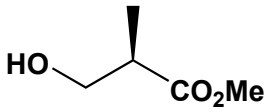
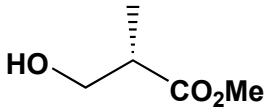
Massachusetts Institute of Technology
Organic Chemistry 5.512

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.

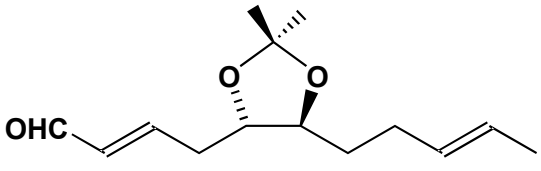




A stereoselective synthesis of each of these target molecules has been reported in the literature and a reference for each synthesis is provided at the end as an appendix. In addition, an outline of these literature syntheses will be posted on the MIT server for your reference. Note, however, that the 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)



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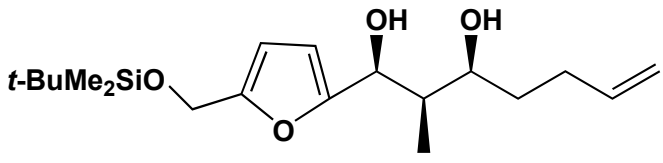
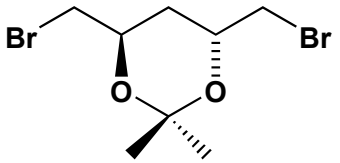
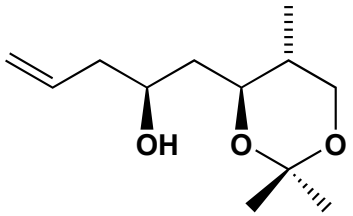
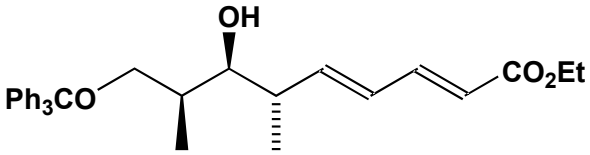
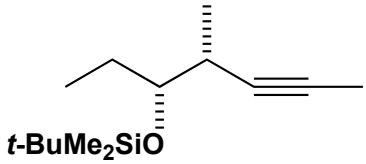
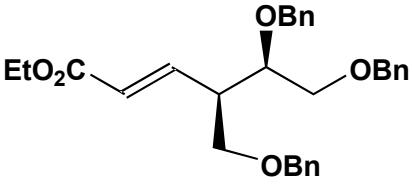


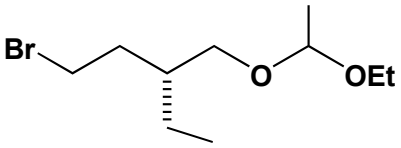
(3) 
Br
Br
O
O

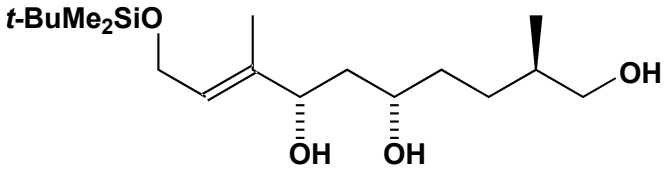
(4) 
OH
O
O

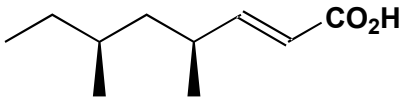
(5) 
OH
Ph3CO
CO2Et

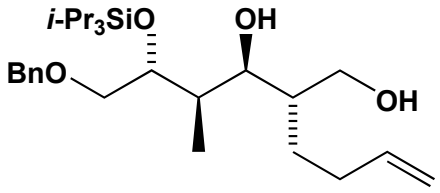
(6) 
t-BuMe2SiO

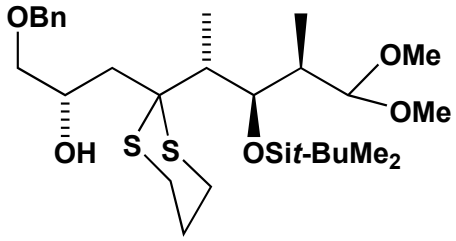
(7) 
OBn
EtO2C
OBn
OBn

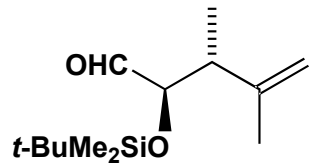
(8) 
Br
O
OEt

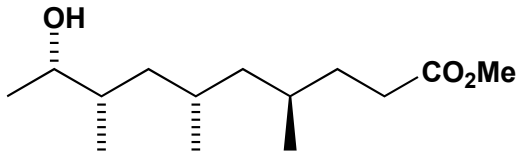
(9) 
t-BuMe2SiO
OH
OH
OH

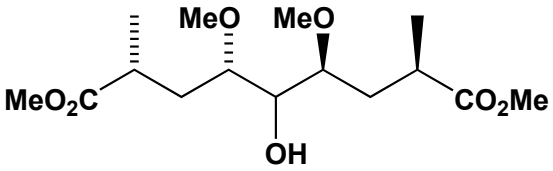
(10) 
CO2H

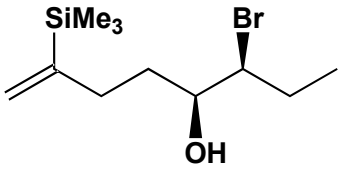
(11) 

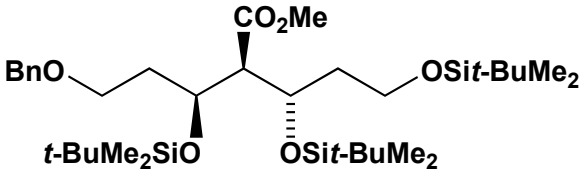
(12) 

(13) 

(14) 

(15) 

(16) 

(17) 

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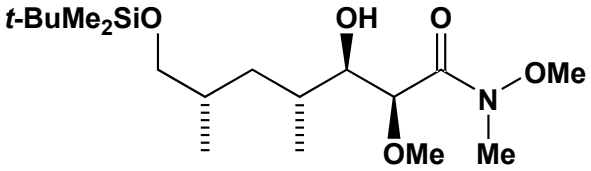

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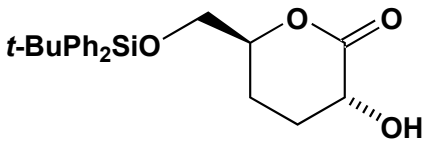

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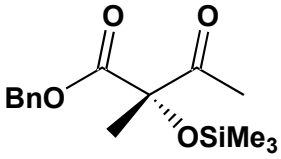

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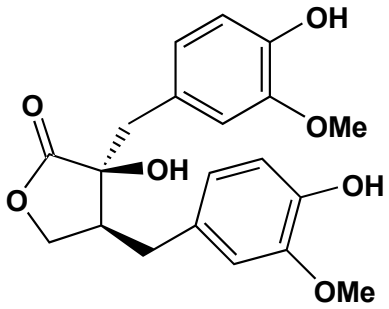
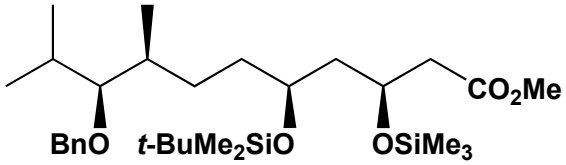


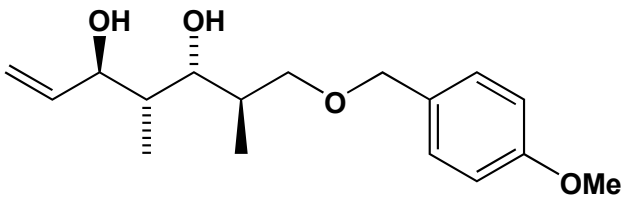
The following problems are taken from the second exam in previous years. The instructions were identical to those on page 1.

(22)

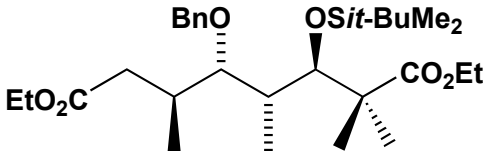


See total synthesis of roflamycoin, S. Rychnovsky *J. Am. Chem. Soc.* **1994**, *116*, 175

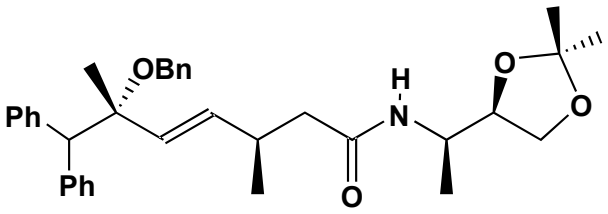
(23)

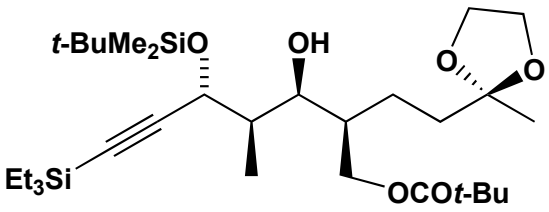


See synthesis of C(1)-C(14) fragment of callipeltoside A, T. R. Hoye *Org. Lett.* **1999**, *1*, 169

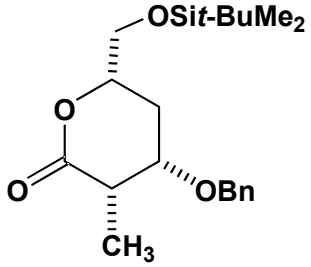
(24) 

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

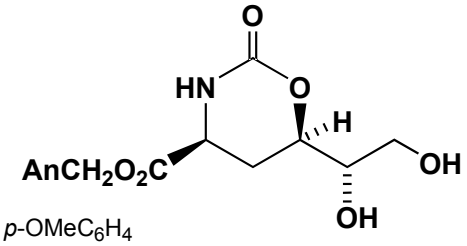
(25) 

(26) 

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

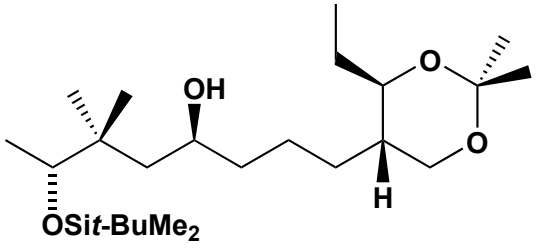
(27) 

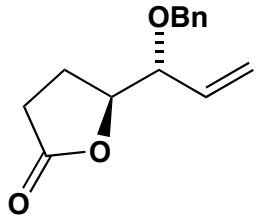
See synthetic studies on miyakolide, S. Masamune et al. *J. Org. Chem.* **1997**, *62*, 8978

(28) 

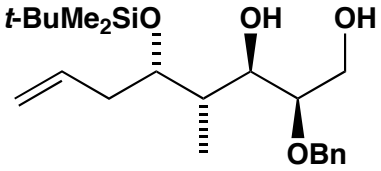
An = *p*-$OMeC_6H_4$

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

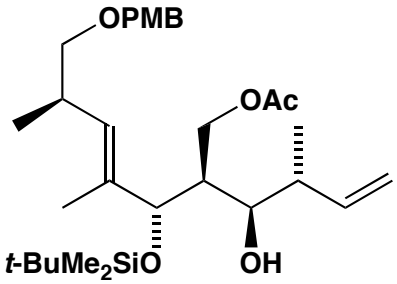
(29) 

(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)