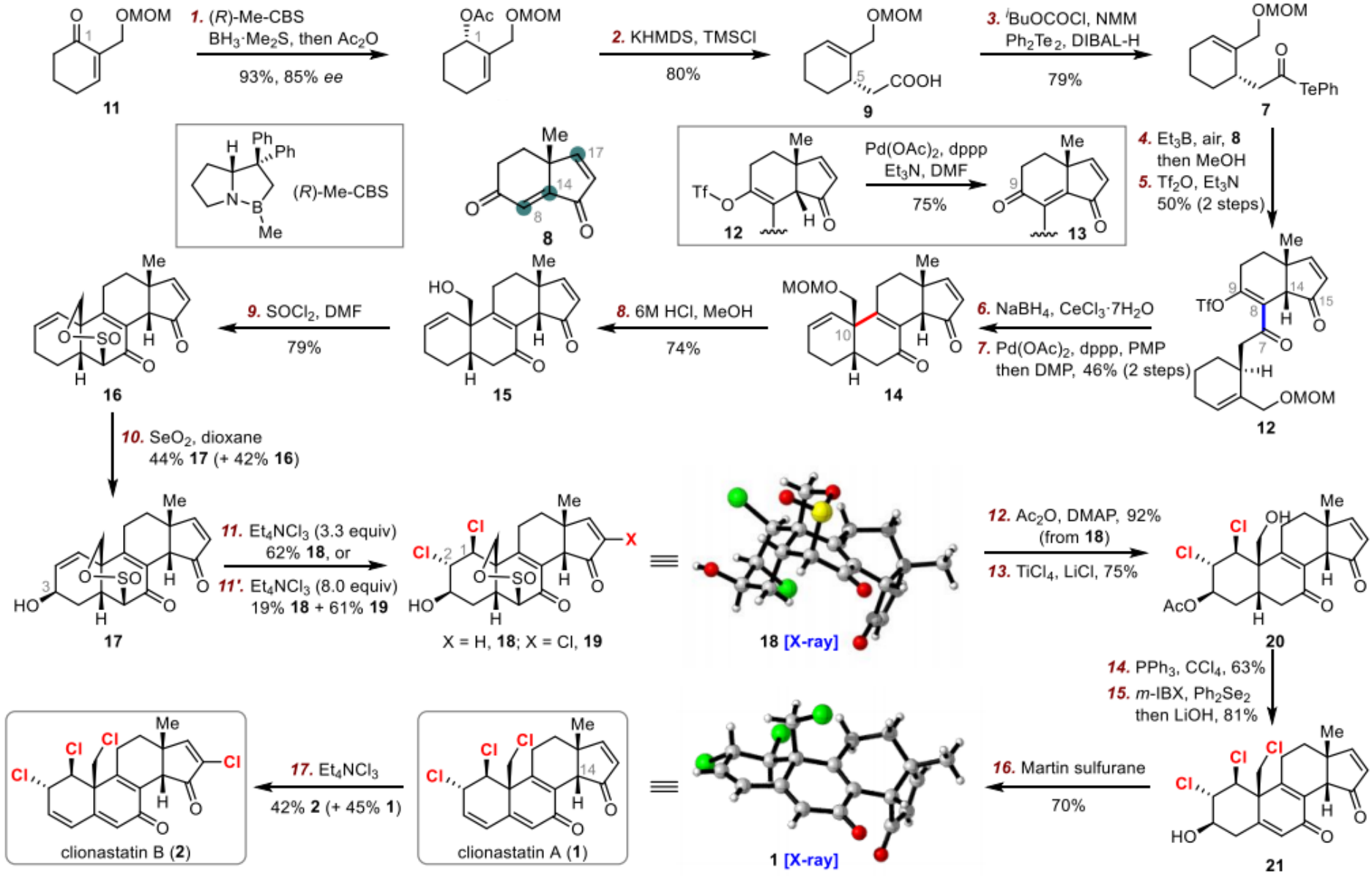
[various conditions]



1

B. Possible pathway for dichlorination of 16 to afford 27 (with conformational lock by sultine):

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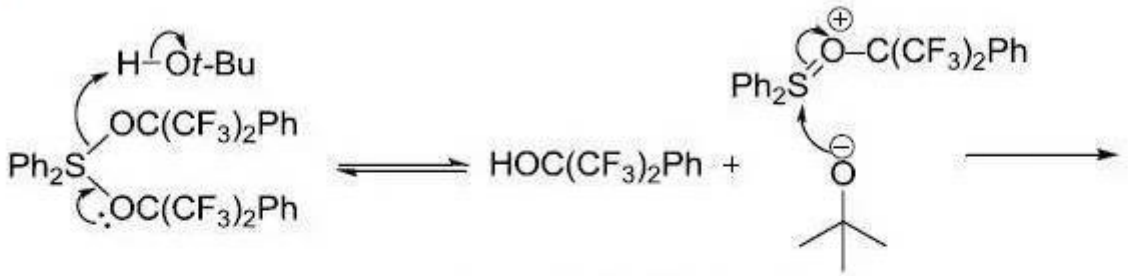
BH3·Me2S, then Ac2O
93%, 85% ee
2. KHMDS, TMSCl
80%
9
3. tBuOCOCl, NMM
Ph2Te2, DIBAL-H
79%
7
4. Et3B, air, 8
then MeOH
5. Tf2O, Et3N
50% (2 steps)
12
6. NaBH4, CeCl3·7H2O
7. Pd(OAc)2, dppp, PMP
then DMP, 46% (2 steps)
14
8. 6M HCl, MeOH
74%
15
9. SOCl2, DMF
79%
16
10. SeO2, dioxane
44% 17 (+ 42% 16)
17
11. Et4NCl3 (3.3 equiv)
62% 18, or
11'. Et4NCl3 (8.0 equiv)
19% 18 + 61% 19
X = H, 18; X = Cl, 19
18 [X-ray]
12. Ac2O, DMAP, 92%
(from 18)
13. TiCl4, LiCl, 75%
20
14. PPh3, CCl4, 63%
15. m-IBX, Ph2Se2
then LiOH, 81%
21
16. Martin sulfurane
70%
1 [X-ray]
17. Et4NCl3
42% 2 (+ 45% 1)
clionastatin A (1)
clionastatin B (2)
(R)-Me-CBS
8
12
13

Martin硫化物脱水试剂可以将叔醇或仲醇脱水得到烯烃，但伯醇主要得到醚。机理与Burgess脱水试剂类似。

反应机理

HOC(CF3)2Ph酸性很强可以提供质子。



The alcohol is acidic