Cascade reactions in total synthesis[1]

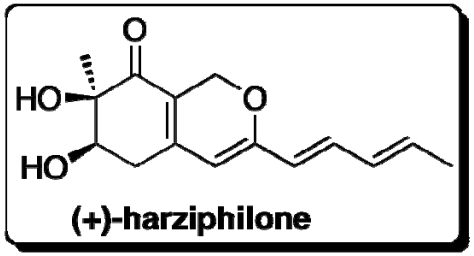
or

an organic chemist dream

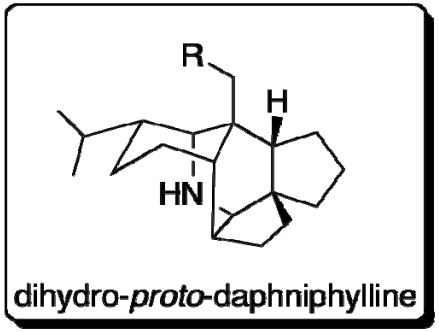
Fabien RODIER

1: Nicolaou *et al*. *Angew. Chem. Int. Ed*. **2006**, *45*, 7134
2: Andersen, E. A. *Org. Biomol. Chem*. **2011**, *9*, 3997

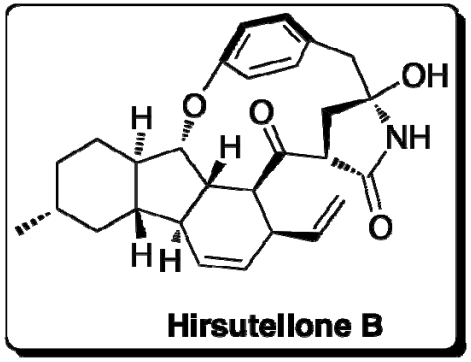
- Cascade reaction = growing field in organic chemistry
- Not an exhaustive report but a glimpse on 3 molecules



(+)-harziphilone



dihydro-*proto*-daphniphylline



Hirsutellone B

- Cascade for domino and consecutive process

Why doing cascade reactions in total synthesis?

- Significant intellectual challenge
- Atom economy
- Economy of time and labour
- Resource management
- Waste economy

« Green chemistry »

Why doing cascade reactions in total synthesis?

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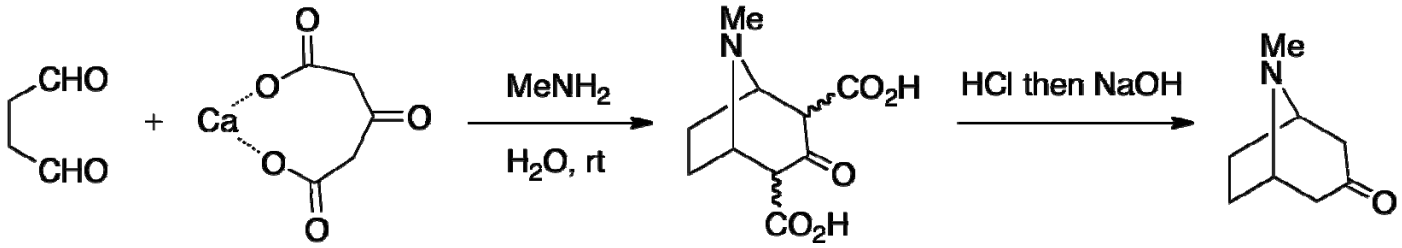
- Economy of time and labour
- Resource management
- Waste economy

To contribute to both the **SCIENCE** and **ART** of synthesis

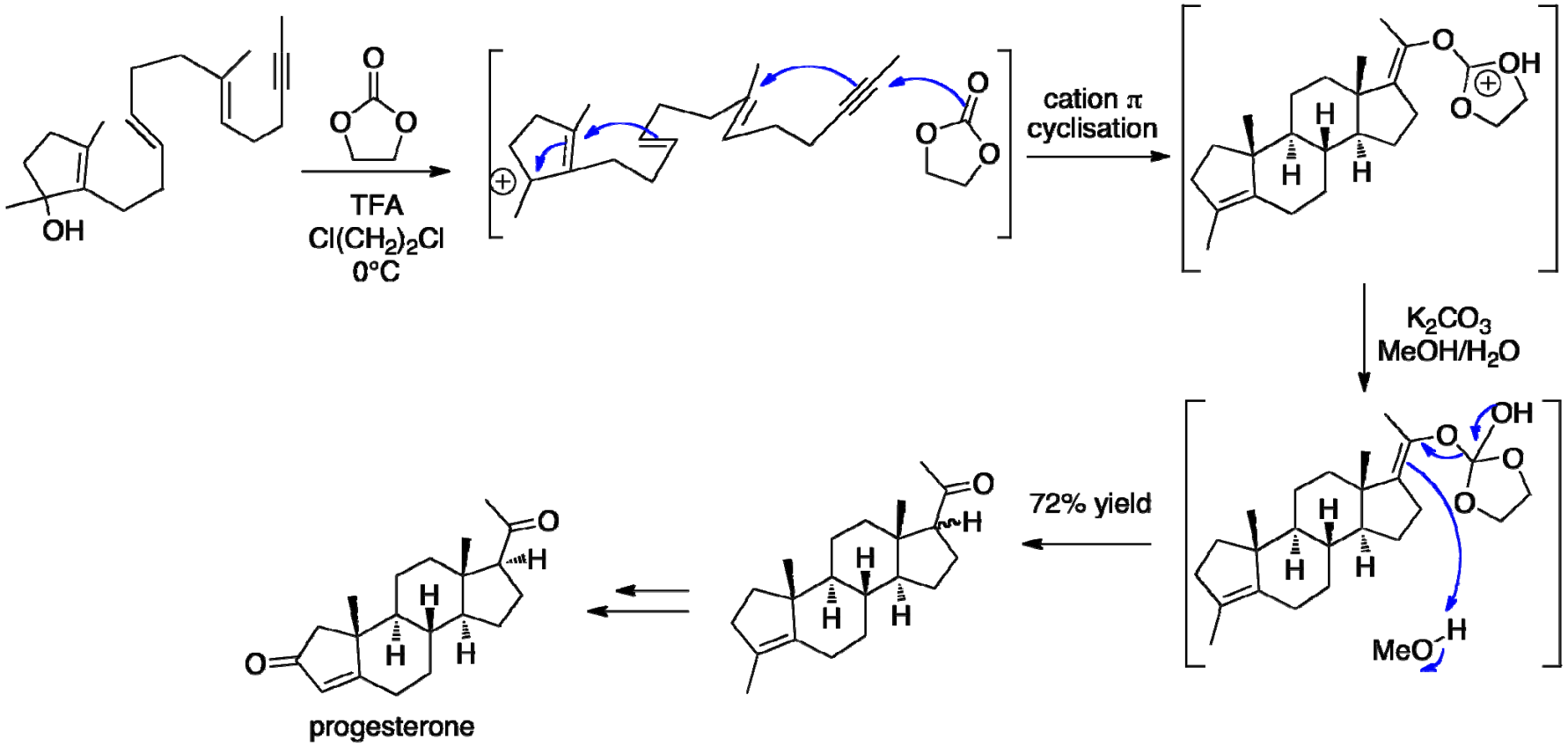
1917 = Robinson's one pot synthesis of tropinone……



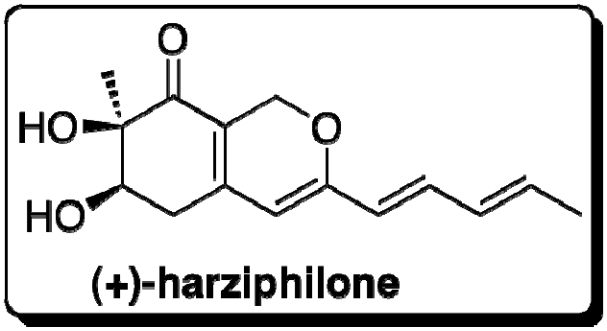
- 1917 = Robinson's one pot synthesis of tropinone……

- Organic chemistry were passionated about cascade reactions...

  -> 1971 = total synthesis of progesterone by Johnson *et al*



Total synthesis of (+)-harziphilone[1]

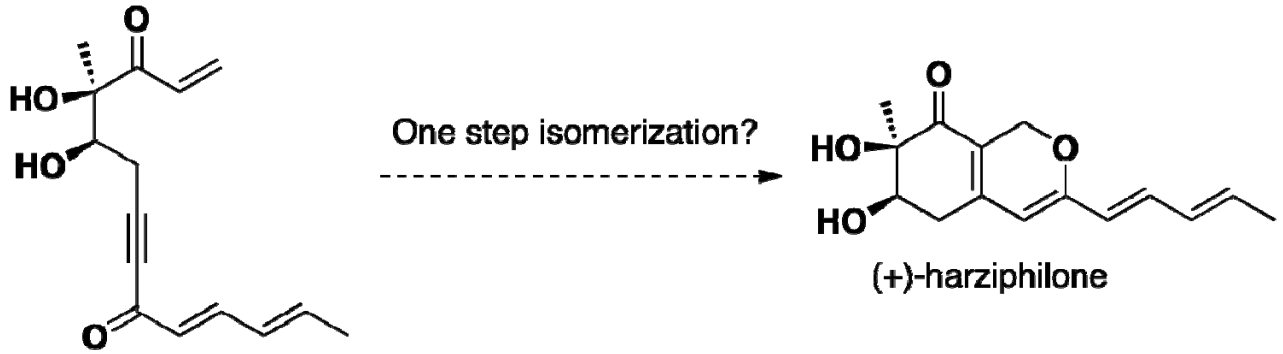


Biology = action against HIV

Chemistry =

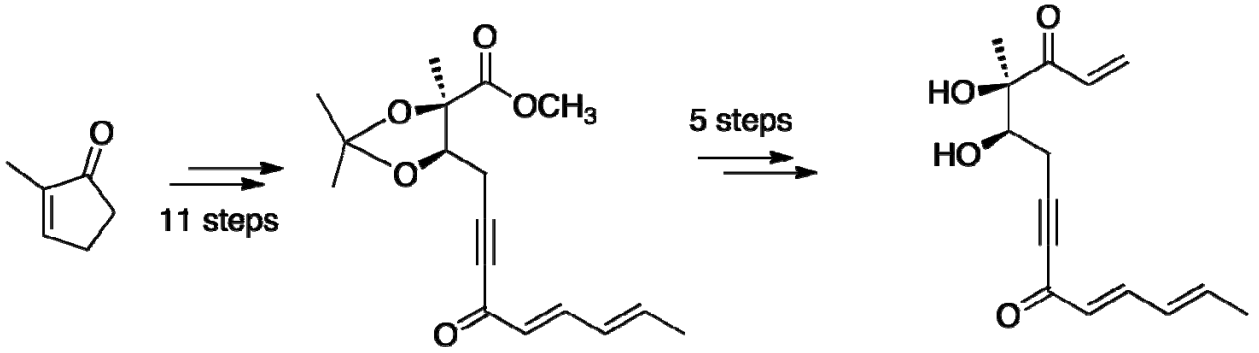
- 15 carbon atoms
- two six-membered ring systems
- two contiguous hydroxyl bearing stereocenters
- pentadienyl side system

Strategy

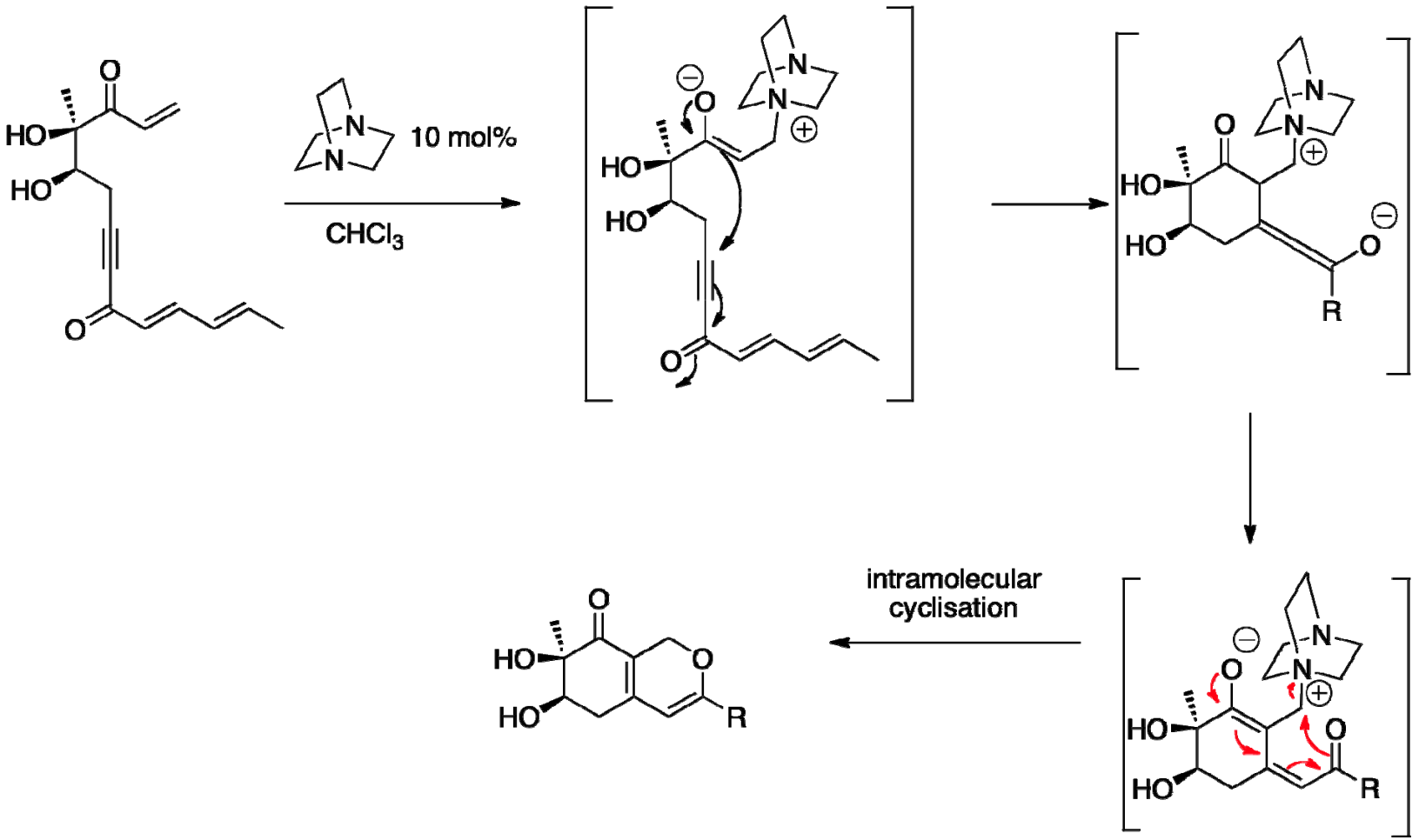


1: Sorensen *et al. Proc. Natl. Acad. Sci*. **2004**, 12064

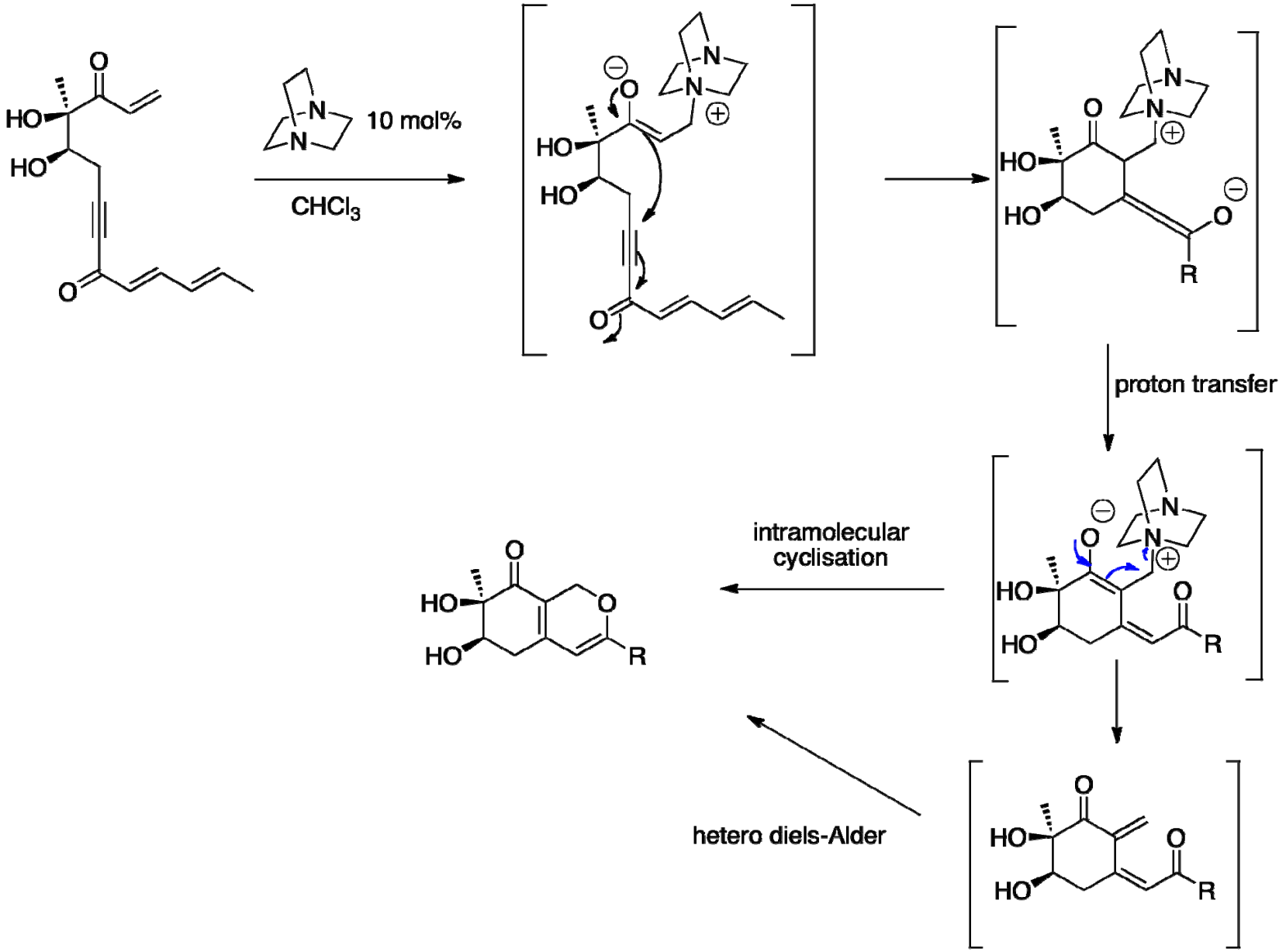
Synthetic approach



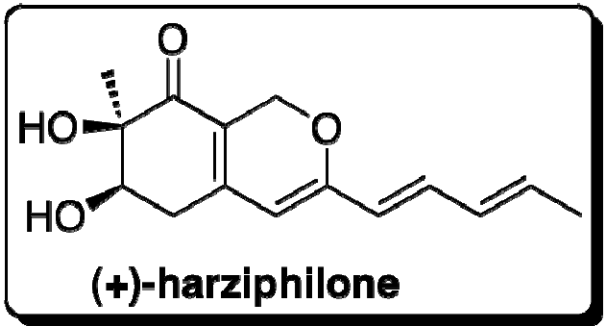
Nucleophilic cascade



Nucleophilic cascade

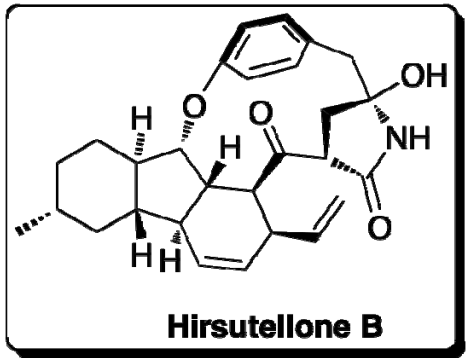


Conclusion: total synthesis of (+)-harziphilone



17 steps
one reaction cascade: 2 cycles in one step
This strategy allows further biological studies

Total synthesis of Hirsutellone B



Hirsutellone B

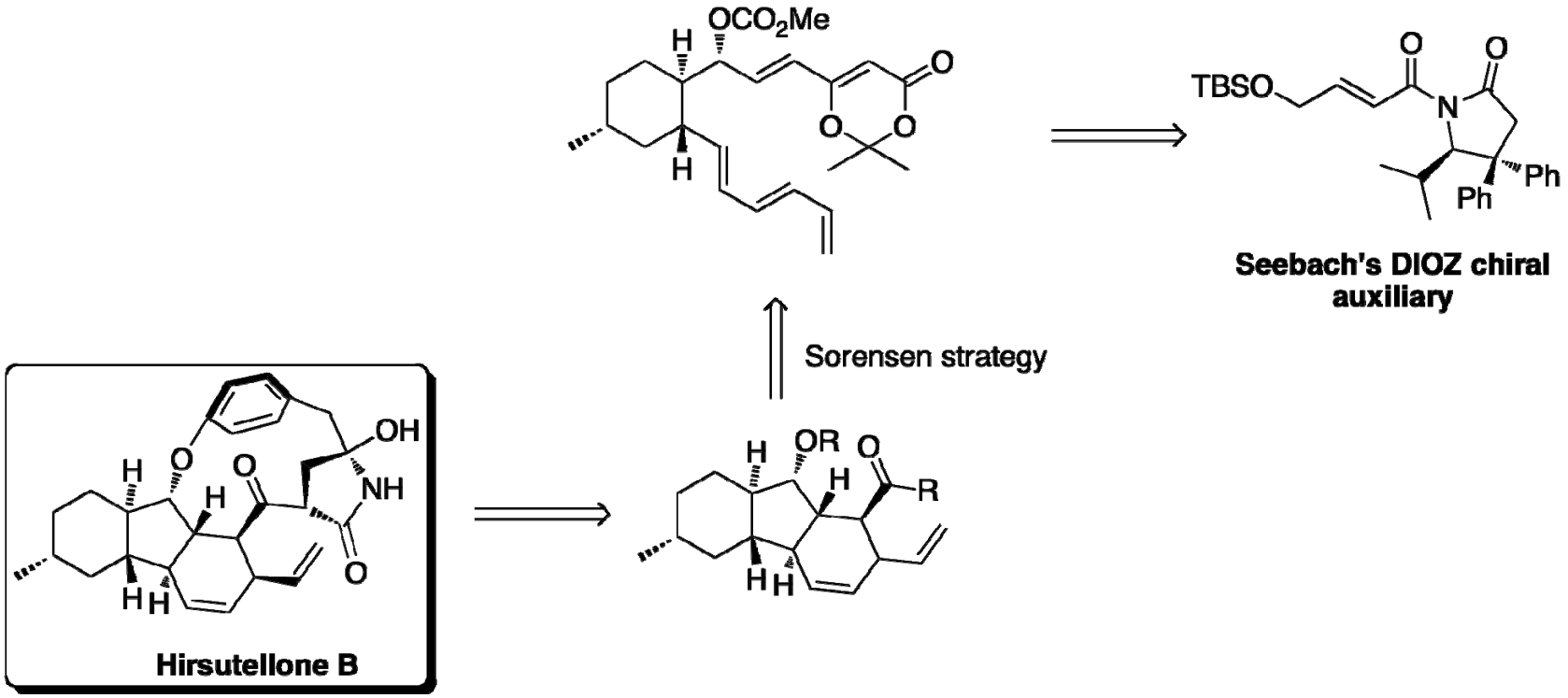
Biology =

- belong to a growing class of fungal secondary metabolites
- antifungal and antibiotic activities
- impressive activity against *Mycobacterium tuberculosis*

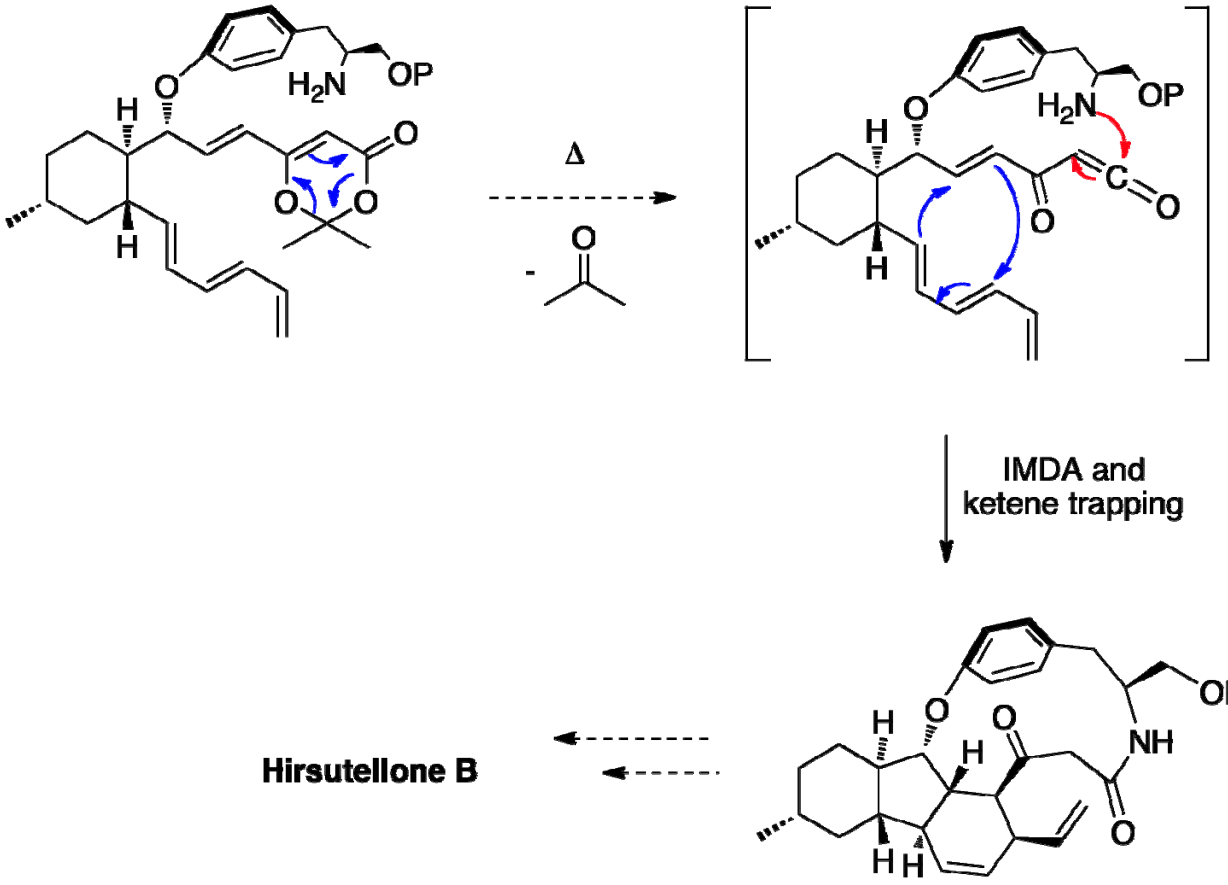
Chemistry =

- unique structural features
- (6,5,6)-fused tricyclic core
- δ-lactam or succinimide containing moiety
- 12- or 13-membered *p*-cyclophane structural motif with 10 stereogenic centers and aryl ether linkage

2 groups used almost the same strategy: Nicolaou and Sorensen



Sorensen strategy :[1]

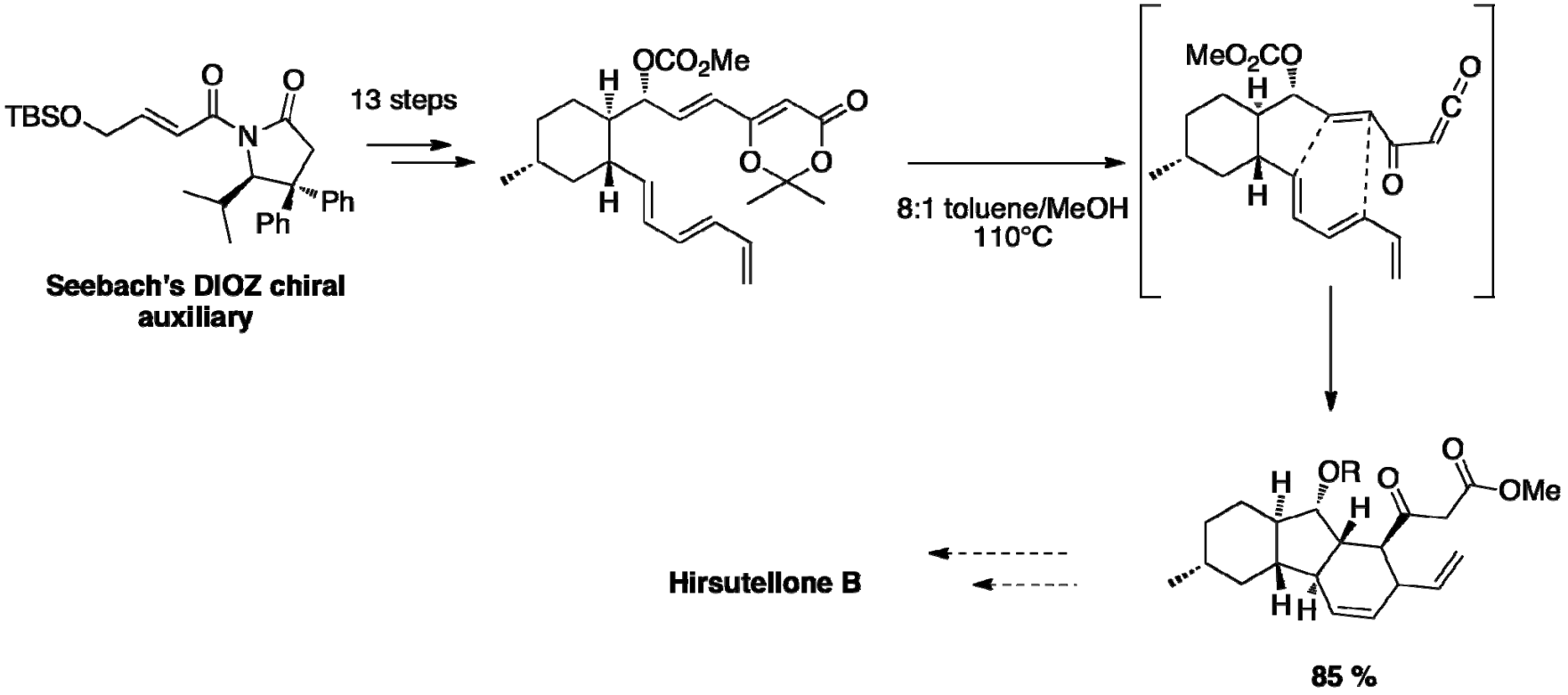


- Impressive cascade reaction
- First tandem ketene trapping and IMDA

- reactivity of intermediate 2

1: Sorensen *et al*. *Org. Lett*. **2009**, 701

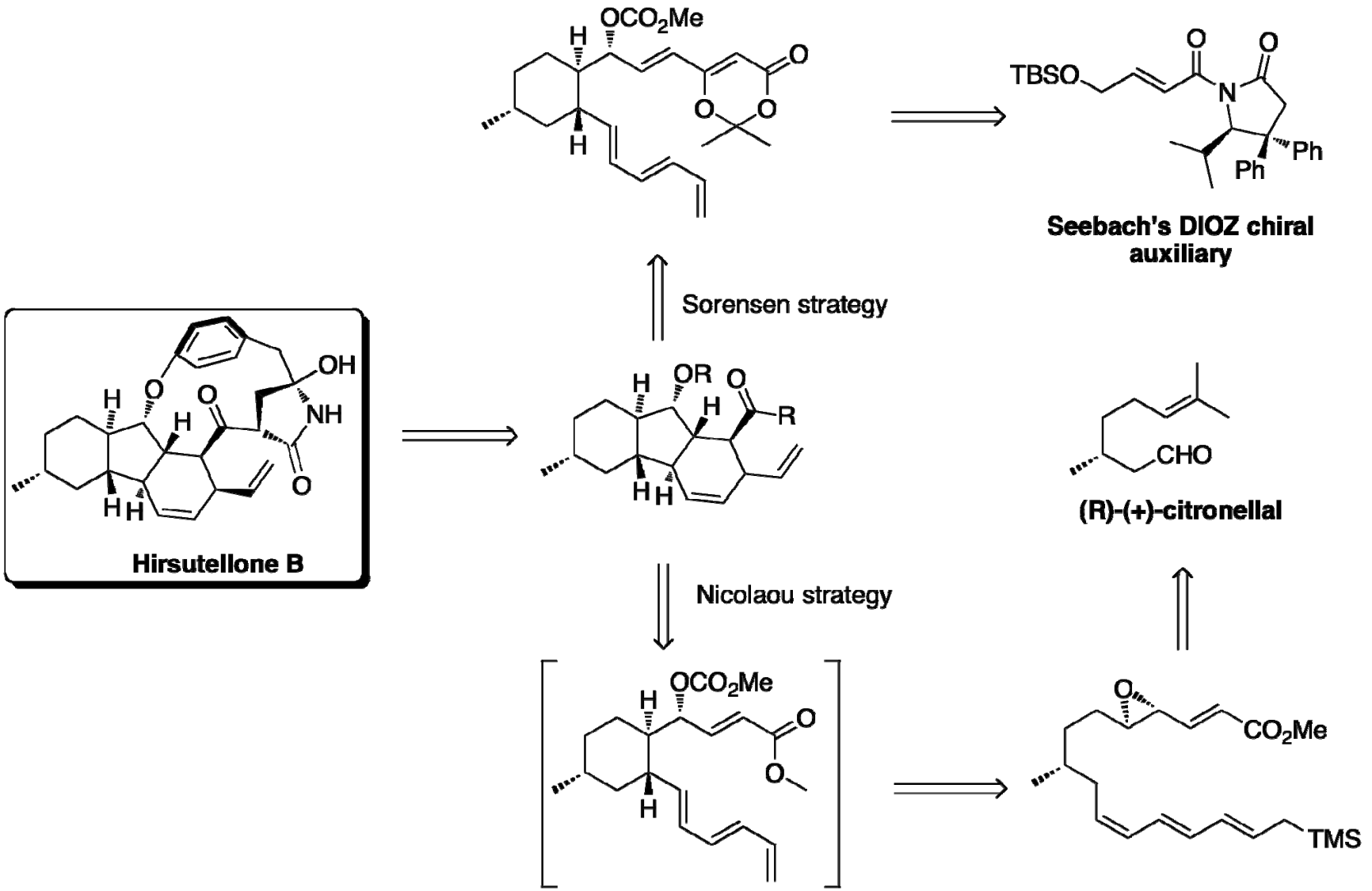
Model study:



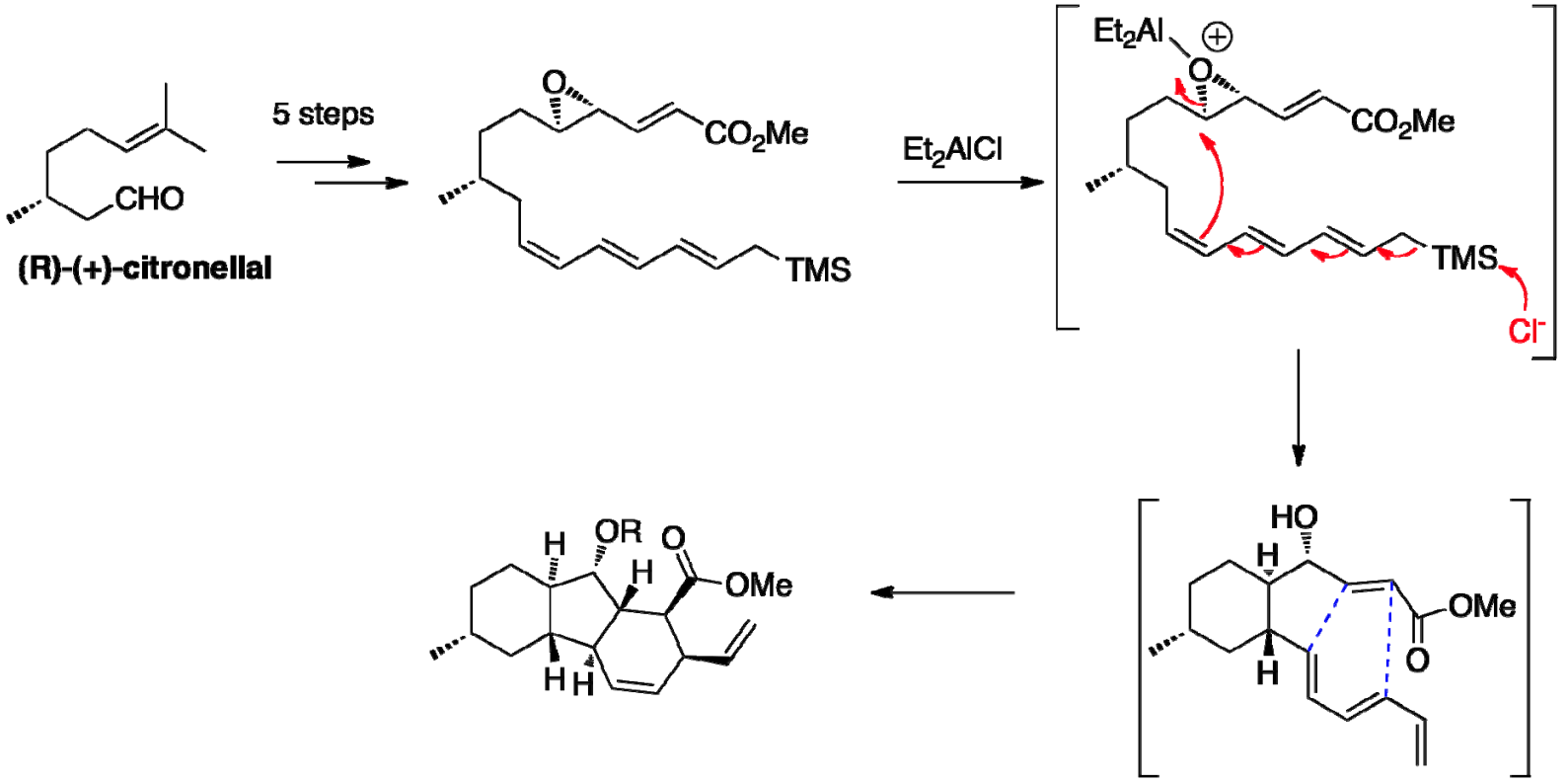
Seebach's DIOZ chiral auxiliary

85 %

Formation of the tricyclic core
Only one diastereomer
3 contiguous stereogenic centers

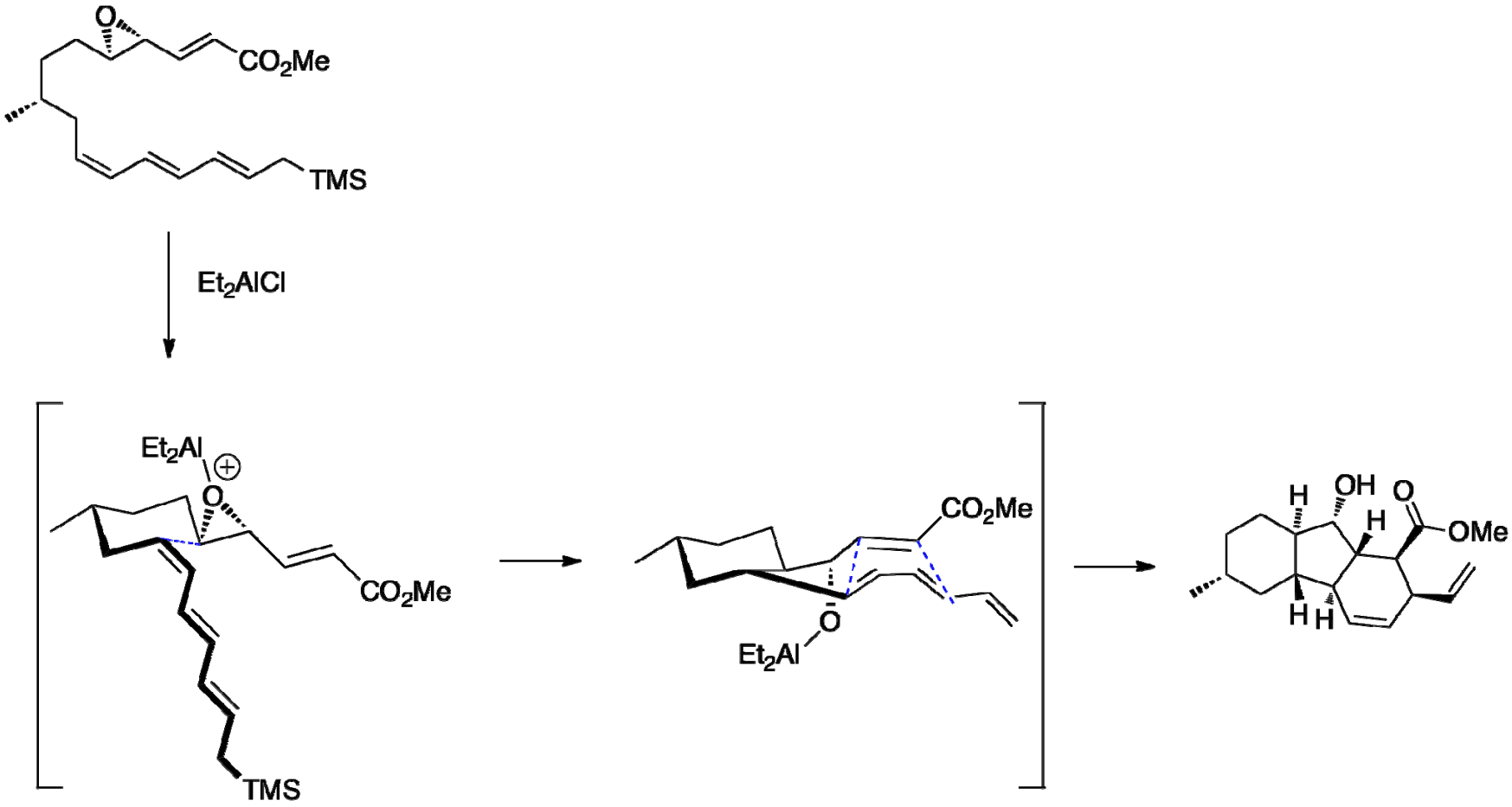

OCO2Me
H
O
O
O
H
TBSO
O
O
N
Ph
Ph
Seebach's DIOZ chiral auxiliary
Sorensen strategy
OH
O
H
O
NH
H
H
O
Hirsutellone B
H
OR
O
H
R
H
H
CHO
(R)-(+)-citronellal
Nicolaou strategy
OCO2Me
H
O
O
H
O
CO2Me
TMS

Nicolaou strategy : First cascade synthesis of the tricyclic core[1]

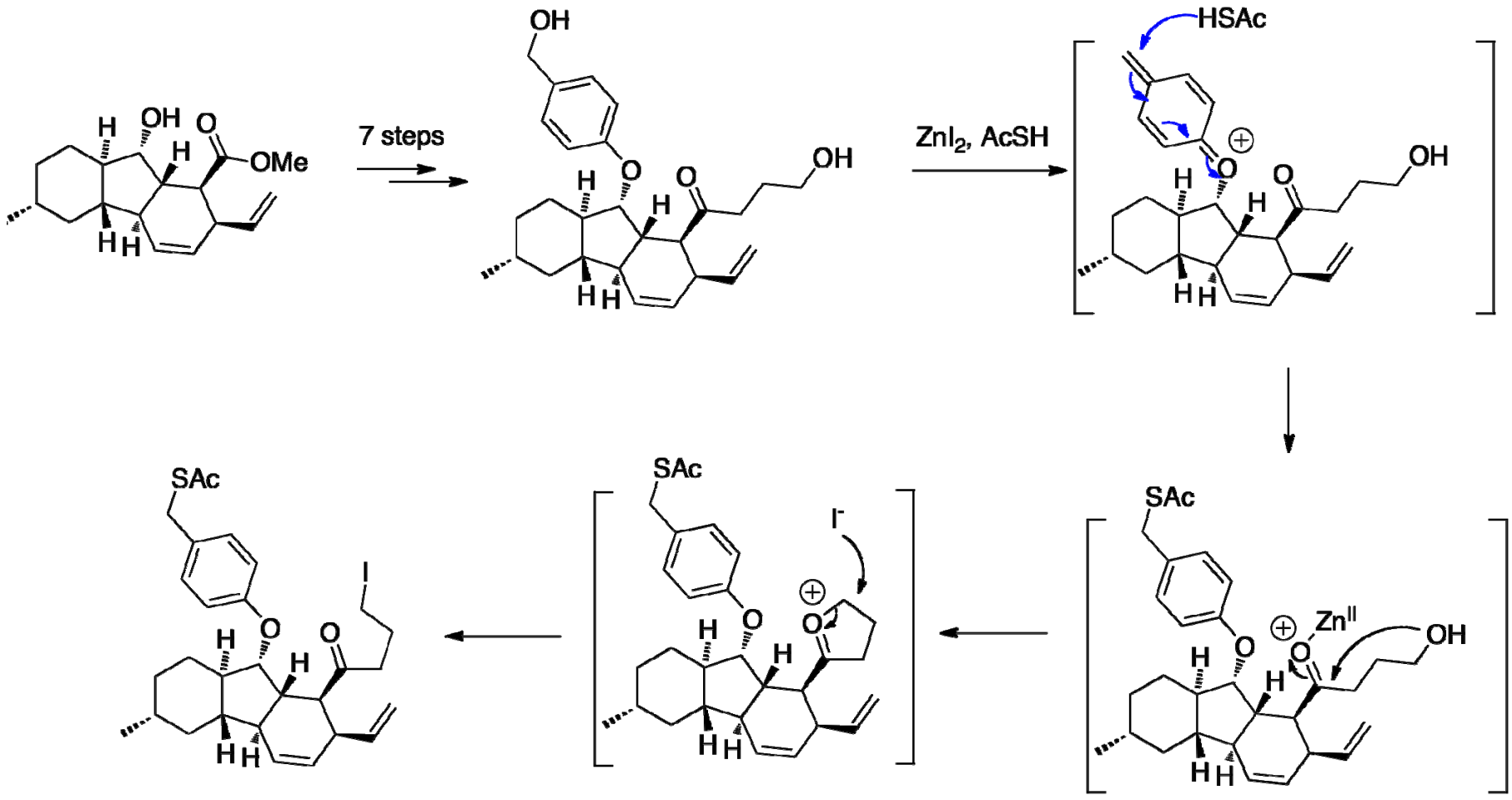


1: Nicolaou *et al*. *Angew. Chem. Int. Ed*. **2009**, 6870

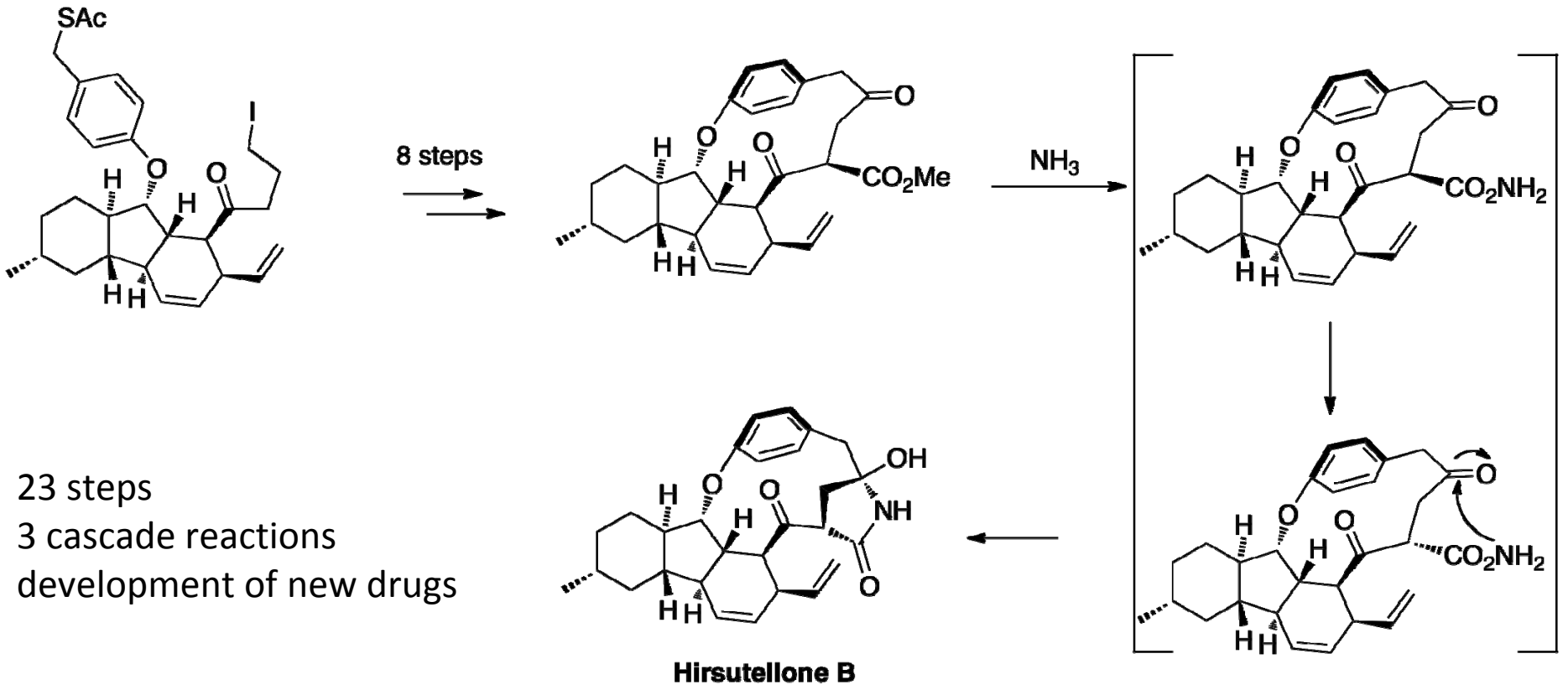
Transition state



Nicolaou strategy : 2nd cascade



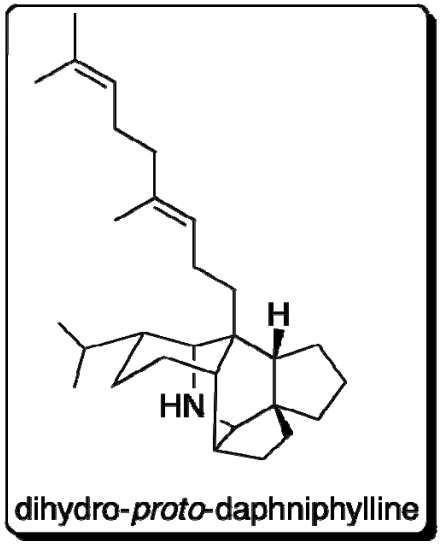
Nicolaou strategy : 3rd cascade



Hirsutellone B

23 steps
3 cascade reactions
development of new drugs

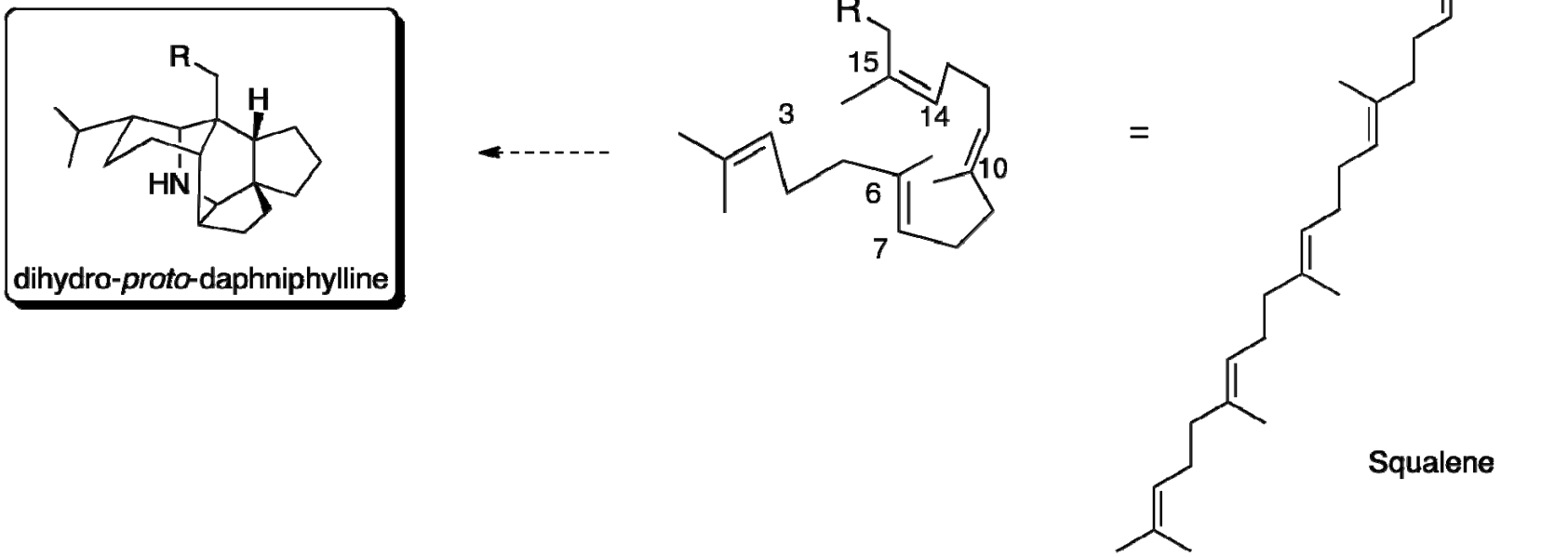
Total synthesis of dihydro-*proto*-daphniphylline[1]



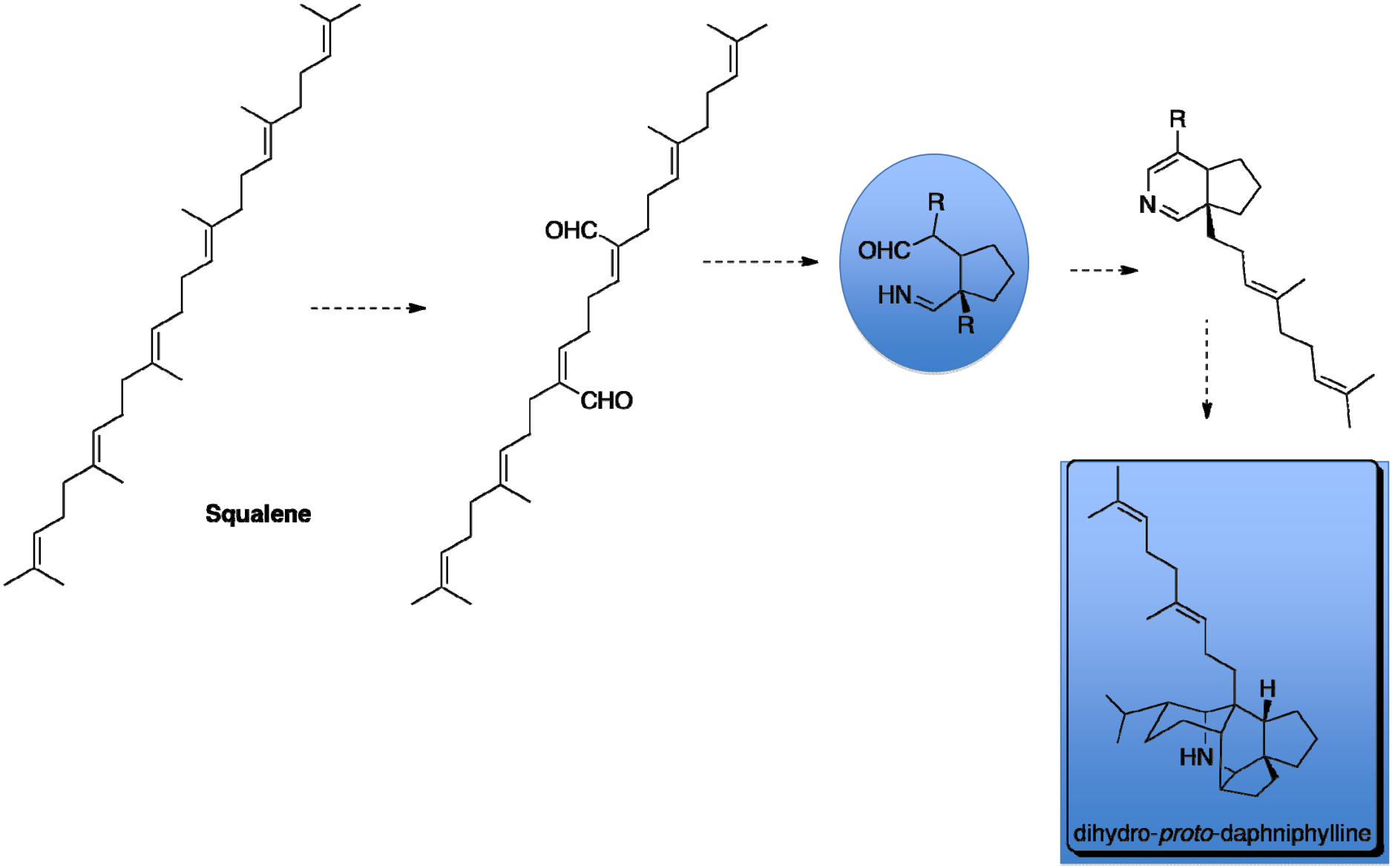
Belong to a family of *Daphniphyllum* alkaloïd
Isolated from tree of *Daphniphyllum macopodum*
4 fused membered rings
8 stereogenic centers

1: Heathcock, C. H. *Proc. Natl. Acad. Sci*. **1996**, 14323

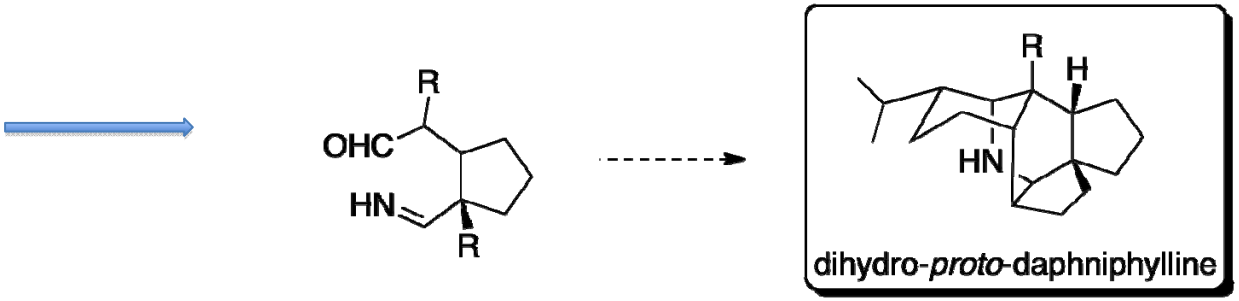
Biosynthetic approach: this molecule comes from squalene?????

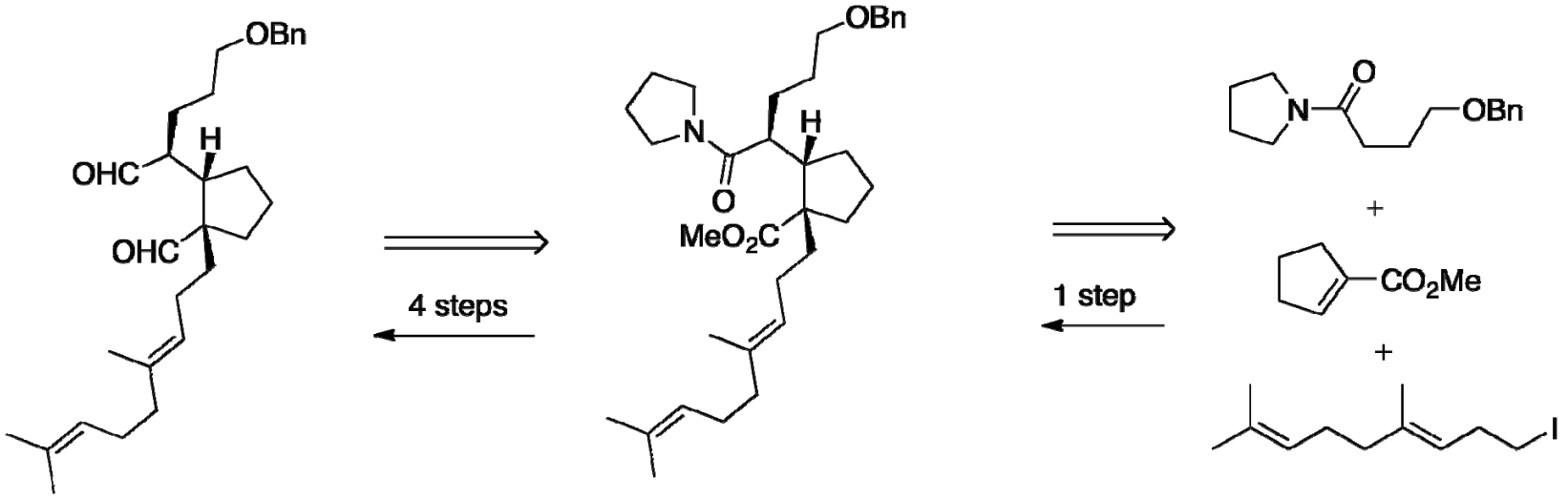


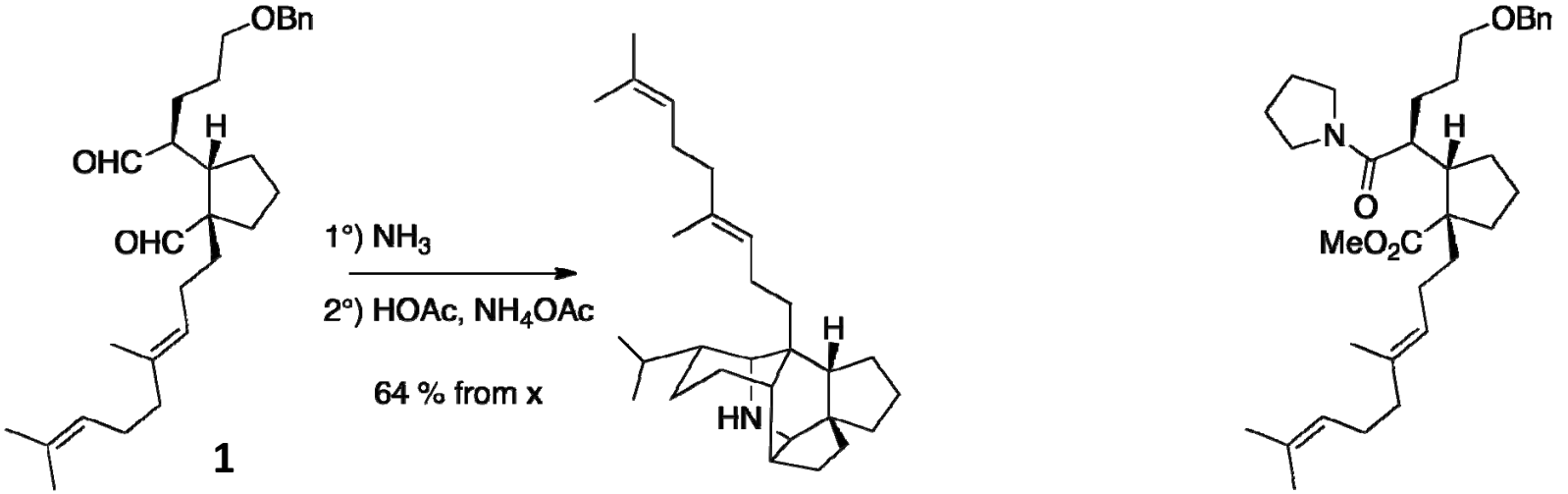
More precisely….



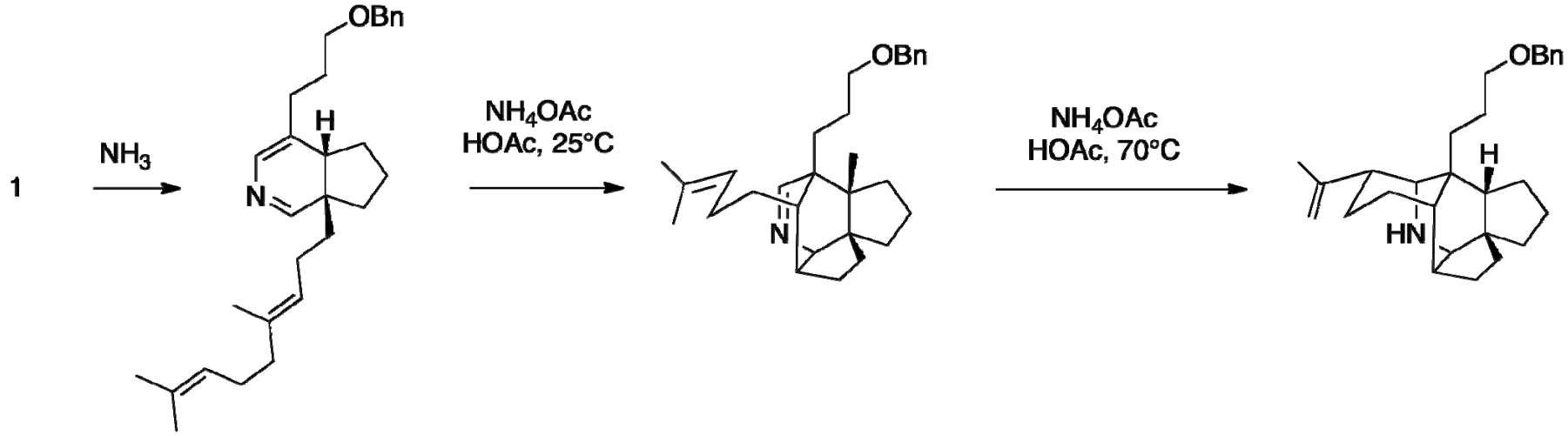
Check the feasibility of the process



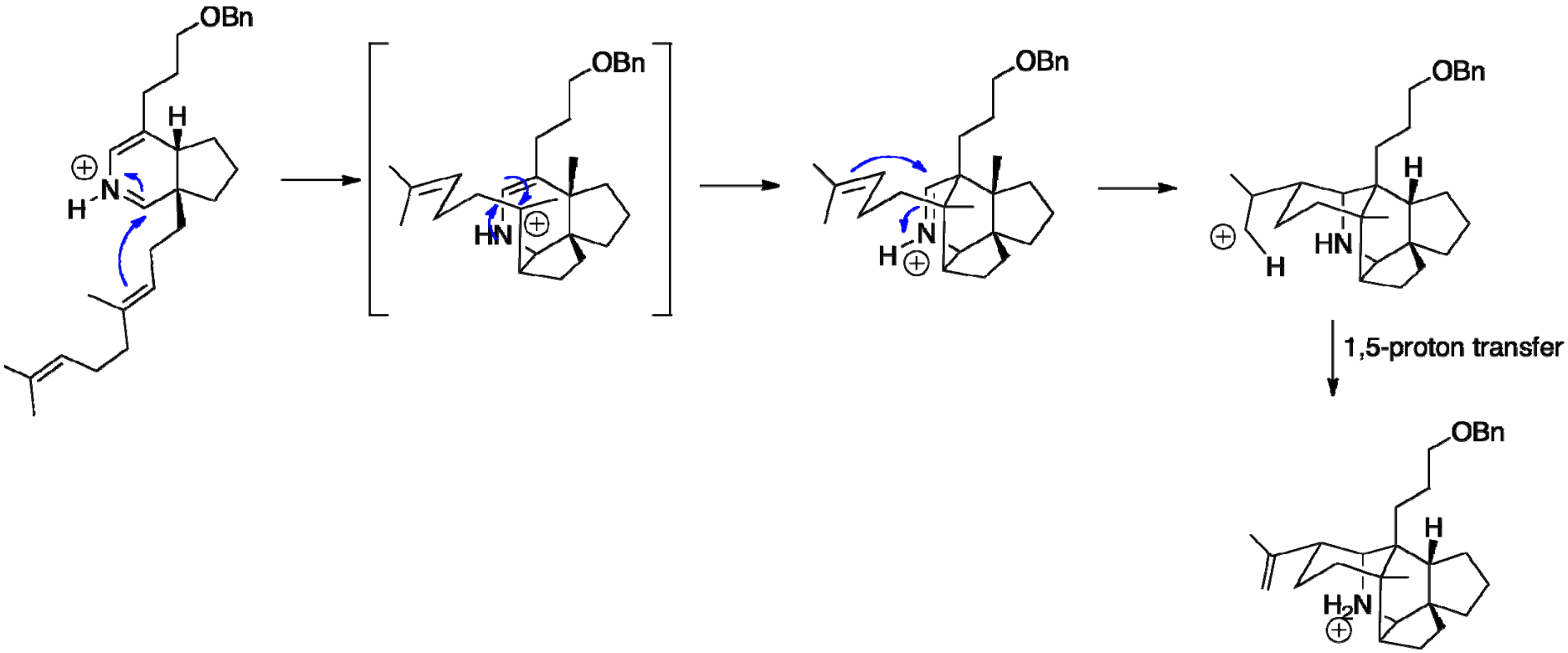



OBn
H
OHC
OHC
1
1°) NH3
2°) HOAc, NH4OAc
64 % from x
H
HN
OBn
N
H
O
MeO2C

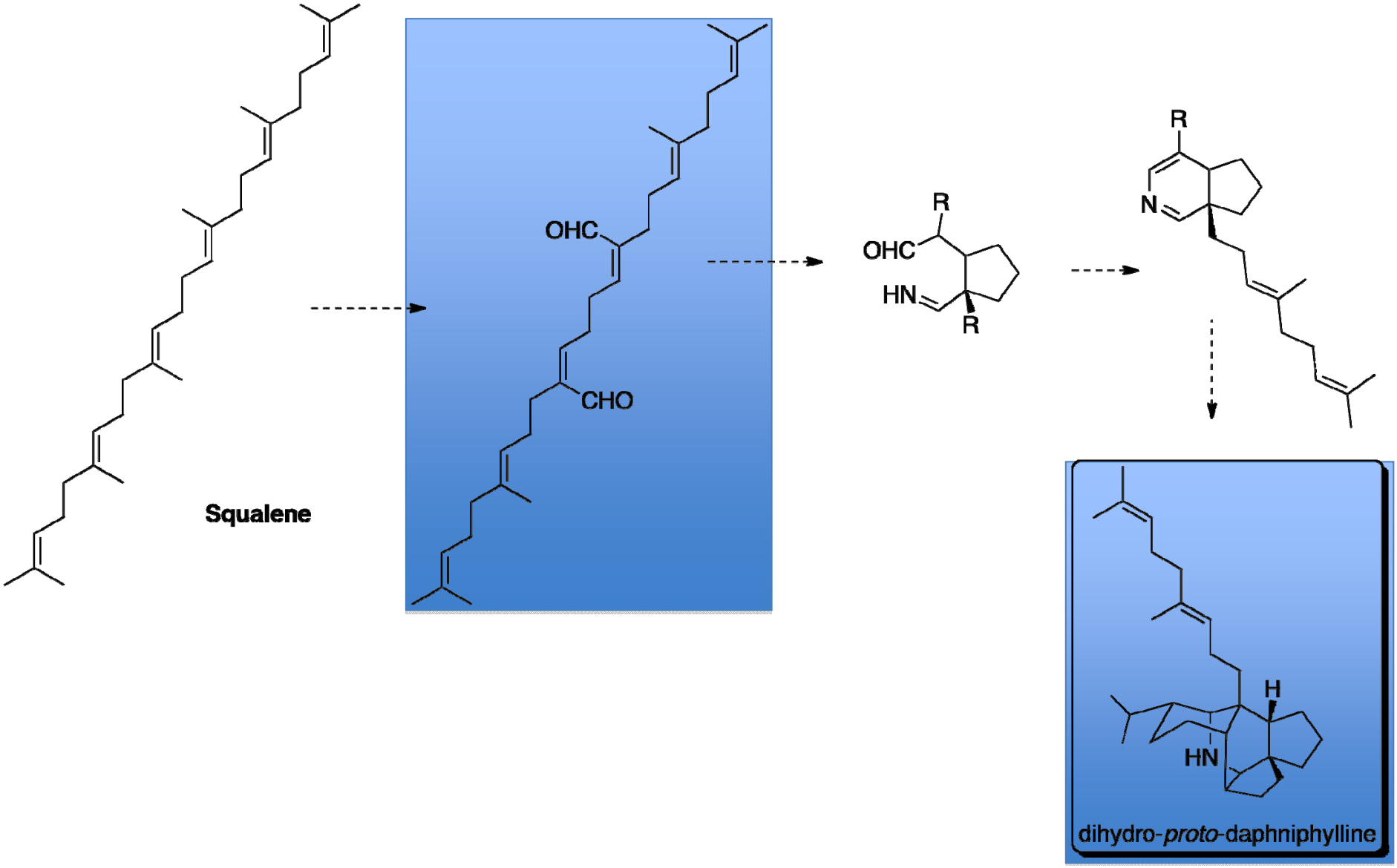
Mechanism:

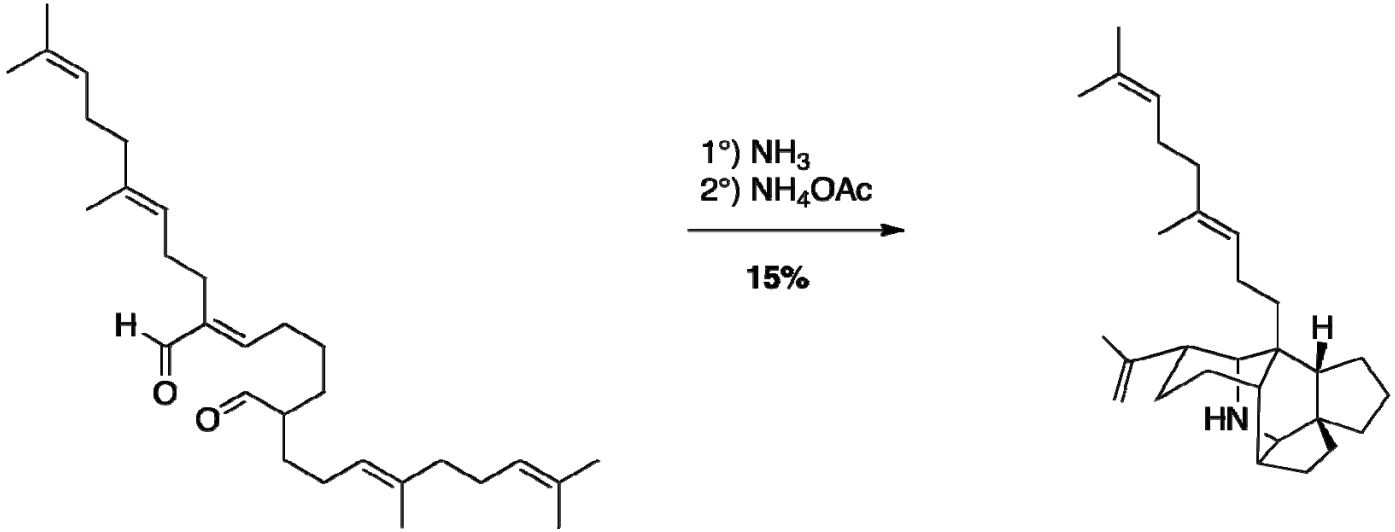

1
NH3
OBn
H
N
NH4OAc
HOAc, 25°C
OBn
N
NH4OAc
HOAc, 70°C
OBn
H
HN

More precisely..

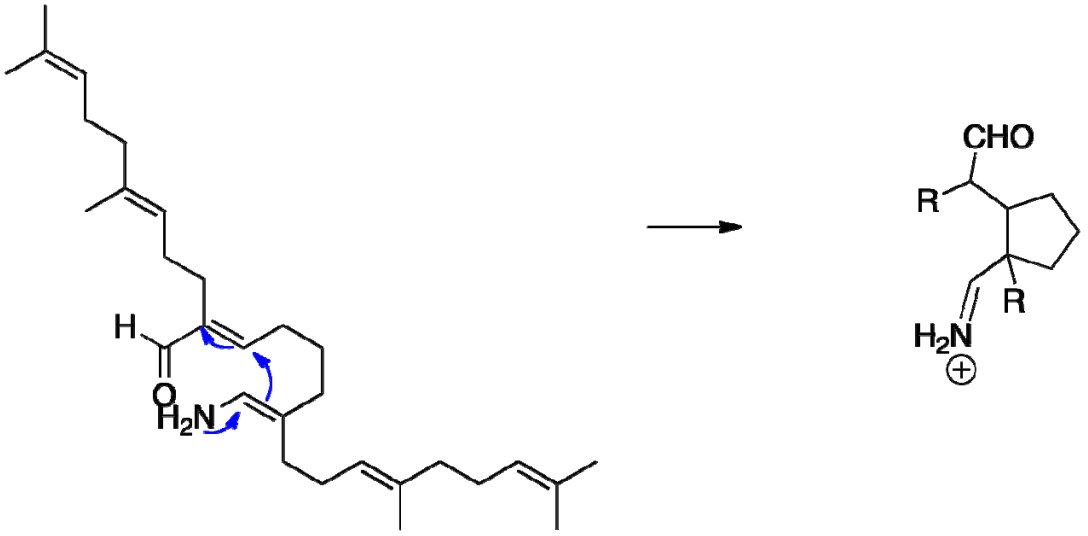


More precisely….



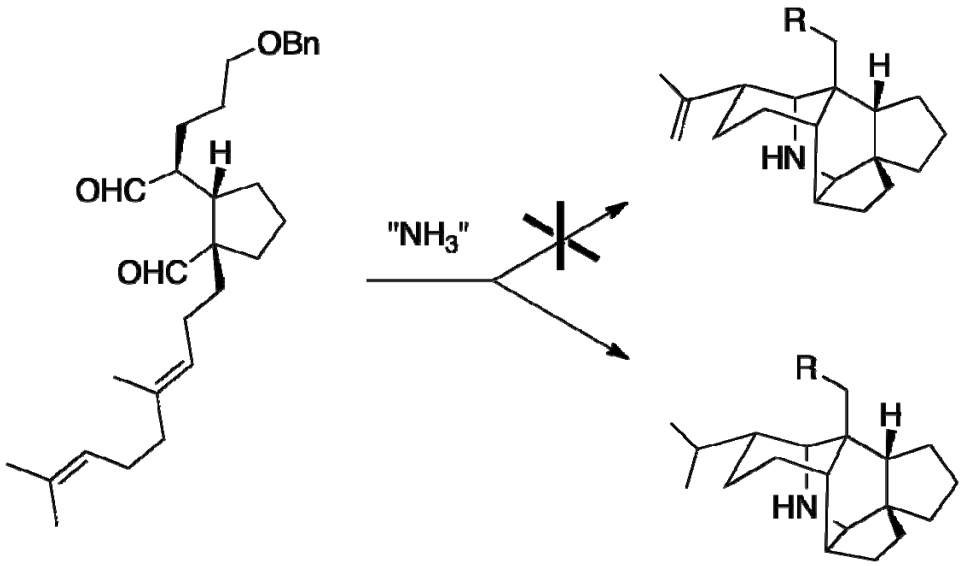


Problem comes from the first step…..

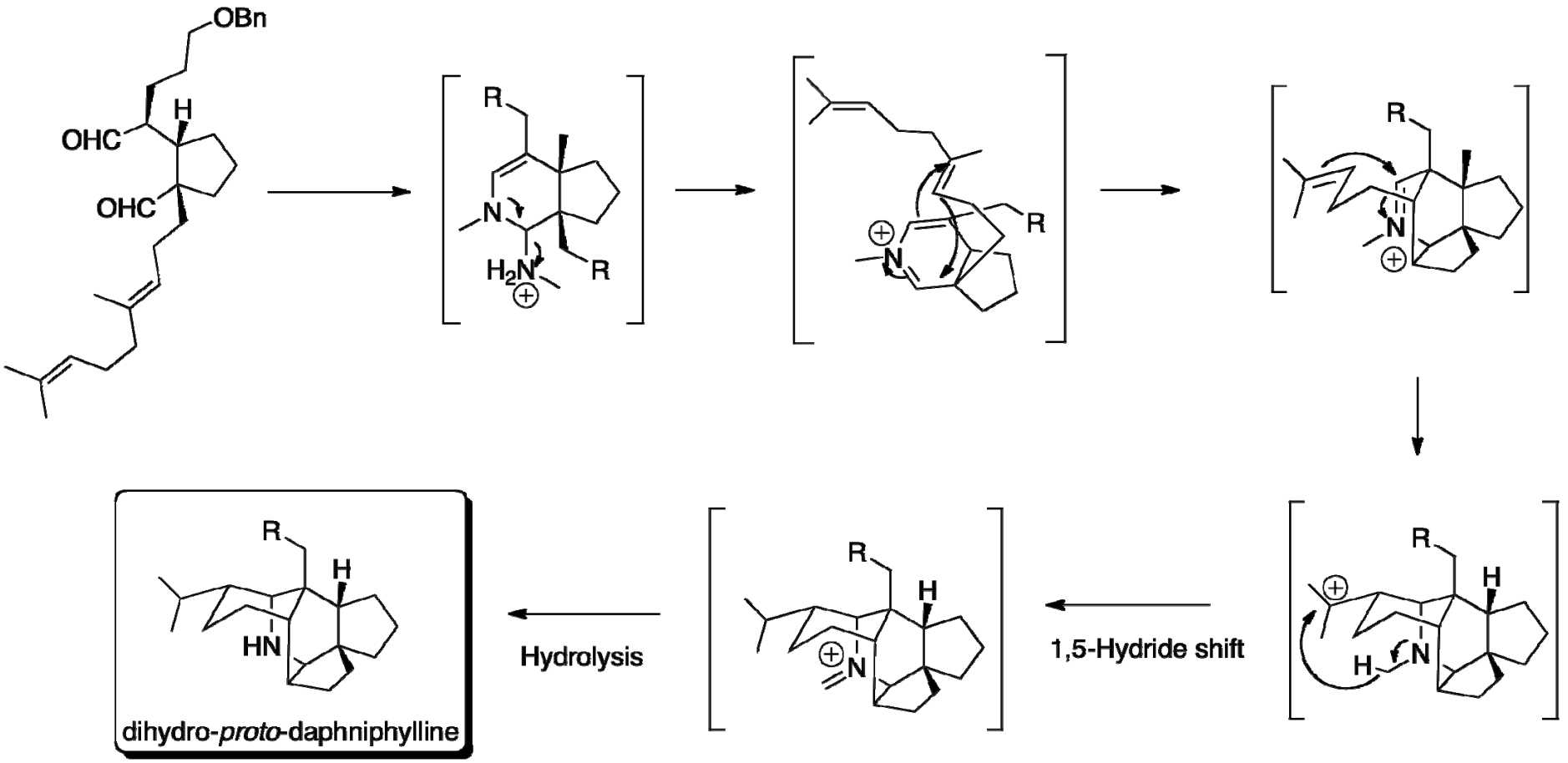


Serendipity…….

The solution arises from a student's mistake…….



Mechanism:


OBn
H
OHC
OHC
R
N
H2N
R
R
N
R
N
R
H
N
1,5-Hydride shift
R
H
N
Hydrolysis
R
H
HN
dihydro-proto-daphniphylline

Conclusion

- Cascade reactions= useful tool in organic chemistry
- Cascade reactions= must be developped…….

Thanks for your attention