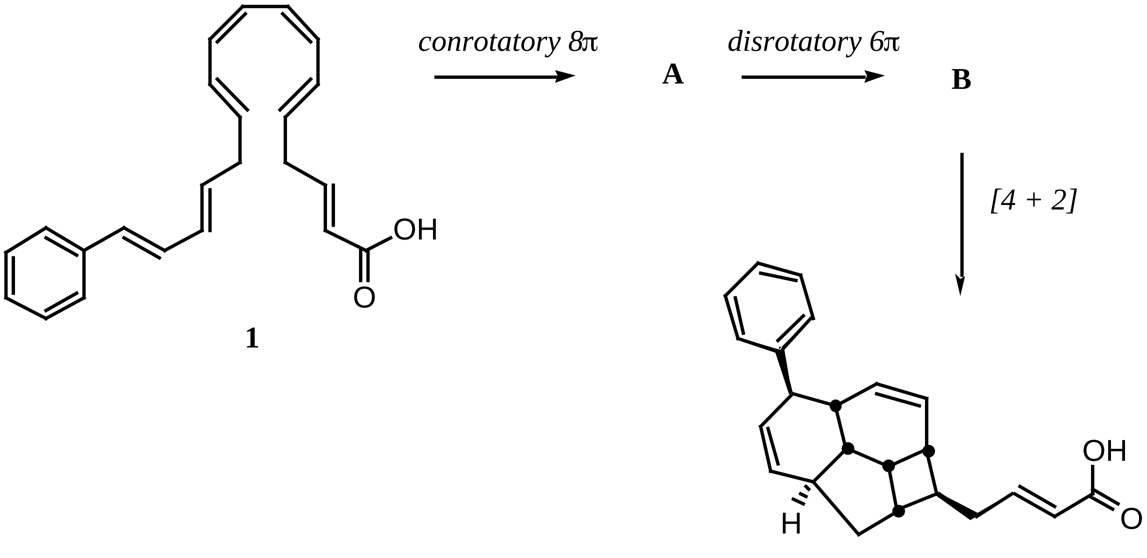
CHE 452
Winter, 2001
EXAM 2

1. Isolated in the early 1980s, the endiandric acids comprise an impressive class of natural secondary metabolites, with an interesting molecular architecture containing four fused carbocyclic rings and eight contiguous stereogenic centers (*J. Chem. Soc., Chem. Commun.*, **1980**, 902). Endiandric acid B, shown below, is one of these compounds. The chemist, D. St. C. Black, who isolated these natural products from an Australian plant (*Endiandra introrsa*) hypothesized that they were formed in nature from achiral polyunsaturated precursors, such as **1**, through a series of electrocyclizations. Black postulated that **1** could undergo a conrotatory 8π electron electrocyclization to give intermediate **A**. Compound **A** could subsequently undergo a disrotatory 6π electron electrocyclization to give a new product, **B**. An *intramolecular* [4 + 2] cycloaddition reaction of **B** would then afford Endiandric acid B. Intrigued by this extraordinary hypothesis, the K.C. Nicolaou group at Scripps Research Institute initiated a program directed towards a total synthesis of the Endiandric acids, and ultimately demonstrated the power of electrocyclic reactions in organic synthesis (*J. Am. Chem. Soc.* **1982**, *104*, 5555).

   Give structures for intermediates **A** and **B** and show how Endiandric acid B is generated from an intramolecular [4 + 2] cyclization of compound **B**.

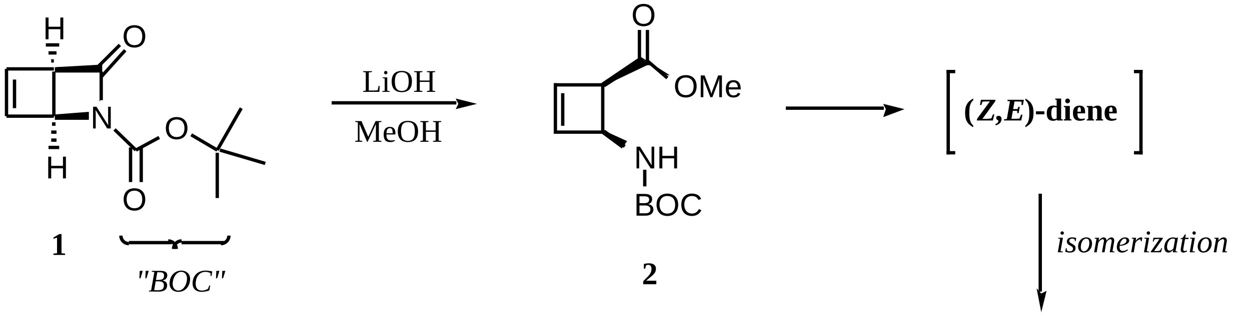


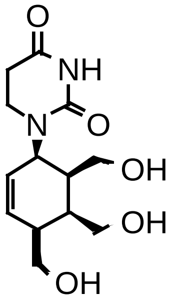
1

Endiandric Acid B

2. A recent report in the *Journal of Organic Chemistry* (*J. Org. Chem.* **2001**, *66*, 583) documents the preparation of a novel cyclohexene nucleoside (**3**) through a Diels-Alder cycloaddition of an (*E*,*E*)-N-acylamino-1,3-diene as the key reaction. The authors prepared the diene for their Diels-Alder reaction through the thermally-allowed electrocyclic ring-opening of cyclobutene **2**. Cyclobutene **2** was prepared from the base-catalyzed hydrolysis of lactam **1**. Cyclobutene **2** undergoes a thermally-allowed electrocyclic ring-opening reaction to give a (*Z*,*E*)-diene, which quickly isomerizes under the reaction conditions to give the more stable (*E*,*E*)-diene. Subsequent treatment of the (*E*,*E*)-diene with methyl acrylate (CH_2=$CHCO_2Me$) gives a Diels-Alder adduct with complete regioselectivity and a high degree of stereoselectivity.

Show how the *(Z,E)*-diene is formed from **2.** Is this a conrotatory or disrotatory process? Show the corresponding (*E*,*E*)-diene (you don't need to show a mechanism for the isomerization) and the Diels-Alder adduct.





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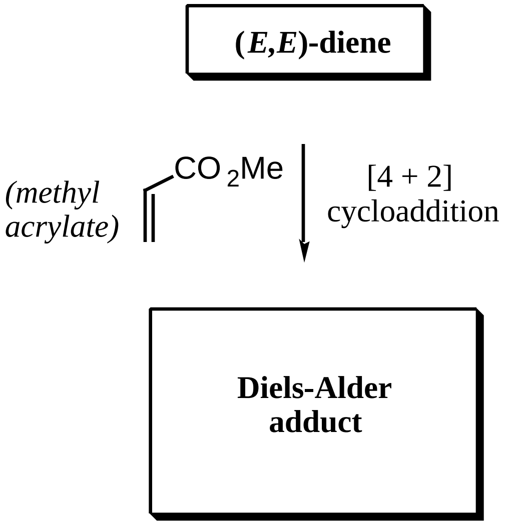
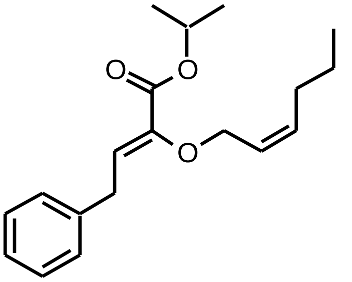
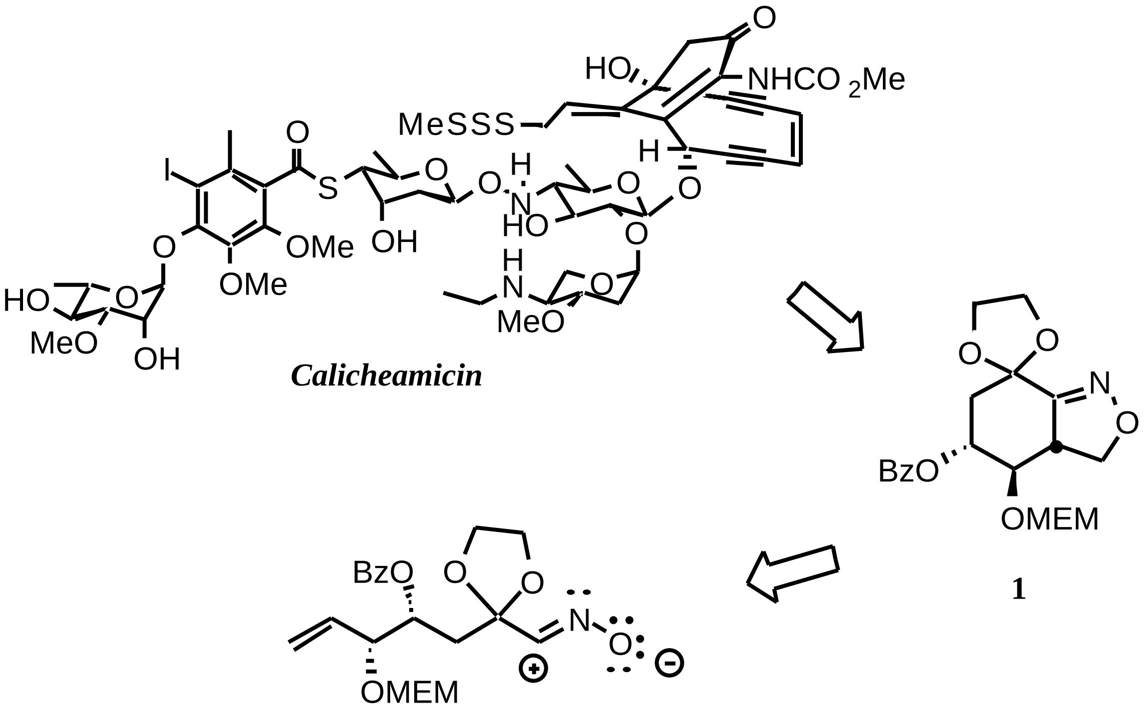


3. A recent report in *Organic Letters* (*Org. Lett.* **2000**, *3*, 49) documents the novel catalytic enantioselective Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers. Show a transition state and predict the product stereochemistry for the [3, 3] sigmatropic rearrangement of the allyl vinyl ether substrate shown below.



4. Calicheamicin is the most prominent member of the enediyne class of natural anti-tumor agents. One of the key intermediates in the Nicolaou synthesis (*J. Am. Chem. Soc.* **1990**, *112*, 8193) of Calicheamicin is **1**, which was generated through an intramolecular 1,3-dipolar cycloaddition of nitrile-oxide **2**. Show a mechanism for the conversion of **2** → **1.**



Calicheamicin

1

2

("MEM" and "Bz" are protecting groups)