1. In each case, the Cram model is shown first and then the Felkin-Anh model, both in Newman projection. The diastereomer that is predicted to be the major product is also shown.

(a)

(b)

(c) In this case, reduction does not generate a chiral center, so the model used is irrelevant. Nonetheless, the models are shown.

(d)
2. (a) The conformation of this molecule is shown in the usual half-chair of a cyclohexenone derivative. Since cerium borohydride will give selective 1,2-reduction, the main issue is stereochemistry. The bulky siloxymethyl group on the bottom blocks approach from that face. Therefore, approach is from the top to give the stereochemistry shown for the alcohol product.

(b) To predict the stereochemistry of this reduction, we can examine a 3D model of the ketone. The gem-dimethyl unit as well as the other bridgehead methyl sterically block path A, but path B is relatively open and predicts the major product. Alternatively, a LUMO map of the ketone shows a more intense blue color exposed to face B, so delivery of hydride will be from that face.

(c) Coordination of the alcohol moiety with zinc borohydride modifies the conformation, as shown, to deliver
hydride from behind. The result is the diastereomeric trans diol shown.

(d) The ethyl group effectively blocks one face of the azabicyclooctane ring. Delivery of hydride from the direction of the arrow leads to the diastereomeric alcohol shown.

3. Cerium borohydride gives selective 1,2-reduction of the conjugated ketone, delivering hydride from the bottom face to give the alcohol. This alcohol unit then reacts with the free carboxyl to form the lactone. Examination of the 3D figure clearly suggests that attack from the top face (A) is blocked by both the methyl group and the -CH₂COOH group. The bottom face (B) is unencumbered, leading to the stereochemistry indicated for reduction of the ketone to the alcohol and shown in the lactone. The LUMO map shows that attack from the bottom face, to give the alcohol precursor required to give the lactone product, is slightly preferred.

4. The first step is to look at the actual conformation of the steroid. Using the usual model for conjugated ketones with R being the steroid ring, predictions can be made for reduction of the carbonyl. Diisobutylaluminum hydride
will coordinate to the carbonyl oxygen, restricting the angle from which hydride will be delivered. This coordination leads to delivery of hydride via a complex that gives anti-Cram selectivity and generates the diastereomer labeled $\alpha$. Selectride, however, does not coordinate, and delivery will be from the less sterically hindered pathway (Cram selectivity), as shown, to give the $\beta$-diastereomer.

\[ \text{See Tetrahedron Lett., 1985, 26, 69.} \]

5. The first step of this reaction is reduction of the ketone unit to give an alcohol. Treatment with the basic reagent \( \text{tert-butoxide} \) leads to an alkoxide product, as shown. With the tosylate unit properly positioned, a Grob-like fragmentation is possible, leads to the aldehyde and the alkene units in the final product.

\[ \text{See J. Org. Chem., 1999, 64, 4304} \]

6. The reaction products shown are taken from the cited reference. The first step is epoxidation of the C=C unit with \( \text{meta-chloroperoxybenzoic acid} \). The Spartan model shown can be interpreted in several way: the methyl group on the adjacent allylic carbon can provide steric hindrance, or the bridgehead methyl on the lower face could block the reaction. In fact, the lower face is more hindered, and epoxidation occurs from the top face, in 81% yield. Lithium borohydride opens the epoxide, this time from the lower face, and regioselectively at the less sterically hindered carbon (see model) to give the alcohol shown.
7. Inspection of the 3D model shows that path A is blocked by the methyl group, so reduction with LiAlH₄ occurs by attack via path B, which gives the stereochemistry shown for the allylic alcohol. Both 1,2- and 1,4-addition are possible, so LiAlH₄ is used in ether at low temperature to maximize 1,2-addition. The second reaction is simply a Mitsunobu reaction with the alcohol, first forming the benzoate ester with inversion of configuration, and the treatment with methanolic KOH to give the requisite alcohol.

8. (a) Aluminum hydride coordinates effectively to the oxygen of the carbonyl. 1,4-Reduction demands delivery of hydride to carbon via path B, whereas 1,2-reduction demands delivery via path A. Once bound to oxygen, the distance between H and the terminal C of the C=C unit via path B is rather long, making delivery difficult. Delivery via path A is facile due to the relatively short distance between the carbonyl C and H.
Coordination to oxygen therefore inhibits 1,4-addition and promotes 1,2-addition.

(b) L-Selectride is much more bulky than sodium borohydride. On approach to the carbonyl carbon, this steric bulk will maximize steric interactions with the indane ring system and lead to greater selectivity relative to NaBH₄. Using the Cram model, the diastereomer shown is predicted to be the major product.

(c) In this reaction, sodium transfers an electron to benzene to generate radical anion A. The proximity of the single electron and the negative charge (2 electrons localized on that carbon) destabilize A due to electrostatic repulsion. The resonance form (B) diminishes electrostatic interactions and is energetically favored. Transfer of hydrogens to B leads to the final product, 1,4-cyclohexadiene.

(d) Transfer of an electron from sodium to anisole can generate two different regioisomeric radical anions, A and B. The proximity of the negative charge to the electron donating OMe group destabilizes A, making B energetically more favorable. This leads to the product shown. Similar reaction with benzoic acid leads to C and D as the possible radical anions. In this case, the electron withdrawing carboxylate group stabilizes the adjacent negative change in C, making it more stable than D where the charge is distal to the carboxylate group. For this reason, C leads to the major product shown.
(e) Lithium aluminum hydride is a powerful reducing agent due to the charge distribution and polarity of the Al—H moiety. It will reduce ester groups, acid groups, and carboxylate anion groups. Since LiAlH₄ will reduce both the ester and the acid, the product is a diol. Borane coordinates with the acid but not with the ester. It will therefore transfer hydride only to the acid and not to the ester, and the acid is reduced and the ester is not. The product is a hydroxy-ester.

(f) This reduction occurs via a six-centered transition state, as shown.

![Six-centered transition state diagram](image)

When the alkene is symmetrical and not polarized, electron density is readily transferred to hydrogen, leading eventually to expulsion of N₂, which drives the reaction. When the alkene is conjugated to a carbonyl, the electron donating ability of the alkene is diminished, slowing the reaction by destabilizing the requisite six-centered transition state. See *J. Am. Chem. Soc.*, 1961, 83, 4302.

(g) In A there is a neighboring group effect where the OH group coordinates with zinc borohydride and delivers hydride from the same face as the hydroxyl group. When the OH is blocked as the silyl derivative, zinc borohydride cannot coordinate, and the usual steric effects lead to delivery of hydride from the face opposite the OSiR₃ group.

(h) This transformation is taken from *J. Am. Chem. Soc.*, 2002, 124, 12416. Birch reduction of the naphthalene unit containing the electron releasing OMe groups is expected to give the reduced product shown. Aqueous hydrolysis converts the vinyl ether to the ketone, but the C=C unit in the ketone-bearing ring will move into the other ring to form the aromatic ring, rather than into conjugated with the carbonyl. Aromatization is the driving force leading to the major product.
9. The first transformation can be effected with Sn/HCl (Stephen reduction) or with LiAlH(O-t-Bu)_3. The second transformation can be effected with LiAlH_4 or with LiBHEt_3.

10.

(a) 

(b) 

CHO

(c) 

PMB = p-methoxybenzyl
Piv = pivaloyl

(d) 

MeO

MeO

CO_2H

NH_2


(e) 

MeO

N

CO_2Me

CO_2t-Bu

Org. Lett., 2003, 5, 999

(f) 

MeO

MeO

Br

NHPMB


PMB = p-methoxybenzyl

(g) 

(t-Bu)Me_2SiO

OH


(h) 

Ph

MeO

CO_2t-Bu

Org. Lett. 2003, 5, 1927

(i) 

Br

HO

11. In each case a synthesis is shown. These are not necessarily the only approaches. It is very likely there are
many approaches for several of these questions.

(a) The acid hydrolysis of the vinyl ether to the ketone may also convert the methyl ester to the acid. If this
occurs, an esterification step (thionyl chloride; methanol) would be required. Mild acid hydrolysis of the vinyl
ether should be possible, however.

(b) The first step requires a chain extension and converting the alcohol to its tosylate introduces the requisite
leaving group, allowing a subsequent reaction with NaCN to give the corresponding nitrile. DIBAL-H reduction of
the nitrile gives the aldehyde.

(c) All steps in this synthesis are taken from *Org. Lett.*, 2002, 4, 1379. Bromination of the allylic alcohol (2.8)
and S_N2 displacement with cyanide gives the nitrile (2.6.A.i). Basic hydrolysis to the carboxylic acid, and
esterification with diazomethane (2.5.C; 13.9.C), was followed by selenium dioxide oxidation to the aldehyde
(3.8.A). Reduction of both the ester and aldehyde with LiAlH4 gave the diol (4.2.B), and selective chlorination of
the allylic alcohol with N-chlorosuccinimide (2.8) gave the final target.
(d) The Wittig olefination step is discussed in chapter 8.

(e) All reagents are taken from the cited reference. The first reaction reduces the ester unit to an alcohol. This is followed by conversion to a tosylate that allows Super-Hydride reduction to give the methyl group. The O-SiR₃ unit is cleaved with aqueous acid to give the corresponding alcohol (see chap. 7, sec. 7.3.A.i). The primary alcohol is then converted to the aldehyde by a Swern oxidation (see chap. 3, sec. 3.2.C.i).

(a) DIBAL-H, toluene, –78°C  (b) TsCl, DMAP, NEt₃  (c) LiEt₂BH, THF  (d) AcOH, aq THF  (e) DMSO, (COCl)₂, NEt₃

see *Tetrahedron Lett.*, 2000, 41, 403
(f) All reagents are taken from the cited reference. Initial reduction of the acid to the alcohol was followed by treatment with tosic acid. This led to an internal transesterification to the lactone, and conversion of the dioxolone to the alcohol. Treatment with the dimethyl acetal of formaldehyde led to the ether shown (a MOM group - see chap. 7, sec. 7.3.A.i), and DIBAL-H reduction converts the lactone to a lactol.

\[
\text{CO}_2\text{H} \quad \text{O} \quad \text{O} \\
\text{O} \quad \text{O} \quad \text{OH} \\
\text{OO} \quad \text{O} \quad \text{OO}
\]

(a) BH₃, THF; H₂O⁺  (b) p-TsOH, CHCl₃  (c) CH₂(OMe)₂, P₂O₅  (d) DIBAL-H, CH₂Cl₂

*see J. Org. Chem, 2000, 65, 9129*

(g) All reagents are taken from the cited reference. Initial reduction of the ester unit (using DIBAL-H) gives the allylic alcohol. To insert the proper stereochemistry for the new alcohol unit, Sharpless asymmetric epoxidation using (-)-DIPT (see Sec. 3.4.D.i) gives the epoxide and selective reduction of the less sterically hindered carbon of the epoxide with Red-Al gives the final product.

\[
\text{CO}_2\text{Et} \quad \text{O} \quad \text{O} \\
\text{O} \quad \text{SiMe}_3 \\
\text{OH} \\
\text{OH} \\
\text{OH}
\]

(a) DIBAL-H, CH₂Cl₂, –78°C  (b) (-)-DIPT, t-BuOOH, Ti(OiPr)₄  (c) Red-Al, THF

*see Tetrahedron Lett., 2000, 41, 2821*

(h) A Friedel-Crafts acylation inserts the ketone moiety, and the Wolff-Kishner reduction removes the carbonyl. Catalytic hydrogenation reduces not only the benzene ring but also the nitro group in a single step.

\[
\text{O} \quad \text{n-C}_3\text{H}_7 \\
\text{n-C}_3\text{H}_7 \\
\text{n-C}_3\text{H}_7 \\
\text{NH}_2
\]

(a) butanoyl chloride, AlCl₃  (b) N₂H₄, KOH  (c) HNO₃, H₂SO₄; separate ortho product  (d) excess H₂, Ni(R)

*Section 12.4.D p 1090*

(i) All reagents were taken from *Eur. J. Org. Chem., 2003*, 4445. Reduction of the acid with borane (4.6.A) was
followed by bromination with carbon tetrabromide and triphenylphosphine (2.8.A).

(j) All reagents are taken from the cited reference. The first problem is how to remove the OH group. If the OH is first converted to a tosylate, Finkelstein exchange (chap. 2) generates an iodide that can be reduced with tin hydride. The ester is reduced to an alcohol with LiBH₄, and aqueous acid converts the dioxolane unit (a ketal) to the carbonyl (see chap. 7, sec. 7.3.B.i). The final step is an oxidation. Several methods can be used from chap. 3, sec. 3.2, but the Dess-Martin periodinane reagent was used in this citation.

(k) Hydrogenation with a Lindlar catalyst sets the cis alkene geometry.

12. In each case a synthetic solution is shown. There are other approaches based on other disconnections. The Aldrich catalog (2000-2001) was used as a source for the starting material for convenience. There are, obviously, other sources of chemicals.
(a) An attractive starting material is the commercially available benzylacetone at $95.40/Kg, but it has more than the required five carbons. One more disconnection leads to acetone, which can be converted to benzylacetone via enolate alkylation (see Sec. 9.3.A). Acetone is available from Aldrich ($18.30/L) and has less than five carbons. The Wittig olefination step(a) is discussed in Section 8.8.A.

(b) The starting material is 3-methyl-2-butanol at $43.10/100 mL. Initial conversion to a mesylate allows an S_N2 reaction with the anion of 1-propyne. The alcohol could also be converted to a bromide using PBr_3 or a similar reagent. Lindlar reduction of the alkyne leads to the cis-alkene.

(c) The requirement that the starting material be five carbons or less makes this a very cumbersome synthesis. The point of this exercise is first to give practice for various reactions but also to show that setting arbitrary starting material requirements can have profound consequences. A shorter approach, for example, would use phenetole (ethoxy benzene) and Birch reduction. In the synthesis shown, 2-ethoxy-propanoic acid was not found to be commercially available (someone probably sells it if sufficient time was taken to find a source), but the expensive β-propiolactone at $76.20/5 mL can be opened with ethanol (transesterification) to give the requisite alcohol-ester. Wittig olefination (see Sec. 8.8.A) can be done with a carboxyl substituent.
(d) This synthesis begins with benzene at \$31.00/L and bromination followed by reaction with cuprous cyanide gives benzonitrile. Rosenmund reduction gives benzaldehyde (remember that we had to begin with material containing only 6 carbons). A Wittig olefination (see Sec. 8.8.A) gives styrene and a radical HBr addition gives the primary bromide. An S_N2 displacement with cyanide allows selective reduction to the aldehyde.

13. (a) NaBH_4  
(b) Na, NH_3, EtOH  
(c) LiAlH(Or-Bu)_3 - some diol will also be formed with virtually any reagent  
(d) NaBH_3CN, pH 7

(e) The first step requires reduction of the ketone to an alcohol, and the mild reagent NaBH_4 was used. The second step uses NBS to form a bromonium ion, which is opened by the proximal alcohol unit to give the bromo-ether shown. Both reagents used here were taken from the cited reference.
(f) LiAlH₄ will reduce the ester to the alcohol, the azide to the amide, and the lactam to the cyclic amine. See *J. Org. Chem.*, **1996**, *61*, 4572.