

# **Solution Manual for Organic Synthesis 4th Edition – Michael Smith**

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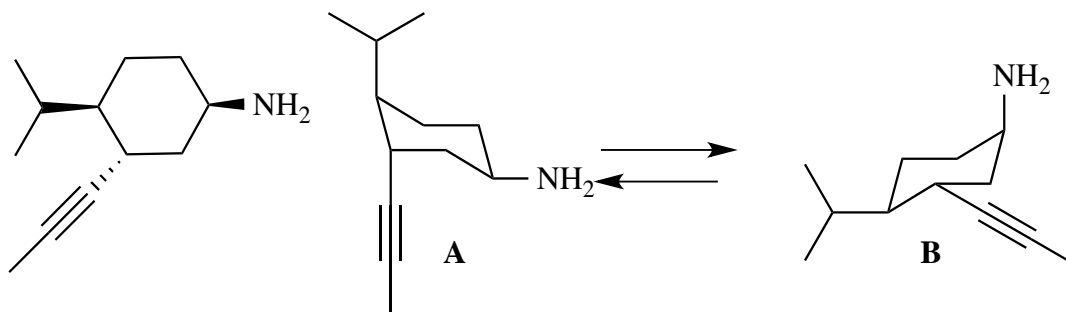
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## CHAPTER 1

1. The calculations are shown for each molecule using values from Table 1.4 in Chapter 1.



$$(a) \quad H^{\circ}_A = A_{CHR_2} + A_{C\equiv} = 2.1 + 0.2 = 2.3 \text{ kcal mol}^{-1}$$

$$H^{\circ}_B = A_{NHR} + G_{C\equiv} + G_{CHR_2} = 1.3 + 0 + 0.8 = 2.1 \text{ kcal mol}^{-1}$$

$$\Delta H^{\circ} = H^{\circ}_B - H^{\circ}_A = 2.1 - 2.3 = -0.2 \text{ kcal mol}^{-1}$$

$$\text{At } 150^{\circ}\text{C}, 2.303 RT = 2.303(1.987)(423)^* = 1.936 \text{ kcal mol}^{-1}$$

[\* T is in Kelvin =  $^{\circ}\text{C} + 273$ ]

$$\text{therefore, } \Delta G^{\circ} = -0.2 = -1.936 \log K_{eq}$$

$$\log K_{eq} = \frac{-0.2}{-1.936} = +0.103$$

$$K_{eq} = 10^{0.103} = 1.27$$

$$1.27 = B(2.27)$$

$$\text{If } A + B = 1$$

$$\text{then, } A = 1 - B$$

$$K_{eq} = \frac{B}{A} = \frac{B}{1 - B}$$

$$K_{eq}(1 - B) = B$$

$$\text{and } B = \frac{K_{eq}}{1 + K_{eq}}, \text{ via}$$

$$1.27(1 - B) = B$$

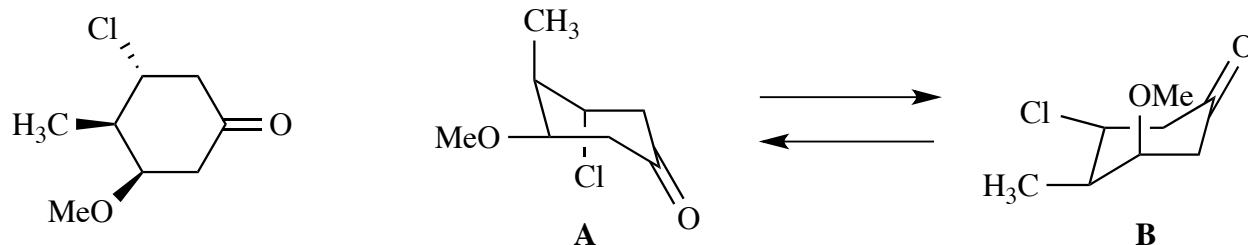
$$1.27 - 1.27B = B$$

$$1.27 = B + 1.27B$$

$$\frac{1.27}{2.27} = B = 0.56$$

Therefore, 56% of B and 100-56 = 44% of A.

Since A has two axial groups and B has only one, an initial glance suggests that B will be lower in energy and be the greatest contributor to the chair population. Conformation A has one axial group ( $\text{CHMe}_2$ ) on the top and one axial group ( $\text{C}\equiv\text{CMe}$ ) on the bottom so  $A_{CHR_2}$  and  $A_{C\equiv}$  are used from Table 1.4. In B there is only one axial group ( $\text{NH}_2$ ) so  $A_{OR}$  is used. The two equatorial groups in B ( $\text{CHMe}_2$  and  $\text{C}\equiv\text{CMe}$ ) are on adjacent carbons, so there are two G terms,  $G_{C\equiv}$  and  $G_{CHR_2}$ .



$$(b) \quad H^{\circ}_A = \frac{3}{4}(A_{CH_2R} + A_{Cl}) = 0.1.8 + 0.4 = 1.65 \text{ kcal mol}^{-1}$$

$$H^{\circ}_B = \frac{3}{4}(A_{OR} + G_{CH_2R} + G_{Cl}) = \frac{3}{4}(1.8 + 0.4 + 0.5) = 2.03 \text{ kcal mol}^{-1}$$

$$\Delta H^{\circ} = H^{\circ}_B - H^{\circ}_A = 2.03 - 1.65 = 0.38 \text{ kcal mol}^{-1}$$

$$\text{at } 25^{\circ}\text{C}, \Delta G^{\circ} = 0.38 = -1.364 \log K_{eq}$$

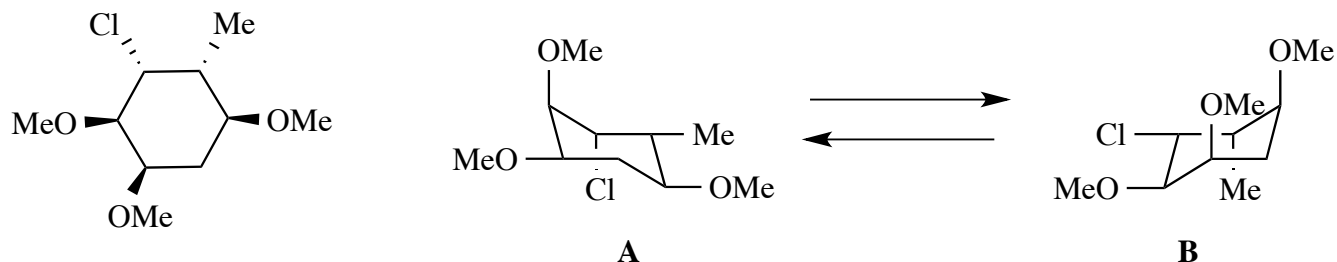
$$\log K_{eq} = \frac{0.38}{-1.364} = -0.279$$

$$K_{eq} = 10^{-0.279} = 0.526$$

$$\frac{0.526}{1.526} = B = 0.345$$

Therefore, 34.5% of B and 100-34.5 = 65.5% of A.

Although B has two axial groups, it is actually lower in energy because the axial chlorine has a lower interaction than the combined G value interactions in B. It accounts for only 35% of the population of chair conformers. Conformation B has two adjacent and diequatorial groups, so  $G_{CH_2R}$  and  $G_{Cl}$  are used from Table 1.4. Since B has one axial methoxy group,  $A_{OR}$  is used.



$$(c) \quad H^{\circ}_A = A_{OR} + A_{Cl} + G_{CH_2R} + G_{OR} = 0.8 + 1.8 + 0.4 + 0.2 = 3.2 \text{ kcal mol}^{-1}$$

$$\text{If } A + B = 1$$

$$H^{\circ}_B = U_{OR} + U_{OR} + A_{CH_2R} + G_{Cl} + G_{OR} = 0.8 + 0.8 + 1.8 + 0.5 + 0.2 = 4.1 \text{ kcal mol}^{-1} \quad \text{then, } A = 1 - B$$

$$\Delta H^{\circ} = H^{\circ}_B - H^{\circ}_A = 4.1 - 3.2 = 0.9 \text{ kcal mol}^{-1}$$

$$\text{at } 25^{\circ}\text{C}, \Delta G^{\circ} = 0.9 = -1.364 \log K_{eq}$$

$$\log K_{eq} = \frac{0.9}{-1.364} = -0.66$$

$$K_{eq} = 10^{-0.66} = 0.22$$

$$K_{eq} = \frac{B}{A} = \frac{B}{1-B}$$

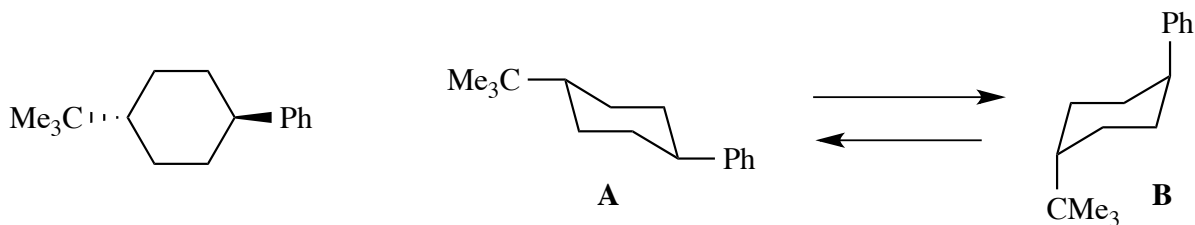
$$K_{eq}(1-B) = B$$

$$\text{and } B = \frac{K_{eq}}{1+K_{eq}}$$

$$\frac{0.22}{1.22} = B = 0.18$$

Therefore, 18% of B and 100-18 = 82% of A.

The three axial groups in B, along with the two G-interactions make it much more sterically demanding than the two axial groups and the two G-interactions in A. Therefore, A accounts for the greater percentage of chair conformations.



(d)  $H^\circ_A = \text{no interactions} = 0 \text{ kcal mol}^{-1}$   
 $H^\circ_B = A_{\text{aryl}} + A_{\text{CR}_3} = 3.0 + 6.0 = 9.0 \text{ kcal mol}^{-1}$

$\Delta H^\circ = H^\circ_B - H^\circ_A = 9.0 - 0 = 9.0 \text{ kcal mol}^{-1}$

at  $25^\circ\text{C}$ ,  $\Delta G^\circ = 9.0 = -1.364 \log K_{\text{eq}}$

$\log K_{\text{eq}} = \frac{9.0}{-1.364} = -6.598$

$K_{\text{eq}} = 10^{-6.598} = 3 \times 10^{-7}$

If  $A + B = 1$

then,  $A = 1 - B$

$K_{\text{eq}} = \frac{B}{A} = \frac{B}{1-B}$

$K_{\text{eq}}(1-B) = B$

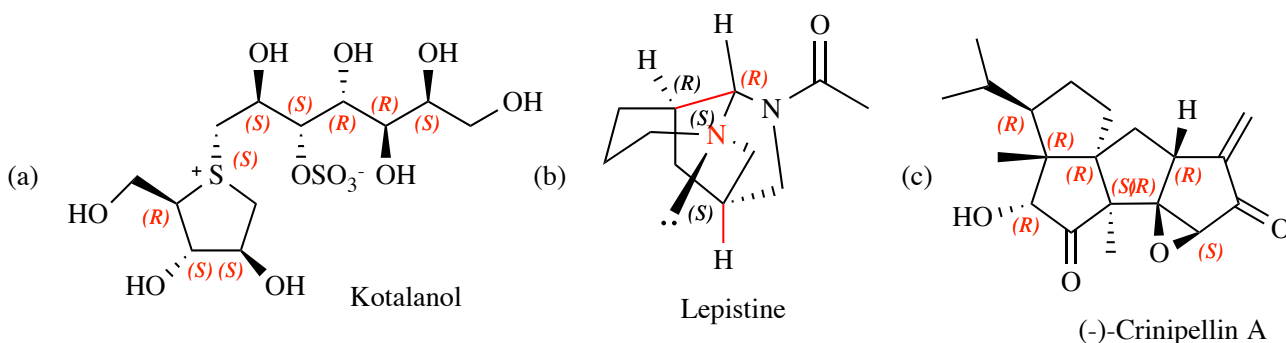
and  $B = \frac{K_{\text{eq}}}{1+K_{\text{eq}}}$

$\frac{3 \times 10^{-7}}{1.00} = B = 3 \times 10^{-7}$

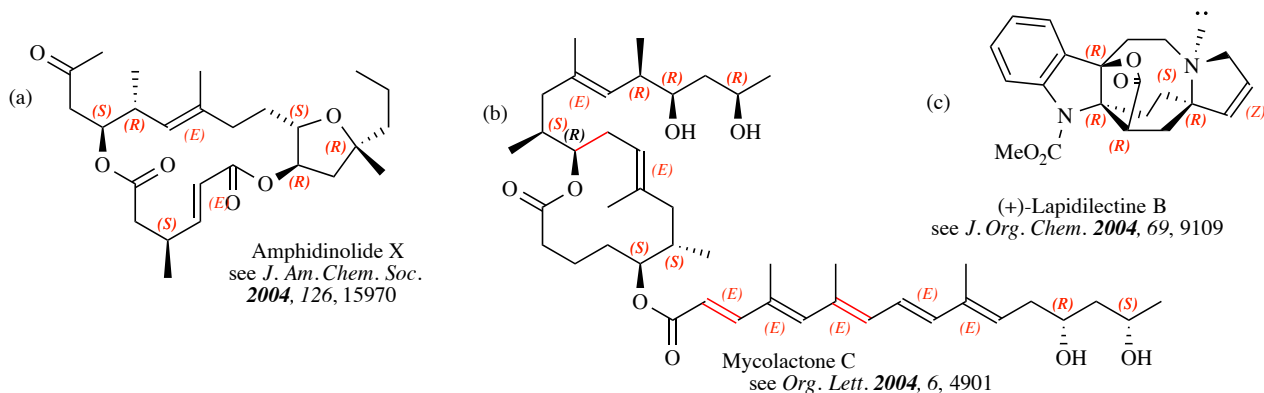
Therefore, **0.00003% of B and 100-0.00003 = 99.99997% of A.**

Since A has two large equatorial groups and B has two large axial groups, the equilibrium is pushed in the direction of A, in essentially 100%.

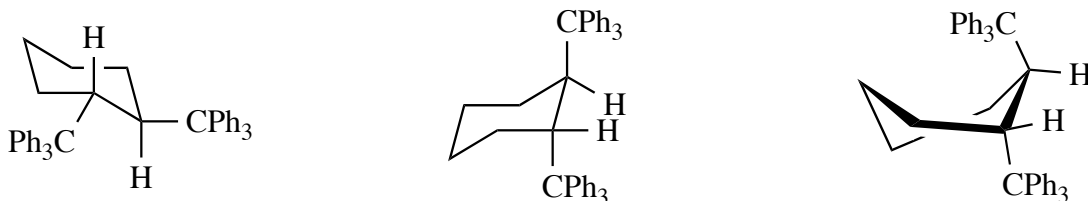
**2. The absolute configuration for each chiral center in the following molecules is shown beside the appropriate chiral center.**



**3. Determine the absolute configuration for every stereogenic center in the following molecules:**

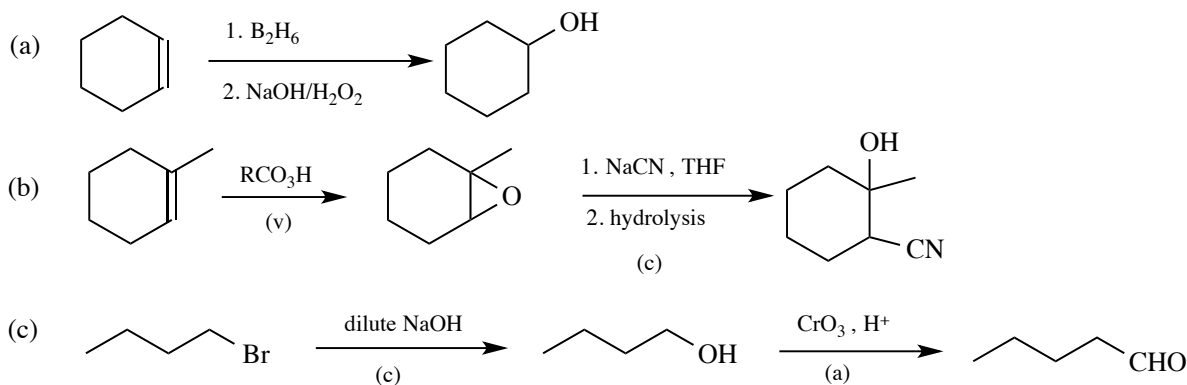


4. Draw both chair conformations and one twist-boat conformation for *trans*-1,2-di(triphenylmethyl)cyclohexane.

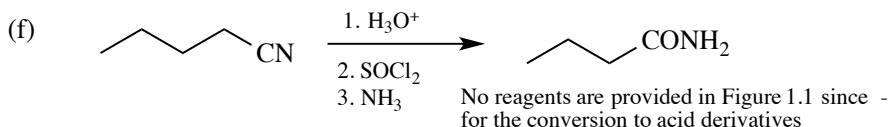
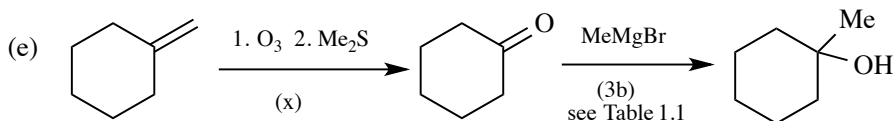
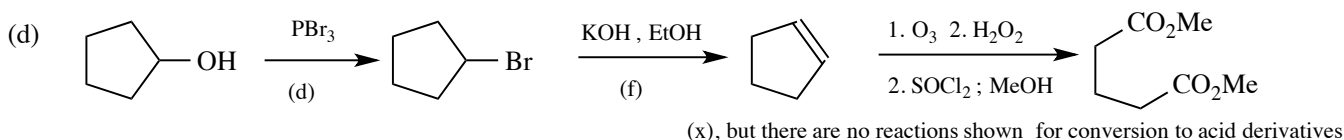


5. Using the reaction wheel (Fig. 1.2) give reasonable syntheses, including reagents and all intermediates (no mechanisms).

There is more than one "correct" answer. One possible solution is shown for each transformation. The letters (a), (f), etc., beside each reagent refer to the lettered transformations from Figure 1.2 in Chapter 1.



The first reaction is a poor one since elimination will be a major process. Limiting the choices to those in Figure 1.1 is a problem since there are other ways to do this.



**6. Use the *Compendium of Organic Synthetic Methods* (Vol. 13) to give three *different* reactions (with literature references and reactions) for each of the following.**

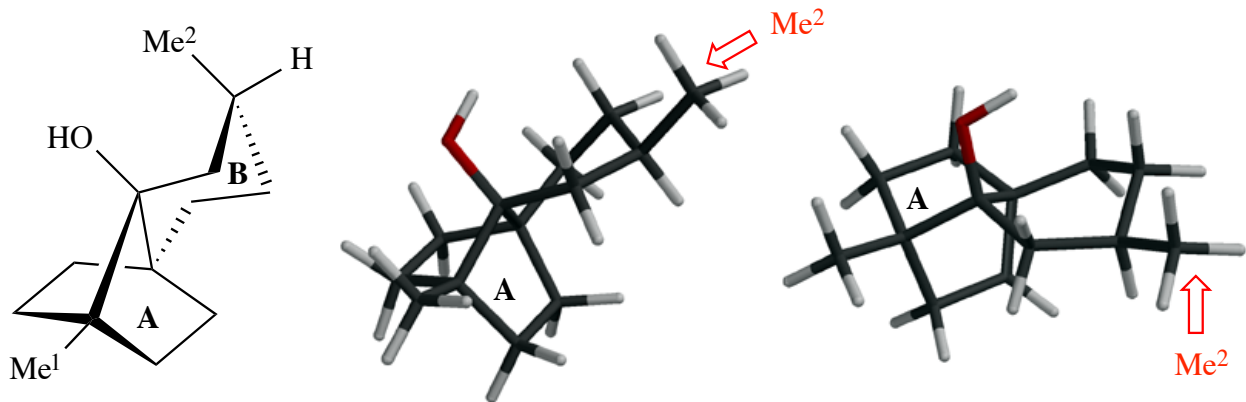
There are potentially many examples for each part (but not always; see the last sentence for this answer). This is a literature-searching question, and there are no correct or incorrect answers. The appropriate sections and pages from Vol. 13 of the *Compendium* are indicated for each category.

- (a) Acids from Nitriles. Section 28. Volume 13: p. 18 (1 example).
- (b) Aldehydes from Nitriles. Section 58. Volume 13: p. 84 (0 examples).
- (c) Amines from Halides. Section 100. Volume 13: pp. 283-290 (43 examples).
- (d) Amides from Nitriles. Section 88. Volume 13: pp. 248-249 (6 examples).
- (e) Ethers from Halides. Section 130. Volume 13: pp. 353-354 (28 examples).
- (f) Halides from Amines. Section 142. Volume 13: pp. 369 (4 examples)
- (g) Ketones from Olefins. Section 179. Volume 13: pp. 393-395 (14 examples).
- (h) Olefins from Aldehydes. Section 199. Volume 13: pp. 419-421 (16 examples + 1 review).

The real lesson from this exercise, apart from learning to use this literature resource, is that some functional group exchange reactions are well studied and there are many variations. Others yield only a handful of possibilities. Despite the request for three examples in the question, 0 examples were found for (b) and only 1 example was found for (a). In these cases, further literature searching in the older literature is a necessity.

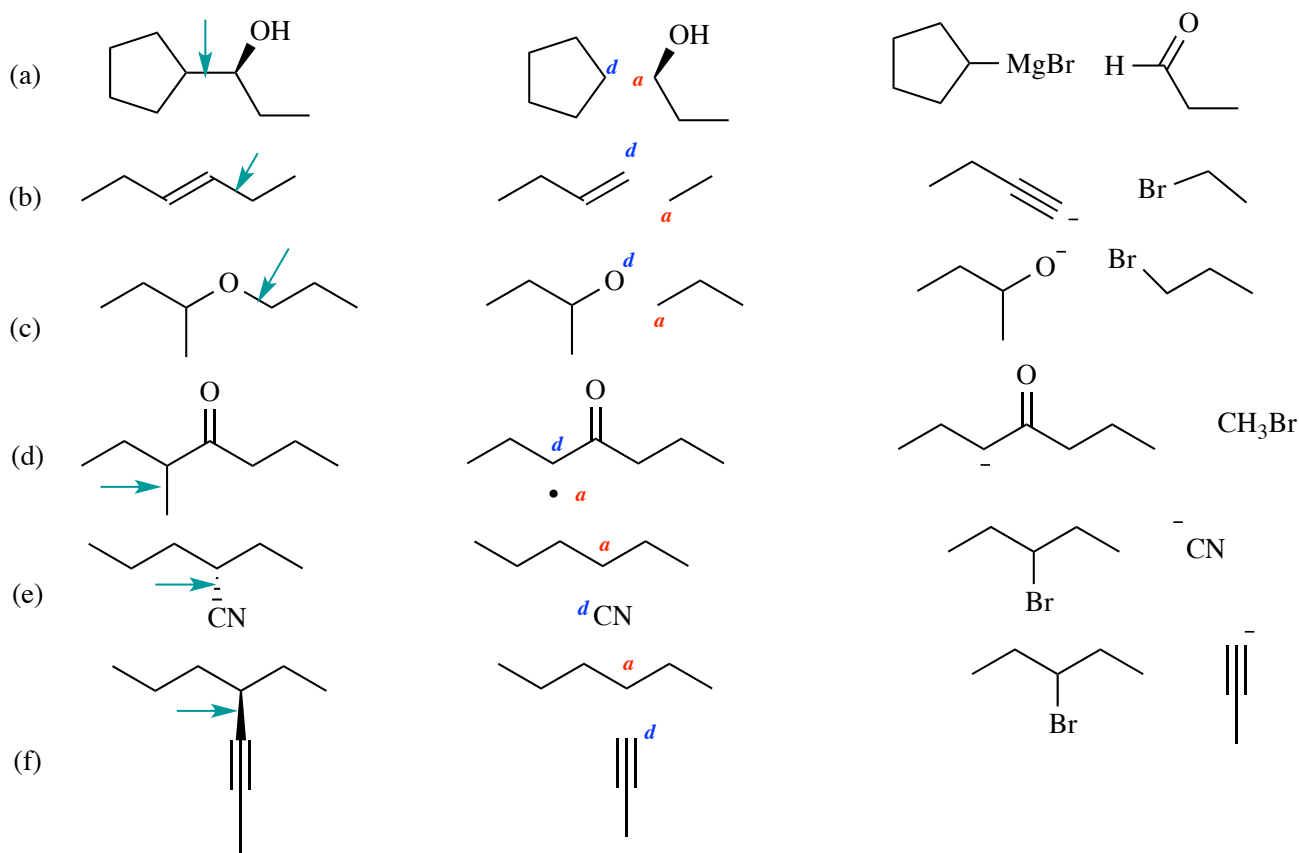
**7. Draw molecule A in what should be the low-energy conformation. Briefly discuss the conformation for the highlighted ring in molecule A. Also discuss the conformational preference (axial or equatorial) for both methyl groups (1 and 2) as well as the hydroxyl.**

The bicyclo[2.2.1]heptane unit (A) is very rigid and greatly influences the stereochemistry for the molecule. The appended six-membered ring B assumes a conformation that is close to a twist-boat, and it cannot 'ring flip' easily due to the conformationally immobile bicycloheptane unit. This constraint forces the methyl group (Me<sup>2</sup>) into a pseudo-axial position. The other methyl group (Me<sup>1</sup>) is at a bridgehead position of the bicycloheptane and is effectively perpendicular to that ring, as shown. The hydroxyl group is formally in a pseudo-axial position relative to ring B.



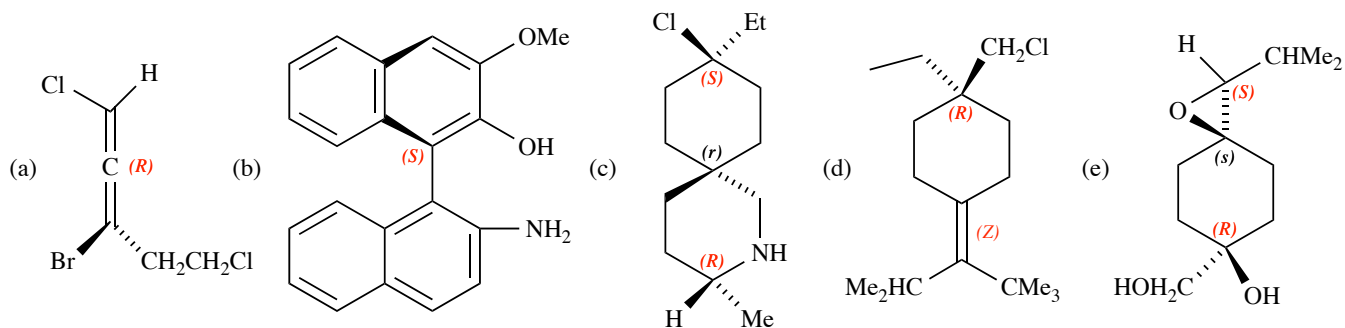
8. In each of the following disconnect the indicated bond and draw the disconnect products. Assign d/a based on any natural bond polarization. If there is no bond polarization, assign a reasonable d/a. Correlate the disconnect products with real reagents using the concept of synthetic equivalents in Table 1.2.

Donor and acceptor sites are assigned based on known reaction types, and the reagents will generate the requisite bond from those fragments. Other reactions may be required in some cases to manipulate the functional group (e.g., reduction of the alkyne unit to a trans alkene in (b)).



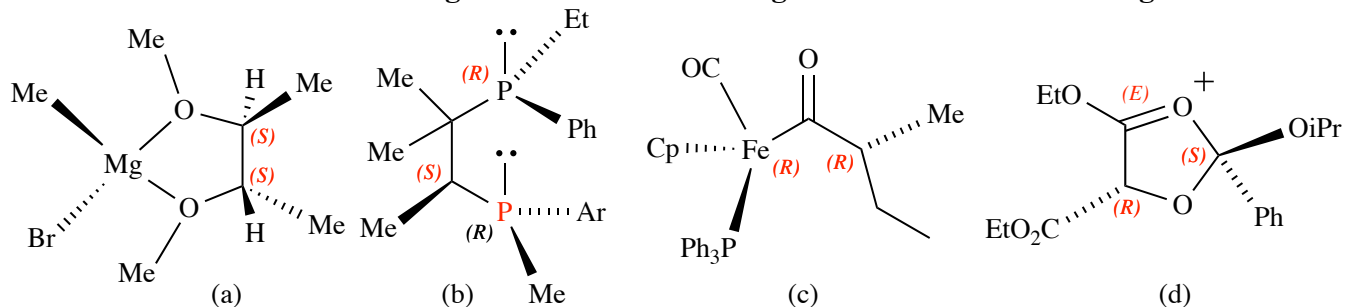
9. Determine the absolute configuration (R or S) for each chiral axis in the following molecules:

The R or S configuration for the chiral axis of each molecule that has a chiral axis rather, as well as that of stereogenic centers chiral center, is shown for (a) - (e).



For (a), Cl is 1 and H is 2; Br is 3 and  $\text{CH}_2\text{CH}_2\text{Cl}$  is 4. For (b), OH is 1 and  $\text{C}^{\text{aryl}}$  is 2;  $\text{NH}_2$  is 3 and  $\text{C}^{\text{aryl}}$  is 4. For (c), Cl is 1 and Et is 2; Me is 3 and H is 4. For (d),  $\text{CH}_2\text{Cl}$  is 1 and Et is 2;  $\text{CMe}_3$  is 3 and  $\text{CHMe}_2$  is 4. For (e) the epoxy O is 1 and  $\text{CHMe}_2$  is 2; OH is 3 and  $\text{CH}_2\text{OH}$  is 4.

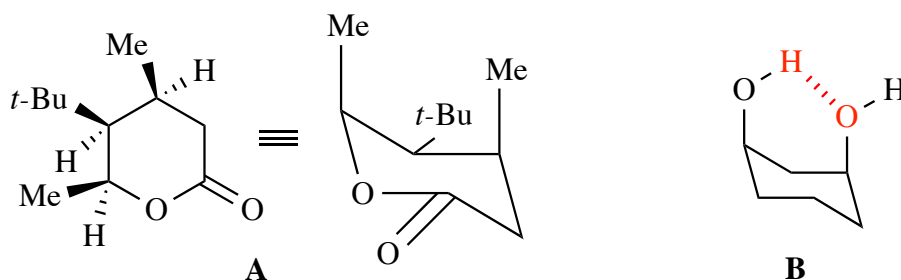
**10. Determine the absolute configuration for each stereogenic center in the following molecules:**



**11. The conversion of the hydroxy-acid shown to the corresponding lactone is rather slow. When pushed under aqueous acid conditions, epimerization at the carbon bearing the hydroxyl can occur. Draw the lactone and explain the observations noted in this question.**

When the hydroxy-acid cyclizes to form the lactone (see A) the two methyl groups are 1,3-diaxial, with the *tert*-butyl group equatorial. In the presence of acid, the hydroxyl group can be protonated and eliminate water and form a cation.

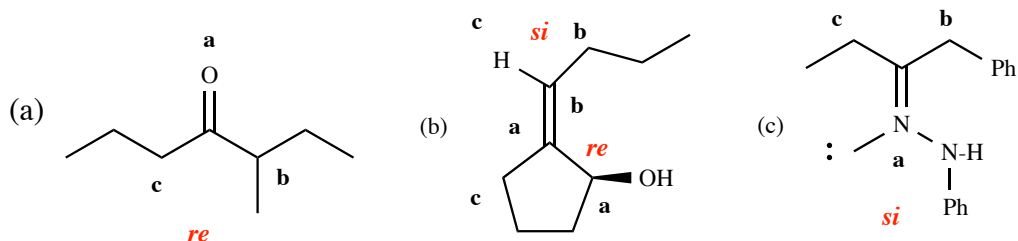
In the presence of water, the alcohol is regenerated, but both epimers are generated since reaction with water leads to the methyl group being axial or equatorial in the lactone. Under equilibration conditions, the lactone with one axial methyl and one equatorial methyl will be lower in energy due to diminished A-strain, and the equilibrium will shift to favor that lactone (net epimerization of the alcohol-bearing carbon in the hydroxy-acid). Acid catalyzed opening of the lactone gives, of course, the hydroxy-acid.



12. Explain why *cis*-1,3-cyclohexanediol exists mainly in the diaxial conformation in aqueous ethanol solution, when by Corey's  $\Delta G$  calculations (see Table 1.4), the diequatorial conformation should be lower in energy.

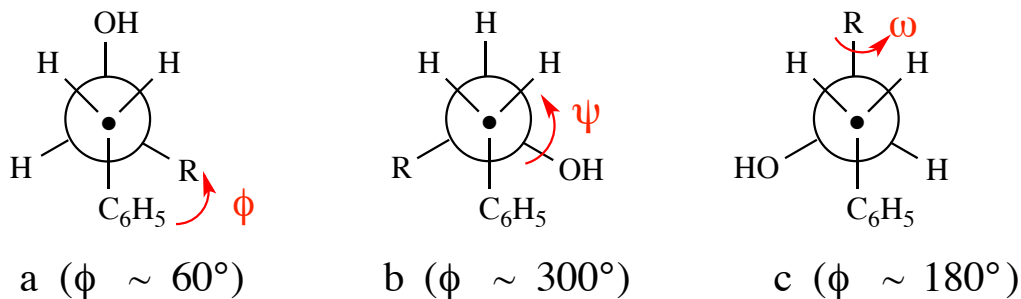
The diaxial conformation allows hydrogen bonding (see **B**). Such hydrogen bonding counterbalances the energy difference of the diaxial (which has U-strain) vs. diequatorial conformations. The net result is that although the diaxial conformation has U-strain, the hydrogen bonding makes it the dominant species.

13. Determine the correct *re/si* label for each prochiral atom in the following molecules.



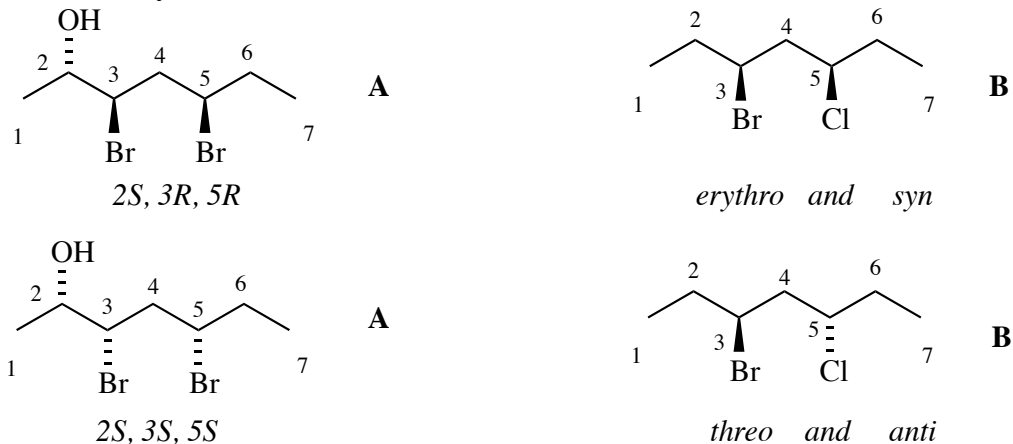
14. Draw the three most significant anti-rotamers of 1-phenylethan-1-ol ( $R = \text{Me}$  in the accompanying diagram), and correlate them with the rotamers marked a-c on the energy curve.

The correlation is



Taken from *Eur. J. Org. Chem.* 2004, 2398

15. (a) Draw the (2*S*, 3*R*, 4*R*) and the (2*S*, 3*S*, 4*S*) derivative of molecule A. (b) Draw both the erythro/threo and the syn/anti forms of molecule B.



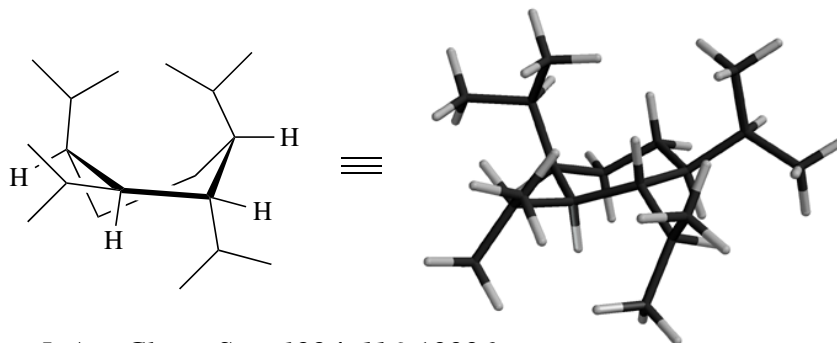
16. Classify each of the following reactions as stereospecific/stereoselective and/or regiospecific/regioselective.

- (a) Diastereoselective      (b) Enantiospecific      (c) Regiospecific and diastereoselective.

17. Explain why the ground state energy of cyclodecane is higher than that of cyclooctadecane. Why is cyclopentadecane higher in energy than cyclohexadecane?

Cyclodecane has a relatively small internal cavity where transannular interactions are maximized. This transannular interaction disappears in cyclooctadecane where the additional carbons make the internal cavity large enough for the "internal" hydrogen atoms to have little interaction. Compare crown cyclodecane and cyclononane in the text, in Section 1.5.B. Inspection of Figure 1.23 of the text can answer the second part of this question. Cyclohexadecane is an even-membered ring and, as such, will fit better on the diamond lattice. Since cyclopentadecane has an odd-membered ring, there is a "twist" in the ring when attempting to "lay it on the diamond lattice". This "twist" makes the energy of the ring slightly higher.

18. Draw the boat conformation of *cis*-,*trans*-,*trans*-1,2,3,4-tetraisopropylcyclohexane.



See *J. Am. Chem. Soc.* **1994**, *116*, 10306

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