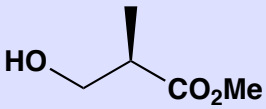
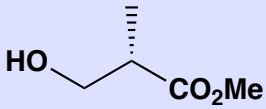
Massachusetts Institute of Technology
Organic Chemistry 5.511

December 7, 2007
Prof. Rick L. Danheiser

Problem Set 10
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.

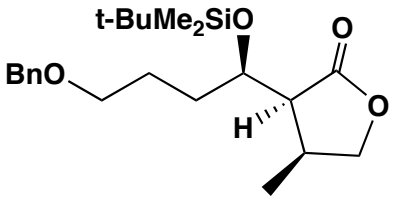




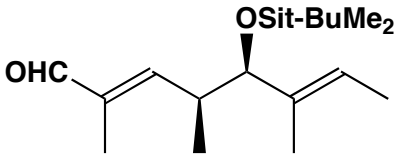
A stereoselective synthesis of most of these target molecules has been reported in the literature and in these cases a reference for the synthesis is provided next to the molecule. In addition, an answer key for this problem set will be posted on the 5.512 website for your reference. Note that the original route to each molecule may not be the optimal approach, especially in view of new methods that may have been developed since the literature route was originally reported. 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 5.511, and then critically compare your viable approaches and decide which would be most practical and efficient.

Although the emphasis in this problem set is on the chemistry we studied during the last several units, keep in mind that the second exam will cover chemistry discussed over the entire semester.

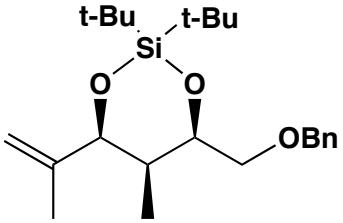
(1)



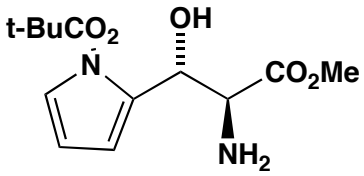
Intermediate in the synthesis of (-)-stemoamide by Williams, see *Tetrahedron Lett*. **1994**, *35*, 6417

(2) 

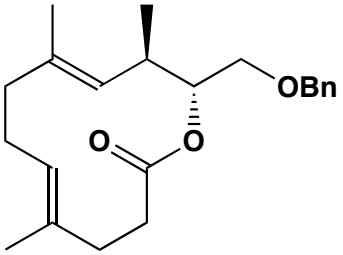
Intermediate in the synthesis of hexadepsipeptide GE3 by Hamada, see *Synlett* **2002**, *4*, 613

(3) 

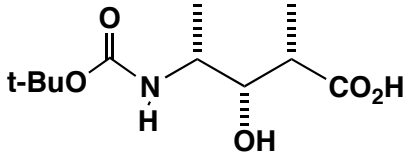
Intermediate in the synthesis of the macrolide antibiotic cytovaricin by Evans, see *J. Am. Chem. Soc*. **1990**, *112*, 7001

(4) 

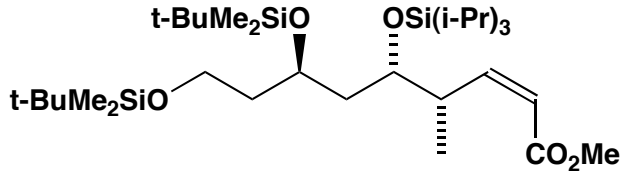
Intermediate in the synthesis of bleomycin by Boger, see *Angew. Chem. Int. Ed*. **1999**, *38*, 449

(5) 

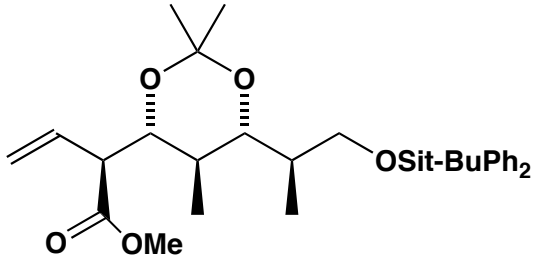
Intermediate in the synthesis of polyether antibiotic lonomycin A by Evans, see *J. Am. Chem. Soc*. **1995**, *117*, 3454

(6) 

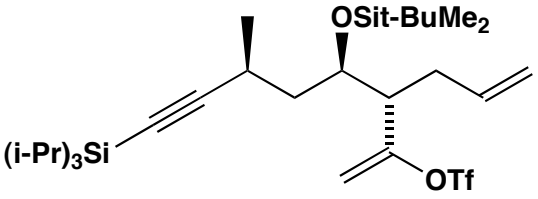
Intermediate in the synthesis of bleomycin by Boger, see *Angew. Chem. Int. Ed*. **1999**, *38*, 449

(7) 

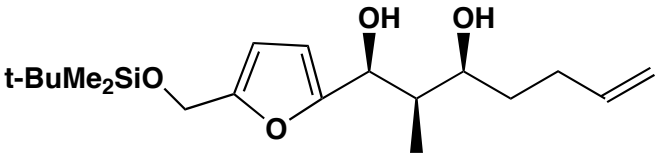
Intermediate in the synthesis of polycavernoside A by J. D. White, see *J. Am. Chem. Soc*. **2001**, *123*, 8593

(8) 

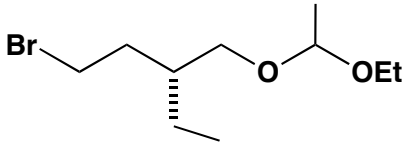
Intermediate in the synthesis of (+)-damavaricin D by Roush, see *J. Am. Chem. Soc*. **1997**, *119*, 11331

(9) 

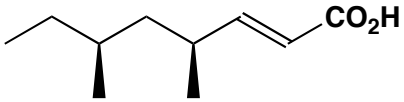
Intermediate in the synthesis of (+)-8-*epi*-xanthatin by Martin, see *Org. Lett.* **2005**, *7*, 4621

(10) 

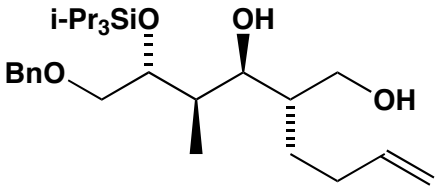
See total synthesis of phorbol,
P. A. Wender *J. Am. Chem. Soc.* **1997**, *119*, 7897

(11) 

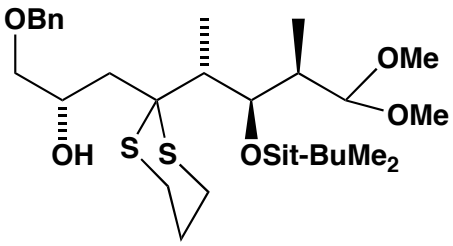
See total synthesis of (-)-talaromycins A and B,
A. B. Smith *J. Org. Chem.* **1984**, *49*, 1469

(12) 

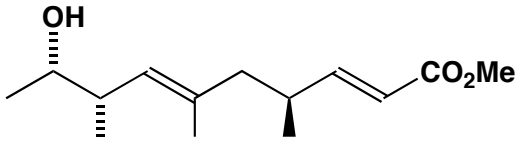
See synthetic studies on zaragozic acid A,
K. C. Nicolaou *Angew. Chem. Int. Ed.* **1994**, *33*, 2184

(13) 

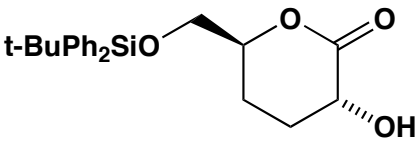
See total synthesis of sanglifehrin A,
K. C. Nicolaou *J. Am. Chem. Soc.* **2000**, *122*, 3830

(14) 

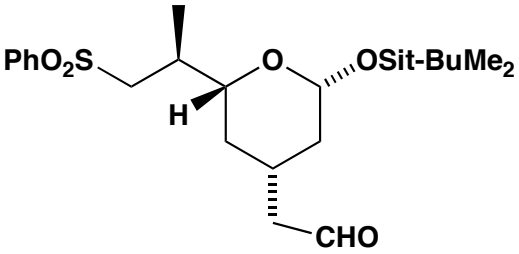
See total synthesis of (+)-discodermolide,
A. B. Smith *J. Am. Chem. Soc.* **2000**, *122*, 8654

(15) 

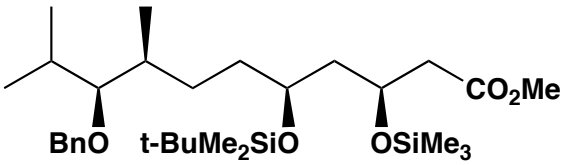
See total synthesis of ionomycin,
D. A. Evans *J. Am. Chem. Soc.* **1990**, *112*, 5290

(16) 

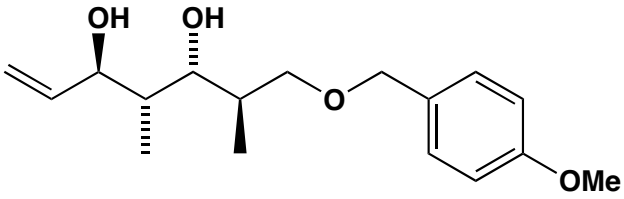
See C1-C27 fragment of okadaic acid,
C. J. Forsyth *J. Org. Chem.* **2001**, *66*, 925

(17) 

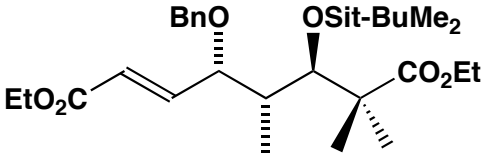
See total synthesis of rhizoxin D,
G. E. Keck *Angew. Chem. Int. Ed.* **2001**, *40*, 231

(18) 

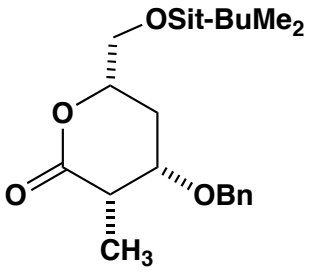
See total synthesis of roflamycoin
S. Rychnovsky *J. Am. Chem. Soc.* **1997**, *119*, 205

(19) 

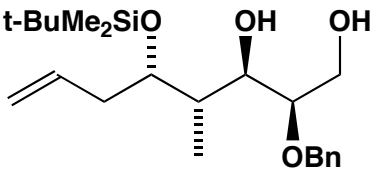
See synthesis of C1-C14 fragment
of callipeltoside A,
T. R. Hoye *Org. Lett.* **1999**, *1*, 169

(20) 

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

(21) 

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

(22) 

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

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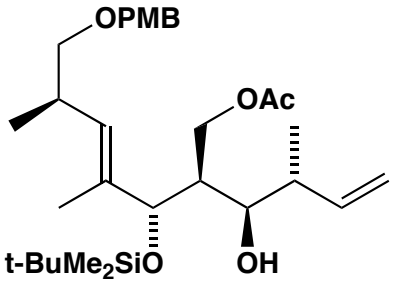
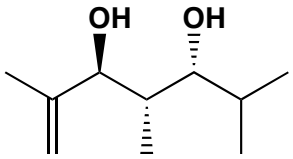


See total synthesis of (+)-13-deoxytedanolide,
A. B. Smith *J. Am. Chem. Soc.* **2003**, *125*, 350

(24)



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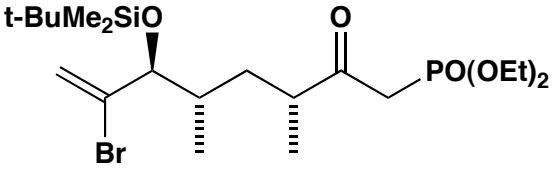

Intermediate for the synthesis of azaspiracid-1, see
Zhou, X.-T.; Carter, R. G. *Chem. Commun.* **2004**, 2138

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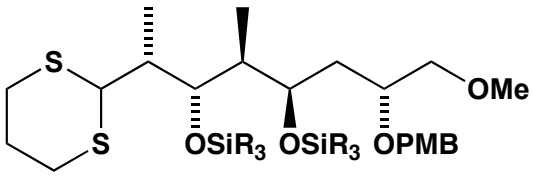

R_3SiO = *t*-$BuMe_2SiO$

Intermediate for the synthesis of apoptolidin, see
Nicolaou, K. C. et al. *J. Am. Chem. Soc.* **2003**, *125*, 15,433

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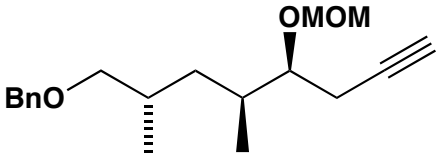

See synthetic studies on (-)-kendomycin
White, J. D.; Smits, H.
Org. Lett. **2005**, *7*, 235