

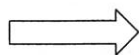
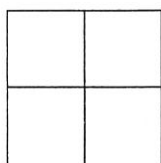
Fenestrane

~From the Synthetic View of the Natural Product~

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§1 Introduction

1-1 Introduction



Window (Lat. fenestra) structure alkane.
Febestra alkane •••• "Fenestrane"

Vlasios Georgian and Martin Saltzman, *TL*, 1972, 13, 4315-4317

tetracyclo [3.3.1.0^{3,9}.0^{7,9}] nonane (1)

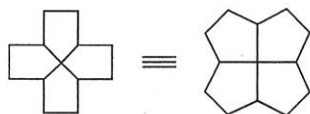
(This compound has never been synthesized, so far.)

cf. Pyramidane (tetracyclo[2.1.0.0^{1,3}.0^{2,5}] pentane)
 Minimum fenestrane.



2

Staurane (from Greek stauros, cross)
 tetracyclo[5.5.1.0^{4,13}.0^{10,13}]tridecane



4

Propellane



3

Paddlane

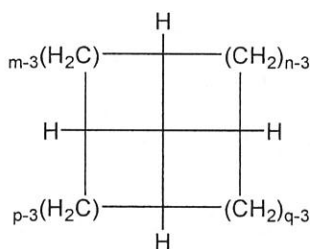


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1-2 Naming Rule

[m.n.p.q]fenestrane

1. Start with smallest ring number (m).
2. Second number (n) is smaller one which ring touches the smallest ring.
3. Third number (p) is the next one in the round manner.
4. Last number (q) is decided automatically.



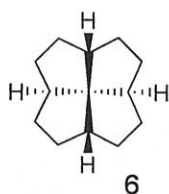
description of *cis/trans*

- cis*: Relationship of proton to bridge-head carbon and bridge-head carbon to central carbon are same. (up-up or down-down)
trans: Relationship of proton to bridge-head carbon and bridge-head carbon to central carbon are different. (up-down or down-up)

cis/trans is written before [m.n.p.q], its order is same as [m.n.p.q].

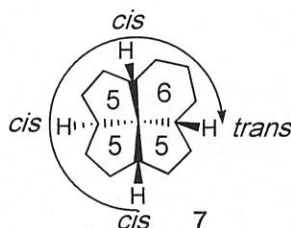
Normally, if there are many same number, they ordered as *cis* comes front.
 Some people says olefin containing fenestrane as "fenestrene", but it is not major.

Examples



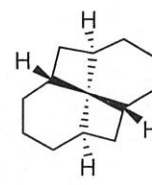
6

all-*cis*-[5.5.5.5]fenestrane



7

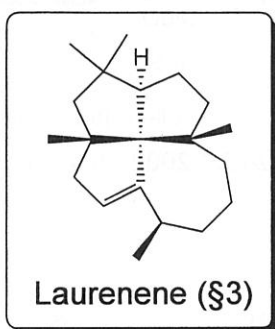
cis,cis,cis,trans-[5.5.5.6]fenestrane



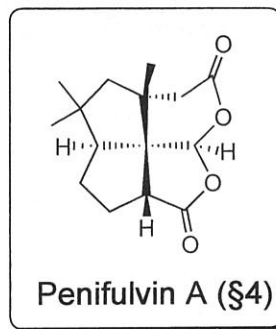
8

all-*cis*-[4.6.4.6]fenestrane

In natural product, there are only two compounds which have fenestrane structure. Both of them are terpene compound.



diterpene
all-*cis*-[5.5.5.7]fenestrane



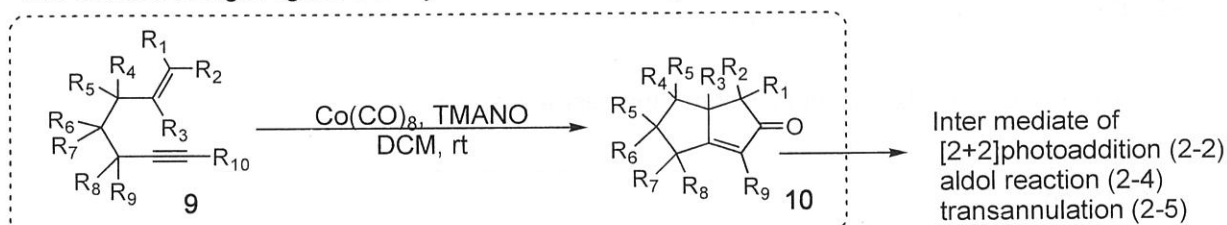
sesquiterpenoid
all-*cis*-Dioxa[5.5.5.6]fenestrane

All-*cis* fenestrane is most stable.

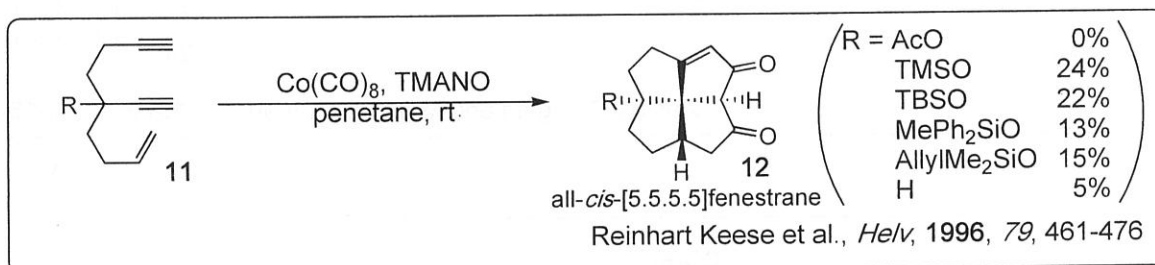
§2 Synthetic approach

2-1 Pauson-Khand Reaction ([2+2+1]addition)

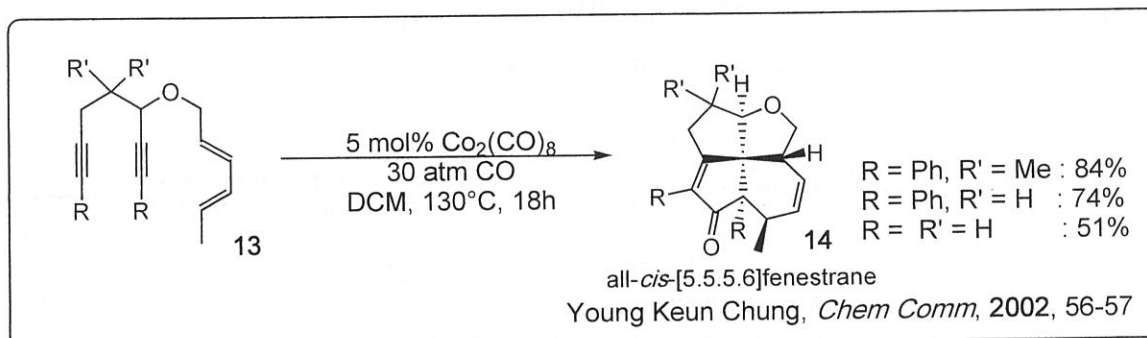
Intramolecular Pauson-Khand Reaction is fine way to make bicyclo[3.3.0]octane. This reaction is high regioselectivity and stereoselectivity.

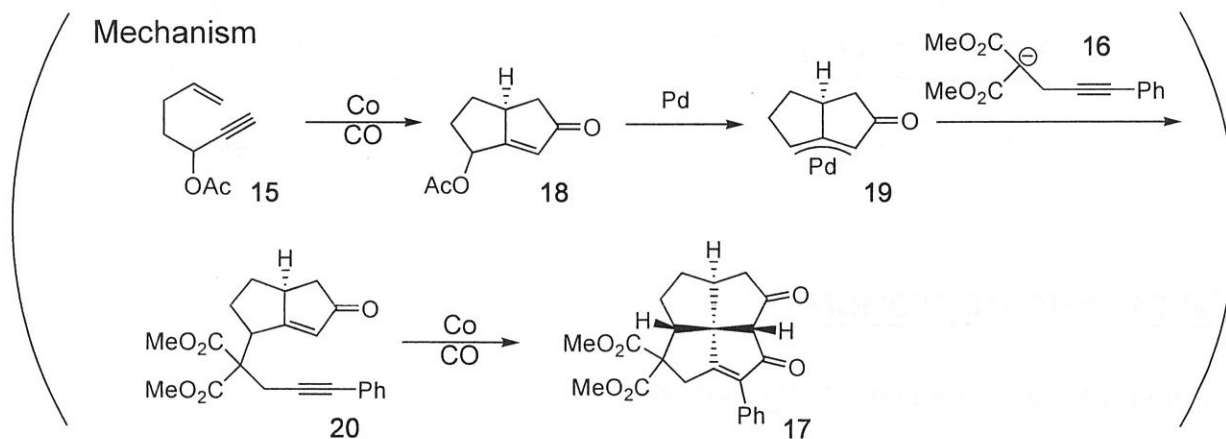
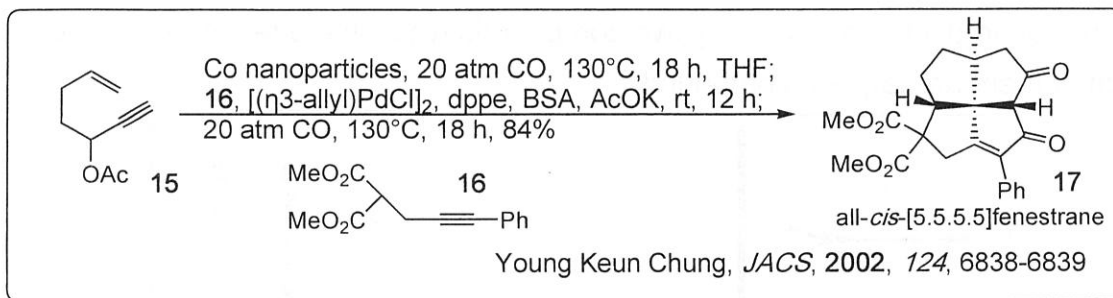


Moreover, intramolecular tandem Pauson-Khand Reaction gives fenestrane structure in one step.



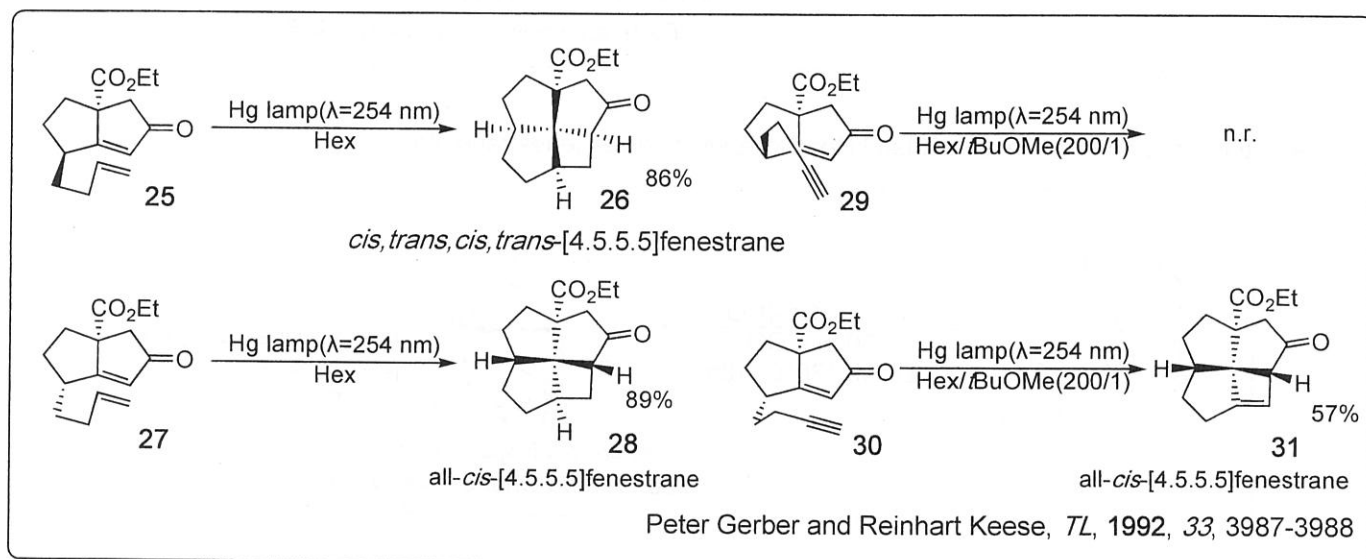
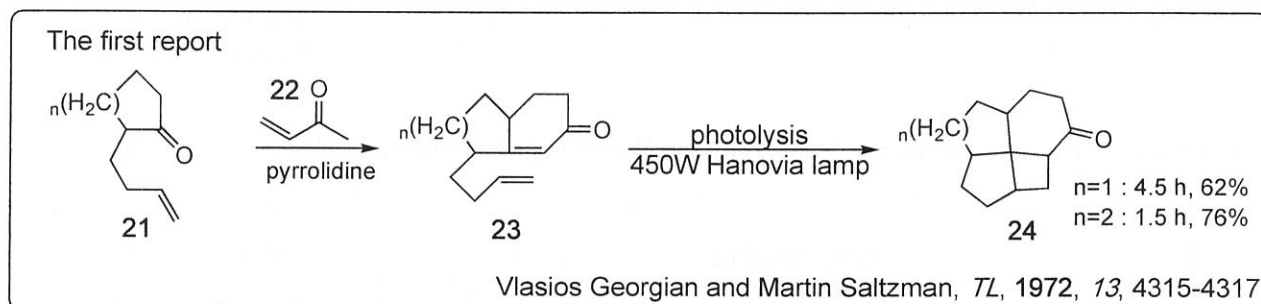
And there are one pot Pauson-Khand Reactions which gives fenestrane structure.





2-2 [2+2]photoaddition

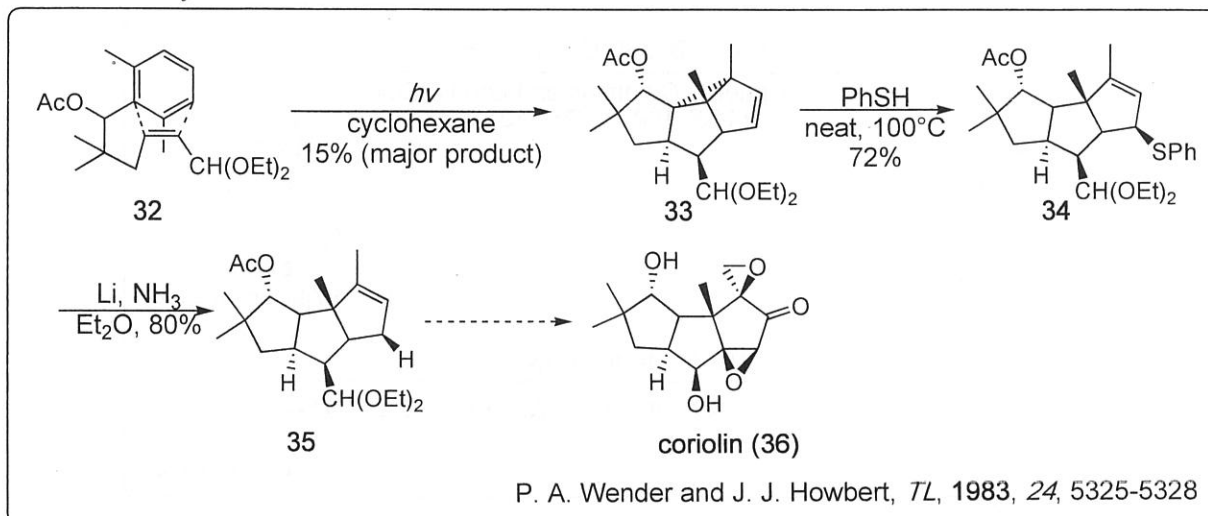
To make [4.m.n.p]fenestrane, [2+2]photoaddition is the best way so far.



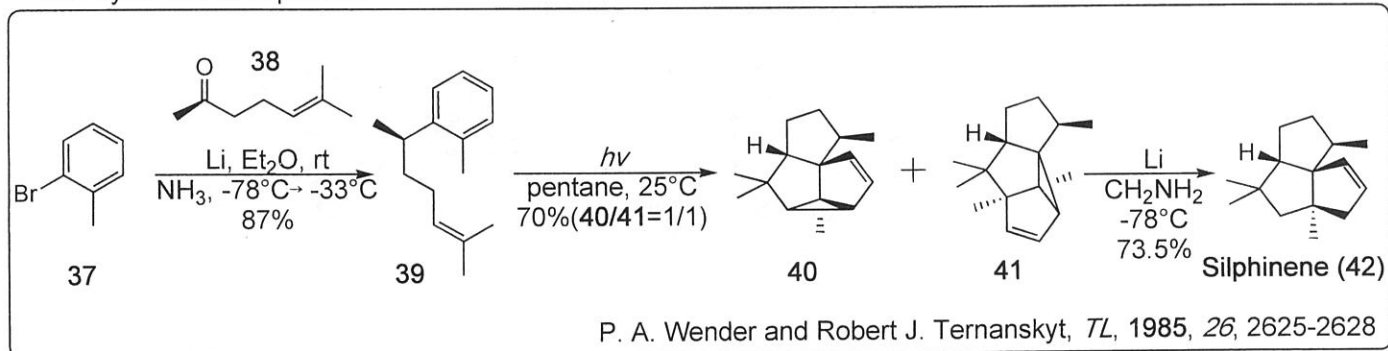
2-3 [2+3]photoaddition

[2+3]photoaddition is very convenient to synthesize the natural products.

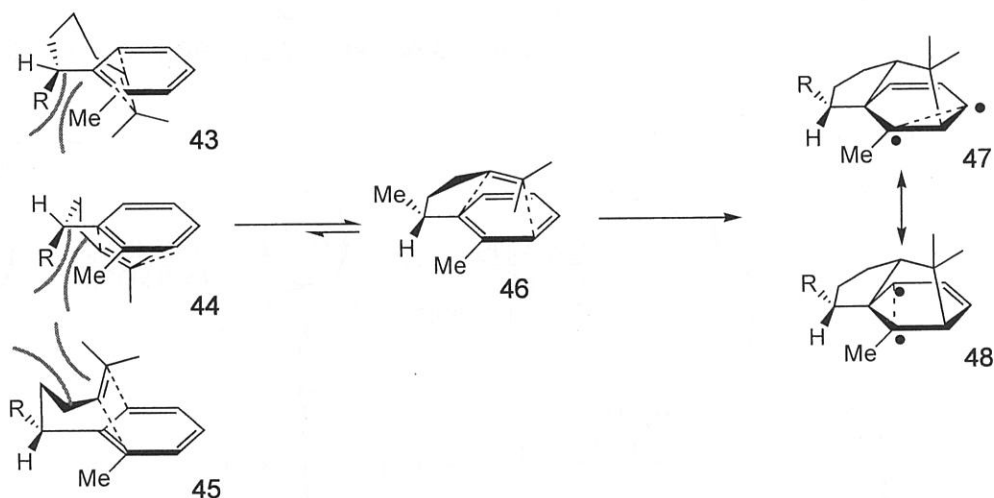
Toward to synthesis of coriolin



Total synthesis of Silphinene



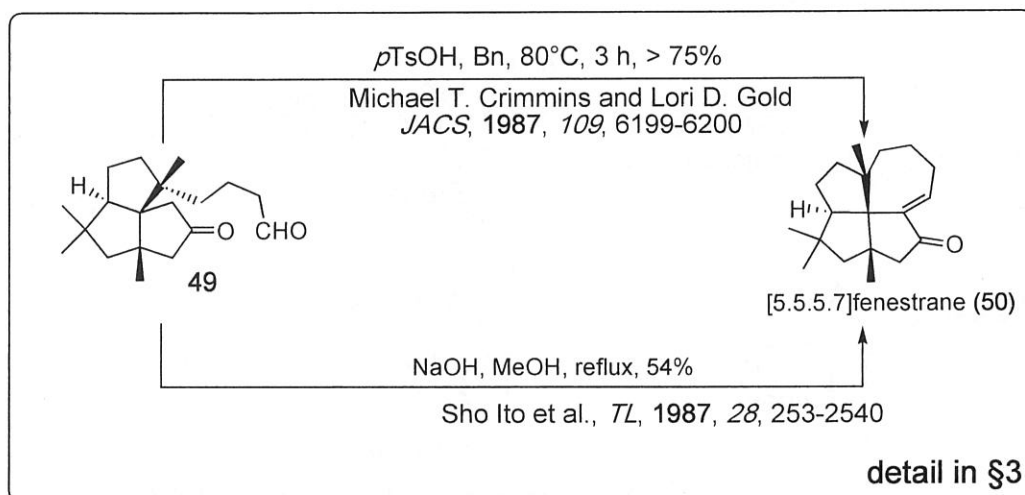
These reactions have good regioselectivity.
But selectivity of electric transition is not controlled.



[2+3] photocyclization was used in the total synthesis of Laurenene and Penifulvin A.
Those schemes are written in §3 and §4.

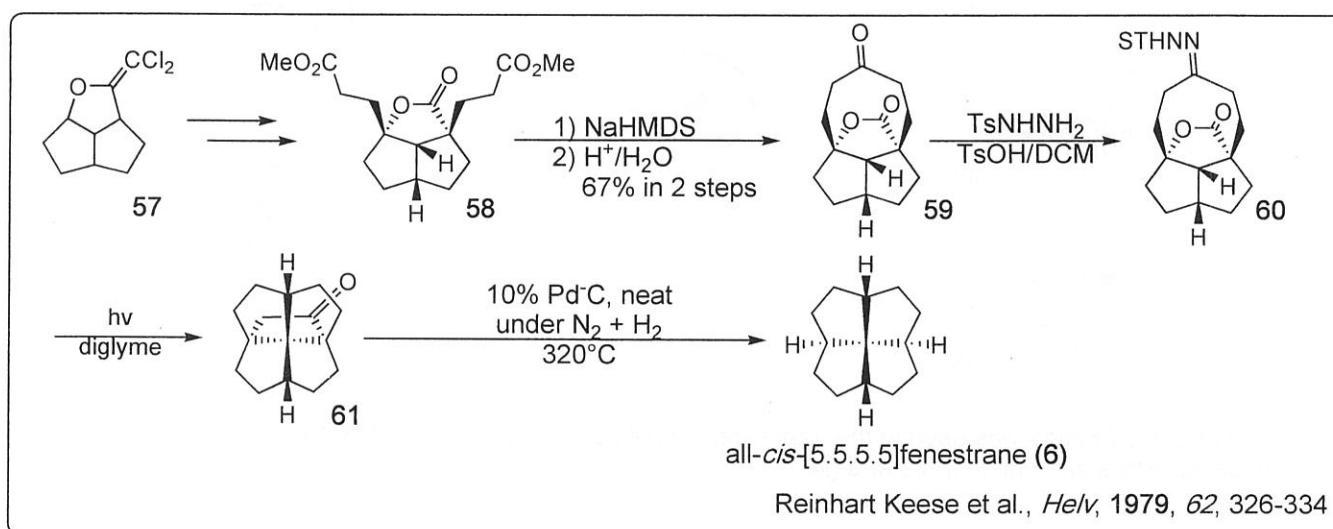
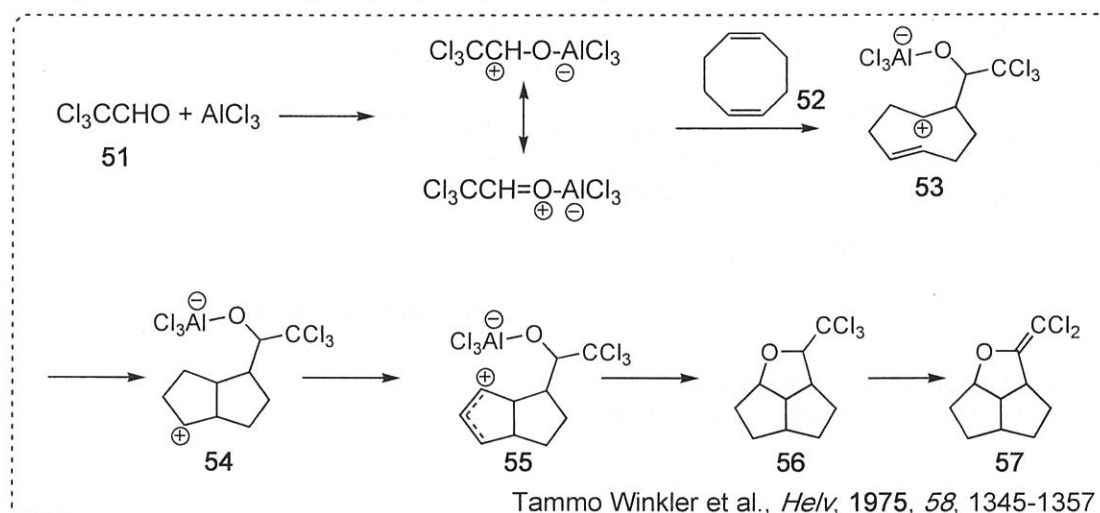
2-4 aldol reaction

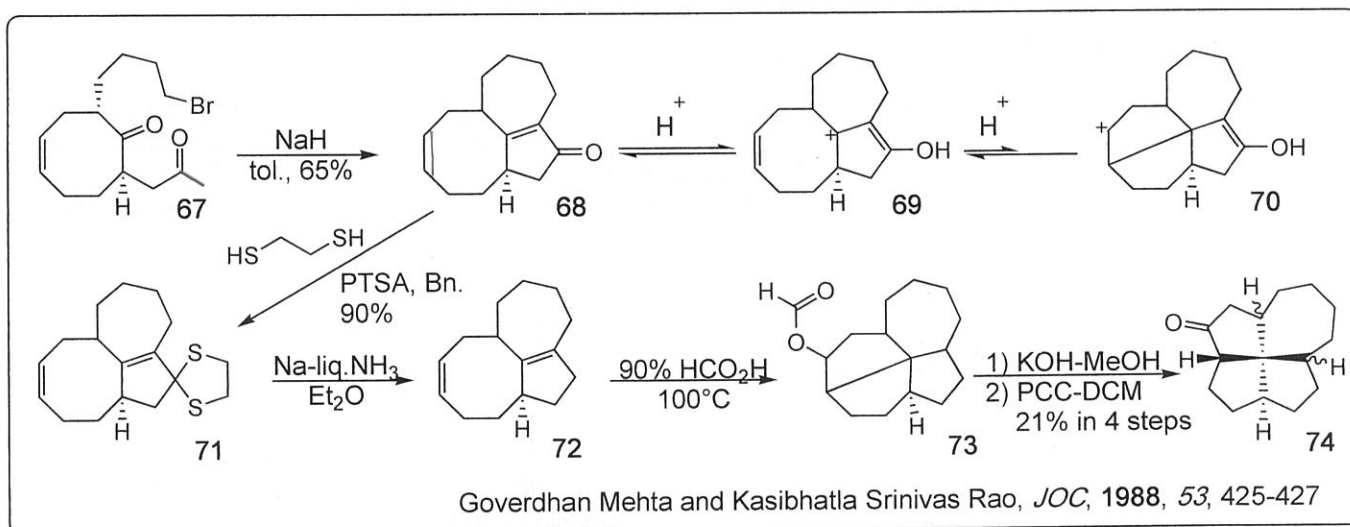
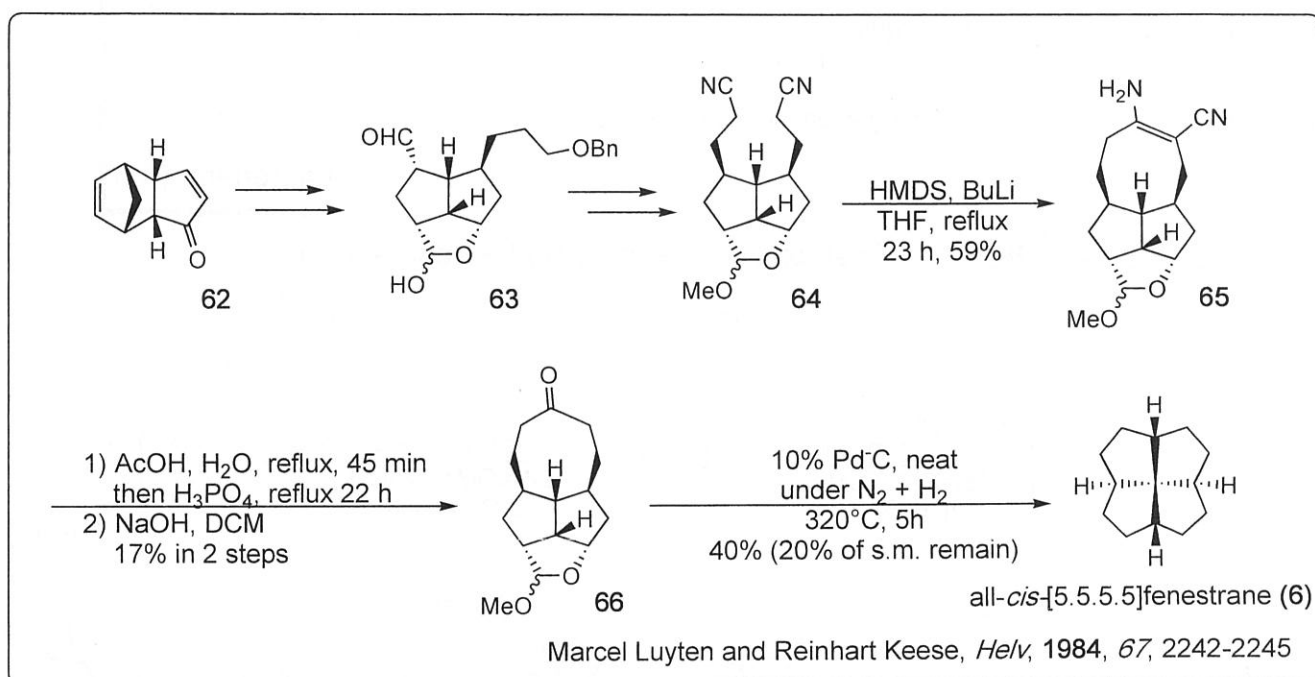
In laurene synthesis, to make the 7-membered-ring, aldol reaction was used.



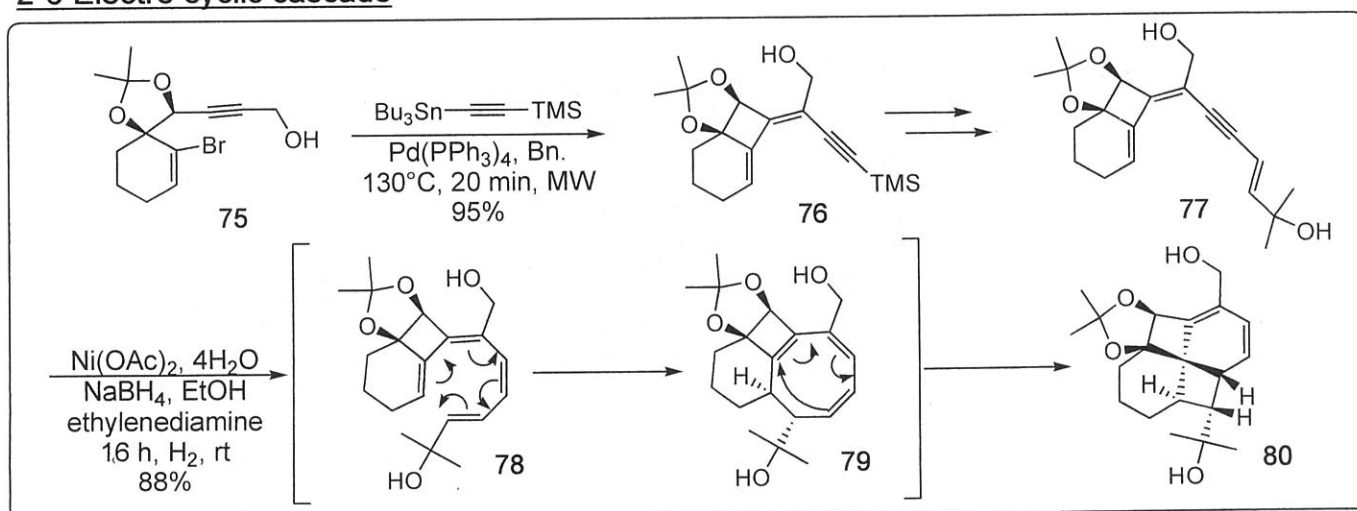
2-5 Transannulation

From cyclooctane/-ene ring, bicyclo[3.3.0]octane is produced.





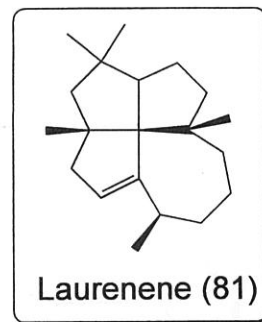
2-6 Electro cyclic cascade



§3 Total Synthesis of Laurenene

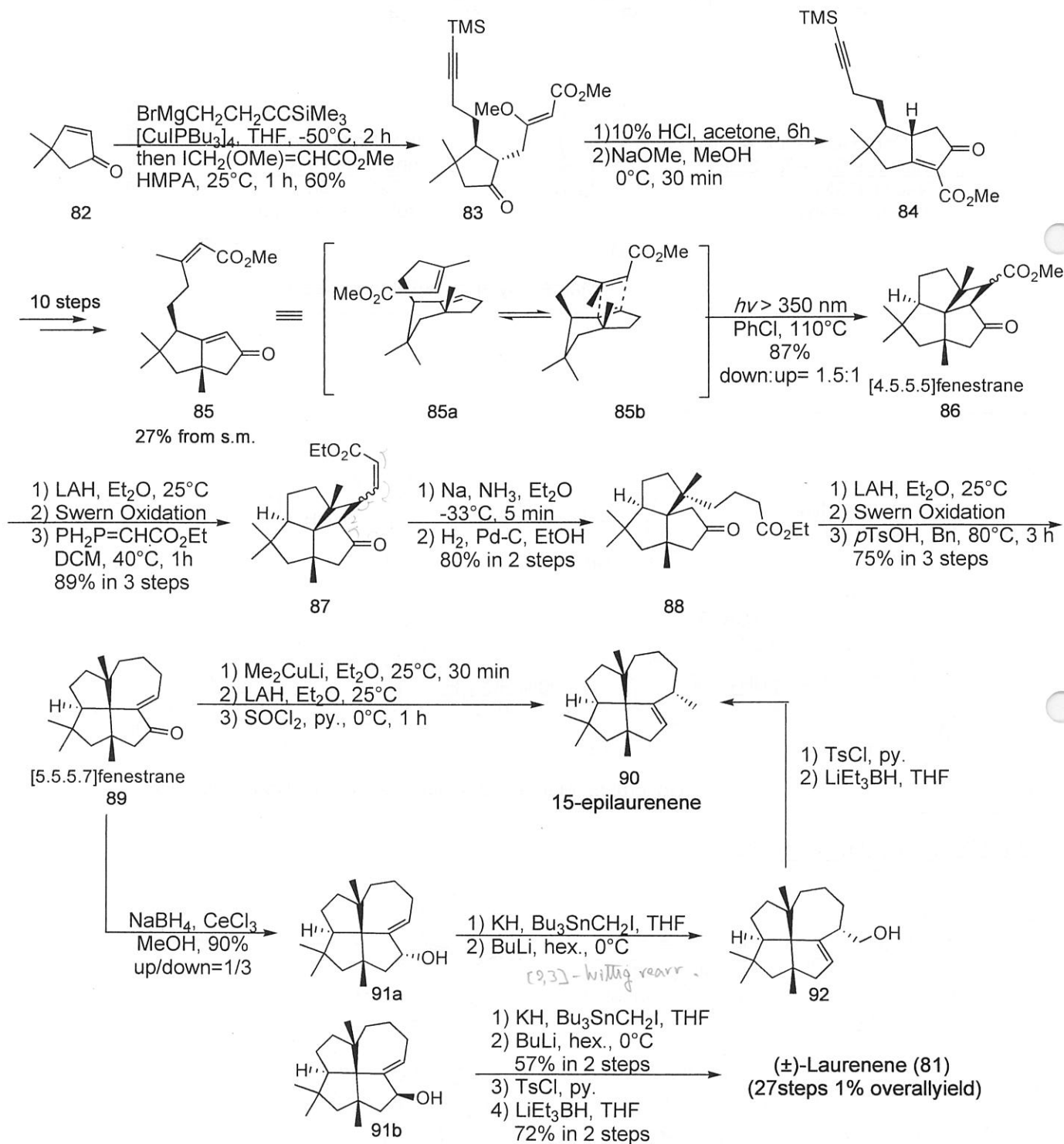
Isolation : from *Dacrydium cupressinum*
 Isolator : Denis R. Lauren et al. in 1971

First natural product containing a fenestrane ring system.

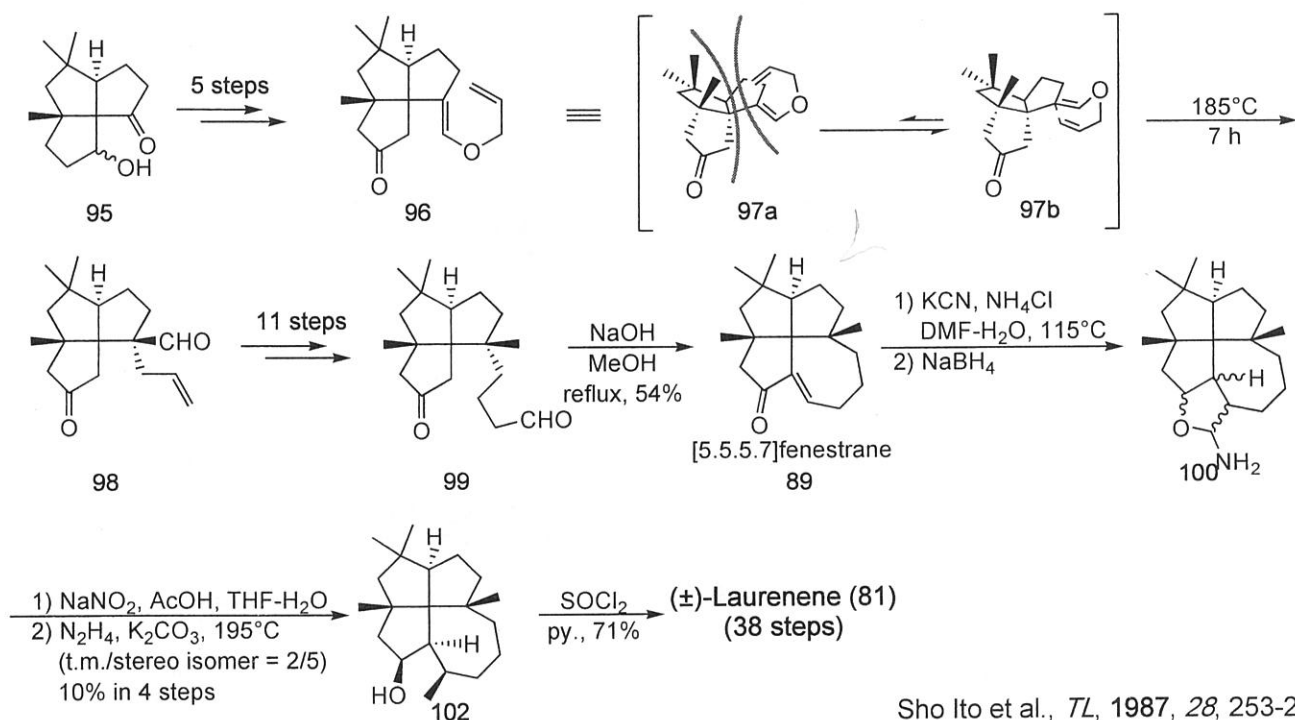
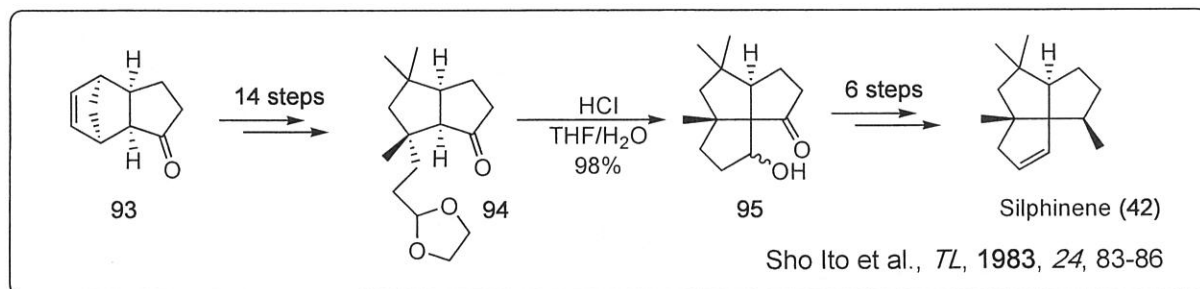


3-1 Gould's Route

First total synthesis of (±)-Laurenene (81)

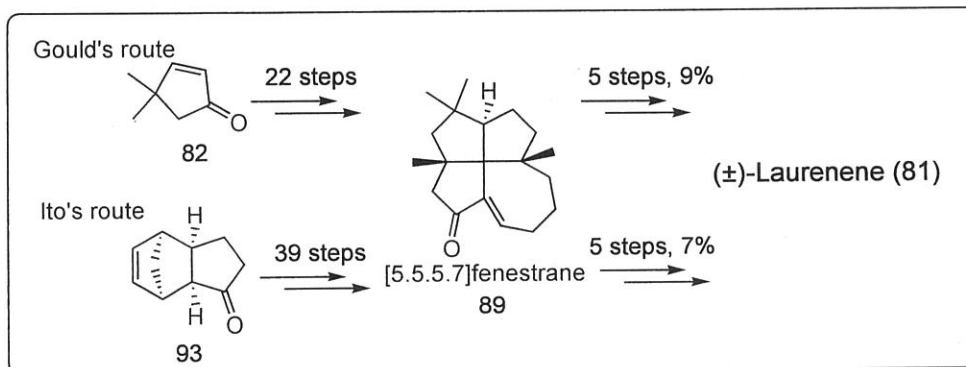


3-2 Ito's Route



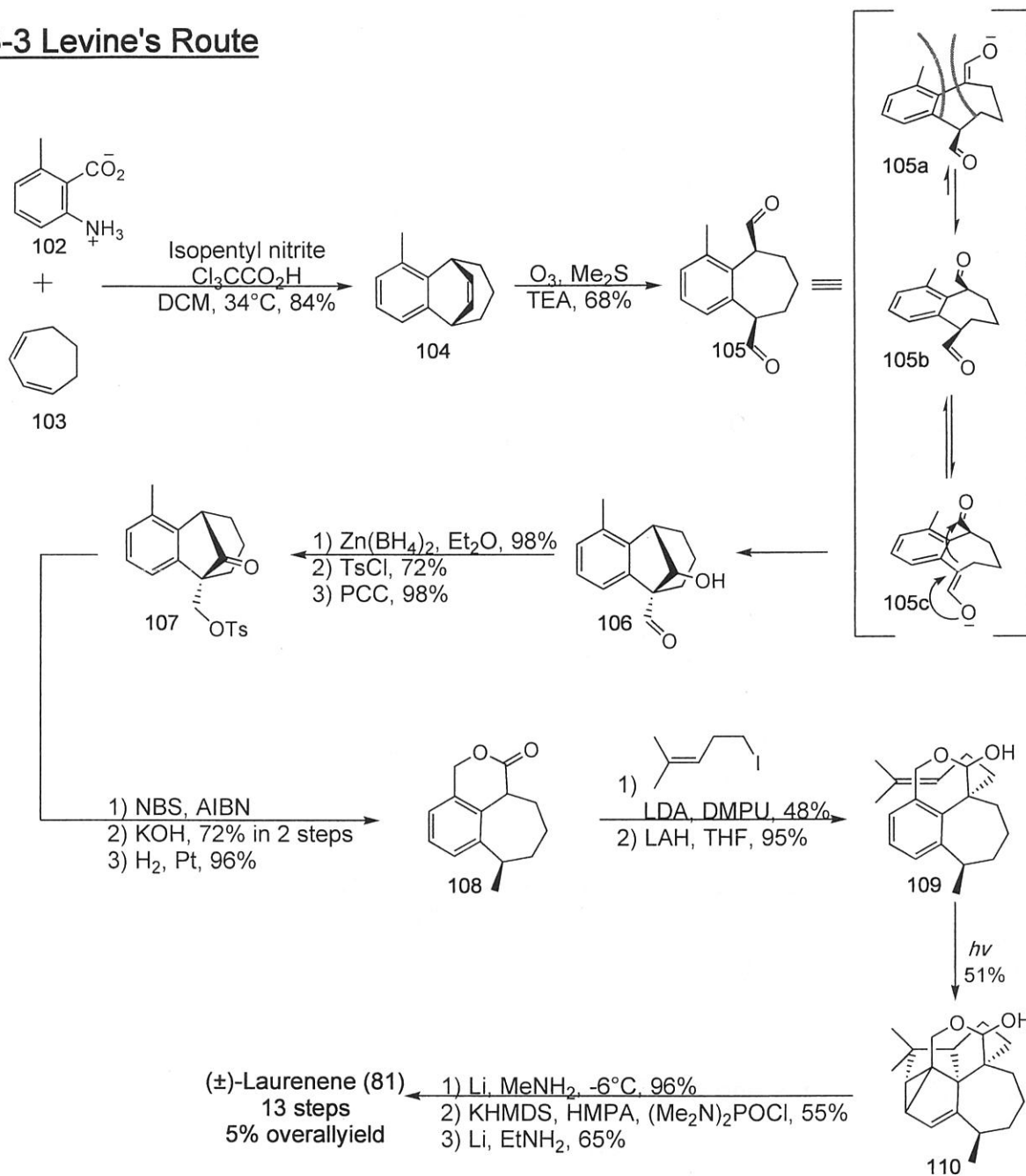
Summary of Gould's Route and Ito's Route

- Both routes have the same intermediate [5.5.5.7]fenestrane (89). Ito's route was started from Silphinene's precursor, their route was not practical. Moreover, after the same intermediate, Gould's route is better than Ito's route.



- Needless to say, how to make the fenestrane structure is the most important, so both routes were deeply thought about it. On the other hand, they depreciated the methyl group. So, as a result, fenestrane structure was easily synthesized, but they lost more than 90% materials in the methylation step.
- Though it is a trivial story, Gould's paper was received by ACS on 24 Mar. 1987. Gould's lab was at North Carolina. Ito's paper was received in UK on 26 Mar. 1987. Ito's lab was at Tohoku Univ.. Which was the real first report??

3-3 Levine's Route



Barry H. Levine et al., *JACS*, 1988, 110, 4858-4860

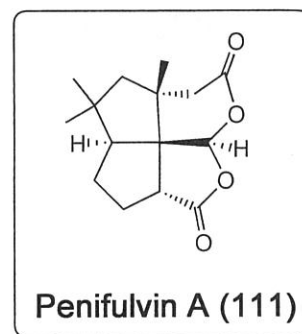
Summary of Levine's Route

- To introduce the homoprenyl group, they take long way (105-109).
Because 105 and its derivatives were not introduced the homoprenyl group.
(i.e. 105a was not formed because of peri-methyl group sterically inhibits enolization)

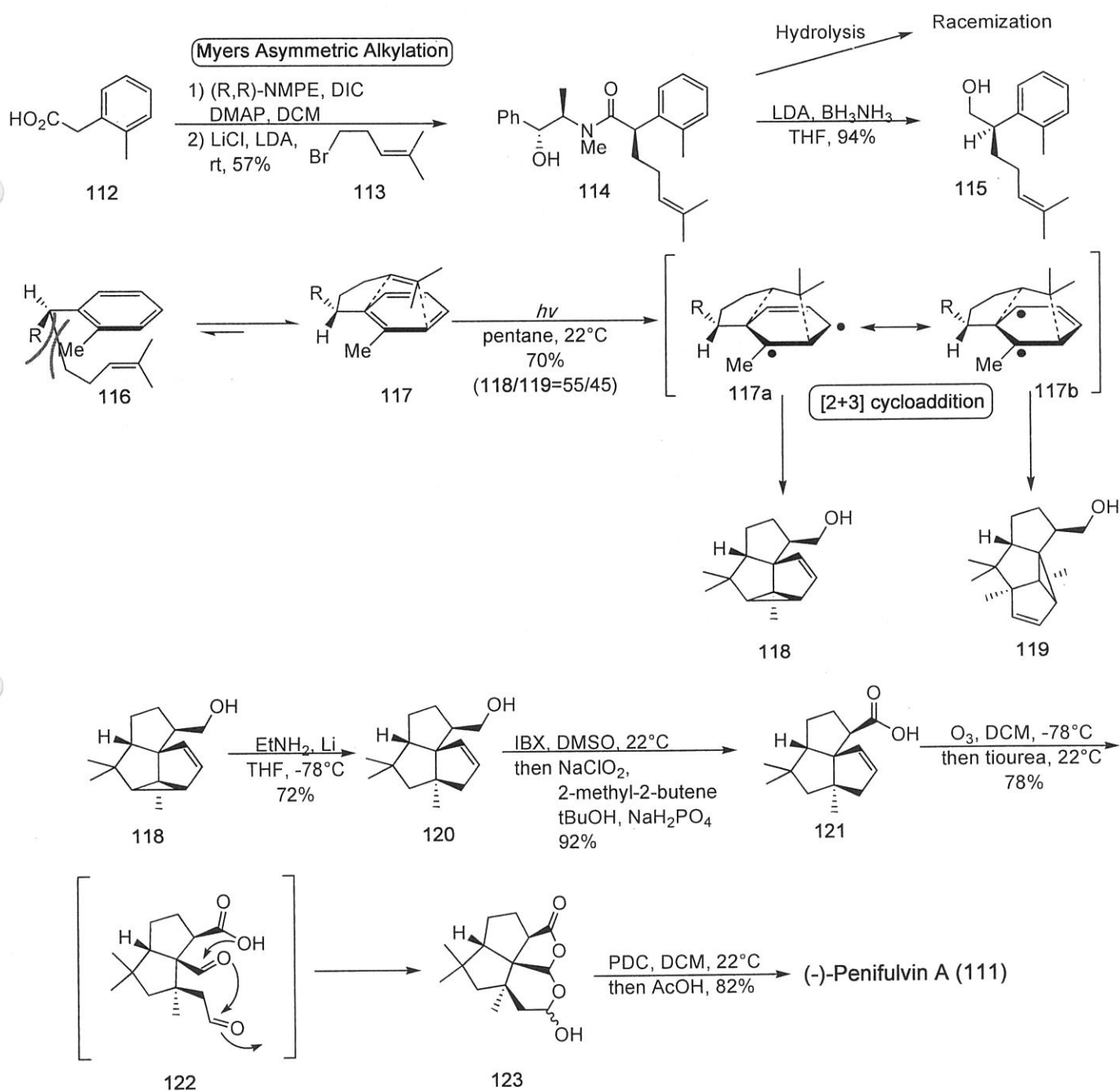
\$4 Total Synthesis of Penifulvin A

Isolation : from *Penicillium griseofulvum*

Activity : against the fall armyworm (*Spodoptera frugiperda*)

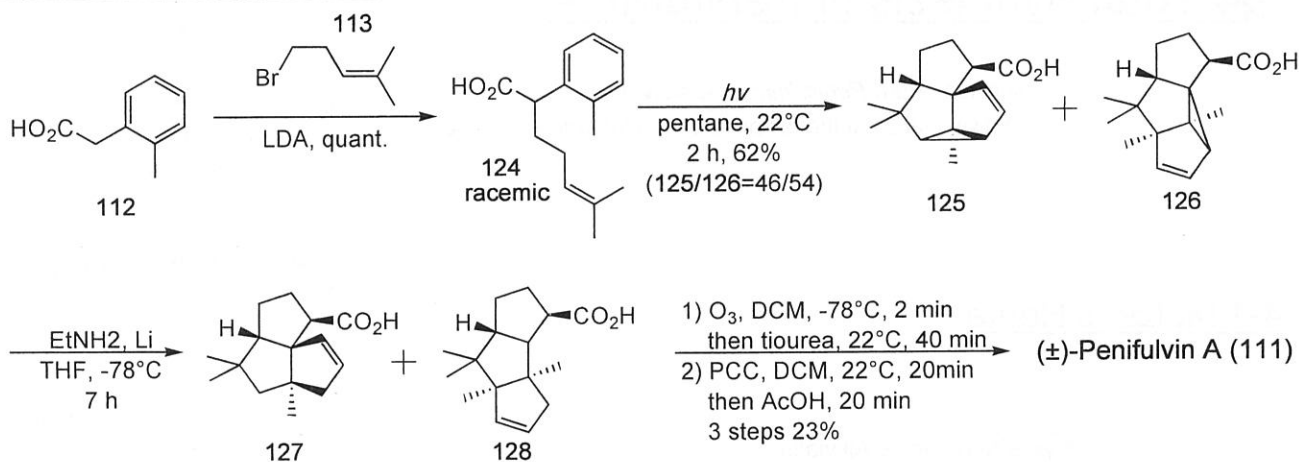


4-1 Mulzer's Route



Tanja Gaich and Johann Mulzer, *J. Am. Chem. Soc.*, 2009, 131, 452-453

4-2 Racemic Synthesis



Summary of Mulzer's Route

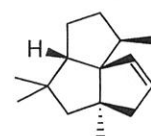
(-)-Penifulvin A (111) was synthesized in 8 steps, 8% yield.

(±)-Penifulvin A was synthesized in 5 steps, 14% yield.

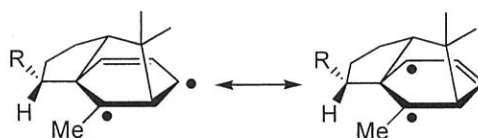
Without using protective group.

Summary of Levine's Route and Mulzer's Route

- They also used [2+3] photocyclization. Because isoration report of each compound, Silphinene was written as a intermediate candidate of biosynthetic route.
- [2+3] photocyclization is good way to synthesize the multi-ring compounds. Regioselectivity is very high, but electron transition is not controlled, so yield was halved.



Silphinene (42)



§5 Final section

5-1 Summary of Total Syntheses

Although, there are many approaches to Fenestrane structure (in §2), there are only reports of aldol reaction (§3-1,2) or [2+3]photocyclization (§3-3, §4). Moreover, half of them were synthesized via Silphinene derivative (§3-2, §4), same as biosynthetic intermediate.

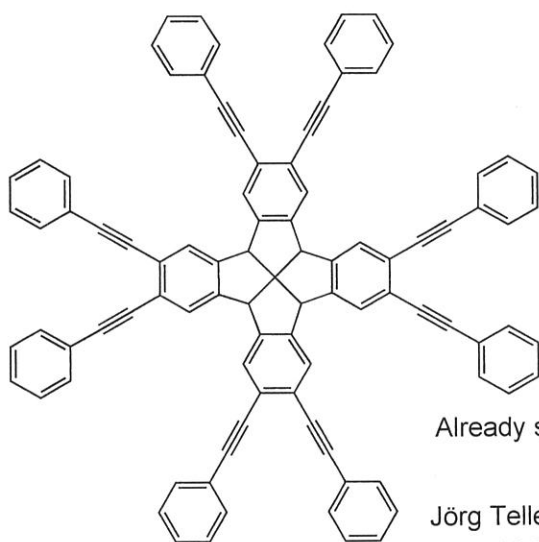
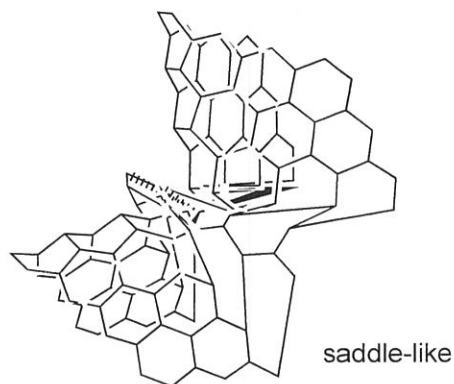
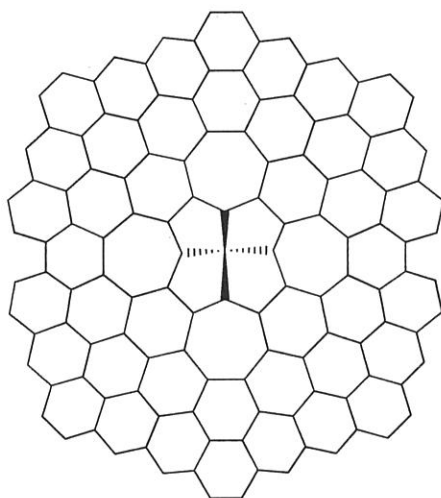
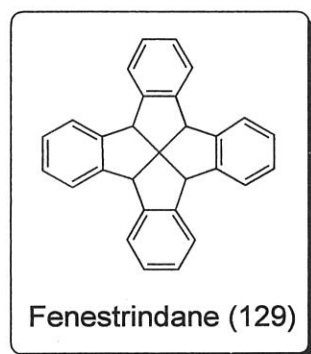
Fenestrane structure is very strained, so ring formation is rather easy (§4), because formation of stereoisomer is difficult.

On the other hand, after formation of the fenestrane structure, alkylation or other stereoselective functionalization is difficult (§3-1,2).

[2+3]photocyclization is the best way to access natural fenestrane compound, so far. If we can control the electron transition, this route will be the perfect.

5-2 Another study of Fenestrane

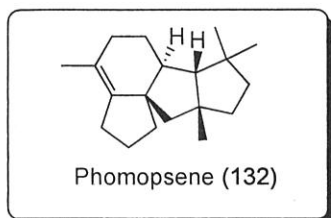
In this seminar, I talked only from the synthetic view of the natural product. But there are another study of fenestrane, so now I introduce it simply.



5-3 Future of Fenestrane

In those way, fenestrane study is advanced day by day.
Fenestrindane's saddle like form will give us the new quality material.

And, new fenestrane-like compound Phomopsene (132) was discovered by Japanese Group.



Isolation : from *Phomopsis amygdali*

Total synthesis of Phomopsene (132) will be finished before too long, and its activity will be clear.

But the essential and the final problem is to make the [4.4.4]fenestrane.



When we can make flat carbon, this compound will be synthesized.

Epilogue

I'm glad to have a Lit. seminar on total solar eclipse day (next chance in japan : AD2035)
I never used pdf image as copy&paste, its make résumé dirty.

If you want to study fenestrane more, this review will help you.
Bhaskar Rao Venepalli and William C. Agosta, *Chem. Rev.*, 1987, 87, 399-410