1. The initial reaction with BF$_3$ leads to elimination of the methoxy unit with formation of an iminium salt. The iminium salt reacts with MeMgBr from the less hindered side to give the methylated final product, with the stereochemistry shown. The stereochemistry is predicted from the conformational model in which path B is blocked by the bicyclic ring system and the TBDMS protected alcohol. Delivery of the Grignard reagent from the less hindered path A leads to the product shown.

2. This reaction is taken from *J. Org. Chem.*, 2004, 68, 619. Inspection of the model suggests that face A is less sterically hindered. Delivery of the methyl group from that face is consistent with product formation. The acetoxy group provides the steric hindrance to the bottom face.

3. A reasonable mechanism involves formation of a ketone moiety via the alkoxide, with transfer of the negative charge to the carbon adjacent to the sulfur. An internal Michael addition of this carbanion gives an enolate anion (see Sec. 9.7.A), which is hydrolyzed to the final product.

4. See Sec. 4.7.B for a discussion of these models.

(a) All models predict the same incorrect stereochemistry for all nucleophiles since the actual product will have
the R and OH stereochemistry reversed (see Sec. 4.7.C).

(b) The models predict the same angle of approach for all five nucleophiles. Note that each model predicts a different product. The Cram and Karabatsos models predict the same diastereomer, but different enantiomers. Assuming each reaction is not enantioselective, these two models predict the same diastereomer. The Felkin-Ahn model, however, predicts a different diastereomer.

(c) In this molecule, the OMe group can interact with both Grignard reagents but probably not very well with the sodium or lithium derivatives. The Cram chelation model is used nonetheless. In the other models, the OMe group is positioned as close as possible to the carbonyl oxygen. The same major product is predicted by all three models. Unfortunately, the steric hindrance provided by methyl vs. ethyl is minimal, and this lack of facial bias means that the reaction is predicted to proceed with poor diastereoselectivity.

(d) Both the Cram and Karabatsos models predict the same diastereomer. The Felkin-Ahn model predicts the diastereomer with the opposite stereochemistry of the alcohol moiety.
e) All three models predict the same diastereomer.

5. The selectivity is explained by the Cram model. Attack of BuLi over the less steric hindered H, as shown in the model, leads to the diastereomer indicated as the major product.

6. Initial reaction with the strong base generates the α-carbanion of the sulfoxide. Acyl addition to the ketone generates the alkoxide as it forms the new C—C bond. The alkoxide regenerates a carbonyl with concomitant breakage of the bond to generate an ester enolate (see Sec. 9.4.B). In the second step, acetic acid protonates the carbanion to give the final product.
Organic Synthesis Solutions Manual

1. \( \text{LiN(SiMe}_3\text{)}_2 \) → see *Tetrahedron Lett.*, 2000, 41, 377

7.

(a) \[
\begin{array}{c}
\text{Me} \\
\end{array}
\]
(b) \[
\begin{array}{c}
\text{Me} \\
\end{array}
\]
(c) \[
\begin{array}{c}
\text{Me} \\
\end{array}
\]
(d) \[
\begin{array}{c}
\text{Me} \\
\end{array}
\]
(e) \[
\begin{array}{c}
\text{Me} \\
\end{array}
\]

8.

(a) \[
\begin{array}{c}
\text{MgBr} \\
\text{CdCl}_2 \\
\text{Cp}_2\text{TiMe}_2 \\
\text{BuMgCl, CeCl}_3 \\
\text{Br CO}_2\text{H} \\
\text{Br} \\
\end{array}
\]

(b) \[
\begin{array}{c}
\text{O} \\
\end{array}
\]

(c) \[
\begin{array}{c}
\text{O} \\
\text{OH} \\
\text{Bu} \\
\text{Bu} \\
\end{array}
\]

(d) \[
\begin{array}{c}
\text{O} \\
\text{SPh} \\
\text{N-Li} \\
\text{2-butaneone} \\
\text{SPh} \\
\text{SPh} \\
\text{OH} \\
\text{OH} \\
\end{array}
\]

(e) \[
\begin{array}{c}
\text{Br} \\
\text{Mg}^+ \text{, THF} \\
\text{CO} \\
\text{H}_3\text{O}^+ \\
\text{CO}_2\text{H} \\
\end{array}
\]

(f) \[
\begin{array}{c}
\text{Br} \\
\text{r-BuLi} \\
\text{CuCN} \\
\text{n-Bu}_2\text{Cu(CN)Li}_2 \\
\text{-78°C} \\
\text{I} \\
\text{n-Bu} \\
\end{array}
\]

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(g) \[ \text{1. } n\text{-BuLi, TMEDA} \]
\[ \text{2. allyl bromide} \]
\[ \rightarrow \]

(h) \[ \text{1. } n\text{-BuMgBr, FeCl}_3 \]
\[ \text{2. } H_3O^+ \]
\[ \rightarrow \]

(i) \[ \text{Br} \]
\[ \text{NaCN, DMF} \]
\[ \rightarrow \]

(j) \[ \text{C} \]
\[ \text{1. } \text{NaNH}_2 \]
\[ \text{2. MeI} \]
\[ \rightarrow \]

(k) \[ \text{O} \]
\[ \text{PhCu} \bullet \text{BF}_3 \]
\[ \rightarrow \]

(l) \[ \text{Br} \]
\[ \text{1. } \text{Na}_3\text{Fe(CO)}_4 \]
\[ \text{2. EtI} \]
\[ \text{3. CO} \]
\[ \rightarrow \]

(m) \[ n\text{-Bu} \]
\[ \text{DIBAL-H, heptane, 50°C} \]
\[ \text{MeLi, ether} \]
\[ \text{CO}_2 \]
\[ \text{H}_3\text{O}^+ \]
\[ \rightarrow \]

(n) \[ \text{Br} \]
\[ \text{PPh}_3 \]
\[ \rightarrow \]
\[ \text{1. } n\text{-BuLi} \]
\[ \text{2. PhCHO} \]

(o) \[ \text{EtO} \]
\[ \text{CO}_2\text{Et} \]
\[ \text{PhCHO, NaH} \]
\[ \rightarrow \]

(p) \[ \text{OMe} \]
\[ \text{1. NaH} \]
\[ \text{2. PhCHO} \]
\[ \rightarrow \]
9. Taken from *Org. Lett.* 2000, 2, 11. Initial acyl substitution of the Weinreb amide generated the conjugated ketone, along with the amine (MeONHMe). Subsequent Michael addition gave the enolate anion, and workup with water gave the final β-amino ketone product.

10. In reaction (a), the first equivalent of ethyllithium reacts with the more acidic H-O, but the second equivalent deprotonates at a carbon of the benzene ring, leading to the two dilithio derivatives shown.


In reaction (b), the first equivalent of ethyllithium removes the more acidic H-N, but the second equivalent deprotonates at the carbon α- to the imine moiety.


11. The following are reasonable reagents for each transformation.

   A. 1. DIBAL-H, −78°C  2. H₂O
   B. 1. aq NaOH  2. pH 7
   C. 1. excess PhMgBr  2. H₂O
   D. 1. aq NaOH  2. pH 7  3. SOCl₂  4. n-Pr₂Cd
12. (a) In general, exo attack is preferred in bicyclic systems such as this (see Sec. 4.7.E). If the exo face is the lowest energy face for approach of the organocuprate, the major product will be the exo methyl derivative shown.

(b) Initial addition of the cuprate occurs from the less sterically hindered exo face (see answer in a). This conjugate addition leads to an enolate anion (see Sec. 9.7.A). Since the bromide moiety is on a face easily accessible by the enolate, displacement of the bromide is facile, leading to a five-membered ring and the tricyclic ketone shown.

(c) The epoxidation of the alkene occurs from the face opposite the sterically blocking methyl group to give A. Once the epoxide stereochemistry is set, reaction with butylmagnesium bromide occurs from the less hindered face, and at the less hindered carbon (distal to the bridgehead carbon bearing the methyl group).

13. (a) For a spirodecane derivative, see Bull. Chem. Soc. Jpn., 1978, 51, 3590

(b) J. Am. Chem. Soc., 2002, 124, 5380

(c) Org. Lett., 2003, 5, 991
14. In each case, a possible synthesis is presented. Other solutions are possible for each problem.

(a) This sequence is taken from the cited paper.

\[
\begin{align*}
\text{C}_8\text{H}_{17} & \rightarrow \text{C}_8\text{H}_{17} (\text{a, b}) \\
\text{C}_8\text{H}_{17} & \rightarrow \text{C}_{11}\text{H}_{23} (\text{c, d, e}) \\
\text{C}_{11}\text{H}_{23} & \rightarrow \text{C}_8\text{H}_{17} \text{C}_{18}\text{H}_{35} (\text{f})
\end{align*}
\]

Weinreb amide

(a) SOCl$_2$  (b) MeNHOMe  (c) C$_{11}$H$_{23}$MgBr , THF  (d) TsNHNH$_2$  (e) NaBH$_4$  (f) m-CPBA

(b) All reagents are taken from *J. Am. Chem. Soc.*, 2003, 125, 4048. Initial deprotection of the acetate group (7.3.A.ii) was followed by a tetrapropylammonium perruthenate oxidation (3.2.F.i) to give the aldehyde. Wittig olefination (8.8.A.i) and reduction of the ester with Dibal (4.6.C), gave the alcohol. Deprotection of the O-silyl group with tetrabutylammonium fluoride (7.3.A.i) allowed "switching" of the protecting groups, with the more reactive allylic alcohol being converted to the triisopropylsilyl ether (7.3.A.i). A second TPAP oxidation to the aldehyde, was followed by a Grignard reaction (8.4.C.i) to give the target.

\[
\begin{align*}
\text{OAc} & \rightarrow \text{OH} (\text{a}) \\
\text{OH} & \rightarrow \text{CHO} (\text{b}) \\
\text{CHO} & \rightarrow \text{CO}_2\text{Et} (\text{c}) \\
\text{OH} & \rightarrow \text{CHO} (\text{d}) \\
\text{CHO} & \rightarrow \text{OH} (\text{e}) \\
\text{OH} & \rightarrow \text{OTIPS} (\text{f}) \\
\text{OH} & \rightarrow \text{CHO} (\text{g}) \\
\text{CHO} & \rightarrow \text{OH} (\text{h})
\end{align*}
\]

(a) K$_2$CO$_3$ , MeOH  (b) TPAP , NMO  (c) Ph$_3$P=CHCO$_2$Et , toluene , 100°C  (d) Dibal-H , CH$_2$Cl$_2$ , –78°C  
(e) TBAF , THF  (f) TIPS-Cl , imidazole  (g) TPAP , NMO  (h) allylMgbr , ether , –78°C
(c) This sequence is taken from *J. Org. Chem.*, 2003, 68, 9533. Initial protection of the alcohol as the triisopropylsilyl ether (7.3.A.i) was followed by a Wittig reaction (8.8.A.i), which gave a 4:1 Z:E mixture of the alkene. Deprotection of the alcohol (7.3.A.i) allowed oxidation to the aldehyde with the Dess-martin reagent (3.2.D). A second Wittig reaction gave a vinyl ether, and hydrolysis liberated the ketone product.

(d) All reagents are taken from *J. Am. Chem. Soc.*, 2003, 125, 12836. Initial protection of the alcohol as the benzyl ether (7.3.A.i) allowed the Grignard reaction (8.4.C) to form the homoallylic alcohol. This alcohol was protected as the triethylsilyl ether (7.3.A.i), and ozonolysis (3.7.B) generated the ketone.

(e) All reagents are taken from *J. Am. Chem. Soc.*, 2002, 124, 9718. Asymmetric dihydroxylation (3.5.B.ii), followed by protection of the diol as an acetonide (7.3.A.iii), allowed removal of the para-methoxyphenyl protecting group with ceric ammonium nitrate (7.3.A.ii). TPAP oxidation (3.2.F.i) and reaction with ethylmagnesium bromide (8.4.C.i) was followed by a second TPAP oxidation to the ketone, and reaction with vinylmagnesium bromide. Deprotection liberated the diol.
(f) Reaction \( d \) will generate ortho and para isomers. The para isomer must be separated chromatographically. A milder Lewis acid may be used for this Friedel-Crafts acylation since phenol is highly activated (12.4.D).

(g) All reagents are taken from the *J. Am. Chem. Soc.*, **2003**, 125, 15433. Protection of the alcohol as the \( t \)-butyldimethylsilyl ether (7.3.A.i) allowed ozonolysis to the aldehyde (3.7.B). Wittig reaction (8.4.C) gave the conjugated ester, which was reduced to the alcohol with diisobutylaluminum hydride (4.6.C) and then oxidized to the aldehyde with tetrapropylammonium perruthenate (3.2.F.i). Horner-Wadsworth-Emmons olefination (8.8.A.i) gave a new conjugated ester, which was reduced and then oxidized as above. A second Horner-Wadsworth-Emmons olefination (8.8.A.iii) gave the requisite triene unit, and both the alcohol and the alkyne were deprotected with tetrabutylammonium fluoride (7.3.A.i).
(h) This sequence is taken from *J. Org. Chem.*, 2003, 68, 9983. Initial oxidation with tetrapropylammonium perruthenate (3.2.F.i) was followed by addition of the sulfone anion (8.6.A) to the aldehyde. Deprotection of pivaloyl group (7.3.A.ii) and a second oxidation to the aldehyde with the Dess-Martin reagent (3.2.D) was followed by addition of the alkyne anion (8.3.C) to give the propargyl alcohol. Lindlar hydrogenation provided the *cis*-alkene (4.8.B) and a final Dess-Martin oxidation to the ketone completed the sequence.

(i) All reagents in this sequence are taken from *Org. Lett.*, 2002, 4, 1715. Conjugate addition of divinyl cuprate (8.7.A.vi) was followed by reduction of the ester with Super hydride (4.5.B). The resulting alcohol was oxidized to the aldehyde with the Swern oxidation (3.2.C.i), followed by Wittig olefination (8.8.A.i), and catalytic
hydrogenation of both vinyl groups (4.8.B). The silyl protecting group was removed with tetrabutylammonium fluoride (7.3.A.i), and a Swern oxidation to the aldehyde (3.2.C.i), followed by NaClO₂ oxidation to the acid, and esterification with diazomethane (2.5.C; 13.9.C), was followed by introduction of the phenylselenide via the enolate anion (9.2) and syn elimination (2.9.C.vi). A second conjugate addition with divinyl cuprate (8.7.A.vi) and reduction of the ester with Super hydride (4.5.B), allowed formation of the alkoxide with sodium hydride. The alkoxide attacked the carbamate unit, and acyl substitution (2.5.C) led to the oxazolidinone product shown.

(j)

(k) All reagents are taken from the cited reference. Wittig olefination gives the conjugated ester, allowing conjugate addition with the higher order cuprate, in the presence of the trapping agent chlorotrimethylsilane. DIBAL-H reduction of the ester gives an aldehyde, which reacts with the alkyne anion to give the diastereomeric mixture of alcohols shown.
(l) All reagents are taken from *J. Am. Chem. Soc.*, 2003, 125, 4680. This sequence includes a "cheat", in that phosphonate ester is used, containing the Weinreb's amide unit. Horner-Wadsworth-Emmons olefination with a (8.8.A.iii) leads to the conjugated amide, and reduction to the aldehyde with diisobutylaluminum hydride (4.6.C) was followed by a Wittig reaction (8.8.A.i) to give the diene. Deprotection of the trityl group (7.3.A.i) and iodination (2.8.A) gave the target.

(m) All reagents in this sequence are taken from *J. Am. Chem. Soc.*, 2002, 124, 9682. Reduction of the ester with LiAlH₄ (4.2.B) was followed by PCC oxidation (3.2.B.ii) to the aldehyde. Wittig olefination (8.8.A.i) gave the vinyl group, and hydroboration generated the anti-Markovnikov alcohol (5.4.A). Reaction with thionyl chloride converted the alcohol to the chloride (2.8.A).

(n) All reagents are taken from *J. Org. Chem.*, 2003, 68, 6905. Oxidation of the secondary alcohol with the Dess-Martin periodinane (sec 3.2.D) was followed by mild basic hydrolysis of the acetate. Oxidation of the resulting alcohol with tetrapropylammoniumperruthenate (TPAP - sec 3.2.F.i) gave a ketone. Ozonolysis under reductive conditions led to the aldehyde unit, and intramolecular aldol condensation gave the targeted compound as a mixture.
of diastereomeric alcohols.

(a) Dess-Martin periodinane, Py, CH₂Cl₂  (b) K₂CO₃, aq MeOH  (c) TPAP, NMO, MS 4Å, CH₂Cl₂  
(d) O₃, Py, CH₂Cl₂ ≠ MeOH, Me₂S  (e) NaOH, MeOH

(o) All reagents are taken from J. Org. Chem., 2003, 68, 2376. Asymmetric reduction of the ketone unit by hydrogenation (sect 4.8.C, 4.8.G) using a chiral catalyst was followed by protection of the resulting alcohol and an SN₂ displacement (sect 2.6.A) of the chloride to give the azide. DIBAL-H reduction (sect 4.6.C) of the ester stopped at the aldehyde, and a simple Wittig olefination (sect 8.8.A) gave the alkene unit. Dihydroxylation using osmium tetroxide (sect 3.5.B) gave the final product.

(p) All reagents are taken from Org. Lett. 2002, 4, 2125. Reduction of both ester units with LiAlH₄ gave the diol (4.2.B), and the symmetry of the molecule allowed on hydroxyl to be protected as the OTBDMS ether (7.3.A.i). Swern oxidation (3.2.C.i), followed by Wittig olefination (8.8.A.i) gave the conjugated ester, which was reduced with diisobutylaluminum hydride (4.6.C) to the allylic alcohol. Another Swern oxidation gave the aldehyde, and this was followed by a second Wittig olefination and Dibal reduction of the ester. Final Swern oxidation to the conjugated aldehyde completed the synthesis.
(q) This sequence is taken from *J. Am. Chem. Soc.*, 2002, 124, 6981. Swern oxidation (3.2.C.i) of the primary alcohol unit was followed by a Wittig reaction (8.8.A.i). Dibal reduction of the ester (4.6.C) to the primary alcohol, allowed an allylic manganese dioxide oxidation (3.2.F.iii) to the aldehyde. Subsequent Horner-Wadsworth-Emmons olefination (8.8.A.iii) and deprotection of the O-silyl group with tetrabutylammonium fluoride (7.3.A.i) gave the target.

15. In each case a synthesis is shown. There are other syntheses based on other starting materials. In each of the provided solutions, the source of starting material was the 2000-2001 Aldrich Chemical catalog. There are, obviously, other sources of organic chemicals. Other synthetic routes are available based on other starting materials.

(a) This is a very simple synthesis. Disconnection to the commercially available cyclopentane carboxaldehyde
Cyclopentanecarbonitrile (Aldrich, $154.40/10g) is another obvious starting material.

The cyclohexenone starting material is available from Aldrich, $60.40/100 mL.

The hexanal starting material is available from Aldrich, $42.90/500 mL.
Cyclohexanone is available from Aldrich ($19.70/L). The enolate chemistry used here is described in greater detail in Section 9.4.A.ii. Reduction of the alkene (step e) used diimide, described in Section 4.10.B, and was chosen to be compatible with the SPh moiety which is known to poison many hydrogenation catalysts and is itself subject to hydrogenolysis.

Pentanal is available as valeraldehyde from Aldrich, $33.80/L.

Friedel-Crafts acylation is described in Sections 12.4.D, 12.4.E. Benzene is available from Aldrich, $28.80/L.
(g)  
(a) \text{MeMgBr} \; \text{H}_3\text{O}^+  \quad (b) 1. \text{TsCl}, \text{pyridine} \quad 2. \text{NaCN}, \text{DMF}  \quad (c) \text{n-PrMgBr} \; \text{H}_3\text{O}^+, \text{heat} \quad (d) \text{Ph}_3\text{P=CHCH}_2\text{Ph}

Cyclopentene oxide is available from Aldrich, $118.60/25g.

(h)  
(a) [\text{SPh}_2/\text{n-BuLi}] \quad (b) \text{HClO}_4

The hexanal starting material is available from Aldrich, $42.90/500 \text{mL}.