Synthetic Efforts Toward Ryanodine and Ryanodol

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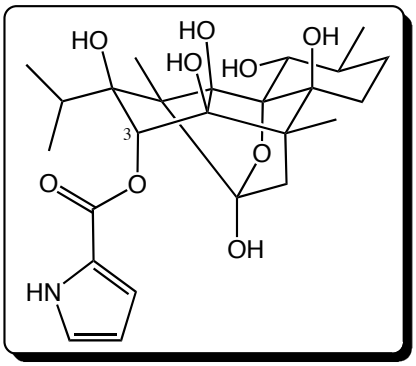


(+)-Ryanodine

Molecule Features/ Synthetic Challenges

- Sterically congested pentacyclic core
- Eleven contiguous stereocenters
- Five free hydroxyl functional groups, all present on the same face of the molecule
- Instability of the hemiketal
- α-Pyrrole carboxylic ester at C3

History of the Ryanoids

- Extracts from *Ryania* family members were used by local Central/South American natives as poison for arrowheads. The toxic nature of the shrubs were such that even termites would not feed on them.
- Ryanoid formulations were first patented and marketed by Merck & Co., Inc. (Ryanex) in 1943 as potent insecticides.
- Ryanodine was first isolated by Folkers and coworkers in 1948 from extracts of the tropical shrub *Ryania speciosa* Vahl. It was found that pure ryanodine had 700x the insecticidal potency of crude extracts.
- Absolute structure was determined in 1967 based on chemical degradation studies and x-ray analysis.
- First total synthesis of (+)-Ryanodol achieved by Deslongchamps and coworkers in 1979; ryanodine has not yet been synthesized.
- Ryanodine has allowed the identification and partial characteriation of a family of intracellular calcium release channels, termed Ryanodine Receptors (RyRs).

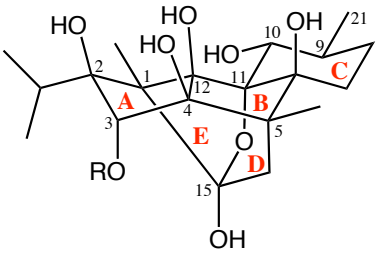
Isolation/Biology:

Folkers, K., et al *J. Am. Chem. Soc*. **1948**, *70*, 3086.
Weisner, K. et al *Tet. Lett*. **1967**, 221.
Sutko, J. L. et al *Pharmacol. Rev*. **1997**, *49*, 53.

Synthetic Efforts:

Deslongchamps, P. et al *Can. J. Chem.* **1979**, *57*, 3348.
Deslongchamps, P. et al *Can. J. Chem.* **1990**, *68*, 115-192.
Wood, J. L. et al *Tetrahedron* **2003**, *59*, 8855.
Graeber, J. K. *Yale University Graduate Thesis* **2003**.

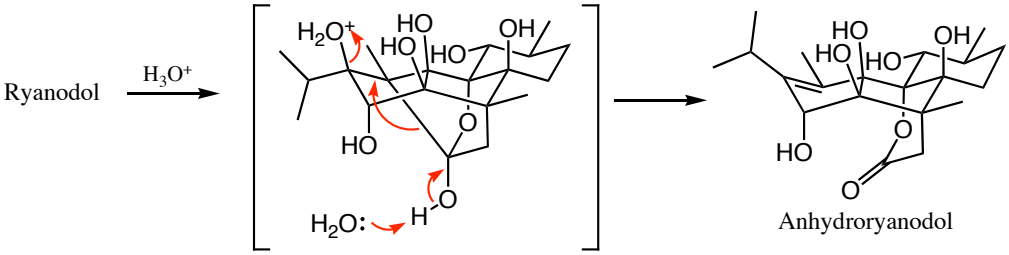
Ryanodine Reactivity



R=H, Ryanodol

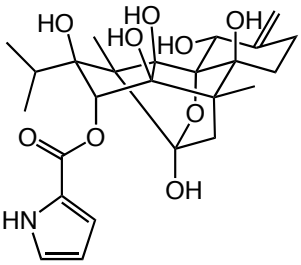
R=  , Ryanodine

- Cage-like shape of molecule prevents selective ester formation at C3; esterification occurs at C10.
- Dehydration occurs in the presence of acid to form anhydroryanodine. This major degradation product was key to elucidation of absolute structure.
- Due to the bridgehead nature of the molecule, stereocenters at C1, C5, C11, C12, and C15 are geometrically related.
- Deslongchamps uses this rationale to focus on setting the other six stereocenters en route to anhydroryanodol, the targeted precursor to (+)-ryanodol.

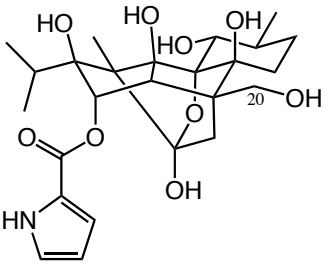


Anhydroryanodol

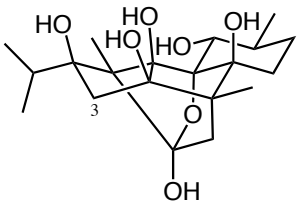
Related Ryanoids



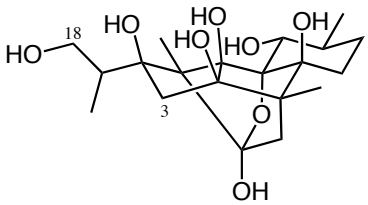
9,21-didehydroryanodine
Major component of ryania extracts; equipotent insecticide as ryanodine.



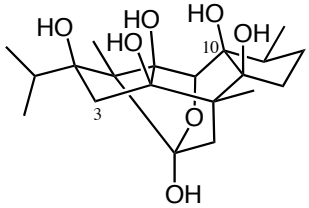
Spiganthine
Isolated from *Spigelia anthelmia*; found with ryanodine.



Cinnzeylanol



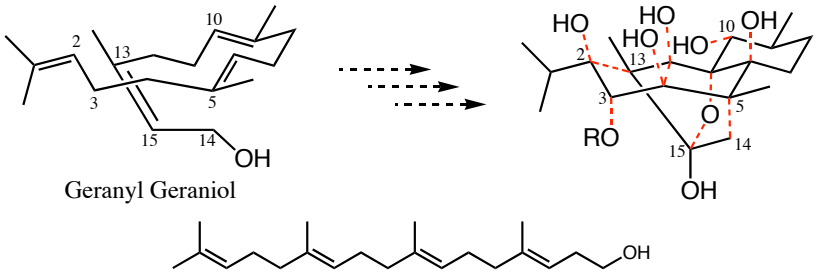
Cincassiol B



Perseanol
Isolated from *Persea indica*, the tree that ryanodol was first isolated.

Non-alkaloidal ryanoids isolated from the Cinnamonum genus; insecticidal.

Biosynthesis and Biological Activity



Geranyl Geraniol

- Thought to be derived from geranyl geraniol; however, "the mechanism of carbon-carbon bond formation... is not obvious... nor is that of introducing the required hydroxyl functionalities."

- Effects on calcium levels were known for some time, but it wasn't until 9,21-didehydroryanodine was isolated that the receptor could be identified (*via* [^{3}H]-labeled derivative)

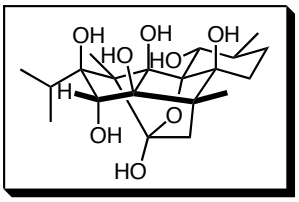
- RyRs are a family of calicum channels that release Ca^{2+} from intracellular stores; physically the largest ion channel known, RyRs exist as a homotetramer.

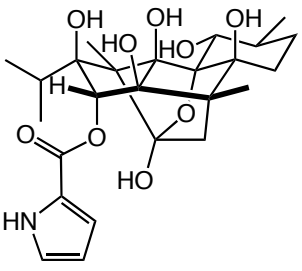
- Understanding of the binding site is unclear; at low [ryanodine], the receptor is at partial (50%) to full conductance; however, at high [ryanodine], the channel is in a closed state.

- The α-pyrrole ester is necessary for biological activity; ryanodol has lost all affinity for RyR. The next most important feature is the shape of the ryanoid skeleton. It is believed that ryanodine binds the receptor with the hydrophobic surface, exposing the polar alcohol functionalities.

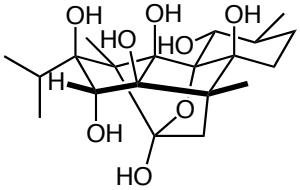
- Total synthesis efforts could provide analogs not accessible through degradation, facilitating elucidation of binding models, biosynthesis, binding site characteristics, and provide clues about endogenous RyR ligands.

Retrosynthesis of Ryanodine

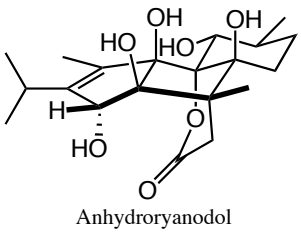




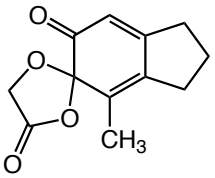
Ryanodine



Ryanodol



Anhydroryanodol



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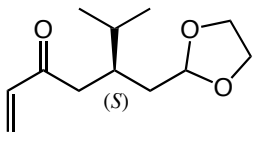
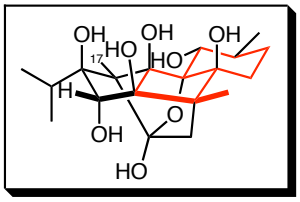
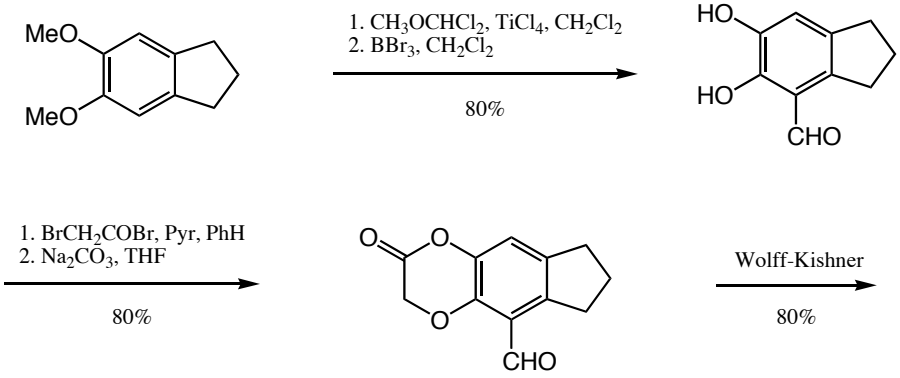
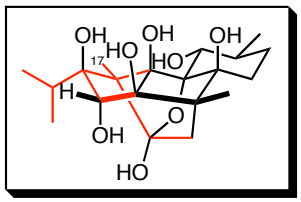


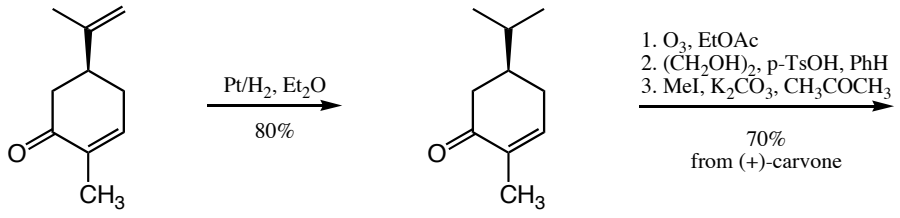
Synthesis of o-Spirolactone Dienone

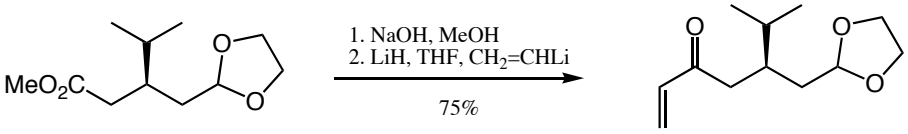




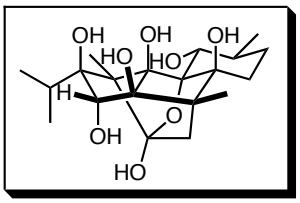
Synthesis of Vinylketone Acetal

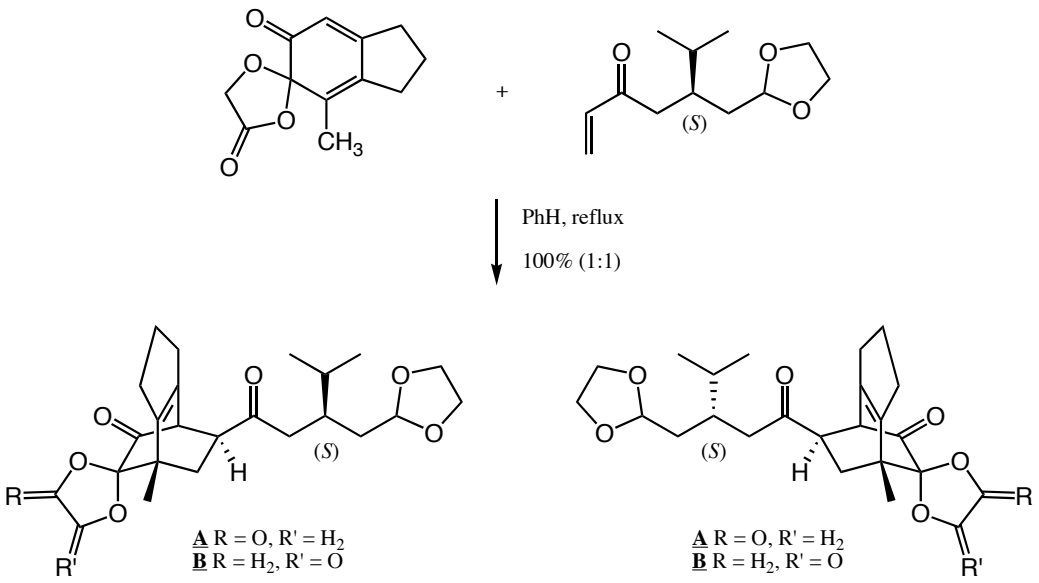




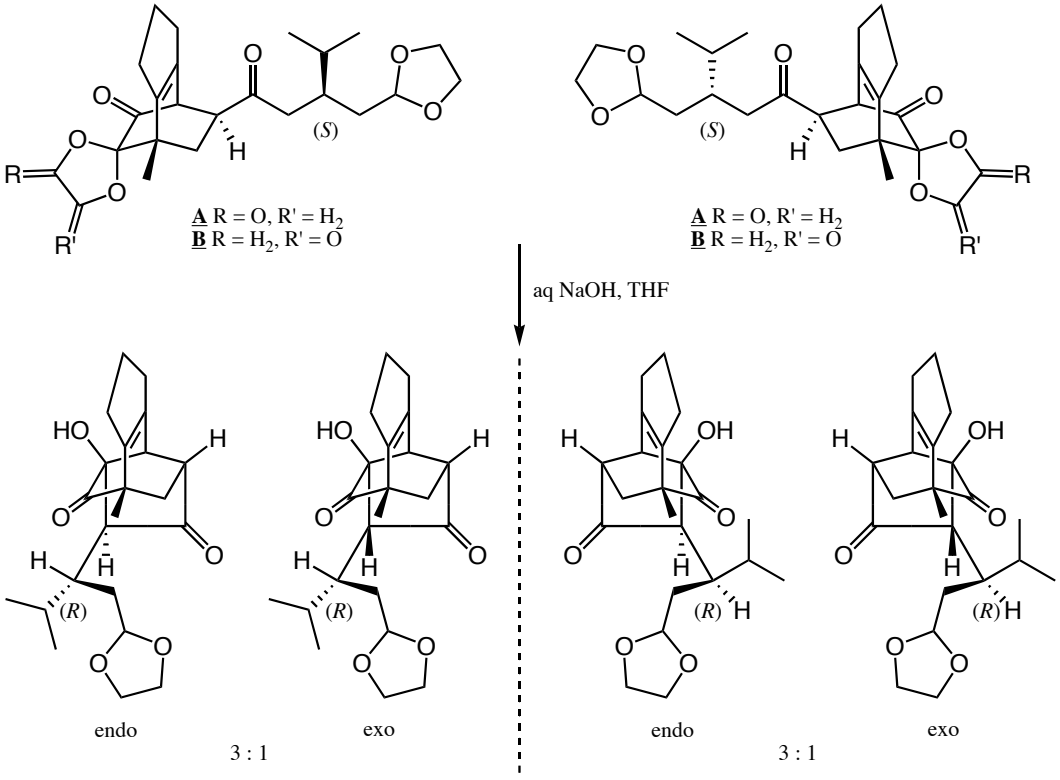


Diels-Alder Reaction

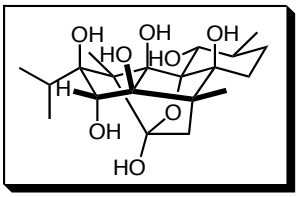


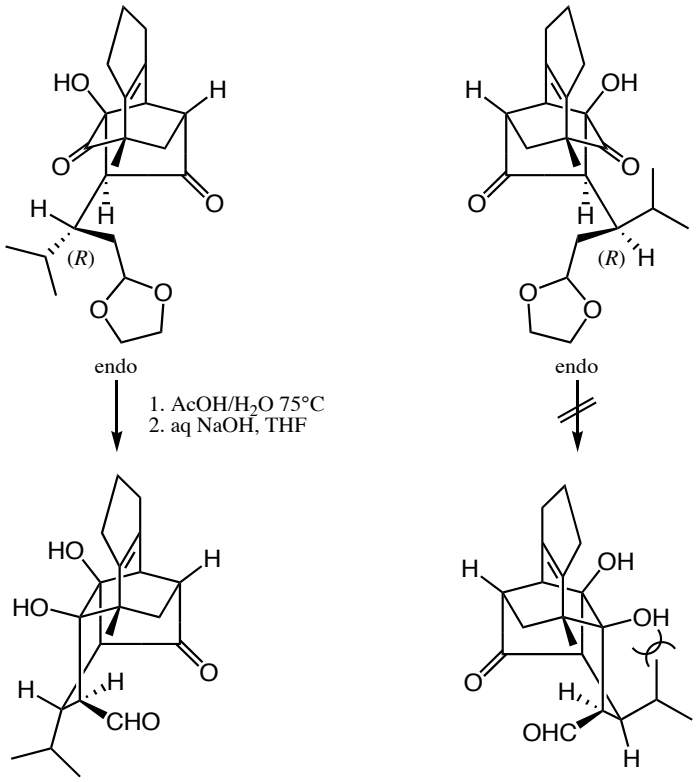


Intramolecular Aldol Reaction

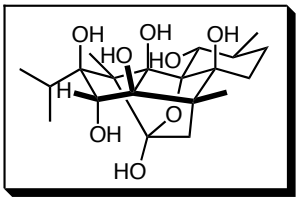


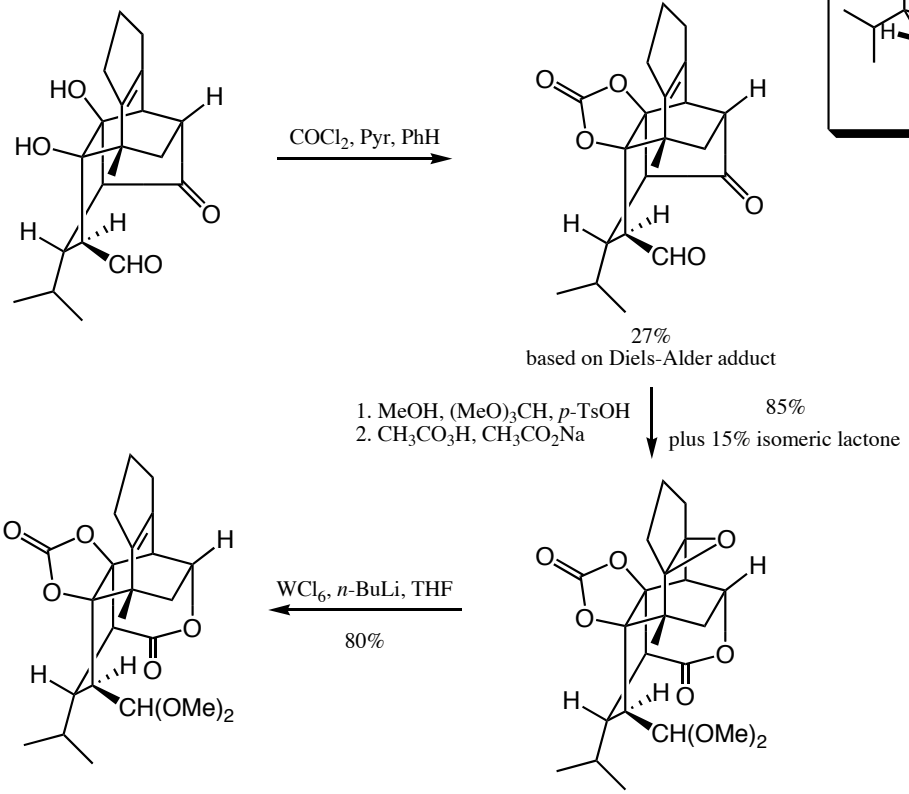
Second Aldol Reaction



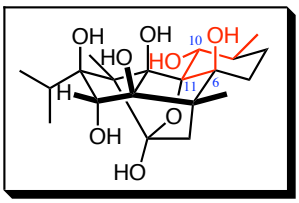


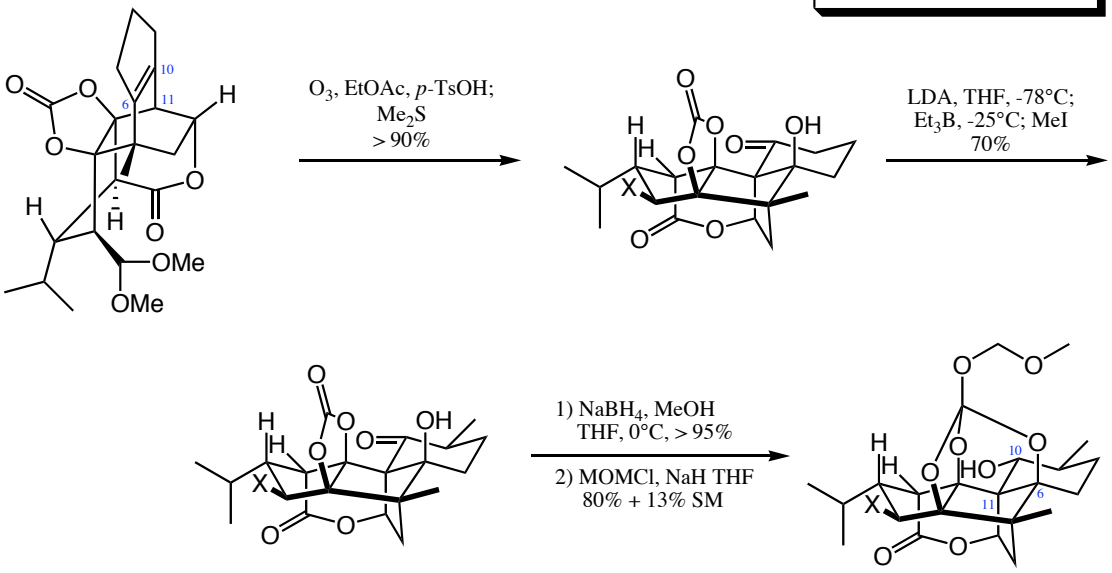
Key lactone Intermediate





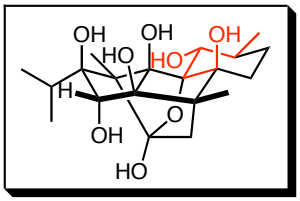
Ozonolysis and Aldol Condensation – the C Ring

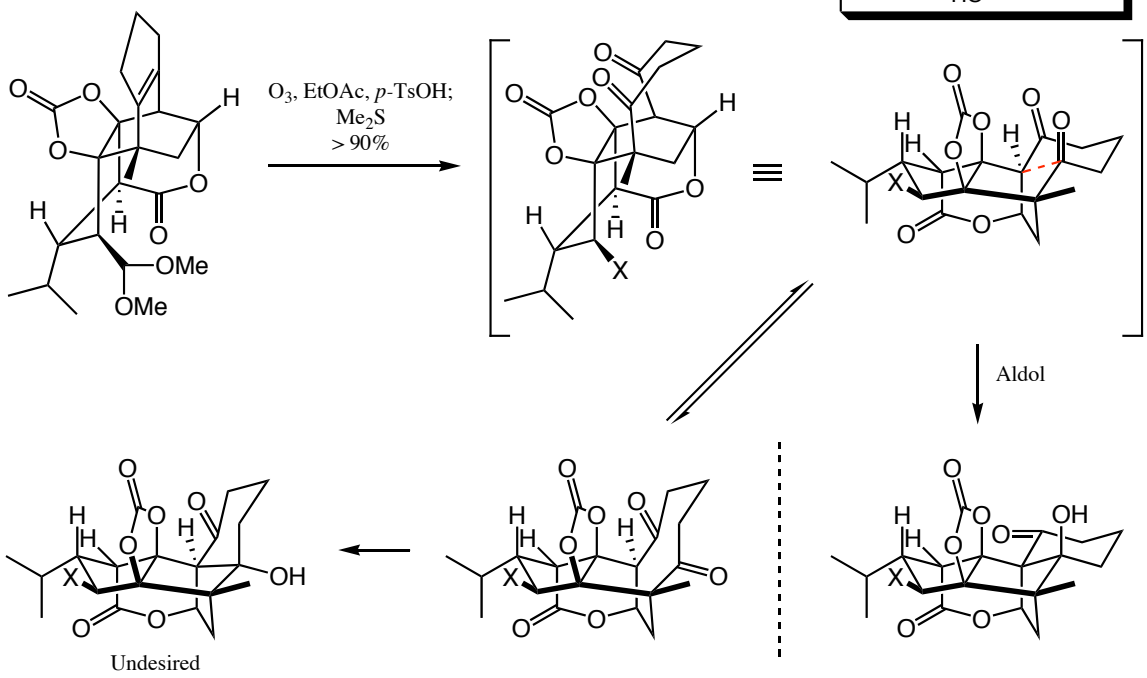




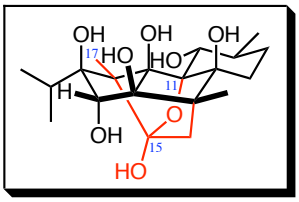
X = –CH(OCH$_3$)$_2$

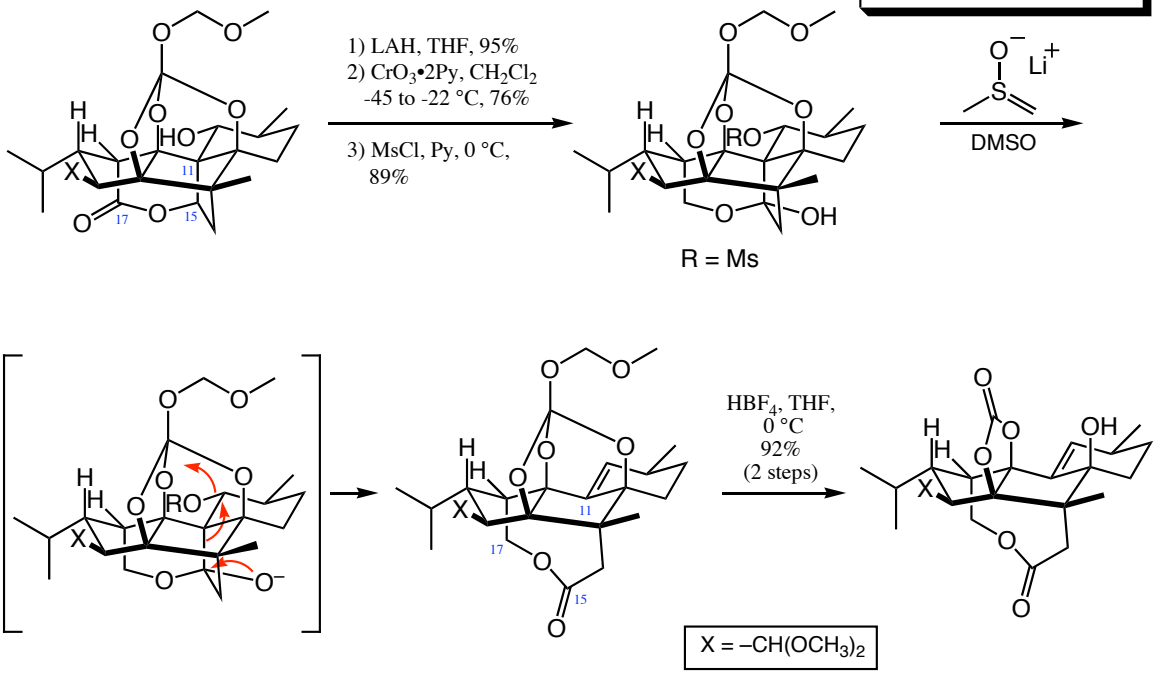
Ozonolysis and Aldol Condensation



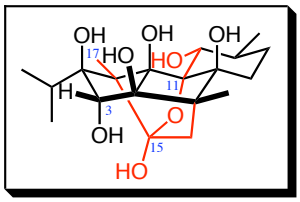


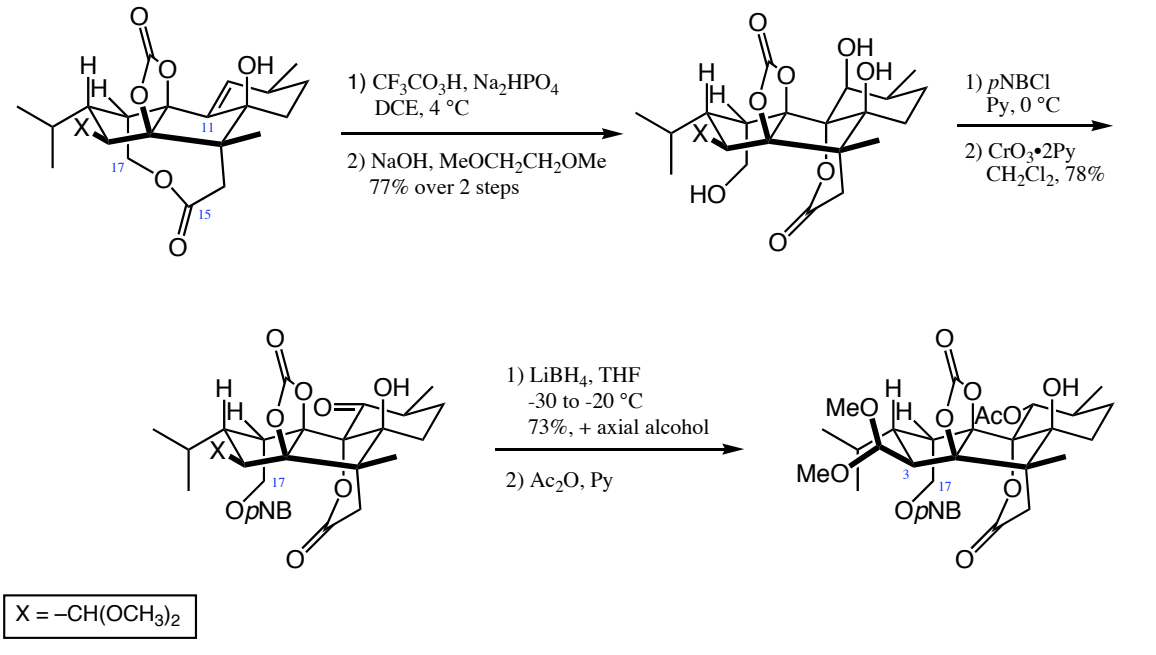
Grob Fragmentation to a Macrolactone – Strategy for the D Ring



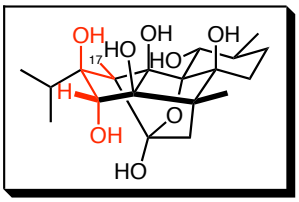


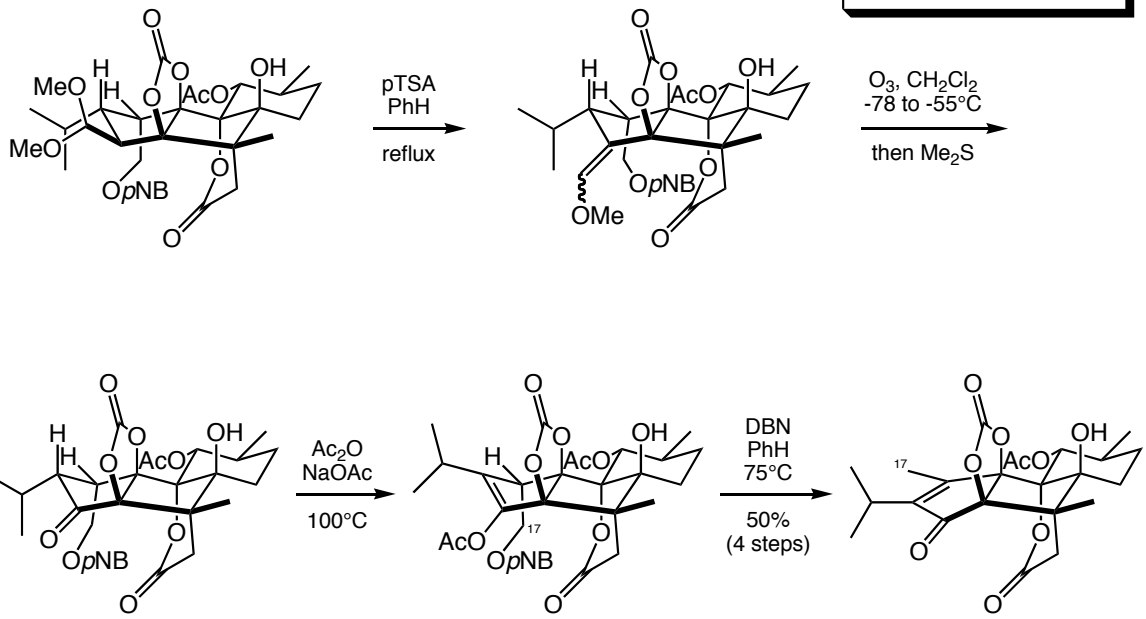
D Ring Formation and FGI



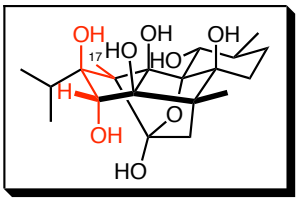


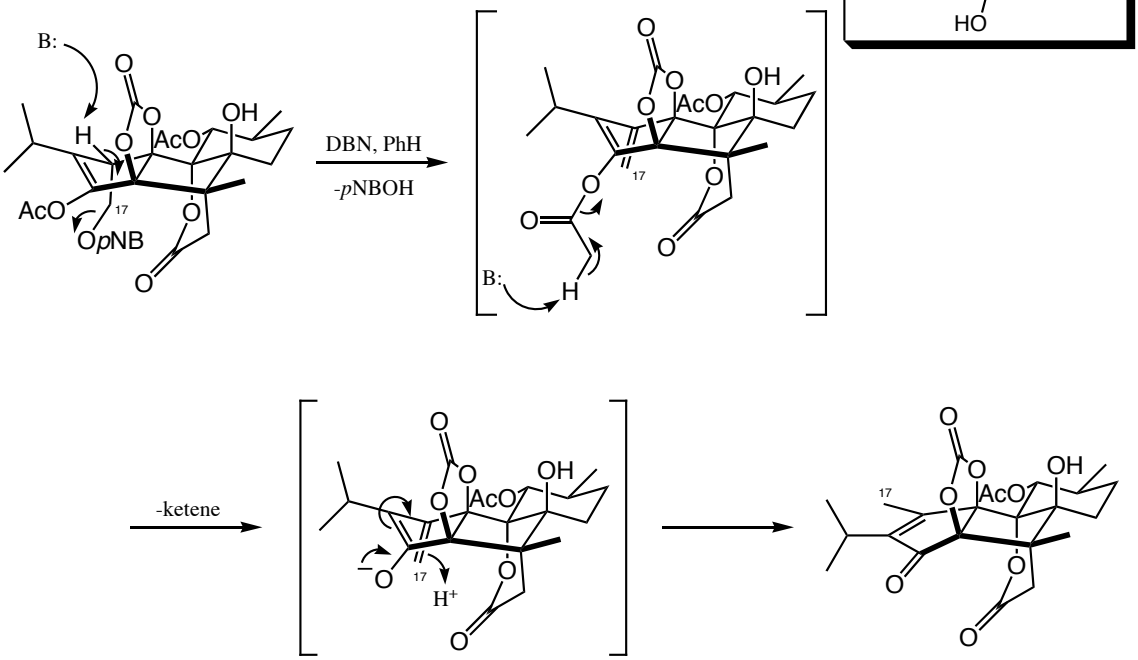
Degradation of Ring A



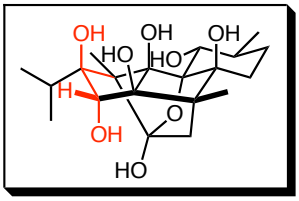


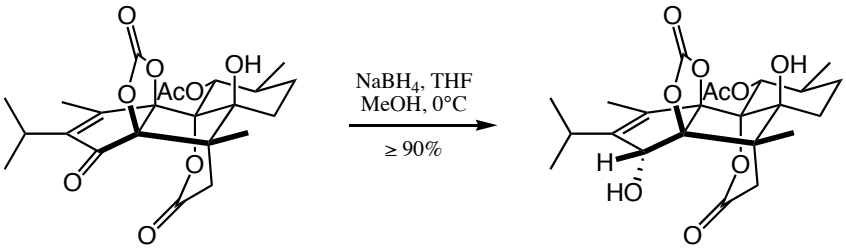
Enone Formation Details

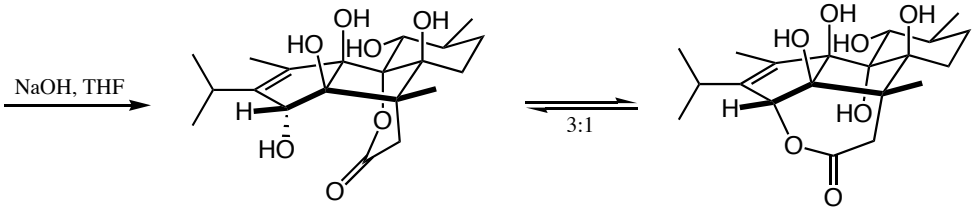




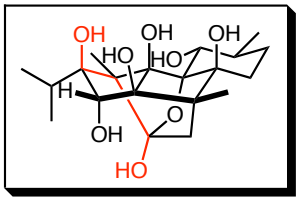
Synthesis of Anhydroryanodol





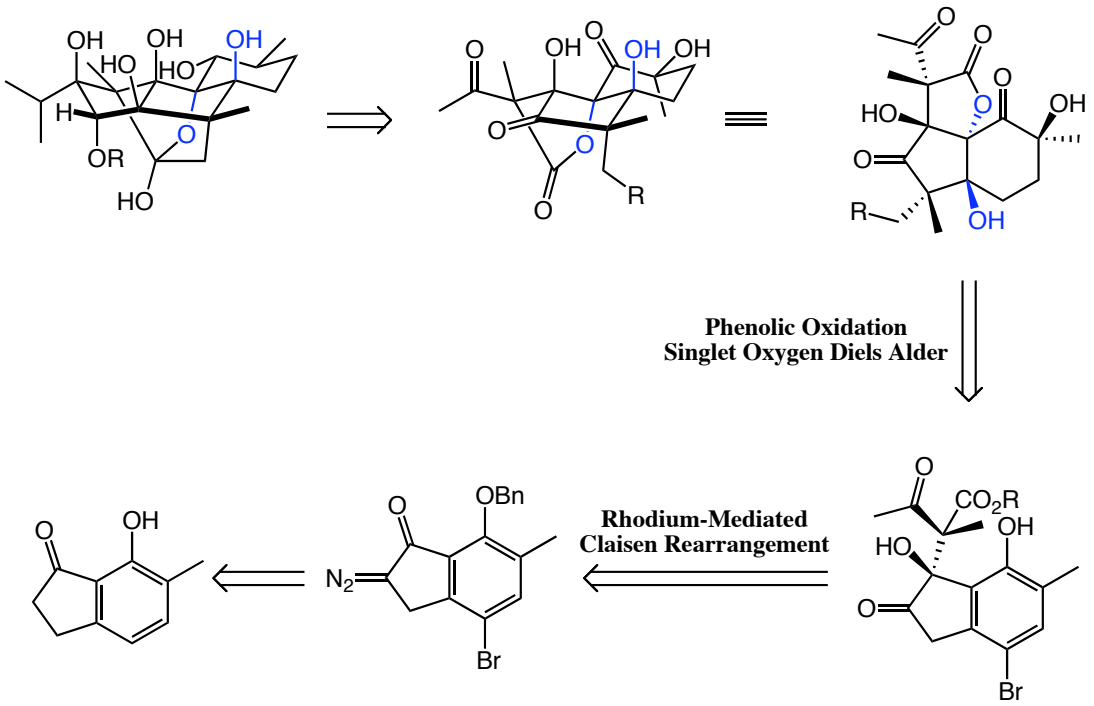


Completion of the Synthesis

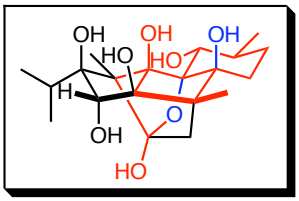


Wood's Retrosynthetic Analysis of Ryanodine

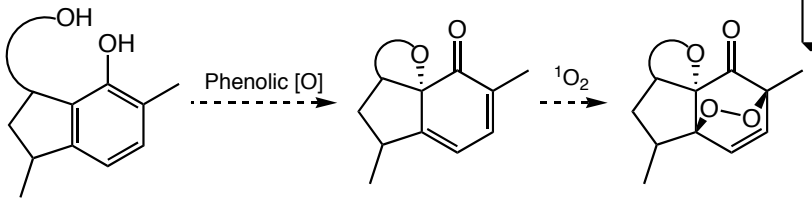
Rhodium-Mediated Claisen Rearrangement and Phenolic Oxidation / Singlet Oxygen Diels Alder



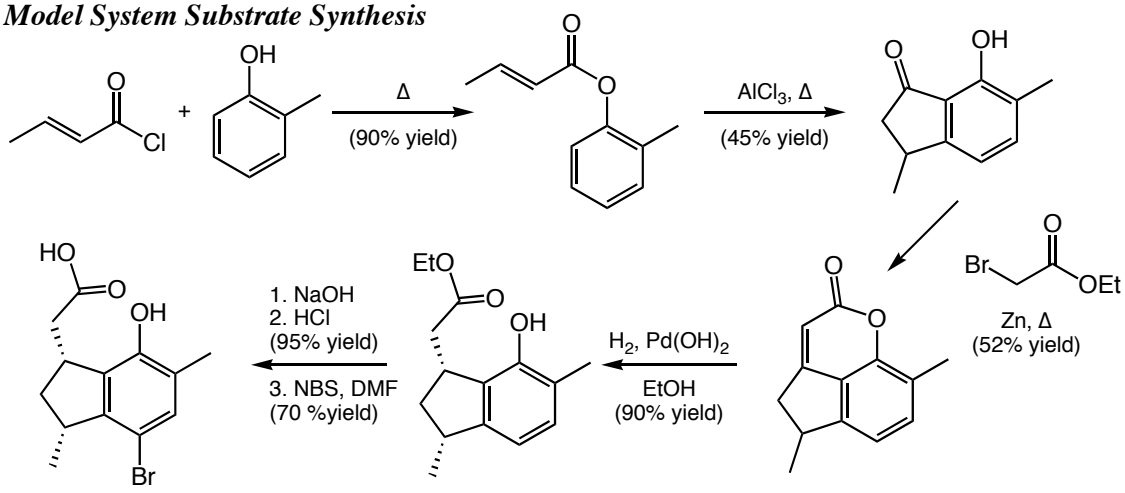
Wood's Phenolic Oxidation/ Singlet Oxygen Diels Alder



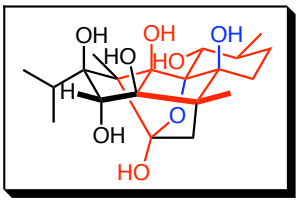
General Strategy



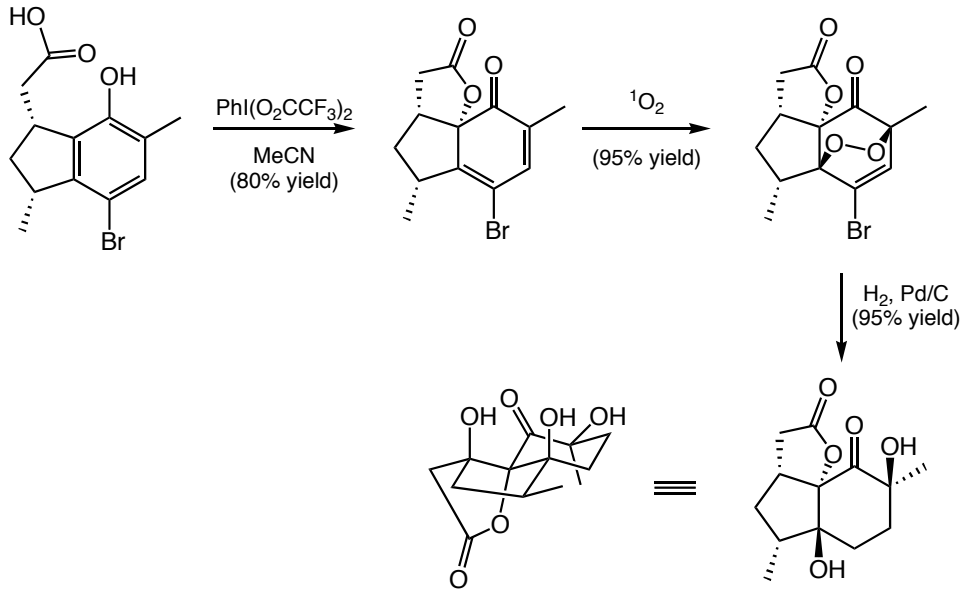
Model System Substrate Synthesis



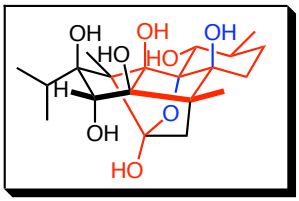
Wood's Phenolic Oxidation/ Singlet Oxygen Diels Alder (cont.)



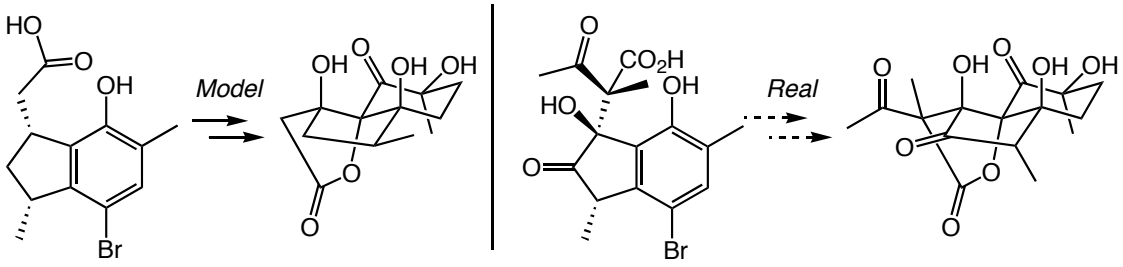
Model System Validates the Strategy



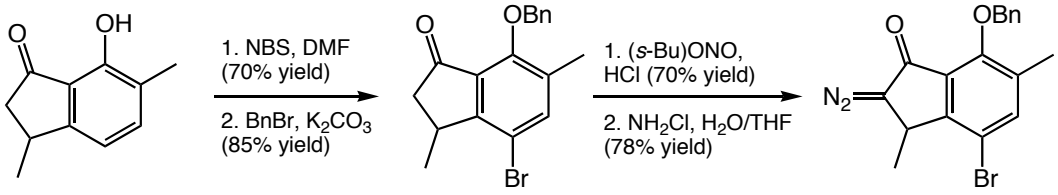
Wood's Phenolic Oxidation/ Singlet Oxygen Diels Alder (cont.)



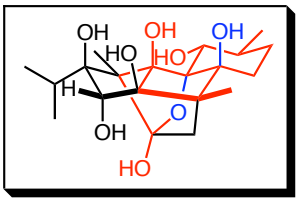
Strategy for the Real System



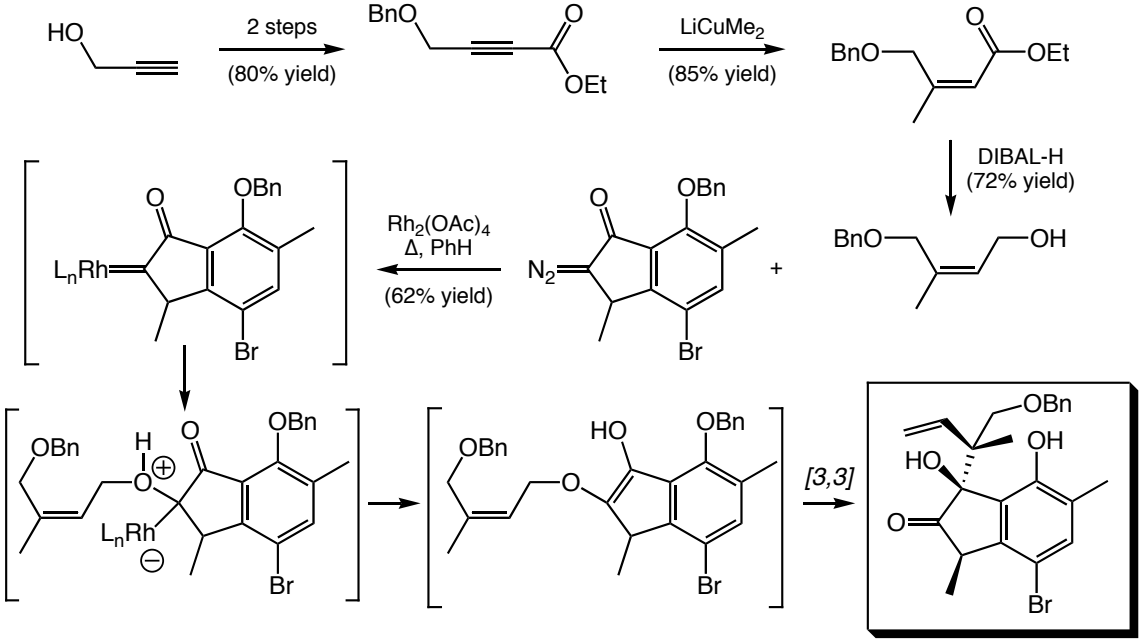
Real System Substrate Synthesis



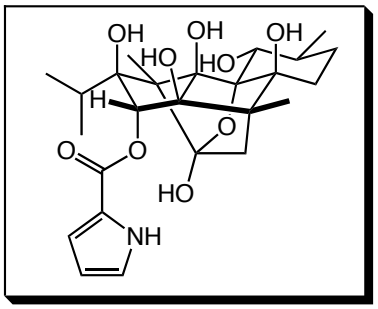
Wood's Phenolic Oxidation/ Singlet Oxygen Diels Alder (cont.)



Real System Validates the Strategy



Concluding Remarks



– Lack of obvious disconnections

– Many hydroxyls vs. compact polycyclic structure

– Inclusion/installation of the pyrrole ester moiety

– Synthesis of the C_6–C_{11} trans diol

"...it can be concluded from this analysis that ryanodol is indeed a very complex diterpene..." – Deslongchamps