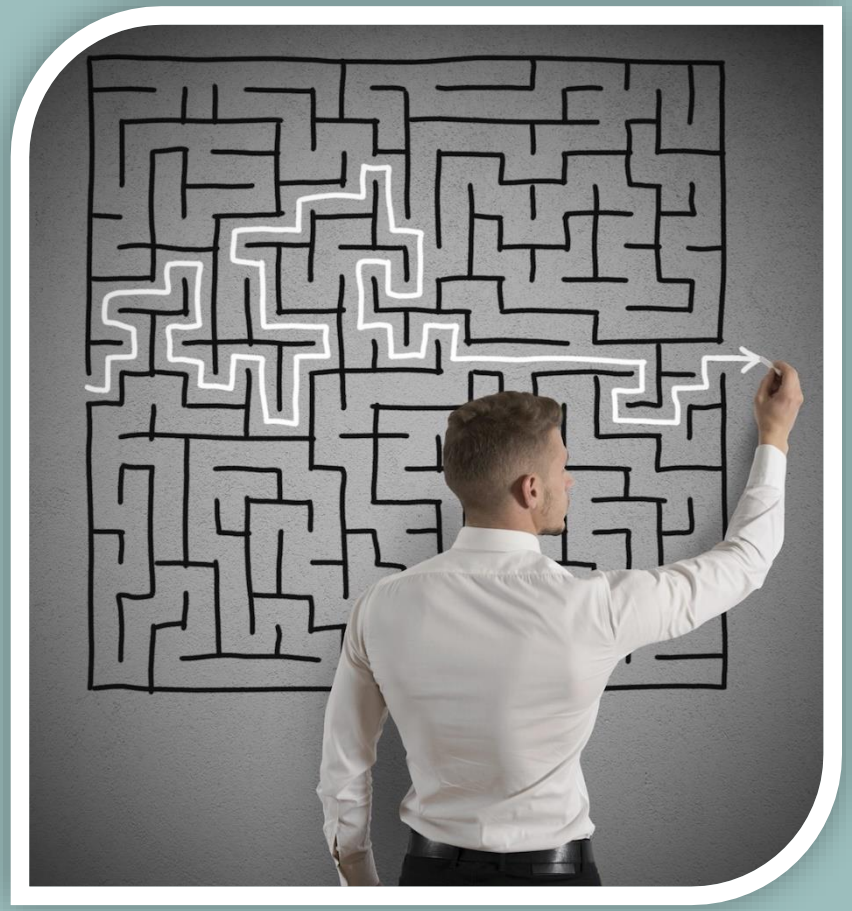


STORY OF RYANODOL

FROM 1943 TO 2018

Beltran Raphaël

CONTENT

- Introduction
- Isolation and Structure Determination of (+)-ryanodol
- Total Synthesis of ryanodol
- Summary
  - The presentation will not focus on the bioactivity of ryanodol.

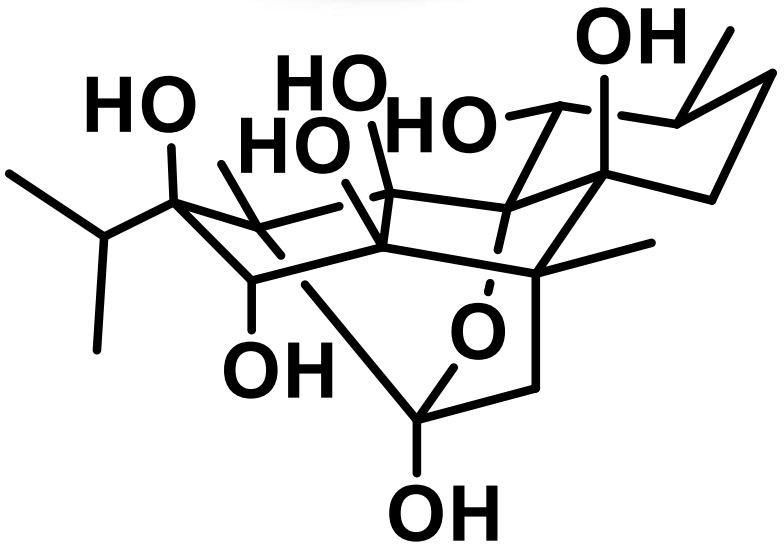
INTRODUCTION

- Among the most highly oxidized & synthetically challenging diterpenoid reported to date.

- Sterically congested pentacyclic core with eleven contiguous stereocenters

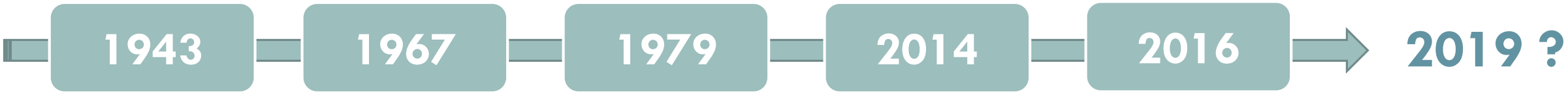
- 5 free hydroxyl group in the same face of the molecule.

- Unstable hemiketal, three methyl groups & one isopropyl group.



(+)-ryanodol

STORY LINE



ISOLATION AND STRUCTURE DETERMINATION

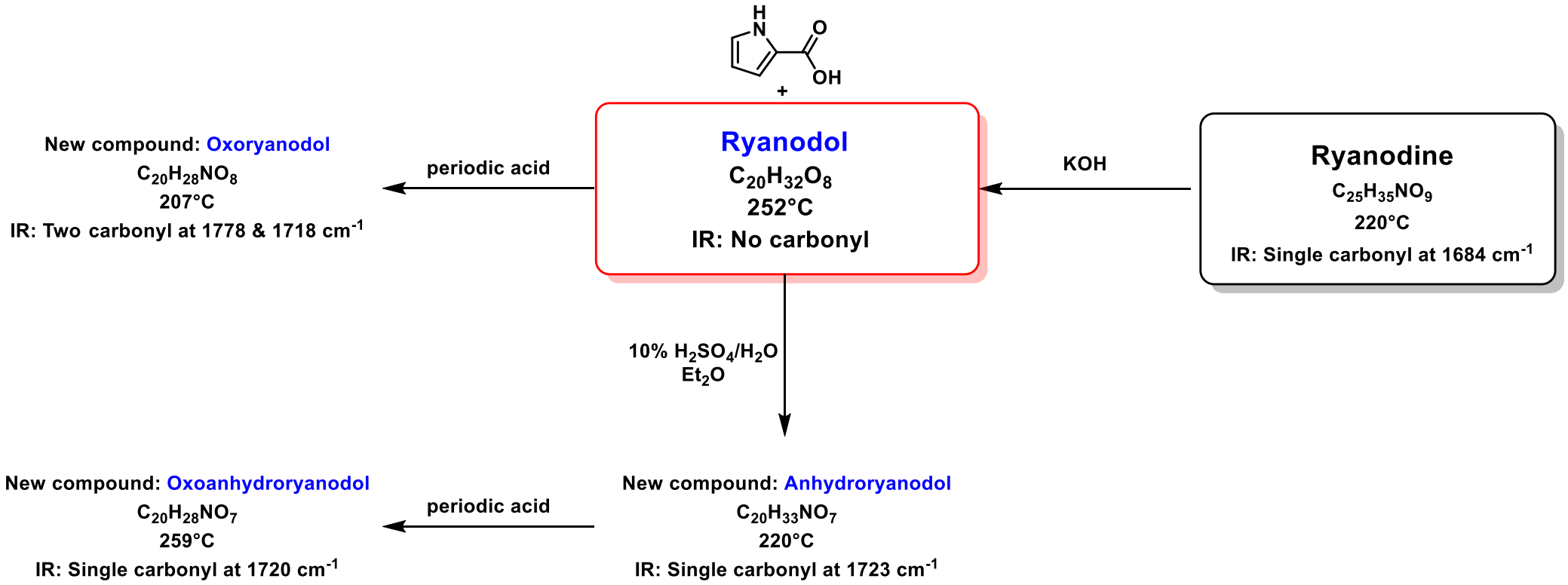
- In 1943 collaborators from Merck and the Department of Entomology at Rutgers University found that **extract** from the stem and root of Ryania Speciosa Vahl were very active as potent insecticides.

- The crude extract was crystallized from ether until a pure product was obtained: Ryanodine.
  - M.p. 219-220°C; $[\alpha]_D$ +26° in methanol. ~ 700 times more active than the stem wood of Ryania speciose Vahl.

- What about the structure?
  - Presence of a pyrrole-like ring system.
  - Neutral to litmus and form no precipitates with other common alkaloids.
  - Determination of formula: $C_{25}H_{33}NO_9$ or $C_{26}H_{37}NO_9$ with 6 or 7 active hydrogens.

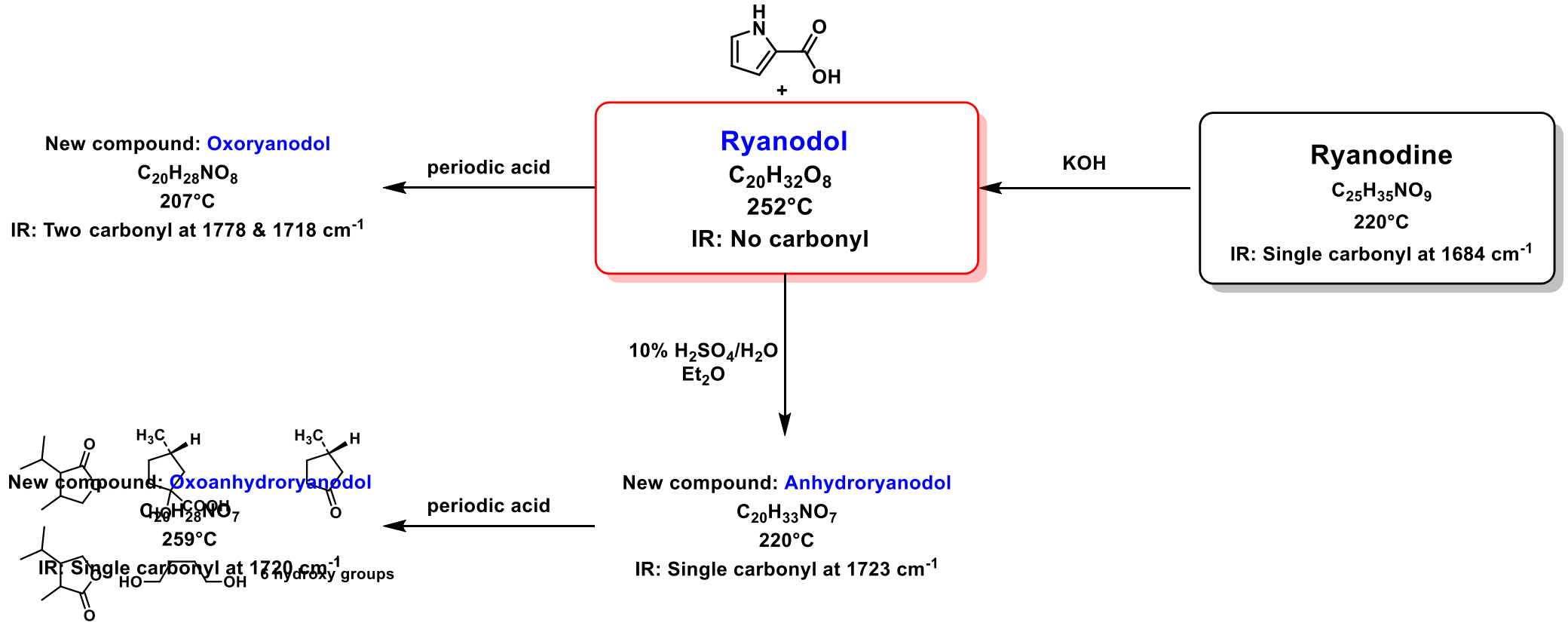
ISOLATION AND STRUCTURE DETERMINATION

- 1951- K. Wiesner contribution



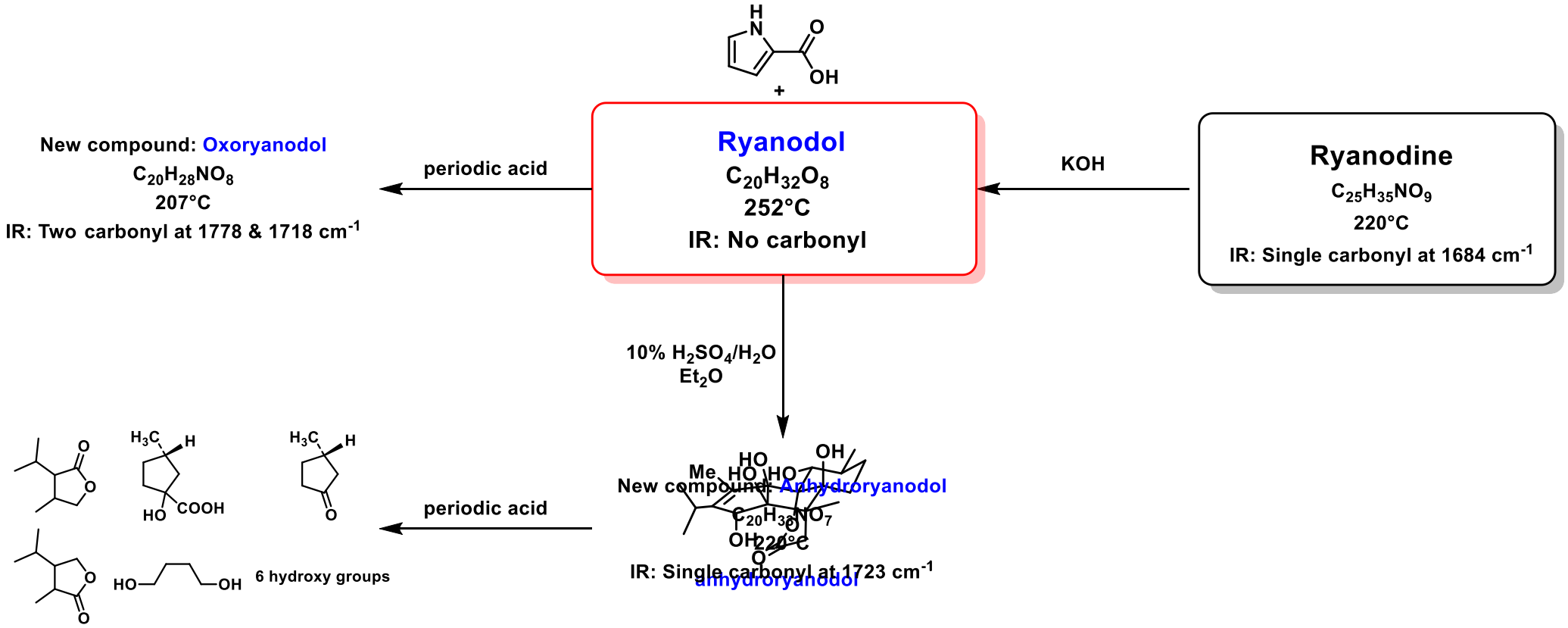
ISOLATION AND STRUCTURE DETERMINATION

- 1951- K. Wiesner contribution
- In 1960 cleavage of oxoanhydroryanodol into several fragments



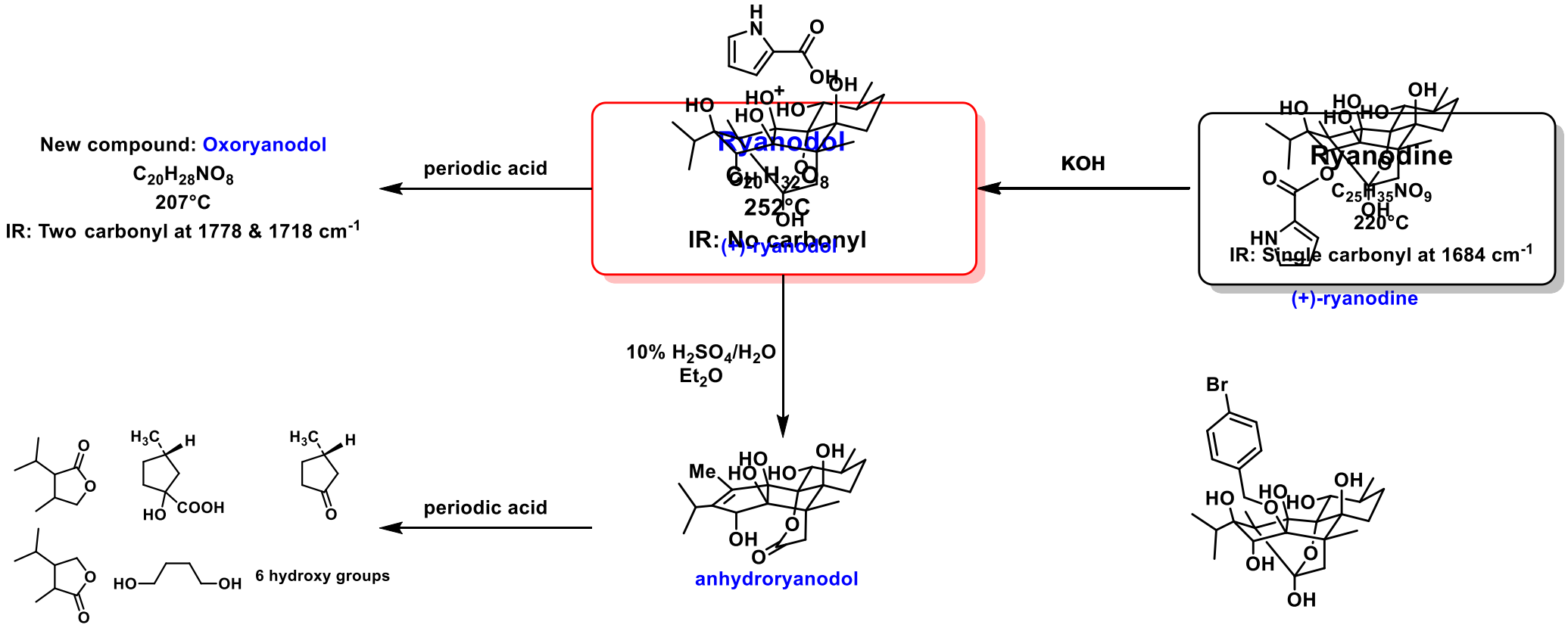
ISOLATION AND STRUCTURE DETERMINATION

- 1951- K. Wiesner contribution
- In 1960 cleavage of oxoanhydroryanodol into several fragments
- In 1962 he solved the structure of anhydroryanodol.



ISOLATION AND STRUCTURE DETERMINATION

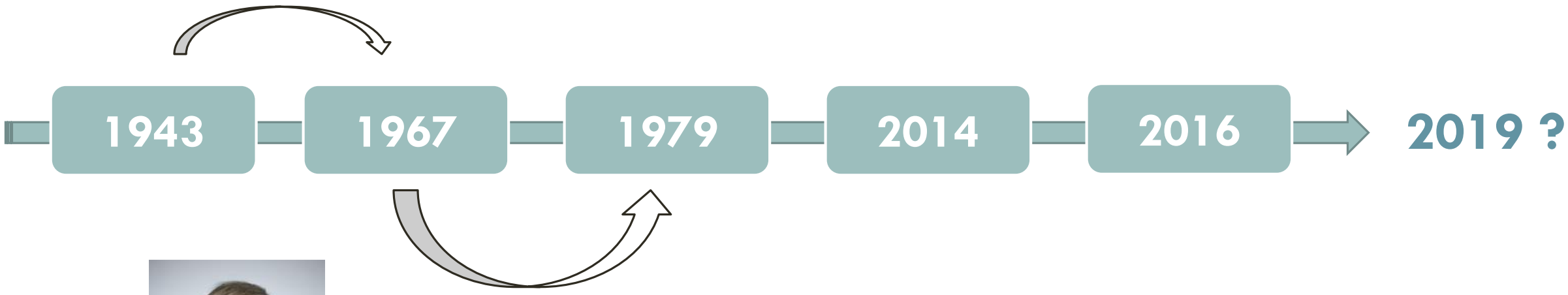
- 1951- K. Wiesner contribution
- In 1960 cleavage of oxoanhydroryanodol into several fragments
- In 1962 he solved the structure of anhydroryanodol.
- In 1967 he solved the structure of ryanodine



In 1972 Xray of p-bromobenzyl of ryanodol

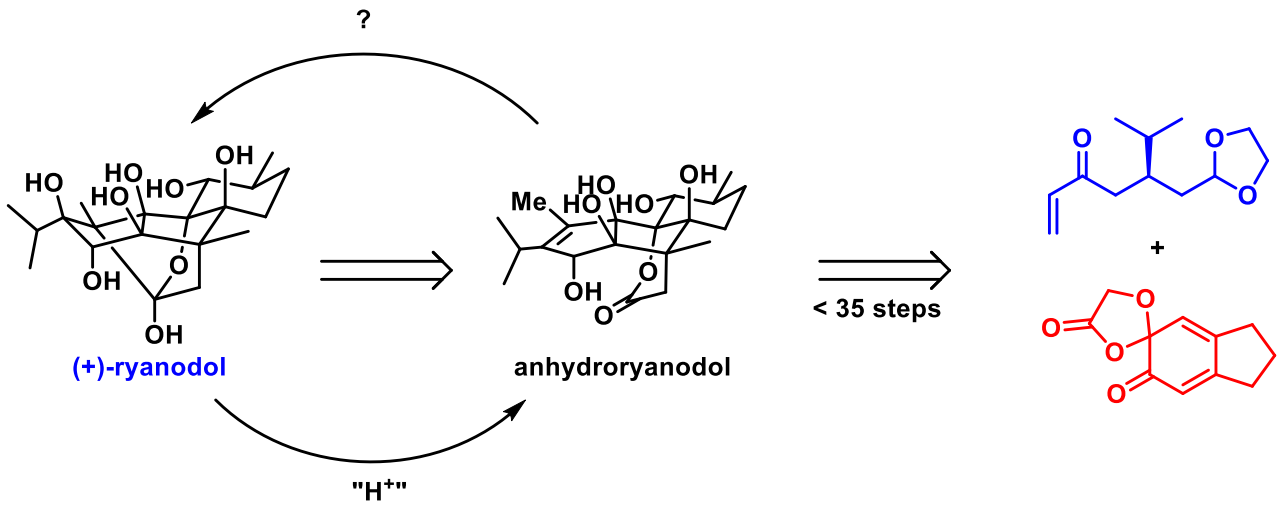
STORY LINE

24 years from
isolation to
Structure determination

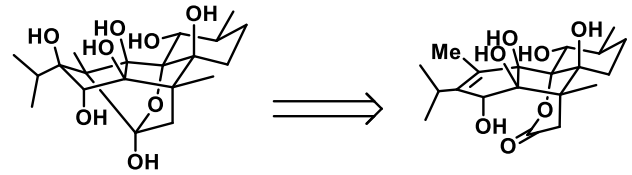


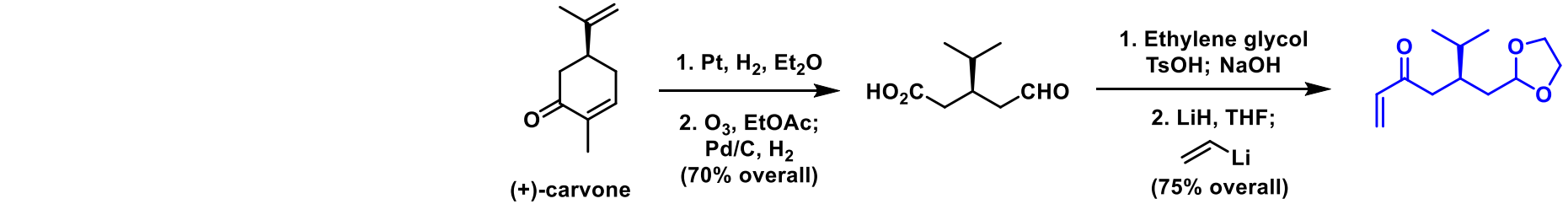
1979. Prof. Pierre Deslongchamps
First total synthesis of Ryanodol.
12 years after structure
determination.

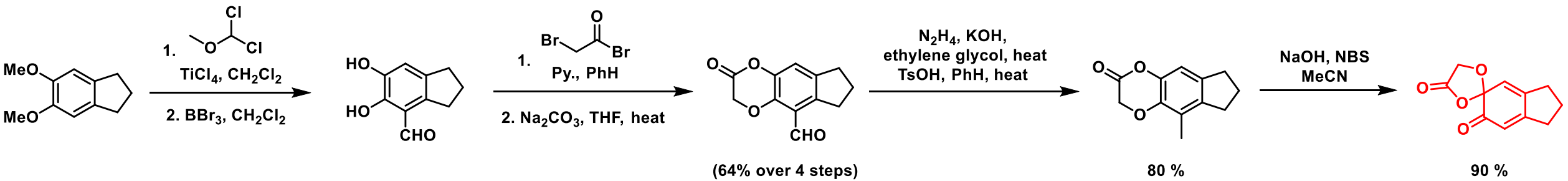
SYNTHESIS BASED ON PREVIOUS OBSERVATION



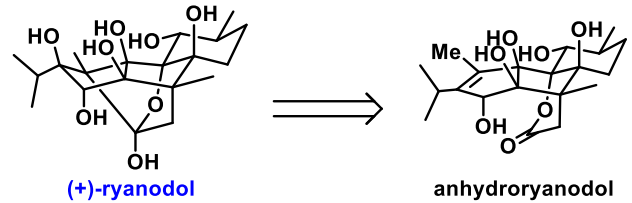
DESLONGCHAMPS SYNTHESIS







DESLONGCHAMPS SYNTHESIS



A: R=O; R'=H_2
B: R'=O; R=H_2

+

A: R=O; R'=H_2
B: R'=O; R=H_2

PhH
Reflux, 1h

A: R=O; R'=H_2
B: R'=O; R=H_2

+

A: R=O; R'=H_2
B: R'=O; R=H_2

Use as crude

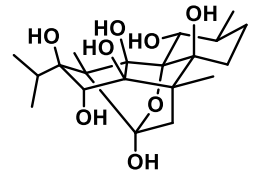
NaOH
THF, rt

Intra Aldol

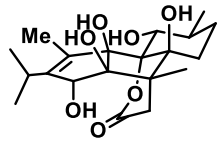
3:1

3:1

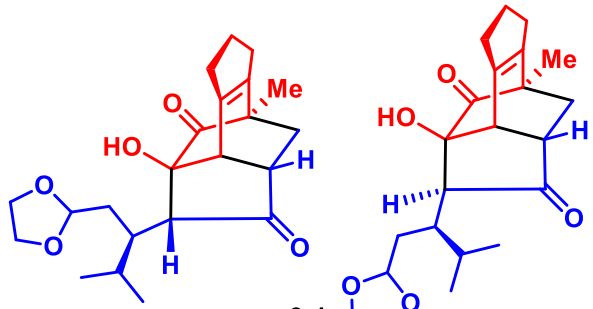
DESLONGCHAMPS SYNTHESIS



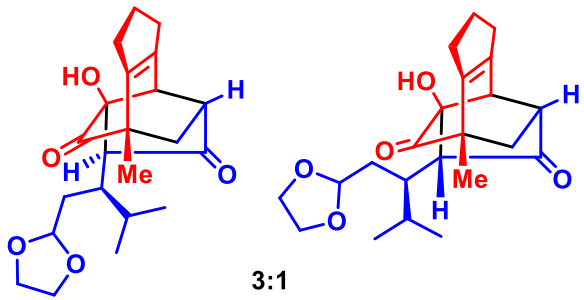
(+)-ryanodol



anhydroryanodol



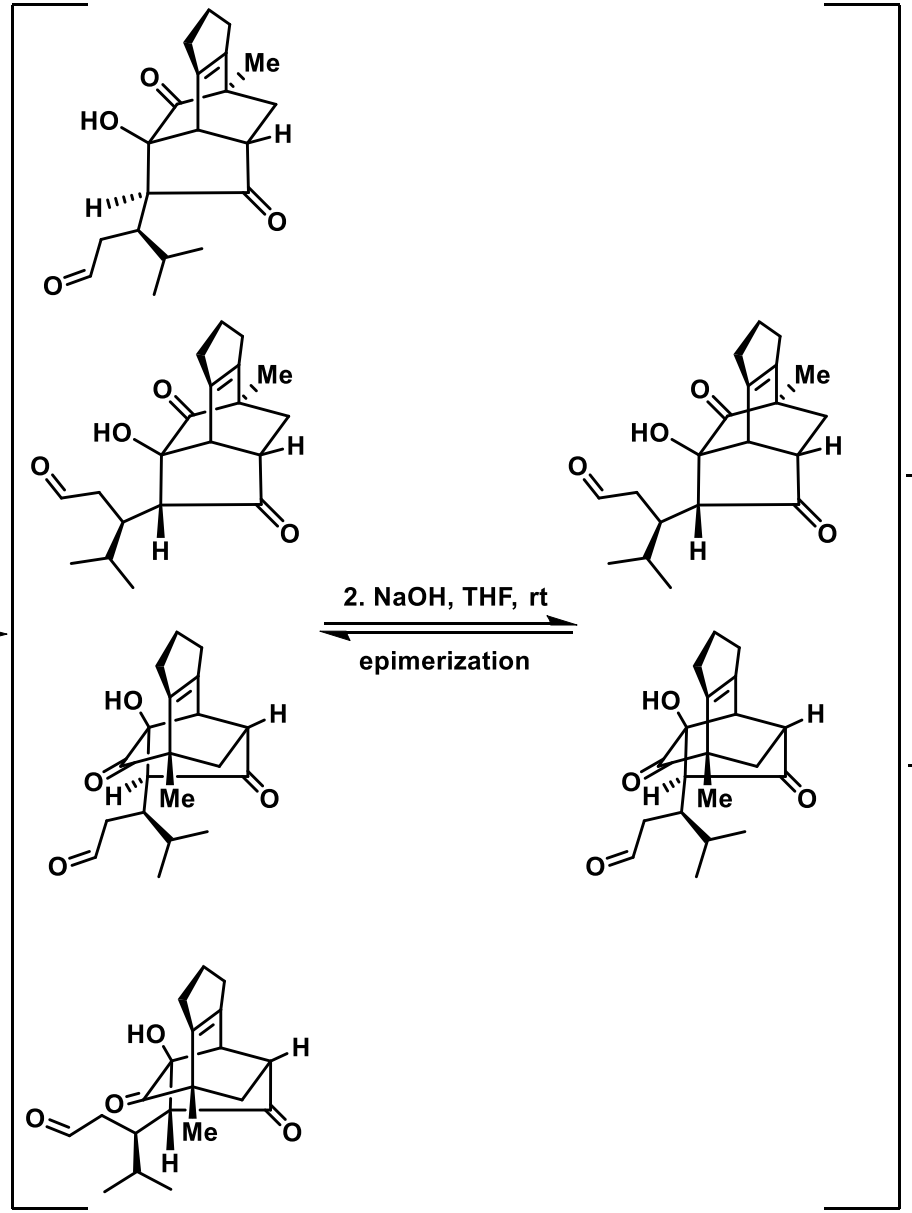
3:1



3:1

Use as crude

1. AcOH, H_2O

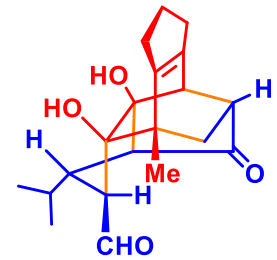


2. NaOH, THF, rt

epimerization

No information

Intra aldol

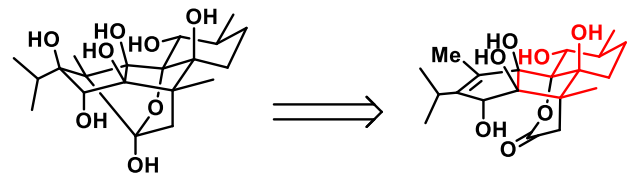


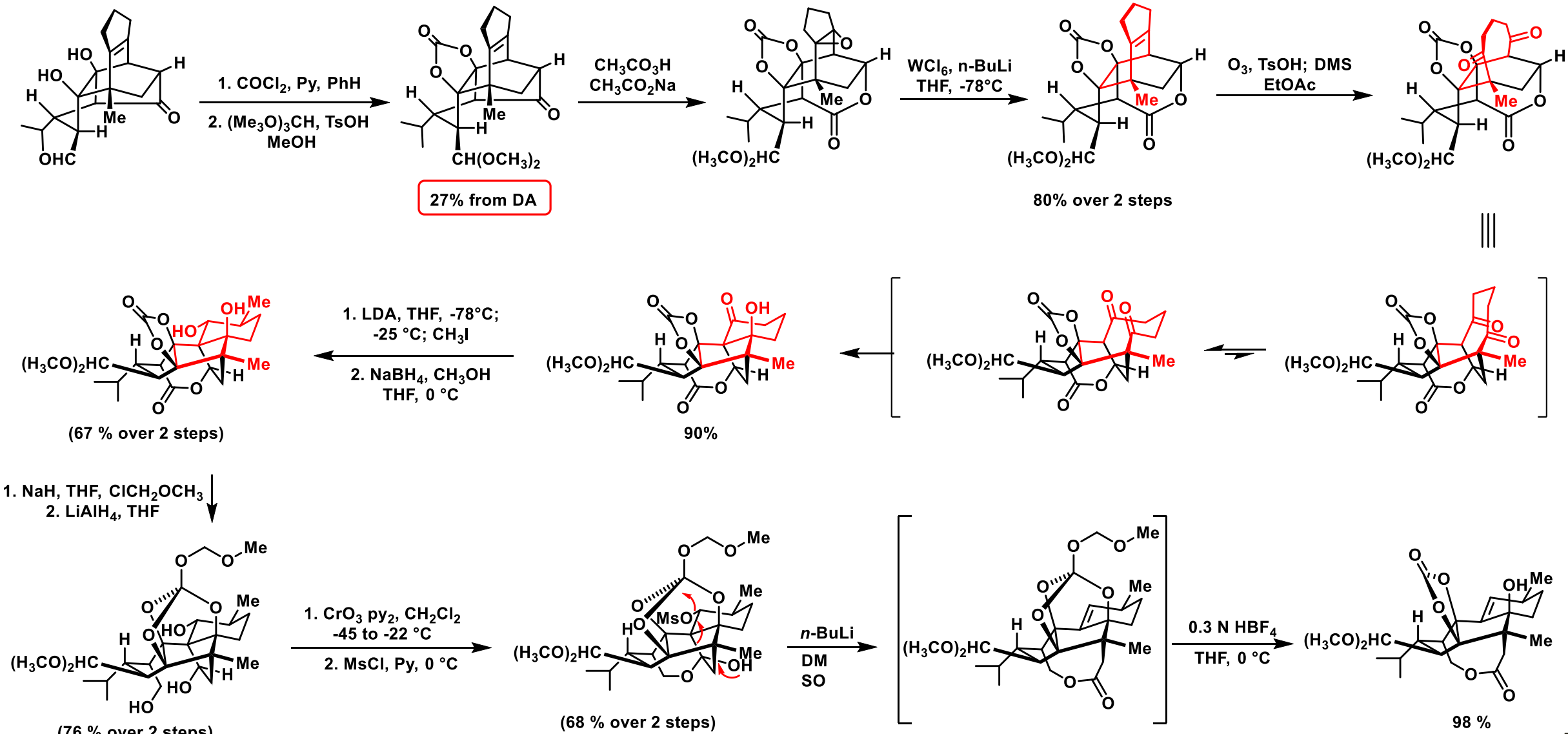
. Diels Alder reaction
. 2 deprotections
. 2 sequence of epimerization/ intra aldol.

Generation of 4 new c-c bonds (in orange).

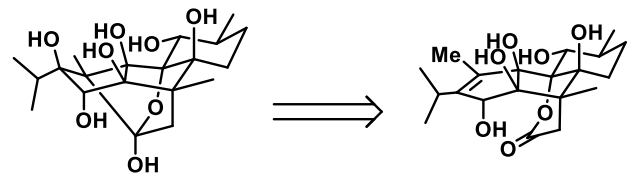
Formation of the tetracyclic scafold

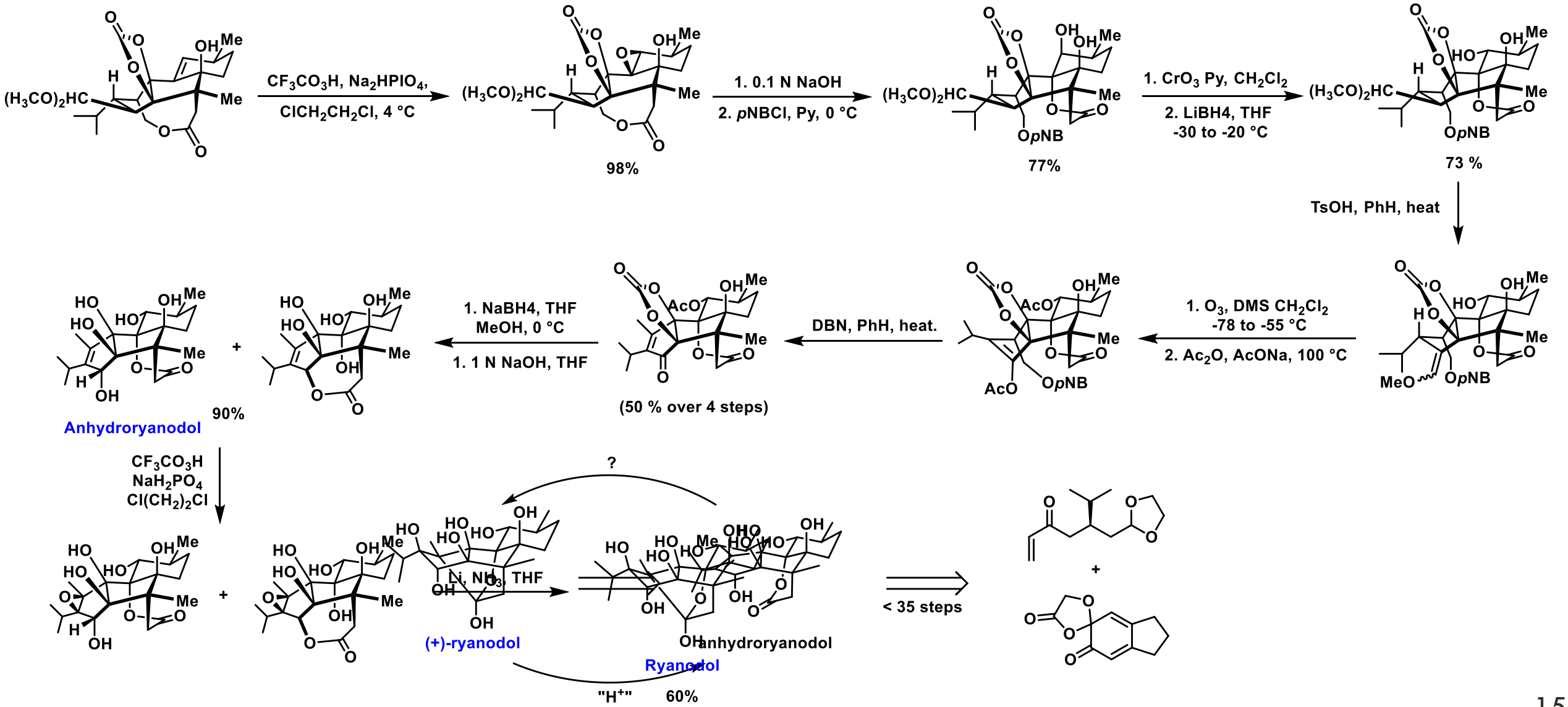
DESLONGCHAMPS SYNTHESIS





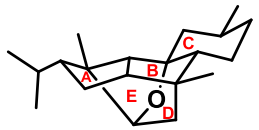
DESLONGCHAMPS SYNTHESIS





SUMMARY DESLONGCHAMPS SYNTHESIS

Key Diels-Alder cycloaddition & elegantly designed intramolecular aldol reactions to generate the ABCD framework.



Relay synthesis using the degradation product to reach Ryanodol in two-step sequence.

Construction of the key hemiacetal at the end of the synthesis.

37 steps for the longest linear sequence.

Many protecting groups & many functional groups manipulation

STORY LINE

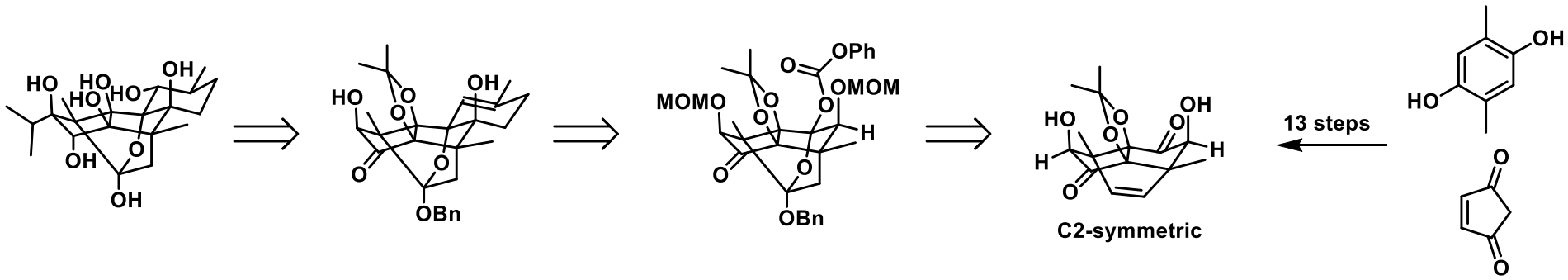
2014. Prof. Masayuki Inoue
Second total synthesis of Ryanodol.
The only group to succeed after Deslongchamps 35 years ago.

24 years from
isolation to
Structure determination

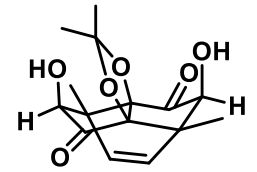
1943 → 1967 → 1979 → 2014 → 2016 → 2019 ?

1979. Prof. Pierre Deslongchamps
First total synthesis of Ryanodol.
12 years after structure determination.

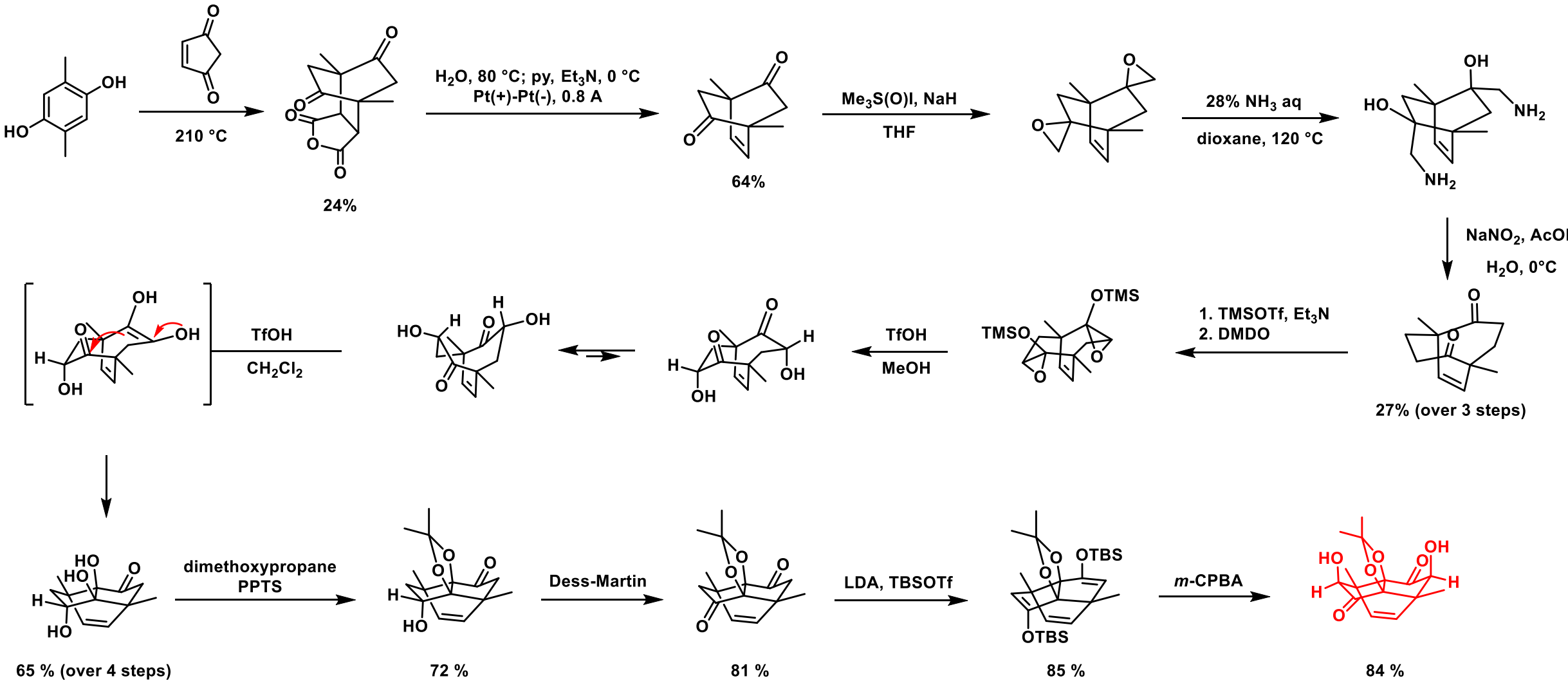
INOUE RETRO-SYNTHESIS



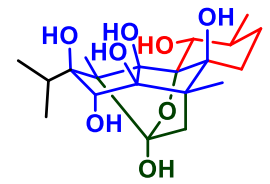
INOUE SYNTHESIS



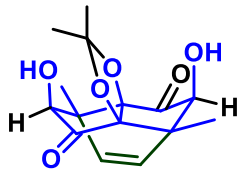
C2-symmetric



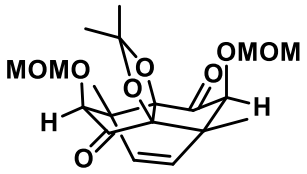
INOUE SYNTHESIS



(+)-ryanodol

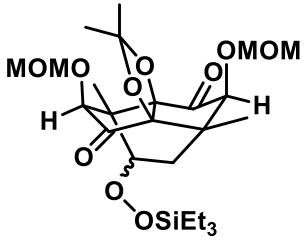


1. NaH, MOMCl; $NaHSO_3$

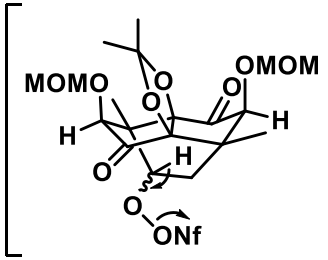


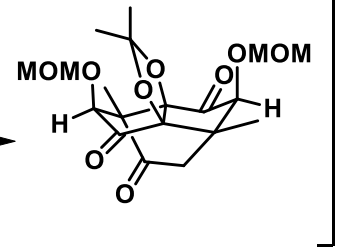
92%

2. O_2, $Co(acac)_2$ Et_3SiH, *t*-BuOOH

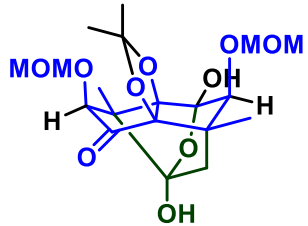


3. NfF, DBU



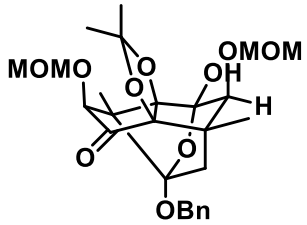


SiO_2 column

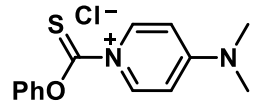


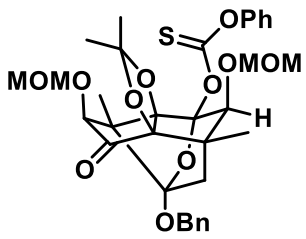
58% Over 2 steps

4. BnOH, 4A MS SiO_2



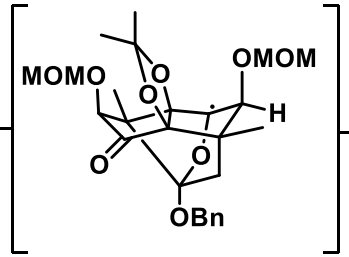
5. KH

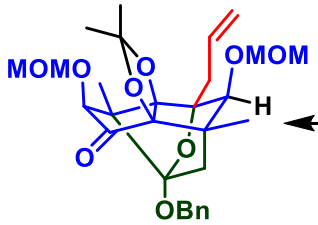




68% over 2 steps

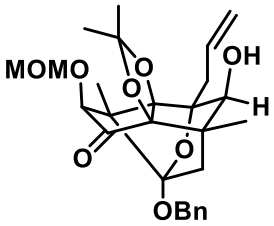
6. AIBN $SnBu_3$



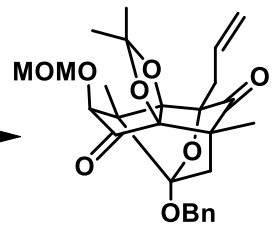


66%

7. $BF_3.OEt_2$, Me_2S

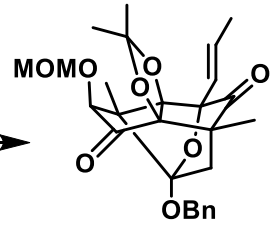


8. Dess-Martin

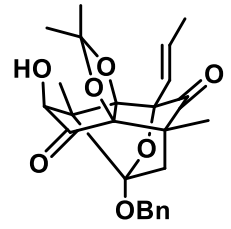


65% over 2 steps

9. $PdCl_2(MeCN)_2$

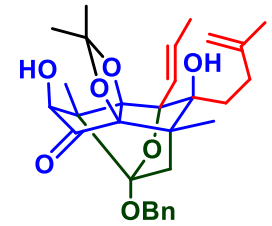


10. $BF_3.OEt_2$, Me_2S



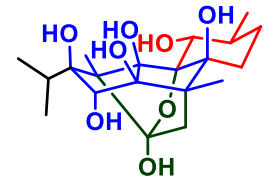
86% over 2 steps

10. Li

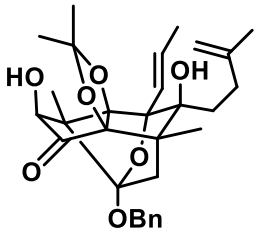


84%

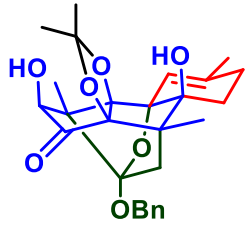
INOUE SYNTHESIS



(+)-ryanodol

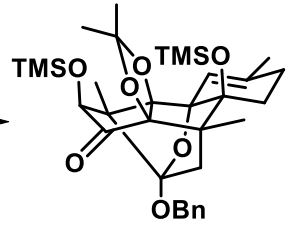


11. Metathesis



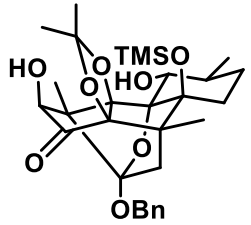
75%

12. TMSOTf, py



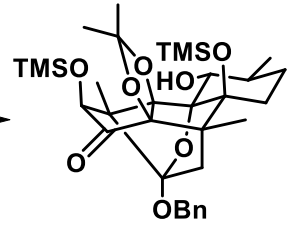
89%

13. BH_3.THF; $NaBO_3$



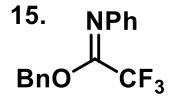
91%

14. TMSOTf, Py
HCl

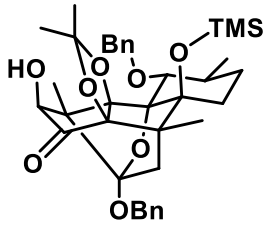


87%

15.

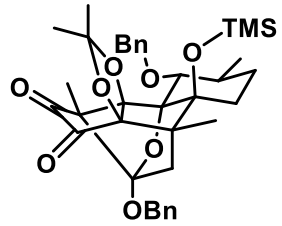


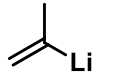
$Sc(OTf)_3$; NaOH



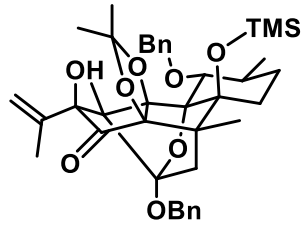
90%

16. Dess-Martin



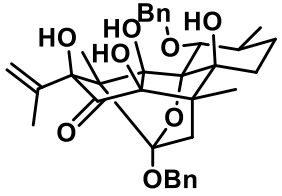
17. 

$CeCl_3$

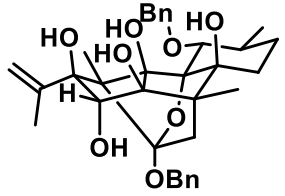


21% over 2 steps
(recover diketone: 53%)

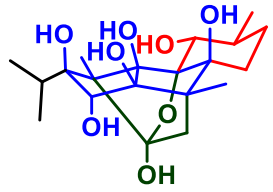
18. TASF (72%)
19. HCl



20. $NaBH(OAc)_3$



21. H_2, Pd/C



87% over 3 steps

Ryanodol

SUMMARY INOUE SYNTHESIS

Reduce the use of protecting groups & redox process (In comparision with Deslongchamps).

Key hemiacetal was formed in the middle of the synthesis.

Synthesis highlighted the utility of radical chemistry in the total synthesis of complex natural product.

35 steps for the longest linear sequence

STORY LINE

2014. Prof. Masayuki Inoue
Second total synthesis of Ryanodol.
The only group to succeed after Deslongchamps 35 years ago.

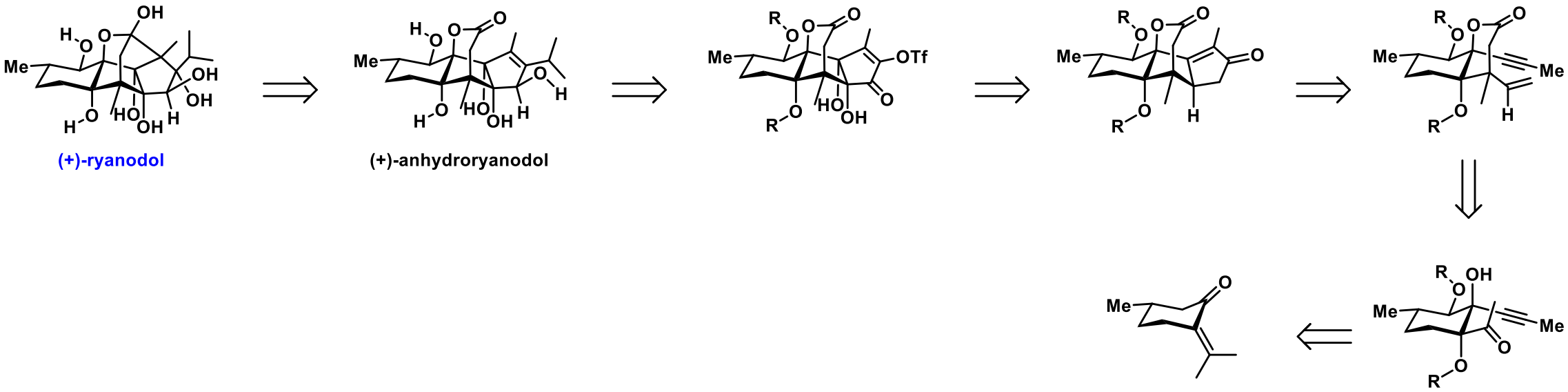
24 years from
isolation to
Structure determination

1943 → 1967 → 1979 → 2014 → 2016 → 2019 ?

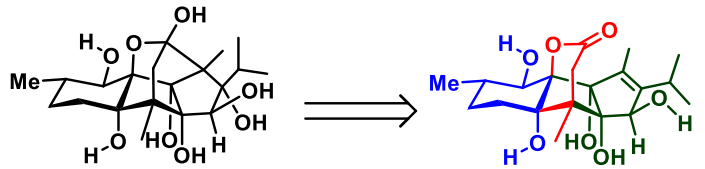
1979. Prof. Pierre Deslongchamps
First total synthesis of Ryanodol.
12 years after structure determination.

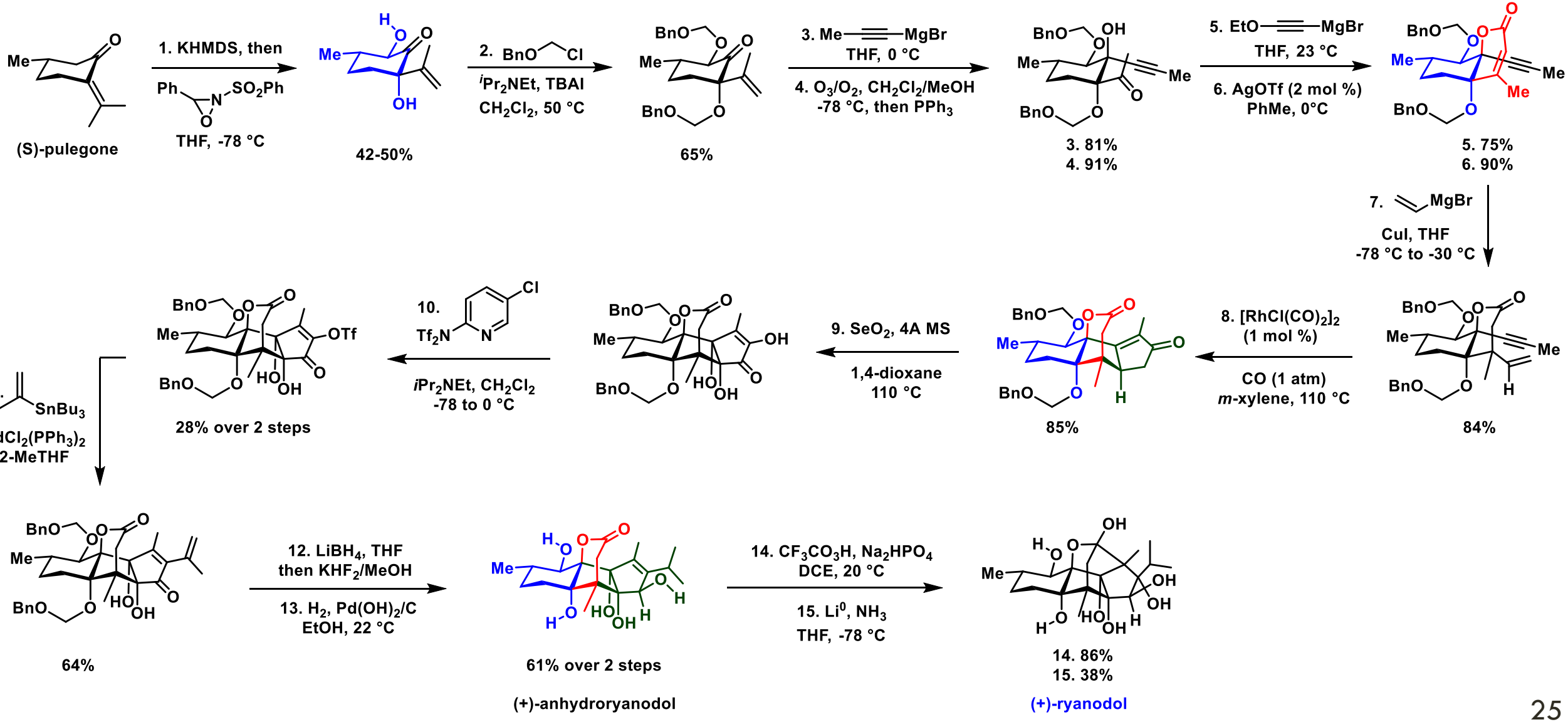
2016. Prof. Sarah E. Reisman
Third total synthesis of Ryanodol.
The last one reported to date.

REISMAN RETRO-SYNTHESIS



REISMAN SYNTHESIS





SUMMARY REISMAN SYNTHESIS

15 steps from the commercially available (S)-pulegone.

Pauson-Khand reaction to build the carbon framework and SeO_2 - oxidation to install three oxygen atoms in a single step.

Minimum of protecting groups & redox adjustments.

SUMMARY

2014. Prof. Masayuki Inoue
Second total synthesis of Ryanodol.
The only group to succeed after Deslongchamps 35 years ago.

24 years from
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REFERENCES

For the Isolation & Structure:

- *J. Am. Chem. Soc.*, **1948**, *70* , 3086–3088
- *Can. J. Chem.*, **1951**, *29*, 905.
- *Tetrahedron Lett.*, **1960**, *15*, 31.
- *Tetrahedron Lett.*, **1967**, *3*, 221.

For Deslongchamps Synthesis:

- *Can. J. Chem.*, **1979**, *57*, 3348.

For Inoue Synthesis:

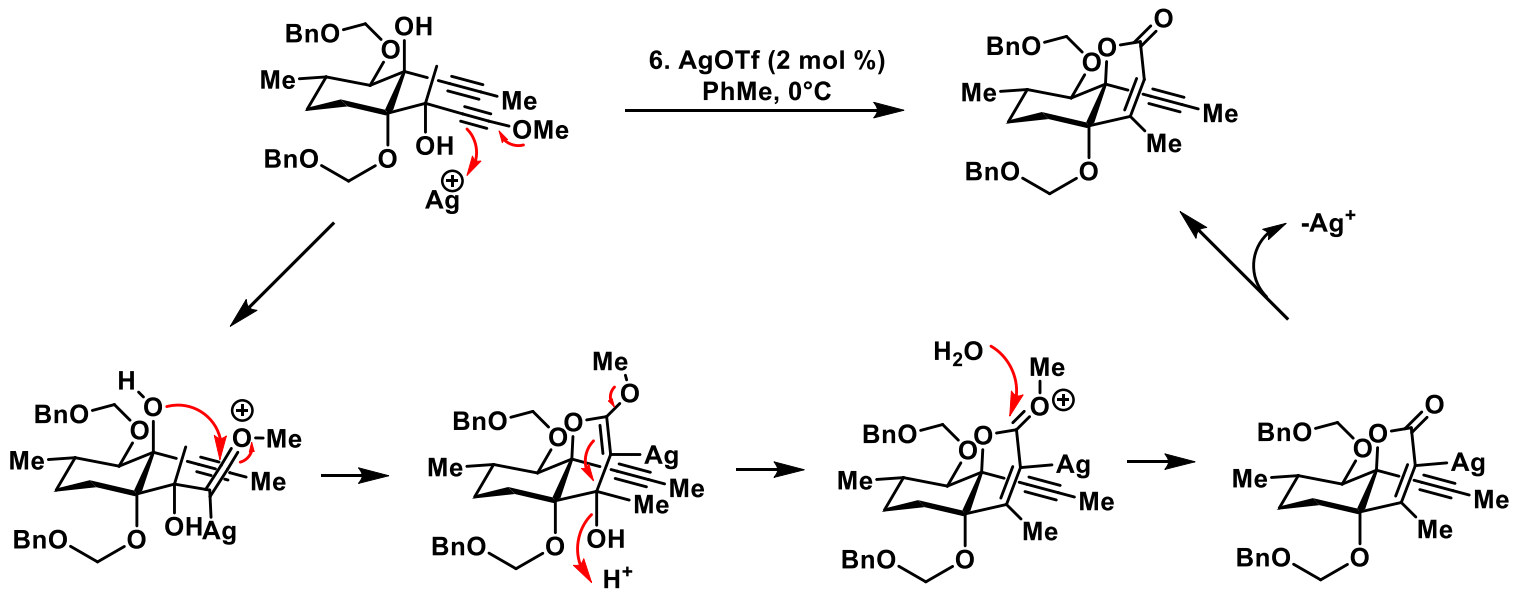
- *Tetrahedron Lett.*, **2009**, *50*, 1035.
- *Chem. Sci.*, **2013**, *4*, 1615.
- *J. Am. Chem. Soc.*, **2014**, *136*, 5916.
- *Chem. Eur. J.*, **2016**, *22*, 230–236 (also ryanodine)

For Reisman Synthesis:

- *Science,* **2016**, *353*, 912.
- ACS Cent. Sci. 2017, 3, 278−282 (also ryanodine)

STORY OF RYANODOL

FROM 1943 TO 2018


6. AgOTf (2 mol %)
PhMe, 0°C
-Ag+