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SOLVED PROBLEMS IN ADVANCED ORGANIC SYNTHESIS
 (FOR CSIR NET & GATE)
1st EDITION
 (First released on: 7th, May 2012)

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This book is intended for the aspirants of CSIR NET, SLET, SET, GATE, IISc and other University entrance exams. Most of the advanced level problems in organic synthesis from previous year question papers are solved and are thoroughly explained with mechanisms.

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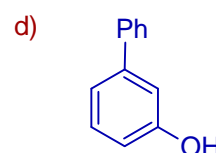
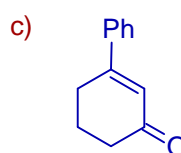
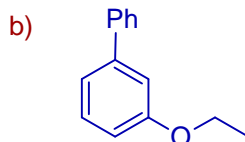
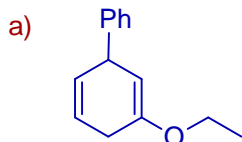
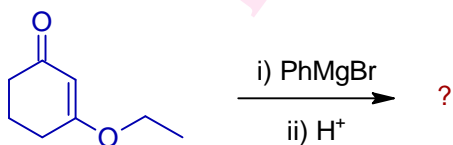
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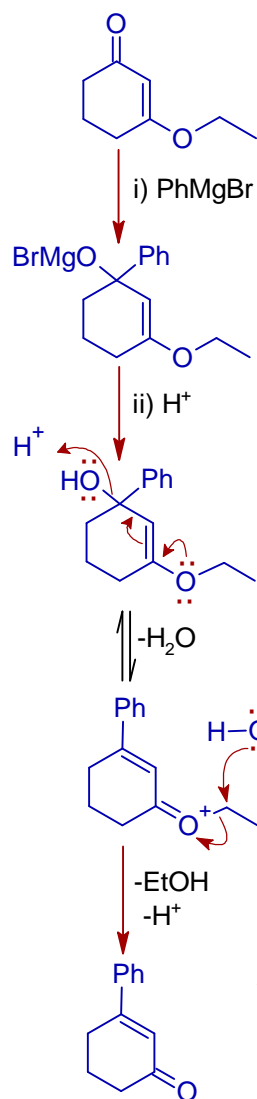
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Problem 1.1 (IISc 2011)



Answer: c

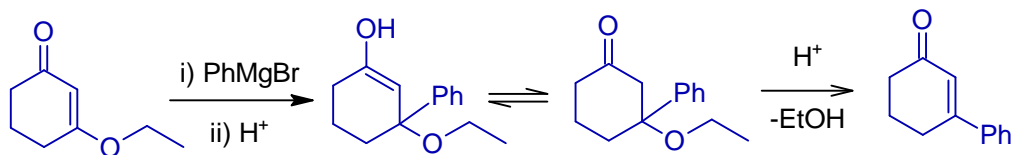
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Explanation

1,2 addition of Grignard reagent

acid catalysed and conjugate π bond assisted removal of OH groupfinal removal step of EtOH **Think different:**

What will happen if 1,4 addition occurs?

1, 4 - addition of PhMgBr

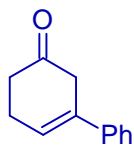
Same product! So it might be the actual mechanism? But slim chances. Why? The possible explanation might go like this:

i) the positive charge on 4th position is diminished due to contribution of p-electrons of adjacent ethoxy 'O' through conjugation (+M effect).

ii) The enolate ion form is less stable due to -I effect of 'O'.

iii) We also know that: 1,2 addition is kinetically more favorable than 1,4-addition in case of Grignard reagents. It is because the R group attached to Mg in GR is a hard nucleophile and prefers carbonyl carbon with considerable positive charge (hard electrophile).

And if this is the mechanism, the removal of ethanol may give another product, though less likely, as shown below.



Now start arguing!

Web Resource:

<http://www.adichemistry.com/organic/organicreagents/grignard/grignard-reagent-reaction-1.html>

Problem 1.2

The most appropriate set of reagents for carrying out the following conversion is:



a) i) EtMgBr; ii) HCl

b) i) $(C_2H_5)_2CuLi$; ii) HCl

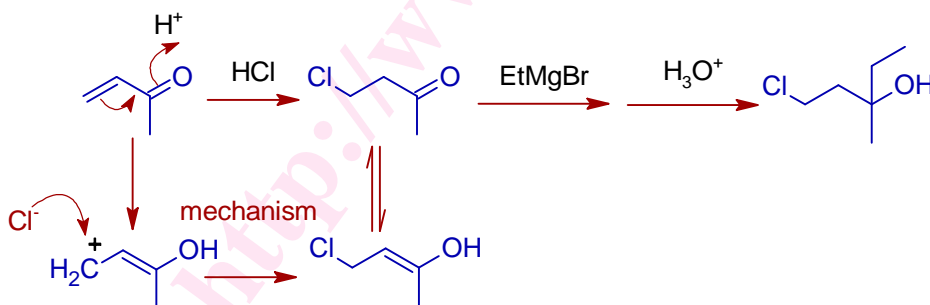
c) i) C_2H_5Li ; ii) HCl

d) i) HCl; ii) EtMgBr

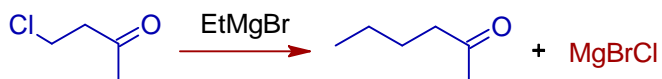
Answer: d

Explanation:

1,4-addition of HCl furnishes 4-chlorobutanone, which reacts with Grignard reagent to get the desired product.

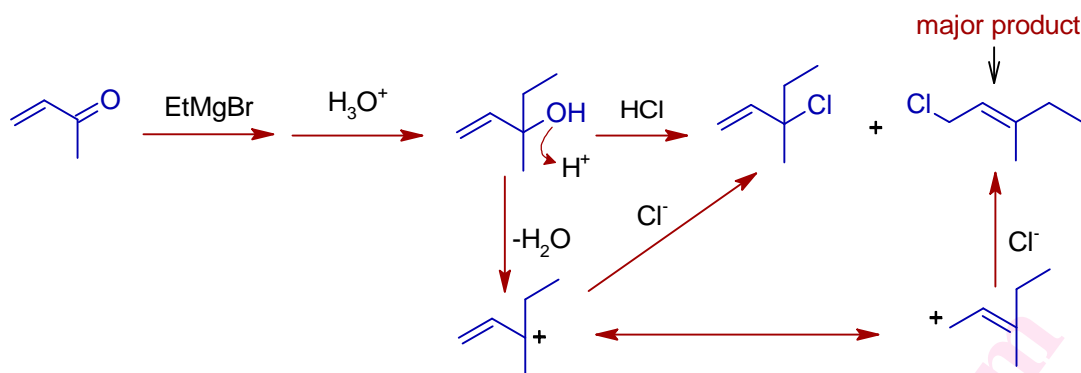


However, the yields may not be satisfactory due to side reaction that is possible in the second step with Grignard reagent. It may undergo Wurtz like coupling reaction with $-CH_2Cl$ group.



What about other options?

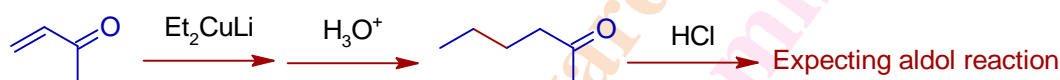
Option - a :



* 1,2-addition occurs with Grignard reagent, since the ethyl group attached to Mg has considerable positive charge and is a hard nucleophile. It prefers to attack 2nd carbon (hard electrophile).

* In the reaction of allylic alcohol with HCl, the Cl^- prefers to attack the allylic carbocation from less hindered end. Hence the major product is 1-chloro-3-methyl-2-pentene.

Option - b



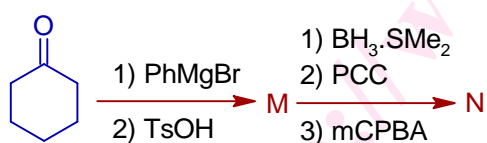
1,4-addition occurs with Lithium diethyl cuprate, since ethyl group attached to copper is a soft nucleophile and prefers carbon at 4th position (soft electrophile).

Option-c :

The products are same as in case of option-a. Ethyl lithium also shows 1,2 addition like Grignard reagent.

Problem 1.3 (CSIR DEC 2011)

Choose the correct option for M & N formed in reactions sequence given below.

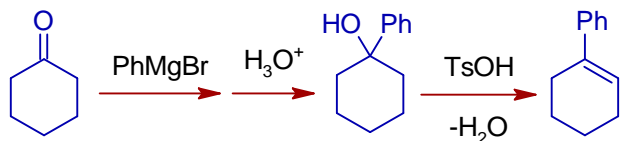


- a) M = N =
- b) M = N =
- c) M = N =
- d) M = N =

Answer: a

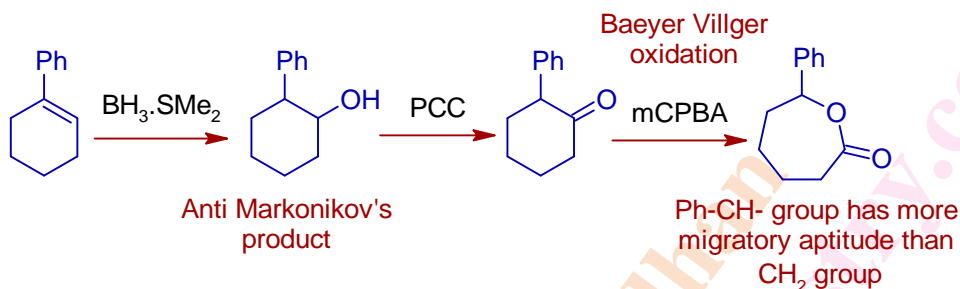
Explanation:

* A tertiary alcohol is formed upon 1,2 addition of PhMgBr and is dehydrated in presence of Tosylic acid.



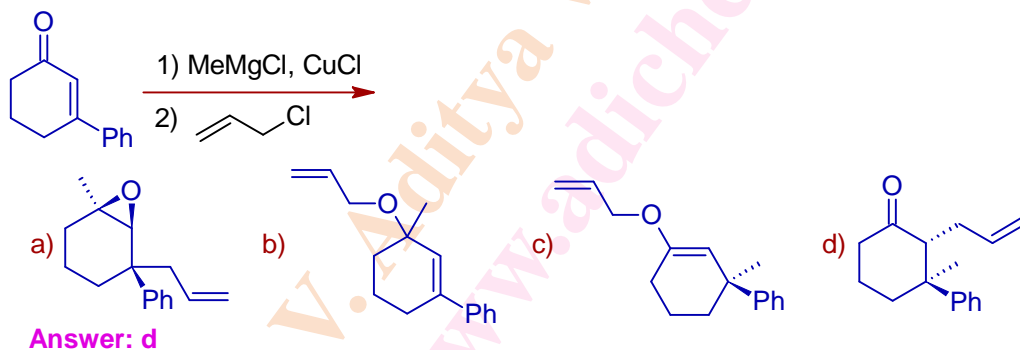
* Thus formed product is subjected to hydroboration with $\text{BH}_3 \cdot \text{Me}_2\text{S}$ complex to yield 2-phenylcyclohexanol, an anti-Markonikov's product, which is oxidized to a ketone in presence of PCC.

The keto compound is subjected to Baeyer Villiger oxidation with mCPBA to get a lactone. The PhCH- group is migrated onto oxygen in preference to CH_2 group.



Problem 1.4 (CSIR JUNE 2011)

The major product formed in the following transformation is:



Answer: d

Explanation:

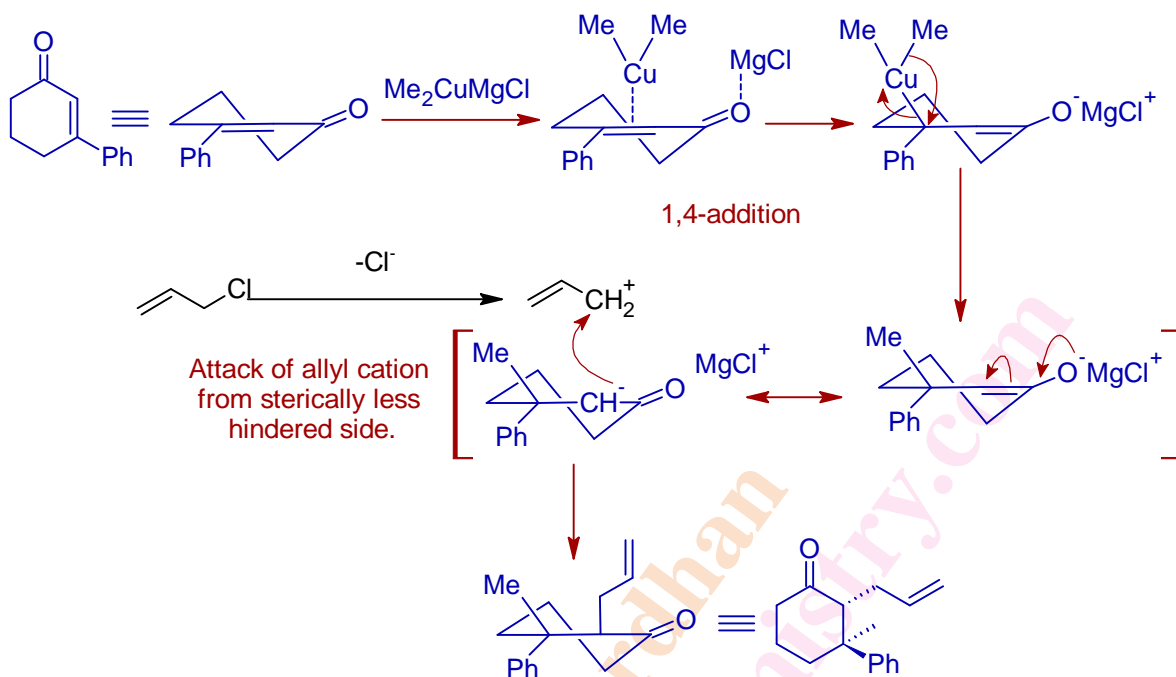
* The Grignard reagent reacts with CuCl to give Me_2CuMgCl , an organocopper compound also known as Gilman reagent that is added to the α, β -unsaturated ketone in 1,4-manner.

Initially copper associates with the double bond to give a complex, which then undergoes oxidative addition followed by reductive elimination.

Thus formed enolate ion acts as a nucleophile and substitutes the Cl group of allyl chloride.

The attack on allyl chloride is done from the opposite side of more bulky phenyl group.





Why 1,4-addition occurs with Gilman reagent?

The methyl group on copper is a softer nucleophile and hence prefers softer electrophile. The carbon at 4th position is less polar and hence is a softer electrophile. That is why the attack of Me group occurs at 4th position.

Whereas the carbonyl carbon is more polar and a hard electrophile.

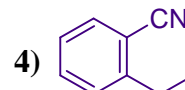
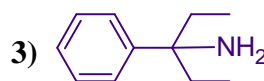
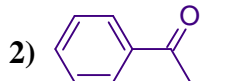
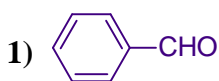
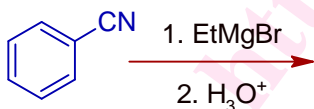
Note: The atoms with more polarity i.e., high charge are harder.

Why not the O⁻ end of the enolate ion forms bond with allyl group?

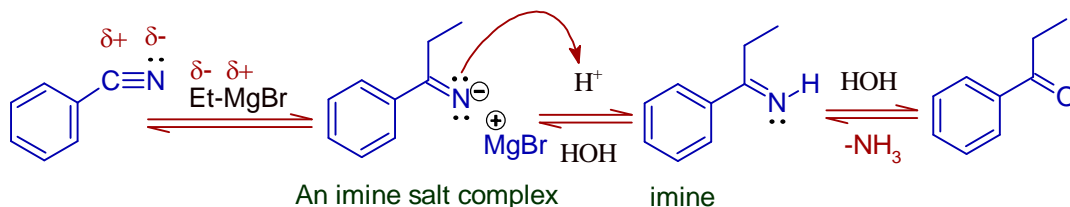
The very polar O⁻ end is a hard nucleophile whereas the CH⁻ end is a softer nucleophile. The allyl group with positive charge on carbon is also a softer electrophile and hence the bond is formed preferentially between the C-end of enolate and allyl group.

Problem 1.5 (CSIR OLD MODEL PAPER)

The major product formed in the reaction, given below, is

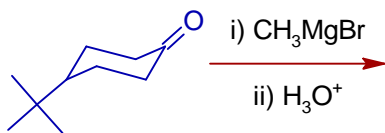


Explanation:



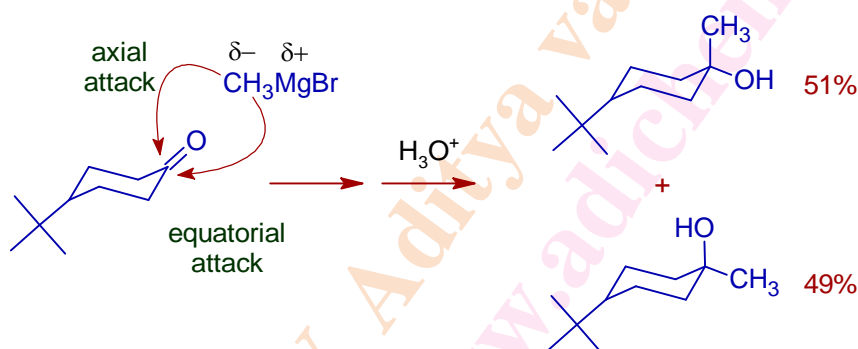
Problem 1.7 (GATE 1991)

Predict the major product in the following reaction.



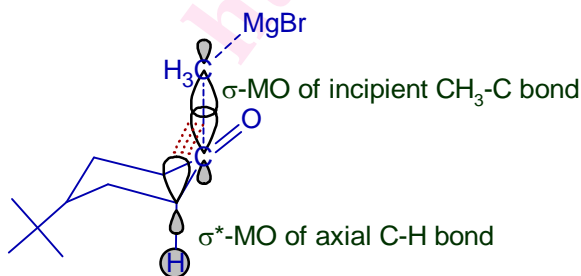
Explanation:

* The product mixture contains both axial and equatorial alcohols in equal proportions. There is no diastereoselectivity observed during this addition reaction due to steric and stereoelectronic effects operating equally.



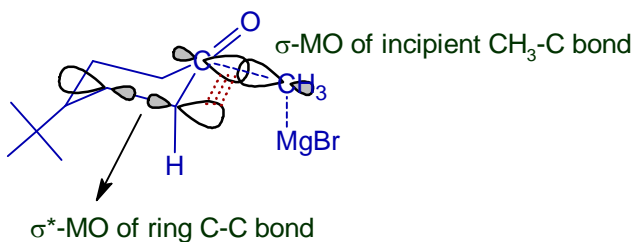
* When steric factor alone is considered, the moderately bulkier methylmagnesium bromide (GR) prefers to attack the cyclohexane ring from the convex side i.e. equatorial.

However this steric factor is cancelled out by stereoelectronic effect which favors axial attack of GR. The stereoelectronic effect can be explained by relatively stronger hyperconjugative interaction between σ -MO of incipient CH_3 -C bond and σ^* -MO of axial C-H bond on the adjacent carbon during late transition state when the GR approaches axially.



Relatively stronger hyperconjugative interaction between σ -MO of incipient CH_3 -C bond and σ^* -MO axial C-H bond during axial attack.

Hyperconjugative interaction between σ -MO of incipient CH_3 -C bond and σ^* -MO of ring C-C bond is also possible during equatorial attack. However this is relatively less effective and hence axial attack is more favored on stereoelectronic grounds.

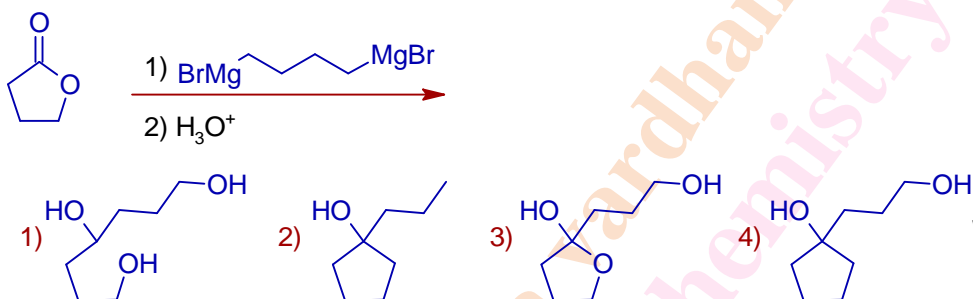


Relatively weaker hyperconjugative interaction between σ -MO of incipient CH_3 -C bond and σ^* -MO of ring C-C bond during equatorial attack.

However steric factor will outweigh stereoelectronic factor and improves the diastereoselectivity by favoring more equatorial attack, if alkyllmagnesium sulfonates (otherwise known as Reetz-Grignard reagents) are used. The larger the sulfonate group, the more it favors an equatorial approach.

Problem 1.8

Which of the following options is the most likely product formed in the following reaction?

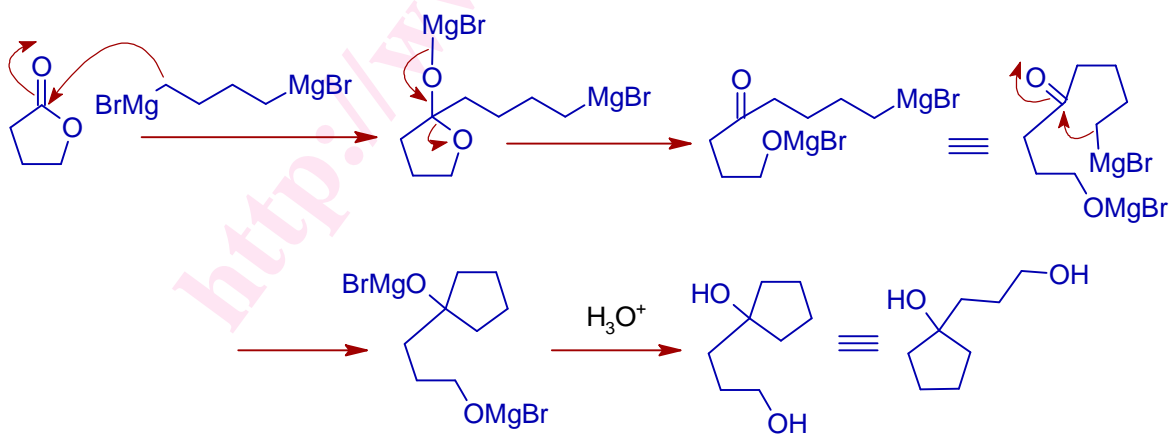


Answer: 4

Explanation:

* In this reaction, a lactone is made to react with a bis-Grignard reagent to get a diol. One of the alcoholic group is tertiary and is derived from the carbonyl group of lactone. The other hydroxyl group is primary and takes on shape from the ring oxygen of lactone.

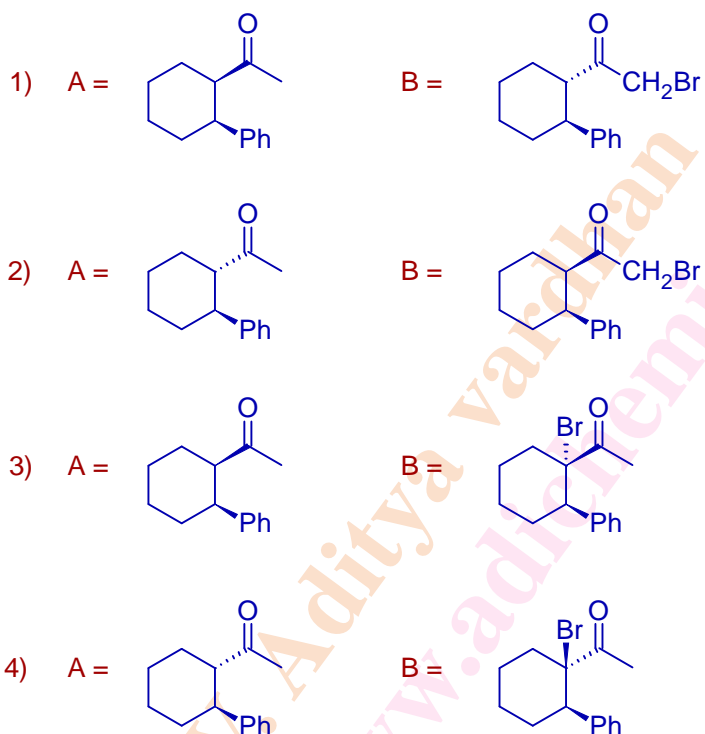
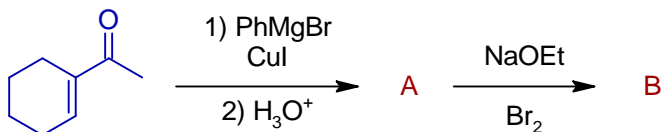
This conversion is akin to the reaction of esters with excess of GR.



Problem 1.9

(CSIR NET JUNE 2015)

The major products A and B in the following synthetic sequence are:



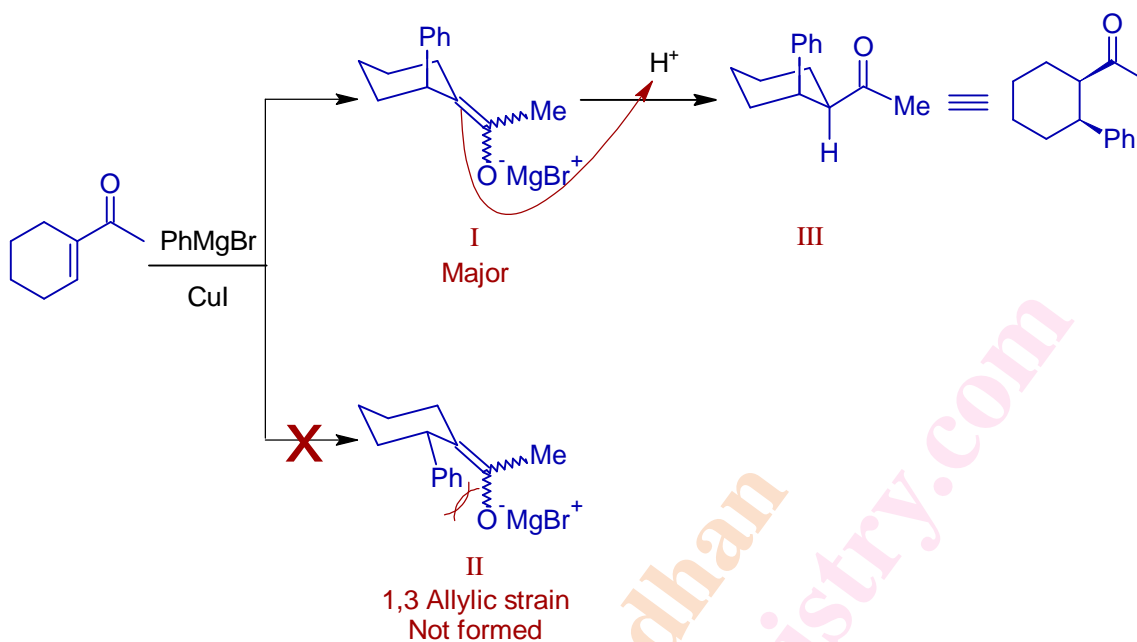
Answer: 1

Explanation:

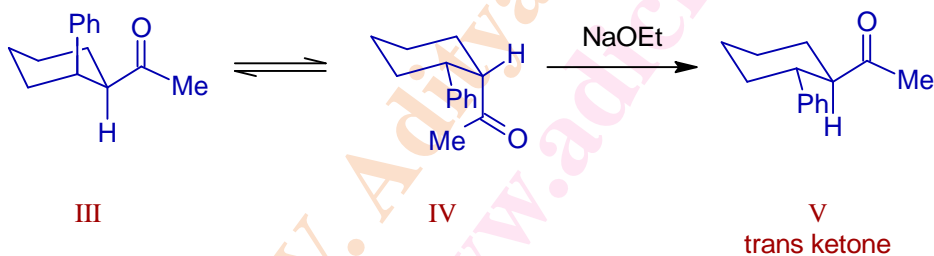
* The reactant, 1-acetylcyclohexene undergoes 1,4-conjugate addition with GR in presence of CuI to give a bromomagnesio complex (I) in which the phenyl group is axially oriented.

(II) is not formed due to 1,3-Allylic strain.

* Protonation of complex (I) takes place from axial side to give a cis ketone (II).

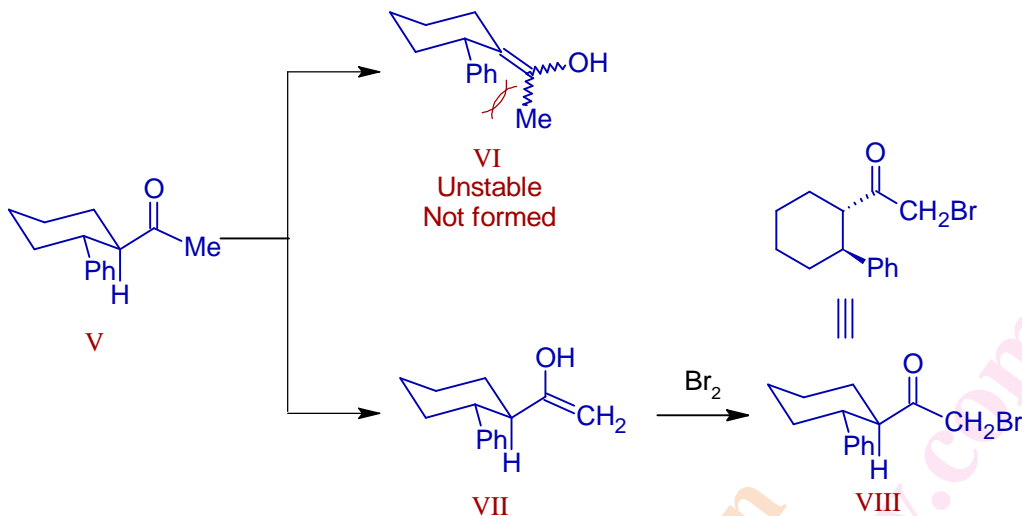


* The cis ketone, (III) can exist in another conformer, (IV), which is epimerized in presence of NaOEt to give more stable trans ketone (V).



* The trans ketone, V can be enolized either by removal of axial ring proton or one of the methyl proton to give VI or VII.

However, VI is not stable due to 1,3-Allylic strain and hence VII is formed exclusively, which upon bromination gives VIII.



Followup questions

* What is the major product formed if 'A' is brominated in presence of acid?

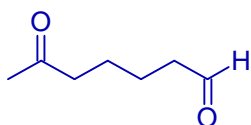
Hint: (III) is enolized by the removal of ring proton. Thus bromination of ring takes place.

* What is the product formed if COMe is replaced by CPh in (V)?

Hint: No enolization

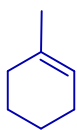
Problem 2.1

(GATE 2012)

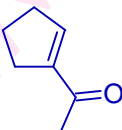


what is the major product?

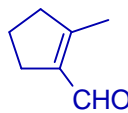
a)



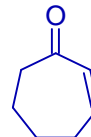
b)



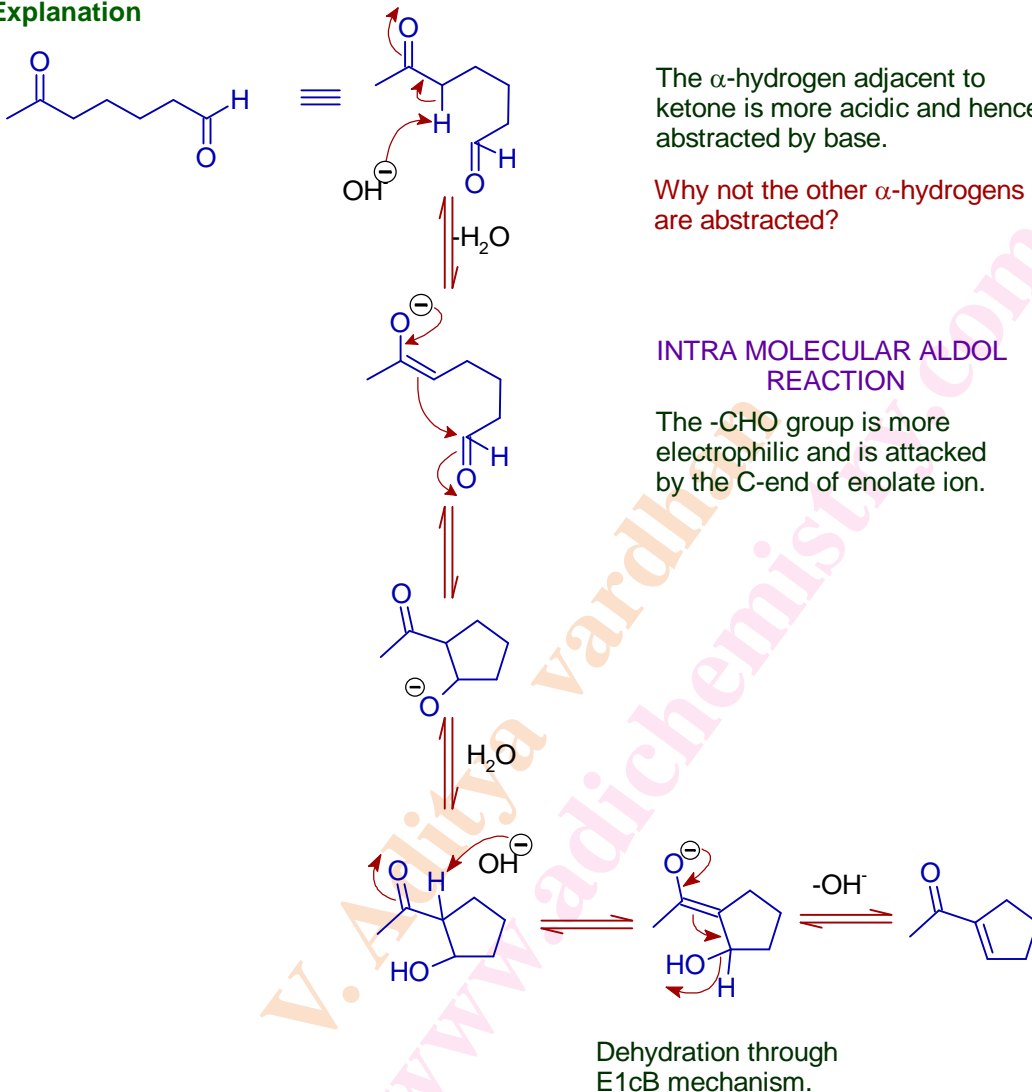
c)



d)



Answer: b

Explanation**Web Resource:**

<http://www.adichemistry.com/organic/namedreactions/aldol/aldol-addition-condensation-1.html>

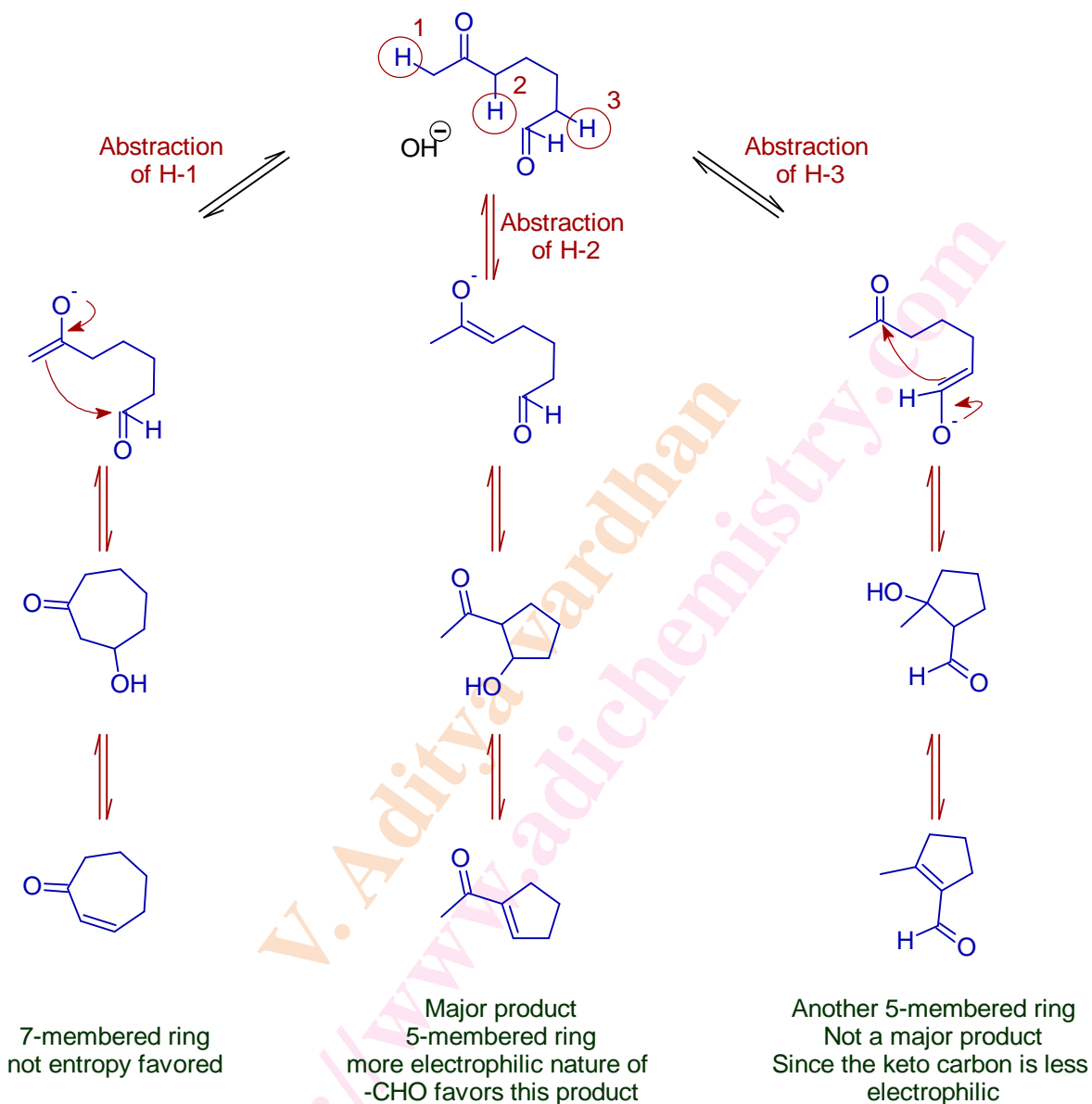
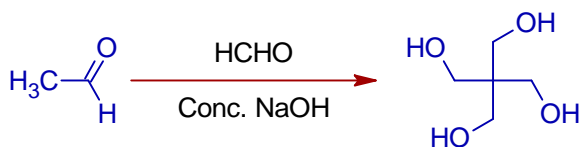
Think different:

Why not other α -hydrogens are abstracted leading to different products?

There are three different types of α -hydrogens, one adjacent to -CHO group and two adjacent to keto group. If these hydrogens are abstracted, three different types of products are possible as explained below.

However formation of 7-membered ring is not favorable due to entropy considerations, even though the abstraction of proton from CH_3 group adjacent to keto group is kinetically favored.

Abstraction of proton adjacent to -CHO group also leads to formation of five membered ring. But keto group is less electrophilic and the equilibrium does not move in forward direction.

**Problem 2.2****(IIT JEE 2012)****The number of aldol reaction(s) that occurs in the given transformation is:**

a) 4

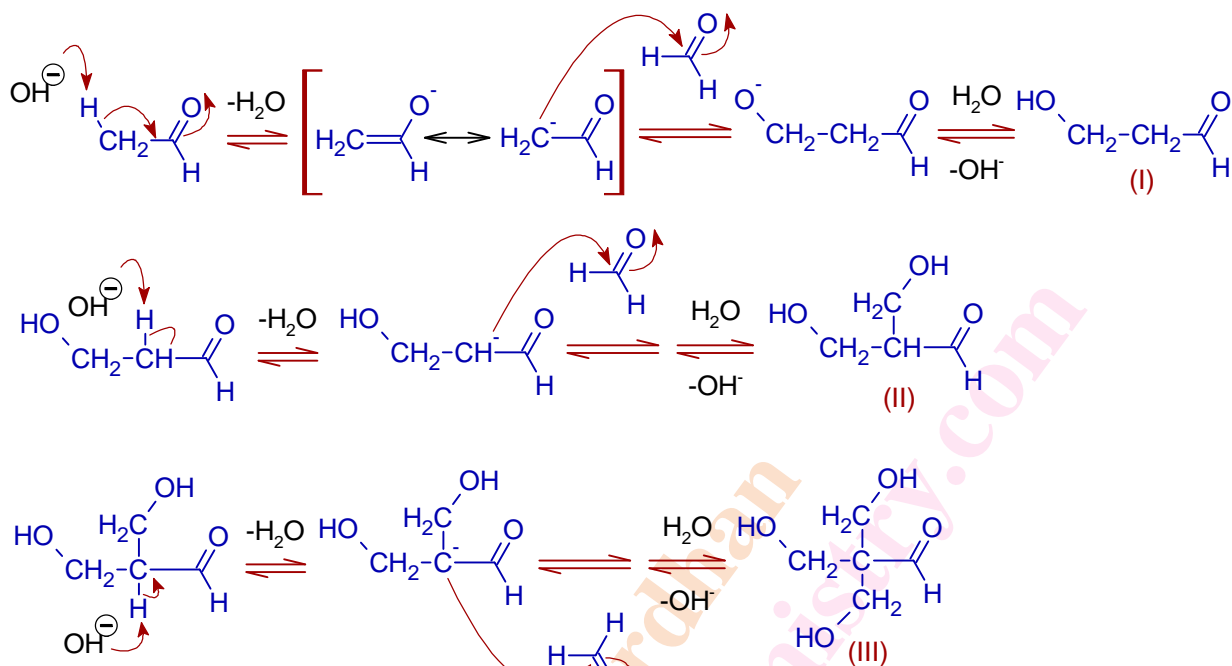
b) 3

c) 2

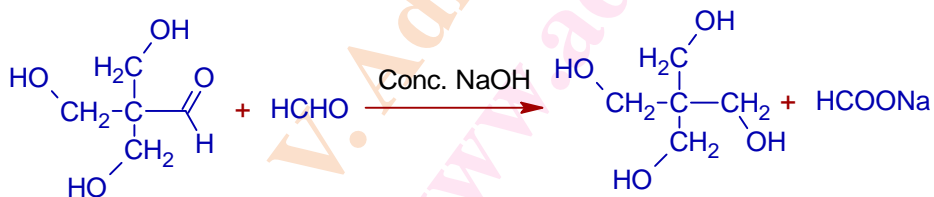
d) 1

Answer: b**Explanation:**

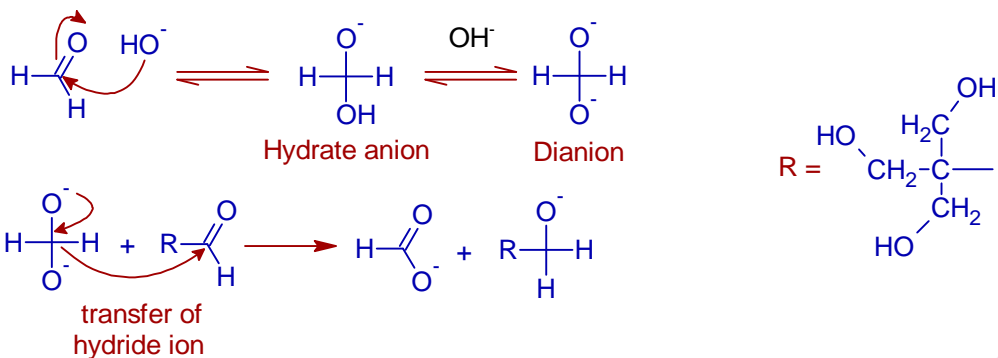
* Since there are 3 α -hydrogens in acetaldehyde it undergoes crossed aldol reactions with 3 moles of formaldehyde i.e., three aldol reactions.



* Thus formed product (III) contains **no** α -hydrogens and hence undergoes crossed Cannizzaro reaction with formaldehyde. In this step, formaldehyde is oxidized and $-\text{CHO}$ group of (III) is reduced to CH_2OH . The final product formed is also known as pentaerythritol.



Mechanism:



What are the other products possible in this reaction?

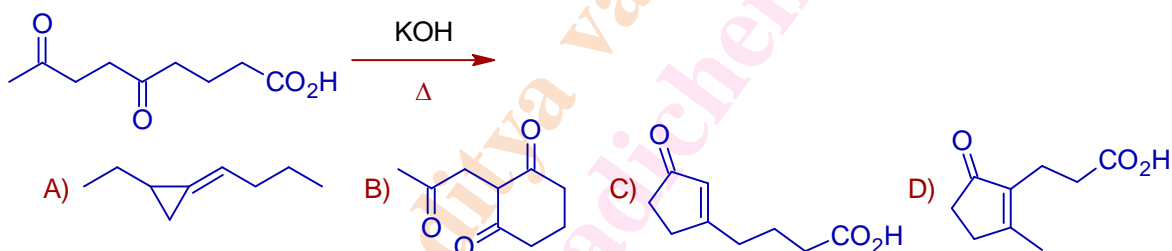
* Aldol and crotonaldehyde are also formed due to self condensation of acetaldehyde.

Why formaldehyde is preferentially oxidized in the final step?

* The carbonyl group of formaldehyde is more electrophilic due to absence of electron withdrawing groups and hence the initial attack of OH^- occurs on formaldehyde.

Problem 2.3 (UOH MSC 2012)

The most favorable product obtained in the following reaction is:

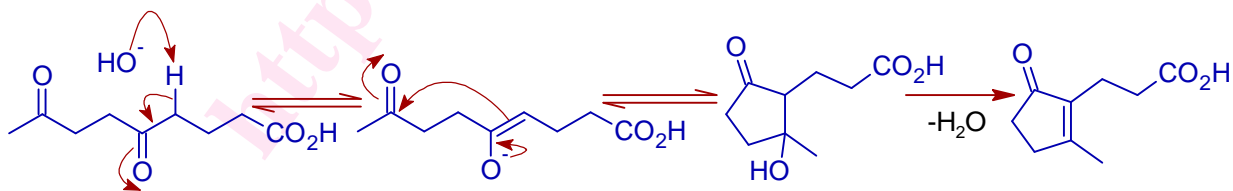


Answer: D

Explanation:

* 2,5-diketones undergo aldol condensation reactions in presence of a strong base to give cyclized products. Among the possible cyclizations, those result in 5 membered ring are more favored over 3 membered ones.

There are two acidic hydrogens on C-1 and C-6, abstraction of which lead to 5 membered rings. However the abstraction of more acidic hydrogen on C-6 carbon is kinetically more favored.



Problem 2.4 (GATE 2005)

In the given reactions, identify the correct combination of their major products P and Q.

[LDA = $\text{LiN}(\text{i-Pr})_2$]

