Massachusetts Institute of Technology
Organic Chemistry 5.512

February 28, 2005
Prof. Rick L. Danheiser

Problem Set 1
Review of Stereochemical Principles

1. Define "stereogenic center". What is the difference between a chiral center and a stereogenic center?

2. Define the terms "stereoselective reaction" and "stereospecific reaction" and give an example of each.

3. Define the terms "diastereotopic face" and "enantiotopic face" and give an example of each.

4. Why is the following title nonsensical: "A Chiral Total Synthesis of Strychnine"?

5. Define "allylic strain". Give an example of a molecule with $A^{1,2}$ strain and a molecule with $A^{1,3}$ strain.

6. Why will we discuss the products of reactions in terms of "enantiomeric purity" rather than "optical purity" in 5.512?

7. Define "kinetic resolution".

8. Define "antiperiplanar" and "synclinal" and illustrate each using both Newman projections and sawhorse representations for *n*-butane.

9. Define "prochiral faces" and illustrate with an example.

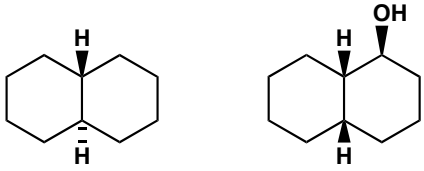
10. What is the barrier to rotation (in kcal/mol) about the carbon-carbon bond in ethane?

11. Draw the *s-trans* and *s-cis* conformations of acrolein. Which is lower in energy?

12. Rank the following substituents in terms of conformational free energies on cyclohexane rings: CH_3, OH, CN, OMe, ethynyl, *i*-Pr, CHO, Br, CO_2Et, H.

13. Define "anomeric effect" and provide an example.

14. Draw an artistic and accurate three-dimensional representation of *trans* decalin and the two alternative conformers of the hydroxy *cis*-decalin shown below.



15. Draw the cis and trans conformational isomers of methyl acetate. Which is lower in energy? By roughly how much?

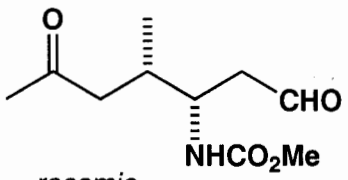
Massachusetts Institute of Technology
Organic Chemistry 5.512

March 9, 2005
Prof. Rick L. Danheiser

Problem Set 2
Strategies for Synthesis of Acyclic Molecules Based on Desymmetrization, Chirality Transfer, the "Chiron Approach", and "Ring Template" Strategies

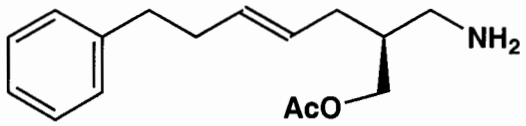
I. Design a highly stereoselective synthesis of the following target molecules beginning with commercially available materials and employing one of the strategies listed above. For the compounds indicated, a route to the target molecule in racemic form will be sufficient. Be sure to explicitly identify all reagents necessary for each transformation. Enantiomerically enriched reagents may be used if they are commercially available; however, each stereogenic center in the target molecule must be generated in your synthetic route. In other words, the stereogenic carbons in the chiral reagents you employ cannot be directly incorporated in the final product.

(1)

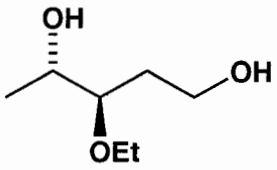


racemic

(3)

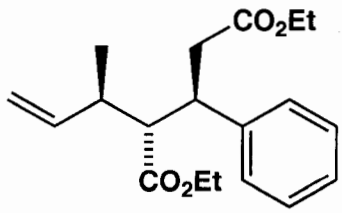


(2)



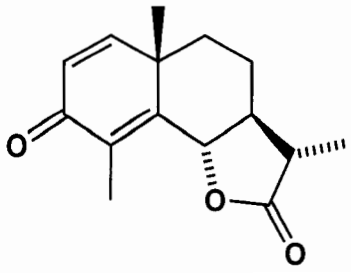
racemic

(4)



racemic

II. In 1944, Paranjape and coworkers in India announced a "total asymmetric synthesis" of the anthelmintic sesquiterpene santonin (see attached article). They reported that treatment of racemic 2-formylcyclohexanone with sodium ethoxide (to form the sodium enolate) followed by alkylation with methyl iodide (in either benzene, toluene, or ethanol as solvent) afforded 2-methyl-2-formylcyclohexanone as a liquid with an optical rotation of -26.2°! How do you account for these results?



Please Refer to

Paranjpe, K. D., N. L. Phalnikar, B. V. Bhide, and K. S. Nargund. “A Case of Total Asymmetric Synthesis.” *Nature*, no. 3874 (January 29, 1944): 141.

Massachusetts Institute of Technology

Organic Chemistry 5.512

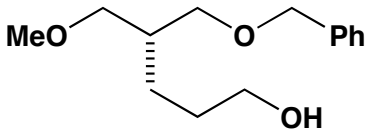
March 28, 2005
Prof. Rick L. Danheiser

Problem Set 3
Stereocontrolled Alkylation and Related Strategies

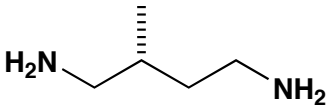
Design a highly stereoselective synthesis of the following target molecules beginning with commercially available materials. Be sure to explicitly identify all reagents necessary for each transformation. Enantiomerically enriched reagents may be used if they are commercially available; however, each stereogenic center in the target molecule must be generated in your synthetic route. In other words, the stereogenic carbons in the chiral reagents you employ cannot be directly incorporated in the final product.

---

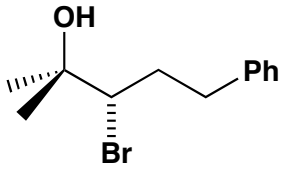
(1)



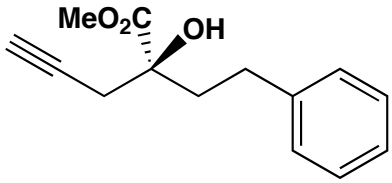
(2)



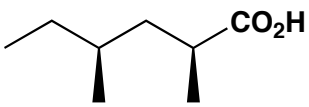
(3)

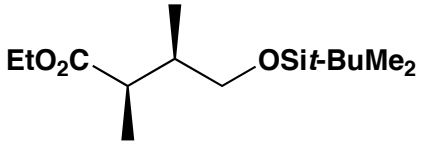


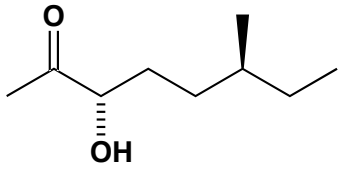
(4)

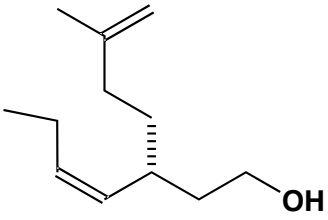


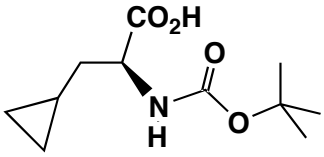
(5)

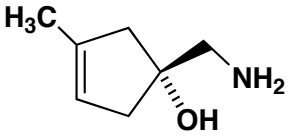


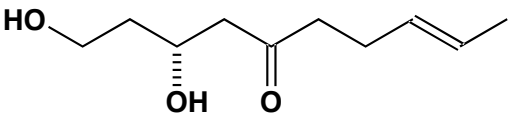
(6) 
EtO2C
OSit-BuMe2

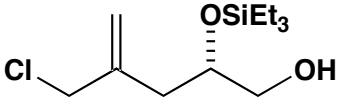
(7) 
O
OH

(8) 
OH

(9) 
CO2H
O
N
H
O

(10) 
H3C
NH2
OH

(11) 
HO
OH
O

(12) 
OSiEt3
Cl
OH

Massachusetts Institute of Technology

Organic Chemistry 5.512

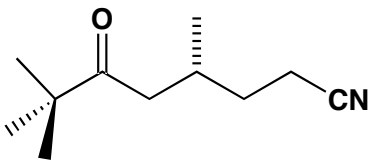
April 4, 2005
Prof. Rick L. Danheiser

Problem Set 4
Practice Problems for First Exam

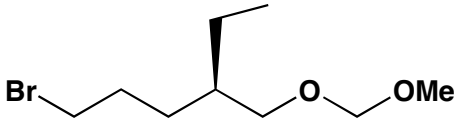
Design a highly stereoselective synthesis of the following target molecules beginning with commercially available materials. Be sure to explicitly identify all reagents necessary for each transformation. Enantiomerically enriched reagents may be used if they are commercially available; however, each stereogenic center in the target molecule must be generated in your synthetic route. In other words, the stereogenic carbons in the chiral reagents you employ cannot be directly incorporated in the final product.

---

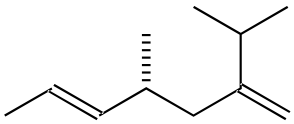
(1)



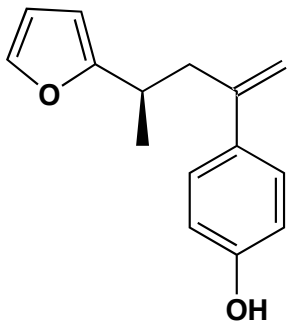
(2)

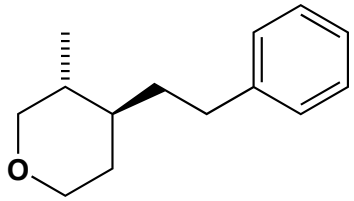


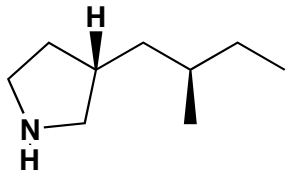
(3)

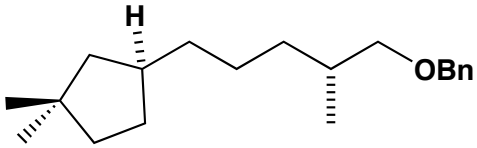


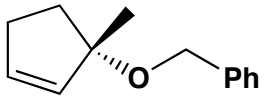
(4)

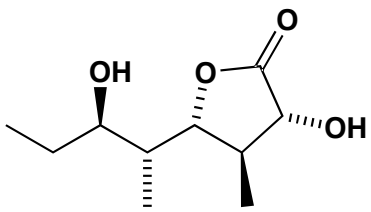


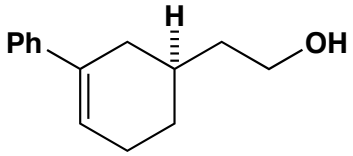
(5) 

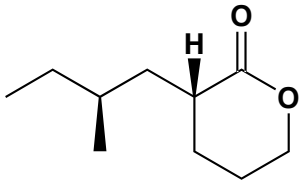
(6) 

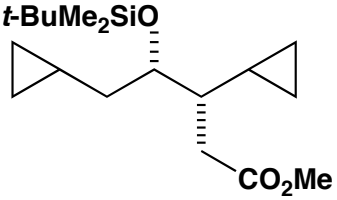
(7) 

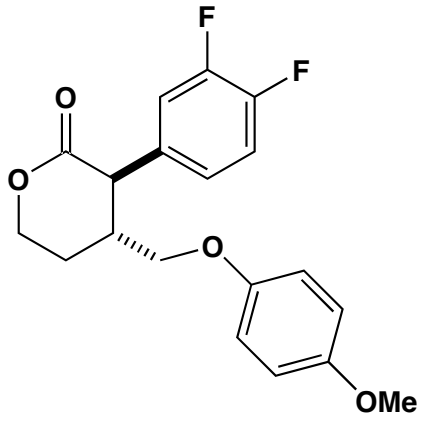
(8) 

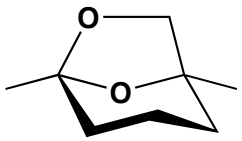
(9) 

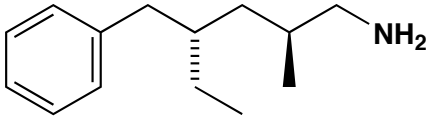
(10) 

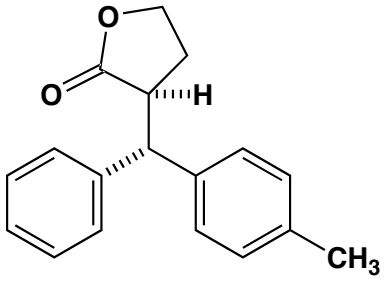
(11) 

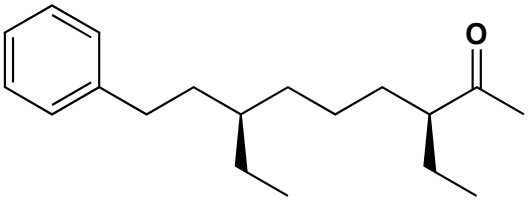
(12) 

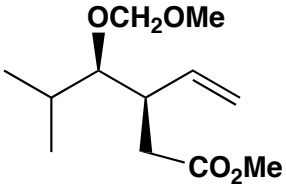
(13) 

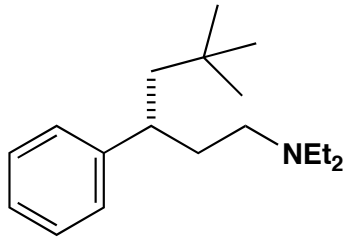
(14) 

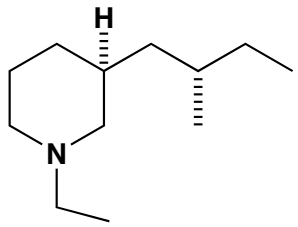
(15) 

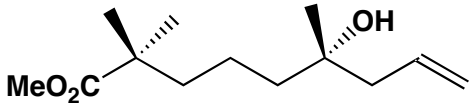
(16) 

(17) 

(18) 

(19) 

(20) 

(21) 

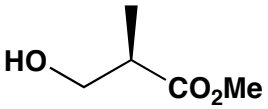
Massachusetts Institute of Technology

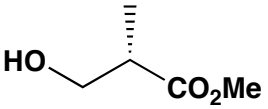
Organic Chemistry 5.512

April 20, 2005
Prof. Rick L. Danheiser

Problem Set 5
Stereocontrolled Addition to Carbonyl Compounds

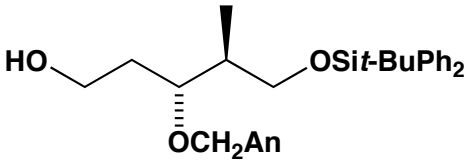
Design a highly stereoselective synthesis of the following target molecules beginning with commercially available materials. Be sure to explicitly identify all reagents necessary for each transformation. Enantiomerically enriched reagents may be used if they are commercially available; however, with the exception of the two compounds shown below, each stereogenic center in the target molecule must be generated in your synthetic route. In other words, the stereogenic carbons in the chiral reagents you employ cannot be directly incorporated in the final product. The exceptions are (S) and (R) methyl 3-hydroxy-2-methylpropionate, which are commercially available and have been widely employed in total synthesis. A stereoselective synthesis of each of most of these target molecules has been reported in the literature and a reference for each synthesis will be provided with the solutions posted on the MIT Server.



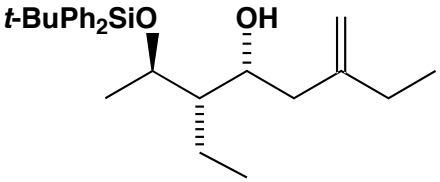


---

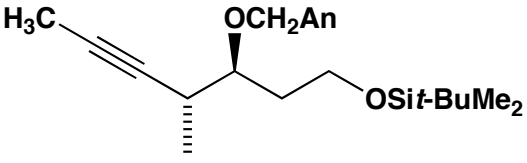
(1)



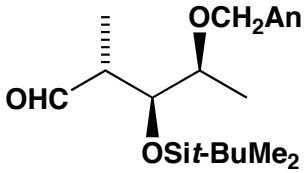
(2)



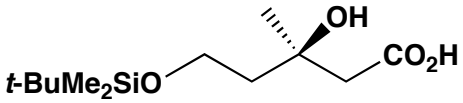
(3)



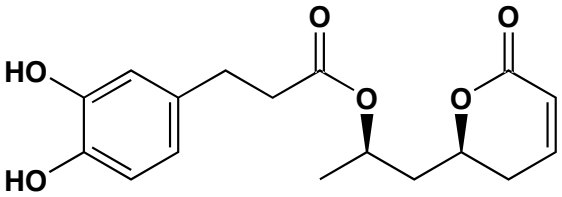
(4)


OCH2An
OHC
OSit-BuMe2

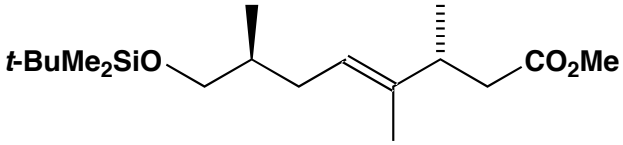
(5)


OH
CO2H
t-BuMe2SiO

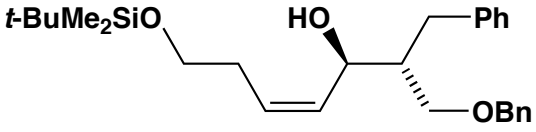
(6)


O
O
HO
O
O
HO

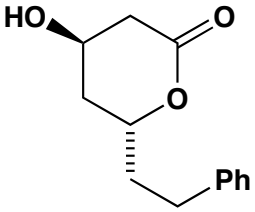
(7)


t-BuMe2SiO
CO2Me

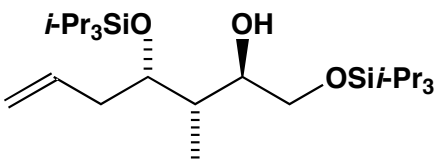
(8)


t-BuMe2SiO
HO
Ph
OBn

(9)


HO
O
O
Ph

(10)

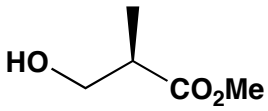

i-Pr3SiO
OH
OSii-Pr3

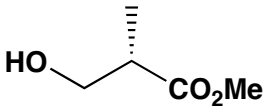
Massachusetts Institute of Technology
Organic Chemistry 5.512

April 27, 2005
Prof. Rick L. Danheiser

Problem Set 6
Stereocontrolled Carbonyl Reduction and Aldol Reactions

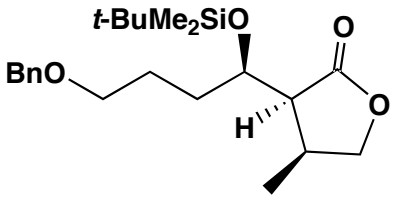
Design a highly stereoselective synthesis of the following target molecules beginning with commercially available materials. Be sure to explicitly identify all reagents necessary for each transformation. Enantiomerically enriched reagents may be used if they are commercially available; however, with the exception of the two compounds shown below, each stereogenic center in the target molecule must be generated in your synthetic route. In other words, the stereogenic carbons in the chiral reagents you employ cannot be directly incorporated in the final product. The exceptions are (S) and (R) methyl 3-hydroxy-2-methylpropionate, which are commercially available and have been widely employed in total synthesis. A stereoselective synthesis of each of most of these target molecules has been reported in the literature and a reference for each synthesis will be provided with the solutions posted on MIT Server.



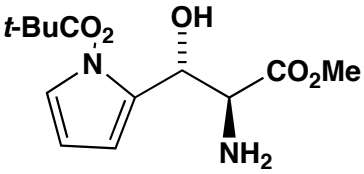


---

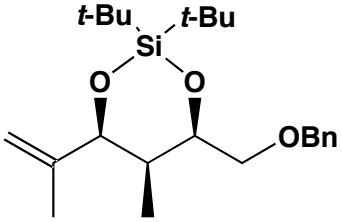
(1)



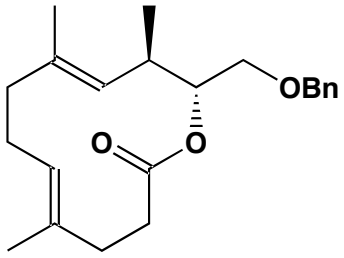
(3)



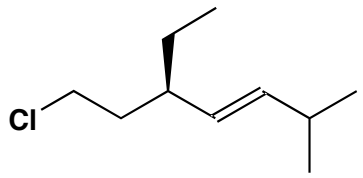
(2)



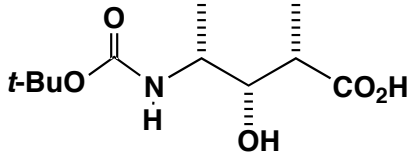
(4)



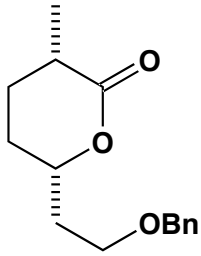
(5)


Cl

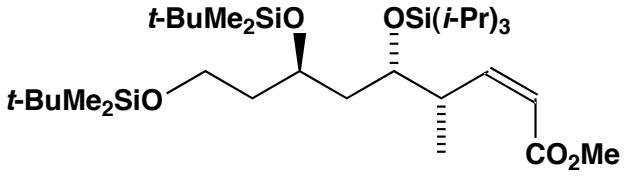
(6)


O
t-BuO
N
H
CO2H
OH

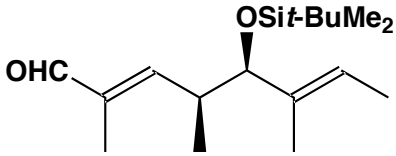
(7)


O
O
OBn

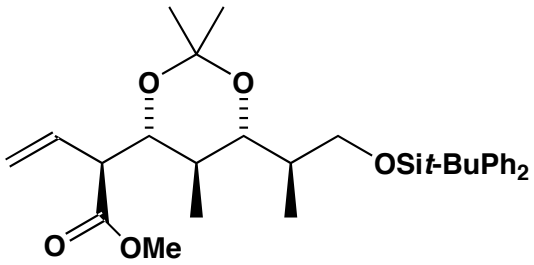
(8)


t-BuMe2SiO
OSi(i-Pr)3
t-BuMe2SiO
CO2Me

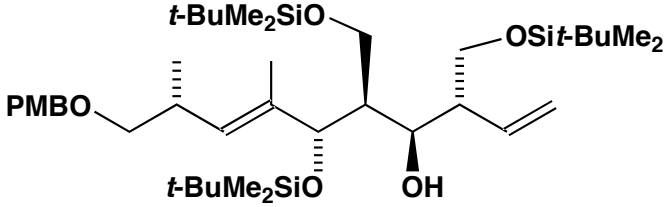
(9)


OSit-BuMe2
OHC

(10)


O
O
OSit-BuPh2
O
OMe

(11)

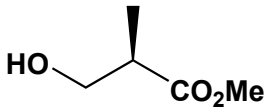

t-BuMe2SiO
OSit-BuMe2
PMBO
t-BuMe2SiO
OH

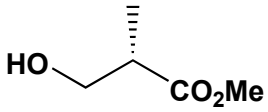
Massachusetts Institute of Technology
Organic Chemistry 5.512

May 4, 2005
Prof. Rick L. Danheiser

Problem Set 7
Stereocontrolled Synthesis of Acyclic Molecules
Review Problems for Second Exam

Design a highly stereoselective synthesis of the following target molecules beginning with commercially available materials. Be sure to explicitly identify all reagents necessary for each transformation. Enantiomerically enriched reagents may be used if they are commercially available; however, with the exception of the two compounds shown below, each stereogenic center in the target molecule must be generated in your synthetic route. In other words, the stereogenic carbons in the chiral reagents you employ cannot be directly incorporated in the final product. The exceptions are (S) and (R) methyl 3-hydroxy-2-methylpropionate, which are commercially available and have been widely employed in total synthesis.

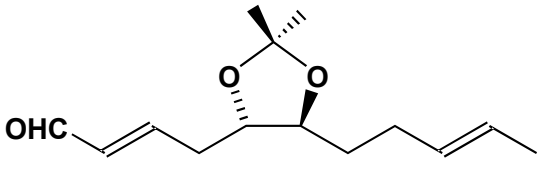




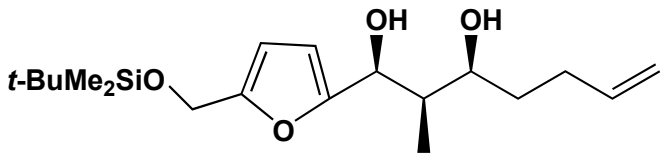
A stereoselective synthesis of each of these target molecules has been reported in the literature and a reference for each synthesis is provided at the end as an appendix. In addition, an outline of these literature syntheses will be posted on the MIT server for your reference. Note, however, that the original route to each molecule may not be the optimal approach, especially in view of new methods that have been reported since the literature route was developed!

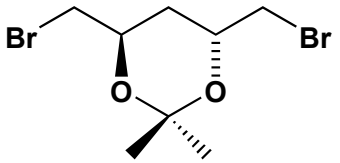
To derive maximum benefit from these problems, I recommend that for each target you consider all possible synthetic routes that can be envisioned based on the methods and strategies studied in 5.512, and then critically compare your viable approaches and decide which would be most practical and efficient.

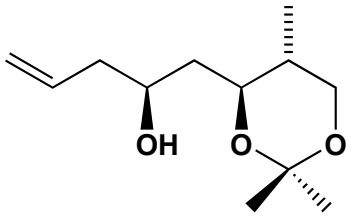
(1)

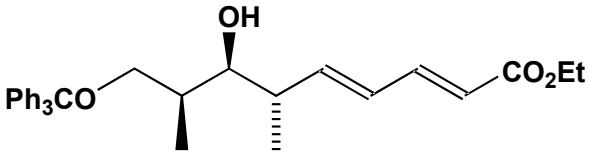


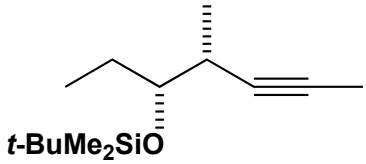
(2)

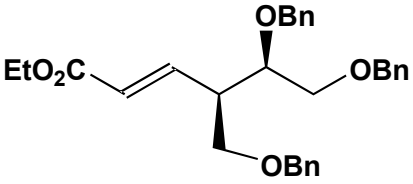


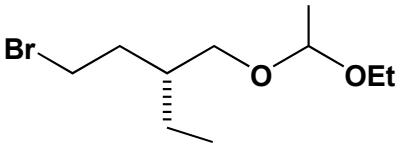
(3) 
Br
Br
O
O

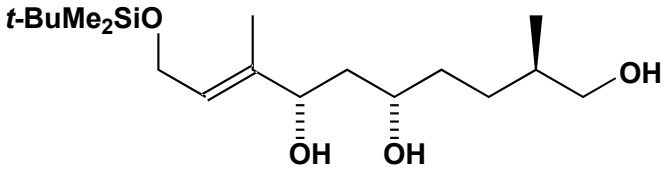
(4) 
OH
O
O

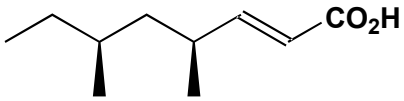
(5) 
OH
Ph3CO
CO2Et

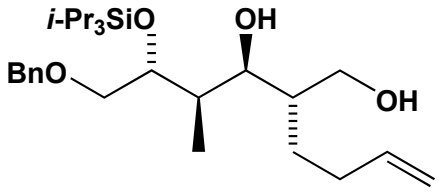
(6) 
t-BuMe2SiO

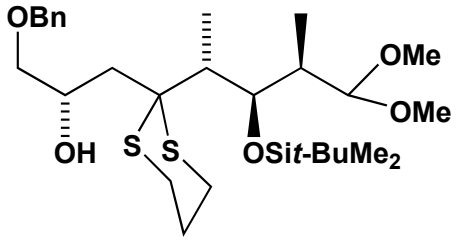
(7) 
OBn
EtO2C
OBn
OBn

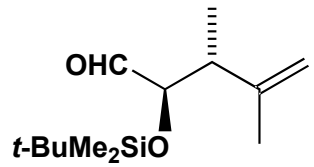
(8) 
Br
O
OEt

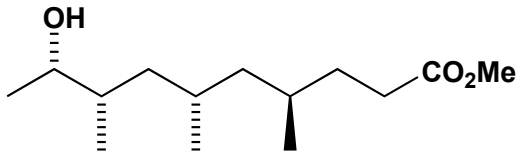
(9) 
t-BuMe2SiO
OH
OH
OH

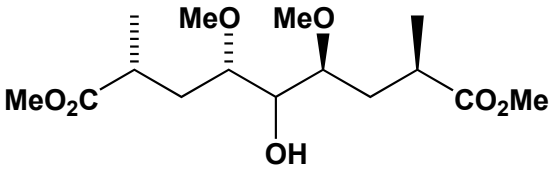
(10) 
CO2H

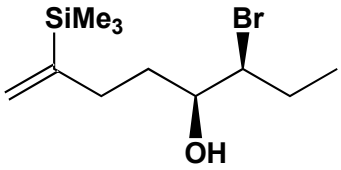
(11) 

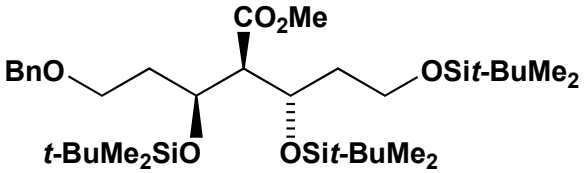
(12) 

(13) 

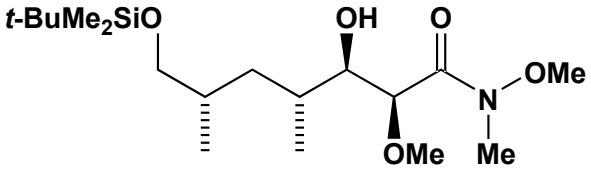
(14) 

(15) 

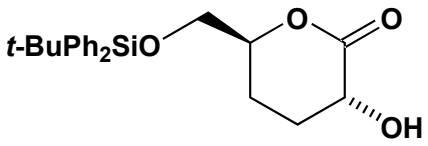
(16) 

(17) 

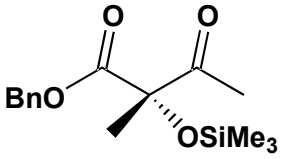
(18)



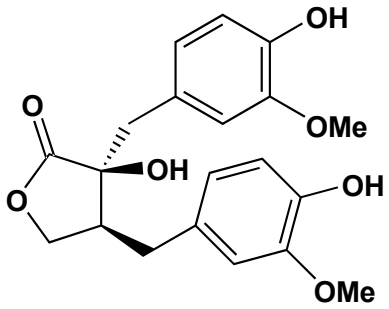
(19)



(20)

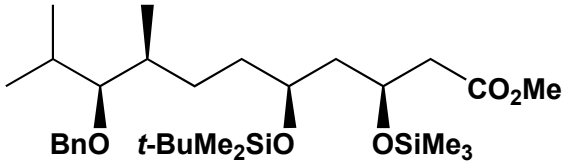


(21)



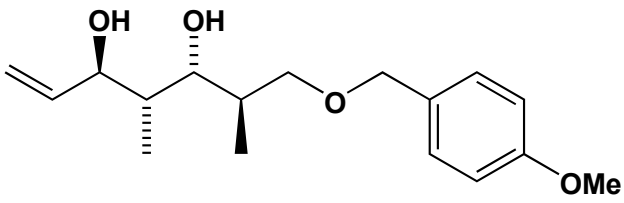
The following problems are taken from the second exam in previous years. The instructions were identical to those on page 1.

(22)

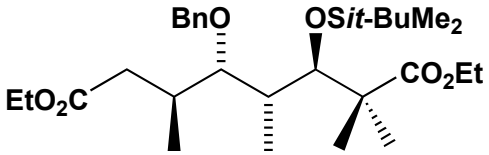


See total synthesis of roflamycoin, S. Rychnovsky *J. Am. Chem. Soc.* **1994**, *116*, 175

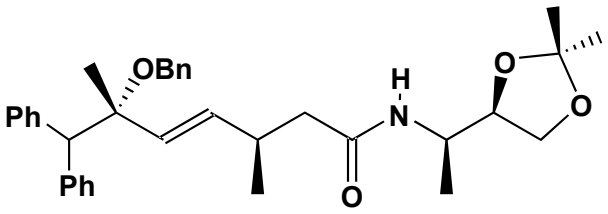
(23)

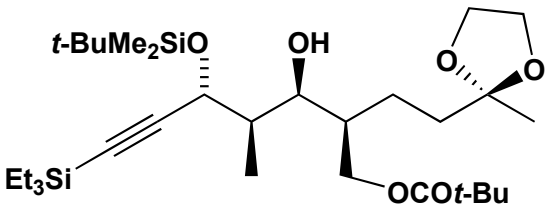


See synthesis of C(1)-C(14) fragment of callipeltoside A, T. R. Hoye *Org. Lett.* **1999**, *1*, 169

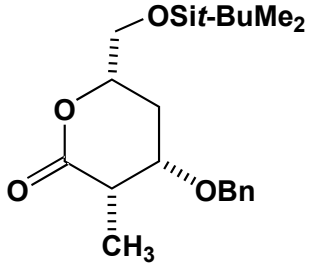
(24) 

Intermediate for synthesis of epothilone A; see, for example J. S. Panek *Org. Lett.* **2000**, *2*, 2575

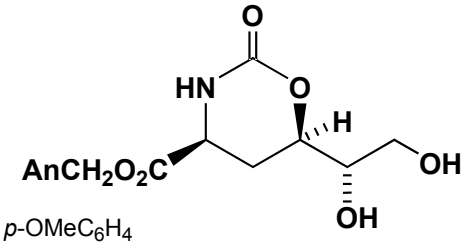
(25) 

(26) 

See total synthesis of sanglifehrin A, K. C. Nicolaou et al. *J. Am. Chem. Soc.* **2000**, *122*, 3830

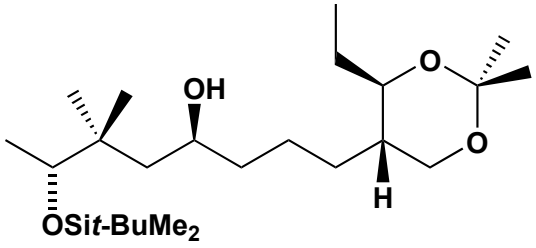
(27) 

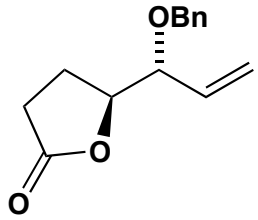
See synthetic studies on miyakolide, S. Masamune et al. *J. Org. Chem.* **1997**, *62*, 8978

(28) 

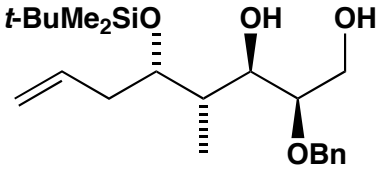
An = *p*-$OMeC_6H_4$

See J. E. Baldwin et al. *Tetrahedron Lett.* **1987**, *28*, 3605

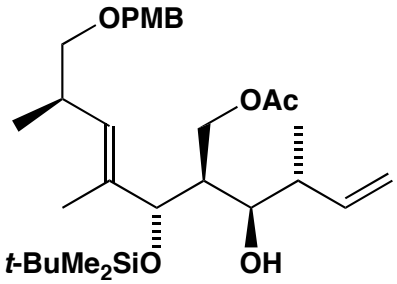
(29) 

(30) 

See total synthesis of resiniferatoxin,
P. A. Wender et al.
J. Am. Chem. Soc. **1997,** *119*, 12976

(31) 

See synthetic studies on spongistatin 1,
M. T. Crimmins et al.
Org. Lett. **2001**, *3*, 949

(32) 

See total synthesis of (+)-13-deoxytedanolide,
A. B. Smith et al.
J. Am. Chem. Soc. **2003**, *125*, 350

(33)