# 10.10: AN INTRODUCTION TO MULTIPLE STEP SYNTHESIS

> **Learning Objective**
> - use retrosynthetic analysis to design a multi-step synthesis with correct regiochemistry and stereochemistry using the reactions studied to date

## INTRODUCTION

The study of organic chemistry introduces students to a wide range of interrelated reactions. Alkenes, for example, may be converted to structurally similar alkanes, alcohols, alkyl halides, epoxides, glycols and boranes; cleaved to smaller aldehydes, ketones and carboxylic acids; and enlarged by carbocation and radical additions as well as cycloadditions. Most of these reactions are shown in the Alkene Reaction Map below. All of these products may be subsequently transformed into a host of new compounds incorporating a wide variety of functional groups. Consequently, the logical conception of a multi-step synthesis for the construction of a designated compound from a specified starting material becomes one of the most challenging problems that may be posed. Functional group reaction maps like the one below for alkenes can be helpful in designing multi-step syntheses. It can be helpful to build and design your own reaction maps for each functional group studied.

## ALKENE REACTION MAP

Please note: The reagents for each chemical transformation have been intentionally omitted so that this map can be used as a study tool. The answers are provided at the end of this section as part of the exercises.
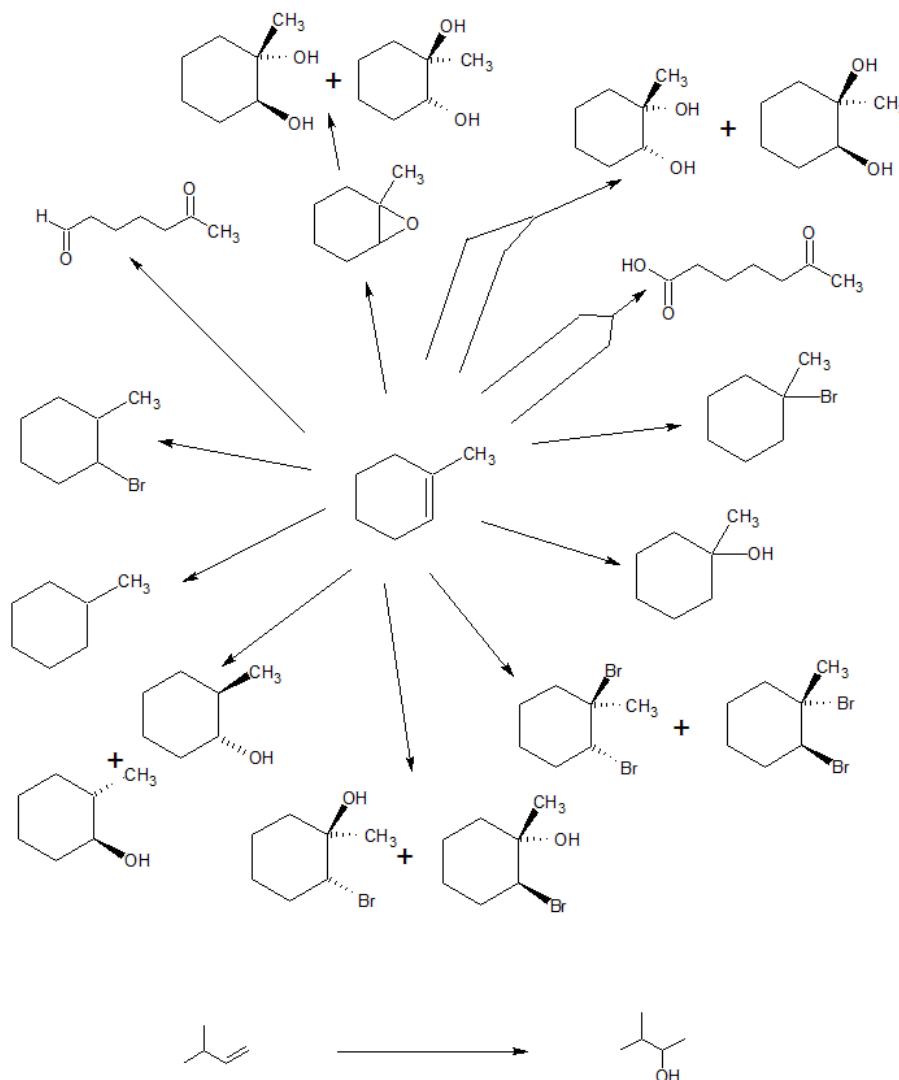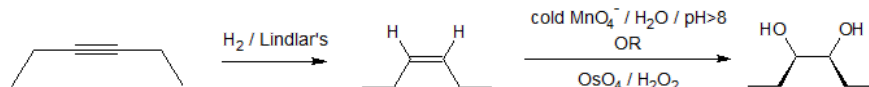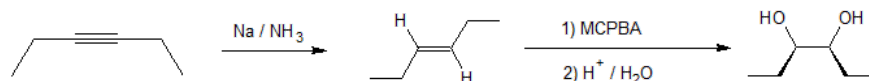
## SIMPLE MULTI-STEP SYNTHESES

A one or two step sequence of simple reactions is not that difficult to deduce. For example, the synthesis of meso-3,4-hexanediol from 3-hexyne can occur by more than one multi-step pathway.
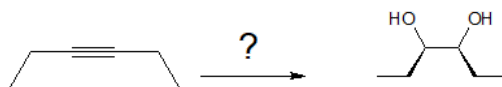
One approach would be to reduce the alkyne to cis or trans-3-hexene before undertaking glycol formation. Permanaganate or osmium tetroxide hydroxylation of cis-3-hexene would form the desired meso isomer.

From trans-3-hexene, it would be necessary to first epoxidize the alkene with a peracid followed by ring opening with acidic or basic hydrolysis.

Longer multi-step syntheses require careful analysis and thought, since many options need to be considered. Like an expert chess player evaluating the long range pros and cons of potential moves, the chemist must appraise the potential success of various possible reaction paths, focusing on the scope and limitations constraining each of the individual reactions being employed. The skill is acquired by practice, experience, and often trial and error.

### THINKING IT THROUGH WITH 3 EXAMPLES

The following three examples illustrate strategies for developing multi-step syntheses from the reactions studied in the first ten chapters of this text. It is helpful to systematically look for structural changes beginning with the carbon chain and brainstorm relevant functional group conversion reactions. Retro-synthesis is the approach of working backwards from the product to the starting material.
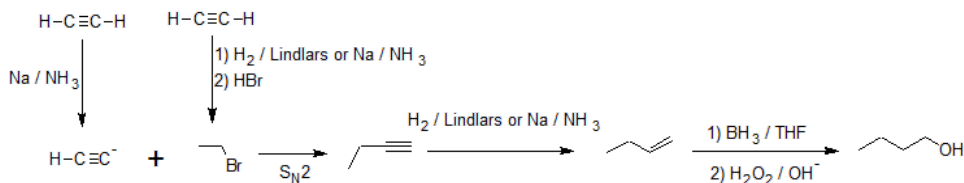
In the first example, we are asked to synthesize 1-butanol from acetylene.
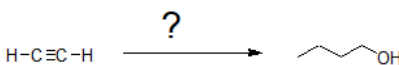
The carbon chain doubles in size indicating an acetylide $S_N2$ reaction with an alkyl halide. Primary alcohol formation from an anti-Markovnikov alkene hydration reaction (hydroboration-oxidation) is more likely than a substitution reaction. Applying retro-synthesis, we work backwards from the alcohol to the alkene to the alkyne from an acetylide reaction that initially builds the carbon chain.
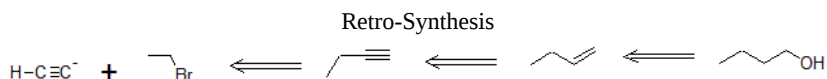
Retro-Synthesis

Working forwards, we specify the reagents needed for each transformation identified from the retro-synthesis. The ethylbromide must also be derived from acetylene so multiple reaction pathways are combined as shown below.

In the second example, we are asked to synthesize 1,2-dibromobutane from acetylene.
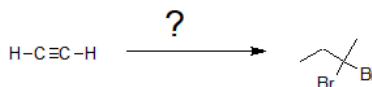
Once again there is an increase in the carbon chain length indicating an acetylide $S_N2$ reaction with an alkyl halide similar to the first example. The hydrohalogenation can be subtle to discern because the hydrogen atoms are not shown in bond-line structures. Comparing the chemical formulas of 1-butyne with 1,2-dibromobutane, there is a difference of two H atoms and two Br atoms indicating hydrohalogenation and not halogenation. The addition of both bromine atoms to the same carbon atom also supports the idea that hydrohalogenation occurs on an alkyne and not an alkene. The formation of the geminal dihalide also indicates hydrohalogenation instead
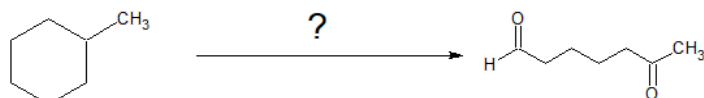
of halogenatioin because halogenation produces vicinal dihalides. With this insight, the retro-synthesis indicates the following series of chemical transformations.

### Retro-Synthesis
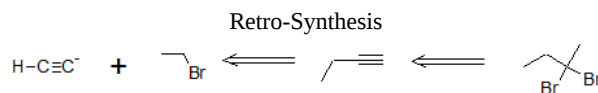


Working forwards, we specify the reagents needed for each transformation.
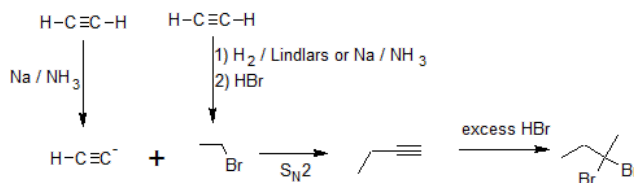


In the third example, we are asked to produce 6-oxoheptanal from methylcyclohexane.



Counting the carbons, the starting material and product both contain seven carbon atoms and there is a cleavage reaction of an alkene under reductive conditions. One important missing aspect of this reaction is a good leaving group (LG). Alkanes are chemically quite boring. We can burn them as fuel or perform free-radical halogenation to create alkyl halides with excellent leaving groups. With these observations, the following retro-synthesis is reasonable.

### Retro-Synthesis
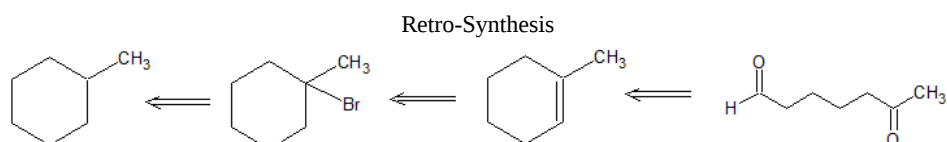


Working forwards, we specify the reagents needed for each reaction. For the initial free-radical halogenation of the alkane, we have the option of chlorine ($Cl_2$) or bromine ($Br_2$). Because methylcyclohexane has several different classifications of carbons, the selectivity of $Br_2$ is more important than the faster reactivity of $Cl_2$. An strong base with heat can be used for the second step to follow an E2 mechanism and form 1-methylcyclohexene. The aldehyde group on the final product indicates gentle oxidative cleavage by any of several reaction pathways. These reactions can be combined in to the following multi-step synthesis.
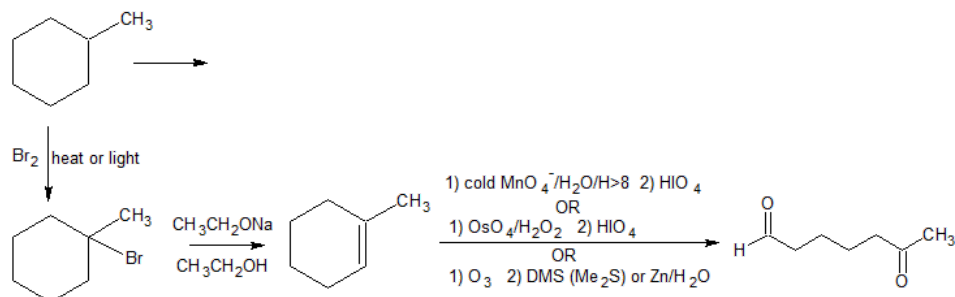


## REACTION MAPS TO BUILD FUNCTIONAL GROUP CONVERSION MASTERY

After working through the examples above, we can see how important it is to memorize all of the functional group reactions studied in the first ten chapters. We can apply the knowledge of these reactions to the wisdom of multi-step syntheses.

Please note: The reagents for each chemical transformation have been intentionally omitted so that these maps can be used as a study tools. The answers are provided at the end of this section as part of the exercises.

## ALKANE AND ALKYL HALIDE REACTION MAP
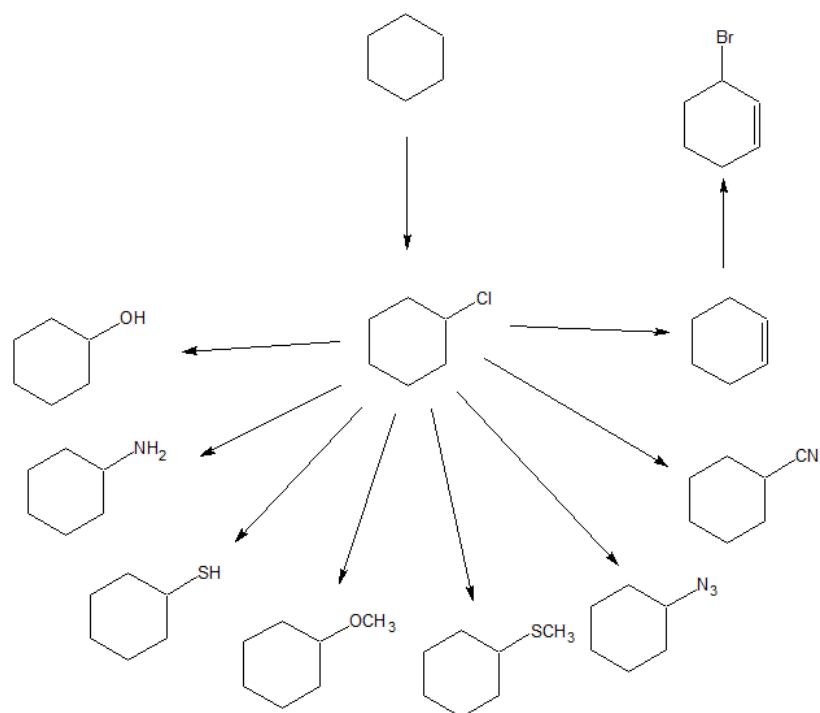
ALKYNE REACTION MAP
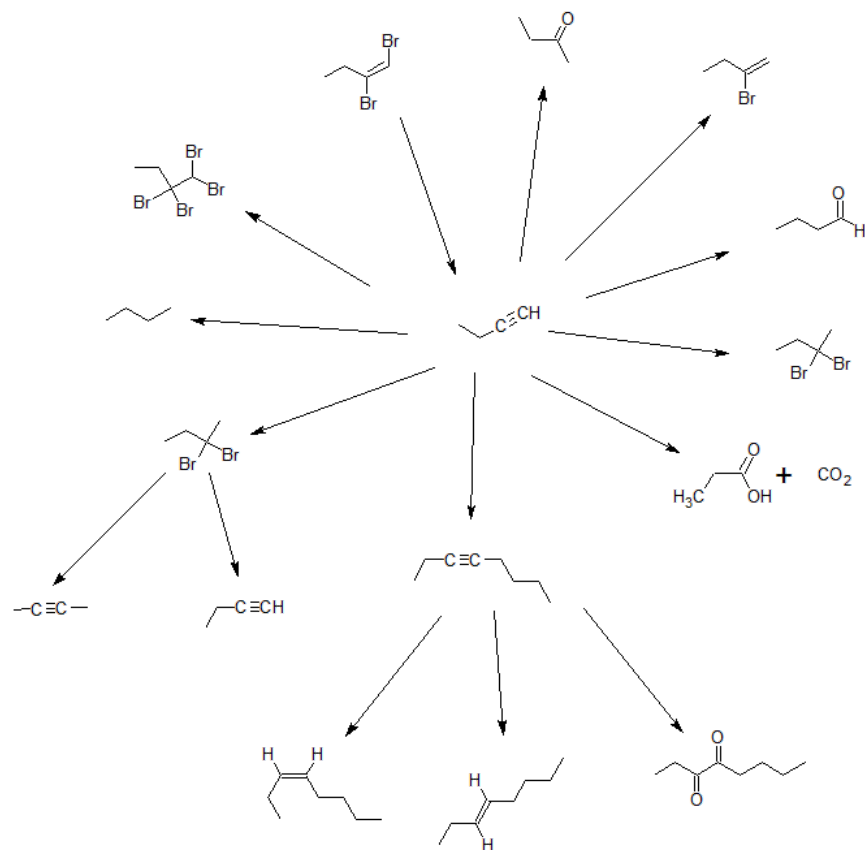
## Exercise

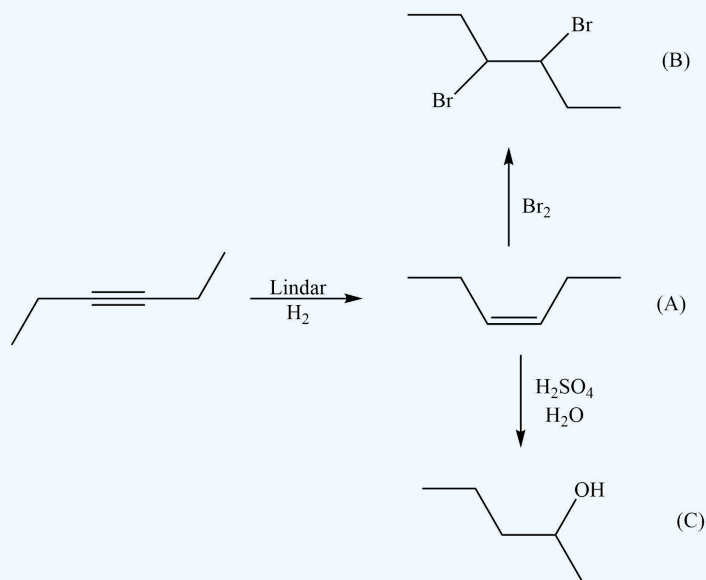**1.** Starting at 3-hexyne predict synthetic routes to achieve:

*a) trans*-3-hexene

b) 3,4-dibromohexane

c) 3-hexanol.

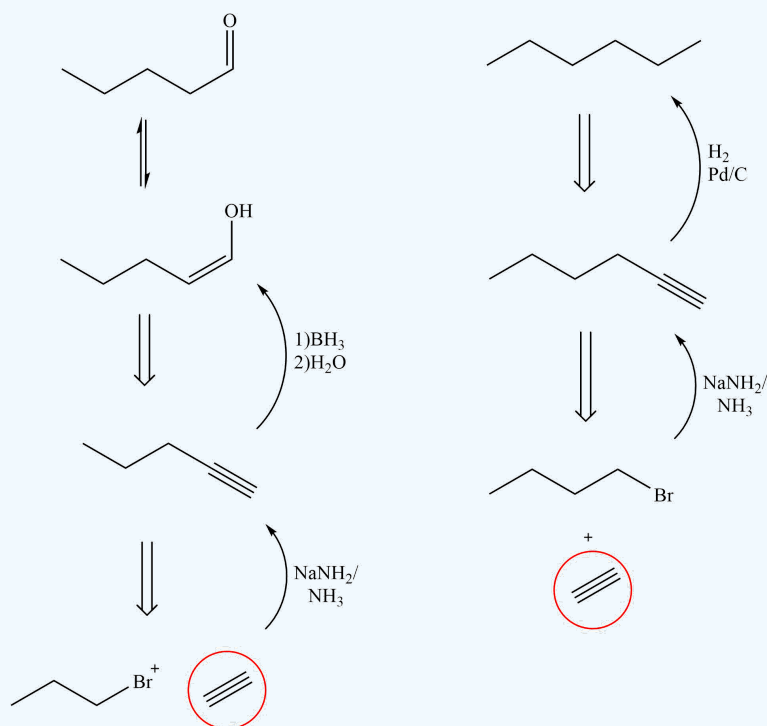**2.** Starting with acetylene and any alkyl halides propose a synthesis to make

a) pentanal

b) hexane.

**Answer**

**1.**



**2.**

## CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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