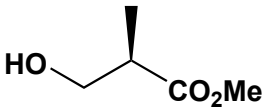
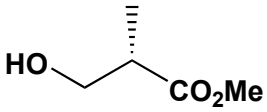
Massachusetts Institute of Technology
Organic Chemistry 5.512

May 12, 2006
Prof. Rick L. Danheiser

Problem Set 8
Stereocontrolled Synthesis of Acyclic Molecules
Review Problems for Second Exam

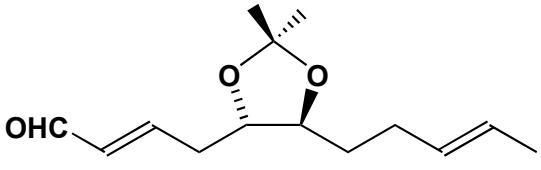
Design a highly stereoselective synthesis of the following target molecules beginning with commercially available materials. Be sure to explicitly identify all reagents necessary for each transformation. Enantiomerically enriched reagents may be used if they are commercially available; however, with 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.





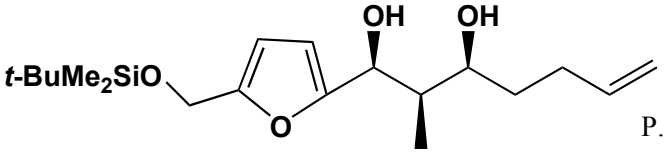
A stereoselective synthesis of each of these target molecules has been reported in the literature and a reference for each synthesis is provided. In addition, an outline of these literature syntheses will be posted on the 5.512 website later this week for your reference. Note, however, that the original 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)

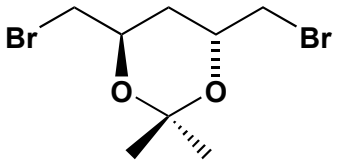


See total synthesis of phomoidride B,
T. Fukuyama *J. Am. Chem. Soc.* **2000**, *122*, 7825

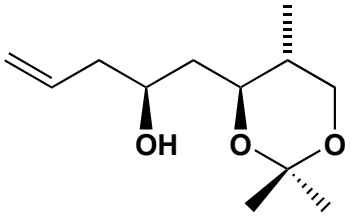
(2)



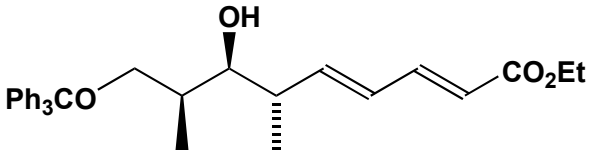
See total synthesis of phorbol,
P. A. Wender *J. Am. Chem. Soc.* **1997**, *119*, 7897

(3) 

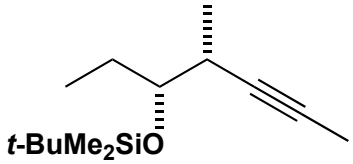
See total synthesis of (-)-roxaticin,
S. Rychnovsky *J. Am. Chem. Soc.* **1994**, *116*, 1753

(4) 

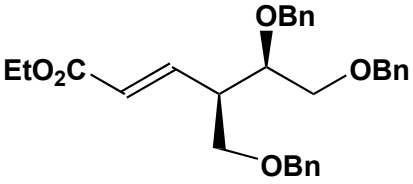
See total synthesis of (-)-roxaticin,
S. Rychnovsky *J. Am. Chem. Soc.* **1994**, *116*, 1753

(5) 

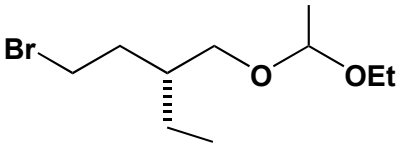
See total synthesis of elaiophylin aglycon,
D. A. Evans *J. Org. Chem.* **1997**, *62*, 454

(6) 

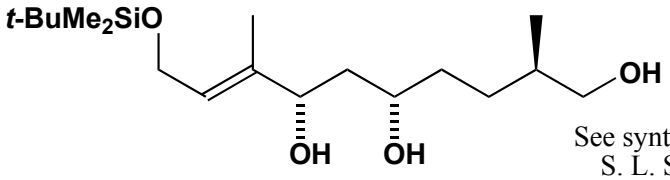
Intermediate to erythronolide B fragment,
E. J. Corey *J. Am. Chem. Soc.* **1978**, *100*, 4618

(7) 

See total synthesis of amphotericin B,
K. C. Nicolaou *J. Am. Chem. Soc.* **1987**, *109*, 2205

(8) 

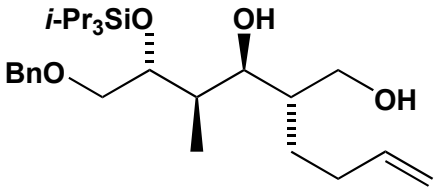
See total synthesis of (-)-talaromycins A and B,
A. B. Smith *J. Org. Chem.* **1984**, *49*, 1469

(9) 

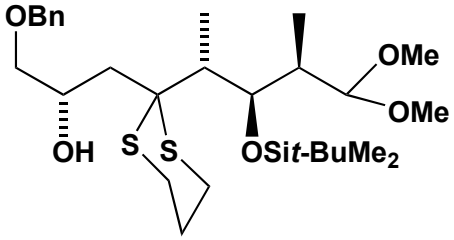
See synthesis of C10-C21 fragment of rapamycin,
S. L. Schreiber *J. Org. Chem.* **1992**, *57*, 5058

(10) 

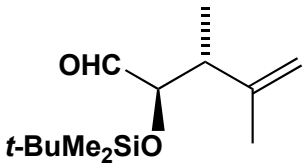
See synthetic studies of zaragozic acid A,
K. C. Nicolaou *Angew. Chem. Int. Ed.* **1994**, *33*, 2184

(11) 

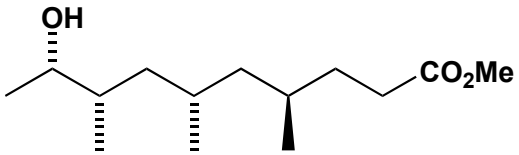
See total synthesis of sanglifehrin A,
K. C. Nicolaou *J. Am. Chem. Soc.* **2000**, *122*, 3830

(12) 

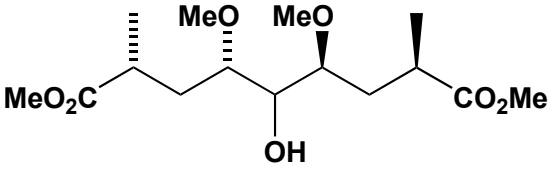
See total synthesis of (+)-discodermolide,
A. B. Smith *J. Am. Chem. Soc.* **2000**, *122*, 8654

(13) 

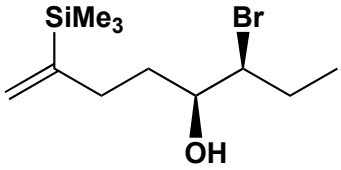
See total synthesis of (-)-amphidinolide P,
D. R. Williams *Org. Lett.* **2000**, *2*, 945

(14) 

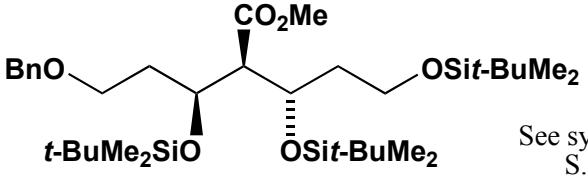
See total synthesis of ionomycin,
D. A. Evans *J. Am. Chem. Soc.* **1990**, *112*, 5290

(15) 

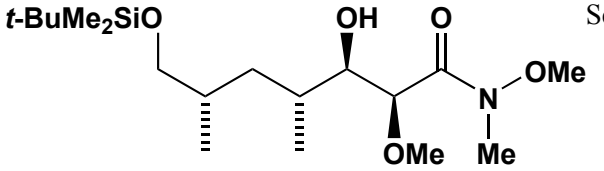
See total synthesis of FK506,
S. L. Schreiber *J. Am. Chem. Soc.* **1990**, *112*, 5583

(16) 

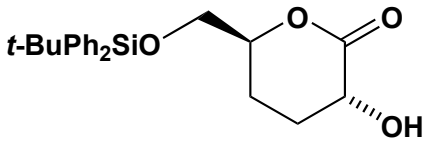
See total synthesis of (+)-isolaurepinnacin,
L. E. Overman *J. Am. Chem. Soc.* **1997**, *119*, 2446

(17) 

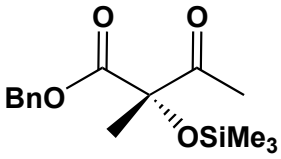
See synthesis of 3-hydroxyl-2-vinylcarbonyl compounds,
S. Masamune *J. Am. Chem. Soc.* **1982**, *104*, 5521

(18) 

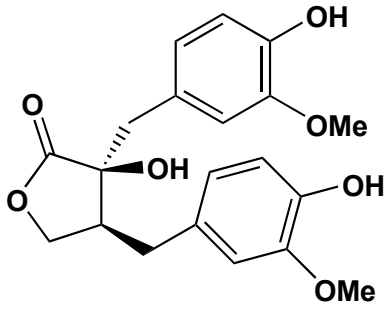
See synthesis of C22-C42 fragment of rapamycin,
S. L. Schreiber *J. Org. Chem.* **1992**, *57*, 5060

(19) 

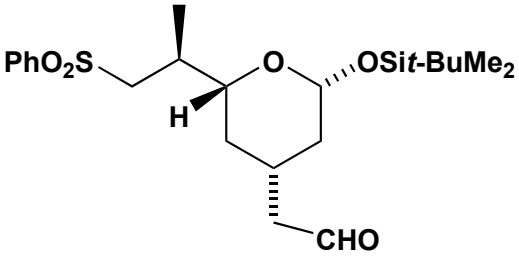
See C1-C27 fragment of okadaic acid,
C. J. Forsyth *J. Org. Chem.* **2001**, *66*, 925

(20) 

See synthetic studies on hexadepsipeptide GE3,
Y. Hamada *Syn. Lett.* **2002**, 613

(21) 

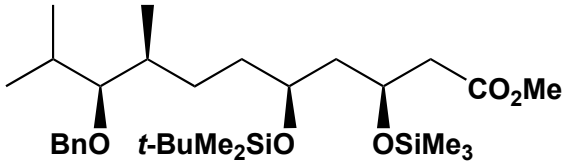
See total synthesis of (-)-wikstromol,
M. Sefkow *J. Org. Chem.* **2001**, *66*, 2343

(22) 

See total synthesis of rhizoxin D,
G. E. Keck *Angew. Chem. Int. Ed.*
2001, *40*, 231

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

(23)



See total synthesis of roflamycoin, S. Rychnovsky *J. Am. Chem. Soc.* **1997**, *119*, 205

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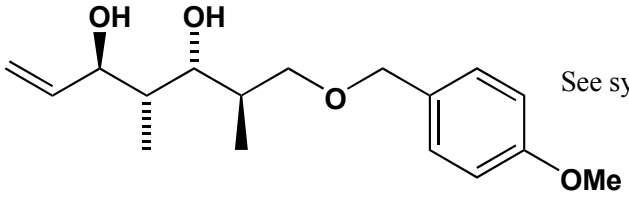
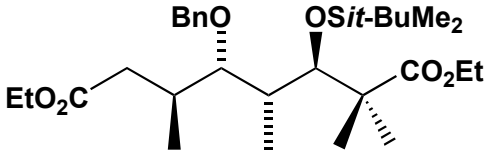


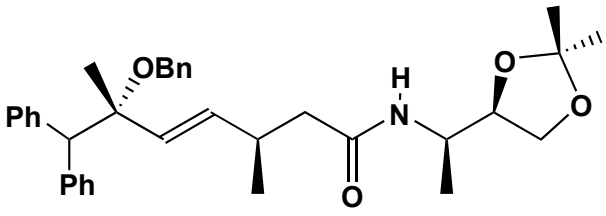
See synthesis of C1-C14 fragment of callipeltoside A, T. R. Hoye *Org. Lett.* **1999**, *1*, 169

(25)



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

(26)



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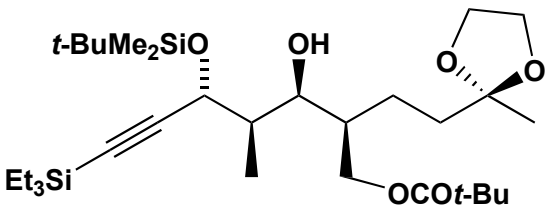
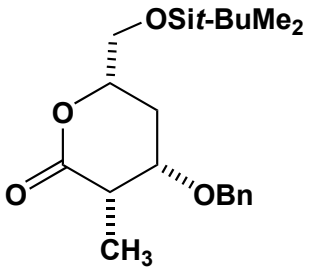


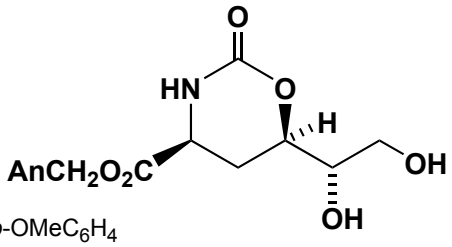
See total synthesis of sanglifehrin A, K. C. Nicolaou *J. Am. Chem. Soc.* **2000**, *122*, 3830

(28)



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

(29)



An = *p*-OMeC$_6$H$_4$

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

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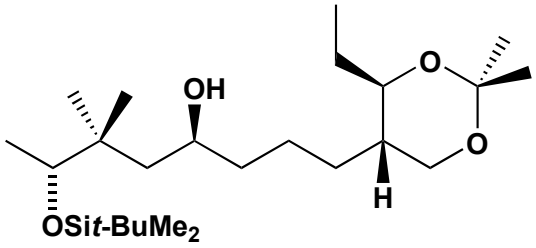

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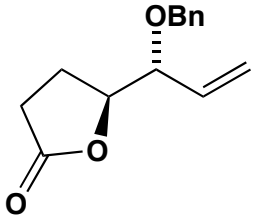
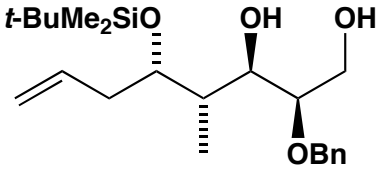
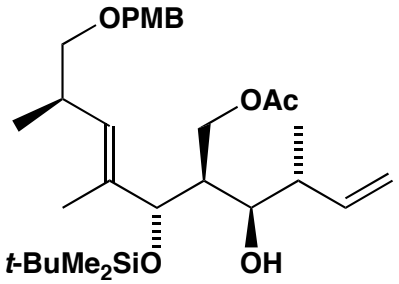


See total synthesis of resiniferatoxin, P. A. Wender *J. Am. Chem. Soc.* **1997,** *119*, 12976

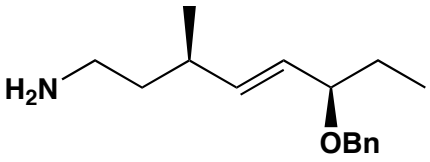
(32)

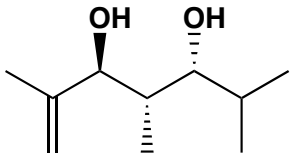


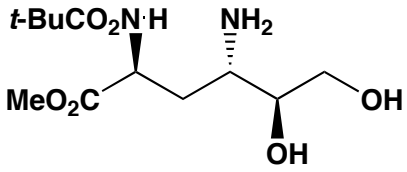
See synthetic studies on spongistatin 1,
M. T. Crimmins *Org. Lett.* **2001**, *3*, 949

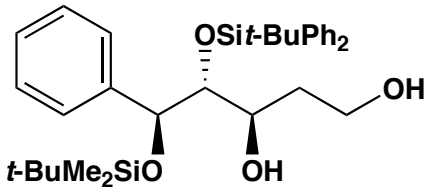
(33) 

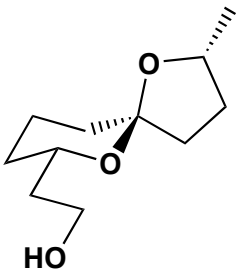
See total synthesis of (+)-13-deoxytedanolide,
A. B. Smith *J. Am. Chem. Soc.* **2003**, *125*, 350

(34) 

(35) 

(36) 

(37) 

(38) 

Fragment of (+)-spirolaxine methyl ether
for a recent total synthesis, see
M. A. Brimble *Chem. Commun.* **2005**, 1560