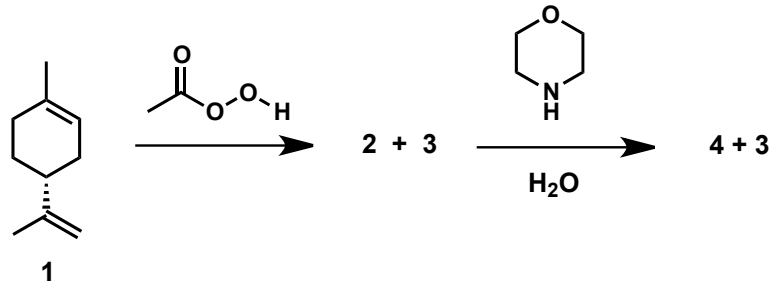
Reactivity in Organic Chemistry

Mid term test October 31st 2011, 9:30-12:30

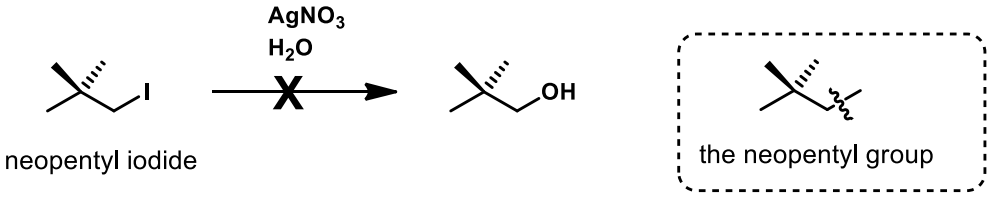
Problem 1 (25p)

R-(+)-Limonone can be epoxidized (using peracetic acid) to give an inseparable mixture of two diastereomeric limonene oxides. Provide the structures of these two compounds. When this mixture is reacted with morpholine in the presence of water (under controlled conditions), one chirally pure amino alcohol was formed and one (chirally pure) limonene oxide remained in the mixture. Provide the structure of the aminoalcohol and the remaining limonene oxide.



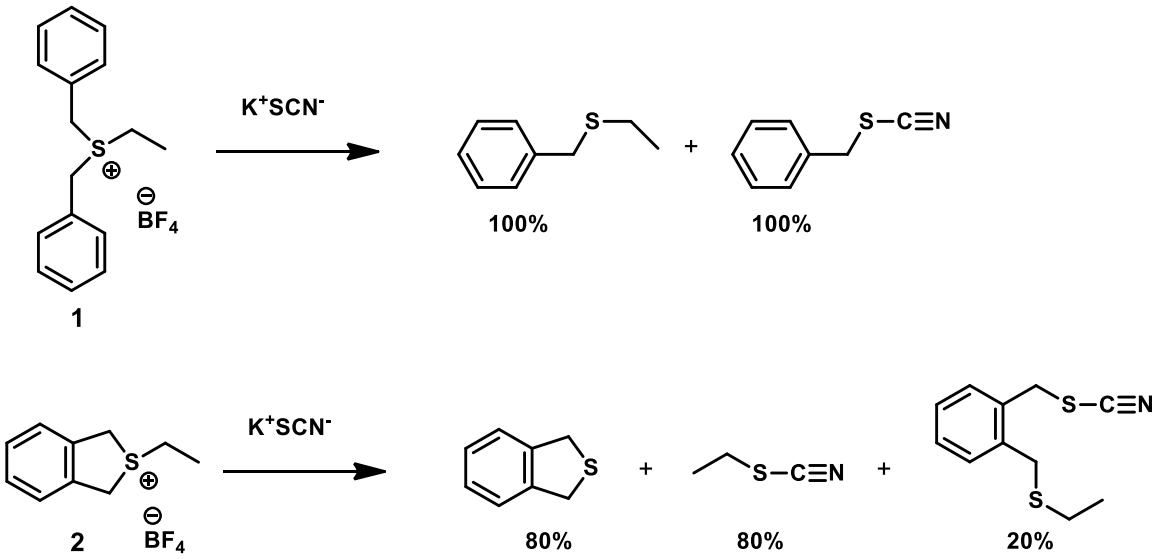
Problem 2 (10 p)

Substitution reactions on neopentylic systems proceed very sluggishly. Provide an explanation for this fact considering both S_N1 and S_N2-mechanisms. In the description of the S_N2-process, use a Newman projection to indicate steric interactions.



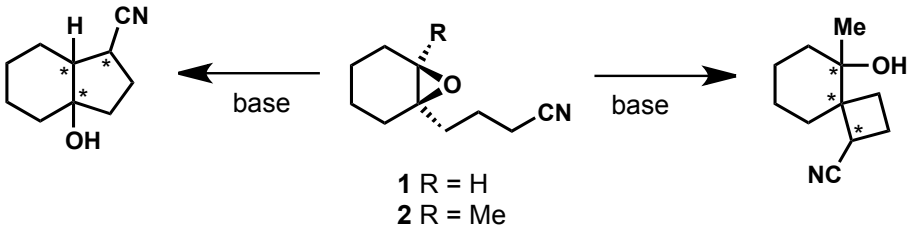
Problem 3 (20 p)

Explain why the substitution of dibenzylsulfonium salt **1** is 8000 times faster than the substitution of dibenzylsulfonium salt **2**. Explain the formation of the different substitution products.



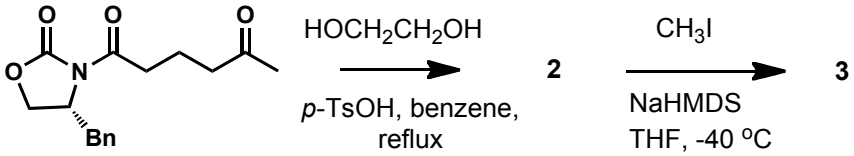
Problem 4 (25p)

When the epoxynitriles **1** and **2** are treated with strong base, opening of the epoxides occurs at different positions. Provide an explanation for the observed regioselectivity. Predict the stereochemistry of the newly formed chiral centers.



Problem 5 (20p)

Chiral amide **1** was treated with ethylene glycol under acidic conditions to give compound **2**. Provide the structure of compound **2** and the mechanism of its formation. Intermediate **2** was isolated and subsequently converted into product **3.** Give the structure of **3** and the mechanism of its formation. Show the stereochemistry of **3** and explain how it arises.



1

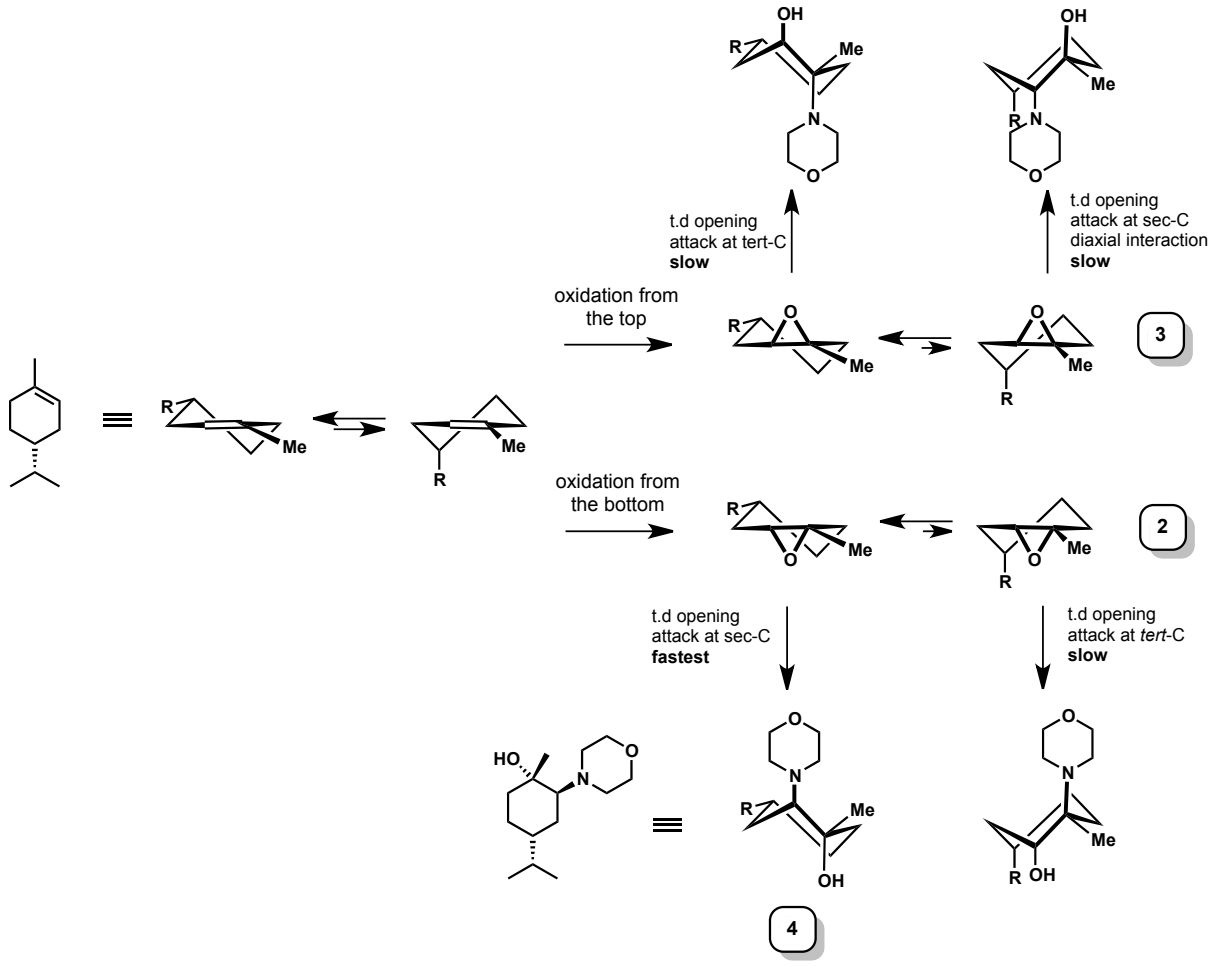
Reactivity in Organic Chemistry

Mid term test October 31st 2011, 9:30-12:30

Problem 1

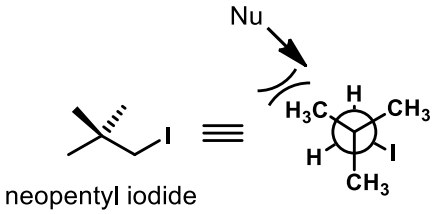
Epoxidation of limonene occurs at the double bond with the highest HOMO: the most substituted one. It can be epoxidized from the "top" and "bottom" face. Both faces are sterically equally accessible so no selectivity can be expected. Opening of the resulting epoxide preferentially occus at the secondary C (it is an basic nucleophilc opening, development of partial positive charge is not the determining factor under these conditions!) in a trans diaxial fashion to provide the chair product. In epoxide **3** this type of opening can occur but only from the unfavorable conformer, placing the large R-group in a axial fashion. Epoxide opening suffers here from a substantial 1,3-diaxial interaction.

Opening of epoxide **2** on the other hand can proceed at the secondary C-atom, on the most favorable half chair conformer, without developing 1,3-diaxial interactions.



Problem 2

An S_N1-substitution on a primary carbon is very unfavorable, because the primary cation is unstable. An S_N2-substitution suffers from severe steric interactions as can be clearly seen in the newman projection of the neopentylic iodide. Backside attack of the iodide is hampered by an eclipsed interaction with one of the methyl groups. (Also see Claydon, Greeves, Warren & Wothers, p 978-979).



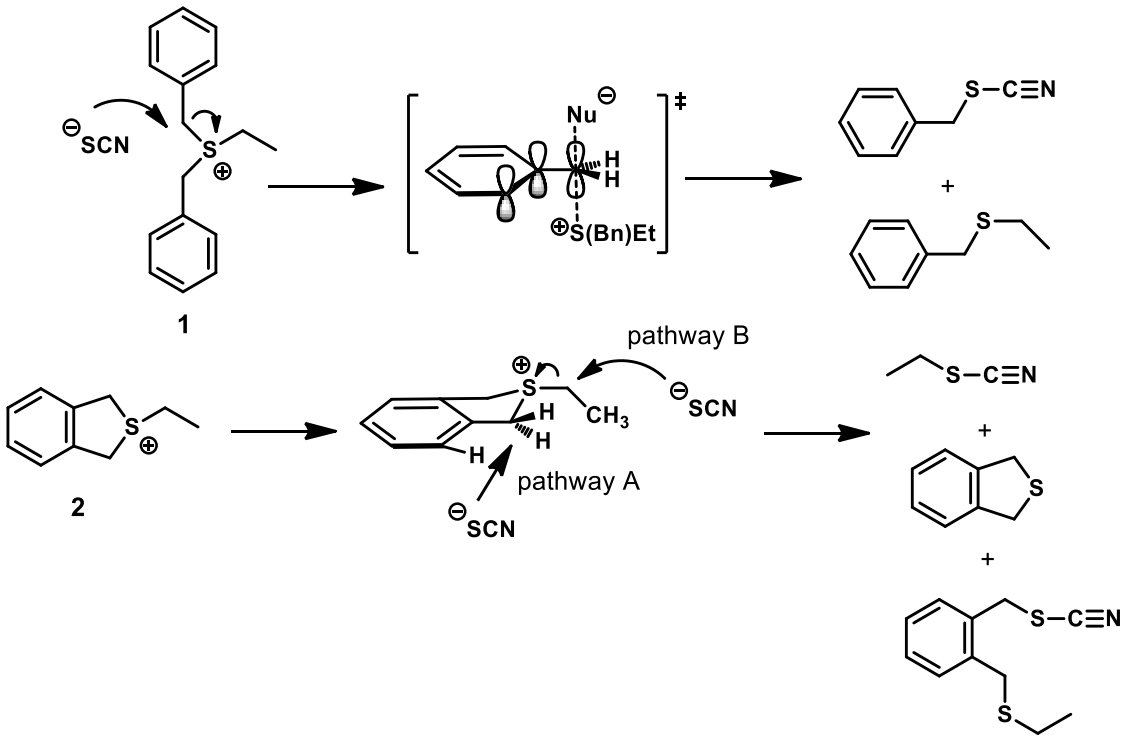
neopentyl iodide

Problem 3

S_N2-like substitutions at benzylic positions are accelerated by the favorable conjugation of the π-system of the benzene ring with the p-orbital in the transition state.

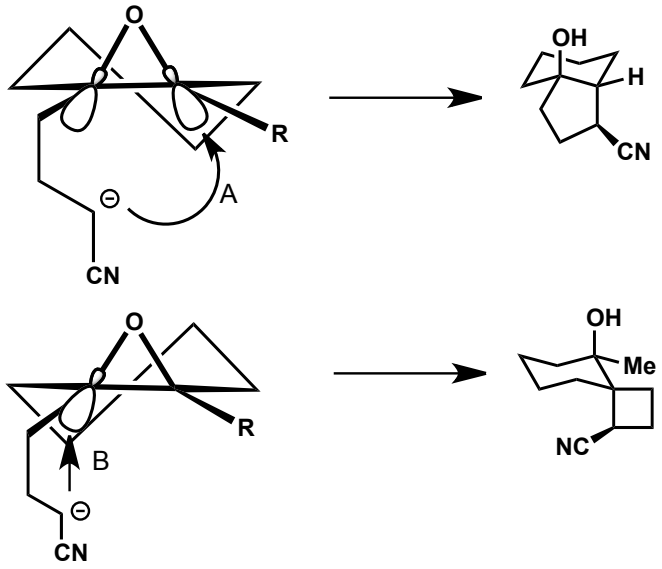
In order to provide efficient overlap between the orbitals involved, the benzene ring and the reaction center must be properly aligned: the π-system of the benzene ring must be perpendicular to the trajectory of the incoming nucleophile and the substitution of the leaving group. Substitution of sulfonium salt **1** at either benzylic center can benefit from stabilization from this overlap.

In sulfonium salt **2** backside attack of the sulfonium group in an S_N2-like fashion cannot benefit from this overlap because now the attack is not perpendicular to the π-system of the benzene ring. Instead attack occurs at the ethyl group because pathway B is favored over pathway A (See Figure) because of unfavorable steric interaction in pathway A.


SCN
S
Nu
H
H
S(Bn)Et
S–C≡N
+
S
1
pathway B
S
H
CH3
H
H
SCN
pathway A
SCN
2
S–C≡N
+
S
+
S–C≡N
S

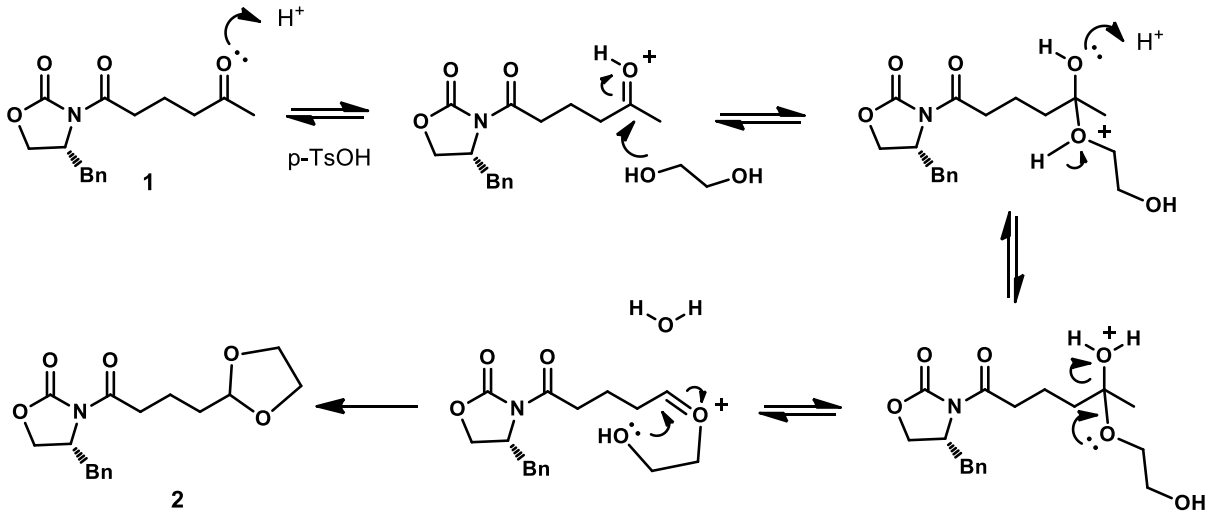
Problem 4

The ***trans* diaxial** intramolecular epoxide opening can occur at two positions, following pathway A or B (see picture). Pathway A is formally *anti*-Baldwin (6-endo *tet*), in other words, the nucleophile has to come all the way around to the far side of the epoxide to efficiently overlap with the σ^* on this side. Pathway B is "Baldwin allowed" (4-exo-*tet*). However, this pathway involves nucleophilic attack at a tertiary C-atom (which is inherently slow). Thus pathway A, even though this is anti-Baldwin, will be favored if R = H, because this involves nucleophilic attack on a secondary C, as opposed to the tertiary C. If R = Me, both epoxide carbons are tertiary and the reaction will proceed following the Baldwin rules. The stereochemistry of the products is as shown, because in these products (and the transition states leading to these products) the CN group will take up a position with the least steric hindrance (*exo* in the 5,6-bicycle, away from the tertiary alcohol function in 6,4-bicycle).

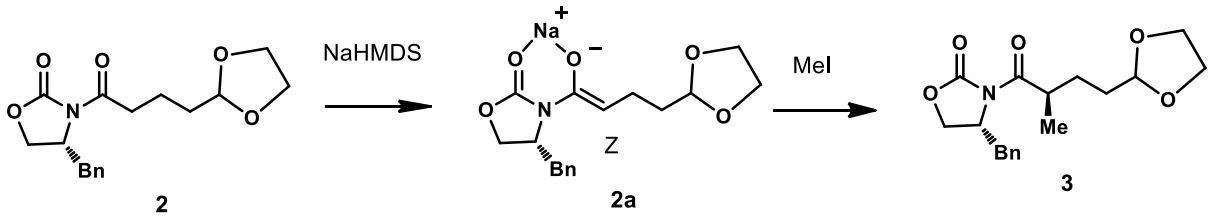


Problem 5

The first step is an acid catalyzed ketal formation. Only the keton function in **2** reacts with ethylene glycol, the less electrophilic amide and carbamate functions remain intact. The reaction starts with protonation of the carbonyl of the ketone function, subsequent steps are equlibria. The reaction is driven to completion by expulsion of water. The last step is also entropically favorable for a five ring is formed and the number of particle does not increase in the forward reaction.



Compound **2** is converted into Z-enolate **2a** that is subsequently alkyated with MeI to give **3** as the major diastreomer.



The stereochemistry of enolate can be explained by invoking a Claisen-Ireland chair-like transition state. The favoured chair lacks the 1,2-interaction between the chiral auxiliary and the substituent α to the carbonyl of the amide. The subsequent alkylation takes place stereoselectively from the less hindered face of the molecule *anti* to the benzyl group.