CASCADE PERICYCLIC REACTIONS IN TOTAL SYNTHESIS

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Group Meeting

3/23/2021

Outline of Presentation

-Introduction to Pericyclic Reactions

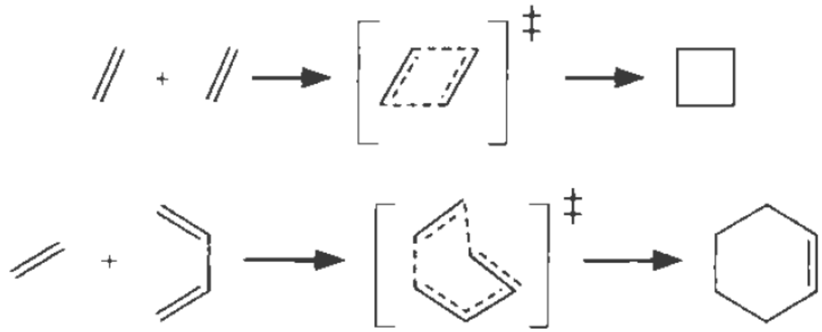
-Classes of Pericyclic Reactions w/ stereochemical considerations

- Electrocyclic ring opening/closing
- Cycloaddition Reactions
- Sigmatropic rearrangements
- Ene Reactions

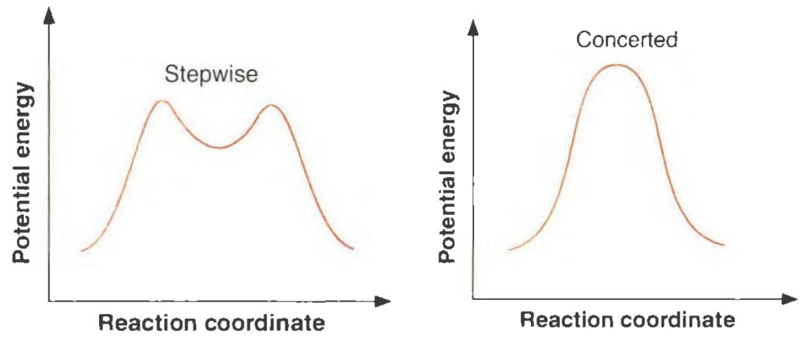
-Group Problems

What is a Pericyclic Reaction?

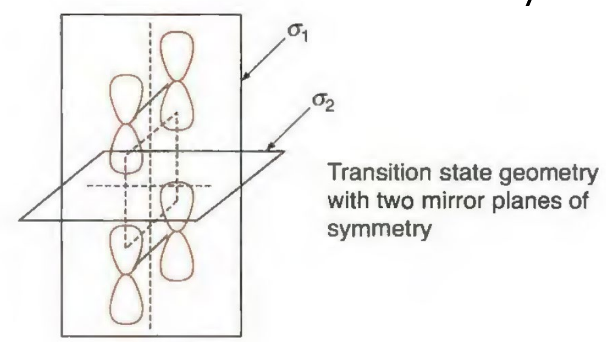
A **Pericyclic reaction** is one that involves a transition state with a cyclic array of atoms and an associated cyclic array of interacting orbitals



1. Must be concerted



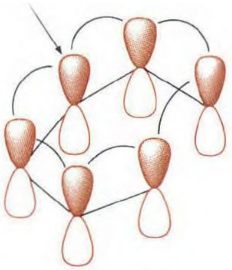
2. Must have conservation of orbital symmetry



Anslyn, E. V., & Dougherty, D. A. (2005). *Modern physical organic chemistry*. University Science Books.

Aromatic Transition State Theory/Topology

Zimmerman and Evans (1965): Developed the theory of Aromatic Transition state for pericyclic reaction. The theory states that if a reaction, with a simple array of 4n + 2 electrons in a pericyclic transition will be stabilized by aromaticity.

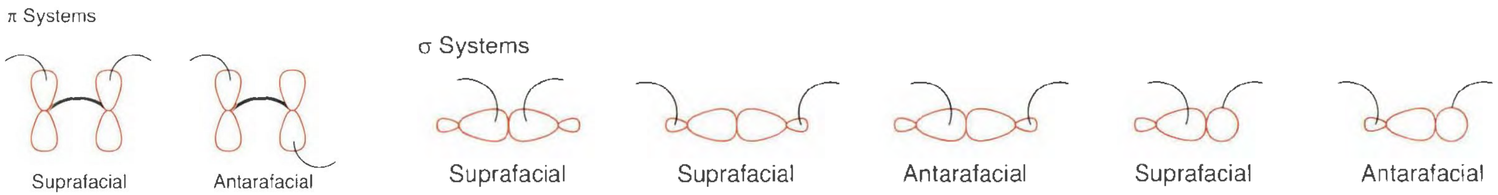


No nodes

This theory was further extended to accommodate systems with “twisted ribbon natures”. A transition state can be characterized as having Huckel topology (even nodes) or Mobius Topology (odd nodes) and based on the reaction conditions can predict whether a reaction will be pericyclic or stepwise.

Number of nodes	**Δ**	**hv**
Odd	Mobius Topology (4n)	Mobius Topology (4n+2)
Even	Huckel Topology (4n+2)	Huckel Topology (4n)

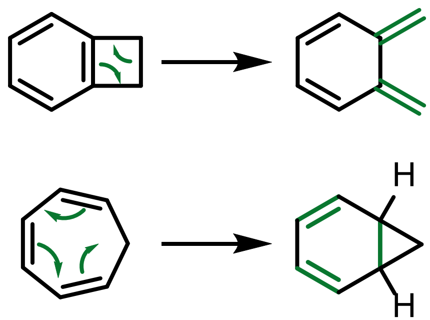
Suprafacial vs. Antarafacial- Which face of the orbital will participate in the transition state



Anslyn, E. V., & Dougherty, D. A. (2005). *Modern physical organic chemistry*. University Science Books.

Four Classes of Pericyclic Reactions

Electrocyclization

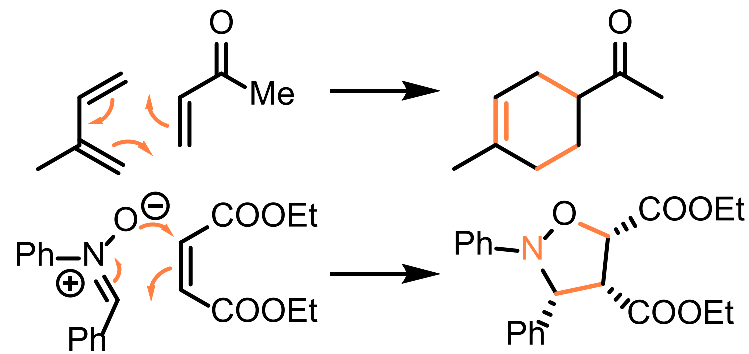


4 π Electrocyclic ring opening

6 π Electrocyclic ring closing

A bond forms/breaks between two conjugated systems

Cycloaddition

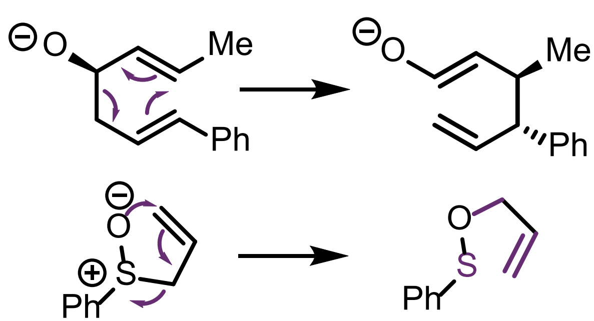


[4+2] Diels-Alder

[3+2] 1,3-dipolar

σ bonds are formed between two ends of two π systems to give a cyclic product

Sigmatropic Rearrangement

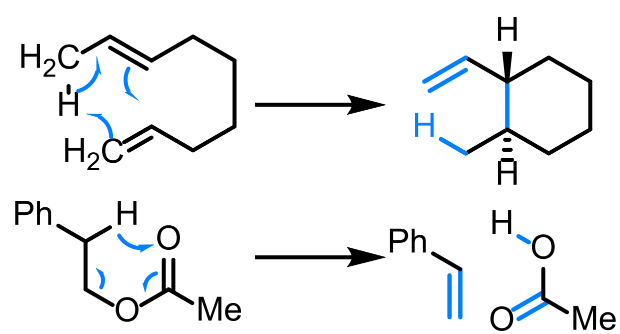


[3,3] (Cope)

[2,3]

Cleavage of a σ bond connecting ends of a fragments and concerted formation of a σ bond at the other end

Ene Reaction



Alder ene reaction

Retro-ene reaction

6 electron reaction with a four-electron component (ene) and two-electron component (enophile)

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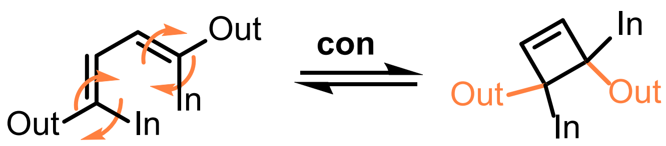
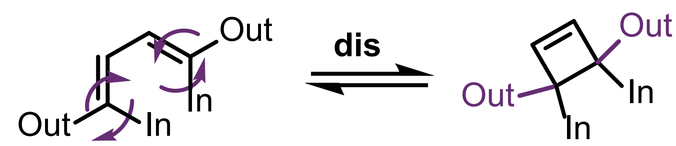
Electrocyclization Stereochemistry Considerations

The stereochemistry of reaction depends on how the termini rotate

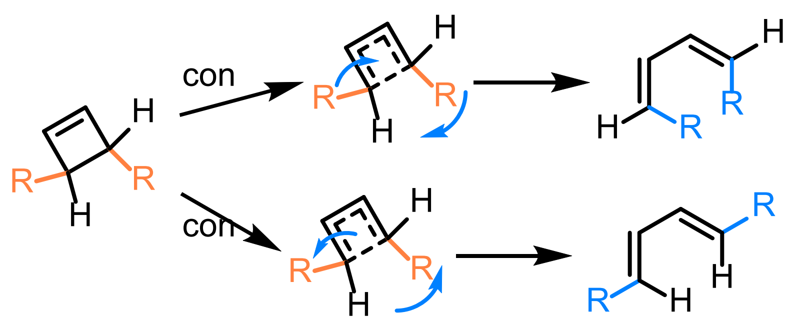




Woodward-Hoffman Rules predicts in which reactions one will have certain stereospecificity based on odd (4n+2) or even (4n) electron pairs

Number of electron pairs	Δ	hv
Odd	disrotatory	conrotatory
Even	conrotatory	disrotatory

Another stereochemistry consideration for electrocyclic ring opening can be the **torque selectivity**



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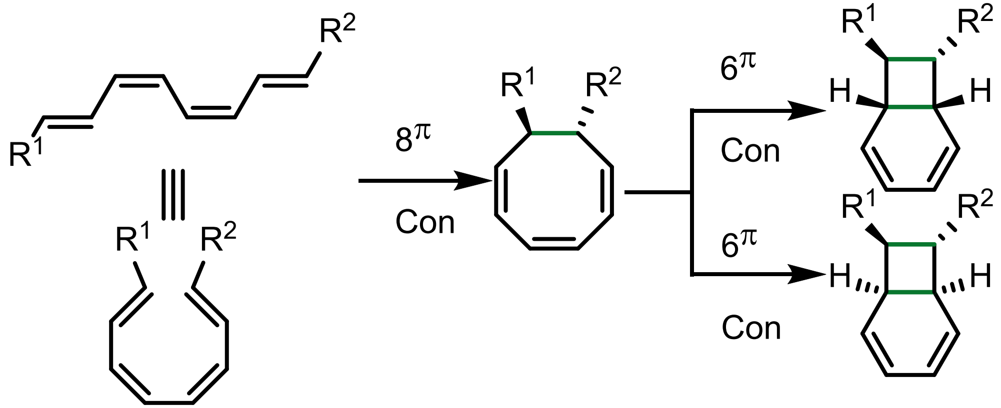
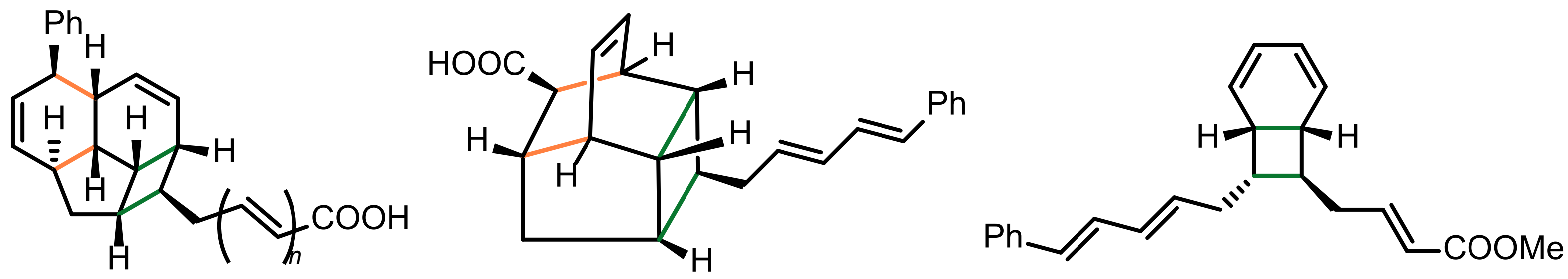
8π-6π Electrocyclizations in Biosynthesis

8π-6π Electrocyclizations are believed to be common biosynthesis pathway in nature.



Nicolaou (1982): Wanted to show validity of 8π-6π Electrocyclizations as a biosynthetic pathway by synthesizing Endiandric acid family.



n=0, Endriandric acid A
n=1, Endriandric acid B

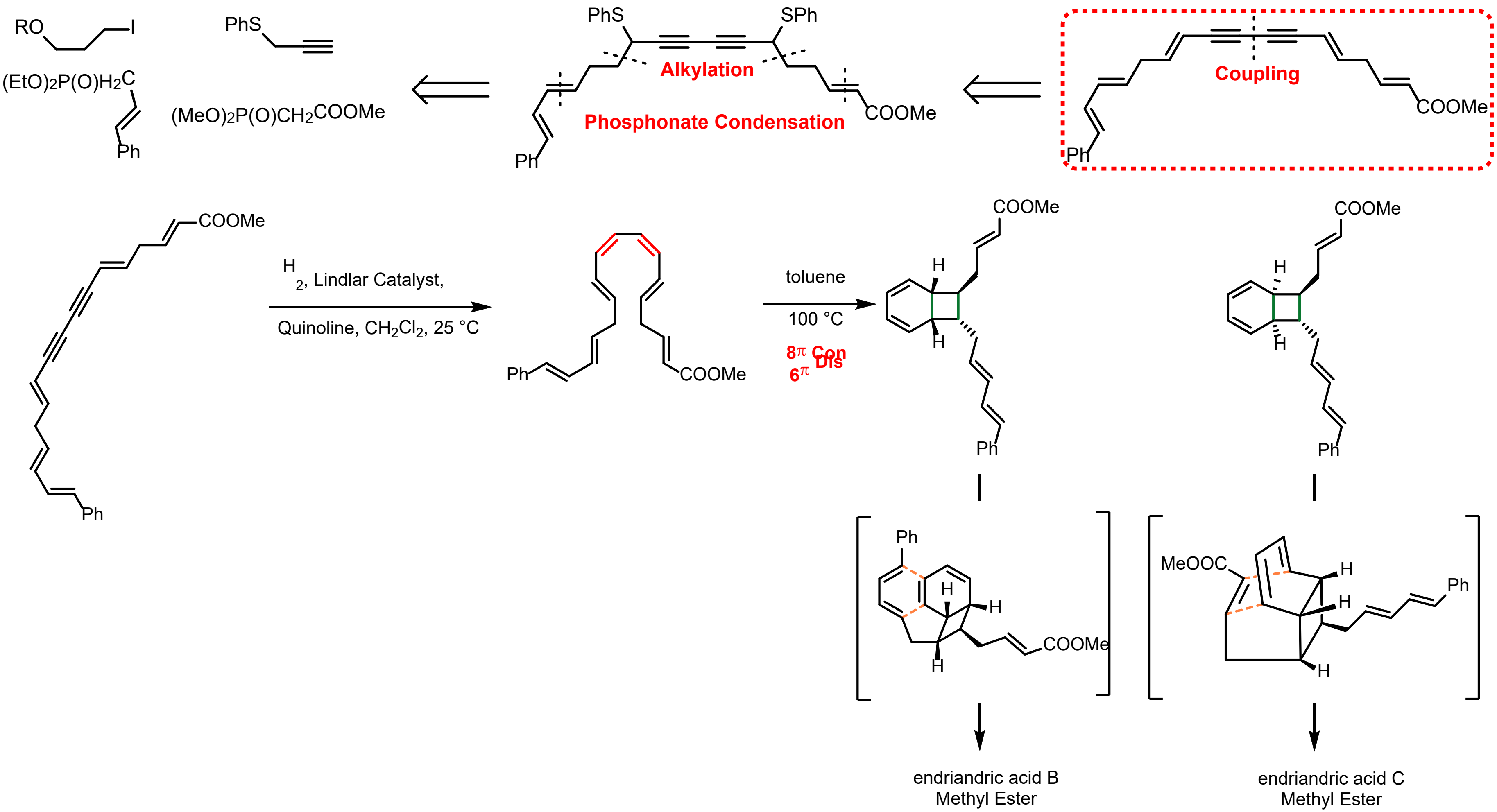
Endriandric acid C

Endriandric acid D (Hypothesized)

J. Am. Chem Soc. 1982, 104, 5557. J.Am Chem. Soc. 1982, 104, 5558. J. Am chem. Soc. 1982, 104, 5560.

Total Synthesis of Endiandric Acid family

Nicolau exhibited that 8π-6π Electrocyclization pathway was viable for synthesis.



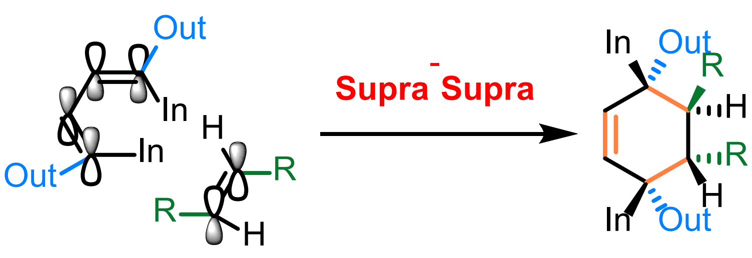
J. Am. Chem Soc. 1982, 104, 5557. J.Am Chem. Soc. 1982, 104, 5558. J. Am chem. Soc. 1982, 104, 5560.

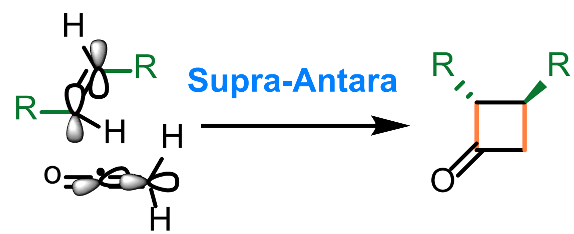
4.5:1 B:C, 30% Yield

Cycloaddition Stereochemistry Considerations

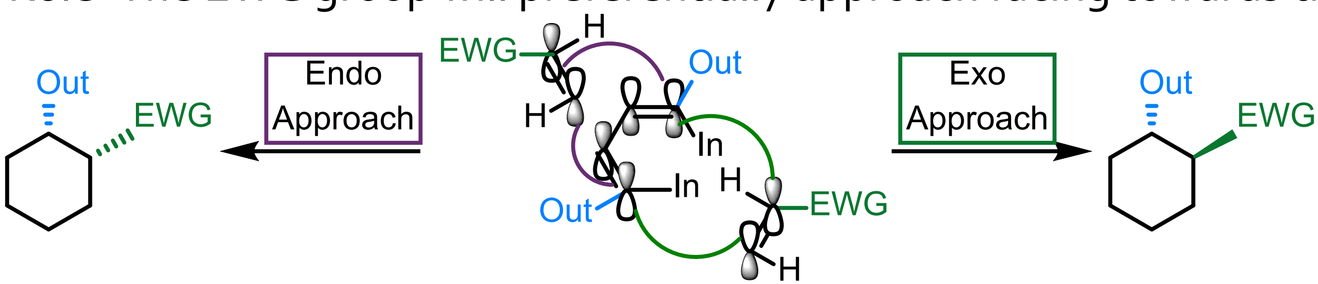
Woodward-Hoffman Rules have been developed for cycloadditions and are based on how the orbitals will approach

Number of electron pairs	Δ	hv
Odd	Supra-Supra	Supra-Antara
Even	Supra-Antara	Supra-Supra





Endo Rule- The EWG group will preferentially approach facing towards the diene



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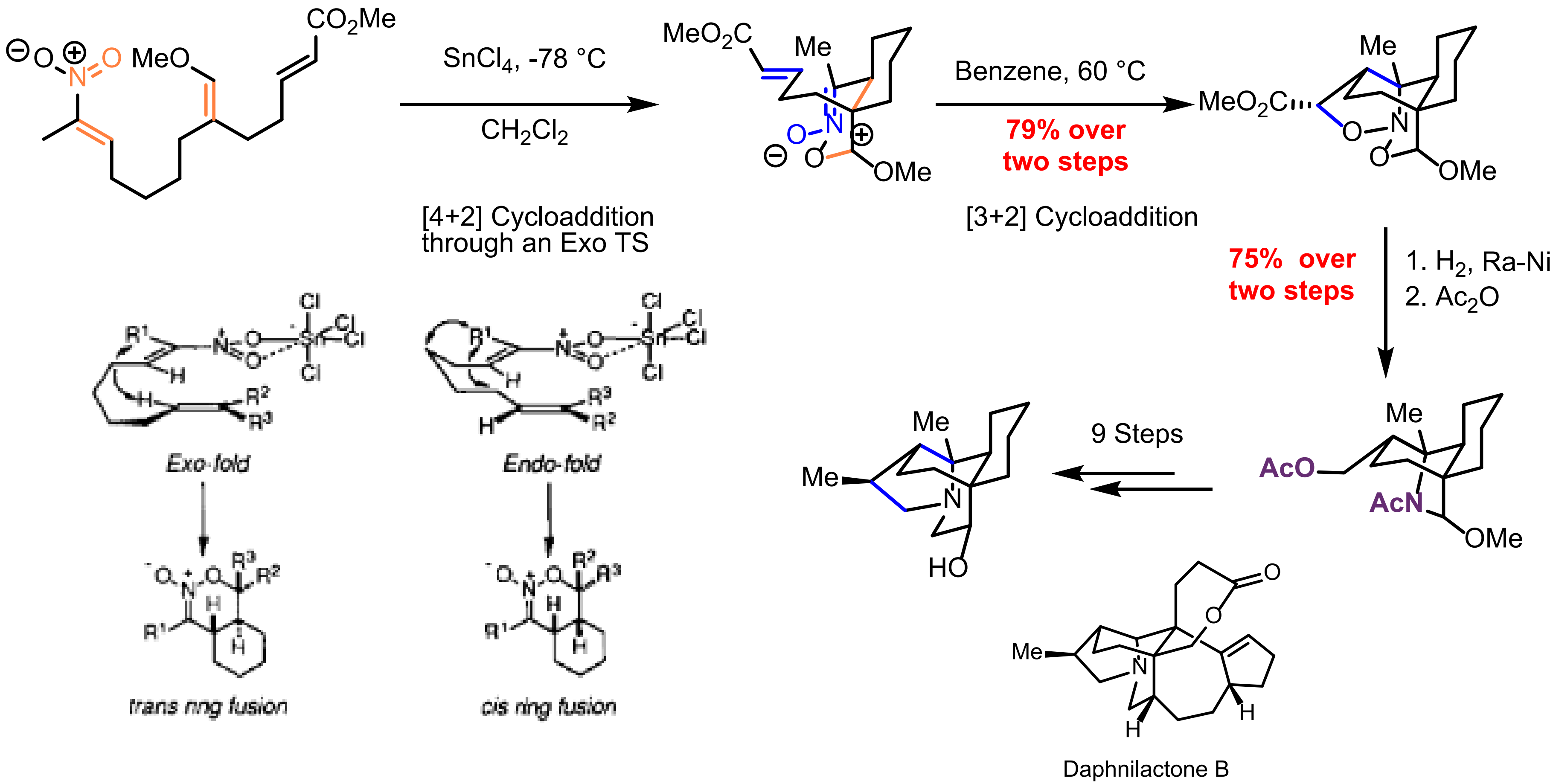
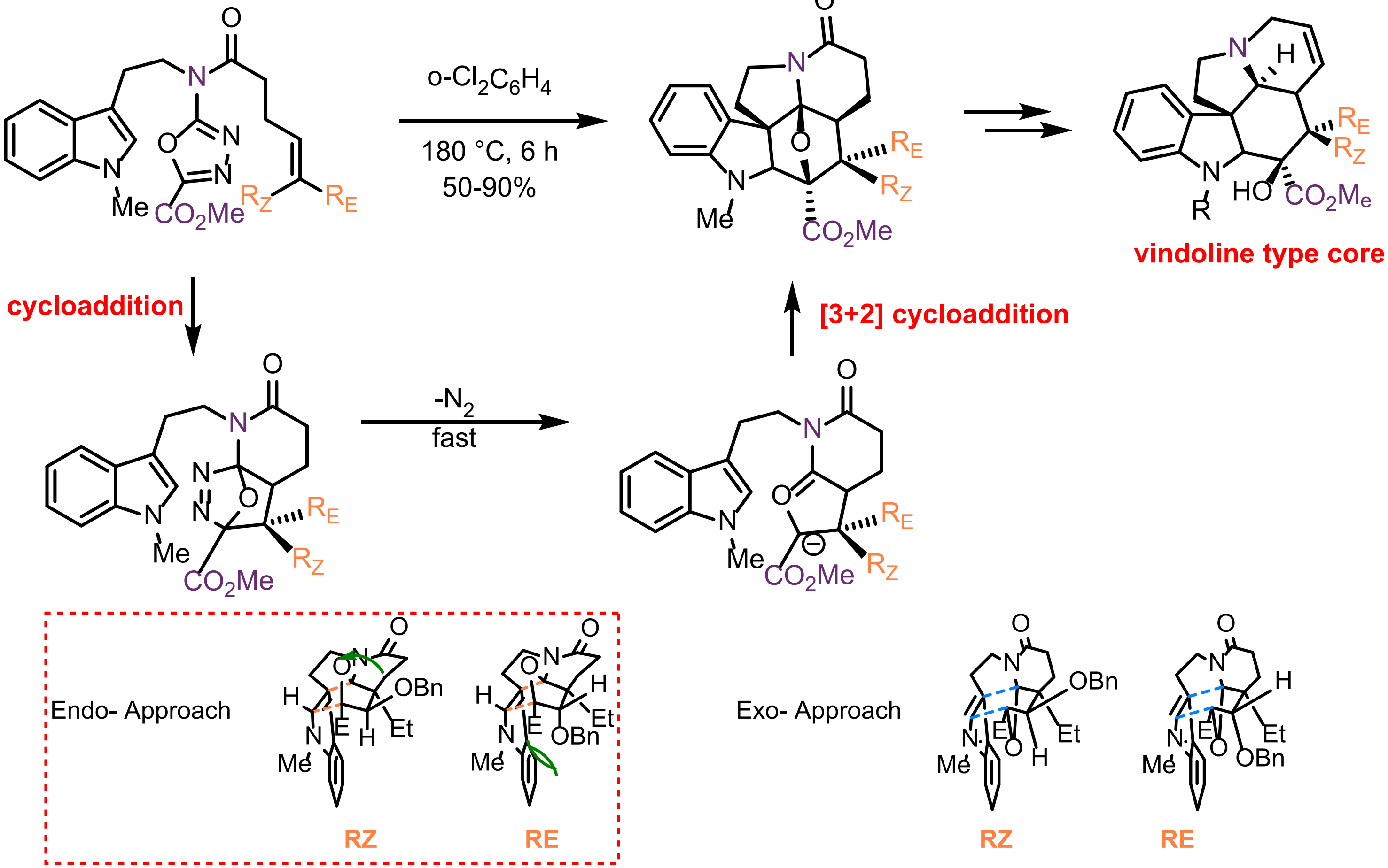
Application of tandem cycloadditions

Denmark (2006): Published a synthesis towards the core of Daphnilactone B. The key step in the synthesis is a tandem/cascade [4+2]/[3+2] cycloaddition



Synthesis example of Stereochemistry

Boger (2006): Published a concise synthesis towards Vindoline which is an intermediate towards the Vinca-Alkaloids

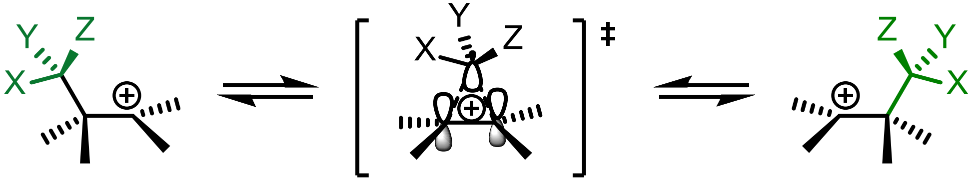


J. Am. Chem. Soc. 2006, 128, 32, 10589–10595.

Sigmatropic Rearrangement Stereochemistry

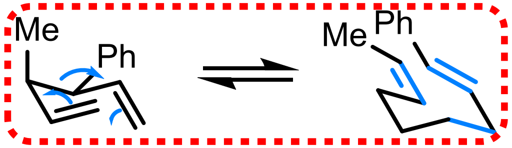
Woodward-Hoffman Rules have been developed for sigmatropic rearrangements which can require a suprafacial or antarafacial migration of the group

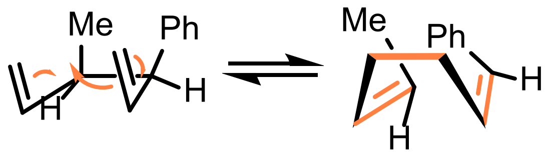
Number of electron pairs	Δ	hv
Odd	Supra-Supra	Supra-Antara
Even	Supra-Antara	Supra-Supra



[1,2] cationic **Supra-Supra**

The stereoselecitivity of the reactions is based on whether it will go through a chair or a boat transition state





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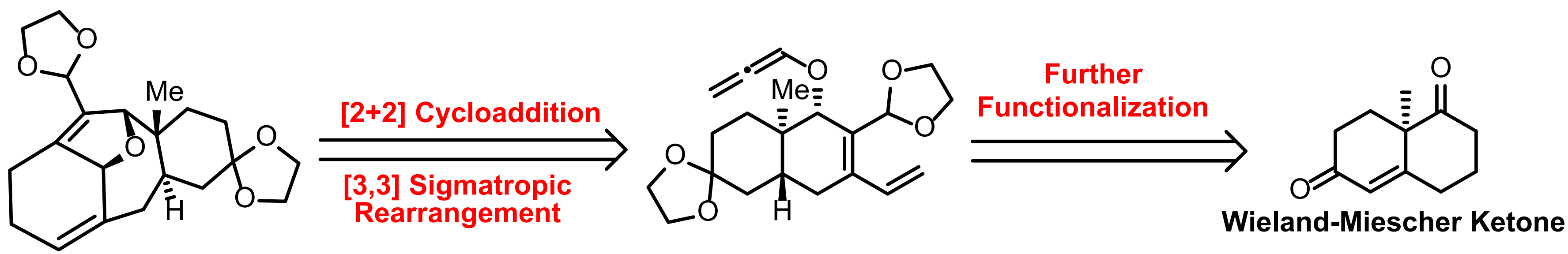
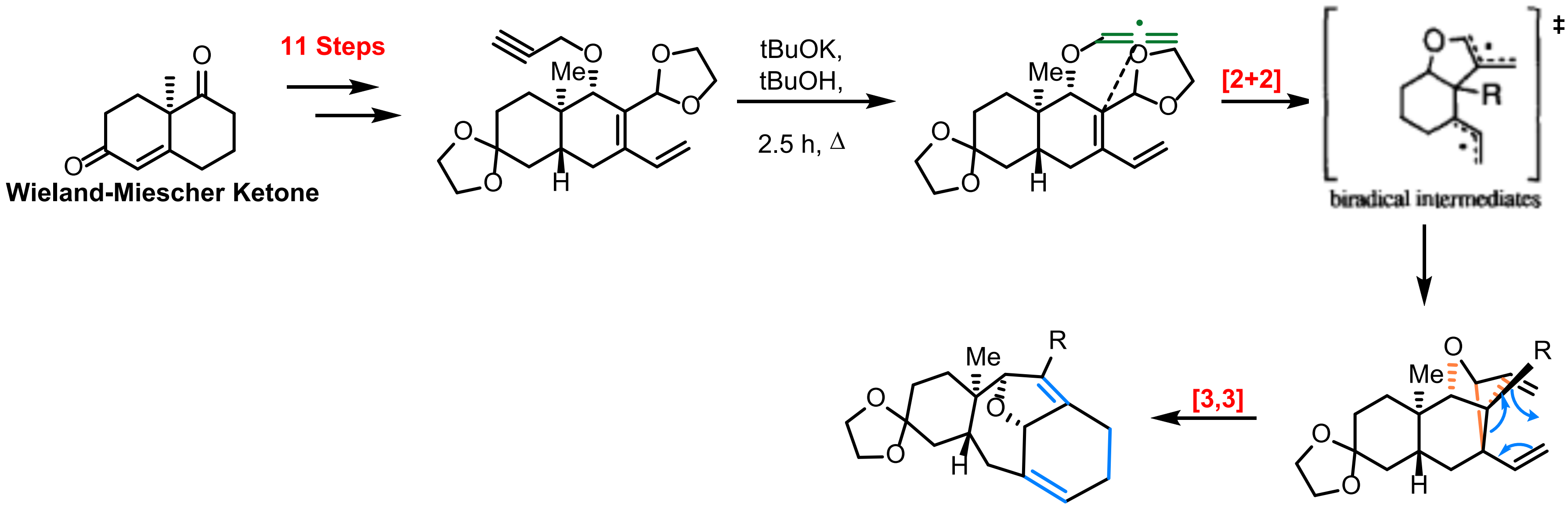
Synthesis example of Stereochemistry

Kanematsu (1995): Published a partial synthesis towards the Oxa-Tane type scaffold

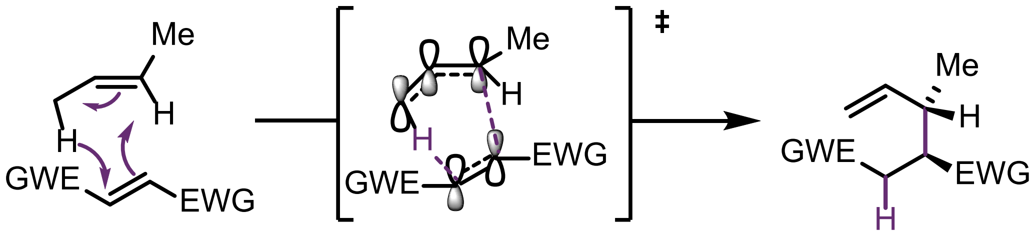




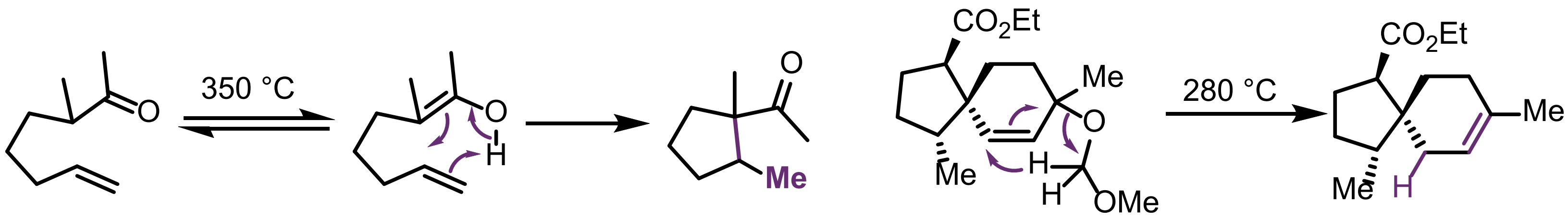
Tetrahedron 1995, 51, 3499-3506.

Ene Reaction

Ene reaction is a six-electron process- it usually has one four-electron component (ene) and the one two-electron component (enophile) and must always be **Supra-Supra**



There are many different types of ene reactions such as: enol type enes and the retro ene reactions.



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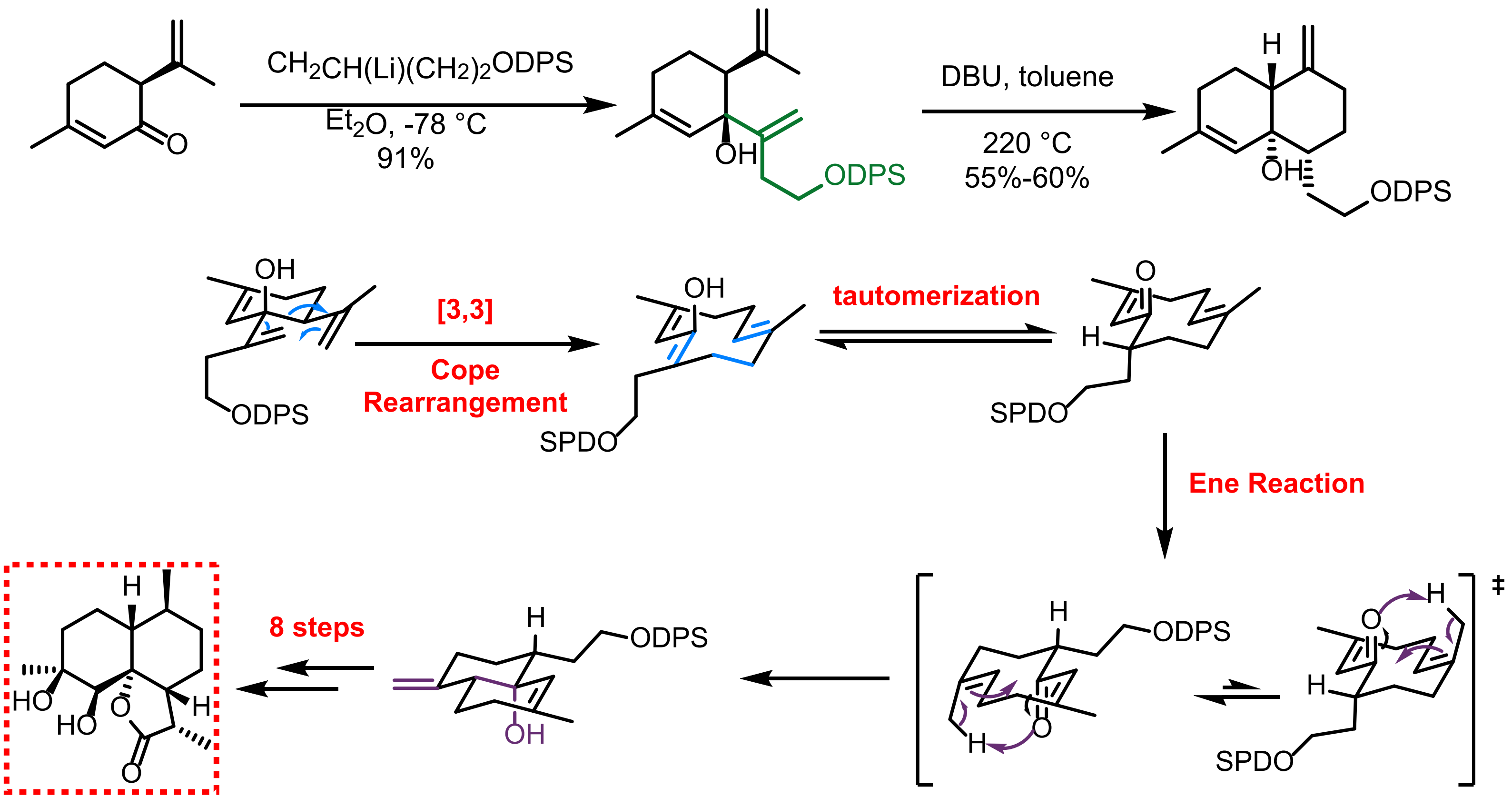
Pericyclic Cascade with Ene Reaction

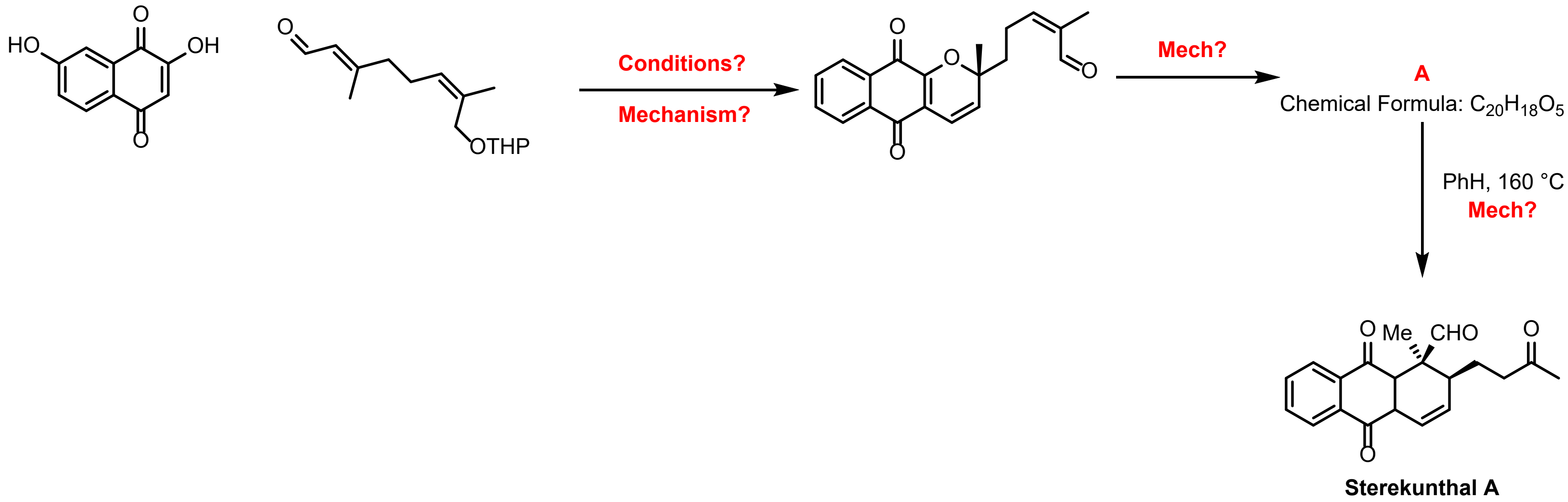
Barrilaut (2001): Towards the synthesis of (+)-Arteannium M an anti-Malarial.



Org. Lett. 2001, 3, 12, 1925–1927

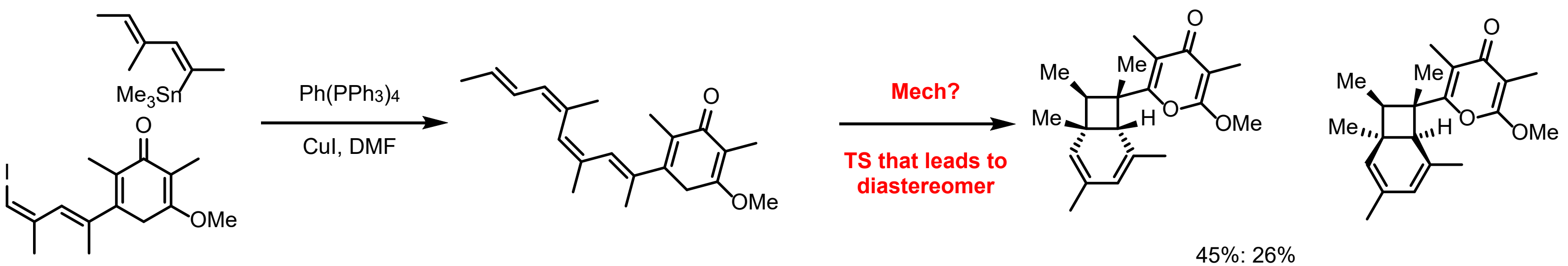
Problem 1

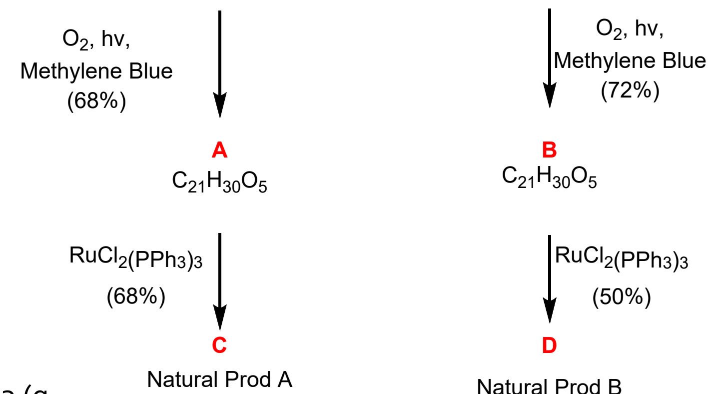
In 2005, Dirk Trauner published a biomimetic synthesis of Naphthoquinones, natural products isolated from the Bignoniaceae plant family. This family of natural productshas interesting antimalarial properties and Trauner et. Al wanted to study thie biosynthesis.



Problem 2

In 2005, Dirk Trauner published a hypothesized Biomimetic total synthesis to natural products isolated from a bacteria, *Streptomyces spectabilis.*





Natural Product A

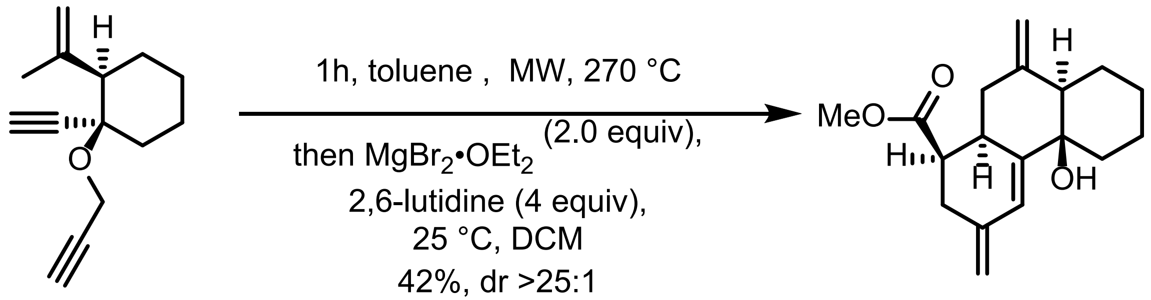
IR (thin film) 2960, 2296, 1659, 1615 cm-1;
1H NMR (500 MHz): δH 3.98 (s, 3 H), 3.18 (s, 1 H), 2.45-2.38 (m, 2 H), 2.27 (s, 1 H), 1.93 (s, 3H), 1.89 (s, 3 H), 1.55 (s, 3 H), 1.38 (s, 3 H), 1.19 (m, 6 H), 1.02 (s, 3 H);
13C NMR (125 MHz): δC 182.6, 166.2, 163.3, 119.0, 105.5, 62.3, 61.3, 60.6, 59.4, 56.9, 54.1, 45.0, 44.0, 35.9, 23.6, 22.2, 20.5, 18.6, 11.4, 11.2, 7.6;
HRMS (EI) calcd for C21H28O5 (M+): 360.193674; found: 360.194119.

Natural Product B

IR (thin film) 2924, 2466, 1657, 1613 cm-1;
1H NMR (500 MHz): δH 4.05 (s, 3 H), 3.09 (s, 1 H), 2.94 (s, 1 H), 2.83 (s, 1 H), 2.53 (q, J = 7.3 Hz, 1 H), 2.02 (s, 3 H), 1.88 (s, 3 H), 1.60 (s, 3 H), 1.41 (s, 3 H), 1.38 (s, 3 H), 1.18 (s,1 H), 1.16 (m, 1 H);
13C NMR (125 MHz): δC 181.7, 162.3, 162.2, 117.8, 100.9, 60.3, 57.8, 57.2, 56.8, 56.2, 46.9, 46.1, 44.3, 34.0, 26.2, 21.4, 21.1, 15.7, 10.8, 10.1, 7.1;
HRMS (EI) calcd for C21H28O5 (M+): 360.193674; found: 360.193884.

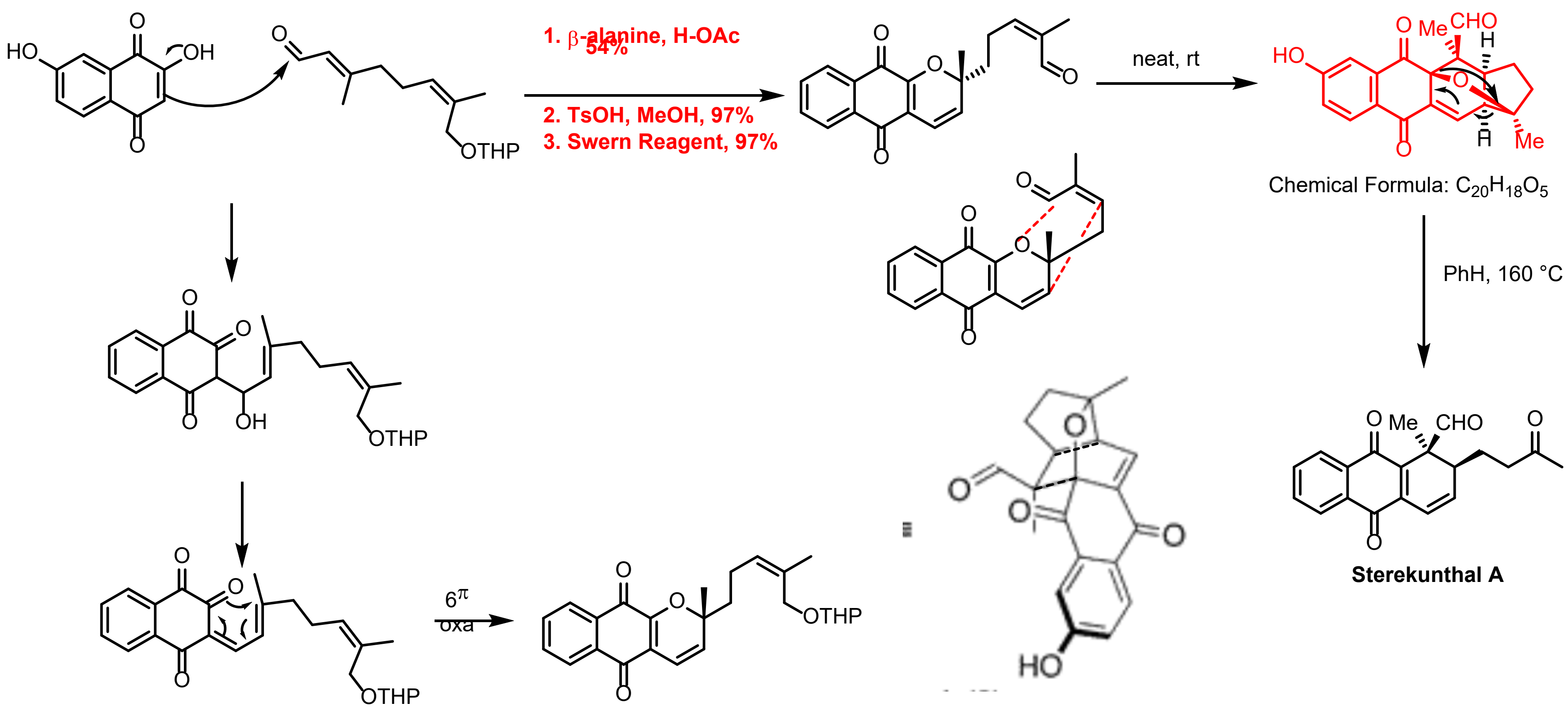
Problem 3

Barriault et. al. published a paper in 2008 towards the a novel approach to construct dieterpenes and 14-β-hydroxysteroids by successive pericyclic reactions.

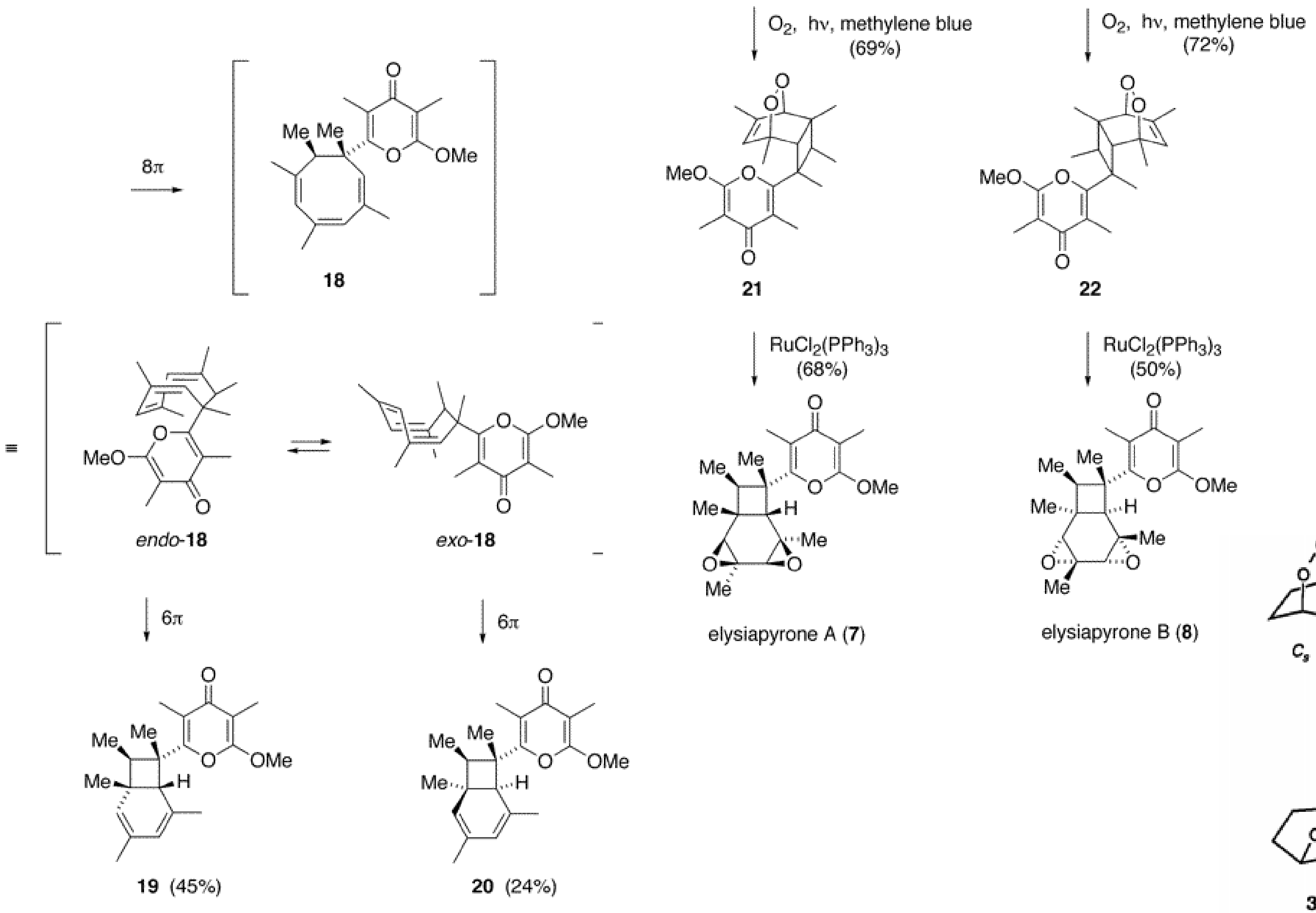


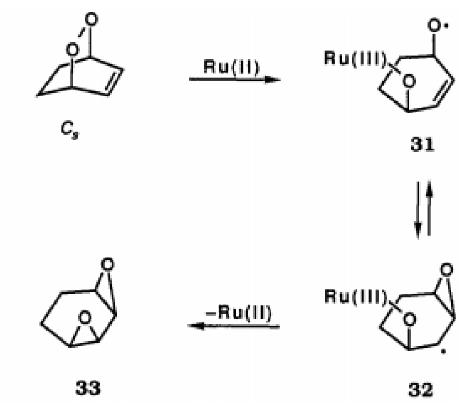
Mechanism? Stereochemistry?
Why was the $MgBr_2{\cdot}OEt_2$ needed?

Answer to Problem 1



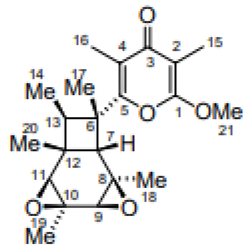
Answer to Problem 2





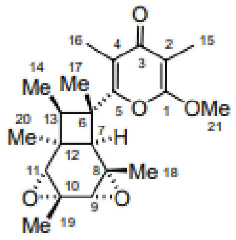
Org. Lett. 2005, 7, 14, 2901–2903

Answer to Problem 2



7

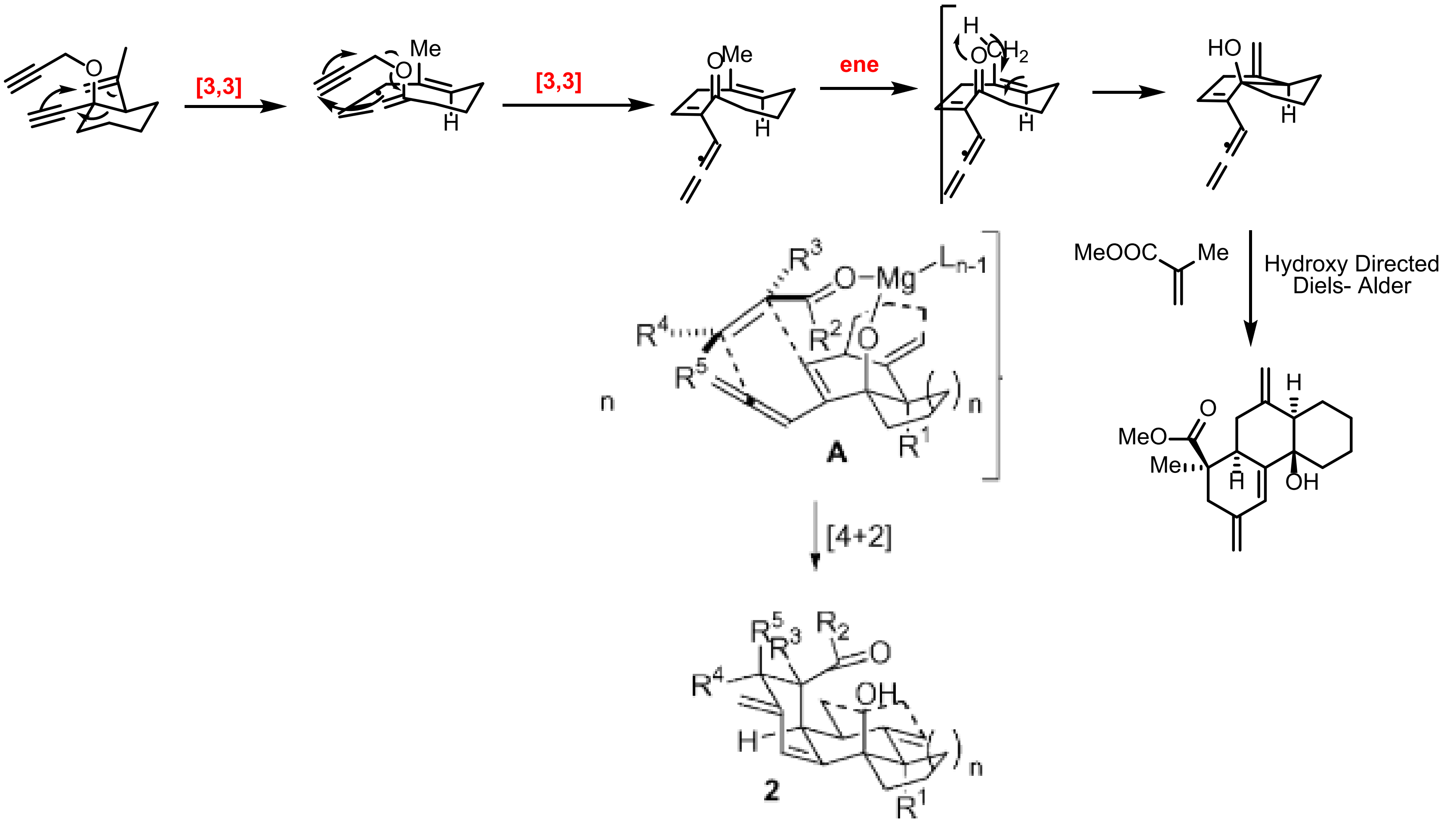
Position	^{13}C (Lit.)	^{13}C (Current)	^{1}H (Lit.)	^{1}H (Current)
1	163.2	163.3		
2	105.4	105.5		
3	182.5	182.6		
4	118.9	119.0		
5	166.1	166.2		
6	44.9	45.0		
7	54.0	54.1	2.27 s	2.27 s
8	59.2	59.4		
9	61.1	61.3	3.18 s	3.18 s
10	56.7	56.9		
11	62.1	62.3	2.39 s	2.39 s
12	35.7	35.9		
13	43.8	44.0	2.43 q (7.5)	2.45 q (7.5)
14	20.3	20.5	1.19 d (7.5)	1.19 m
15	7.4	7.6	1.93 s	1.93 s
16	11.0	11.2	1.89 s	1.89 s
17	23.4	23.6	1.38 s	1.38 s
18	22.0	22.2	1.55 s	1.55 s
19	11.2	11.4	1.20 s	1.20 s
20	18.4	18.6	1.03 s	1.02 s
21	60.4	60.6	3.98 s	3.98 s



8

Position	^{13}C (Lit.)	^{13}C (Current)	^{1}H (Lit.)	^{1}H (Current)
1	162.0	162.2		
2	100.9	100.9		
3	181.7	181.7		
4	117.8	117.8		
5	162.3	162.3		
6	44.3	44.3		
7	46.9	46.9	2.93 s	2.94 s
8	56.2	56.2		
9	60.3	60.3	3.08 s	3.09 s
10	56.7	56.8		
11	57.8	57.9	2.82 s	2.83 s
12	34.0	34.1		
13	46.0	46.1	2.52 q (6.8)	2.53 q (7.3)
14	10.0	10.1	1.16 d (6.8)	1.16 m
15	7.1	7.1	1.86 s	1.88 s
16	10.8	10.8	2.08 s	2.02 s
17	15.7	15.7	1.37 s	1.38 s
18	21.4	21.4	1.40 s	1.41 s
19	21.0	21.1	1.58 s	1.60 s
20	26.1	26.2	1.17 s	1.18 s
21	57.3	57.3	4.03 s	4.05 s

Answer to Problem 3



Chem. Commun., 2008, 3004–300

More Reading

- Review your Pericyclic Reactions-

Anslyn, E. V., & Dougherty, D. A. (2005). *Modern physical organic chemistry*. University Science Books.

Grossman, R. B. *The Art of Writing Reasonable Organic Reaction Mechanisms*, 3rd ed.; Springer, 2019.

Reviews with Pericyclic Cascade Reactions-

Chem. Soc. Rev., 2016, 45, 1557-1569- Cascade polycyclizations in natural product synthesis

Org. Biomol. Chem., 2014, 12, 4192- Pericyclic domino reactions: concise approaches to natural carbocyclic frameworks

Angew. Chem. Int. Ed. 2014, 53, 2556 – 2591- Toward a symphony of Reactivity: Cascades involving Catalysis and Sigmatropic Rearrangements

Chem. Rev. 2005, 105, 4757−4778. Biosynthetic and Biomimetic Electrocyclizations.