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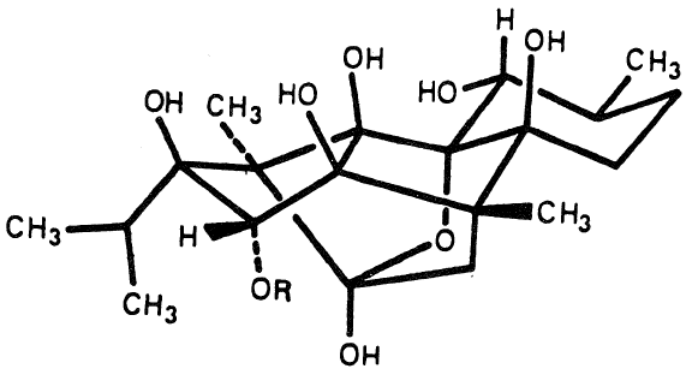
Total Synthesis of Ryanodol

Masanori Nagatomo, Masaki Koshimizu, Kengo Masuda, Toshiki Tabuchi, Daisuke Urabe, and **Masayuki Inoue***

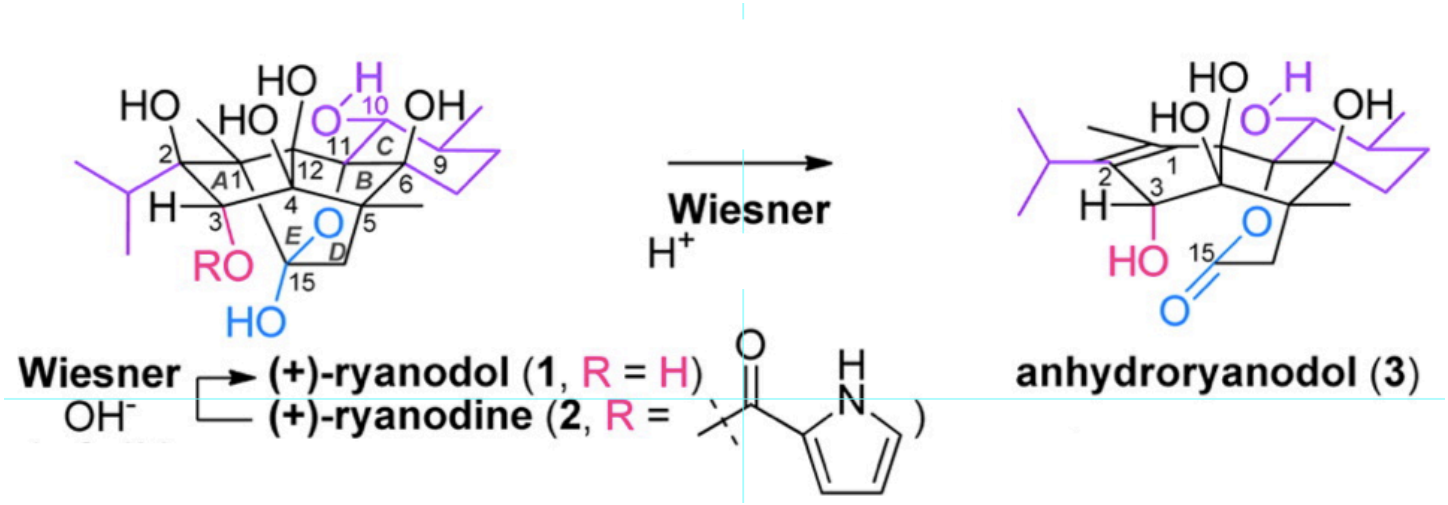
(*J. Am. Chem. Soc.* **2014**, *ASAP,* DOI: 10.1021/ja502770n)



1 R = H

(+)-Ryanodine & (+)-Ryanodol

- *Isolated in 1948, Structure established in 1968.*



- *Polyhydroxylic Diterpenes, recognised for insecticidal properties.*

Rogers, E. F.; Koniuszy, F. R.; Shavel, J., Jr.; Folkers, K. *J. Am.Chem. Soc.* **1948**, *70*, 3086.
Wiesner, K. Collect. *Czech. Chem. Commun.* **1968**, *33*, 2656.

(+)-Ryanodine

- *Central & South America: Amazonia.*

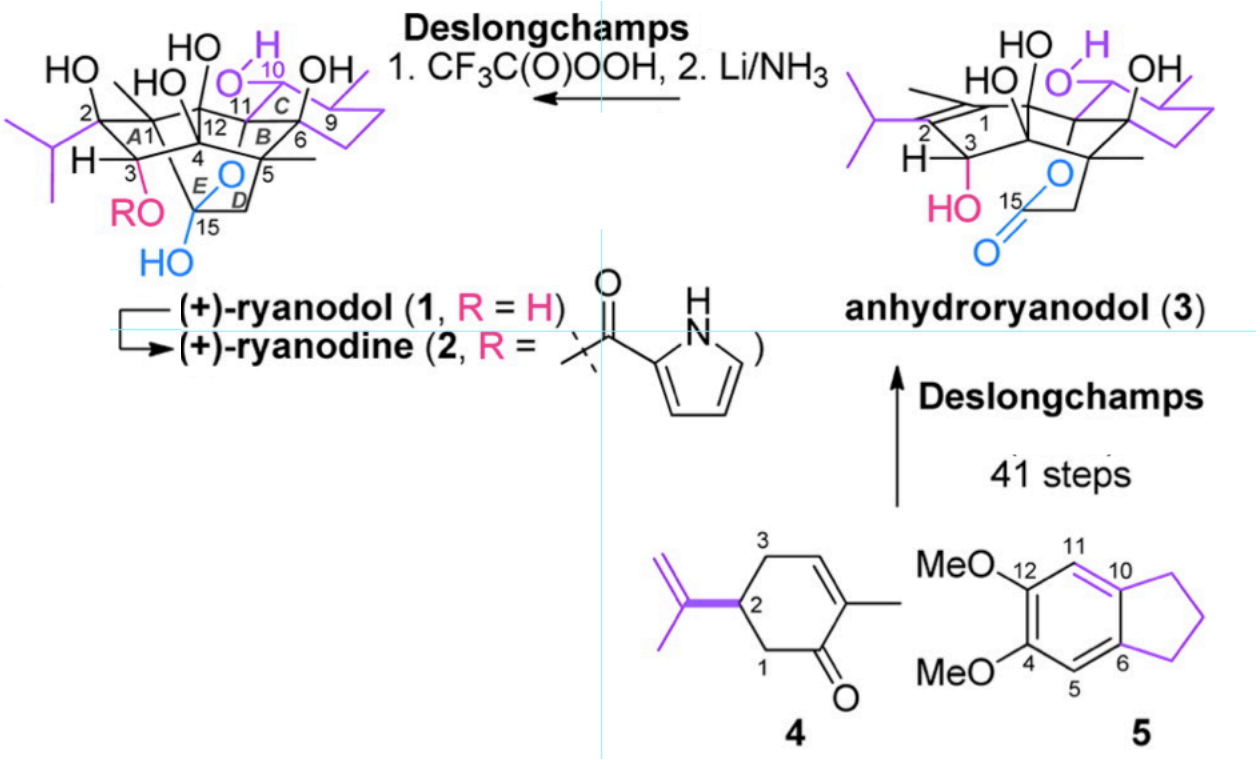
- *Strong affinity for Ryanodine Receptors, Ca^{2+} channels, skeletal & cardiac muscles.*

- *Potential for treatment for associated diseases.*

Mackrill, J. *J. Biochem. Pharmacol.* **2010**, *79*, 1535.
Van Petegem, F. *J. Biol. Chem.* **2012**, *287*, 31624.

(+)-Ryanodol

- *Only 1 total synthesis reported: P.* ***Deslongchamps*** *(&* ***19 co-workers)*** *from* ***1979*** *to* ***1990.***

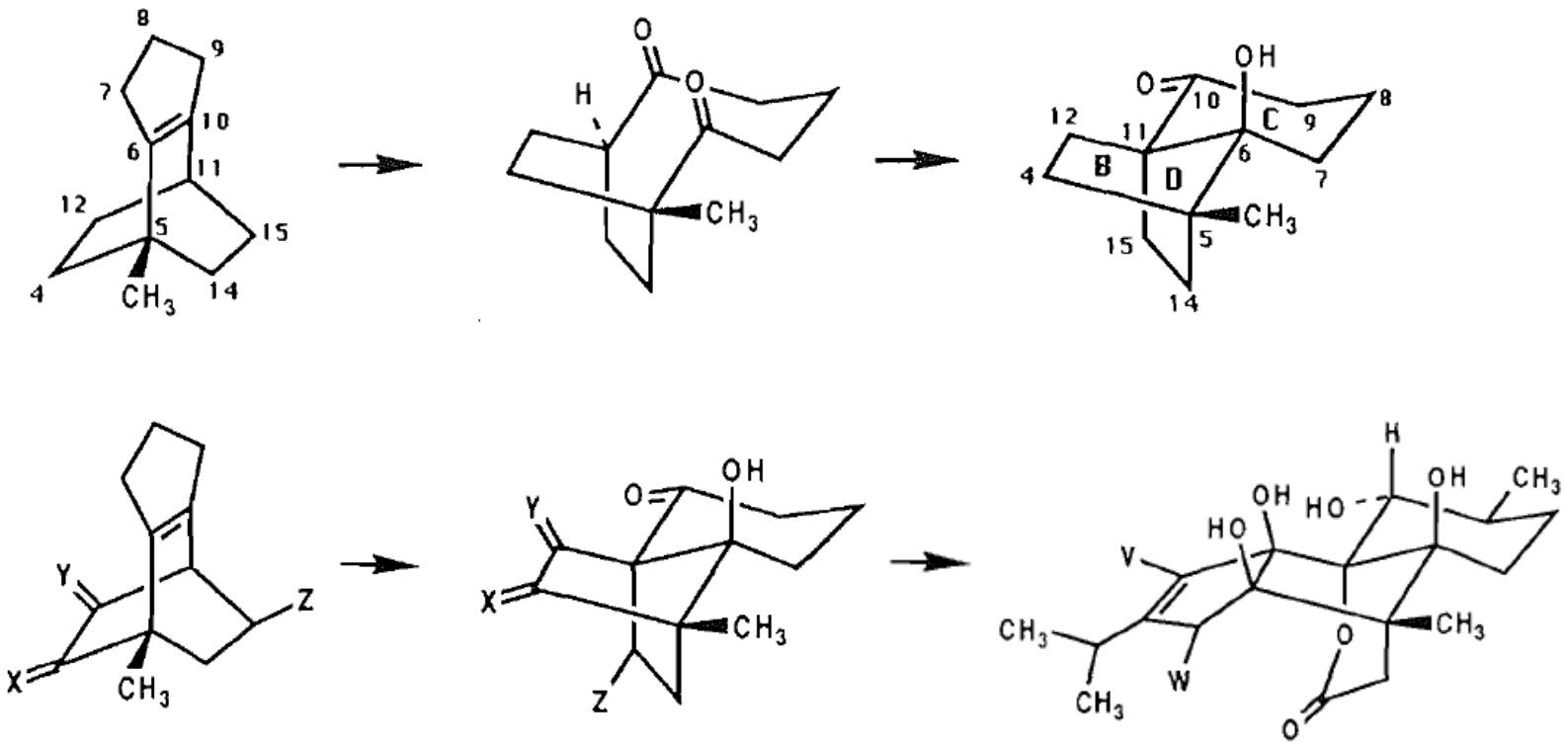


- *5 rings, 11 contiguous asymmetric carbons, 5 geometrically related.*

J. L. Sutko, J. A. Airey, W. Welch, Luc Ruestvan *Pharmacol. Rev.* **1997**, *49*, 53.
M. Inoue and co-workers, *J. Am. Chem. Soc.* **2014**, *ASAP,* DOI: 10.1021/ja502770n.

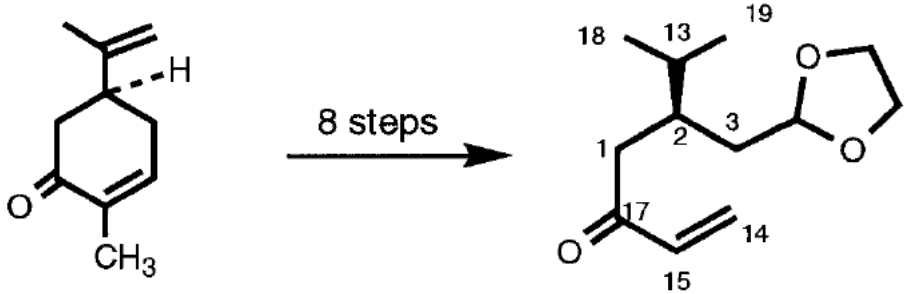
(+)-Ryanodol, Deslongchamps et al.

- *Synthetic plan:*



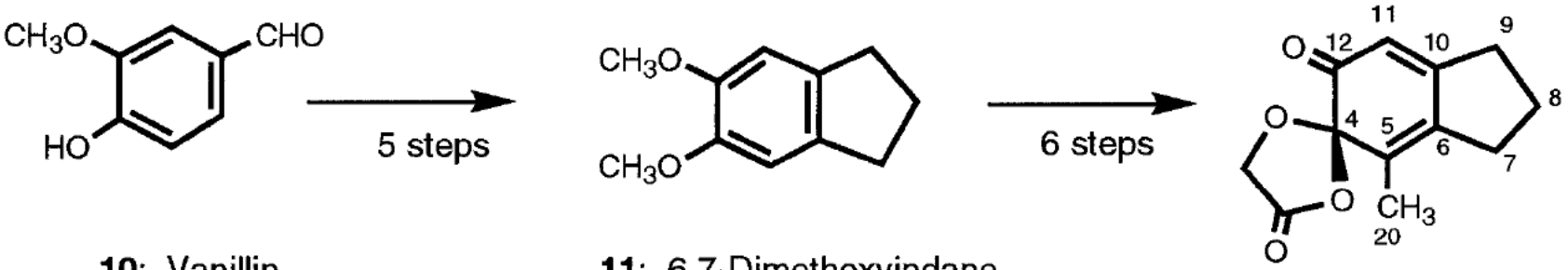
(+)-Ryanodol, Deslongchamps et al.

- *Major assembling: Diels-Alder reaction.*



8: S(+)-Carvone

9: Dienophile



10: Vanillin

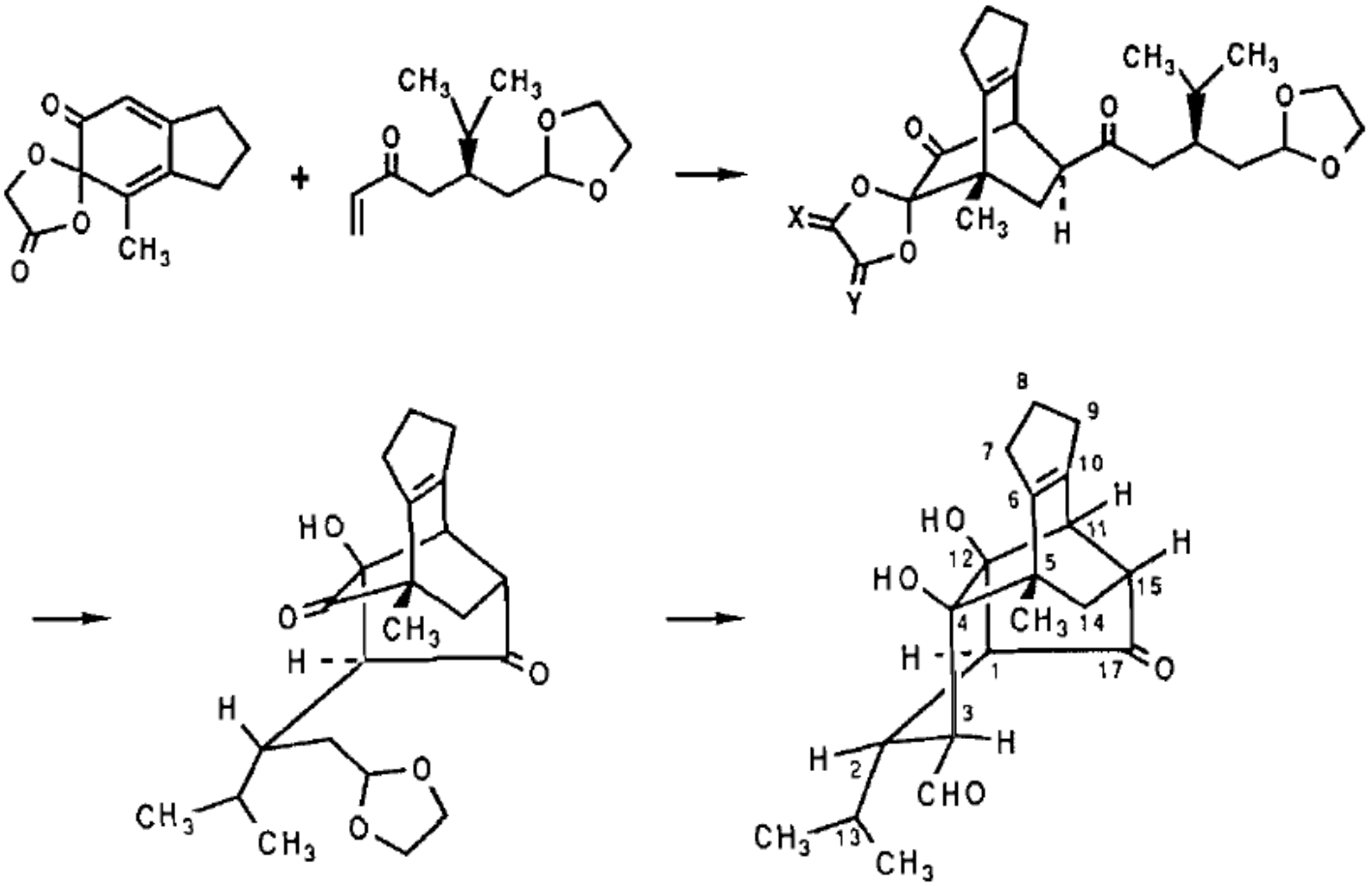
11: 6,7-Dimethoxyindane

12: Diene, one enantiomer shown

Deslongchamps *et al. Can. J. Chem.* **1990**, *68*, 115.

(+)-Ryanodol, Deslongchamps et al.

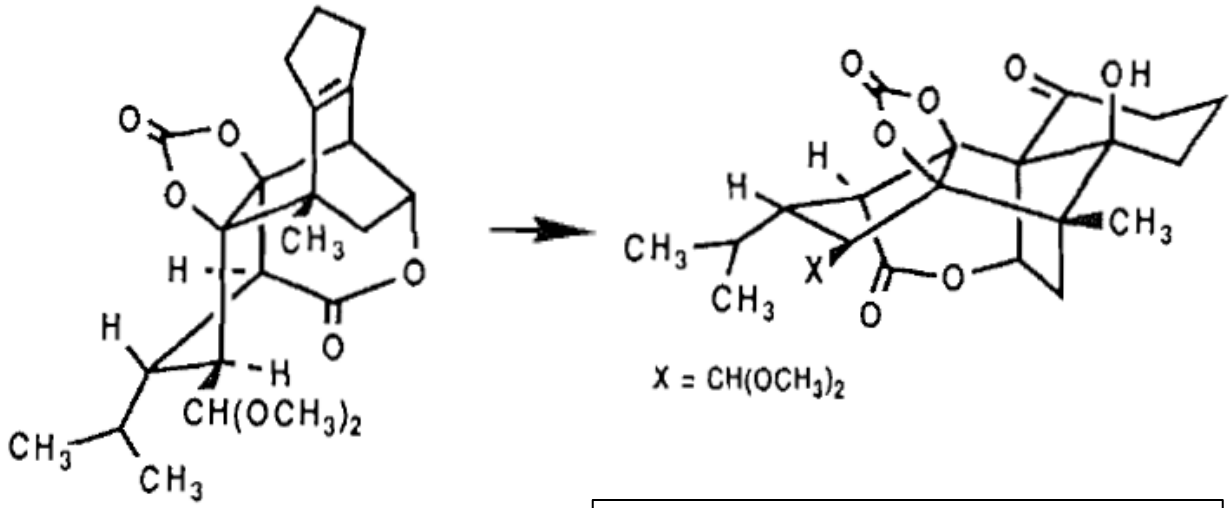
- *Diels-Alder & aldol reactions sequence.*

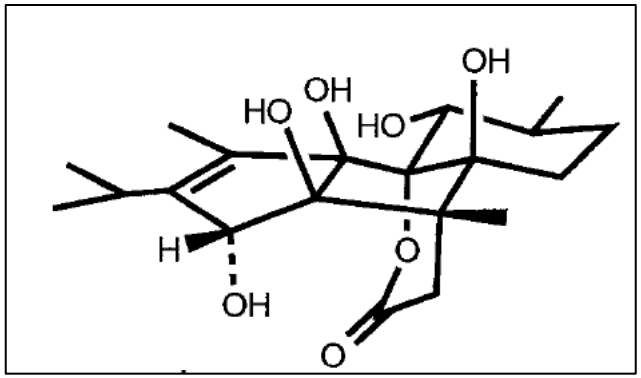


Deslongchamps *et al. Can. J. Chem.* **1990**, *68*, 115.

(+)-Ryanodol, Deslongchamps et al.

- *(+)-anhydroryanodol:*



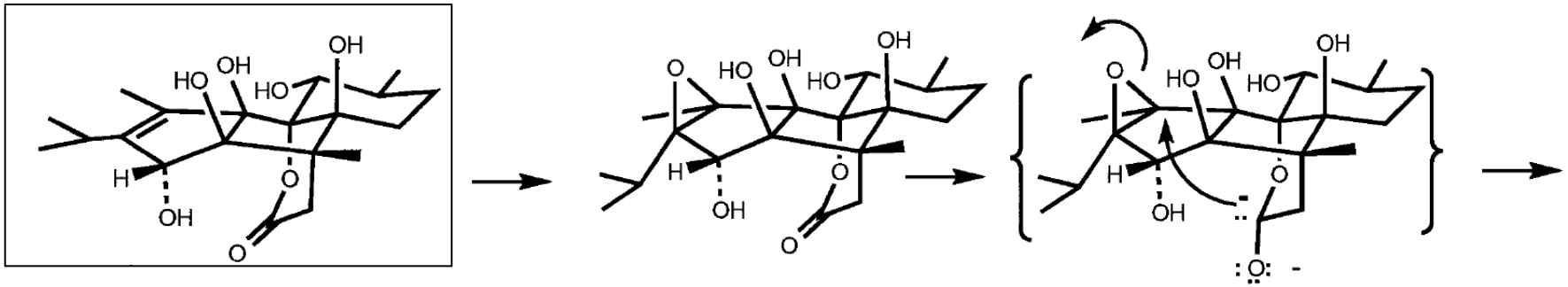


(+)-anhydroryanodol

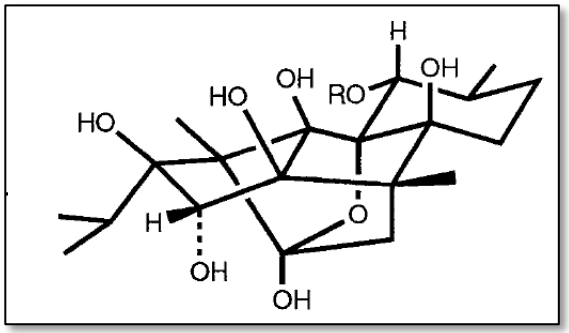
Deslongchamps *et al. Can. J. Chem.* **1990**, *68*, 153.

(+)-Ryanodol, Deslongchamps et al.

- *From (+)-anhydroryanodol to (+)-ryanodol:*



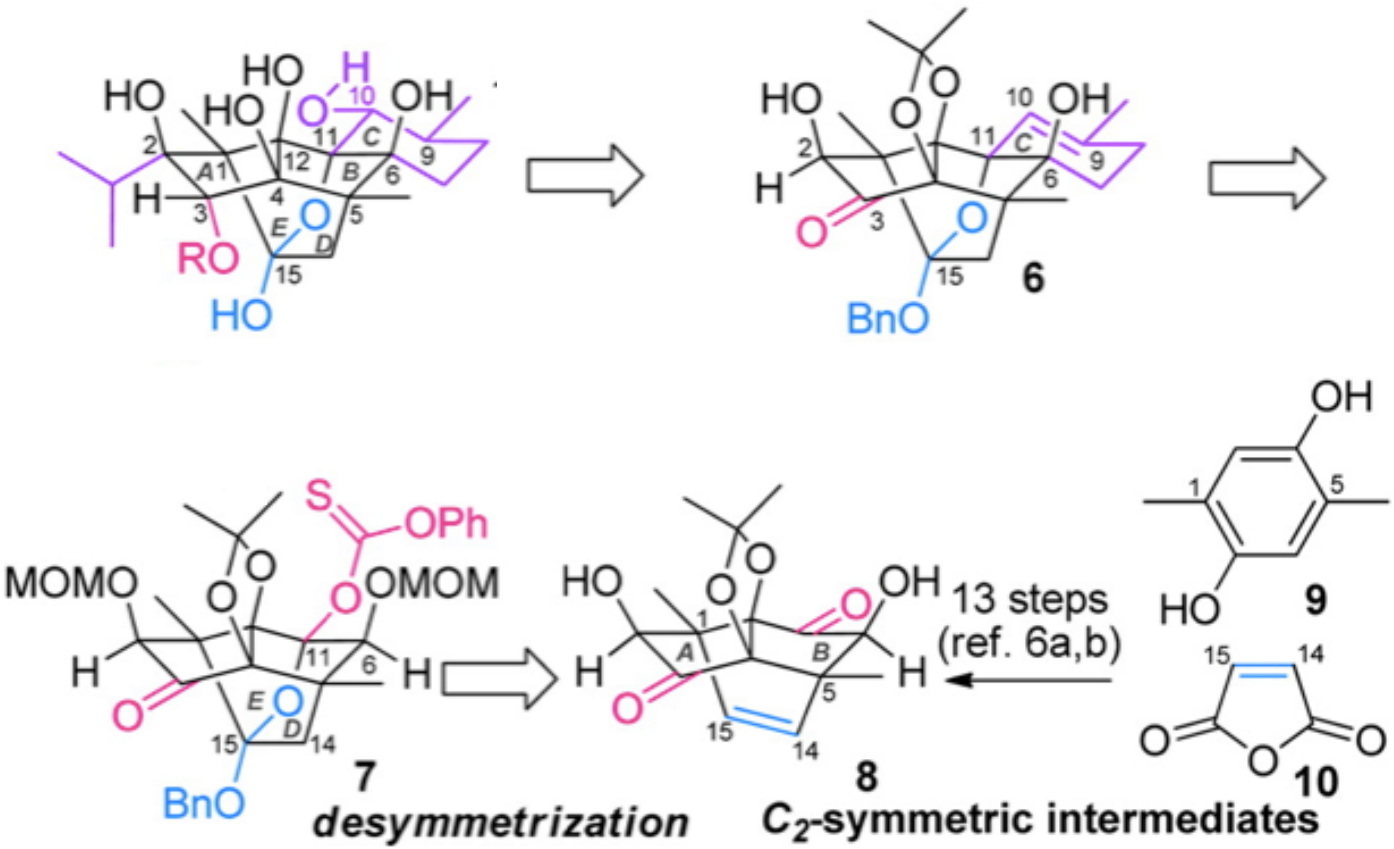
(+)-anhydroryanodol



(+)-ryanodol

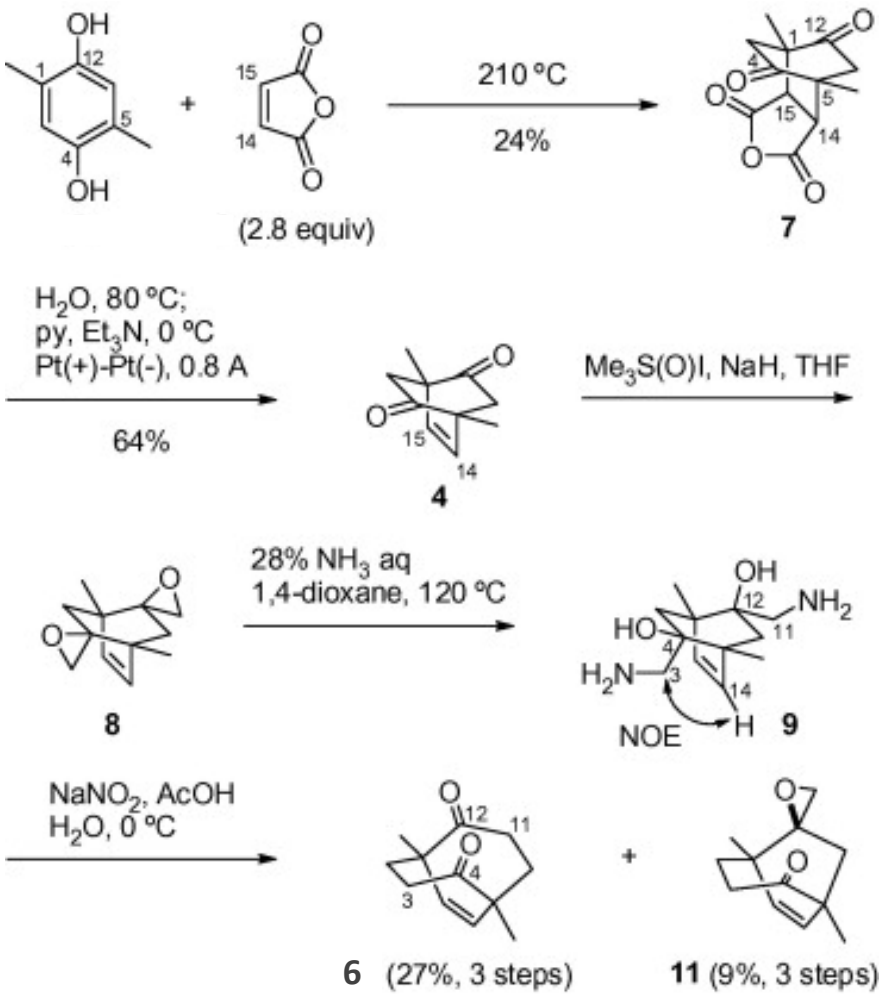
(+)-Ryanodol, Inoue's synthesis.

- *Retrosynthetic proposal:*



(+)-Ryanodol, Inoue's synthesis.

- *Synthesis of the C_2-symmetric key intermediate:*



"Poor yield, but routinely provides multi-gram quantities"

Hagiwara, K.; Himuro, M.; Hirama, M.; Inoue, M. *Tetrahedron Lett.* **2009**, *50*, 1035.
Urabe, D.; Nagatomo, M.; Hagiwara, K.; Masuda, K.; Inoue, M. *Chem. Sci.* **2013**, *4*, 1615.

(+)-Ryanodol, Inoue's synthesis.

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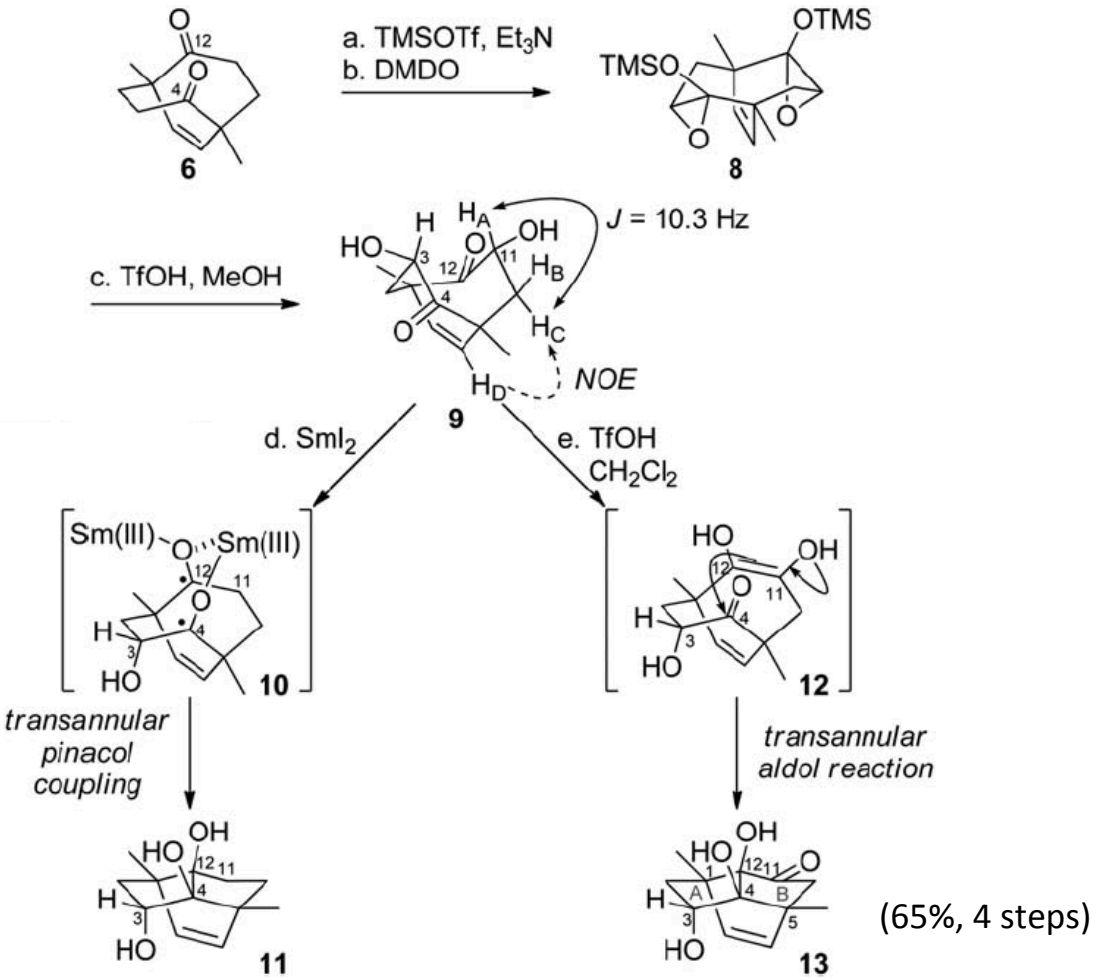

Hagiwara, K.; Himuro, M.; Hirama, M.; Inoue, M. *Tetrahedron Lett.* **2009**, *50*, 1035.
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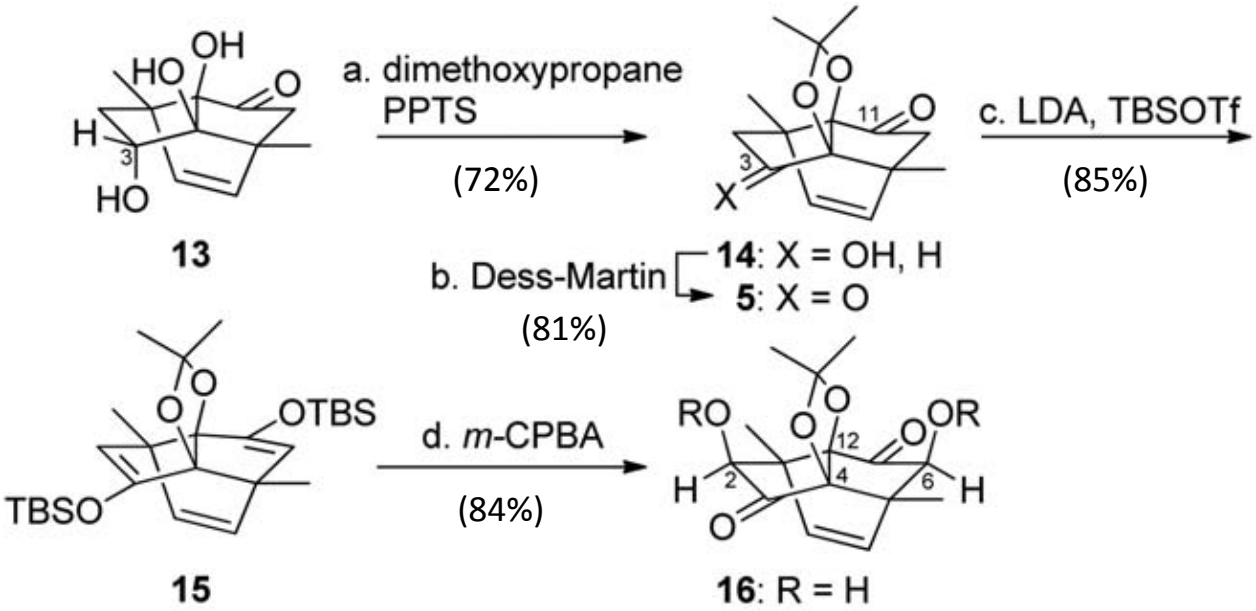

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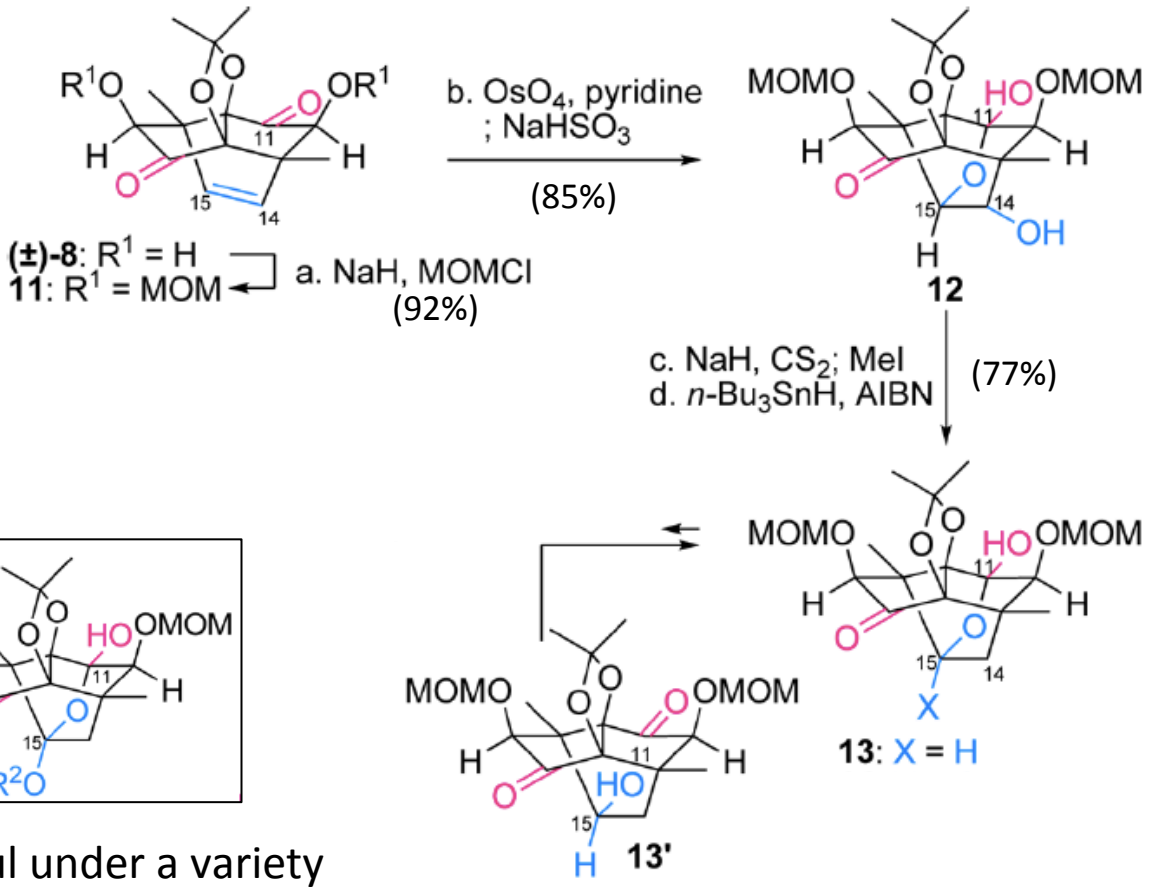
Urabe, D.; Nagatomo, M.; Hagiwara, K.; Masuda, K.; Inoue, M. *Chem. Sci.* **2013**, *4*, 1615.

(+)-Ryanodol, Inoue's synthesis.

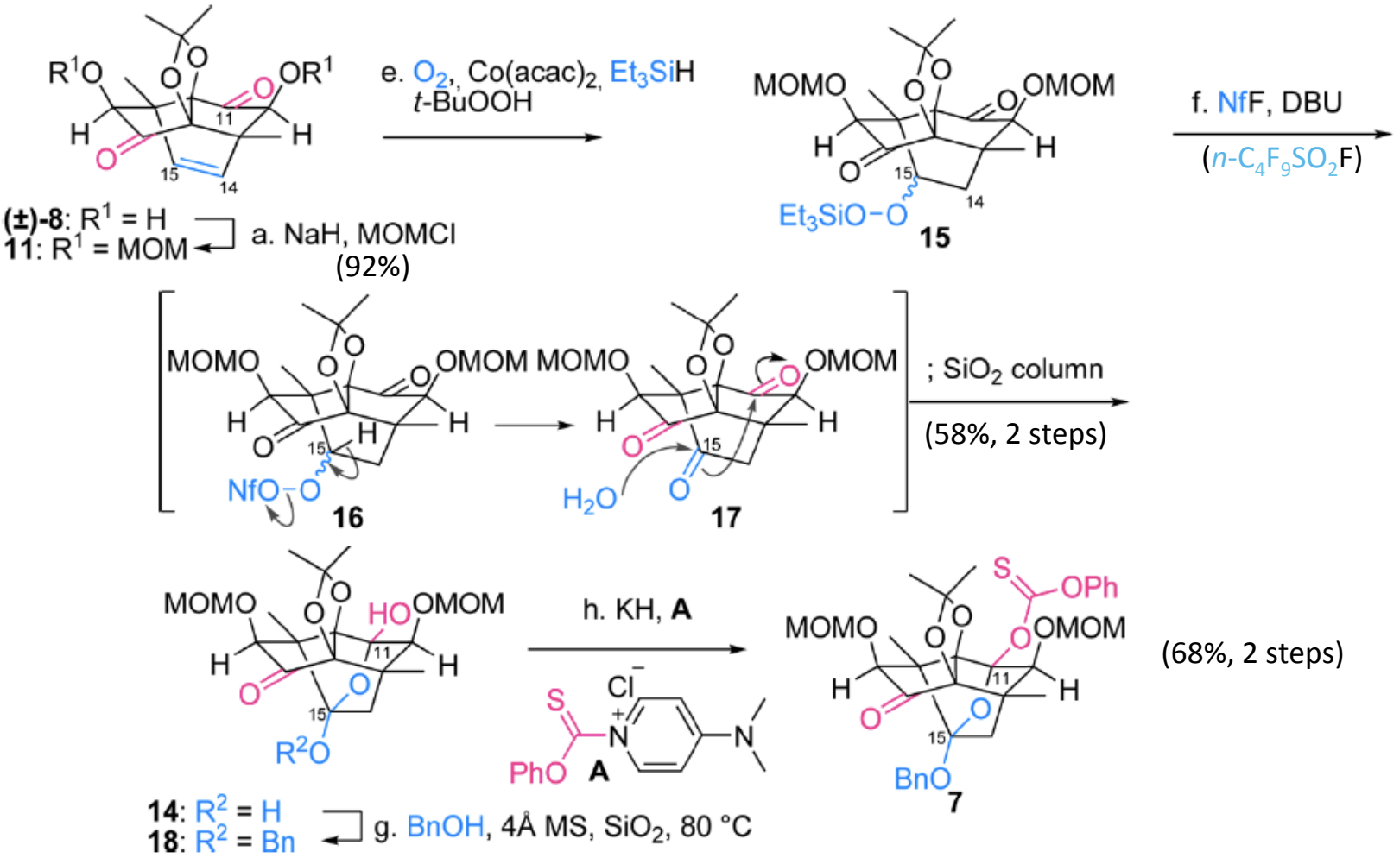
- *Development of the C15-Oxidation Protocol:*



"Unsuccessful under a variety of conditions"

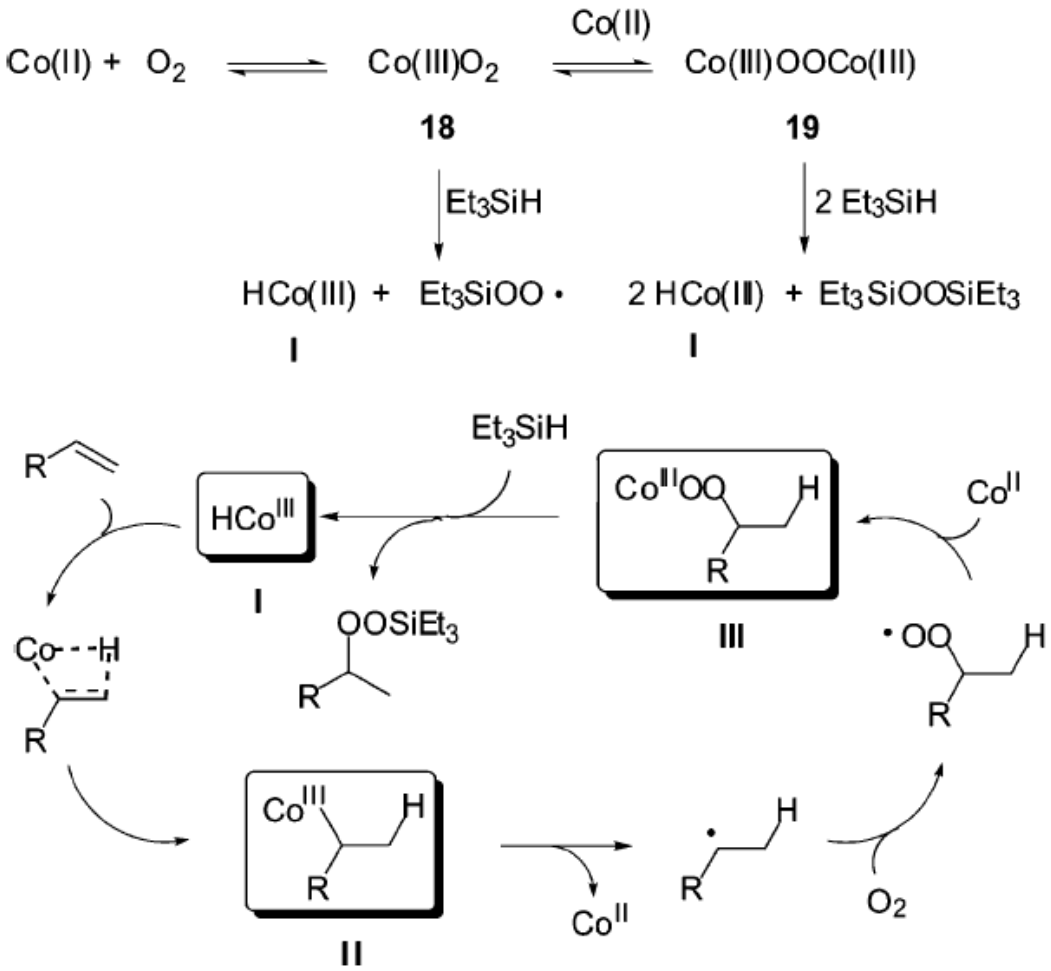
(+)-Ryanodol, Inoue's synthesis.

- *Need to oxidize C15 without going through a free hydroxy group:*



(+)-Ryanodol, Inoue's synthesis.

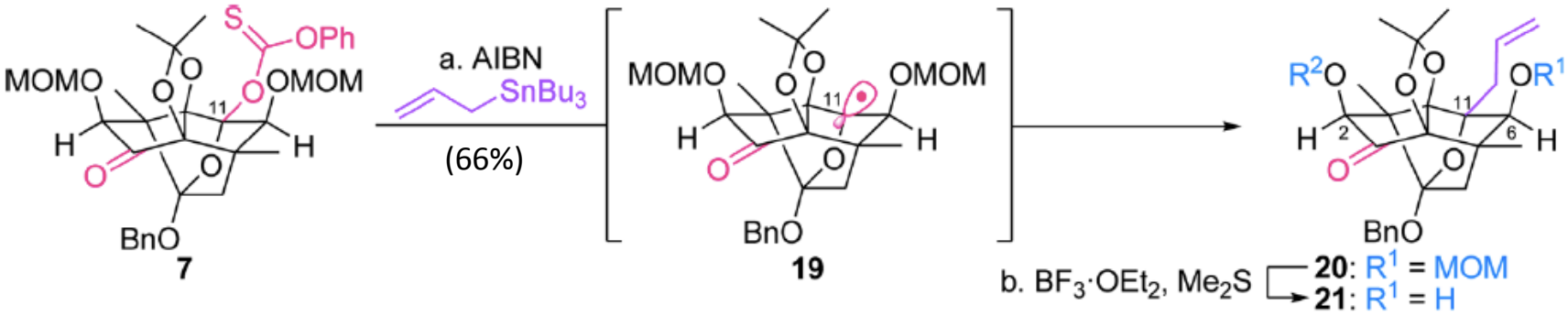
- *Triethylsilylperoxidation of alkenes, proposed mechanism:*

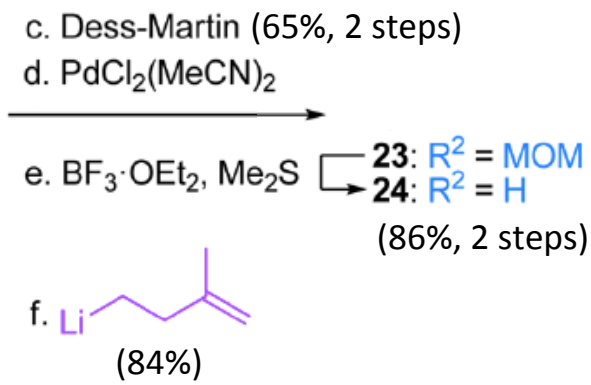


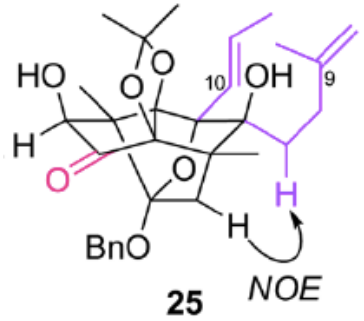
Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 573.
Tokuyasu,T.; Kunikawa, S.; Masuyama, A.; Nojima, M. *Org. Lett.* **2002**, *4*, 3595.

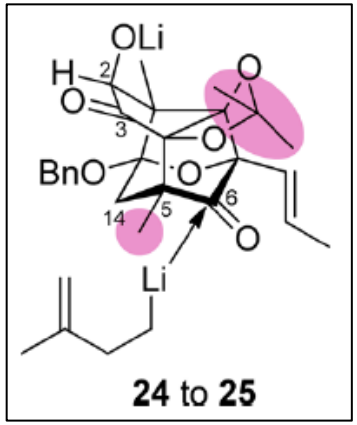
(+)-Ryanodol, Inoue's synthesis.

- *Construction of the C ring:*



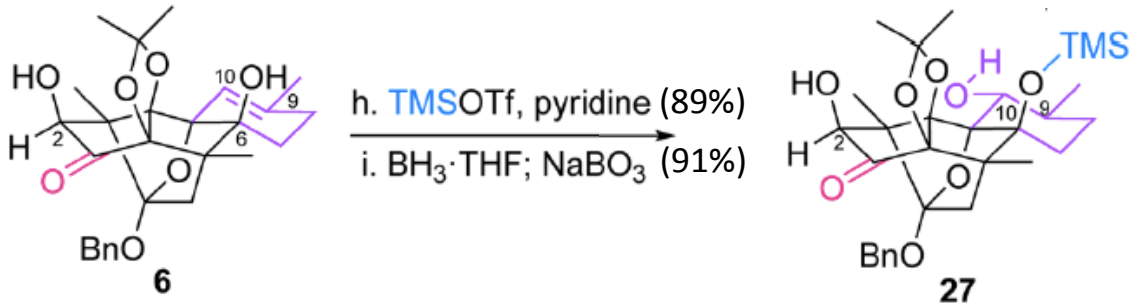


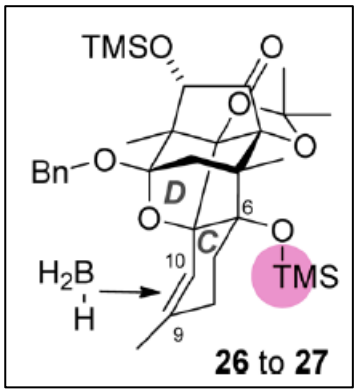




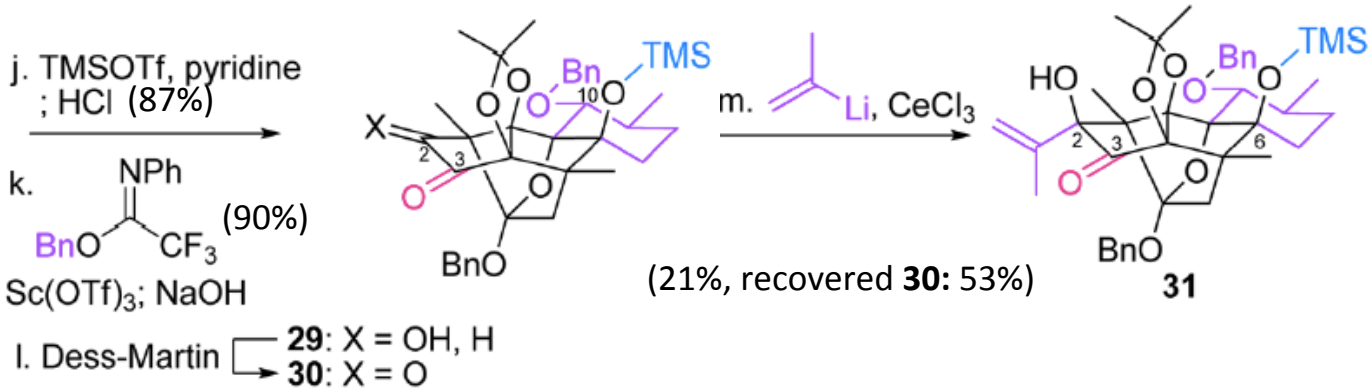
(+)-Ryanodol, Inoue's synthesis.

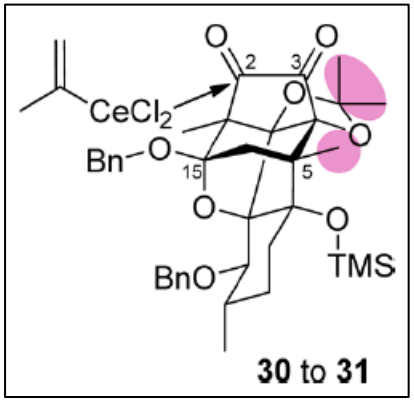
- *Last functionalisations:*





"C6-OH TMS ether was required to ensure the desired stereoselectivity"

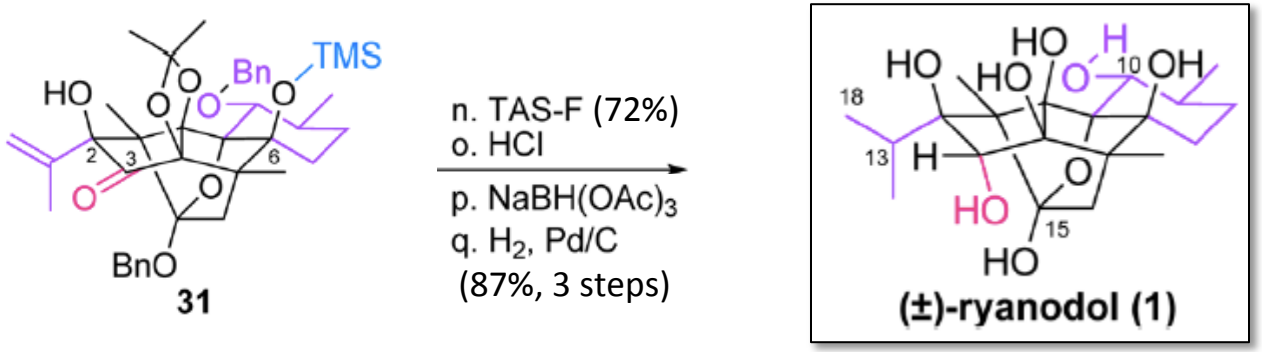




M. Inoue and co-workers, *J. Am. Chem. Soc.* **2014**, *ASAP,* DOI: 10.1021/ja502770n.

(+)-Ryanodol, Inoue's synthesis.

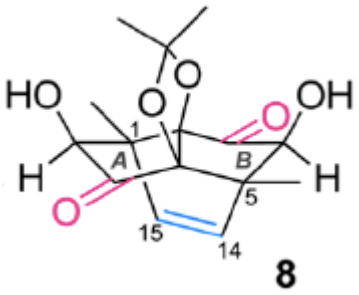
- *Completion of the synthesis:*



Summary / Conclusion

- *Deslongchamps' approach:* ***43 steps, 1st synthesis, asymmetric.***

- *Inoue's approach:* ***35 steps, 2nd synthesis, racemic,*** *including:*



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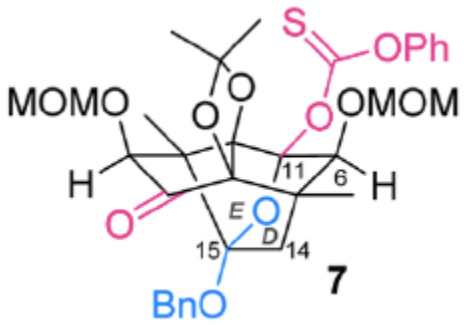
- Desymmetrizing C15-oxidation
- Differential functionalization of bis-hemiacetal
- Alpha-alkoxy bridgehead radical reaction
- RCM for installing the C-ring
- Stereoselective hydroboration/oxidation
- Isopropyl chain introduced as the cerium reagent
- Hydroxy-directed reduction at C3



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